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Stereoselective synthesis of quaternary α-amino acids. Part 1: Acyclic compounds

Carlos Cativiela * and María Dolores Díaz-de-Villegas ‡

Department of Organic Chemistry, ICMA, Universidad de Zaragoza-CSIC, 50009 Zaragoza, Spain

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Contents

1. Introduction

Construction of novel peptidic sequences with tailor-made enhanced properties with respect to natural active peptides and proteins is the ultimate, and one of the most challenging, goals in biomimetic research. In recent years, therefore, the *de novo* design of peptides and proteins with a high propensity to fold with predetermined secondary and tertiary structures has rapidly become a subject of major interest and importance in the area of bioorganic chemistry,[1–10] as the introduction of conformational constraints into peptides may provide useful information on their bioactive conformation and result in beneficial physiological effects. Among the variety of non-coded amino acids used to optimise the biological

* Corresponding author. E-mail: cativiela@posta.unizar.es

† A list of abbreviations used in this report is given in Appendix A.

‡ E-mail: loladiaz@posta.unizar.es

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properties of bioactive peptides, α-alkyl α-amino acids have played a special role in the design of peptides with enhanced properties.[11–25]

Structure stabilisation in peptides by the incorporation of non-coded amino acid residues possessing specific conformational preferences for inducing particular conformations when inserted into a polypeptidic chain is mainly due to severe restrictions of the rotational freedom around their N–C(α) and C(α)–C=O bond. α-Alkyl α-amino acids[26–34] have been shown to impart well-defined conformational constraints to a peptide backbone; it has been shown, for example, that the achiral α-methylalanine (Aib) strongly prefers folded conformations, preferentially inducing helical secondary structures of either the 3_{10}- or α-helical type.[35–42] Chiral isovaline (Iva) seems to be more versatile and is able to achieve extended conformations in addition to showing behaviour similar to that of α-methylalanine residues.[43–48] α-Methylvaline [(α-Me)Val] residues are strong β-turn and right-handed helix conformers that are able to induce the same helicity as that of C^{α}-monosubstituted protein amino acids.[49–55] α-Methylphenylalanine [(α-Me)Phe] is an efficient β-turn and helix former, much stronger than its non-methylated parent compound phenylalanine, and in general the relationship between the chirality of α-methylphenylalanine and the handedness of the helix is opposite to that exhibited by protein amino acids[56–60] and the same is true for α-methylleucine [(α-Me)Leu].[61,62] Finally, α-methylserine [(α-Me)Ser] seems to be a promising residue in the design of peptides presenting a well-defined and specific conformation.[63–65]

Moreover, these α-alkylamino acids are known to be powerful enzyme inhibitors. Evidence for this is provided, for example, by the inhibition of aromatic acid decarboxylase by α-methyldopa,[66] the fact that α-methyltryptophan [(α-Me)Trp] is a substrate for tryptophan hydrolase[67] and its 5-hydroxy derivative is a potent inhibitor, in vivo, of tyrosine hydrolase,[68] or the competitive inhibition of aspartate amino transferase by α-methylaspartic acid [(α-Me)Asp].[69]

Recent reviews in the literature have covered the diastereoselective syntheses of various kinds of amino acids. In 1989 the splendid monograph by Williams[70] collected the existing approaches to the synthesis of amino acids, and this was complemented in 1994 by the work of Duthaler[71] covering new approaches to these compounds but excluding methods for enantioselective preparation of α-substituted quaternary α-amino acids. In 1996 Seebach et al. published their review on self-regeneration of stereocentres, a part of which was dedicated to alkylation of α-amino acids to produce α-alkylamino acids by application of this synthetic principle[72] and, in addition, an article by Wirth was published in 1997 that described some new strategies to α-alkylated α-amino acids.[73]

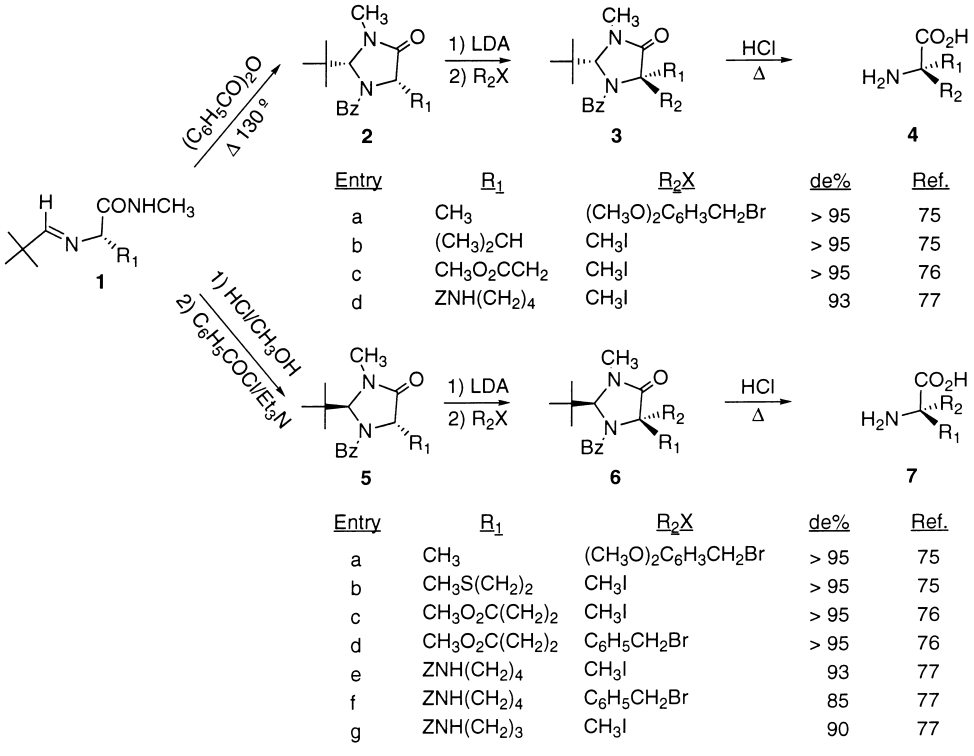
The present review covers the literature related to the synthesis of α-substituted quaternary α-amino acids with an acyclic backbone skeleton. Cycloaliphatic quaternary α-amino acids or heterocyclic quaternary α-amino acids are not included as the literature on this subject will be covered in Part 2 of this review.

2. Diastereoselective alkylation of α-amino acids. Self-reproduction of chirality

α-Amino acids can be α-alkylated stereoselectively with retention or inversion of configuration through *cis*- or *trans*-imidazolidinones **2** and **5**, respectively, without any external chiral auxiliary in a synthetic route developed by Seebach and called self-reproduction of the centre of chirality.

In order to obtain *cis*- or *trans*-imidazolidinones, methyl or ethyl esters of amino acid hydrochlorides were converted into *N*-methyl amides that, by condensation with pivalaldehyde and subsequent cyclisation of the obtained Schiff bases **1**, afforded either *cis*- or *trans*-imidazolidinones as the major compounds depending on the reaction conditions.[74] A simple recrystallisation afforded the desired starting material

in optically pure form. Deprotonation of imidazolidinones with lithium diisopropylamide (LDA) to give non-racemic lithium enolates, followed by addition of the appropriate electrophile, yielded α-alkylamino acid precursors **3** or **6** with a high stereoselectivity. In order to obtain the free α-alkylamino acid **4** and **7**, rather severe hydrolysis is required in concentrated acid at 175–180°C in a sealed tube, a factor that limits this synthetic methodology to amino acids without acid-labile substituents (Scheme 1).



Entry	R_1	R_2X	de%	Ref.
a	CH_3	$(CH_3O)_2C_6H_3CH_2Br$	> 95	75
b	$(CH_3)_2CH$	CH_3I	> 95	75
c	$CH_3O_2CCH_2$	CH_3I	> 95	76
d	$ZNH(CH_2)_4$	CH_3I	93	77

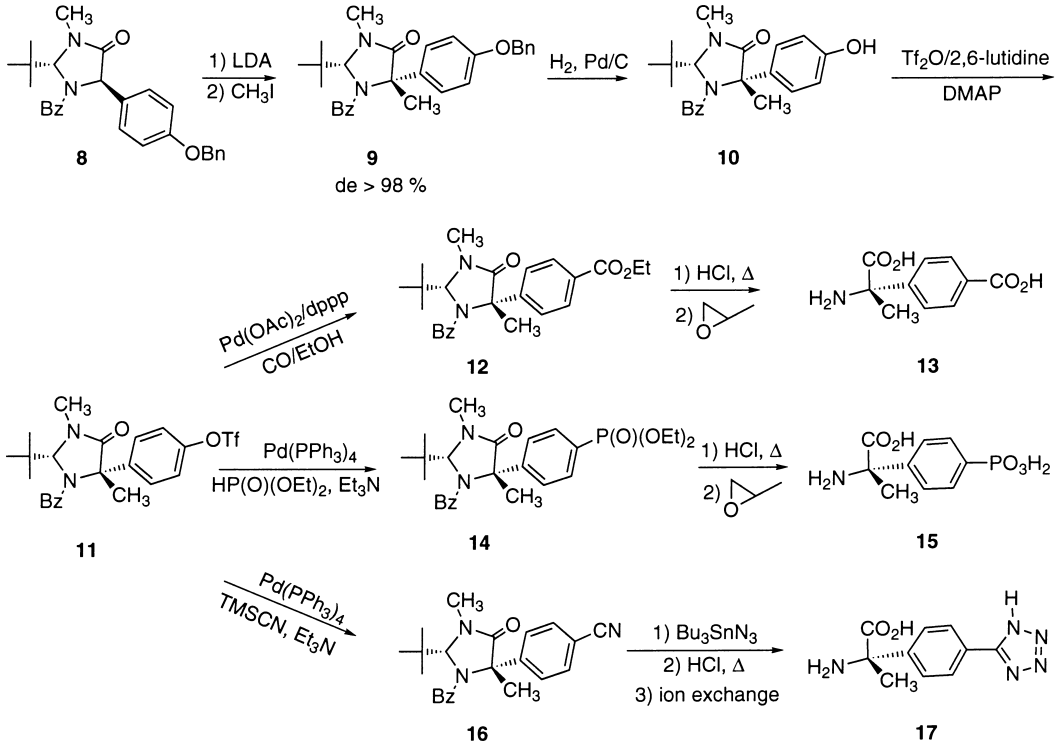
Entry	R_1	R_2X	de%	Ref.
a	CH_3	$(CH_3O)_2C_6H_3CH_2Br$	> 95	75
b	$CH_3S(CH_2)_2$	CH_3I	> 95	75
c	$CH_3O_2C(CH_2)_2$	CH_3I	> 95	76
d	$CH_3O_2C(CH_2)_2$	$C_6H_5CH_2Br$	> 95	76
e	$ZNH(CH_2)_4$	CH_3I	93	77
f	$ZNH(CH_2)_4$	$C_6H_5CH_2Br$	85	77
g	$ZNH(CH_2)_3$	CH_3I	90	77

Scheme 1.

This general and elegant asymmetric synthesis of α-alkylamino acids has been applied by Seebach and co-workers to the synthesis of a wide variety of highly valuable compounds such as both enantiomers of α-methyldopa[75] from (*S*)-alanine, (*S*)-α-methylvaline[75] from (*S*)-valine, (*R*)-α-methylmethionine[75] from (*S*)-methionine, (*S*)-α-methyl aspartic acid[76] from (*S*)-aspartic acid, (*R*)-α-methyl and (*S*)-α-benzyl glutamic acid[76] from (*S*)-glutamic acid, (*R*)- and (*S*)-α-methyl and (*R*)-α-benzyllysine[77] from (*S*)-lysine, (*R*)-α-methylornithine[77] from (*S*)-ornithine and, more recently, to the stereoselective synthesis of (*S*)-α-methyl-4-carboxyphenylglycine **13**,[78,79] (*S*)-α-methyl-4-phosphonophenylglycine **15**,[79] and (*S*)-α-methyl-4-(tetrazol-5-yl)phenylglycine **17**,[79] from (*R*)-4-hydroxyphenylglycine (Scheme 2).

cis-Imidazolidinones are less readily available than *trans*-imidazolidinones and so, in order to obtain both enantiomers of an α-alkylamino acid, it is more convenient to use both enantiomers of an α-amino acid when possible, as described by Hruby et al.[80] for the synthesis of all the isomers of α,β-dimethylphenylalanine from (*S*)- and (*R*)-alanine *N*-methylamide.

In this case, the authors observed kinetic resolution when an equivalent of racemic (1-bromoethyl)benzene was used as the electrophile, and a 1:3 mixture of the two possible stereoisomers on the stereogenic carbon of the side chain at C_5 was obtained on alkylation of both *trans*-imidazolidinones. By using a large (3-fold) excess of (1-bromoethyl)benzene, high overall yields of a mixture 7.7/92.3 of (*S*,*S*)-imidazolidinones **20** and **21** from the (*S*,*S*)-imidazolidinone **18**, or 3/97 of (*R*,*R*)-imidazolidinones



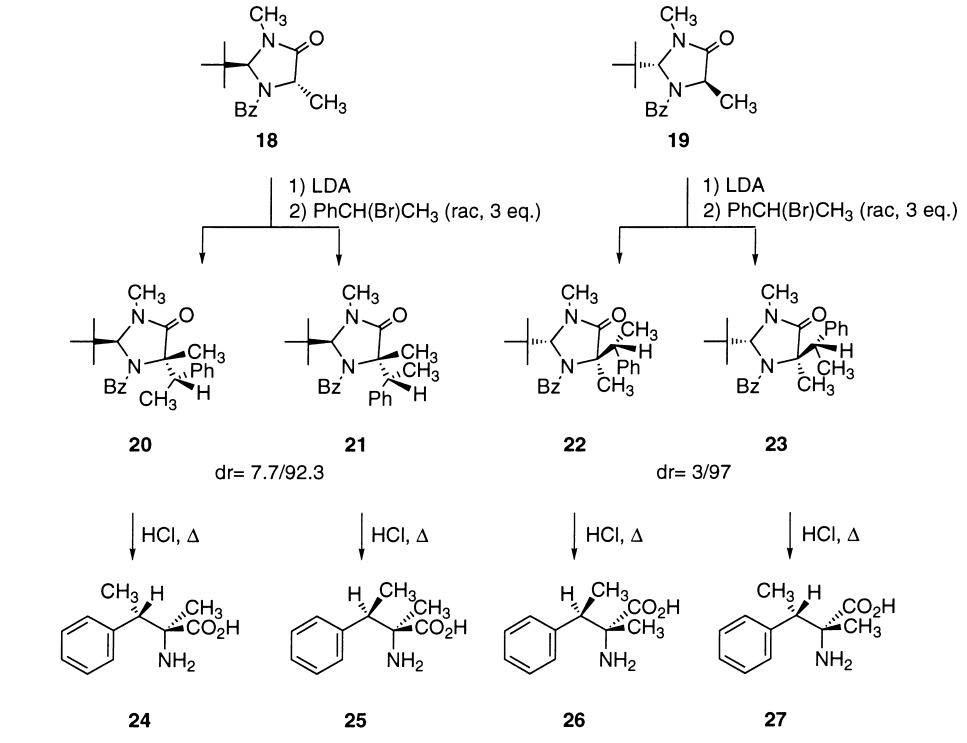
Scheme 2.

22 and **23** from the (*R*,*R*)-imidazolidinone **19**, of the two possible stereoisomers on $C_{5\alpha}$ was obtained. Hydrolysis of each of the four enantiomerically pure alkylated imidazolidinones afforded the corresponding four diastereoisomers of α,β-dimethylphenylalanine **24**–**27** (Scheme 3).

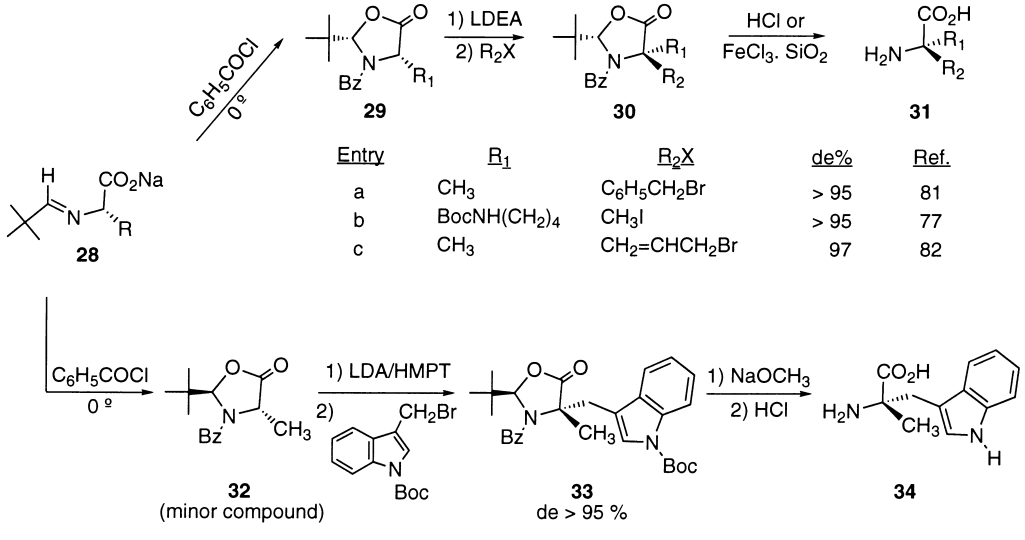
Alternatively, sodium salts of α-amino acids can be condensed with pivalaldehyde to give Schiff bases that, upon treatment with benzoyl chloride in dichloromethane at or below room temperature, were cyclised to afford oxazolidinones of *cis* configuration **29** in a highly diastereoselective manner. In this case LDA is not a good base to deprotonate oxazolidinones and lithium diethylamide (LDEA) was used in order to obtain high yields of the alkylated products **30** by treatment with an electrophile. The free amino acid can be obtained under much milder conditions that those necessary for imidazolidinones, i.e. 6 N HCl under reflux conditions and in the presence of $FeCl_3 \cdot SiO_2$, giving more simple access to α-alkyl amino acids than for the analogous imidazolidinones. The following amino acids have been obtained using this synthetic protocol: (*R*)-α-methylphenylalanine[81] from (*S*)-alanine, (*S*)-methyllysine[77] from (*S*)-N^6-Boc-lysine, and (*S*)-α-allylalanine[82] from (*S*)-alanine (Scheme 4). (*S*)-α-Methyltryptophan **34**,[77] has been obtained from (*S*)-alanine through *trans*-oxazolidinone **32** (Scheme 4).

In order to obtain (*R*)-α-methyltryptophan Zhang et al.[83] synthesised the *cis*-oxazolidinone by cyclisation of the Schiff base of (*R*)-tryptophan and pivalaldehyde in the presence of ethyl chloroformate. Direct methylation of this compound can be achieved without protection of the indole moiety by treatment with two equivalents of LDA followed by one equivalent of methyl iodide. Under these conditions the reaction occurs only at the α carbon in good yield and with excellent diastereoselectivity (>98%). Final hydrolysis in refluxing 6 N HCl furnished the amino acid in good yield (Scheme 5).

Hirschmann and co-workers[84,85] obtained several α-(3,3-dimethylallyl)amino esters through the Seebach protocol by using allyl chloroformate to induce cyclisation to furnish *cis*-oxazolidinones. Alkylation of *cis*-oxazolidinones derived from (*R*)-phenylalanine, (*R*)-leucine and (*R*)-valine with 1-

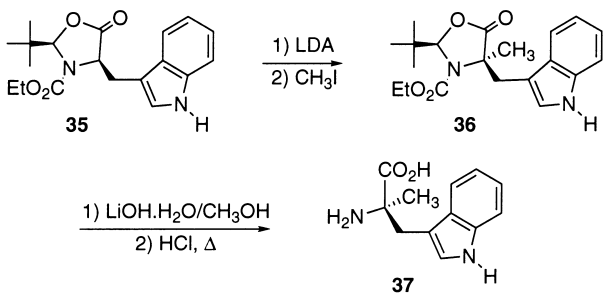


Scheme 3.

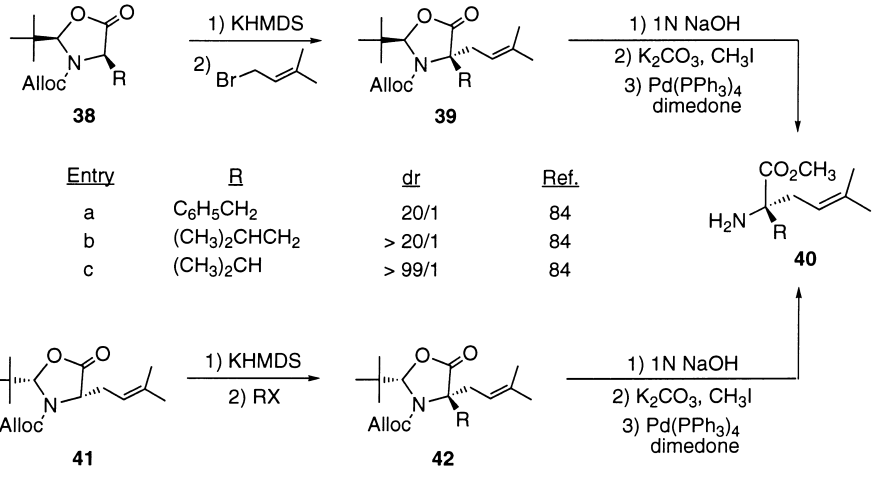


Scheme 4.

bromo-3-methyl-2-butene afforded the corresponding oxazolidinones with >95% diastereoselectivity.[84] Alternatively, alkylation of *cis*-oxazolidinones derived from (*S*)-prenylglycine with several electrophiles provided the alkylated oxazolidinones with a very high diastereoselectivity (>95%).[85] Hydrolysis of these compounds to give the final amino esters was performed in several steps: basic hydrolysis to the alloc-protected amino acids, transformation of the amino acids into the corresponding amino esters and removal of the alloc protecting group with a catalytic amount of $Pd(PPh_3)_4$ (Scheme 6).



Scheme 5.



Entry	R	dr	Ref.
a	$C_6H_5CH_2$	20/1	84
b	$(CH_3)_2CHCH_2$	> 20/1	84
c	$(CH_3)_2CH$	> 99/1	84

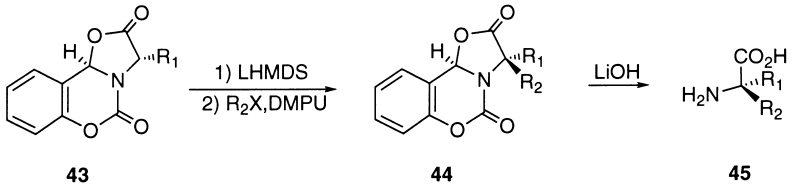
Entry	RX	dr	Ref.
a	$C_6H_5CH_2Br$	> 99/1	85
b	4-$BnOC_6H_4CH_2Br$	> 99/1	85
c	$BnOCH_2I$	> 99/1	85
d	$I(CH_2)_4I$, NaN_3	> 99/1	85

Scheme 6.

A tricyclic version of Seebach's oxazolidinones was developed by Zydowsky et al.[86] and this started from *trans*-oxazolidinones **43** derived from condensation of amino acids with salicylaldehyde and triphosgene under anhydrous conditions. Alkylation of these compounds with alkyl halides using lithium bis(trimethylsilyl)amide as a base proceeded in good yields and, in most cases, excellent diastereoselectivity with predominant, if not exclusive, retention of configuration. Hydrolysis of the alkylated oxazolidinones with lithium hydroxide in aqueous dioxane afforded the free amino acids **45** in good to excellent yields (Scheme 7).

Imidazolidinones and oxazolidinones, after deprotonation, can both react with carbonyl compounds as electrophiles to afford the corresponding hydroxyalkylation compounds, and in some cases by-products arising from 1,4-migration of the benzoyl group to the hydroxyl group are also obtained. In the addition of aldehydes to chiral enolates four diastereoisomers can be formed, although hydroxyalkylation of imidazolidinones and oxazolidinones derived from methionine with acetaldehyde cleanly afforded a single diastereoisomer.[87] Desulfurisation and hydrolysis of oxazolidinone yielded (2*S*,3*R*)-2-ethylthreonine **48**. Several attempts to hydrolyse imidazolidinone with 6 N HCl at 150°C in a sealed tube afforded tetrahydrothiophene **49** (Scheme 8).

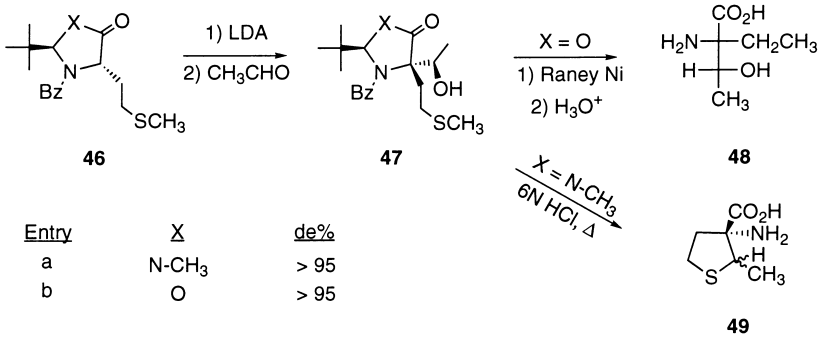
The imidazolidinone derived from methionine has been converted to the vinylglycine derivative **50**



43 44 45

Entry	R_1	R_2X	dr
a	C_6H_5	$CH_2=CHCH_2Br$	> 31/1
b	C_6H_5	CH_3CH_2I	31/1
c	C_6H_5	CH_3I	8/1
d	$(CH_3)_2CH$	$CH_2=CHCH_2Br$	> 31/1
e	$(CH_3)_2CH$	CH_3I	5/1

Scheme 7.



46 47 48 49

Entry	X	de%
a	N-CH_3	> 95
b	O	> 95

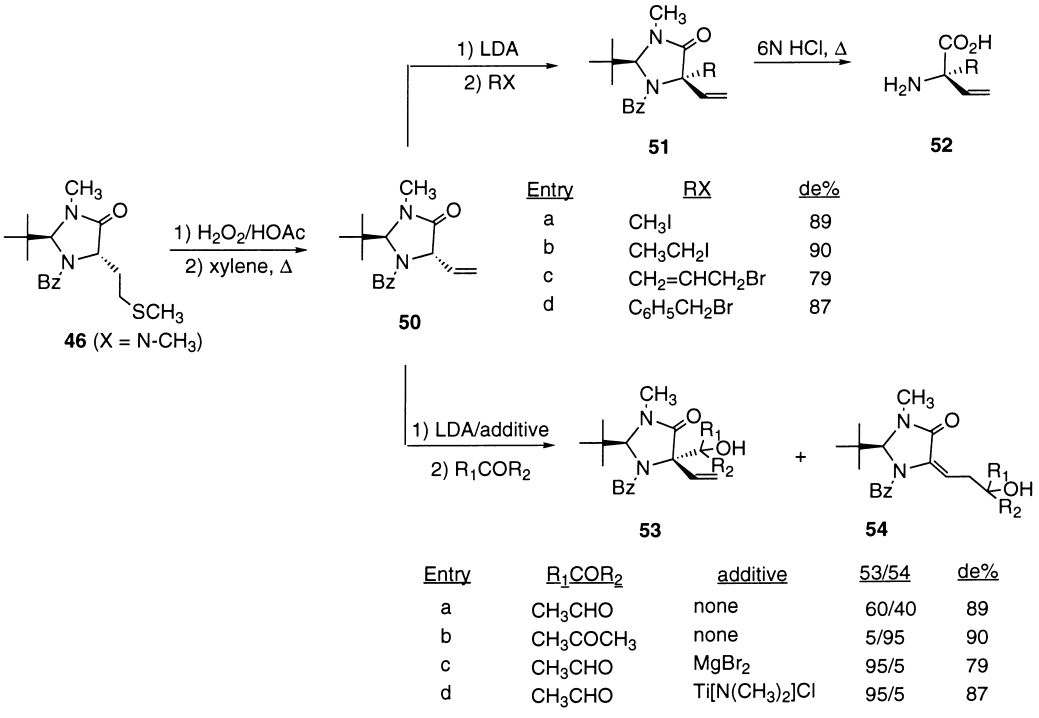
Scheme 8.

by oxidation and subsequent pyrolysis of the sulfoxide.[87] Deprotonation of this compound followed by reaction with electrophiles cleanly afforded α-alkylation compounds **51** when alkyl halides were used as electrophiles.[88] Nevertheless, the use of carbonyl compounds as electrophiles[87] led to hydroxyalkylation in the α (**53**) and γ (**54**) positions (acetaldehyde), or exclusively in the γ (**54**) position (acetone) unless magnesium or titanium enolates were generated in the reaction medium prior to the addition of the acetaldehyde; in this case α-alkylation compounds were preferentially obtained (Scheme 9).

Hydrolysis of alkyl vinyl imidazolidinones **51** in 6 N HCl at 100°C in a sealed tube afforded the corresponding α-alkylated vinylglycines **52**. These compounds can be also obtained through α-alkylated imidazolidinones **55**, derived from methionine, by oxidation and subsequent pyrolysis of the sulfoxide[88] (Scheme 10).

Alkylation of imidazolidinones and oxazolidinones occurs *anti* to the C_2 substituent. This stereochemical behaviour has been explained by Seebach et al. in the case of imidazolidinones by taking into account the steric requirements of the C_2 substituent, which hinders the approach to the *cis*-face and favours the attack of electrophiles at the *anti*-face, as well as invoking stereoelectronic effects that lower the transition-state energy of the approach of the electrophile from the face opposite to the C_2 substituent. Moreover, the aggregation state of the reagent, as well as the chelation of the metal, may play an important role in controlling the stereochemical course of the reaction and must also be taken into account.

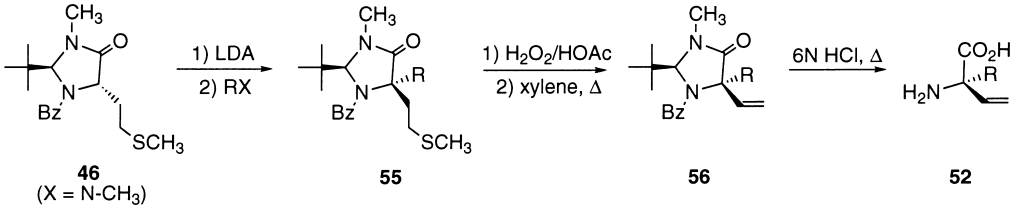
Chiral oxazolidinones obtained from amino acids and aromatic aldehydes (benzaldehyde or 2,3-dichlorobenzaldehyde) are also versatile intermediates in the synthesis of α-alkyl amino acids following the 'principle of self-reproduction of chirality centres' and require milder hydrolysis conditions that those used to deprotect pivalaldehyde acetals. *cis*-Oxazolidinones or *trans*-oxazolidinones were deprotonated



Entry	RX	de%
a	CH_3I	89
b	CH_3CH_2I	90
c	$CH_2{=}CHCH_2Br$	79
d	$C_6H_5CH_2Br$	87

Entry	R_1COR_2	additive	53/54	de%
a	CH_3CHO	none	60/40	89
b	CH_3COCH_3	none	5/95	90
c	CH_3CHO	$MgBr_2$	95/5	79
d	CH_3CHO	$Ti[N(CH_3)_2]Cl$	95/5	87

Scheme 9.

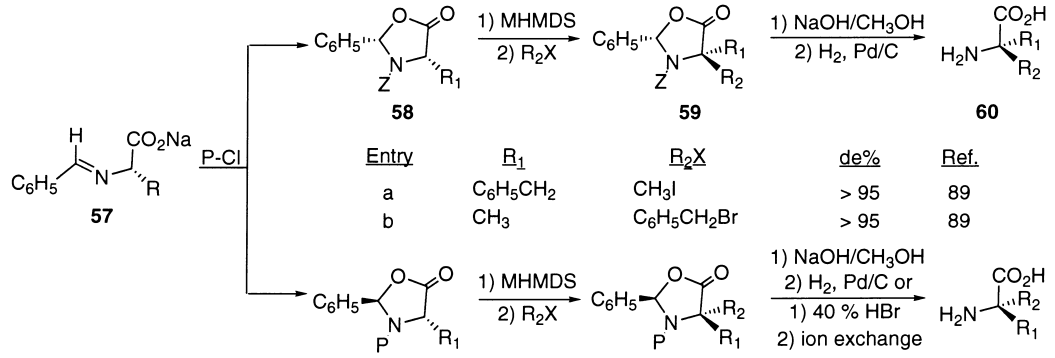


Entry	RX	de%
a	CH_3I	95
b	CH_3CH_2I	95
c	$(CH_3)_2CHI$	93

Scheme 10.

with potassium or lithium hexamethyldisilylamide (KHMDS or LHMDS) and neutralised with an electrophile to afford the corresponding alkylation compound as a single diastereoisomer. The ratio of *cis*- to *trans*-oxazolidinones obtained in the cyclisation of sodium salts of Schiff bases derived from amino acids with acyl chlorides depends on the nature of the acyl chloride used. The use of benzyloxycarbonyl chloride leads preferentially to *N*-benzyloxycarbonyloxazolidinones of *cis*-configuration, whereas the use of benzoyl chloride preferentially gives *N*-benzoyloxazolidinones of *trans*-configuration. Depending on the *N*-protecting group, the free alkyl amino acid is obtained by hydrolysis of the oxazolidinone with sodium hydroxide and hydrogenolysis of the carbobenzoxyl group (P=Z), or by hydrolysis with 40% HBr at reflux (P=Bz). This approach has been applied to the synthesis of both enantiomers of α-methylphenylalanine[89] from (*S*)-phenylalanine or (*S*)-alanine, several (*S*)-α-alkyl aspartic acids[90] from the corresponding (*S*)-mino acid, conveniently protected (*R*)-α-methylaspartic acid and (*R*)-α-methylleucine[91] from (*R*)-alanine, conveniently protected (*R*)-α-methylglutamic from (*R*)-alanine by Michael addition[91] and, more recently, (*R*)-allylmethionine[92] from (*R*)-methionine and (*R*)- or (*S*)-2-

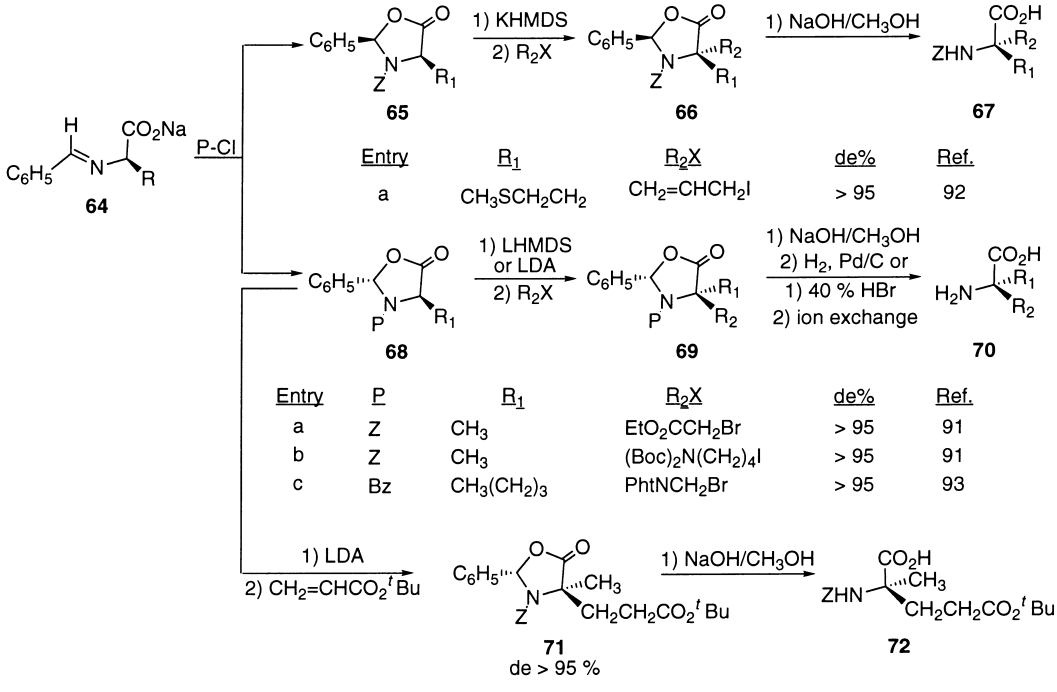
aminomethylnorleucine from (*R*)- or (*S*)-norleucine, respectively[93] (Schemes 11 and 12). In each case the electrophile entered from the side opposite the aryl group.



Entry	R_1	R_2X	de%	Ref.
a	$C_6H_5CH_2$	CH_3I	> 95	89
b	CH_3	$C_6H_5CH_2Br$	> 95	89

Entry	P	R_1	R_2X	de%	Ref.
a	Z	$C_6H_5CH_2$	CH_3I	> 95	89
b	Bz	CH_3	EtO_2CCH_2Br	> 95	90
c	Bz	$C_6H_5CH_2$	EtO_2CCH_2Br	> 95	90
d	Bz	$(CH_3)_2CH$	EtO_2CCH_2Br	> 95	90
e	Bz	$CH_3SCH_2CH_2$	EtO_2CCH_2Br	> 95	90
f	Bz	$CH_3(CH_2)_3$	$PhtNCH_2Br$	> 95	93

Scheme 11.



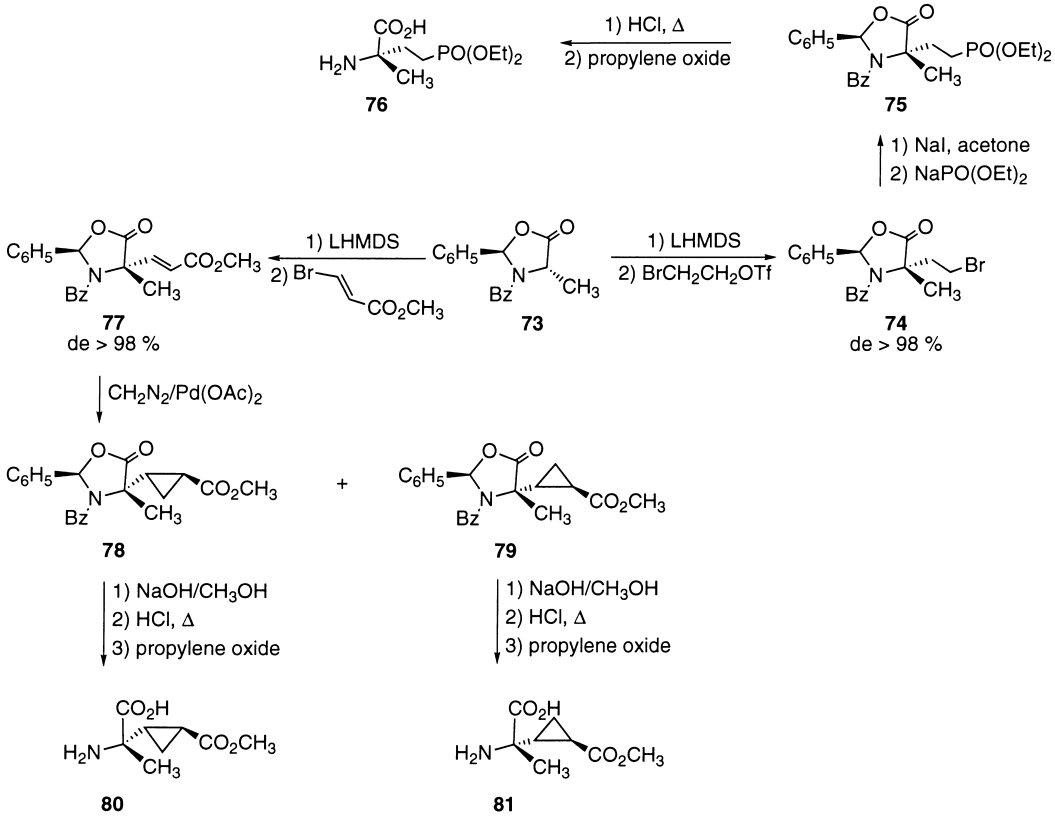
Entry	R_1	R_2X	de%	Ref.
a	$CH_3SCH_2CH_2$	$CH_2=CHCH_2I$	> 95	92

Entry	P	R_1	R_2X	de%	Ref.
a	Z	CH_3	EtO_2CCH_2Br	> 95	91
b	Z	CH_3	$(Boc)_2N(CH_2)_4I$	> 95	91
c	Bz	$CH_3(CH_2)_3$	$PhtNCH_2Br$	> 95	93

Scheme 12.

This methodology has also been applied to the synthesis of two isotype-selective antagonists of glutamate receptors.[94] Alkylation of chiral oxazolidinone **73**, derived from (*S*)-alanine, with 2-bromoethyltriflate, followed by conversion of the resulting bromide into the diethylphosphite through an

intermediate iodide and hydrolysis, provided (*S*)-2-amino-2-methyl-4-phosphonobutyric acid, (*S*)-MAP4 **76** in high overall yield. Michael addition of the enolate obtained from oxazolidinone **73** to methyl *E*-3-bromopropenoate, followed by elimination of HBr, afforded α,β-unsaturated ester **77**. Treatment of this ester with diazomethane led to a mixture of diastereomeric oxazolidinones **78** and **79** in a 3:4 ratio, and these compounds were separated by column chromatography. From the isolated compounds two enantiomerically pure 2-methyl-2-carboxycyclopropylglycines were obtained (Scheme 13).



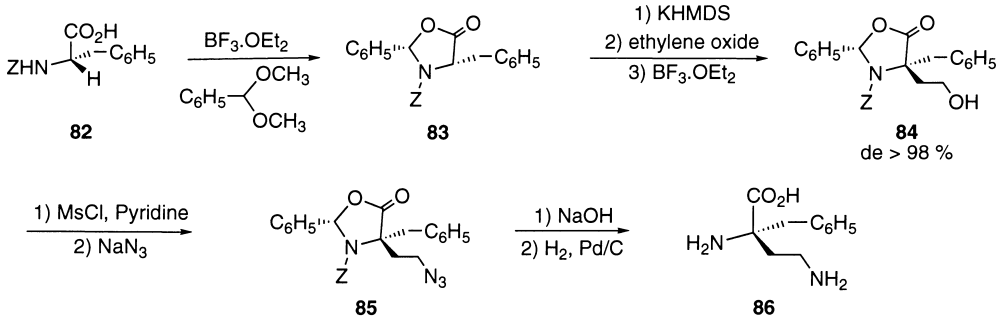
76 **75** **77** **73** **74** **78** **79** **80** **81**

Scheme 13.

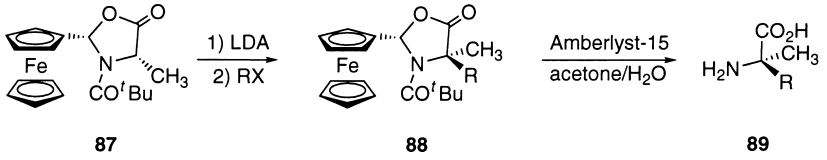
The use of benzaldehyde dimethylacetal instead of benzaldehyde to obtain oxazolidinones has proven to be a better procedure to obtain the oxazolidinone derived from *N*-benzyloxycarbonylphenylalanine as a twofold improvement in the yield is observed.[95] Neutralisation of the enolate generated from this oxazolidinone with ethylene oxide procedeed with high efficiency. From this alkylated compound, (*R*)-benzyl-2,4-diaminobutyric acid has been obtained through standard procedures (Scheme 14).

In the same context, Davies[96,97] has developed a practical route to (*R*)-α-methylamino acids from (*S*)-alanine via *cis*-*N*-pivaloyl-1,3-oxazolidin-5-one **87** derived from ferrocene carboxaldehyde. Alkylation of the lithium enolate of this compound, obtained by deprotonation with LDA, with an appropriate alkyl bromide led to the corresponding alkylation compound. This compound arises from the attack of the electrophile opposite to the ferrocenyl group and is obtained as a single diastereoisomer in good yield. Hydrolysis of compound **88** under mild conditions (amberlyst-15) released the free amino acid, ferrocene carboxaldehyde and pivalic acid (Scheme 15).

The principle of self-reproduction of chirality has also been applied to β-heterosubstituted amino acids such as serine,[98–100] threonine[99,101,102] and cysteine.[103,104] In these cases, in order to avoid undesired β-



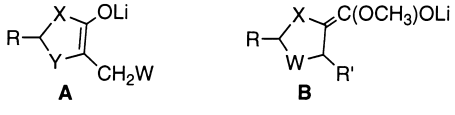
Scheme 14.



Entry	RX	de%	Ref.
a	$C_6H_5CH_2Br$	> 98	96, 97
b	$CH_2=CHCH_2Br$	> 96	97
c	$CH_3CH=CHCH_2Br$	92	97
d	2-$CH_3C_6H_4CH_2Br$	96	97
e	$C_6H_5CH=CHCH_2Br$	> 98	97
f	2-naphthyl-CH_2Br	> 98	97
g	*N*-Boc-3-indolyl-CH_2Br	96	97
h	$NCCH_2Br$	92	97

Scheme 15.

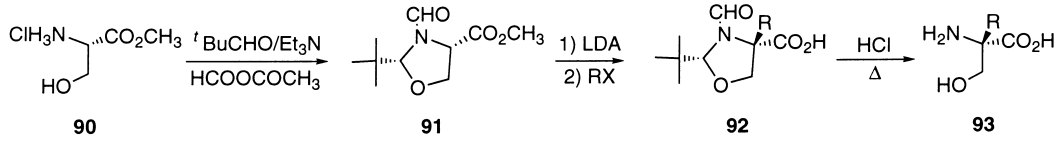
elimination reactions as the heteroatom W is tied into the heterocyclic ring, alkylation does not occur through enolates of the type **A** with an endocyclic double bond but through enolates of the type **B** with an exocyclic double bond (Scheme 16).



Scheme 16.

The methyl ester hydrochloride of (*S*)-serine reacted with pivalaldehyde/triethylamine to afford *cis*- and *trans*-methyl 2-*tert*-butyloxazolidine-4-carboxylate, which was formylated to afford *cis*-**91** as the major diastereoisomer. Deprotonation of this compound with lithium diisopropylamide (LDA), followed by reaction with an electrophile, usually in the presence of a cosolvent such as hexamethylphosphotriamide (HMPA) or dimethylpropyleneurea (DMPU), gives the α-alkylated compounds **92** in satisfactory yields and with excellent diastereoselectivity. In this case, the attack of the electrophile occurs almost exclusively *anti*- to the *tert*-butyl residue. The hydrolysis of the alkylated oxazolidines to α-alkylserines has been achieved by refluxing in 6 N HCl (Scheme 17).

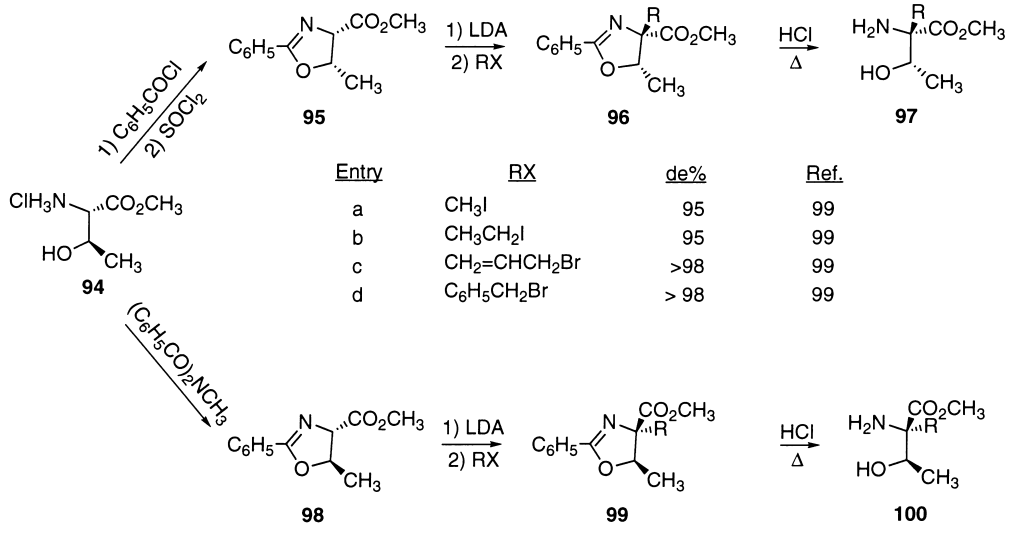
L-Threonine has been converted into α-alkylallothreonines of both senses of chirality through 2-phenyloxazolines of *cis* and *trans* configuration, **95** and **98** respectively, which can be stereoselectively obtained.[99] Deprotonation of oxazolines with lithium diisopropylamide (LDA) generates the enolates, which react with reactive electrophiles to afford the corresponding alkylation compounds **96** and **99** with high diastereoselectivity. The electrophile approaches the enolate from the face *anti* to the threonine



Entry	RX	de%	Ref.
a	CH_3I	> 98	99
b	CH_3CH_2I	> 98	99
c	$CH_2=CHCH_2I$	>98	99
d	$C_6H_5CH_2Br$	97	99
e	C_6H_5COCl	> 95	99
f	$CH_3(CH_2)_{16}COCl$	> 98	100

Scheme 17.

methyl residue and the presence of a cosolvent greatly improves the yield. The free amino acids resulting from Cα-alkylation, (2*S*,3*S*)- and (2*R*,3*R*)-2-alkylallothreonines, are obtained in high yields by refluxing the corresponding oxazoline with 6 N HCl followed by ion exchange chromatography (Scheme 18).



Entry	RX	de%	Ref.
a	CH_3I	95	99
b	CH_3CH_2I	95	99
c	$CH_2=CHCH_2Br$	>98	99
d	$C_6H_5CH_2Br$	> 98	99

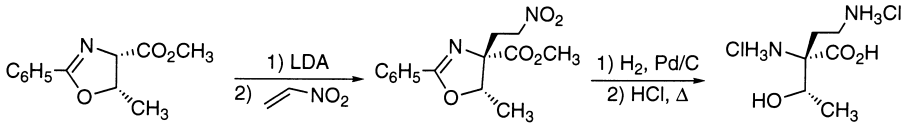
Entry	RX	de%	Ref.
a	CH_3I	93	99
b	CH_3CH_2I	95	99
c	$(CH_3)_2CHCH_2CH_2Br$	>98	99
d	$(CH_3)_2CHI$	> 98	99
e	C_6H_5COCl	> 95	99

Scheme 18.

The use of carbonyl compounds as electrophiles has also been tested, although hydrolysis to the final amino acids has not been performed. Both oxazolidine **91** and oxazoline **95** react with acetone through an intermediate enolate to give a single diastereoisomer.[98,99,101] On addition of benzadehyde to oxazolidine **91**, one of the four possible diastereoisomers is obtained preferentially,[98] and oxazoline **95** adds benzaldehyde to afford only two of the four possible diastereoisomers, i.e. those that are epimeric at the chiral carbon on the newly introduced side chain.[99,101]

(2*S*,3*S*)-2-Aminoethylallothreonine **102** has been obtained by the addition of the lithium enolate

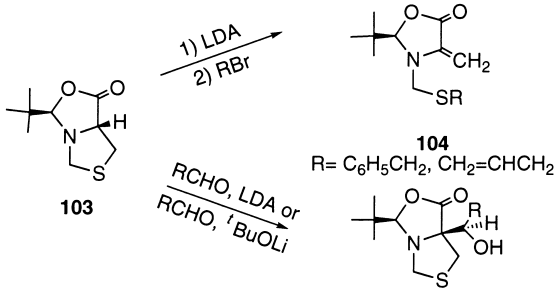
generated from the oxazoline **95** to nitroethene,[102] as conjugate addition occurs in high yield and with excellent diastereoselectivity. Hydrogenation and hydrolysis of the Michael adduct leads to the free amino acid according to Scheme 19.



95 **101** de 95 % **102**

Scheme 19.

In the case of cysteine, β-elimination strongly competes with the formation of the enolate despite the sulfur atom being tied into a heterocyclic ring. Compound **104** is isolated from the reaction mixture even after short reaction times with base at −78°C and quenching with very reactive electrophiles. This undesired process can be avoided by addition of the starting bicyclic compound **103**, which is easily obtained from (*R*)-cysteine, formaldehyde and pivalaldehyde, to a solution of the aldehyde used as the electrophile and LDA or *tert*-butyllithium at −78°C. Of the four possible diastereomeric adducts, only one is usually formed with a high diastereoselectivity[103,104] (Scheme 20).

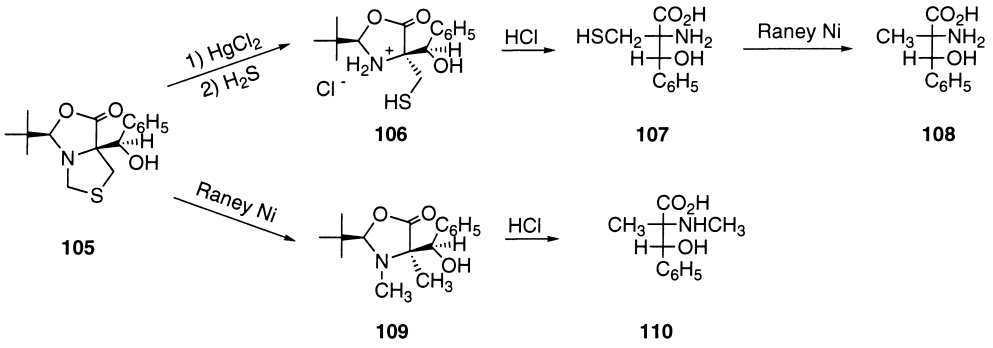


103 **104** R= $C_6H_5CH_2$, CH_2=$CHCH_2$ **105**

Entry	aldehyde	de%	Ref.
a	cinnamaldehyde	89	103
b	benzaldehyde	92	103
c	4-bromobenzaldehyde	82	103
d	anisaldehyde	96	103
e	piperonal	96	103
f	furfural	88	103
g	thenaldehyde	94	103
h	1-methylpyrrol-2-carbaldehyde	90	104
i	pyridin-3-carbaldehyde	65	104

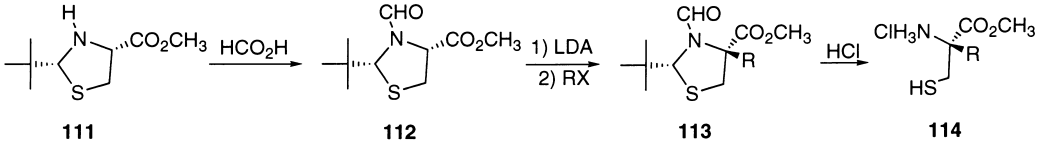
Scheme 20.

The alkylation compound obtained by the reaction with benzaldehyde has been used to exemplify the various possible transformations in α,α-dialkyl open-chain amino acids.[104] Cleavage of the ring containing the S atom, followed by acidic hydrolysis of the cyclic *N*,*O*-acetal, leads to the corresponding (2*R*,3*R*)-α-hydroxyalkylcysteine **107**, which on treatment with Raney nickel cleanly affords (2*R*,3*R*)-α-methyl-β-phenylserine. Alternatively, desulfurisation with Raney nickel followed by acidic hydrolysis affords *N*-methyl-(2*R*,3*R*)-α-methyl-β-phenylserine (Scheme 21). These results indicate that the attack has occurred with retention of the relative stereochemistry of substituents at Cα and with absolute topicity *si*, *si*.



Scheme 21.

Pattenden et al. have succeeded in alkylating (*R*)- or (*S*)-cysteine by a slight modification of the Seebach procedure.[105,106] *N*-Formylation of the thiazolidine **111**, derived from condensation of cysteine methyl ester hydrochloride and pivalaldehyde, led to the key reaction intermediate as a single *cis*-diastereoisomer. Deprotonation at −90°C with LDA in the presence of DMPU afforded the corresponding lithium enolate, which was quenched at −90°C with a range of reactive electrophiles to produce the corresponding 4-alkylthiazolidines **113** with excellent diastereoselectivity. Treatment with 5 M hydrochloric acid releases the hydrochloride salt of the 2-methyl-, 2-ethyl- or 2-benzylcysteine of the same configuration as the starting amino acid (Scheme 22).

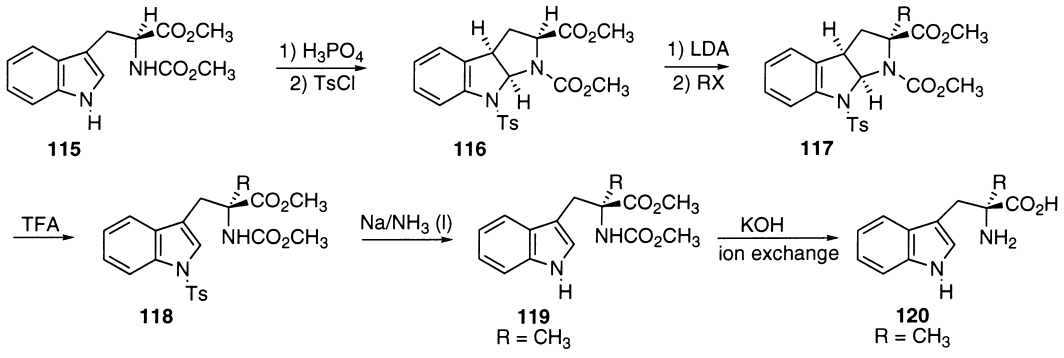


Entry	RX	de%	Ref.
a	CH_3I	> 95	105, 106
b	CH_3CH_2I	> 95	105
c	$C_6H_5CH_2Br$	> 95	105
d	$CH_2{=}CHCH_2Br$	> 95	105
e	$CH_3O_2CCH_2Br$	> 95	105

Scheme 22.

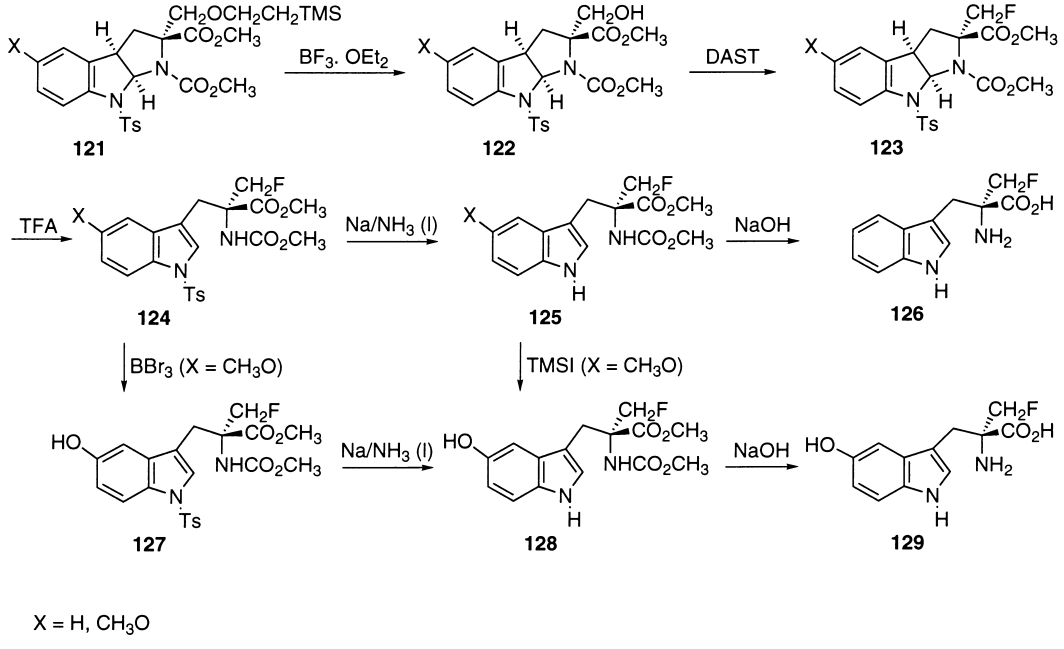
Crich at al. have developed a variation of the Seebach concept of 'self reproduction of chirality' based on the reactive nature of the indole group in tryptophan.[107,108] In this methodology, hexahydropyrrolo[2,3-*b*]indole, obtained from N_b-methoxycarbonyl-L-tryptophan methyl ester **115**, was protected by transformation into the *N*-tosyl derivative **116**. This compound can be deprotonated at −78°C with LDA to generate a lithium enolate that reacts with various electrophiles to give excellent yields of alkylated compounds in which the electrophile has entered from the *exo*-face of the enolate with complete diastereoselectivity. In this way different substituents could be introduced with retention of configuration. In order to regenerate the tryptophan ring, hexahydropyrroloindoles were stirred at room temperature in trifluoroacetic acid to release N_b-sulfonamido α-alkyltryptophan derivatives in excellent yields. In the case of the α-methyl compound, removal of the sulfonamide protecting group was achieved by treatment of **118** in refluxing liquid ammonia with sodium metal. Subsequent refluxing with potassium hydroxide led to complete deprotection (Scheme 23).

The same protocol, when applied to (*S*)-5-hydroxytryptophan, led to the corresponding α-alkyl derivatives[109] and, from hexahydropyrroloindoles **121**, Ames et al.[110] have developed enantiospecific syntheses of α-(fluoromethyl)tryptophan analogues (Scheme 24).



Entry	RX	de%	Ref.
a	CH_3I	> 98	107, 108
b	$C_6H_5CH_2Br$	> 98	107, 108
c	$CH_3SCH_2CH_2I$	> 98	107, 108
d	$CH_2{=}CHCH_2Br$	> 98	107, 108
e	EtO_2CCH_2Br	> 98	107, 108
e	$TMSCH_2CH_2OCH_2Cl$	> 98	107, 108

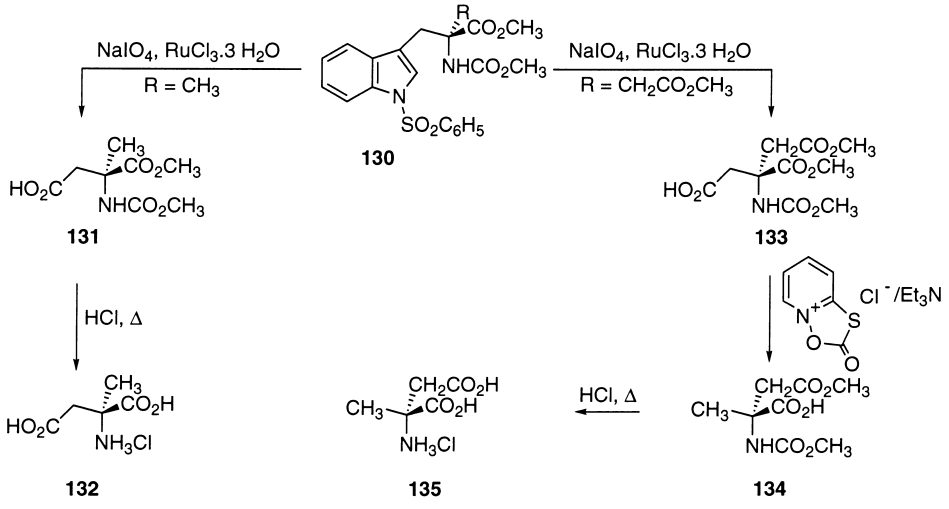
Scheme 23.



Scheme 24.

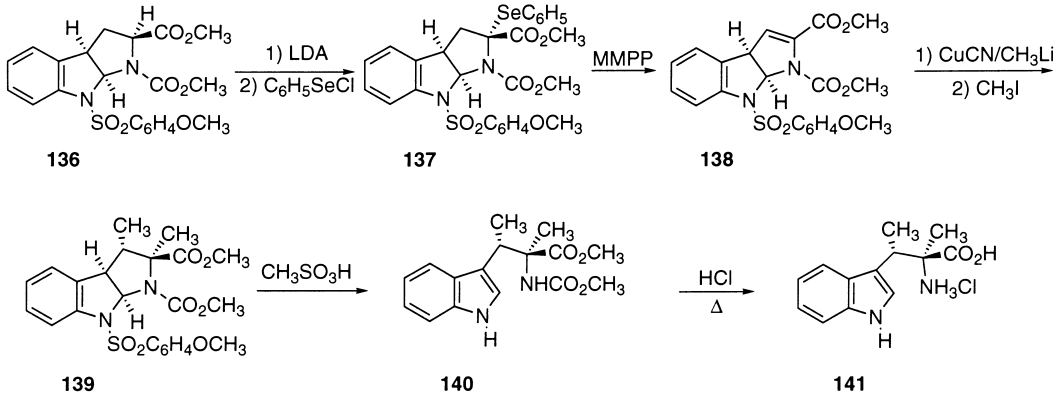
Both enantiomers of α-methylaspartic acid have been obtained from benzene sulfonamides **130**.[111] The (*S*)-enantiomer was obtained from the α-methyl compound by transforming the indole ring into a carboxylic acid moiety through an oxidative cleavage with sodium metaperiodate and ruthenium trichloride hydrate. The same procedure applied to an α-carbomethoxymethyl compound afforded a selectively protected tricarboxylic compound, which was decarboxylated to give (*R*)-α-methylaspartic acid (Scheme 25).

Quenching of the enolate generated from **136** and LDA with phenylselenylchloride afforded the



Scheme 25.

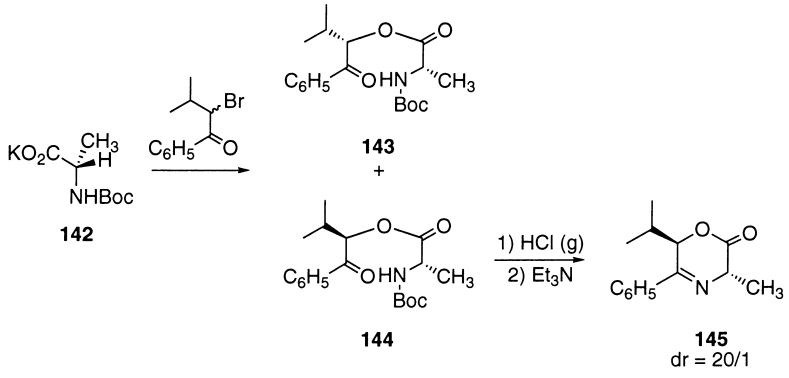
corresponding phenylselenide **137**, from which dehydroderivative **138** was obtained in nearly quantitative yield.[112] This intermediate was submitted to conjugate addition with several nucleophiles and the quenching of the enolate, obtained from the reaction of **138** with lithium dimethylcyanocuprate, with methyl iodide gave the double α,β-dimethylated adduct **139** as only one of the four possible diastereoisomers. Both conjugate addition and enolate trapping were found to have occurred from the *exo*-face. In this case, cycloreversion of the adduct to the tryptophan nucleus and desulfurisation could be achieved in a single step by treatment with methanesulfonic acid. Subsequent hydrolysis with 6 N HCl under reflux conditions allowed the synthesis of α,β-dimethyltryptophan as its hydrochloride salt (Scheme 26).



Scheme 26.

In a recent approach to this concept Nájera et al.[113] obtained the chiral oxazinone **145** by reaction of α-bromoisovalerophenone with the potassium salt of *N*-Boc-L-alanine. In the first instance, an equimolecular mixture of esters **143** and **144** was obtained, from which the (3*S*,6*R*) compound was isolated by flash chromatography. Treatment of compound **144** with hydrogen chloride in ethyl acetate, followed by treatment with base in the presence of molecular sieves, provided the chiral oxazinone **145** as a 1:20 mixture of diastereoisomers at C_3, from which the *trans*-diastereoisomer was isolated. The (3*S*,6*R*) chiral oxazinone has also been obtained as a single diastereoisomer by esterification of *N*-Boc-L-alanine with (*R*)-α-hydroxyvalerophenone and subsequent cyclisation as above. When the same procedure was applied to the (3*S*,6*S*) ester, a mixture of *cis–trans* oxazinones was obtained, but in this case epimerisation

at C_6 also occurred, a fact that limits the access to the oxazinone of *S* configuration at C_6 as a synthetic intermediate (Scheme 27).

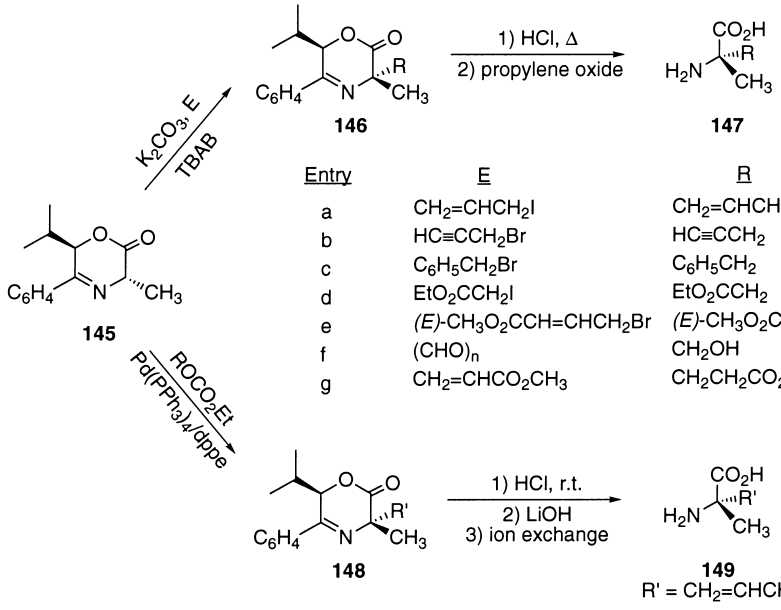


Scheme 27.

Reaction of oxazinone **145** with different electrophiles in the presence of potassium carbonate and tetra *n*-butylammonium bromide afforded the corresponding alkylated oxazinones in good yields and with good diastereoselectivities. It is also possible to perform alkylation of oxazinone **145** with allylic carbonates in the presence of $Pd(PPh_3)_4$ and 1,2-bis(diphenylphosphino)ethane as a catalyst. In this case, regioselective and stereoselective allylation of oxazinone took place and the diastereoisomer arising from the attack of the allylic carbonate in the less substituted position to the face of the enolate opposite to the isopropyl group was preferentially obtained. Final hydrolysis afforded α-methylamino acids in enantiomerically pure form (Scheme 28).

Oxazaborolidinones[114] have also been used as intermediates in the synthesis of chiral α-alkylamino acids. In this case the L-amino acid sodium salts were transformed into α-amidino carboxylates, which were treated with potassium phenyltrifluoroborate and trimethylsilylchloride to afford the corresponding oxazaborolidinone as a mixture of diastereoisomers. Slow evaporation of the solution afforded the less soluble diastereoisomer **151** with a high diastereoselectivity. Alkylation on trapping the enolate generated by treatment with base (potassium *tert*-butoxide or potassium hexamethyldisilylamide) at −78°C with allyl or benzyl halides gave the corresponding alkylated compounds with excellent diastereoselectivity. The adduct derived from the attack of the electrophile at the less hindered face, i.e. *syn*-face to fluoride, was obtained preferentially. Other alkylating agents, such as methyl or *n*-propyl iodide, showed less selective behaviour. Methanolysis to cleave the boron complex and amidine cleavage with ethylene diamine gave enantiomerically pure amino acids in good yields; in this way (*R*)-α-methylphenylalanine or (*R*)-α-methylvaline were obtained (Scheme 29).

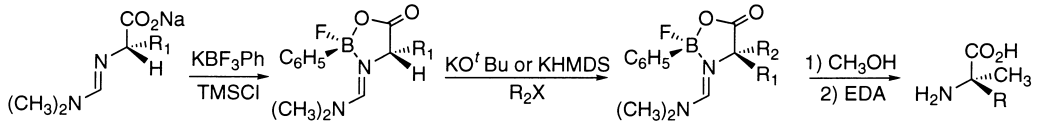
Chiral borane–amine adducts[115] have also proved to be potential intermediates for the asymmetric synthesis of α-methyl amino acids, allowing the synthesis of α-methyl amino acid derivatives from methyl (*S*)-*N*-benzyl-*N*-methylalaninate. Treatment of this compound with a borane–dimethylsulfide complex in hexane led to a mixture of diastereomeric borane–amino ester adducts. The less soluble diastereoisomer, **155**, was isolated by crystallisation during the reaction provided that equilibration of the more soluble diastereoisomer remaining in solution occurred. The isolated diastereoisomer was alkylated with various alkyl halides, using KHMDS as a base, on reaction with reactive electrophiles, allyl or benzyl bromides. In the cases when less reactive electrophiles were used, LDA and the addition of a complexing agent prior to neutralisation proved to be a more practical protocol. Diastereofacial selectivities were in the range of 68–82%. Hydrolysis with ammonium chloride solution led to the corresponding *N*-benzyl-*N*-methylamino ester with acceptable to good yields (Scheme 30).



Entry	E	R	dr
a	$CH_2=CHCH_2I$	$CH_2=CHCH_2$	96/4
b	$HC\equiv CCH_2Br$	$HC\equiv CCH_2$	> 98/2
c	$C_6H_5CH_2Br$	$C_6H_5CH_2$	> 98/2
d	EtO_2CCH_2I	EtO_2CCH_2	95/5
e	*(E)*-$CH_3O_2CCH=CHCH_2Br$	*(E)*-$CH_3O_2CCH=CHCH_2$	92/8
f	$(CHO)_n$	CH_2OH	80/20
g	$CH_2=CHCO_2CH_3$	$CH_2CH_2CO_2CH_3$	95/5

Entry	$ROCO_2Et$	R'	dr
a	$CH_2=CHCH_2OCO_2Et$	$CH_2=CHCH_2$	> 98/2
b	$CH_2=C(CH_3)CH_2OCO_2Et$	$CH_2=C(CH_3)CH_2$	> 98/2
c	*(E)*-$C_6H_5CH=CHCH_2OCO_2Et$	*(E)*-$C_6H_5CH=CHCH_2$	91/9
d	$CH_2=CHCH(CH_3)OCO_2Et$	*(E)*-$CH_3CH=CHCH_2$	92/8
e	*(E)*-$CH_3CH=CHCH_2OCO_2Et$	*(E)*-$CH_3CH=CHCH_2$	92/8
f	$(CH_2=CH)_2CHOCO_2Et$	*(E)*-$CH_2=CHCH=CHCH_2$	85/15
g	*(E)*-$CH_3(CH_2)_2CH=CHCH_2OCO_2Et$	*(E)*-$CH_3(CH_2)_2CH=CHCH_2$	94/6

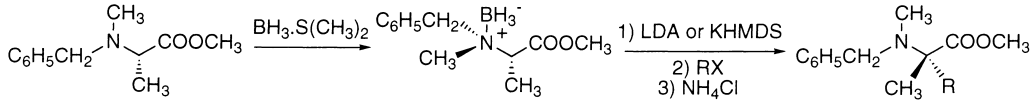
Scheme 28.



Entry	R_1	R_2X	dr
a	$C_6H_5CH_2$	CH_3I	5.8/1
b	$C_6H_5CH_2$	$CH_2=CHCH_2Br$	142/1
c	$C_6H_5CH_2$	$CH_3CH_2CH_2Br$	4/1
d	$(CH_3)_2CH$	CH_3I	4/1
e	$(CH_3)_2CH$	$CH_2=CHCH_2Br$	≥ 20/1
f	$(CH_3)_2CH$	$C_6H_5CH_2Br$	99/1
g	C_6H_5	$CH_2=CHCH_2Br$	14/1
h	C_6H_5	CH_3I	1/1

Scheme 29.

Enolates generated from optically active α-amino acids have been enantioselectively alkylated without the addition of any external chiral source, according to the concept of 'memory of chirality' proposed by Fuji et al.[116,117] In this way, *N*-methyl-*N*-Boc-phenylalanine ethyl ester has been transformed into the corresponding α-methylphenylalanine derivative, without the addition of any external chiral source, by deprotonation with base followed by neutralisation with methyl iodide. The level of asymmetric induction

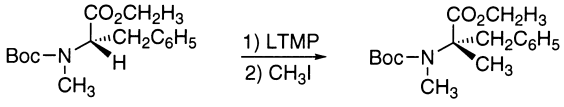


154 155 156

Entry	RX	ee%
a	$C_6H_5CH_2Br$	82
b	*(E)*-$C_6H_5CH{=}CHCH_2Br$	82
c	$CH_2{=}CHCH_2Br$	74
d	$CH_3(CH_2)_4I$	68
e	$CH_3O_2CCH_2Br$	80

Scheme 30.

and the absolute configuration of the final amino acid derivative depended on the nature and amount of base. It was found that KHMDS promoted inversion of configuration whereas with LTMP or LDA asymmetric methylation proceeded with retention of configuration. The best results were observed with the use of an equimolecular amount of LTMP as a base at low temperatures and quenching after 15 min (Scheme 31).



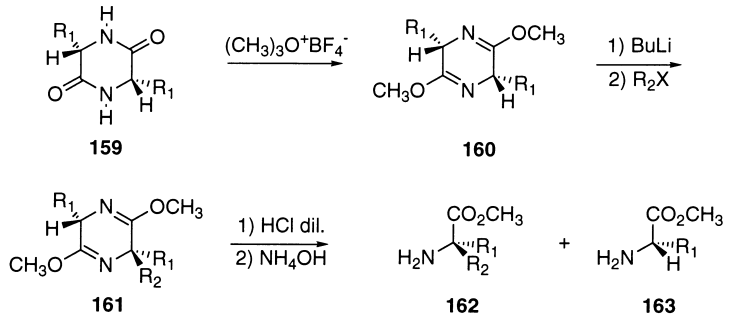
157 158 ee 82 %

Scheme 31.

3. Diastereoselective alkylation of chiral amino acid enolates

Alkylation of glycine or amino acid anion chiral equivalents is one of the most convenient general methodologies for the synthesis of non-racemic amino acids and, in particular, α-alkylamino acids. This approach is based on the following concept. A chiral amino acid equivalent is built up from a racemic lower amino acid (or synthetic equivalent) and a chiral auxiliary; this compound must possess an acidic CH adjacent to the potential amino acid group. Treatment with base generates an anion intermediate that is neutralised with an electrophile to diastereoselectively afford a higher amino acid. Subsequent hydrolysis of the alkylated compound liberates the chiral auxiliary and the newly formed optically active amino acid.

The bis-lactim ether methodology developed by Schöllkopf et al.[118–120] is one of the most notable examples of this approach. The pioneering work of these authors involved condensation of two molecules of L-alanine methyl ester on heating to give a diketopiperazine that, on treatment with trimethyloxonium-tetrafluoroborate, is converted into (3*S*,6*S*)-2,5-dimethoxy-3,6-dimethyl-3,6-dihydropyrazine **160**, its bis-lactim ether. This bis-lactim ether can be alkylated, after deprotonation with butyllithium, with a wide variety of electrophiles in a highly diastereoselective manner. Hydrolysis of the alkylated bis-lactim ethers yielded L-alanine methyl ester and the corresponding (*R*)-α-methylamino acid. This indicates that the electrophile had entered *anti* to the methyl group of the alanine, which acted as a chiral auxiliary. In this way different α-methylamino acids of *R* configuration have been obtained.[121,122] To obtain α-alkylleucine derivatives, the bis-lactim ether of L-leucine has been used as starting material[123] (Scheme 32).



Entry	R_1	R_2X	de%	Ref.
a	CH_3	$C_6H_5CH_2Br$	93	121,122
b	CH_3	3,4-$(CH_3O)_2C_6H_3CH_2Br$	95	121,122
c	CH_3	2-naphthyl-CH_2Br	93	121,122
d	CH_3	2-quinolyl-CH_2Br	94	121,122
e	CH_3	3-pyridyl-CH_2Cl	> 95	121,122
f	CH_3	CH_2=$CHCH_2Br$	92	121,122
g	CH_3	$(CH_3)_2CHBr$	92	121,122
h	CH_3	CH_3CH_2Br	95	122
i	CH_3	$CH_3(CH_2)_7Br$	92	122
j	CH_3	C_6H_5CH=$CHCH_2Br$	91	122
k	$(CH_3)_2CHCH_2$	$C_6H_5CH_2Br$	> 95	123
l	$(CH_3)_2CHCH_2$	2-naphthyl-CH_2Br	> 95	123
m	$(CH_3)_2CHCH_2$	CH_2=$CHCH_2Br$	> 95	123
n	$(CH_3)_2CHCH_2$	$C_6H_5CH_2OCH_2CH_2Br$	> 95	123
o	$(CH_3)_2CHCH_2$	HC≡CCH_2Br	> 95	123
p	$(CH_3)_2CHCH_2$	$CH_3(CH_2)_3I$	85	123
q	$(CH_3)_2CHCH_2$	CH_3I	84	123
r	$(CH_3)_2CHCH_2$	CH_3SCH_2Cl	88	123

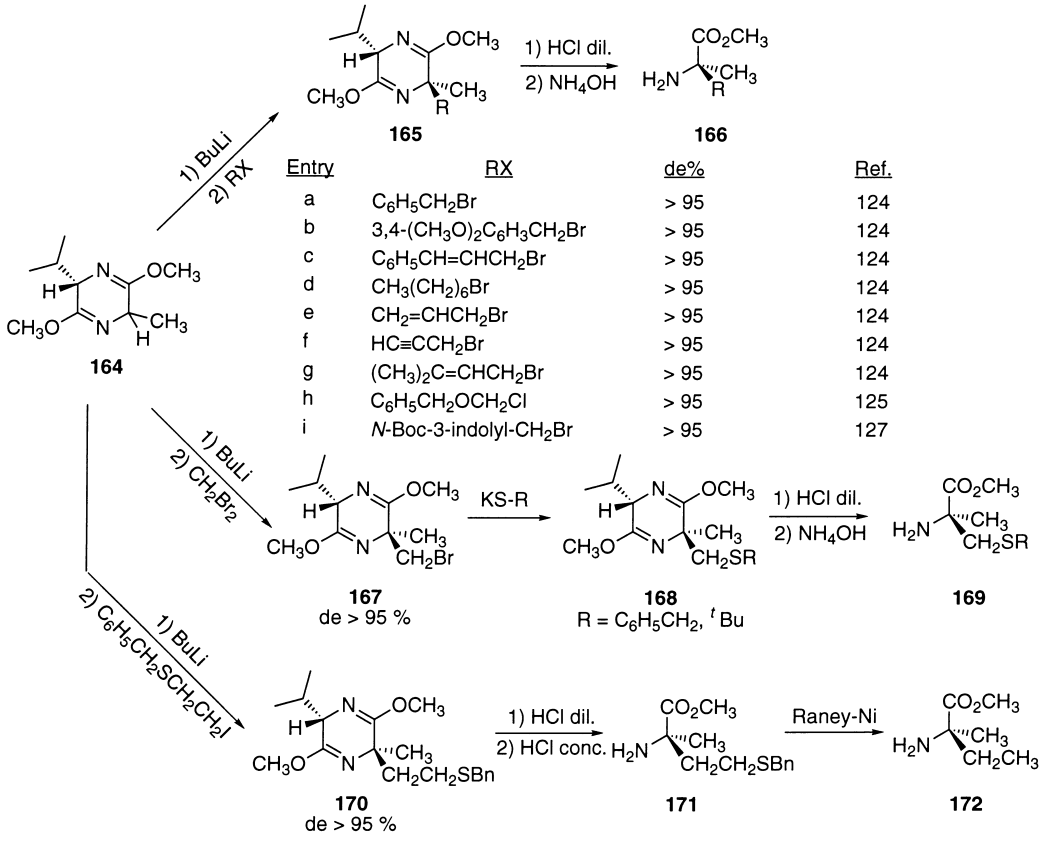
Scheme 32.

The procedure was subsequently improved with the use of mixed bis-lactim ethers derived from a chiral amino acid (e.g. L-valine) and racemic alanine, obtained from dipeptide L-Val-D,L-Ala-OCH_3. The mixed bis-lactim ether **164** is metallated regioselectively in the alanine moiety by treatment with butyllithium at −70°C and subsequently alkylated with excellent diastereoselectivity (e.d. >95%). This procedure has been applied to the synthesis of several amino acids such as (*R*)-α-methylphenylalanine, (*R*)-α-methyldopa, several (*R*)-α-methyl-α-allylglycines,[124] (*R*)-α-methylserine,[125] (*R*)-α-methyl-S-alkylcysteines,[126] (*R*)-α-methyltryptophan[127] and (*R*)-isovaline[128] (Scheme 33).

The use of acrylates that carry a leaving group in the β-position makes possible an addition–elimination process that gives precursors of β,γ-didehydro-α-methylglutamates[129] (Scheme 34).

When oxiranes are used as electrophiles (*R*)-α-methylhomoserine methyl esters are finally obtained.[130] The diastereofacial selectivity of the nucleophilic oxirane ring opening is, in all cases, almost total. In addition, the use of chiral racemic oxiranes means that one enantiomer reacts faster than the other with a very high degree of kinetic resolution (Scheme 35).

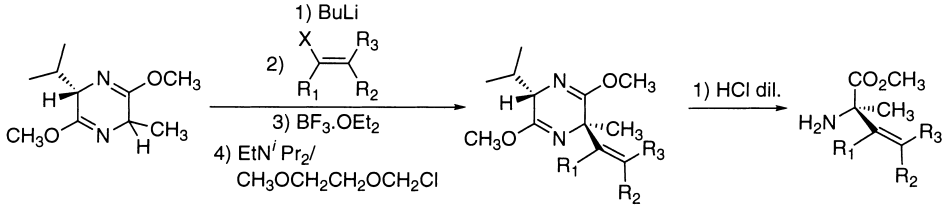
Bis-lactim ethers are also capable of giving aldol condensations with both aldehydes and ketones with a high level of asymmetric induction on C_α but low asymmetric induction on C_β. Surprisingly the level of enantiofacial discrimination on the attack of the carbonyl group does not depend on the size of the substituent. In this way the symmetrical bis-lactim ether derived from L-alanine[131,132] and the mixed bis-lactim ether derived from L-valine and D,L-alanine[133] reacted with ketones and aldehydes



165 **166** **164** **167** de > 95 % **168** R = $C_6H_5CH_2$, ^{t}Bu **169** **170** de > 95 % **171** **172**

Entry	RX	de%	Ref.
a	$C_6H_5CH_2Br$	> 95	124
b	3,4-$(CH_3O)_2C_6H_3CH_2Br$	> 95	124
c	$C_6H_5CH{=}CHCH_2Br$	> 95	124
d	$CH_3(CH_2)_6Br$	> 95	124
e	$CH_2{=}CHCH_2Br$	> 95	124
f	$HC{\equiv}CCH_2Br$	> 95	124
g	$(CH_3)_2C{=}CHCH_2Br$	> 95	124
h	$C_6H_5CH_2OCH_2Cl$	> 95	125
i	*N*-Boc-3-indolyl-CH_2Br	> 95	127

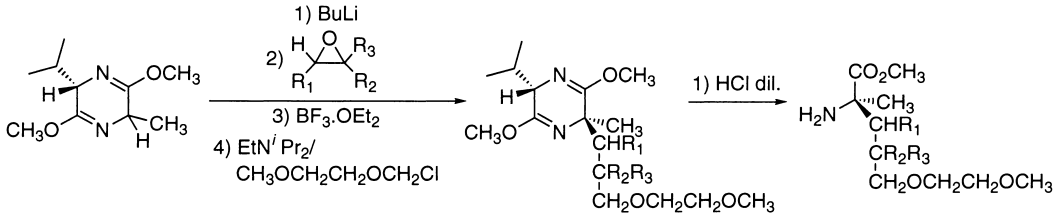
Scheme 33.



164 **173** **174**

Entry	X	R_1	R_2	R_3	dr
a	Cl	H	H	CO_2CH_3	97.5/2.5
b	Cl	H	CO_2CH_3	H	99/1
c	Cl	CH_3	H	CO_2CH_3	99.5/0.5
d	Cl	CH_3	CO_2CH_3	H	99.5/0.5
e	Br	CH_3	CO_2CH_3	H	99.5/0.5
f	OPO_3Et_2	CH_3	H	CO_2CH_3	99.5/0.5
g	Cl	C_6H_5	H	CO_2CH_3	> 99.5/0.5
h	Cl	H	CO_2CH_3	C_6H_5	99/1
i	Cl	-$(CH_2)_3$-		CO_2CH_3	99.5/0.5

Scheme 34.

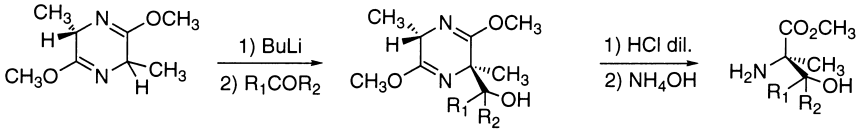


164 **175** **176**

Entry	R_1	R_2	R_3	de %	Epimeric ratio
a	H	H	H	> 95	-
b	H	CH_3	H	> 95	>97.5/2.5
c	CH_3	H	CH_3	> 95	>97.5/2.5
d	-$(CH_2)_4$-		H	> 95	>97.5/2.5

Scheme 35.

to give synthetic precursors of α-methyl serines (Schemes 36 and 37). α-Alkenylalanine precursors have been obtained by treatment of hydroxy derivatives with thionyl chloride/pyridine. On the other hand, reaction of bis-lactim ethers with acid chlorides leads to the formation of ketones **185**, which have been alternatively synthesised by Swern oxidation of the corresponding alcohol **186** (obtained by condensation of bis-lactim ethers with aldehydes). Reaction of compounds **185** with methylene triphenylphosphorane followed by subsequent hydrolysis, furnishes α-methyl-β-substituted vinylglycine derivatives[134] (Scheme 37).



160 **177** **178**

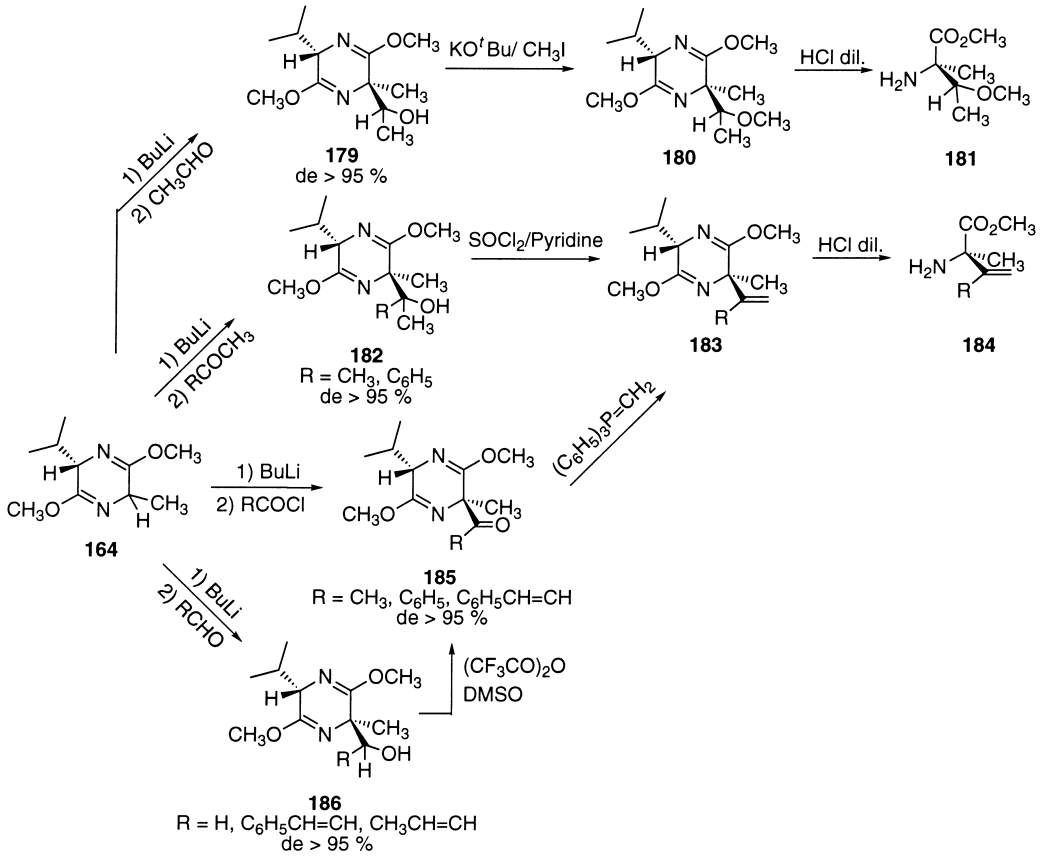
Entry	R_1	R_2	de %	Epimeric ratio	Ref.
a	H	H	90	-	131, 132
b	CH_3	CH_3	85	-	131, 132
c	C_6H_5	C_6H_5	> 95	-	131, 132
d	C_6H_5	CH_3	> 95	70.5/29.5	131, 132
e	C_6H_5	H	82	76/24	131, 132
f	4-$CH_3OC_6H_4$	H	85	87/13	131, 132

Scheme 36.

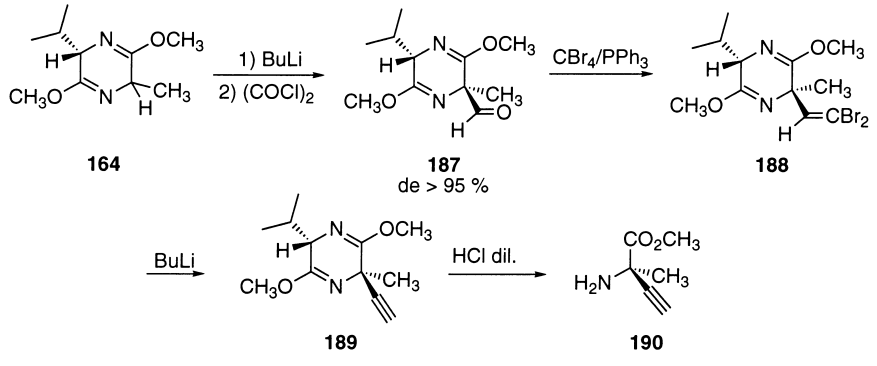
Bis-lactim **187**, obtained from the reaction with oxalyl chloride, has been transformed into a 2-ethynyl-substituted bis-lactim and, from this compound, (*R*)-2-ethynylalanine methyl ester can be isolated by hydrolysis under standard conditions (Scheme 38).

This extremely useful methodology has a wide application for the synthesis of unusual α-methylamino acids and has recently been applied to the synthesis of α,α′-bridged bis(α-alanine) derivatives from bis-lactim **164**[135] (Scheme 39).

Schöllkopf et al. have also described the use of optically active imidazolinones as intermediates in the synthesis of α-alkylamino acids.[136,137] Cyclisation of chiral α-isocyanoamides with 1 equivalent of base leads to the in situ formation of the metallated imidazolinone, which can be stereoselectively alkylated at C_4 with good yields and stereoselectivities when benzylic halides are used. Hydrolysis of



Scheme 37.

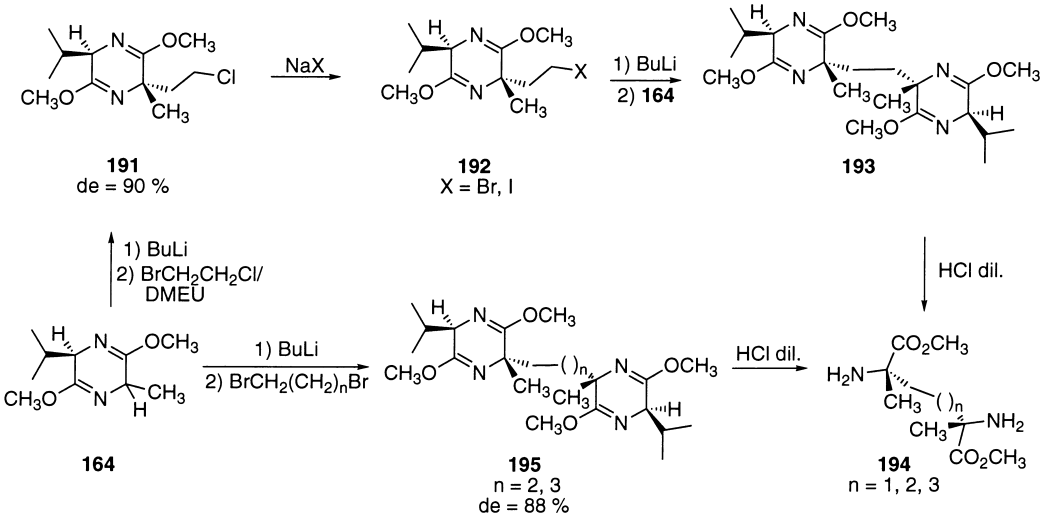


Scheme 38.

the 4,4-disubstituted imidazolinones under harsh acid or alkaline conditions affords the corresponding α-alkylamino acids (Scheme 40).

An alternative approach used by the same authors for the synthesis of α-alkylamino acids is based on diastereoselective alkylation with activated electrophiles of 3,6-dihydro-2*H*-1,4-oxazin-2-ones, prepared from optically active α-hydroxy acids and arylglycines. Mild acid treatment of the alkylated compounds has led to a wide variety of α-alkylated phenylglycines[138] and α-alkylated furylglycines[139] (Scheme 41).

Seebach et al. have developed a chiral glycine derivative, *tert*-butyl 2-*tert*-butyl-3-methyl-4-oxo-1-imidazolidinecarboxylate **206**, an imidazolidinone derived from glycine,[140] that can be geminally



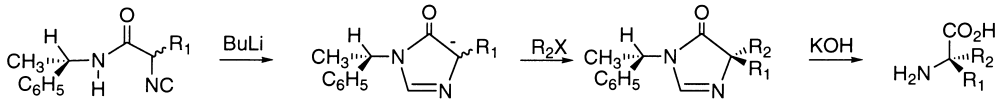
Scheme 39.

dialkylated in excellent yields and selectivities in a one pot procedure. Depending on the order of addition of the two electrophiles, both enantiomers of an α-alkylamino acid, or its *N*-methylamide, can be obtained after successive hydrolysis with TFA and HCl[141,142] (Scheme 42).

Hydrolysis of 5,5-dialkylated imidazolidinones to give the free amino acid in an acidic medium is impossible in these cases when the bulk of the side chains (R_1/R_2) is greater than $CH_3/C_6H_5CH_2$. The bulk of these side chains hampers the access to some α-alkylamino acids. The authors have succeeded in this step by simply transforming aminomethylamides, obtained by hydrolysis in 6 N HCl/methanol, into *N*-benzoylamino acid amides. These compounds can be converted into free amino acids by hydrolysis of the *N*-methylamide with 4 N HCl/dioxane followed by hydrolysis of the *N*-benzoyl amino acid with concentrated aqueous HCl at 100°C in a sealed tube. In this way α-alkylamino acids with bulky substituents have been obtained and this is now the procedure of choice for the synthesis of α-alkylamino acids[48,143] (Scheme 43). This synthetic protocol has been recently applied to the synthesis of enantiomerically pure (*S*)-α-methylphenylalanine, (*S*)-α-methyldopa and (*S*)-α-methyltyrosine labelled with fluorine-18.[144]

Deprotonation of unsaturated imidazolidinones **213** with LDA generates a lithium dienolate intermediate that can be subsequently alkylated with different alkyl halides as well as aldehydes to afford products derived from electrophilic attack in the α-carbonyl compound.[145] Hydrolysis of some of these compounds led to the synthesis of some unusual amino acids (Scheme 44).

Chiral *N*-*tert*-butoxycarbonyl or *N*-benzyloxycarbonyl 5,6-diphenyltetrahydro-1,4-oxazin-2-ones initially obtained from chiral 1,2-diphenyl-2-hydroxyethylamine and ethyl bromoacetate,[146] and whose syntheses have been recently improved,[147,148] have proven to be extremely useful starting materials for the synthesis of α-alkylamino acids with high enantiomeric purity.[149–151] Generation of the enolate with lithium or sodium hexamethyldisilylamide followed by addition of an alkyl halide results in the formation of alkylation products from the attack, with high diastereoselectivity, of the electrophile *anti* to the two phenyl substituents on the oxazinone ring. To perform alkylation of 3-monosubstituted oxazinones it is necessary to generate the enolate in the presence of the electrophile using potassium hexamethyldisilylamide as base and avoiding the use of HMPA as cosolvent. Alkylation of highly hindered 3-substituted oxazinones requires the use of a large excess of base to promote the reaction.[149] As an alternative to this procedure, Baldwin has recently described[152] that generation of the sodium enolate



196 197 198 199

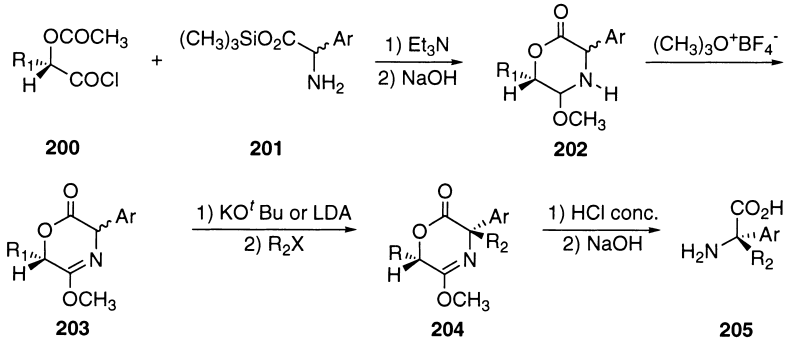
Entry	R_1	R_2X	de%	Ref.
a	CH_3	$C_6H_5CH_2Br$	> 95	136, 137
b	CH_3	3,4-$(CH_3O)_2C_6H_3CH_2Br$	66-80	136, 137
c	CH_3	4-$CH_3OC_6H_4CH_2Br$	72	136
d	CH_3	3-$CH_3OC_6H_4CH_2Br$	81	137
e	CH_3	4-$NO_2C_6H_4CH_2Br$	> 95	137
f	CH_3	3-$NO_2C_6H_4CH_2Br$	> 95	137
g	CH_3	4-$NCC_6H_4CH_2Br$	> 95	137
h	CH_3	1-naphthyl-CH_2Br	> 95	136, 137
i	CH_3	2-naphthylCH_2Br	> 95	136, 137
j	CH_3	2-thienyl-CH_2Br	> 95	136, 137
k	CH_3	3-benzothienyl-CH_2Br	>95	136, 137
l	CH_3	2-bromo-3-benzofuranyl-CH_2Br	>95	136, 137
m	CH_3	CH_2=$CHCH_2Br$	17	137
n	CH_3	$(CH_3)_2C$=$CHCH_2Br$	35	137
o	CH_3	*c*-$C_6H_{11}CH_2Br$	35	137
p	CH_3CH_2	$C_6H_5CH_2Br$	95	136
q	CH_2=$CHCH_2$	$C_6H_5CH_2Br$	90	136
r	$CH_3CH_2CH_2$	$C_6H_5CH_2Br$	90	136
s	$(CH_3)_2CH$	$C_6H_5CH_2Br$	95	136
t	$CH_3(CH_2)_3$	$C_6H_5CH_2Br$	95	136
u	4-$BrC_6H_4CH_2$	$C_6H_5CH_2Br$	100	136
v	$C_6H_5CH_2$	CH_3I	20	136
w	$C_6H_5CH_2$	CH_2=$CHCH_2Br$	43	136
x	$C_6H_5CH_2$	$(CH_3)_2CHI$	65	136
y	$C_6H_5CH_2$	$CH_3(CH_2)_3Br$	55	136
z	$C_6H_5CH_2$	EtO_2CCH_2Br	31	136
a'	$C_6H_5CH_2$	4-$BrC_6H_4CH_2Br$	100	136

Scheme 40.

in the presence of 15-crown-5 also resulted in the formation of alkylation compounds, even when non-activated alkyl halides were used to trap the enolate. In all of the cases described, dialkylation occurs with total diastereoselectivity and, as expected, the second alkylation also proceeded *anti* to the two phenyl rings of the oxazinone (Scheme 45).

The Baldwin protocol has proven to be very useful in the synthesis of (2*S*,6*S*)-2,6-diamino-6-(hydroxymethyl)pimelic acid[152] and led to an improvement on the results described by Williams for the synthesis of the same compound[153] (Scheme 46).

In a related approach, Remuzon et al.[154] obtained (6*R*)-*N*-*tert*-butoxycarbonyl- and *N*-benzyloxycarbonyl-3,6-diphenyl-1,4-oxazin-2-ones and tested their methylation under different reaction conditions. However, all attempts to obtain the dialkylated compounds in high yields and stereoselectivities were unsuccessful. Nevertheless, when the starting compound possesses an additional chiral substituent at the *N*-atom, e.g. a phenylethyl group, and a 4-methoxyphenyl group at C_3, alkylation occurs with acceptable yields and excellent diastereoselectivity. Yields were better when the electrophile was added prior to the addition of base and an increase in the size of the electrophile resulted in an increase in the stereoselectivity of the alkylation reaction (Scheme 47). Final hydrolysis to afford 2-



Entry	Ar	R_1	R_2	de %	Ref.
a	C_6H_5	$(CH_3)_2CH$	$C_6H_5CH_2Br$	> 95	138
b	C_6H_5	$(CH_3)_2CH$	$CH_2=CHCH_2Br$	83	138
c	C_6H_5	$(CH_3)_2CH$	CH_3I	60	138
d	C_6H_5	$(CH_3)_3C$	$C_6H_5CH_2Br$	> 95	138
e	C_6H_5	$(CH_3)_3C$	CH_3I	90	138
f	C_6H_5	C_6H_5	CH_3I	77	138
g	C_6H_5	C_6H_5	$C_6H_5CH_2Br$	> 95	138
h	C_6H_5	$C_6H_5CH_2$	CH_3I	49	138
i	2-furyl	$(CH_3)_2CH$	$C_6H_5CH_2Br$	> 95	139
j	2-furyl	$(CH_3)_2CH$	4-pyridyl-CH_2Cl	> 95	139
k	2-furyl	$(CH_3)_2CH$	2-thienyl-CH_2Br	> 95	139
l	2-furyl	$(CH_3)_2CH$	2-naphthyl-CH_2Br	> 95	139
m	2-furyl	$(CH_3)_2CH$	$CH_2=CHCH_2Br$	70	139
n	2-furyl	$(CH_3)_2CH$	CH_3I	58	139
o	2-furyl	$(CH_3)_2CH$	CH_3CH_2I	61	139
p	2-furyl	$(CH_3)_2CH$	$(CH_3)_2CHI$	62	139
q	2-furyl	$(CH_3)_2CH$	*c*-$C_6H_{11}CH_2I$	62	139
r	2-furyl	$(CH_3)_3C$	$C_6H_5CH_2Br$	> 95	139
s	2-furyl	$(CH_3)_3C$	$CH_2=CHCH_2Br$	> 95	139
t	2-furyl	$(CH_3)_3C$	CH_3I	> 95	139

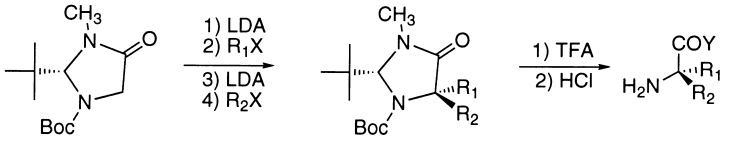
Scheme 41.

alkyl-2-(4-methoxyphenyl)glycine derivatives have proved to be troublesome and undesired by-products are also obtained.

Very recently, Sandri et al.[155] have used a lactim containing a glycine moiety as the starting material for the synthesis of α-alkylamino acid-containing dipeptides. Alkylation of this compound with an alkyl halide affords a diastereomeric mixture of lactims in which the predominant compound is that possessing an *anti* configuration of substituents at C_3 and C_6.[156] A second alkylation of this diastereomeric mixture yields the corresponding 3,3-disubstituted lactim with a good 1,4-*trans* induction with respect to the methyl group on C_6. A change in the absolute configuration of the 1-phenethyl group leads to a slight decrease in the stereoselectivity, although the sense of asymmetric induction is the same. Debenzylation of the lactim followed by acidic hydrolysis easily afforded dipeptides containing sterically hindered amino acids (Scheme 48).

Chiral amidine esters obtained from amino acids and (*S*)-1-dimethoxymethyl-2-methoxymethylpyrrolidine (SDMP) have been used by Kolb and Barth as amino acid equivalents in alkylation reactions.[157,158] These reactions give moderate yields and low diastereoselectivities. Final deprotection yields α-alkylamino acids (Scheme 49).

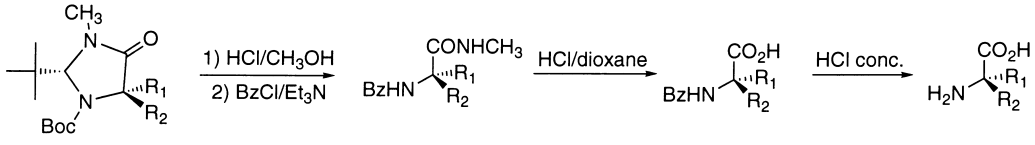
Slightly better results are obtained on double alkylation of an amidine derived from



206 **207** **208**

Entry	R_1X	R_2X	de%	Y	Ref
a	CH_3CH_2I	$Br(CH_2)_4Cl$	> 95	OH	141
b	CH_3I	$Br(CH_2)_5Cl$	> 95	OH	141
c	CH_3I	CH_3CH_2I	> 95	-	142
d	CH_3CH_2I	$C_6H_5CH_2Br$	> 95	NCH_3	142
e	$C_6H_5CH_2Br$	$(CH_3)_2CHI$	> 95	NCH_3	142
f	$C_6H_5CH_2Br$	*c*-$C_6H_{11}CH_2Br$	> 95	NCH_3	142
g	CH_3I	4-$CH_3OC_6H_4CH_2I$	> 95	-	142
h	3,4-$(CH_3O)_2C_6H_3CH_2I$	CH_3CH_2I	> 95	-	142
i	3,4-$(CH_3O)_2C_6H_3CH_2I$	$(CH_3)_2CHI$	> 95	-	142
j	3,4-$(CH_3O)_2C_6H_3CH_2I$	*c*-$C_6H_{11}CH_2Br$	> 95	-	142
k	3,4-$(CH_3O)_2C_6H_3CH_2I$	$C_6H_5CH_2Br$	> 95	-	142

Scheme 42.



209 **210** **211** **212**

Entry	R_1	R_2
a	CH_3	CH_3CH_2
b	CH_3	$C_6H_5CH_2$
c	CH_3CH_2	$C_6H_5CH_2$
d	$C_6H_5CH_2$	$(CH_3)_2CH$
e	3,4-$(CH_3O)_2C_6H_3CH_2$	$(CH_3)_2CH$
f	$C_6H_5CH_2$	*c*-$C_6H_{11}CH_2$

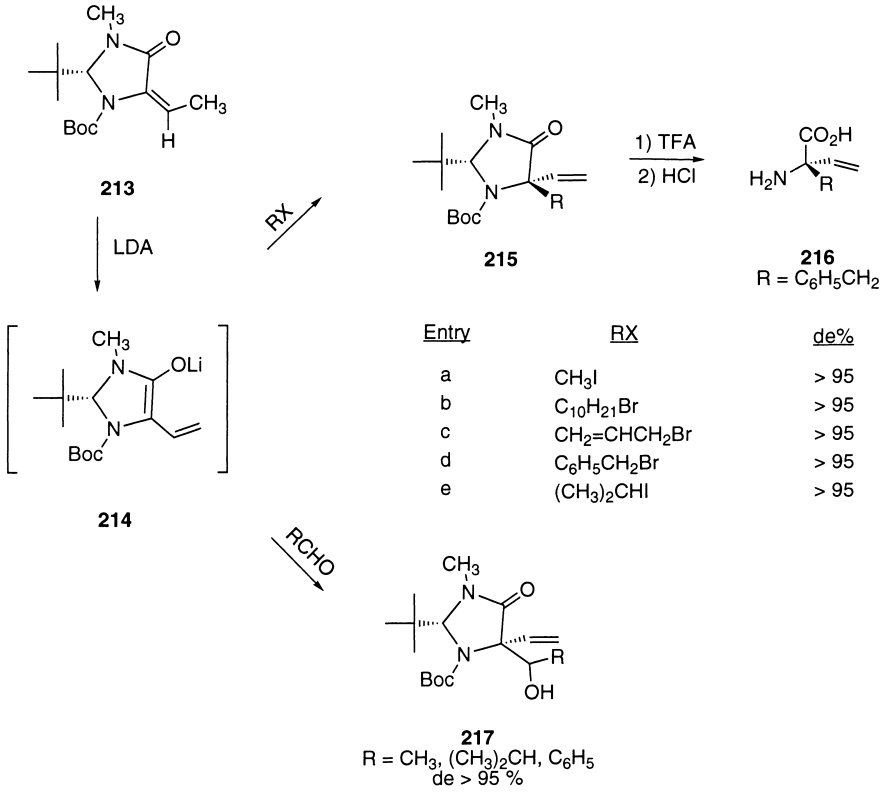
Scheme 43.

propargylamine.[158,159] In this case the ethynyl group behaves as a masked carboxylic acid, as it is transformed into this group by oxidation with $RuO_2/NaIO_4$ after hydrolysis of the amidine function with hydrazine hydrate and cleavage of the silyl protecting group with sodium methoxide (Scheme 50).

Enolate alkylation of Schiff bases derived from glycine, or other amino acids, and chiral carbonyl compounds, as a chiral matrix, to obtain starting aldimines has also been used to obtain α-alkylamino acids.

One of the first examples to appear in the literature describing the synthesis of α-alkylamino acids using a chiral Schiff base derived from an amino acid was reported by Schöllkopf et al.[160] In this work, the authors obtained galactodialdehyde aldimines **253** derived from valine, leucine and isoleucine. These compounds, after deprotonation with LDA, reacted with activated alkyl halides to afford the corresponding alkylated aldimines **254** with high yields and stereoselectivities varying from 23 to >95%. After acidic hydrolysis, methyl esters of α-alkylamino acids are obtained with good yields (Scheme 51).

Viallefont et al.[161,162] have attempted the synthesis of α-alkylamino acids via Schiff bases derived from 2-hydroxypinan-3-one. These compounds, which are easily obtained from α-amino acid esters,



Entry	RX	de%
a	CH_3I	> 95
b	$C_{10}H_{21}Br$	> 95
c	$CH_2{=}CHCH_2Br$	> 95
d	$C_6H_5CH_2Br$	> 95
e	$(CH_3)_2CHI$	> 95

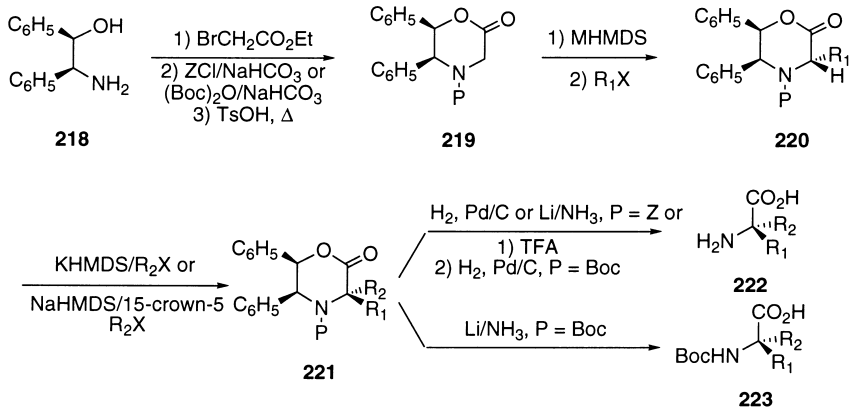
Scheme 44.

are deprotonated with LDA and subsequently alkylated with alkyl halides. Although Schiff bases derived from alanine give α-methylamino acids in good yields with a predictable stereochemistry and a moderate diastereoselectivity (52–83%), when Schiff bases possessing bulky substituents are used the results obtained are less convenient as the diastereoselectivity decreases and the absolute configuration of the major compound depends on the shielding effect of the side chain of the starting amino acid. Acidic hydrolysis of the alkylated compounds releases the corresponding amino acid and chiral auxiliary, which can be recovered (Scheme 52).

More recently Lavergne et al.[163] described the synthesis of α-substituted arylamino acids through the addition of fluorobenzene tricarbonyl chromium complexes to α-imino esters derived from 2-hydroxypinan-3-one. Lactones arylated at C_α are obtained in this reaction, although in some cases arylation on the pinane ring competes to a significant extent. Once again, the absolute configuration of arylated compounds depends on the nature of the amino acid side chain. Decomplexation of diastereomerically pure C_α-arylated lactones followed by hydrolysis gives 2-phenylamino acids (Scheme 53).

Aldimines derived from a complex chiral aldehyde of the pyridoxal type and amino acid benzyl esters have also been alkylated at C_α with low yields but acceptable stereoselectivities when sodium hydride is used as a base.[164] The use of aldimino compounds with an *R*-ansa structure largely increases the optical yield. Final hydrolysis is achieved smoothly with dilute hydrochloric acid at room temperature (Scheme 54).

Another recent approach is the use of Schiff bases obtained from amino acid chiral carboxylic acid derivatives. Diastereoselective alkylation of aldimines derived from 4-chlorobenzaldehyde and sultam-derived amino acids has been achieved by Lavielle et al.[165] The deprotonation–alkylation sequence



218 **219** **220** **221** **222** **223**

Entry	P	R_1X	R_2X	de%	Ref.
a	Boc	CH_3I	$CH_2{=}CHCH_2I$	100	149,150
b	Boc	CH_3I	$(CH_3)_2C{=}CHCH_2I$	100	149,150
c	Boc	$CH_3CH_2CH_2I$	$CH_2{=}CHCH_2I$	100	149,150
d*	Boc	$C_6H_5CH_2Br$	$CH_2{=}CHCH_2Br$	100	151
e*	Boc	$CH_2{=}CHCH_2Br$	$C_6H_5CH_2Br$	100	151
f	Boc	CH_3I	$CH_3(CH_2)_3I$	100	152
g	Boc	CH_3I	$(CH_3)_2CHCH_2I$	100	152
h	Boc	CH_3CH_2I	$CH_3(CH_2)_6I$	100	152
i	Z	CH_3I	$C_6H_5CH_2Br$	100	149,150
j	Z	CH_3I	$C_6H_5CH{=}CHCH_2Br$	100	149,150
k	Z	$CH_3CH_2CH_2I$	$C_6H_5CH_2Br$	100	149,150
l	Z	$CH_2{=}CHCH_2I$	$C_6H_5CH_2Br$	100	149,150
m*	Z	CH_3I	$C_6H_5CH_2Br$	100	152
n*	Z	$C_6H_5CH_2Br$	$CH_2{=}CHCH_2I$	100	152
o	Z	CH_3I	$CH_2{=}CHCH_2I$	100	152

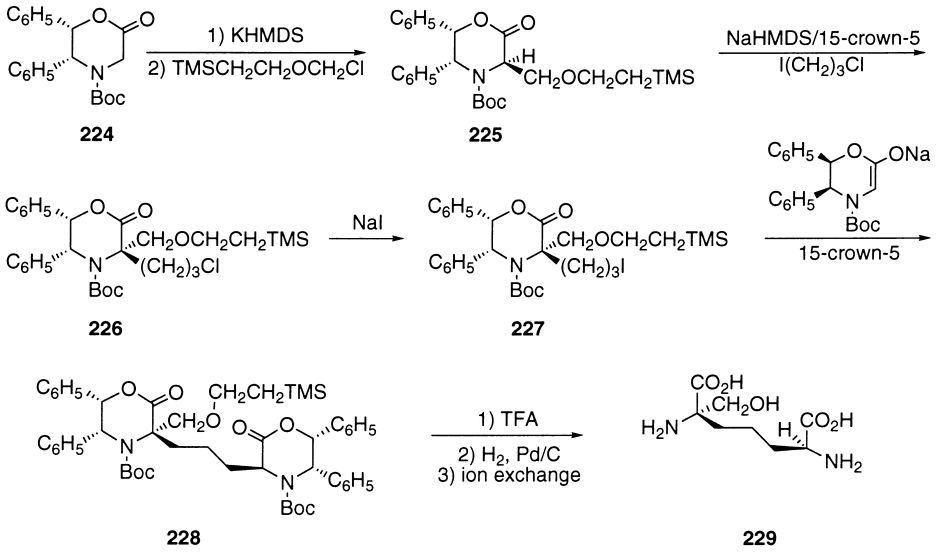
* ent-**218**

Scheme 45.

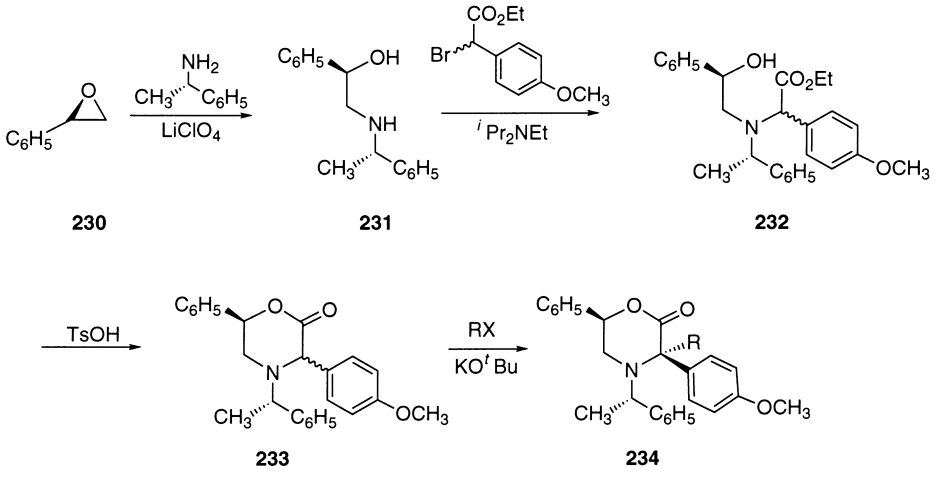
is totally stereoselective for the methionine derivative, and is quite diastereoselective in the case of leucine, phenylalanine and alanine. Although the authors use chiral amino acids as starting compounds, the stereochemical course of the alkylation reaction is directed by the sultam chiral auxiliary and both enantiomers of an amino acid afforded the same α-alkylamino acid after acidic hydrolysis (Scheme 55).

Chiral nickel complexes of (*RS*)-alanine Schiff base with (*S*)-*N*-(*N′*-benzylprolyl)aminobenzaldehyde and (*S*)-2-*N*-(*N′*-benzylprolyl)aminobenzophenone are interesting α-amino acid moieties that can be easily alkylated to afford α-methylamino acid precursors in excellent yields.[166–168] With the use of a nickel complex of the Schiff base derived from (*S*)-2-*N*-(*N′*-benzylprolyl)aminobenzaldehyde, the diastereoselectivities are quite low. Better results are obtained with the use of the nickel complex of the Schiff base derived from (*S*)-2-*N*-(*N′*-benzylprolyl)aminobenzophenone as the chiral intermediate and sodium or potassium hydroxide in DMF as a base, and under these conditions large diastereoselectivities (>80%) are observed. Several optically pure α-methylamino acids have been obtained after alkylation, separation of the diastereomeric mixtures on silica gel and hydrolysis with dilute hydrochloric acid and, in all cases, amino acids of *S* configuration were obtained preferentially (Scheme 56).

Hydroxymethylation of the nickel complex of the Schiff base derived from (*S*)-2-*N*-(*N′*-benzylprolyl)aminobenzophenone with a large excess of formaldehyde and a high concentration



Scheme 46.

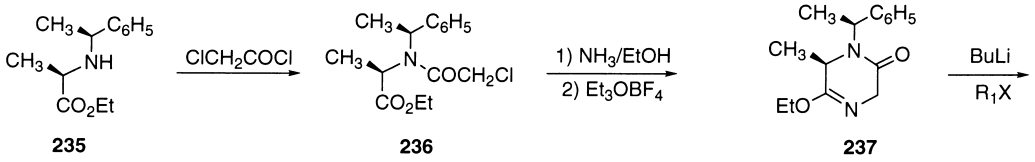


Entry	RX	de%
a	CH_3I	84
b	CH_3CH_2I	98
c	$CH_2{=}CHCH_2Br$	100
d	$C_6H_5CH_2Br$	94

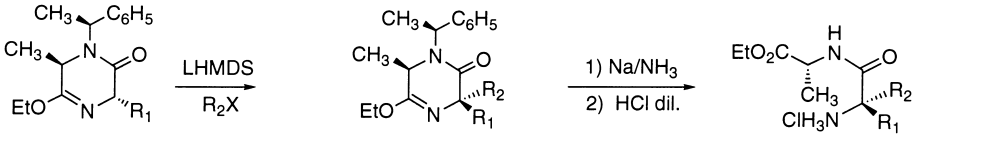
Scheme 47.

of sodium methoxide affords two diastereomeric compounds.[169] The diastereoselectivity of this reaction is subject to both kinetic and thermodynamic control and, at the end of the reaction, the ratio between the diastereoisomers approaches unity. After preparative column chromatography of both diastereoisomers and hydrolysis by the action of hydrochloric acid in aqueous alcoholic solution, both enantiomers of α-methylserine were obtained.

Berkowitz and Smith[170] have recently reported a different strategy based upon the diastereoselective double alkylation of the dianion derived from a chiral *N*-benzoyl α-amino ester. When 8-phenylmenthol is used as a chiral auxiliary, alkylation takes place with a high level of diastereoselectivity and moderate



235 **236** **237**



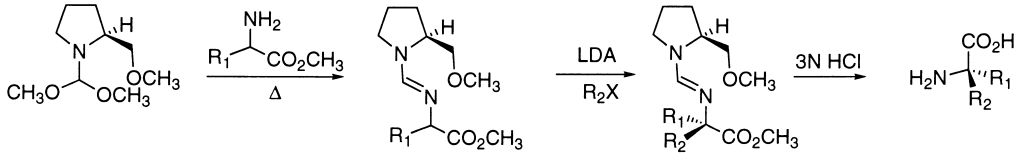
238 **239** **240**

$R_1 = CH_3CH_2$, $R_2 = CH_2{=}CHCH_2$

Entry	R_1X	R_2X	dr	dr*
a	CH_3I	CH_3CH_2I	93/7	85/15
b	CH_3I	$CH_2{=}CHCH_2I$	95/5	88/12
c	CH_3I	$C_6H_5CH_2Br$	90/10	75/25
d	CH_3CH_2I	CH_3I	90/10	75/25
e	CH_3CH_2I	$CH_2{=}CHCH_2I$	97/3	97/3
f	CH_3CH_2I	$C_6H_5CH_2Br$	95/5	54/46
g	$CH_2{=}CHCH_2I$	CH_3I	82/18	81/19
h	$CH_2{=}CHCH_2I$	CH_3CH_2I	98/2	85/15
i	$CH_2{=}CHCH_2I$	$C_6H_5CH_2Br$	98/2	86/14
j	$C_6H_5CH_2Br$	CH_3I	83/17	75/25
k	$C_6H_5CH_2Br$	CH_3CH_2I	98/2	88/12
l	$C_6H_5CH_2Br$	$CH_2{=}CHCH_2I$	98/2	92/8

* **238** with the *N*-phenethyl group possessing *R* configuration

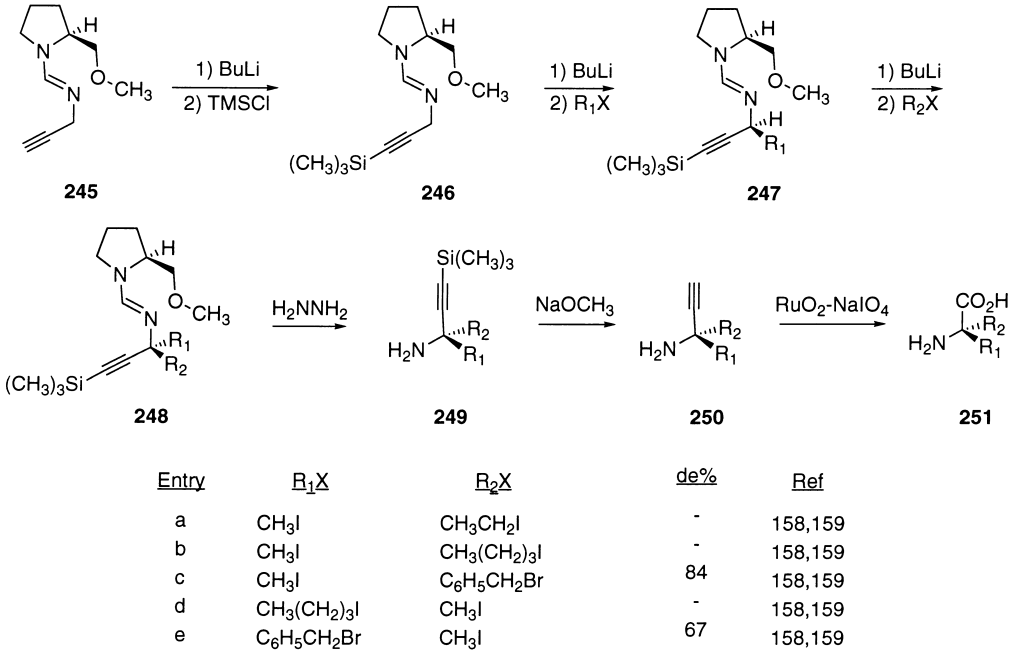
Scheme 48.



241 **242** **243** **244**

Entry	R_1	R_2X	de%	Ref
a	CH_3	CHF_2Cl	-	157,158
b	CH_3	CH_3CH_2I	-	157,158
c	CH_3	$CH_3(CH_2)_3I$	-	157,158
d	CH_3	$C_6H_5CH_2Br$	-	157,158
e	CH_3	$3,4\text{-}(CH_3O)_2C_6H_3CH_2Br$	51	157,158
f	$(CH_3)_2CHCH_2$	CH_3I	30	158
g	$C_6H_5CH_2$	CH_3I	-	157,158
h	$C_6H_5CH_2$	CH_3CH_2I	15	157,158
i	$C_6H_5CH_2$	$CH_2{=}CHCH_2Br$	-	158
j	$C_6H_5CH_2$	CHF_2Cl	-	158
			-	

Scheme 49.



Entry	R_1X	R_2X	de%	Ref
a	CH_3I	CH_3CH_2I	-	158,159
b	CH_3I	$CH_3(CH_2)_3I$	-	158,159
c	CH_3I	$C_6H_5CH_2Br$	84	158,159
d	$CH_3(CH_2)_3I$	CH_3I	-	158,159
e	$C_6H_5CH_2Br$	CH_3I	67	158,159

Scheme 50.

yields that are significantly improved in the presence of 10% HMPA. This procedure has been used to obtain a considerable variety of α-methylamino acid derivatives, which can be purified by recrystallisation, with diastereomeric excesses varying from 78 to 88%. Enantiomerically pure α-methylamino acids are obtained by ester cleavage with KO_2/18-crown-6 followed by acidic hydrolysis allowing the recovery of the chiral auxiliary (Scheme 57).

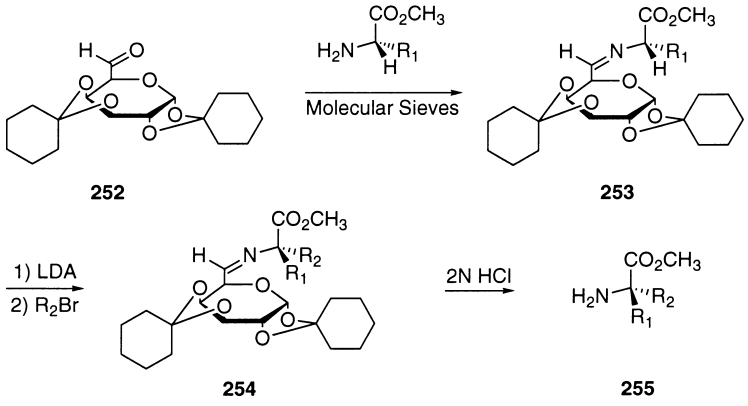
4. Chiral β-lactams as building blocks

Enantiomerically pure β-lactams have proven to be versatile intermediates for the synthesis of a wide variety of compounds of biological interest and have given rise to what has been called the β-lactam synthon method.[171,172] This methodology provides an efficient route to α-alkylamino acids through different approaches.

The asymmetric ketene–imine [2+2] cycloaddition attaching a chiral auxiliary to the ketene allows the asymmetric synthesis of 3-amino β-lactams. In this reaction, oxazolidinones derived from (*S*)- or (*R*)-phenylglycine behave as excellent chiral auxiliaries, so that the reaction of their derivatives with *N*-benzylimines derived from aromatic aldehydes provides chiral intermediates for the synthesis of aromatic α-alkylamino acids. Treatment of an enantiomerically pure β-lactam with base followed by neutralisation with methyl iodide gives rise to methylation at the C_3 carbon from the opposite side to the C_4 aryl group. Cleavage of the N–C_4 bond by hydrogenolysis and subsequent acidic hydrolysis of the amide group releases the α-alkylamino acids. In particular (*S*)-α-methylphenylalanine and (*S*)-α-methyldopa have been obtained in this way[173–175] (Scheme 58).

The same approach has been applied to the synthesis of (2*S*,3*R*)-2,3-diamino-2-methyl-5-phenylpentanoic acid using a chiral 3-amino-4-styryl-β-lactam as a synthetic intermediate[176] (Scheme 59).

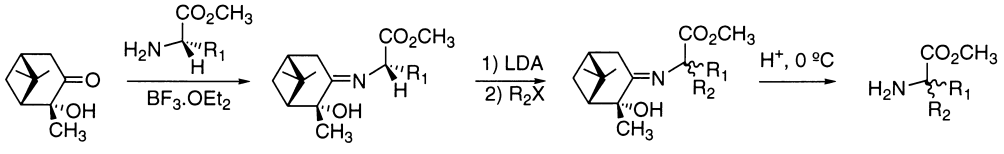
Chiral β-lactam **287** has been diastereoselectively alkylated at C_3 with reactive alkyl halides. The usual



252 253 254 255

Entry	R_1	R_2X	de%
a	$(CH_3)_2CH$	$C_6H_5CH_2Br$	80
b	$(CH_3)_2CH$	2-naphthyl-CH_2Br	> 95
c	$(CH_3)_2CH$	2-quinolyl-CH_2Br	74
d	$(CH_3)_2CH$	4-$BrC_6H_4CH_2Br$	75
e	$(CH_3)_2CH$	$C_6H_5CH{=}CHCH_2Br$	76
f	$(CH_3)_2CH$	$CH_2{=}CHCH_2Br$	76
g	$(CH_3)_2CH$	CH_3I	23
h	$(CH_3)_2CHCH_2$	$C_6H_5CH_2Br$	75
i	$(CH_3)_2CHCH_2$	$CH_2{=}CHCH_2Br$	57
j	$(CH_3)_2CHCH_2$	$HC{\equiv}CCH_2Br$	48
k	*(S)* -$CH_3CH_2(CH_3)CH$	$C_6H_5CH_2Br$	88
l	*(S)* -$CH_3CH_2(CH_3)CH$	2-naphthyl-CH_2Br	96
m	*(S)* -$CH_3CH_2(CH_3)CH$	2-quinolyl-CH_2Br	90
n	*(S)* -$CH_3CH_2(CH_3)CH$	$CH_2{=}CHCH_2Br$	75
o	*(S)* -$CH_3CH_2(CH_3)CH$	CH_3I	29

Scheme 51.



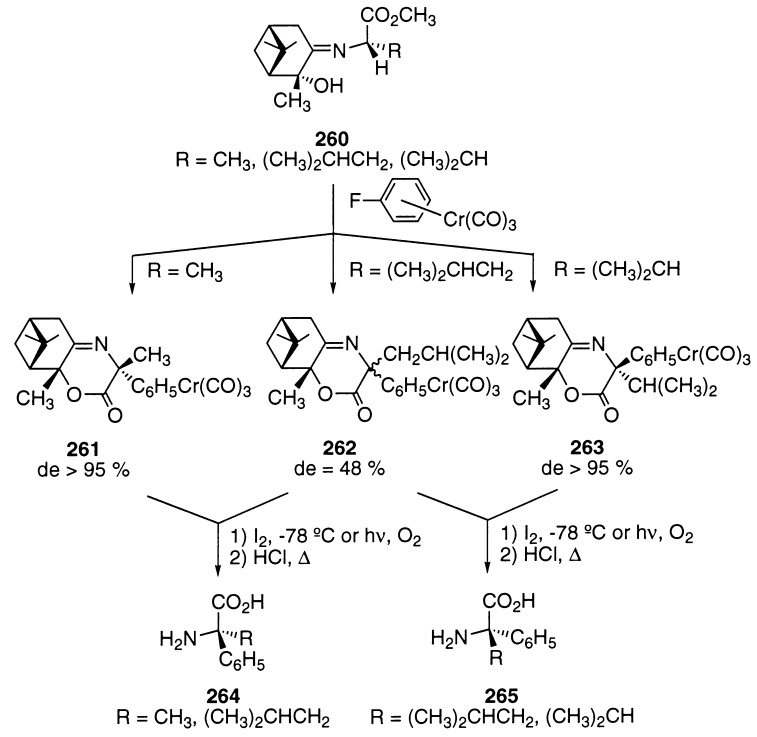
256 257 258 259

Entry	R_1	R_2X	de%	Abs. Conf.
a	CH_3	$CH_3(CH_2)_2I$	83	*S*
b	CH_3	$HC{\equiv}CCH_2Br$	52	*S*
c	$CH_3(CH_2)_2$	CH_3I	90	*R*
d	$CH_3(CH_2)_2$	$CH_2{=}CHCH_2Br$	15	*R*

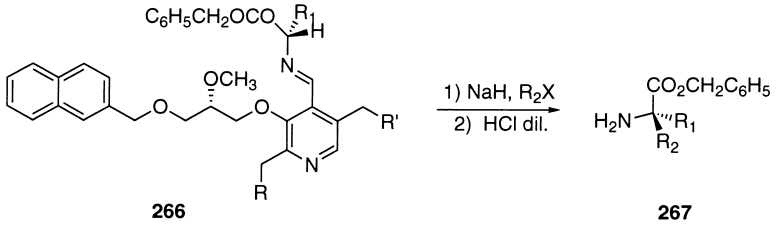
Scheme 52.

work-up of the alkylated compounds gave α-alkylphenylalanines and liberated the (*S*)-leucinol used as a chiral matrix in the preparation of the starting compound[175] (Scheme 60).

Hegedus uses as a chiral starting compound an extremely hindered bicyclic β-lactam, obtained by photolysis of a carbene complex with a dihydrooxazine and subsequent conversion of the oxazolidine to an oxazolidinone. Oxazolidinone **293** is alkylated at C_3 with complete retention of configuration,



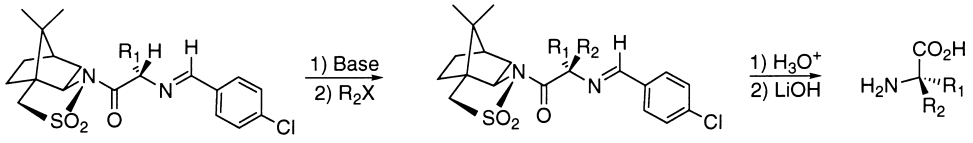
Scheme 53.



Entry	R	R'	R_1	R_2	de%
a	H	$OCH_2C_6H_5$	CH_3	$C_6H_5CH_2Br$	86
b	H	$OCH_2C_6H_5$	CH_3	$4\text{-}NO_2C_6H_4CH_2Br$	83
c	H	$OCH_2C_6H_5$	CH_3	$CH_2{=}CHCH_2Br$	17
d	H	$OCH_2C_6H_5$	$C_6H_5CH_2$	CH_3I	82
e	*(S)* S-$(CH_2)_5$-S		CH_3	$C_6H_5CH_2Br$	8
f	*(R)* S-$(CH_2)_5$-S		CH_3	$C_6H_5CH_2Br$	96
g	*(R)* S-$(CH_2)_5$-S		CH_3	$4\text{-}NO_2C_6H_4CH_2Br$	84
h	*(R)* S-$(CH_2)_5$-S		CH_3	$CH_2{=}CHCH_2Br$	82
i	*(R)* S-$(CH_2)_5$-S		$C_6H_5CH_2$	CH_3I	90

Scheme 54.

although this reaction is limited to very reactive electrophiles.[177,178] Compound **294**, obtained by methylation, has been hydrolysed with gaseous hydrogen chloride in methanol to give an aminal that was further hydrolysed to an aldehyde, and this is the key intermediate in the synthesis of a variety of α-methylamino acids (Scheme 61). Starting from compound **296**, (*R*)-α-methylserine, (*R*)-

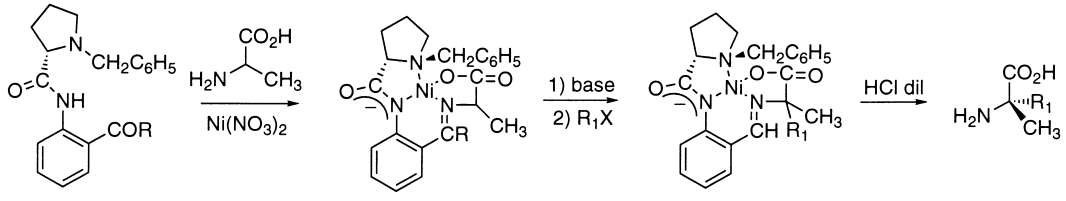


268 269 270

Entry	Base	R_1	R_2X	dr	Abs. Conf.
a*	BuLi	$CH_2CH_2SCH_3$	CH_3I	> 99/1	*R*
b	BuLi	$(CH_3)_2CHCH_2$	CH_3I	87/13	*S*
c	BuLi	$C_6H_5CH_2$	CH_3I	85/15	*S*
d	BuLi	CH_3	$C_6H_5CH_2Br$	92/8	*R*
e	NaH	CH_3	$C_6H_5CH_2Br$	97/3	*R*
f*	K_2CO_3	CH_3	$C_6H_5CH_2Br$	97/3	*S*
g**	K_2CO_3	CH_3	$C_6H_5CH_2Br$	97/3	*S*
h	K_2CO_3	CH_3	$C_6H_5CH_2Br$	90/10	*R*
i	BuLi	$C_6H_5CH_2$	CH_3I	90/10	*S*
j	BuLi	$C_6H_5CH_2$	CH_3I	90/10	*S*
k	NaH	$C_6H_5CH_2$	CH_3I	90/10	*S*
l	NaH	$C_6H_5CH_2$	CH_3I	90/10	*S*

* **268** with (+)-sultam as chiral auxiliary
** **268** with (+)-sultam as chiral auxiliary and alanine of *(R)*-configuration

Scheme 55.



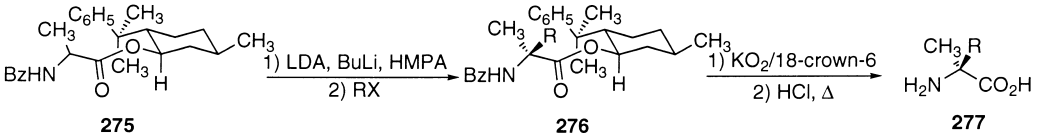
271 272 273 274

Entry	R	Base	R_1X	dr	Ref.
a	H	BuLi	$C_6H_5CH_2Br$	56/44	166,167
b	H	TBAI	$C_6H_5CH_2Br$	66/34	166,167
c	H	BuLi	$CH_2=CHCH_2Br$	61/39	166,167
d	H	TBAI	$CH_2=CHCH_2Br$	70/30	166,167
e	H	NaOH	$CH_2=CHCH_2Br$	61/39	167
f	C_6H_5	BuLi	$C_6H_5CH_2Br$	90/10	167
g	C_6H_5	NaOH	$C_6H_5CH_2Br$	93/7	167
h	C_6H_5	NaOH	$CH_2=CHCH_2Br$	92/8	167
i	C_6H_5	NaOH	4-$C_6H_5CH_2OC_6H_4CH_2Cl$	91/9	167
j	C_6H_5	KOH	2-$FC_6H_4CH_2X$	> 95/5	168
k	C_6H_5	KOH	3-$FC_6H_4CH_2X$	> 95/5	168
l	C_6H_5	KOH	4-$FC_6H_4CH_2X$	> 95/5	168

Scheme 56.

α-methylglutamic acid, (*R*)-α-methylornithine, (*R*)-α-vinylalanine, (*R*)-α-ethynylalanine and (*R*)-2-methyl-2,3-diaminopropanoic acid have all been obtained (Scheme 62).

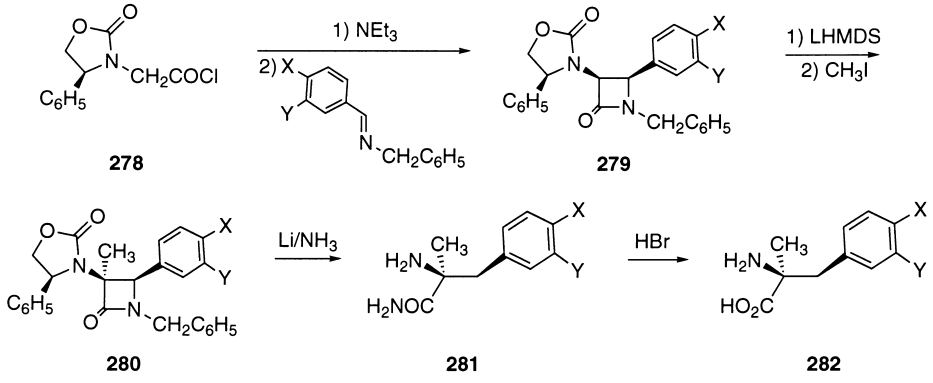
Alternatively, β-lactams can be stereoselectively alkylated on the side chain bonded to the N_1 atom and, in this case, the β-lactam ring acts as the chiral auxiliary. The starting compounds for the synthesis of



275 276 277

Entry	RX	dr
a	$C_6H_5CH_2Br$	94/6
b	CH_3CH_2I	93/7
c	$^tBuO_2CCH_2Br$	91/9
d	$C_6H_5CH_2OCH_2Br$	89/11
e	$HC{\equiv}CCH_2Br$	93/7
f	$CH_2{=}CHCH_2Br$	94/6
g	$(CH_3)_2CHCH_2I$	89/11
h	3,4-(TBDMSO)$_2$C$_6$H$_5$CH$_2$Br	94/6

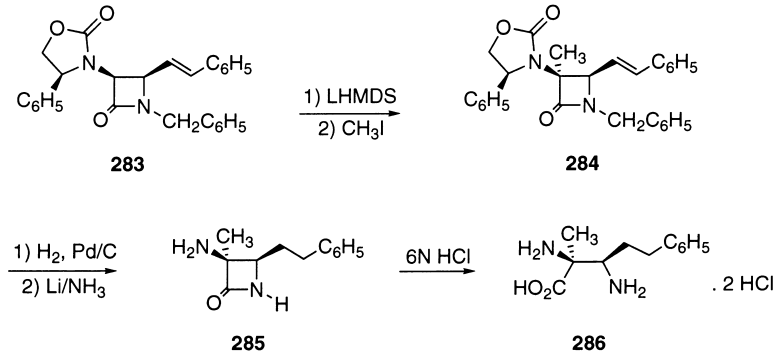
Scheme 57.



278 279 280 281 282

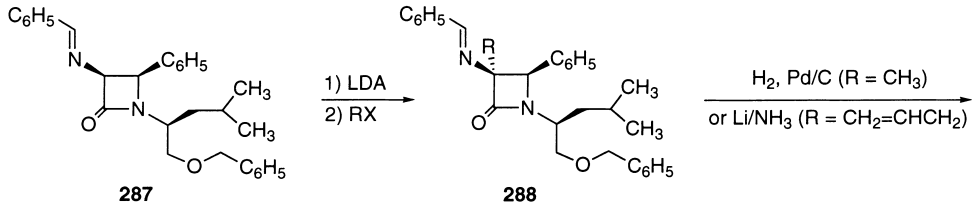
Entry	X	Y	de%
a	H	H	> 99.5
b	CH_3O	CH_3O	> 99.5

Scheme 58.

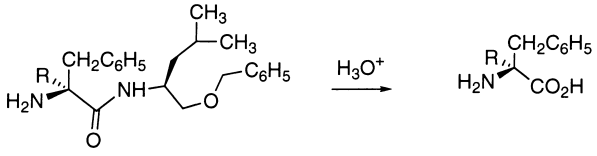


283 284 285 286

Scheme 59.



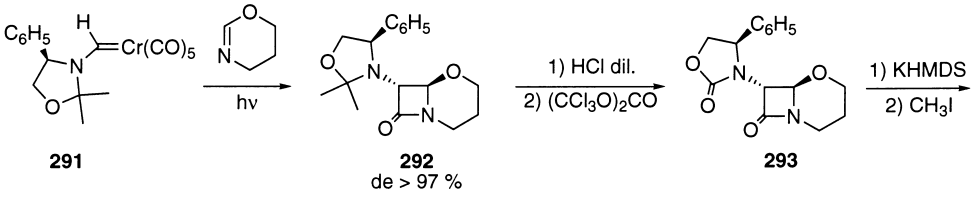
287 288



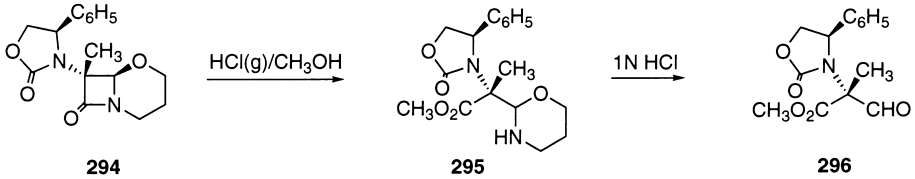
289 290

Entry	RX	de%
a	CH_3I	> 99.5
b	$CH_2{=}CHCH_2Br$	> 99.5

Scheme 60.



291 292 de > 97 % 293



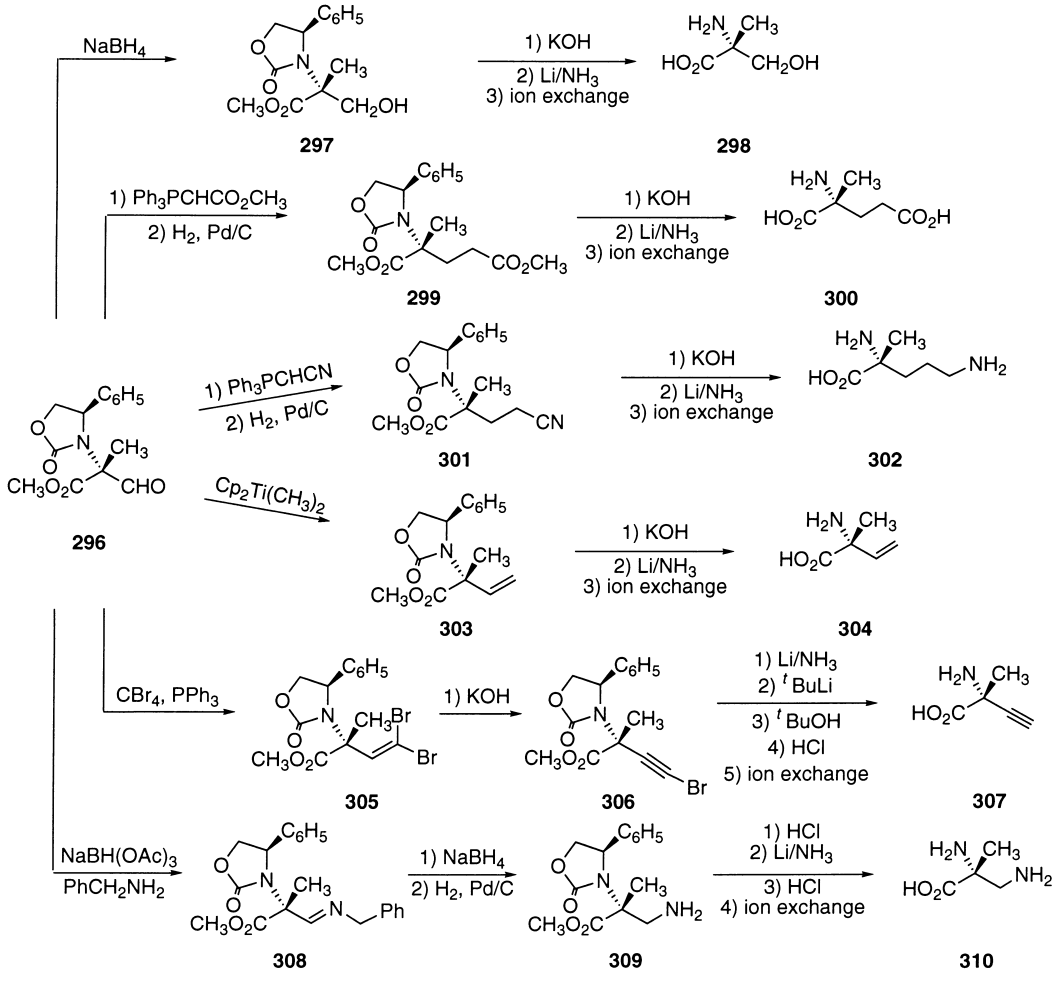
294 de > 97 % 295 296

Scheme 61.

α-methylamino acids are obtained by a [2+2] cycloaddition between a chiral imine derived from alanine *tert*-butyl ester and a ketene generated from 2-phenoxyacetylchloride.[173,174,179] The β-lactam enolate, generated by treatment with LDA, is alkylated with almost total stereoselectivity and in high yield when the reaction is carried out under thermodynamic control allowing the formation of a rigid chelate structure. Hydrogenolysis of the β-lactam ring followed by acidic hydrolysis affords the corresponding α-methylamino acid in high yield (Scheme 63).

When the phenoxy group at C_3 is replaced by a benzyloxycarbonylamino group poor results are observed in the alkylation reaction, unless this group was trimethylsilylated before generation of the enolate. In this case, benzylation on the side chain occurs with a diastereoselectivity of 14:1 in the formation of the (*S*)-methylphenylalanine precursor[173,179] (Scheme 64).

When the 3-amino group of the β-lactam was in an oxazolidinone structure, as in the case of β-lactam **318**, obtained from the [2+2] cycloaddition of chiral (*S*)-(4-phenyloxazolidinyl)ketene with *tert*-butyl *N*-benzylidenealaninate, asymmetric alkylation proceeded with extremely high stereoselectivity and only one diastereoisomer was detected by HPLC.[173,174] Deprotection of alkylated compound



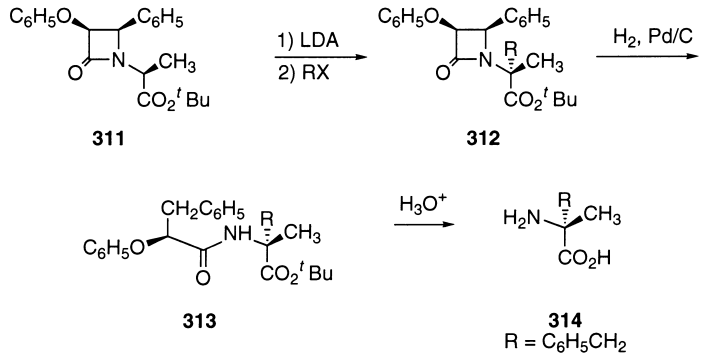
Scheme 62.

319 with trifluoroacetic acid and reduction with lithium/ammonia gave (*R*)-phenylalanyl-(*S*)-α-methylphenylalanine **320** (Scheme 65).

The use of chiral (*S*)-(4-phenyloxazolidinyl)ketene to perform the [2+2] cycloaddition with *tert*-butyl *N*-benzylideneglycinate gave a chiral glycine equivalent that is doubly alkylated at C_α.[180] The choice of the order of addition of the two alkyl halides gives control over the absolute configuration of the final compound. The first alkylation has to be performed at −78°C to achieve good yields and stereoselectivities, and the second alkylation under thermodynamic control occurs with excellent diastereoselectivity. The doubly alkylated compounds are transformed into dipeptides incorporating α-alkylamino acids by Birch reduction (Scheme 66).

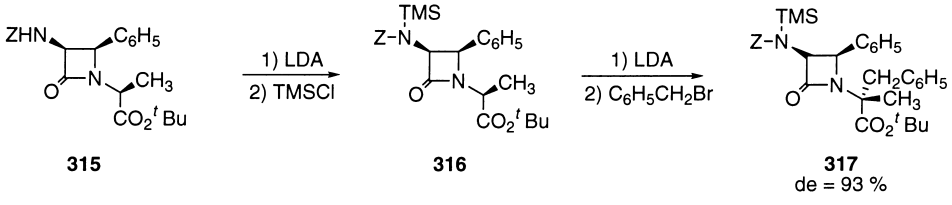
Once alkylation on the side chain at N_1 has occurred, alkylation at C_3 of the β-lactam ring can be performed and, in this way, a combination of both types of alkylation allows the synthesis of dipeptides consisting of two α-alkylamino acids[180] (Scheme 67).

The approach developed by Palomo et al. is based on the stereoselective [2+2] cycloaddition of imines, derived from a chiral α-alkoxy ketone, with (benzyloxy)ketene and subsequent transformation of the chiral β-lactam into an amino acid *N*-carboxy anhydride.[181,182] *N*-Benzylimines **328** react with (benzyloxy)ketene to afford the corresponding β-lactams as single diastereoisomers. These compounds,

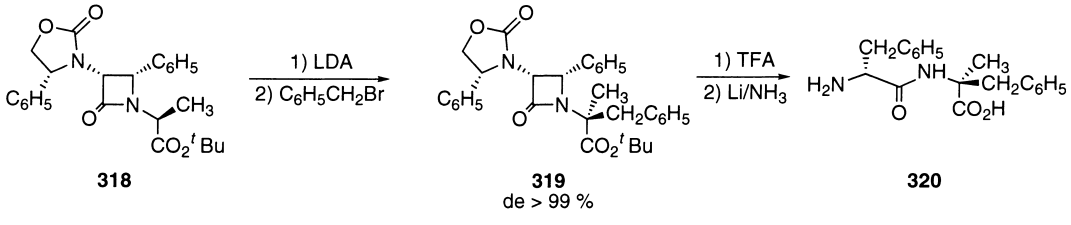


Entry	RX	de%
a	$CH_2=CHCH_2Br$	> 95
b	$C_6H_5CH_2Br$	> 98
c	CH_3CH_2Br	> 98
d	$3,4\text{-}(CH_3O)_2C_6H_3CH_2Br$	93

Scheme 63.



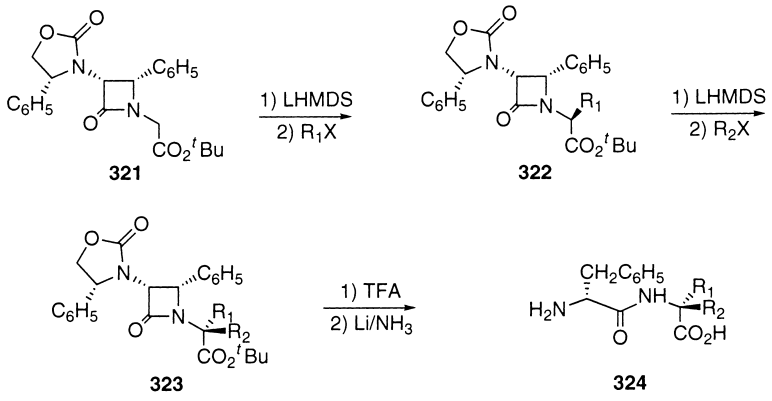
Scheme 64.



Scheme 65.

after hydrogenolysis, on exposure to commercial bleach and a catalytic amount of tetramethylpiperidine-*N*-oxyl (TEMPO) generate *N*-carboxy anhydrides of α-methyl-β-alkylserines, which can be coupled with amino acid benzyl esters in the presence of potassium cyanide to yield dipeptides containing α-alkylamino acids[181] (Scheme 68).

[2+2] Cycloaddition of (benzyloxy)ketene and *N*-benzylimine **333** generates a β-lactam that incorporates a masked formyl group at C_4 and this formyl group is generated by hydrolysis of the isopropylidene group and cleavage of the diol with sodium periodate. Wittig olefination followed by hydrogenolysis of the benzyl group with concomitant hydrogenation of the double bond of this 4-formyl-β-lactam, and subsequent treatment with commercial bleach in the presence of a catalytic amount of TEMPO generates the *N*-carboxy anhydrides of the corresponding α-methylamino acid, which can be coupled with amino acid esters as described above[182] (Scheme 69).

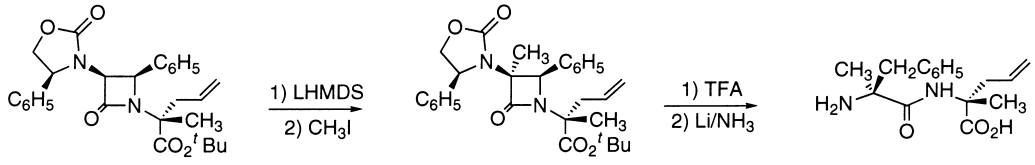


321 322 323 324

Entry	R_1X	R_2X	de%
a	CH_3I	$CH_2{=}CHCH_2Br$	> 99
b*	CH_3I	$CH_2{=}CHCH_2Br$	> 99
c	$CH_2{=}CHCH_2Br$	CH_3I	> 99
d	CH_3I	$C_6H_5CH_2Br$	> 99

* ent-**321**

Scheme 66.



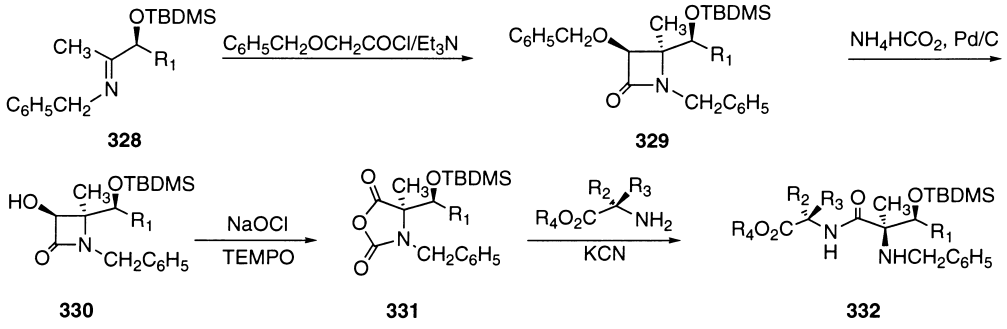
325 326 de > 99 % 327

Scheme 67.

5. Quaternary α-amino acids by rearrangement of β-carbonyl carboxylic acid derivatives

Another approach to the asymmetric synthesis of α-alkylamino acids is based on the rearrangement of β-carbonyl compounds to α-amino acid derivatives, a process that proceeds with total retention of configuration. Based on this approach, Fukumoto et al.[183,184] obtained chiral 8-phenylmenthyl α,α-dialkylmonomalonic esters by diastereoselective alkylation of 8-phenylmenthyl α-alkylmonomalonic esters. The reaction, performed by the addition of more than two equivalents of LDA and neutralisation of the dianion with an alkyl halide, occurs with high levels of diastereoselectivity, especially when allyl or benzyl halides are used. The major compound isolated is submitted to Curtius rearrangement followed by hydrogenolysis of the obtained urethane. Subsequent hydrolysis of the 8-phenylmenthyl ester using KOH and 18-crown-6 in toluene released the corresponding α-alkylamino acid in enantiomerically pure form. Surprisingly, the same diastereoisomer is obtained on methylation of 8-phenylmenthyl α-alkylmonomalonic esters and on alkylation of 8-phenylmenthyl α-methylmonomalonic ester (Scheme 70).

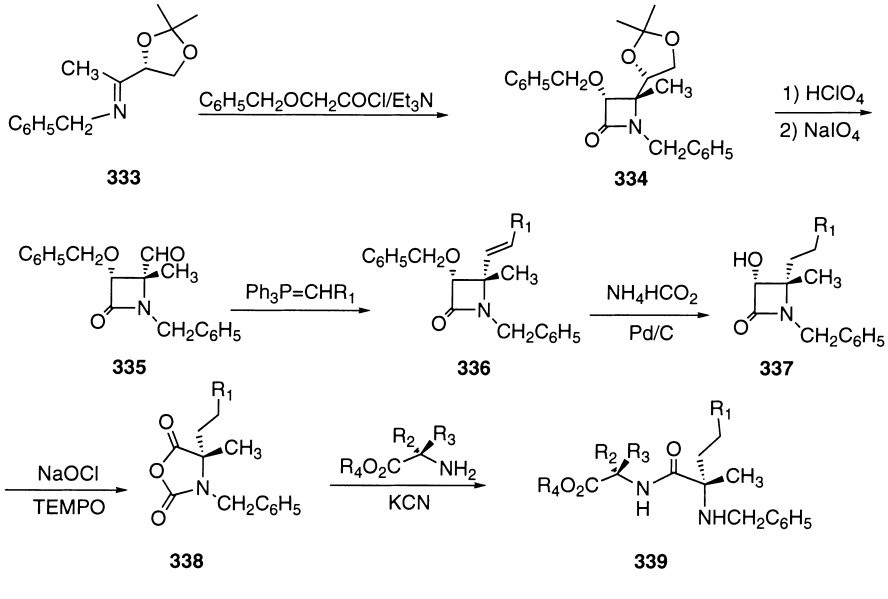
Diastereoselective alkylation of chiral cyanoesters derived from (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoyl-isoborneol provides key intermediates in the synthesis of α-alkylamino acids. By using this methodology, developed by our group, both enantiomers of the same amino acid can be obtained using different synthetic strategies. Alkylation of chiral 2-cyanopropanoate and methylation of chiral 2-



328 **329** **330** **331** **332**

Entry	R_1	R_2	R_3	R_4
a	CH_3	$C_6H_5CH_2$	H	CH_3
b	CH_3	$(CH_3)_2CH$	H	CH_3
c	$C_6H_5CH_2$	$C_6H_5CH_2$	H	$C_6H_5CH_2$
d	$C_6H_5CH_2$	$(CH_3)_2CH$	H	$C_6H_5CH_2$
e	$(CH_3)_2CH$	$C_6H_5CH_2$	H	$C_6H_5CH_2$
f	$(CH_3)_2CH$	CH_3	CH_3	$C_6H_5CH_2$

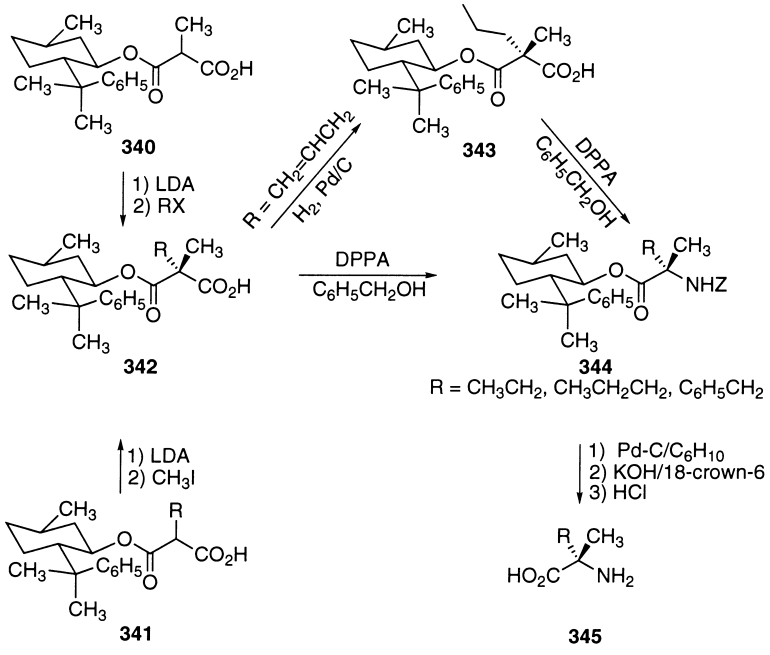
Scheme 68.



333 **334** **335** **336** **337** **338** **339**

Entry	R_1	R_2	R_3	R_4
a	H	$C_6H_5CH_2$	H	CH_3
b	C_6H_5	$(CH_3)_2CH$	H	$C_6H_5CH_2$
c	CH_3	CH_3	CH_3	$C_6H_5CH_2$

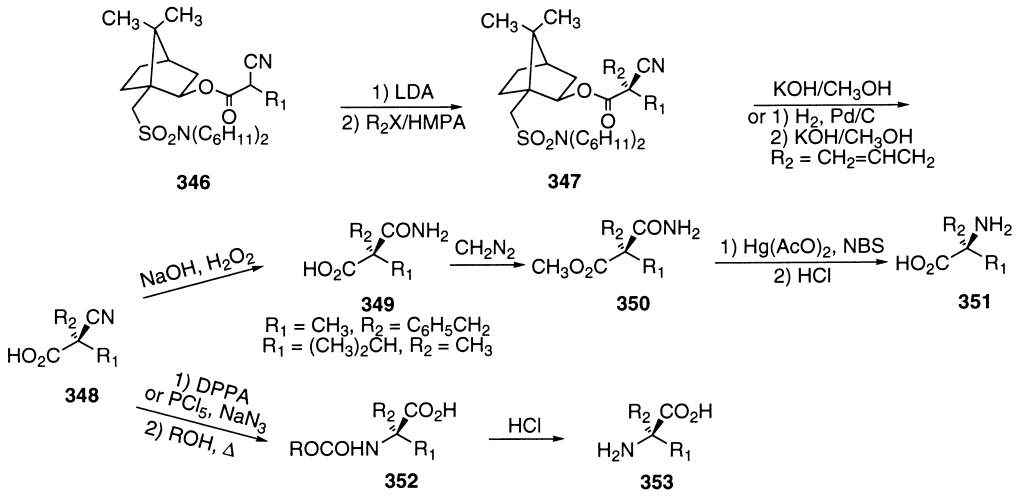
Scheme 69.



Entry	RX	R	dr
a	CH_3CH_2I		4/1
b	$CH_3CH_2CH_2I$		4/1
c	$CH_2=CHCH_2I$		7/1
d	$CH_2=C(CH_3)CH_2I$		6/1
e	$C_6H_5CH_2Br$		12/1
f	2-$NO_2C_6H_4CH_2Br$		10/1
g	4-$NO_2C_6H_4CH_2Br$		8/1
h	3,4-$(CH_3O)_2C_6H_3CH_2Br$		12/1
i	4-$CH_3OC_6H_4CH_2Br$		12/1
j	2-$CH_3OC_6H_4CH_2Br$		16/1
k		CH_3CH_2	5/1
l		$CH_3CH_2CH_2$	5/1
m		$C_6H_5CH_2$	15/1

Scheme 70.

alkylcyanoacetate provides both stereoisomers of the same α,α-dialkylcyanoacetate with high yields and stereoselectivities.[185] Moreover, a diastereomerically pure α,α-dialkylcyanoacetate can be conveniently elaborated to afford both enantiomers of the same amino acid. Basic hydrolysis of the diastereomerically pure α,α-dialkylcyanoacetate affords an enantiomerically pure α,α-dialkylcyanoacetic acid, which when submitted to Curtius rearrangement yields one of the two possible enantiomers of the final α-alkylamino acid after acidic hydrolysis. On the other hand, basic hydrolysis of the cyano group to an amide group followed by esterification of the carboxylic acid with diazomethane affords an amido ester, which is submitted to Hofmann rearrangement to yield, after acidic hydrolysis, the opposite enantiomer of the same α-alkylamino acid. This synthetic strategy has proven to be extremely versatile and amino acids with different side chains such as (*R*)-isovaline,[186] both enantiomers of α-methylphenylalanine,[187] and α-methylvaline,[188] (*R*)-α-methyltryptophan,[189] (*R*)-α-methyldiphenylalanine,[190] and several (*R*)-α-phenylamino acids[191] have been obtained in good chemical yields (Scheme 71).



346 347 348 349 350 351 352 353

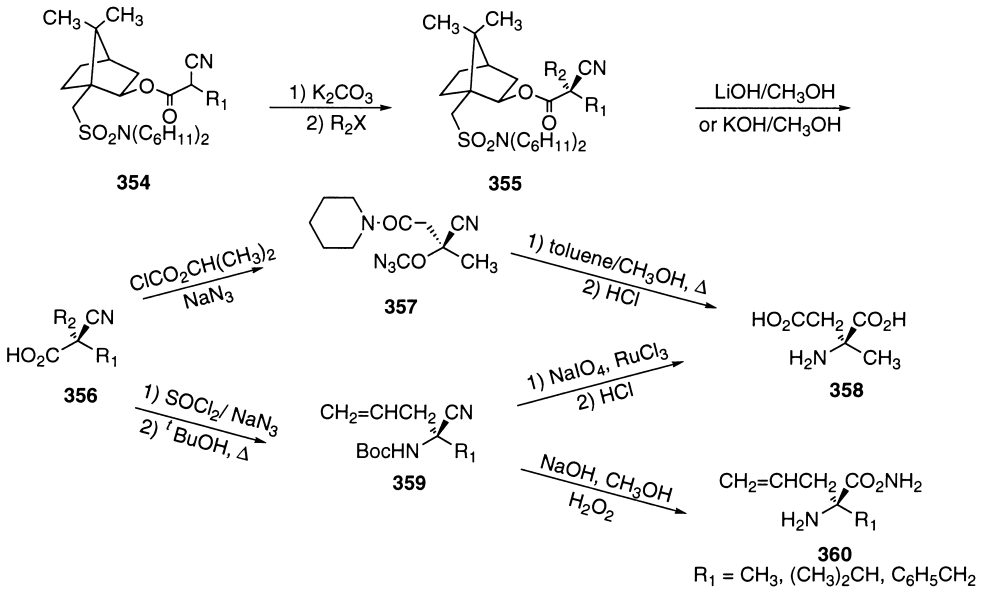
Entry	R_1	R_2X	dr	Ref.
a	CH_3CH_2	CH_3I	80/20	186
b	$C_6H_5CH_2$	CH_3I	80/20	187
c	CH_3	$C_6H_5CH_2I$	91/9	187
d	$(CH_3)_2CH$	CH_3I	82/18	188
e	*N*-Boc-3-indolyl-CH_2	CH_3I	60/40	189
f	CH_3	*N*-Boc-3-indolyl-CH_2Br	85/15	189
g	$(C_6H_5)_2CH$	CH_3I	86/14	190
h	C_6H_5	CH_3I	90/10	191
i	C_6H_5	CH_3CH_2I	> 98/2	191
j	C_6H_5	$CH_3CH_2CH_2I$	93/7	191
k	C_6H_5	$CH_2=CHCH_2I$	>98/2	191

Scheme 71.

To obtain (*S*)-α-methylaspartic acid, several electrophiles have been tested using potassium carbonate as a base. The alkylated compounds obtained in the reaction of (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl-2-cyanopropanoate with *N*-(bromoacetyl)piperidine[192] or allylbromide[193] were elaborated to (*S*)-α-methylaspartic acid. Moreover, allylation compounds of chiral 2-cyanoesters have been transformed into *N*-Boc-(*R*)-α-allylamino acid amides, which are suitable precursors for the synthesis of peptide isosteres and peptidomimetics[193] (Scheme 72).

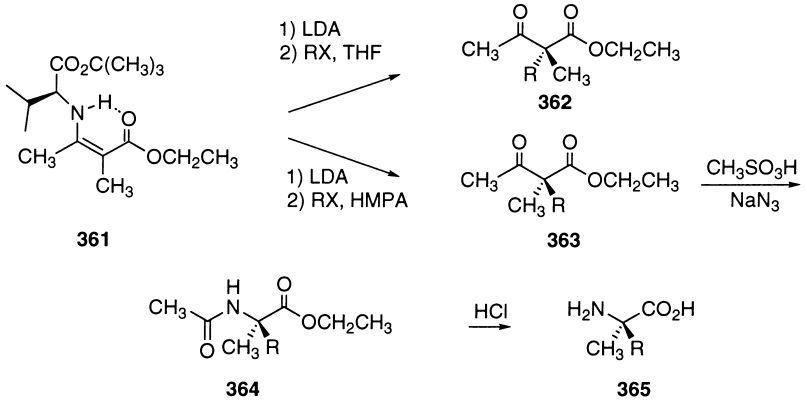
Asymmetric alkylation of chiral enamines obtained from β-ketoesters and L-valine *tert*-butyl ester affords optically active α,α-disubstituted-β-ketoesters. The diastereofacial selectivity of this reaction depends on the set of external ligand–toluene solvent systems, and complementary results are obtained by the use of one equivalent of HMPA as a ligand and by the use of three equivalents of THF, trimethylamine or dioxolane as a ligand.[194–196] Enantiomerically pure α,α-disubstituted-β-ketoesters are submitted to Schmidt rearrangement followed by acidic hydrolysis, and this process allows the asymmetric synthesis of (*R*)-α-methylphenylalanine, (*R*)-α-(2-naphthylmethyl)alanine and (*R*)-α-methylaspartic acid in excellent chemical yields[197] (Scheme 73).

Finally, Frutos et al.[198] have converted enantiomerically pure α,α-disubstituted-β-ketoesters into oximes, which have been submitted to Beckmann rearrangement, after being *N*-tosylated, to afford chiral *N*-acyl-α,α-disubstituted-α-aminoacid esters (Scheme 74).



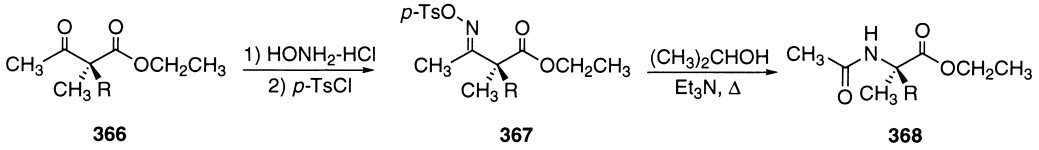
Entry	R_1	R_2X	dr	ref.
a	CH_3	$CH_3O_2CCH_2Br$	75/25	192
b	CH_3	$^tBuO_2CCH_2Br$	80/20	192
c	CH_3	$C_6H_5CH_2O_2CCH_2Br$	82/18	192
d	CH_3	1-piperidylcarbonyl-CH_2Br	92/8	192
e	CH_3	$CH_2{=}CHCH_2Br$	75/25	193
f	$(CH_3)_2CH$	$CH_2{=}CHCH_2Br$	95/5	193
g	$C_6H_5CH_2$	$CH_2{=}CHCH_2Br$	92/8	193

Scheme 72.



Entry	RX	de %
a	$C_6H_5CH_2$	92
b	2-naphthylCH_2Br	-
c	$CH_3O_2CCH_2Br$	76

Scheme 73.



366 367 368

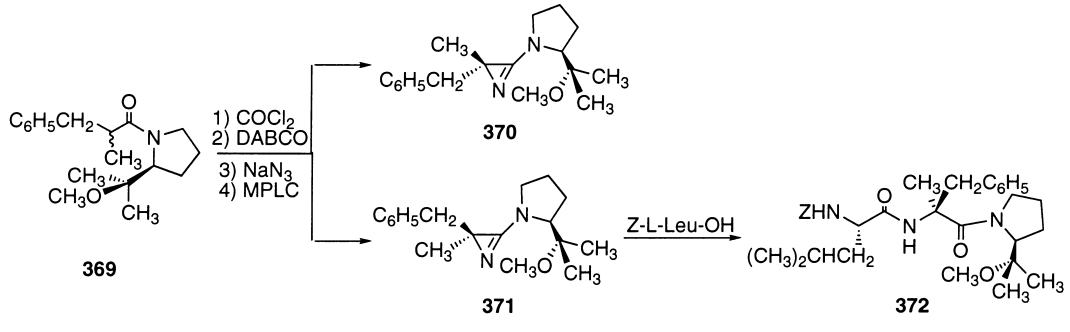
Entry	R	ee %
a	$C_6H_5CH_2$	99.7
b	4-Br$C_6H_4CH_2$	98.5
c	3-Cl$C_6H_4CH_2$	99
d	2-naphthylCH_2	97.8
e	CH_2=$CHCH_2$	95

Scheme 74.

6. Chiral 2*H*-azirines and aziridines as building blocks

In recent years chiral azirines and aziridines have been used as intermediates for the synthesis of α,α-dialkylamino acids. 3-Amino-2*H*-azirines have proven to be valuable synthetic equivalents of α,α-dialkylamino acids in peptide synthesis as their reactions with carboxylic acids and amino acids give α,α-dialkylamino acid derivatives. The acid-catalysed cyclisation of these derivatives affords 1,3-oxazol-5(4*H*)-ones, which act as intermediates in a subsequent amino acid coupling. This is known as the 'aziridine/oxazolone method' and was developed by Heimgartner.[199]

Although this reaction has been developed as a methodology for peptide synthesis, it can also be regarded as an asymmetric synthesis of the α,α-dialkylamino acid moiety. To obtain starting compounds, the authors developed a synthetic strategy based on the reaction between amide enolates and phosgene followed by reaction with sodium azide. When chiral amide **369**, derived from (*S*)-2-(1-methoxy-1-methylethyl)pyrrolidine and 2-methyl-3-phenylpropanoic acid, is used, a mixture of diastereoisomers is obtained from which chiral synthons for both (*S*)- and (*R*)-phenylalanine can be isolated by column chromatography. Azirine ring opening with *N*-benzyloxycarbonyl-L-leucine affords the corresponding dipeptide[200] (Scheme 75).

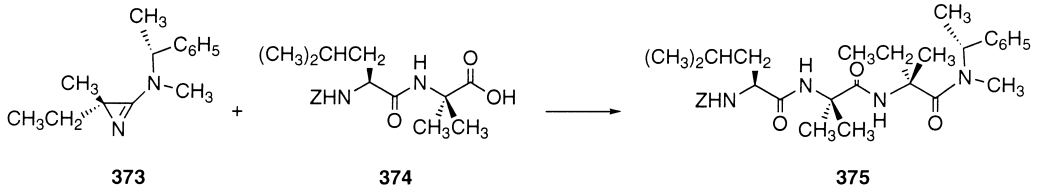


369 370 371 372

Scheme 75.

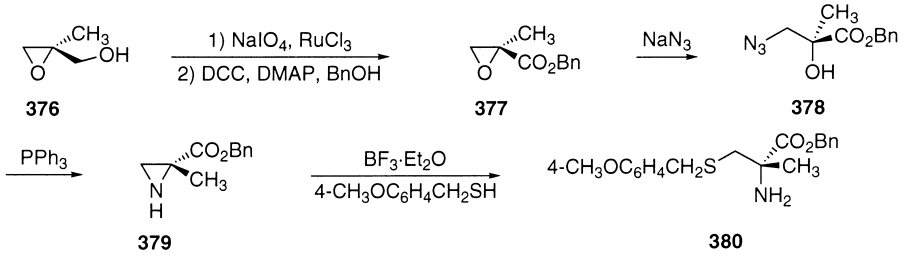
(*S*)-Iva and (*R*)-Iva synthons have also been obtained in diastereomerically pure form and incorporated into small peptides by reaction with *N*-benzyloxycarbonyl-L-leucyl-2-aminoisobutiric acid[201] (Scheme 76).

Chiral 2-aziridine carboxylates are also very useful synthetic intermediates as their regioselective ring opening leads to unusual amino acids.[202] In order to obtain α-alkylamino acids, 2-alkyl-2-aziridine carboxylates have to be used as starting compounds and several approaches have recently been described for the synthesis of such compounds in enantiomerically pure form.



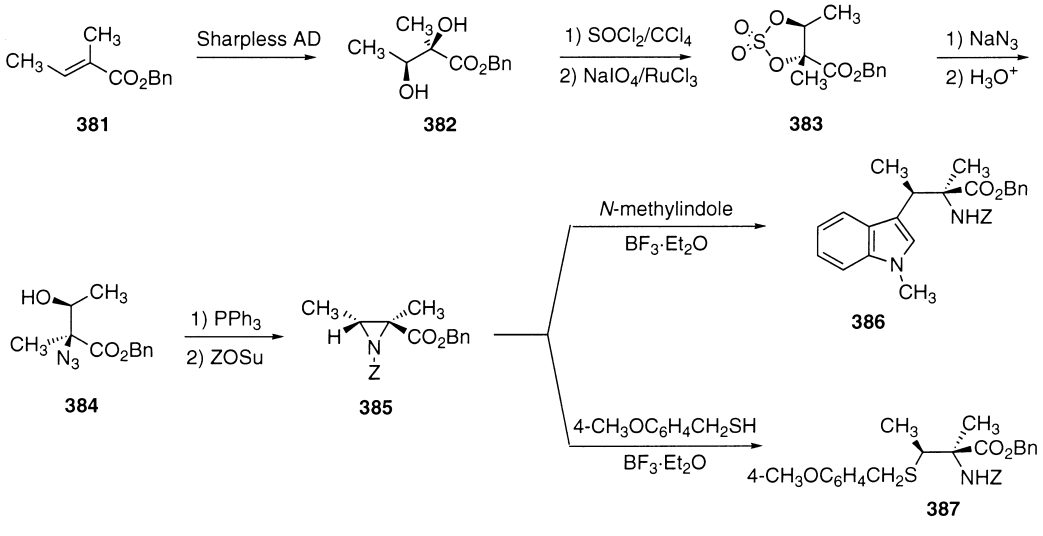
Scheme 76.

From (*R*)-2-methylglycidol, Goodman et al. obtained benzyl (*S*)-2-methyl-2-oxirane carboxylate. Regioselective ring opening of this compound with sodium azide followed by treatment with triphenylphosphine generated enantiomerically pure benzyl (*R*)-2-methyl-2-aziridine carboxylate in excellent chemical yield. From this compound, α-methylcysteines were obtained by regioselective Lewis acid-catalysed ring opening of the aziridine ring with 4-methoxy-α-toluenethiol[203] (Scheme 77).



Scheme 77.

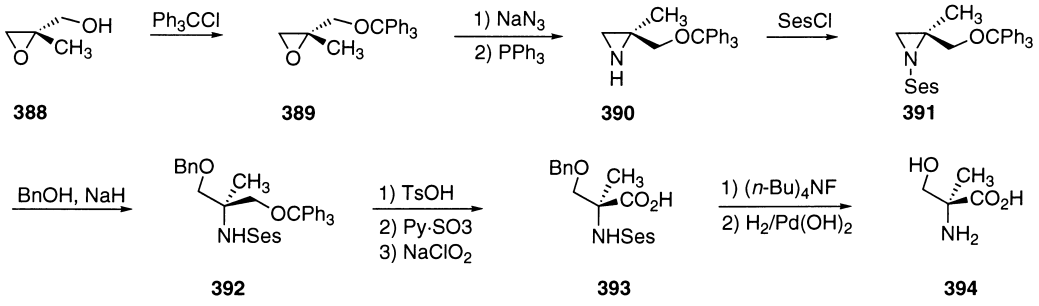
From enantiomerically pure benzyl *N*-benzyloxycarbonyl-2,3-dimethyl-2-aziridinecarboxylate **385**, obtained from benzyl tiglate **381** in five consecutive steps, α,β-dimethyltryptophan and α,β-dimethylcysteine derivatives have been obtained in a similar way[204] (Scheme 78).



Scheme 78.

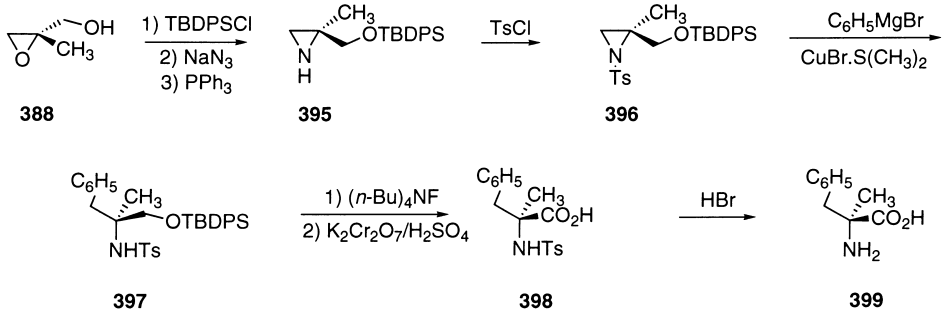
From commercially available (*S*)-2-methylglycidol, Wipf et al.[205,206] obtained the *O*-trityl derivative, which was submitted to ring opening with sodium azide followed by an in situ Staudinger reaction and cyclisation to afford the corresponding aziridine. *N*-Sulfonylation of aziridine with β-trimethylsilylethanesulfonyl chloride gives an activated aziridine that allows the smooth regioselective ring opening with sodium benzyloxide. Subsequent conversion of the *O*-trityl-protected primary alcohol

to the carboxylic acid yields an *N*,*O*-bisprotected (*S*)-α-methylserine derivative. From this derivative, the α-methylamino acid was obtained in enantiomerically pure form after removal of the protecting groups with fluoride anions and catalytic hydrogenolysis (Scheme 79).



Scheme 79.

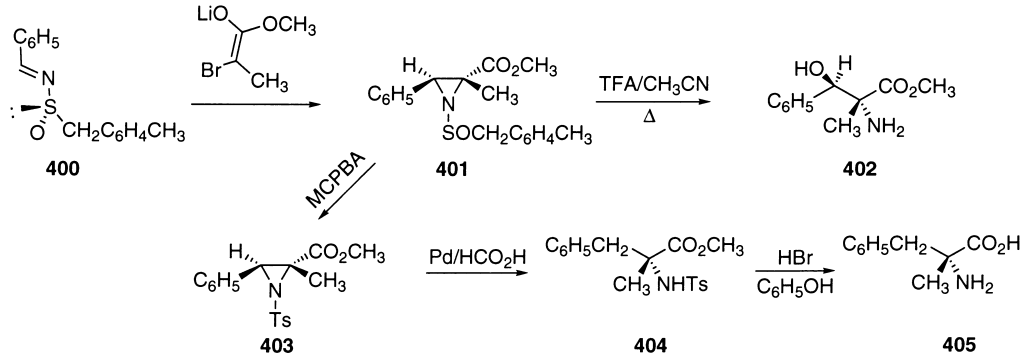
Pritchard[207] has also developed a synthetic strategy that allows the synthesis of chiral aziridines from (*S*)-2-methylglycidol. In this case, *O*-*tert*-butyldiphenylsilylglycidol is transformed into 2-*tert*-butyldiphenylsilyloxy-2-methyl-*N*-tosylaziridine by nucleophilic ring opening with sodium azide followed by a Staudinger reaction and *N*-tosylation with *p*-toluenesulfonyl chloride. Ring opening of the activated aziridine occurs regioselectively at C_3 when nitrogen, sulfur and carbon nucleophiles, i.e. soft nucleophiles, are used. This provides precursors of α-methylamino acids in good chemical yields. The potential of this methodology has been demonstrated by the transformation of the product obtained in the ring opening of the aziridine using a phenyl-organometallic reagent as the nucleophile, to give (*S*)-α-methylphenylalanine by removal of the silyl protecting group followed by oxidation of the primary alcohol and acidic *N*-tosyl cleavage (Scheme 80).



Scheme 80.

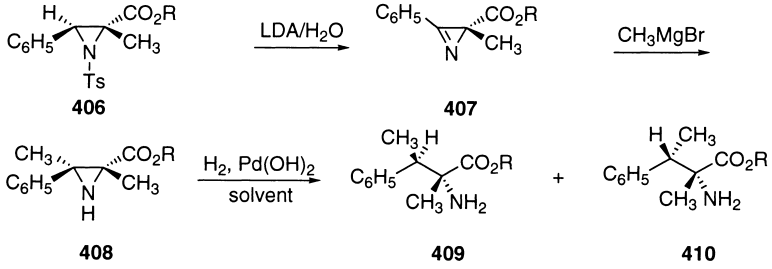
Davis et al.[208] obtained chiral 2-methyl-2-aziridinecarboxylic acid derivative **401** by a Darzens-type condensation between (*S*)-benzylidene-*p*-toluenesulfinamide and the lithium enolate generated from methyl α-bromopropionate. The major compound, obtained with a 90% diastereomeric excess, has a *trans* configuration. Acidic hydrolysis of *N*-sufinylaziridine under the appropriate reaction conditions cleanly affords (2*R*,3*R*)-α-methyl-β-phenylserine methyl ester. On the other hand, treatment of *N*-sufinylaziridine with *meta*-chloroperbenzoic acid readily affords activated *N*-tosylaziridine, and hydrogenation of this compound gives a quantitative yield of an (*R*)-α-methylphenylalanine derivative from which the free amino acid was isolated by acidic hydrolysis (Scheme 81).

N-Tosylaziridine **406** has been transformed into chiral methyl (*R*)-2*H*-azirin-2-carboxylate **407** by treatment with LDA. This compound adds Grignard reagents to afford more substituted aziridin-2-carboxylates from which 2,3-dimethylphenylalanine has been obtained. In the last step of the synthesis,



Scheme 81.

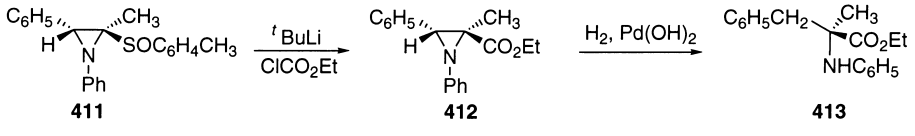
mixtures of *erythro* and *threo* compounds are obtained and the stereoselectivity for the hydrogenolysis of aziridines is highly dependent on the solvent and the substitution pattern of the substrate[209] (Scheme 82).



Entry	R	solvent	409/410
a	CH_3	CH_2Cl_2	67/33
b	CH_3	hexane	10/90
c	^{t}Bu	CH_2Cl_2	90/10
d	^{t}Bu	hexane	40/60

Scheme 82.

Finally, treatment of chiral 2-sulfinylaziridines with *tert*-butyllithium generates aziridinyllithiums that react with electrophiles to afford 2-substituted aziridines. When ethyl chloroformate is used as the electrophile, the aziridine obtained can be further elaborated to α,α-dialkylamino acids. In this way (*S*)-*N*-phenyl-α-methylphenylalanine ethyl ester has been obtained in moderate yields[210] (Scheme 83).



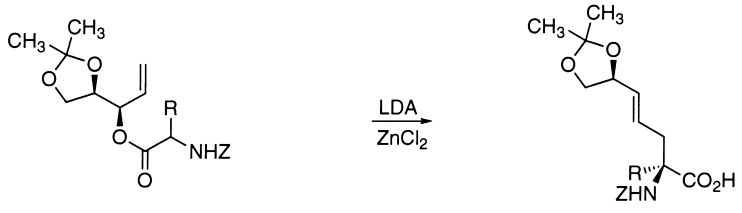
Scheme 83.

7. Sigmatropic rearrangements

The first synthesis of allylic amino acids by the Claisen rearrangement was described in 1975 by Steglich[211] and later by Barlett et al.,[212] but the general application of this method to the synthesis of γ,δ-unsaturated amino acid derivatives has been developed by Kazmaier et al.[213,214] To this end, allylic

esters of *N*-protected amino acids are deprotonated with LDA in the presence of a metal salt to afford a chelated enolate that, on heating, undergoes a Claisen rearrangement to give α-allylamino acids.

Although this methodology has been applied to the synthesis of a wide variety of α-alkyl-α-allylamino acids with high control of the stereochemistry, there are only a few examples of its application to the asymmetric synthesis of α-alkylamino acids. To obtain these compounds in enantiomerically pure form, allylic esters derived from chiral allylic alcohols have been used. When chiral allylic ester **414** is used as the starting compound, the rearrangement occurs with a high degree of chirality transfer, as one would expect, giving rise to α-alkyl-α-allylamino acids with high diastereomeric excesses[215] (Scheme 84).

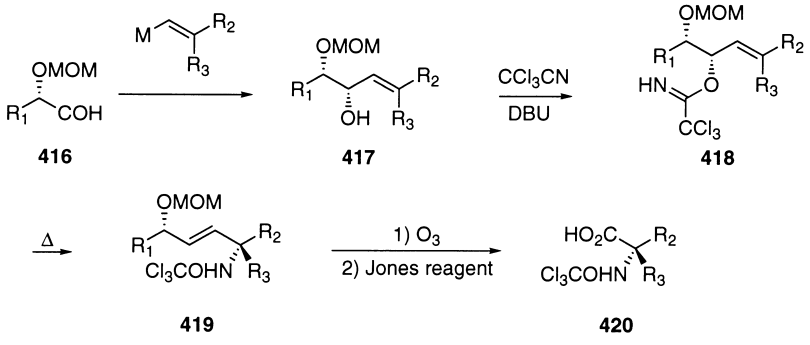


414 **415**

Entry	R	de%
a	CH_3	94
b	CH_3CH_2	90

Scheme 84.

Larchevêque et al.[216] have also developed a synthetic strategy based on a sigmatropic rearrangement. Condensation of vinylalanes with chiral α-alkoxyaldehydes gives chiral monoprotected diols in good yields and with a high diastereoselectivity. Reaction of these compounds with trichloroacetonitrile in the presence of base gives trichloroacetimidates, which on heating rearrange to allylic amines. The oxidative cleavage of these amines allows access to α,α-dialkylamino acids with high enantiomeric purity (Scheme 85).



416 **417** **418** **419** **420**

M	R_1	R_2	R_3	*syn/anti*
$Al(CH_3)_3Li$	C_6H_5	$CH_3(CH_2)_3$	CH_3	100/0
1/2 CuLi	$(CH_3)_2CH$	CH_3	$CH_3(CH_2)_3$	95/6
1/2 CuLi	$(CH_3)_2CH$	CH_3	CH_3CH_2	96/4
$Al(CH_3)_2$	$(CH_3)_2CH$	C_6H_5	CH_3	80/20

Scheme 85.

8. Addition of nucleophiles to the C=N bond

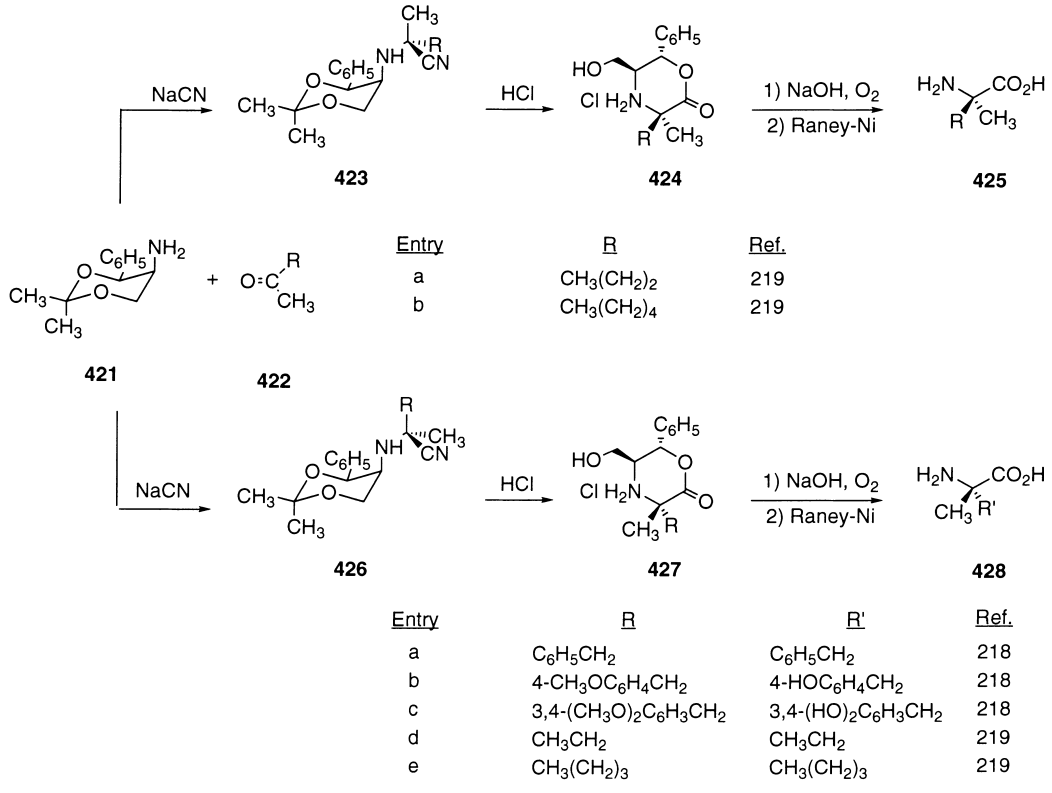
The Strecker synthesis, which involves the addition of cyanide or its equivalent to an imine and subsequent hydrolysis of the amino nitrile, is a well known and widely used procedure for the preparation of α-amino acids. In spite of the well documented use of the Strecker synthesis for the synthesis of chiral α-hydrogenamino acids,[70,71,217] very little literature describes the asymmetric synthesis of α-alkylamino acids using this synthetic strategy, and the first examples in this field were reported by Weinges et al. In this approach (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane[218,219] and other related compounds[220] were used as chiral amines to obtain chiral imines derived from methyl ketones. These imines react smoothly with sodium cyanide, after addition of acetic acid, to afford the corresponding α-methylamino nitriles in high yield and with excellent diastereoselectivity. Although the stereoselectivity in the addition of cyanide is almost total, equilibrium mixtures of both possible diastereoisomers are obtained on standing in solution due to a reversible Strecker reaction, and the ratio of products depends on the substitution pattern.[220,221]

Transformation of the amino nitrile into the corresponding amino acid is performed by treatment with concentrated hydrochloric acid. This leads to hydrolysis of both the nitrile and the acetal group and eventual cyclisation to a 2-oxomorpholine, which is followed by oxidative cleavage with sodium hydroxide, air and Raney nickel. In this way, (*S*)-α-methylphenylalanine, (*S*)-α-methyltyrosine, (*S*)-α-methyldopa[218] and several α-methylamino acids possesing aliphatic side chains[219] have been obtained. When methyl ketones with an even number of carbon atoms in the alkyl chain are used as starting compounds, the final amino acids are of *S*-configuration. However, ketones with an uneven number of carbon atoms in the alkyl chain are synthetic precursors of (*R*)-α-methylamino acids (Scheme 86).

(*S*)-Phenylethylamine has also been used as the chiral amine in the asymmetric Strecker synthesis of α-methylamino nitriles from methyl ketones.[222] Once again the amino nitriles, on standing in solution, afford equilibrium mixtures of both diastereoisomers. Fortunately, on cooling the mixture to 0°C, one of the diastereoisomers crystallises from the solution and this allows its isolation in diastereomerically pure form. The synthesis of the corresponding α-methylamino acid is then achieved by hydrolysis with concentrated sulfuric acid followed by hydrogenolysis. The absolute configuration of the final amino acid depends on the substitution pattern on the aromatic ring, which causes preferential crystallisation of the *R* or *S* diastereoisomers; when R_1 and R_2 are hydrogen, (*R*)-configured amino acids are obtained, whereas one or two methoxy substituents on the aromatic ring leads to (*S*)-amino acids (Scheme 87).

By using (*S*)-phenylethylamine hydrochloride instead of the free amine in the synthesis of α-methylphenylalanine from benzyl methyl ketone, Woodard et al.[223] avoided the equilibration of diastereomeric amino nitriles obtained in the addition of sodium cyanide to the chiral imine.

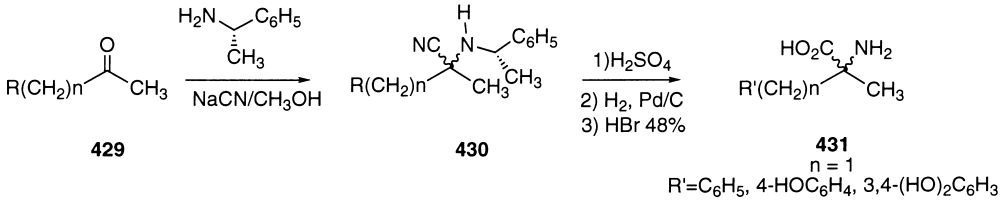
Another approach to the asymmetric synthesis of amino acids by the Strecker synthesis that allows the synthesis of α-methyl-β-hydroxyamino acids has recently been developed by Ohfune et al. Esterification of α-hydroxyketones with chiral *N*-*tert*-butoxycarbonylamino acids leads to an intermediate that, after removal of the *N*-Boc protecting group with trifluoroacetic acid and treatment of the resulting trifluoroacetate salt with sodium cyanide, gives a mixture of diastereomeric amino nitriles from which the major diastereoisomer has been isolated. Starting from acetol and (*S*)-*N*-*tert*-butoxycarbonylphenylalanine, (*S*)-*N*-*tert*-butoxycarbonylvaline or (*S*)-*N*-*tert*-butoxycarbonylalanine, cyclic amino nitriles were obtained diastereoselectively in high yield. The diastereoselectivity of the reaction depends on the bulk of the side chain of the amino acid, (*S*)-amino acid acetol esters preferentially give cyclic amino nitriles of 5*S* configuration. Treatment of the amino nitrile with *tert*-butyl hypochlorite and triethylamine, followed by hydrolysis with concentrated hydrochloric acid, leads to (*R*)-α-methylserine. The use



Entry	R	Ref.
a	$CH_3(CH_2)_2$	219
b	$CH_3(CH_2)_4$	219

Entry	R	R'	Ref.
a	$C_6H_5CH_2$	$C_6H_5CH_2$	218
b	4-$CH_3OC_6H_4CH_2$	4-$HOC_6H_4CH_2$	218
c	3,4-$(CH_3O)_2C_6H_3CH_2$	3,4-$(HO)_2C_6H_3CH_2$	218
d	CH_3CH_2	CH_3CH_2	219
e	$CH_3(CH_2)_3$	$CH_3(CH_2)_3$	219

Scheme 86.

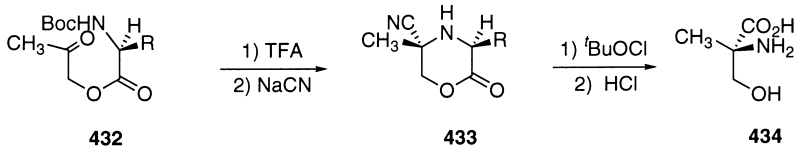


Entry	n	R	Abs. Conf.
a	1	C_6H_5	*R*
b	1	4-$CH_3OC_6H_4$	*S*
c	1	3,4-$(CH_3O)_2C_6H_3$	*S*
d	2	C_6H_5	*R*
e	2	4-$CH_3OC_6H_4$	*S*
f	2	3,4-$(CH_3O)_2C_6H_3$	*S*

Scheme 87.

of (*R*)-valineacetol as the starting material allows the synthesis of the opposite enantiomer of α-methylserine[224,225] (Scheme 88).

A mixture of two diastereomeric cyclic amino nitriles was obtained in the same way from racemic acetoin and (*S*)-*N*-*tert*-butoxycarbonylphenylalanine. Both compounds possess the same 5*S* configuration, and the major compound, obtained with 60% diastereomeric excess, was the 6*S* isomer. Prolonged reaction times at room temperature led to an almost equimolecular mixture of both diastereoisomers and under acidic conditions the mixture was further equilibrated to afford a 1/9 mixture of the 6*R*

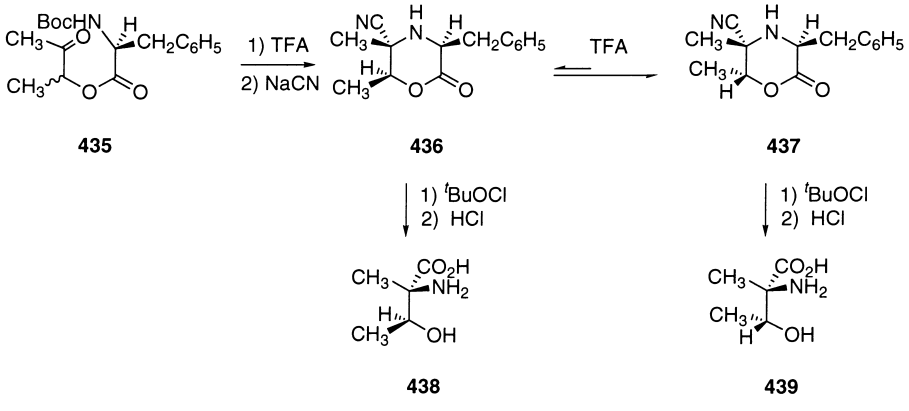


432 **433** **434**

Entry	R	dr
a	CH_3	3/1
b	$C_6H_5CH_2$	10/1
c	$(CH_3)_2CH$	25/1

Scheme 88.

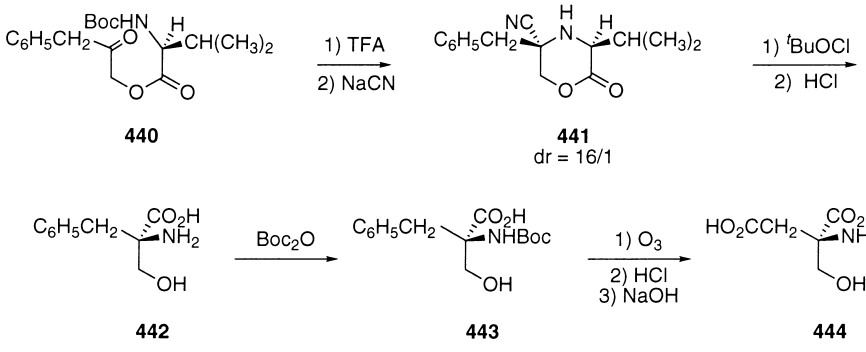
configured diastereoisomer. Removal of the phenylalanyl moiety from each of the diastereoisomers with *tert*-butyl hypochlorite and triethylamine followed by hydrolysis with concentrated hydrochloric acid led to (2*R*,3*S*)-2-methylthreonine and (2*R*,3*R*)-2-methyl*allo*threonine respectively[224,225] (Scheme 89).



435 **436** **437** **438** **439**

Scheme 89.

Under similar reaction conditions a 16/1 diastereomeric mixture of 5*S* and 5*R* cyclic amino nitriles was obtained from phenylacetol and (*S*)-*N*-*tert*-butoxycarbonylvaline. The major diastereoisomer was converted into (*R*)-α-benzylserine as above. Oxidative degradation of the phenyl group, after protection of the amino group, and final hydrolysis gave rise to (*R*)-α-carboxymethylserine. *S* enantiomers were obtained using (*R*)-*N*-*tert*-butoxycarbonylvaline[226] (Scheme 90).

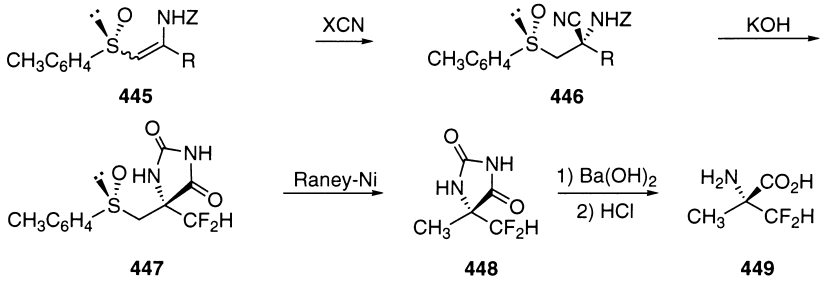


440 **441** dr = 16/1 **442** **443** **444**

Scheme 90.

Chiral *N*-carbobenzyloxy-α-fluoroalkyl-β-sulfinylenamines **445** also have been used as starting materials in the asymmetric Strecker synthesis to afford *N*-benzyloxycarbonyl-α-amino-β-sulfinyl

nitriles in excellent yields, but with only modest diastereoselectivity in favour of the *syn* diastereoisomer, without any influence of the geometry of the double bond. (*R*)-α-Difluoromethylalanine has been obtained from diastereomerically pure isolated (R_S,2*R*)-3-[(4-methylphenyl)sulfinyl]-2-[*N*-(benzyloxycarbonyl)amino]-2-difluoromethyl propionitrile by basic hydrolysis followed by desulfinylation by treatment with Raney nickel and hydrolysis of the hydantoin[227] (Scheme 91).

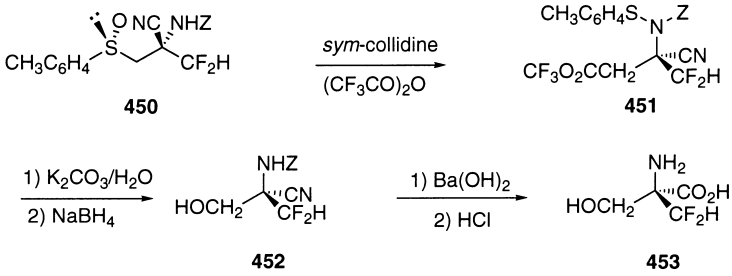


445 446 447 448 449

Entry	Geometry	XCN	R	dr
a	*Z*	KCN	CF_3	65/35
b	*Z*	KCN	CF_2H	65/35
c	*E*	KCN	CF_2H	65/35
d	*Z*	$(EtO)_2P(O)CN$	CF_2H	70/30
e	*E*	$(EtO)_2P(O)CN$	CF_2H	70/30
f	*Z*	TMSCN	CF_2H	70/30
g	*E*	TMSCN	CF_2H	70/30
h	*Z*	KCN	CF_2Cl	55/45

Scheme 91.

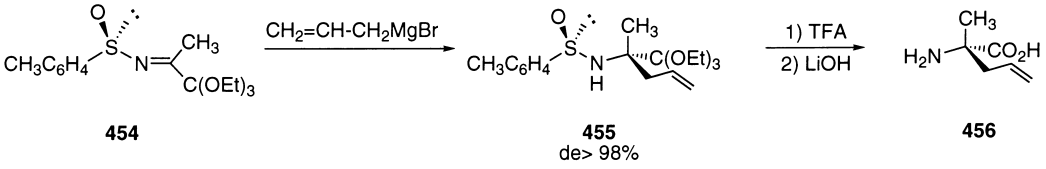
Alternatively, diastereomerically pure isolated (R_S,2*R*)-3-[(4-methylphenyl)sulfinyl]-2-[*N*-(benzyloxycarbonyl)amino]-2-difluoromethylpropionitrile under trifluoroacetic anhydride-promoted Pummerer reaction conditions undergoes a non-oxidative rearrangement to give an α-trifluoroacetoxysulfenamide, which is transformed into (*S*)-α-difluoromethylserine in two successive steps (Scheme 92).



450 451 452 453

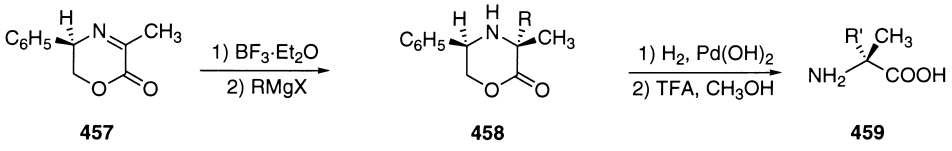
Scheme 92.

Stereoselective addition of organometallic reagents to the C=N bond of chiral compounds constitutes a recent methodology that has been applied to the asymmetric synthesis of α-alkylamino acids. In this context, chiral sulfinimines, imines and oximes have been used as starting compounds. Hua et al.[228] have recently reported that chiral sulfinimine **454**, obtained by the addition of methyllithium to triethoxyacetonitrile followed by treatment with (*R*)-menthyl-*p*-toluenesulfinate, undergoes a completely stereoselective addition reaction with allylmagnesium bromide. The obtained adduct, on hydrolysis of the sulfinamide and orthoester moieties, affords (*S*)-2-amino-2-methylpentenoic acid in enantiomerically pure form (Scheme 93).



Scheme 93.

(5*R*)-5-Phenyl-3-methyl-3,4-dehydromorpholinone, obtained by direct condensation of (*R*)-phenylglycinol with ethyl pyruvate, reacts with organomagnesium reagents in the presence of a Lewis acid to afford imine addition compounds as single diastereoisomers.[229] Hydrogenolysis of the morpholinone with palladium hydroxide under a pressure of 5 atmospheres furnishes enantiomerically pure α-methylamino acids (Scheme 94).



Entry	R	R'	de%
a	CH_3CH_2	CH_3CH_2	> 98
b	$CH_3(CH_2)_5$	$CH_3(CH_2)_5$	> 98
c	$(CH_3)_2CH$	$(CH_3)_2CH$	> 98
d	$(CH_3)_3C$	$(CH_3)_3C$	> 98
e	$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2$	> 98
f	$C_6H_5CH_2$	$C_6H_5CH_2$	> 98
g	$C_6H_5C{\equiv}C$	$C_6H_5(CH_2)_2$	> 98

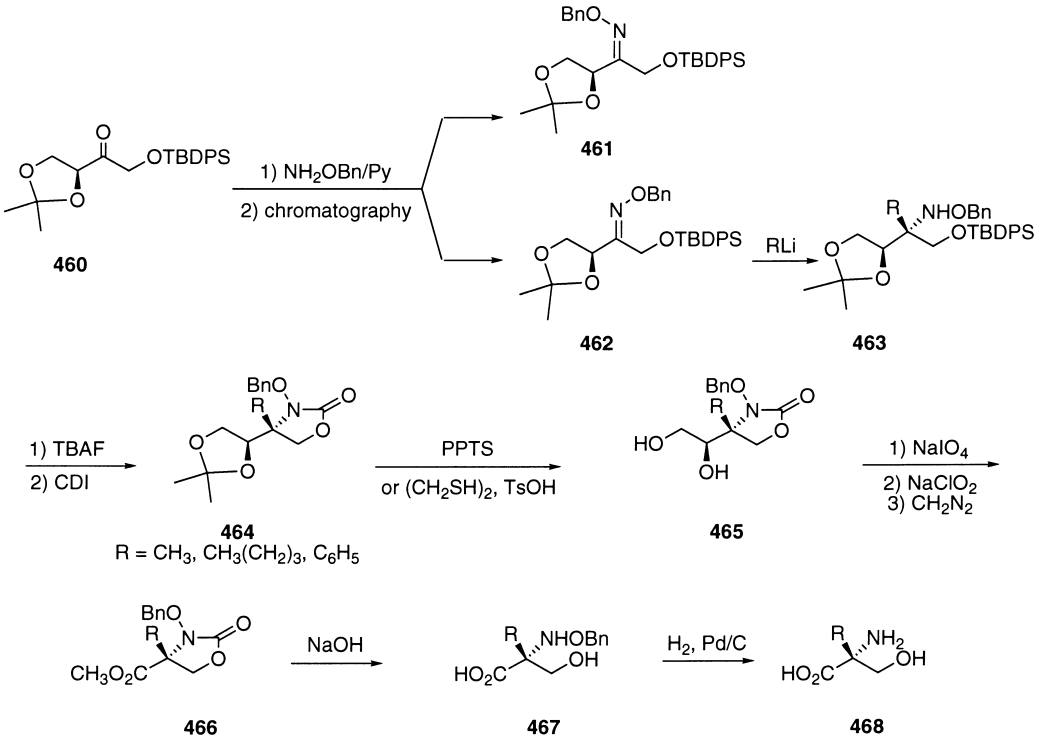
Scheme 94.

Suitably protected erythrulose reacts with *O*-benzylhydroxylamine to afford an equimolecular mixture of ketoxime ethers, which can be separated into geometrical isomers. Whereas addition of organolithium reagents to the C=N bond of *Z*-configured ketoximes **461** occurs with modest stereoselectivity, the addition of the same reagents to ketoximes of *E*-configuration **462** occurs quite stereoselectively and, in most cases, the minor diastereoisomer is not detected by NMR spectroscopy.[230,231] (*R*)-α-Substituted serines have been obtained in enantiomerically pure form from addition compounds.[232] To this end, *O*-benzylhydroxylamines **463** are desilylated and converted into oxazolidinones by treatment with carbonyldiimidazole. Cleavage of the acetonide, two-step oxidation of the diol and esterification then yields a 4-carboxymethyl-2-oxazolidinone that, upon hydrolysis and subsequent hydrogenolysis, furnishes the α-alkylamino acid (Scheme 95).

Finally, diastereoselective addition of butyllithium to chiral (*E*)-*O*-[(*R*)-1-phenylbutyl]ketoxime, derived from benzylidene acetone, affords the corresponding hydroxylamine in moderate yield and with about 80% diastereomeric excess. Cleavage of the N–O bond and acylation with benzylchloroformate gives the *N*-benzyloxycarbonyl-protected amine **471**, which is submitted to oxidative cleavage of the double bond to afford (*R*)-*N*-benzyloxycarbonyloxy-α-methylnorleucine[233] (Scheme 96).

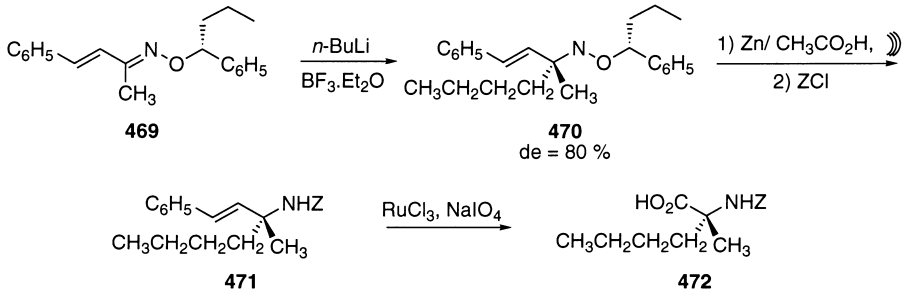
9. Enantioselective syntheses

In recent years there has been great progress in asymmetric synthesis employing a chiral organometallic compound as a catalyst, so-called catalytic asymmetric synthesis, and this constitutes one of the most



Entry	R	dr
a	CH_3	93/7
b	$CH_3(CH_2)_3$	> 95/5
c	$(CH_3)_3C$	> 95/5
d	C_6H_5	> 95/5
e	$CH_2{=}CHCH_2$	80/20

Scheme 95.

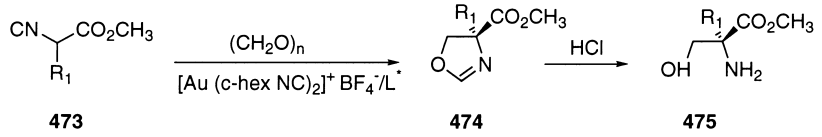


Scheme 96.

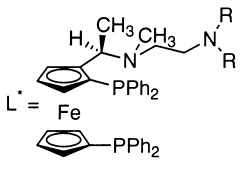
promising methods of obtaining an optically active compound since a small amount of chiral catalyst can produce a large amount of chiral compound. Despite the great potential of this synthetic strategy only a few examples have appeared in the literature dealing with the catalytic asymmetric synthesis of α-alkylamino acids.

Pioneering work in this field has been performed by Ito et al.[234] who have developed an enantioselective synthesis of α-alkylserines through a gold(I)-catalysed asymmetric aldol reaction of methyl α-

isocyanocarboxylates with formaldehyde, using (aminoalkyl)ferrocenylphosphines as chiral ligands. The reaction affords chiral methyl 4-alkyl-2-oxazoline-4-carboxylates with enantiomeric excesses varying from 44 to 81% depending on the chiral ligand. Among the various chiral ligands tested, those bearing an ethylamino or piperidino group at the terminal position of the ferrocene side chain were found to be more effective. Acidic hydrolysis of chiral methyl 4-alkyl-2-oxazoline-4-carboxylates gives the corresponding (*S*)-α-alkylserine in nearly quantitative yield (Scheme 97).



473 **474** **475**



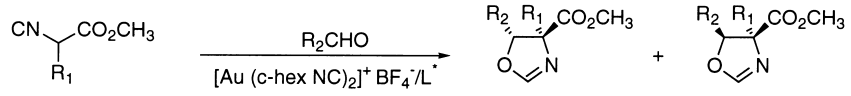
Entry	R-N-R	R_1	ee%
a	$N(CH_3)_2$	CH_3	64
b	1-piperidyl	CH_3	63
c	$N(CH_3)_2$	CH_3CH_2	70
d	1-piperidyl	CH_3CH_2	66
e	$N(CH_3)_2$	$(CH_3)_2CH$	71
f	1-piperidyl	$(CH_3)_2CH$	81
g	$N(CH_3)_2$	C_6H_5	67

Scheme 97.

This synthetic methodology has been applied to the synthesis of α-methylphenylalanine, α-alkyl-β-phenylserines and α-alkylthreonines.[235] In these cases, methyl α-isocyanocarboxylates were condensed with benzaldehyde and acetaldehyde to give a mixture of *cis* and *trans* oxazolines whose ratio depends on the substitution pattern of the starting α-isocyanocarboxylate. In the reaction with benzaldehyde, the predominant stereoisomer, obtained with a high enantiomeric excess, has a *trans* geometry except when the α-alkyl substituent is an isopropyl group. The reaction with acetaldehyde is less selective and also less enantioselective with the *cis* stereoisomer, obtained with mediocre or poor enantiomeric excess, being predominant in the mixture when non-equimolecular mixtures of *cis* and *trans* isomers are obtained (Scheme 98).

Enantioenriched oxazolines have been conveniently elaborated to the corresponding α-alkylamino acid. In this way, 5-phenyl substituted oxazolines have been submitted to palladium-catalysed hydrogenolysis to afford α-alkylphenylalanine derivatives. Moreover, enantioenriched oxazolines can be transformed into α-alkylphenylserines and α-alkylthreonines by acidic methanolysis (Scheme 99).

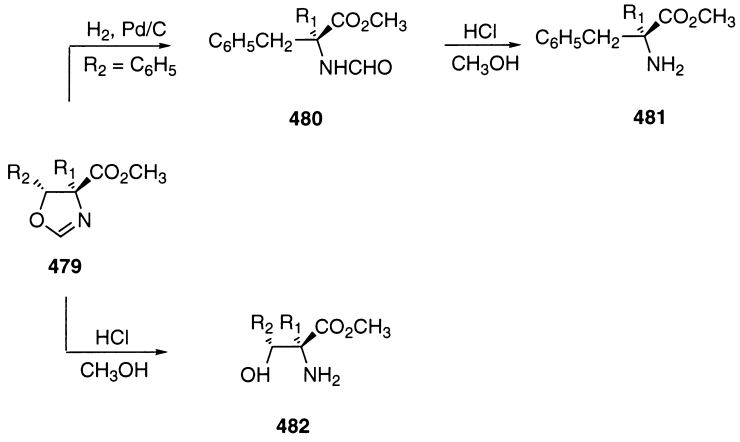
O'Donnell et al. have also developed an enantioselective route to α-alkylamino acids based on the well known strategy developed by the authors and applied to the asymmetric synthesis of monoalkylamino acids.[236] Asymmetric synthesis of α-methylamino acids is performed by phase-transfer catalytic alkylation, using cinchonine and cinchonidine as a chiral catalyst, of Schiff bases derived from aromatic aldehydes and alanine *tert*-butyl ester.[237] Optimal results were obtained using KOH/K_2CO_3 as the base and the *p*-chlorobenzaldehyde-derived imine as the substrate. Under these reaction conditions alkylation with several alkyl halides gave the corresponding alkylation products in good yields and with enantiomeric excesses in the range of 36–50% in favour of the enantiomer of *R* configuration when the cinchonine-derived chiral catalyst was used. With the use of *pseudoenantiomeric* cinchonidine-derived catalyst, the corresponding enantiomer of *S* configuration is obtained as the major compound although the enantiomeric excesses obtained are worse. Purification of the major enantiomer by crystallisation and subsequent deprotection releases the α,α-dialkylamino acid (Scheme 100).



476 477 478

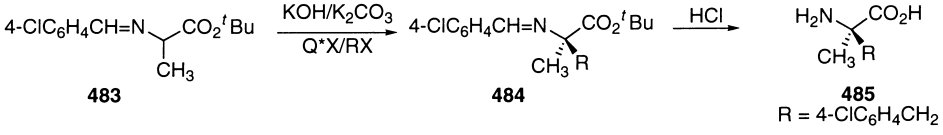
Entry	R-N-R	R_1	R_2	477/478	ee% 477	ee% 478
a	$N(CH_3)_2$	CH_3	C_6H_5	82/18	92	44
b	NEt_2	CH_3	C_6H_5	77/23	82	26
c	1-piperidyl	CH_3	C_6H_5	88/12	90	5
d	1-morpholyl	CH_3	C_6H_5	97/3	94	53
e	$N(CH_3)_2$	$(CH_3)_2CH$	C_6H_5	50/50	88	48
f	NEt_2	$(CH_3)_2CH$	C_6H_5	52/28	85	42
g	1-piperidyl	$(CH_3)_2CH$	C_6H_5	54/46	92	28
h	1-morpholyl	$(CH_3)_2CH$	C_6H_5	62/38	88	17
i	$N(CH_3)_2$	CH_3	CH_3	38/62	46	49
j	1-piperidyl	CH_3	CH_3	44/56	44	6
k	1-morpholyl	CH_3	CH_3	56/44	86	54
l	1-morpholyl	CH_3CH_2	CH_3	54/46	87	66
m	1-piperidyl	$(CH_3)_2CH$	CH_3	22/78	35	23
n	1-morpholyl	$(CH_3)_2CH$	CH_3	24/76	26	51

Scheme 98.

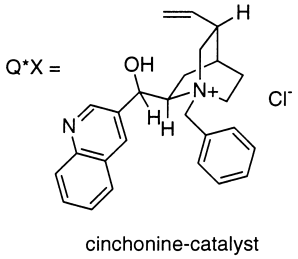


480 481 479 482

Scheme 99.



483 484 485
R = 4-ClC6H4CH2

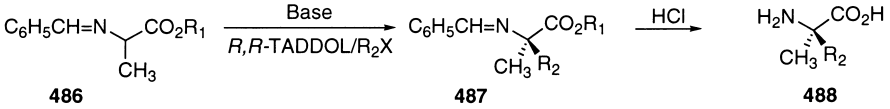


cinchonine-catalyst

Entry	RX	ee%
a	$4\text{-}FC_6H_4CH_2Br$	50
b	$4\text{-}ClC_6H_4CH_2Br$	48
c	$4\text{-}BrC_6H_4CH_2Br$	44
d	$C_6H_5CH_2Br$	44
e	2-naphthylCH$_2$Br	42
f	$CH_2{=}CHCH_2Br$	36

Scheme 100.

In a similar approach, Belokon' et al.[238] performed *C*-alkylation of Schiff bases derived from benzaldehyde and alanine esters under phase-transfer catalysis using (4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol, TADDOL, as the chiral promoter. The alkylation reaction proceeded with enantiomeric excesses varying from 24 to 82% and the best results were obtained when a stoichiometric amount of TADDOL was used. Final deprotection of the alkylation compounds allows the synthesis of enantioenriched (*R*)-α-methylphenylalanine and (*R*)-α-allylalanine (Scheme 101).



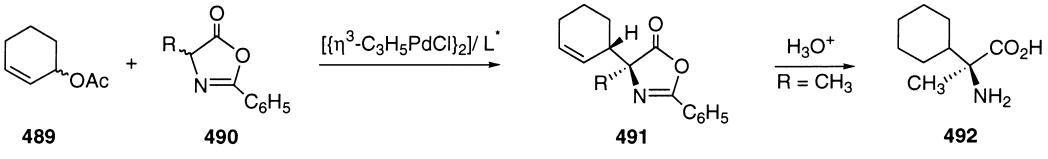
486 **487** **488**

Entry	R_1	R_2X	Base	ee%
a	CH_3	$C_6H_5CH_2Br$	NaH	70
b	$(CH_3)_2CH$	$C_6H_5CH_2Br$	NaH	60
c	$(CH_3)_2CH$	$CH_2=CHCH_2Br$	NaH	75
d	$(CH_3)_2CH$	$C_6H_5CH_2Br$	NaOH	82
e	$(CH_3)_2CH$	$C_6H_5CH_2Br$	KOH	24
f*	$(CH_3)_3C$	$C_6H_5CH_2Br$	NaH	40
g*	$(CH_3)_3C$	$C_6H_5CH_2Br$	NaOH	38

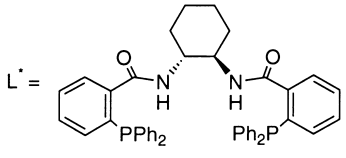
*S-alanine

Scheme 101.

Allylation of azlactones derived from *N*-benzoylamino acids with 3-acetoxycyclohexene using chiral palladium catalysts generated in situ, triethylamine as the base and acetonitrile as solvent gave the corresponding alkylation product in high yield, with a good stereoselectivity and a high enantioselectivity for both the major and the minor diastereoisomers. Removal of the minor diastereoisomer by column chromatography allowed the isolation of the major compound in enantiomerically pure form. As the size of the side chain of the amino acid increases, the diastereomeric excess increases. Hydrogenation of the double bond, followed by hydrolysis of azlactone gave the corresponding α,α-dialkylamino acid[239] (Scheme 102).



489 **490** **491** **492**

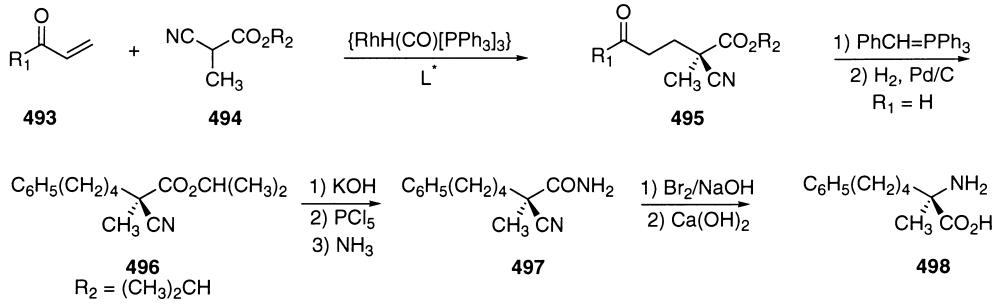


Entry	R	ee%
a	CH_3	99
b	$C_6H_5CH_2$	99
c	$(CH_3)_2CHCH_2$	99
d	$(CH_3)_2CH$	95

Scheme 102.

Finally, asymmetric Michael addition between α-cyanocarboxylates and vinylketones or acrolein, catalysed by rhodium complexes with a diphosphine as a chiral ligand, affords optically active Michael adducts in high yield and with enantiomeric excesses varying from 73 to 92% working at a temperature of 3–5°C and using benzene as a solvent.[240] The Michael adduct obtained in the reaction of isopropyl α-cyanopropanoate with acrolein has been further elaborated to (*R*)-2-amino-2-methyl-6-phenylhexanoic acid by treatment with benzyltriphenylphosphonium ylide, subsequent hydrogenation of the Wittig

olefination product and transformation of the ester moiety into the amino group through a Hofmann rearrangement (Scheme 103).



Entry	R_1	R_2	ee%
a	H	$(CH_3)_2CH$	87
b	H	$(^iPr)_2CH$	92
c	CH_3	CH_3	73
d	CH_3	CH_3CH_2	81
e	CH_3	$(CH_3)_2CH$	86
f	CH_3	$(CH_3)_3C$	81
g	CH_3	$(^iPr)_2CH$	93
h	CH_3CH_2	$(CH_3)_2CH$	85
i	CH_3CH_2	$(^iPr)_2CH$	91
j	C_6H_5	$(CH_3)_2CH$	83
k	4-$CH_3OC_6H_4$	$(CH_3)_2CH$	89
l	2-$CH_3OC_6H_4$	$(CH_3)_2CH$	86
m	4-ClC_6H_4	$(CH_3)_2CH$	85

Scheme 103.

The same research group has also described the asymmetric aldol reaction[241] and asymmetric allylic alkylation[242] of 2-cyanopropanoates to afford the corresponding aldol adduct and allylation compound respectively. However, further elaboration of these compounds, which would allow the asymmetric synthesis of α-alkyl-β-hydroxyamino acids and α-allyl amino acids, has not been described.

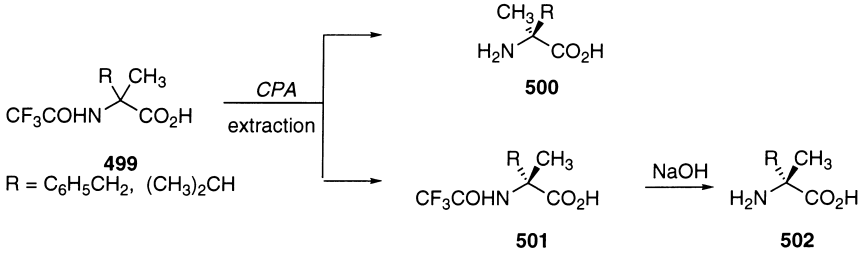
10. Resolution procedures

In addition to the procedures described above for the asymmetric synthesis of chiral non-racemic α,α-dialkylamino acids by asymmetric synthesis using either chiral auxiliaries or asymmetric catalysts, resolution procedures also allow their isolation in enantiomerically pure form from racemic mixtures obtained by non-asymmetric procedures. The resolution into enantiomers of a racemic mixture of α,α-dialkylamino acids can be performed using two major types of resolution procedure: enzymatic resolution of racemic amino acid derivatives or chemical resolution of diastereoisomers obtained from racemic amino acids.

The resolution of racemic compounds by enzyme-catalysed reactions has become a powerful tool in organic synthesis.[243–246] Hydrolytic enzymes are the biocatalysts most commonly used in organic synthesis and of particular interest among hydrolytic enzymes are amidases, proteases, esterases and lipases. These enzymes catalyse the hydrolysis and formation of ester and amide bonds and have been used extensively for the large-scale resolution of racemic mixtures of α-amino acid derivatives.[247]

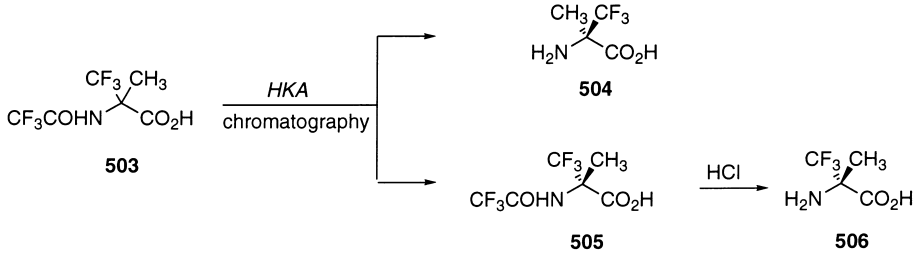
Despite the fact that the rate of enzymatic digestion of α,α-dialkylamino acid derivatives is often slow compared to the corresponding α-hydrogenamino acid derivatives, it is possible to obtain these compounds in enantiomerically pure from using hydrolytic enzymes.

One of the first examples that appeared in the literature was reported by Marshall et al.,[248] who performed the digestion of *N*-trifluoroacetyl-α-methylphenylalanine and *N*-trifluoroacetyl-α-methylvaline using bovine carboxypeptidase A (*CPA*). Protected derivatives of *R*-configuration were separated from the free (*S*)-amino acids obtained in the reaction mixture by a simple extraction procedure. Finally, (*R*)-α-methylphenylalanine and (*R*)-α-methylvaline were obtained from their *N*-trifluoroacetyl derivatives by mild hydrolysis in 1 N NaOH (Scheme 104).



Scheme 104.

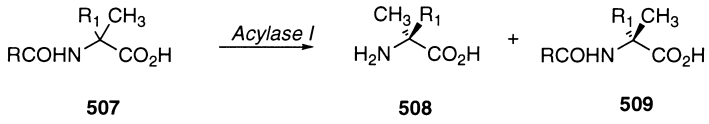
Racemic *N*-trifluoroacetyl-α-trifluoromethylalanine has also been resolved into enantiomers by partial hydrolysis with hog kidney aminoacylase (*HKA*). In this case, the (*R*)-amino acid derivative is selectively hydrolysed with 98% enantioselectivity and the unreacted *N*-trifluoroacetyl derivative has an optical purity of 97%[249] (Scheme 105).



Scheme 105.

Although acylase I, isolated from porcine kidney, shows poor reactivity towards α,α-dialkylamino acid amides, Whitesides et al.[250] have developed a new methodology to efficiently perform enzymatic resolutions, the so-called membrane-enclosed enzymatic catalysis (MEEC),[251] that uses enzymes placed in commercially available dialysis membranes. This methodology allows the use of large quantities of protein in small reaction volumes and the recovery of the soluble enzyme. By using this technique, α-methylmethionine, α-methylphenylalanine and α-methyltyrosine have been efficiently resolved with membrane-enclosed acylase I (Scheme 106).

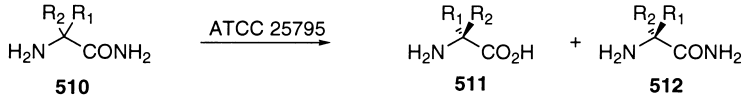
The enzymatic hydrolysis of α,α-dialkylamino acid amides using aminopeptidase from *Mycobacterium neoaurum* ATCC 25795 has also been reported. This enzyme is capable of selectively hydrolysing (*S*)-amino acid amides of a wide variety of α,α-dialkylamino acids to give the (*R*)-amide. Selectivity for substrates with two small substituents is only moderate, but for substrates with sterically more demanding substituents the enzyme is almost completely stereoselective. Separation of the two compounds can be performed by solubility differences of the (*S*)-acid and the (*R*)-amide in organic solvents[252–255] (Scheme 107).



507 **508** **509**

Entry	R_1	ee % 508	ee% 509
a	$CH_3SCH_2CH_2$	93	-
b	$C_6H_5CH_2$	91	80
c	4-$HOC_6H_4CH_2$	95	47

Scheme 106.



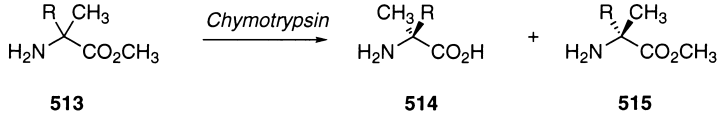
510 **511** **512**

Entry	R_1	R_2	ee % 511	ee% 512
a	CH_3	CH_3CH_2	80	73
b	CH_3	CH_2=$CHCH_2$	78	54
c	CH_3	$(CH_3)_2CH$	> 98	> 98
d	CH_3	$CH_2(CH_2)_5$	> 99	89
e	CH_3	$CH_2(CH_2)_8$	> 99	99
f	CH_3	$C_6H_5CH_2$	> 99	99
g	CH_3	C_6H_5CH=$CHCH_2$	> 98	48
h	CH_3	C_6H_5	95	86
i	CH_3CH_2	$C_6H_5CH_2$	> 96	62
j	CH_3CH_2	C_6H_5	94	14
k	CH_2=$CHCH_2$	$C_6H_5CH_2$	85	20

Scheme 107.

The amidase from *Ochrobactrum anthropi* can resolve heavily substituted α,α-dialkylamino acid amides that could not be efficiently resolved by *Mycobacterium neoaurum*[255–258] due to the fact that it hydrolyses (*S*)-amides selectively.

Roeske et al.[259] found that chymotrypsin hydrolyses the (*S*)-isomer of some α-methylamino acids, having deacylated the amino group, and this method has allowed the enzymatic resolution of α-methylphenylalanine methyl ester, α-methyltryptophan methyl ester and α-methyl-4-fluorophenylalanine methyl ester (Scheme 108).



513
R = 3-indolylCH$_2$, $C_6H_5CH_2$, 4-$FC_6H_4CH_2$

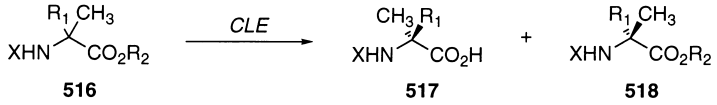
514 **515**

Scheme 108.

Candida lipolitica esterase (*CLE*) efficiently resolves α-methyl-α-benzylamino acid esters and *N*-acetamido derivatives, in most cases with the enantioselectivity of the recovered ester exceeding 98–99% at 50% substrate conversion[260] (Scheme 109).

Pig liver esterase (*PLE*) can be used for the resolution of α,α-dialkylamino acid esters. In this case, the *S* enantiomer of the amino ester is preferentially hydrolysed and enantioselectivities are low except for α-allyl-α-phenylglycine methyl ester and α-butyl-α-phenylglycine methyl ester.[253,255,258]

Humicola amino esterase[261] successfully catalyses the resolution of straight chain aliphatic α,α-dialkylamino acid esters in which both chains are larger than methyl. This method is especially useful

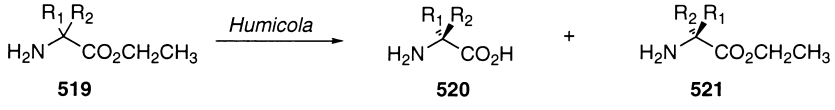


516 517 518

Entry	R_1	X	R_2	ee% 518
a	3,4-$(CH_3O)_2C_6H_3CH_2$	H	CH_3CH_2	> 99
b	$C_6H_5CH_2$	H	CH_3CH_2	> 99
c	$C_6H_5CH_2$	H	$CH_3(CH_2)_3$	> 99
d	3-indolylCH_2	H	$CH_3(CH_2)_3$	95
e	$C_6H_5CH_2$	Ac	CH_3CH_2	> 99
f	$(CH_3)_2CHCH_2$	Ac	CH_3CH_2	92

Scheme 109.

as these amino acids are difficult to resolve by chemical and biochemical means due to the flexibility of the two large alkyl groups, which become indistinguishable to most resolving agents. Most of the amino esters digested by this esterase are resolved into (*R*)-amino acids and (*S*)-amino esters (Scheme 110).



519 520 521

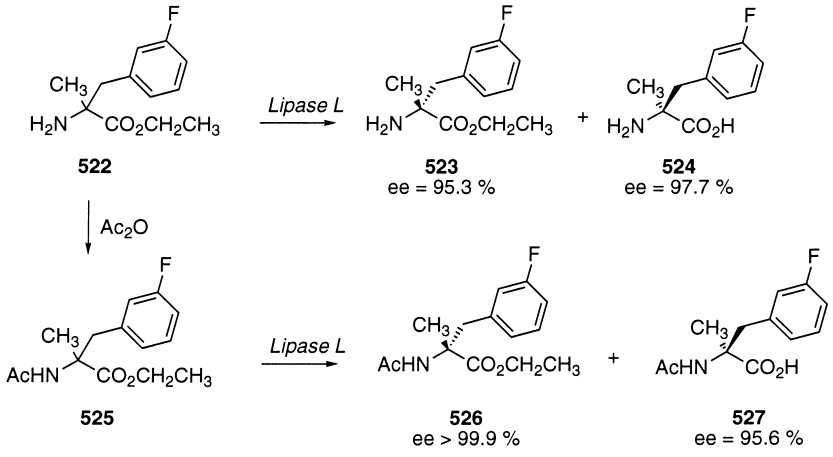
Entry	R_1	R_2	ee% 520	ee% 521
a	$CH_3(CH_2)_8$	CH_3CH_2	91	-
b	$CH_3(CH_2)_5$	CH_3CH_2	90	99
c	$CH_3(CH_2)_5$	$CH_3(CH_2)_2$	92	60
d	$C_6H_5CH_2$	CH_3CH_2	85	-
e	$C_6H_5CH_2$	CH_3	32	88
f	$CH_3(CH_2)_3$	CH_3CH_2	92	-
g	$CH_3CH{=}CH$	CH_3CH_2	94	66
h	$CH_3(CH_2)_2$	CH_3CH_2	26	53
i	CH_3	CH_3CH_2	36	100

Scheme 110.

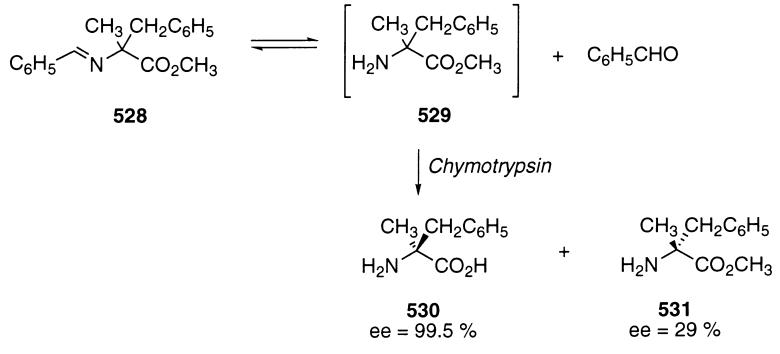
Spero et al.[262] have described the use of lipase L in the synthesis of α-methyl-3-fluorophenylalanine by enzymatic resolution of the ethyl ester or the *N*-acetyl ethyl ester. Starting from the ethyl ester, the *S* enantiomer was hydrolysed to the acid and the *R* enantiomer remained as the ester. Whereas the amino ester can be easily isolated from the reaction by extraction, the amino acid had to be acetylated to achieve their isolation. Starting from the *N*-acetyl derivative the (*R*)-acetylamino ester remained unreacted, whereas the *S* enantiomer was saponified to the acid; in this case the isolation of both enantiomers was easily performed in high yields (Scheme 111).

Belokon' et al.[263] have described the use of Schiff bases derived from amino acid esters as substrates towards chymotrypsin and lipases. The procedure has the inherent advantage of the lability of the *N*-protected group and the increased solubility in organic and aqueous–organic solvents and it has been successfully applied to the resolution of α-methylphenylalanine. The (*S*)-amino acid with a 98% enantiomeric excess precipitated out from the solution as the reaction progressed and the liberated aldehyde and unhydrolysed (*R*)-ester, with 29% enantiomeric excess, remained in solution (Scheme 112).

Lipase-mediated transesterification of 2-alkyl-2-benzoylamino-3-butenols using vinyl acetate as an acyl donor preferentially acetylates one enantiomer of the substrate.[264] Among the variety of enzymes tested, lipase AK-20 appeared to be the most enantioselective catalyst and optimal results were obtained working with water-saturated benzene as a cosolvent. Deacetylation of acetates **534** followed by oxida-



Scheme 111.



Scheme 112.

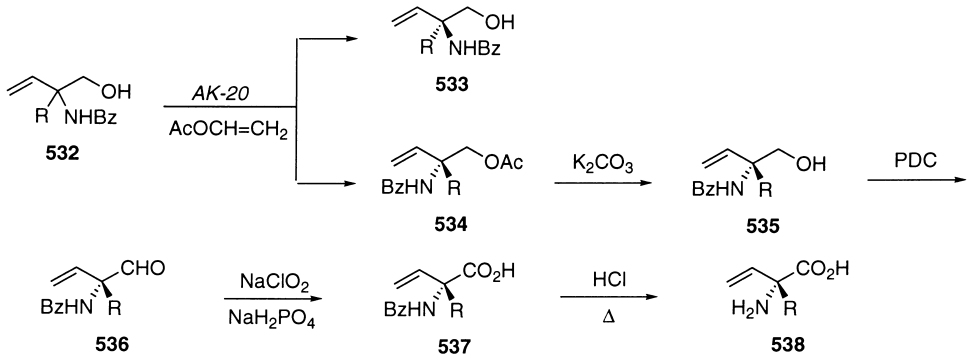
tion of the hydroxymethyl side chain to acid and final acidic hydrolysis provides the free α-vinylamino acids (Scheme 113).

Pig liver esterase has been used to resolve cyclic β-ketoesters bearing a quaternary carbon centre. Enantiomerically pure unreacted β-ketoesters have been submitted to Beckmann rearrangement promoted by silica gel through an intermediate tosylated oxime. The lactams, obtained in excellent yields as enantiomerically pure compounds, are *N*-Boc protected and treated with a nucleophile to afford the corresponding esters or acids[265] (Scheme 114).

Björkling et al.[266] obtained α-methylphenylalanine, α-methyltyrosine and α-methyldopa by Curtius rearrangement of enantiomerically pure methyl α,α-dialkylmonomalonic esters obtained by enzyme-catalysed hydrolysis of their corresponding dimethyl esters using pig liver esterase (*PLE*) or chymotrypsin. Enantioselectivity in the resolution procedure using *PLE* is not total. The use of chymotrypsin gives enantiomerically pure monoesters after incubation times of several weeks (Scheme 115).

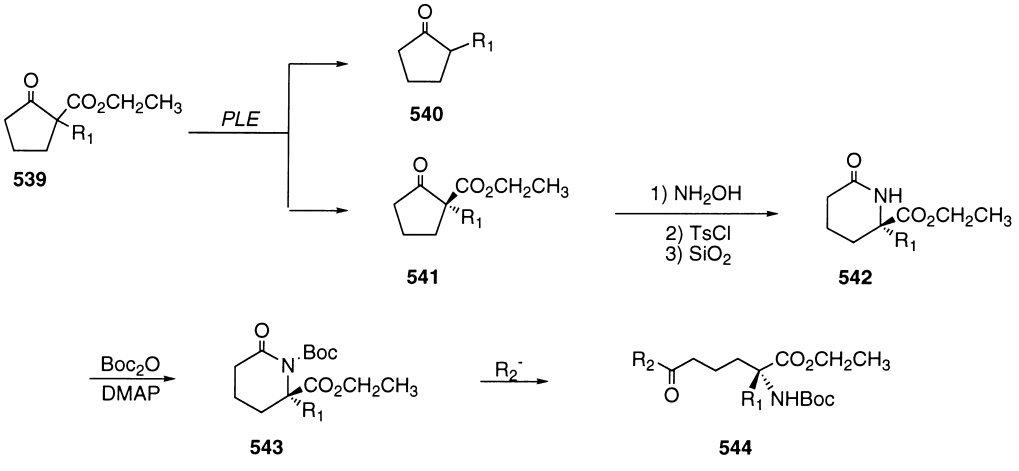
Nagao et al.[267] have recently reported a new synthesis of α-substituted serines based on enantioselective enzymatic hydrolysis of diethyl α-alkyl-α-(benzyloxycarbonylamino)malonates using pig liver esterase or rabbit liver esterase (*RLE*). Subsequent reduction of the carboxy or the carbethoxy moiety of the (*R*)-ethyl α-alkyl-α-(benzyloxycarbonylamino)malonates obtained in this way allows the synthesis of both enantiomers of the amino acid (Scheme 116).

Compound **552** has been further elaborated to give the longer chain α-substituted serine derivative **555** through ozonolysis of the allylic moiety and subsequent Horner–Wadsworth–Emmons olefination of the resulting aldehyde with methyl bis(trifluoroethyl)phosphonate (Scheme 117).



Entry	R	ee% 534
a	3,4-(TBDMSO)$_2$C$_6$H$_3$CH$_2$	67
b	C$_6$H$_5$CH$_2$	60 (1st cycle)
c	C$_6$H$_5$CH$_2$	86 (2nd cycle)
d	CH$_3$	80 (1st cycle)
e	CH$_3$	98 (2nd cycle)

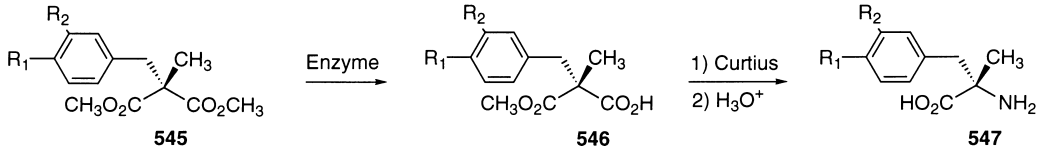
Scheme 113.



Entry	R_1	R_2	ee%
a	CH_3CH_2	CH_3CH_2O	100
b	CH_3CH_2	HO	100
c	CH_3CH_2	CH_3	100
d	CH_2=$CHCH_2CH_2$	CH_3CH_2	100

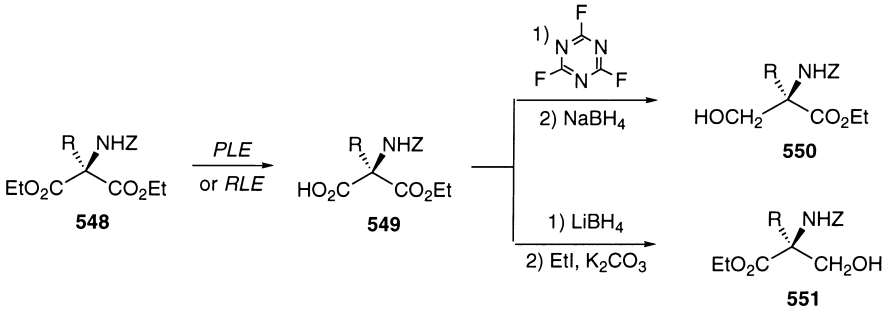
Scheme 114.

On the other hand, the difunctional nature of α,α-dialkylamino acids also allows their chemical resolution through direct crystallisation of diastereomeric compounds obtained from the racemic amino acid and a chiral resolving agent such as brucine,[268,269] cinchonidine,[270] phenylethylamine,[271] 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (BNPPA)[272] or the resolving agent chlocyphos.[273] Nevertheless, these classical resolution procedures are often tedious and time consuming as diastereomerically pure compounds are only obtained after several crystallisation cycles.



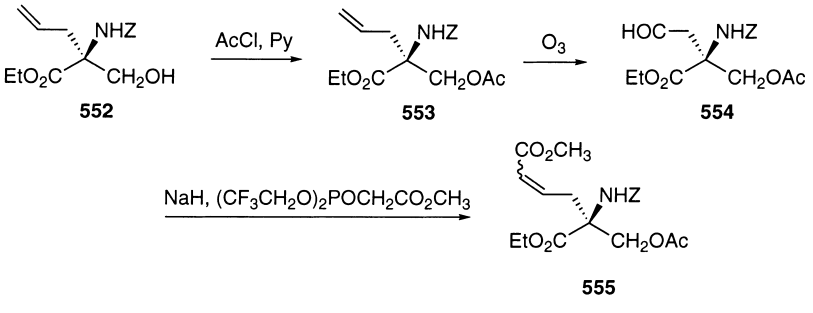
Entry	Enzyme	R_1	R_2	ee%
a	*PLE*	H	H	45
b	*PLE*	CH_3O	H	82
c	*PLE*	CH_3O	CH_3O	93
d	*chymotrypsin*	H	H	100
e	*chymotrypsin*	CH_3O	H	100
f	*chymotrypsin*	CH_3O	CH_3O	100

Scheme 115.



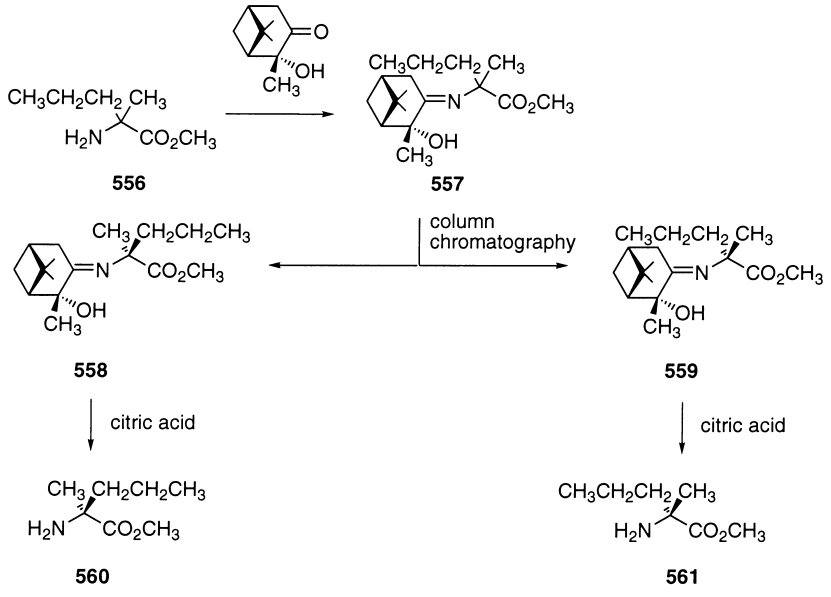
Entry	Enzyme	R	ee%
a	*PLE*	CH_3	97
b	*PLE*	$C_6H_5CH_2$	95
c	*PLE*	$CH_2{=}CHCH_2$	60
d	*RLE*	$CH_2{=}CHCH_2$	90

Scheme 116.



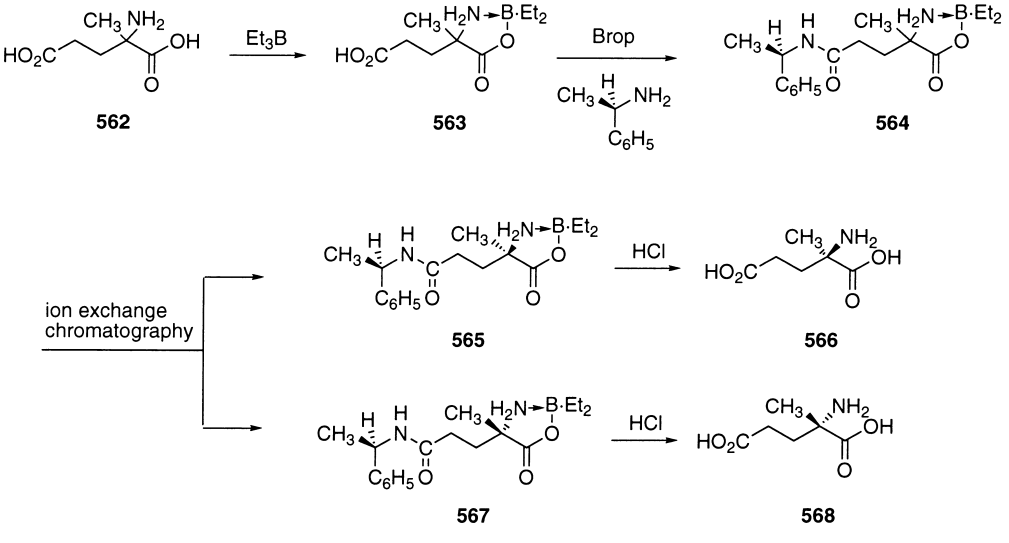
Scheme 117.

In certain cases it is possible to isolate both diastereomeric compounds obtained in the reaction of the racemic α,α-dialkylamino acid with a chiral compound by using chromatographic techniques that are nowadays more convenient. For example, α-methylnorvaline and α-propyl-2-bromophenylalanine have been resolved by simple column chromatography on silica gel through Schiff bases of their methyl esters with 2-hydroxypinan-3-one. After column chromatography, acidic hydrolysis of the Schiff bases under mild conditions provides the corresponding amino esters in enantiomerically pure form[274] (Scheme 118).



Scheme 118.

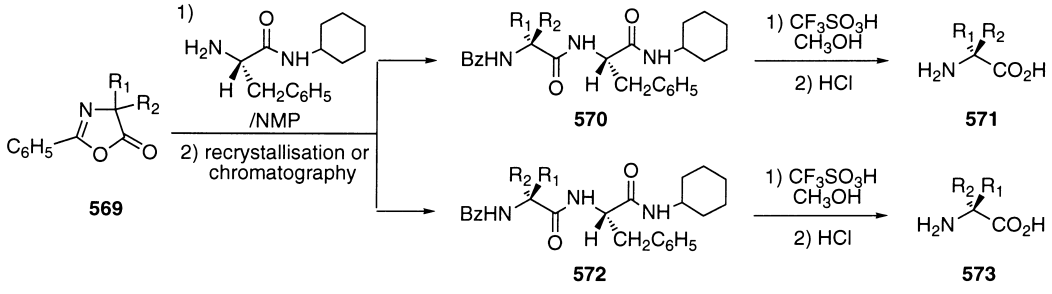
α-Methylphenylalanine has been resolved by simple column chromatography of its diastereomeric α-boroxazolidinone-ɣ-phenylethylamide or ɣ-phenylethanolamide. The amino acid reacts with triethylborane to afford quantitatively the corresponding boroxazolidinone derivative, which is coupled efficiently with (*R*)-1-phenylethylamine with the reagent Brop. This compound is chromatographed on a silica gel column to afford both isolated diastereoisomers in quantitative yield. The same procedure can be applied to the corresponding amides derived from (*R*)-phenylglycinol. Final hydrolysis to the free amino acids is achieved after treatment with 6 N hydrochloric acid[275] (Scheme 119).



Scheme 119.

Among the most recent studies on the chemical resolution of diastereomeric compounds derived from racemic α,α-dialkylamino acids, it is worth mentioning the methodology developed by Obrech et al. based on the easy separation of di- and tripeptides, containing a phenylalanine residue, derived

from *N*-acyl-α,α-dialkylamino acids. 4,4-Disubstituted-2-phenyloxazolones can be obtained by cyclisation of the corresponding *N*-benzoylamino acid by the action of an activating agent such as *N*,*N*-dicyclohexylcarbodiimide or 1,1′-carbonyldiimidazole, or by alkylation of 4-monosubstituted-2-phenyloxazolones with an electrophile in the presence of sodium hydride.[276] Treatment of this compound with a chiral amide derived from phenylalanine provides diastereomeric dipeptides that can be easily separated by crystallisation or column chromatography.[277] The most efficient and versatile of the chiral amides used to resolve α,α-dialkylamino acid derivatives is the cyclohexylamide derived from phenylalanine, which has allowed the isolation of both enantiomers of α-methylphenylalanine, α-methylvaline, α-methylphenylglycine,[278] 2-(aminomethyl)alanine, 2-(aminomethyl)leucine,[279] α-methylglutamic acid, α-methylaspartic acid and α-isobutylaspartic acid[280] (Scheme 120).



Entry	R_1	R_2	Ref.
a	CH_3	$C_6H_5CH_2$	278
b	CH_3	$(CH_3)_2CH$	278
c	CH_3	C_6H_5	278
d	CH_3	NHBz	279
e	$(CH_3)_2CHCH_2$	NHBz	279
f	CH_3	$CH_2CH_2CO_2{}^tBu$	280
g	CH_3	$CH_2CO_2{}^tBu$	280
h	$(CH_3)_2CHCH_2$	$CH_2CO_2{}^tBu$	280

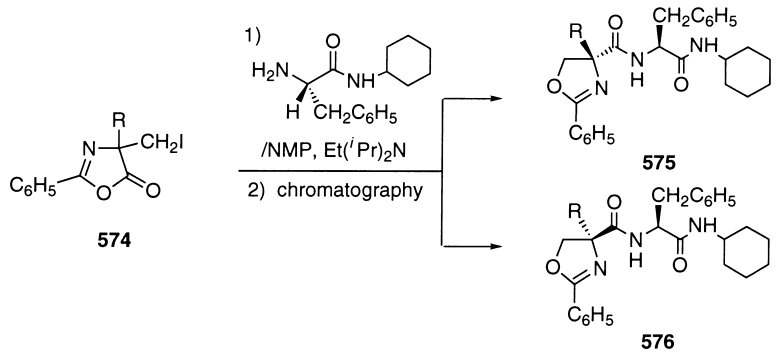
Scheme 120.

When the authors applied the same procedure to racemic 4-alkyl-4-iodomethyl-2-phenyloxazolone, a diasteromeric mixture of oxazolines was obtained. Diastereoisomers were separated by flash chromatography, after which they were transformed into dipeptides incorporating an α-alkylserine residue[281,282] (Scheme 121).

Treatment of racemic azlactone **577** with the cyclohexylamide derived from phenylalanine under the same reaction conditions gave a separable mixture of diastereomeric succinimide derivatives. In this case the resolved amino acid contains the side chains of aspartic acid and glutamic acid[282] (Scheme 122).

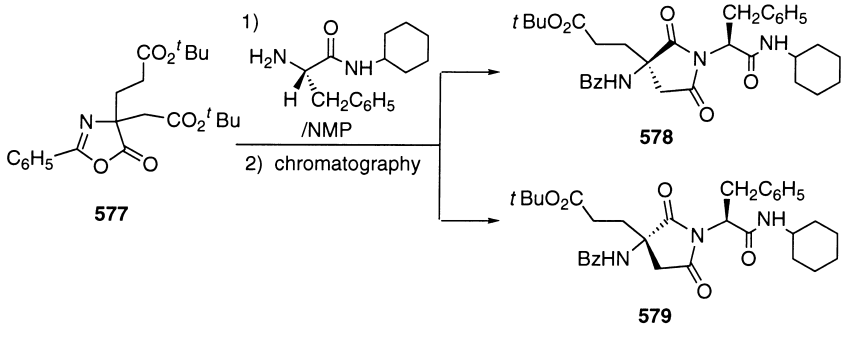
α-Methyl-4-carboxyphenylglycine has been resolved into enantiomers by anion exchange chromatography through its dipeptide with the amino acid (*S*)-leucine.[283] (*S*)-Leucyl-(*S*)-α-methyl-4-carboxyphenylglycine was first eluted in a pure form in 35% yield and more than 99.5% diastereomeric excess. Nevertheless, diastereomerically pure (*S*)-leucyl-(*R*)-α-methyl-4-carboxyphenylglycine was obtained in only 3% yield unless the middle fraction containing both diastereoisomers was eluted again (Scheme 123).

Other resolution procedures have been used to obtain α-alkylamino acids in enantiomerically pure form. For example, α-methylcysteine has been obtained by preparative high performance liquid chromatography separation of racemic 4-ethoxycarbonyl-4-methyl-2-phenylthiazoline, obtained by methyl-

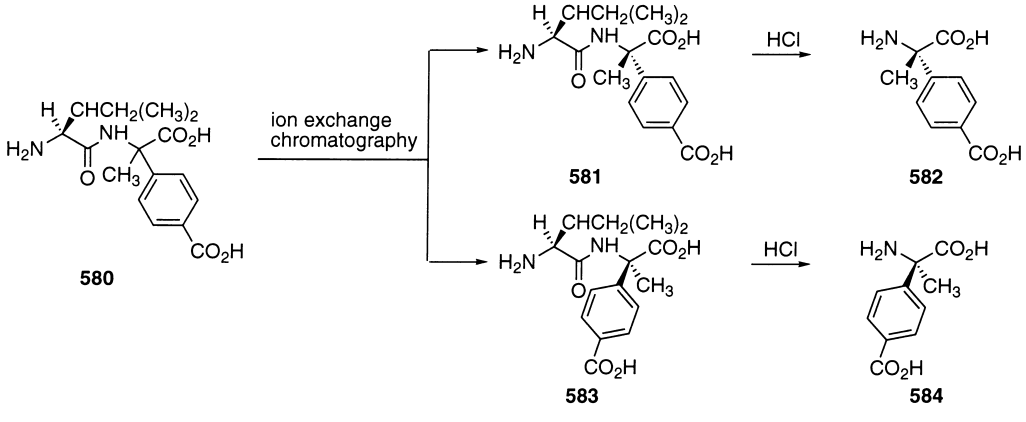


Entry	R	Ref.
a	CH_3	281, 282
b	C_6H_5	281, 282
c	$(CH_3)_2CH$	281, 282
d	$(CH_3)_2CHCH_2$	281, 282
e	$CH_2CO_2{}^tBu$	282

Scheme 121.

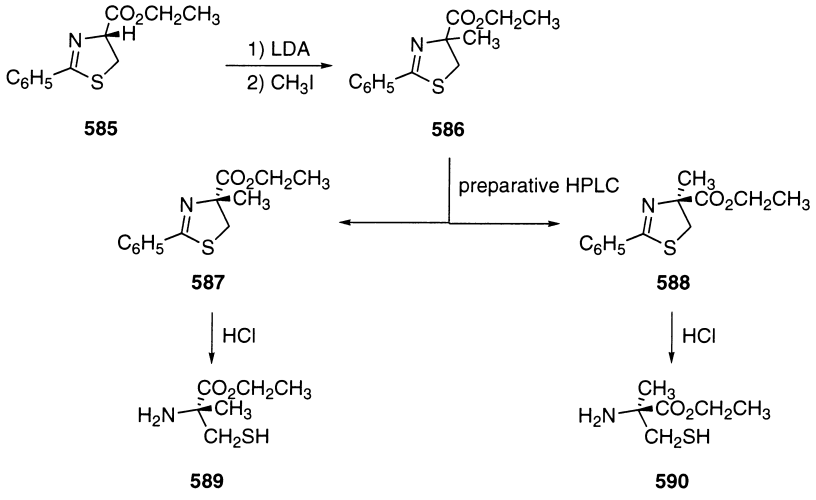


Scheme 122.



Scheme 123.

ation of 4-ethoxycarbonyl-2-phenylthiazoline, using cellulose triacetate as a chiral stationary phase followed by acidic hydrolysis[284] (Scheme 124).



Scheme 124.

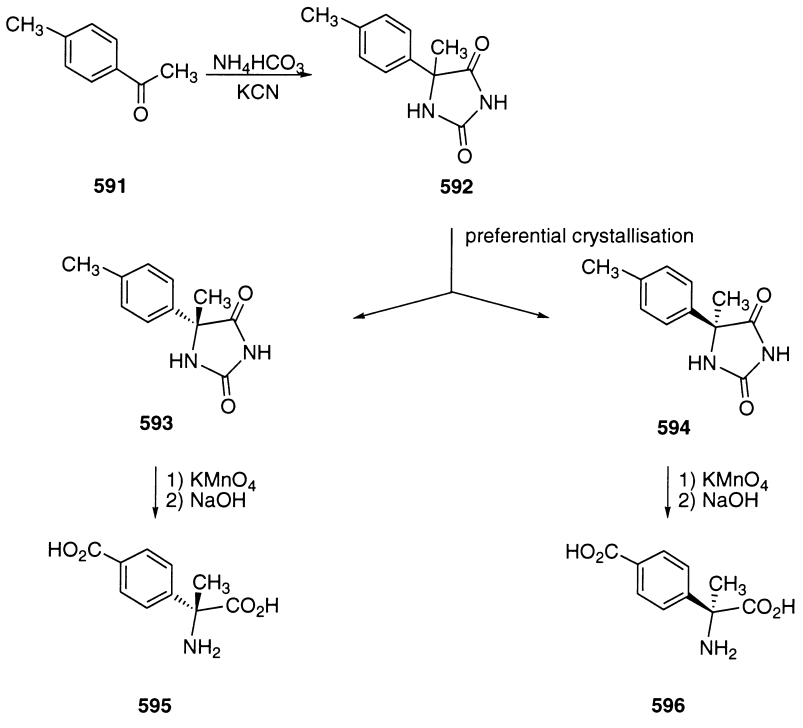
α-Methyl-4-carboxyphenylglycine has been resolved into enantiomers by auto-seeded programmed polythermic preferential crystallisation, a variant of preferential crystallisation, of the hydantoin obtained in the Bücherer–Bergs reaction of 4-methylacetophenone. This technique works due to the fact that 5-methyl-5-(4-methylphenyl)hydantoin crystallises as a conglomerate. The technique is based on alternate successive crystallisation of each enantiomer of the mixture from a supersaturated mother liquor containing a slight excess of one enantiomer. After the hydantoin had been resolved, oxidation of the *para* methyl group and hydrolysis under basic conditions afforded the amino acid[285] (Scheme 125).

11. Miscellaneous

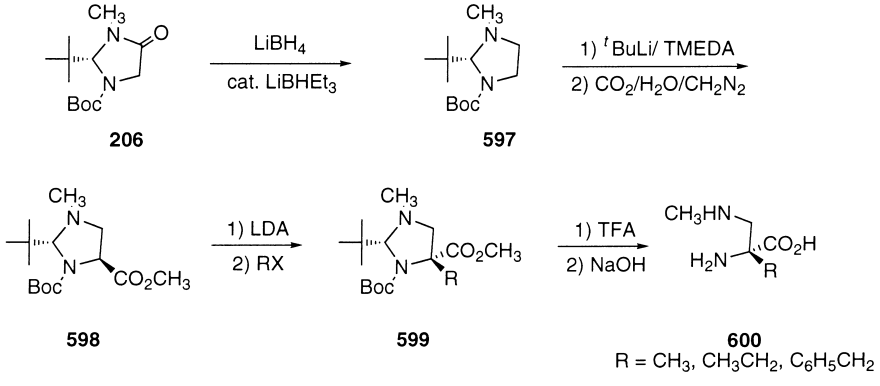
A number of synthetic methodologies have appeared in the literature that do not fit any of the groups described above and these are discussed now.

Firstly, the chiral imidazolidinone derived from glycine and pivalaldehyde, developed by Seebach et al. as a glycine building block for the synthesis of α-amino acids and described at the beginning of this review, has been converted into 5-carboxymethylimidazolidine essentially as a single diastereoisomer with the *trans*-configuration as shown in Scheme 126.[286] Treatment of this compound with LDA gives an enolate intermediate that adds different electrophiles with total stereoselectivity with the newly introduced R group in a *trans* disposition with respect to the *tert*-butyl group. Sequential treatment of the alkylated compounds with trifluoroacetic acid and sodium hydroxide, followed by ion exchange chromatography, gives the corresponding α-alkyl-α,β-diamino acids (Scheme 126).

Cyano esters derived from (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisoborneol, used by our group as synthetic precursors for α,α-dialkylamino acids through asymmetric alkylation and subsequent rearrangement to the desired compounds, have also been submitted to electrophilic amination.[287] The use of *O*-(diphenylphosphinyl)hydroxylamine as the amination reagent and lithium hexamethyldisilylamide as a base led to α-aminocyano esters in good yields and with acceptable diastereoselectivities. From diastereomerically pure compounds, α-alkyl-α,β-diamino acids are easily obtained by hydrogenation of the cyano group followed by basic hydrolysis (Scheme 127).

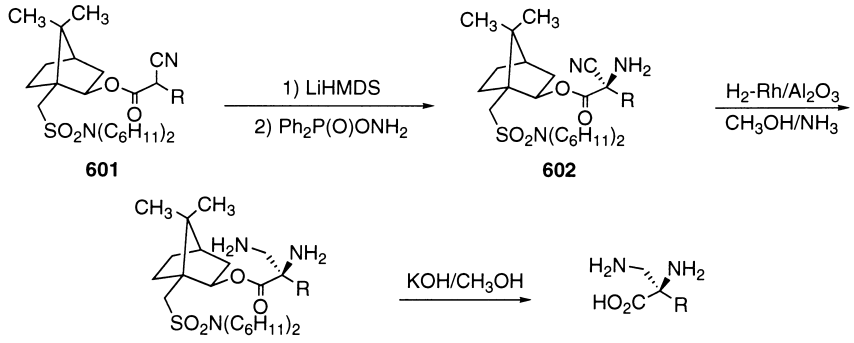


Scheme 125.



Entry	RX	dr
a	CH_3I	> 98/2
b	CH_3CH_2I	> 98/2
c	$(CH_3)_2CHI$	> 98/2
d	$CH_3(CH_2)_3I$	> 98/2
e	$CH_2{=}CHCH_2Br$	> 98/2
f	$C_6H_5CH_2Br$	> 98/2
g	C_6H_5SCl	> 98/2
h	C_6H_5SeCl	> 98/2

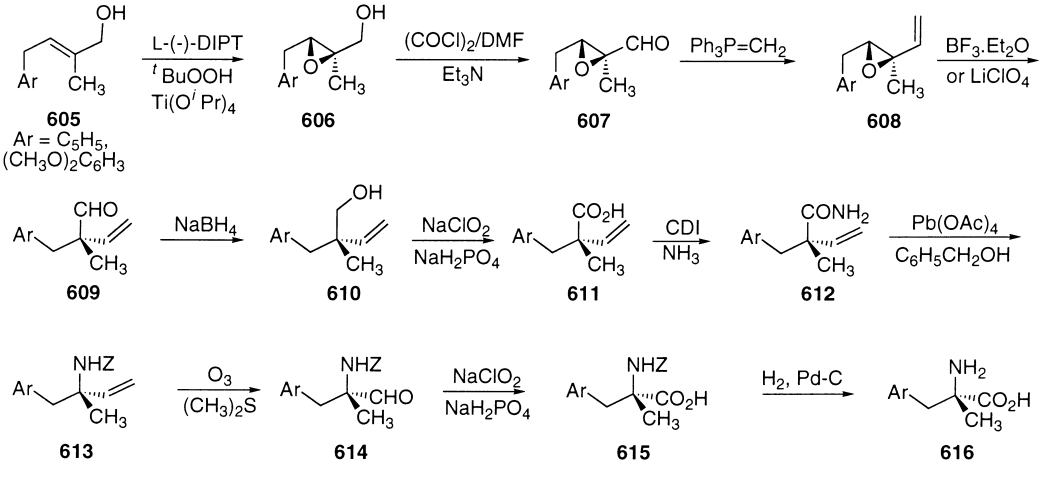
Scheme 126.



Entry	R	dr
a	CH_3	78/22
b	$CH_3CH_2CH_2$	76/24
c	$(CH_3)_2CH$	70/30
d	$(CH_3)_2CHCH_2$	77/23
e	$C_6H_5CH_2$	80/20

Scheme 127.

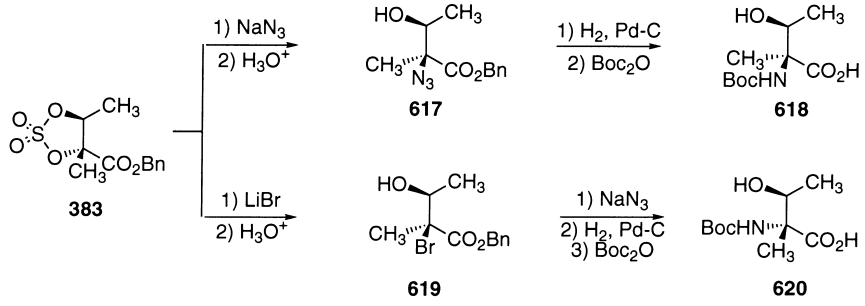
Asymmetric epoxidation of *E*-allylic alcohols under Sharpless conditions yields optically active epoxy alcohols in excellent yields and with optical purities ranging from 90 to 96% enantiomeric excess. Swern oxidation to epoxy aldehydes followed by Wittig methylenation affords vinyl epoxides **608**, which rearrange to aldehydes under mild conditions using boron trifluoride etherate at −78°C for 2 min. With substituted benzyl systems these reaction conditions give unsatisfactory yields of aldehyde and better results are obtained with the use of 5 M $LiClO_4$ in refluxing ether. Aldehydes are oxidised to acids and subsequently converted into amides **612**, which are then rearranged to carbamates by the action of lead tetraacetate in the presence of benzyl alcohol. Finally, ozonolysis of the vinyl moiety followed by reductive work-up, oxidation of the aldehyde with sodium chlorite and hydrogenolysis with palladium on carbon gives (*S*)-α-methylphenylalanine and (*S*)-α-methyldopa[288] (Scheme 128).



Scheme 128.

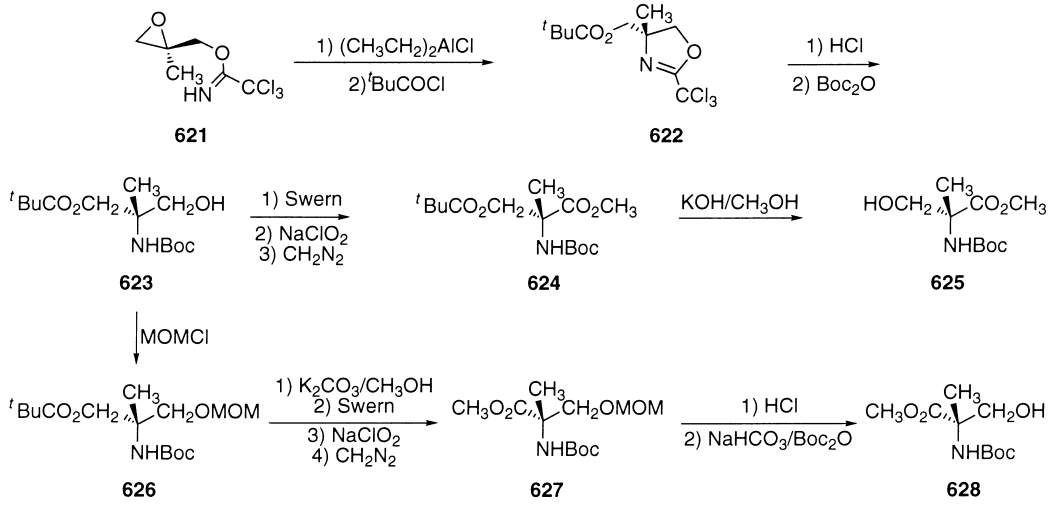
Goodman et al.[204] have developed a synthetic route to α-methylthreonine derivatives starting from benzyl tiglate. The Sharpless epoxidation of this compound gives the corresponding diol with excellent

optical purity. The homochiral diol was transformed into a cyclic sulfite and oxidised to cyclic sulfate **383**, and this compound was submitted to nucleophilic substitution. Depending on the nucleophile and the subsequent reaction sequence to the final amino acid, the four stereoisomers of *N*-*tert*-butoxycarbonylamino-α-methylthreonine can be obtained (Scheme 129).



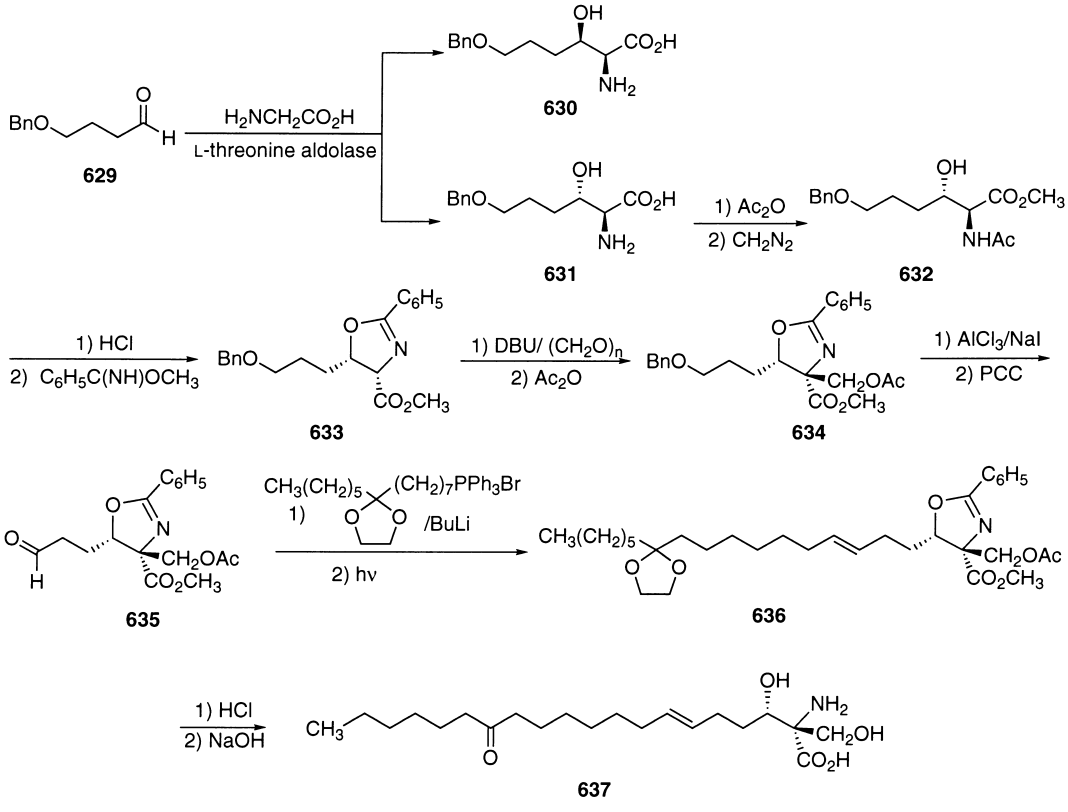
Scheme 129.

Hatakeyama et al.[289] obtained chiral α-methylserine from 2-methyl-2,3-epoxytrichloroacetylimidates synthesised from (*R*)-methylglycidol. Diethylaluminium chloride-promoted cyclisation of trichloroacetylimidate and subsequent pivaloylation gave the corresponding oxazoline, which was hydrolysed to the *N*-Boc protected amino alcohol **623**. From this compound, a divergent synthesis to both enantiomers of *N*-*tert*-butoxycarbonylamino-α-methylserine methyl ester has been developed and this is shown in Scheme 130.



Scheme 130.

Mycestericin D has been synthesised from γ-benzyloxybutanal in several steps.[290] The aldehyde has been condensed with glycine in the presence of L-threonine aldolase to afford a mixture of 2*S*,3*R* and 2*S*,3*S* compounds. Under kinetically controlled reaction conditions the 2*S*,3*R* compound predominates in the mixture whereas under thermodynamically controlled conditions the 2*S*,3*S* isomer is the major compound. The α-amino-β-hydroxy acids obtained in this way are *N*-acetylated and isolated by chromatography. Compound **632** is then hydrolysed and treated with benzimidate to afford an oxazoline derivative which is stereoselectively *C*-alkylated by treatment with formaldehyde in the presence of DBU with retention of configuration. Mycestericin D **637** was obtained from this compound in several steps according to Scheme 131.



Entry	time	631/630
a	15 h	40/60
b	15 m	90/10

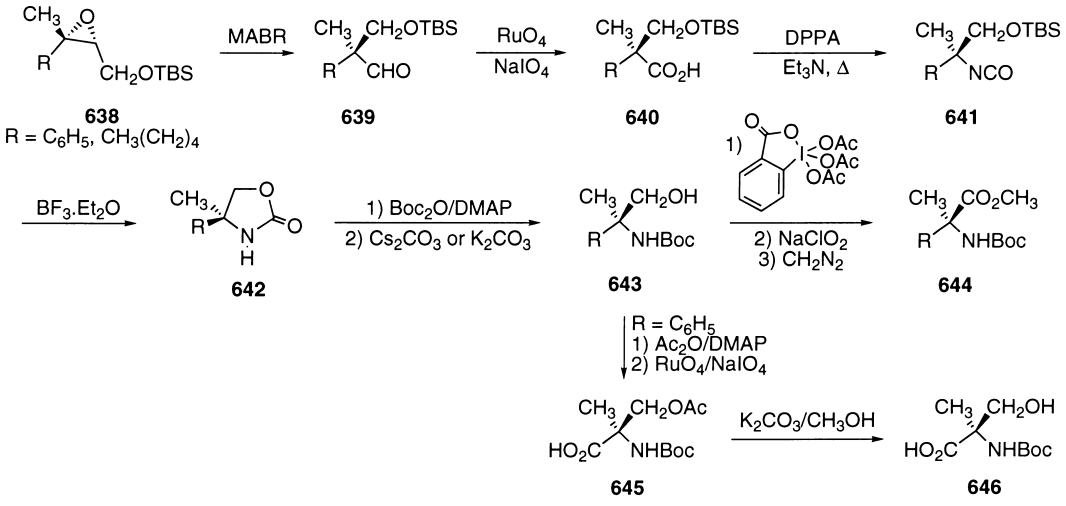
Scheme 131.

Chiral epoxy silyl ethers smoothly rearrange to β-silyloxy aldehydes by the action of methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR). Oxidation of the aldehydes to carboxylic acids and subsequent Curtius rearrangement yield the corresponding isocyanates, which can be further elaborated to (*S*)-α-methylphenylglycine, (*S*)-α-pentylalanine and (*R*)-α-methylserine[291] (Scheme 132).

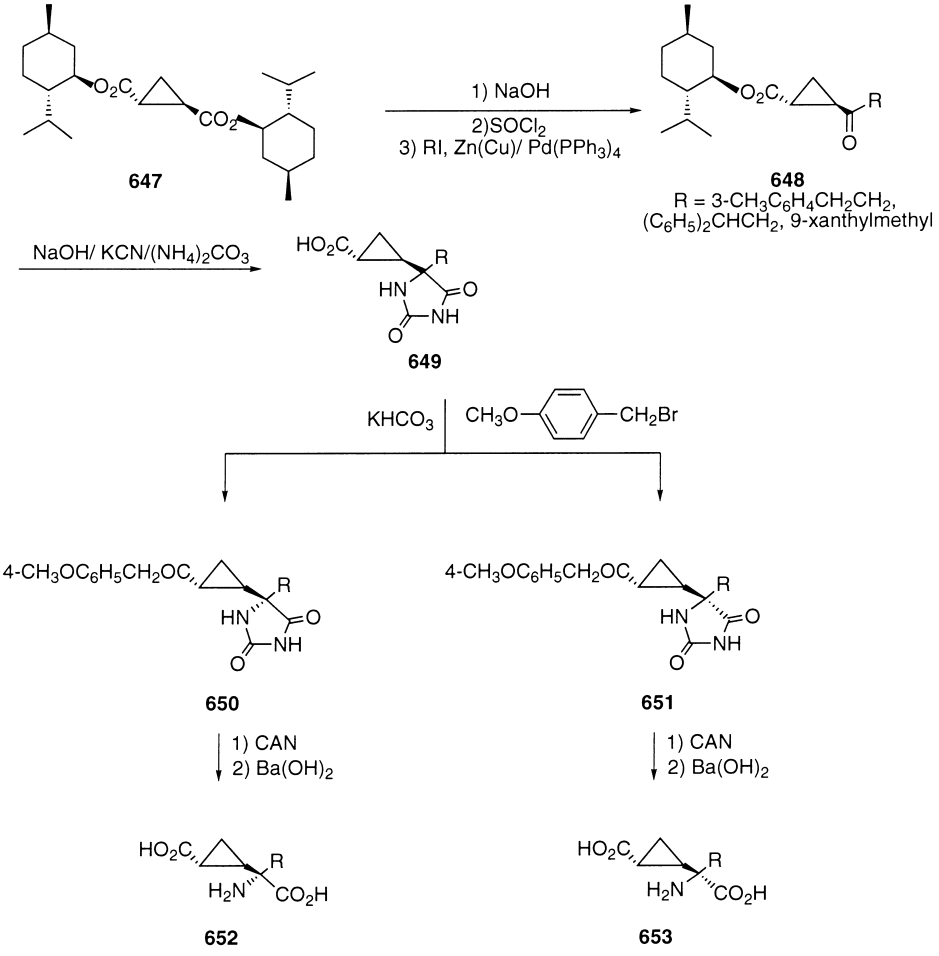
Finally, stereochemically homogeneous *trans*-dimenthylcyclopropane-1,2-dicarboxylate has been converted into chiral 2-substituted-2-amino-2-(2-carboxycyclopropyl)glycines according to Scheme 133.[292] Selective hydrolysis to the acid-ester followed by acid chloride formation and palladium-mediated coupling with an organozincate affords non-racemic ketones that are transformed into an equimolecular mixture of hydantoins. These hydantoins can be separated into diastereoisomers by chromatography and further elaborated to enantiomerically pure amino acids.

12. Concluding remarks

α,α-Dialkylamino acids are an important class of non-proteinogenic amino acids that play an important role in the inhibition of enzyme activities and in the design of conformationally modified bioactive peptides. Their extensive use is only limited by the availability of enantiomerically pure compounds in large quantities.



Scheme 132.



Scheme 133.

As we have shown in this article, a wide variety of synthetic approaches to these compounds has been developed, most which are based on stereoselective syntheses using chiral auxiliaries. Such an approach allows the synthesis of almost any imaginable compound on a laboratory scale.

The use of enzymes for the resolution of racemic compounds is an attractive approach to the synthesis of compounds on a large scale that, combined with racemisation to recycle the undesired enantiomer, has been applied to the synthesis of α-hydrogenamino acids. Although in some cases enzymes can resolve α,α-dialkylamino acids, this type of process is generally slow and less stereoselective and the undesired enantiomer cannot be racemised, which is a significant drawback when only one of the stereoisomers is required.

Enantioselective synthesis using chiral catalysts would allow the synthesis of large quantities of optically active compounds using only small amounts of optically active catalysts. However, this technique has not been extensively used in the synthesis α,α-dialkylamino acids in enantiomerically pure form. Nevertheless, the usefulness of this methodology makes its exploitation a worthwhile pursuit and, in our opinion, this technique offers excellent prospects for the future.

Acknowledgements

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Appendix A. Abbreviations

Ac = CH_3CO
Aib = 2-aminoisobutyric acid
Alloc = $CH_2{=}CHCH_2OCO$
Bn = $C_6H_5CH_2$
BNPPA = 1,1′-binaphthyl-2,2′-diylhydrogen phosphate
Boc = $(CH_3)_3COCO$
Brop = bromotris(dimethylamino)phosphonium hexafluorophosphate
BTEAC = benzyltriethylammonium chloride
Bu = $CH_3CH_2CH_2CH_2$
^{t}Bu = $(CH_3)_3C$
Bz = C_6H_5CO
CAN = ceric ammonium nitrate
CDI = carbonyldiimidazole
CLE = *Candida lipolitica* esterase
Cp = cyclopentadienyl
CPA = bovine carboxypeptidase A
DABCO = 1,4-diazabicyclo[2.2.2]octane
DAST = diethylaminosulfur trifluoride
DCC = dicyclohexylcarbodiimide
DIPT = diisopropyl tartrate
DMAP = dimethylaminopyridine
DMPU = *N*,*N*′-dimethylpropyleneurea

DMSO = dimethylsulfoxide
de = diastereomeric excess
dppe = 1,2-bis(diphenylphosphino)etane
dppp = 1,3-bis(diphenylphosphino)propane
dr = diastereomeric ratio
ee = enantiomeric excess
EDA = ethylenediamine
Et = CH_3CH_2
c-Hex = cyclohexyl
HKA = hog kidney aminoacylase
HMPT = hexamethylphosphorous triamide
HPLC = high performance liquid chromatography
KHMDS = potassium hexamethyldisilylamide
Iva = isovaline
LDA = lithium diisopropylamide
LDEA = lithium diethylamide
Leu–OH = leucine
LHMDS = lithium hexamethyldisilylamide
LTMP = lithium 2,2,6,6-tetramethylpiperidine
MABR = methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide)
MCPBA = *m*-chloroperoxybenzoic acid
MEEC = membrane enclosed enzymatic catalysis
MOM = methoxymethyl
MPLC = medium pressure liquid chromatography
Ms = CH_3SO_2
NMP = *N*-methylpirrolidone
PCC = pyridinium chlorochromate
PDC = pyridinium dichromate
Ph = C_6H_5
PhtN = phthalimidoyl
PLE = pig liver esterase
PPTS = pyridinium *p*-toluenesulfonate
^{i}Pr = $(CH_3)_2CH$
PTC = phase transfer catalyst
Py = pyridine
RLE = rabbit liver esterase
SDMP = (*S*)-1-dimethoxymethyl-2-methoxymethylpyrrolidine
Ses = β-trimethylsilylethanesulfonyl
TADDOL = (4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol
TBAB = tetrabutylammonium bromide
TBAF = tetrabutylammonium fluoride
TBAI = tetrabutylammonium iodide
TBDMS = *tert*-butyldimethylsilyl
TBDPS = *tert*-butyldiphenylsilyl
TEMPO = tetramethylpiperidine-*N*-oxyl
Tf = CF_3SO_2

TFA = trifluoroacetic acid
TMDEA = tetramethylethylenediamine
TMS = trimethylsilyl
Ts = *p*-toluenesulfonyl
Z = $C_6H_5CH_2OCO$
Z-OSu = *N*-(benzyloxycarbonyloxy)succinimide

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