Recent Advances in the Catalytic Asymmetric Synthesis of .beta.-Amino Acids

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

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In this *critical review*, the progress in catalytic asymmetric synthesis of β-amino acids is discussed, covering the literature since 2002. The review treats transition metal catalysis, organocatalysis and biocatalysis and covers the most important synthetic methods, such as hydrogenation, the Mannich reaction and conjugate additions (160 references).

1.1 Introduction

β-Amino acids are key structural elements of peptides, peptidomimetics and many other physiologically active compounds.[1] Notably, β-amino acids are precursors for β-lactams, the most important class of antibiotics.[2] Although some β-amino acids themselves show interesting pharmacological properties, usually they are intermediates *en route* to more complex products with biological and pharmacological activity. In recent years, it has become clear that peptides based on β-amino acids have secondary structures comparable to their α-amino acid analogues, but are not vulnerable towards proteases.[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-aminopropionic acid core (Fig. 1).[4] In addition, cyclic amino acids have the amino group integrated in a ring, as is the case in β-proline.[5]

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 the asymmetric synthesis of β-amino acids before 2002 has been reviewed by Liu and Sibi,[6] and described in the book *Enantioselective synthesis of β-amino acids* edited by Juaristi and Soloshonok in 2005.[7,8] Seebach and co-workers recently described the preparation of β^2-amino acids for β-peptide synthesis.[9] Ma discussed earlier developments in the catalytic asymmetric synthesis of α- and β-amino acids in 2003 in a minireview.[10] Therefore, this review is focused on catalytic asymmetric synthesis using transition metals, organocatalysts and biocatalysts, covering the literature since 2002. Methods based on chiral auxiliaries and kinetic resolution (biocatalysis) are not discussed herein.

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1.2 Metal catalysis

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

1.2.1 Hydrogenation

The enantioselective hydrogenation of β-substituted-β-(amino)-acrylates has been extensively discussed (Scheme 1).[11] Therefore,

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Wiktor Szymański

Wiktor Szymański received his PhD degree from The Warsaw University of Technology, Poland, in 2008, under the supervision of Prof. Ryszard Ostaszewski. Since then, he has been working with Prof. Dick B. Janssen and Prof. Ben L. Feringa at the University of Groningen. His work focuses on the use of biotransformations in organic chemistry and the construction of bioconjugates.

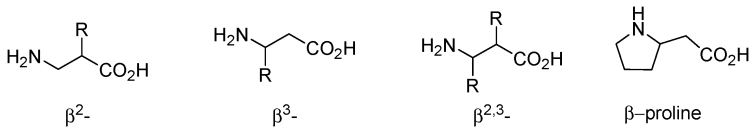
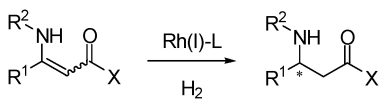


Fig. 1 General structure of β-amino acids.

this part concerning catalytic asymmetric hydrogenation is kept relatively brief, focusing on key recent contributions.

The geometrical isomers of the β-(amino)acrylates show different reactivity and selectivity in metal-catalyzed hydrogenations: reactions of (*E*)-isomers generally lead to higher enantioselectivities, and (*Z*)-isomers frequently react faster, although the enantioselectivity is sometimes lower.[11]



Scheme 1 Rhodium-catalyzed hydrogenation of (*E*)- and (*Z*)-β-dehydroamino acid derivatives.

Dick B. Janssen

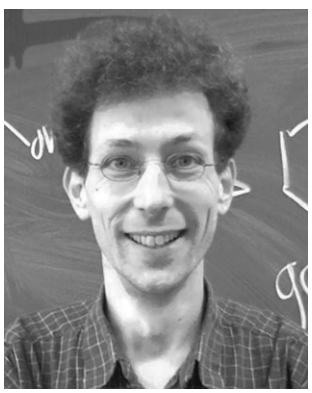
Dick B. Janssen received an MSc in chemistry (1977) and a PhD in microbiology (1982) from the University of Nijmegen. After post doctoral work with Prof. Bernard Witholt in Groningen and a fellowship of the Royal Netherlands Academy of Sciences (KNAW) he became professor of Biotechnology at the University of Groningen in 1993. His research interests are enzyme discovery and engineering, biocatalysis, and biotransformation of synthetic compounds.

The first example of an asymmetric hydrogenation of *N*-acyl-β-(amino)acrylates was published in 1991 by Noyori and co-workers using $Ru(O_2CCH_3)_2$ and (*R*)-BINAP, providing >90% *ee*.[12] The advances in Ru- and Rh-catalyzed homogeneous hydrogenations have since then provided the standard procedure for the synthesis of β-amino acids, using a variety of chiral bidentate and monodentate phosphorous ligands.[11–13] An important breakthrough by Hsiao and co-workers was the use of chiral ferrocenylphosphine ligand **3** in the hydrogenation of (*Z*)-enamine esters **1** with an unprotected amine group in trifluoroethanol (TFE) as solvent to yield the corresponding amino esters **2** with excellent *ee* (up to 97%) (Scheme 2).[14] This represents the first example of a high yielding enantioselective hydrogenation of unprotected β-enamine esters without the use of a directing protecting group.

A chiral BoPhoz-type ligand **5** was employed for the Rh-catalyzed hydrogenation of alkyl-(*E*)-β-phenyl-α-(phthalimidomethyl)acrylates **4** (Scheme 3).[15] The products were obtained in high yields and with excellent *ee*'s. In one of the cases, the corresponding β-amino acid was obtained in good yield upon cleavage of the phthalimide protecting group and hydrolysis of the ester functionality.

TangPhos **10** was employed in the synthesis of *N*-aryl-β-amino acids by Zhang and co-workers.[16] Starting from (*Z*)-enamines, the products were obtained with up to 96% *ee* using Rh-**10** in TFE (Scheme 4a). Furthermore, (*Z*)- and (*E*)-*N*-acyl-β-dehydroamino esters **1** were used as substrates for the hydrogenation with **10** as catalyst to give protected β^3-amino esters with high *ee*'s (Scheme 4b).[17]

The Rh-catalyzed enantioselective hydrogenation of (*E*)- and (*Z*)-β-acylamino acrylates using BDPMI **13** gave under

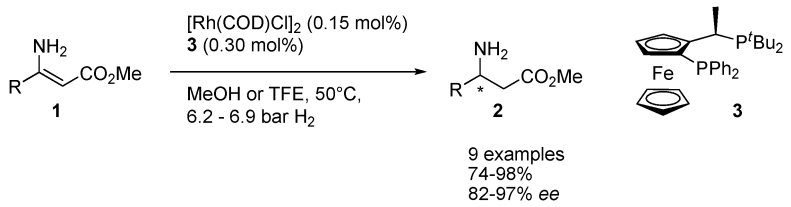


Adriaan J. Minnaard

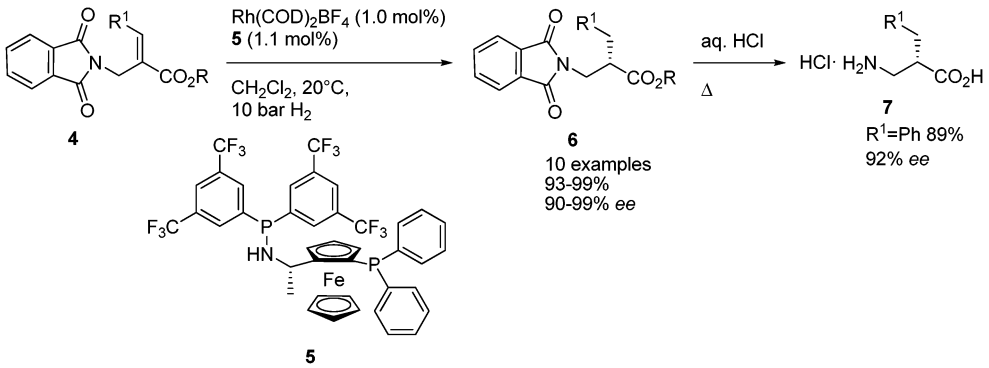
Adriaan J. Minnaard received his PhD degree from Wageningen Agricultural University, The Netherlands. He was a scientist at DSM-Research, from 1997 to 1999. Subsequently, he joined the University of Groningen in 1999 as an Assistant Professor in the department of Prof. Ben L. Feringa. In 2005, he was appointed Associate Professor and in 2009 Full Professor in Bio-organic Chemistry. In 2006 he was a guest researcher in the group of Prof. H. Waldmann at the Max Planck Institute for Molecular Physiology in Dortmund, Germany. His work focuses on asymmetric catalysis and natural product synthesis.

Ben L. Feringa

Ben L. Feringa obtained his PhD degree in 1978 at the University of Groningen in the Netherlands under the guidance of Professor Hans Wynberg. After working as a research scientist at Shell he was appointed full professor at the University of Groningen in 1988 and named the distinguished Jacobus H. van't Hoff Professor of Molecular Sciences in 2004. He was elected foreign honorary member of the American Academy of Arts and Sciences and member of the Royal Netherlands Academy of Sciences. His research interests include stereochemistry, organic synthesis, asymmetric catalysis, molecular switches and motors, self-assembly and nanosystems.



Scheme 2 Rhodium-catalyzed hydrogenation of unprotected enamines.



Scheme 3 Rh-BoPhoz-catalyzed hydrogenation of phthalimide-protected enamines.

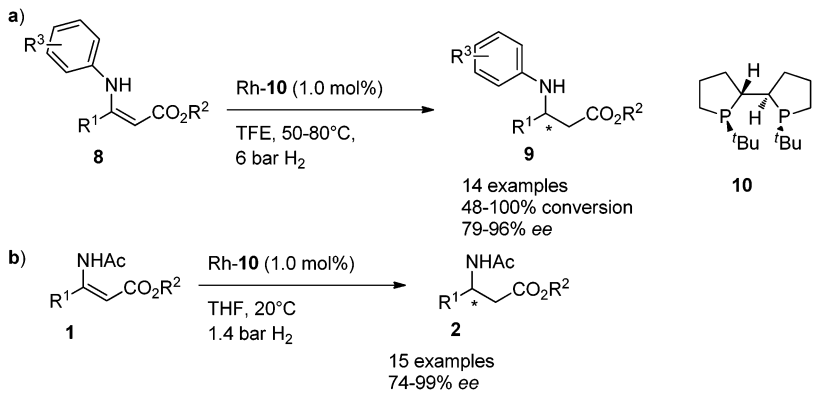
mild conditions *ee*'s of up to 97% and 92%, respectively (Scheme 5).[18]

Börner and co-workers used 1,3-diphenyl-1,3-bis(diphenylphosphino)propane **15** in the hydrogenation of (*E*)-enamines to give β^3-amino esters with up to 97% *ee* (Scheme 6).[19,20] The use of (*Z*)-enamines as substrates leads to significantly lower enantioselectivities (*ee*'s up to 75%).[19]

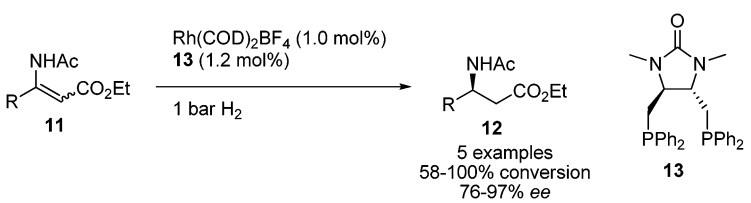
MalPhos **17** was very effective in the Rh-catalyzed hydrogenation of (*E*)-enamines, providing 99% *ee* and for the corresponding (*Z*)-enamines up to 90% *ee*'s were reached (Scheme 7).[21] Me-DuPhos **18** also gave high *ee*'s with these (*E*)-enamines, but the *ee*'s in the hydrogenation of (*Z*)-enamines were lower (up to 88%).

Et-Duphos gave high *ee*'s in the hydrogenation of α-aminomethyl acrylates **19** yielding β^2-amino acid derivatives (Scheme 8),[22] while Tangphos gave similar *ee*'s.

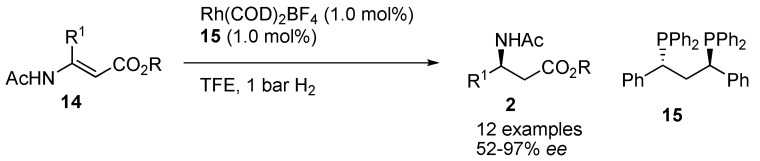
Moreover, Chan and co-workers used the Ru-complex of dipyridyl–phosphine ligand **22** for the hydrogenation of (*E*)- and (*Z*)-β-(acylamino)acrylates **11** (Scheme 9).[23] The use of (*E*)-substrates leads to high conversion and *ee*'s in MeOH as solvent, while the (*Z*)-enamines gave the best results in THF as solvent, but in general lower *ee*'s were found.



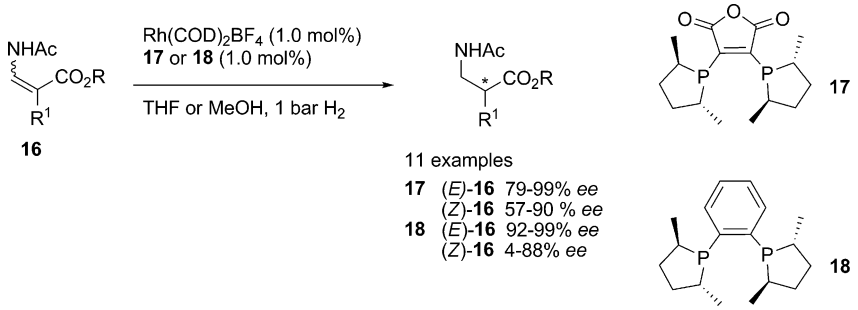
Scheme 4 Rhodium–Tangphos-catalyzed hydrogenation of (*Z*)-enamines.



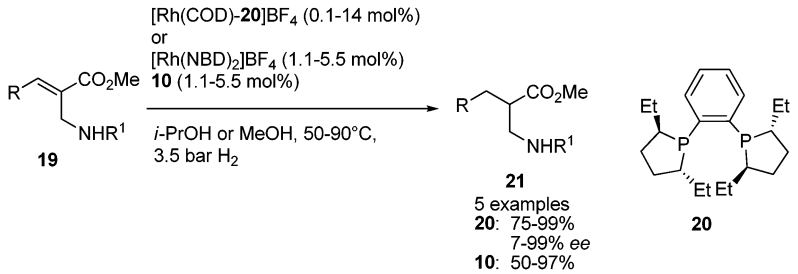
Scheme 5 Rhodium–BDPMI-catalyzed hydrogenation of (*E*)- and (*Z*)-enamines.



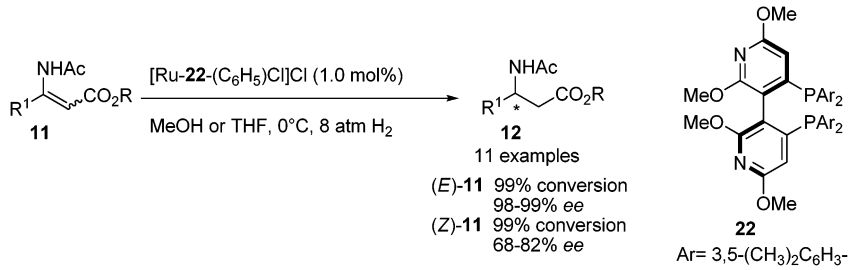
Scheme 6 Rhodium–bis-diphenylphosphino-propane-catalyzed hydrogenation of (*E*)-enamines.



Scheme 7 Rhodium-catalyzed hydrogenation of (*E*)- and (*Z*)-enamines with MalPhos and Me-DuPhos.



Scheme 8 Hydrogenation of α-aminomethyl acrylates catalyzed by Et-Duphos and Tangphos.



Scheme 9 Ru–dipyridyl-phosphine ligand-catalyzed hydrogenation of (*E*)- and (*Z*)-enamines.

An *ortho*-substituted BINAPO ligand **23** was used by Zhang and co-workers for the Ru-catalyzed hydrogenation of β-aryl-substituted β-(acylamino)acrylates **11** with high *ee*'s (Scheme 10).[24]

Chan and co-workers also investigated different diastereomers of bridged atropisomeric biphenyl-based diphosphine ligands for the Ru-catalyzed hydrogenation of (*E*)-*N*-acyl-protected enamines **14** (Scheme 11).[25] The use of ligands **24–27** provides the β-amino ester derivatives **12** with excellent *ee*'s.

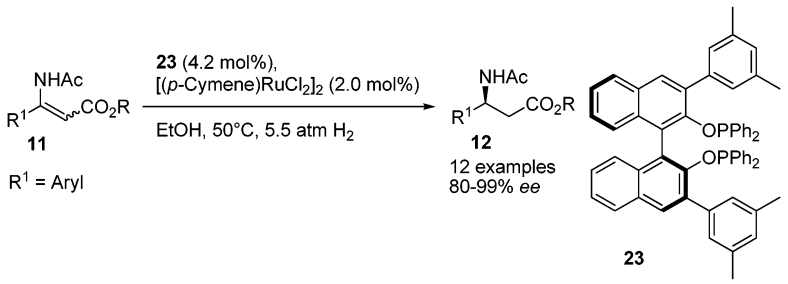
Zhang and co-workers introduced bisphosphepine ligand **29**, that was used in the catalytic hydrogenation of (*Z*)-enamines with excellent enantioselectivity (*ee* >99%) (Scheme 12).[26] In contrast, (*E*)-enamines give only low enantioselectivity (*ee* 32%) using the same catalyst system.

Using (*S*)-C3-TunaPhos **32** as ligand in a ruthenium catalyzed reaction, Zhang and co-workers prepared cispentacin analogues with excellent *ee* (up to 99%) (Scheme 13).[27] In the same reaction, TangPhos **10** and Me-DuPhos **18** gave cispentacin derivative **33** with significantly lower enantiomeric excess.

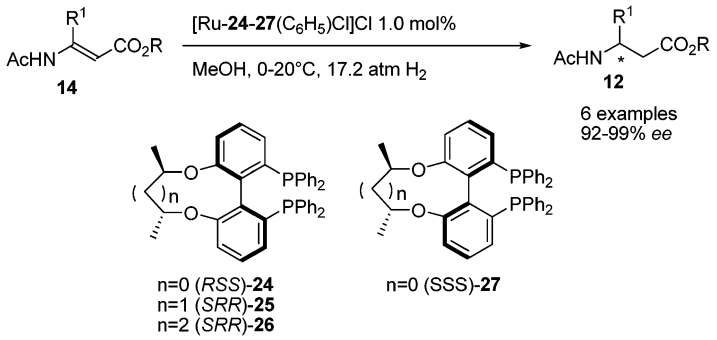
The use of monodentate ligands such as phosphites, phosphoramidites and other phosphorous ligands has also resulted in high enantioselectivities in Rh-catalyzed hydrogenations.[28] β^2-Amino acid derivatives are formed with up to 99% *ee* when phthalimide protected acrylates are hydrogenated using carbohydrate-phosphite **35** (Scheme 14).[29]

Several phosphite ligands were screened for the hydrogenation of **11**; compound **37** was identified as the optimal ligand (Scheme 15). Hydrogenation of (*E*)-enamines with ligand **37** gave the products **2** with up to 98% *ee*, but the corresponding (*Z*)-enamines led to amino esters with only up to 61% *ee*.[30]

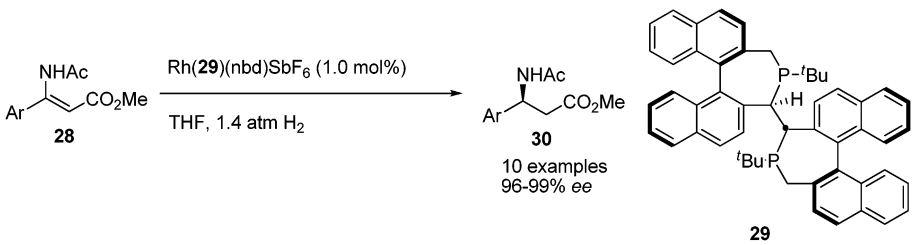
The use of monodentate phosphoramidite ligands in the rhodium-catalyzed hydrogenation of (*E*)/(*Z*)-β-dehydroamino



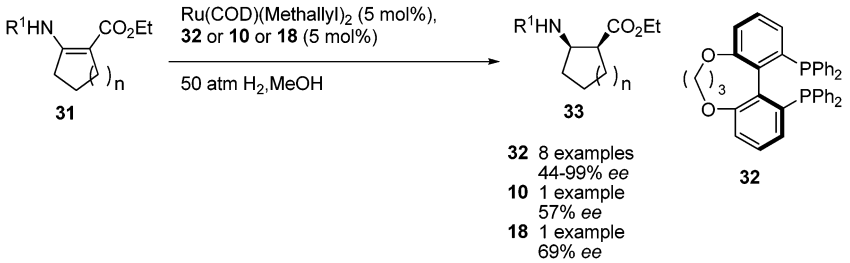
Scheme 10 Ru-catalyzed hydrogenation of enamines with a BINAPO ligand.



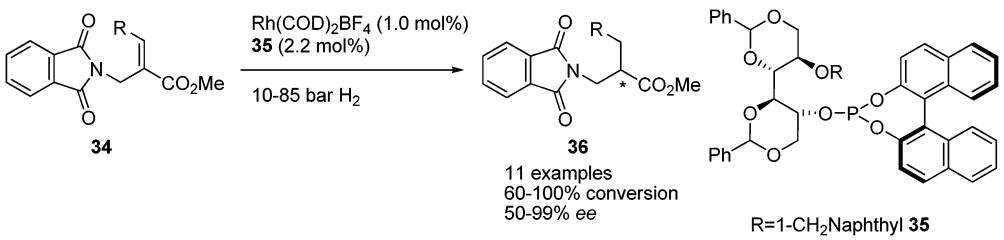
Scheme 11 Ru-bridged biphenyl-based diphosphine-catalyzed hydrogenation of (*E*)-enamines.



Scheme 12 Rhodium-catalyzed hydrogenation of (*Z*)-enamines using bisphosphepine ligands.

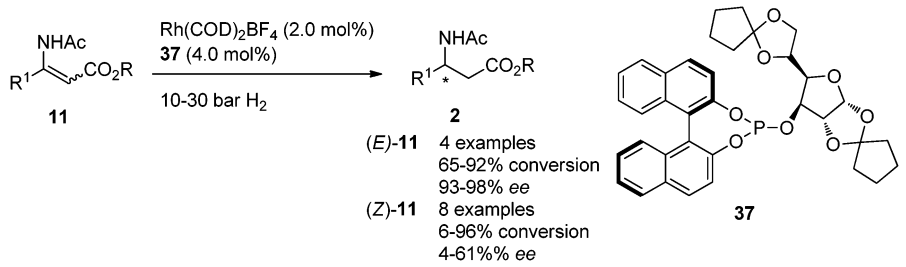


Scheme 13 Ru-catalyzed hydrogenation towards cyclic β-amino acids.



Scheme 14 Rh-catalyzed hydrogenation of phthalimide-protected aminoacrylates.

acids has been described by Feringa, Minnaard, de Vries and co-workers (Scheme 16).[11,31] The use of ligand **38** leads to β-amino acid precursors with excellent enantioselectivities for (*E*)-substrates, while a slight modification in the amine



Scheme 15 Rh–phosphite-catalyzed hydrogenation of aminoacrylates.

backbone of the ligand leads to very high enantioselectivities in the hydrogenation of (*Z*)-substrates.

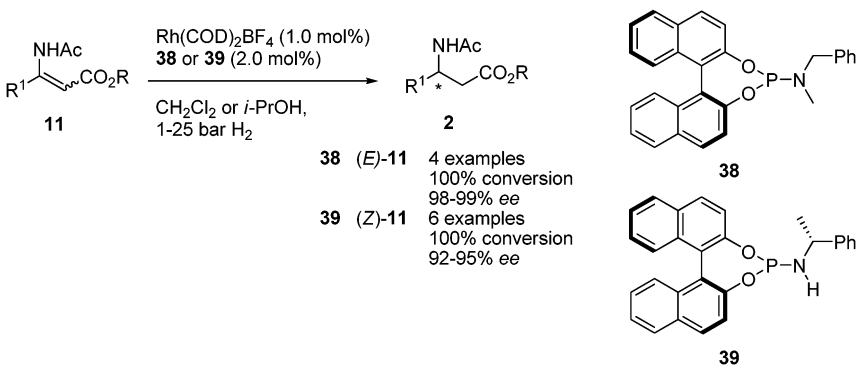
The mixed ligand approach has been employed in the hydrogenation catalyzed by rhodium–phosphoramidite complexes in order to further enhance the enantioselectivity (Scheme 17).[11,31,32] Hereby, three different catalysts are in equilibrium with one another, namely the two homo-complexes Rh–L^AL^A and Rh–L^BL^B and the hetero combination Rh–L^AL^B. Enhanced enantioselectivities are observed when Rh–L^AL^B is more active and more selective than each of the homo combinations.[33] Chiral phosphoramidite **41** in combination with achiral tris-*o*-tolyl-phosphine was used for the synthesis of β^2-amino acids using the unprotected carboxylic acids **40** (Scheme 17).

The combination of Ir(I) and phosphoramidite ligand **43** has been used by Beller and co-workers in the hydrogenation of (*E*)- and (*Z*)-*N*-(acylamino)acrylates, giving the product with up to 94% and 67% *ee*, respectively (Scheme 18).[34]

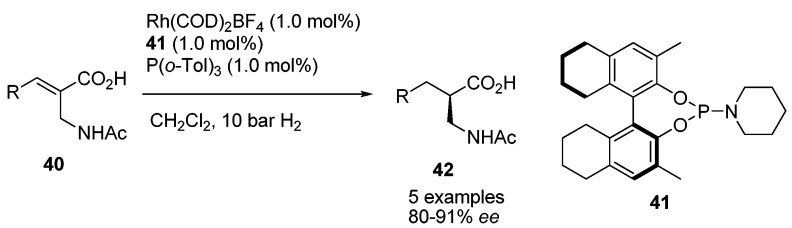
As demonstrated previously[11] and discussed in the preceding paragraphs, the catalytic asymmetric hydrogenation of β-dehydroamino acids represents an important, highly atom-economical tool for the synthesis of β^2- and β^3-amino acids. Excellent enantioselectivities have been achieved starting from both (*E*)- or (*Z*)-*N*-acyl enamines while the catalyst loading usually does not exceed 1.0 mol%. Asymmetric hydrogenation, in addition, is a reaction that can be easily scaled up. Up to now, the widest scope was obtained with bidentate phosphine and monodentate phosphoramidite ligands in combination with rhodium and ruthenium. Moreover, the mixed ligand approach offers new prospects in asymmetric hydrogenation, in particular for the combination of chiral and achiral monodentate ligands. *N*-acyl enamido esters are the most frequently used substrates, which implies the necessity to remove these protecting groups afterwards. Therefore, strategies in which these protecting groups are avoided are very important. A drawback of asymmetric hydrogenation is the use of transition metals, which are expensive and can limit their use in the pharmaceutical industry, where strict regulations apply to the levels of heavy metals in drug intermediates.

1.2.2 Mannich reaction

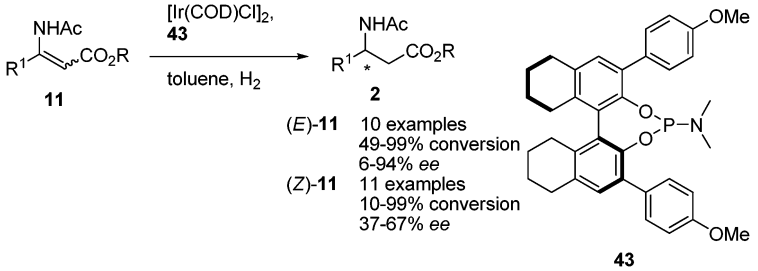
The Mannich reaction is an important C–C bond-forming reaction involving the addition of metal enolates of carbonyl



Scheme 16 Rh–phosphoramidite-catalyzed hydrogenation of *N*-acyl-(*E*)- and (*Z*)-enamines.



Scheme 17 Mixed ligand approach towards β-amino acids.



Scheme 18 Ir–phosphoramidite-catalyzed asymmetric hydrogenation.

compounds to imines.[35,36] 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.[35] Earlier work relied on the stoichiometric use of chiral auxiliaries.

Sodeoka and co-workers published in 2005 the addition of β-ketoesters to various imines catalyzed by a chiral cationic palladium complex (Scheme 19).[37] The catalysts derived from SegPhos **46** and BINAP **47** were investigated. Two vicinal stereogenic centers are created in this reaction; high diastereomeric ratios (up to 95 : 5) are obtained, along with excellent *ee*'s (up to 99%). Besides 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 excellent selectivities, *i.e.* up to 99% *ee* and a *dr* of 95 : 5.

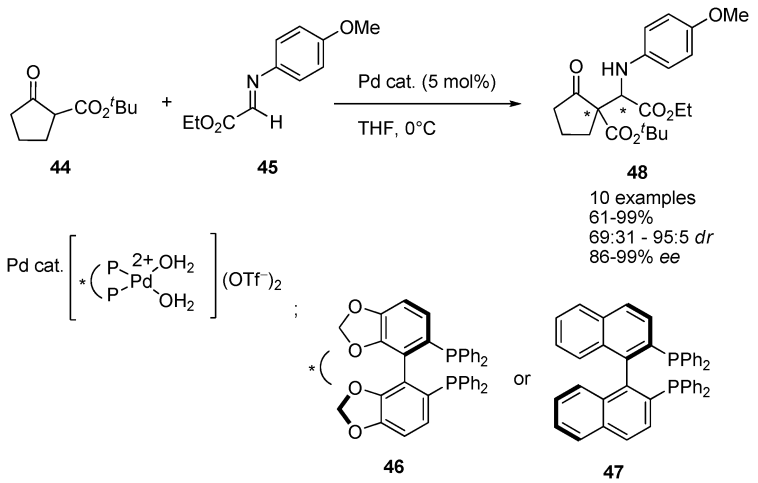
Diethylzinc and bridged-Binol **51** form *in situ* the active catalyst that has been used by Shibasaki and co-workers in the *anti*-selective Mannich reaction of hydroxyketone **50** with *N*-substituted imines **49** (Scheme 20).[38] The *anti*-Mannich products **52** are obtained with high diastereomeric ratio and high enantiomeric excess from imines with aromatic, heteroaromatic, (*E*)-cinnamyl and cyclopropyl groups. The β-amino ketones were transformed into the corresponding β-amino ester derivatives **53** by Baeyer–Villiger oxidation.

Trost and co-workers used chiral dinuclear catalysts **56–58** for the synthesis of β-*syn*-amino-α-hydroxy ketones **59** from α-hydroxy ketones and glyoxalate imines or aldimines (Scheme 21).[39] The adducts were obtained with moderate to high *dr*'s and with high *ee*'s, and could be transformed into β-amino acid derivative **60** in three steps. The structure of the ligand had to be slightly modified in order to achieve high *ee*'s for all classes of substrates.

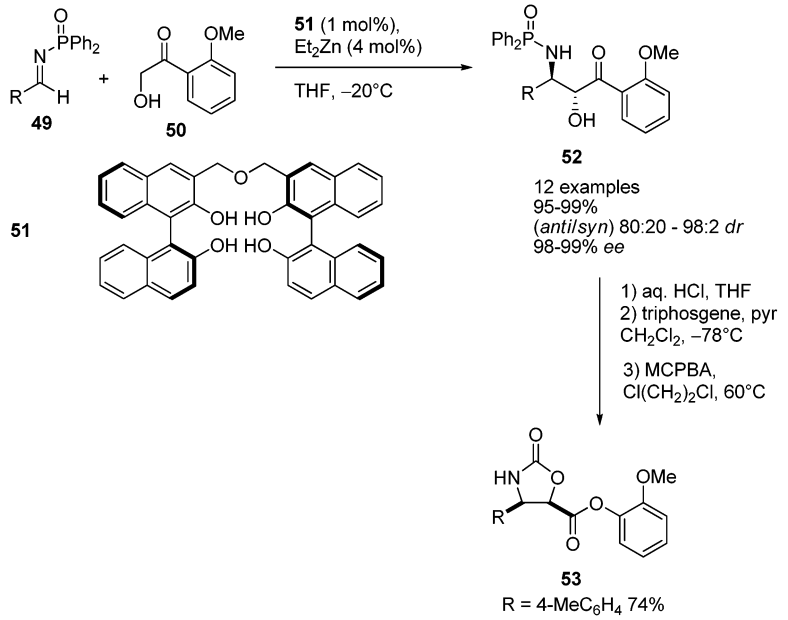
Shibasaki and co-workers also used the bridged-binol complex **51** with In(III) as a catalyst in the addition of *N*-(2-hydroxyacetyl)pyrrole **62** to various imines **61** (Scheme 22).[40] The diastereomeric ratio was found to depend on the imine used. In general, the *syn* adducts **63** were obtained 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*-substituted aryl imines. The *N*-acyl-pyrrole group was transformed under basic conditions to the corresponding ethyl ester to give *syn*-α-hydroxy-β-amino esters **64**.

Moreover, La(III)–*i*Pr-pybox **67** was studied by Shibasaki and co-workers in the direct asymmetric Mannich reaction of trichloromethyl ketones **66** and pyridyl- or thienylsulfonyl-protected imines **65** (Scheme 23).[41] The *syn* isomers were preferentially formed with high *ee* (up to >99%) using the thienylsulfonyl protecting group. Aliphatic, aromatic and heteroaromatic imines were employed as substrates. The product **68** was transformed into the *N*-Boc protected β^2-amino ester **69** by a nucleophilic displacement of the trichloromethyl anion and subsequent Boc-protection of the amino group.

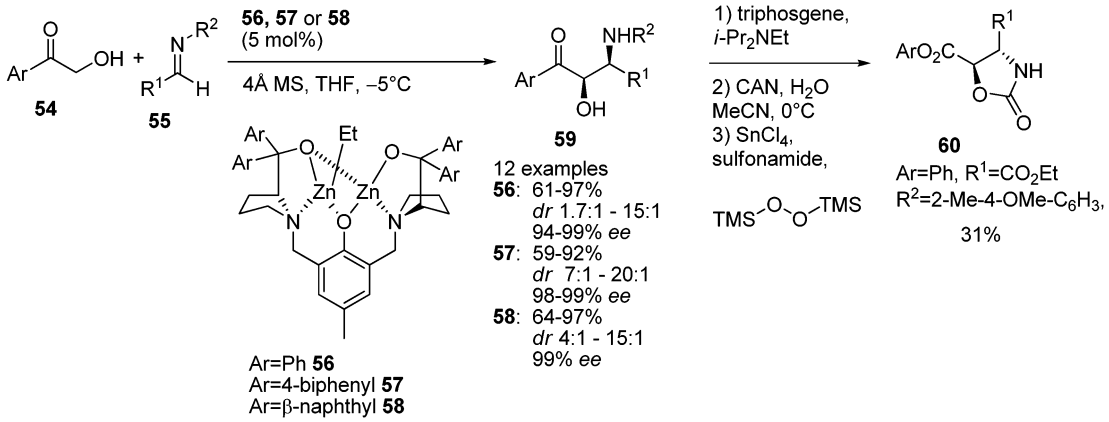
The same group investigated homodinuclear Ni–Schiff base complex **72** for the synthesis of tetrasubstituted *anti*-α,β-diamino acids (Scheme 24).[42] Boc-protected aromatic, heteroaromatic



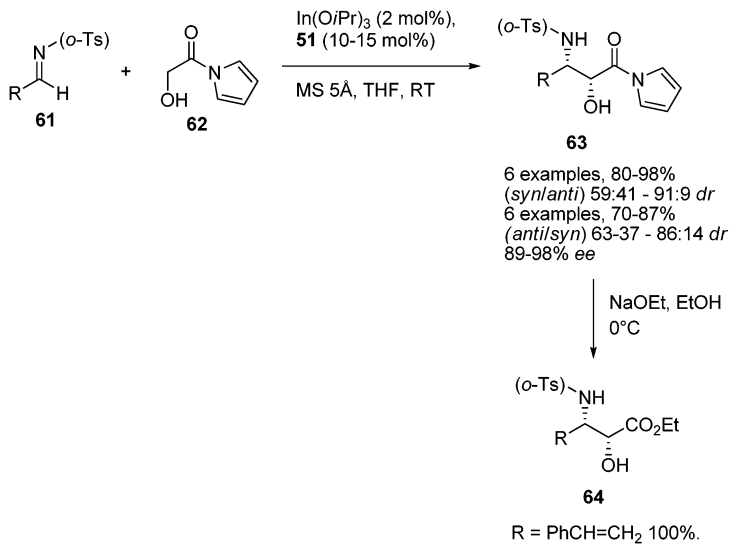
Scheme 19 Pd-catalyzed addition of β-ketoesters to α-imino esters.



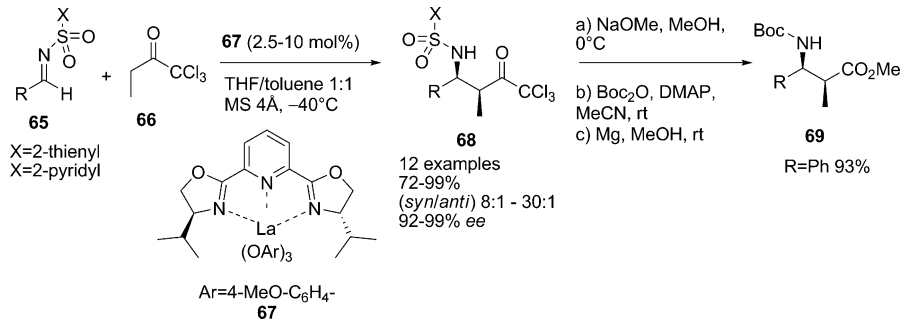
Scheme 20 Zn-catalyzed addition of hydroxyketones to imines.



Scheme 21 Mannich reaction of hydroxy ketones and imines catalyzed by a dinuclear Zn-species.



Scheme 22 In-catalyzed addition of *N*-(2-hydroxyacetyl)pyrrole to imines.



Scheme 23 La-catalyzed addition of trichloromethyl ketones to imines.

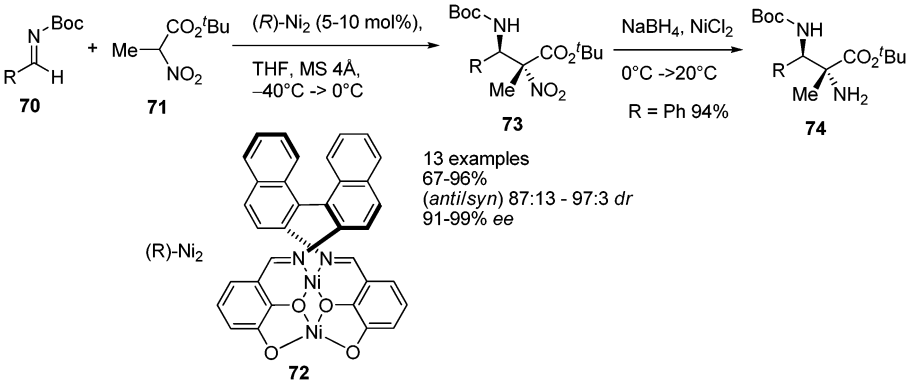
and aliphatic imines **70** gave with **71** the corresponding adducts **73** with high *dr*'s (up to 97 : 3) and high *ee*'s (up to 99%). Using $NaBH_4$–$NiCl_2$, the nitro group was reduced to provide the α,β-diamino esters **74**.

The Jørgensen group introduced Cu–phosphino–oxazoline complex **76** for the catalytic asymmetric Mannich reaction of glycine derivatives **75** and imines **61** (Scheme 25).[43] 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 **77** were obtained with $CuClO_4$ as a metal salt in the presence of molecular sieves.

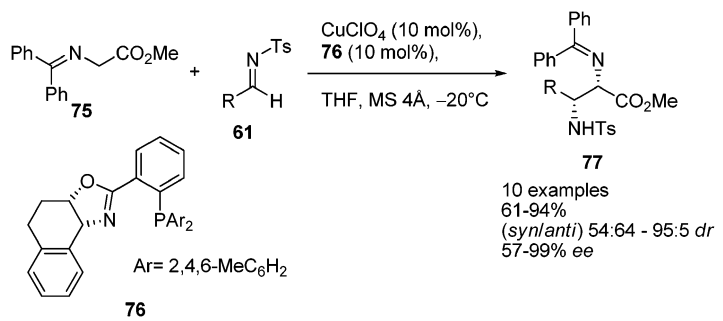
Furthermore, the group of Kobayashi investigated copper salts in the direct three-component Mannich reaction producing protected α,β-diamino esters using Me-Duphos **18** as a ligand (Scheme 26).[44] A simple aromatic and enolizable aliphatic aldehyde **78**, a secondary amine **79** and a glycine derivative **75** are used as starting materials in this transformation. The use of (*R*,*R*)-Me-Duphos leads to a 1 : 1 mixture of *syn*/*anti* diastereoisomers with 75% and 77% *ee*, respectively.

The Shibasaki group used a copper complex of ligand **82** to catalyze the direct Mannich reaction of thioamides **81** to yield β-amino-thioamides **83** with good *ee*'s (Scheme 27).[45] The corresponding β-amino thioester derivative **84** could be synthesized in one step from these Mannich adducts.

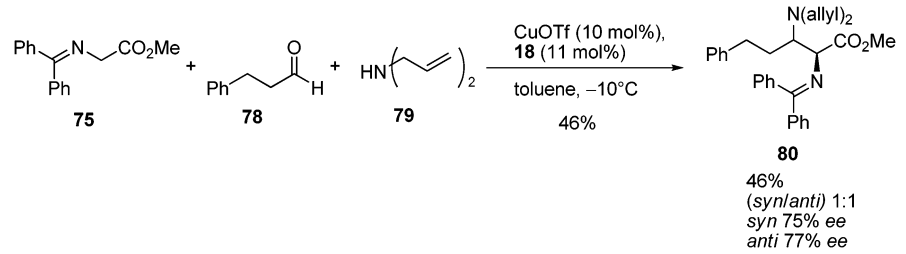
In the asymmetric Mannich-type reaction of *N*-acylimino esters **85** and silyl enol ethers **86**, Kobayashi and co-workers have studied copper–diamine complex **87** as catalyst (Scheme 28).[46] The Mannich adducts were obtained in high yields and frequently with high *ee*'s. In the reactions of α-substituted silyl enol ethers, the desired *syn* adducts were obtained again with high enantio- and diastereomeric excess.



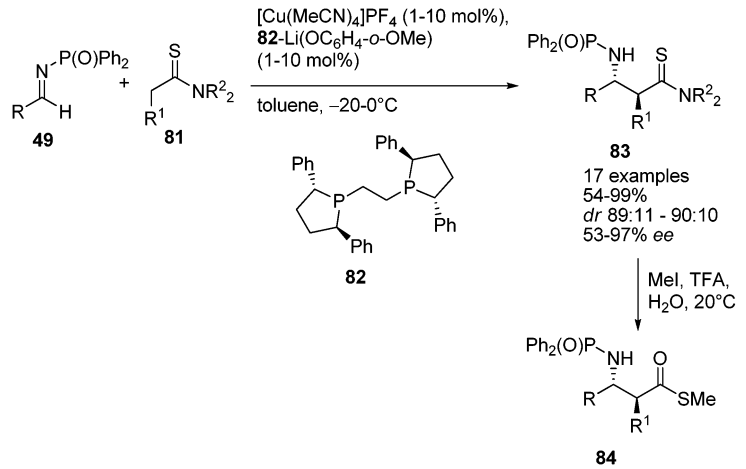
Scheme 24 Ni-catalyzed addition of nitroacetate to imines.



Scheme 25 Cu-catalyzed addition of glycine derivatives to imines.



Scheme 26 Cu-catalyzed three-component Mannich reaction of a glycine derivative, aldehyde and amine.

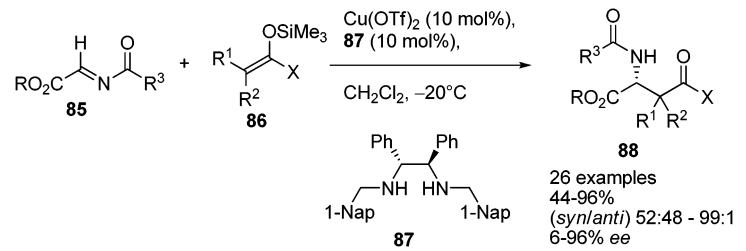


Scheme 27 Cu-catalyzed Mannich reaction of protected-imines and thioamides.

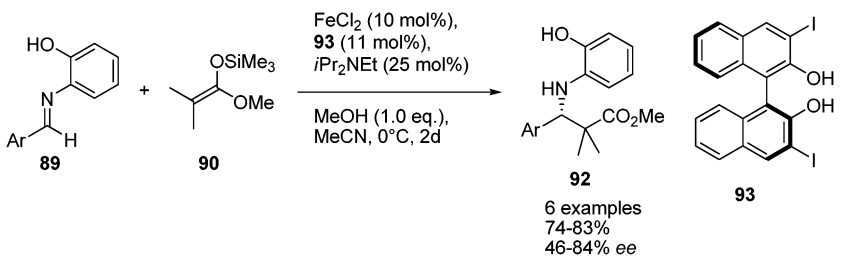
When $CuClO_4$–(*S*)-xylyl-BINAP was used as a catalyst in the addition of *tert*-butylthio-trimethylsiloxypropene and *N*-benzoylimino esters, the *syn* adducts were formed with high diastereo- and enantioselectivity starting from (*Z*)-enolates, and the *anti* adducts starting from (*E*)-enolates.[46] In general, considerably higher *ee* values were obtained when bulky substituents were present in **86** (R^1, R^2 or X).

The same group also studied the iron(II)-complex of 3,3′-I_2Binol **93** in the asymmetric Mannich reaction (Scheme 29).[47] The reaction of α-dimethyl silylenol ethers **90** with protected aromatic imines **89** provided the *N*-protected β-amino esters **92** with good *ee*'s (up to 84%).

Willis and co-workers studied bisoxazoline ligand **95** and $Mg(ClO_4)_2$ as catalyst for the Mannich reaction of imides **94**



Scheme 28 Cu-catalyzed addition of silyl enol ethers to *N*-acylimino esters.



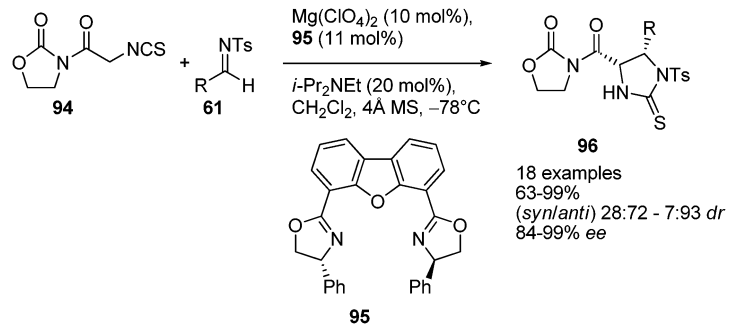
Scheme 29 Fe-catalyzed addition of silyl enol ethers to aromatic imines.

and aldimines **61** (Scheme 30).[48] The *anti* adducts **96** were obtained with good *dr*'s and high *ee*'s.

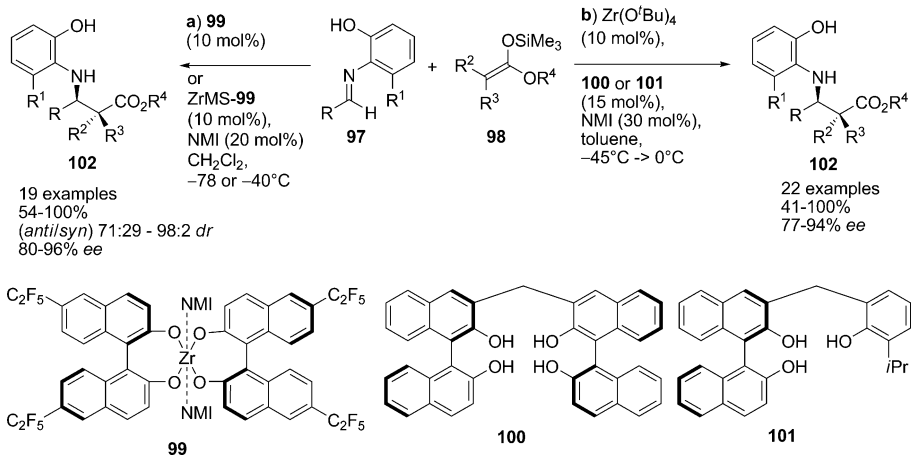
Kobayashi and co-workers also used chiral catalysts based on Binol and Zr(IV) in the Mannich reaction.[49] In the synthesis of α-methyl-β-amino acid derivatives by condensation of (*E*)-silyl ketene acetals **98** with aldimines **97**, the chiral zirconium catalyst **99** prepared from $Zr(O^tBu)_4$, 6,6′-dipentafluoroethyl-1,1′-bi-2-naphthol and *N*-methylimidazole (NMI) was used (Scheme 31a).[49a,50] Aromatic and aliphatic imines were employed as substrates, giving the *anti* adducts **102** 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 molecular sieves (ZrMS-**99**), could be stored for 53 d under air without loss of activity, and used for a second catalytic cycle.[49b] The enantioselectivity was enhanced in the presence of molecular sieves; from the (*E*)-silyl enol ether **98** the *syn*-adduct is formed, while from the (*Z*)-silyl enol ether the *anti*-adduct is obtained, both in good yield, and with high *dr* and *ee* (Scheme 31a).

Moreover, a Sc catalyst based on a chiral bis-amine-*N*-oxide ligand **106** was studied in the three component Mannich reaction of aromatic aldehydes, 2-hydroxyaniline and silyl enol ethers (Scheme 32).[51] The Mannich adducts **107** were obtained with moderate to good yields and high *ee*'s. Further optimization studies identified bridged bis-Binol **100** and ligand **101** as the best ligands, but the enantioselectivity could not be further increased (Scheme 31b).[49c] When this catalytic system was applied in the Zr-catalyzed reactions, the Mannich adducts **102** of various aromatic imines were provided in high yield with up to 94% *ee*.

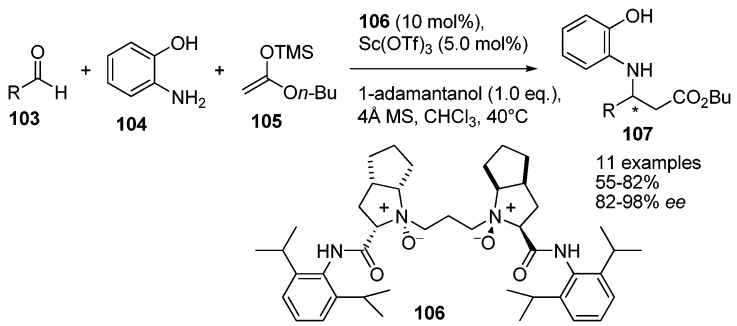
In conclusion, chiral Lewis acid complexes are useful catalysts for the asymmetric Mannich reaction to produce β-amino acid derivatives. Many combinations of metals, such as Cu(I), Cu(II), Fe(II), In(III), La(III), Ni(II) and Zr(IV), and various ligands as the source of the chiral information, have been developed. The Mannich reactions discussed here (see also paragraph 1.3.1 for organocatalysts) represent highly stereoselective and frequently extremely versatile atom-economic methods for the synthesis of chiral β^2- and $\beta^{2,3}$-amino acid derivatives, and diamino acids. Up to now, the best results, both in terms of scope and selectivity, were obtained with Binol-type ligands combined with Zr(IV). The Mannich reaction requires, however, an activation of the nucleophile, and does not accept esters as substrates. The activation can be achieved by the use of the second carboxy group precursor (arylketone, trihalomethylketone, *etc.*), the introduction of an extra electron-withdrawing group, or the pre-formation of the silyl enol ether. These approaches, however, imply the necessity for further transformations of the Mannich reaction products to give the desired β-amino acids.



Scheme 30 Mg-catalyzed addition of imides to imines.



Scheme 31 Zr-catalyzed addition of silyl enol ethers to imines.



Scheme 32 Sc-catalyzed three component Mannich reaction.

1.2.3 Conjugate addition

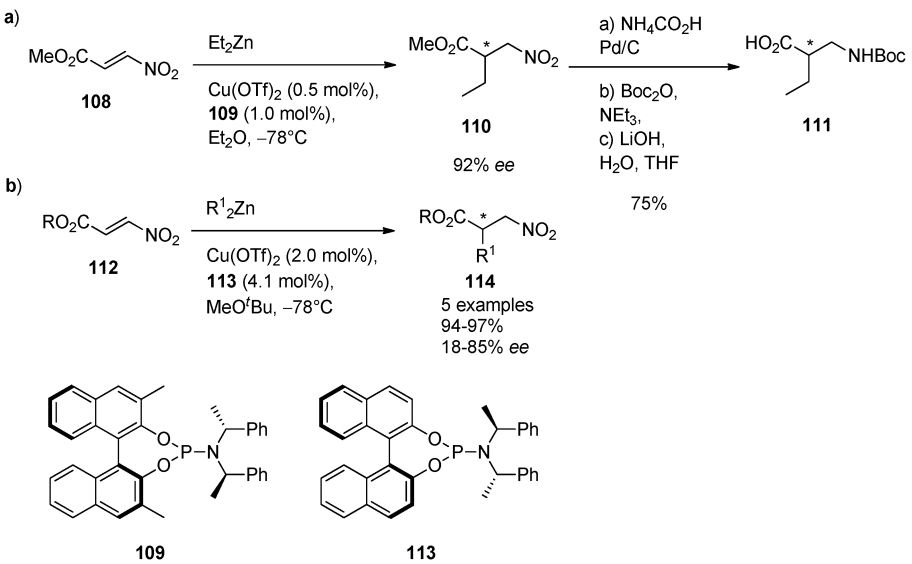
The catalytic asymmetric conjugate addition, when applied in the synthesis of β-amino acids, can be achieved in two ways: (1) addition of carbon nucleophiles, such as organometallic reagents, cyanide or Michael donors, and (2) addition of nitrogen nucleophiles, such as aromatic amines, hydroxylamines, and carbamates.[52]

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.[53] 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).[54] In particular, nitro-olefins are versatile acceptors for the synthesis of β-amino acids.

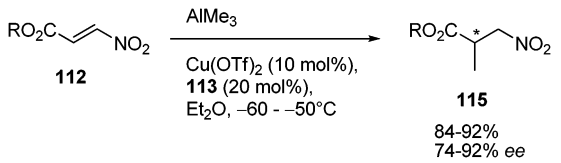
Organozinc species have been successfully applied in copper-catalyzed 1,4-additions to form chiral β-substituted esters and enones.[55] The use of phosphoramidite ligands derived from 2,2′-binaphthol resulted in a breakthrough that provided catalysts that show high activity and excellent chemo- and regio-selectivity. The groups of Sewald,[56] Wendisch[57] and Feringa[58] have successfully used 3-nitropropenoates or acetal-substituted nitropropenoates as acceptors and dialkylzinc reagents as nucleophiles to synthesize β-amino acid precursors.[59] In 2002, Rimkus and Sewald reported the addition of diethyl zinc to methyl 3-nitropropenoate **108** catalyzed by a Cu–phosphoramidite **109** complex (Scheme 33a).[56] Adduct **110** 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 **111**.

Around the same time, Wendisch and co-workers reported the addition of dialkylzinc reagents to nitropropenoates **112** using phosphoramidite **113** as chiral ligand (Scheme 33b).[57] In MeO^{t}Bu as solvent, the adducts were obtained in high yield with up to 85% *ee* using diethylzinc as nucleophile. Furthermore, phosphoramidite **113** was employed in the Michael addition of trimethyl aluminium to nitro-olefin **112** (Scheme 34).[60] At low temperature in ether as solvent, enantioselectivities up to 92% were obtained.

Excellent enantioselectivities (up to 98%) were obtained by Feringa and co-workers in the addition of dialkyl zinc reagents to acetal-substituted nitropropenoates (Scheme 35).[58] The adducts of Et_2Zn, Me_2Zn and Bu_2Zn were obtained with high



Scheme 33 Cu-catalyzed addition of dialkyl zinc reagents to nitro-olefins.



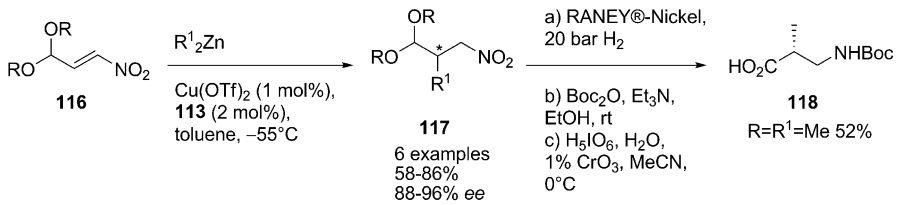
Scheme 34 Cu-catalyzed addition of trimethyl aluminium to a nitro-olefin.

yields and *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 **118**.

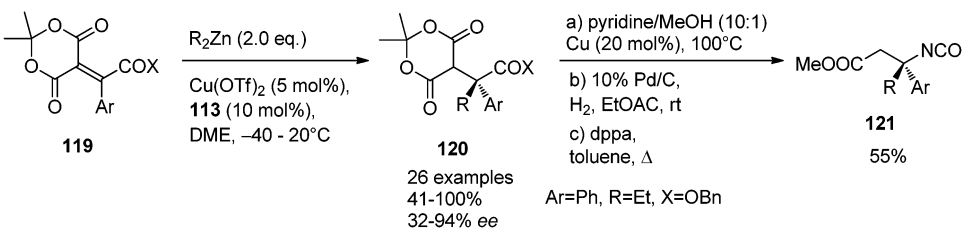
Recently, carboxylic acid derivatives that have all-carbon quaternary stereocentres have been synthesized through copper-catalyzed asymmetric conjugate addition of dialkyl zinc reagents to 2-aryl acrylates **119** (Scheme 36).[61] Fillion and co-workers used phosphoramidite ligand **113** to obtain the adducts in high yields with up to 94% *ee*. β-Amino acid precursor **121** was synthesized through deprotection of adduct **120**, followed by a Curtius rearrangement of the succinic acid derivative.

Trost and Hisaindee reported a heterodinuclear chiral catalyst **124** comprising Mg^{2+} and Zn^{2+} and a chiral proline-derived ligand for the addition of α-hydroxyketones to β-substituted nitroalkenes **123** (Scheme 37).[62] As substrates, aromatic, aliphatic and alkynyl-β-substituted nitroalkenes, and phenyl- and furyl-hydroxyketones were employed leading up to 99% *ee* and good diastereoselectivities in favour of the *anti*-products. Reduction of the nitro group and the ketone to the corresponding amino-diol, followed by *N*-Boc-protection and oxidative cleavage of the diol, gave the corresponding β^2-amino acids **118**.

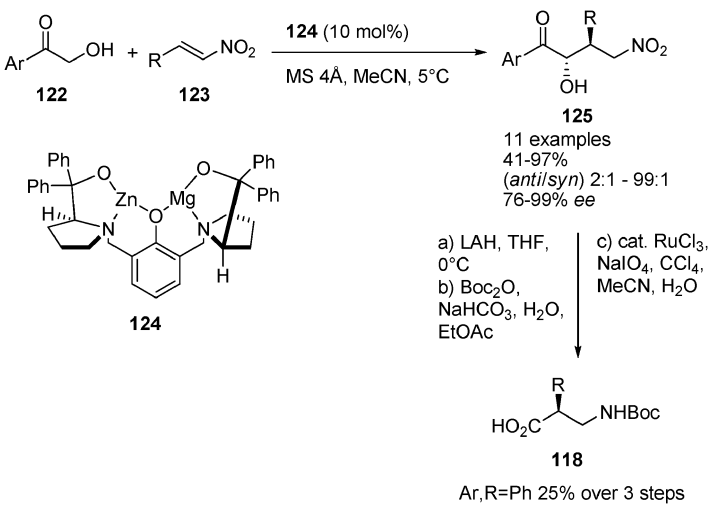
An enantioselective rhodium-catalyzed enolate protonation method for the synthesis of β^2-amino acids was reported by Sibi and co-workers (Scheme 38).[63] A complex prepared from Rh(acac)(ethylene)$_2$ and difluoroPhos **127** catalyzed the conjugate addition of arylboronic acids to β-acrylates **126**.



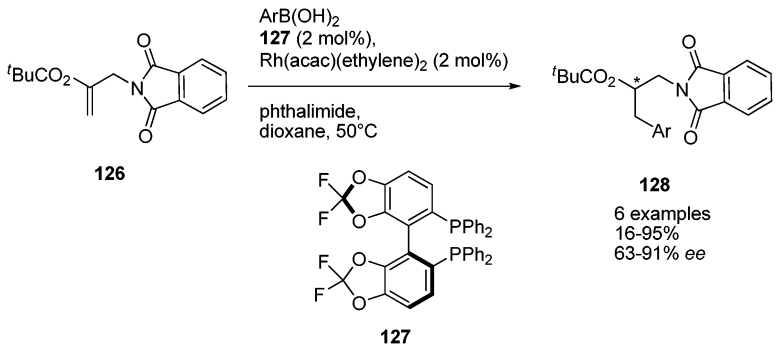
Scheme 35 Cu-catalyzed addition of dialkyl zinc reagents to acetal substituted nitropropenoates.



Scheme 36 Cu-catalyzed addition of dialkyl zinc reagents to 2-aryl-acrylates to form quaternary stereocentres.



Scheme 37 Heterodinuclear catalyst for the addition of α-hydroxyketones to nitroalkenes.



Scheme 38 Rhodium-catalyzed conjugate addition and enantioselective protonation.

Enantioselective protonation of the chiral oxa-π-allyl-rhodium intermediate resulted in good yields and with high enantioselectivities (*ee* up to 91%) using one equivalent of phthalimide as proton source.

Sammis and Jacobsen reported the enantioselective conjugate addition of cyanide to α,β-unsaturated imides using aluminium salen catalyst **130** (Scheme 39).[64] The adducts **131** 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.

In summary, the asymmetric additions of dialkylzinc and aluminium reagents as well as α-hydroxyketones to α,β-unsaturated nitro alkenes represent valuable methods to prepare β^2-amino acid precursors with high enantioselectivities. Monodentate phosphoramidites are the ligands of choice in these transformations. Some of theses methods can be applied in the construction of all-carbon quaternary stereocenters, which is a valuable tool for the preparation of such compounds. Most of the methods described in this chapter rely, however, on the availability of the activated nucleophiles, such as dialkylzinc and aluminium reagents or boronic acids. This may somewhat limit the variety of β-amino acid structures, that can be obtained by the conjugate addition of *C*-nucleophiles to activated double bonds.

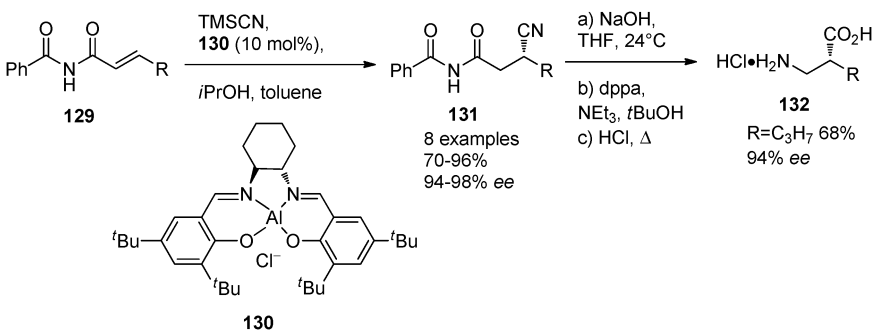
1.2.3.2 Nitrogen nucleophiles. Conjugate addition of amine nucleophiles to α,β-unsaturated carboxylic acid derivatives is one of the most attractive and atom-economic methods for the synthesis of β-amino acids. In the past, mostly chiral Michael acceptors or chiral amines have been used for diastereoselective conjugate additions.[52] Recently, several groups have reported significant progress towards catalytic asymmetric versions of conjugate additions of amines.[52,65]

For the enantioselective addition of primary aromatic amines to α,β-unsaturated oxazolidinones **133**, Li and Hii investigated cationic palladium–BINAP complex **134** (Scheme 40a).[66] Using aniline derivatives and crotonyloxazolidinone, the adducts were obtained in very 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.

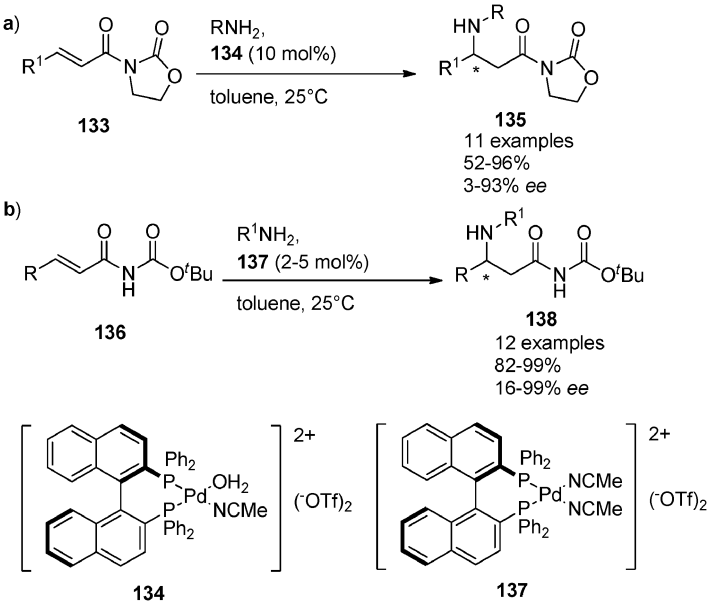
A similar cationic palladium complex **137** was tested in the addition of aromatic amines to *N*-alkenoylcarbamates (Scheme 40b).[67] High enantioselectivities and high yields were achieved using various aliphatic substrates (R = Me, Et, Pr). The products were converted to *N*-aryl-β^3-amino acids by the hydrolysis of the imide under basic conditions. Moreover, the authors compared isolated and *in situ*-formed complexes, and found similar results.[68]

Also, Sodeoka and co-workers employed a cationic catalyst derived from BINAP, which was used in its dimeric form **138** (Scheme 41).[69] Aromatic amines substituted with electron donating or withdrawing groups gave the adducts in high yield with high *ee*'s (up to 97%).

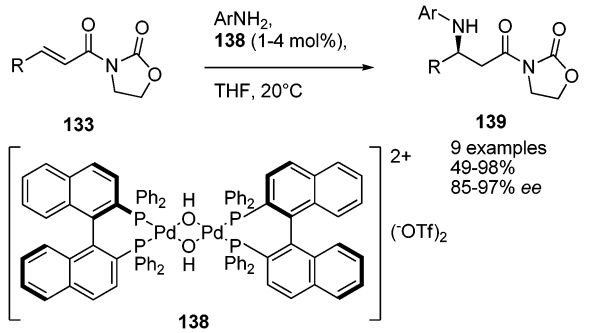
The Jørgensen group investigated a Ni(II)–bisoxazoline **95** catalyst in the addition of secondary aromatic amines to oxazolidinones **133** (Scheme 42).[70] Various β-substituted aliphatic α,β-unsaturated oxazolidinones were used, resulting in the formation of amine adducts **140** in good yields and *ee*'s up to 96%.



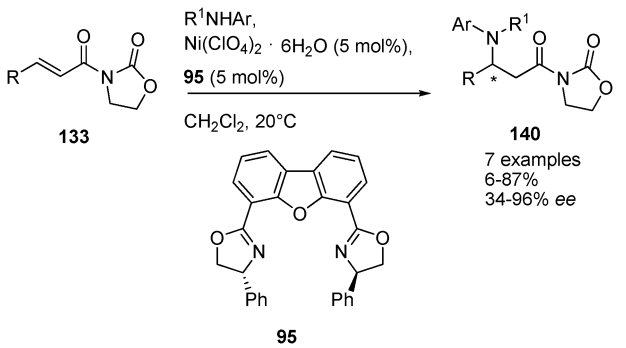
Scheme 39 Al–Salen-catalyzed addition of cyanide to α,β-unsaturated imides.



Scheme 40 Pd-catalyzed addition of aromatic amines to α,β-unsaturated imides.

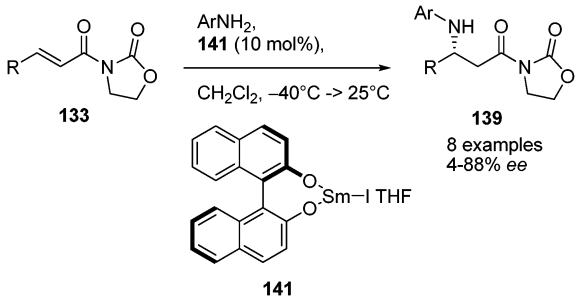


Scheme 41 Enantioselective addition of aromatic amines to α,β-unsaturated oxazolidinones catalyzed by a dimeric palladium species.



Scheme 42 Ni-catalyzed addition of aromatic amines to α,β-unsaturated oxazolidinones.

Iodo(binaphtholate)samarium complex **141** has been used in the addition of aromatic amines to *N*-alkenoyl-oxazolidinones (Scheme 43).[71] Substrates with aromatic substituents and *p*-anisidine as nucleophile resulted in the adducts **139** with *ee*'s up to 76%, but only low *ee*'s were obtained using oxazolidinones with aliphatic substituents.

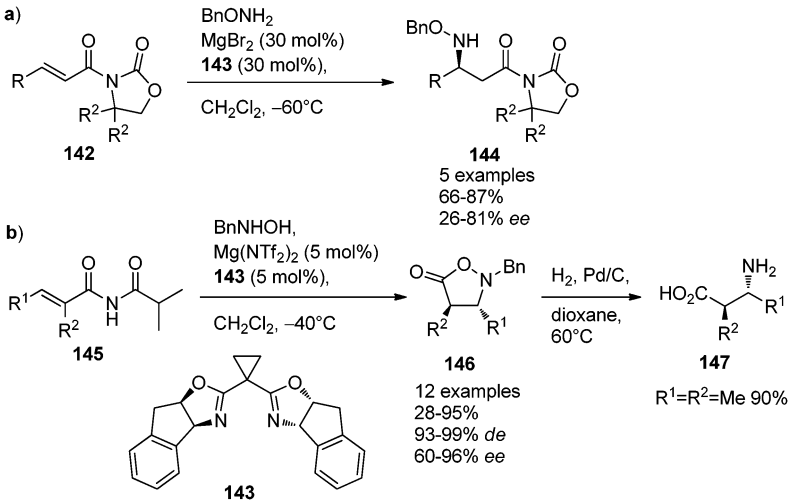


Scheme 43 Sm-catalyzed addition of aromatic amines to oxazolidinones.

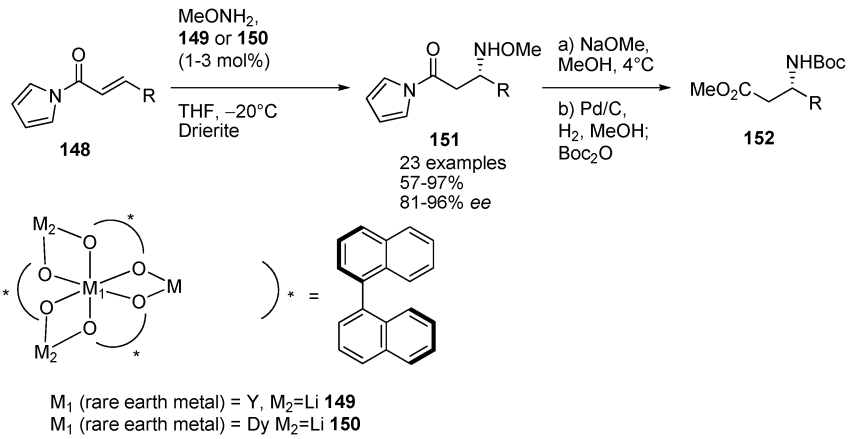
Besides aromatic amines, hydroxylamines have been widely used in catalytic enantioselective conjugate additions. Sibi and co-workers employed Mg–bisoxazoline catalyst **143** in the addition of *O*-benzyloxy amine to oxazolidinones **142** (Scheme 44a).[72] However, only moderate enantioselectivities (up to 81% *ee*) were observed with high catalyst loadings of 30 mol%. The stereochemical outcome of this transformation depends on the temperature, *i.e.* at 0 °C or room temperature the configuration is reversed compared to that of the product obtained at −60 °C, and the *ee* was in general lower at elevated temperatures. β^3-Amino esters were obtained upon hydrolysis of the imide to the corresponding methyl ester.

The addition of *N*-benzyloxy amines to α,β-disubstituted imide **145** catalyzed by bisoxazoline ligand **143** and $Mg(NTf_2)_2$ leads to the formation of isoxazolidinones **146** (Scheme 44b).[73] The *anti* adducts were obtained in high yields and excellent diastereo- and enantiomeric excess. Upon hydrogenolysis, the $\beta^{2,3}$-amino acids **147** were obtained in high yield.

Shibasaki and co-workers studied lithium–lanthanide-based catalysts **149** and **150** in the enantioselective aza-Michael addition of methoxylamine (Scheme 45).[74] Heterobimetallic catalysts are often combinations of rare earth metals and



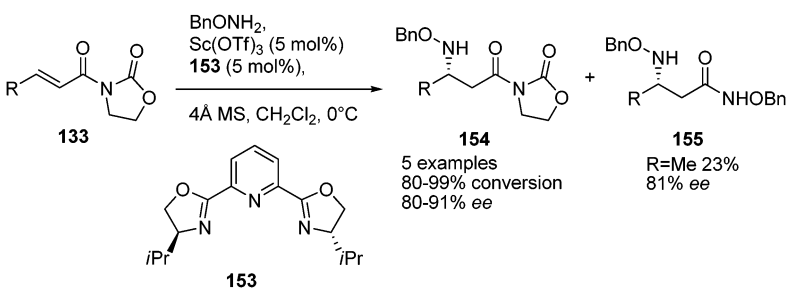
Scheme 44 Mg-catalyzed addition of hydroxylamines to α,β-unsaturated imides.



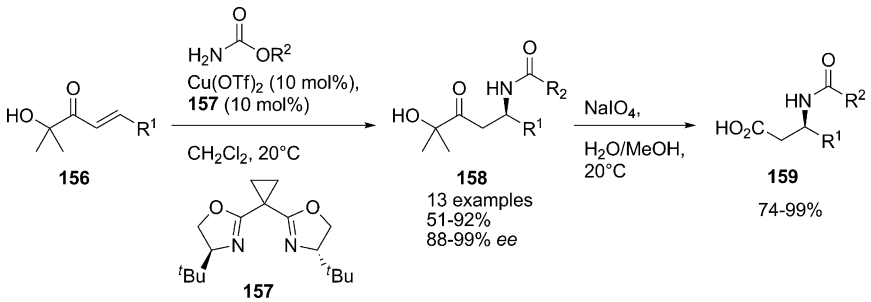
Scheme 45 Heterobimetallic catalysts for the aza-Michael addition of methoxylamine.

alkali metals. In particular they show a cooperative effect of the two metal centers, *i.e.* a Lewis acid site to activate the electrophiles and a basic site to deprotonate the nucleophiles to form activated metal nucleophiles.[75] 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 ions are activating the α,β-unsaturated compound and control the orientation of the amine in the addition step, while mechanistic studies revealed that the ionic radius of the rare earth metals plays a major role. Drierite ($CaSO_4$) was added as desiccant, because traces of water decreased the rate of the reaction.[76] The enantiomeric excess of the adducts reaches up to 96%. The *N*-acylpyrrole group of **151** was easily transformed into the corresponding methyl ester, and after hydrogenolysis of the hydroxylamine, β^3-amino esters **152** were obtained.

$Sc(OTf)_3$–*i*-Pr-pybox **153** catalyst has also been used for the enantioselective addition of *O*-benzyloxyamine to α,β-unsaturated 3-acyloxazolidinones (Scheme 46).[77] The adduct **154** was obtained in good yield with high *ee*'s (up to 91%); using crotonoyl oxazolidinone as substrate, **155** was also formed in 23% yield with 81% *ee* besides **154**.



Scheme 46 Sc-catalyzed addition of benzyloxyamine to oxazolidinones.



Scheme 47 Cu-catalyzed addition of carbamates to α-hydroxy enones.

Palomo and co-workers investigated Cu(II)-bisoxazoline **157** complex for the addition of carbamates to α-hydroxy-enones (Scheme 47).[78] Benzyl, *t*butyl, methyl and ethyl carbamate were successfully added to aliphatic and aromatic α-hydroxy-enones **156** providing the adducts in high yield and high *ee*. The α-hydroxy ketone was oxidatively cleaved using $NaIO_4$ to yield the corresponding *N*-protected β^3-amino acid **159**.

In summary, aromatic amines, hydroxylamines, alkoxylamines and carbamates were successfully added to α,β-unsaturated carbonyl compounds using Lewis acids as catalysts. The best results were obtained with BINAP and BOX ligands. However, all methods described here and in the older literature[52] rely on modified carbonyl compounds as acceptors. Simple carboxylic esters were not yet successfully employed as substrates to give β-amino esters *via* highly enantioselective conjugate additions. This implies the necessity for further transformations of conjugate addition reaction products towards β-amino acids.

1.2.4 Miscellaneous

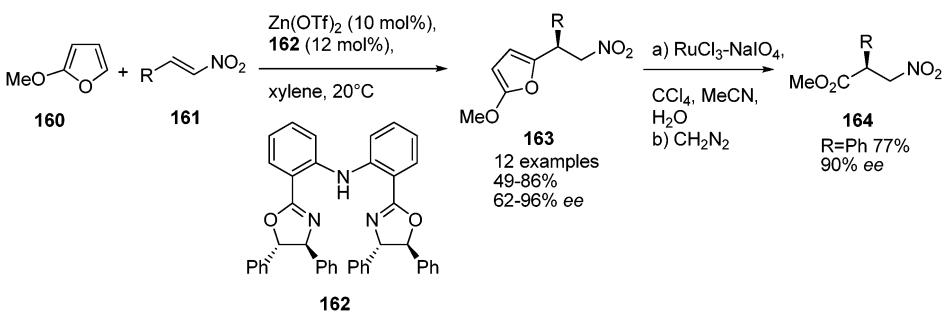
Several reactions to form β-amino acids in an enantioselective manner, which do not fit in the above described categories are discussed herein.

In 2007, an asymmetric Friedel–Crafts alkylation of methoxyfuran with nitroalkenes was described (Scheme 48).[79] A diphenylamine-tethered bisoxazoline **162**–Zn(II) complex was used to catalyze the addition of methoxyfuran **160** to aromatic nitro-olefins **161** with *ee*'s up to 96%. The furan ring was subsequently oxidatively cleaved and the intermediate treated with diazomethane to form the protected β-nitro ester derivatives **164**, which could be further transformed into the corresponding β^2-amino acids.

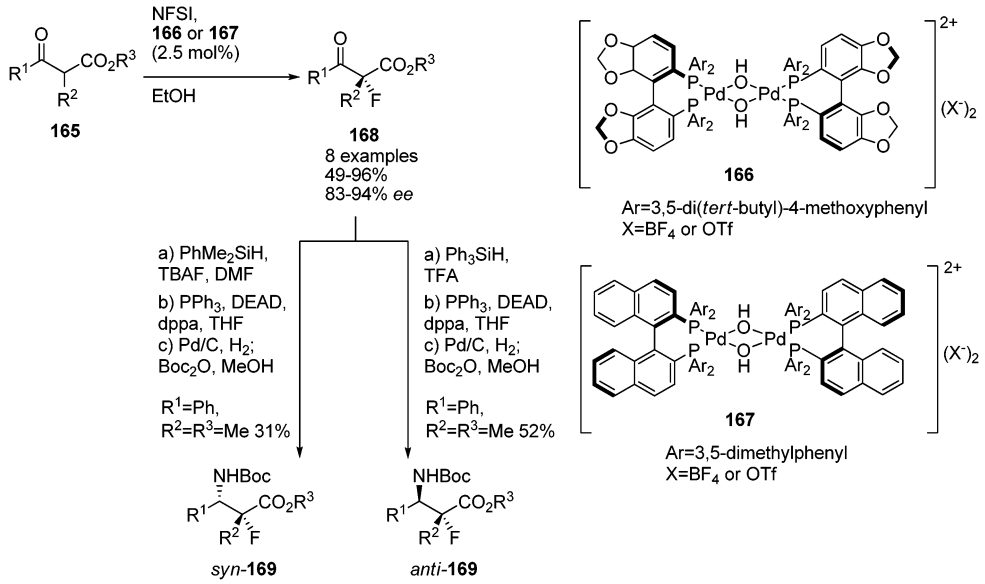
Sodeoka and co-workers have tested chiral cationic dimeric palladium catalysts for the α-fluorination of β-ketoesters with *N*-fluorobenzenesulfonamide (NFSI) (Scheme 49).[80] Catalyst **166** derived from DTBM-SegPhos gave high enantioselectivities (up to 91% *ee*). A similar catalyst **167** in which the chiral part was derived from BINAP, gave comparable *ee*'s 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 ketones to the corresponding *anti*-fluoro-alcohols or $PhMe_2SiH$–TBAF for the reduction to the *syn*-fluoro-alcohols. Both diastereomers were subsequently transformed into the respective azides using a Mitsunobu reaction, followed by reduction and *in situ* Boc protection to give the α-fluoromethyl-β-amino esters.

β^2-Amino acids were also synthesized by rhodium-catalyzed C–H insertion of diazoacetates **171** into *N*-Boc-*N*-benzyl-*N*-methylamine (Scheme 50).[81] Benzylamine **170** proved to be the optimal substrate for the insertion of various aromatic, heteroaromatic and alkenyl diazoacetates, which proceeds with up to 96% *ee*.

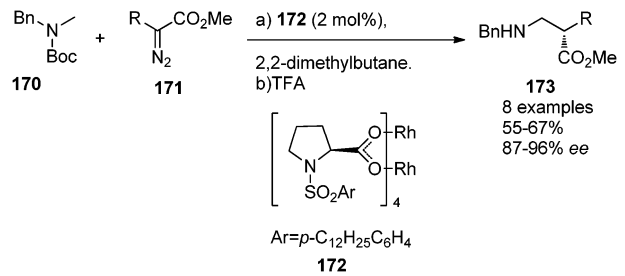
Lurain and Walsh have developed a multi-step procedure for the synthesis of γ-unsaturated β^2-amino acid derivatives with high *ee* (Scheme 51).[82] First, an enantioselective vinylzinc addition to aldehydes yields allylic alcohol **176**, followed by Overman's [3,3]-sigmatropic imidate rearrangement and a one-pot deprotection–oxidation sequence to yield **178**. The vinylzinc reagents were generated *in situ via* hydroboration of terminal alkyne **174** with dicyclohexylborane and transmetalation of the vinylborane with diethylzinc. Ligand **175** catalyzes the addition of the vinylzinc reagent to aromatic and aliphatic aldehydes in high yield with excellent *ee*'s (up to 99%). Subsequently, the trichloroacetimidate was synthesized using trichloracetonitrile in DBU and heated to reflux, yielding the rearranged product **177**. 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 **178**.



Scheme 48 Zn-catalyzed Friedel–Crafts reaction of methoxyfuran with nitroalkenes.



Scheme 49 Pd-catalyzed enantioselective fluorination of β-ketoesters.

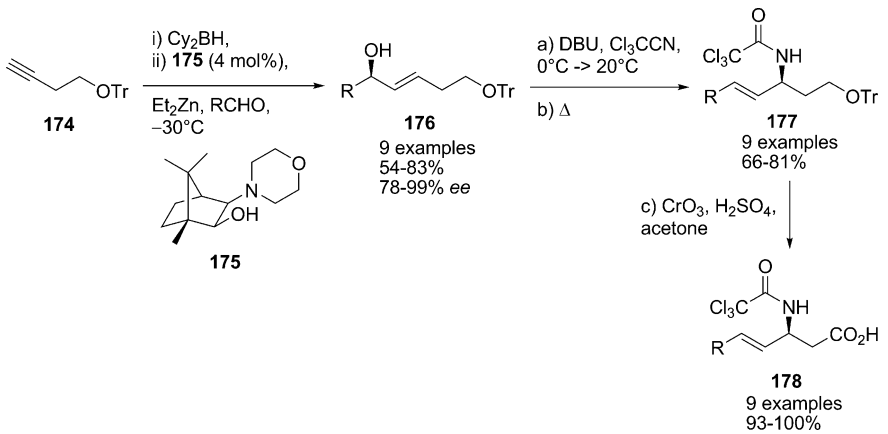


Scheme 50 Rh-mediated C–H-activation for the synthesis of β^2-amino acids.

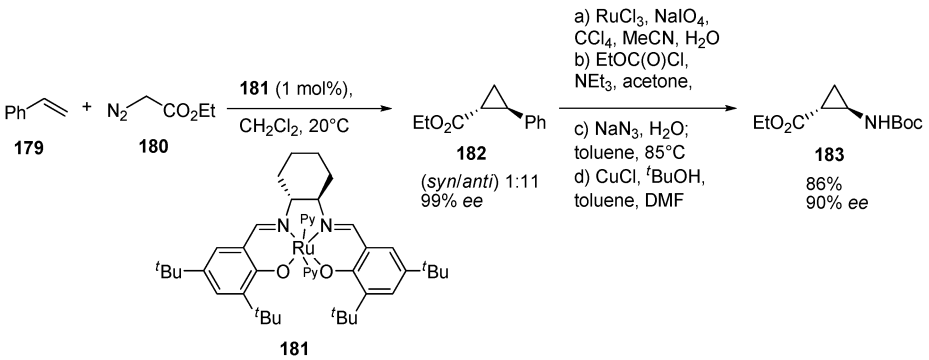
Ru–salen catalyst **181** was tested in an enantioselective cyclopropanation in order to prepare β^2-cyclopropyl amino acids (Scheme 52).[83] The cyclopropanation of styrene with ethyl diazoacetate **180** proceeded with good diastereo- and enantioselectivity. For the synthesis of *trans*-cyclopropyl 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 **183**.

Johnson and co-workers 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 53).[84] Using cyanoformate **185**, acylsilane **184** and 15 mol% of salen–aluminium complex **186**, high enantioselectivities in the formation of **187** were achieved. First, enantioselective cyanation of the acylsilane occurs, leading to a chiral alkoxide that undergoes a 1,2-Brook-rearrangement to give the product **187** upon reaction with a second molecule of the cyanoformate. The nitrile group was subsequently reduced to the free amine **188**.

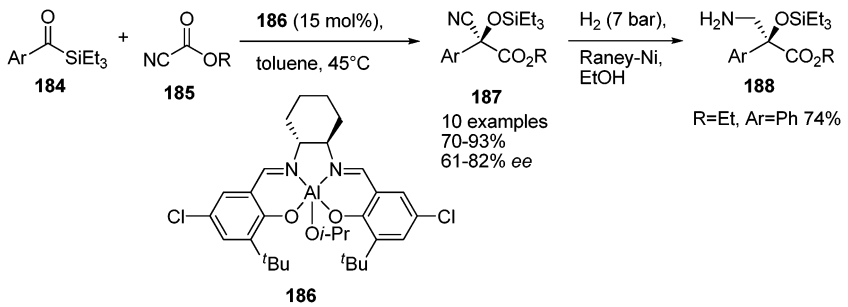
Feringa and co-workers developed the catalytic asymmetric allylic substitution of Grignard reagents using Taniaphos **190** as a chiral ligand and used this transformation as a key step in a new route to β^2-amino acids (Scheme 54).[85] Allylic amine **189** was treated with methylmagnesium bromide in the presence of the chiral copper catalyst to give **191** in high yield with 95% *ee*. The olefin was oxidatively cleaved with



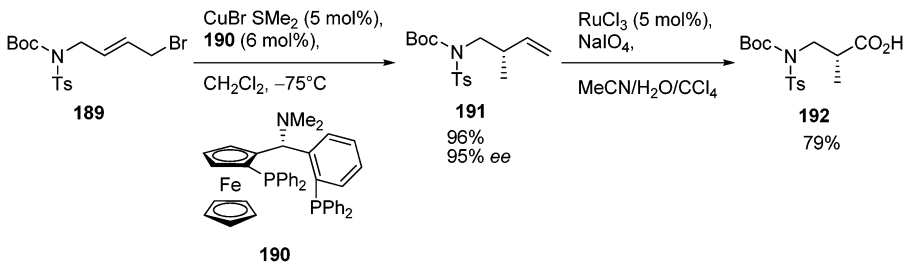
Scheme 51 Enantioselective addition of vinylzinc reagents to aldehydes as a key step for the synthesis of β^2-amino acids.



Scheme 52 Enantioselective Ru-catalyzed cyclopropanation as a key step in the synthesis of β^2-cyclopropyl-amino acids.



Scheme 53 Enantioselective cyanation–1,2-Brook-rearrangement–C-acylation for the synthesis of β-amino acids.



Scheme 54 Cu-catalyzed asymmetric allylic substitution using Grignard reagents.

$RuCl_3$–$NaIO_4$, and the *N*-Boc-*N*-tosyl protected β-amino acid **192** was obtained in 79% yield.

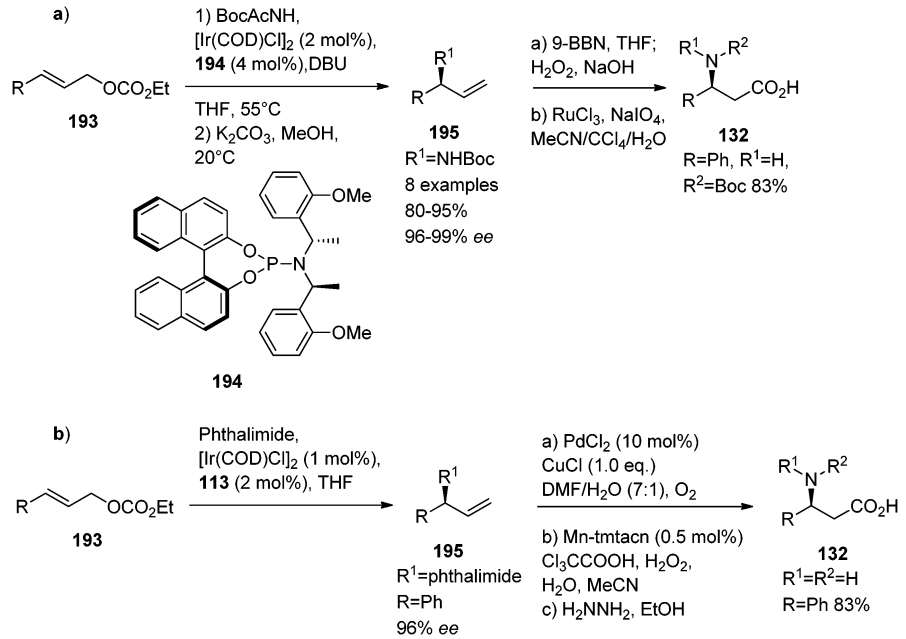
Moreover, the catalytic asymmetric allylic amination of allylic carbonates catalyzed by Ir–phosphoramidite **194** was used for the preparation of β^3-amino acid derivatives by Singh and Han (Scheme 55a).[86] *N*-Boc-*N*-acetylamine was employed as nucleophile giving the branched products with high regioselectivity (>99 : 1) and excellent *ee* (up to 99%). The product was deacylated *in situ* 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 **132**.

Asymmetric allylic amination has also been employed in a synthetic route towards β^3-amino acids presented by Feringa and co-workers (Scheme 55b).[87] The use of phthalimide as a nucleophile in an Ir–phosphoramidite **113**-catalyzed reaction gave the *N*-phthalimide-protected precursor **195**. Aldehyde selective Wacker oxidation, followed by the *N*-deprotection yielded product **132** with high overall yield.

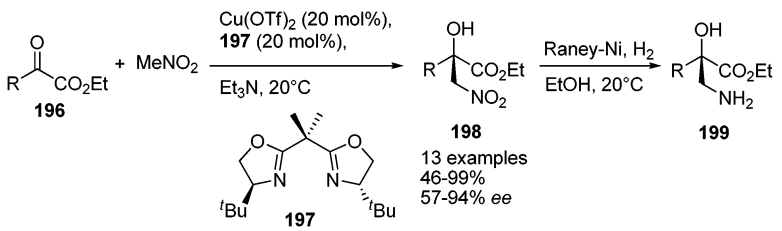
Jørgensen and co-workers employed the asymmetric Henry reaction to synthesize α-hydroxy-β^2-amino acid esters (Scheme 56).[88] Copper–bisoxazoline **197** complex was used to add nitromethane to aliphatic and aromatic α-ketoesters to give the adducts in good yield with high *ee*'s (up to 94%). Upon reduction of the nitro group, the corresponding β-amino acid esters **199** were obtained.

Enantioselective [3 + 2]-cycloadditions of nitrones and α,β-unsaturated 2-acyl imidazoles **201** were used to synthesize $\beta^{2,3}$-hydroxy-amino acid derivatives (Scheme 57).[89] Evans and co-workers employed Ce(IV)-bisoxazoline catalyst **202** to achieve the addition of aliphatic and aromatic nitrones **200** to 2-acyl imidazoles **201** in high yield and up to 99% *ee* with an *endo* : *exo* ratio >99 : 1. The isoxazolidines **203** were reductively cleaved using $Pd(OH)_2/C$ and hydrogen to give $\beta^{2,3}$-amino acid derivatives **204**.

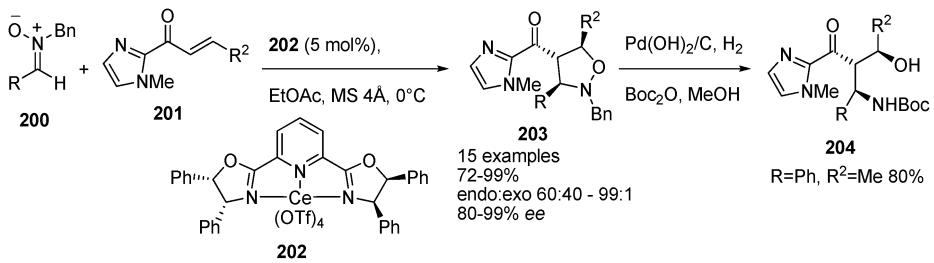
Chiral nucleophilic quinuclidine alkaloid-derived catalyst **208** in combination with $Ti(OiPr)_4$ as Lewis acid has been employed in the asymmetric aza-Baylis–Hillman reaction (Scheme 58).[90] Starting from aromatic aldehydes, tosylamide and methyl acrylate, Balan and Adolfsson applied catalyst **208** to obtain the Baylis–Hillman adducts **209** in good yield, albeit with moderate enantioselectivities.



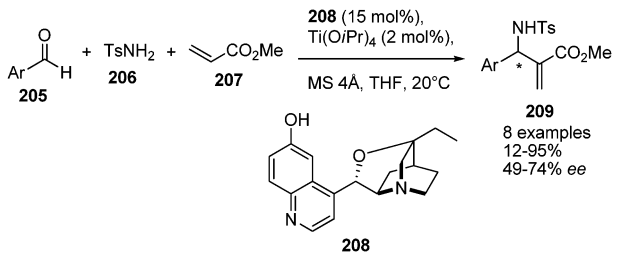
Scheme 55 Ir-catalyzed asymmetric allylic amination.



Scheme 56 Cu-catalyzed asymmetric Henry reaction.



Scheme 57 Catalytic asymmetric [3 + 2]-cycloaddition.

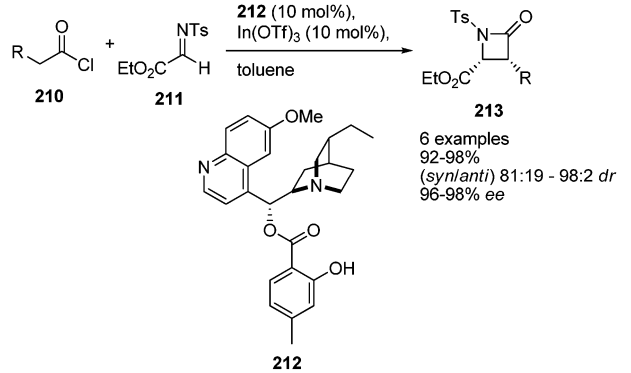


Scheme 58 Catalytic asymmetric Baylis–Hillman reaction.

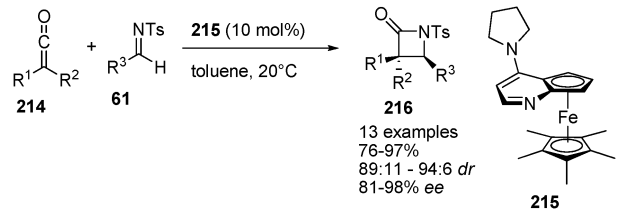
Using bifunctional asymmetric catalyst **212**, Lectka and co-workers synthesized β-lactams from acyl chlorides **210** and imine **211** (Scheme 59).[91] A combination of $In(OTf)_3$ and quinidine derivative **212** gave the *syn*-β-lactam **213** with high *dr* (up to 98 : 2) and high *ee* (up to 98%).

Hodous and Fu developed an enantioselective version of the Staudinger reaction for the synthesis of β-lactams (Scheme 60).[92] Symmetric and unsymmetric ketenes **214** added to a range of imines **61** in a reaction catalyzed by planar-chiral nucleophile **215** to give the *N*-Ts-protected-β-lactams **216** in high yields and with high *ee*'s.

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 *e.g.* Taxol analogues. α-Trifluoromethylisoserine **220** was obtained by dihydroxylation of 2-(trifluoromethyl)



Scheme 59 In–quinidine-catalyzed asymmetric formation of β-lactams.



Scheme 60 Synthesis of β-lactams *via* a Staudinger reaction catalyzed by a planar-chiral nucleophile.

acrylic amide **217**. Amide **218** was hydrolysed, esterified and treated with sulfuryl chloride to give cyclic sulfate **219**. This compound was treated with NaN_3, followed by hydrolysis and reduction, to give the β-amino acid **220** with 90% *ee* (Scheme 61a).[93] The asymmetric aminohydroxylation was used in the synthesis of polyhydroxylated β-amino acid constituents of microsclerodermic cyclic peptides (Scheme 61b).[94] γ-Alkoxy-(*E*)-alkene **221** was transformed into *syn*-β-amino-α-hydroxy ester **222** with 97% *ee* using $(DHQD)_2PHAL$ as catalyst and *tert*-butylcarbamate as nucleophile.

In this section, a number of versatile catalytic enantioselective methods to synthesize β^2- or β^3-amino acids were discussed. Among the most frequently employed are those based on addition to nitroolefins and Sharpless aminohydroxylation and dihydroxylation. However, these methods have most often been used for the synthesis of specific amino acids, for example as key steps in natural product synthesis.

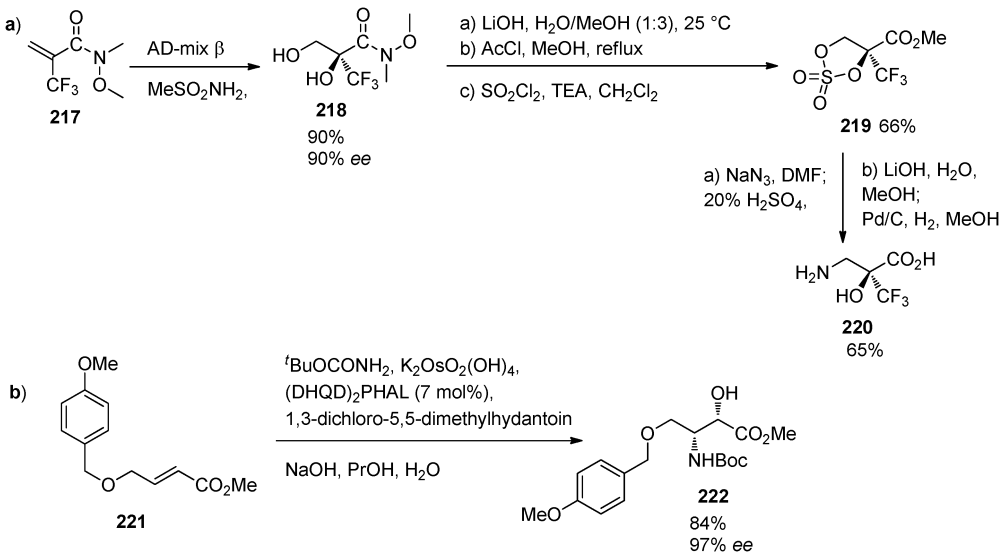
1.3 Organocatalysis

Asymmetric transformations promoted by small chiral organic molecules have become very useful among the recently developed methods for the synthesis of β-amino acids.[95] Important catalysts used for this purpose are proline, proline-derived amines, chiral Brønsted acids, (thio)ureas, and *Cinchona* alkaloids.[96] In this section, Mannich reactions, conjugate additions and miscellaneous organocatalytic synthesis of β-amino acids are presented, covering the recent literature since 2002.

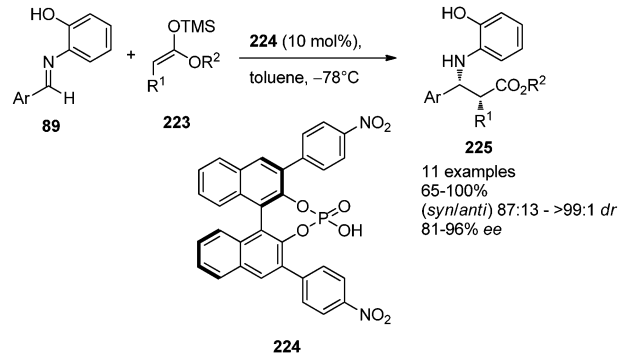
1.3.1 Mannich reaction

Organocatalytic Mannich reactions represent a direct entry into β-amino carbonyl compounds.[97] Low molecular weight synthetic molecules that have hydrogen-bond donor abilities and a secondary interaction site, such as aromatic, acidic or basic functionalities, can catalyze a variety of C–C and C–heteroatom bond-forming reactions with high enantioselectivity.[98] Chiral Brønsted acids are an important class of organocatalysts. Hydrogen bonds are formed between the catalyst and the electrophile to activate the substrate and to organize the transition-state.[99] Chiral Brønsted acids are classified into two categories: (1) neutral Brønsted acids, such as thiourea and Taddol derivatives which are denoted hydrogen-bonding catalysts, and (2) stronger Brønsted acids, such as Binol derivatives and phosphoric acids.

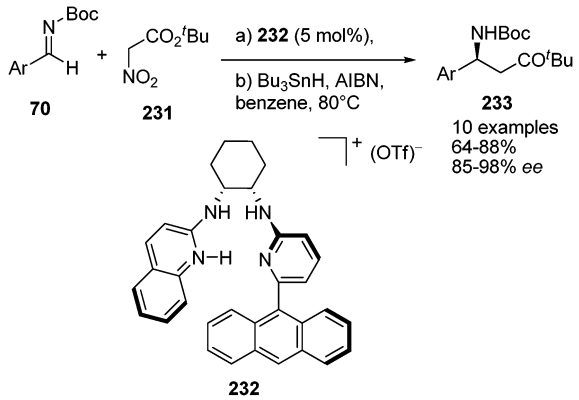
Chiral phosphoric acid **224** derived from Binol gave high levels of stereocontrol in the reaction of aromatic aldimines with silyl enol ethers (Scheme 62).[100] High diastereoselectivities (*dr* up to $>99:1$) and high enantioselectivities (*ee* up to 96%) were achieved.



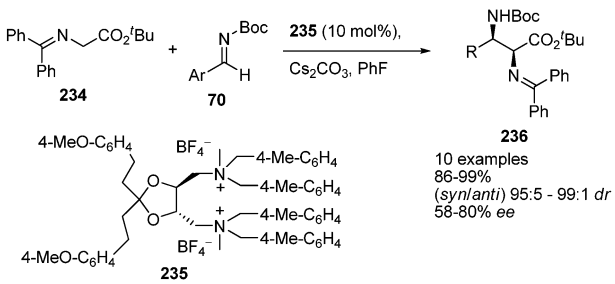
Scheme 61 Aminohydroxylation and dihydroxylation for the synthesis of β-amino acid derivatives.



Scheme 62 Mannich reaction catalyzed by a chiral Binol-derived phosphoric acid.



Scheme 64 Mannich reaction catalyzed by a chiral amine.



Scheme 65 Mannich reaction catalyzed by a chiral phase transfer catalyst.

Yamamoto and co-workers studied chiral Brønsted acid **227**, which was proposed to activate imine **55** through hydrogen bonding (Scheme 63a).[101] An achiral Brønsted acid (R^3OH) protonates the amine moiety of the intermediate after the addition step to give the adducts **228** with good *ee* (up to 87%). Taddol-derived phosphoric acid **229** was also used to catalyze the addition of silyl enol ethers **226** to aromatic aldimines with good yield and high *ee*'s (Scheme 63b).[102] In both of these methods only the addition of the isobutyric acid-derived silyl enol ether is described.

The reaction of aromatic *N*-Boc-protected aldimines with nitroacetate **231** using amine catalyst **232** gave the products in good yield and high *ee* (up to 98%) (Scheme 64).[103] Using tributyltin hydride and AIBN, the nitro group was removed to provide the corresponding β^3-amino ester **233**.

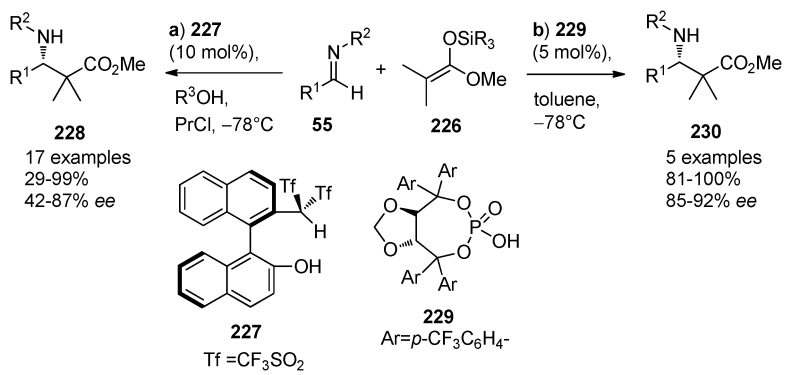
Phase transfer catalyst **235**, developed by Shibasaki and co-workers, is effective in the addition of glycine–Schiff-base **234** to aromatic imines (Scheme 65).[104] The glycine–Schiff-base is deprotonated by Cs_2CO_3, presumably at the interface between the liquid and solid phase, where counterion exchange with **235** takes place, followed by the asymmetric C–C-bond formation. The Mannich adducts **236** were obtained with good diastereomeric and enantiomeric excess.

Furthermore, Maruoka and co-workers used phase transfer catalyst **238** for the Mannich reaction of glycine derivative **234** and imine **237** (Scheme 66).[105] The α,β-diamino-diester **239** was obtained with good *dr* and *ee*.

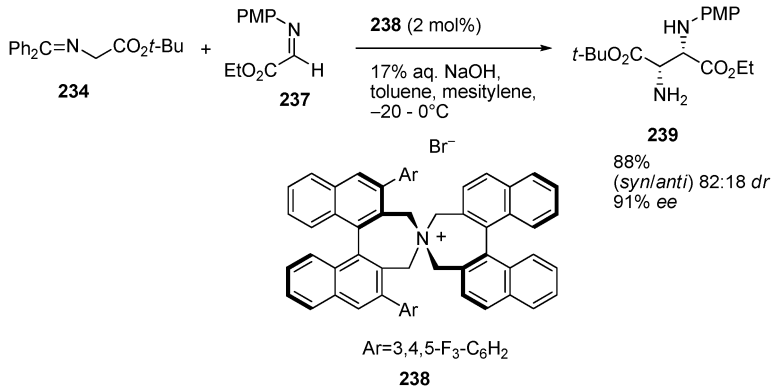
Jacobsen and co-workers studied thiourea **241** as catalyst in the Mannich reaction of silyl enol ethers **240** with *N*-Boc-protected aldimines **70** (Scheme 67).[106] Aromatic β^3-amino acid derivatives were obtained in high yields with up to 98% *ee*. Variation in the amine part of the catalyst, *i.e.* thiourea **242**, gave comparable enantioselectivities for the Mannich reaction.[107]

The organocatalytic enantioselective Mannich-type reaction of phosphorous ylides **244** with *N*-Boc-protected imines catalyzed by bis-thiourea **245** leads, after reaction with formaldehyde, to *N*-Boc-β-amino-α-methylene esters **246** (Scheme 68).[108] Various substituted aromatic, heteroaromatic, cyclic and branched aliphatic imines were tested, which gave the corresponding esters with high *ee*'s.

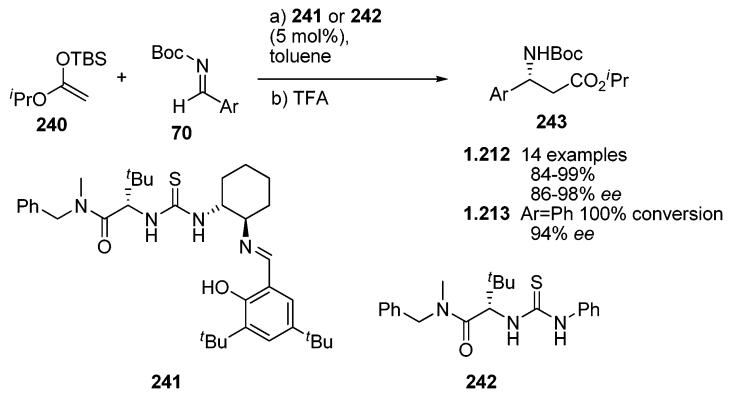
Deng and co-workers tested catalyst **248** with a thiourea and a quinine alkaloid moiety (Scheme 69a).[109] The thiourea group is proposed to activate and direct the electrophilic imine, and the tertiary nitrogen of the quinine moiety



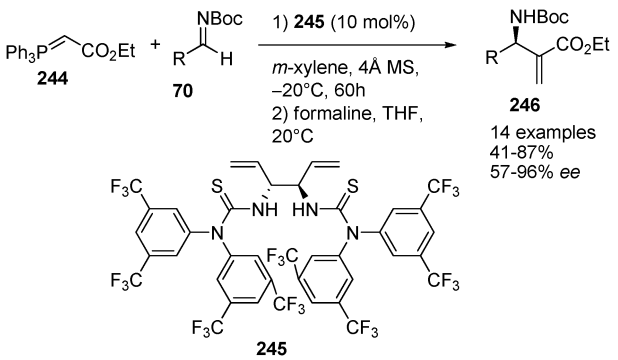
Scheme 63 Brønsted acid-catalyzed Mannich reactions for the synthesis of $\beta^{2,2,3}$-amino acids.



Scheme 66 Mannich reaction mediated by a phase transfer catalyst for the synthesis of an α-β-diamino-diester.



Scheme 67 Thiourea-catalyzed asymmetric Mannich reaction.



Scheme 68 Mannich-type reaction of phosphorous ylides mediated by a thiourea catalyst.

activates the nucleophile.[110] The products **249** resulting from the addition of malonates to *N*-Boc-protected 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 **132** in high yield. The same group also tested catalyst **248** for the Mannich reaction with *in situ*-generated carbamate-protected imines (Scheme 69b).[111] The Mannich adducts **252** were obtained in high yield with up to 96% *ee* starting from α-amino sulfone **251**, dibenzyl malonate **250** and catalyst **248**.

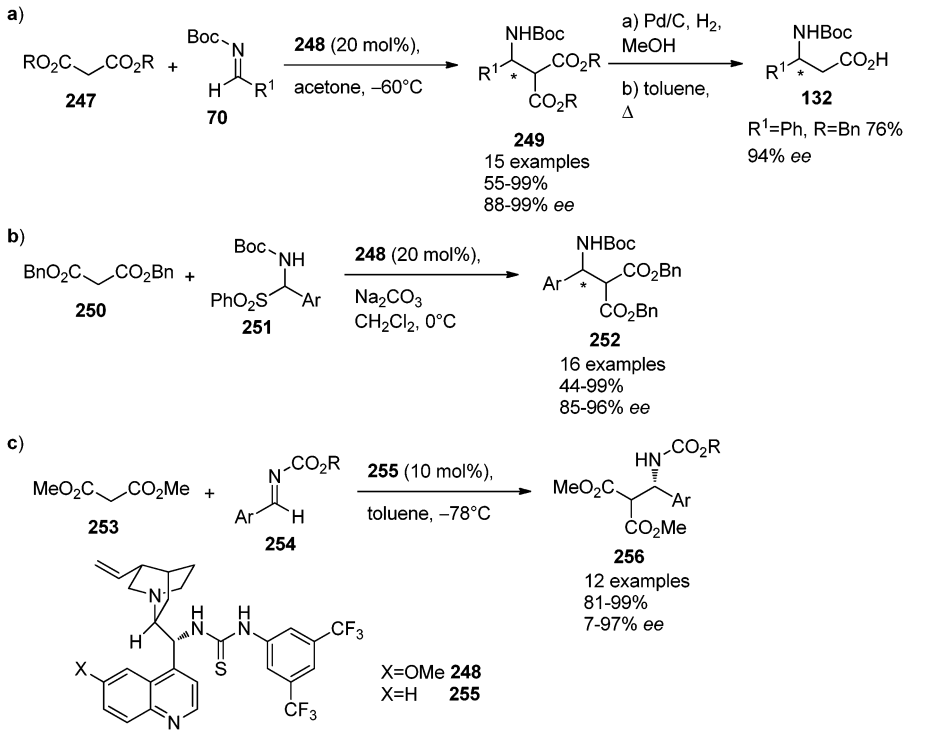
Dixon and co-workers used a similar thiourea–cinchonine alkaloid catalyst **255** for the addition of malonates to *N*-Boc- and *N*-Cbz-protected aldimines **254** (Scheme 69c),[112] providing the Mannich adducts in high yield with up to 97% *ee*.

A related asymmetric Mannich reaction of β-keto esters with imines catalyzed by cinchonine alkaloid **259** was reported by Schaus and co-workers (Scheme 70a).[113] Cinchonine **259** 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 **261** was obtained. The same catalyst was also successful in the addition of cyclic β-keto esters, providing high yield, and high diastereo- and enantioselectivities (Scheme 70b).[114]

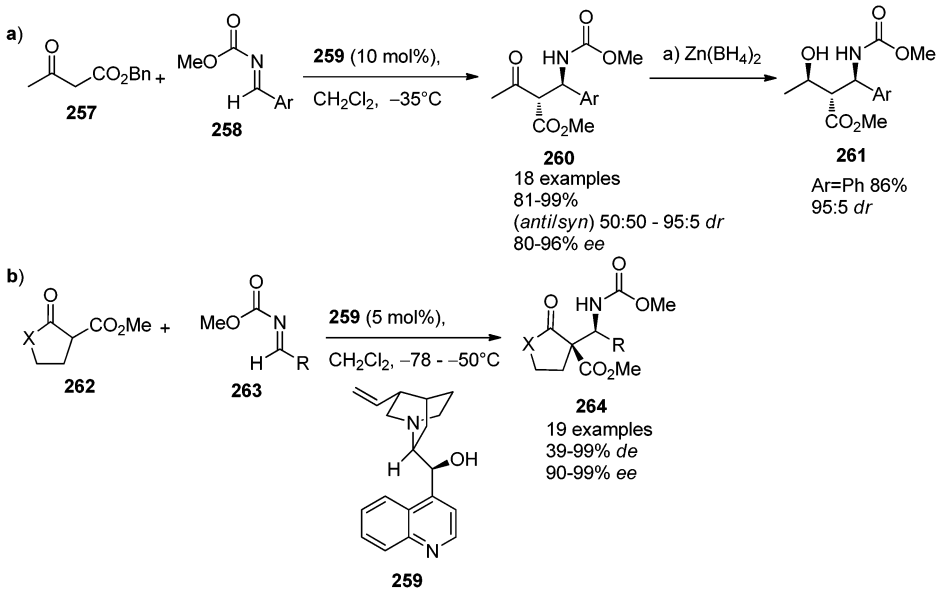
Jørgensen and co-workers investigated quinidine alkaloid derivative **267** in the reaction of α-cyanoacetates **265** with α-imido carboxylates **266** (Scheme 71).[115] Aromatic α-cyanoacetates **265** gave the corresponding Mannich adducts **268** in high yield in a highly diastereo- and enantioselective transformation; the highest *ee* and *dr* were obtained starting from α-cyanobenzyl carboxylate.

Barbas III and co-workers studied the Mannich reaction of thioesters with an *in situ*-generated *N*-Boc imine catalyzed by *Cinchona* alkaloid **271** (Scheme 72).[116] However, the Mannich adduct was only obtained with moderate enantioselectivity.

Proline and proline derivatives are important catalysts for organocatalytic transformations.[117] Proline acts hereby as a multifunctional catalyst.[118] The amine group of proline reacts with the carbonyl group of the substrate to generate an



Scheme 69 Thiourea–quinine and cinchonine-derived catalysts for the asymmetric Mannich reaction.

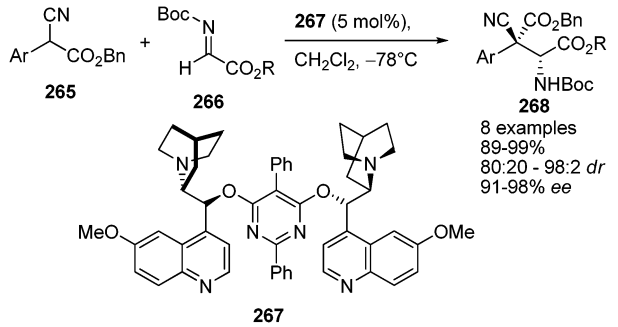


Scheme 70 Cinchonine-catalyzed asymmetric Mannich reaction of cyclic and acyclic β-ketoesters.

enamine, while the carboxylic acid functionality activates the electrophile *via* hydrogen-bonding to provide a highly ordered transition state.[96] 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 co-workers have used L-proline **275** as catalyst in the addition of aliphatic aldehydes **273** to PMP-protected glyoxylate-derived imine **274** (Scheme 73).[119] The *syn*-products **276** were obtained with high *dr*'s and *ee*'s, and subsequently oxidized and cyclized to provide β-lactams **277**. When an aqueous medium, such as THF–H_2O (9 : 1), was used in this Mannich reaction and the catalyst loading was increased to 10 mol%, the *syn*-adduct was obtained with high diastereo- (95 : 5) and high enantioselectivity (up to 99%).[120]

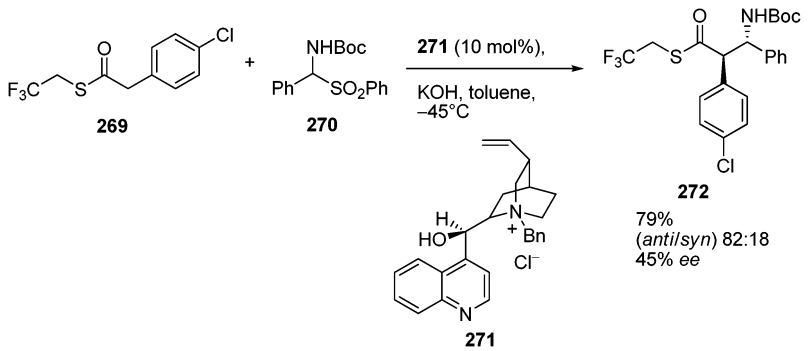
Quaternary all carbon stereocentres were also synthesized *via* a Mannich reaction using proline catalysis and α-branched aldehydes (Scheme 74).[121] α,α-Disubstituted aldehydes **278**



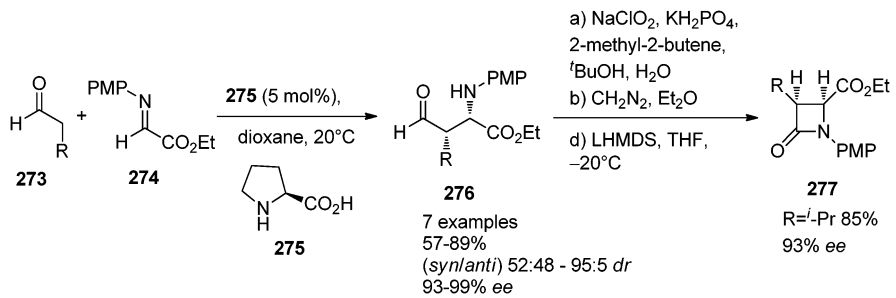
Scheme 71 Quinidine alkaloid-catalyzed asymmetric Mannich reaction of α-imido carboxylates with α-cyanoacetates.

were used as donor reagents in the addition to glyoxylate-derived imine **274** 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*). However, high catalyst loadings (30 mol%) were required. In one example, product **279** was converted into the β-lactam **280**.

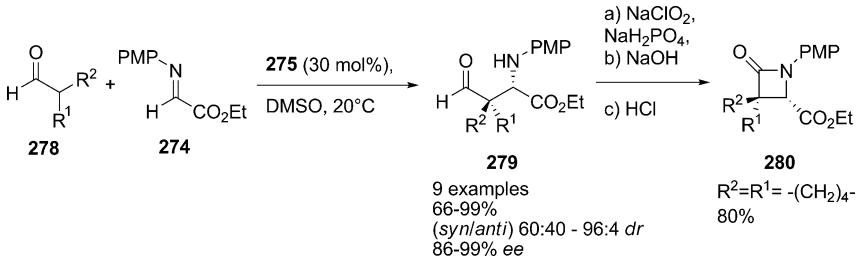
An extension of the scope of the direct asymmetric Mannich reaction of unmodified aldehydes was reported in 2003 by Barbas III (Scheme 75).[122] Several substituted proline derivatives were investigated in the addition of aldehydes to α-imino ethyl glyoxylate, revealing that proline gives the best diastereoselectivities for the formation of the *syn*-adduct with high enantioselectivity (up to 99% *ee*). However, (*S*)-2-methoxymethylpyrrolidine shows reversed diastereoselectivity, *i.e.* the *anti*-adduct is formed preferentially with good enantioselectivity (74–92% *ee*). 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 stereochemistry of the products. For substituted aromatic amines (with electron withdrawing functional groups), a diastereomeric ratio of up to 95 : 5 for the *syn*-adduct is obtained. Furthermore, the authors describe a 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 75).



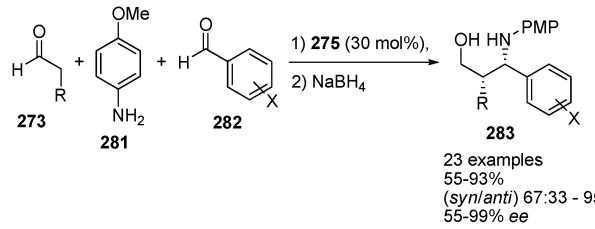
Scheme 72 *Cinchona* alkaloid-catalyzed asymmetric Mannich reaction.



Scheme 73 Proline-catalyzed asymmetric Mannich reaction of aldehydes and α-imido carboxylates to yield β-lactams after three consecutive steps.



Scheme 74 Proline-catalyzed asymmetric Mannich reaction to form quaternary all carbon stereocentres.



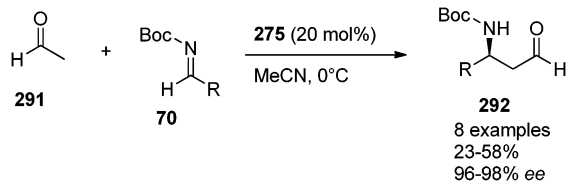
Scheme 75 Proline-catalyzed asymmetric one-pot-three component Mannich reaction.

Hayashi and co-workers 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 75).[123] The same three-component Mannich reaction has been described by Córdova for the synthesis of γ-amino alcohols.[124] 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 (Scheme 75).[125]

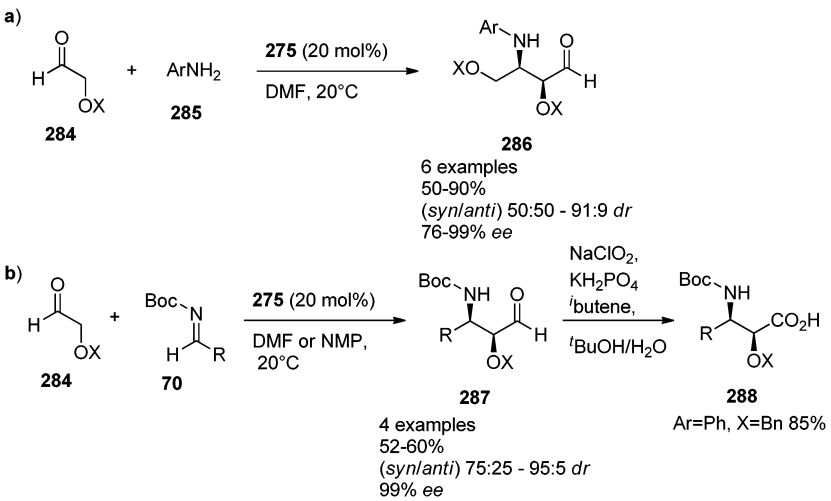
Using glycol aldehydes as substrates, protected amino-tetroses **286** (Scheme 76a)[126] and *syn*-α-hydroxy-β-amino acids **288** (Scheme 76b)[127] were prepared. However, high catalyst loadings of proline are necessary to achieve excellent enantio-selectivities (*ee* up to 99%) and good diastereoselectivity. The diastereomeric ratio is in some cases up to 91 : 9 but for most substrates it does not exceed 80 : 20 (*syn* : *anti*). 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 76b). The products were converted by oxidation to the corresponding *N*-protected-β-amino acids.

List and co-workers reported excellent diastereoselectivities (*dr* up to 99 : 1) and enantioselectivities (*ee* > 98%) towards the *syn*-adduct for the proline catalyzed addition of aldehydes to aromatic *N*-Boc-protected imines **70** (Scheme 77a).[128] Employing slightly different reaction conditions, Córdova and co-workers also reported this transformation (Scheme 77b).[129] For a variety of aliphatic and allylic aldehydes the *syn*-products **290** were obtained in a highly diastereo- and enantioselective transformation.

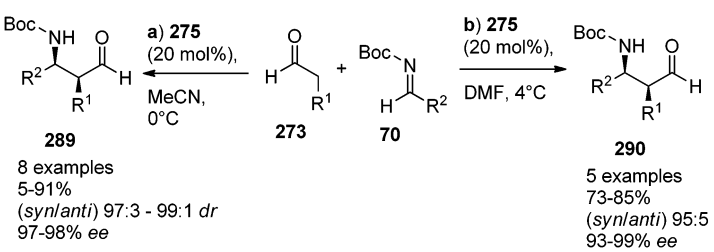
In 2008, the List group reported the proline-catalyzed reaction of *N*-Boc-imines with acetaldehyde (Scheme 78).[130] Various aromatic, heteroaromatic and aliphatic β-amino aldehydes are obtained with excellent *ee* (up to 99%); however, the yields are low (23–58%), and a high catalyst loading of proline (20 mol%) is employed.



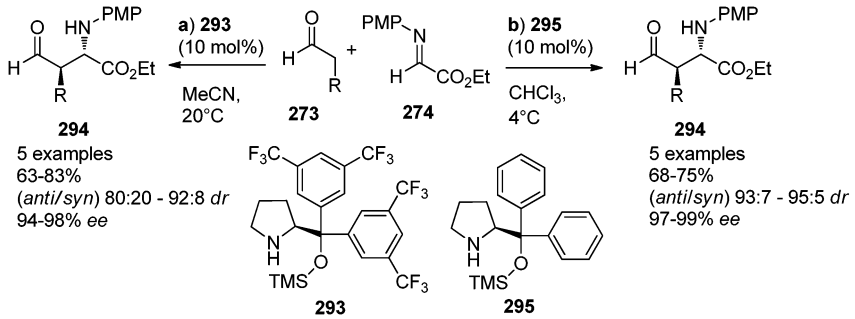
Scheme 78 Proline catalyzed Mannich reaction of acetaldehyde.



Scheme 76 Proline-catalyzed asymmetric synthesis of α-hydroxy-β-amino aldehydes.



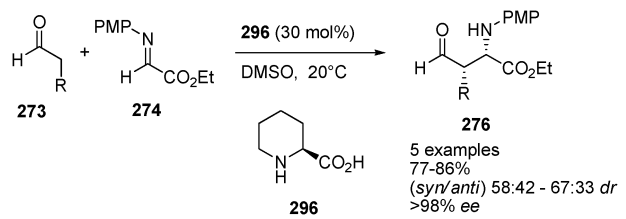
Scheme 77 Proline-catalyzed asymmetric Mannich reaction of *N*-Boc-imines (a) by List and (b) by Córdova.



Scheme 79 Mannich reaction of aldehydes catalyzed by proline derivatives (a) by Jørgensen and (b) by Córdova.

Hayashi and co-workers performed experimental studies towards the mechanism and compared the reactivity of aldimines to aldehydes employing NMR spectroscopy and theoretical methods.[131] 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 favorable than protonation of the aldehyde.

Several alternative organocatalysts based on proline have been designed in recent years. Jørgensen and co-workers used TMS-protected catalyst **293** in the Mannich reaction of PMP-protected α-imino ethylglyoxylate **274** and aliphatic aldehydes **273** (Scheme 79a).[132] 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 co-workers using related catalyst **295** giving the *anti* adducts with good selectivity (Scheme 79b).[133]

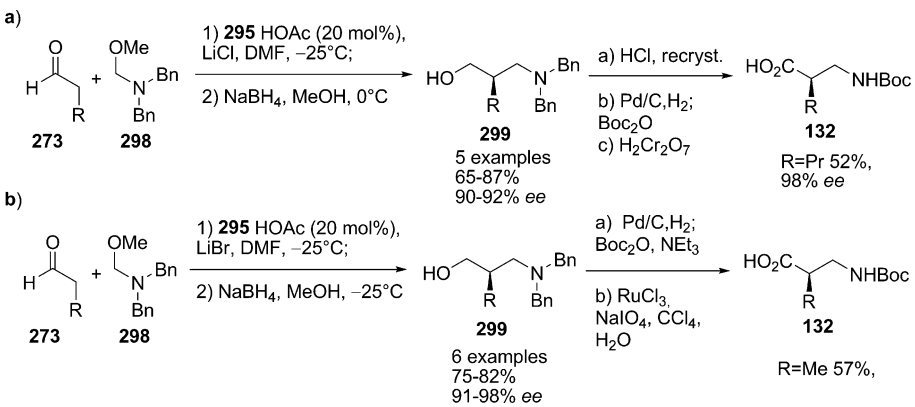


Scheme 80 Mannich reaction catalyzed by pipecolic acid.

Hayashi and co-workers performed calculations and experiments on the Mannich reaction with catalyst **293** and **295**. The addition of acetaldehyde to *N*-Bz-, *N*-Boc- and *N*-Ts-protected aromatic imines revealed that in the presence of *p*-$NO_2C_6H_4CO_2H$ as additive, better yields and excellent enantioselectivities were obtained.[134]

Moreover, pipecolic acid **296**, the 6-membered ring analogue of proline, was used by Barbas III and co-workers in the addition of aliphatic aldehydes **273** to α-imino ethylglyoxylate **274** (Scheme 80).[135] The *ee*'s are high for both diastereoisomers (*ee* >98%), but the selectivity towards *syn* adducts is usually low (*dr* up to 67 : 33).

The enantioselective aminomethylation of aldehydes was investigated by Gellman and co-workers for the synthesis of β^2-amino acid building blocks for peptide synthesis (Scheme 81a).[136] An iminium species was *in situ*-generated by elimination of MeOH from aminal **298**. Proline derivative **295** catalyzed the addition of aliphatic aldehydes to give the adducts in good yield with high *ee* (up to 92%). The β-amino aldehydes were reduced *in situ* to the corresponding alcohols. For the synthesis of β^2-amino acids, the amino alcohol was recrystallized as a 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 **132**. Córdova and co-workers screened further additives and found that LiBr increases the enantioselectivity (*ee* up to 98%) (Scheme 81b).[137] The corresponding β^2-amino acid **132** was synthesized by removal of the benzyl protecting group and reprotection of the amine using Boc_2O, followed by oxidation of the alcohol to the carboxylic acid providing *N*-Boc-β-amino acid **132** with an overall yield of 57%.



Scheme 81 Organocatalytic aminomethylation for the synthesis of β^2-amino acids (a) by Gellman and (b) by Córdova.

In summary, in recent years the organocatalytic Mannich reaction has found widespread application in the synthesis of β-amino acids. Both β^2- and β^3-amino acids, as well as $\beta^{2,3}$-amino acids, are accessible with high diastereoselectivities towards the *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. Furthermore, simple carboxylic esters have not yet been used as substrates to give β-amino esters *via* Mannich reaction. Therefore, further transformations of Mannich reaction products into β-amino acids are usually necessary.

1.3.2 Conjugate addition

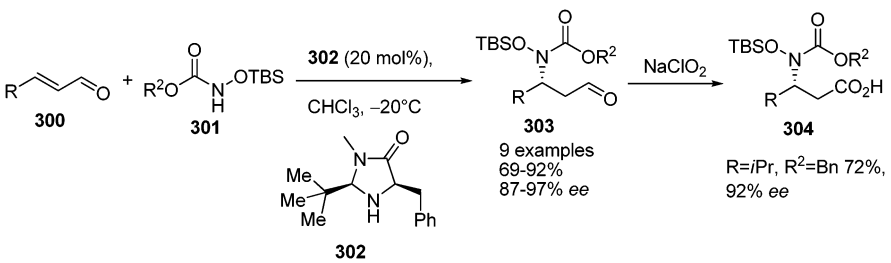
Organocatalytic C–N bond formations *via* conjugate addition are especially important for the synthesis of β-amino acids. MacMillan and co-workers designed nitrogen nucleophile **301** that readily undergoes a conjugate addition to α,β-unsaturated aldehydes (Scheme 82).[138] In the presence of an imidazolidinone organocatalyst **302** (as TFA-salt), benzyl *tert*-butyldimethylsiloxycarbamate **301** was added to aliphatic and benzyloxy-substituted α,β-unsaturated aldehydes **300**. 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 a weak base ($pK_a \sim 9$). The products **303** are obtained in high yield with up to 97% *ee*, and were subsequently oxidized to *N*-protected β^3-amino acids **304**.

Following a similar approach, Córdova and co-workers reported that proline-derived chiral amine **295** catalyzes the conjugate addition of *N*-Cbz-methoxylamine **305** to α,β-unsaturated aldehydes (Scheme 83a).[139] The β-amino aldehydes were obtained in high yield with high enantiomeric excess (up to 98%). A subsequent oxidation of the aldehyde **306** to the corresponding carboxylic acid and deprotection of the amine provided β^3-amino acids **307**. When carbamate-protected hydroxylamines **308** were used as nucleophiles, the cyclic 5-hydroxy-isooxazolidinones **309** were obtained with high *ee* up to 99% (Scheme 83b).[140] These intermediates were subsequently cleaved by hydrogenolysis to give β^3-amino acid **307** with high *ee*.

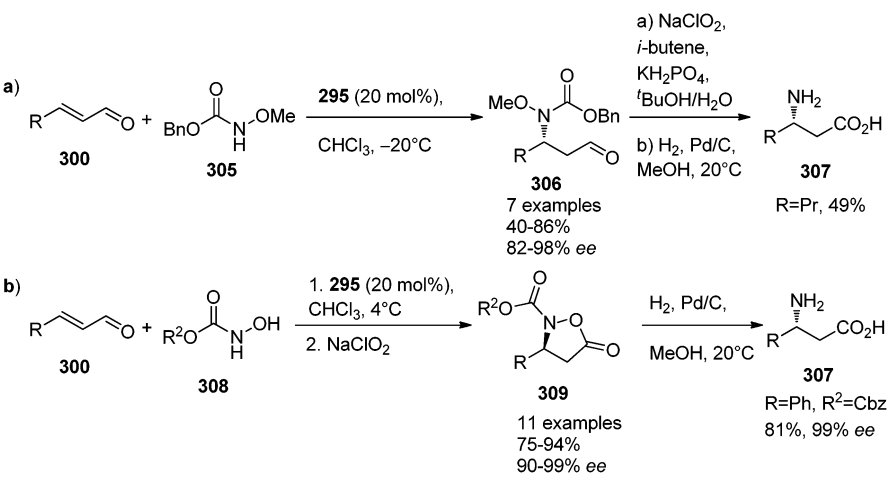
Proline derivative **293** has also been used for the intramolecular aza-Michael addition (Scheme 84).[141] Piperidines and pyrrolidines were synthesized with up to 95% *ee*. The aldehydes were oxidized to the corresponding carboxylic acids, such as homopipecolic acid derivative **312**.

Sibi and Itho used thiourea catalyst **314** for the conjugate addition of *O*-substituted hydroxylamines to pyrazole-functionalized Michael acceptors **313** (Scheme 85).[142] Aliphatic α,β-unsaturated substrates (R = alkyl) gave high enantioselectivities but phenyl-substituted substrates (R = Ph) gave the adducts with only moderate *ee*.

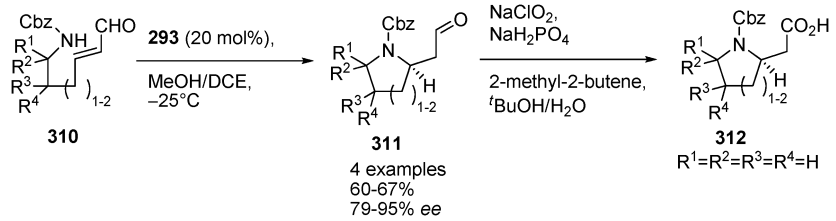
Moreover, carbon nucleophiles have been added to α,β-unsaturated substrates using organocatalysts. An illustrative example leading to β-amino acids pertains to the addition of



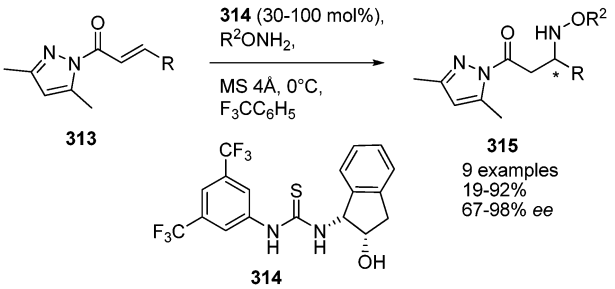
Scheme 82 Organocatalytic aza-Michael addition.



Scheme 83 Organocatalytic aza-Michael addition.



Scheme 84 Intramolecular organocatalytic aza-Michael addition; yields correspond to those of the alcohols obtained by the reduction of products **311**.



Scheme 85 Thiourea catalyzed aza-Michael addition of hydroxylamines.

malonates to α,β-unsaturated nitroalkenes catalyzed by thiourea **318** (Scheme 86).[143] The products **319** were obtained with high enantioselectivity using only 1 mol% of the organocatalyst. Subsequent Baeyer–Villiger oxidation gave the corresponding ester **320**, and a subsequent reduction with DIBAL-H provided the diol **321**, which was oxidatively cleaved. Finally, the nitro group was reduced to give the free amino acid **307**.

The organocatalytic addition of amines to α,β-unsaturated carbonyl compounds represents a fast and atom-economic entry into the synthesis of β-amino acids, which generally proceeds with very high enantioselectivities. Many synthetically useful Michael adducts can be made readily in enantiomerically pure form *via* conjugate addition. However, relatively high catalyst loadings of 20–30% are usually employed. A major challenge is to further optimize the organocatalytic conjugate addition of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds with regard to both catalyst loading and substrate scope.

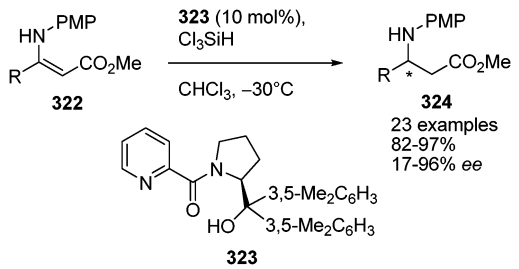
1.3.3 Miscellaneous

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

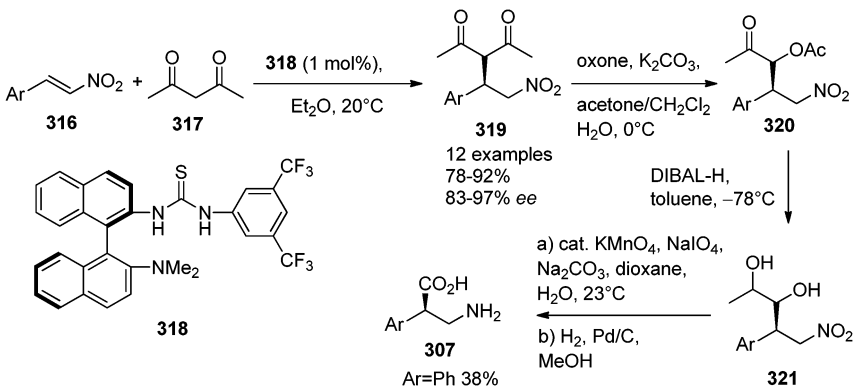
For instance, Lewis base **323** catalyzes the hydrosilylation of β-enamino esters (Scheme 87).[144] The aromatic, aliphatic or cyclic (*Z*)-enamino esters **322** were hydrosilylated using trichlorosilane to give the corresponding β^3-amino esters **324** in high yield with high enantiomeric excess.

List and co-workers studied the transfer hydrogenation of β-nitroalkenes catalyzed by thiourea **326** (Scheme 88).[145] The Hantzsch ester was used as hydrogen source, leading to β-amino acid precursors **327** with high enantiomeric excess when (*E*)-alkenes were used, and high *ee* of the opposite enantiomer starting from (*Z*)-alkenes.

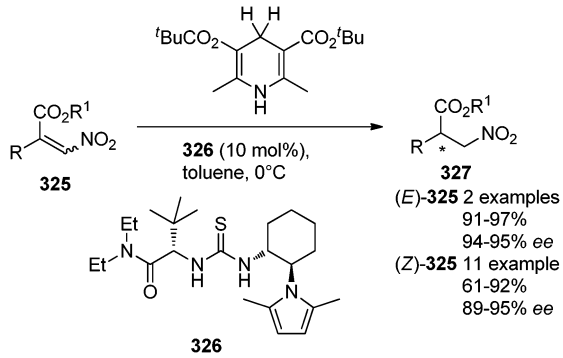
An alternative approach to β-amino acids based on a dynamic kinetic resolution was applied in the reduction of enamines with trichlorosilane (Scheme 89).[146] α-Amino acid-derived amide **330** was used in the reduction with trichlorosilane of imines **329**,



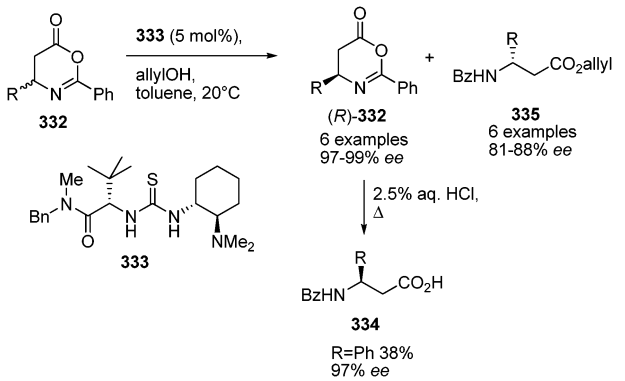
Scheme 87 Organocatalytic hydrosilylation of enamino esters.



Scheme 86 Thiourea catalyzed aza-Michael addition of malonates to nitroalkenes.



Scheme 88 Thiourea-catalyzed conjugate reduction of nitroalkenes.



Scheme 90 Organocatalytic kinetic resolution of oxazinones.

which are in equilibrium with the corresponding enamines **328**. The *syn*-$\beta^{2,3}$-amino esters **331** were isolated with high *dr* ($>99:1$) and high *ee* (90%).

Thiourea catalyst **333** was studied by Berkessel and co-workers for the kinetic resolution of racemic oxazinones **332** (Scheme 90).[147] With up to 57% conversion, the remaining chiral oxazinones **332** were isolated with $>99\%$ *ee* and the ring-opened β^3-amino ester **335** with 88% *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 **334** was isolated, frequently with 97% *ee*.

Córdova and co-workers reported that proline derivative **295** catalyzes the aziridination of α,β-unsaturated aldehydes (Scheme 91).[148] The α,β-aziridine aldehydes **336** were obtained in a highly enantioselective transformation (up to 99%), and were converted in one step into the corresponding Cbz-protected amino esters **338** in the presence of an *in situ*-generated thiazolium catalyst **337**.

A multistage, one-pot procedure was used for the synthesis of α,β-amino diesters (Scheme 92a).[149] A proposed mechanism involves the elimination of HCl from **347** catalyzed by benzoylquinine (BQ) **341** and stoichiometric amounts of proton sponge (PS) **342**, resulting in the formation of imine **348** (Scheme 92b). This reacts subsequently with enolate **346** derived from carboxylic acid chloride **339** *via* ketene **345**. The obtained β-lactam **343** undergoes ring opening upon treatment with methanol to yield aspartic acid derivative **344**. Moreover, in one step, β-lactams **350** were synthesized from preformed imines **349** and acyl chloride catalyzed by benzoylquinine **341** in the presence of stoichiometric amounts of base and 15-crown-5 (Scheme 92c).[150]

Jørgensen and co-workers used the [1,3]-sigmatropic rearrangement of racemic *O*-allylic trichloroacetimidates **351** to synthesize *N*-protected β-amino esters **352** catalyzed by dihydroquinidine $(DHQD)_2PHAL$ (Scheme 93).[151] The products of the rearrangement were obtained in good yield with high *ee* (up to 92%).

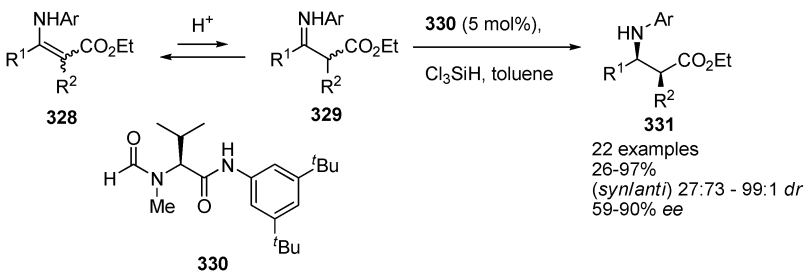
Chiral nucleophilic quinidine-derived catalyst **208** has been employed in the asymmetric aza-Baylis–Hillman reaction (Scheme 94).[152] Aromatic imines **49** and activated acrylate **353**, were reacted to give the Baylis–Hillman adducts **354** in moderate yield with moderate enantiomeric excess (up to 73%). Subsequent hydrolysis and ring closure upon treatment with BOPCl **355** gave β-lactams **356**.

N-Heterocyclic carbene **358** was shown to catalyze the addition of α,β-unsaturated aldehydes **300** to nitrosobenzene **357** *via* a reaction involving an umpolung of **300**. This transformation gives isooxazolidinone intermediates **359** which were transformed under acidic conditions to the corresponding methyl esters **360** (Scheme 95).[153]

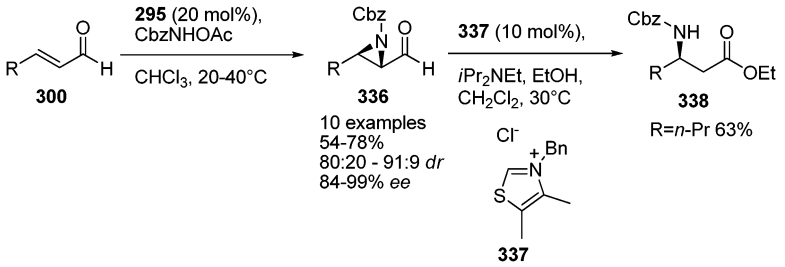
In summary, the routes to β^2- and β^3-amino acids and β-lactams based on a variety of methods including (transfer) hydrogenation, aziridination, (dynamic) kinetic resolution, one-pot reactions of imines with enolates, 1,3-sigmatropic rearrangement, aza-Baylis–Hillman reaction and umpolung of α,β-unsaturated aldehydes were discussed. In most cases, these reactions have limited scope so far, and are useful only in the synthesis of specific β-amino acid precursors or β-lactams.

1.4 Biocatalytic routes

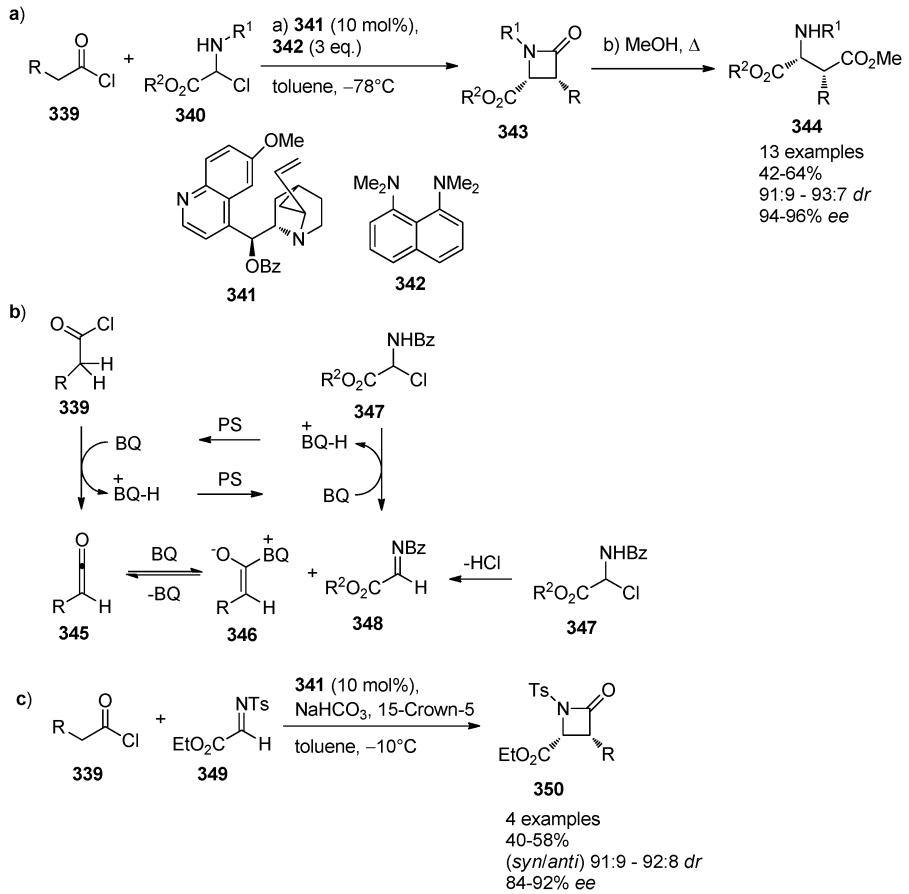
There are only few recent biocatalytic methods reported for the synthesis of β-amino acid apart from kinetic resolutions.[154] The biocatalytic preparation of enantiopure β-amino acids was reviewed in 2006;[154] therefore, this part will focus on non-kinetic resolutions since 2006.



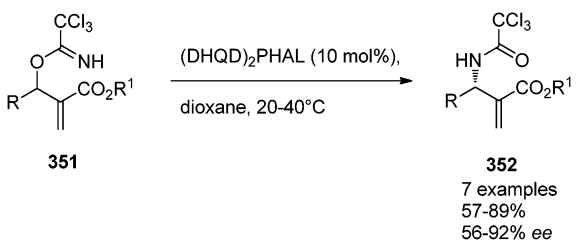
Scheme 89 Dynamic kinetic resolution of enamines towards β-amino acid derivatives.



Scheme 91 Organocatalytic aziridination of α,β-unsaturated aldehydes.



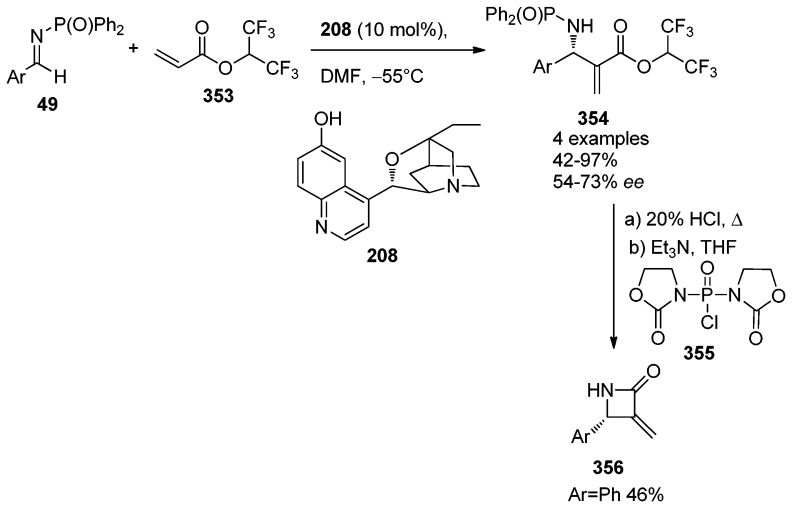
Scheme 92 Multistage one-pot procedure for the synthesis of β-lactams catalyzed by benzoylquinine.



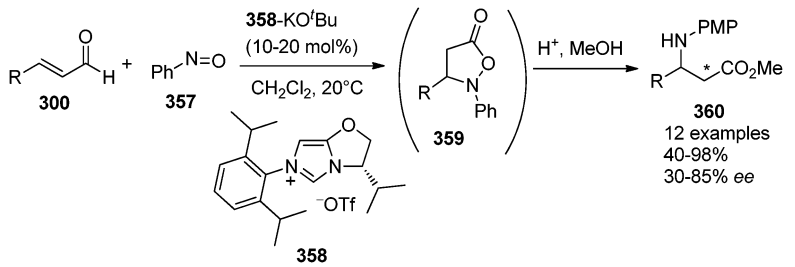
Scheme 93 [1,3]-Sigmatropic rearrangement for the synthesis of β-amino esters.

A β-transaminase from *Mesorhizobium* sp. LUK was cloned and characterized as a new biocatalyst for the synthesis of β-amino acids (Scheme 96).[155] However, only phenyl-substituted β-ketoester **361** was screened as a precursor in combination with a lipase from *Candida rugosa*, which catalyzes the hydrolysis of **361** to β-keto acid **362** being the substrate for the transamination. Racemic β-alanine **363** was used as nitrogen source and β-phenylalanine **365** was obtained after low conversion (20%) albeit with 99% *ee*.

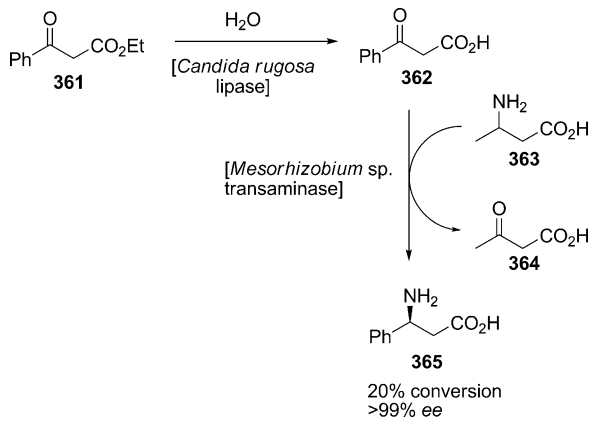
Saccharomyces carlsbergensis old yellow enzyme was studied in the asymmetric bioreduction of β-nitroacrylates (Scheme 97).[156] NADPH was supplied by a cofactor regeneration system (glucose-6-phosphate/bakers yeast glucose-6-phosphate dehydrogenase). (*Z*)-Alkenes **366** substituted α to the carboxylate 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 **367**. The scope is limited to small aliphatic substituents (Me, Et, *n*-Pr, *i*-Pr)



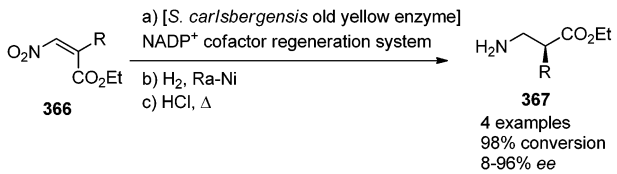
Scheme 94 Aza-Baylis–Hillman reaction for the synthesis of β-lactams.



Scheme 95 Addition of α,β-unsaturated aldehydes to nitrosobenzene catalyzed by *N*-heterocyclic carbenes.

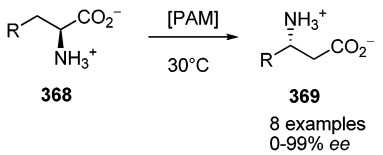


Scheme 96 Transaminase-catalyzed synthesis of β-phenylalanine.



Scheme 97 Synthesis of β^2-amino acids *via* bioreduction.

β-Styryl- and β-aryl-β-alanine derivatives have been synthesized using phenylalanine amino mutase (PAM) (Scheme 98).[157] Aromatic and heteroaromatic α-amino acids

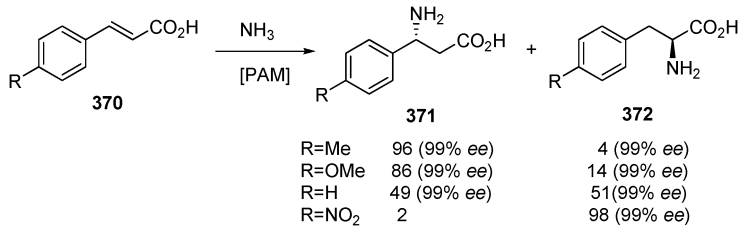


Scheme 98 PAM-catalyzed synthesis of β-amino acids from α-amino acids.

were employed to synthesize the corresponding β-amino acids with high enantioselectivity;[158] however, no isolation of the β-amino acids was described.

Janssen, Feringa and co-workers reported the use of PAM to catalyze the amination of cinnamic acid derivatives in a synthetic procedure for β-amino acids (Scheme 99).[159] A mixture of α- and β-amino acids is obtained which were not separated from each other or isolated. With electron donating substituents in the *para*-position of the aromatic ring, predominantly β-amino acids are formed with excellent *ee*'s. In PAM catalyzed addition of ammonia to the cinnamic acid **370** the mixture of unsubstituted α- and β-phenylalanines can be obtained with 50% yield. A convenient method for the separation of these isomers has been reported.[160]

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 limited substrate scope so far.



Scheme 99 PAM-catalyzed synthesis of β-amino acids form cinnamic acid derivatives.

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 pharmaceutical intermediates and peptidomimetics. In the past 15 years, tremendous progress has been made as shown in this review and preceding overviews.[6–8] Using many different methodologies, β^2- and β^3-amino acids with various substitution patterns are available. In many cases, rhodium- and ruthenium-catalyzed hydrogenation is the method of choice, due to very low catalyst loadings (down to 0.1 mol%), high selectivities (usually over 90% *ee*) and the formation of products that do not require a multi step functionalization to β-amino acids. Therefore, these methods should be considered first in the planning of the syntheses. Other transition-metal catalyzed processes, such as Mannich reaction or conjugate addition, are limited by the accessibility of the nucleophiles. They also usually require higher catalyst loadings (1–15 mol%). Nevertheless, they present a valuable tool for the preparation of β-amino acids with quaternary stereocenters and α,β-diamino acids.

In recent years, organocatalysis started to play 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 in transformations based on the Mannich reaction. However, in many cases high catalyst loadings have to be used (5–30 mol%), reaction times are in some cases rather long, and further transformations are needed to prepare the desired β-amino acids. On the other hand, one of the more promising catalysts, (*S*)-proline, is a naturally occurring amino acid, and therefore very cheap.

The need for environmentally friendly methods that would not require high catalyst loadings could be fulfilled by biocatalysis. However, up to now, most enzymatic methods rely on kinetic resolutions, which means that only 50% of the desired enantiomer of the product can be obtained, unless a dynamic kinetic resolution protocol is used. Only a few examples of direct enzymatic addition of ammonia to α,β-unsaturated carboxylic acids have been reported. Therefore, the catalytic asymmetric synthesis of β-amino acids starting from simple and cheap starting materials and using recyclable sustainable catalysts remains an important challenge for synthetic organic chemists.

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