**Table1:** summary of various synthetic methods and procedures in chronological order of their development.

|  |  |  |
| --- | --- | --- |
| **Year** | **Auther(s)** | **Description** |
| **1973** | Eggelte TA *et al*. | Research showed reaction(s) of furan and maleic acid was carried out in several solvents. The *endo-*adduct was isolated and the structure established by its spectral properties and their conversion into compounds. The adducts of furan with fumaric acid, diethyl fumarate and diethyl maleate were reported. |
| **1989** | Bose AK *et al*. | Here morpholines were synthesized by an efficient molecular rearrangement of appropriate derivatives ofα-hydroxy-β-lactams included optically active β-lactams prepared from homochiral Schiff bases. |
| **1993** | Varma RS *et al*. | The research focused on simple high-yielded method(s) for deprotection of acetylated phenols and alcohols which occurs under mild conditions on an alumina surface using microwave irradiation**.** Here, authors’ reported a simplistic and trouble-free procedure to affect the deacetylation of a variety of such esters on neutral alumina under solvent-free reactions conditions which could be further accelerated safely by using an unmodified common household microwave oven. |
| **1994** | Crawford LA *et al*. | This communication discussed the synthesis of λ-aminobutyric acid in response to treatments reducing cytosolic *pH*. The proposal investigates by using isolated asparagus (*Asparagus sprengeri Regel*) mesophyll cells. The cell acidification was promoted by using hypoxia, H+/L-glutamic acid symport and addition of butyrate or other weak acids. |
| **1994** | Coles MP *et al.* | This communication deals with reaction of homochiral norbornene monomers which were derived from amino acids that undergo ring-opening metathesis polymerisation with [Mo(=CHCMe2Ph)(=NC6H3Pri2-2,6)(OBut), to give homochiral polymers with narrow molecular mass distributions. Here, they described the synthesis of homochiral polymers derived from norbornenes functionalised with optically pure alanine ester residues. |
| **1994** | Ortiz AD *et al*. | They showed the reaction in microwave irradiation ketene acetals that undergo 1,3-dipolar and hetero- Diels-Alder cycloadditions within 5-12 min to give excellent yields of easily purified heterocyclic products. |
| **1996** | Hanessian *et al.* | Resercher(s) developed an enantiomerically selective synthesis of allyl containing amino acids (Figure **1**). The starting sultam derivatives of *O*-benzyl glyoxylic acid oximes were reacted with allyl bromides in the presence of zinc in aqueous ammonium chloride. After selective cleavage of the N-O bond in the presence of Mo(CO)6, the sultam auxiliary was removed by treatment with LiOH in THF/H2O solution to afford the corresponding free allylglycine derivatives without any loss of stereochemical purity.    Figure **1** |
| **1996** | Fuji *et al.* | Scientists performed a diastereoselective alkylation of the (*S*)-glycine equivalent**,** which includes axially chiral bi-naphthol (Figure **2**) as an auxiliary, with several electrophiles yielding (*R)*-α-amino acid derivatives.    Figure. **2** |
| **1996** | Andersson *et al.* | Study described the preparation of the unnatural, bicyclic proline derivatives (Figure 3**a**)and (Figure 3**b**), along with their utility as chiral ligands in the copper-catalyzed enantioselective allylic oxidation of cyclohexene with *tert*-butyl perbenzoate.    n= 3a=1; 3b =2  Figure **3** |
| **1997** | Ondrus V and  Fisera L | Research proposed newroutes for the synthesis of various novel chiral maleimides. The oxabicyclic anhydride, *exo*-Diels-Alder adduct of furan and maleic anhydride was used as a vehicle, which in turn reacted with hydrochlorides of amino acids in the presence of Et3N with the release of furan to give the requisite novel chiral imides in good to moderate yields. The stereoselectivity of 1,3-dipolar cycloaddition of nitrile oxides with prepared chiral imides were also investigated. |
| **1998** | Sandhu S *et al*. | This communication tried to focus on howmaleic and phthalic anhydride condensed with amino acids and alkylamines to undergo microwave irradiation technique. The reaction afforded N-substituted maleimides and phthalimides in excellent yields. |
| **1998** | Lectka T *et al.* | This communication reported, an operationally convenient and efficient, catalytic, enantioselective iminoene reaction of R-imino ester with various alkenes which were catalyzed by Lewis acid complex and show that the reaction could be a useful new pathway to get R-amino acid derivatives. They initiated the study with the reaction between R-imino esterand R-methylstyrene. |
| **1998** | Kokotos *et al.* | Chemist prepared enantiopure lipophilic α-amino (Figure **4**) acids and also their other functionalized derivativesand  some bis α-amino acids. The key intermediate was protected glutamic acid aldehydewhich was utilized in a Wittig reaction with trityloxy alkylidene triphenylphosphoranes. After hydrogenation of the obtained β-hydroxy-α-amino acid was used as starting material in the synthesis of functionalized α-amino acids.    Figure **4** |
| **2001** | Shieh *et al* | Study discussed a facile synthetic route to (*R*)-4 piperidinylglycine. It offers a promising alternative to the previously published 8-step synthesis for the same compound. The Cbzenamides **(**Figure **5a)** and **(**Figure **5b)** were prepared from commercially available *N*-Cbz-phosphonoglycine trimethyl ester and *N*Boc-4-piperidone using the Schmidt protocol.    **5a**=R=*t*-Bu; **5b**=R=*i*-Pr  Figure. **5** |
| **2001** | Davis *et al.* | Scientest described an asymmetric synthesis which was reported with α-substituted serines (Figure **6**)*via* the regioselective hydrogenolysis of 2-benzyloxyaziridine 2- carboxylate. The starting (2*S*, 3*S*) *N*-sulfinylaziridine carboxylate was treated with TFA to remove the *N* sulfinyl group without ring-opening.    Figure **6** |
| **2001** | Li and Huang | Developed an interesting method for the synthesis of amino acid derivatives (Figure **7a,7b,7c**)*via* carbon-carbon bond formation in water and air atmosphere. Rhodium-catalyzed (catalyst: Rh2(COD)2Cl2) conjugated addition of ethyl alpha-phthalimido aminoacylate with various organotin reagents proceeded smoothly in water under ambient conditions and concurrent sonication to give the desired compounds.    R= 7a=Cl, 7b=Me, 7c= *t*-Bu  Figure. **7** |
| **2001** | Park *et al.* | Described chiral auxiliary mediated stereoselective alkylation reaction of *N*‘-[(*S*)-1’-phenylethyl]-*N*-(diphenylmethylene) glycinamide **,** using a phase transfer catalyst (PTC). **(**Figure **8a,8b and 8c)**    R=8a=Cl; 8b=I; 8c= CH2  Figure 8 |
| **2001** | Gilbertson *et al.* | Discussed incorporation of phosphine containing amino acids into rigid secondary structures such as α-helixes and ß-strands, that allows the generation of large libraries of bis- and monophosphine ligands for screening in asymmetric catalytic reactions. As because these ligands are produced by a solid phase approach, a wide variety of ligands with different structures and chiral environments can be made. **(**Figure **9a,9b)**    **9a 9b**  Figure.9 |
| **2001** | Ondrus V *et al*. | Showed a new route for the synthesis of novel chiral and achiral maleimides. A cheap and readily available *exo*-Diels-Alder adduct of furan and maleic anhydride reacted with amino acids in water that undergo classical heating or microwave irradiation with the release of furan to give maleimide products in good to excellent yields. |
| **2001** | Davis *et al.* | Reported the first example of asymmetric synthesis of α-alkyl-α-amino(arylmethyl)phosphonate derivatives (Figure **10**)from enantiopure ketosulfinimines.    Figure 10 |
| **2002** | Carlier *et al.* | Reported a catalytic asymmetric synthesis of Trp regioisomers (Figure 11) where the alanine unit is attached, not to C-3 of indole, but to C-2, C-4, C-5, C-6, or C-7. The most convenient catalyst was Burk DuPhos system, with the EtDuPhos ligand affording the greatest enantiomeric selectivity. The reactions were conducted in methanol, ethyl acetate, dichloromethane and acetone, all these solvents providing suitable reaction conditions.    Figure 11 |
| **2002** | Kokotos G *et al*. | Describedanefficient route for the synthesis of enantiopure unnatural α-amino acids and 2-amino alcohols. The synthesis was based on the Wittig-type olefination of 3-benzyloxy-2-(tertbutoxycarbonylamino) propanal with various ylides. |
| **2003** | Gallos *et al.* | Reported the synthesis of racemic nonproteinogenic alpha amino acids. Hetero Diels-Alder addition of a starting compound ethyl 2-nitrosoacrylate to electron rich alkenes such as enol esters, enamines and allylsilanes yields oxazines. The stereochemistry of the reaction is controlled by epimerization of the thermodynamically less stable isomer to the more stable one. (Figure 12a, 12b)    12a 12b  Figure 12 |
| **2003** | Wasserman *et al.* | Successfully showed the preparation of heterocyclic non-proteinogenic derivatives of α-amino acids (Figure 13a & 13b) by reacting alpha,beta-diketo nitrile with diamines and related dinucleophiles. alpha,beta -Diketo nitrile was prepared from mono Boc-protected amino dicarboxylic acid and phosphoranylidenacetonitrile, followed by ozonolysis of the obtained product at low temperature in CH2Cl2/MeOH.    13a R=OH; X=H  13b R=CN; X=Cl  Figure 13 |
| **2003** | Gellerman *et al.* | Published a rapid synthesis of ring A-disubstituted, Fmoc and Boc protected *L*-tryptophan derivatives (Figure **14a-d**)The synthesis starts from the appropriate 2,4- or 2,3 disubstituted phenylhydrazinesand optically active *N,N*-diprotected *L-*glutamic a-aldehydeand it utilizes Fischer-indole synthesis as a key step affording the mixture of mono- Boc/di-Boc tryptophan esters.    **14a**=R1 = Me, R2 = H, R3 = Me  **14b=** R1 = OMe, R2 = H, R3 = Me  **14c=** R1 = H, R2 = Me, R3= Me  **14d=** R1 = Et, R2 = H, R3 = Ph  Figure 14 |
| **2003** | Soloshonok *et al.* | Describe synthesis of sterically constrained α,α-symmetrically disubstituted α-amino acids. Showed interesting approach of dialkylating the Ni (II) complex of a glycine derivative resulted in symmetrical-α,α-amino acids. **(**Figure **15 a-h)**    **Alk** =  **a :** CH2-CH=CH2 **e :**(CH2)2CH3  **b:** CH2-C6H5 **f:** (CH2)3CH3  **c:** *trans* CH2-CH=CH-C6H5 **g :** CH3  **d:** CH2-CH3 **h :** (CH2)4CH3  Figure 15 |
| **2003** | Rutjes *et al.* | Described an interesting approach to the synthesis of proline derivatives, by Pd- catalyzed *5-endo-dig*  cyclization of lipophilic acetylene-containing amino acid derivatives. **(**Figure **16)**    Figure16 |
| **2003**  **and**  **2004** | Kabalka and coworkers | Successfully snthesized boronated novel 1-aminocyclobutane-1-carboxylic acid derivatives (ACBC). The skeleton was constructed by a [2+2] cycloaddition reaction. All presented boron-containing unnatural amino acids are currently being evaluated as potential agents for boron neutron capture therapy. **(**Figure **17)**    Figure 17 |
| **2004** | Chang *et al.* | A novel class of pseudoaromatic amino acids, namely tetrahydroindazol-3-yl alanine and benzisoxazole-3- ylalanine derivatives, was reportedSequential acylation of cyclic 1,3-diketones or cyclic enamines by side chain carboxyl functionalities of appropriately protected aspartic or glutamic acids followed by regioselective cycloaddition with dinucleophiles such as hydrazine, *N*-benzylhydrazine and hydroxylamine, yielded various derivatives . These novel homochiral amino acids, offer unique opportunities, not only as structural surrogates of tryptophan, but also as novel amino acid building blocks for the design of molecular probes. |
| **2004** | Wang *et al.* | The novel pyrrolidine-sulfonamide (Figure **18)** has been prepared and used successfullyto catalyze asymmetric Mannich-type reactions in DMSO between various ketones and PMP (*p*-methoxyphenol) alpha-imino ester. Other possible solvents were also explored and all could be employed in this reaction. The reaction is used to efficiently synthesize functionalized alpha-amino acid derivatives.    Figure 18 |
| **2004** | Dondoni *et al* | Study shows a family of heterocyclic amino acids comprising highly functionalized ß-(2-pyridyl)- and ß-(4-pyridyl)-alanines and the corresponding *N*-oxide derivatives that have been developedby a convenient one-pot thermal Hantzsch-type cyclocondensation of aldehyde–ketoester enamine systems . |
| **2004** | De Riccardis *et al.* | Disclosed an asymmetric synthesis of N,O-diprotected (2*S*,3*S*)-*N*-methyl-delta hydroxyisoleucine,a building block required for the asymmetric synthesis of halipeptin A. **(**Figure **19)**    Figure 19 |
| **2004** | Esaki *et al.* | Described coupled enzymatic synthesis of *N*-methyl-*L*-phenyl alanine from phenylpyruvic acid and methylamine by using a novel enzyme *N-*methyl-*L*-amino acid dehydrogenase (NMAADH) from *Pseudomonas putida*, NADP+ and glucose dehydrogenase (GDH) from *Bacillus subtilis* as a co factor recycling system. **(**Figure **20)**    Figure.20 |
| **2005** | Garbay *et al* | Described an enantioselective synthesis of malonylphenylalanyl and malonylmethylphenylalanyl derivatives uses 4-bromobenzaldehydediethyl acetal as a starting material andconverts it to the corresponding products by a four step synthetic pathway as published |
| **2005** | Boto *et al* | In present communication arylglycine derivatives (Figure **21a and 21b)** were prepared in one step, starting from readily available serine derivatives. The method involves treating the starting protected serine with iodine and DIB (di acetoxyiodo benzene) at room temperature. The reaction mixture was then cooled and BF3 Et2O, together with an excess of different nucleophiles, was added. These building blocks can be used to develop novel antineurodegenerative drugs, as they possess the ability to selectively modulate metabotropic glutamate receptors.    **21a 21b**  Figure 21 |
| **2005** | Pedatella *et al.* | An orthogonally protected 2,3-amino acid (Figure **22)** was reported.The starting enolates of *N,N*-dibenzylated ß3-amino esterswere treated with di *tert*- butyl azodicarboxylate (DBAD) to give *N`,N*``-di-Boc-2-hydrazino derivativeswith excellent *anti* diastereomeric ratios.    Figure 22 |
| **2005** | Pellicciari *et al.* | First time synthesized 2-(tetrahydrofuran-2-yl)glycine (Figure **23**) is a conformationally constrained amino acid. The first enantiodivergent synthesis of all four possible 2-(tetrahydrofuran-2-yl) glycine stereoisomers was described. The key synthetic step is a highly stereo-controlled allylboration.    Figure.23 |
| **2005** | Ballini *et al* | A useful and fast microwave-assisted synthesis of α-nitro-α-amino esters (Figure **24)** and the corresponding acids, under mild conditions and without solvent, was reported. The desired products were obtained *via* Michael addition from methyl *N*-(diphenylmethylene)-2,3 didehydroalaninate.    Figure 24 |
| **2005** | Tanaka *et al.* | Prepared a new class of α-disubstituted α-amino acids (Figure **25)** bearing a pendent chiral centre. Derivatives of 4-aminopiperidine-4-carboxylic acid are achiral α-amino acids bearing a nitrogen group. The focus on this amino acid has been due to the antimicrobial activity of its helical peptides.    Figure.25 |
| **2005** | Takemoto *et al.* | Published a tandem reaction yielding dehydroamino acid derivatives. Afforded α-disubstituted amino acids*via* radical and anionic carbon–carbon bond-forming processes. The authors disclosed the reductive allylation reaction of *N-*phthaloyl dehydroalanine with allyl acetatewhich was accomplished by using Bu3SnH and Pd(PPh3)4 yielding. |
| **2005** | Kessler *et al.* | Reported a three-step synthesis of *N*α-methyl-*N*α-(*o* nitrobenzenesulfonyl)-α-amino acids (Figure **26)** without extensive purification. The procedure is based on previously known *N*-alkylation of *N*α-arylsulfonylamino esters, which was improved by utilizing dimethyl sulfate and DBU as base.    Figure 26 |
| **2005** | Konopelski *et al.* | Published a complementary method for the synthesis of optically pure *N*-methyl amino acids esters (Figure **27)** that requires no protection of the functionalized amino acid side chain. The method comprises two consecutive reductive aminations, first with benzaldehyde, then with paraformaldehyde. An important feature of the reaction is that both sequences of imine formation and subsequent reduction were performed in the same flask and without isolation.    Figure 27 |
| **2005** | Tandon *et al* | Presenting a series of (*S*)-*N*-(1,4-naphthoquinon-2-yl)-α-amino acid methyl esters. The reaction of 1,4-naphthoquinonesand their bromo derivatives with enantiomerically pure *L*-amino acid methyl ester hydrochlorides produce *N*-modified-α-amino acid methyl esters |
| **2007** | Perdih A and Dolenc MS | This review focuses on the selected recent synthetic methodologies leading to unnatural amino acids including chiral catalysts that enabled enantioselective synthesis and microwave-assisted synthesis. It also focused on solid phase synthesis and construction of organometallic amino acids. |
| **2007** | Matthew JG *et al.* | The present communication shows an interesting topic of enantioselective organocatalysis. They discussed the impact of enamine, iminium, nucleophilic and bronsted acid catalysts in organic synthesis, and highlighted key strategic methods to assemble useful molecules with high enantiomeric purity. |
| **2007** | Corvo MC and Pereira MMA | Describes the synthesis of λ-amino acid analogues from natural α-amino acids by a radical pathway. They present a new λ-amino esters and amides preparation by a radical method. This was the first time that any radical species generated from natural α-amino acids and are used to synthesize λ-amino acid derivatives. |
| **2008** | Sha Y and Li J | The present study develops a convenient synthesis of amino acid methyl esters. All compounds are prepared in a good to excellent yields by room temperature reactions of amino acids with methanol in the presence of trimethylchlorosilane. The method is not only compatible with natural amino acids, but also with other aromatic and aliphatic unnatural amino acids. |
| **2008** | Parra M *et al.* | Described an efficient synthesis of γ-amino acids and here attempts made to drive its enantioselectivity. The present communication describes a general procedure for the addition of dianions of carboxylic acids to bromoacetonitrile. This methodology, with saturated carboxylic acids, is a new approach to the synthesis of γ-aminoacids that are obtained with higher yields than those earlier described. Unfortunately, here poor yield resulted in their attempts which drive the enantioselectivity by chiral amide induction. |
| **2009** | Cobb AJA *et al.* | Presents an enantioselective intramolecular michael addition of nitronates onto conjugated esters for access to cyclic *γ*-amino acids with up to three stereocenters. They have shown the first use of bifunctional organocatalysis in the intramolecular michael addition of nitronates to conjugated esters. They have also demonstrated its utility in peptide chemistry, and mechanistic investigations of the reaction. |
| **2011** | Narsaiah AV *et al.* | The study describes the use of a catalyst named Amberlyst-15 which is an efficient, cost-effective and recyclable hetero generous solid acid catalyst for the synthesis of β-enaminones and β-enamino esters. The β-keto carbonyl compounds rapidly react with a variety of amines in the presence of Amberlyst-15 to produce beta-enamino compounds with excellent yields. |
| **2012** | R. Saladino *et al*. | In this review authors were tried to describe the recent advances in the amino acid side-chain transformations and backbone modifications by oxidative and fluorination procedures. They also emphasizes about how modified amino acids with enhanced biological activity, proteolitic stability and bioavailability are of increasing interest in protein design and engineering as drug candidates. |
| **2012** | Rudat J *et al.* | Presents a mini review on transaminases an enzyme for the synthesis of enantio-pure β-amino acids. This review gives an overview over microbial transaminases with activity towards β-amino acids and their substrate spectra. It also outlines current strategies for the screening of new biocatalysts. As optically pure β-amino acids constitute interesting building blocks for peptidomimetics and a great variety of pharmaceutically important compounds. Their efficient synthesis still poses a major challenge. Transaminases (also known as aminotransferases) possess a great potential for the synthesis of optically pure β-amino acids. |
| **2012** | Murthy LN *et al.* | Presents a brief review on synthesis and applications of β-enamino carbonyl compounds owing to the wide range applications in pharmaceuticals and as building blocks for the synthesis of a variety of heterocyclic compounds, β-amino esters, β-amino acids, β-amino alcohols, peptides and alkaloids. They developed a number of methods so far for the synthesis of these compounds. |
| **2016** | Lei Liu *et al*. | Reviewed surveys the recent advances of synthesis of chiral unnatural α-amino acids and peptides through palladium-catalyzed functionalization of un-activated C(sp3)–H bonds. The review represents all the available methods for direct C–H functionalization of simple amino acids that represents one of the most attractive approaches because it exhibits good atom-economy and step-efficiency. |