New Methods towards the synthesis of beta-amino acids

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Chapter 1

Recent advances in the catalytic asymmetric synthesis of β-amino acids

This chapter describes the progress in catalytic asymmetric synthesis of β-amino acids covering the literature since 2002. The chapter is structured into three parts: 1) transition metal catalysis, 2) organocatalysis and 3) biocatalysis. The respective paragraphs are subdivided into the most important synthetic methods, such as hydrogenation, the Mannich reaction and conjugate additions.

1.1 Introduction

β-Amino acids are key structural elements of peptides, peptidomimetics and other natural products.[1] In addition, they are essential chiral building blocks for the synthesis of pharmaceuticals.[1] Furthermore, β-amino acids are presursors for β-lactams which are potentially biologically active and of interest as antibiotics.[2] Some β-amino acids show interesting pharmacological properties by themselves, but most are valuable intermediates in routes to novel molecules with biological and pharmacological activity. β-Peptides have secondary structures comparable to their α-amino acid analogues.[3] β-Amino acids are subdivided into β^2-, β^3- and $\beta^{2,3}$-amino acids depending on the position of the side chain at the 3-aminocarboxylic acid core (figure 1.1).[4] Additionally, cyclic amino acids have the amino and ester moiety as substituents or the amino group is integrated into the heterocyclic structure, such as β-proline.[5]

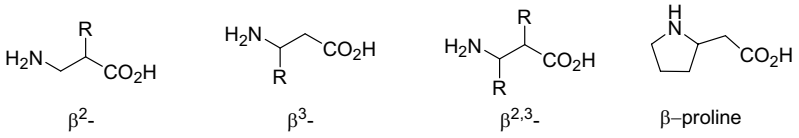


Figure 1.1. General structure of β-amino acids.

Until recently, methods for the synthesis of β-amino acids relied predominantly on classical resolution, stoichiometric use of chiral auxiliaries or homologation of α-amino acids. Much of the work related to asymmetric synthesis of β-amino acids before 2002 has been reviewed by Sibi,[6] and summarized in the book *Enantioselective synthesis of β-amino acids* edited by Juaristi and Soloshonok in 2005[7,8]. Seebach and coworkers described recently the preparation of β^2-amino acids for β-peptide synthesis.[9] Therefore, this chapter is focussed on catalytic asymmetric synthesis using transition metals, organocatalyst and biocatalysts covering the literature since 2002. Methods using chiral auxiliaries and kinetic resolution (biocatalysis) are not discussed herein.

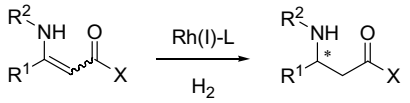
1.2 Transition metal catalysis

Various transition metals and chiral ligands have been used for the synthesis of β-amino acids. The most frequently employed methods are catalytic asymmetric hydrogenation, conjugate addition of carbon- and nitrogen nucleophiles to α,β-unsaturated systems and the Mannich reaction.

1.2.1 Hydrogenation

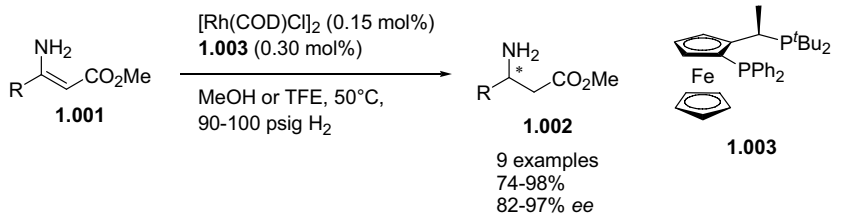
The enantioselective hydrogenation of β-substituted-β-(amino)acrylates has been extensively discussed (scheme 1.01).[10] Therefore, this part concerning catalytic asymmetric hydrogenation is kept relatively brief, focussing on key contributions since 2002. The geometrical isomers of the β-(amino)-acrylates show different reactivity and

selectivity in metal-catalyzed hydrogenations: (*E*)-isomers generally lead to higher enantioselectivities, and (*Z*)-isomers frequently react faster, although the enantioselectivity is sometimes lower.



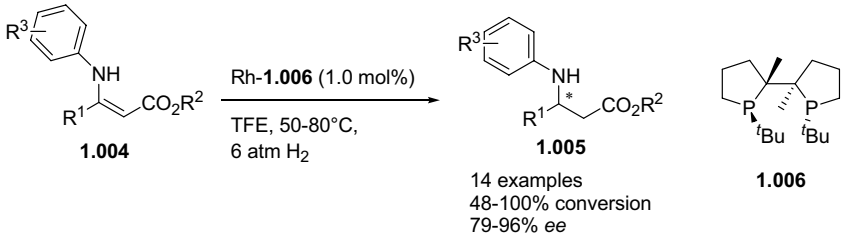
*Scheme 1.01. Rhodium catalyzed hydrogenation of (*E*)-and (Z)-β-dehydroamino acid derivatives.*

The first example of an asymmetric hydrogenation of *N*-acyl-β-(amino)acrylates was published in 1991 by Noyori and coworkers using $Ru(O_2CCH_3)_2$ and (*R*)-Binap, providing >90% *ee*.[11] Their advances in Ru- and Rh-catalyzed homogeneous hydrogenations have since then become a standard procedure for the synthesis of β-amino acids, using a variety of chiral bidentate and monodentate phosphorous ligands.[10-12] An important breakthrough by Hsiao and coworkers was the use of chiral ferrocenylphosphine ligand **1.003** 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 *ee* (up to 97%) (scheme 1.02).[13] This represents the first example of a high yielding enantioselective hydrogenation of unprotected β-enamine esters without the use of a directing protecting group.



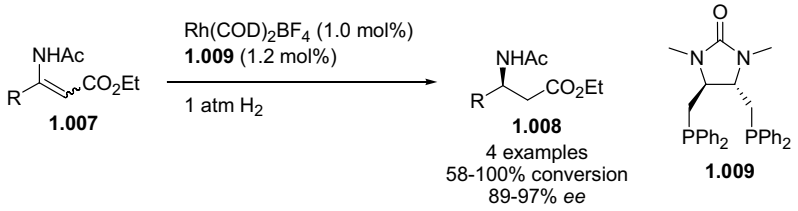
Scheme 1.02. Rhodium-ferrocenylphosphine catalyzed hydrogenation of unprotected enamines.

TangPhos **1.006** was employed in the synthesis of *N*-aryl-β-amino acids by Zhang and coworkers.[14] Starting from (*Z*)-enamines, the products were obtained with up to 96% *ee* using Rh-**1.006** in TFE (scheme 1.03).



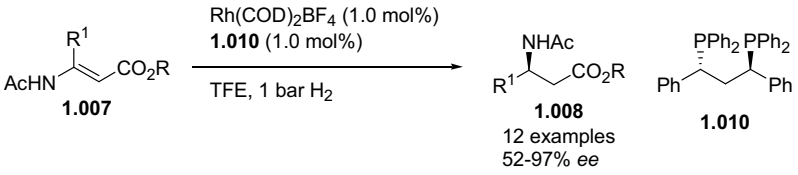
Scheme 1.03. Rhodium-Tangphos catalyzed hydrogenation of (Z)-enamines.

The Rh-catalyzed enantioselective hydrogenation of (*E*)- and (*Z*)-β-acylamino acrylates using BDPMI **1.009** gave under mild conditions *ee*'s of 97% and 92%, respectively (scheme 1.04).[15]



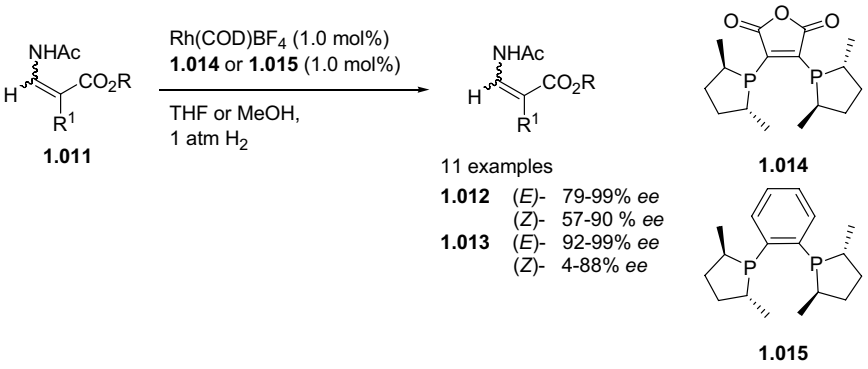
Scheme 1.04. Rhodium-BDPMI catalyzed hydrogenation of (Z)-enamines.

Börner and coworkers used 1,3-diphenyl-1,3-bis(diphenylphosphino)propane **1.010** in the hydrogenation of (*E*)-enamines to give β^3-amino esters with up to 97% *ee* (scheme 1.05).[16,17] (*Z*)-Enamines as substrates lead to significantly lower enantioselectivities (*ee* up to 75%).[16]



*Scheme 1.05. Rhodium-diphenylphosphino-propane catalyzed hydrogenation of (*E*)-enamines.*

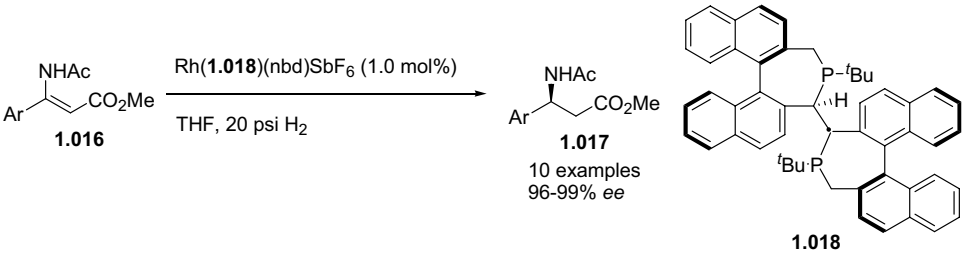
MalPhos **1.014** catalyzed the hydrogenation of (*E*)-enamines with 99% *ee* and of the corresponding (*Z*)-enamines with up to 90% *ee* (scheme 1.06).[18] Me-DuPhos **1.015** gave also high *ee* with these (*E*)-enamines, but the *ee* in the hydrogenation of (*Z*)-enamines was lower (*ee* up to 86%).



*Scheme 1.06. Rhodium catalyzed hydrogenation of (*E*)- and (Z)-enamines with MalPhos and Me-DuPhos.*

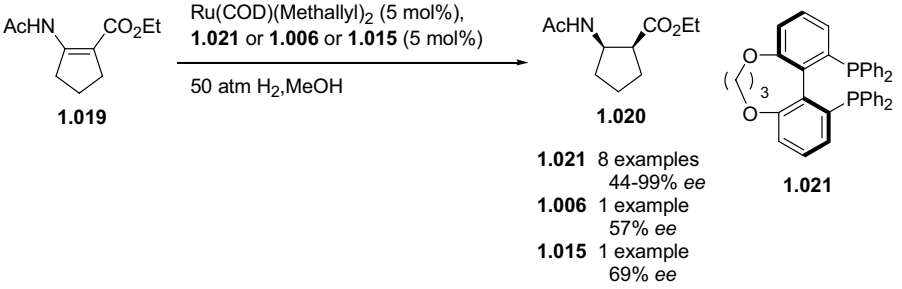
Zhang and coworkers synthesized bisphosphepine ligand **1.018**, that catalyzes the hydrogenation of (*Z*)-enamines with very high enantioselectivity (*ee* >99%) (scheme

1.07).[19] On the contrary, (*E*)-enamines give only low enantioselectivity (*ee* 32%) using the same catalyst system.



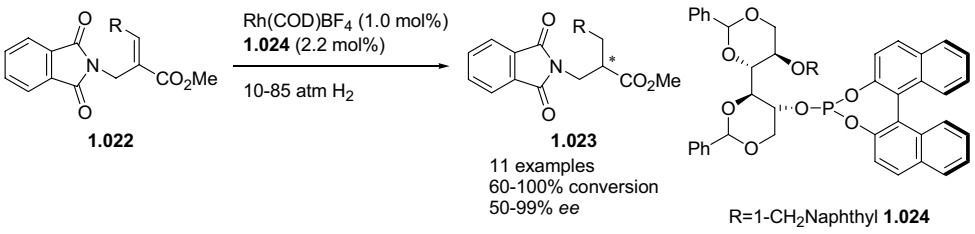
Scheme 1.07. Rhodium-bisphosphepine catalyzed hydrogenation of (Z)-enamines using bisphosphepine lignds.

Using (*S*)-C3-TunaPhos **1.021** as ligand in a ruthenium catalyzed reaction, Zhang and coworkers synthesized cispentacin with excellent *ee* (up to 99%) (scheme 1.08).[20] In the same reaction, TangPhos **1.006** and Me-DuPhos **1.015** gave cispentacin derivative **1.020** with significantly lower enantiomeric excess.



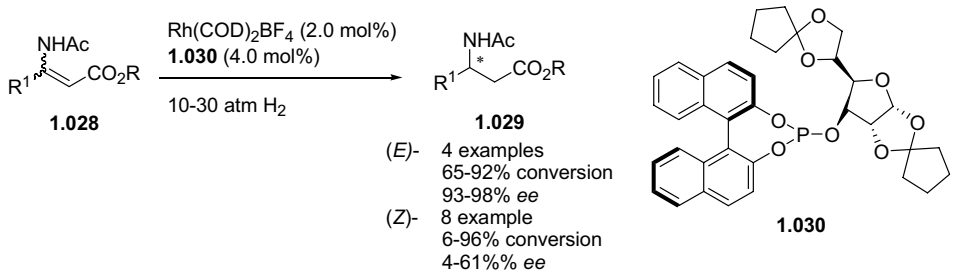
Scheme 1.08. Ru-catalyzed hydrogenation towards cyclic β-amino acids.

Monodentate ligands such as phosphites and other phosphorous ligands can also result in high enantioselectivities in Rh-catalyzed hydrogenations.[21] Phosphite-based ligands with a carbohydrate moiety have been applied in the Rh-catalyzed homogeneous hydrogenation. β^2-Amino acid derivatives are formed with up to 99% *ee* when phthalimide protected acrylates are hydrogenated using carbohydrate-phosphite **1.024** (scheme 1.09).[22]



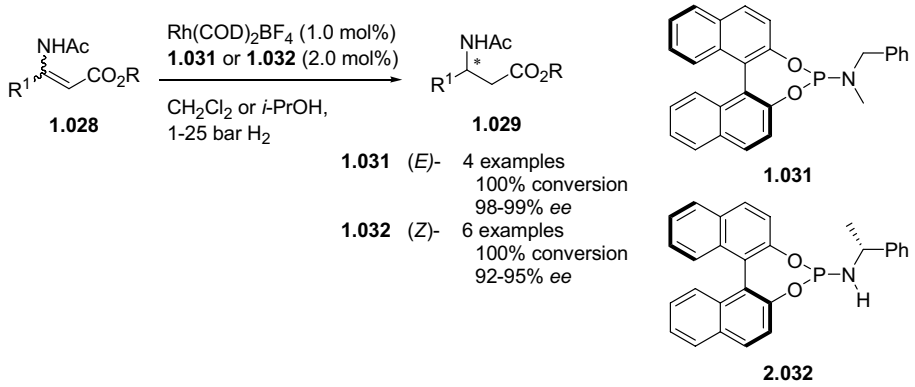
Scheme 1.09. Rh-catalyzed hydrogenation of phthalimide protected acrylates.

Several phosphite ligands were screened for the hydrogenation of **1.028** identifying **1.030** as optimal ligand (scheme 1.10). Hydrogenation of (*E*)-enamines with ligand **1.030** gave the products **1.029** with up to 93% *ee*, but the corresponding (*Z*)-enamines lead to amino esters with only 61% *ee*.[23]



Scheme 1.10. Rh-phosphite catalyzed hydrogenation of acrylates.

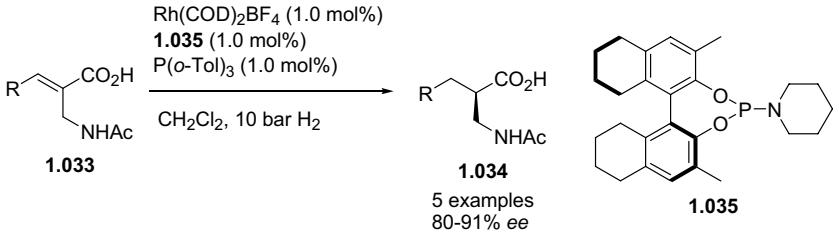
The use of monodentate phosphoramidite ligands in the rhodium-catalyzed hydrogenation of (*E*)/(*Z*)-β-dehydroamino acids has been described by Feringa, Minnaard, de Vries and coworkers (scheme 1.11).[10,24] Ligand **1.031** leads to β-amino acid precursors with excellent enantioselectivities for (*E*)-substrates, while a slight modification in the amine backbone of the ligand leads to very good enantioselectivities in the hydrogenation of (*Z*)-substrates.



*Scheme 1.11. Rh-phosphoramidite catalyzed hydrogenation of (*E*)- and (Z)-enamines.*

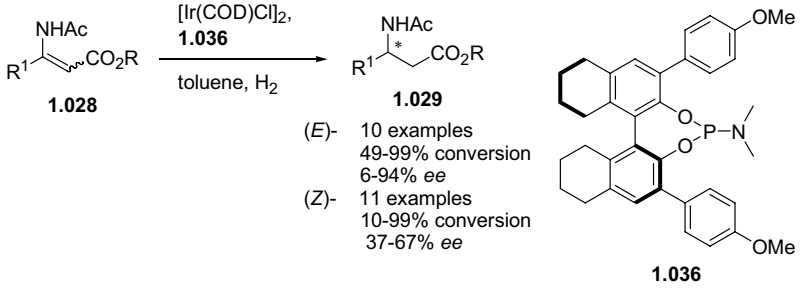
The mixed ligand approach has been employed in the hydrogenation catalyzed by rhodium-phosphoramidite complexes in order to further enhance the enantioselectivity (scheme 1.12).[10,24,25] Hereby, three different catalysts are in equilibrium with one another, namely the two homo-complexes Rh-L^AL^A and Rh-L^BL^B and the hetero combination L^AL^B. Enhanced enantioselectivities are observed when Rh-L^AL^B is more active and more selective than each of the hetero combinations.[26] Chiral phosphoramidite **1.035** in combination with achiral tris-*o*-tolyl-phosphine was used for

the synthesis of β^2-amino acids using the unprotected carboxylic acid **1.034** (scheme 1.12).



Scheme 1.12. Mixed ligand approach towards β-amino acids.

Furthermore, the combination of Ir(I) and phosphoramidite ligand **1.036** has been used by Beller and coworkers in the hydrogenation of (*E*)- and (*Z*)-*N*-(acylamino)acrylates, giving the product with up to 94% and 67% *ee*, respectively (scheme 1.13).[27]



Scheme 1.13. Ir-phosphoramidite catalyzed asymmetric hydrogenation.

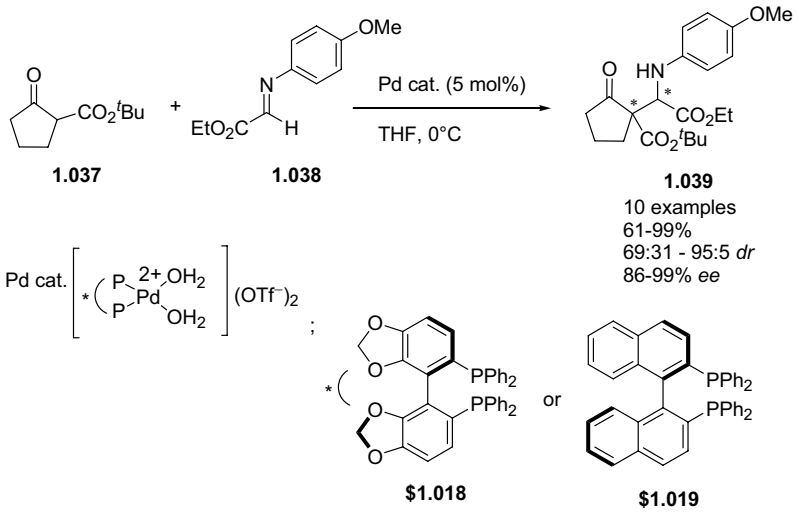
As demonstrated previously[10] and discussed in the preceeding paragraphs, the hydrogenation of β-dehydroamino acids represents an important tool for the synthesis of β-amino acids. High enantioselectivities have been achieved starting from both (*E*)- or (*Z*)-enamines.

1.2.2 Mannich reaction

The Mannich reaction is an important C-C-bond forming reaction involving the addition of metal enolates of carbonyl compounds to imines.[28,29] The versatility and potential of the Mannich reaction to form β-amino carbonyl compounds has made it an important method to synthesize β-amino acids. Recently, several successful examples of catalytic asymmetric Mannich reactions have been developed.[28] Earlier work relied on the stoichiometric use of chiral auxiliaries.

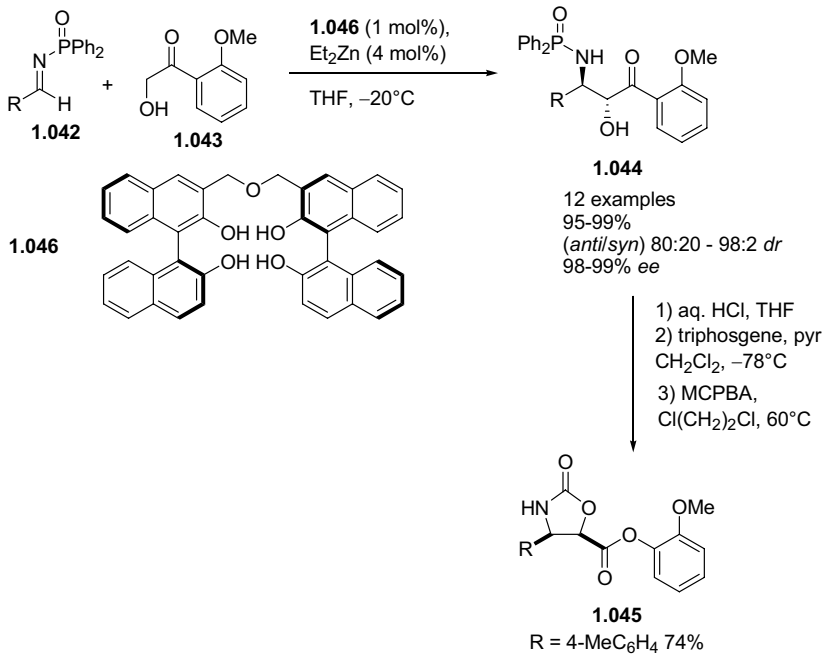
Sodeoka and coworkes published in 2005 the addition of β-ketoesters to various imines catalyzed by a chiral cationic palladium complex (scheme 1.14).[30] The catalysts derived from SegPhos **1.040** and Binap **1.041** were investigated. Two stereogenic centers are created in this reaction; high diastereomeric ratios (up to 95:5) are obtained, along with

excellent *ee*'s (up to 99%). Next to the *p*-methoxyphenyl (PMP) protecting group, Boc and tosyl protecting groups for the imine could be employed. Moreover, the three component coupling, using *p*-anisidine, α-aldehyde esters and cyclic β-keto esters, gave the product with up to 99% *ee* and a *dr* of 95:5.



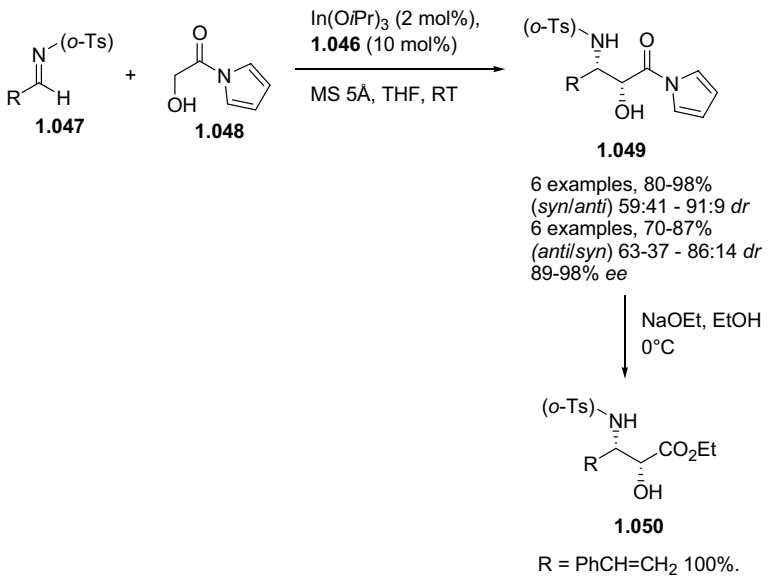
Scheme 1.14. Pd-catalyzed addition of β-ketoesters to α-imino esters.

Diethylzinc and bridged-Binol **1.046** form *in situ* the active catalyst that has been used by Shibasaki and coworkers in the *anti*-selective Mannich reaction of hydroxyketone **1.043** with *N*-Dpp imines **1.042** (scheme 1.15).[31] The *anti*-Mannich products **1.044** are obtained with high diastereomeric ratio and high enantiomeric excess from imines with aromatic, heteroaromatic and cyclopropyl-groups. The β-amino ketone was transformed into the corresponding β-amino ester by Baeyer-Villiger oxidation.



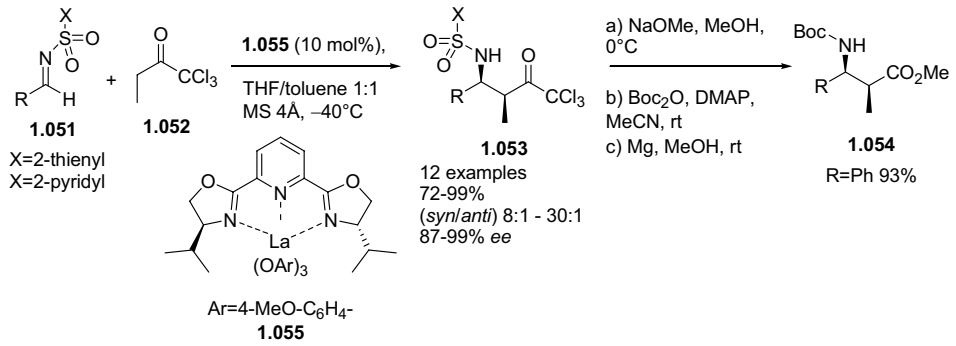
Scheme 1.15. Zn-catalyzed addition of hydroxyketones to imines.

Shibasaki and coworkers also used the bridged-binol complex **1.046** with In(III) that catalyzes the addition of *N*-(2-hydroxyacetyl)pyrrole **1.048** to various imines **1.047** (scheme 1.16).[32] The diastereomeric ratio depends on the imine used. In general, the *syn*-adducts were obtained with good *dr* and high *ee* with alkenyl and phenyl substituted imines and the *anti*-adducts with a moderate diastereomeric ratio and high enantiomeric excess using *o*-aryl-substituted imines. The *N*-acyl-pyrrole group was transformed under basic conditions to the corresponding ethylester to give *syn*-α-hydroxy-β-amino esters **1.050**.



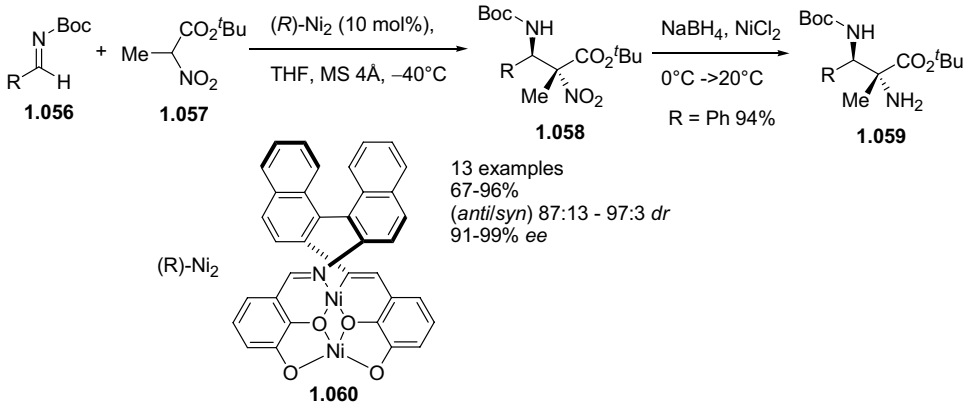
Scheme 1.16. In-catalyzed addition of N*-(2-hydroxyacetyl)pyrrole to imines.*

Moreover, La(III)-*i*Pr-pybox **1.055** was studied by Shibasaki and coworkers in the direct asymmetric Mannich reaction of trichloromethyl ketones **1.052** and pyridyl- or thienylsulfonyl-protected imines **1.051** (scheme 1.17).[33] The *syn*-isomers were preferentially formed with high *ee* (>99%) using the thienylsulfonyl protecting group. Aliphatic, aromatic and heteroaromatic imines were employed as substrates. The product **1.053** was transformed into the *N*-Boc-protected β^2-amino ester **1.054** using esterification under basic conditions and subsequent Boc-protection of the amino group.



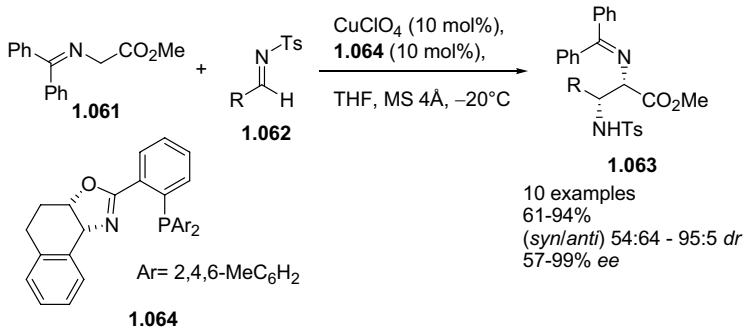
Scheme 1.17. La-catalyzed addition of trichloromethyl ketones to imines.

The same group investigated the homonuclear Ni_2-Schiff base complex **1.060** for the synthesis of tetrasubstituted *anti*-α,β-diamino acids (scheme 1.18).[34] Boc-protected aromatic and aliphatic imines **1.056** gave with nitro-acetate **1.057** the corresponding adducts **1.058** with high *dr*'s (up to 97:3) and high *ee*'s (up to 99%). Using $NaBH_4/NiCl_2$, the nitro group was reduced to give the α,β-diamino ester **1.059**.



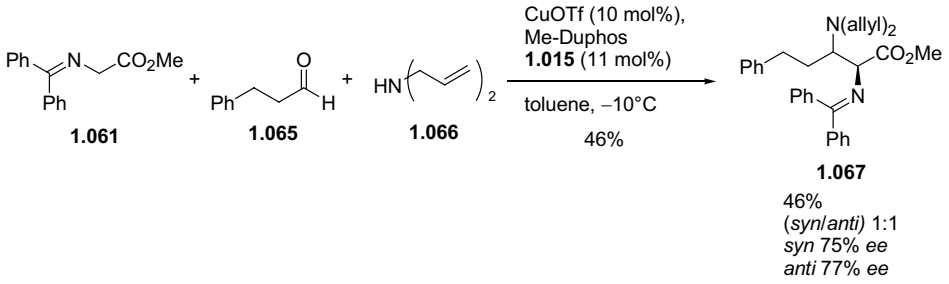
Scheme 1.18. Ni-catalyzed addition of nitroacetate to imines.

The Jørgensen group developed Cu-phosphino-oxazoline complex **1.064** that catalyzes the asymmetric Mannich reaction of glycine derivatives **1.061** and imines **1.062** (scheme 1.19).[35] Preferentially, *syn*-adducts were formed with high diastereomeric- and enantiomeric excess using aromatic and aliphatic imines as substrates. The highest selectivities in the synthesis of the α,β-diamino ester derivatives **1.063** were obtained with $CuClO_4$ as metal salt in the presence of molecular sieves.



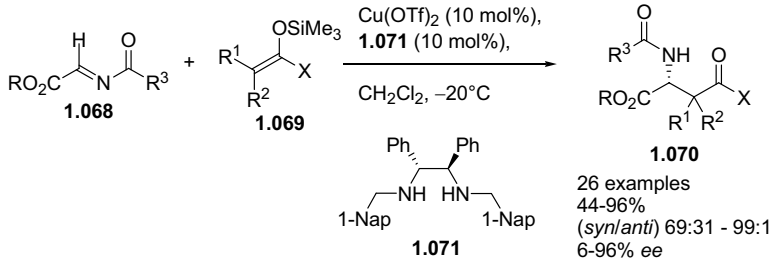
Scheme 1.19. Cu-catalyzed addition of glycine derivatives to imines.

Furthermore, the group of Kobayashi investigated copper salts in the direct three-component Mannich reaction producing protected α,β-diamino esters using Me-Duphos **1.015** as ligand (scheme 1.20).[36] Simple aromatic and enolizable aliphatic aldehydes **1.065**, secondary amines **1.066** and glycine derivatives **1.061** are used as starting materials in this reaction. (*R*,*R*)-Me-Duphos leads to a 1:1 mixture of *syn*/*anti* diastereomers with 75% and 77% *ee*, respectively.



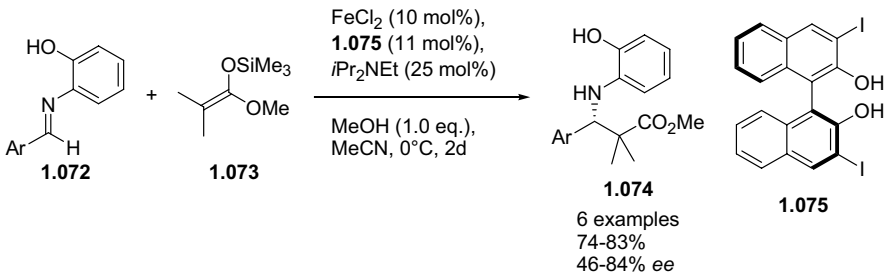
Scheme 1.20. Cu-catalyzed three-component Mannich reaction of a glycine derivative, aldehyde and amine.

In the asymmetric Mannich type reaction of *N*-acylimino esters **1.068** and silyl enol ethers **1.069**, Kobayashi and coworkers have studied copper-diamine complexes **1.071** as catalysts (scheme 1.21).[37] The Mannich adducts were obtained in high yields with high *ee*'s. In the reactions of α-substituted silyl enol ethers (X = α-methyl or benzyloxy), the desired *syn*-adducts were obtained again with high enantio- and diastereomeric excess. When $CuClO_4$-(*S*)-xylyl-Binap was used as a catalyst system in the addition of *tert*-butylthio-trimethylsiloxy-propene and *N*-benzoylimino esters, the *syn*-adduct was obtained with high diastereo- and enantioselectivity starting from (*Z*)-enolates, and the *anti*-adduct starting from (*E*)-enolates.[37]



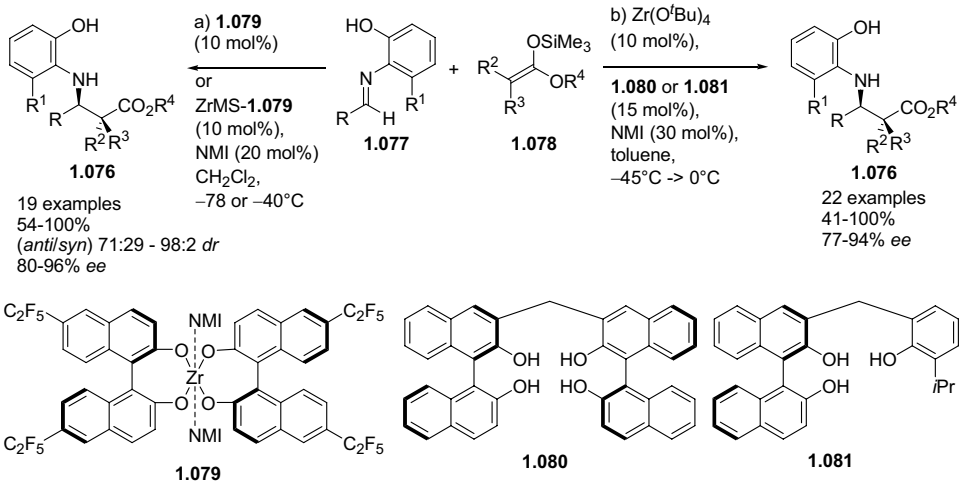
Scheme 1.21. Cu-catalyzed addition of silylenol ethers to N*-acylimino esters.*

The same group studied also the iron(II)-complex of 3,3'-I_2Binol complex **1.075** in the asymmetric Mannich-reaction (scheme 1.22).[38] The reaction of α-dimethyl silyl enolethers **1.073** with protected aromatic imines **1.072** provided the adducts **1.074** with good *ee*'s (up to 84%).



Scheme 1.22. Fe-catalyzed addition of silylenol ethers to aromatic imines.

Kobayashi and coworkers also used chiral catalysts based on Binol and Zr(IV) in the Mannich reaction.[39] In the synthesis of α-methyl-β-amino acid derivatives by condensation of (*E*)-silyl ketene acetals **1.078** with aldimines, the chiral zirconium catalyst **1.079** prepared from $Zr(O^tBu)_4$, 6,6'-dipentafluoroethyl-1,1'-bi-2-naphthol and *N*-methylimidazole (NMI) was used (scheme 1.23a).[39a,40] Aromatic and aliphatic imines were employed as substrates, giving the *anti*-adducts in good yields with high diastereo- and enantiomeric excess. The products were transformed into α-methyl-β-amino esters by transesterification of the Mannich adduct followed by deprotection of the amino group *via* a sequence involving methylation of the phenolic OH-group and deprotection using $AgNO_3$ in the presence of excess $(NH_4)_2S_2O_8$. This chiral air-stable zirconium catalyst as a mixture with powdered moleculars sieves (ZrMS-**1.079**) could be stored for 53 d under air without loss of activity, and be recycled for a second catalytic cycle.[39b] The enantioselectivity was enhanced in the presence of molecular sieves; from the (*E*)-silyl enolether **1.078** the *syn*-adduct is formed, while from the (*Z*)-silyl enolether the *anti*-adduct is obtained, both in good yield with high *dr* and *ee* (scheme 1.23a).



Scheme 1.23. Zr-catalyzed addition of silylenol ethers to imines.

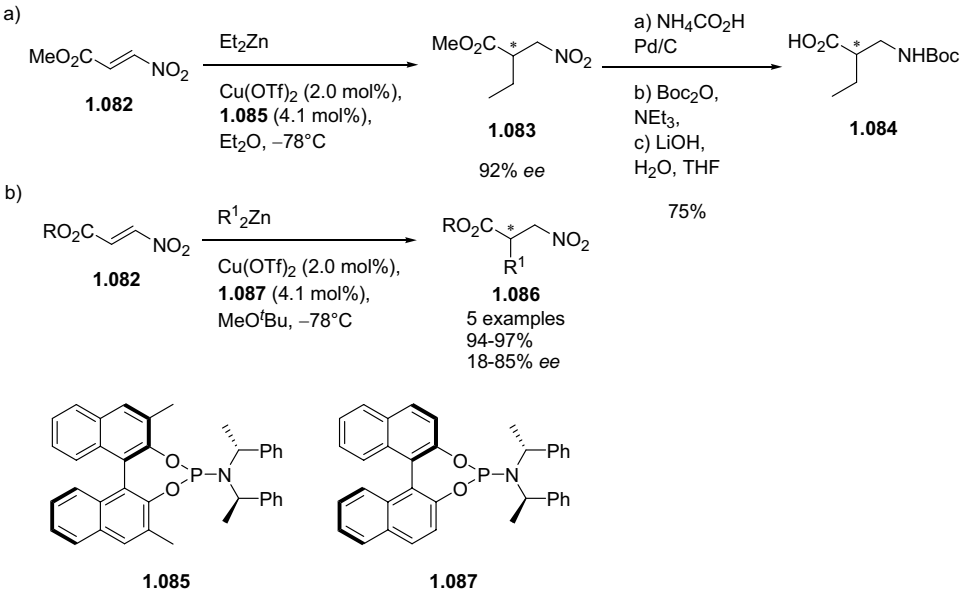
Further optimization studies identified bridged-bis-Binol **1.080** and ligand **1.081** as the best ligands, but the enantioselectivity could not be further increased (scheme 1.23b).[39c] When they were applied in the Zr-catalyzed reactions, the Mannich adducts **1.076** of various aromatic imines were provided in high yield with up to 94% *ee*.
In conclusion, chiral Lewis acids are useful catalysts for the asymmetric Mannich reaction to produce β-amino acid derivatives. Many combinations of metals, such as Cu(I), Cu(II), Fe(II), In(III), La(III), Ni(II), Zr(IV), and various ligands as source of the chiral information have been developed. The Mannich reactions discussed here (see also paragraph 1.3.1 for organocatalysts) represent highly stereoselective and frequently atom-economic methods for the synthesis of chiral β^2- and $\beta^{2,3}$-amino acid derivatives and diamino acids.

1.2.3 Conjugate addition

The catalytic asymmetric conjugate addition when applied in the synthesis of β-amino acids can be achieved in two ways: 1) addition of carbon nucleophiles, such as organometallic reagents, cyanide or Michael donors, and 2) nitrogen nucleophiles, such as aromatic amines, hydroxylamines, and carbamates.[41]

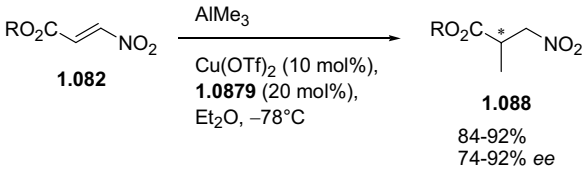
1.2.3.1 Carbon nucleophiles

The conjugate addition of carbon nucleophiles to α,β-unsaturated compounds is an important C-C-bond formation reaction.[42] This transformation shows a broad scope due to the large variety of acceptors (α,β-unsaturated aldehydes, esters, ketones, phosphonates, sulfones, thioesters and nitroalkenes) and nucleophiles (organometallic reagents, Michael donors, other carbanions).[43] In particular, nitro-olefins are versatile acceptors for the synthesis of β-amino acids.
Organozinc species have been successfully applied in copper-catalyzed 1,4-additions to form chiral β-substituted esters and enones. The use of phosphoramidite ligands derived from 2,2'-binaphthol resulted in a breakthrough providing catalysts thats show high activity and excellent chemo- and regio-selectivity. The groups of Sewald[44], Wendisch[45] and Feringa[46] have successfully used 3-nitropropenoates or acetal substituted nitropropenoates as acceptors and bisalkyl zinc reagents as nucleophiles to synthesize β-amino acid precursors.[47] In 2002, Sewald and coworkers reported the addition of diethyl zinc to methyl-3-nitropropenoate **1.082** catalyzed by a Cu-phosphoramidite **1.085** complex (scheme 1.24a).[44] Adduct **1.083** was obtained with 92% *ee*, and the nitro group could easily be reduced by catalytic transfer hydrogenation using ammonium formate. The amino group was *N*-Boc protected and subsequent ester hydrolysis gave *N*-Boc-β^2-amino acid **1.084**.



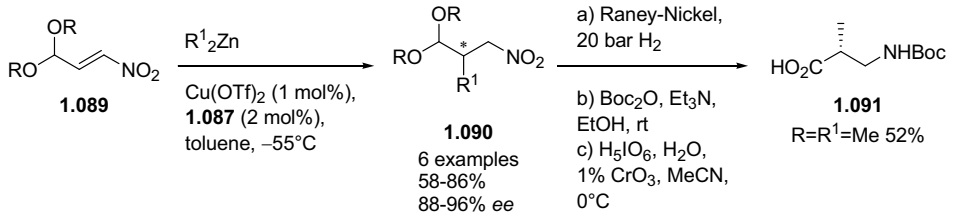
Scheme 1.24. Cu-catalyzed addition of diethyl zinc to a nitro-olefin.

Around the same time, Wendisch and coworkers reported the addition of bisalkyl zinc reagents to nitropropenoate **1.082** using phosphoramidite **1.087** as chiral ligand (scheme 1.24b).[45] In MeO^{t}Bu as solvent, the adduct was obtained in high yield with up to 85% *ee* using diethyl zinc as nucleophile. Furthermore, phosphoramidite **1.087** was employed in the Michael addition of trimethyl aluminium to nitroolefin **1.082** (scheme 1.25).[48] At low temperature in ether as solvent, enantioselectivities up to 92% were obtained.



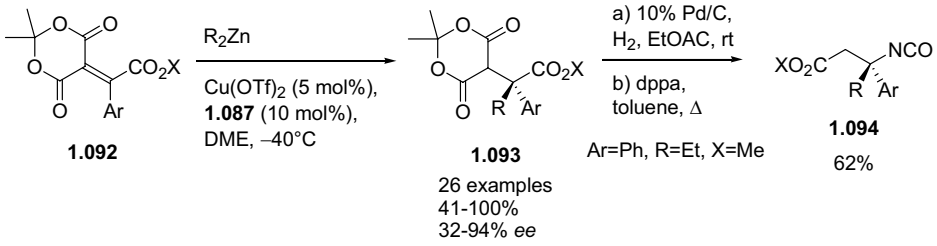
Scheme 1.25. Cu-catalyzed addition of trimethyl aluminium to a nitro-olefin.

Excellent enantioselectivities (up to 98%) were obtained by Feringa and coworkers in the addition of dialkyl zinc reagents to acetal-substituted nitropropenoates (scheme 1.26).[46] The adducts of Et_2Zn, Me_2Zn and Bu_2Zn were obtained with high yields and high *ee*'s. The corresponding *N*-Boc protected β^2-amino acids were formed *via* 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 **1.091**.



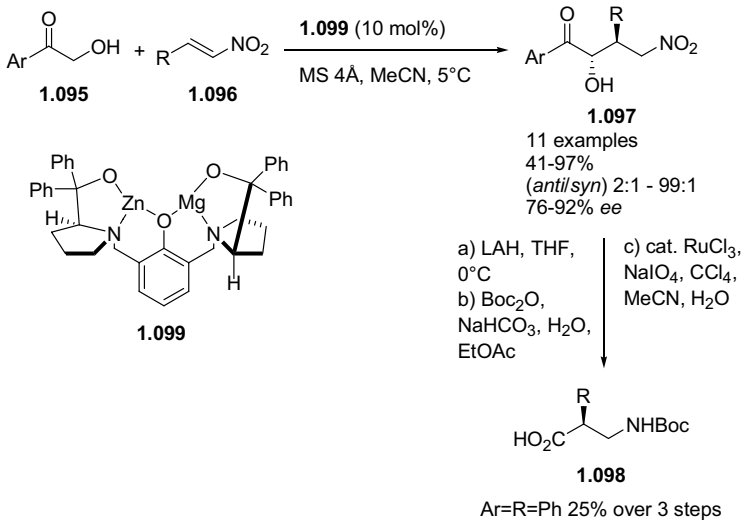
Scheme 1.26. Cu-catalyzed addition of dialkyl zinc reagents to acetal-substituted nitropropenoates.

Recently, carboxylic acid derivatives that have all carbon quaternary stereocenters have been synthesized through copper catalyzed asymmetric conjugate addition of dialkyl zinc reagents to 2-aryl acrylates **1.092** (scheme 1.27).[49] Fillion and coworkers tested phosphoramidite ligand **1.087** to obtain the adducts in high yields with up to 94% *ee*. β-Amino acid derivative **1.094** was synthesized through deprotection of adduct **1.093**, followed by a Curtius rearrangement of the succinic acid derivative.



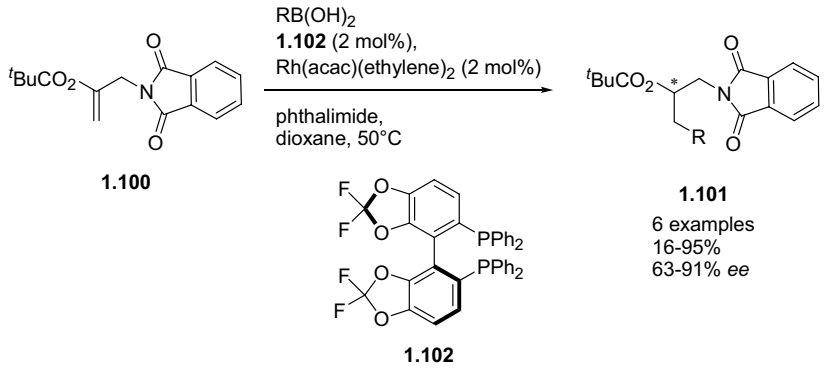
Scheme 1.27. Cu-catalyzed addition of dialkyl zinc reagents to 2-aryl-acrylates to form quaternary stereocenters.

Trost and coworkers reported a heterodinuclear asymmetric chiral catalyst **1.099** comprising Mg and Zn and a chiral proline-derived ligand for the addition of α-hydroxyketones to β-substituted nitroalkenes **1.096** (scheme 1.28).[50] As substrates aromatic, aliphatic and alkynyl-β-substituted nitroalkenes and phenyl- and furyl-hydroxyketones were employed leading to up to 92% *ee* and good diastereoselectivities in favor of the *anti*-products. Reduction of the nitro group and of the ketone to the corresponding amino-diol, followed by Boc-protection and oxidative cleavage of the diol gave the corresponding β^2-amino acid **1.098**.



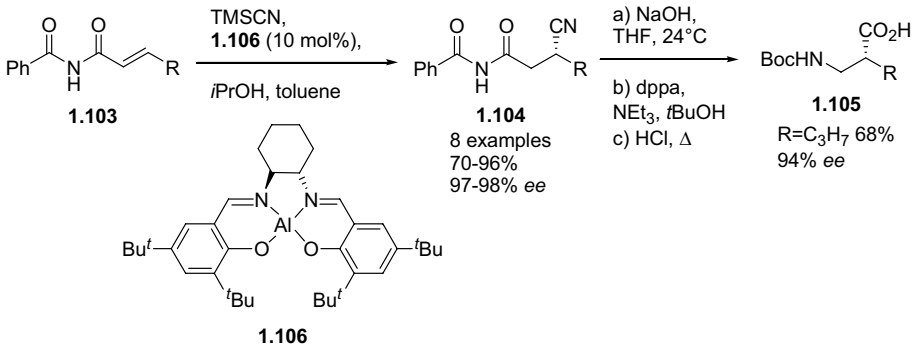
Scheme 1.28. Heterodinuclear catalyst for the addition of α-hydroxyketones to nitroalkenes.

An enantioselective rhodium catalyzed enolate protonation method for the synthesis of β^2-amino acids was reported by Sibi and coworkers (scheme 1.29).[51] A complex prepared from Rh(acac)(ethylene)$_2$ and difluoroPhos **1.102** catalyzed the conjugate addition of aryl boronic acids to β-acrylates **1.100**. Enantioselective protonation of the oxa-π-allyl-rhodium intermediate resulted in good yields with high enantioselectivitites (*ee* up to 91%) using one equivalent of phthalimide as proton source.



Scheme 1.29. Enantioselective rhodium catalyzed conjugate addition and protonation.

Jacobsen and coworkers reported the enantioselective conjugate addition of cyanide to α,β-unsaturated imides using aluminium salen catalyst **1.106** (scheme 1.30).[52] The adducts were obtained with up to 98% *ee* in high yields and were transformed into β-amino acids by basic hydrolysis of the imide to the corresponding carboxylic acid, followed by Curtius rearrangement with diphenylphosphoryl azide (dppa) and hydrolysis of the nitrile group to the corresponding carboxylic acid under acidic conditions.



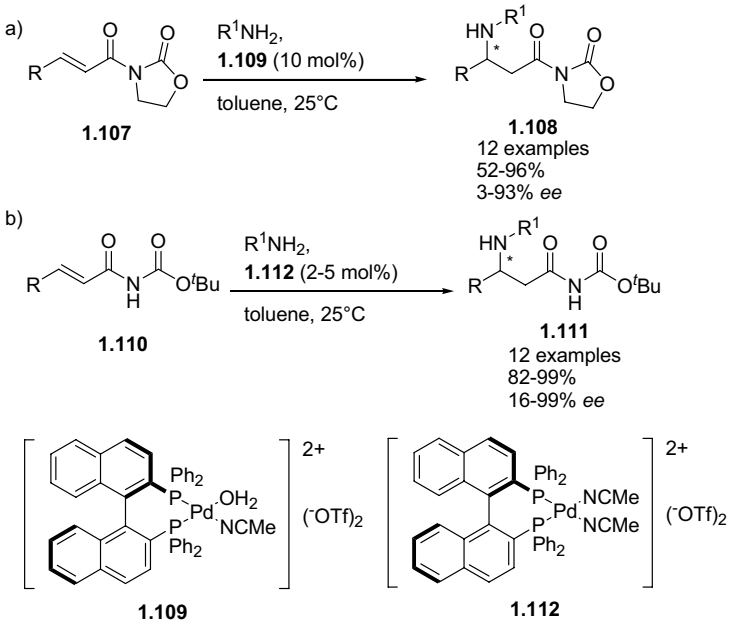
Scheme 1.30. Al-Salen catalyzed addition of cyanide to α,β-unsaturated imides.

The addition of dialkyl zinc and aluminium reagents as well as α-ketoesters to α,β-unsaturated nitro alkenes represent valuable methods to synthesize β^2-amino acid precursors with high enantioselectivities. Some methods can also be applied in the construction of all carbon quaternary stereocenters. Moreover, cyanide could be used in the addition to α,β-unsaturated imides to yield β^2-amino acids after three subsequent transformations. Furthermore, a rhodium-catalyzed addition of aryl boronic acids followed by enantioselective protonation gave optically active β^2-amino acid derivatives.

1.2.3.2 Nitrogen nucleophiles

Conjugate addition of amine nucleophiles to α,β-unsaturated carboxylic acid derivatives is one of the most attractive and atom-economic methods for the synthesis of β-amino acids. In the past, mostly chiral Michael acceptors or chiral amines have been used for diastereoselective conjugate additions.[41] Recently, several groups have reported significant progress towards catalytic asymmetric versions of conjugate additions of amines.[41,53]

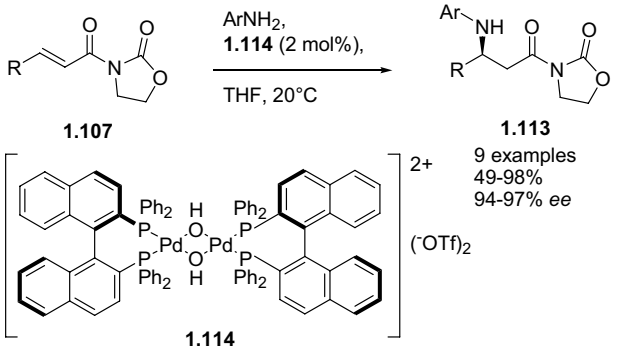
For the enantioselective addition of primary aromatic amines to α,β-unsaturated oxazolidinones **1.107**, Hii and coworkers investigated cationic palladium-Binap complex **1.109** (scheme 1.31a).[54] Using aniline and crotonyl-oxazolidinone, the adducts were obtained in good yield with *ee*'s up to 93%. However, when the substrate incorporated longer aliphatic chains than methyl, i.e. ethyl and propyl, a significantly lower *ee* was observed.



Scheme 1.31. Pd-catalyzed addition of aromatic amines to α,β-unsaturated imides.

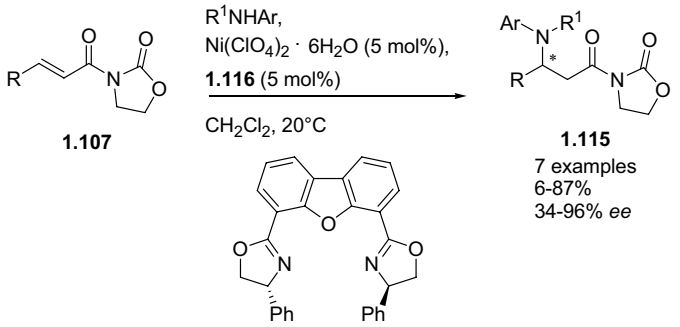
A similar cationic palladium complex **1.112** was tested in the addition of aromatic amines to *N*-alkenoylcarbamates (scheme 1.31b).[55] High enantioselectivities and high yields were achieved using various aliphatic substrates (R = Me, Et, Pr). The products were converted to *N*-aryl-β[3]-amino acids by hydrolysis of the imide under basic conditions. Moreover, the authors compared isolated and *in situ* formed complexes, and the obtained results being comparable.[56]

Also, Sodeoka and coworkers employed a cationic catalyst derived from Binap, which was used in its dimeric form **1.114** (scheme 1.32).[57] Aromatic amines substituted with electron donating or withdrawing groups gave the adducts in high yield with high *ee*'s (up to 97%.)



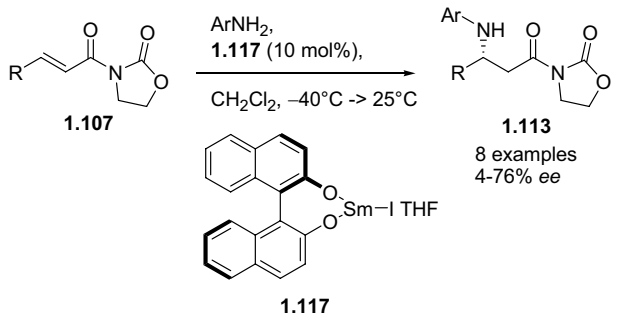
Scheme 1.32. Enantioselective addition of aromatic amines to α,β-unsaturated imides catalyzed by a dimeric palladium species.

The Jørgensen group investigated Ni(II)-bisoxazoline catalyst **1.116** in the addition of secondary aromatic amines to oxazolidinones **1.107** (scheme 1.33).[58] Various β-substituted aliphatic α,β-unsaturated oxazolidinones were used resulting in the amine adducts **1.115** in good yields and *ee*'s up to 96%.



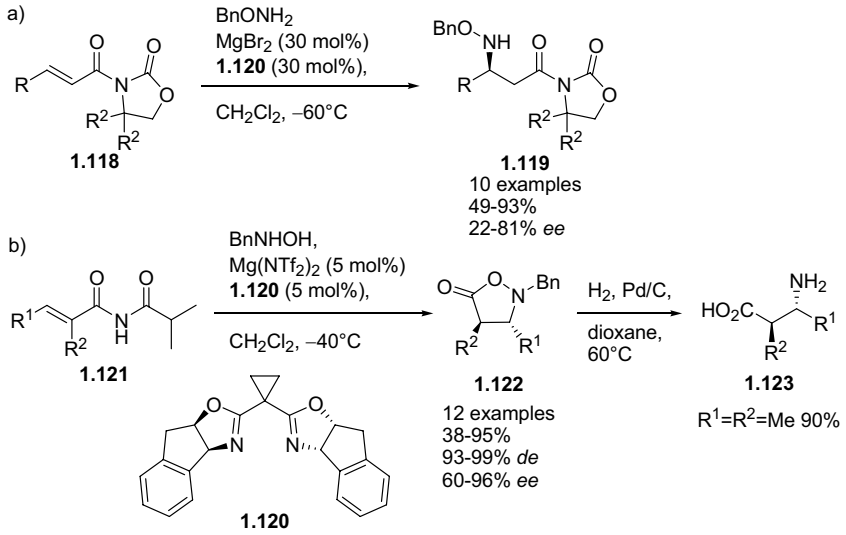
Scheme 1.33. Ni-catalyzed addition of aromatic amines to α,β-unsaturated imides.

Iodo(binaphtholate)samarium complex **1.117** has been used in the addition of aromatic amines to *N*-alkenoyloxazolidinones (scheme 1.34).[59] Substrates with aromatic substituents and *p*-anisidine as nucleophile resulted in the adducts **1.113** with *ee*'s (up to76%), but only low *ee*'s were reached using oxazolidinones with aliphatic substituents.



Scheme 1.34. Sm-catalyzed addition of aromatic amines to oxazolidinones.

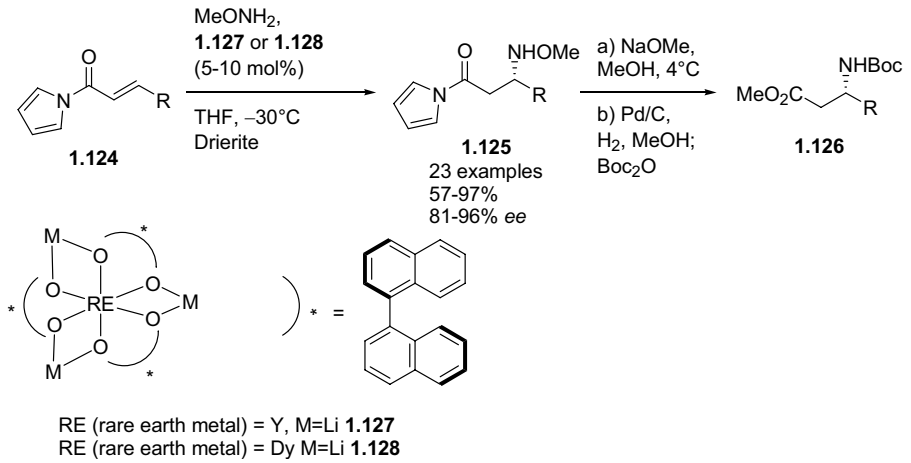
Besides aromatic amines, hydroxylamines have been widely used in catalytic enantioselective conjugate additions. Sibi and coworkers used Mg-bisoxazoline complex **1.120** in the addition of *O*-benzylhydroxyl amine to oxazolidinones **1.118** (scheme 1.35a).[60] However, only moderate enantioselectivities (up to 81%) were observed with high catalyst loadings of 30 mol%. The sterechemical outcome of this transformation depends on the temperature, *i.e.* at 0°C or room temperature the configuration reversed compared to the reaction at –60°C, and the *ee* was in general lower. β^3-Amino esters were synthesized upon hydrolysis of the imide to the corresponding methyl ester.



Scheme 1.35. Mg-catalyzed addition of hydroxylamines to α,β-unsaturated imides.

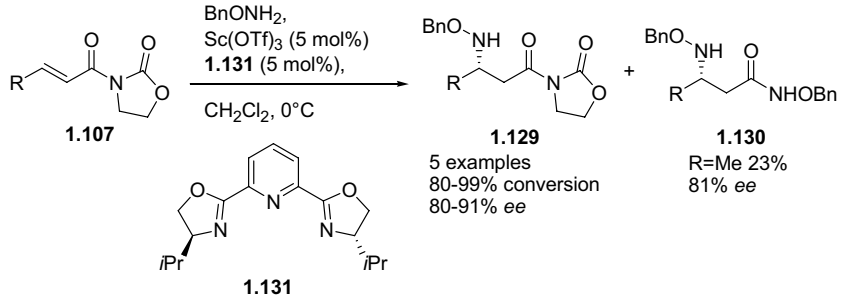
The addition of *N*-benzylhydroxyl amines to α,β-disubstituted imide **1.121** catalyzed by bisoxazoline ligand **1.120** and $Mg(NTf_2)_2$ lead to the formation of isoxazolidinones **1.122** (scheme 1.35b).[61] The *anti*-adducts were obtained in high yields with high diastereo- and enantiomeric excess. Upon hydrogenolysis, the $\beta^{2,3}$-amino esters **1.123** were obtained in high yield.

Shibasaki and coworkers studied heterobimetallic catalysts **1.127** and **1.128** in the enantioselective aza-Michael addition of methoxylamine (scheme 1.36).[62] Heterobimetallic catalysts are often combinations of rare earth metals and alkali metals. For instance, they show a cooperative effect of the two mutual centers, i.e. a Lewis acid to activate the electrophiles and a Brønsted base to deprotonate the nucleophiles to form activated metal nucleophiles.[63] Herein, Lewis acid-Lewis acid cooperative catalysis is employed using Li as alkali metal and Y or Dy as rare earth metal. Both Li and the rare earth metal are activating the α,β-unsaturated compound and control the orientation of the amine. Drierite ($CaSO_4$) was added as dessicant because traces of water decreased the rate of the reaction. Molecular sieves could not be used due to the absorption of methoxylamine. Mechanistic studies revealed that the ionic radius of the rare earth metals plays a major role. The enantiomeric excess of the adducts reaches up to 96%. The *N*-acylpyrrole group of **1.125** was easily transformed into the corresponding methyl ester. After hydrogenolysis of the hydroxylamine, β^3-amino esters **1.126** were obtained.



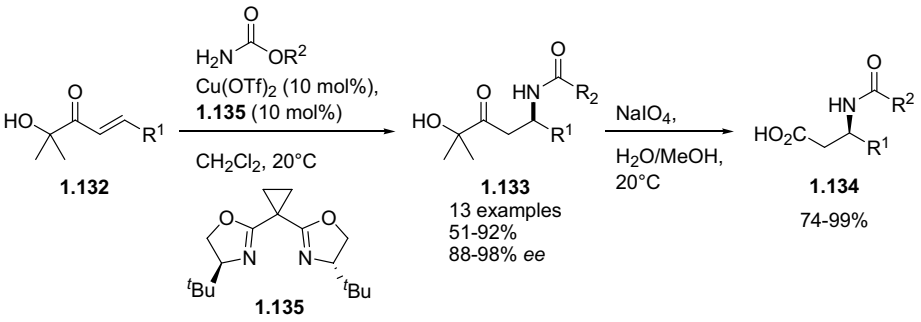
Scheme 1.36. Heterobimetallic catalysts for the aza-Michael addition of hydroxylamines.

$Sc(OTf)_3$/*i*-Pr-pybox complex **1.131** has been used for the enantioselective addition of *O*-benzylhydroxylamine to α,β-unsaturated 3-acyloxazolidinones (scheme 1.37).[64] The adduct **1.129** was obtained in good yield with high *ee*'s (up to 91%); using crotonoyloxazolidinone as substrate, *N*-benzyloxyamide **1.130** was also formed in 23% yield with 81% *ee* next to 77% of **1.129**.



Scheme 1.37. Sc-catalyzed addition of benzylhydroxylamine to oxazolidinones.

Palomo and coworkers investigated Cu(II)-bisoxazoline **1.135** for the addition of carbamates to α-hydroxy-enones (scheme 1.38).[65] Benzyl-, *t*butyl, methyl and ethyl carbamate were successfully added to aliphatic and aromatic α-hydroxy-enones **1.132** providing the adducts in high yield with high *ee*. The α-hydroxy ketone was oxidatively cleaved using $NaIO_4$ to yield the corresponding β^3-amino acid **1.134**.



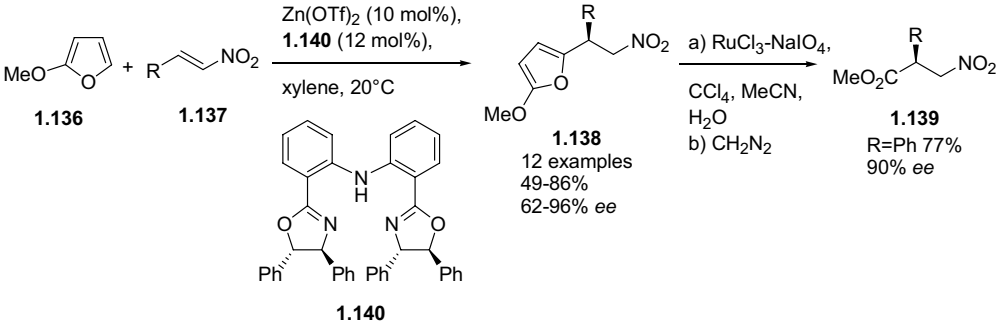
Scheme 1.38. Cu-catalyzed addition of carbamates to α-hydroxy enones.

Aromatic amines, hydroxylamines and carbamates were successfully added to α,β-unsaturated carbonyl compounds using Lewis acids as catalyst. However, all methods described here and in the older literature[41] use activated carbonyl compounds as acceptors. Simple carboxylic esters were not yet successfully employed to give β-amino esters *via* highly enantioselective conjugate additions.

1.2.4 Miscellaneous

Several reactions to form β-amino acids in an enantioselective manner which do not fit in the above described categories are discussed herein.

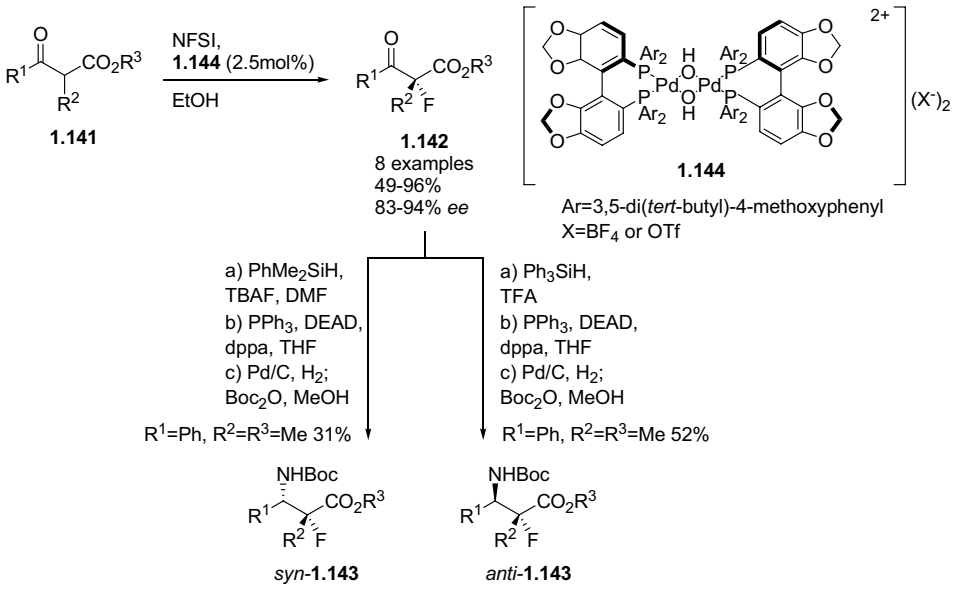
In 2007, an asymmetric Friedel-Crafts alkylation of 2-methoxyfuran with nitroalkenes was described (scheme 1.39).[66] A diphenylamine-tethered bisoxazoline **1.140**-Zn(II) complex was used to add methoxyfuran **1.136** to aromatic nitroolefins **1.137** with *ee*'s up to 96%. The furan-ring was subsequently oxidatively cleaved and the intermediate treated with diazomethane to form the β-nitro ester **1.138** which could be further transformed into the corresponding β^2-amino acids.



Scheme 1.39. Zn-catalyzed Friedel-Crafts reaction of 2-methoxyfuran with nitroalkenes.

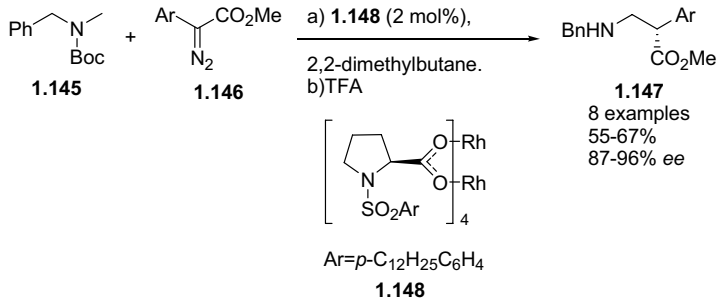
Sodeoka and coworkers have tested chiral cationic dimeric palladium catalysts for the α-fluorination of β-ketoesters with *N*-fluorobenzenesulfonamide (NFSI) (scheme 1.40).[67] Catalyst **1.144** derived from DTBM-SegPhos gave excellent enantioselectivities up to 94%. The products were converted to β-amino esters using a sequence involving

Ph_3SiH/TFA for the diastereoselective (*dr* >95:5) reduction of the ketone to the corresponding *anti*-fluoro-alcohol or Ph_3SiH/TBAF for the reduction to the *syn*-fluoro-alcohol. Both diastereomers were subsequently transformed into the respective azides using the Mitsunobu reaction, followed by reduction and *in situ* Boc-protection to give the α-fluoromethyl-β-amino esters.



Scheme 1.40. Pd-catalyzed enantioselective fluorination of β-ketoesters.

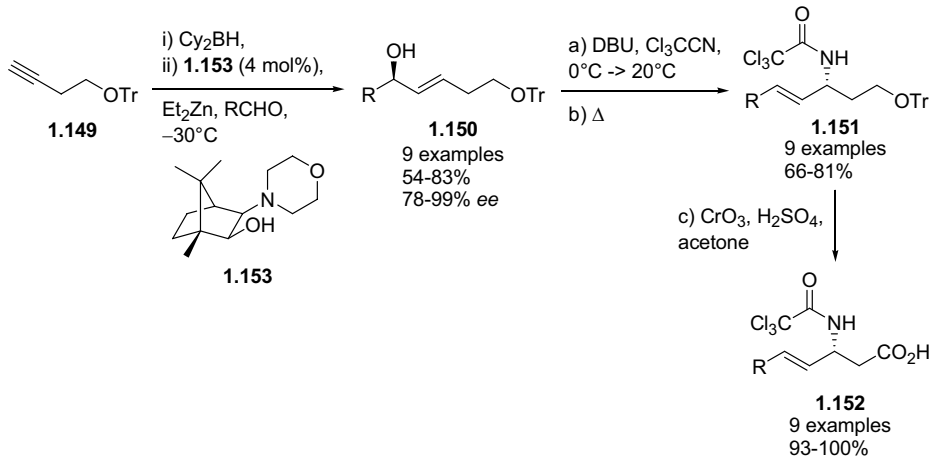
β^2-Amino acids were also synthesized by rhodium-catalyzed C-H insertion of aromatic diazoacetates **1.146** into *N*-Boc-*N*-benzyl-*N*-methylamine (scheme 1.41).[68] Benzylamine **1.145** is the optimal substrate for the insertion of various aromatic, heteroaromatic and alkenyl diazoacetates which proceeds with up to 96% *ee*.



Scheme 1.41. Rh-catalyzed C-H-activation for the synthesis of β^2-amino acids.

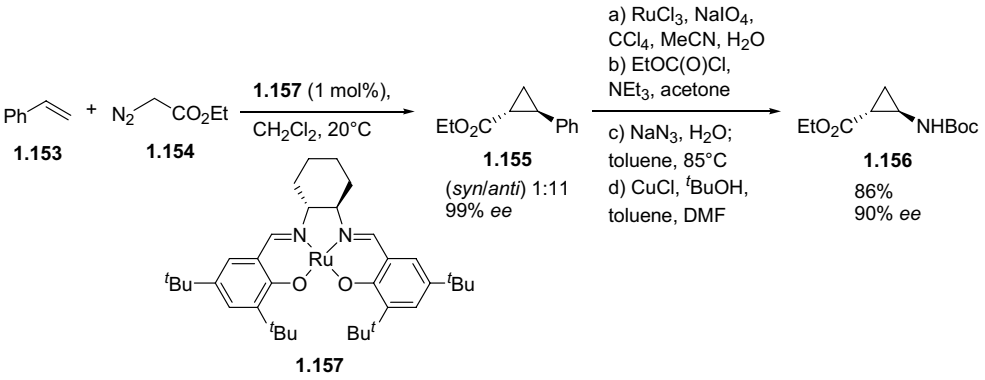
Walsh and coworkers have developed a multi-step procedure for the synthesis of γ-unsaturated β^2-amino acid derivatives with high *ee* (scheme 1.42).[69] First, an enantioselective vinylzinc addition to aldehydes yields allylic alcohol **1.150**, followed by

Overman's [3,3]-sigmatropic imidate rearrangement to yield **1.151** by a one-pot deprotection-oxidation sequence. The vinylzinc reagents were generated *in situ via* hydroboration of terminal alkyne **1.149** with dicyclohexylborane and transmetalation of the vinylborane with diethylzinc. Ligand **1.153** catalyzes the addition of the vinylzinc reagent to aromatic and aliphatic aldehydes in high yield with excellent *ee*'s (up to 99%). Then, the trichloroacetimidate was synthesized using trichloracetonitrile in DBU and heated to reflux yielding the rearranged product **1.151**. One-pot deprotection of the trityl alcohol and oxidation of the free hydroxy-group using chromium trioxide in sulfuric acid gave the *N*-protected amino acid **1.152**.



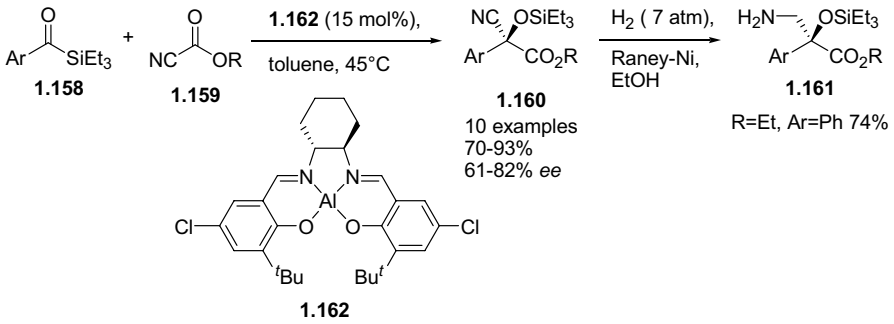
Scheme 1.42. Enantioselective addition of vinylzinc reagents to aldehydes as a key step for the synthesis of β^2-amino acids.

Ru-salen catalyst **1.157** was tested in an enantioselective cyclopropanation in order to prepare β^2-cyclopropane amino acids (scheme 1.43).[70] The cyclopropanation of styrene with ethyl diazoacetate **1.154** proceeded with good diastereo- and enantioselectivity. For the synthesis of *trans*-cyclopropyl β-amino acid derivatives, the phenyl ring was oxidatively cleaved giving the free carboxylic acid which was used in a subsequent Curtius rearrangement. The resulting isocyanate was converted into *N*-Boc-protected amino ester **1.156**.



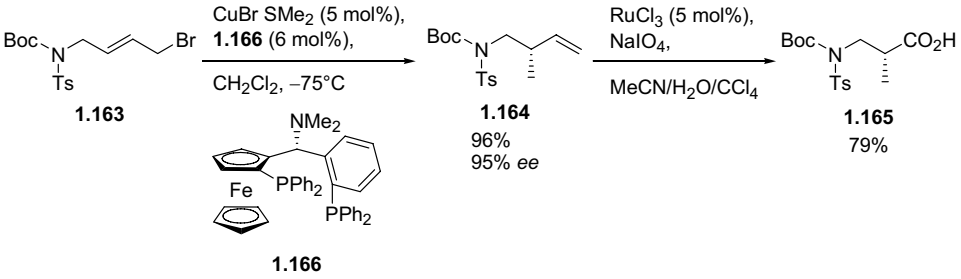
Scheme 1.43. Enantioselective Ru-catalyzed cyclopropanation as a key step in the synthesis of β²-cyclopropane-amino acids.

Johnson and coworkers developed an asymmetric cyanation/1,2-Brook-rearrangement/C-acylation reaction sequence for the synthesis of β-amino-α-hydroxy-α-phenyl amino acid derivatives (scheme 1.44).[71] Using cyanoformate **1.159**, acylsilane **1.158** and 15 mol% of salen-aluminium complex **1.162**, high enantioselectivities in the formation of **1.160** were achieved. First, enantioselective cyanation of the acylsilane occurs, leading to a chiral metaloxide that undergoes a 1,2-Brook-rearrangement to give the product **1.160** upon reaction with a second molecule of the cyanoformate. The nitrile group was subsequently reduced to the free amine **1.161**.



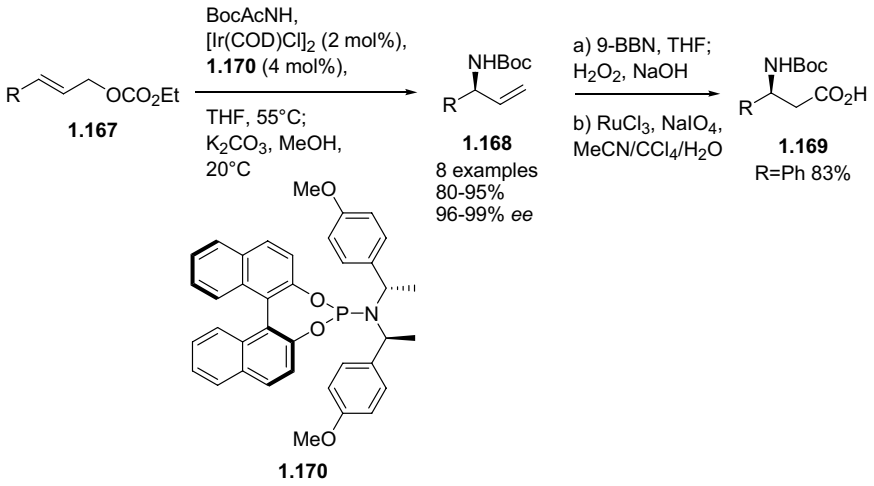
Scheme 1.44. Enantioselective cyanation/1,2-Brook-rearrangement/C-acylation for the synthesis of β-amino acids.

Feringa and coworkers developed the catalytic asymmetric allylic substitution of Grignard reagents using Taniaphos **1.166** as a chiral ligand and used this transformation as a key step in a new route to β²-amino acids (scheme 1.45).[72] Allylic amine **1.163** was treated with methylmagnesium bromide in the presence of the chiral copper catalyst to give **1.164** in high yield with an 95% *ee*. The olefin was oxidatively cleaved with $RuCl_3$-$NaIO_4$, and the *N*-Boc-*N*-tosyl protected β-amino acid **1.165** was obtained in 79% yield.



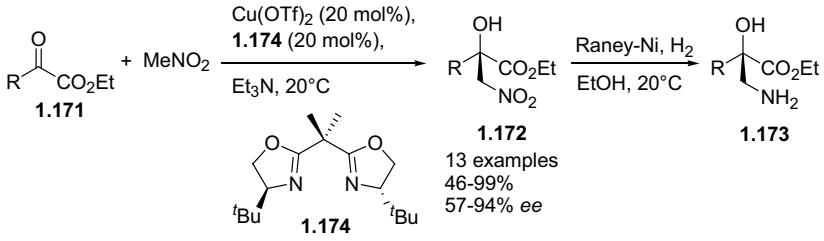
Scheme 1.45. Cu-catalyzed asymmetric allylic substitution using Grignard reagents.

Moreover, the catalytic asymmetric allylic amination of allylic carbonates catalyzed by Ir-phosphoramidite **1.170** was used for the preparation of β^3-amino acid derivatives (scheme 1.46).[73] *N*-Boc-*N*-acetylamine was employed as nucleophile giving the branched products with high regioselectivity (>99:1) and excellent *ee* (up to 99%). The product was *in situ* deacylated under basic conditions to give *N*-Boc-protected aliphatic and aromatic allylic amines. Hydroboration-oxidation and subsequent oxidation of the resulting alcohol gave the *N*-Boc-protected-β^3-amino acid **1.169**.



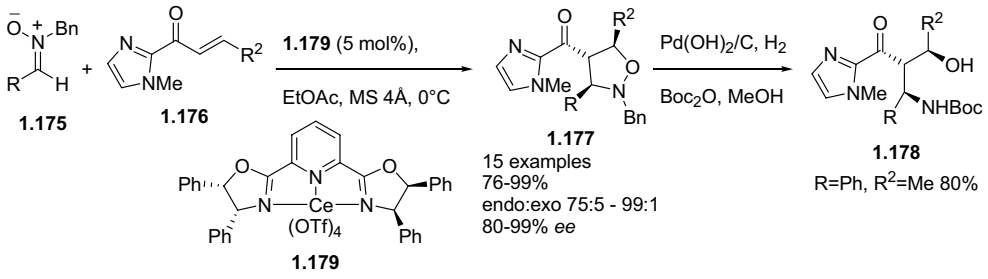
Scheme 1.46. Ir-catalyzed asymmetric allylic amination.

Jørgensen and coworkers employed the asymmetric Henry reaction to synthesize α-hydroxy-β^2-amino acid esters (scheme 1.47).[74] Copper-bisoxazoline **1.174** complex was used to add nitromethane to aliphatic and aromatic α-ketoesters to give the adducts in good yield with high *ee*'s (up to 94%). Upon reduction of the nitro group, the corresponding β-amino acid esters **1.173** were obtained.



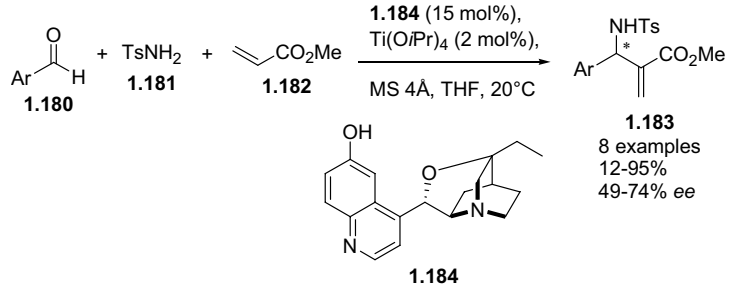
Scheme 1.47. Cu-catalyzed asymmetric Henry reaction.

Enantioselective [3+2]-cycloadditions of nitrones and α,β-unsaturated 2-acyl imidazole **1.176** were used to synthesize $\beta^{2,3}$-hydroxy-amino acid derivatives (scheme 1.48).[75] Evans and coworkers employed Ce(IV)-bisoxazoline catalyst **1.179** to achieve the addition of aliphatic and aromatic nitrones **1.175** to 2-acyl imidazoles **1.176** in high yield with up to 99% *ee* with an *endo*:*exo* ratio >99:1. The isoxazolidines **1.177** were reductively cleaved using $Pd(OH)_2/C$ and hydrogen to give $\beta^{2,3}$-amino acid derivatives **1.178**.



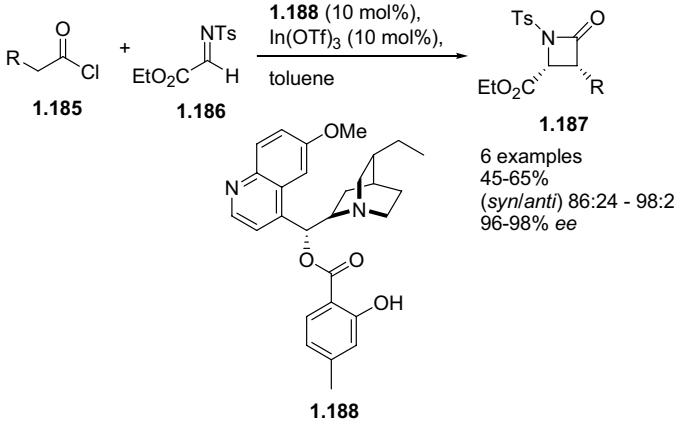
Scheme 1.48. Catalytic asymmetric [3+2]-cycloaddition.

Chiral nucleophilic quinuclidine alkaloid derived catalyst **1.184** in combination with $Ti(OiPr)_4$ as Lewis acid has been employed in the asymmetric aza-Baylis-Hillman reaction (scheme 1.49).[76] Starting from aromatic aldehydes, tosylamide and methyl acrylate, Adolfsson and coworkers studied catalyst **1.184** to obtain the Baylis-Hillman adducts **1.183** in good yield with moderate enantioselectivities.



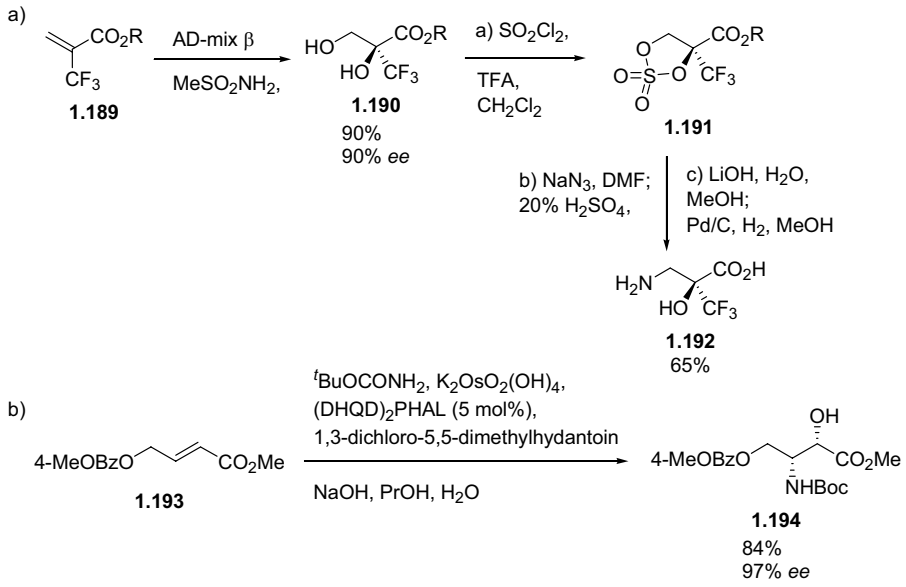
Scheme 1.49. Catalytic asymmetric Baylis-Hillman reaction.

Using bifunctional asymmetric catalyst **1.188**, Lectka and coworkers synthesized β-lactams from acyl chlorides **1.185** and imine **1.186** (scheme 1.50).[77] A combination of $In(OTf)_3$ and quinidine derivative **1.188** gave the *syn*-β-lactam **1.187** with high *dr* (up to 98:2) and high *ee* (up to 98%).



Scheme 1.50. In-quinidine catalyzed asymmetric formation of β-lactams.

The catalytic asymmetric Sharpless aminohydroxylation and dihydroxylation of α,β-unsaturated carboxylic acid derivatives are important methods for the synthesis of α-hydroxy-β-amino acids which are key building blocks for the synthesis of Taxol analogues. α-Trifluoromethylisoserine **1.192** was synthesized by dihydroxylation from 2-(trifluoromethyl) acrylic ester **1.189**, followed by treatment with Burgess reagent to give sulfamidate **1.191** which was hydrolyzed in acidic medium to give the β-amino acid with 90% *ee* (scheme 1.51a).[78] The aminohydroxylation was used in the synthesis of polyhydroxylated β-amino acid constituents of microsclerodermic cyclic peptides (scheme 1.51b).[79] γ-Alkoxy-(*E*)-alkene **1.193** was transformed into *syn*-β-amino-α-hydroxy ester **1.194** with 97% *ee* using $(DHQD)_2PHAL$ as catalyst and *tert*-butylcarbamate as nucleophile.



Scheme 1.51. Aminohydroxylation and dihydroxylation for the synthesis of β-amino acid derivatives.

There are many versatile catalytic enantioselective methods to synthesize β^2- or β^3-amino acids. Among the most frequently employed are those based on cycloadditions and Sharpless amino- and dihydroxylation. However, these methods are most often used for the synthesis of specific amino acids, for example as key step in natural product synthesis.

1.3 Organocatalysis

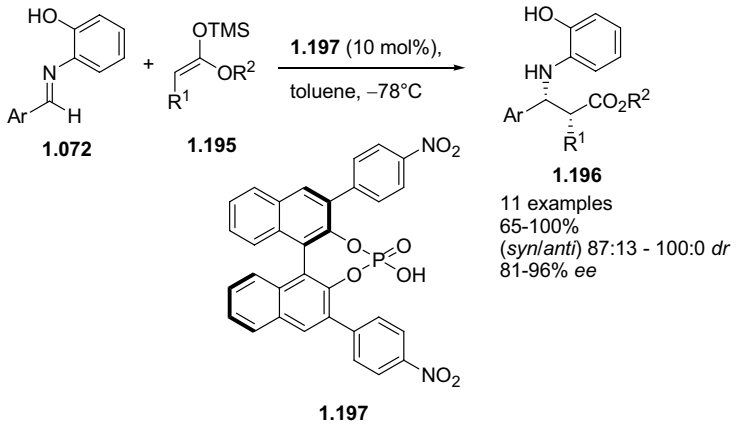
Asymmetric transformations promoted by small chiral organic molecules have become very useful among the recently developed methods for the synthesis of β-amino acids.[80] Important catalysts used for this purpose are proline, proline-derived amines, chiral Brønsted acids, (thio)ureas, and cinchona alkaloids.[81] In this paragraph Mannich reactions, conjugate additions and miscellaneous organocatalytic synthesis of β-amino acids are presented, covering the recent literature since 2002.

1.3.1 Mannich reaction

Organocatalytic Mannich reactions represent a direct entry into β-amino carbonyl compounds.[82] Low-molecular weight synthetic molecules that have hydrogen-bond donor abilities and a secondary interaction side, such as aromatic, and acidic or basic functionalities, can catalyze a variety of C-C and C-heteroatom bond forming reactions with high enantioselectivity.[83] Chiral Brønsted acids are an important class of organocatalysts. Hydrogen bonds are formed between the catalyst and the electrophile to activate it and to organize the transitionstate.[84] Chiral Brønsted acids are classified into two categories: 1) neutral Brønsted acids, such as thiourea and Taddol derivatives which

are called hydrogen-bonding catalysts, and 2) stronger Brønsted acids, such as Binol derivatives and phosphoric acids.

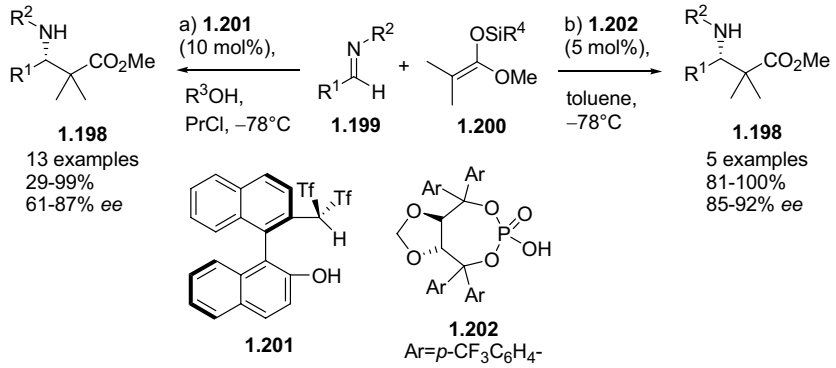
Chiral phosphoric acid **1.197** derived from Binol gave high stereoinduction in the reaction of aromatic aldimines with silylenol ethers (scheme 1.52).[85] High diastereoselectivities (*dr* up to 100:0) and high enantioselectivities (*ee* up to 96%) were achieved.



Scheme 1.52. Mannich reaction catalyzed by a chiral Binol-derived phosphoric acid.

Yamamoto and coworkers studied chiral Brønsted acid **1.201** which was proposed to activate imine **1.199** through hydrogen bonding (scheme 1.53a).[86] An achiral Brønsted acid (R^3OH) protonates the amine moiety of the intermediate to give the adducts **1.198** with good *ee* (up to 78%).

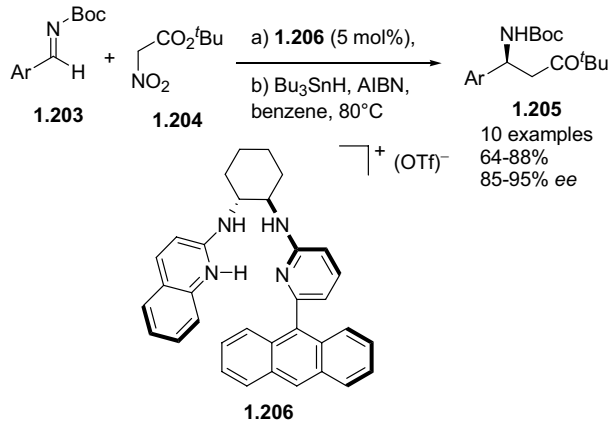
Taddol-derived phosphoric acid **1.202** was also used to catalyze the addition of silylenol ethers **1.200** to aromatic aldimines with good yield and high *ee*'s (scheme 1.53b).[87]



Scheme 1.53. Brønsted acid catalyzed Mannich reactions for the synthesis of $\beta^{2,2,3}$-amino acids.

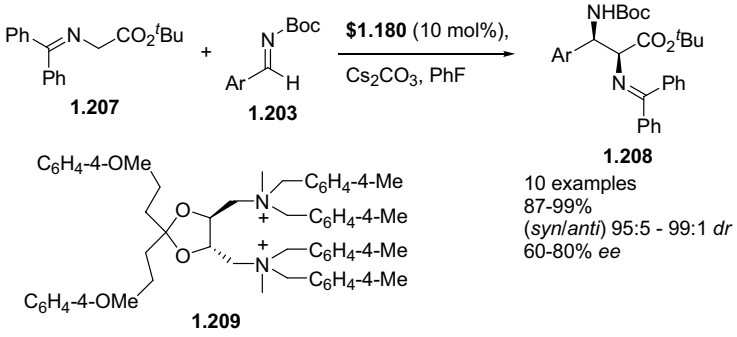
The reaction of aromatic *N*-Boc-protected aldimines with nitroacetate **1.204** using amine catalyst **1.206** gave the products in good yield and high *ee* (up to 98%) (scheme 1.54).[88]

Using tributyl tinhydride and AIBN, the nitro group was removed to provide the corresponding β^3-amino ester **1.205**.



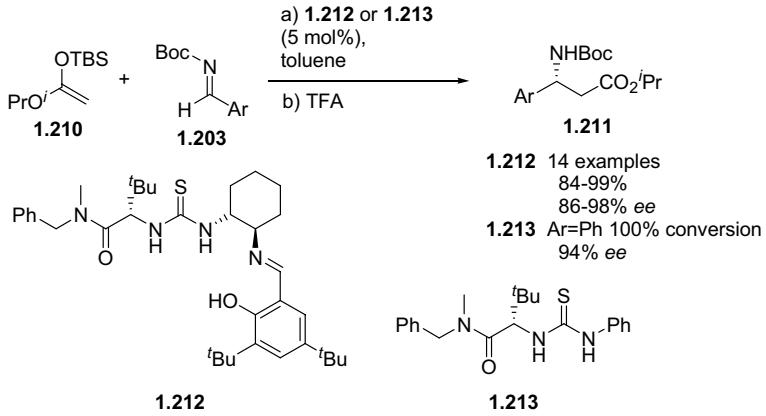
Scheme 1.54. Mannich reaction catalyzed by a chiral amine.

Phase transfer catalyst **1.209**, developed by Shibasaki and coworkers, is effective in the addition of glycine-Schiff-base **1.207** to aromatic imines (scheme 1.55).[89] The glycine-Schiff-base is deprotonated by Cs_2CO_3, presumably at the interface between liquid and solid phase, where upon counterion exchange with **1.209** takes place, followed by the asymmetric C-C-bond formation. The Mannich adducts **1.208** were obtained with good diastereomeric- and enantiomeric excess.



Scheme 1.55. Mannich reaction catalyzed by a chiral phase transfer catalyst.

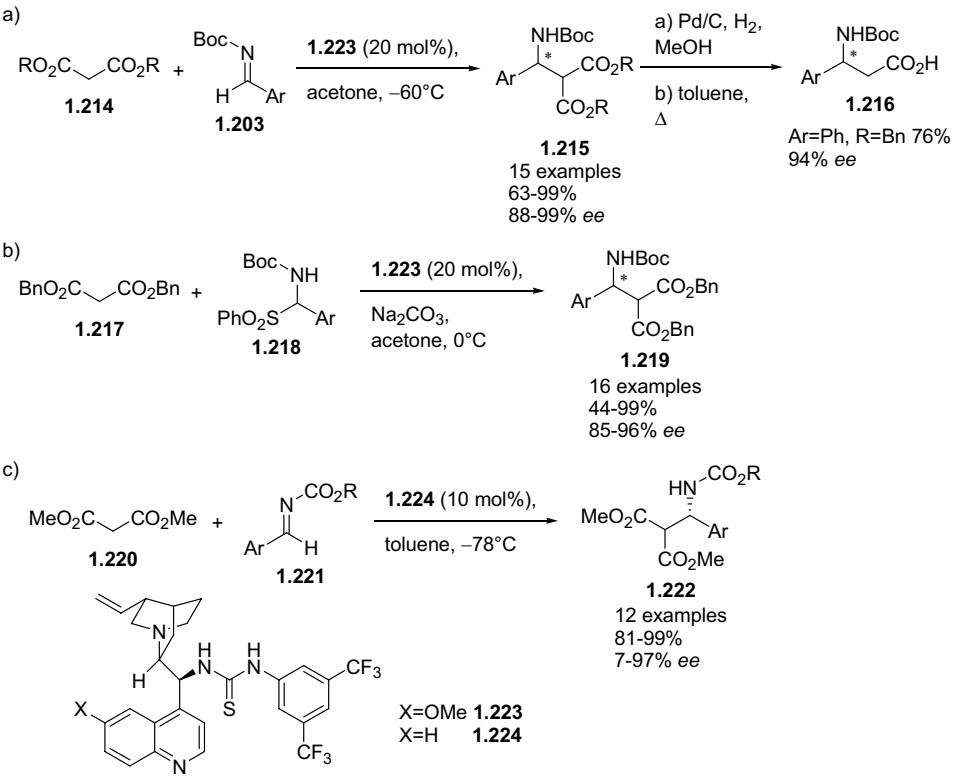
Jacobsen and coworkers studied thiourea **1.212** as catalyst in the Mannich reaction of silylenol ethers **1.210** with *N*-Boc-aldimines **1.203** (scheme 1.56).[90] Aromatic β^3-amino acid derivatives were obtained in high yields with up to 98% *ee*. Variation in the amine part of the catalyst, i.e. thiourea **1.213**, gave comparable enantioselectivities for the Mannich reaction.[91]



Scheme 1.56. Thiourea catalyzed asymmetric Mannich reaction.

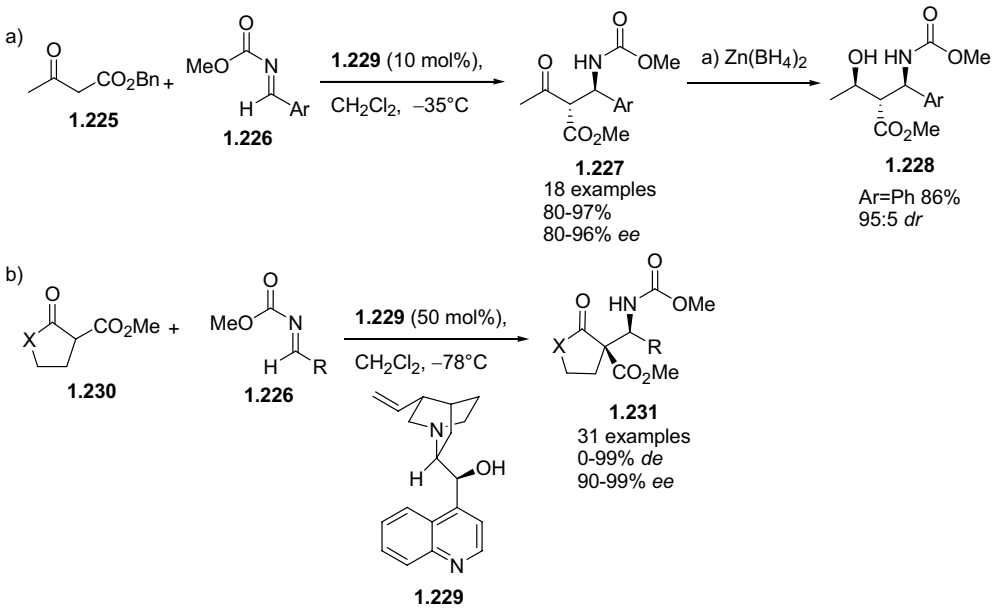
Deng and coworkers tested catalyst **1.223** with a thiourea and a quinine alkaloid moiety (scheme 1.57a).[92] The thiourea-group is proposed to activate and direct the electrophilic imine, and the tertiary nitrogen of the quinine moiety activates the nucleophile. The products **1.215** resulting from the addition of malonates to *N*-Boc-protected aromatic aldimines were obtained in high yield with high *ee* (up to 99%). Upon hydrogenation, the benzyl ester was deprotected and subsequent decarboxylation provided the *N*-protected β^3-amino acid **1.216** in high yield. The same group also tested catalyst **1.223** for the Mannich reaction with *in situ* generated carbamate-protected imines **1.218** (scheme 1.57b).[93] The Mannich adducts were obtained in high yield with up to 96% *ee* starting from α-amino sulfone **1.218**, dibenzyl malonate **1.219**, and catalyst **1.223**.

Dixon and coworkers used a similar thiourea-cinchonine alkaloid catalyst **1.224** for the addition of malonates to *N*-Boc- and *N*-Cbz protected aldimines **1.221** (scheme 1.57c).[94] The Mannich adducts of dimethyl malonate **1.220** and the protected aromatic aldimines **1.221** were obtained in high yield with up to 97% *ee*.



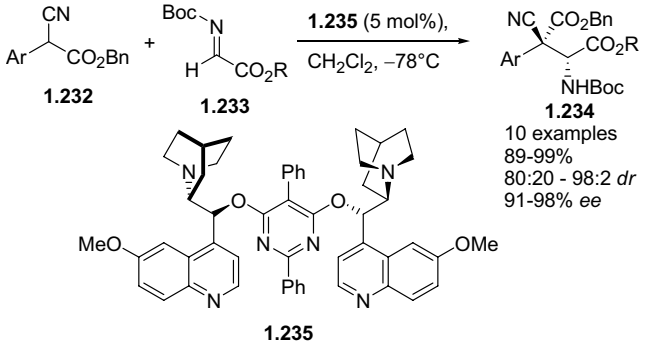
Scheme 1.57. Thiourea-quinine and cinchonine derived catalysst for the asymmetric Mannich reaction.

The asymmetric Mannich reaction of β-keto esters with imines catalyzed by cinchonine alkaloid **1.229** was reported by Schaus and coworkers (scheme 1.58a).[95] Cinchonine **1.299** catalyzed the formation of the Mannich adducts with high diastereoselectivity (*dr* up to 20:1) and high enantioselectivity (*ee* up to 96%). Upon reduction with $Zn(BH_4)_2$ the *syn*-amino alcohol derivative **1.228** was obtained. The same catalyst was also tested in the addition to cyclic β-keto esters, providing high yield and high diastereo- and enantioselectivities (scheme 1.58b).[96]



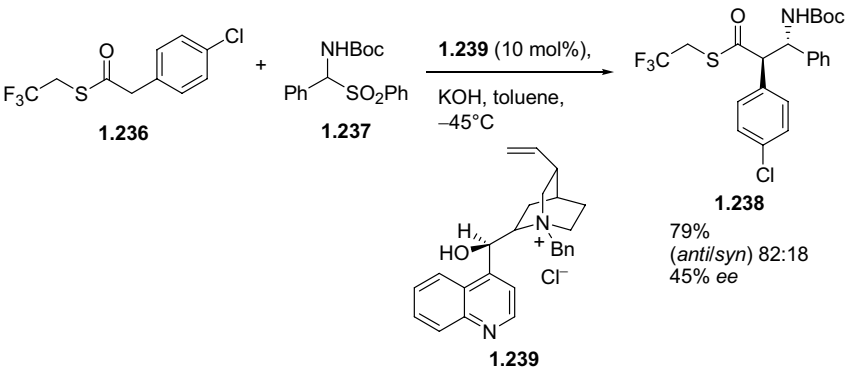
Scheme 1.58. Cinchonine catalyzed asymmetric Mannich reaction of cyclic and acyclic β-ketoesters.

Jørgensen and coworkers investigated quinidine alkaloid derivative **1.235** in the reaction of α-cyanoacetates **1.232** with α-imido carboxylates **1.233** (scheme 1.59).[97] Aromatic α-cyanoacetates **1.232** gave the corresponding Mannich adducts **1.234** in high yield in a highly diastereo- and enantioselective transformation; the highest *ee* and *dr* were obtained starting from α-cyano-*tert*-butyl-carboxylate.



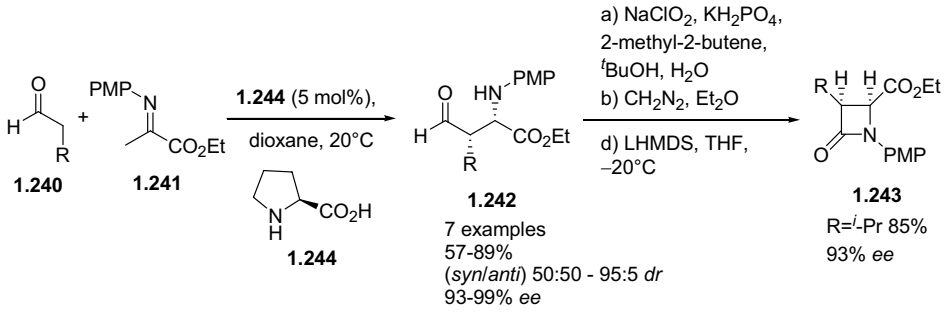
Scheme 1.59. Quinidine alkaloid catalyzed asymmetric Mannich reaction of α-imido carboxylates and α-cyanoacetates.

Barbas III and coworkers studied the Mannich reaction of thioesters with *in situ* generated *N*-Boc imines catalyzed by cinchona alkaloid **1.239** (scheme 1.60).[98] However, the Mannich adduct was only obtained with moderate enantioselectivity.



Scheme 1.60. Cinchonina alkaloid catalyzed asymmetric Mannich reaction.

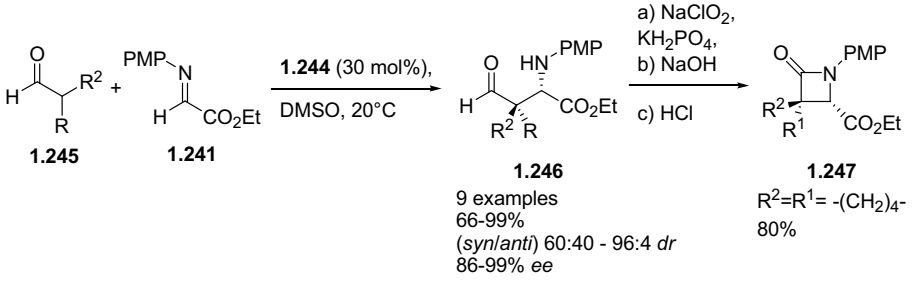
Proline and proline derivatives are important catalysts for organocatalytic transformations.[99] Proline acts hereby as a multifunctional catalyst.[83] The amine group of proline condensates with the carbonyl group of the substrate to generate an enamine, the carboxylic acid functionality activates the electrophile *via* hydrogen-bonding in a higly ordered transition state.[81] The H-donor functionality was found to be important to arrange the electrophile relative to the pyrrolidine ring and thus lowering the activation barrier for the C-C-bond formation by stabilizing charge build up in the transition state.
Barbas III and coworkers have used proline **1.244** as catalyst in the addition of aliphatic aldehydes to PMP-protected α-imido ethylesters **1.241** (scheme 1.61).[100] The *syn*-products **1.242** were obtained with high *dr*'s and *ee*'s, and subsequently oxidized and cyclized to obtain β-lactam **1.243**. When an aqueous medium, such as THF/H_2O (9:1), was used in this Mannich reaction, the *syn*-adduct was obtained with high diastereo- (95:5) and high enantioselectivity (up to 99%).[101]



Scheme 1.61. Proline catalyzed asymmetric Mannich reaction of aldehydes and α-imido carboxylates to form β-lactams.

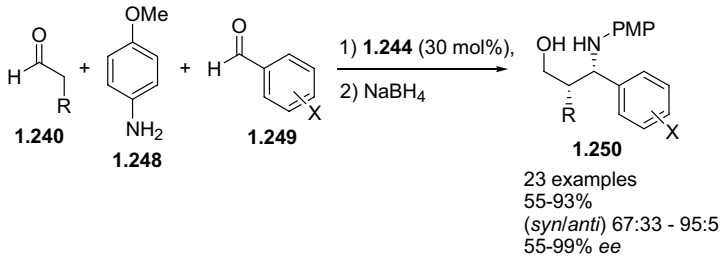
Quaternary all carbon stereocenters were synthesized *via* a Mannich reaction using proline catalysis and α-branched aldehydes (scheme 1.62).[102] α,α-Disubstituted aldehydes **1.245** were used as donor reagents in the addition to α-imido ethylester **1.241** to provide quaternary β-formyl substituted α-amino acid derivatives in high yield with

excellent *dr*'s (up to 96:4 *syn:anti*) and high *ee*'s (up to 99%, *syn*). The products were further converted to form spiro-lactams **1.247**. However, high catalyst loadings (30 mol%) were required.



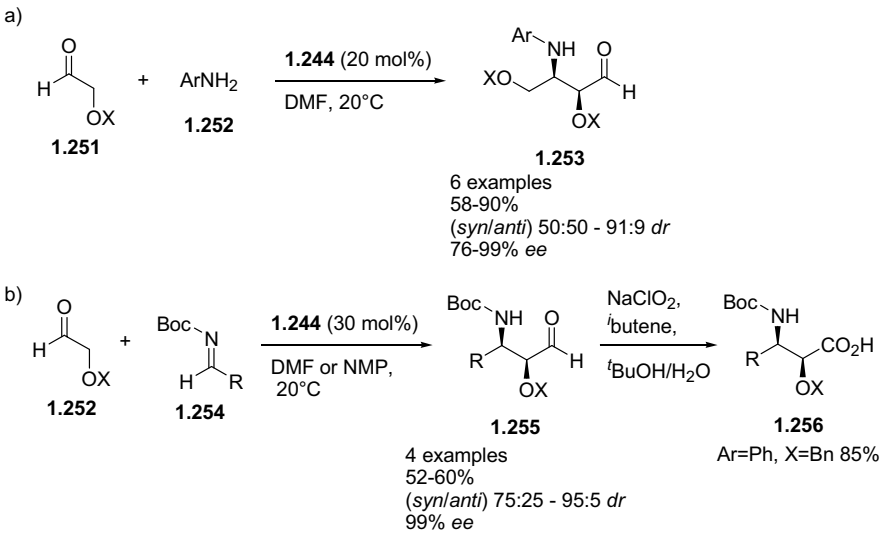
Scheme 1.62. Proline catalyzed asymmetric Mannich reaction to form quaternary all carbon stereocenters.

An extension of the scope of the direct asymmetric Mannich reaction of unmodified aldehyde donors was reported in 2003 by Barbas III (scheme 1.63).[103] Several substituted proline derivatives were investigated in the addition of aldehydes to α-imino ethyl glyoxylate, revealing that proline gives the best diastereoselectivities for the formation of the *syn*-adduct with high enantioselectivity. However, (*S*)-2-methoxymethylpyrrolidine shows reversed diastereoselectivity, *i.e.* that the *anti*-adduct is formed preferentially but with only moderate enantioselectivity. The effect of water on the Mannich reaction with preformed aromatic aldimines was also studied: the reaction tolerates a significant amount of water (up to 10%) without affecting the enantioselectivity. For substituted aromatic amines (with electron withdrawing functional groups) a diastereomeric ratio (up to 91:9) for the *syn*-adduct is obtained. Furthermore, the authors describe the one-pot-three-component reaction of aliphatic aldehydes, *p*-anisidine and substituted aromatic aldehydes to give adducts with high diastereomeric ratio (up to 95:5) and high *ee* (up to 99%) (scheme 1.63). Hayashi and coworkers also reported the three component Mannich reaction of aromatic and heteroaromatic aldehydes, *p*-anisidine and aliphatic aldehydes to give the *syn*-adducts with high diastereomeric ratio (up to 95:5) and high *ee* (scheme 1.63).[104] The same three-component Mannich reaction has been described by Córdova and coworkers for the synthesis of γ-amino alcohols.[105] Córdova investigated a broader aldehyde scope such as heteroaromatic, aliphatic aldehydes and ethyl glyoxylate which gave the corresponding Mannich adducts again with high *syn*-selectivity and high *ee*'s.[106]



Scheme 1.63. Proline-catalyzed asymmetric one-pot-three component Mannich reaction.

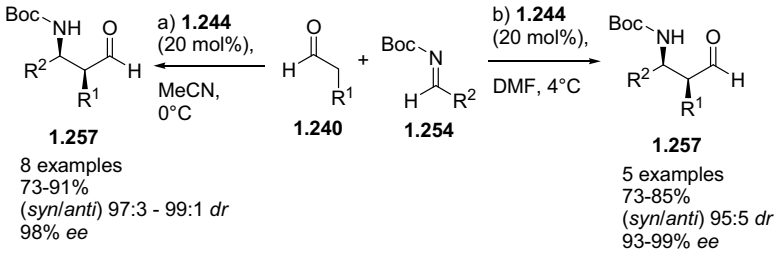
Using glycol aldehydes as substrates, Córdova and coworkers describe an entry into the synthesis of protected amino-tetroses **1.253** (scheme 1.64a) and *syn*-α-hydroxy-β-amino acids **1.256** (scheme 1.64b).[107] However, high catalyst loadings of proline are necessary to achieve excellent enantioselectivities (*ee* up to 99%) and good diastereoselectivity. The diastereomeric ratio is in some cases up to 91:9 but for most substrates it does not exceed 80:20 (*syn*/*anti*). In 2008, the synthesis of α-hydroxy-β-amino acid derivatives was improved using higher catalyst loadings and preformed imines to yield higher enantioselectivities (*ee* up to 99%) (X=TBS and PG=Boc) and diastereoselectivities (*dr* up to 95:5) for the *syn*-adducts (scheme 1.64b).[108] The products were converted by oxidation to the corresponding β-amino acids.



Scheme 1.64. Proline-catalyzed asymmetric synthesis of α-hydroxy-β-amino aldehydes.

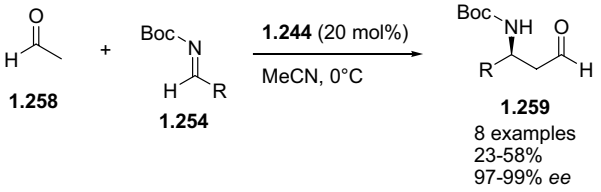
List and coworkers reported excellent diastereoselectivities (*dr* up to 99:1) and enantioselectivities (*ee* up to 99%) towards the *syn*-adduct for the proline catalyzed addition of aldehydes to aromatic *N*-Boc-protected imines **1.254** (scheme 1.65a).[109] A scope of aliphatic, heteroaromatic and aromatic imines is described. Employing slightly different reaction conditions, Córdova and coworkers also reported this transformation

(scheme 1.65b).[110] For a variety of aliphatic and allylic aldehydes the *syn*-products **1.257** were obtained in a highly diastereo- and enantioselective transformations.



Scheme 1.65. a) Proline catalyzed asymmetric Mannich reaction of N*-Boc-imines by List and b) by Córdova.*

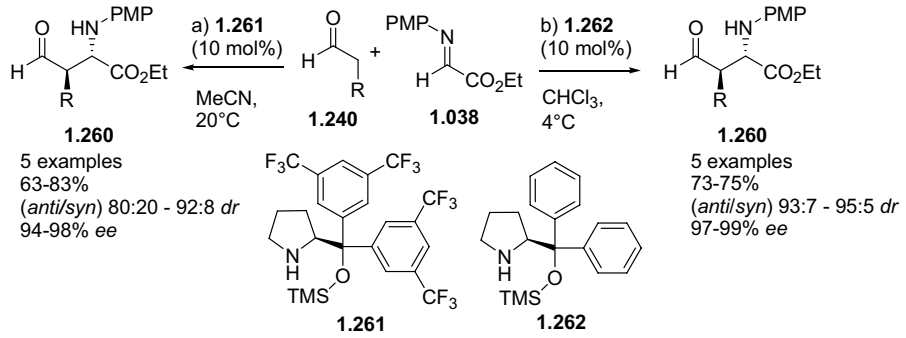
In 2008, the List group reported the proline catalyzed reaction of *N*-Boc-imines with acetaldehyde (scheme 1.66).[111] The β-amino aldehydes are obtained with excellent *ee* (up to 99%), however, the yields are low (23-58%), and a high catalyst loading of proline (20 mol%) has to be employed.



Scheme 1.66. Proline-catalyzed Mannich reaction of acetaldehyde.

Hayashi and coworkers conducted experimental studies towards the mechanism and compared the reactivity of aldimines to aldehydes employing NMR-spectroscopy and theoretical calculations using density functional theory (B3LYP/6-31G*).[112] In the Mannich reaction of *p*-anisidine and two equivalents of benzaldehyde, the formed imine reacts seven times faster with the second equivalent of aldehyde than the aldehyde enol would react with itself (aldol reaction). The authors attribute their findings to the fact that a protonation of the basic nitrogen atom of the aldimine by the carboxylic acid group of proline is more favourable than protonation of the aldehyde.

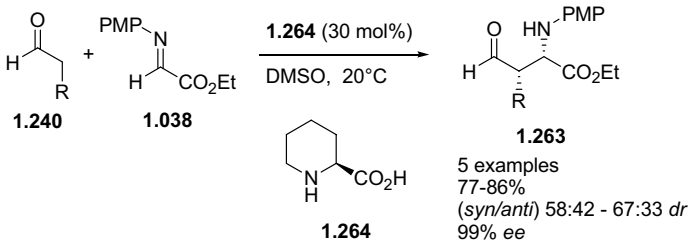
Several alternative organocatalysts based on proline have been designed in recent years. Jørgensen and coworkers used TMS-protected catalyst **1.261** in the Mannich reaction of PMP-protected α-imino ethylglyoxylate **1.038** and aliphatic aldehydes **1.240** (scheme 1.67a).[113] This catalyst gives the *anti*-adducts with high *dr*'s and high *ee*'s. Direct asymmetric Mannich reactions of aliphatic aldehydes with α-imino ethylglyoxylate were also described by Córdova and coworkers using related catalyst **1.262** giving the *anti*-adducts with good selectivity (scheme 1.67b).[114]



Scheme 1.67. a) Mannich reaction of aldehydes catalyzed by proline derivatives by Jørgensen and b) by Córdova.

Hayashi and coworkers performed calculations using density functional theory (B3LYP) and experiments on the Mannich reaction with catalyst **1.261** and **1.262**. The addition of acetaldehyde to *N*-Bz-, *N*-Boc- and *N*-Ts-protected aromatic imines revealed that in the presence of *p*-NO_2PhCO_2H as additive better yields and excellent enantioselectivities were obtained.[115] Experimentally, *N*-Boc- and *N*-Bz protected imines were investigated; all reactions gave the *anti*-adducts in good yield with high enantioselectivity (up to 98%).

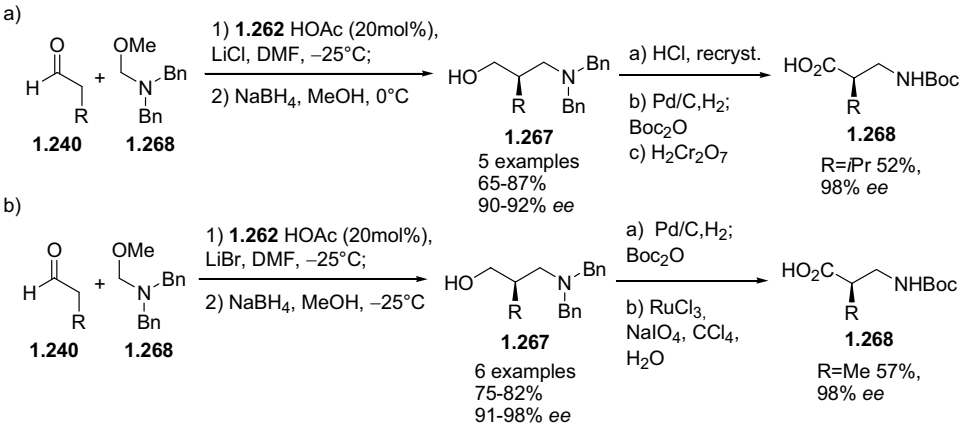
Moreover, pipecolic acid **1.264**, the 6-ring analogue of proline, was used by Barbas III and coworkers in the addition of aliphatic aldehydes to α-imino ethylglyoxylate (scheme 1.68).[116] The *ee*'s are high for both diastereomers (*ee* >99%), but the selectivity towards *syn*-adducts is usually low (*dr* up to 67:33).



Scheme 1.68. Mannich reaction catalyzed by pipecolic acid.

The enantioselective aminomethylation of aldehydes was investigated by Gellman and coworkers for the synthesis of β^2-amino acid building blocks for peptide synthesis (scheme 1.69a).[117] An iminium species was *in situ* generated by elimination of MeOH from aminal **1.268**. Proline derivative **1.262** catalyzed the addition of aliphatic aldehydes to give the adducts in good yields with high *ee*'s (up to 92%). The β-amino aldehydes were *in situ* reduced to the corresponding alcohols. For the synthesis of β^2-amino acids, the amino alcohol was recrystallized as hydrochloride salt to increase the *ee*, the protecting groups removed by hydrogenation followed by Boc-protection, and the alcohol oxidized to the corresponding carboxylic acid **1.268**. Córdova and coworkers

screened further additives and found that LiBr increases the enantioselectivity (*ee* up to 98%) (scheme 1.69b).[118] The corresponding β^2-amino acid **1.268** was synthesized by deprotection of the benzyl-protecting group and reprotection using Boc_2O, followed by oxidation of the alcohol to the carboxylic acid providing *N*-Boc-β-amino acid **1.268** with an overall yield of 57%.



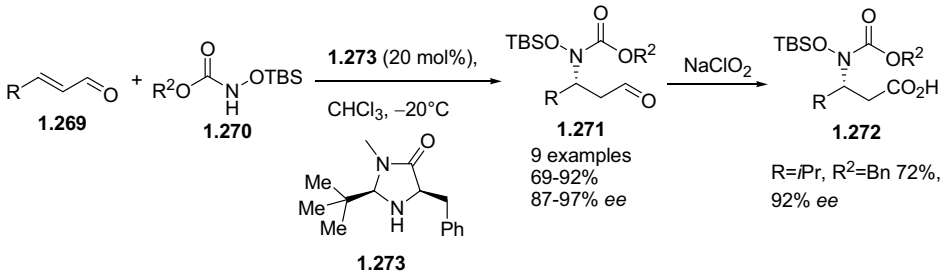
Scheme 1.69. a) Organocatalytic aminomethylation for the synthesis of β^2-amino acids by Gellman and b) by Córdova.

In recent years, the organocatalyzed Mannich reaction has found widespread application in the synthesis of β-amino acids. Both, β^2- and β^3-amino acids are accessible with high diastereoselectivities towards *syn*- or *anti*-Mannich products depending on catalyst source and substrate. However, when proline or its derivatives are used as catalysts, in most cases high catalyst loadings of 20-30% are still needed to achieve a highly stereoselective transformation.

1.3.2 Conjugate addition

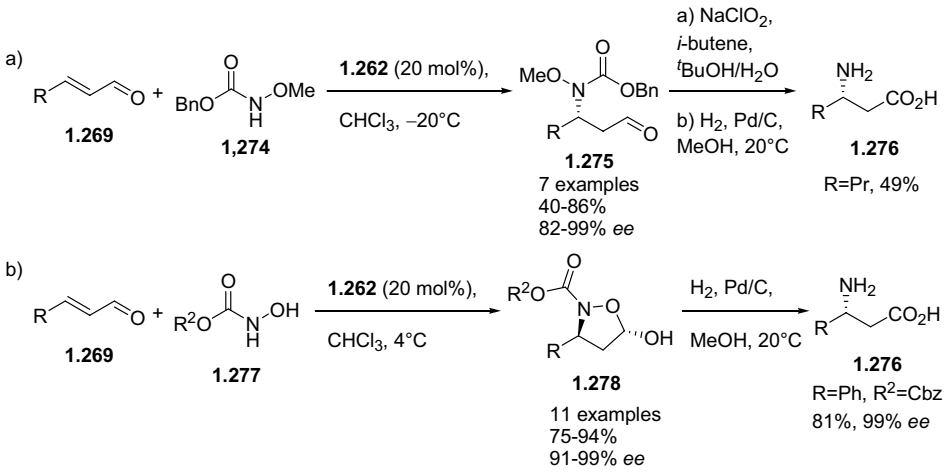
The addition of carbon and nitrogen nucleophiles to α,β-unsaturated compounds is an important organic transformation for the synthesis of pharmaceuticals and natural products. Organocatalytic C-N bond formations are especially important for the synthesis of β-amino acids *via* conjugate addition.

MacMillan and coworkers designed nitrogen nucleophile **1.270** that readily undergoes a conjugate addition to α,β-unsaturated aldehydes (scheme 1.70).[119] In the presence of an imidazolidinone organocatalyst **1.273** (as TFA-adduct), benzyl *tert*-butyldimethylsiloxycarbamate **1.270** was added to aliphatic and benzyloxy-substituted α,β-unsaturated aldehydes **1.269**. The nucleophile was designed to enhance the nucleophilicity through the N-O functionality *via* the α-effect while the carbamate moiety renders the amino aldehyde product effectively nonbasic ($pK_a \sim 9$). The products **2.171** are obtained in high yield with up to 97% *ee*, and were subsequently oxidized to *N*-protected β^3-amino acids **1.272**.



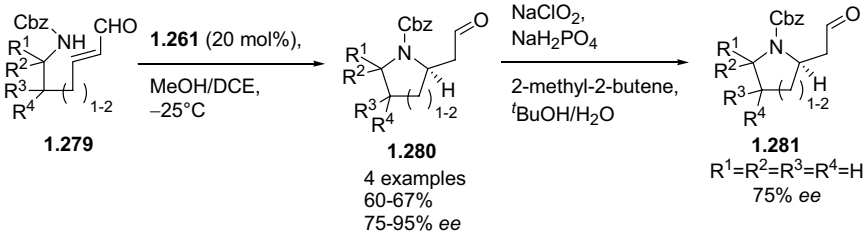
Scheme 1.70. Organocatalytic aza-Michael addition.

Following a similar approach, Córdova and coworkers reported that proline-derived chiral amine **1.262** catalyzes the conjugate addition of *N*-Cbz-methoxylamine **1.274** to α,β-unsaturated aldehydes (scheme 1.71a).[120] The β-amino aldehydes were obtained in high yield with high enantiomeric excess (up to 99%). A subsequent oxidation of the aldehyde **1.274** to the corresponding carboxylic acid and deprotection of the amine provided β^3-amino acids **1.276**. When carbamate-protected hydroxylamines **1.277** were used as nucleophile, the cyclic 5-hydroxy-isooxazolidinones **1.278** were obtained with high *ee* up to 98% (scheme 1.71b).[121] They were subsequently cleaved by hydrogenolysis to give β^3-amino acid **1.276** with high *ee*.



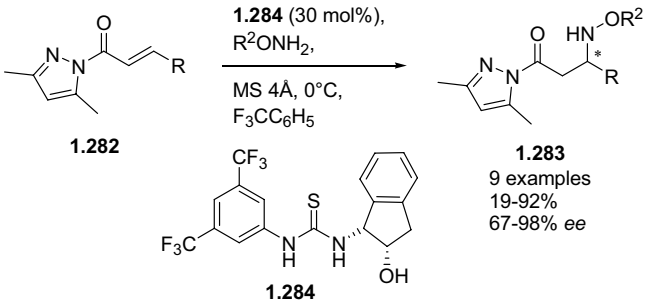
Scheme 1.71. Organocatalytic aza-Michael addition.

Proline derivative **1.261** has also been used for intramolecular aza-Michael addition (scheme 1.72).[122] Piperidines and pyrrolidines were synthesized with up to 95% *ee*. The aldehydes were oxidized to the corresponding carboxylic acids, such as homopipecolic acid derivative **1.281**.



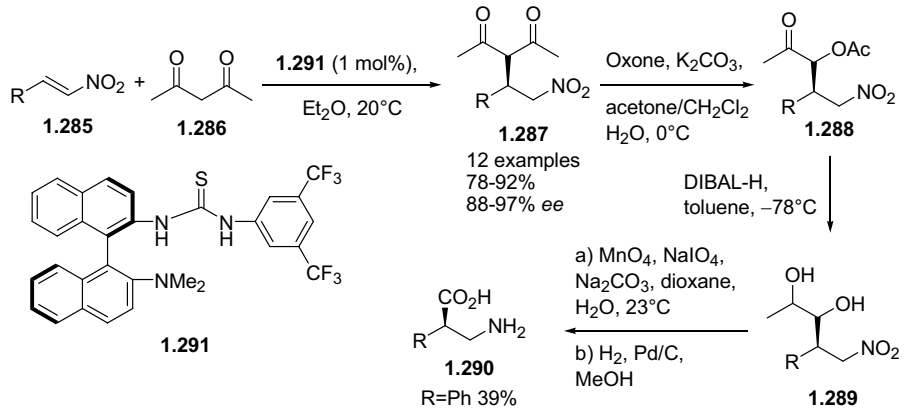
Scheme 1.72. Intramolecular organocatalytic aza-Michael addition.

Sibi and coworkers used thiourea catalyst **1.284** for the conjugate addition of *O*-substituted hydroxylamines to pyrazole crotonates **1.282** (scheme 1.73).[123] Aliphatic α,β-unsaturated compounds gave high enantioselectivities but phenyl-substituted substrates gave the adducts with only moderate *ee*.



Scheme 1.73. Thiourea catalyzed aza-Michael addition of hydroxylamines.

Moreover, carbon-nucleophiles have been added to α,β-unsaturated substrates using organocatalysts. An illustrative example leading to β-amino acids pertains to the addition of malonates to α,β-unsaturated nitroalkenes catalyzed by thiourea **1.291** (scheme 1.74).[124] The products **1.287** were obtained with high enantioselectivity. Subsequent Baeyer-Villiger oxidation gave the corresponding ester **1.288**, and a subsequent reduction with DIBAL-H provided the diol **1.289**, which was oxidatively cleaved. Finally, the nitro group was reduced to give the free amino acid **1.290**.



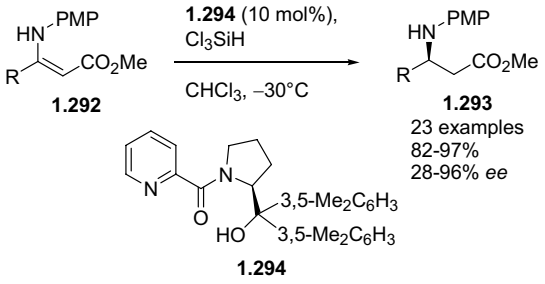
Scheme 1.74. Thiourea-catalyzed aza-Michael addition of malonates to nitroalkenes.

The organocatalytic addition of amine nucleophiles to α,β-unsaturated carbonyl compounds proceeds generally with very high enantioselectivities. However, relatively high catalyst loadings of 20-30% are employed. A major challenge is to further optimize the organocatalyzed conjugate addition of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds with regard to catalyst loading and substrate scope. This reaction represents a fast atom-economic entry towards the synthesis of β-amino acids; many synthetically useful Michael adducts might be made readily in enantiomerically pure form *via* conjugate additions.

1.3.3 Miscellaneous

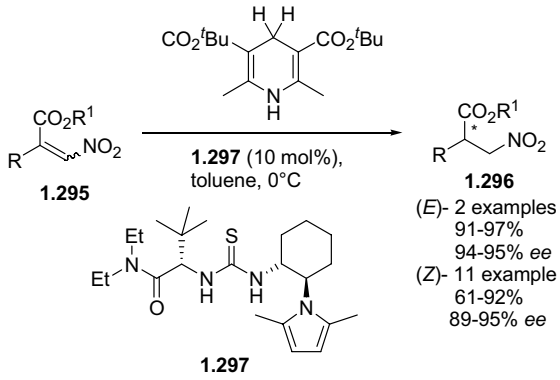
Several other reaction types were used for the synthesis of β-amino acids using organocatalysts such as substituted proline derivatives, cinchona alkaloids, thioureas and *N*-heterocyclic carbenes.

For instance, Lewis base **1.294** catalyzes the hydrosilylation of β-enamino esters (scheme 1.75).[125] The aromatic, aliphatic or cyclic (*Z*)-enamino esters **1.292** were hydrosilylated using trichlorosilane to give the corresponding β^3-amino esters **1.293** in high yield with high enantiomeric excess.



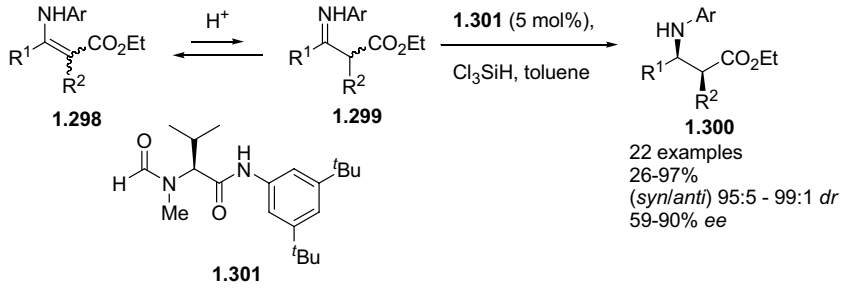
Scheme 1.75. Organocatalytic hydrosilylation of enamino esters.

List and coworkers studied the transfer hydrogenation of β-nitroalkenes catalyzed by thiourea **1.297** (scheme 1.76).[126] The Hantztsch ester was used as hydrogen source, leading to β-amino acid precursors **1.296** with high enantiomeric excess when (*E*)-alkenes were used, and high *ee* of the opposite enantiomer starting from (*Z*)-alkenes.



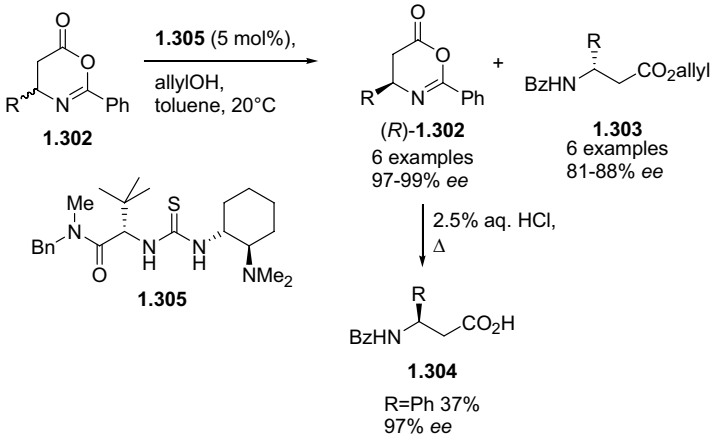
Scheme 1.76. Thourea catalyzed conjugate reduction of nitroalkenes.

An alternative approach to β-amino acids based on a dynamic kinetic resolution was applied in the reduction of enamines with trichlorosilane (scheme 1.77).[127] α-Amino acid derived amide **1.301** was used in the reduction with trichlorosilane of imines **1.299** which are in equilibrium with the corresponding enamines **1.298**. The *syn*-$\beta^{2,3}$-amino esters **1.300** were isolated with high *dr* (>99:1) and high *ee* (90%).



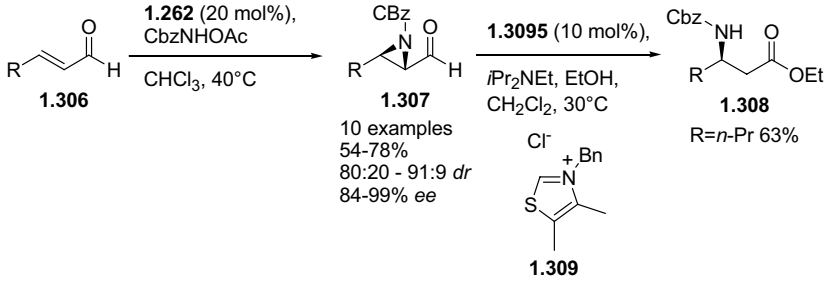
Scheme 1.77. Dynamic kinetic resolution of enamines towards β-amino acid derivatives.

Thiourea catalyst **1.305** was studied by Berkessel and coworkers for the kinetic resolution of racemic oxazinones **1.302** (scheme 1.78).[128] With up to 57% conversion, the chiral remaining oxazinones **1.302** were isolated with >99% *ee* and the ring-opened β^3-amino ester **1.303** with 84% *ee*. When the reaction was driven to 25% conversion, the ring-opened product had 96% *ee*. Using hydrolytic workup, the *N*-benzoyl-β-amino acid **1.304** was isolated with 97% *ee*.



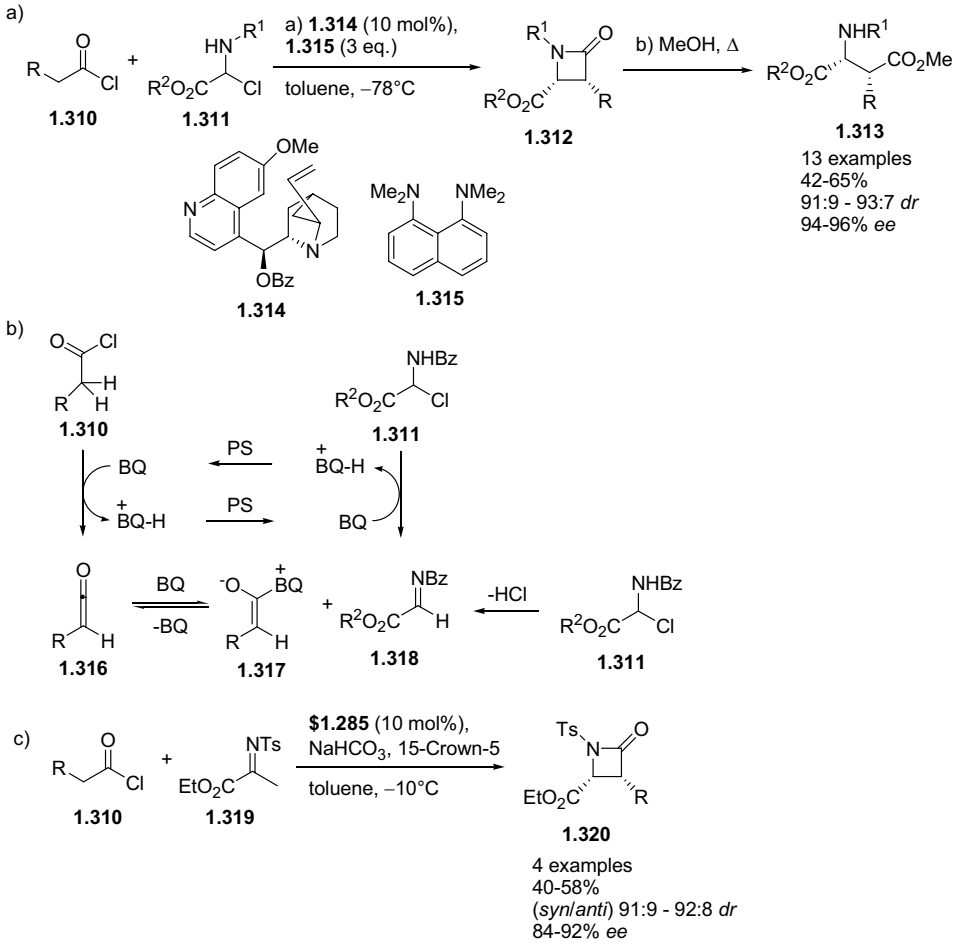
Scheme 1.78. Organocatalytic kinetic resolution of oxazinones.

Córdova and coworkers reported that proline derivative **1.262** catalyzes the aziridination of α,β-unsaturated aldehydes (scheme 1.79).[129] The α,β-aziridine aldehydes **1.307** were obtained in a highly enantioselective transformation (up to 99%), and were converted in one step into the corresponding Cbz-protected amino esters **1.308** in the presence of an *in situ* generated thiazolium catalyst **1.309**.



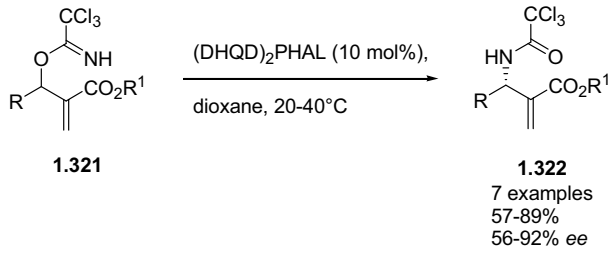
Scheme 1.79. Organocatalytic aziridination of α,β-unsaturated aldehydes.

A multistage, one-pot procedure was used for the synthesis of α,β-amino diesters (scheme 1.80a).[130] A proposed mechanism involves dehalogenation of **1.310** catalyzed by benzoylquinine (BQ) **1.314** and stoichiometric amounts of proton sponge (PS) **1.315**, resulting in the formation of imine **1.318** (scheme 1.80b). This reacts subsequently with enolate **1.317** derived from carboxylic acid chloride **1.310** *via* ketene **1.316**. The obtained β-lactam **1.312** undergoes ring opening upon treatment with methanol to yield aspartic acid derivative **1.313**. Moreover, in one step, β-lactams were synthesized from preformed imines **1.319** and acylchloride catalyzed by benzoylquinine **1.320** in the presence of stoichiometric amounts of base and 15-crown-5 (scheme 1.80c).[131]



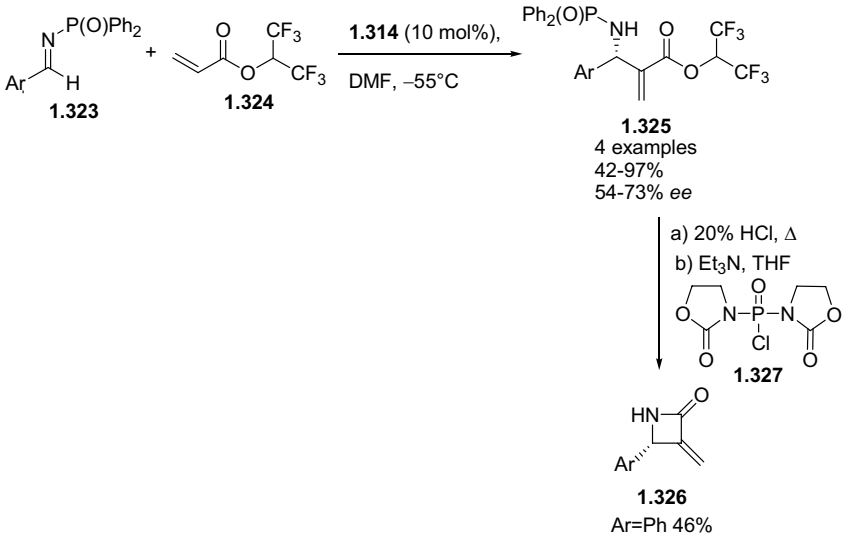
Scheme 1.80. Multistage one-pot procedure for the synthesis of β-lactams catalyzed by benzoylquinine.

Jørgensen and coworkers used the [1,3]-sigmatropic rearrangement of *O*-allylic trichloroacetimidates **1.321** to synthesize *N*-protected β-amino esters **1.322** catalyzed by dihydroquinidine $(DHQD)_2PHAL$ (scheme 1.81).[132] The products of the rearrangement were obtained in good yield with *ee* (up to 92%).



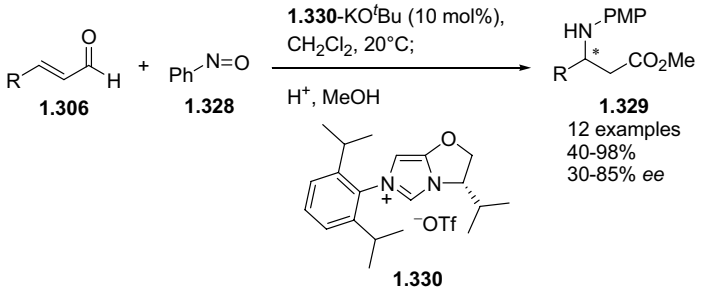
Scheme 1.81. [1,3]-Sigmatropic rearrangement for the synthesis of β-amino esters.

Chiral nucleophilic quinidine catalyst **1.314** has been employed in the asymmetric aza-Baylis-Hillman reaction (scheme 1.82).[133] Aromatic imine **1.323** and activated alkene **1.324**, 1,1,1,3,3,3-hexafluoroisopropyl acrylate, were reacted to give the Baylis-Hillman adducts **1.325** in moderate yield with moderate enantiomeric excess (up to 73%). Subsequent hydrolysis and and ring closure upon treatment with BOPCl **1.327** gave β-lactam **1.326**.



Scheme 1.82. Aza-Baylis-Hillman reaction for the synthesis of β-lactams.

N-Heterocyclic carbene **1.330** was shown to catalyze the addition of nitrosobenzene to α,β-unsaturated aldehydes *via* a reaction involving umpolung of **1.306**. This transformation gives isooxazolidinone intermediates which were hydrolyzed under acidic conditions to the corresponding methyl ester **1.329** (scheme 1.83).[134]



Scheme 1.83. Addition of α,β-unsaturated aldehydes to nitrosobenzene catalyzed by N*-heterocyclic carbenes.*

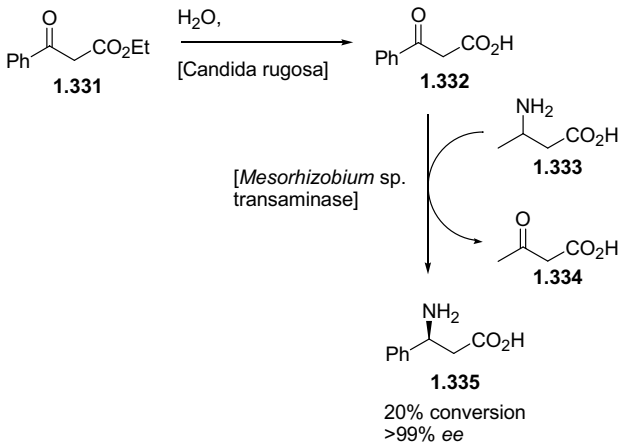
In this section routes to β^2- and β^3-amino acids and β-lactames based on a variety of methods including (transfer)hydrogenation, aziridination, (dynamic) kinetic resolution, one-pot reactions of imines with enolates, 1,3-sigmatropic rearragement, aza-Baylis-

Hillman reaction and umpolung of α,β-unsaturated aldehydes were discussed. In most cases, this reactions have limited scope so far to prepare specific β-amino acid presursors or β-lactams.

1.4 Biocatalytic routes

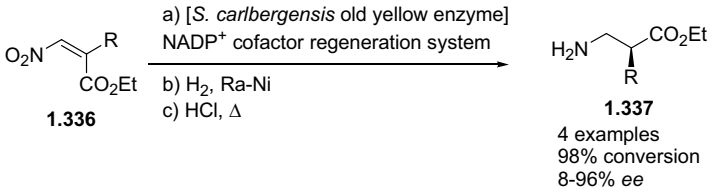
There are only few recent biocatalytic methods reported for the synthesis of β-amino acid apart from kinetic resolutions.[135] The biocatalytic preparation of enantiopure β-amino acids has been reviewed in 2006,[135] therefore, this part will focus on non-kinetic resolutions since 2006.

A β-transaminase from *Mesorhizobium* sp. LUK was cloned and characterized as new biocatalyst for the synthesis of β-amino acids (scheme 1.84).[136] However, only phenyl substituted β-ketoester **1.331** was screened as presursor in combination with a lipase from *Candida rugosa* which catalyzes the hydrolysis of **1.331** to β-keto acid **1.332** being the substrate for the transamination**.** Racemic β-alanine was used as nitrogen source and β-phenylalanine **1.335** was obtained after low conversion (20%) albeit with 99% *ee*.



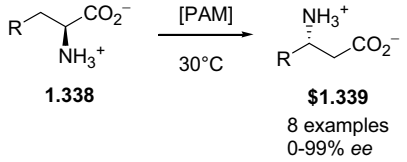
Scheme 1.84. Transaminase catalyzed synthesis of β-phenylalanine.

Saccharomyces carlsbergensis old yellow enzyme was studied in the asymmetric bioreduction of β-nitroacrylates (scheme 1.85).[137] NADPH was supplied by a cofactor regeneration system (glucose-6-phosphate/bakers yeast glucose-6-phosphate dehydrogenase). (*Z*)-Alkenes substituted in α-position to the carboxylate with ethyl-, propyl or *iso*-propyl groups were reduced with high conversion and high *ee* (up to 96%). Subsequent hydrogenation and acidic hydrolysis gave the corresponding β^2-amino acids **1.337**. The scope is limited to short aliphatic substituents (Me, Et, *n*-Pr, *i*-Pr)



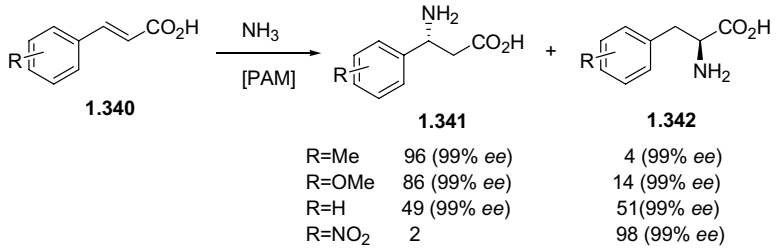
Scheme 1.85. Synthesis of β²-amino acids via *bioreduction.*

β-Styryl- and β-aryl-β-alanine derivatives have been synthesized using phenylalanine amino mutase (PAM) (scheme 1.86).[138] Aromatic and heteroaromatic α-amino acids were employed to synthesize the corresponding β-amino acids with high enantioselectivity,[139] however no isolation of the β-amino acids was described.



Scheme 1.86. PAM catalyzed synthesis of β-amino acids from α-amino acids.

Janssen, Feringa and coworkers reported the use of PAM to catalyze the amination of cinnamic acid derivatives in a synthetic procedure for β-amino acids (scheme 1.87).[140] A mixture of α- and β-amino acids is obtained which were not separated from each other or isolated. With electron donating substituents in *para*-position of the aromatic ring, predominantly β-amino acids are formed.



Scheme 1.87. PAM catalyzed synthesis of β-amino acids form cinnamic acid derivatives.

Biocatalytic processes are a valuable addition to the organocatalytic and transition metal catalyzed methods for the synthesis of β-amino acids. Enantioselectivities are in general very high (>99%), but most enzymes have a small substrate scope so far. Additionally, in the reports discussed here, frequently the β-amino acids were not isolated, but only conversion was measured, and substantial work is required to make these methods applicable to synthetic organic chemistry.

1.5 Conclusion and outlook

The synthesis of β-amino acids remains a challenging target for organic chemists due to the importance of these building blocks as pharmaceuticals intermediates and peptidomimetics. In the past 15 years, tremendous progress has been made as shown in this review and preceeding overviews.[6-8] Using many different methodologies, β^2- and β^3-amino acids with various substitution patterns are now available. Organocatalysis has played an important role in recent years in the field of catalytic asymmetric synthesis and quickly provided a useful method to prepare β-amino acids, especially transformations based on the Mannich reaction. However, in many cases high catalyst loadings have to be used, and reaction times are in some cases rather long. On the other hand, one of the more promising catalysts, (*S*)-proline, is a naturally occuring amino acid, and therefore very cheap. Homogeneous catalysis using transition metals provided the most important methods in recent years to synthesize β-amino acids. Among them, the hydrogenation of enamines has been applied in industrial synthesis of β-amino acids because high turnover, high enantioselectivity and low catalyst loadings can be used. However, some transition metals are highly toxic and harmful for the environment. Therefore, biocatalysis would provide an important alternative, but up to now no enzymes are known that have a broad substrate scope in combinations with high turnover numbers. Most enzymatic methods rely on kinetic resolutions, which means that only 50% of the starting materials can be converted, unless a dynamic kinetic resolution protocol is used. Therefore, the catalytic asymmetric synthesis of β-amino acids starting from simple and cheap starting materials and using recycable sustainable catalysts remains an important challenge for synthetic organic chemists.

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