Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 12, pp. 1895–1946, 1997

Printed in Great Britain
PII: S0957-4166(97)00208-5
0957-4166/97 $17.00 + 0.00

TETRAHEDRON: ASYMMETRY REPORT NUMBER 26

Asymmetric synthesis of amines by nucleophilic 1,2-addition of organometallic reagents to the CN-double bond

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1. Introduction

The amine group is one of the fundamental structures in organic chemistry. In particular enantiomerically pure amines bearing a stereogenic centre at the α-position play a crucial role as characteristic srtuctural features in bioactive natural products and pharmaceutically important compounds. Thus the development of stereoselective syntheses of diastereo- and enantiopure amines has been a major objective for organic chemists in recent years. Especially, the synthetically flexible concept of asymmetric synthesis under C–H, C–C and C–N bond formation is of growing importance. Beside strategies such as reduction of imino derivatives, electrophilic and nucleophilic amination by C–N

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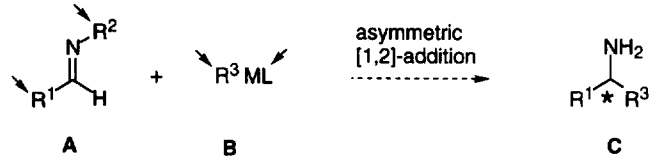
connection or reductive coupling of imines, the generation of amines by 1,2-addition of nucleophiles to a C=N imino group in an asymmetric fashion provides a C–C connective and attractive direct route to amines.[1] In comparison to the nucleophilic addition to carbonyl compounds the aza-analogous reaction has been investigated much less. Some general problems are the poor electrophilicity of the imino group, the abstraction of acidic α-protons forming an azaenolate or the formation of reductive coupling products. Promising improvements have been reached in overcoming these problems by activation of the imino group or by means of more selective reagents.

In this report we wish to present a brief summary of truly asymmetric variants with stoichiometric or catalytic amounts of a chiral auxiliary. The chirality information can be incorporated into the carbonyl part or the amine part of the imino substrate **A**, in the nucleophilic reagent or in external chiral ligands as is depicted in the general equation.



$R^1 = R^3$ = alkyl, aryl, allyl, vinyl, etc.
R^2 = alkyl, aryl, $-SiR_3$, $-NR_2$, POR_2, -OR, $-S(O)_xR$, $-BR_2$, etc.
M = Li, Mg, Ba, B, Sn, Si, Ce, Yb, Cd, Cu, Zn, Zr, etc.

↘ = possible incorporation of chirality information

Asymmetric synthesis of amines by nucleophilic 1,2-addition to the imino group

So as not to broaden the scope of this review[2] we have limited it to the reaction of organometallics with uncharged imines and imino derivatives covering the literature up to 1997. For reviews on related Aldol-, Strecker-, Mannich-, and Ugi-type reactions the reader is referred to the literature.[3]

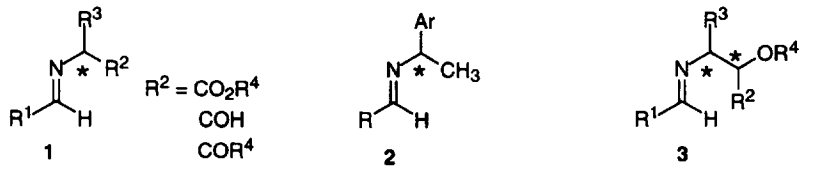
2. Addition to imines

The nucleophilic attack of organometallic reagents to the CN-double bond of imines is the most popular strategy for generating amines by nucleophilic 1,2-addition.

2.1 N-*Alkyl/arylimines*

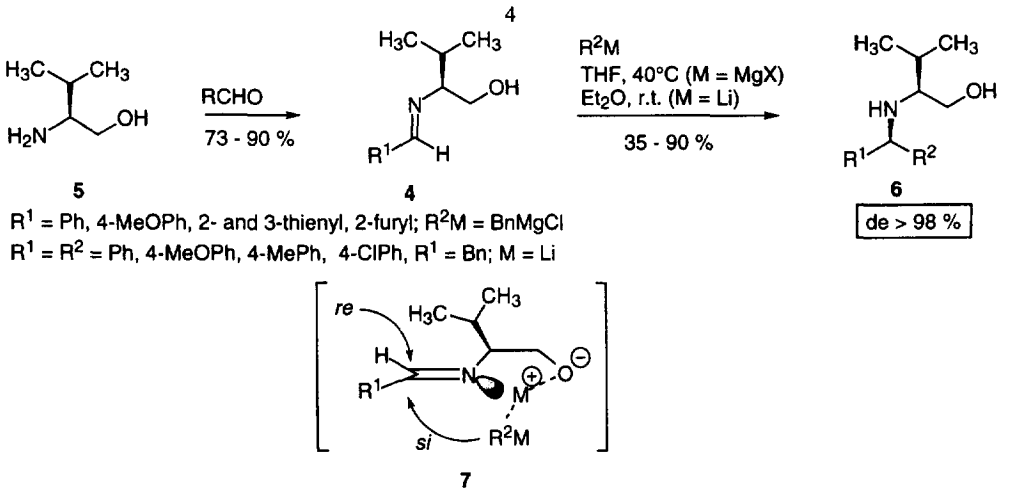
2.1.1 Auxiliary group in the amine

The use of readily available enantiopure amines as auxiliaries is a widely employed strategy. It is desirable that both enantiomers are easily accessible. The enantiopure acyclic and cyclic imines can be prepared by condensation with the corresponding carbonyl compound. Widely employed amines bear a second heteroatom, usually an *O*-atom, for possible chelation of the bidentate imine to rigidify the transition state of the 1,2-addition. Typical auxiliaries are α-amino acids and their derivatives **1**, α-arylethyl amines **2**, e.g. (*R*)- or (*S*)-α-phenylethylamine, and β-amino alcohols **3**, e.g., ephedrines and their derivatives. Sugar derived auxiliaries have also been used successfully.



β-Amino alcohols as auxiliary. High diastereoselectivities have been reached in the pioneering work of Takahashi *et al.*[4] The non-enolisable arylimines **4** were obtained as a single isomer by condensation of (*S*)-valinol **5** and the corresponding aldehydes. Benzylmagnesium chloride or

aryllithium compounds were added under 1,3-induction to the imino group in acceptable to high yields forming a single diastereomeric adduct **6**. By appropriate selection of the imino and nucleophilic agent, both diastereomeric adducts could be obtained. As transition state a metallo-chelate **7** was proposed. Coordination of the alkoxy group and the lone pair of the imino function led to a preferred *si*-attack of the organometallic reagents. For the removal of the auxiliary group several methods have been described in the literature (Scheme 1).[4e]



5 **4** **6**

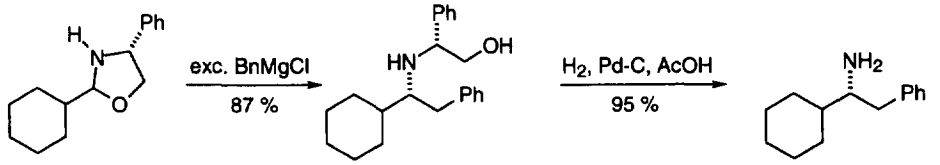
R^1 = Ph, 4-MeOPh, 2- and 3-thienyl, 2-furyl; R^2M = BnMgCl
R^1 = R^2 = Ph, 4-MeOPh, 4-MePh, 4-ClPh, R^1 = Bn; M = Li

7

Scheme 1. Diastereoselective synthesis of amines according to Takahashi *et al.*[4]

Change of the auxiliary to other amino alcohols, e.g. (*S*)-alaninol, showed the importance of the sterically demanding *i*-propyl group at the resident stereogenic centre for the diastereofacial selection.[4b] Also the use of smaller nucleophiles, e.g. EtMgBr, led to lower selectivities (*de*=56%, R=Ph). Valino methyl ether gave better results (*de*=83%).[4b]

During the investigations of the synthesis of enantiomerically pure *N*-alkyl-1-cyclohexyl-2-phenylethylamines the enantiopure primary amine **8** was prepared.[4e] Benzyl Grignard addition to the 1,3-oxazolidine **9** as masked imine derivative, prepared from phenylglycinol and cyclohexylcarbaldehyde, gave the adduct **10** as a single diastereomer. Hydrogenation led to the enantiopure (*R*)-1-cyclohexyl-2-phenylethylamine **8** in excellent yield (Scheme 2).



9 **10** **8**

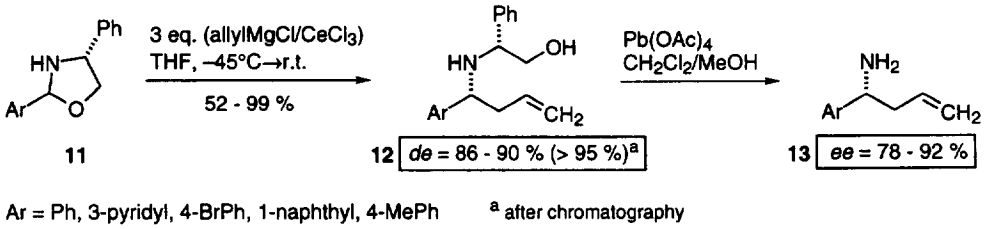
single diastereomer

Scheme 2. Synthesis of enantiopure primary amine **3** according to Takahashi *et al.*[4e]

Takahashi's asymmetric synthesis[4] was the basis on which Pridgen *et al.* explored the scope of this reaction.[5] In several studies phenylglycinol has been used as auxiliary. The formed 1,3-oxazolidines as masked imine showed a solvent dependent equilibrium with the corresponding imines.

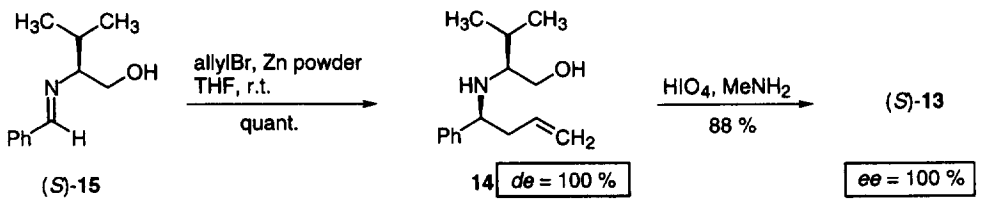
Initially the synthesis of homoallyl amines was described.[5a] Nucleophilic allyl organocerium (allylMgCl/$CeCl_3$) was added to enantiopure 2-aryl-4-phenyl-1,3-oxazolidines **11** in a highly stereo-

controlled manner. Amine **12** was oxidized with lead tetraacetate to homoallylamine **13** under partial racemization for R=tolyl (Scheme 3).



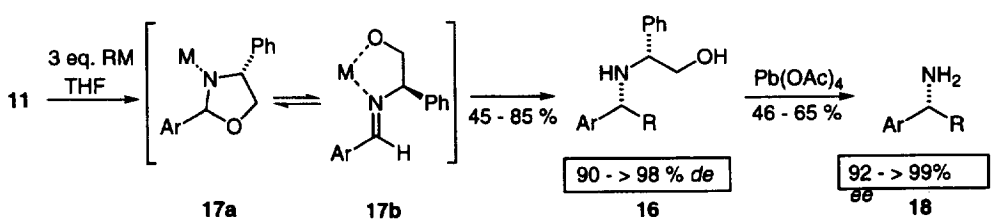
Scheme 3. Asymmetric synthesis of homoallylamines **13** according to Pridgen and Wu.[5a]

Alternatively, the homoallylamine (*S*)-**14** was obtained by applying a Barbier-type addition of allylzinc bromide to the imine **15**, derived from (*S*)-valinol and benzaldehyde, with quantitative diastereoselectivity and yield.[6] Treatment of the adduct with periodic acid in the presence of aqueous methylamine allowed the enantiomerically pure **13** to be obtained directly in 88% yield (Scheme 4).



Scheme 4. Barbier type allylation of imine **15** according to Umani-Ronchi, Savoia *et al.*[6]

Addition of several organomagnesium, organolithium and organocerium reagents to **11** was performed in high diastereoselectivity (de=90–>98% for **16**) followed by removal of the auxiliary as depicted in Scheme 5.[5b] Interestingly, addition to the imino group did not take place until at least 1.5 equivalents of Grignard reagent had been added. Actually 2.5–3.0 equivalents were required to force the reaction to completion and to obtain high diastereoselectivity. The formation of the metallated species **17a** and **17b** is assumed. Chelation of the metal ion by the alkoxy substituent and the imino nitrogen could form a highly ordered transition state. An optimized procedure without racemization was described for the oxidative cleavage of the auxiliary, to afford the amines **18**.[5d]

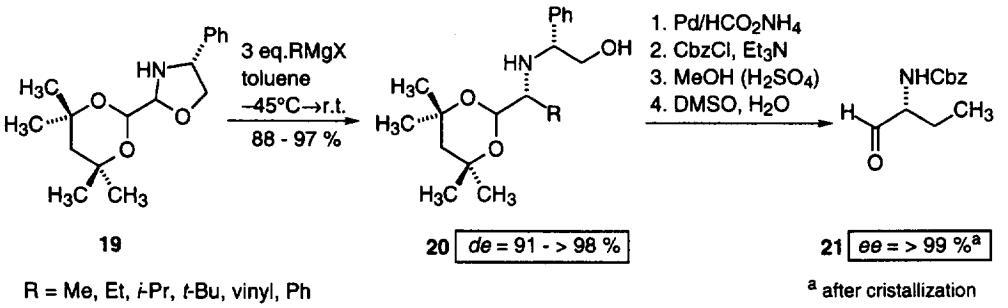


Scheme 5. Synthesis of virtually enantiopure amines according to Pridgen *et al.*[5b]

Pridgen *et al.* described the selective 1,2- *vs* 1,4-addition of nucleophilic organometallics to enantiopure 2-(1-naphthyl)- and 2-cinnamyl-1,3-oxazolidines.[5c] Organoceriums (R=Me, Et) were the organometallics of choice for the selective nucleophilic 1,2-addition with good yields (75%) and with

outstanding diastereoselectivities (96–>99% *de*). Grignard reagents added predominantly in a 1,4-addition but also with high diastereofacial discrimination.

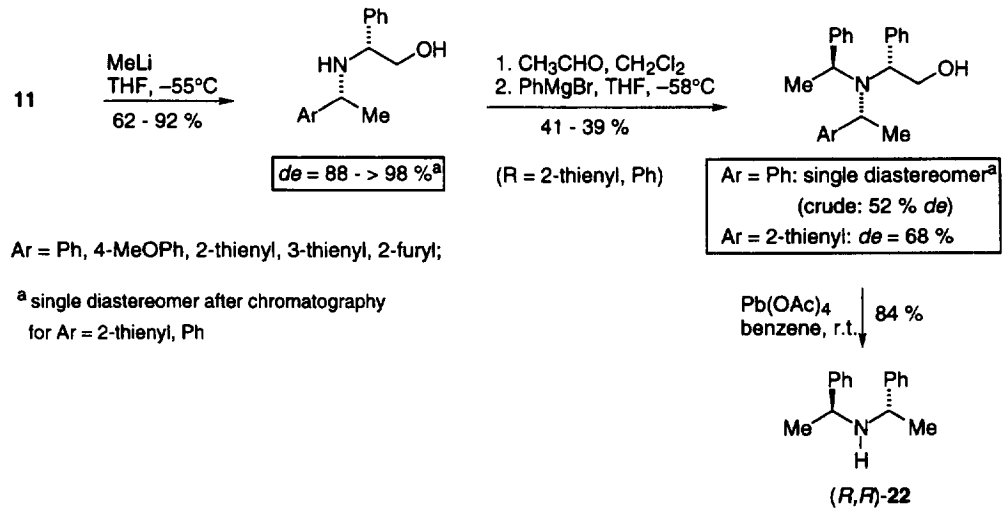
A general procedure for the highly diastereoselective addition of Grignard reagents to the chiral 1,3-oxazolidines **19** (Scheme 6) was described in order to prepare α-amino acid precursors (*de*=91–>98% for **20**).[5d] In one case (R=Et) the resulting amino alcohol **20** was transferred to the Cbz-protected amino acetal by applying palladium catalyzed hydrogenolysis without racemization. A transformation to the Cbz-protected α-amino aldehyde **21** was described with slight epimerization (98 *vs* 92% *ee*).



Scheme 6. Enantioselective synthesis of α-amino acetals and aldehydes according to Pridgen *et al.*[5d]

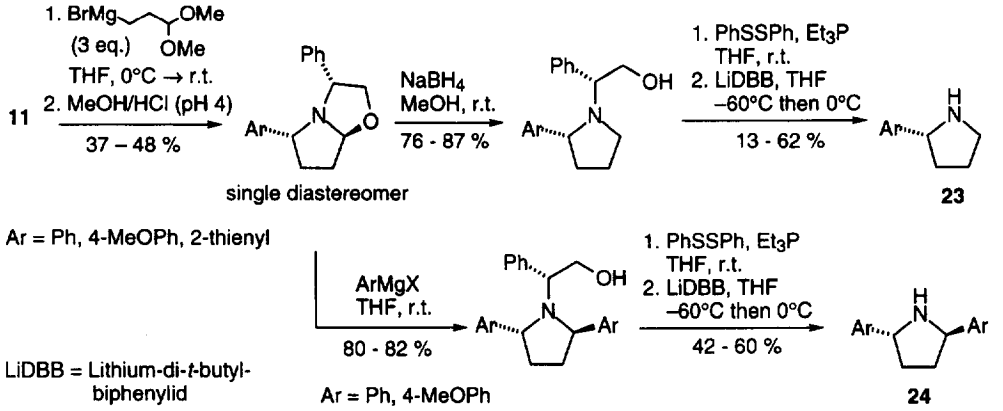
This method was employed in the highly stereoselective asymmetric synthesis of both enantiomers of 2-(1′-amino-2′-methylpropyl)imidazole, a key synthon in the synthesis of a protease inhibitor.[5f]

Applications of 1,3-oxazolidines for the synthesis of various non-racemic primary amines have been reported by other researchers.[7–9] This type of reaction was used as a key step in the stereoselective synthesis of bis(1-phenylethyl)amine **22** as depicted in Scheme 7.[7c] The second newly formed stereogenic centre was generated by nucleophilic addition to an *in situ* formed iminium ion.



Scheme 7. Enantioselective synthesis of bis(1-phenylethyl)amine **22**.[7c]

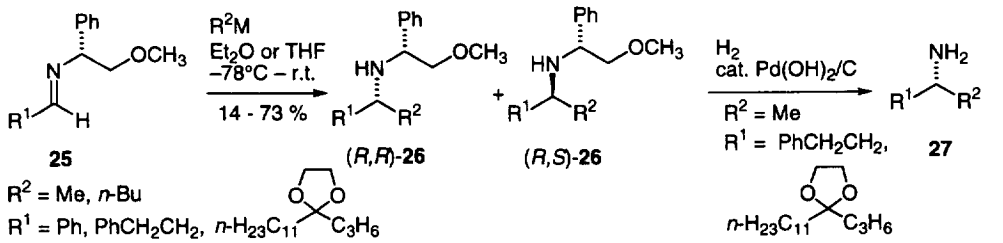
Formation of (*R*)-2-arylpyrrolidines **23** and the C_2-symmetric (*R,R*)-2,5-bis(aryl)pyrrolidines **24** was initiated by addition of a Grignard reagent bearing an acetal group to various arylimines **1** with complete diastereoselectivities.[7b] The whole reaction sequence with a new cleavage of the auxiliary group in moderate to low yields 13–62% is shown in Scheme 8.



Scheme 8. Enantioselective synthesis of (*R*)-2-arylpyrrolidines **23** and the C_2-symmetric (*R,R*)-2,5-bis(aryl)pyrrolidines **24**.[7b]

Another example of an allyl cerium reagent addition leads to a phenylogous amino acid mimicking an extended dipeptide.[9]

β-Alkoxy amines as auxiliary. A reversal of the diastereofacial 1,2-addition to the enolisable and nonenolisable imines **25** derived from (*R*)-2-methoxy-1-phenylethylamine has been reported by Fujisawa *et al.*[10] Organolithium and organocerium reagents added from the *re*-face of the imine **25** in a highly diastereoselective manner (90–>98% *de* of **26**). In contrast to these results organocopper reagents attacked the opposite *si*-face in low to acceptable yields (14–56%). A summary of the results is given in Scheme 9. The obtained stereoselectivity might be explained in terms of a chelation-controlled model for the organolithium and cerium reagents (see **7**, Scheme 1) and an open-chain model for the cuprate additions. The auxiliary can be removed easily by hydrogenation to form the primary amines **27** which was demonstrated in two cases.

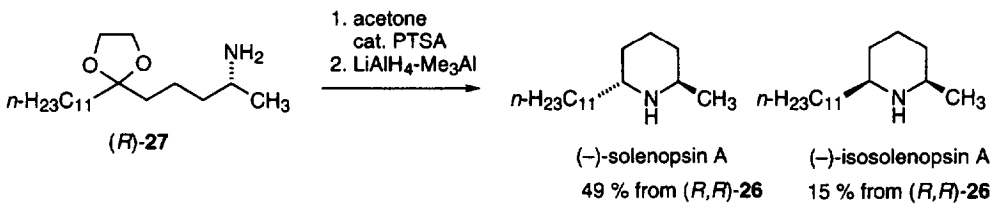


R^2M	yield (**26**)	*de* (**26**)	configuration
R^2Li	45 - 73 %	90 - > 98 %	(*R,R*)
$R^2Li/CeCl_3$	55 - 65 %	> 94 %	(*R,R*)
$R^2{}_2CuLi/BF_3$	14 - 56 %	74 - 94 %	(*R,S*)

Scheme 9. Enantioselective synthesis of primary amines **27** according to Fujisawa *et al.*[10]

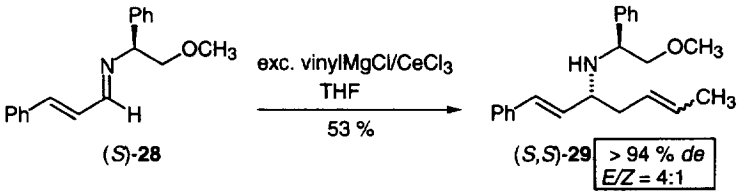
As a first application of the sequence, the synthesis of (−)-solenopsin A and (−)-isosolenopsin A was performed (Scheme 10).

The scope of the reaction was extended by Higashiyama *et al.*[11] The reaction of organocerium reagents ($R^2MgBr/CeCl_3$; R^2=Me, Et, *i*-Pr, Ph) with aliphatic imines (R^1=Me, Et, *i*-Pr) proceeded with high diastereoselectivities (*de*=88–>98%) and yields ranging from 60 to 90%.



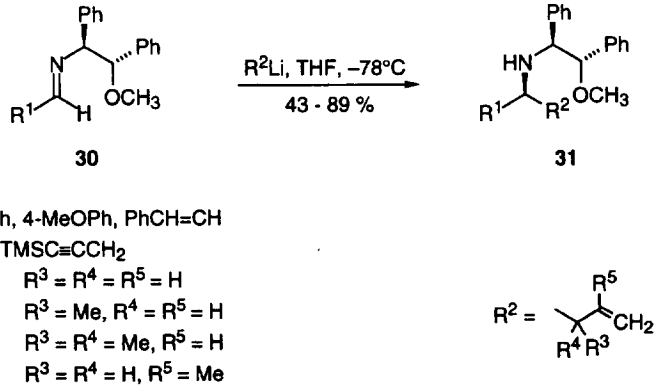
Scheme 10. Asymmetric synthesis of (−)-solenopsin A and (−)-isosolenopsin A by Fujisawa *et al.*[10]

The same auxiliary was employed in the addition of the vinylcerium agent prepared from vinyl magnesium bromide and cerium trichloride to imine **28**.[12] Unexpectedly homoallylamines, e.g. **29**, were formed (Scheme 11). Two different mechanisms are proposed. One suggests the successive reaction of two vinyl nucleophiles and the other the reaction of a preformed dimerized cerium agent. This reaction could be an alternative route to the rarely successful α-selective addition of crotylmetallic compounds to imines.



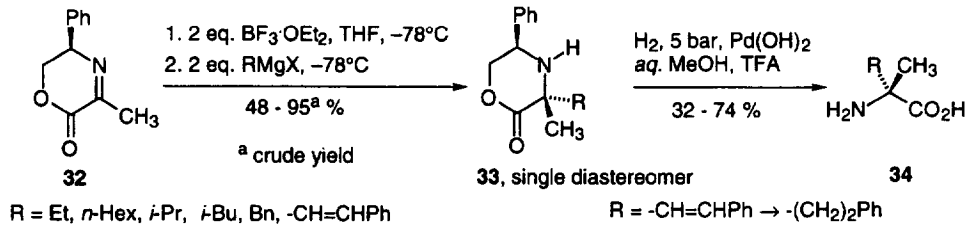
Scheme 11. α-Selective synthetic equivalent for the crotyl anion in addition to imines.[12]

The diastereofacial addition of alkyl-, allyl- and propargyllithium reagents to chiral imines **30** derived from *erythro*-2-methoxy-1,2-diphenylethylamine has been investigated.[13] High diasteroselectivities (88–100% *de* of **31**) related to the newly formed α-amino stereogenic centre can be obtained. A cleavage of the auxiliary was not described (Scheme 12).



Scheme 12. Diastereoselective addition of organolithium reagents to imine **30**.[13]

An asymmetric synthesis of enantiopure α-substituted alanine derivatives by quarternization of the cylic imine **32** has been described by Harwood *et al.*[14] Reaction of the dehydromorpholinone (**32**)–BF_3 complex with Grignard reagents lead to a single diastereomer in all cases in moderate to high yield. Cleavage of the morpholinone was performed using hydrogenolytic conditions (Scheme 13).



Scheme 13. Asymmetric synthesis of α-substituted alanines **34** by Harwood *et al.*[14]

α-Amino esters as auxiliary. Torii *et al.*[15] have described the 'Barbier-type' allylation of the imine **35** by the action of aluminum and a catalytic amount of titanium tetrachloride in THF without reaction of the ester group. High diastereoselectivity (*de*=90%) and good yields (91%) could be achieved (Table 1, Entry 1). Phenylimine **35**, activated with $BF_3 \cdot OEt_2$ reacted with allylic bromide in the presence of chromium dichloride to give the corresponding homoallylic amine **36** (*de*=86%) as a modified Nozaki–Hiyama reaction (Scheme 14).[16] The reaction can be performed in a single step starting from benzaldehyde and (*S*)-valino methyl ester (Table 1, Entry 2).

A bismuth promoted allylation has been described in a $Bi/Bu_4NBr/MeCN$ system with moderate diastereofacial discrimination (*de*=40%).[17]

Umani-Ronchi, Savoia *et al.* have investigated 'Grignard'- and 'Barbier'-type procedures for the addition of several allylmetal (Zn, Cu, Pb, Bi, Al, In) species to alkyl- and arylimines **35** (Table 1, Entry 4–6).[6,18] The addition of allyl bromide and zinc in tetrahydrofuran afforded homoallylamines **36** in excellent to complete diastereoselectivities, but in the case of aromatic imines the diastereoselectivity is diminished by reversibility of the reaction, which caused the lowering of the diastereomeric excesses with increasing reaction time. The retroallylation reaction could be avoided by performing the addition in the presence of a trace amount of water, or by using $CeCl_3 \cdot 7H_2O$ as catalyst.

Also several allylmetal (Pb, Bi, Cu, Al) species, employed as 'Grignard' type reagents at low temperature gave highly diastereoselective additions to imine **35** combined with good to complete conversion.[18a,c]

The bimetallic redox systems $Al–PbBr_2$ and $Al–BiCl_3$ were successfully applied in the allylation of aromatic imines **35**. Diastereomeric excesses of 92 to 96% for the adduct **36** were obtained.[18a]

The addition of several allylmetal reagents to the imine **35** (R=2-pyridyl) and its metal salt complexes have been performed.[18b] Allyllead bromide, prepared by transmetallation of allylmagnesium chloride and $PbBr_2$, although being unreactive toward phenyl imine **35** (R=Ph), reacted with a high level of diastereoselectivity [*de*=92% of (*S,S*)-**36**]. The opposite sense of asymmetric induction was observed with allyltin trihalides with a diastereomeric excess up to 94% of (*S,R*)-**36** (Table 1, Entry 7).

The catalytic allylation of chiral imines prepared from benzaldehyde and an enantiopure amine [(*S*)-1-phenylethylamine and (*S*)-valino methyl ester] with allyltributylstannane in the presence of catalytic amounts of lanthanide triflates has been reported.[19] The best diastereoselectivities were obtained for the allylation of **35** (R=Ph) with scandium triflate (*de*=82%) combined with low yield (36%, Table 1, Entry 8).

A simple highly stereoselective one-pot synthesis of homoallylic amines has been described by Loh *et al.*[20] The indium-mediated allylation is performed by addition of a preformed allylic indium solution in DMF to crude imine **35** derived from (*S*)-valino methyl ester and various amines. In all cases good to excellent diastereoselectivities were observed for both aromatic and aliphatic amines (*de*=90–98%). Starting from glyoxylic acid monohydrate the corresponding α-amino acid was obtained in 52% yield (Table 1, Entry 9).

With one exception (Entry 7b) the *si*-face of the imines was always attacked by the allylnucleophiles. In order to rationalize the stereochemical outcome several stereochemical models have been proposed.

Table 1. Diastereoselective allylation of imine **35**

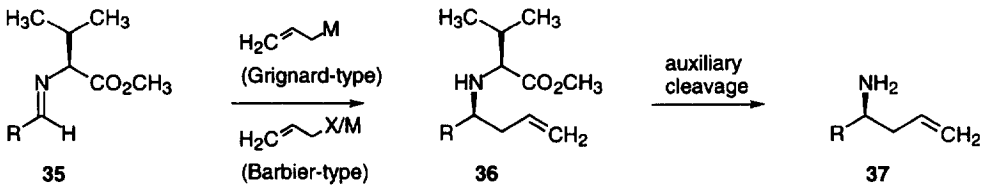
Entry	R	allylation condition	*de* **36** [%]	yield **36** [%]	lit.
1	Ph	1.25 eq. allyl bromide $TiCl_4$ (0.05 eq.)/Al, THF, r.t.	90	91	15
2	Ph	1.2 eq. allyl bromide 1 eq. BF_3 OEt_2, 2.5 eq. $CrCl_2$, THF, r.t.	86	75	16
3	Ph	1.4 eq. allyl bromide 1 eq. Bu_3NBr, 1 eq. Bi powder, CH_3CN, r.t.	40	85	17
4	Ph, 4-MeOPh, 3-pyridyl, *i*-Pr, *n*-C_5H_{11}	1.5 eq. allyl bromide 2 eq. Zn powder, 0.1 eq. $CeCl_3$, THF, 0°C	96 - 100	100	6,18a
5	Ph, *n*-C_5H_{11}	allyl (Pb, Bi, Cu, Al) species THF	94 - 100	70 - 100	18a,c
6	Ph[a], 3-pyridyl	1.2 eq. allyl bromide 1.5 eq. Al, 0.1 eq. ($BiCl_3$ or $PbBr_2$), THF, r.t.	92 - 96	56 - 100	18a
7	2-pyridyl	a) 1.1 eq. allylPbBr-MgICl, THF b) 1.5 eq. allyl$SnCl_3$, THF	92 94[b]	80 85	18b
8	Ph	1.5 eq. allyl$SnBu_3$ 0.15 eq. $Sc(OTf)_3$, CH_2Cl_2, r.t.	82	36	19
9	Ph, 3-pyridyl, *c*-C_6H_{11}, TMSC≡C, $HO_2CCHO \cdot H_2O$	1.5 eq. allyl bromide 2 eq. In powder, DMF/CH_2Cl_2, r.t.	90 - 98	52 - 80	20

a. By use of valine *t*-butyl ester as auxiliary a diastereoselectivity of > 98 % was obtained.

b. The opposite (*R*) configuration was generated.

A cyclic chair transition state is envisaged in the addition of allylzinc, or any allylmetal compound, to the amine **35** in the absence of Lewis acids. In addition, the zinc metal is coordinated to the ester group (**38**). The bulky *i*-propyl group is disposed externally. In the case of Lewis acid mediated reactions, in which a chelate complex with the nitrogen and oxygen heteroatoms of the imine can be formed, the stereocontrol is determined by a preferential attack of the allyl reagents from the bottom side as depicted in Figure 1 (**39**).

In order to obtain the primary homoallylamine **37**, a precursor for β-amino acids and β-lactams, removal of the auxiliary was performed by alkaline hydrolysis followed by electrolytic decarboxylation.[15] Also a multistep procedure could be followed from the acid, involving the Curtius



Scheme 14. Asymmetric synthesis of homoallylamines by addition of allylmetallics to imine **35**.[6,15-20]

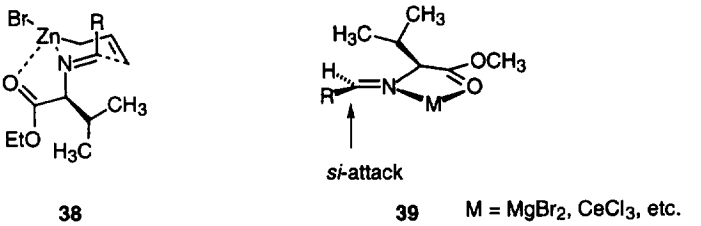


Figure 1. Proposed transition states for chelating allylation reactions.

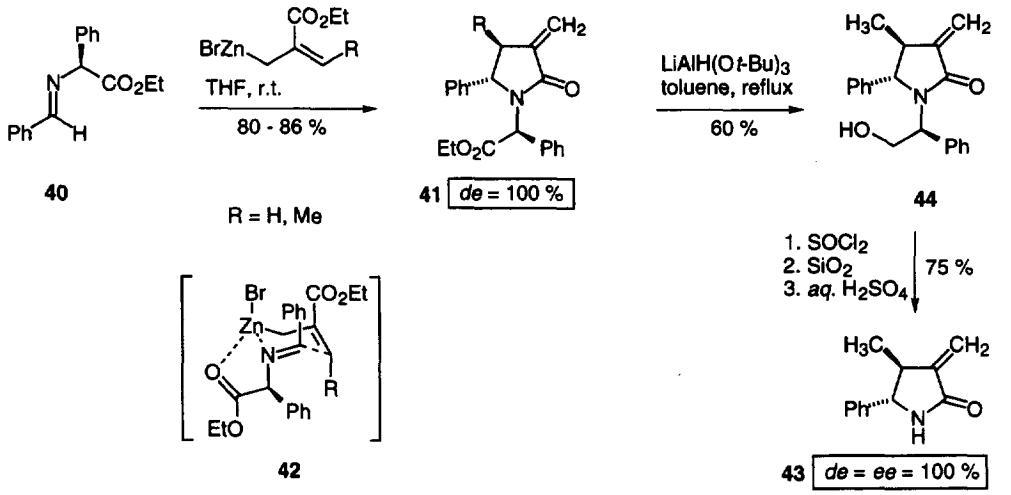
rearrangement of the corresponding acyl azide as the key step.[21] Alternatively reduction of the ester function of **2** with $LiAlH_4$, followed by the oxidative cleavage of the β-hydroxy amines with periodic acid in the presence of methylamine gave the primary homoallylamine **37**.[18]

Stereocontrolled addition of functionalized allyl- and crotyl reagents to the chiral imine **40** derived from *D*- or *L*-phenylglycine furnished exclusively cyclized adducts **41** as single diastereomers in very good yields.[22a,b] The complete stereocontrol at one (R=H) or two (R=Me) stereogenic centres in lactam **41** may be caused by the compact cyclic chair transition state **42** in which the maximum stabilization is attained. The synthesis of the enantiopure α-methylene-β-substituted-γ-lactam **43** has been performed by selective reduction of **41** using lithium tri(*t*-butyloxy)aluminium hydride to afford the lactam **44**. Finally, reaction with thionyl chloride followed by elimination of hydrochloric acid on silica gel led to an enamine which was hydrolyzed to give **43** in 40% overall yield for the removal of the auxiliary (Scheme 15). Similar selectivities were obtained for the addition of the zinc reagents by employing the bidentate auxiliary phenylglycinol (*de*=92–>95%).[22b,c]

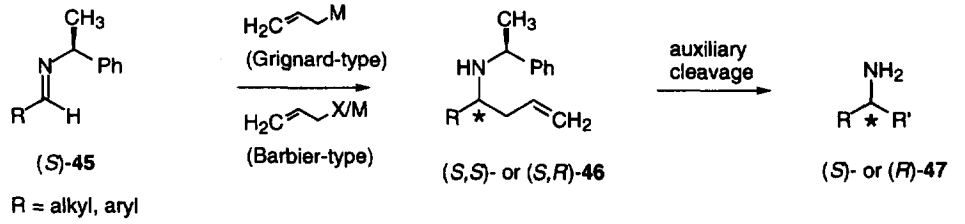
It was noted that in the presence of $BF_3 \cdot Et_2O$ (perfluor-*n*-hexyl)lithium reacted with the optically active imine prepared from benzaldehyde and (*S*)-valino methyl ester to afford the corresponding amine in diethylether as solvent and at −78°C with high diastereoselectivity (*de*=96%) and moderate yield (54%).[23]

α-Arylethyl amines as auxiliary. Enantiomerically pure 1-arylethylamines, in particular 1-phenylethylamine, are widely used as auxiliaries, owing to the availability of both enantiomers and the possible reductive removal of the 1-arylethyl group. The allylation of alkyl- and aryl *N*-phenylethylimines **45** with different types of organometallics to afford homoallylamines **46** is of particular interest (Scheme 16).

Yamamoto *et al.*[24] were the first to describe the Lewis-acid induced addition of allylstannanes to imines derived from 1-phenylethylamine and *i*-butyraldehyde. The reactions proceeded with moderate diastereoselectivities (e.g. 64% *de* for $TiCl_4$ and 34% *de* for BF_3Et_2O). The diastereoselectivity could be pushed up to 84% *de*, if *B*-allyl-9-borabicyclo[3.3.1]nonan (allyl-9-BBN) was used (Table 2, Entry 1 and 2). In the case of allyl-9-BBN and other allyl metal reagents, a cyclic chair transition state can be used as an extended Cram model to explain the observed selectivity. A sort of 1,2-axial–equatorial interaction between the 1-phenylethyl group and the ligand L in **48** may create the level of

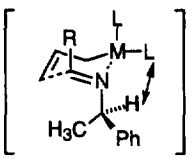


Scheme 15. Enantioselective synthesis of α-methylene-β-substituted-γ-lactams according to Villieras *et al.*[22a,b]



Scheme 16. Asymmetric allylation of 1-phenylethylimine **45**.

asymmetric 1,3-induction. Reaction of (*R*)-**45** (R=Et) with (*E*)-crotyl-9-BBN predominantly produced the corresponding *syn*-homoallylamine in a γ-selective *re*-attack of the imino group (*syn:anti*=4:1).



Several research groups have investigated the type of reaction in dependence of the nature of the imine and of the metal. A summary is given in Table 2. Moderate stereocontrol (*de* of **46**=60%) was observed when the imine **45** (R=Ph) was allylated under Barbier-type conditions using allylbromide and indium powder in THF.[25] The diastereoselectivity was not improved when the phenyl substituent of the chiral amine was replaced by the more bulky 1-naphthyl group (*de* of **46**=33%). The magnesium and zinc mediated Barbier reaction of **45** (R=Ph, 2- and 4-MeOPh) gave only racemic or low induced adducts **46** (*de*=0–43%).[26b] Also the allylation of aldimines with allylstannane activated by chlorotrialkylsilane afforded the homoallylamine **46** in low diastereomeric excess (*de*=20%).[26a]

Sato and Gao have reported on the highly diastereoselective addition of allylic titanium componds to alkylimines **45** (R=Et, *i*-Pr).[27] The reaction of the *in situ* prepared reagents [Ti(O*i*-Pr)4, i-PrMgCl and allylic halides or alcohol derivatives in diethylether] with **45** provided the corresponding homoallylic amine **46** according to the transition state **48** with very high 1,3-asymmetric induction (90–92% *de*) and in good yields (Entry 6, Table 2). The method was extended for the synthesis of chiral β-substituted

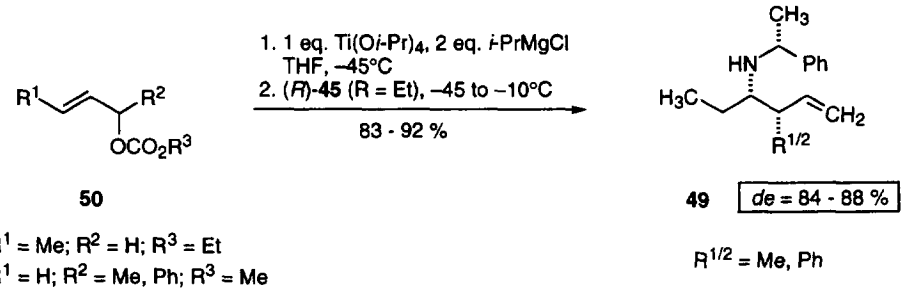
Table 2. Diastereoselective allylation of imine **45**

No.	R	allylation conditions	*de* **46** [%]	yield **46** [%]	lit.
1	*i*-Pr	allyl-9-BBN, Et_2O, –78°C	84	88 - 89	[24]
2	*i*-Pr	allylSnBu_3, $TiCl_4$, CH_2Cl_2, –78°C	64	60 - 70	[24]
3	Ph	2.25 eq. allylBr 1 eq. In-powder, THF, r.t.	60[b]	25[a]	[25]
4	Ph, 2- and 4-MeOPh	1.1 eq. allylBr 1.2 eq. Mg or Zn powder, THF, r.t.	0 - 43	77 - 93	[26b]
5	4-ClPh,	1 eq. allylSnBu_3, 1 eq. Me_3SiCl CH_3CN, 0°C - r.t.	20[b]	63 (85)[c]	[26a]
6	Et, *i*-Pr	1 eq. allyl(Br, OPh, OCO_2Et) 1 eq. Ti(O*i*-Pr)4, 2 eq. *i*-PrMgCl THF, –45 to –10°C	90 - 92	78 - 88	[27]
7	*i*-Pr	a) 1.5 eq. allylMgCl b) 3 eq. $(allyl)_2CuMgCl$-MgICl THF, –78°C	80 90	80 -100	[28]
8	Ph, 2- and 4-MeOPh 3- and 4-pyridyl 2,4-$(MeO)_2$Ph	a) 2 eq. allyl-9-BBN, Et_2O,–78°C b 3 eq. $(allyl)_2CuMgCl$-MgICl) THF, –78°C	98 - 86 94 - 48	80 -100	[28]
9	2-pyridyl	a) 3 eq. allylZnBr, THF, –78°C b) 1 eq. allyl$SnCl_2I$, THF, –78°C	74 70	80 -100	[28]

a. A partial reaction was observed. b. The absolute configuration was not determined. c. Value in brackets: yield obtained by use of Bu_3SiCl instead of Me_3SiCl.

homoallylic amines **49**. Branched allylic titanium compounds prepared from the carbonates **50** gave predominantly the *syn*-product **49** in excellent selectivities (*de*=84–88%) as illustrated in Scheme 17).

The diastereoselective addition of allylmetal compounds to imines derived from (*S*)-1-phenylethylamine was also investigated intensively by Umani-Ronchi, Savoia *et al.* Allyl-9-BBN, -MgX, -Cu, and diallylcuprate attacked the *si*-face of the imine **45** derived from 2-methylpropane. Beside the reaction of allylmagnesium chloride in THF (*de* of **46**=80%), diallylcuprate proved to be a reagent superior even to allyl-9-BBN, and afforded the homoallylic amine (*S,S*)-**46** with 90% *ee*. Conversely, the *re*-face of aromatic aldimines was generally attacked. Best results were achieved with allyl-9-BBN and diallyl cuprate with a diastereomeric excess up to 98%. Allyl-9-BBN was also the most selective reagent concerning aromatic amines, exept for pyridine-2-imine **45**. Addition of allyl(dichloro)iodotin or allylzinc bromide to this bidentate imine gave best diastereoselectivities (70–74% *de*). A SET mechanism was proposed under formation of a chelate complex with organometallic reagents. The opposite sense of asymmetric induction observed in the reaction of



50

R^1 = Me; R^2 = H; R^3 = Et
R^1 = H; R^2 = Me, Ph; R^3 = Me

49 *de* = 84 - 88 %

R$^{1/2}$ = Me, Ph

Scheme 17. Diastereoselective addition of branched allylic titanium compounds according to Gao and Sato.[27]

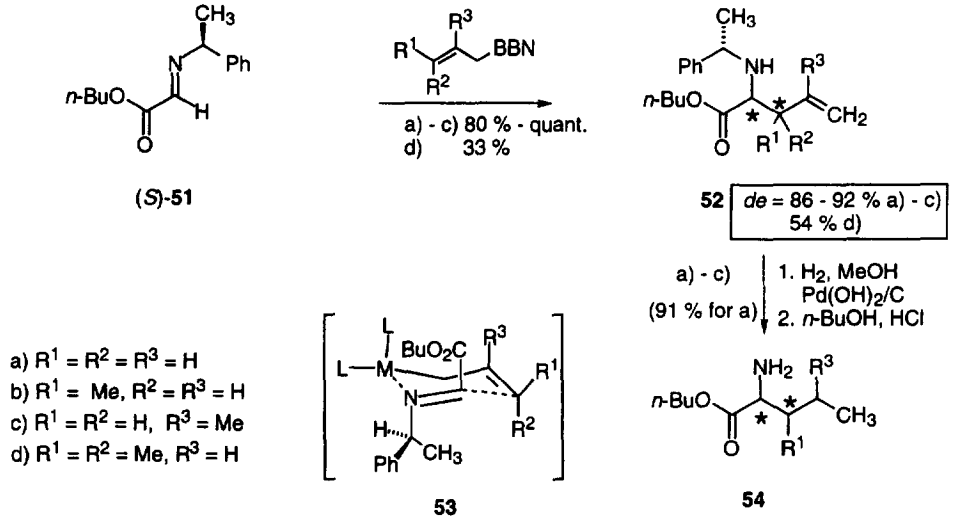
aliphatic *vs* aromatic aldimines was rationalized by isomerization of *E*- to *Z*-aromatic imines prior to the C–C bond formation (for a detailed discussion of the mechanism see the original literature).[28] A synthetic route to optically active α-arylsubstituted amines was given by regioselective removal of the 1-phenylethyl auxiliary, with concomitant hydrogenation of the unsaturated chain (HCO_2NH_4, Pd–C, MeOH, 65°C).

The high 1,3-asymmetric induction was applied to the synthesis of non-racemic amino acids and their derivatives. Yamamoto *et al.* have examined the enantioselective synthesis of amino acids by the reaction of allyl and branched allyl nucleophiles with α-imino ester **51** derived from (*S*)-1-phenylethylamine.[24b,29] The reaction of allyl-9-BBN proceeded regioselectively at the imine carbon in high yield and provided the corresponding amino acid derivative (*S,S*)-**52** in high diastereomeric excess (*de*=92%). The stereochemical outcome is in agreement with the cyclic chair transition state model **53**. Higher diastereoselection (*de*=96%) was obtained in the addition to the α-imino ester derived from (−)-1-cyclohexylethylamine. The reaction proceeded with crotyl-9-BBN in quantitative yield to give the Cram-*syn*-adduct **52** in a diastereomeric excess of 86%. Diastereofacial selectivity is reversed in methallyl-9-BBN (R^1=R^2=H, R^3=Me) addition to **51** (*de* of **52**=90%). In this case a boat transition state is assumed in order to avoid the 1,3-diaxial interaction arising from the methallyl methyl group (R^3=Me) in transition state **53**. The addition of prenyl-9-BBN resulted in low yields and selectivities (*de* of **52**=54%). The reaction of allylzinc reagents with **51** gave low diastereomeric excesses in all cases. The adducts **52** were transformed into the saturated α-amino butylesters **54** by hydrogenolytic reductive removal of the 1-phenylethyl group (H_2, cat. $Pd(OH)_2/C$) (Scheme 18).

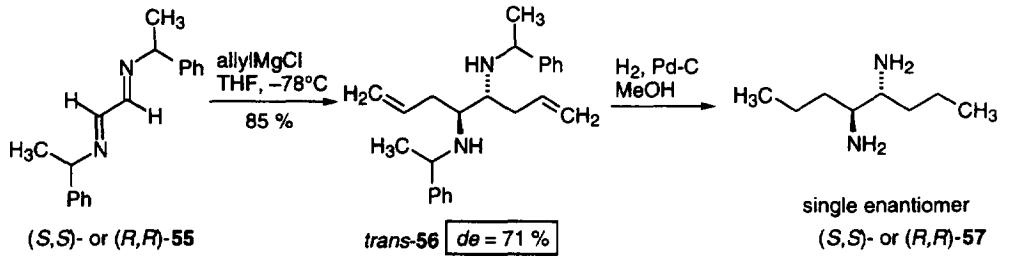
Thomas and Hallet investigated the reaction between allytin trichloride, generated from allyltributylstannane and tin tetrachloride, and imines.[30] The activated imine (*R*)-**51** reacted stereoselectively to give the (*R,S*) stereoisomer **52** (*de*=86%) in 89% yield. The stereoselectivity is remarkable because the analogous reaction with allyl-9-BBN proceeds with the opposite configuration. The newly generated stereocentre can be converted by equilibration in presence of KO*t*-Bu (70% *de*).

Neumann *et al.* have used the allylation reaction to generate enantiopure bisamine **57** (Scheme 19).[31] The double allylation of 1,2-bisimine **55**, prepared by condensation of (*S*)- or (*R*)-1-phenylethylamine with glyoxal, was performed with allylic magnesium chloride in THF to afford the *trans*-adduct **56** (*de*=71%) and traces of other diastereomers. Chromatographic separation of the diastereomers, followed by hydrogenation of the double bonds during hydrogenolysis of the *N*-benzyl group afforded enantiomerically pure (*R,R*)- or (*S,S*)-4,5-diaminooctanes. The absolute configuration was not unambiguously determined.

Other Grignard additions (MeMgCl and PhMgCl) were performed in ether/THF with moderate yields (35 and 47%) and selectivities (*de*=40 and 80%).[32] In case of the phenyl reaction starting from (*R*)-1-phenylethylamine the newly generated (*S,S*)-configuration of the corresponding adduct was determined. It is assumed that the first attack of the phenyl reagent is based on an acyclic Cram or Felkin–Anh type model which was introduced by Yamamoto and Ito[29b] to explain the

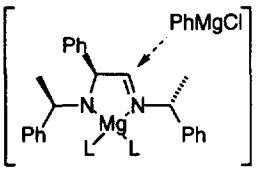


Scheme 18. Diastereoselective addition of allylic boron compounds to α-imino ester **51** according to Yamamoto *et al.*[24b,29]



Scheme 19. Asymmetric synthesis of vicinal diamine **57** according to Neumann *et al.*[31]

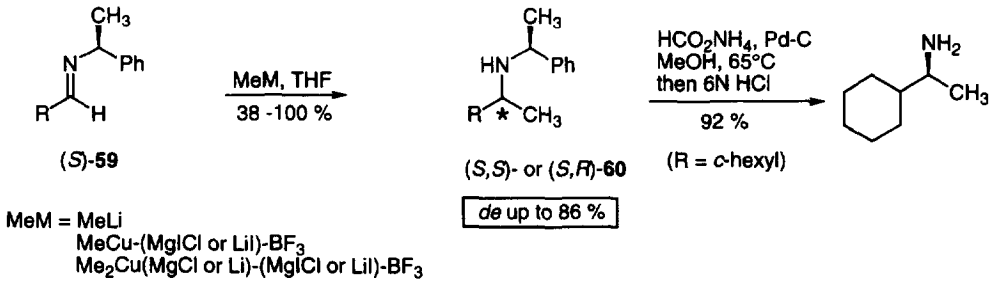
diastereoselectivity (*de*=48%) observed in the addition of benzylzinc chloride reagent to α-imino ester **51**. The stereoselectivity in the second addition is presumably enforced by both 1,3- and 1,2-induction in a chelated intermediate **58**.



58

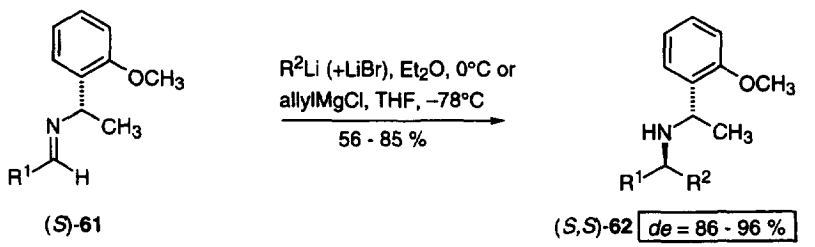
Umani-Ronchi, Savoia *et al.* have investigated the diastereoselective addition of methylmetal reagents to alkyl- and arylimines **59** derived from (*S*)-1-phenylethylamine.[33] Best results were obtained by using methyllithium and methylcopper- and dimethylcuprate-boron trifluoride reagents in THF. Mainly the (*S,S*)-configurated amine **60** was obtained in diastereomeric excesses up to 86% (R=Ph, *c*-hexyl) by dimethylcuprate methylation. In case of the corresponding addition of methyllithium to strongly chelating bidentate imines **59** having a heteroatom in the *ortho* position (R=2-pyridyl and 2-furyl), reversed asymmetric induction (*de*=40–64%) was observed (Scheme 20). A detailed discussion of the mechanism is given in the literature cited.

Other 1-arylethylamines have been employed in order to reach better results in the addition step.



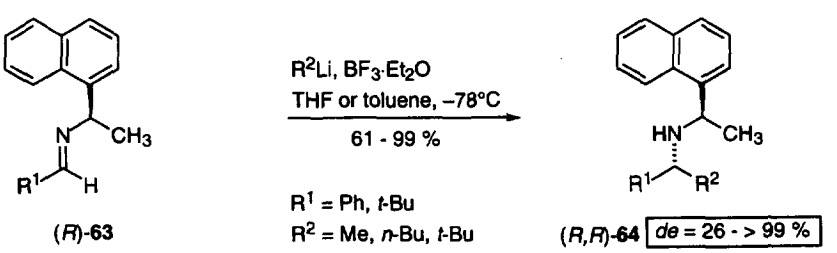
Scheme 20. Diastereoselective methylation of imine **59** according to Umani-Ronchi, Savoia *et al.*[33]

Hashimoto, Saigo *et al.* described the reaction of alkyl- and allyllithium reagents to imine **61** derived from an *o*-methoxy-modified 1-phenylethyl amine as depicted in Scheme 21.[34] Best results were obtained when the reaction with organolithium reagents was carried out in diethylether at 0°C. Allylmagnesium chloride gave a much higher induction than allyllithium (86% *vs* 34% *de* of **62**). The preferred *si*-attack observed was explained by a rigidified transition state model based on a six-membered chelation ring of the methoxy group and the nitrogen of the imino group bridged by the lithium. A selective removal of the auxiliary has not been described.



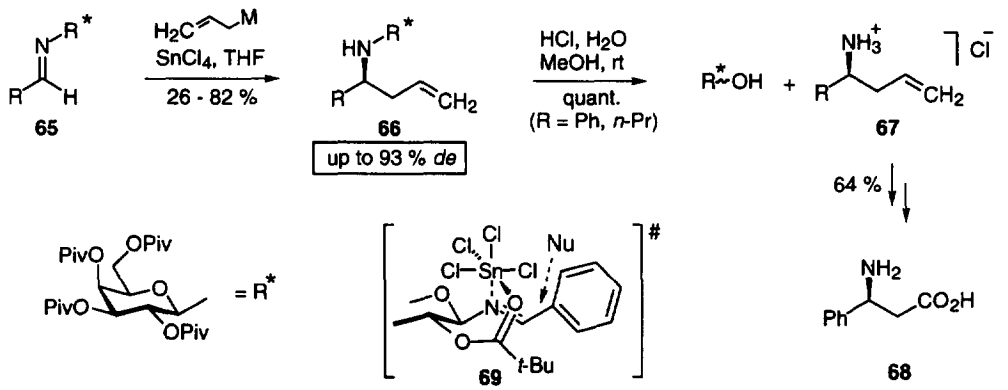
Scheme 21. Diastereoselective addition to chiral imine **61** according to Hashimoto, Saigo *et al.*[34]

Nakagawa *et al.*[35] have reported on the diastereoselective alkylation of imine **63** with alkyllithium reagents in the presence of $BF_3 \cdot OEt_2$. (*R*)-α-Naphthylethyamine is used as a enantiopure amine. The level of diastereoselectivity obtained in the reaction is strongly related to the employed nucleophile. MeLi gave the best diastereomeric excess (>99%) whereas the reaction of *tert*-butyllithium afforded the adduct **64** with a low diastereomeric ratio (*de*=26%) as shown in Scheme 22.



Scheme 22. α-Naphthylethylamine as chiral auxiliary according to Nakagawa *et al.*[35]

Miscellaneous auxiliaries. A highly stereoselective synthesis of chiral homoallylamines **67** has been reported by Kunz and Laschat.[36] A Lewis acid induced addition of allyl trimethylsilane (R=aryl) or trimethylstannane (R=alkyl) to the imino derivative **65** was performed by employing the polyfunctional 2,3,4,6-tetra-*O*-pivaloyl-β-*D*-galactopyranosyl amine as chiral auxiliary. The reaction provided the homoallylamine **65** with low to high diastereofacial discrimination (≤93% *de*) in dependence of the imine substrate in yields ranging from 26–82%. The preferred formation of the homoallylamine **66** can be rationalized by a *si*-attack of the allylic nucleophile. A transition state **69** forming a *N,O*-chelate with an octahedral coordinated tin was assumed. The low yields were caused by partial anomerization of the β-anomer under the Lewis acidic conditions. The resulting α-anomer did not react with allylsilane. Aliphatic homoallylamines **66** were synthesized by using allyltributylstannane in the presence of $SnCl_4$. Both α- and β-anomeric aliphatic imines **65** reacted with the allylstannane and showed the same diastereomeric ratio for **66**. The homoallylamines **67** could be obtained by acidic release. Oxidative conversion led to optically active β-amino acids **68** (Scheme 23).

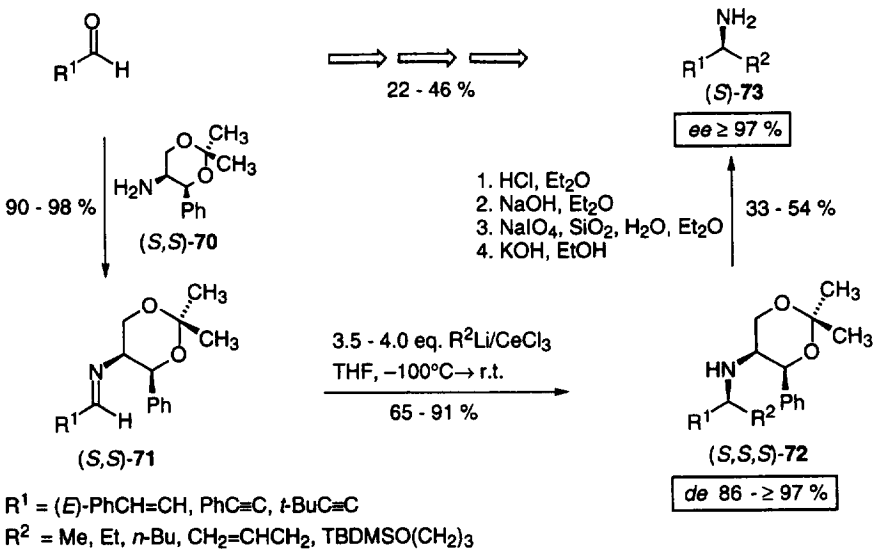


Scheme 23. Asymmetric synthesis of homoallylamines and β-amino acids by Kunz and Laschat.[36]

Enders and Schankat reported on the enantioselective synthesis of allyl-, propargyl and 4-en-2-inylamines **73** in high enantiomeric purity (≥97% *ee*) as depicted in Scheme 24.[37] The key step is the diastereoselective 1,2-addition (86–≥98% *de*) of organocerium reagents to chiral α,β-unsaturated aldehyde imines **71** derived from the commercially available auxiliary (+)-(*S,S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane-(*S,S*)-**70** to produce amine (*S,S,S*)-**72**. The opposite (*R*)-configuration of the generated stereogenic centre can be obtained by the addition of methyllithium. Other organolithium and Grignard reagents led to a mixture of regioisomers (1,2 *vs* 1,4-addition). The chiral auxiliary (*S,S*)-**70** is removed in 3 steps affording the amines (*S*)-**73** in moderate to acceptable yields (33–54%). A summary of the method is given in Scheme 24. A diastereoisomeric enrichment is possible by crystallization. The propargylamine **72** (R^1=TMSC≡C, R^2=Me, 93% *de*, ≥98% *de* after chromatography) is substrate for Pd-catalyzed coupling with alkenyl and 2-thienyl halides to produce enynylamines and thienyl-substituted alkynylamines.

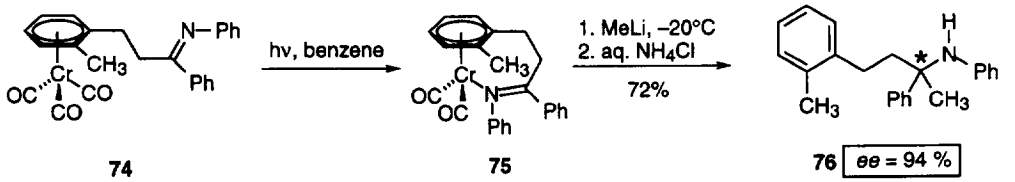
2.1.2 Auxiliary group in the carbonyl compound

Solladié-Cavallo *et al.* have described an asymmetric synthesis of amine **76** employing the enantiopure chromium tricarbonyl complex **74**.[38] Irradiation of the arene complex **74** gave the chelate **75** and subsequent addition of methyllithium proceeded with 94% enantiomeric excess of the resulting amine **76** (Scheme 25). Treatment of **74** with alkyllithium reagents led to a racemic mixture of the



Scheme 24. Asymmetric synthesis of allyl-, propargyl and 4-en-2-inyl-amines by Enders and Schankat.[37]

corresponding amine **76** indicating the importance of the imino chelation to reach a high asymmetric induction.

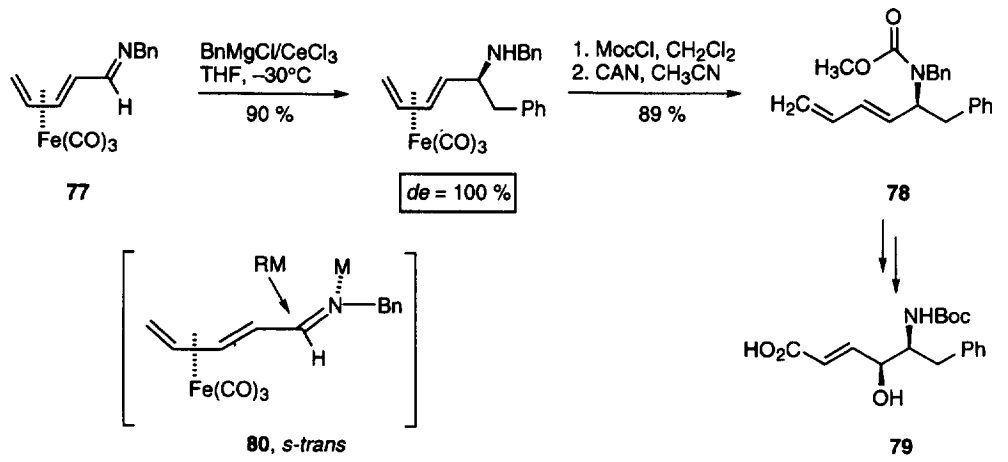


Scheme 25. Arene(dicarbonyl)chromium-chelate **75** in the asymmetric synthesis of amines according to Solladié-Cavallo.[38]

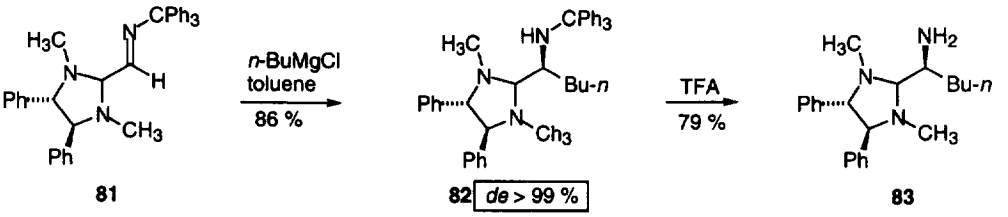
Excellent diastereoselectivities were obtained by 1,2-addition of various organometallic nucleophiles to the racemic 1-iminobutadiene-iron tricarbonyl [$Fe(CO)_3$] complex **77** by Iwata *et al.* (Scheme 26).[39] In particular, by using organocerium reagents [Me, *n*-Bu, Ph, allyl (Li or MgBr)/$CeCl_3$] only single secondary amine complexes **2** were obtained in good yields. As an application of this methodology, benzylcerium reagents were added to the enantiopure complex **77** with complete diastereoselectivity followed by oxidative decomplexation to the protected amine **78**. The transformation to the hydroxyethylene isostere **79** was described. The stereochemical outcome of the addition to the imine complexes can be rationalized as follows. NOE experiments showed an equilibrium mixture of both *s-trans* and *s-cis* conformers of **77**. In cases using Lewis acidic organometallic reagents and also in the presence of Lewis acids, the coordinated complex of conformer **80** is more stable and the nucleophiles attack from the opposite face of the bulky tricarbonyl iron unit takes place stereoselectively.

A highly diastereoselective addition of *n*-butylmagnesium chloride solution in toluene to the iminoaminal **81**, a glyoxal derivative, has been reported by Alexakis *et al.* (Scheme 27).[40] Treatment of adduct **82** with TFA gave the deprotected primary amine **83** which can be transferred to the *N*-Boc-protected α-amino aldehyde. For the analogous hydrazone transformation see Chapter 3.2.

Utimoto, Matsubara *et al.* have reported on the addition of several organometallic reagents to the imino group of the enantiopure 1,3-oxathiane **84**.[41] Independently of the character of the nucleophiles outstanding diasteroselectivities (>98% *de*) were achieved for the amine **85**. Cleavage of the oxathiano

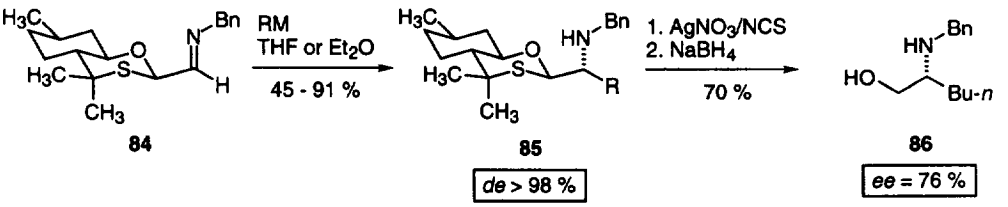


Scheme 26. Enantioselective synthesis of hydroxyethylene isostere **79** according to Iwata *et al.*[39]



Scheme 27. Aminal-directed addition to imine **79** according to Alexakis *et al.*[40]

group was performed in one case (R=*n*-Bu) to yield the amino alcohol **86** in considerablely lowered enantiomeric excess (Scheme 28).



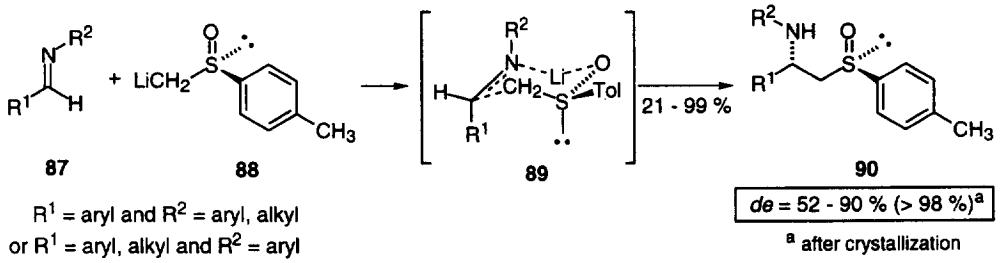
RM = *n*-Bu[Li, MgBr, Li/$CeCl_3$, Li/Yb$(OTf)_3$], PhLi, $H_2C{=}C(CH_3)Li$, $CH_3(CH_2)_4C{\equiv}CLi$

Scheme 28. Asymmetric synthesis of amino alcohols according to Utimoto, Matsubara *et al.*[41]

2.1.3 Auxiliary group in the nucleophile

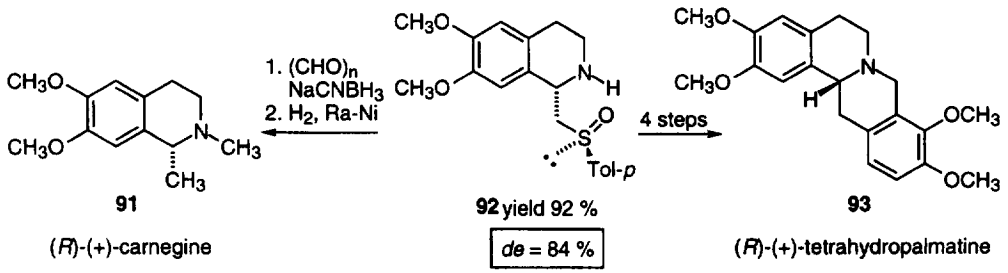
In 1973, Tsuchihashi *et al.*[42] reported on the addition of the lithium carbanion of (*R*)-methyl *p*-tolyl sulfoxide **88** to *N*-benzylideneaniline **87** ($R^1{=}R^2{=}Ph$) at −10 to −20°C as a highly diastereoselective process. The generality of this method was not demonstrated. More recently, Kagan[43] and Pyne[44a,b] have investigated the diastereoselective addition of **88** to various imines **87**. Attempts to extend these reactions to nonaromatic amines were unsuccessful. The reaction temperature as well as the reaction time is a crucial variable in determining the product diastereoselectivity of **90** in this type of reaction. The reaction showed good to moderate product diastereoselection under kinetically controlled

conditions (−45°C to 0°C) as illustrated in Scheme 29. The authors suggested a chair-like transition state **89**. Under thermodynamically controlled conditions poor diastereoselectivities were obtained.



Scheme 29. Diastereoselective additions of chiral α-sulfoxide carbanion **88** to imines according to Kagan[43] and Pyne.[44a,b]

This methodology permits the construction of (*R*)-carnegine **91**[44c] and (*R*)-tetrahydropalmatine **93**.[44b] The best diastereoselectivity of the β-amino sulfoxide **92** was obtained by addition of **88** to 3,4-dihydroxy-6,7-dimethoxyisoquinoline under equilibrium controlled conditions. The interconversion of the diastereomers was explained *via* a retro-Michael addition–Michael addition reaction sequence. The alkaloids **91** and **93** were elaborated in 2 and 4 steps by reductive desulfuration as illustrated in Scheme 30.



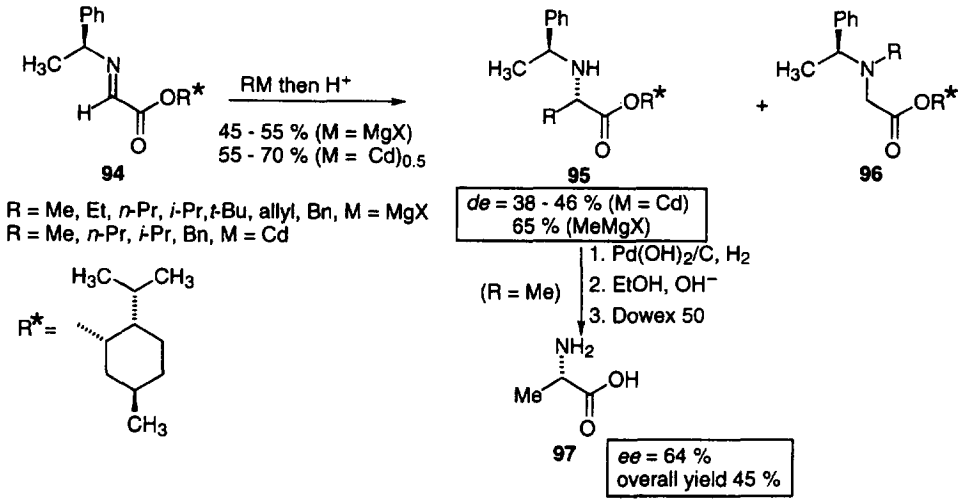
Scheme 30. Asymmetric synthesis of carnegine **91** and tetrahydropalmatine **93**.[44b,c]

2.1.4 Double-induced stereoselectivity

In the early seventies Fiaud and Kagan[45] reported the first asymmetric addition of organometallic reagents to enantiomerically pure α-imino ester **94**, prepared from glyoxalic acid, (*R*)- or (*S*)-α-phenylethylamine and (−)-menthol in order to generate the α-amino ester **95**. Depending on the character of the Grignard nucleophile either **95** (R=Me, *t*-Bu, allyl) or **96** (R=Et, Pr, *i*-Bu, Bn) was regioselectively formed in low to moderate optical and chemical yields. The formation of **94** can be explained by a Michael-type reaction. It was shown that (−)-menthol as auxiliary is dominant over the chiral imine group. Replacement of (*S*)-α-phenylethylamine by the (*R*)-enantiomer gave a similar diastereoselectivity.[45a] Organolithium agents can not be used in this reaction because of their favoured addition to the ester group. The use of the corresponding organocadmium reagents led exclusively to the desired product **95** in acceptable yields (55–70%) but low diastereoselectivities (38–46% *de*).[45b] Removal of the auxiliaries by hydrogenolysis and basic hydrolysis gave the α-amino acid **97** (Scheme 31).

2.1.5 Ligand-induced stereoselectivity

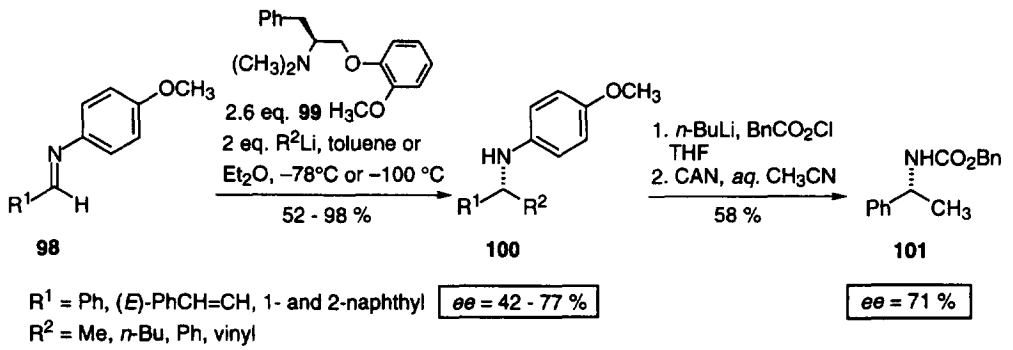
The ligand-induced enantioselective synthesis avoids the auxiliary attachment and removal steps It also holds the potential for direct recovery and reuse of the unchanged chiral reagents. The next innovative step was the exploration of useful synthetic 1,2-additions controlled by catalytic amounts



Scheme 31. Enantioselective synthesis of α-amino acids according to Fiaud and Kagan.[45]

of chiral additives. In recent years several stoichiometric asymmetric reactions as well as successful first catalytic attempts have been described in the literature.

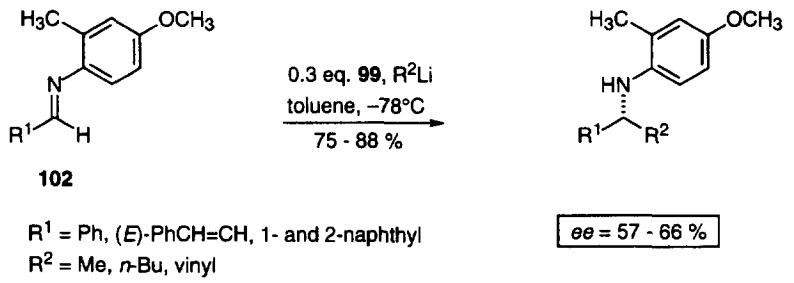
The first report of external chiral-ligand-mediated addition of organometallic reagents to a CN double bond appeared in 1990 by Tomioka *et al.*[46a] The reaction of organolithium compounds (R=Me, Bu, Ph, vinyl) with aromatic or unsaturated *N*-4-methoxyphenylimines **98** in the presence of the chiral β-amino alcohol derivative **99** afforded selectively the corresponding 1,2-addition products **100** with an enantiomeric excess of up to 77%. The chiral tridentate aminoether **99** is superior to bidentate ligands.[46e] The reaction was performed in toluene or diethylether at low temperatures (−78°C or −100°C). The imines **98** derived from cinnamaldehyde (R^1=PhCH=CH) exhibited lower enantioselectivities of 42–48% *ee* in contrast to the aryl imine (R^1=Ph, 1- and 2-naphthyl). The 4-methoxyphenyl group of the amine **100** was removed in one case (R^1=Ph, R^2=Me, 70% *ee*) by a two step sequence.[46a,d] After protection of the amine with the benzyloxycarbonyl group the oxidative removal of the 4-methoxyphenyl group was carried out by cerium ammonium nitrate (CAN) to provide the protected primary amine **101** without loss of optical purity in 58% yield (Scheme 32).



Scheme 32. Enantioselective ligand-mediated addition to imine **98** according to Tomioka *et al.*[46a,d,e]

In a recent paper the influence of substituted *N*-4-methoxyphenylimines (R^1=Ph) has been investigated.[46c] Alkyl substituents in the 2-position of the aromatic moitey led to an enantiomeric excess of up to 90% under the described reaction conditions.

Tomioka *et al.* disclosed a catalytic process for the enantioselective addition reaction (Scheme 32), by the use of a substoichiometric amount of the chiral ligand **99** with excellent yield.[46b] The enantiomeric excess of **100** decreased in direct relation to the amount of employed ligand. For instance, the chiral catalyst **99** of 0.05 equivalent still exhibited a remarkable catalytic effect on the asymmetric induction to give **100** with 40% *ee*. For butyllithium additions, the choice of the reaction solvent was critical for the catalytic asymmetric induction. The use of lithium bromide complexed methyllithium for the catalytic enantioselective methylation of imine **98** at −42°C significantly decreased the enantioselectivity of this reaction. Reaction conditions and results for the catalytic 1,2-addition of organolithiums to the imine **102** derived from 4-methoxy-2-methylaniline are shown in Scheme 33.



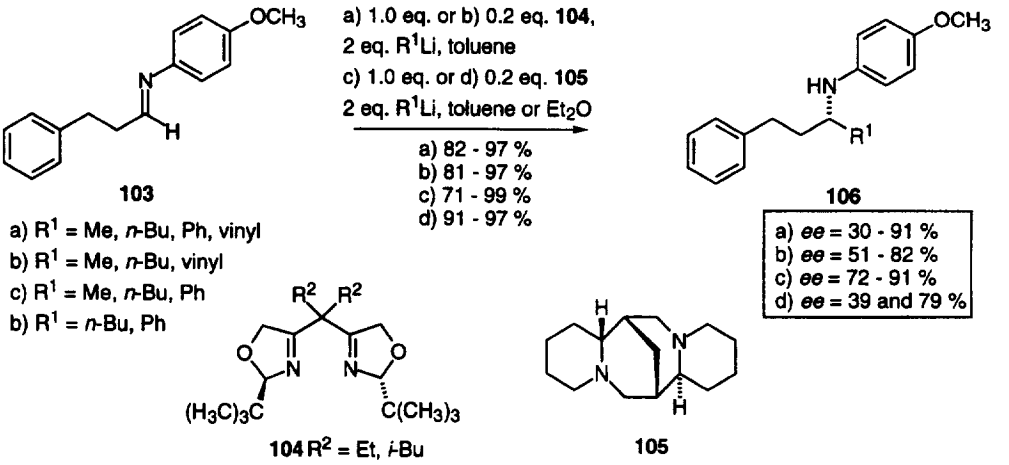
Scheme 33. Catalytic asymmetric 1,2-addition of organolithiums to imine **102** according to Tomioka *et al.*[46d]

The lower selectivities in the catalytic process can be rationalized by the competing noncatalyzed reaction and a possible disorder of the reactive ligand–organolithium complex by the formed chiral lithiumamide.

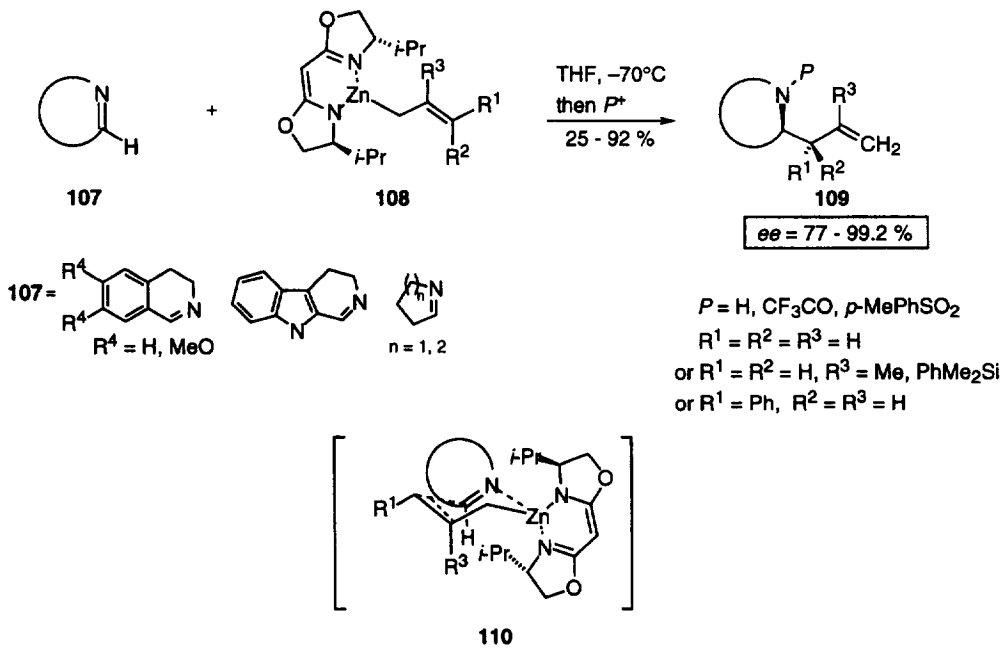
The bidentate C_2-symmetric bis(oxazoline) ligands **104**[47b] have been described as efficent external ligands for the stoichiometric and substoichiometric enantioselective methylation of **98** (Scheme 32).[47a] The adduct **100** (R^2=Me) was obtained under similar reaction conditions with good enantiomeric excesses (*ee*=60–85%) and very high yields (90–98%). The process was extended to the enantioselective addition of several organolithiums to the enolisable imine **103** with use of the chiral ligand **104** (R^2=Et). It was found that MeLi provided the highest enantioselectivity (91% *ee*) compared to the use of *n*-BuLi (57% *ee*), PhLi (30% *ee*) and vinyllithium (89% *ee*) for the stoichiometric reaction. In all additions, ligand **104** was recovered in enantiomerically pure form in 91–100% yield. Substoichiometric amounts of **104** (R^2=Et) gave reduced enantioselectivities (*ee*=51–82%). The bidentate tertiary amine (−)-sparteine **105** was found to serve effectively as external ligand in both stoichiometric and catalytic quantities as shown in Scheme 34. The enantioselectivity of both butylation and phenylation of **103** was significantly improved by employing one equivalent of sparteine, affording the amines **106** in 91% and 82% *ee* respectively.

The asymmetric addition of organolithium reagents to imine **102** (Scheme 34) gave the opposite configuration (*S*)-amine **106** with an enantiomeric excess up to 21% by the use of a modified (*S*)-proline derived tridendate catalyst.[48]

A highly enantioselective allylation of cyclic aldimines **107** has been investigated by Nakamura *et al.*[49] Allylic zinc reagent **108**, prepared by reaction of an enantiopure lithiated bisoxazoline and allylzinc bromide, added to the mono-, di- and tricyclic imines **107** in high to excellent enantioselectivity (*ee*=77–99%) at −70°C. The homoallylic adducts were obtained as free or acylated secondary amines **109**. The best selectivities were obtained with the bisoxazoline ligand derived from (*S*)-valinol. Poor enantioselectivities were observed in the allylation of acyclic (*E*)-imines, ketimines and acylpyridinium salts. Under the assumption of the chair transition state **110** with equatorial disposition of substituents and reduced interaction of the *i*-propyl group *si*-attack of the imine group was rationalized (Scheme 35).



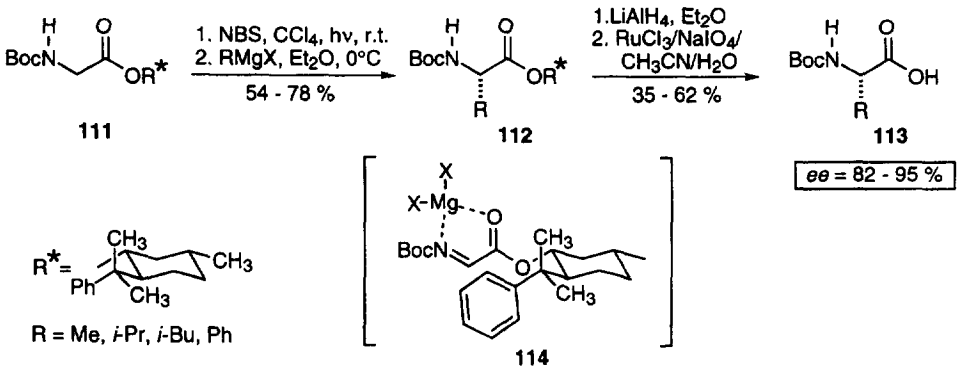
Scheme 34. Enantioselective addition of organolithium reagents to imine **103** according to Denmark *et al.*[47]



Scheme 35. Enantioselective allylation of cyclic aldimines **107** according to Nakamura *et al.*[49]

2.2 N-*Acylimines*

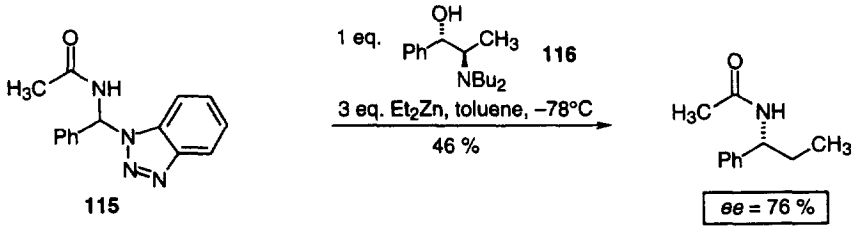
Obrecht *et al.*[50a] have examined the addition of Grignard reagents to α-bromo *N*-glycine-(−)-phenylmenthyl ester **111** based on a methodology developed by Steglich *et al.*[50b–d] *N*-Boc iminoacetate is generated before the Grignard nucleophile regio- and diastereoselectively attacks the C–N-imino bond. Since removal of the auxiliary by transesterfication led to racemization, the enantiopure alcohol was cleaved off by reduction and recovered quantitatively. The resulting *N*-Boc-protected amino alcohol could be oxidized to the *N*-Boc amino acids **112**. The high diastereoselectivities (82–95%) of **112** can be rationalized firstly, by a 5-membered chelate **114** of the magnesium cation with the acylimino and the carbonyl group and secondly, by the face discrimination of the imine double bond by the aromatic ring of the auxiliary moiety, as depicted in Scheme 36.



Scheme 36. Enantioselective synthesis of *N*-Boc-α-amino acids according to Obrecht *et al.*[50]

The scope of this reaction was extended by Hamon *et al.*[51] Aryl and alkyl Grignard reagents (R=Me, Et, *i*-Pr, *n*-Pr, Ph, Bn) gave high to complete diastereoselectivities of **113** (90–>98% *de*) at −78°C, whereas lower diastereofacial selectivity was achieved by the use of allyl and vinyl magnesiumhalides (51–57% *de*). Conditions were described for the direct hydrolysis of these derivatives without racemization of the resulting amino acid (TFA, then 6N HCl, reflux).

Enantioselective ethylation of *N*-(acetamidobenzyl)benzotriazole **115**, acting as masked activated *N*-acylimine, was described by Katritzky and Harris.[52] The addition of diethylzinc complexed with (−)-*N,N*-dibutylnorephedrine **116**, an efficient chiral catalyst for the addition of diethylzinc to carbonyl substrates, is performed with enantioselctivities up to 76%. Optimized conditions are given in Scheme 37. A loss of selectivity is reported with an increase in the size of the amide **115** and with less then one equivalent of the amino alcohol or three equivalents of the zinc nucleophile, respectively. For enantioselective addition of organozinc reagents see also Chapter 2.5.

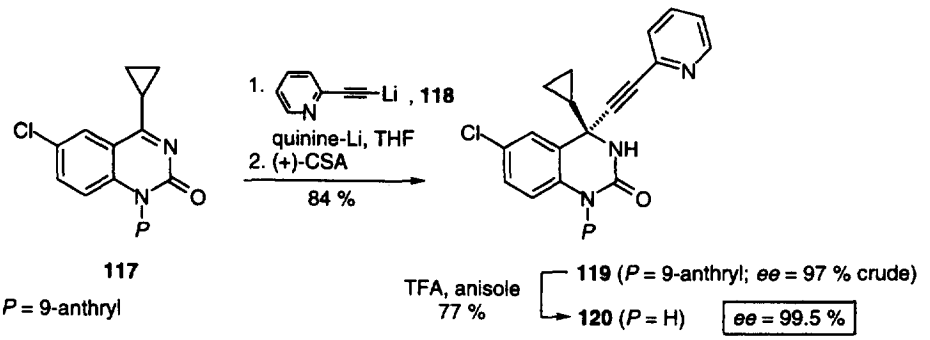


Scheme 37. Enantioselective addition of diethylzinc to benzotriazole **115**.[52]

The ligand induced enantioselective synthesis of the HIV reverse transcriptase inhibitor **120**, involving a lithium acetylide addition of **118** to the cyclic *N*-acyl ketimine **117**, has been described by Huffman *et al.*[53] As chiral controller the lithium alkoxide of the alkaloid quinine was used. Quinidine can be employed to give the opposite enantiomer. For the high enantiomeric excess (97% *ee*) of the adduct the bulky 9-anthryl protecting group (*P*) and optimized temperature conditions were required. Purification of the (+)-CSA salt **119** and deprotection of the 9-anthranyl group afforded the nearly enantiopure inhibitor **120** (Scheme 38).

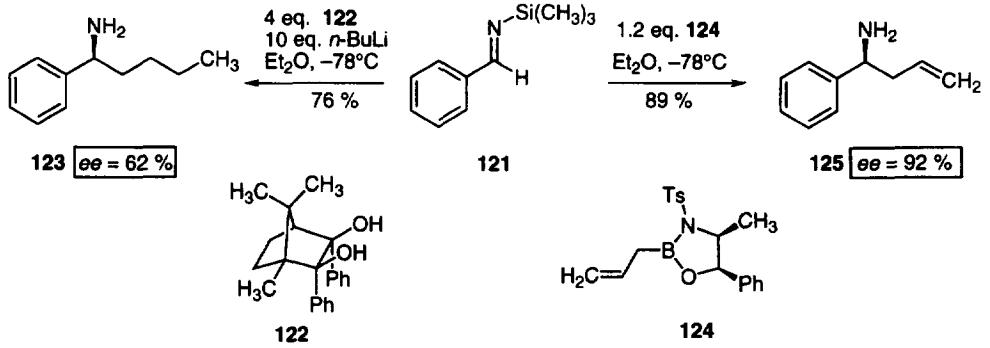
2.3 N-*Silylimines*

Pioneering work in the area of ligand-induced enantioselective alkyl- and allyl addition to the C–N double bond was reported by Itsuno *et al.* (Scheme 39).[54] *N*-(trimethylsilyl)benzaldehyde imine **121** was alkylated with *n*-butyllithium in the presence of the chiral lithium alkoxide prepared from the diol **122**.[54a] After aqueous work-up the primary amine **123** was obtained in good yield (76%) and with an



Scheme 38. Enantioselective acetylide addition to cyclic *N*-acyl ketimine **117**.[53]

enantiomeric excess of 62%. It is noteworthy that two equivalents of diol **122** were necessary to obtain high asymmetric inductions. Organolithium reagents afforded both higher yield and greater selectivity compared to the corresponding Grignard reagents. Silyl imine **121** failed to react with diethylzinc in the presence of amino alcohols or diols.

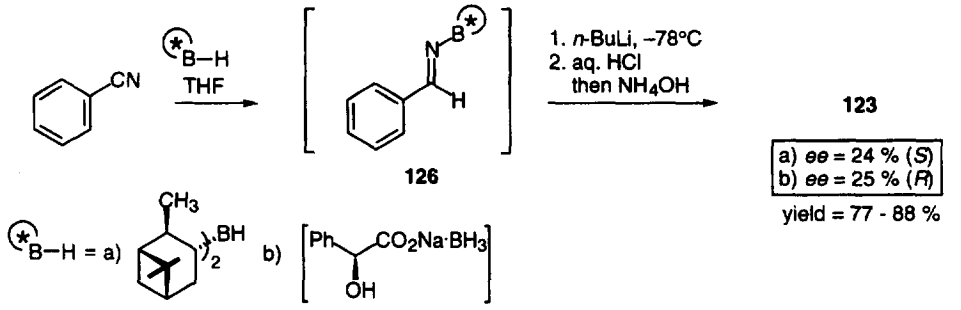


Scheme 39. Enantioselective addition to *N*-(trimethylsilyl)benzaldehyde imine **121** according to Itsuno *et al.*[54]

Also the enantioselective allylation of the *N*-trimethylsilyl imine **121** by chirally modified allylboron reagents has been investigated.[54b,c] *B*-allyldiisopinocampheylborane was prepared starting from the commercially available (−)-*B*-chlorodiisopinocampheylborane. After addition of the enantiopure allylborane under optimized conditions, the adduct was hydrolyzed to give directly the enantiomerically enriched homoallylamine **125** with an enantiomeric excess of 73%. Recently, a more efficient chiral allylboron reagent has been described.[54c] The *B*-allyloxazaborolidine **124** prepared from (−)-norephedrine gave the best results (92% *ee*) in 89% yield.

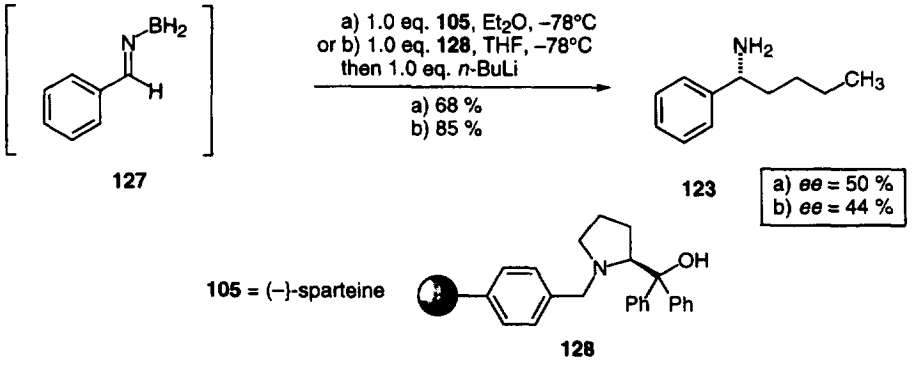
2.4 N-*Borylimines*

A rarely investigated type of reaction is the asymmetric 1,2-addition to *N*-borylimines. Beside a general strategy for the synthesis of racemic pimary amines, an asymmetric variant has been carried out (Scheme 40).[55] The chirality information was incorporated into the boryl part of **126** by partial reduction of benzonitrile with enantiopure boranes. Diisopinocampheylborane[55a] as well as the reducing agent prepared from sodium borohydride and the optically active carboxylic acid (*S*)-mandelic acid[55b] were used for the in situ preparation of borylimines **126** which can be seen as masked imine derivatives of ammonia. Alkylation with *n*-butyllithium at low temperatures and acidic hydrolysis afforded the (*R*)- or (*S*)-configured amine **123** in high yields (77–88%) but only poor enantioselectivities (*ee*=24–25%).



Scheme 40. Diasteroselective addition to chiral *N*-borylimines **126** according to Itsuno *et al.*[55]

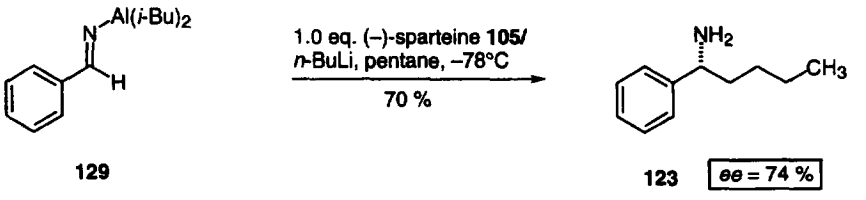
Recently the same group has reported new results on the reaction of *n*-butyllithium and *N*-(metallo)imines (Scheme 41).[56] *N*-Borylbenzaldehyde imine **127**[56a] was alkylated after complexation with one equivalent (−)-sparteine **105** in diethylether with enantioselectivities up to 50% *ee* and good yields. Also the enantioselective alkylation with a polymer supported amino alcohol **128** was examined. An enantiomeric excess of 44% for **123** was obtained in high yield (85%).



Scheme 41. Enantioselective addition to *N*-borylimine **127** according to Itsuno *et al.*[56b]

2.5 N-*Alumino imines*

Beside investigations of the ligand-induced addition of *n*-butyllithium to *N*-silyl- and *N*-borylimine (see section 2.3 and 2.4) the reaction of *N*-(diisobutylalumino)benzaldehyde imine **129** has been examined.[56b] Addition of the *N*-alumo imine **129**, prepared in situ from partial reduction of benzonitrile with diisobylaluminium hydride, to the preformed (−)-sparteine **105**/*n*-BuLi complex at −78°C in pentane gave best selectivities of the obtained primary amine **123** (*ee*=74%) as depicted in Scheme 42.



Scheme 42. Enantioselective addition to *N*-alumino imine **129** according to Itsuno *et al.*[56]

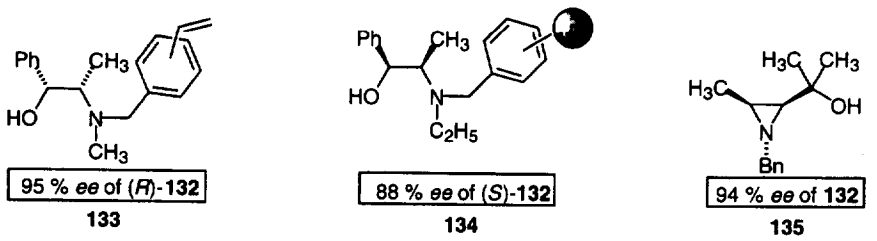


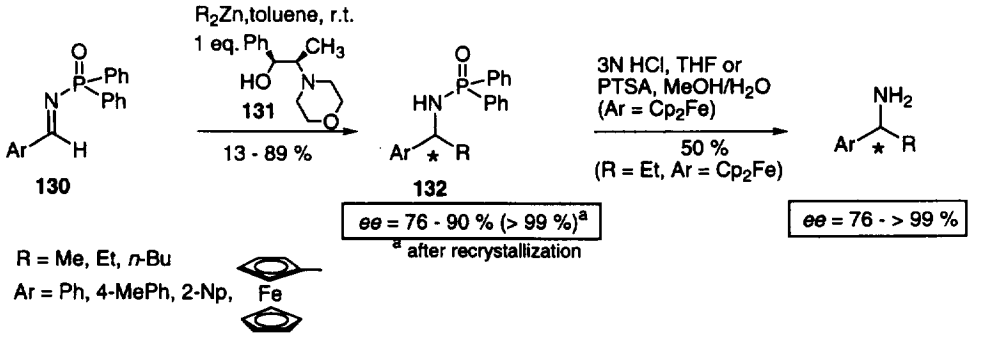
Figure 2. Optimized ligands for the addition of dialkylzinc to *N*-phosphinoylimines **130**.[58c,d]

2.6 N-*Phosphinoylimines*

The catalytic enantioselective addition of dialkylzinc reagents to aldehydes is a well investigated reaction.[57] Soai *et al.* reported on the corresponding highly enantioselective addition to the reactive *N*-diphenylphosphinoylimines **130** in the presence of enantiopure β-amino alcohols derived from norephedrine.[58a,b] In general, the use of one equivalent of **131** as ligand led to the corresponding phosphoramide **132** in high enantiomeric excess (up to 91% *ee*) and good yields. Substoichiometric amounts of the ligand (0.5 eq.) gave slightly lower stereoselectivities but considerably lower yields. The (*S*)-configuration of the new stereogenic centre was determined in one case. Acidic treatment afforded the free amine without racemization. Also optically active ferrocenylamines, important synthetic intermediates for the synthesis of chiral catalysts, can be prepared in the described way starting from ferrocenyldiphenylphosphinyl imines.[58b] Good yields for the addition step seem to be limited with the diethylzinc reagent.

Recently other ligands have been described for the enantioselective addition of diethylzinc to *N*-phosphinoylimines **130** (Ar=Ph).[58c,d] In order to find a polymer catalyst *N*-alkyl-*N*-vinylbenzylnorephedrines were optimized for the ethylation. The amino alcohol **133** (Figure 2) gave the best enantioselectivity (ee=95%, 81% yield). Also the polymer **134**,[58c] synthesized by the copolymerization of the chiral monomer with styrene and divinylbenzene, was found to be highly enantioselective (*ee*=88%, 60% yield). After work-up and separation by filtration the chiral ligand **134** was recovered and can be employed again as chiral catalyst.

Enantiopure aziridino alcohols, e.g. **135**,[58d] were used as catalyst for the same reaction with enantiomeric excesses of up to 94% of **132** (Scheme 43, Ar=Ph, R=Et).

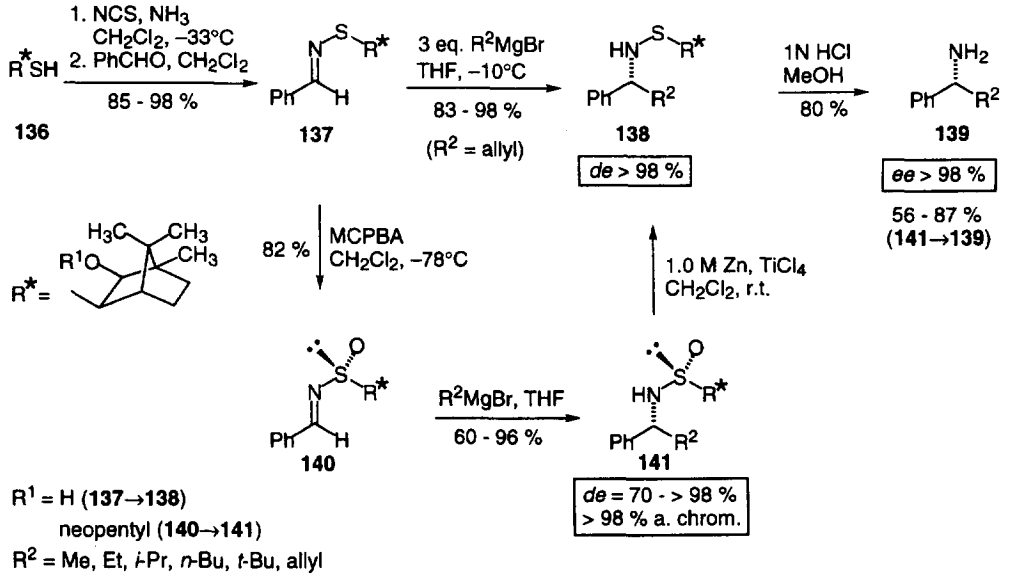


Scheme 43. Enantioselective synthesis of amines by addition of dialkylzinc to *N*-phosphinoylimines **130** according to Soai *et al.* [58a,b]

2.7 N-*Thioimines*

N-Thioimines, e.g. *N*-sulfenyl-, *N*-sulfinyl- or *N*-sufonylimines, are a relativly unexplored group of imino compounds. So far only a few asymmetric examples of stereoselective additions of organometallics to the C–N double bond have been reported.[59–61]

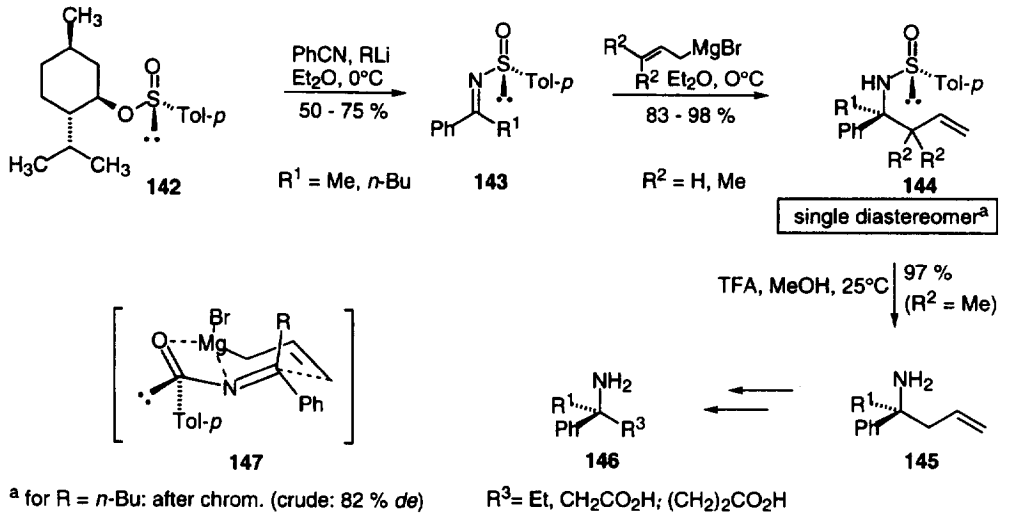
The nucleophilic addition to sulfenyl- and sulfinylimines (**137**, **140**) bearing camphor-derived mercapto auxiliaries **136** has been investigated by Yang *et al.*[59] Allyl Grignard addition to the chiral sulfenimine led to a single diastereomer of **138**. Advantageous is the smooth cleavage of the N–S bond. The enantiopure amines (*S*)-**139** and the recycable mercapto auxiliary **136** were obtained in good yields after acidic treatment. Diastereo- and enantiomerically pure sulfinylimines **140** can be synthesized by oxidation of the sulfenylamine **137** with MCPBA followed by chromatographical separation of the diastereomers (*de*=72%). The observed high to complete diastereoselectivities of the asymmetric Grignard addition was influenced by the nucleophilic character of different alkyl-, aryl- and allyl Grignard reagents as well as the chirality of the sulfinyl group. Size difference of the 2-alkoxy group of the chiral template seems to have little effect on the diastereoselectivity. The sulfinamide **141** was reduced to the sulfenamide **138** and hydrolyzed to afford the enantiopure amine (*S*)-**139** without any racemization as depicted in Scheme 44. For the allylation, a chair-like transition state is proposed that can be rigidified by chelation of the oxygen atom of the sulfinyl group or the oxy group of the camphor derivative.



Scheme 44. Synthesis of enantiopure primary amines by addition to sufenyl-/sulfinylimines **137**, **140** according to Yang *et al.*[59]

The stereoselective addition of allyl Grignard reagents to enantiopure *N*-benzylidene-*p*-toluenesulfinamides **143** has also been examined by Hua *et al.*[60] The chiral sufinylimines **143** were prepared by the reaction of a generated lithio ketimine and (−)-*L*-menthyl (*S*)-*p*-tolylsulfinat **142**. Treatment of **143** with allylmagnesium bromide gave the adduct **144** in good (82% *de*) to complete stereoselectivity. **144** was converted easily into the homoallylamine **145** by treatment with TFA in methanol. Addition reactions with other nucleophiles failed (*n*-BuLi or vinylmagnesium bromide) because of deprotonation at the α-imino carbon. A transformation into α- and β-amino acids **146** bearing a quarternary stereogenic α-centre was described. For the addition reaction a six-membered-ring transition state was proposed (**147**, Scheme 45). The magnesium chelates with both N- and

O-atoms of sulfonylimine **143** and therefore the addition of the allyl Grignard reagent occurs from the *re*-face.



Scheme 45. Enantioselective synthesis of homoallylamines **145** according to Hua *et al.*[60]

An asymmetric synthesis of α-amino acids and *N*-protected α-amino aldehydes by addition of an auxiliary bearing vinylanion **148** to aryl and alkyl *N*-mesitylsulfonylimines **149** has been described by Braun and Opdenbusch.[61] The chiral vinyllithium **148** is elaborated from (*S*)-ethyllactate in four steps and can be regarded as chiral synthetic equivalent of a carboxyl group. Addition to the *N*-sufonylimines **149** at low temperatures afforded the adduct **150** in high diastereofacial selectivity (*de*=92–96%) but in low to moderate yields (20–63%). Ozonolysis of **150** (R=aryl) led directly to the *N*-sulfonyl amino acid ester **151**. After hydrolysis of the ester the nonhydrolyzed sulfonyl group can be removed by sodium–naphthalene to obtain enantiopure (*S*)-phenylglycine **152** in good yield. Also *N*-sulfonyl-α-amino aldehydes **153** can be prepared by Br/H exchange of **150** followed by ozonolysis in nearly quantitative yield. In this reaction the *O*-protected lactate aldehyde **154** is recycled (Scheme 46).

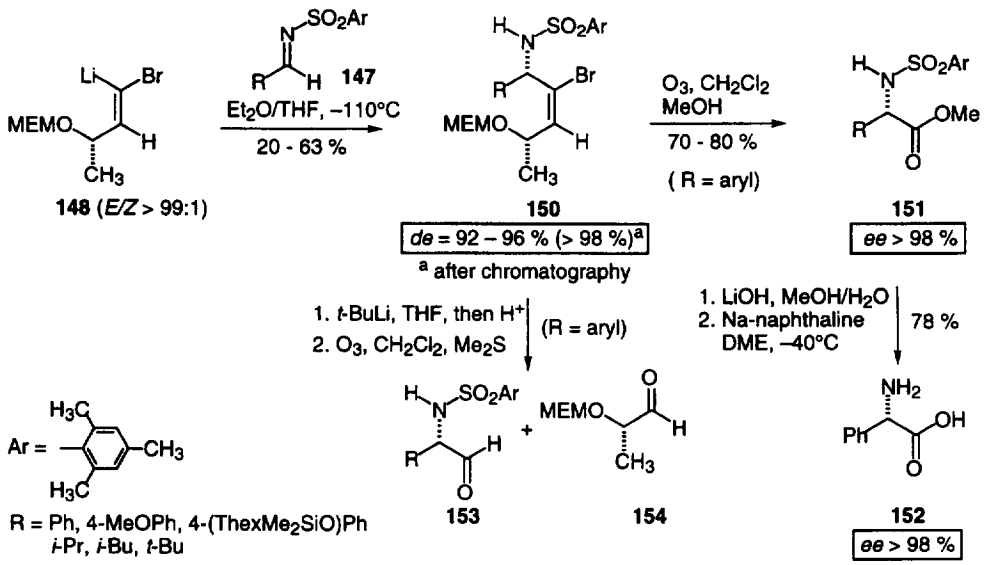
3. Addition to hydrazones

The addition of nucleophilic reagents to the CN-double bond of hydrazones leads to hydrazines. The N–N-bond can then be cleaved under reductive conditions to obtain the optically active amines. Some of the described procedures appear limited to aryl imines.

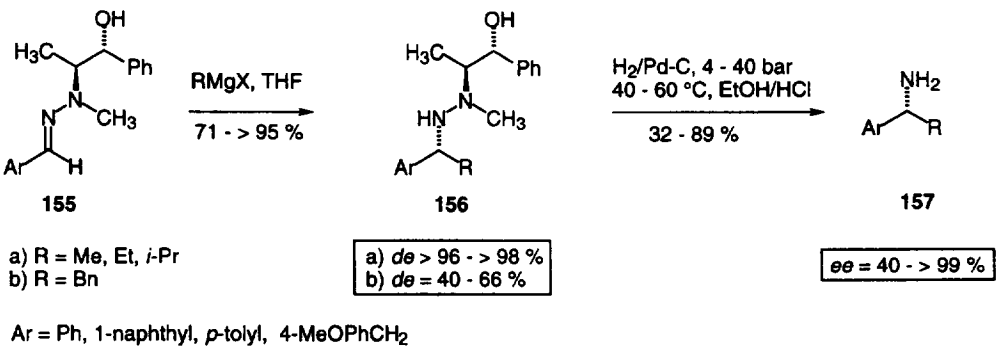
3.1 Auxiliary group in the hydrazine compound

Takahashi *et al.* have described methods for the asymmetric synthesis of primary amines by Grignard addition to chiral hydrazones employing *L*-ephedrine (Scheme 47)[62a–c] and *L*-valine derivatives[62d] as auxiliaries. The chiral *E*-configurated hydrazone **155**, obtained by condensation of (−)-*N*-aminoephedrine with aryl aldehydes, reacted with alkyl Grignard reagents to give the chiral hydrazines **156** as single diastereomers in good yields.[62a] The addition of benzylmagnesium chloride gave the hydrazine in significantly lower diastereoselectivity. Hydrogenolysis of the hydrazines **156** using a Pd/C catalyst in HCl–EtOH produced the α-arylalkylamine **157**. In one case (Ar=Ph, R=*i*-Pr) partial racemization was observed during the high pressure hydrogenolysis. The cleavage allows the recovery of the chiral auxiliary reagents without loss of enantiomeric excess.

Surprisingly, the nucleophilic addition of phenyllithium to phenylacetaldehyde and 4-methoxybenzaldehyde hydrazones led to a single diastereomer (*de*>98%) with the inverted configuration resulting through a complete change of the diastereofacial attack.[62c]



Scheme 46. Enantioselective synthesis of α-amino acids and amino aldehydes according to Braun *et al.*[61]

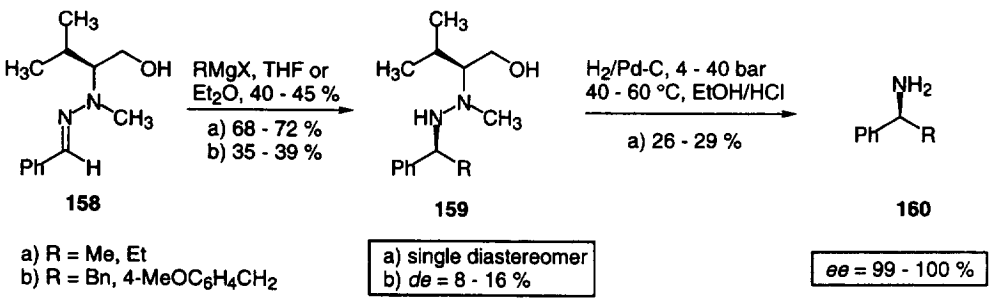


Scheme 47. Enantioselective synthesis of primary amines **157** according to Takahashi *et al.*[62a–c]

A similar route to enantiomerically pure α-phenylalkyl amines **160** starting from (*S*)-valinol was elaborated (Scheme 48).[62d] The chiral hydrazone **158** was prepared in a five step reaction sequence (overall 40%). The obtained diastereoselectivity for the hydrazine **159** is excellent after 1,2-addition of aliphatic Grignard reagents (R=Me, Et) to **158** whereas benzyl reagents reacted with low selectivity. The N–N-bond cleavage by hydrogenation proceeded without racemization but in low yields.

The stereochemical course of the Grignard addition can be rationalized by the magnesium chelated intermediates **161** and **162**, involving the hydroxyl group and nitrogen atom of the hydrazones.[62] These chelate intermediates are six-membered rings where the isopropyl group and the phenyl group are oriented equatorially. It is possible that a second Grignard reagent approaches the lone pair of the oxygen atom, and the alkyl nucleophile attacks from the bottom face of the C=N bond controlled by the conformation of the chelated intermediates **161** and **162** as shown in Figure 3.

The described procedures appear limited mainly to aryl imines. The SAMP/RAMP hydrazone method[63] provides a more general route to enantiomerically pure amines. A wide range of enantiomerically pure hydrazones, obtained from condensation of aldehydes and (*S*)-1-amino-2-(methoxymethyl)pyrrolidine **163** (SAMP) or (*R*)-1-amino-2-(methoxymethyl)pyrrolidine (RAMP)



Scheme 48. Enantioselective synthesis of primary amines **160** according to Takahashi *et al.*[62d]

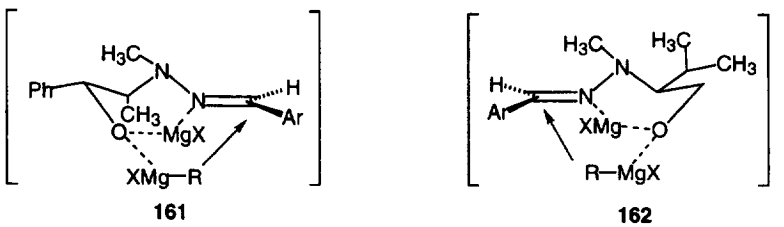


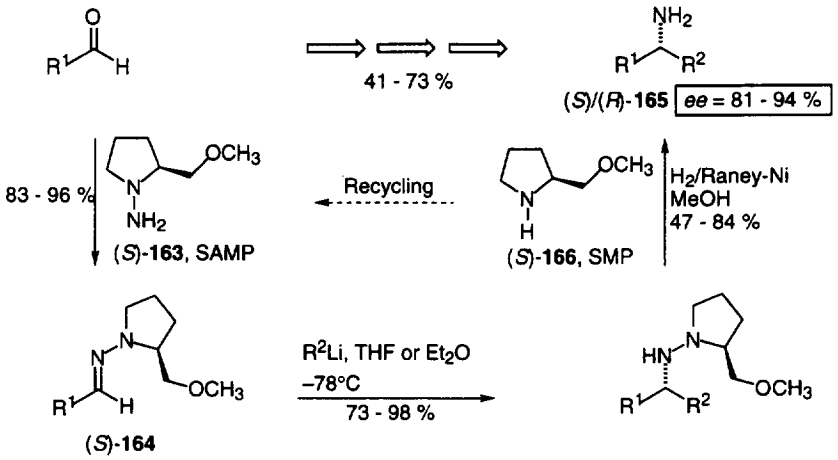
Figure 3. Transition states for the diastereoselective Grignard addition to hydrazones **155** and **158**.[62]

react with non-functionalized and functionalized organometallic reagents in a highly stereoselective manner. Reductive N–N-bond cleavage of the resulting hydrazines afford the primary amines or their derivatives in good overall yield and in high diastereo- and enantioselectivities

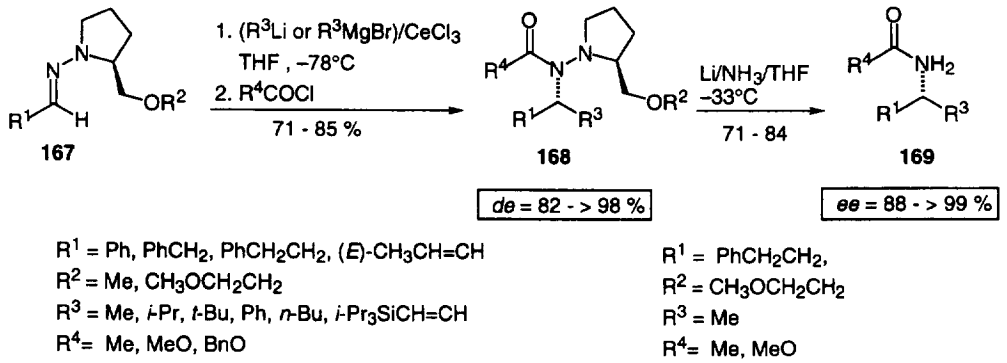
Firstly, Enders *et al.* (Scheme 49)[64] have described the addition of organolithium compounds to the aldehyde hydrazones **164** leading to the hydrazine. The N–N-bond cleavage was performed with H_2/Raney nickel in methanol to afford the enantiomerically enriched primary amines **165** in good enantioselectivities (*ee*=81–94%) and an overall yield of 40–73%. The enantiopure auxiliary (*S*)-2-(methoxymethyl)pyrrolidine (SMP) **166** can be recovered. Both enantiomers of **165** are separately accessible either by change of the auxiliary (SAMP *vs* RAMP) or by appropriate change of the introduced substituents.

Denmark *et al.* (Scheme 50)[65a] and Nübling[66a] have described the addition of in situ prepared organocerium reagents (RLi/$CeCl_3$ or RMgX/$CeCl_3$) to SAMP-aldehyde hydrazones. The initial adducts were trapped with either methyl or benzylchloroformate to afford the stable *N*-aminocarbamates, which were obtained in 67–83% yield and with diastereoselectivities ranging from 82% to 98% *de*.[65a] In two cases free amines were prepared by hydrogenolysis of the N–N-bond of the unprotected hydrazine similar to the method described above. It was shown that slightly increased diastereoselection can be achieved with a modified proline auxiliary (*S*)-1-amino-2-(methoxyethoxymethyl)pyrrolidine (SAMEMP)[63a] in certain additions of organocerium reagents to hydrazones.[65b] The influence of the reagent stoichiometry on efficiency and selectivity of organocerium addition to chiral and achiral hydrazones was reported in detail for the organocerium reagents MeLi/$CeCl_3$.[65c] For the chiral SAMEMP hydrazone at least two equivalents of methyl nucleophile are required to obtain an acceptable yield. It was suggested that the reactivity of the first equivalent is inhibited by chelation with the auxiliary side chain and that binding of the reagent to one of the hydrazone nitrogen atoms facilitates addition.

The auxiliaries of the acylated (Ac or Moc) SAMP[66a] and SAMEMP[66b] hydrazines can be removed by treatment with an excess of lithium in refluxing ammonia. The acyl group of the hydrazide **168** is necessary as an activating group for the N–N-bond cleavage. Thus acylated amines **169** were obtained in good yields and with complete preservation of configuration on both sides of the hydrazines.



Scheme 49. Enantioselective synthesis of α-substituted primary amines by Enders *et al.*[64]

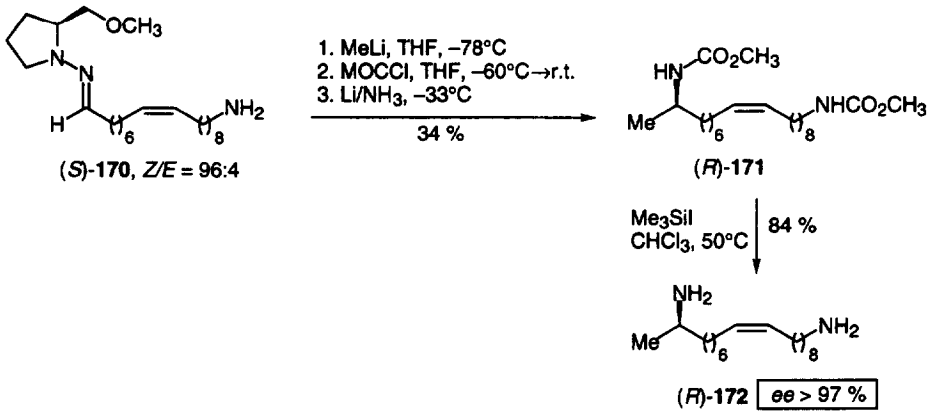


Scheme 50. Diastereoselective addition of organocerium reagents to hydrazone **167** according to Denmark *et al.*[65,66b]

This cleaving method seems to be applicable even to hydrazines where a hydrogenation cleavage is not possible. Although aromatic rings are not reduced, benzylic or allylic hydrazines suffer from hydrogenolysis of the C–N-bond.

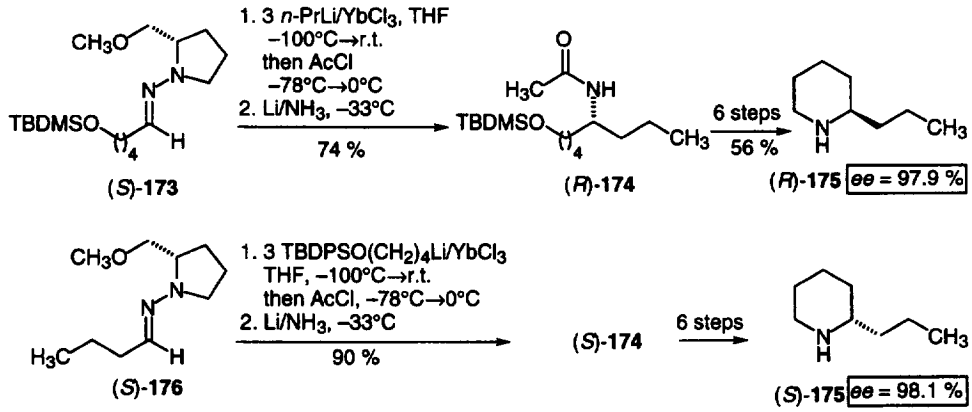
An efficient and highly enantioselective (*ee* >97%) total synthesis of the harmonine **172**, a defence alkaloide of ladyugs, in good overall yield has been described.[67] As a key step for the generation of the stereogenic centre, an asymmetric C–C-bond formation by nucleophilic addition of three equivalents of methyllithium to the unsaturated SAMP hydrazone **170** was used. After quenching with methyl chloroformate (MOCCl), the protected hydrazine amine was obtained. Cleavage of the MOC-protected hydrazine with Li/NH_3 gave the biscarbamate **171** which was finally transferred to the diamine **172** as shown in Scheme 51.

As another application of the method in natural product synthesis both enantiomers of the hemlock alkaloid coniine have been prepared using SAMP.[68] Hydrazone **173** was converted into the acetyl hydrazide in 83% yield by treatment with three equivalents of a propylytterbium reagent ($RLi:YbCl_3$=3:1) in THF and subsequent quenching of the reaction with acetyl chloride. The reaction proceeded with very high diastereoselectivity (*de* ≥98%). The N–N-bond cleavage was carried out with an excess of lithium in refluxing ammonia, furnishing the acetamide **174** in 89% yield. The acetamide **174** was transferred to (*R*)-coniine **175** (*ee*=98%) in six steps (56% yield). The opposite (*S*)



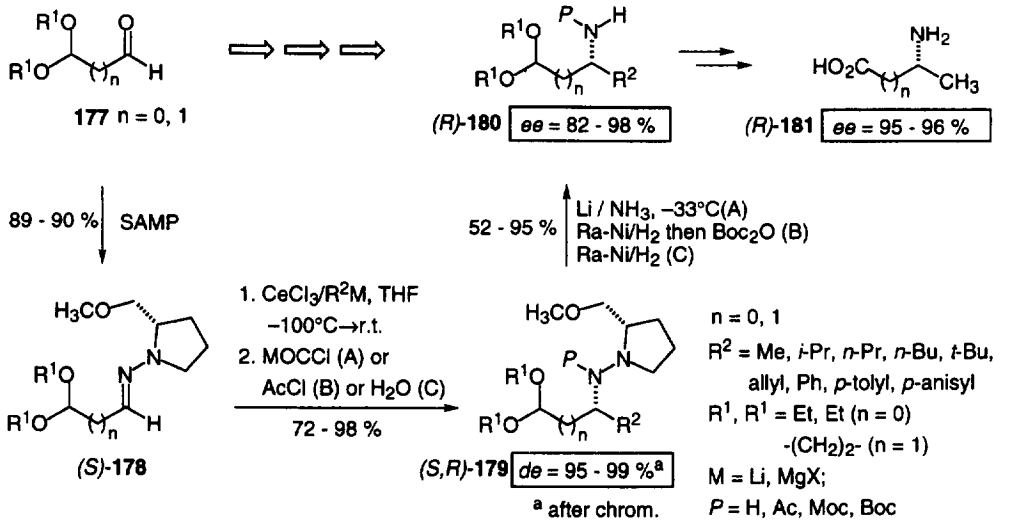
Scheme 51. Enantioselective total synthesis of harmonine by Enders and Bartzen.[67]

enantiomer **175** can be obtained with the same enantiomerically purity by synthon control starting from propanal SAMP hydrazone **176** as illustrated in Scheme 52. Interestingly, organoytterbium reagents seem to be more selective but less reactive than the corresponding cerium reagents. Species of the type 'RYbCl$_2$' do not appear to add to the hydrazone C–N-double bond.



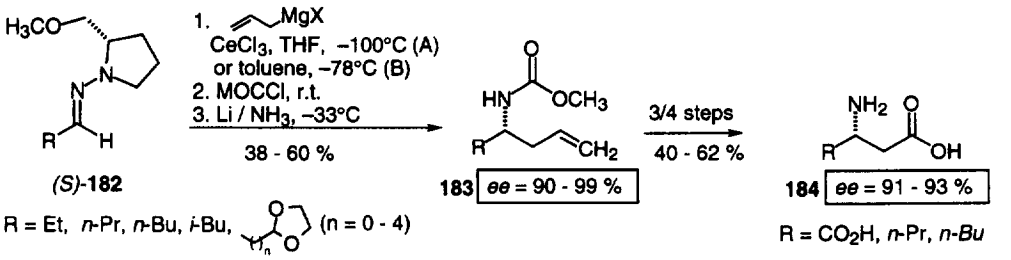
Scheme 52. Enantioselective synthesis of both enantiomers of coniine **175** by Enders and Tiebes.[68]

The hydrazone method has also been successfully applied to the enantioselective synthesis of α-amino acetals and α-amino acids[69a] as well as to β-amino acetals and β-amino acids[69b] as shown in Scheme 53. The key step is the diastereoselective nucleophilic 1,2-addition of organocerium reagents to the CN-double bond of α- and β-hydrazono acetals **178** which were prepared by condensation of bifunctional α,α- or β,β-dialkoxy aldehydes **177** with the enantiopure hydrazine SAMP. After trapping with acylchlorides (AcCl or MocCl) or aqueous work up and chromatography, the hydrazines **179** were obtained in good to excellent yield (72–98%) and high diastereomeric excesses (95–99% *de*). Reductive removal of the auxiliary SMP gave enantiomerically enriched α- and β-amino acetals **180**. Oxidative transformation of the acetal functionality into the acid group by ozonolysis opens up a novel highly enantioselective entry to both α-amino acids and β-amino acids **181** (Scheme 53). A similar strategy for the synthesis of *N*-protected α-amino acetals and α-amino aldehydes was later described by Denmark *et al.*[70]



Scheme 53. Enantioselective synthesis of α- and β-amino acetals and α- and β-amino acids according to Enders *et al.*[69]

An alternative access to enantiomerically enriched β-amino acids has been developed.[71] Nucleophilic 1,2-addition of allyl cerium reagents in THF or allyl Grignard reagents in toluene to SAMP/RAMP hydrazones **182**, partly bearing an 1,3-dioxolane moiety, led to methoxycarbonyl protected homoallylamins and homoallylamino acetals **183** in high enantiomeric excesses (*ee*=90–98%). Subsequent ozonolysis of the double bond and the acetal group afforded β-amino acids and diacids **184** of high enantiomeric purity as depicted in Scheme 54 (*ee*=91–93%).

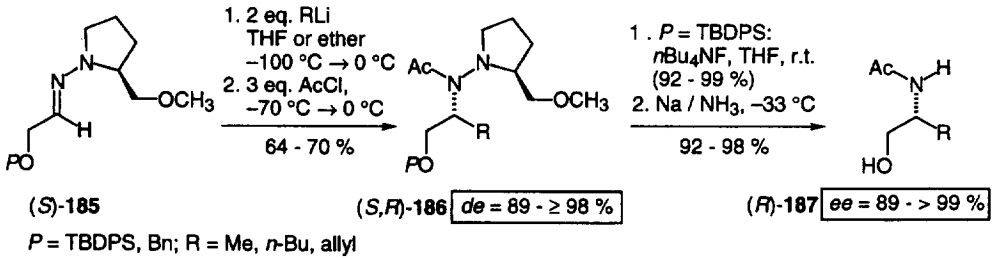


Scheme 54. Enantioselective synthesis of β-amino acids according to Enders *et al.*[71]

Yamamoto *et al.* has reported on the regioselective allylation of imines and hydrazones with allylic barium reagents.[72] Treatment of the benzaldehyde SAMP hydrazone with the prenylbarium chloride reagent in THF at 0°C almost exclusively afforded the α-allylated hydrazine with 60% *de*. When the reaction was carried out at −78°C, the γ-adduct was obtained as the major product in 98% diastereomeric excess and 51% yield.

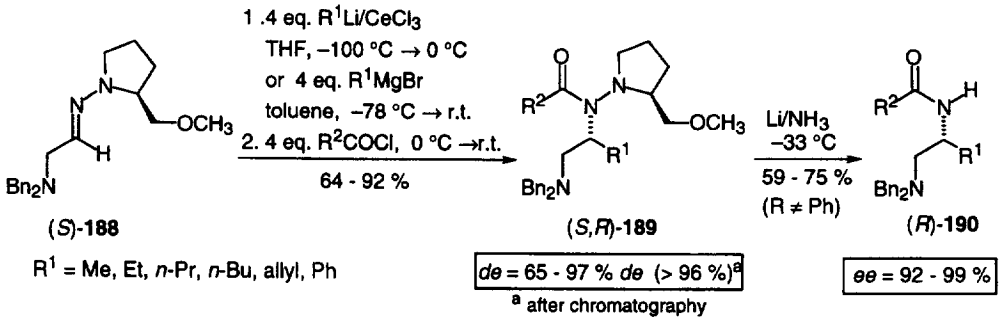
An efficient enantioselective synthesis of *N*-acetyl protected 1,2-amino alcohols **187** has been described starting from the readily available benzyl or TBDPS protected glycol aldehyde SAMP hydrazones **185**.[73] These were treated with two equivalents of alkyl- and allyllithium reagents at low temperatures, and the lithium hydrazide formed was trapped with acetyl chloride. The *N*-acetyl protected hydrazines **186** were obtained with high to very high diastereomeric excesses (89–≥98% *de*). The silyl-protected acetyl hydrazides **186** (*P*=TBDPS) were desilylated prior to cleavage of the N–N-bond. Reductive N–N-bond cleavage with concomitant removal of the benzyl protecting group

was carried out with sodium in ammonia without racemization, giving excellent yield of the amino alcohol **187** (Scheme 55).



Scheme 55. Enantioselective synthesis of β-amino alcohols according to Enders and Reinhold.[73]

Also 1,2-diamines bearing one stereogenic centre were obtained *via* nucleophilic 1,2-addition of organoceriums in THF or allyl Grignard reagents in toluene to dibenzylamino-acetaldehyde SAMP hydrazones **188** (Scheme 56).[74] Separation of the minor diastereomer of the acyl protected hydrazine **189** (*de*=65–97%) by chromatography and reductive N–N-bond cleavage led to differently protected 1,2-diamines **190** in good yields and of high enantiomeric purity (*ee*=92–99%).

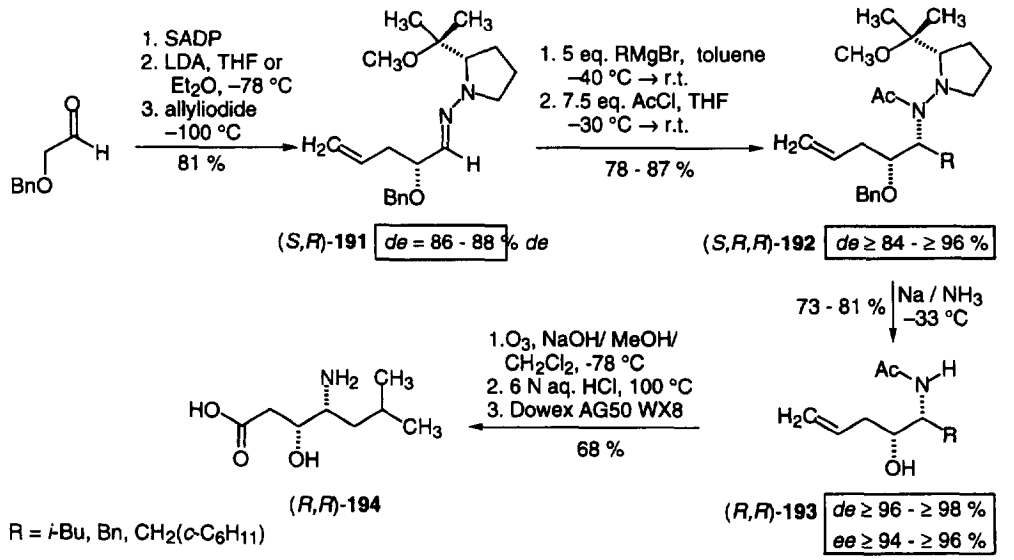


Scheme 56. Enantioselective synthesis of vicinal diamines by Enders and Chelain.[74]

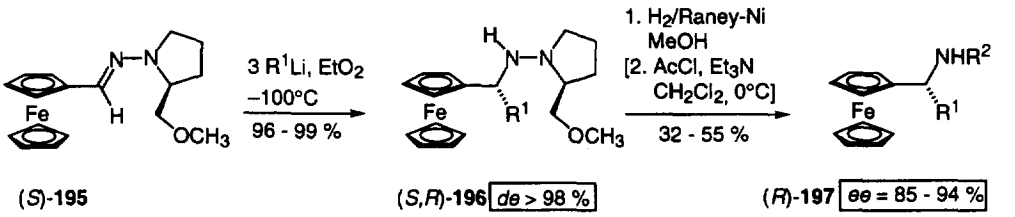
A C–C bond forming, flexible, *syn*-diastereo- and enantioselective synthetic strategy of *N*-acetyl protected functionalized 1,2-amino alcohols **193**, which are direct precursors of γ-amino-β-hydroxy amino acids, e.g. statin, has been reported starting from benzyloxyacetaldehyde.[73] Key steps are the successive electrophilic α-allylation of the corresponding (*S*)-1-amino-2-(1-methyl-1-methoxyethyl)pyrrolidine (SADP) hydrazone[73b,c] and the nucleophilic 1,2-addition of Grignard reagents in toluene to the allylated hydrazone **191** with high to complete diastereoselectivity. After cleavage of the N–N-bond (Na/NH_3) of **192**, the total synthesis of (*R,R*)-statin **194** was performed by oxidative transformation of the C–C-double bond into the corresponding methyl ester as shown in Scheme 57.

Based on the SAMP/RAMP-hydrazone method, an enantioselective synthesis of 1-ferrocenylalkylamines **197** has been reported.[75] Nucleophilic 1,2-addition of organolithium compounds (R=Me, Et, *n*-Bu, *t*-Bu, *n*-Hex) to ferrocenecarboxaldehyde–SAMP–hydrazone **195** led to hydrazine **196** in almost quantitative yield and with complete asymmetric induction (*de* ≥98%). Subsequent N–N-bond cleavage with Raney-nickel promoted hydrogenolysis gave 1-ferrocenylalkylamines **197** in acceptable to good overall yield (30–54%, 4 steps) and with high enantiomeric excess (85–94%) as shown in Scheme 58.

As an extension of the described sequence the diastereo- and enantioselective synthesis of protected 1,1′-bis(1-aminoalkyl)ferrocenes **199** has been developed starting from the bis-SAMP–hydrazone **198** (Scheme 59).[75b] After addition of organolithium reagents, the N–N-cleavage was performed with an

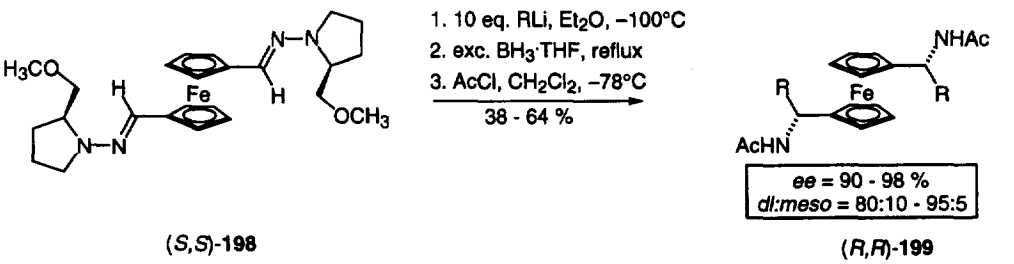


Scheme 57. Diastereo- and enantioselective synthesis of γ-amino-β-hydroxy amino acids, e.g. statin **190**.[73]



Scheme 58. Enantioselective synthesis of 1-ferrocenylalkylamines **197** by Enders and Lochtman.[75a]

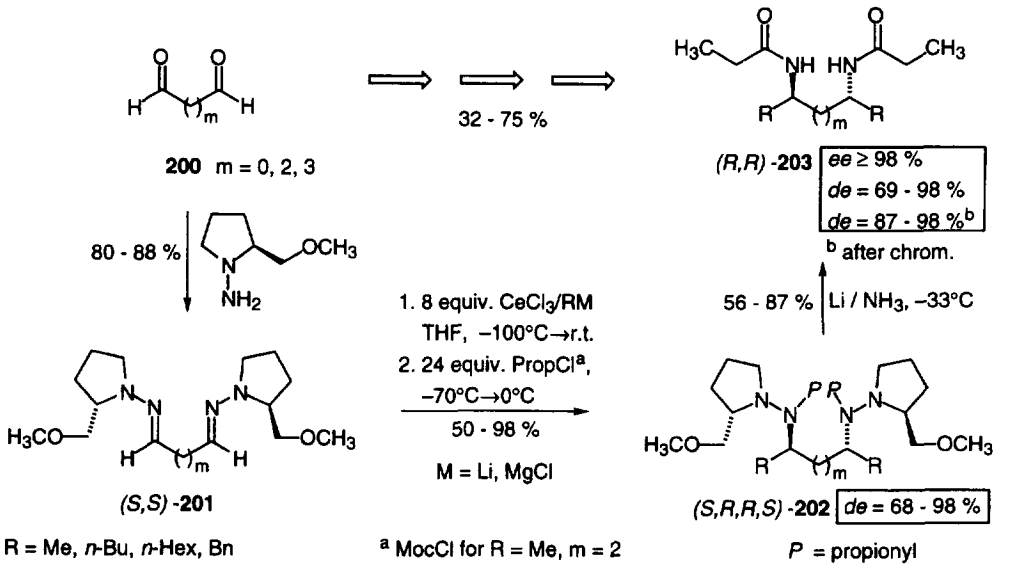
improved reductive procedure (exc. BH_3·THF). The acetyl protected organometallic diamines **199** were obtained in good overall yields (38–64%), with high enantiomeric excesses (*ee*=90–98) and *dl:meso* ratios (up to 95:5).



Scheme 59. Enantioselective synthesis of *N*-protected 1,1′-bis(1-aminoalkyl)ferrocene **199**.[75b]

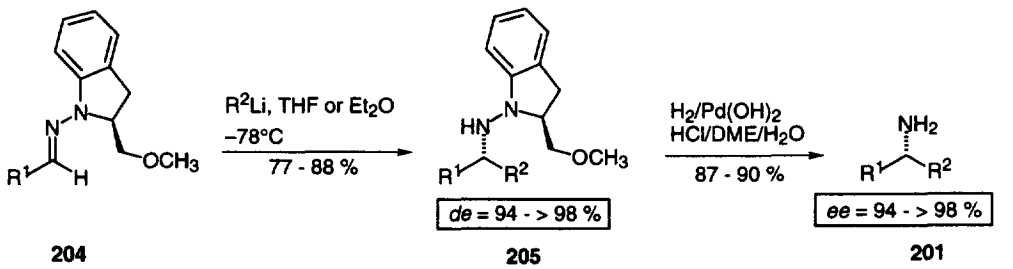
Another important application is the flexible diastereo- and enantioselective synthesis of C_2-symmetric, protected 1,*n*-diamines **203** (n=2,4,5) from dialdehydes **200**.[76] The bis-SAMP–hydrazones **201** were treated with organocerium compounds formed *in situ* at low temperatures followed by

trapping of the resulting lithiumhydrazides with propionyl chloride (PropCl) or methyl chloroformate (MocCl) to give the *N*-protected hydrazines **202** with good to excellent diastereoselectivities (*de*=68–98%). After treating with Li/NH_3 the *meso* compound can be separated by chromatography in order to obtain the C_2-symmetric diamines **203** with high diastereomeric excesses (*de*=87–98%) and very high enantiomeric excesses (*ee* ≥98%) as shown in Scheme 60. The overall yield over three steps is 32–75%.



Scheme 60. Diastereo- and enantioselective synthesis of protected C_2-symmetric 1,*n*-diamines **203**.[76]

Recently, the highly diastereoselective addition of organolithium reagents to (*S*)-1-amino-2-methoxymethylindoline (SAMI) hydrazones **204** derived from (*S*)-indoline-2-carboxylic acid has been examined.[77] Hydrogenation of the formed hydrazines **205** (*de*=94–>98%) was carried out at room temperature under atmospheric pressure using a $Pd(OH)_2$/C catalyst in dimethylether–water containing hydrochloric acid. The amines **206** as well as the auxiliary precurser (*S*)-2-methoxymethylindoline were obtained without loss of enantiomeric excess in high yields (Scheme 61). The method was applied to the synthesis of the alkaloid (−)-coniine.

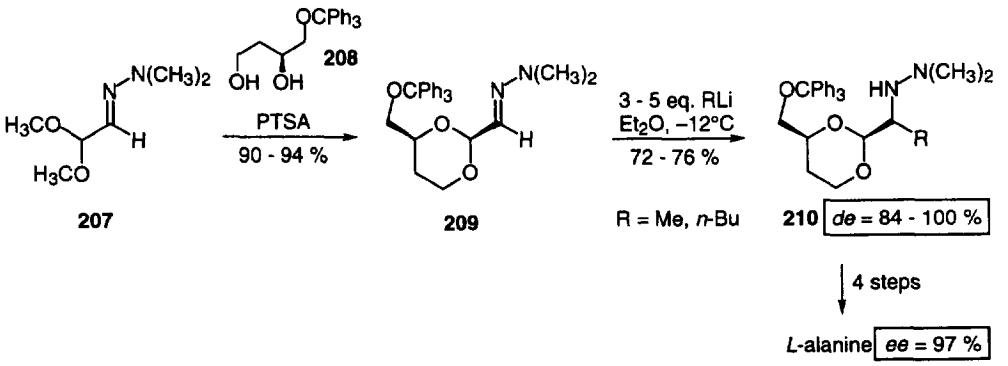


Scheme 61. Enantioselective synthesis of amines **206** *via* organolithium addition to hydazones **204** according to Kim and Choi.[77]

3.2 Auxiliary group in the carbonyl compound

Several investigations dealing with the incorporation of the auxiliary in the carbonyl part of the hydrazones have been reported. In addition, the covalently connected auxiliary can be used as protecting group for functional groups.

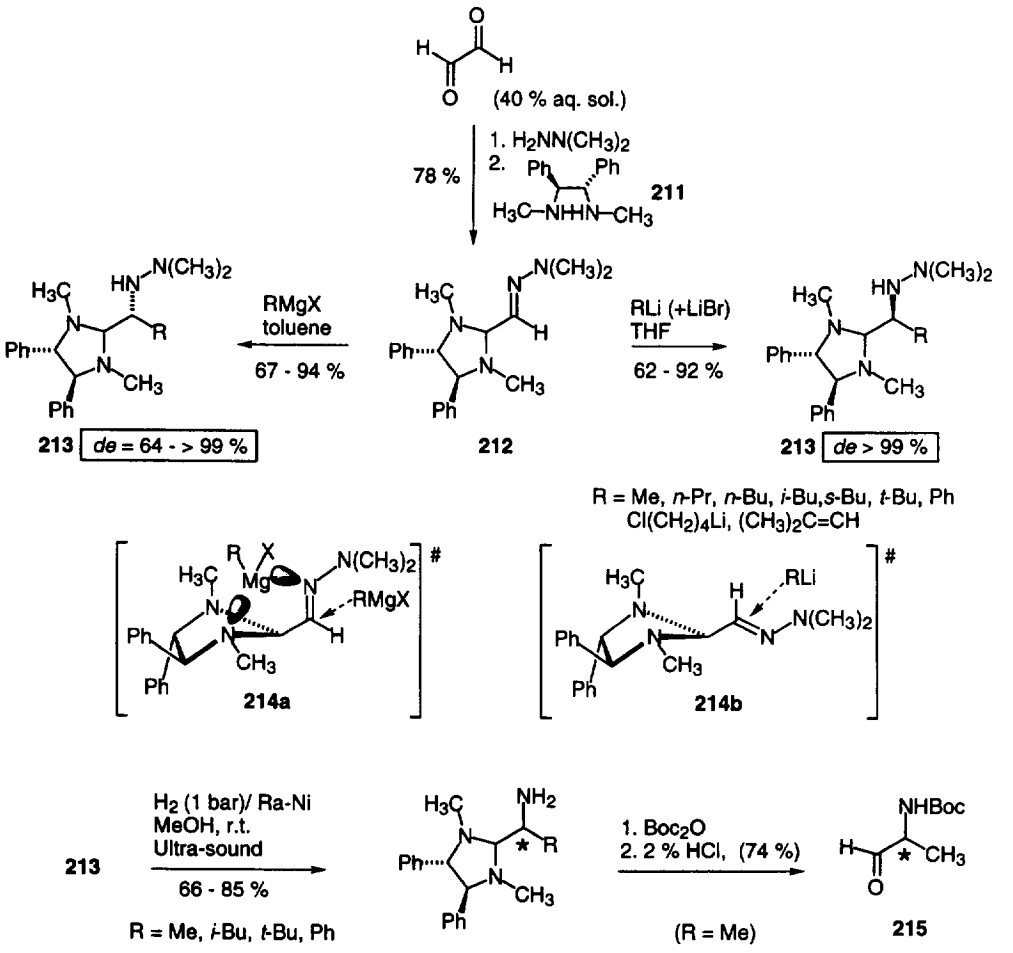
A predestined substrate is the bifunctional glyoxal. Thiam and Chastrette (Scheme 62)[78] have described the synthesis of enantiopure dimethylhydrazones **209**, prepared by transacetalization of the desymmetrized glyoxal derivative **207** with the 1,3-diol **208**[78b] derived from (*S*)-malic acid. Diastereoselective addition of organolithium reagents provided the hydrazinoacetals **210** with high diastereoselectivities (84–100%). The sterically demanding triphenylmethyl group is crucial for the high level of diastereofacial discrimination. Similar selectivities were obtained employing methyl-α-2,3-dimethylglucoside as diol whereas the transesterfication proceeded in low yield. Reductive cleavage of the hydrazine **210** (H_2, Ra-Ni, EtOH) followed by oxidation of the phthalimido derivative was mentioned providing *L*-alanine in 97% enantiomeric excess.



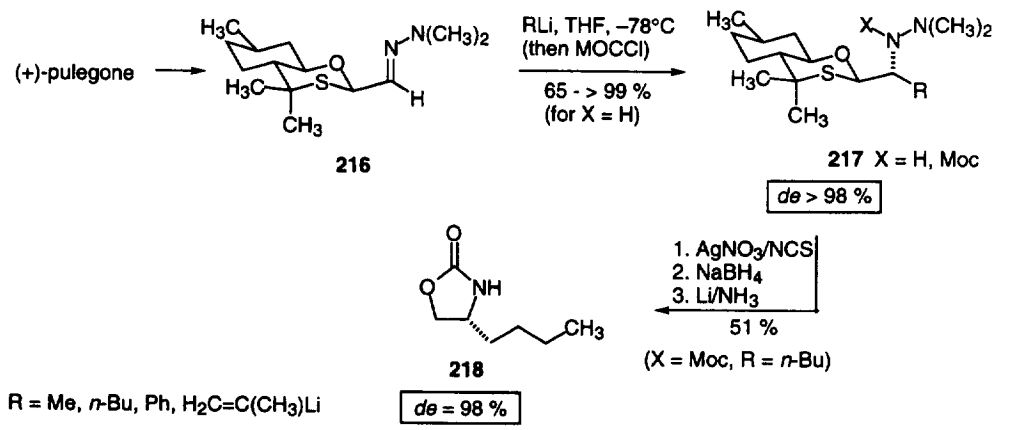
Scheme 62. Diastereoselective synthesis of hydrazinoacetals **210** according to Thiam and Chastrette.[78]

Alexakis *et al.* have elaborated on a general asymmetric entry to α-amino aldehydes by employing chiral aminals.[40,79] The desymmetrization of glyoxal by formation of the monodimethylhydrazone followed by aminalization of the remaining aldehyde group with the enantiopure C_2-symmetric diamine **211** was smoothly done. The resulting crystalline aminal **212** gave the single diastereomer (*S,S,S*)-**213** upon reaction with a wide range of organolithium reagents in THF. A sterically controlled transition state **214b** is assumed, therefore rationalizing the observed stereochemistry.[79a] By contrast, with Grignard reagents, in toluene as solvent, **212** gave the epimeric adduct (*S,S,R*)-**213** with opposite stereochemistry in moderate to complete stereoselectivity (64–>99% *de*).[40] Allyl Grignard reagents gave lower diastereoselectivities (64–85% *de*) in contrast to the otherwise generally high to complete diastereofacial selectivity. The formation of the opposite diastereomer can be ascribed to a chelate control by the lone pair of one of the two nitrogens of the imidazolidine ring and the hydrazone nitrogen (**214a**). In such a rigid conformation, the pseudoequatorial *N*-methyl group masks the *si*-face of the hydrazone functionality. The hydrazines **213** are direct precursors of *N*-Boc-protected α-amino aldehydes **215** as shown in Scheme 63. The cleavage of the N–N-bond of **213** was best achieved with Raney nickel under ultrasonic conditions.[79b] Sterically hindered hydrazines were also cleaved and no racemization or debenzylation was observed.

Matsubara *et al.* have reported a highly diastereoselective 1,2-addition to hydrazones and imines (Scheme 28) containing 1,3-oxathiane as a chiral group.[41] Reaction of organolithium reagents and the hydrazone **216** derived from (+)-pulegone afforded exclusively the hydrazine **217**. Reversal of the diastereoselectivity was observed by use of organolithium (R=Me, *n*-Bu, Ph)-lanthanoid salt [$CeCl_3$, $Yb(OTf_3)$] complexes (*de*=32–72%). Interestingly, the alkylation of the corresponding *N*-benzylimine with organolithium reagents as well as organocerium reagents was performed with complete diastereoselectivity under generation of the same configuration. In one case the methoxycarbonyl (MOC) protected hydrazine **217** was transferred into the β-amino alcohol derivative **218** without any significant racemization in moderate yield (51%) as illustrated in Scheme 64.



Scheme 63. Asymmetric synthesis of α-amino aldehydes according to Alexakis *et al.*[40,79]



Scheme 64. Enantioselective synthesis of 1,2-amino alcohol derivatives according to Matsubara *et al.*[41]

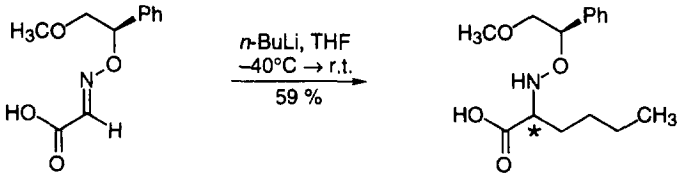
4. Addition to oxime ethers

In general, oxime ethers are often less electrophilic and less easily activated than the corresponding imines. Nucleophilic addition to oxime ethers leads to hydroxylamines and, after reductive clevage

of the N–O bond, to amines. General problems are, besides proton abtraction in the α-position, the existence of mixtures of *E/Z*-isomers, poor electrophilic reactivity of the oxime and the lability of the N–O bond.

4.1 Auxiliary group in the alkoxyamine

Reaction of organolithium reagents with glyoxylate derived oximes provides a direct route to α-*N*-hydroxyamino acids. First investigations of an asymmetric sequence have been described by Kolasa, Miller *et al.* (Scheme 65).[80] A chiral alkoxy amine as auxiliary and glyoxylic acid were condensed in high yield to afford the oxime ether (e.g. **219**). Addition of butyllithium gave the hydroxylamine **220** in modest diastereoselectivity. The attack of the carbonyl substituent by the strongly nucleophilic reagents was avoides by selection of the free acid function. Neither the determination of the absolute configuration nor the removal of the auxiliary has been described. An alternative mode by the same group employing chiral glyoxylamides is mentioned in section 4.2.



219 **220** *de* = 33 %

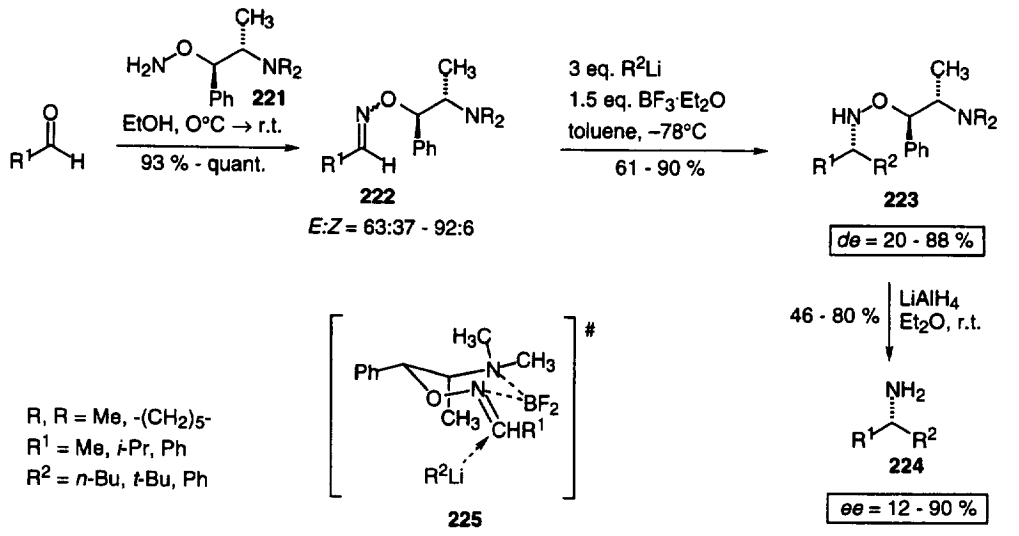
Scheme 65. Diastereoselective addition to chiral oxime ether **219** according to Kolasa, Miller *et al.*[80]

The enantiomerically pure alkoxyamines **221** prepared from *L*-ephedrine or norephedrine were used as chiral auxiliary by Dieter and Datar (Scheme 66).[81] Reaction of **221** with aliphatic aldehydes or benzaldehyde using ethanol as solvent afforded the corresponding oxime ethers **222** as mixtures of *E/Z*-isomers. Several types of nucleophilic reagents were investigated in the addition reaction. Organolithium and Grignard reagents as Grignard–zinc bromide complex ($PhMgBr/ZnBr_2$), cerium reagent ($BuLi/CeCl_3$), cuprate (Bu_2CuLi) or lithium perchlorate adduct ($PhMgBr/LiClO_4$) failed to react in the desired way. Activation of the oxime ether **222** by addition of the Lewis acid boron trifluoride–diethylether complex and reaction with organolithium reagents in toluene at −78°C led to the desired alkoxyamines **223** in good yields (61–90%). The diastereomeric excess mirrors the initial *E/Z*-ratio of the starting oxime **222**. Interestingly three equivalents were nessecary to obtain complete conversion, presumably due to competing destruction of the alkyllithium reagents affording alkylfluoroboranes. The use of less organolithium reagents led to a preferred addition to the more reactive *Z*-isomer. The method seems to be sensitive to the nucleophilic character. The reaction of methyl- and 2-thienyl lithium failed under the optimized conditions, whereas the addition of the less nucleophilic 1-hexenyllithium gave partial conversion (37% yield). Reduction of the alkoxyamine **223** by lithium aluminium hydride afforded the corresponding amine **224**, obviously, under partial racemization for the benzylic alkoxyamine (R^2=Ph).

The stereochemical outcome of the reaction can be rationalized by a chair-like conformation of the six-membered chelate **225**. It was assumed that the nucleophile preferentially attacks from the bottom face of the complex because of the steric demand of the axial *N*-methyl group.

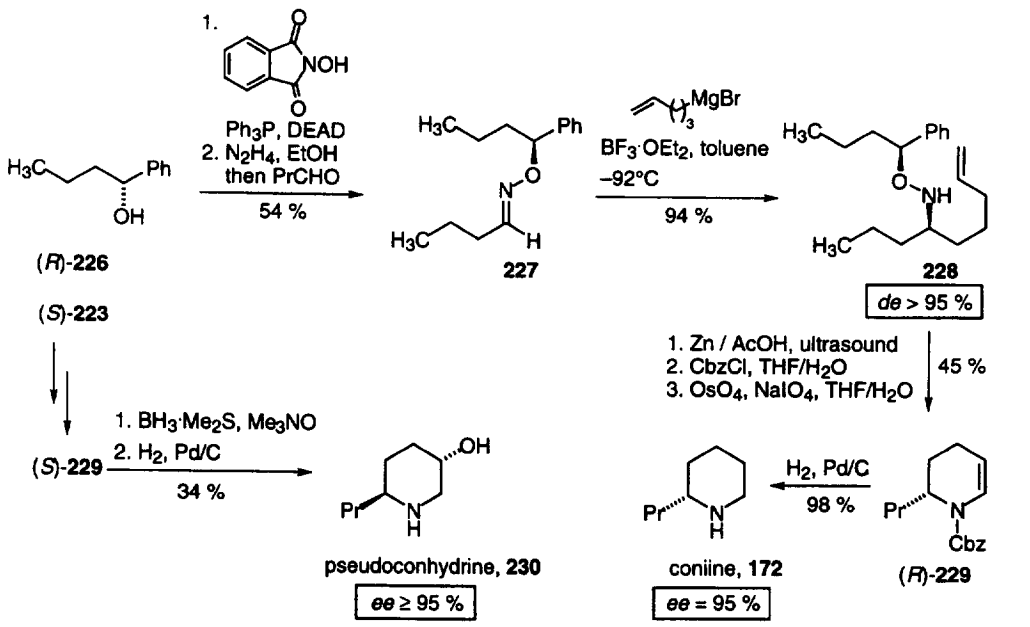
Moody *et al.*[82a,b] have described the addition of Grignard and organolithium reagents to racemic *E*-configurated *O*-phenylethyl aldoximes under the same BF_3-condition. The secondary hydroxylamines were obtained in 21–84% yield and 38–95% diastereomeric excess. In one case the addition of *n*-butyl lithium to enantiopure (*R*)-1-phenylethyl benzaldoxime was described.

Recently, the asymmetric synthesis of the alkaloids (−)-coniine and (+)-pseudoconhydrine has been reported.[82c] A key step is the addition of pent-4-enylmagnesium bromide to the chiral oxime ether **227**. The enantiopure hydroxylamines (*R*)- and (*S*)-*O*-(1-phenylbutyl)hydroxylamines (ROPHy and



Scheme 66. Asymmetric synthesis of amines *via* oxime ether according to Dieter and Datar.[81]

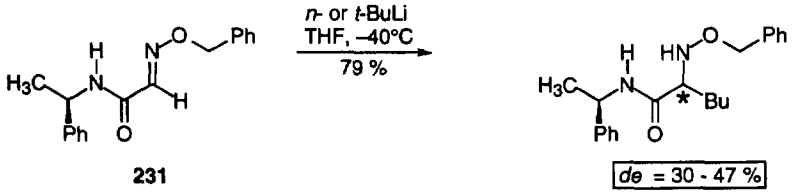
SOPHy) were prepared from the commercial 1-phenylbutanols **226** by Mitsonobu reaction with *N*-hydroxyphthalimide followed by hydrazinolysis and condensation with butyraldehyde. The pure *E*-oxime ether **227** was obtained after chromatographic separation from the *Z*-isomer. Addition of the pentenyl Grignard reagent (3 eq.) to a solution of oxime ether **227** and borone trifluoride etherate (3 eq.) gave the hydroxylamine **228** in excellent yield and diastereoselectivity. After N–O-bond cleavage using a zinc/acetic acid/ultrasound method the compound was transferred to (*R*)-(−)coniine **172** in three steps. Pseudoconhydrine **230** can be elaborated starting from the (*S*) configured alcohol **226** as shown in Scheme 67.



Scheme 67. Asymmetric synthesis of 2-substituted piperidines according to Moody *et al.*[82c]

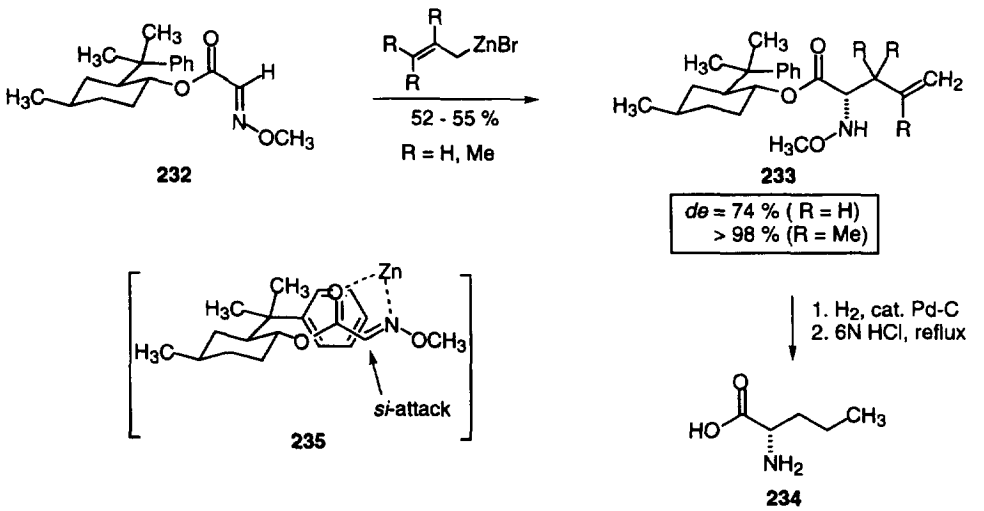
4.2 Auxiliary group in the carbonyl compound

Reaction of alkyllithium reagents with chiral amide derivatives of the *O*-benzyl oxime of glyoxylic acid **231** proceeded in low diastereoselectivity.[80] Beside α-phenylethylamine, as depicted in Scheme 68, the bidentate auxiliaries derived from norephedrine, prolinol derivatives and *L*-valine were tested as chiral substitutents in the glyoxalate framework.



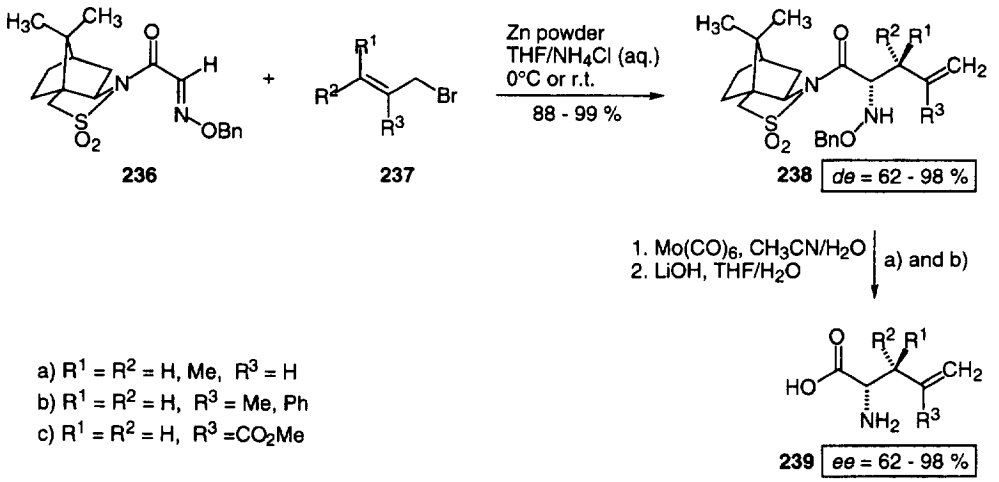
Scheme 68. Diastereoselective addition to chiral oxime ethers according to Kolasa, Miller *et al.*[80]

(−)-8-Phenylmenthol was used as auxiliary to reach high stereocontrol in the addition of allyl and 2,3-dimethyl-2-butenyl zinc reagents to the *N*-methoxyiminoester **232**.[83] The predominant formation of the (*S*)-configurated hydroxylamine **233** was rationalized by a chelation controlled allylation to the less hindered *si*-face of **235**. The methoxyamine **233** was transferred into norvaline **234** by hydrogenation (H_2, $Pd(OH)_2$–C) followed by hydrolysis of the resulting saturated ester (6N HCl, reflux). The auxiliary 8-phenylmenthol was recovered (Scheme 69).



Scheme 69. Diastereoselective allylation of *N*-methoxyiminoacetate **232** according to Yamamoto and Ito.[83]

With the same intention to build up allylglycine and its chain-substituted analogues Hanessian and Yang have investigated a zinc-mediated *C*-allylation of *O*-benzyl oximes **236** in aqueous media (Scheme 70).[84] Reaction of Oppolzer's (1*S*)-(−)-2,10-camphorsultam analogue **236** with the organometallic reagents, prepared *in situ* from powdered zinc and allyl bromides **237** in the biphasic system THF–water gave exclusively the γ-adduct **238** with high diastereoselectivity (up to 98% *de*) and excellent yields. The degree of diastereoselectivity seems to depend of the substitution in the allylic moiety. Allylation with γ-substituents led to nearly complete diastereoselectivities. After cleavage of the N–O-bond in the presence of $Mo(CO)_6$ the sultam auxiliary was removed by basic hydrolysis with LiOH to afford the free allylglycine derivatives **239** without loss of enantiomeric excess.



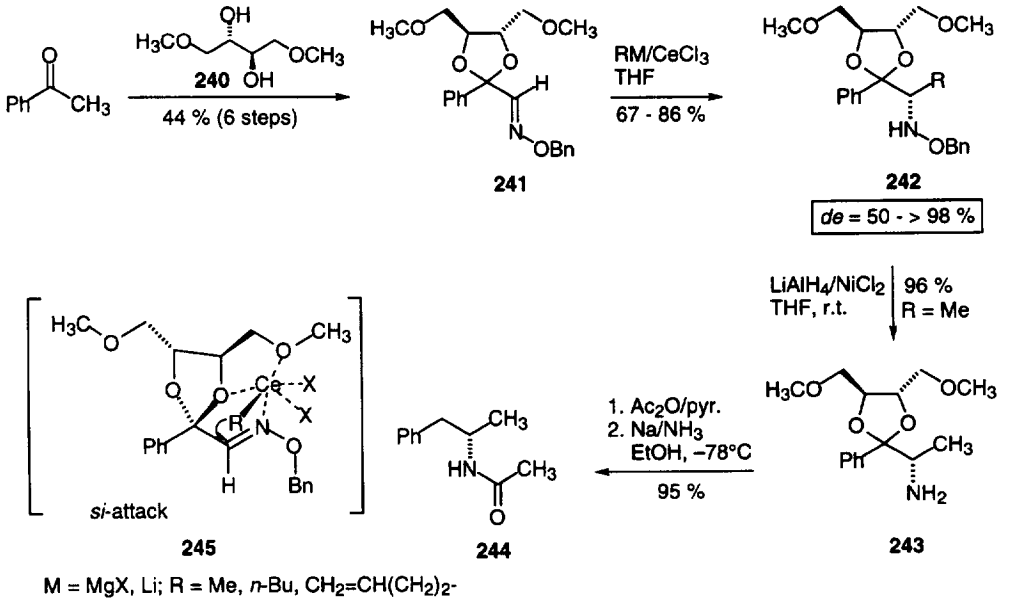
Scheme 70. Asymmetric synthesis of allylglycine and related derivatives according to Hanessian and Yang.[84]

A highly stereoselective 1,2-addition of organocerium reagents ($RMgX/CeCl_3$, $RLi/CeCl_3$) to the chiral aldoxime acetal **241** has been described by Fujioka, Tamura *et al.*[85] The oxime **241** was prepared in 6 steps starting from acetophenone with (−)-(*S,S*)-1,4-dimethoxy-2,3-butanediol **240** as auxiliary. Nucleophilic addition of organocerium reagents generated from $CeCl_3$ and Grignard or organolithium compounds proceeded in high chemical yields and with high diastereoselectivities to afford *N*-oxygenated amines **242**. Generally higher diastereoselectivities were reached by organocerium reagents prepared from Grignard solutions (86–>98% *de*) in contrast to the use of organolithium reagents/$CeCl_3$ (50–80% *de*). N–O-bond fission was achieved by lithium aluminium hydride–nickel chloride reduction to give the amine **243** which was transfered to the *N*-acetylprotected amphetamine **244** as illustrated in Scheme 71. The *si*-face selectivity in the addition reaction may be rationalized by assuming a preformed chelation model of the α-keto acetal **241** and the cerium reagent.[85] Chelation of the cerium metal between the nitrogen atom, the methoxy oxygen atom, and one of the acetal oxygen atoms may form a rigid structure in the transition state **245**.

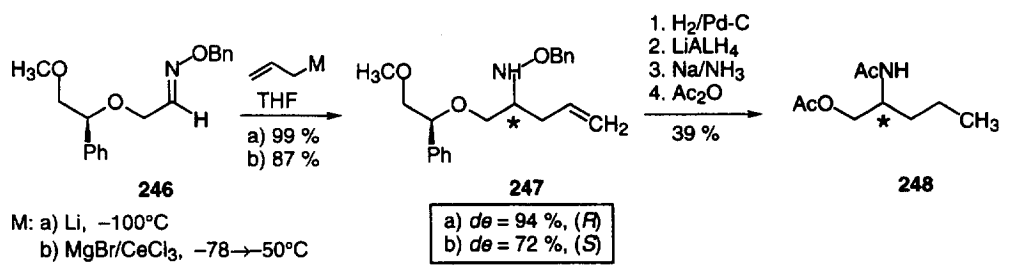
An enantioselective synthesis of β-amino alcohols has been described by Fujisawa *et al.*[86] A key step is the diastereofacial selective reaction of allyl metallic reagents to the enantiopure alkoxymethyl oxime ether **246** to afford benzyloxyamine **247**. The oxime ether **246** was prepared from (*S*)-2-methoxy-1-phenylethanol in three steps (72% yield) as a 1:1 mixture of *E/Z* isomers which were separated by chromatography. Both the stereoselectivity and the reactivity were affected by the configuration of the oxime ethers **246**. As allylic nucleophiles allyllithium, allyl Grignard reagents and their corresponding cerium reagents were tested. Allyllithium reacted with (*E*)-**246** in high diastereoselectivity (*de*=94%) and with nearly quantitative yield. The opposite (*S*)-configuration of the newly generated stereogenic centre was obtained by use of a cerium reagent prepared from Grignard solution in THF and cerium trichloride (*de*=72%). Surprisingly, the addition reaction to (*E*)-**246** by allyllithium complexed with cerium trichloride also furnished the (*R*)-product stereoselectively (*de*=84%). The reaction of the (*Z*)-oxime ether of **246** showed only poor facial discrimination. The transformation of **247** to the *N,O*-acetylated norvalinol **248** is shown in Scheme 72.

4.3 Ligand-induced stereoselectivity

In the field of enantioselective synthesis of amines by ligand-induced addition to oximes and oxime ethers very few investigations have been reported in the literature. Beside the diastereoselective allylation to prepare optically active allylglycine and its derivatives according to Hanessian and Yang (see chapter 4.2, Scheme 70), the enantioselective allylation of α-ketoester oximes with an external



Scheme 71. Diastereoselective addition to chiral α-aldoxime acetal according to Fujioka, Tamura *et al.*[85]



Scheme 72. Diastereoselective allylation of enantiopure alkoxymethyl oxime ether according to Fujisawa *et al.*[86]

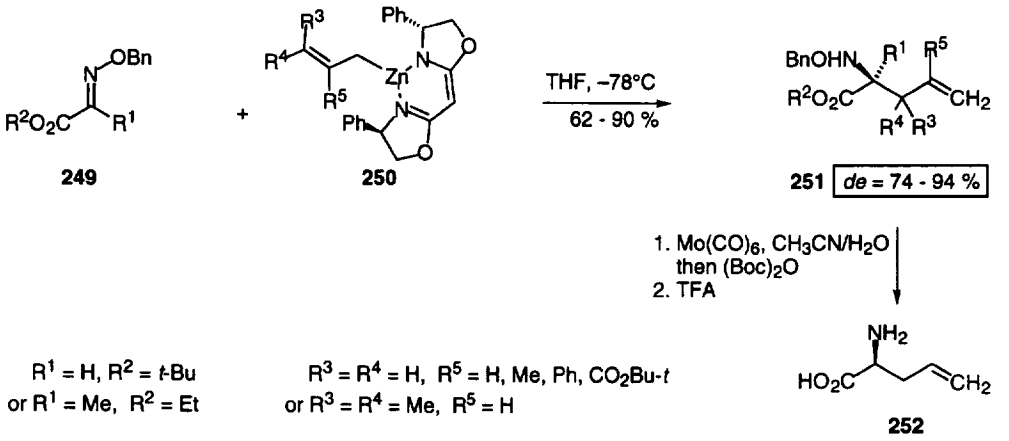
chiral ligand has been examined by the same group (Scheme 73).[87] Phenylsubstituted bis(oxazoline) allyzinc and α- or γ-substituted allylzinc reagents **250** underwent a γ-selective reaction with *O*-benzyl glyoxylic and pyruvic ester oximes **249** to give the benzyloxyamine **251** in high yields and enantioselectivities (*ee*=74–94%). The chiral bis(oxazoline) ligand was separated from the product and recovered without loss of optical activity. For the high inductions the *t*-butyl ester group and the phenyl substituted bis(oxazoline) as well as the low temperature are essential. The adducts **251** are precursors for allylglycines and allyalanine. The selective cleavage of the N–O-bond can be performed by $Mo(CO)_6$ followed by transformation, e.g. into *L*-allylglycine **252**.

5. Addition to nitrones

There have been several investigations to overcome the low reactivity of imines concerning the stereoselective addition of organometallics by use of nitrones. In general, nitrones show a higher electrophilic reactivity due to the highly polarized C–N-double bond. A few concepts have been described in the literature.

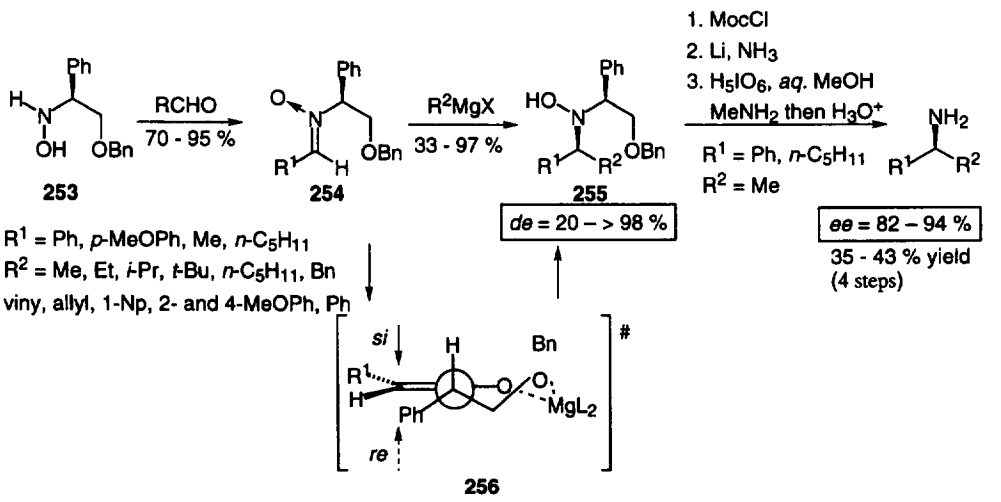
5.1 Auxiliary group in the substrate

Chang and Coats[88] have investigated the addition of Grignard reagents to C-aryl and C-alkyl-*N*-(α-phenyl-β-(benzyloxy)ethyl nitrones **254** prepared by condensation of the corresponding aldehydes



Scheme 73. Asymmetric synthesis of allylglycine and allylalanine derivatives according to Hanessian and Yang.[87]

and hydroxylamine **253**. High and very high diastereoselectivities (up to >98% *de*) and acceptable to good yields were observed for the addition of Grignard reagents in most cases. A solvent effect to more nonpolar solvents leading to higher diastereoselectivities was achieved. Significantly lower diastereomeric ratios were found for allyl and *o*-methoxyphenyl Grignard reagents (*de*=20–56%). The configuration of the major product can be rationalized by assuming that the Grignard reagents attack the nitrone face opposite to the pseudoequatorial *N*-(α-phenyl) group in a six-membered magnesium chelate **256**. ^{1}H NMR spectral investigations indicate a 1:1 complex of nitrone **254** and magnesium bromide in the solvent CD_2Cl_2. A four step path was developed in order to convert the hydroxylamines **255** to the optically active (*S*)-1-phenylethylamine (94% *ee*) and (*S*)-2-heptylamine (82% *ee*) in 33–39% overall yield from (*S*)-nitrone **254** (Scheme 74).

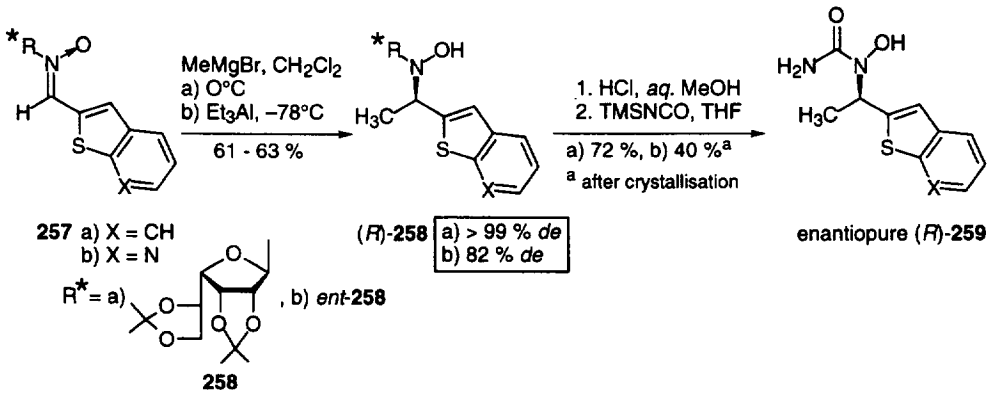


Scheme 74. Enantioselective synthesis of primary amines *via* Grignard additions to nitrones according to Chang and Coates.[88a]

Also the diastereoselectivities of organometallic additions to racemic and enantiopure nitrones bearing stereogenic α-arylethyl, β-methoxy- and β-silyloxyalkyl substituents on nitrogen, prepared from α-arylethylamine, valinol and phenylglycinol, have been investigated.[88b] The diastereoselectivity of Grignard reagents with racemic nitrones bearing a non-chelating α-arylethyl groups on nitrogen

were low. High diastereoselectivity was observed in the addition to nitrone bearing the potentially chelating β methoxyalkyl group. A reversal or decrease of stereoselectivity can be reached by the reaction of Grignard reagents with the corresponding TBDPS ether. A loss of chelation control in the reaction is proposed.

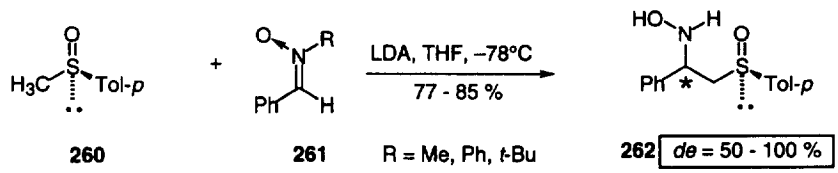
Another performed strategy incorporated a sugar derived auxiliary into the nitrone.[89] The synthesis of the (*R*)-enantiomer of 5-lipoxygenase inhibitor zileuton **259** is based upon Grignard alkylation of β-configurated (*Z*)-nitrones **257** bearing a 2,3,5,6-di-*O*-isopropylidene-gulofuranose auxiliary.[89] Both of its enantiomers can be prepared starting from commercially available material. After the methyl Grignard addition forming the hydroxylamine **258** in complete diastereoselectivity and good yields (61%) the sugar group can be cleaved off by acidic hydrolysis. Carbamoylation gave the final product zileuton. Precomplexation by the use of the Lewis acid trimethylaluminium resulted in a reversal of the stereochemical outcome. The pyrido analogue (*R*)-RS-27871 was prepared in this manner starting from the *L*-gulofuranose derived nitrone **257** (X=N, *ent*-R*)(Scheme 75).[89]



Scheme 75. Enantioselective synthesis of 5-lipoxygenase inhibitors using a gulofuranose auxiliary.[89b]

5.2 Auxiliary group in the nucleophile

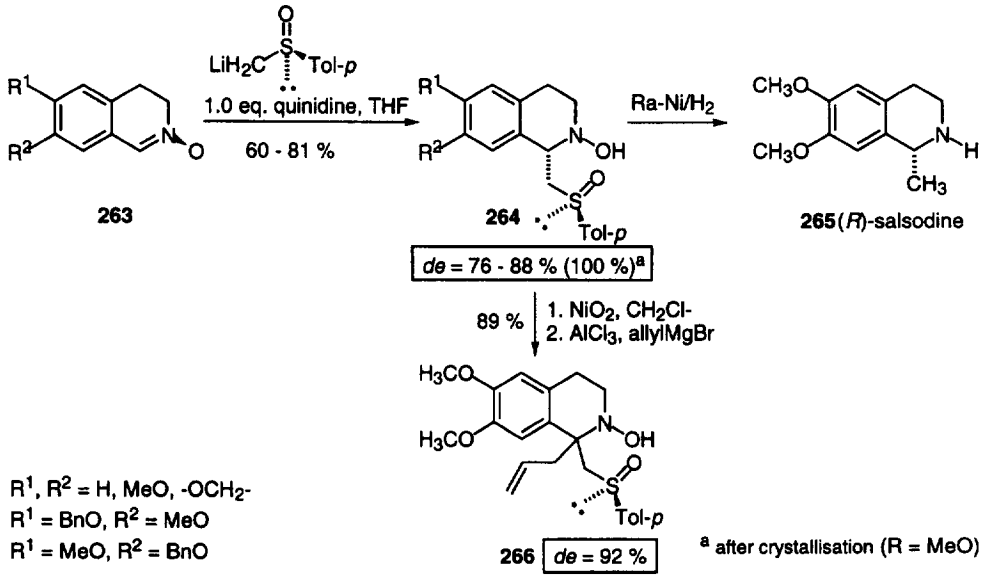
Optically active sulfoxides are of interest in a number of stereoselective processes, e.g. C–C bond formation. In 1982, Annunziata and Cinquini[90] reported the addition of lithiated (*R*)-*p*-tolyl methyl sulfoxide **260** to the nitrones **261** at −78°C in high yields (77–85%). The diastereoselectivity of these reactions increased up to completion (R=*t*-Bu) as a function of the steric demand of the R group. The stereochemical outcome of **262** was not determined (Scheme 76).



Scheme 76. Stereoselective synthesis of β-hydroxylamino sulfoxides according to Annunziata and Cinquini.[90]

Addition of optically active (*R*)- and (*S*)-methyl *p*-tolyl sulfoxid anions to 3,4-dihydroisoquinoline *N*-oxides **263** has been studied to obtain precursors of various isoquinoline alkaloids such as (*R*)-salsodine **265** or (*R*)-homolaudanosine.[91] Typically, treatment of the cyclic *N*-oxide **263** (R^1=R^2=OMe) with the lithiated sulfoxide according to literature conditions[90b] gave a poor diastereomeric ratio (28% *de*). The addition of one equivalent of lithium salt of quinidine in THF as co-auxiliary improved the diastereoselectivities (76–88% *de*). The sulfoxide group can be easily removed by hydrogenation yielding the alkaloid **265**. Starting fom sulfony hydroxylamine **264** (R^1=R^2=OMe) the alkaloid

homolaudanosine can be elaborated.[91b] Furthermore, the induction of a stereogenic quarternary carbon α to the amine was described. Oxidation of hydroxylamine **264** (R^1=R^2=OMe) with nickel peroxide and diastereoselective addition of allyl Grignard reagents gave the sulfinyl hydroxylamine **266** in high diastereoselectivity (*de*=92%) and excellent yield (89%, two steps) as illustarated in Scheme 77. Addition of the Lewis acid $AlCl_3$ is neccessary to achieve high diastereofacial selectivity. The absolute configuration of the newly generated stereogenic centre was not determined.



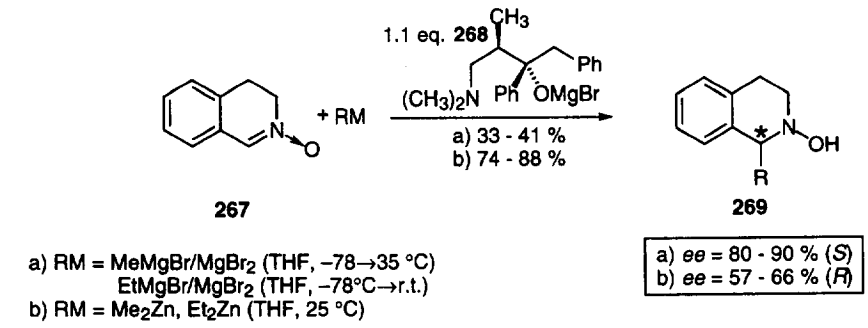
Scheme 77. Asymmetric synthesis of tertahydroisochinoline by addition of lithiated *p*-tolyl methyl sulfoxids according to Murahashi *et al.*[91]

5.3 Ligand-induced stereoselectivity

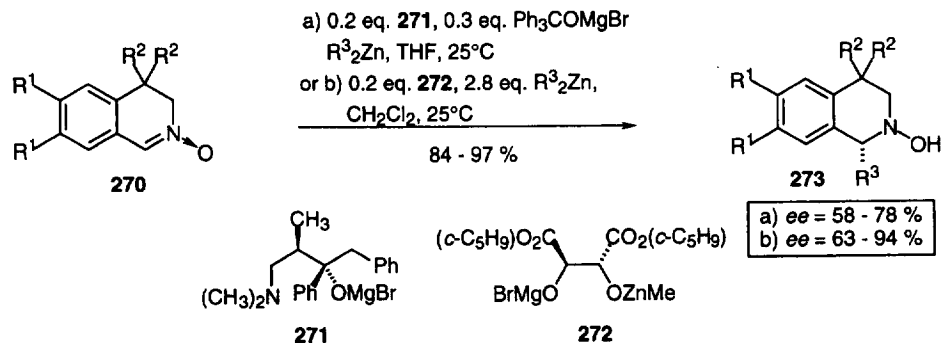
A remarkable example of ligand-induced stereoselectivity is the enantioselective addition of Grignard and alkylzinc reagents to the 3,4-dihydroisoquinoline *N*-oxide **267**.[92a] The external auxiliary bromomagnesium (2*S*,3*R*)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butoxide **268** was prepared from the enantiopure alcohol (Chirald®) and alkylmagnesium bromide.[92a] Addition of Grignard reagents in the presence of in situ generated magnesium bromide led to the (*R*)-configurated product **269** in enantioselectivities up to 90%. On the other hand in the absence of a magnesium salt the reaction of dialkylzinc reagents and the chiral ligand **268** gave the opposite configuration of **269**. A summary of the optimized conditions and results is given in Scheme 78. The stereochemistry of the newly formed chiral centre was determined by conversion of **269** to the corresponding amine (Pd/C, H_2; 75%). Although the mechanism is still an open question the predominantly *si*-attack of the Grignard reagents was rationalized by alkyl transfer of a nucleophile which is aggregated to a nitrone–ligand–$MgBr_2$ complex. Dialkylzinc could not be complexed with **268** and would approach from the less hindered *re*-face.

Two catalytic variants of ligand-induced addition of dialkylzinc to the 3,4-dihydroisoquinoline *N*-oxides **270** have been described recently by Ukaji *et al.* (Scheme 79).[92b,c] Catalytic amounts of the enantiopure ligand **271** (0.2 eq.) in the presence of bromomagnesium triphenylmethoxide were used to reach enantioselectivities up to 78% in excellent yields.[92b] The role of the achiral alkoxide might be explained as a co-ligand which leads to an more effective face discrimination and/or acceleration of the catalytic cycle.

The enantioselectivity could be further improved by employing magnesium zinc alkoxide **272** derived from tartric acid as catalyst.[92c] The 1-alkyl tetrahydroisoquinolines **273** were obtained in



Scheme 78. Ligand induced addition to a nitrone according to Ukaji *et al.*[92a]



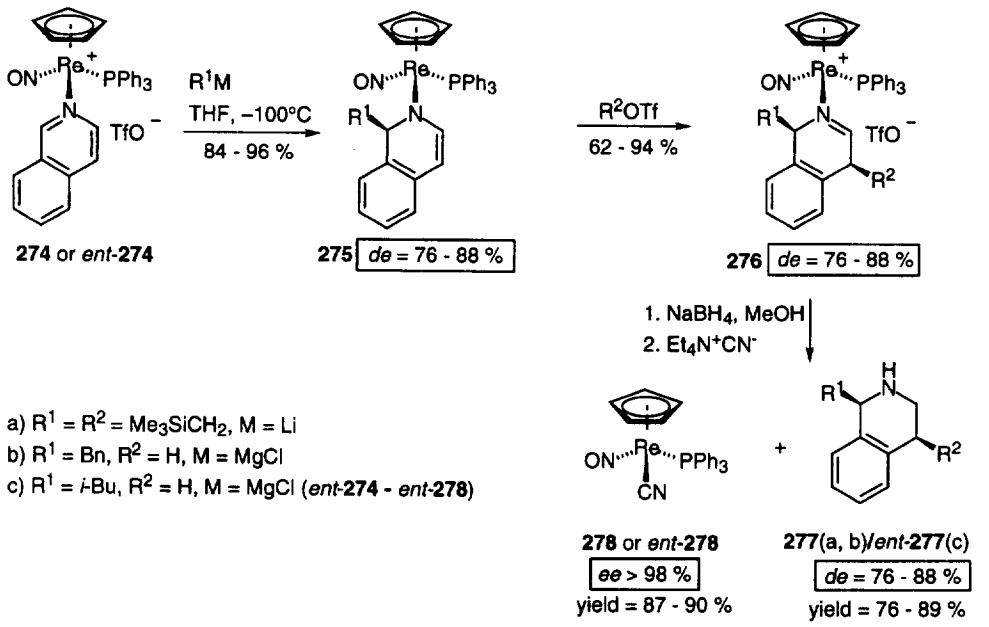
Scheme 79. Catalytic asymmetric addition of organozinc reagents to nitrones according to Ukaji *et al.*[92b,c]

very good yields (84–95%)and with enantioselectivities up to 94% *ee*. It was suggested that the alkylgroup is transferred from complexed dialkylzinc reagent since a reversal of the enantiofacial selection was observed by use of less then 2 equivalents of diethyl zinc and a stoichiometric amount of magnesium–zinc ligand.

6. Miscellaneous additions

A new strategy for the enantioselective synthesis of 1-alkyl- and 1,4-dialkyl-1,2,3,4-tetrahydroisoquinolines has been described by Gladysz *et al.* (Scheme 80).[93] Addition of both organolithium and Grignard reagents to the enantiopure rhenium isochinoline complex **274** gave exclusivly the enamino complex **275** with high diastereomeric excesses (76–88% *de*). The adduct **275** was protonated or treated with an electrophilic triflate reagent in order to obtain the *cis* substituted 1,4-dialkyl-1,2,3,4-tetrahydroisoquinoline complex **276**. Reaction with sodiumborane and substitution with a cyanide source gave the desired alkaloide **277** and the cyanid complex **278** in excellent yield and without loss of enantiomeric excess. The rhenium complex can be recycled to form the enantiopure substrate **274**.

Continuing investigations have been reported to apply the method to the analogous optically active quinoline complexes.[94] Alkylation with organolithium reagents seemed to react in a highly diastereoselective way. However, subsequent reaction with HOTf gave mixtures of amine complexes and alkene complexes.



Scheme 80. Enantioselective synthesis of 1-alkyl- and 1,4-dialkyl-1,2,3,4-tetrahydroisoquinolines according to Gladysz *et al.*[93]

7. Conclusion

In summary, impressive progress has been made in the field of asymmetric 1,2-addition to the CN double bond. A number of efficient and practical synthetic methods for the synthesis of enantiomerically enriched amines have been developed. The reaction can be applied to a wide range of functionalized organometallics and imino compounds. Several natural products and biologically active compounds employed as drugs containing amino groups have been synthesized in convincing ways. Most of them are auxiliary-based asymmetric reactions using internal chirality to reach a high degree of selectivity. Recently, the ligand-induced stereoselectivity connected with its advantages in a stoichiometric or even catalytic fashion seem to be a promising strategy. Despite the results achieved, the remaining need for new and useful asymmetric syntheses of enantiomerically enriched amines demands intensive and challenging research in this area in the future.

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2. In spite of our intensive literature search to gather all relevant publications we want to apologize to the research groups whose work are not mentioned in this paper. We would be very pleased if the researchers inform us about missing papers.
3. Review about stereoselective addition to *N*-acyliminium ions: a) de Koning, H.; Speckamp, W. N. [1a], p. 1953. b) Hiemstra, H.; Speckamp, W. N. [1b], Vol. 2, p. 1047. Mannich-type reaction: c) Kleinman E. F. [1b], Vol. 2, p. 893. d) Heaney, H. [1b], Vol. 2, p. 953. d) Overman, L. E.; Ricca, D. J. [1b], Vol. 2, p.1007. Aldol-type reaction: e) Risch, N.; Arend, M. [1a], p. 1894. f) Gennari, C. [1b], Vol. 2, p. 629. Strecker and Ugi reaction: g) Kunz, H. [1a], p. 1931, h) Ugi, I.; Lohberger, S.; Karl, R. [1b], Vol. 2, p. 1083.
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(Received in UK 12 May 1997)