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Recent Developments in the Stereoselective Synthesis of α-Aminoacids

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Contents

1. INTRODUCTION

The α-amino-carboxylic-acids are one of the five major classes of natural products and they exhibit important and diverse biological functions.[1,2] Historically, the aminoacids have been subdivided into the 20 proteinogenic and the non-proteinogenic representatives.[3] The number of known naturally occurring unusual, *i.e.* non-proteinogenic, structures is constantly increasing, and had reached 700 when counting was discontinued in 1985.[3c] Besides their role as constituents of peptides, proteins, and peptidoglycans in bacterial cell-walls, aminoacids have also a function for neuronal signal transduction (glycine, glutamate) and are further metabolized, *e.g.* to polyamines. The unusual structures are mainly produced by various microorganisms and have evolved to interfere with biochemical pathways of other organisms. In close analogy a large number of man-designed unusual aminoacids find pharmaceutical applications or are used to control plant growth and plant diseases.

Except for glycine, α-aminoacids are chiral structures and most naturally occurring compounds belong to the L-series, which in most cases corresponds to the (*S*)-configuration according to the *C.I.P*-rules. A lot of effort has therefore been devoted to the preparation of aminoacids in enantiomerically pure form of either configuration, a subject already covered by many general reviews[4,5] and reviews covering selected aspects including their *industrial production*[6]; *specific methods* such as chiral glycine templates,[7] kinetic resolution by enzymes,[8] chromium aminocarbene complexes,[9] carbohydrates as chiral auxiliaries,[10] partial synthesis from carbohydrates[11] or other aminoacids;[12] *specific compounds* such as α,β-unsaturated,[13] β,γ-unsaturated,[14] and acetylenic aminoacids,[15] aryl-glycines,[16] fluorine-containing structures,[17] 1-aminocyclopropane-carboxylic acids,[18] and α-aminoaldehydes;[19] *mechanistic aspects* like allylic strain[20] and catalyst structure in asymmetric hydrogenations;[21] and *the use of aminoacids as chiral starting materials*,[19a, 22] *auxiliaries* and *catalysts*.[23]

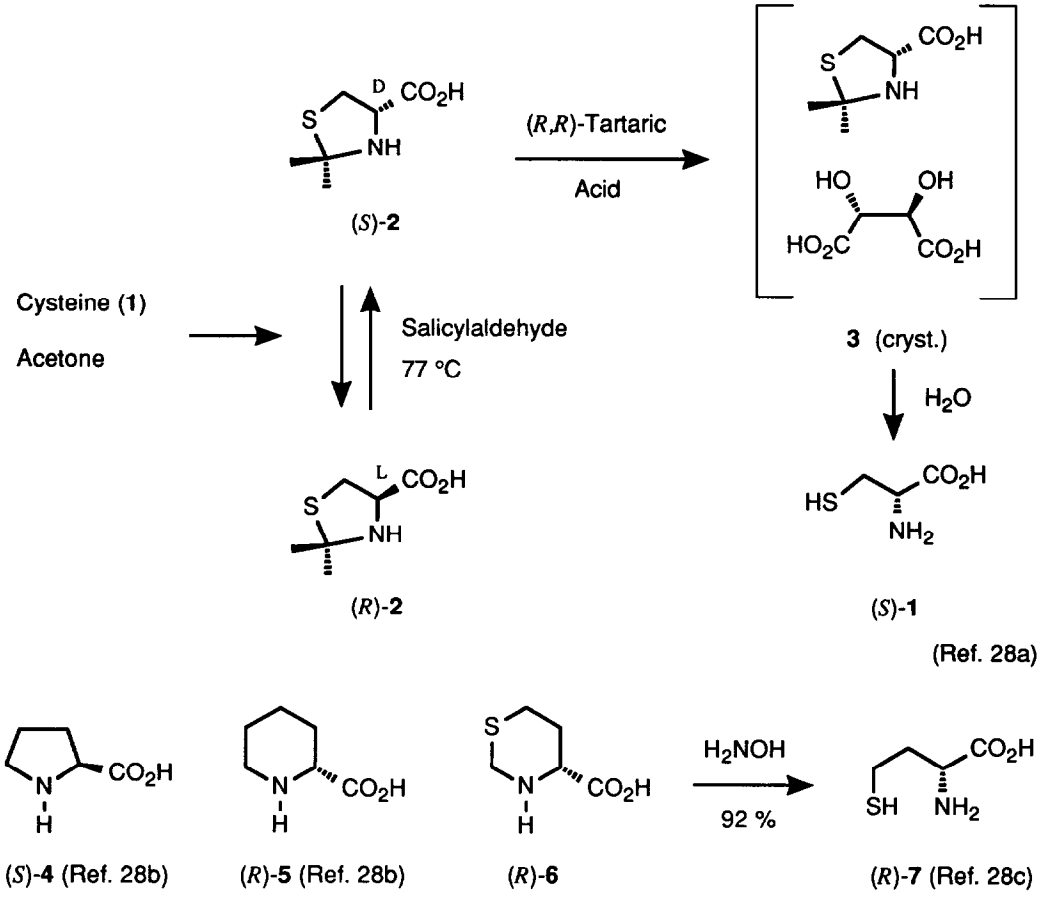
The present review covers the literature which has appeared since the monograph of Williams[5] in 1989, including all methods for obtaining optically active aminoacids with the exception of the classical resolution of racemates. Whenever possible the corresponding chapters of reference 5 are referred to. The classification is strictly according to methods and not structure types. **Not included** are methods for the enantioselective preparation of α-*substituted quaternary* α-aminoacids, β-*aminoacids*, α-amino-*phosphonic* and α-amino-*boronic* acids. The (*L*)-enantiomers of the proteinogenic aminoacids can be produced on an industrial scale,[6] mostly by using biotechnological methods. Suitable derivatives of most common aminoacids [24] including cysteine[25] allow, furthermore, the direct separation of their racemates without the need of a chiral auxiliary for the formation of diastereomeric derivatives. The currently developed methods are therefore aiming at the reliable and expedient preparation of the more complex non-proteinogenic representatives. It has to be noted that one of the major hurdles is still the final deprotection and purification, especially in the case of sensitive compounds, *e.g.* β,γ-unsaturated aminoacids[14] or aryl-glycines[16].

2. KINETIC RESOLUTION OF RACEMATES

In contrast to the classical resolution by crystallization or chromatographic separation of diastereomeric derivatives, and as opposed to the direct separation by preferential crystallization,[24, 25] chromatography using chiral stationary phases,[26] or enantioselective transport through chiral membranes,[27] kinetic resolution makes use of enantiomer selective reactions. A racemate is thereby chemically transformed by a chiral reagent or catalyst. The optical purities of product and remaining starting material are a function of the different rates for the enantiomers. In ideal cases the reaction stops after 50% conversion. If concomitant racemization of only the starting material is possible, a complete transformation to one enantiomer can be achieved.

2.1. Chemical Methods

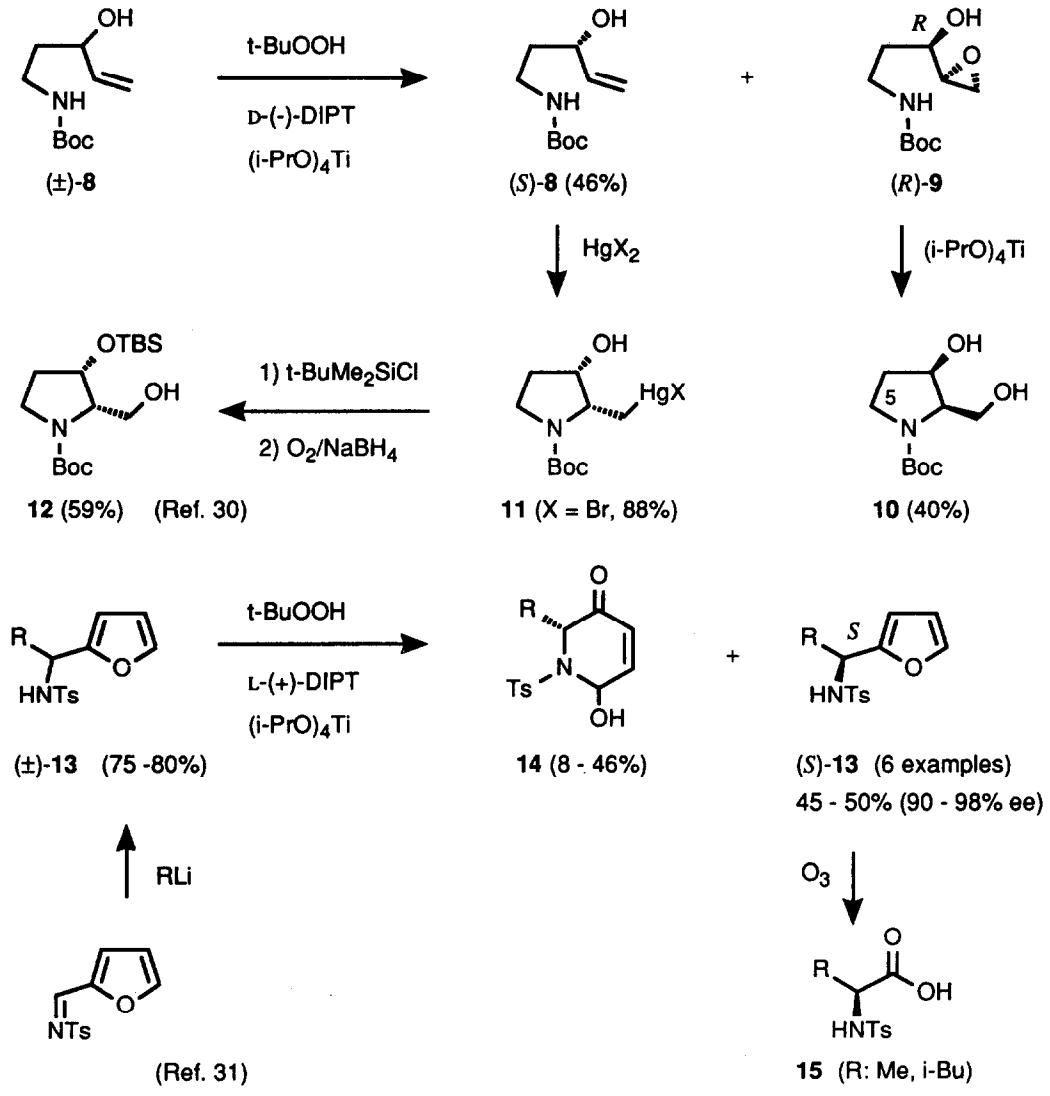
Cyclic aminoacids can be racemized smoothly by heating in carboxylic acids with an aldehyde as catalyst. Protonated Schiff's bases are proposed as intermediates of this epimerization. In combination with enantioselective salt precipitation using (*R,R*)- or (*S,S*)-tartaric acid Shiraiwa and coworkers have applied this principle for the deracemization of aminoacids.[28] As shown in *Scheme 1* (*R/S*)-cysteine (**1**) was transformed with acetone/AcOH to 2,2-dimethylthiazolidine-4-carboxylic acid (**2**). By heating with one equivalent of (*R,R*)-tartaric acid in the presence of salicylaldehyde the salt **3** was precipitated in high yield. Hydrolysis gave (*S*)-cysteine (**1**) of 98% ee in 80% overall yield.[28a] Using the same method (*S*)-proline (**4**, 80%),[28b] (*R*)-pipecolic acid (**5**, 70%),[28b] and (*R*)-1,3-thiazane-4-carboxylic acid (**6**, 80%), a precursor of (*R*)-homocysteine (**7**)[28c] could be obtained in optically pure form.



Scheme 1

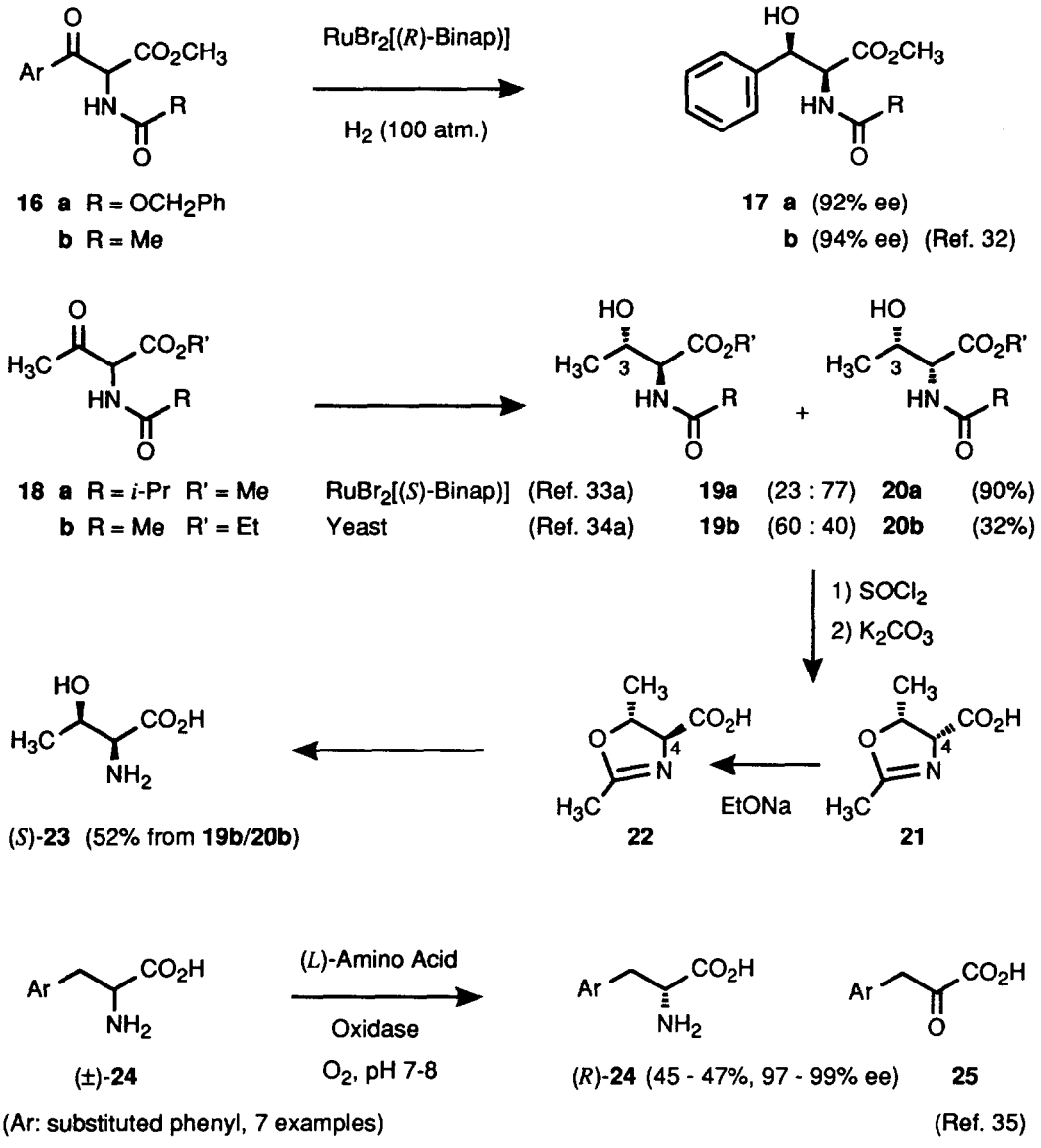
Not surprisingly, the catalytic oxidation system developed by Sharpless and coworkers for enantioselective epoxidations[29] has also been applied for kinetic resolution of aminoacid precursors (*Scheme 2*). Using (*D*)-(-)-DIPT (diisopropyl tartrate) the (*R*)-enantiomer of the racemic allyl alcohol **8** was selectively oxidized to the epoxide **9**, which formed hydroxy-L-prolinol **10** by $Ti(O\text{-}i\text{-}Pr)_4$ assisted ring closure. Amidomercuration

of (*S*)-**8** (→ **11**) followed by *O*-protection and oxidative demercuration gave the enantiomeric prolinol **12**, selectively protected at O-C(3).[30] By *O*-silylation and RuO_2-mediated oxidation of C(5) the diol **10** was transformed into an intermediate for *threo*-3-hydroxyglutamate. Swern oxidation of **12** affords 3-hydroxyprolinal.



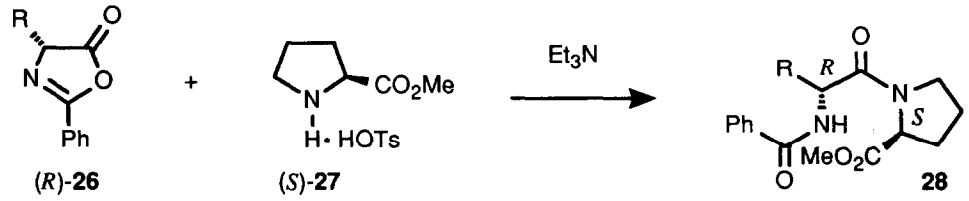
Scheme 2

The α-furyltosylamides **13** are readily obtained from N-tosylfurfuralimine. Enantiomer-selective oxidation with L-(+)-tartrate as auxiliary afforded the unstable dihydropyridones **14** and the (*S*)-enantiomers of **13** (R: Me, Et, n-Pr, n-Bu, i-Bu, n-Hex) in high optical purity (90 - 98% ee). Oxidative degradation of two representatives (R: Me, i-Bu) with O_3 or $RuCl_3/NaIO_4$ afforded the N-tosyl aminoacids **15**.[31]



Scheme 3

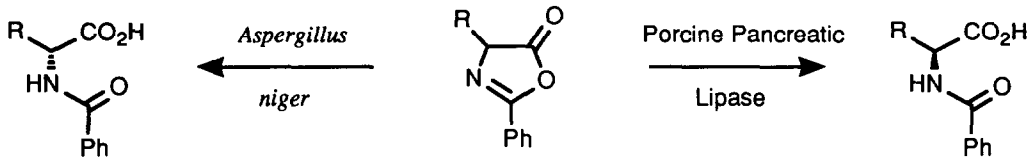
The enantiomers of α-amido-β-ketoesters are in rapid equilibrium, due to the acidity of the α-hydrogen. Reduction of the keto-function generates a new stereocenter and the facile racemization is stopped simultaneously, an ideal situation for kinetic resolution. The Ru/Binap hydrogenation catalyst developed by Noyori and associates is ideally suited for this transformation and the arylketone **16** is converted quantitatively to the (*L*)-*threo*-β-hydroxyphenylalanine derivative **17** with excellent induction (92 - 94% ee, *Scheme 3*).[32] While cationic Rh-complexes turned out to be less discriminating, the Ru/Binap system was successfully applied for the reductive resolution of various α-acylamino-β-oxocarboxylates as well,[33] *e.g.* acetoacetate



(*R*)-**26** (*S*)-**27** **28**

R	% de (CH_2Cl_2)	% de (DMF)
i-Pr	84	72
i-Bu	90	72
s-Bu	79	83
t-Bu	86	80
Ph	89	68

(*S*)-**26** (Ref. 36b)



(*R*)-**29** (±)-**26** (*S*)-**29**

% ee	R	% ee
83	$MeS(CH_2)_2$	80
37	4-$HOC_6H_4CH_2$	19
99	$C_6H_5CH_2$	**99**
34	Indol-3-CH_2	55
6	i-Bu	87
80	C_6H_5	76
15	4-HOC_6H_4	67
20	$C_6H_5CH_2SCH_2$	20

(Ref. 37a)

Scheme 4

18a.[33a] In this case, however, 23% of *erythro*-epimer **19a** was formed in addition to the major diastereomer **20a**. The same transformation can also be effected by microbial reduction (*Saccharomyces rouxii*, baker's yeast).[34a] The 3 : 2 mixture of **19b** and **20b** could be transformed to the oxazolines **21** and **22**, involving an inversion of C(3). Equilibration at C(4) and oxazoline cleavage gave L-threonine **23** in 52% overall yield from **19b/20b** (*Scheme 3*). *Cis*-3-Hydroxy-(*R*)-proline[34b-e] and the six-membered analog[34f] can be produced by microbial reduction of the corresponding cyclic ketoesters as well. D-Configurated phenylalanines **24** with va-

rious substituents on the aromatic ring have been obtained in excellent yield and with high optical purity by subjecting the racemates to L-aminoacid oxidase (*Scheme 3*).[35] The L-enantiomers are thereby transformed into the α-ketoacids **25**.

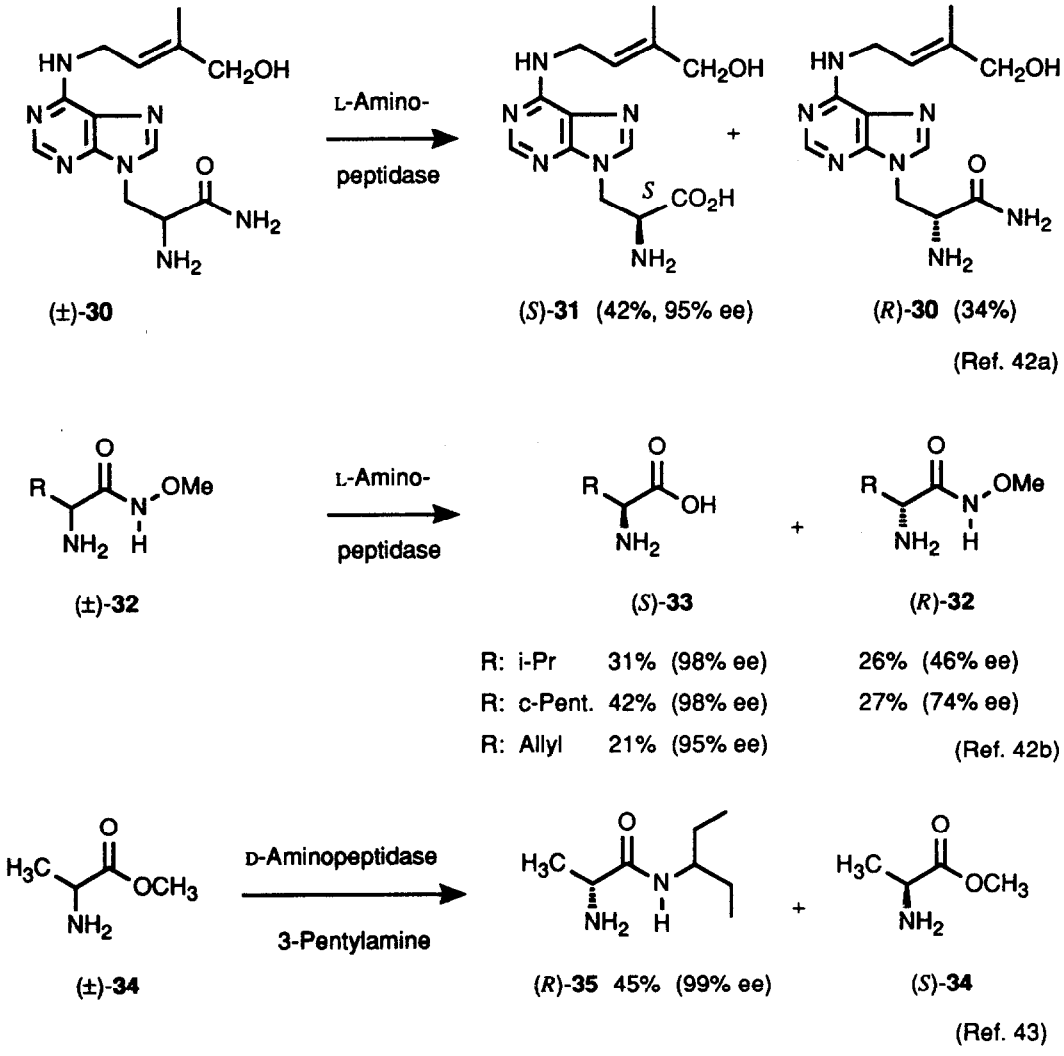
Oxazolin-5-ones (azlactones), derivatives of *N*-acyl-aminoacids, are especially prone to racemization and therefore suited for kinetic resolution with concomitant isomerization. Miyazawa and coworkers used α-aminoesters for the enantiomer-selective aminolysis of such oxazolinones (*Scheme 4*).[36] 2-Phenyl-5-oxazolinones **26**[36a,b] gave thereby better results than the corresponding azlactones derived from formic, acetic, pivalic[36c], or trifluoroacetic[36d] acid; and proline methyl ester **27** was more selective in forming the (*R,S*)-configurated *N*-benzoyl dipeptides **28** than other α-amino-esters. The diastereomeric excess is generally better in non-polar solvents like CH_2Cl_2 or xylene than in DMF and can be increased by lowering the temperature.[36a] In a recent report Sih and coworkers demonstrated that the same 2-phenyloxazolinones (±)-**26** can also be hydrolyzed enzymatically with high enantiomer selectivity (*Scheme 4*).[37] By testing ten different lipases it was found that porcine pancreatic lipase (PPL) affords the (*S*)-enantiomers of the *N*-benzoylaminoacids **29**, while the *Aspergillus niger* enzyme is (*R*)-selective. In some cases like phenylalanine the induction is impressive; for some substrates, however, uncatalyzed hydrolysis appears to compete with the enzymatic process. In a recent report a more general method for the enantiomer-selective hydrolysis of (±)-**26** is described:[37b] in a first step methanolysis catalyzed by *Pseudomonas cepacia* lipase gives *N*-benzoyl methyl esters in 46 - 91% yield and with 66 - 95% ee. Further treatment with *Protease N* or *Prozyme 6*, two commercially available enzyme preparations, affords (*S*)-**29** of > 99% ee and often in more than 50% overall yield. The same proteases also catalyze the hydrolysis of C(4)-substituted 2-phenylthiazolin-5-ones to L-*N*-thiobenzoylaminoacids (14 - 98%, 57 - 98% ee).[37b] The alcoholysis (n-BuOH) of (±)-**26** has also been catalyzed by a fungal lipase (*Mucor miehei*).[38] The induction is, however, not as high (43 - 69% ee, *S*) and the racemization too slow to allow a complete conversion.

Closely related to these studies are the efforts of a Russian group (Karpeiskaya, Klabunovskii, and coworkers) put forward in a series of publications[39] on the reductive amination of azlactones derived from α,β-unsaturated amino acids. Hydrogenation to the saturated azlactones catalyzed by $PdCl_2$/amine precedes the enantiomer selective aminolysis by a chiral amine, which can be the same as used for the hydrogenation. The best inductions (50% de) have been observed with phenethylamine or phenylglycinol. Azlactones derived from 2-aminotetralin-2-carboxylic acid and a series of related compounds have been resolved by aminolysis with L-Phe-L-Phe-amides followed by separation of the corresponding tripeptides and hydrolysis.[40] In this case the fully substituted α-carbons prevented an asymmetric transformation by *in situ* racemization.

2.2. Use of Hydrolytic Enzymes

Hydrolytic enzymes are especially well suited for the kinetic resolution of racemic aminoacid derivatives (*cf.* ref. 5; *chapter 7*, pp. 257 - 279). This method has therefore found numerous industrial applications and has also recently been reviewed.[6,8] The different approaches are best classified according to the bond cleaved by enzymatic assistance. The major processes are amide or nitrile hydrolysis by *aminopeptidases* or *nitrilases*, cleavage of N-acyl groups by *acylases*, and ester hydrolysis by *lipases* or *proteases*. A disadvantage of enzymatic methods is often the narrow substrate tolerance; the determination of scope and limitation is therefore of crucial importance. As most enzymes selectively process the L-configurated enantiomers, recent effort has been directed towards finding D-selective enzymes. The availability of the enzymes from natural sources is no longer a major issue, as sequencing, cloning, and expression can now be done routinely. Enzy-

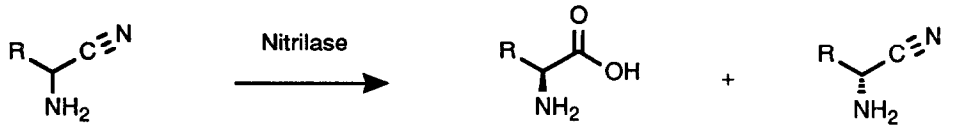
mes with improved properties, *e.g.* higher stability, become available from site-specific mutations.



Scheme 5

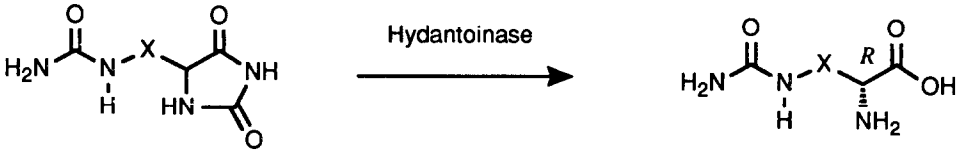
The versatility of the L-specific aminopeptidases from *Pseudomonas putida* and *Mycobacterium neoaurum* has been illustrated in several recent reviews[6b,c,41] and articles.[42] Complex substrates such as amide **30** are smoothly converted into (*S*)-lupinic acid **31** leaving the D-enantiomer (*R*)-**30** untouched (*Scheme 5*).[42a] *N*-Methoxy-amides **32** are more soluble than the unsubstituted counterparts and are therefore easier to handle. Their successful kinetic resolution by the L-specific aminopeptidase affording L-aminoacids **33** is therefore of high practical value.[42b] With the aid of the D-specific aminopeptidase from *Ochrobacterium anthropi* aminolysis of racemic amino acid esters **34** in aprotic solvents affords selectively the (*R*)-configurated amides, *e.g.* alanine-3-pentylamide (*R*)-**35** (*Scheme 5*).[43] The substrate tolerance of this thiol-peptidase is, however, rather narrow, and branched-chain aminoacids as well as serine, threonine, and methionine are not processed. While

3-pentylamine can be replaced by n-butylamine, neopentylamine, or benzylamine (slow!), laurylamine and aniline are not tolerated.



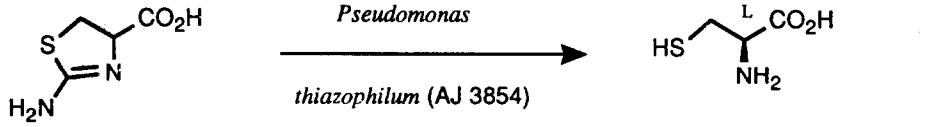
R:		
	i-Pr	> 99% ee
	n-Pr	92% ee
	i-Bu	89% ee
	n-Bu	> 99% ee
	$MeS(CH_2)_2$	96% ee

(Ref. 44)



X:			
	CH_2	69%	98% ee
	$(CH_2)_2$	73%	96% ee
	$(CH_2)_3$	79%	96% ee
	$(CH_2)_4$	70%	20% ee
	$(CH_2)_2SCH_2$	71%	96% ee
	$(CH_2)_2S(CH_2)_2$	78%	96% ee

(Ref. 46)



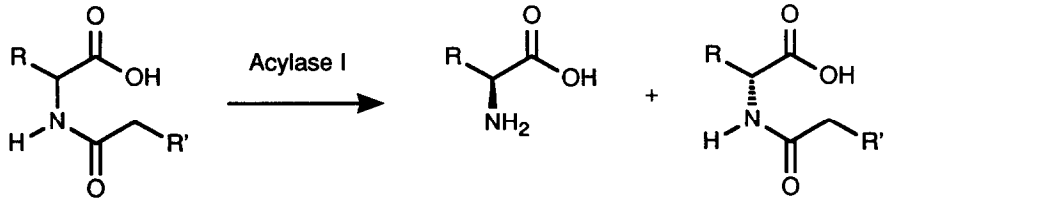
(Ref. 47)

Scheme 6

Racemic α-aminonitriles **36** are efficiently prepared by the Strecker synthesis. Their enantiomer selective hydrolysis to α-aminoamides or aminoacids **37** is therefore of great practical value. The nitrilase from *Rhodococcus rhodochrous* converts several substrates **36** with high L-selectivity to (*S*)-configurated acids **37** (*Scheme 6*).[44] In the case of R = CH_3, however, D-alanine of 57% ee is produced. The enantiomer-selective α-aminonitrile hydrolysis has also been attempted with chiral ketones as catalysts.[45] For phenylalanine amide the maximal enantiomeric excess obtained was 42%.[45a] With the aid of a new D-selective hydantoinase (EC 3.5.2.2) from *Agrobacterium radiobacter* racemic hydantoins with an ω-ureido function **38** can be cleaved to

(*R*)-configurated acids **39**.[46] Due to *in situ* racemization of **38** the yields exceed 50% (*Scheme 6*). Thiazoline **40**, a synthetic intermediate for racemic cysteine, can be transformed quantitatively to L-cysteine (**1**) by fermentation with *Pseudomonas thiazophilum* under carefully optimized conditions.[47]

Table 1: Enantiomer Selective Hydrolysis of Racemic *N*-Acetyl or *N*-(Chloroacetyl) Aminoacids with Acylase I (EC 3.5.1.14).[48]



R	R'	Enzyme	(*S*)-42	Yield (% ee)	(*R*)-42	Yield (% ee)
Et	H	Porcine kidney		40% (99.5)		32% (99.5)
Et	Cl	Porcine kidney		40% (99.5)		41% (99.5)
n-Pr	H	*Aspergillus*		33% (99.5)		32% (99.5)
Allyl	Cl	Porcine kidney		41% (99.5)		33% (99.5)
trans-Butenyl	H	*Aspergillus*		33% (99)		38% (93)
cis-Butenyl	H	Porcine kidney		44% (99.5)		47% (99.5)
cyclo-Pr	Cl	Porcine kidney		37% (99)		42% (84)
cyclo-PrCH$_2$	H	*Aspergillus*		50% (95)		50% (98)
2-FurylCH$_2$	H	*Aspergillus*		45% (99)		41% (-)[a]
MeS(CH$_2$)$_2$	Cl	Porcine kidney		51% (93)		31% (-)[a]
PhCH$_2$	Cl	Porcine kidney		43% (91)		46% (80)
4-HOC$_6$H$_4$CH$_2$	Cl	Porcine kidney		17% (95)		64% (47)

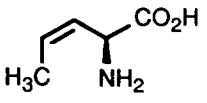
a) The free amino acid (*R*)-**42** was not isolated.

One of the most versatile acylases for the L-selective cleavage of N-acetyl, chloroacetyl, or methoxyacetyl groups is acylase I (EC 3.5.1.14), obtained either from *porcine kidney* or *Aspergillus oryzae*. Whitesides and associates have reported an exhaustive study involving over 50 substrates (±)-**41**; some of their re-

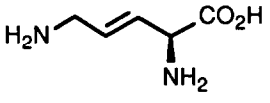
sults are summarized in *Table 1*.[48] The selectivity is generally excellent, and after separation of L-**42**, D-**41** can often be hydrolyzed chemically, affording the enantiomer D-**42** in high optical purity as well. The two enzymes show some complementarity, as only the fungal enzyme tolerates α-methyl-α-aminoacids, while the O_2-sensitive acylase from porcine kidney is to be preferred for aromatic and β-branched sidechains. Aminoacids with additional functionalities (lysine, histidine, arginine) are poor substrates; aspartic acid and secondary aminoacids (proline, pyroglutamate) are not tolerated.

It is therefore not surprising, that this method has found rather broad application, and further structures resolved with acylase I are shown in *Chart 1*. Enzymatic hydrolysis is probably the best method for obtaining the L-enantiomers of delicate β,γ-unsaturated aminoacids like **43 - 48**, used for labelling with ^3H (**43**, **44**)[49] or as enzyme inhibitors and antimetabolites (**44 - 48**).[50,51] Trifluoro-norvaline **49**,[52] the bornyl-alanine **50**, used for artificial sweeteners,[53] and cyclooctatetraenyl-alanine **51**, designed as a metal ligand[54a], have been resolved with acylase I as well as furyl- and thienyl-alanine.[54b]

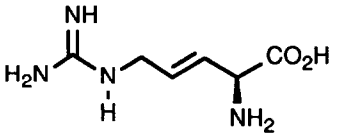
Chart 1: Aminoacids Resolved by Acylase I (EC 3.5.1.14)



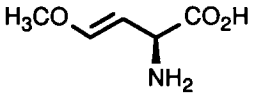
43 (Ref. 49)



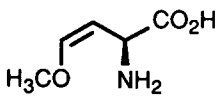
44 (Refs. 49, 50)



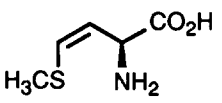
45 (Ref. 50)



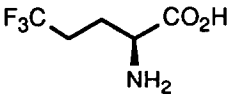
46 (Ref. 51)



47 (Ref. 51b)



48 (Ref. 51c)



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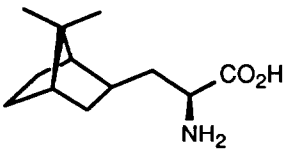

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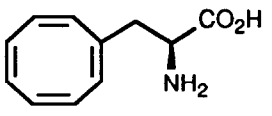
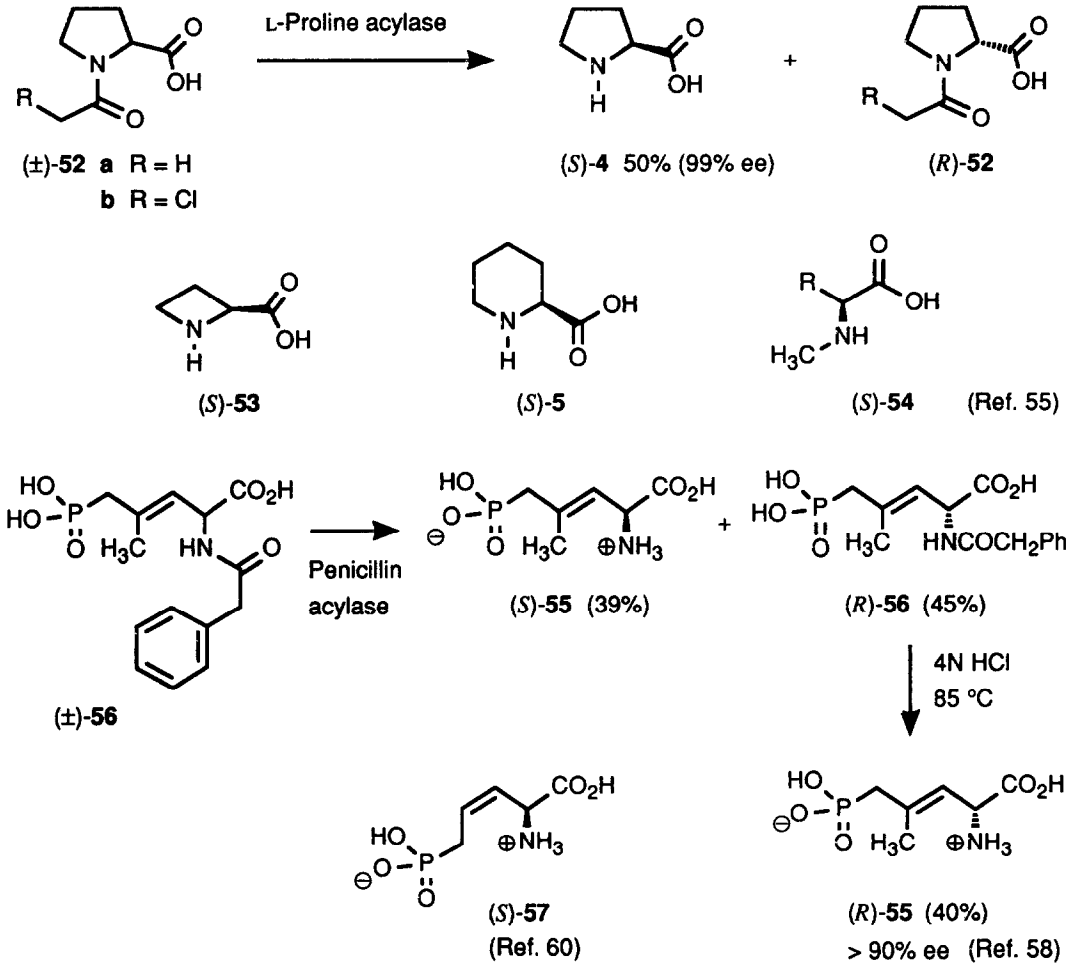


51 (Ref. 54a)

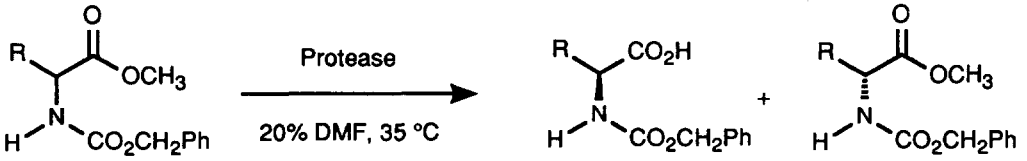
While acylase I does not process proline or other cyclic aminoacids, an L-selective proline-acylase was found in *Bacterium comamonas testosteroni* (DSM 5416).[55] As shown in *Scheme 7*, this enzyme not only converts L-configurated *N*-acetyl or *N*-chloroacetyl-proline **52a,b** into L-proline (**4**), but can also be used to resolve azetidine-carboxylic acid **53**, pipecolic acid **5**, and some *N*-methyl-α-aminoacids **54**.[55c] *Penicillin acylase* (EC 3.5.1.11) is another enzyme, readily available from bacterial sources, which cleaves *N*-phenylacetyl derivatives of α-aminoacids with high L-selectivity.[56] This enzyme has also found use for selective deprotec-

tion in peptide and carbohydrate chemistry,[57] and was successfully applied for the resolution of 5-phosphono-α-amino-pentenoate **55** *via* the phenylacetamide (±)-**56**.[58] Chemical hydrolysis of (*R*)-**56**, not processed by the enzyme, gave (*R*)-**55** of high optical purity, a potent glutamate antagonist.[59] The (*S*)-enantiomer of *cis*-2-amino-5-phosphono-3-pentanoic acid (**57**) was obtained by the same method.[60] The specific rotation of (*S*)-**57** ($[\alpha]_D$ = + 198, c: 0.5/H_2O) is much higher than reported for the material obtained by acidic hydrolysis of the peptidic antibiotics plumbemycine[61] or rhizocticin.[62] Moreover, by applying the Clough-Lutz-Jirgenson rule[63] to **57** the wrong absolute configuration was deduced;[61] the correct configuration of (*S*)-(+)-**57** was corroborated by an independent synthesis from (*R*)-serine (*cf.* below, chapter 7.1.).[64] The fact that the original erroneous rotation value for (*S*)-**57** is reported in connection with a recently claimed total synthesis of (*S*)-**57**,[65d] adds to doubts over this work and related publications.[65]



Scheme 7

Table 2: L-Selective Ester Hydrolysis of Racemic *N*-Benzyloxycarbonyl Protected Aminoacid Methyl Esters (±)-**58** with Microbial Proteases.[66]



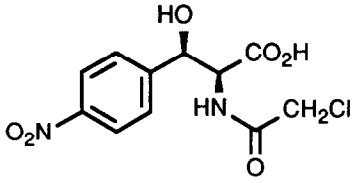
(±)-**58** (*S*)-**59** (*R*)-**58**

	Aspergillus oryzae		*Bacillus subtilis*	
R	conv.	% ee (**59**)	conv.	% ee (**59**)
Et	45%	78	40%	95
n-Pr	40%	83	40%	91
n-Bu	40%	98	40%	99
i-Bu	40%	93	40%	97
n-Pentyl	33%	94	40%	98
n-Hexyl	30%	97	38%	99
$HOCH_2$	38%	21	40%	78
$ZNH(CH_2)_4$	21%	98	40%	93
$C_6H_5CH_2$	40%	94	45%	98
$4\text{-}FC_6H_4CH_2$	17%	75	40%	85
$4\text{-}ClC_6H_4CH_2$	40%	98	40%	94
$4\text{-}BrC_6H_4CH_2$	32%	97	40%	90
i-Pr	-	-	40%	98
$MeS(CH_2)_2$	-	-	40%	99
C_6H_5	-	-	25%	41
$C_6H_5(CH_2)_3$	-	-	40%	99

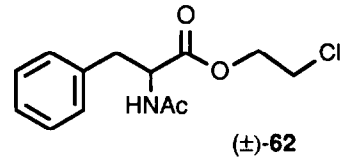
The third method for enzymatic resolution of amino acids makes use of proteolytic enzymes for enantiomer selective ester hydrolysis of *N*-acyl aminoacid esters. Among the best studied enzymes are the microbial proteases of *Bacillus subtilis* and *Aspergillus oryzae*. The scope of these enzymes has recently been surveyed and some of the results are collected in *Table 2*.[66] These hydrolytic enzymes apparently have a broader substrate tolerance than the acylases, and benzyloxycarbonyl protected derivatives (±)-**58** with unusual residues are cleaved L-selectively to the (*S*)-configurated acids **59**. The protease from *Bacillus subtilis* gives generally better results. Low optical purity is observed with serine and phenylglycine, and amino acids with

long aliphatic sidechains are processed at slow rates.

Site-directed mutation has yielded a subtilisin mutant (8350) with 100-fold enhancement of stability in H_2O and 50-fold higher stability in DMF, exhibiting similar or even moderately better catalytic activity.[67] The *Bacillus subtilis* protease was the only enzyme which allowed resolution of the chloroamphenicol precursor **60**,[68] and the *O*-phosphotyrosine analogs **61** have also been obtained by L-selective hydrolysis of the corresponding methyl or ethyl esters with this enzyme (*Scheme 8*).[69] In aprotic media the transesterification of β-chloroethyl ester (±)-**62** with n-propanol (→ **63**) is catalyzed by the *Aspergillus oryzae* protease.[70a] Interestingly, the preference of the enzyme changes from moderate L-selectivity in polar solvents to moderate D-selectivity in apolar media. It has recently been reported that bovine carbonic anhydrase (EC 4.2.2.1), a Zn-enzyme, cleaves methyl esters of *N*-acetyl-phenylalanine, -aspartate, and -glutamate with high D-selectivity.[70b]

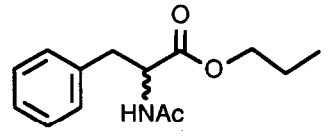


(*S*)-*threo*-**60** (Ref. 68)

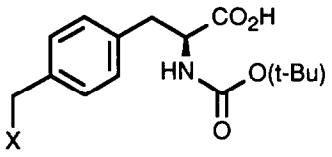


(±)-**62**

Aspergillus oryzae protease



63



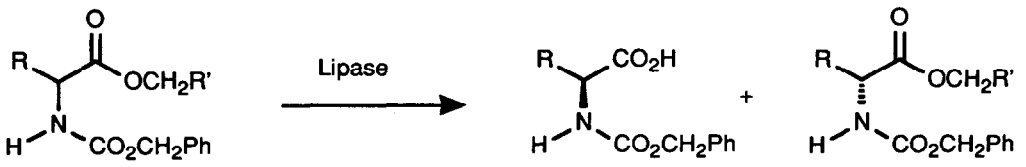
61 **a** X = CO_2CH_3
b X = CONHOH
c X = SO_3Na
d X = $PO(OEt)_2$ (Ref. 69)

Solvent	v_L/v_D (initial rates)	
CH_3CN	7.1 : 1	
Toluene	1 : 3.8	
Octane	1 : 4.2	
CCl_4	1 : 5.2	(Ref. 70a)

Scheme 8

Besides α-chymotrypsin,[68b,71] papain,[71b] and bromelain,[68b] *porcine pancreatic lipase* (PPL) is successfully used for enantiomer-selective ester hydrolysis, if trifluoroethyl esters are used.[72] In *Table 3* the results with PPL (EC 3.1.1.3)[72a] are compared with lipases from *Aspergillus niger*, *Pseudomonas fluorescens*, and *Candida cylindracea*.[73] Substrates are the benzyloxycarbonyl protected 2,2,2-trifluoroethyl esters (±)-**64a** in the case of PPL and the corresponding β-chloroethyl esters for the other lipases. With the exception of alanine, valine, n-hexylglycine PPL is more selective than the three microbial enzymes. In sharp contrast to the *Bacillus subtilis* protease (*cf.* above, *Table 2*[66]) the conversion to L-phenylglycine proceeds well and with excellent selectivity.

Table 3: L-Selective Hydrolysis of α-Amino Esters (±)-**64** with Different Lipases.[72a,73]



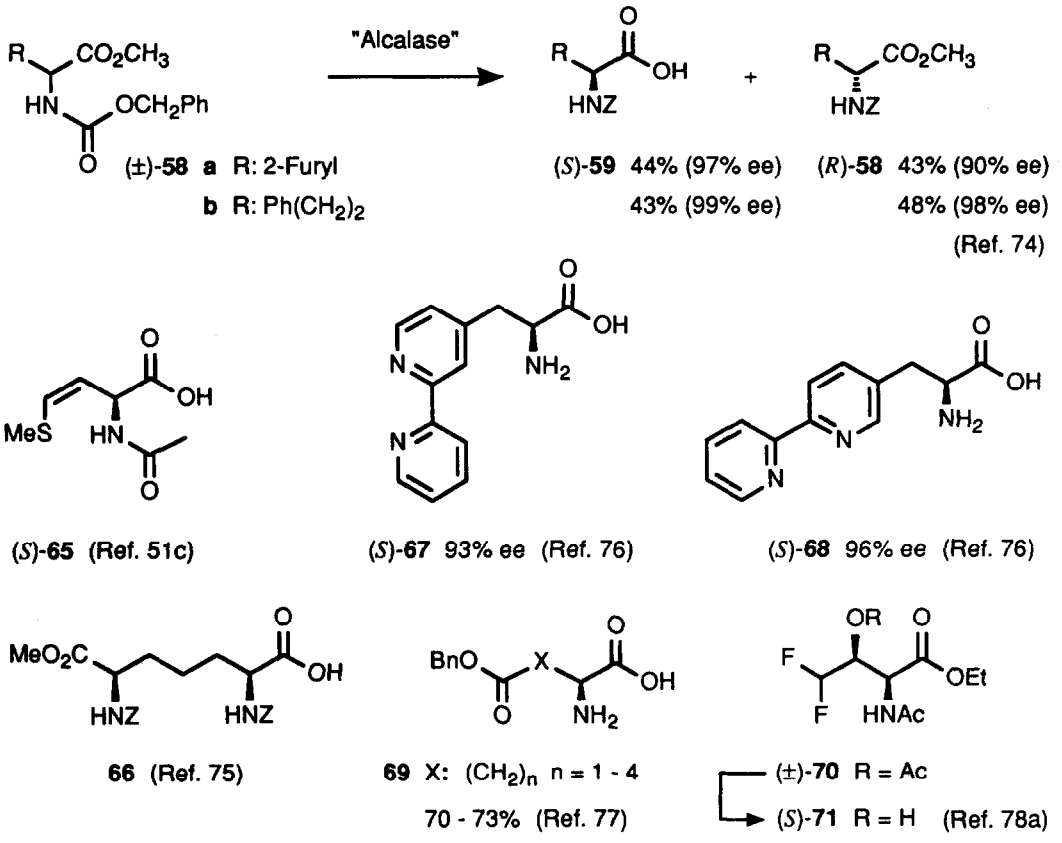
(±)-**64** **a** R': CF_3 (PPL) (*S*)-**59** (*R*)-**64**
b R': CH_2Cl (other lipases)

R	*PPL* conv.	(% ee)	*A.Niger* conv.	(% ee)	*P. fluorescens* conv.	(% ee)	*C. cylindracea* conv.	(% ee)
Me	31%	(21)	36%	(89)	46%	(16)	38%	(7)
Et	40%	(97)	40%	(96)	49%	(52)	36%	(7)
n-Pr	40%	(97)	27%	(86)	43%	(58)		
n-Bu	38%	(92)	32%	(85)	52%	(60)	42%	(30)
i-Bu	40%	(98)						
n-Pentyl	40%	(87)	44%	(95)	25%	(80)	27%	(66)
i-Pentyl	40%	(95)						
n-Hexyl	33%	(61)	31%	(94)	47%	(87)		
n-Heptyl	21%	(52)						
i-Pr	a)		14%	(92)	8%	(53)		
Allyl	38%	(93)	34%	(86)	40%	(52)	31%	(27)
$MeS(CH_2)_2$	40%	(90)						
C_6H_5	44%	(97)						
$C_6H_5CH_2$	40%	(99)	32%	(94)	12%	(57)	35%	(63)
Thiazol-4-CH_2	44%	(89)	37%	(94)	40%	(70)	35%	(43)
$C_6H_5(CH_2)_2$	30%	(71)						
$C_6H_5(CH_2)_3$	17%	(36)						
2-$FC_6H_4CH_2$	40%	(97)						
4-$FC_6H_4CH_2$	40%	(90)						
4-$ClC_6H_4CH_2$	28%	(94)						

a) not a substrate

The alkaline protease preparation "Alcalase" from *Bacillus licheniformis* (mainly *subtilisin Carlsberg*) is emerging as another useful enzyme for L-selective ester cleavage, converting (±)-**58** to (*S*)-configurated

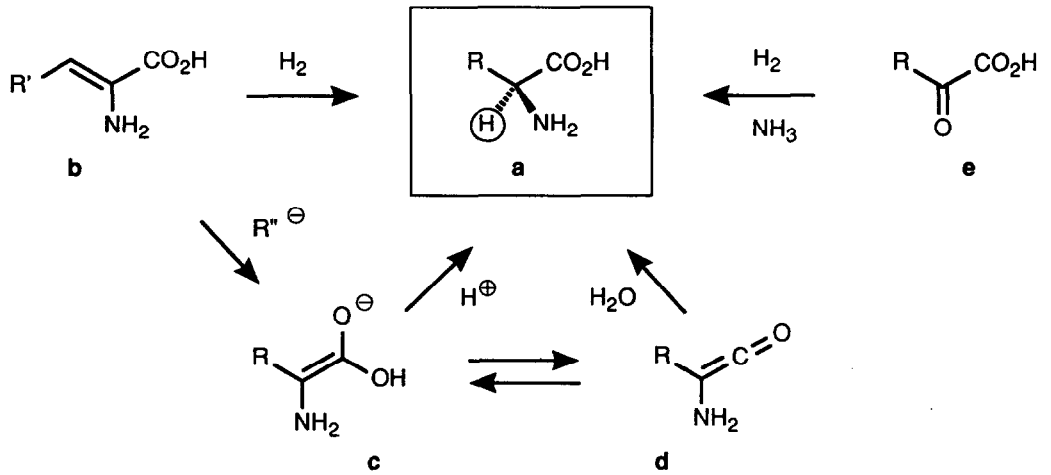
acid **59** and (*R*)-**58** (*Scheme 9*).[74] While unprotected esters are best hydrolyzed in water without buffer by adjusting the pH to 7 with 5N NaOH, a cosolvent (acetone or dioxane) is advisable for the lipophilic *N*-benzyloxycarbonyl protected derivatives (±)-**58**. In this case the enzyme should be stabilized by immobilization on *Amberlite XAD-8*.[74b] After L-selective ester-cleavage with subtilisin Carlsberg it is advantageous to cleave *N*-acetyl derivatives with acylase I, resulting in a further upgrading of enantiomeric purity.[74c] Alcalase was also used for the liberation of (*S*)-**65**,[51c] for the regioselective monohydrolysis of *meso*-2,7-diaminoheptanedioic acid monoester (→ **66**)[75] and for the resolution of the bipyridyl-alanines (*S*)-**67** and (*S*)-**68**.[76] The enzyme *pronase* (EC 3.4.24.4) converted the dibenzyl esters of α-amino diacids regioselectively to the monoesters **69**.[77] Treatment of racemic *N*,*O*-diacetyl-4-difluorothreonine (±)-**70**[78a] as well as the 4,4,4-trifluoro-analog[78b] with a *cellulase* from *Trichoderma viride* gave the monoprotected derivatives, *e.g.* **71**, with moderate L-selectivity (*Scheme 9*). D-4-Trifluorothreonine and L-4-trifluoro-*allo*-threonine are obtained by *O*-deacetylation with lipase MY from *Candida cylindracea*.[78b]



Scheme 9

3. ENANTIOSELECTIVE INTRODUCTION OF THE α-HYDROGEN

The principal transformations leading to α-aminoacids **a** by enantioselective introduction of the α-hydrogen are depicted in *Scheme 10*. Depending on whether the β-carbon, the nitrogen, or the carboxylate is involved in the unsaturation, the chiral α-carbon is obtained from α,β-unsaturated aminoacids **b** either by hydrogenation or 1,4-addition of nucleophiles (*via* **c**), protonation of enolates **c**, hydration of α-amino-ketenes **d**, or by reductive amination of α-keto-acids **e**.



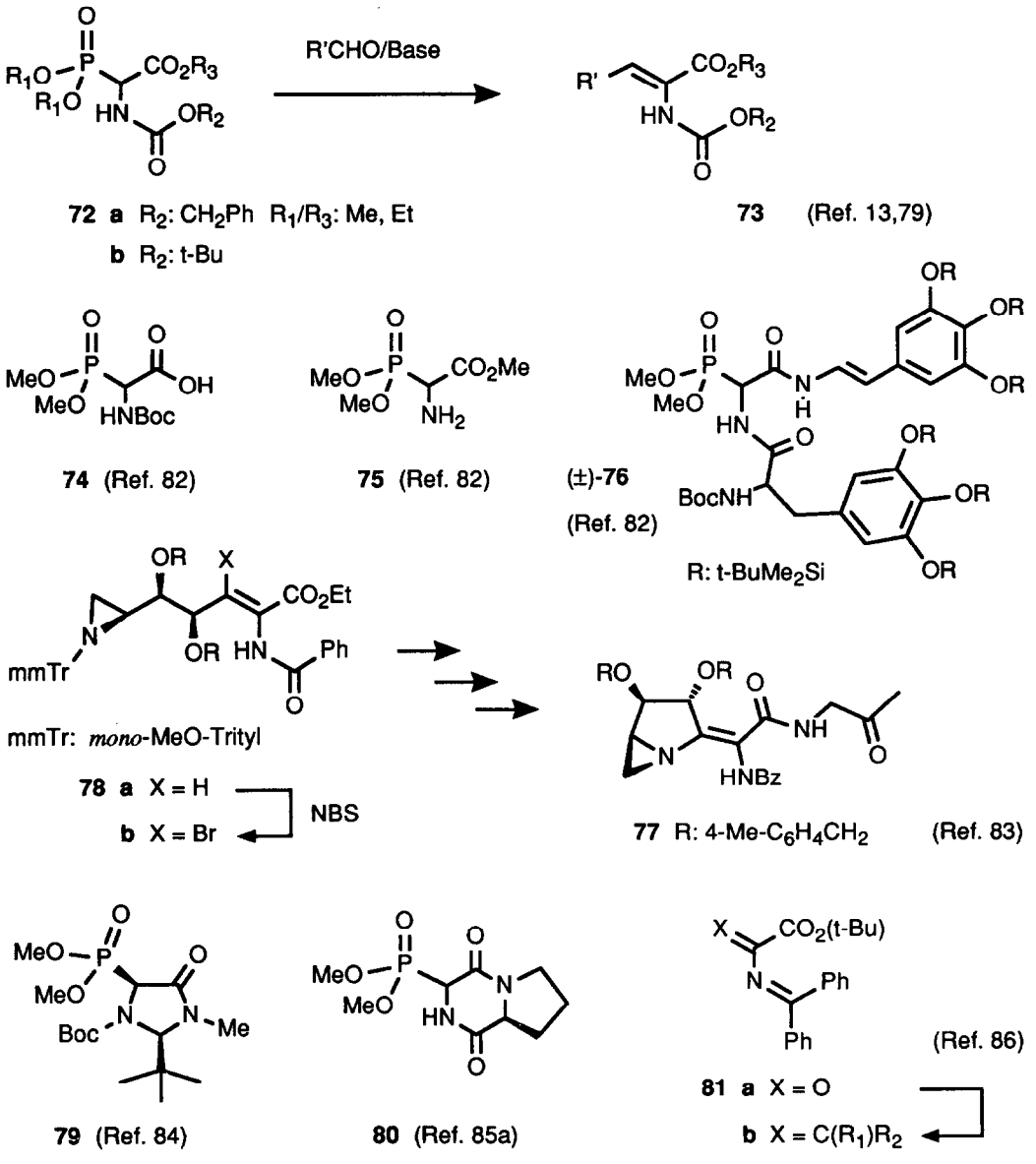
Scheme 10

3.1. Asymmetric Hydrogenation of α,β-Didehydro-Aminoacids

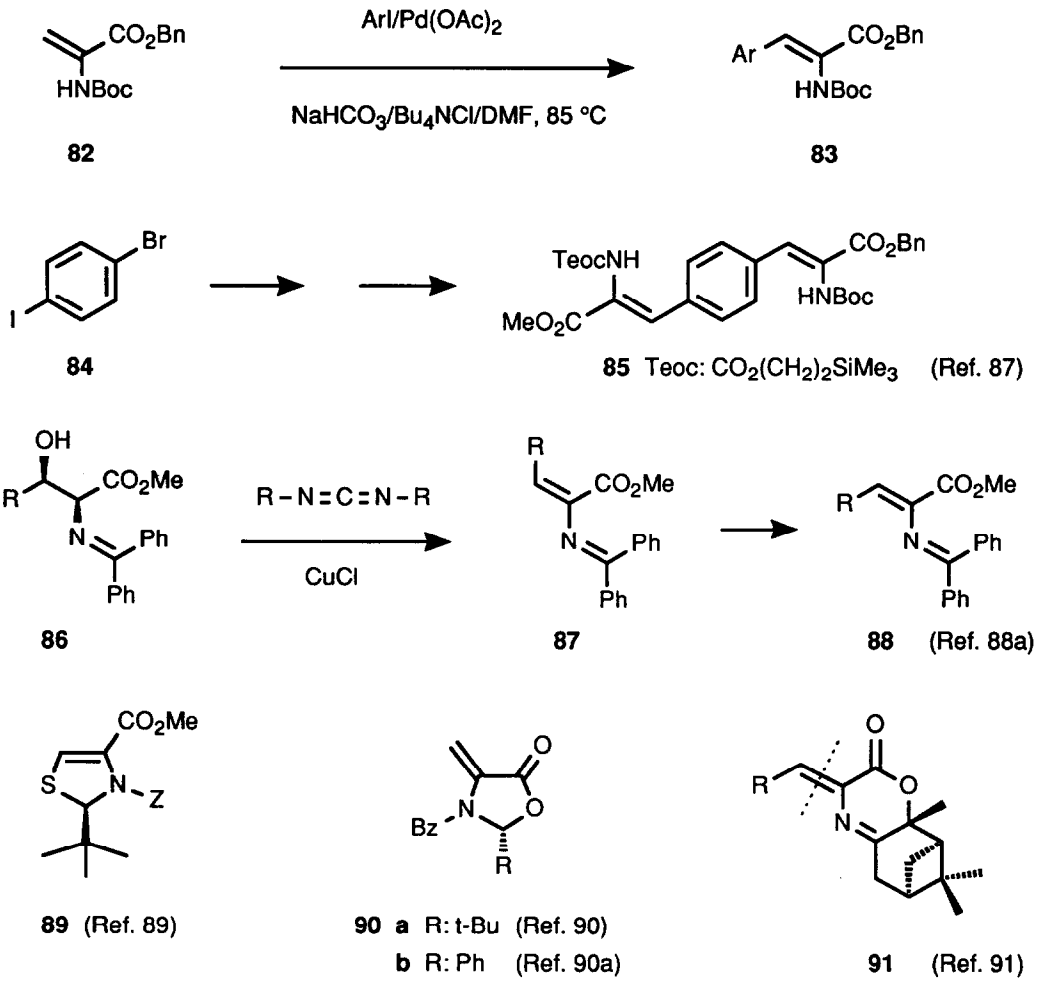
The synthesis of α,β-didehydro-α-aminoacids including spectroscopy, isolation from natural sources, and reactions has been reviewed by Schmidt *et al.* and more recently by Shin and coworkers.[79] Among the more recently developed methods, one of the most versatile is the Wittig-Horner reaction of phosphonates **72** with aldehydes, affording Cbz- or Boc-protected dehydro-aminoacids **73** with preference for the (*Z*)-isomers (*Scheme 11*).[80] For various aldehydes 20% NaOH as base is applicable under phase-transfer conditions,[80a] but tetramethylguanidine[80b] or DBU[81] have also been used, the latter to avoid racemization in the case of α-chiral aldehydes.[81] The free acid **74** and the free amine **75** have been prepared for the synthesis of more advanced phosphonates like **76**, an intermediate of the tunichrome An-1 synthesis.[82] Dehydro-aminoacids can be further processed, *e.g.* the complex bicyclic structure **77**, related to the antitumor antibiotic azinomycin, has been obtained from **78a** *via* the bromide **78b**.[83] Dehydro-aminoacids with chiral centers for further diastereoselective transformations have been prepared from the phosphonates **79**,[84] **80**,[85a] and related oxazinones.[85b,c] Wittig olefination of the delicate oxalic acid derivative **81a** below 0°C affords dehydro-aminoacids **81b** in 25 - 90% yield, again with (*Z*)-preference in the case of monosubstituted ylids.[86]

Additional methods for the preparation of α,β-didehydro-aminoacids are depicted in *Scheme 12*. A versatile method is the Heck coupling of aryl iodides or bromides with α-amido-acrylate **82**, giving (*Z*)-isomers **83**.[87] Most rewardingly, this also works for dihalides, and by either adjusting the reaction conditions or by exploiting the different reaction rates of bromides and iodides (*e.g.* **84**) differentially protected *bis*-α,β-didehydro-aminoacids like **85** can be obtained.[87b] Dehydration of β-hydroxy-α-aminoacid derivatives shows some complementarity to other methods.[88] *Threo*-isomers **86** can thereby be transformed into the (*E*)-isomers

87, which often are only minor products of other methods. Isomerization to the thermodynamically more stable (*Z*)-isomers **88** is possible.[88a,b] The chiral dehydro-aminoacids **89**[89] and **90**[90] have been obtained from (*R*)-cysteine, **90a** also from (*S*)-alanine[90a], and analogs of **90a** by using the phosphonate **79** (*cf. Scheme 11*).[84] Aldol condensation of the 2-hydroxypinan-3-one derivative of glycine with aldehydes gives dehydro-aminoacids **91**.[91]



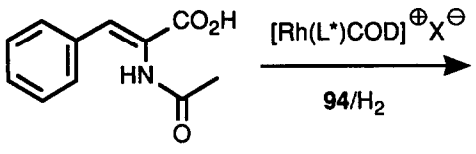
Scheme 11



Scheme 12

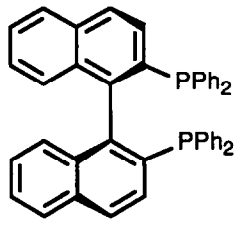
The enantioselective hydrogenation of dehydro-aminoacids, classically the conversion of α-acetamido-cinnamic acid **92** to phenylalanine **93** (*Scheme 13*), is catalyzed by chirally modified Wilkinson catalysts **94**. This is one of the most efficient processes for the preparation of optically active aminoacids, and therefore is used also for industrial production.[6d] Several reviews of this field[92] include *chapter 6* of ref. 5 (pp. 239 - 256). Higher catalytic activity is generally observed for cationic Rh(I)-complexes, *i.e.* by using non-associating counter-ions such as $ClO_4^{\ominus}$, $BF_4^{\ominus}$, $CF_3SO_3^{\ominus}$, or $PF_6^{\ominus}$.[93] The steric requirements for chiral *bis*-phosphine ligands affording highly enantioselective complexes have been carefully studied by X-ray analysis,[21a] calculations,[21b] NMR-analysis,[94] and mechanistic considerations.[95] It is therefore to be expected, that numerous chiral *bis*-phosphines have been prepared for this purpose; 87 structures are listed in reference 92a. The most successful ligands, their abbreviations, the configuration for (*S*)-induction, and the enantiomeric excess for the conversion of **92** to **93** are listed in *Scheme 13*. It has, however, to be noted, that the order of induction is substrate-dependent and that catalytic activity might be more important than a 5% difference in enantiose-

lectivity. In many cases Binap **95** gives only moderate induction[21a,93,96] and is better suited as a ligand for Ru(II) (*cf.* above *Scheme 3*).[97]

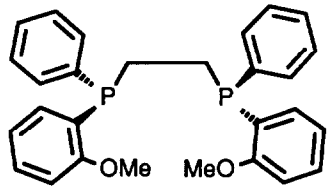


92 **93** (Ref. 92a)

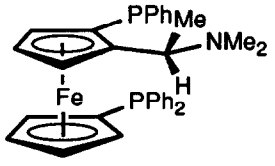
L*: Chiral Diphosphine
COD: 1,5-Cyclooctadiene
X: ClO_4, BF_4, PF_6, CF_3SO_3



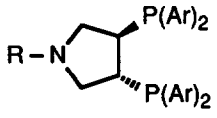
95 (*R*)-Binap (99% ee)



96 (*R,R*)-Dipamp (94% ee)



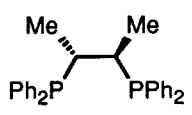
(*S,R*)-Bppfa (93% ee)



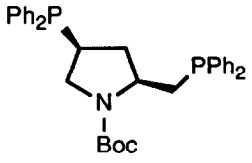
100 $(Ar)_2$: Ph_2 (*R,R*)-Deguphos
(99% ee, Ref. 99a)

102 $(Ar)_2$: $(3,5\text{-}Me_2\text{-}4\text{-}MeOC_6H_2)_2$ (Ref. 99b)

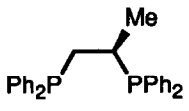
103 $(Ar)_2$: Ph, $2\text{-}MeOC_6H_4$ (Ref. 95b)



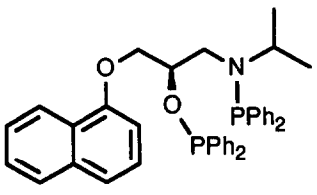
(*R,R*)-Chiraphos
(99% ee)



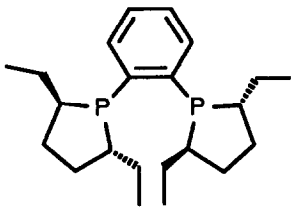
101 (*S,S*)-Bppm
91% ee



105 (*R*)-Prophos
(90% ee)



109 (*R*)-Propraphos
(90 - 95% ee, Ref. 102c)

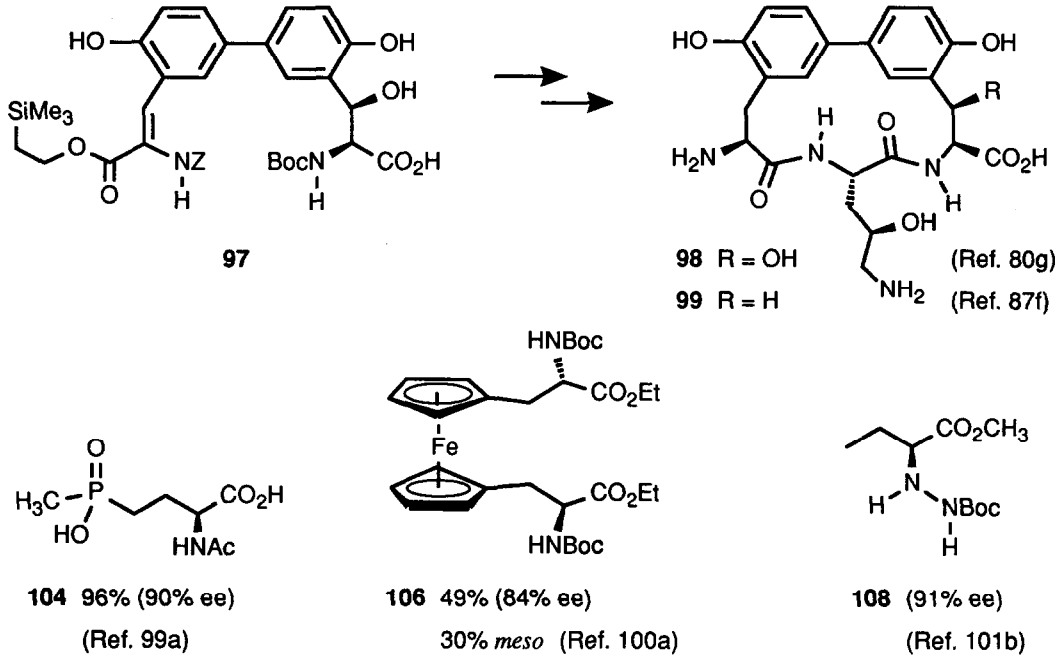


107 (*R*)-Duphos
(99% ee, Ref. 94)

Scheme 13

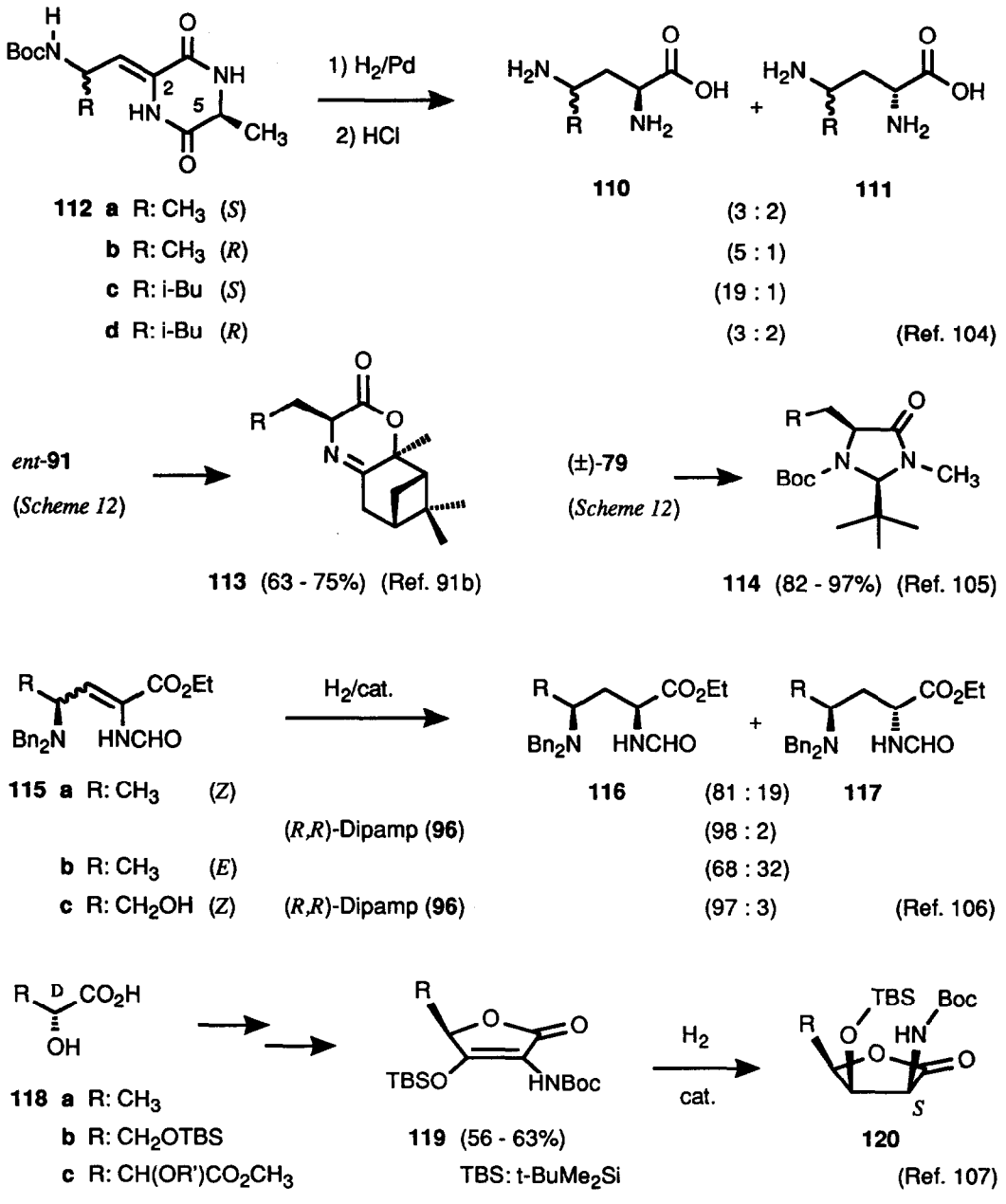
The most frequently used ligand appears to be Dipamp **96** (*Scheme 13*), and it has been used for the enantioselective preparation of many complex amino acids,[52,80c,d,87d] for enantioselective deuteration,[98] and on a large scale as well.[87e] Hydrogenation of the multifunctional compound **97** and similar structures led to

intermediates which could be transformed to the antibiotics biphenomycin A **98**[80g], biphenomycin *B* **99**[80e,f,87f] and a related structure[87c] (*Scheme 14*). It has been claimed that Deguphos **100** and Bppm **101** are the only ligands of industrial significance, due to their excellent catalytic activity (up to 10 000 catalytic cycles).[99a] Deguphos has also been modified by introduction of various *N*-substituents,[92a] or by quaternization of the nitrogen, to get solubility in water.[99a] Replacing the phenyl groups by the electron releasing 3,5-Me_2-4-MeO-C_6H_2-substituents resulted in enhanced catalytic activity and better stereoselectivity of complex **102** and related systems[99b,c] (*cf.* also ref. 99d); and the additional chirality on phosphorus of **103** is expected to improve the enantioselectivity of the corresponding Rh(I)-complex.[95b] An example of an unusual amino acid obtained by using Deguphos **100** is the ω-phosphinate **104** (*Scheme 14*).[99a] The tetrahydrofuran analog of Deguphos[99e] was used for the preparation of ferrocenylalanine.[99f] Most surprising is the high induction obtainable with Prophos **105**, the simplest chiral biphosphine. While up to 99% ee has been obtained for α-amido-cinnamates,[93] hydrogenation of a ferrocenyl derived *bis*-α,β-didehydro-aminoacid gives the optically active diastereomer **106** in 84% ee (49%) and 30% of *meso*-isomer (*Scheme 14*).[100a] A recent communication describes the preparation of ornithine stereospecifically deuterated at C(3) using the catalyst derived from **105**.[100b]



Scheme 14

The excellent results obtained with Duphos **107** demonstrate, that aryl substituents on phosphorus are not a prerequisite for high induction.[94,101] With Rh(I)/Duphos as catalyst the α-hydrazino acid **108** could be obtained by enantioselective hydrogenation of the α,β-unsaturated precursor (*Scheme 14*).[101b] Esters and amides of diphenylphosphinic acid can replace the *bis*-phosphines as ligands for Wilkinson type of Rh catalysts. Chiral ligands can thereby be prepared straightforwardly by derivatization of diols or amino alcohols. Among the most successful representatives are glucopyranose-2,3-diphosphinite[95c,102b] and Propraphos **109** derived



Scheme 15

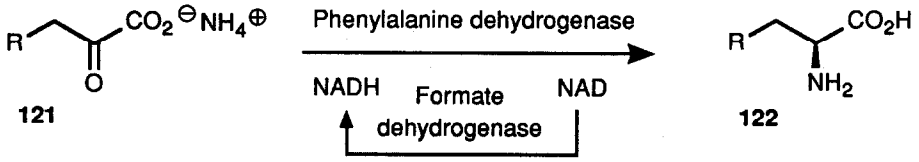
from propranolol.[102] Various substituted arylalanines[102c] including fluorinated derivatives[102d], as well as furyl-[102e], and thienyl-alanines[102f] have been obtained with high enantiomeric excess using **109** as chiral ligand. A major disadvantage of the homogeneous Rh(I) catalysts, when compared to heterogeneous catalysis, is the often difficult separation of the chiral ligand from the product. To circumvent these problems, efforts have

been made to render these ligands water soluble, *e.g.* by incorporation of quaternary ammonium ions.[99b,103a,b] However, these ligands generally afford less selective catalysts. Reductions with Bppm **101** can be conducted in water, provided that an amphiphile is added.[103c] Another promising approach is to adsorb the cationic Rh(I)-complexes on sulfonated ion-exchange resins.[102b] In this case the catalytic results are better, but especially in the case of Propraphos **109** leaching of the ligand and Rh(I) is a major problem.

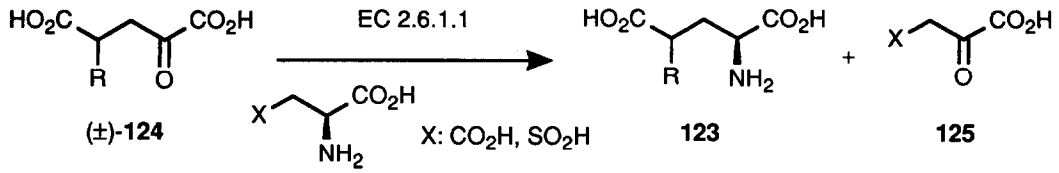
As an alternative to chiral hydrogenation catalysts, reduction of α,β-didehydro-aminoacids can also be controlled by chiral auxiliaries or asymmetric centers in the sidechain (*cf.* ref. 5; *chapter 6*, pp. 230 - 236) (*Scheme 15*). 2,4-Diaminoacids **110/111** have been obtained by hydrogenation of 2-alkylidene-diketopiperazines **112**.[104] While the ratio **110** : **111** is clearly influenced by the stereogenic center in the sidechain, the influence of C(5) prevails and **110** with α-(*S*)-configuration is the major product. Hydrogenation of the heterocycles *ent*-**91** and (±)-**79** proceeds with good yield and the amino acid precursors **113**[91b] and **114**[105] are obtained with excellent diastereocontrol (> 95% de). Not unexpectedly the stereocontrol by an asymmetric center in the sidechain is less pronounced and a chiral catalyst is needed, if the dehydro-aminoacids **115**, obtained from α-aminoaldehydes, were to be reduced with high stereocontrol to 2,4-diamino acids **116/117**.[106] A higher *lk* : *ul* ratio **116/117** is observed for small residues R and for (*Z*)-**115**. Chiral α-hydroxy carboxylic acids **118** can be transformed in a few steps to the unsaturated α-amido-γ-lactones **119**, which afford *lyxo*-configurated saturated lactones **120** with excellent stereocontrol (less than 5% *ribo*-isomer).[107] The lactones **120** are versatile intermediates for amino sugars (*e.g.* L-daunosamine[107a]) and L-configurated β-hydroxy-α-amino acids (*e.g.* mugineic acid[107b]).

3.2. Reductive Amination of α-Ketoacids and Related Processes

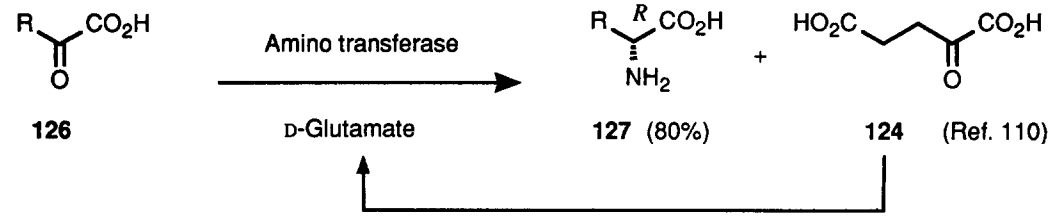
The reductive amination of α-ketoacids **121** is a biosynthetic step and therefore the corresponding enzymes are efficient catalysts for their transformation into L-amino acids **122** (*cf.* ref. 5; *chapter 7*, pp. 270 - 275) (*Scheme 16*). The specificity of phenylalanine dehydrogenases from *Bacillus sphaericus* (SCRC-1279a)[108a] and a *Rhodococcus* sp. [108b] expressed by relative activity has been tested for various substrates **121**. Considerable differences are observed between the two enzymes, especially for the transformations to tyrosine and homophenylalanine (**122**, R: 4-HO-C_6H_4, $C_6H_5CH_2$). *Alcaligenes faecalis* (IAM 1015, whole cells) was used for the preparation of (4*R*/*S*,2*S*)-5,5,5-trifluoroleucine[108c]. Glutamates **123** substituted at C(4) are obtained from α-ketoglutarates **124** and aspartate or cysteine-sulfinate using glutamic-oxalacetic amino transferases (EC 2.6.1.1) from different sources.[109] The resulting α-ketoacids **125** are withdrawn from the equilibrium either by decarboxylation (slow) or reduction with malate dehydrogenase in the case of aspartate, and by loss of SO_2 with cysteine-sulfinate as nitrogen donor. As the (*R*)-enantiomers of **124** are processed faster, (2*S*, 4*R*)-**123** can be isolated at low conversion (40%). After long incubation times, on the other hand, the (2*S*, 4*S*)-diastereomers of **123** prevail. As most natural amino acids are L-configurated, the D-enantiomers are less readily available by biochemical methods. Exceptions are bacterial peptidoglycans (cell wall), which incorporate D-amino acids. The D-amino-acid amino transferase from a thermophilic *Bacillus* species (YM-1), an enzyme with broad substrate tolerance, has been used for the transformation of α-ketoacids **126** to D-amino acids **127** with high efficiency.[110] The nitrogen source, D-glutamate, can be recycled *in situ* from 2-ketoglutarate **124** with glutamate dehydrogenase, glutamate racemase, and formate dehydrogenase, a combination of highly specific enzymes not affecting the product **127**.



R	Relative Activity	
	Bacillus sphaericus (Ref. 108a)	*Rhodococcus sp.* (Ref. 108b)
$4\text{-}HOC_6H_4$	100%	5%
C_6H_5	74%	100%
$MeSCH_2$	8%	33%
$C_6H_5CH_2$	2%	72%



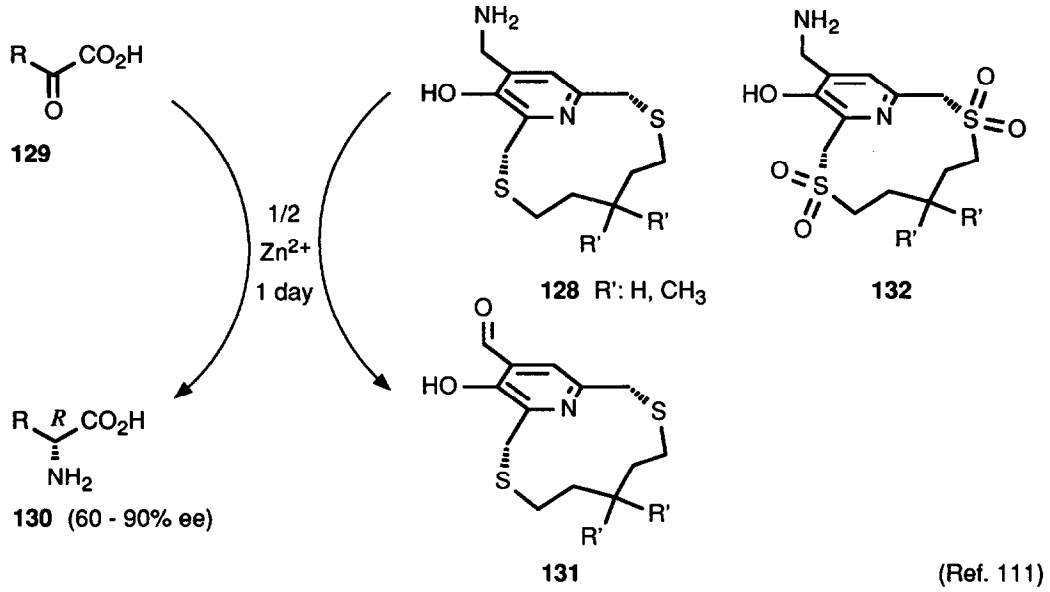
R	Pig heart	V^{rel}: (*R*)-124 *Escherichia coli*	*Pseudomonas aeruginosa*
H		100%	
CH_3	90%	93%	87%
C_2H_5	130%	50%	31%
OH	70%	8%	(Ref. 109)

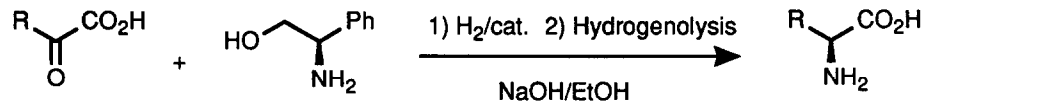


Scheme 16

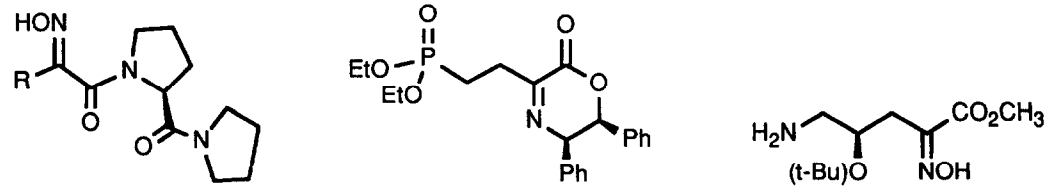
The stereocontrolled reductive amination of α-ketoacids has also been approached by chemical means (*Scheme 17*). The pyridophane **128**, a pyridoxamine analog of planar chirality, efficiently mediates the enantioselective conversion of **129** to **130** in the presence of 0.5 equivalents of Zn^{2+}, while being converted to the aldehyde **131**.[111] With the corresponding *bis*-sulfone **132** the transamination is roughly 10-times slower, and, with the exception of alanine (**130**, R: CH_3), the induction is lower. Schiff's bases formed *in situ* from **129**

and phenylglycinol **133** can be reduced to aminoacids **134** by catalytic hydrogenation (H_2/Pd-C).[112] The stereocontrol is dependent on solvent, amount and nature of base added, and is better for small residues. α-Phenethylamine is less efficient as a chiral auxiliary than **133**. Reduction of oximes **135** with SmI_2 in methanol[113] and of the heterocycle **136** with Al-Hg[114] affords (*S*)-configurated aminoacid derivatives with high stereocontrol. The oxime **137**, derived from 4-hydroxyproline, can be reduced with (*R*)-induction by using Na/NH_3, while a 1 : 1 (*R*,*S*)-mixture results upon catalytic hydrogenation.[115a] Fluoro-derivatives of threonine have been obtained by reduction of β-hydroxy-α-(*N*-methoxyimino)butyrates.[115b]





129 R: CH_3 — **133** — **134** 40% (85% ee) (Ref. 112)
C_2H_5 — 35% (87% ee)
$PhCH_2$ — 17% (17% ee)
Ph — 21% (21% ee)

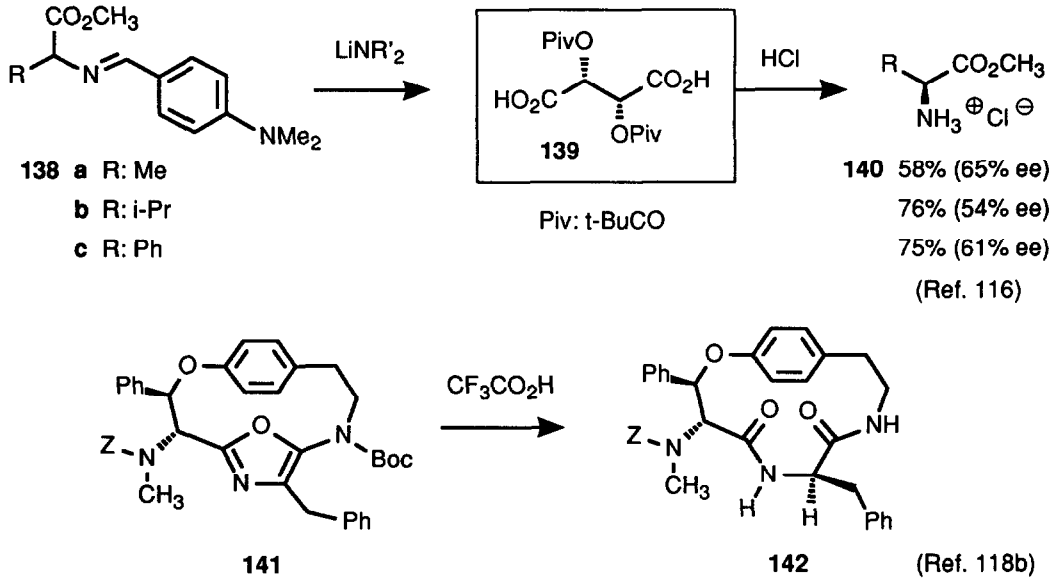


135 (Ref. 113) **136** (Ref. 114) **137** (Ref. 115a)

Scheme 17

3.3. Asymmetric Protonation of Enolates and Asymmetric Hydration of α-Amino-Ketenes

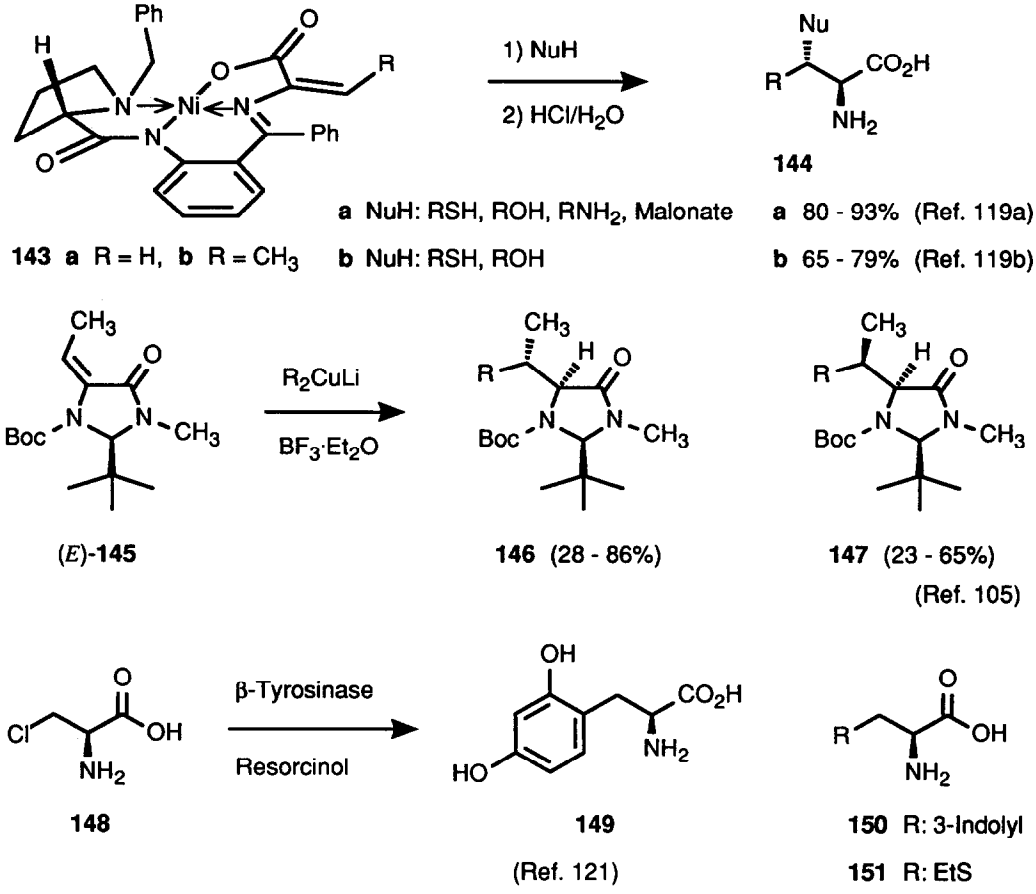
Protonation of the Li-enolates generated from Schiff's bases **138** with (*R,R*)-dipivaloyl-tartaric acid **139**, a chiral proton source, gives L-configurated aminoacid esters **140** of moderate optical purity (*Scheme 18*).[116] The magnitude of the induction depends on the structures of the Schiff's base aldehyde and the Li-base, and is also affected by temperature variations. Equilibration of Schiff's bases derived from aminoacids and a chiral carbonyl component *via* their Cu-chelates followed by hydrolysis results in moderate optical induction (22 - 53% ee).[117] Hydrolysis of oxazoles derived from aminoacids gives (*S,S*)-dipeptides with 72% de.[118a] In the case of the macrocyclic compound **141** the strained cyclic peptide **142**, a model for crenatine, is obtained as a single isomer.[118b]



Scheme 18

Addition of a nucleophile to an α-amino-acrylate **b** affords an enolate **c**, derived from an α-aminoacid **a** (*cf. Scheme 10*). This transformation, allowing for the generation of two new asymmetric centers, has been realized with the Ni-chelates **143a** and **143b** (*Scheme 19*).[119] After hydrolysis of the adducts, L-configurated amino acids **144** are isolated in good yield. Suitable nucleophiles are thiols and alcohols, and in case of **143a** amines and malonate as well. The trisubstituted olefin **143b**, (*E*)-isomer only, leads to *erythro*-diastereomers **144b** with high stereocontrol.[119b] Selectride reduction of *ent*-**91** (*cf. Schemes 12* and *15*) proceeds with 95% de[91b] and phenylcuprate addition to α-acetamido-acrylates of chiral alcohols gives only moderate stereocontrol (44% ee).[120] Much better selectivity is observed for the heterocycle **145** .[105] While the (*E*)-isomer affords selectively the diasteromers **146** upon cuprate addition, the epimers **147** are obtained from (*Z*)-**145** (*Scheme 19*). The addition of a nitronate to the oxazolidinone **90a** (*Scheme 12*) was, however, less selective (68% de).[90c] Some rather substrate specific PLP-dependent enzymes cleave the bond to the β-carbon of α-amino acids *via* an amino-acrylate intermediate. These catalysts can therefore be used to add or exchange different β-substituents.[121] Mediated by β-tyrosinase (EC 4.1.99.2) β-chloroalanine **148** can be substituted by different

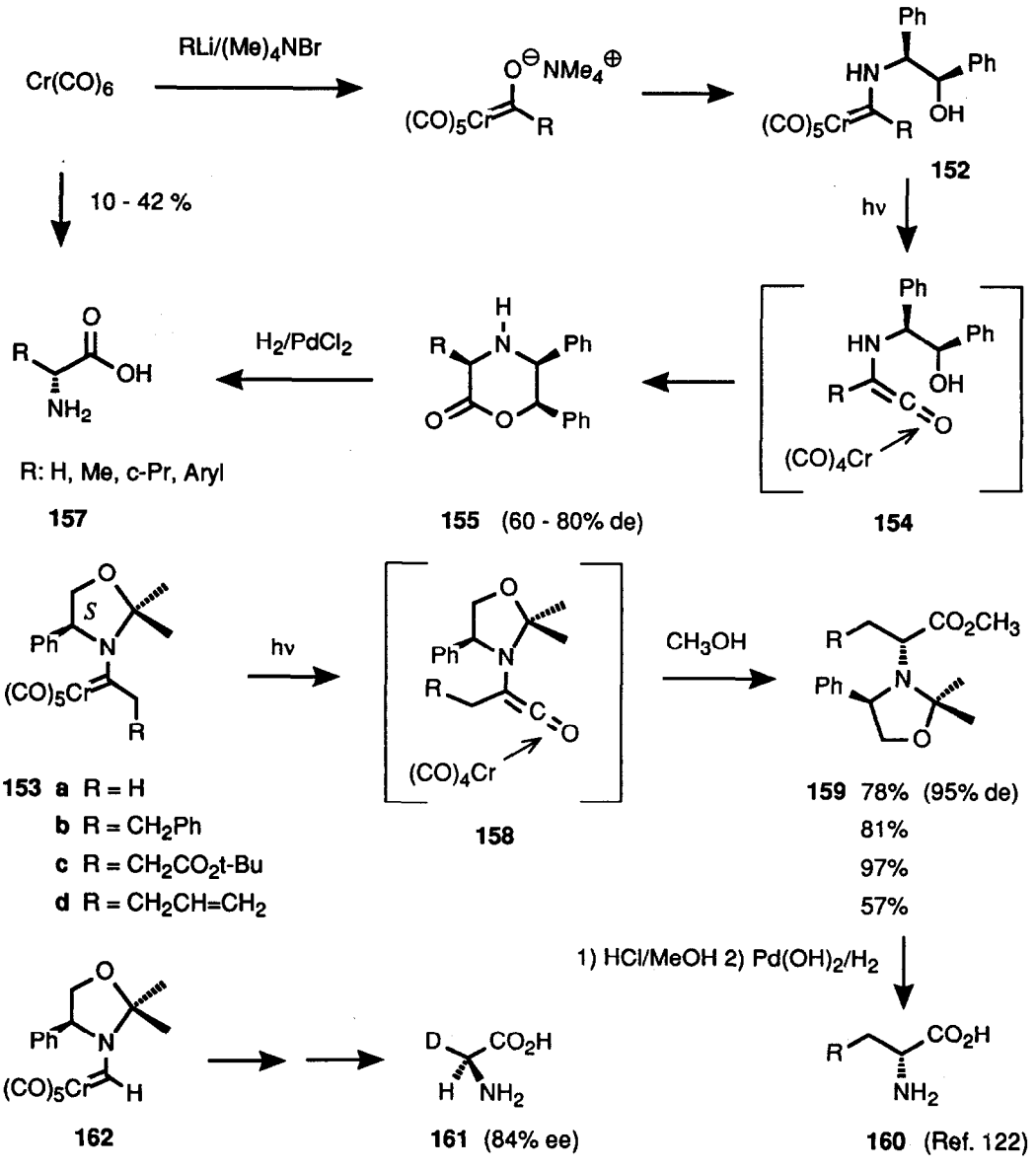
phenols (*e.g.* resorcinol), affording tyrosine derivatives (*e.g.* **149**). With tryptophanase (EC 4.1.99.1) and cysteine desulfhydrase (EC 4.4.1.1), respectively, pyruvic acid can be transformed into tryptophane **150** or *S*-ethylcysteine **151**.



Scheme 19

The stereocontrolled addition of alcohols to amino ketenes has been developed by Hegedus and coworkers (*Scheme 20*).[122] This method is based on irradiation of chromium aminocarbene complexes[9] **152** and **153**, available from $Cr(CO)_6$, Li-organic compounds and the corresponding chiral amines. Photolysis of **152** affords the putative ketene intermediate **154**, which cyclizes with 60 - 80% de to the oxazinones **155**.[122a-c] Separation of diastereomers and hydrogenolysis gives (*R*)-amino acids **157** in 10 - 42% overall yield. The aminocarbene **153a** is prepared analogously using the phenylglycinol-derived oxazolidine as chiral auxiliary. Deprotonation of **153a** (n-BuLi) and alkylation gives the derivatives **153b-d**.[122d,e] Addition of methanol to the ketene **158**, generated by irradiation, gives the esters **159** with excellent yield and stereoselectivity. Other alcohols (*e.g.* t-BuOH) can be used as well,[122d] and a dipeptide results, if the complex **153** is irradiated in the presence of t-butyl alaninate.[122e] The amino function is finally liberated by acetal cleavage and hydrogenoly-

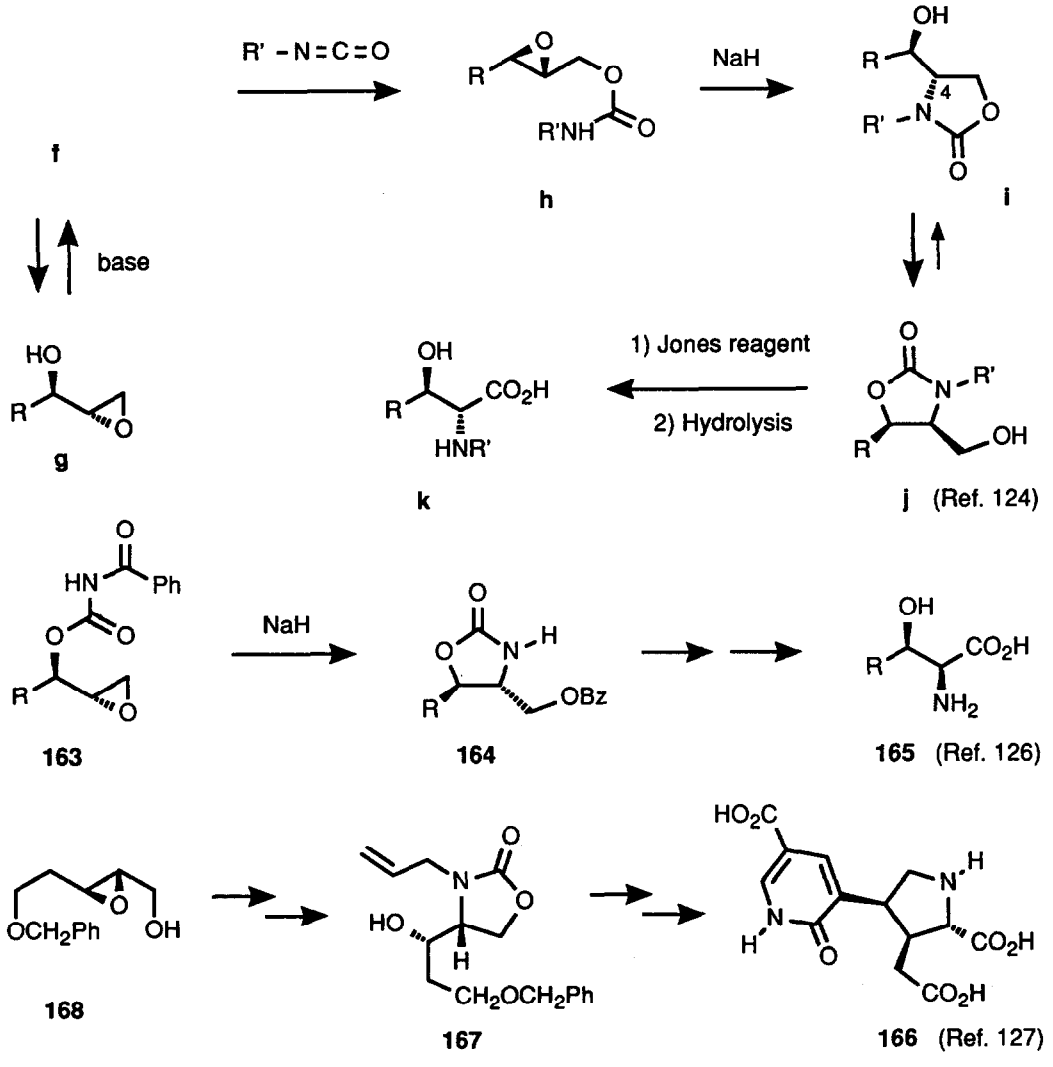
sis (→ **160**).[122c] This method is well suited for the preparation of labelled amino acids. By using $Cr(^{13}CO)_6$, amino acids with labelled carboxyl- and α-carbon are obtained.[122e] Enantioselectively monodeuterated glycine **161**, on the other hand, is obtained by quenching the ketene derived from **162** with CH_3OD.[122c] The enantiomer of **161** prevails (75% de), if the acetonide of **162** is replaced by a carbamate carbonyl.



Scheme 20

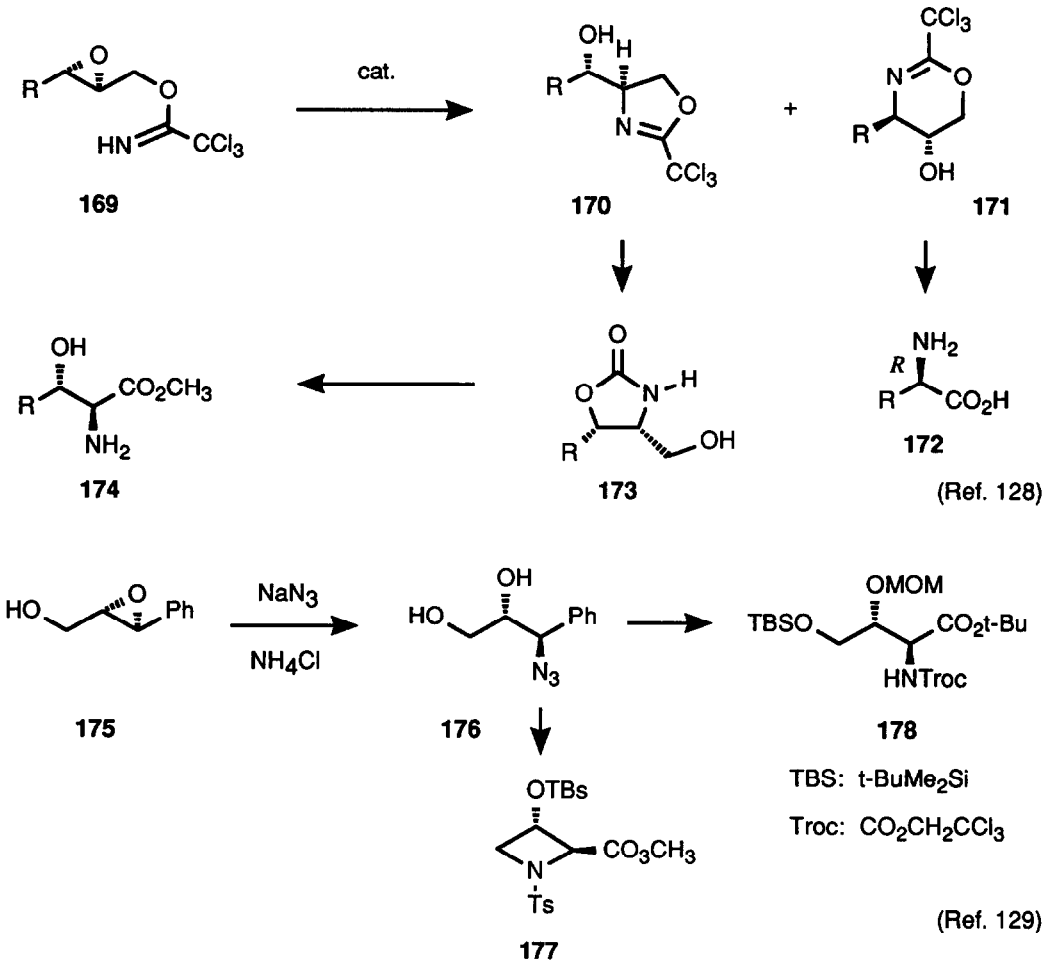
4. ENANTIOSELECTIVE INTRODUCTION OF THE α-AMINO-FUNCTION

4.1. Nucleophilic Amination



Scheme 21

The generation of α-aminoacids by introducing the NH_2-group with nucleophilic aminating agents (*cf.* ref. 5; *chapter 4*, pp. 186 - 207) is generally based on S_N2 displacements, *i.e.* the chirality is introduced prior to the nucleophilic amination. Versatile intermediates for this purpose are chiral epoxides, *e.g.* the α-hydroxymethyl epoxides **f** conveniently obtained from allylic alcohols by the Sharpless procedure.[29] Due to the facile Payne rearrangement (→ **g**) catalyzed by bases the regioselectivity of nucleophilic epoxide-openings with amines is rather low, giving at best a high yield of terminal amines from **g**, intermediates which are not suited

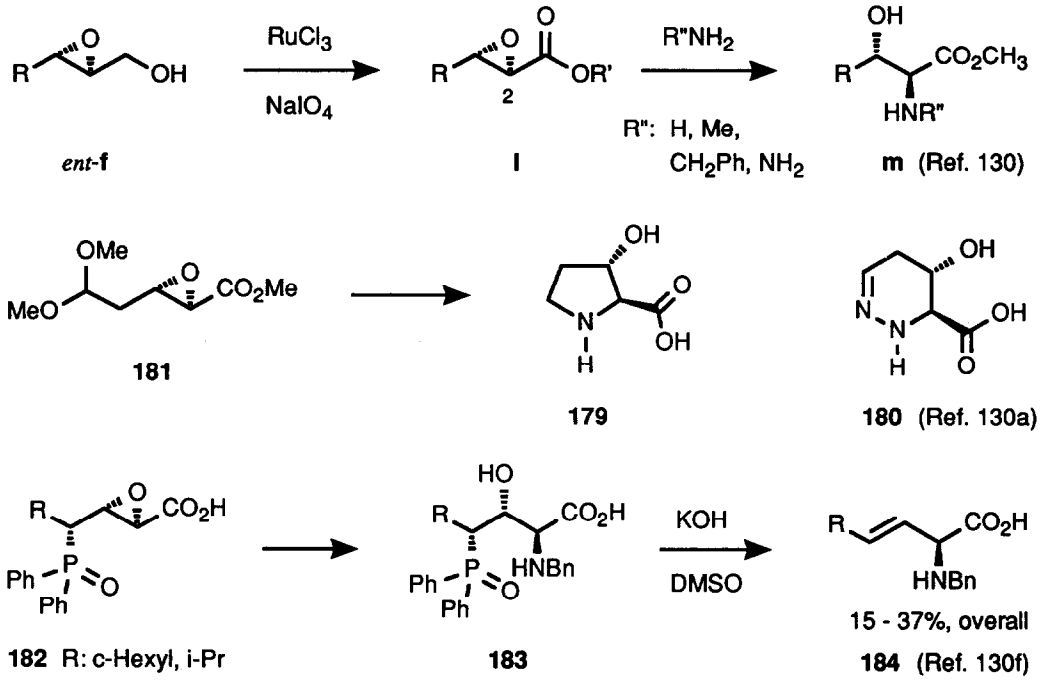


Scheme 22

for amino acid syntheses (*Scheme 21*).[123a] Better results have, however, been obtained with $(i\text{-PrO})_2Ti(N_3)_2$ (*cf.* ref. 5, p. 203),[123b] and with (diarylmethyl)amines/$(i\text{-PrO})_4Ti$.[123c] The rearrangement of **f** can, however, be avoided, and high regiocontrol of the amination is achieved if carbamates **h** are generated by reaction with isocyanates. Deprotonation with NaH leads to the cyclic carbamates **i**, which isomerize in most cases to the regioisomeric oxazolidinones **j**. *N*-Substituted β-hydroxy-aminoacids **k** are obtained by Jones oxidation and carbamate hydrolysis.[124] The *threo*-isomers of **k** are either derived from *cis*-epoxides[124a] or can be generated by equilibrating the *cis*-oxazolidinones to the *trans*-isomers after oxidation of the hydroxymethyl group to the carboxylate.[124b,c] Using methyl isocyanate, this principle was applied to the synthesis of MeBmt, the unusual amino acid of cyclosporin.[124] On the other hand the *N*-substituent can be removed hydrogenolytically, if benzyl isocyanate is applied for this sequence.[124d] Epoxides with an α-phosphine oxide function have recently been transformed into the corresponding oxazolidinones **i** according to this protocol. In this case concomitant olefination led to vinylic C(4)-substituents, intermediates for β,γ-unsaturated aminoacids.[125] The *N*-acyl-car-

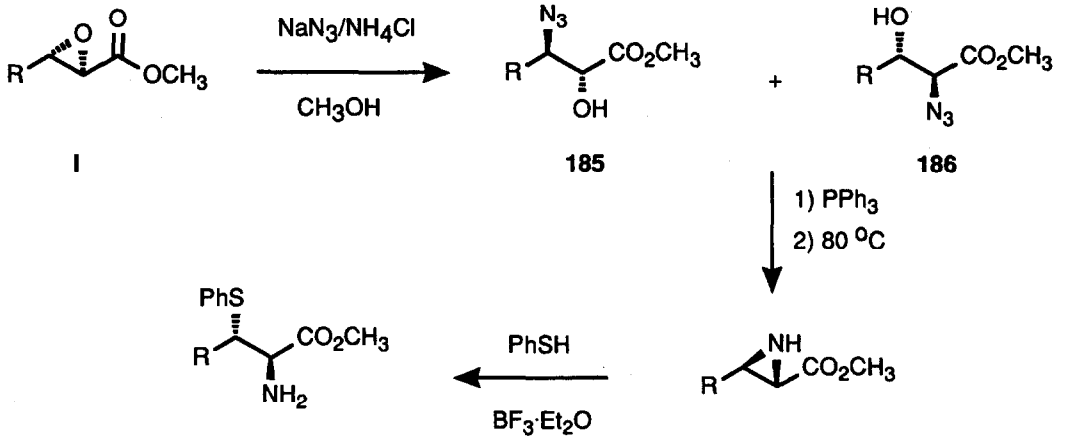
bamates **163** are obtained from the epoxides **g** by treatment with benzoyl-isocyanate. The NaH mediated ring closure is followed by an acyl shift from N to O (→ **164**, *Scheme 21*). The conversion of **164** into *threo*-β-hydroxy-α-aminoacids **165** is straightforward.[126] This method was introduced by Baldwin for the synthesis of acromelic acid A (**166**).[127] The intermediate **167** was obtained from epoxide **168** by derivatization with allyl isocyanate and base-mediated ring closure. The unwanted oxazolidinone regioisomer corresponding to **j** could be reverted to **167**.

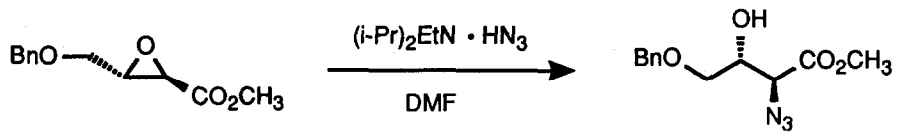
Under Lewis-acid catalysis the trichloro-acetimidates **169** are transformed into mixtures of oxazolines **170** and the regioisomeric oxazines **171** (*Scheme 22*).[128] The ratio of **170** and **171** can be influenced with the catalyst: BF_3-Et_2O and CH_3SO_3H favor **170**, $SnCl_4$ **171**. Exclusive formation of **171** is observed in the case of trisubstituted epoxides. Both isomers, **170** and **171**, can be transformed into aminoacids. Hydrolysis of the heterocycle, periodate cleavage of the glycol, and $MnO_4^{\ominus}$ oxidation affords the (*R*)-amino acids **172** from **171**. The oxazolines **170**, on the other hand, are transformed *via* the oxazolidinones **173** to (*S*)-configurated *erythro*-β-hydroxy-α-amino acids **174**. This protocol was also part of the first total synthesis of frangulanine, a strained 14-membered cyclic peptide alkaloid.[128b] The phenyl-substituted epoxide **175** is an exception, as opening with NaN_3/NH_4Cl in CH_3OH proceeds with high regiocontrol giving the azide **176** in quantitative yield.[129] Conversion of **176** to the azetidine carboxylate **177** and to differentially protected derivatives of 2-amino-L-threonic acid (*e.g.* **178**) involved oxidative degradation of the phenyl substituent to the carboxylate ($RuCl_3/NaIO_4$).These intermediates have been converted to the phytosiderophores mugineic acid[129a,c], *epi*-hydroxy-mugineic acid, and distichonic acid.[129b]

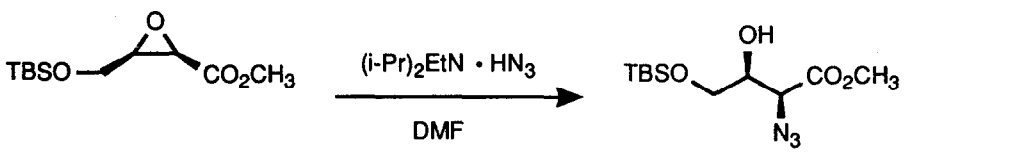


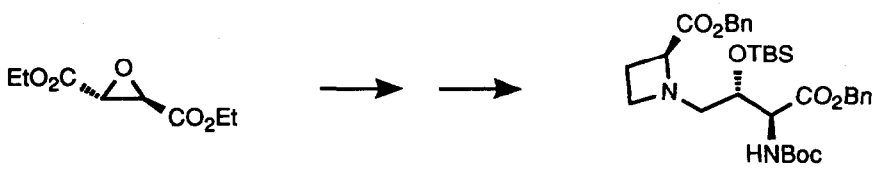
Scheme 23

By oxidation of the glycidols **f** (or *ent*-**f**) to the corresponding acids **l** the problem of nonregioselective epoxide opening is avoided, as ammonia, primary amines, and hydrazine[130a] attack exclusively at C(2) (→ **m**)[130], with the exception of unsubstituted glycidic acid and the phenyl derivative[131] (*cf.* ref. 5; pp. 197 - 202) (*Scheme 23*). Following this protocol, 3-hydroxyproline **179** and the tetrahydropyridazine **180**, a constituent









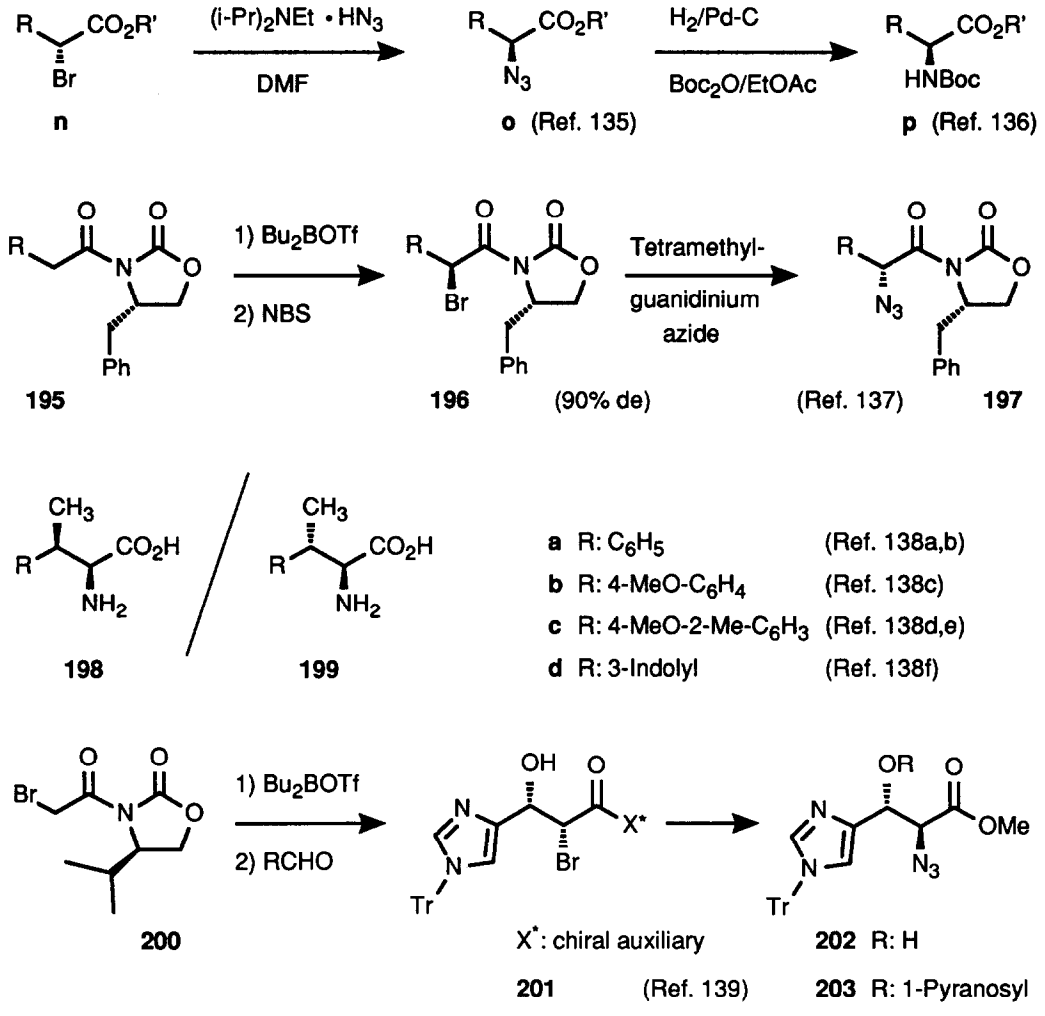
Scheme 24

of the antitumor agent luzopeptin A, have been obtained successfully, both from the epoxide **181**.[130a] A recent example is the conversion of the α-phosphinoxy-epoxides **182** *via* **183** to β,γ-unsaturated *N*-benzylaminoacids **184**.[130f] The epoxides **182** and all the other possible stereoisomers are obtained from the corresponding allyl alcohols by kinetic resolution with the Sharpless reagent[29] (*cf.* ref. 125). This allows the preparation of *ent*-**184** and of the *cis*-isomers as well in 15 - 37% overall yield from the allyl alcohols. The authors claim that no racemization is observed during the rather harsh basic conditions needed for the final olefination step.[130f]

Reaction of glycidic acids **l** with NaN_3/NH_4Cl in CH_3OH is again less selective and mixtures of regioisomers **185** and **186** are generally isolated (*Scheme 24*).[132] These mixtures can, however, be converted to isomerically homogeneous aziridine-carboxylates **187**, which in turn can be further transformed by Lewis-acid catalyzed ring opening with nucleophiles, *e.g.* to the β-thioether **188**[132a,b,134b] (for further examples see below: chapter 7.2, *Scheme 68*). Saito and associates have recently introduced diisopropylethylammonium azide as an ideal reagent for epoxide opening.[133] Attack at C(3) (→ **185**) and α-epimerization are minimized, and even for the phenyl substituted epoxide **l** (R: C_6H_5) a considerable amount of **186** is formed (**185** : **186** = 3 : 2). Using this reagent the epimeric epoxides **189** and **190** have been converted smoothly to *erythro*- and *threo*-α-azido-β-hydroxy esters **191** and **192**.[133] 2,3-Epoxysuccinate **193**, readily prepared in both enantiomeric forms from the corresponding tartrates,[134a] is a versatile intermediate for β-hydroxy-α-amino acids without bias for regiocontrol, due to its C_2-symmetry.[134] A recent example is its conversion to **194**, an advanced intermediate for the synthesis of mugineic acid.[134d]

In addition to epoxides other leaving groups, *e.g.* bromides **n**, are also well suited for azide substitution (→ **o**, *Scheme 25*). The Hünig's base salt of hydrazoic acid has again turned out to be superior to other azidation reagents (LiN_3, NaN_3, $[Bu_4N]N_3$).[135] The observation that protection with Boc_2O (→ **p**) appears to be accelerated, when performed *in situ* with catalytic (10% Pd-C/H_2) azide reduction, is worth mention.[136] One of the best methods, the use of chiral *N*-acyloxazolidinones **195**, for the generation of α-bromides **196** with high optical purity, has been developed by Evans and coworkers[137] (*cf.* ref. 5, pp. 190 - 192). A full account, including the substitution using tetramethylguanidinium azide (→ **197**), has now appeared.[137b] Hruby and associates have used this method for the synthesis of several β-methyl-substituted amino acids of either *syn*- **198** or *anti*- **199** relative configuration in both enantiomeric forms.[138a-f] These derivatives have been designed to study the effects of conformational restriction in peptide side-chains. In the case of the phenylalanine and tyrosine derivatives **198a,b/199a,b** the chiral β-carbon resulted from resolution before attatchment to the oxazolidinone.[138a-c] For the other compounds the Evans auxiliary was used to generate this center as well by diastereoselective cuprate addition to α,β-unsaturated *N*-acyloxazolidinones.[138d-f] The chirality of the β-carbon had only a marginal influence on the stereoselectivity of the C(α)-bromination. In case of **198a/199a** the 99 : 1 ratio for the matched pair (→ *anti*-bromide, → **198**) dropped to 94 : 6 for the mismatched case (→ *syn*-bromide, → **199**).[138a,c] This method has recently been applied for the synthesis of fluorinated aminoacids.[138g] The boron-aldol reaction of the bromoacetyl derivative **200** offers another entry to chiral *syn*-α-bromo-β-hydroxyacids and hence to *anti*-α-amino-β-hydroxyacids (*cf.* ref. 5, pp. 186 - 189). *Erythro*-β-Hydroxyhistidine is a pivotal amino acid constituent of the DNA-cleaving antibiotic bleomycin. The bromide **201** has been obtained by this method from **200** and was further transformed to azide **202**, an ideal substrate for *O*-glycosylations (→ **203**).[139a,b] This protocol has recently been incorporated in the synthesis of a model for the carboxylate-binding pocket of the antibiotic vancomycine.[140] By using the appropriate counterion, enolates of **200** can afford *anti*-aldols as well, especially in the case of aromatic aldehydes.[139c] These bromides are

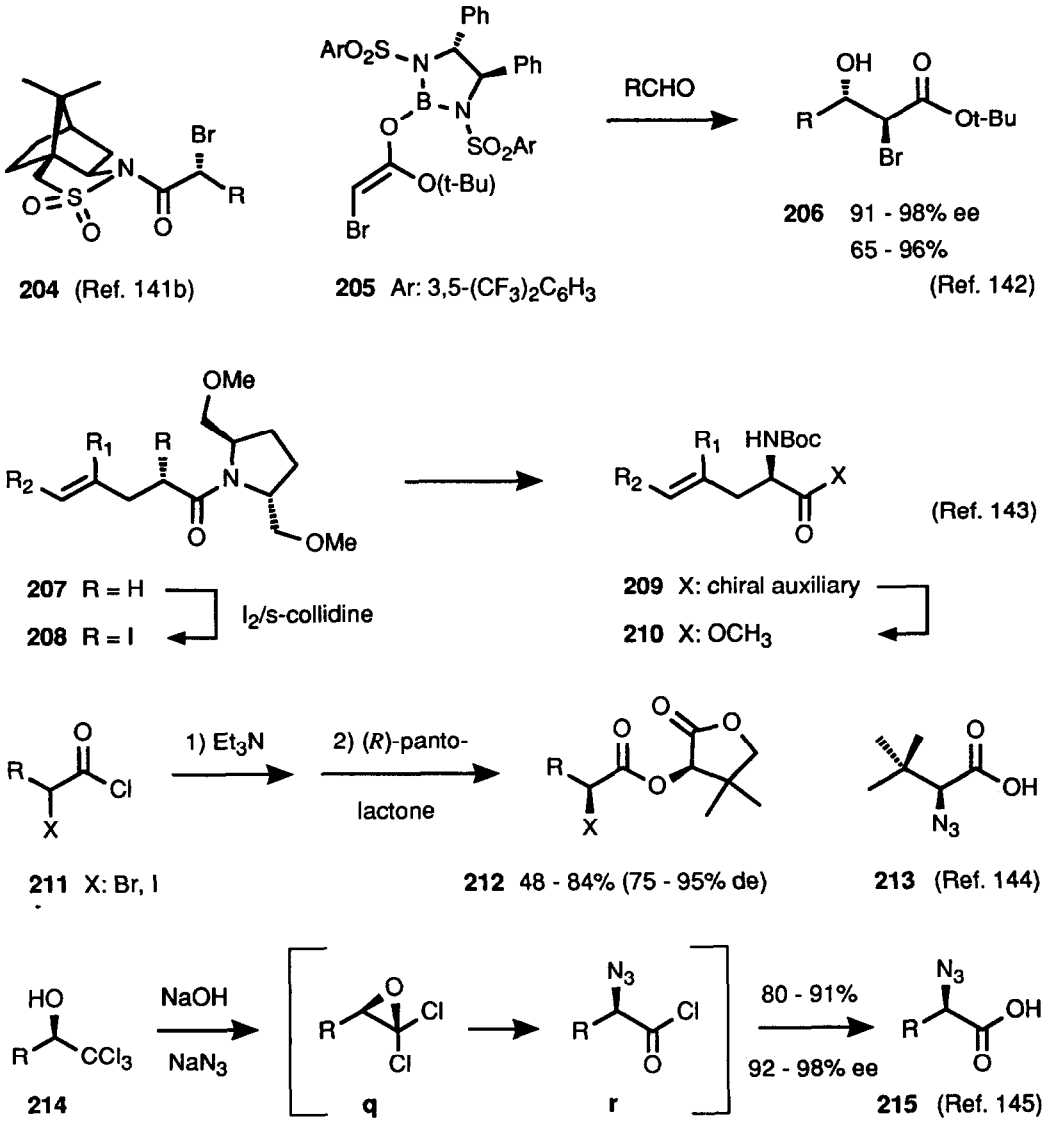
in turn intermediates for *syn*-α-amino-β-hydroxyacids.



Scheme 25

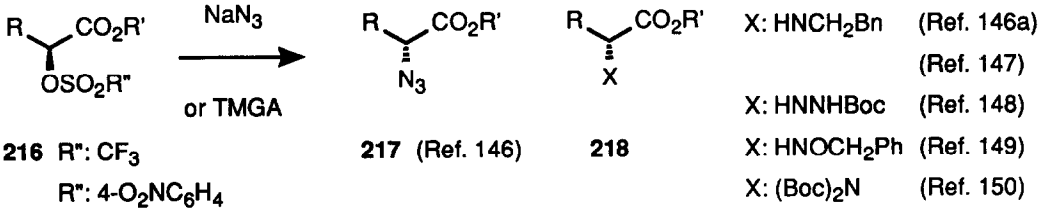
Several other systems for the preparation of optically active α-halo-acids are depicted in *Scheme 26*. The camphor-sultam **204** introduced by Oppolzer and coworkers[141b] is more readily removed than the sulfonamide substituted ester used previously for the same purpose (*cf.* ref. 5, pp. 193 - 195).[141a] The enolate **205** is generated from a chiral boron reagent, therefore the steps for introduction and removal of chiral auxiliaries are avoided.[142] Reaction of **205** with aldehydes affords bromohydrins **206** with excellent stereocontrol.[142] The bromides **204** and **206** have been converted into aminoacids by azide substitution and reduction.[141,142] Iodination of the unsaturated amides **207** proceeds with good stereocontrol, and the resulting iodides **208** can be transformed *via* azides to the t-butyl carbamates **209**.[143] The cleavage of the auxiliary (→ **210**) is not trivial and can only be effected *via* iodolactonization. When α-haloketenes generated from the acid chlorides **211** are

quenched with optimal timing by (*R*)-pantolactone, (*S*)-configurated esters **212** are obtained with good stereocontrol.[144] As an exception the t-butyl substituted ketene gave the (*R*)-bromide (87% de), which was transformed to the tert.-leucine precursor **213**. In a recent communication Corey and Link descibed a novel aminoacid synthesis from the trichloromethyl carbinols **214**, readily obtained by catalytic enantioselective reduction of the corresponding ketones.[145] Alkaline azide treatment gives the amino acid precursors **215** *via* the putative intermediates **q** and **r**.



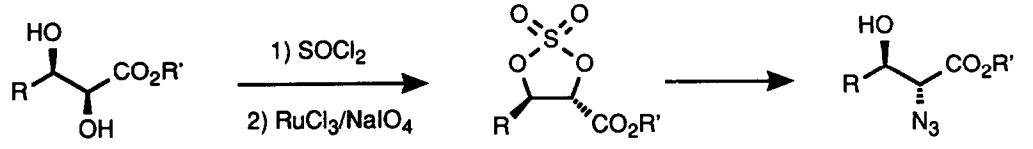
Scheme 26

α-Hydroxy-carboxylates are readily available chiral compounds. Their substitution with *N*-nucleophiles is therefore an efficient method for the preparation of α-aminoacids. The sulfonic esters **216** are optimally suited for azide displacement (→ **217**, *Scheme 27*).[146] The reactions are generally clean, although problems (racemization) have been encountered with mandelic acid derivatives.[146a] The sodium or tetramethylguanidinium azide can be replaced by other nucleophiles: amines[146a,147], hydrazines[148], hydroxylamines[149] or imides[150], affording the derivatives **218**. The di-*N*-Boc-imide is especially effective and has been found to be preferred to the corresponding Mitsunobu-reaction (see below).[150] Closely related is the conversion of chiral diols **219** *via* cyclic sulfates **220** to β-hydroxy-α-azido-acids **221** with clean inversion and excellent regiocontrol.[151] Direct substitution of alcohols **222** by nitrogen nucleophiles **223** is achieved under Mitsunobu conditions (→ **224**).[150a,152] Usually phthalimide **223a** is used for this purpose, but the harsh conditions for unmasking the amino function led to the search for other nucleophiles. Numerous candidates were tested for the conversion of lactate **222** (R: CH_3) into D-alanine, and their efficiency turned out to be directly related to the pK_a-values, which should be below 13.5, when measured in DMSO. Among the best substitutes are the imide **223b**[150a] and the *N*-sulfonyl-carbamate **223c**,[152b] which allows selective removal of either the Boc- or the SES (trimethylsilylethylsulfonyl) group. The $Zn(N_3)_2$-pyridine complex **223d** has recently been introduced as a substitute for hydrazoic acid in Mitsunobu-reactions.[152c]

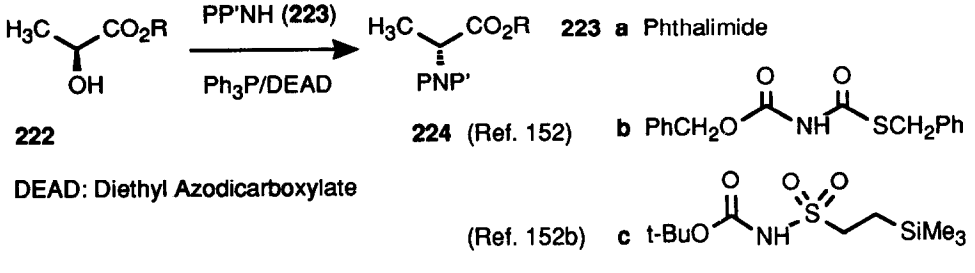


216 R": CF_3
R": 4-$O_2NC_6H_4$

217 (Ref. 146) **218**



219 R: c-C_6H_{11}, $C_{15}H_{31}$, CH_2OH, n-C_5H_{11}, CO_2R' **220** **221** (Ref. 151)



222

DEAD: Diethyl Azodicarboxylate

224 (Ref. 152)

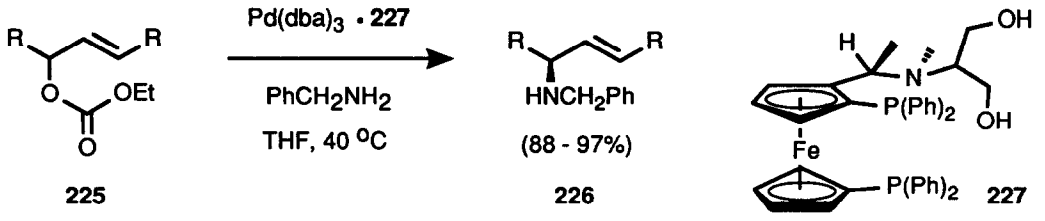
223 **a** Phthalimide

b

(Ref. 152b) **c** t-BuO, NH, $SiMe_3$

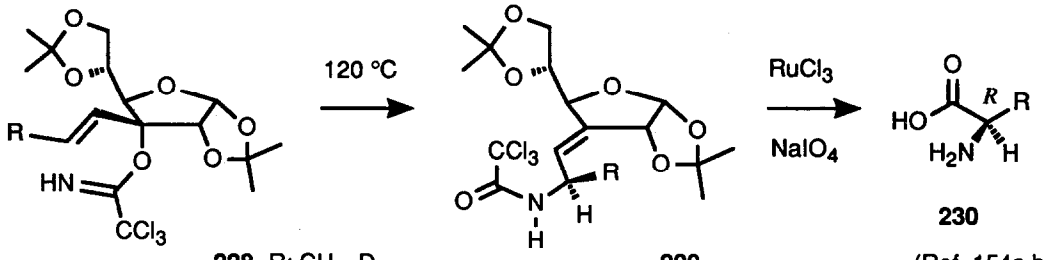
(Ref. 152c) **d** $Zn(N_3)_2 \cdot (Pyridine)_2$

Scheme 27

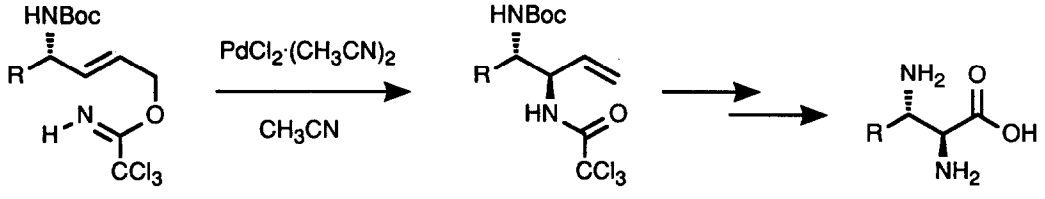


225 226 227

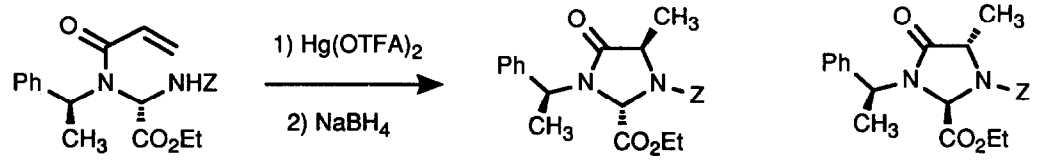
R: CH_3 (70% ee), n-Pr (82% ee), i-Pr (97% ee), Ph (97% ee) (Ref. 153)



228 R: CH_3, D 229 230 (Ref. 154a,b)



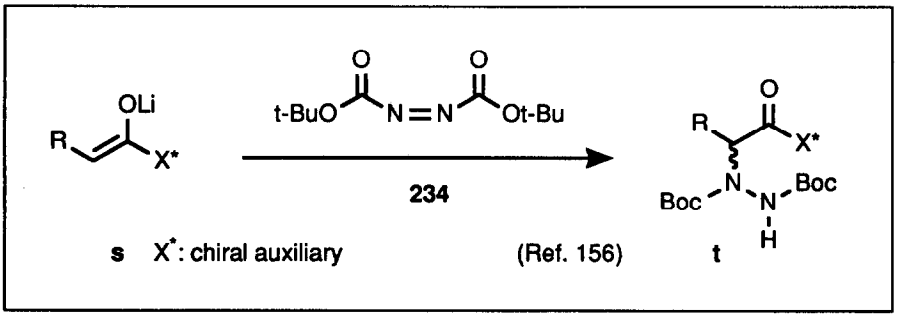
228a 228b 228c (Ref. 154c)

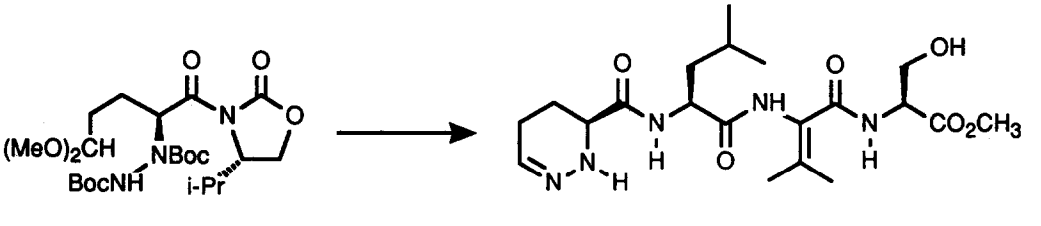


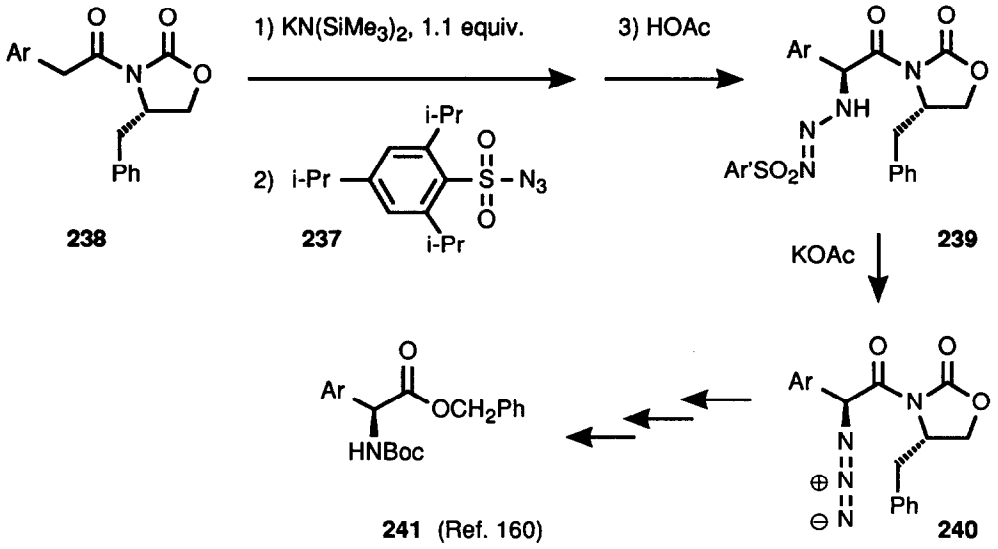
231 (Ref. 155a) 232 (80%) 233 (75%)

Scheme 28

Allylic symmetrical carbonates **225** or the corresponding phosphates readily form η^3-allyl-Pd(II) compounds upon reaction with Pd(0)-complexes. Addition of benzylic amines liberates the allylamines **226** in high yield, regenerating the Pd(0)-reagent at the same time. With the aid of the chiral diphosphine ligand **227**, especially designed for this reaction, this catalytic process becomes highly enantioselective (*Scheme 28*).[153] Some of the allylamines **126** have been oxidatively degraded to *N*-benzyl-aminoacids. Carbohydrates are attractive templates for stereoselective transformations.[10] Overman rearrangement of the glucose derivative







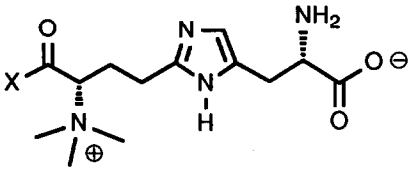
Scheme 29

228 proceeds with excellent chirality transfer (94 : 6, → **229**) even for R = D.[154a,b] Oxidative cleavage not only liberates the (*R*)-configurated aminoacids **230**, but at the same time regenerates the starting material for **228**. In the case of the (*Z*)-isomer of **228** the stereoselectivity of the rearrangement is even better (> 99% ds), affording precursors for (*S*)-aminoacids from the same auxiliary. While the thermal rearrangement of the trichloroacetimidates **228a** derived from Boc-protected α-aminoaldehydes proceeds unselectively, the Pd-catalyzed version affords differentially protected *threo*-1,2-diamines **228b** with excellent diastereoselectivity.[154c]

This method has been used for the transformation of alanine to 2,3-diaminobutanoic acid **228c**. The chiral glyoxylic acid *bis-N*-acyl-aminal **231** is converted by an amidomercuration - demercuration sequence to the imidazolidinone **232**.[155a] Experiments with analogs of **231**,[155c,d] lacking the carbethoxy group, show, that the phenethyl residue introduced to separate the diastereomeric aminals **231**, has no influence on the excellent stereocontrol of the conversion **231** → **232**. This is corroborated by the cyclization of *epi*-**231**, affording **233** as the only product.[155a] The radical intermediate of the demercuration step can be intercepted with acrylate or acrylonitril before hydride reduction.[155b]

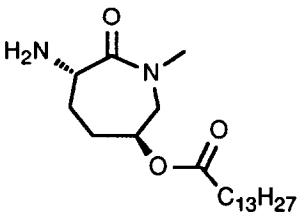
4.2. Electrophilic Amination of Enolates

Chart 2: Aminoacids obtained by Electrophilic Amination with Trisyl Azide **237**.

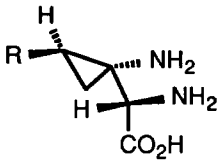


242 X: OH Diphthine (Ref. 161d)

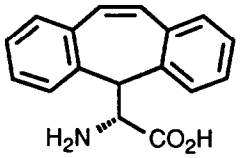
243 X: NH_2 Diphthamide



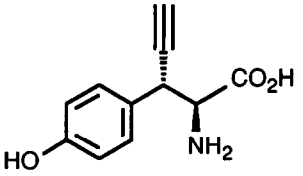
244 (Ref. 161c)



245 (Ref. 161g)



246 (Ref. 161f)

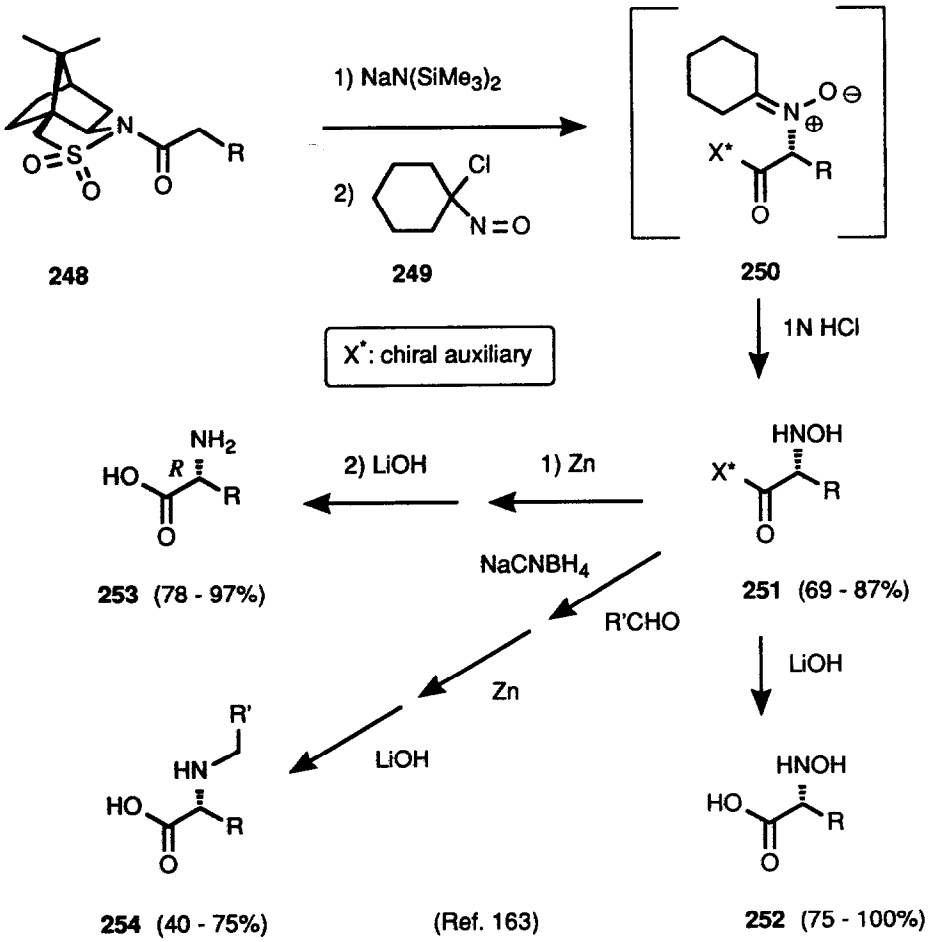


247 (Ref. 161a)

One of the most direct approaches to α-aminoacids is the amination of enolates with electrophilic reagents (*cf.* ref. 5, *chapter 3*, pp. 167 - 185). Unfortunately only a few suitable reagents have so far been identified. One of the first was di-t-butyl azodicarboxylate **234**, which converts the Li-enolates **s** to α-hydrazido acids **t**.[156] This method has subsequently been applied to β-hydroxy esters with preferential formation of *erythro*-β-hydroxy-α-aminoacids.[157] Due to the rather harsh conditions needed to break the N-N bond, this method is now mainly used for the synthesis of α-hydrazino-acids, *e.g.* the masked aldehyde **235**, a precursor for tetrahydropyridazine carboxylate, which could be incorporated into the peptide **236**, the right-hand fragment of the DNA-intercalating peptide antibiotic antrimycin.[158] The saturated analog, piperazic acid, a constituent of azinothricin, has been prepared analogously.[159] A much more promising electrophilic amination agent is trisyl azide **237**, introduced by Evans and coworkers, mainly for the preparation of complex aromatic amino acids, *e.g.* vancomycin.[137b,160] After careful optimization studies the protocol shown in *Scheme 29* was developed. The potassium enolate generated from the *N*-acyl-oxazolidinone **238** is treated for a short time (2 - 3 min.) with **237** before quenching with 4 - 6 equivalents of AcOH at low temperature. Upon warming the pro-

tonated adduct **239** is fragmented by KOAc/HOAc to the azide **240**. Further high yielding transformations give access to aminoacid derivatives such as **241**.

Owing to its versatility this method is now being applied quite frequently.[138f,161,162] Some examples are shown in *Chart 2*: diphthine **242** and diphthamide **243** are essential, histidine-derived aminoacid constituents of the elongation factor 2[161d], and the lysine derivative **244** has been converted to the anthelmintic natural product bengamide B.[161c] The other structures are man-designed: **245**[161g] and **246**[161f] as aminoacid analogs with conformationally constrained side-chains, **247**[161a] as a prodrug, which should give a dopamine β-hydroxylase inhibitor upon decarboxylation.

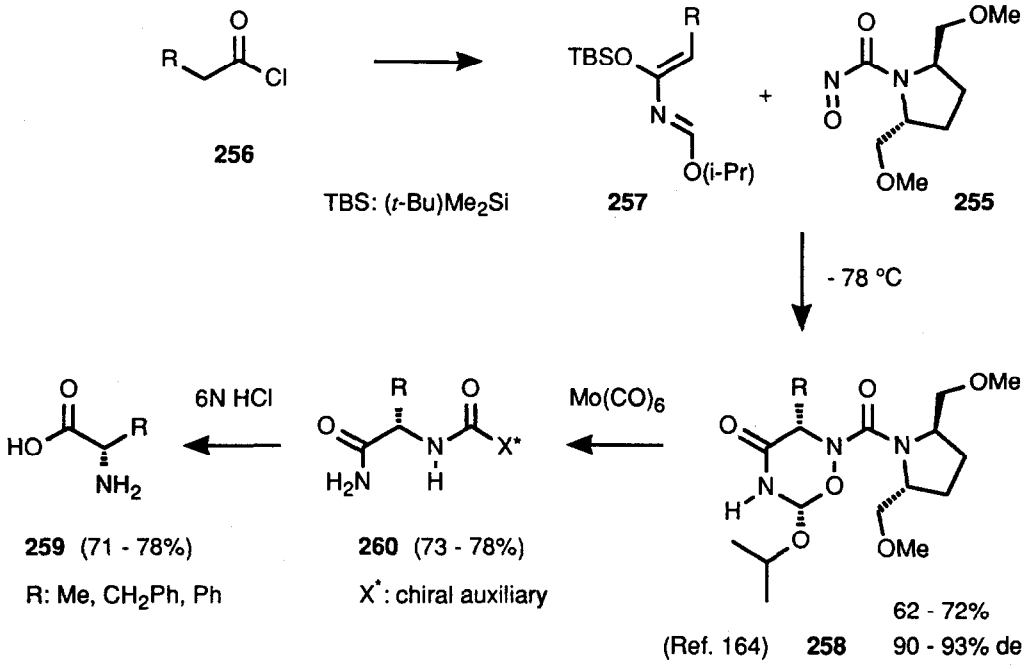


Scheme 30

Oppolzer and associates have recently disclosed another procedure for enantioselective electrophilic amination of enolates based on the *N*-acyl camphor sultam **248** as chiral template and on 1-chloro-1-nitrosocyclohexane **249** as electrophile (*Scheme 30*).[141b,163] Hydrolysis of the primary adducts, the nitrones **250**, affords the corresponding hydroxylamines **251** in excellent yield and with good stereocontrol. After purifica-

tion, in many cases by crystallization, removal of the auxiliary affords the N-hydroxy-aminoacids **252**. Amino acids **253** can be obtained, if the *N*-hydroxy bond is reduced with Zn and *N*-alkyl-aminoacids **254** are available, when the hydrogenolysis and cleavage steps are preceded by reductive amination of an aldehyde.

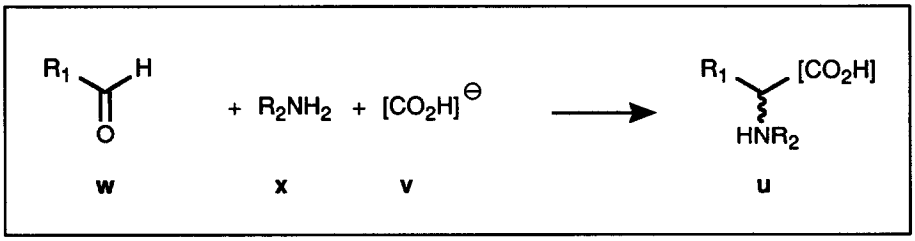
The acylnitroso reagent **255**, generated *in situ* by oxidation of the corresponding hydroxamic acid, can also be used as a chiral aminating agent, provided that the acid to be aminated is converted *via* the acid chloride **256** to the electron-rich heterodiene **257** (*Scheme 31*).[164] Cycloaddition gives the heterocycles **258** in good yield and with high stereocontrol. In order to unravel the aminoacid **259**, the N-O bond has first to be cleaved, preferentially with $Mo(CO)_6$. The resulting urea **260** is hydrolyzed with 6N HCl. Very recently enantioselective aziridination of cinnamate has been achieved with (*N*-tosylimino)phenyliodinane, catalyzed by a chiral Cu(I)-complex (*cf.* below, chapter 7.2., ref. 303a). Addition of *N*-phthalimido-nitrene to camphorsultam derivatives of α,β-unsaturated acids leads to *N*-phthalimido-aziridines, precursors of β-substituted α-hydrazino-acids (33 - 95% de).[303b]

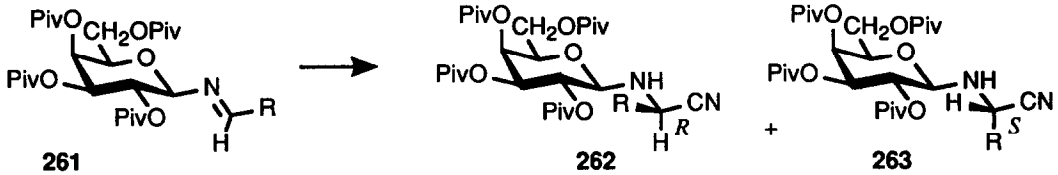


Scheme 31

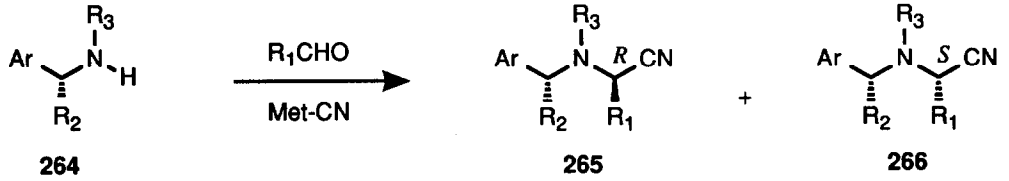
5. ASYMMETRIC STRECKER SYNTHESIS AND UGI CONDENSATION

Aminoacid precursors **u** are most efficiently assembled by addition of a nucleophilic carboxylate synthon **v** to a Schiff's base generated from aldehydes **w** and amines **x** (*Scheme 32*). The most frequently used carboxylate synthons **v** are cyanides (Strecker synthesis) and isocyanates (Ugi condensation). Stereocontrol can be expected by incorporating chirality in the aldehyde **w**, the amine **x**, the nucleophile **v**, or by using a chiral catalyst. From these possibilities the use of chiral amines **x** appears to be most popular (*cf.* ref. 5, *chapter 5*, pp. 208 - 229). One of the best studied auxiliaries is 1-amino-tetra-*O*-pivaloyl-β-D-galactopyranose introduced by Kunz and coworkers.[10b,165] The Schiff's bases **261**, either preformed or generated *in situ*, are



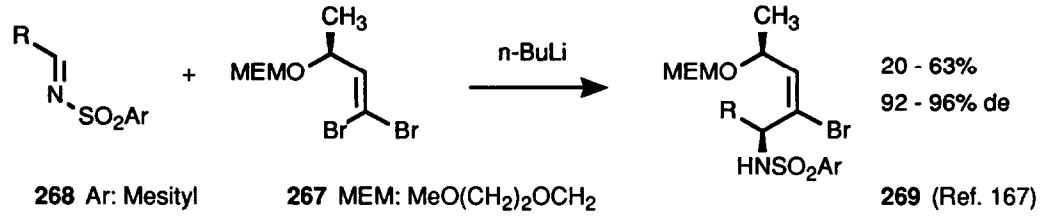


	Conditions	Solvent	ratio 262/263
Piv: t-BuCO	NaCN	i-PrOH/AcOH	(3 - 11) : 1
	$Me_3SiCN/ZnCl_2$	i-PrOH	(4 - 13) : 1
	$Me_3SiCN/ZnCl_2$	$CHCl_3$	1 : (3 - 9)
(Ref. 165)	$Me_3SiCN/SnCl_4$	THF	(7 - 13) : 1

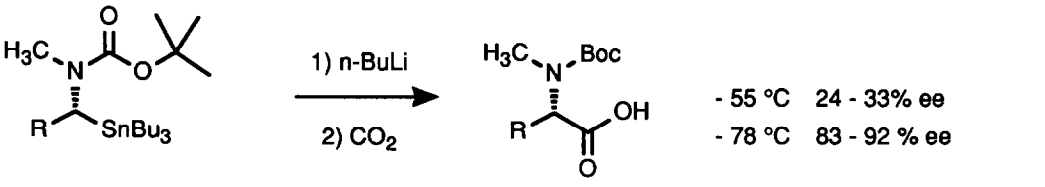


Ar	R_2	R_3	Met		ratio 265/266	(Ref.)
Ph	Me	H	Fe-Hemin	kinetic	1 : (6 - 19)	(Ref. 166a)
Ph	Et	H	Fe-Hemin	kinetic	1 : (24 - 99)	(Ref. 166a)
2-Naphthyl	Me	H	Fe-Hemin	kinetic	1 : (9 - 32)	(Ref. 166a)
Ph	CH_2OH	CH_2Ph	Et_2Al	kinetic	1 : (4 - 13)	(Ref. 166c)
L-Amino Acid		H	$Me_3Si/ZnCl_2$	kinetic	(1 - 9) : 1	(Ref. 166d)
Ph	Me	H	K	thermodyn.	1 : (3 - 4)	(Ref. 166f)
Ph	t-Bu	H	K	thermodyn.	1 : 9	(Ref. 166f)
Ph	CH_2OH	H	K	thermodyn.	(4 - 6) : 1	(Ref. 166g)

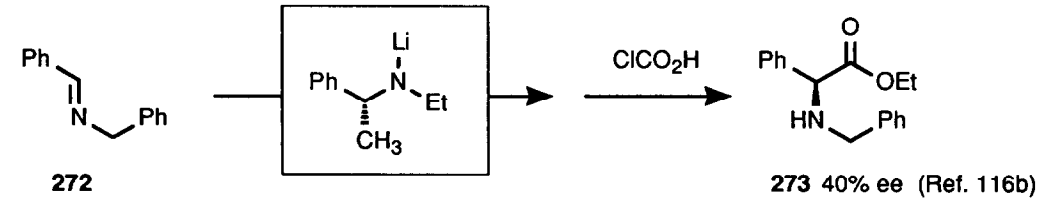
Scheme 32



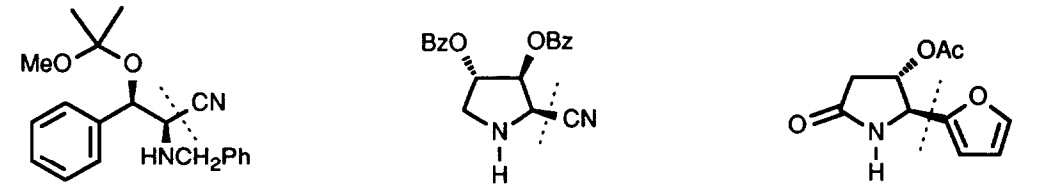
268 Ar: Mesityl **267** MEM: $MeO(CH_2)_2OCH_2$ **269** (Ref. 167)



270 R = Et, i-Pr **271** (Ref. 168a,b)



272 **273** 40% ee (Ref. 116b)

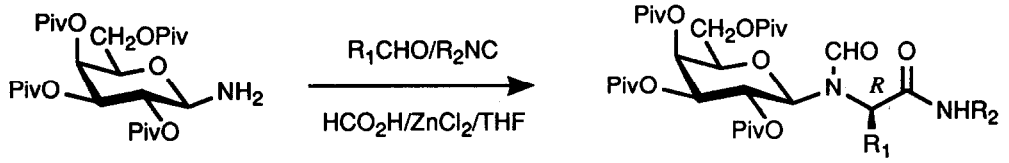


274 76% de (Ref. 169a) **275** 20% de (Ref. 169b) **276** 34% de (Ref. 169c)

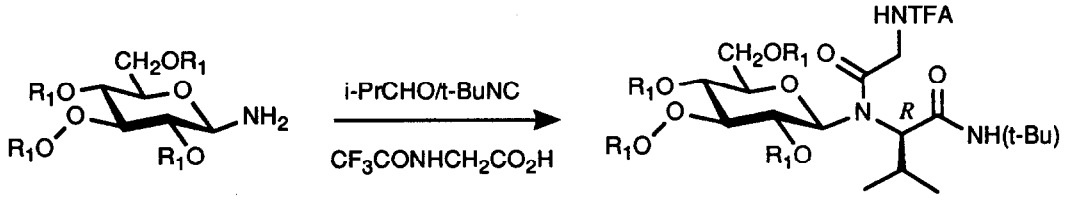
Scheme 33

thereby transformed to the α-cyano-amines **262** and **263** (*Scheme 32*). After separation of the diastereomers by crystallization, the aminoacids are unraveled under rather harsh acidic conditions: 1) HCl/HCO_2H; 2) HBr/AcOH. The use of Me_3SiCN in combination with a Lewis acid is preferable over the conventional NaCN/AcOH(cat.) method. By changing the solvent from i-PrOH to $CHCl_3$ the (*R*)-selectivity of the $ZnCl_2$-catalyzed reaction is reversed to (*S*)-preference. For R = C_6H_5 $SnCl_4$/THF induces better stereocontrol than $ZnCl_2$/i-PrOH. (*S*)-Configurated α-aminonitriles are also formed with good stereocontrol, when the 1-amino-glycosides **281** and **282** derived from D-arabinose and L-fucose are used (see below, *Scheme 34*).[173b] Suitable auxiliaries for asymmetric Strecker reactions are benzylic amines **264**, since the free amino function can be obtained by hydrogenolysis; some recent results are shown in *Scheme 32*.[166] By using polymer-supported hemin-cyanide especially high diastereoselectivity was obtained with α-phenylpropylamine (**265** : **266** = 1 : (24 - 99)).[166a] *N*-Benzylphenylglycinol and various L-amino acid esters or dipeptides have been used in combina-

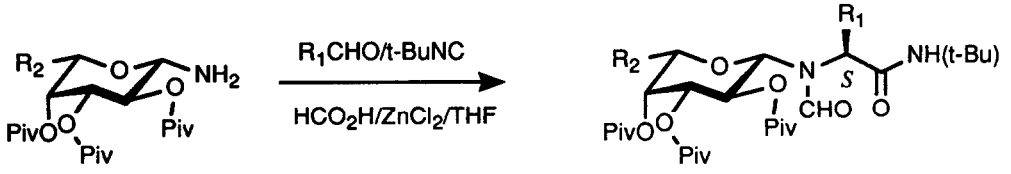
tion with Et_2AlCN[166c] and $Me_3SiCN/ZnCl_2$.[166d] Ogura and associates have demonstrated that the diastereomeric α-aminonitriles **265** and **266** can be equilibrated in methanolic solution.[166f,g] This offers interesting possibilities for the kinetic resolution of α-amino-nitriles (see above, chapter 2.2, *Scheme 6*, refs. 44,45), which have not yet been exploited. The equilibrium ratio, which has also been approached by MM2-calculations[166f], is highly influenced by the residue R_2 of **264**.



277 Piv: t-BuCO R_2: t-Bu, Ph **278** 75 - 93% (88 - 94% de) (Ref. 171)

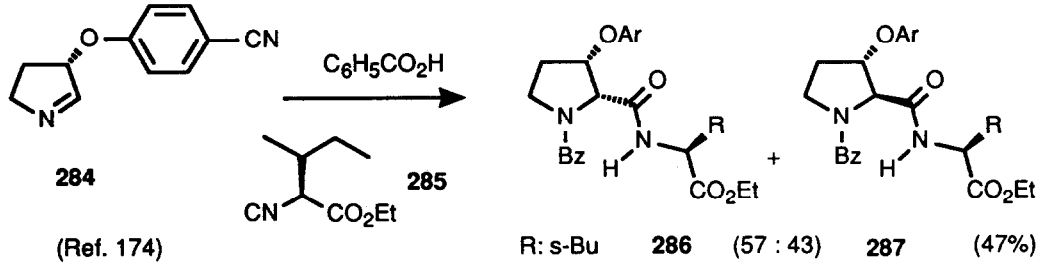


280 R_1: i-Pentyl **279** (98% de) (Ref. 172)



281 R_2 = H (Ref. 173)
282 R_2 = CH_3 (Ref. 173b)

283 85 - 91% (92 - 94% de)



284 **285**

(Ref. 174) R: s-Bu **286** (57 : 43) **287** (47%)

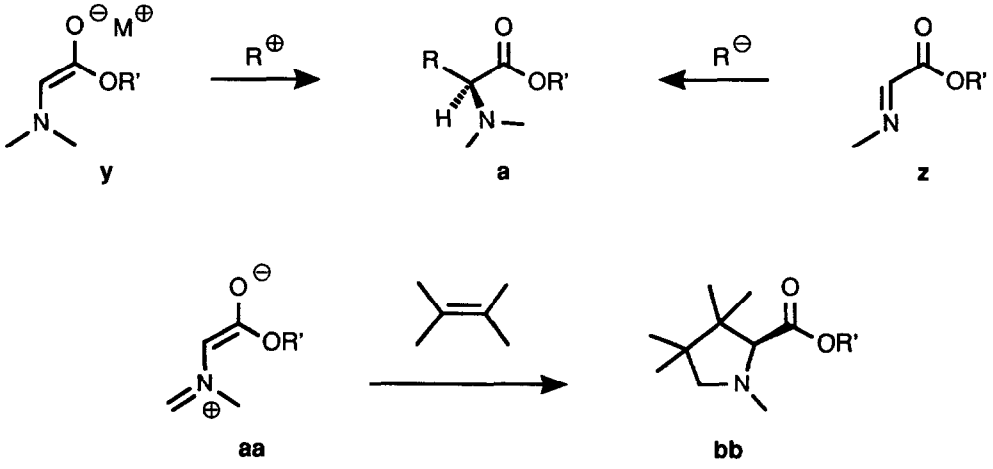
Scheme 34

The L-lactic acid derivative **267** can be considered as a chiral carboxylate synthon. Regiocontrolled lithiation and addition to sulfonylimines **268** gives the allylic sulfonamides **269** with excellent stereocontrol (*Scheme 33*).[167] Aminoacids or amino aldehydes are liberated by ozonolysis, and the mesitylene sulfonyl

group can be cleaved by reduction with Na-naphthalenide in DME. α-Amido-organolithium compounds can be generated from the corresponding stannanes **270** with retention of configuration.[168a,b] Their carboxylation at low temperature, affording amino acids **271** of high optical purity, can be considered a Strecker-type process with reversed polarity. Recently α-lithiated *N*-methylpiperidine and *N*-methylpyrrolidine have been prepared analogously. These non-chelated α-amino-organolithiums are configurationally more stable and carboxylation at -40 °C affords aminoacids of high optical purity.[168c] Related is the deprotonation of the benzylimine **272** with a chiral Li-base.[116b] Addition of chloroformate affords phenylglycine ester **273** of maximally 40% ee. Schiff's bases derived from aldehydes with chiral α-carbons induce only moderate to low diastereoselectivity in the preparation of the aminoacid precursors **274**[169a], **275**[169b], and **276**[169c]. The precursor for **274** is readily prepared from protected mandelonitrile. (*R*)-Configurated cyanohydrins of high optical purity (63 - 97% ee) are conveniently obtained from aliphatic aldehydes using mandelonitrile lyase (EC 4.2.1.0).[170]

The same galactose template **277** used for the asymmetric Strecker-synthesis induced the (*R*)-configuration to an even greater extent, when applied for the Ugi four-component condensation (→ **278**, *Scheme 34*).[171] Deprotection is achieved by sequential treatment with HCl/CH_3OH to cleave the formamide, H_2O for deglycosylation, and 6N HCl for amide hydrolysis. The Gly-Val dipeptide **279** was obtained with excellent stereocontrol using tetra-*O*-isopentyl-1-aminoglucose **280** as auxiliary.[172] With other carboxyl components and *O*-tetramethyl- or *O*-tetraethyl-glucopyranose the induction was, however, lower (59 - 74% de). The virtue of the *O*-alkyl protected carbohydrate is that the aminoglycoside can be cleaved under milder conditions (CF_3CO_2H/thiourea), thus allowing the synthesis of dipeptides. *Pseudo*-enantiomers of the D-galactoside **277** are the readily available aminopyranosides of D-arabinose **281** and L-fucose **282**. Both auxiliaries therefore induce the (*S*)-configuration (→ **283**) very efficiently, when applied for Ugi condensations.[173] The combination of the chiral pyrroline **284**, the isocyanide **285** derived from L-isoleucine and benzoic acid gives a close to 1 : 1 mixture of the epimeric dipeptides **286** and **287** in model experiments aiming at the synthesis of 14-membered cyclopeptide alkaloids (*e.g.* numularine F).[174] The stereocontrol of **284** in similar condensations with achiral isocyanides and chiral acid components was not much better.

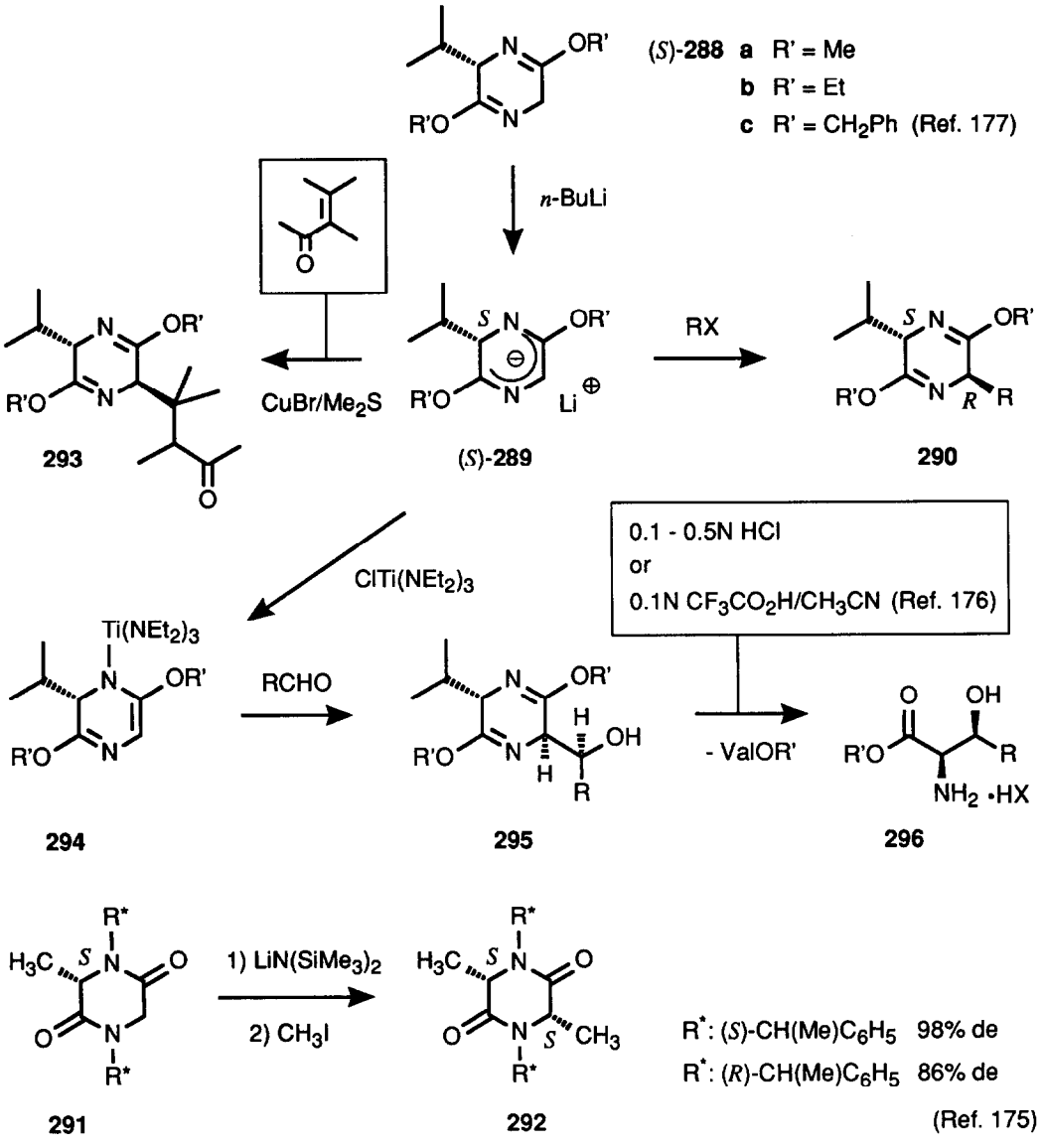
6. STEREOSELECTIVE INTRODUCTION OF THE SIDE-CHAIN



Scheme 35

A last possibility for the retrosynthetic disconnection of the α-carbon of amino acids corresponds to the introduction of the sidechain R (*Scheme 35*) (*cf.* ref. 5, *chapter 1*, pp. 1 - 133, and ref. 7c). Aminoacids **a** are thereby obtained either by reaction of glycine anion synthons **y** with electrophiles $R^{\oplus}$ or by adding nucleophiles $R^{\ominus}$ to glyoxylic-imine equivalents **z**. In addition to bond formation involving radicals or carbenes, addition of olefins to α-carboxy azomethine ylids **aa** leads to pyrrolidine-2-carboxylates **bb**.

6.1. Glycine α-Anion Equivalents



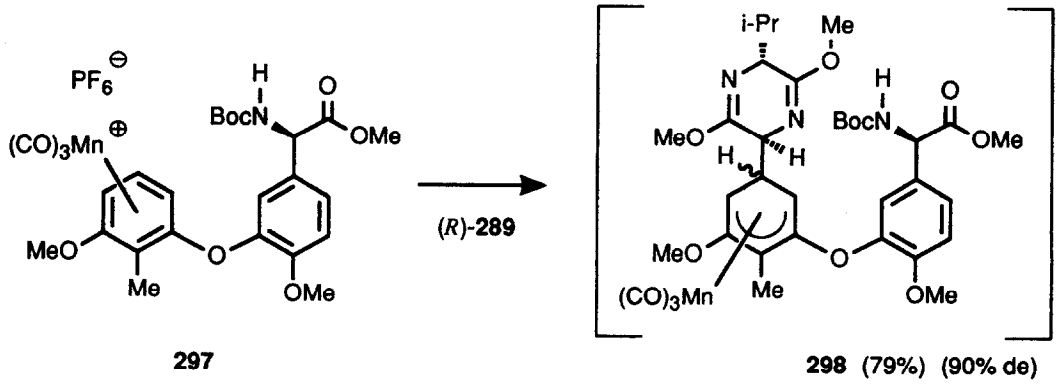
Scheme 36

One of the most versatile and apparently the most prolific chiral glycine equivalent is Schöllkopf's *bis*-lactim ether **288** derived from *cyclo*-Val-Gly (*Scheme 36*). Its use has been reviewed by Schöllkopf[7a] and up to 1989 by Williams (ref. 5, pp. 1 - 33). Alkylation of the Li-salt **289** gives the *trans*-disubstituted derivatives **290**, *i.e.* (*S*)-valine induces the (*R*)-configuration. This is in sharp contrast to the *N*-alkyldiketopiperazine **291**, affording *cyclo*-(*S*)-Ala-(*S*)-Ala **292** upon methylation.[175] The chirality of the *N*-phenethyl substituents of **291** has thereby only a marginal influence. In the presence of CuBr-Me_2S the anion **289** can also be used for 1,4-additions to α,β-unsaturated carbonyl compounds (→ **293**) or, after transmetalation with $ClTi(NEt_2)_3$ (→ **294**) for aldol reactions, yielding the *syn*-adducts **295** with excellent stereocontrol of both newly formed chiral centers. The unraveling of the amino acids **296** is probably the most tricky step of the sequence, and optimal conditions have to be found for each substrate. It has recently been reported, that dilute trifluoroacetic acid (3 equivalents) is often preferable to hydrochloric acid, and that CH_3CN as cosolvent has a beneficial effect.[176] The valine ester formed upon hydrolysis can often be removed by distillation. The final ester cleavage, which is usually done under more harsh acidic conditions, can most advantageously be effected by hydrogenolysis, if the recently introduced benzyl derivative **288c** is used.[177]

An exhaustive treatment of all the recent applications of the Schöllkopf method would be outside the scope of this review. Only a selection of highlights is therefore given in the following. Cationic aryl-manganese complexes are a novel type of electrophile, and their use for the preparation of sophisticated arylglycines has been pioneered by Pearson and coworkers (*Scheme 37*).[162b,178] Addition of the Li-salt (*R*)-**289** to the diaryl ether **297** gives the η^5-dienyl-$Mn(CO)_3$ complex **298** with good stereo- and regiocontrol. Oxidative demetalation, hydrolysis of the *bis*-lactim ether and *N*-protection gives the ristomycinic acid derivative **299**.[162b] The *bis*-amino acid **300** has been prepared analogously.[178a] The stereocontrolled synthesis of either pure (*S,S*)-2,6-diaminoheptanedioic acid or unsymmetrical derivatives of the *meso*-form is a problem which has recently been solved by the Schöllkopf methodology.[179] The fluoro-olefin **301** has been prepared *via* the *bis*-lactim ether **302**.[179a] Hypoglycine A **303**[180a] and *S*-protected ovothiol A **303a**[180b] are further amino acids prepared by *bis*-lactim ether alkylations. Successful recent examples include the synthesis of phosphinothricin,[181a] phosphono analogs of *O*-phosphotyrosine[181b] and *O*-phosphoserine,[181c] an episulfide analog of methionine,[181d] the phenylalanine substitute trimethylsilylalanine,[181e] and several isotopically labelled aminoacids.[182]

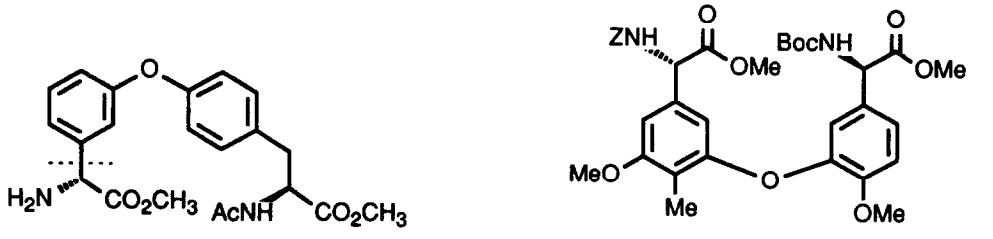
The aldol reaction of the titanated *bis*-lactim ether **294** (*Scheme 36*)[176,183] is often preferable to the alkylation, especially when the corresponding alkyl halides are unreactive or not available. In this case deoxygenation of the aldol **295** leads to the desired derivative **290**.[184] If *syn*-selectivity is not an issue, the Li-salt **289** can also be used for aldol additions. In the case of **304**, an intermediate for D-*erythro*-sphingosine **305**, 45% of *anti*-isomer has been isolated (*Scheme 38*).[185a] Addition of (*S*)-**289** to a glutamic acid semialdehyde derivative proceeded, however, with 83% *syn*-preference. The adduct **306** was further transformed to *meso*-3-fluorodiaminoheptanedioic acid **307**.[185b] An interesting application of the cuprate derived from (*R*)-**289** is the 1,6-addition to the dienone **308** yielding 40% of **309** and 24% of 1,4-adduct.[186a] This intermediate was further transformed to the dipeptide chlorotetain **310** and *epi*-chlorotetain, the isomer which has before been erroneously assigned to this natural product. The correct structure of anticapsin, an antibiotic which is closely related to chlorotetain, could be determined recently, also by total synthesis using the Schöllkopf methodology.[186b] Addition of the titanium derivative **294** to nitro-olefins gives the 1,4-adducts **311** in good yield and diastereoselectivity.[186c] The *syn/anti*-control is much inferior with the Li-salt **289** or the $(i\text{-PrO})_3Ti$-derivative. Reduction of the nitro group afforded γ-lactams, cycloaddition with the corresponding nitrile oxides the is-

oxazoline **312**.

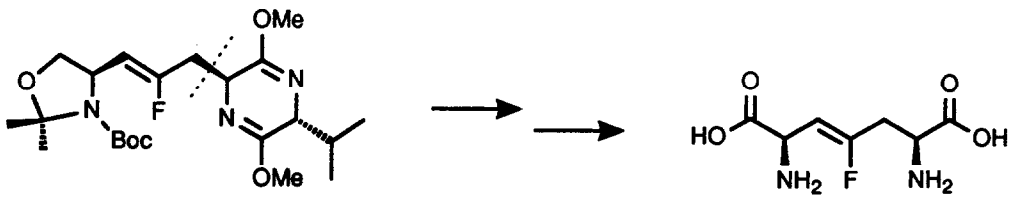


297 **298** (79%) (90% de)

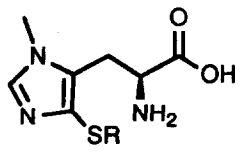
1) NBS, 2) 0.25N HCl, 3) $ClCO_2CH_2Ph$



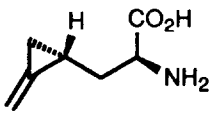
300 (Ref. 178a) **299** 27% (Ref. 162b)



302 **301** (Ref. 179a)

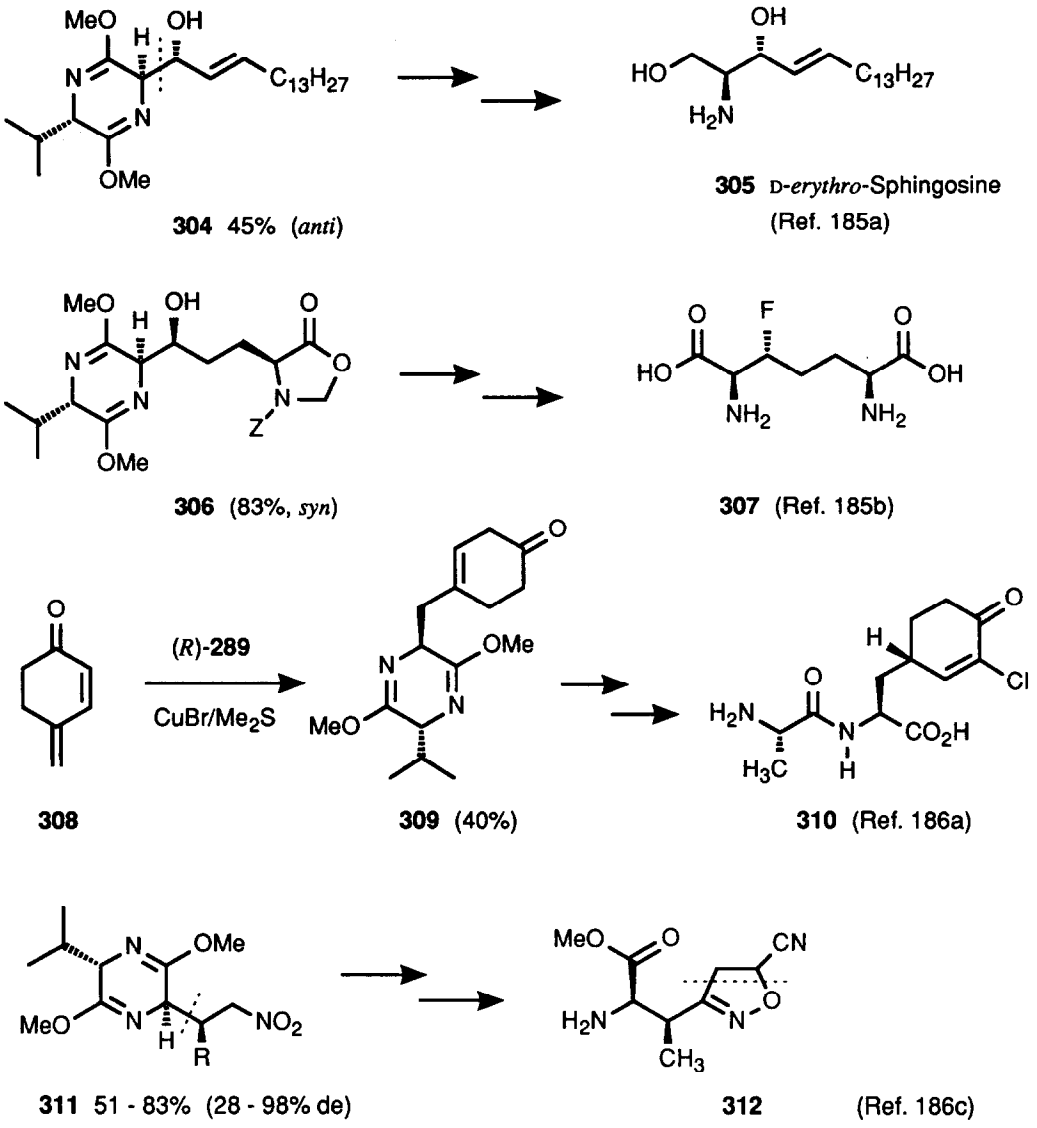


303a (Ref. 180b)
R: 4-$MeOC_6H_4CH_2$



303 (Ref. 180a)

Scheme 37



304 45% (*anti*) **305** D-*erythro*-Sphingosine (Ref. 185a)

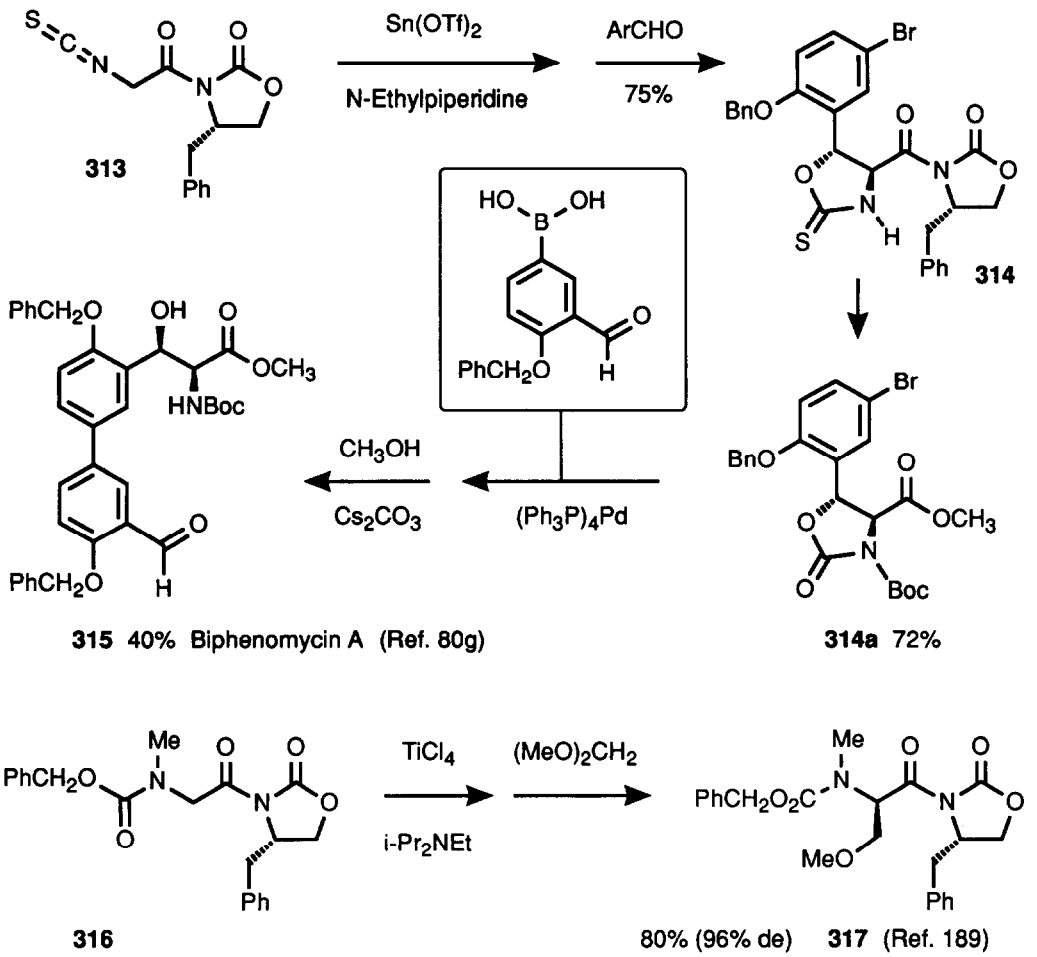
306 (83%, *syn*) **307** (Ref. 185b)

308 **309** (40%) **310** (Ref. 186a)

311 51 - 83% (28 - 98% de) **312** (Ref. 186c)

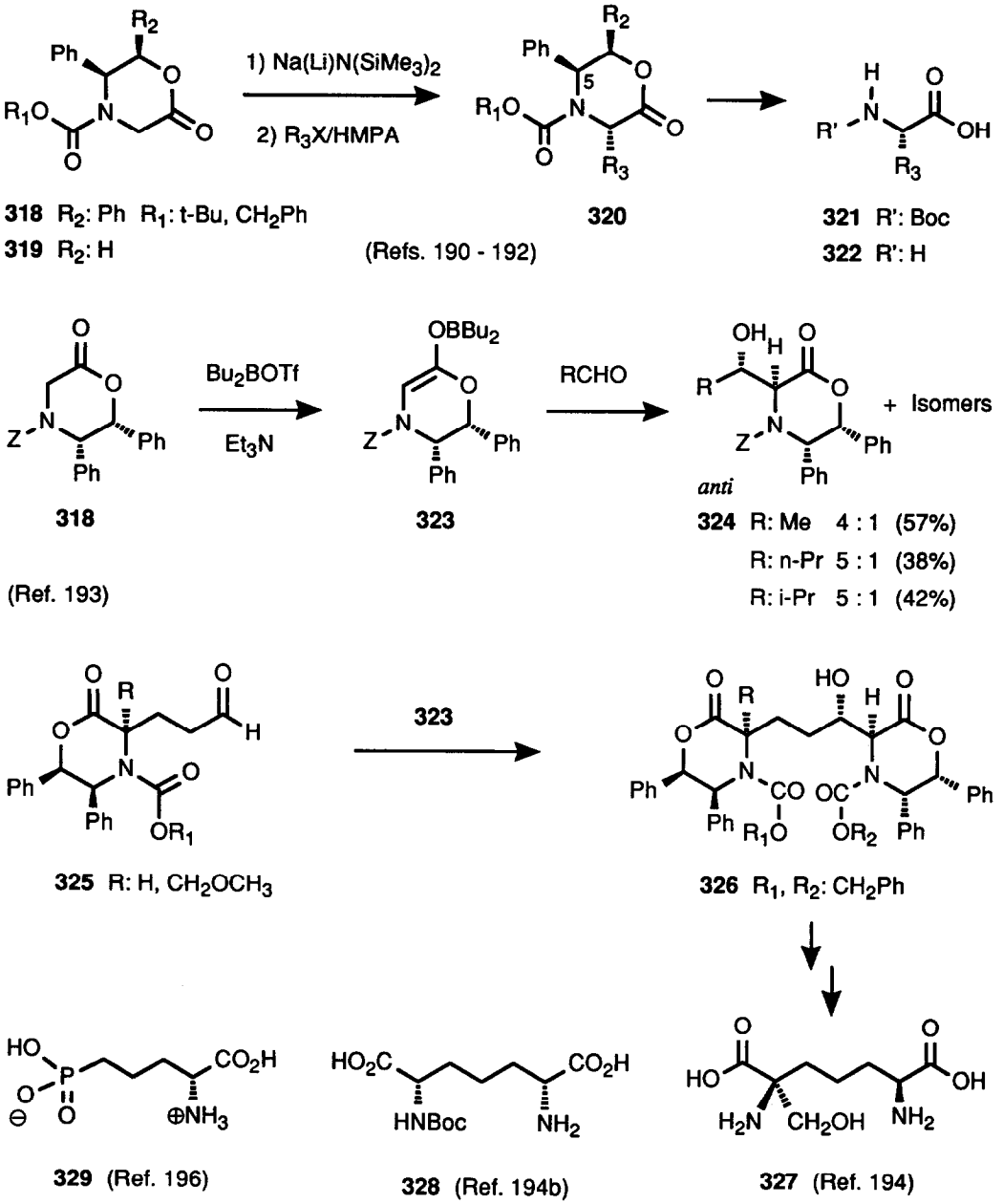
Scheme 38

One of the major hurdles of the enolization of glycine derivatives is the nitrogen protection. An elegant solution is the use of isothiocyanate **313** introduced by Evans and Weber (*cf.* ref 5, pp. 41 - 43).[187] Its Sn-aldol reaction leads to thiocarbamates, *e.g.* compound **314**, which was further elaborated *via* **314a** and Suzuki coupling to the complex biphenyl-alanine **315**, an intermediate of a total synthesis of biphenomycin A (*Scheme 39*).[80g] For the enolization of the *N*-benzyloxycarbonyl-sarcosine derivative **316** the $TiCl_4/(i\text{-}Pr)_2NEt$ protocol[188] was applied. Reaction of the resulting Ti-enolate with dimethoxymethane gave the *N,O*-dimethylserine derivative **317**.[189] The corresponding aldehyde served as a chiral building unit for a total synthesis of caliculin A.



Scheme 39

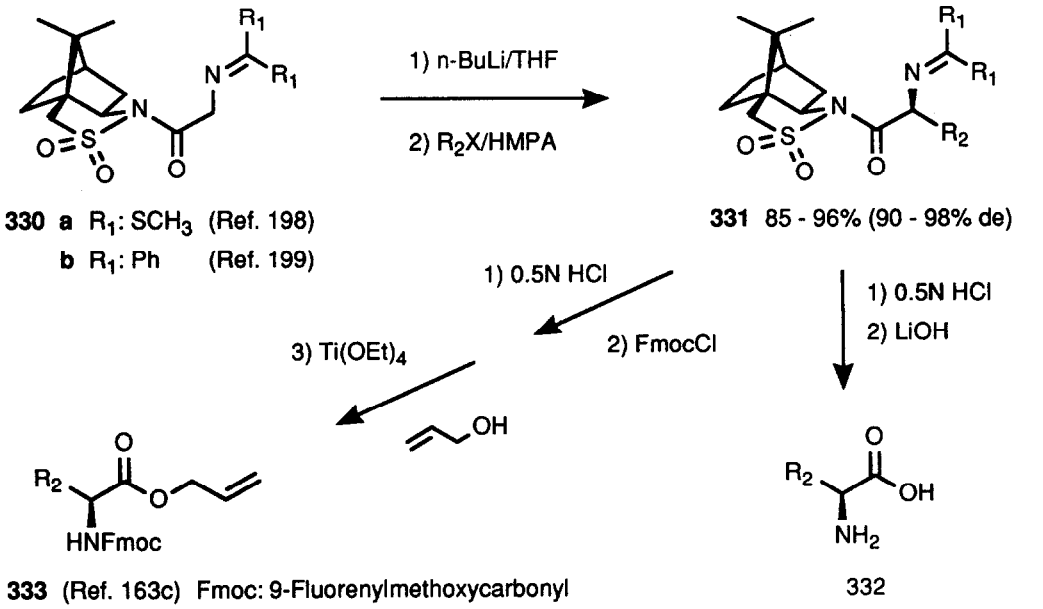
Alkylation of the two *N*-acyl-oxazinones **318**[190] and **319**,[191] available in both enantiomeric forms, was described almost simultaneously (*cf.* ref. 5, pp. 87 - 90) (*Scheme 40*). For the deprotonation only disilazides are successful, and temperature, mode of addition, and other parameters have to be adjusted carefully. The counterion is important, and, according to a recent communication, $NaN(SiMe_3)_2$ is preferable to the Li-salt, especially in combination with 15-crown-5, enabling deprotonation at - 100 °C.[192] Common with other enolate alkylations the reactivity of the halide R_3X is essential and addition of HMPA (10%) to the solvent is advisable in case of non-activated electrophiles.[190b] For both systems the products **320** are obtained with high diastereoselectivity (98 - 99% de), the substituent being introduced *anti* to the C(5)-phenyl residue. Allylic strain exerted by the carbamoyl function is thereby important (*cf.* ref. 20), as the *N*-benzyl analog is preferentially attacked from the opposite (*syn*) side (86% de).[191] The auxiliary is conveniently removed by hydrogenolysis. Dissolved metal reduction (Li/NH_3) of **320** (R_1: t-Bu) affords *N*-Boc aminoacids **321**,[190] while $H_2/PdCl_2$ directly leads to free aminoacids **322** from **320** (R_1: CH_2Ph).[190,191] Enolization of **318** with $(Bu)_2BOTf/Et_3N$



Scheme 40

proceeds exceptionally well for an ester. The resulting (*E*)-boron-enolate **323** reacts readily with aldehydes.[193] The facial selectivity is excellent for the oxazinone and acceptable (4 : 1) for the aldehyde carbonyl in favor of the *anti*-aldols **324**, which can be isolated pure by crystallization (38 - 57%). The versatility of this method has recently been demonstrated by the stereocontrolled synthesis of 2,6-diaminoheptanedioic acid

derivatives.[192,194] Problems with alkylations were avoided with the aldehydes **325**, prepared by ozonolysis of the corresponding allyl derivatives. Boron-aldol reaction (→ **326**), deoxygenation, hydrogenolysis, and demethylation of the CH_2OCH_3-group (48% HBr) afforded the α-hydroxymethyl derivative **327** with excellent stereocontrol. By using 15-crown-5 in the deprotonation step the same compound was obtained by *bis*-alkylation with a propane-1,3-dihalide as well.[192] The use of **318** (R_1: t-Bu) and **318** (R_1: CH_2Ph) allowed the regioselective preparation of the differentially protected *meso*-compound **328**.[194b] This auxiliary was also used to prepare α,ω-diamino acids[195] and (*R*)-configurated 2-amino-5-phosphonovaleric acid **329**.[196] Analogs of **319** (R_2: H) have been prepared from several amino alcohols, obtained conveniently by reduction of abundant aminoacids.[197] The diastereoselectivity of the alkylation is excellent in many cases, but the auxiliary cannot be removed at the end. Some intermediates have been transformed into peptide isosteres, potential inhibitors of aspartyl proteases.[197b]

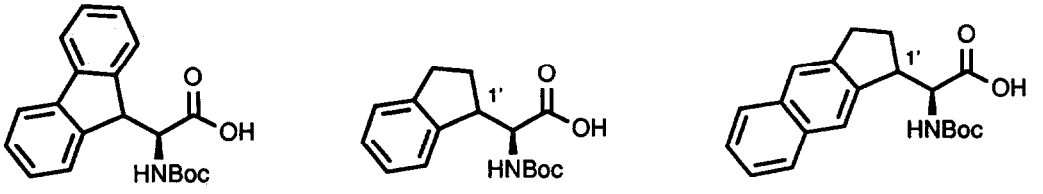


330 **a** R_1: SCH_3 (Ref. 198)
b R_1: Ph (Ref. 199)

331 85 - 96% (90 - 98% de)

333 (Ref. 163c) Fmoc: 9-Fluorenylmethoxycarbonyl

332



334 (Ref. 199a)
> 95% de

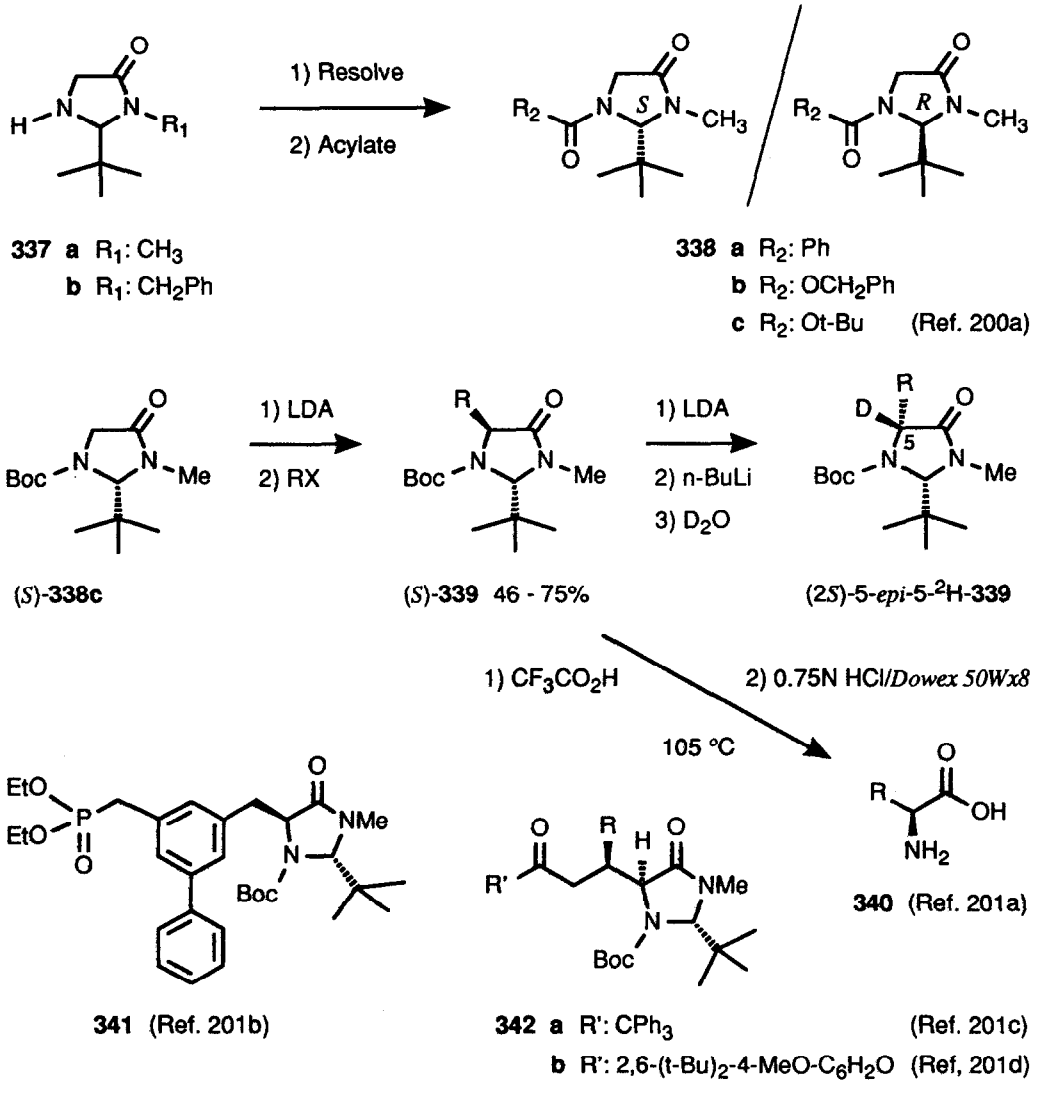
335 (Ref. 199b)
> 95% de, C(1'): 2% de

336 (Ref. 199c)
C(1'): 33% de

Scheme 41

The camphor sultam introduced by Oppolzer[141b] has been used for asymmetric derivatization of glyci-

ne as well (*Scheme 41*). Deprotonation of the imino-derivatives **330a**[163c,198] or **330b**[199] followed by alkylation with an iodide or bromide in the presence of HMPA gives the aminoacid derivatives **331** with good diastereoselectivity (90 - 98% de) and excellent yield, even in the case of rather unreactive electrophiles (*e.g.* i-PrI, 80%). After purification and diastereomer separation, imine hydrolysis under acidic conditions and removal of the auxiliary with LiOH affords aminoacids **332**. *N*-Fluorenylmethoxycarbonyl-protected allyl esters **333**, on the other hand, are obtained by imine cleavage, N-protection and $(i\text{-PrO})_4Ti$ catalyzed esterification.[163c] Recent examples include the phenylalanine and naphthylalanine analogs **334**, **335**, and **336**[199] with conformationally restricted side-chains.



337 **a** R_1: CH_3
b R_1: CH_2Ph

338 **a** R_2: Ph
b R_2: OCH_2Ph
c R_2: Ot-Bu (Ref. 200a)

(*S*)-**338c**

(*S*)-**339** 46 - 75%

(2*S*)-5-*epi*-5-^{2}H-**339**

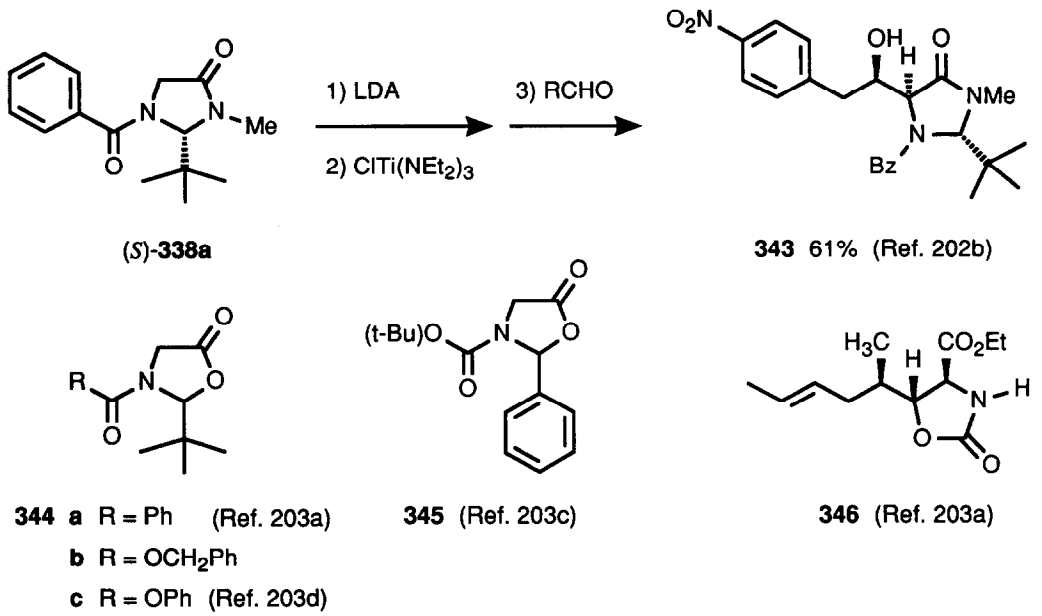
340 (Ref. 201a)

341 (Ref. 201b)

342 **a** R': CPh_3 (Ref. 201c)
b R': 2,6-(t-Bu)$_2$-4-MeO-C_6H_2O (Ref, 201d)

Scheme 42

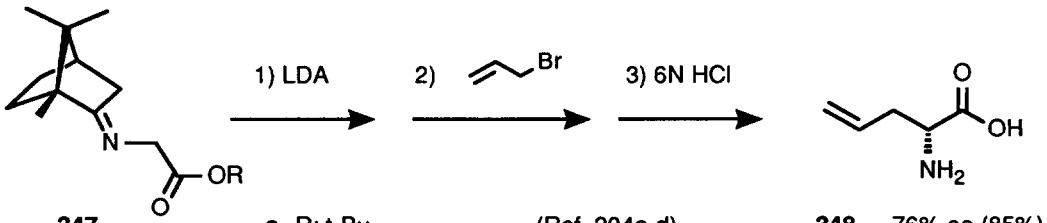
2-t-Butylimidazolidin-4-ones react with high diastereoselectivity at C(5) (*cf. Scheme 19*, ref.105). The parent compound **337** has therefore been resolved into its enantiomers. *N*-Acylation afforded the chiral glycine equivalents **338a - c** (*cf.* ref. 5, pp. 71 - 75) (*Scheme 42*).[200] Deprotonation of Boc-BMI **338c** and alkylation with halides proceeds as expected, affording the (*S*)-aminoacid precursors **339** from (*S*)-**338c**.[201] The attack of the electrophiles is kinetically controlled, as deprotonation of (*S*)-**339** and reprotonation with D_2O proceeds with inversion of C(5) (→ (2*S*)-5-*epi*-5-^{2}H-**339**). The aminoacids **340** are obtained by sequential treatment with CF_3CO_2H and 0.75N HCl/*Dowex 50Wx8* (H^+) at 105 °C. This method has been applied for the preparation of glutamate antagonists, *e.g.* **341**.[201b] The 1,5-dicarbonyl compounds **342** are obtained with excellent stereocontrol by Michael addition to unsaturated tritylketones[201c] or hindered aryl esters.[201d]



Scheme 43

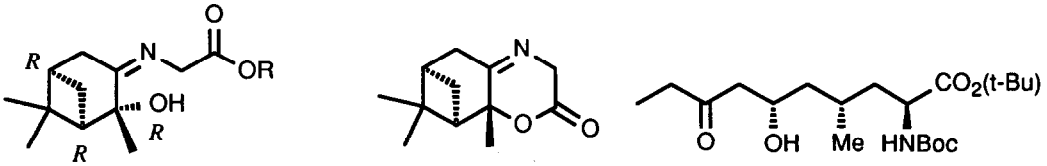
The Li-enolates derived from the imidazolidinones **338** can also be used for aldol reactions (*Scheme 43*).[202] While the stereoselectivity at C(5) of the heterocycle is excellent, the enantioface discrimination of the aldehyde is not always good (36 - 92% de), with the *threo*- or *syn*-adduct being favored.[202a] As in the case of the Schöllkopf reagent (*cf. Scheme 36*) the selectivity can be improved by transmetalation with $ClTi(NEt_2)_3$. Under these conditions reaction with the acidic *p*-nitrophenacetaldehyde yields 61% of pure *threo*-adduct **343**.[202b] A further problem of the Li-aldolization is the *N*(1)-*O*-benzoyl shift, which is not observed with the Ti-derivative. In another application of this method, the synthesis of *threo*-β-hydroxylysine, this transacylation was prevented by quenching the Li-alkoxide with 3,5-dinitrobenzoyl chloride.[130c] With L-glutamate-γ-semialdehyde this protocol was used for the preparation of the *threo*-β-hydroxy derivatives of either *meso*- (matched) or L,L- (mismatched) 2,6-diaminoheptanedioic acids.[185b] The epimeric *erythro*-β-hydroxy-α-aminoacids are obtained, when the *N*-Boc-protected imidazolidinone **338c** is acylated with acid chlorides, followed by $LiHBEt_3$-reduction of the resulting ketones.[202c] The hydrolysis of the *N*-methylimidazolidinones deri-

ved from **338** is sometimes met with difficulties. Therefore the oxazolidinone analogs **344** and **345** have been prepared and separated into the enantiomers by preparative HPLC (*Scheme 43*).[203] These heterocycles are best deprotonated with $LiN(SiMe_3)_2$ at -75 °C. The resulting enolates are rather unstable, and are treated with an aldehyde at -100 °C. In case of the benzyloxycarbonyl derivative **344b** transacylation of the Li-aldolates gives 2-oxazolidinones, especially with branched aliphatic aldehydes.[203b] This is an advantage for the preparation of *N*-alkyl aminoacids, and **346** was transformed to MeBmt, the unusual *N*-methyl aminoacid of cyclosporin.[203a] The deprotection to the free aminoacids is much easier, especially for **344b** and **345**. In case of **345** direct hydrogenolysis affords *N*-Boc-*N*-benzyl aminoacids.[203c] The influence of the *N*-acyl substituent on the stereoselective methylation of **344** was studied recently. Small residues are generally preferrable and excellent stereoselectivity was obtained for the phenylcarbamate **344c** (R = OPh).[203d]



347

a	R: t-Bu	(Ref. 204a-d)	**348**	76% ee (85%)
b	R: c-C_6H_{11}	(Ref. 205a)		66% ee (70%)
c	R: (+)-Menthyl	(Ref. 205a,b)		85% ee (81%)
d	R: (-)-Menthyl	(Ref. 205a)		3% ee (70%)

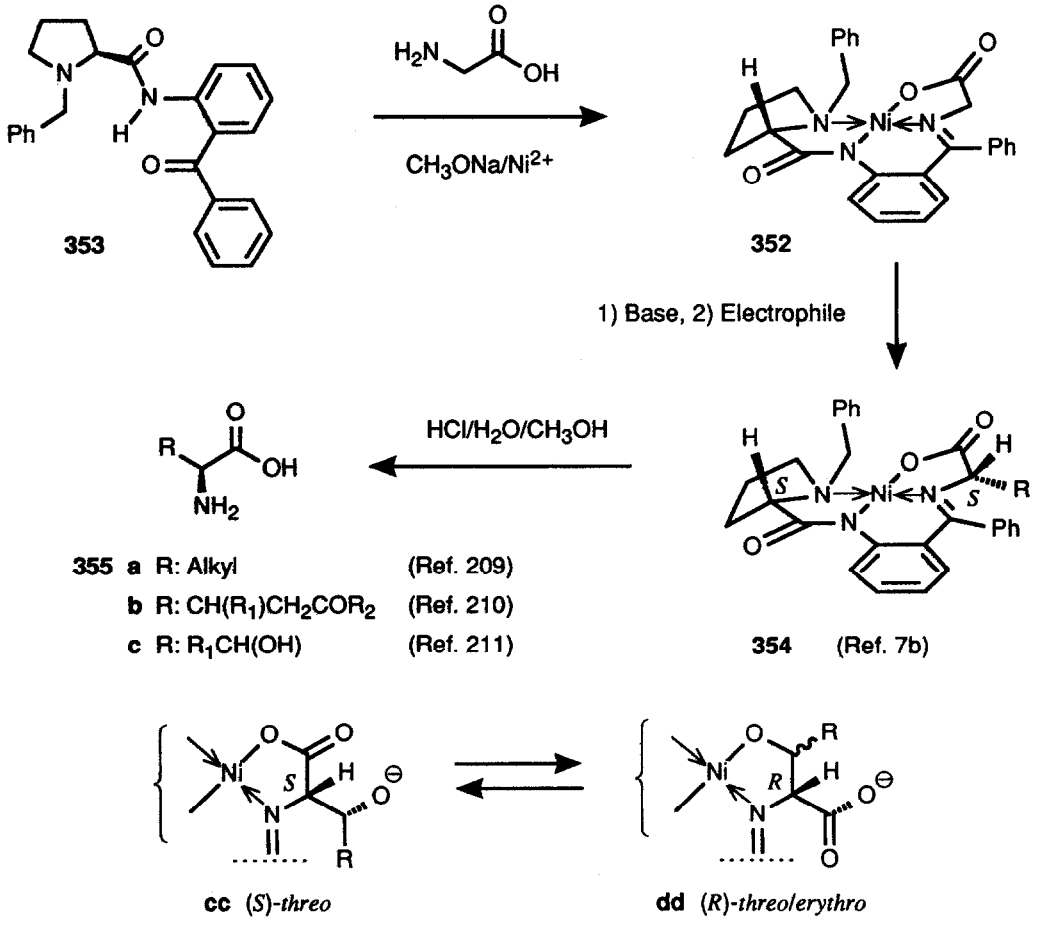


349	**a** R: Et	(Ref. 207a,b,h)	**350**	**351** 92% ee
	b R: t-Bu	(Ref. 207c,e)	(Ref. 91b)	(Ref. 207c)
	c R: Me	(Ref. 207d,e)		
	d R: i-Bu	(Ref. 207e)		
	e R: (-)-Menthyl	(Ref. 205a,c,d)		

Scheme 44

An efficient asymmetric derivatization of glycine esters is the formation of Schiff's bases with chiral ketones, effecting simultaneous acidification of the α-protons (*cf.* ref. 5, pp. 34 - 38). Among the better studied systems is the camphor imine **347**, which gives (*R*)-aminoacids upon deprotonation with LDA, alkylation, and acidic hydrolysis (*Scheme 44*).[204,205] Successful applications include the synthesis of 7-azatryptophane (98% de)[204c] and 1,4-additions to α,β-unsaturated esters (90 - 95% de for C(α)), giving access to substituted pyroglutamates upon cleavage of the imine with H_2NOH.[204d] The ester group has a marked influence on the stereoselectivity, as exemplified for the allylation of **347a - d** (→ **348**). The beneficial effect of a bul-

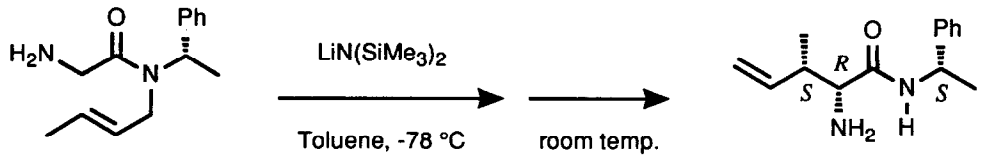
ky ester can be enhanced by incorporating chirality, and thus the best induction (85% ee) is observed for **347c**, the (+)-menthyl ester, as opposed to the mismatched (-)-menthyl derivative (3% ee).[205] Similar results have been reported for *N,N*-diisopropyl-10-camphorsulfonamide[206a] and (+)-ketopinic acid as chiral carbonyl auxiliaries.[206b] The latter system has also been used for aldol reactions, exhibiting rather moderate diastereo- and enantioselectivity. Another frequently used system is the 2-hydroxypinan-3-one derivative **349**, which induces (*S*)-configuration in case of the (*R,R,R*)-enantiomer (*Scheme 44*).[205,207] The sense of the induction is rather puzzling and its magnitude is influenced by numerous factors, including additives (*e.g.* $MgBr_2$).[207a] A possible explanation, which is, however, not generally accepted, invokes different aggregation states of the Li-enolate.[207b,h] Rather startling, furthermore, is the observation that the cyclic analog **350** induces the opposite configuration.[91b] The fact that the order of the addition of two electrophiles, either two different alkyl substituents,[207e] or an alkyl halogenide and a proton,[91b] is unimportant, *i.e.* the same configuration results with the alternate mode of addition, awaits a convincing explanation. Nevertheless, good results have been reported with this auxiliary, *e.g.* the synthesis of *AHMOD* (**351**), a constituent of leucinostatins,[207c] and highly



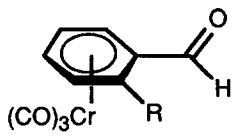
Scheme 45

erythro-selective aldol reactions with sugar aldehydes.[207d] The influence of the ester appears to be less pronounced[207e] and for (*R,R,R*)-**349** the (-)-menthyl derivative **349e** is the matched pair.[205a,c,d] The Schiff's base from glycine and the pyridoxal analog with planar chiralty, **131** *cf. Scheme 17*, has been used for aldol reactions with simple unhindered aldehydes.[208] Under optimized conditions (0.6 equivalents of $Zn(OAc)_2$) a slight excess of *erythro*-isomer (75 - 77% ee) is isolated in addition to the *threo*-epimer (50 - 54% ee).[208a]

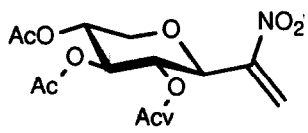
One of the best studied systems is the Ni-complex **352**, readily obtained from the proline amide **353** and glycine (*cf* ref. 5, pp. 91 - 95) (*Scheme 45*). Its various uses, including deprotonation with base followed by reaction with electrophiles leading to (*S*)-configurated products **354** has recently been reviewed.[7b] In this case it could be demonstrated that the generally good induction is thermodynamically controlled. After separation of the diastereomers by chromatography, acidic hydrolysis of **354** yields aminoacids **355** of high optical purity. Alkylation with reactive halides affords **355a**,[209] *e.g.* fluoro-substituted phenylalanines[209b,c] or ω-phosphono-α-aminoacids.[209d] The power of this method is exemplified by the expedient and fast preparation of β-^{11}C-labelled aminoacids for positron emission tomography (PET) in 12 - 60% radiochemical yield and 80 - 90% ee.[209e] 1,4-Addition to α,β-unsaturated carbonyl compounds leads to the Michael adducts **355b** with good stereocontrol of C(α), C(β), and sometimes also of C(γ).[210] The products **355b**, glutamate derivatives, can be transformed to substituted prolines. The Ni- or Cu-template **352** is also well suited for aldol reactions with various aldehydes giving rise to β-hydroxy-α-aminoacids **355c**.[211] In this case the configuration of **355c** is dependent on the equilibrium of two alternative aldolate intermediates: **cc** and **dd** (*Scheme 45*). While the alcoholate **cc** and therefore (*S*)-*threo*-configuration is favored at high pH and for fluorinated residues R,[211d] the (*R*)-enantiomers are prevailing at lower base concentration *via* carboxylate **dd**, often with high *threo*-preference as well.[211c]



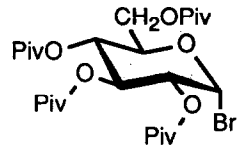
356 (Ref. 212) **357** 89% (78% de)



358 **a** R: OMe (Ref. 213)
b R: Me



359 (Ref. 214a)

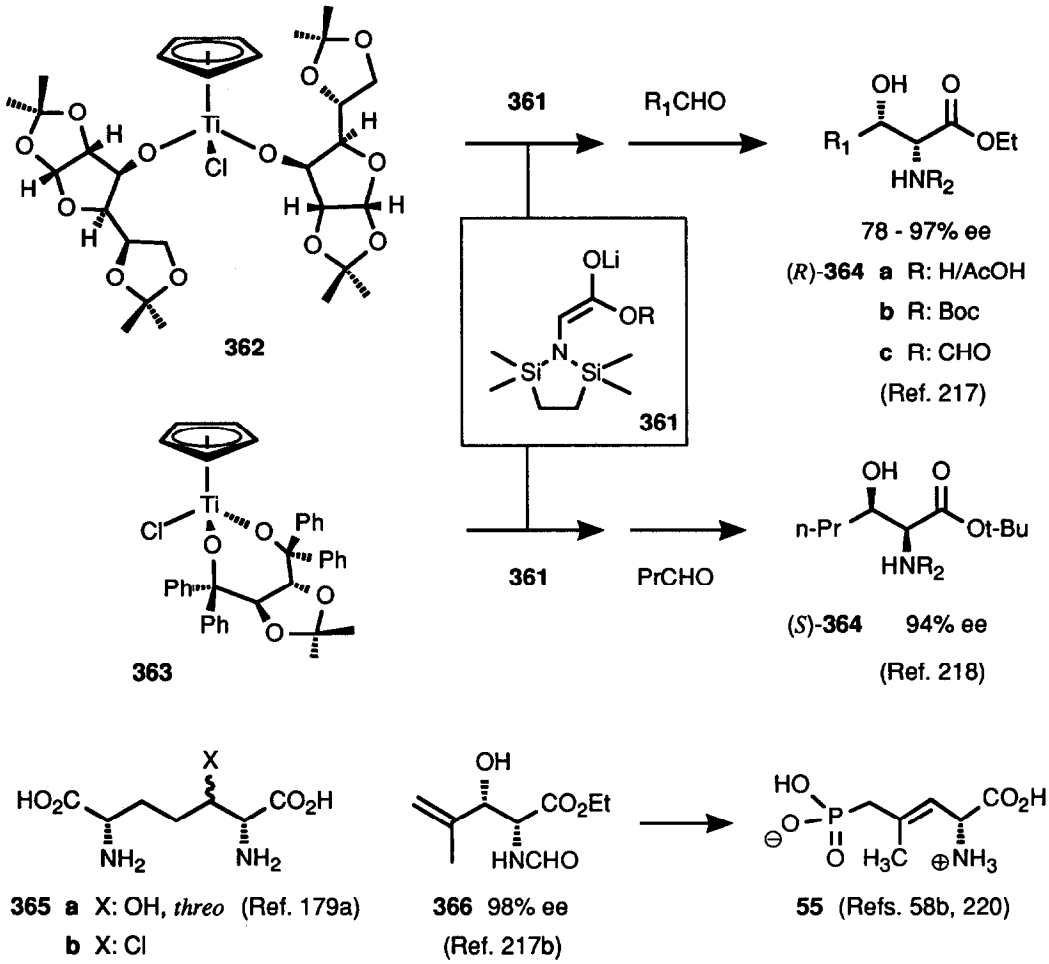


360 (Ref. 214b)
Piv.: t-BuCO

Scheme 46

A very special case is the aza-Claisen rearrangement of glycine allylamide **356** proceeding with high *syn*-selectivity (*Scheme 46*).[212] The enantiofacial selectivity exerted by the (*S*)-*N*-phenethyl residue is remar-

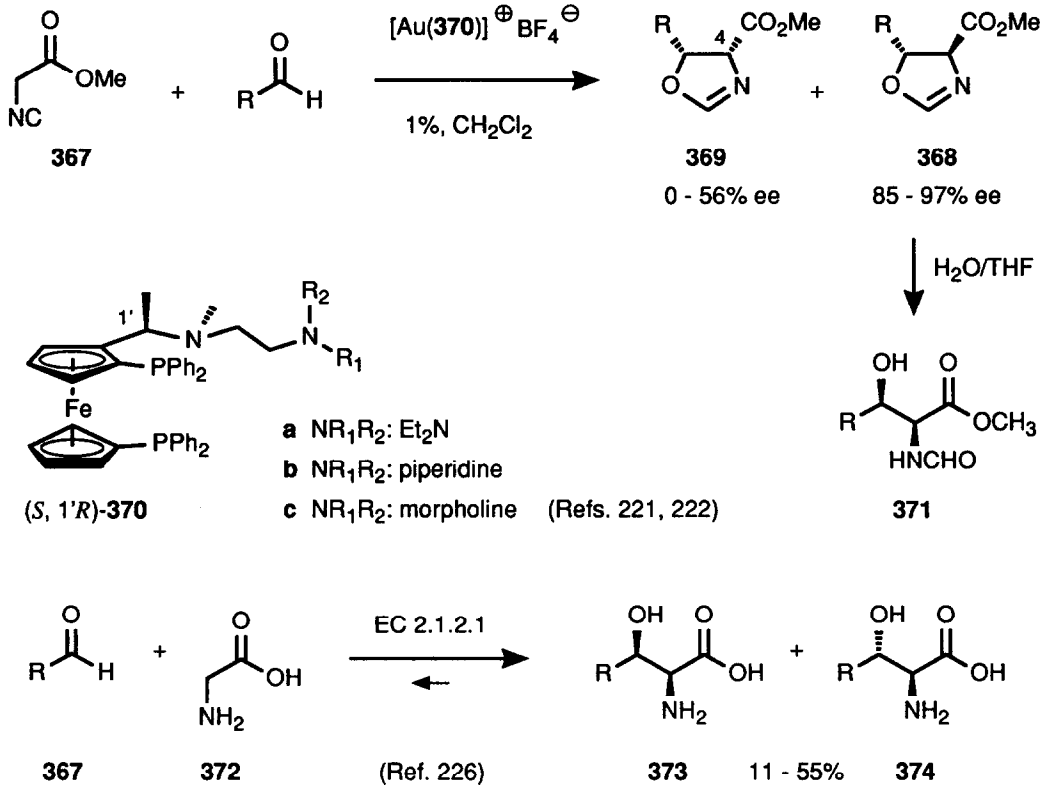
kable, giving 78% excess of (*R*)-configurated *allo*-isoleucine **357** in excellent yield. The use of chiral electrophiles has so far met with limited success. While good control has been achieved by the aldehyde **358a** having planar chirality (92% de),[213] the stereoselectivity exhibited by **358b**[213], the sugar derivatives **359** and **360**,[214] or by applying chiral methyl sulfates[116b,215] was moderate at best.



Scheme 47

The use of non-covalently bound chiral auxiliaries has the advantage of reducing the number of intermediates and is a first step towards enantioselective catalysis. In case of glycine enolates the counterion is the most obvious choice for such non-covalent chiral modifications, *e.g.* by using chiral metal ligands. Transition metals with well defined coordination geometry and aggregation properties, strong ligand to metal bonds, and correspondingly slow ligand exchange rates, are better suited to this purpose than alkali metals. Transmetalation of the silyl-protected glycine enolate **361** with the cyclopentadienyl-Ti-complexes **362** or **363**[216] and addition to aldehydes thus gives *threo*-β-hydroxy-α-aminoacids **364** with high (*R*)-selectivity in case of the D-glucose derived ligand (**362**),[179a,217] or with (*S*)-configuration, when the chelating tetraphenyl-threitol li-

gand is used (**363**).[216b,218] Applications include the *meso*-2,6-diaminoheptanedioic acid **365a**, its chloro derivative **365b**,[179a,217b,219] and the methacrolein adduct **366**[217b], an intermediate for the glutamate antagonist **55**[58b,220] (*cf. Scheme 7*).

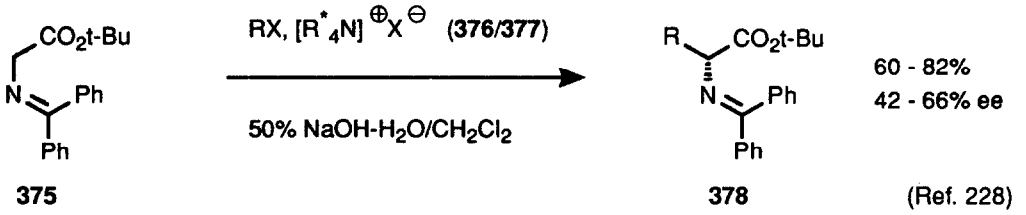


Scheme 48

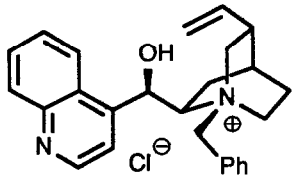
The addition of isocyanoacetate **367** to various aldehydes mediated by a cationic Au(I)-complex was developed by Hayashi and associates, and was the first catalytic enantioselective aldol-type reaction reported (*Scheme 48*, *cf.* ref. 5, pp. 49 - 53).[221] The main product with 60 - 99% de and 85 - 97% ee is the *trans*-oxazoline **368**, which in most cases is isolated with better optical purity than the minor C(4)-epimer **369**. The best ligands for this transformation are the chiral *bis*-diphenylphosphino-ferrocenes **370**, especially **370b** and **370c** reported later.[221b,e] Hydrolysis of oxazoline **368** gives *threo*-*N*-formyl-β-hydroxy-α-aminoacid esters **371**, which are L-configurated, if **370** with (*R*)-configurated side-chain and (*S*)-planar chirality is used. The main problem of this very elegant process is the formation of the epimer **369** of opposite α-configuration and lower optical purity. So far attempts for optimization have not been very fruitful, as improvements for **368** and **369** often do not run in parallel,[221c,222] *e.g.* a bulky amine substituent NR_1R_2 in the side-chain of the ligand **370** can enhance the optical purity of **369** to 70% ee, while reducing the yield and enantiomeric excess of **368**.[221e] Preparation of the diastereomeric ligand (*S*,1'-*S*)-**370**, a tricky task, since the asymmetric center of the side-chain is used to induce the planar chirality, led to the interesting observation that the induction is mainly go-

verned by the side-chain.[222b,c] Despite much effort,[221e,222c] the mechanism of this complex process has not been clarified, and the supposed chelating property of the *bis*-phosphines **370** could not be verified by X-ray analysis of the chloro complex, a catalyst with only slightly inferior properties, when compared to the tetrafluoroborates.[222a] While the size of the ester group of the isocyanoacetate **366** has a beneficial effect mainly on the optical purity of the minor *cis*-epimer **369**,[222d] the stereoselectivity of isocyanoacetamides is generally better.[221d] Bulky aldehydes give better results; however, the course of additions to heterocyclic substrates is also governed by electronic effects.[222d] The Au(I)-complex catalyzes additions to α-keto-esters as well, but with somewhat lower stereocontrol.[221f] Good to intermediate results have also been reported for substituted α-isocyano esters,[223] except for the addition to formaldehyde.[223b] Applications of this process include the syntheses of sphingosines,[224a] the unusual aminoacid MeBmt of cyclosporin,[224b] and of the glutamate antagonist **55** *via* the intermediate **366** (*cf, Scheme 47*).[58b] Experiments with Ag-catalysts led to mechanistically interesting conclusions.[205] As opposed to Au(I), Ag(I) can be coordinated by two isocyanides in addition to the diphosphine **370**. This complex is kinetically more stable and could be analyzed by NMR.[225a] The proximity of the ligand side-chain to the isocyanoacetate could thereby be verified with NOE-measurements, thus confirming the proton-abstracting function of the terminal amino-group. In contrast to the *mono*-isocyanido-Au(I) complex, catalysis by the *bis*-isocyanido-Ag(I) complex proceeds with much lower stereocontrol, but its concentration can be kept low by slow addition of isocyanoacetate **366**. By further optimization of the reaction temperature good enantioselectivity can be obtained with Ag(I) as well.[225b] This method gives thus access to a variety of β-hydroxy-α-aminoacids, a class of aminoacids found in numerous natural products. It is therefore not surprising, that an enzyme, serine hydroxymethyl transferase (EC 2.1.2.1), catalyzes the same process. Its substrate specificity has recently been evaluated with a number of heterocyclic, aromatic, and aliphatic aldehydes (*Scheme 48*).[226] With 10 equivalents of glycine **372** the conversion is rather slow and 11 - 55% of *threo/erythro* mixtures **373/374** are isolated after 20 - 60 days of incubation. While indol-3-aldehydes and 4-formylimidazole are not recognized as substrates, 2-formylimidazole is converted into 55% of product within 60 days.

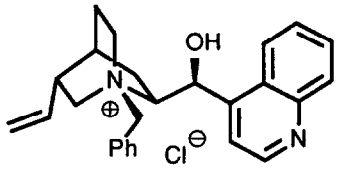
While the Pd-catalyzed allylation of the acidic Schiff's base **375** is restricted to the synthesis of allylglycines,[227] its alkylation in a two-phase system, mediated by chiral phase-transfer catalysts has a broader scope (*Scheme 49*, *cf.* ref. 5, *chapter 8*, pp. 280 - 284).[76,228] Chiral tetraalkylammonium chlorides are obtained by *N*-benzylation of the alkaloids cinchonine (→ **376**) or its ψ-enantiomer cinchonidine (→ **377**). In the presence of the cinchonine-derived catalyst **376** (*R*)-configurated aminoacid derivatives **378** are obtained in good yield and with moderate enantioselectivity. The optical purity of the products can, however, often be upgraded by selective crystallization of racemate, or after cleavage of the imine by kinetic resolution with a protease.[76] The ammonium salt **376**[229a] and chiral Cu-chelates such as **379**[229b] have recently been used for the enantioselective alkylation of glycine- or alanine- derived Schiff's bases fixed as Ni-chelates.[7b,229] A chiral environment for enantioselective alkylation of Schiff's bases can also be generated in macroreticular polymers either by incorporating chiral pendant groups[230a] or by chiral imprinting.[230b] In the latter case a derivatized aminoacid such as **380** is copolymerized with styrene. Subsequent hydrolysis of the imine and borate leaves a chiral cavity within the polystyrene, which presents functions to help reassemble the corresponding aminoacid by alkylation or aldolization of glycine. The optical yields are still low (0.7 - 35% ee), but chemical yields up to 92% have been reported.



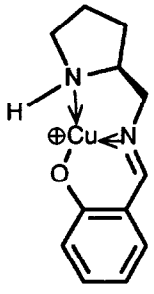
375 378 (Ref. 228)



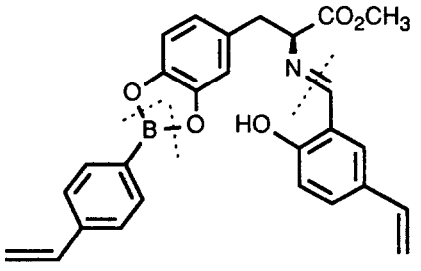
376 *N*-Benzylcinchoninium chloride



377 *N*-Benzylcinchonidinium chloride



379
(Ref. 229b)



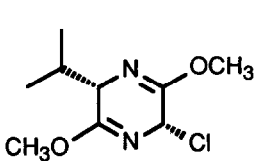
380
(Ref. 230b)

Scheme 49

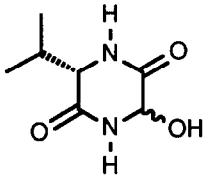
6.2. Glycine α-Cation Equivalents

The heterocycles which serve as chiral glycine-anion equivalents can be reversed in polarity simply by oxidation to glyoxylic acid derivatives (*Scheme 50*, *cf.* Ref. 5, *chapter 1*, pp. 95 - 133). Thus the chlorinated *bis*-lactim ether **381** could be converted into aromatic aminoacids by $SnCl_4$-catalyzed Friedel-Crafts alkylations of electron-rich aromatics.[231] More recently the diketopiperazine **382** and the analog derived from proline were subjected to electrophilic substitution with styrenes and a 1,3-diketone under the catalysis of CF_3CO_2H or sulfonic acids.[232] While radical couplings of the bromide **383** with allylstannane proceeds with retention of configuration, its deuteration catalyzed by $PdCl_2$ appeared to have occured with inversion.[233] One of the most thoroughly studied glycine cation equivalents is the 3-bromo-oxazinone **384** (*cf.* ref. 5, pp. 87 - 90; refs. 7c, 16).[190a,234] It has been substituted efficiently by alkyl thiolates, malonate, alkyl-Zn halides and cuprates.[234a] Under Lewis-acid catalysis reactions with allylsilanes and silyl enol ethers[190a,134], as well as Friedel-Crafts alkylations[234a] and couplings with trialkylstannylacetylides[234b] could also be effected. A more recent report describes couplings with arylcuprates (→ **385**).[234c] Deprotection of the products **385/386** is either done with Li/NH_3 giving Boc-protected aminoacids **387a**, or by catalytic hydrogenolysis leading to the free aminoacids **387b** from *N*-benzyloxycarbonyl-protected intermediates (R_1: CH_2Ph). The bromo derivative of Boc-BMI **388** could also be substituted with a variety of oxygen, nitrogen, sulfur, and phosphorus nucleophiles.[84] Successful carbon nucleophiles include cyanide, malonate, allylsilane, silyl enol ethers and electron

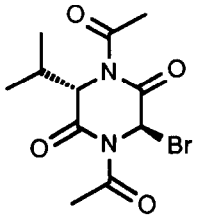
rich aromatics. Reactions of **388** with cuprates proceeded, however, with low yields and stereoselectivity. In sharp contrast to the related heterocycles **381**, **383**, and **384**, the substitutions with the imidazolidinone **388** involved inversion at C(5). The Ni-complex **389** is obtained by bromination of **352** (*cf. Scheme 45*) with Br_2/Et_3N as a 2 : 1 (*R*)/(*S*)-mixture.[235] Substitution with oxygen and nitrogen nucleophiles, as well as with diethyl malonate occurs with excellent stereocontrol (90 - 98% ee (*S*)) and good yields (60 - 90%).



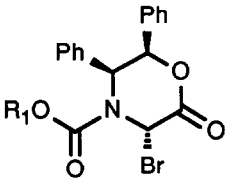
381 (Ref. 231)



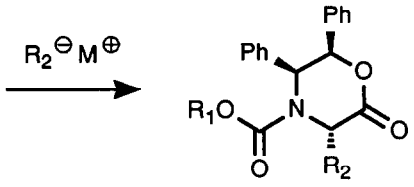
382 (Ref. 232)



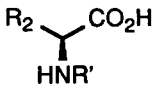
383 (Ref. 233)



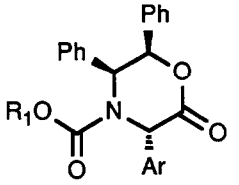
384 a R_1: t-Bu
b R_1: CH_2Ph



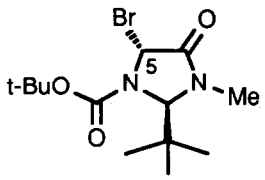
386



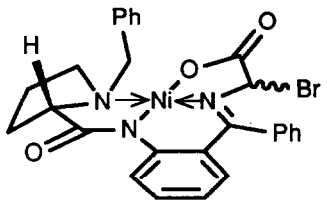
387 a R': Boc
b R': H
(Ref. 234)



385 (Ref. 234c)



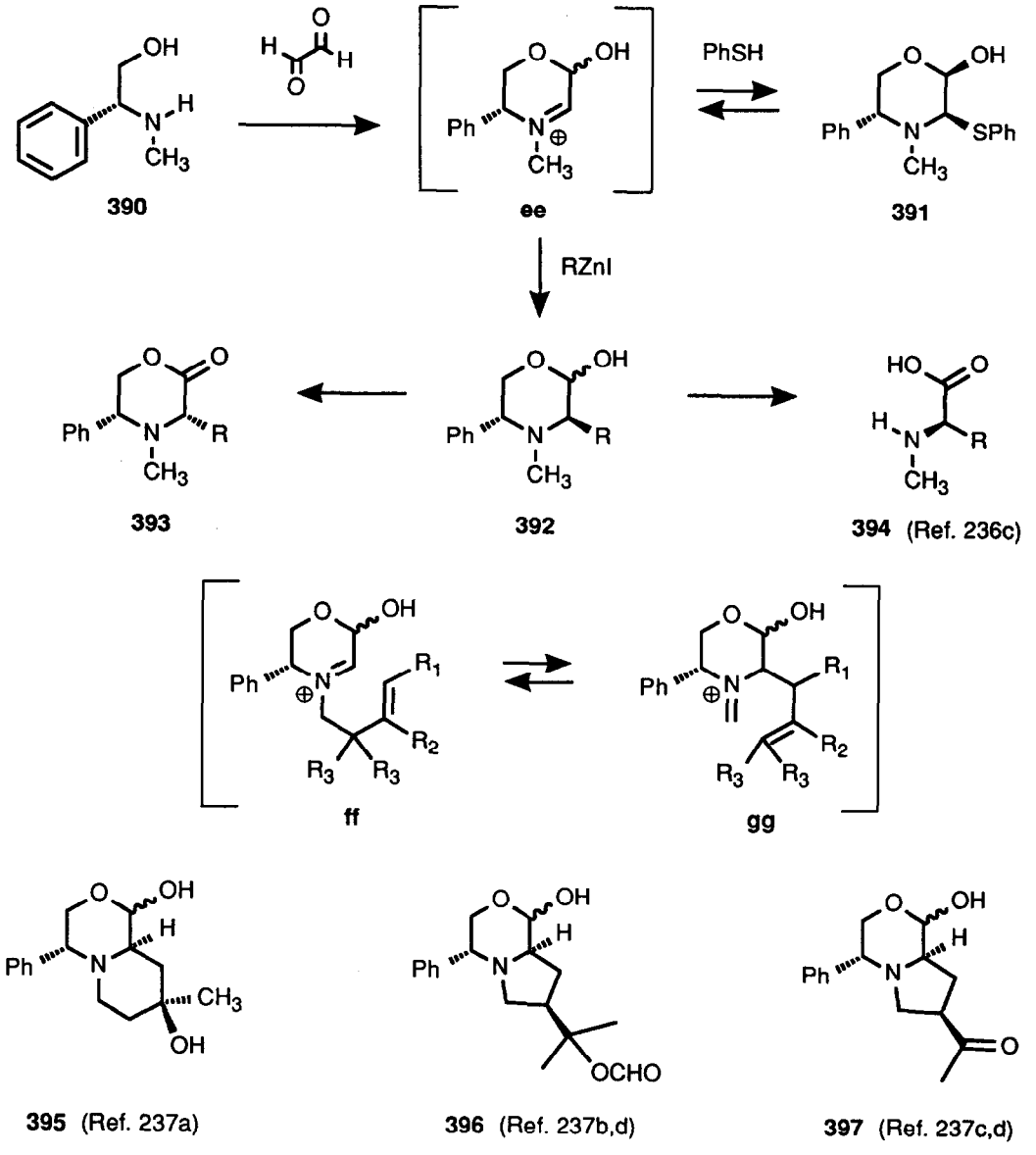
388 (Ref. 84)



389 (Ref. 235)

Scheme 50

Agami and associates developed recently a novel electrophilic glycine synthon from *N*-methyl-phenylglycinol **390** and glyoxal (*Scheme 51*).[236] The resulting cation **ee**, which dimerizes or disproportionates to the corresponding oxazinone in the absence of a nucleophile,[336b,d] is best trapped *in situ* with thiophenol (→ **391**).[236b] Reaction of **391** with Lewis-acidic organometallics like alkyl-Zn halides proceeds *via* iminium intermediate **ee** and affords the *trans*-disubstituted oxazinols **392** by kinetically controlled attack of the nucleophile. The *cis*-isomers are, on the other hand, the favored products of alkyl-Cu reagents, which might be formed by an S_N2-type substitution of the phenylthio group. Swern oxidation of the hemiacetals **392** leads to the

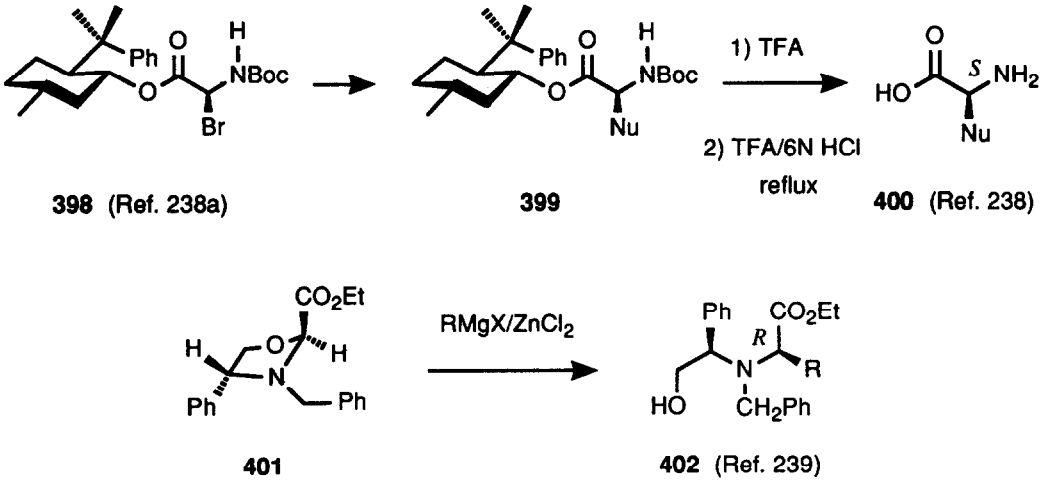


Scheme 51

corresponding lactones, which can be equilibrated with t-BuOK to the thermodynamically favored *cis*-isomers **393**. Deprotection to the *N*-methyl-aminoacids **394** is initiated by acylative *N*-dealkylation with vinyl chloroformate.[236c] Cyclic aminoacids can be obtained, when the phenylglycinol is substituted with a homoallyl group.[237] The corresponding endocyclic iminium ion **ff** is thereby in equilibrium with **gg** *via* an aza-Cope rearrangement. The products depend on the substituents R_1, R_2, R_3; *e.g.* for R_1, R_3 = H and R_2 = CH_3 piperidine **395** is formed from the primary intermediate **ff**.[237a] Geminal substituents $R_3 \neq H$, on the other hand, fa-

vor the rearrangement and the proline precursors **396** and **397** are isolated for R_1, R_2 = H and R_3 = CH_3/CH_3 or CH_3/OH, respectively.[237b,c,d] In one case the intermediate **gg** could be intercepted by hydrolysis before cyclization.[237b,d]

The (-)-8-phenylmenthyl ester **398**, originally introduced by Obrecht and associates,[238a] has been used for the synthesis of various (*S*)-aminoacids by Hamon and coworkers (*Scheme 52*).[238b,c] A new deprotection protocol for converting the adducts **399** to the acids **400** is a real improvement, when compared to the original $LiAlH_4$-reduction, $RuCl_3/NaIO_4$-oxidation sequence. In addition to Grignard reagents[238d] the bromide **398** has been substituted with propargyl-, allenyl-, and allyl-tin compounds[238c], as well as with tin deuteride, giving monodeuterated glycine with 90% de.[238b,e] Reaction of the oxazolidine **401**, derived from glyoxylic acid and phenylglycinol, with Grignard reagents has to be catalyzed by $ZnCl_2$.[239] The (*R*)-aminoacid derivatives **402** are thereby obtained with 72 - 94% de. Aminoacid esters of high optical purity are obtainable by separation of the diastereomers and hydrogenolytic *N*-deprotection.



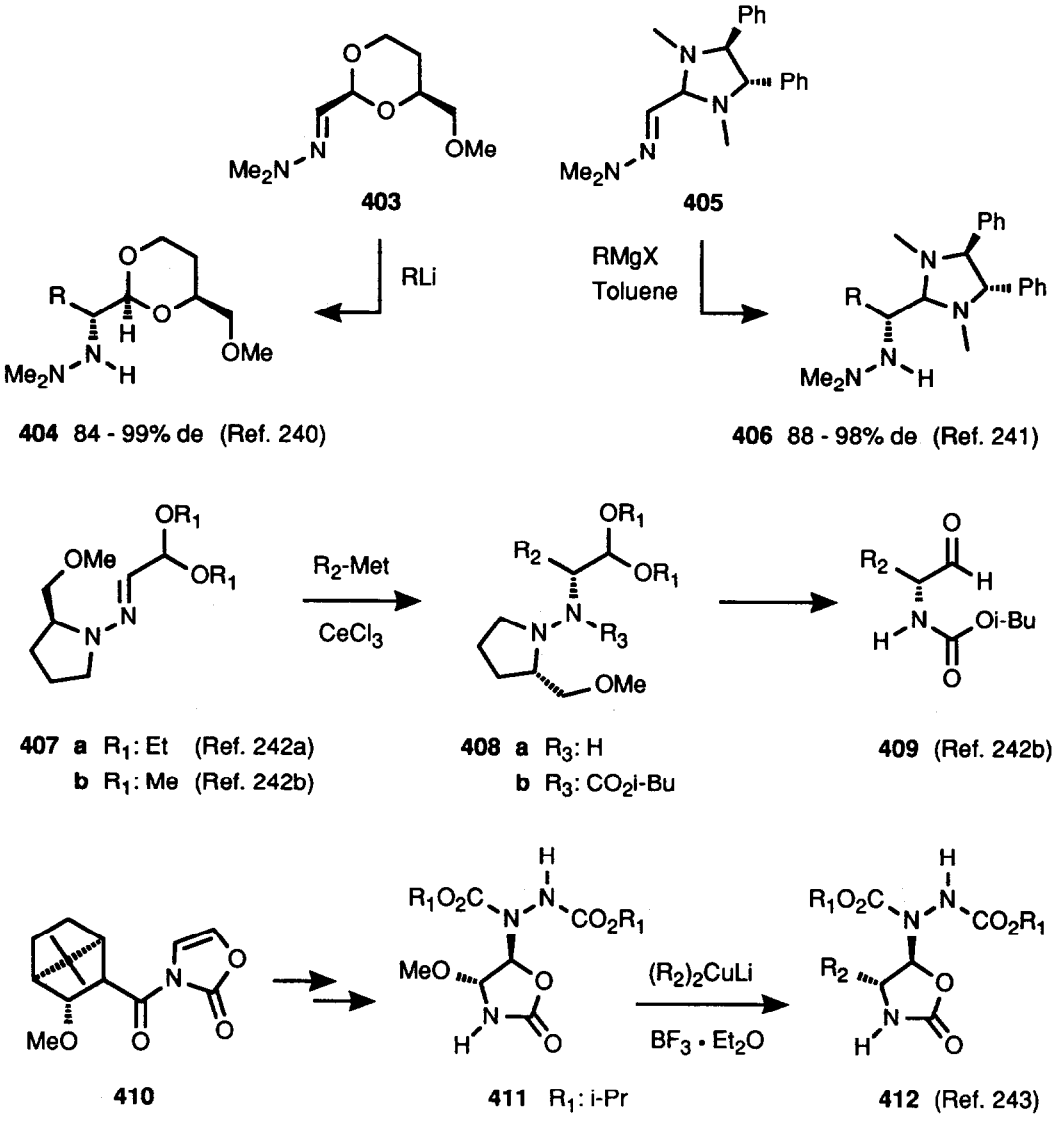
398 (Ref. 238a) **399** **400** (Ref. 238)

401 **402** (Ref. 239)

Scheme 52

Chiral glycine aldehyde equivalents have recently been described by several groups (*Scheme 53*). Among a series of chiral diols used for transacetalization the acetal **403** derived from malic acid induced the best stereocontrol upon addition of CH_3Li and n-BuLi (→ **404**).[240] Addition of Grignard reagents to the aminal **405** proceeded with excellent stereoselectivity (→ **406**), when conducted in toluene with a minimal amount of ether.[241] With allylmagnesium bromide good results were, however, obtained only after transmetalation with $TiCl_4$.[241b] Organocerium reagents have been found to add with high diastereocontrol to the prolinol-derived glyoxal hydrazones **407a,b**.[242] Trapping of the primary adducts with isobutyl chloroformate gives the hydrazides **408b** and facilitates the ensuing reductive *N-N* bond cleavage with Li/NH_3. Acetal cleavage (Me_3SiI) affords the aldehydes **409**, which can be oxidized to the corresponding aminoacids.[242b] The *N*-acyloxazolinone **410** is converted in three steps to the chiral amidoalkylating agent **411**.[243] The crucial step is a [4 + 2]-cycloaddition of azodicarboxylic ester proceeding with 52 - 72% de. Reaction of **411** with cuprates/$BF_3.Et_2O$ gives the aminoaldehyde derivatives **412** in high yield (75 - 85%). Carbamoylation, $NaBH_4$-reduction and oxidation with pyridinium dichromate provided (*R*)-valine and (*R*)-t-leucine from the corresponding-

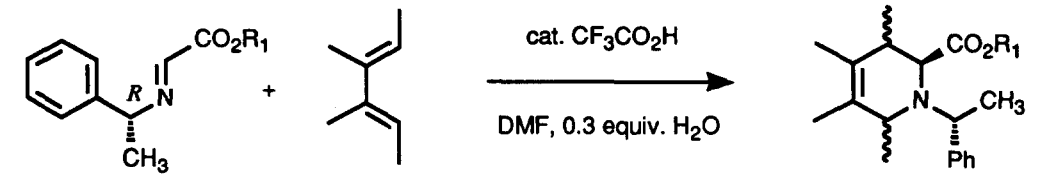
ly substituted intermediates **412**.



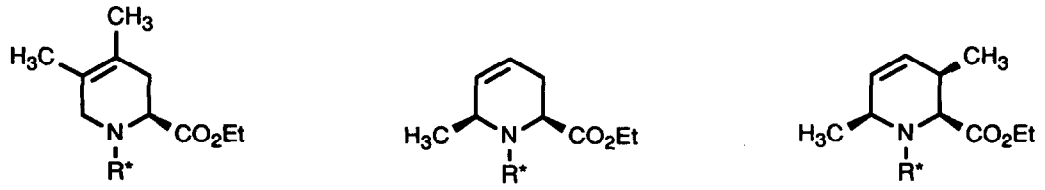
Scheme 53

The chiral glyoxylimine **413** originally introduced by Mukaiyama and coworkers[244] has been used by several groups for [4 + 2]-cycloadditions, thus providing access to various *N*-phenethylpiperidine-2-carboxylates **hh** (*Scheme 54*).[245] The aza-dienophile **413** has to be activated and 1 equivalent of each of CF_3CO_2H and BF_3-Et_2O in CH_2Cl_2,[245a,b] or 1 equivalent of CF_3CO_2H and 0.3 equivalents of H_2O in DMF[245c,d] seem to be equally well suited for optimal yields and diastereoselectivity. The examples **414** - **416**, prepared in DMF, show an appealing degree of regio- and *exo*-selectivity.[245c,d] The diastereoselectivity induced by the

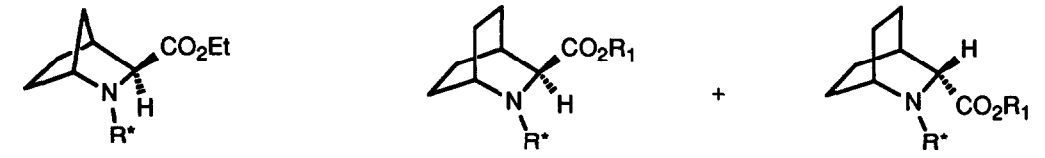
(*R*)-phenethyl residue is, however, rather moderate, but chromatographic separation and hydrogenolysis gives the saturated and deprotected aminoacids in high optical purity. In the case of cyclic dienes the diastereomeric purity of both *exo*- and *endo*-adducts **417** - **419** is better, especially when the reaction is conducted in CH_2Cl_2 at low temperature.[245a,b] When activated with Lewis acids or in liquid SO_2 the 8-phenylmenthyl glyoxyl imine **420** participates in [4 + 2]-cycloadditions, *e.g.* with cyclopentadiene to give the polycyclic aminoacid **421** with excellent stereocontrol.[246a] Ene-reactions with 94 - 96% de have recently been reported for the *N*-benzyl- and *N*-tosyl-analogs of **420**.[246b]



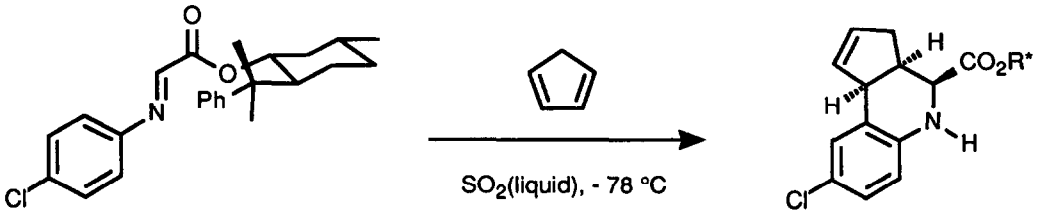
413 **hh** (Ref. 245d)



414 69% (68% de) **415** 35% (36% de) **416** 55% (26% de)



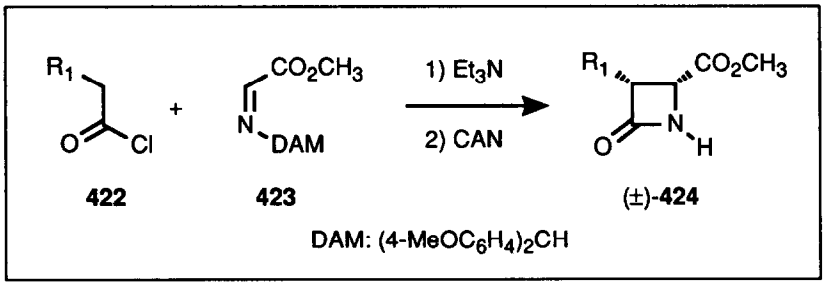
417 94% (96% de) **418** 50% (76% de) (78 : 22) **419** (Ref. 245b)

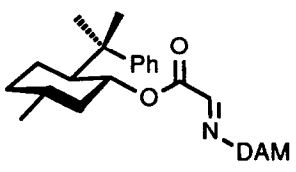


420 **421** 92% de (Ref. 246a)

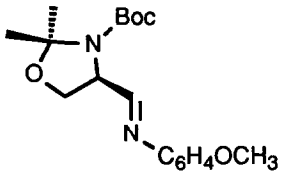
Scheme 54

The [2 + 2]-cycloaddition of ketenes generated from acid chlorides **422** and glyoxylimine **423** proceeds with perfect diastereoselectivity and single isomers of racemic *cis*-β-lactams (±)-**424** are isolated after oxidative cleavage of the di-p-anisylmethyl (DAM) group (*Scheme 55*).[247] In order to obtain optically active products, chirality was introduced into the reactants. The diastereofacial discrimination of the (-)-8-phenylmenthyl ester **425** was low (30% de)[247b], but excellent results were reported with the imine **426** derived from (*R*)-serine[247a] and with the chiral acid chloride **427**.[247b] The resulting β-lactams were transformed into the β-substituted aspartic acids **428**,[247a] **429**,[247b] and 2-deoxy-2-aminothreonate **430**.[247a]

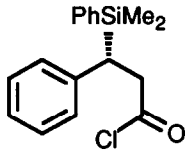




425



426



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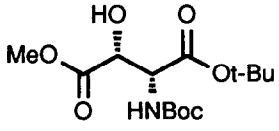
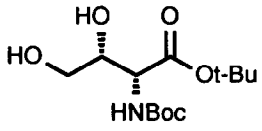
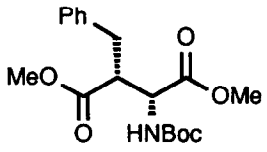


428



430



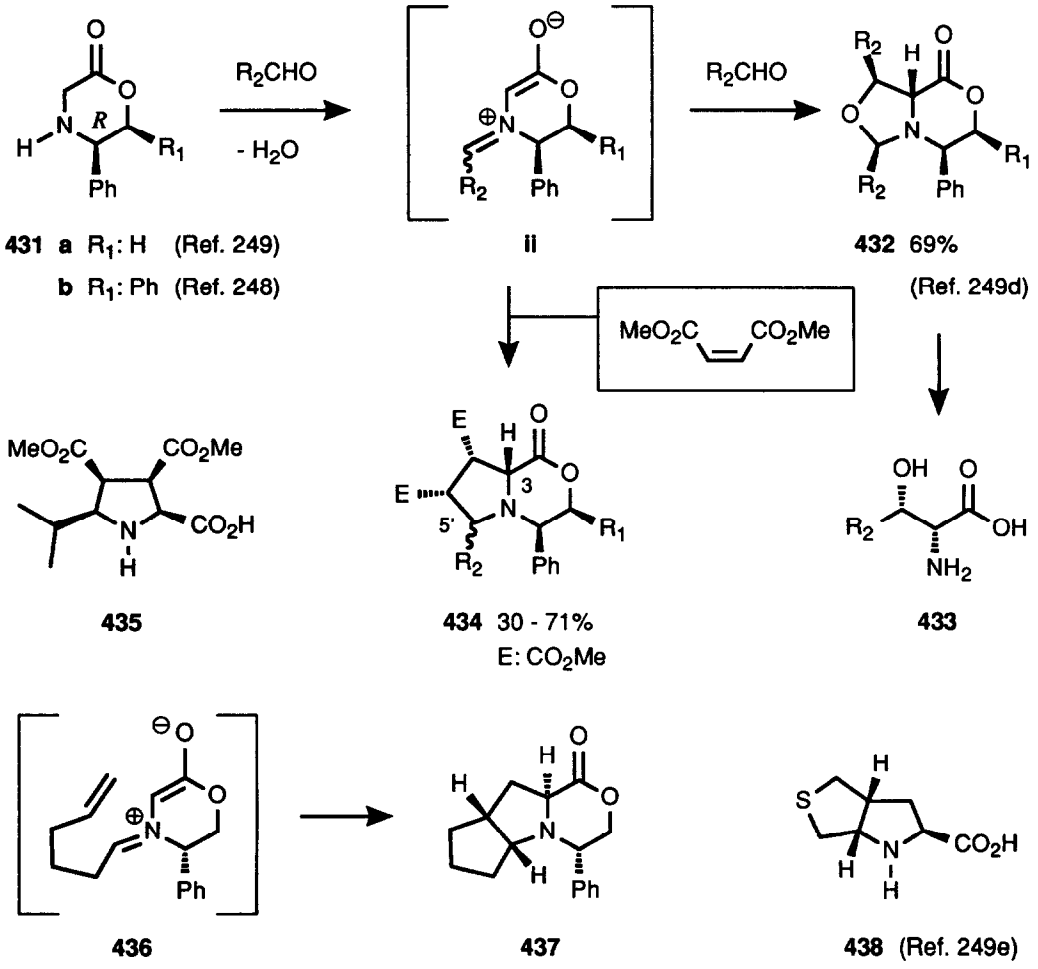
429 (Ref. 247)

Scheme 55

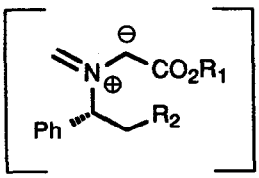
6.3. α-Carboxy Azomethine Ylids

Two groups have independently reported on the use of the closely related oxazinones **431a**[249a-e] and **431b**[248] for the generation of azomethine ylids **ii** upon reaction with formaldehyde[249a-c] and various other aldehydes[248,249d,e] (*cf.* ref. 5, pp. 113 - 115) (*Scheme 56*). Prolonged treatment with 3 equivalents of aldehyde induces anelation to oxazolidines **432** with good yield and stereoselectivity.[249d] Hydrolysis followed by hydrogenolytic cleavage of the auxiliary unravels *threo*-β-hydroxy-α-aminoacids **433**. The nitrogen ylids **ii** can also be intercepted with 1,3-dipolarophiles, *e.g.* with maleates giving fused pyrrolidines **434** in moderate to good yields.[248,249a-c] The stereocontrol at C(3), α to the carbonyl, is always perfect as well as the *endo*-posi-

tion of the two ester groups, provided that $R_2 \neq H$. Epimeric mixtures are, however, formed with respect to C(5'), the former aldehyde carbonyl-C. An exception is isobutyraldehyde (R_2: i-Pr) and the all-*syn* substituted proline **435** is obtained from *ent*-**431** as the only product.[248] Similar results are obtained with other dipolarophiles like maleic anhydride, maleimide, propiolic ester, and acetylene dicarboxylate.[249a-c] Intramolecular cyclizations of ylids such as **436**, generated from unsaturated aldehydes, give polycyclic derivatives, *e.g.* **437** and **438** in excellent yield and with good stereocontrol. Provided that cysteine-derived 2-phenylthiazolidine-4-carboxylates could be obtained diastereomerically pure, the excellent stereocontrol of azomethine ylids derived from these templates should give enantiomerically pure products upon cycloaddition.[249f] Optically active products are, however, formed with 1,3-dipoles derived from 1,2,3,4-tetrahydroisoquinoline-3-carboxylate, as the deprotonation upon ylid formation occurs exclusively at C(1).[249g]

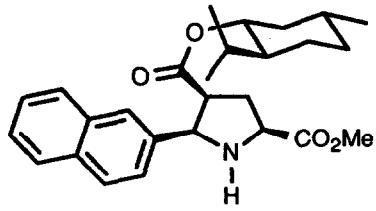


Scheme 56

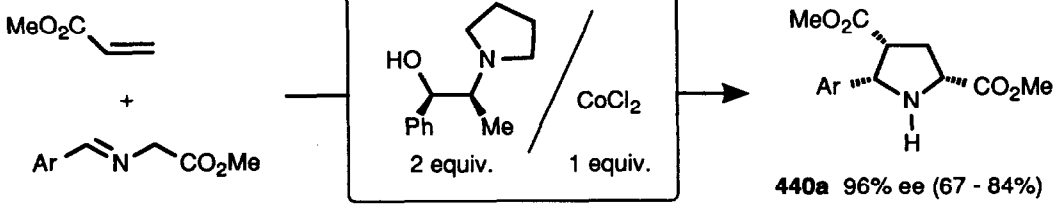


439 **a** R_1: 4-$MeOC_6H_4O$ R_2: H (Ref. 250)

b R_1: Et R_2: $OSiMe_3$ (Ref. 251)

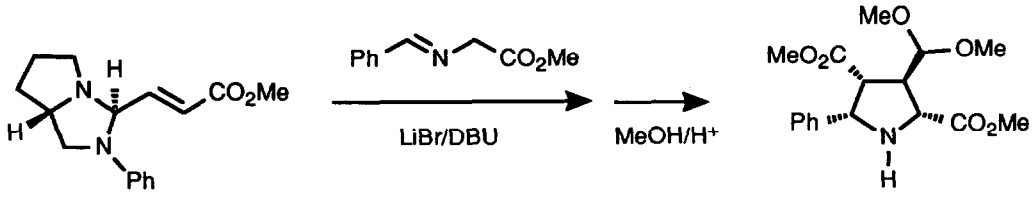


440 (Ref. 252a)



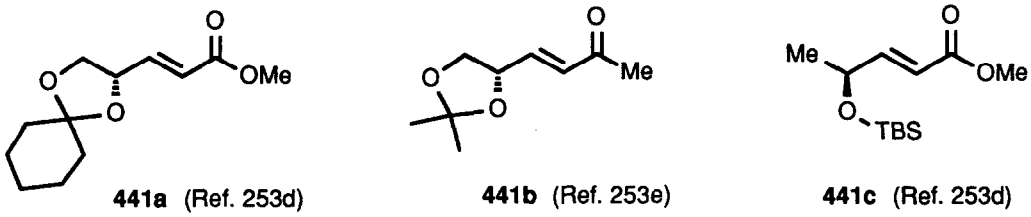
440a 96% ee (67 - 84%)

(Ref. 252b)



441

442 54% (Ref. 253a-c)



441a (Ref. 253d) **441b** (Ref. 253e) **441c** (Ref. 253d)

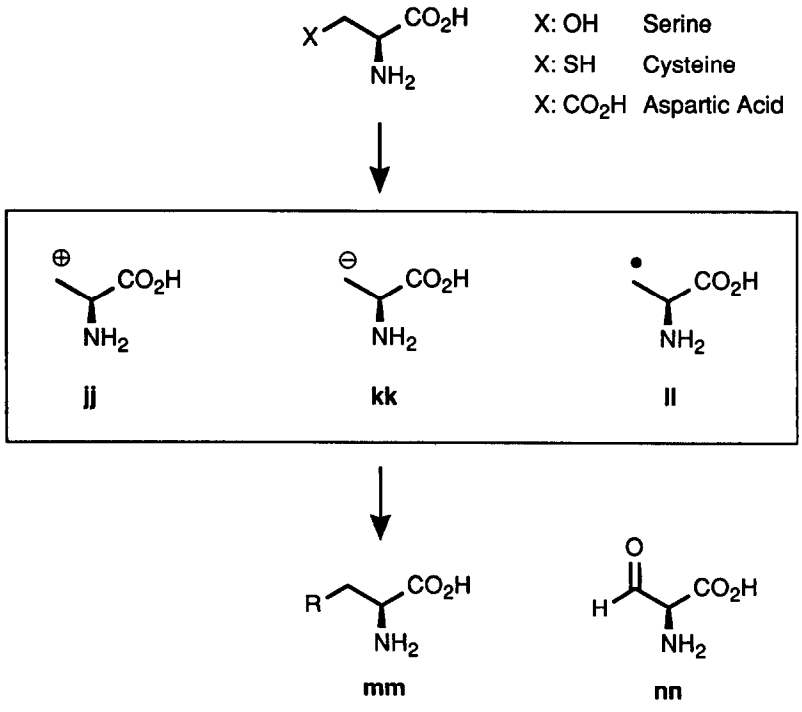
Scheme 57

Other acyclic chiral azomethine ylids, *e.g.* **439a**[250] and **439b**[251], have been generated, but their additions to dipolarophiles exhibited very low facial selectivity. The concept of chirally modified dipolarophiles was, on the other hand, very successful and addition of (-)-menthyl acrylate to the glycinate imine of 2-naphthaldehyde catalyzed by AgOAc gave the proline **440** as single diastereomer in 50% yield.[252a] The cycloaddition of glycine derived ylids to methyl acrylate is efficiently catalyzed by one equivalent of $CoCl_2$ in the presence of two equivalents of an aminoalcohol. By using a chiral base derived from *nor*-ephedrine, the products **440a** (Ar = 2-naphthyl, 4-Br-phenyl, 4-Me-phenyl) are thereby obtained with 96% optical purity.[252b] The chi-

ral aminal derivative of fumarate semialdehyde **441** and related compounds add with high diastereoface selectivity as well.[253a-c] After methanolytic cleavage of the proline derived auxiliary, the elaborated pyrrolidine **442** was isolated as single diastereomer. Similar chiral dipolarophiles have been prepared from glyceraldehyde (**441a,b**) or lactaldehyde (**441c**).[253d,e] The stereocontrol in cycloadditions depends on the reaction conditions, but diastereoisomer ratios up to 9 : 1 have been reported for **441c**[253d], and up to 95 : 5 for **441b**.[253e]

7. PARTIAL SYNTHESIS FROM α-AMINOACIDS

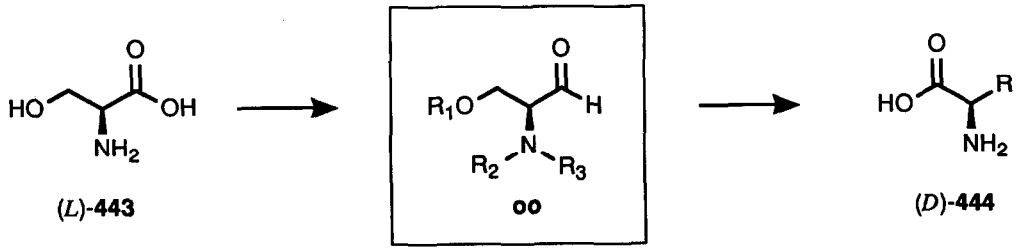
The transformation of a chiral compound to the target structure is often more direct than an asymmetric synthesis using a chiral auxiliary. The number of α-aminoacid syntheses from chiral precursors is enormous, and only the most general principles with broad applicability are therefore treated below. The scope is further restricted to aminoacids as optically active precursors, since the partial syntheses from carbohydrates, the other obvious source for suitable precursors, has been reviewed not too long ago.[10a,11] The basic chiral aminoacid synthons are the alanine-β-cation **jj**, the corresponding anion **kk**, and the radical **ll**, which are generally derived from either serine, cysteine, or aspartic acid. These intermediates are usually involved in transformations leading to substituted alanines **mm** of identical absolute configuration (*cf.* ref. 5, *chapter 2*, pp. 134 - 166) (*Scheme 58*). Formylglycine equivalents **nn** are derived from serine or cysteine and can also be considered as carbenoid alanine synthons. Their net conversion into other aminoacids frequently involves a formal inversion of configuration.



Scheme 58

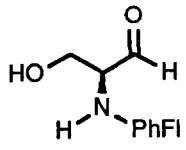
7.1. Formylglycine Equivalents

The most common formylglycine equivalents are serine aldehydes **oo**, which are obtained in protected form from L-serine **443** (*Scheme 59*). Elaboration of the formyl substituent into an aminoacid side-chain **R** and oxidation of the hydroxymethyl group to a carboxylic acid concludes the transformation of L-serine **443** to D-amino acids **444**. Conversely, D-serine can be converted analogously to L-amino acids.

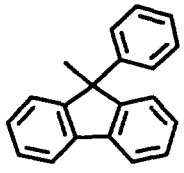


Scheme 59

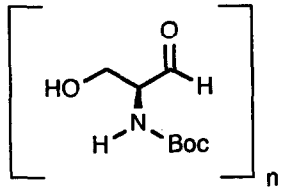
Chart 3: Serine-derived α-Aminoaldehydes.



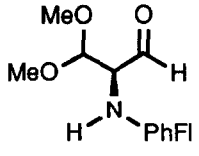
445 (Ref. 254)



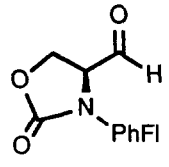
PhFl: 9-Phenylfluorenyl



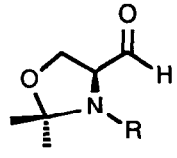
446 (Ref. 255)



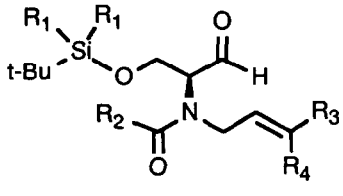
447 (Ref. 254)



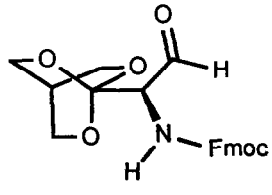
448 (Ref. 254)



449 **a** R: CO_2t-Bu (Refs. 179a, 256, 259)
b R: CO_2CH_2Ph (Ref. 257)
c R: CO_2CH_3 (Ref. 258a)
d R: CH_2Ph (Ref. 258b)



450 (Refs. 260, 261)

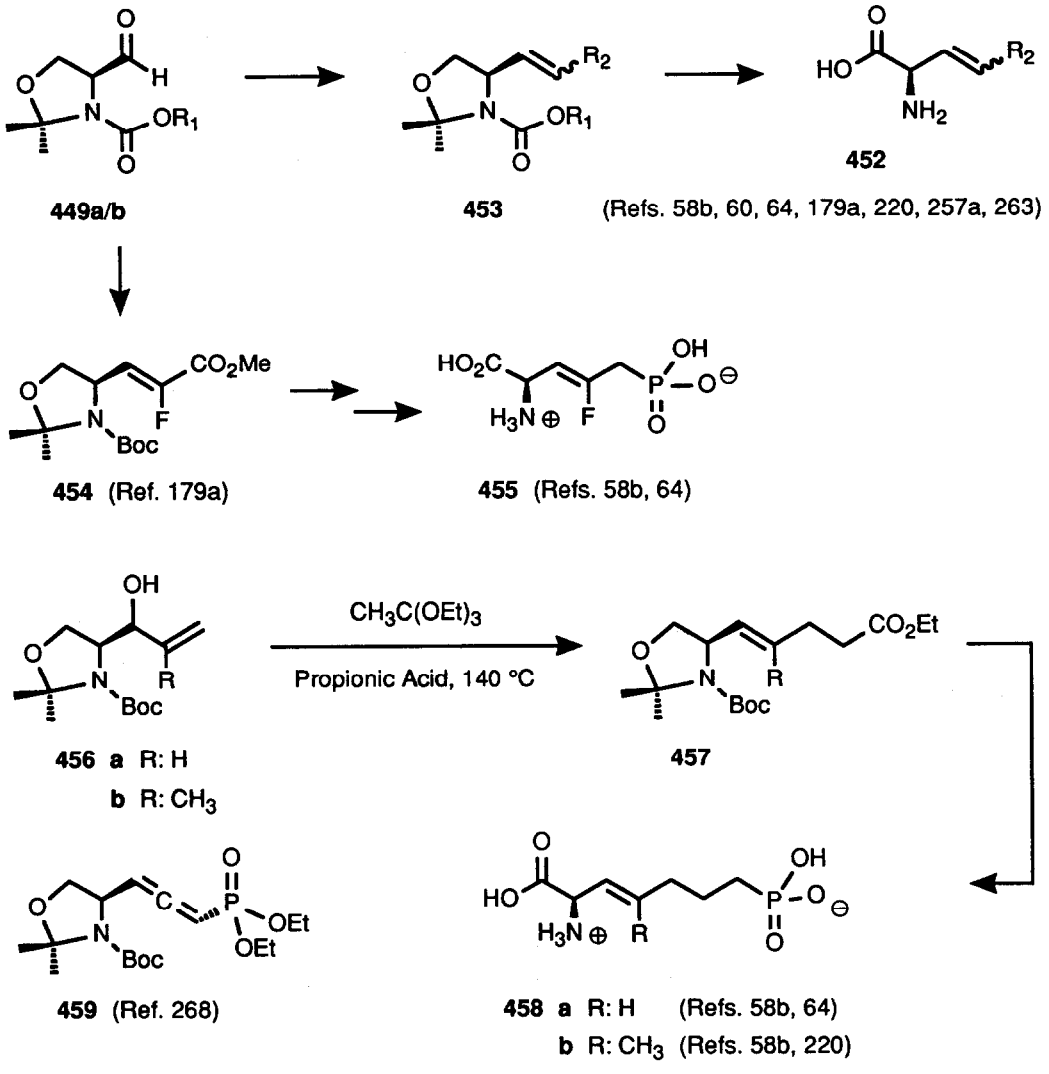


451 (Ref. 262)

The most important serine-derived aldehydes which have been designed and used for this purpose are depicted in *Chart 3* ((*S*)-enantiomers). The derivatives with non-protected hydroxymethyl group, **445**[254] and **446**[255], are remarkably robust, but due to the free hydroxy function only of limited use for further synthetic transformations. The *N*-Boc derivative **446**, obtained from glucosamine, is considered to be stabilized by *poly*-hemiacetal formation. It has been converted into the (*R*)-glutamic acid monoester by Wittig olefination with stabilized phosphoranes for the introduction of the side-chain.[255a] The stability of **447** and **448** is ascribed to the N-(9-phenylfluorenyl) group (PhFl) and has been tested by converting both aldehydes into the *N*-PhFl derivative of vinylglycinal of 98 - 99% ee.[254] Probably the most versatile intermediates are the acetonides **449a** introduced by Garner,[256a] the *N*-benzyloxycarbonyl analog **449b**,[257] and **449c**.[258] The *N*-benzyl protected 4-formyloxazolidine **449d** has recently been prepared in connection with an elegant construction of kainoids by tandem Michael additions (see below).[258b,c] The original procedure for **449a** has been disclosed recently as an *Organic Syntheses* preparation[256c], but alternative procedures have also been developed.[259] The advantages of the synthesis reported by us[179a] are that reagents like diazomethane, methyl iodide, or PPh_3/-DEAD are avoided, that no chromatographic purifications are necessary, and that the final reduction can be conducted at 0°C instead of -78°C. The applications of **449** will be further discussed below. Kainic acid and related compounds have been prepared from serine according to *Scheme 59*. The general structure **450** represents the aldehyde intermediates of these syntheses[260] or of related model studies[261]. The orthoester **451**, a protected formylglycine, has recently been prepared.[262] So far, it has been converted into threonine, *allo*-threonine, *threo*- and *erythro*-phenylserine, and *threo*-β-hydroxyglutamate.[262b]

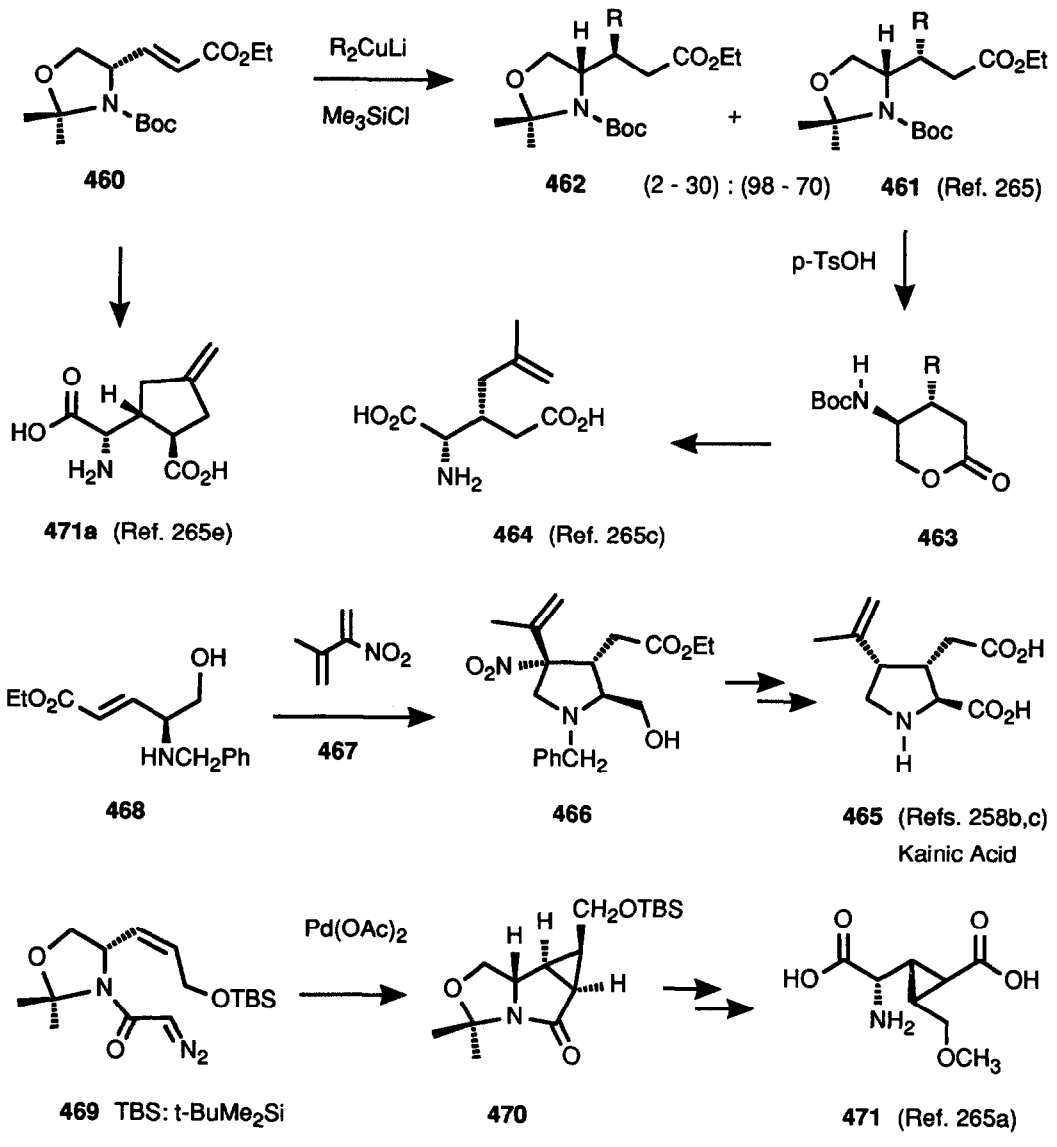
A distinctive advantage of the conversion of serine shown in *Scheme 59* is that manipulations can be performed in the absence of the carboxyl function. This method is therefore especially suited for the preparation of β,γ-unsaturated aminoacids **452**, and both acetonide protected aldehydes **449a**[58b,60,64,179a,220,263] and **449b**[257a,263] have been used for this purpose (*Scheme 60*). The unsaturated side-chain (→ **453**) can be conveniently introduced by Wittig olefinations with unstabilized ylids,[179b,257a,258,263,264]stabilized phosphoranes,[58b,64] and α-phosphonocarboxylates[60,64,259a,265] with the exception of methylenetriphenylphosphorane, which caused racemization of **449a**.[266] The methylene derivative was, however, successfully obtained with $CH_2I_2/Me_3Al/Zn$.[266] Reformatsky-type conditions were also used for the preparation of the α-fluoro ester **454**, which served as an intermediate not only for the *bis*-α-aminoacid **301** (*Scheme 37*)[179a] but also for the 5-phosphono-3-pentenoate **455**.[58b,64] Vinyl substituted oxazolidines **453** are also obtainable by 1,3-allylic rearrangements, *e.g.* in the course of the bromination of an allylic alcohol[179a], or from allyl carbamates.[267] Orthoester-Claisen rearrangement of the allylic alcohols **456a,b** gave the γ,δ-unsaturated esters **457** without affecting the t-butyl carbamate protection. Further transformations gave access to the glutamate antagonists **458a,b**.[58b,64,220] The allenylphosphonate **459** was recently obtained by rearrangement of the corresponding propargyl phosphite with relative *anti*- or *erythro*-configuration.[268]

While β,γ-unsaturated aminoacids **452** are primarily of interest as conformationally constrained aminoacid analogs and as potential mechanism based inhibitors of PLP-dependent enzymes, the precursors **453** are also versatile intermediates for further transformations. Simple reduction has been used for the preparation of (*R*)-2-amino-5,5-difluoro-5-phosphonopentanoate,[64] or to obtain differentially protected *meso*-2,6-diaminoheptanedioic acids[179b] and lysine homologs.[257a] Conjugate addition of benzyl phenyl sulfide[259a] and R_2CuLi/Me_3SiCl in Et_2O[265b-d,269] has been used to prepare substituted glutamates, *e.g.* additions to the unsaturated ester **460**, also obtainable from glutamate,[265d] proceed with good *syn*-selectivity (→ **461**), and the mi-



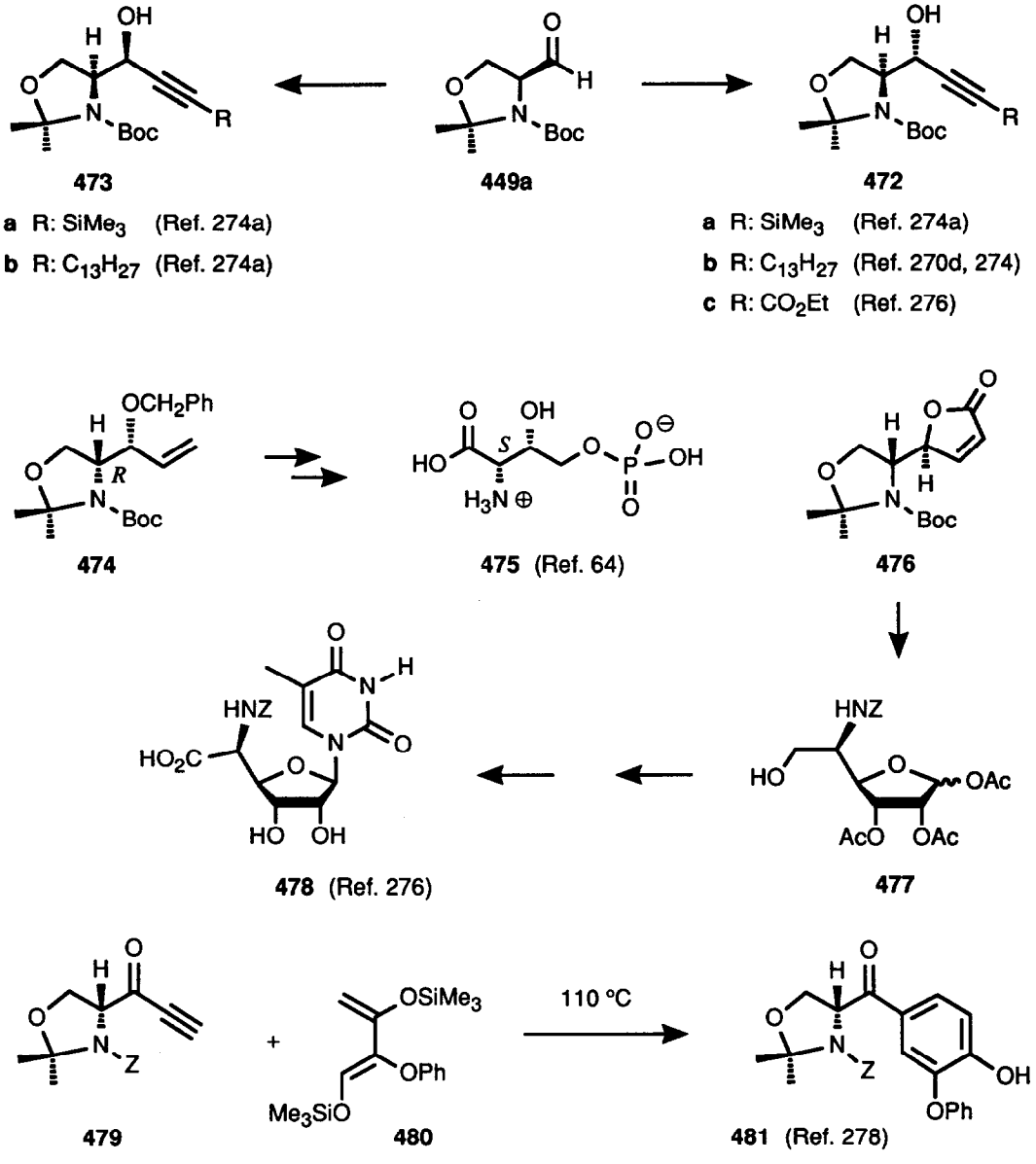
Scheme 60

nor isomers **462** can be separated by cyclization to the lactones **463**. This protocol has been used for the synthesis of the *seco-nor*-kainoid **464** (*Scheme 61*).[265c] Benetti and associates have recently reported an elegant synthesis of *allo*-kainic and kainic acid **465** from **449d**.[258b,c] The basic skeleton **466** is thereby constructed in quantitative yield by a double Michael addition between the nitrodiene **467** and the unsaturated ester **468**. Cyclopropanation has also been used, mainly for the preparation of constrained glutamate analogs.[264,265a] Intramolecular Pd-catalyzed cyclization of the diazoketone **469** gave the tricyclic compound **470**, a single isomer in this case. The cyclopropanoglutamate **471** derived from **470** is a glutamate agonist of the NMDA-subtype.[265a] Cycloaddition of trimethylenemethane or equivalents thereof is the key step for the conversion of **460** to **471a** and two stereoisomers, designed as conformationally restricted glutamate analogs.[265e]



Scheme 61

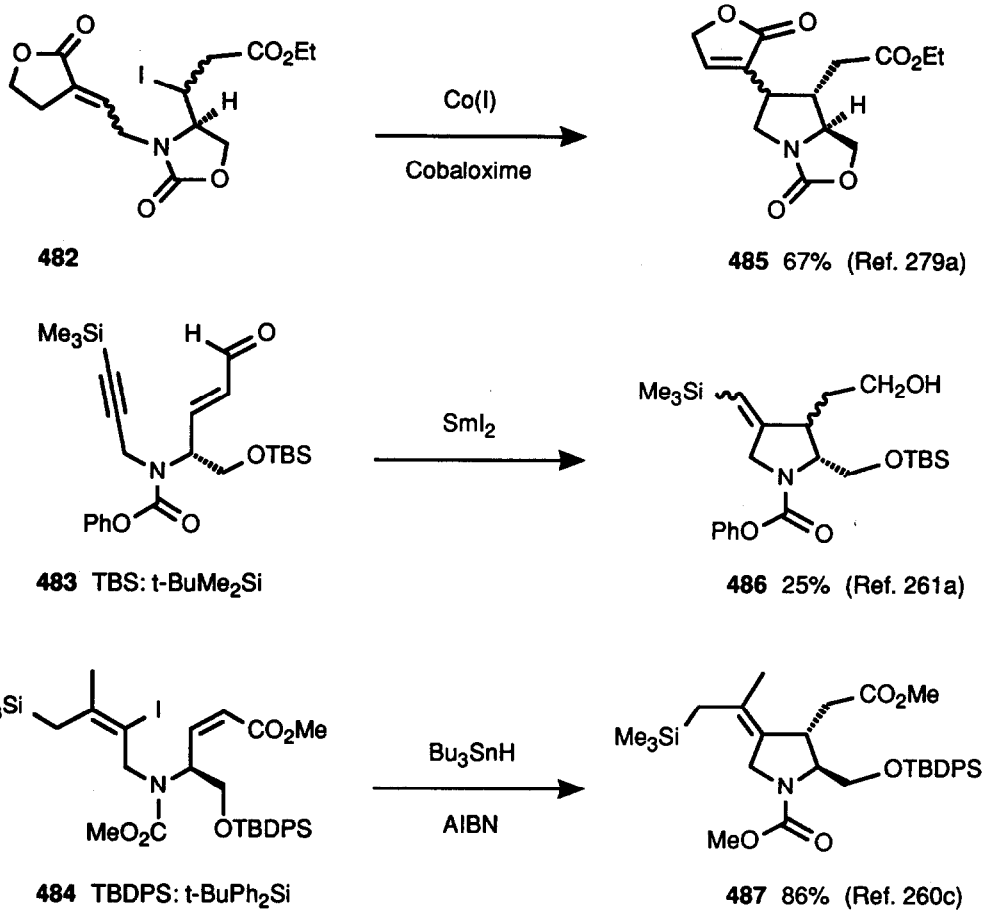
Addition of nucleophiles to the aldehydes **449a,b**, *e.g.* vinyl organometallic species,[270] CH_3Li or CH_3MgBr,[257b] and allylboranes,[271] usually leads to *syn/anti*-mixtures with *anti*-preference. The selectivity can of course be improved with chiral reagents,[271] and perfect stereocontrol has been achieved with allyl-Ti-complexes, chelated by a diol ligand derived either from (*R,R*)- or (*S,S*)-tartrate.[272] With 2-trimethylsilylthiazole the *anti*-selectivity is already more pronounced (92 : 8),[273] but by far the best selectivity with achiral nucleophiles is exhibited by Li-acetylides, and the *anti*-isomers **472** are formed with 90% de if the reactions are carried out in THF/HMPA (*Scheme 62*).[270d,274] Most rewardingly, this ratio can almost be reversed in a less polar medium (Et_2O) and by transmetalation with $ZnBr_2$, thus allowing the efficient preparation of the



Scheme 62

syn-epimers **473** as well.[274a] This has not only been exploited for the synthesis of sphingosines[270d,274] but also for the preparation of aminoacids, *e.g.* the *syn*-isomer *ent*-**473a** has been converted to regioselectively protected *threo*-β-hydroxyaspartate[275], or *via* the benzylated allyl-alcohol **474** to *threo*-β-hydroxyhomoserine-*O*(4)-phosphate **475**.[64] Addition of propiolic ester to (*R*)-**449a** gave *ent*-**472c**.[276] Hydrogenation with Lindlar catalyst afforded the unsaturated lactone **476**, which, in an elegant sequence of steps, could be converted *via* **477** to thymine polyoxine C **478**. Casiraghi and associates used a similar approach, with 2-trimethylsiloxyfuran as

nucleophile, for model studies aiming at the synthesis of amipurimycin.[277] While a hetero Diels-Alder cycloaddition with the Danishefsky diene was involved in the conversion of (*R*)-**449a** to *threo*-β-hydroxyglutamate,[256a] cycloaddition between the acetylenic ketone **479** and elaborated dienes such as **480** led to aromatic ketones, *e.g.* **481**, which are intermediates for the *bis*-aminoacid isodityrosine, a constituent of several cyclic peptide antibiotics.[278]



482 **485** 67% (Ref. 279a)

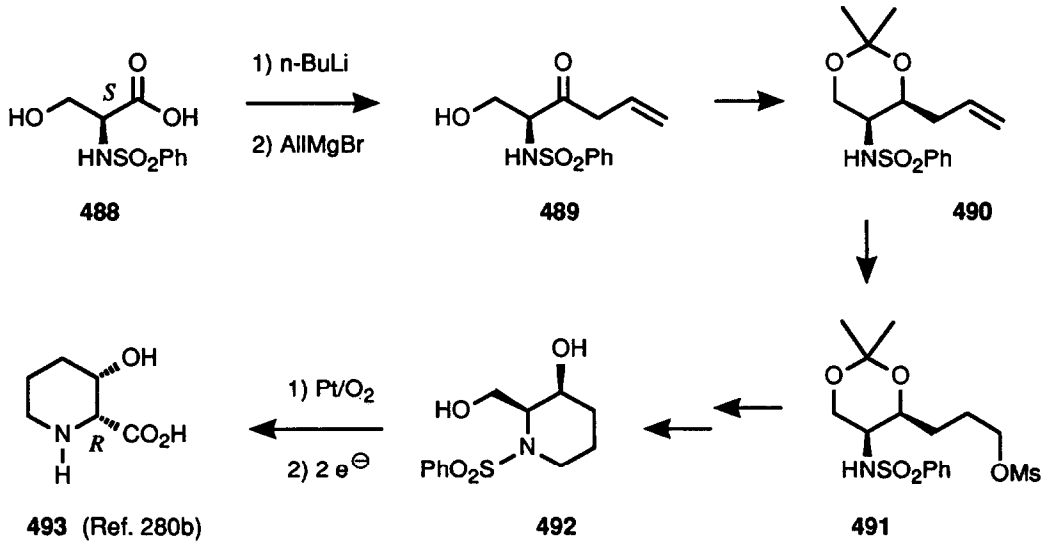
483 TBS: t-BuMe$_2$Si **486** 25% (Ref. 261a)

484 TBDPS: t-BuPh$_2$Si **487** 86% (Ref. 260c)

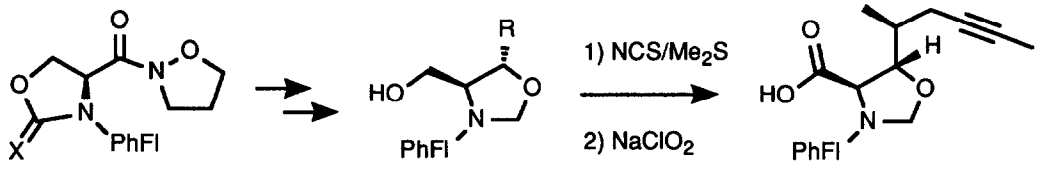
Scheme 63

For the synthesis of kainoids and other substituted prolines the serine-derived aldehydes **450** (*cf. Chart 3*) have been further elaborated to structures such as **482**, **483**, and **484**, the immediate precursors for the key cyclization step (*cf.* ref. 5, pp. 306 - 320) (*Scheme 63*). As exemplified for the amine **468** (*Scheme 61*), anionic 1,4-additions give the best yields of such cyclizations, but with the incorrect stereochemistry at C(4), corresponding to *allo*-kainic acid.[258b,c,261b] The Co(I) mediated cyclization of unsaturated iodides, studied by Baldwin and coworkers, is heavily influenced by the substituents of the participating olefin, and side-reactions, especially elimination of iodide, lead to low yields (30 - 40%) of the desired products.[260a,b] Better results are obtained with unsaturated esters, and the ratio of cyclization (→ **485**) to elimination is 17 : 1 for the

lactone **482**.[279a] Ketyl-anion radicals generated by reduction with SmI_2 can induce cyclization. The alkyne **483** is thereby transformed to the trimethylsilyl-methylidene prolinol **486**, a promising intermediate for the introduction of the correct C(4) configuration.[261a] An excellent result has recently been reported for the reductive cyclization of vinyl iodide **484** induced by tin hydride.[260c] The product **487** could be transformed either to *allo*-kainic or kainic acid by stereoselective 1,3-protiodesilylations assisted transannularly by the carboxylic



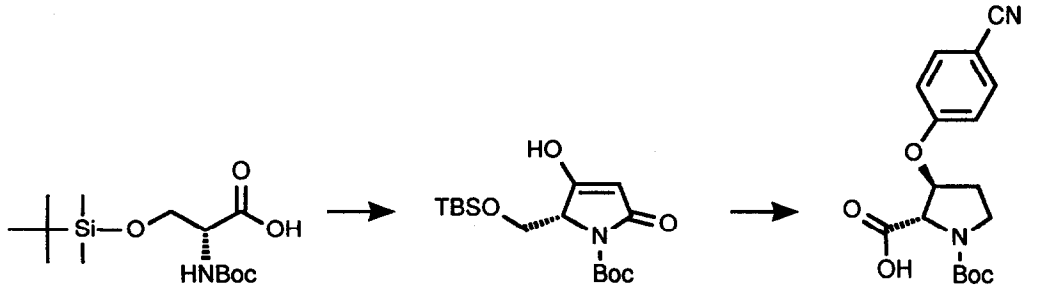
488 **489** **490** **491** **492** **493** (Ref. 280b)



494 **a** X: H, H PhFl: 9-Phenylfluorenyl
b X: O

495 R: $C(Me)CH_2C{\equiv}CMe$

496 75% (Ref. 280c)



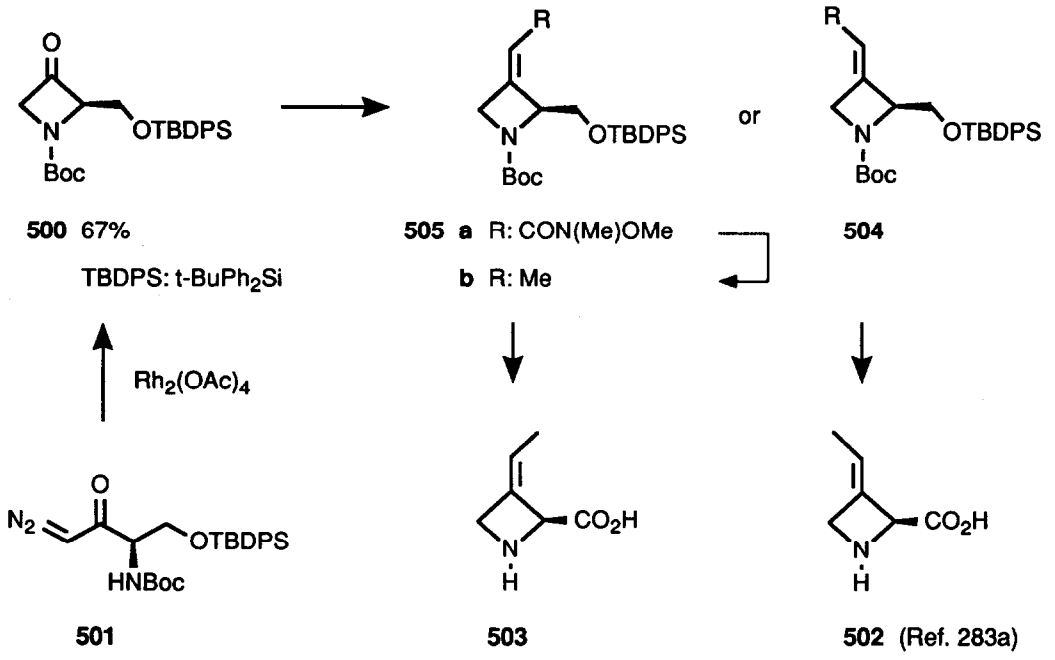
497 **498** (Ref. 281) **499** (Ref. 282)

Scheme 64

acid functions. Tin hydride mediated cyclization to trisubstituted pyrrolidinones has been achieved from α-chloro-amide analogs of vinyl iodide **484** as well.[279b] The precursors are obtained conveniently by *N*-acylation of the serine derivative **468** (*Scheme 61*) after *O*-silylation.

The actual pioneering work on the transformation of L-serine to D-aminoacids, reported by Rapoport and coworkers in 1984 (*cf.* ref. 5, pp. 146 - 150), did not proceed *via* an α-aminoaldehyde intermediate **oo** as depicted above in *Scheme 59*, but α-sulfonamido ketones were obtained directly from the acid **488** with an excess of organo-Li, or with combinations of organo-Li and Grignard reagents (*Scheme 64*).[280] Reduction of these ketones gives precursors for β-hydroxy-α-aminoacids with preferred relative *threo*-configuration, when L-selectride is used. The *erythro*-epimers result upon reduction with $LiBH_4$.[280b] Following these lines, the allyl adduct **489** has been transformed *via* 1,3-dioxane **490** and the mesylate **491** to the α-hydroxymethyl-*N*-sulfonylpiperidine **492**. The crucial steps to the D-amino acid **493** are the chemoselective oxidation of the primary alcohol to the acid with Pt/O_2 and the reductive desulfonation.[280b] In addition to **492** this method has been applied for the synthesis of D-*threo*-β-hydroxyglutamate, lysine, and methionine, as well as for D-*erythro*-3-hydroxyproline.[280b] To avoid the excess of organometallic reagent needed for the introduction of the side-chain and also to circumvent the problematic desulfonation step at the end, the *N*-(9-phenylfluorenyl)-protected hydroxamates **494a,b** have been developed as substitutes for **488**.[280c] In this case, however, the amine and the secondary hydroxy group have to be protected by formation of the thermodynamically favored oxazolidine regioisomer **495**. Otherwise the final oxidation by a two stage process, *N*-chlorosuccinimide/Me_2S treatment affording the aldehyde and chlorite oxidation to the acid, would not be successful. The unsaturated acid **496** is thereby obtained in 75% yield without affecting the triple bond. Further steps led to MeBmt, the unusual aminoacid of cyclosporin.[280c] Activation of the selectively protected *N*-Boc serine **497** with 2-propenyl chloroformate allows the condensation with Meldrum's acid. Decarboxylation of the primary product affords the optically active tetramic acid **498**, which had also served as an intermediate for statine and detoxinine.[281] The proline **499** was then obtained by reduction of the 1,3-dicarbonyl function, Mitsunobu etherification and oxidation of the primary alcohol *via* aldehyde, obtained by the Swern method, and $KMnO_4$-treatment.[282] This *erythro*-3-hydroxyproline derivative was an intermediate of the first total synthesis of the strained *ansa*-cyclopeptide numularine-F.[282b]

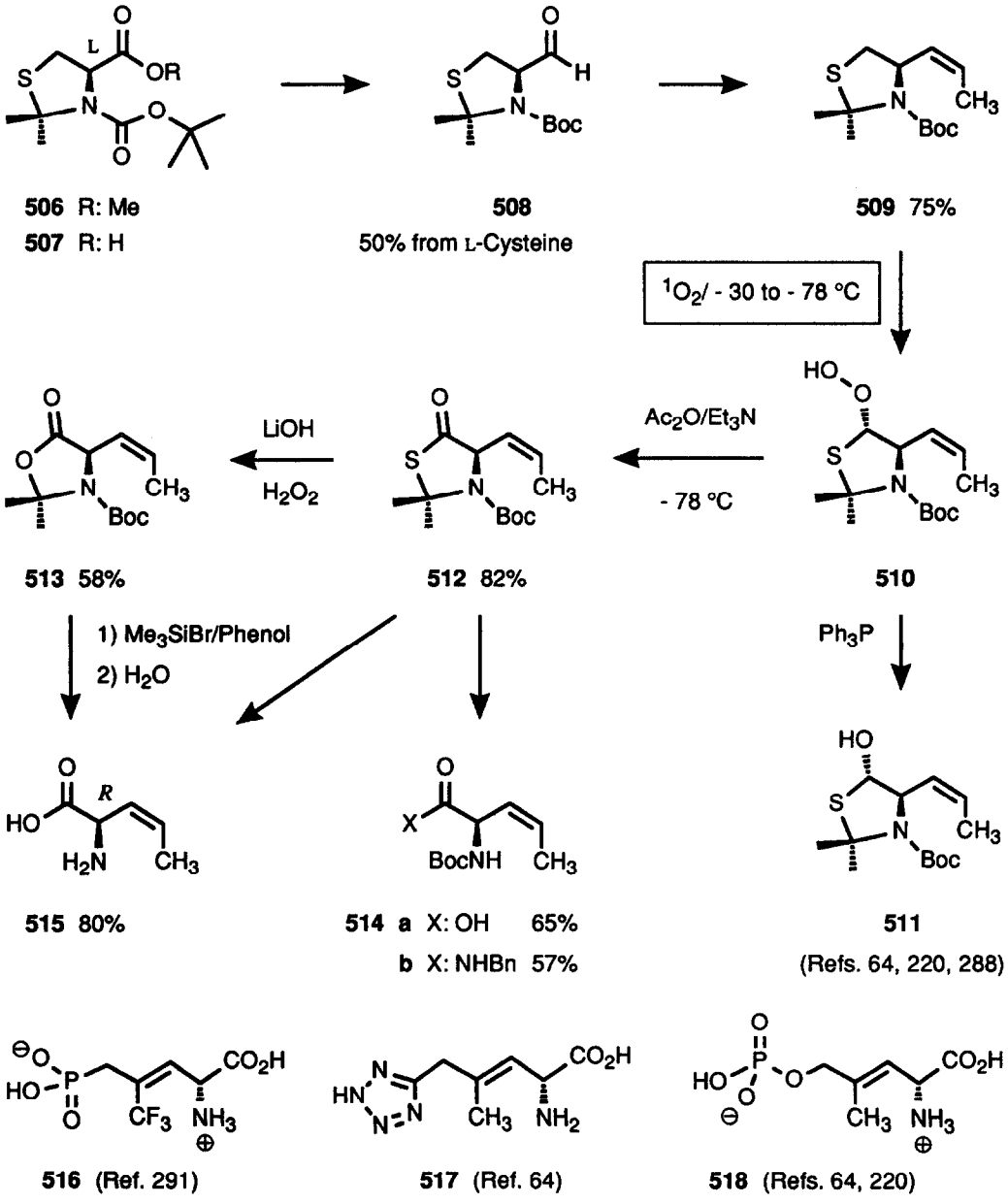
In a very recent report Hanessian and coworkers have demonstrated, that D-serine can also be applied to the synthesis of L-azetidine-2-carboxylates.[283] The crucial step, affording the protected 2-hydroxymethyl-3-azetidinone **500** is the Rh(I)-catalyzed cyclization of the diazoketone **501** derived from D-serine (*Scheme 65*). The aim of this work was the synthesis of optically pure polyoximic acid of *trans*- (**502**) and *cis*- (**503**) double bond geometry.[283a] The precursors **504** and **505** could be prepared either with diethylphosphono-*N*-methyl-*N*-methoxyacetamide (95% preference of **504a**) or with the corresponding triphenylphosphorane (89% preference of **505a**). After the separation of the isomers, the syntheses were completed by reduction of the carboxamides **504a/505a** to methyl groups (→ **504b/505b**), cleavage of the silyl ethers, and oxidation to the acids with Jones reagent. Interestingly, the *cis*-isomer **503** turned out to be the constituent of polyoxin A and not **502**, as previously claimed. This could also be verified by NMR-analysis of the tripeptidic antibiotic polyoxin A.



Scheme 65

For all transformations of L-serine to D-amino acids the crucial step is the oxidation of the former hydroxymethyl side-chain to the carboxylic acid. The best methods, $RuCl_3/NaIO_4$[284], $KMnO_4$[285], and $NaClO_2$[280c], are, however not applicable on olefinic substrates or in the presence of otherwise sensitive functionalities. The other methods have severe disadvantages; the Pt/O_2 oxidation is extremely sluggish for substrates with *N*-protection other than sulfonamides,[58b] and the Cr(VI)-based methods, quite apart from the toxicity of chromium, give low yields and partial racemization in the case of β,γ-unsaturated α-aminoacids.[58b,64,179a] A better solution for a masked carboxylate than the hydroxymethyl group was therefore looked for. The thiomethyl group appeared most promising, as cysteine-derived thiazolidines can undergo Pummerer-type oxidations, *e.g.* the $^1O_2$-mediated C(5)-hydroxylation of **506**, first reported by Ando and associates.[286] The sulfur analog **508** of the Garner aldehyde was prepared in 50% overall yield from L-cysteine *via* the known acid **507**.[287] Following the same protocol as for the synthesis of **449a**[179a] (*cf. above, Scheme 61, Chart 3*) this could again be achieved without the need for chromatographic purification (*Scheme 66*).[288] The aldehyde **508** is somewhat less reactive than the oxygen analog **449a**, but Wittig olefination was found suited for the preparation of **509** and various other derivatives with unsaturated side-chains.[64,220,288] The key step, the $^1O_2$-oxidation, turned out to be a very clean process, leading to the hydroperoxide **510** without any detectable attack of the double bond. This turned out to be general, and selective oxidation at sulfur is possible in the presence of trisubstituted olefins, unsaturated esters, allylsilanes, allyl bromides, and alkynes, functions which are sensitive to singlet oxygen. The hydroperoxides are generally stable below -20°C and can either be reduced to hemiacetals, *e.g.* **511**, or fragmented with Ac_2O/NEt_3 to thiol lactones such as **512**. Whereas the reduction to hemiacetals was successful in all cases studied so far, double bond migration into the exocyclic position occurs in the case of the 4-alkynyl derivative and the unbranched *trans*-acrylic sidechain upon trans-

formation to the lactones.[64,220] Treatment of the thiol-lactone **512** with one equivalent of $LiOH/H_2O_2$ in THF gives the lactone **513**, which is more slowly transformed into the *N*-Boc protected acid **514a** with an excess of reagent.[64,220] The amide **514b** is obtained with $Me_2AlNHCH_2Ph$ in toluene, according to the procedure of Weinreb.[289] The t-butyl carbamates of both heterocycles **512** and **513** can be cleaved with Me_3SiBr/phenol[290]



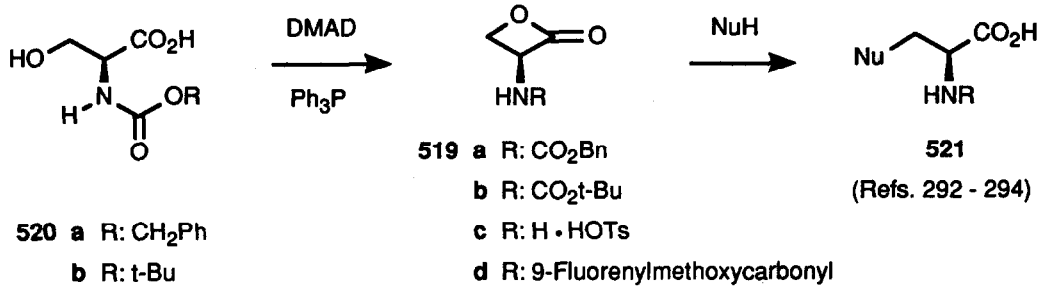
Scheme 66

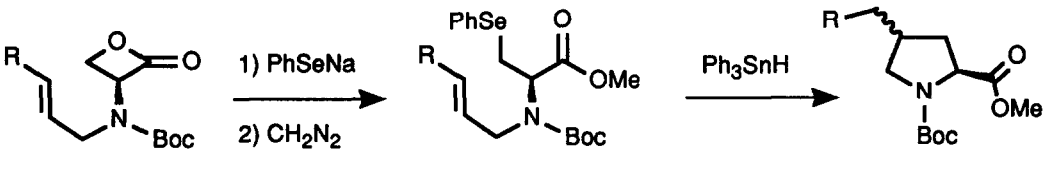
without affecting the acetonides. While the hydrolytic cleavage of the *N*-deprotected lactone derived from **513** is immediate (→ **515**), the thio analog derived from **512** needs prolonged treatment either with 1N HCl or acidic ion-exchange resin for the liberation of the free aminoacid **515**. All the derivatives of *cis*-dehydronorvaline **515** have been isolated with > 95% optical purity. Applications of this method include the preparation of the ω-phosphono-aminoacid **55** (*cf.* above, *Scheme 7*), the trifluoroanalog **516**,[291] the tetrazole **517**,[64] and the allylic phosphate **518**.[64,220]

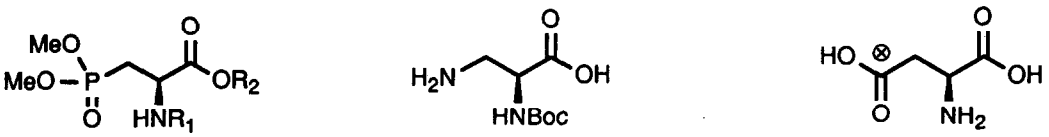
7.2. Alanine β-Cation Equivalents

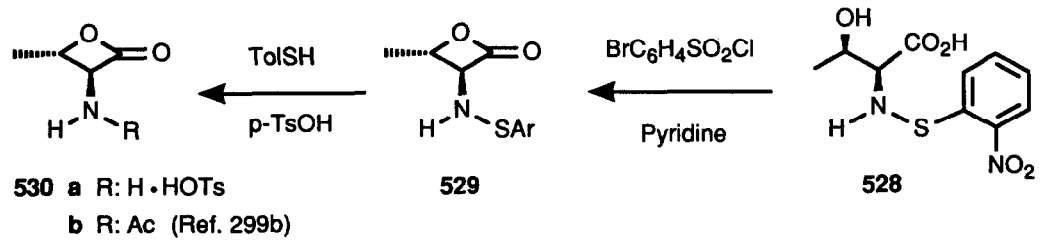
This concept is most readily realized by substitution of the serine OH-function after suitable activation. To avoid the competing elimination Vederas and coworkers prepared the β-lactones **519a-c** by Mitsunobu esterification from *N*-benzyloxycarbonyl- and *N*-Boc-serine **520a,b**. Deprotection afforded the stable salt **519c**. Substituted alanines **521** were obtained with various heteronucleophiles and also with cuprates (*cf.* ref. 5, pp. 134 - 139) (*Scheme 67*).[292] This elegant method has recently been described in an *Organic Synthesis* preparation,[293] and the Fmoc-derivative **519d** has been introduced as a further derivative.[294] The β-lactone **519a** has been *N*-alkylated with allyl halides/Ag_2O (→ **522**, 65 - 90%) before being substituted with PhSeNa.[295] The selenides **523** underwent radical cyclization when treated with tin hydride, albeit with low stereocontrol, affording the 4-substituted prolines **524** as *cis/trans*-mixtures. Heating of **519** with phosphites resulted in an Arbusov-like substitution to β-phosphono alanines **525** with simultaneous esterification of the departing carboxylate.[294,296] The substitution of lactone **519a** with ammonia, giving access to 2,3-diaminopropanoate **526** is in competition with serine amide formation *via* attack at the carbonyl group. This side reaction could be suppressed by inverse addition (**519** to NH_3), increasing the yield of **526** from 26% to 96%.[297] By using labelled cyanide as nucleophile, the resulting nitrile could be hydrolyzed to L-[4-^{13}C]-aspartate **527**.[298] Neither threonine, *allo*-threonine or homologs can be transformed to β-lactones under Mitsunobu conditions.[299] Cyclization can, however, be effected by treating either phenylsulfonamide derivatives[299a] or 2-nitrophenylsulfenyl amides **528**[299b] with *p*-bromophenylsulfonyl chloride in pyridine. The resulting β-lactones, *e.g.* **529**, can be deprotected to sulfonate salts, *e.g.* **530a**. The free amines can then be reacylated (→ **530b**) and even coupled to dipeptides. Substitution at C(4) is heavily biased and could only be observed with HBr, in case of the sulfonamides also with thiourea and magnesium halides.

Aziridine-2-carboxylic acid derivatives are another class of α-aminoacid β-cation equivalents (*cf.* ref. 5, pp. 139 - 140). These compounds are readily obtained from vicinal azido alcohols by a modified Staudinger reaction (*cf.* above, chapter 4.1, *Scheme 24*).[132a,b,134c] Other methods include treatment of serine esters with diethoxytriphenylphosphorane,[300] the Darzens type addition of chloroacetate Li- or Zn-enolates to imines[301] and the treatment of serine or threonine with sulfuryl chloride/Et_3N, possibly proceeding *via* the cyclic sulfamidate **531**.[302] Very recently Evans and associates have reported on the enantioselective aziridination of cinnamic esters with [*N*-(p-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) using 5% of a Cu(I) catalyst, chelated by a chiral *bis*-oxazoline.[303a] The aziridinecarboxylate obtained with 94 - 97% ee (63 - 76% yield) was converted into *N*-tosylphenylalanine and *erythro*-phenylserine. *N*-Phthalimido-aziridinecarboxylic acids are available by diastereoselective addition of *N*-phthalimidonitrene to camphorsultam derivatives of unsaturated acids (33 - 95% de).[303b] They are amenable to $BF_3.Et_2O$-catalyzed nucleophilic opening by mercaptanes. Recent studies on the reactivity of aziridine carboxylates in nucleophilic ring-opening reactions have shown that, with the exception of 3-arylaziridine-2-carboxylate,[304a] activation by *N*-acylation or sulfonation is necessa-



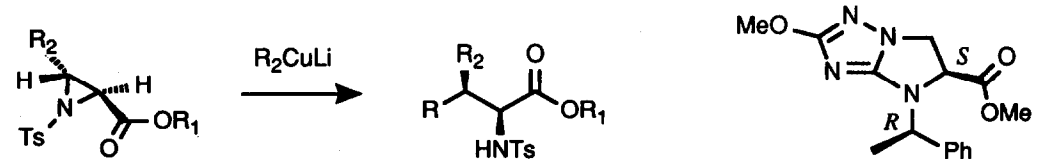






Scheme 67

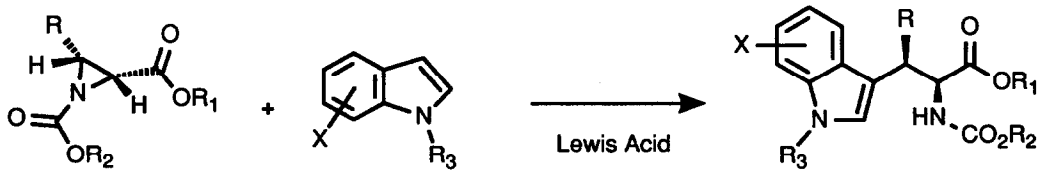
ry.[304] As in the case of the serine-β-lactones **519** (*cf. Scheme 67*) the best results are obtained with hetero-nucleophiles, especially with thiols (*cf.* above *Scheme 24*, compound **188**).[132] An appealing recent application is the double substitution with ethylene-glycol giving a differentially protected ethylene-bridged serine, an interesting *bis*-α-aminoacid for crosslinking of peptides.[305a] Reaction of *N*-Fmoc-protected aziridine carboxylate with 4,5-dimethoxy-2-nitrobenzylalcohol affords a serine derivative with photolytically cleavable side-chain



533 **a** R_1: t-Bu R_2: H
b R_1: Et R_2: CO_2Et

534 32 - 47% (Ref. 307)
54 - 68% (Ref. 134b)

532 20% (Ref. 306)

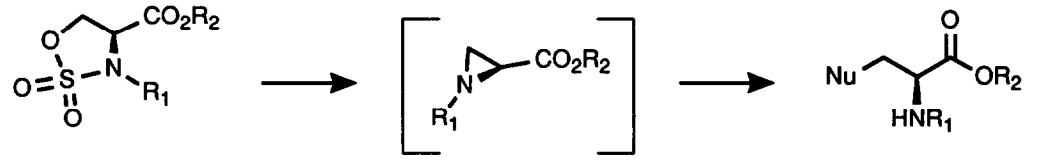


536 R_2: CH_2Ph, t-Bu
a R: H R_1: Me
b R: Me R_1: CH_2Ph

535
a R_3: H
b R_3: Me, Et

$Zn(OTf)_2$
$BF_3 \cdot Et_2O$

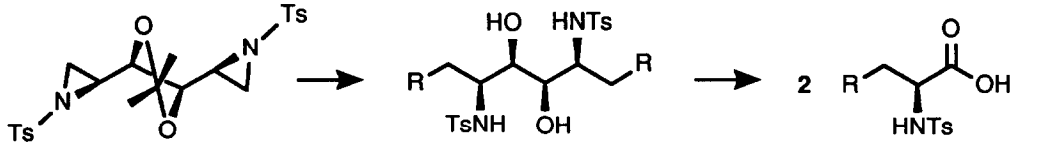
537
a 3 - 46% (Ref. 308a)
b 44 - 69% (Ref. 308b)



531 **a** R_1: CH_2Ph R_2: t-Bu
b R_1: CPh_3 R_2: CH_2Ph

539

538 (Ref. 309)
(Ref. 302)



540

541

542 (Ref. 310)

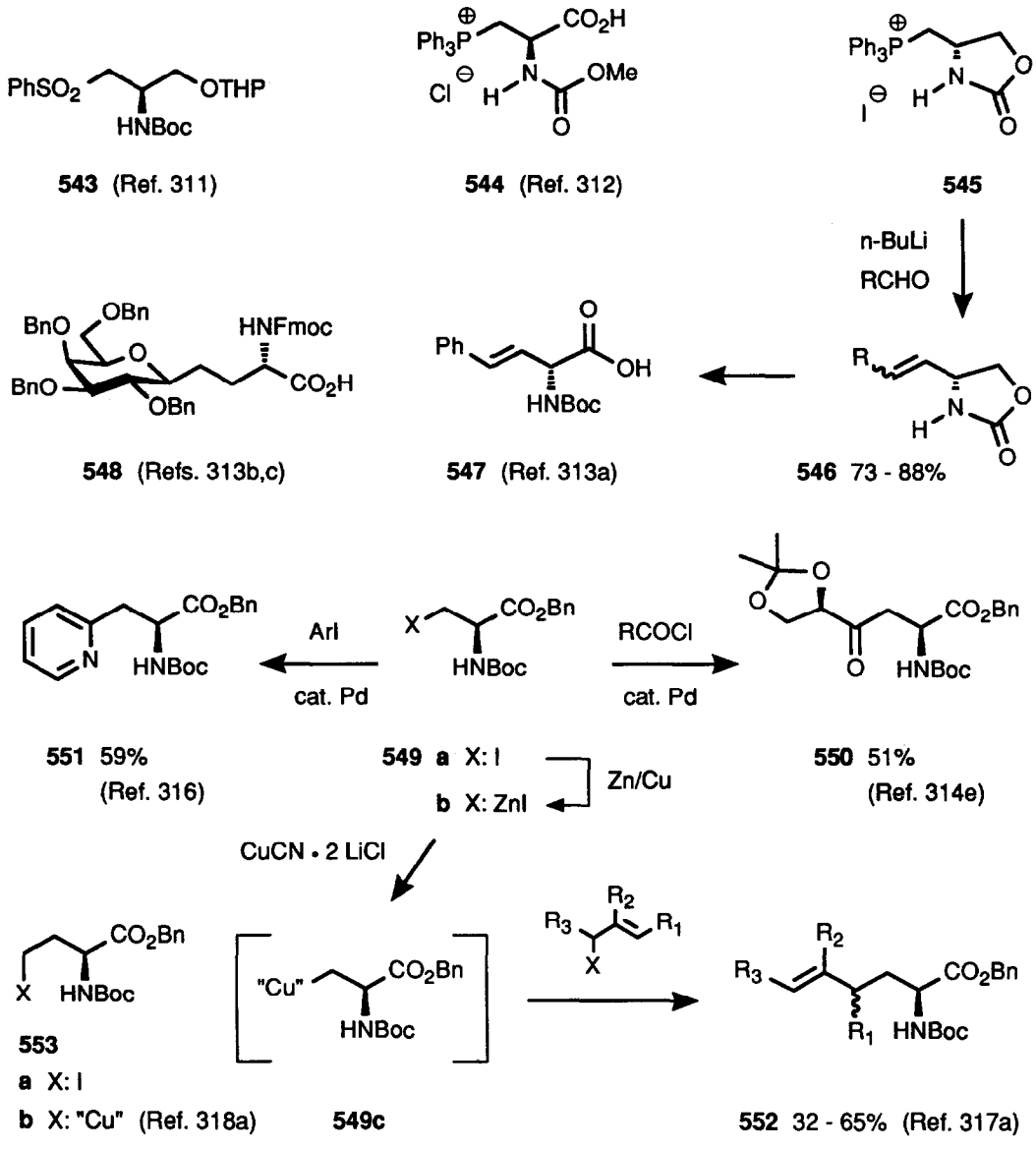
Scheme 68

protection.[305b] An exception is the condensation of *N*-phenethylaziridine-2-carboxylate with 2-bromo-5-methoxy-1,3,5-triazole giving the fused heterocycle **532**, but in low yield and only from the (*S,R*)-diastereomer (*Scheme 68*).[306] The reaction of aziridinecarboxylates with organocuprates is sluggish and activation as *N*-tosyl derivatives **533** is necessary.[134b,307] The reason for the somewhat better yields of **534b** obtained from the tartrate derived aziridine **533b** are not clear. Side reactions are attack at C(2) (28 - 55%) and reductive opening (21 - 25%).[307] A very interesting process is the Lewis acid catalyzed alkylation of various indoles **535**

with aziridines **536a**[308a] and **536b**.[308b] Despite the methyl group at C(3) the yields of substituted tryptophanes **537b** obtained from **536b** are better than for **537a**. This is probably related to the *N*-alkyl group of indoles **535b**. Baldwin and coworkers used the serine sulfamidate **531a** as a substitute for aziridinecarboxylate in substitutions with a variety of nucleophiles including cyanide, pyrazole, and malonate.[309] Judging from the observations reported by van Boom and associates[302] these reactions to **538** might proceed *via* an aziridine intermediate **539**. Duréault and coworkers have used the *bis*-aziridine **540** as a substitute for aziridine carboxylate.[310] Cuprate addition gives the glycols **541** in excellent yield, (75 - 92%) after acetonide hydrolysis. Periodate cleavage and CrO_3 oxidation of the resulting aldehydes leads to aminoacids **542**.

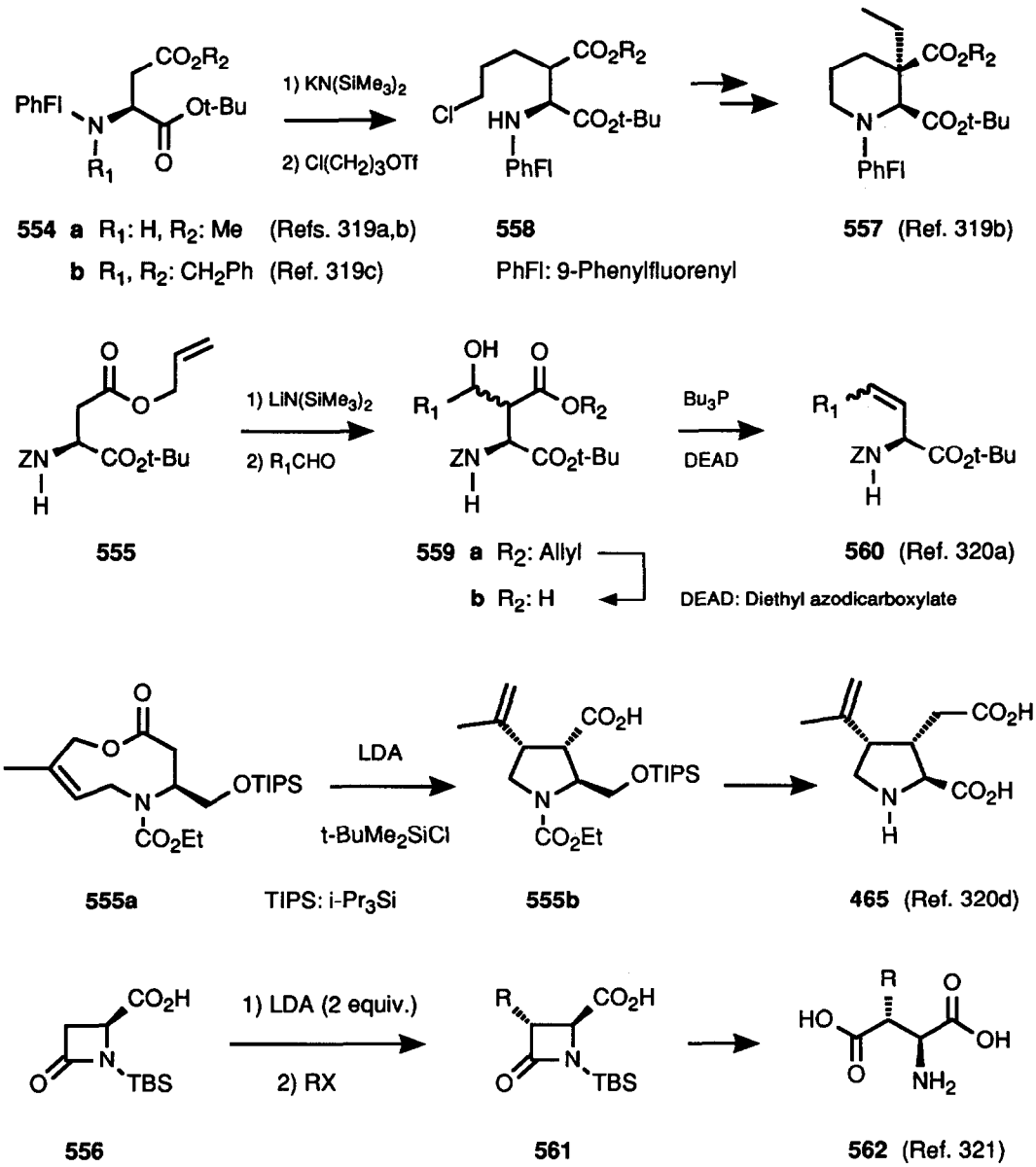
7.3. Alanine β-Anion Equivalents

The polarity of the serine side-chain can be reversed from electrophilic to nucleophilic by substitution to the sulfone **543**[311] or to the phosphonium salts **544**[312] and **545**[313] (*Scheme 69*). The Wittig ylid prepared from the oxazolidinone **545** appears now to be the most versatile reagent of the three for olefination of aldehydes. The vinyl derivatives **546** are obtained in good yield (73 - 88%) and good *trans*-selectivity in case of aromatic aldehydes. The resulting oxazolidinones **546** are intermediates for β,γ-unsaturated aminoacids such as **547**.[313a] Reagent **545** has recently been used for the preparation of the C-glycosyl aminoacid **548**, the C-analog of *O*-galactopyranosylserine.[313b,c] In a series of papers Jackson and coworkers have reported on the preparation of β-iodoalanine **549a** and on the use of the derived Reformatsky reagent **549b**, an alanine homoenolate. Various γ-keto-α-aminoacids are obtained by Pd-catalyzed coupling of **549b** with acid chlorides,[314] a representative example being the preparation of the glyceric acid derivative **550**.[314e] The preparation of **549b** has recently been improved by using a different method for zinc activation.[314f] Fourney and associates reported recently that the *N*-benzyloxycarbonyl protected analog of **549b** could be obtained with Zn-Cu couple simply by using a "vibromixer" instead of sonication. The resulting reagent was used *in situ* for conjugate addition to a carbohydrate derived unsaturated nitrile.[315] The coupling of **549b** with aromatic iodides or vinyl triflates requires Pd catalysis as well.[316] The yields of these reactions are generally not high, but interesting compounds such as the pyridine analog of phenylalanine **551** can be obtained expediently. A more reactive species **549c** of undefined nature is obtained upon addition of the soluble Cu-salt CuCN/2 LiCl.[317] This reagent combines without further catalysis with a variety of allylic halides, giving the unsaturated aminoacids **552**.[317a] Coupling with 3-bromopropiolic ester is successful as well.[314f] An allylic shift is involved with this coupling, and allenes are therefore obtained from propargylic halides.[314f] The reagent **549c** reacts as well with cationic iron-dienyl and iron-trienyl complexes, albeit with low diastereocontrol concerning newly generated asymmetric centers; *i.e.* better selectivity is expected with resolved iron complexes.[317b] This methodology has now been extended to the homologous series as well, and the reagent corresponding to **549c**, **553b**, has been prepared from the glutamate derived iodide **553a** and has also been successfully coupled with allylic halides.[318a] A similar organo-Zn reagent had been prepared before from a *N*-benzyloxycarbonyl protected 5-oxazolidinone analog of **553a**. After addition of CuCN it was used for 1,4-additions to α,β-unsaturated carbonyl compounds.[318b] Pd-Catalyzed coupling of the Reformatsky reagent derived from **553a** with protected 2'-iodohistidine is the key step of a recent synthesis of diphthamide **243** (*cf.* above, *Chart 2*, ref. 161d).[318c]



Scheme 69

Aspartate can be considered as an alanine β-anion equivalent, and regioselective β-enolate formation is possible, when the α-carbon is either protected with the bulky *N*-(9-phenylfluorenyl) group (→ **554**[319]), by deprotonation of an amide NH (→ **555**[320a-c]) or of the free carboxylic acid (→ **556**[321]) (*Scheme 70*). The *N*-PhFl derivative **554a** is best deprotonated with $KN(SiMe_3)_2$. While aldol reactions are not successful, alkylation gives *syn/anti* mixtures in acceptable yields.[319a] An impressive example is the conversion to the piperidine-dicarboxylate **557** *via* **558** in the context of a total synthesis of (+)-vincamine.[319b] Alkylation of the *N*-diprotected analog **554b** exhibits better stereoselectivity. The β-benzyl ester ensures regioselective ester cleava-



Scheme 70

ge for the ensuing Curtius degradation to 2,3-diaminoacids.[319c] Hydroxylation of the β-enolate of *N*-PhFl-protected dimethyl aspartate with MoOPH gave β-hydroxy aspartate with high *erythro*-selectivity in THF, and with *threo*-preference, when conducted in THF/HMPA(10%).[322] The β-Li-enolate of *N*-benzyloxycarbonyl protected aspartate **555** could be alkylated with reactive halides only,[320b,c] but in this case reaction with aldehydes proceeded in 32 - 50% yield, affording the aldols **559a** as mixtures of 2 stereoisomers.[320a] Cleavage of the allyl ester under Pd-catalysis (→ **559b**) allowed the decarboxylative elimination mediated by the

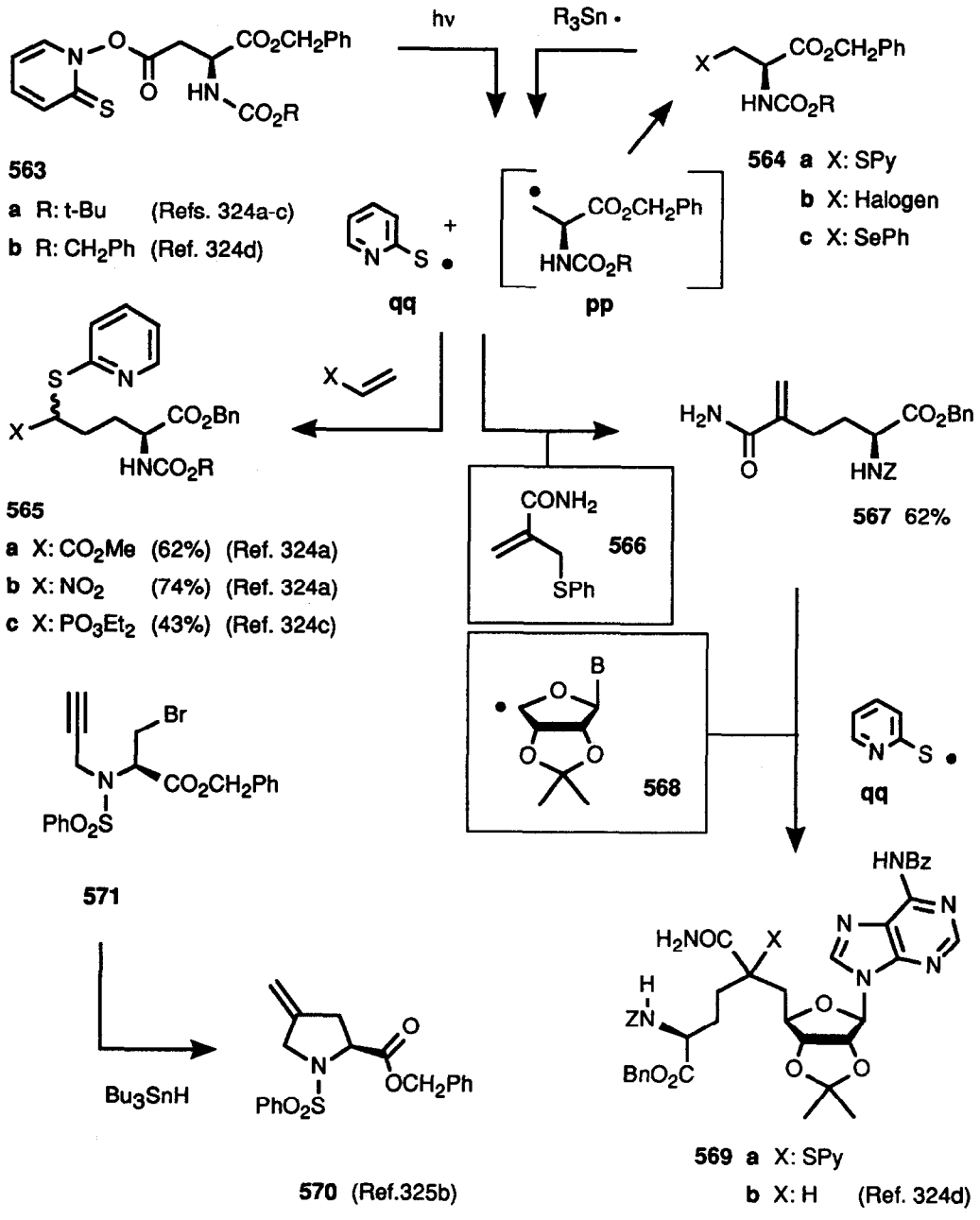
Mitsunobu reagent couple, affording *cis/trans*-mixtures of β,γ-unsaturated aminoacids **560**. Analogous aldol additions were successful with *N*-tritylated glutamic acid diesters as well.[323] Elimination to γ,δ-unsaturated α-aminoacids, substituted allylglycines, was effected with orthoformamide in this case. Ireland-Claisen rearrangement of the cyclic allyl ester **555a** derived from aspartate afforded the pyrrolidine **555b**, an advanced intermediate for the synthesis of kainic acid **465**.[320d] In this case racemization was prevented by reduction of the 1-carboxylate. The β-lactam **556** is obtained from dibenzyl aspartate in 4 steps and 67% overall yield.[321a] Its dilithium salt can be alkylated with excellent stereocontrol giving the *trans*-disubstituted β-lactams **561** in 57 - 60% yield.[321b] Hydrolysis with 6N HCl leads straightforwardly to unprotected β-alkyl aspartates **562**[321b], whereas β-lactam cleavage with regioselective acid derivatization is more difficult.[321a]

7.4. Alanine β-Radical Equivalents

The C(β)-radical of alanine **pp** can be generated either by photolysis of aspartic acid *N*-hydroxy-2-thiopyridone ester **563**[324] or from β-halo-alanines **564b** with trialkyl-Sn radicals generated from the corresponding tin hydrides[325a,b] or allyltriphenyltin reagents[325c] (*Scheme 71*). Radical intermediates are also involved in the borohydride reduction of 3-mercurio-alanine derivatives (*cf.* above, *Scheme 28*, ref. 155b). The amide protected radical **pp** appears to be long-lived enough for interception with radicophiles before rearranging to the C(α)-radical. It has recently been found, that radical bromination of phthalimidoyl derivatives of α-aminoacids occurs at benzylic or tertiary positions with preference to C(α).[326] Without any additives the radical-pair **pp/qq**, generated from **563** with extrusion of CO_2, recombines to **564a**.[324b] Halides **564b** are obtained with trichloromethyl halides and the selenide **564c** in the presence of diphenyl diselenide. While reduction to alanine is mediated by thiols or tin hydrides, addition to electrophilic olefins leads to extended radicals, which are in turn trapped by **qq**, affording the adducts **565** in good yields.[324a,c] The thiopyridine substituent can either be removed by tin hydride reduction[324c], or be eliminated after *m*-chloroperbenzoic acid oxidation to the sulfoxide.[324a] Application of the acceptor **566** with a radical leaving group directly leads to the unsaturated amide **567**, which in turn is an acceptor for 5-noradenosyl **568**, completing an elegant synthesis of (*S*)-sinefungin **569b** *via* the *S*-pyridyl adduct **569a**.[324d] The glutamate derived analog of **563** can be transformed to the homologous products of those depicted in *Scheme 71*.[324a-c] Treatment of *N*-allyl- or *N*-propargyl-β-halo-alanine derivatives with tributyltin hydride leads to proline derivatives, *e.g.* 4-methyleneproline **570** from **571**.[325b] Photolysis of *N*-carbobenzyloxy-3-iodo-alanine benzyl ester and allyltriphenylstannanes results in coupling to δ,ϵ-unsaturated aminoacids. A putative biosynthetic precursor of tabtoxinine β-lactam has been obtained by this method.[325c]

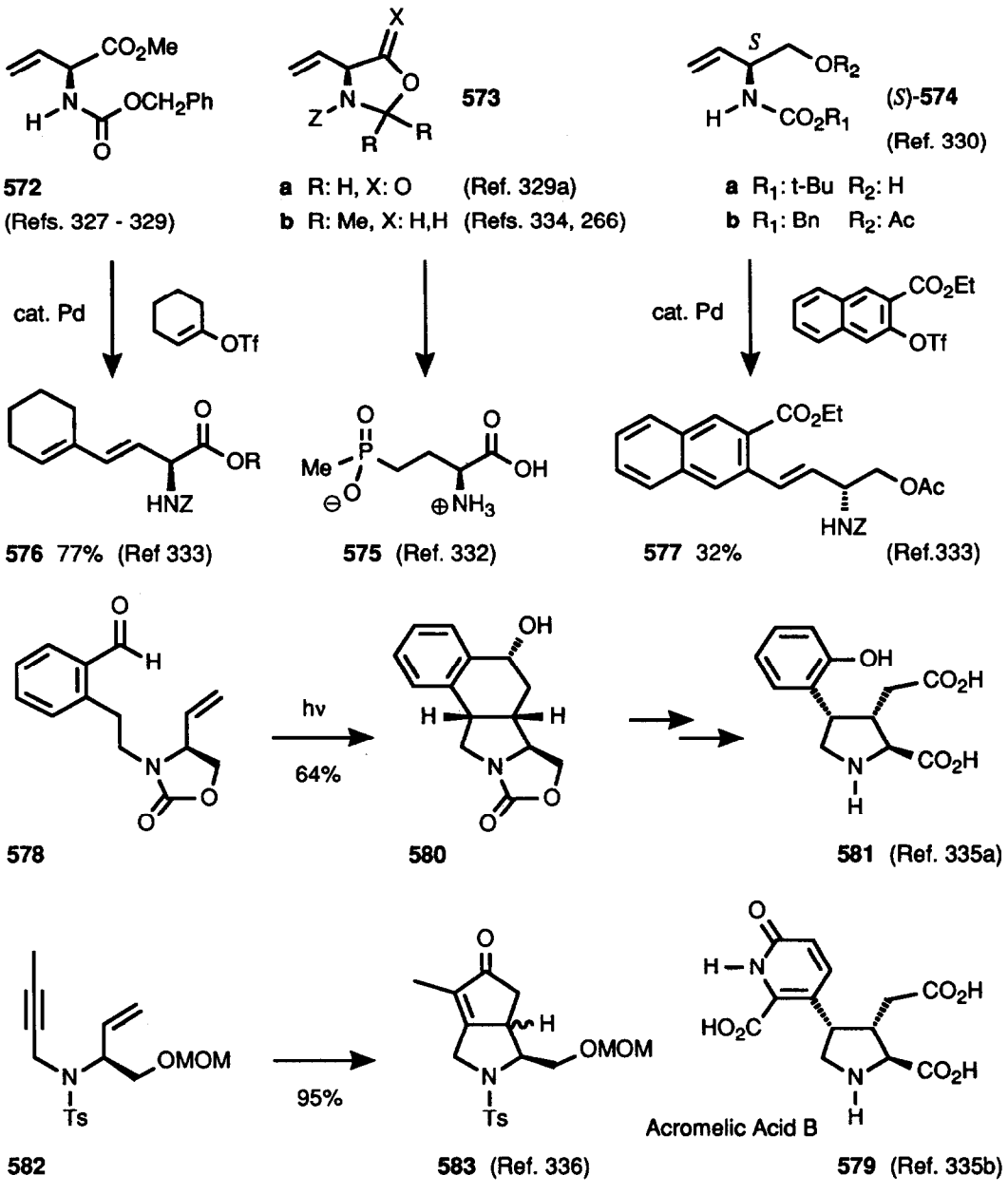
7.5. Miscellaneous Protocols

Vinylglycine is not only an interesting compound for studying enzyme inhibition, it has also served as a versatile synthetic intermediate (*Scheme 72*). Vinylglycine is conveniently obtained in differently protected forms **572/573a** either by elimination from methionine sulfoxide[327], recently disclosed as an *Organic Syntheses* preparation,[327c] from the analogous phenylselenide,[324a,328] or by oxidative decarboxylation of glutamate.[329] The vinylglycinols **573b** and **574** are obtained similarly by elimination from L-methioninol.[330] However, the acetonide **573b**, especially the (*R*)-configurated enantiomer, is more readily obtained from the Garner-serine aldehyde **449a** (*cf. Chart 3*) according to Moriwake and coworkers,[266] or most probably even better by using dimethyltitanocene, the novel methylenation reagent recently introduced by Petasis and associates.[331] β-Hydroxy-ornithines have been prepared from **572** *via* isoxazolidines obtained by nitrone cycloaddi-



Scheme 71

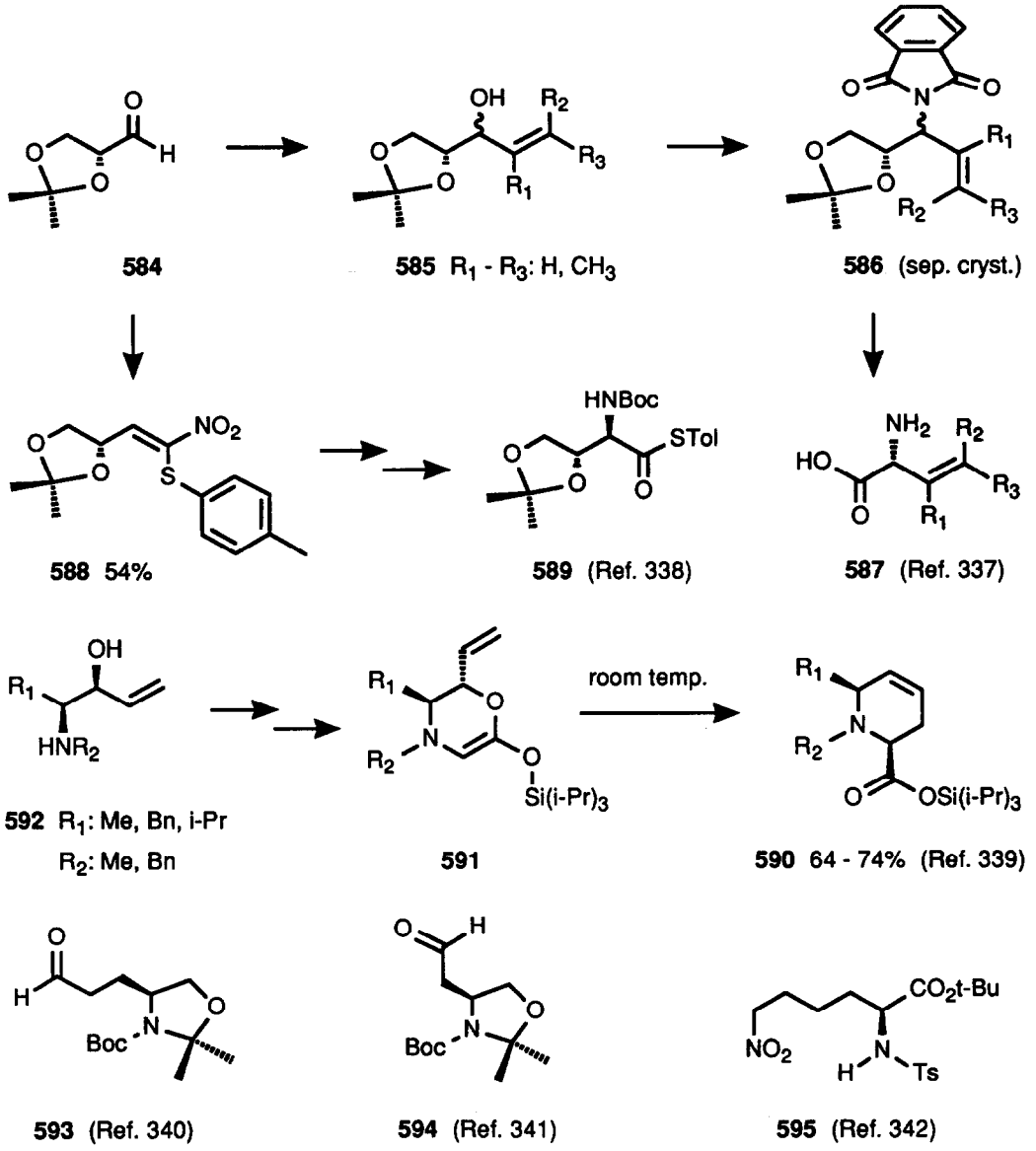
tion.[329b] Radical mediated addition of P(III)-compounds led to 4-phosphoryl substituted α-aminobutanoate, *e.g.* the herbicidal phosphinate phosphinothricin **575**.[332] Vinylglycine **572** or the acetyl protected vinylglycinol **574b** undergo efficient Heck coupling with a variety of vinyl and aryl triflates (*e.g.* → **576** and **577**).[333]



Scheme 72

All possible isomers of (2-carboxycyclopropyl)glycine, conformationally restricted glutamate analogs, have been obtained by cyclopropanation of **573b** with diazoacetic acid derivatives[334] (*cf.* also *Scheme 61*, **469** → **471**[265a]). Vinylglycinol (*S*)-**574a** has been transformed to *threo*-β-hydroxy-homotyrosine, a constituent of the peptidic antibiotics echinocandin C and D.[130g] In a series of very interesting papers Shirahama and associates

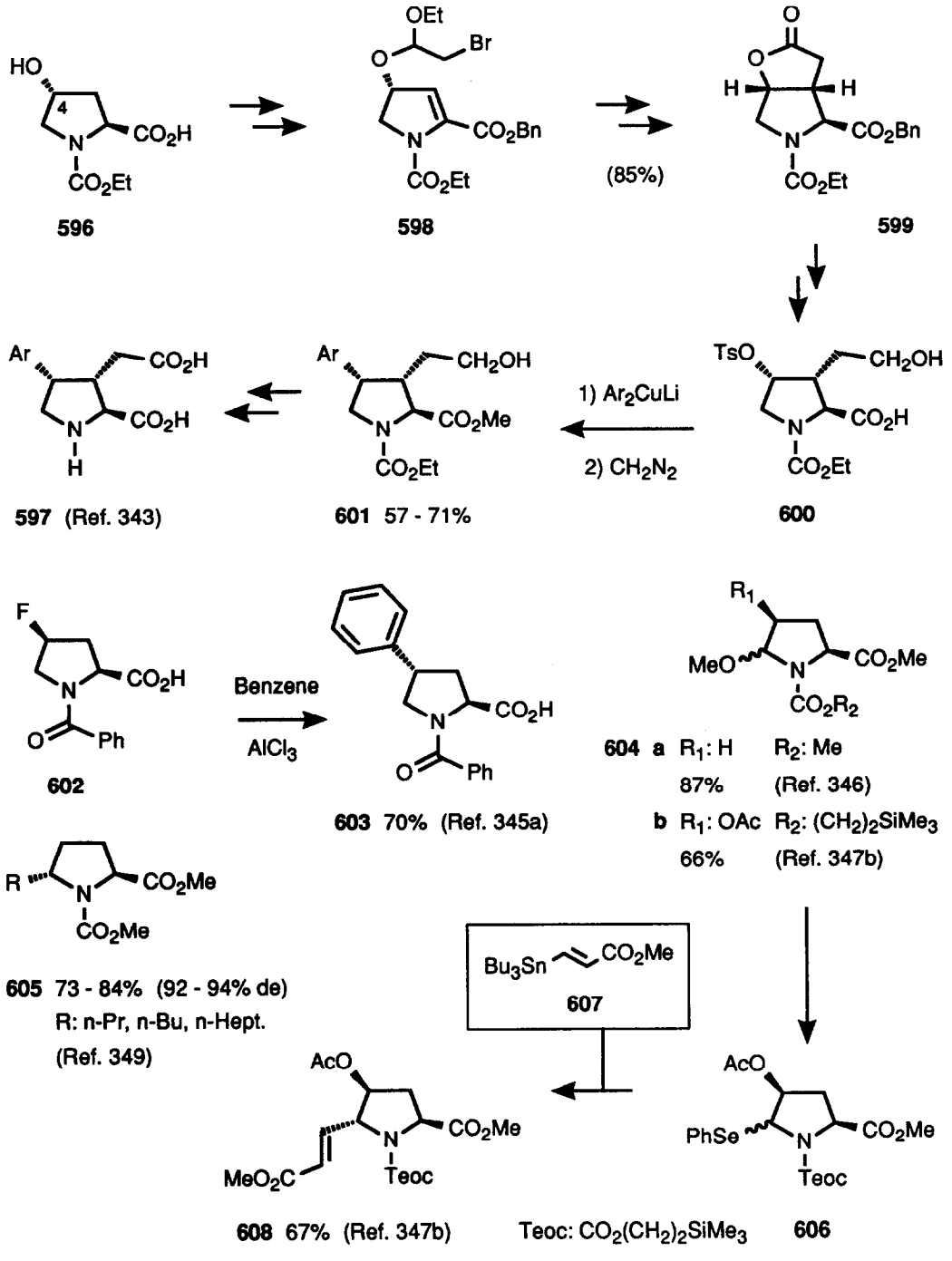
have disclosed the elaboration of vinylglycinol *via* 4-vinyloxazolidinones such as **578** to acromelic acids (*e.g.* **579**) and analogs, kainate-type glutamate agonists[335] (*cf.* ref. 5, pp. 306 - 320). Cyclization of **578**, a [8 + 2]-process, is initiated by photo-enolization of the aromatic aldehyde. The tricyclic alcohol **580**, obtained with excellent and correct stereoselectivity, is oxidized to the aromatic ketone, which is then readily cleaved by a Baeyer-Villiger oxidation, giving a close precursor of **581**.[335a] The *N*-propargyl compound **582** gives the enone **583** under Pauson-Khand conditions, in excellent yield but with rather low stereoselectivity (63 : 47).[336] The major isomer has been further transformed to kainic acid (**465**, *cf. Scheme 61*).



Scheme 73

Glyceraldehyde acetonide **584** is one of the simplest chiral building blocks, readily obtainable from natural sources in both enantiomeric forms. It has therefore also been used efficiently for the preparation of aminoacids. Mulzer and coworkers have converted the addition products of vinylic organometallics **585** to the phthalimides **586** by the Mitsunobu-reaction.[337] The major *syn*-epimers of **586** could often be separated by crystallization and have subsequently been transformed to β,γ-unsaturated aminoacids **587** of high optical purity (97% ee) by unraveling of the masked carboxylate, involving oxidative glycol cleavage using $Pb(OAc)_4$ and Jones-reagent. Knoevenagel-condensation with nitromethyl tolyl sulfide leads to interesting nitro-olefins, which can be considered as electrophilic ketene equivalents. The adduct of ribose-5-aldehyde has been converted to an aminoacid by conjugate addition of $KOSiMe_3$ and azide substitution of the resulting α-hydroxy acid.[146c] With glyceraldehyde acetonide **584** the nitro-olefin **588** is formed. Stereoselective epoxidation with either *t*-BuOOLi (→ *syn*) or *t*-BuOOK (→ *anti*) followed by opening with various nitrogen nucleophiles directly afforded tolylthio esters of α-aminoacids, *e.g.* **589**.[338] The piperine-carboxylates **590**, intermediates for indolizidine alkaloids, are smoothly obtained by Claisen-Ireland-rearrangement of the silyl ketene-acetals **591**, which proceeds at room temperature.[339] The heterocyclic precursors **591** are readily prepared from the vinyl Grignard adducts **592** of α-aminoaldehydes. Potentially useful synthetic intermediates are the homologs **593**[340] and **594**[341] of the Garner-serine aldehyde. They have been obtained from aspartate and glutamate, respectively, and were transformed to glutamate analogs[340] and 5-hydroxylysine, a constituent of bengamide A.[341] The nitro compound **595**, obtained in 50 - 60% yield by *m*-chloroperbenzoic acid treatment of *N*-tosyl-ornithine t-butyl ester, was used for a synthesis of sinefungin **569** (*cf. Scheme 71*).[342]

Given the importance of cyclic aminoacids, some effort has been put into synthetic transformations of proline **4** and 4-hydroxyproline **596** (*Scheme 74*). Several characteristic aspects are represented by the conversion of **596** to Acromelic acid and congeners **597**.[343] Although the stereochemistry of C(2) is lost upon dehydrogenation with hypochlorite (→ **598**), it is restored after radical cyclization and epimerization with DBU giving **599** in 85% yield. Substitution of the tosylate **600** with arylcuprates occurs with retention of configuration at C(4) (→ **601**), a fact which has been explained before by nitrogen-assisted double inversion.[344] Fluorination of **596**, on the other hand, gives the fluoride **602** with inverted configuration.[345] Some uncertainties concerning the NMR spectra of **602** could recently be clarified as effects of hindered amide rotation.[345d] The Friedel-Crafts-arylation to **603** proceeds with inversion as well.[345a] 5-Methoxyproline **604a** is readily obtained by anodic oxidation of proline.[346] This transformation is, however, much less clean for either epimer of 4-hydroxyproline,[347] and only by systematic optimization of protecting groups could a 66% yield of **604b** be obtained.[347b] *Lewis*-acid catalyzed substitution at C(5) of **604a,b** with allylsilanes,[346b,347] propargylsilane,[347b] silyl enol ethers,[346b] malonate,[346b] trimethylsilyl cyanide,[347b] trimethylsilylacetylene,[348] and dialkylcuprates[349] all proceeded with low diastereoselectivity. Only the addition of alkylcopper reagents, catalyzed by $BF_3.Et_2O$, gave the 5-alkylprolines with excellent stereocontrol and good yield.[349] High selectivity was also observed in radical reactions of phenyl selenides, *e.g.* **606**, derived from **604**.[347b] Initiated by $(Bu_3Sn)_2$ under irradiation, the addition to β-tributylstannyl-acrylate **607** gave 67% substitution to **608**, a precursor for the synthesis of the β-lactam synergist bulgecin C.


HO
4
CO2H
N
CO2Et
596
OEt
Br
O
CO2Bn
N
CO2Et
598
(85%)
O
O
H
H
CO2Bn
N
CO2Et
599
TsO
CH2OH
CO2H
N
CO2Et
600
1) Ar2CuLi
2) CH2N2
Ar
CH2OH
CO2Me
N
CO2Et
601 57 - 71%
Ar
CO2H
CO2H
N
H
597 (Ref. 343)
F
CO2H
N
O
Ph
602
Benzene
AlCl3
CO2H
N
O
Ph
603 70% (Ref. 345a)
R1
MeO
CO2Me
N
CO2R2
604 a R1: H R2: Me
87% (Ref. 346)
b R1: OAc R2: (CH2)2SiMe3
66% (Ref. 347b)
R
CO2Me
N
CO2Me
605 73 - 84% (92 - 94% de)
R: n-Pr, n-Bu, n-Hept.
(Ref. 349)
Bu3Sn
CO2Me
607
AcO
CO2Me
N
MeO2C
Teoc
608 67% (Ref. 347b)
AcO
PhSe
CO2Me
N
Teoc
606
Teoc: CO2(CH2)2SiMe3

Scheme 74

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