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(*S*)-1-Aminoindane: synthesis by chirality transfer using (*R*)-phenylglycine amide as chiral auxiliary

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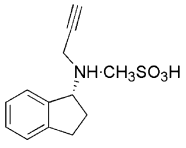
Abstract—A practical asymmetric synthesis of nearly enantiomerically pure (*S*)-1-aminoindane has been developed. The key step involves the diastereoselective heterogeneous metal-catalyzed reduction of the ketimine of 1-indanone with the chiral auxiliary (*R*)-phenylglycine amide. The selectivity of the asymmetric hydrogenation step was optimized with regard to metal catalyst, solvent and catalyst loading. The chiral auxiliary was removed by means of a novel non-reductive procedure. Thus, (*S*)-1-aminoindane with an ee of 96% was prepared in 58% overall yield from (*R*)-phenylglycine amide in an effective three-step procedure.

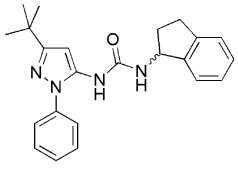
1. Introduction

Enantiomerically pure (*R*)-phenylglycine amide [(*R*)-PGA] is readily available at DSM as a result of its application on an industrial scale as key intermediate in the enzymatic synthesis of β-lactam antibiotics.[1] Recently, the versatility of (*R*)-PGA as a chiral auxiliary has been demonstrated. High diastereoselectivities were found in addition reactions to imines of (*R*)-PGA. For example, addition of HCN via a diastereoselective Strecker reaction in combination with a crystallization-induced asymmetric transformation, gave nearly diastereomerically pure aminonitriles.[2] As an example, the aminonitrile obtained from pivaldehyde was converted into (*S*)-*tert*-leucine in 73% yield and with >98% ee. In another application, homoallylamines with high enantiomeric excesses were obtained from diastereoselective additions of allylzinc reagents to aldimines derived from (*R*)-PGA. Diastereoselective ratio's of >99:1 were typically observed.[3]

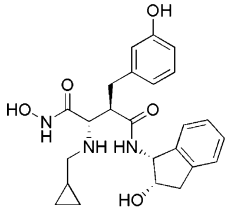
Herein, we present the application of (*R*)-PGA as a chiral auxiliary in the preparation of (*S*)-1-aminoindane.[4] This chiral amine is of pharmaceutical importance as a key structural element in therapeutic agents under clinical investigations. Examples are Rasagiline mesylate for the treatment of Parkinson's disease,[5] and derivatives thereof either with antimalarial activity[6] or with the potential for treatment of Alzheimer's disease,[7] pyrazole urea-based p38 MAP kinase inhibitors as candidates for treatment of inflammatory diseases,[8] orally bioavailable aggrecanase inhibitors,[9] or irindalone, which displays potent antihypertensive activity.[10]



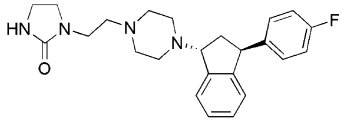
Rasagiline mesylate



p38 MAP kinase inhibitor



aggrecanase inhibitor



Irindalone

Methodologies employed for the synthesis of enantiomerically pure (*R*)- or (*S*)-1-aminoindane include classical or enzymatic resolutions. For example, resolutions of racemic *N*-benzyl-1-aminoindane with (*S*)-mandelic acid[11] or (*R*,*R*)-tartaric acid[12] furnished, after hydrogenation, (*R*)-1-aminoindane with >99% ee (overall yields were 21–39 and 15–19%, respectively). Enzymatic resolution of racemic 1-aminoindane through

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acylation with 2,2,2-trifluoroethyl butyrate using the rather expensive enzyme subtilisin afforded (*R*)-1-aminoindane in 40% yield with an ee of 98%.[13] An evident limitation of these resolution methods is that the yield never exceeds 50%.[14]

Recently, much effort has been directed towards developing procedures for asymmetric synthesis of enantiopure 1-aminoindane. For example, routes using chiral rhodium[15] and ruthenium catalysts[16] have been described for the enantioselective hydrosilylation of 1-indanoxime with Ph_2SiH_2 to yield, after hydrolysis, (*R*)-1-aminoindane. However, ee values and yields were low, 8–35 and 10–41%, respectively. Using indene as starting material, (*S*)-1-aminoindane was synthesized in three steps in 61% isolated yield and 77% ee via hydroboration involving a chiral rhodium catalyst.[17]

For the preparation of enantiopure amines, diastereoselective synthesis using a chiral auxiliary can be a viable alternative. In this concept, an imine is formed in the first step by reaction of a prochiral ketone with a chiral auxiliary. The second step consists of a diastereoselective reaction (chirality transfer) followed by cleavage of the chiral auxiliary. Previously, this approach has been employed in the synthesis of enantiomerically pure 1-aminoindane. For example, (*R*)-phenylethylamine has been used for the synthesis of (*R*)-1-aminoindane from 1-indanone in three steps, with an overall yield of 5% and >99% ee.[18] This route was hampered by the non-selective removal of the chiral auxiliary after its use. In a similar approach, (*R*)-phenylglycinol has been employed as a chiral auxiliary in the synthesis of (*S*)-1-aminoindane from 1-indanone. The three-step procedure afforded the product in 39% overall yield; the specific rotation of the (*S*)-1-aminoindane indicated that nearly enantiomerically pure material was obtained.[19] The limited availability and cost of this chiral auxiliary are the main drawbacks of this compound, especially when use on industrial scale is envisaged. Furthermore, chromatography is used to obtain diastereomerically pure intermediates, followed by removal of the chiral auxiliary by procedures unsuitable for large-scale preparations, e.g. oxidation with $Pb(OAc)_4$.

We now report the application of (*R*)-phenylglycine amide as a highly efficient chiral auxiliary in an asymmetric transamination reaction for the synthesis of (*S*)-1-aminoindane, which involves three steps: imine formation, diastereoselective reduction and removal of the chiral auxiliary.

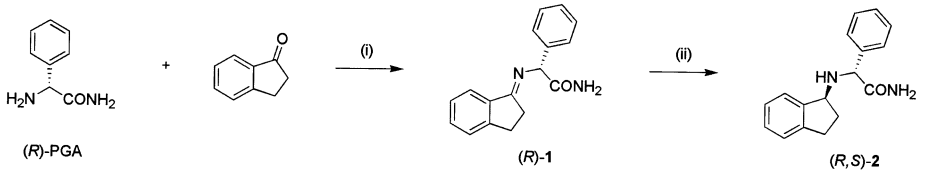
2. Results and discussion

2.1. Synthesis of the amine (*R*,*S*)-2

On treatment of (*R*)-PGA with 1-indanone in the presence of a catalytic amount of *p*-TsOH·H_2O in boiling *i*-PrOAc, (*R*)-**1** was isolated in 90% yield and 99% ee (Scheme 1, conversion >98%). ^{1}H NMR spectroscopic analysis of (*R*)-**1** gave no evidence for the formation of a *cis*/*trans* mixture. Therefore, on the basis of steric hindrance, it is assumed that solely *trans*-(*R*)-**1** was formed. Removal of water during the reaction via a Dean–Stark trap proved essential in order to obtain high yields. As soon as the calculated amount of water was collected, the reaction was terminated, usually after ca. 6 h. Prolonged reflux of the mixture resulted in slight racemization of the product.

The second and key step in the preparation of (*R*,*S*)-**2**, and eventually (*S*)-**5**, is the diastereoselective metal-catalyzed hydrogenation[20] of (*R*)-**1** to afford the desired amine (Scheme 1). Hydrogenation of (*R*)-**1** at 3.5 bar H_2 and 40°C in *i*-PrOAc using Raney-nickel as catalyst afforded the diastereomers (*R*,*S*)-**2** and (*R*,*R*)-**2** in a 94:6 ratio. The diastereomeric ratio of (*R*,*S*)-**2** and (*R*,*R*)-**2** was determined by ^{1}H NMR analysis on the basis of the relative integration of the aminoindanyl-CH triplets of (*R*,*S*)-**2** at 4.39 ppm and (*R*,*R*)-**2** at 4.19 ppm. The diastereomeric ratio was confirmed by HPLC analysis. Purification via one efficient crystallization of the HCl-salt provided a single diastereomer identified as (*R*,*S*)-**2** in 84% overall yield, based on the imine (*R*)-**1**, and 98% ee. The assignment of the absolute configuration was made by conversion of (*R*,*S*)-**2** to (*S*)-1-aminoindane (vide infra).

Disadvantages of this approach were the necessity to use large amounts of Raney-nickel (>100 w/w%) to ensure complete conversion of (*R*)-**1** into (*R*,*S*)-**2** and the low solubility of (*R*)-**1** in *i*-PrOAc. Therefore, we



Scheme 1. Synthesis of amine (*R*,*S*)-**2**. *Reagents and conditions*: (i) *p*-TsOH·H_2O, *i*-PrOAc, reflux, ca. 6 h; (ii) Ra-Ni, 3.5 bar H_2, 40°C, 45 h.

sought to optimize this reduction step in terms of catalyst loading, solvent and type of catalyst by using Argonaut's parallel pressure reactor, the Endeavor.[21] The effect of solvent and catalyst loading[22] on the hydrogenation of (*R*)-**1** with Raney-nickel was examined (Table 1).

The influence of the catalyst loading on the reaction time is significant: decrease of the amount of catalyst results in an increase in reaction time, entries 1–3. The conversion using 25 w/w% Raney-nickel was still not complete after 20 h (entry 1). However, the influence on the de is only marginal.[23]

In a protic solvent (entry 4), the reaction time decreased, but unfortunately the de decreased as well. The rather low solubility of (*R*)-**1** in *i*-PrOAc and *i*-PrOH could possibly have an effect on the speed of reaction. For this reason, alternative solvents were sought. It was found that (*R*)-**1** was readily soluble in THF and NMP. Hydrogenation in the former is fast (entry 5), with a de of the product that is comparable to that obtained from reactions in *i*-PrOAc. However, in NMP, the reaction is slow and the diastereoselectivity is low, entry 6.

As the amount of Raney-nickel that is needed to hydrogenate (*R*)-**1** effectively is high and handling of this large amount on production scale would be difficult, we focused our attention on palladium and platinum catalysts for the formation of (*R*,*S*)-**2**.

The results of the first screening are shown in Table 2. In general, nearly complete conversions with the Pd, Pt and Pd/Pt mixed catalysts (10 w/w%) in *i*-PrOAc were reached in 2–10 h, but the de values of the product were lower than those with Raney-nickel.

The best result was found by using the 5% Pd/C catalyst in *i*-PrOAc; (*R*,*S*)-**2** was formed with a de of 82% at complete conversion after 5 h (entry 2). Most importantly, hydrogenations with the Pd- or Pt-catalysts required a significantly lower amount of catalyst than reactions with Raney-nickel (10 versus 100 w/w%, respectively). Additionally, the Pd- and Pt-catalyzed reductions can be performed at room temperature, whereas hydrogenations with Raney-nickel required elevated temperatures.

This promising result prompted us to investigate further the possibilities and a series of experiments with the 5% Pd/C catalyst was conducted with variation of the solvent. The results are summarised in Table 3.

Toluene is the most suitable solvent (entry 2): (*R*,*S*)-**2** was obtained with a de of 89% at complete conversion in 3 h. The de is comparable to the result with Raney-nickel in *i*-PrOAc (Table 1). A high yield crystallization procedure to obtain diastereomerically pure (*R*,*S*)-**2** via the HCl salt had already been developed for the Raney-nickel hydrogenations (vide supra).

Interestingly, a clear correlation between solvent polarity (as measured by the dielectric constant ε) and the de is found (Fig. 1).

Entries 7–11 clearly show that an increase in polarity of the alcohol decreases the de, from 63% for *n*-octanol to 42% for ethanol. Generally, the de in polar solvents is low. Also, the diastereoselectivity in MTBE is high (entry 3), but the conversion is not complete. In 2-methyltetrahydrofuran (CH_3-THF; entry 5), the reduction is fast with complete conversion, and the de is comparable to the reduction in *i*-PrOAc, entry 4. Hep-

Table 1. The effect of solvent and catalyst loading on the hydrogenation of (*R*)-**1** with Raney-nickel[a] at 50°C, 3.5 bar H_2

Entry	Loading (w/w%)	Solvent	Time (h)	Conversion (%)	De (%)
1	25	*i*-PrOAc	>20	98	93
2	50	*i*-PrOAc	10	>99	92
3	100	*i*-PrOAc	8	>99	89
4	100	*i*-PrOH	4.5	>99	82
5	100	THF	3.5	>99	88
6	100	NMP	>20	86	38

[a] Doduco ACTIMET 'S', charge 768-18071.

Table 2. The effect of type of catalyst on the hydrogenation of (*R*)-**1** in *i*-PrOAc

Entry	Catalyst	Loading (w/w%)	Conditions	Time (h)	Conversion (%)	De (%)
1	Ra-Ni[a]	100	50°C, 3.5 bar H_2	8	>99	89
2	5% Pd/C[b]	10	25°C, 3.5 bar H_2	5	>99	82
3	5% Pt/C[c]	10	25°C, 3.5 bar H_2	2	98	64
4	1% Pt/C[d]	10	25°C, 3.5 bar H_2	>10	98	68
5	8% Pd/2% Pt/C[e]	10	25°C, 3.5 bar H_2	5	>99	76

[a] Doduco ACTIMET 'S', charge 768-18071.
[b] Engelhard ESCAT 142, moist-reduced, 52% moisture.
[c] Aldrich, dry.
[d] Engelhard ESCAT 261, moist-reduced, 51% moisture.
[e] Johnson-Matthey, 1130/8, batch 10, type 464, 51% moisture.

Table 3. The effect of the solvent on the hydrogenation of (*R*)-**1** with 5% Pd/C[a] (8 w/w%) at 25°C, 3.5 bar H_2

Entry	Solvent	ε	Time (h)	Conversion (%)	De (%)
1	Heptane	1.92	>10	37	50
2	Toluene	2.38	3	>99	89
3	MTBE	4.5	>10	74	85
4	*i*-PrOAc	5[b]	6	98	80
5	CH_3-THF[c]	5.26	2	>99	79
6	THF	7.58	2	97	68
7	*n*-Octanol	10.34	8	99	63
8	*n*-Pentanol	13.9	6	98	57
9	*s*-BuOH	16.56	6	>99	53
10	*i*-PrOH	19.92	7	>99	47
11	EtOH	24.55	2	97	42

[a] Engelhard ESCAT 142, moist-reduced, 52% moisture.
[b] Not found in the literature. The value given here is estimated from the values of 4.63 for *i*-pentyl acetate and 6.68 for MeOAc.
[c] 2-Methyltetrahydrofuran.

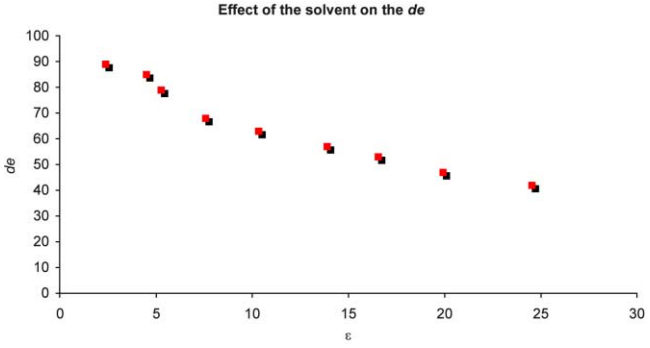


Figure 1. Correlation of the solvent polarity (ε) with the de of the hydrogenation of (*R*)-**1** with 5% Pd/C[a] (8 w/w%) at 25°C, 3.5 bar H_2. From left to right: toluene (ε=2.38), MTBE (ε=4.5), CH_3-THF (ε=5.26), THF (ε=7.58), *n*-octanol (ε=10.34), *n*-pentanol (ε=13.9), *s*-BuOH (ε=16.56), *i*-PrOH (ε=19.92) and EtOH (ε=24.55). [a]Engelhard ESCAT 142, moist-reduced, 52% moisture.

tane is a clear exception, which is probably due to the fact that (*R*)-**1** is completely insoluble in this solvent (hence, the low conversion).

Next, we decided to study improvement of the reduction of (*R*,*S*)-**2** in toluene by variation of the amount of catalyst (Table 4).

Upon increase of the amount of catalyst, the reaction time to obtain >99% conversion decreases, but the de value is not significantly affected. The best conditions were found at 4–6 w/w% of 5% Pd/C, which ensured short reaction times, complete conversion and high de values. Furthermore, in preliminary experiments, it was demonstrated that concentrations of the imine (*R*)-**1** in toluene could be increased to 0.25 g mL^{-1} without any effect on hydrogenation rate and diastereoselectivity.[24] These high substrate concentrations, low catalyst loadings (Pd/C might be recycled, a point that has not yet been tested) in combination with high diastereoselectivity and easy enrichment via crystallization leads to an industrially viable procedure for this step.

Table 4. The effect of catalyst loading on the hydrogenation of (*R*)-**1** with 5% Pd/C[a] in toluene at 25°C, 3.5 bar H_2

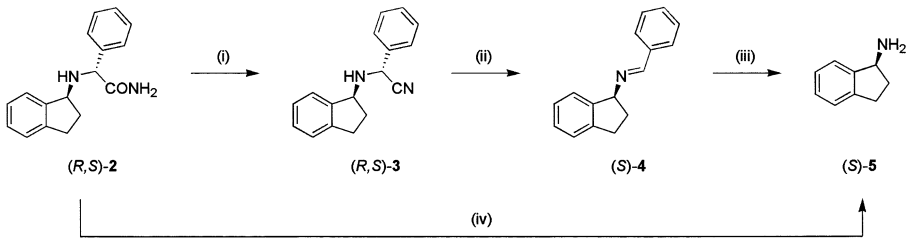
Entry	Loading (w/w%)	Time (h)	Conversion (%)	De (%)
1	2	15	>99	91
2	4	7	>99	91
3	6	4	>99	89
4	8	3	>99	89
5	10	2.7	>99	88
6	12	2.4	>99	88
7	14	2.3	>99	88

[a] Engelhard ESCAT 142, moist-reduced; 52% moisture.

In order to prove the reaction conditions on larger scale [Endeavor runs were carried out using 2 mmol of (*R*)-**1**], the reduction of (*R*)-**1** was performed on a 100 mmol scale, employing the conditions represented by entry 3 in Table 4. Thus, 26.4 g of the imine was suspended in 250 mL of toluene and 1.7 g of 5% Pd/C was added. The mixture was hydrogenated for 3 h at 3 bar H_2 and 25°C. Filtration and evaporation of the solvent, afforded (*R*,*S*)-**2** as a yellow oil in quantitative yield with a de of 90%. Purification to diastereomerically pure (*R*,*S*)-**2** in 85% overall yield has been done via the HCl-salt as described in the experimental section for a Raney-nickel reduction.

2.2. Non-reductive chiral auxiliary removal

Catalytic hydrogenolysis of (*R*,*S*)-**2** to remove the chiral auxiliary afforded (*S*)-1-aminoindane (*S*)-**5** in 40% yield (5% Pd/C, 5 bar H_2, 40°C, EtOH, AcOH). In this specific case, the regioselectivity of the *N*-debenzylation step was in favor of cleavage of the other N–C bond, thus affording (*R*)-PGA and indane. Therefore, we sought for alternative routes for the conversion of (*R*,*S*)-**2** to (*S*)-**5**. For this purpose, we developed the *retro*-Strecker method. Initially, the (*R*)-PGA chiral auxiliary was removed in three separate steps from (*R*,*S*)-**2**, affording (*S*)-**5** (Scheme 2).



Scheme 2. Non-reductive chiral auxiliary removal furnishing (*S*)-**5**. *Reagents and conditions*: (i) $POCl_3$, Et_3N, CH_2Cl_2, 0°C→rt, 1 h; (ii) K_2CO_3, EtOH, reflux, 1 h; (iii) $NH_2OH{\cdot}HCl$, THF/H_2O 1:1, 20 h; (iv) $POCl_3$, Et_3N, THF, 0°C→reflux, 5 h; $NH_2OH{\cdot}HCl$, H_2O, 16 h.

Dehydration of (*R*,*S*)-**2** with $POCl_3$ in CH_2Cl_2 in the presence of Et_3N afforded the nitrile (*R*,*S*)-**3**. Crude (*R*,*S*)-**3** generally contained residual Et_3N and invariably, minor quantities of (*S*)-**4** were detected, probably since excess base is used in the procedure, thus effecting the subsequent *retro*-Strecker reaction. Previously, in the syntheses of chiral homoallylamines, we performed the dehydration step according to the Vilsmeier procedure (oxalyl chloride and DMF in CH_2Cl_2).[3] In the case of (*R*,*S*)-**2**, dehydration with $POCl_3$ is less time-consuming, cleaner, and the yield is improved.

Treatment of crude (*R*,*S*)-**3** with K_2CO_3 in boiling ethanol, the *retro*-Strecker procedure, furnished the imine (*S*)-**4** in 94% yield from (*R*,*S*)-**2**, which was subjected to $NH_2OH{\cdot}HCl$ to afford (*S*)-**5** in 82% yield, 96% ee. The configuration of (*S*)-**5** was established by comparison of the HPLC analysis with that of an authentic sample.

This three-step sequence was greatly improved by performing the procedure in one pot without isolation of the intermediates (*R*,*S*)-**3** and (*S*)-**4**. Thus, treatment of (*R*,*S*)-**2** with $POCl_3$ in THF at 0°C in the presence of a large excess of Et_3N resulted in dehydration. Subsequently, the mixture was heated at reflux to effect the *retro*-Strecker reaction. Finally, addition of an aqueous solution of $NH_2OH{\cdot}HCl$ afforded (*S*)-**5** as a partly crystalline, brown oil in 70% isolated yield from (*R*,*S*)-**2** and 96% ee. The deprotection of (*S*)-**4** can also be accomplished by acidic hydrolysis using an excess of 30% HCl at reflux temperature for 24 h, furnishing (*S*)-**5** in 73% isolated yield from (*R*,*S*)-**2**, 96% ee.

3. Conclusions

The method presented here allows the asymmetric synthesis of (*S*)-1-aminoindane (*S*)-**5** from 1-indanone, employing (*R*)-phenylglycine amide as the chiral auxiliary. Thus, (*S*)-**5** was prepared in 58% overall yield from (*R*)-PGA and 1-indanone in an effective three-step procedure. As (*R*)-phenylglycine amide is readily available within DSM, scale-up of this procedure is envisaged. Obviously, (*S*)-phenylglycine amide is also accessible and can be used for the preparation of (*R*)-1-aminoindane.

More examples of this chirality transfer approach to enantiomerically pure amines using (*R*)- or (*S*)-phenylglycine amide are currently under investigation.

4. Experimental

4.1. Materials and methods

All reactions were performed using commercially available solvents and reagents, purchased from Acros Organics, which were used without further purification. (*R*)-Phenylglycine amide is provided by DSM Geleen, the Netherlands. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer at 200 MHz. Chemical shifts are denoted in ppm and were referenced to residual solvent resonances. HPLC analyses were performed on a HP1100 apparatus.

4.2. Synthetic procedures

4.2.1. Synthesis of the Schiff base (*R*)-1. A one-neck flask of 2 L, fitted with a Dean–Stark trap, was charged with (*R*)-PGA (101.9 g, 0.68 mol), 1-indanone (97.9 g, 1.1 equiv.) and *p*-$TsOH{\cdot}H_2O$ (6.50 g, 5 mol%). The mixture was suspended in *i*-PrOAc (500 mL) and boiled under reflux until the expected amount of water had collected in the Dean–Stark trap (ca. 6 h; 50 mL of solvent and water was removed via the trap in total). The mixture was allowed to cool to room temperature and stirred for 3 h, then the residue was filtered off. The cream-colored solid was stirred in H_2O (500 mL) for 5 min to remove unreacted (*R*)-PGA. The product was filtered off, washed with *i*-PrOAc (2×150 mL) and dried under reduced pressure, affording (*R*)-**1** as a white solid (160.7 g, 90%); ^1H NMR ($CDCl_3$, 200 MHz): δ 2.42–2.59 (m, 1H, indane-CH_2), 2.82–3.00 (m, 1H, indane-CH_2), 3.08–3.21 (m, 2H, indane-CH_2), 5.11 (s, 1H, PGA-CH), 5.96 (br s, 1H, $CONH_2$), 7.35–7.60 (m, 8H, aryl-CH), 7.67 (br s, 1H, $CONH_2$), 7.99 (d, 1H, aryl-CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.6, 29.2, 70.3, 122.9, 125.7, 126.1, 127.4, 127.9, 128.1, 128.3, 129.0, 129.3, 132.3, 139.7, 150.7, 175.7, 176.6; HPLC (Crownpak) 99% ee; $[\alpha]_D^{23} = -45.0$ (*c* 1.0, $CHCl_3$).

4.2.2. Synthesis of the amine (*R*,*S*)-2. In a 500 mL high-pressure hydrogenation flask, (*R*)-**1** (11.97 g, 45.3

mmol) was suspended in *i*-PrOAc (200 mL). Raney-nickel (ca. 15 g, 125 w/w%) was washed with MeOH (2×50 mL) and *i*-PrOAc (2×50 mL) and added to the reaction mixture. The flask was charged with 3.5 bar H_2, heated to 40°C and shaken for 45 h. At room temperature, the mixture was filtered over a P3 glass frit covered with Celite® and the residue was extracted with *i*-PrOAc (300 mL). The volatiles were removed under reduced pressure and the residual yellow oil was dissolved in acetone (500 mL). Under vigorous mechanical stirring, 15 mL of 6N HCl was added dropwise, during which a white precipitate formed. The thick slurry was stirred for 15 min, then filtered over a P3 glass frit and washed with acetone (50 mL). The resulting white solid was dissolved in demineralised water (500 mL) and EtOAc (300 mL). To this, anhydrous Na_2CO_3 was added in portions to pH 10, after which the layers were separated. The aqueous layer was extracted with EtOAc (300 mL); the combined organic fractions were dried on Na_2SO_4, filtered, and the volatiles were removed under reduced pressure, furnishing (*R*,*S*)-**2** as a slightly yellow oil (10.13 g, 84%); ^{1}H NMR ($CDCl_3$) δ 1.78–1.88 (m, 1H, indane-CH_2), 1.97 (br s, 1H, NH), 2.56–2.71 (m, 1H, indane-CH_2), 2.80–3.14 (m, 2H, indane-CH_2), 4.39 (t, 1H, indane-CH), 4.52 (s, 1H, PGA-CH), 6.43 (br s, 1H, $CONH_2$), 7.28–7.57 (m, 10H, aryl-CH/$CONH_2$); (*R*,*R*)-**2** δ 4.19 (t, indane-CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.5, 34.5, 62.8, 65.9, 124.5, 125.3, 126.8, 127.6, 127.9, 128.1, 128.2, 128.6, 129.3, 139.9, 143.8, 144.7, 175.8; HPLC-MS (Discovery C18) 99% pure, 99% de. HPLC (Chiralcel OD) 98% ee; $[\alpha]_D^{23} = -6.00$ (*c* 1.0, $CHCl_3$).

4.2.3. Synthesis of the nitrile (*R*,*S*)-3 and the imine (*S*)-4. A 250 mL one-neck flask was charged with (*R*,*S*)-**2** (6.16 g, 23.1 mmol), CH_2Cl_2 (100 mL) and Et_3N (16 mL, 5 equiv.). The mixture was cooled to 0°C and $POCl_3$ (4.8 mL, 2.2 equiv.) was added dropwise. The solution adopted an orange-brown color and was stirred at 0°C for 10 min. Subsequently, the mixture was allowed to warm to room temperature and stirred for 1 h. Water (100 mL) was added carefully, followed by Na_2CO_3 to pH 8. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried on Na_2SO_4 and the volatiles were removed in vacuo, affording (*R*,*S*)-**3** as a brown oil; ^{1}H NMR ($CDCl_3$) δ 1.98–2.17 (m, 1H, indane-CH_2), 2.12 (br s, 1H, NH), 2.52–2.67 (m, 1H, indane-CH_2), 2.89–3.03 (m, 1H, indane-CH_2), 3.09–3.23 (m, 1H, indane-CH_2), 4.64 (t, 1H, indane-CH), 4.99 (s, 1H, PGA-CH), 7.22–7.57 (m, 7H, aryl-CH), 7.61–7.69 (m, 2H, aryl-CH). Crude (*R*,*S*)-**3** was dissolved in EtOH (250 mL) and K_2CO_3 (6.81 g, 2 equiv.) was added. The mixture was boiled under reflux for 1 h and subsequently, EtOH was removed in vacuo. The residue was partitioned between CH_2Cl_2 and H_2O (2×200 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (200 mL). The combined organic layers were washed with brine (200 mL), dried on Na_2SO_4 and the volatiles were removed in vacuo, furnishing (*S*)-**4** as a brown, partly crystalline solid (4.79 g, 94%); ^{1}H NMR ($CDCl_3$) δ 2.33–2.45 (m, 1H, indane-CH_2), 2.51–2.65 (m, 1H, indane-CH_2), 2.97–3.15 (m, 1H, indane-CH_2), 3.16–3.32 (m, 1H, indane-CH_2), 5.02 (t, 1H, indane-CH), 7.19–7.40 (m, 4H, aryl-CH), 7.45–7.58 (m, 3H, aryl-CH), 7.84–7.95 (m, 2H, aryl-CH), 8.57 (s, 1H, N=CH).

4.2.4. Synthesis of (*S*)-1-aminoindane (*S*)-5. Imine (*S*)-**4** (10.00 g, 45.2 mmol) was dissolved in THF/H_2O 1:1 (250 mL) and NH_2OH·HCl (9.42 g, 3 equiv.) was added. The mixture was stirred for 20 h and subsequently, THF was removed in vacuo. The residual emulsion was acidified with 1N HCl to pH 1 and washed with EtOAc (200 mL). 10% NaOH was added to pH 8 and the aqueous layer was extracted with CH_2Cl_2 (250 mL). The organic layer was dried on Na_2SO_4 and the volatiles were removed in vacuo, yielding (*S*)-**5** as a brown oil (4.96 g, 82%); ^{1}H NMR ($CDCl_3$) δ 1.73 (br s, 2H, NH_2), 1.74–1.84 (m, 1H, indane-CH_2), 2.51–2.66 (m, 1H, indane-CH_2), 2.80–2.95 (m, 1H, indane-CH_2), 2.97–3.15 (m, 1H, indane-CH_2), 4.43 (t, 1H, indane-CH), 7.27–7.35 (m, 3H, aryl-CH), 7.38–7.45 (m, 1H, aryl-CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ. 30.1, 37.0, 57.0, 123.5, 124.4, 126.5, 127.2, 142.9, 147.3; HPLC (Crownpak) 96% ee; $[\alpha]_D^{23} = +20.0$ (*c* 1.0, $CHCl_3$).

4.2.5. One-pot chiral auxiliary removal to afford (*S*)-5. In a 250 mL one-neck flask, (*R*,*S*)-**2** (5.54 g, 20.8 mmol) was dissolved in THF (75 mL) and Et_3N (35 mL, 12 equiv.). The mixture was cooled to 0°C and $POCl_3$ (4.3 mL, 2.2 equiv.) was added dropwise, during which the solution slowly adopted an orange-brown color. After the addition was completed, the mixture was stirred at 0°C for 15 min, then allowed to warm to room temperature at which it was stirred for 1 h. Subsequently, the reaction mixture was boiled under reflux for 5 h, then allowed to cool to room temperature. A solution of NH_2OH·HCl (4.34 g, 3 equiv.) in H_2O (75 mL) was added and the mixture was stirred at room temperature for 16 h. Subsequently, THF was removed in vacuo and a 30% HCl solution was added dropwise to pH 1. The aqueous layer was washed with MTBE (2×75 mL) and subsequently, CH_2Cl_2 (100 mL) and a 33% NaOH solution were added successively (the latter dropwise) to pH 9. The layers were separated and the organic layer was dried on Na_2SO_4. Removal of the volatiles in vacuo afforded (*S*)-**5** as a brown oil (1.93 g, 70%), which partly crystallized on standing; analytical data as above (Section 4.2.4).

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24. All Endeavor experiments were conducted with a concentration of (*R*)-**1** of 0.1 g mL^{-1}.