Discovery and development of inhibitors selective for human constitutive proteasome and immunoproteasome active sites

Xin, B.; Xin B.

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Asymmetric synthesis of aliphatic α-amino acids

2.1 Introduction

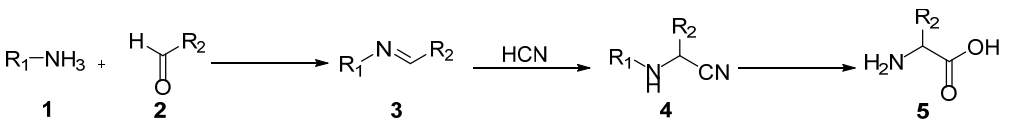
Amino acids are characterized by an amine (-NH_2) and a carboxylic acid (-COOH) functionality. In nature, 21 proteinogenic α-amino acids, which are also termed natural amino acids, exist and that are the building blocks of proteins. Non-proteinogenic α-amino acids are much more diverse in nature and besides this numerous synthetic α-amino acids have been prepared in the past decades. These are often used as substitutes for natural α-amino acids in the design of bioactive compounds. For instance, various aliphatic unnatural α-amino acids were incorporated in peptide-based proteasome inhibitors, which amongst others led to the discovery of potent and selective inhibitors of the chymotryptic activity (β5c) of human constitutive proteasomes. These and related studies require access to a wide array of aliphatic α-amino acids, and for this purpose numerous synthesis strategies have been explored in the past decades. In this chapter general synthesis strategies towards aliphatic α-amino acids are reviewed, with a focus on identifying conceptually distinct strategies, rather than on providing a complete overview of all research efforts in this field.

2.2 Synthetic methods

2.2.1 The Strecker reaction

The Strecker reaction is named after the German chemist Adolph Strecker who first reported this reaction in 1850.[1] The reaction starts with the condensation of an amine and an aldehyde to form a Schiff base. After the addition of HCN and subsequent hydrolysis, an amino acid is obtained, in which the side chain (R_2) functionality is derived from the nature of the aldehyde applied in the reaction (Scheme 1). The asymmetric Strecker reaction was first explored by Michael Worsley to prepare unnatural aliphatic α-amino acids.[2]

Scheme 1. General scheme of the Strecker reaction.



In the Worsley procedure, chiral amines such as *R*(+) and *S*(-)α-methylbenzylamine (Figure 1, **6** and **7**) were used to prepare chiral Schiff bases by condensation with achiral aldehydes. These Schiff bases were next reacted with HCN to obtain asymmetric Strecker products for further elaboration towards the target amino acids in high enantiomeric excess (>97%) (Scheme 2A). This methodology has been used to prepare a variety of amino acids also by other research groups.[3] For instance, 2,3,4,6-O-pivaloyl-β-D-galactopyranosyl imine (**19**) was reacted with trimethylsilyl cyanide with $SnCl_4$ as the Lewis acid in THF to give compound **20** (Scheme 2B).[4] Using the same Schiff base (**19**), but in combination with $ZnCl_2$ as the Lewis acid and $CHCl_3$ as solvent, the S-configured Strecker product was obtained predominantly (80% de). Schiff base **21**, which was prepared from *R*-α-phenylglycinol (**9**), was applied in the preparation of compound **22** and **23** (Scheme 2C).[5]

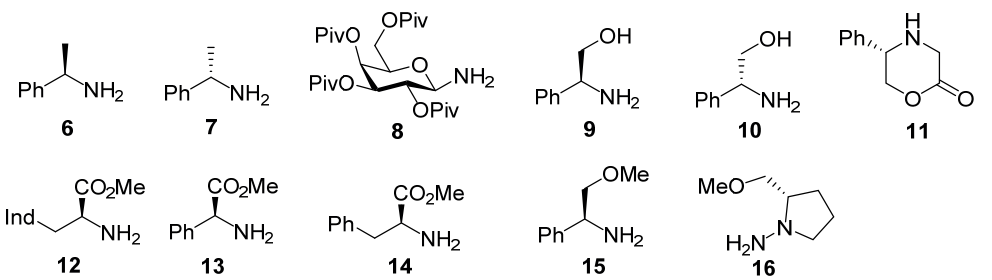
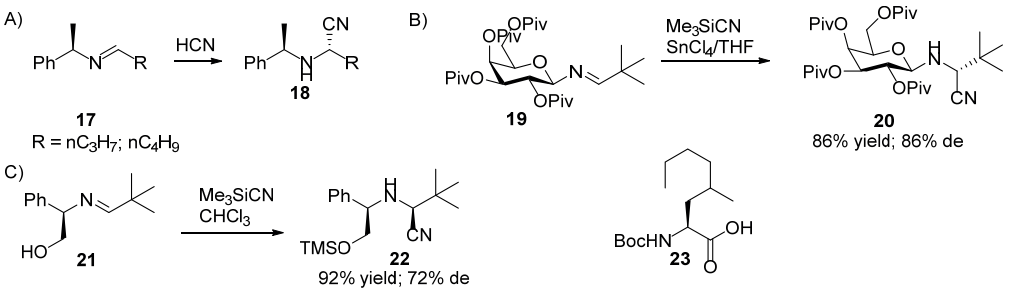
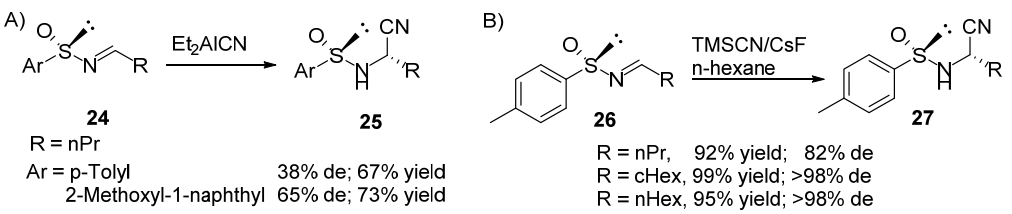


Figure 1. The structures of some chiral amines that have been applied in asymmetric Strecker reactions.[6]



Scheme 2. Application of chiral amines in diastereoselective Strecker reactions.

Chiral sulfinimimes were first developed by Davis and co-workers[7] for diastereoselective Strecker reactions using Et_2AlCN (Scheme 3A) as the cyanide source. Two chiral auxiliaries were explored for this reaction, which both gave low to medium de values. Later on, the same research group[8] found that when the imine (R = *t*Bu, Ar = *p*-Tolyl), Et_2AlCN and 2-propanol were used in a 1:1.5:1 (eq.) ratio, the de value increased to 80% and the product was obtained in 91% yield. This improved method was applied[9] in the preparation of β-fluoro α-amino acids. The combination of TMSCN and CsF was also applied in this process, also with high diastereoselectivity (Scheme 3B).[10]

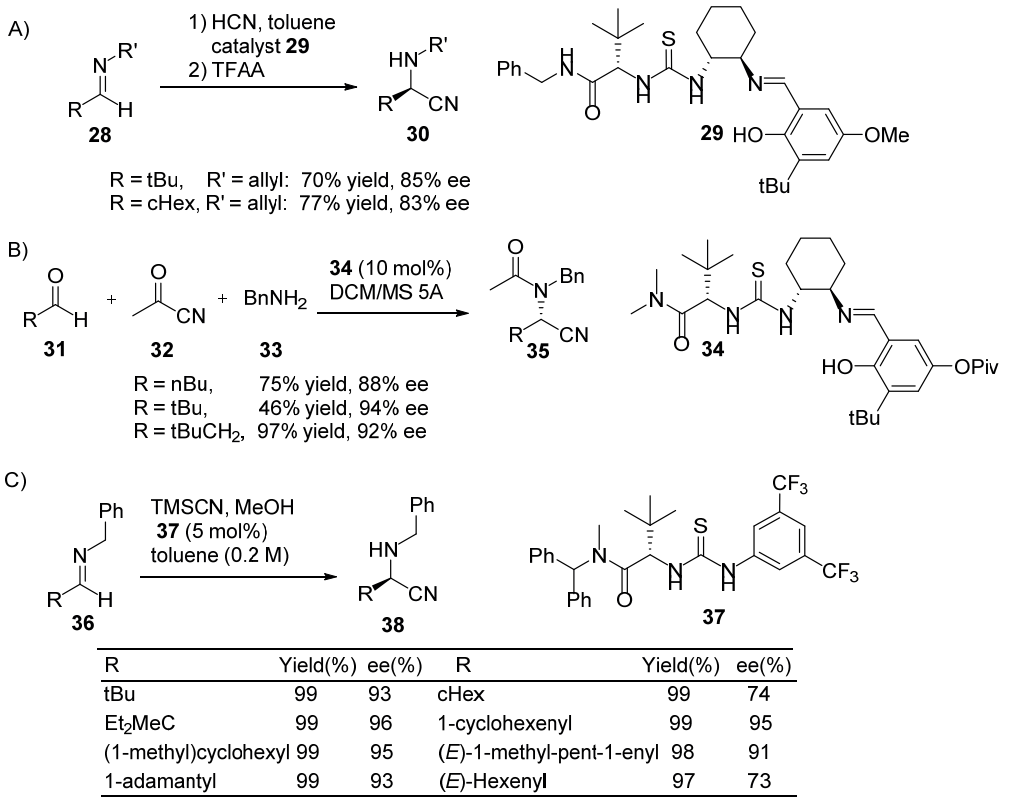


Scheme 3. Application of chiral sulfinimines in diatereoselective Strecker reactions.

The preparation of both enantiomers of adamantylalanine and carboranylalanine by asymmetric Strecker reaction on Ellmans tert-butyl sulfinimines was reported recently.[11] In preparing the adamantylalanine precursors, ethylisopropoxyaluminium cyanide was used as cyanide source[12] and the Strecker reaction proceeded in high enantioselectivity (92% enantiomeric excess, >99% enantiomeric excess after crystallization). This method was also used in the preparation of cis and trans bicyclohexylalanine.[13] In the asymmetric synthesis of carboranylalanine TMSCN was used as cyanide source in presence of CsF and the reaction proceeded in up to 85% de.

Various chiral catalysts have been developed for asymmetric Strecker reactions (Scheme 4). Several chiral imine-containing catalysts were found to catalyze this type of reaction.[14] Jacobsen and co-workers[14a] found that compound **29** is an effective catalyst for asymmetric Strecker reactions (Scheme 4A). The amino nitriles (**30**) were obtained with *R* configuration and in good enantiomeric excess. Catalyst **34** was used in one-pot asymmetric Strecker

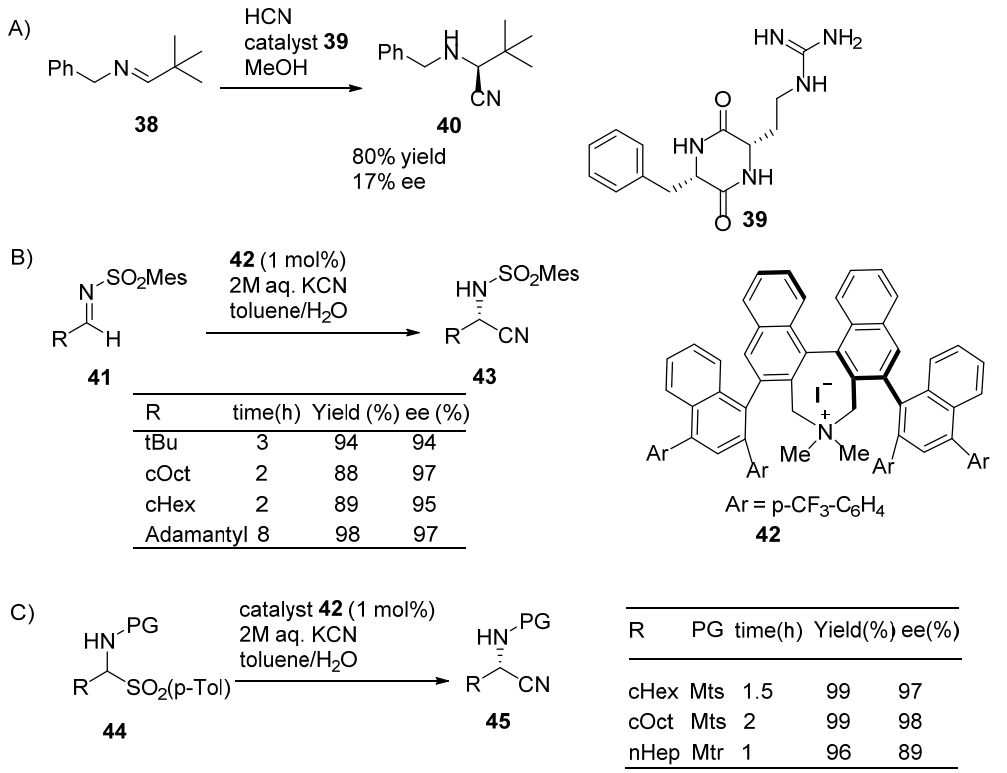
reaction, also in good ee (Scheme 4B).[15] Catalyst **37** is different from the other catalysts in this series as it does not have an imine moiety. Various substrates and reaction conditions were explored for this catalyst (Scheme 4C).[16]



R	Yield(%)	ee(%)	R	Yield(%)	ee(%)
tBu	99	93	cHex	99	74
Et_2MeC	99	96	1-cyclohexenyl	99	95
(1-methyl)cyclohexyl	99	95	(*E*)-1-methyl-pent-1-enyl	98	91
1-adamantyl	99	93	(*E*)-Hexenyl	97	73

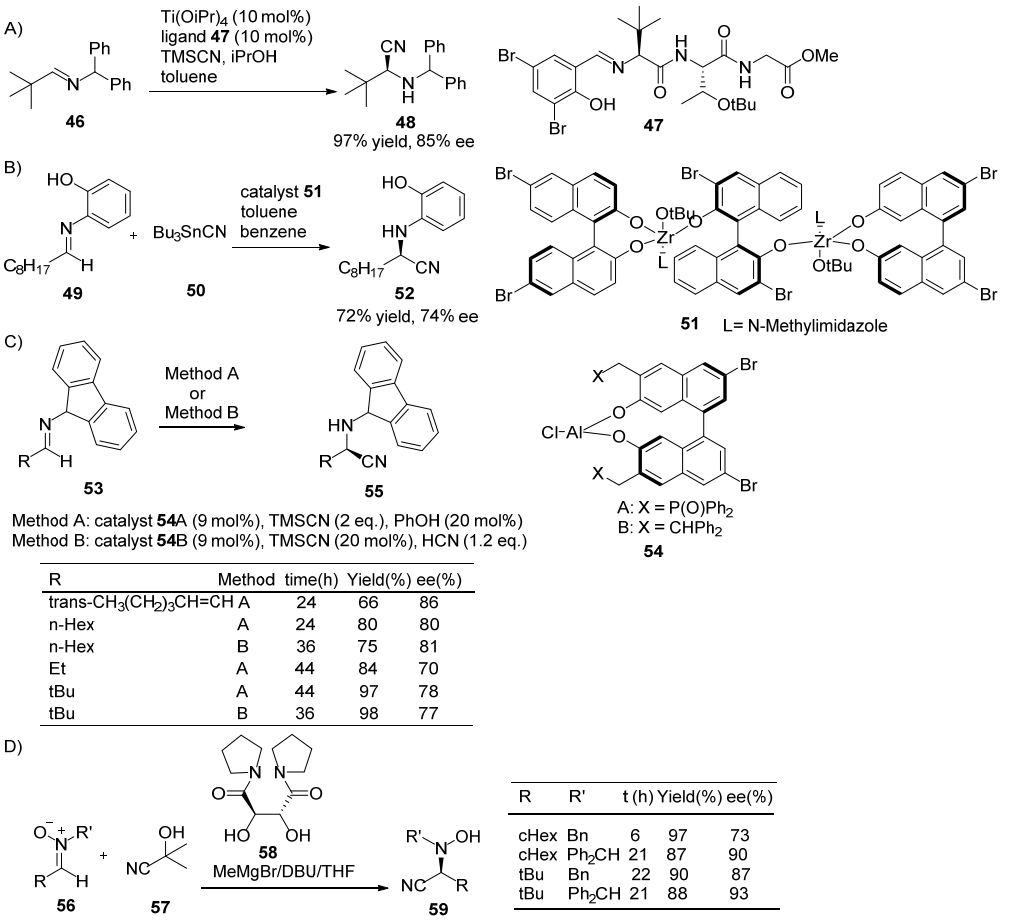
Scheme 4. Application of chiral catalysts in enantioselective Strecker reactions.

The cyclic dipeptide **39** was reported to catalyze asymmetric Strecker processes (Scheme 5A). However, the enantiomeric excess appeared to be very low (17%).[17] Catalyst **42** was developed as phase transfer catalyst (PTC) for the asymmetric Strecker-type reaction using aqueous KCN as cyanide source (Scheme 5B). Bulkyl groups (R = adamantyl) required longer reaction times and all product were obtained in high enantiomeric excess.[18] Later on, they used the same PTC system in the Strecker synthesis with compound **44** as starting material which could generate the reactive N-sulfonyl imines *in situ*, and the products were prepared in high enantiomeric excess (Scheme 5C).[19]



Scheme 5. Application of cyclic chiral catalysts in diatereoselective Strecker reactions.

Metal-containing catalysts were also developed for asymmetric Strecker reactions. $Ti(OiPr)_4$ was used in combination with various ligands to catalyze this reaction.[20] For example, this metal in combination with ligand **47** could catalyze the enantioselective addition of cyanide to imine **46** with high yield and enantiomeric excess (Scheme 6A).[20a] Chiral zirconium catalyst **51** was also reported to catalyze this reaction with tribuyltin cyanide **50** (Scheme 6B).[20b] The one-pot strategy was also developed for this asymmetric reaction.[21] The aluminium-containing bifunctional catalyst system was also explored for this asymmetric Strecker reactions.[22] Shibasaki and co-workers[22a] developed catalyst **54** for this type of asymmetric reaction. The products were obtained in modest enantiomeric excess (Scheme 6C). the magnesium-tartramide complex generated from compound **58** and MeMgBr, could catalyze the asymmetric cyanide addition to compound **56** using compound **57** as cyanide source and the products were obtained with medium to high enantiomeric excess (Scheme 6D).[23]



R	Method	time(h)	Yield(%)	ee(%)
trans-$CH_3(CH_2)_3CH$=CH	A	24	66	86
n-Hex	A	24	80	80
n-Hex	B	36	75	81
Et	A	44	84	70
tBu	A	44	97	78
tBu	B	36	98	77

R	R'	t (h)	Yield(%)	ee(%)
cHex	Bn	6	97	73
cHex	Ph_2CH	21	87	90
tBu	Bn	22	90	87
tBu	Ph_2CH	21	88	93

Scheme 6. Application of metal-containing chiral catalysts in diatereoselective Strecker reactions.

2.2.2 Catalytic hydrogenation of aromatic amino acids

Catalytic hydrogenation of aromatic amino acids is the most direct and concise method to prepare their aliphatic counterparts (Figure 2). Various catalyst and catalytic systems have been developed to carry out this type of reaction. H-Cha-OH (**60**) was prepared through the hydrogenation of H-Phe-OH in AcOH and H_2O with PtO_2 as the catalyst and the reaction was carried out at 50 psi H_2.[24] This catalytic system was also used by several other groups[25] to prepare H-Cha-OH and its analogs, and these studies investigated the influence of different solvent systems.[26] Rhodium on carbon (5% Rh/C) can also catalyze the hydrogenation of H-Phg-OH to H-Chg-OH (**61**) in aqueous HCl and under 3.6 bar H_2 pressure.[27] Various catalytic conditions for the reduction of H-Phe-OH to H-Cha-OH with Rh/C were investigated.[28] It appeared that catalyst loading (5% or 10%) did not affect the reaction. The reaction also went on smoothly in various solvent systems. However, no conversion was observed when pure acetic acid was used as solvent and also when the reaction was carried out in a big batch. Prakash and co-worker[29] found that hydrogenation of H-Phe-OH required acidic conditions

(hydrochloride, sulfuric or phosphoric acids) when using Rh/C. When replacing Rh/C with rhodium on alumina (Rh/Al), no acid was needed to obtain high yield. In reducing H-Phg-OH to H-Chg-H, basic conditions proved superior to acidic conditions. Furthermore, other catalysts, such as 5% ruthenium on active carbon,[30] Raney nickel,[31] (CAAC-1)Rh(COD)Cl complex[32] and 5% Rh/Al (rhodium on activated aluminum)[13,33] can also be used to catalyze this type of reactions, yielding various aliphatic amino acids.

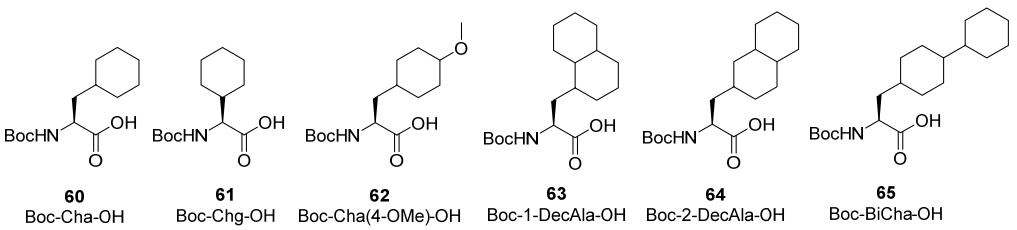
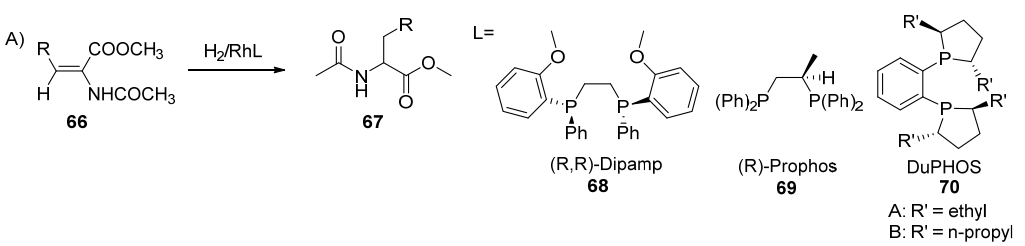


Figure 2. Representative structures of amino acids, prepared through catalytic hydrogenation of their aromatic counterparts.

2.2.3 Catalytic asymmetric hydrogenation of dedydroamino acid

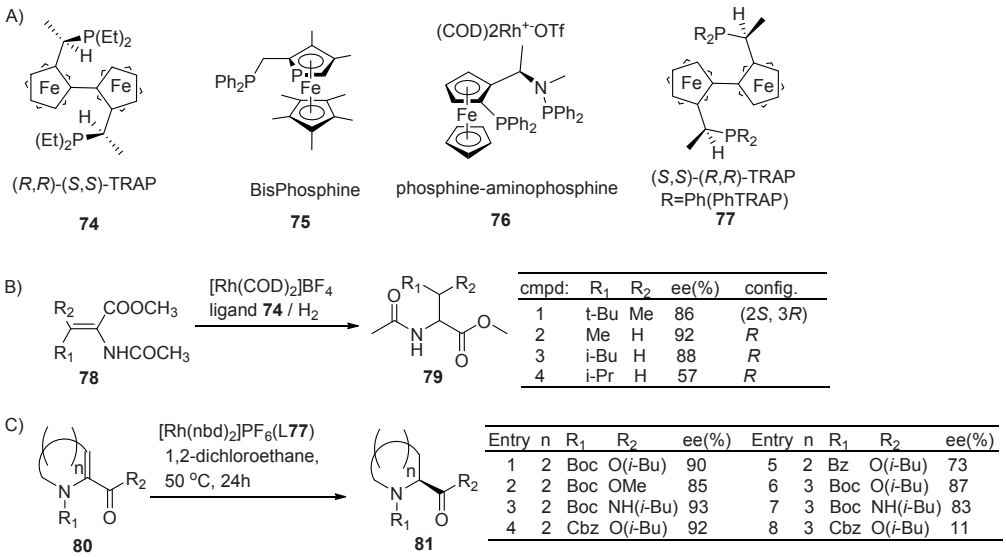
The preparation of enantiomerically pure α-amino acids from asymmetric hydrogenation of the corresponding dehydroamino acid has been reported for a long time and various rhodium-containing catalyst systems were developed. Various phosphine containing ligands have been used to form complexes with rhodium.[34] Rhodium-chiral phosphine (**68**, **69** and **70**) complexes can catalyze the homogeneous hydrogenation of dehydroamino acid with aliphatic side chains (Scheme 7A).[34a] Different substrates were explored in this reaction.[34b] Rhodium-chiral phosphine (**73**) complex was used to catalyze the hydrogenation of cyclic dehydroamino acids (**71**) with different ring sizes (Scheme 7B). Small ring size (n=1,2) gave low enantiomeric excess but large ring size (up to n=12) gives good enantioselectivities and high yields.[34c]



n	yield(%)	ee(%)	n	yield(%)	ee(%)
1	84	0.4	5	97	94.5
2	95	26.5	9	96	91.3
3	96	94.8	12	86	86.0
4	96	97.0			

Scheme 7. Catalytic hydrogenation of dehydroamino acids catalyzed by rhodium-chiral phosphine complex.

Ferrocene-containing ligands were also developed for this reaction (Figure 3A).[35] The rhodium-(*R*,*R*)-(*S*,*S*)-TRAP(**74**) complex was used to catalyze the asymmetric hydrogenation of compound **78** to **79** (Figure 3B). The products were obtained with different configurations.[35a] The trans-chelating chiral ligand **77**-Rh complex was also applied to asymmetric catalytic hydrogenation of the cyclic dehydroamino acids (Figure 3C). Aliphatic six- and seven-membered ring substrates with different protecting group were subjected to these reaction conditions.[35b]



cmpd:	R_1	R_2	ee(%)	config.
1	t-Bu	Me	86	(2*S*, 3*R*)
2	Me	H	92	*R*
3	i-Bu	H	88	*R*
4	i-Pr	H	57	*R*

Entry	n	R_1	R_2	ee(%)	Entry	n	R_1	R_2	ee(%)
1	2	Boc	O(*i*-Bu)	90	5	2	Bz	O(*i*-Bu)	73
2	2	Boc	OMe	85	6	3	Boc	O(*i*-Bu)	87
3	2	Boc	NH(*i*-Bu)	93	7	3	Boc	NH(*i*-Bu)	83
4	2	Cbz	O(*i*-Bu)	92	8	3	Cbz	O(*i*-Bu)	11

Figure 3. Catalytic hydrogenation of didehydroamino acids catalyzed by rhodium-ferrocene complex.

Riley and co-workers[36] reported 1,2-bis(diphenylphosphino)-cyclohexylethane (**83**) as a new chiral ligand in catalyst [Rh((R)-cycphos)-(norbornadiene)]PF_4 (Figure 4A). This catalyst was used in the preparation of L-2-amino-5-methylhexanoic acid precursor **84** through asymmetric hydrogenation. The chiral mixed rhodium-phosphorus/sulfur (**85** and **86**) system could also enantioselectively catalyze the hydrogenation of dehydroamino acids (Figure 4B). By using different ligands, the products with *R* and *S* configurations can be obtained with high enantiomeric excess.[37] (*S*)-pipecolic acid methyl ester **89** was prepared through the asymmetric catalytic hydrogenation of the cyclic dehydroamino acid **87** using the Noyori's ruthenium catalyst, $RuCl_2$-(*R*)-BINAP (Figure 4C).[38]

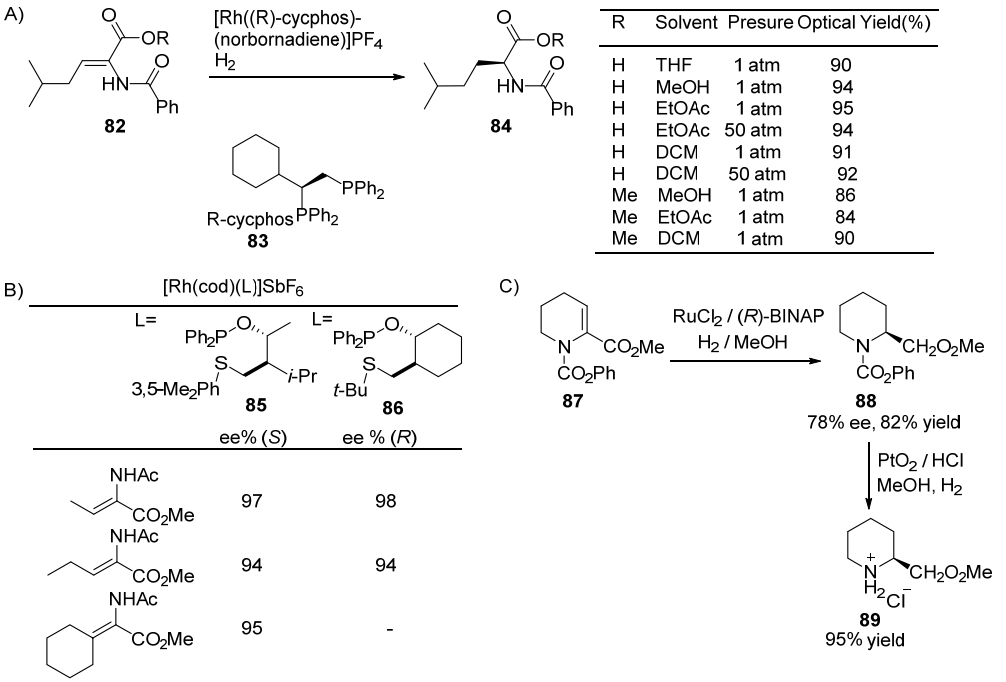


Figure 4. Rhodium-catalyzed hydrogenation of dehydroamino acids.

2.2.4 Alkylation of glycine

Cinchonidine and its derivatives are widely used in the preparation of non-natural amino acids by asymmetric alkylation of glycine derivatives (Figure 5).[39] Compound **100** could be enantioselectively alkylated when using catalyst **90** (Scheme 8A). The obtained product can be further transformed into the corresponding amino acids.[39a] Organoboranes (**103**), together with catalyst **94** were also used for the synthesis of *S* and *R* amino acids (Scheme 8B). A variety of aliphatic substituents including cyclic side chains of different ring size could be used in this strategy.[39b]

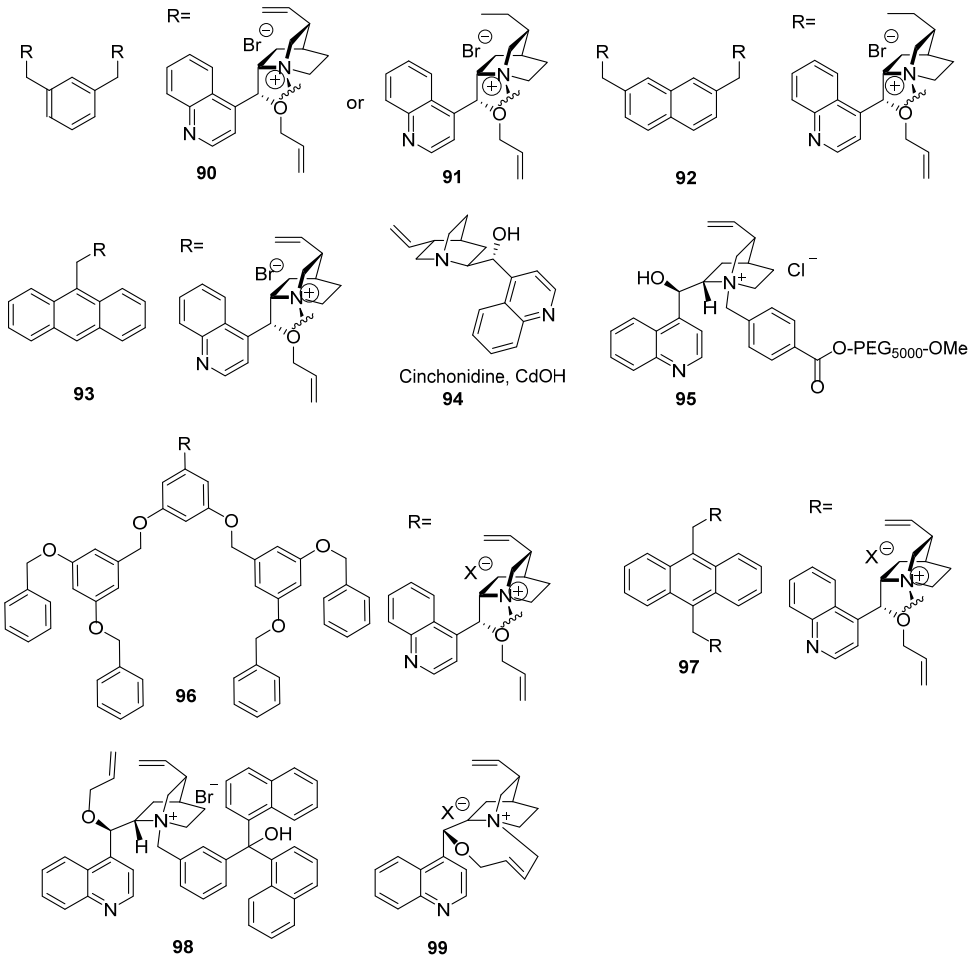
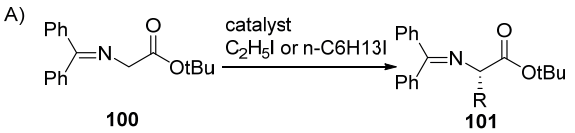
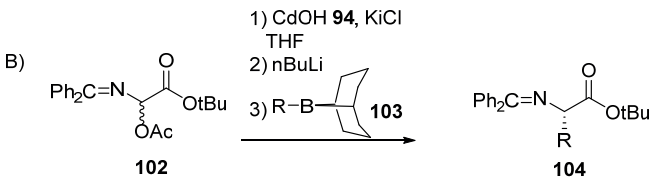
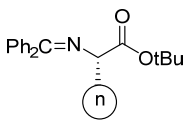


Figure 5. Structures of cinchonidine–containing catalysts.

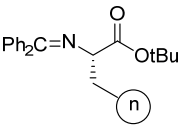


RX	Catatyst	Time(h)	Yield(%)	ee(%)
$C2H_5$**I**	**90**	10	50	92
n-C_6H13I	**90**	5	64	99
n-C_6H13I	**91**	12	81	>99
$C2H_5$**I**	**92**	12	83	97
n-C_6H13I	**92**	12	80	>99

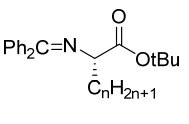




	Yield	ee
n=3	84%	54%(*S*)
n=4	57%	55%(*S*)
n=5	78%	95%(*S*)
	80%	92%(*R*)
n=6	84%	92%(*S*)
n=7	81%	89%(*S*)
n=8	79%	90%(*S*)



	Yield	ee
n=4	74%	65%(*S*)
n=5	89%	62%(*S*)
n=6	69%	62%(*S*)
	63%	59%(*R*)

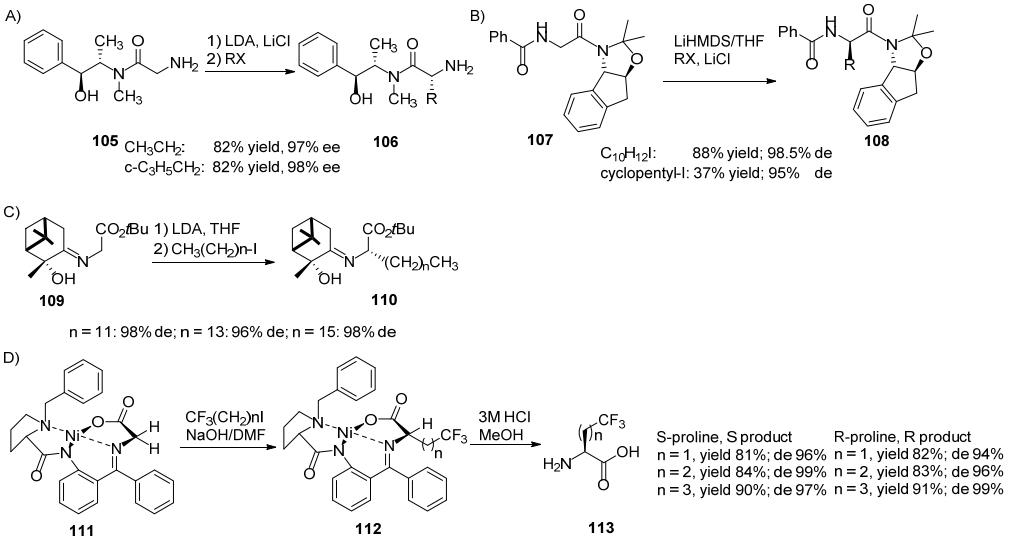


	Yeld	ee
n=4	80%	80%(*S*)
n=6	74%	85%(*S*)
	85%	82%(*R*)
n=8	92%	75%(*S*)

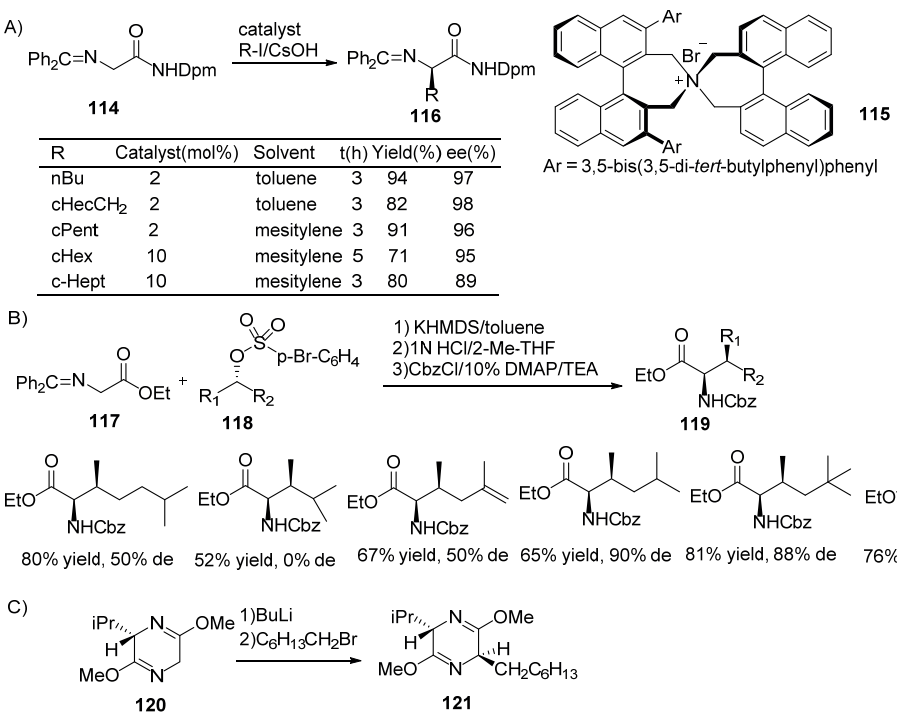
Scheme 8. Examples of alkylation of glycine derivatives using cinchonidine-containing catalysts.

Diastereoselective alkylation of pseudoephedrine glycinamide **105** was reported to give compound **106,** which was refluxed in H_2O to give the *S* configured amino acids (Scheme 9A).[40] In a related strategy, the enantioselective synthesis of *R* configured amino acids was accomplished starting from the hippuric acid amide **107** (Scheme 9B).[41] Chiral Schiff base **109** was explored for diastereoselective alkylation reactions (Scheme 9C).[42] Asymmetric alkylation of a Ni-containing glycine complex was also explored to prepare unnatural amino acids.[43] Wang and co-workers[43a] reported the asymmetric alkylation of a Ni-containing glycine complex **111** (Scheme 9D). Various trifluoromethyl containing *S* and *R* α-amino acids were obtained in high diastereomeric excess.

Several chiral quaternary ammonium cations were investigated on their properties to transfer chirality in the alkylation of imines.[44] Compound **114** was alkylated with catalyst **115** and **116** was obtained with high enantiomeric excess (Scheme 10A). Lou and co-workers[45] reported the preparation of β-branched α-amino acids through asymmetric alkylation of glycine imine **117** with compound **118**. After acidic hydrolysis and treatment with CbzCl, various β-branched Cbz protected α-amino acids were obtained (Scheme 10B). The alkylation of cyclized glycine derivatives was also reported,[46] as was the alkylation of cyclo-(L-Val-Gly) **120** (Scheme 10C).[46a]



Scheme 9. Alkylation of glycine derivatives.



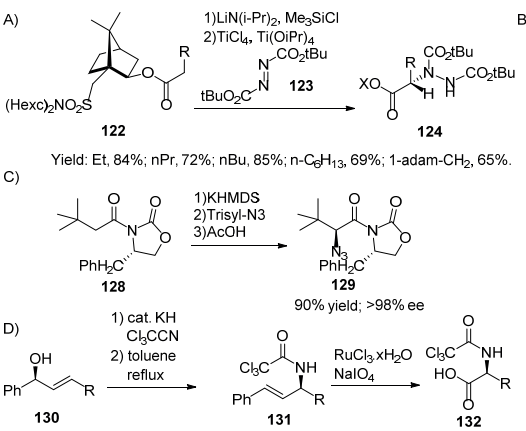
R	Catalyst(mol%)	Solvent	t(h)	Yield(%)	ee(%)
nBu	2	toluene	3	94	97
cHecCH$_2$	2	toluene	3	82	98
cPent	2	mesitylene	3	91	96
cHex	10	mesitylene	5	71	95
c-Hept	10	mesitylene	3	80	89

Scheme 10. Alkylation of glycine derivatives through other strategies.

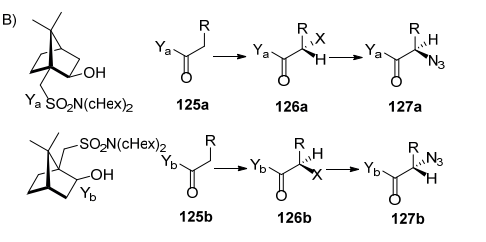
2.2.5 Asymmetric amination

Diazene **123** can be used for the diastereoselective amination of chiral ester **122** and after removal of the protecting groups, the corresponding *S*-amino acids were obtained (Scheme 11A).[47] The amine could also be introduced via the azide, which in turn can be obtained from chiral halide or hydroxyl precursors.[48] Oppolzer and co-workers[48a] reported on the azide substitution of chiral α-haloesters (**126ab**, Scheme 11B) and the corresponding amino acids were obtained via the transesterification of the azidoesters (**127ab**) and successive hydrogenolysis.

Direct electrophilic azide transfer was also explored for this reaction.[49] In this way, compound **129** was obtained in high yield and enantiomeric excess from compound **128**. Compound **129** was further transformed to *S*-*tert*-butylglycine (Scheme 11C).[49a] Walsh and co-workers[50] prepared various allylic alcohols **130** in an enantioselective fashion and these alcohols were transformed to the allylic amide through Overman's [3,4]-sigmatropic rearrangement of imidates with high enantiomeric excess (Scheme 11D). The corresponding *S* amino acids were obtained after oxidative cleavage of the allylic amines.



Entry	R	yield(%)	ee(%)	Entry	R	yield(%)	ee(%)
1	n-Bu	64	95-99	4	tBu	90	96-99
2	c-Pr	93	89	5	ada	83	97-99
3	c-Hexyl	96	95-99	6	$Cl(CH_2)_4$	66	93

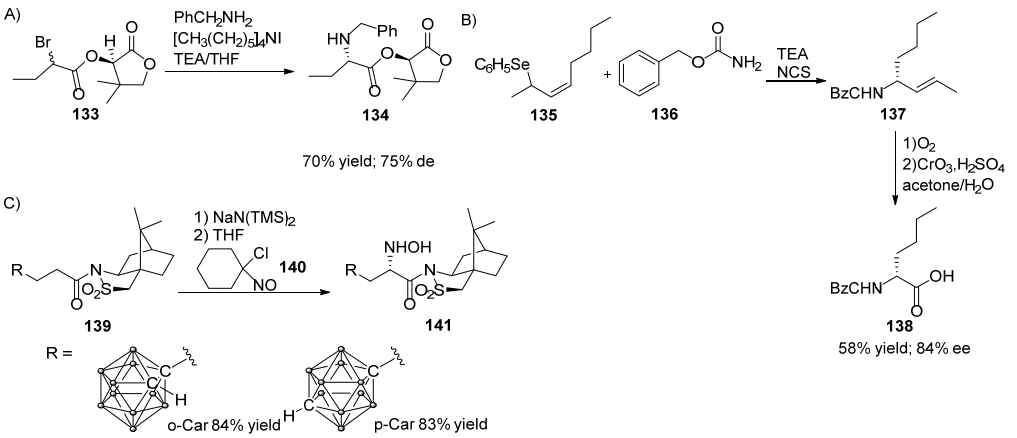


			2		3		4	
R	Y	X	Yield(%)	ee(%)	Yield(%)	ee(%)	Yield(%)	ee(%)
Et	a	Cl	75	>99	87	-	72	94
nPr	a	Cl	75	97	93	97	87	94
nBu	a	Br	77	96	88	96	72	94
n-C_6H_{13}	a	Cl	82	>94	89	100	78	98
1-adam-CH_2	b	Cl	54	-	88	-	73	96

Scheme 11. Asymmetric amination reactions**.**

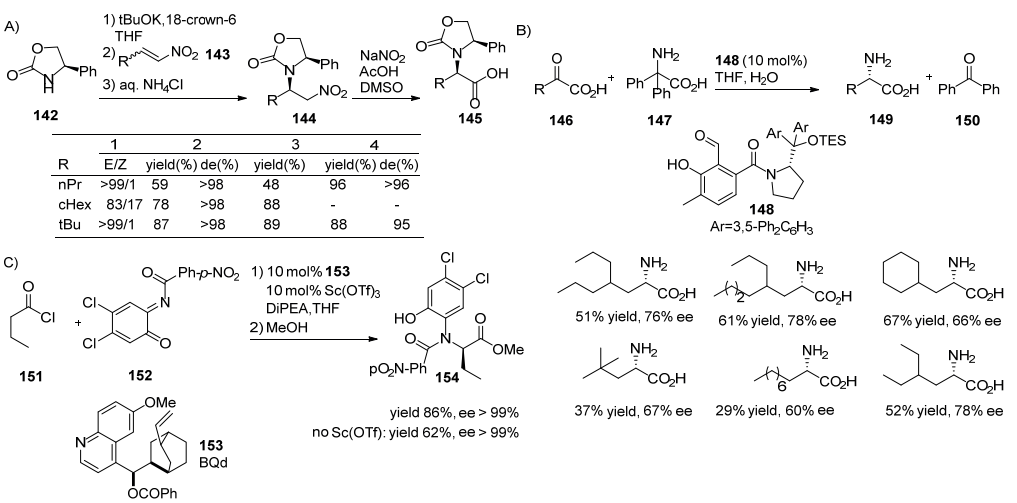
Dynamic kinetic resolution of racemic α-bromo acid *S* **133** with various amines has been shown to give one major stereoisomer (Scheme 12A).[51] Hopkins and co-workers[52] prepared *R*-Cbz-Nle-OH **138** though the asymmetric amination of **135** with compound **136** and after oxidative cleavage of **137**, product **138** was obtained (Scheme 12B). The *o*-carboranylalanine and *m*-carboranylalanine were prepared via asymmetric amination of compound **139** and the

obtained product **141** could be further transferred to the corresponding amino acids (Scheme 12C).[53]



Scheme 12. Asymmetric amination reactions through other strategies.

The conjugate addition of 4-phenyl-2-oxazolidinone potassium salt of **142** to nitroalkenes **143** yields the corresponding nitro 2-amino-nitroalkanes **144** (Scheme 13A). After oxidation and Birch reduction, the desired amino acids were obtained.[54] Compound **148** catalyzes the asymmetric transamination of the α-ketone acids **146** with amine **147** and various aliphatic amino acids were prepared (Scheme 13B).[55] The direct asymmetric amination of butyryl chloride **151** with compound **152** was carried out with Lewis acid $Sc(OTf)_3$ and BQd **153** (Scheme 13C).[56]

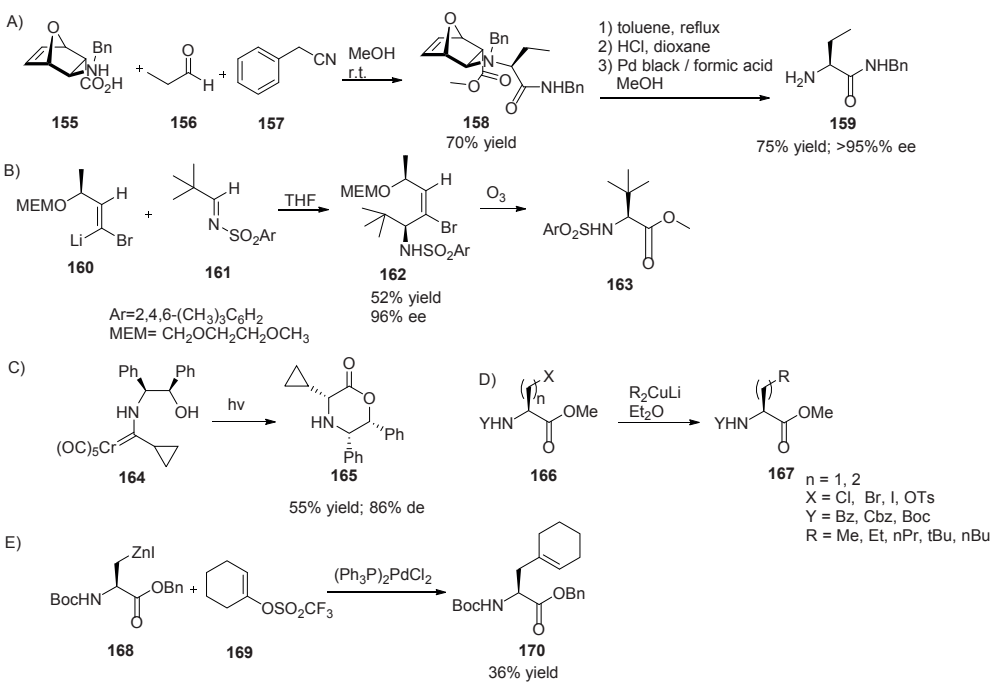


	1		2		3	4	
R	E/Z	yield(%)	de(%)	yield(%)	yield(%)	de(%)
nPr	>99/1	59	>98	48	96	>96
cHex	83/17	78	>98	88	-	-
tBu	>99/1	87	>98	89	88	95

Scheme 13. Asymmetric amination reactions through other strategies.

2.2.6 Other methods

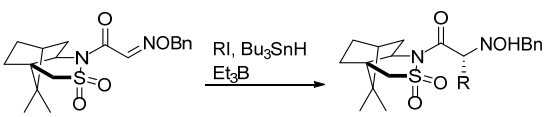
Ugi multicomponent reactions were also explored for the preparation of aliphatic unnatural amino acids.[57] Guanti and co-workers reported the application of the bicyclic β-amino acid scaffold **155** as a chiral auxiliary in the Ugi multicomponent reaction to prepare the *S* amino acid (Scheme 14A).[57d] Asymmetric addition of the organolithium reagent **160** which contains the precursor of the carboxyl group, to the mesityl sulfonylimine **161** gave the precursor **162**. After ozonolysis, the protected *S*-*tert*-butylalanine **163** was obtained (Scheme 14B).[58] The aminocarbene **164** could be diastereoselectively converted to lactone **165** in good enantiomeric excess and acceptable yield. The lactone can be further transformed to the corresponding *R* amino acid **163** (Scheme 14C).[59] The protected serine could also be modified to non-natural amino acids. Various aliphatic amino acids were prepared via reaction of lithium diorganocuprate with serine (n=1) and homoserine (n=2) derivatives (Scheme 14D).[60] Cyclohexen-1-yl triflate (**168**) was coupled with organozinc reagent (**169**) with $(Ph_3P)_2PdCl_2$ as the catalyst (Scheme 14E). The obtained product (**170**) can be further reduced to prepare Boc-Cha-OBn.[61]



Scheme 14. The application of Ugi multicomponent reactions in the preparation of amino acids.

Various imine derivatives of glycine were asymmetrically added to various reagents and after the removal of the protecting groups, the corresponding amino acids were obtained.[62] Naito and co-workers[62ad] reported highly stereocontrolled radical addition to Oppolzer's camphor sultam derivative of glyoxylic oxime ether **171** (Scheme 15A). The addition of n-butyllithium to imine **173** gave compounds **174** with a carboxyl precursor and after the changing the protecting group and oxidative cleavage, Cbz protected S amino acids **175** were obtained (Scheme 15B).[62bh] The asymmetric addition of organolithium reagents to *S*-O-(1-phenylbutyl) oximes **176** gave compound **178** and the corresponding amino acids **179** were obtained after oxidative cleavage (Scheme 15C).[62i]

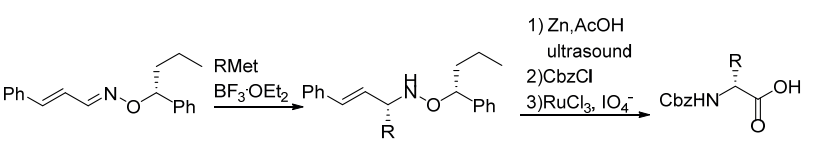
A)



171 **172**

Entry	RI	Lewis acid	Solvent	Yield(%)	de(%)
1	EtI	none	Et_2O	54	92
2	EtI	$BF_3{\cdot}OEt_2$	DCM	80	90
3	tBuI	none	Et_2O	25	>96
4	tBuI	$BF_3{\cdot}OEt_2$	DCM	83	>96
5	iBuI	none	Et_2O	39	94
6	iBuI	$BF_3{\cdot}OEt_2$	DCM	83	94
7	c-Hexyl-I	none	Et_2O	74	92
8	c-Hexyl-I	$BF_3{\cdot}OEt_2$	DCM	86	92

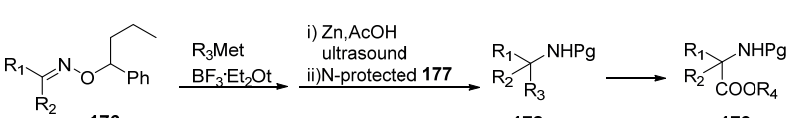
B)



173 **174** **175**

R = n-Bu 174, yield 92% / de 93%; 175, yield 47%
R = i-Bu 174, yield 93% / de 92%; 175, yield 31%

C)



176 **178** **179**

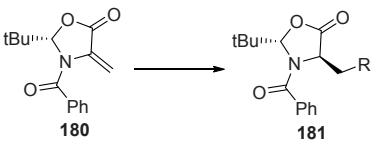
Entry	R_1	R_2	R_3	R_4	Pg	yield(%)	ee or de(% cfg.)
2a	tBu	H	Ph	-	Ac	9	>98 (R)
3a	tBu	H	-	H	Ac	63	-
2b	n-Pr	H	$CH{=}CH_2$	-	Cbz	77	84*.(R)
3b	n-Pr	H	-	Me	Cbz	59	-
2c	c-Hex	H	$CH{=}CH_2$	-	Cbz	38	92* (S)
3c	c-Hex	H	-	Me	Cbz	70	-

*Note: de values are measured after the 1st step reaction.

Scheme 15. Asymmetric addition to imine derivatives.

Stereoselective conjugate addition to dehydroalanine derivatives (Michael acceptors) was developed as an alternative strategy to prepare amino acids.[63] Bechwith and co-workers[63a] reported the diastereoselective radical addition of alkyl iodides or alkylmercuric halide to compound **180** (Scheme 16A). Pedrosa *et al*. reported the diastereoselective nucleophilic ring opening of compound **182** with dialkylzinc reagents. After Pd/C catalyzed bis-debenzylation, *R* amino acids **184** were obtained with good to high enantiomeric excess, although the yields were not high (Scheme 16B).[64] *S*-cycloalkylglycine (**188**) and *S*-*N*-heterocyclic amino acids (**190**) were prepared from **185** with *S* configuration. The alkylated intermediates (**186**) were converted to two different cyclic products when using different bases (Scheme 16C). If the starting material **185** is in *R* configuration, the corresponding *R* products were obtained.[65]

A)

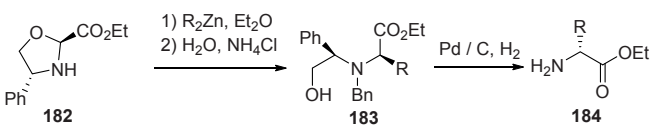


180 **181**

Method A:
R-I,azobisiosbutyronitrile
tributylstannane
Method B:
alkylmercuric halide
sodium cyanoborohydride
Method C:
R-I, tributyltin chloride (10% mol)
sodium cyanoborohydride

R	Method	Yield (%)	de (%)
cycolhexyl	A	52%	82%
cycolhexyl	B	89%	68%
1-adamantyl	A	66%	90%
1-adamantyl	B	>95%	84%
Me	C	63%	84%
tBu	A	70%	>96%
$(CH_2)_3CF_3$	A	63%	84%

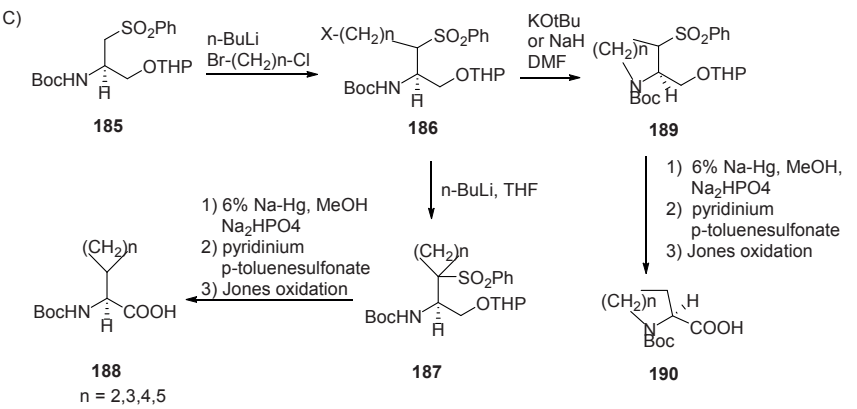
B)



182 **183** **184**

Entry	R	ee (%)	yield (%)	Entry	R	ee (%)	yield (%)
1	Me	72	45	4	iPr	72	45
2	Et	74	42	5	nBu	74	42
3	Pr	76	47	6	i-Bu	76	47

C)



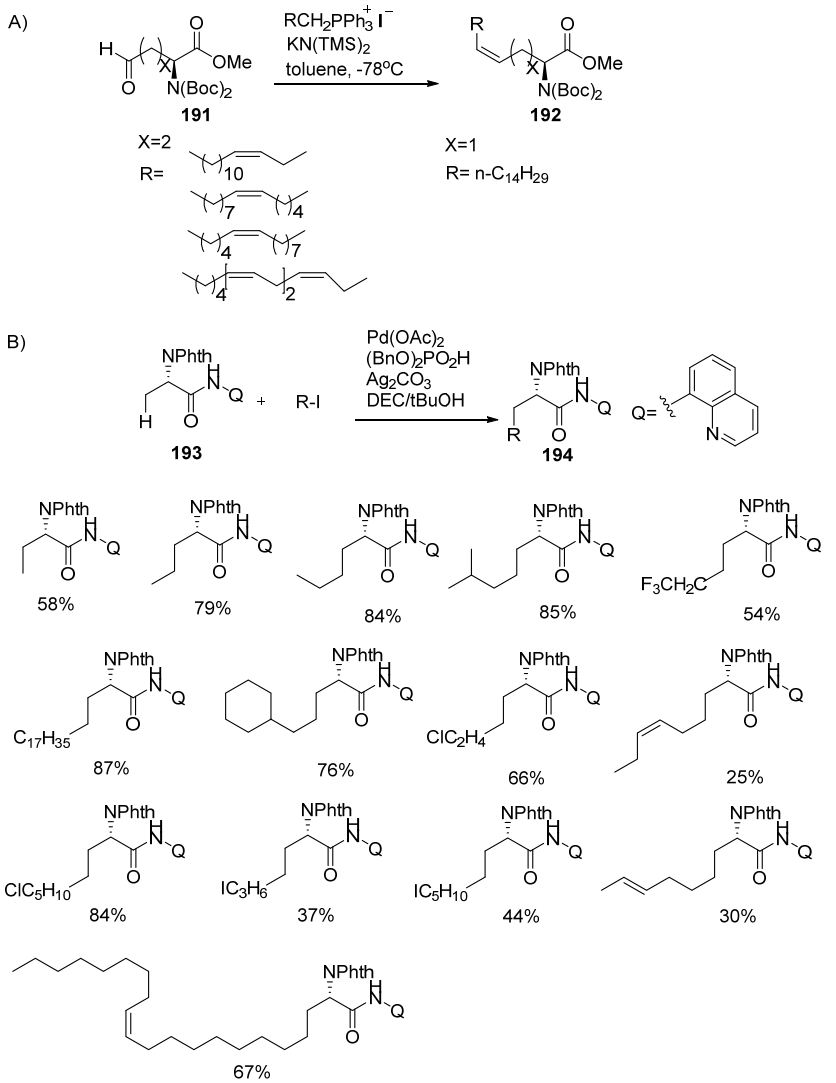
185 **186** **189**

188 **187** **190**

n = 2,3,4,5

Scheme 16. Other methods to prepare the non-natural amino acids.

Various lipophilic *S* amino acids were also prepared though Wittig reaction of the aldehyde containing *S* amino acids **191**, which are prepared from L-glutamic acid (X=2) or L-aspartic acid (X=1) (Scheme 17A).[66] Direct alkylation of protected alanine **193** was developed as an efficient method to synthesize optically active amino acids and various aliphatic sides could be introduced (Scheme 17B).[67] Various aliphatic unnatural amino acids has been prepared through this method.



Scheme 17. Other methods to prepare the non-natural amino acids.

2.3 Conclusion

Various synthetic methods and procedures are presented in this review to prepare enantiomerically pure aliphatic α-unnatural amino acids. The enantioselectivity can vary considerably with different side chains and different reaction conditions. There is not a reaction condition that could fit the preparation of most amino acids, but at the same time the broad array of synthetic methodology available ascertains that the synthesis of a desired chiral aliphatic amino acid can be done with confidence, provided that the appropriate methodology is selected.

2.4 References

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