Selected Recent Developments in the Enantioselective Reduction of Imines by Asymmetric Transfer Hydrogenation

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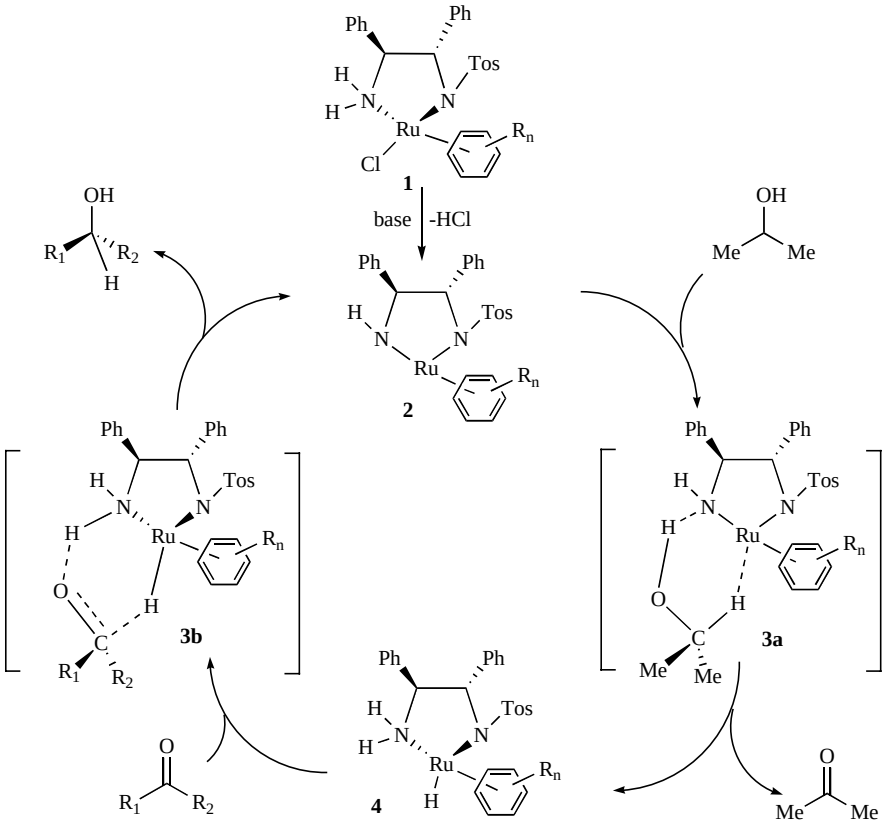
Abstract: The asymmetric transfer hydrogenation is a highly versatile tool for the stereoselective reduction of C=O and C=N prochiral groups. Carbonyl compounds have been the most frequently used as the synthetic substrates but imines were much less popular despite their importance as the sources of chiral amines. This review summarizes recent development in a search for more effective ligands and conditions of the reduction procedure. Particularly useful appear the mono-tosylated 1,2-diamines as the chirality inductors in the presence of a mixture of formic acid and triethylamine as a hydrogen source. Also, the structure of the substrates plays very important role. The cyclic endogenous imines usually give highest optical yield of the products.

Keywords: Imines, chiral amines, stereoselective synthesis, alkaloids.

1. INTRODUCTION

Synthetic organic chemistry has been aimed on stereoselective construction of complex derivatives for the last few decades since it was proven that enantiomers of a given molecule differ usually in their bioactivity.

Nitrogen containing bases are widely distributed in nature and also many synthetic amines are valuable pharmaceuticals and therefore methods directed toward their stereoselective preparation have been the subject of a number of investigations. Among a variety of developed methods, the stereoselective synthesis of target molecules exploiting carbon-nitrogen double bond reduction is of particular interest. The asymmetric transfer hydrogenation (ATH) procedure has gained a prominent position due to its experimental simplicity and usually high efficiency of the chiral induction. Since 2-propanol or formic acid (usually in the presence of triethylamine) is used as a hydrogen source, a dangerous manipulation with molecular hydrogen can be avoided. This reaction was initially designated for ketones reduction and indeed a tremendous amount of successful examples of enantioselective preparations of secondary alcohols can be found in the literature and is the subject of in-depth reviews [1-7]. In the mid 1990s, Noyori reported [8] that Ru(II) complexes of monosulfonylated 1,2-diamines, such as (1*R*,2*R*)-*N*-(*p*-toluenesufonyl)-1,2-diphenylethylenediamine (TsDPEN) or its enantiomer could be



Scheme 1.

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1570-193X/07 $50.00+.00

applied for the reduction of prochiral imines with an excellent enantioselectivity. Also, Noyori and co-workers studied the mechanism of ATH process in the case of ketones using 1,2-amino alcohols and monotosylated diamines as ligands [9-23] and the same group first described the mechanism as a *metal-ligand bifunctional catalysis* [11]. The reaction involves the formation of ruthenium hydride **4** from a 16-electron precursor **2** and a hydrogen donor (2-propanol or formate). The 18-electron complex **4** that was formed is subsequently involved in a simultaneous hydride transfer from Ru-H and a protonation from N-H moiety in a cyclic transition state **3b** (Scheme **1**).

The chiral information is transferred to the reduced substrate from the ligand molecule which may be anionic or neutral depending on its ability to donate proton during the reduction step [7]. This feature seems to be beneficial to the efficiency of the process. A variety of structures of possible ligands have been investigated and some general remarks can be addressed. Among various combinations of nitrogen, oxygen, phosphorus and sulphur atoms, the amino alcohols and diamine moieties are usually the most readily accessible and are able to give good-to-excellent enantioselectivity. Since the complete coverage of all ligands used in asymmetric transfer hydrogenation is far beyond the scope of this article, only selected examples of popular chiral inductors will be mentioned (Fig. **1**).

All ligands listed in Fig. (**1**), formed a well defined complexes containing ruthenium, rhodium or iridium as a central atom (Fig. **2**).

Also, a new generation of "so-called" tethered complexes **13**-**15** have recently been introduced by Wills and co-workers [21, 23-25] (Fig. **3**).

Prochiral ketones are reduced very effectively using all the above catalytic systems, but the most remarkable enantiocontrol is achieved with monotosylated 1,2-diamines. Interestingly, it was

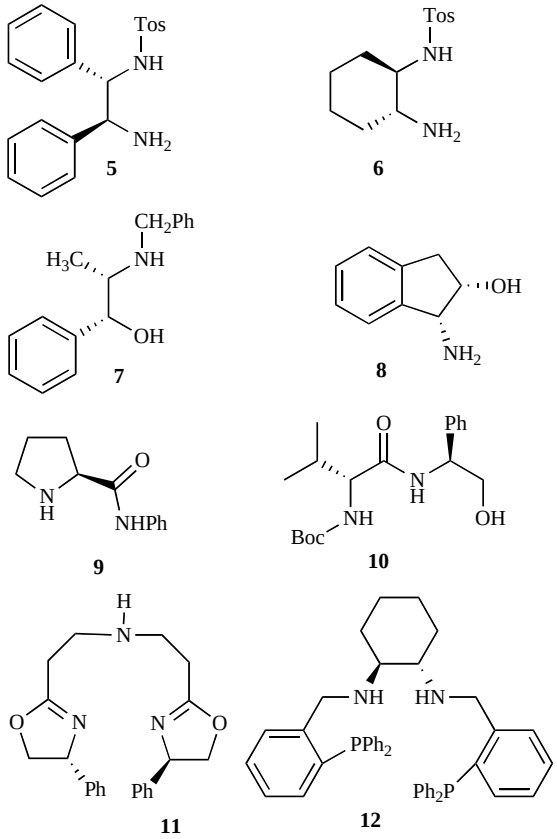


Fig. (1).

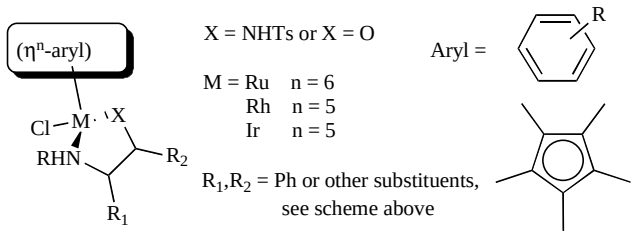


Fig. (2).

demonstrated by Wills [26] that the configuration of the resultant alcohol follows that present at the carbon atom adjacent to the *N*-tosyl group in the ligand molecule. In the case of these ligands, 2-propanol (IPA) or formic acid/triethylamine (TEAF) is used as a hydrogen source and even as a solvent. If 2-propanol is employed as the hydrogen donor, it is often added in a large excess and is used in the combination with strong bases like NaOH, KOH, K_2CO_3 at various concentrations. Although 2-propanol is environmentally friendly and easy to handle, the reversibility of the reaction remains a major drawback that can be avoided using formates as hydrogen donors. Moreover, when 1,2-diamine moiety is present in the ligand molecule, TEAF serves as a preferential and the most effective reagent. It appears that of β-amino alcohols are incompatible with the formic acid/triethylamine reduction system. Also TEAF allows better stereoinduction and a higher rate of the reduction of prochiral C=N bond.

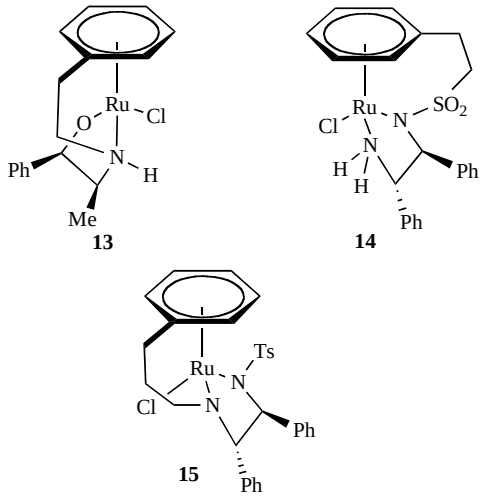


Fig. (3).

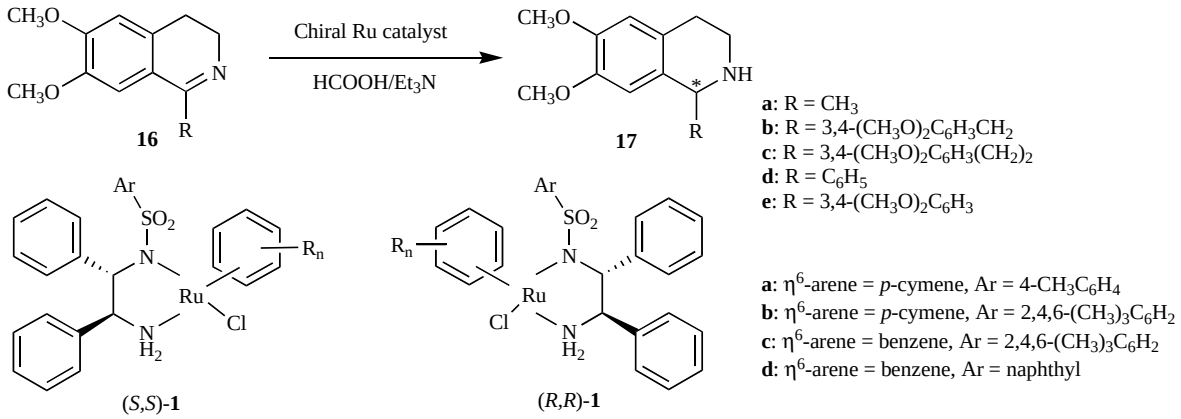
In general, imines are far less popular as substrates in the asymmetric hydrogen transfer reaction and only a limited number of applications of this process to imines are cited in the literature [8,27-37].

The research group of Blackmond reported detailed kinetic studies of the asymmetric transfer hydrogenation of imines with formic acid using Rh-chiral diamine catalysts [38]. They discussed the role of bases like Et_3N in metering HCOOH into the catalytic cycle and showed that the rate behaviour strongly depends on the reaction conditions, including the type of the solvent and the method of addition of the transfer agent. The authors suggested that the reaction protocol involving controlled addition of formic acid gave high yields even at high substrate/catalyst ratio (S/C).

The scope and generality of the ATH method was recently been extended even on the use water as the solvent [39].

2. ENANTIOSELSCTIVE REDUCTION OF 3,4-DIHYDROISOQUINOLINES

The Bischler-Napieralski cyclization of the phenylethylamides furnishes cyclic imines that are suitable as substrates for enantioselective reductions [40]. Starting from the fundamental work of



Scheme 2.

Noyori *et al.* [8], the asymmetric transfer hydrogenation created an attractive alternative to the existing procedures of stereoinduction due to its experimental simplicity, safety reasons and usually excellent enantiocontrol.

In his study, Noyori selected the reduction of imine **16a** to amine **17a** in the presence of ruthenium (II) catalysts **1** as the model reaction, as shown in Scheme **2**.

The best results for the reduction was obtained using 5:2 formic acid-triethylamine azeotropic mixture in acetonitrile containing (*S*,*S*)-**1a** at 28°C. The reaction led to the product **17a** in 95% ee and in quantitative yield. The ATH process was conducted equally well in various aprotic solvents including DMF, DMSO and CH_2Cl_2 but not in ethereal or alcoholic media.

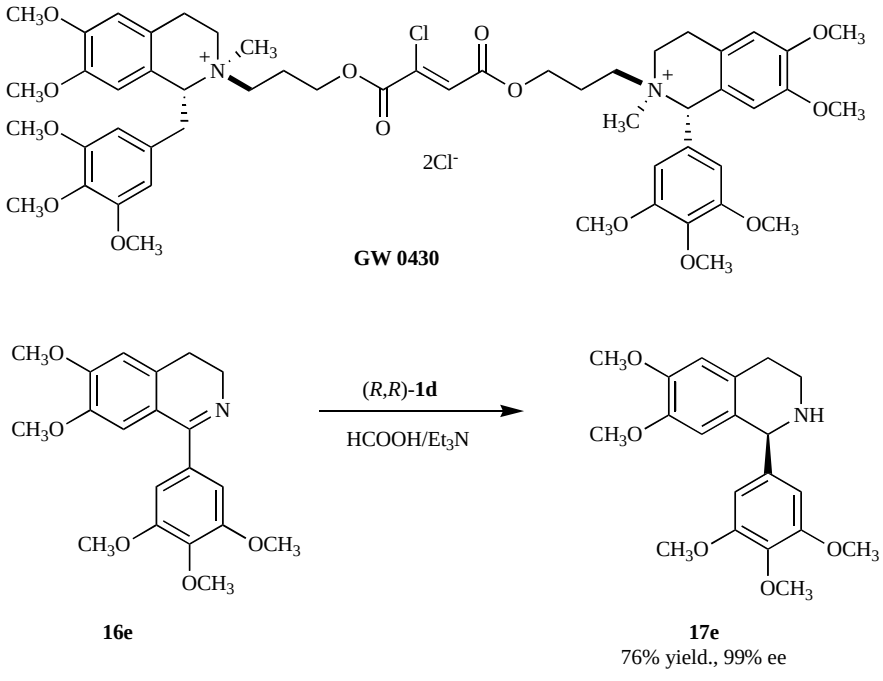
Both NH_2 and $ArSO_2$ groups play crucial role for high reactivity, while the structure of the Ar group and the substitution pattern of the η^6-arene ligand may be fine-tuned depending on the imine substrates. The reaction is normally performed with an S/C ratio of 200, but the ratio can be as high as 1000. This catalytic method is particularly useful for the enantioselective reduction of other 3,4-dihydroisoquinoline derivatives **16b-e** to corresponding amines with excellent ee, as illustrated in Table **1**.

Table 1. Asymmetric Transfer Hydrogenation of 3,4-Dihydroisoquinolines

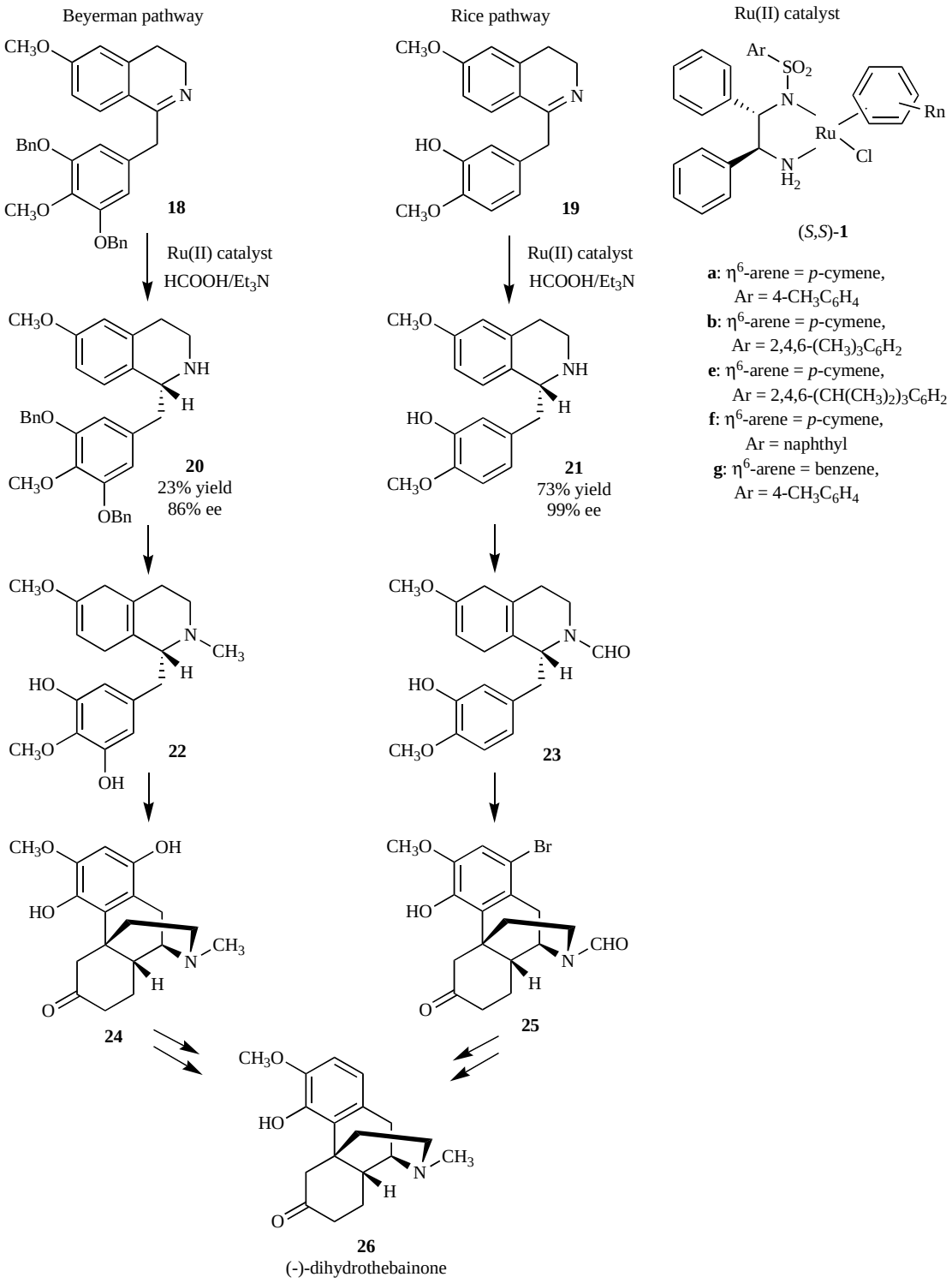
Imine	Catalyst	S/C	Solvent	Time [h]	Yield [%]	Ee [%]	Config.
16a	(*S*,*S*)-**1a**	200	CH_3CN	3	>99	95	*R*
16a	(*S*,*S*)-**1a**	1000	CH_3CN	12	97	94	*R*
16b	(*R*,*R*)-**1b**	200	DMF	7	90	95	*S*
16c	(*R*,*R*)-**1b**	200	CH_2Cl_2	12	99	92	*S*
16d	(*S*,*S*)-**1d**	200	CH_2Cl_2	8	99	84	*R*
16e	(*R*,*R*)-**1d**	100	CH_2Cl_2	12	>99	84	*S*

The same result for the asymmetric reduction of imine **16b** with chiral Ru(II) (*R*,*R*)-**1b** catalyst was obtained by Mujahidin and Doye [41]. The key intermediate in the enantioselective synthesis of (*S*)-laudanosine and (*S*)-xylopinine was amine **17b**, that was obtained in 92% yield with 93% ee.

The asymmetric transfer hydrogenation was used as a key step in synthesis of ultra-short-acting non-depolarizing neuromuscular blocker GW 0430 described by Samano *et al.* [29]. The synthetic pathway for



Scheme 3.



Scheme 4.

this compound involves the enantioselective reduction of imine **16e** – Scheme 3. The amine **17e** was prepared *via* ATH of imine **16e** with Noyori's catalyst (*R*,*R*)-**1d** in the presence of azeotropic mixture of formic acid – triethylamine. The HPLC analysis on a chiral stationary phase of the crude reaction mixture showed, that the desired product **17e** is formed in 83% ee and this was further improved when the formic acid salt of **17e** precipitated from the reaction mixture in 76% yield and in 99% ee [29].

The imine moiety was subjected to the ATH process in a stereoselective synthesis of morphine [28]. Meuzelaar *et al.* used this method to the synthesis of chiral 1,2,3,4-tetrahydroisoquinoline intermediates **20** and **21** in the Rice [42] and Beyerman [43] routes to morphine (Scheme **4**). The asymmetric hydrogen transfer reaction of the "Rice imine" **19** was best carried out in DMF at 20-30^{o}C. When the reaction was performed in acetonitrile or dichloromethane or at the temperature higher than 30^{o}C, the deactivation of the catalyst was observed. The experiments showed that complex (*S*,*S*)-**1b** was the best catalyst for the transfer hydrogenation of imine **19** and gave tetrahydroisoquinoline **21** with 99% ee and in 73% yield.

The synthesis of amine **20**, the intermediate in the Beyerman's route to morphine, was performed under the same conditions (DMF as a solvent, 20°C) that were applied for compound **21**. Some representative results obtained with complexes **1a**,**b**,**e**-**g**, in the presence of TEAF as hydrogen source, are summarized in Table **2**.

Table 2. Results of the Asymmetric Transfer Hydrogenation of Imine 18 Catalyzed by Ruthenium Complexes

Imine	Catalyst	Cat. [mol %]	Time [h]	Ee [%]
18	(*S*,*S*)-**1a**	5	2	86
18	(*S*,*S*)-**1a**[a]	5	2	84
18	(*S*,*S*)-**1b**	5	1.5	81
18	(*S*,*S*)-**1e**	10	2	62
18	(*S*,*S*)-**1f**	10	4	67
18	(*S*,*S*)-**1g**	5	2	81

[a] The complex was prepared *in situ*.

Vedejs *et al.* [30] used the ATH procedure for the enantioselective synthesis of several *ortho*-substituted amines that can be applied as chiral proton donors in other processes. These authors prepared two tetrahydroisoquinoline series: H-series (Z=H) and dimethoxy series (Z=CH_3O), with *ortho*-substituents, like NH_2 and its derivatives **34**-**37**, or other groups X like **33** and **38**, that can be converted into amino group (Scheme **5**).

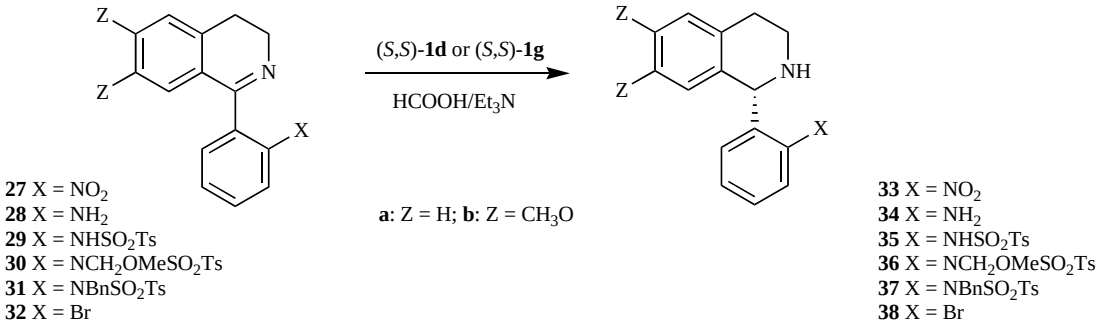
Most of the subsequent studies were performed using (*S*,*S*)-**1g** as the catalyst. The nitrophenyl imine **27a** was not reduced at a useful rate using 1 mol % of (*S*,*S*)-**1g** as the catalyst, while compound **27b** afforded ca. 20% of **33b** with excellent enantioselectivity of 97.1% ee. The asymmetric reduction of **29b** gave no product within 16h using 2 mol% of the catalyst (*S*,*S*)-**1g** and afforded only 11% conversion after 72h with 7.5 mol% of the catalyst. Again, the amine **35** was obtained with an excellent enantiomeric excess (≥96% ee). The reduction of bromophenyl derivative provided the best route to diamine **34**. The asymmetric hydrogenation of **32** proceeded without any of the complications encountered with *o*-amino derivatives and gave amine **38** with 94-98% ee and with good conversion.

The chiral rhodium complexes (*S*,*S*)-**39** and (*R*,*R*)-**39**, generated from $[Cp^*RhCl_2]_2$ and both enantiomers of *N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine were found to provide superior catalysts for the asymmetric transfer hydrogenation of some other heterocyclic imines, as illustrated in Scheme **6** [27].

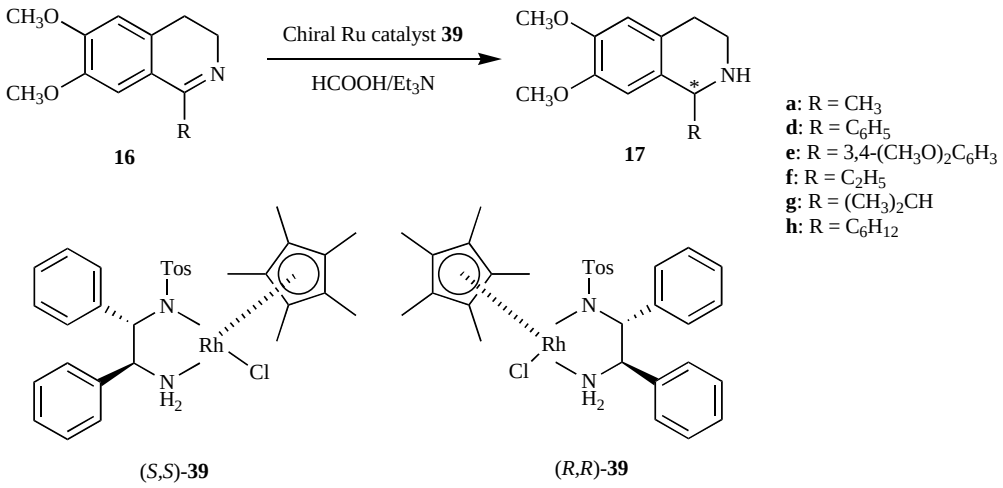
Using 3,4-dihyroisoqunoline **16g** as a model substrate, the conditions for ATH procedure catalyzed by (*S*,*S*)-**39** were optimized. The reactions were carried out using TEAF as hydrogen source at a S/C molar ratio from 200:1 up to 1000:1 without decreasing the yield of the process, see Table **3**. The reaction with **16g** proceeded rapidly and it was completed in 10min at 20°C, with an excellent ee value (99%). The catalyst was still active at -20°C, and furthermore did not show any decrease in the enantioselectivity at the temperature as high as +40°C in acetonitrile. The reaction failed when isopropanol with triethylamine was used as hydrogen source. Only in two cases the ATH gave tetrahydroisoqiunolines **17d** and **17e** with very low enantioselectivity.

In the first enantioselective synthesis of tubulosine **44** and emetine **45**, the enantioselective catalytic reduction was again used as the key step [32]. The C-1 substituted 3,4-dihydroisoquinoline **40**, an important intermediate in both synthetic pathways, was transformed into the enantiopure compound **41** using the ATH catalytic system with (*R*,*R*)-**1a** as the catalyst and TEAF as the hydrogen source (Scheme **7**). The product was obtained in 93% yield and 95% ee.

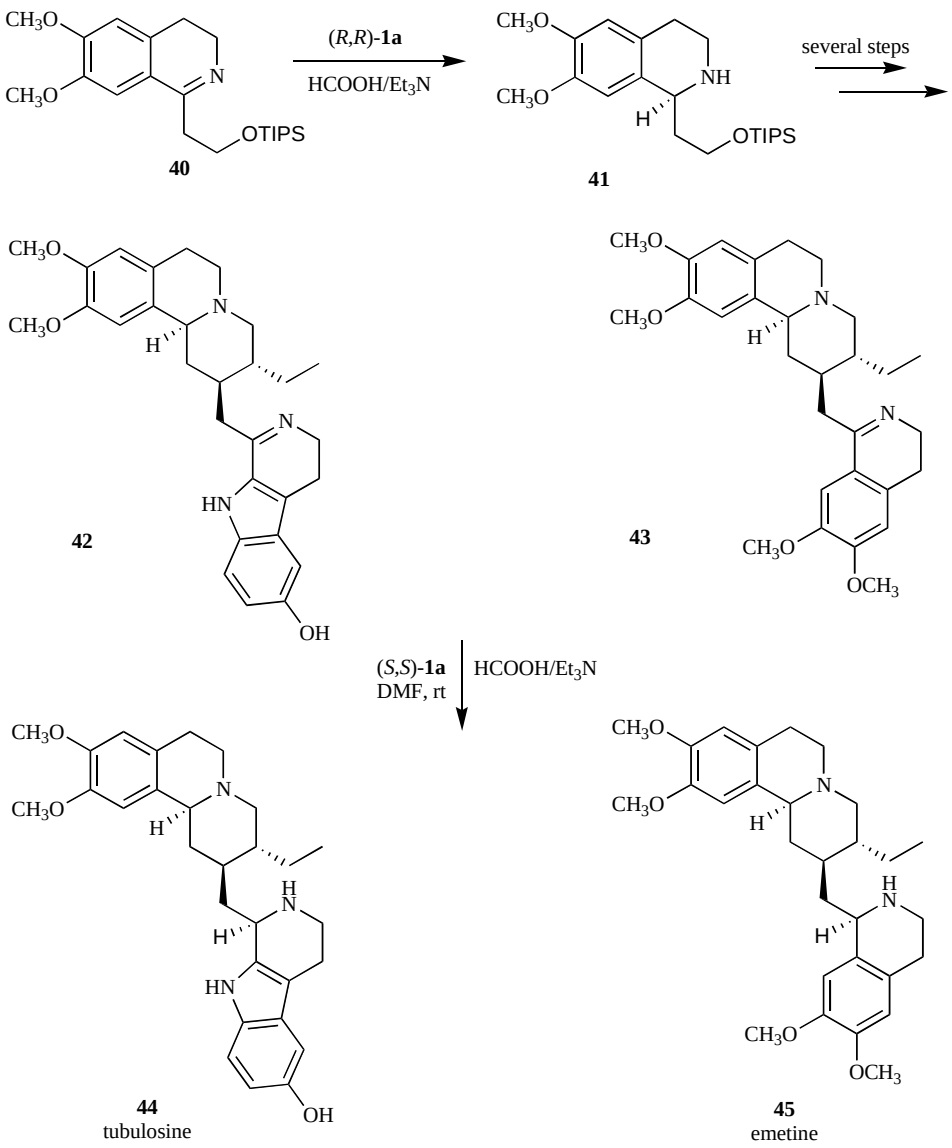
In the next step, the amine **41** was used in a domino Knoevenagel/hetero-Diels-Alder reaction to afford imines **42** and **43**. In the final step, the hydrogenation of imine **42** using (*S*,*S*)-**1a** in the



Scheme 5.



Scheme 6.



Scheme 7.

presence of triethylamonium formate, gave the corresponding amine in the yield of 78% and 95% ee. After the cleavage of the benzyl ether by hydrogenolysis, tubulosine **44** was obtained. The asymmetric reduction of imine **43** gave emetine **45** with 95% ee and 73% yield.

Table 3. Asymmetric Transfer Hydrogenation of Imines 16 Catalyzed by Rhodium Complexes

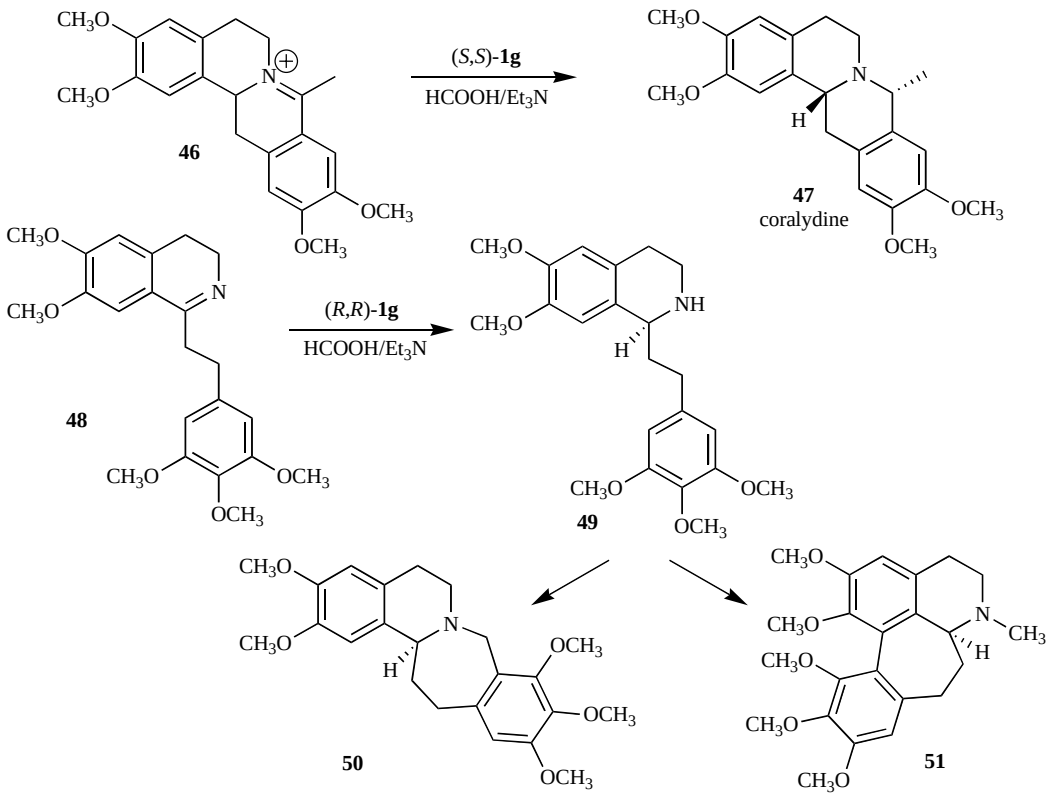
Imine	Catalyst	S/C	Solvent	Time [min]	Yield [%]	Ee [%]	Config.
16a	(*S*,*S*)-**39**	200	CH_3CN	10	96	89	*R*
16a	(*R*,*R*)-**39**	200	CH_2Cl_2	10	95	90	S
16f	(*S*,*S*)-**39**	200	CH_2Cl_2	10	93	83	R
16g	(*S*,*S*)-**39**	200	CH_2Cl_2	10	96	99	*R*
16g	(*S*,*S*)-**39**	1000	CH_2Cl_2	60	94	93	*R*
16g	(*S*,*S*)-**39**	1000	CH_3CN	60	94	97	*R*
16d	(*S*,*S*)-**39**	100	CH_2Cl_2	180	90	4.4	R
16e	(*S*,*S*)-**39**	100	CH_2Cl_2	180	89	3.2	*R*
16h	(*S*,*S*)-**39**	200	CH_2Cl_2	10	94	97	R

We have also adopted the ATH methodology in our laboratory to the enantioselective synthesis of tetrahydroisoquinoline and tetrahydro-β-carboline alkaloids or their synthetic congeners [35-37,44].

The protoberberine alkaloid (*R*,*R*)-coralydine **47** was obtained employing the conditions for the asymmetric hydrogen transfer proposed by Noyori (Scheme **8**) [8]. Thus, the reduction of imine **46** with TEAF in acetonitrile containing chiral ruthenium complex (*S*,*S*)-**1g** gave (*R*,*R*)-coralydine **47** in 85% yield and 63% ee. The final alkaloid can be easily purified to a high degree of the optical purity by the crystallization of its hydrochloride salt [36].

Much better results were obtained in the asymmetric synthesis of other isoquinoline alkaloids – homoprotoberberine **50** and homoaporphine **51** [36]. An intermediate in the preparation of these compounds, the amine **49** was obtained in the enantioselective reduction of imine **48** using (*R*,*R*)-**1g** as the chiral catalyst. Under the same conditions as before, the reaction was completed in 12h to afford (*S*)-**49** in 87% chemical yield and excellent optical purity (98.6% ee).

Having been encouraged by positive results in the enantioselective formation of isoquinoline derivatives with the use of the asymmetric transfer hydrogenation protocol [8], we applied this method to the stereoselective synthesis of an anthelmintic drug praziquantel **59**. The



Scheme 8.

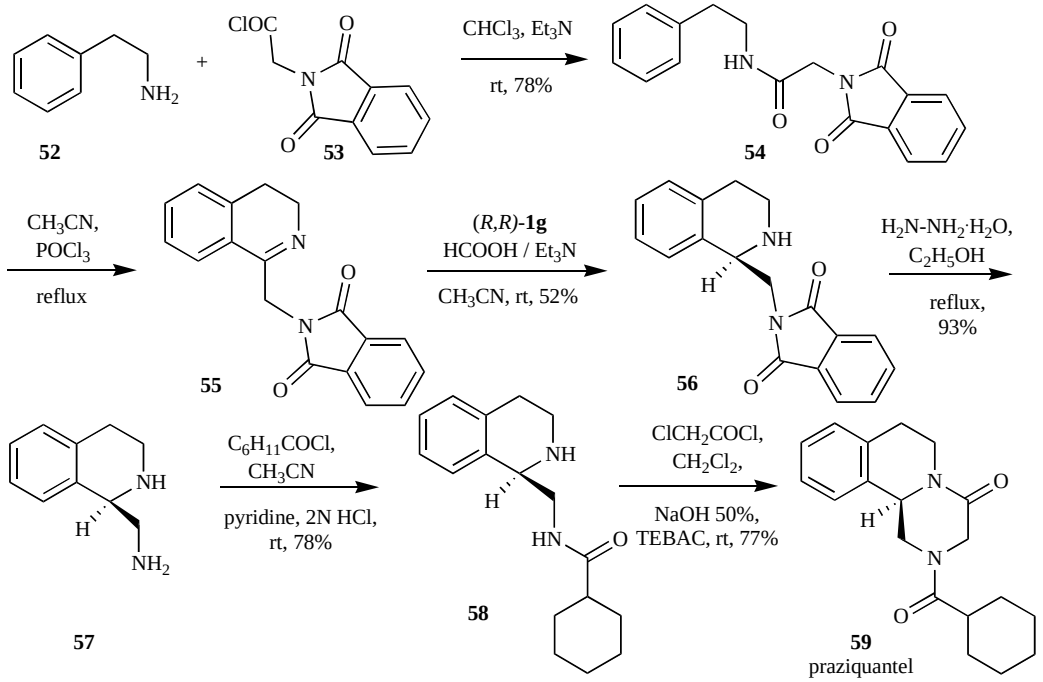
asymmetric hydrogen transfer to imine **55** was used in a key step to settle the chirality at C-1 position in intermediate **56** [35] – Scheme **9**.

The enantioselective reduction of imine **55** performed with (*R*,*R*)-**1g** as the catalyst and formic acid – triethylamine azeotropic mixture as the hydrogen source provided the amine **56** in 52% yield and fair optical purity (64% ee). The crystallization of this product gave (*R*)-**56** as a pure enantiomer.

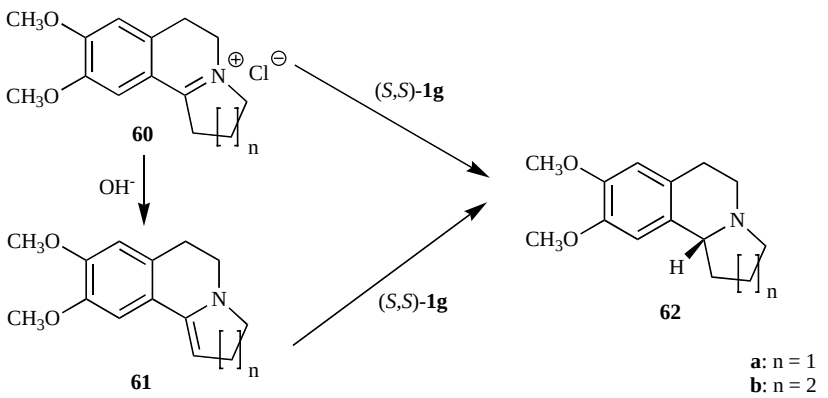
The final product (*R*)-**59** was obtained in several subsequent steps in enatiomerically pure form [35].

In a similar experiments, the ATH methodology was applied by us for the preparation of two other tetrahydroisoquinoline alkaloids **62a** and **62b**, as shown in Scheme **10** [37,44].

These two alkaloids can be prepared using compounds **60** and **61** as the substrates for the asymmetric reduction.



Scheme 9.



Scheme 10.

The best results in the enantioselective synthesis of crispine A **62a** were obtained when enamine **61a** was used as a starting material (Table **4**). The reduction was carried out in CH_3CN at 0°C to give crispine A **62a** with 99% ee and in 90% yield but when the reaction was performed using the iminium salt **60a**, the desired crispine A was isolated in 96% yield and with 92% ee.

The second alkaloid containing benzo[a]quinolizidine ring system (**62b**, n=2) was analogously prepared from its prochiral precursors **60b** or **61b**. In these cases, the amine **62b** was obtained in high chemical yield of 97% but only in 87% ee. The enantiomeric excess of both products **62a**,**b** were determined on the basis of the ^1H NMR experiments with (+)-(*R*)-*tert*-butylphenylphosphinothioic acid as chiral solvating agent [37].

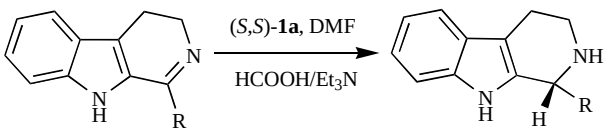
Table 4. Enantioselective Synthesis of Amines 62a,b

Imine or Enamine	Catalyst	T[°C]	Yield [%]	Ee [%]	Config.
60a	(*S*,*S*)-**1g**	22	95	77	*R*
60a	(*S*,*S*)-**1g**	0	96	92	R
61a	(*S*,*S*)-**1g**	0	90	>99	R
60b	(*S*,*S*)-**1g**	22	97	87	*R*
60b	(*S*,*S*)-**1g**	0	83	85.8	*R*
61b	(*S*,*S*)-**1g**	22	80	68.7	*R*
61b	(*S*,*S*)-**1g**	0	89	82.7	R

3. ENANTIOSELSCTIVE REDUCTION OF 3,4-DIHYDRO-β-CARBOLINES

The tetrahydro-β-carboline skeleton-containing compounds form a class of tryptamine derivatives, which have been extensively studied since this skeleton is a common structural feature of numerous secondary metabolites, like indole alkaloids. Many of these bases are very important to pharmacology and are attractive synthetic targets to both academic and industrial research groups. Due to a significant biostereodiscrimination, the asymmetric methods of their construction are of particular importance.

Already in his fundamental work from 1996, Noyori described two successful examples of an enantioselective ATH procedure on 3,4-dihydro-β-carbolines [8], (Scheme **11**).

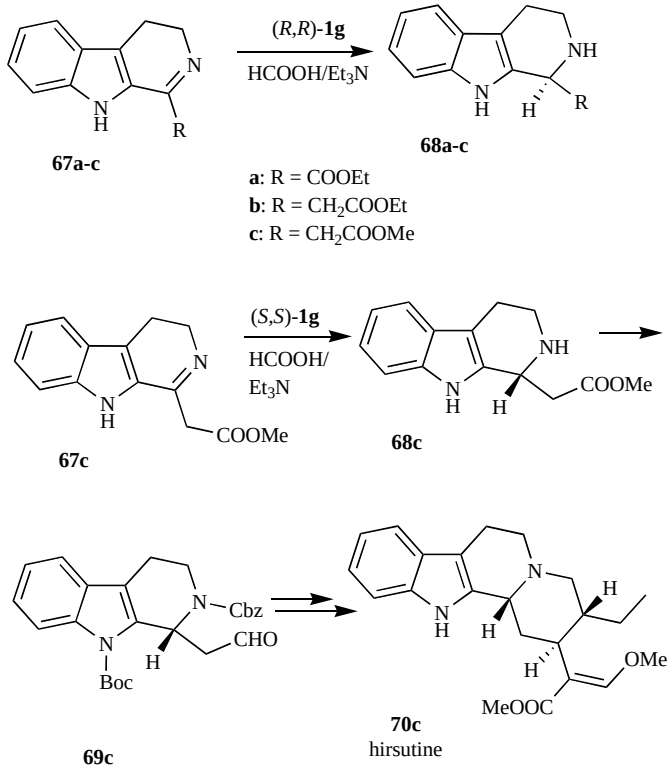


63 R = CH_3 **65** R = CH_3 89% yield, 93% ee
64 R = C_6H_5 **66** R = C_6H_5 83% yield, 96% ee

Scheme 11.

The asymmetric reduction of imines **63** and **64** in the presence of (*S*,*S*)-**1a** as the catalyst and TEAF as hydrogen source, gave amines (*R*)-**65** and (*R*)-**66** in excellent optical purity, 93-96% ee and in high yield 83-89%.

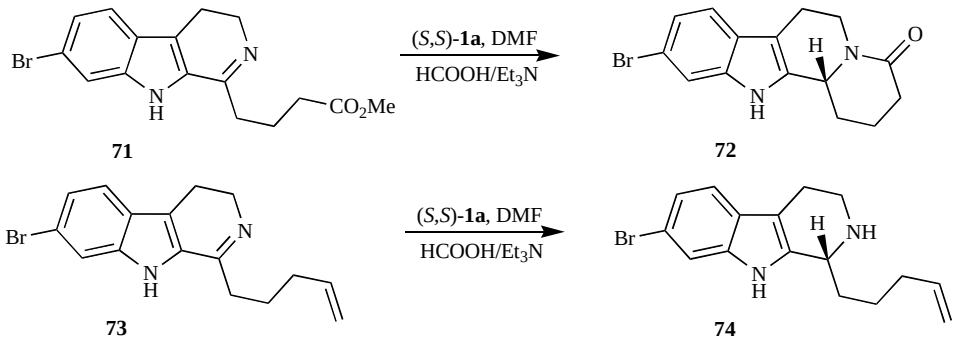
The stereoselective synthesis of amines **68a-c** (Scheme **12**) *via* the asymmetric transfer hydrogenation was also described by Tietze and coworkers [31]. The amine **67c** was an intermediate in the total synthesis of hirsutine **70c**. The reaction with imines **67a-c** proceeded under standard conditions and gave products **68a-c** with 95-97% ee.



Scheme 12.

Santos *et al.* [33] took advantage on the Noyori's protocol for the asymmetric transfer hydrogenation of appropriately functionalized β-carboline derivatives **71** and **73** to the stereoselective synthesis of arborescidine-type alkaloids (Scheme **13**).

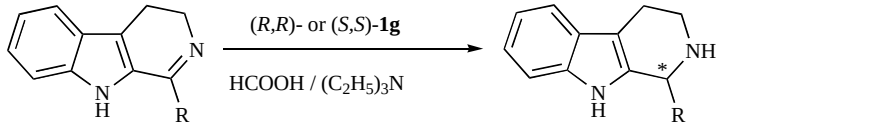
The enantioselective reduction of imine **71** was accomplished with the complex (*S*,*S*)-**1a** in DMF in the presence of HCOOH-Et_3N mixture. After the *in situ* cyclization, the lactam **72** was obtained in 89% yield and 96% ee. The hydrogenation of imine **73** in DMF resulted in the formation of amine **74** in 96% yield. Interestingly, when the imine was subjected to ATH reaction in acetonitrile as the solvent,



Scheme 13.

following the procedure described by Tietze [31], no reaction took place, only the starting material being recovered.

We have recently communicated that the asymmetric hydrogen transfer process is very effective in the enantioselective synthesis of various fatty acid 1-substituted-tetrahydro-β-carbolines **76**, as illustrated in Scheme **14** [34].

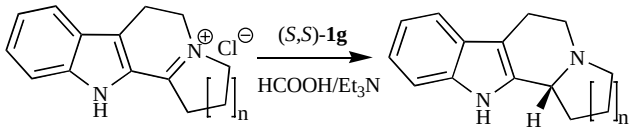


a: R= CH_3; **b:** R= $(CH_2)_2CH_3$; **c:** R= $(CH_2)_7CH_3$; **d:** R= $(CH_2)_{16}CH_3$;
e: R= (*Z*)-$(CH_2)_7(CH=CH)(CH_2)_7CH_3$; **f:** R= (*Z*)-$(CH_2)_3[(CH=CH)CH_2]_4(CH_2)_3CH_3$

Scheme 14.

The asymmetric reduction of imines **75a-f** under the conditions utilized by Tietze [31], using both enantiomers of the chiral catalyst (*S*,*S*)-**1g** or (*R*,*R*)-**1g**, gave the corresponding amines **76a-f** in excellent enantioselectivity >98% ee and high yield 70-88%. Of course, the stereochemistry of the catalyst determined the stereochemistry of the amine, and the products with (1*R*) configuration were obtained when (*S*,*S*)-**1g** were used, whereas the (1*S*) isomers were formed under the influence of (*R*,*R*)-**1g**, what is in full accordance with Noyori results [8].

Following our interest in the preparation of naturally occurring β-carboline derivatives, we completed the synthesis of two indole alkaloids: harmicine **78a** and desbromoarborescidine **78b** [41] – Scheme **15**.

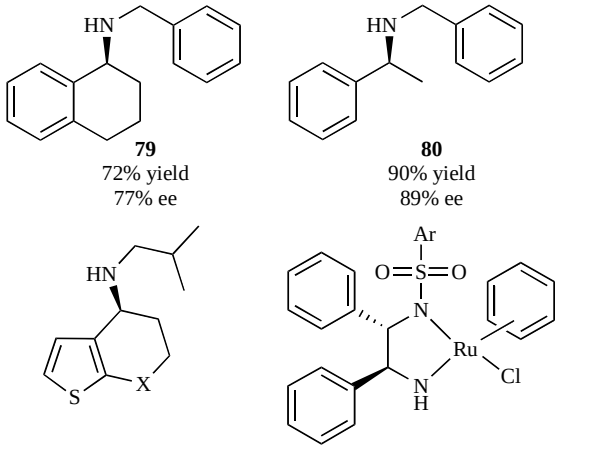


Scheme 15.

Thus, the asymmetric transfer hydrogenation of imine **77a** under standard conditions (acetonitrile as a solvent and TEAF as hydrogen source) using (*S*,*S*)-**1g** as the catalyst, gave (*R*)-harmicine (*R*)-**78a** in 81% chemical yield and 79% ee, determined on the basis of ^{1}H NMR experiments with phosphinothioic acid used as chiral solvating agent [37]. Fortunately, after a single crystallization, an almost enantiopure alkaloid could be obtained. The hydrogenation of imine **77b** under analogous conditions afforded (*R*)-desbromoarborescidine **78b** in 84% yield and 90.5% ee. Again, a single crystallization gave the enantiopure material. In contrast to the determination of the enantiomeric excess for compound **78a**, the ^{1}H NMR differentiation using substituted phosphonothioic acid was unsuccessful. However, employing its selenium analogue, we were able to observe a very good separation of the signals of the formed dynamic diastereomeric associates [44].

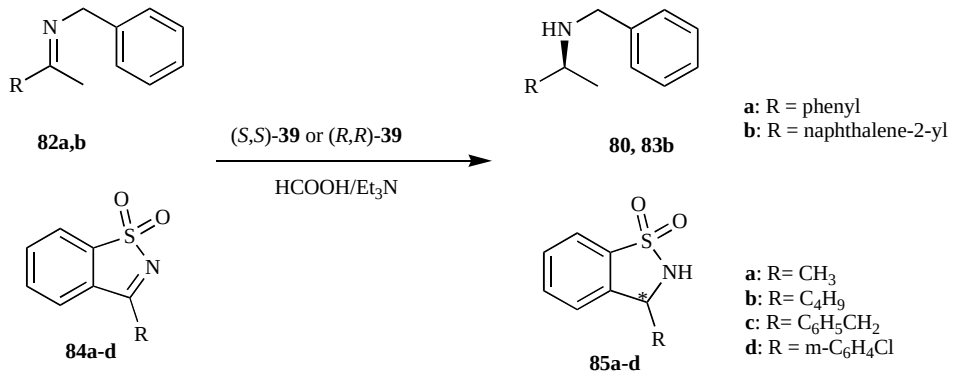
4. ENANTIOSELSCTIVE REDUCTION OF OTHER IMINES

The enantioselective reduction of selected acyclic imines was also described by Noyori *et al.* [8]. The ATH reaction in this case was somewhat less stereoselective but using chiral catalyst (*S*,*S*)-**1c** or (*S*,*S*)-**1d** they were able to obtain the appropriate amines **79**-**81** with a high value of enantiomeric excess, as shown in Scheme **16**.



Scheme 16.

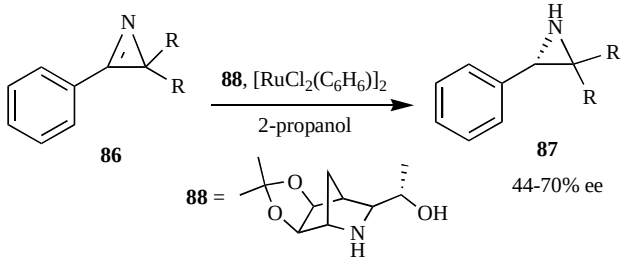
The ATH reduction of prochiral sulfonamides **84a-d** (Scheme **17**) proceeds rapidly and in excellent yield under the same conditions as in the case of isoquinolines **16a-h**, but the enantioselectivity of this process was only good, giving products in 67-81% ee [27].



Scheme 17.

Unexpectedly, the hydrogenation of acyclic imines **82a**,**b** afforded amines **80** and **83b** with an excellent chemical yield too, but the asymmetric induction decreased dramatically to 8.4% ee. These results seem to indicate that the highest degree of the chirality induction during the ATH procedure is probably reserved for cyclic, endogenous imines.

An interesting example of the enantioselective reduction of aromatic 2*H*-azirines using aminoalcohol **88**-$[RuCl_2(p\text{-cymene})]_2$ catalyzed asymmetric transfer hydrogenation was reported recently (Scheme **18**) [45]. The hydrogenation of azirine **86** (R = H) using this catalytic system and 2-propanol as the hydrogen source afforded the product with high stereoselectivity 70% ee and with 70% yield. The use TEAF as the hydrogen donor caused a complete decomposition of azirine **86**.



Scheme 18.

5. CONCLUSIONS

There have been numerous advances in the development of asymmetric hydrogenations in recent years. However, starting from an early stage of the development of ATH procedure, the reduction of carbonyl group was mainly explored. Imines, albeit also very important substrates for the stereoselective synthesis, were much less popular. However, during the last decade, a series of important contributions to this area have been published. It was firmly proven that cyclic endogenous imines, containing mainly 3,4-dihydroisoqunoline or 3,4-dihydro-β-carboline framework, were excellent prochiral substrates for ATH reductions. The best results can be obtained when monotosylated 1,2-diamine as ligands and the azeotropic $HCOOH/Et_3N$ mixture as the hydrogen source were used.

6. ACKNOWLEDGEMENT

This work was supported in part by grants PBZ-KBN-126/T09/2004/13 and KBN-1315/T09/2005/29.

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Received: March 07, 2007 **Revised: April 17, 2007** **Accepted: May 16, 2007**