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Stereoselective reduction of endocyclic carbon–nitrogen double bond: application to the synthesis of biomolecules

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Abstract

Recent advances in the stereoselective synthesis of nitrogen containing heterocyclic compounds using the reduction of endocyclic double carbon–nitrogen bond are surveyed.

Contents

1. Introduction

One of the most important advances in synthetic organic chemistry of the last few decades is stereoselective synthesis. Since it was realised that each enantiomeric form of a molecule can possess different biological activities, stereoselective synthesis methodology is particularly important for the synthesis of heterocyclic compounds.

The synthesis of target molecules with a high enantiomeric purity exploiting carbon–nitrogen double bond reduction reactions of acyclic substrates was earlier studied in detail, but the interest for similar transformations of endocyclic C=N bond has but recently arisen. Such transformations are frequently

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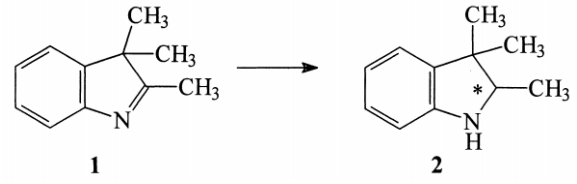
used as the key step to the stereoselective synthesis of alkaloids, their synthetic analogues and biologically active substances. This review considers mostly the advances in this field of organic chemistry achieved in the last five years.

2. Stereoselective catalytic reduction

2.1. Enantioselective catalytic reduction

Enantioselective catalysis using chiral metal complexes is the most efficient method for the preparation of chiral molecules. Its main advantage consists of the fact that the stereochemical information is transferred from a single molecule of chiral ligand of the catalyst to thousands of molecules of the product. Metal complex catalysis is more flexible than catalysis by organic chiral compounds, as both the chiral ligand and the nature of the metal centre can be varied while maintaining control of the process. Metal complex catalysts are also convenient to easily obtain both enantiomeric forms of product, when both enantiomeric forms of the ligands are available.[1] Complexes of group 8 transition metals with the chiral phosphine ligands are used for the asymmetric hydrogenation of cyclic imines. The influence of metal and the chiral ligand structure on the efficiency of asymmetric hydrogenation has been studied in the reduction of 2,3,3-trimethylindolenine **1** (Scheme 1).[2–5] The best results were obtained using the complexes of iridium(III) with (*S*,*S*)-BDPP and (4*R*,5*R*)-MOD-DIOP (≈80% *ee*), whereas the catalysts containing rhodium failed in asymmetric hydrogenation of indolenine **1** (Table 1).



Scheme 1.

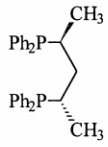
The catalyst system of Ir(I)–MOD-DIOP 3-tetrabutylammonium iodide and Ir(I)–BCPM 1-bismuth(III) iodide are efficient for the asymmetric hydrogenation of a cyclic ketimine, 2,3,3-trimethylindoline, and a high enantiomeric excess of up 91% *ee* has been attained.[3] It is well known that neutral Ir(I) complexes usually show higher enantioselectivity than the cationic ones. In contrast, some prochiral ketimines were hydrogenated in high enantioselectivity with neutral rhodium or iridium complexes in the presence of iodine. These facts imply that the selection of iodine or other additives which can coordinate to the vacant site of the iridium complex (forming a neutral complex) is important for the improvement of enantioselectivity in the hydrogenation of imines.[6] However, six-membered imines could not be hydrogenated in high *ee* by using these catalyst systems (Table 2).

The use of a catalytic system of iridium complex with diphosphine in the presence of different imides or amides as co-catalysts was found to be very efficient.[6,7] The best results on the asymmetric hydrogenation of 3,4-dihydroisoquinoline (**3a**) were achieved while using (2*S*,4*S*)-BCPM in the presence of phthalimide as co-catalyst at 2–5°C. (*S*)-Salsolidine (**4a**) was obtained in this case with an enantiomeric excess of 79% (Table 2, Scheme 2).

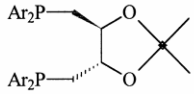
The influence of the solvents in this case is worth noting. Thus the high enantiomeric excess of salsolidine, obtained on the reduction of **3** (20°C, (2*S*,4*S*)-BCPM, phthalimide) was achieved in toluene (79% *ee*), whereas in THF, under similar conditions, only 41% *ee* was observed. The data presented in Table 2 demonstrate that the most efficient co-catalysts are five membered cyclic imides.

Table 1
The asymmetric hydrogenation of 2,3,3-trimethylindolenine with chiral complexes of rhodium and iridium[2,3]

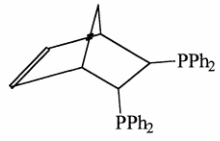
Reaction conditions	Ligand L	Catalyst	*ee* (%)
$S:Ir_2$= 1000 H_2 (40 psig) 30 °C THF, CH_2Cl_2	(*S,S*)-BDPP	$[Ir(L)H(I)]_2$	80 (+)
	(4*R*,5*R*)-DIOP	″	51(-)
	(-)-NORPHOS	″	47 (-)
L: metal complex : substrate = 2,4 : 1 : 200 benzene : MeOH = 1 : 1	(4*R*,5*R*)-DIOP	$[Ir(COD)Cl]_2$*	66 (+)
	(4*R*,5*R*)-MOD-DIOP	″	81 (+)
	(4*R*,5*R*)-DIOP	$[Rh(COD)Cl]_2$	0
	(4*R*,5*R*)-MOD-DIOP	″	0



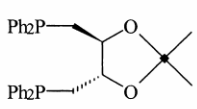
(*S,S*)-(-)-BDPP



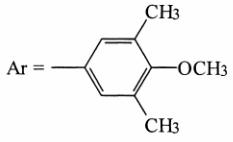
(4*R*,5*R*)-MOD-DIOP



(-)-NORPHOS



(*4R,5R*)-DIOP



COD - cyclooctadiene

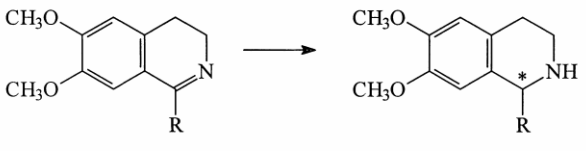
An optically active 1-hydroxymethyl-substituted tetrahydroisoquinoline alkaloid, (*S*)-calycotomine (**4b**), was conveniently synthesised by using catalytic asymmetric hydrogenation of 1-benzyloxymethyl-3,4-dihydro-6,7-dimethoxyisoquinoline (**3b**) (R=CH_2OBn) with 0.5% of an iridium(I) complex of (*R*)-BINAP in the presence of 3,4,5,6-tetraflurophthalimide (100 atm H_2, 2–5°C, toluene–MeOH, S/C=200, 86% *ee*) (Scheme 2).[8]

Asymmetric hydrogenation of 1-[3-(benzyloxy)propyl]-3,4-dihydro-6,7-dimethoxyisoquinoline (**3c**) was also performed under similar conditions using (*S*)-BINAP and parabanic acid (as an additive), leading to the corresponding tetrahydroisoquinoline (**4c**) with 89% *ee* (estimated to be *S*) in quantitative yield (Scheme 2).[8]

The chiral titanocene catalysts are particularly valuable for the asymmetric hydrogenation of cyclic imines.[9,10] The Ti(III) hydride is presumably the active catalyst obtained in situ from (*R,R,R*)-**6** by action of 2 equiv. butyllithium and 3 equiv. phenylsilane under hydrogen atmosphere. It is known that the asymmetric reduction of cyclic imines with many late transition metal catalysts is less successful than in the case of acyclic imines.[10] In contrast, the asymmetric hydrogenation of cyclic imines, performed with a chiral titanocene catalyst affords cyclic (*S*)-amines with excellent levels of enantiomeric excess in all cases investigated (Table 3, Scheme 3).[10]

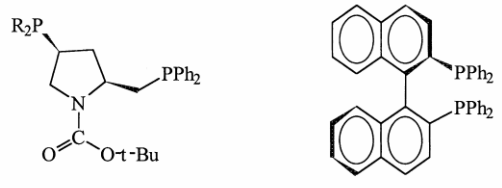
Table 2
The asymmetric hydrogenation of isoquinoline **3a**[6]

Ligand	Co-catalyst	Solvents	T (°C)	Time (h)	Yield (%)	*ee* (%)
(2*S*,4*S*)-BCPM	none	benzene-MeOH	20	24	90	18(*R*)
(2*S*,4*S*)-BCPM	Bu_4NI	benzene-MeOH	20	50	97	10(*S*)
(2*S*,4*S*)-BCPM	succinimide	benzene-MeOH	-10	72	94	67(*S*)
(2*S*,4*S*)-BCPM	hydantoin	benzene-MeOH	20	30	96	49(*S*)
(2*S*,4*S*)-BCPM	phthalimide	MeOH	20	24	97	43(*S*)
(2*S*,4*S*)-BCPM	phthalimide	benzene-MeOH	-10	48	98	76(*S*)
(2*S*,4*S*)-BCPM	phthalimide	toluene	2~5	24	95	93(*S*)
(2*S*,4*S*)-BCPM	phthalimide	iHF	20	20	95	41(*S*)
(2*S*,4*S*)-BCPM	4-chlorophthalimide	toluene	20	20	97	81(*S*)
(2*S*,4*S*)-BCPM	4,5-dichloro-phthalimide	toluene	20	20	95	76(*S*)
(2*S*,4*S*)-BCPM	2,3-naphthalene-carboximide	toluene	20	11	46	74(*S*)
(2*S*,4*S*)-BCPM	2-pyrrolidone	benzene-MeOH	20	48	85	12(*R*)
(2*S*,4*S*)-BPPM	Bu_4NI	benzene-MeOH	20	90	100	7(*S*)
(2S,4*S*)-BPPM	phthalimide	toluene	20	20	87	7(*S*)
(4*R*,5*R*)-DIOP	phthalimide	toluene	20	20	52	26(*S*)
(4*R*,5*R*)-MOD-DIOP	phthalimide	benzene-MeOH	-10	60	51	68(*S*)
(4*R*,5*R*)-MOD-DIOP	Bu_4NI	benzene-MeOH	20	90	91	28(*S*)



3a-c **4a-c**

a R=Me, **b** R= CH_2OH, **c** R=$(CH_2)_3OBn$

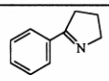
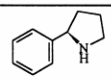
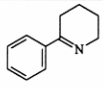
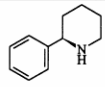
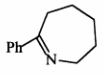
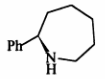
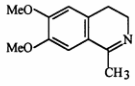
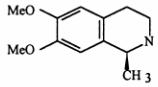
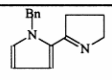
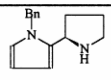
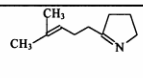
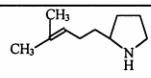
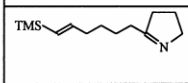
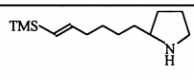
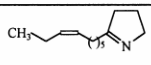
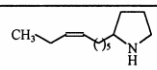
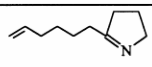
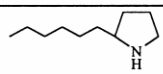
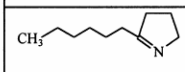
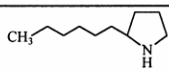
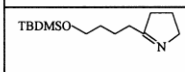
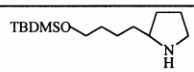
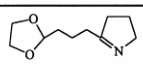
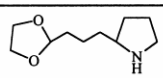
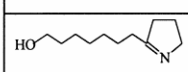
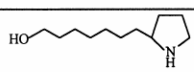


(2*S*,4*S*)-BCPM R = *c*-C_6H_{11} (*R*)-BINAP

(2*S*,4*S*)-BPPM R = Ph

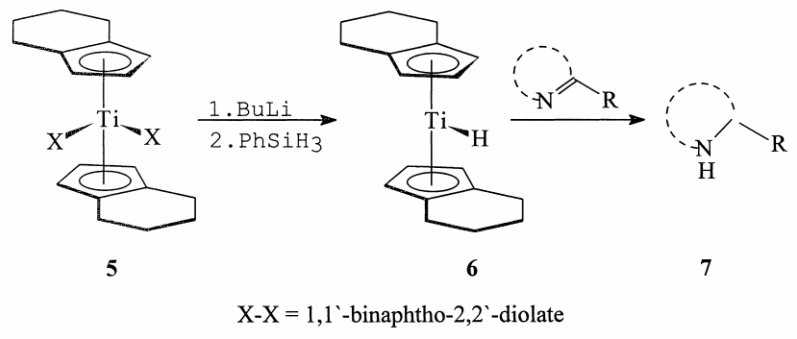
Scheme 2.

Table 3
Asymmetric hydrogenation of cyclic imines with chiral titanocene catalysts[8]

Imine	Amine	Pressure(psig)	T (°C)	Yield (%)	*ee* (%)	(±)
		2000 500 80 80	65 21 65 65	77 86 84 83	98 99 99 99	(+)-*R* (+)-*R* (+)-*R* (+)-*R*
		2000 500	65 65	70 78	97 98	(+)-*R* (+)-*R*
		50 80	45 65	71 74	98 97	(+)-*R* (+)-*R*
 *Z*-imine		2000 80	65 65	82 79	98 95	(-)-*S* (-)-*S*
		500 80	23 65	83 72	99 99	(+)-*R* (+)-*R*
		80	50	79	99	(+)-*R*
		80	50	73	99	(+)-*R*
		80	45	69	99	(+)-*R*
		80	45	72	99	(+)-*R*
		2000	65	81	98	(+)-*R*
		80	65	82	99	(+)-*R*
		80	65	82	99	(+)-*R*
		80	65	84	99	(+)-*R*

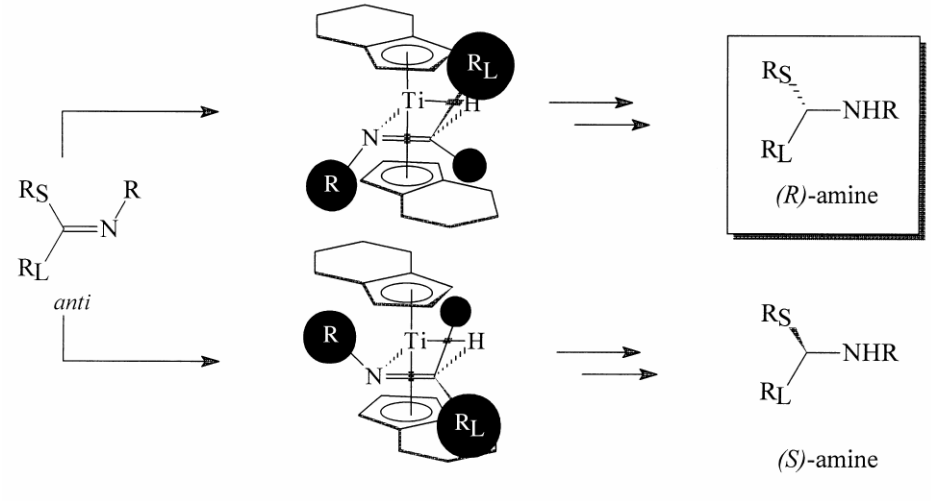
In addition, in almost all cases, the reaction could be carried out under much lower hydrogen pressure than for acyclic imines. A difference between the reduction of cyclic imines and that of acyclic imines is that the enantiomeric excesses for cyclic imines are insensitive to charges in hydrogen pressure.[10]

As can be seen from Table 3, the hydrogenation of cyclic *E* imines (2-substituted pyrrolines and related compounds with six and seven membered rings) with (*R*,*R*)-catalyst yields cyclic (*R*)-amines, whereas cyclic *Z* imines (1-methyl-6,7-dimethoxy-2,3-dihydroquinoline) affords (*S*)-amines. The reason for this



Scheme 3.

seems to be connected with the fact that the interaction of an *E* imine with (*R,R*)-titanium complex leads to two possible intermediates, A and B (Scheme 4). In A, the nitrogen substituent is strictly down away from the cyclohexyl ring in the titanocene complex while in B the nitrogen substituent is up and interacts unfavourably with the tetrahydroindenyl ligand.

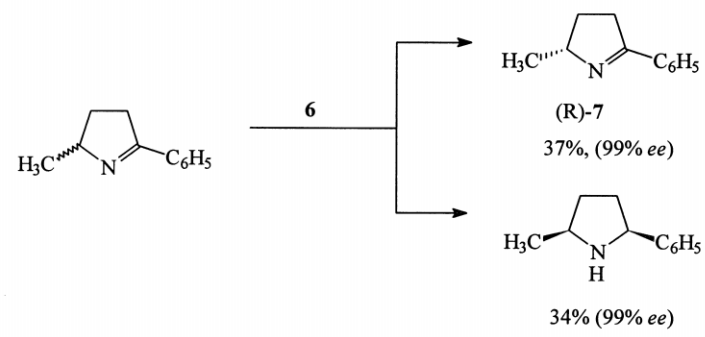


Scheme 4.

Thus, A should be favoured with respect to B so that, starting from an *E* imine, the (*R*)-amine is expected when the (*R,R*) catalyst is employed. This model can be used for prediction of the stereochemical outcome in the cyclic imines hydrogenation.[10]

The kinetic resolution in 2,5-disubstituted-1-pyrrolines hydrogenation was shown to be very efficient when the chiral titanocene catalyst (*R,R*)-**5** was employed. For example, (±)-5-methyl-2-phenyl-1-pyrroline under ≈50% conversion provides both (2*R*,5*S*)-pyrrolidine and (*R*)-**7** in good yields, and with excellent enantiomeric excesses (Scheme 5).[11]

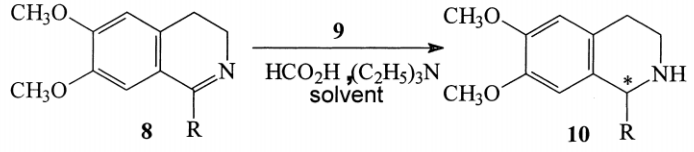
Asymmetric transfer hydrogenation of a number of 3,4-dihydroisoquinolines (**8**) exploiting chiral Ru(II) catayst (**9**) was used in the stereodirected synthesis of isoquinoline alkaloids.[10] Reduction was carried out with a formic acid–triethylamine system in polar aprotic solvents (DMF, DMSO, CH_2Cl_2, CH_3CN) containing catalyst **9**, with a substrate:catalyst ratio ranging from 100:1 to 1000:1. Tetrahydroisoquinolines (**10**) were obtained under these conditions with 72–95% yield and with 84–95% *ee* (Table 4, Scheme 6).[12]



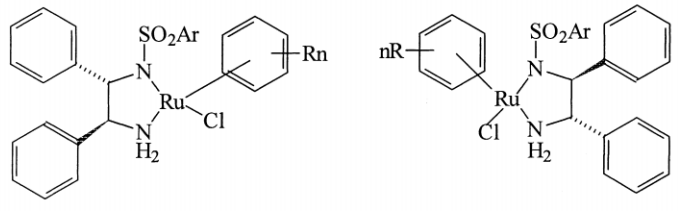
Scheme 5.

Table 4
Asymmetic transfer hydrogenation of 3,4-dihydroisoquinolines **8**[12]

8	Catalyst	Ratio substrate: catalyst	Time (h)	Yield (%)	*ee* (%)	Configuration
a	(*S,S*)-**9a**	200	3	99	95	*R*
a	(*S,S*)-**9a**	1000	12	97	94	*R*
b	(*R,R*)-**9b**	200	7	90	95	*S*
c	(*R,R*)-**9b**	200	12	99	92	*S*
d	(*S,S*)-**9d**	200	8	99	84	*R*
e	(*R,R*)-**9d**	100	12	99	84	*R*



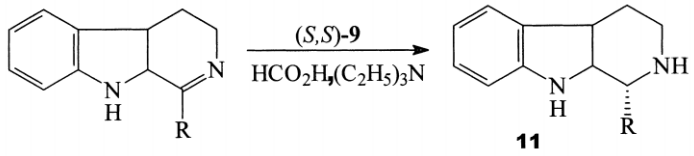
a R=CH_3, **b** R=3,4-$(CH_3O)_2C_6H_3CH_2$, **c** R=3,4-$(CH_3O)_2C_6H_3(CH_2)_2$, **d** R=C_6H_5,
e R=3,4-$(CH_3O)_2C_6H_3$



a η^6-aryl=*p*-cymene, Ar=4-$CH_3C_6H_4$, **b** η^6-aryl= *p*-cymene, Ar=2,4,6-$(CH_3)_3C_6H_2$,
c η^6-aryl=benzene, Ar=2,4,6-$(CH_3)_3C_6H_2$, **d** η^6-aryl=benzene, Ar = 1-naphthyl

Scheme 6.

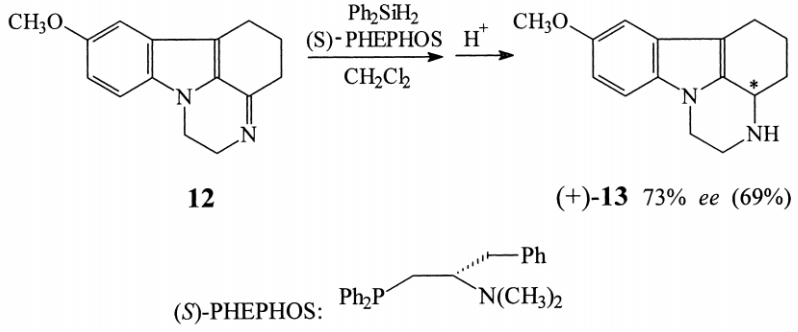
In addition, this asymmetric procedure can be extended to the synthesis of optically active 1,2,3,4-tetrahydro-β-carbolines (**11**; Scheme 7).[12]



11a R=CH_3 (86%, 97% *ee*), **b** R=C_6H_5 (83%, 96% *ee*)

Scheme 7.

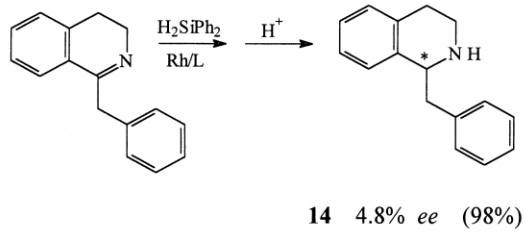
The homogeneous catalysis by transition metal complexes allows an asymmetric hydrosilylation, in order to obtain non-racemic nitrogen heterocycles.[13] Thus, catalytic hydrosilylation of **12**, performed with diphenylsilane and [Rh(COD)Cl]$_2$–(*S*)-PHEPHOS [(*S*)-PHEPHOS=(*S*)-(2-dimethylamino-3-phenylpropyl)diphenylphosphine] yields (+)-2,3,3a,4,5,6-hexahydro-8-methoxy-(1H)-pyrazino[3,2,1-jk]carbazole (**13**) — the enantiomer of the antidepressant 'Pyrazidole' with 73% *ee* (Scheme 8).



Scheme 8.

The enantiomeric purity depends to a large extent on the substrate/catalyst ratio, stereoselectivity generally increasing with an increase in this ratio. The maximum *ee* was obtained at the ratio S/Rh=400.

This method, however, is not always successful, since the hydrosilylation with subsequent hydrolysis of 1-benzyl-3,4-dihydroisoquinoline leads to the corresponding tetrahydroisoquinoline (**14**) with only 4.8% *ee* (Scheme 9).



Scheme 9.

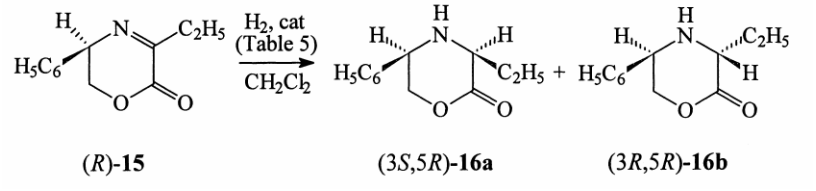
2.2. Diastereoselective catalytic reduction

This section deals with heterogeneous catalytic hydrogenation of cyclic imines containing a stereogenic centre in the β-position (1,3-asymmetric induction).

Table 5
Catalytic hydrogenation of (*R*)-5-phenyl-3,4-dehydromorpholin-2-one **15**[14]

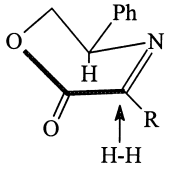
Catalyst	(3*S*,5*R*)-**16** : (3*R*,5*R*)-**16**
Pd/C	3.6 : 1.0
Rh/C	1.5 : 1.0
Ru/C	no reaction
Pt/C	3.2 : 1.0
PtO_2	>15 : 1.0
$(Ph_3P)_2RhCl$	no reaction

(*R*)-5-Phenyl-2-ethyl-3,4-dehydromorpholin-2-one (**15**) was converted to (3*S*,5*R*)-**16** with 78% diastereomeric purity (Scheme 10, Table 5).[14]



Scheme 10.

The observed stereoselectivity can be explained by assuming that **15** in the preferred conformation exists as a folded system, so that the hydrogen addition occurs at the less hindered side (Schemes 10 and 11).



Scheme 11.

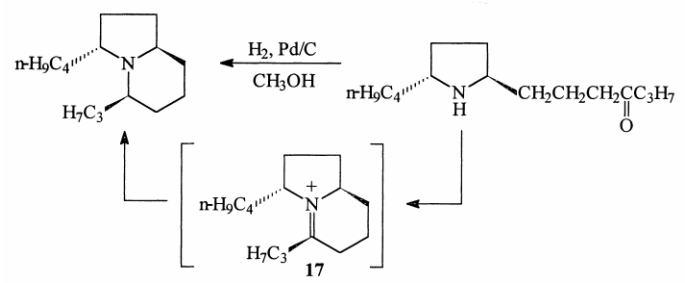
This synthetic strategy is commonly used in the stereoselective synthesis of a number of 3,5-disubstituted indolizine alkaloids. For instance, the key step in an easy and highly enantioselective route to (−)-gephyrotoxine 223 AB involves the hydrogenation of iminium intermediate **17** by Pd/C in methanol. This procedure makes (−)-(3*R*,5*R*,9*R*)-3-butyl-5-propyloctahydroindolizine available in an enantiomerically pure form (Scheme 12).[15]

Further examples of using this methodology are given in Schemes 13 and 14.[16]

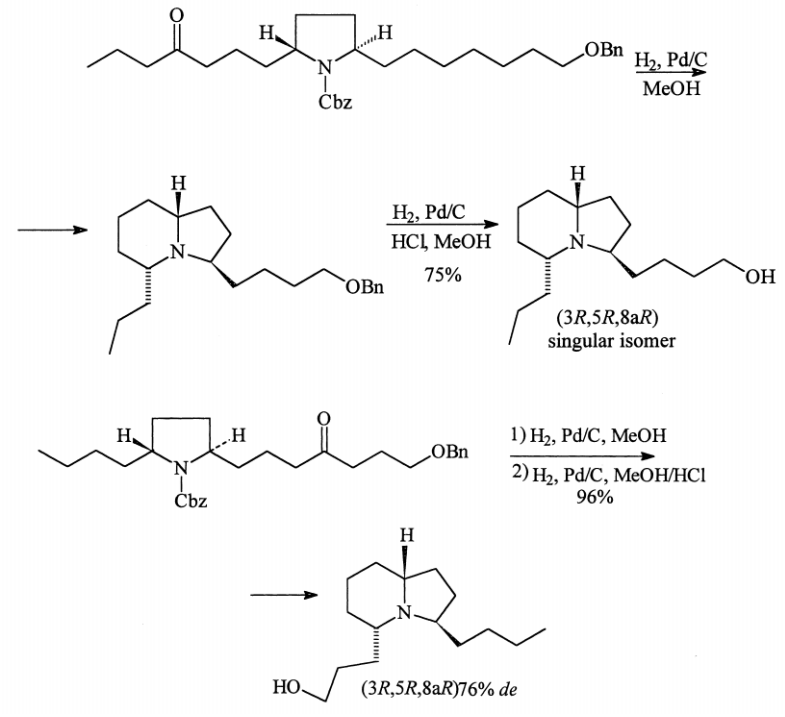
3. Stereoselective hydride reduction

3.1. Enantioselective hydride reduction

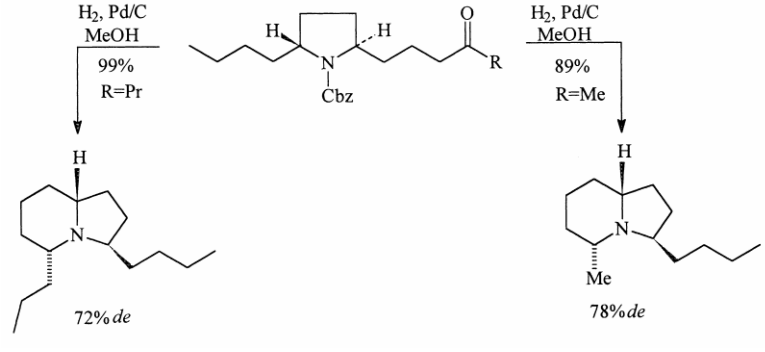
The stereoselective reduction of the carbon–nitrogen double bond discussed in this part of the review deals with the use of chiral sodium acyloxyborohydrides. Thus, 3,4-dihydropapaverine **18** underwent



Scheme 12.



Scheme 13.

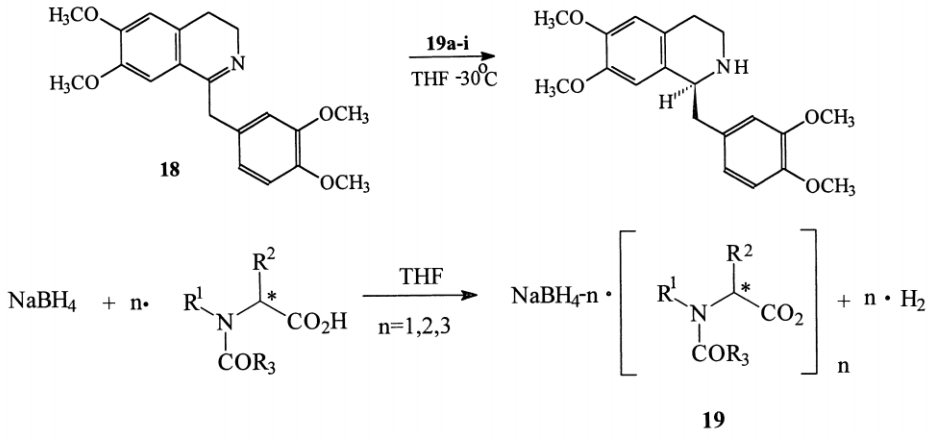


Scheme 14.

Table 6
Enantioselective reduction of dihydropapaverine **18** with chiral sodium alkoxyborohydrides **19a–i**[17]

19	R^1	R^2	R^3	n	Time (h)	Yield (%)	*ee* (%)
a	-[CH$_2$]$_3$-		OCH_2Ph	1	20	54	0
b	-[CH$_2$]$_3$-		OCH_2Ph	2	20	46	18
c	-[CH$_2$]$_3$-		OCH_2Ph	3	12	68	60
d	-[CH$_2$]$_3$-		CH_3	3	12	72	55
e	-[CH$_2$]$_3$-		Ph	3	12	68	60
f	-[CH$_2$]$_3$-		OBu-t	3	9	57	58
g	H	CH_3	OCH_2Ph	3	7	64	16
h	H	$CH(CH_3)_2$	OCH_2Ph	3	9	54	10
i	H	CH_2Ph	OCH_2Ph	3	6	83	8

enantioselective reduction with these new agents **19a–i**, which are easily prepared by reaction of $NaBH_4$ with N-acyl α-amino acids (Table 6, Scheme 15).[17]



Scheme 15.

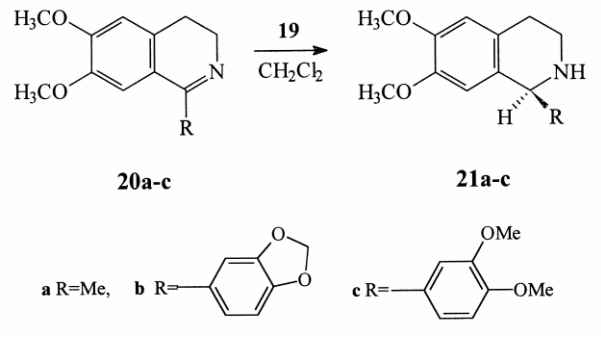
As evident from Table 6, the highest *ee*s (55–60%) of (*S*)-norlaudanosine were achieved when triacyloxyborohydrides **19c–f**, prepared from (*S*)-N-acylproline, were used. Moreover, it is noteworthy that the size of N-acyl groups (substituent R^3) in these derivatives slightly influences the outcome of the reaction (Scheme 15).

The solvent effect on this enantioselective reduction was also examined. The imine **18** was treated with **19c** in different solvents, and both dichloromethane and 1,1-dichloroethane afforded better *ee*s (70%) (Table 7).[17]

The simple and highly effective enantioselective reduction of other cyclic imines was carried out using **19c**. Thus, 1-substituted 3,4-dihydroisoquinoline derivatives **20a–c** were reduced with **19c** (2,5 equiv.) in CH_2Cl_2 at room temperature for 22 h, to give the corresponding (*S*)-amines (salsolidine **20a**, norcryptostyline **20b**, and norcryptostyline II **20c**, respectively) with high yields (85–90%) and with excellent enantioselectivities (70–86% *ee*) (Scheme 16).[17]

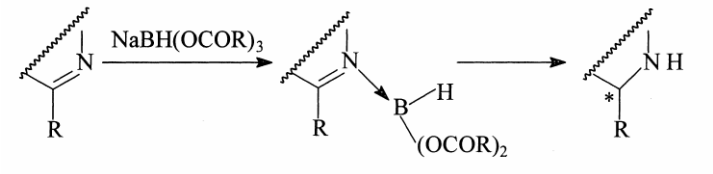
Table 7
Influence of solvents on the efficiency of the dihydropapaverine **18** reduction with **19c**

Solvent	Time (h)	Yield (%)	*ee* (%)
C_2H_5O	8	35	66
DME	144	60	42
CH_3CN	144	60	48
$PhCH_3$	8	53	65
$AcOC_2H_5$	44	74	63
CH_2Cl_2	6	70	71
CH_3CHCl_2	44	79	70
$Cl_2CHCHCl_2$	30	89	6



Scheme 16.

This reduction was assumed to proceed via formation of an imine–borane complex followed by intra- or intermolecular hydride reduction of the imino group (Scheme 17).



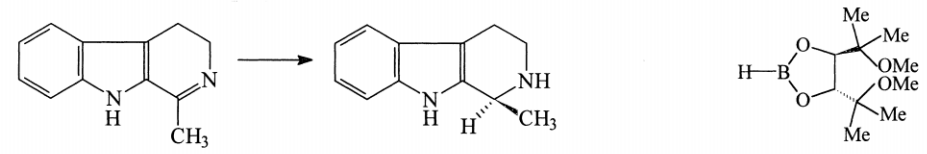
Scheme 17.

In analogy, under the same conditions, 1-methyl-3,4-dihydro-β-carboline (**22**) gave tetrahydroharman (**23**) with 85% chemical yield and 79% *ee*.

In contrast, when the imine **22** underwent reduction with dialkoxyborane **24** at −78°C, after 10 min, **23** was obtained with 98% yield but with 42% *ee* (Scheme 18).[18]

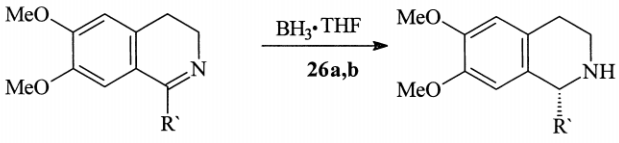
Recently, a fundamentally different approach for the enantioselective reduction of dihydroisoquinoline derivatives **25** utilising enantioface-selective coordination on the imine nitrogen was reported.[19] Thus, thiazazincolidine complex **26**, was shown to be an excellent catalyst for enantioselective reduction of **25** with $BH_3 \cdot THF$ to the corresponding amines **27** in good *ee* (Scheme 19, Tables 8 and 9).[19]

The absolute configuration of the newly generated stereogenic centre in products **27** was found to be *R* in all cases, which would be expected from the presumed working model **28A**. These results may be



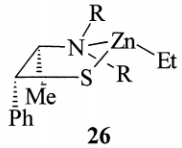
22 **23** **24**

Scheme 18.



25a-d (*R*)-**27-a-d**

a R`=Me, **b** R`=3,4-(Meo)$_2$C$_6$H$_3$CH$_2$-, **c** R`=3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$-, **d** R`=3,4-(MeO)$_2$C$_6$H$_3$-



26

R,R=(CH$_2$)$_5$

Scheme 19.

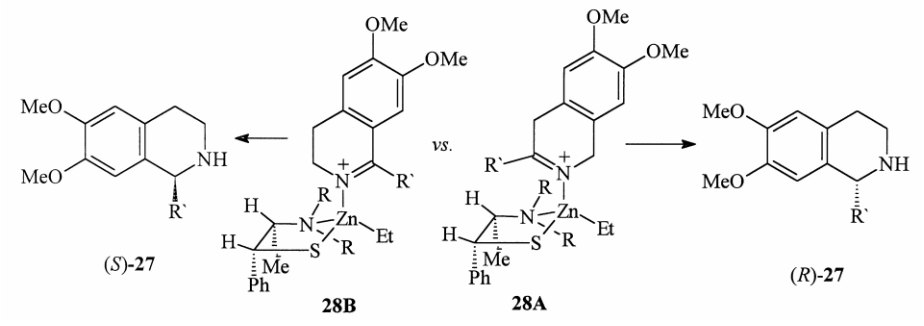
Table 8
Reduction of 3,4-dihydoisoquinoline with 2 equiv. of $BH_3 \cdot THF$ with thiazazincolidine catalyst in toluene[19]

Substrat	Temp. (°C)	Time (h)	*ee* (%)	Yield (%)
25a	10	12	62	81
	0	12	79	75
	-5	12	86	65
25b	-5	4	78	83
25c	0	4	68	65
	-5	4	76	25
25d	-5	4	24	92

rationalised by assuming that the unfavourable $A^{1,3}$ strain between the alkyl group (R') and the ethyl group on the zinc atom in **28B** is more severe than the steric interaction between the alkyl group (R') and two hydrogens on the catalyst ring in **28A** (Scheme 20). In addition to this steric reason, the anti-relationship between the C=N bond in the substrate and the Zn–C bond in the catalyst seems to make complex **28A** the lower-energy species presumably due to electronic reasons.[19]

Table 9
Products ratio in the reduction of iminium ions **29**[20]

R	Ar		
	C_6H_5	2-ClC_6H_4	2,6-$Cl_2C_6H_3$
	30a : 30b	**30a : 30b**	**30a : 30b**
CH_3	91 : 9	100 : 0	98.4 : 1.6
C_2H_5	92 : 8	95 : 5	100 : 0
i-C_3H_7	88 : 12	98,6 : 1,4	98,6 : 1,4
3,4-dimethoxybenzyl	94 : 6	87 : 13	99 : 1



Scheme 20.

3.2. Diastereoselective hydride reduction

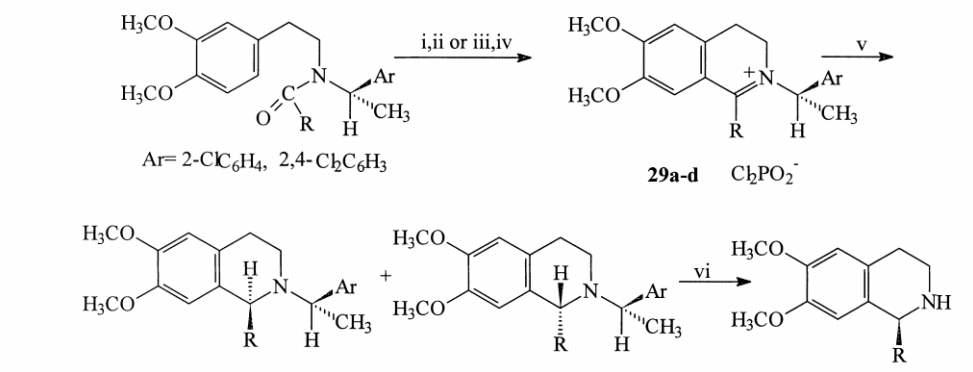
The contemporary methodology based on the hydride reduction of an endocyclic carbon–nitrogen double bond constitutes a powerful tool for the synthesis of saturated nitrogen containing heterocycles with high *de*. In particular, reduction with boron hydride of iminium ions prepared either before or in situ (for instance in acidic medium) is often very effective. In this case, the stereocontrolled formation of an iminium ion–borohydride ion pair prior to hydrogen reduction seems highly probable. Consequently, during the last few years numerous stereoselective syntheses based on this methodology were developed, making use of various chiral auxiliaries and reagents.

Polniaszek and co-workers[20] have extensively investigated the stereoselective nucleophilic addition of hydride ion to the carbon–nitrogen double bond of chiral iminium ions (**29**) derived from chiral amines. The iminium salts reacted with excess solid $NaBH_4$ at −78°C to give chiral 1-substituted tetrahydroisoquinolines. Depending on the relative size difference between methyl and aryl groups in iminium ions, a varying isomer ratio was observed (Table 9).

As shown in the Table 9, good to excellent diastereoselectivity was observed for all entries. For steric reasons the iminium ions **29** are preferentially attacked by hydride ion from the *re* diastereoface. (*S*)-(−)-Salsolidine (**4a**) and (*S*)-(−)-noraudanosine (**30**) were prepared with high enantiomeric purity by this synthetic methodology after removing the chiral auxiliary (Scheme 21).[20]

Reactants and conditions: (i) $BH_3 \cdot THF$, $BF_3 \cdot Et_2O$, THF, reflux, 2–4 h; (ii) Ac_2O **29a**, propionyl chloride **29b**, DMAP, Et_3N, CH_2Cl_2, rt; (iii) for **29d** (3,4-dimethylphenyl)acetic acid, DCC, CH_2Cl_2, rt; (iv) benzene–$POCl_3$, 90°C; v. 4–5 equiv. $NaBH_4$, 3 h, −78°C; (vi) H_2, 10% Pd/C, EtOAc–EtOH, 10% HCl.

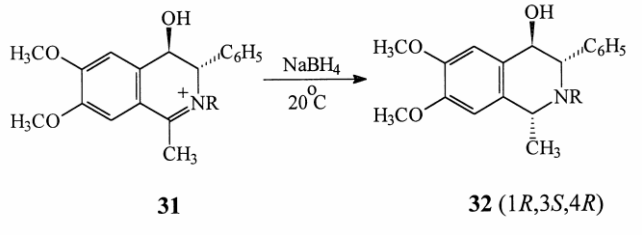
Similarly, the hydride reduction of homochiral (3*S*,4*R*)-1-methyl-3-phenyl-4-oxy-6,7-dimethoxy-3,4-



Reactants and conditions: i. BH_3-THF, BF_3•Et_2O, THF, reflux, 2-4 h; ii.Ac_2O **29a**, propionyl chloride **29b**, DMAP, Et_3N, CH_2Cl_2, r.t.; iii. For **29d** (3,4-dimethylphenyl)acetic acid, DCC, CH_2Cl_2, r.t.; iv.Benzene-$POCl_3$, 90 °C; v. 4-5 equiv. $NaBH_4$, 3h, -78 °C; vi.H_2, 10% Pd/C, EtOAc-EtOH, 10% HCl

Scheme 21.

dihydroisoquinoline **31** with $NaBH_4$ in MeOH at 20°C led to (1*R*,3*S*,4*R*)-tetrahydroisoquinoline **32** in high *ee* (Scheme 22).[21]



Scheme 22.

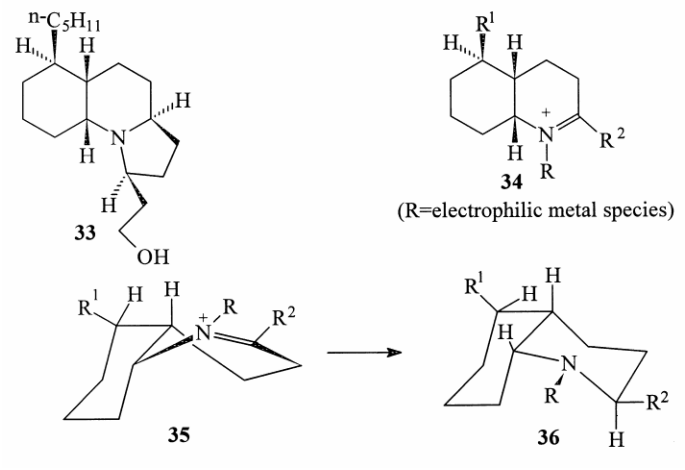
The key step of the total synthesis of (±)-perhydrogephyrotoxin **33** consists of the stereocontrolled reduction of iminium ion like **34**. It was anticipated that iminium ion **34** would be preferentially reduced via a transition-state conformer related to **35**, since the other conformer would be destabilised by an $A^{1,2}$ interaction between *R* and C-9 (Scheme 23).[22]

The stereoelectronic preference for initial *trans*-diaxial alignment of the entering hydride nucleophile and for the nitrogen lone pair formation would then lead to decahydroquinoline **36**. This approach was applied to the stereocontrolled synthesis of (±)-**33** from *trans*-1,3-butadiene-1-carbamate (Scheme 24).

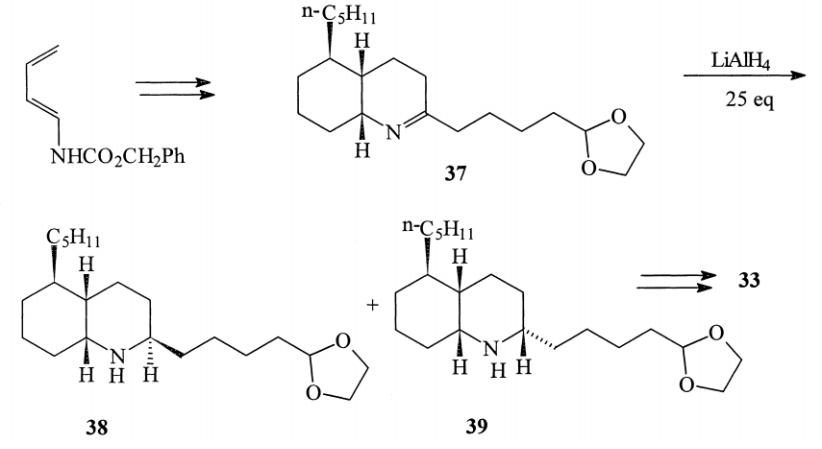
Treatment of imine **37** with ≈25 equiv. of $LiAlH_4$ in diethyl ether at −15°C gave *cis*-decahydroquinolines **38** and **39** with 80% *de* (Scheme 23).[22]

The observed stereoselectivity can be explained by assuming that a transition-state conformer related to **35** is preferred and stereoselective reduction of **34** takes place from the sterically hindered concave face.[22]

Diastereoselective reduction of dehydroprotoberberines **40** with $NaBH_4$ in THF provided the tetrahydroprotoberberines **41a** and **41b** (as a 4:1 ratio of α/β C-8 diastereomers) and **42** (as a single C-8 diastereomer), respectively. The study of stereochemistry of **37** and **38** by NOE difference spectroscopy and ^1H–^1H decoupling experiments revealed that the major isomer of **41a** and **42** presents a *trans*-fused D/C ring system in a chair-like arrangement with the C-8 substituent in an equatorial disposition. The

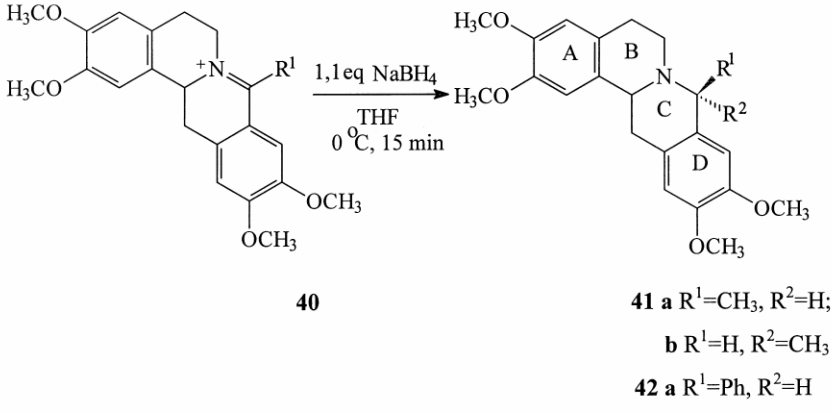


Scheme 23.



Scheme 24.

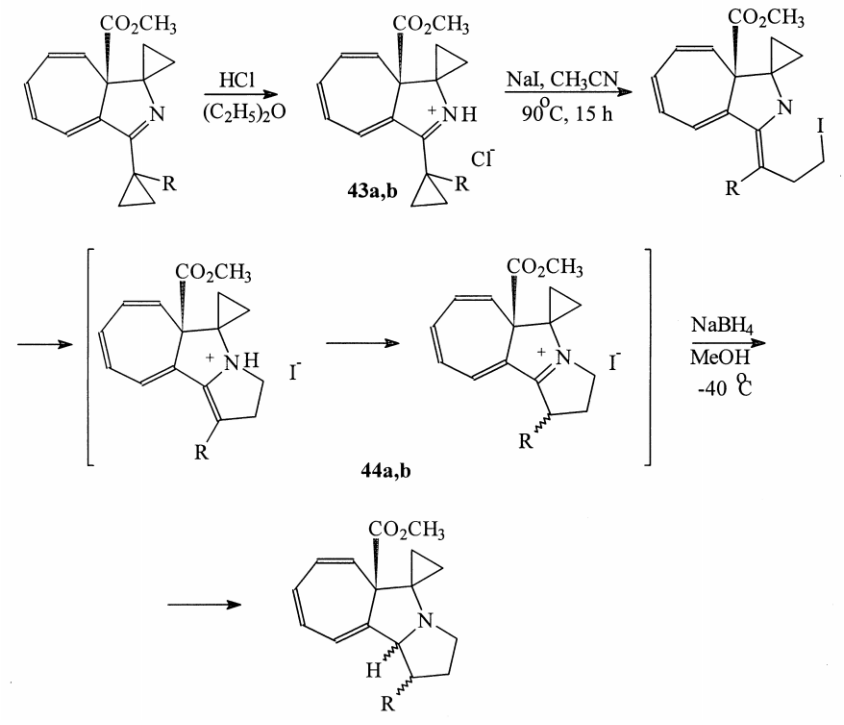
minor isomer **42b** most likely adopts a *cis* form at the B/C ring system with the C-8 Me group in pseudoaxial disposition (Scheme 25).[23]



Scheme 25.

An analogous stereoselective reduction was used in the synthesis of methyl 1,2,3,5,5a,10b-hexahydrospiro[cyclohepta[a]pyrrolizine-5,1′-cyclopropane]-5a-carboxylates. The iminium ion **43a** (R=H) was rearranged by nucleophilic attack of iodide and subsequent borohydride reduction (MeOH, −40°C) of the resulting iminium–enammonium salt **44** to give the tricyclic amine **45a** with 75% yield as a diastereomeric mixture, A:B (1:1.3) (Scheme 24).[22] The reduction of **44b** (R=Me) led to amine **45b** as a mixture of all four diasteremers (with ratio 4.7:3.2:2.9:1) with a total yield of 51%.[24]

The same method was applied to the dihydroisoquinoline derivatives **46**. After rearrangement and subsequent reduction with $NaBH_4$ in methanol at 0°C, 1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolines *cis*- and *trans*-**47** were isolated with 78% yield and a (1*R*,5*S*,10b*S*)-**47**:(1*S*,5*S*,10b*S*) ratio of 1.8:1 (Schemes 26 and 27).[24]



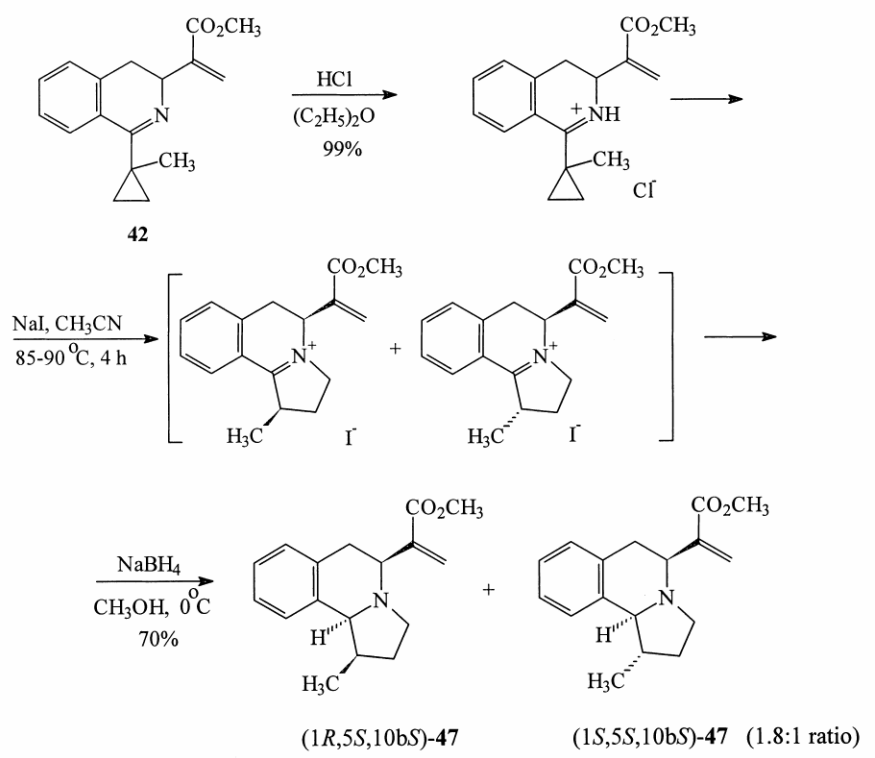
Scheme 26.

A total synthesis of (−)-mitragine **48** (Scheme 28), an analgesic indole alkaloid, starting from an enantiomerically pure alcohol (*R*)-(+)-**49** was reported by Takayama and co-workers.[25]

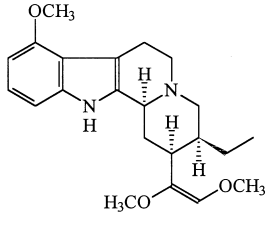
The key step of the synthesis involves the reduction of pyridinium salt **50** with sodium borohydride to yield two diastereomers **51a** and **51b** with 33% and 27% yields, respectively (Scheme 29).[25]

The stereoselective hydride reduction of iminium ion **52** was used in the biomimetic approach towards the pumiliotoxin C.[24] Reaction of **52** with $NaBH_4$ in MeOH led to the formation of two isomeric products in a 15:85 ratio, which were also obtained by using $NaBH_3CN$ in THF/HCl at pH 4.0, although with low stereoselection (45:55). The subsequent reaction of this mixture with sodium in liquid NH_3 and hydrogenolytic cleavage of the N-benzyl group then gave decahydroquinolines **53a**,**b** in a 15:85 ratio (Scheme 30).[26]

Stereoselective reduction of iminium ion is a key step in the enantiospecific synthesis of (+)- and (−)-coniine.[25] Reaction of **54** with $NaBH_4$ in EtOH gave alcohols **56a** and **56b**. Under hydrogenolysis conditions the chiral auxiliary was cleaved giving (2*S*)-(+)-coniine with 95% yield and enantiomeric



Scheme 27.

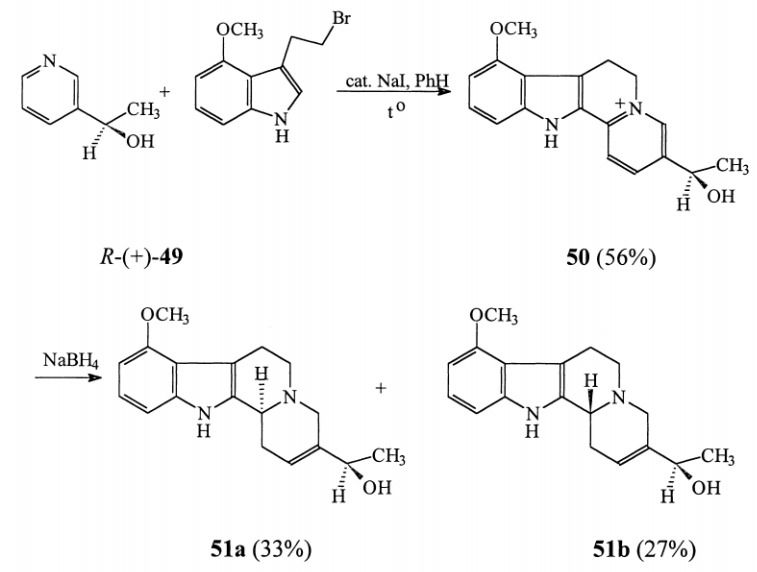


Scheme 28.

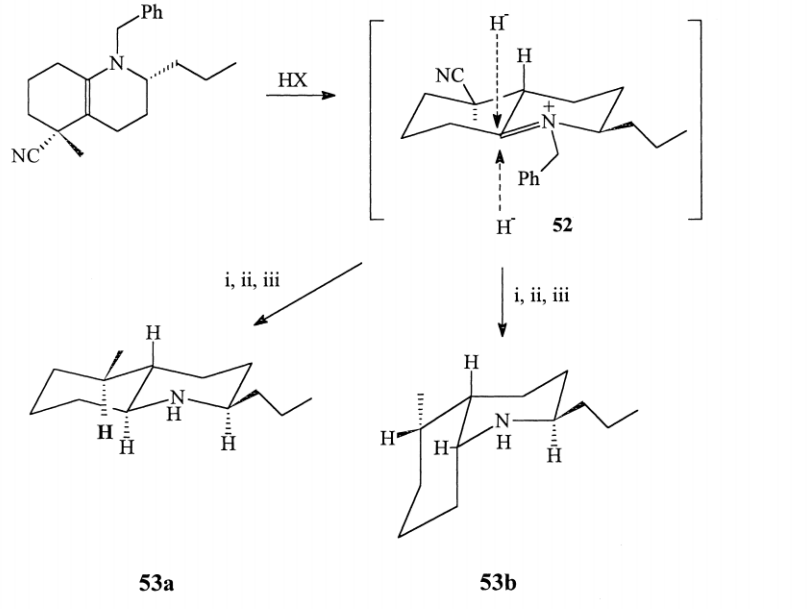
purity ≈98%. The high stereoselectivity observed in the reaction of **54** with hydride ion involves first formation of an iminium ion by elimination of the CN group, followed by approach of the hydride ion under complete stereoelectronic control from the axial direction to the iminium conformer **55** (Scheme 31).[27]

The diastereoselective hydride reduction of chiral indoles represents an efficient method to prepare indolines. The reduction of indoles by boron hydrides in an acid medium is known to proceed via intermediate formation of an indoleninium ion.[28] The reaction of (*S*)-1-(1-methylbenzyl)-2-alkylindoles **57** with various boron hydrides was investigated in detail.[29,30]

As shown in Table 10, moderate to good diastereoselectivity was observed for all entries. As expected, when complex boron hydrides are used the reaction diastereoselection increases. Probably, the stereo-controlled formation of an indoleninium ion–borohydride ion pair precedes the hydride reduction step. In contrast, when borane–amine complexes were used, only poor stereoselectivity was observed ($de \leq 40\%$) (Scheme 32).[29]



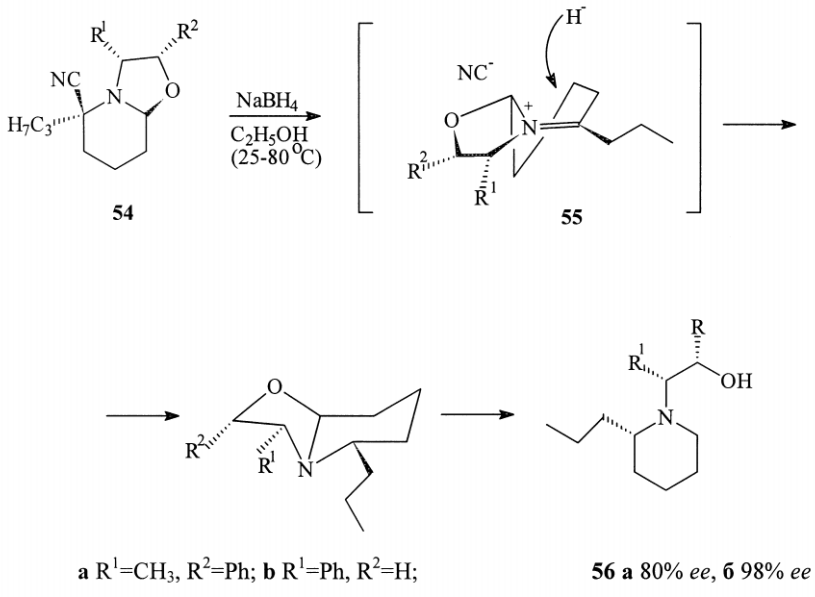
Scheme 29.



Reactants and conditions: i. a) $NaBH_4$, MeOH, r.t. , 20 h; b) $NaBH_3CN$, THF, pH 4, r.t., 2 h;
ii. Na/NH_3, THF, -78 °C, 1 h ; iii. H_2, Pd/C 10%, MeOH, H^+, 12 h.

Scheme 30.

The nucleophilic addition reaction of the hydride ion to the carbon–nitrogen double bond of the indoleninium ion **58** presents an example of 1,3-asymmetric induction. In contrast, the reaction of indole **60** with $NaBH_3CN$ in CF_3CO_2H is characterised by low diastereoselection,[31] controlled by 1,2-asymmetric induction (Scheme 33).



Scheme 31.

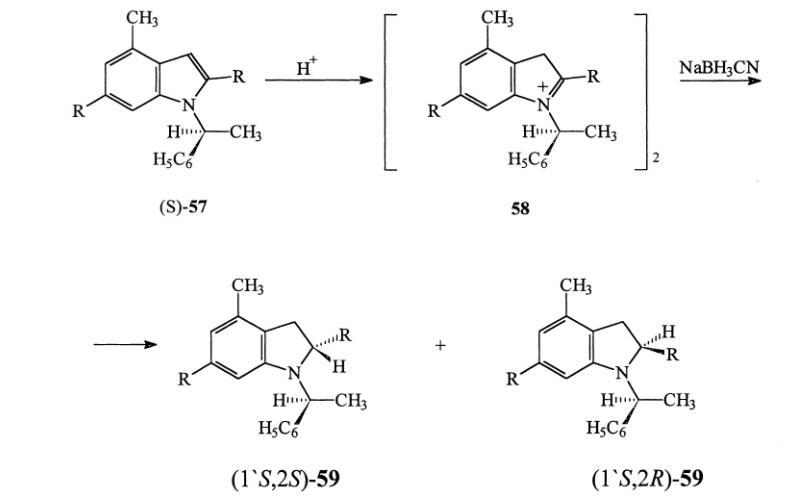
Table 10
Reduction of indole (*S*)-**57a** with boron hydrides[29]

entry	boron hydride (BH)	Conditions				(1`*S*,2*S*)-**59**: (1`*S*,2*R*)-**59**	*de* (%)	yield (%)
		molar ratio BH:**57**	solvent	temp (°C)	time (h)			
1	$NaBH(OAc)_3$	2	AcOH	r.t.	1	2.6:1	44	85
2	$NaBH_3CN$	2.5	MeOH-HCl	-50	1	5:1	67	90
3	$NaBH_3CN$	2	MeOH-HCl	-80	1	9:1	80	88
4	Bu_4NBH_4	3	CH_2Cl_2	reflux	20			*
5	$NaBH_4$	4	MeOH-HCl	-80	2	6:1	71	
6	$C_2H_5N{\bullet}BH_3$	3	MeOH-HCl	-50	1.5	2:1	33	
7	*t*-$BuNH_2{\bullet}$ BH_3	8	MeOH-HCl	-80	1.5	2.3:1	39	

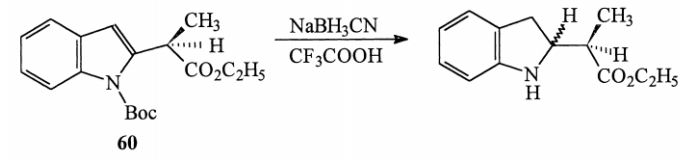
*no reaction

4. Conclusion

The examples collected in this review demonstrate that stereoselective reduction of a carbon–nitrogen double bond is widely used in the construction of saturated nitrogen-containing heterocycles. Non-racemic target chiral compounds can be obtained by homo- and heterogeneous hydrogenation, hydrosilylation as well as hydride reduction. These synthetic techniques make the desired products available with high stereoisomer ratios, and they open convenient routes to the preparation of various heterocyclic compounds which can be used as intermediates in the construction of natural products, pharmaceuticals, food additives and other interesting molecules.



Scheme 32.



Scheme 33.

Acknowledgements

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