Recent approaches towards the asymmetric synthesis of α,α-disubstituted α-amino acids

Henning Vogt[a] and Stefan Bräse*[b]

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The class of α,α-disubstituted α-amino acids has gained considerable attention in the past decades and continues doing so. The ongoing interest in biological and chemical properties of the substance class has inspired the development of many new methodologies for their asymmetric construction, which have not found their way into the general focus of organic chemistry yet. The aim of this review is to provide an overview of the developments in the field since 1998.

Introduction

Amino acids and their derivatives play a central role in the design of life. The importance of the twenty proteinogenic L-amino acids as building blocks in peptides and proteins is self-evident, but also the class of non-proteinogenic α,α-disubstituted α-amino acids has moved into the focus of biochemical research, drug discovery, and even geochemistry. Thus, α,α-disubstituted α-amino acid residues have been found to exhibit a pronounced helix-inducing potential when present in peptides. This property is for example responsible for the membrane destabilisation exerted by peptaibols, a class of peptidic broad-spectrum antibiotics.[1,2]

[a]*Center for Sustainable and Green Chemistry, Department of Chemistry, Building 201, Technical University of Denmark, DK-2800, Lyngby, Denmark*
[b]*Institute of Organic Chemistry, University of Karlsruhe (TH), Fritz-Haber-Weg 6, D-76131 Karlsruhe, Germany*

Moreover, peptides containing α,α-disubstituted α-amino acid residues were found to often display enhanced resistance against chemical[3] and enzymatic[4] degradation. This led to the exploitation of this substance class for the elucidation of various receptor models,[5] as well as the structural optimisation of potential receptor ligands, not only peptides,[6] but also conformationally related compounds, which were accordingly named peptidomimetics or peptoids.[7]

Other α,α-disubstituted α-amino acids are capable of acting as enzyme inhibitors, by mimicking the ligand properties of their natural analogues, but preventing subsequent enzymatic reaction due to their increased rigidity or their inability to form enolate intermediates.[8] α-Methyl-4-carboxyphenylglycine (M4CPG) was the first compound reported to express antagonist action at group II and group III metabotropic glutamate receptors.[9] Following the discovery of the potency of M4CPG, a whole range of mutations was carried out on the initial structure to obtain more detailed

Henning Vogt was born in Koblenz, Germany in 1975. He received his diploma in chemistry from the RWTH Aachen in 2002 and changed to the University of Bonn for his postgraduate studies under the supervision of Stefan Bräse, where he received his PhD in 2006 for his work on organocatalytic strategies towards α,α-disubstituted α-amino acids. He is currently holding a post-doctoral position in Robert Madsen's group at the Technical University of Denmark.

Henning Vogt

Stefan Bräse

Stefan Bräse was born in Kiel, Germany in 1967. He studied at the Universities of Göttingen, Bangor (UK) as well as Marseille. He received his PhD in 1995 after working with Armin de Meijere in Göttingen. After post-doctoral appointments at Uppsala University (Jan E. Bäckvall) and The Scripps Research Institute (K. C. Nicolaou) as DAAD fellow, he began his independent research career at the RWTH Aachen in 1997 (associated to Dieter Enders). In June 2001, he finished his Habilitation and moved to the University of Bonn as a Professor of Chemistry. Since 2003, he has held a chair at the University of Karlsruhe (TH). He was the recipient of the OrChem prize of the Gesellschaft Deutscher Chemiker (2000) and Eli Lilly Lecturer (2001).

information about structure–activity relationships. In the field of plant protection research, (*S*)-fenamidone was found to be a highly efficient fungicide.[10]

On a more academic level, L-isovaline (Iva), the least complex chiral α,α-disubstituted α-amino acid, has gained considerable attention, after samples of organic material obtained from carbonaceous meteorites were found to contain traces of this compound in up to 15% ee.[11]

The growing interest in α,α-disubstituted α-amino acids motivated extensive research into the development and refinement of efficient methods for their preparation. Although a number of asymmetric strategies, such as Schöllkopf's bislactim ether method[12] or Seebach's self-reproduction of stereocentres (SRS),[13] can undeniably be regarded as classic approaches in asymmetric synthesis, and nowadays are established as regulars in chemistry text books, the construction of the fully substituted stereocentre in α,α-disubstituted α-amino acids still constitutes a challenge for the organic chemist. Therefore, the field of α,α-disubstituted α-amino acid synthesis has lost none of its attractiveness and remains growing to the present day. A comprehensive review about synthetic approaches towards α,α-disubstituted α-amino acids was published by Cativiela and Díaz-de-Villegas in two parts in 1998 and 2000.[14,15] Since then, astonishing progress has been achieved by the introduction of modern strategies, most of which have not been covered in any review yet. The present article will therefore comprise literature published after 1998. Due to the almost infinite amount of literature in the field of amino acid synthesis, this review will be limited to approaches dealing with the asymmetric construction of the fully substituted stereocentre in α,α-disubstituted α-amino acids. It will therefore not consider reactions leading to achiral or racemic products, resolution processes, enzymatic or biological methods, or derivatisations of α,α-disubstituted α-amino acids, which have been previously prepared by known procedures, although many noteworthy contributions have certainly also been made in these areas.

Most approaches that have been devised for the asymmetric synthesis of α,α-disubstituted α-amino acids can be divided into three categories, depending on the nature of the bond which is formed in the asymmetric step. Thus, it is possible to formally attach either one of the two alkyl substituents to the central carbon atom of the task compound (Fig. 1, path A). This is most often accomplished by electrophilic alkylation of amino acid enolate equivalents. Especially catalytic approaches have received considerable attention in recent years, but also auxiliary-controlled methods keep on emerging, as will be shown in Section 1. On the other hand, one of the two functional groups—amino group (path B) or carboxylic group (path C)—may be introduced into the molecule in the asymmetric step. The asymmetric construction of the C–N bond in α,α-disubstituted α-amino acids by electrophilic α-amination (path B) has gained attention only in recent years, largely due to the emergence of organocatalytic procedures. This will be discussed in Section 2. Although asymmetric variants of the Strecker synthesis—formally introducing the carboxylic group into the molecule—were developed very early in the history of asymmetric synthesis, impressive progress has been made since asymmetric catalytic variants started to emerge in the mid-nineties of the last century. Section 3 is dedicated to these efforts as well as methods involving the nucleophilic alkylation of C–N multiple

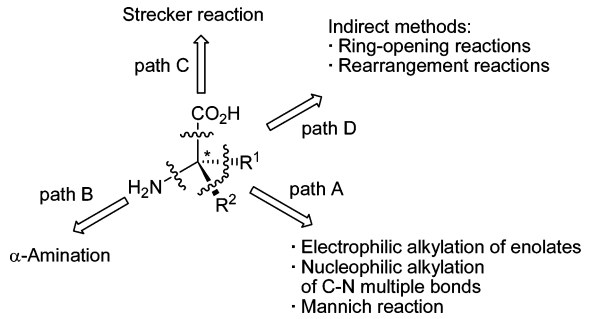
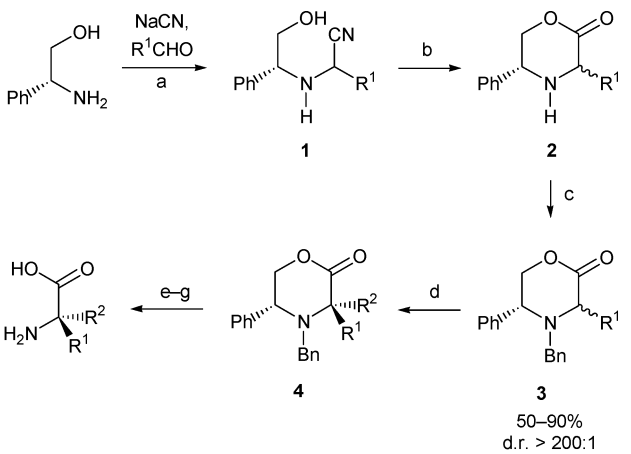


Fig. 1 Possible approaches towards α,α-disubstituted α-amino acids.

bonds (Fig. 1, path A). Path D comprises indirect methods, which may partly also be classified as belonging to one of the previous categories, but are more conveniently described as a class of their own, since they usually involve stereospecific transformations of existing stereocentres. These methods are presented in Section 4.

1 Electrophilic alkylation of amino acid enolates

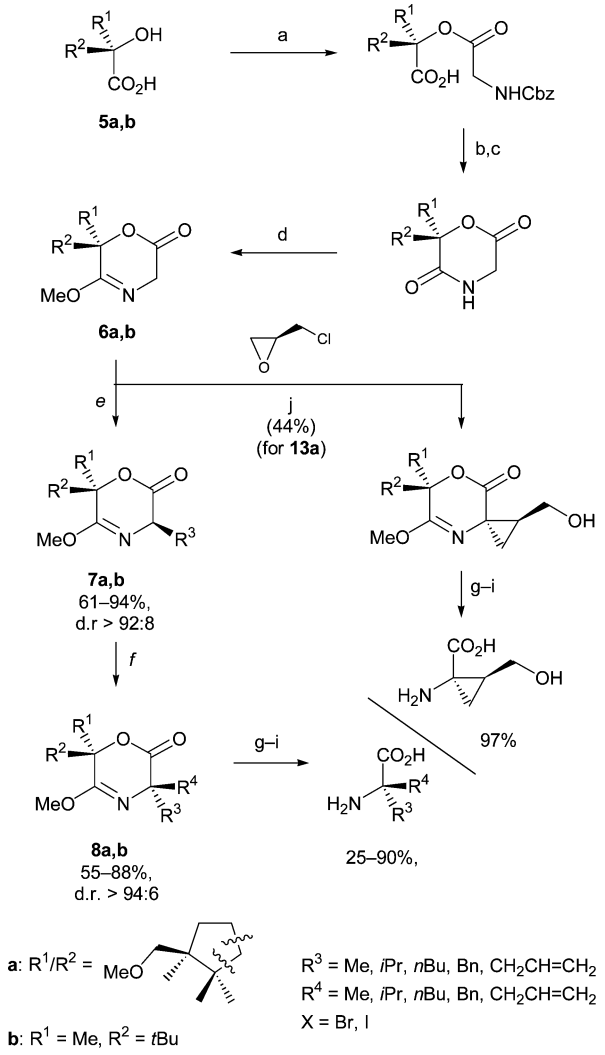
By far the most strategies that have been developed for the asymmetric synthesis of α,α-disubstituted α-amino acids involve the electrophilic α-alkylation of amino acid enolate equivalents.[14] Ma and Ding demonstrated that oxazinones **2**, which were derived from the Strecker products **1**, can be used as substrates for the diastereoselective alkylation towards α,α-disubstituted α-amino acids (Scheme 1).[16] The alkylation of the benzyl-protected oxazinone **3** with electrophiles delivered the dialkylated species **4** in diastereomeric ratios over 200 : 1. The incoming electrophile was generally directed to the *cis*-position relative to the auxiliary phenyl group, with the exception of methyl bromoacetate. Aldehydes were also applied in the reaction with **3**, resulting in two



Scheme 1 Alkylation of Strecker products according to Ma and Ding.[16] *Reagents and conditions*: (a) NH_4Cl, MeOH–H_2O 1 : 1, 0 °C, 12 h; (b) HCl–MeOH, then TsOH, toluene, reflux, 2 d; (c) BnBr, K_2CO_3, DMF, 60–65 °C, 8 h (33–48%, 3 steps); (d) NaHMDS, DME, −78 °C, 1 h, then R^2X or aldehyde, 0.1–24 h; (e) NaOH–MeOH; (f) H_2 (40 atm), Pd/C, EtOH, 40 °C, 36 h; (g) Dowex-50W (62–80%, 3 steps).

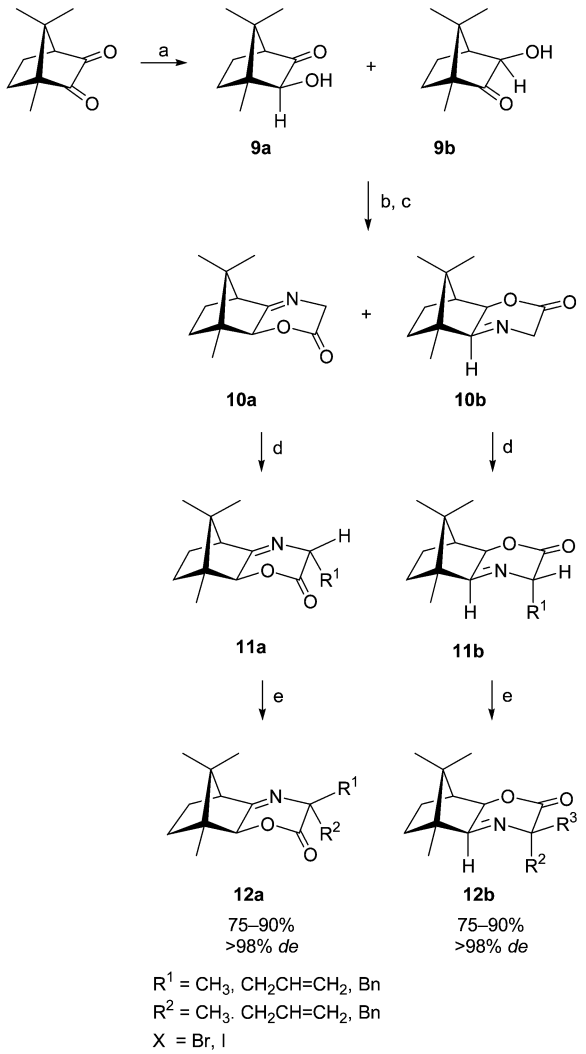
diastereomers in ratios ranging from 8 : 1 to 10 : 1, displaying opposite configuration at the secondary carbinol centre.

Wanner *et al.* introduced two related auxiliaries, **5a** and **5b**, for the derivatisation of glycine-derived Schiff base oxazolines **6a** and **6b**, which were prepared from the auxiliary in four steps (Scheme 2).[17] Deprotonation, followed by treatment with alkyl halides, afforded the monoalkylated product **7** in high diastereoselectivity. The electrophile entered the enolate *trans* to the *tert*-butyl-group (in the case of **6b**). The dialkylated products **8a**,**b** were synthesised from the monoalkylated oxazinones **7a**,**b** in an analogous reaction. Cleavage of the imidate function in **8** with TFA was followed by basic saponification to liberate the α,α-disubstituted α-amino acid. The authors also performed cyclopropanation reactions between the enolate of **6a** and enantiopure epichlorohydrin. Interestingly, the reaction did not seem to commence with the substitution of chloride, but with an addition to the terminal epoxide carbon, to result in products with unexpected stereochemistry.



Scheme 2 Alkylation of chiral oxazinones according to Wanner *et al.*[17] *Reagents and conditions*: (a) *N*,*N*′-carbonyldiimidazole, Cbz-Gly-OH, THF, rt, 4 h, then 12, rt, 20 h (86–96%); (b) H_2, Pd/C, EtOH, rt, 12 h (88–96%); (c) 2-chloro-1-methylpyridinium iodide, Et*N*iPr_2, CH_2Cl_2, reflux, 4 h (84–89%); (d) Me_3O^+ BF_4^-, CH_2Cl_2, rt, 12 h (89–91%); (e) *s*BuLi, THF, −78 °C, 30 min, then R^3X, −78 °C, 12 h; (f) *s*BuLi, −78 °C, 30 min, then R^4X, −78 °C, 12 h; (g) TFA–H_2O, 60 °C, 20 h; (h) $NaOH_{aq}$, 20 h; (i) Dowex; (j) NaHMDS, (*S*)-epichlorohydrin, THF, −20 °C, 46 h.

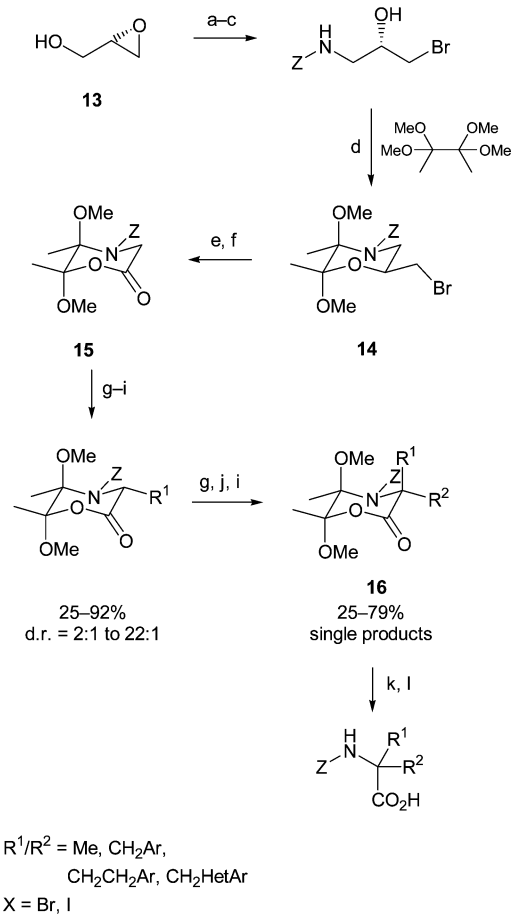
Lu *et al.* demonstrated that the camphor-based tricyclic Schiff base oxazinone **10**[18] can be dialkylated in good yield and excellent diastereoselectivity (Scheme 3).[19] The oxazinone was obtained from camphorquinone by monoreduction with sodium borohydride and subsequent cyclisation with glycine. The inseparable intermediates **9a** and **9b** were obtained in a 1 : 1.85 ratio. Oxazinones **10a** and **10b** could be isolated as pure diastereomers in a 1 : 1.59 ratio. Deprotonation of either oxazinone with lithium diisopropylamide (LDA) and subsequent alkylation delivered exclusively the *endo*-product **11a** or **11b**, which was in the next step deprotonated with a slightly higher excess of LDA and treated with a different alkyl halide to furnish the dialkylated product **12a** or **12b** in good yield and excellent diastereoselectivity. The incoming electrophile always entered the substrate in the axial



Scheme 3 Alkylation of camphor-derived oxazinones according to Lu *et al.*[19] *Reagents and conditions*: (a) $NaBH_4$, Et_2O–CH_3OH, 0 °C, 30 min (87%); (b) Z-Gly-OH, DMAP, DCC, THF, rt, 16 h (98%); (c) H_2, Pd/C, EtOH, rt, 16 h (65%); (d) LDA, THF, −30 °C, 90 min, then HMPA, R^1X, −78 °C, 12 h; (e) LDA, THF, −30 °C, 90 min, then HMPA, R^1X, −78 °C, 12 h.

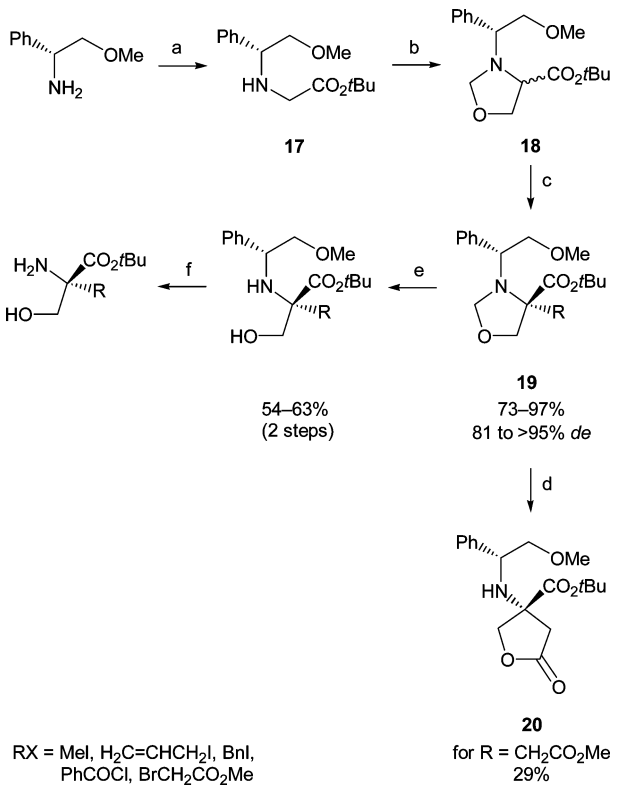
position, leading to the *endo*-product, regardless of the size of the electrophile or the order of addition. The free amino acid was finally released by successive treatment with 2 N sodium hydroxide solution at room temperature and 6 N hydrochloric acid at 92 °C. The auxiliary was recovered in good yield.

Ley *et al.* developed a six step synthesis to obtain chiral oxazinone **15** from the Sharpless epoxide **13** under self reproduction of stereocentres.[20] The entire stereochemistry of the chiral glycine equivalent **15** is solely determined by the absolute configuration of the initial epoxide. The key-step in this sequence is the cyclisation towards **14**, which makes use of the anomeric effect of the methoxy-groups to obtain the isomer shown in Scheme 4 in 10 : 1 selectivity. Deprotonation of oxazinone **15** with LDA and addition of electrophiles generally proceeded in good diastereoselectivity. However, the addition of hexamethylphosphoric triamide (HMPA) or tetramethylethylenediamine (TMEDA) was necessary to enhance reactivity. After the second deprotonation–alkylation sequence, only single diastereomers were detected. Cleavage of the dialkylated oxazinone **16** to release the *N*-protected amino acid was accomplished by treatment with aqueous TFA, followed by neutralisation with methanolic sodium hydroxide solution.



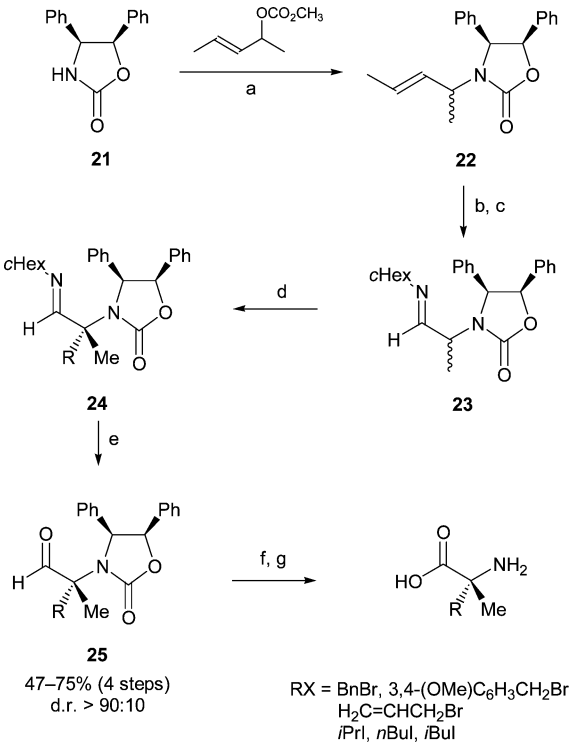
Scheme 4 Alkylation of oxazinones under self-reproduction of stereocentres according to Ley *et al.*[20] *Reagents and conditions*: (a) phthalimide, PPh_3, DTBAD, THF, reflux, 16 h; (b) 48% HBr, reflux, 16 h; (c) $ClCO_2Bn$, $EtNiPr_2$, MeOH 0 °C to rt, 2 h, (54%, 3 steps); (d) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 30 °C, 2 h (69%); (e) KHMDS, THF, −78 °C to rt, 2 h (64%); (f) $NaIO_4$, $RuCl_3$, $NaHCO_3$, H_2O–CH_3CN–CCl_4, rt (85%); (g) LDA, HMPA or TMEDA, THF, −78 °C, 1 h; (h) R^1X, −55 °C, 22 h; (i) AcOH, Et_2O, −78 °C to rt; (j) R^2X, −55 °C, 22 h; (k) TFA–H_2O, rt, 30 min; (l) 1 N NaOH–MeOH, rt, 30 min.

Serine-derivatives carrying a second alkyl-substituent in the α-position can be synthesised from glycine-derivative **17** in good yield and stereoselectivity by a protocol provided by Husson *et al.* (Scheme 5).[21] Thus, a [3 + 2]-cycloaddition with paraformaldehyde resulted in a 1 : 1 diastereomeric mixture of oxazolidine **18**, which was then deprotonated with potassium hexamethyldisilazide (KHMDS) and treated with electrophiles to give the alkylated oxazolidine **19**. Careful acidic hydrolysis and hydrogenation delivered the free serine derivative. The product arising from the reaction with methyl α-bromoacetate underwent spontaneous cyclisation towards lactone **20** upon hydrolysis.

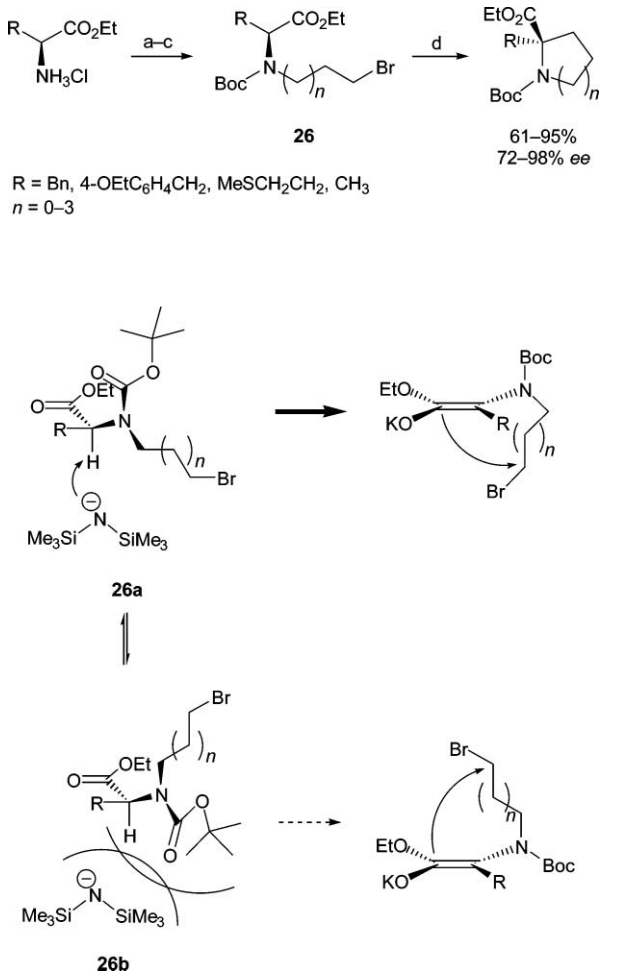


Scheme 5 Alkylation of oxazolidines according to Husson *et al.*[21] *Reagents and conditions*: (a) $BrCH_2CO_2tBu$, K_2CO_3, MeCN (73%); (b) $(CH_2O)_n$, toluene, Δ (87%); (c) KHMDS, THF, −78 °C, then RX; (d) H^+ (29–63%, 2 steps); (e) H_2, Pd/C, MeOH–HCl (79–89%).

A somewhat different approach, using the Evans-type oxazolidinone **21** as the carrier of chiral information in the synthesis of α-methylated amino acids, was chosen by Wenglowsky and Hegedus (Scheme 6).[22] After a palladium-catalysed allylic amination, compound **22** was converted to the imine **23** by ozonolysis and condensation of the resulting aldehyde with cyclohexylamine. The latter was subjected to a deprotonation–alkylation sequence to give the dialkylated imine **24**. To avoid side reactions, deprotonation had to be carried out in the presence of the electrophile and the reaction had to be quenched at low temperature. The best results were finally obtained when the whole four step sequence leading from **21** to **25** (including hydrolysis of the imine **24**) was carried out without purification of the intermediates. A number of alkylation reactions was thus carried out, leading to products in 47–75%



Scheme 6 Alkylation of imines according to Wenglowsky and Hegedus.[22] *Reagents and conditions*: (a) $Pd(PPh_3)_4$–dppe, DMF, 25 °C, 12 h (89–95%); (b) O_3, Me_2S, CH_2Cl_2, −78 °C to rt, 4 h; (c) cyclohexylamine, $MgSO_4$, CH_2Cl_2; (d) RX–KHMDS, THF, −78 °C to −45 °C; (e) HCl–THF (47–75%, 4 steps); (f) $NaClO_2$, NaH_2PO_4; (g) H_2, $Pd(OH)_2$ (82–94%, 2 steps).



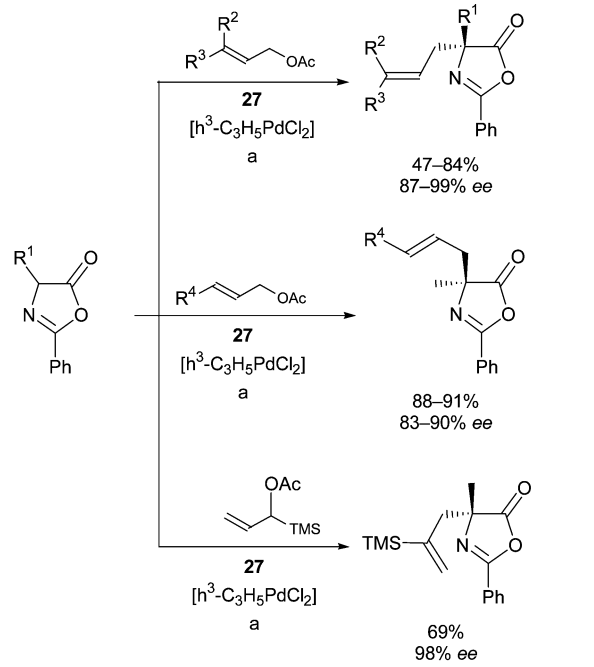
Scheme 7 Intramolecular alkylation of amino acids according to Kawabata *et al.*[23] *Reagents and conditions*: (a) $Br(CH_2)_{2+n}OH$, K_2CO_3, DMF; (b) Boc_2O, $EtNiPr_2$; (c) CBr_4, PPh_3 (63%, 3 steps); (d) KHMDS, DMF, −60 °C, 30 min.

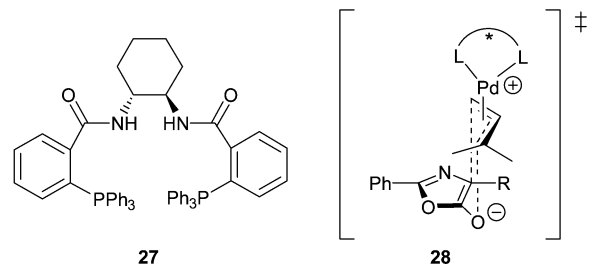
overall yield and diastereomeric ratios over 9 : 1. Conversion towards the free amino acid was achieved in two additional steps by oxidation of the aldehyde and hydrogenation.

An interesting self-reproductive approach towards cyclic α-alkylated amino acids was presented by Kawabata *et al.* (Scheme 7)[23] Thus, intramolecular alkylation of *N*-Boc-protected amino acids **26** delivered the cyclic products in good to excellent yield and enantioselectivity. KHMDS proved to be superior over lithium bases such as LiHMDS or lithium tetramethylpiperidide (LTMP) for deprotonation. This method allowed not only for the synthesis of proline-derivatives, but also of different ring-sizes, *i.e.* four-, six-, and seven-membered ring-systems, although reaction towards the latter was significantly slower, and a decay in stereoselectivity was noted with increasing reaction time. The authors attributed the at first glance surprising stereoselectivity to the preference of the bulky base for deprotonation of rotamer **26a** over deprotonation of rotamer **26b**, since in the latter the α-proton is shielded by the bulky protective-group.

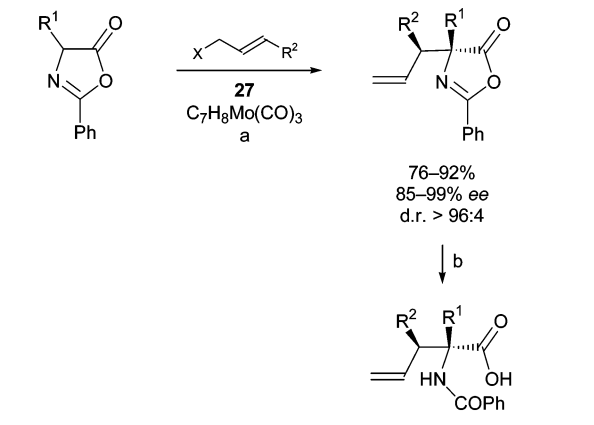
Azlactones (3-oxazolin-5-ones), which can be regarded as cyclic Schiff bases, have only been recognised as suitable substrates for asymmetric amino acid synthesis since asymmetric catalysis allowed for the introduction of the stereoinformation into the target compound by means of a chiral catalyst. Thus, the palladium-catalysed allylic alkylation of azlactones with asymmetric, 1-monosubstituted or 1,1-disubstituted allyl species in the presence of C_2-symmetric ligands such as **27** delivered products in more than 90% ee (Scheme 8).[24] Terminally unsymmetrically substituted allylating species led to *E*–*Z*-mixtures, with the *Z*-product displaying high enantiomeric excess. Silylated allylating agents were partly desilylated, and in some cases the formation of regioisomers was observed. Facial discrimination in the coordination of the allylic species to the metal centre, in combination with the minimalisation of charge separation in transition state **28**, is thought to be responsible for the selectivity observed. Interestingly, the reaction with prenylating agents displayed opposite stereoselectivity to that observed in the reaction with cinnammylating species. This was explained by steric interactions between the larger allyl-substitutents and the ligand in the catalyst's coordination sphere, resulting in a different transition state and, consequently, a different facial selectivity for the azlactone. The palladium-catalysed allylic alkylation of azlactones was successfully utilised in the total synthesis of sphingofungin F.[25] The regioselectivity of the reaction could be generally altered to result in β-branched products by exchange of palladium for molybdenum (Scheme 9).[26]

The direct palladium-catalysed allylic alkylation of α-acetamido-β-ketoesters **29** to result in α,α-disubstituted α-amino acid esters was demonstrated by Kuwano and Ito (Scheme 10). Using (*R*)-BINAP as the ligand, they obtained α-alkylated products in good yields and enantiomeric excess.[27]

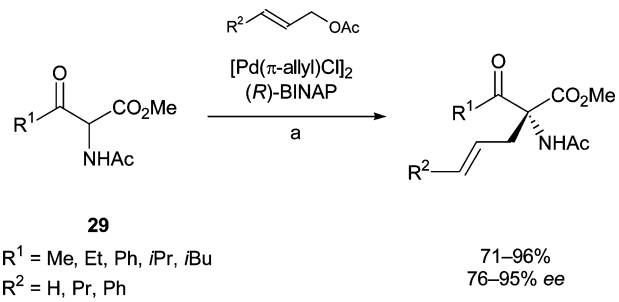




Scheme 8 Palladium-catalysed allylic alkylation of azlactones according to Trost *et al.*[24] *Reagents and conditions*: (a) NEt_3, toluene, rt, 3 h–3 d.



Scheme 9 Molybdenum-catalysed allylic alkylation of azlactones according to Trost *et al.*[26] *Reagents and conditions*: (a) LDA, THF, 0 °C, 3–6 h; (b) MeOH–K_2CO_3 (quant. for Ar = Ph, R = CH_3).



Scheme 10 Palladium-catalysed allylic alkylation of α-amino-β-ketoesters according to Kuwano and Ito.[27] *Reagents and conditions*: (a) *t*BuOK, toluene, −30 °C.

The past 15 years have witnessed a number of interesting developments in the field of phase transfer catalysis (PTC).[28,15b] This approach generally involves the alkylation of amino acid enolates, derived from Schiff bases with inorganic bases such as sodium hydroxide or sodium hydride in organic solvents. Since O'Donnell first introduced cinchona-derived quaternary ammonium catalysts for the synthesis of α-alkylated alanine derivatives in up to 50% ee,[29] considerable improvement has been achieved by the introduction of new catalysts, such as the modified cinchonidinium catalyst **30a**[30] and **30b**,[31] TADDOL (**31**),[32] and NOBIN (**32**) (Fig. 2).[33] While these catalysts were all used for the alkylation of alanine-derived Schiff bases only, copper(II)–salen complex **33**[34] has also been applied in the alkylation of amino acids carrying α-substituents different from a methyl-group.[34c,35] The latter variant also provides the advantage that readily available amino acid methyl esters can be used as substrates without any significant loss in stereoselectivity compared to bulkier isopropyl or *tert*-butyl esters, which proved to be essential for high enantioselectivity in earlier PTC reactions.

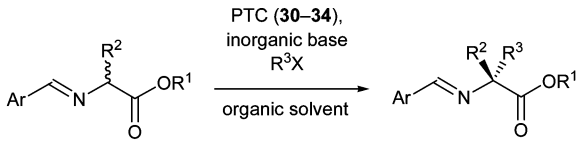
The latter advantage also applies to the C_2-symmetric quaternary ammonium salt **34a**, which was found to be a very potent catalyst for the stereoselective sequential double alkylation of glycine-derived Schiff bases, as well as the alkylation of alanine-, isobutyl- and phenylglycine-derivatives.[36] An interesting example in this context is the synthesis of cyclic amino and imino acids **35** and **36**, respectively, as shown in Scheme 11.[37]

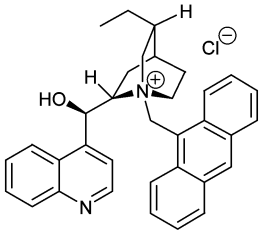
Jew and Park showed that the closely related catalyst **34b** can be used for the synthesis of α-alkylated serine derivatives (Scheme 12).[38] The oxazoline moiety in **37** fulfilled a twofold function: the activation of the α-proton and protection of the side chain hydroxy group. While the alkylation with ethyl iodide proceeded only in moderate yield, activated electrophiles such as allylic, propargylic, or benzylic halides gave yields above 85%, with generally excellent enantioselectivity. Hydrolysis of the benzylated product with 6 M hydrochloric acid proceeded in 98% yield.

The same catalyst, **34b**, was also used for the stereoselective alkylation of cyclic α-amino-β-ketoesters **39** (Scheme 13).[39] Thus, reaction with different electrophiles in a 4 : 3-mixture of *o*-xylene and saturated aqueous potassium carbonate solution delivered the α-alkylated products in high yield and enantiomeric excess.

Catalyst **34c** allowed for the enantioselective modification of *N*-terminal amino acid residues in dipeptide **38a**,[40] as well as alanine- and phenylalanine-derived amides **38b** (Scheme 14).[41]

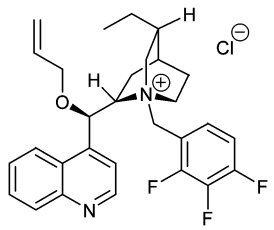
Shibasaki *et al.* introduced the tartrate-derived diammonium salt (TaDiAS) **41** as phase transfer-catalyst for the alkylation





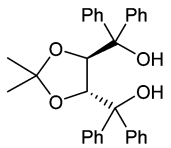
30a
(Lygo *et al.*)
58–95%
19–87% *ee*

Ar = 4-ClC_6H_4
R^1 = *t*Bu, R^2 = Me
R^3 = Bn, 2-$NaphCH_2$,
4-$ClC_6H_4CH_2$, *t*$BuOCOCH_2$
X = Br,I



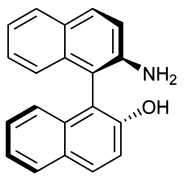
30b
(Jew, Park, *et al.*)
86–93%
84–96% *ee*

Ar = 2-Naph
R^1 = *t*Bu, R^2 = Me
R^3 = H_2C=$CHCH_2$, $H_2CC{\equiv}CCH_2$,
4-$BrC_6H_4CH_2$, 4-*t*$BuC_6H_4CH_2$,
4-$CF_3C_6H_4CH_2$, 2-$FC_6H_4CH_2$,
2,4-$FC_6H_3CH_2$, 2,6-$FC_6H_3CH_2$,
3-$MeC_6H_4CH_2$, 1-$NaphCH_2$
X = Cl, Br



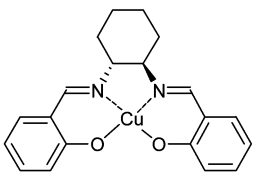
TADDOL, **31**
(Belokon *et al.*)
81–91%
75–82% *ee*

Ar = Ph
R^1 =iPr, R^2 = Me
R^3 = Bn, H_2C=$CHCH_2$
X = Br



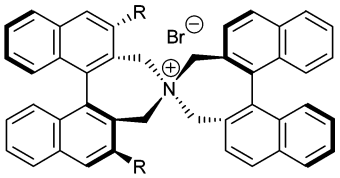
NOBIN, **32**
(Belokon *et al.*)
60–>90%
18–68% *ee*

Ar = Ph
R^1 = *i*Pr, R^2 = Me
R^3 = Bn, H_2C=$CHCH_2$,
1-$NaphCH_2$
X = Cl, Br



33a
(Belokon *et al.*)
25–95%
10–96% *ee*

Ar = Ph, 4-ClC_6H_4,
R^1 = Me, *i*Pr, *t*Bu
R^2 = Me, Et, *i*Bu, Bn, H_2C=$CHCH_2$,
$MeOCOCH_2$, $MeOCO(CH_2)_2$
R^3 = Bn, H_2C=$CHCH_2$, H_3CCH=$CHCH_2$,
4-$FC_6H_4CH_2$, 4-$NO_2C_6H_4CH_2$,
4-$OMeC_6H_4CH_2$, 1-$NaphCH_2$,
2-$NaphCH_2$, PhCH=CH
X = Cl, Br



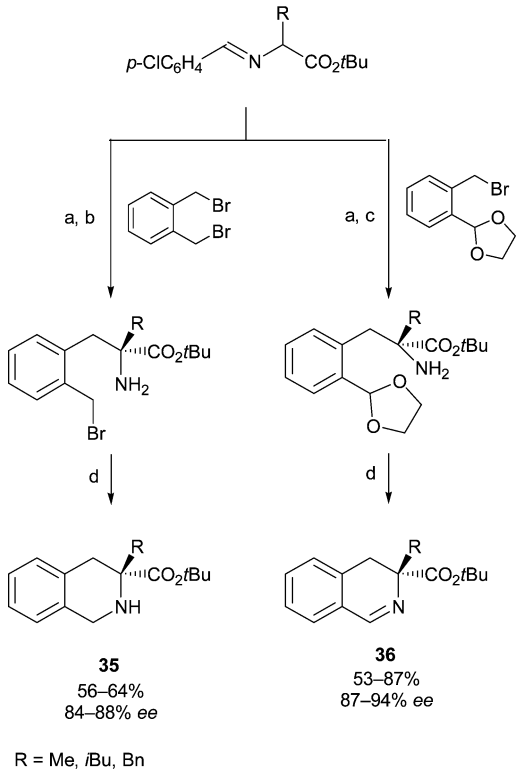
34a: R = 3,4,5-FC_6H_2
b: R = 3,5-$CF_3C_6H_3$
c: R = 3,5-(3,5-*t*BuC_6H_3)C_6H_3
(Maruoka *et al.*)
58–89%
82–99% *ee*

Ar = 4-ClC_6H_4,
R^1 = Me, Et, *t*Bu
R^2 = Me, Ph, Bn, *i*Bu, H_2C=$CHCH_2$
R^3 = Et, *t*$BuOCOCH_2$, Bn, H_2C=$CHCH_2$,
H_2C=$C(CH_3)CH_2$, $H_2CC{\equiv}CCH_2$,
1-$NaphCH_2$, PhCH=$CHCH_2$,
N-Boc-2-indolylmethyl
X = Cl, Br

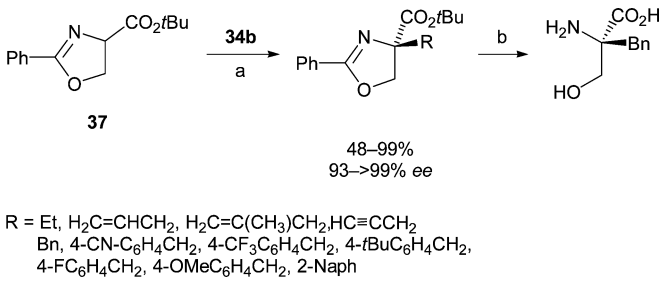
Fig. 2 Phase transfer-catalysts for the alkylation of amino acid-derived Schiff bases.[30–36]

of alanine-derived Schiff bases **40** (Scheme 15).[42] Interestingly, the tetrafluoroborate catalyst proved to be considerably more powerful than the originally employed iodide in the alkylation of both glycine- and alanine-derived Schiff bases. This effect even applied under phase transfer conditions using excess hydroxide. However, considerably prolonged reaction times were required for the alkylation of alanine-derived **40** under optimised conditions in comparison to α-unsubstituted Schiff bases. Based on molecular orbital calculations, the authors suggested that the catalyst provides a chiral environment by forcing the substrate enolate into the *Z*-configuration through fixation of the two cationic moieties *via* hydrogen bonding to the α-methylene units.

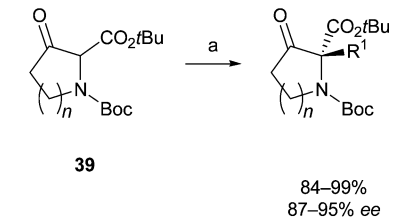
Takemoto *et al.* demonstrated the application of an achiral palladium-catalyst in combination with the chiral phase transfer-catalyst **42** for the asymmetric allylic alkylation of amino acid-derived Schiff bases (Scheme 16).[43] Apart from glycine equivalents, also the alanine imino ester **40** was alkylated with allylic acetate in moderate yield but good enantiomeric excess.



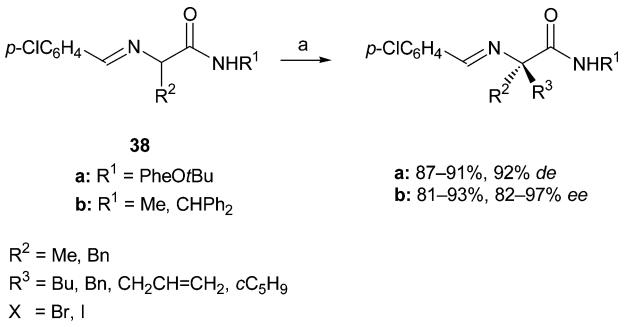
Scheme 11 Synthesis of benzocyclic amino acids by PTC according to Maruoka *et al.*[37] *Reagents and conditions*: (a) **34a** (1 mol%), $CsOH{\cdot}H_2O$, toluene, 0 °C, 0.5–1 h; (b) 0.5 M citric acid; (c) 1 N HCl–THF; (d) $NaHCO_3$.



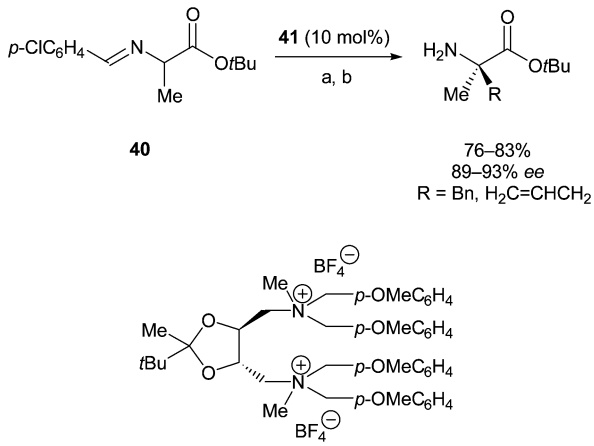
Scheme 12 PTC alkylation of oxazolines according to Jew and Park.[38] *Reagents and conditions*: (a) **34b**, RX (X = Br, I), KOH, toluene, 0 °C, 3–20 h; (b) 6 M HCl (98%).



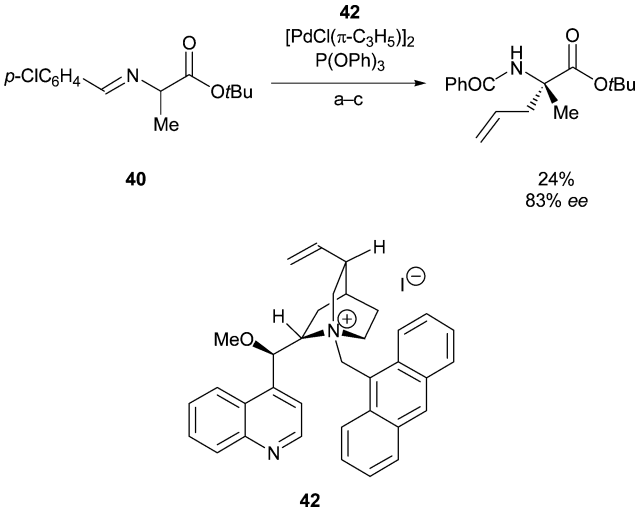
Scheme 13 PTC alkylation of cyclic α-amino-β-ketoesters according to Maruoka *et al.*[39] *Reagents and conditions*: (a) **34b** (1 mol%), R^1X, satd. K_2CO_3–H_2O, *o*-xylene, 0 °C, 3–24 h.



Scheme 14 PTC alkylation of amides according to Maruoka *et al.*[40,41] *Reagents and conditions*: (a) **34c** (2 mol%), R^3X, $CsOH{\cdot}H_2O$, toluene, 0 °C, 1–10 h.



Scheme 15 PTC alkylation of Schiff bases according to Shibasaki *et al.*[42] *Reagents and conditions*: (a) RX, $CsOH{\cdot}H_2O$, toluene–CH_2Cl_2, −70 °C, 148–168 h; (b) 0.2 M citric acid, THF, rt, 1 h.

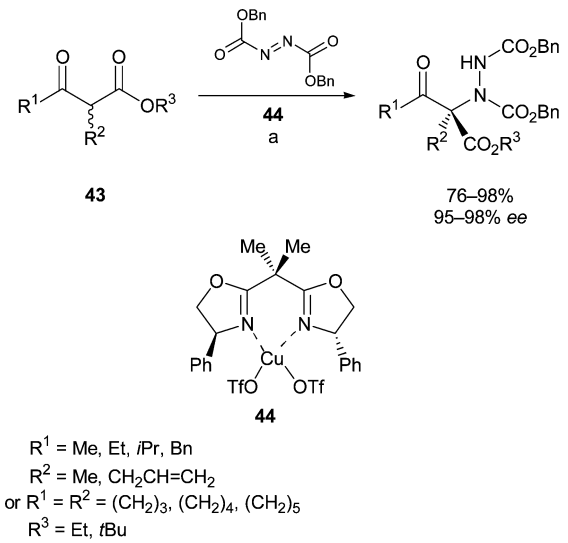


Scheme 16 Combined PTC and palladium-catalysed allylic alkylation of Schiff bases acccording to Takemoto *et al.*[43] *Reagents and conditions*: (a) Allylic acetate, 50% KOH–H_2O, toluene, 0 °C; (b) 15% citric acid; (c) PhCOCl, Et_3N.

2 Electrophilic α-amination of α-branched carbonyl compounds

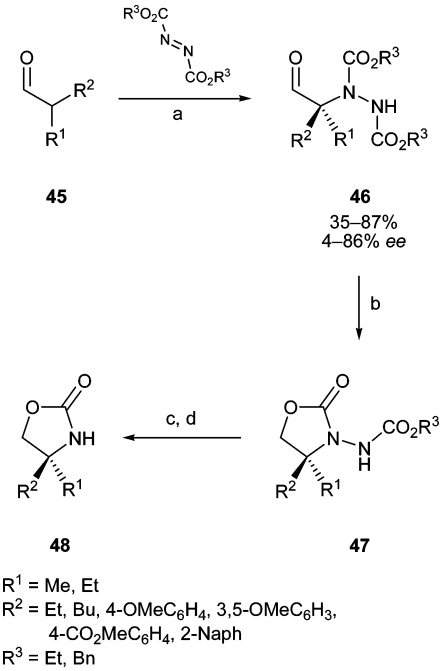
Although a multitude of approaches have been devised in the past to utilise nitrogen electrophiles, such as chiral and achiral nitroso compounds, oxaziridines, sulfonyloxycarbamates, sulfonyl azides, and especially azodicarboxylates for the asymmetric α-amination of carbonyl compounds under "umpolung" principles,[44] only a few considered the possibility of using α-branched substrates in order to open access to α,α-disubstituted α-amino acids,[45] before organocatalytic strategies were developed for this task.[46]

Jørgensen *et al.* reported on the use of Cu(II)-BOX complex **44** in the reaction of different racemic α-alkyl-β-ketoesters **43** with diethyl azodicarboxylate (DEAD) and dibenzyl azodicarboxylate (DBAD) to obtain products in excellent yield and enantiomeric excess (Scheme 17).[47] A variety of different substitution patterns for the starting material were evaluated, making this reaction the first general approach towards α,α-disubstituted α-amino acids *via* α-amination of α-branched carbonyl species. This approach was later extended to include different cyclic α-acylated ketones as substrates.[48]



Scheme 17 First general strategy towards α,α-disubstituted α-amino acids *via* electrophilic α-amination according to Jørgensen *et al.*[47] *Reaction conditions*: (a) CH_2Cl_2, rt, 16 h.

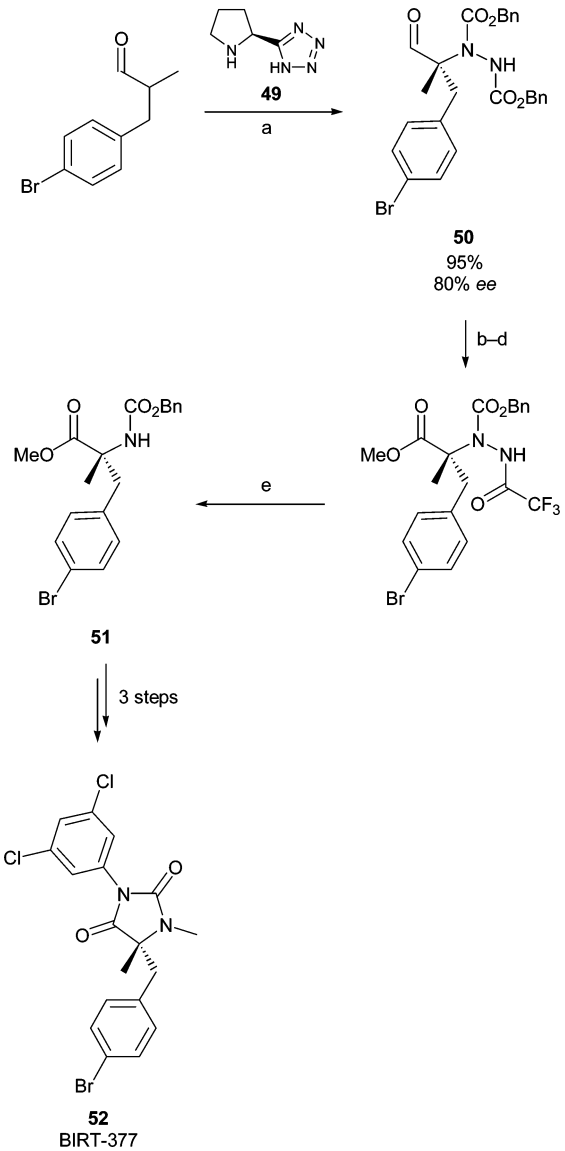
In 2002, List and Jørgensen simultaneously reported on the proline-catalysed α-amination of α-monosubstituted aldehydes with azodicarboxylates to give α-monosubstituted amino acid-derivatives in excellent yields and enantioselectivity.[49] Seeing the potential of this reaction for the preparation of more demanding α,α-disubstituted α-amino acid derivatives, the applicability of this reaction to racemic α,α-disubstituted aldehydes **45** was explored in our group (Scheme 18).[50] The reaction with DEAD and DBAD in dichloromethane proceeded in good yields and enantioselectivities up to 86% ee, thus representing the first example for the successful utilisation of α,α-disubstituted aldehydes in enamine catalysis. The stereoselectivity of the reaction, however, only reached satisfying levels, when the α-carbon was directly substituted by an aryl-group. Moreover, the reaction time was considerably prolonged in



Scheme 18 First organocatalytic α-amination of α,α-disubstituted aldehydes.[50] *Reagents and conditions*: (a) L-Proline, CH_2Cl_2, rt, 2.5–9 d; (b) $NaBH_4$, CH_2Cl_2–EtOH, 0 °C, 30 min (for R^3 = Bn); (c) H_2, Pd/C, AcOH–MeOH, rt, 12 h (76%, for R^1 = Me, R^2 = Ph); (d) $NaNO_2$, AcOH–HCl, reflux, 30 min (59%).

comparison to α-monosubstituted aldehydes, indicating that the acceleration of the reaction rate observed for the reaction of linear aldehydes did not apply in that case.[51] While *in situ*-reduction had to be carried out on the α-monosubstituted amination products, due to their susceptibility to racemisation, the α-aminated α,α-disubstituted aldehydes **46** were configurationally stable, due to the absence of an acidic α-proton. If nevertheless reduction with sodium borohydride was carried out after completion of the amination reaction, the product in most cases underwent spontaneous cyclisation to form oxazolidinone **47**. In the cases in which DBAD had been used in the amination step, the free oxazolidinones **48** could be obtained by hydrogenation and subsequent treatment with sodium nitrite. Unfortunately, oxazolidinone **48** proved to be extremely resistant against any attempt at opening. Moreover, although oxidation of the aldehyde **46** towards the corresponding acid is easily achieved, the conversion of the hydrazide towards the free amino acid was generally found to be rather tedious and inefficient, thus imposing a limit on the feasibility of the method.

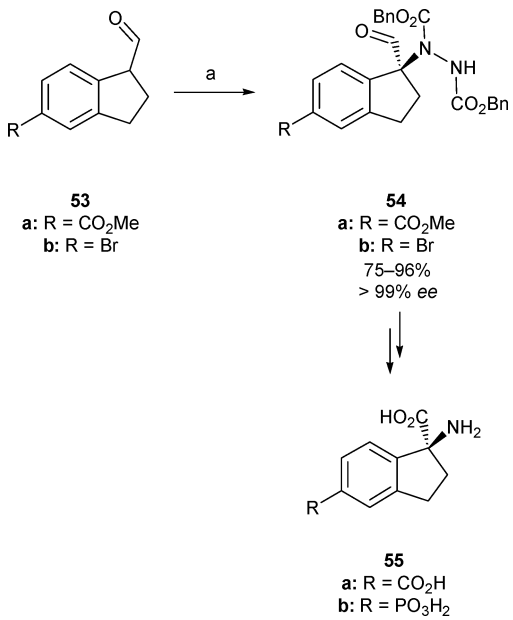
The problem connected to the conversion of the amination product towards the free amino acid was addressed by Barbas *et al.* in the total synthesis of cell adhesion inhibitor BIRT-377 (**52**, Scheme 19).[52] Using tetrazole-catalyst **49** instead of proline, they managed to synthesise the aminated aldehyde **50** in 95% yield and 80% ee. Recrystallisation delivered the enantiopure product in 71% yield. After oxidation and esterification, the corresponding amino ester was subjected to a *one pot*-trifluoro acetylation–selective benzyloxycarbonyl deprotection sequence to give, after treatment with samarium iodide, the Cbz-protected amino acid **51**. The task compound **52** was then obtained in three additional steps.



Scheme 19 Organocatalytic α-amination in the synthesis of BIRT-377 by Barbas *et al.*[52] *Reagents and conditions*: (a) DBAD, CH_3CN, rt, 3 h; (b) $NaClO_2$, 4 °C, 12 h (86%); (c) $TMSCHN_2$ (99%); (d) Tfa_2O, pyridine, 40 °C, 16 h (99%); (e) SmI_2, 30 min (98%).

Barbas further extended the scope of this reaction type with the synthesis of the metabotropic glutamate receptor ligands (*S*)-AIDA (**55a**) and (*S*)-APICA (**55b**) from aldehydes **53a** and **53b** (Scheme 20). In these syntheses, L-proline proved to be a highly efficient catalyst, providing **54a** and **54b** in excellent yield and enantioselectivity.[53]

In 2004, several groups introduced cinchona-alkaloid derivatives **56–58** as highly efficient organocatalysts for the α-amination of α-substituted α-cyanoacetates (Fig. 3) and β-dicarbonyl compounds (Fig. 4) with azodicarboxylates. Thus, Jørgensen *et al.* reported β-isocupreidine (β-ICD, **56**) to catalyse the α-amination of α-substituted α-cyanoacetates in excellent yields and enantioselectivities (Fig. 3).[54] The combination of di-*tert*-butyl azodicarboxylate (D*t*BuAD) and the *tert*-butyl ester at low temperatures (−78 °C) proved to be the most favourable for high conversion and selectivity, although higher temperatures, such as −20 °C or



Scheme 20 Organocatalysed α-amination in the synthesis of (*S*)-AIDA and (*S*)-APICA by Barbas *et al.*[53] *Reagents and conditions*: (a) L-Proline, DBAD, CH_3CN, rt, 3 h.

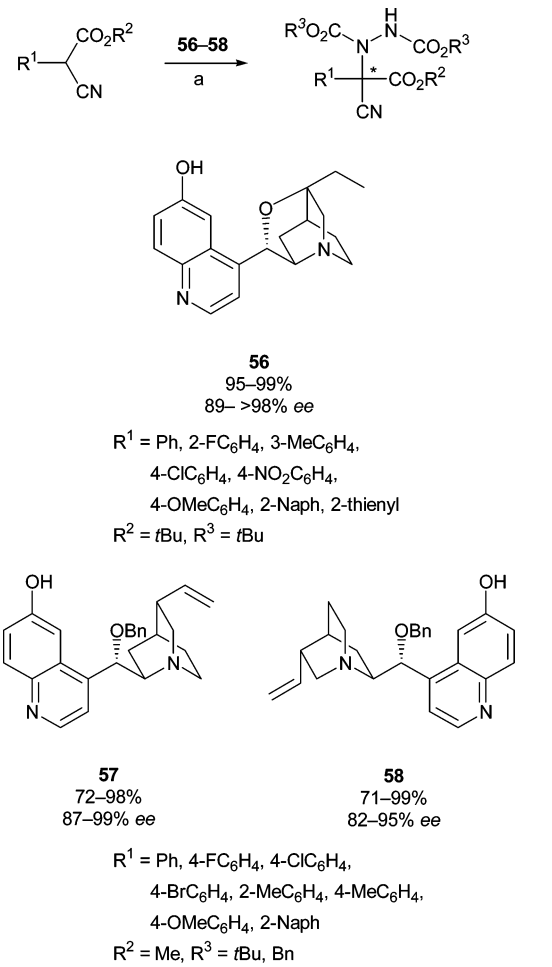


Fig. 3 Cinchona-derived organocatalysts for the α-amination of α-cyanoesters. *Reagents and conditions*: (a) DBAD (R^3 = Bn) or D*t*BuAD (R^3 = *t*Bu), toluene, −78 to −50 °C.

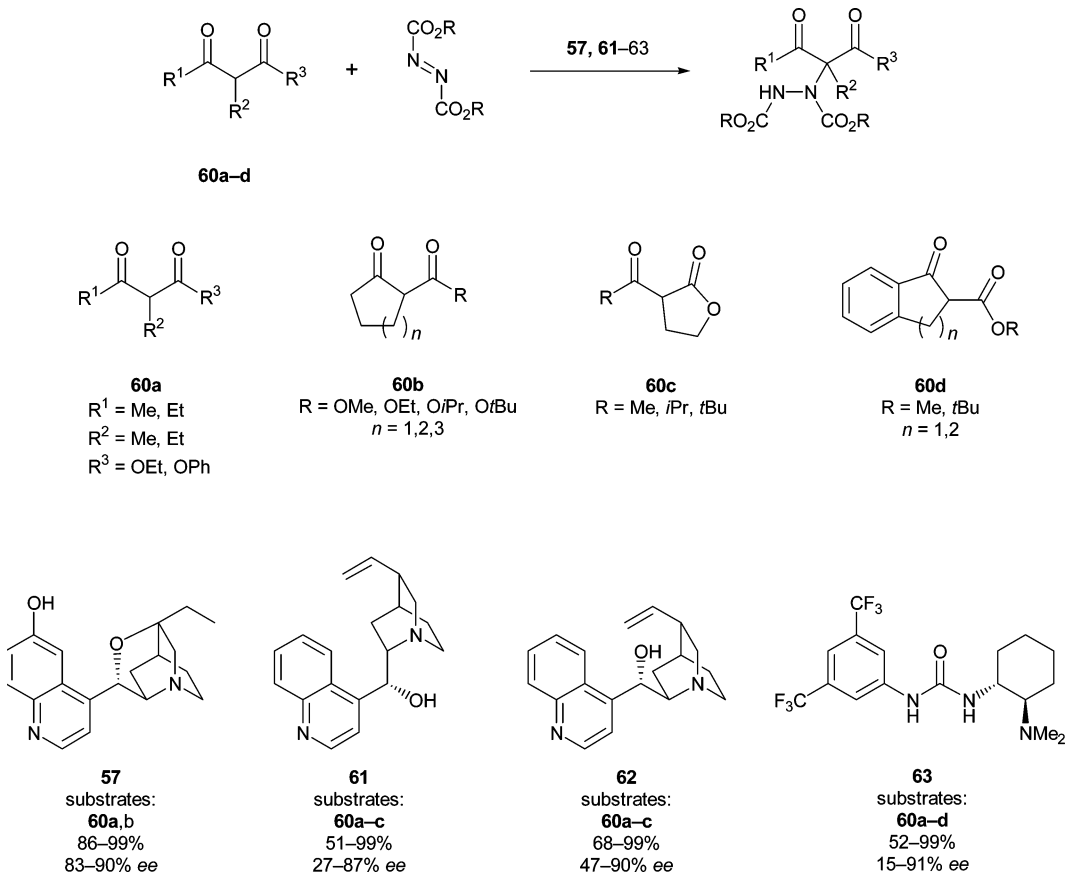
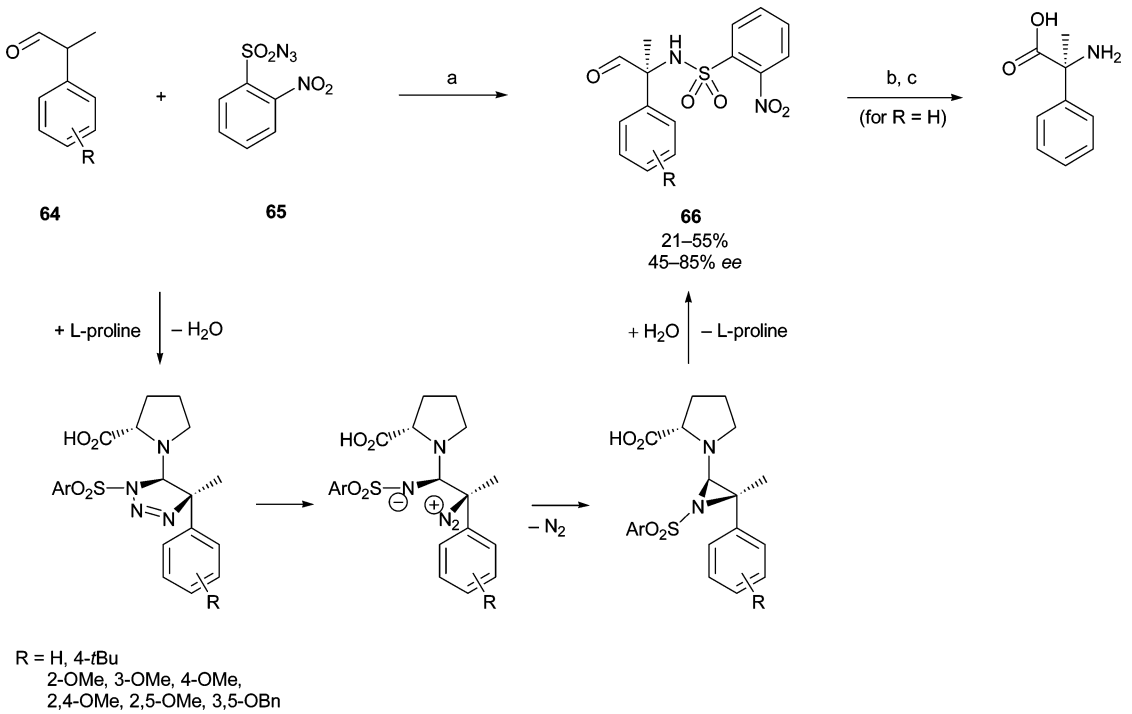


Fig. 4 Organocatalysed α-amination of β-ketoesters and appropriate organocatalysts.

room temperature, still led to acceptable results. The catalyst loading could be reduced to as little as 0.5 mol%. However, a much lower reaction rate was observed in this case. A wide range of α-aryl-substituted α-cyanoacetates, including heterocyclic species, were aminated with excellent results. In contrast, α-alkylated substrates gave products only in low stereoselectivity. Deng *et al.* demonstrated that—in contrast to the unprotected analogues—benzyl-protected cinchona alkaloids **57** and **58** are suitable catalysts for the α-amination of α-cyanoethylacetates (Fig. 3).[55] In their case, the application of the pseudo-enantiomers **57** and **58** led to different products in opposite absolute configuration.

Catalyst **57** was also shown to be capable of catalysing the enantioselective α-amination of β-carbonyl compounds (Fig. 4).[54] Thus, compounds of the type **60a**,**b** were aminated with D*t*BuAD in 86–99% yield and 83–90% ee. Pihko and Pohjakallio reported cinchonidine (**61**) and cinchonine (**62**) to catalyse the α-amination of β-ketoesters with DBAD.[56] While open-chained substrates of the type **60a** gave products in only moderate enantiomeric excess, cyclic substrates of the type **60b** were aminated in 77–90% ee. In these cases, esterification with an ethyl group was favourable over esterification with a benzyl group. Lactones **60c** were aminated in 42–64% ee. However, the presence of a *tert*-butyl-substituent led to a considerable decrease in yield. In all these reactions, application of **61** resulted in products with the opposite absolute configuration to products arising from reactions catalysed by **62**. Takemoto *et al.* introduced the urea catalyst **63** (Fig. 4) for the amination of β-dicarbonyl compounds with D*t*BuAD.[57] The best results were obtained with cyclic substrates. In addition, the reaction was carried out using α-phenyl-substituted α-cyanoacetate to give the corresponding product in 93% yield and 73% ee.

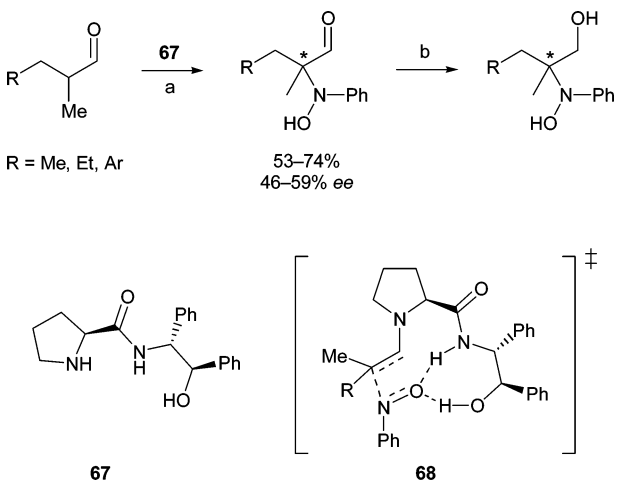
The difficulties encountered in connection with the cleavage of the hydrazides emerging from the amination with azodicarboxylates initiated the search for different nitrogen electrophiles, which would enable a more straightforward route towards the free amino acids. To our surprise, the reaction of α-branched aldehydes **64** with sulfonyl azides in the presence of L-proline did not result in triazene formation or azide transfer as expected, but in α-sulfamidation towards **66** (Scheme 21).[58] Since yields and enantioselectivity of the reaction reached only moderate levels, a careful optimisation was performed, including an extensive screening of solvents, catalysts, and sulfonyl azides. The best results were generally obtained when the reaction was carried out in ethanol. If tosyl azide was employed, the enantiomeric excess of the product was increased from 59 to 72% ee by use of the ionic liquid *N*-butyl-*N*′-methylimidazolium tetrafluoroborate ([bmim][BF_4]) as the solvent. Of a range of pyrrolidine-based catalysts tested in the reaction, proline gave the best results with regards to the combination of yield and stereoselectivity. Due to side reactions withdrawing the catalyst from the catalytic cycle, stoichiometric amounts of the catalyst were generally required for maximum conversion. A range of different α-branched aldehydes reacted with nosyl azide to afford products between 21 and 55% yield and enantioselectivities up to 86% ee. Similar to the proline-catalysed reaction of α-branched aldehydes with azodicarboxylates, satisfying levels of stereoselectivity were only reached, when α-aryl-substituted aldehydes were applied. Methoxy-substituents



Scheme 21 Organocatalysed α-sulfamidation of α-branched aldehydes.[58] *Reagents and conditions*: (a) L-Proline, EtOH, rt, 1–7 d; (b) $NaClO_2$, NaH_2PO_4, CH_3CN–H_2O, rt, 1 d (92%); (c) NaOMe, MeOH, rt, 1 d (quant.).

on the aromatic moiety further enhanced the product's enantiomeric excess. However, the yields dropped significantly when the aldehyde was carrying an *ortho*-substituent. Since the emergence of the product cannot be satisfactorily explained by the classical enamine catalysis pathway, a new mechanism was proposed, which includes as the key-step a 1,3-dipolar cycloaddition of the sulfonyl azide to the *in situ*-formed enamine, followed by a number of rearrangement steps as shown in the bottom line of Scheme 21. Deprotection of **66** was easily achieved, after oxidation of the aldehyde, by treatment with sodium methylate.

Nitroso aldol reactions can either exhibit *N*- or *O*-selectivity with respect to the nitroso compound. Most pyrrolidine-derived organocatalysts,[59] as well as chiral α-hydroxycarboxylic acids,[60] were reported to generally furnish aminohydroxylated products, until very recently Gong and Jiang published the regio- and stereoselective organocatalysed α-hydroxyamination of α-branched aldehydes using proline-amide **67** as the catalyst (Scheme 22).[61] They reasoned that the stabilisation of transition state **68** through hydrogen bonding might be responsible for the *N*-selectivity, whereas in other organocatalysed nitroso aldol reactions, *N*-protonation by the catalyst is preferred due to the higher basicity of the nitroso nitrogen.

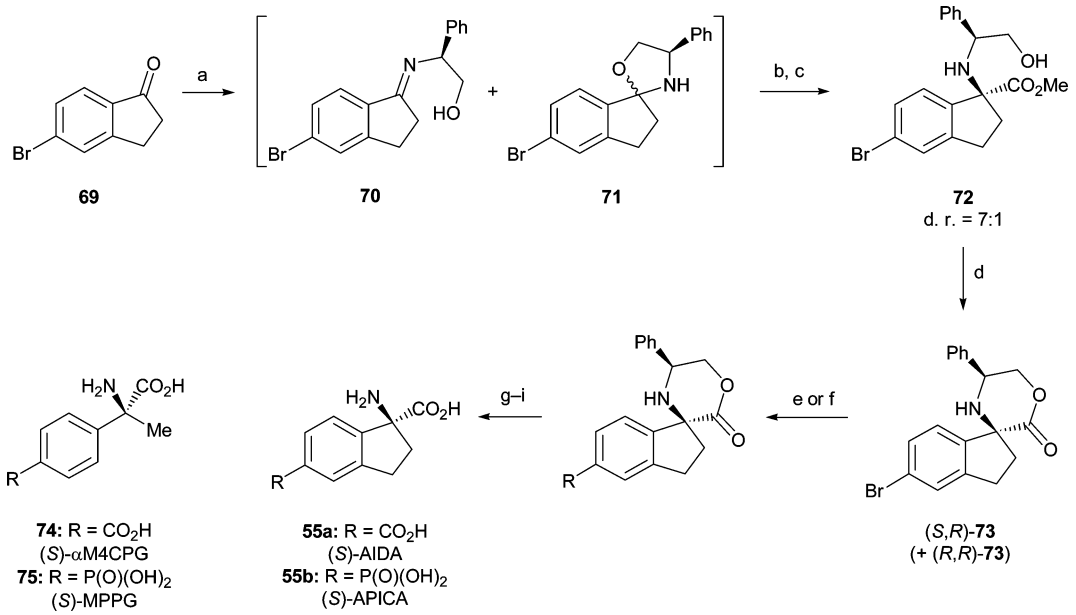


Scheme 22 Organocatalysed *N*-nitroso aldol reaction according to Gong and Jiang.[61] *Reagents and conditions*: (a) PhNO, toluene, 2–3 h; (b) $NaBH_4$.

3 Nucleophilic addition to C–N-multiple bonds

The starting point in amino acid synthesis was set in 1850, when Strecker developed the first (racemic) amino acid synthesis. Condensation of aldehydes, ammonia and hydrocyanic acid delivered aminonitriles, which were converted to the amino acids by acidic hydrolysis.[62]

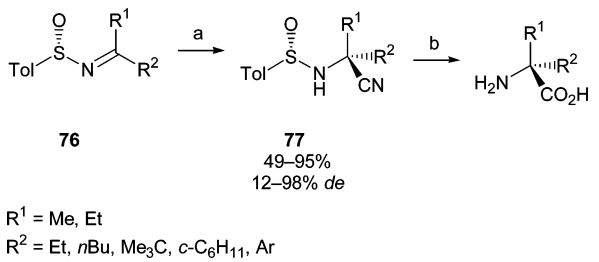
In 1999, Ma *et al.* reported the first asymmetric synthesis of the metabotropic glutamate receptor antagonists (*S*)-AIDA (**55a**) and (*S*)-APICA (**55b**, Scheme 23).[63] By refluxing bromo-substituted indanone **69** and (*R*)-2-phenylglycinol in toluene with azeotropic removal of water, they obtained a mixture of imine **70** and the 1,3-oxazolidine **71**. These were successively treated with trimethylsilyl cyanide and saturated methanolic hydrogen chloride to give the *N*-protected amino ester **72** in a 7 : 1 diastereomeric ratio. After conversion of the inseparable diastereomers towards the separable cyclisation products (*S*,*R*)-**73** and (*R*,*R*)-**73**, the task compounds **55a** and **55b** were synthesised from the main product (*S*,*R*)-**73** by palladium-catalysed carbonylation or phosphonation, followed by basic cleavage of the resulting oxazolinone and removal of the



Scheme 23 Application of the asymmetric Strecker reaction in the synthesis of metabotropic glutamate receptor antagonists by Ma *et al.*[63] *Reagents and conditions*: (a) (*S*)-phenylalaninol, toluene, reflux; (b) TMSCN, MeOH, rt, 24 h; (c) HCl–MeOH, rt, 12 h (61%, 3 steps); (d) toluene, reflux, 24 h (59%), (e) $Pd(OAc)_2$–dppp, CO, EtOH, Et_3N, DMSO, 70 °C, 3 h (67%, R = CO_2Et); (f) $Pd(PPh_3)_4$, $HP(O)(OEt_2)$, Et_3N, MeOH, 0 °C, 30 min (83%, R = $P(O)(OEt)_2$).

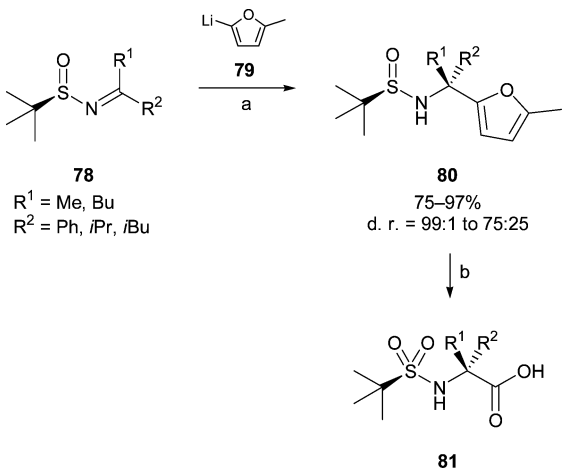
auxiliary. The metabotropic glutamate receptor antagonists (*S*)-αM4CPG (**74**) and (*S*)-MPPG (**75**) were prepared in a similar manner using the same chiral auxiliary. The diastereoselectivity of the Strecker reaction, however, was rather low in these cases, leading to diastereomeric ratios of 2 : 1 and 2.5 : 1, respectively.

Chiral sulfinamides have been reported to be suitable auxiliaries for the asymmetric Strecker reaction towards α,α-disubstituted α-amino acids by Davis *et al.*[64] Chiral sulfinyl ketimines **76**, obtained from the reaction of ketones with the auxiliary, were converted to diastereomerically enriched sulfinylaminonitriles **77** with the aid of ethylaluminium cyanoisopropylate (Scheme 24). No epimerisation was observed for the Strecker products, a phenomenon that had been observed in earlier approaches. However, a general limitation was found in the occurrence of isomeric mixtures of *E*- and *Z*-ketimines, which resulted in a decrease of diastereoselectivity. Moreover, while the sulfinyl group could be easily removed under acidic conditions, the cyano-group in products with very bulky substituents (*e.g. tert*-butyl) proved to be highly resistant against hydrolysis.



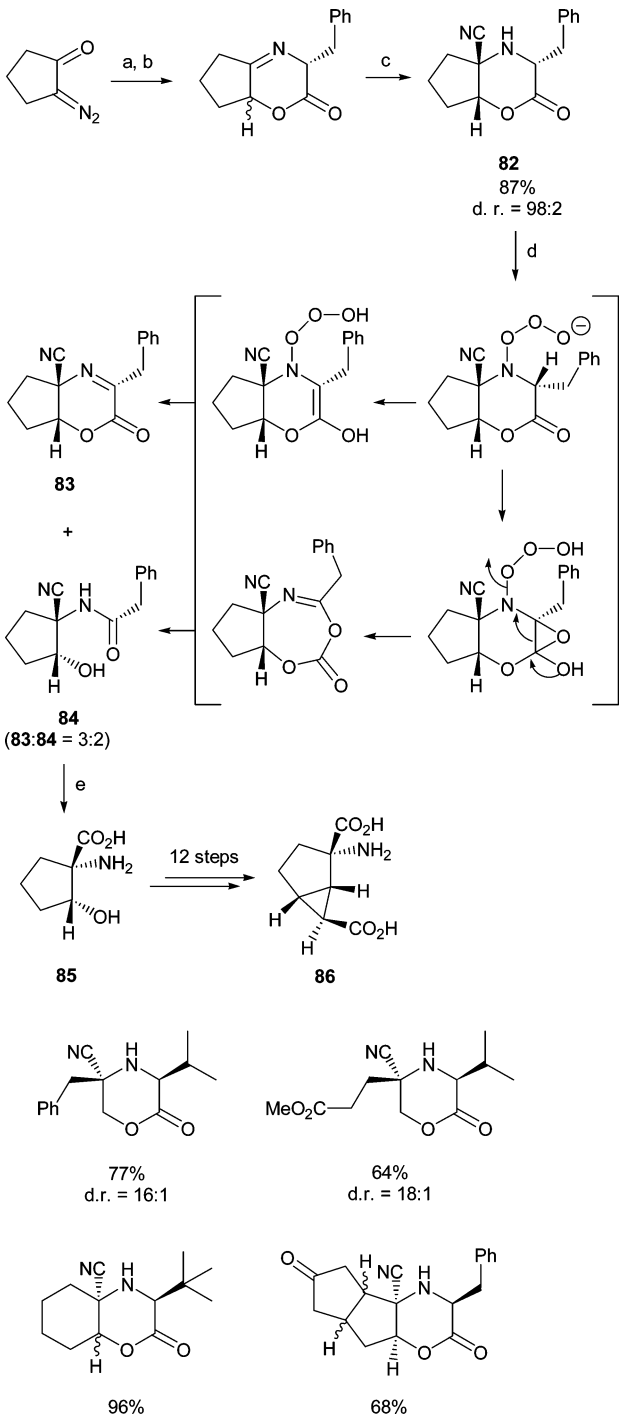
Scheme 24 Strecker reaction with sulfinyl ketimines according to Davis *et al.*[64] *Reagents and conditions*: (a) "EtAl(O*i*Pr)CN", THF, −78 °C to rt, 15 h; (b) 6 N HCl, reflux, 15 h, up to 69%.

A related Strecker-analogous reaction, involving the addition of furyl lithium species **79** to chiral *tert*-butanesulfinyl ketimines **78**, was devised by Ellman *et al.* (Scheme 25).[65] In analogy to the reaction described by Davis, diastereomeric ratios of the addition product **80** were excellent, when substrates with highly differentiated substituents were employed, but decreased with growing similarity in steric size. The attractiveness of this reaction lies in the conversion of the addition product **80** to the (sulfonyl-protected) amino acid **81**, since the carboxylic group is formed by oxidation of the furyl-moiety with sodium iodate under ruthenium catalysis, thus avoiding the harsh conditions required for the hydrolysis of the aminonitriles obtained in conventional Strecker reactions using cyanide as the nucleophile.



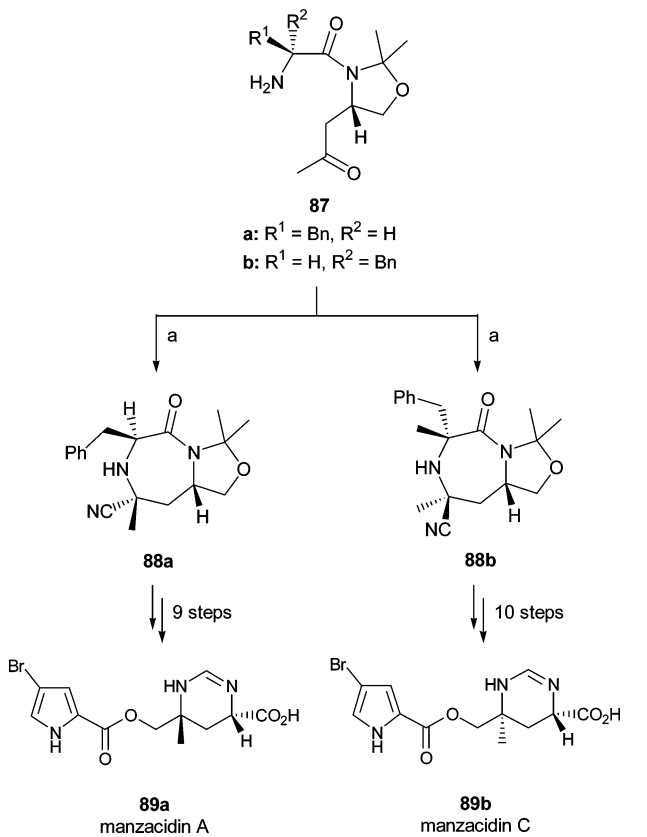
Scheme 25 Strecker-analogous reaction according to Ellman *et al.*[65] *Reagents and conditions*: (a) $AlMe_3$, toluene, 0 °C, 3–4 h; (b) $RuCl_3 \cdot H_2O$, $NaIO_4$, CH_2Cl_2, CH_3CN, H_2O, rt, 1 h (62–69%).

After Ohfune *et al.* had developed an asymmetric Strecker approach towards all diastereomers of α-methylthreonine and both enantiomers of α-methylserine,[66] they elaborated on this strategy to open access to other cyclic[67] and acyclic serine-derivatives (Scheme 26).[68] A crucial step in this strategy was the oxidation of the aminonitrile **82** to the iminonitrile **83**. Since the classical chlorination–dehydrochlorination method using *tert*-butyl chlorite and triethylamine resulted in a decrease in yield or even failed completely for sterically congested aminonitriles, the authors introduced ozone as a bidentate base. Under these conditions, they obtained mixtures of the desired iminonitrile **83** and the amide **84**, which could both be cleaved by treatment with concentrated hydrochloric acid to give the free amino acid in high yield. The cyclic Strecker product **85** was converted in a 12 step sequence to the metabotropic glutamate receptor agonist (+)-LY354740 (**86**).[69]



Scheme 26 Asymmetric Strecker reaction according to Ohfune *et al.*[69] *Reagents and conditions*: (a) D-Phe-OH, $Cu(acac)_2$, toluene; (b) TFA; (c) TMSCN, $ZnCl_2$, *i*PrOH, rt, 18 h (87%); (d) O_3, EtOAc, −78 °C (98%); (e) conc. HCl (98%).

A similar approach was chosen for the synthesis of **88a** and **88b** from **87a** and **87b**, respectively, which were used as intermediates for the total synthesis of manzacidin A (**89a**) and manzacidin C (**89b**) (Scheme 27). In contrast to the reactions above, the Strecker reaction was performed on a seven-membered lactam instead of a six-membered lactone. In addition, the presence of a second stereocentre rendered the stereochemical outcome of the reaction rather unpredictable. However, the Strecker reaction proceeded smoothly and resulted in only one diastereomer. The occurrence of a diastereomeric product mixture when a glycine-residue was used instead of the initial phenylalanine-residue indicated that the stereochemical influence of the β-stereocentre was overruled by the stereochemistry of the amino acid. This synthesis helped to establish the absolute configuration of natural (−)-manzacidin and (+)-manzacidin.[70]



Scheme 27 Asymmetric Strecker reaction in the total synthesis of manzacidin A and C by Ohfune *et al.*[70] *Reagents and conditions*: (a) TMSCN, $ZnCl_2$, *i*PrOH, rt, 18 h, (81–87%, single diastereomers).

The procedure presented above was also successfully utilised for a number of natural product syntheses.[71] Thus, an asymmetric Strecker reaction was used for the synthesis of the Corey

intermediate **90** of lactacystin (**91**, Fig. 5).[72,73] Further natural products which have been successfully synthesised using Ohfune's asymmetric Strecker approach are kaitocephalin (**92**)[74] and altemicidin (**93**).[71b]

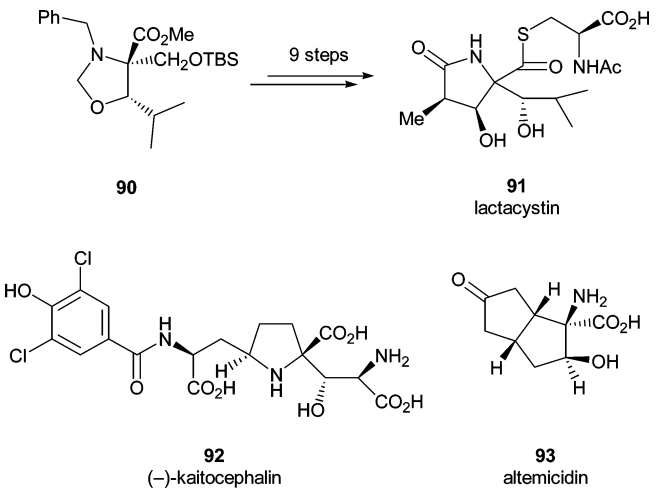
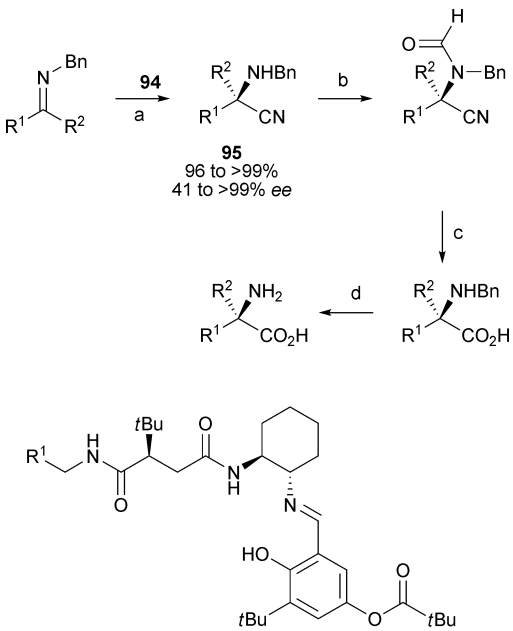


Fig. 5 Natural products synthesised *via* Ohfune's asymmetric Strecker approach.

Starting in the mid-nineties, impressive achievements were made in the catalytic asymmetric Strecker reaction towards α-monosubstituted amino acids.[75] Thus, it was just a question of time until related approaches towards α,α-disubstituted α-amino acids would be reported. The first reaction of this kind was published in 2000 by Vachal and Jacobsen.[76] By reaction of *N*-protected ketimines with hydrocyanic acid under the influence of a resin-bound or soluble Schiff base catalyst (**94a** and **94b**, respectively), they prepared different α-methyl-α-arylglycine-derivatives in essentially quantitative yield and 88–95% ee (Scheme 28). A decrease in stereoselectivity was noted, when the ketimine carried exclusively non-aromatic substituents. *ortho*-Substituted aryl substituents, on the other hand, effected the destabilisation of the resulting aminonitriles **95**. Hydrolysis of **95** succeeded only after formylation of the amine, since the unformylated species underwent a retro-Strecker reaction under the required reaction conditions. The free amino acid was subsequently obtained by hydrogenation.

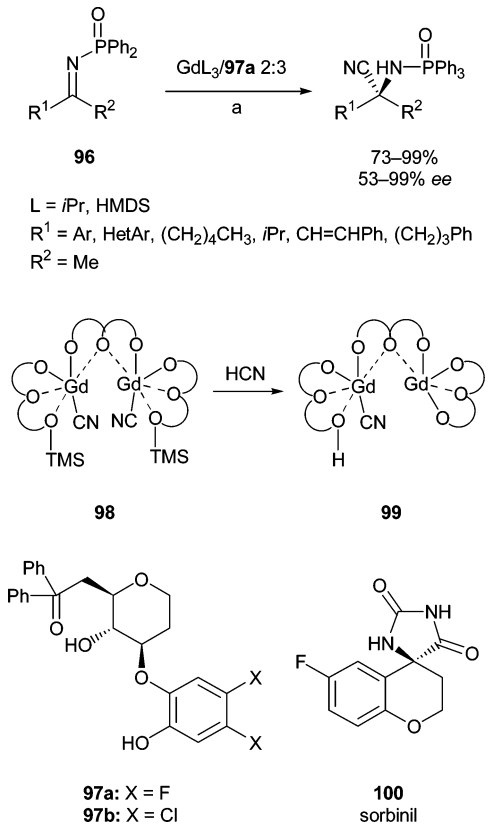
Shibasaki *et al.* developed a highly efficient gadolinium-catalysed Strecker reaction using phosphinoyl imines **96** and the chiral ligand **97a** (Scheme 29).[77] Phosphinoyl imines proved to be favourable for high enantioselectivity over *N*-alkylated ketimines,[78] since they easily equilibrate between *E*- and *Z*-configuration under the reaction conditions applied.[77b] Consequently, the cyanide adds to the more reactive isomer, presumably *E*, leaving the other isomer to equilibrate. The stoichiometric addition of 2,6-dimethylphenol (DMP) as a proton source led to a considerable improvement in reactivity and enantioselectivity.[79] This was attributed to the formation of the active catalyst **99** from the silylated species **98**, which would act as an internal proton donor in the course of the reaction. Further improvement was made when the proton source and the reagent were combined and stoichiometric amounts of hydrocyanic acid were used together with only catalytic amounts of trimethylsilyl cyanide.[80] These catalytic amounts of the latter, however, proved to be essential



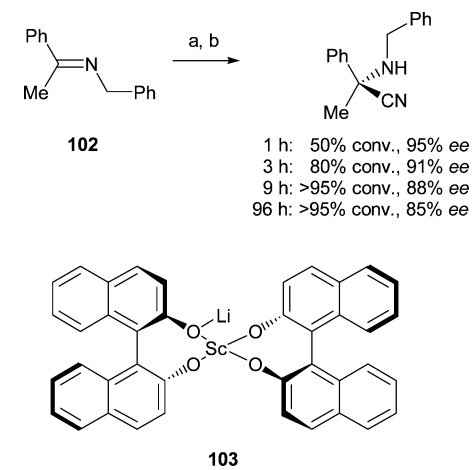
Scheme 28 First catalytic asymmetric Strecker synthesis towards α,α-disubstituted α-amino acids according to Vachal and Jacobsen.[76] *Reagents and conditions*: (a) HCN, toluene, −75 °C, 15–90 h; (b) HCO_2H–Ac_2O (97–98%); (c) conc. HCl, 105 °C (95%); (d) H_2, Pd/C, HCl, MeOH–H_2O (92–93% overall).

for the reaction, since the active catalyst **99** was generated only from the silylated species, whereas hydrocyanic acid did not add to the precatalyst directly. The active catalytic species in these reactions was shown by ESI-MS measurements to be a 2 : 3 gadolinium : ligand complex. When gadolinium isopropylate was used as the gadolinium source, minor amounts of a 4 : 5 complex were also detected in the catalyst solution. In contrast, hexamethyldisilazyl gadolinium exclusively furnished the 2 : 3 complex.[81] This gadolinium source led to a further enhancement in stereoselectivity. By variation of crystallisation conditions, the authors succeeded in isolating a 4 : 5 complex of gadolinium and the ligand **97b**.[82] This complex surprisingly catalysed the Strecker reaction to give products of the opposite absolute configuration, although the stereochemistry of the ligand was essentially the same as in the former reactions. The gadolinium-catalysed Strecker reaction exhibited a broad substrate scope. Besides different aryl- and heteroaryl-substituted imines, also indanone- and tetralinone-derived substrates reacted in high yields and enantiomeric excess. The applicability of this reaction to the synthesis of compounds of higher complexity was demonstrated in the total synthesis of sorbinil (**100**, Scheme 29)[79] and (+)-lactacystin (**91**, see Fig. 5).[81]

Vallée *et al.* reported the heterobimetallic scandium binol-complex **103** to catalyse the asymmetric Strecker reaction of ketimine **102** (Scheme 30) with 95% ee at 50% conversion.[83] At



Scheme 29 Asymmetric catalytic Strecker reaction according to Shibasaki *et al.*[77] *Reagents and conditions*: (a) TMSCN, DMP or TMSCN, HCN, EtCN, −40 °C, 0.25–54 h.

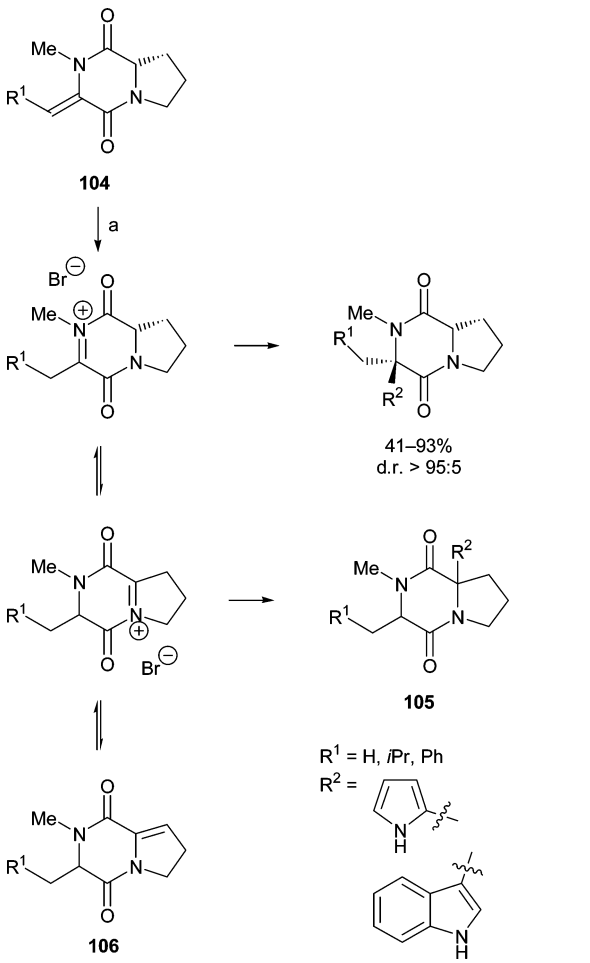


Scheme 30 Asymmetric catalytic Strecker synthesis according to Vallée *et al.*[83] *Reagents and conditions*: (a) **103**, TMSCN, toluene, −20 °C; (b) H_2O.

longer reaction times, however, a decrease in the reaction rate and in enantioselectivity was observed, which was attributed to a possible catalyst poisoning or decay.

While the Strecker reaction makes use of the nucleophilic addition of a "CO_2H^-"-synthon to imines, it is also possible to add alkyl-groups to C=N double bonds (compare Fig. 1, path A). If the substrate carries a carboxylic group or a suitable precursor, this is another possibility to open access to amino acids.

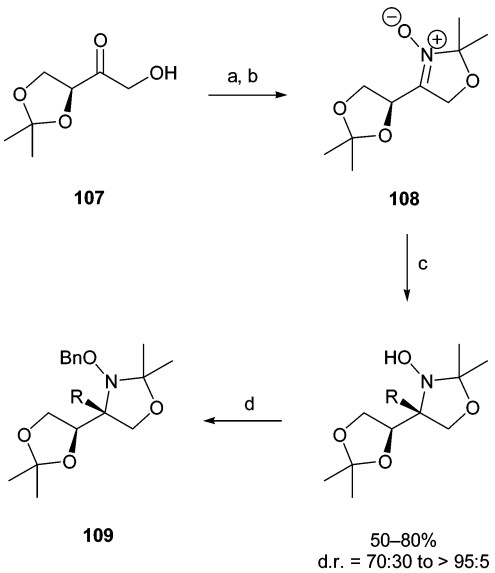
Thus, L-proline-derived diketopiperazine **104** reacted in the presence of hydrogen bromide with nitrogen heterocycles to give disubstituted products in more than 95 : 5 diastereoselectivity (Scheme 31).[84] In some cases, isomerisation of the diketopiperazide was observed to result in the racemic products **105** or **106**.



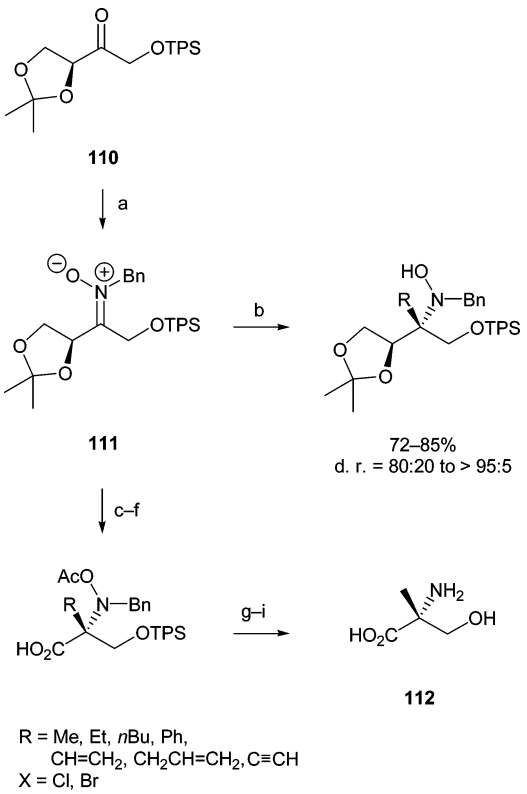
Scheme 31 Addition of *N*-heterocycles to diketopiperazines according to Jin and Liebscher.[84] *Reagents and conditions*: (a) 48% HBr, R^2X, dioxane, rt or reflux.

After Carda and Marco had presented the synthesis of serine-derivatives by nucleophilic addition of organolithium reagents to protected erythrulose oximes,[85] they also demonstrated the nucleophilic addition of organolithium and organomagnesium reagents to cyclic nitrone **108**, derived from erythrulose acetonide **107** (Scheme 32).[86] Thus, the reaction of **108** with different organometallic reagents delivered the product in 50–80% yield and diastereomeric ratios of 70 : 30 to >95 : 5. The addition of a bulky *tert*-butyl-group could not be accomplished. The products were converted to the benzyl-protected oximes **109**, the transformation of which towards the corresponding α-alkylated serines had already been shown in preceding publications (see also Scheme 33, steps c–i).[85]

Since the preparation of precursor **108** was rather inefficient, the same research group introduced acyclic nitrone **111**, which was obtained from silyl-protected erythrulose acetonide **110** in 78% yield (Scheme 33).[87] The addition of different Grignard



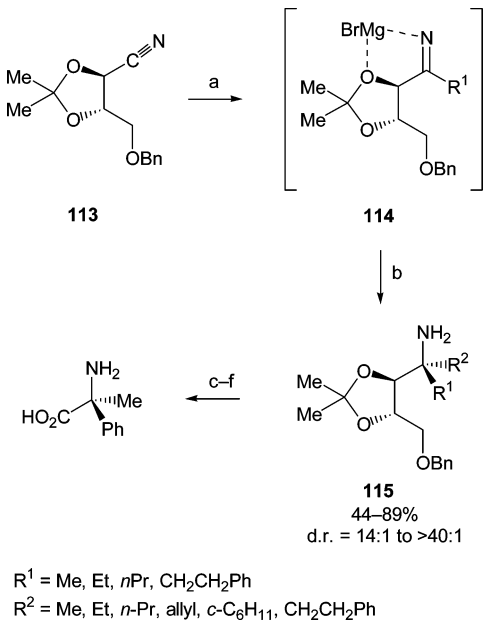
Scheme 32 Nucleophilic alkylation of cyclic nitrones according to Carda and Marco.[86] *Reagents and conditions*: (a) NH_2OH (74%); (b) acetone, 2,2-dimethoxypropane, TsOH (30%); (c) RM, Et_2O, −78 °C, 1 h; (d) NaH; BnBr, TBAI, THF, rt, 12 h.



Scheme 33 Nucleophilic alkylation of acyclic nitrones according to Carda and Marco.[87] *Reagents and conditions*: (a) BnNHOH (78%); (b) RMgX, THF, −78 °C, 5 h; (c) RMgX, THF, −78 °C, 5 h, then Ac_2O, rt, 30 min (50–96%); (d) HIO_4; (e) $NaClO_2$; (f) CH_2N_2 (50–70%, 3 steps); (g) TBAF, THF (87%); (h) H_2 (70 psi), $Pd(OH)_2$; (i) NaOH, EtOH (64%, 2 steps, for R = Me).

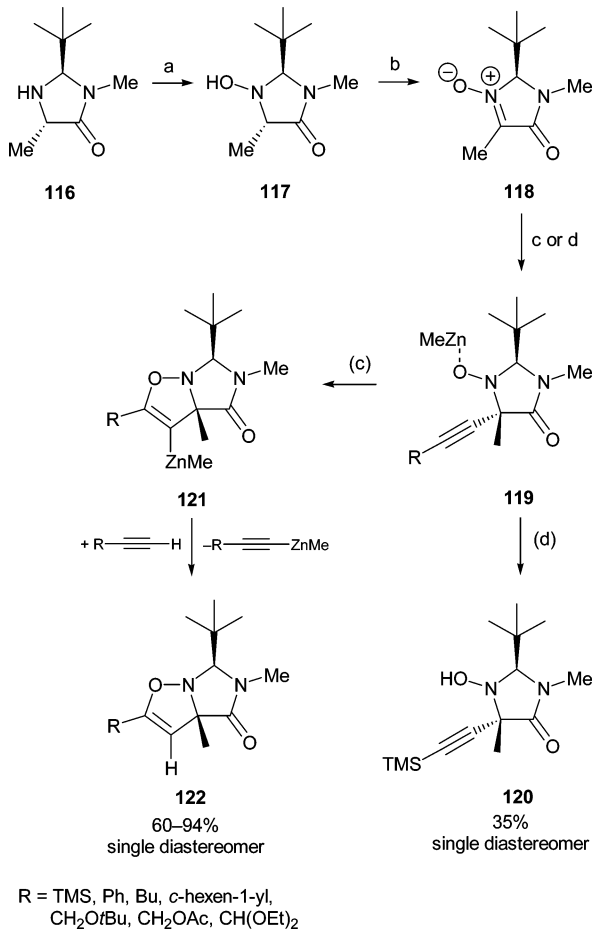
reagents delivered the corresponding product in diastereomeric ratios higher than 80 : 20. In most cases, the presence of equimolar amounts of zinc bromide resulted in enhanced diastereoselectivity. This was attributed to the stronger chelating effect exerted by zinc compared to magnesium, and thus the better stabilisation of the Cram's chelated transition state. The conversion towards the free amino acid was demonstrated in the synthesis of α-methylserine (**112**).

A related strategy was pursued in the sequential double alkylation of tartaric acid-derived nitrile **113**.[88] The key reaction in this approach is shown in Scheme 34. After the addition of a Grignard reagent, the second alkyl-group was introduced by means of an organocerium species. Chelation-control in the intermediate imine anion **114** is thought to be responsible for the stereoselectivity of the second addition step. The diastereomeric ratio of **115** was between 14 : 1 and >40 : 1, depending on the size difference of the substituents and the order of addition. Conversion to the corresponding *N*-protected α,α-disubstituted α-amino acid was accomplished in four additional steps by *N*-protection, cleavage of the acetal and the resulting diol, and final oxidation of the resulting aldehyde.

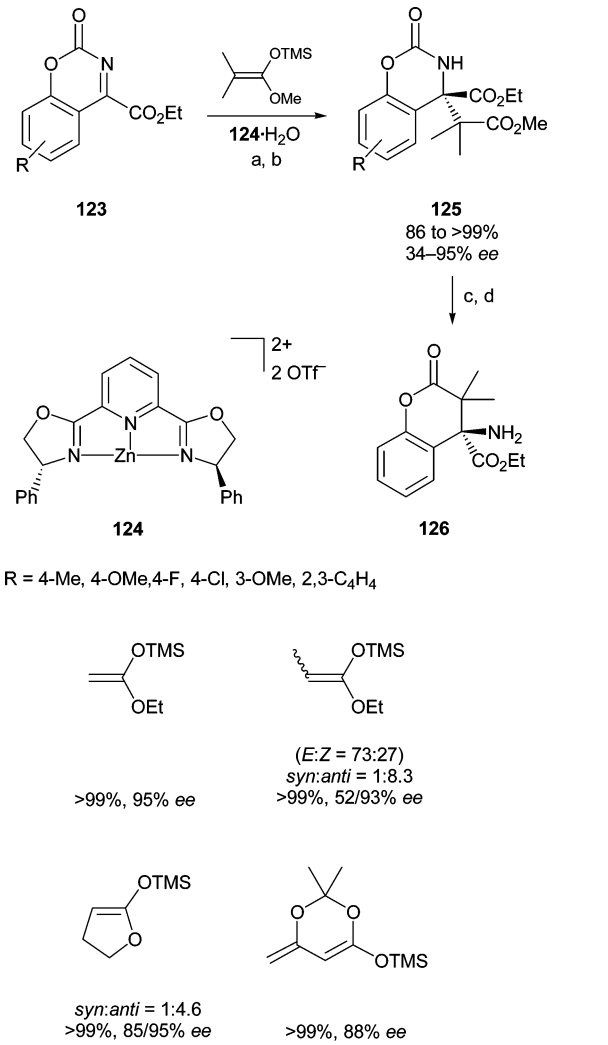


Scheme 34 Diastereoselective sequential nucleophilic double alkylation of nitriles under chelation control according to Charette and Mellon.[88] *Reagents and conditions*: (a) R^1MgBr, toluene, 0 °C to rt; (b) $R^2CeCl_2 \cdot MgClBr$, toluene, −78 °C to rt; (c) CbzCl, $EtNiPr_2$, CH_2Cl_2 (95%); (d) TsOH, MeOH; (e) $NaIO_4$, THF, H_2O; (f) $KMnO_4$, NaH_2PO_4, *t*BuOH, H_2O (80%, 3 steps, for R^1 = Ph, R^2 = Me).

The nucleophilic addition of alkynes to cyclic nitrone **118** under self-reproduction of stereocentres was demonstrated by Chavant *et al.* (Scheme 35).[89] Nitrone **118** was prepared from Seebach's imidazolidinone **116** by a two step oxidation. Since **118** proved to be configurationally unstable, the storable precursor **117** was synthesised in large quantities and oxidised immediately before application. The addition of the alkynyl zinc species was highly stereoselective and delivered only one diastereomer. However, only alkylation with the trimethylsilyl species resulted in a stable adduct (**120**). All other alkynes tested in the reaction delivered the



Scheme 35 Nucleophilic alkylation of cyclic nitrones under self reproduction of stereocentres according to Chavant *et al.*[89] *Reagents and conditions*: (a) urea–H_2O_2, $MeReO_3$, CH_2Cl_2, 20 °C, 10 h (65%); (b) MnO_2, CH_2Cl_2, 20 °C, 2 h; (d) RC≡CH, Me_2Zn, toluene, 20 °C, 18 h, then NH_4Cl; (e) TMSC≡CH, Me_2Zn, toluene, 6 h, then NH_4Cl.



Scheme 36 Catalytic Mannich reaction according to Jørgensen *et al.*[90] *Reagents and conditions*: (a) CH_2Cl_2, −78 °C; (b) EtOH or H_2O, −78 °C to rt; (c) Boc_2O, DMAP, CH_3CN, rt, 17 h (78%, for R = H); (d) Cs_2CO_3, MeOH, rt, 2 h (79%, for R = H).

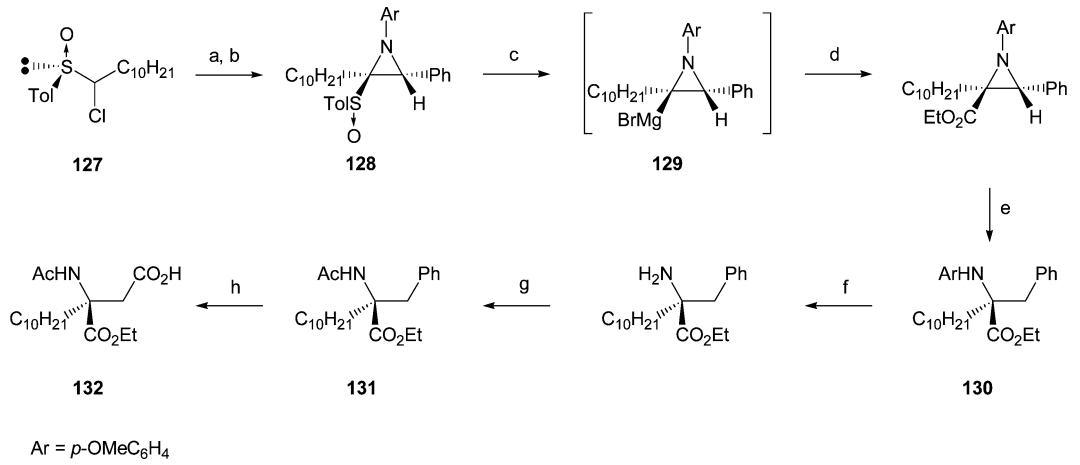
cyclisation product **122**. Since these products can theoretically also arise from a 1,3-dipolar cycloaddition, mechanistic experiments were carried out to confirm a tandem addition–cyclisation process involving the intermediates **119** and **121**.

The Mannich reaction is another example for a reaction involving the addition of nucleophiles—in this case enolates—to imines. However, ketimines are rather demanding substrates, due to increased steric hindrances compared to aldimines. Moreover, the *E*–*Z*-equilibrium of the imine double bond often hampers control over the stereochemistry of the reaction.

This problem was addressed by Jørgensen *et al.*, who introduced cyclic ketimines of the type **123** as substrates for the catalytic asymmetric Mannich reaction (Scheme 36).[90] By integration into a cyclic system, the imine double bond is fixed in *Z*-configuration. The presence of a carbamate protective group additionally enhances the electrophilicity of the substrate. Moreover, the absence of α-protons suppresses enamine formation, which would result in the deactivation of the substrate. The reaction of **123** with silyl enol ethers under catalysis of the zinc bisoxazolidine complex **124** delivered products in excellent yield and generally high enantiomeric excess above 80% ee. One exception was the 3-methoxy-substituted substrate with only 34% ee, which was most probably due to electronic effects. Different enolates were tested in the reaction with unsubstituted **123**. In the cases, where mixtures of *syn*- and *anti*-products were obtained, moderate diastereoselectivity was observed towards the *syn*-product, which also displayed the higher enantiomeric excess. The unsubstituted carbamate **125** was cleaved, after Boc-protection, with caesium carbonate. Spontaneous cyclisation of the cleavage product led to lactone **126**.

4 α,α-Disubstituted α-amino acids *via* stereospecific ring-opening and rearrangement reactions

Various methods have been devised in the past utilising stereoselective ring-opening reactions of chiral aziridines to open access to α,α-disubstituted α-amino acids.[14] Satoh and Fukuda presented the synthesis of long chain-substituted phenylalanine- and aspartic acid-derivatives **131** and **132**, respectively, by reaction of aziridinyl species **129** with ethyl chloroformate and subsequent ring-opening hydrogenation towards **130** (Scheme 37).[91] The



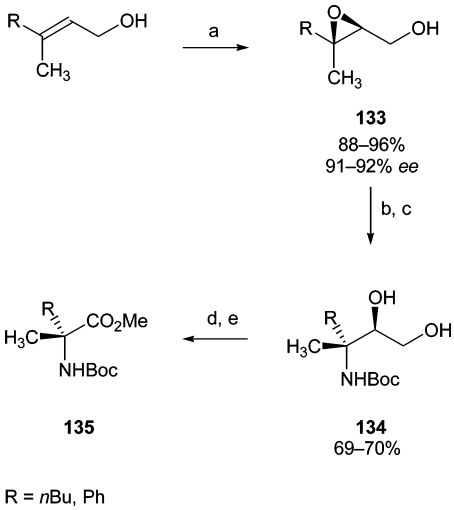
Scheme 37 Stereospecific ring-opening reaction of aziridines according to Satoh and Fukuda.[91] *Reagents and conditions*: (a) LDA, PhC=NAr, THF, −78 °C, 30 min (78%); (b) *t*BuOK, *t*BuOH, 70 °C, 40 min (94%); (c) MeMgBr, then *t*BuLi, THF, −78 °C, 1 min; (d) EtOCOCl, THF, −78 °C, 1 min (64%, 2 steps); (e) H_2, $Pd(OH)_2$–C, MeOH, EtOAc; (f) ceric(IV) ammonium nitrate, CH_3CN, H_2O, 0 °C, 30 min (54%, 2 steps); (g) Ac_2O, DMAP, pyridine (97%); $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O (60%).

synthesis of the aziridine **128** using chiral sulfoxide **127** was highly diastereoselective and resulted in only one diastereomer. All subsequent reactions in the sequence were stereospecific, and **131** was obtained in an optically pure state. Aspartic acid-derivative **132** was obtained from phenylalanine-derivative **131** by oxidation with ruthenium chloride and sodium iodate.

Due to their broad applicability, numerous strategies have been developed for the preparation of chiral epoxides, rendering this substance class a very attractive starting material for asymmetric transformations. Consequently, various methods have also been developed for the conversion of chiral epoxides into α,α-disubstituted α-amino acids.

Probably the most widely used asymmetric reaction towards chiral epoxides is the Sharpless epoxidation.[92] Sharpless demonstrated that chiral 3-hydroxyepoxides undergo stereospecific ring-opening upon treatment with azides to afford 1-azido-2,3-diols, which can act as amino acid-precursors.[93] However, the ring-opening reaction of disubstituted epoxides of the type **133** by various protocols proved to be rather difficult and gave the undesired regioisomer due to the increased steric hindrance.[94] The reaction finally proceeded with the desired regioselectivity, when sodium azide was used in combination with a mild Lewis acid (Scheme 38). The products were immediately submitted to catalytic hydrogenation in the presence of Boc-anhydride to give the *N*-protected diol **134**. This was converted to the protected amino acid **135** in two additional steps.

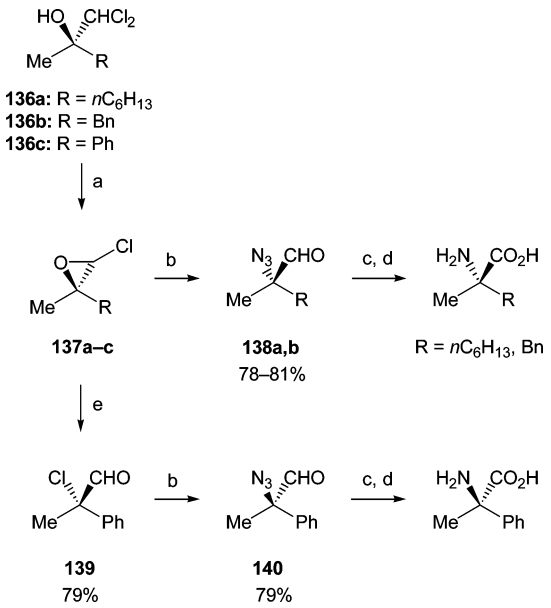
The stereospecific ring-opening reaction of α-chloroepoxides **137a** and **137b**, derived from stereochemically defined dichloromethylcarbinols **136a** and **136b**, respectively, with sodium azide gave α-azidoaldehydes **138a** and **138b** (Scheme 39).[95] Oxidation and subsequent hydrogenation then furnished the free amino acid in good yield. Interestingly, the phenylsubstituted epoxide **137c** resulted in products of the opposite absolute configuration. The authors explained this result with a double inversion involving the intermediate **139**, which was also identified after stirring **137c** at room temperature in THF for 12 h. Treatment of **139** with sodium azide resulted in aldehyde **140**, which was transformed into the free amino acid in the same manner as described above.



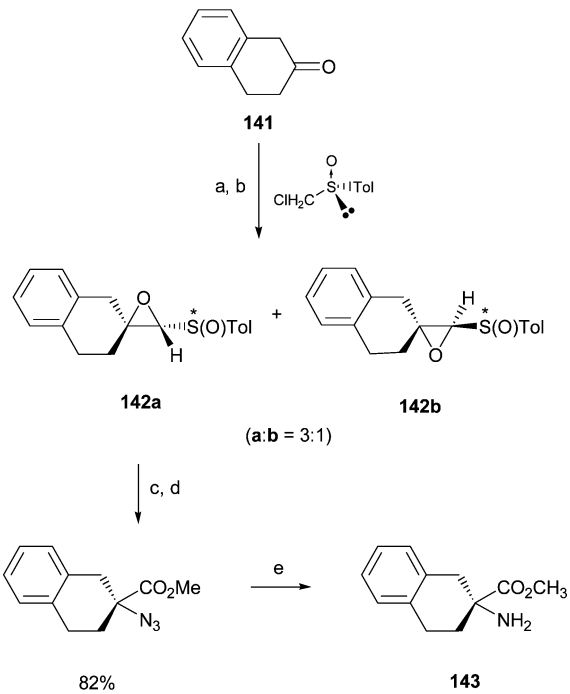
Scheme 38 Stereospecific ring-opening reaction of Sharpless epoxides according to Pericás, Riera *et al.*[94] *Reagents and conditions*: L-(+)-DET, *t*BuOOH, $Ti(OiPr)_4$, CH_2Cl_2, −20 °C, 4 h; (b) NaN_3, $LiClO_4$, CH_3CN, 65 °C, 24 h; (c) H_2, Pd/C, Boc_2O, EtOAc, rt, 5 h; (d) $KMnO_4$, $NaIO_4$, Na_2CO_3, dioxane, H_2O, rt, 12 h (71–87%); (e) CH_3I, $KHCO_3$, DMF, rt, 12 h (72–95%).

A similar procedure was published by Satoh *et al.*, who prepared a 3 : 1 diastereomeric mixture of the sulfinyloxiranes **142a** and **142b** from tetralone (**141**, Scheme 40).[96] The main product **142a** was submitted to a stereospecific ring-opening reaction with sodium azide, and the resulting aldehyde converted to the amino acid ester **143** by oxidation and subsequent hydrogenation.

Unsaturated γ,δ-epoxy esters can be stereospecifically opened with azides under palladium-catalysis and double inversion of configuration (Scheme 41).[97] In the course of their studies, Miyashita *et al.* also demonstrated the use of this reaction for the synthesis of both enantiomers of α-methyglutamic acid-derivative **146**. Stereospecific epoxidation of the chiral unsaturated compound **144** was followed by a palladium-catalysed azide substitution to furnish (*R*)-**146** in 93% yield. The reaction is thought to

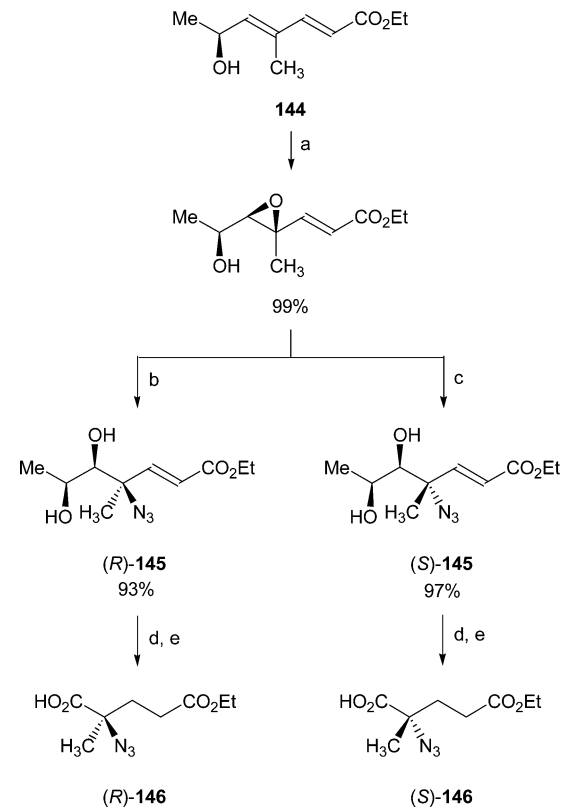


Scheme 39 Stereospecific ring-opening reaction of α-chloroepoxides according to Masaki *et al.*[95] *Reagents and conditions*: (a) K_2CO_3, MeOH, rt, 10 min; (b) NaN_3, 15-crown-5, THF, rt, 12 h; (c) Jones oxidation; (d) H_2, Pd/C, EtOH, rt, 16 h; (e) THF, rt, 12 h.



Scheme 40 Stereospecific ring-opening reaction of epoxides according to Satoh *et al.*[96] *Reagents and conditions*: (a) LDA, THF, −78 °C (99%); (b) *t*BuOK, *t*BuOH, THF, 0 °C (93%); (c) NaN_3, NH_4Cl; (d) I_2, KOH, MeOH; (e) H_2, Pd/C, EtOAc (98%).

proceed through coordination of the intermediate allylic cation to the palladium centre, followed by an intramolecular transfer of the azide from the silyl-group to the uncoordinated face of the allylic moiety. Concomitant hydrogenation of the double bond and the azide in the presence of Boc-anhydride and subsequent cleavage of the diol delivered (*R*)-**146** in 68% yield. The opposite

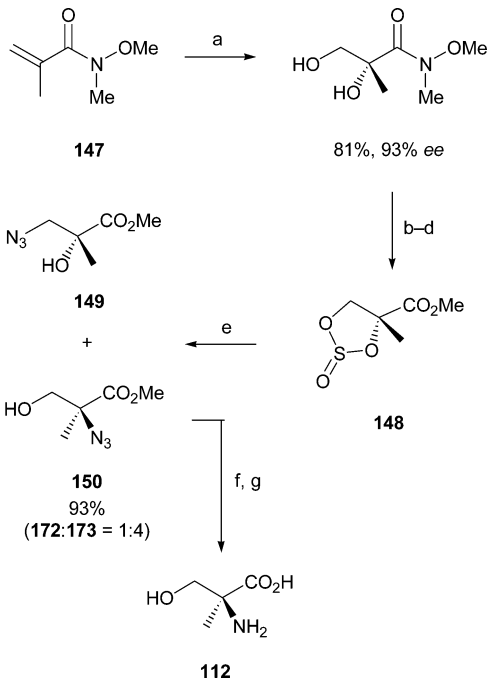


Scheme 41 Palladium-catalysed stereospecific ring-opening reaction of epoxides according to Miyashita *et al.*[97] *Reagents and conditions*: (a) *m*CPBA, CH_2Cl_2, 0 °C, 1 h; (b) $TMSN_3$, $Pd(PPh_3)_4$, THF, rt, 1 h; (c) NaN_3, $Ti(OEt)_4$, DMF, rt, 1 h; (d) H_2, PtO_2, Boc_2O, EtOAc, rt; (e) $RuCl_3$, $NaIO_4$, CCl_4, CH_3CN, H_2O, rt, 2 h (68% overall).

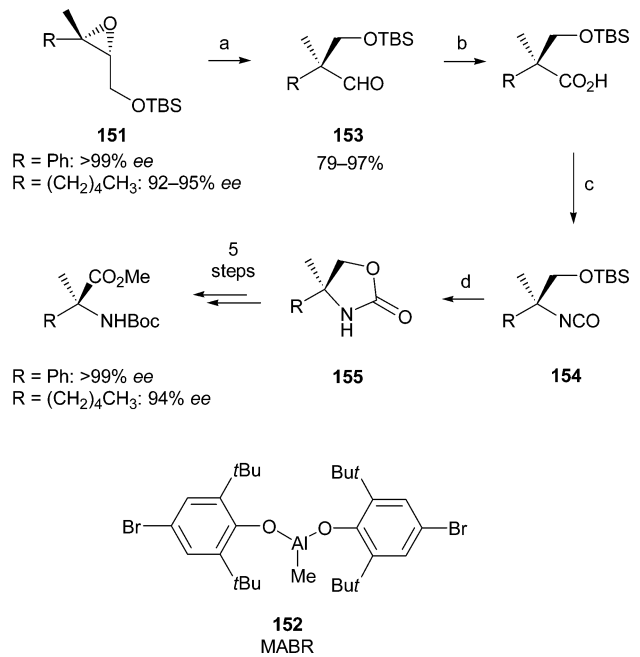
enantiomer was prepared by reaction with sodium azide and titanium tetraethylate under modified Sharpless conditions[98] to yield (*S*)-**145** in 97%. The conversion to (*S*)-**146** was carried out under the same conditions as above.

The stereospecific ring-opening of the chiral cyclic sulfite **148** was demonstrated in the enantioselective synthesis of both enantiomers of α-methylserine (Scheme 42).[99] Sulfite **148** was prepared in 93% ee from **147** by Sharpless dihydroxylation with AD-mix α, basic hydrolysis, and esterification. Treatment of **148** with sodium azide resulted in a 1 : 4 mixture of the regioisomers **149** and **150**, with an excess of the desired α-substituted product **150**. Similar yields were obtained, when the sulfite **147** was first oxidised to the corresponding sulfate and then treated with sodium azide. Hydrolysis of the ester and subsequent hydrogenation of the azide delivered the free amino acid **112** in 39% overall yield with respect to **147**. By application of AD-mix β in the Sharpless dihydroxylation step, the opposite enantiomer of **112** was synthesised in equal yield and enantioselectivity.

An approach combining the stereospecific rearrangement of Sharpless epoxides with a stereospecific Curtius rearrangement was proposed by Matsushita *et al.* (Scheme 43).[100] Thus, the MABR-promoted rearrangement of **151** (MABR = methylaluminium bis(4-bromo-2,6-di-*tert*-butyl-phenoxide, **152**) afforded the aldehyde **153** in good to excellent yields. After oxidation, the resulting acid was submitted to a Curtius rearrangement. Since the addition of *tert*-butanol to cyanate **154** towards the



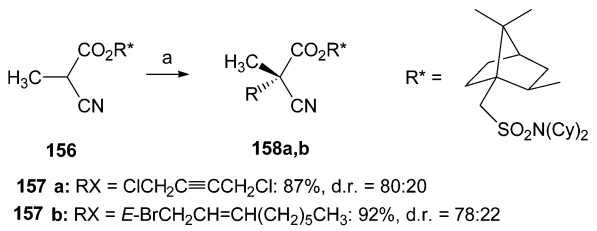
Scheme 42 Stereospecific ring-opening reaction of cyclic sulfites according to Avenoza, Peregrina *et al.*[99] *Reagents and conditions*: (a) AD-mix α, $MeSO_2NH_2$, *t*BuOH, H_2O, 0 °C, 12 h; (b) $LiOH{\cdot}H_2O$, H_2O, MeOH, rt, 2 h; (c) AcCl, MeOH, reflux, 12 h (85%); (d) $SOCl_2$, CCl_4, reflux, 4 h (90%); (e) NaN_3, DMF, 50 °C, 2 d; (f) 6 N HCl, reflux, 12 h; (g) H_2, Pd/C, MeOH, rt, 24 h (83%, 2 steps).

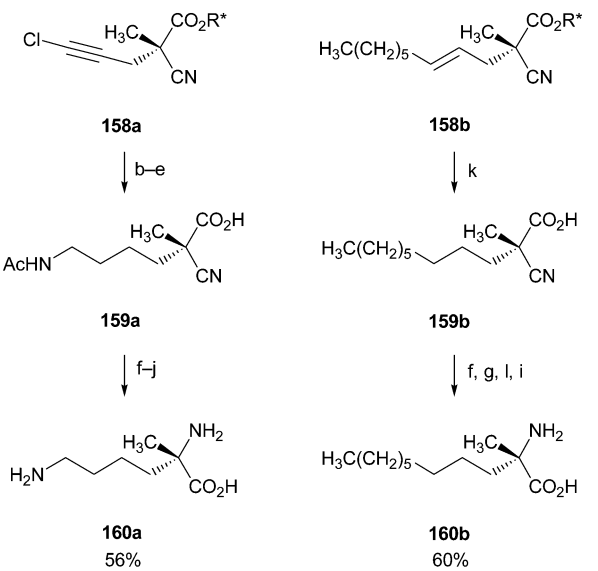


Scheme 43 Stereospecific MABR-promoted rearrangement of epoxides according to Matsushita *et al.*[100] *Reagents and conditions*: (a) 152, CH_2Cl_2, −78 °C; (b) RuO_4, $NaIO_4$, CCl_4, CH_3CN, H_2O (78–87%); (c) DPPA, Et_3N, toluene, reflux (62–75%); (d) $BF_3{\cdot}OEt_2$, THF (81–98%).

N-Boc-protected amino alcohol did not occur, **154** was converted to oxazolidinone **155** by treatment with boron trifluoride, which was then, after Boc-protection, cleaved with caesium or potassium carbonate, oxidised in 2 steps and esterified to furnish the *N*-protected amino ester in high enantiomeric excess.

Cativiela *et al.* developed a methodology involving the auxiliary-controlled asymmetric alkylation of α-cyanoesters, followed either by Hofmann rearrangement of the corresponding amide, obtained by hydrolysis of the cyano-group, or by Curtius rearrangement of the previously hydrolysed carboxylic group, to yield both enantiomers of α,α-disubstituted α-amino acids.[101] However, this strategy was limited to highly reactive electrophiles in the alkylation step. To open access also to long-chain substituted α,α-disubstituted α-amino acids, such as α-methyllysine (**160a**), or 2-amino-2-methylundecanoic acid (**160b**), the chiral α-cyanoester **156** was diastereoselectively alkylated with propargyl or allyl halides **157a** or **157b**, respectively (Scheme 44). After separation of the diastereomers, the main product was hydrogenated (after substitution of the terminal halide by sodium azide in the case of **158a**) and saponified. The resulting α-cyano acid **159** was subjected to a Curtius rearrangement and subsequently hydrolysed to furnish **160a** and **160b** in 56 and 60% yield, respectively.

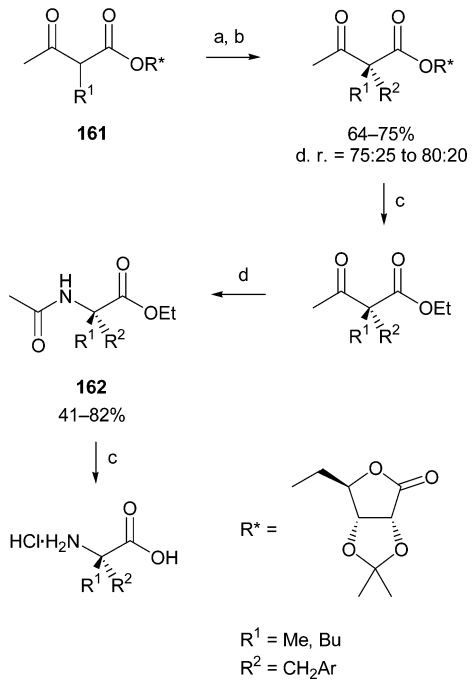




Scheme 44 Stereospecific Curtius rearrangement of α-cyanoesters according to Cativiela *et al.*[101] *Reagents and conditions*: (a) **157a** or **157b**, K_2CO_3, acetone; (b) NaN_3, TBAI, DMF (85%); (c) H_2, Pd/C; (d) Ac_2O, pyridine (86%, 2 steps); (e) KOH, MeOH (56%); (f) $SOCl_2$; (g) NaN_3; (h) toluene, MeOH, Δ; (i) HCl, Δ; (j) ion exchange; (k) H_2, Pd/C (88%); (l) toluene, Δ.

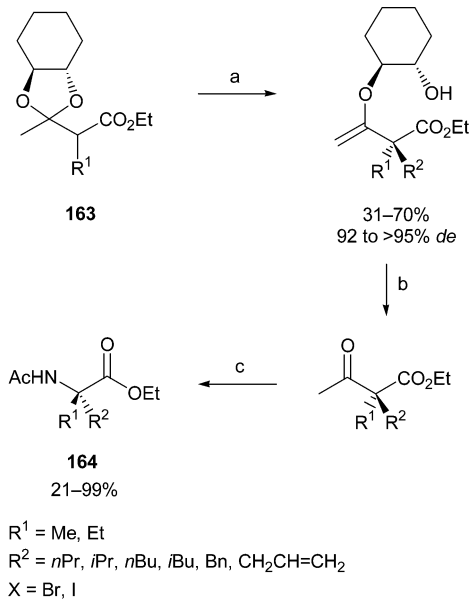
Vallribera *et al.* suggested a strategy using easily accessible D-ribonolactone acetonide as chiral auxiliary for the diastereoselective alkylation of α-monosubstituted β-ketoesters **161**, followed by transesterification and subsequent stereospecific Schmidt

rearrangement towards α,α-disubstituted α-amino esters **162** (Scheme 45).[102]



Scheme 45 Stereospecific Schmidt rearrangement of β-ketoesters according to Vallribera *et al.*[102] *Reagents and conditions*: (a) NaH; (b) R^2Br, THF, −78 °C to rt; (c) $Ti(OEt)_4$, EtOH, reflux, 5 h (37–93%); (d) NaN_3, CH_3SO_3H, DME, −30 °C to rt, 24 h; (e) 6 N HCl, reflux, 24 h (65–81%).

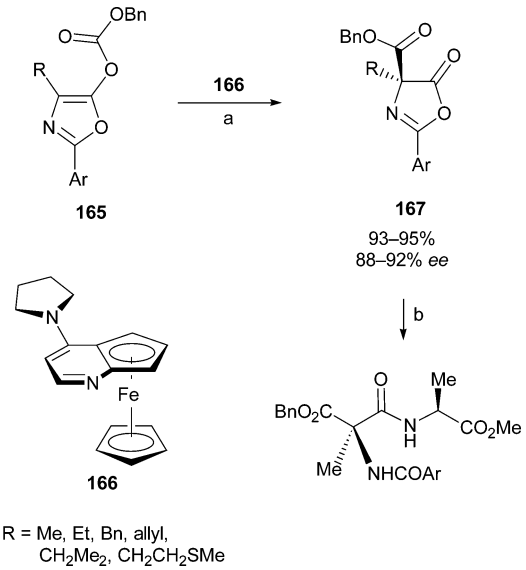
A similar strategy was pursued by Tanaka *et al.*[103] In this case, α,α-disubstituted β-ketoesters were synthesised by diastereoselective alkylation of the acetal **163** (Scheme 46). While the originally envisioned Beckmann rearrangement failed to deliver



Scheme 46 Stereospecific Schmidt rearrangement of β-ketoesters according to Tanaka *et al.*[103] *Reagents and conditions*: (a) LDA, R^2X, THF, HMPA, −78 °C to −40 °C; (b) $BF_3{\cdot}OEt_2$, EtOH, H_2O, rt, 3 h (73–85%); (c) NaN_3, CH_3SO_3H, $CHCl_3$, reflux, 6 h.

the corresponding α,α-disubstituted α-amino acid in acceptable yield, stereospecific Schmidt rearrangement furnished the *N*-acylated amino ester **164** in moderate to excellent yield, depending on the nature of substituents.

Ruble and Fu reported a catalytic asymmetric approach to the Steglich rearrangement of *O*-acylated azlactones **165** to give C^5-acylated oxazinones **167** (Scheme 47).[104] The application of the planar chiral, ferrocene-derived 4-(pyrrilidino)pyridine-catalyst **166** gave rise to the products in 93–95% yield and 88–92% ee.

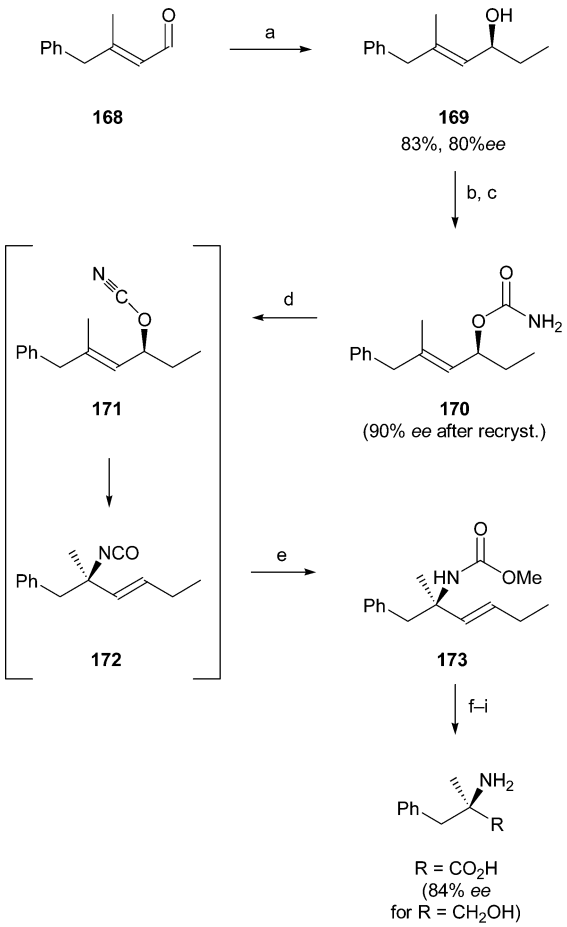


Scheme 47 Asymmetric catalytic Steglich rearrangement of azlactones according to Ruble and Fu.[104] *Reagents and conditions*: (a) *t*-amyl alcohol, 0 °C; (b) L-Ala-OMe (95%, for R = Me).

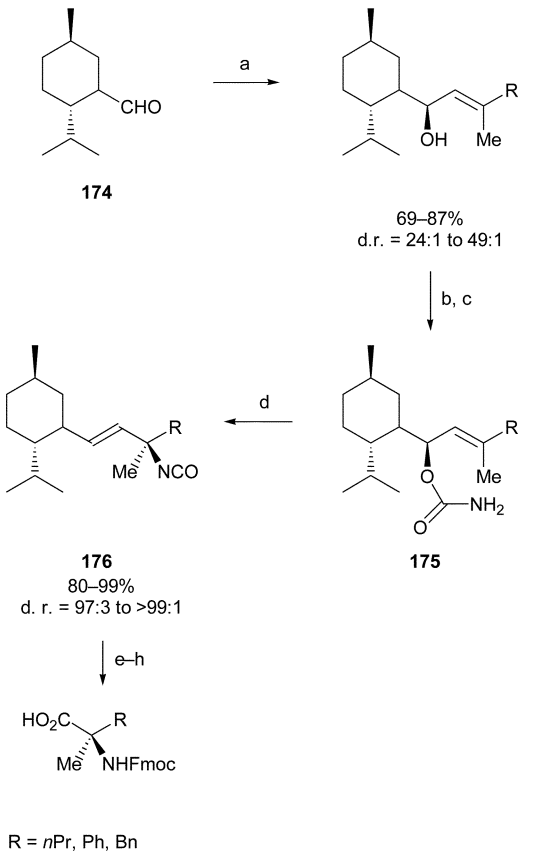
The final class of stereospecific rearrangement reactions to be discussed herein is the class of [3,3]-sigmatropic rearrangements. Very recent approaches in this context involve the formation of a C-N bond by a [3,3]-sigmatropic rearrangement reaction.

Ichikawa *et al.* presented the stereospecific rearrangement of isocyanate **171** towards cyanate **172** in the synthesis of α-methylphenylalanine (Scheme 48).[105] Stereoselective addition of diethylzinc to the α,β-unsaturated aldehyde **168** afforded the chiral allylic alcohol **169** in 80% ee. After the conversion to carbamate **170**, the enantiomeric excess was increased to 90% ee by recrystallisation. Dehydration of **170** delivered isocyanate **171**, which underwent a [3,3]-sigmatropic rearrangement reaction towards cyanate **172**. Due to its susceptibility towards hydrolysis, **172** was not isolated, but immediately converted to carbamate **173**. Oxidative cleavage and hydrolysis finally furnished the free amino acid. The enantiomeric excess of the corresponding amino alcohol was determined to be 84% ee. Thus, the rearrangement step was found to be 97% stereospecific. The applicability of this rearrangement type was also demonstrated in the synthesis of different natural products.[106]

A very similar strategy involving the same rearrangement type was developed almost simultaneously by Roy and Spino.[107] The rearrangement of chiral carbamates **175** towards allylic cyanates **176** proceeded highly stereospecifically (Scheme 49). The chiral carbamates **175** were obtained by diastereoselective addition of vinyllithium or vinylalanes to *p*-menthanecarboxaldehyde (**174**)



Scheme 48 3,3-Sigmatropic rearrangement of isocyanates according to Ichikawa *et al.*[106] *Reagents and conditions*: (a) (*S*)-*N*-methyl-α,α-diphenylprolinol, $ZnEt_2$, Et_3N, cyclohexane, 5 °C, 16 h; (b) $Cl_3CCONCO$, CH_2Cl_2, 0 °C; (c) MeOH, K_2CO_3, 0 °C to rt (92%, 2 steps); (d) PPh_3, Et_3N, CBr_4, CH_2Cl_2, 0 °C, 20 min; (e) Bu_3SnOMe, MeOH, 12 h (85%, 2 steps); (f) O_3, CH_2Cl_2, −78 °C, 10 min; (g) $NaClO_2$, NaH_2PO_4, *t*BuOH, H_2O, isoprene (87%, 2 steps); (h) 6 N HCl, reflux, 6 h; (i) ion exchange (93%, 2 steps).



Scheme 49 3,3-Sigmatropic rearrangement of isocyanates according to Roy and Spino.[107] *Reagents and conditions*: (a) ICH=C(CH_3)R, *t*BuLi, $AlMe_3$, THF; (b) $Cl_3C(O)OCN$, CH_2Cl_2, 0 °C; (c) K_2CO_3, MeOH, H_2O (88 to >99%, 2 steps); (d) Tfa_2O, Et_3N, CH_2Cl_2, 0 °C; (e) 9-fluorenemethanol, $Ti(OtBu)_4$, benzene, 45 °C (84–95%); (f) O_3, CH_2Cl_2; (g) PPh_3; (h) $NaClO_2$, NaH_2PO_4, *t*BuOH, H_2O, isoprene (81–98%).

and subsequent protection of the hydroxy-group. The cyanates **176** resulting from the rearrangement reaction were converted to Fmoc-protected amino acids by titanium-catalysed addition of 9-fluorenemethanol and subsequent oxidative cleavage of the double bond.

Conclusion

The incorporation of α,α-disubstituted α-amino acids has proved to be very useful for influencing the conformational behaviour of peptides and peptoids. This led to the targeted synthesis of many substances with enhanced receptor affinity and physiological properties. Moreover, previously unknown natural products containing α,α-disubstituted α-amino acid moieties are constantly being discovered, causing a growing demand for efficient methods for their preparation.

Despite the existence of many powerful methods for the synthesis of α,α-disubstituted α-amino acids, the challenge to asymmetrically construct their fully substituted stereogenic carbon centre therefore keeps on inspiring many synthetic chemists. Especially the emergence of asymmetric catalytic approaches, such as the phase transfer-catalysed alkylation of Schiff base enolates, the organocatalysed α-amination of α-disubstituted carbonyl compounds, or asymmetric catalytic Strecker reactions, has given a new edge to amino acid synthesis, and further breakthroughs are to be expected in these areas. At the same time, auxiliary-controlled methods—well-established strategies as well as newly developed concepts—have lost none of their relevance, and still find widespread application in natural product synthesis. Thus, the field of α,α-disubstituted α-amino acid synthesis will remain vivid and continue to inspire future generations of organic chemists.

Acknowledgements

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