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Stereo- and regioselectivity in asymmetric synthesis of α-amino substituted benzocyclic compounds

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Abstract

The enantiomerically pure chiral benzocyclic amines **6–8** were obtained by asymmetric transamination of the corresponding prochiral ketones **9a–c**. The method involves: (a) formation of chiral imines **10a–c** from the prochiral ketones **9a–c** and the inexpensive chiral auxiliary (*R*)- or (*S*)-phenylethylamine (PEA); (b) asymmetrically induced reduction of these imines to the diastereomeric amines **11a–c** and **12a–c**; (c) catalytic hydrogenation to remove the benzylic fragment of the chiral PEA auxiliary. The stereoselectivity of the imine reduction, as well as the regioselectivity of the catalytic hydrogenation, are strongly dependent on the size of the saturated ring condensed with the benzene ring. This approach was used to develop a convenient, high yielding, and stereoselective route to several practically important optically active α-amino substituted benzocyclic compounds.

1. Introduction

Chiral amines are intermediates for many commercial and developmental drugs, and are also used as chiral auxiliaries and resolving agents.[1] In many cases, the corresponding prochiral ketone is the key intermediate in the conventional manufacture of the racemic amine. The desired stereoisomer can then be obtained by the resolution of the racemic amine via: (a) fractional crystallisation of the diastereomeric salt of that amine with a chiral acid;[2] (b) by chromatography on a chiral stationary phase;[3] and (c) more recently, by enzyme catalysed aminolysis in organic solvents.[4] The disadvantage of all these resolution procedures is the fact that the unwanted enantiomer has to be recycled or discarded, which means that the desired chiral amines may be isolated in yields not higher than 50%. This problem may be avoided if it is possible to use asymmetric synthesis.

Recognising the strategic importance of the corresponding prochiral ketones, much effort has been directed toward developing methodologies for their asymmetric transamination into chiral amines,

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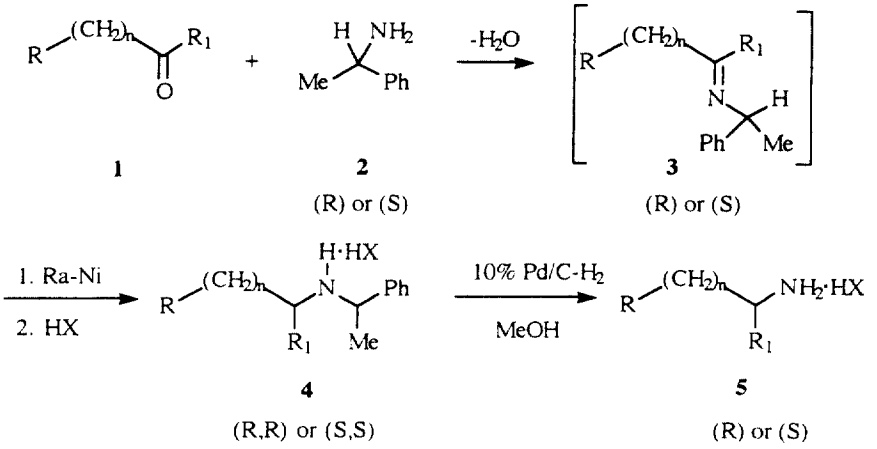
using readily available chiral benzylic amines as auxiliaries. This concept involves formation of the intermediate chiral imine **3** from the key prochiral ketone **1** and the chiral benzylic amine auxiliary **2**, asymmetrically induced catalytic or stoichiometric reduction of this imine into the diastereomeric amine **4**, followed by removal of the no longer needed benzylic auxiliary fragment by catalytic hydrogenation (Scheme 1).

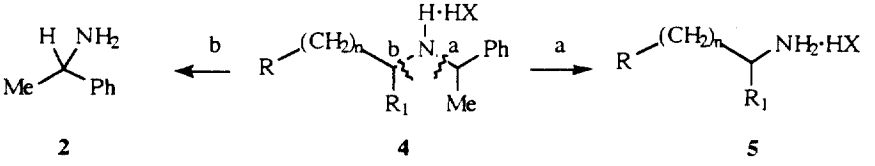


Scheme 1.

The absolute configuration of the newly generated stereogenic centre in the amine **5** is determined by the configuration of the chiral auxiliary, and since both enantiomers of the phenylethylamine (PEA) are available, either configuration of this centre could be generated at will.

This approach was successfully used for the synthesis of psychotomimetic phenylisopropylamines,[5] chiral alkyl amines,[6] derivatives of mescaline,[7] as well as taxol's side chain[8] and natural amino acids.[9]

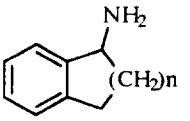
The case when n=0 and R or R^1 is an aromatic moiety is a special problem because the intermediate diastereomeric amine **4** is 'dibenzylic' and its catalytic hydrogenation may cause the cleavage of either of the two benzylic C–N bonds (Scheme 2). While hydrogenation promoted cleavage according to route (a) would result in the desired product **5**, cleavage according to route (b) would be completely unproductive and wasteful. Only one attempt was reported to apply this transamination approach to the synthesis of chiral benzylic amines (n=0, R is an oxygenated phenyl, R^1=Me). This is the work of Bringmann and Geisler,[10] who succeeded in obtaining enantiomerically pure oxygenated 1-phenylethylamines using oxygenated acetophenones as substrates.



Scheme 2.

Chiral benzocyclic amines (Fig. 1) are playing an increasingly important role in pharmaceutical chemistry and provide key intermediates for a number of valuable pharmaceutical preparations with mostly neurotropic and psychotropic activity.[2d,11,12]

Of particular interest to us is the chiral (*R*)-1-aminoindane **6**, which is the key intermediate in the synthesis of (*R*)-*N*-propargyl-1-aminoindan (PAI), a potent irreversible inhibitor of the B form of monoamine oxidase which could be used in the treatment of Parkinson's disease.[11,12] In view of the growing importance of this class of compounds and, in particular, because of our continuing interest



6 n=1
7 n=2
8 n=3

(R) or (S)

Figure 1.

in developing a practical synthesis of (*R*)-1-aminoindane **6**, we undertook a study of the scope and limitations of the asymmetric synthesis approach to the synthesis of chiral α-substituted benzocyclic amines.

2. Results and discussion

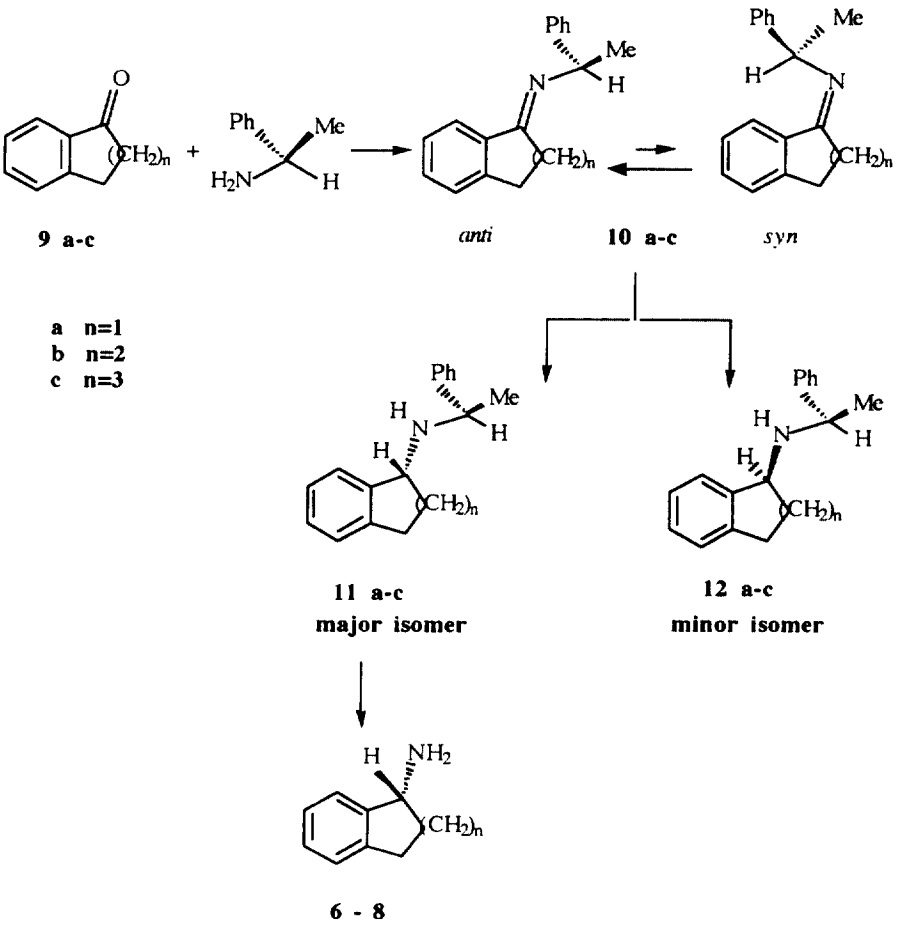
We now report the applicability of the asymmetric transamination approach, with enantiomerically pure phenylethylamines (PEA) as chiral auxiliaries, to the synthesis of chiral α-substituted benzocyclic amines. The practically important (*R*)-1-aminoindane **6**, (*R*)- and (*S*)-1,2,3,4-tetrahydro-1-naphthylamine **7** and (*R*)- and (*S*)-5-amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene **8** were chosen as target molecules for this study (Fig. 1).

Our approach includes three steps which are summarised in Scheme 3: (a) synthesis of chiral imines **10a–c** by condensation of ketone **9a–c** with (*R*)-(+)-PEA; (b) stereoselective reduction of the chiral imine C=N bond with an achiral reductive agent to predominantly one diastereomer of the mixture of diastereomeric amines **11a–c** and **12a–c**; and (c) regioselective removal of the chiral auxiliary by catalytic hydrogenolysis to obtain **6–8**.

2.1. Synthesis and analysis of imines *10a–c*

The imines **10a–c** were prepared by condensation of ketones **9a–c** with (*R*)-(+)-(PEA) in the presence of catalytic amounts of trifluoroacetic acid (TFA) by refluxing in toluene or xylene with azeotropic removal of water. The imines were not isolated from the reaction mixture in pure form because of decomposition during distillation or purification on silica gel, so the crude reaction mixtures (which contained according to GC analysis about 5–7% of unreacted PEA, 5–7% of unreacted ketones and 76–85% of the main product) were subjected to IR, GC–MS, HRMS and NMR analysis. These analyses indicated that imines **10a–c** were the only main products (Table 1).

Analysis of ^{1}H NMR spectra of the reaction mixtures revealed that in the case of **10a** or **10b** only one quartet for Hα at 4.84 or 4.88 ppm and only one doublet for the Me group at 1.59 or 1.54 ppm were observed. This indicates that only one geometrical isomer of **10a** and **10b** is present in the reaction mixtures. In the case of **10c**, two quartets were observed at 4.82 and 4.60 ppm, which could belong to two geometrical isomers of the imine in the ratio 1.2:1. We suppose that for imines **10a–b**, when a five- or a six-membered ring is fused with a benzene ring, the *syn* isomer could not exist due to steric hindrances, whereas in the case of imine **10c**, the larger and more flexible seven-membered ring makes possible the existence of *anti* as well as *syn* isomers. At this stage we do not have enough information for the conclusive identification of various isomers, but this problem is of considerable theoretical interest and its investigation is currently in progress in our laboratory.



Scheme 3.

2.2. Asymmetric hydrogenation of imines 10a–c

In the next step of the synthetic sequence, the imine can be hydrogenated in several ways to induce the formation of the second chiral centre. To find the optimal conditions providing the best stereoselectivity for this transformation, we studied the catalytic reduction of the chiral imines **10a–c** over palladium on charcoal (Pd/C), as well as the stoichiometric reduction with sodium borohydride. The results are given in Table 2.

Reduction of imines **10a** and **10b** with sodium borohydride proceeded with a high diastereoselectivity (*de*>92%) and gave as the main products (*R*,*R*) amines **11a** and **11b**. The configuration of newly created stereogenic centres was tentatively assigned as (*R*) by comparison of specific rotations of 1-aminoindane and 1,2,3,4-tetrahydro-1-naphthylamine, obtained after hydrogenolysis of **11a** and **11b**, with specific rotations of pure enantiomers.[2,13]

Asymmetric reduction of Shiff's bases using B_2H_6 has been reported by Charles et al.[14] The steric course of the reaction was discussed and it was concluded that the conformation of the substrate in the transition state includes the four-centred complex with the M–H bridge from the less hindered side. Applying this model permits an explanation of the predominant creation of the (*R*,*R*) diastereomer in the reduction of imine **10a** with sodium borohydride (Fig. 2).

If the configuration of **10a** is *anti*, and in the most favoured transition-state conformation the hydrogen

Table 1
Spectral characteristics of crude imines **10a–c**

	IR(cm^{-1})	HRMS $(M)^+$	Calcld. M. W.	^1H NMR δMe	δHα*
10a	1651	235.1348	235.1361	1.59	4.84
10b	1629	249.1498	249.1518	1.54	4.88
10c	1638	263.1647	263.1674	1.55	4.82 4.50

*- the chemical shift of H-atom from the phenylethyl moiety

Table 2
The ratio of diastereomers **11a–c/12a–c** obtained by catalytic and stoichiometric reduction of imines **10a–c***

Reagent	Temp. °C	Solvent	from **10a**	from **10b**	from **10c**
H_2/Pd/C	25	Hexane	93:7	92:8	81:19
-	-	Toluene	92:8	91:9	78:22
-	-	EtOAc	89:11	89:11	77:23
-	-	MeOH	92:8	93:7	71:29
NaBH4	20	EtOH/Tol	94:6	94:6	58:42
-	-20	EtOH/Tol	96:4	97:3	58:42

* The ratio of diastereomers was determined by GC as described in the experimental part

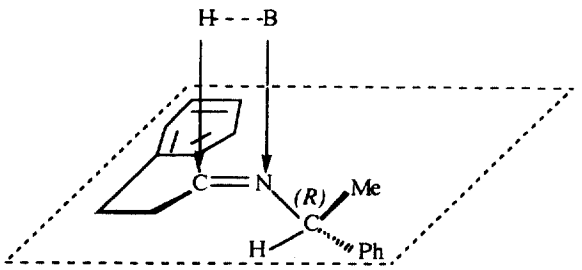


Figure 2. Transition state will yield the (*R*,*R*)-isomer

from the phenylethyl moiety is lying in the plane of the molecule, the reduction takes place from the less hindered side, i.e. from the side of the methyl group, which results in an (*R*) configuration of the new stereogenic centre. We believe that this model can also be applied to the reduction of **10b**, in spite of the fact that the six-membered ring is not planar. However, if the C=N double bond, together with the two α-carbons and the hydrogen from the phenylethyl moiety are lying in the same plane, the reduction of the *anti* isomer of **10b** from the side of the methyl group, will result in (*R*) induction.

In the case of imine **10c**, the diastereoselectivity of the reduction with sodium borohydride was very poor (*de* 16%), which is probably due to either the existence of **10c** in two isomeric forms *anti* and *syn*, with reduction of each form from the less hindered side resulting in a new stereogenic centre with an opposite configuration, or because applying the model discussed above is not warranted in this case because of the complex and unpredictable conformation of the seven-membered ring.

As it is possible to see from Table 2, the diastereoselectivity of the reduction of **10c** increased substantially when catalytic reduction over Pd/C was employed. Moreover, the diastereoselectivity was influenced by the solvent used. The best results were obtained when hexane was used as a solvent (62% *de*), and the diastereoselectivity decreased in more polar solvents: toluene (56% *de*) ethyl acetate (54% *de*) and methanol (42% *de*). In each case the major product was the (*R*,*R*) diastereomer. The absolute configuration of the new stereogenic centre predominantly formed in **11c** was established as (*R*) by X-ray analysis of its perchlorate salt (Fig. 3).

To explain the results of the catalytic hydrogenation of **10c**, we used the model proposed by Harada et al.,[15] who studied the diastereoselectivity of catalytic reduction of (±)-*N*-(ethylbenzylidene)-α-ethylbenzylamine over Pd/C and found that the ratio of (±) to *meso* forms of the product is not dependent on the *anti* to *syn* ratio in the precursor imines. On this basis they proposed a mechanism of hydrogenation, whereby the substrate is isomerised rapidly by the catalyst bringing about an equilibrium of *syn* and *anti* isomers. Each isomer is then hydrogenated at a different rate from the least hindered side. Thus, if the catalyst causes the *syn/anti* isomerisation of **10c** (K_{eq}), and every isomer is hydrogenated from the less hindered side to give with different rates (k_{syn}, k_{anti}) the (*R*,*R*)- and (*R*,*S*)-diastereomers, the ratio between them is defined, according to Curtin–Hammet equation, by K_{eq}, k_{syn}, k_{anti}.

If an isomer (*syn* or *anti*), which gives the (*R*,*R*)-diastereomer is hydrogenated faster than the equilibrium between isomers (*syn/anti*) is shifted, then the main product will be the (*R*,*R*) diastereomer. In non-polar hexane, where the interaction between the substrate and the surface of the catalyst is stronger than in the polar methanol, this process is more active and the diastereoselectivity of the reduction is better.

2.3. Catalytic debenzylation of amines 11a–c

N-Debenzylations via catalytic hydrogenation are widely used in organic synthesis.[16] Competitive *N*-debenzylation (as exemplified by routes 'a' and 'b' in Scheme 2, i.e. the influence of α-substituents and substituents in the benzene ring on the regioselectivity of *N*-debenzylation was studied.[17] It was found that the presence of a methyl group as an α-substituent to nitrogen reduces the reactivity of the adjacent C–N benzylic bond.

We found that the regioselectivity of *N*-debenzylation depends critically on the size of the saturated ring condensed with the benzene ring. The regioselectivity of *N*-debenzylation toward the benzocyclic amines (*R*)-**6–8** is enhanced in the order **11a**<**11b**<**11c** (Table 3). In the case of the five-membered ring **11a**, the regioselectivity of the hydrogenolysis was not satisfactory, which means that a planar five-membered ring unsuccessfully competes with the methyl group from the phenylethyl moiety for the stabilisation of the adjacent C–N benzylic bond. Enlargement of the saturated ring, which amounts to

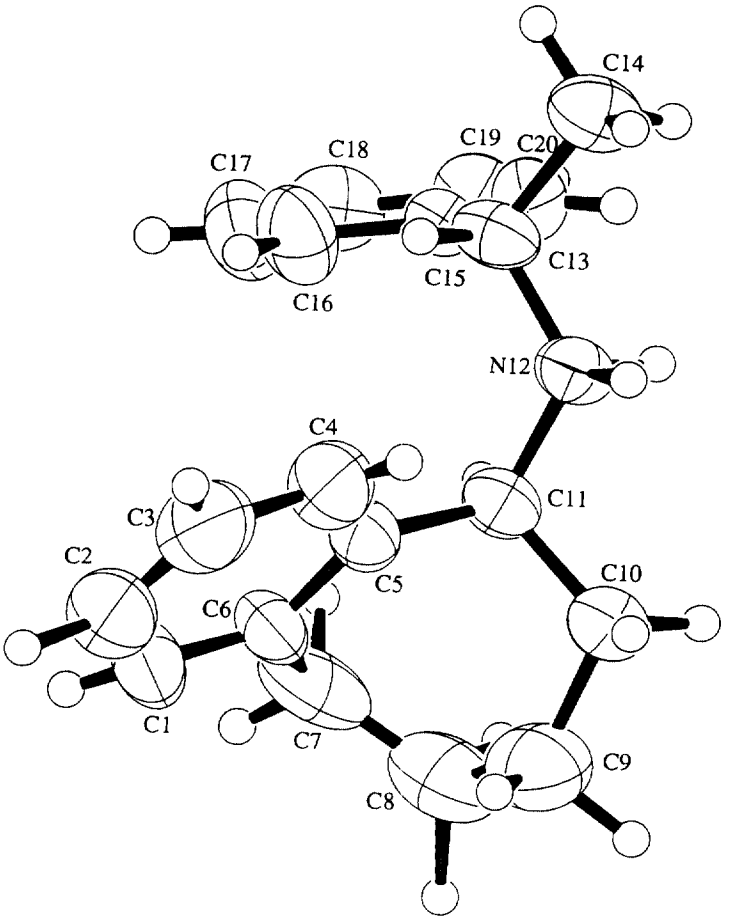


Figure 3. X-Ray structure of **11c** — perchlorate (only a cation is shown)

increasing the size of alkyl substituent, improves the regioselectivity. Thus, in the case of a six-membered ring the ratio (*R*)-**7**:(*R*)-PEA was 3.5:1, and in the case of a seven-membered ring the ratio (*R*)-**8**:(*R*)-PEA increased to 45.5:1.

Catalytic removal of the phenylethyl moiety from the secondary amines (*R*)-**11a–c** was performed on Pd/C, in methanol–water solution with an excess of acetic acid (about 4 equivalents), under a hydrogen pressure of about 4 atm and at 18°C. The reaction was monitored by HPLC and it was found that the hydrogenolysis is not accompanied by racemisation. Amines (*R*)-**6–8** were separated from (*R*)-PEA, via crystallisation with (*R*,*R*)-tartaric or hydrochloric acid.

3. Conclusions

The method of asymmetric transamination of benzocyclic ketones **9a–c** using (*R*)-(+)-PEA as a chiral auxiliary was applied to the synthesis of enantiomerically pure benzocyclic amines **6–8**, which are potentially useful pharmaceutical syntones.

(i) Imines **10a–c** were obtained with high yields from the prochiral ketones **9a–c** and the chiral auxiliary (*R*)-(+)-PEA. The *anti* to *syn* ratio of **10a–c** depends on the size of the saturated ring fused

Table 3
Catalytic hydrogenation of amines (*R,R*)-**11a–c**

11(1g)	Reaction time (h)	Ratio of (R)-benzocyclic amine /(R)-PEA (GC)	Unreated **11a-c** (%, GC)
a	189	(R)-**6**/(R)-PEA 2.2:1	4
b	53	(R)-**7**/(R)-PEA 3.5:1	5
c	24	(R)-**8**/(R)-PEA 45.5:1	<1

with the benzene ring and changes from predominantly *anti* (>95%) for five- and six-membered rings **10a–b** to a virtually 50:50 ratio for the seven-membered ring **10c**.

(ii) The diastereoselectivity of the reductions of **10a–c** with sodium borohydride and catalytic reduction over Pd/C was studied. It was found that for **10a–b** the diastereoselectivity of reduction with sodium borohydride is high (*de*>92%) and gives the (*R,R*)-diastereomer as a major product which corresponds to the reduction of the *anti*-isomer from the less hindered side. For **10c**, the diastereoselectivity of the reduction with sodium borohydride was low (*de* 16%), but increased substantially under catalytic hydrogenation conditions with Pd/C (*de*>42%). A dependence of the *de* on the solvent used was observed with the best diastereoselectivity obtained in non-polar solvents (hexane, *de* 62%).

(iii) The absolute configuration of the newly created stereogenic centre in **11c** was established as (*R*) with the help of X-ray analysis, which means that the major product of **10c** reduction is also the (*R,R*)-diastereomer.

(iv) The regioselectivity of hydrogenolytic cleavage of (*R,R*)-**11a–c** to (*R*)-**6–8** over Pd/C was studied. It was found that the regioselectivity of the reaction increases from **11a** [(*R*)-**6**:(*R*)-PEA 2.2:1] to **11c** [(*R*)-**8**: (*R*)-PEA 45.5:1].

4. Experimental section

4.1. General details

Melting points and boiling points are uncorrected. ^{1}H NMR spectra were determined with Bruker-200 AM (200 MHz) and Bruker 400-AM WB (400 MHz) instruments in $CDCl_3$ solutions with TMS as an internal standard. ^{13}C NMR spectra were determined with a Brucker 400 AM WB (100.614 MHz) instrument in $CDCl_3$ solutions. IR spectra were run on a Nicolet Impact 400. HRMS spectra were measured on a Varian Mat-711 at 70 eV. GC–MS spectra were measured on a Magnum (Finnigan) with a DB-5 column. Gas chromatographic analyses were obtained on a Hewlett–Packard 5890 Series II chromatograph using a DB-210 capillary column (30 m/0.25 mm), stationary phase OV-210, carrier gas — helium (2.0 ml/min), detector FID (250°C). Program A — 100°C (5 min), 10°/min (14 min),

240°C (10 min). Program B — 100°C (5 min), 1°/min (60 min), 20°/min (4 min), 240°C (10 min). HPLC was performed on a Merck–Hitachi instrument (pump 6200A, UV detector L-4000, integrator D-2500) on a Crownpack chiral column, eluent $HClO_4$–water (pH 2). Optical rotations were measured on a JASCO DIP-370 polarimeter. Commercially available (*R*)-(+)-phenylethylamine (Fluka) 99%+ (GC), bp 187–189°C, $[\alpha]_D^{20}$ +38.6 (d 0.952) was used as a chiral auxiliary. 1-Indanone (Aldrich) 99%+, bp 243–245°C. α-Tetralone (Aldrich) 98%, bp 113–116°C (6 mmHg). 1-Benzosuberon (Aldrich) 99%, bp 270°C. Pd/C catalyst, Type 487, Johnson Matthey, %Pd 9.95; $\%H_2O$ 0.5.

4.2. *Synthesis of amines **11a–b** via asymmetric reduction of imines **10a–b** with sodium borohydride*

4.2.1. (R,R)-N-*(1-Indanyl)-1-phenylethylamine **11a***

A mixture of 1-indanone (20.0 g, 0.152 mol), (*R*)-(+)-PEA (18.4 g, 0.152 mol) and 100 mg of trifluoroacetic acid (TFA) was refluxed in toluene (200 ml) with azeotropic removal of water during 7 h. The solution was cooled to room temperature and added dropwise at −20 to −30°C during 30 min to the stirred solution of sodium borohydride (6 g, 0.159 mol) in absolute ethanol (150 ml). The resulting mixture was stirred at −20 to −30°C during an additional 2–3 h period and then kept at −16°C for two days. Water was added to the mixture and the solvents were removed in vacuo. The residue was extracted with ether (150 ml), dried over sodium sulphate, concentrated in vacuo and distilled at 115–120°C (0.1 mmHg) to obtain 20 g of the diastereomeric mixture **11a** and **12a** in the ratio 96:4. A solution of amines **11a** and **12a** (20 g, 0.084 mol) in methanol (100 ml) was added to the solution of (*R,R*)-tartaric acid (12.6 g, 0.084 mol) in methanol, the mixture was stirred for ca. 15 min and the solvent was evaporated. The solid crude product was crystallised twice from ethanol to obtain 15 g of the tartrate salt of **11a** with *de*>99%, mp 161–163°C, $[\alpha]_D^{20}$ +50 (*c* 0.85, MeOH). The free amine **11a** (9 g, 25% yield based on 1-indanone, was isolated from the salt by the standard procedure, $[\alpha]_D^{20}$ +91 (*c* 0.945, MeOH).

^{1}H NMR δ ppm 1.46 (d, 3H); 1.60 (s, 1H); 1.74–1.82 (m, 1H); 2.26–2.34 (m, 1H); 2.75–2.82 (m, 1H); 2.98–3.05 (m, 1H); 4.15–4.22 (m, 2H); 7.24–7.52 (m, 9H). ^{13}C NMR δ ppm (aliphatic region) 24.42 (CH_3); 30.02 (CH_2); 34.87 (CH_2); 56.27 (CH); 60.74 (CH). HRMS (*m/z*) 237.1505. $C_{17}H_{19}N$ calcd 237.1517.

4.2.2. (R,R)-N-*1-(1,2,3,4-Tetrahydronaphthyl)-1-phenylethylamine **11b***

A mixture of 1-tetralone (20.0 g, 0.14 mol), (*R*)-PEA (19.8 g, 0.16 mol) and 100 mg of TFA was refluxed in xylene (150 ml) with azeotropic removal of water during 8 h. The cooled solution was added dropwise during 40 min, at −20 to −30°C, to the stirred solution of sodium borohydride (5.2 g, 0,18 mol) in absolute ethanol (150 ml) and the mixture was stirred for an additional 2 h at −20 to −30°C and after this was kept overnight at −16°C. Water was added to the mixture, the solvents were removed in vacuo, and the product extracted with ether, dried over sodium sulphate and the ether was removed in vacuo. The crude mixture of **11b** and **12b** in the ratio 97:3 was dissolved in ethanol (50 ml) and added to the solution of (*R,R*)-tartaric acid (24 g, 0.16 mol) in ethanol (250 ml). The resulting solution was concentrated to dryness to give 38 g of the salt. Additional crystallisation from ethanol gave 16 g of tartaric salt of (*R,R*)-isomer with *de*>99%, mp 72–75°C, $[\alpha]_D^{20}$ +59 (*c* 0.92, MeOH). **11b** (9.5 g, the yield 27% based on 1-tetralone) was isolated from the salt by standard procedure, $[\alpha]_D^{20}$ +94 (*c* 1.09, MeOH).

^{1}H NMR δ ppm 1.36 (d, 3H); 1.65–1.77 (m, 3H); 1.84–1.93 (m, 1H); 2.69–2.80 (m, 2H); 3.70 (dd, 1H); 4.04 (q, 1H); 7.07–7.49 (m, 9H). ^{13}C NMR δ ppm (aliphatic region) 24.77 (CH_3); 18.73 (CH_2); 29.13 (CH_2); 29.56 (CH_2); 53.25 (CH); 56.18 (CH). HRMS (*m/z*) 251.1660. $C_{18}H_{12}N$ calcd 251.1674.

4.3. Hydrogenation of imines **10 a–c** on Pd/C in various solvents — general procedure

The hydrogenation was carried out in hexane, toluene, ethyl acetate and methanol at 25–27°C and at a hydrogen pressure of about 4 atm.

A solution of imine **10a–c** (1 g/30 ml) and Pd/C (10% from the weight of imine) was shaken until absorption of hydrogen ceased. The analysis of the reaction mixtures was performed by GC.

4.3.1. (R,R)-N-[5-(6,7,8,9-Tetrahydro-5H-benzocycloheptenyl)]-1-phenylethylamine **11c**

A mixture of benzosuberone (9.42 g, 0.06 mol), (*R*)-(+)-PEA (7.11 g, 0.06 mol) and TFA (100 mg) in toluene (150 ml) was refluxed with azeotropic removal of water during 8 h.

The solution was cooled to room temperature, mixed with Pd/C (1.5 g), and shaken under a hydrogen pressure of about 4 atm during 30 h. The catalyst was filtered off through Celite, the solvent evaporated and the residue (16.5 g) was dissolved in methanol and mixed with a methanolic solution of (*R,R*)-tartaric acid (9.25 g). The solution was stirred during 15 min, methanol was removed and the residue was triturated with ether and crystallised three times from ethanol to obtain 4.5 g of the salt with *de*>98%, mp 192–193°C, $[\alpha]_D^{20}$ +69 (*c* 0.945, MeOH). **11c** (2.85 g, 18% yield based on 1-benzosuberone) was isolated from the salt, $[\alpha]_D^{20}$ +120 (*c* 0.94, MeOH).

^{1}H NMR δ ppm 1.47 (d, 3H); 1.67–2.11 (m, 7H); 2.80–2.86 (m, 1H); 3.18 (dd, 1H); 3.75–3.82 (m, 2H); 7.23–7.49 (m, 9H). ^{13}C NMR δ ppm (aliphatic region) 25.01 (CH_3); 27.00 (CH_2); 27.92 (CH_2); 34.73 (CH_2); 35.50 (CH_2); 55.05 (CH); 59.21 (CH). HRMS (*m/z*) 265.1787. $C_{19}H_{23}N$ calcd 265.1831.

4.4. Hydrogenolysis of amines **11a–c** on Pd/C — general procedure

Hydrogenolysis of **11a–c** was performed in a methanol–water solution in the presence of 4 equivalents of acetic acid at a hydrogen pressure of about 4 atm, at 17–20°C, on Pd/C. At the end of the reaction, the mixture was passed through Celite to remove the catalyst and the methanol was evaporated. Free amines were isolated by standard procedure and separation of amines **6–8** from PEA were performed via crystallisation of their tartrates or hydrochloride salts.

4.4.1. (R)-(−)-1-Indanamine **6**

A mixture of **11a** (*de*>99%) (6 g, 0.025 mol), Pd/C (0.6 g), acetic acid (5.7 ml), water (6 ml) and methanol (60 ml) was shaken at 25°C, during 62 h under a hydrogen pressure of about 4 atm. The catalyst was filtered off, the methanol was removed in vacuo and the residue dissolved in chloroform. The chloroform solution was extracted with 25% aqueous solution of NH_4OH, the organic layer separated, dried over sodium sulphate and the solvent removed. The crude oil (4.2 g) contained (*R*)-**6** and (*R*)-PEA in the ratio about 64:36. The mixture was dissolved in methanol and HCl (gas) was passed through the solution. Methanol was removed, the crude crystalline residue was refluxed with 40 ml of ethyl acetate during 15 min, crystals (3 g) with the ratio of (*R*)-**6**:(*R*)-PEA about 83:17 were filtered off, dissolved in 6 ml of hot methanol and ethyl acetate (6 ml) was added to the hot solution. 1.4 g (20% yield) of the salt with the ratio of (*R*)-**10**:(*R*)-PEA about 96.5:3.5 was separated, *ee* of (*R*)-**6**>99%, $[\alpha]_D^{20}$ −17 (*c* 1.3, MeOH) {lit.,[2] $[\alpha]_D^{20}$ −16.5 (*c* 1.5, MeOH)}.

^{1}H NMR δ ppm 1.60–1.71 (m, 1H); 1.66 (s, 2H); 2.41–2.54 (m, 1H); 2.69–3.00 (m, 2H); 4.32 (t, 1H); 7.19–7.31 (m, 4H).

4.4.2. (R)-(−)-1,2,3,4-Tetrahydro-1-naphthylamine 7

A mixture of **11b**, *de*>99%, (8 g, 0.032 mol), Pd/C (0.8 g), water (4 ml), acetic acid (7.3 ml) and methanol (160 ml) was shaken during 24 h under a hydrogen pressure of about 4 atm. The mixture was worked up as described for (*R*)-**6** and distilled at 120–140°C/5 mmHg to give 2 g (43%) of (*R*)-**7**, *ee*>99%, which contained about 10% of PEA. The crude product was dissolved in methanol, mixed with the methanolic solution of (*R*,*R*)-tartaric acid (2 g), stirred for about 15 min, methanol was removed in vacuo, the residue washed with ether and the solid crystallised twice from ethanol to give 2 g of the (*R*)-**7**-tartrate salt), $[\alpha]_D^{20}$ +17 (*c* 1.10, MeOH), which gave 0.9 g of (*R*)-**7** (yield 18%), $[\alpha]_D^{20}$ −26 (*c* 1.32, MeOH), *ee*>99% {lit.[13] $[\alpha]_D^{20}$ −42.1 (d 1.0240)}.

^{1}H NMR δ ppm 1.63 (s, 2H); 1.67–1.81 (m, 2H); 1.88–2.01 (m, 2H); 3.97 (t, 1H); 7.04–7.41 (m, 4H).

4.4.3. (R)-5-Amino-6,7,8,9-tetrahydro-5H-benzocycloheptene 8

A mixture of **11c** (96% *de*) (1.5 g, 0.0057 mol), Pd/C (0.15 g), water (0.9 ml), acetic acid (1.3 ml) and methanol (30 ml) were shaken during 25 h at 25°C. The mixture was worked up as described for (*R*)-**6** and **7** to obtain 1 g of crude (*R*)-**8**, which was purified via crystallisation of its tartrate. 0.95 g (53%) of the salt, which did not melt till 210°C was separated, $[\alpha]_D^{20}$ +26 (*c* 1.125, MeOH).

^{1}H NMR δ ppm (free base) 1.51 (s); 1.48–2.10 (m, 6H); 2.79–2.84 (m, 2H); 4.21 (d, 1H); 7.08–7.19 (m, 3H); 7.40 (d, 1H).

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