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Recent advances in the stereoselective synthesis of β-amino acids

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1. Introduction

During the last decade, stereoselective synthesis of β-amino acids has gained considerable attention due to their biologically important properties, their occurrence in natural products, and as potential precursors for β-lactams.[1] The β-amino acids in free form show interesting pharmacological properties. For instance, hypoglycemic and antiketogenic activities were observed in rats after oral intake of emeriamine (**1**) (Scheme 1).[2] Cispentacin (**2**) is an antifungal antibiotic.[1] Functionalized β-amino acids are key components of a variety of bioactive molecules such as taxol (**3**) one of the most active antitumor agents which contains phenylisoserine as its side chain.[3] Unsaturated β-amino acid ADDA (**4**) is present in the antibiotics cyanovinfin RR, nodularin, as well as microcystin LR.[4] Furthermore, β-amino acids, although not as abundant as their α-analogues, are also segments in peptidic natural products with various biological activities. Steglich et al. have demonstrated that (*R*)-β-dopa (**5**,3,4-dihydroxy-β-phenylalanine) is contained in mushroom *Cortinarius*

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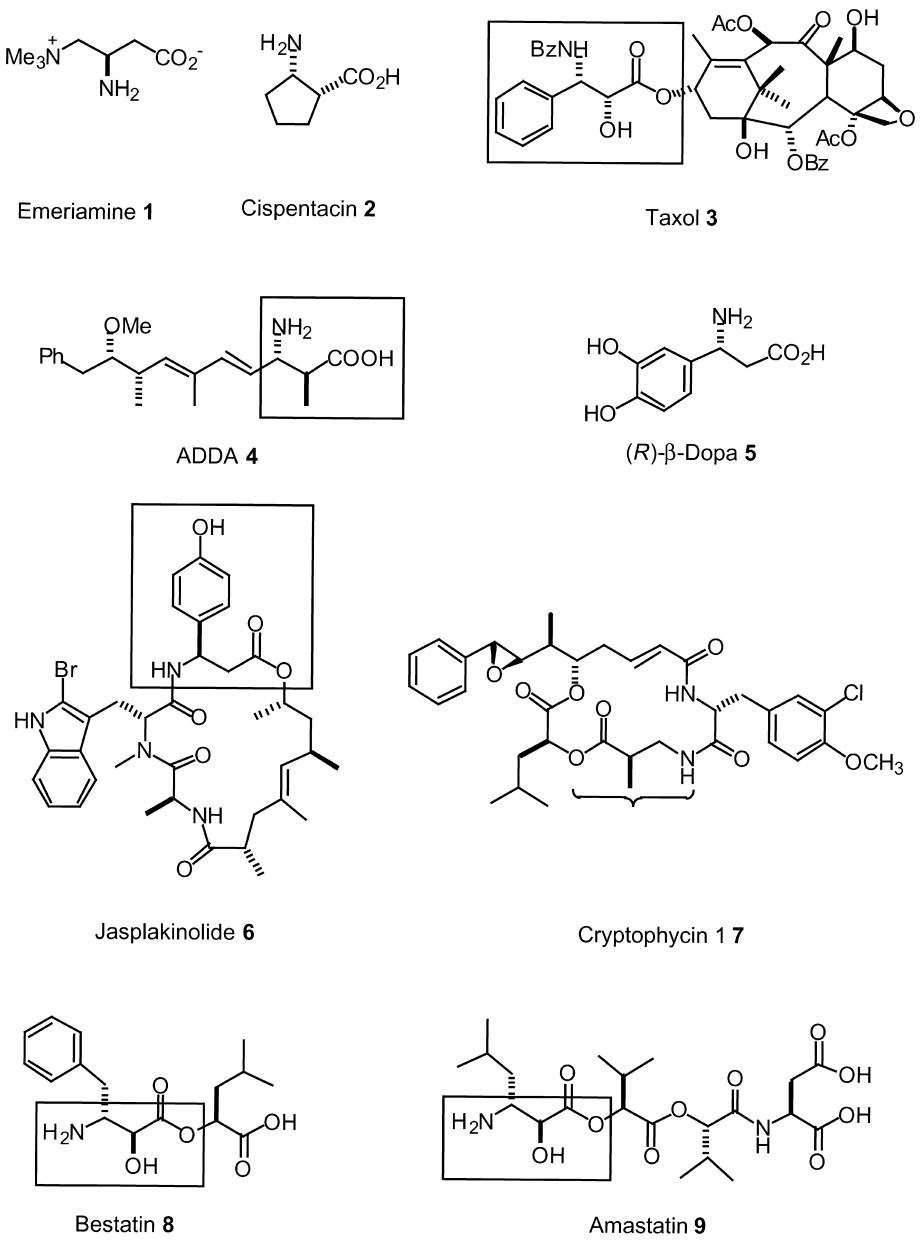


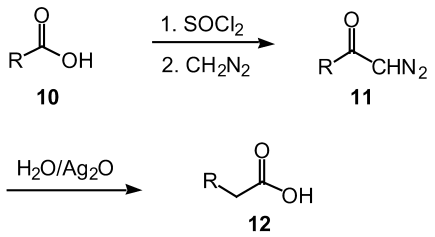
Scheme 1.

violaceus as the Fe(III)–catechol complex, which gives the fruit its blue-violet color.[5] β-Tyrosine, a β-aryl-β-amino acid, is present in jasplakinolide (**6**) which is a sponge metabolite with potent insecticidal, antifungal, and anti-helminthic properties.[6] Other representative examples include cryptophycin 1 (**7**) a potent tumor-selective depsipeptide,[7] and aminopeptidase inhibitors bestatin (**8**) and amastatin (**9**).[8]

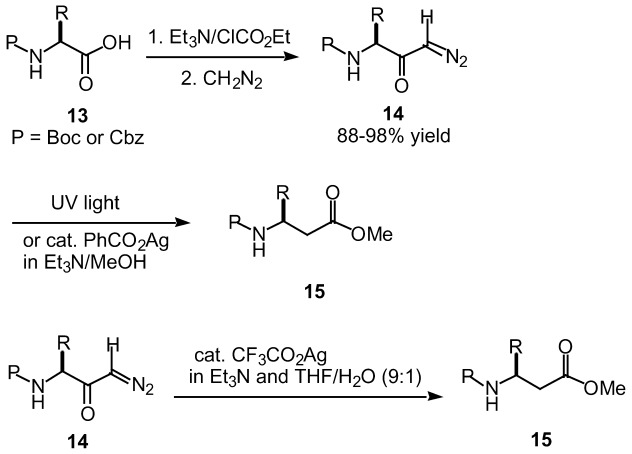
Given the significance of β-amino acids, it is not surprising that the development of their synthesis in optically pure form has become an important and challenging endeavor for organic chemists in recent years. Numerous methodologies have emerged, and most of the work prior to 1998 has been extensively reviewed.[9] This compilation is intended to give an overview of the key advances achieved from 1995 to the present. There are eight main approaches available till date for stereoselective synthesis of β-amino acids including homologation of α-amino acids, enzymatic resolution, addition of enolates (or equivalents) to imines, Curtius rearrangement, conjugate addition of a nitrogen nucleophile to α,β-unsaturated esters or imides, hydrogenation, amino hydroxylation and β-lactam synthesis. All these reactions will be discussed in the following sections along with a few other promising miscellaneous strategies.

1.1. The chiral pool approach: α-amino acids as starting materials

1.1.1. Arndt–Eistert homologation. The Arndt–Eistert reaction is considered to be the best method for one carbon chain elongation of a carboxylic acid (Scheme 2).[10] Taking the advantage of ready availability, low cost, and high enantiomeric purity of α-amino acids, the direct



Scheme 2.



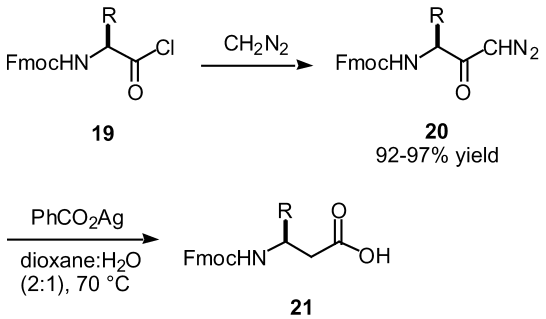
Scheme 3.

homologation to prepare β-amino acids following the Arndt–Eistert procedure has found many applications in small molecule as well as natural product synthesis.

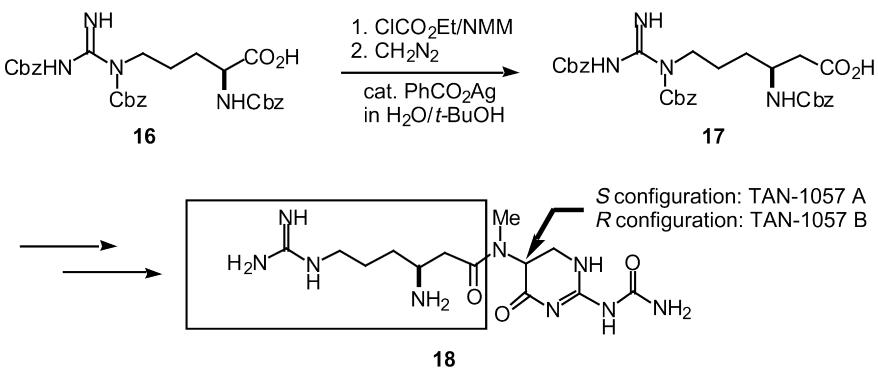
Seebach and co-workers have utilized this approach in β-peptide synthesis. As illustrated in Scheme 3, the *N*-protected α-amino acids were converted to the mixed anhydride using $Et_3N/ClCO_2Et$, followed by addition of CH_2N_2 to afford **14** with good yield and in enantiomerically pure form. Wolff rearrangement of the corresponding diazoketones to β-amino acid derivatives was then achieved by UV light initiation or by the use of a catalytic amount of silver benzoate in triethylamine and methanol.[11] In addition, diazoketone **14** may be trapped with the amine terminus of another carboxyl protected β-amino acid fragment to provide β-peptide directly. Ellmermer-Müller et al. have reported an alternate procedure to convert diazoketone **14** to β-amino esters using a mixed-solvent THF/H_2O (9:1) in the presence of a catalytic amount of silver trifluoroacetate added as a homogeneous solution in Et_3N.[12] A modified procedure using *N*-Fmoc-protected α-amino acids and *i*-BuOCOCl/*N*-methylmorpholine to form the mixed anhydride was later proposed by Seebach et al. for solid phase synthetic applications.[13]

Yuan and Williams have successfully applied the Arndt–Eistert reaction in the total synthesis of TAN-1057 A,B, anti MRSA (methicillin-resistant *Staphylococcus aureus*) antibiotics. TAN-1057 A,B (**18**) are dipeptides containing a β-arginine fragment as shown in Scheme 4. The β-amino acid was prepared in 58% yield by chain elongation of tri-*N*-Cbz-L-arginine via diazoketone formation using NMM/$ClCO_2Et$, followed by silver benzoate catalyzed rearrangement.[14] A 1:1 mixture of *tert*-butyl alcohol and water was used as the solvent. This procedure has the advantage of preparing the free acid without a saponification step and preventing deprotection of the *N*-Cbz group.

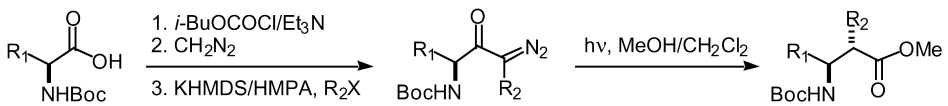
The aminoacyldiazomethanes are sometimes produced in low yields using the mixed anhydride procedure described above. Racemic starting amino acids and their methyl esters are often obtained as side products whose removal is at times very difficult. To overcome this problem, Liguori et al. have succeeded in converting the *N*-Fmoc-α-aminoacylchlorides **19** to diazomethanes in almost quantitative yields, and with complete retention of configuration.[15] The diazomethanes **20** formed in this reaction may be used in the rearrangement step without any purification. Since the Fmoc protecting group is base labile, a base-free condition (catalytic $PhCO_2Ag$ in dioxane and water at 70°C) was used to decompose the diazoketones (Scheme 5). Sewald and co-workers have reported another very interesting account where base-free, Ag^+ mediated and ultrasonic



Scheme 5.



Scheme 4.



R_1	d.r. (*anti* : *syn*)	yield (%)
Me	6:1	25
i-Pr	>10:1	48
Bn	6:1	49
$(Ph)_2CH$	6:1	45
CH_2-1-Naph	6:1	77

Scheme 6.

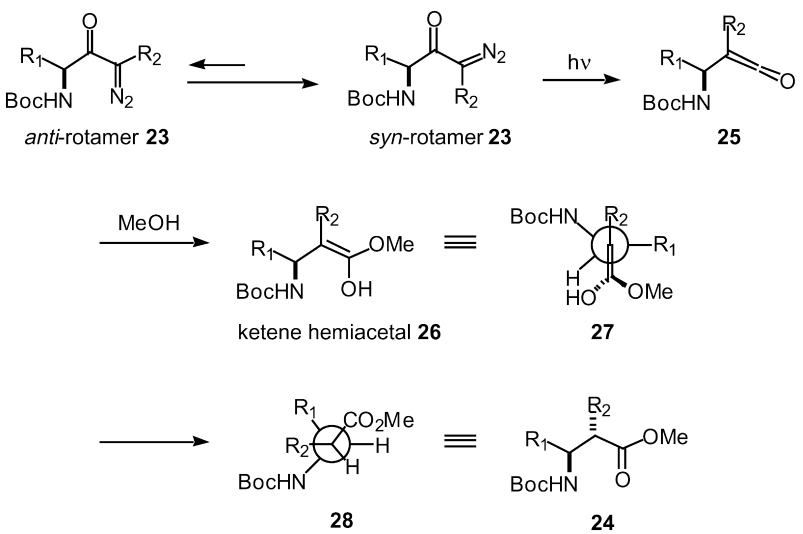
promoted Wolff rearrangement was applied to the Arndt–Eistert chain elongation of Fmoc protected α-amino acids.[16] The desired β-amino acids were prepared in moderate to good yields (65–82%) within minutes at room temperature.

Photo induced Wolff rearrangement was also featured in the asymmetric synthesis of α-substituted β-amino acid derivatives.[17] α-Alkyl-diazoketones **23** were readily prepared in two steps from the corresponding α-amino acid as depicted in Scheme 6. The rearrangement took place smoothly at −78°C under UV light irradiation. After trapping with methanol, α-substituted-β-amino esters were produced in good yield (up to 77%) favoring the *anti* products.

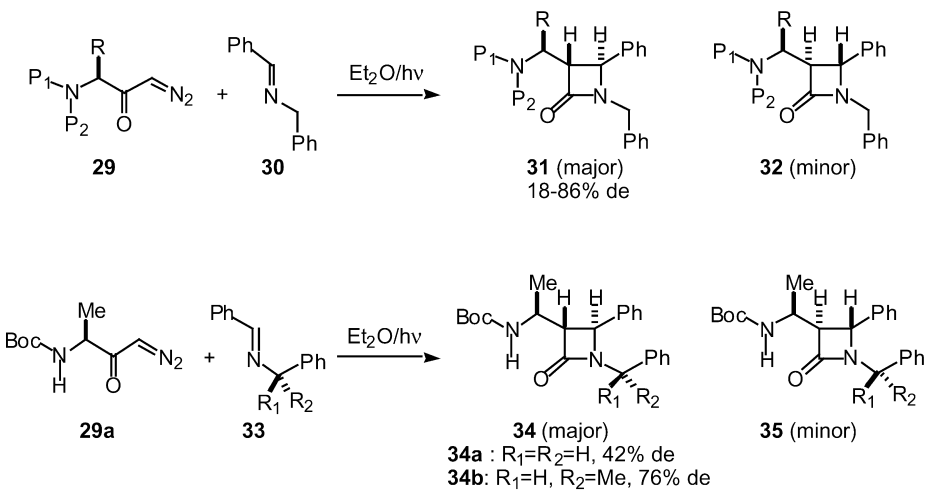
The rearrangement was believed to take place preferentially from the *syn*-rotamer of the diazoketones **23** (Scheme 7) where concerted backside attack of the nitrogen by the migrating group was possible. A ketene hemiacetal intermediate **26** was most likely generated during the course of the reaction, which then tautomerized to give the desired product **24**. A possible transition state (**27**) was also proposed by the authors based on solution NMR and molecular modeling studies (Scheme 7).

Podlech and Linder extended the Wolff rearrangement strategy to the synthesis of β-lactams.[18] In this example, diazoketones **29** were subjected to the photo Wolff rearrangement condition to afford the corresponding ketenes, which were then trapped with *N*-benzylbenzaldimine **30** to furnish β-lactams. Two of the four possible diastereomers **31** and **32** were produced with the *trans* configuration at the ring junction. The size of the amino acid side chain was the sole factor in determining the selectivity of the reaction, with the bulkier *tert*-leu providing the highest de (86%). The selectivities could be further improved by the use of a chiral imine. For instance, when the alanine-derived diazoketone **29a** was used, the diastereoselectivity was increased from 42 to 76% by the use of (*S*)-*N*-phenethylbenzaldimine **33** (Scheme 8).

While the Arndt–Eistert protocol works very well for the preparation of enantiomerically pure β-substituted as well as α-substituted β-amino acids, it is not suitable for large scale synthesis due to the high cost of the silver catalyst and difficult handling of the hazardous reagent CH_2N_2. Longobardo and co-workers[19] have developed a new way to synthesize β-amino acid via reduction of *N*-protected α-amino acid **36**, followed by conversion of the corresponding β-amino alcohol **37** to β-amino iodide **38**, then β-amino cyanide **39** (Scheme 9). The key step of this transformation



Scheme 7.



Scheme 8.

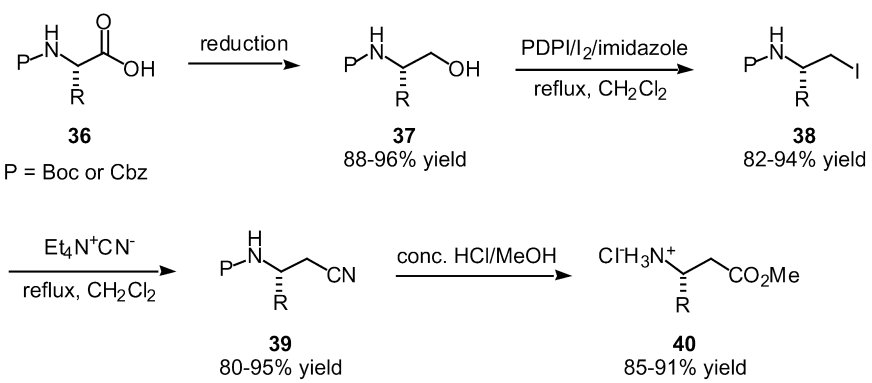
was to generate the iodide in high yields and without racemization using polystyryl diphenylphosphine-iodide (PDPI) complex.

1.1.2. Stereoselective synthesis of β-amino acids starting from aspartic acid. Aspartic acid is a naturally occurring α-amino acid which possesses a β-amino carboxylic acid fragment. This feature makes aspartic acid an attractive precursor for the preparation of many β-amino acid derivatives. Jefford and co-workers discovered that 3-(*N*-tosylamino)butano-4-lactone **42**, which is derived from aspartic acid **41** via tosylation, anhydride formation and selective $NaBH_4$ reduction, was a useful template for the stereoselective synthesis of β-amino acid derivatives.[20] The key intermediate **43** was obtained by treatment of **42** with TMSI in $EtOH/CH_2Cl_2$. Nucleophilic displacement on **43** with various Gilman reagents furnished γ-substituted β-amino acid derivatives **44** in high yields and >99% ee (Scheme 10). The same methodology was also extended to the synthesis of α-hydroxy β-amino acid, where lactone **42** was hydroxylated followed by ring opening with TMSI and substitution with organocuprates to yield **46** with *syn*-configuration. It is worth noting that when R=Ph, the resulting α-hydroxy β-amino acid derivative is a fragment of Bestatin (**8**) a well-known immunoregulation and amino peptidase B inhibitor.

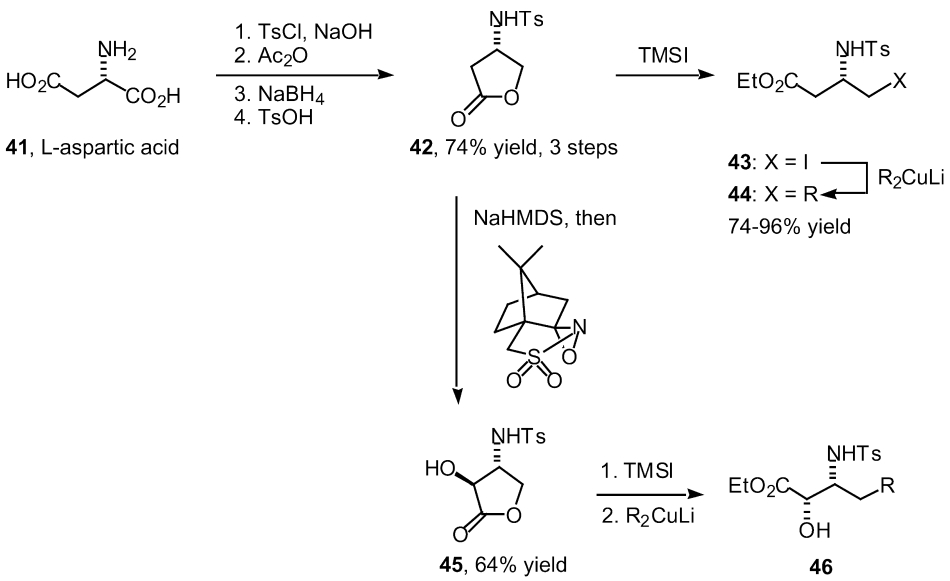
Dexter and Jackson reported a mild and convenient method for the synthesis of functionalized zinc reagent **48**.[21] The use of a dipolar aprotic solvent such as DMF was important in this transformation. The iodide precursor **47** was easily prepared from L-aspartic acid following a similar method as described above (see Scheme 10). Palladium catalyzed coupling reaction with aromatic iodides **49** produced β-amino esters **50** in moderate to good yields (Scheme 11).

Seki and Matsumoto have explored the utility of oxazolidin-2-one-4-acetic acid derivative **51**, derived from L-aspartic acid, in β-amino acid synthesis.[22] Stereoselective alkylation of **51** or **54**, obtainable from **51** in a single transformation (Scheme 12),[23] was the key step, where an inversion of stereochemistry was observed. Therefore, the Seki protocol provides an efficient route for easy access to either diastereomer of the α,β-disubstituted β-amino acid derivatives **53**.

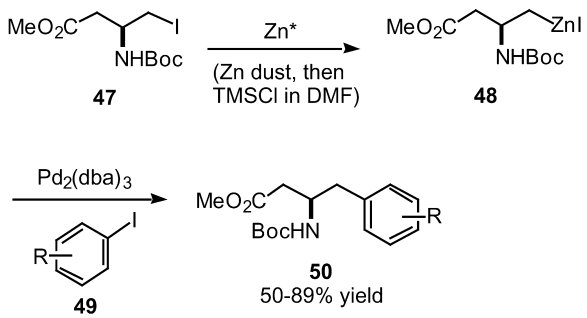
1.1.3. Stereoselective synthesis of β-amino acids from asparagine and derivatives. Diastereoselective alkylation to introduce substitution at the α-carbon is by far the most efficient method for preparing α,α-disubstituted β-amino acid derivatives. Better diastereoselectivities are often obtained using cyclic auxiliaries, which allow for superior differentiation of the two diastereotopic faces. The alkylation of heterocyclic compound perhydropyrimidin-4-one **57**, derived from inexpensive α-amino acid L-asparagine,[24] has been extensively studied by Juaristi et al.[25] Various electrophiles were added to **57** with almost complete stereocontrol (>95% de) providing the *trans* alkylated



Scheme 9.



Scheme 10.

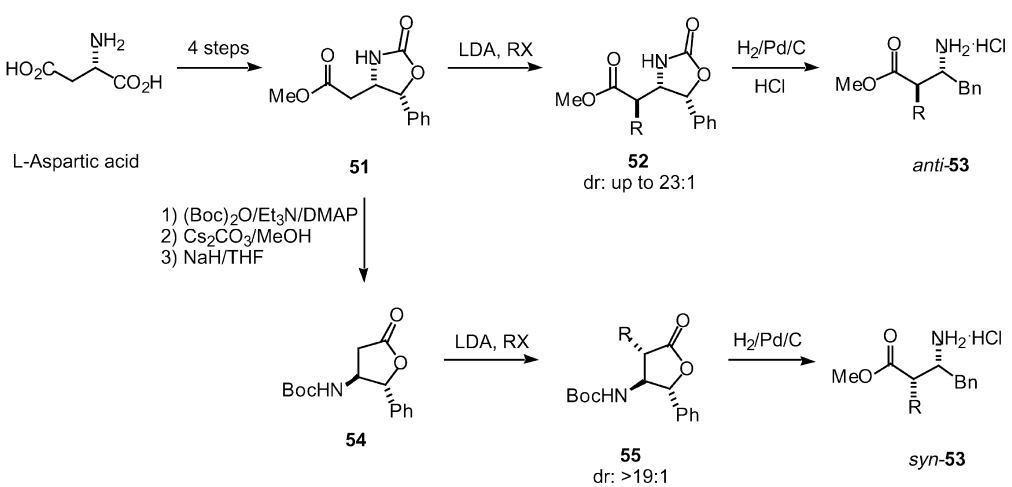


Scheme 11.

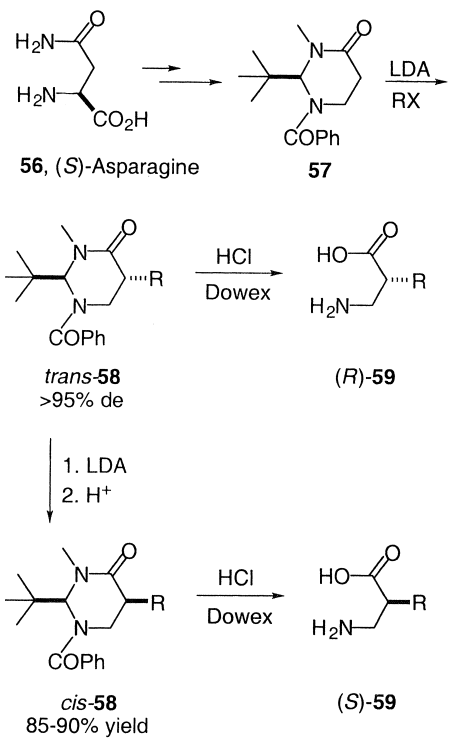
product **58** in good yields, which upon hydrolysis using HCl gave the α-substituted β-amino acids **59** with *R* configuration (Scheme 13). Alternatively, the β-amino acids with *S* configuration were conveniently prepared by epimerization of the *trans* adducts. The key step in this transformation was the highly diastereoselective protonation of enolates generated from *trans*-**58**.

In an extension to their methodology, Juaristi and coworkers demonstrated the application of the same chiral auxiliary **57** in the synthesis of α,α-disubstituted β-amino acids.[26] Dialkylation of **57** proceeded with >95% diastereoselectivity. Acid hydrolysis of the dialkylated adducts **60** yielded enantiopure β-amino acids **61** in high yields (Scheme 14(A)). Furthermore, the same authors also investigated the alkylation of iminoester **62**. Different electrophiles were added to **62** with excellent diastereoselectivities to furnish the *trans* products **63**, precursors to β,β-disubstituted β-amino acids **64** (Scheme 14(B)).[27]

A highly diastereoselective synthesis of functionalized β-amino acids following an entirely different approach is outlined in Scheme 15.[28] The key feature of this strategy is the radical mediated 1,5-hydrogen atom transfer and subsequent trapping with electrophilic olefins. The β-amino acid derivatives **67** were obtained with high ee's through 1,3-asymmetric induction. Large amounts of the reduction product **68** was also observed in this process, which led to low yields of the desired products **67**.



Scheme 12.



56, (*S*)-Asparagine
57
trans-58
>95% de
(*R*)-59
cis-58
85-90% yield
(*S*)-59

Scheme 13.

1.2. β-Amino acids as starting materials

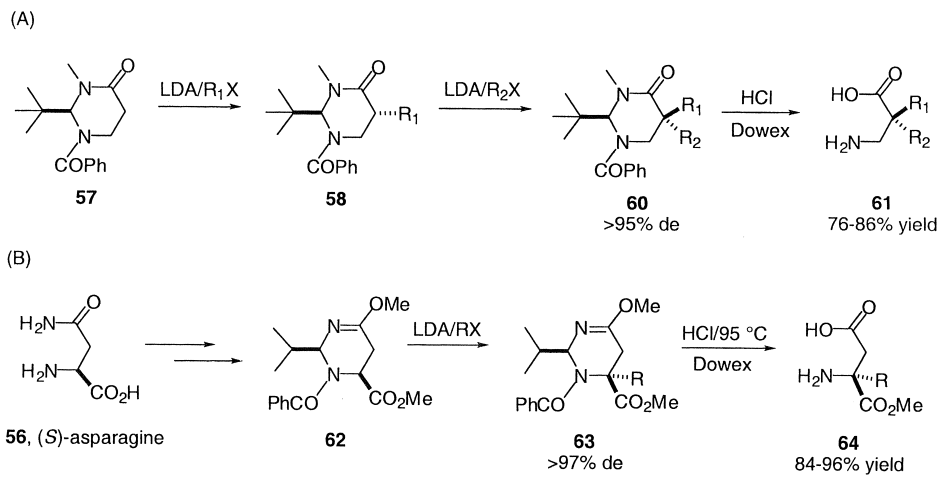
1.2.1. Classic resolution of β-amino acids. A traditional method to resolve a carboxylic acid is to transform its racemic mixture into diastereomeric salts via complexation with a chiral base.[29] As illustrated in Scheme 16, upon treatment of racemic **69** with a base, for example, (−)-ephedrine (**70**) two diastereomeric salts **71**, **72** will be produced which can then be separated by fractional crystallization due to their difference in solubility in a suitable solvent. After separation, the resulting diastereochemically pure salt can be easily converted back to the free acids while the chiral base can be recovered and reused. However, multistep fractional recrystallization is often required, and therefore the sequence is long and tedious. Ephedrine is among the most commonly used bases in this process, as it is readily available and inexpensive. Following this methodology, *N*-protected-(*S*)-3-amino-4-pentenoic acid **73** and both enantiomers of *cis*-2-aminocyclopentanecarboxylic acid **74** were resolved in enantiopure form by Zablocki[30] and Samuelsson,[31] respectively.

Alternatively, β-amino esters were resolved through diastereomeric salt formation between the amino group and a chiral acid, such as tartaric acid, mandelic acid or camphorsulfonic acid.[9c] β-Amino ester **77**, prepared by conjugate addition of (*S*)-α-methylbenzylamine **75** to methyl methacrylate **76**, was resolved by multiple recrystallizations of its tosylate salt **78** (Scheme 17).[32]

1.2.2. Enzymatic resolution of β-amino acids. Enzymatic resolution plays an important role in the production of α-amino acids, and the hydrolytic enzymes are among the most popular ones used in this context. On the other hand, the biocatalytic preparation of β-amino acids in their enantiopure form is less explored. This is mainly due to the fact that the enzymes commonly used to resolve α-amino acids have narrow substrate tolerance of β-amino acids and often exhibit low selectivity in the process.[9e,33]

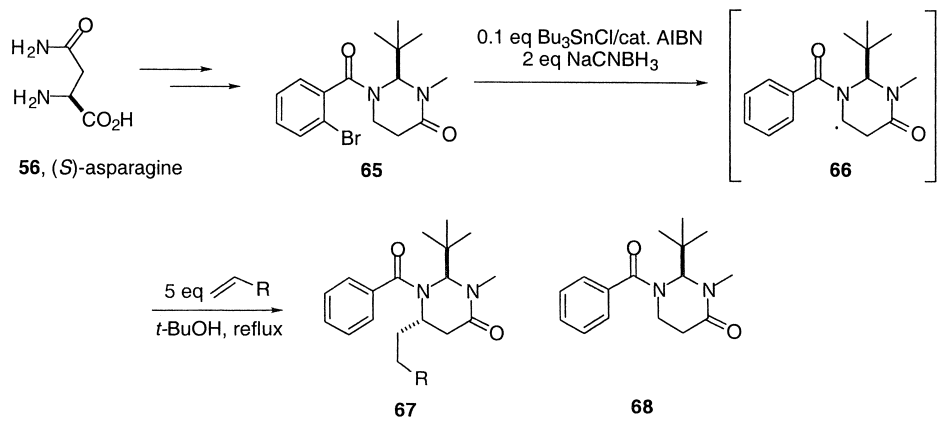
There are several types of enzymatic resolutions available for asymmetric synthesis of β-amino acids and derivatives. One such process involves stereoselective acylation of one enantiomer of the racemic β-amino esters or *N*-hydroxymethylated β-lactams. For instance, Kanerva and Fülöp et al., utilizing *Pseudomonas cepacia* lipase PS or *Candida antarctica* lipase A, were able to resolve 10 cyclic β-amino carboxylic acids via enantioselective amide formation between the amino group of the racemic substrates and 2,2,2-trifluoroethyl esters in diisopropyl ether.[34] As outlined in Scheme 18, the acylation of the amino group preferentially occurred at the *R* center, leading to *S*-enriched unreacted substrates **79** and various *R*-enriched amides **80**.

Recently, Kanerva and co-workers have reported *Candida antarctica* lipase A catalyzed kinetic resolution of aliphatic β-substituted β-amino esters.[35] Their method allowed for gram-scale synthesis of the corresponding β-amino acids with high enantiomeric purity (Scheme 19(A)). Gotor et al.



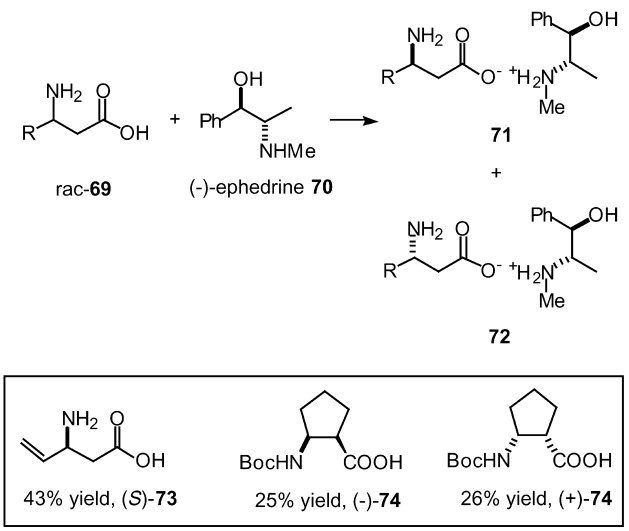
57
58
60
>95% de
61
76-86% yield
56, (*S*)-asparagine
62
63
>97% de
64
84-96% yield

Scheme 14.



R	yield **67** (%)	ee (%)	reduction **68** (%)
CO_2Me	56	97	10
CN	59	97	20
SO_2Ph	50	98	41

Scheme 15.



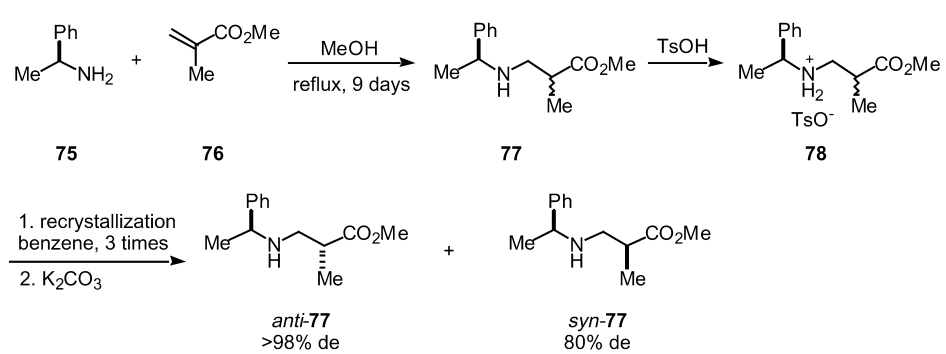
Scheme 16.

have described a similar enzymatic route to prepare enantiopure 3-aminobutyric acid (**84**) (Scheme 19(B)).[36]

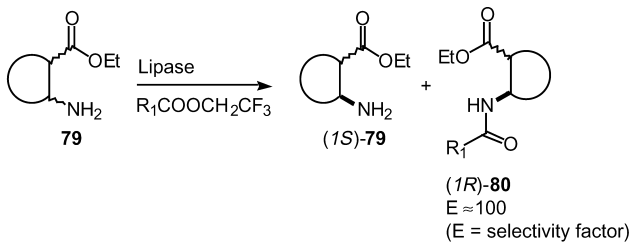
The efficiency of lipase in catalyzing the asymmetric acylation of *N*-hydroxymethylated β-lactams has also been explored.[37] Various cyclic substrates as illustrated in Scheme 20 were resolved in high enantioselectivities when the reactions were carried out in acetone and vinyl butyrate as the acyl donor. More importantly, hydrolysis of azetidinones (1*R*,5*S*)-**87a** and (1*S*,5*R*)-**86a** provided both enantiomers of β-amino acid cispentacin (**2**) an antifungal antibiotic.

Theil and Ballschuh have also developed a useful chemoenzymatic route for the preparation of both enantiomers of cispentacin.[38] The resolution was based on the lipase PS catalyzed transesterification of silyloxyalcohol **88** (Scheme 21). Furthermore, Lee and Kim described a similar strategy for the enantioselective synthesis of taxol side chain **92a** (Scheme 22) and analogs.[39]

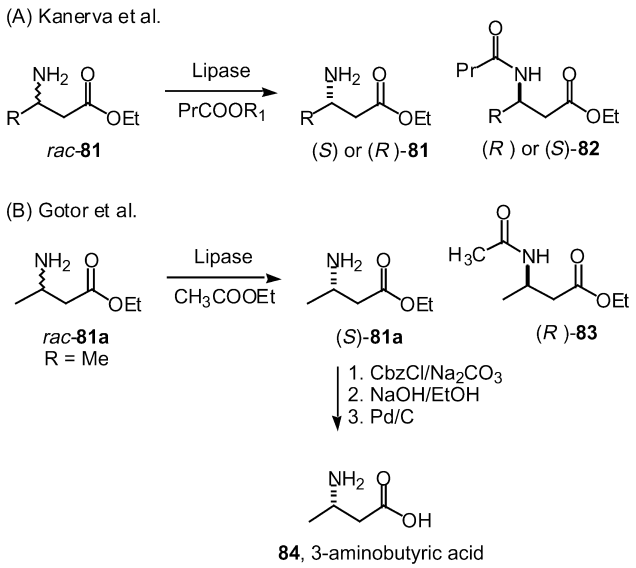
Until now, the most efficient method for enzymatic resolution of β-amino acids seems to be the penicillin acylase (PA) catalyzed hydrolysis of *N*-phenylacetyl derivatives. Soloshonok and Cardillo are the key players in this area. Soloshonok et al. prepared racemic β-aryl-β-amino acids **96** through the condensation of aromatic aldehydes **93** and malonic acid **94** in the presence of ammonium acetate **95**. PA mediated hydrolysis of the corresponding *N*-phenylacetyl derivatives **97** provided the



Scheme 17.



Scheme 18.



Scheme 19.

(*R*)-β-amino acids in >95% ee (Scheme 23).[40] The *S* enantiomers were also prepared in enantiopure form via hydrolysis of *S*-**97**.

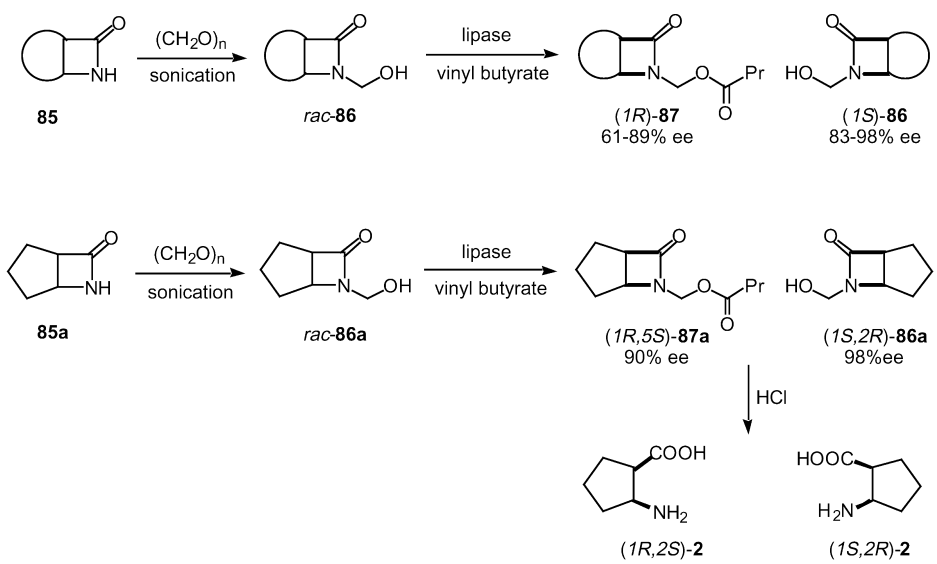
Similarly, Cardillo and Tomasini have resolved the α-alkyl *N*-phenylacetyl β-amino acid derivatives *anti*-**99**, prepared from alkylation of 3-aminobutanoic acid *rac*-**84**, using immobilized penicillin G acylase (PGA).[41] Both enantiomers of **101** were obtained in good yields and excellent enantioselectivities (Scheme 24).

1.3. Simple β-amino acids to functionalized derivatives

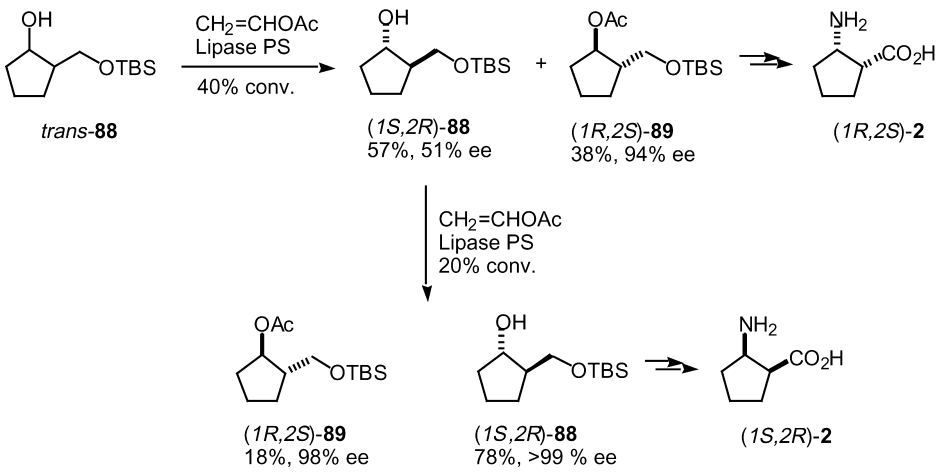
α-Hydroxy β-amino acids are a class of compounds which show high pharmaceutical and medicinal interest.[42] Both the *syn* and *anti* stereoisomers are known to possess interesting bioactivities. A noted example of the *syn* stereoisomers is the antitumor agent taxol, which contains phenylisoserine side chain as its key pharmacophore. Consequently, enormous efforts have been expended to develop efficient routes for their synthesis. Cardillo and Gentilucci reported a facile two-step approach for the preparation of *syn*-α-hydroxy β-amino acids.[43] The key step was the highly diastereoselective formation of *trans*-oxazoline **106** from iodination of the dianion of **104** (Scheme 25). Enantiopure 3-amino-3-phenylpropanoic acid (**103**) was obtained by PGA catalyzed kinetic resolution of *rac*-**102**.

The same methodology was also extended to the synthesis of *anti*-α-alkyl-α-hydroxy-β-amino acids.[44] Enolization of oxazoline **106** with LiHMDS followed by quenching with different alkyl halides afforded the desired alkylated products **107** in good yields. The diastereoselectivity increased with the size of the electrophile whereas methylation proceeded with poor de (16%). As depicted in Scheme 26, *re* face electrophile attack was favored to avoid steric interaction with the C-4 phenyl group, thus *syn* isomers **107** were produced as the major products, which upon hydrolysis under mild acidic condition furnished β-amino esters **108** in quantitative yields.

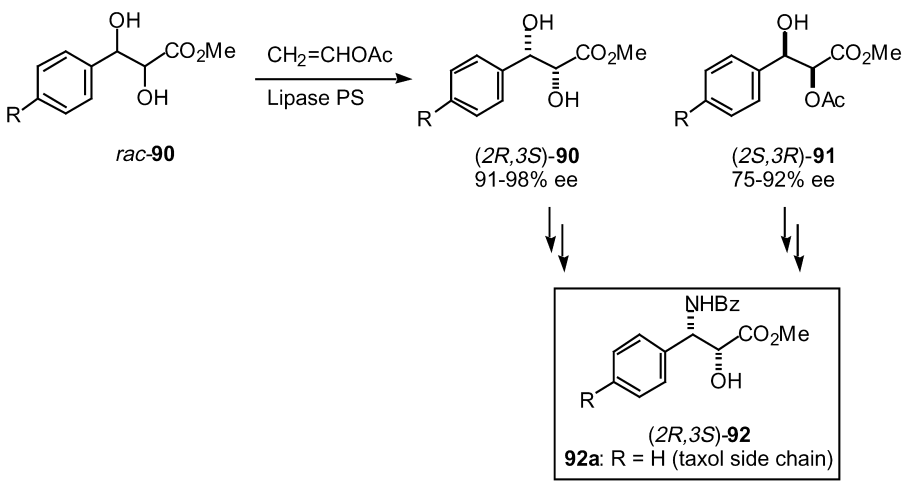
As a complementary method to the one discussed above, stereoselective preparation of *syn*-α-alkyl-α-hydroxy-β-amino acids were accomplished following a slightly different reaction sequence: alkylation of **109**, *cis*-oxazoline **111** formation, and hydrolysis (Scheme 27).[45] The *syn* stereoselectivity can be envisioned by an *anti*-iodine addition to the sodium dianion **113**, providing the *anti*-2-iodo derivative **114**, which was then cyclized to give the



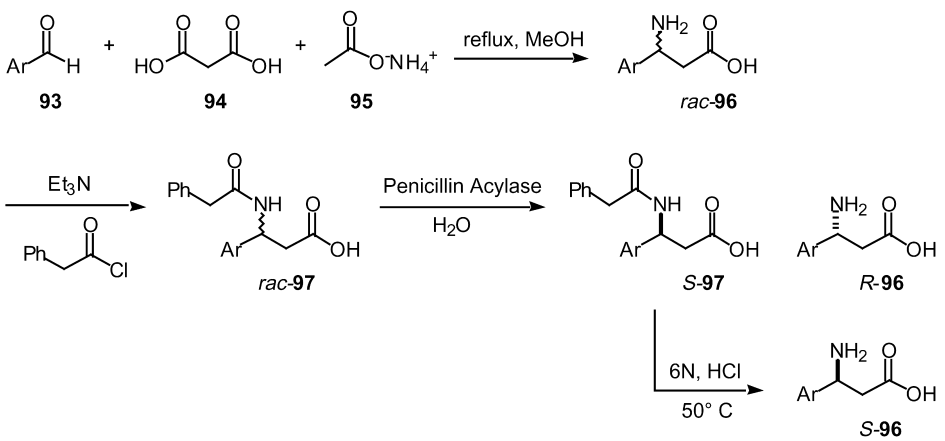
Scheme 20.



Scheme 21.



Scheme 22.

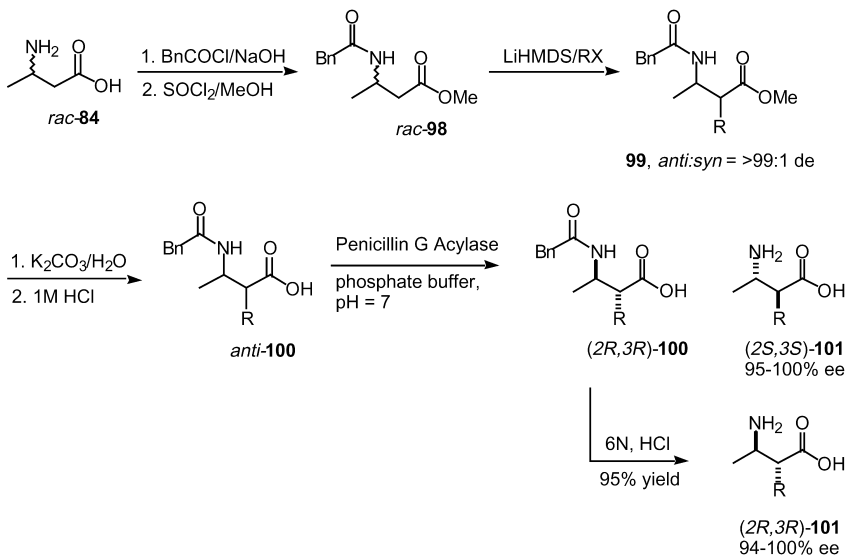


Scheme 23.

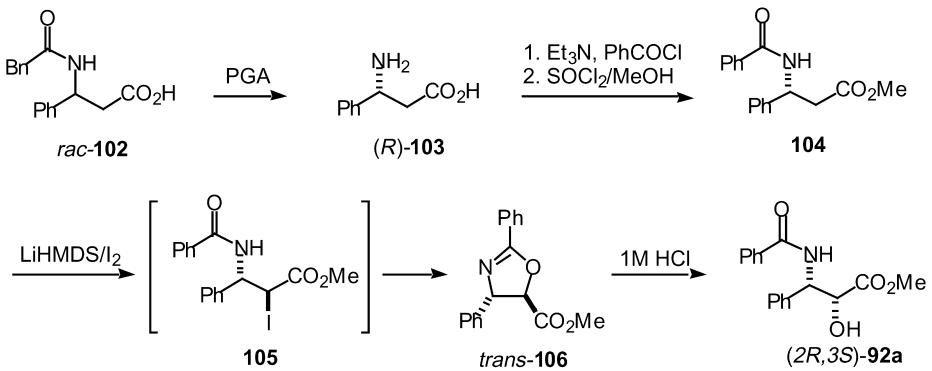
cis-**111**. Ruano and Paredes have also reported a convenient procedure for the synthesis of optically pure *syn*-α-alkyl-α-hydroxy-β-amino acids through hydrolysis of chiral 2-oxazolines.[46]

Pyrimidinones have been extensively used in asymmetric synthesis of β-amino acid derivatives.[47] Escalante and Juaristi have demonstrated the efficiency of perhydropyrimidinone **115**, derived from (*S*)-3-amino-3-phenylpropionate, in stereoselective hydroxylation reaction to prepare the stereoisomer of taxol side chain (2*R*,3*R*)-**92a** (Scheme 28).[48]

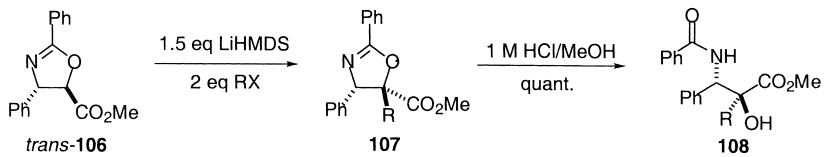
In another recent development, Seebach et al. have



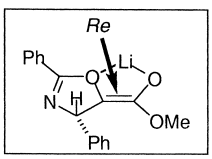
Scheme 24.



Scheme 25.



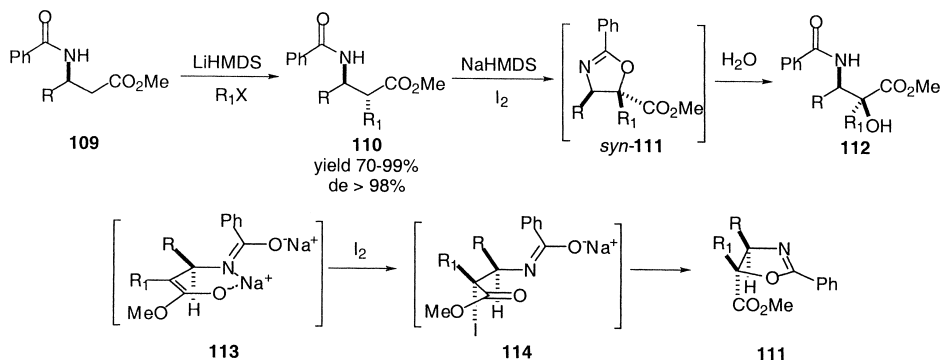
RX	Yield (%)	de (%)
MeI	94	16
EtI	90	48
PrI	89	74
Allyl iodide	98	84
BnBr	98	84



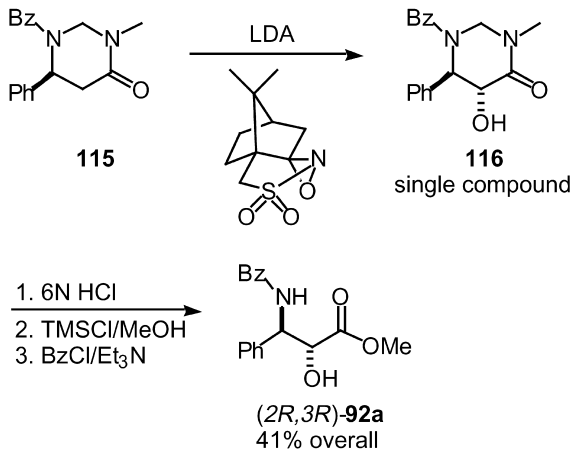
Scheme 26.

described a useful process for the preparation of α-substituted β-amino acids based on highly stereoselective alkylation of hydropyrimidine **119**.[49] This chiral auxiliary was readily available in gram quantities from 3-amino propanoic acid, and subsequent resolution via preparative HPLC, followed by reaction with Me_3OBF_4 (Scheme 29). Alkylation of **119** using LDA as the base proceeded smoothly with complete stereocontrol. High yields were obtained with primary alkyl, allyl, propargyl, benzyl and carbalkoxymethyl halides. Conversion of the heterocycle **120** to α-branched β-amino esters **121** was achieved by a 3-step deprotection, hydrolysis and protection sequence.

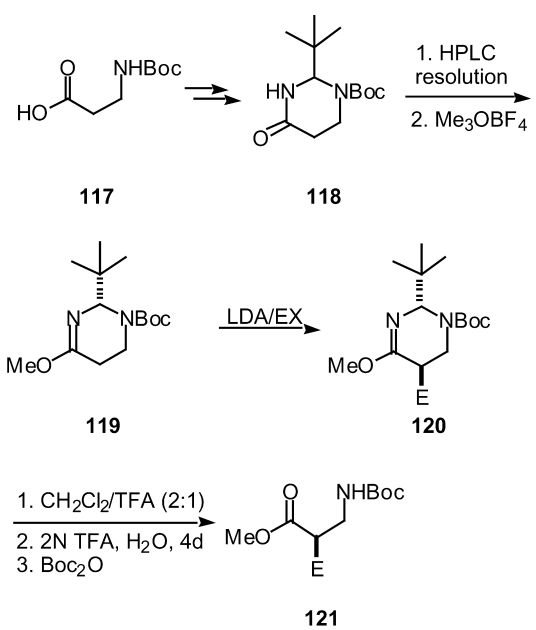
Lavielle and co-workers have successfully demonstrated the use of sultam-β-alaninate-derived Schiff base **123** as a novel precursor for the synthesis of α-substituted β-amino acid derivatives.[50] The lithium enolate generated from **123** was trapped with different electrophiles to give the desired



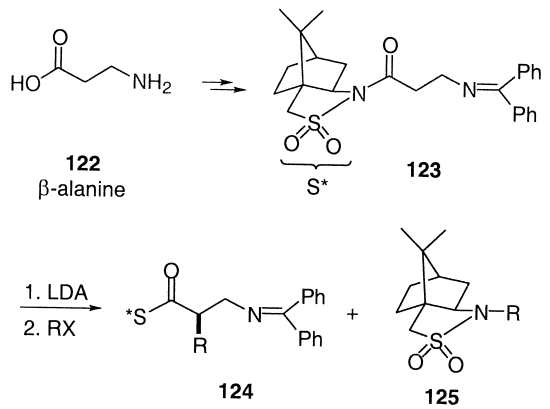
Scheme 27.



Scheme 28.



Scheme 29.



Scheme 30.

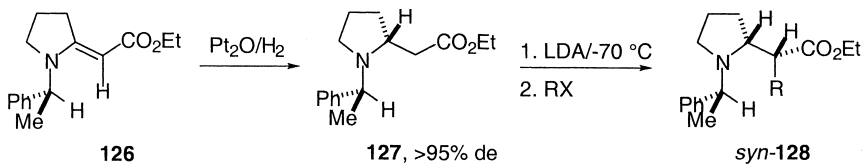
product **124** as a single diastereomer (Scheme 30). The reaction must be performed at −45°C or below to avoid formation of byproduct **125**.

Diastereoselective alkylation of β-amino ester **127** toward α-substituted β-amino acid derivatives was investigated by Lhommet et al.[51] Catalytic hydrogenation of β-enamino ester **126** gave **127** with >95% de in 60% yield (Scheme 31). This product was then alkylated at −70°C with a series of halides leading to *syn*-**128** as the only product. A point to note was that secondary halides gave no product (entry 5, Scheme 31) and the yield of the product decreased dramatically with the chain length of the alkyl halide (compare entries 1–3, Scheme 31). On the other hand, the alkylation reaction proceeded smoothly with allylic halides, which upon hydrogenation provided an alternate route to the synthesis of **128** with long alkyl chains. The high *syn* diastereoselectivity could be envisioned by the formation of the *E* enolate, which led to the most stable conformation **129** for stereoelectronic reasons. Alkylation would then occur opposite to the bulky methylbenzyl group, providing the final product as a single diastereomer.

1.4. Curtius rearrangement

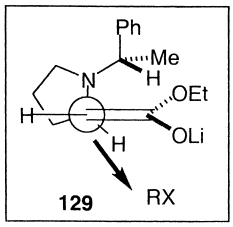
Functionalized succinates are ideal precursors for asymmetric synthesis of β-amino acids if one can selectively transform one of the carboxy groups into an amino group by means of a Curtius rearrangement (Scheme 32).

Sibi and Deshpande have showcased this methodology in the stereoselective preparation of iturinic acid (**137**) and 2-methyl-3-aminopropanoic acid **140** (R=Me) components of biologically important peptides iturin and cryptophycin.[52] Alkylation of **133** attached with Sibi's chiral auxiliary provided **134** in good to excellent diastereoselectivities



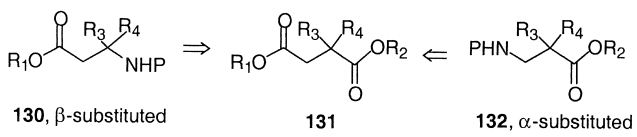
126 127, >95% de *syn*-128

Entry	Substrate	X	Yield (%)
1	R = Me	I	75
2	R = Et	I	60
3	R = Pr	I	25
4	R = allyl	Br	68
5	R = *i*-Pr	Br	N.R.



129

Scheme 31.



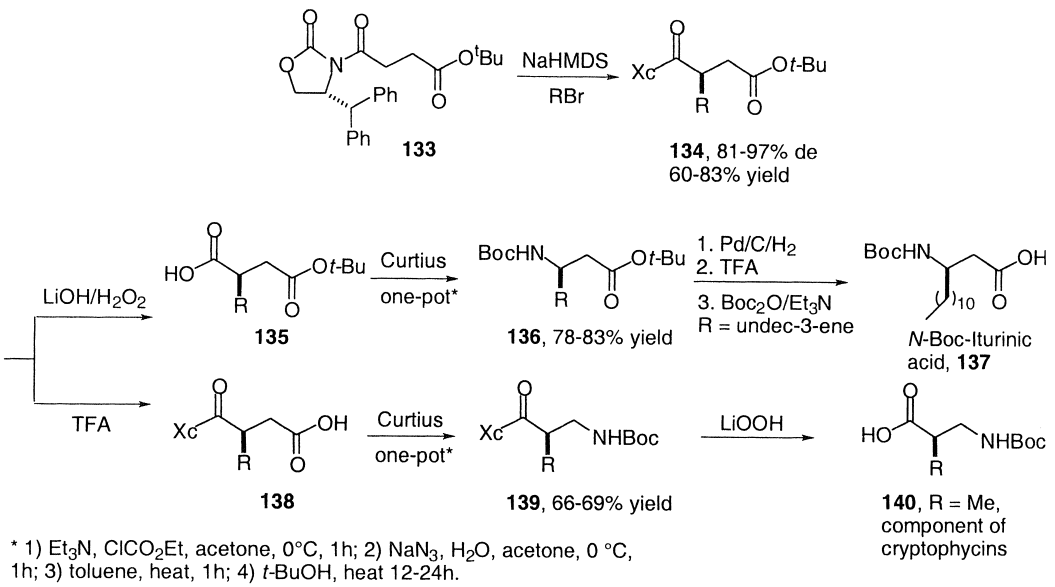
130, β-substituted **131** **132**, α-substituted

Scheme 32.

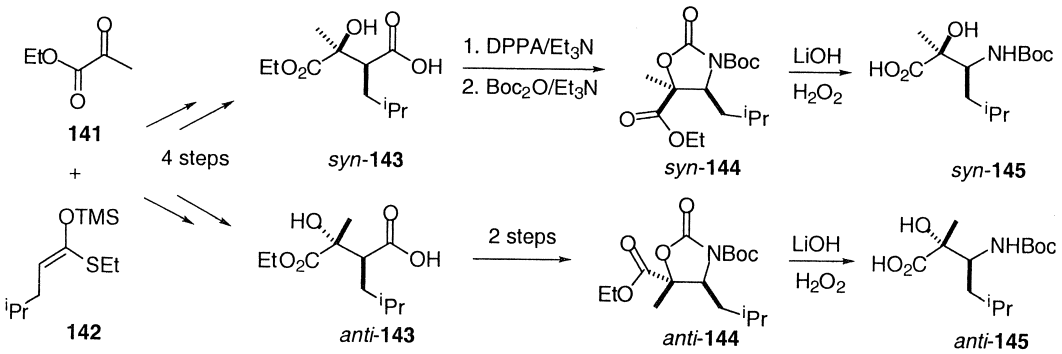
(Scheme 33). The imide or ester end of **134** was then selectively hydrolyzed using $LiOH–H_2O_2$ or TFA, respectively. Finally, Curtius rearrangement proceeded with retention of stereochemistry to give **137** and **140** with high overall yield in four steps.

The Curtius protocol described above provided a practical route toward a variety of α or β-substituted β-amino acid derivatives due to its generality of the alkylation, hydrolysis and Curtius rearrangement steps. The Evans' group has also successfully employed a similar sequence, where β-alkyl and β-aryl amino acids were produced with high enantiomeric purities.[53] Roers and Verdine have synthesized *syn* and *anti* α-hydroxy β-amino acids **145** via a modified Curtius rearrangement procedure using DPPA as an azide source.[8] The key steps included the asymmetric aldol reaction to produce the chiral succinates **143**, and the formation of oxazolidinones **144**, which could be chemoselectively opened to give the desired β-amino acids containing a tertiary hydroxyl group at the α-carbon (Scheme 34).

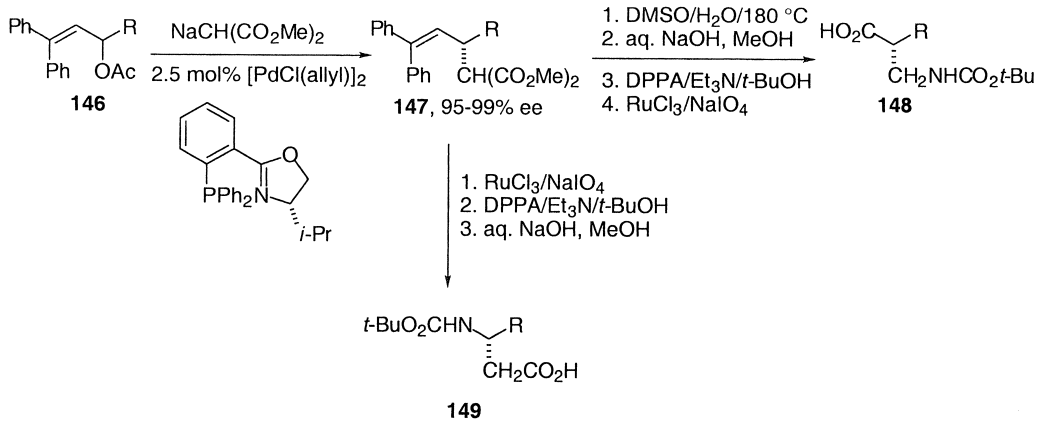
A palladium catalyzed asymmetric allylic substitution followed by Curtius rearrangement sequence to β-amino acid derivatives was explored by Williams and coworkers.[54] Taking advantage of the well established Pd-mediated substitution reaction with allylic acetate **146**, compounds **147** were prepared with complete regio- and enantiocontrol (Scheme 35). Decarboxylation of **147**, Curtius rearrangement, and oxidation of the double bond led to α-substituted β-amino acid derivatives **148** without loss of ee. Alternatively, **147** was oxidized first, then underwent Curtius rearrangement smoothly to give enantiopure β-substituted β-amino acid derivatives **149**. The dihydroxylated *trans*-aminocyclohexane β-amino acid **153** was recently prepared by Wipf and Wang.[55] The titanium catalyzed asymmetric Diels–Alder reaction with desymmetrized fumarate **150**, and subsequent Curtius rearrangement were the highlights of their synthesis (Scheme 36). On the



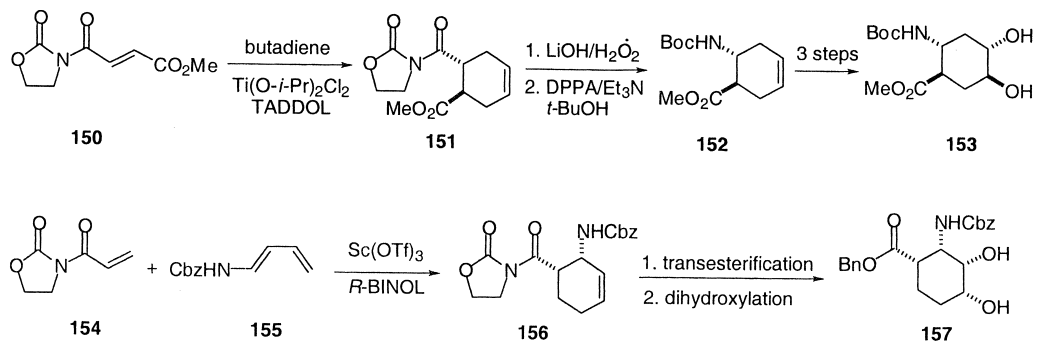
Scheme 33.



Scheme 34.



Scheme 35.



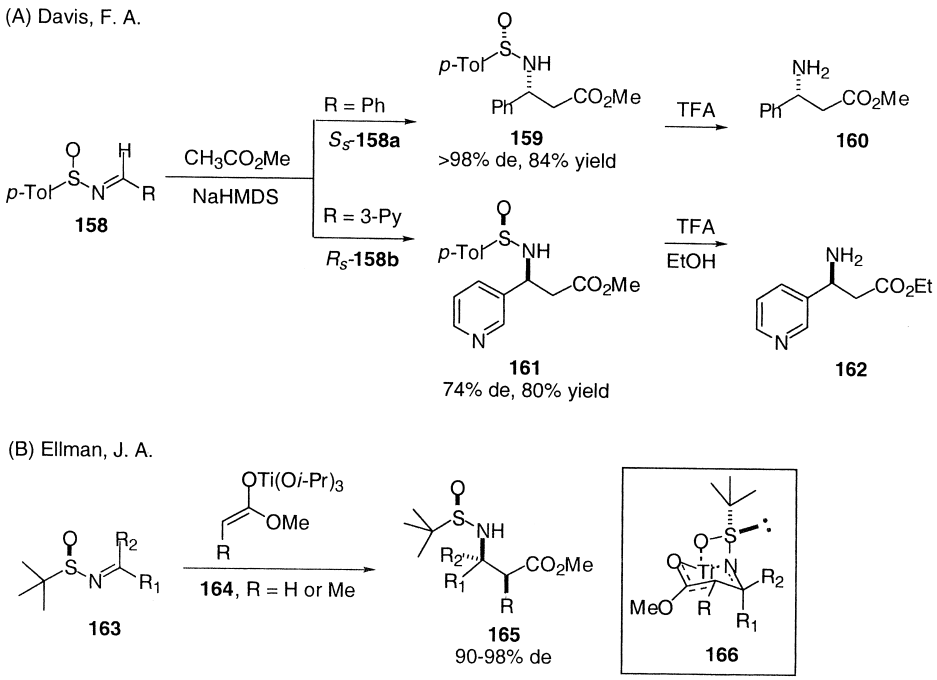
Scheme 36.

other hand, again featuring asymmetric Diels–Alder reaction, the *cis* β-amino acid **157** was obtained in 3 steps from aminodiene **155** and acyl oxazolidinone **154**. The above examples illustrate that Curtius rearrangement is a versatile method for the construction of functionalized β-amino acid derivatives with either β or α-substitution. Additionally, this process was utilized by Samuelsson in the synthesis of *trans* 2-aminocyclopentanecarboxylic acid,[31] and by Ortuño in the preparation of constrained cyclopropane and cyclobutane β-amino acids.[56]

1.5. Addition to carbon–nitrogen double bonds

1.5.1. Asymmetric addition of enolates to imines. The asymmetric Mannich-type reaction provides a general access to β-amino acids. It involves the condensation of an imine and an ester enolate or equivalent. The diastereoselective version of this reaction has been extensively studied, where a chiral controller is either attached to the imine nitrogen, the enolate, or both.

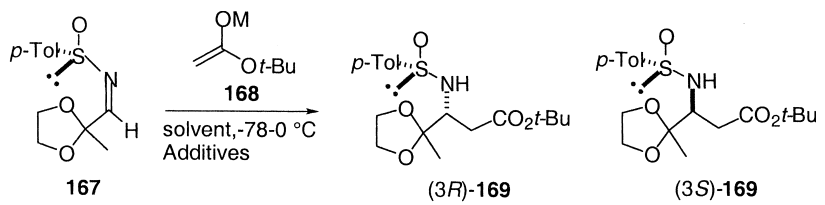
The use of sulfoxides as chiral auxiliaries in asymmetric synthesis has received increased attention in recent years.[57] Diastereoselective addition of sodium enolate to chiral sulfinimine **158** has been investigated by Davis et al. in the preparation of (*R*)-(+)-β-phenylalanine **160** and (*S*)-(+)-ethyl-β-amino-3-pyridinepropanoate **162** (Scheme 37(A)).[58] The carbon–nitrogen double bond is activated by the sulfinyl group, and therefore facilitates the addition of various nucleophiles. Another advantage of using sulfinimines in β-amino acid synthesis is that it is highly stereodirecting and can be easily removed without



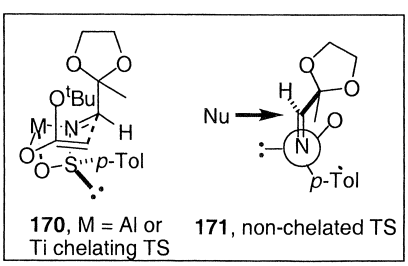
Scheme 37.

epimerization. Ellman and Tang applied a similar methodology for the construction of β,β-disubstituted and α,β-disubstituted β-amino acids with satisfactory results.[59] As shown in Scheme 37(B), titanium enolate **164** added to *tert*-butanesulfinyl imine **163** with high *syn* diastereoselectivity, which was consistent with the Zimmerman–Traxler model **166**.

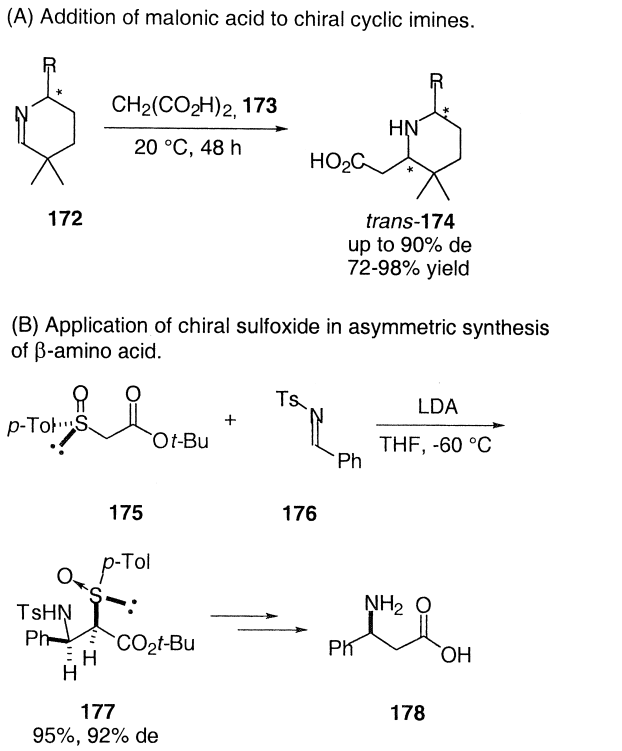
Fujisawa and co-workers have found that the selectivity of the reaction between **167** and **168** was dependent on the enolate metal species, additives, as well as the solvents used.[60] The use of lithium enolate in the presence of 3 equiv. of HMPA in THF provided the 3*S* product with 96% de, whereas titanium or aluminum enolates gave 3*R* product up to 92% de (Scheme 38). A non-chelated model **171** was proposed in the case of lithium enolate, and the reversed selectivities obtained with other metal enolates were rationalized by the chelation-controlled Zimmerman–Traxler transition state **170**. A switchover of diastereoselectivity was also observed when the reaction was



Entry	Metal	Additive (eq)	Solvent	Yield (%)	3*R* : 3*S*
1	Li	None	THF	65	14 : 86
2	Li	HMPA (3.0)	THF	68	02 : 98
3	Li	None	Et_2O	75	82 : 18
4	$Ti(Oi\text{-}Pr)_3$	None	THF	89	96 : 04
5	AlEtCl	None	THF	79	77 : 23



Scheme 38.



Scheme 39.

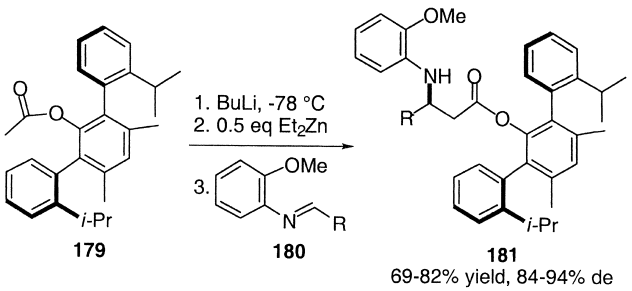
performed in ether instead of THF (compare entries 1 and 3, Scheme 38).

On the other hand, cyclic β-amino acid **174** was obtained in high *trans* diastereoselectivity by addition of malonic acid **173** to cyclic imines **172** (Scheme 39(A)).[61] In addition, Bhat et al. synthesized enantiopure β-amino-β-phenylpropionic acid **178** through the application of chiral enolate of *tert*-butyl (+)-(*R*)-*p*-toluenesulfinylacetate (**175**) (Scheme 39(B)).[62]

Diastereoselective Mannich reaction of chiral enolates and achiral imines has been examined by several research groups. One recent example reported by Yamamoto et al. involved the addition of lithium enolate generated from chiral acetate **179** to aldimines **180**.[63] The use of a Lewis acid additive (0.5 equiv. of Et_2Zn) was important to activate the imine functionality, and therefore provided the desired product **181** in high yield and selectivity (Scheme 40).

Badía and co-workers, utilizing readily available (*S*,*S*)-(+)-pseudoephedrine **182** as the chiral auxiliary, were able to prepare different α-methyl-β-substituted β-amino esters **185** with excellent diastereoselectivities (Scheme 41(A)).[64] Additionally, the reactions of imines and chiral enolates were explored by Wang,[65] Roos,[66] Zanda,[67] and Wyatt,[68] respectively, in asymmetric preparation of β-substituted-β-amino acids (Scheme 41(B) and (C)) α-trifluoromethyl-β-hydroxyaspartic acid **192** (Scheme 41(D)) and 2-substituted 3-aminopropanoic acids **196** (Scheme 41(E)).

In a related study, Kise and Ueda described the synthesis of *anti*-α,β-disubstituted β-amino ester **200** via the use of lithium enolate of chiral oxazolidinone **197**.[69] A key aspect



Scheme 40.

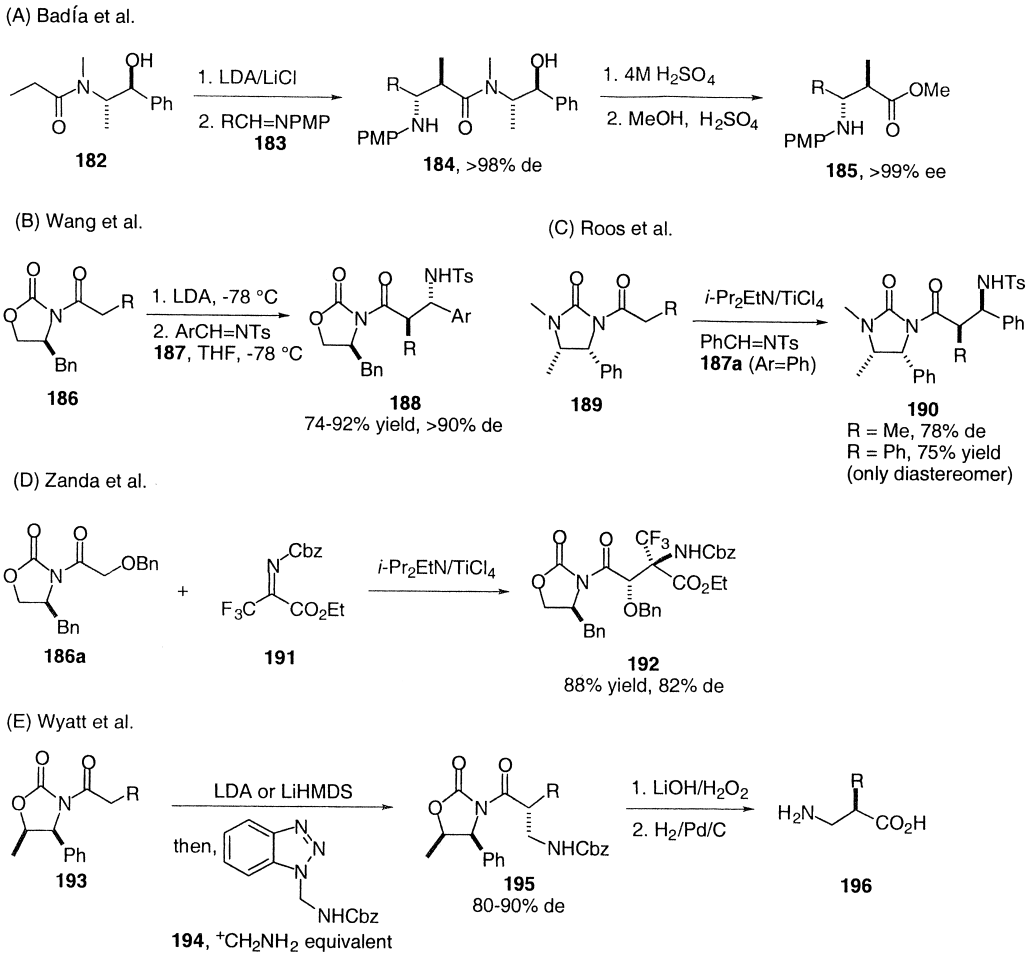
of this method was the simultaneous in situ generation of the enolate and *N*-alkoxycarbonylimine (Scheme 42).[70] Compound **200** was then converted to β-lactam **201** in 2 steps, a useful precursor of β-lactam antibiotic PS-5.

A novel diastereoselective Mannich-type reaction involving chiral enolate of **204** and carbamate **205** was developed by Palomo and co-workers.[71] As depicted in Scheme 43, non-racemic **204** was easily prepared from acetylene **202** and camphor **203**,[72] which upon treatment with an excess amount of LDA, reacted with **205** to furnish β-amino acid derivative **206** with up to 98% de. An additional feature of this transformation was that the camphor chiral auxiliary **203** was recovered along with the enantiopure *N*-protected β-amino acids **207** after desilylation and oxidative cleavage of the acyloin moiety of **206**.

Gennari, Vulpetti and Pain have shown that chiral boron enolates, prepared from α-halosubstituted thioacetates **207** and menthone-derived ligands **208**, reacted with silyl imines **209** with excellent diastereocontrol to give *syn*-α-halo-β-aminothioesters **210** (Scheme 44(A)).[73] On the other hand, for the first time, Barbas and co-workers have successfully demonstrated the use of unmodified aldehyde donors in catalytic asymmetric Mannich reactions (Scheme 44(B)).[74] In the presence of L-proline, a number of aliphatic aldehydes were added to *N*-protected α-imino ethyl glyoxylate **212** to afford β-formyl functionalized amino acids **213** with high ee's, presumably through an aldehyde enamine intermediate. Compound **213** could be readily transformed into β-amino acid derivatives **214** in two easy steps.

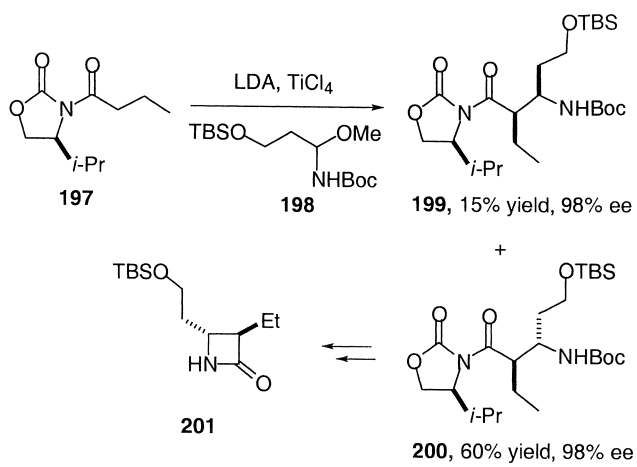
1.5.2. Asymmetric addition of silyl enolates to imines. As previously discussed, the asymmetric Mannich reaction represents a powerful route to stereoselective synthesis of β-amino esters. However, until now this reaction is considerably less developed due to two main reasons: the poor electrophilicity of the imine functionality, and its tendency to undergo α-deprotonation leading to the formation of an enamine. One way to address these limitations is through the use of preformed enolates, such as silyl enolates as the nucleophiles.

Kunz et al. have found that $ZnCl_2$ promoted asymmetric Mannich reaction between silyl ketene acetal **216** or bis(silyl) ketene acetal **217** and *N*-galactosyl imines **215** provided a convenient access to β-amino esters **220** (Scheme 45).[75] An advantage of their protocol was the easy removal and recovery of the chiral auxiliary by simple hydrolysis of the glycosidic bond.



Scheme 41.

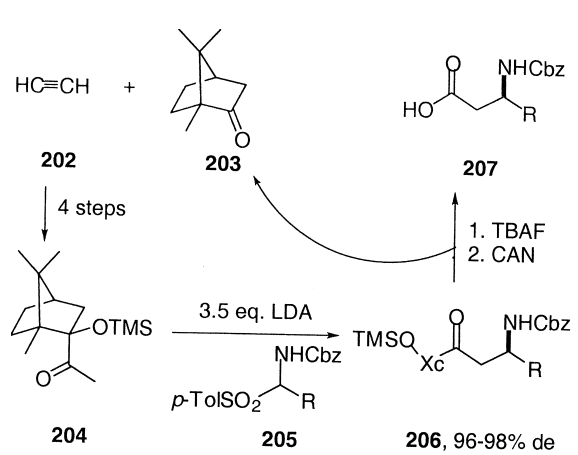
An efficient one-pot procedure involving the addition of silyl enol ether **216** to chiral imine generated in situ from aldehydes **221** and (*S*)-valine methyl ester **222** was applied to the asymmetric synthesis of β-amino esters with moderate to good selectivities.[76] All reactions were carried out at room temperature with a catalytic amount of $Yb(OTf)_3$ to activate the imine (see model **224**, Scheme 46) and anhydrous $MgSO_4$ to remove the water produced in the reaction.



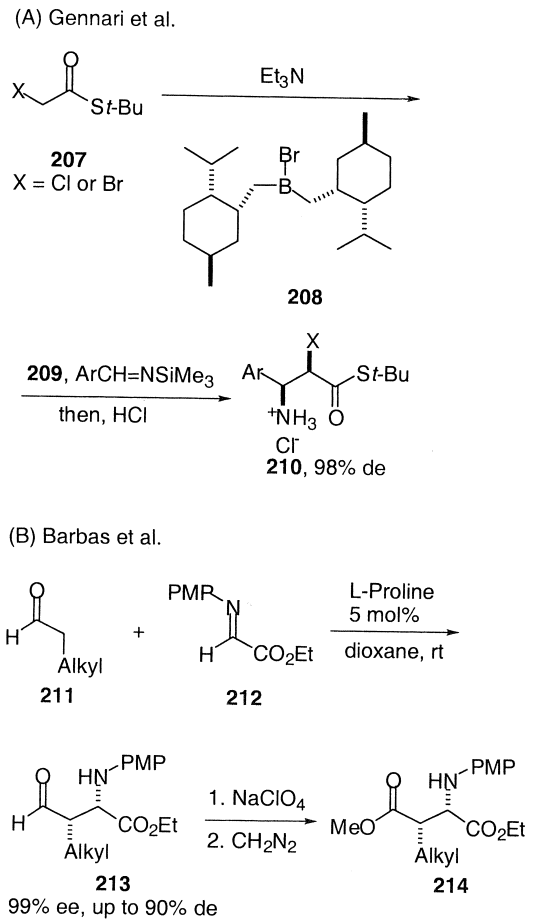
Scheme 42.

Recently, Viallefont,[77] Kawecki,[78] Ha[79] and Brigaud[80] have independently reported a similar Lewis acid-mediated condensation of silyl enolates and chiral imines in stereoselective preparation of β-amino esters **226** (Scheme 47(A)) and **228** (Scheme 47(B)) α-hydroxy-β-amino acid **231** (Scheme 47(C)) as well as trifluoromethylated β-amino acids **235** (Scheme 47(D)).

Another elegant example of stereoselective synthesis of β-amino acids via asymmetric Mannich reaction can be discerned from the work of Waldmann et al.[81] Imines **236**

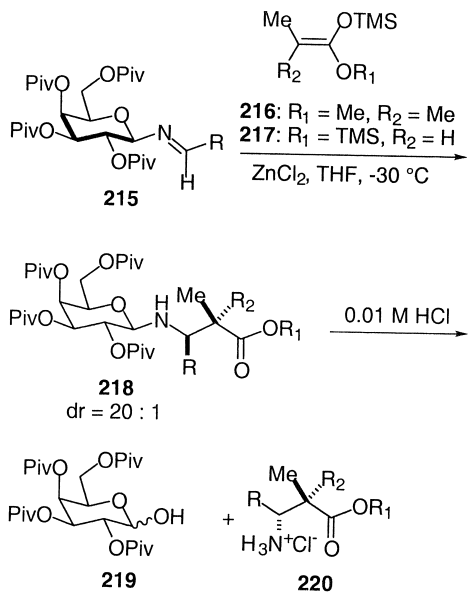


Scheme 43.

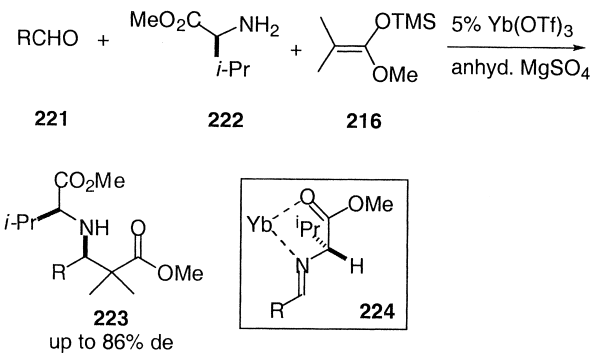


Scheme 44.

were activated by reacting with *N*,*N*-phthaloyl-protected amino acid chloride **237** to lead to the *N*-acyliminium intermediate **238**, which was then subjected to nucleophilic attack by **216** or **234** (Scheme 48). It is interesting to note that complete diastereocontrol could be achieved if either of



Scheme 45.



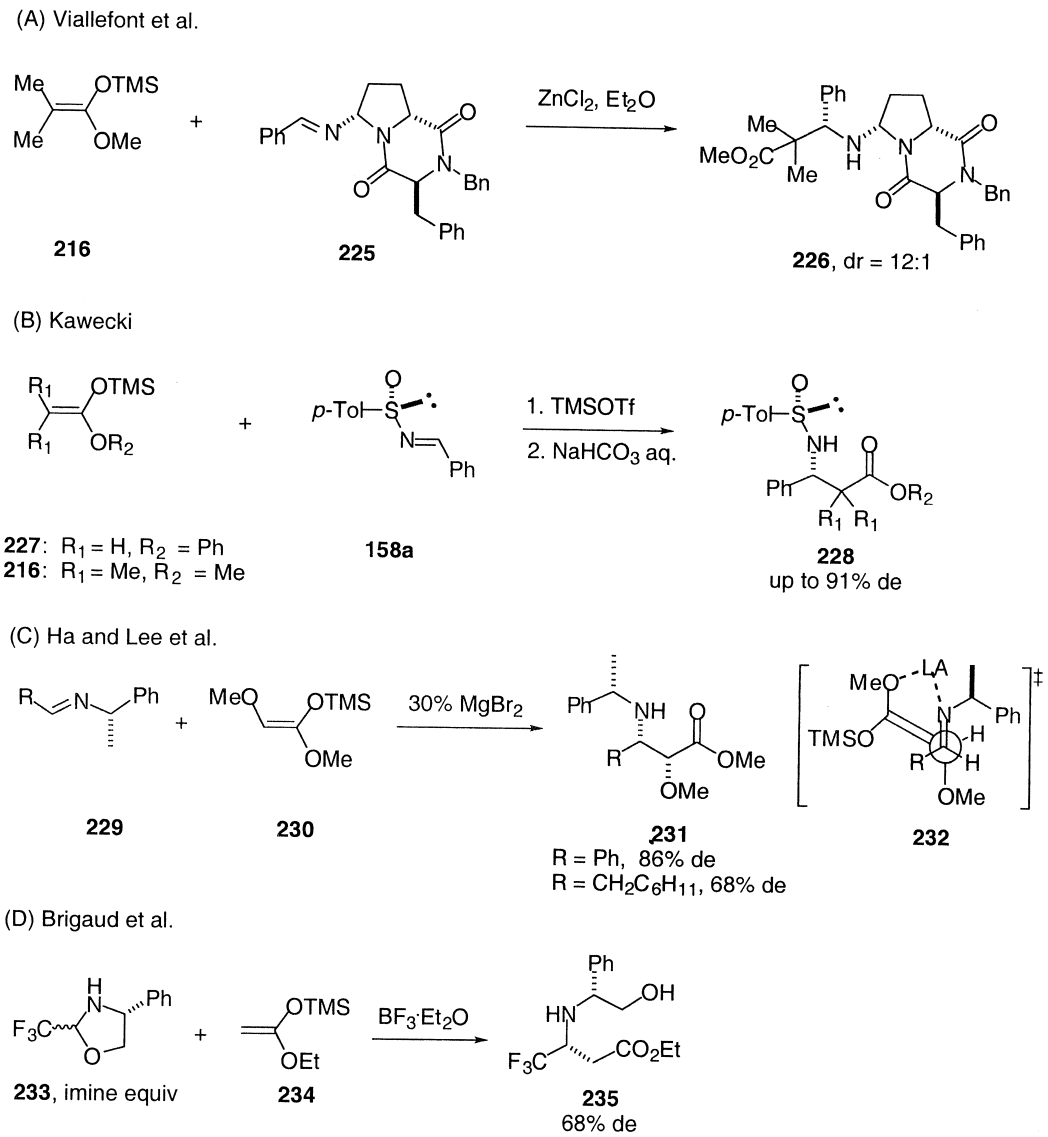
Scheme 46.

the aromatic groups of the imine **236** carried an *ortho*-substituent. It was assumed that *E*-imines **236** were converted to *Z*-iminium salts **238** prior to the addition of nucleophiles, and the high de's observed were in agreement with transition state **240**, where the imine and carbonyl double bonds were in a coplanar *s-trans* arrangement.

An excellent account regarding chiral Lewis acid-mediated reaction of **216** and imines **241** was recently described by Kobayashi and co-workers.[82] The effect of Lewis acids, additives, as well as catalyst's structure on the enantioselectivity of the reaction was carefully investigated. The use of a bidentate Lewis acid Zr(O*t*-Bu)$_4$ was necessary. The dimeric complex **243**, prepared by mixing 1 equiv. Zr(O*t*-Bu)$_4$, 2 equiv. BINOL and 2 equiv. *N*-methylimidazole (NMI) was shown to be a remarkable catalyst in promoting the addition of silyl enolate **216** to various aryl or heterocyclic substituted aldimines **241** (Scheme 49). Moreover, the introduction of electron withdrawing groups at the 6,6′-positions of BINOLs helped to increase the Lewis acidity of Zr, and thus improved the selectivity and the catalyst turnover (compare entries 1–3, Scheme 49). A stereochemical model **244** was proposed by the authors, where one face of the imine was sufficiently blocked by one of the phenyl groups, hence the nucleophiles approached from the opposite face.

1.5.3. Asymmetric addition of Reformatsky reagents to imines. The nucleophilic addition of Reformatsky reagents to Schiff bases offers another strategy for the synthesis of enantiopure β-amino esters or lactams. Ukaji, Inomata and co-workers demonstrated this reaction with success using diisopropyl tartrate (DIPT, **245**) as the chiral auxiliary.[83] The Reformatsky-type reagent, generated in situ from diethylzinc and *tert*-butyliodoacetate, added to imine **246** stereoselectively to furnish β-amino ester **247** in up to 98% ee (Scheme 50). Interestingly, the addition of small amount of water (0.8 equiv.) helped to improve the ee of **247** (R=Ph) from 45 to 93%, possibly due to the breakup of the initial highly aggregated complex of the metal salt of DIPT and imine **246**.

Quirion et al. reported the synthesis of α,α-difluoro-β-amino acid via asymmetric Reformatsky-type reaction of ethyl bromodifluoroacetate with chiral 1,3-oxazolidines **248**, stable equivalents of imines (Scheme 51(A)).[84] A similar methodology was also utilized by Buttero in the addition of bromoesters to imines **251** attached to a



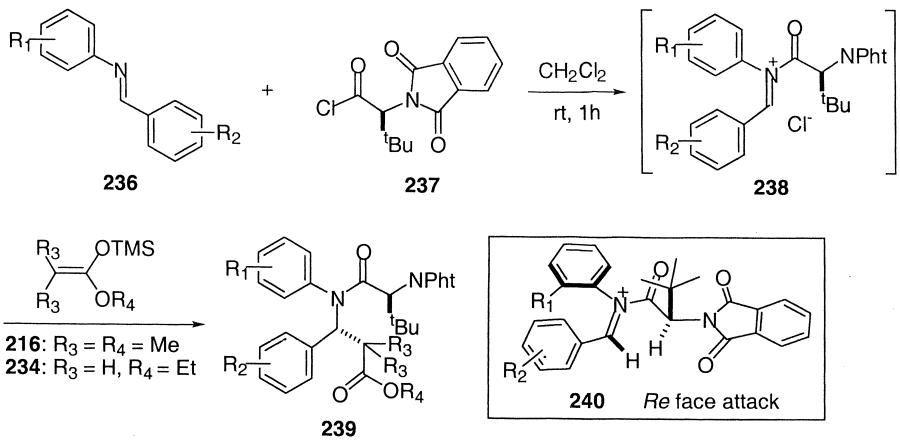
Scheme 47.

tricarbonyl(η^6 arene)chromium(0) complex (Scheme 51(B)).[85] Alternatively, Shankar and co-workers applied the diastereoselective Reformatsky reaction between chiral bromoacetate **254** and imines **255** in the synthesis of β-lactams **257** which were analogs of cholesterol absorption inhibitor SCH 48461 (Scheme 51(C)).[86]

1.5.4. Asymmetric addition of carbon-nucleophiles to nitrones or oximes. The preparation of optically pure β-amino acid derivatives can be accomplished via asymmetric addition of a nucleophile to nitrones. This method offers an attractive alternative to Mannich-type reaction of imines, because of the inherent stability of nitrones, and their ready availability.

Murahashi and co-workers have made important contributions to this area. They first explored the possibility of using *N*-acyloxyiminium species **259** as an activated nitrone equivalent to react with chiral enolates **260** providing β-amino acid derivatives **261** with moderate selectivities.[87] It was noteworthy that the use of the boron enolate instead of the titanium enolate inverted the product stereochemistry, thus both *anti* and *syn* isomers of α-methyl-β-phenylalanines were obtained in enantiomeric forms using the same chiral source (Scheme 52(A)). The reversal of stereochemistry could be explained by invoking open and closed transition state models **262** and **263**, respectively. The effectiveness of this protocol was also demonstrated by the enantioselective synthesis of indolizidine alkaloid **267**, which is a key intermediate for a series of compounds with interesting biological properties (Scheme 52(B)).[88]

An enantioselective variant of the above transformation was recently developed by the same authors.[89] Complex **270**, prepared from (*S*)-BINOL, Ti(O*i*-Pr)$_4$ and 4-*tert*-butylcatechol, catalyzed the addition of silyl ketene acetal **269** to nitrones with good yields and up to 92% ee (Scheme 53(A)). In another report by Murahashi, ZnI_2-mediated highly diastereoselective addition of 1,3-bis(triethylsilyloxy)-1-methoxy-1-butene to nitrones was realized in the asymmetric synthesis of *N*-hydroxy-β-amino esters as illustrated in Scheme 53(B).[90] It should be noted that a single diastereomer was obtained in all cases.

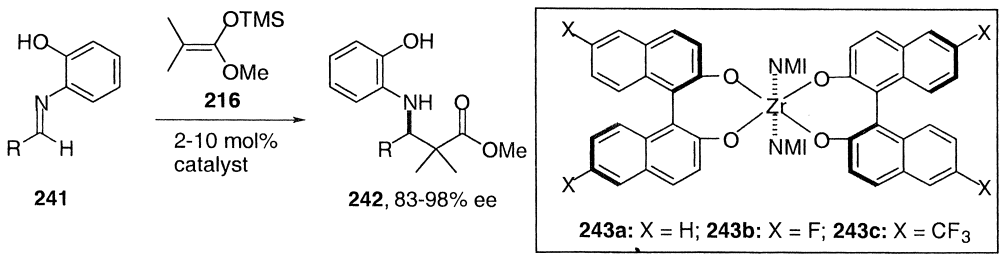


Entry	Nu	R_1	R_2	de (%)
1	**216**	H	4-MeO	82
2	**216**	4-MeO	H	82
3	**216**	2-OMe, 6-Me	H	>98
4	**216**	2-OMe, 6-Me	2-OMe	>98
5	**234**	2-OMe, 6-Me	H	94
6	**234**	2-OMe, 6-Me	4-MeO	>98
7	**234**	2-OMe, 6-Me	2-MeO	>98

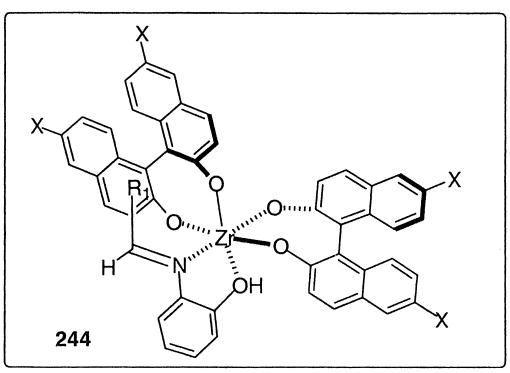
Scheme 48.

On the other hand, Aggarwal et al. have completed the synthesis of enantiopure cispentacin (**2**) emphasizing a highly diastereoselective, intramolecular nitrone [3+2] cycloaddition process with chiral ketene equivalent **275** as the key step (Scheme 54).[91]

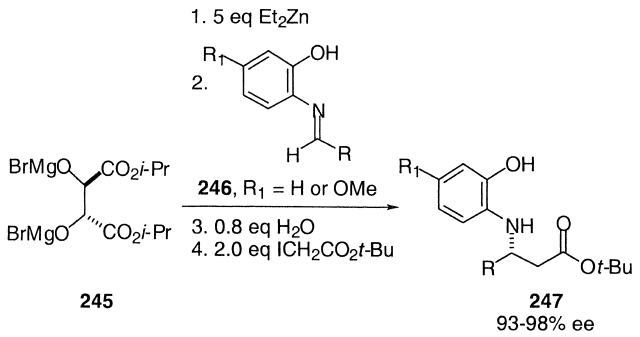
The nucleophilic addition to oxime ethers opened up another novel entry for stereoselective synthesis of β-amino acid derivatives. Naito and co-workers have succeeded in adding carbon radicals to unactivated oxime ethers that were attached to a camphorsultam chiral auxiliary.[92] In the presence of $BF_3{\cdot}OEt_2$, monoalkylated derivative **279** underwent facile reaction with a variety of radicals to produce α,β-dialkyl substituted β-amino acid precursors with excellent diastereoselectivities (Scheme 55(A)). A radical addition-cyclization sequence was later described by the same authors in the asymmetric construction of γ-butyrolactones **282**, and their further conversion to β-amino acids.[93] The high points of this process were the formation of two chiral centers in one single transformation, and its tolerance in aqueous media:



Entry	catalyst(mol%)	R	ee (%)
1	**243a** (10%)	Ph	58
2	**243b** (10%)	Ph	87
3	**243c** (2%)	Ph	87



Scheme 49.



Scheme 50.

good de's were observed when reactions were performed in a mixed-solvent, water/methanol (1:4) (Scheme 55(B)).

1.6. Conjugate addition

Among various strategies available to date, conjugate addition of an amine nucleophile to α,β-unsaturated carboxylic acid derivatives represents one of the most attractive methods for the stereoselective synthesis of β-amino acids.[94] There are basically three ways to achieve asymmetric induction utilizing this methodology: (1) addition of a 'chiral ammonia' equivalent to an acceptor; (2) addition of a nitrogen nucleophile to a chiral acceptor; (3) asymmetric catalysis (Scheme 56).

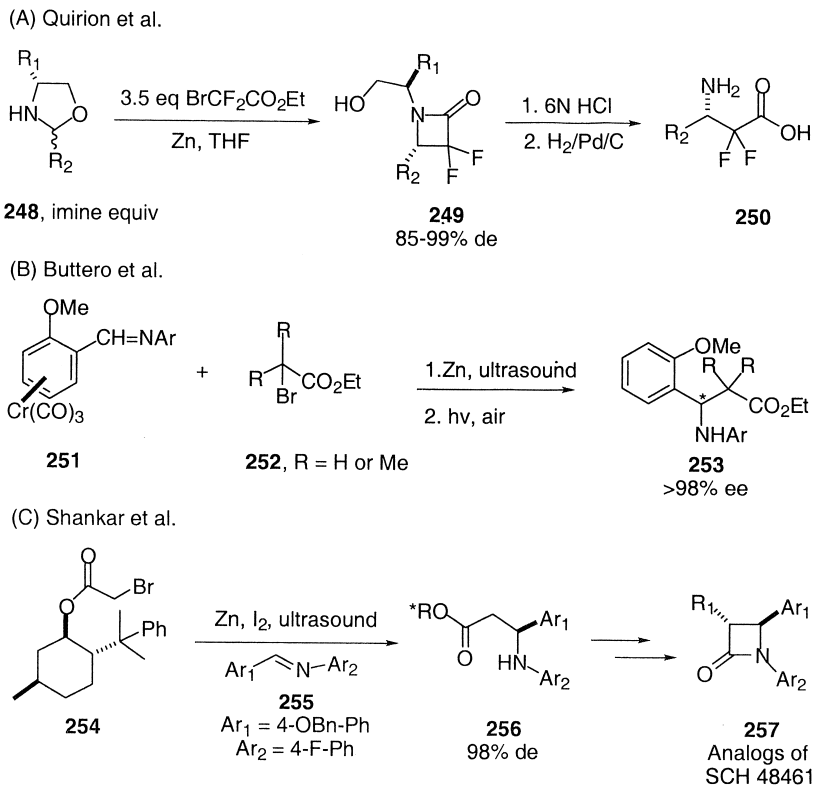
1.6.1. Diastereoselective conjugate addition of chiral nucleophiles. Recently, asymmetric synthesis of β-amino acids via conjugate addition of chiral metallated amines has attracted several research groups' interest. Lithium amides, derived from readily available chiral amines **286**–**290**, have been extensively used as synthetic equivalents of ammonia in these transformations (Scheme 57).

Davies and co-workers were the first to demonstrate that lithium *N*-benzyl-phenylethylamide **292** underwent stereoselective addition to different enoates, which after debenzylation with $Pd(OH)_2$ and subsequent hydrolysis, provided β-amino acids and α-methyl-substituted β-amino acids with high enantiomeric purity (Scheme 58(A)).[95] Additionally, electrophilic hydroxylation of the intermediate enolate afforded α-hydroxy β-amino acids with excellent diastereoselectivities (Scheme 58(B)).[96]

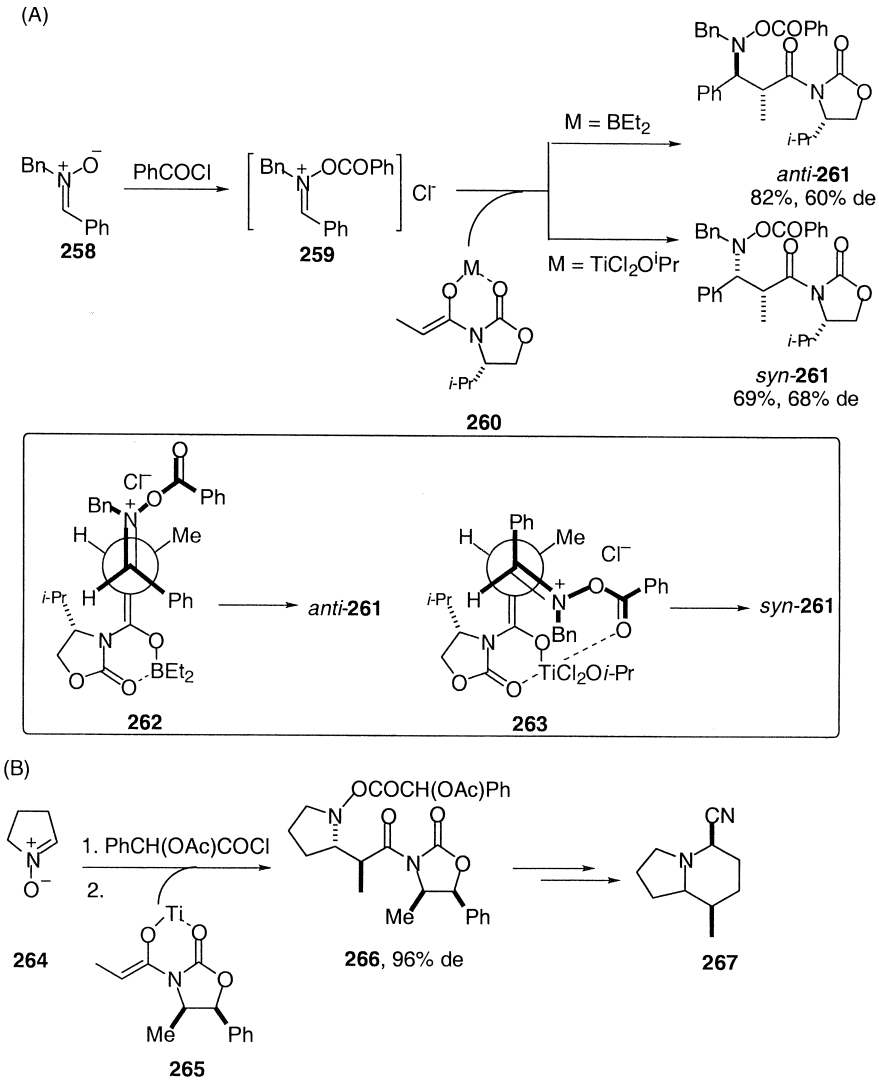
A model **298** was proposed to account for the high de observed in the conjugate additions of **292** (Scheme 58). Based on molecular modeling studies, the lowest energy transition state was one where the α,β-unsaturated acceptor adopts an *s-cis* conformation, lithium is chelated to the carbonyl oxygen as well as the nitrogen lone pair, and the two phenyl groups are almost parallel to each other. As shown in Scheme 58, the *si* face addition is favored.[97]

One limitation of the above methodology is that hydrogenolysis is required for the removal of the protecting groups in the final step of the amino acid synthesis. The hydrogenolysis condition is often not compatible with a few other important functional groups, such as alkenes, which may also be present in the molecule. To overcome this difficulty, the same authors have examined the efficiency of lithium allylamide **299** in the conjugate addition reactions.[98] The allyl protecting group could be selectively deprotected using Wilkinson's catalyst (Scheme 59).

The synthetic utility of the protocol described in Schemes



Scheme 51.



Scheme 52.

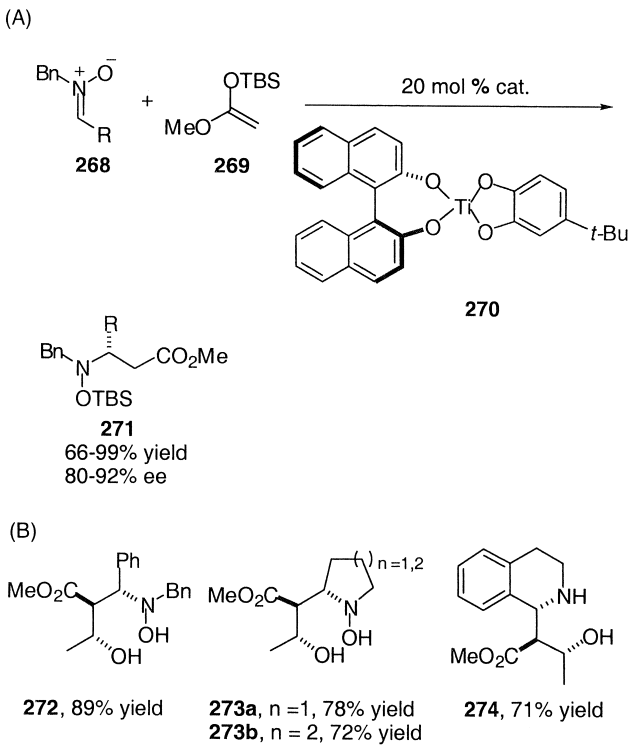
58 and 59 was further elegantly demonstrated by Davies and others in the construction of key component of antibiotic ADDA (**302**),[99] sperabillins B and D (**303**),[100] β-haloaryl-β-amino acids **304**,[101] peptidomimetics **305**–**307**,[102] cyclic β-amino acids **308**,[103] ultra-broad spectrum carbapenem **309**,[104] pyrrolizidine alkaloids **312**–**313**,[105] as well as many other applications (Scheme 60).

Enders et al. have explored the use of TMS-SAMP as a nucleophile in an aza analogous Michael addition process, which yielded *N*-silylated β-hydrazinoesters **314** in high diastereoselectivity (Scheme 61(A)).[106] In order to suppress the competing 1,2-addition pathway, silylated SAMP as well as *tert*-butyl esters **295** were required in this transformation. The same reaction sequence was also applied to the synthesis of cyclic β-amino acids **318** and heterocyclic β-amino acids **320** via tandem aza Michael addition/intramolecular cyclization (Scheme 61(B)).[107]

Analogously, conjugate addition of homochiral amidocuprates, derived from phenylethyl trimethylsilylamine **288**, to enoates **321** provided an easy access to enantiopure β-amino acid derivatives.[108] Trapping of the intermediate enolates with D_2O or alkyl halides furnished α-deuterated β-amino acid **323** or *anti*-α-alkyl β-amino acid derivatives **324** with excellent diastereoselectivity (Scheme 62).

1.6.2. Diastereoselective conjugate addition of an achiral amine to a chiral trap. Stereoselective 1,4-additions involving an achiral nucleophile and a chiral acceptor have been investigated by a number of scientists.[9e,94] d'Angelo and co-workers have succeeded in the addition of diphenylmethanamine to chiral crotonates **325** with excellent diastereoselectivity under high pressure conditions.[109] A π-stacking model **327** was proposed to rationalize the observed high selectivities, which were consistent with the preferential attack of the amine from the less hindered enoate π-face of **325** residing in its *s-trans* conformation (Scheme 63). An *anti* addition of the amine across the double bond was also suggested by the authors via addition of Ph_2CHND_2.

Similarly, Matsuyama et al. were able to add different acyclic nitrogen nucleophiles to chiral *p*-tolylsulfinyl cinnamate **328** with moderate to good selectivities (Scheme 64(A)).[110] Most notably, the addition of NH_3 to **328** proceeded smoothly at room temperature, followed by reductive removal of the sulfinyl group to give **329** (R=H)

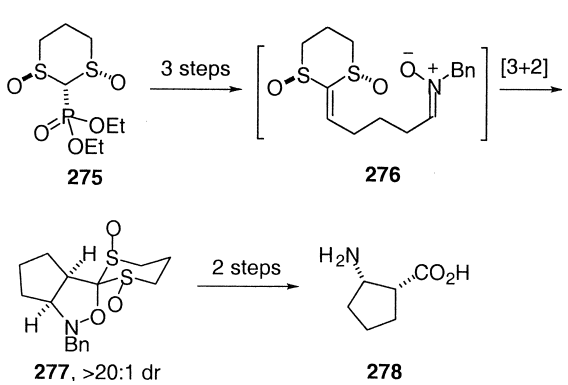


Scheme 53.

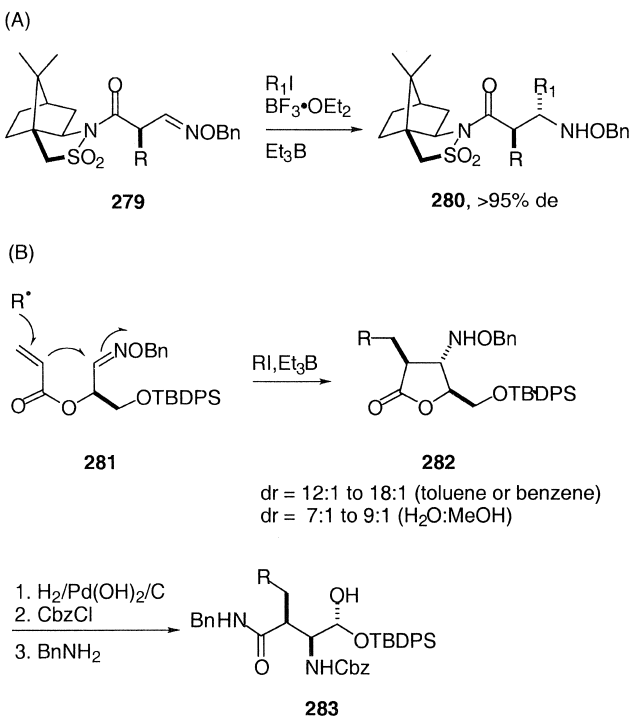
in 81% ee. Furthermore, the addition of achiral lithium amides to chiral enoates were reported in the literature as well, such as the two systems described by Yamamoto[111] and Meyers,[112] respectively, as outlined in Scheme 64(B) and (C).

Perlmutter and Tabone reported the synthesis of *anti*-α-substituted-β-amino esters based on diastereoselective conjugate addition of $BnNH_2$ via 1,3-asymmetric induction (Scheme 65(A)).[113] In another recent report, Costa et al. were also able to add $BnNH_2$ to chiral ester **339** in 90% yield (Scheme 65(B)).[114] The use of TBAF as an efficient base in promoting the aza–Michael addition of $BnNH_2$ to sugar-based γ-alkoxy α,β-unsaturated esters **341** was recently described by Sharma and co-workers.[115] The presence of TBAF was important, as it not only enhanced the reactivity of the amine nucleophile, but also helped to suppress the 1,2-addition pathway (Scheme 65, C).

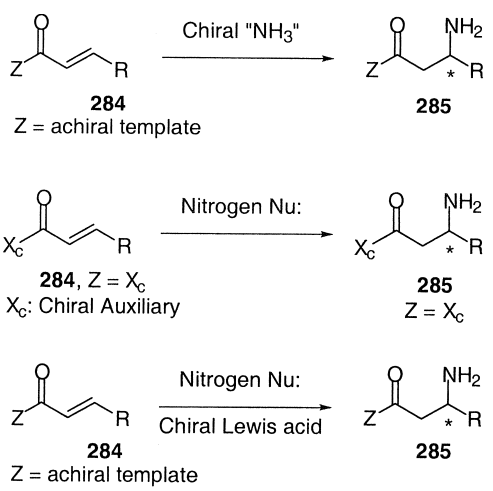
Cardillo et al. have also made significant contributions to



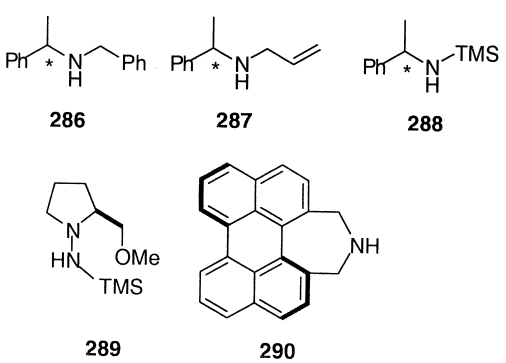
Scheme 54.



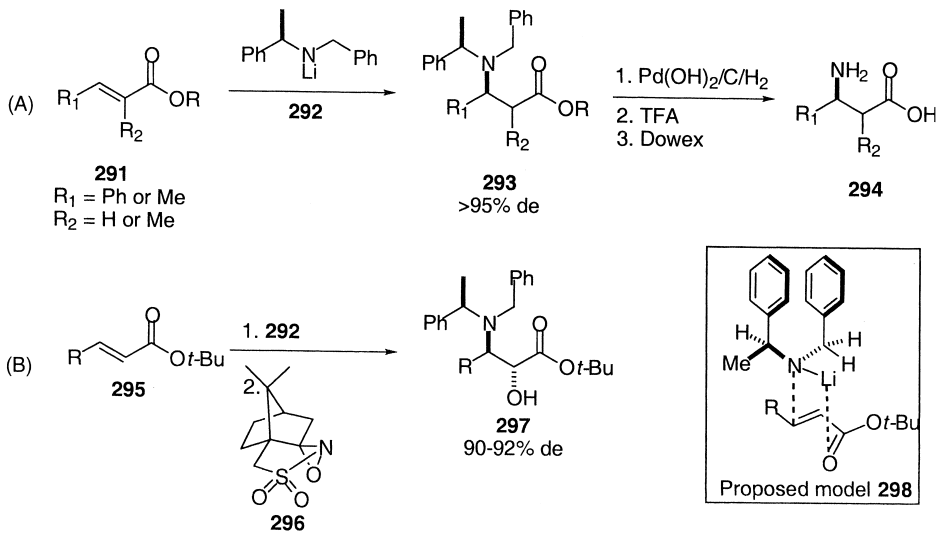
Scheme 55.



Scheme 56.



Scheme 57.

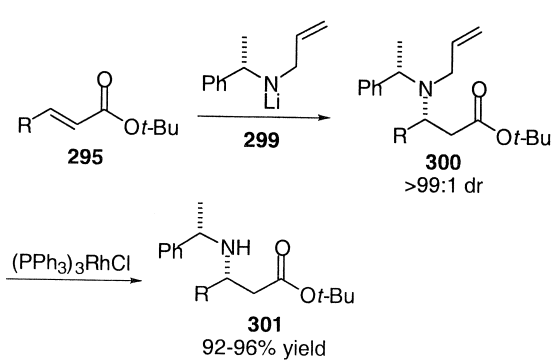


Scheme 58.

this area. They have developed an elegant protocol for the addition of *O*-benzylhydroxylamine to chiral imide **343** in the presence of a Lewis acid.[116] The role of the Lewis acid was two-fold: to control the rotamer population and to enhance the reactivity of the substrate. In addition, an inversion of product stereochemistry was observed when changing the Lewis acid from $TiCl_4$ to $AlMe_2Cl$ (Scheme 66).

Saito et al. described the addition of chiral methylbenzylhydroxylamine **347** to chiral esters **346** with up to 84% de as a result of double diastereoinduction (Scheme 67).[117] The isoxazolidinones **348** produced in this process were easily converted to β-amino acids by reductive cleavage of the N–O bond. Volonterio, Bravo and Zanda applied a similar double stereodifferentiation approach in the asymmetric construction of retropeptides.[118]

One drawback of the above process was that the stereocenter in the chiral source was destroyed during the deprotection step in order to generate the free β-amino acids. To overcome this difficulty, Saito and co-workers have designed a recyclable chiral amine source called Lewis acid hydroxylamine hybrid reagent (LHHR) **349**, where a chiral auxiliary was tethered to the hydroxylamine through an appropriate metal, such as Al or B (Scheme 68).[119] Conjugate addition of **349** to esters **284** gave the desired products in up to 71% ee.



Scheme 59.

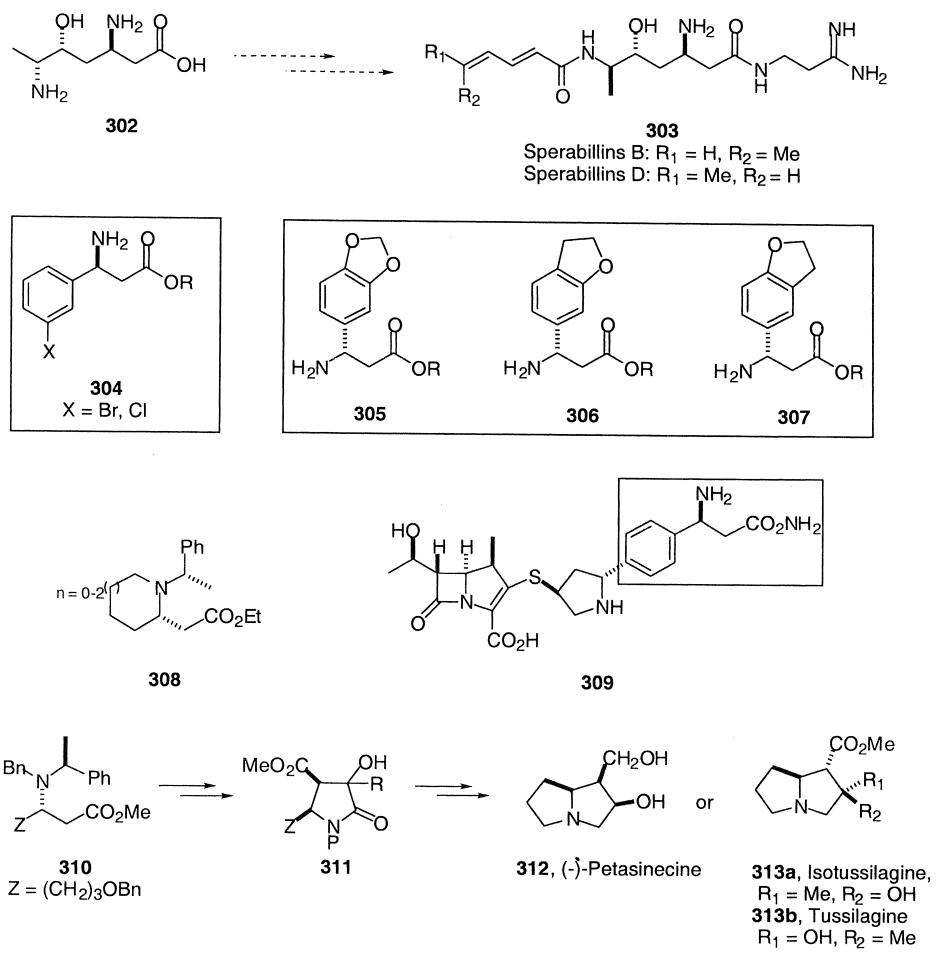
1.6.3. Enantioselective conjugate amine additions. Despite the numerous diastereoselective examples of conjugate amine additions reported in the literature, the development of efficient enantioselective processes for the synthesis of β-amino acids remains a significant challenge. Only in the last four years have tremendous achievements been made in this area.

The first enantioselective example of conjugate amine addition was reported by Jørgensen in 1996.[120] A titanium BINOL catalyst **354** was used to catalyze the addition of $BnONH_2$ to *N*-acyloxazolidinones **353**. High conversions were obtained, but, with only up to 42% enantioselectivity (Scheme 69).

In a similar manner, Sibi and co-workers have recently developed a highly enantioselective protocol for the conjugate addition of *O*-benzylhydroxylamine to 3,5-dimethylpyrazole-derived enoate **356** using catalytic amounts of a chiral Lewis acid prepared from $MgBr_2{\cdot}OEt_2$ and a bisoxazoline **359**.[121] β-Amino acid derivatives **357** were synthesized in good chemical yields and up to 97% ee (Scheme 70). The high ee's obtained in this example were partially accounted for by a selective 1,2-addition of excess amine to the minor isomer of the conjugate addition adduct **357** to give byproduct **358**, thereby increasing the ee of **357** by kinetic resolution. The control of the product configuration by the Lewis acid was also noteworthy. Opposite enantiomer of the product was produced in 59% ee when a lathanide Lewis acid was employed in conjunction with the same ligand.

In a recent account by Cardillo, low ee's (up to 29%) were reported in the conjugate addition of $BnONH_2$ to doubly activated acceptors, alkylidene or arylidene malonates **360**, in the presence of a Cu(II)-box-complex **361**.[122] The selectivity was further increased to as high as 76% by the use of a bulkier amine nucleophile, *N*,*O*-bis(trimethylsilyl) hydroxylamine (Scheme 71).

As discussed earlier, *N*-substituted hydroxylamines, which are more nucleophilic than *O*-substituted hydroxylamines,



Scheme 60.

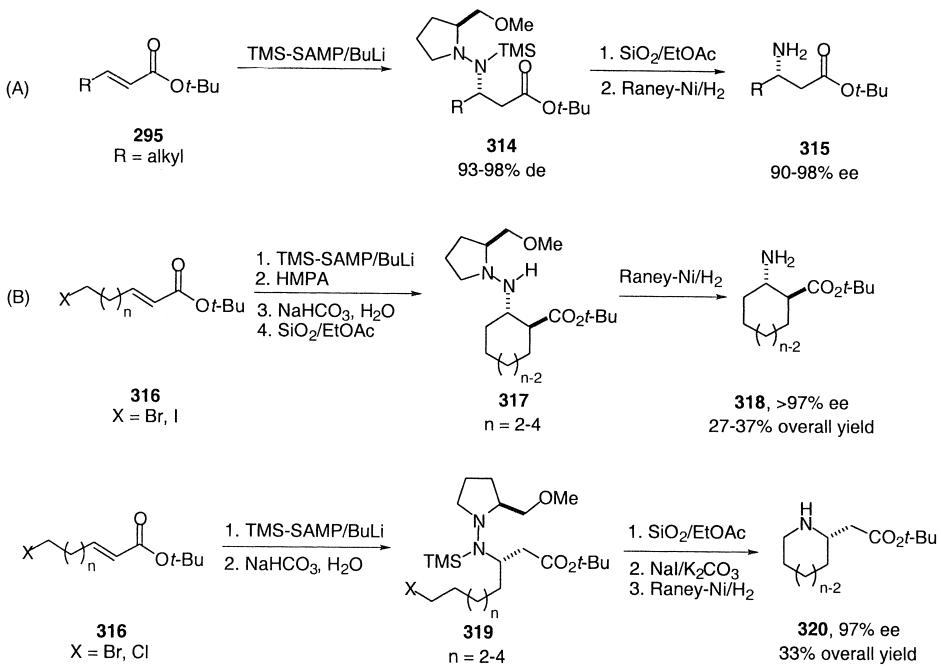
can undergo conjugate addition to α,β-unsaturated enoates to generate isoxazolidinones, precursors for β-amino acids.[123] Zhao[124] and Ortuño[125] have independently studied the conjugate addition of *N*-alkylhydroxylamine to enoates in some detail, and have proposed a concerted mechanism for the reaction. Later, O'Neil et al. confirmed this mechanism in their study of BnNHOH addition to nitriles, sulfones as well as nitro compounds.[126]

Taking advantage of the high reactivity of BnNHOH, Sibi and Liu developed a highly efficient method for the conjugate addition of BnNHOH to pyrrolidinone-derived enoates **363**.[127] For the first time, β-aryl-β-amino acid derivatives were obtained in high enantiomeric purity using catalytic amounts of a chiral Lewis acid (Scheme 72(A)). In view of the increasing demand for large-scale synthesis of enantiopure β-amino acids, the same authors have reported another interesting account of how to improve the selectivity of conjugate addition at moderate reaction temperatures and using simple ligands.[128] The use of a novel class of achiral templates, pyrazolidinones, to perform chiral relay[129] was the highlight of this report. Furthermore, catalysts **359** and **368** provided enantiomeric products with high purity at practical reaction conditions (Scheme 72(B)).

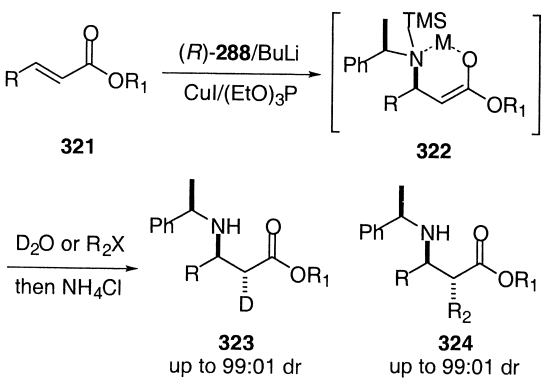
Stereoselective addition of secondary aromatic amines **370** to acyl pyrrolidinones **369** was investigated by Jørgensen et al.[130] The selectivity and chemical efficiency were found to be dependent on the reaction conditions including solvents, catalysts and Lewis acids. Better yields were obtained using CH_2Cl_2 as the solvent. Catalyst DBFOX-Ph **372** was the most effective in catalyzing the addition of substituted *N*-methyl anilines to **369**, providing β-amino acid derivatives **371** in up to 90% ee (Scheme 73). The absolute configuration of the product was determined to be *S*, which agreed with a trigonal bipyramidal geometry around the metal with ligand **372** occupying three sites while the substrate taking up the other two, leaving the *Re* face of the alkene available for amine additions. Ligand **372** and Zn(II) perchlorate catalyzed enantioselective addition of aldoximes to acyl oxazolidinone or imidazolidinone was recently accomplished in moderate ee's by Kanemasa et al.[131]

Likewise, Sundararajan and Prabagaran succeeded in the 1,4-addition of $BnNH_2$ to ethyl cinnamate **373** in the presence of a novel polymer-supported chiral catalyst **376** (Scheme 74).[132] It should be noted that only a simple filtration was needed for purification of the final product, and the catalyst could be easily recovered by washing with 1N HCl.

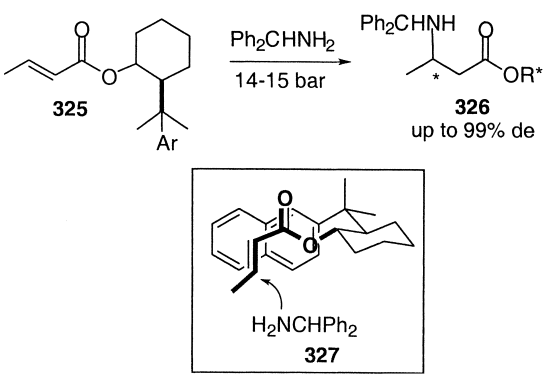
The use of azide as a nucleophile in conjugate addition reactions is well documented.[133] Chiral (salen)Al(III) complex **379** catalyzed conjugate addition of hydrazoic acid (HN_3) to α,β-unsaturated imides was recently



Scheme 61.



Scheme 62.



Scheme 63.

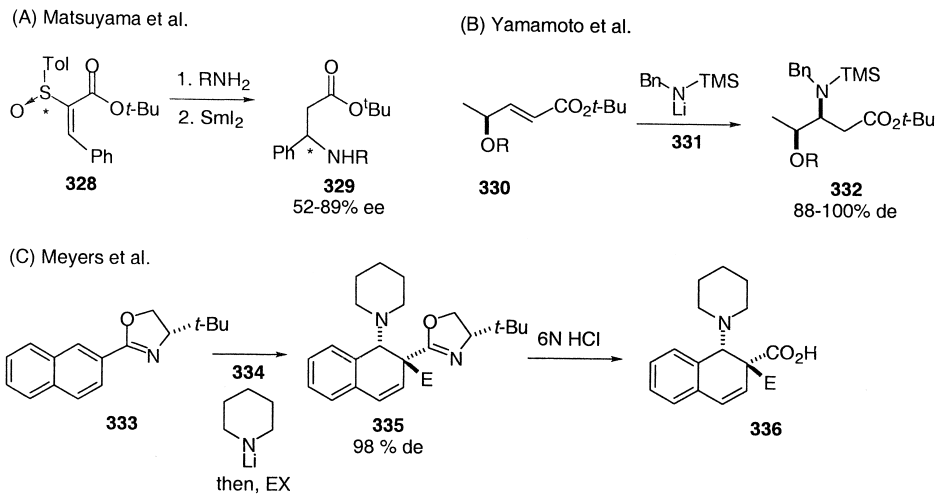
described by Jacobsen et al.[134] This procedure provided access to a variety of enantiopure β-alkyl-β-azido compounds. However, the addition to cinnamate **377** (R=Ph) was inefficient, and reaction was incomplete after 24 h at room temperature (Scheme 75).

Recently, Miller and co-workers developed a milder reaction condition for azidation, in which the azide was generated from a 3.8:1 mixture of $TMSN_3$ and *t*-BuCOOH in toluene.[135] Simple β-turn tripeptide **381** mediated conjugate addition of azide to enoate **369** yielded β-amino acid derivatives **380** in up to 92% ee (Scheme 76(A)). Metal-free catalysis was the key feature of this process. Nelson and Spencer have reported an alternate method for the preparation of enantiopure β-substituted β-azido carboxylic acids **383** via azide-mediated S_N2 ring opening of chiral β-lactones **382** (Scheme 76(B)).[136]

1.6.4. Conjugate addition of carbon-nucleophiles. An alternative strategy for the synthesis of β-amino acids is the conjugate addition of a carbon-nucleophile to a substrate containing pre-installed nitrogen. Sibi and Asano have demonstrated this process with success in the 1,4-addition of chiral ionic nucleophiles to enamidomalonates **384**.[137] The organomagnesium amides **387** and **388** were prepared by treatment of the corresponding bisoxazoline ligand with 1 equiv. of *n*-BuLi followed by different Grignard reagents. This procedure allowed for the enantioselective preparation of a variety of β-amino acids after decarboxylation of the addition products (Scheme 77). More importantly, the sense of stereoinduction were reversed with these two chiral nucleophiles.

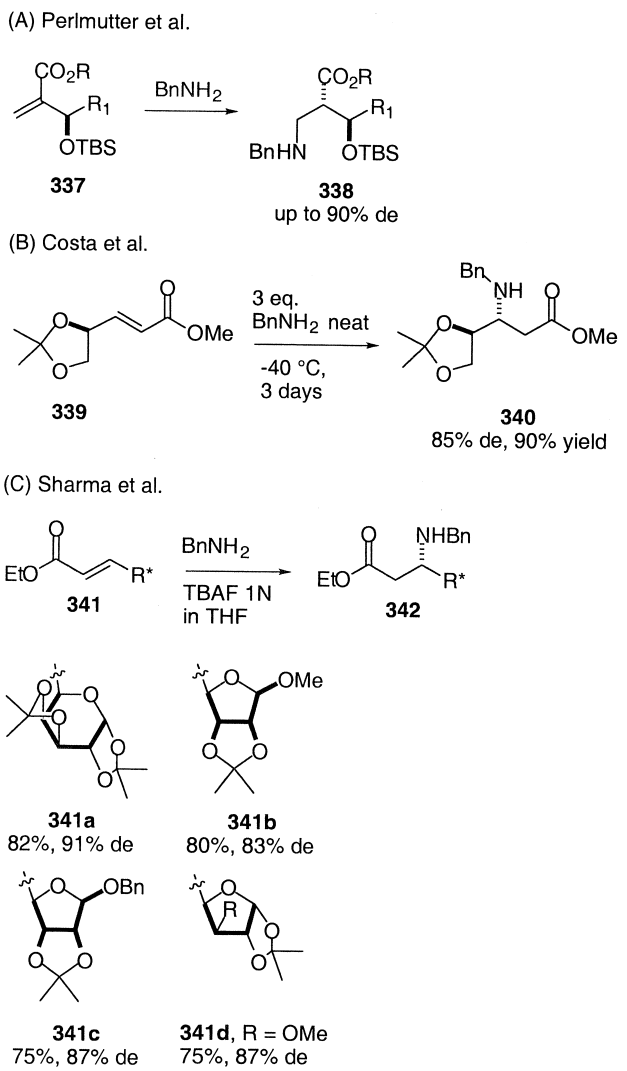
The reaction between neutral nucleophiles, silylketene acetals **390a–c**, and enamidomalonates **389** was also investigated by the same group.[138] β-Amino acid derivatives **391** were produced in excellent chemical efficiency and good enantioselectivity in the presence of $Cu(OTf)_2$ and ligand **359** (Scheme 78).

Dechoux et al. have accomplished the asymmetric synthesis of β-amino acids by means of conjugate addition of organocuprates **393** to chiral acceptor **392**.[139] *Anti* addition



Scheme 64.

of **393** to **392** proceeded with almost complete diastereocontrol, and the use of TMSCl as an additive was necessary to prevent the formation of byproduct **396** via a β-elimination process (Scheme 79). The resulting adducts were converted to β-amino acids **395** in two easy steps.

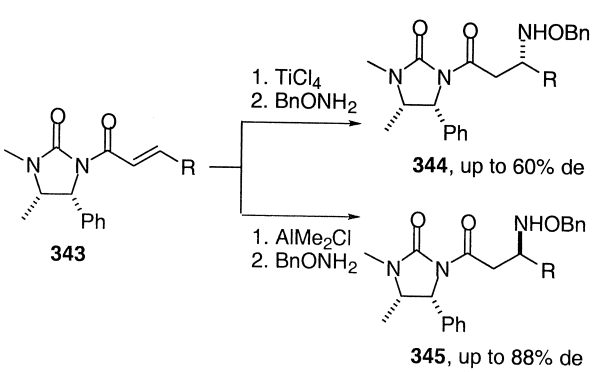


Scheme 65.

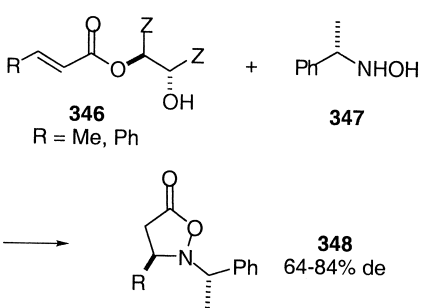
A highly selective 1,2-asymmetric induction process was realized in the conjugate radical addition of **398** to chiral acrylate **397** followed by hydrogen transfer.[140] Both *syn* and *anti* α,β-disubstituted β-amino ester **399** were obtained in >98% ee with *syn*-**399** being the predominant diastereomer (Scheme 80).

1.7. Reduction of α,β-unsaturated esters or nitriles

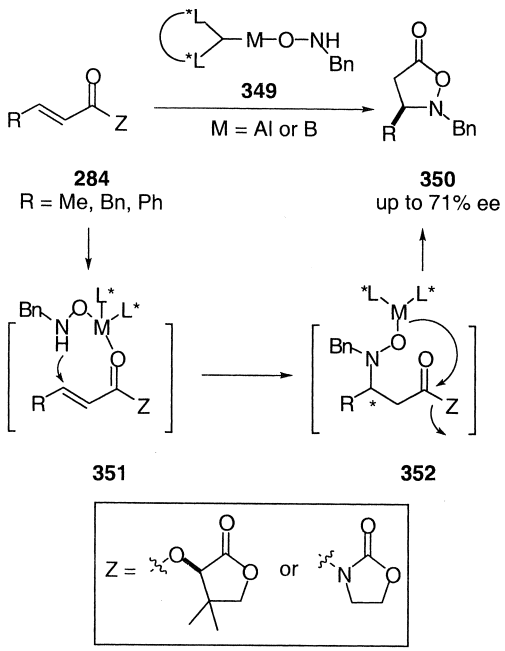
1.7.1. Catalytic hydrogenation. Another attractive approach to prepare enantiopure β-amino acid derivatives involves asymmetric hydrogenation of acrylic acid or nitrile



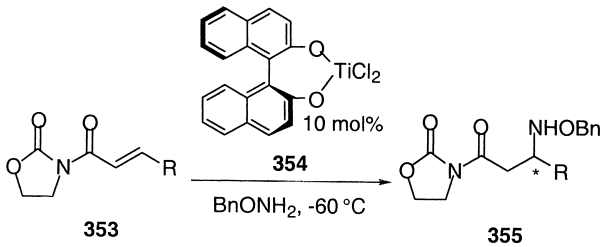
Scheme 66.



Scheme 67.



Scheme 68.



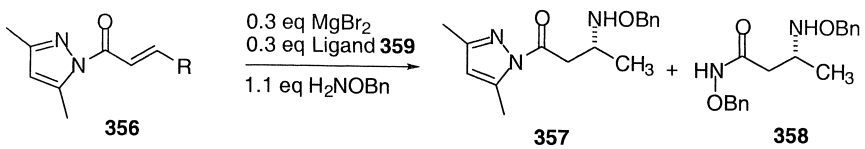
Scheme 69.

derivatives. Recently, Zhang et al. developed a straightforward process to prepare β-amino esters via rhodium catalyzed hydrogenation of 3-aminoacrylates **400**.[141] Two catalysts Rh-BICP **401** and Rh-DuPhos **402** were chosen for their study and all reactions were carried out in toluene under high H_2 pressure (Scheme 81). High enantioselectivities were obtained for **402** catalyzed hydrogenation of *E*-**400**, and **401** catalyzed hydrogenation of both *E*/*Z* isomers of **400**. In addition, (*E*)-**400** isomers were found to be more reactive than the corresponding (*Z*)-**400** isomers, and much higher pressure (294 psi) was required for complete reduction of *Z*-**400**. Their methodology was applied for the synthesis of a variety of aliphatic β-amino esters (R=Me, Et, Pr, *i*-Pr and *i*-Bu). However, only moderate ee's (65–66%) were achieved for hydrogenation of β-(acylamino)-acrylates with a phenyl substituent.

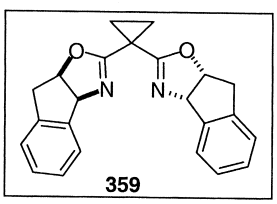
Heller and co-workers have found that the use of polar solvents, such as MeOH, accelerated the hydrogenation of (*Z*)-β-aminoacrylates.[142] In the presence of a catalytic amount of Et-DuPHOS-Rh **404**, both *E* and *Z* isomers of **400a** were hydrogenated to give β-amino ester **403a** in up to 97% ee. Surprisingly, a dramatic increase in ee was observed when decreasing the H_2 pressure from 30 to 1 bar (Scheme 82(A)). In addition, Gridnev and Imamoto achieved excellent (*R*)-enantioselectivity using electron-rich P-chirogenic diphosphines-Rh complexes **407** and **408** mediated asymmetric hydrogenation of (*E*)-β-alkyl-β-aminoacrylates **405** (Scheme 82(B)).[143]

Very recently, Zhang et al. have designed a novel class of bisphosphinite ligands **411** (*o*-BINAPO) for enantioselective hydrogenation of β-aryl-substituted 3-aminoacrylates.[144] Fine-tuning of ligand was one of the goals of this study. The introduction of bulky aryl groups at the 3,3′-positions of the binaphthyl backbones was crucial, as this would help to reduce the flexibility of the ligands and thus provided the most efficient face shielding. Indeed, a range of β-aryl-β-amino esters **410** were obtained in high enantiomeric purity utilizing a catalytic amount of ligand **411** along with [Ru(*p*-cymene-Cl_2]$_2$ (Scheme 83). Another noteworthy feature was that their catalytic system tolerated an *E*/*Z* mixture of the substrates, which simplified the starting material preparation process.

Enantioselective hydrogenation of α,β-unsaturated nitriles **412** and their methyl esters **415** bearing an α-phthalimidomethyl substituent was investigated by Jackson and coworkers.[145] It was hypothesized that rhodium-catalyzed hydrogenation of **412** could be facilitated through the formation of a six-membered chelate **414** between the imide carbonyl group and Rh (Scheme 84). Surprisingly, only up to 48% ee were observed for Rh-DuPhos mediated hydrogenation of phthalimido nitriles **412**. An improved selectivity (84%) was achieved in the hydrogenation of phthalimido ester **415** (R=H) using Ru-BINAP as the

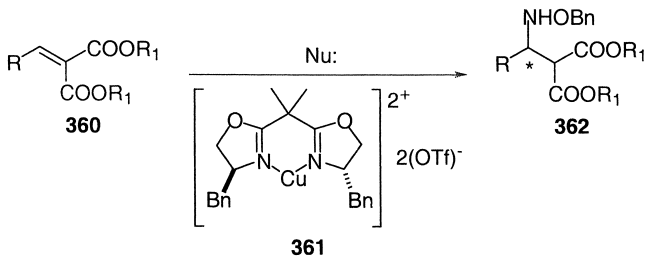


R	yield (%)	ee (%)
Me	80	92 (*R*)
CH_2Ph	80	95 (*R*)
i-Pr	76	87 (*R*)
Me[a]	67	59 (*S*)
Ph[b]	24	83



[a] 1 eq Y(OTf)$_3$ used.
[b] 60% of the starting material was recovered

Scheme 70.



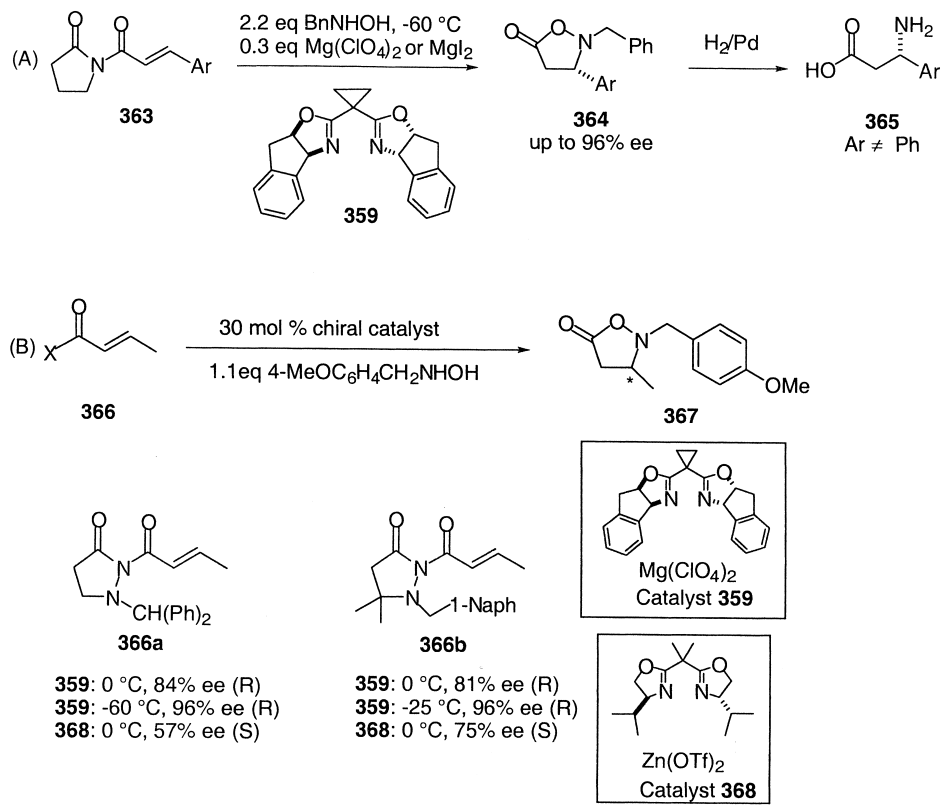
Substrate	Amine Nu:	Temp. (°C)	Yield (%)	ee (%)
R = Ph, R_1 = Me	$BnONH_2$	10	66	20
R = *i*-Pr, R_1 = Me	$BnONH_2$	-10	60	00
R = *i*-Pr, R_1 = Et	$BnONH_2$	-20	71	29
R = *i*-Pr, R_1 = Me	TMSNHOTMS	-10	73	76
R = CH_2*i*-Pr, R_1 = Me	TMSNHOTMS	-10	52	74

Scheme 71.

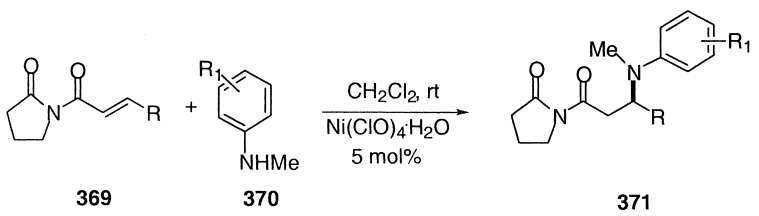
catalyst. However, the introduction of a β-substituent (**415**, R=Me) resulted in a drastic decrease in ee (only 10%).

1.7.2. Reductive amination. Several recent reports have documented the reductive amination route to enantiopure β-amino esters and derivatives. Cimarelli and Palmieri described a practical and convenient method for chemoselective reduction of β-enamino esters **418** with sodium triacetoxyborohydride in acetic acid.[146] Different substrates were reduced smoothly with good diastereo- and enantioselectivities (Scheme 85). Pyrrolidines **423**, **424** and cispentacin **425**, compounds which possess known biological activity, were produced using this methodology (Scheme 85). Intermediate **419**, formed by ligand exchange between the β-enamino esters and one of the acetoxy ligands, was proposed to explain the observed high stereoselectivity. The hydride was intramolecularly transferred *anti* to the bulky amine substituent, leading to the reduced intermediate **420**, which would decompose to the final product in the presence of HOAc.

Xu et al. have successfully employed a modified Palmieri's approach in large-scale asymmetric synthesis of *cis*-2-amino-1-cyclohexanecarboxylate **426** (Scheme 86).[147] The highest selectivity was obtained when the reaction was carried out in neat isobutyric acid and $NaBH_4$ as the hydride



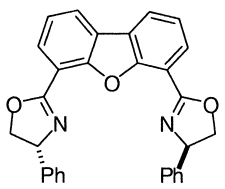
Scheme 72.



369 370 371

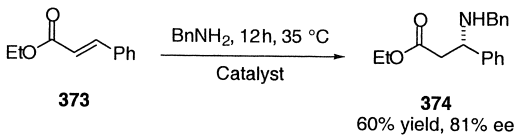
Substrate	Amine R_1	Yield (%)	ee (%)
R = Me	R_1 = H	62	90
R = Me*	R_1 = H	19	84
R = Me	R_1 = *m*-MeO	73	89
R = Me	R_1 = *p*-Cl	23	96
R = Pr	R_1 = H	25	95
R = COOEt	R_1 = H	93	00

* THF was used as the solvent

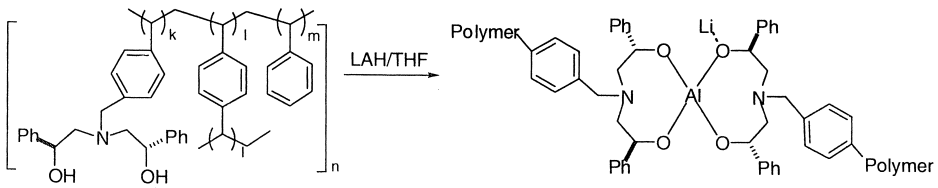


372

Scheme 73.

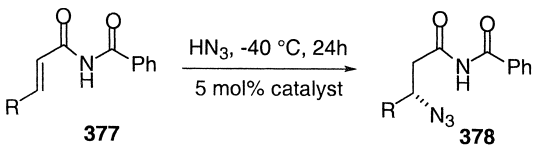


373 374
60% yield, 81% ee



375 376

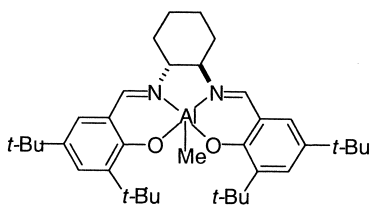
Scheme 74.



377 378

Substrate	Yield (%)	ee (%)
R = Me	96	96
R = Pr	97	95
R = *i*-Pr	98	97
R = *t*-Bu	99	97
R = Bn	97	95
R = Ph	60	58*

* 10 mol% catalyst, at rt

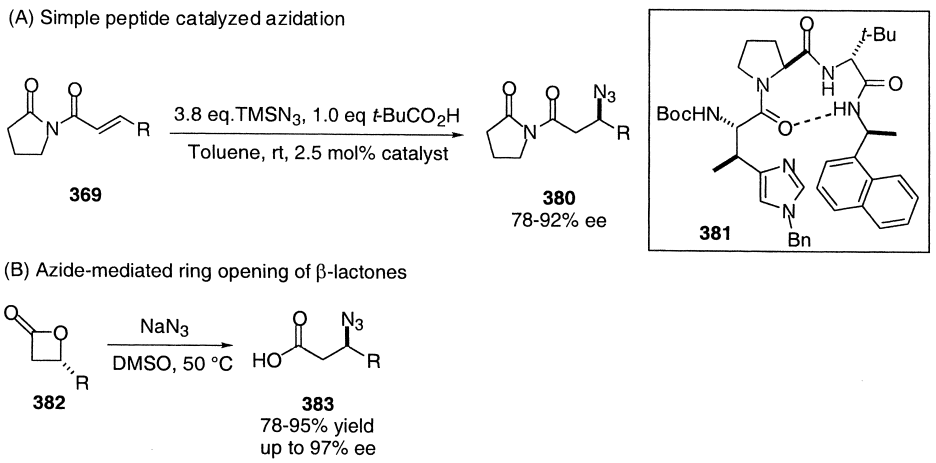


379

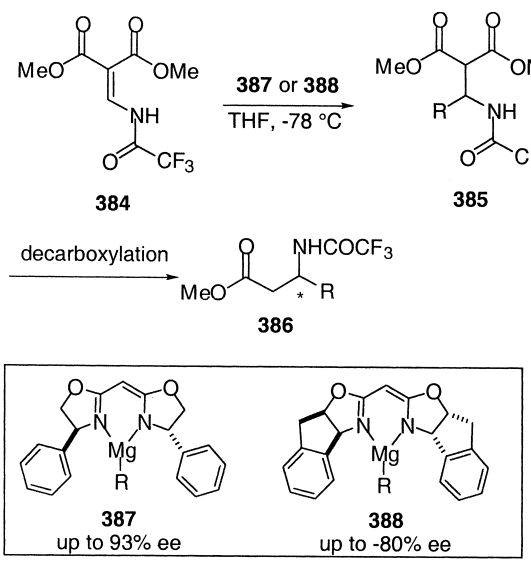
Scheme 75.

donor. A similar method has also been explored by Gellmans' group using $NaCNBH_3$ as the reducing agent to prepare β-peptide building blocks **427** and **428** (Scheme 86).[148] More importantly, in both Xu and Gellman's procedure, the major diastereomer was isolated in optically pure form by a simple crystallization as its HBr or HCl salt.

Cohen et al. utilized an analogous approach in a large scale synthesis of β-aryl-β-amino esters **432**.[149] The enamine **431** was obtained by heating a mixture of the corresponding β-ketoesters **429** and 4-methoxyphenylethylamine **430** in toluene at 65°C under reduced pressure, thus water was removed completely and any potential amide byproduct formation was avoided. Hydrogenation of **431** using Pearlman's catalyst afforded **432** in >98% ee (Scheme 87). It is important to note that the isomerization of *Z*-**431** to



Scheme 76.



Scheme 77.

E-**431** using 2 equiv. of $BF_3{\cdot}Et_2O$ before hydrogenation was crucial in achieving high selectivity in this transformation.

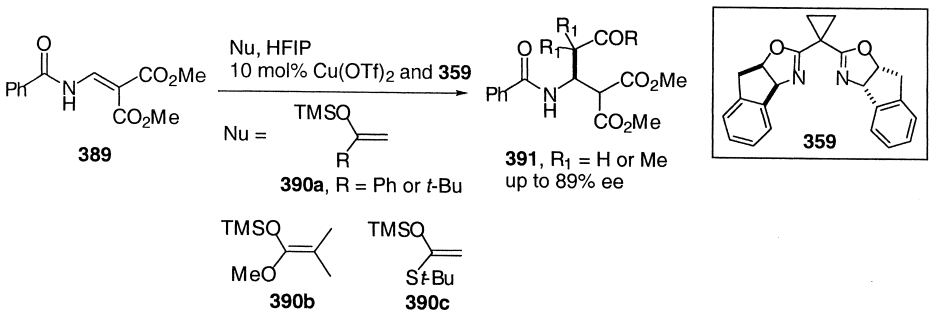
1.8. Aminohydroxylation

Sharpless asymmetric aminohydroxylation (AA) of olefins is a versatile methodology for enantioselective synthesis of *N*-protected amino alcohols.[150] If the substrate is an α,β-unsaturated ester (R_2=ester) *syn*-α-hydroxy-β-amino acids, an important pharmacophore found in many bioactive compounds, are produced in enantiopure form (Scheme 88). In general, the reaction is carried out in an alcohol/water mix-solvent using a catalytic amount of $K_2OsO_2(OH)_4$ and an alkaloid ligand. It is important to note that dihydroquinidine (DHQD) **435a** and dihydroquinine (DHQ) **435b** provide products with opposite configurations. In addition, sulfonamides, amides, carbamates[150b] and various amino-substituted heterocycles[151] have been utilized as nitrogen sources in this process.

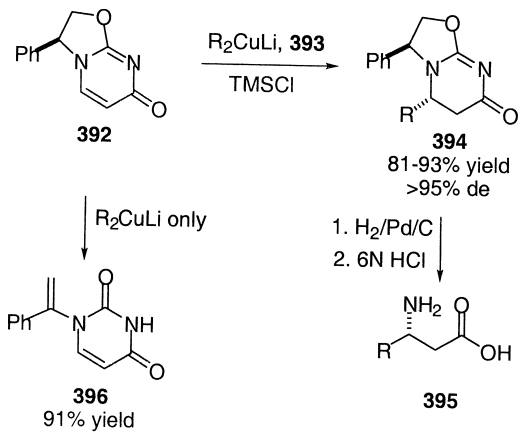
Selected results of aminohydroxylation of α,β-unsaturated esters to prepare α-hydroxy-β-amino acids are presented in Scheme 89(A). Among these, **439** is the key component of renin inhibitor cyclohexylnorstatine,[152] and **440** is the key skeleton of antibiotic Loracarbef.[153] The fact that more and more examples have appeared in the literature utilizing this protocol in natural product synthesis suggests that a promising future for the Sharpless AA in complex molecule synthesis is likely. An outstanding case was the Sharpless' elegant large-scale preparation of the taxol side chain **442**.[154] In two steps, the target molecule was obtained in 68% yield and 99% ee starting from isopropyl cinnamate **441** (Scheme 89(B)).

1.9. Asymmetric synthesis of β-lactams

The nucleophilic cleavage of N(1)–C(2) bond of β-lactams provides β-amino acid derivatives directly (Scheme 90).[155] The development of efficient methods for asymmetric synthesis of β-lactams is an active area of research.[156]



Scheme 78.

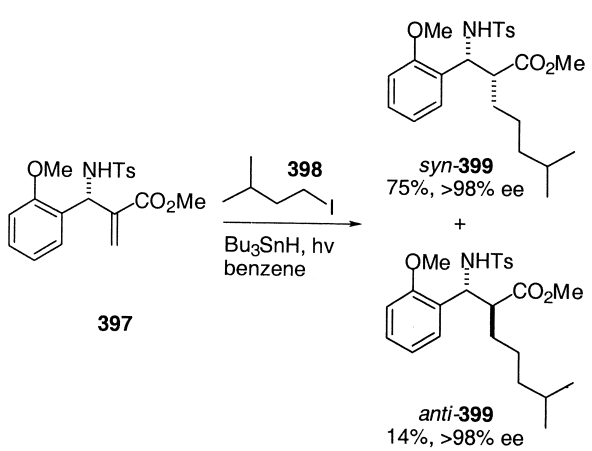


Scheme 79.

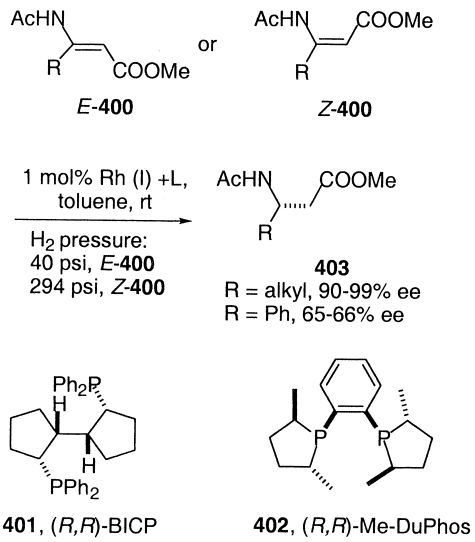
Some examples have already been discussed throughout the review, thus this section will only focus on the most recent advances.

The Staudinger reaction, which involves a [2+2] ketene–imine cycloaddition, is one of the most reliable methods available for the construction of β-lactam rings.[157] A remarkable catalytic system including a chiral nucleophile and a Lewis acid was developed by Lectka et al. in the synthesis of optically pure β-lactams.[158] Unlike the classic Staudinger reaction, a nucleophilic ketene **448** was generated in the presence of 10 mol% of benzoylquinine (BQ) **447**, leading to increased reactivity of the original substrate **445**. The addition of 10 mol% of In(III) triflate resulted in a dramatic enhancement of the reaction rate as well as chemical yields, presumably through chelation to imine **446** (Scheme 91).

A highly enantioselective synthesis of β-lactams was recently described by Hodous and Fu.[159] In this study, a novel planar chiral heterocycle **453** was found to be very effective in promoting the [2+2] cycloaddition of symmetrical or asymmetrical disubstituted ketenes **451** with a range of imines **452** (Scheme 92). The reaction was proposed to proceed through intermediate **455**, similar to what Lectka has observed. It is important to



Scheme 80.



Scheme 81.

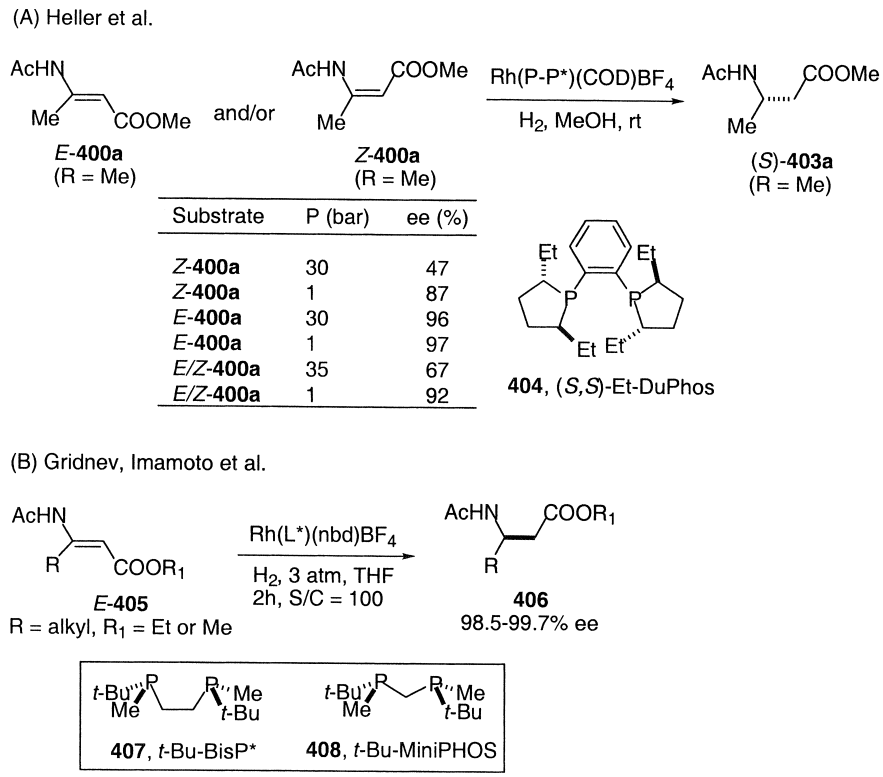
note that β-lactams **454** were easily transformed into β-amino acid derivatives via ring opening with amines, such as **456**.

Several recent accounts have showcased the utility of the enolate–imine condensation reaction in β-lactam synthesis.[160] One excellent example reported by Braun and co-workers is outlined in Scheme 93. The addition of chiral dianion derived from *R*-triphenylglycol propionate **459** to imines **458** provided *trans*-β-lactams **461** with good chemical efficiency and up to 97% ee. Surprisingly, when ester enolate or silyl ester enolate obtained from a similar chiral source **460** were used, *cis*-β-lactams **461** were produced in 85–97%ee (Scheme 93).[161]

Tomioka et al. demonstrated the asymmetric preparation of β-lactams **465** via enantioselective addition of lithium enolate **462** to imine **463** based on a ternary complex reagent.[162] An interesting observation of their study was that the addition of 2.2 equiv. of another lithium amide improved the selectivity as well as the reactivity of the reaction (compare entries 1 and 2–4, Scheme 94). β-Lactam **465** were produced directly in this transformation, and the use of lithium cyclohexylisopropylamine or lithium dicyclohexylamine as the additive provided **465** with the highest enantioselectivity (entries 2 and 3). Good selectivities were also obtained in the presence of 20 mol% of **464** (entry 4).

An intramolecular C–H insertion protocol was investigated by Hashimoto et al.[163] A series of chiral Rh(II) complexes **467** were found to be outstanding catalysts in promoting the cyclization of **466**, yielding *trans*-**468** as the sole product with high enantiomeric purity. The same authors have also extended this methodology to the construction of key intermediate **470** for carbapenem antibiotics (Scheme 95).

Stimulated by the outcome of Kinugasa's[164] convergent route to β-lactams via couplings of an alkyne and a nitrone in the presence of copper, Lo and Fu have examined the

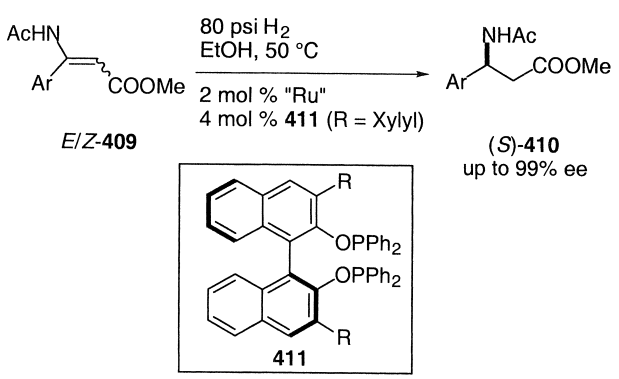


Scheme 82.

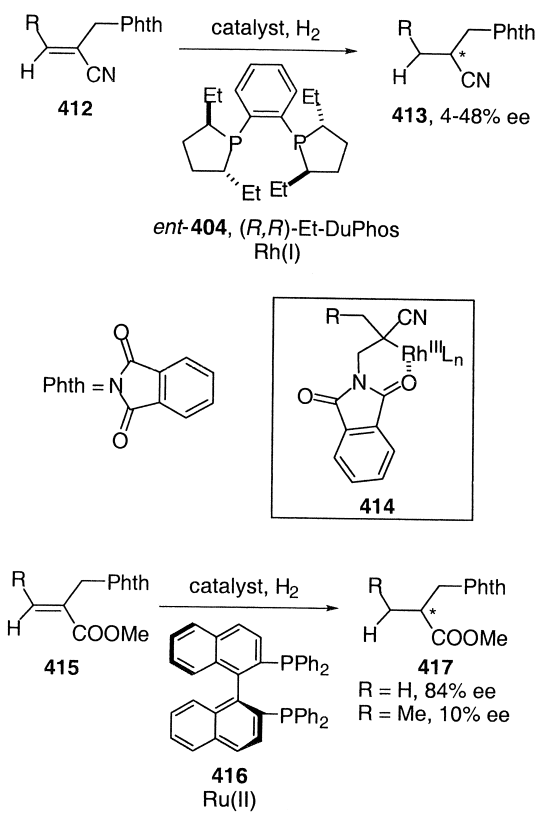
enantioselective version of the Kinugasa reaction in some detail.[165] Planar chiral bis(azaferrocene)ligand **474** in conjunction with CuCl (1–2.5%) catalyzed the reaction of a variety of alkynes **471** with nitrones **472** to give β-lactams in excellent enantioselectivities (Scheme 96). The most appealing characteristics of this method were the broad substrate scope and the easy accessibility of the starting materials.

1.10. Miscellaneous methods

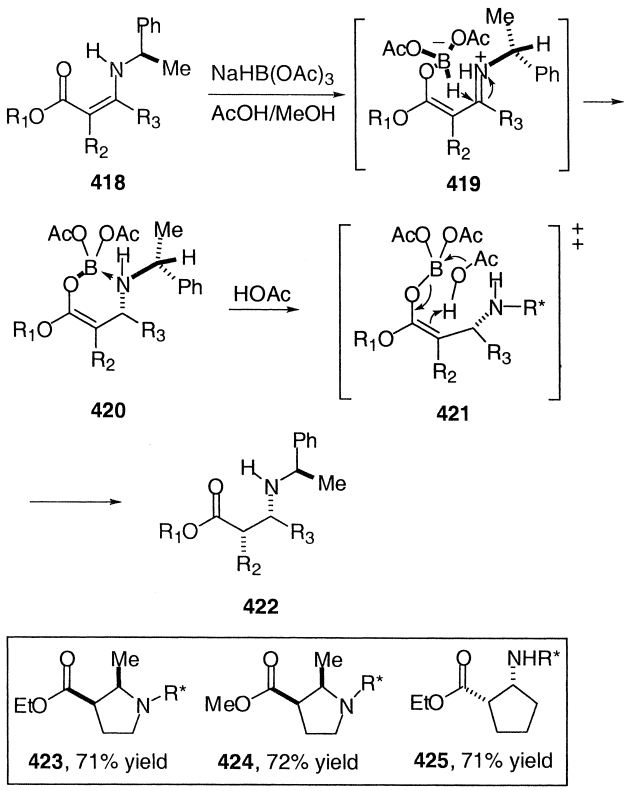
β-Amino acid ADDA (**4**) is a common component of several cyanobacterial toxins, such as nodularin, motuporin and microcystins. An elegant and stereoselective synthesis of this molecule was recently completed by Rinehart et al.[166] Asymmetric aldol reactions were employed to establish all the chiral centers in ADDA (Scheme 97). A 'one-pot'



Scheme 83.



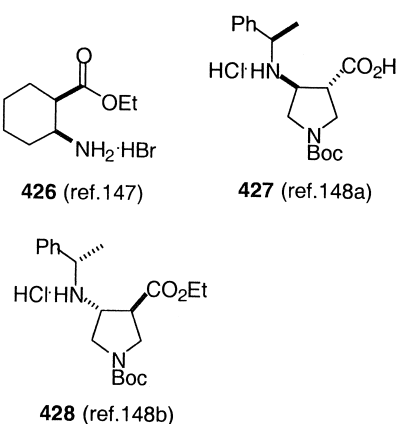
Scheme 84.



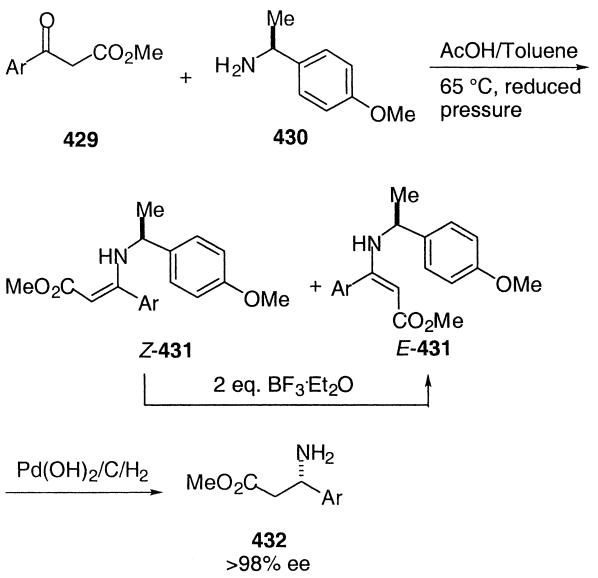
Scheme 85.

Mitsunobu reaction and SmI_2 reduction to allylic amines via isoxazolidin-5-one **483** formation was the highlight of their synthesis, which led to *N*-Boc-ADDA **475** in 40% overall yield in 13 steps. The importance of Adda has stimulated several research groups' interest in developing an efficient method for its synthesis. Other representative syntheses of ADDA include Toogood's Claisen rearrangement route with 9% yield in 15 steps,[167] Chamberlin's convergent approach featuring stereoseletive alkylation of aspartate and a novel Suzuki coupling method with 5% overall yield in 21 steps,[168] as well as Schreiber's method via modified Julia olefination and Lewis acid promoted crotylstannane addition with 12% overall yield in 23 steps.[169]

Juhl and Jørgensen presented a new route to *syn*-α-

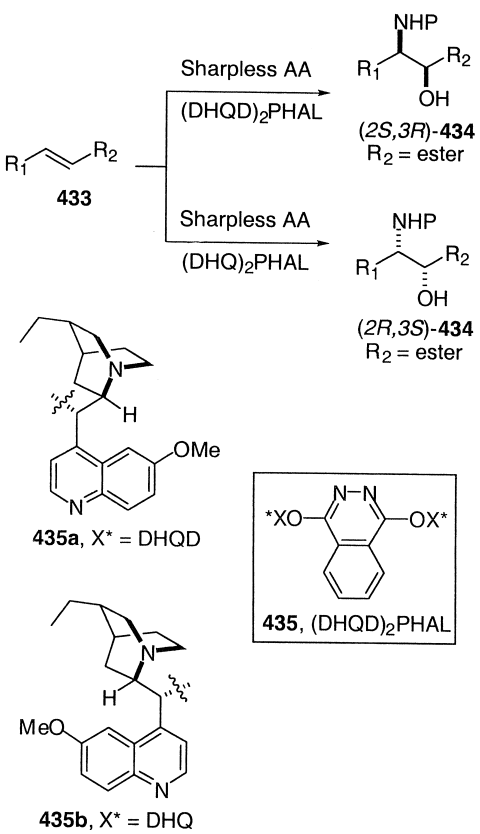


Scheme 86.

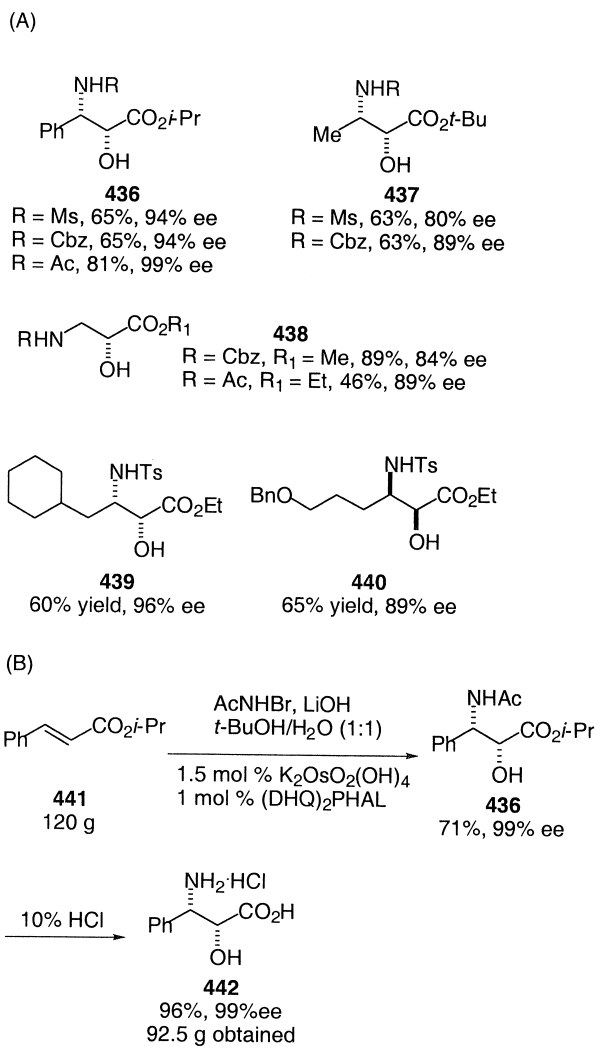


Scheme 87.

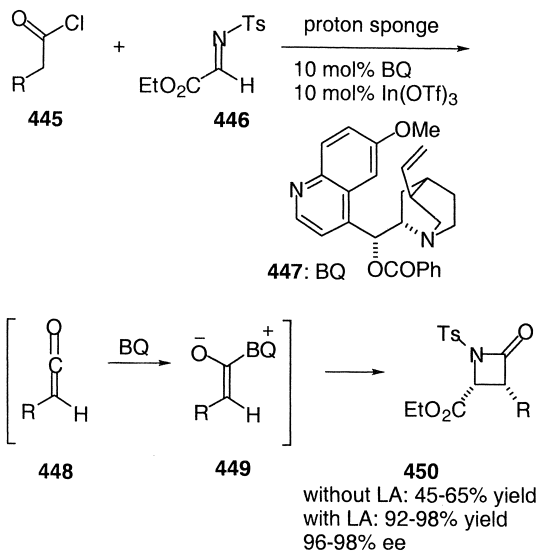
hydroxy β-amino esters via asymmetric α-amination reaction of 2-keto esters **484**.[170] Dibenzyl azodicarboxylate **485** was chosen as the electrophilic nitrogen source. Higher chemical yields were obtained when reactions were carried out in THF instead of CH_2Cl_2 (Scheme 98). Among various bisoxazoline–Cu(II) catalysts examined, **489** was the most effective. This process provided a novel entry to the α-aminated products in four reaction steps with moderate to good chemical efficiency and excellent



Scheme 88.



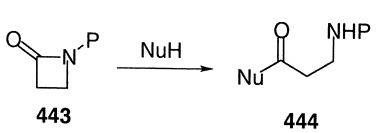
Scheme 89.



Scheme 91.

levels of enantioselectivities. The authors have also demonstrated the easy accessibility to protected α-hydroxy β-amino esters from **484** as outlined in Scheme 98. The absolute configuration of the newly formed chiral center was determined to be *S*, which accounted for a six-membered chair like transition state **491** with the *R*-substituent of **484** oriented in the less crowed pseudo-equatorial position. Recently, Jørgensen et al. have also observed high levels of enantioselectivities in *t*-Bu-bisoxazoline mediated Henry reaction of α-keto esters and nitromethane.[171]

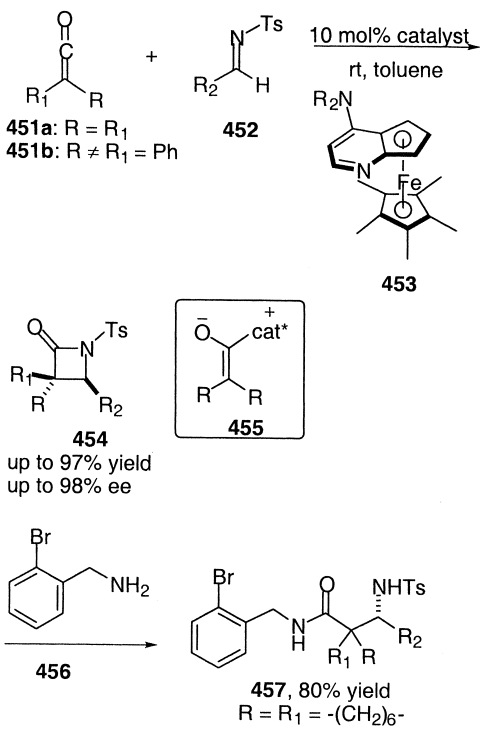
Brussee and co-workers have investigated the use of chiral cyanohydrin **492**, available from *R*-oxynitrilase mediated addition of HCN to 2-butenal, as potential precursor for the synthesis of α-hydroxy-β-amino acids.[172] In principle, Grignard addition to nitrile could be used to introduce a



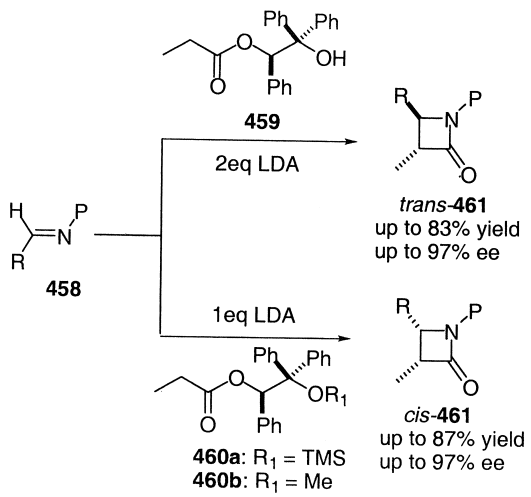
Scheme 90.

variety of substituents next to the nitrogen diastereoselectively through 1,2-asymmetric induction. Ozonolysis of **494** followed by Jones oxidation would then furnish the required carboxylic acid functionality (Scheme 99). This process was successfully applied to enantioselective preparation of **496** (R=Ph) the side chain of taxol.

Pericàs and Riera have developed another effective method for enantioselective synthesis of all four isomers of α-hydroxy-β-amino acid starting from the same allyl alcohol.[173] Their sequence included Sharpless asymmetric epoxidation, regioselective epoxide opening with benzylamine, and subsequent oxidation of the primary alcohol to



Scheme 92.

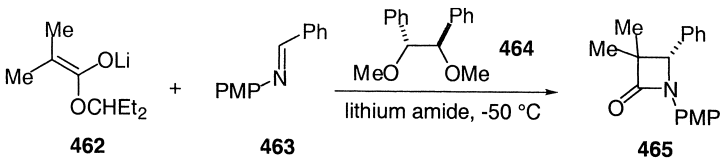


Scheme 93.

give the enantiopure *anti* products **502** and **506**. The corresponding *syn* stereoisomers **503** and **507** were obtained via Mitsunobu reaction of **502** and **506**, respectively (Scheme 100).

(*S*)-3-Amino-2-phenyl propanoic acid **515** is of particular interest because it is present as the side chain of penicillin betacin, whereas its ethyl ester has neurological activity.[9b] Lavielle and co-workers reported the asymmetric synthesis of its *N*-Boc protected derivative (**510**) featuring acylation of metallated phenylacetonitrile as the key step (Scheme 101(A)).[174] Another stereoselective approach to **515** following an entirely different strategy was later described by Calmes and Escale.[175] Amino acid **515** was obtained in enantiopure form via base catalyzed addition of (*R*)-pantolactone **513** to *N*-phthalyl ketene **512** (Scheme 101(B)).

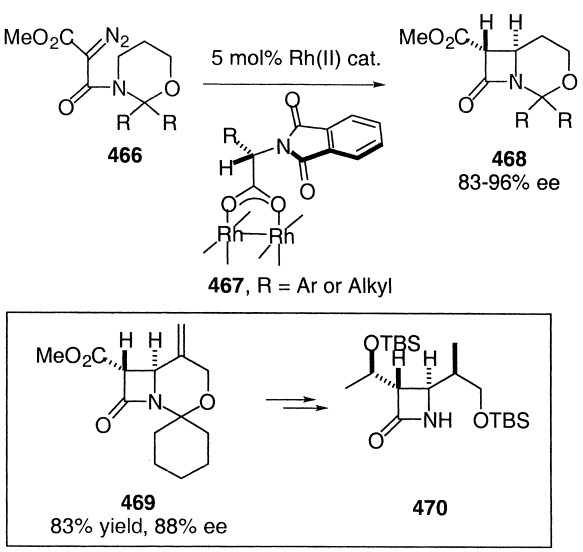
(+)-Methylphenidate hydrochloride (**518**) a cyclic β-amino acid, is a mild nervous system stimulant used for the treatment of attention deficit hyperactivity disorder. Prashad and co-workers completed the first enantioselective synthesis of **518** in nine steps with 13% overall yield from phenylacetic acid (Scheme 102(A)).[176] In contrast, a SmI_2-promoted aziridine ring



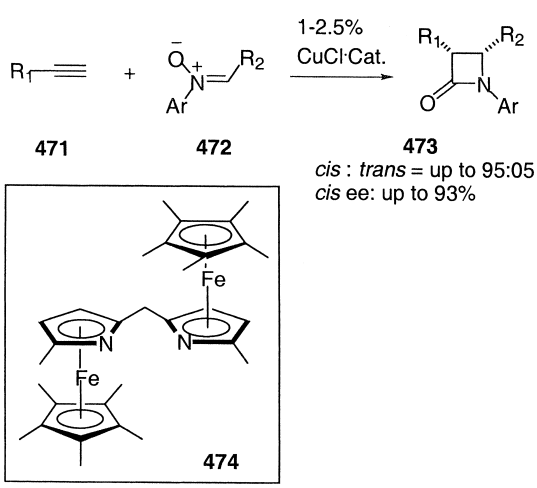
Entry	Li Amide	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	none	-20	7	95	60
2	LICA	-50	4	85	88
3	$LiNHex_2$	-50	4	76	86
4	LICA	-78	20*	80	75

* 20 mol% of **464** was used.

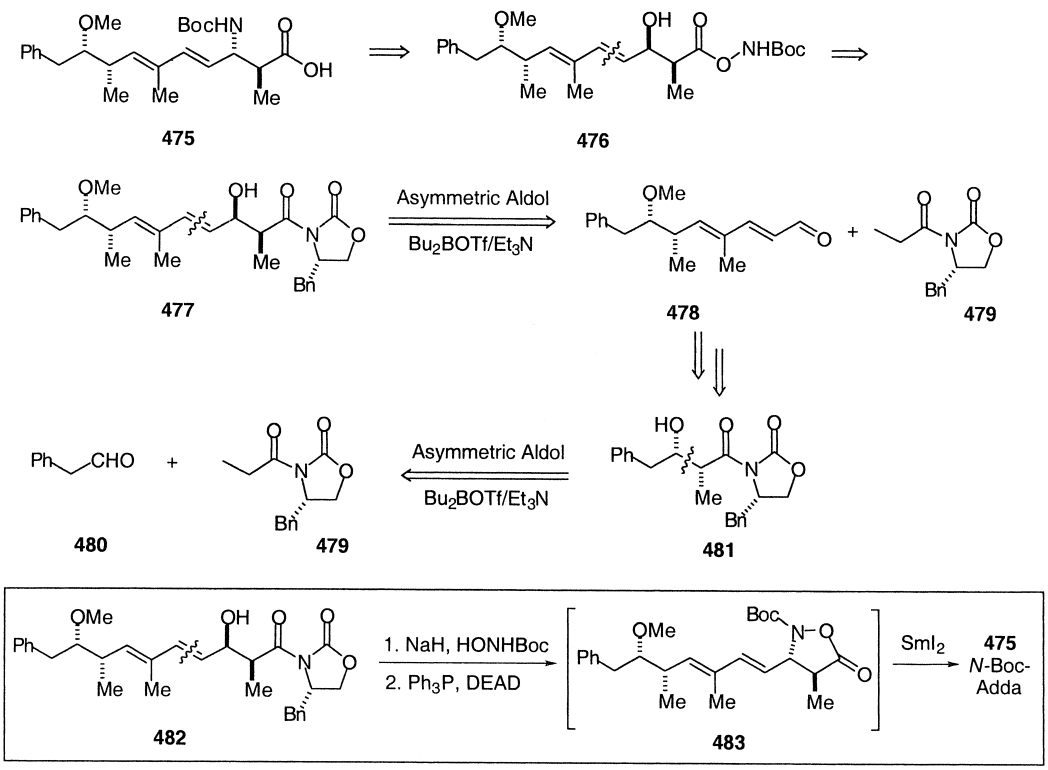
Scheme 94.



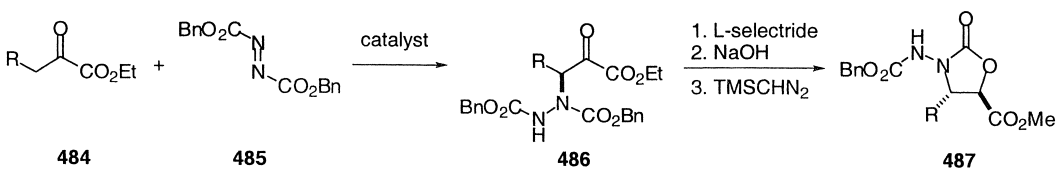
Scheme 95.



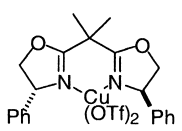
Scheme 96.



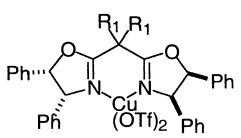
Scheme 97.



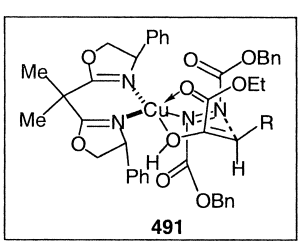
R	Cat.	Solvent	yield (%)	ee (%)
Bn	**488**	CH_2Cl_2	39	90
Bn	**488**	THF	60	82
Bn	**489**	THF	57	89
Bn	**490**	THF	58	88
Pentyl	**489**	THF	48	97
allyl	**489**	THF	38	90
i-pr	**489**	THF	60	95
c-hexylmethyl	**489**	THF	72	96



488

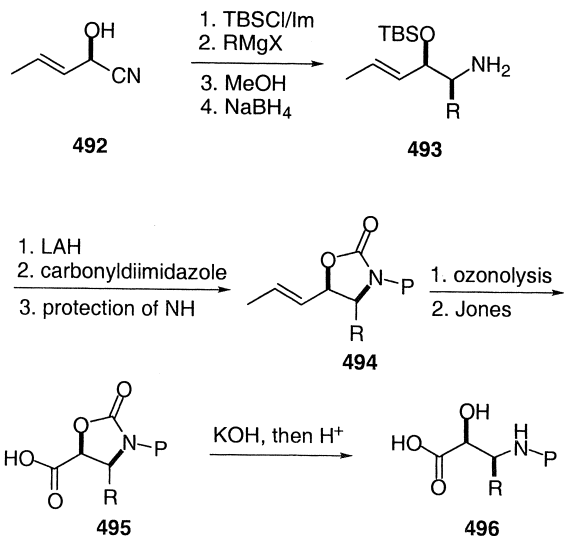


489, R_1 = H
490, R_1 = Me



491

Scheme 98.



Scheme 99.

opening protocol was described by Kawahata and Goodman in asymmetric synthesis of constrained phenylalanine analogs **520** (Scheme 102(B)).[177]

Recently, enantiopure β-phenyl amino acid was prepared by Kim, Park and Beak[178] in 76% overall yield from *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine **521** via (−)-sparteine (**523**)/BuLi catalyzed diastereoselective alkylation with substituted vinyl bromide **522**, and subsequent oxidation with ozone, followed by Jones reagent (Scheme 103).

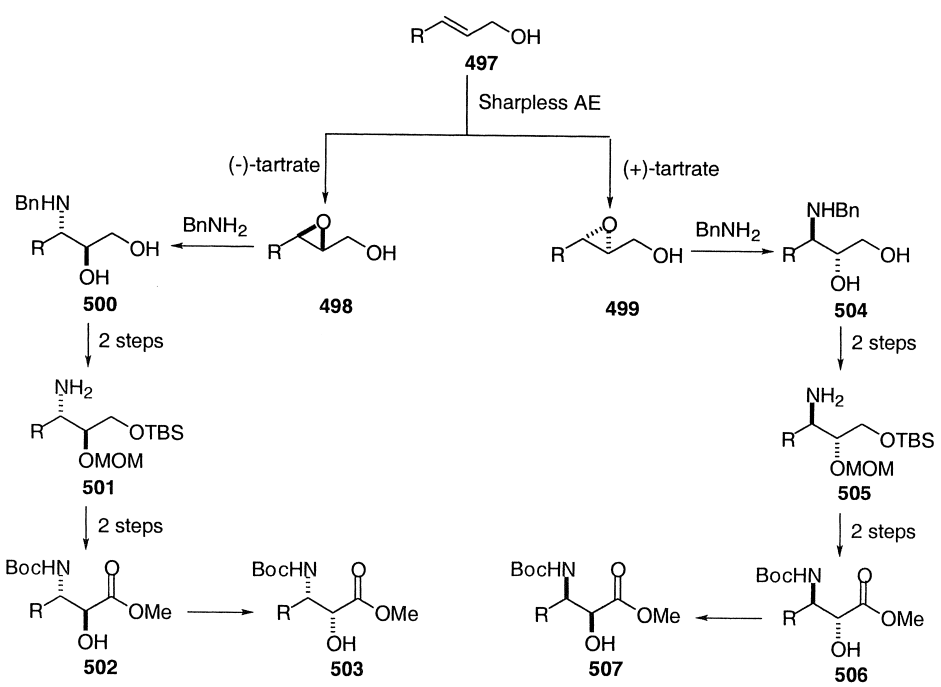
Gais and co-workers, utilizing sulfonimidoyl *anti*-homoallylic alcohols **526** and **532**, were able to synthesize β,β-disubstituted or β-substituted δ-hydroxy β-amino acids.[179] Carbamate **528**, easily derived from hydroxy sulfoximines **526**, was subjected to Hirama–Itô cyclization condition to provide the key intermediate **529** as a single diastereomer (Scheme 104). Alkylation of **529** with ClCOOMe proceeded with good diastereocontrol to give **530**, which upon reductive removal of the sulfonimidoyl group afforded the protected β-amino ester **531** in high yield. This sequence was also applied to the synthesis of cyclic β-amino ester derivative **534**.

A novel biomimetic protocol for the preparation of β-fluoroalkyl-β-amino acids was developed by Soloshonok and co-workers.[180] This process involved two consecutive base catalyzed 1,3-proton shift of enamine to aldimine, which was hydrolyzed to β-amino acids in 6N HCl. Asymmetric induction could be achieved in the presence of a chiral base. However, only up to 36% ee was observed when chiral bases (*R*)-*N*,*N*-dimethyl-1-phenylethylamine, (1*R*,2*S*)-*N*-methyl ephedrine and (−)-cinchonidine were employed.[180a] In contrast, high ee's were obtained by DBU catalyzed isomerization of chiral enamines **537** (Scheme 105).[180b]

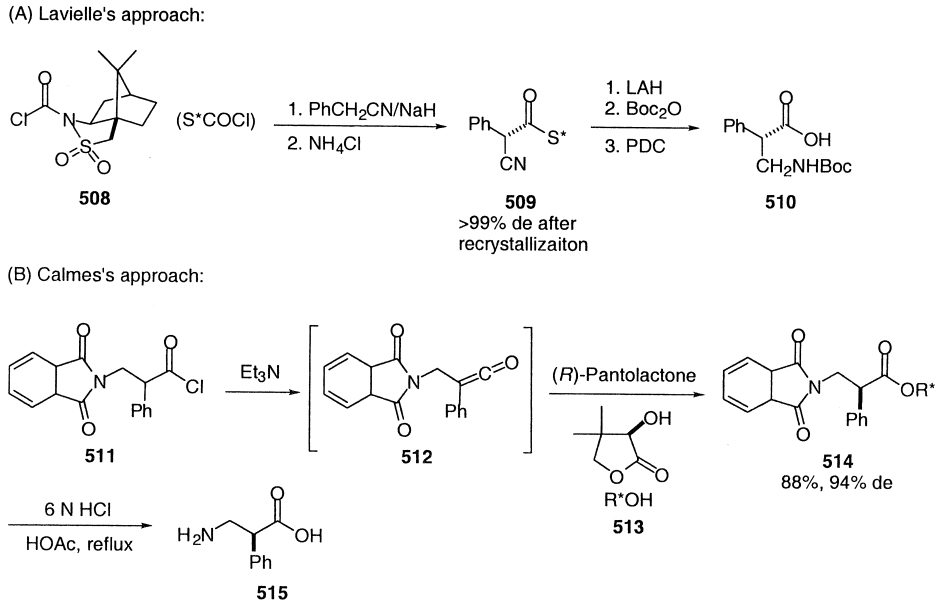
Finally, in a recent synthesis reported by Mazaleyrat et al.,[181] ethylcyanoacetate **542** was bisalkylated by the chiral binaphthyl derivative **541** in 79% yield. Cobalt mediated selective reduction of the cyano group, followed by a two-step protection and deprotection sequence led to the α,α-disubstituted β-amino acid, (*R*)-β^{2,2}-HBin **544**. This was the first enantiomerically stable β-amino acid with axial chirality (Scheme 106).

1.11. Conclusions

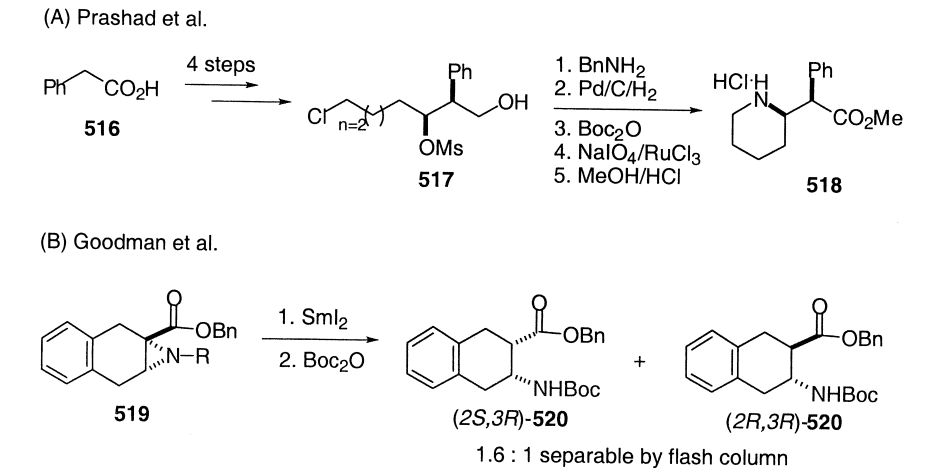
It is evident from the examples discussed in this review that



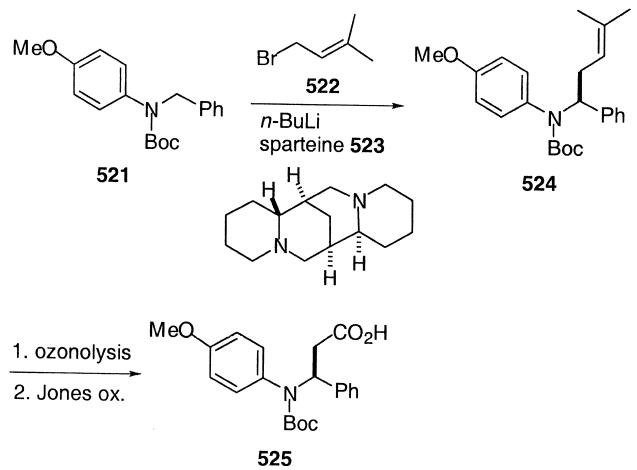
Scheme 100.



Scheme 101.



Scheme 102.



Scheme 103.

tremendous progress has been made in the past decade for the stereoselective synthesis of β-amino acids and derivatives. Many methodologies are now available for the asymmetric preparation of β-amino acids with various substitution patterns. Each approach has its own advantages and limitations. The development of an efficient process suitable for large-scale synthesis, which is easy to operate, practical and inexpensive, remains a significant challenge. No doubt, the growing interest in enantiopure β-amino acids will stimulate new and improved methods for their synthesis in the near future.

Acknowledgements

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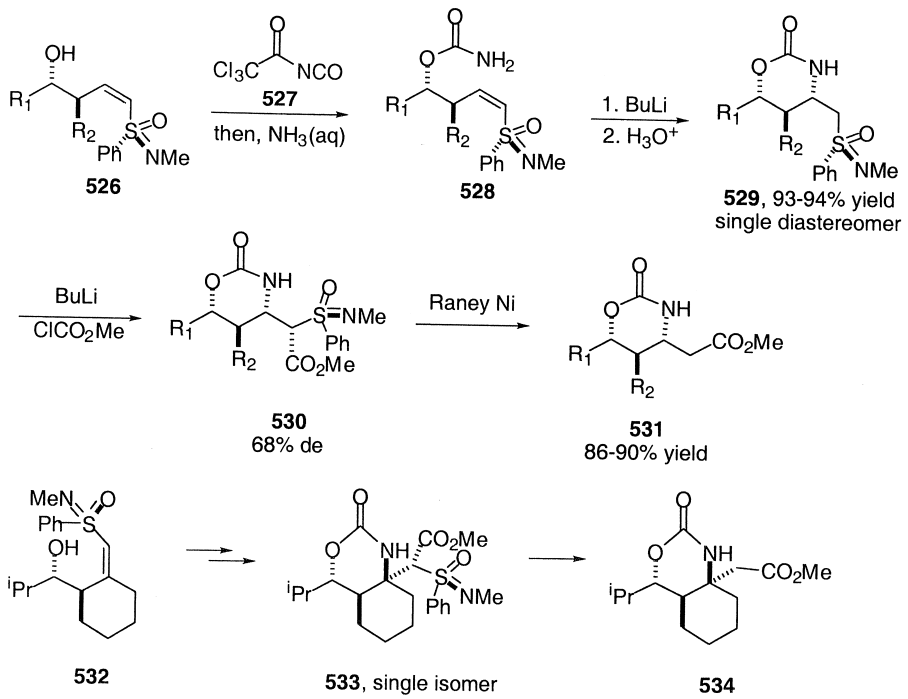
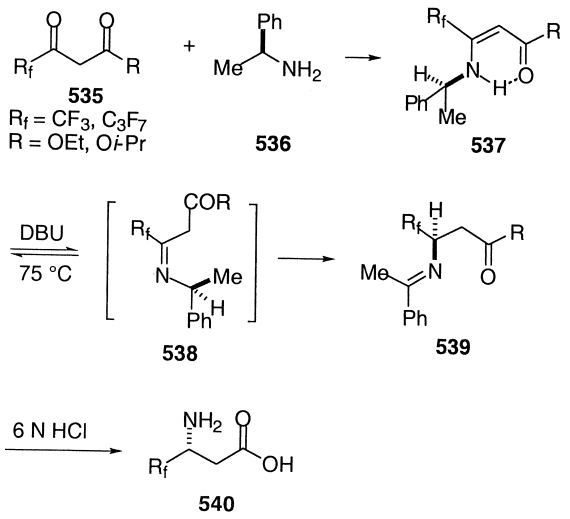
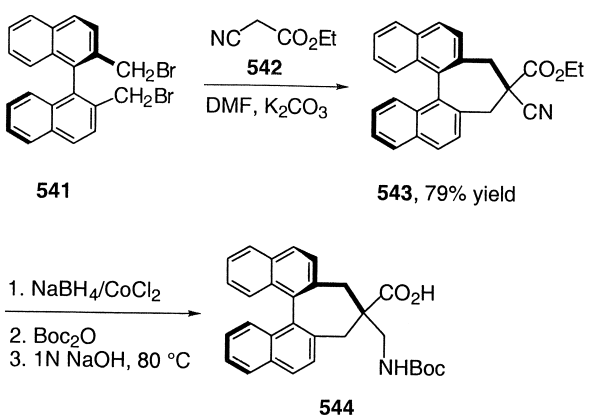


Scheme 104.



Scheme 105.



Scheme 106.

program. Mei Liu thanks ND-EPSCoR for a doctoral dissertation fellowship. We would also like to thank Professors Franklin Davis (Temple University) and Joseph Konopelski (University of California-Santa Cruz) for helpful discussions.

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Biographical sketch

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