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# Recent progress on the stereoselective synthesis of acyclic quaternary α-amino acids

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**Abstract**—The most recent papers describing new procedures for the synthesis of acyclic α,α-dialkylamino acids are collected in this review along with coverage of extensions of well established procedures.


**Contents**



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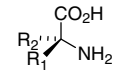
## 1. Introduction

Linear peptides are highly flexible molecules that can adopt a multitude of conformations in solution and, of these, very few are responsible for their biological activity. As a result, the construction of novel peptidic sequences with tailor-made enhanced properties with respect to natural active peptides and proteins is a worthwhile goal, and one of the most challenging, in biomimetic research. In this context, the incorporation of rigid amino acid surrogates with conformational constraints into peptides with biological activity is a very useful tool for the construction of new molecules with improved properties, which, at the very least, may provide useful information on their bioactive conformation and result in beneficial physiological effects.[1–11]

Among these conformational restrictions, the use of quaternary amino acids has proved to be one of the most interesting and promising strategies and, for this reason, it is very important to have a knowledge of the most important procedures that allow the synthesis of desired quaternary amino acids in enantiomerically pure form. In fact, we have previously collected stereoselective syntheses of quaternary amino acids into two reviews. The first review dealt with the stereoselective synthesis of acyclic compounds[12] and the second collected the reported procedures for the synthesis of cyclic amino acids.[13] Although reviews focused on asymmetric synthesis of quaternary α-amino acids have not appeared since, a couple of reviews dealing with some particular constrained amino acids have been published. Gibson et al.[14] collected the synthesis of β-substituted and cyclic conformationally constrained analogues of phenylalanine (Phe), tyrosine (Tyr), tryptophan (Trp) and histidine (His). Furthermore, Park and Kurth[15] collected recent approaches to the synthesis of some cyclic amino acid derivatives. More recently,[16] a review covering the enantio- and diastereoselective construction of some α-substituted serine analogues used in the synthesis of biologically active compounds has been published.

Due to the great importance of this topic, we have included an update of the most important procedures involving the stereoselective synthesis of acyclic quaternary amino acids (Fig. 1), covering papers that have appeared in the literature since our last review up to the end of 2005.




acyclic quaternary α-amino acids

**Figure 1.**

Before describing procedures directed to the stereoselective synthesis of chiral acyclic derivatives, it is worth mentioning that among the wide variety of non-coded amino acids used to optimise the biological properties of bioactive peptides, α-alkyl α-amino acids have played a special role in the design of peptides with enhanced properties. In this context there have been many structural analyses reported concerning the influence of conformational restriction of the amino acids on the structure of model peptides in which they are incorporated. Among them achiral dialkylglycines have been extensively studied and, in particular, reports on dimethylglycine (Aib),[17,18] diethylglycine or 2-amino-2-ethylbutanoic acid (Deg),[19,20] dipropylglycine (Dpg),[19] dibenzylglycine (Dbg)[21] and diphenylglycine[22] have been published.

Numerous reports concern the behaviour of model peptides containing chiral quaternary α-amino acids in special α-methyl derivatives. Among these compounds, peptides containing isovaline, 2-amino-2-methylbutanoic acid or 2-aminoisobutyric acid (Iva),[17,23] α-methyl valine

[(αMe)Val],[23–26] α-methyl phenylalanine [(αMe)Phe], α-methyl asparagine [(αMe)Asn][27] or combined residues[28–30] are the most frequently studied.

In the same context, different studies concerning peptides that contain some particular α-methyl derivatives, such as α-methyl norvaline or 2-amino-2-methylpentanoic acid [(αMe)Nva],[23,31,32] 2-methyl-2-allylglycine or 2-amino-2-methyl-4-pentenoic acid (Mag),[33,34] α-methyl-α-cyclohexylglycine [(αMe)Chg],[35] α-methylphenylglycine [(αMe)Phg],[36] 2-methyl-2-diphenylmethylglycine [(αMe)Dip],[37] 2-amino-2-methyloctanoic acid [(αMe)Aoc][38] and 2-amino-2-methylundecanoic acid [(αMe)Aun][39] have also been reported.

Other compounds containing α-ethyl amino acids, such as butylethylglycine or 2-amino-2-ethylhexanoic acid (Beg),[40,41] 2-amino-2-ethyl-4-methylpentanoic acid [(αEt)-Leu][42] or sequences composed of diverse α-ethyl amino acids,[43] have also been studied.

In this review, we have collected the most recently described synthetic strategies directed towards the synthesis of constrained quaternary acyclic amino acids as well as the extension of previously described methodologies for the synthesis of new α,α-dialkyl amino acids.

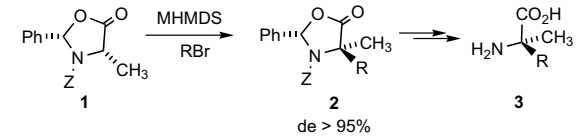
## 2. Self-regeneration of stereocentres

The principle of 'self-regeneration of stereocentres' (SRS)[44]—in which the stereogenic centre of a chiral molecule generates a temporary centre of chirality, which in turn is used to introduce diastereoselectively a new ligand at the original stereogenic centre—has been applied to the synthesis of various acyclic quaternary amino acids. α-Amino acids are usually converted into chiral heterocyclic intermediates from which chiral heterocyclic enolates with diastereotopic faces are generated and then diastereoselectively alkylated. The different approaches collected in this part of the review have been grouped together according to the structure of the intermediate heterocyclic compound.

### 2.1. Self-regeneration of stereocentres via oxazolidinones

Oxazolidinones are common intermediates in this methodology and several variants, differing in the nature of the substituents on the oxazolidinone ring and/or their relative configuration, have been described.

Some authors describe the stereoselective synthesis of the starting oxazolidinone to have a confusing trend regarding stereoselectivity. The formation of the *cis*-compound has been optimised using thionyl chloride in the presence of anhydrous zinc chloride to promote cyclisation of the amino acid derivative and the aldehyde intermediate using THF as the solvent.[45] An alternative approach involves combining the formation of the chiral template with a crystallisation-induced asymmetric transformation.[46] Alkylation of *cis*-oxazolidinone **1**, obtained from *N*-benzyloxycarbonyl-L-alanine, takes place opposite to the phenyl ring[45,47,48] and in some cases it is necessary to generate the enolate in the presence of the alkylating agent to obtain a good yield of compound **2**, the hydrolysis of which gave the corresponding amino acid (Scheme 1).




**Scheme 1.**

Alkylated compounds have been transformed into BIRT-377, a hydantoin that could play an important role as an anti-inflammatory,[45] and (2*S*,3*S*,4*S*)-2-methyl-2-(carboxycyclopropyl)glycine (MCCG), a potent group II metabotropic glutamate receptor antagonist[47] (Fig. 2).

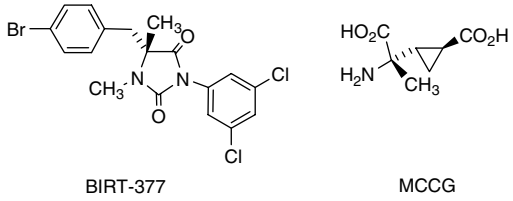
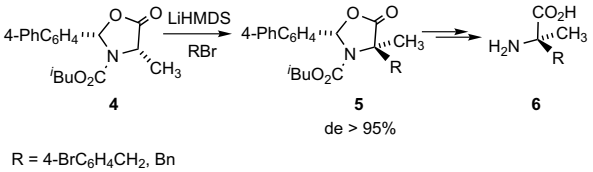



**Figure 2.**

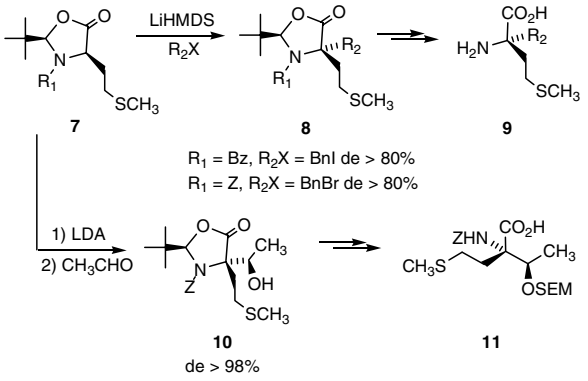
Deprotonation of *cis*-oxazolidinone **4**, obtained from *N*-isobutoxycarbonyl-L-alanine and 4-phenylbenzaldehyde in a crystallisation-controlled reaction, in the presence of the corresponding electrophile leads to alkylation opposite to the aryl group with excellent yield and complete diastereoselectivity.[46] Treatment of oxazolidinone **5** and subsequent hydrolysis cleanly afforded the amino acid (Scheme 2).




**Scheme 2.**

Oxazolidinones **7**, obtained from (*R*)-methionine and pivalaldehyde, are the starting compounds in the synthesis of (*R*)-benzylmethionine.[49] The yield of alkylated oxazolidinone **8** was found to depend on the nature of the N-protecting group and the electrophile. When using benzyl bromide as the alkylating agent, the yield of alkylated *N*-benzyloxazolidinone **8** remained below 24% regardless of the base used for enolisation, but increased to 80% when benzyl iodide was the electrophile. Alkylation of *N*-benzyloxycarbonyloxazolidinone with benzyl bromide provided the alkylated compound in moderate yield. Final hydrolysis with hydrobromic acid or potassium trimethylsilanolate gave (*R*)-benzylmethionine with 80% diastereomeric excess. Trapping of the lithium enolate of oxazolidi-

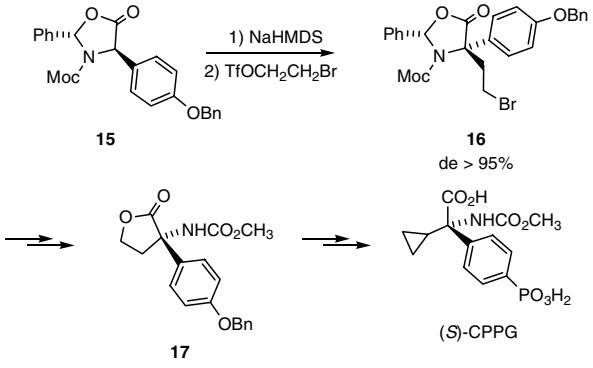
none **7** ($R_1 = Z$) with acetaldehyde gave compound **10** as a single diastereoisomer.[50] This compound was protected and hydrolysed to give unnatural amino acid **11** (Scheme 3).



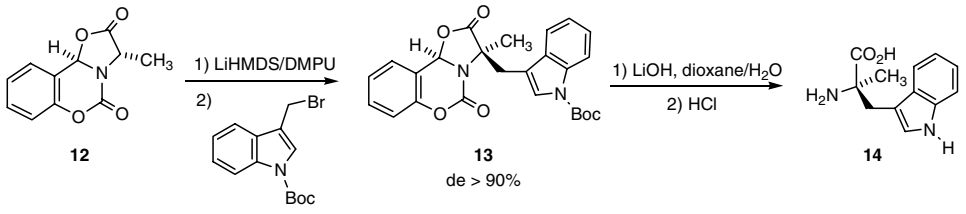

**Scheme 3.**

Condensation of L-alanine with salicylaldehyde, under conditions appropriate to avoid racemisation, gave tricyclic *trans*-oxazolidinone **12**, which was used as an intermediate in the synthesis of orthogonally protected (*R*)-α-methyltryptophan[51] (Scheme 4).

Ma and Zhu[52] described the synthesis of (*S*)-α-cyclopropyl-4-phosphonophenylglycine [(*S*)-CPPG] using the SRS principle. To this end, *trans*-oxazolidinone **15**—prepared from (*R*)-4-benzyloxyphenylglycine—was alkylated with 2-bromoethyl trifluoromethanesulphonate with total diastereoselectivity. Chiral lactone **17** was obtained by hydrolysis of compound **16** and appropriate reaction of this compound led to the target amino acid (Scheme 5).

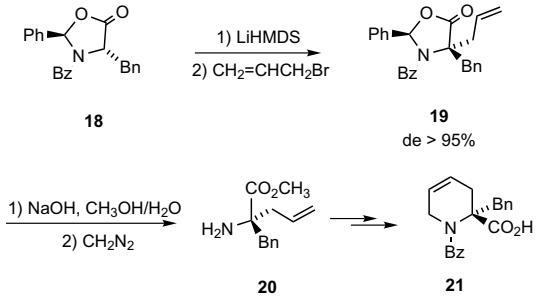



**Scheme 5.**




**Scheme 4.**

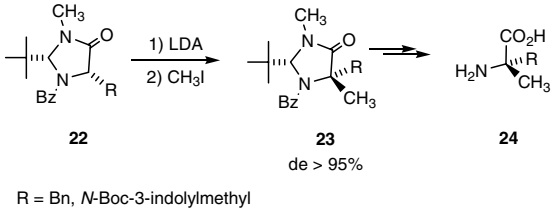
Finally, *trans*-oxazolidinone **18**, derived from L-phenylalanine, proved to be a convenient synthetic precursor in the synthesis of (*R*)-α-allylphenylalanine, from which a 1,2,3,6-tetrahydropyridine-based phenylalanine mimetic was obtained by combining the SRS principle and ring-closing metathesis[53] (Scheme 6).




**Scheme 6.**

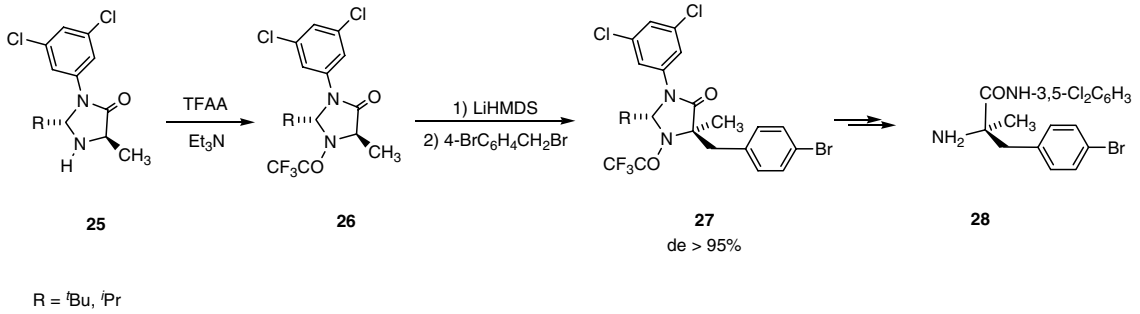
## 2.2. Self-regeneration of stereocentres via imidazolidinones

Lithium enolates derived from imidazolidinones are extremely useful intermediates in the synthesis of α-alkyl α-amino acids, an approach that makes use of the self-regeneration of stereocentres. In this context, *cis*-imidazolidinones **22**, obtained by reaction of Schiff bases of pivalaldehyde and L-phenylalanine *N*-methyl amide or L-1-*tert*-butoxycarbonyltryptophan *N*-methyl amide with benzoic acid anhydride, have been converted into the corresponding α-methyl amino acids.[54] In both cases diastereoselectivity in the electrophilic attack was total and subsequent hydrolysis under the appropriate conditions led to the amino acid in enantiomerically pure form (Scheme 7).




**Scheme 7.**

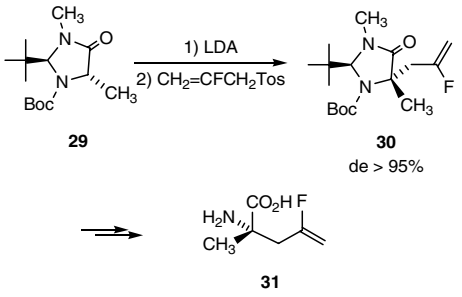
In studies directed towards the synthesis of BIRT-377, Yee et al.[55–57] investigated the synthesis and alkylation of chiral




**Scheme 8.**

imidazolidinones derived from D-alanine. These authors described the stereoselective formation of *trans*-imidazolidinones **25** by a crystallisation-driven dynamic transformation, that was efficiently conducted in non-polar solvents, such as isooctane. After N-protection the imidazolidinones were converted into lithium enolates and alkylated with bromobenzyl bromide. This reaction gave the α,α-disubstituted imidazolidinones derived from the attack of the electrophile opposite to the directing group, in each case as a single diastereoisomer, and from these compounds, amino acid derivative **28** was obtained (Scheme 8). Alkylated compound **27** (R = $^t$Bu) is an appropriate precursor for the synthesis of BIRT-377 on a multikilogram scale.

This methodology has been applied to the synthesis of (*S*)-2-amino-4-fluoro-2-methyl-4-pentenoic acid.[58] Allylation of imidazolidinone **29** with allyltosylate led to exclusive formation of compound **30**, which upon acidic hydrolysis followed by basic hydrolysis provided the desired amino acid (Scheme 9).

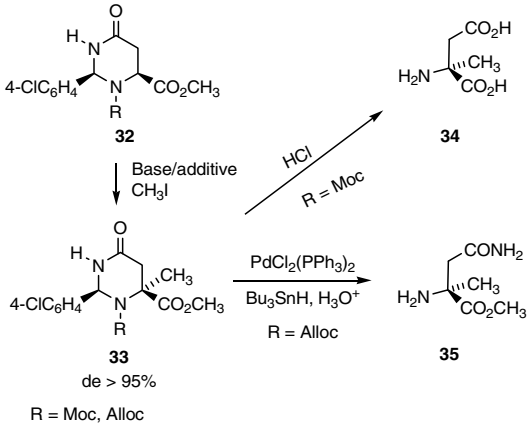



**Scheme 9.**

## 2.3. Self-regeneration of stereocentres via tetrahydropyrimidinones

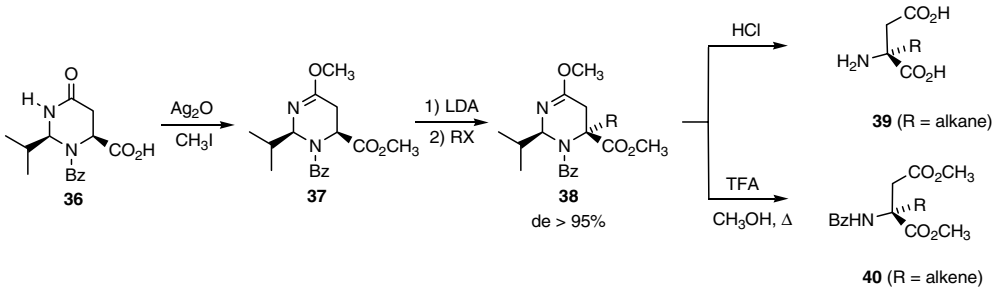
L-Asparagine was the starting material in the synthesis of *cis*-tetrahydropyrimidinones **32**—a new class of heterocyclic systems from which α,α-dialkyl amino acids can be obtained through the SRS concept.[59] The $C_2$ aromatic substituent directs the alkylation process and the electrophile enters in a *trans* disposition. The main problem in the alkylation step is the choice of both a suitable base and the reaction conditions to achieve monoalkylation.

The use of LDA and an excess of lithium chloride in the presence of DMPU gave monoalkylated compound **33** as a single diastereoisomer in high yield and a reasonable reaction time. When R = $CO_2CH_3$, subsequent hydrolysis led to (*S*)-α-methylaspartic acid in enantiomerically pure form. *N*-Alloc tetrahydropyrimidinone proved to be a more suitable intermediate for the synthesis of (*S*)-α-methyl asparagines. In this case, the optimum alkylation conditions involved the use of potassium *tert*-butoxide and in situ quenching of the enolate at low temperature; subsequent deprotection of the carbamate and acidic hydrolysis allowed the isolation of (*S*)-α-methyl asparagine methyl ester (Scheme 10).




**Scheme 10.**

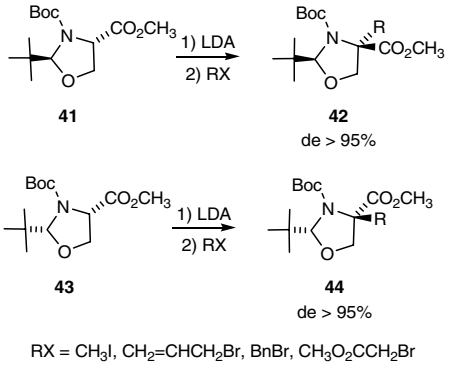
*cis*-Tetrahydropyrimidinone **36** (obtained from L-asparagine, isobutyraldehyde and benzoyl chloride) has been converted into the corresponding iminoester **37**, which has been found to be a more convenient intermediate for the synthesis of α-methylaspartic acid derivatives.[60,61] Lithium enolates were generated by treatment of the heterocycle with LDA and quenched with various electrophiles to afford *trans* alkylated compounds with complete diastereoselectivity. Hydrolysis in acidic media and ion exchange chromatography led to the free α-alkyl amino acids. Partial hydrolysis can be performed under relatively mild conditions to afford α-alkyl aspartic acid derivatives with preservation of the alkene moiety (Scheme 11).




**Scheme 11.**

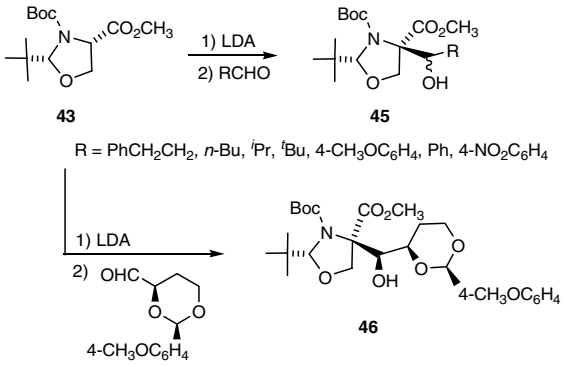
## 2.4. Self-regeneration of stereocentres via oxazolidines

β-Heterosubstituted amino acids have been converted into valuable heterocyclic intermediates for the synthesis of α-alkyl amino acids using the SRS principle. In this context *cis*- and *trans*-oxazolidines obtained from serine have been used as substrates in alkylation reactions (Scheme 12).[62] In each case the alkylation took place with a total diastereoselectivity opposite to the *tert*-butyl group, although 2 equiv of base were necessary to obtain useful yields. Alkylated compounds derived from the reaction of *cis*-oxazolidine were systematically obtained with higher yields that those derived from the reaction of *trans*-oxazolidine.



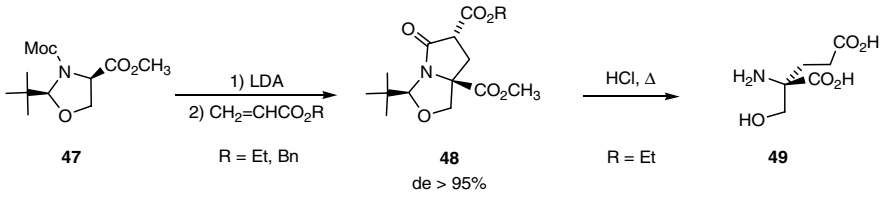

**Scheme 12.**

The lithium enolate obtained from oxazolidine **43** was also reacted with several aliphatic and aromatic aldehydes to afford mixtures of the corresponding *syn*- and *anti*-aldol adducts with low *syn*/*anti*-diastereoselectivity.[63] The use of simple unbranched aliphatic aldehydes gave equimolecular mixtures of *syn*- and *anti*-aldols in high yields. The presence of substituents on the skeleton increased the *syn*/*anti*-diastereoselectivity, but lowered the degree of conversion. Aromatic aldehydes showed improved behaviour and very good conversions and higher diastereoselectivities, which depended on the nature of the substituent(s) on the benzene ring, were observed. The same oxazolidine reacted with a chiral aldehyde in a double stereodifferentiation process to afford *syn*-compound **46** as a single diastereoisomer, albeit in low yield (Scheme 13). Transformation of the alkylated oxazolidines into the corresponding α-alkyl amino acids has not been described.

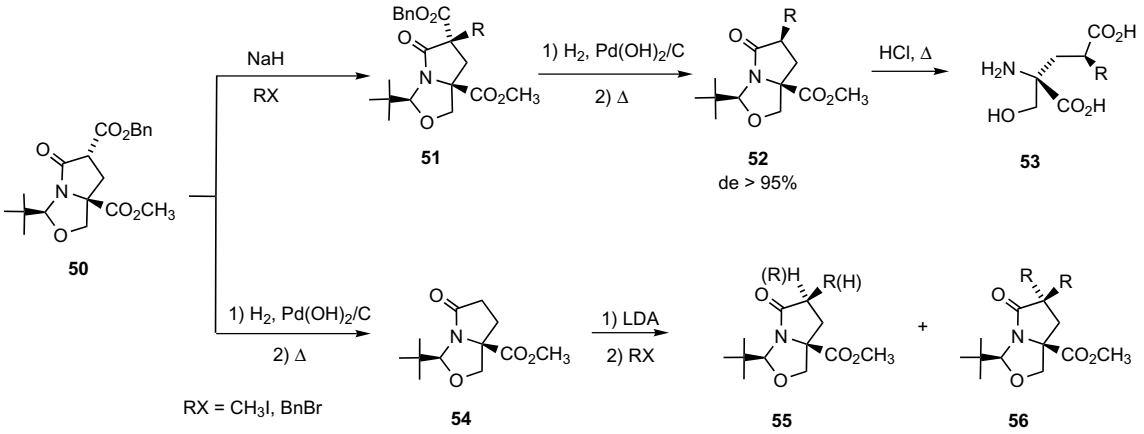



**Scheme 13.**

The nature of the N-protecting group in oxazolidines obtained from serine has been shown to strongly influence the course of the reaction. For example, it was necessary to use *N*-Moc oxazolidine **47** (obtained from D-serine) to achieve the synthesis of (*R*)-α-hydroxymethylglutamic acid and some γ-substituted analogues.[64] In this case the reaction of the lithium enolate generated from the oxazolidine with acrylates led to bicyclic compound **48** as a single diastereoisomer, the hydrolysis of which gave the free amino acid (Scheme 14).



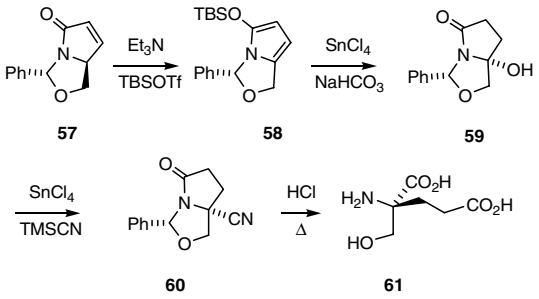

**Scheme 14.**




**Scheme 15.**

γ-Substituted analogues were obtained by alkylation of 6-benzyloxycarbonyl bicycle **50** to afford the corresponding derivatives in which the alkyl group has a *cis*-disposition with respect to the methoxycarbonyl group. Hydrogenolysis, decarboxylation and final hydrolysis led to γ-alkyl-α-hydroxymethylglutamic acids **53**. Hydrogenolysis of compound **50** followed by decarboxylation and treatment with electrophiles led to mixtures of *cis*- and *trans*-monoalkylated and dialkylated products **55** and **56** (Scheme 15).

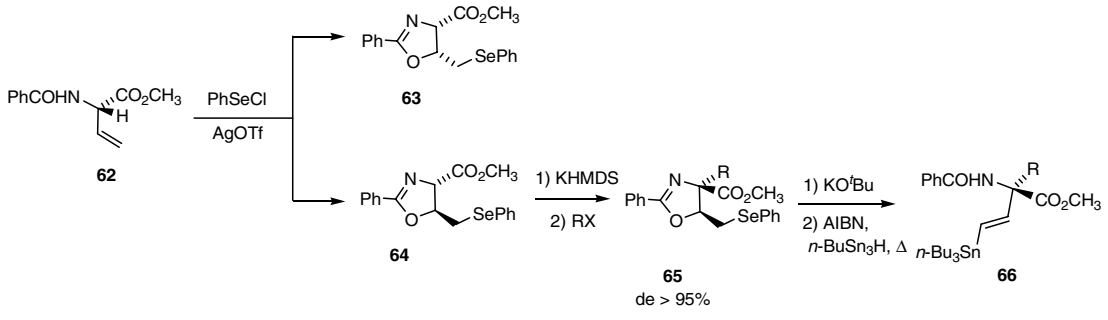
Langlois et al.[65] described an alternative procedure for the synthesis of (*S*)-α-hydroxymethylglutamic acid and this was also based on the SRS principle. In this case (*S*)-pyroglutaminol was the chiral starting material from which bicyclic compound **57** was obtained. Introduction of the carboxy group was achieved through silyloxypyrrole **58** by trapping its iminium ion with hydroxide, subsequent addition of cyanide and hydrolysis (Scheme 16).




**Scheme 16.**

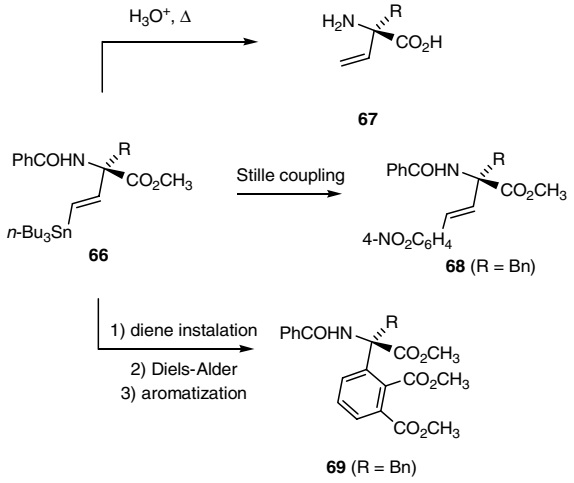
## 2.5. Self-regeneration of stereocentres via oxazolines

In an approach that can be considered similar to the SRS principle, *N*-benzoyl-L-vinylglycine methyl ester was converted into a mixture of *cis*- and *trans*-oxazolines that, after isolation, serve as synthetic precursors for α-substituted vinyl amino acids.[66,67] Each oxazoline reacted with alkyl halides to afford the corresponding α-alkylated compound, in which the electrophile entered opposite to the phenylselenomethyl group with total diastereoselectivity. The original α-vinyl moiety was recovered in three steps: basic hydrolysis of the oxazoline, stereoselective substitution of the phenylselenyl group by a tributylstannyl group and final protodestannylation. In this way the entire sequence, which is shown in Scheme 17 for a *trans*-oxazoline, provided the corresponding α-alkyl vinyl amino acids. In addition, the α-tributylstannylvinyl group proved to be extremely versatile for obtaining α,α-dialkyl amino acids through Stille coupling or conversion to a diene moiety followed by a Diels–Alder reaction (Scheme 18).




RX = $CH_3I$, BnBr, $BnOCH_2Br$, $EtO_2CCH_2Br$, *m*-$TBSOC_6H_4CH_2I$, *trans*-$PhCH{=}CHCH_2Br$

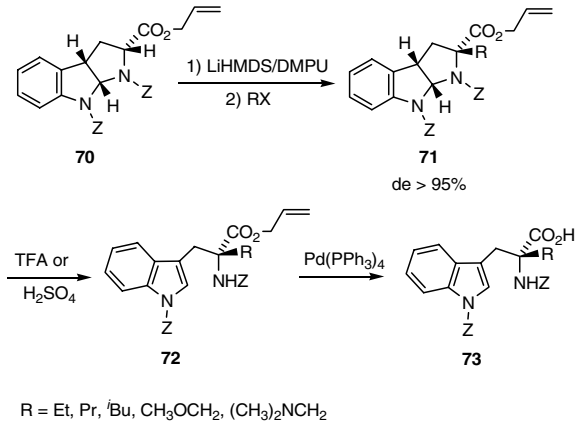
**Scheme 17.**




Scheme 18.

## 2.6. Self-regeneration of stereocentres via tetrahydropyrroloindoles

Tryptophan can be diastereoselectively α-alkylated using a tetrahydropyrroloindole as a chiral intermediate in an SRS process.[68] The synthesis of this chiral intermediate was performed by cyclisation of conveniently protected (*R*)-tryptophan and subsequent *N*-benzyloxycarbonylation of the indoline nitrogen. Alkylation at the α carbon of the original amino acid moiety gave a good yield and complete diastereoselectivity at room temperature, using LiHMDS as the base and DMPU as a cosolvent. Alkylated tetrahydropyrroloindoles were easily converted to the corresponding *N*-benzyloxycarbonyl α,α-dialkyl amino acids by treatment first with trifluoroacetic or sulfuric acid to recover the indole ring and then with tetrakis(triphenylphosphine)palladium(0) to remove the allyl protecting group from the carboxylic acid moiety (Scheme 19).




Scheme 19.

Several alkyl-substituted derivatives of the neurokinin-1 receptor antagonist CI 1021 were obtained from compound **72** (Fig. 3).

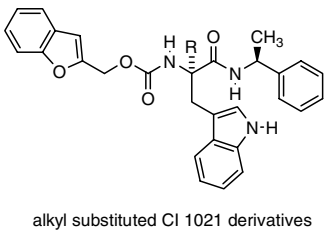
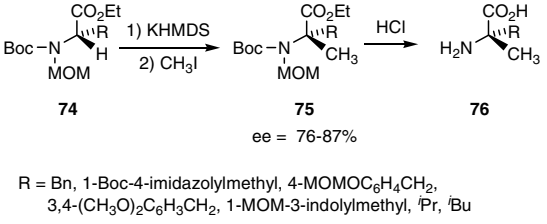



Figure 3.

## 3. Memory of chirality

Memory of chirality is a phenomenon that occurs in processes where an initial stereogenic centre is destroyed during the generation of the corresponding reactive intermediate, but this intermediate is able to 'remember' the configuration of its precursor to transfer the chirality to the final compound without using any external chiral source.[69] This concept has proven to be a useful approach for the asymmetric synthesis of acyclic α,α-dialkyl amino acids.

In the methylation of N,N-disubstituted phenylalanine derivatives it was found that the enantiomeric excess of the final methylated compound depended on the substituents on the nitrogen atom. These substituents have to be different, with the combination of *tert*-butoxycarbonyl/methoxymethyl being the most effective in terms of enantioselectivity. Taking into account these premises, methylation of several amino acids with different aliphatic and aromatic side chains was carried out and afforded α-methyl amino acid derivatives with retention of configuration in good yields and with enantiomeric excess values of 76–87%. Acidic hydrolysis provided the corresponding α-methyl amino acids[70] (Scheme 20).




Scheme 20.

The stereochemical course of the α-methylation was controlled by the initial configuration at $C_2$ even when an adjacent stereogenic centre was present. This was proved by the fact that L-isoleucine and D-*allo*-isoleucine *N*-Boc-*N*-MOM derivatives were methylated with retention of configuration and comparable diastereoselectivity[71,72] and the same result was found when *N*-Boc-*N*-MOM derivatives of (2*R*,3*R*)- and (2*S*,3*R*)-β-methylphenylalanine were used as substrates.[72]

The solvent dependence of the enantioselectivity in the alkylation of compound **74** (R = Bn) led the authors to the conclusion that enantioselectivity could be controlled by the regulation of the aggregate structure of chiral enolate intermediates.[73] One strategy to control the formation

of intramolecular aggregates is to use amino acid dimers as substrates (Fig. 4). In this case alkylation led to mixtures of chiral and *meso* isomers in which the effect of solvent on enantioselectivity was not very significant.

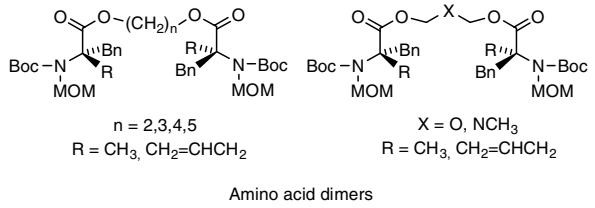
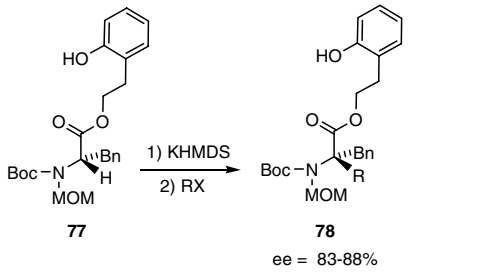



**Figure 4.**

An alternative strategy to control the formation of intramolecular aggregates is to use an ester derived from an alcohol with an additional hydroxy group. This strategy has allowed the extension of this methodology to the synthesis of α-allyl amino acids,[73,74] as enantioselectivities were quite good when esters with a free phenol group able to form stable intramolecular aggregates were used as starting materials. α-Allylation took place with retention of configuration and the degree of asymmetric induction was comparable with that obtained when using different allyl halides as electrophiles (Scheme 21).

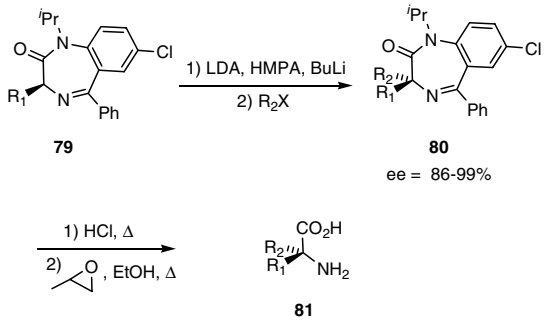



**Scheme 21.**

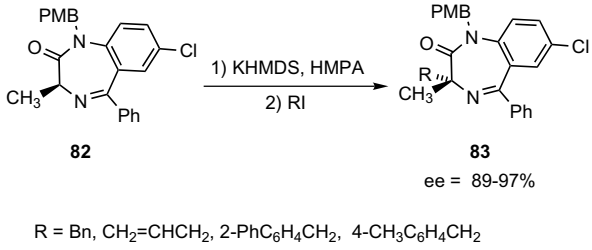
A change in the length of the phenol linker or the use of an anisole instead of a phenol group was detrimental in terms of enantioselectivity.

Finally, the intrinsic chirality of the benzodiazepin-2-one ring has been used to obtain α,α-dialkyl amino acids enantioselectively by deprotonation/alkylation of 3-alkyl-1,4-benzodiazepin-2-ones **79**, derived from (*S*)-*tert*-butoxycarbonylalanine and (*S*)-*tert*-butoxycarbonylphenylalanine.[75] The degree of enantioselectivity was dependent on the bulkiness of the $N_1$ substituent to such an extent that alkylation of *N*-methyl benzodiazepin-2-one led to a racemic compound, whereas *N*-isopropyl benzodiazepin-2-ones were alkylated in a highly enantioselective manner with retention of the spatial disposition of the starting amino acid. Acidic hydrolysis of the alkylated compounds provided the corresponding α,α-dialkyl amino acids (Scheme 22).

The convenience of using *N*-4-methoxybenzyl-1,4-benzodiazepin-2-ones as starting compounds led to the development of an alternative protocol to achieve enantioselective alkylation.[76] Deprotonation at −109 °C with KHMDS followed by the addition of an excess of an allylic or benzylic iodide led to the corresponding α-alkyl derivative with excellent enantiomeric excess through a transformation in which the original spatial distribution was retained (Scheme 23). Alkylation with less reactive iodides occurred with substantial enolate racemisation with the enantiomeric excess values of the resulting compounds, as well as the yields, being very low.




**Scheme 22.**




**Scheme 23.**

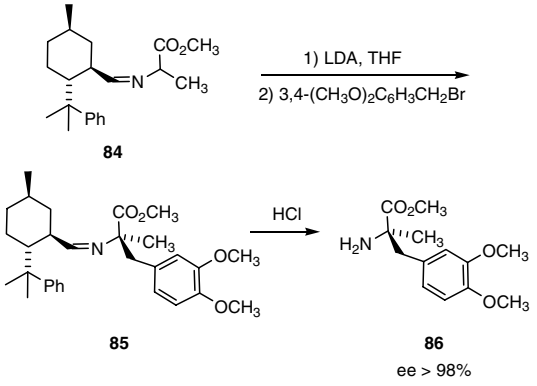
## 4. Diastereoselective alkylation

Diastereoselective syntheses involve the use of appropriate synthetic equivalents incorporating a covalently bonded chiral auxiliary. In this respect, dialkylation of chiral glycine equivalents or alkylation of chiral amino acid equivalents is one of the most useful and versatile methodologies for the asymmetric synthesis of α,α-dialkyl amino acids. To this end both acyclic and cyclic chiral derivatives have been widely used. Iminoglycinates in the acyclic series, as well as a wide variety of chiral heterocyclic glycine equivalents in the cyclic series, have been described in the literature as excellent precursors for enantiomerically pure α,α-dialkyl amino acids.

### 4.1. Diastereoselective alkylation of acyclic chiral amino acid equivalent enolates

Imines derived from α-amino acids and aldehydes are reactive substrates for alkylation and the use of chiral

aldehydes enables this reaction to be performed diastereoselectively. In this context, enantiomerically pure (*R*)-α-methyldopa has been obtained by alkylation of an enolate derived from chiral iminoalaninate **84** and subsequent hydrolysis according to Scheme 24.[77]

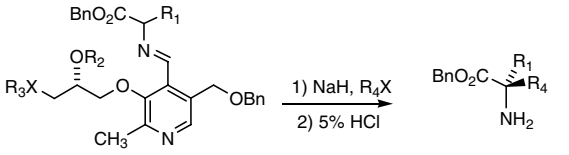



**Scheme 24.**

Alkylation of aldimines derived from chiral aldehydes of the pyridoxal type with an *R*-ansa structure has been applied to the stereoselective alkylation of the N-terminal residue of small peptides[78,79] (Scheme 25).

Neither the absolute configuration nor the size of the side chain of the contiguous residue influence the stereochemical course of the alkylation. Indeed, compounds with an (*R*)-configuration at the N-terminal α-methyl amino acid have been obtained upon alkylation with alkyl bromides in the presence of $LiClO_4$ and DBU. In the absence of $LiClO_4$ or in the presence of other alkali metal ions, the corresponding alkylated compounds of (*S*)-configuration at the N-terminal α-methyl amino acid have been obtained with comparable levels of diastereoselectivity.

In a related approach, aldimines derived from chiral aldehydes of the pyridoxal type with a chiral side chain at $C_3$ have been deprotonated and quenched with an alkyl halide to afford the corresponding α-alkylated compounds with different levels of diastereoselectivity, which depend on the structure of the side chain and the metal ion.[80] Optimal results were obtained when $R_3 = 2$-naphthylmethyl and $R_2 = CH_3$ with sodium hydride as the base (Scheme 26).

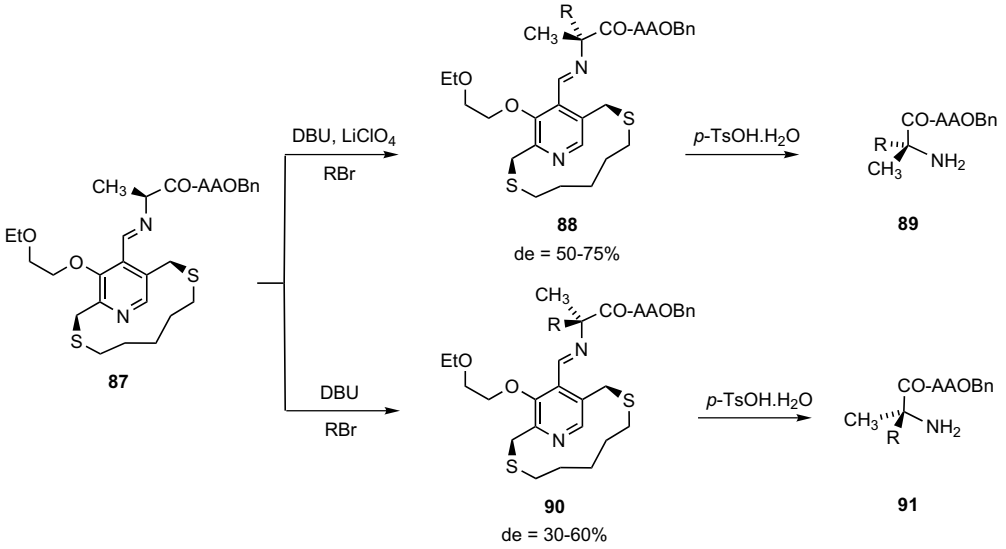



$R_1 = CH_3$, Bn,
$R_2 = CH_3$, Bn
$R_3X$ = BnO, BnS, 1-naphthylmethylO, 2-naphthylmethylO
$R_4X$ = BnBr, 4-$NO_2C_6H_4CH_2Br$, $EtO_2CCH_2Br$, $CH_2$=$CHCH_2Br$, $CH_3I$

**Scheme 26.**

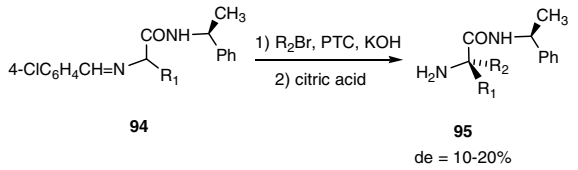
The appropriate combination of the chiral ansa-structure and a chiral side chain at $C_3$ (matched pair) in most cases gave the corresponding alkylated compounds with better diastereoselectivities in a double stereodifferentiation process.[81]

Schiff bases derived from 4-chlorobenzaldehyde and phenylalanine, phenylglycine and alanine chiral amides have been alkylated using 18-crown-6, 15-crown-5, TBAB or TBPB as phase-transfer catalysts to afford, after hydrolysis, the corresponding α,α-dialkyl amino acids in low to moderate yields and with very poor diastereoselectivity (Scheme 27).[82]



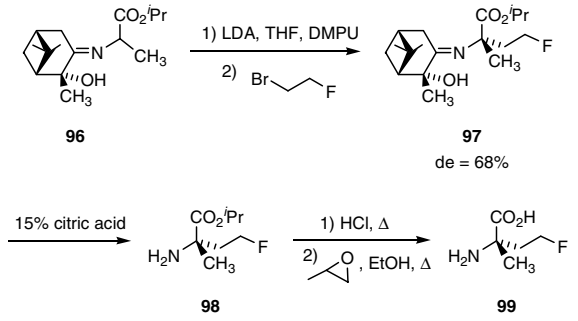

AA = L-Ala, D-Ala, Gly, L-Val, D-Val, L-Ala-L-Ala R = Bn
AA = L-Ala R = Bn, 4-$NO_2C_6H_4CH_2$, $CH_2$=$CHCH_2$, HC≡$CCH_2$

**Scheme 25.**




**Scheme 27.**

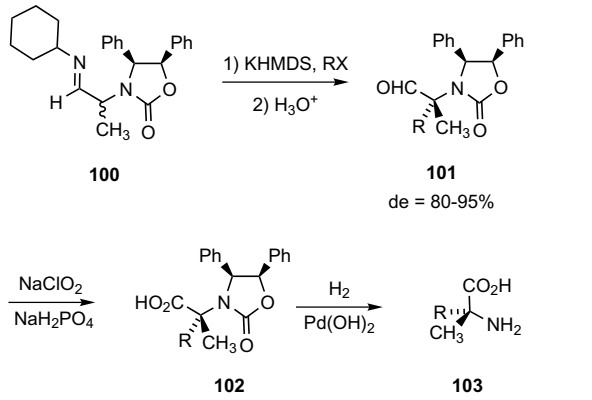
Imines derived from α-amino acids and chiral ketones have also been used as substrates in the synthesis of α,α-dialkyl amino acids. Haufe applied the diastereoselective alkylation of iminoglycinates derived from (*R*,*R*,*R*)-2-hydroxy-3-pinanone to the synthesis of γ-fluorinated α-methyl-α-amino acids.[83] The low yield and poor diastereoselectivity obtained in the alkylation step with LDA in THF was increased to some extent by varying the reaction conditions. Ultimately, alkylation in the presence of DMPU led to compound **97** in moderate yield and diastereoselectivity (Scheme 28). This compound was used to obtain (*S*)-2-amino-4-fluoro-2-methylbutanoic acid with an 85% enantiomeric excess, although the overall yield of the entire sequence was very poor.




**Scheme 28.**

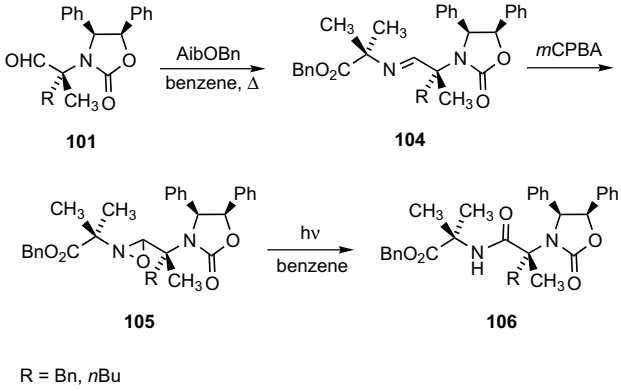
Apart from Schiff bases derived from amino acids there are other acyclic chiral amino acid synthons that have been used in diastereoselective alkylations. For example, alkylation of chiral α-aminoimine **100** under carefully controlled reaction conditions, which require deprotonation with an excess of base at low temperature in the presence of the electrophile, proceeded smoothly to afford, after hydrolysis, the corresponding α-methyl-α-aminoaldehyde with high diastereoselectivity.[84] Oxidation of the aldehyde moiety and subsequent hydrogenolysis provided α-methyl-α-amino acids in good overall yield (Scheme 29).

The amount of electrophile required depended on its reactivity; with activated benzyl or allyl bromides, 1 or 2 equiv of the reagent were sufficient for clean alkylation, whereas with less reactive alkyl iodides 10 equiv of reagent were required to inhibit the formation of undesired by-products. The use as a chiral auxiliary of the 4,5-diphenyl-2-oxazolidinone with a (4*R*,5*S*)-configuration led to alkylated compounds with an (*R*)-configuration. Aldehydes **101** also




**Scheme 29.**

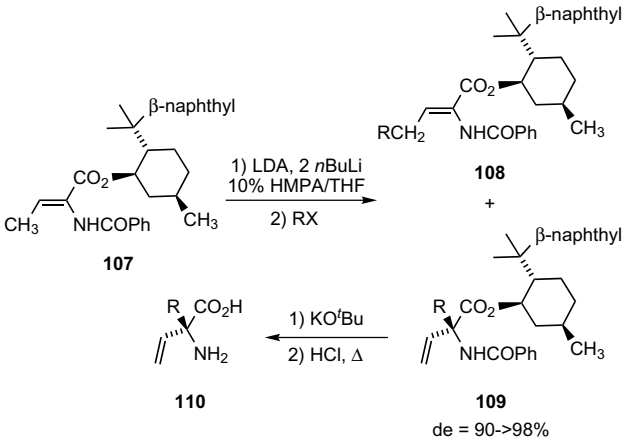
serve as α-amino acid synthons in the preparation of dipeptides containing sterically hindered residues. This approach involves imine formation, oxidation to an oxaziridine and a thermal or photochemical rearrangement (Scheme 30).




**Scheme 30.**

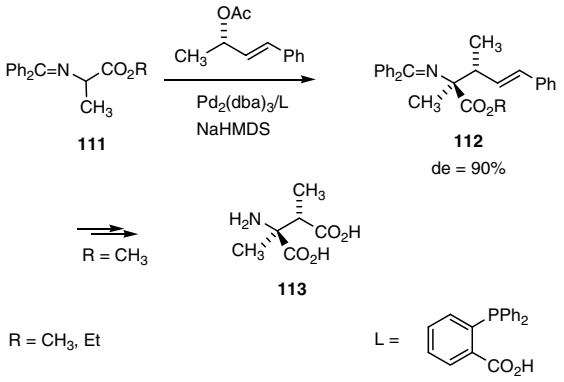
In their approach to the synthesis of higher α-vinyl amino acids, Berkowitz et al. studied the alkylation of dianionic dienolates generated from chiral esters derived from *N*-benzoyl-α,β-didehydroaminobutyric acid.[85] (−)-8-(β-Naphthyl)-menthol was the best chiral auxiliary and alkylation of ester **107** gave mixtures of α and γ alkylated compounds with excellent diastereoselectivity. The α/γ ratios were found to be better on using hard electrophiles. γ-Alkylated compounds decomposed during alkaline hydrolysis, allowing the recovery of the chiral auxiliary and isolation of the methyl esters of α-alkylated compounds, which were further hydrolysed to the free amino acid (Scheme 31).

Finally, the alkylation of *N*-(diphenylmethylene)alaninates with (*R*)-2-acetoxy-4-phenyl-3-butene, a chiral reagent, catalysed by palladium and using 2-(diphenylphosphino)-benzoic acid as the ligand was investigated. The reaction proceeded with almost total regioselectivity and high diastereoselectivity when methyl and ethyl esters were used as substrates.[86] From these compounds (2*S*,3*S*)-3-methyl-aspartic acid was obtained (Scheme 32).




RX = 3-TBSOC$_6$H$_4$CH$_2$I, $^i$BuI, EtI, Cl(CH$_2$)$_4$I, PhCH=N(CH$_2$)$_2$I, BnBr, EtO$_2$CCH$_2$Br, $^i$PrI, PrI, TMSC≡CCH$_2$Br

**Scheme 31.**



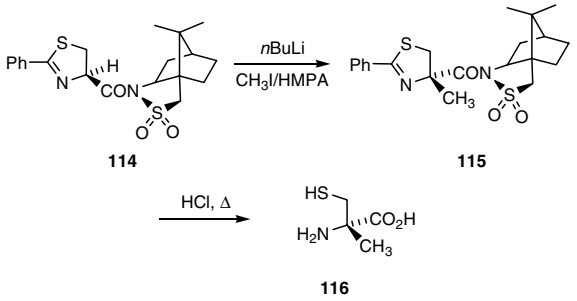

**Scheme 32.**

The lack of diastereoselectivity in the alkylation of *tert*-butyl esters under the same reaction conditions was circumvented by using 1-(diphenylphosphino)-2-naphthoic acid as the ligand. In this case the reaction led to the corresponding α,α-dialkyl-β-substituted amino acid derivative of (2*S*,3*R*)-configuration with a diastereomeric excess of 82%.

## 4.2. Diastereoselective alkylation of cyclic chiral amino acid equivalent enolates

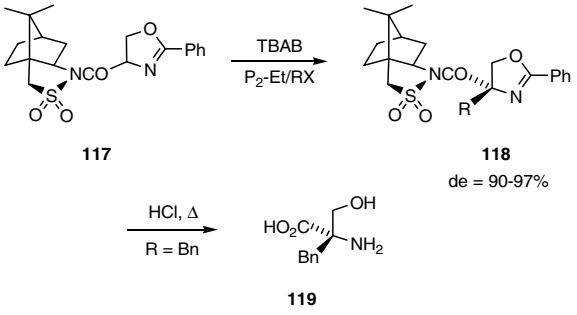
In recent years a plethora of α-amino acid synthetic equivalents have been used to obtain α,α-dialkyl amino acids in enantiomerically pure form in diastereoselective alkylation processes.

In some approaches the chiral auxiliary in the cyclic amino acid synthetic equivalent is an exocyclic chiral appendage so that the enolate generated by treatment with a base can be alkylated diastereoselectively. In one of these approaches, 2,10-camforsultam was used as a chiral auxiliary in the synthesis of α-methylcysteine from cysteine.[87] The amino acid was converted into 2-phenylthiazoline **114**, which possesses a labile acidic proton for ease of alkylation. The best results were obtained when the enolate, previously generated at −78 °C using *n*BuLi as a base, was trapped with methyl iodide in the presence of HMPA (Scheme 33). Contrary to the expectations, alkylation and subsequent hydrolysis of phenylthiazolinyl (*R*)-camforsultam led to (*S*)-α-methylcysteine, while alkylation of phenylthiazolinyl (*S*)-camforsultam followed by acidic hydrolysis led to (*R*)-α-methylcysteine.




**Scheme 33.**

Benzylation of the related substrate **117**, derived from (*S*)-camforsultam and 2-phenyl-2-oxazoline-4-carboxylate, under the same reaction conditions was unsuccessful and phase-transfer catalysis conditions were tested.[88] Among the different bases used to perform benzylation, optimal results were obtained with phosphazene base P$_2$-Et working at −78 °C as the diastereoselectivity was markedly higher when decreasing the reaction temperature. This methodology was extended to other alkyl halides. Alkylation with active halides led to the corresponding α-alkyl derivative with high yield and diastereoselectivity, whereas aliphatic alkyl halides, with the exception of methyl iodide, did not react (Scheme 34).



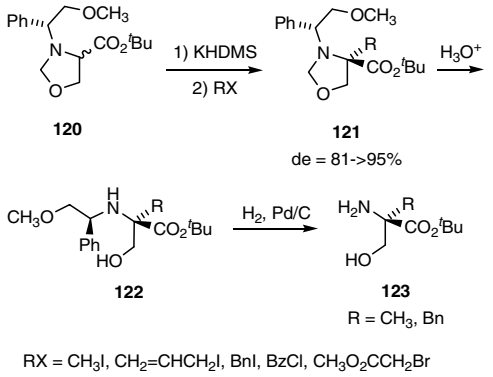

R = Bn, CH$_3$, CH$_2$=CHCH$_2$, CH$_2$=C(CH$_3$)CH$_2$, HC≡CCH$_2$, 4-FC$_6$H$_4$CH$_2$, 4-CH$_3$C$_6$H$_4$CH$_2$, 2-naphthylmethyl

**Scheme 34.**

On the other hand, compound **117** reacted with *tert*-butyl acrylate to afford the corresponding (*S*)-2-hydroxymethylglutamic acid precursor, from which the amino acid was obtained in 88% yield and 85% enantiomeric excess.

Oxazolidine **120** possesses a chiral N-protecting group and has proven to be a suitable precursor in the preparation of α-alkyl serine derivatives.[89] The potassium enolate gener-

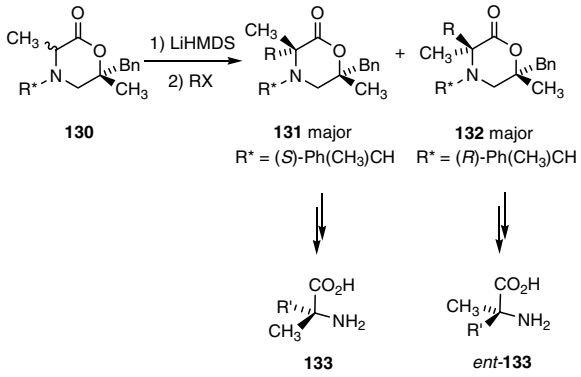
ated by deprotonation with KHMDS reacted with several alkyl halides to afford the corresponding α-alkyl serine precursors, which were directly submitted to acidic hydrolysis to give the desired products in good yield and with good diastereoselectivity. Subsequent hydrogenolysis gave α-alkyl serine *tert*-butyl esters, as shown in Scheme 35.




**Scheme 35.**

Sandri et al.[90–92] have constructed 2-alkyl-2,6-diaminopimelic acid surrogates from piperazine-2,5-dione **124**. This glycine-derived chiral synthon was first submitted to alkylation with a dihalide to afford the corresponding bicyclic derivative, usually as an enriched diastereomeric mixture that can be separated easily by column chromatography. Bicyclic compounds can be further alkylated and, depending on their structure and stereochemistry, alkylation at the bridgehead is complicated by alkylation at the benzylic position of the *N*-phenethyl group, especially in bicyclic derivatives with a $C_3$ bridge. In some cases this undesired reaction can be overcome by using *n*BuLi, a bulkier base, instead of $CH_3Li$. Final hydrolysis under the appropriate conditions led to enantiomerically pure 2,6-diaminopimelic acid surrogates with an alkyl group at the $C_2$ position (Scheme 36).

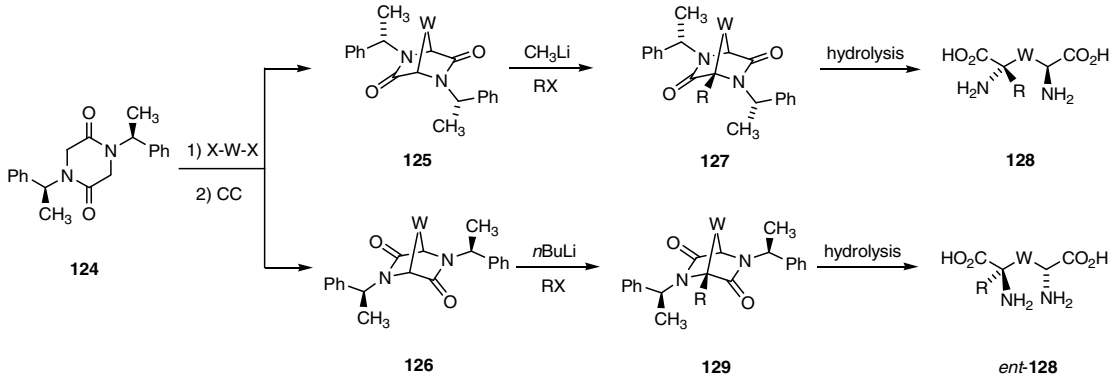
The same authors reported a new approach to the stereoselective synthesis of α,α-dialkyl amino acids by alkylation of diastereomeric mixtures of chiral morpholinones **130**.[93,94] The stereochemical course of the alkylation reaction was directed by the absolute configuration of the *N*-phenethyl group. On using (*R*)-*N*-phenethyl morpholinones good levels of *trans* induction were observed whereas with (*S*)-*N*-phenethyl morpholinones, *cis*-compounds were preferentially obtained. The major products were converted into the corresponding amino acids as shown in Scheme 37.




**Scheme 37.**

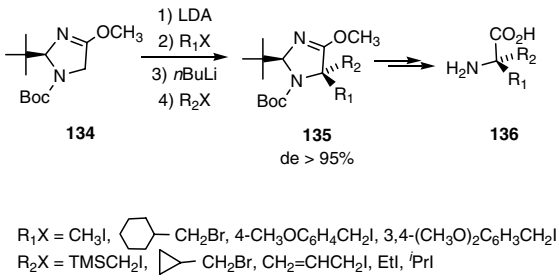
Undoubtedly amongst the most efficient approaches to the asymmetric synthesis of α,α-dialkyl amino acids by diastereoselective alkylation are those that use chiral cyclic α-amino acid synthetic equivalents such as chiral imidazolidinones, oxazinones, bislactim ethers or tetrahydropyrazinones.

The in situ double alkylation of (*S*)-*tert*-butyl 2-*tert*-butyl-4-methoxy-2,5-dihydroimidazole-1-carboxylate (BDI), a new chiral glycine synthetic equivalent, led to α,α-dialkyl amino acids.[95] Dialkylated compounds **135** are obtained as single diastereoisomers, usually in high overall yields that depend on the level of crowding. The mildness of the conditions required for hydrolysis allows the



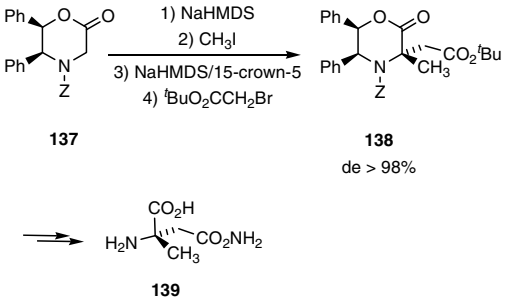

**Scheme 36.**

preparation of amino acid esters with acid-labile side chains, with the absolute configuration determined by the sequence in which the two alkylating agents are added (Scheme 38).




**Scheme 38.**

Williams' oxazinone **137** with a (5*S*,6*R*)-configuration is the glycine synthetic equivalent from which (*S*)-α-methyl-asparagine was obtained by sequential alkylation with methyl iodide and *tert*-butyl bromoacetate.[96] The yields of the second alkylation were optimised by enolate generation using a combination of NaHMDS and 15-crown-5 and subsequent quenching with the alkyl halide. The same enantiomer of α-methylasparagine was obtained starting from *ent*-**137** and inverting the alkylation steps. Both synthetic routes led to the corresponding dialkylated compound as a single diastereoisomer, from which the desired amino acid was obtained in enantiomerically pure form by acidic hydrolysis followed by amination and final hydrogenolysis (Scheme 39).




**Scheme 39.**

Dialkylation of oxazinone **137** has been used as a synthetic strategy to obtain enantiomerically pure *N*-Boc-α-methyl-4-diethylphosphonophenylalanine (Fig. 5).[97]

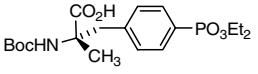
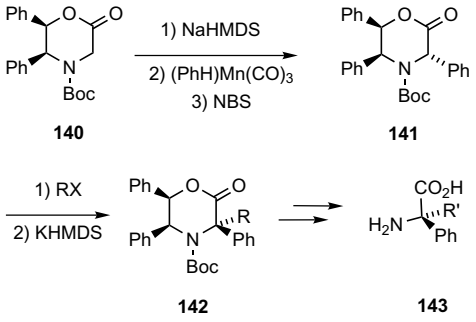


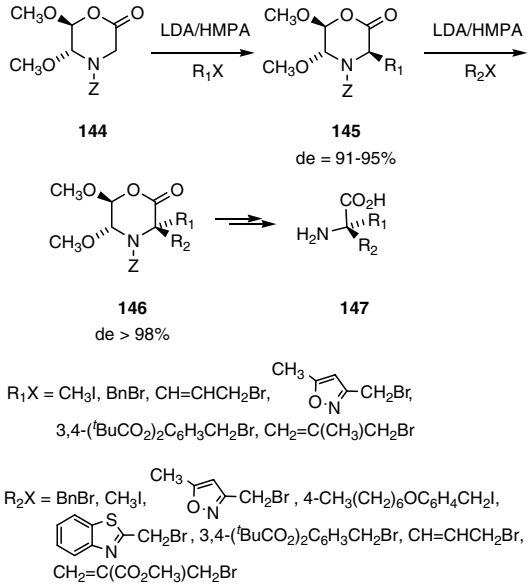

**Figure 5.**

Arylation of oxazinone **140** with a benzene–$Mn(CO)_3$ complex led to the corresponding 3-phenyloxazinone, from which α-alkyl-α-phenylglycines were obtained asymmetrically with high yields and total stereoselectivity by deprotonation followed by the addition of an alkyl halide and subsequent hydrolysis and hydrogenolysis (Scheme 40).[98]




**Scheme 40.**

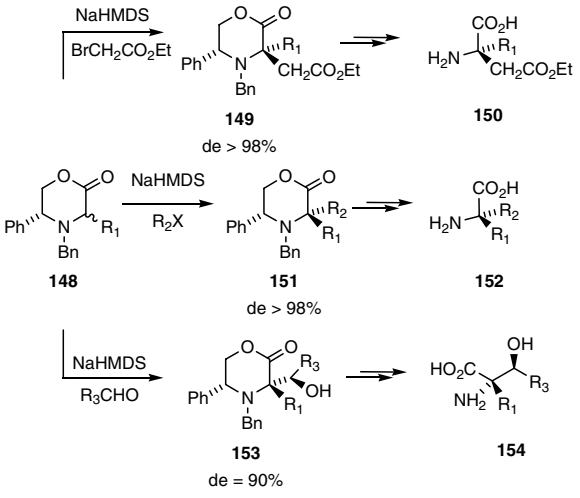
Ley et al. have prepared the new chiral glycine synthetic equivalent **144** (with a 1,4-oxazin-2-one ring) from glycidol.[99] In general, sequential alkylation of this compound proceeds to give good to excellent yields and excellent diastereoselectivity in the presence of HMPA. This route allowed the synthesis of enantiomerically pure α,α-dialkyl amino acids with different side chains (Scheme 41).[100]




**Scheme 41.**

Sodium enolates generated from oxazinone **148** reacted with active electrophiles to give the corresponding alkylated products, which were deprotected in a convenient manner to generate α,α-dialkyl amino acids.[101,102] Alkyl halides reacted with almost total diastereoselectivity and reaction with aldehydes gave preferentially one of the four possible aldol adducts with excellent diastereoselectivity. The absolute configuration of the newly formed stereogenic

centre depended on the electrophile. Whereas aldehydes and simple alkyl halides provided 3*R*,5*S* oxazinones as products, the reaction with methyl bromoacetate led to the product with (3*R*,5*R*)-configuration (Scheme 42).



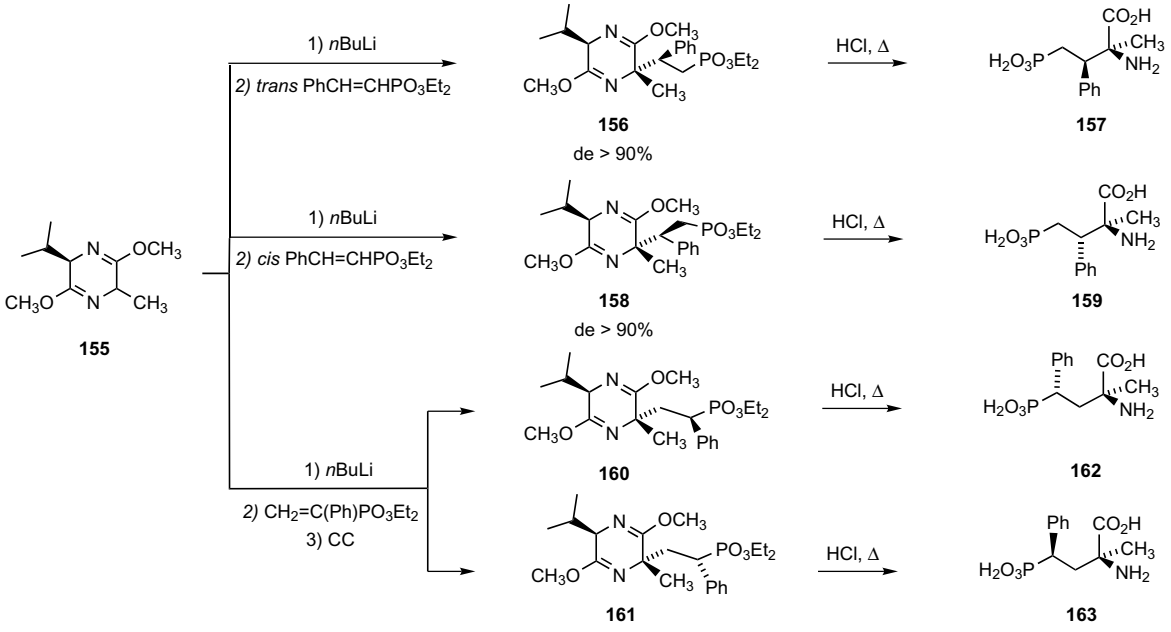

**Scheme 42.**

Schöllkopf bislactim ethers have been used as chiral precursors in the new syntheses of several α,α-dialkyl amino acids. In the synthesis of 2-amino-2-methyl-3-phenyl-4-phosphonobutanoic acids, potential antagonists of glutamic acid at group III receptors, a key step involved the conjugate addition of the lithium salt of bislactim **155** to 2-phenylethenylphosphonates. This afforded Michael adducts with a 2,5-*trans* disposition with good yields.[103] The diastereoselectivity in the formation of the stereogenic centre at $C_{2'}$ was very high and its absolute configuration depended on the stereochemistry of the vinylphosphonate (Scheme 43). When 1-phenylethenylphosphonate was the Michael acceptor, a mixture of adducts epimeric at $C_{2'}$ was obtained with a diastereomeric excess of 50% in favour of the 2,5-*trans*-2,2′-*anti* isomer. When the reaction was quenched at room temperature, a ca. 60:40 epimeric mixture was obtained, from which both epimers were isolated on a multigram scale. Final hydrolysis of bislactim ethers in acidic media provided the desired amino acids.

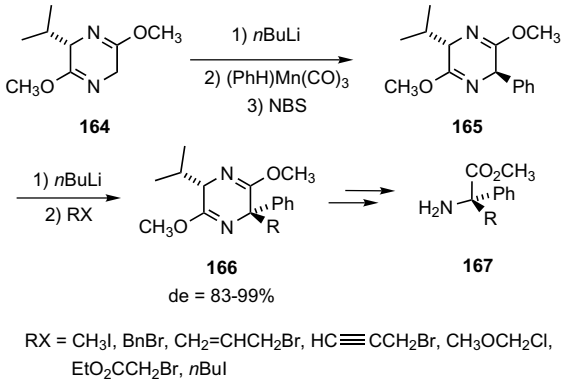
Arylation of the bislactim ether derived from *cyclo*[Gly-L-Val] provided the key intermediate in the synthesis of enantiomerically pure α-alkyl-α-phenylglycine derivatives.[104] Treatment of this compound with *n*-butyllithium, followed by addition of an alkyl halide led to the corresponding alkylated compound as a single diastereoisomer. The product had a *trans* disposition between the isopropyl and the alkyl group in all cases, except when methyl iodide was the reagent. Acid hydrolysis required mild conditions and the corresponding α-alkyl-α-phenylglycine methyl esters were obtained after long reaction times (Scheme 44).

The alkylation of Schöllkopf bislactim ethers has been applied to the synthesis of quaternary α-alkylaspartic acid derivatives as intermediates in the synthesis of quaternary β-lactams. It was observed that alkylation yields with α-haloacetates as electrophiles improved when deprotonation was performed with *tert*-butyllithium instead of *n*-butyllithium.[105] The same is true for alkylation with other electrophiles.

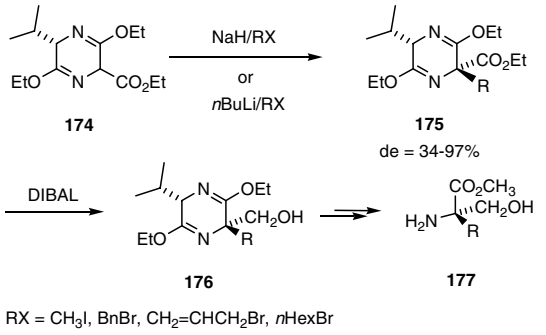
Alkylation of bislactim **168** led to the appropriate synthetic intermediates from which enantiomerically pure novel α-alkyl-α-cyclopentyl glycines were obtained according to




**Scheme 43.**




Scheme 44.



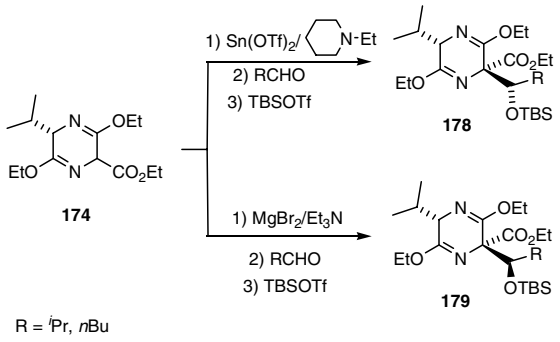

Scheme 46.

Scheme 45.[106] The vinyl moiety in bislactim **169** was submitted to Wacker oxidation conditions to afford a methyl ketone, which was then converted into an α-diazoketone by activation with trifluoroethyl trifluoroacetate (TFEA) followed by reaction with tosyl azide. The α-diazoketone in the presence of $Rh_2(OAc)_4$ gave chemoselective and regioselective intramolecular carbenoid insertion to afford a five-membered ring. Hydrolysis to the corresponding α-alkyl-α-cyclopentyl glycines under mild conditions was sensitive to steric interactions so that hydrolysis of propyl bislactim **172** required strongly acidic conditions, which led to the formation of diketopiperazines.

Nagao et al.[107] designed new bislactim ether **174** as a masked serine to perform the asymmetric synthesis of α-alkyl serine methyl esters by deprotonation, reaction with alkyl halides and subsequent hydrolysis (Scheme 46).

Compound **174** was submitted to tin- or magnesium-mediated aldol-type reactions with achiral aldehydes.[108] When aliphatic aldehydes were used as reagents tin-promoted aldol reaction led to the preferential formation of compounds of (2*R*,1′*S*)-configuration, whereas the similar aldol reaction in the presence of magnesium bromide and triethylamine led to compounds with the (2*R*,1′*R*)-configuration as the major products (Scheme 47).

In contrast, the reaction with benzaldehyde or 3-methyl-2-butenal afforded the diastereoisomer with a (2*R*,1′*R*)-con-

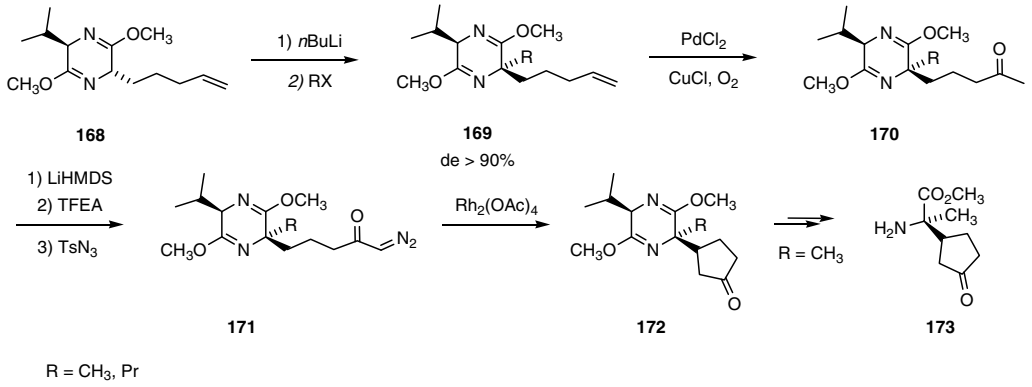



Scheme 47.

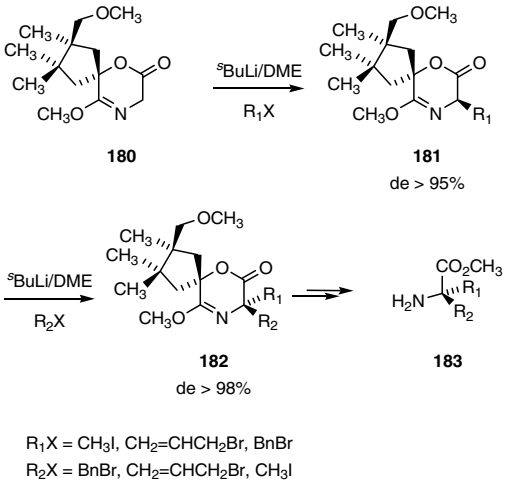
figuration as the major product in both tin- and magnesium-promoted reactions. In all cases, reduction with DIBAL and subsequent hydrolysis led to new α-substituted serine derivatives.

Sequential alkylation of chiral oxazinone **180** led to α,α-disubstituted compounds from which α,α-dialkyl amino acid methyl esters were obtained by basic hydrolysis (Scheme 48).[109] An appropriate choice of solvent was crucial to avoid dialkylation competing in the first step of the synthesis and dimethoxyethane proved to be the best, although yields of the monoalkylation did not exceed 76%.

The same group also designed oxazinone **184** as a new chiral glycine equivalent, which is accessible in both enantiomeric forms.[110] After deprotonation, alkylation of this

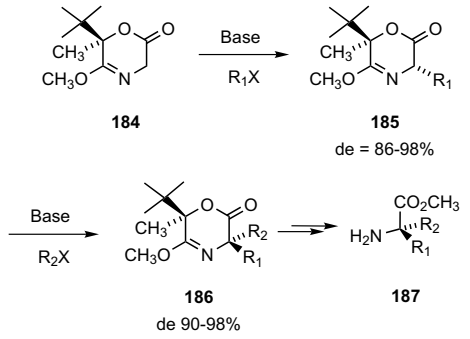



Scheme 45.



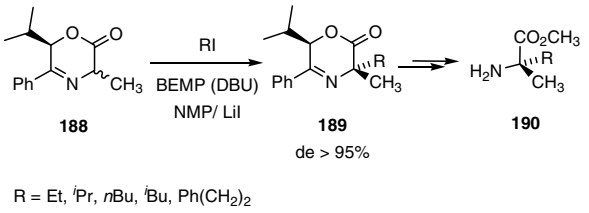

**Scheme 48.**

compound led to the corresponding monoalkylated compounds with good to excellent yields and excellent diastereoselectivities when the reaction was carried out at low temperature. The second alkylation proceeded smoothly and oxazinones **186** were generally obtained in good yields and with high diastereoselectivities. Non-activated alkyl halides required the use of phosphazenic base $^{t}$Bu–P$_4$ for deprotonation. Final hydrolysis provided α,α-dialkyl amino acid methyl esters in enantiomerically pure form (Scheme 49).



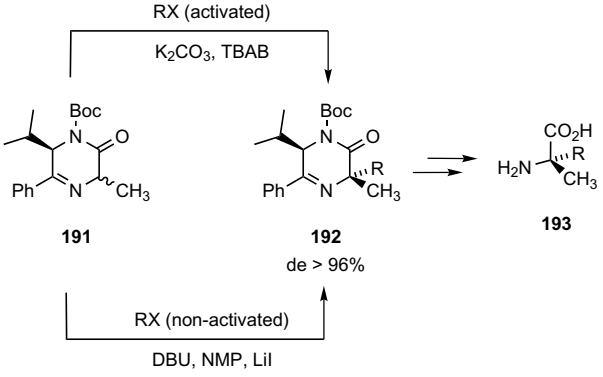

**Scheme 49.**

Nájera et al. reviewed the use of new chiral oxazinones and pyrazinones as chiral intermediates for the asymmetric synthesis of α,α-dialkyl amino acids.[111,112] The reaction of chiral oxazinone **188** with non-activated alkyl halides was possible using organic bases such as BEMP or DBU, a method that has allowed the synthesis of enantiomerically pure (*S*)-α,α-dialkyl amino acids.[113] O-Alkylation competed with C-alkylation to a variable extent that depended upon the reaction conditions. The use of a slight excess of BEMP (1.1 equiv) as base, NMP as solvent, and lithium iodide as an additive usually gave the best C/O alkylation rate (Scheme 50). The versatility of oxazinone **188** as a chiral alanine equivalent in the asymmetric synthesis of (*S*)-α-methylamino acid derivatives by alkylation under phase-transfer catalysis conditions, organic base conditions and allylation under Pd(0) catalysis has been discussed in a feature article.[114]



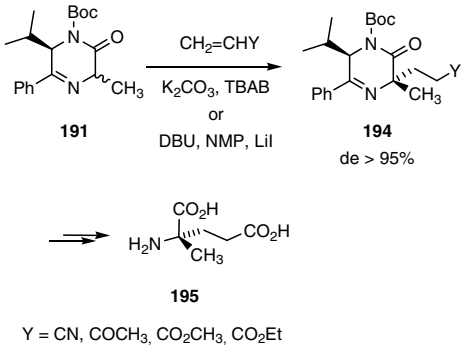

**Scheme 50.**

In a related approach that slightly improved the results obtained with oxazinone **188**, pyrazinone **191** was reacted with several electrophiles to give α-methyl-α-amino acid precursors with high diastereoselectivity.[115,116] Alkylation with activated halides could be performed under phase-transfer catalysis conditions, whereas non-activated halides required the use of organic bases (Scheme 51).



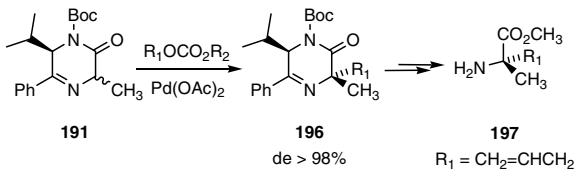

**Scheme 51.**

Electrophilic olefins underwent Michael addition using either phase-transfer catalysis conditions or organic bases, to promote the reaction (Scheme 52).[115]




**Scheme 52.**

Pyrazinone **191** can also be allylated with allylic carbonates by means of palladium(0) catalysis (Scheme 53).[115]




$R_1$ = $CH_2$=CHCH$_2$, $CH_2$=CHCHCH$_3$, $CH_2$=C($CH_3$)$CH_2$, *trans*-PhCH=CHCH$_2$

$R_2$ = $CH_3$, Et

**Scheme 53.**

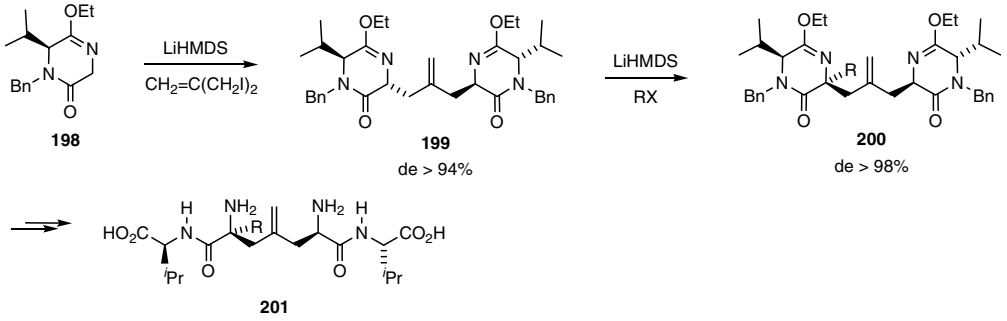
In all cases, final hydrolysis under the appropriate reaction conditions provided α-methyl-α-amino acids or their methyl esters—even when an allyl side chain was present.

In order to gain access to α-alkyl-γ-methylene derivatives of 2,6-diaminopimelic acid, synthon **198** was deprotonated and alkylated with 2-iodomethyl-3-iodopropene to afford compounds derived from double 1,4-*trans* induction with high diastereoselectivity. A second alkylation gave compound **200**, which underwent Birch reduction and hydrolysis to give the desired α,α-dialkyl amino acid derivatives in enantiomerically pure form (Scheme 54).[117]

The chiral Schiff base of alanine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone acts as a tetradentate ligand to afford a Ni(II) complex that can be considered a cyclic chiral amino acid equivalent. Diastereoselective alkylation of this Ni(II) complex was applied to the large-scale asymmetric synthesis of (*S*)-α-*trans*-cinnamylalanine[118] and (*S*)-α-methyl-2′,6′-dimethyltyrosine.[119] The diastereoselectivity of the reaction was very high and, in addition, the major diastereoisomer could be easily isolated by column chromatography. Decomposition of the Ni(II) complex gave the corresponding amino acid in enantiomerically pure form and allowed recovery of the chiral ligand, from which the starting alanine complex **202** can be readily prepared (Scheme 55).

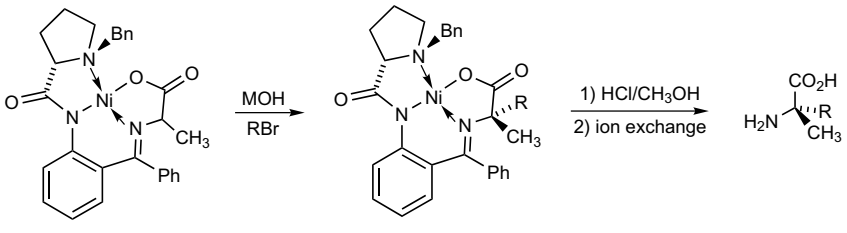
Deprotonation of complex **202** followed by quenching with an excess of a racemic α-alkylbenzylbromide led to stereoselective alkylation, which allowed the asymmetric synthesis of α-methyl-β-substituted phenylalanines.[120] At room temperature, the diastereoselectivity was moderate and decreased as the steric bulk of the alkylating agent increased. However, when the reaction was carried out at −10 °C the diastereoselectivity was very good and the amino acid with a (2*S*,3*S*)-configuration was obtained in enantiomerically pure form, simply by washing the reaction mixture with ether and subsequent decomposition of the Ni(II) complex (Scheme 56).

New Ni(II) complexes with chiral ligands have recently been synthesised for use as chiral alanine synthons (Fig. 6).[121]




RX = $CH_3$I, BnBr, $CH_2$=CH$CH_2$Br, $CH_3OCH_2$Br

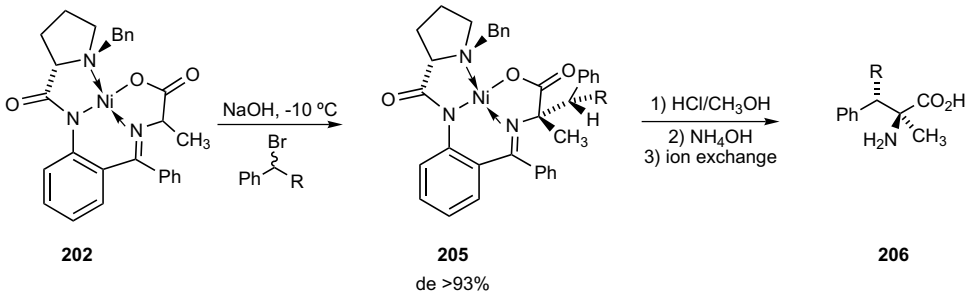
**Scheme 54.**




M = K, Na

R = *trans*-PhCH=CHCH$_2$, 2,6-($CH_3$)$_2$-4-BnO$C_6H_2CH_2$, 2,6-($CH_3$)$_2$-4-HO$C_6H_2CH_2$

**Scheme 55.**




**Scheme 56.**

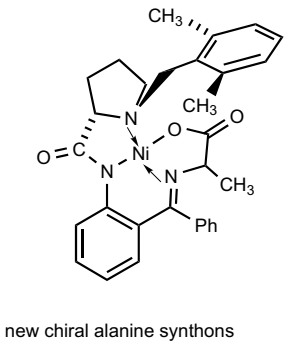
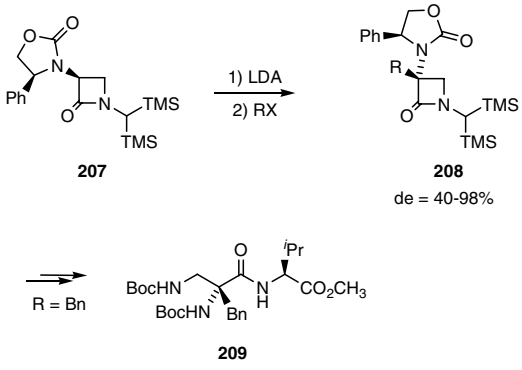



**Figure 6.**

## 5. Chiral β-lactams as building blocks

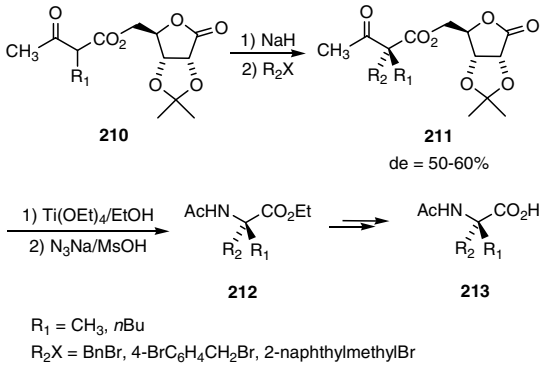
β-Lactams can be considered useful intermediates in the synthesis of diverse functionalised α- and β-amino acids and examples of their use as synthetic intermediates have recently been reviewed by Palomo et al.[122] A new approach[123] to the synthesis of α,α-dialkyl amino acids using this methodology has been developed starting from 4-unsubstituted 3-amino-β-lactams. In this process, the stereochemical course of the reaction cannot be directed by the $C_4$ substituent on the β-lactam ring as in previously reported approaches. Diastereoselective alkylation of the lithium enolate generated from β-lactam **207** with both reactive and unreactive alkyl halides took place to give moderate to good yields. The diastereomeric purity of $C_3$ in the alkylated β-lactam obtained in this way was dependent on the electrophile; the use of alkyl halides gave only moderate diastereoselectivity but alkylation with allyl and benzyl halides led to the formation of only one diastereoisomer. The resulting compounds were used as building blocks in the synthesis of dipeptides containing α,α-dialkyl amino acids (Scheme 57).




**Scheme 57.**

## 6. Rearrangement of β-carbonyl carboxylic acid derivatives

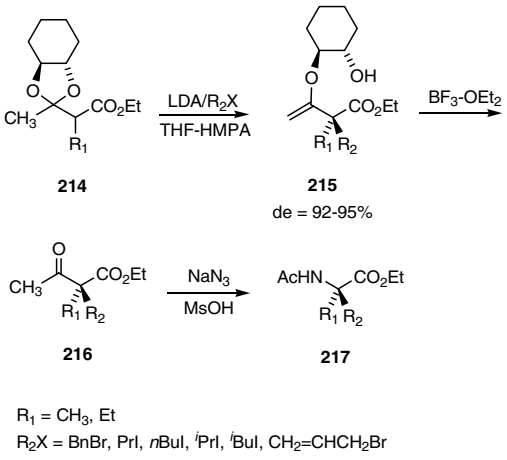
The asymmetric synthesis of α,α-dialkyl amino acids has also been performed by diastereoselective alkylation of activated methylene groups in compounds possessing masked amino and carboxylic acid groups, with the amino acid moiety generated after alkylation through a rearrangement process. This approach has been applied to the synthesis of α,α-dialkyl amino acids by alkylation of chiral β-keto esters derived from 2,3-*O*-isopropylidene-D-ribonolactone and subsequent transesterification, Schmidt rearrangement and hydrolysis of the isolated major compound[124] (Scheme 58).




**Scheme 58.**

In the same context, chiral cetals **214**, obtained via reaction of ethyl β-keto esters with (*S*,*S*)-cyclohexane-1,2-diols, have been alkylated to afford enol ethers in moderate yields. The diastereoselectivity of the alkylation was very

high, as demonstrated by the high enantiomeric excess of keto esters obtained from enol ethers **215**. α,α-Dialkyl-β-keto esters were transformed into the corresponding α,α-dialkyl amino acids using the Schmidt rearrangement (Scheme 59).[125]



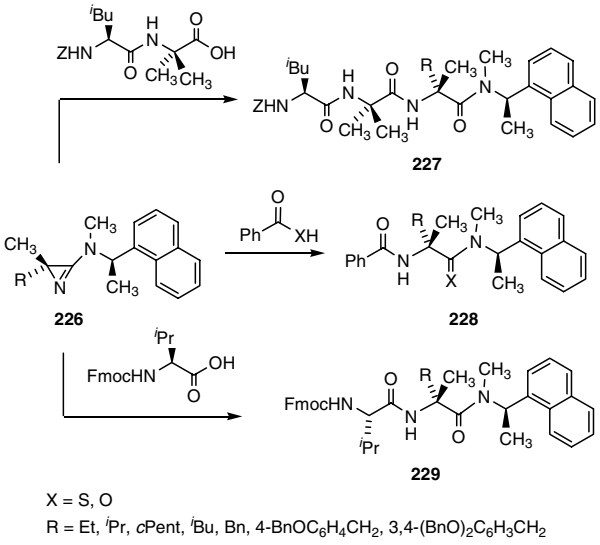

**Scheme 59.**

α-Ethylleucine obtained in this way has been introduced into Aib- or Deg-containing peptides in order to study their conformational preferences.[42]

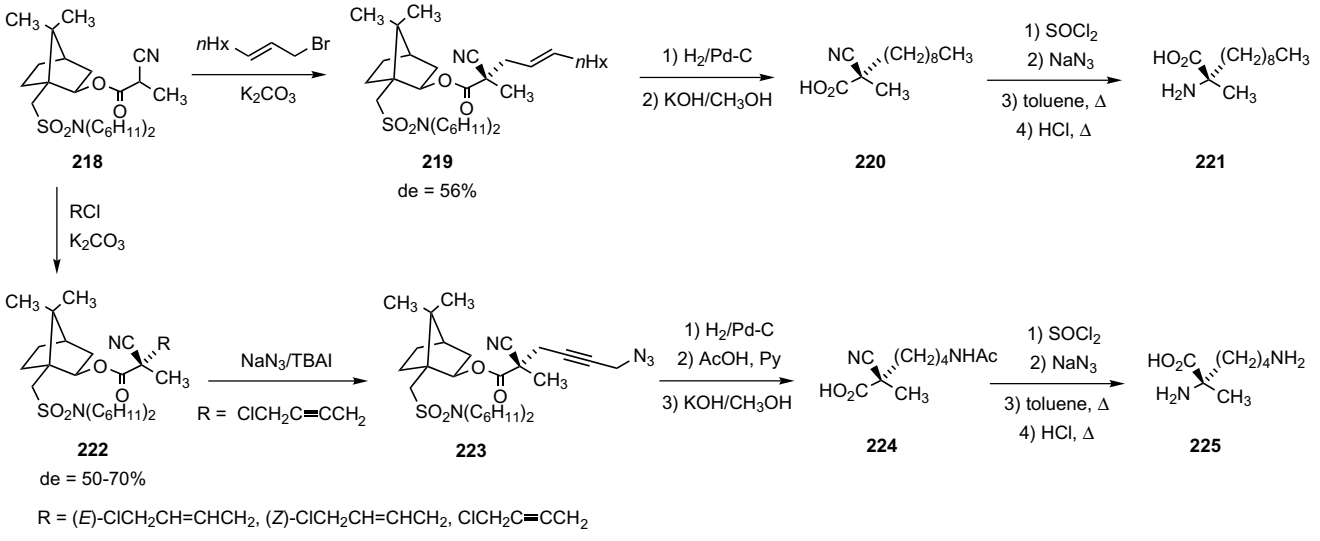
α-Methyllysine and 2-amino-2-methyl undecanoic acid have been obtained by diastereoselective alkylation of chiral cyanopropanoates with allyl halides or propargyl halides as the key step to introduce the long side chain of the target amino acid.[126] The appropriate transformation of the introduced alkyl chain, subsequent hydrolysis of the ester moiety and Curtius rearrangement provided the desired amino acid, as shown in Scheme 60.

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

The use of 3-amino-2*H*-azirines as synthetic equivalents of α,α-dialkyl amino acids in peptide synthesis using the 'azirine/oxazolone' method, as developed by Heimgartner,[127] has great potential. This approach was used for the preparation and isolation and of new α,α-dialkyl amino acids for use in peptide synthesis.[128,129] (*R*)-1-(1-Naphthyl)ethylamine has been used as a chiral auxiliary for preparing synthons **226** for isovaline (R = Et), α-methylvaline (R = $^{i}$Pr), α-cyclopentylalanine (R = *c*Pent), α-methylleucine (R = $^{i}$Bu), α-methylphenylalanine (R = Ph), α-methyltyrosine (R = 4-BnOC$_6$H$_4$CH$_2$) and α-methyldopa (R = 3,4-(BnO)$_2$C$_6$H$_3$CH$_2$). These compounds were reacted with carboxylic acid amino acid derivatives (Scheme 61).



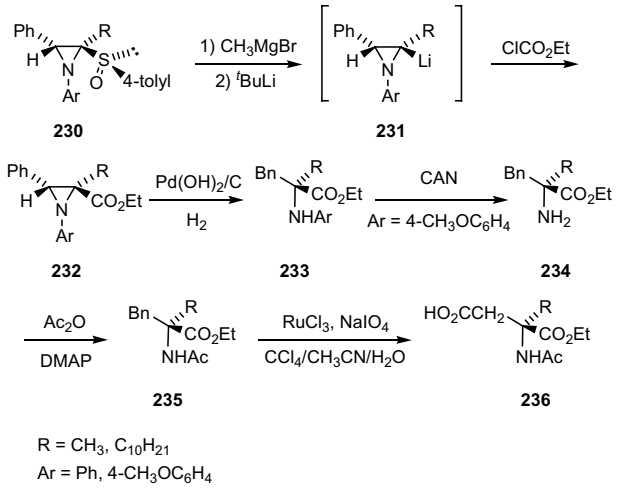

**Scheme 61.**




**Scheme 60.**

The development of efficient routes to chiral 2-aziridines has contributed to their widespread use in the synthesis of organic compounds in enantiomerically pure form.[130]

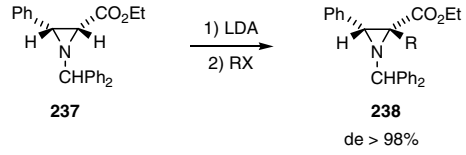
Aziridinyl anions, generated by treatment of sulfinylaziridines with organometallic reagents, are used in organic synthesis. These anions react with iodoalkanes in the presence of copper(I) iodide in cross-coupling reactions and are capable of adding electrophiles. The latter behaviour has allowed the synthesis of α,α-dialkyl amino acids. Chiral sulfinylaziridine **230**, on treatment with methylmagnesium bromide and subsequent metal exchange with *tert*-butyllithium, gave an aziridinyllithium intermediate that reacted with ethyl chloroformate to give the corresponding ethoxycarbonylated aziridine as a single diastereoisomer.[131,132] This compound was used in the synthesis of enantiomerically pure α-alkylphenylalanine and α-alkylaspartic acid derivatives **235** and **236** (Scheme 62).




**230** **231** **232** **233** **234** **235** **236**

**Scheme 62.**

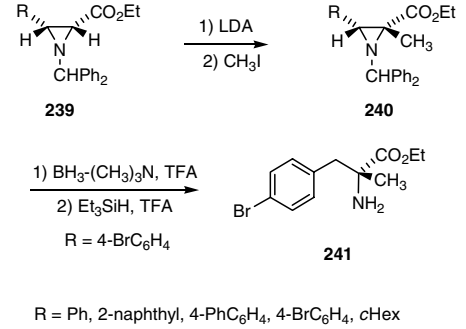
Alkylation of chiral aziridine-2-carboxylates **237** with different electrophiles could be performed by using an excess of LDA as the base.[133] In all cases, the attack of the electrophile occurred with retention of configuration at $C_2$ (Scheme 63). When aldehydes were used as electrophiles, selectivity was not observed in the formation of the alcohol stereogenic centre.




**237** **238**

**Scheme 63.**

The methylation reaction has been extended to other chiral aziridine-2-carboxylates with different substituents at $C_3$. From these compounds, α-methyl amino acid derivative **241**, an intermediate in the synthesis of BIRT-377, was obtained by reductive ring opening (Scheme 64).

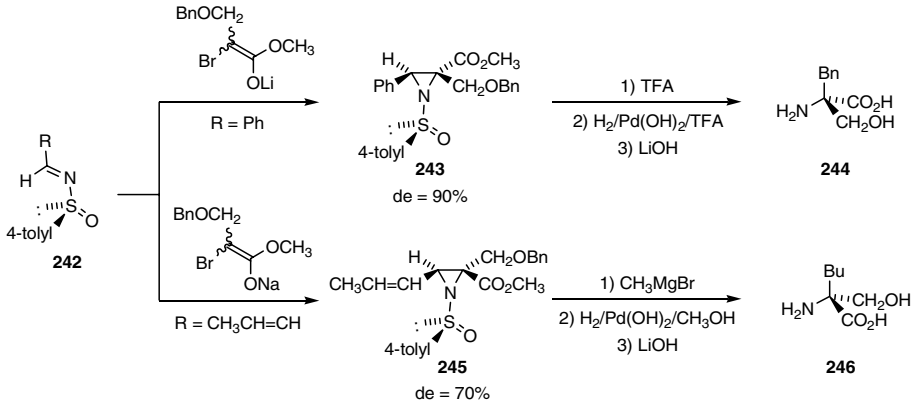



**239** **240** **241**

**Scheme 64.**

When chiral 2-substituted aziridine-2-carboxylates are used as synthetic intermediates, the attack of the nucleophiles at $C_3$ gives α,α-dialkyl amino acid derivatives. In this way α-alkylserines have been prepared by regioselective hydrogenolysis of enantiomerically pure 2-benzyloxymethylaziridine-2-carboxylates, obtained by aza-Darzens synthesis.[134] Aziridines of either *E*- or *Z*-configuration were obtained as the major products, depending on the nature of the substituents in sulfinimine **242** and on the reaction conditions (Scheme 65).

Benzaldehyde derived sulfinimine **242** (R = Ph) reacted with the lithium enolate generated from methyl 3-benzyloxy-2-bromopropanoate to afford aziridine **243**, with an



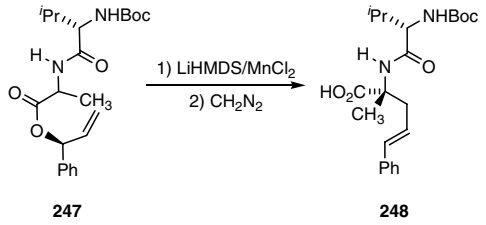

**242** **243** **244** **245** **246**

**Scheme 65.**

*E*-configuration, in excess. In contrast, the reaction of crotonaldehyde derived sulfinimine **242** (R = $CH_3CH{=}CH$) with the sodium enolate generated from methyl 3-benzyloxy-2-bromopropanoate afforded aziridine **245** (*Z*-configuration) as the major product. These compounds were used to prepare (*S*)-α-benzylserine and (*R*)-α-*n*-butylserine by removal of the *N*-sulfinyl group under the appropriate reaction conditions and subsequent hydrogenolysis (Scheme 65). The reaction conditions require the use of a large excess of methylmagnesium bromide in the case of compound **244** to avoid the formation of any side products.

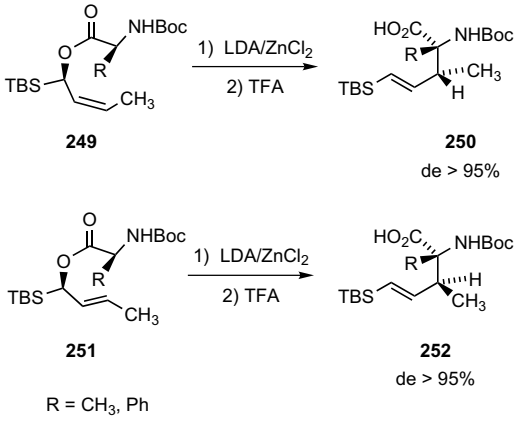
## 8. Sigmatropic rearrangements

A Claisen rearrangement of chelated enolates generated from allylic esters of N-protected amino acids gives α-allylamino acid derivatives.[135] This reaction has been used to perform modifications at the CO terminal residue of dipeptides and allows the direct introduction of α-alkylamino acids into the dipeptide. When esters derived from chiral allylic alcohols were used as the starting materials, the rearrangement took place asymmetrically and the corresponding α-alkylamino acid residue was generated with total stereoselectivity (Scheme 66).[136,137]




**Scheme 66.**

This protocol has also been applied to the synthesis of optically active vinylsilane-containing amino acids starting from 1-acyloxy-2-butenylsilanes.[138] Depending on the geometry of the double bond of the starting compound, vinylsilanes containing α,α-dialkyl amino acids of *syn*- or *anti*-configuration were obtained as single diastereoisomers (Scheme 67). The absolute configuration of the final amino




**Scheme 67.**

acid was independent of the absolute configuration of the starting amino acid, meaning that a racemic amino acid can be used as the acyloxy group.

A convenient elaboration of the vinylsilane moiety led to the synthesis of 2,3-dimethylaspartic acid of (2*S*,3*S*)- and (2*S*,3*R*)-configurations (Fig. 7).[139]

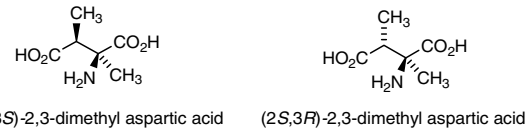
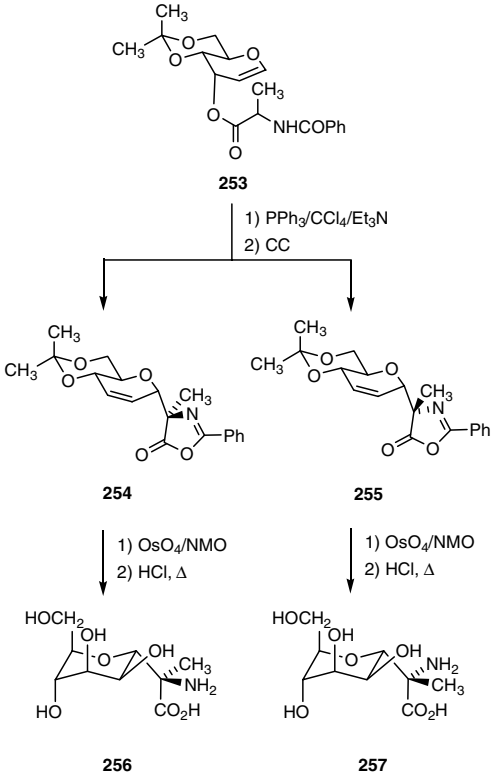


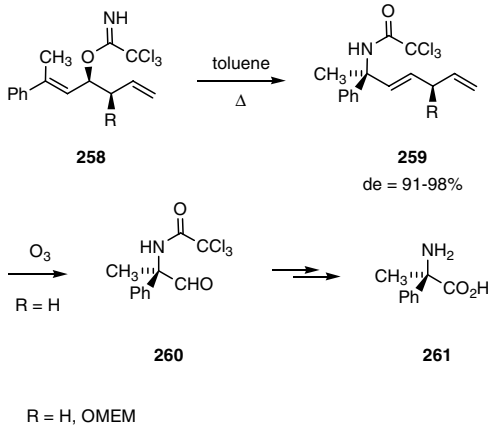

**Figure 7.**

Esterification of alanine with acetonide-protected D-ribo-hex-1-enitol provided a chiral allyl ester that rearranged to a mixture of diastereomeric oxazolones upon treatment with triphenylphosphine, carbon tetrachloride and triethylamine.[140] The diastereoselectivity was moderate and isolated oxazolones were transformed into α-D-*C*-mannosylalanine of (2*R*)- and (2*S*)-configuration by dihydroxylation and hydrolysis, as shown in Scheme 68.




**Scheme 68.**

On heating trichloroacetimidates **258**, derived from chiral homoallylic allylic alcohols, amides **259** were obtained through an Overman rearrangement, which took place with complete retention of configuration.[141] Subsequent ozonolysis of the alkene moiety, oxidation of the resulting aldehyde and hydrolysis provided the corresponding α,α-dialkyl amino acid (Scheme 69).



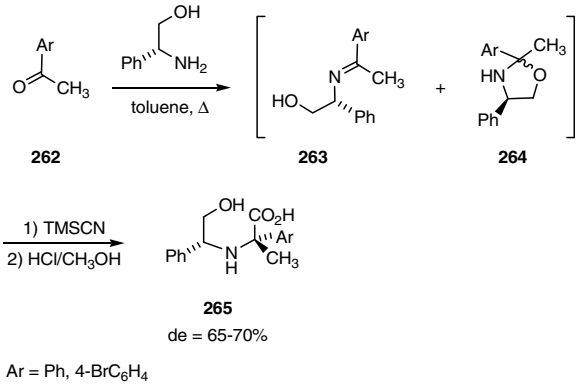

**Scheme 69.**

## 9. Addition of nucleophiles to the C=N bond

The addition of nucleophiles to the C=N bond of chiral compounds is a useful tool for the creation of a C–C bond in an asymmetric fashion. This methodology allows the introduction of the carboxylic acid moiety by the Strecker synthesis or the side chain of the amino acid by the addition of organometallic reagents. In this part of the review we have grouped together the different approaches developed in this area on the basis of the type of compounds in which the C=N bond is present.

### 9.1. Addition of nucleophiles to imines

Cyanide addition to the C=N bond of ketimines bearing a chiral N-substituent that acts as a removable chiral auxiliary constitutes an appealing methodology for obtaining α,α-dialkyl amino acids. To this end, (*R*)-phenylglycinol has been used as a chiral auxiliary and the imine/1,3-oxazolidine mixture obtained by heating an α-arylketone and this amino alcohol was treated with trimethylsilyl cyanide to afford, after hydrolysis, the corresponding amino acid derivative through a Strecker-type reaction.[142] Amino esters were obtained with moderate diastereoselectivity, with the (*R*,*S*)-diastereoisomer obtained in excess (Scheme 70).




**Scheme 70.**

The major compound was isolated to provide key intermediates in the synthesis of metabotropic glutamate receptor antagonists (*S*)-2-methyl-2-(4-carboxyphenyl)glycine [(*S*)-αM4CPG] and (*S*)-2-methyl-2-(4-phosphonophenyl)glycine [(*S*)-MPPG] (Fig. 8).

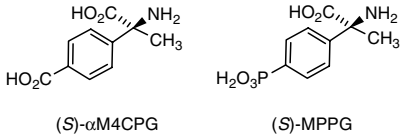
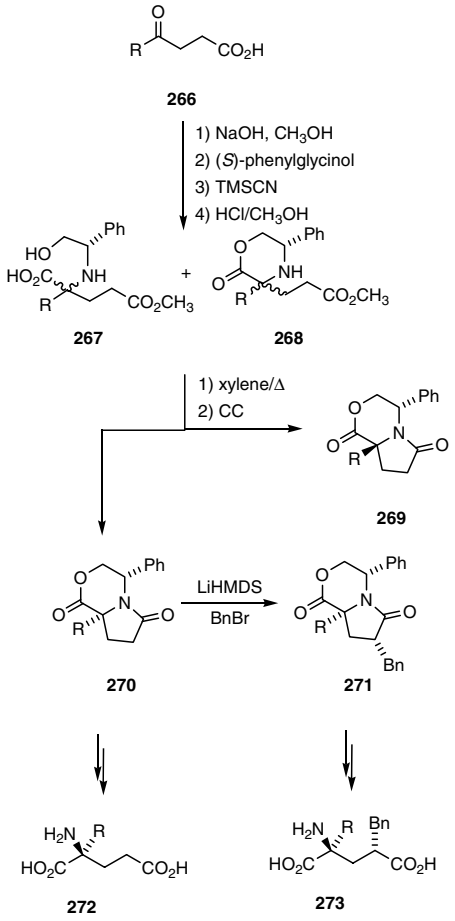



**Figure 8.**

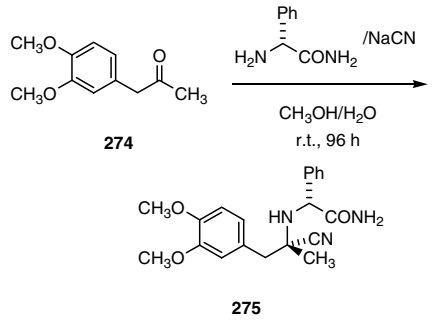
The same reaction starting from γ-keto acid sodium salts led to a mixture of amino esters, which were converted into two separable diastereomeric bicyclic compounds **269** and **270**.[143,144] The diastereoselectivity was dependent upon the size of the R substituent and decreased as the size of the substituent increased. The isolated major compound was benzylated to give α,γ-disubstituted glutamic acid precursors, although the diastereoselectivity in the alkylation was not very high. Final hydrolysis of the bicyclic compound led to α-substituted and α,γ-disubstituted glutamic acids (Scheme 71).




**Scheme 71.**

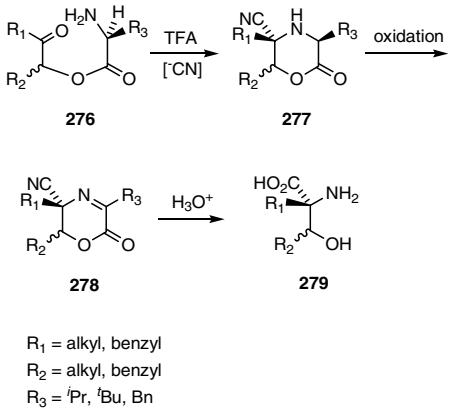
The Strecker synthesis has successfully been used in the synthesis of chiral α-monosubstituted α-amino acids from

imines derived from aldehydes. However, the application of this approach to the synthesis of α,α-dialkyl amino acids starting from imines derived from ketones has usually been limited by the low reactivity of the substrate and the low diastereoselectivity of the products. One way to overcome this drawback involves crystallisation-induced asymmetric transformations in which one diastereoisomer selectively precipitates and the other epimerises in solution so that the equilibrium is shifted to the formation of the less soluble diastereoisomer. This approach has been applied to the synthesis of α-methyl dopa by Strecker reaction of the imine derived from 3,4-dimethoxyacetophenone and (*R*)-phenylglycine amide.[145] On stirring the reaction mixture for 96 h, nearly diastereomerically pure amino nitrile of (2*S*)-configuration was isolated as a solid in 76% yield (Scheme 72).




**Scheme 72.**

The use of chiral cyclic ketimines, generated in situ from α-acyloxyketones with an amino acid as the acyloxy group, as intermediates in Strecker reactions usually gives the corresponding α-amino nitriles in a highly stereoselective manner. This approach was developed by Ohfune[16,146] and has been applied to the asymmetric synthesis of biologically active α,α-disubstituted amino acids (Scheme 73).




**Scheme 73.**

The low yields obtained in the oxidation of sterically congested α-amino nitriles to α-imino nitriles using *tert*-butyl hypochlorite/triethylamine was a serious drawback that could be overcome by using ozone as the reagent. This modification converted this synthetic procedure into a highly useful tool for the synthesis of β-hydroxy α,α-disubstituted amino acids (Fig. 9).[147–149]

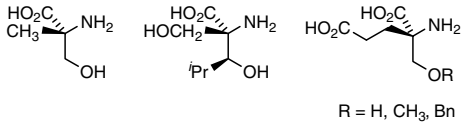
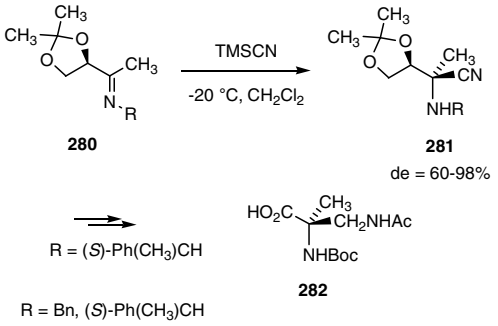



**Figure 9.**

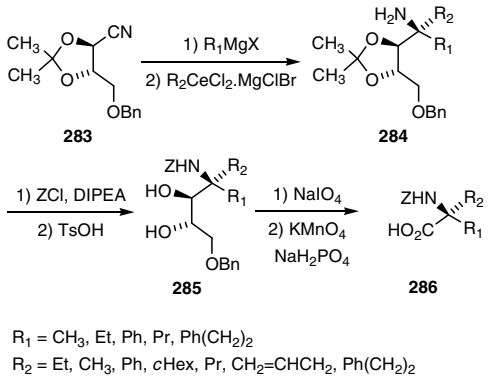
Ketimines derived from (*R*)-2,2-dimethyl-1,3-dioxolan-4-yl methyl ketone add cyanide to afford α,α-dialkyl amino acid precursors.[150] The stereoselectivity of the addition depended on the solvent and reaction temperature. In kinetically controlled processes, amino nitriles with a *syn*-configuration were obtained preferentially, whereas in thermodynamically controlled processes *anti*-amino nitriles were the major products. Double stereodifferentiation under kinetic control led to *syn*-amino nitrile **281** [R = (*S*)-Ph(CH$_3$)CH] with complete diastereoselectivity. This amino nitrile subsequently gave (*R*)-(2-aminomethyl)alanine derivative **282** (Scheme 74).




**Scheme 74.**

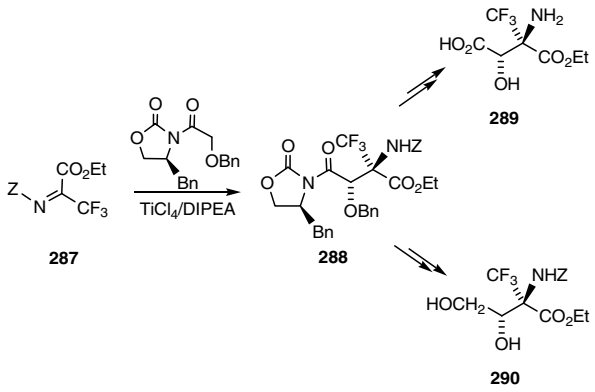
Alternatively, it is possible to introduce the side chain of the amino acid by addition of an organometallic reagent to an imine containing a masked carboxylic acid moiety. In the approach developed by Charette and Mellon[151] for the asymmetric synthesis of α,α-dialkyl amino acids, the imine is generated by addition of a Grignard reagent to a chiral cyanohydrin. The addition of a second organometallic reagent led to the corresponding amines with moderate to good yields and excellent diastereoselectivity. Organomagnesium and organolithium reagents were unreactive as second nucleophiles and organocerium reagents had to be used in this reaction. The carboxy group was generated from the 5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane moiety and the use of the appropriate combination of organometallic reagents gave precursors for the synthesis of amino acids of (*R*)- and (*S*)-configuration (Scheme 75).

A complementary approach involved the addition of chiral nucleophiles to ketimines. In this context chiral chlorotitanium enolates derived from (*S*)-(α-benzyloxy)acetyl 2-oxazolidinone reacted with the *N*-benzyloxycarbonylimine of ethyl trifluoropyruvate to afford a mixture of two out of



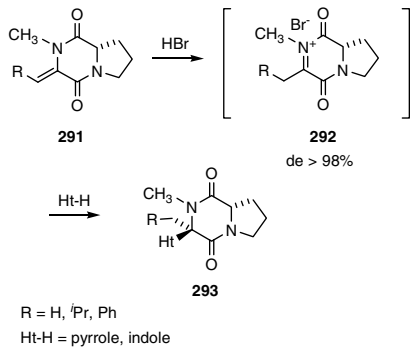

**Scheme 75.**

the four possible Mannich adducts, which had an *anti*-configuration.[152] Under optimal conditions the diastereoselectivity was very high and adduct **288**, which proved to be a versatile intermediate for the synthesis of α-trifluoromethyl-β-hydroxyamino acids, was obtained as the major product in a 91/9 ratio (Scheme 76).




**Scheme 76.**

Protonation of 3-alkylidene or 3-benzylidene diketopiperazines led to the formation of cyclic *N*-acyliminium salts that were able to add nucleophiles to afford α,α-dialkyl amino acid precursors.[153] In general, diketopiperazines derived from proline as the chiral auxiliary add nucleophiles with high stereoselectivity when the reactions are carried out in dioxane at room temperature (Scheme 77).

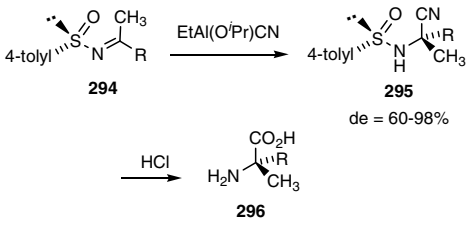



**Scheme 77.**

## 9.2. Addition of nucleophiles to sulfinimines

Chiral sulfinimines are very useful substrates in diastereoselective synthesis as they display excellent reactivity and usually lead to the corresponding products in a highly diastereoselective manner. As a result, they have been used as intermediates in the asymmetric synthesis of chiral nitrogen-containing compounds.[154–156]

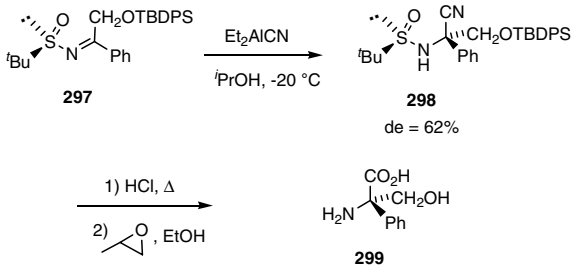
Chiral ($S_S$)-*p*-toluenesulfinyl ketimines have been used as substrates in the asymmetric Strecker syntheses with ethylaluminium cyanoisopropoxide as the cyanation reagent.[157] When the difference in size between $R_1$ and $R_2$ was sufficiently large the starting sulfinimine was present as a single *E*-isomer and cyanide addition took place with very high diastereoselectivity (Scheme 78).




**Scheme 78.**

When the starting sulfinimine existed as a mixture of *E*:*Z* isomers the diastereoselectivity was low because cyanide addition to each isomer led to the amino nitrile of opposite configuration at $C_2$. This behaviour has also been observed on using chiral *tert*-butanesulfinyl ketimines as substrates. Final acidic hydrolysis of the isolated major diastereoisomers was performed easily in most cases to afford the corresponding α,α-dialkyl amino acids.

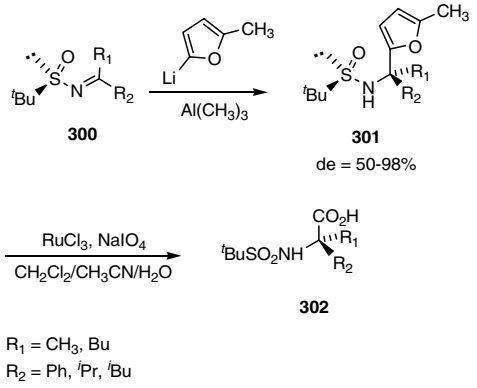
The chiral ($S_R$)-*tert*-butanesulfinyl ketimine **297** (derived from 2-hydroxyacetophenone) is present exclusively as the *Z*-isomer. This compound added cyanide at −20 °C with moderate diastereoselectivity in favour of the amino nitrile of (*R*,*R*)-configuration.[158] The major product was isolated and converted into (*S*)-α-phenylserine, as shown in Scheme 79.




**Scheme 79.**

Ellman et al.[159] obtained *tert*-butanesulfonyl-protected α,α-dialkyl amino acids by the addition of 5-methyl-2-

furyllithium, an alternative equivalent of the carboxylic acid moiety, to *tert*-butanesulfinyl ketimines followed by oxidation (Scheme 80).

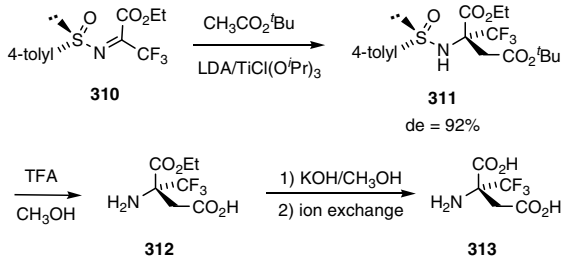



**Scheme 80.**

The diastereoselectivity depended on the difference in the sizes of the imine substituents, with imines bearing highly differentiated substituents giving very high diastereoselectivity but imines with substituents of similar size providing only moderate diastereoselectivity.

($S_S$)-*p*-Toluenesulfinimines derived from trifluoropyruvates smoothly reacted with Grignard reagents to provide the corresponding *N*-sulfinyl amino esters with moderate diastereoselectivity.[160,161] Compounds with an opposite configuration were obtained preferentially depending on the organomagnesium reagent. Whereas allyl and benzylmagnesium halides led to compounds with a (2*R*)-configuration as the major products, alkylmagnesium halides gave compounds of (2*S*)-configuration in excess. Diastereoselectivity increased on increasing the steric bulk of the alkyl chain of the organomagnesium reagent. The isolated major compounds subsequently gave enantiomerically pure α-trifluoromethyl amino acids (Scheme 81).

Reaction of a related sulfinimine with titanium enolates allowed the synthesis of enantiomerically pure α-trifluoromethylaspartic acid with good overall yield (Scheme 82).[162] Sodium, potassium or lithium enolates were less effective in terms of yield and diastereoselectivity.



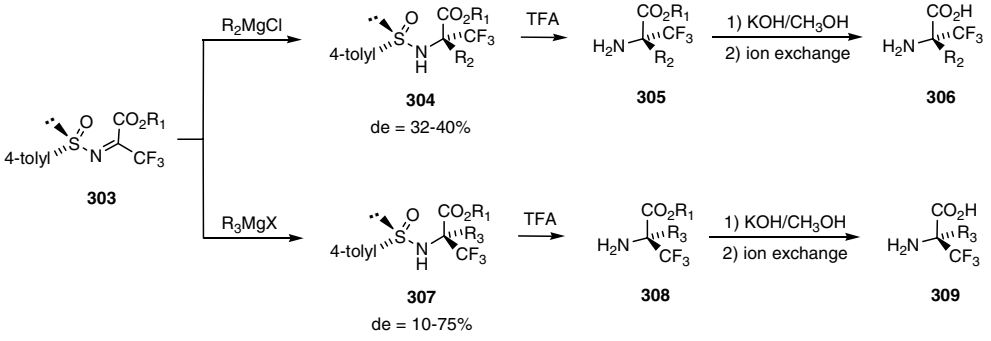

**Scheme 82.**

### 9.3. Addition of nucleophiles to oxime ethers

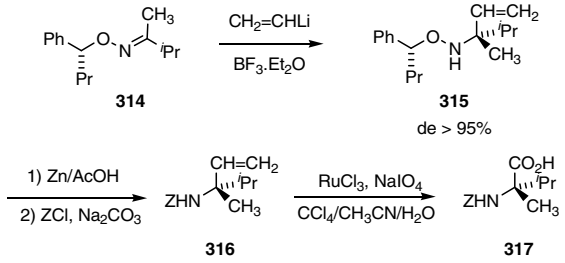
Moody et al. have proposed two alternative routes for the synthesis of α-amino acids starting from oxime ethers. One approach is based on the addition of carboxyl synthons to oxime ethers[163] and the other is based on the addition of organometallic reagents to oxime ethers that incorporate a carboxylic acid precursor.[164] The use of chiral ketoxime ethers derived from (*R*)-*O*-1-phenylbutylhydroxylamine (ROPHy) as starting compounds has extended these methodologies to the synthesis of α,α-dialkyl amino acids.

Among the carboxyl synthons tested in the first approach, cyanide and acetylide did not react with oxime ethers and 2-furyllithium added with low yields. Vinyllithium gave the most satisfactory results and hydroxylamine **315** was obtained with moderate yield and excellent diastereoselectivity. Cleavage of the N–O bond, N-protection and conversion of the vinyl moiety into a carboxyl group afforded *N*-benzyloxycarbonyl α-methylvaline (Scheme 83).[163]

In the second approach, the oxime ether derived from benzylidene acetone and (*R*)-*O*-(1-phenylbutyl)hydroxylamine (ROPHy) was obtained as a separable mixture of *Z*- and *E*-isomers. The addition of butyllithium to the isolated

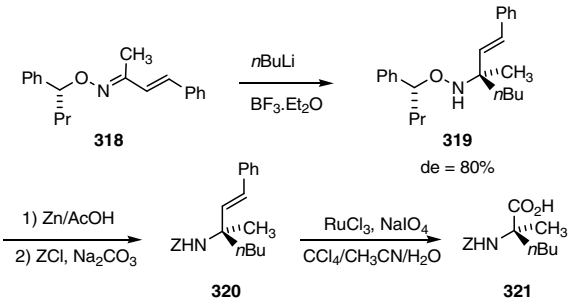



**Scheme 81.**




Scheme 83.

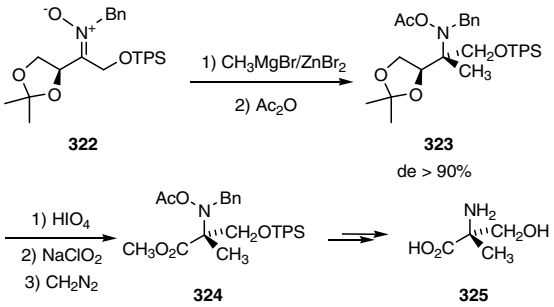
oxime ethers gave the corresponding hydroxylamine, which was converted into 2-benzyloxycarbonylamino-2-methylhexanoic acid, with the benzylidene moiety acting as the carboxylic acid precursor.[164] Addition to oxime ethers of *Z*- and *E*-configuration led to hydroxylamines of opposite configuration at the new stereogenic centre as the major products with good diastereoselectivity. This process is shown in Scheme 84 for the oxime ether of *E*-configuration.




Scheme 84.

### 9.4. Addition of nucleophiles to nitrones

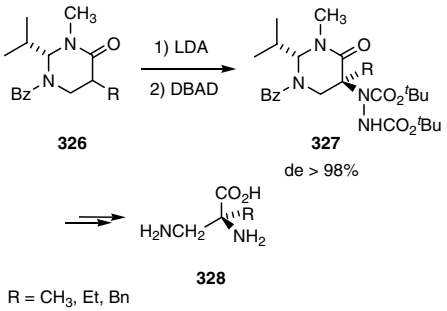
Chiral keto nitrones containing a masked carboxylic acid have also been used as precursors in the asymmetric synthesis of α,α-dialkyl amino acids. For example, nitrone **322**—prepared from L-erythrulose—reacted with several organomagnesium reagents to give mixtures of diastereomeric hydroxylamines. The diastereoselectivity and the stereochemical course of the reaction were highly dependent on the reaction conditions and the organometallic reagent.[165] In the absence of Lewis acids or in the presence of zinc bromide, compounds with an (*S*)-configuration at the new stereogenic centre were obtained in good yield and with good diastereoselectivity, which was normally higher in the presence of the Lewis acid. The addition of organomagnesium reagents in the presence of diethylaluminium chloride took place with lower diastereoselectivity and in some cases a reversal in the stereochemical course of the addition was observed. When allylmagnesium bromide was the reagent, compounds with (*R*)- and (*S*)-configuration at the new stereogenic centre were obtained in the absence of Lewis acid or in the presence of zinc bromide, respectively. The application of this synthetic methodology to the synthesis of (*R*)-α-methylserine is shown in Scheme 85.




Scheme 85.

## 10. Diastereoselective α-amination of carbonyl compounds

The amino moiety of the α,α-dialkyl amino acid has been introduced by electrophilic amination. Starting from chiral tetrahydropyrimidinones, amination was performed by treatment of the corresponding lithium enolates with di-(*tert*-butyl)azodicarboxylate (Scheme 86).[166]




Scheme 86.

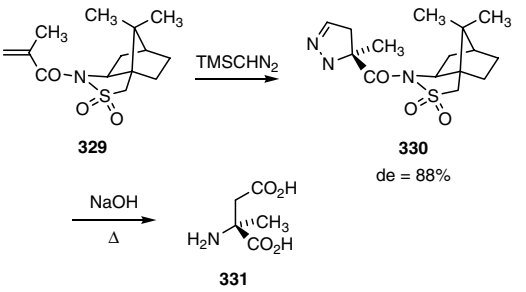
The nitrogen substituent entered opposite to the isopropyl group to give the corresponding adduct as a single diastereoisomer, from which enantiomerically pure α,α-dialkyl amino acids were obtained. Both (*S*)- and (*R*)-α,α-dialkyl amino acids were obtained from tetrahydropyrimidinones of (*R*)- and (*S*)-configuration, respectively.

## 11. Diastereoselective 1,3-dipolar cycloaddition

A new asymmetric synthesis of (*S*)-α-methylaspartic acid has been developed and this takes advantage of the highly diastereoselective 1,3-dipolar cycloaddition of trimethylsilyldiazomethane and the *N*-methacrylate derivative of (1*R*)-10-camforsultam. Diastereomerically pure pyrazoline **330** was isolated on a multigram scale and converted into the desired amino acid by alkaline fragmentation of the heterocyclic ring (Scheme 87).[167]

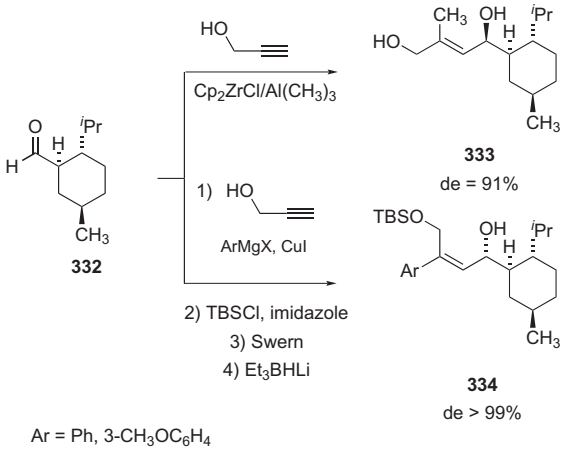
## 12. Diastereoselective $S_N2'$ substitution

The $S_N2'$ displacement of an allylic leaving group in chiral pivalate esters is a stereospecific reaction that has been used in the creation of quaternary stereogenic centres. A stereodivergent approach to α,α-dialkyl amino acids has been developed starting from chiral allylic esters with the appropriate substituents.[168,169]




**Scheme 87.**

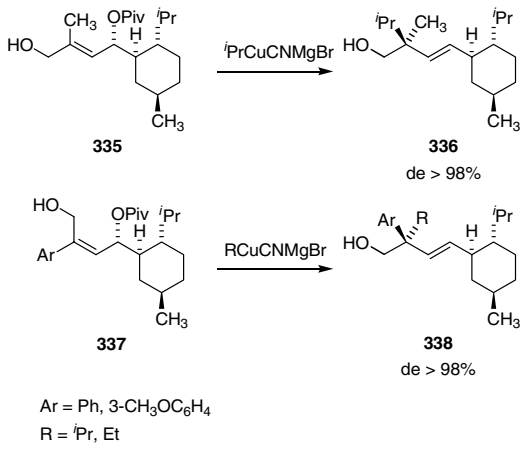
The source of chirality in this approach was *p*-menthane-3-carboxaldehyde, which reacted with propargyl alcohol and organometallic reagents to afford the corresponding diols. In cases where the diastereoselectivity in this reaction was not very good, oxidation of the secondary alcohol and reduction of the resulting ketone gave the desired diol with complete stereoselectivity (Scheme 88).




**Scheme 88.**

$S_N2'$ displacement in pivalate esters **335** and **337** with monoalkylcyanocuprates occurred with total stereocontrol (Scheme 89).

Oxidation of the primary alcohol, Curtius rearrangement on the resulting acid and ozonolysis of the alkene moiety led to the corresponding α,α-dialkyl amino acid in enantiomerically pure form. The enantiomer of opposite configuration can be obtained from compound **336** by protection of the primary alcohol, ozonolysis of the alkene moiety, Curtius rearrangement of the resulting acid and final oxidation of the free the primary alcohol. Both reaction sequences are shown in Scheme 90 for α-methylvaline.

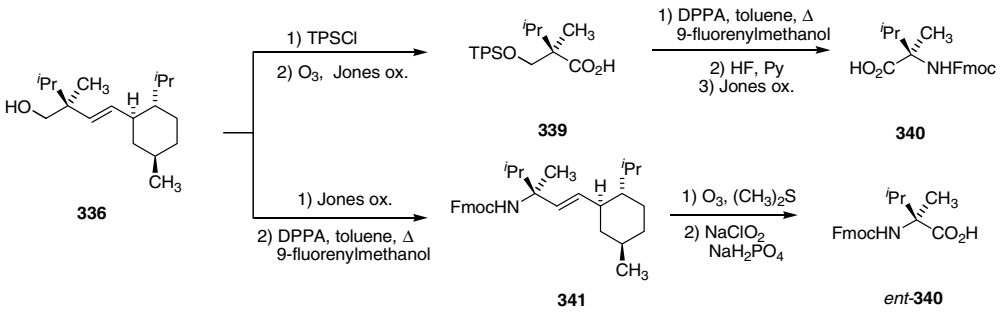



**Scheme 89.**

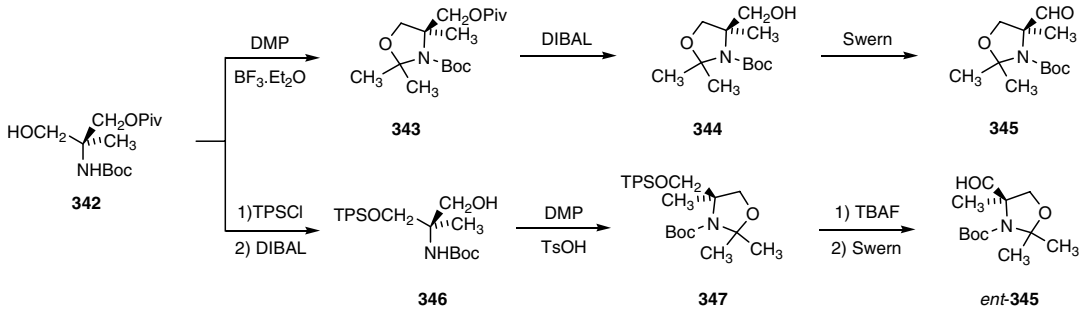
## 13. Chiron approach

(*R*)- and (*S*)-*N*-Boc-*N*,*O*-isopropylidene serinal, known as Garner's aldehyde, is one of the most versatile chiral synthons used in the preparation of chiral compounds. α-Methyl homologues can be regarded as ideal chirons for the synthesis of α,α-dialkyl amino acids. The oxazolidine ring can act as a masked α-methyl amino acid moiety and convenient manipulation of the formyl group at $C_4$ can generate the side chain of the target amino acid. The synthetic utility of *N*-Boc-*N*,*O*-isopropylidene-α-methylserinal was investigated by carrying out stereodivergent syntheses of both enantiomers from selectively protected diol **342**, obtained in turn from (*R*)-methylglycidol; this route has been performed on a large scale (Scheme 91).[170,171]

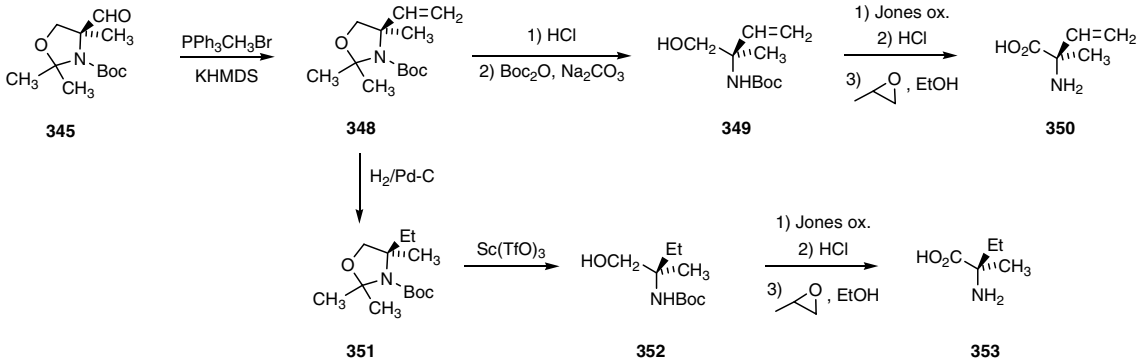
Convenient manipulation of the formyl group at $C_4$ in compound **345** led to the efficient syntheses of several α-methyl amino acids of (*R*)- or (*S*)-configuration depending on the configuration of the starting compound. Cleavage of




**Scheme 90.**



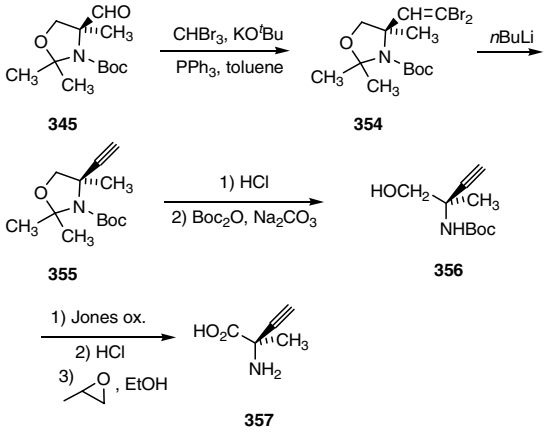

**Scheme 91.**




**Scheme 92.**

the acetonide moiety, N-protection and Jones oxidation of the primary alcohol was the common strategy used to generate the amino acid moiety at the end of the synthesis. Wittig olefination with methyltriphenylphosphonium bromide was the synthetic tool used to introduce the side chain of vinyl glycine[172] and isovaline[170] (Scheme 92).

The Corey–Fuchs strategy for the conversion of a formyl group to an ethynyl group was used to obtain the ethynylglycine precursor[172] (Scheme 93).

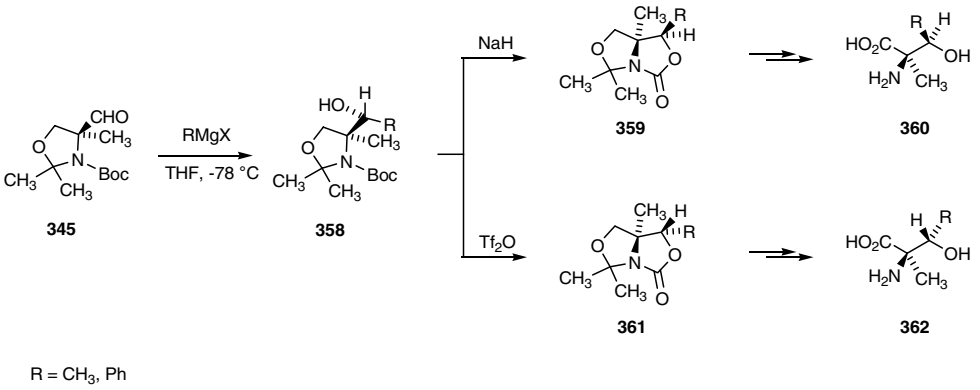



**Scheme 93.**

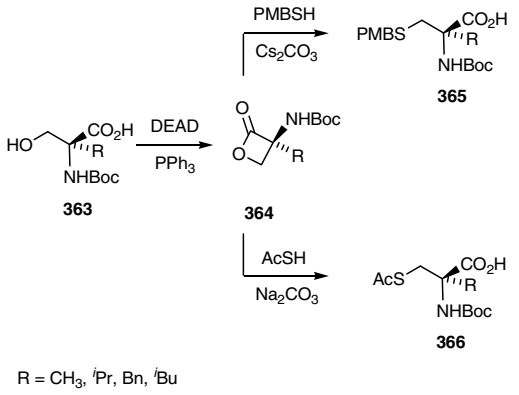
The addition of nucleophiles to the formyl group led to preferential formation of *anti*-adducts and the stereoselectivity in the creation of the new stereocentre depended on the reaction conditions. In the absence of Lewis acids at low temperature and using THF as the solvent the reaction gave excellent levels of stereocontrol in the addition of phenyl[173] and methylmagnesium bromide[174] to **345**. Intramolecular cyclisation of adduct **358** with sodium hydride gave a cyclic urethane with retention of configuration. Application of the standard protocol for the generation of the amino acid moiety provided (2*R*,3*R*)-α-methyl-β-hydroxyamino acids whereas the formation of cyclic urethane by treatment with triflic anhydride took place with inversion of configuration, which led to the formation of precursors for α-methyl-β-hydroxyamino acids of (2*R*,3*S*)-configuration (Scheme 94).

The appropriate choice of the starting compound and reaction conditions provided access to the four diastereoisomers of α-methyl-β-phenylserine and α-methylthreonine.

*N*-Boc-α-alkylserines were the starting materials used by Olma in the synthesis of α-alkylcysteine derivatives.[175] Compound **363** were converted into their corresponding α-alkyl-β-lactones under Mitsunobu reaction conditions. Whereas diisopropyl azodicarboxylate was ineffective for this reaction, diethyl azodicarboxylate provided the desired β-lactones in excellent yield. Ring opening of lactones **364** with sulfur nucleophiles led to the corresponding S-protected *N*-Boc-α-alkylcysteines (Scheme 95).

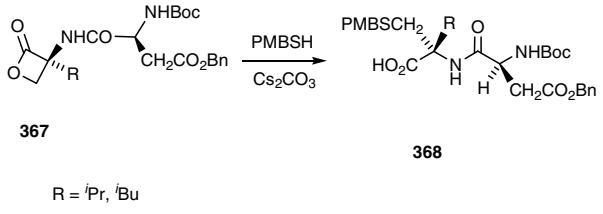



**Scheme 94.**




**Scheme 95.**

β-Lactones **364** have been converted into their corresponding *p*-toluenesulfonic acid salts and coupled with *N*-Boc-aspartic acid benzyl ester to afford **367**—an interesting intermediate in the synthesis of peptides containing α,α-dialkylamino acids through nucleophilic ring opening[176] (Scheme 96).




**Scheme 96.**

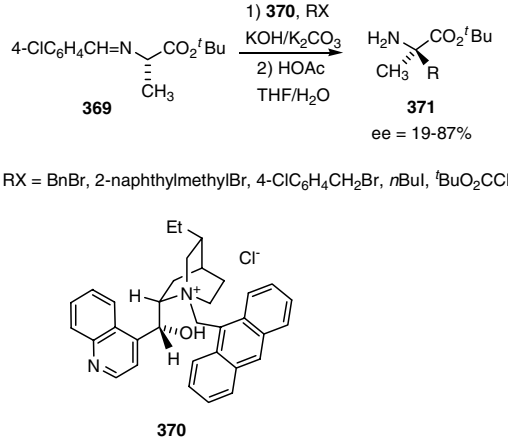
## 14. Enantioselective syntheses

Amongst the different approaches for the asymmetric synthesis of chiral compounds, that mediated by a chiral catalyst have enormous synthetic utility due to the possibility of producing large quantities of enantioenriched or enantiomerically pure compounds through mediation of a relatively small quantity of chiral catalyst. Several different synthetic routes have been developed for the asymmetric synthesis of α-amino acids using chiral catalysts to induce the preferential formation of one of the two possible enantiomers.[177] Unfortunately, most of these methodologies cannot be extended to the creation of a quaternary stereogenic centre. Nevertheless, in recent years some progress has been made in this field and new catalysts that allow the enantioselective synthesis of α,α-dialkylamino acids have been developed.

### 14.1. Alkylation under phase-transfer conditions

Suitable chiral catalysts to perform the enantioselective synthesis of optically active amino acids under phase-transfer conditions have been described.[178–180] This methodology has been extended to the asymmetric synthesis of α,α-dialkylamino acids.

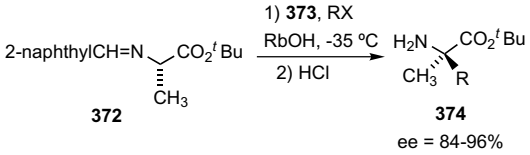
Ammonium salts derived from *cinchona* alkaloids are the most common catalysts used in phase-transfer catalysed reactions. Lygo et al.[181] have used *N*-anthracenylmethyl-substituted cinchonidine as a catalyst in the alkylation of aldimines derived from alanine esters (Scheme 97). Optimal results were obtained with these catalysts on using toluene as the organic phase and finely ground solid base, freshly prepared by fusing potassium hydroxide and anhydrous potassium carbonate. As far as the substrate is concerned, the imine obtained from alanine *tert*-butyl ester and 4-chlorobenzaldehyde pro-




**Scheme 97.**

vided the best yield and enantioselectivity in the benzylation reaction. When using other arylmethyl halides, the enantioselectivities were moderate while with alkyl halides the yields were very poor and enantioselectivities very low.

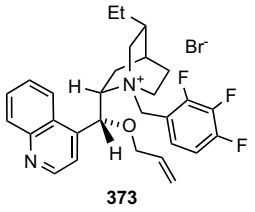
Hydrocinchonidinium bromide derivative **373** behaves as an excellent phase-transfer catalyst in the alkylation of imines derived from alanine *tert*-butyl ester and enantiomeric excesses of up to 96% were obtained depending on the substrate and the reaction conditions.[182] As far as the arylmethylene moiety of the imine is concerned, imines prepared from 2-naphthaldehyde gave the best results in the benzylation reaction using KOH as the base at 0 °C. The enantiomeric excess increased on lowering the reaction temperature, which required the use of a different base. Excellent enantioselectivities were obtained with RbOH at −35 °C in the alkylation of compound **372** with different alkyl halides (Scheme 98).




**372** **374**

ee = 84-96%

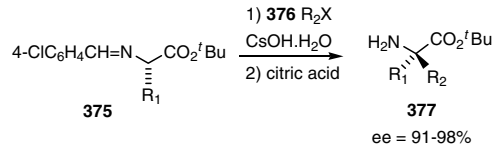
RX = 4-$BrC_6H_4CH_2Br$, BnBr, 4-$^tBuC_6H_4CH_2Br$, 4-$CF_3C_6H_4CH_2Br$, 3-$CH_3C_6H_4CH_2Br$, 2-$FC_6H_4CH_2Br$, 1-naphthylmethylCl, 2,6-$F_2C_6H_3CH_2Br$, 2,4-$Cl_2C_6H_3CH_2Br$, $CH_2$=$CHCH_2Br$, HC≡$CCH_2Br$




**373**

**Scheme 98.**

Maruoka et al.[183–185] designed a $C_2$-symmetric chiral quaternary ammonium salt that can be used in the enantioselective alkylation of amino acid Schiff bases (Scheme 99) as well as in the double alkylation of iminoglycinates,

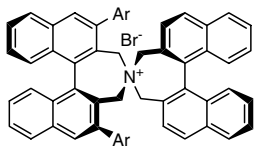



**375** **377**

ee = 91-98%

$R_1$ = $CH_3$, Bn, $^t$Bu

$R_2$ = BnBr, $CH_2$=$CHCH_2Br$, EtI, $^tBuO_2CCH_2Br$, 1-Boc-3-indolylmethylBr

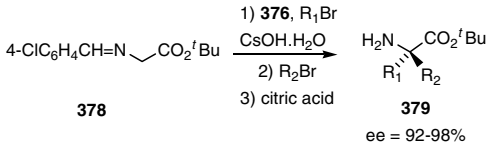



Ar = 3,4,5-$F_3C_6H_2$

**376**

**Scheme 99.**

which allows the synthesis of α,α-dialkylamino acids (Scheme 100).




**378** **379**

ee = 92-98%

$R_1$ = $CH_2$=$CHCH_2$, Bn

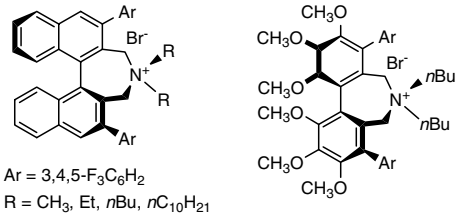
$R_2$ = Bn, $CH_2$=$C(CH_3)CH_2$, HC≡$CCH_2$, $CH_2$=$CHCH_2$

**Scheme 100.**

Double alkylation of glycine allows the synthesis of α,α-dialkylamino acids that contain two side chains different to those of the natural amino acids, with the absolute configuration of the product dependent upon the order of addition of the halides.

Enantiomeric excesses were very high in both the alkylation of amino acids and double alkylation of glycine and yields, modest in some cases in aerobic conditions,[184] were greatly increased when air was rigorously excluded.[185]

The same authors have recently designed new catalysts of the same type by replacing one (Type A catalysts) or both (Type B catalysts) rigid binaphthyl moieties by more flexible alkyl or aryl groups in order to obtain less lipophilic systems[186,187] (Fig. 10). These newly designed catalysts are highly active in the asymmetric alkylation of Schiff base **369**.



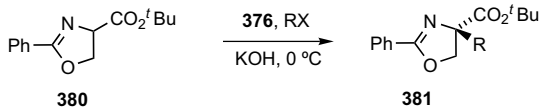

Ar = 3,4,5-$F_3C_6H_2$

R = $CH_3$, Et, *n*Bu, *n*$C_{10}H_{21}$

type A catalysts type B catalysts

**Figure 10.**

Enantioselective alkylation of 2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester under optimised phase-transfer catalysis conditions,[188] using chiral ammonium salt **376** as the catalyst, provided α-alkylserine precursors with excellent enantioselectivities (Scheme 101).



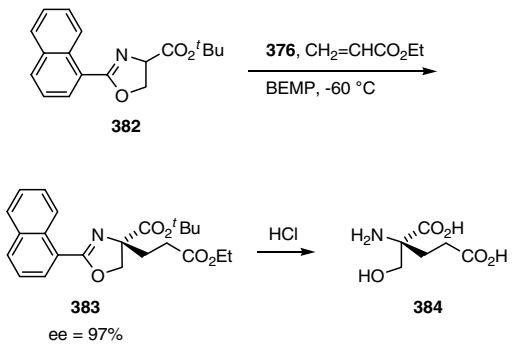

**380** **381**

ee = 93-99%

RX = EtI, $CH_2$=$CHCH_2Br$, $CH_2$=$C(CH_3)CH_2Br$, HC≡$CCH_2Br$, BnBr, 4-$NCC_6H_4CH_2Br$, 4-$CF_3C_6H_4CH_2Br$, 4-$^tBuC_6H_4CH_2Br$, 4-$FC_6H_4CH_2Br$, 4-$CH_3OC_6H_4CH_2Br$, 2-naphthylmethylBr

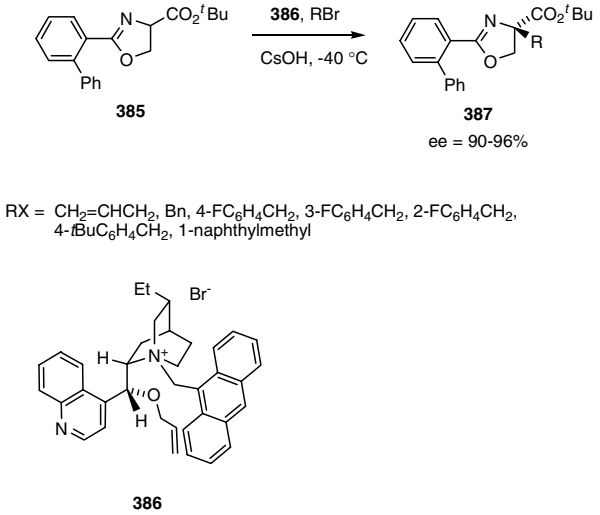
**Scheme 101.**

Phase-transfer catalysed Michael addition using the same substrate and catalyst with ethyl acrylate as the electrophile was not enantioselective. However, when 2-(1-naphthyl)-2-oxazoline-4-carboxylic acid *tert*-butyl ester **382** was used as the substrate the corresponding alkyl derivative was obtained with an enantiomeric excess of 97%.[189] Hydrolysis of this compound led to (*S*)-α-(hydroxymethyl)glutamic acid (Scheme 102).



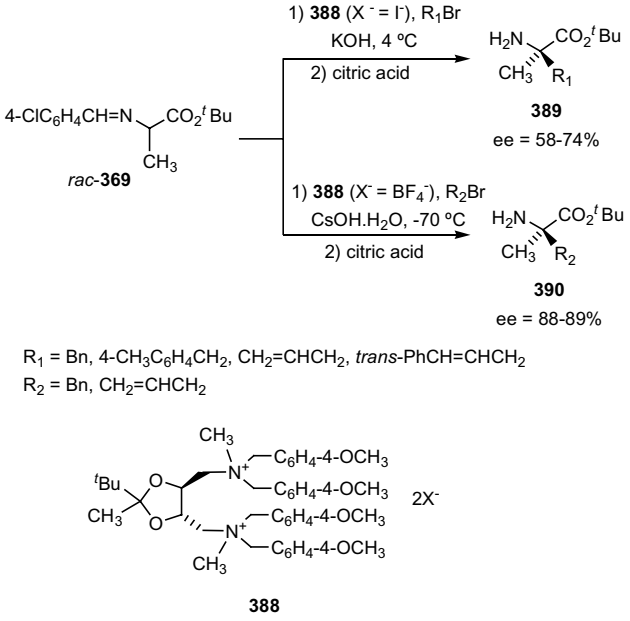

**Scheme 102.**

Replacement of the 2-phenyl group in oxazoline **380** by an *ortho*-biphenyl group allowed the phase-transfer catalysed alkylation using *cinchona* derived catalyst **386** to be performed in a highly enantioselective manner when cesium hydroxide was used as the base working at low temperature (−40 °C)[190] (Scheme 103).




**Scheme 103.**

TaDiAs, which are new tartrate-derived diammonium salts, have recently been developed for use in catalytic asymmetric phase-transfer alkylation.[191] A variety of catalysts have been obtained by changing the arylmethyl moiety on the nitrogen or the counter ion. These compounds have been tested in phase-transfer catalysed reactions. Alkylation of imine **369** with different alkyl halides in the presence of iodide chiral ammonium salt **388** ($X^- = I^-$) at 4 °C gave the corresponding α,α-dialkylamino acid derivatives with moderate enantioselectivities. Tetrafluoroborate chiral ammonium salt **388** ($X^- = BF_4^-$) dramatically accelerated the reaction and promoted alkylation at low temperature, a process that provided α,α-dialkylamino acid derivatives with improved yields and enantioselectivities (Scheme 104).




**Scheme 104.**

Alkylated compound **390** ($R_2 = CH_2{=}CHCH_2$) has been used to obtain the L-Argol portion of aeruginosin 298-A analogues (Fig. 11).[191]

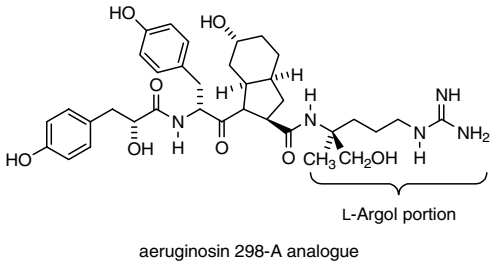
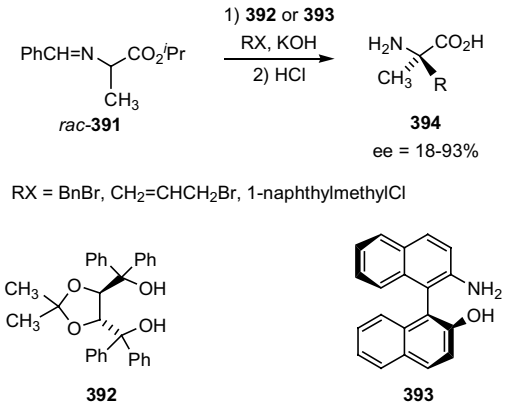



**Figure 11.**

In recent years, other types of chiral phase-transfer catalysts have been used to obtain α,α-dialkylamino acids enantioselectively. Chiral organic compounds capable of functioning as sodium cation chelating agents have proven to be useful as catalysts in enantioselective phase-transfer catalysis reactions. The resulting ion pair formed between the chiral ligand and the substrate is soluble in toluene and provides a rigid complex in the transition state. This phenomenon makes asymmetric induction possible.

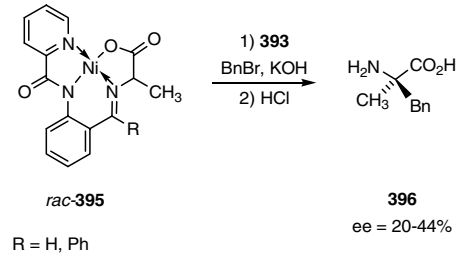
TADDOLs (chiral diols obtained from tartaric acid), BINOLs and NOBINs (chiral aminonaphthols) have been

tested as promoters in the benzylation of imines derived from alanine isopropyl ester and benzaldehyde. TADDOL **392** and NOBIN **393** were found to be the most efficient promoters in terms of activity and asymmetric induction.[192–194] The level of asymmetric induction was dependent upon the nature of the base and the best results were obtained with NaOH. Modification of the TADDOL or NOBIN did not improve the performance of the catalyst. The procedure has been extended to other reactive alkylating agents, as shown in Scheme 105.




**Scheme 105.**

NOBIN also promoted the asymmetric benzylation of Ni(II) complexes **395**, which contain imines derived from alanine and PBP or PBA as ligands.[195] However, the reaction was very slow and the asymmetric induction very low (Scheme 106).

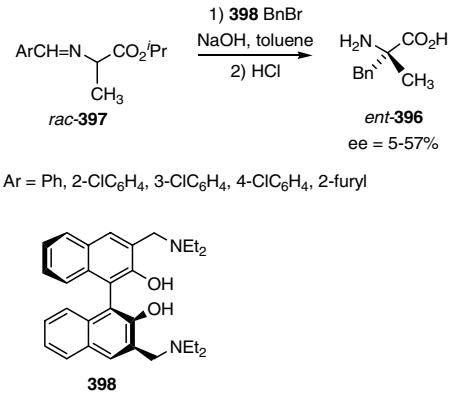



**Scheme 106.**

BINOLAMs are new bis(aminomethyl)binaphthols and these have also been prepared and tested in the enantioselective benzylation of imines obtained from alanine isopropyl esters and aromatic aldehydes.[196] In the case of BINOLAM **398**, the best results were obtained using NaOH as base, toluene as the solvent and the imine obtained from benzaldehyde as the substrate (Scheme 107).

In an attempt to improve the enantioselectivity of the reaction, BINOLAM was modified by changing the substituents on the nitrogen.[196] However, similar results to those found for previous examples were obtained.

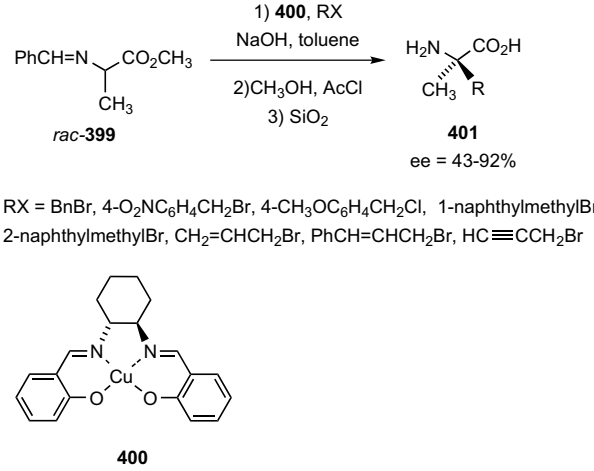
Chiral metal complexes are extremely efficient as catalysts in enantioselective synthesis, as they possess the ability to fix the orientation of the substrate and the chiral ligand




**Scheme 107.**

in the sphere of the complex, thus providing optimal chiral templates for high asymmetric induction. A chiral metal complex able to chelate metal ions could be an efficient catalyst in asymmetric phase-transfer catalysis. In this context, the use of nickel(salen) and copper(salen) complexes has recently been reviewed.[197] Initial results in this field show that they were active catalysts for the benzylation of compound **399** under phase-transfer catalysis conditions.[198] Asymmetric induction with nickel complexes was very low but the performance of the catalysts increased on using copper(salen) complexes. Indeed, enantiomeric excesses of up to 92% were achieved with a copper catalyst derived from (1*S*,2*S*)-[*N*,*N*′-bis(2′-hydroxybenzylidene)]-1,2-diaminocyclohexane. Any modification in the structure of the salen ligand proved detrimental in terms of enantioselectivity.[199]

The procedure has been extended to the synthesis of different α-methyl-α-amino acids, optimizing the use of the easily obtained imine derived from alanine methyl ester and benzaldehyde as the starting material.[200] To this end a re-esterification step was introduced as part of the reaction and the final hydrolysis of the product was performed using a non-aqueous work-up (Scheme 108). The enantioselectivity of the reaction was moderate to good depending on the electrophile. In an effort to explain



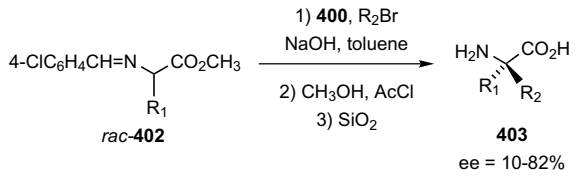

**Scheme 108.**

this behaviour, mechanistic studies were performed[201] and showed that those alkylating agents that are reactive under $S_N2$ conditions and able to stabilise a charged transition state led to the best results.

Variations in the structure of the starting imine led to improved results when imines derived from alanine methyl ester and 4-halobenzaldehydes were used as substrates, with the imine derived from 4-chlorobenzaldehyde being the most effective.[202,203]

Catalysts with substituents of various sizes and at various positions on the salen ligand aromatic rings[203] and catalysts with a different metal ions have also been tested.[204] It seems that the formation of square-planar complexes is necessary for catalytic activity and copper(II) and cobalt(II) complexes led to the best enantioselectivities. On the other hand, (1*S*,2*S*)-[*N*,*N*′-bis(2′-hydroxybenzylidene)]-1,2-diaminocyclohexane continued to be the best chiral ligand.

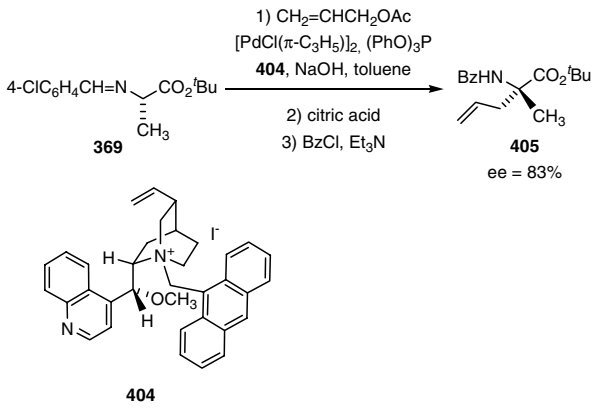
Catalyst **400** can be used in the asymmetric alkylation of imines derived from different α-amino acid methyl esters to obtain α,α-dialkylamino acids (Scheme 109).[205,206] In this case the enantioselectivity of the reaction depends on the amino acid side chain and usually decreases with increasing chain size.




$R_1$ = Et, $^t$Bu, Bn, Ph, $CH_2$=$CHCH_2$, $CH_3O_2CCH_2$
$R_2$ = $CH_2$=$CHCH_2$, Bn, 4-$O_2NC_6H_4CH_2$, $CH_3C{\equiv}CCH_2$, $HC{\equiv}CCH_2$

**Scheme 109.**

Finally, palladium(II)-mediated allylic alkylation of compound **369** in the presence of a chiral phase-transfer catalyst led to the corresponding α-allylated compound, from which (*S*)-*N*-benzoyl-α-allylalanine *tert*-butyl ester was obtained in low yield but with good enantioselectivity (Scheme 110).[207]

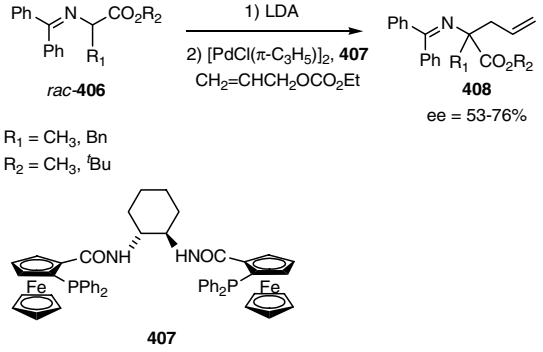



**Scheme 110.**

## 14.2. Transition metal-catalysed allylic alkylation

Allylic substitution mediated by a transition metal is a useful reaction in the enantioselective synthesis of chiral compounds when the appropriate combination of transition metal and chiral ligand is used. This methodology has been applied to the synthesis of α,α-dialkylamino acids using different amino acid synthetic equivalents, different transition metals and different chiral ligands.

Chiral ferrocene ligands have been tested in the palladium(II)-catalysed asymmetric allylic alkylation of imino esters. Among the several ligands tested,[208] compound **407**, which combines planar chirality with a chiral pocket matching their chiralities, was the most efficient ligand in the allylation of imino esters derived from alanine and phenylalanine (Scheme 111). The absolute configuration of the resulting compounds was not determined.

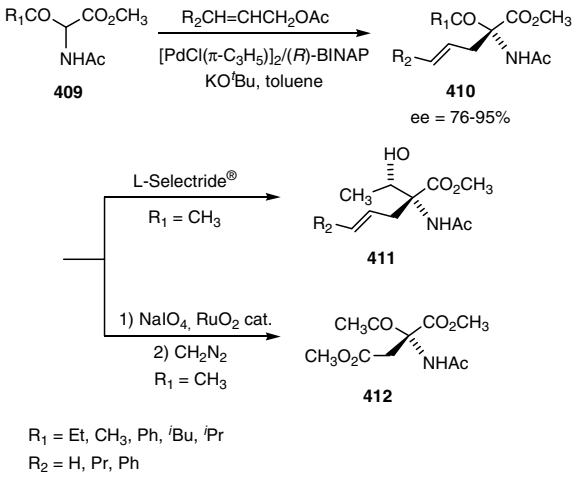



**Scheme 111.**

The palladium(II) complex catalyst generated from [Pd(π-allyl)Cl]$_2$ and (*R*)-BINAP promoted highly enantioselective allylation of α-acetamido-β-ketoesters.[209] When γ-substituted allyl acetates were used as reagents the reaction was completely regio- and diastereoselective, leading to α-(γ-substituted allyl)-α-acetamido-β-ketoesters with good yields and enantioselectivities. Reduction of the resulting compounds with L-Selectride® or oxidative cleavage of the olefin moiety followed by treatment with diazomethane gave α,α-dialkyl-β-hydroxyamino acid or α-acetyl aspartic acid derivatives, respectively (Scheme 112).

A combination of [Ir(COD)Cl]$_2$ and chiral phosphinate **414** catalysed the enantioselective allylic alkylation of imino alaninates to afford mixtures of compounds **415** and **416**.[210] Diastereoselectivity and enantioselectivities in the formation of **415** and **416** depended on the reaction conditions. The use of THF as the solvent, LiHMDS as the base and the appropriate ratio of reagents gave acceptable diastereoselectivities and enantioselectivities (Scheme 113).

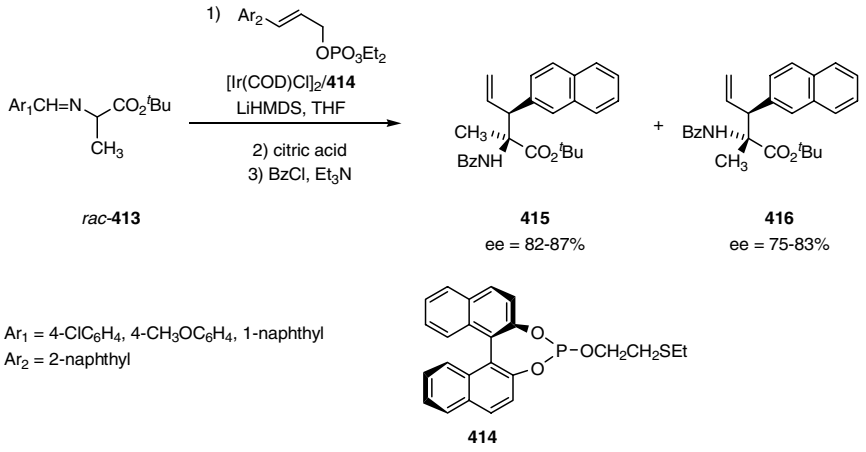
Palladium-catalysed allylic alkylation of oxazolones using bis-2-diphenylphosphinobenzamides derived from (*R*,*R*)-1,2-diaminocyclohexane or related compounds as chiral ligands has proven to be a versatile methodology for the enantioselective synthesis of α,α-dialkylamino acids.[211–213] The reaction proceeded with excellent enantioselectivity when 1-monosubstituted or 1,1-disubstituted allyl systems



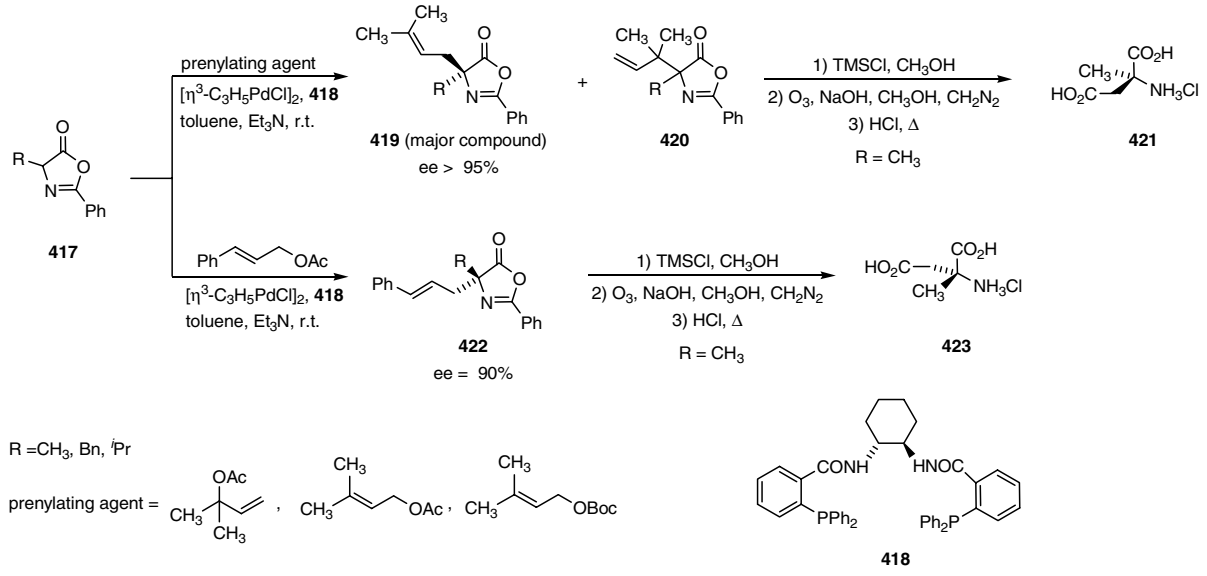

Scheme 112.

were used as reagents. The regioselectivity depended on the ligand and the steric demand of the nucleophile as well as on the reaction conditions. Optimal results were obtained working at room temperature with toluene as the solvent, triethylamine as the base and a 0.1% loading of catalyst when **418** was used as a ligand. It is worth mentioning that facial selectivity in the attack on the oxazolone depended on the alkylating agent, meaning that prenylenation and cinnamylation of the same oxazolone using the same catalyst provided compounds with opposite configuration (Scheme 114). Subsequent methanolysis of allylated oxazolones and ozonolysis of the allyl moiety led to α-methylaspartic acid derivatives.

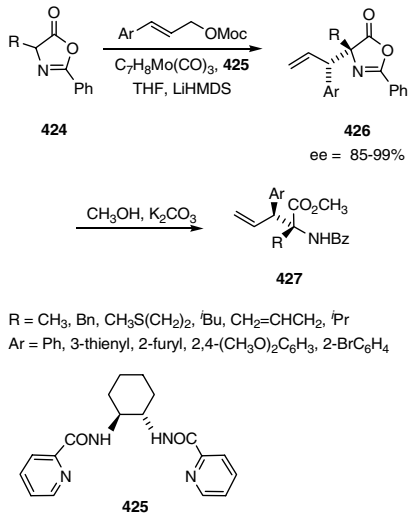
Molybdenum catalysts have been tested to control the regioselectivity of the allylation reaction[214] and in nearly all cases, the branched products were the only ones obtained and these were formed as single diastereoisomers (Scheme 115).




Scheme 113.



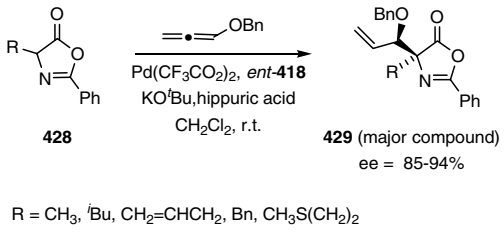

Scheme 114.




**Scheme 115.**

Palladium and molybdenum asymmetric allylic alkylation are complementary processes to obtain linear and branched allylated compounds.

In a related approach, the palladium-catalysed reaction of oxazolones with α-alkoxyallenes to afford the corresponding α-alkoxyallylated compounds has been studied.[215] The results were found to depend upon the reaction conditions and on working at the appropriate pH, which could be achieved by using potassium *tert*-butoxide in conjunction with hippuric acid, compounds **429** were obtained with good isolated yields and excellent diastereo- and enantioselectivities (Scheme 116).



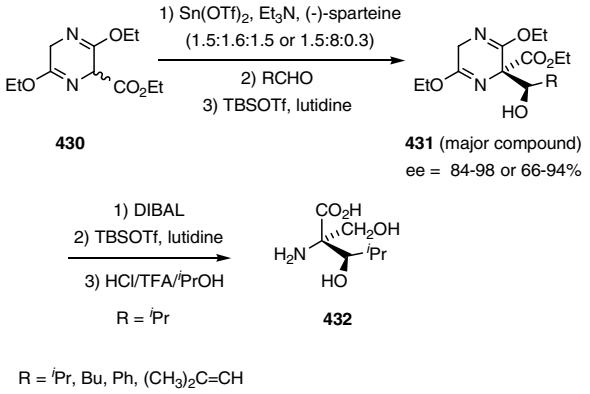

**Scheme 116.**

## 14.3. Aldol-type reactions

The Sn(II)-mediated aldol condensation of aldehydes with bislactim ethers derived from diethyl aminomalonate and glycine in the presence of an excess amount of (−)-sparteine afforded preferentially diastereoisomers **431** with good enantioselectivities.[216] Good levels of enantioselectivity were also obtained with 0.3 equiv of chiral ligand provided that triethylamine was used in a large excess. The major compound obtained in the reaction of bislactim **430** with isobutyraldehyde was converted to α-substituted serine **432** (Scheme 117).

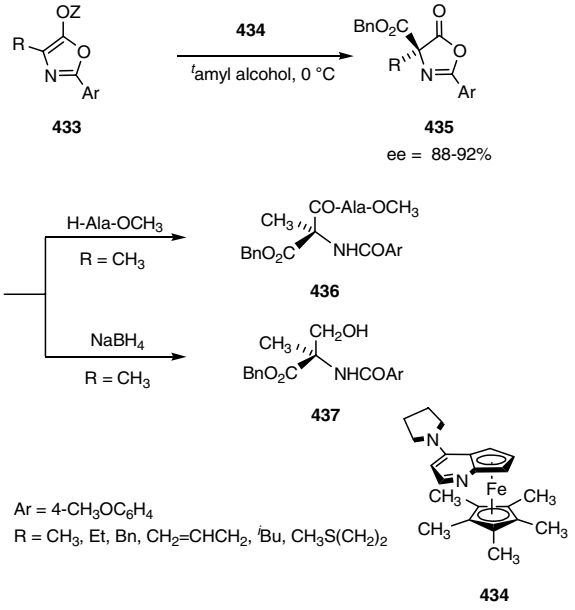
## 14.4. Enantioselective rearrangements

Chiral derivatives of 4-(dimethylamino)pyridine or 4-(pyrrolidino)pyridine catalysed the enantioselective



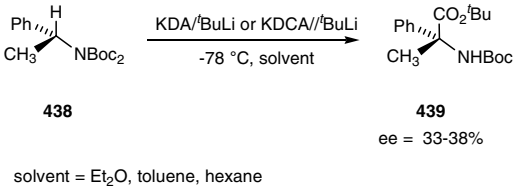

**Scheme 117.**

rearrangement of O-acylated azlactones into C-acylated azlactones, with the most selective being the 4-(pyrrolidino)pyridine derivative **434**.[217,218] The enantioselectivity of the rearrangement depended on the substituent at $C_2$ and on the migrating group at $C_5$. Optimal results were obtained with 2-(4-methoxyphenyl) derivatives as starting compounds and benzyl carbonate as the migrating group. Under optimised conditions, azlactones **435** were obtained in excellent yield and with high enantioselectivity. These compounds are valuable synthetic intermediates in the synthesis of α,α-dialkylamino acids and their derivatives (Scheme 118).




**Scheme 118.**

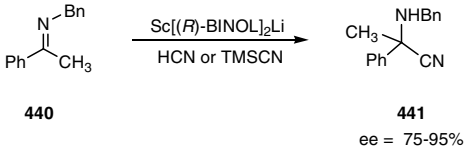
*N*,*N*-Di-Boc-protected (*R*)-phenylethylamine underwent [1,2] Boc migration upon treatment with base.[219] The enantioselectivity of the migration reaction, which was low in any case, depended on the solvent. The reaction in THF was not enantioselective whereas in less polar solvents migration occurred enantioselectively to afford the α,α-dialkylamino acid derivative of (*R*)-configuration as the major product (Scheme 119).




**Scheme 119.**

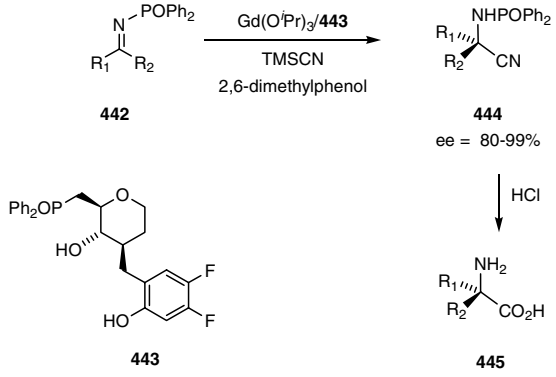
## 14.5. Addition of nucleophiles to the C=N bond

The catalytic enantioselective Strecker reaction is an attractive methodology for the synthesis of optically active α-amino acids and this topic has recently been reviewed.[220] The synthesis of α,α-dialkylamino acids using this methodology requires the use of a ketimine as the substrate and, in this respect, several enantioselective Strecker reactions starting from ketimines and using a chiral catalyst have recently been developed. Chiral heterobimetallic complexes of the type M(BINOL)$_2$Li have been used as catalysts in the enantioselective addition of cyanide to *N*-benzyl imine **440**.[221] The use of Al[(*R*)-BINOL]$_2$Li as the catalyst gave low to moderate enantioselectivities and these depended on the cyanide source and the coordinating ability of the solvent. The best results were obtained with trimethylsilyl cyanide as the cyanide source and toluene as a non-coordinating solvent. Sc[(*R*)-BINOL]$_2$Li proved to be a more efficient catalyst and induced high enantioselectivity in the first stage of the addition of trimethylsilyl cyanide. As the reaction evolved, both the reaction rate and the enantiomeric excess decreased—probably due to catalyst poisoning or decay. In any case, the enantioselectivity was clearly superior with the scandium catalyst regardless of the cyanide source used (Scheme 120). The resulting amino nitrile was not transformed into the corresponding α,α-dialkylamino acid and the absolute configuration of the major product was not determined.




**Scheme 120.**

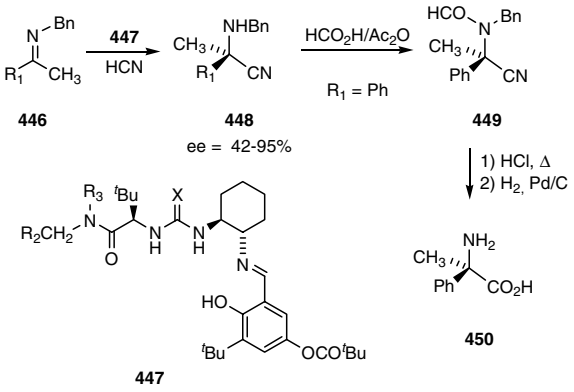
Shibasaki et al. described a general catalytic enantioselective Strecker reaction of ketimines using a chiral gadolinium complex prepared from Gd(O$^i$Pr)$_3$ and ligand **443**, derived from D-glucose, in a 1:2 ratio.[222,223] The enantioselectivity depended on the N-protecting group, the order of the addition of the reagents and the presence of protic additives. Optimal results were obtained using *N*-phosphinoyl imines by adding the substrate to the dried pre-catalyst, followed by solvent and trimethylsilyl cyanide as the cyanide source in the presence of 2,6-dimethylphenol. High enantioselectivities were achieved under these conditions with a wide variety of substrates, including aryl and hetaryl methyl ketimines, propiophenone-derived *N*-phosphinoylketimine, alkyl-substituted ketimines, α,β-unsaturated ketimines and even cyclic ketimines. Hydrolysis of the resulting amino nitriles led to the corresponding α,α-dialkylamino acids (Scheme 121). Excellent enantioselectivities were obtained on reducing the catalyst loading to levels as low as 0.1% and using a catalytic amount of trimethylsilyl cyanide and a stoichiometric amount of HCN, which proved to be much more advantageous for the large-scale synthesis of chiral α,α-dialkylamino acids.[224]




**Scheme 121.**

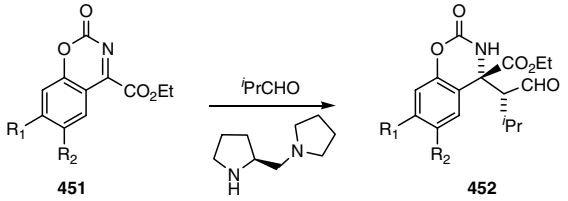
Chiral Schiff bases derived from (*S*,*S*)-1,2-diaminocyclohexane have been used as organocatalysts in the enantioselective addition of HCN to ketimines.[225,226] Resin-bound catalyst **447** ($R_2$ = polystyrene beads, $R_3$ = H, X = S) required long reaction times to reach high yields and higher reactivities were observed with soluble catalysts **447** ($R_2$ = Ph, $R_3$ = H, X = O or $R_2$ = H, $R_3$ = $CH_3$, X = O). The use of *N*-allyl imines as substrates led to the formation of unstable amino nitriles, but the use of *N*-benzyl imines gave stable amino nitriles, generally with high enantioselectivities. In cases where compounds **449** are crystalline, a single recrystallisation led to enantiomerically pure compounds. Enantiomerically pure α-methylphenylglycine has been obtained by N-formylation (to avoid decomposition), hydrolysis and N-debenzylation (Scheme 122).

The addition of Mannich bases to the C=N bond of imines has enormous utility for the synthesis of nitrogen-containing compounds in general and α-amino acids in particular, but it is only recently that this approach has been extended to the use of ketimines as starting compounds. In this context Jorgensen et al. have developed enantioselective Mannich reactions starting from cyclic α-ketimino esters in which the anchoring of the protecting group favours their reaction with the nucleophile. Cyclic ketimino esters **451** reacted with isobutyraldehyde in the presence of chiral secondary amines using diethyl ether as the solvent to enantioselectively afford α,α-dialkylamino acid precursors **452**.[227] Among the different amines tested as organocatalysts, (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine led to optimal results (Scheme 123). For other aldehydes the best results were obtained using dichloromethane as the solvent.




$R_1$ = Ph, 4-$CH_3C_6H_4$, 4-$BrC_6H_4$, 4-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$, 4-$CF_3C_6H_4$, 3-$BrC_6H_4$, 2-$BrC_6H_4$, $^t$Bu
$R_2$ = polystyrene bead, Ph, H
$R_3$ = H, $CH_3$
X = S, O

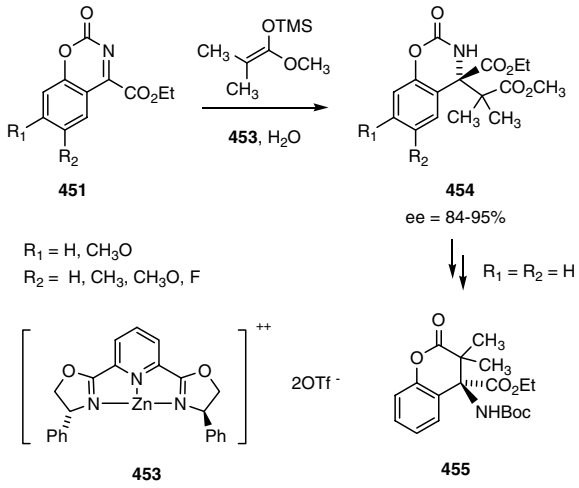
**Scheme 122.**




$R_1$ = H, $CH_3O$
$R_2$ = H, $CH_3$, $CH_3O$, F

**Scheme 123.**

The same substrates reacted with methyl trimethylsilyl dimethylketene acetal in the presence of zinc chiral catalyst **453**.[228] The rate of the addition of the reagents and the presence of a catalytic amount of water was essential for obtaining compounds **454** in good yields and with high enantioselectivities. Mannich adducts have been transformed into α,α-dialkylamino acid derivatives (Scheme 124). Other silylketene acetals reacted with compound



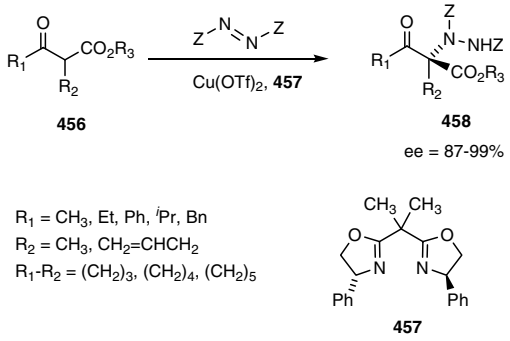

$R_1$ = H, $CH_3O$
$R_2$ = H, $CH_3$, $CH_3O$, F

**Scheme 124.**

**451** ($R_1 = R_2 = H$) to afford the corresponding Mannich adducts with excellent enantiomeric excess and good *syn*/*anti*-diastereoselectivity on using α-monosubstituted silylketene acetals.

### 14.6. Electrophilic amination

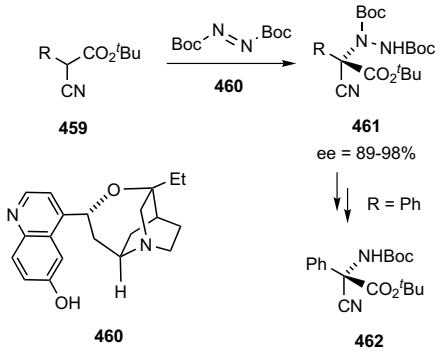
Electrophilic amination of enolates, probably one of the simplest approaches to α-amino acids, is relatively uncommon due to the paucity of electrophilic nitrogen sources. The direct α-amination of α-substituted β-ketoesters catalysed by chiral copper bisoxazoline **457** complex has recently been reported.[229] Compounds **458** were obtained in excellent yields and with enantiomeric excesses usually greater than 95% upon reaction of both acyclic and cyclic α-substituted β-ketoesters with dibenzyl azodicarboxylate (Scheme 125).




$R_1$ = $CH_3$, Et, Ph, $^i$Pr, Bn
$R_2$ = $CH_3$, $CH_2$=$CHCH_2$
$R_1$-$R_2$ = $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$

**Scheme 125.**

Alkaloid β-isocupreidine **460** also catalysed this reaction although the enantioselectivities were somewhat lower.[230] This alkaloid catalysed the electrophilic amination of α-cyanoesters, and compounds **461** were obtained with high enantioselectivities using di-*tert*-butyl azodicarboxylate as the nitrogen source. Hydrazine cleavage led to the synthesis of α-cyanophenylglycine derivatives (Scheme 126).

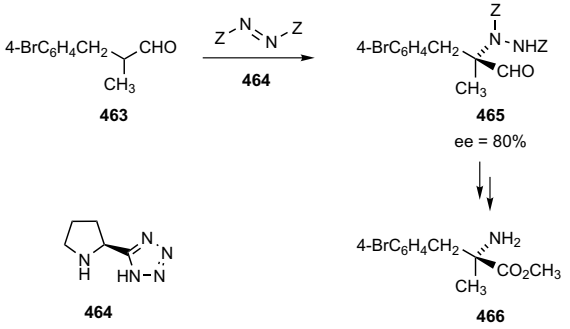



R = Ph, 2-$FC_6H_4$, 3-$CH_3C_6H_4$, 4-$ClC_6H_4$, 4-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$, 2-naphthyl, 2-thienyl

**Scheme 126.**

More recently Chowdari and Barbas[231] have described the highly enantioselective amination of 3-(4-bromophenyl)-

2-methylpropanal with dibenzyl azodicarboxylate. The reaction was catalysed by chiral tetrazole **464**, which was obtained from proline. Other proline-derived organocatalysts were less effective in terms of yield and enantioselectivity. Convenient elaboration of the resulting aminoaldehyde led to α,α-dialkylamino acid derivative **466**, from which BIRT-377 has been efficiently obtained (Scheme 127).

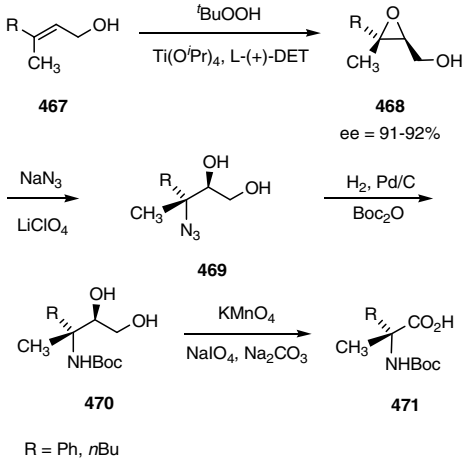



**Scheme 127.**

## 14.7. Olefin epoxidation and dihydroxylation

Chiral epoxides and diols have proven to be useful synthetic intermediates in the synthesis of α,α-dialkylamino acids. These chiral synthons have been obtained in enantiomerically pure form from olefins using enantioselective Sharpless epoxidation or enantioselective asymmetric dihydroxylation.

Pericas et al.[232] used 3,3-disubstituted allyl alcohols **467** as substrates in Sharpless epoxidations. The enantiomeric excess of the resulting epoxide depended on the tartrate used in the preparation of the catalyst, with better results obtained when using L-(+)-DET, ca. 92%, rather than L-(+)-DIPT, ca. 83%. Epoxides were converted into the desired α,α-dialkylamino acids by azide nucleophilic ring opening, which was not trivial and required the use of a mild Lewis acid, immediate catalytic hydrogenation of the azidodiol in the presence of *tert*-butyldicarbonate and oxidation (Scheme 128).




**Scheme 128.**

Sharpless epoxidation of 2-ethynylpropenol is the key step in the synthesis of (+)-lactacystin (Fig. 12) as developed by Pattenden et al.[233]

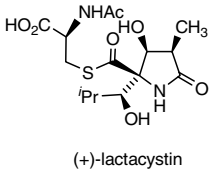
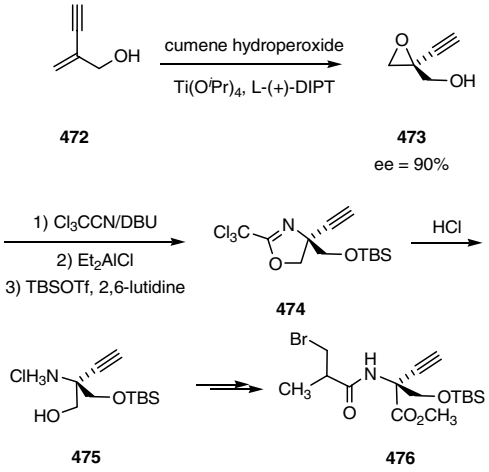



**Figure 12.**

The epoxide was converted into oxazoline **474** via a trichloromethylacetamidate. Hydrolysis of the oxazoline released aminoalcohol **475** and further elaboration of this compound led to α,α-dialkylamino acid derivative **476**, from which (+)-lactacystin was obtained (Scheme 129).

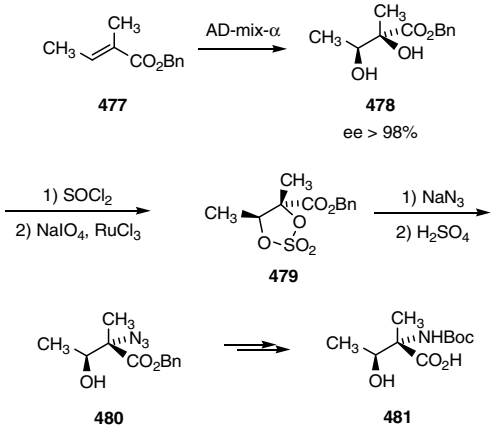



**Scheme 129.**

Goodman et al.[234] have developed enantioselective syntheses of α,β-dimethylserines and α,β-methylcysteines using Sharpless asymmetric dihydroxylation to generate the two stereogenic carbons present in the final compound. These reactions gave excellent enantioselectivities. (2*S*,3*S*)- And (2*R*,3*R*)-α,β-dimethylserine were obtained from benzyl tiglate using $(DHQ)_2PHAL$ (AD-mix-α) or $(DHQD)_2PHAL$ (AD-mix-β), respectively, to promote asymmetric dihydroxylation. The amino group is introduced with inversion at $C_2$ through nucleophilic substitution by azide via a cyclic sulfate. Final hydrogenation provided the desired amino acid, as shown in Scheme 130 for the (2*S*,3*S*)-stereoisomer.

All attempts to obtain (2*S*,3*R*)-α,β-dimethylserine from cyclic sulfate **479** by two consecutive nucleophilic displacements failed and, ultimately, (2*S*,3*R*)-α,β-dimethylserine was obtained from angelic acid *tert*-butyl ester using a similar sequence to that shown in Scheme 130. Asymmetric dihydroxylation using AD-mix-β led to the (2*R*,3*R*)-diol with an enantiomeric excess of 60%.

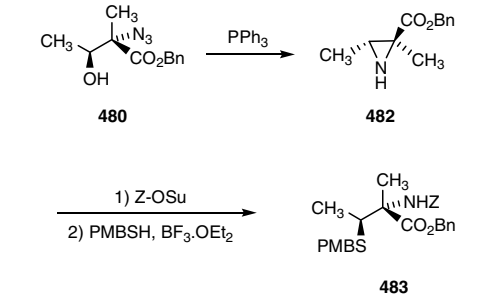
Fully protected (2*S*,3*S*)-α,β-dimethylcysteine was obtained by conversion of azido alcohol **480** into an activated




477 478 ee > 98% 479 480 481

**Scheme 130.**

*N*-benzyloxycarbonylaziridine followed by ring opening with a thiol (Scheme 131).




480 482 483

**Scheme 131.**

Asymmetric Sharpless dihydroxylation of the Weinberg amide of 2-methyl-2-propenoic acid led to the corresponding amidodiol of either (*R*)- or (*S*)-configuration, depending on the reagent, with complete enantioselectivity.[171,235] These compounds were used to prepare useful chiral intermediates such as chiral azido alcohols or *N*-Boc-*N*,*O*-isopropylidene-α-methylserinals, whose synthetic versatility has been exemplified in Section 13. The synthetic route to (*R*)-amidodiol **485** is shown in Scheme 132. An AD-mix-β was used as the reagent in the dihydroxylation step in order to obtain the (*S*)-enantiomer.

Azidoalcohol **487** is a suitable precursor for β,β-disubstituted-α-methyl amino acids and β-branched α-methylserine derivatives.[236] The double addition of organomagnesium reagents to the carbomethoxy group in compound **488** led to compound **489**. The use of the appropriate organometallic reagent enabled the synthesis of α-methyl-β,β-diphenylalanine, protected α-methyl-β,β-diphenylserine and α-methyl-β,β-dimethylserine according to Scheme 133.

Compound **485** has been converted into the conveniently protected β-D-glucopyranosyl-(*S*)-α-methylserine,[238] which can be regarded as a building block to gain access to new constrained glycopeptides. To this end, azido compound **497** was obtained for use in the glycosidation step (Scheme 134).

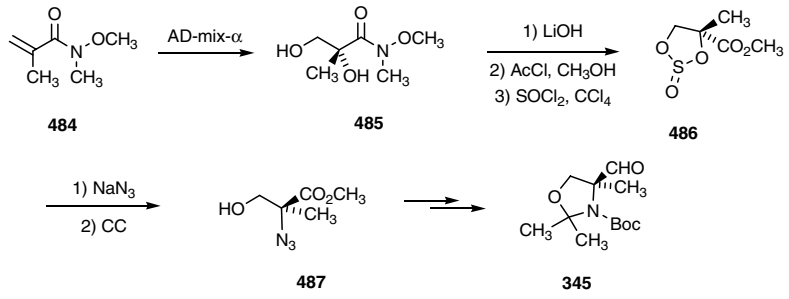
Compound *ent*-**487** has been converted into (*R*)-α-methylserine-β-lactone,[238] a versatile building block for the synthesis of (*R*)-α-methylcysteine and lanthionines (Scheme 135).

In order to perform the lactone ring opening with carbon nucleophiles, α-methylserine methyl ester, obtained from **487**, has been converted into *N*,*N*-dibenzyl-α-methylserine-β-lactone.[239] Lactonisation under Mitsunobu conditions was unsuccessful and, among the different reagents tested for lactonisation, HBTU was by far the best activating agent. Ring opening of lactone **505** with alkyl cuprates generated from primary alkylmagnesium halides or indole Grignard reagent led to the corresponding α,α-dialkylamino acid derivatives with complete regioselectivity (Scheme 136).

The use of alkyl cuprates generated from arylmagnesium halides, or other Grignard reagents such as isopropyl, vinyl or allylmagnesium chloride, led to competition with undesired processes involving *O*-alkyl fission. The regioselectivity of *O*-alkyl fission was notably improved for arylmagnesium halides by the presence of trimethylsilylchloride in the reaction mixture.

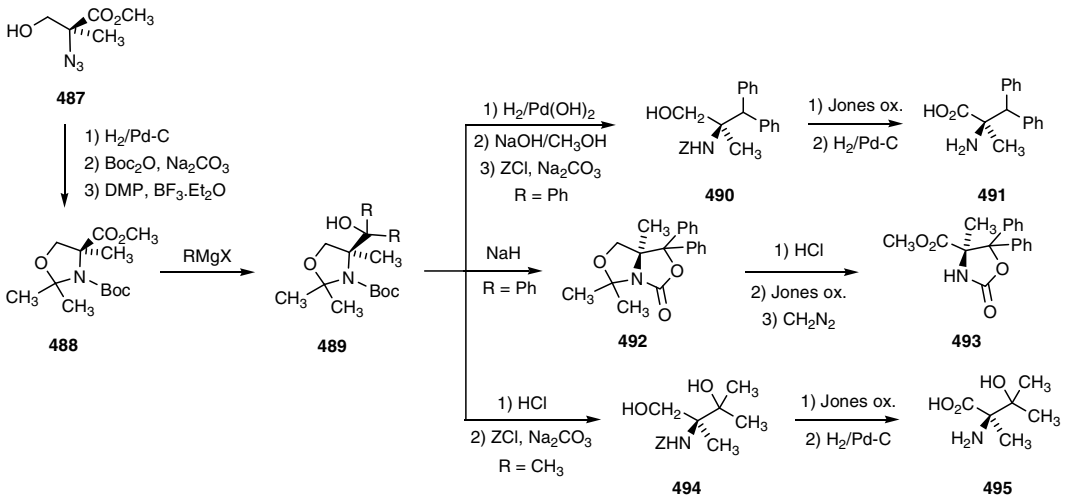
## 14.8. Desymmetrisation procedures

The desymmetrisation of compounds having a symmetry plane by stereoselective differentiation between two enantiotopic groups has become a useful and elegant approach for the synthesis of enantiomerically pure compounds. Most desymmetrisation approaches for the asymmetric

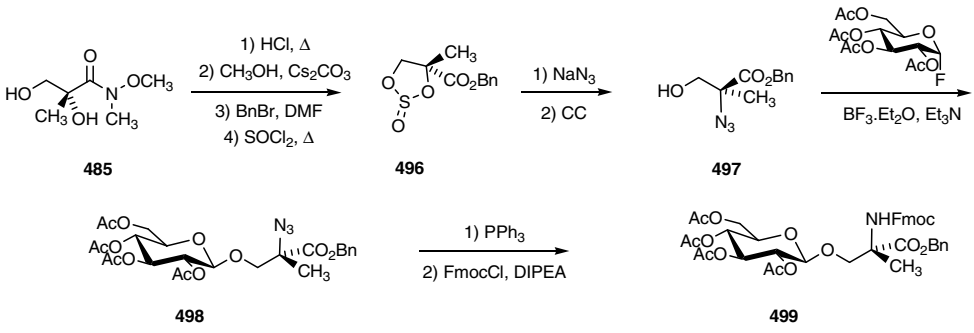



484 485 486 487 345

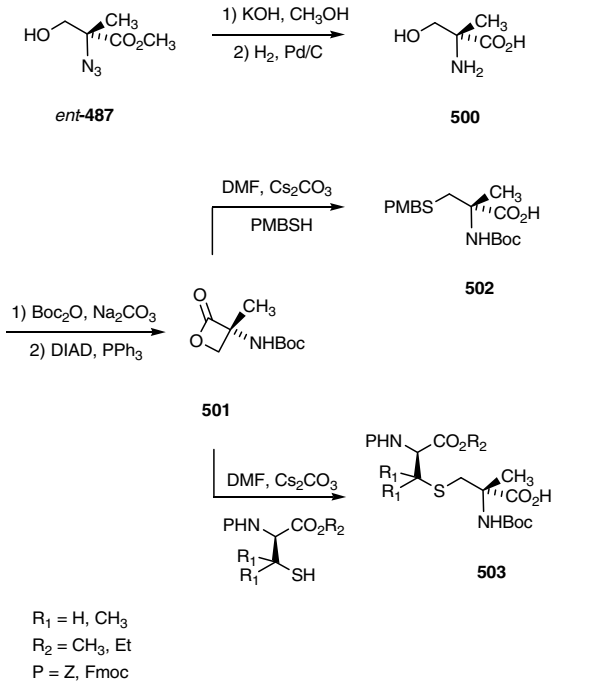
**Scheme 132.**



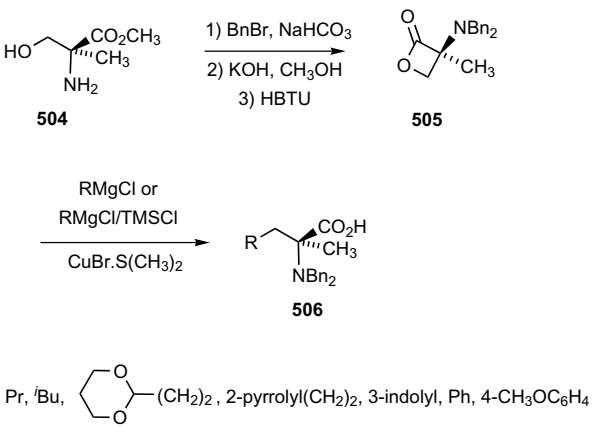
Scheme 133.



Scheme 134.



Scheme 135.

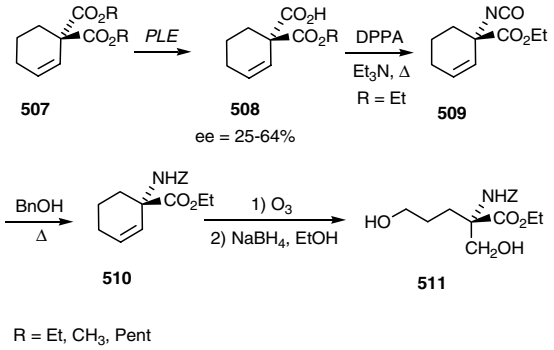


Scheme 136.

synthesis of α,α-dialkylamino acids are based upon enzymatic processes, as enzymes are capable of differentiating enantiotopic groups with high levels of enantioselectivity.

Honda et al.[240] described the enantioselective hydrolysis of the pro-*S* ester group of malonates **507** catalysed by pig liver estearase. Hydrolysis led to the corresponding

hemiesters of (*R*)-configuration with excellent yields and enantioselectivities, which depended on the bulkiness of the ester group. Hemiester **508** (R = Et) has been converted into α-substituted serine derivative **511**, as shown in Scheme 137.




**Scheme 137.**

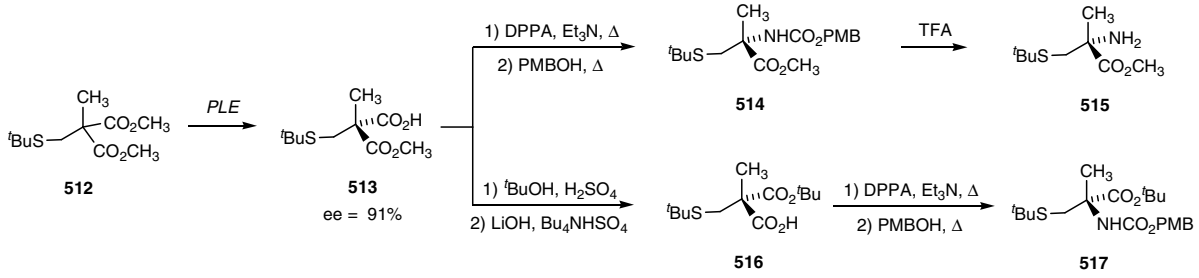
(*R*)- And (*S*)-2-methylcysteine derivatives have been synthesised from common intermediate **513**, obtained by desymmetrisation of a 2,2-disubstituted malonate diester using pig liver estearase to perform a highly enantioselective hydrolysis of the pro-*S* ester group.[241] This enantiodivergent procedure (Scheme 138) is amenable to large-scale preparations.

Enzymatic desymmetrisation of diacetate **518** catalysed by pig liver estearase led to chiral monoacetate **519** in good yield and high enantioselectivity.[242] This chiral compound is the common intermediate in the synthesis of α-substituted serine analogues. The terminal alkyne in the protected, enantiomerically pure diol intermediates was transformed into a variety of side chains through acetylide addition to electrophiles or palladium-catalysed Sonogashira couplings (Scheme 139).[243]

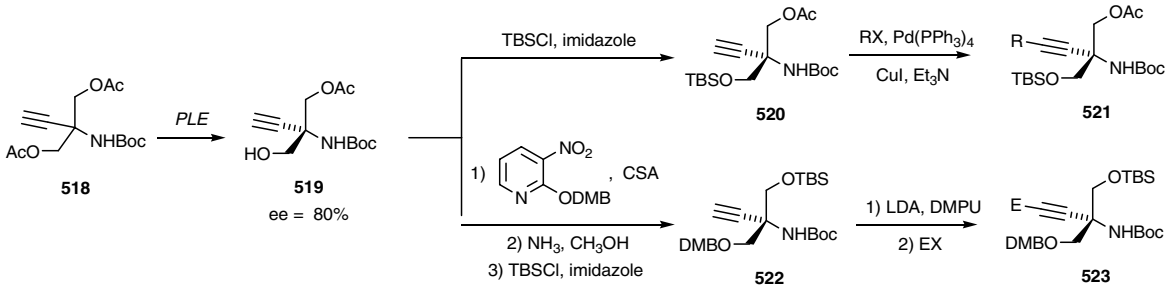
Once the alkyne moiety had been reduced, oxidation of one of the two selectively deprotected primary hydroxyl groups generated the carboxylic acid group of the amino acid moiety. A choice of the appropriate order for the manipulation gave compounds with (*R*)- or (*S*)-configuration from **521** (Scheme 140).

α,α-Disubstituted malononitriles behave as substrates in enantioselective hydrolysis catalysed by the nitrile-converting enzyme *Rhodococcus* sp. CGMCC 0497. The reaction led to a mixture of compounds from which almost enantiomerically pure (*R*)-α,α-disubstituted malonamic acids could be isolated. The yields of the desired compounds increased when increasing the reaction time and decreasing the reaction temperature; the optimal results were obtained at 20 °C after 7 days.[244] Alternatively, α,α-disubstituted malonamides have been submitted to enantioselective hydrolysis catalysed by *Rhodococcus* sp. CGMCC 0497. With these substrates the hydrolysis was much faster and more efficient, with compounds **529** obtained in nearly quantitative yield and total enantioselectivity, in most cases after 1 day (Scheme 141).[245]

The resulting (*R*)-α,α-disubstituted malonamic acids could afford both enantiomers of the corresponding α,α-dialkylamino acid using standard procedures (Scheme 142).

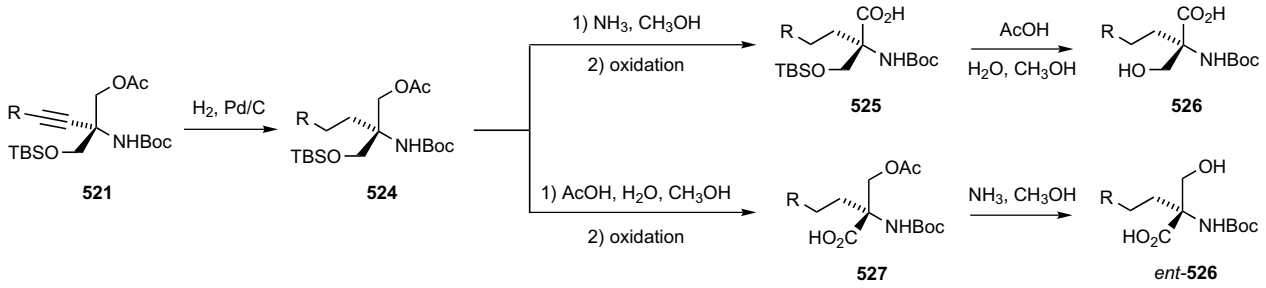



**Scheme 138.**

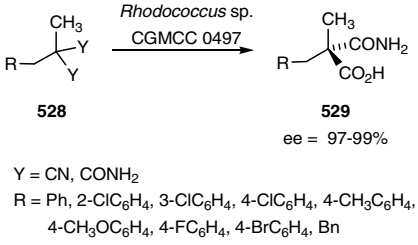



RX = PhI, 4-$CH_3OC_6H_4I$, 4-$FC_6H_4I$, 2-thienylI, 2-pyridylBr, $CH_3(CH_2)_3CH{=}CHI$
EX = TMSCl, $CH_2{=}CHCH_2Br$, $^tBuCOCl$

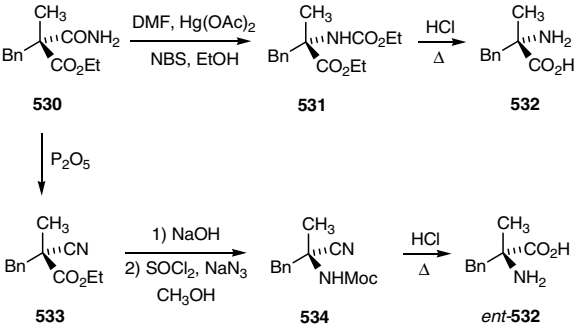
**Scheme 139.**




**Scheme 140.**




**Scheme 141.**

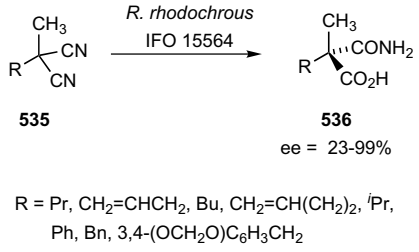



**Scheme 142.**

On the other hand, attempts to obtain cyanoamides or cyanoacids from dinitriles **528** (Y = CN) using the same nitrile-converting enzyme led to worse results, with the conversion of substrates was incomplete and the enantiomeric excesses of products were usually low to medium.[246]

*Rhodococcus rhodochrous* IFO 15564 also catalysed the enantioselective hydrolysis of α,α-disubstituted malononitriles to α,α-disubstituted malonamic acids.[247] The substrate specificity of the nitrile hydratase was rather broad while the rate of hydrolysis and enantioselectivity depended on the substrate. With substituents larger than ethyl, the *pro*-(*R*)-carbamyl group was preferentially hydrolysed and compounds with an (*R*)-configuration were obtained (Scheme 143).

Compound **536** [R = 3,4-(OCH$_2$O)C$_6$H$_4$CH$_2$], obtained in 95% yield and 98% enantiomeric excess, was used to synthesise (*S*)-α-methyldopa through Hoffman rearrangement of the amide moiety.




**Scheme 143.**

## 15. Resolution of racemic mixtures

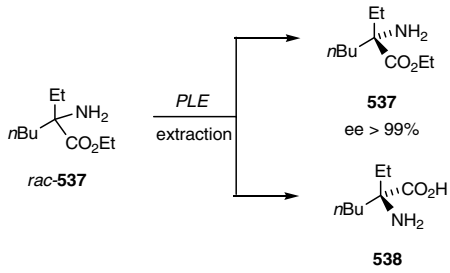
In addition to the diastereoselective and enantioselective syntheses described above for the asymmetric synthesis of α,α-dialkylamino acids, it is possible to obtain these compounds in enantiomerically pure form from racemic mixtures.

### 15.1. Enzymatic procedures

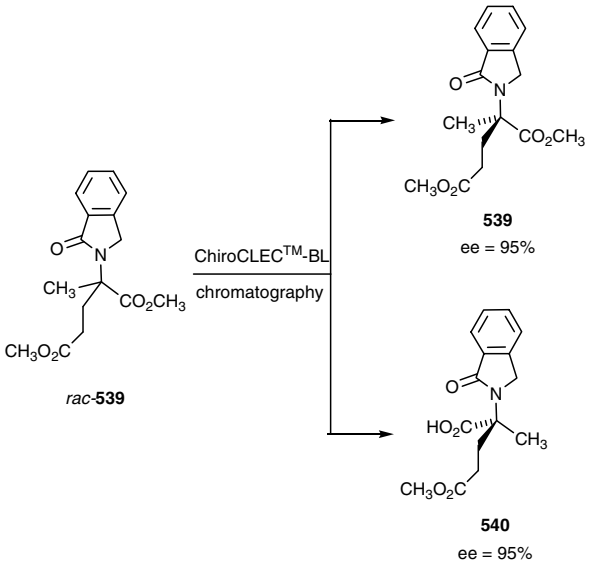
Among the resolution procedures, those using hydrolytic enzymes, such as lipases, amidases, proteases and esterases are the most commonly used in amino acid synthesis. Nevertheless, the biocatalytic resolution of esters bearing an adjacent quaternary stereogenic centre is not a trivial task. This is because hydrolytic enzymes usually do not accept these compounds as substrates and several strategies have been developed to circumvent this limitation.[248] As a consequence, some racemic α,α-dialkylamino acids were resolved into enantiomers using whole cells of *Mycobacterium neoaurum* or pig liver estearase, as discussed in a recent review.[249]

One recent contribution in this field,[40] is the synthesis of racemic butylethylglycine (Beg) from butyl ethyl ketone by Strecker synthesis and subsequent resolution using pig liver estearase. The unreacted enantiomerically pure (*S*)-amino ester was recovered in 31% yield (Scheme 144).

ChiroCLEC™-BL, a biocatalyst consisting of cross-linked enzyme crystals, hydrolysed the carboxylic acid of the amino acid moiety of the (*S*)-enantiomer of racemic 2-methyl-2-phthalimidinoglutaric acid dimethyl ester to afford the hemiester of (*S*)-configuration and left the diester of (*R*)-configuration unreacted (Scheme 145).[250]

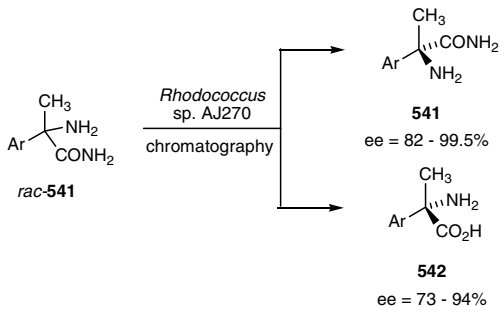



**Scheme 144.**



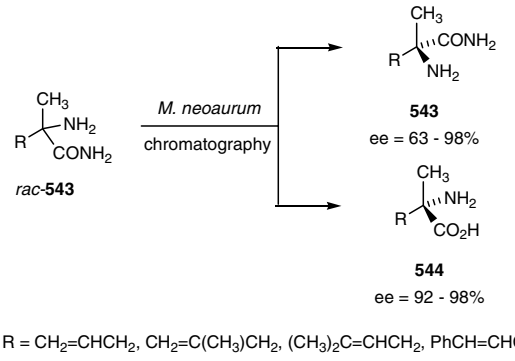

**Scheme 145.**

α,α-Dialkylamino acid amides have proven to be appropriate substrates for biocatalysed kinetic resolutions. Amidases within *Rhodococcus* sp. AJ270 catalysed the hydrolysis of α-arylalanine amides and racemic mixtures were transformed into amides of (*R*)-configuration and acids of (*S*)-configuration (Scheme 146).[251,252] The reaction rate and enantioselectivity depended on the electronic nature and substitution pattern of the aryl side chain. The enantiomeric excess of the amide increased and the enantiomeric excess of the acid decreased as the reaction progressed and, after the appropriate reaction time, α,α-dialkylamino acid amides with enantiomeric excesses higher than 99.5% were isolated.




**Scheme 146.**

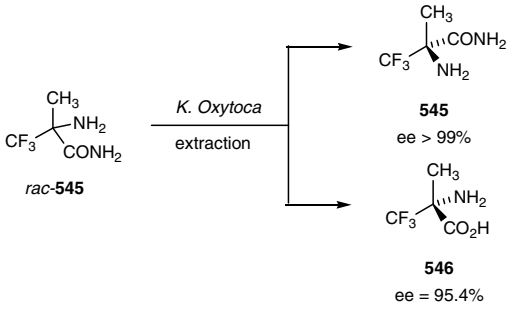
Amidases from *M. neoaurum* ATCC 25795 and *Ochrobactrum anthropi* NCIMB 40321 are capable of resolving α,α-dialkylamino acid amides with an unsaturated side chain with high (*S*)-selectivity (Scheme 147).[33,253] *O. anthropi* possesses a more open active site than *M. neoaurum* and this means that, despite having a lower stereoselectivity, it can accept substrates in which both side chains are larger than methyl.




**Scheme 147.**

*O. anthropi* or *M. neoaurum* also catalysed the resolution of $^{15}$N-labelled D-isovaline amide,[254] α,α-dialkylamino acid amides with a fluoroalkyl side chain[255] and 2-azido-2,4-dimethylpentanamide,[256] a valuable equivalent for α-methylleucine in peptide synthesis.

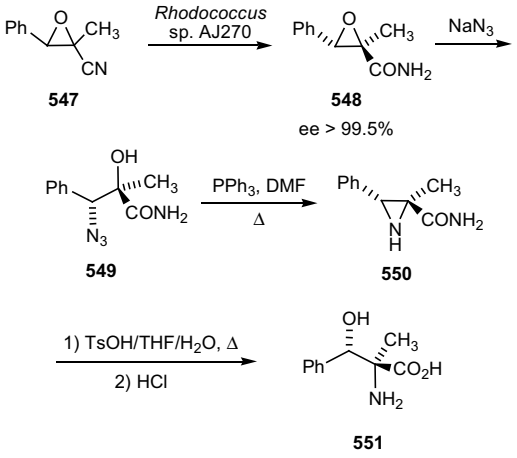
Heat-stable amidase from *Klebsiella oxytoca* can accept α-trifluoromethyl alanine amide as a substrate,[257] a property that allows the isolation of the amide of (*S*)-configuration in 50% yield and with an enantiomeric excess higher than 99% and the acid of (*R*)-configuration in 42% yield and 95.4% enantiomeric excess. The time required for complete conversion is only 1 min (Scheme 148).




**Scheme 148.**

The combination of the nitrile hydratase and the amidase in *Rhodococcus* sp. AJ270 whole cells has proven to be a powerful tool for obtaining enantiomerically pure carboxylic acids from nitriles. The nitrile hydratase catalyses the hydration of the nitrile to the amide and the amidase catalyses the enantioselective hydrolysis of the amide. This methodology has been applied to the synthesis of α-methylserine derivatives starting from racemic *trans*-2-methyl-

3-phenyloxiranecarbonitrile.[258] Incubation of this substrate for 7.5 h led to enantiomerically pure amide **548** of (2*R*,3*S*)-configuration in 45% yield. The hydrolysed compound was not isolable because it spontaneously decomposed. α-Methylserine derivative **551** was obtained from this oxiranecarboxamide as shown in Scheme 149.




**Scheme 149.**

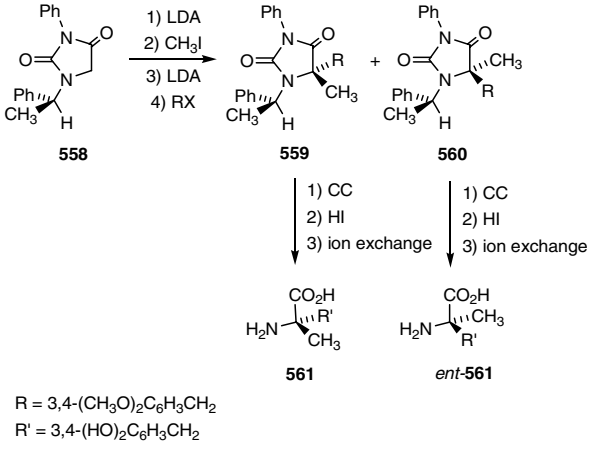
## 15.2. Separation of diastereoisomers

α,α-Dialkylamino acids or their precursor racemic mixtures have also been resolved by physical procedures after conversion into diastereoisomers. Racemic *N*-benzoyl-α-hydroxymethyl amino acids have been resolved by fractional crystallisation of diastereomeric salts using (−)-cinchonidine[259] or (−)-quinine[260] as resolving agents, in order to replace the parent amino acid in deltorphin I and in a cyclic opioid peptide.

Both enantiomers of 2-cyano-2-methyl-3-phenylpropanoic acid have been obtained from the racemic compound by fractional crystallisation of the corresponding (1*R*,2*S*)-norephedrine diastereomeric salts.[261] These enantiomerically pure compounds were then converted into (*S*)-α-methylphenylalanine on a large laboratory scale through the enantioconvergent synthesis shown in Scheme 150.

In some cases, the reaction of a chiral substrate with an achiral reagent or an achiral substrate with a chiral reagent gives almost equimolecular mixtures of diastereomeric compounds that can be separated and subsequently elaborated upon to afford enantiomerically pure α,α-dialkylamino acids. A potential diastereoselective synthesis therefore becomes a resolution of enantiomers through diastereoisomers.

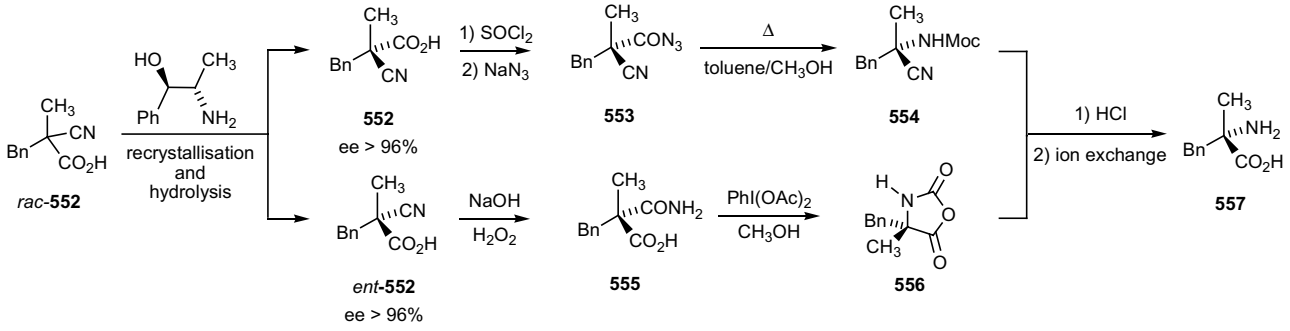
This is the case for the synthesis of α-methyldopa from chiral hydantoin **558** by double alkylation, as reported by Juaristi et al.[262] Whereas the lithium enolate generated from **558** was methylated in high yield and with excellent diastereoselectivity, the second alkylation was not diastereoselective and an equimolecular mixture of hydantoins **559** and **560** was obtained. These compounds were readily separated by flash chromatography and hydrolysed to (*S*)- and (*R*)-methyldopa, respectively (Scheme 151).



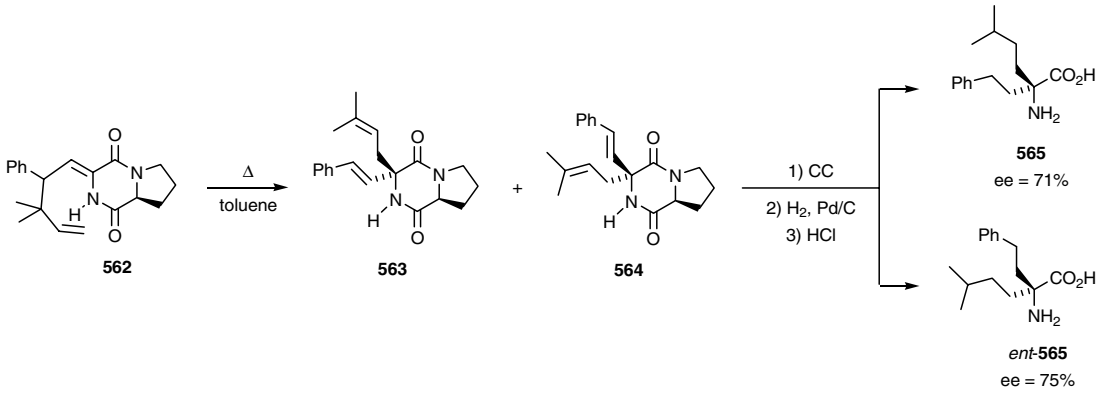

**Scheme 151.**

On heating 3-ylidenepiperazine-2,5-dione **562** in toluene, an equimolecular mixture of diastereomeric 3,3-alkenylpiperazinediones was obtained by Cope rearrangement.[263] After partial separation by column chromatography, both compounds were hydrogenated and subsequently hydrolysed to yield the corresponding enantioenriched α,α-dialkylamino acids (Scheme 152).

Finally, the reaction of the *N*-benzyloxycarbonyl imine of methyl trifluoropyruvate with α-lithium (*R*)-ethyl *p*-tolylsulfoxide was not completely diastereoselective and an equimolecular mixture of two of the four possible diastereoisomers was obtained.[264] The two diastereoisomers were




**Scheme 150.**



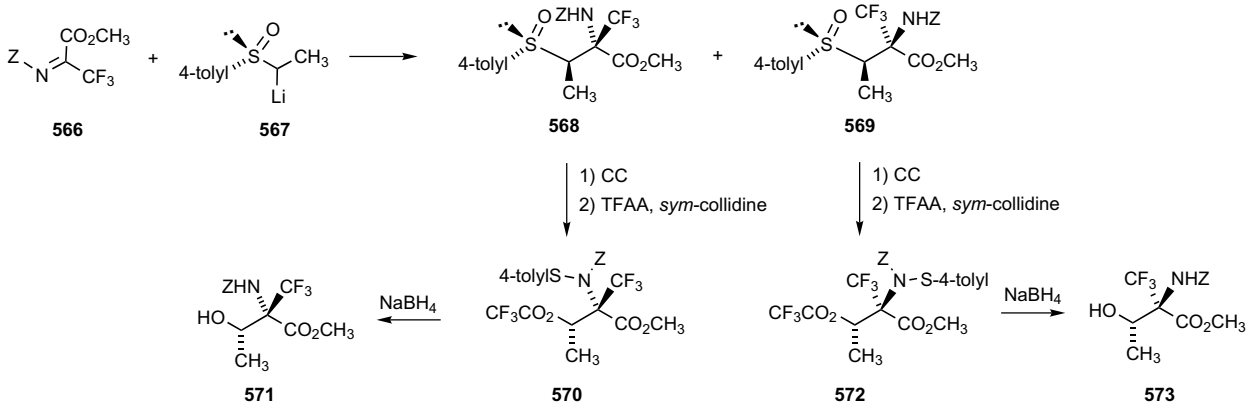

**Scheme 152.**

separated by flash chromatography and treated with trifluoroacetic anhydride in the presence of *sym*-collidine to rearrange to diastereomerically pure trifluoroacetoxysulfenamides **570** and **572**. From these compounds α-trifluoromethyl-*allo*-threoninate **571** and α-trifluoromethylthreoninate **573** were obtained by reduction with sodium borohydride (Scheme 153).

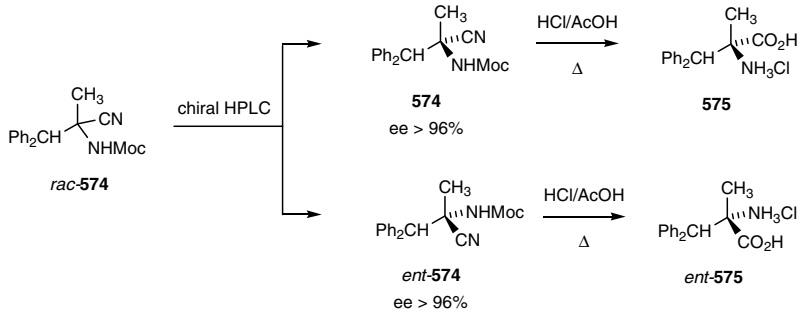
## 15.3. Chiral chromatography

The development of new chiral stationary phases has made it possible to resolve racemic α,α-dialkylamino acids into enantiomers by semi-preparative HPLC. Welk-01, a Pirkle-type phase, is the chiral stationary phase used in the resolution of 2-methyl-2-phthalimidinoglutaric acid.[250]

Both enantiomers of 2-methoxycarbonylamino-2-methyl-3,3-diphenylpropanonitrile, a synthetic precursor for 2-methyl-2-diphenylmethylglycine [(αMe)Dip], have been isolated in enantiomerically pure form using a cellulose-derived chiral stationary phase.[265] Subsequent hydrolysis of the resolved enantiomers led to (*R*)-[(αMe)Dip] and (*S*)-[(αMe)Dip] (Scheme 154).




**Scheme 153.**




**Scheme 154.**

## 16. Total synthesis of complex α,α-dialkylamino acids

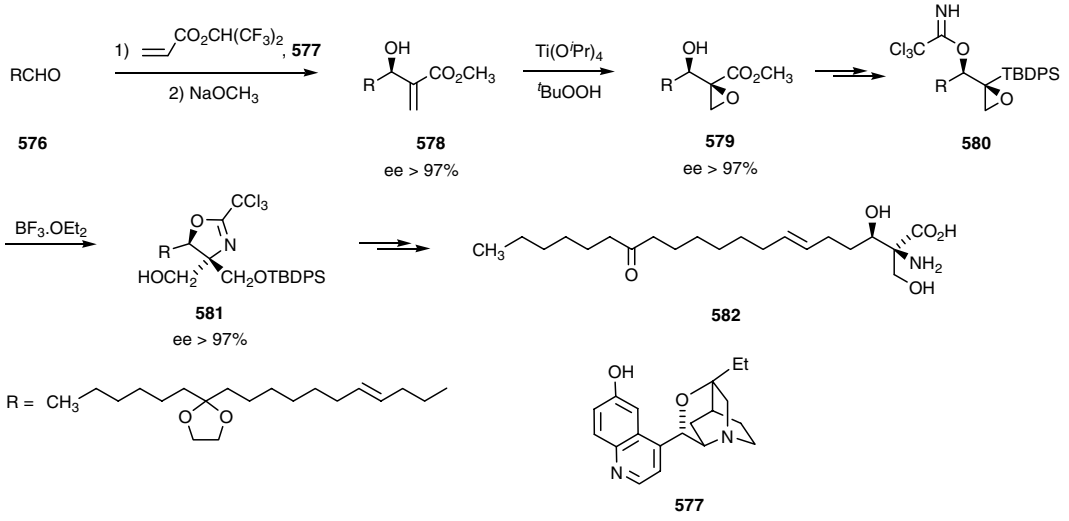
There are a number of important products of biological interest, such as sphingofungins, mycestericin or myriocin, whose structures can be considered as an α-alkylserine or an α-alkylalanine. The total synthesis of these compounds has been described and reviewed[266] in recent years.

The synthesis of (*S*)-mycestericin E **582**, a potent immunosuppressant, has been carried out from achiral aldehyde **576** in 12 steps with an overall yield of 4.7%.[267] The stereogenic β-carbon of the final amino acid was generated by an asymmetric Baylis–Hillman reaction catalysed by cinchona alkaloid **577** and the α-alkylserine moiety was constructed through titanium tetraisopropoxide-mediated epoxidation of chiral allylic alcohol **578** and Lewis acid-promoted cyclisation of epoxytrichloroacetylimidate **580**. The key steps and key intermediates are shown in Scheme 155.

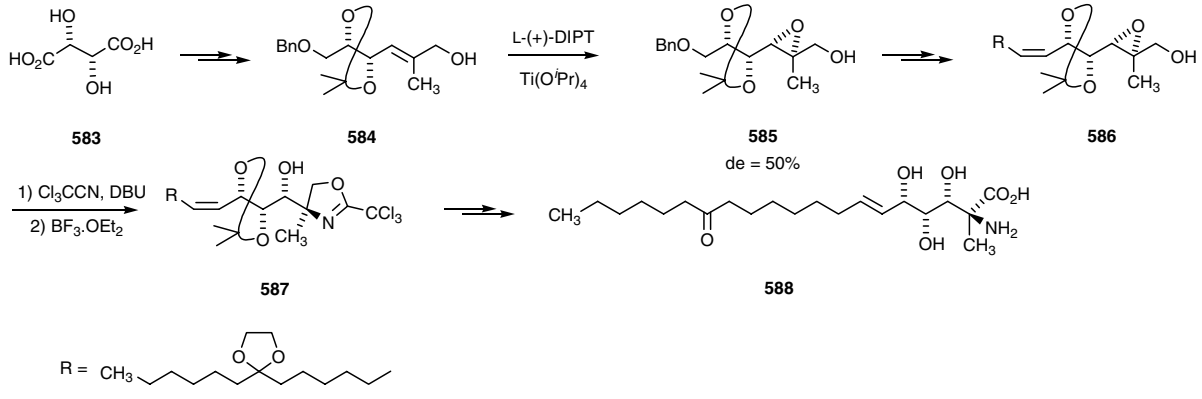
Sphingofungin F **588**, an inhibitor in the biosynthesis of sphingolipids, has been obtained from L-(+)-tartaric acid in 22 steps and 3.7% overall yield.[268] Key steps in the synthesis of this compound with the appropriate stereochemistry at stereogenic carbons are Sharpless asymmetric epoxidation of allylic alcohol **584** and intramolecular ring opening of the epoxide **586** with an *N*-nucleophile (Scheme 156).

Alternatively, sphingofungin F has been obtained from *cis*-2-butene-1,4-diol in 15 steps and 17% overall yield.[269,270] In this case the synthesis of the compound with the appropriate stereochemistry relies on asymmetric palladium-catalysed alkylation of 5(4*H*)-oxazolones using bis-2-diphenylphosphinobenzamides derived from (*R*,*R*)-1,2-diaminocyclohexane **418** as chiral ligands, as developed by Trost, and dihydroxylation of alkene **591**: This route affords a single product (Scheme 157).

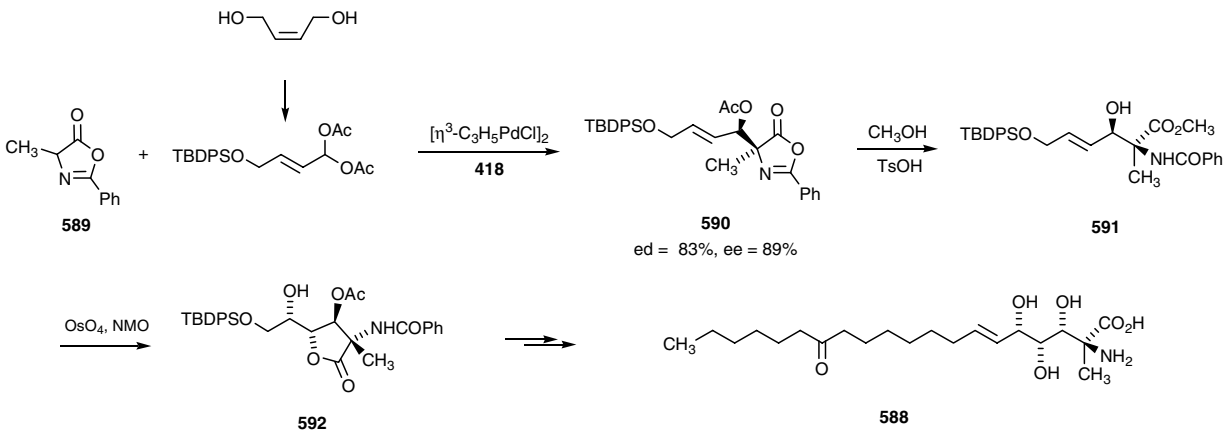
A similar synthetic scheme, using 5(4*H*)-oxazolone **593** as the substrate allowed the synthesis of sphingofungin E **597** in 17 steps and 5.1% overall yield (Scheme 158).[270] In



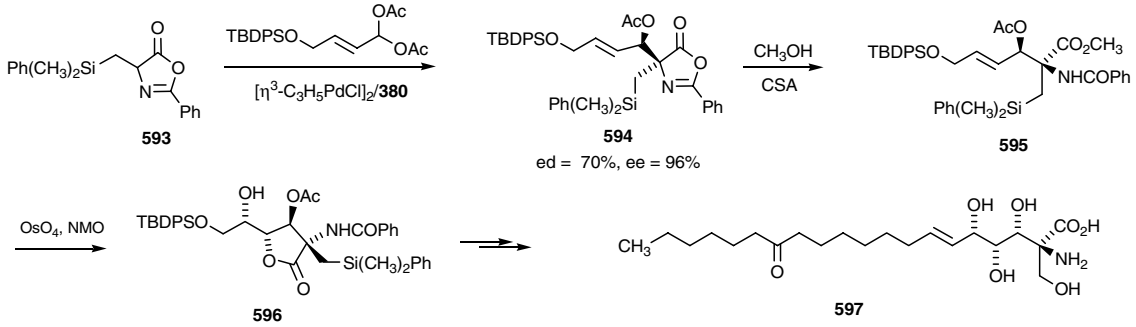

**Scheme 155.**




**Scheme 156.**




**Scheme 157.**

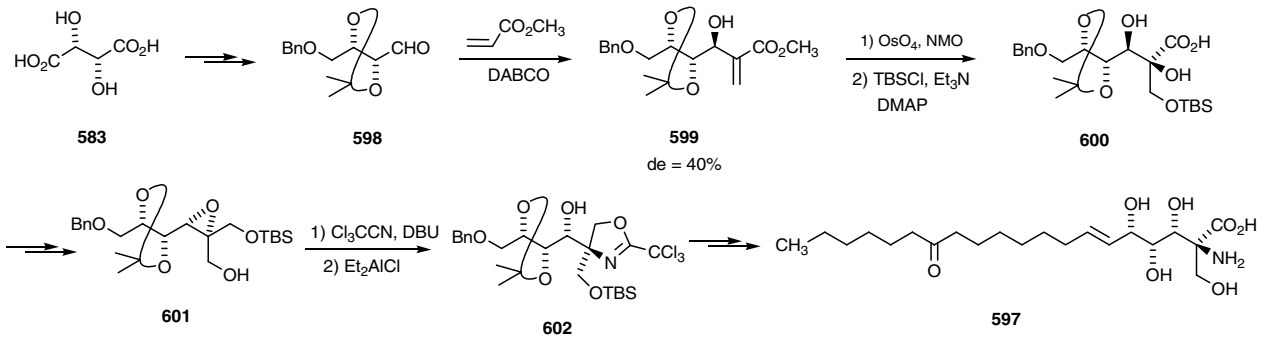



**Scheme 158.**

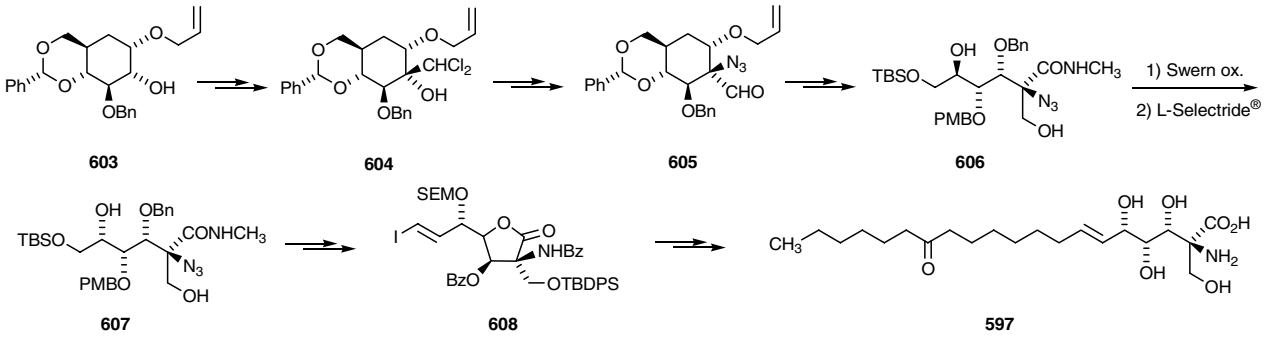
this case, palladium-catalysed alkylation of the 5(4*H*)-oxazolone was less effective and the major compound was obtained with a 70% diastereomeric excess and a 96% enantiomeric excess under optimised reaction conditions.

Sphingofungin E has also been obtained from L-(+)-tartaric acid in 19 steps and 8.1% overall yield.[271] A Baylis–Hillman reaction of aldehyde **598** led to the creation of a new stereogenic centre with moderate diastereoselectivity. Subsequent dihydroxylation of allylic alcohol **599** occurs with complete stereoselectivity; intramolecular ring opening of epoxide **601** with an *N*-nucleophile gave access to the masked amino acid moiety, also with complete stereoselectivity (Scheme 159).

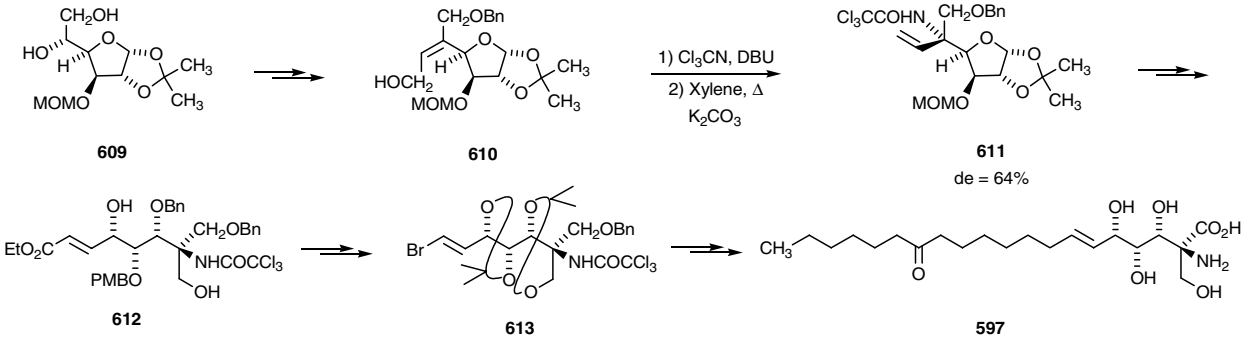
D-Glucose derivative **603** is the starting compound in the synthesis of sphingofungin E developed by Shiozaki et al.[272,273] Manipulation of the hydroxy group at $C_5$ resulted in dichloromethylated tertiary alcohol **604** with the appropriate stereochemistry. This compound was converted into azide-aldehyde **605** by nucleophilic ring opening of an intermediate spiro 2-chloroepoxide. This compound was converted to alcohol **606** by reduction and successive protection/deprotection steps. The configuration of $C_5$ was then inverted by an oxidation/reduction sequence. Further manipulation of this compound led to iodoalkene **608**, which was coupled with an organoborane and further elaborated to obtain sphingofungin E in 29 steps and 1.1% yield from starting compound **603** (Scheme 160).



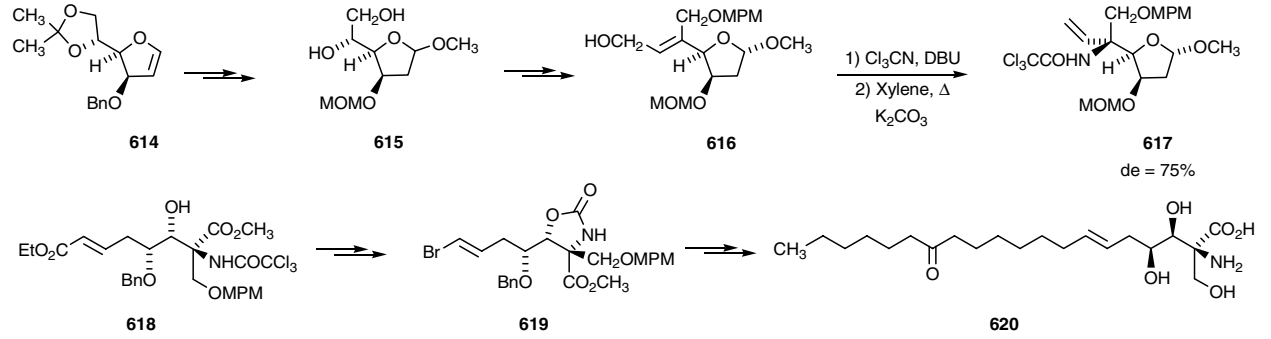

**Scheme 159.**




**Scheme 160.**




**Scheme 161.**




**Scheme 162.**

Diol **609**, also obtained from D-glucose, has been converted into sphingofungin E in 24 steps and 3.7% yield.[274] The key step in the creation of the quaternary stereogenic centre is an Overman rearrangement of the trichloroacetylimidate obtained from allylic alcohol **610**. The resulting compound was converted into tetrol **612**, from which conveniently protected bromide **613** was obtained. Coupling of this fragment with a sulfone and further elaboration led to sphingofungin E (Scheme 161).

This is the methodology developed by the same authors[274,275] to perform the total synthesis of (+)-myriocin **620** from glycal **614**, which is obtained from D-mannose. The optimal reaction conditions for the 22 steps required to transform the starting compound into (+)-myriocin gave 10.35% overall yield (Scheme 162).

## 17. Concluding remarks

In this review, we have covered recent progress in the development of new synthetic methodologies for the synthesis of α,α-dialkylamino acids and have also discussed extensions to well established synthetic routes to new α,α-dialkylamino acids.

The existing methodologies for diastereoselective enolate alkylation, self-regeneration of stereocentres, memory of chirality and alkylation of chiral substrates have been

widely and effectively applied to the synthesis of α,α-dialkylamino acids with very different side chains. The addition of nucleophiles to the C=N bond has proven to be efficient for the preparation of various compounds. Convenient elaboration of versatile chiral synthons has emerged as a useful strategy for the construction of target molecules. Enantioselective syntheses mediated by chiral catalysts have also proven to be powerful tools for the construction of the quaternary stereogenic centre.

All of these methodologies give the synthetic organic chemist the opportunity to select the most appropriate way to obtain the desired α,α-dialkylamino acid in enantiomerically pure form on both a laboratory scale and a multigram scale.

## 18. Abbreviations

Ac = acetyl
Aib = dimethylglycine
AIBN = 2,2′-azobisisobutyronitrile
Ala = alanine
Alloc = allyloxycarbonyl
BDI = (*S*)-*tert*-butyl-2-*tert*-butyl-4-methoxy-2,5-dihydroimidazole-1-carboxylate
Beg = butylethylglycine or 2-amino-2-ethylhexanoic acid
BEMP = 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2- diazaphosphorine
Bn = benzyl
Boc = *tert*-butoxycarbonyl
Bu = butyl
$^{i}$Bu = isobutyl
$^{s}$Bu = *sec*-butyl
$^{t}$Bu = *tert*-butyl
Bz = benzoyl
CC = column chromatography
CSA = camforsulfonic acid
COD = cyclooctadiene
Cp = cyclopentyl
(*S*)-CPPG = (*S*)-α-cyclopropyl-4-phosphonophenylglycine
*m*-CPBA = *meta*-chloroperbenzoic acid
DABCO = 1,4-diazabicyclo[2.2.2]octane
Dba = dibenzylamine
DBAD = di-(*tert*-butyl)azodicarboxylate
DBU = 1,8-diazabicyclo[5.4.0]udec-7-ene
de = diastereomeric excess
Deg = diethylglycine or 2-amino-2-ethylbutanoic acid
DEAD = diethylazodicarboxylate
DET = dietyl tartrate
DIBAL = diisobutylaluminum hydride
DIPEA = diisopropylethylamine
DIPT = diisopropyl tartrate
DMB = 3,4-dimethoxybenzyl
DME = dimethoxyethane
DMP = 2,2-dimethoxypropane
DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DPPA = diphenylphosphoryl azide
Dpg = dipropylglycine
Et = ethyl
(αEt)Leu = 2-amino-2-ethyl-4-methylpentanoic acid
Fmoc = 9-fluorenylmethoxycarbonyl
Gly = glycine
HBTU = *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
His = histidine
Iva = isovaline, 2-amino-2-methylbutanoic acid or 2-amino-isobutyric acid
KDA = potassium diisopropylamide
KDCA = potassium dicyclohexylamide
KHMDS = potassium hexamethyldisilylamide
Hex = hexyl
HMPA = hexamethylphosphoramide
LDA = lithium diisopropylamide
LiHMDS = lithium hexamethyldisilylamide
Mag = 2-methyl-2-allylglycine or 2-amino-2-methyl-4-pentenoic acid
MCCG = (2*S*,3*S*,4*S*)-2-methyl-2-(carboxycyclopropyl)glycine
αM4CPG = 2-methyl-2-(4-carboxyphenyl)glycine
MPPG = 2-methyl-2-(4-phosphonophenyl)glycine
(αMe)Aoc = 2-amino-2-methyloctanoic acid
(αMe)Asn = α-methyl asparagine
(αMe)Aun = 2-amino-2-methylundecanoic acid
(αMe)Chg = α-methyl-α-cyclohexylglycine
(αMe)Dip = 2-methyl-2-diphenylmethylglycine
(αMe)Nva = α-methylnorvaline or 2-amino-2-methylpentanoic acid
(αMe)Phe = α-methylphenylalanine
(αMe)Phg = α-methylphenylglycine
(αMe)Ppp = α-methyl-4-phosphonophenylalanine
(αMe)Val = α-methylvaline
Moc = methoxycarbonyl
MOM = methoxymethyl
MPM = *p*-methoxyphenylmethyl
NaHMDS = sodium hexamethyldisilylamide
NBS = *N*-bromosuccinimide
NMO = 4-methylmorpholine-*N*-oxide
NMP = 1-methyl-2-pyrrolidone
PBA = pyridine-2-carboxylic acid(2-formyl-phenyl)amide
PBP = pyridine-2-carboxylic acid(2-benzoyl-phenyl)amide
Oct = octyl
Pent = pentyl
Ph = phenyl
Phe = phenylalanine
PLE = pig liver estearase
PMB = *p*-methoxybenzyl
Ppp = 4-phosphonophenylalanine
Pr = propyl
$^{i}$Pr = isopropyl
Py = pyridine
ROPHy = (*R*)-*O*-1-phenylbutylhydroxylamine
rt = room temperature
SEM = 2-(trimethylsilyl)ethoxymethyl
SRS = self-regeneration of stereocentres
TBAB = tetrabutylammoniumbromide
TBAF = tetrabutylammoniumfluoride
TBAI = tetrabutylammoniumiodide
TBPB = tetrabutylphosphomiumbromide
TBDPS = *tert*-butyldiphenylsilyl
TBS = *tert*-butyldimethylsilyl
TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate

TBTU = *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate
Tf = trifluoromethanesulfonyl
TFA = trifluoroacetic acid
TFAA = trifluoroacetic anhydride
TFEA = trifluoroethyl trifluoroacetate
THF = tetrahydrofuran
TMSCN = trimethylsilyl cyanide
TPS = *tert*-butyldiphenylsilyl
Trp = tryptophan
Ts = *p*-toluenesulfonyl
Tyr = tyrosine
Val = valine
Z = benzyloxycarbonyl

## 19. Note added in proof

After the submission of this manuscript an excellent review on the asymmetric synthesis of α,α-disubstituted α-amino acids has appeared in Organic Biomolecular Chemistry [Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406–430].

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