Methods for the asymmetric preparation of amines

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Reviewing the literature published up to January 1995

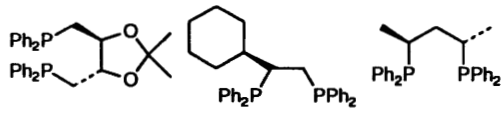
1 Introduction

In light of the development of asymmetric synthesis during the past twenty years, it may seem surprising that the asymmetric preparation of amines is still met with such difficulties and is so unpredictable. However, the problems associated with asymmetric aminations are several. One is the lack of an apparent prochiral functional group as a precursor. Another is the different behaviour of what at first glance seem to be quite similar nitrogen-containing prochiral compounds. Nevertheless, several promising methods have emerged. It is noteworthy that completely different approaches have become useful in the past few years, both when it comes to the choice of prochiral functional group and method to convert it into an amino group. Hence, in this review, I have tried to cover the literature within the field as broadly as possible, but I soon realized that a few limitations were necessary, and so decided to deal only with general methods in which a new chiral centre is created as the amine is produced. The methods covered are divided into three categories: reductions, alkylations, and additions to double bonds. Of these, additions to double bonds is the smallest category as cycloaddition reactions are not included. Furthermore, I have excluded asymmetric syntheses of amino acids, because I considered this a topic of its own.

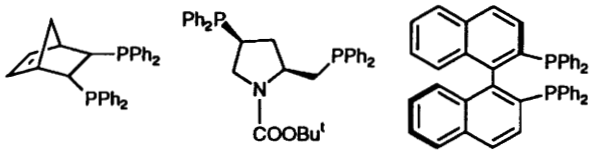
2 Reduction of the C=N bond

2.1 Catalytic processes

So far, all asymmetric catalytic processes for the reduction of C=N double bonds have been based on the use of transition metals. A majority of the reported catalytic systems consist of transition metals with a chiral diphosphine ligand.[1] A selection of ligands used in these C=N reductions are shown below. Some of the results obtained with these ligands are summarized in **Table 1**.



(+)-DIOP (*R*)-(+)-cycphos (−)-BDPP

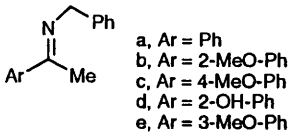


(−)-NORPHOS (2*S*,4*S*)-BPPM (+)-BINAP

Et-DuPHOS NBD COD

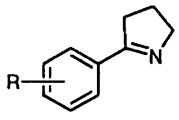
In an early example, the (+)-DIOP ligand together with $[RhCl(C_2H_4)]_2$ and Ph_2SiH_2 was used for hydrosilylations of prochiral imines.[2] The silyl amines were not isolated, but hydrolysed *in situ* to produce amines. In all cases, the yields are excellent. The highest selectivity reported (65% e.e.) is achieved with the imine **1a** when the reaction is performed at around 0 °C. Raising the temperature to 60 °C results in a dramatic decrease in selectivity, as an e.e. of only about 27% is observed. In a later paper, the same catalytic system was used for the asymmetric reduction of enamines.[3] A modification, in which $[Rh(COD)Cl]_2$ was used instead of $[RhCl(C_2H_4)]_2$, appeared several years later.[4] In this study, five-membered cyclic imines **2** were

hydrosilylated but, contrary to the paper by Kagan *et al.*,[2] the amines could not be isolated after hydrolysis. Instead, the silylamines were treated with trifluoroacetic anhydride to yield the trifluoroacetamide derivatives. The best result (64% e.e.) is obtained with an unsubstituted phenyl group at the 2-position, although bromine in the *para*-position does not decrease the selectivity significantly. When the phenyl moiety contains a methoxy group in one or several positions, the optical yield is considerably lower. This observation is ascribed to intra- and inter-molecular coordination of the methoxy substituent to rhodium. Hydrosilylations of oximes with this catalyst system have also been studied, but substantially lower selectivities were observed (1.4–18.7% e.e.).[5]



a, Ar = Ph
b, Ar = 2-MeO-Ph
c, Ar = 4-MeO-Ph
d, Ar = 2-OH-Ph
e, Ar = 3-MeO-Ph

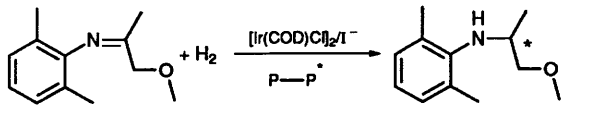
1



2

The (*R*)-(+)-cycphos ligand has been used together with $[Rh(NBD)Cl]_2$ and KI for the reduction of aromatic imines **1a–d**.[6] Here, the presence of a methoxy substituent in the *para*-position increases the e.e. Thus, imine **1c** can be hydrogenated to give an e.e of 91% and imine **1a** gives 71% e.e. For the *ortho*-substituted imine **1b**, the optical yield is somewhat lower and no asymmetric induction was observed with imine **1d**. The catalyst is not effective for the asymmetric hydrogenation of aliphatic imines. An interesting observation is that the selectivity is significantly lower without KI. A similar decrease in selectivity has been reported earlier,[7] although the effect of halide was less dramatic. In a detailed structural study of (−)-(*S,S*)-BDPP, Bakos and co-workers[8] reported a 73% e.e. in hydrogenations of **1a**. In a later paper,[9] they examined the effect of sulfonation at the *meta*-position of one or several phenyl groups in the (−)-BDPP ligand. The sulfonated ligands were not purified, but used as a mixture. The compositions were determined with HPLC. When performing the hydrogenation with $[Rh(NBD)Cl]_2$ and partly sulfonated (−)-BDPP, they were able to obtain high enantioselectivities of aromatic benzylamines **1a–c** and **1e** (89–96% e.e.).

In a comparative study,[10] several chiral diphosphines were used together with $[Ir(COD)Cl]_2$ (**Scheme 1**). The most effective ligands are those capable of forming a flexible six- or seven-membered metallacycle, *e.g.* BDPP, DIOP and BPPM. With these ligands, both reactivity and enantioselectivity are high. Quite contrary, 1,2-diphosphino compounds, such as NORPHOS, are considerably less efficient. Furthermore, a strong halogen effect is observed, as the halogen-free catalytic system $[Ir(COD)_2]BF_4$/(*S,S*)-DIOP produces the (*R*)-amine with only 4% e.e. and only 30% conversion. Also, the two methyl substituents



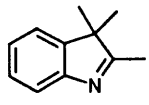
3

*(2*S*, 3*S*)-DIOP 70% e.e.
(2*S*, 4*S*)-BPPM 73% e.e.
(2*S*, 4*S*)-BDPP 84% e.e.

Scheme 1

in the *ortho*-positions of the phenyl group of **3** are important, presumably by hindering the rotation about the *N*-aryl bond.

Another type of iridium-reagent, the dimeric $[Ir(P–P)HI_2]_2$, in which P–P is a diphosphine, has been investigated by Osborn *et al.*[11] The reagent was investigated with (+)-DIOP, (−)-BDPP, (+)-BINAP and (−)-NORPHOS as chiral diphosphine ligands. Osborn's findings indicate dissociation of the dimeric catalyst to the monomer and an equilibrium between free imine and monomer and an imine/monomer complex. Moreover, by studying the hydrogenation of deuterated imine **3**, they concluded that addition occurs almost exclusively (>95%) to the C=N bond and not to the enamine tautomer. Of the substrates studied, the highest selectivity is observed in hydrogenation of **4** with (−)-BDPP as the ligand (80% e.e.).



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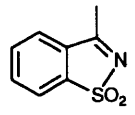
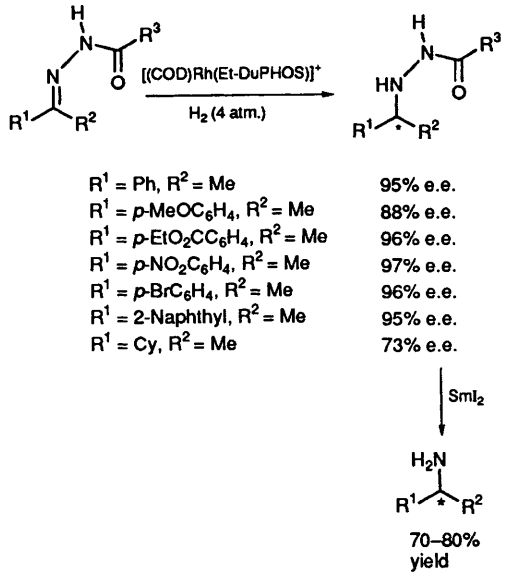


5

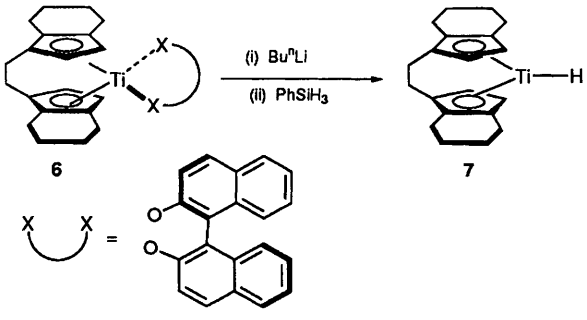
Oppolzer and co-workers have reported the reduction of **5** with $Ru_2Cl_4[(R)-(+)-BINAP]_2$, which proceeds with exclusive formation of one enantiomer.[12]

A very efficient rhodium-based catalyst has been reported by Burk[13,14], who used a cationic rhodium complex together with the chiral 1,2-bis(phospholano)-benzene, Et-DuPHOS (**Scheme 2**). The hydrogenations are performed on *N*-benzoylhydrazones to yield hydrazines in 72–97% e.e. After the hydrogenation, the N–N bond is readily cleaved with SmI_2 to produce amines in high yields without loss of optical purity. An interesting observation is that no hydrogenation takes place without the carbonyl functionality of the hydrazones present. This observation is ascribed to chelation of the *N*-benzoylhydrazone functionality to the cationic rhodium centre. Furthermore, the hydrogenations are highly chemoselective. For example, little or no reduction is observed for alkenes, alkynes, ketones, aldehydes, esters, nitriles, carbon–halogen bonds, nitro groups, or even imines in competition experiments. This is attributed to the aforementioned substrate chelation of the *N*-benzoyl hydrazone and the fact that *N*-benzoylhydrazine inhibits the reduction of aldehydes, alkenes and alkynes among others.



Scheme 2

Another excellent asymmetric hydrogenation catalyst based on titanium has been developed by Buchwald and co-workers.[15–17] The active catalyst is the titanium(III)hydride **7**, which is formed *in situ* by treating the chiral air stable *ansa*-titanocene **6**[18] with Bu^nLi and phenylsilane (**Scheme 3**). The catalyst works extraordinarily well for the reduction of cyclic imines (97–98% e.e.). Though still respectable in several cases, the selectivity is generally lower (53–85% e.e.) when the substrate is an acyclic imine. The observed e.e.s correlate roughly with the *anti*/*syn* ratios of the investigated imines. For this observation the authors suggest that both the *anti* and *syn* isomers are reactive, giving rise to opposite enantiomers of the product amines.[19] The catalyst has also been used for asymmetric hydrogenations of enamines.[20]



Scheme 3

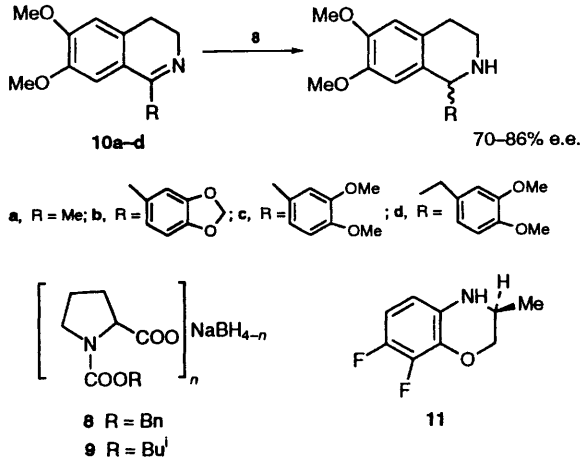
The last two mentioned methods are the subject of an excellent review by Bolm.[21]

2.2 Non-catalytic processes

2.2.1 Reductions with chiral reagents

There are examples of asymmetric reductions of imines and oxime ethers using aluminium hydrides.[22,23] However, the asymmetric induction is at best fair and, hence, these reagents have given way to boron-based reagents, in some cases combined with Lewis acids, such as $ZrCl_4$ or $ZnCl_2$/$AlCl_3$. Hitherto, no reports have appeared in which boron reagents are used in a catalytic fashion, as is the case with carbonyl reductions.[24]

Chiral sodium triacyloxyborohydrides such as **8** and **9** can be prepared from $NaBH_4$ and *N*-carboxyl derivatives of optically active α-amino acids. These reducing agents have proven useful for reductions of certain cyclic imines. Iwakuma *et al.*[25,26] have described asymmetric reductions of imines **10a–d**. In their study, several acyloxyborohydrides were investigated of which **8** in CH_2Cl_2 produces the highest optical yield (**Scheme 4**). In another investigation,[27] the amine **11**, a precursor to the antibacterial agent (*S*)-(−)-ofloxacin,[28] has been prepared in 95% e.e. from the corresponding imine using **9** as the reducing agent.

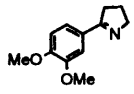
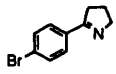
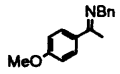
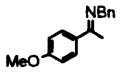
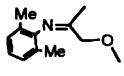
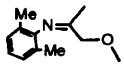
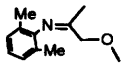
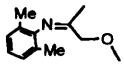


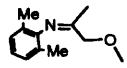
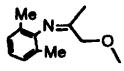
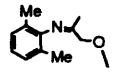
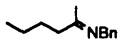
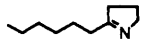
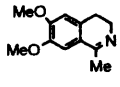
Scheme 4

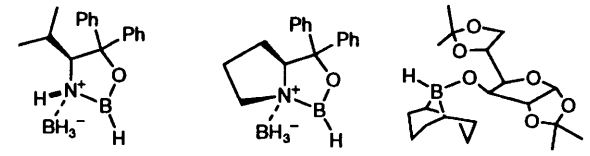
A comparative study of several reducing agents efficient in asymmetric ketone reduction has been undertaken by Cho and Chun.[29] The asymmetric reducing characteristics of Itsuno's reagent **12**,[30] Corey's reagent **13**,[31] K-glucoride (Brown's reagent) **14**,[32] Sharpless' reagent **15**[33] and Mosher's reagent **16**,[34] were compared with propiophenone *N*-phenylimine **17** as the substrate (**Scheme 5**). Under the same conditions as those found most successful for ketone reductions. Itsuno's reagent is the most effective (87% e.e.), whereas **14** and **16** did not reduce the examined imine **17**. Further reductions with Itsuno's reagent show that aromatic *N*-phenyl imines can be reduced with good to high selectivity (71–88% e.e.). Lower optical yields are observed for aromatic *N*-alkyl imines (*ca.* 50% e.e.) and for aliphatic *N*-phenyl imines the selectivity drops significantly. The cyclic imine **10a** was inert to the reagent.

The chiral dialkoxyborane **18** has been investigated for several different imines.[35,36] The e.e.s obtained range from 12 to 73% and it is notable that the only alkyl ketimine in the study, **19**,

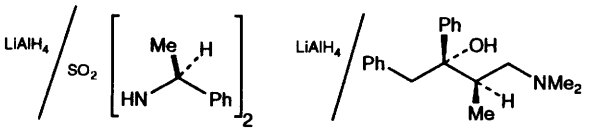
Table 1 Asymmetric catalytic reductions of imines

Catalyst	Substrate	e.e.	Ref.
DIOP/$[RhCl(C_2H_4)_2]_2$		65%	1
DIOP/$[Rh(COD)Cl]_2$		64%	3
DIOP/$[Rh(COD)Cl]_2$		31%	3
DIOP/$[Rh(COD)Cl]_2$		33%	3
DIOP/$[Rh(COD)Cl]_2$		60%	3
(*R*)-cycphos/$[Rh(NBD)Cl]_2$/KI		79%	5
(*R*)-cycphos/$[Rh(NBD)Cl]_2$/KI		91%	5
(*R*)-cycphos/$[Rh(NBD)Cl]_2$/KI		71%	5
(*R*)-cycphos/$[Rh(NBD)Cl]_2$/KI		0%	5
(–)-BDPP/$[Rh(NBD)Cl]_2$		73%	7
(–)-BDPP*)/$[Rh(COD)Cl]_2$		96%	8
(–)-BDPP*)/$[Rh(COD)Cl]_2$		95%	8
(–)-BDPP*)/$[Rh(COD)Cl]_2$		89%	8
(–)-BDPP*)/$[Rh(COD)Cl]_2$		91%	8
(–)-NORPHOS/$[Ir(COD)Cl]_2$		27%	9
(+)-DIOP/$[Ir(COD)_2BF_4]/I^-$		68%	9
(+)-DIOP/$[Ir(COD)Cl]_2/I^-$		70%	9
(2*S*, 4*S*)-BPPM/$[Ir(COD)Cl]_2$		73%	9

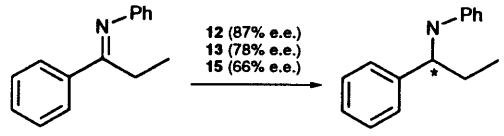
Catalyst	Substrate	e.e.	Ref.
(–)-BDPP/$[Ir(COD)Cl]_2/I^-$		84%	9
(+)-DIOP/$[Ir(COD)Cl]_2/I^-$		66%	9
(+)-DIOP/$[Ir(COD)Cl]_2/I^-$		52%	9
(+)-DIOP/$[Ir(COD)Cl]_2/I^-$		16%	9
(–)-BDPP/$[Ir(P\text{-}P)HI_2]_2$		40%	10
(–)-BDPP/$[Ir(P\text{-}P)HI_2]_2$		80%	10
NORPHOS/$[Ir(P\text{-}P)HI_2]_2$		47%	10
DIOP/$[Ir(P\text{-}P)HI_2]_2$		63%	10
BINAP/$[Ir(P\text{-}P)HI_2]_2$		22%	10
7		58%	13, 14
7		76%	13, 14
7		76%	13, 14
7		98%	13, 14
7		97%	13, 14
7		98%	13, 14
7		98%	13, 14
7		85%	13, 14



12 Itsuno's reagent 13 Corey's reagent 14 K-glucoride



15 Sharpless' reagent 16 Mosher's reagent

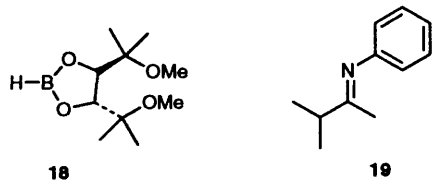


17

Scheme 5

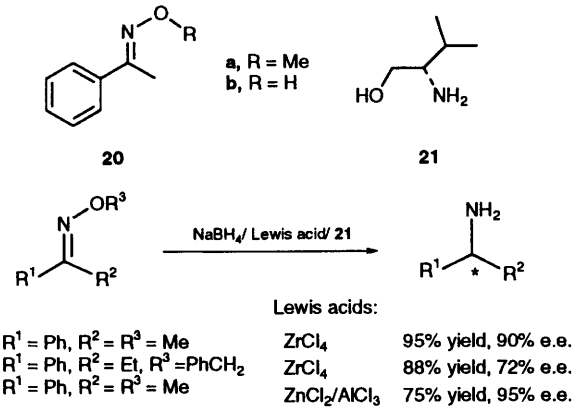
was reduced to the (*S*)-amine with 71% e.e. No reaction takes place without the addition of $MgBr_2 \cdot OEt_2$. Oxime ethers are unreactive to these reaction conditions. A selection of asymmetric reductions of imines with chiral reagents are shown in Table 2.

While the (*E*)- and (*Z*)-isomers of an imine are in equilibrium with each other through inversion of the nitrogen, oxime ethers have distinct *syn*- and *anti*-isomers,[37] as the energy barrier for inversion of the nitrogen is considerably higher. Although the oxygen of the oxime functionality offers an additional stereochemical control element through coordination to the reagent, one must also take into consideration the issue of performing the reduction on pure *syn*- or *anti*-isomer, as a mixture of these might decrease the optical yield substantially. Asymmetric reductions of oxime ethers have been reported by Itsuno and co-workers.[38] Using Itsuno's reagent **12**, the *anti*-oxime ether **20a** is reduced to



18 19

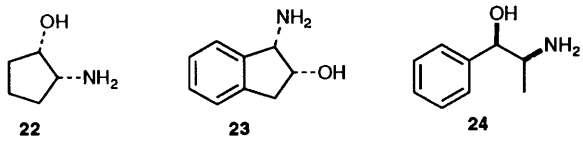
the corresponding amine with 99% e.e. In addition to Itsuno's reagent **12**, other chiral amino alcohols were used to prepare analogues of **12**. All of the amino alcohols examined give a high degree of asymmetric induction. The study also includes the effect of various *O*-substituents and suggests that both bulkier groups such as $SiMe_3$, and more electron-withdrawing groups such as COMe, decrease the optical yields considerably. When the reaction is performed on the oxime **20b**, no asymmetric induction at all is observed. The same type of chiral ligand has been used for reductions with hydride reagents.[39,40] The chiral amino alcohol **21** has been used as a ligand together with $NaBH_4$ and $ZrCl_4$ or $ZnCl_2/AlCl_3$ (**Scheme 6**). The amino alcohol is inert to suspensions of $NaBH_4$ in THF and, furthermore, no reduction of the oxime ethers take place under these conditions. Thus, the reducing species is thought to be a mixture of zirconium aminalkoxy borohydrides. It is also noteworthy that no amine is produced with Lewis acids such as $CuCl_2$, $ZnCl_2$ or $AlCl_3$ alone, or $ZnBr_2$.



20 21

Scheme 6

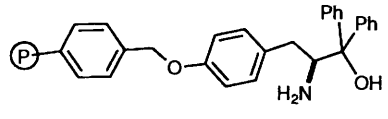
Several other amino alcohols have been examined by Didier *et al.*[41] The substrate studied, the oxime ether **20a**, is reduced to the corresponding amine with BH_3 and the chiral amino alcohols **22**, **23** and **24** [(–)-norephedrine] with 95, 94.5 and 93.2% e.e.



22 23 24

respectively. In some cases, the reduction of the oxime ether is not complete and a mixture of oxime ether, amine and hydroxylamine methyl ether is obtained. However, after elimination of the oxime ether, the hydroxylamine can be treated with an excess of BH_3 to produce the amine without loss of optical purity.

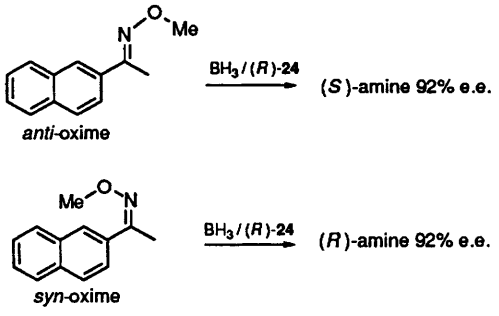
Itsuno and co-workers[42] have also reported reductions with the polymer supported chiral alcohol **25** and borane, but here the selectivities are lower (6–67% e.e.).



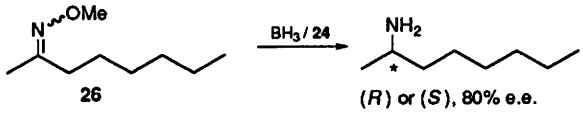
25

A systematic investigation of reduction of *syn*- or *anti*-ketoxime ethers has been undertaken by Sakito, Yoneyoshi, and Suzukamo.[43] They examined the reduction of several oxime ethers with BH_3 and

(–)-norephedrine, **24**, and obtained either enantiomer of the amine depending on the *syn*- or *anti*-configuration of the oxime ether. The most spectacular example is shown in **Scheme 7**. Thus, the difference in bulkiness of the two R-groups attached to the prochiral carbon seems to be of little importance and, accordingly, oxime ethers in which this steric difference is small can be reduced with high enantioselectivity, as exemplified by the reduction of the oxime ether of octan-2-one (**26**; 80% e.e., **Scheme 8**). For a summary of asymmetric reductions of oxime ethers, see **Table 3**.

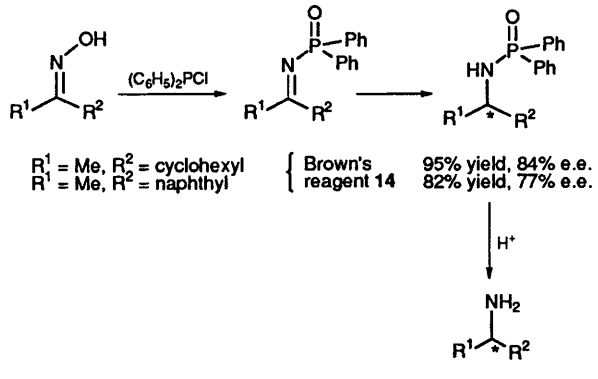


Scheme 7



Scheme 8

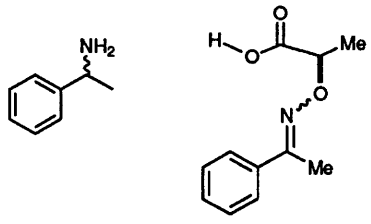
In a different approach,[44] the oximes were first converted into phosphinyl imines (**Scheme 9**). The introduction of the diphenylphosphinyl group enhances the electrophilicity of the imine carbon, thus making it more susceptible to nucleophilic attack. After the reduction, the phosphinyl moiety is easily removed. The reductions were performed on a number of substrates with Mosher's reagent **16**, (*R*)- or (*S*)-bi-2-naphthol/$LiAlH_4$ (Noyori's reagent),[45] and K-glucoride **14** (Brown's reagent) as reducing agents. The results are somewhat varying, but in some cases both high yields and high optical purities are obtained. The best results are shown in **Scheme 9**.



Scheme 9

2.2.2 Reductions using internal chiral auxiliaries

As a substrate bonded chiral auxiliary in C=N bond reductions, phenylethyl amine (**27**) is by far the most commonly employed. One reason is that it is easily removed with Pd/C to produce primary amines. Also, both enantiomers of **27** are commercially available. Using borane as the reducing agent, a 20 α-steroid is produced with 84% e.e. by reduction of the corresponding phenylethyl imine.[46] Other applications of **27** as a chiral promoter include reductions of fluoroalkylated imines,[47] the use of an NADH model as reducing agent,[48] and $NaBH_4$ reductions of cyclic iminium ions.[49] A number of imines derived from **27** have been studied in reductions with lithium aminoborohydrides. Reduction of the *tert*-butylmethylimine derivative proceeds with 92% d.e.[50] Oxime ethers with chiral promoters derived from β-pinene or α-amino acids have been used in reductions with $LiAlH_4$ and $BH_3 \cdot SMe_2$.[51] However, the degree of asymmetric induction is generally quite low. For example, the oxime ether **28** is reduced with 44% e.e. using $LiAlH_4$.



27 **28**

3 Alkylations

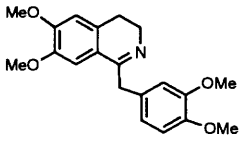
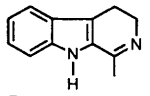
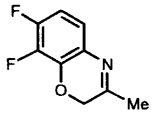
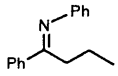
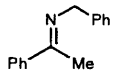
3.1 Nucleophilic alkylations

3.1.1 Alkylations using internal chiral auxiliaries

Yamamoto and co-workers have studied the addition of allylic metal compounds to aldimine **29**,[52,53] derived from 1-(*R*)-phenylethylamine and 2-methylpropanal. With allyl-9-BBN, the Cram product[54] is obtained in a 92:8 ratio (**Scheme 10**). They suggest that the reaction proceeds through transition state **30** (**Figure 1**), in which the steric repulsions between the methyl group (and/or the phenyl group) and the other ligands on the metal are minimized. Further experimental data from Hoffmann and Eichler[53] indicatate that increased size of the ligands (L) leads to higher diastereoselectivity. With allylstannane, the selectivity depends strongly on the Lewis acid, as $TiCl_4$ gives a 82:18 and BF_3 a 67:33 ratio in favour of the Cram isomer. All metals investigated give the Cram isomer as the major product.

Addition of crotyl-9-BBN to the propanal derivative **32**, gives exclusively the Cram isomer in a *syn*:*anti* ratio of 75:25 (**Scheme 11**). Both enantiomers of the vicinal diamine **33** have been prepared by double addition of allylic Grignard reagents to dialdimines prepared from glyoxal and (*R*)- or (*S*)-phenylethylamine followed by removal

Table 2 Non-catalytic asymmetric reductions of imines

Reducing agent	Substrate	e.e.	Ref.
8		70%	25
8		79%	25
9		95%	26
12		87%	29
12		88%	29
12		71%	29
12		73%	29
12		46%	29

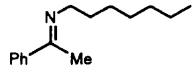
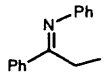
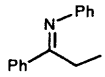
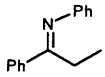
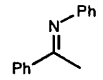
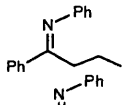
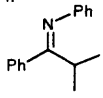
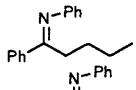
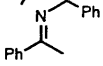
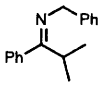
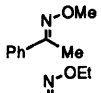
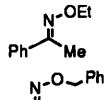
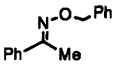
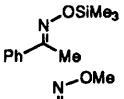
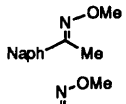
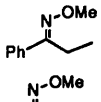
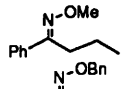
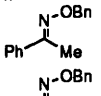
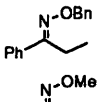
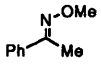
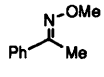
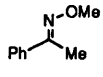
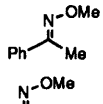
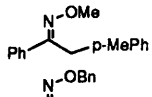
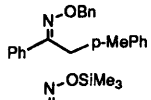
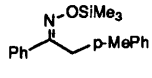
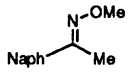
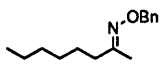
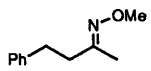
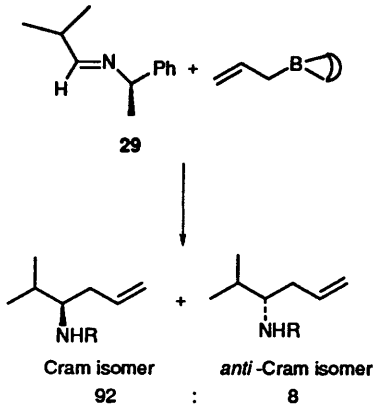
Reducing agent	Substrate	e.e.	Ref.
12		52%	29
13		78%	29
15		66%	29
18		73%	35, 36
18		56%	35, 36
18		65%	35, 36
18		18%	35, 36
18		65%	35, 36
18		71%	35, 36
18		72%	35, 36
18		36%	35, 36

Table 3 Non-catalytic asymmetric reductions of oxime ethers

Reducing agent	Substrate	e.e.	Ref.
12		99%	38
12		81%	38
12		91%	38
12		62%	38
12		70%	38
$22/NaBH_4/ZrCl_4$		66%	39, 40
$22/NaBH_4/ZrCl_4$		61%	39, 40
$22/NaBH_4/ZrCl_4$		69%	39, 40
$22/NaBH_4/ZrCl_4$		72%	39, 40
$22/NaBH_4/ZrCl_4$		92%	40

Reducing agent	Substrate	e.e.	Ref.
BH_3·THF/ 22		95%	41
BH_3·THF/ 23		94.5%	41
BH_3·THF/ 24		93.2%	41
BH_3·THF/ 24		92%	43
BH_3·THF/ 24		90%	43
BH_3·THF/ 24		91%	43
BH_3·THF/ 24		92%	43
BH_3·THF/ 24		80%	43
BH_3·THF/ 24		86%	43

of the chiral auxiliary with Pd/C.[55] The (*R*,*R*)- or (*S*,*S*)-diamines were produced in 6:1 ratios, respectively. It was not determined which enantiomer of phenethylamine gives which diamine, but in both cases only trace amounts of the *meso*-compound were detected. These findings are in accordance with those cited above. With this substrate, double chelation to the metal is suggested to take place, thus forming a bicyclic transition state (**Figure 2**).



Scheme 10

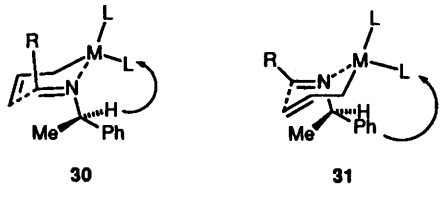
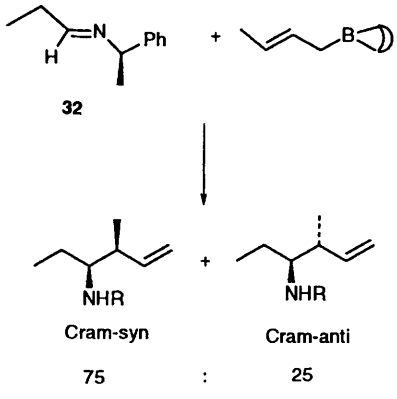


Figure 1 Interactions between the metal ligands and the chiral auxiliary[54]



Scheme 11

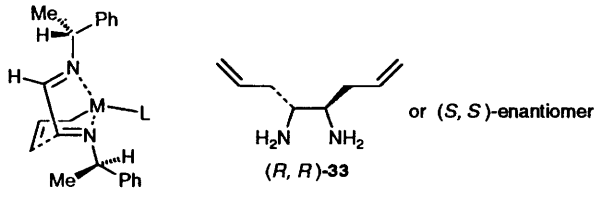
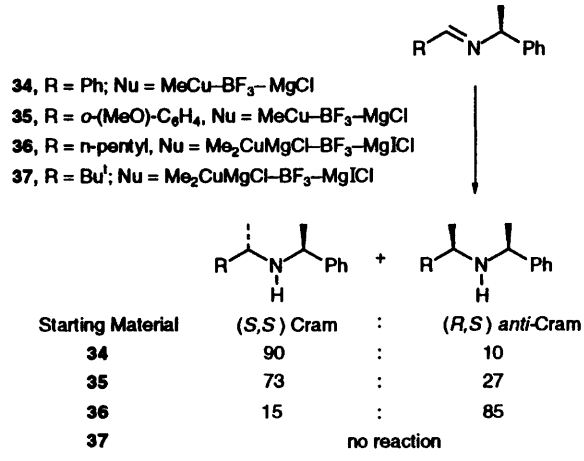


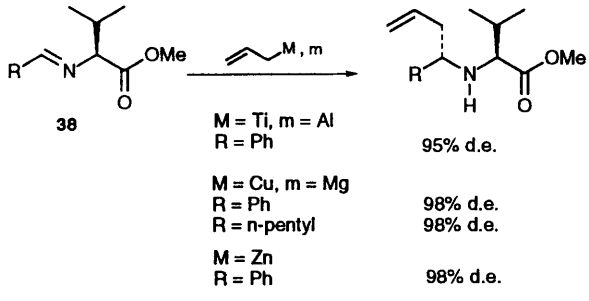
Figure 2 [55]

Addition of methylcopper and dimethyl cuprate to the aromatic aldimines **34** and **35** follow the same pattern[56] (Cram:*anti*-Cram up to 90:10; **Scheme 12**), whereas the aliphatic aldimine **36** shows reversed selectivity (15:85). No reaction was observed with compound **37**. Addition of allylic Grignard and copper reagents to **34** and **35** followed no general trend and the diastereoselectivity was found to be moderate.[57]



Scheme 12

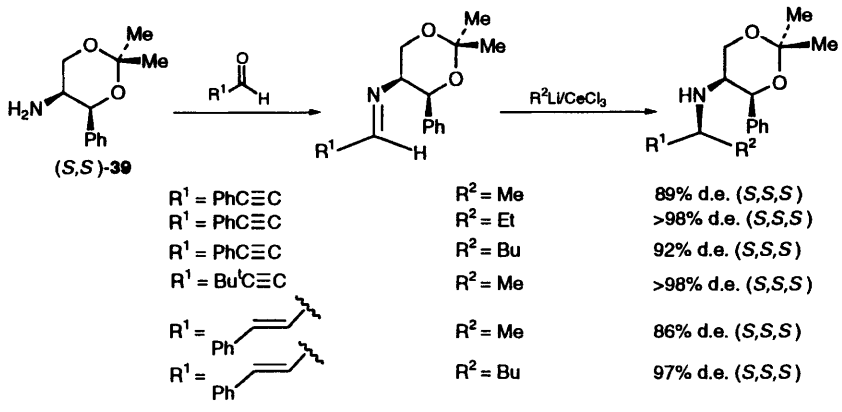
Allylic metal reagents based on Al/Ti[58], Zn[59] and Mg/Cu[57] have been added with excellent diastereoselectivity to imines derived from (*S*)-valine (**38**, **Scheme 13**). The allylic metal species is suggested to add to a five-membered cyclic chelate between the imino ester and Al or Mg. The chiral auxiliary can be removed electrolytically in high yields.



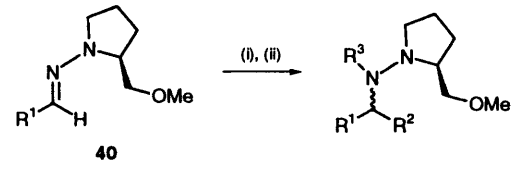
Scheme 13

Additions of aliphatic (Me, Et, Bu) organocerium reagents to allylic and prop-2-ynylic imines prepared from amine **39** and an aldehyde,[60] provide secondary amines of high diastereoisomeric purity (86–98% d.e. **Scheme 14**). The auxiliary **39** can be removed without loss of diastereoisomeric purity, although the yields are not excellent.

Turning away from imines, the SAMP-hydrazones **40** are very useful for highly asymmetric additions of organolithium[61] and organocerium[62] reagents to yield optically active hydrazines (**Scheme 15**). The hydrazines are prone to air oxidation and, hence,



Scheme 14



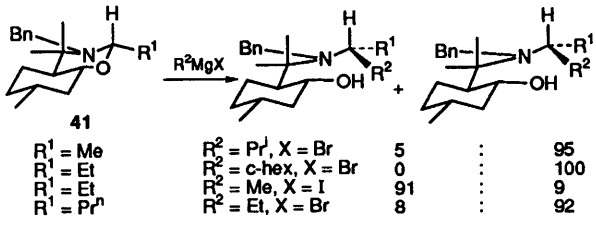
(i) R^2Li/THF, (ii) H_2O	e.e. of amine after reduction:
R^1 = Bu^t, R^2=cyclohexyl	90%
R^1= Bu^t, R^2= Bu^n	93%
R^1= Pr^i, R^2 = cyclohexyl	90%
(i) R^2Li/$CeCl_3$/THF, (ii) $ClCO_2R$	d.e. of carbamates: (R^3 = CO_2R)
R^1 = $PhCH_2CH_2$, R^2 = Me	96%
R^1 = $PhCH_2CH_2$, R^2 = Ph	96%
R^1 = (*E*)-CH_3CH =CH, R^2 = Me	92%

Scheme 15

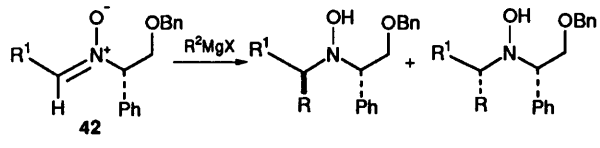
the yields are generally higher for the organocerium protocol, according to which the initially formed metallohydrazines are quenched with methyl or benzyl chloroformate before work-up to obtain the more stable carbamates. The N–N bond is readily cleaved with Raney-Ni without loss of optical purity. If desired, the auxiliary can be recycled.

The chiral 1,3-oxazolidine **41**, easily prepared in two steps from commercially available (+)-pulegone,[63] has been used by Pedrosa *et al.* to prepare aminoalcohols of high diastereoisomeric purity through nucleophilic ring-opening with Grignard reagents.[64] Thus, additions of phenyl and alkyl (Et, Pr^i, Pr^n, Me and cyclohexyl) Grignard reagents proceed with high diastereoisomeric discrimination (**Scheme 16**). When the nucleophile is a bromide-based Grignard reagent, the attack occurs from the nitrogen side of the heterocycle and, surprisingly, when the Grignard reagent is prepared from an alkyl iodide, the nucleophilic attack comes from the opposite side. A non-polar solvent such as hexane gives higher diastereoselectivity than diethyl ether. Removal of the chiral auxiliary is effected in a two-step procedure with high yields (the yield for each step is 96–98%).

Additions of Grignard reagents to the nitrone **42** to yield hydroxylamines (**Scheme 17**) were found to



Scheme 16



Scheme 17

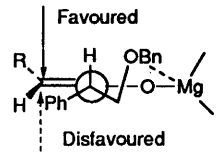
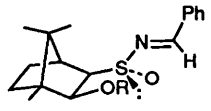


Figure 3 Addition of Grignard reagents to nitrone 42; chelated transition state model[65]

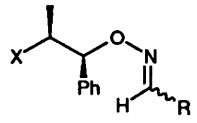
take place with high selectivity in most cases (60–96% d.e.).[65] Notable exceptions are allyl- and (*o*-methoxyphenyl)-magnesium bromides, which give high yields but low selectivity (56 and 59% d.e., respectively) and *tert*-butyl- and isopropyl-magnesium chlorides, where the yields remain low, but the selectivities are respectable (90 and 88% d.e., respectively). The stereochemical outcome was explained by invoking a chelated transition state model (**Figure 3**) which was supported by NMR investigations. Both steric and stereoelectronic

considerations predict nucleophilic attack from the same side. The hydroxylamines from the Grignard additions are converted into carbamates, reduced with lithium in liquid ammonia, cleaved with periodic acid, and hydrolysed with aqueous hydrochloric acid to yield primary amines.

Addition of allyl magnesium bromide to camphor-derived sulfenimines **43** proceeds with high diastereoselectivity (98% d.e.).[66] However, alkyl Grignard reagents show varying degrees of asymmetric induction (20–88% d.e.). Chiral oxime ethers **44**, prepared from ephedrine and norephedrine, undergo 1,2-nucleophilic addition reactions with alkyllithium reagents with 64–88% d.e. The diastereoselectivity was found to mirror the *syn/anti* ratio of the starting oxime ethers.[67]



43 R = benzyl or neopentyl

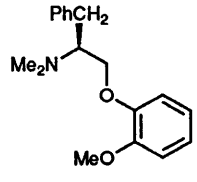


44a X = NMe_2, R = Me, Pr^i or Ph

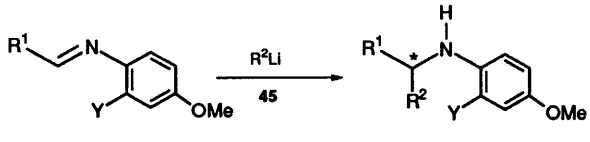
b X = N⬡, R = Pr^i

3.1.2 Alkylations using external chiral auxiliaries

Compound **45** has been used as an external chiral auxiliary in alkylations of *N*-(4-methoxyphenyl) imines with organolithium reagents.[68] When organolithium reagents are added to *N*-*p*-methoxyphenyl-substituted imines in the presence of a stoichiometric amount of **45**, asymmetric addition to the C=N bond is observed. The authors have also shown that it is possible to further enhance the enantioselectivity of the reaction by alkylsubstitution of the *ortho*-position of the *N*-*p*-methoxyphenyl moiety (**Scheme 18**).[69] The



45

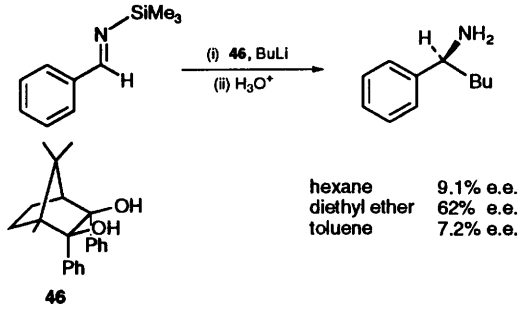


	Y = H	Y = Me
R^1 = Ph, R^2 = Me	75% e.e.	90% e.e.
R^1 = Ph, R^2 = Bu	71% e.e.	70% e.e.
R^1 = Ph, R^2 = vinyl	77% e.e.	90% e.e.
R^1 = PhCH=CH, R^2 = Me	48% e.e.	90% e.e.
R^1 = 1-Naph, R^2 = Me	70% e.e.	78% e.e.
R^1 = 2-Naph, R^2 = Me	74% e.e.	-
R^1 = 1-Naph, R^2 = Bu^n	68% e.e.	-

Scheme 18

p-methoxyphenyl group can be oxidatively removed to produce a primary amine.[70] The N-*p*-methoxyphenyl imine of cinnamaldehyde shows lower enantioselectivity and, interestingly, exchange of the *N*-substituent to cyclohexyl results in 1,4-addition instead of 1,2-addition. When performing the reaction with catalytic amounts of the auxiliary **45**, the asymmetric induction is lower.[71]

Several other chiral additives have been examined in enantioselective alkylations of *N*-(trimethylsilyl) benzaldehyde by Itsuno *et al.* (**Scheme 19**).[72] The chiral dialcohol **46** gives up to 62% e.e. when butyllithium is used in the alkylation of *N*-(trimethylsilyl)benzaldehyde imine, although it is necessary to use four equivalents of the ligand. Surprisingly, the enantioselectivity is substantially lower in non-coordinating solvents such as hexane and toluene.

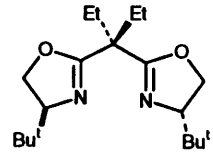


hexane	9.1% e.e.
diethyl ether	62% e.e.
toluene	7.2% e.e.

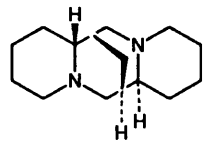
46

Scheme 19

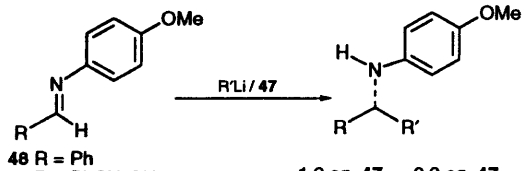
Denmark *et al.* have investigated the bis-isoxazoline **47** (**Scheme 20**).[73] Without the ligand, little or no reaction takes place between methyllithium and **48** at −78 °C, whereas in the presence of **47** the addition is complete after 1 h. Using stoichiometric amounts of **47**, the reaction selectivities are generally good (71–89% e.e.) for additions of methyllithium and vinyllithium to the examined imines. The enolizable imine **49** could be alkylated with a comparable level of enantio-selectivity, using a substoichiometric amount (0.2 eq.) of the bis-oxaline **47**. Lesser selectivity is



47



50



48 R = Ph
49 R = $PhCH_2CH_2$

	1.0 eq. 47	0.2 eq. 47
R'Li = MeLi: **48**	75% e.e.	68% e.e.
R'Li = MeLi: **49**	91% e.e.	82% e.e.
R'Li = CH_2=CHLi: **49**	89% e.e.	82% e.e.

Scheme 20

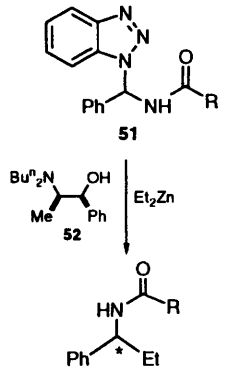
observed in additions of butyllithium (57% e.e.) and phenyllithium (30% e.e.), which is speculated to arise from weaker coordination of these lithium reagents to the ligand. With these reagents, the bidentate tertiary amine (–)-sparteine (**50**)[74] was found to be effective (butyllithium and phenyllithium added with 91 and 82% e.e., respectively).

Unlike lithium reagents, alkylzinc reagents do not react with imines or silylimines in the presence of aminoalcohol promotors and, therefore, imine analogues have to be used together with these reagents. In one approach the *N*-(amidobenzyl) benzotriazoles (masked N-acylimines) **51** are used as substrates (**Scheme 21**).[75] In the presence of (1*S*,2*R*)-(–)-*N*,*N*-dibutylnorephedrine (**52**), diethylzinc can be added with good selectivity (76% e.e. is the highest reported). The yields seem to drop as the selectivity goes up, though. In another approach, the *N*-diphenylphosphinoylimines **53** serve as electrophiles (**Scheme 22**).[76] Hydrolysis of the initial products affords primary amines. The chiral auxiliary used in this study is the chiral aminoalcohol **54**. Using diethylzinc, the alkylation proceeds with good selectivity (75–89% e.e.). Other alkyl groups, such as butyl and methyl, show about the same selectivity, but the yields are lower. When using **54** in catalytic amounts, a considerable drop in selectivity could be noted, although the enantiomeric mixture could be refined by crystallization.

3.2 Electrophilic alkylations

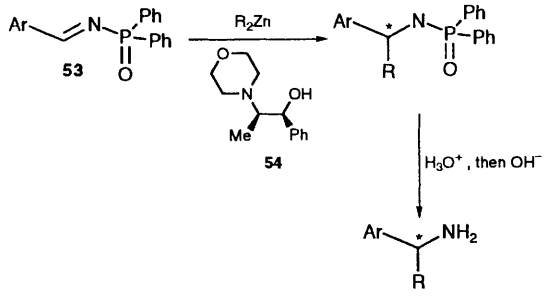
The SAMP-hydrazones **55** (**Scheme 23**), previously mentioned in section 3.1.1, have also been used in diastereoselective electrophilic alkylations.[77] When treated with lithium diisopropylamide and quenched with alkyl halides, these compounds provide a convenient route to β-chiral amines. After reduction of the C=N-bond and cleavage of the chiral 1-substituted pyrrolidine moiety with Raney-Ni/H_2, the resulting amines are produced in 90–95% e.e.

Another paper has dealt with the heterocycle **56** (**Scheme 24**).[78] The carboxylic group in the α-position directs the incoming electrophile to the opposite face of the ring system. Thus, the dianion of **56** yields only one diastereoisomer when treated with methyl iodide or benzyl bromide. In contrast, reaction of dilithiated **56** with benzaldehyde afforded two diastereoisomers in a 1:1 mixture. However, this could be overcome by transmetallation of the dianion with $MgBr_2$-etherate prior to addition of benzaldehyde: only one of four possible diastereoisomers was formed. The product



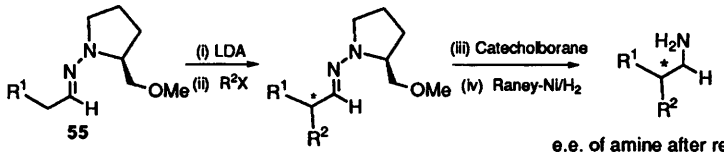
R = Me 46% yield, 76% e.e.
R = Pr^i 80% yield, 41% e.e.
R = Bu^t 96% yield, 0% e.e.

Scheme 21



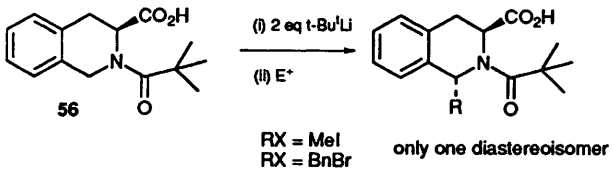
Ar = Ph, R = Et	90% e.e.
Ar = 2-Naphthyl, R = Et	91% e.e.
Ar = Ph, R = Me	85% e.e. (46% yield)
Ar = Ph, R = Bu^n	87% e.e. (56% yield)
Ar = 4-MeC$_6$H$_4$, R = Et	90% e.e.

Scheme 22



	e.e. of amine after reduction:
R^1 = Me, R^2 = n-pentyl	>95%
R^1 = n-pentyl, R^2 = Me	>90%
R^1 = Me, R^2 = benzyl	>90%
R^1 = benzyl, R^2 = Me	>95%
R^1 = Me, R^2 = iso-hexyl	>95%
R^1 = , R^2 = Me	>95%
R^1 = phenyl, R^2 = Me	95%

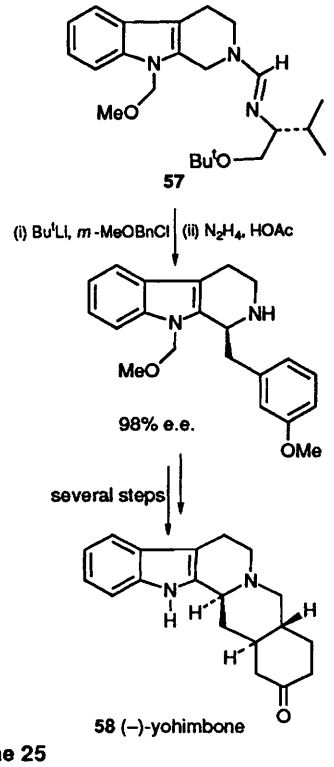
Scheme 23



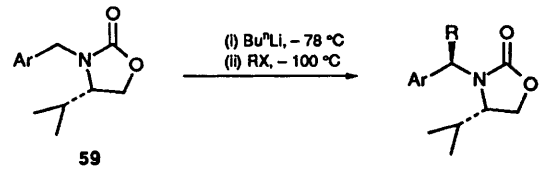
Scheme 24

can be decarboxylated electrochemically. Meyers and co-workers have published several studies of chiral formamidines as vehicles for the production of optically active secondary amines.[79] The strategy has been applied to the total syntheses of morphine,[80] isoquinoline alkaloids[81] and (+)-anisomycin.[82]

In another example, the same group has applied this strategy to the stereoselective alkylation of the formamidine **57** (**Scheme 25**).[83] The anion of **57** is alkylated with 3-methoxybenzyl chloride and the formamidine part removed by treatment of the alkylation product with a mixture of hydrazine–ethanol–acetic acid. The e.e. of the resulting amine is 98%. The cyclic amine is then elaborated into the historically important alkaloid yohimbone **58**. The *N*-benzyloxazolidinone **59** has also been used for asymmetric alkylations.[84] Lithiation of **59** and subsequent treatment with an alkyl halide affords alkylation products with e.e.s between 75% and 99% (**Scheme 26**). Thereafter, the amine is liberated in three steps. In the same paper, electrophilic alkylations of the aminooxazoline **60** are described, but the diastereoselectivity is lower. The auxiliary has been employed for sequential asymmetric alkylations of isoindoline.[85]

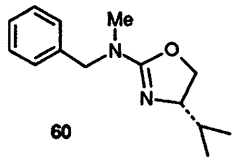


Scheme 25



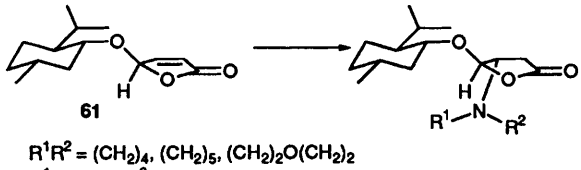
Ar = Ph	RX = MeI	99% d.e.
Ar = Ph	RX = EtI	99% d.e.
Ar = α-naphthyl	RX = MeI	99% d.e.
Ar = Ph	RX = Bu^{n}Br	75% d.e.
Ar = Ph	RX = BnCl	87% d.e.
Ar = *p*-BnOC$_6$H$_4$	RX = BrCH$_2$CO$_2$Bu^t	93% d.e.

Scheme 26



4 Double bond manipulations

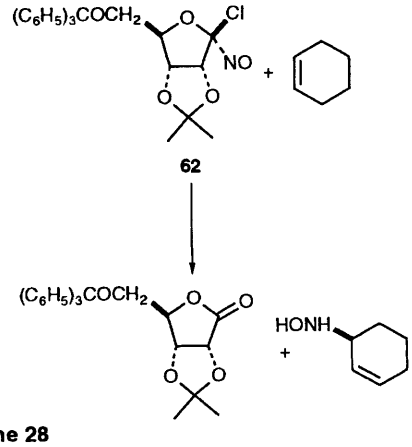
Diastereoselective 1,4-addition of amines to the furanone **61** has been shown to provide aminolactones (**Scheme 27**) which can be reduced to 2-amino-1,4-diols.[86] The addition takes place *anti* to the menthoxy group and proceeds with high diastereoselectivity (more than 96% in all cases studied). Treatment of the adducts with lithium aluminium hydride affords (*R*)-2-amino-butane-1,4-diols in good yields.



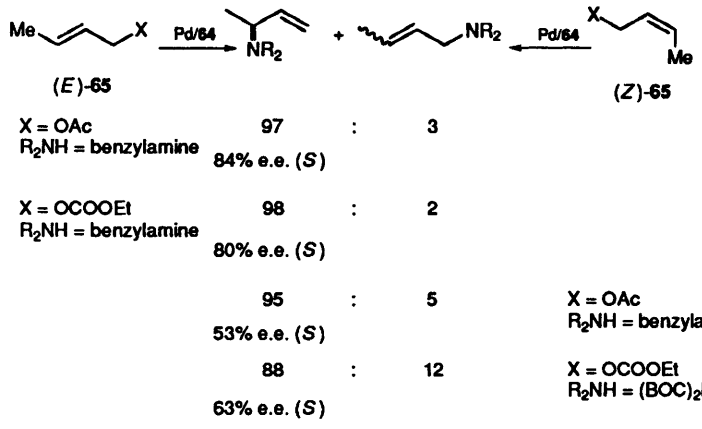
R^1R^2 = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$
R^1 = C_2H_5, R^2 = C_2H_5
R^1 = H, R^2 = n-C_4H_9
R^1 = H, R^2 = $C_6H_4C_2$
> 96% d.e. in all cases

Scheme 27

Both cyclic and acyclic alkenes have been shown to react with the chiral chloronitroso sugar **62** as shown in **Scheme 28**. The resulting hydroxylamines can be reduced to allylic amines.[87] The observed enantioselectivity is generally greater than 80%.

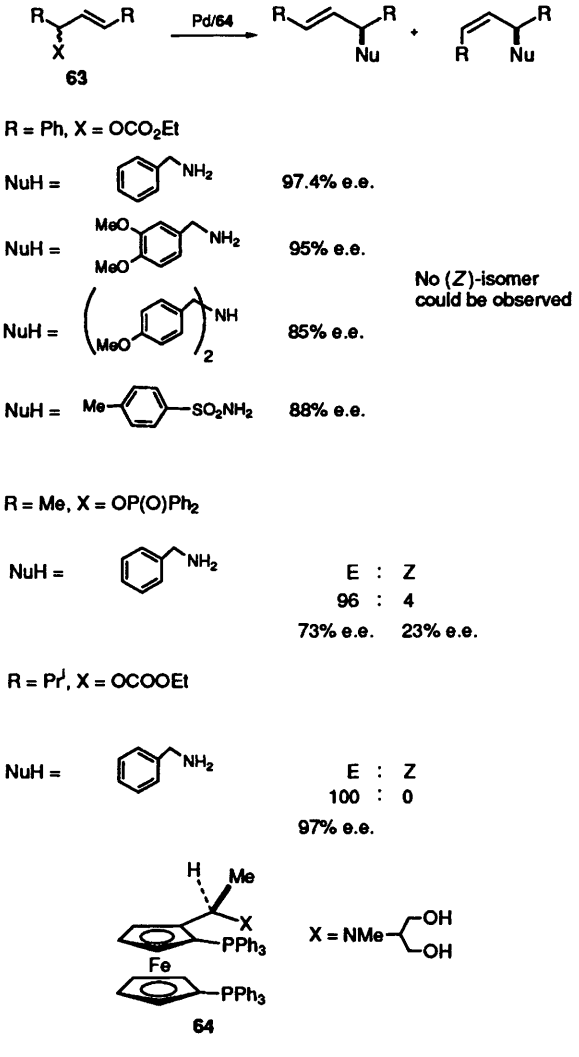


Scheme 28



Scheme 30

Asymmetric allylic amination has also been performed on substrates of the type **63** (**Scheme 29**).[88] The chiral ferrocenylphosphine **64** is used together with Pd to form a chiral π-allyl complex of **63**, which is converted into an optically active allylic amine by nucleophilic attack by a benzylic amine. When the R-groups of **63** are phenyl, the reaction



Scheme 29

proceeds with high enantioselectivity (85–98% e.e.) producing the (*E*)-isomer exclusively. With methyl groups, the enantioselectivity is somewhat lower and small amounts of the (*Z*)-isomer can be detected [73% e.e., 4% (*Z*)-isomer]. For other alkyl groups (Pr^i and Pr^n), the enantioselectivity is again higher (97 and 82% e.e., respectively) and essentially one geometrical isomer is formed.

In a later paper,[89] the authors describe the use of the (*E*)- and (*Z*)-isomers of **65** for the same operation (**Scheme 30**). The nucleophilic attack was found to be γ-selective, leading to the S_N2' products. However, (*Z*)- or (*E*)-geometry around the double bond of **65** does not unambiguously lead to opposite configurations of the chiral carbon produced. Also, the degree of asymmetric induction varies, but is somewhat higher for the reactions performed on the (*E*)-isomer.

Acknowledgement

Several people have read and commented on this manuscript. My gratitude goes especially to Dr Thomas Olsson, Magnus Eriksson, Dr Kaye Stern, and Professor Martin Nilsson for their advice and assistance during the preparation of this text.

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