

## Enantioselective Synthesis of $\beta$ -amino acids: A Review

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### Abstract

The synthesis of enantioselective  $\beta$ -amino acids is being reported in this review on account of their significant properties as proteinogenic, non-proteinogenic role such as neurotransmitter, biosynthesizer and nutritional supplementing materials etc. They are extensively used as chiral starting materials, auxiliaries and catalysts in organic synthesis. According to literature evidences, extensive research has been carried out to develop the methodologies for the synthesis of stereoselective  $\beta$ -amino acids. In this review, we describe recent advances in synthetic routes of enantioselective  $\beta$ -amino acids derivatives with chemical reactions during the last decades and to provide the most suitable route of their synthesis to compete the future challenges.

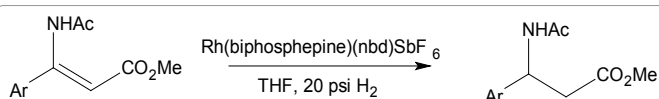
**Keywords:**  $\beta$ -amino acids; Enantioselective; Synthesis

### Introduction

Enantioselective synthesis of  $\beta$ -amino acids has gained significant importance because of their interesting pharmacological applications as hypoglycaemic and antiketogenic properties, antibacterial and antifungal activities, antihelminthic as well potent insecticidal properties activities [1-3].  $\beta$ -amino acids are fundamental building blocks for the preparation of pharmaceutical and agrochemical target molecules. They have displayed a high tendency towards the formation of  $\beta$ -peptides stable secondary structures (turns, sheets, and helices) and they are extensively used as chiral starting materials, auxiliaries and catalysts in organic synthesis [4-6]. Enantioselectively defined  $\beta$ -amino acids are applied in drug development, molecular recognition, bimolecular structure and functional studies [3-7]. However, the synthesis of  $\beta$ -amino acids bearing various functional groups on the  $\beta$ -carbon with thiadiazole ring systems have been well studied due to having variety of biological activities, including antifungal, antitubercular, antibacterial, anticancer, and analgesic properties [8,9].

Different methodologies have been tried out for their synthesis to maintain desired chirality is a big challenge. Several different catalytic asymmetric approaches to synthesize  $\beta$ -amino acids involving carbon-carbon, carbon-nitrogen, and carbon-hydrogen bond forming reactions have been developed [10]. As per literature evidences, the enantioselective derivative of  $\beta$ -amino acid like *N*-acyl- $\beta$ -(amino) acrylates was prepared by using  $\text{Ru}(\text{O}_2\text{CCH}_3)_2$  as catalyst [1]. Similarly Ru and Rh chiral mono- and bi-dentate phosphorous homogeneous catalysts were used for their synthesis through hydrogenation standard procedure. The hydrogenation of (*Z*)-enamines catalysed by bisphosphopine ligand was proceeded by Zhang et al. (Scheme 1) with 90% high yield. On the contrary, using the same catalyst system, (*E*)-enamines give only low yield [11].

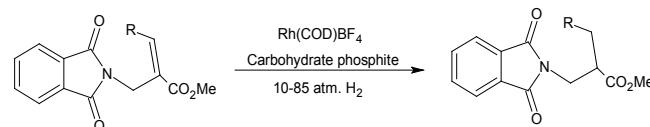
High enantioselectivity in Rh-catalyzed hydrogenations can also be obtained by phosphite and other phosphorous ligands [12]. When phthalimide protected acrylates are hydrogenated using carbohydrate-phosphite  $\beta^2$ - amino acid derivatives are formed with 99% yield (Scheme 2) [13].



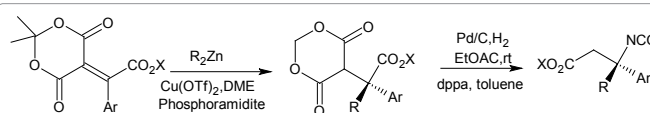
**Scheme 1:** Rhodium-bis phosphopine catalyzed hydrogenation of (*Z*)-enamines.

Phosphoramidite ligand was used to obtain adducts in high yields with up to 94% by Fillion et al. through conjugate addition of dialkylzinc reagents to 2-aryl acrylate (Scheme 3). Deprotection of adduct, followed by a Curtius rearrangement of the succinic acid derivative resulted in the formation of  $\beta$ -amino acid derivative [14].

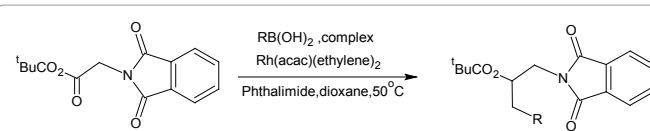
Sibi et al. reported an enantioselective rhodium catalyzed enolate protonation method for the synthesis of  $\beta^2$ -amino acid (Scheme 4).  $\text{Rh}(\text{acac})(\text{ethylene})_2$  and difluorophos used to form a complex which catalyzed the conjugate addition of aryl boronic acids to  $\beta$ -acrylates. The intermediate oxa- $\beta$ -allyl-Rh resulted in good yields using one equivalent of phthalimide as proton source [15].



**Scheme 2:** Rh-catalyzed hydrogenation of phthalimide protected acrylates.



**Scheme 3:** Cu-catalyzed dialkylzinc to 2-aryl-acrylates to form quaternary stereo centers.



**Scheme 4:** Enantioselective rhodium catalyzed conjugate addition and protonation.

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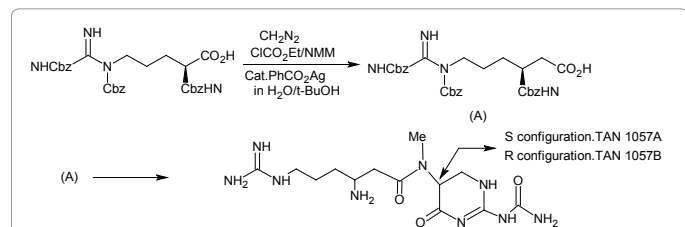
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A dipeptide antibiotic TAN-1057 A,B was synthesized (58% yield) via tri-N-Cbz-L-arginine and diazoketone in 1:1 molar ratio while the tert-butyl alcohol/water is used as solvent. The overall chemical reaction is given in Scheme 5 [16].

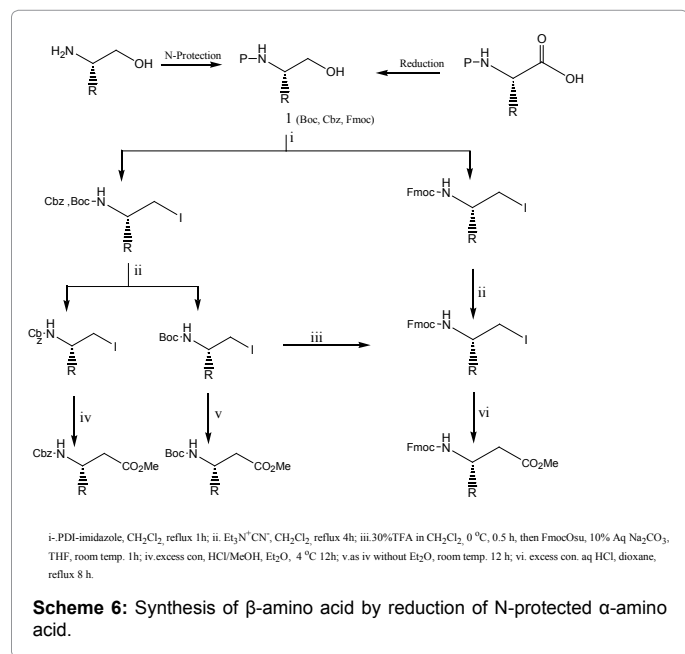
On the other hand enantioselective  $\beta$ -amino acids were synthesized in good yield from N-protected amino acids via reduction of carboxyl function,  $\beta$ -amino alcohol into corresponding  $\beta$ -amino iodide and cyanides (Scheme 6) [17].

The conjugate addition of cyanide to  $\alpha, \beta$ -unsaturated imides using aluminium-salen catalyst was reported by Jacobsen et al. (Scheme 7). The basic hydrolysis of the imide to the corresponding carboxylic acid resulted in the formation of adducts which were transformed into  $\beta$ -amino acids, under acidic conditions the  $\beta$ -amino acids are converted to corresponding carboxylic acid followed by Curtius rearrangement with diphenylphosphoryl azide (dppa) and hydrolysis of the nitrile group [18].

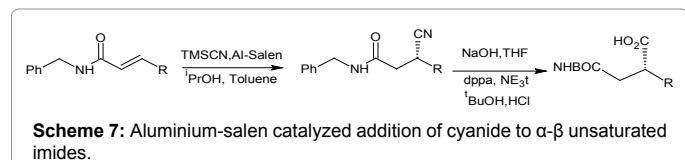
2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) in its dimeric form used to derive cationic catalyst which was employed by Sodeoka et al. in the synthesis of  $\beta$ -amino acids. The adducts in high



**Scheme 5:** Arndt-Eistert reaction in the total synthesis of TAN-1057A, and TAN-1057B.



**Scheme 6:** Synthesis of  $\beta$ -amino acid by reduction of N-protected  $\alpha$ -amino acid.



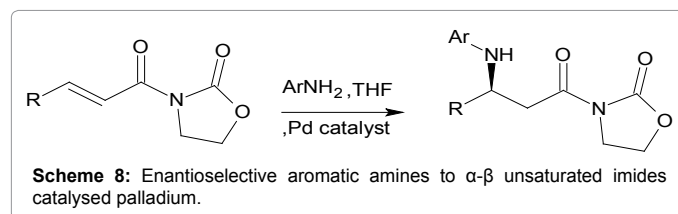
**Scheme 7:** Aluminium-salen catalyzed addition of cyanide to  $\alpha$ - $\beta$  unsaturated imides.

yield are obtained from aromatic amines substituted with electron donating or withdrawing groups (Scheme 8) [19].

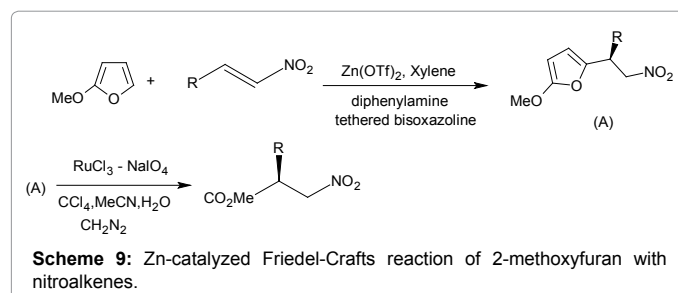
In 2007, a diphenylamine-tethered bisoxazoline Zn(II) complex was used to add methoxyfuran to aromatic nitro olefins in an asymmetric Friedel-Crafts alkylation of 2-methoxyfuran with nitroalkenes with yield upto 96% (Scheme 9). The furan ring oxidatively give an intermediate which is then treated with diazomethane to form the  $\beta$ -nitro ester from which the corresponding  $\beta^2$ -amino acids are obtained [20].

In the following scheme 10, *Candida antarctica* lipase A and B enzymes played a vital role in synthesis of enantiomeric (S and R)  $\beta$ -amino acids, because lipase can achieve resolution of a racemic substrate [21-23].

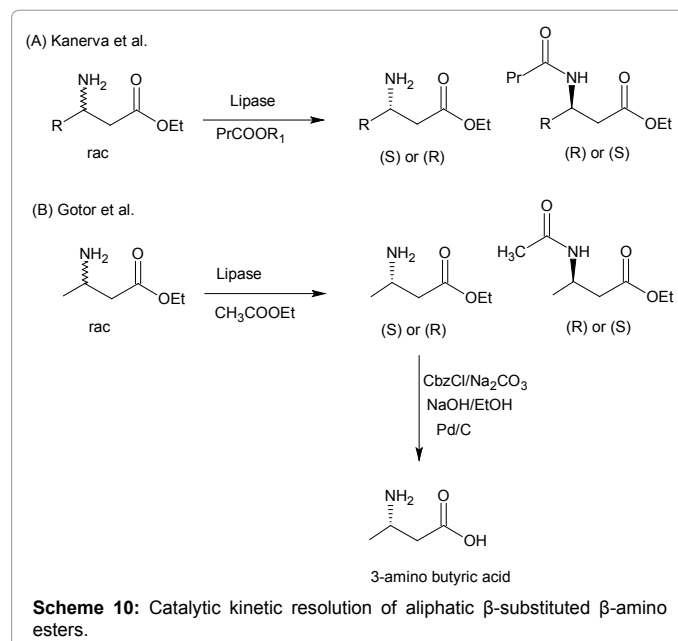
Another way to easy synthesis of S and R  $\beta$ -amino acids were prepared and reported by Soloshonok et al. The N-phenylacetyl and malonic acid was taken as reactants in the presence of ammonium acetate. Penicillin acylase enzyme in aqueous media used to produce enantiomers. The scheme 11 describes the key steps of their synthesis [24].



**Scheme 8:** Enantioselective aromatic amines to  $\alpha$ - $\beta$  unsaturated imides catalysed palladium.



**Scheme 9:** Zn-catalyzed Friedel-Crafts reaction of 2-methoxyfuran with nitroalkenes.



**Scheme 10:** Catalytic kinetic resolution of aliphatic  $\beta$ -substituted  $\beta$ -amino esters.

A rhodium-catalyzed C-H insertion of aromatic diazoacetates into *N*-Boc-*N*-benzyl-*N*-methylamine was also used in the synthesis of  $\beta^2$ -amino acids (Scheme 12) [25]. Benzylamine which will give up to 96% yields used for insertion of various aromatic, heteroaromatic and alkenyldiazoacetates.

Aromatic  $\beta^3$ -amino acid derivatives were obtained with up to 98% yield in the reaction of silylenol ethers with *N*-BOC-aldimines having thiourea as a catalyst (Scheme 13) [26]. Comparable enantioselectivities were given by the catalyst i.e. thiourea due to variations in the amine part.

A multi-step procedure for the synthesis of  $\beta$ -unsaturated  $\beta^2$ -amino acid derivatives was described by Walsh et al. (Scheme 14). First, enantioselective vinylzinc addition to aldehydes yield allylic alcohol, followed by Overman's 3,3-sigmatropic imidate rearrangement by one-pot deprotection-oxidation sequence. The hydroboration of terminal alkyne with dicyclohexylborane and transmetalation of the vinylborane with diethylzinc generated vinylzinc reagents. The addition of the vinylzinc reagent to aromatic and aliphatic aldehydes was catalyzed by ligands in high yield 99% using the trichloroacetimidate in 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to synthesize trichloroacetimidate and heated to reflux yielding the rearranged product. One-pot deprotection of the trityl alcohol and

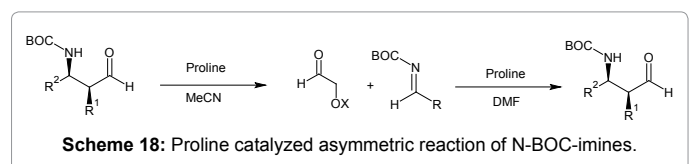
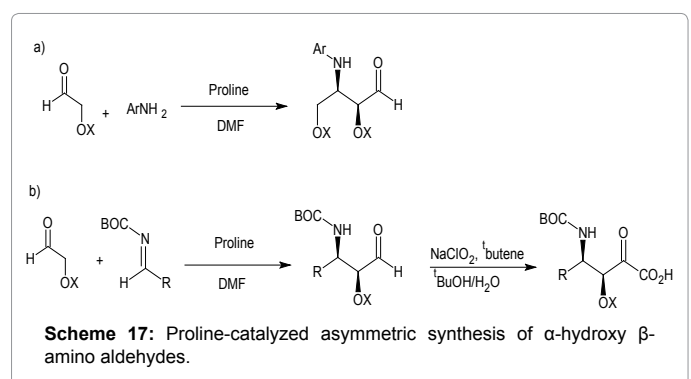
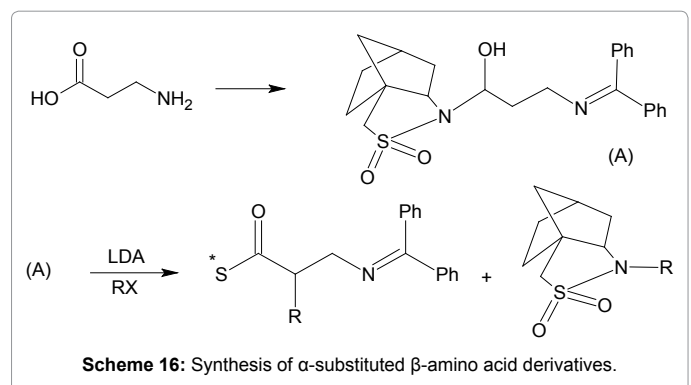
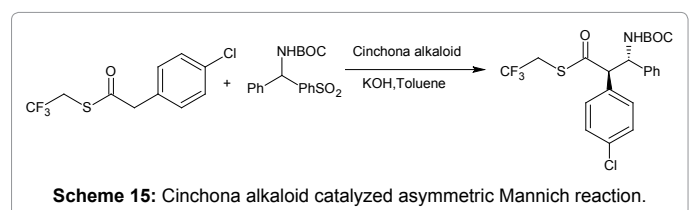
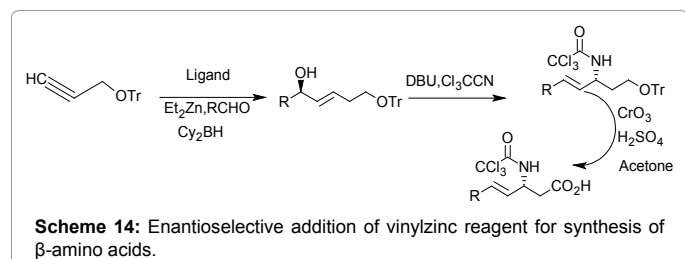
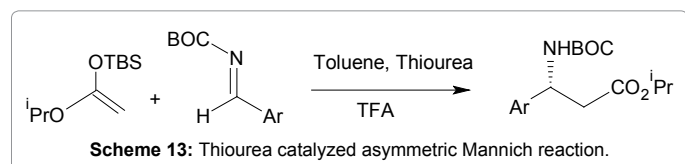
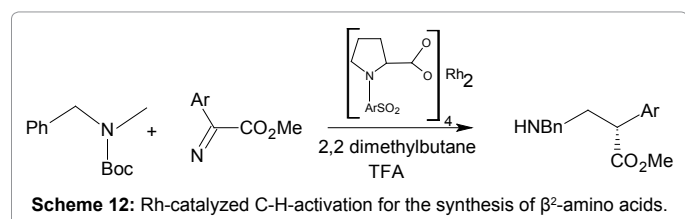
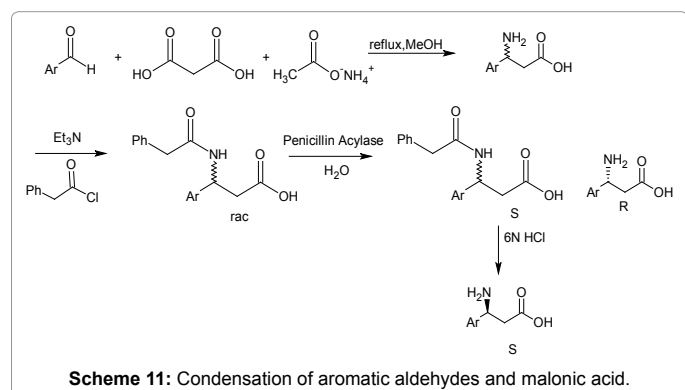
oxidation of the free hydroxyl group gave *N*-protected amino acid using chromium trioxide in sulphuric acid [27].

In another reaction, synthesis of *N*-BOC imines were catalysed by Cinchona alkaloid given in scheme 15 are moderate enantioselective amino acids [28].

Lavielle and co-workers used sultam- $\beta$ -alaninate-derived Schiff base for the synthesis of  $\alpha$ -substituted  $\beta$ -amino acid derivatives. Lithium enolate was produced as a bi-product which is trapped with electrophiles. The reaction is given in scheme 16 [29].

The synthesis of protected aminotetroses and *syn*- $\beta$ -hydroxy- $\beta$ -amino acids was successfully described by Córdova et al. using glycol aldehydes (Scheme 17a, b). They are enantioselective and diastereoselective in nature [30, 31].

The proline catalysed addition of aldehydes to aromatic *N*-BOC-protected imines gave *syn*-adduct (Scheme 18) with excellent diastereoselectivities and enantioselectivities. This was reported by List et al. [32].



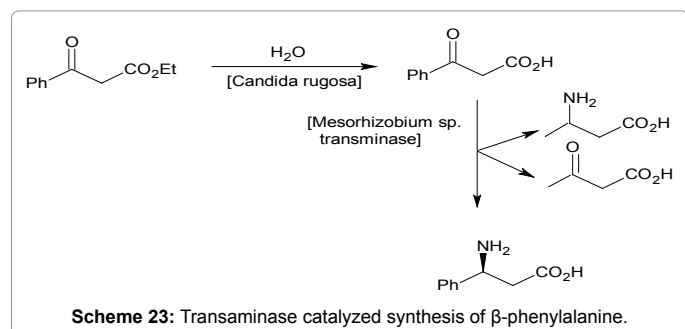
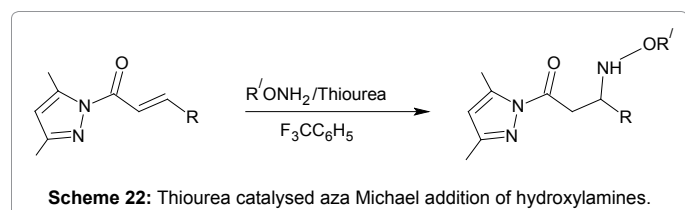
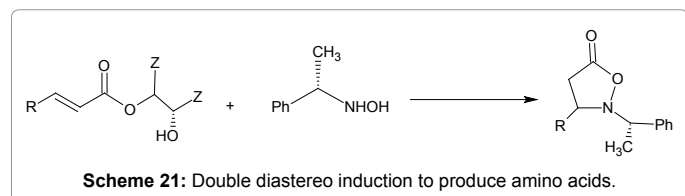
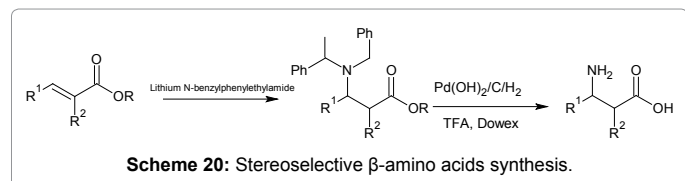
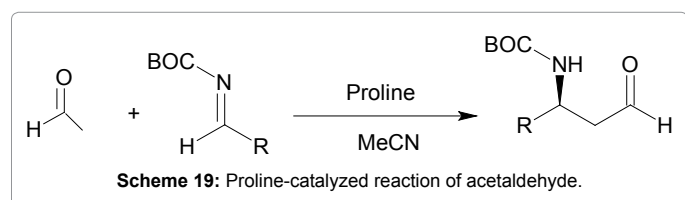
The same group reported the proline catalyzed reaction of *N*-BOC-imines with acetaldehyde (Scheme 19) [32].

Versatile asymmetric *syn*- $\alpha$ -alkyl- $\beta$ -amino esters may be generated in good yield and with excellent stereocontrol. Several examples illustrate these products may be debenzylated and hydrolysed to afford homo chiral *syn*- $\alpha$ -alkyl- $\beta$ -amino acids (Scheme 20) [33, 34].

In the following scheme 21, Saito et al. produced isoxazolidinones which were converted to  $\beta$ -amino acids by reductive cleavage of the N-O bond by double diastereo induction of chiral methyl benzyloxyamine to chiral esters [35].

Thiourea was used as a catalyst for the conjugate addition of *O*-substituted hydroxylamines to pyrazolecrotonates by Sibi et al. (Scheme 22). The yield of adducts is higher with aliphatic  $\alpha$ ,  $\beta$ -unsaturated compounds as compared to the phenyl substituted substrates [36].

The synthesis of  $\beta$ -amino acids was also characterized by a new

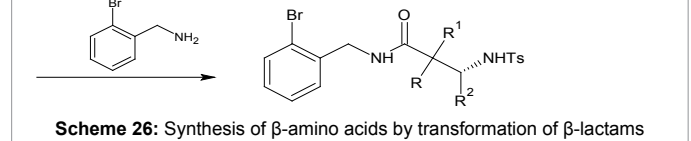
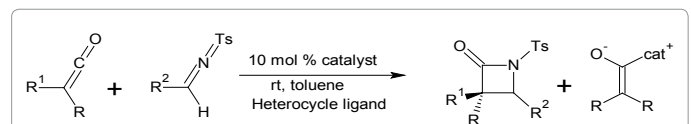
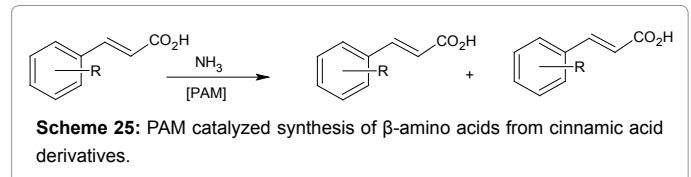
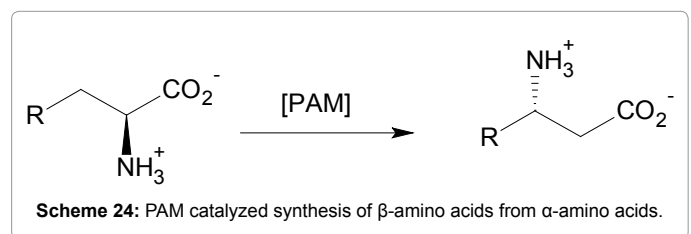


biocatalyst which was named as  $\beta$ -transaminase (Scheme 23). The lipase from *Candida rugosa* catalyzes the hydrolysis of  $\beta$ -keto acid being the substrate for the transamination. The final product obtained was  $\beta$ -phenylalanine while the racemic  $\beta$ -alanine was used as nitrogen source [37].

Aromatic and heteroaromatic  $\beta$ -amino acids were employed to synthesize the corresponding  $\beta$ -amino acids. Phenylalanine amino mutase (PAM) has been used to synthesize  $\beta$ -Styryl- and  $\beta$ -aryl- $\beta$ -alanine derivatives (Scheme 24) [38].

PAM was used by Janssen and Feringa et al. in a synthetic procedure for  $\beta$ -amino acids to catalyze the amination of cinnamic acid derivatives (Scheme 25). A mixture of  $\alpha$ - and  $\beta$ -amino acids which remained unisolated or un-separated was obtained. By the substitution of electron donating groups in *para*-position of the aromatic ring corresponding  $\beta$ -amino acids are obtained [39].

$\beta$ -amino acids were synthesized by transformation of enantioselective  $\beta$ -lactams. In this method, the di-substituted symmetric or asymmetric ketenes react with imines effectively to



produce  $\beta$ -lactams which is preceded further to get enantioselective of high purity  $\beta$  amino acids (Scheme 26) [40].

High enantiomeric and diastereomeric purity *N*-benzoyl  $\alpha$ -hydroxy  $\beta$ -amino acids was prepared by excellent chiral starting material cyanohydrin [(-)-(R,E)-*p*-2-hydroxy-3-pentenitrile] which was prepared by R-oxynitrilase catalytic addition of HCN to 2-butenal, reaction is described in the scheme 27 [41].

The use of chiralferrocenylphosphine ligand in the hydrogenation of (*Z*)-enamine esters with an unprotected amine group in trifluoroethanol (TFE) as solvent to yield the corresponding amino esters with excellent yield 98% (Scheme 28) [42].

MalPhos catalyzed (*E*)-enamines with 99% yield and of the corresponding (*Z*)-enamines with 90% yield is reported (Scheme 29). In a similar reaction, Me-DuPhos gave also high yields with these (*E*)-enamines, but (*Z*)-enamines gave correspondingly lower yields [43].

The mixed ligand approach has been employed in the synthesis of  $\beta$ -amino acid catalyzed by rhodium-phosphoramidite complexes in order to further enhance the enantioselectivity. The combination of chiral phosphoramidite with achiral tris-*o*-tolyl-phosphine using the unprotected carboxylic acid was used for the synthesis of  $\beta^2$ -amino acids (Scheme 30) [44].

In 2005, the addition of  $\beta$ -ketoesters to various imines catalyzed by a chiral cationic palladium complex was described by Sodeoka et al. (Scheme 31) [45]. The catalyzed addition of  $\beta$  ketoesters to  $\alpha$ -imino esters gave the corresponding  $\beta$ -amino acids.

Shibasaki et al. in the direct asymmetric reaction of trichloromethyl ketones and pyridyl- orthienylsulfonyl-protected imines studied

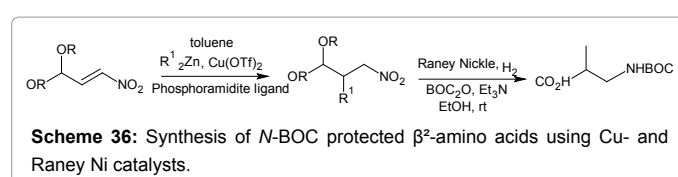
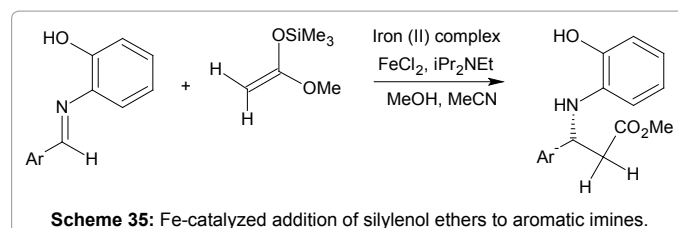
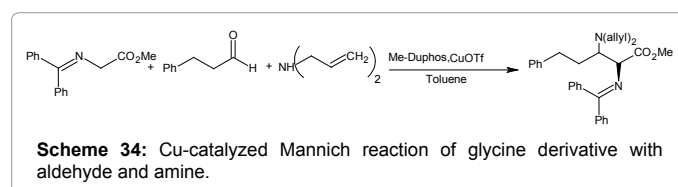
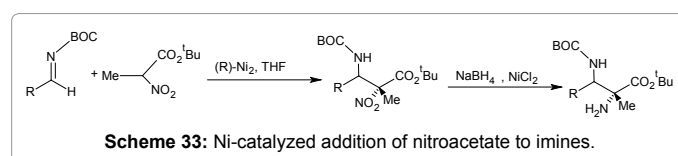
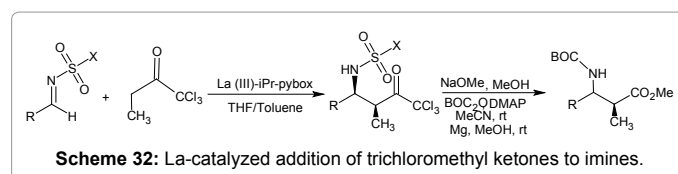
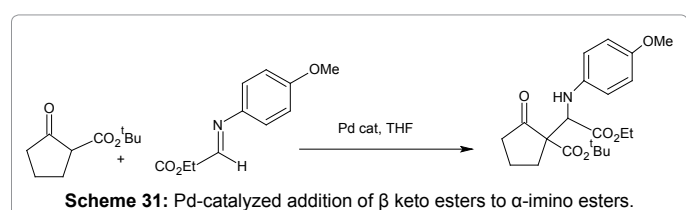
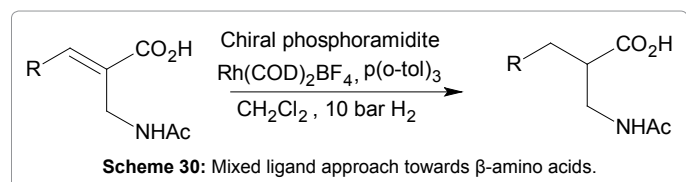
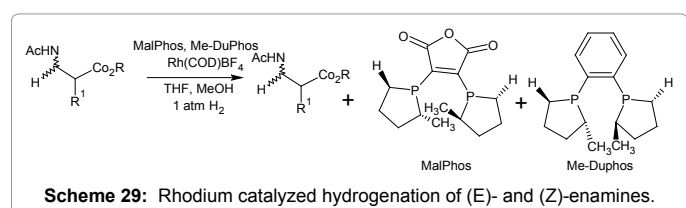
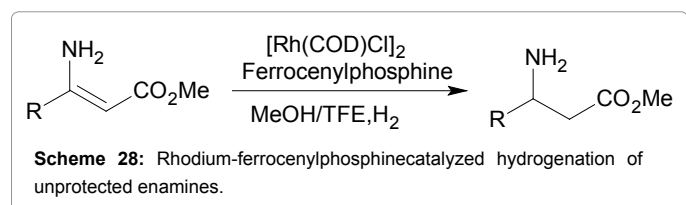
La(III)-*i* Pr-pybox (Scheme 32). The trend of the reaction was to use the aliphatic, aromatic and heteroaromatic imines as substrates. Using esterification the product was transformed into the *N*-BOC-protected  $\beta^2$ -amino ester under basic conditions [46].

Homonuclear Ni<sub>2</sub>-Schiff base complex was also reported by Shibasaki et al. for the synthesis of tetra substituted *anti*- $\alpha$ ,  $\beta$ -diamino acids (Scheme 33). The corresponding adducts were obtained with high yields from BOC-protected aromatic and aliphatic imines with nitroacetate. The nitro group was reduced to give  $\alpha$ ,  $\beta$ -diamino ester using NaBH<sub>4</sub>/NiCl<sub>2</sub>, which was transformed to the corresponding acid [47].

Simple aromatic and enolizable aliphatic aldehydes, secondary amines and glycine derivatives are used as starting materials producing protected  $\alpha$ ,  $\beta$ -diamino esters using Me-Duphos as ligand by Kobayashi (Scheme 34) [48].

Kobayashi et al. have also studied the asymmetric Mannich reaction (Scheme 35). The adducts with yield 84% are obtained by the reaction of  $\beta$ -dimethyl silylenol ethers with protected aromatic imines [49].

Feringa et al. obtained adducts of Et<sub>2</sub>Zn, Me<sub>2</sub>Zn and Bu<sub>2</sub>Zn with high yield by the addition of dialkyl zinc reagents to acetal-substituted nitropropenoates (Scheme 36) [50]. Raney-Nickel reduction of the nitroalkane, followed by BOC-protection of the amine group and oxidation of the acetal under acidic conditions to the corresponding carboxylic acid gave the corresponding *N*-BOC protected  $\beta^2$ -amino acids.

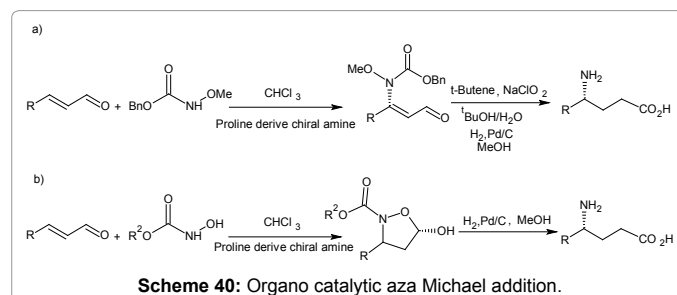
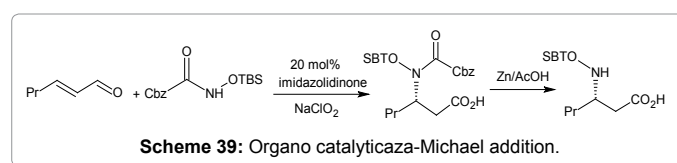


Hii et al. investigated cationic palladiumbinap complex using aniline and crotonyloxazolidinone, to get enantioselective addition of primary aromatic amines to  $\alpha, \beta$  unsaturated oxazolidinones (Scheme 37a) [51]. Similarly high yield 98% obtained when cationic palladium complex was investigated in addition to aromatic amines to *N*-alkenylcarbamates (Scheme 37b) using various aliphatic substrates (R = Me, Et, Pr). By the hydrolysis of the imide under basic conditions, the products were converted to *N*-aryl- $\beta^3$ -aminoacids [52].

The synthesis of  $\beta^2$ -amino acids was reported by Gellman et al. by the enantioselective aminomethylation of aldehydes (Scheme 38a). The  $\beta$ -amino aldehydes were reduced to the corresponding alcohols by reaction with Proline derivative. For the synthesis of  $\beta^2$ -amino acids, the amino alcohol was recrystallized as hydrochloride salt to increase the yield, the protecting groups removed by hydrogenation followed by BOC-protection, and the alcohol oxidized to the corresponding carboxylic acid [53, 54]. High yields up to 98% were obtained by Córdova et al. by using LiBr (Scheme 38b). The corresponding  $\beta^2$ -amino acid was synthesized by oxidation of the alcohol to the carboxylic acid after deprotection of the benzyl-protecting group re-protection using BOC<sub>2</sub>O [55].

A demonstration of the organocatalytic amine addition and the accompanying products is presented in the one pot conversion of simple aldehydes to enantio enriched  $\beta$ -amino acids. The 2-hexenal reacts with asymmetric amination conditions followed by *in situ* Pinnick oxidation provided the corresponding  $\beta$ -amino acids with excellent enantioselective (92%). *N*-O bond removal can be accomplished under mild reduced conditions (Zn/AcOH) (Scheme 39) [56].

Similarly, in another report by Córdova et al. the  $\alpha, \beta$ -unsaturated aldehydes were obtained by the reaction of proline-derived chiral amine with *N*-Cbz-methoxylamine as a nucleophile (Scheme 40a) [57]. The  $\beta$ -amino aldehydes obtained in high yield up to 99% undergo oxidation to the corresponding carboxylic acid and deprotection of the amine provided  $\beta^3$ -amino acids. When carbamate-protected hydroxylamines were used as nucleophile, the cyclic 5-hydroxy-isooxazolidinones were obtained with high yield up to 98% (Scheme 40b). The corresponding  $\beta^3$



amino acids were obtained by subsequent cleavage by hydrogenolysis with high yield up to 97% [58].

The derivatives of  $\beta$ -amino acid were obtained with high yields through 1,3-asymmetric induction through radical mediated 1,5-hydrogen atom transfer and trapped by electrophilic olefins (Scheme 41) [59].

The preparation of syn- $\alpha$ -hydroxy  $\beta$ -amino acids was reported in two steps by Cardillo and Gentilucci. The key step of this synthesis was the formation of transoxazoline (Scheme 42). The PGA catalyzed kinetic resolution gave 3-amino-3-phenylpropanoic acid [60].

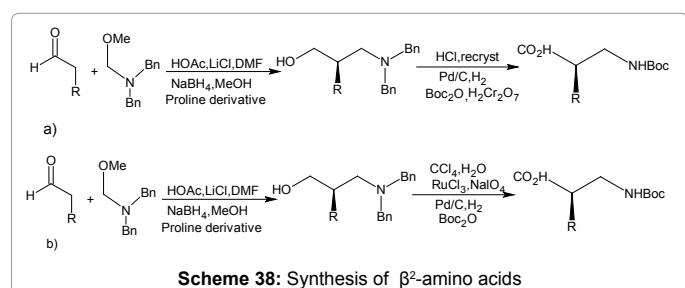
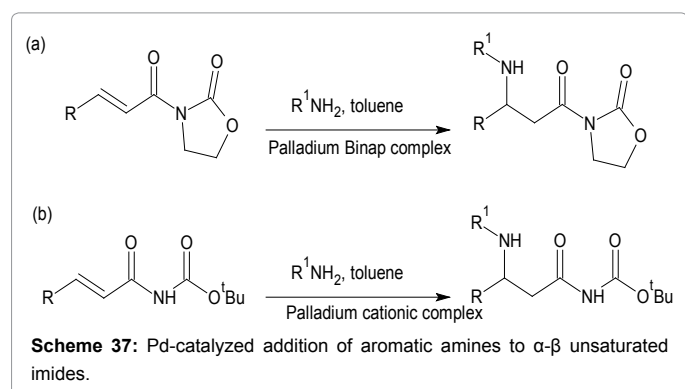
The enantioselective (*R*)-(+)- $\beta$ -phenylalanine and (*S*)-(+)-ethyl- $\beta$ -amino-3-pyridinepropanoate have been prepared elsewhere in literature (Scheme 43). The reaction was completed by the addition of sodium enolate to chiral sulfinimine [61,62]. The sulfinyl group activated the carbon-nitrogen double bond, and therefore facilitates the addition of various nucleophiles. In similar methodology titanium enolate was added to tertbutanesulfinylimine by Ellman and Tang for the construction of  $\beta, \beta$  disubstituted and  $\alpha, \beta$  disubstituted  $\beta$ -amino acids [63].

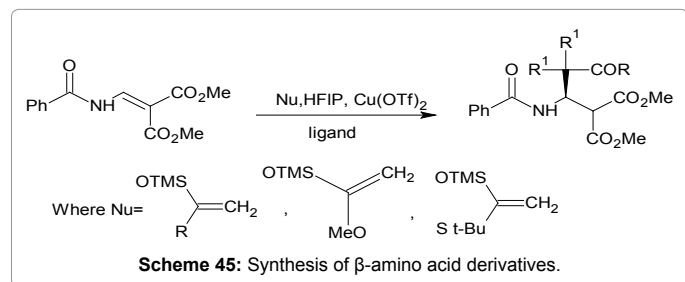
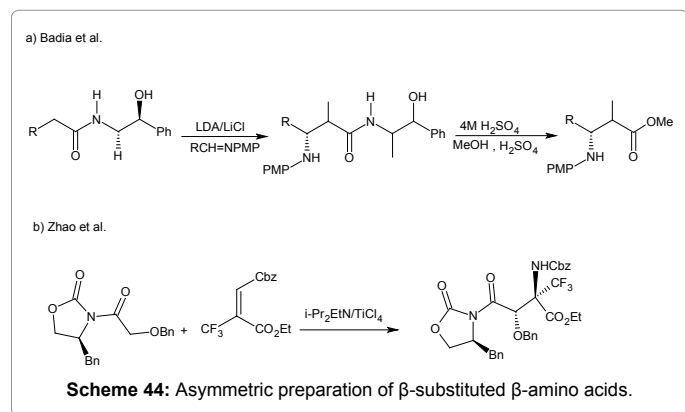
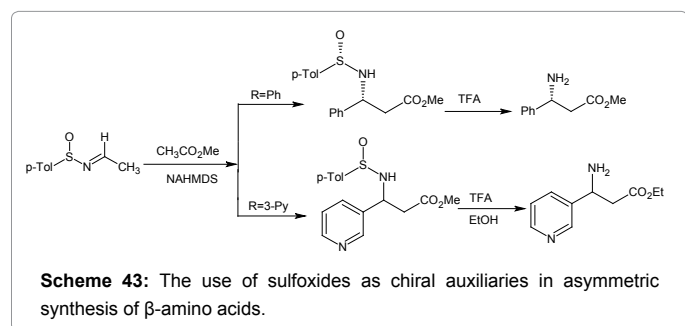
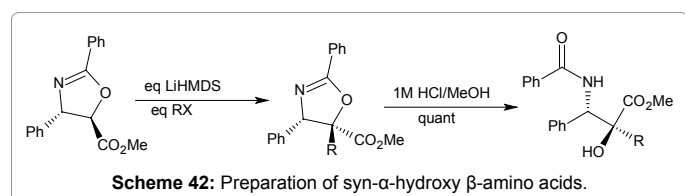
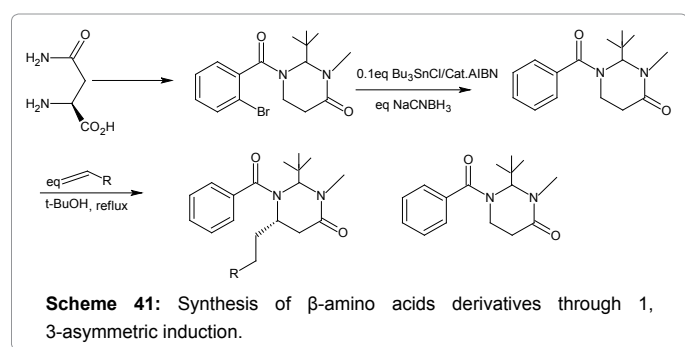
In another approach  $\alpha$ -methyl- $\beta$ -substituted  $\beta$ -amino esters were prepared by Badia et al., utilizing readily available (*S, S*)-(+)-pseudoephedrine as chiral auxiliary (Scheme 44a) [64]. An asymmetric preparation of  $\beta$ -substituted  $\beta$ -aminoacids were explored by reactions of imines and chiral enolates (Scheme 44b) [65,66].

TMS-SAMP as a nucleophile was used by Enders et al. to synthesis *N*-silylated  $\beta$ -hydrazino-esters as aza analogous Michael addition process [67]. In a Tandem aza Michael addition intramolecular cyclization, the same reaction sequence was also applied to the synthesis of cyclic  $\beta$ -amino acids and heterocyclic  $\beta$ -amino acids [68]. Sibi et al. reported  $\beta$ -amino acid derivatives with 97% yield (Scheme 45) [69].

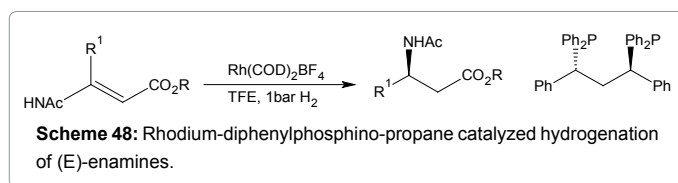
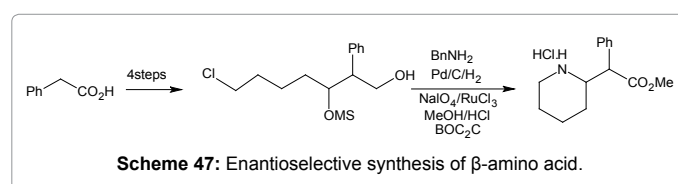
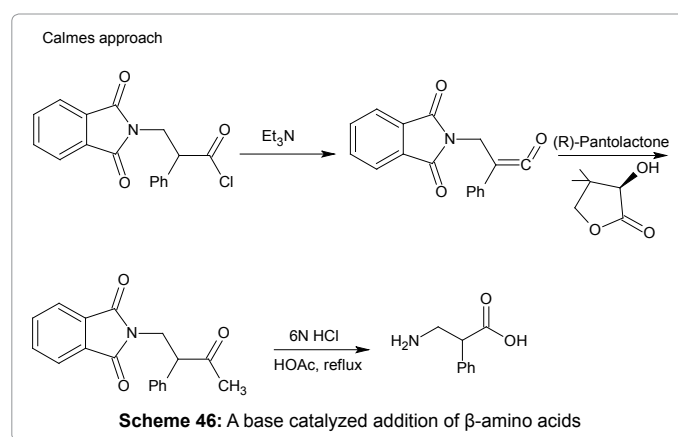
Lavielle et al. reported the asymmetric synthesis of the *N*-BOC protected derivative of (*S*)-3-Amino-2-phenyl propanoic acid featuring acylation of metallated phenylacetonitrile as the key step [70]. Another approach involved base catalyzed addition of (*R*)-pantolactone to *N*-phthaloyl ketene following an entirely different strategy was later described by Calmes and Escale (Scheme 46) [71].

Prashad et al. reported the first enantioselective cyclic  $\beta$ -amino acid (+)-methylphenidate hydrochloride, which is a mild nervous system stimulant used for the treatment of attention deficit hyperactivity disorder (Scheme 47) [72, 73].





$\beta^3$ -amino esters were obtained by Börner et al. using 1, 3-diphenyl-1,3-bis(diphenylphosphino) propane in the hydrogenation of (E)-enamines (Scheme 48). The esters were then converted to the corresponding  $\beta^3$ -amino acids [74].



Kim, Park and Beak recently synthesized  $\beta$ -phenyl amino acids from N-BOC-N-(p-methoxy-phenyl) benzylamine via (-)-sparteine/BuLi catalysed diastereoselective alkylation with substituted vinyl bromide, and subsequent oxidation with ozone, followed by Jones reagent (Scheme 49) [75].

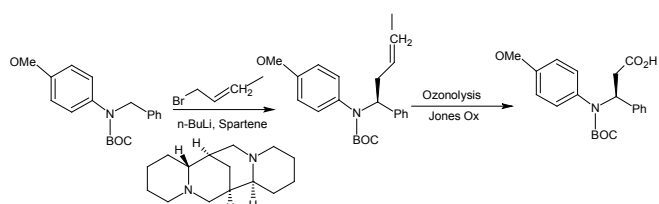
Berkessel et al. studied thiourea catalyst for the kinetic resolution of racemic oxazinones (Scheme 50). The N-benzoyl- $\beta$ -amino acid was isolated with 97% yield using hydrolytic environment [76].

The  $\alpha$ -amino acid derived amide was reduced with imines with trichlorosilane which are in equilibrium with the corresponding enamines (Scheme 51). The  $\beta$ -amino esters obtained were converted to the corresponding  $\beta$ -amino acids [77].

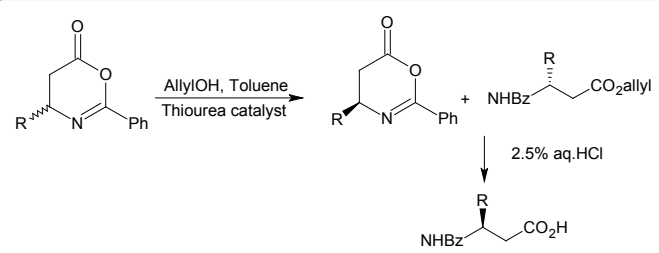
The polar solvents accelerate the hydrogenation of (Z)- $\beta$ -aminoacrylate in the presence of Et-DuPHOS-Rh as a catalysts reported by Heller and co-workers. The corresponding  $\beta$ -amino acids were obtained from the E and Z isomers which were hydrogenated to give  $\beta$ -amino esters (Scheme 52) [78].

Various aminomutases have been used for the conversion of aliphatic and aromatic  $\alpha$ -amino acids to the corresponding  $\beta$ -isomers [39]. Various aromatic (S)- $\beta$  amino acids can be obtained by using phenylalanine aminomutase (PAM) in tandem with phenylalanine ammonialyase (PAL). The stereoselective hydrolysis of racemic phenyldihydrouracil to D- and L-N-carbamoyl- $\beta$ -phenylalanine on further hydrolyse to corresponding  $\beta$ -amino acid [79].

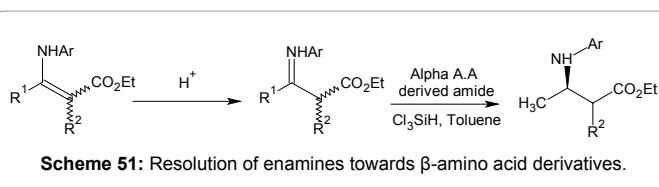
Transaminases (also known as aminotransferases) possess a great potential for the synthesis of optically pure-amino acids [80]. Transaminases can be applied either for the kinetic resolution of racemic compounds or the asymmetric synthesis starting from a prochiral substrate. The catalytic ring-expansive carbonylation of



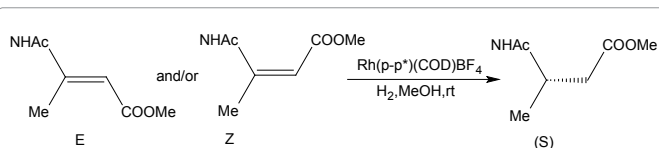
**Scheme 49:** Synthesis of  $\beta$ -phenyl amino acid from N BOC- N-(p-methoxyphenyl) benzylamine.



**Scheme 50:** Organo catalytic resolution of oxazinones.



**Scheme 51:** Resolution of enamines towards  $\beta$ -amino acid derivatives.



**Scheme 52:** The hydrogenation of (Z)- $\beta$ -aminoacrylate towards  $\beta$ -amino acid synthesis.

oxazolines, easily derived from  $\alpha$ -amino acids, to yield  $\beta$ -amino acid derivatives is described in Scheme 53 [81].

A new set of reaction conditions has been established to facilitate the copper-catalyzed enantioselective 1,4-reduction of  $\beta$ -(acylamino) acrylates toward a selection of  $\beta$ -alkyl- $\beta$ -amino acid derivatives in high yield 99% (Scheme 54) [82].

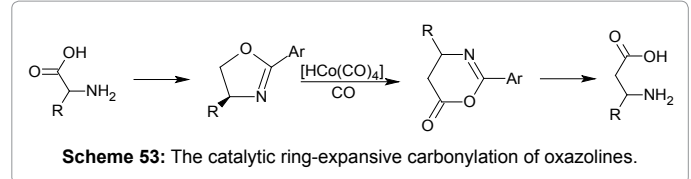
The chlorosulfonylisocyanate was reacted with cycloalkene to give fused  $\beta$ -lactams. The ring opening of the lactams was easily carried out with hydrochloric acid (Scheme 55) [83].

*Cis*- and *trans*- cyclohexane based  $\beta$ -amino acids, have also been prepared from the Diels-Alder adduct tetrahydroanthranilic anhydride (Scheme 56) [84-87]. The *cis*-isomer was prepared by ring-opening of this cyclic anhydride with aqueous ammonia to give the monoamide. Hoffman degradation of the resulting amide with hypobromite (or hypochlorite if a double bond was present) gave the  $\beta$ -amino acid. The synthesis of *trans*-cyclohexane required three additional steps. Esterification of anhydride gave the *cis*-diester and this was epimerised with sodium methoxide to give the *trans*-diester. Dehydration of this ester afforded the *trans*-anhydride, which was reacted to give the amine in two steps [88].

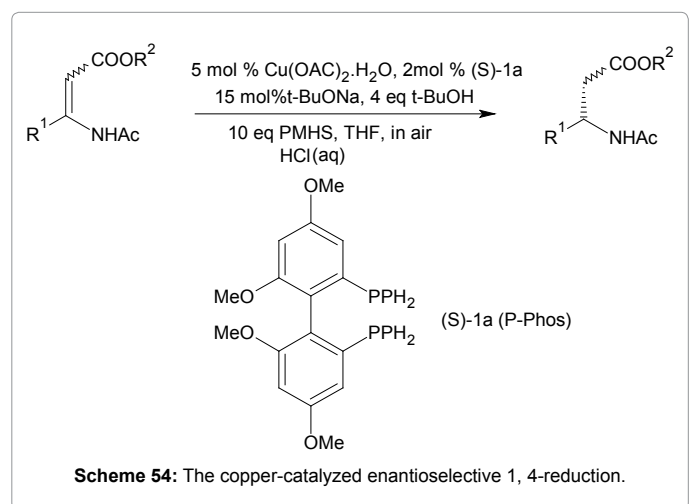
Enantiomerically pure *cis*  $\beta$ -amino acid was synthesised from

diester (Scheme 57). This diester was region specifically hydrolysed using pig liver esterase to give the monoester [89, 90]. Reaction of this ester with sodium azide afforded the azide intermediate. A subsequent Curtius rearrangement of the azide gave the enantiomerically pure *cis*  $\beta$ -amino acid. In a related synthesis, epimerisation of the methyl ester to the *trans*-analogue gave the enantiomerically pure *trans*- $\beta$ -amino acid [91].

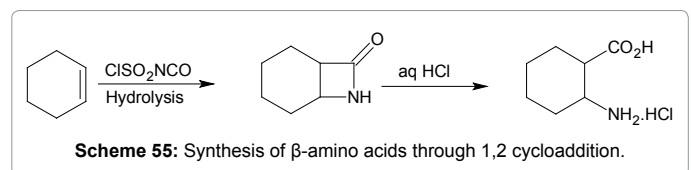
A general enzymatically-catalysed synthesis of cyclic  $\beta$ -amino acids was reported by Forro et al. The  $\beta$ -lactam ( $\pm$ ) was enantioselectively hydrolysed with alipase B enzyme, giving *cis*  $\beta$ -amino acid. This resolved



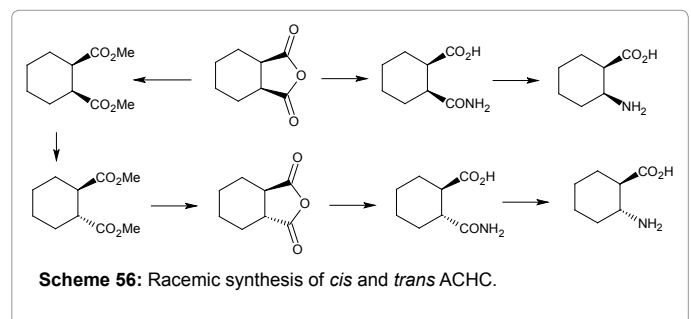
**Scheme 53:** The catalytic ring-expansive carbonylation of oxazolines.



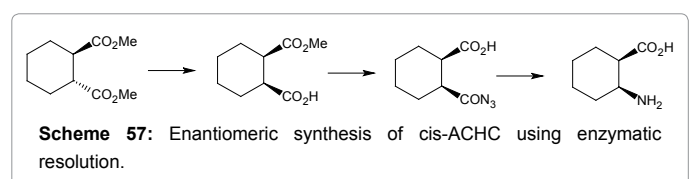
**Scheme 54:** The copper-catalyzed enantioselective 1,4-reduction.



**Scheme 55:** Synthesis of  $\beta$ -amino acids through 1,2 cycloaddition.



**Scheme 56:** Racemic synthesis of *cis* and *trans* ACHC.



**Scheme 57:** Enantiomeric synthesis of *cis*-ACHC using enzymatic resolution.

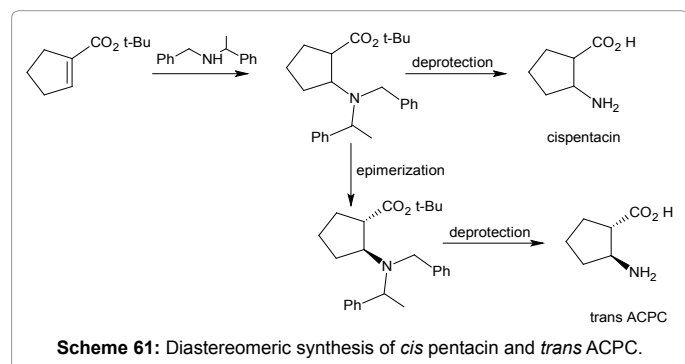
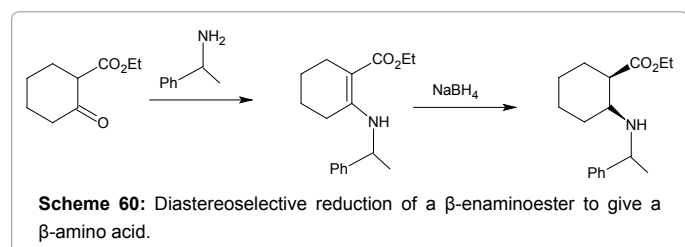
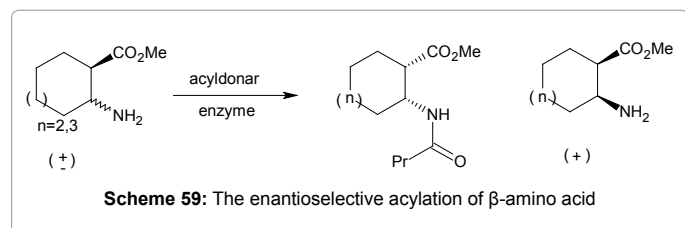
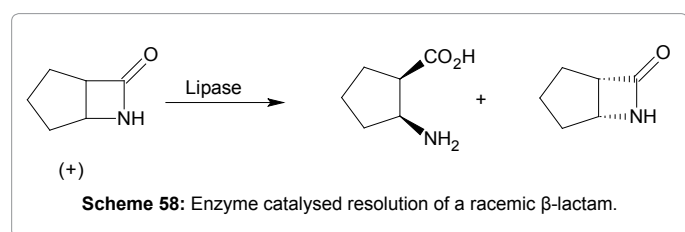


the other  $\beta$ -lactam enantiomer, which could then be hydrolysed non-enzymatically (Scheme 58) [92].

Another sequence which includes an enzymatic resolution involves the enantioselective acylation of  $\beta$ -amino acid ( $\pm$ ), to give the amide and resolving the other enantiomer (Scheme 59) [93, 94].

The use of chiral auxiliaries to introduce stereocentres into achiral molecules has proven very successful in the synthesis of  $\beta$ -amino acids. The racemic ketone ( $\pm$ ) was reacted with chiral  $\alpha$ -methyl benzylamine, to give the enantiomerically pure  $\beta$ -enamino ester intermediate was reduced by using sodium borohydride (Scheme 60) [95]. An alternative reduction at the more hindered face of enaminoester with sodium cyanoborohydride gave the corresponding *trans*  $\beta$ -amino acid [96, 97].

Davies et al. synthesized enantiomerically pure cyclic  $\beta$ -amino acids in 98% diastereomeric excess via conjugate addition of a chiral amine to cyclic  $\alpha$ ,  $\beta$ -unsaturated esters (Scheme 61) [98, 99]. Stereoselective addition of the chiral amine, followed by aqueous quenching of the lithium enolate gave the *cis* as major isomer. The chiral amine moiety was hydrogenated with  $\text{Pd}(\text{OH})_2$  to give the cyclopentane-based *trans*  $\beta$ -amino acid. This versatile general method was also used to synthesize novel heterocyclic  $\beta$ -amino acids [100].



Enders et al. synthesised cycloheptane based  $\beta$ -amino acids using a conjugate addition/alkylation reaction of  $\alpha,\beta$ -unsaturated ester (Scheme 62). This gave the cyclic chiral intermediate in  $>96\%$  yield was cleaved to  $\beta$ -amino acid [67, 68].

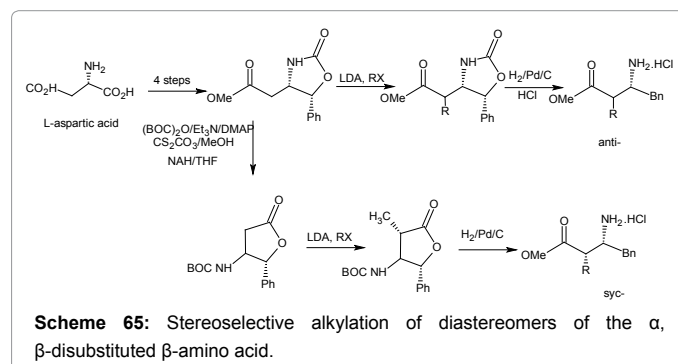
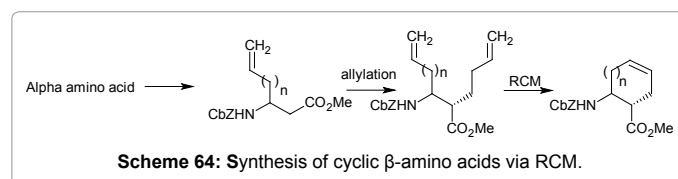
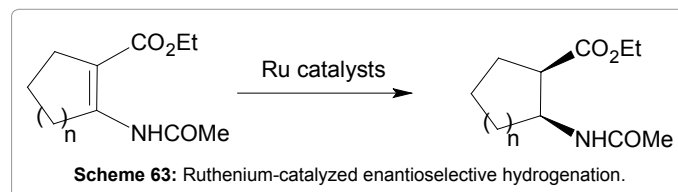
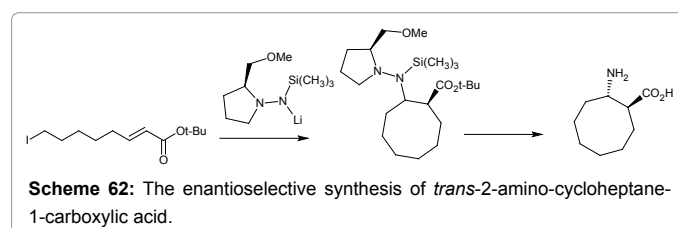
Enantioselective hydrogenation of the  $\beta$ -unsaturated ester using a ruthenium catalyst gave the  $\beta$ -amino ester, in up to 99% yield (Scheme 63). This reaction proved efficient for the synthesis of cyclopentane and cyclohexane. However, hydrogenation of seven- and eight-membered cycles gave lower diastereoselectivity [100].

A versatile method to synthesize *cis* or *trans*  $\beta$ -amino acids utilises a RCM approach using Grubb's 1<sup>st</sup> and 2<sup>nd</sup> generation ruthenium catalysts (Scheme 64). Allylation at the  $\beta^2$  position gave the *trans*-diene, necessary for cyclization using Grubb's catalyst [101].

The stereoselective alkylation of oxazolidin 2-one-4-acetic acid derivative with inversions of stereochemistry is the main step for the synthesis of diastereomer of  $\alpha$ ,  $\beta$ -disubstituted  $\beta$ -amino acid derivatives (Scheme 65) [102,103].

Such type of synthesis of stereoselective preparation of iturinic acid and 2-methyl-3-aminopropanoic acid also reported via alkylation mechanism is being described in scheme 66 [104].

Similar asymmetric synthesis of  $\beta$ -amino esters involved by the addition of silylenol ether to chiral imine generated *in situ* from



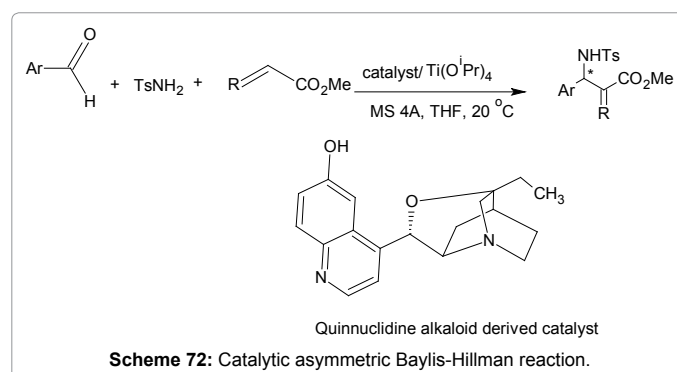
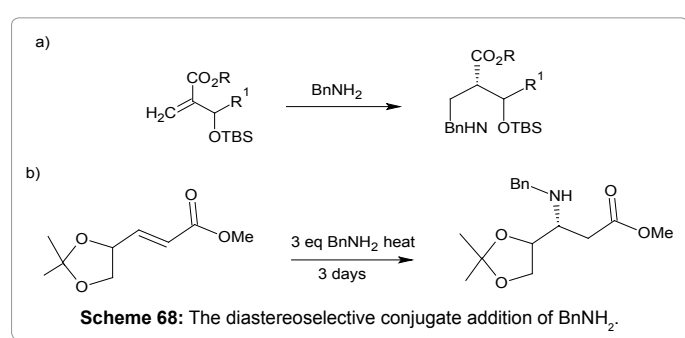
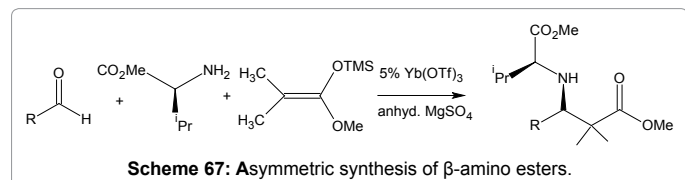
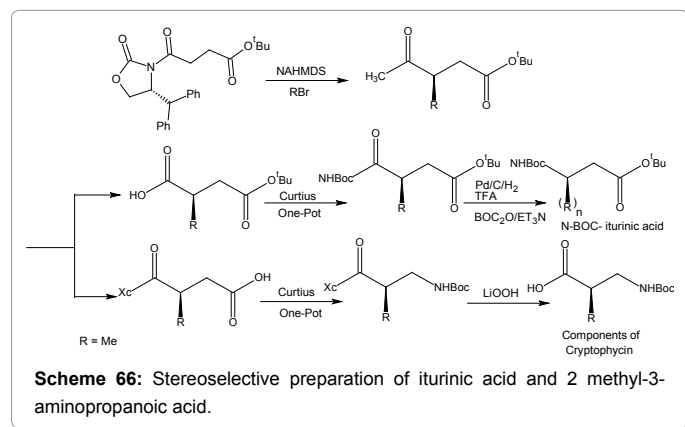
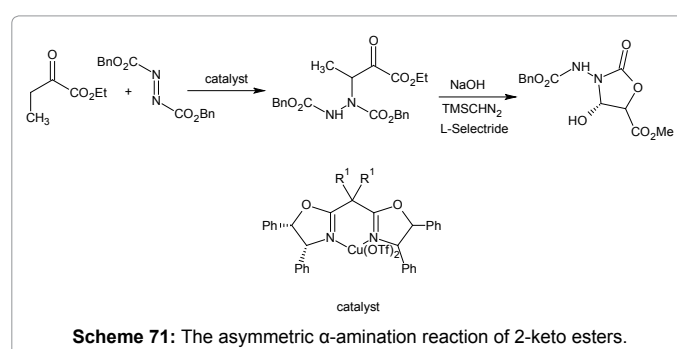
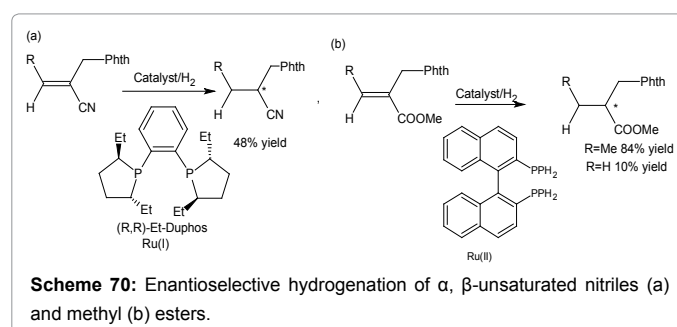
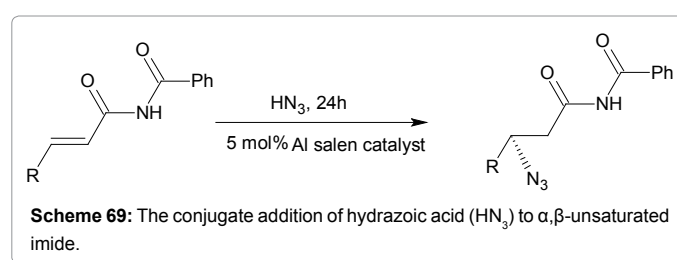
aldehydes and (S)-valine methyl ester described in scheme 67. All reactions were carried out at room temperature in  $\text{Yb}(\text{OTf})_3$  catalyst to activate the imine and anhydrous  $\text{MgSO}_4$  to remove the water [105].

The synthesis of anti- $\alpha$ -substituted- $\beta$ -amino esters based on diastereoselective conjugate addition of  $\text{BnNH}_2$  was reported by Perlmutter and Tabone scheme 68 (a) [106]. In another recent report, Costa et al. were also able to add  $\text{BnNH}_2$  to choral ester in 90% yield scheme 68 (b) [107].

The conjugate addition of hydrazoic acid ( $\text{HN}_3$ ) to  $\alpha,\beta$ -unsaturated imide catalyzed by Chiral (salen)Al(III) complex was also described by Jacobsen et al. (Scheme 69). This procedure provided access to a variety of enantiopure  $\beta$ -alkyl- $\beta$ -azido compounds. However, the addition to cinnamate was inefficient and reaction was incomplete [108].

Enantioselective hydrogenation of  $\alpha,\beta$ -unsaturated nitriles and their methyl esters bearing  $\beta$ -phthalimidomethyl substituents were reported by Jackson et al. (Scheme 70a,b). Surprisingly, only up to 48% yield was observed for Rh-DuPhos mediated hydrogenation of phthalimido nitriles. An improved selectivity (84%) was achieved in the hydrogenation of phthalimido ester (R=H) using Ru-BINAP as the catalyst. However, the  $\beta$ -substituent phthalimido ester (R=Me) resulted in a drastic decrease in yield (only 10%) [109].

Juhl and Jørgensen reported anovel method to synthesize  $\alpha$ -hydroxy  $\beta$ -amino esters via asymmetric  $\alpha$ -amination and 2-keto esters (Scheme 71). Dibenzyldiazodicarboxylate was acted as electrophilic



nitrogen source. When THF gave higher % yields with excellent levels of enantioselectivities [110].

When aromatic aldehydes added to silylamide and methylacrylate in the presence of nucleophilic quinuclidine alkaloid derived catalyst in combination with  $\text{Ti}(\text{O}^i\text{Pr})_4$  as Lewis acid, a good yield with moderate enantioselectivities were obtained (Scheme 72) [111].

Lectka et al. used bifunctional asymmetric catalyst and synthesized  $\beta$ -lactams from acyl chlorides and imine (Scheme 73). A combination of  $\text{In}(\text{OTf})_3$  and quinidine derivative was used to obtain the syn- $\beta$ -lactam with high yield [112].

Chiral Brønsted acid which was proposed to activate imine through hydrogen bonding was studied by Yamamoto et al. An achiral

Brønsted acid ( $R^3OH$ ) protonates the amine moiety of the intermediate to give adducts in good yields. The addition of silylenolethers to aromatic aldimines was also catalyzed by Taddol-derived phosphoric acid with good yield as well (Scheme 74) [113,114].

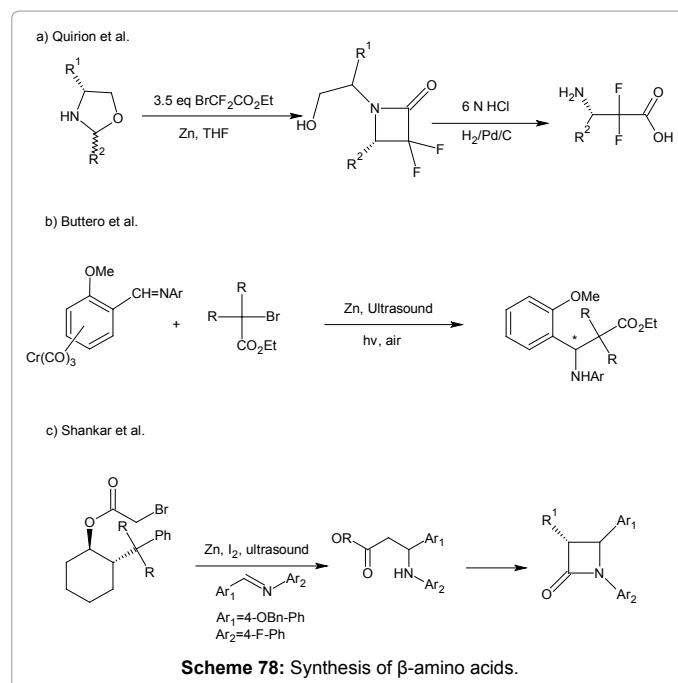
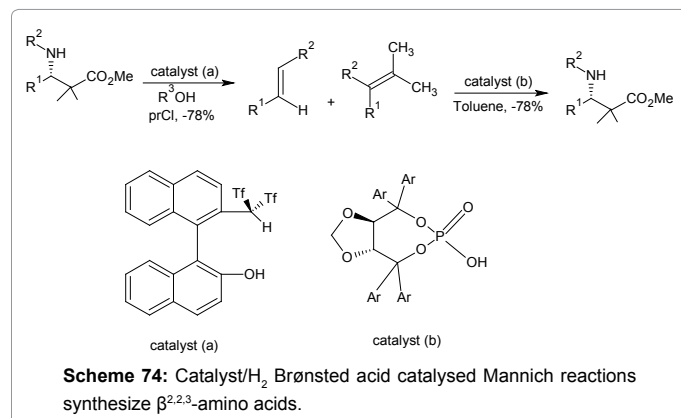
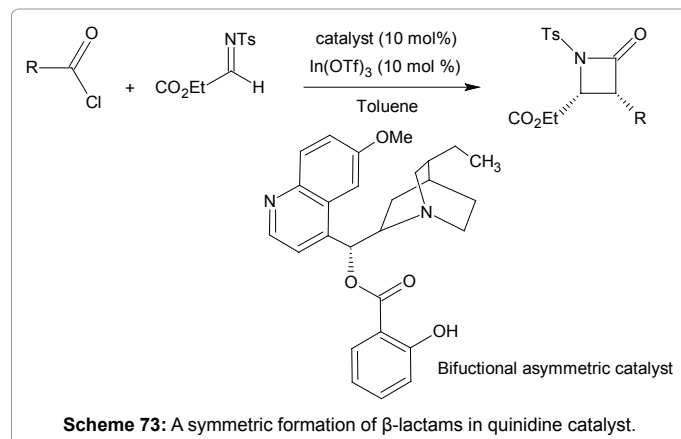
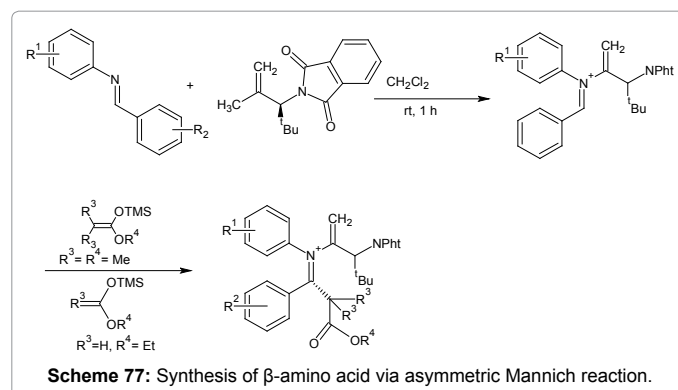
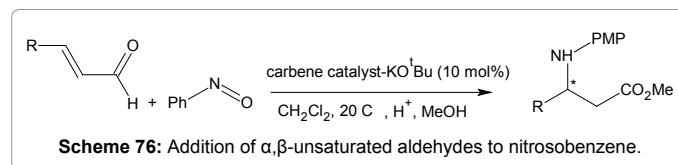
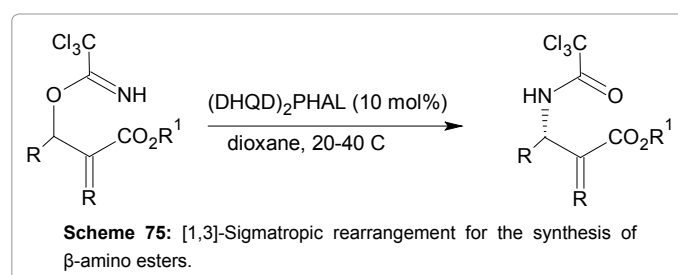
N-protected  $\beta$ -amino esters have been synthesized in good yield by Jørgensen et al. using the [1,3]-sigmatropic rearrangement of O-allyltrichloroacetimidates catalyzed by dihydroquinidine (DHQD)<sub>2</sub>PHAL (Scheme 75) [115].

The addition of nitrosobenzene to  $\alpha, \beta$ -unsaturated aldehydes was catalyzed by N-Heterocyclic carbene. This transformation gives isooxazolidinone intermediates which were hydrolyzed under acidic conditions to the corresponding methyl ester (Scheme 76) [116].

Waldmann et al. developed that imines while reacting with N, N-phthaloyl protected amino acid chloride lead to the N-acyliminium intermediate, which was then subjected to nucleophilic attack (Scheme 77). It is interesting to note that excellent results were obtained if the aromatic groups of the imine carried an *ortho*substituent [117].

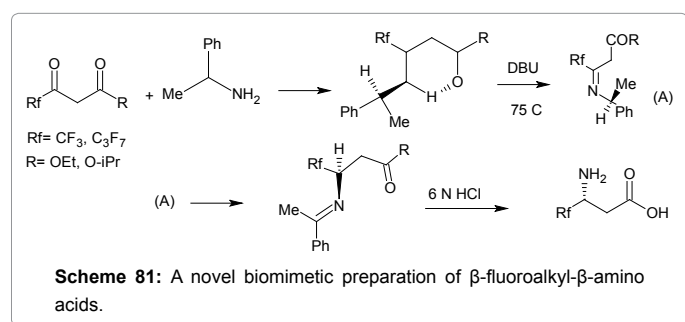
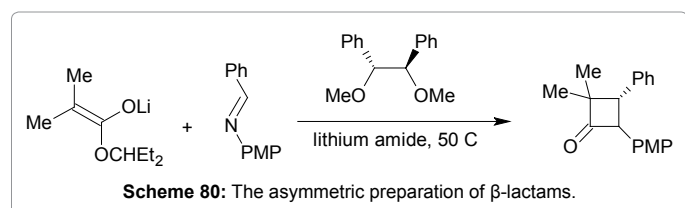
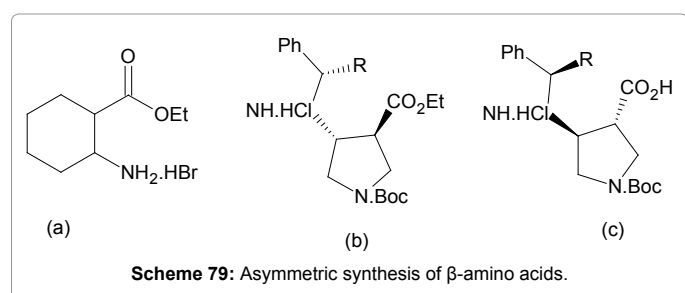
The synthesis of  $\alpha, \alpha$ -difluoro- $\beta$ -amino acid was reported by Quirion et al. using ethyl bromodifluoroacetate with chiral 1, 3-oxazolidines (Scheme 78a) [118]. Buttero et al. used a similar procedure in the addition of bromo esters to imines attached to atricarbonyl chromium(0) complex (Scheme 78b) [119]. Shankar et al. synthesized  $\beta$ -lactams which were analogs of cholesterol absorption inhibitor SCH 48461 using chiral bromoacetate and imines (Scheme 78c) [120].

A large-scale asymmetric synthesis of cis-2 amino-1-cyclohexane carboxylate was reported by Xu et al. (Scheme 79a) [95]. Highest selectivity was obtained when the reaction was carried out in isobutyric acid and  $NaBH_4$  as hydride. A similar method using  $NaCNBH_3$  as the



reducing agent to prepare  $\beta$ -peptide building blocks (b) and (c) has also been explored by Gellmans' group (Scheme 79b,c) [96,97].

The enantioselective addition of lithium enolate to imine based on a ternary complex reagent was reported by Tomioka et al.  $\beta$ -Lactams were produced directly by the use of lithium cyclohexylisopropyl



amine or lithium dicyclohexyl amine as the additives with the highest enantioselectivity (Scheme 80) [121, 122].

A novel biomimetic preparation of  $\beta$ -fluoroalkyl- $\beta$ -amino acids is given in scheme 81. The process involved two consecutive base catalyzed 1,3-proton shift of enamine to aldimine, which was hydrolyzed to  $\beta$ -amino acids in 6N HCl [123-125].

## Conclusions

A tremendous progress has been made in the past decades for the enantiopure synthesis of  $\beta$ -amino acids and derivatives on account of bearing varieties of biological activities including antifungal, antitubercular, antibacterial and anticancer. They are also used in the treatment of many diseases and health issues. Therefore, enantioselective  $\beta$ -amino acids have potential therapeutic values and are a great challenge for chiral synthesis. Therefore,  $\beta$ -amino acids with various substitution patterns are now available. Each approach has its own advantages and limitations while more than 80 numbers of different approaches have been discussed here but the organo-Rh based and heterogeneous catalyzed approach is found to be more effective (Scheme 1, 2, 4, 11, 12, 13, 28, 29) and (Scheme 8, 9, 33, 34, 35, 36, 37, 45, 54, 63). Other approaches can also be considered to synthesize enantioselective amino acids (Scheme 11, 13, 15, 40, 45, 50, 61, 62, 68, 70, 74). No doubt, the growing interest in enantioselective  $\beta$ -amino acids will stimulate new and improved methods for their synthesis in near future.

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