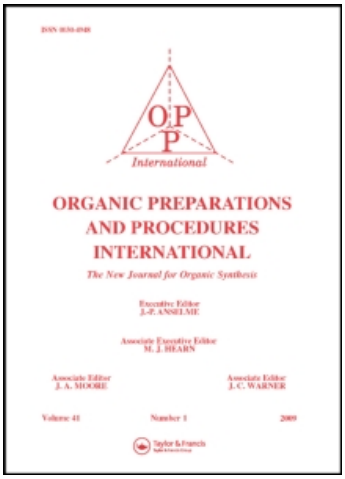

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

ASYMMETRIC REDUCTIONS OF CARBON-NITROGEN DOUBLE BONDS. A REVIEW

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To cite this Article Zhu, Qi-Cong , Hutchins, Robert O. and Hutchins, Marygail K.(1994) 'ASYMMETRIC REDUCTIONS OF CARBON-NITROGEN DOUBLE BONDS. A REVIEW', Organic Preparations and Procedures International, 26: 2, 193 — 235
To link to this Article: DOI: 10.1080/00304949409458026
URL: http://dx.doi.org/10.1080/00304949409458026

ORGANIC PREPARATIONS AND PROCEDURES INT., 26 (2), 193-236 (1994)

ASYMMETRIC REDUCTIONS OF CARBON-NITROGEN DOUBLE BONDS. A REVIEW

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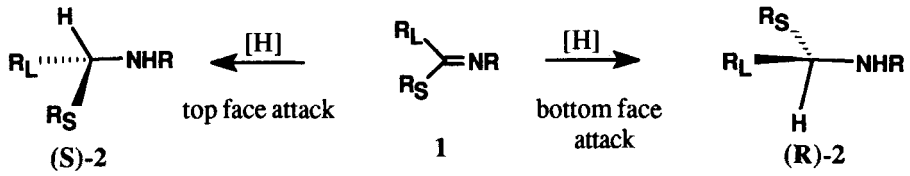
INTRODUCTION

The development of various methodologies for the enantio- and diastereoselective production of amine functionalities remains an active synthetic endeavor since amino groups are ubiquetous in chiral, non-racemic natural products, pharmaceuticals and other physiologically active materials. One important approach to the introduction of such groups involves the asymmetric reduction of heterotopic carbon-nitrogen double bonds to diastereo- or enantioenriched amine or amino acid products (**2**) from a wide variety of related imines, oximes, and other derivatives (**1**).[1]

This review describes the various approaches to asymmetric reductions of carbon-nitrogen π systems (i. e. **Scheme 1**) in which the chiral information is provided by: 1) imines or iminium salts bearing non-racemic stereogenic centers and/or heterotopic faces; 2) covalently bound chiral auxiliary groups or; 3) reagents/catalysts bearing non-racemic stereogenic centers in attached ligands.

Scheme 1



R= a) alkyl; b) R'R'' c) NHR d) OH, OR
e) OCOR; f) POR_2 g) SOR, SO_2R.

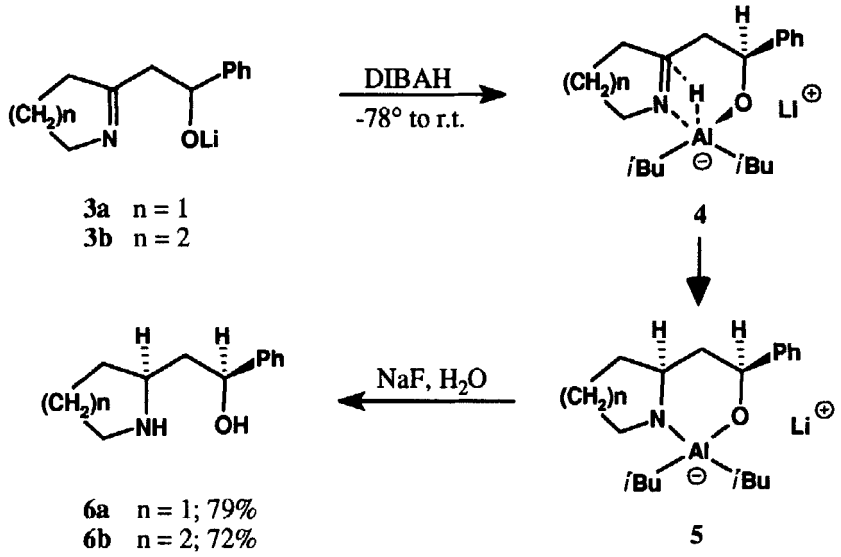
I. REDUCTIONS OF IMINES

A. Diastereoselective Reductions

1. Reductions of Cyclic Imines

An efficient stereoselective synthesis of γ–aminoalcohols has been reported,[2] which was applied to the total synthesis of (±) nor-sedamine **6b** and the pyrrolidino analog **6a**. This protocol employed ligand assisted nucleophilic additions by internal hydride delivery *via* the intermediacy of alkoxide-aluminum hydride complexes (**Scheme 2**).[3,4]

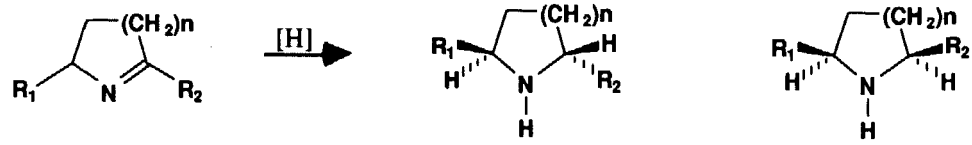
Scheme 2



From a steric standpoint, the internal delivery of hydride to the carbon nitrogen double bond in the chelate **4** leading to **5** occurs from the opposite side of the phenyl group and this led to high 1,3 asymmetric induction in reduction to the corresponding γ-amino-alcohols **6**.

The diastereoselective reduction of 2,5-dialkylpyrrolines **7a-f** and 2,6-dialkylpiperidines **7g-h** played a key role in a synthesis of certain natural insecticides (e.g. **8**, **Scheme 3**). Such reductions are reported to afford 1/1 *cis/trans* mixtures of **8a/9a** with $NaBH_3CN$[5] or to favor the *cis* diastereomer by treatment of **7i** with PtO_2/H_2 (>99%).[6]

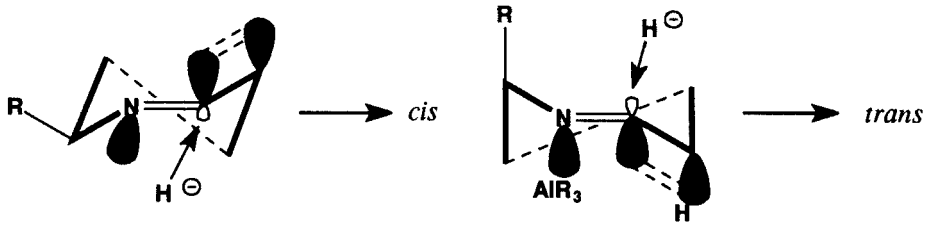
Scheme 3



	n	R_1	R_2
a	1	$-(CH_2)_7-CH=CH_2$	$-(CH_2)_4-CH=CH_2$
b	1	$-(CH_2)_8-Me$	$-(CH_2)_4-CH=CH_2$
c	1	$-(CH_2)_8-Me$	$-(CH_2)_5-Me$
d	1	-Me	$-(CH_2)_8-Me$
e	1	-Me	$-(CH_2)_{14}-Me$
f	1	-Me	$-(CH_2)_9-CH=CH_2$
g	2	$-(CH_2)_{10}-Me$	-Me
h	2	-Me	$-(CH_2)_{10}-Me$
i	1	$-CO_2t-Bu$	$-(CH_2)_6-Me$

In 1982, Yamamoto[7] reported highly stereoselective reductions of the 2,6-dialkylpiperidine **7g** leading to the *cis* piperidine **9g** (>99%) with DIBAH, $LiAlH_4$ (>99%), $NaBH_3CN$/HCl (98%) or to the *trans* isomer **8g** (95%) using $LiAlH_4/Me_3Al$. These results were rationalized as an outcome of a high preference for *anti*-periplaner attack of hydride with respect to the vicinal σ_{C-H} bond to the imino group.[8a,b] Thus, hydride approach to the imino π bond is preferred *trans* to the 5 alkyl group due to stabilization of the σ^* orbital (low-lying vacant imine orbital) *via* electron delocalization from the σ_{C-H} bond into the σ^* bond orbital which gives the *cis* isomer as indicated below (**Scheme 4**). However,

Scheme 4



with a trialkylaluminum reagent present, complexation with the imine nitrogen introduces allylic strain ($A^{1,2}$)[8c] which favors the 5-R axial conformation and hydride attack *cis* to the R group is favored leading to the *trans* isomer.

Lhommet and co-workers[9a] observed the same *trans* stereoselectivity in the reduction of the 2,6-dialkylpiperidine **7h** with $LiAlH_4$-Me_3Al to **8h** (95%) but the reduction of 2,5-dialkylpyrrolidenes with $LiAlH_4$-Me_3Al or DIBAH was found to always yield the *cis* isomers as major products. With 5-membered rings, complexation of Lewis acids (e.g. R_3Al) does not alter the direction of hydride approach since no comparable conformational change is available. Similar *trans* stereoselectivity in the reduction of an analog of **7** (with $NaBH(OAc)_3$) was exploited in route to the ant venom alkaloid xenovenine.[9b]

2-Aza-1,3-dienes react with aldehydes *via* a [4+2]-cycloaddition processes[10,11] to afford 5,6-dihydro-2H-1,3-oxazines **10**. Reduction of **10** with Na/*i*-PrOH in THF at 25° followed by acid hydrolysis led to the 1,3-amino alcohols **11** and **12** as a mixture of diastereoisomers (**Scheme 5**, **Table 1**). Treatment of **10** with $LiAlH_4$ in THF resulted in reductive cleavage to N-alkylated-1,3-amino alcohols **13** in nearly quantitative yields. Among the four possible diasteroisomers, only the ratio of epimers **13a** and **13b** was reported (**Table 1**).

Stereoselective reductions of 3- and 4-substituted cyclohexyl imines with various hydride reagents have revealed that small reagents ($NaBH_4$, $NaBH_3CN$) favor axial approach,[12a] as observed with the corresponding ketones. Likewise, electrochemical reduction provides predominately net hydride deliverance from the axial direction.[12b] However, even moderately bulky reagents [e.g. $NaBH(OAc)_3$, $LiAlH_2(OCH_2CH_2OCH_3)_2$] attack preferentially from the equatorial side in contrast to the results observed for the same reagents with the corresponding ketones. This was interpreted[12a] as implying that additional steric interactions induced by the nitrogen substituents encumber axial attack

by substituted hydride reagents and force approach from the equatorial direction. The very bulky tri-*sec*-butylborohydride anion affords highly stereodiscriminating equatorial attack (>95%). Reduction of 2-alkylcyclohexyl and 2-alkycyclopentyl imines also proceed with high stereoselectivity to give *cis* 2-alkyl cyclic amines with both hindered and unhindered reagents.[12a]

Scheme 5

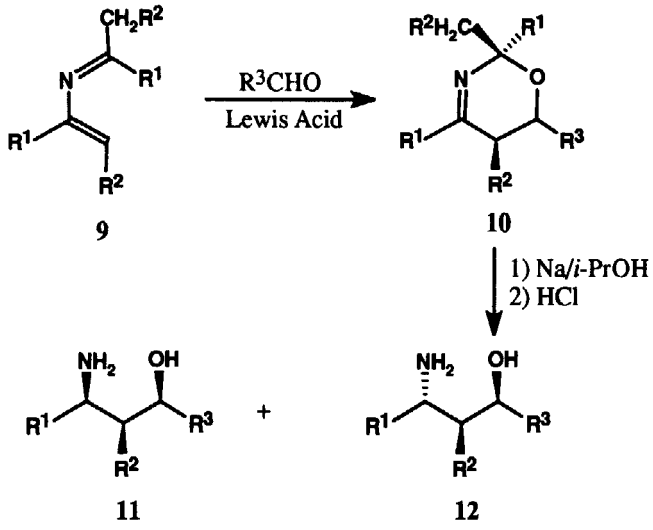
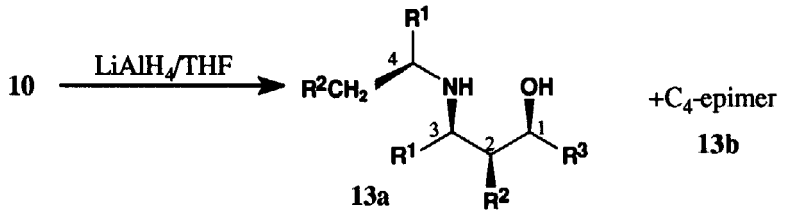


TABLE 1. Reduction of 5,6-Dihydro-2H-1,3-Oxazines **10** with Hydride Reagents.



Entry[a]	R^2	R^3	yield (%)[b]	**11/12**	yield (%)[c]	**13a/13b**
1	Me	Ph	99[d]	61/39	95	90/10
2	Me	2-thienyl	100	59/41	93	87/13
3	Me	PhCHMe	98	60/40	90	81/19
4	Et	Ph	97	65/35	98	89/11

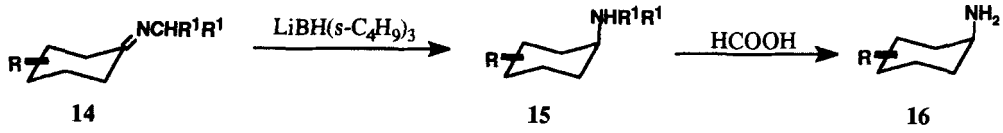
a R^1 = Ph. b) Reduction with Na/*i*-PrOH/THF, at 25° c) Reduction with $LiAlH_4$/THF/reflux d) Reduction with Na/*i*-PrOH/THF, at -30°, **11/12** = 76/24

Subsequently, the reductions of *p,p'*-dimethoxybenzhydryl imines of 2-alkyl (**14a**), 3-alkyl (**14b**) and 4-alkyl cyclohexanones (**14c**, **Scheme 6**) with the highly hindered reagents lithium tri-*sec*-butyl- or triethylborohydride were disclosed[13] to provide highly stereoselective (>90%) routes to axial secondary amines[12a] (**15a-c**). Subsequent cleavage of the resulting secondary amines with formic acid

affords the corresponding axial cyclohexyl primary amines **16a-c** in high yields. A predominance of axial amine diastereomers is also obtained using hindered alkylcyanoborohydride with substituted cyclohexyl systems.[14]

Related studies[15] found that the reduction of the bicyclic imine **17** (**Scheme 7**) with Li/CH_3NH_2 or lithium tri-*sec*-butylborohydride produced the amine **18b** with 99% diastereoselectivity ($LiAlH_4$ and $NaBH_3CN$ afforded 1/1 ratios of **18a** and **18b**). Likewise, reduction of imine **19** with Li/CH_3NH_2 probably yielded **20b** with 90% stereoselectivity.[15a] Since both bicyclic imines **17** and **19** are conformationally labile, the stereochemical course of reduction in these instances is ambiguous. However, the stereoselectivities can be rationalized as due to expected equatorial attack[16] on the conformations of **17** and **19** which provide access to the convex faces of the molecule.

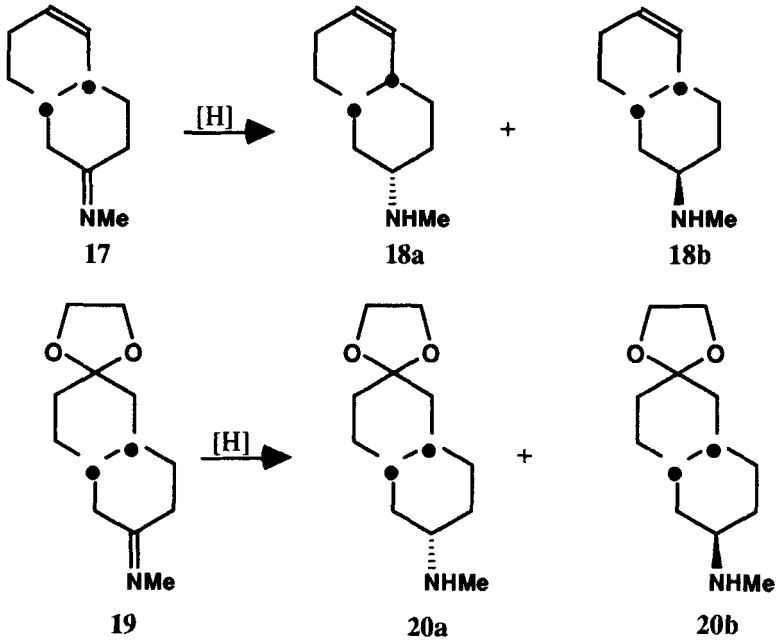
Scheme 6



14 **15** **16**

	R	R^1
a	2-Me	p-C_6H_4-OMe
b	3-Me	p-C_6H_4-OMe
c	4-*t*-C_4H_9	p-C_6H_4-OMe
d	4-Me	p-C_6H_4-OMe

Scheme 7

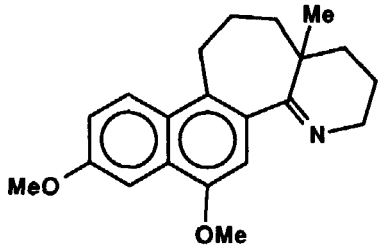


17 **18a** **18b**

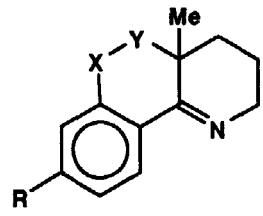
19 **20a** **20b**

Another category of diastereoselective *exo*-imine reductions involves those also contained within a cyclic structure such as found in certain tetrahydropyridine derivatives (e.g. **21** and **22**, **Figure 1**).[17,18] The stereoselectivity obtained (at the ring-fusion of the *trans* and the *cis* amines) upon reduction of such derivatives vary greatly with the reducing system. Thus, Pd-C/H_2 and PtO_2/H_2 afforded only the *trans* amines with **21** and **22**, while $LiAlH_4$ reduction of **21** and **22a-f** gave the

Figure 1



21



22a-g

22	R	X	Y
a	OMe	CH_2	$(CH_2)_2$
b	H	CH_2	$(CH_2)_2$
c	OMe	O	$(CH_2)_2$
d	H	O	$(CH_2)_2$
e	H	S	$(CH_2)_2$
f	OMe	CH_2	CH_2
g	H	S	CH_2

cis isomers predominantly, with **21**, **22a**, and **22b** giving only the *cis* stereoisomers. On the other hand, $NaBH_4$ stereoselectively reduced **22a**, **22b**, **22f**, and **22g** to the *trans* isomers and also Na/NH_3 afforded predominantly the *trans* isomers with the oxygen containing derivatives **22c** and **22d**.

2. Reductions of Acyclic Imines

A fruitful approach to the synthesis of acyclic 2-amino alcohol diastereomers involves reaction of silylether protected cyanohydrins (**23**) with Grignard reagents to generate intermediate metalloimines which are subsequently reduced with $NaBH_4$ or $Zn(BH_4)_2$ to diastereomeric hydroxyamines **24** (**Scheme 8**).[18]

The *erythro* diastereomers are obtained predominately (**Table 2**), which was rationalized as involving a chelated intermediate as indicated in **Scheme 8**.[18a] The selectivity observed appears to be solvent dependent in that $NaBH_4$ gives higher *erythro/threo* ratios in CH_3OH than in ether,[18a,c] while the opposite is observed with $Zn(BH_4)_2$.[18b] Likewise, alkylimines corresponding to **23a** are also reduced to N-alkylaminoalcohols with high diastereoselectivity with $Zn(BH_4)_2$.[18b]

Scheme 8

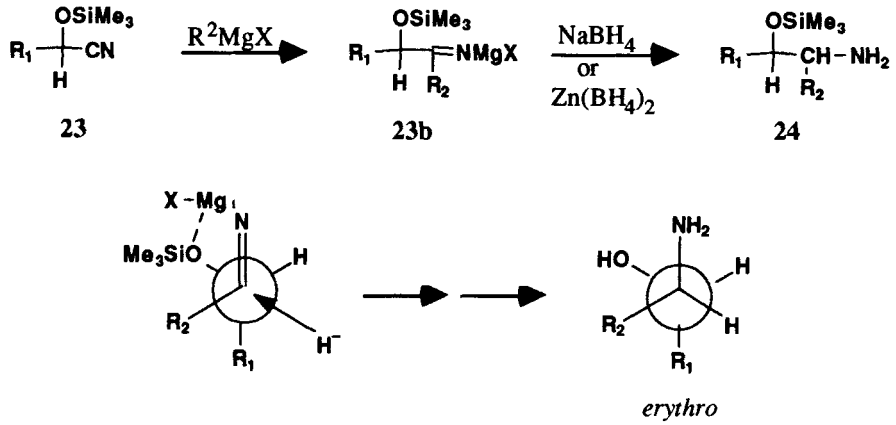


TABLE 2. Reduction of Trimethylsilyl–Protected Cyanohydrins **23.**

23	R^1	R^2	Reducing Agent	24, Ratio erythro/threo	Ref.
a	$-C_6H_5$	$-C_6H_5$	$NaBH_4$, MeOH, rt	16	18a
a			$NaBH_4$, ether, -78°	7	18b
a			$Zn(BH_4)_2$, ether, -78°	100	18b
b	$3,4\text{-}(MeO)_2C_6H_3$	-Me	$NaBH_4$, MeOH, -78°	24	18a
b			$Zn(BH_4)_2$, MeOH, -78°	13	18a
c	$4\text{-}MeC_6H_4$	$-C_6H_5$	$Zn(BH_4)_2$, ether, -78°	100	18b

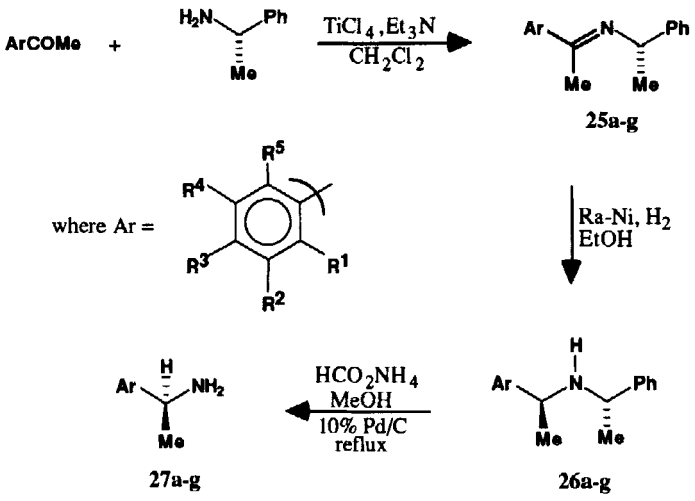
3. Using Chiral Auxiliary Groups

The formation of chiral, enantioenriched imines by the utilization of optically active amines, and subsequent reduction of the diastereotopic imine faces with achiral reagents provides a powerful method for introduction of new stereogenic centers, often with high diastereomeric excesses. New, optically active amines are then obtained by removal of the chiral auxiliary group. Thus, an efficient method for the asymmetric synthesis of chiral 1-arylethylamines, in essentially two steps has been reported[19a] in which substituted acetophenones were reductively aminated with optically active 1-phenylethylamine, *via* the corresponding imines **25b-g**. These could be directly hydrogenated with high diastereoselectivities to the secondary amines **26** (73-83% yields), and cleaved with surprisingly high regio-selectively by hydrogenolysis, leading to the desired primary amines **27** in 93-98% yields (86-97 %e.e., **Scheme 9**). The (S)-configuration of 1-phenylethyl amine induced the (S)-configuration of the product while the (R)-amine induced the (R) products. Lower optical purities resulted[19a] when the hydrogenation of imine **25a** was conducted with $CoCl_2/NaBH_4$ (74% e.e.) or $Pd/C/H_2$ (76% e.e.). Similarly, trifluoromethyl acetophenone was converted to the trifluoromethyl derivative of **27** in 80% e.e. *via* reduction of the corresponding chiral 1-phenylethyl imine. In this case, reduction was accom-

plished using $NaAlH_2(OCH_2CH_2OMe)_2$ followed by catalytic debenzylation.[20]

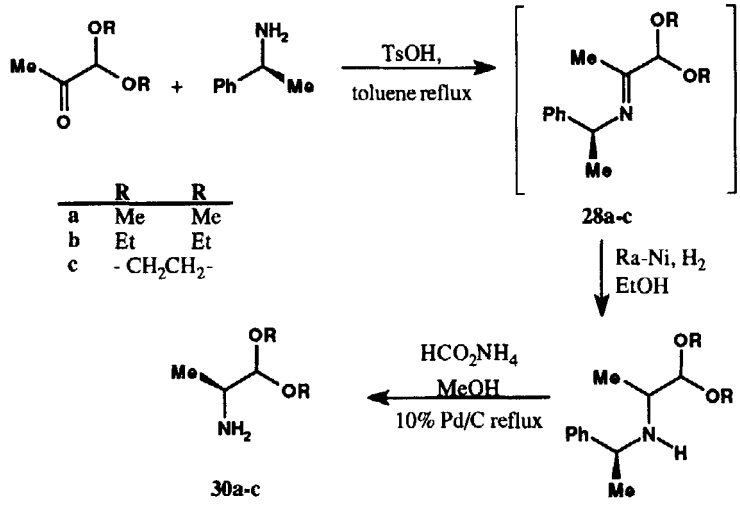
Likewise, enatiomerically pure (**R**)- or (**S**)-1,1-dialkoxy-2-propanamines **30** (>95% e.e.) were obtained[21] by asymmetric reduction of chiral imines **28a-c** (**Scheme 10**) prepared from 1,1-dialkoxy-2-propanones, using (**R**)- or (**S**)-1-phenylethylamine.

Scheme 9



	R^1	R^2	R^3	R^4	R^5
a	H	H	H	H	H
b	Me	H	H	H	OMe
c	OMe	OMe	OMe	H	H
d	H	OMe	OMe	OMe	H
e			OMe	H	H
f	OPr	OMe	OMe	H	H
g	OH	OMe	OMe	H	H

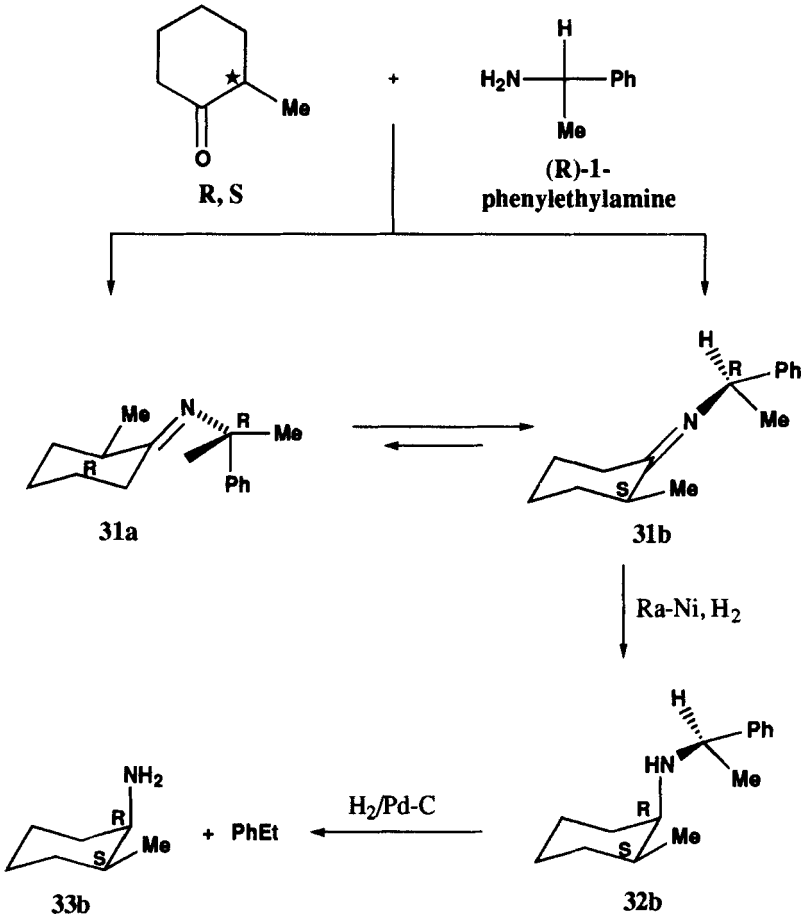
Scheme 10



	R	R
a	Me	Me
b	Et	Et
c	- CH_2CH_2-	

An asymmetric synthesis of 2-substituted cyclohexylamines was obtained from the corresponding racemic ketones by means of reductive amination in a three step procedure.[22,23] Thus, condensation of 2-alkylcyclohexanones with optically active 1-phenylethylamine yielded mixtures of imines **31a** and **31b** which were hydrogenated over Raney nickel to give essentially only one, optically active, diasteromerically enriched *cis* secondary amine (**32b**). Hydrogenolysis over Pd/C led to highly enantiomerically enriched *cis* primary amines **33b** in good yields (**Scheme 11**). These results require that an asymmetric interconversion of the diastereomeric imines (**31a**, **31b**) occurs prior to hydrogenation and that either the diastereomer **31b** is greatly favored at equilibrium or that the reduction rate of **31b** (or the conformational isomer) is much faster than for **31a**.

Scheme 11

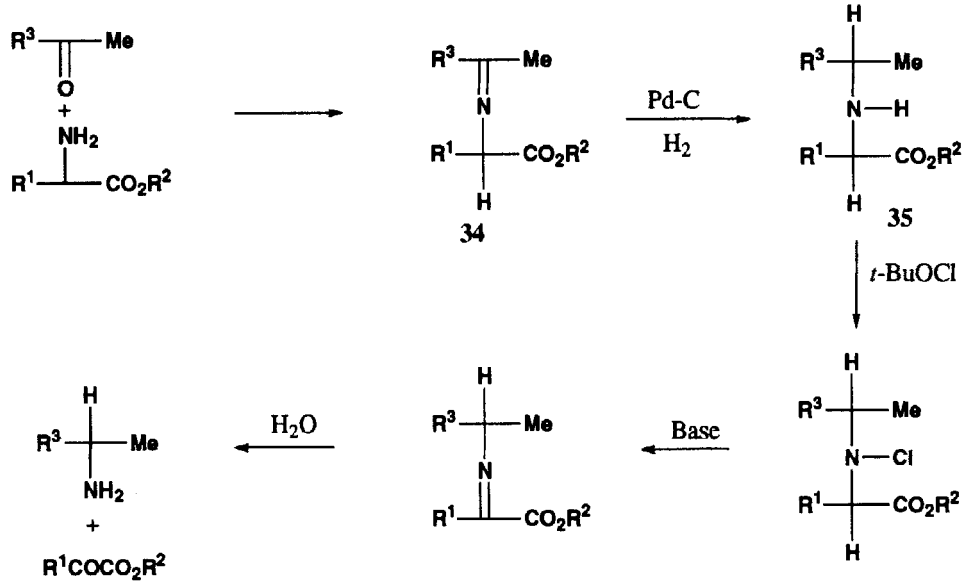


The use of optically active 1-phenylethylamine as a chiral auxiliary group has also been successfully applied to the synthesis of steroidal amines *via* reduction of corresponding imines with BH_3 and subsequent catalytic hydrogenolysis.[23a] In addition, the same chiral auxiliary group has been

utilized to prepare acyclic amine diastereomers *via* reduction with H_2/Pd, $LiAlH_4$ and $NaBH_4$.[23b]

Readily available optically active amino acids also may serve as effective chiral auxiliaries.[24] Thus, imines **34** (**Scheme 12**) were prepared from the reaction of optically active amino acid esters with ketones, and reduced by catalytic hydrogenation (5% Pd/C) in ethanol. A new stereogenic center is produced by 1,3 asymmetric induction to afford diastereo-isomeric mixtures of **35** which were cleaved by treatment with alkaline *t*-butyl hypochlorite, and subsequently hydrolyzed to give optically active amines **36** in enantiomeric excesses of 49-87%. With L-amino acid esters, the absolute configurations of the amines obtained were S. Best results were obtained when the ester alcohol was bulky (e.g. with O-*t*-Bu).

Scheme 12



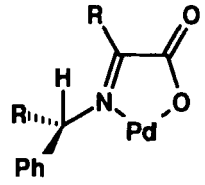
R^1	CH_2Ph	CH_2Ph	Me	*i*-Pr	CH_2CH_2OCOEt
R^2	Me	Et	*t*-Bu		
R^3	Ph	CH_2Ph			

Sheehan[25] and Hiskey[26] demonstrated the synthesis of optically active amino acids in 12-80% e.e. by catalytic hydrogenation of the imines formed from α-keto acids and (**R**)-(+)- and (**S**)-(−)-1-phenylethylamine followed by hydrogenolysis. Kanai and Mitsui[27] applied this technology using (**R**)-(+)- and (**S**)-(−)-1-phenylpropylamine to obtain optically active alanine (51-67% e.e.), α-amino-n-butyric acid (33-39% e.e.), phenylglycine (24-30% e.e.), phenylalanine (10-14% e.e.), and glutamic acid (6-12% e.e.). The results indicated that the optical induction obtained in the α-amino acids decreased in the order: Me> Et> Ph> CH_2Ph> $CH_2CH_2CO_2H$.

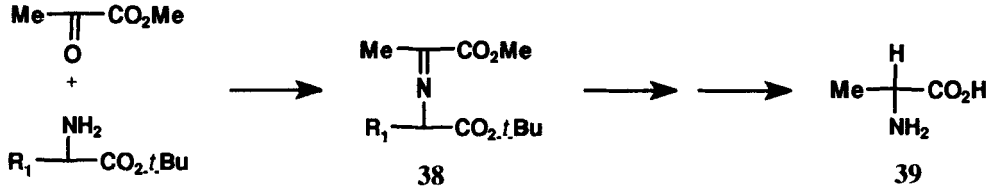
The steric course of catalytic hydrogenation was rationalized to occur by formation of a five-membered ring chelation structure (e.g. **37**)[28] with subsequent hydrogenation taking place from the less bulky side of the chelated substrate. This mechanism was supported by the results of various hydrogenolytic catalytic asymmetric transaminations.[29,30] Solvent effects in the hydrogenolytic asymmetric transaminations of α-keto acids with optically active 1-alkylbenzylamines has also been studied.[31]

Likewise, sterically controlled syntheses of optically active α-amino acids were obtained from the corresponding α-keto acids and optically active phenylglycine (40-60% e.e.),[32] or from α-keto acid esters **38** and L-amino acid *t*-butyl esters (**Scheme 13**, 53-71% e.e.)[33] by reduction with Pd-C/H_2. The results are explained by the same chelation model **37** based on initial substrate-catalyst complexation.[34] Diastereoselective reduction of cyclic imines has also been utilized to prepare the useful optically active bicyclic amines **41** and **43**.

Figure 2



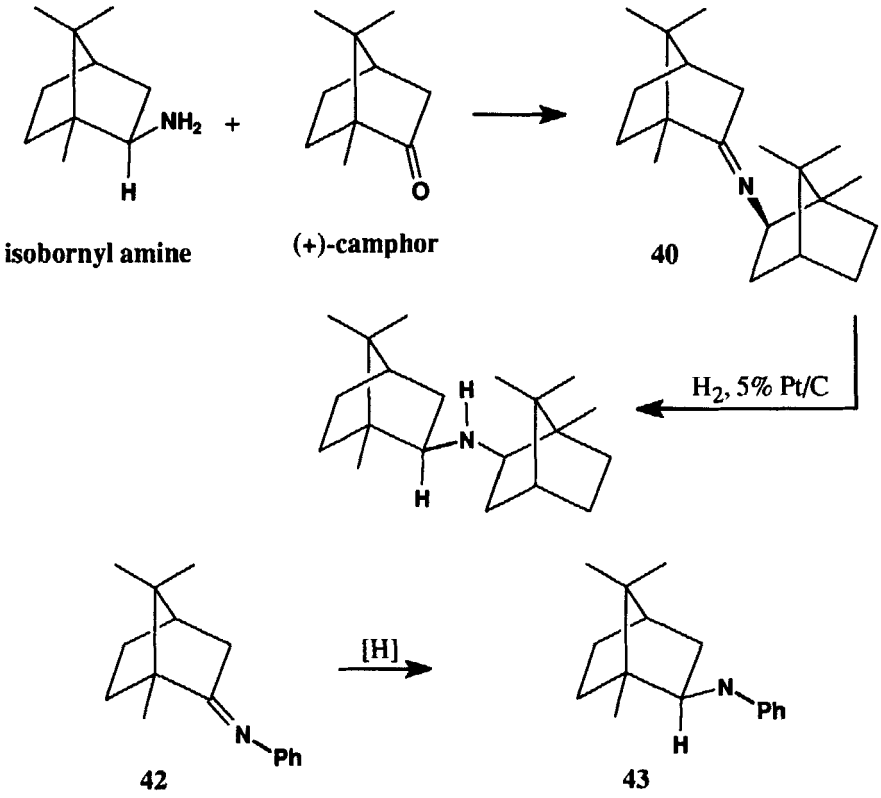
Scheme 13



R^1 =	*i*-Pr	-CH_2Ph
	-CH_2CHMe_2	-CH_2OCO-*t*-Bu
	-CH_2CH_2OCO-*t*-Bu	

Thus, condensation of isobornyl amine with (+)-camphor (**Scheme 14**) in the presence of titanium tetrachloride afforded imine **40**.[35,36] Catalytic hydrogenation of this imine gave diisobornyl amine **41** in 88% yield.[37] Likewise, isobornyl aniline **43** was obtained[20] in 74% yield by reduction of the camphor-anil **42** with $CoCl_2$/$NaBH_4$/MeOH.

Scheme 14



isobornyl amine (+)-camphor 40 42 43

B. Enantioselective Reductions

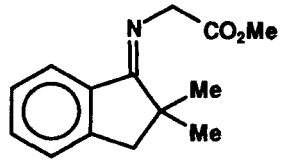
1. Reductions with Chiral, Enantioenriched Catalysts

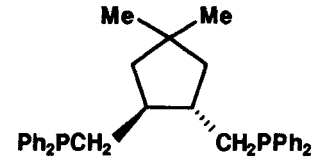
The asymmetric reduction of imines with enantiotopic faces using optically active catalysts or reagents conceptually provides a valuable protocol to enantiomerically enriched amines. Several approaches are described in this section.

The imines $ArC(Me)=NCH_2Ph$ **44a-c** (Ar=Ph, $2\text{-}MeOC_6H_4$, $4\text{-}MeOC_6H_4$) were hydrogenated to the corresponding secondary amines (1000 psi H_2, –25°) using an *in situ* generated chiral RhI(R)-cyclophos system[38] [cyclophos=$Ph_2PCH(C_6H_{11})CH_2PPh_2$]; a maximum of 91% e.e. (**45c**) was achieved in the presence of iodide as a co-catalyst. However, this catalyst system was not effective for asymmetric hydrogenation of dialkyl prochiral imines.

Hydrogenation of the prochiral faces of imine **46** (**Figure 3**) with Pd/H_2 in the presence of an iridium catalyst modified with the chiral phosphine ligand DIOP (**Figure 3**) yielded the corresponding optically active secondary amine (configuration not specified) with 23% enantiomeric excess and 99% conversion.[39]

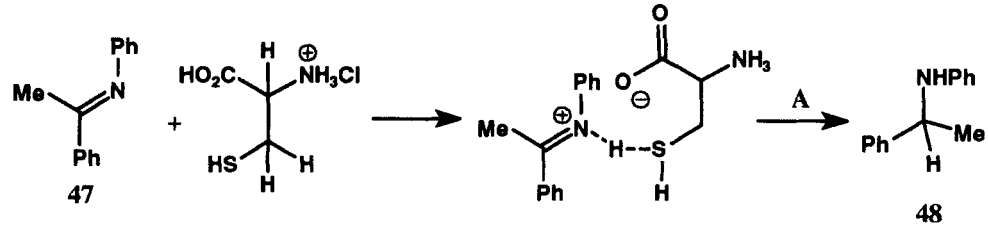
Figure 3

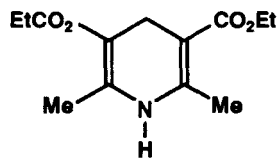




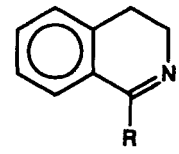
The prochiral imine **47** could be reduced by 3,5-dicarboethoxy-1,4-dihydro-2,6-dimethylpyridine (**Scheme 15**, **A** was used as the 1,4-dihydropyridine to mimic NADH) in the presence of optically active α-amino acid hydrochlorides, camphor sulfonic acid, abeitic acid, or tartaric acid to give amines with varying degrees of enantiomeric excesses (2.4-62% e.e.). The best result (62% e.e.) was obtained using an α-amino acid with side chain carrying a group capable of H-bond formation (e.g. L-cysteine·HCl, **Scheme 15**), and this was employed to prepare the isoquinoline alkaloids **50a,b** in up to 65% enantiomeric excess from the corresponding imines **49**.[40a]

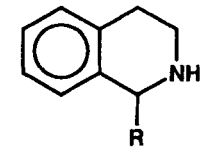
Scheme 15





A





49a-b **50a-b**

	R
a	CH_3
b	3,4-methylenedioxyphenyl

Horner and Skaletz[40b] investigated the electrochemical reduction of imines to the corresponding chiral amines. Asymmetry was induced by use of various chiral salts derived from ephredrine, pseudoephedrine and deoxyephedrine derivatives as electrolytes. Although chemical yields generally were in the 60-80% range, the best enantiomeric excess was 11% with the average being about 5%.

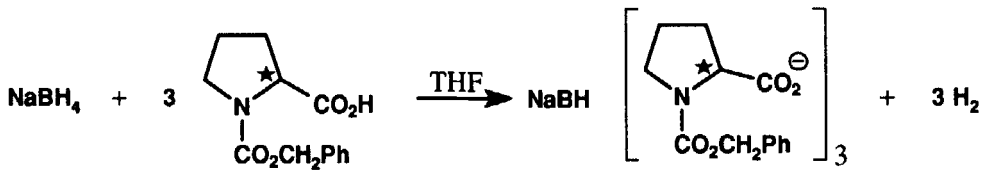
Chiral amines were produced in poor to moderate enantiomeric excesses (3-50% e.e.) by the hydrosilation of prochiral imines in the presence of [Rh-(+)-DIOP] as catalyst at ambient temperature.[40c] The induction was enhanced to 65% e.e. by lowering the temperature to 2°.

2. Reductions with Chiral Metal Hydride Reagents

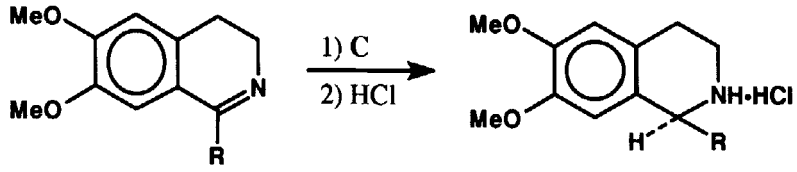
The incorporation of stereogenic, non-racemic fragments into hydride reducing reagents offers another attractive approach for the asymmetric reduction of imines bearing prochiral faces. Thus, Grundon and co-workers[41] reported that lithium alkyl(hydro)dipinan-3α-yl borates reduce prochiral cyclic imines asymmetrically, but in only 4-25% enantiomeric excesses. Improved results for optically active alkaloids [**52a** (60% e.e.), **52b** (70% e.e.), and **52c** (86% e.e.)] were obtained by Yamada and co-workers[42a,b] using chiral sodium triacyloxyborohydrides (**B, Scheme 16**). A solvent effect was observed in that reductions with halogenated alkanes (*e. g.* dichloromethane or 1,1-dichloroethane), afforded the best enantiomeric excesses of **52a** (70% e.e.).

Reagents prepared from reaction of $LiAlH_4$ with (–)-menthol or (+)-borneol were used to reduce several aliphatic imines to the corresponding amines, but the enantiomeric excesses obtained were low (i.e. 1.8-9.9% e.e.).[42c] Also, the use of optically active α-phenylethylamine-borane complex for the reductive amination of prochiral ketones to produce chiral amines has also been investigated but gave very low enantioselectivities (1.1-1.6% e.e.).[42d]

Scheme 16



B

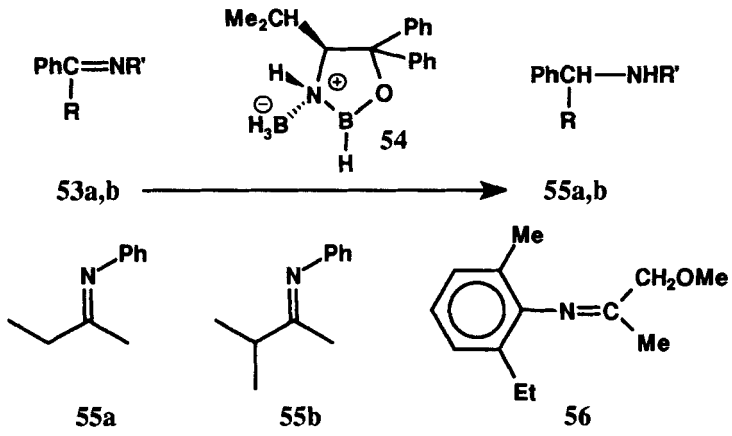


51 **52**

	R
a	3,4-methoxyphenyl
b	Me
c	3,4-methylenedioxyphenyl

A series of N-substituted aryl ketimines **53** were sucessfully asymmetrically reduced to the corresponding amines in excellent yields (87-98%) and generally good enantiomeric excesses (46-88% e.e., R configurations)[42e] using the chiral borane reagent **54**[42f] (**Scheme 17**). Reduction of N-substituted alkyl ketimines **53a** and **53b** with **54** was less effective, and afforded the corresponding amines **55a** and **55b** in 9 and 14% e.e., respectively.[42e] The process has been utilized to reduce **56** enroute to the herbicide metolachlor.[43g]

Scheme 17



3. Enzymatic Reductions

Although few synthetically useful enzymatic, enantioselective reductions of imines are available,[43] a large scale process for the reductive amination of 2-oxo-4-methylpentanoic acid to L-leucine has been disclosed. This involves use of L-leucine dehydrogenase coupled with a co-enzyyme (NADH) covalently bound to polyethylene glycol to enable recyclization.[43a]

II. REDUCTION OF IMINIUM SALTS

A. Diastereoselective reductions

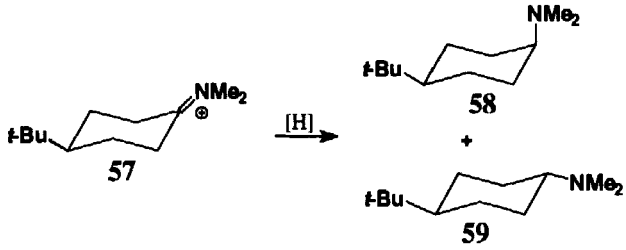
1. Reductions of Cyclic Iminium Salts

The reduction of heterotopic faces of iminium salts represents another approach for the asymmetric production of amine stereoisomers. In fact, the increased electrophilicity of the iminium ion carbon, compared to imines, enhances the rates of nucleophilic hydride attack. Iminium salts[44] are readily prepared from ketones or aldehydes and amine salts.

Diastereoselective reduction (**Table 3**) of 4-substituted cyclohexyl iminium salts (**57**) with various hydride reagents affords essentially the same stereoselective results as the previously discussed reduction of the corresponding 4-substituted cyclohexyl imines.[12a] Thus, "small" reagents (e.g. $NaBH_4$,[12a] $LiAlH_4$[45]) afford predominantly axial attack to give equatorial tertiary amines (or no selectivity, e.g. $NaBH_3CN$[12a]) while even moderately bulky reagents show high preference for equatorial attack leading to axial isomers.[12a] This same preference for equatorial approach is observed in reductive aminations (which proceed through iminium ions) of 4-*t*-butylcyclohexanone using $(n\text{-}Bu)_4BH_3CN$,[12e] $NaBH(OAc)_3$[12c] or Na-9-BBNCN-H[14] while essentially no selectivity is observed with $NaBH_3CN$.[12d]

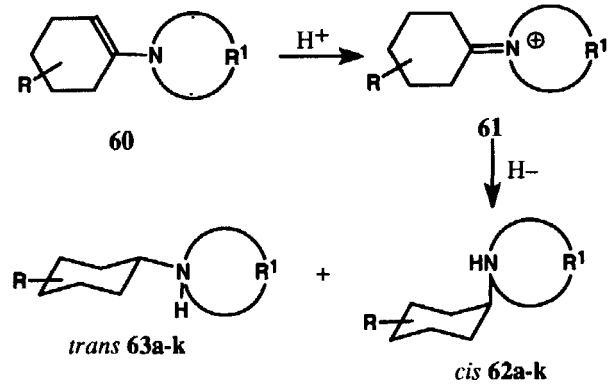
Similarly, reduction of iminium salts of 4-*t*-butylcyclohexanone with an NADH model (*e.g.* **A**), in which hydride is transferred from the 4-position of a 1,4-dihydropyridine, results in approach predominantly from the equatorial side to give 73-95% of the *cis* isomer.[46] In addition, reduction of

TABLE 3. Reduction of Iminium Salt **57** with Hydride Reagents



Hydride Reagent	Solvent	Yield (%)	**58/59**	Ref.
$NaBH_4$	*i*-PrOH	70	16/84	12a
$LiAlH_4$	-	-	10/90	46
$NaBH_3CN$	MeOH, H^+	75	42/58	12a
t-$BuNH_2BH_3$	$MeCO_2H$	85	51/49	12a
$(MeOCH_2CH_2O)_2AlH_2/Na$	THF	74	72/28	12a
Hantsch Ester	MeCN	-	75/25	45
$LiBH(sec\text{-}Bu)_3$	THF	76	94/6	12a

Scheme 18



trans **63a-k**

cis **62a-k**

	R	R^1
a	2-Me	$-(CH_2)_4-$
b	2-Me	$-(CH_2)_5-$
c	2-Me	$-CH_2CH_2OCH_2CH_2-$
d	2-Et	$-(CH_2OCH_2-$
e	2-cyclohexyl	$-(CH_2)_4-$
f	3-Me	$-(CH_2)_4-$
g	3-Me	$-(CH_2)_5-$
h	4-Me	$-(CH_2)_4-$
i	4-Me	$-(CH_2)_5-$
j	4-*t*-Bu	$-(CH_2)_4-$
k	4-*t*-Bu	$-(CH_2)_5-$

enamines (**60a-k**) in acidic media (which proceed through iminium ions, (**Scheme 18**), also essentially mimic results with 2-, 3-, and 4-substituted imines examples (**Table 4**).[12a]

Stereoselective reductions of other enamines, including indoles, and iminium salts with borohydride reagents in carboxylic acid solvents have been reviewed.[46e]

2. Using Chiral Auxiliary Groups

The reductions of the chiral iminium ions **64a-c** to the diastereomers **65a** and **65b** have been described.[47] The results indicated that the preferred conformation is that in which the *re* diasteroface (bottom face in **64**) is less hindered to nucleophilic approach than the *si* (top) face.

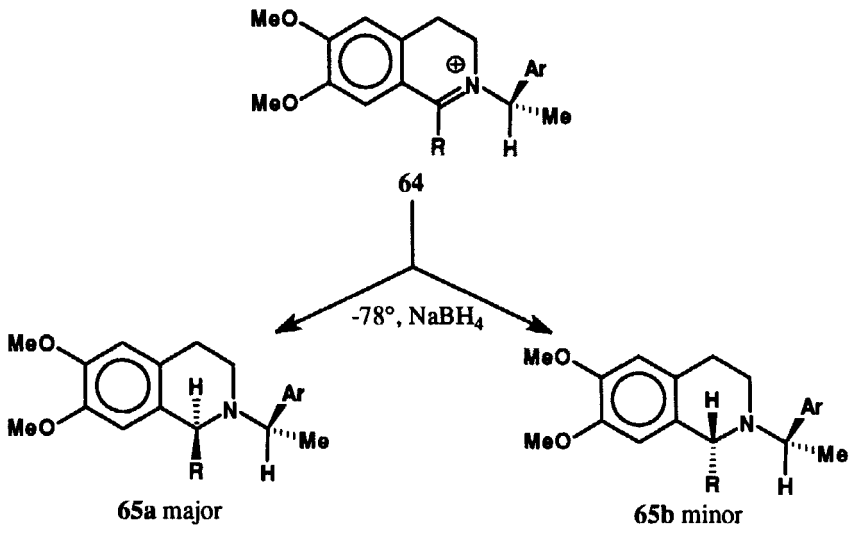
TABLE 4. Reduction of Enamines (**60a-k**) with Hydride Reagents in Acetic Acid[12a]

	Ratio of **62/63** (yield %)				
60	$NaBH_4$	$NaBH_3CN$	NH_3BH_3	*t*-$BuNH_2BH_3$	*i*-Pr_2NHBH_3
a	–	66/34 (75)	66/34 (59)	68/32 (73)	70/30 (85)
b	82/18 (63)	79/21	80/20	80/20	72/18
c	82/18 (63)	82/18 (82)	80/20 (85)	80/20 (85)	74/26 (70)
d	–	82/18	81/19	82/18 (60)	68/32
e	–	–	72/28	94/6	96/4
f	–	74/26 (86)	86/14 (87)	89/11 (84)	81/19 (78)
g	86/14	83/17	88/12	92/8	88/12
h	–	84/16 (80)	80/20 (60)	82/18 (84)	71/29 (50)
i	79/21	77/23	84/16	86/14 (80)	82/18
j	72/28 (78)	79/21 (86)	83/17 (89)	87/13 (89)	74/26 (87)
k	–	86/14 (75)	89/11	91/9	88/12

Thus highly diastereoselective hydride reductions (up to *ca.* 100% selection of the major isomer **65a**) were obtained to give chiral, enantioenriched 1-substituted tetrahydroisoquinolines **65a** and **65b** (**Scheme 19**). Hydrogenolysis of **65a** and **65b** was accomplished by treatment with H_2 and 10% Pd/C in acidic EtOH-EtOAc, to afford the corresponding enantioenriched secondary amines.

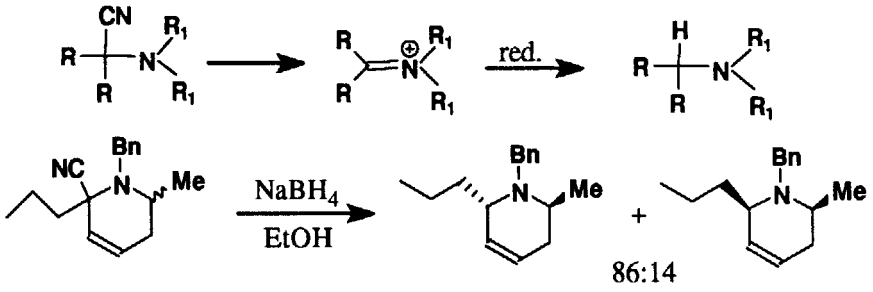
Iminium salts may also be generated and reduced *in situ* by treatment of α-cyanoamines with a variety of hydride reagent systems (e.g. $LiAlH_4$/THF[48a], $NaBH_4$/EtOH,[48b] $Zn(BH_4)_2$/EtOH[48c] or THF[48c,d], $AgBF_4$[48d], AlH_3/ether). The process can occur with high stereoselectivity as illustrated in **Scheme 20**.

Scheme 19



Ar = phenyl, 2-chlorophenyl, 2,6-dichlorophenyl
R = Me, Et, *i*-Pr, 3,4-DMB

Scheme 20



III. REDUCTIONS OF HYDRAZONES AND RELATED DERIVATIVES

A. Diastereoselective Reductions

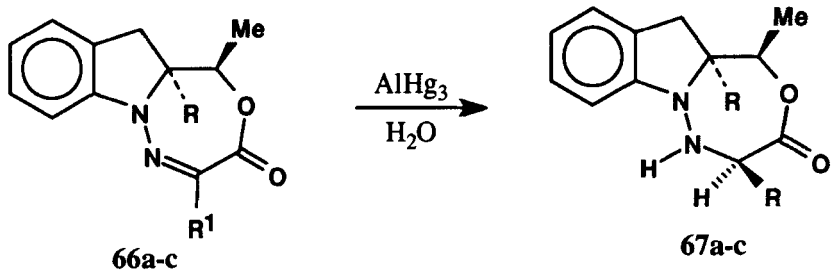
1. Reductions of Chiral Substrates

Asymmetric synthesis of α-amino acids *via* reduction of the chiral hydrazono lactones **66a-c** to the desired products **67** has been described[49a] using aluminum amalgam ($AlHg_3$) as the reducing reagent. Conversion to the corresponding α-amino acids **68** was accomplished by hydrogenolysis of the N-N bond with Pd/C as catalyst and hydrolysis of the lactone to afford the products in 78-90% e.e. (**Scheme 21**).

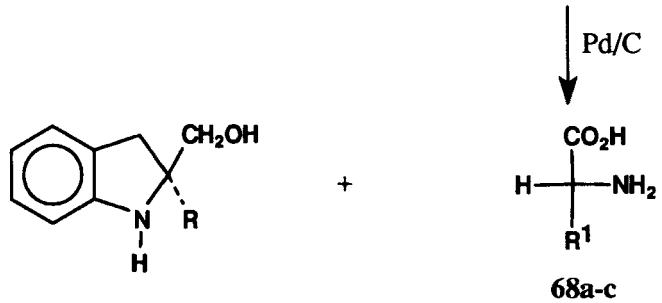
The diastereoselective reductions of hydrazone derivatives has also been utilized to prepare chiral, enantioenriched amine ligands, useful for other asymmetric reductions. Thus, condensation of (+)-camphor and (–)-menthone with ethyl carbohydrazide afforded carboethoxyhydrazones **69** and **71**.

Hydrogenation with platinum oxide yielded the corresponding products, **70** in 96% yield (exo/endo= 98:2) and **72a,b** in 95% yield (10:1 mixture, respectively **Scheme 22**).[37]

Scheme 21



66a-c **67a-c**



68a-c

	R	R^1
a	H	Me
b	H	Et
c	Me	Me

2. Using Chiral Auxiliary Groups

Miyazawa and co-workers[49b] have reported the synthesis of *t*-leucine *via* hydrogenation of phenylhydrazones in which an amino acid was incorporated as an amide to serve as the source of chirality. It was suggested that the results[26, 27] could be explained by assuming a preferred conformation of the intermediate complex (i.e. **73**, **Scheme 22**), as described previously, formed prior to hydrogenation. The choice of catalyst was found to have a significant influence on the asymmetric hydrogenation. Thus, the use of palladium black or palladium oxide resulted in higher enantioenrichment of the product *t*-leucine than with palladium/carbon (**Table 5**).

Scheme 22

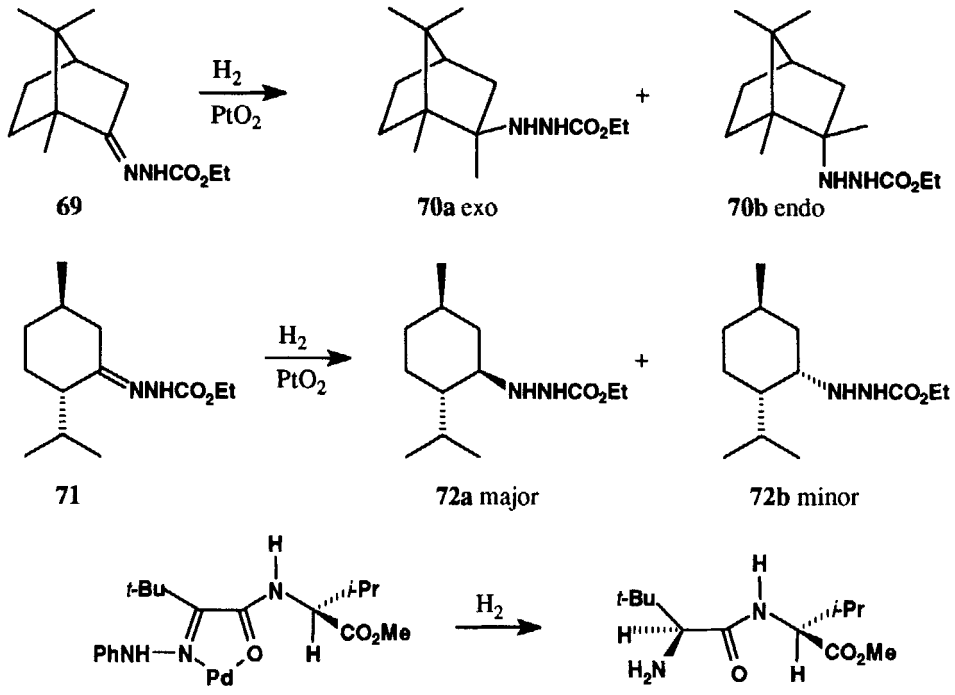


TABLE 5. Hydrogenation of Phenylhydrazones.

Entry	Catalyst	Temperature °C	Yield %	Ratio of Diastereomers **74** L-L %	D-L %
1	Pd-C	10	43	66	34
2	Pd-C	50	45	67	33
3	Pd-C	60	52	66	34
4	Pd-C	100	52	64	36
5	Pd/black	50	44	77	23
6	PdO	50	48	78	22

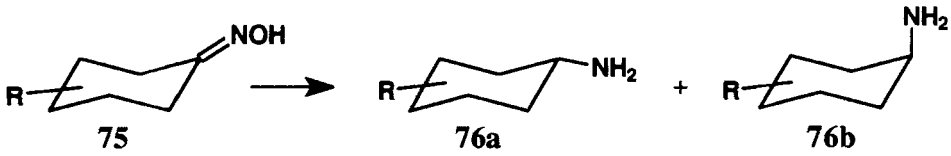
IV. REDUCTIONS OF KETOXIMES

A. Diastereoselective Reductions

1. Reductions of Cyclohexyl Oximes

Although systematic studies are sparse, reduction of cyclohexyl oximes with $NaBH_4$ in combination with $NiCl_2$ or MoO_3 afford the corresponding amines with moderate, but opposite selectivities (**Table 6**). Thus, $NaBH_4/NiCl_2$ gives predominately axial amines with most examples while $NaBH_4/MoO_3$ affords predominately the equatorial isomers or no selectivity.[50a]

TABLE 6. Reduction of Cyclohexyl Oximes to Amines



75 76a 76b

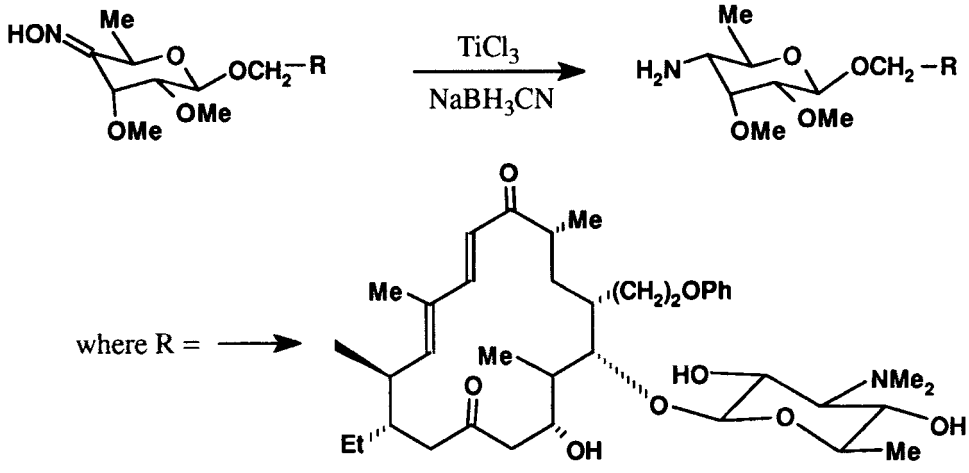
R	Reagent	Ratio 76a:76b (% Yield)
trans-2-*i*-C_3H_7-5-CH_3	$NaBH_4/NiCl_2$	33:67 (92)
4-*tert*-$C(CH_3)_3$	$NaBH_4/NiCl_2$	38:62 (95)
	$NaBH_4/MoO_3$	75:25 (87)
carvone (2-CH_3-5-*i*-C_3H_7-2-ene)	$NaBH_4/NiCl_2$	50:50 (90)
	$NaBH_4/MoO_3$	50:50 (90)

2. Reduction of Chiral Oximes

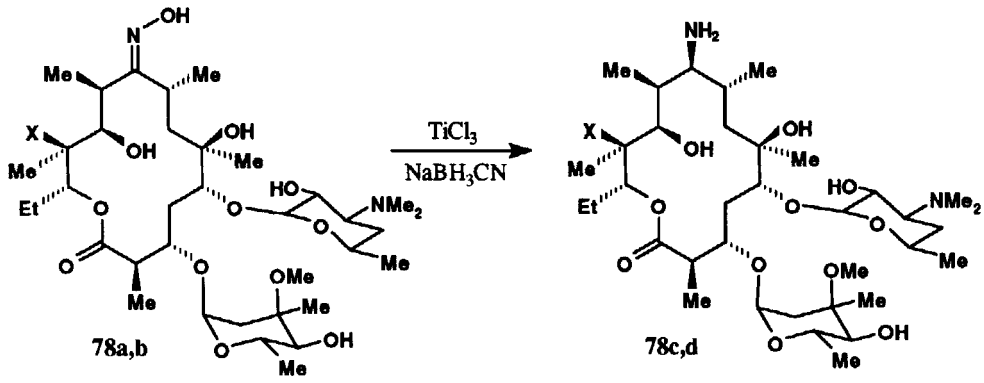
A mild and convenient procedure for direct reduction of oximes to amines involves treatment of oximes with $TiCl_3$ in the presence of $NaBH_3CN$.[50b] This process is compatible with structurally complex substrates containing other reducible functionalities, including ketones.[50c] Thus, the highly functionalized, desmycosin derivative **77b** was obtained from the reduction of the oxime **77a** in 50% yield (**Scheme 23**).

Likewise, conversion of the oxime of erythromycin **78a,b** to erythromycylamine **78c,d** has also been accomplished with this protocol in 50-60% chemical yield with high stereoselectivity (**Scheme 24**).

Scheme 23



Scheme 24

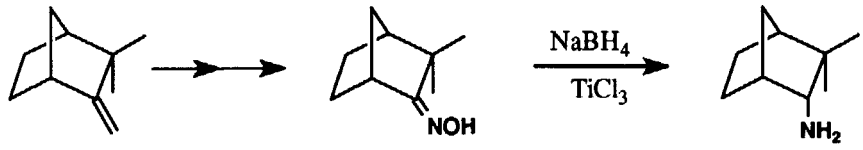


76	X	Name
a	OH	Erythromcyclamine A
b	H	Erythromcyclamine A

A related reduction system for oximes employing $NaBH_4/TiCl_4$ (in glyme) has also been developed.[51,52] This was utilized in a synthesis of *endo*-2-camphenylamine **80** (>99% diastereoselectivity) from camphenelone oxime **79** in 76% yield. A highly diastereoselective reduction was also obtained *via* a dissolving metal process (Na/*n*-PrOH) to afford only **80** in 78% yield (**Scheme 25**).[51]

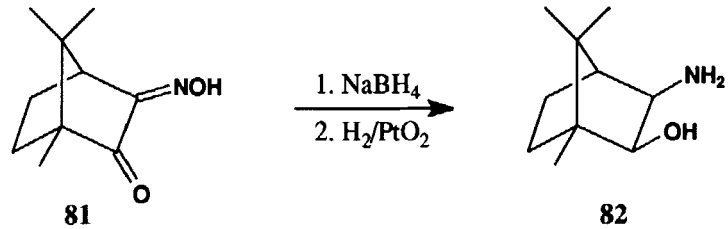
Another related reduction provided amino alcohol **82** in 72-76% yield[53] by treatment of oxime **81** successively with $NaBH_4$ (EtOH) and H_2/PtO_2 (xylene) using a modification of a literature procedure (**Scheme 26**).[54]

Scheme 25



(+) or (-) Camphene — **79** — **80** (endo) (+) or (-)

Scheme 26

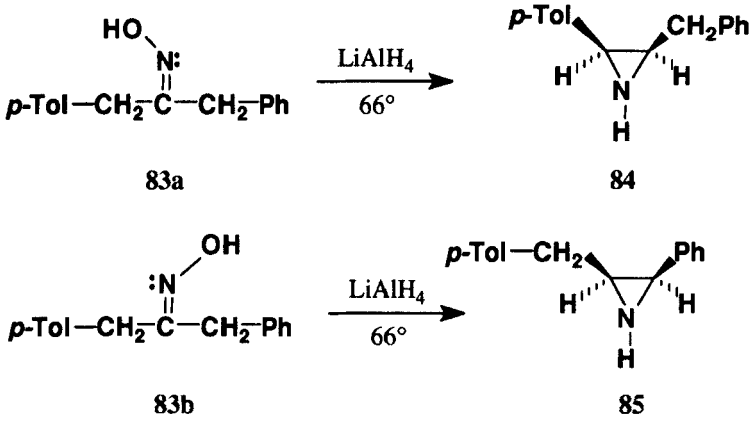


81 — **82**

3. Reduction with Cyclization

The $LiAlH_4$ reduction of the oximes **83a-b** *via* a cyclization process to the corresponding aziridines **84** and **85** represents an interesting deviation from normal reduction of the π bond.[55] The formation of aziridines **84** and **85** as the major products (>80%) indicated high *syn* stereoselectivity (**Scheme 27**).

Scheme 27

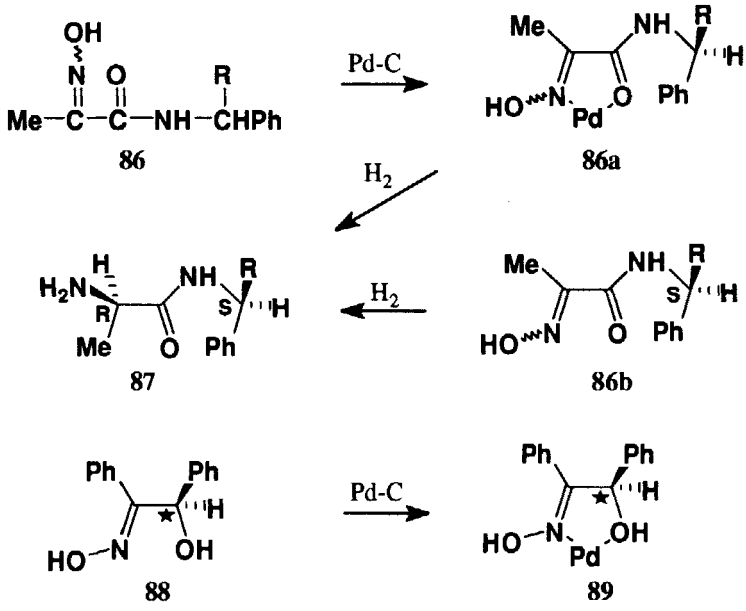


4. Using Chiral Auxiliary Groups

A method has been described[56] in which oximes and benzylimino derivatives of chiral pyruvamides were hydrogenated over $Pd(OH)_2/C$. Oximes of such pyruvamides involving (**R**)-ethylbenzylamine as a chiral auxiliary gave (**S**)-alanine predominantly (up to 70% e.e.) through hydrolyses of the hydrogenated products. The direction of hydrogen addition to the diastereotopic oxime faces of **86** was rationalized as attack on the *re* face (bottom) of the Pd-chelated intermediate **86a**[4, 35] or on the *si* face (top) of the open intermediate **86b**. In either case approach occurs from the side opposite the R substituent (**Scheme 28**).

In a related example, only the (E)-isomer of the racemic benzoin oxime **88** is capable of forming a five-membered chelated structure (**89**) with the catalyst.[57] Subsequent hydrogen-ation of **89** affords a >80% diastereomeric excess of the hydroxyamine product resulting from approach from the less hindered *si* face (away from the phenyl) (**Scheme 28**).[57,58] Similar results were obtained in the hydrogenation of the corresponding (Z)-oximes which presumably proceed through six-membered, intramolecular hydrogen bonded intermediates.[57]

Scheme 28



B. Enantioselective Reductions

1. Enzymatic Reductions

Gibbs and co-workers[59] demonstrated that the asymmetric reduction of 2-butanone oxime could be achieved with baker's yeast to yield optically active 2-aminobutane in 58% e.e. [(**R**)-isomer]. 4-Methyl-2-pentanone oxime yielded 4-methyl-2-aminopentane in 50% e.e. [(**R**)-isomer]. However, the process failed with acetophenone oxime.

2. Reductions with Chiral Reagents and Catalysts

The enantioselective synthesis of primary amines *via* catalytic hydrosilyation of oximes has been reported using $[Rh(COD)Cl]_2$/DIOP (COD = 1,5-cyclooctadiene) as a chiral hydrogenation catalyst.[59b] Hydrolysis of the resulting silylamine products gave the corresponding chiral amines in 4 - 19% enantiomeric excesses.

In a another study,[60,61] an intermediate generated by the reaction of $LiAlH_4$ and 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose was used to reduce oximes, yielding optically active amines in up to 56% enantioenrichment. All the resulting amines obtained had the **S**-configuration. However, a similar $LiAlH_4$-glucofuranose complex, but modified with 1 equivalent of ethanol, gave optically active amines with **R**-configurations.

An asymmetric catalyst was prepared by reduction of a palladium-protein complex formed by deposition of palladium chloride on silk fibroin fiber, a dissymmetric protein. Hydrogenation of α-benzildioxime in the presence of this catalyst gave diphenylethylenediamine which exhibited optical activity, but no enantiomeric excess was presented. Two optically active amino acids were also

prepared *via* hydrogenation of their oxime precursors in the presence of the above catalyst giving glutamic acid and phenylalanine, again in unspecified enantiomeric excesses.[62a]

An electrochemical asymmetric reduction of prochiral pyruvic and phenylglyoxylic acid oximes using a poly-L-valine-coated graphite electrode afforded only low (<17%) enantiomeric excesses of the corresponding amines.[62b] Similar results were obtained in the hydrogenation of the corresponding (Z)-oximes which were attributed to proceed through a six-membered, intramolecular hydrogen bonded, ring intermediate.[62b]

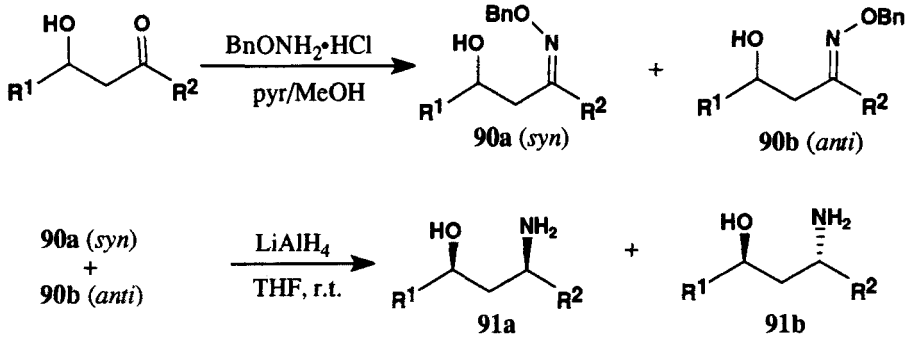
V. REDUCTIONS OF KETOXIME ETHERS

A. Diastereoselecive Reductions

1. Reductions of Chiral Oxime Ethers

Narasaka and Ukaji[63] reported the asymmetric reduction of β-hydroxy ketone-*syn*-O-benzyloximes by $LiAlH_4$ to *syn*-1,3-amino alcohols in good yields. The conversion of β-hydroxy ketones to the corresponding O-benzyloximes **90a** and **b** was performed by treatment of the ketones with O-benzylhydroxylamine hydrochloride and pyridine in refluxing methanol.[64] The resulting *syn* (**90a**) and *anti* (**90b**) isomers were readily separated by column chromatography on silica gel (**Scheme 29**). High stereoselectivity for the *syn* amino alcohols **91a** was observed when the *syn*-O-benzyl oximes **90a** were treated with $LiAlH_4$ in THF. On other hand, reduction of the *anti*-O-benzyloximes **90b** with $LiAlH_4$, gave lower stereoselection (**Table 6**).

Scheme 29



A subsequent improvement[65] has been reported utilizing a mixture of **90a** and **90b**. The mixture was reduced with $LiAlH_4$ in the presence of sodium or potassium methoxide to afford the *syn*-1,3-amino alcohol **91a** in a highly stereoselective manner (**Table 7**). Furthermore, the addition of sodium or potassium methoxide accelerated the $LiAlH_4$ reduction of the *anti* isomer **90b**. These results suggested that the aluminum intermediates **92a** and **92c** equilibrate in the presence of methoxide with the corresponding alkoxides **92b** and **92d.** At this stage, the sodium alkoxide of *anti*-O-benzyloxime **92b** is reduced *via* a six-membered ring sodium chelate (**Scheme 30**). In the case of

the *syn*-isomer (**90a**), however, the formation of a six-membered sodium chelate is configurationally prevented. Thus, an intramolecular reduction proceeds *via* the aluminum complex **92c**.

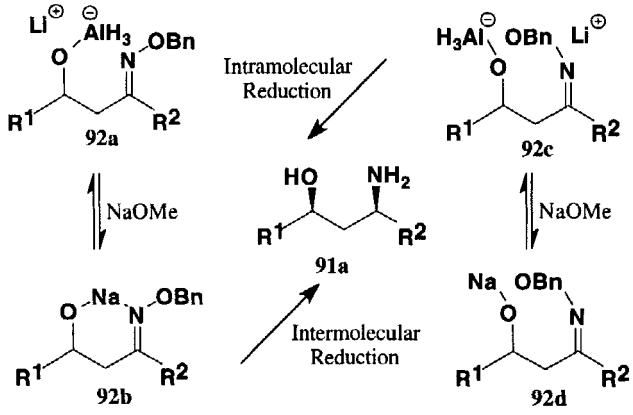
TABLE 6. Reduction of O-benzyl Oximes **90** with $LiAlH_4$

Entry	R^1	R^2	Ratio of **91a/ 91b** (yield %) from *syn*-**90a**	from *anti*-**90b**
1	*n*-Bu	*n*-Bu	95/5 (87)	77/23 (96)
2	*i*-Bu	*i*-Bu	95/5 (77)	77/23 (83)
3	CH_2CH_2Ph	CH_2CH_2Ph	91/9 (85)	79/21 (96)
4	CH_2CH_2Ph	Me	88/12(78)	78/22 (85)
5	Ph	Me	88/12(74)	85/15 (82)
6	Ph	Ph	85/15(82)	88/12 (74)

TABLE 7. Reduction of O-benzyl Oximes **90** with $LiAlH_4$-NaOMe

Entry	R^1	R^2	**90a/90b**	**91a/91b**	Yield (%)
1	*n*-Bu	*n*-Bu	52/48	96/4	92
2	*i*-Bu	*i*-Bu	55/45	95/5	92
3	CH_2CH_2Ph	CH_2CH_2Ph	51/49	94/6	89
4	CH_2CH_2Ph	Me	34/66	97/3	94
5	Ph	Me	28/72	90/10	97

Scheme 30



General syntheses of lythraceae alkaloids include the condensation of isopropelletierine with aromatic aldehydes[66] or a [2+3] cycloaddition of tetrahydropyridine N-oxide.[67] By applying the above efficient methods, new routes to lythraceae alkaloids were achieved.[68,69] The key intermediate, an

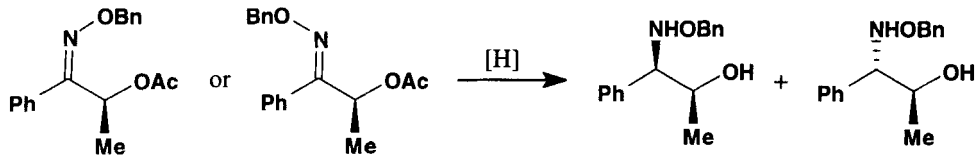
acyclic *syn*-1,3-amino alcohol **94**, was prepared stereoselectively (65% yield) from a β-hydroxyketone derivative **93** by treatment with $LiAlH_4$ in the presence of potassium methoxide (**Scheme 31**).

Scheme 31

93 **94**

In another investigation, 1,2-amino alcohols **96** and **97** were obtained[70a] from the hydrosilane/H^+ reduction of (2-acetoxy-1-phenylpropylidene)-benzyloxyazanes **95a** and **95b**. The *syn*-isomer **95a** gave the *threo* isomer **97** preferentially, while the *anti*-configuration **95b** afforded the *erythro* isomer **96** with high diastereoselectivity. With $LiAlH_4$, both **95a** and **95b** gave the *erythro* isomer **96** predominantly, the latter was much more stereoselective (**Scheme 32, Table 8**).

Scheme 32



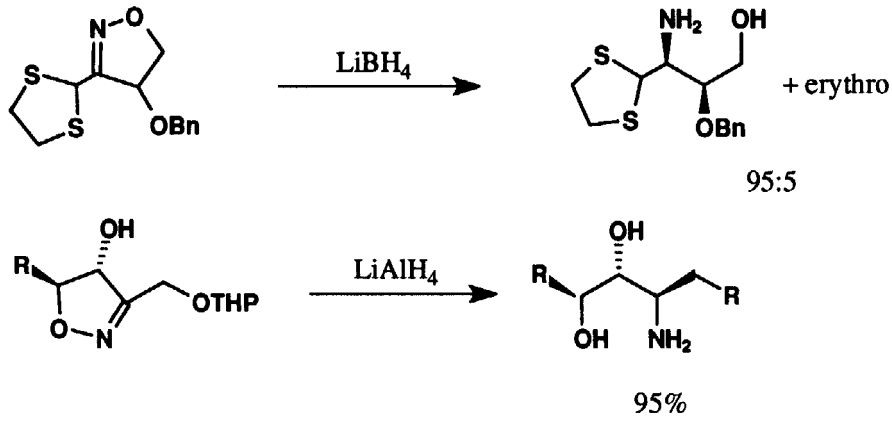
95a (*syn*) **95b** (*anti*) **96** **97**

TABLE 8. Reduction of Oximes **95** with Hydride Reagents

95	Reagent	Solvent	Yield %	**96/97**
a	$HSiMe_2Ph$	TFA	77	24/76
a	$LiAlH_4$	Et_2O	39	58/42
b	$HSiMe_2Ph$	TFA	73	99/1
b	$LiAlH_4$	Et_2O	46	82/18

Related reductions of endo-cyclic oxime ethers (isoxazolines) with concomitant ring cleavage affords diastereomeric β-hydroxyamines, often with high selectivities, using $LiAlH_4$[70b-d] or $LiBH_4$[70e] (**Scheme 33**).

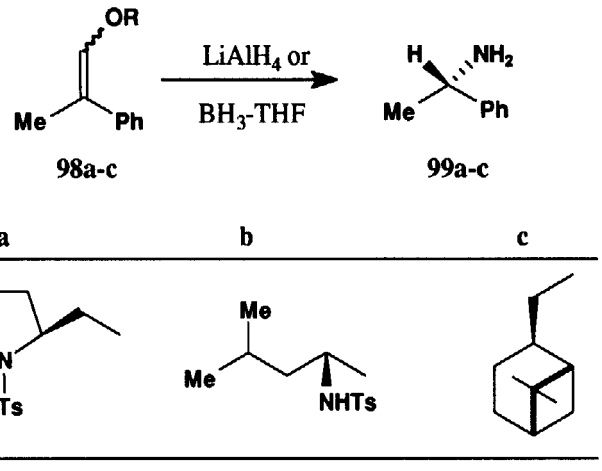
Scheme 33



2. Using Chiral Auxiliary Groups

The chiral oxime ethers **98a-c** were synthesized from the sodium salt of acetophenone oxime and enantioenriched halides, tosylates, or N-tosylaziridines which in turn were derived from optically active β-pinene or α-amino acids.[71] Reduction of **98a-c** with $LiAlH_4$ or BH_3/THF gave the optically active primary amines, albeit in low optical purities [**99a** (4.2% e.e.), **99b** (3.3% e.e.), and **99c** (44 % e.e.)] (**Scheme 34**).

Scheme 34

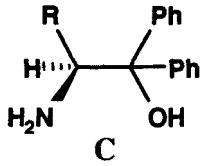


B. Enantioselective Reductions

1. Reductions with Chiral Reagents

Itsuno and co-workers[72] introduced reagents prepared from chiral, enantiomerically enriched amino alcohols (**C, Figure 4**) and borane which asymmetrically reduces ketones to optically active secondary alcohols in high enantioselectivity.[73]

Figure 4



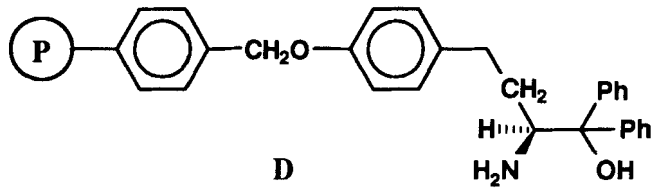
C

where, R =
Me, *t*-Bu, neo-Pe, *s*-Bu, CH_2Ph,
$(CH_2)_2SMe$, p-MeC_6H_4-

Extension of the use of these reagents for the reduction of oxime ethers gave satisfactory results (up to 99% e.e.).[74] The results indicated that the active amino alcohol-borane complex interacts with the oxime ether, and concomitantly accelerates reduction by borane to induce asymmetry. Indeed, borane alone reduced the oxime ether only slowly in THF at ambient temperature. However, 10 equiv of oxime ether was reduced quantitatively with 10 equiv of borane in the presence of only 1 equiv of the chiral complex to give the corresponding chiral amine (52 % e.e.).[75]

Further study was directed toward anchoring the optically active1-1-diphenyl-2-amino alcohol C to a polymer.[76] Thus, the polymer supported chiral amino alcohol (**D**, **Figure 5**) was converted to the corresponding polymeric complex by treatment with borane. Although very effective for the asymmetric reduction of ketones to optically active alcohols (up to 97% e.e.), reduction of oxime ethers to corresponding amines occured in only 18-67% e.e.

Figure 5

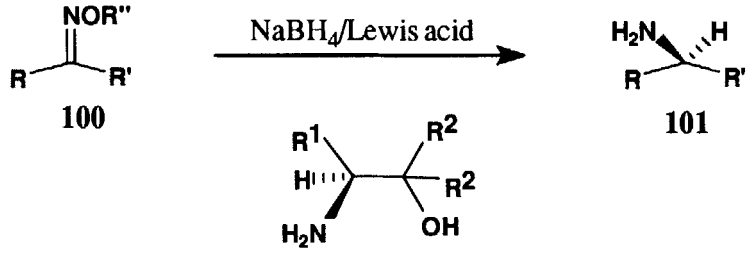


D

Asymmetric conversions of ketoxime ethers have been described[77] which used a chirally modified reducing agent prepared from (–)-norephedrine and two equivalents of BH_3, to give optically active amines in 79-92% e.e. The absolute configuration of the preferred amine was dependent on the geometry of the oxime ether.

Recently,[78,79] reductions were reported using novel hydride agents formed by combining Lewis acids (e.g. $ZrCl_4$, $ZnCl_2$+$AlCl_3$) with sodium borohydride (**Scheme 35**). In the presence of chiral amino alcohols (e.g. **E**), this system reduced various ketoxime O-alkyl ethers **100a-c** to the corresponding optically active primary amines **101a-c** with high enantioselectivities (up to 95% e.e.). The extent of asymmetric reduction was dependent on the solvent, the temperature, the structure of the oxime ether, the structure of chiral amino alcohol, and the $NaBH_4/ZrCl_4$/chiral amino alcohol/oxime ether proportions.[80]

Scheme 35



(E)

	R^1	R^2
a	*i*-Pr	H
b	*i*-Pr	Ph
c	*i*-Pr-CH_2	H

The chiral reagent prepared from $LiAlH_4$ and-3-O-benzyl-1,2-O-cyclohexylidene-D-gluco-furanose[60,61] has been presented previously for the reduction of oximes. This reagent is also successful for the asymmetric reduction of oxime ethers to optically active amines in up to 56% optical purity. Since all the resulting amines obtained have the S-configuration, this method may be used in determining the absolute configurations of amines. As with oximes, the same reductions with the reagent modified with ethanol gives optically active amines with **R**-configurations.

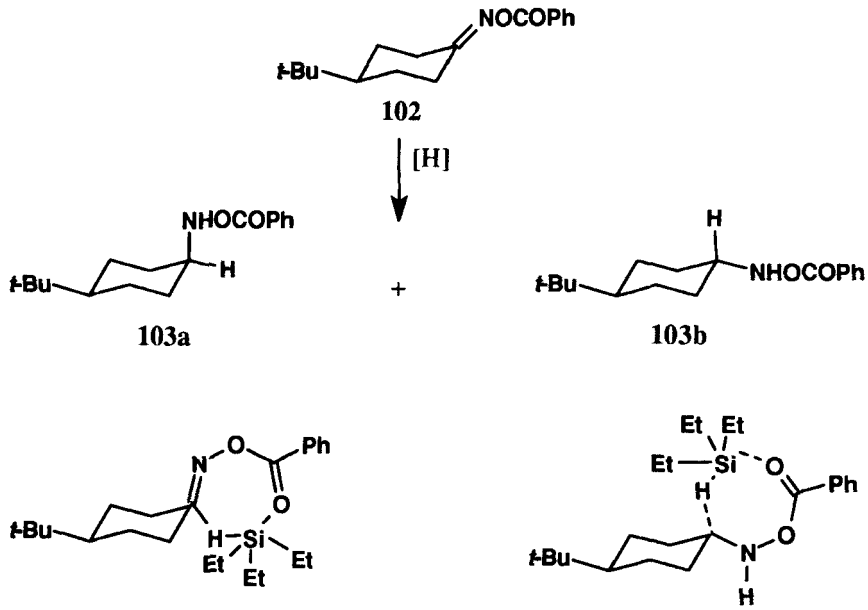
VI. REDUCTIONS OF OXIME ESTERS

A. Diastereoselective Reductions

1. Reductions of Cyclohexanone Oxime Esters

Sternbach and co-workers[81a] reported that O-acyl hydroxylamines could be prepared by the reduction of the corresponding oxime esters with $NaBH_3CN$/AcOH or Et_3SiH/CF_3CO_2H. To probe the stereochemistry of these reductions, 4-*t*-butylcyclohexanone oxime benzoate **102** was reduced by the above reagents, and complementary diastereoselectivities were observed. Thus, Et_3SiH/CF_3CO_2H afforded a 5-fold excess of the axial product **103a** from equatorial attack of hydride while $NaBH_3CN$-AcOH produced a 4-fold excess of the equatorial product **103b** resulting from axial approach. These orientation preferences are consistent with previous results for bulky and small reagents, respectively.[12a] Another explanation was offered which invokes the participation of the benzoyl carbonyl with Et_3SiH so that hydride may be delivered intramolecularly[81a] *via* **102a** or **102b**. The predominance of equatorial attack was attributed to favoring of the less congested **102a** (**Scheme 36**).

Scheme 36



Several amino hexopyranose nucleosides (e.g. **104b**, **Scheme 37**) were prepared *via* reduction of the corresponding oxime acetates (e.g. **104a**) with $NaBH_4/NiCl_2$ or $NaBH_4/MoO_3$.[81b] In all cases with saturated derivatives, the axial amino isomers (e.g. 104b) were the only isolated products, indicating preferential attack from the less hindered side of the hexopyranose ring. However, reduction of α,β-unsaturated derivatives (e.g. **104c**) yielded mixtures of stereoisomers and, in some cases, concomitant reduction of the double bond (**Scheme 37**).[81b]

2. Using Chiral Auxiliary Groups

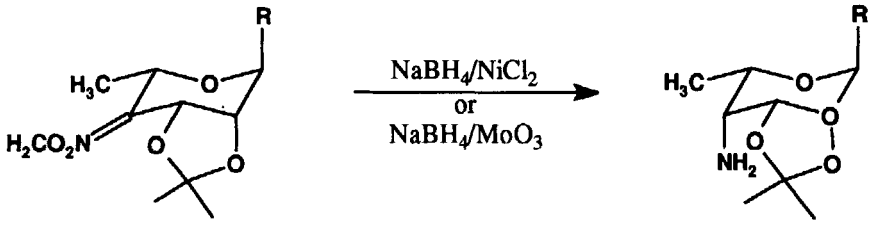
Reductions of chiral esters of oximes (formed by reaction of non-racemic 2-phenylbutanoic acid with oximes), with borane gave, upon hydrolysis, the corresponding amines, but in only 5-7% e.e.[82]

B. Enantioselective Reductions

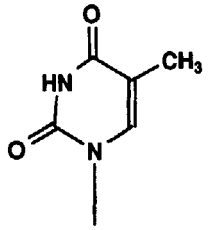
1. Enzymatic Reduction

The enantioselective reduction of 2-butanone oxime acetate **105** by baker's yeast yielded the chiral amine **106** in 24% e.e. of (R)-configuration (**Figure 6**).[59]

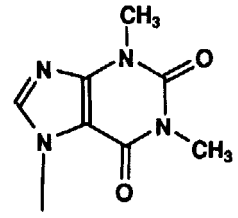
Scheme 37



104a 104b



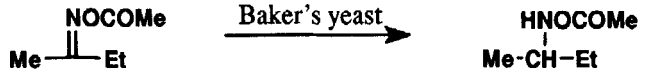
Thyminyl



Theophyllinyl

104c

Figure 6



105 106

VII. REDUCTIONS OF N-SUBSTITUTED PHOSPHINYL IMINES

A. Diastereoselective Reductions

1. Reductions of Cyclic N-Phosphinyl Imines

Diastereoselective reductions of cyclic ketone phosphinyl imines **107** to cyclic phosphinyl amines **108** has been reported.[83] This was accomplished with lithium tri-*sec*-butyl-borohydride and gave high discrimination for equatorial attack to afford axially oriented isomers (**108**). Similar high diastereoselectivities were also observed with cyclopentyl and norbornyl type derivatives. This method provides highly diastereoselective conversions to masked axial primary cyclohexyl amines and analogues. The results are summarized in **Table 9**. The corresponding primary amines are obtained by mild acid hydrolysis.

B. Enantioselective Reductions

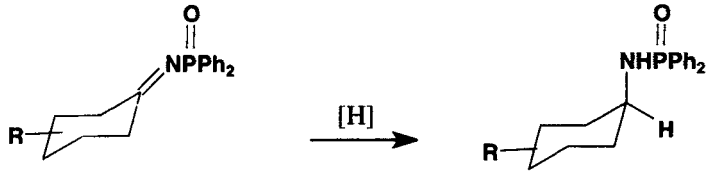
1. Reductions with Chiral Metal Hydride Reagents

N-Substituted phosphinyl imines **109** were reduced by a chiral quinine-$LiAlH_4$ reagent to optical active N-substituted phosphinyl amines **110** by Stec and co-workers.[84] The chemical yields were in the 21-75% range, while the enantiomeric inductions were low to moderate (8-36% e.e., **Scheme 38**).

Additional asymmetric reductions of the prochiral faces in acyclic N-diphenylphosphinyl imines with a variety of chiral aluminum and boron derived hydride reagents to the corresponding chiral phosphinyl amines have also been investigated.[85] The three most successful reagents were BINAL-H, **I**, [Noyori's reagent][86]; K-9-O-DIPGF-9-BBNH, **II**, [Brown's reagent][87]; and, to a lesser extent, Chirald-/LAH, **III**, [Mosher's reagent].[88]

In contrast to the results with ketones, most arylalkyl derivatives provide only low to moderate enantioselectivities (i.e. 7-57% e.e.) while dialkyl phosphinyl imines generally exhibit greater asymmetric inductions with K-9-O-DIPGF-9-BBN (i.e. 50-84% e.e.), again, in contrast to results with ketones in which this reagent generally gave poor selectivities.

TABLE 9. Reduction of Cyclohexylidene N-Diphenylphosphinyl Imines **107** to the Corresponding Phosphinyl Amines **108**.



107 **108**

R	Hydride Reagent	Yield (%)	% Diastereomeric Excess
4-*t*-Bu	$LiBH(s\text{-}Bu)_3$	64	>98
	$NaBH_4$	65	48
4-Ph	$LiBH(s\text{-}Bu)_3$	59	>98
	$NaBH_4$	55	3
4-Me	$LiBH(s\text{-}Bu)_3$	72	>98
	$NaBH_4$	72	20
2-Et	$LiBH(s\text{-}Bu)_3$	67	>98
	$NaBH_4$	63	16

VIII. REDUCTIONS OF SULFINAMIDES AND SULFONYLIMINES

A. Diastereoselective Reductions

1. Reductions of Chiral Substrates

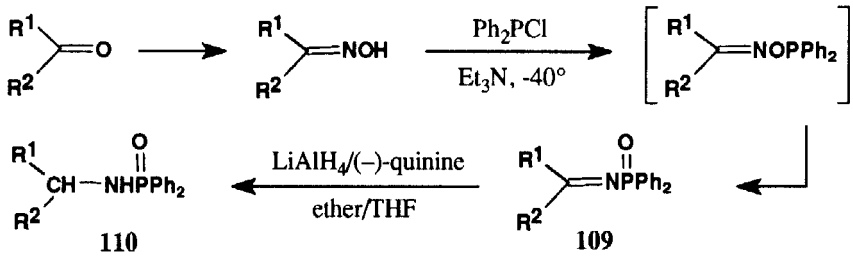
The optically active camphorsultam **112** (**Scheme 39**) was obtained by the diastereoselective reduction of the corresponding camphorsulfonyl-imine **111** with $LiAlH_4$. Because the top face of the

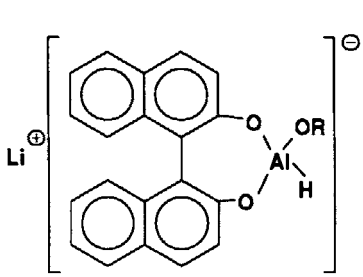
imine double bond is blocked by the bridge methyl group, essentially only one isomer was produced.[89] The product camphorsultam is a chiral auxiliary group widely used in a number of enantioselective organic transformations.

2. Using Chiral Auxiliary Groups

Reductions of optically active sulfur derivatives results in high degrees of asymmetric induction. Thus, Annunziata and co-workers reported[90] the preparation of chiral N-alkylidene sulfinimides *via* the reaction of an alkyl or an aryl Grignard reagent with an aromatic nitrile to give imino-Grignards, which were reacted with a (–)-*l*-menthyl-(S)-*p*-toluenesulfinate (S_1). The resulting sulfinimides were reduced to the corresponding sulfinamides by $LiAlH_4$ in 57-80% e.e. The free amines could be released by vigorous acid cleavage.

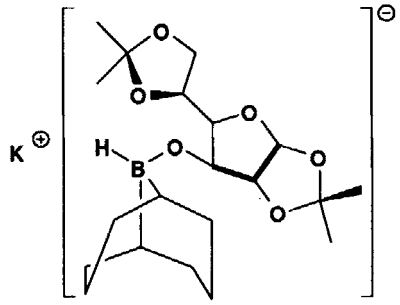
Scheme 38





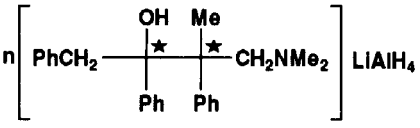
I

(R)- or (S)-bi-2-naphthol/$LiAlH_4$
(R = Me or Et)



II

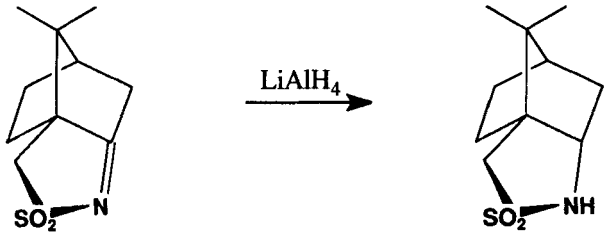
K^+9-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo-3.3.1]-nonane



III

2-(S)-1,3-diphenyl-3-(R)-methyl-4-(dimethylamino)-2-butanol/$LiAlH_4$

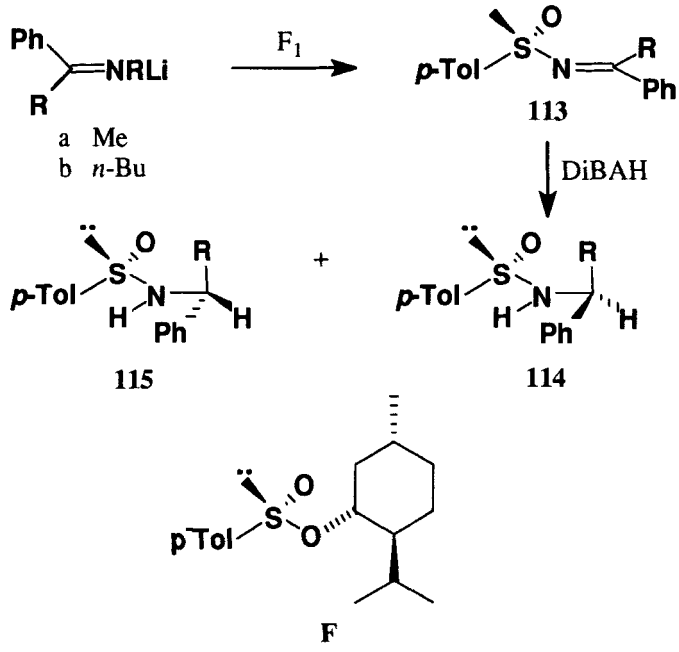
Scheme 39



111 **112**

Similarly, Hua and co-workers[91,92] recently reported that N-benzylidene-p-toluenesulfinimides were also obtained by treating benzonitrile with alkyllithium (CH_3Li or n-BuLi) in ether, followed by the addition of (–)-*l*-menthyl-(S)-*p*-toluenesulfinate (**F**) at 0°. The resulting sulfinimides **113** were then reduced with DIBAH in THF at -30°C to provide mainly sulfinamide diastereomers **114** (**Scheme 40**). From **113a**, a 92% yield of **114a** and **115a** was obtained in a ratio of 96:4, and from **113b**, 96% of **114b** and **115b** (94:6) was obtained. Also, the same procedure could be utilized starting with the corresponding (+)-*d*-menthyl-(**R**)-*p*-toluenesulfinate $\mathbf{R_1}$.

Scheme 40

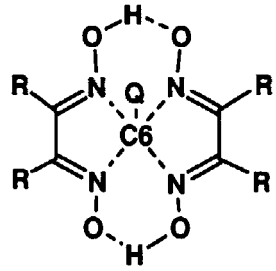


115 **114**

F

A cobalt-mediated catalytic reduction[94] of N-*p*-toluenesufonyl-1-imino-1-phenylacetate in the presence of a quininiun salt was reported to afford the corresponding N-tosyl amino ester with a chemical yield of 80%, but the enantiomeric excess was low (<21% e.e. **Figure 7**).

Figure 7



Q = quinine

Cobalt complex

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(Received August 19, 1993; in revised form October 12, 1993)