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Recent Stereoselective Synthetic Approaches to β-Amino Acids

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1. Introduction

Although much less abundant than their α-analogues, β-amino acids are also present in nature. A number of β-amino acids have been isolated in free form and show interesting pharmacological properties.[1] These β-amino acids can be cyclized to β-lactams,[2] a well-known class of potentially biologically active substances which occur in nature.[3,4]

β-Amino acids are also components of naturally occurring biologically active peptides.[5] For example, α-hydroxy-β-amino acids are present in various peptidic enzyme inhibitors such as bestatin[6] and pepstatin.[7] 3-Amino-2-methylpentanoic acid is present in the structurally related antifungal depsipeptides, majusculamide C[8] and 57-normajusculamide C,[9] and the antitumor agents, aldostatins 11 and 12.[10]

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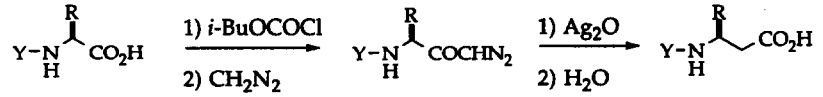
In addition β-amino acids are proving to be useful tools in the synthesis of modified peptides with increased activity and *in vivo* stability.[7, 11]

Taxol, a complex diterpene containing a (-)-*N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine side chain, is currently considered a most exciting lead compound for cancer chemotherapy.[12] It has long been known that natural reserves of taxol are limited; however, a recent report has shown that a taxol precursor 10-deacetyl baccatin which lacks the β-amino acid side chain is readily available from the leaves of *Taxus brevifolia* (western Yew) (1 g / 1 kg).[13] It has been shown that the β-amino acid side chain of taxol is necessary for biological activity.[14] These findings have sparked interest in the synthesis of α-hydroxy-β-amino acids.

A number of previous reviews have been concerned with the occurrence and biochemical properties of β-amino acids,[15] as well as with some early syntheses of racemic materials.[7, 16] This review attempts to focus on the main strategies that have been developed for the synthesis of β-amino acids in diastereo- and enantiomerically enriched form, although a number of procedures for the production of these compounds in racemic form have also been included for completeness. It is impossible to discuss the synthesis of β-amino acids without also mentioning the preparation of β-lactams since the two classes of compounds are so readily interconverted.[2,17] However, since excellent reviews in the area of β-lactam synthesis already exist,[13c,18] an attempt has been made to limit this overlap. Williams has recently written an excellent monograph discussing the synthesis of optically active α-amino acids.[19]

2. Homologation of α-amino acids

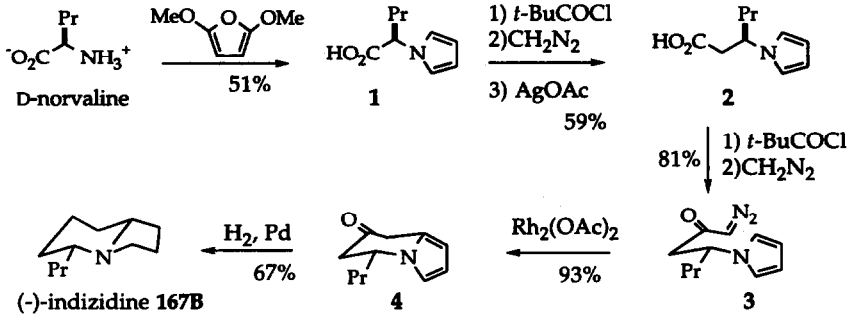
During the 1940's, it was shown that the Wolff rearrangement of diazoketones containing a chiral center next to the carbonyl group occurred with retention of configuration.[20] This finding formed the basis for the use of the Arndt-Eistert reaction for the synthesis of homologous optically active amino acids from their α-amino acid counterparts. **Scheme 2.1** shows the strategy used by Plucinska in his synthesis of a number of β-amino acids.[20] The *N*-protected amino acids were converted to the corresponding diazoketones via reaction of the mixed anhydride derivatives with diazomethane. Treatment with silver oxide then brought about the Wolff rearrangement to give the β-amino acid.



Y = Cbz or Boc
R = α-amino acid side chain

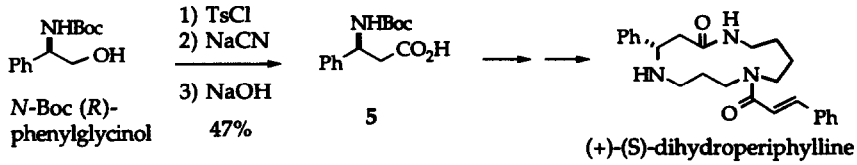
Scheme 2.1

Jefford et al. used the Arndt-Eistert rearrangement in their synthesis of the alkaloid (-)-indolizidine **167B** (**Scheme 2.2**).[21] D-Norvaline was condensed with 2,5-dimethoxytetrahydrofuran to give the 1-pyrrolylacetic acid **1**, which was then converted to the homologous acid **2** via the mixed anhydride and diazoketone. Repetition of the mixed anhydride-diazoketone procedure gave **3**, which was converted into the natural product by carbene *C-H* insertion and hydrogenation.



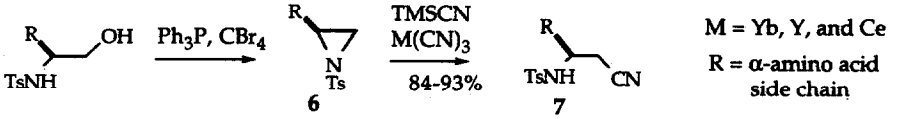
Scheme 2.2

Kibayashi has developed a synthesis of β-phenyl-β-alanine based on the homologation of (*R*)-*N*-*tert*-butoxycarbonyl-phenylglycinol by tosylation, cyanide displacement, and hydrolysis (**Scheme 2.3**).[22] The optically pure β-amino acid **5**, produced in 47% overall yield, was used in the total synthesis of the spermidine alkaloid (+)-(*S*)-dihydroperiphylline.



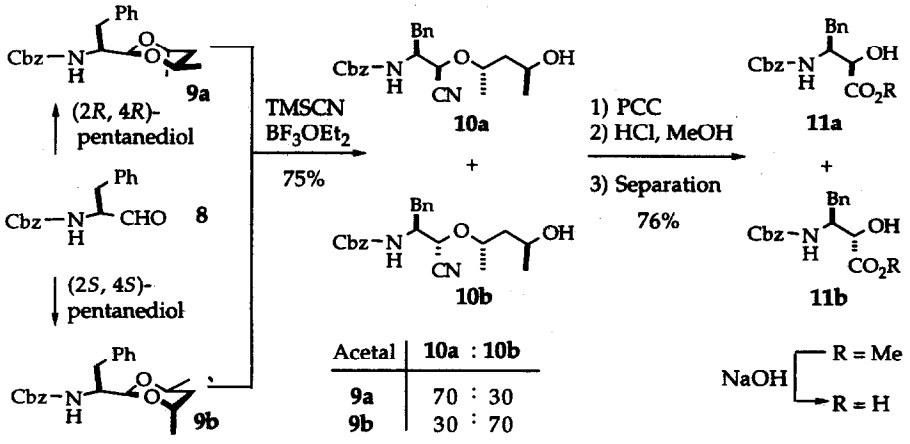
Scheme 2.3

Similarly, it has been shown that α-amino alcohols could be converted into optically pure aziridines (**Scheme 2.4**).[23] Reaction of these *N*-tosylaziridines **6** with trimethylsilyl cyanide in the presence of a lanthanide tricyanide catalyst then gave the cyanoamines **7** with complete regioselectivity and retention of optical purity. $Yb(CN)_3$, $Y(CN)_3$, and $Ce(CN)_3$ were all equally effective catalysts for the aziridine opening reactions. Hydrolysis of the cyanoamines **7** yielded the corresponding β-amino acids.



Scheme 2.4

Herranz et al. have developed a method for the enantioselective synthesis of all four stereoisomers of 3-amino-2-hydroxy-4-phenylbutanoic acid (AHPA) **11**, which are key intermediates in the synthesis of bestatin and its analogues (**Scheme 2.5**).[24] Acetals **9a** and **9b** were prepared in 95% yield by reaction of *N*-protected-L-phenylalaninal **8** with (-)-(2*R*, 4*R*)- and (+)-(2*S*, 4*S*)-pentane-2,4-diol, respectively. Reaction of these acetals **9** with trimethylsilyl cyanide in the presence of boron trifluoride etherate gave the ring opened products **10** in 75% yield as inseparable mixtures.

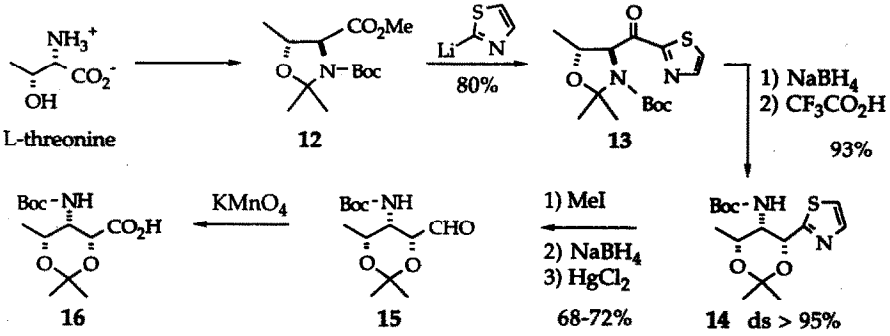


Acetal	10a : 10b
9a	70 : 30
9b	30 : 70

Scheme 2.5

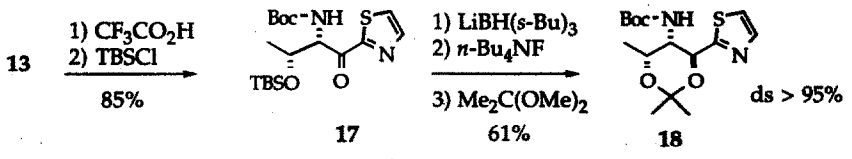
Oxidation with pyridinium chlorochromate (PCC), followed by treatment with dry methanolic hydrochloric acid, and then water gave the hydroxy methyl esters (**11a** and **b**, R = Me). These could be separated by flash chromatography and then saponified to give (2*R*, 3*S*)- and (2*S*, 3*S*)-Cbz-AHPA (**11a** and **b**, R = H). Herranz et al. used the same strategy to prepare the other two isomers, (2*S*, 3*R*)- and (2*R*, 3*R*)-Cbz-AHPA, by starting with Cbz-D-phenylalaninal.

Dondoni et al.[25] have reported a stereoselective route to α-hydroxy-β-amino acids by homologation of protected α-amino acids (**Scheme 2.6**). In the example shown, L-threonine was converted into the 2-thiazolyl amino ketone **13** via its *N*-Boc-2,3-isopropylidene methyl ester **12**. Reduction of **13** with sodium borohydride, followed by acid catalyzed migration of the acetonide protecting group, gave the syn-alcohol **14** with a high degree of diastereoselectivity. Thiazol deblocking by *N*-methylation, reduction, and hydrolysis gave the aldehyde **15**, which was oxidized to give the protected β-amino acid **16**.



Scheme 2.6

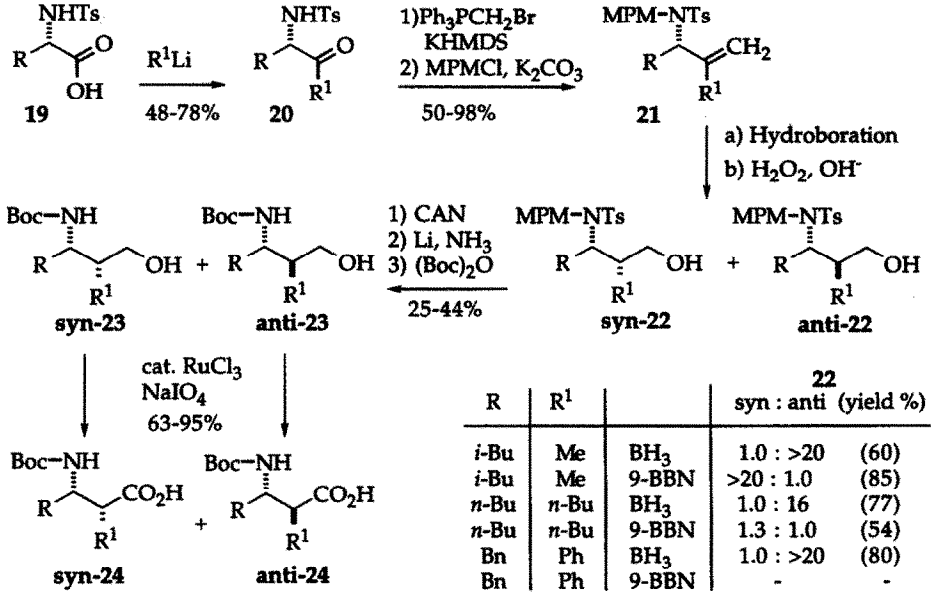
Changing the protecting groups on **13** gave the thiazolyl ketone **17**, which was reduced with *L*-Selectride to give the anti-product **18** after desilylation and protection (**Scheme 2.7**).[25]



Scheme 2.7

Compound **18** was converted into the corresponding amino acid in the same manner as for **14** (**Scheme 2.6**).

Burgess et al. recently reported an alternative method for the preparation of β-amino acids by homologation of the corresponding α-analogue (**Scheme 2.8**).[26] The *N*-tosylated amino acids **19** (R = *i*-Bu, *n*-Bu, and Bn) were reacted with excess alkyllithium (MeLi and n-BuLi) or phenyllithium to afford the ketones **20**. A Wittig reaction gave the allylamines which were protected by reaction with *p*-methoxybenzyl chloride to give **21**. Except for the norleucine derivative, which was obtained in 94% enantiomeric excess, no racemization was detected.



R	R^1		22 syn : anti	(yield %)
i-Bu	Me	BH_3	1.0 : >20	(60)
i-Bu	Me	9-BBN	>20 : 1.0	(85)
n-Bu	*n*-Bu	BH_3	1.0 : 16	(77)
n-Bu	*n*-Bu	9-BBN	1.3 : 1.0	(54)
Bn	Ph	BH_3	1.0 : >20	(80)
Bn	Ph	9-BBN	-	-

Scheme 2.8

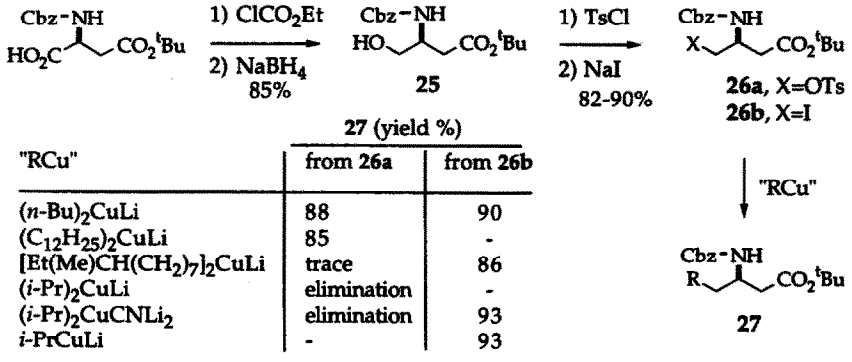
A hydroboration-oxidation sequence was used to introduce the alcohol functionality and set the stereochemistry of the new α-center. When borane was used, the anti-product (**anti-22**) was obtained with good selectivity (> 16 : 1) and high yields. When 9-BBN was used, the syn-product (**syn-22**) predominated, however the yields and selectivity tended to be lower. In both cases, increased selectivity was observed by the use of two *N*-protecting groups. Oxidative removal of the *p*-methoxybenzyl group, followed by removal of the tosyl substituent with lithium in ammonia gave

the free amine, which was protected as the *tert*-butoxycarbonyl derivative **23**. Oxidation furnished the *N*-protected β-amino acids **24**.

3. From aspartic acid, asparagine, and derivatives

Aspartic acid, asparagine, and their derivatives are ideal starting materials for the synthesis of enantiomerically pure β-amino acids, since they already contain the β-amino acid unit and both enantiomers are readily available.

In a method reported by Roumestant. (*S*)-*N*-(benzyloxycarbonyl)-aspartic acid mono *tert*-butyl ester was reduced selectively via its mixed anhydride to the protected homoserine **25** (**Scheme 3.1**).[27] Tosylation of the alcohol gave the primary tosylate **26a**, which could be converted to the iodide **26b** under Finkelstein conditions. Compounds **26a** and **b** were then treated with a variety of alkylcopper reagents to achieve displacement, giving the β-amino esters **27**. The yields of **27**, obtained from both the tosylate **26a** and the iodide **26b**, are tabulated in **Scheme 3.1**. Simple primary alkylcuprates reacted equally well with either electrophile, whereas 8-methyldecylcuprate and the secondary *iso*-propylcuprates only underwent substitution reactions with the iodo derivative.

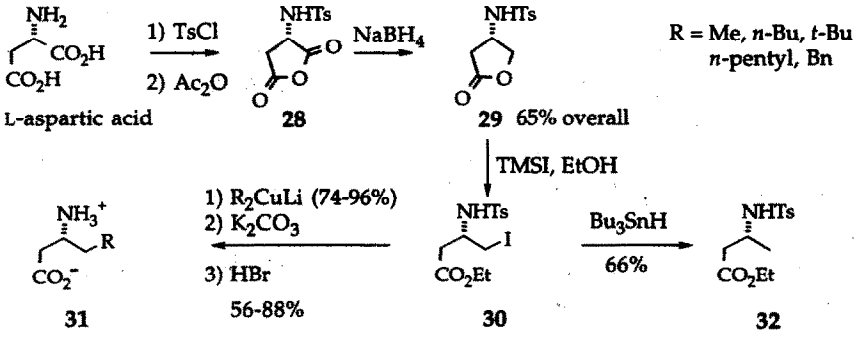


"RCu"	27 (yield %) from **26a**	from **26b**
$(n\text{-Bu})_2CuLi$	88	90
$(C_{12}H_{25})_2CuLi$	85	-
$[Et(Me)CH(CH_2)_7]_2CuLi$	trace	86
$(i\text{-Pr})_2CuLi$	elimination	-
$(i\text{-Pr})_2CuCNLi_2$	elimination	93
i-PrCuLi	-	93

Scheme 3.1

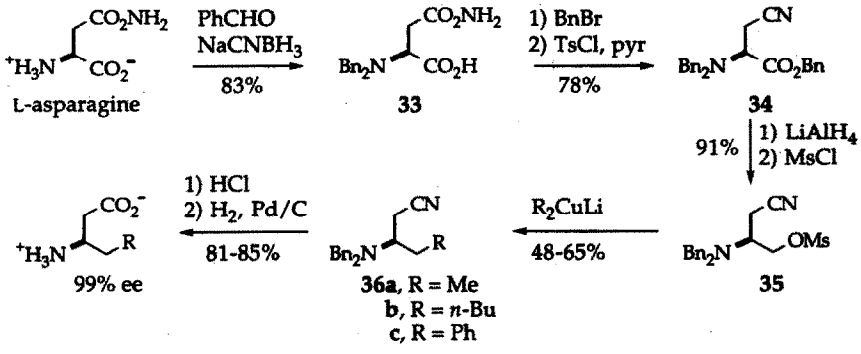
Scheme 3.2 shows how a homoserine derivative **30** can be synthesized from aspartic acid via the succinic anhydride derivative.[28] L-Aspartic acid was protected as its *N*-tosyl derivative, then treated with acetic anhydride to give the anhydride **28**, which underwent selective reduction with sodium borohydride to the lactone **29**. Reaction with iodotrimethylsilane in ethanol gave the homoserine derivative **30**.

Reaction with various organocuprates resulted in efficient incorporation of alkyl groups at the γ-position, leading to compounds **31** after deprotection. Attempted arylation by reaction with lithium diphenylcuprate was unsuccessful. Reduction of **30** with tributyltin hydride gave the β-amino butyrate ester **32**.



Scheme 3.2

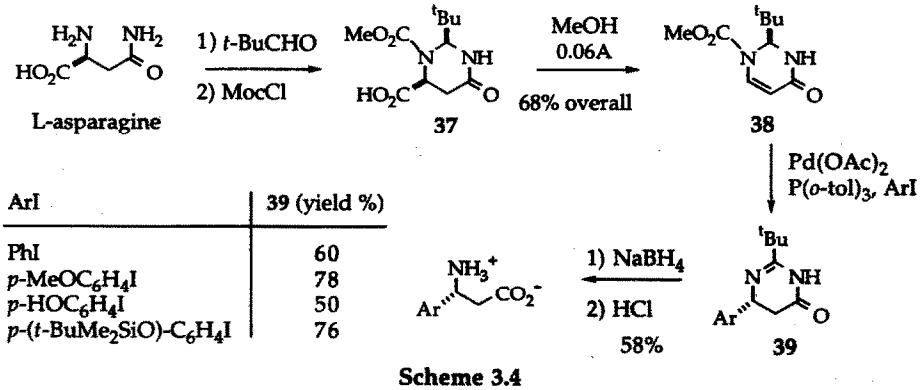
Scheme 3.3 shows work by Gmeimer, in which the two acid functionalities of asparagine were differentiated by conversion of the β-acid to a nitrile group.[29] Reductive amination of L-asparagine with benzaldehyde gave the dibenzyl derivative **33**. Esterification of the acid and dehydration of the amide group furnished the nitrile **34**. Selective reduction of the ester and mesylation of the primary alcohol gave the homoserine derivative **35**, which reacted with the methyl- and *n*-butylcuprates to give products **36a** and **b** in good yields.



Scheme 3.3

In contrast to the preceding work, lithium diphenylcuprate was found to be effective for displacement of the mesylate in **35**, providing access to 3-amino-4-phenylbutanoate derivatives **36c**. Acidic hydrolysis of the nitrile group and hydrogenolysis of the benzyl groups gave the β-amino acids.

Konopelski's method for β-amino acid synthesis from asparagine is fundamentally different from those in the preceding examples (**Scheme 3.4**).[30] Using so-called "self reproduction of chirality", the chiral center of asparagine is used to control the chirality of the *tert*-butyl group in the key intermediate, heterocycle **38**. Thus, reaction of the potassium salt of asparagine with pivaldehyde produced a tetrahydropyrimidine product as a single isomer, which was converted to **37** by protection of the amine group with methyl chloroformate. Oxidative decarboxylation under electrochemical conditions then led to **38** in 68% overall yield from asparagine. The Heck[31] coupling of **38** with aryl iodides produced the coupled products **39** as single isomers with the β-aryl group adding in a formal Michael fashion from the face opposite to the *tert*-butyl group (**Scheme 3.4**). The mechanism of the reduction of the carbon-palladium bond and the oxidation of the carbon-nitrogen bond during the course of this transformation are discussed in detail in the original paper.[30e] Reduction of the imines **39** and acid hydrolysis liberated the β-amino acids as the hydrochloride salts.

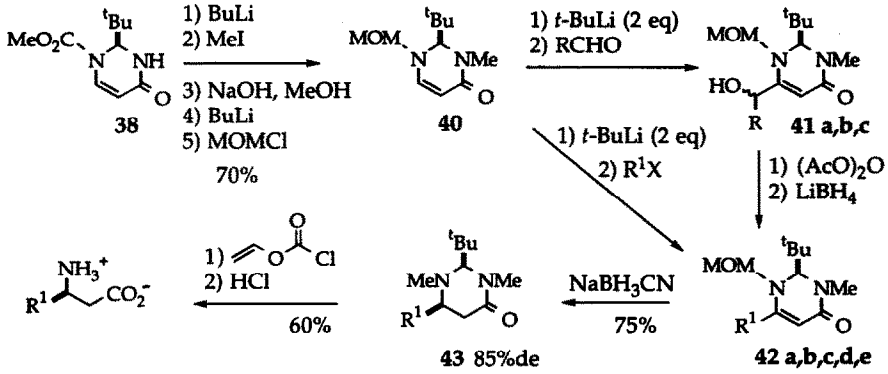


ArI	39 (yield %)
PhI	60
p-$MeOC_6H_4I$	78
p-HOC_6H_4I	50
p-(*t*-$BuMe_2SiO$)-C_6H_4I	76

Scheme 3.4

Heterocycle **38** can also be used for the synthesis of β-alkyl-β-amino acids (**Scheme 3.5**).[30d] Methylation of the free amine, followed by cleavage of the carbomethoxy group with sodium hydroxide, and protection of the resulting amine with a methoxymethyl group gave **40** in which the nitrogen atoms are protected

with base stable groups. Heterocycle **40** was then deprotonated and treated with alkyl halides and aldehydes. Of the alkyl halide electrophiles used, only methyl iodide was found to be very effective (entry 7). The other primary halides afforded the alkylated products in much lower yields (entries 4 &6), or failed to give any product (entry 5). Aldehydes proved to be superior electrophiles and led to the hydroxyl products **41** (entries 1-3). Acetylation and reduction of these alcohols gave the alkylated compounds **42** in higher overall yields (entries 5 & 6). Reaction of aryl iodides with the vinyllithium species, derived from **40**, is not the method of choice for producing β-aryl-β-amino acids; compare entry 8 (**Scheme 3.5**) with the organopalladium coupling with iodobenzene indicated in **Scheme 3.4** (Ar = Ph, 60% yield). Sodium cyanoborohydride reduction of the substituted dihydropyrimidines **42** occurred from the less hindered face to give the saturated heterocycles **43** in highly diastereoselective fashion, with concurrent reduction of the methoxymethyl protecting group. Demethylation of the amine nitrogen and hydrolysis then gave the free β-amino acids.



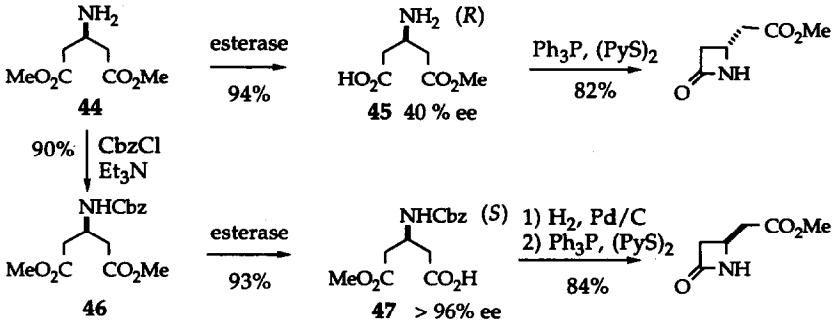
entry	electrophile	**41** ; R ; (yield %)	**42** ; R^1 ; (% yield)
1	CH_3CHO	**a** ; Me ; 81	-
2	*i*-PrCHO	**b** ; *i*-Pr ; 85	-
3	PhCHO	**c** ; Ph ; 84	-
4	EtI	-	**a** ; Et ; 55
5	*i*-BuI	-	**b** ; *i*-Bu ; 0(76)*
6	BnBr	-	**c** ; Bn ; 55(78)*
7	CH_3I	-	**d** ; Me ; 95
8	PhI	-	**e** ; Ph ; 27

* prepared from the corresponding aldehydes via **41b** and **41c**

Scheme 3.5

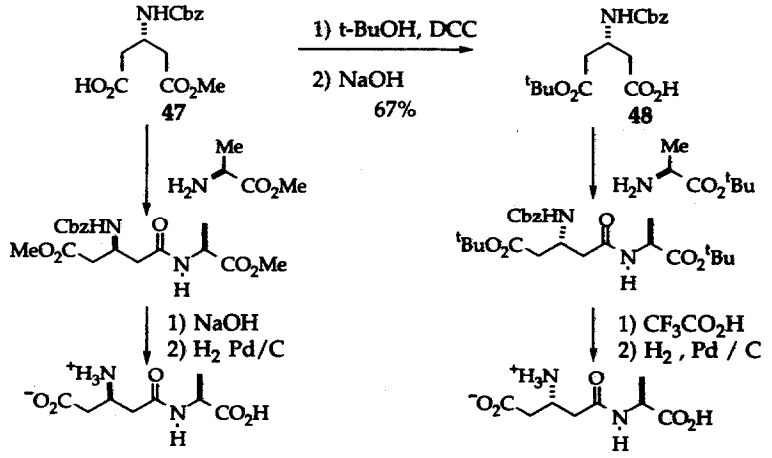
4. Enzymatic resolution

Enzymatic semihydrolysis of a symmetrical diester has been used as a means for preparing β-substituted β-amino acids. For example, dimethyl β-aminoglutarate **44**, prepared by reductive amination of dimethyl β-oxoglutarate, was hydrolyzed by pig liver esterase (PLE) by Ohno and coworkers (**Scheme 4.1**).[32] The reaction was found to be very efficient; however, the (*R*)-half ester **45** was produced in low optical purity (about 40% ee) because the substrate **44** was hydrolyzed slowly even in the absence of PLE. Assuming that the free amine participates in the hydrolysis by hydrogen bonding with the carbonyl group, Ohno and coworkers protected it with a benzyloxycarbonyl group to give **46**. Subsequent incubation with PLE produced the opposite (*S*)-half ester **47** in 93% yield and excellent (> 96%) enantiomeric excess. The β-amino acids **45** and **47** were converted into the corresponding azetidinones in high yield by treatment with triphenylphosphine and dipyridine disulfide.[2a]



Scheme 4.1

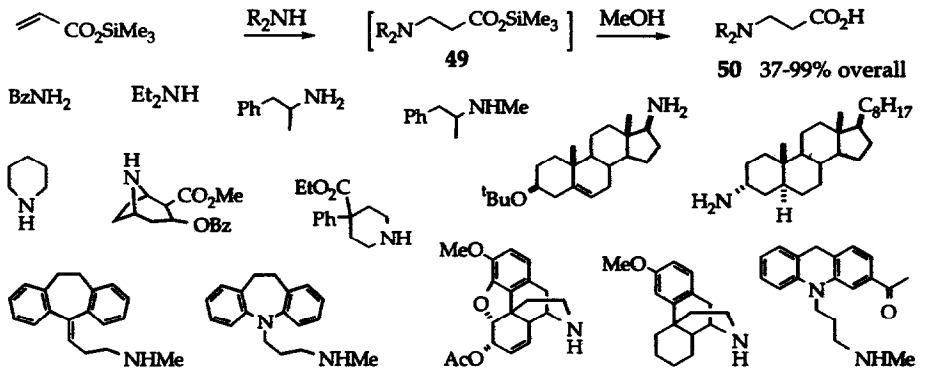
In their synthesis of (3*S*)- and (3*R*)-3-aminoglutaryl-(*S*)-alanine, Crossley et al.[33] used the enzymatic hydrolysis of dimethyl 3-benzyloxycarbonylaminoglutarate reported by Ohno et al.[32] The configuration of the (*S*) half ester **47** could be inverted by chemical reversal of the acid and ester functionalities (**Scheme 4.2**). Thus, esterification of the free acid with *tert*-butyl alcohol under dicyclohexylcarbodiimide conditions followed by selective hydrolysis of the methyl ester gave the (*R*)-half ester **48**. Reaction of the (*S*)- and (*R*)-half esters (**47** & **48**) with (*S*)-alanine methyl and *tert*-butyl esters, respectively, gave the fully protected dipeptides. Base or acid catalyzed hydrolysis of the ester functions, followed by hydrogenolysis of the benzyloxycarbonyl groups gave the free peptides.



Scheme 4.2

5. Michael addition of amines to acrylates and derivatives

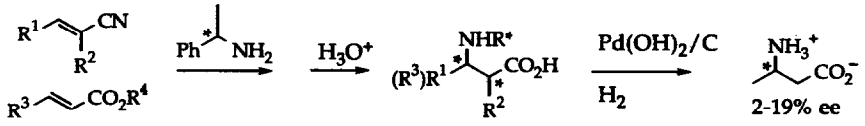
Conceptually, one of the simplest methods for the construction of β-amino acids is through the conjugate addition of amines to acrylic acid derivatives. In a report by Kwiatkowski, several *N*-substituted β-amino acids were synthesized in this manner (**Scheme 5.1**).[34] Michael additions of amines to α,β-unsaturated acids failed, and although addition to acrylonitrile and acrylic esters were known, these methods required basic or acid hydrolysis to liberate the free amino acid.



Scheme 5.1

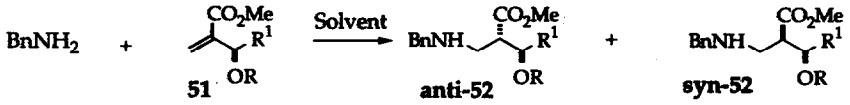
However, Michael addition of amines to trimethylsilyl acrylate afforded an intermediate trimethylsilyl ester **49**, which was readily solvolyzed in aqueous methanol to give *N*-substituted 3-aminopropionic acids **50**. All the amines shown in **Scheme 5.1** were successfully used as nucleophiles.

When the α- or β-positions of the acrylate are substituted, the Michael addition of the amine results in the formation of new chiral center. Most attempts to control the stereochemistry of this new center rely on either addition of a chiral amine or addition to a chiral ester. In one of the first reported examples, Furukawa et al.[35] examined the thermally activated addition of (*R*)- and (*S*)-phenethylamines to crotononitrile (R^1 = Me, R^2 = H), methacrylonitrile (R^1 = H, R^2 = Me), methyl crotonate (R^3 = R^4 = Me), *l*-menthyl crotonate (R^3 = Me, R^4 = *l*-menthyl), and ethyl cinnamate (R^3 = Ph, R^4 = Et) (**Scheme 5.2**). Unfortunately, the additions proceeded only in modest yields (generally 20-40% overall) and with poor diastereoselectivity.



Scheme 5.2

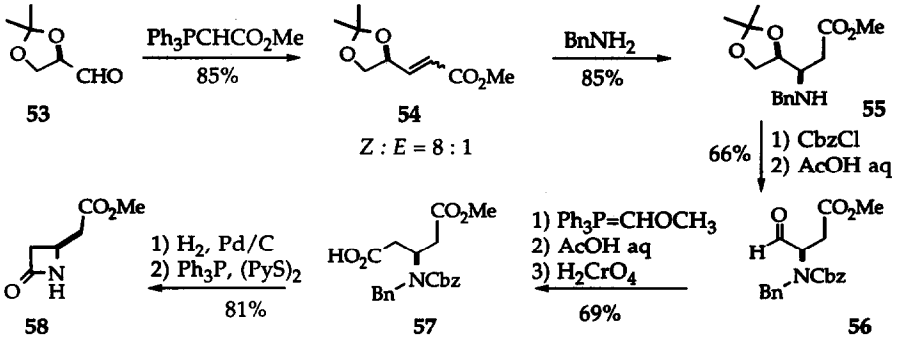
Perlmutter reported the diastereoselective conjugate addition of benzylamine to 2-hydroxyalkylpropenoates **51** (**Scheme 5.3**).[36] When THF was used as solvent **syn-52** was formed preferentially. Changing the solvent to methanol reversed the selectivity in favor of **anti-52**.



	MeOH anti : syn (yield %)		THF anti : syn (yield %)
51a, R = H, R^1 = Ph	4.1 : 1	(98)	1 :3.6 (92)
b, R = H, R^1 = α-Py	4.0 : 1	(92)	1 : 2.3 (52)
c, R = H, R^1 = Me	4.5 : 1	(99)	1 : 2.9 (77)
d, R = TBS, R^1 = Me	>20 : 1	(90)	-

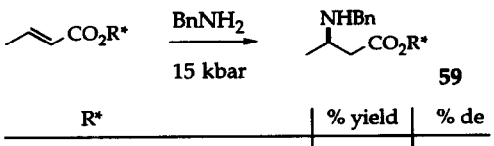
Scheme 5.3

Yamada reported the stereoselective Michael addition of benzylamine to the chiral α,β-unsaturated ester **54**, which was derived from D-glyceraldehyde acetonide **53** (**Scheme 5.4**).[37] Both the *(Z)*- and the *(E)*-isomers of **54** afforded exclusively the (3*R*)-benzylamino ester **55** on reaction with benzylamine. In order to confirm the stereochemistry of **55**, it was converted into β-lactam **58**, an intermediate in the synthesis of (+)-thienamycin. Thus, protection of the amine group in **55**, removal of the acetonide, and diol cleavage gave the aldehyde **56**. Wittig reaction and hydrolysis gave the homologated aldehyde, which was oxidized to the acid **57**. Deprotection of the amine and cyclization gave the β-lactam **58**.



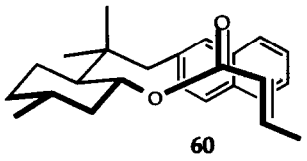
Scheme 5.4

The Michael additions of amines to acrylate derivatives under thermal activation conditions has not always proved to be efficient for the preparation of chiral β-amino acids. An alternative method, reported by d'Angelo et al., involves the high pressure addition of benzylamine to a variety of crotonates derived from the chiral alcohols *l*-menthol, 8-phenylmenthol, 8-(*p*-*t*-butylphenyl)-menthol, 8-(*p*-phenoxyphenyl)-menthol, and 8-(β-naphthyl)-menthol (**Scheme 5.5**).[38] Although the reactions were sluggish under thermal conditions, the use of high pressure (5-15 kbar) produced the addition products **59** in good yields (generally 60-90%). Of the substituted menthyl crotonates listed above, only the latter two, namely 8-(*p*-phenoxyphenyl)-menthyl crotonate and 8-(β-naphthyl)-menthyl crotonate, proved to be effective at controlling the stereochemistry of the addition. The stereochemical outcomes of these additions agree with the "π-stacking " model proposed by Oppolzer in which the aryl group in **60** shields one face of the crotonyl unit, thus directing addition from the other side.[39]



59

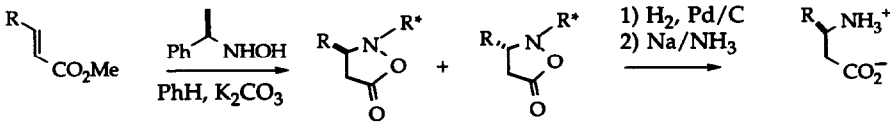
R*	% yield	% de
8-(β-naphthyl)-menthyl	50	>99
8-(*p*-phenoxyphenyl)-menthyl	90	95



60

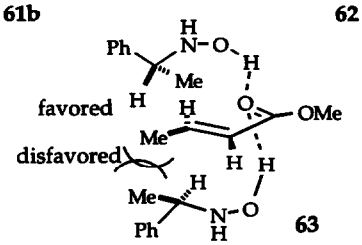
Scheme 5.5

The addition of hydroxylamines to acrylate esters is shown in **Scheme 5.6**.[40] The oxalate salt of (*R*)-phenethylhydroxylamine underwent a 1,4-addition to give the diastereomeric 3-oxazolidinones **61a**, and **b** in good yields, except for the reaction with cis-methyl crotonate (entry 2). The diastereoselectivity for the reaction was generally good (4 : 1 ratio, or better), except for methyl cinnamate (entry 5). Hydrogenolysis of the labile *N-O* bond in **61**, followed by removal of the α-methylbenzyl group by treatment with sodium in ammonia gave the β-amino acid **62**. The origin of the diastereoselectivity is not fully understood; however, it is assumed that the hydroxylamine hydroxyl group plays an important role by hydrogen bonding to the ester carbonyl. Thus, as transition state **63** indicates, attack can occur from either side of the acrylate double bond, but attack from the top face minimizes the steric interactions between the acrylate β-alkyl group and the methyl group of the hydroxyl amine.



61a 61b 62

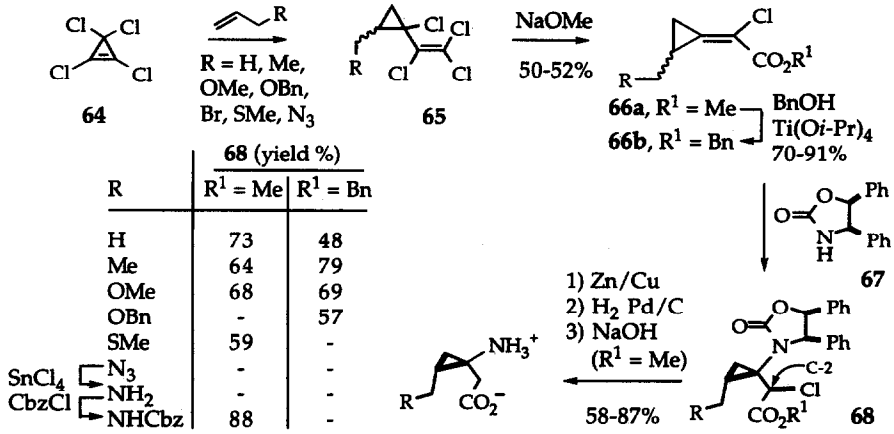
entry	R	yield (%)	61a : 61b
1	Me	91	80:20
2	Me(cis)	22	86:14
3	*n*-Pr	80	82:18
4	*i*-Pr	74	80:20
5	Ph	54	69:31
6	CH_2CH_2OMOM	80	80:20



63

Scheme 5.6

Thermal ring opening of tetrachlorocyclopropene **64** with various alkenes yielded the cyclopropylolefins **65**, which, on treatment with sodium methoxide in methanol afforded 2-chloro-2-cyclopropylideneacetates **66a** with a variety of substituents at the 2' position (**Scheme 5.7**).[41] The methyl esters **66a** were converted to benzyl esters **66b** by treatment with titanium(IV) isopropoxide in benzyl alcohol. These β-cyclopropyl unsaturated esters **66** have been found to be very reactive Michael acceptors. Thus, addition of optically active (4*R*, 5*S*)-4,5-diphenyloxazolidin-2-one **67** to different racemic 2-chloro-2-cyclopropylideneacetates **66** gave the 1,4-adducts **68** with excellent trans-selectivity with respect to the cyclopropane ring, and also good selectivity at the other newly formed stereocenter, C-2. The two major diastereomers can be separated by chromatography, allowing for the resolution of the racemic starting material. Reductive dehalogenation followed by catalytic hydrogenation gave the free amino acids from the benzyl esters, while the methyl esters required a further saponification step. **Scheme 5.7** shows the yields of the Michael addition as the sum of both diastereomers arising from the racemic starting material.

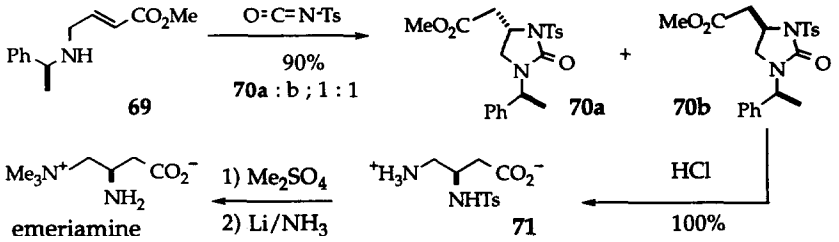


R	68 (yield %) R^1 = Me	R^1 = Bn
H	73	48
Me	64	79
OMe	68	69
OBn	-	57
SMe	59	-
N_3	-	-
NH_2	-	-
NHCbz	88	-

Scheme 5.7

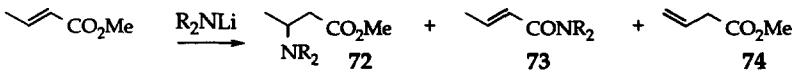
The reaction of the chiral allylamine **69** with *p*-toluenesulfonylisocyanate gave the urea derivative, which cyclized immediately via a Michael addition reaction to afford an equimolar mixture of imidazolidin-2-ones **70** in 90% overall yield (**Scheme 5.8**).[42] These imidazolidinones **70** could be separated by a

combination of crystallization and flash chromatography. Hydrolysis of **70b** gave 3-tosylamido-4-amino acid **71**, which was methylated and deprotected to give the β,γ-diamino acid emeriamine, a potent inhibitor of long chain fatty acid oxidation.



Scheme 5.8

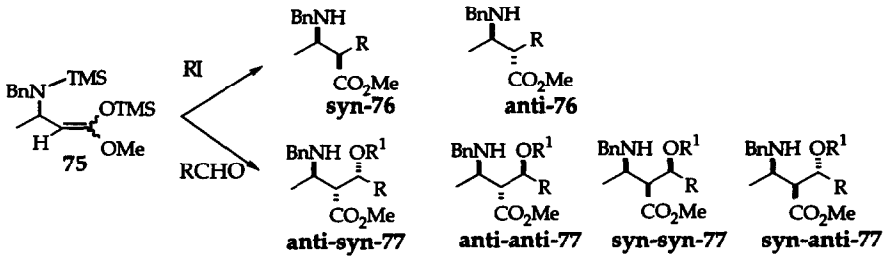
Nucleophilic addition of lithium amides to α,β-unsaturated esters has been the subject of a number of reports by Yamamoto and coworkers (**Scheme 5.9**).[43] Methyl crotonate was reacted with a variety of lithium amides, including lithium diisopropylamide (*i*-Pr_2NLi), lithium *N*-benzyltrimethylsilylamide (Bn(TMS)NLi), lithium benzylamide (BnNHLi), lithium dibenzylamide (Bn_2NLi), and lithium hexamethyldisilazide ((TMS_2)NLi) to produce compounds **72** - **74** in varying amounts. Lithium N-benzyltrimethylsilylamide was shown to be the reagent of choice for such conjugate additions, and gave the β-amino ester **72** in 88% yield.



Scheme 5.9

After the conjugate addition of lithium *N*-benzyltrimethylsilylamide to methyl crotonate, the anion could be trapped with chlorotrimethylsilane to yield the *O*-silylketene acetal having *(Z)*-geometry (**Z-75**) (>99 : 1 / *Z* : *E*) (**Scheme 5.10**). Alternatively, protonation to give the β-aminobutanoate ester and subsequent deprotonation by LDA followed by trapping with chlorotrimethylsilane gave the *(E)*-silyl acetal (**E-75**) (98 : 2 / *E* : *Z*). Since both geometric isomers were available, their reaction with various electrophiles, including alkyl halides and aldehydes, were examined.[43c] The results of these reactions are shown in **Scheme 5.10**. The alkylations with primary iodides proceeded in high yields. Essentially no selectivity was observed with the *(Z)*-enolates (entries 1& 2), while the *(E)*-enolates (**E-75**)

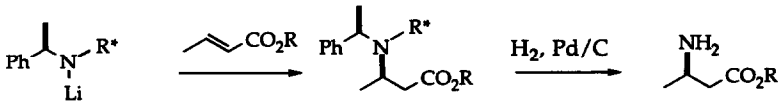
produced moderate to good selectivity in favor of the syn-product (**syn-76**, entries 3 & 4). Reaction of these enolates with benzaldehyde and acetaldehyde was followed by quenching with water or acetyl chloride to yield **77**. The *(Z)*-enolate gave the anti-syn-product (**anti-syn-77**) predominantly (entries 5 & 6), whereas the *(E)*-enolate produced the syn-anti-isomer (**syn-anti-77**) preferentially (entries 7 & 8).



entry	75	electrophile	yield (%)	76 syn : anti	77 anti-syn : anti-anti : syn-syn : syn-anti
1	*Z*	MeI	88	47 : 53	- : - : - : -
2	*Z*	*n*-$C_8H_{17}I$	81	59 : 41	- : - : - : -
3	*E*	MeI	68	69 : 31	- : - : - : -
4	*E*	*n*-$C_8H_{17}I$	60	90 : 10	- : - : - : -
5	*Z*	PhCHO	72	- : -	64 : 11 : 22 : 3
6	*Z*	MeCHO	73	- : -	82 : 0 : 18 : 0
7	*E*	PhCHO	64	- : -	6 : 1 : 13 : 80
8	*E*	MeCHO	39	- : -	0 : 10 : 0 : 90

Scheme 5.10

Addition of the lithium anion of *(R)*-phenethylamine **78a** (R* = H) to acrylate derivatives was unsatisfactory as shown in **Scheme 5.11** (entry 1).[44] However, the lithium amide derivatives of chiral secondary amines **78b - d** (R* ≠ H) added to crotonate esters to afford Michael adducts **79** with excellent diastereoselectivity. The yields were generally high for **78b** and **78c**, and they tended to be lower with the C_2-symmetrical amide **78d** [R* = *(R)*-PhMeCH]. Debenzylation of the amine group afforded the β-amino butanoate esters **83**.

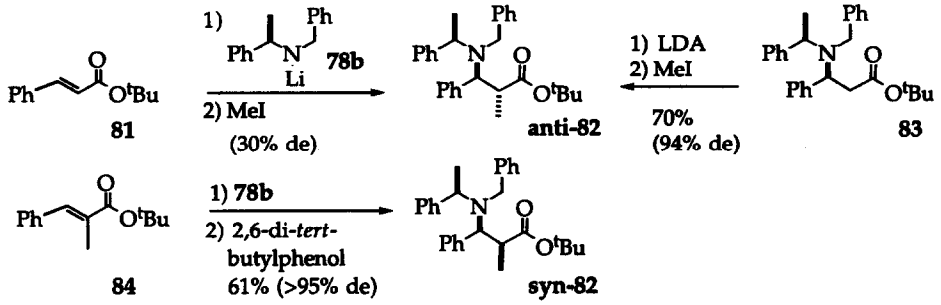


78 79 80

entry	R	78	R* =	yield (%)	de (%)
1	Me	a	H	28	0
2	"	b	$PhCH_2$	85	95
3	"	c	3,4-$(MeO)_2C_6H_3CH_2$	68	95
4	"	d	(*R*)-PhMeCH	57	>99
5	Bn	b	$PhCH_2$	88	95
6	"	c	3,4-$(MeO)_2C_6H_3CH_2$	74	96
7	"	d	(*R*)-PhMeCH	23	98
8	*t*-Bu	b	$PhCH_2$	82	>99
9	"	c	3,4-$(MeO)_2C_6H_3CH_2$	83	>99
10	"	d	(*R*)-PhMeCH	27	>99

Scheme 5.11

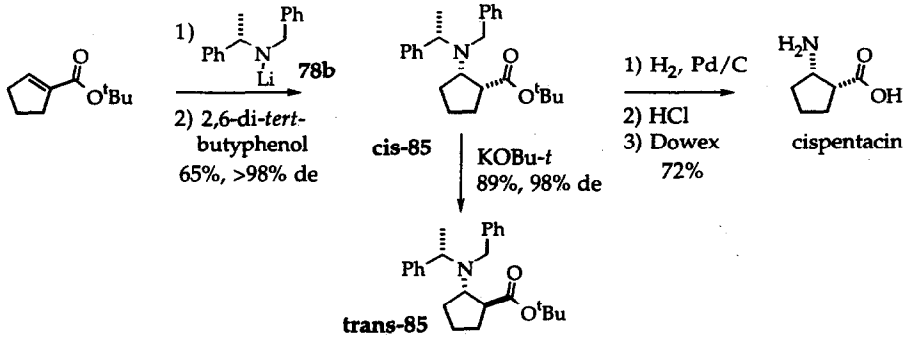
Recently, Davies et al. have reported the extension of this technology to the synthesis of homochiral α-methyl-β-amino acids (**Scheme 5.12**).[45] Michael addition of the chiral lithium amide **78b** to *tert*-butyl cinnamate **81**, followed by trapping of the intermediate enolate with methyl iodide afforded the product **anti-82** with low selectivity at the α-carbon (30% de). However, compound **83**, obtained from **81** in 92% yield and 95% de, could be deprotonated and methylated to give **anti-82** with high selectivity (94% de). The difference between the tandem and sequential selectivities may be governed by the enolate geometry.



Scheme 5.12

Reaction of the lithium amide **78b** with (*E*)-*tert*-butyl 2-methylcinnamate **84**, followed by protonation with the hindered acid, 2,6-di-*tert*-butylphenol, afforded **syn-82** with the opposite chirality at the α-center.

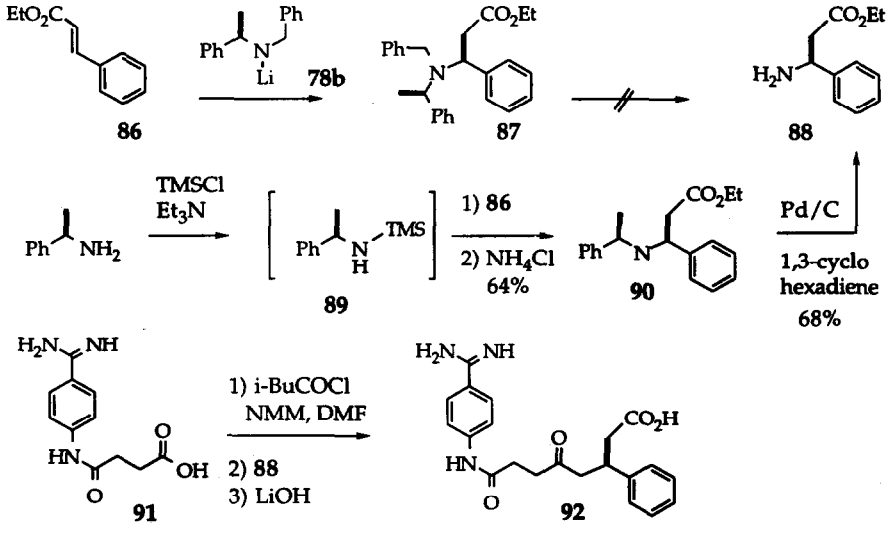
An application of this technology was reported in the asymmetric synthesis of the naturally occurring antifungal agent, cispentacin (**Scheme 5.13**).[46] Michael addition of the chiral lithium amide **78b** to *tert*-butyl 1-cyclopentene-1-carboxylate afforded the cis-2-aminocyclopentane-1-carboxylate ester **cis-85**. Debenzylation and hydrolysis of the addition product gave the natural product, cispentacin. Alternatively, epimerization at the α-center provided access to the trans-2-aminocyclopentane-1-carboxylic acid **trans-85**. An analogous set of reactions was described with the *tert*-butyl 1-cyclohexene-1-carboxylate to prepare cis- and trans-2-aminocyclohexane-1-carboxylic acids.



Scheme 5.13

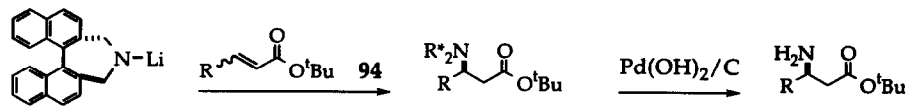
Bovy et al. also hoped to use a Michael addition of the chiral lithium amide **78b** to prepare the β-amino acid portion of the fibrinogen receptor antagonist **92** (**Scheme 5.14**).[47] Excellent selectivity was obtained in the addition reaction to ethyl trans-3-pyridineacrylate **86**, but the product **87** was resistant to debenzylation under hydrogenation conditions, perhaps due to catalytic poisoning by the pyridine moiety. However, when *N*-(trimethylsilyl)-(*R*)-1-phenylethylamine **89**, prepared *in situ*, was deprotonated with butyllithium the lithium amide generated also underwent a highly stereoselective addition to the acrylate derivative. Loss of the TMS group occurred on workup to give **90** and the benzyl group was cleanly removed by catalytic transfer hydrogenation to give the β-amino ester **88**. Coupling

with 4-[[4-(aminoiminomethyl)phenyl]-amino]-4-oxobutanoic acid **91** followed by ester group hydrolysis gave **92**.



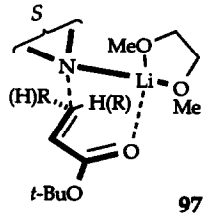
Scheme 5.14

Hawkins et al.[48] have reported some very similar results to those of Davies (see **Scheme 5.11 - 5.13**) using the lithium anion ***S*-93**, of (*S*)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine (**Scheme 5.15**). In order to obtain the optimum conditions, a variety of esters, including methyl, *iso*-propyl, and *tert*-butyl were examined. The effect of using different solvents with additives, such as HMPA, TMEDA, and 12-crown-4 was also studied. It was found that the addition of the anion ***S*-93** to the *tert*-butyl ester **94** in DME gave the optimum results. Generally, the addition occurred in good yields and with excellent diastereoselectivity. The reversal of stereochemistry in the additions to the *(E)*- and *(Z)*-esters (see entries 2 & 3) is consistent with the cyclic transition state **97**, where the chiral amine determines the face of approach and the position of R and H determine the configuration at the β-center.



(R*$_2$N-Li) *S*-**93** **95** **96**

entry	**94** R =	diastereomer ratio (yield %) of **95**	% ee (yield %) configuration of **96**
1	**a** (*E*)-Me	66:1 (83)	>95 (68) *R*
2	**b** (*E*)-Hept	53:1 (80)	96 (80)
3	**c** (*Z*)-Hept	1:8 (39)	-
4	**d** (*E*)-*i*-Bu	69:1 (74)	97 (80)
5	**e** (*E*)-*i*-Pr	34:1 (69)	>99 (57) *S*
6	**f** (*E*)-TBSO	43:1 (86)	>99 (81) *R*
7	**g** (*E*)-TBSO	150:1 (66)^	>99 (78) 3*R*, 4*R*
8		9.4:1 (49)	94 (66) 3*S*, 4*R*

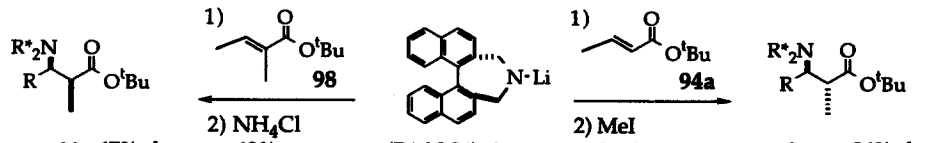


97

^ Reaction with ***R*-93**

Scheme 5.15

This chemistry has also been extended to the asymmetric synthesis of α-methyl-β-amino acids (**Scheme 5.16**).[49] Both C-α epimers of **99** could be obtained, i.e. addition of the chiral lithium amide *S*-**93** to *tert*-butyl tiglate **98**, followed by quenching with a proton source, afforded **syn-99**, whereas, if *tert*-butyl crotonate **94a** was used and the enolate trapped with methyl iodide, then **anti-99** was obtained.

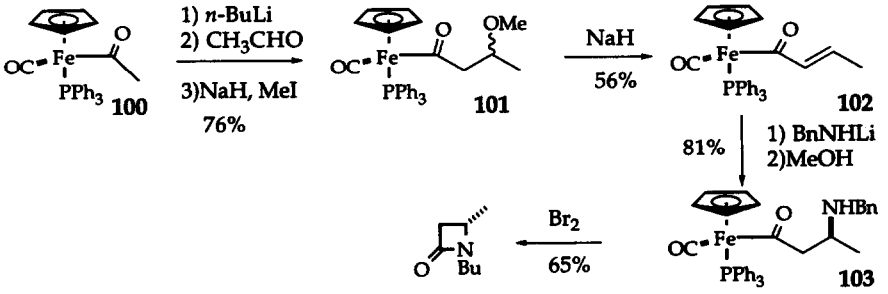


syn-99 67% de (R*$_2$N-Li) *S*-**93** **anti-99** 86% de

Scheme 5.16

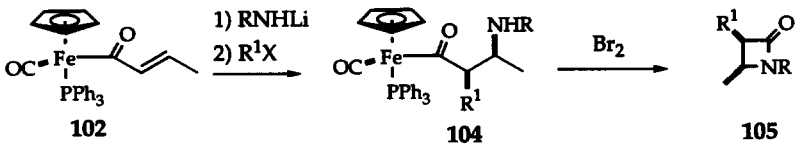
A limited number of examples of asymmetric synthesis of β-amino acids by 1,4-addition of achiral amine anions to chiral α,β-unsaturated acid derivatives have been reported. For example, Davies described a diastereoselective Michael addition of lithium benzylamide to crotonyl derivatives of the chiral auxiliary [(η^5-C_5H_5)Fe(CO)(PPh_3)] (**Scheme 5.17**).[50] The optically pure (*S*)-(+)-acetyl iron complex **100** was successively treated with base, acetaldehyde, and methyl iodide to give a 1 : 1 mixture of β-methoxy complexes **101**. Treatment with base caused an elimination reaction giving the (*E*)-crotonyl complex **102**. Conjugate addition of the lithium

amide followed by methanol quenching gave a single diastereomeric β-amino acetyl complex **103**. Oxidative decomplexation and cyclization with bromine then afforded the (4*S*)-β-lactam.



Scheme 5.17

Alternatively, the anion generated by Michael addition of lithium amide to the acryloyl complex **102** could be trapped with alkyl halides to give the 3-amino-2-alkyl complexes **104** in excellent diastereomeric excess (**Scheme 5.18**).[51] Oxidative cleavage of the iron carbonyl bond liberated the β-lactams **105**.

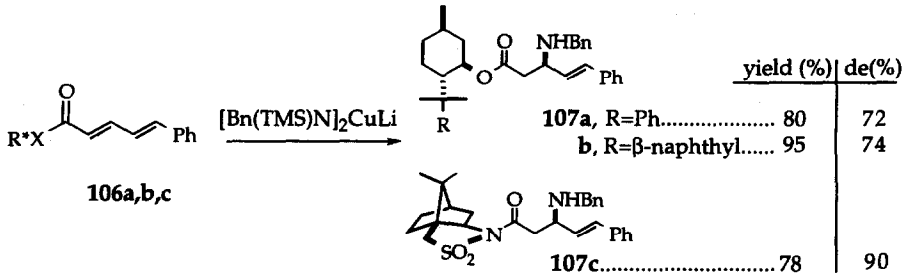


RNH	R^1X	de (%)	**104** (yield %)	**105** (yield %)
BnNH	MeI	98	95	78
"	EtI	97.6	99	80
"	BnBr	96.8	99	63
"		98	92	22
n-PrNH	MeI	95	53	-

Scheme 5.18

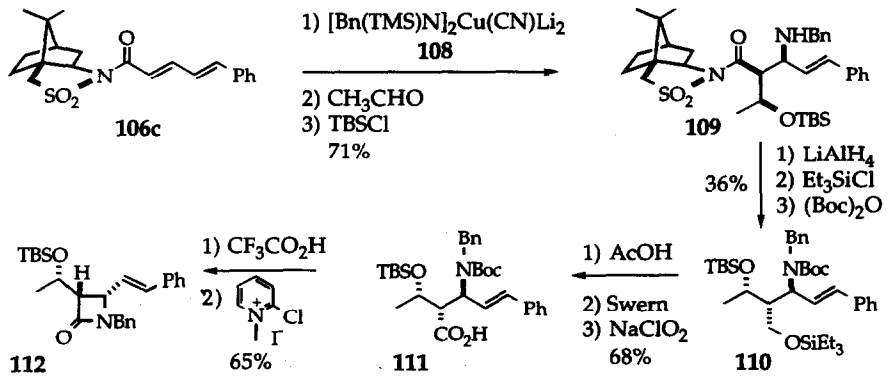
Diaminocuprates, $(R_2N)_2CuLi$, and higher order cyanodiaminocuprates, $(R_2N)_2Cu(CN)Li_2$, are the reagents of choice for 1,4-additions to α,β,γ,δ-dienoate esters **106** (**Scheme 5.19**).[52] Conjugate addition of benzyltrimethylsilyl aminocuprate to the chiral 5-phenyl-2,4-pentadienoate esters derived from (-)-8-phenylmenthol

(**106a**), 8-(β-naphthyl)menthol (**106b**), and (-)-bornanesultam (**106c**) proceeded in high yields and excellent diastereoselectivities. The TMS group was removed during the workup to give the 1,4-adducts **107a-c**.



Scheme 5.19

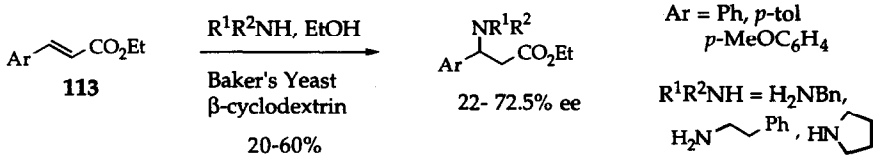
Reaction of the aminocuprate reagent **108** with the (-)-bornanesultam dienoate **106c**, followed by stereoselective trapping with acetaldehyde, and subsequent protection of the hydroxyl group gave the silyl ether **109** as a single diastereomer (**Scheme 5.20**).[52] Thus, the configurations of three contiguous asymmetric centers were set in a single three component coupling process. Removal of the bornanesultam group by lithium aluminum hydride reduction followed by protection of the alcohol and amine groups gave the fully protected β-amino alcohol **110**. Selective deprotection of the primary alcohol and oxidation produced the acid **111**.



Scheme 5.20

Removal of the *tert*-butoxycarbonyl group and cyclization under standard conditions[2b] gave the β-lactam **112**, whose stereochemistry can be converted to that of the natural β-lactam antibiotics through known technology.[18a]

Another method for controlling the stereochemistry of the new chiral center generated in these Michael additions is to carry out the reaction in a chiral medium.[53] One application of this technology is indicated in **Scheme 5.21**. Thus, an ethanol solution of the α,β-unsaturated ester **113** was added to aqueous β-cyclodextrin to form an inclusion complex and fix the geometry of the ester. This solution was then added to a buffered solution of the amine and Baker's yeast. Moderate yields (generally 20-60%) were obtained, and the enantiomeric excess varied from 22% up to 72.5%. The reactions did not take place in the absence of Baker's yeast, and the enantiomeric excesses were lower in the absence of β-cyclodextrin.



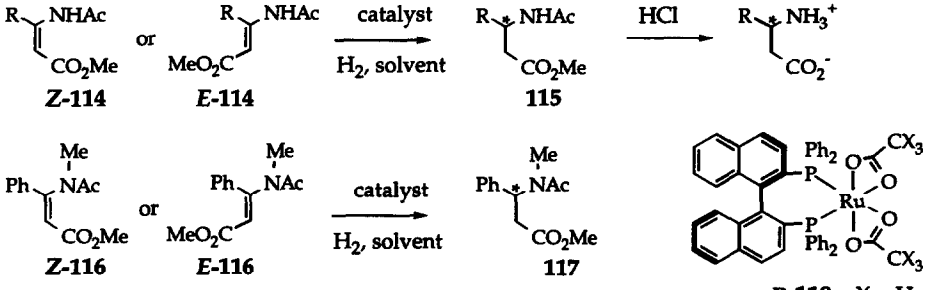
Scheme 5.21

6. Hydrogenation of 3-amino acrylates and derivatives

An alternative method for synthesizing β-amino acid derivatives is by the hydrogenation of 3-amino acrylate derivatives. The stereochemistry of the hydrogenation and hence, the new chiral center, can be controlled by use of either a chiral catalyst or a chiral functionality within the acrylate molecule.

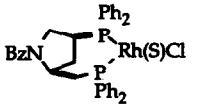
Noyori et al.[54] used BINAP-ruthenium(II) complexes [*R*-**118**] [BINAP = 2,2'-bis(diarylphosphino)-1,1'-binaphthyl] as chiral catalysts for the enantioselective hydrogenation of enamine substrates (**Scheme 6.1**). Acylation of β-amino-α,β-unsaturated methyl esters with acetic anhydride in pyridine provided a mixture of *E* and *(Z)*-enamide esters **114**, which could be separated by chromatography. Alkylation of either ***E***- or ***Z***-**114** with methyl iodide gave the corresponding *(E)-N*-methylenamido esters ***E***-**116**, which could be isomerized photochemically to give the *(Z)-N*-methylenamido esters ***Z***-**116**.

Hydrogenation of a methanol solution of ***Z*-114a** containing 0.5% ***R*-118a** gave the reduced material in only 5% enantiomeric excess (entry 1). However, hydrogenation of the *(E)*-isomer ***E*-114a** with the same catalyst resulted in product formation in 96% enantiomeric excess (entry 2). Slightly lower enantiomeric excesses were obtained at increased hydrogen pressures. The *(Z)*-isomer is more reactive, and hydrogenation of a 1 : 1 mixture of these isomers resulted in selective consumption of that isomer. Hydrogenation of ***E*-114b** under catalysis of ***R*-118a** required 120 hours for completion and provided ***S*-115b** in 87% enantiomeric excess. Use of $Ru(OCOCF_3)_2$[*(R)*-BINAP], ***R*-118b** as catalyst gave ***S*-115b** in 90% enantiomeric excess in 18 hours (entry 3). Reaction of ***E*-114c** under similar conditions with ***R*-118b** required a long period for conversion, during which time the β-amino group was lost and the product was obtained in 25% yield (entry 4). However, hydrogenation of the corresponding *N*-methyl β-acetamidocinnamates ***Z*- and *E*-116** proceeded smoothly with catalyst ***R*-118a** to give **117** with *(R)*-configuration in good enantiomeric excess, 60% and 84%, respectively (entries 5 & 6).



***R*-118a**, X = H
***R*-118b**, X = F

entry	substrate	catalyst	solvent	yield(%)	configuration of 115 or 117 (ee %)
1	***Z*-114a**; R = Me	***R*-118a**	MeOH	quant.	R (5)
2	***E*-114a**; R = Me	***R*-118a**	"	quant.	S (96)
3	***E*-114b**; R = *i*-Bu	***R*-118b**	"	quant.	S (90)
4	***E*-114c**; R = Ph	***R*-118b**	"	25	R (90)
5	***E*-116c**	***R*-118a**	"	quant.	R (60)
6	***Z*-116c**	***R*-118a**	"	97	R (84)
7	***Z*-114c**; R = Ph	**119**	Benzene	91	R (53)
8	***Z*-114a**; R = Me	**119**	MeOH	100	S (55)

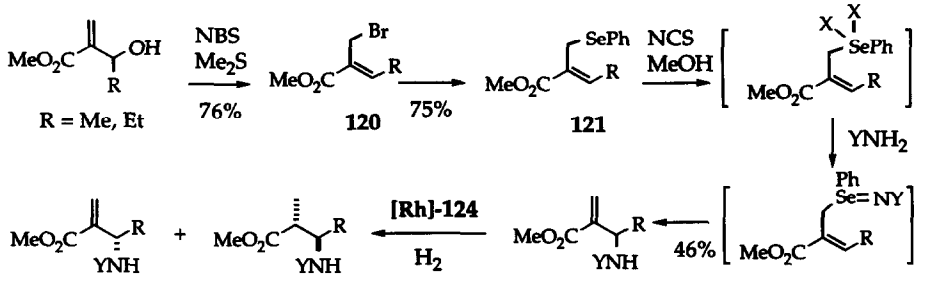


119

Scheme 6.1

Achiwa and Soga[55] have also described the hydrogenation of β-acetylamino acrylic acid derivatives using the biphosphine rhodium complex **119** as the chiral catalyst (**Scheme 6.1**, entry 7 & 8). Generally, a high rate of conversion was obtained; however, the enantiomeric excesses were lower than those obtained by Noyori.[54]

Brown and coworkers used a catalytic hydrogenation of the allylic carbamate **123** to effect a kinetic resolution (**Scheme 6.2**).[56] Treatment of the starting allylic alcohols with *N*-bromosuccinimide led to the allylic bromides **120**, which were converted to the corresponding selenides **121**. Treatment of these selenides with *N*-chlorosuccinimide gave a selenium(IV) species that was trapped by the amine to produce a selenoimine intermediate **122**. This underwent a [2,3]-sigmatropic rearrangement to the allylic carbamate **123**. Hydrogenation of **123** under catalysis by the chiral rhodium complex of the ligand **124** proceeded rapidly but then slowed after consumption of 55-60% of the theoretical amount of hydrogen. Stopping the reaction at this point resulted in the recovery of starting material of high optical purity.



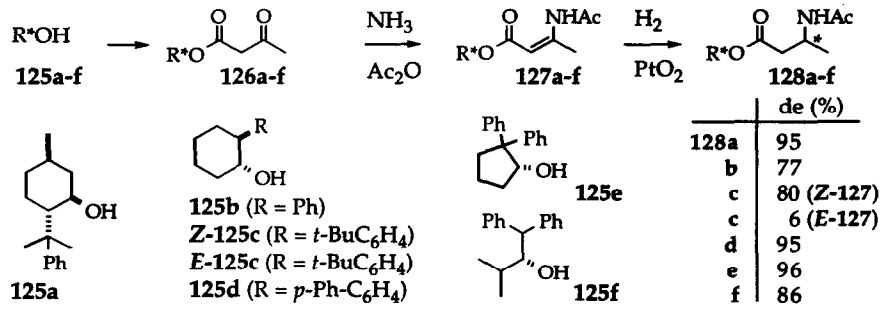
	time (min)	reaction (%)	ee* (%)
123a	60	56	87
b	90	60	98
c	50	58	96

* ee's are for recovered starting material

Scheme 6.2

Catalytic hydrogenation of chiral β-acetamidocrotonate esters **127** with an achiral catalyst has also been used to produce β-amino acids in optically active form (**Scheme 6.3**).[57] The chiral alcohols **125a-f** were transformed into acetoacetates **126**, which were then sequentially treated with ammonia and acetic anhydride to yield

the (*Z*)-β-acetamidocrotonates **127** in all cases, except the trans-2-(*p-tert*-butylphenyl)-cyclohexanol derivative **125c**, which gave a separable mixture of (*E*)- and (*Z*)-isomers. Hydrogenation over platinum oxide at 3-5 bar of hydrogen gave the β-acetamidobutyrates **128**. The authors were hoping to replace the "standard" chiral auxiliary developed by Corey, (-)-8-phenylmenthol **125a**, with a simplified substitute. A substantial decrease in the selectivity of the hydrogenation was observed with derivatives of trans-2-phenyl-cyclohexanol **125b** and trans-2-(*p-tert*-butyl-phenyl)cyclohexanol **125c**. An excellent diastereomeric excess was observed when the ester of trans-2-(4-biphenyl)cyclohexanol **125d** was used. However, the hydrogenated material was contaminated with byproducts from further hydrogenation of the biphenyl moiety. The 2,2-diphenylcyclopentanol **125e** proved to be a highly effective auxiliary, whereas the open chain version, 1,1-diphenyl-3-methyl-2-butanol **125f**, gave slightly lower diastereomeric excesses.

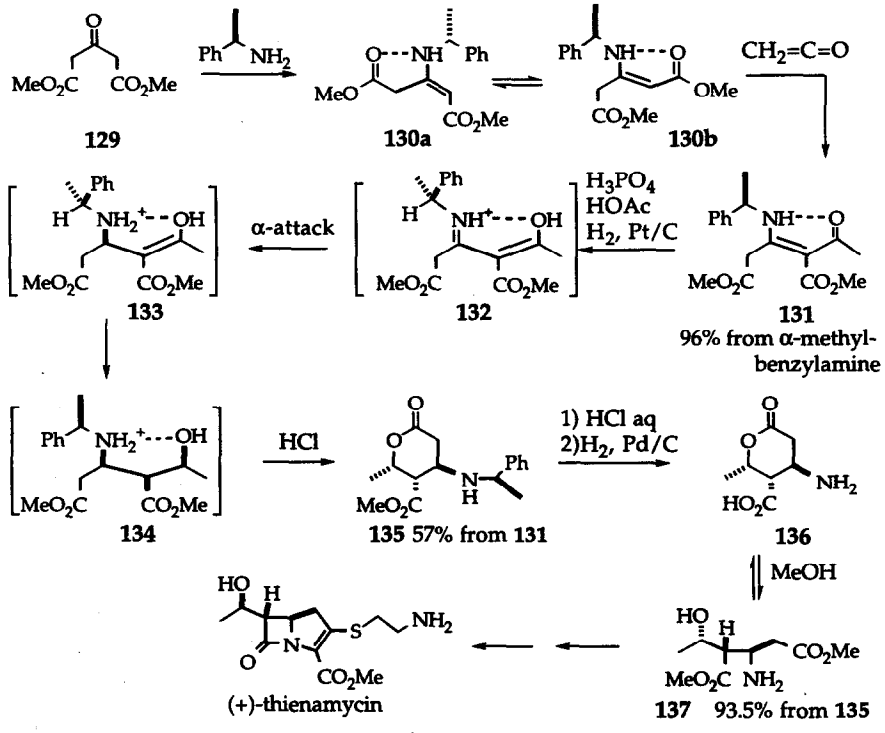


	de (%)
128a	95
b	77
c	80 (*Z*-127)
c	6 (*E*-127)
d	95
e	96
f	86

Scheme 6.3

Melillo et al. described a novel approach to the chiral amino ester **137**, an intermediate used in the synthesis of (+)-thienamycin (**Scheme 6.4**).[58] The key reaction involves the reduction of enamino ketone **131** and sets three consecutive chiral centers. Condensation of (*R*)-(+)-phenethylamine with dimethylacetone dicarboxylate **129** gave an equilibrium mixture of enamines **130a and b**, which upon acylation with ketene gas gave **131** in 96% overall yield from phenethylamine. Enamine **131** was found to be inert to hydrogenation in neutral or basic solvents, however, hydrogenation in a mixture of phosphoric and acetic acids gave the desired lactone **135**. A plausible mechanism for this reduction was proposed to involve initial protonation to form the iminium species **132**. In the conformation drawn, which maximizes hydrogen bonding and minimizes steric interactions,

rotation of the benzylic *C-N* bond is restricted; thus, the large phenyl group blocks the β-face, and the predominant mode of attack of the catalysts is from the α-face of **132**. Subsequent hydrogenolysis of the highly reactive enol intermediate **133**, also from the α-face, gave the all syn-product **134**. This reaction must occur very rapidly before any desorption and re-adsorption can occur. Lactonization of the intermediate **134** gave the product **135**. Hydrolysis of the ester and hydrogenolysis of the benzyl group gave the desired acid **136**, which was converted to the key intermediate **137** by treatment with methanol.

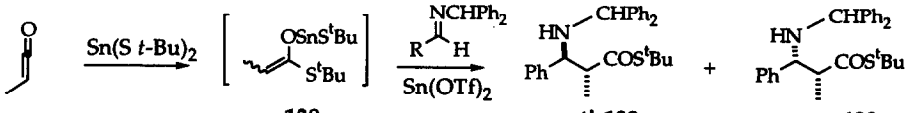


Scheme 6.4

7. Nucleophilic addition to *C-N* double bond equivalents

β-Substituted β-amino acids have been synthesized by nucleophilic 1,2-additions of organometallic reagents or enolates to imines and imine equivalents.

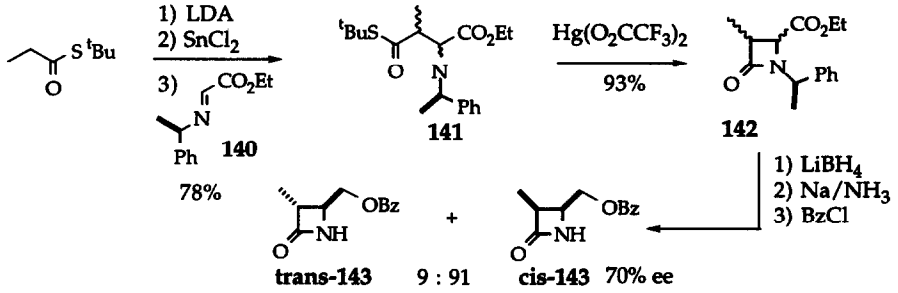
Mukaiyama has found that tin(II) carboxylic thioester enolates **138**, formed *in situ* from stannous *tert*-butylthiolate and methylketene, react with imines in the presence of stannous triflate (**Scheme 7.1**).[59] The resulting β-aminocarboxylic thioesters **139** are formed in good yield with high stereoselectivity in favor of the anti-product.



R	yield(%)	anti : syn
Ph	89	96 : 4
PhCH=CH	60	81 : 19
i-Pr	83	92 : 8
$Ph(CH_2)_2$	65	92 : 8
$(CH_2)_2OBn$	60	88 : 12

Scheme 7.1

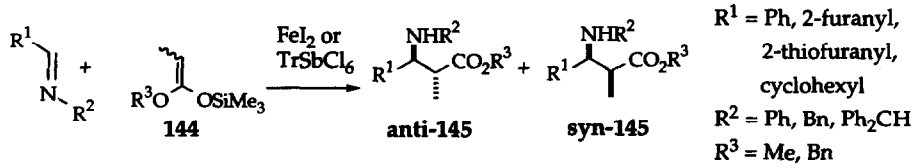
An asymmetric version of this reaction has also been reported by Mukaiyama (**Scheme 7.2**).[60] The tin(II) enolate was formed by metal exchange with the lithium enolate and reacted with the chiral imine **140**, derived from (*R*)-phenethylamine, to produce **141** as a mixture of diastereomers in 78% total yield.



Scheme 7.2

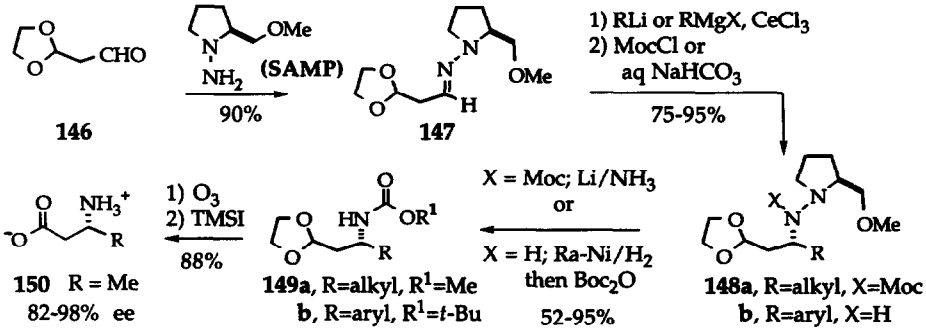
Cyclization with mercury trifluoroacetate gave a mixture of β-lactams **142**. Reduction of the ester, deprotection of the amine, and benzoylation of the alcohol gave the β-lactam **143** as a 91 : 9 mixture of cis- and trans-isomers. The major product **cis-143** was formed in 70% enantiomeric excess.

Mukaiyama has shown that the reaction of ketene silyl acetals **144** with imines can also be promoted with catalytic amount of metal halides (**Scheme 7.3**).[61] A large number of metal halides were screened, and iron(II) iodide and $TrSbCl_6$ were found to be the most successful in terms of yield and selectivity. Generally, the β-amino esters **145** were formed in <90% yield and at least 8 : 2 diastereomeric ratios in favor of the anti-product.



Scheme 7.3

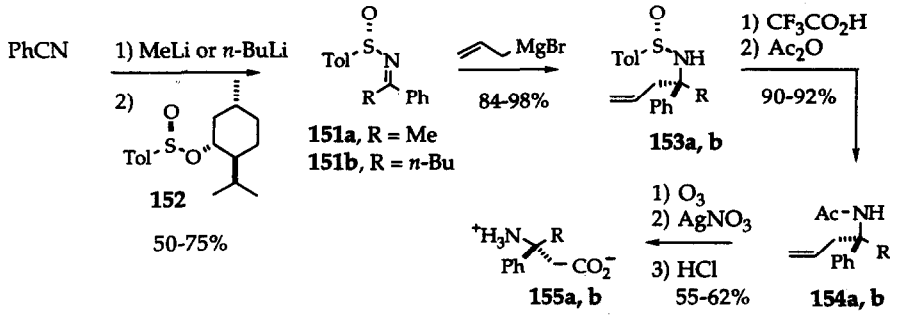
Enders et al.[62] recently described a synthesis of β-amino acids by nucleophilic 1,2-additions of organometallic reagents to 3,3-ethylenedioxypropanal-SAMP-hydrazone **147** [SAMP = (*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine] in the presence of ceric trichloride (**Scheme 7.4**). The reaction of aldehyde **146** with SAMP gave the (*S*)-hydrazone **147**. Addition of the organometallic reagents to the imine bond occurred to give **148** in good yields and with high diastereoselectivities.



Scheme 7.4

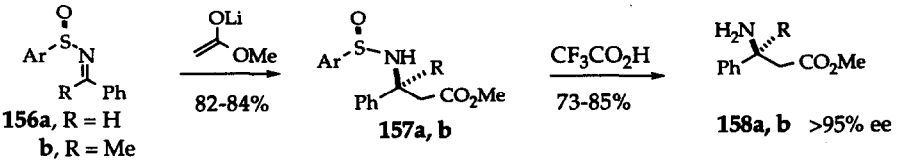
In the alkyl cases (R = Me, Et, *n*-Pr, *n*-Bu and allyl), the reaction was quenched with methyl chloroformate (MocCl). Subsequent *N-N* bond cleavage gave the methoxycarbonyl protected β-amino acetals **149a**. For the aryl substituted derivatives (R = Ph, *p*-tolyl and *p*-anisyl), the order of the reactions was reversed. The 1,2-addition reaction was quenched with aqueous sodium bicarbonate, and then the *N-N* bond cleavage was followed by protection of the free amino acetals as the *tert*-butoxycarbonyl derivatives **149b**. Ozonolysis of the acetal moiety of **149** (R = Me, R^1 = Me) afforded the hydroxyethyl ester derivative, which was converted to the free β-amino acid **150** with trimethylsilyl iodide. Replacement of SAMP with RAMP [(*R*)-(+)-1-amino-2-(methoxymethyl)pyrrolidine] led to the β-amino acids of opposite configuration.

Racemic *N*-alkylidenearenesulfinamides **151** were first prepared by Davis[63] and Burger,[64] and later in optically active form by Cinquini.[65] The synthesis of these reagents reported by Hua et al.[66] relied on the addition of alkyllithium reagents to benzonitrile, with subsequent trapping with (-)-*l*-menthyl-(*S*)-*p*-toluenesulfinate **152** (**Scheme 7.5**). The chiral sulfinamides **151a** and **151b** underwent stereoselective addition reactions with allylmagnesium bromide to yield **153a** in 98% yield as a single diastereomer, and **153b** in 84% yield along with 8% of a diastereomer, which could be separated by chromatography. Hydrolysis with trifluoroacetic acid liberated the free amines which were acylated with acetic anhydride to yield the products **154**. Ozonolysis and subsequent oxidation with silver nitrate and deacetylation with hydrochloric acid gave the free β-amino acids **155**.



Scheme 7.5

Davies et al.[67] have reported a highly diastereoselective 1,2-addition reaction of the lithium enolate of methyl acetate to the chiral sulfinimines **156** to yield the corresponding sulfinamides **157** (**Scheme 7.6**). The product **157a** was obtained as a 9 : 1 mixture of diastereomers which could be separated, while **157b** was formed as the sole product. Thus, enolization of the sulfinimine **156b** (R = Me) does not compete with enolate addition to the *C-N* double bond. Subsequent hydrolysis of the addition products **157** with trifluoroacetic acid liberated the free β-amino esters **158**.



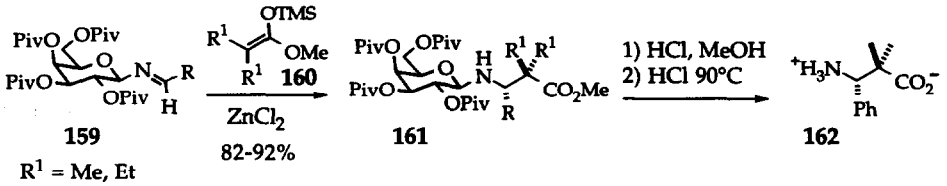
156a, R = H
b, R = Me

157a, b

158a, b >95% ee

Scheme 7.6

Kunz found that *N*-galactosylimines **159**, prepared by the reaction of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine with various aldehydes, underwent a stereoselective addition reaction with silyl ketene acetals **160** in the presence of zinc chloride (**Scheme 7.7**).[68] The products **161** were obtained in excellent yields and the diastereoselectivity was 70-250 : 1. To confirm the *(S)*-configuration of the major diastereomer, the phenyl derivative (R = Ph, R^1 = Me) was converted to the known β-amino acid **162**. Treatment with methanolic hydrochloric acid removed the carbohydrate chiral auxiliary (>90% recovered) to liberate the free amino ester, which was converted to the β-amino acid by treatment with hot aqueous hydrochloric acid.



159

161

162

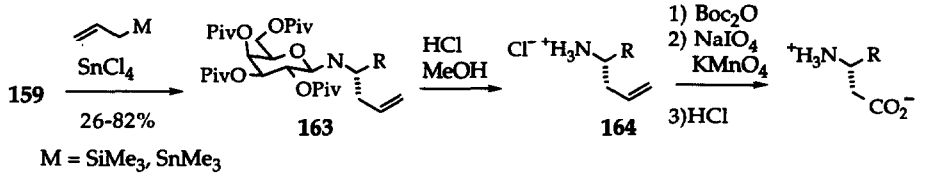
R^1 = Me, Et
R = Ph, *o*-ClC_6H_4, *m*-ClC_6H_4, *p*-FC_6H_4, 2-Naphthyl, *n*-Pr

Scheme 7.7

The Schiff bases **159**, derived from aromatic aldehydes (**Scheme 7.8**, R = *o*-, *m*-, *p*-ClC_6H_4, Ph, *o*-, *p*-$NO_2C_6H_4$, tol, 3-pyridyl, 2-naphthyl, *o*-$MeOC_6H_4$, PhCHCH, *p*-

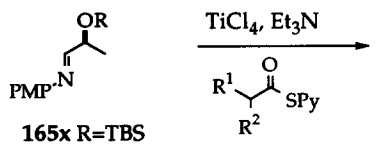
CNC_6H_4, *p*-$MeO_2CC_6H_4$, *p*-FC_6H_4), were found to react with allyltrimethylsilane or allyltrimethyltin in the presence of various Lewis acids to afford the chiral 4-amino-1-butenes **163**.[69] Reactions with allyltrimethylsilane required 2-6 days and the yields tended to be lower (28-82%), and although the more nucleophilic allyltrimethyltin reagent gave better yields, the diastereoselectivities decreased slightly. Thus, for example, reaction of **159** (R = p-ClC_6H_4) with allyltrimethylsilane and allyltrimethyltin under identical conditions, resulted in 49% versus 68% yield and 22 : 1 versus 10 : 1 asymmetric induction, respectively. Both tin tetrachloride and boron trifluoride etherate were effective as catalysts, however the diastereoselectivity was better with the former. After hydrolytic removal of the carbohydrate template, the homoallylamine hydrochloride **164** could be *N*-protected, oxidized, and deprotected to yield the β-aryl-β-amino acids.

Schiff bases **159** of aliphatic aldehydes failed to react with allyltrimethylsilane but did react with allyltrimethyltin (32% and 37% yield, 4 : 1 and 3.5 : 1 diastereoselectivity, for R = *n*-Pr and *n*-C_9H_{19}, respectively).



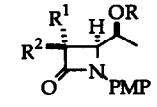
Scheme 7.8

Cinquini et al. have recently reported a highly diastereoselective synthesis of β-lactams by the addition of titanium enolates of 2-pyridyl thioesters **167** to the chiral imines **165** and **166** (**Scheme 7.9**).[70] The resulting β-amino ester intermediates cyclized under the reaction conditions to afford directly the β-lactam products **168** and **169**. The non-stereogenic thioesters **167a** and **b** were shown to add diastereoselectively to the imines **165** and **166** in moderate to good yield (entries 1-5). This reaction was then extended to the stereogenic thioesters **167c-e**, which were condensed with thioesters **165x** and **166** to give the β-lactams **168cx**, **168dx**, **168ex**, and **169e** (entries 6-9). In all cases, the stereoselectivity of the addition was found to be excellent, however the mode of addition was dependent on the stereoelectronic nature of the substituents, R^1 and R^2. For example, a large α-group (*i*-Pr in **167d**) favors trans-product formation **168dx** while the coordinating ligand (BnO in **167e**) gave the product with cis-geometry **168ex**.

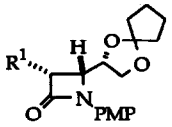


165x R=TBS
y R=Bn

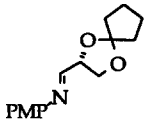
167a R^1=R^2=H
b R^1=R^2=Me
c R^1=Et, R^2=H
d R^1=*i*-Pr, R^2=H
e R^1=OBn, R^2=H



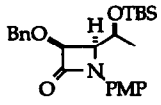
168ax R=TBS, R^1=R^2=H
bx R=TBS, R^1=R^2=Me
ay R=Bn, R^1=R^2=H
by R=Bn, R^1=R^2=Me
cx R=TBS, R^1=Et, R^2=H
dx R=TBS, R^1=*i*-Pr, R^2=H



169a R^1=H
169e R^1=OBn



166

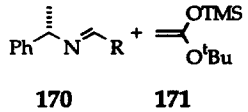


168ex

entry	imine	ester	product	yield (%)	de (%)
1	**165x**	**167a**	**168ax**	42	>99
2	"	**b**	**168bx**	66	96
3	**165y**	**a**	**168ay**	54	82
4	"	**b**	**168by**	80	>99
5	**166**	**a**	**169a**	52	>99
6	**165x**	**c**	**168cx**	50	70
7	"	**d**	**168dx**	70	>99
8	"	**e**	**168ex**	64	98
9	**166**	**e**	**169e**	82	>99

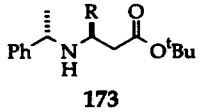
Scheme 7.9

Attempts to obtain stereoselective additions of enolates to chiral imines, derived from phenethylamine, have been only moderately successful (see **Scheme 7.2**). However, Yamamoto recently showed that a highly selective addition can be obtained with phenethylimines **170** by use of double stereodifferentiation techniques (**Scheme 7.10**).[71]

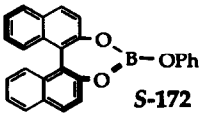


170 **171**

R- or *S*-**172**
50-60%



173



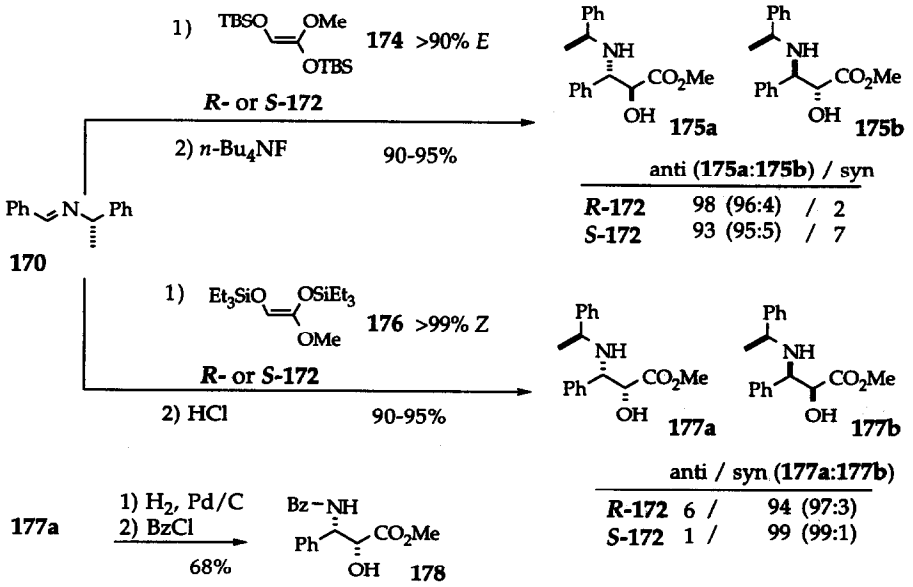
***S*-172**

R	de (%) *R*-172	de (%) *S*-172
Ph	92	74
n-Pr	94	86

Scheme 7.10

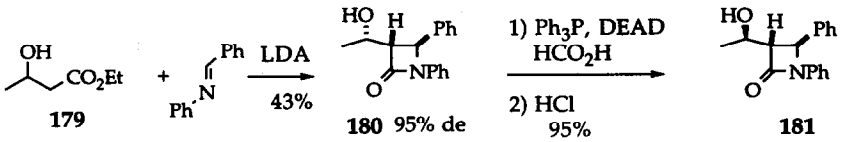
Thus, the chiral boron reagents **172**, derived from (*R*)- or (*S*)-binaphthol and triphenyl borate, promoted condensation of the imines **170** with the ketene acetal **171** to give **173** with good diastereoselectivity.

An application of this technology in the synthesis of the taxol side chain **178** is shown in **Scheme 7.11**.[71] The stereoselectivity of the addition reaction depends upon the geometry of the silyl ketene acetal, thus, the reaction of the (*E*)-ketene acetal **174** with the imine **170** in the presence of either ***R***- or ***S*-172** produced the anti-product **175a** with a high degree of selectivity. In contrast, the (*Z*)-acetal **176** gave the syn-product **177a** selectively with both borate catalysts. Compound **177a** was converted into the *N*-benzoyl-(2*R*, 3*S*)-phenylisoserine methyl ester **178** under standard conditions.



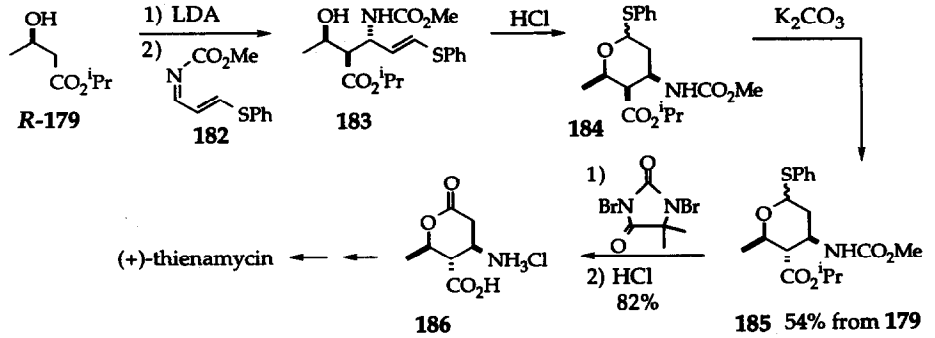
Scheme 7.11

Reaction of the dianion of racemic ethyl-3-hydroxybutyrate **179** with *N*-benzylidenaniline produced the β-lactam **180** in 95% selectivity in favor of the trans-product **180** (**Scheme 7.12**).[72] Inversion of the configuration of the alcohol under Mitsunobu conditions furnished **181** in which the three centers of (±)-thienamycin are set.



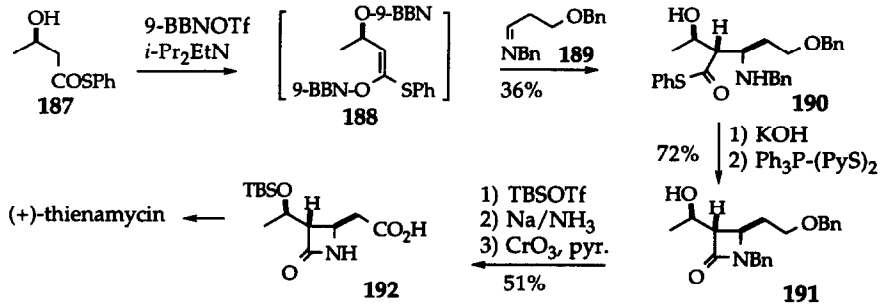
Scheme 7.12

Hatanaka et al.[73] used a similar reaction sequence to achieve a formal synthesis of (+)-thienamycin (**Scheme 7.13**). Addition of the chiral enolate, derived from (*R*)-(-)-*iso*-propyl 3-hydroxybutyrate ***R*-179**, to *N*-methoxycarbonyl (2-phenylthio)ethenylcarboxaldimine **182** afforded a 6 : 1 mixture favoring the syn-anti-product **183**. Cyclization under acidic conditions gave an epimeric mixture of cyclic hemithioacetals **184**. The desired stereochemistry of the ester functionality was obtained by epimerization to give **185** in 54% overall yield from the starting hydroxy ester. Reaction with 1,3-dibromo-5,5-dimethylhydantoin and hydrolysis afforded the lactone **186**.



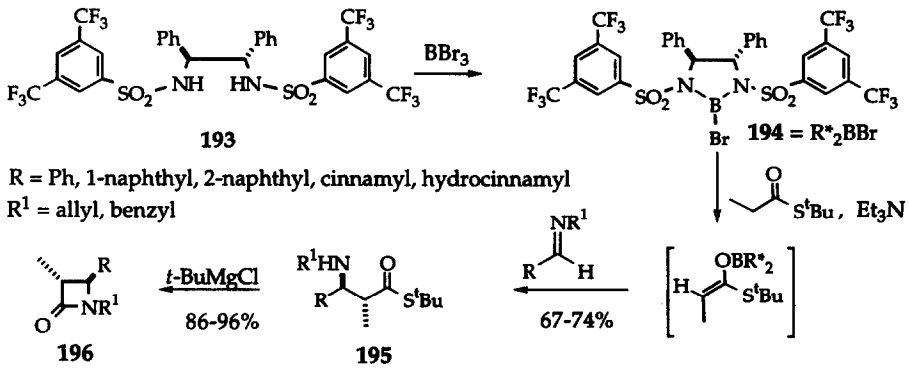
Scheme 7.13

Attempts to carry out addition reactions of the dianion of **179** to enolizable imines, for example, compound **189** in **Scheme 7.14**, were unsuccessful. However, if the corresponding phenylthioester **187** was first converted to the boron enolate **188**, then reaction with imine **189** occurred to produce the β-amino thioester **190**.[74] Hydrolysis of the thioester and cyclization gave the β-lactam **191**, which was converted to the (+)-thienamycin intermediate **192**.



Scheme 7.14

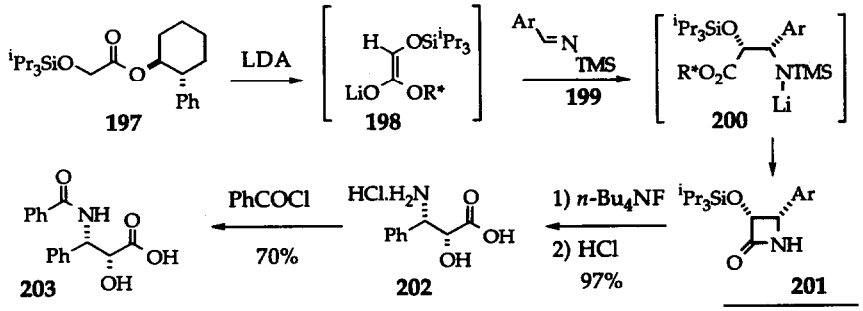
Corey's highly diastereoselective synthesis of β-amino thioesters is also based on the addition of boron enolates to imines (**Scheme 7.15**).[75] (*S, S*)-Diazaborolidine **194**, which was obtained from (-)-*bis*-3,5-di(trifluoromethyl)benzenesulfonamide **193** by treatment with boron tribromide, reacted with *tert*-butyl thiopropanoate in the presence of triethylamine to give the boron enolate, which was then reacted with various imines to produce β-amino thioesters **195** in at least 96% enantiomeric excess in all cases. On treatment with *tert*-butylmagnesium chloride the amino thioesters **195** cyclized to trans-α,β-disubstituted β-lactams **196**.



Scheme 7.15

Ojima has used the reaction of the chiral lithium enolate **198**, derived from the α-siloxyester **197**, with *N*-(trimethylsilyl)imines **199** to generate 3,4-cis-disubstituted β-lactams **201** (**Scheme 7.16**).[76] The chiral auxiliary directs the approach of the imine to the si-face of the enolate forming the *N*-lithiated β-amino

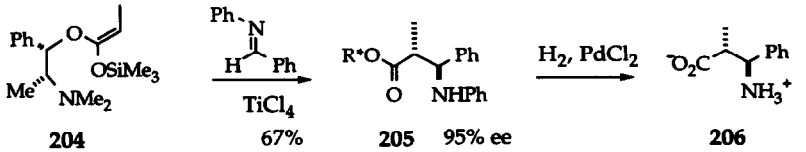
esters **200**, which cyclized *in situ* to the cis-substituted β-lactams **201** in excellent yields and enantiomeric purity. β-Lactam **201a** (Ar = Ph) was converted into α-hydroxy-β-amino acid **202** by deprotection of the alcohol and hydrolysis of the β-lactam ring. Subsequent *N*-benzoylation gave the *N*-benzoyl-(2*R*, 3*S*)-phenylisoserine **203**, the taxol *C*-13 side chain.



	yield (%)	ee (%)
199a, Ar=Ph	85	96
b, Ar=*p*-$MeOC_6H_4$	80	96
c, Ar=3,4-$(MeO)_2C_6H_3$	80	98

Scheme 7.16

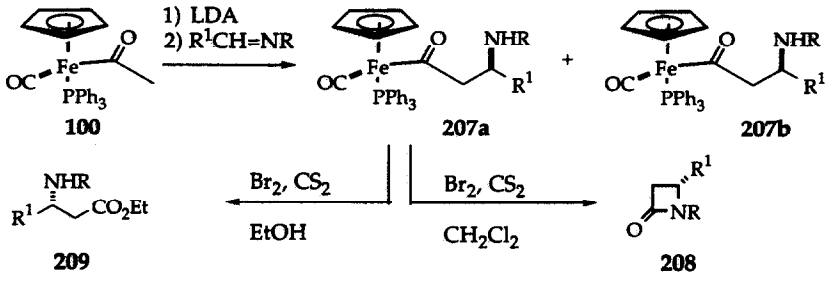
Gennari[3] has reported the reaction of the chiral silyl ketene acetal **204** with benzylidenaniline in the presence of titanium tetrachloride to give only one of the four possible isomers of the β-amino ester **205** (**Scheme 7.17**). The absolute configuration of the product was proven by hydrogenolysis to the known β-amino acid **206**.



Scheme 7.17

Liebeskind et al.[51] have added the enolate, derived from the optically active pseudooctahedral iron(II) complex **100**, to imines (**Scheme 7.18**). Treatment of the lithium enolate with benzylideneaniline (PhCH=NPh, entry 1) gave the β-amino

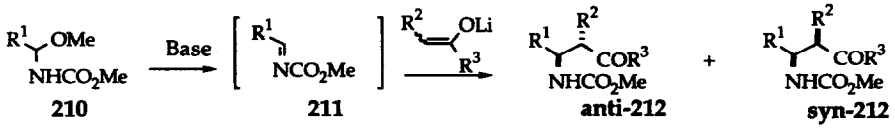
acyl iron product **207** in high yield and with good diastereoselectivity. The lithium enolate of **100** did not react well with other imines, however addition of diethylaluminum chloride produced an enolate species that condensed efficiently, although slowly, with a variety of imines. The β-amino acyl complex **207a** could be converted either to the corresponding β-lactams **208** or the β-amino esters **209** by oxidation with bromine.



entry	$R^1CH=NR$	counterion	yield(%)	**207a : 207b**
1	(*E*)-PhCH=NPh	Li	85	5.7 : 1
2	(*E*)-PhCH=NPr	Et_2Al	80	20 : 1
3	(*E*)-*i*-PrCH=NPr	"	68	20 : 1
4	(*E*)-PhCH=NCH_2Ph	"	75	25 : 1
5	(*E,E*)-PhCH=CHCH=NPr	"	44	2.5 : 1
6	(*E,E*)-PhCH=CMeCH=N-PMP	"	68	1.3 : 1
7	(*E,E*)-EtCH=CMeCH=NPr	"	37	20 : 1

Scheme 7.18

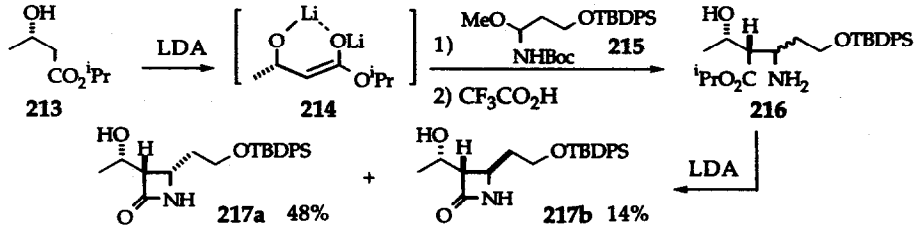
Shono has shown that *N*-methoxycarbonylimines **211** can be generated *in situ* from α-methoxycarbonates **210** and are suitable electrophiles for reactions with lithium enolates (**Scheme 7.19**).[77] A mixture of **210** and a ketone or ester was treated with LDA to give a diastereomeric mixture of β-amino acid derivatives **212**. Enolates of cyclic ketones tended to give anti-products preferentially (entries 1 & 2, **Scheme 7.19**), as did ester enolates (entries 5-7). Acyclic ketones, on the other hand, afforded mainly syn-adducts (entries 3 & 4).



entry	R^1	R^2	R^3	yield (%)	anti : syn
1	*i*-Pr	$-(CH_2)_3-$		52	9 : 1
2	"	$-(CH_2)_4-$		66	9 : 1
3	Me	Me	Et	61	3 : 7
4	*i*-Pr	"	"	76	1 : 9
5	Me	Et	OMe	78	7 : 3
6	*i*-Pr	O*i*-Pr	OMe	92	8 : 2
7	*i*-Bu	Et	OMe	93	9 : 1

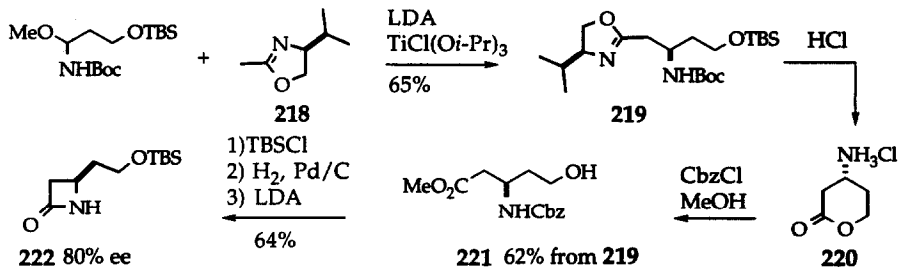
Scheme 7.19

The use of this chemistry for the preparation of homochiral 3,4-disubstituted β-lactams is shown in **Scheme 7.20**.[77] Treatment of the (*S*)-β-hydroxyester **213** with two equivalents of LDA in the presence of α-methoxycarbonate **215** results, after *N*-deprotection, in the formation of the β-amino ester **216** in 65% yield and 80 : 20 syn : anti selectivity. The mixture was cyclized to the separable β-lactams **217** by reaction with LDA. The syn-selectivity is explained by the formation of the intermediate *(Z)*-enolate **214** and alkylation from the si-face of the enolate, opposite the methyl group, and the re-face of the imine.



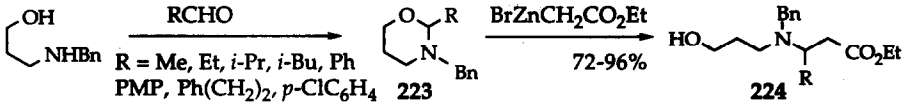
Scheme 7.20

The anion generated from the chiral 2-methyloxazoline **218**, which in turn was derived from L-valinol, was found to react with imine equivalents in a similar fashion (**Scheme 7.21**).[78] Thus, the fully protected β-amino acid **219** was obtained as a single stereoisomer and it could be hydrolyzed to the amino lactone **220**. This was converted to the amino ester **221** and hence, to the β-lactam **222**.



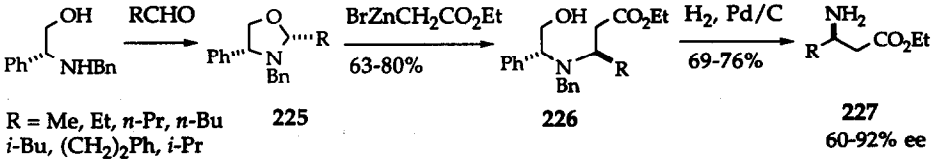
Scheme 7.21

Pedrosa[79] has shown that 3-benzyl-1,3-oxazinanes **223**, obtained by condensation of 3-(benzylamino)propanol with the appropriate alkyl- and aryl-aldehydes (R = Me, Et, *i*-Pr, *i*-Bu, $PhCH_2CH_2$, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, and Ph), react with ethyl bromozinc acetate to afford β-amino ester derivatives **224** in excellent yields (**Scheme 7.22**).



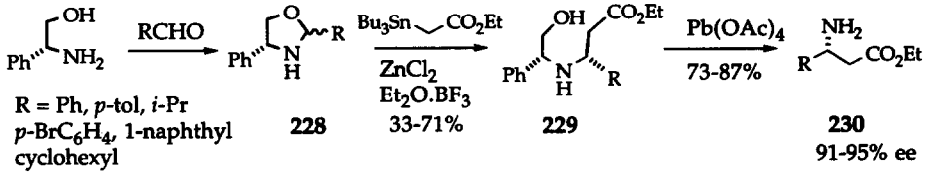
Scheme 7.22

The asymmetric version of this reaction is indicated in **Scheme 7.23**.[80] Thus, the chiral oxazolidines **225**, obtained by the reaction of (-)-(*R*)-*N*-benzylphenylglycinol with various aldehydes, underwent a ring opening reaction with the Reformatsky reagent, usually at 0°C, to give ethyl β-amino carboxylates **226**. The (-)-(2*R*, 4*R*)-4-phenyl-2-isopropyl-1,3-oxazolidine **225** (R = *i*-Pr) failed to react at 0°C, but did react at 35°C, albeit with lower diastereoselectivity (69 : 31). The *N*-protected β-amino esters **226** were easily debenzylated to give the free β-alkyl β-amino esters **227**.



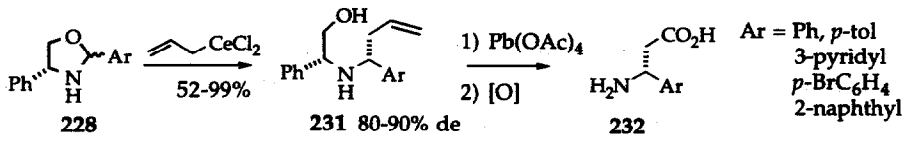
Scheme 7.23

Pridgen and Wu prepared oxazolidines **228** from (*R*)-phenylglycinol as mixtures of diastereomers (**Scheme 7.24**) and found that ethyl tributylstannylacetate added directly to these mixtures under Lewis acid catalyzed conditions, to yield β-amino esters **229**.[81] Various Lewis acids were tested, including zinc chloride, boron trifluoride etherate, chlorotitanium triisopropoxide, titanium(IV) chloride, and tin ditriflate. Zinc chloride provided the best diastereoselectivity at somewhat lower yields, whereas boron trifluoride etherate gave the highest yields, albeit at lower stereoselectivity. The authors reasoned that $ZnCl_2$ was providing good selectivity by complexing both reactants in the transition state, and boron trifluoride etherate was activating the ester by complexing the carbonyl group. Thus, by combination of both Lewis acids (0.5 equiv. of each), best results were obtained. Amino alcohols **229** were isolated in 33-71% yield and 91-99% diastereomeric excess. Compounds **229** (R = Ph, *p*-tol, *p*-BrC_6H_4) were converted into the corresponding β-amino esters **230**. The higher enantiomeric excesses obtained in this work than in that of Pedrosa[80] have been attributed to the fact that the secondary imine from **228** was better able to complex to the zinc in the transition state than is the case with the tertiary imine from **227**. It should also be noted that the β-amino esters produced have the opposite stereochemistry to those formed in **Scheme 7.23**. One disadvantage of this method is that long reaction times (3 - 11 days) were necessary for the ethyl tributylstannylacetate additions to proceed to completion.



Scheme 7.24

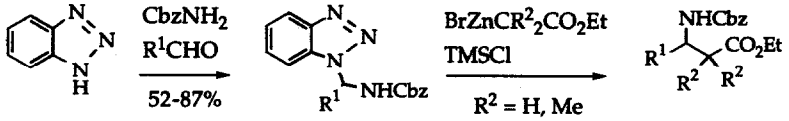
Oxazolidines **228**, derived from arylaldehydes (Ar = Ph, 3-pyridyl, *p*-tol, *p*-BrC_6H_4, and 2-naphthyl), also react with allyldichlorocerium in high yields (≥94%, except for Ar = 3-pyridyl, which went in 52%) and with high diastereoselectivities (**Scheme 7.25**).[82] Lead tetraacetate was used to cleave the chiral auxiliary from the resulting products **231**, and the allylamines were then converted to the corresponding β-aryl β-amino acids **232** through methodology developed by Kunz[68] (see **Scheme 7.8**).



228 231 80-90% de 232

Scheme 7.25

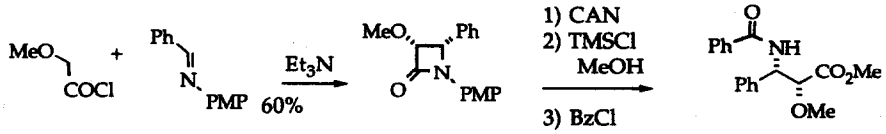
Katritzky and Yannakopoulou[83] used the Reformatsky reaction with 1-benzyloxycarbonylamino-1-(1-benzotriazolyl)alkanes **233** to prepare β-amino esters (**Scheme 7.26**). Compounds **233** were prepared by condensation of benzotriazole, benzyloxycarbonylamine, and the appropriate aldehyde. Subsequent reaction with ethyl 2-bromoalkanoates under Reformatsky conditions yielded the *N*-protected 3-amino esters **234**.



233 R^1 = *i*-Bu, Bn, Ph **234**

Scheme 7.26

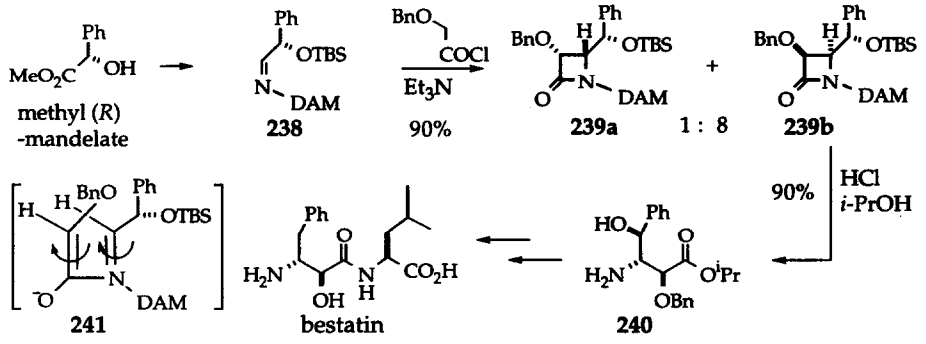
Palomo used a [2 + 2] cycloaddition of the imine **235** with a ketene as the key β-lactam forming step in the synthesis of the taxol side chain **237** in racemic form (**Scheme 7.27**).[84] The reaction of methoxyacetyl chloride with triethylamine led to *in situ* generation of methoxyketene, which underwent a [2 + 2] cycloaddition reaction with the imine **235** to give the β-lactam **236** as a single cis-product. Following removal of the *p*-methoxyphenyl (PMP) protecting group, the lactam was opened to the β-amino ester and the amine was protected as the benzoate to afford **237**.



235 **236** **237**

Scheme 7.27

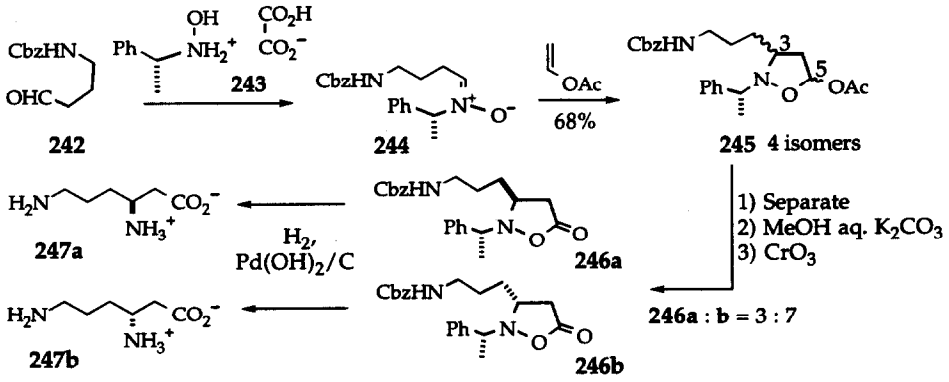
Use of a chiral imine to induce asymmetry in the [2 + 2] cycloaddition reaction was reported by Terashima (**Scheme 7.28**).[85] Methyl (*S*)-mandelate was converted to the chiral imine **238** by protection of the alcohol, reduction of the ester to the corresponding aldehyde, and condensation with di-*p*-anisylmethylamine (DAM-NH_2). The benzyloxyketene, produced *in situ* from the reaction of benzyloxyacetyl chloride and triethylamine, underwent a highly diastereoselective cyclization with the imine to produce the cis-β-lactams as a mixture (8 : 1) in favor of **239b**. Treatment of **239b** with acidic isopropyl alcohol effected opening of the β-lactam ring, along with removal of the silyl and DAM protecting groups, to afford **240**. Compound **240** constitutes a key component of bestatin, an immune response modifier. The mechanism of the [2 + 2] cycloaddition is not clearly understood; however, the initial formation of the zwitter ionic species **241** followed by a conrotatory ring closure, governed by the chiral center, explains the formation of the major product.



Scheme 7.28

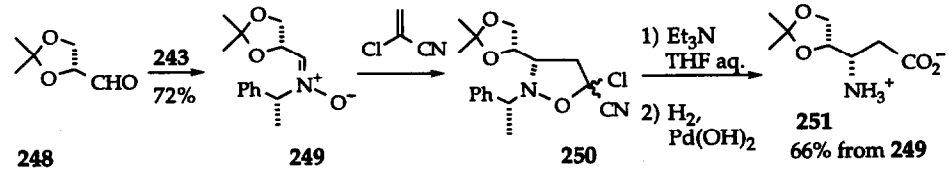
Overton's[86] asymmetric synthesis of β-amino acids is based on a dipolar [2 + 3] cycloaddition reaction of the chiral nitrones **244** with vinyl acetates, ketene acetals, or α-chloroacrylonitrile (**Scheme 7.29**). Reaction of 4-*N*-(benzyloxycarbonyl)butanal **242** with (*R*)-(+)-α-methoxybenzyl hydroxylamine oxalate **243** gave the nitrone **244**. Cycloaddition with vinyl acetate gave four diastereomeric isoxazolidines **245** arising from the reaction in an *endo* or *exo* manner at either the re- or si-face of the vinyl acetate. The four acetates were separated into two pairs of diastereomers, epimeric at C-3, each pair in turn consisting of C-5 epimers. Hydrolysis of the acetate and oxidation of the epimeric alcohols gave pure isoxazolidinones **246a** and **b**. Ensuing

hydrogenolysis afforded (*S*)- and (*R*)-β-lysine **247a** and **247b**, respectively. β-Leucine, 3-amino-3-phenyl propanoic acid, and β-tyrosine were also prepared by this procedure.



Scheme 7.29

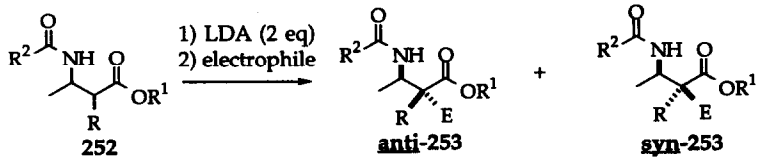
A [2 + 3] cycloaddition reaction was also used in the synthesis of β-amino acid **251**, a potential carbapenem intermediate (**Scheme 7.30**).[87] Condensation of aldehyde **248** with (*R*)-(+)-phenethylhydroxylamine oxalate **243** gave nitrone **249**, which underwent cycloaddition with excess α-chloroacrylonitrile to afford the epimeric oxazolidines **250**. Hydrolysis of this mixture gave the corresponding isoxazolidinone as a single diastereomer and hydrogenolysis afforded the β-amino acid **251**.



Scheme 7.30

8. Reaction at the α-center of β-amino acids

Despite the number of methods that have been developed for the enantiomeric preparation of β-amino acids, access to β-amino acids with α-substitution still remains a challenge. Several workers have been involved in the stereoselective reaction of enolates of β-amino acids to produce these α-substituted-β-amino acids. **Scheme 8.1** shows the alkylation of *N*-protected β-amino esters. The racemic *N*-benzoyl- and *N*-benzyloxycarbonylamino esters **252** were deprotonated and treated with an excess of an electrophile, e.g. reactive primary alkyl halides and aldehydes.[88] Generally, high yields and excellent selectivity in favor of the anti-product **anti-253** was observed. (For α-methylation of *N*,*N*-dibenzyl-β-amino esters see **Scheme 5.12**[45]).

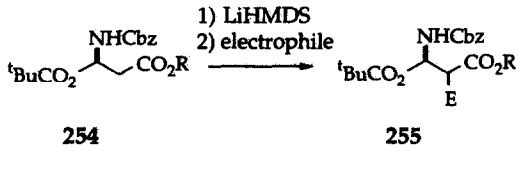


R^2	R^1	R	electrophile	yield (%)	anti : syn
Ph	Et	H	MeI	73	4 : 1
"	"	"	EtI	38	13 : 1
"	"	"	PhCHO	44	3 : 1
"	Me	"	MeI	45-50	4 : 1
"	"	"	EtI	83	16 : 1
"	"	"	AllylBr	70-90	31 : 1
"	"	"	BnBr	70-90	36 : 1
"	"	"	PhCHO	60-70	5 : 1
"	"	Et	BnBr	80	99 : 1
BnO	"	H	MeI	75	7 : 1
"	"	"	BnBr	76	10 : 1
"	"	"	PhCHO	67	2 : 1

Scheme 8.1

In some analogous work by Baldwin and coworkers, (*S*)-aspartic acid was converted into the fully protected *N*-benzyloxycarbonylamino acid diester **254** (**Scheme 8.2**).[89] This compound was deprotonated with lithium hexamethyldisilazide (LHMDS) and then treated with a range of electrophiles.

Moderate yields (45-55%) of the alkylated products **255** were obtained. LDA was an unsuitable base as it caused racemization of **254**.

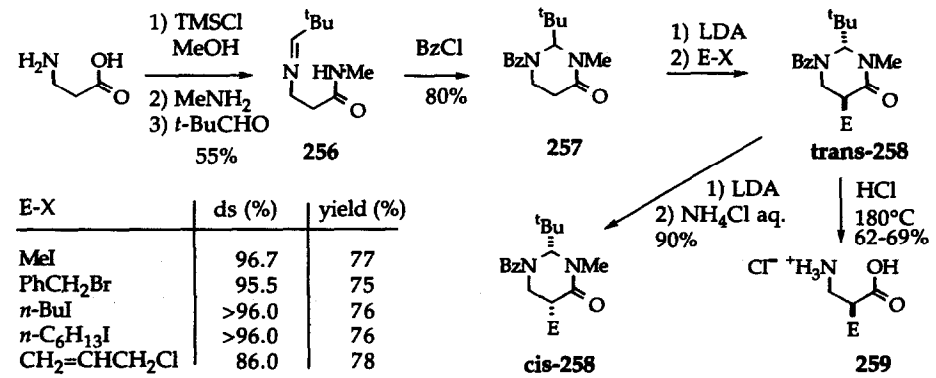


254 **255**

R	electrophile	yield (%)	dr
Me	PhCHO	50	1:1:0:0
"	BnBr	50	5:1
"	EtCHO	55	1:1:0:0
"	AllylBr	45	3:1
Allyl	PhCHO	52	1:1:0:0
"	EtCHO	54	1:1:0:0

Scheme 8.2

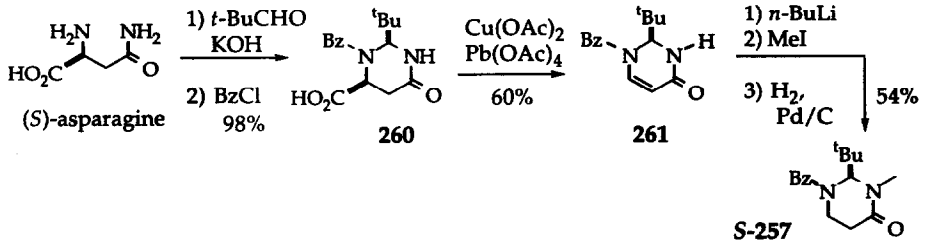
Juaristi and Seebach have explored the α-alkylation of 1-benzoyl-2-*tert*-butyl-3-methylpyrimidin-4-one **257** as a means or synthesizing α-substituted-β-amino acid analogues (**Scheme 8.3**).[90] 3-Aminopropionic acid was converted to the methyl ester and then to the corresponding *N*-methylamide. Subsequent *tert*-butyl imine formation gave compound **256**, which cyclized in the presence of benzoylchloride to give **257**. The X-ray crystal structure of compound **257** shows that the *tert*-butyl group occupies an axial position; thus it is not surprising that excellent diastereoselectivity was obtained in the α-alkylations of the enolate of **257**. The final step in the sequence, the hydrolysis of the alkylated heterocycle **trans-258**, was achieved with hot aqueous hydrochloric acid to give the α-alkylated β-amino acids **259**. Epimerization of **trans-258** was achieved by enolate formation and quenching with a proton source to give **cis-258**.



E-X	ds (%)	yield (%)
MeI	96.7	77
$PhCH_2Br$	95.5	75
n-BuI	>96.0	76
n-$C_6H_{13}I$	>96.0	76
CH_2=$CHCH_2Cl$	86.0	78

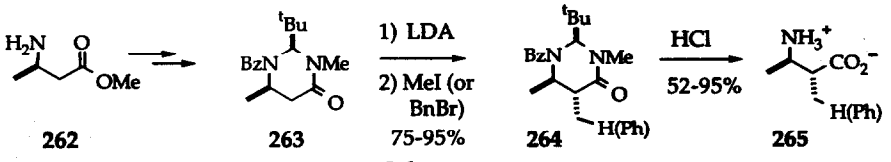
Scheme 8.3

Heterocycle **257** can be prepared in enantiomerically pure form from asparagine (**Scheme 8.4**).[91] (*S*)-Asparagine was condensed with pivalaldehyde and then *N*-benzoylated to give **260** as described by Konopelski.[30e] Oxidative decarboxylation gave enone **261**, which was *N*-methylated and hydrogenated to give 1-benzoyl-2(*S*)-*tert*-butyl-3-methylpyrimidin-4-one ***S*-257** in optically pure form.



Scheme 8.4

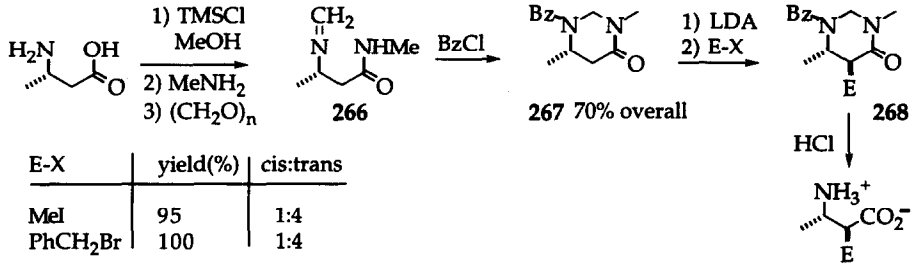
Juaristi and Seebach[92] have prepared 1-benzoyl-2-*tert*-butyl-3,6-dimethylperhydropyrimidin-4-ones **263** in excellent stereoselectivity (95 : 5) in favor of the cis-product from the corresponding methyl (*R*)-3-aminobutanoate **262** (**Scheme 8.5**) using a similar sequence of reactions to that indicated in **Scheme 8.3**. Compound **262** was prepared by the Michael addition of phenethylamine to methylcrotonates as previously reported by Davies.[44] The major isomer of **263** was deprotonated with LDA and then alkylated with methyl iodide and benzyl bromide to give **264** in 75-95% yield. Both the *tert*-butyl and methyl group hinder attack of the electrophile from the si-face of the enolate; thus, exclusive formation of the trans-product **264** was observed. Hydrolysis with hydrochloric acid gave the α-methyl- and α-benzyl-β-amino acids **265**.



Scheme 8.5

Alternatively, 1-benzoyl-3,6(*S*)-dimethyl-perhydropyrimidin-4-one **268** could be prepared from (*S*)-3-aminobutanoic acid (**Scheme 8.6**).[93] Reaction of the methylamide derivative of the acid with paraformaldehyde formed the Schiff base

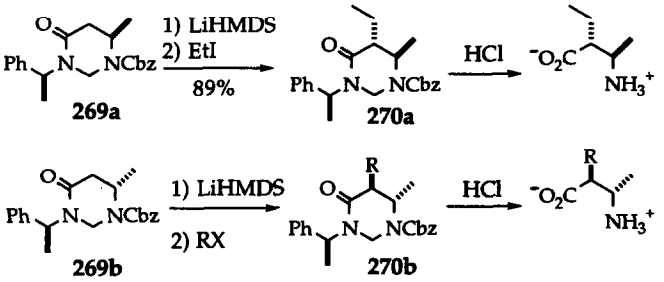
266, which cyclized under treatment with benzoyl chloride to give the heterocycle **267**. Deprotonation with LDA followed by alkylation with methyl iodide and benzyl bromide gave the alkylated products in 95-100% yield and 4 : 1 ratio in favor of the trans-product **268**. In the absence of the *tert*-butyl group, present in **257** and **263**, the asymmetric induction with **267** is due to the C-6 methyl group. Hydrolysis with 6N hydrochloric acid gave the alkylated amino acid.



E-X	yield(%)	cis:trans
MeI	95	1:4
$PhCH_2Br$	100	1:4

Scheme 8.6

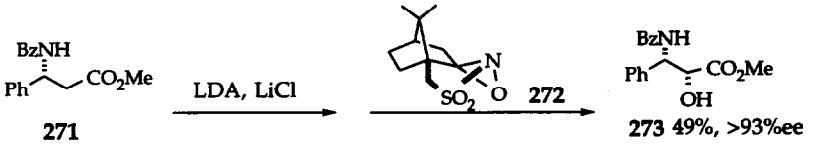
Cardillo et al. have reported a highly diastereoselective alkylation of (1'*S*, 6*R*)- and (1'*S*, 6*S*)-6-methyl-perhydropyrimidin-4-ones **269a** and **b** (prepared as indicated in **Scheme 9.3**) to generate α-substituted β-amino acids (**Scheme 8.7**).[94] The heterocycles **269** were deprotonated with lithium hexamethyldisilazide and alkylated with ethyl iodide, *iso*-butyl iodide, or benzyl bromide. The alkylations occurred preferentially trans to the 6-methyl group giving compounds **270**. Generally, the selectivity was excellent; notably, good yields were obtained using the primary haloalkanes.



RX	yield (%)	trans:cis
EtI	88.5	97:3
i-BuI	56.1	87:13
BnBr	89.8	93:7

Scheme 8.7

An interesting stereoselective α-hydroxylation of a β-amino ester to give the taxol side chain is indicated in **Scheme 8.8**.[67] 3-(*R*)-Benzoylamino-3-phenylpropanoic acid methyl ester **271** was deprotonated by LDA in the presence of lithium chloride and stereoselectively hydroxylated with (+)-(camphorsulfonyl)-oxaziridine **272** to give **273** as a 86 : 14 / syn : anti mixture. Chromatographic separation of the diastereomers gave the methyl ester of the taxol side chain **273** in 49% yield and 93% enantiomeric excess.

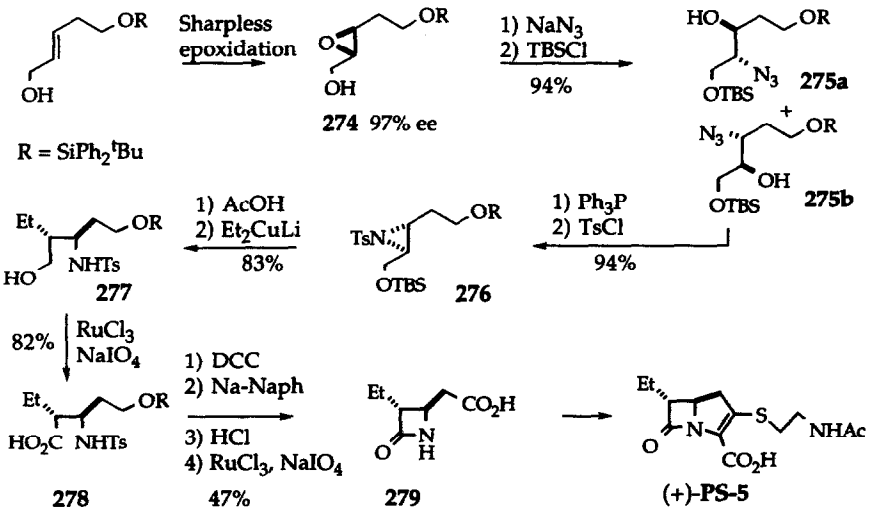


Scheme 8.8

9. Miscellaneous methods

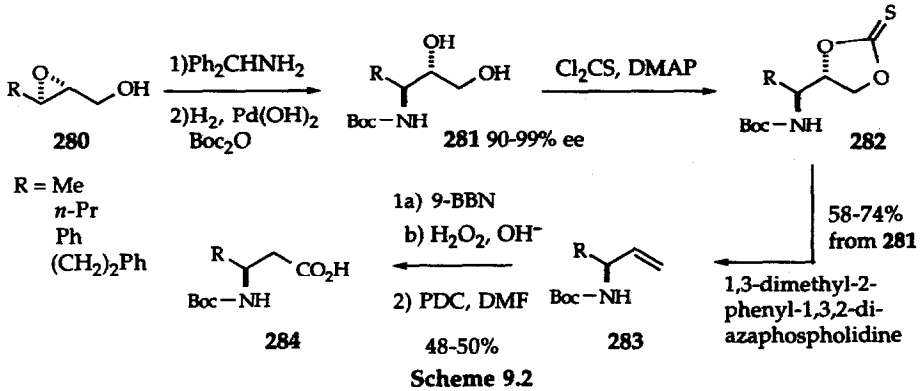
This section contains a number of strategies for the synthesis of β-amino acids that do not fit easily into any of the categories listed above.

Tanner and Somfai[95] used a Sharpless asymmetric epoxidation in a novel preparation of a β-amino acid precursor to the antibiotic (+)-**PS-5** (**Scheme 9.1**). Epoxide **274** was treated with sodium azide to give a mixture of azido alcohols, in which the primary alcohol groups were selectively protected as the *tert*-butyldimethylsilyl ethers **275**. Both compounds **275a** and **b** could be converted into the aziridine **276** and following the deprotection of the *tert*-butyldimethylsilyl ether, a highly regiospecific aziridine ring opening reaction gave the β-toluenesulfonamido alcohol **277**. Oxidization to the acid **278** and cyclization,[2c] followed by deprotection of the amide and alcohol functionalities, and oxidation of the alcohol, gave **279**, which had previously been converted into (+)-**PS-5**. The authors note that varying the starting allylic alcohol (*E* or *Z*) or the tartarate (D or L), used in the Sharpless epoxidation, allows for the enantioselective preparation of all possible diastereomers of the β-amino acid.



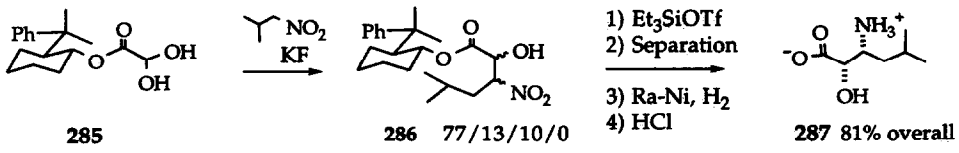
Scheme 9.1

A Sharpless epoxidation was also used by to prepare the epoxides **280** (**Scheme 9.2**).[96] Regioselective ring opening with *N*-diphenylmethylamine followed by a one-pot deprotection-protection procedure gave the *N-tert*-butoxycarbonyl-3-amino-1,2-diols **281**. Reaction with thiophosgene gave the thionocarbonates **282**, which underwent deoxygenation to give the allylamines **283**. Hydroboration and oxidation gave the amino alcohols, which were converted to the β-amino acids **284** by oxidation with PDC.



Scheme 9.2

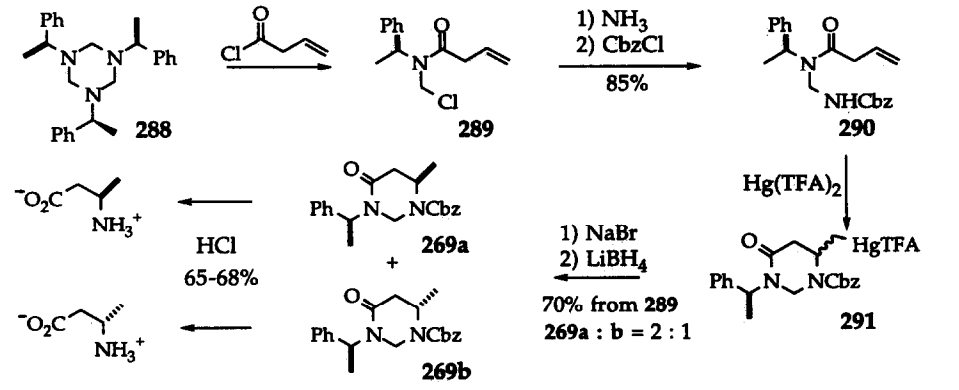
Solladié-Cavallo and Khair[97] used the fluoride ion mediated addition of 1-nitro-3-methylbutane to (-)-8-phenylmenthyl glyoxalate hydrate **285** as the key step in their synthesis of (2*S*, 3*R*)-3-amino-2-hydroxy-5-methylhexanoic acid **287** (**Scheme 9.3**). Compound **286** was formed in 90% yield as a mixture of the four possible diastereomers, with the major isomer accounting for 77% of the mixture. Following protection of the hydroxyl group, the diastereomers were separated and a Raney nickel reduction of the major isomer, followed by hydrolysis gave the recovered chiral auxiliary and the α-hydroxy β-amino acid **287**.



285 **286** 77/13/10/0 **287** 81% overall

Scheme 9.3

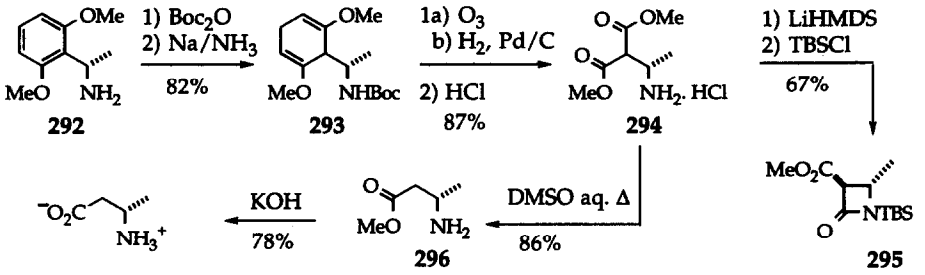
Cardillo et al. have used a mercury promoted cyclization of β,γ-unsaturated amidal **290** to synthesize 6-methylperhydropyrimidin-4-ones **269** (**Scheme 9.4**).[98] These heterocycles can be converted into β-amino acids or used as substrates for the asymmetric synthesis of α-substituted-β-amino acids (see **Scheme 8.7**). Treatment of hexahydrotriazine **288** with 3-butenoyl chloride afforded the corresponding *N*-chloromethyl adduct **289**. This was converted to the amidal by reaction with ammonia; then, protection of the amine as the *N*-benzyloxycarbonyl derivative gave **290** in 85% overall yield.



Scheme 9.4

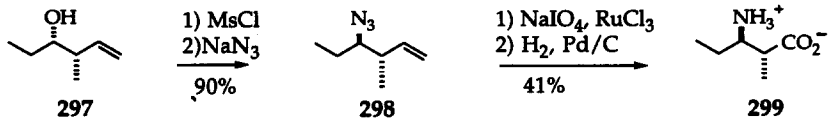
Mercury trifluoroacetate-promoted cyclization gave the cyclized product **291** as a 2 : 1 mixture of diastereomers. Direct reduction of these alkyl mercurialacetate products proceeded in low yields. However, if **291** was first treated with sodium bromide, then reduction gave a mixture of 6-methylperhydropyrimidin-4-ones **269a** and **b** in 70% yield, still as a 2 : 1 mixture. These compounds could be separated and each converted to the corresponding β-amino acids by hydrolysis.

A novel method for the preparation of β-methyl-β-amino acids and β-lactams was described by Bringmann (**Scheme 9.5**).[99] *N*-Protection of the homochiral 1-arylethylamine **292** followed by Birch reduction gave the 1,4-hexadiene **293**. Ozonolysis with reductive workup, followed by deprotection of the amine afforded the 1-aminoethyl malonate **294**, which could be converted into the β-lactam **295**. Alternatively, malonate **294** could be decarboxylated to give the (*S*)-3-methyl-3-amino butyrate **296** in 95% enantiomeric purity. Saponification afforded the corresponding β-amino acid.



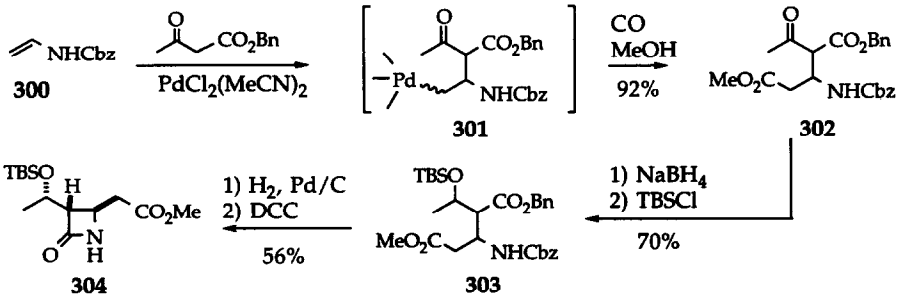
Scheme 9.5

Bates et al. synthesized all four stereoisomers of 3-amino-2-methylpentanoic acid **299** from the corresponding homoallylic alcohols **297** (**Scheme 9.6**).[100] Mesylation of **297** followed by displacement with azide gave **298**. Oxidative cleavage of the olefin followed by catalytic hydrogenation gave the β-amino acids **299** in 37% overall yield from the chiral alcohols.



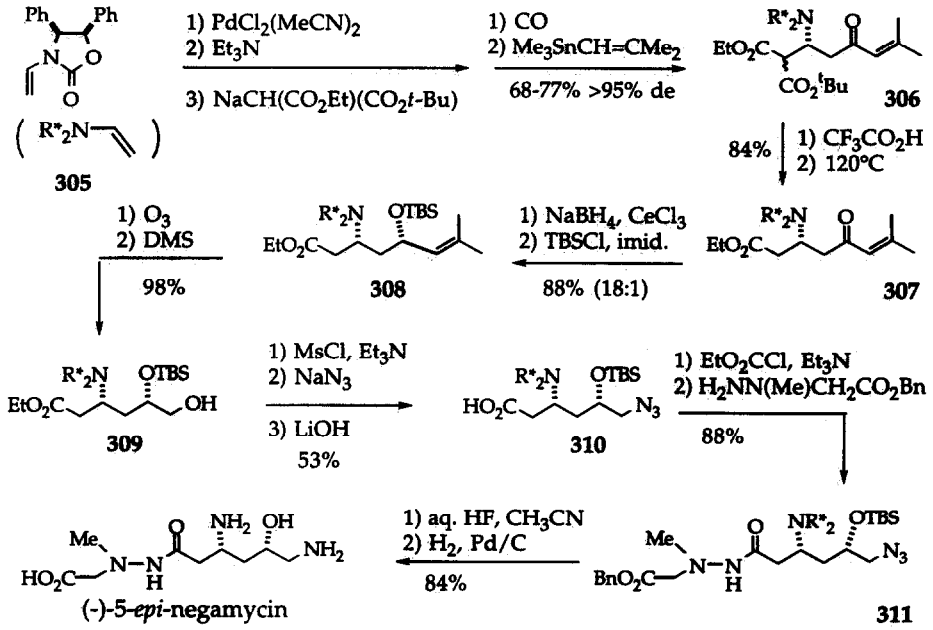
Scheme 9.6

Hegedus et al. used a palladium(II) mediated carboacylation of enamines to produce β-amino acids and a thienamycin intermediate **304** (**Scheme 9.7**).[101] Benzyl *N*-vinylcarbamate **300** reacted with benzyl acetoacetate in the presence of palladium(II) to produce the unstable (σ-alkyl)-palladium(II) complex **301**. This intermediate underwent carbon monoxide insertion and methanol coupling to produce the highly functionalized ketodiester carbamate **302** in excellent yield as a 1 : 1 mixture of diastereomers. Reduction of the ketone and protection of the resultant alcohol gave **303**, which was debenzylated and cyclized to the β-lactam **304**.



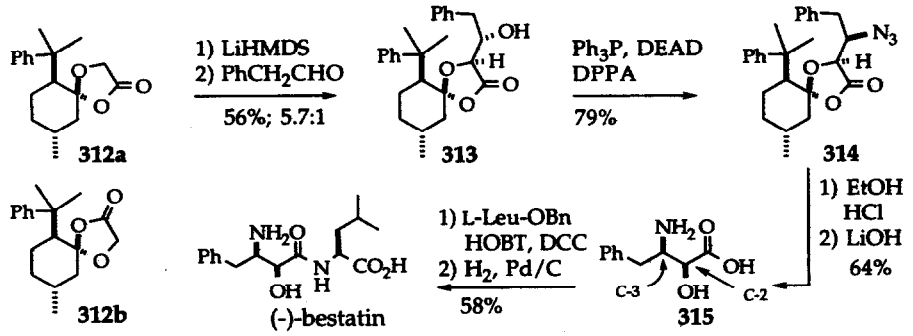
Scheme 9.7

The use of the above methodology in the asymmetric synthesis of the antibiotic (-)-5-*epi*-negamycin has also been reported (**Scheme 9.8**).[102] A palladium-(II)-assisted alkylation of the optically active *N*-vinylcarbamate **305**, followed by carbonylative coupling to isobutenyltrimethylstannane afforded the diester **306**. Hydrolysis of the *tert*-butyl ester with trifluoroacetic acid and decarboxylation gave the β-amino ester **307**. Stereoselective reduction of the keto group followed by protection of the alcohol afforded the silyl ether **308**. Ozonolysis with reductive workup yielded the primary alcohol **309**, which was converted to the corresponding mesylate. Azide displacement and saponification of the ester furnished the acid **310**. Peptide coupling via the mixed anhydride procedure yielded the fully protected product **311**. Finally, removal of the silyl protecting group with hydrogen fluoride, followed by hydrogenolytic cleavage of the benzyl ester and the diphenyl-oxazolidinone with concomitant reduction of the azide, liberated (-)-5-*epi*-negamycin.



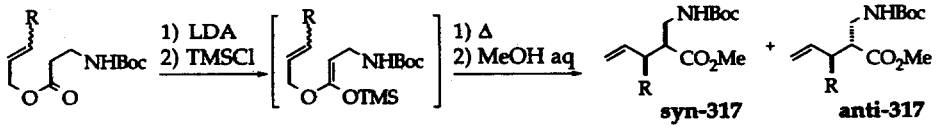
Scheme 9.8

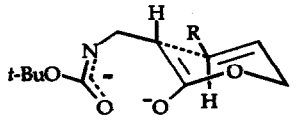
Pearson's asymmetric synthesis of the α-hydroxy-β-amino acid **315** is based on a stereoselective aldol reaction of the enolate of the chiral spirocyclic 1,3-dioxolan-4-one **312a** (**Scheme 9.9**).[103] The absolute stereochemistry at *C*-2 (**315**) is controlled by the alkylation, which occurs preferentially from the re-face of the enolate of **312a**. Good selectivity at *C*-3 (**315**) is obtained by choice of enolate counterion; thus, lithium and magnesium enolates gave anti-aldol products (e.g. **313**) selectively, whereas zirconium enolates favored the syn-aldol products. For the synthesis of (-)-bestatin, the dioxolane **312a** was treated with lithium hexamethyldisilazide and trapped with phenyl acetaldehyde to give **313** selectively (5.7 : 1 ; anti : syn) in moderate yield. Separation of **313** and conversion to the azide **314** occurred under Mitsunobu conditions. Acidic ethanolysis gave the amino ethyl ester, which was hydrolyzed to the acid **315**. Standard peptide coupling and deprotection then gave the dipeptide (-)-bestatin. The authors pointed out that by selection of dioxolane **312a** or **312b** and use of the correct enolate counterion, any of the four diastereomers can be selectively formed.



Scheme 9.9

Knight et al. have recently shown that the enolate Claisen rearrangement can be used as a means of preparing α-allyl-β-amino acids **317** (**Scheme 9.10**).[104] Thus, allylic alcohols were condensed with an *N-tert*-butoxycarbonyl-3-aminopropanoic acid to give the allyl esters **316**. Treatment with LDA and chlorotrimethylsilane gave the intermediate silylenol ether, which underwent rearrangement on heating. Hydrolysis and esterification gave the β-amino esters **317**, generally in high yield. The involvement of a single transition state **318** is likely, since the stereochemistry of the major products is directly related to the starting material *E/Z* geometry.



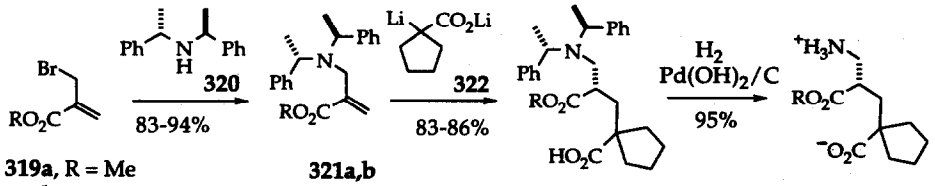


	R	yield (%)	syn : anti
trans-316	Me	88	86 : 14
"	Ph	31	55 : 45
"	*i*-Pr	85	80 : 20
"	CH_2OTBS	77	92 : 8
"	$(CH_2)_2OTBS$	75	93 : 7
cis-316	Me	73	12 : 88
"	Ph	40	77 : 23
"	*i*-Pr	81	81 : 19
"	CH_2OTBS	68	6 : 94
"	$(CH_2)_2OTBS$	70	15 : 85

Scheme 9.10

Exceptions to this rule occur when the allylic alcohol contains a branch α to the six centered transition state, i.e. when R = Ph or *i*-Pr, in which cases the selectivity is lowered or reversed.

The Michael addition of chiral amines to α,β-unsaturated esters to produce β-amino acids with chirality at the β-position has already been discussed. **Scheme 9.11** indicates how Michael addition of enolates to chiral 2-aminomethacrylates can be used to prepare β-amino esters with chirality at the α-center.[105] 2-Bromoacrylates **319** were condensed with the C_2 symmetrical amine **320** to give the chiral acrylates **321**. These were then treated with the lithiodianion of cyclopentanecarboxylic acid **322** to give **323a** and **b** in excellent yield and stereoselectivity. Hydrogenolysis of the products over Pearlman catalyst [$Pd(OH)_2/C$] gave the β-amino esters **324**.



319a, R = Me
319b, R = *t*-Bu

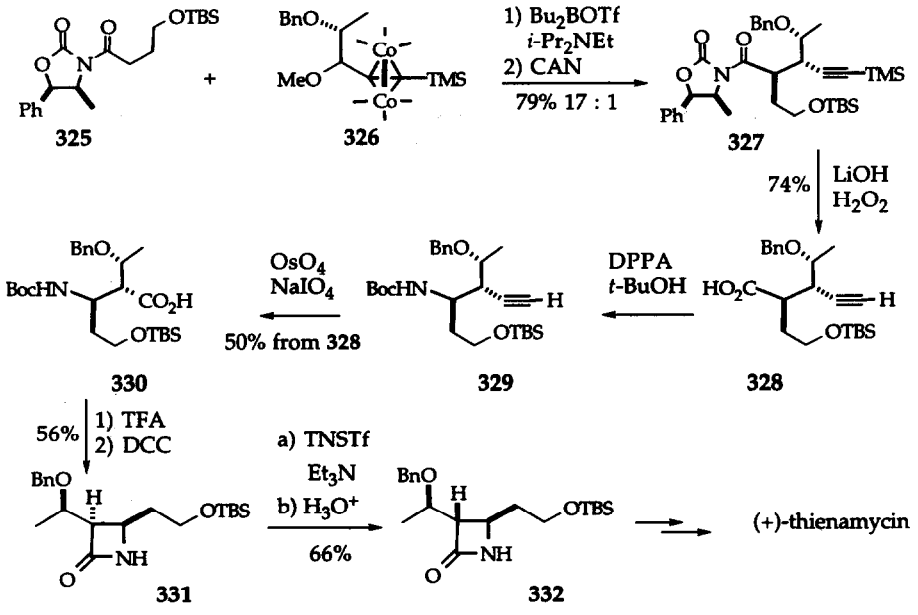
321a,b

323 94-98% de

324

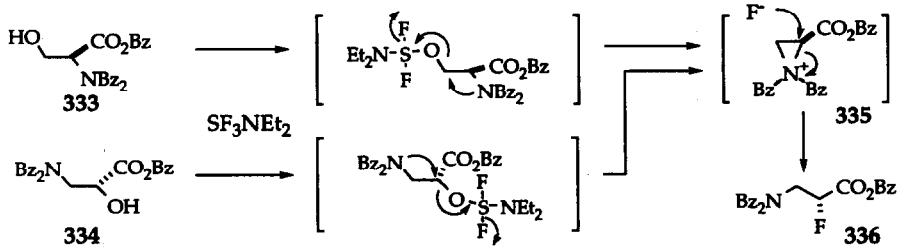
Scheme 9.11

Jacobi and Zheng have recently reported the use of the Nicholas reaction in an interesting synthesis of homochiral β-amino acids (**Scheme 9.12**).[106] The acetylenic cobalt complex **326** was available by condensation of lithium trimethylsilylacetylene with the chiral aldehyde, followed by *in situ* methylation and complexation with $Co_2(CO)_8$. Upon treatment with a Lewis acid catalyst, compound **326** underwent a heterolytic cleavage of the ether functionality affording a cobalt stabilized carbonium ion. This was readily trapped by the *(E)*-enolate of the *N*-acyloxazolidinone **325**, generated by treatment with dibutylborontriflate and Hunig's base (*i*-Pr_2NEt). The major anti-product **327** was obtained in good yield and high diastereoselectivity. Hydrolysis of the amide bond with concomitant cleavage of the TMS group afforded the acid **328**. A Curtius rearrangement was then carried out with diphenylphosphoryl azide (DPPA), followed by trapping with *tert*-butanol to give the *N-tert*-butoxycarbonyl protected amine **329**, with retention of stereochemistry. Oxidative cleavage of the acetylene then liberated the acid **330**. Deprotection and cyclization afforded the cis-β-lactam **331**, which was epimerized to the known (+)-thienamycin precursor **332**.



Scheme 9.12

A facile synthesis of α-fluoro-β-amino acids was described by Shanzer (**Scheme 9.13**).[107] Reaction of either *N,N*-dibenzyl-L-serine-benzyl esters **333** or *N,N*-dibenzyl-D-isoserine benzyl esters **334** with (diethylamino)sulfur trifluoride (DAST) resulted in a rearrangement through a common intermediate **335** to give the α-fluoro-β-amino acid **336** in protected form.



Scheme 9.13

10. Acknowledgment

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12. List of acronyms used

Boc = *tert*-butoxycarbonyl
CAN = ceric ammonium nitrate
Cbz = benzyloxycarbonyl
DCC = dicyclohexylcarbodiimide
de = diastereomeric excess
DEAD = diethyl azodicarboxylate
DMAP = 4-dimethylaminopyridine
DME = dimethoxyethane
DPPA = diphenylphosphoryl azide
dr = diastereomeric ratio
ds = diastereomeric selectivity
ds = diastereoselectively
ee = enantiomeric excess
HOBt = 3-hydroxybenzotriazole
HMPA = hexamethylphosphoramide
KHMDS = potassium hexamethyldisilazide
LiHMDS = lithium hexamethyldisilazide
Moc = methoxycarbonyl
MOM = methoxymethyl
MPM = *p*-methoxybenzyl
NBS = *N*-bromosuccinimide
NCS = *N*-chlorosuccinimide
Piv = *tert*-butylcarbonyl
PMP = *p*-methoxyphenyl
TBDPS = *tert*-butyldiphenylsilyl
TBS = *tert*-butyldimethylsilyl
TFA = trifluoroacetic acid
TMEDA=*N,N,N′,N′*-tetramethylethylene diamine

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