Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 6755–6763

Enantioselective synthesis of *cis*-α-substituted cycloalkanols and *trans*-cycloalkyl amines thereof

Rosario Fernández,[a,*] Abel Ros,[b] Antonio Magriz,[b] Hansjörg Dietrich[c] and José M. Lassaletta[b,*]

[a]*Departamento de Química Orgánica, Universidad de Sevilla, Apdo. de correos 1203, 41071-Seville, Spain*
[b]*Instituto de Investigaciones Químicas (CSIC-USe), Americo Vespuccio s/n, Isla de la Cartuja, E-41092 Seville, Spain*
[c]*Bayer CropScience GmbH, Industriepark Höchst G386, 65926 Frankfurt am Main, Germany*

Received 26 March 2007; revised 19 April 2007; accepted 23 April 2007
Available online 4 May 2007

Abstract—The diastereo- and enantioselective syntheses of *trans*-cycloalkyl amines was accomplished through a three-step sequence consisting of: (1) asymmetric transfer hydrogenation through dynamic kinetic resolution of bicyclic and monocyclic α-substituted ketones using HCO_2H/Et_3N as the hydrogen source and TsDPEN-based Ru(II) catalysts, (2) nucleophilic hydroxyl to azide substitution of the resulting *cis*-cycloalkanols using diphenyl phosphoryl azide under modified Mitsunobu conditions, and (3) reduction of the *trans*-azide intermediates with $LiAlH_4$ of PPh_3/H_2O to the desired targets.
© 2007 Elsevier Ltd. All rights reserved.

1. Introduction

Optically active amines are important building blocks for the synthesis of a variety of biologically active molecules, among other industrial applications. Consequently, numerous methods have emerged in the past few years for their preparation in enantiomerically pure or enriched form.[1] In spite of the considerable advances in asymmetric synthesis and catalysis, the resolution of racemates remains as the most important approach used by the chemical industry for the preparation of this type of compounds. In this context, dynamic kinetic resolution (DKR),[2] not limited by the theoretical 50% maximum yield associated with conventional separation techniques or classical kinetic resolutions, is established as the most efficient technique for the resolution of racemates wherever it is applicable. After the seminal work by the Noyori[3] and Genêt[4] groups on the catalytic hydrogenation of β-keto esters, the hydrogenation through DKR has found a number of applications and stimulated the development of related reactions, including the hydrogenation or transfer hydrogenation[5] of several types of monocyclic[6] and bicyclic[7] cycloalkanones.

On the other hand, cyclic chiral amines are key structural elements in several bioactive compounds such as inhibitors of acyl CoA:cholesterol acyltransferase (ACAT),[8] positive allosteric modulators at the AMPA [2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid] receptors,[9] acetylcholine esterase (AChE), and monoamine oxidase (MAO) inhibitors with potential for treatment of Alzheimer's and Parkinson's diseases,[10] compounds with potent hypoglycemic activity,[11] etc. (Fig. 1).

Inspired by the above-disclosed precedents, we have recently reported on the transfer hydrogenation of α-substituted cyclic ketimines as the first DKR process involving reduction of C=N bonds via DKR.[12] In order to complement this procedure, that is limited to the synthesis of cis products, we envisaged that the corresponding *trans*-α-substituted cyclic amines could be readily available from α-substituted ketones

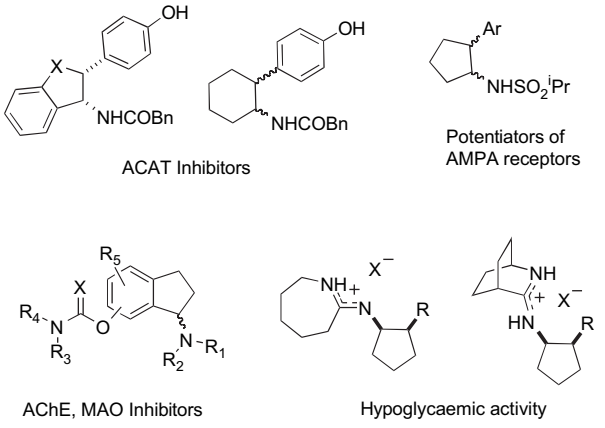
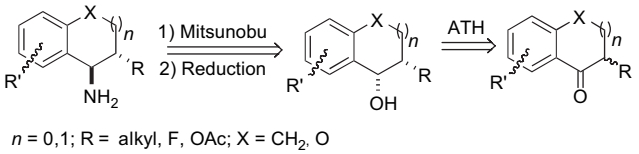


Figure 1. Bioactive cyclic amines.

Keywords: Asymmetric catalysis; Amines; Transfer hydrogenation; Dynamic kinetic resolution.
* Corresponding authors. Tel.: +34 954559727; fax: +34 954624960 (R.F.); tel.: +34 954489560; fax: +34 954460565 (J.M.L.); e-mail addresses: ffernan@us.es; jmlassa@iiq.csic.es

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.04.075

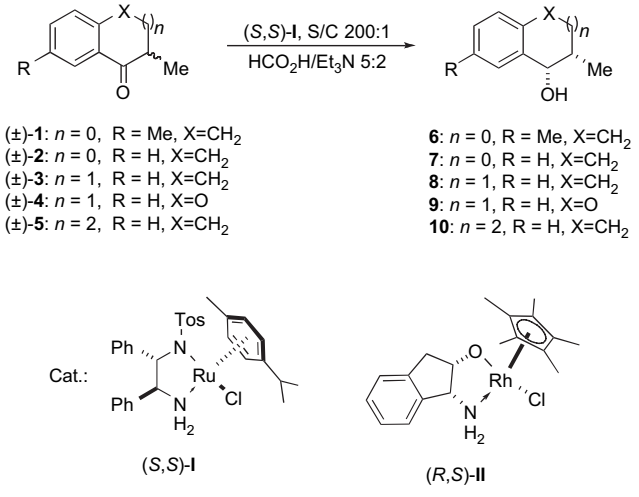
through a three-step synthetic route consisting of: (1) asymmetric transfer hydrogenation to *cis*-α-substituted cycloalkanols, (2) classical[13] or modified[14] Mitsunobu reaction with inversion of the configuration to *trans*-azido intermediates, and (3) reduction of the latter to the desired cycloalkyl amines (Scheme 1). In this paper, we report the results collected on the basis of this hypothesis and its extension to the synthesis of cyclic *cis*-1,2-diols and *trans*-1,2-fluoroamines.



Scheme 1. Retrosynthetic analysis for *cis*-cycloalkanols and *trans*-cycloalkyl amines thereof.

2. Results and discussion

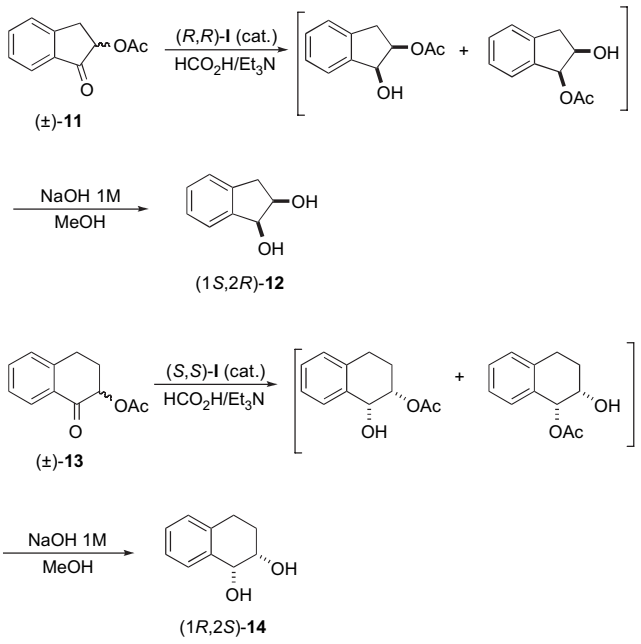
For the synthesis of the desired *cis*-cycloalkanols, initial experiments were performed with readily available racemic 2,6-dimethylindan-1-one (±)-**1** using 0.5 mol % of [RhClCp*(1*R*,2*S*)-*cis*-1-aminoindan-2-ol] [(*R*,*S*)-**II**] as the catalyst and ^{i}PrONa/^{i}PrOH as the hydrogen source.[15] The expected 2,6-dimethylindan-1-ol **6** was isolated in a moderate 45% yield as a 1:3 *cis*/*trans* diastereomeric mixture (Scheme 2), suggesting a thermodynamically controlled formation of the products. On the other hand, the use of Noyori/Ikariya [RuCl(TsDPEN)(*p*-cymene)] catalysts (*R*,*R*)- or (*S*,*S*)-**I** in 5:2 HCO_2H/Et_3N azeotropic mixture as the solvent and hydrogen source (method **A**)[16] was successfully applied to the reduction of racemic indanones (±)-**1**,**2** into the desired *cis*-(1*S*,2*S*)-indan-1-ol derivatives[17] **6** and **7**, obtained in excellent yields and stereoselectivities (Table 1, entries 1 and 2). No reaction was observed from α-aryl substituted indanones, even using substrate/catalyst ratio (S/C)=50 or 1.2:1 HCO_2H/Et_3N mixture (method **B**).[18] This result contrasts with the behavior of monocyclic substrates (see below) and also with that described by Wills and co-workers for 1-aryltetral-2-one derivatives,[7] and can be explained if a large proportion of unreactive enolic form is present in the keto/enol equilibrium in this case.



Scheme 2. Asymmetric transfer hydrogenation of (±)-**1**–**5** using (*S*,*S*)-**I** catalyst and 5:2 HCO_2H/Et_3N azeotropic mixture as hydrogen source.

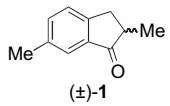
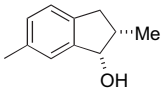
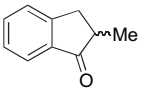
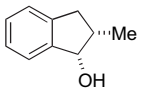
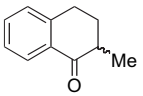
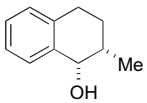
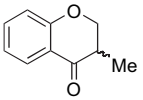
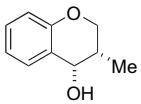
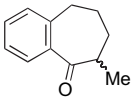
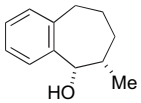
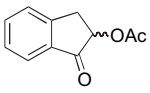
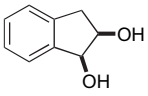
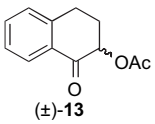
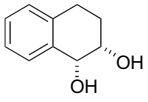
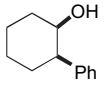
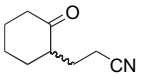
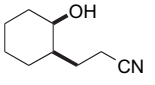
The reactions of tetral-1-one and chroman-4-one derivatives (±)-**3**,**4** were accomplished using (*S*,*S*)-**I** as the catalysts and 5:2 HCO_2H/Et_3N azeotropic mixture to afford, respectively, *cis*-(1*S*,2*S*)-2-methyltetral-1-ol[19] (**8**) and *cis*-(3*S*,4*S*)-3-methylchroman-4-ol (**9**) in high yields, good *cis*/*trans* ratios, and excellent enantioselectivities (Table 1, entries 3 and 4). The longer reaction times required for completion of the reactions and the lower diastereomeric excesses observed with respect to indanone derivatives (±)-**1**,**2** can be explained by a less efficient epimerization of the less reactive (*R*)-**3** or (*R*)-**4** enantiomers. This fact can be in turn tentatively attributed to the lower acidity of the α-proton of tetralone and chromanone rings. Finally, it should also be mentioned that the seven-membered 2-methyl benzosuberone (±)-**5** showed a very poor reactivity under these conditions. By increasing the catalyst loading to 2 mol %, the corresponding alcohol **10** could be isolated in only 30% yield and with moderate diastereo- and enantioselectivity (entry 5).

The behavior of 2-acetoxyindan-1-one (±)-(**11**) and 2-acetoxytetral-1-one (±)-(**13**) as representatives of α-oxygenated cyclic ketones was investigated next. In this cases, use of (*S*,*S*)-**I** or (*R*,*R*)-**I** catalysts and 1.2:1 HCO_2H/Et_3N mixture as hydrogen source and reaction medium afforded the best results concerning reactivity and stereoselectivity, a result in line with that previously observed for the related α-fluoro ketones.[20] The primary products from these reactions were mixture of the expected *cis*-2-acetoxycycloindan-1-ols and *cis*-1-acetoxycycloindan-2-ols, formed through well established 1,2-migration of the acetyl group (Scheme 3). The corresponding *cis* vicinal diols **12**[21] and **14**[22] were obtained by in situ deacetylation using NaOH (1 M)/MeOH (Table 1, entries 6 and 7).



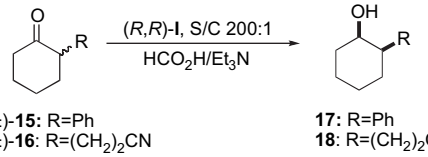
Scheme 3. Synthesis of diols **12** and **14**.

Table 1. Transfer hydrogenation of cyclic α-substituted ketones and enantioselective synthesis of *cis*-cycloalkanols

Entry	Substrate	Method[a]	Catalyst	*T* (days)	Major product	Yield[b] (%)	*cis*/*trans*[c]	er_{cis}[d]
1	 (±)-**1**	**A**	(*S*,*S*)-**I**	7	 (1*S*,2*S*)-**6**	80 (71)	97:3 (99:1)	98:2 (99:1)
2	 (±)-**2**	**A**	(*S*,*S*)-**I**	7	 (1*S*,2*S*)-**7**	78	97:3	98.5:1.5
3	 (±)-**3**	**A**	(*S*,*S*)-**I**	9	 (1*S*,2*S*)-**8**	75	95:5	99:1
4	 (±)-**4**	**A**	(*S*,*S*)-**I**	9	 (3*S*,4*S*)-**9**	92 (80)	86/14 (95:5)	99:1
5	 (±)-**5**	**A**	(*S*,*S*)-**I**[e]	12	 (1*S*,2*S*)-**10**	30	83:17	79:21
6	 (±)-**11**	**B**	(*R*,*R*)-**I**	1	 (1*S*,2*R*)-**12**	80[f]	>99:1	99.5:0.5
7	 (±)-**13**	**B**[g]	(*S*,*S*)-**I**	2	 (1*R*,2*S*)-**14**	80[f]	97:3	96:4
8	 (±)-**15**	**A**	(*R*,*R*)-**I**	6	 (1*R*,2*R*)-**17**	90	>99:1	>99:1
9	 (±)-**16**	**A**	(*R*,*R*)-**I**	6	 (1*R*,2*R*)-**18**	90	85:15	90:10
10	(±)-**16**	**B**	(*R*,*R*)-**I**	6	(1*R*,2*R*)-**18**	80	75:25	80:20

[a] Method **A** uses 5:2 HCO_2H/Et_3N mixture and 0.5% of catalyst; method **B** uses 1.2:1 HCO_2H/Et_3N mixture and 0.5% of catalyst.
[b] Isolated, overall yield from starting ketone. In parenthesis: yield after fractional crystallization.
[c] Determined by ^1H NMR of the crude reaction mixture. In parenthesis: diastereomeric excess after fractional crystallization.
[d] Determined by HPLC or GC on chiral stationary phases. In parenthesis: enantiomeric excess after fractional crystallization.
[e] Catalyst of 2 mol % (S/C 50) was used.
[f] Yields of the diols obtained by in situ deacetylation with NaOH (1 M)/MeOH.
[g] Reaction performed with 2 mmol of ketone in 4 mL of HCO_2H/Et_3N mixture.

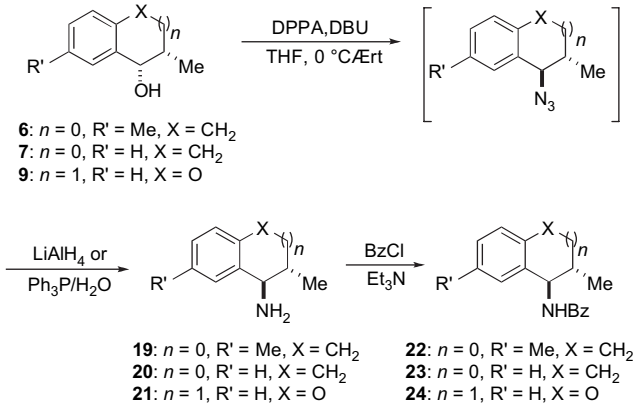
We next turned our attention to monocyclic substrates such as (±)-**15**,**16** (Scheme 4). These are a priori more challenging systems, where the smaller steric and electronic differences at both sides of the carbonyl group constitute additional difficulties. α-Aryl-substituted ketone (±)-**15** was reduced under method **A** using 0.5 mol % catalyst (*R*,*R*)-**I**, to give *cis*-(1*R*,2*R*)-2-phenylcyclohexanol[23] (**17**) in excellent diastereo- and enantioselectivity (Table 1, entry 8). Under the same conditions, ketone (±)-**16** afforded (1*R*,2*R*)-**18** in moderate diastereo- and enantioselectivity (85:15 *cis*/*trans*, 90:10 er, entry 9). Using 1.2:1 HCO_2H/Et_3N mixture (method **B**) a poor result (entry 10) was obtained for ketone (±)-**16**. The minor amounts (10–25%) of trans isomers and the lower er observed for (±)-**16** with respect to (±)-**15** can be explained as a result of the smaller steric repulsion by the alkyl group and the proposed π-interaction between the η^6-arene [on (*R*,*R*)-**I** catalyst] and the aryl ring in (±)-**15**.[24,25]



Scheme 4. Asymmetric transfer hydrogenation of (±)-**15**,**16** using (*R*,*R*)-**I** catalyst and 5:2 or 1.2:1 HCO_2H/Et_3N mixture as hydrogen source.

With the enantiomerically enriched *cis*-cycloalkanols in hand, the synthesis of the target chiral *trans*-cycloalkyl amines was accomplished by nucleophilic substitution of the hydroxy group by an azido group. Modified Mitsunobu conditions using diphenyl phosphoryl azide (DPPA) in the presence of DBU gave rise to azides with complete inversion of configuration at C(1),[14] conditions being mild enough to prevent β-elimination of hydrazoic acid, even in systems as sensitive as the indane and tetraline derivatives. Finally, in situ reduction by $LiAlH_4$/THF or Ph_3P/H_2O (Staüdinger reaction) afforded the desired *trans*-cycloalkyl amines **19**–**21** (Table 2), which were transformed into the corresponding benzamides **22**–**24** for analytical purposes (Scheme 5).

In order to expand the scope of the of the methodology, *trans*-2-fluoro cycloalkyl amines **27** and **28** were also synthesized from the corresponding *cis*-cyclic fluorohydrins **25** and **26** (Scheme 6), that were previously obtained by asymmetric transfer hydrogenation of the corresponding racemic α-fluoroketones via DKR.[20]

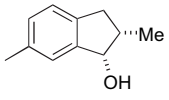
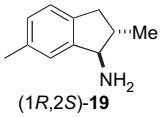
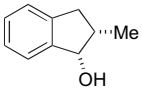
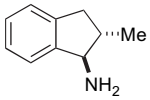
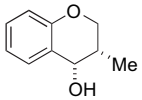
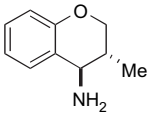
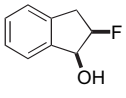
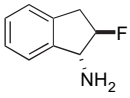
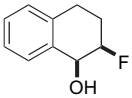
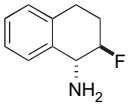


Scheme 5. Synthesis of *trans*-cycloalkyl amines (1*R*,2*S*)-**19**–**21**.

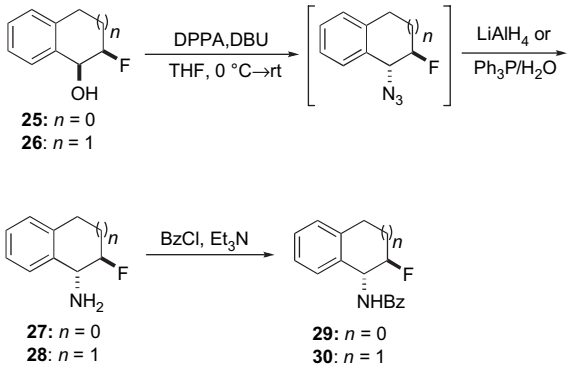
3. Conclusion

Summarizing, the transfer hydrogenation of α-substituted cyclic ketones through DKR is the key step for the synthesis of several *trans*-α-substituted cycloalkyl amines. Using Noyori/Ikariya Ru(arene)TsDPEN catalysts **I** in HCO_2H/Et_3N mixture as the hydrogen source, good reactivities and enantioselectivities were achieved in most cases. The observed yields and the achieved levels of diastereo- and enantioselectivity of the products confer synthetic utility to the methodology.

Table 2. Synthesis of *trans*-cycloalkyl amines

Entry	Substrate	Reducing agent	Product	Yield[a]	*cis*/*trans*[b]	er[c]
1	 (1*S*,2*S*)-**6**	$LiAlH_4$	 (1*R*,2*S*)-**19**	76	96:4	98.5:1.5
2	(1*S*,2*S*)-**6**	Ph_3P/H_2O	(1*R*,2*S*)-**19**	74	97.5:2.5	98.5:1.5
3	 (1*S*,2*S*)-**7**	$LiAlH_4$	 (1*R*,2*S*)-**20**	80	96:4	97.5:2.5
4	(1*S*,2*S*)-**7**	Ph_3P/H_2O	(1*R*,2*S*)-**20**	72	>99:1	98.5:1.5
5	 (3*S*,4*S*)-**9**	Ph_3P/H_2O	 (3*R*,4*R*)-**21**	84	96:4	97.5:2.5
6	 (1*S*,2*R*)-**25**	Ph_3P/H_2O	 (1*R*,2*R*)-**27**	70	>99:1	97.5:2.5
7	 (1*S*,2*R*)-**26**	Ph_3P/H_2O	 (1*R*,2*R*)-**28**	74	>99:1	98.5:1.5

[a] Isolated, overall yield from starting alcohol.
[b] Determined by ^1H NMR of the crude reaction mixture.
[c] Of the major isomer, determined for the corresponding benzamides by HPLC on chiral stationary phases.



Scheme 6. Synthesis of *trans*-2-fluoro-1-cycloalkyl amines **27**–**28**.

4. Experimental section

4.1. General experimental methods

Solvents were purified and dried by standard procedures. Flash chromatography was carried out on silica gel (0.040–0.063 or 0.015–0.040 mm). Melting points were recorded in a metal block and are uncorrected. ^{1}H NMR spectra were recorded at 300, 400 or 500 MHz; ^{13}C NMR spectra were recorded at 75, 100 or 125 MHz with the solvent peak used as the internal reference. The diastereomeric excesses (de) of the products were determined by ^{1}H NMR and the enantiomeric excess (ee) by HPLC on chiral stationary phases with ^{i}PrOH/hexane mixture as the eluant. Catalysts (*R*,*R*)-**I** and (*S*,*S*)-**I**,[25] 2-acetoxyindan-1-one (±)-**11**,[26] and 2-acetoxytetral-1-one (±)-**13**[26] were synthesized according to previously described procedures.

4.2. Transfer hydrogenation of α-substituted ketones. General procedures

*Method **A***. α-Substituted ketone (4 mmol) was added to a solution of catalyst **I** (6.5 mg, 0.02 mmol) in 5:2 HCO_2H/Et_3N (2 mL). The mixture was stirred at rt for 7–12 days, then diluted with CH_2Cl_2 (20 mL) and washed with H_2O (2×15 mL). The organic layer was dried and concentrated, and the residue was purified by flash chromatography.

*Method **B***. α-Substituted ketone (2 mmol) was added to a solution of catalyst **I** (3.3 mg, 0.01 mmol) in 1.2:1 HCO_2H/Et_3N (2 mL). The mixture was stirred at rt for 6–9 days and the reaction was then elaborated as in method **A**.

Starting materials, method used for the synthesis, catalyst, eluants, yields, and spectral and analytical data for compounds **6**–**10**, **12**, **14**, **17**, **18**, and **18**(OBz) are as follows:

4.2.1. (1*S*,2*S*)-2,6-Dimethylindan-1-ol [(1*S*,2*S*)-6]. From 2,6-dimethylindan-1-one (±)-**1** (6.4 g, 40 mmol) and following method **A** with (*S*,*S*)-**I** as the catalyst, after 7 days the residue was purified by flash chromatography (1:12→1:3 EtOAc/hexane) to afford (1*S*,2*S*)-**6** (5.2 g, 80%, 94% de, 96% ee) as a white solid. Crystallization from hexane afforded enriched (1*S*,2*S*)-**6** (71%, >98% de, 98% ee). Mp 112–114 °C. $[\alpha]_D^{20}$ +58.3 (*c* 0.9, $CHCl_3$). Anal. calcd for $C_{11}H_{14}O$: C 81.44, H 8.70; found: C 81.21, H 8.57. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, 3H, *J*=6.8 Hz), 1.41 (br s, 1H), 2.33 (s, 3H), 2.52 (m, 1H), 2.61 (dd, 1H, *J*=15.6, 7.2 Hz), 2.89 (dd, 1H, *J*=15.6, 7.2 Hz), 4.95 (d, 1H, *J*=4.4 Hz), 7.05–7.21 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 21.3, 37.6, 39.5, 77.7, 124.7, 125.4, 129.3, 136.3, 140.3, 144.9. MS (EI): *m*/*z* 162 (M^+, 83), 161 (100), 147 (67), 105 (91). HRMS *m*/*z* calcd for $C_{11}H_{14}O$: 162.1045, found: 162.1044. HPLC (Chiralcel OB, 2-propanol/hexane 4:96, flow 0.35 mL/min, *T*=30 °C): t_R= 15.69 min (minor) and 18.09 min (major).

4.2.2. (1*S*,2*S*)-2-Methylindan-1-ol [(1*S*,2*S*)-7]. From 2-methylindan-1-one (±)-**2** (1 g, 6.85 mmol) and following method **A** with (*S*,*S*)-**I** as the catalyst, after 7 days the residue was purified by flash chromatography (1:8 EtOAc/hexane) to afford (1*S*,2*S*)-**7** (790 mg, 78%, 94% de, 97% ee) as a white solid. Mp 49–51 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (d, 3H, *J*=6.9 Hz), 2.51 (m, 1H), 2.66 (dd, 1H, *J*=15.6, 7.2 Hz), 2.94 (dd, 1H, *J*=15.6, 7.2 Hz), 4.98 (d, 1H, *J*=5.4 Hz), 7.17–7.40 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 38.2, 39.5, 76.9, 125.0, 125.3, 126.9, 128.7, 143.6, 145.0. $[\alpha]_D^{20}$ +40.5 (*c* 0.5, $CHCl_3$) [lit.[17] (1*R*,2*R*)-**7** (>98% ee): $[\alpha]_D^{25}$ −38.0 (*c* 0.3, $CHCl_3$)]. MS (EI): *m*/*z* 148 (M^+, 61), 147 (88), 131 (100). HRMS *m*/*z* calcd for $C_{10}H_{12}O$: 148.0888, found: 148.0882. HPLC (Chiralcel OB, propan-2-ol/hexane 4:96, flow 0.5 mL/min, *T*=30 °C): t_R=11.59 min (minor) and 18.88 min (major). trans Diastereomers: t_R=15.51 min.

4.2.3. (1*S*,2*S*)-2-Methyltetral-1-ol [(1*S*,2*S*)-8]. From 2-methyltetral-1-one (±)-**3** (420 mg, 2.6 mmol) and following method **A** with (*S*,*S*)-**I** as the catalyst, after 9 days the residue was purified by flash chromatography (1:10 EtOAc/hexane) to afford (1*S*,2*S*)-**8** (316 mg, 75%, 90% de, 98% ee) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, 1H, *J*=6.8 Hz), 1.47 (br s, 1H), 1.53–1.94 (m, 3H), 2.74 (ddd, 1H, *J*=16.8, 10.6, 6.4 Hz), 2.85 (ddd, 1H, *J*=16.8, 5.2, 3.2 Hz), 4.55 (d, 1H, *J*=2.8 Hz), 7.06–7.35 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.0, 24.8, 28.9, 34.2, 71.5, 126.1, 127.9, 129.1, 129.9, 136.8, 138.7. $[\alpha]_D^{20}$ −43.7 (*c* 0.45, C_6H_6) [lit.[6d] (1*R*,2*R*)-**8** (97% de, 87% ee): $[\alpha]_D^{25}$ +65.5 (*c* 2.10, C_6H_6)]. MS (CI): *m*/*z* 162 (M^+, 22), 161 (13), 144 (70), 119 (100). HRMS *m*/*z* calcd for $C_{11}H_{14}O$: 162.1045, found: 162.1040. GC (Chirasil-Dex CB, T_{column}=120 °C, helium (90 kPa), $T_{injector}$=250 °C, split ratio 20:1): t_R=35.56 min (minor) and 36.46 min (major). trans Diastereomers: t_R=39.08 and 40.13 min.

4.2.4. (3*S*,4*S*)-3-Methylchroman-4-ol [(3*S*,4*S*)-9]. From 3-methylchroman-4-one (±)-**4** (1 g, 6.2 mmol) and following method **A** with (*S*,*S*)-**I** as the catalyst, after 9 days the residue was purified by flash chromatography (1:16 EtOAc/hexane) to afford (3*S*,4*S*)-**9** (935 mg, 92%, 78% de, 98% ee) as a white solid. Crystallization from hexane afforded enriched (3*S*,4*S*)-**9** (80%, 90% de, 98% ee). Mp 66–68 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (d, 3H, *J*=7.0 Hz), 1.80 (br s, 1H), 2.13 (m, 1H), 3.95 (t, 1H, *J*=11.0 Hz), 4.00 (dd, 1H, *J*=11.0, 3.5 Hz), 4.53 (s, 1H), 6.82–7.25 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.0, 33.0, 66.8, 67.2, 117.1, 120.8, 124.6, 130.1, 130.5, 154.4. $[\alpha]_D^{20}$ −126.8 (*c* 0.69, $CHCl_3$). MS (EI): *m*/*z* 164 (M^+, 74), 162 (8), 122 (100). HRMS *m*/*z* calcd for $C_{10}H_{12}O_2$: 164.0837, found: 164.0837. Anal. calcd for $C_{10}H_{12}O_2$: C 73.15, H 7.37; found: C 73.10, H 7.28. HPLC (Chiralcel OB, 2-propanol/hexane

5:95, flow 0.5 mL/min, T=30 °C): t_R 14.96 min (minor) and 20.95 min (major).

4.2.5. (1*S*,2*S*)-2-Methylbenzosuber-1-ol [(1*S*,2*S*)-10]. From 2-methylbenzosuberon-1-one (±)-**5** (216 mg, 1.35 mmol) and following method **A** with (*S*,*S*)-**I** as the catalyst, after 12 days purification of the residue by flash chromatography (1:10 EtOAc/hexane) afforded (1*S*,2*S*)-**10** (66 mg, 30%, 66% de, 58% ee) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81 (d, 3H, J=6.5 Hz), 1.61–2.04 (m, 5H), 2.64 (m, 2H), 2.95 (m, 1H), 4.86 (s, 1H), 7.06–7.33 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.6, 24.8, 34.5, 35.6, 37.7, 78.3, 125.9, 126.0, 127.2, 129.6, 141.2, 142.0. $[\alpha]_D^{20}$ −115.0 (*c* 0.8, $CHCl_3$). MS (EI): *m*/*z* 176 (M^+, 80), 122 (40), 105 (100). HRMS *m*/*z* calcd for $C_{12}H_{16}O$: 176.1201, found: 176.1210. HPLC (Chiralcel OJ, 2-propanol/hexane 3:97, flow 0.5 mL/min, T=30 °C): t_R=9.24 min (minor) and 11.67 min (major). trans Diastereomers: t_R=10.24 and 18.72 min.

4.2.6. (1*S*,2*R*)-Indane-1,2-diol [(1*S*,2*R*)-12]. From 2-acetoxyindan-1-one (±)-**11** (380 mg, 2 mmol) and following method **B** with (*R*,*R*)-**I** as the catalyst, after 1 day the reaction was elaborated as described. The residue was dissolved in MeOH (6 mL), treated with NaOH 1 M (4 mL), stirred for 15 min, neutralized with HCl (1 N), diluted with H_2O, and extracted with CH_2Cl_2 (3×15 mL). Flash chromatography (2:3 EtOAc/hexane) afforded (1*S*,2*R*)-**12** (240 mg, 80%, >98% de, 99% ee) as a white solid. Mp 100–102 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.45 (d, 1H, J=5.5 Hz), 2.54 (d, 1H, J=7.0 Hz), 2.94 (dd, 1H, J=16.5, 3.5 Hz), 3.11 (dd, 1H, J=16.5, 6.0 Hz), 4.48 (m, 1H), 4.99 (t, 1H, J=5.5 Hz), 7.22–7.42 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 38.7, 73.5, 76.0, 125.1, 125.4, 127.2, 128.9, 140.2, 142.0. $[\alpha]_D^{20}$ −46.5 (*c* 0.8, $CHCl_3$) [lit.[21]: $[\alpha]_D^{25}$ −48.0 ($CHCl_3$)]. MS (EI): *m*/*z* 150 (M^+, 17), 133 (92), 104 (100). HRMS *m*/*z* calcd for $C_9H_{10}O_2$: 150.0681, found: 150.0671. Anal. calcd for $C_9H_{10}O_2$: C 71.98, H 6.71; found: C 71.94, H 6.69. HPLC (Chiralcel OK, 2-propanol/hexane 10:90, flow 0.8 mL/min, T=30 °C): t_R 10.81 min (minor) and 12.90 min (major).

4.2.7. (1*R*,2*S*)-Tetral-1,2-diol [(1*R*,2*S*)-14]. From 2-acetoxytetral-1-one (±)-**13** (408 mg, 2 mmol) and following modified method **B** (2 mmol haloketone/4 mL 1.2:1 HCO_2H/Et_3N mixture) with (*S*,*S*)-**I** as the catalyst, after 2 days the reaction was elaborated as described. The residue was dissolved in MeOH (6 mL), treated with NaOH 1 M (4 mL), stirred for 15 min, neutralized with HCl (1 N), diluted with H_2O, and extracted with CH_2Cl_2 (3×15 mL). Flash chromatography (1:1 EtOAc/hexane) afforded (1*R*,2*S*)-**14** (260 mg, 80%, 94% de, 92% ee) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88 (m, 1H), 2.00 (m, 1H), 2.57 (d, 2H, J=5.2 Hz), 2.76 (ddd, 1H, J=17.2, 9.6, 6.4 Hz), 2.94 (dt, 1H, J=17.2, 5.6 Hz), 3.97 (m, 1H), 4.66 (t, 1H, J=5.2 Hz), 7.08–7.40 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 27.2, 69.8, 70.2, 126.7, 128.4, 128.9, 130.2, 136.5, 136.6. $[\alpha]_D^{20}$ −23.8 (*c* 0.96, $CHCl_3$) [lit.[22]: $[\alpha]_D^{25}$ −38.0 (*c* 0.9, $CHCl_3$, >98% ee)]. MS (EI): *m*/*z* 164 (M^+, 18), 147 (76), 118 (100). HRMS calcd for $C_{10}H_{12}O_2$: 164.0837, found: 164.0832. Anal. calcd for $C_{10}H_{12}O_2$: C 73.15, H 7.37; found: C 73.03, H 7.10. HPLC (Chiralcel OK, 2-propanol/hexane 5:95, flow 1.5 mL/min, T=30 °C): t_R 11.0 min (major) and 13.90 min (minor).

4.2.8. (1*R*,2*R*)-2-Phenylcyclohexanol [(1*R*,2*R*)-17]. From 2-phenylcyclohexanone (±)-**15** (350 mg, 2 mmol) and following the general method **A** with (*R*,*R*)-**I** as the catalyst, after 6 days the residue was purified by flash chromatography (1:10 EtOAc/hexane) to afford (1*R*,2*R*)-**17** (320 mg, 90%, >98% de, >98% ee) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15–7.42 (m, 5H), 3.97–4.08 (m, 1H), 2.74 (dt, 1H, J=12.9, 2.7 Hz), 1.30–2.15 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.9, 24.6, 26.5, 33.3, 48.3, 70.9, 126.8, 128.1, 128.8, 144.3. $[\alpha]_D^{20}$ −106.1 (*c* 0.7, MeOH) [lit.[23]: $[\alpha]_D^{25}$ −106.0 (*c* 0.2, MeOH, >98% de, >98% ee)]. Anal. calcd for $C_{12}H_{16}O$: C 81.77; H 9.15; found: C 81.42; H 9.15. MS (EI): *m*/*z* 176 (M^+, 85), 130 (84), 91 (100). HRMS *m*/*z* calcd for $C_{12}H_{16}O$: 176.1201, found: 176.1195. HPLC (Chiralcel OB, 2-propanol/hexane 1:99, flow 0.5 mL/min, T=30 °C): t_R=12.7 min (minor) and 14.4 min (major).

4.2.9. 3-[(1*R*,2*R*)-2-Hydroxycyclohexyl]propanenitrile [(1*R*,2*R*)-18]. From 3-(2-oxocyclohexyl)propanenitrile (±)-**16** (906 mg, 6.0 mmol) and following method **A** with (*R*,*R*)-**I** as the catalyst, after 6 days the residue was purified by flash chromatography (1:9 EtOAc/hexane) to afford (1*R*,2*R*)-**18** (850 mg, 90%, 70% de, 80% ee) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82–3.90 (m, 1H), 2.26–2.50 (m, 2H), 1.15–1.85 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1, 20.5, 25.0, 26.4, 27.7, 33.2, 40.2, 68.5, 120.4. $[\alpha]_D^{20}$ +20.4 (*c* 1.0, $CHCl_3$). MS (CI): *m*/*z* 154 (M^++1, 20), 153 (M^+, 11), 136 (100). HRMS *m*/*z* calcd for $C_9H_{16}NO$: 154.1233, found: 154.1232.

4.2.9.1. *O*-Benzoyl derivative (1*R*,2*R*)-18(OBz). To a solution of (1*R*,2*R*)-**18** (153 mg, 1.0 mmol) in dry CH_2Cl_2 was added benzoyl chloride (1.2 equiv) and Et_3N (1.2 equiv). After for 8 h, the mixture was concentrated and the residue was purified by flash chromatography (1:9 EtOAc/hexane) to afford (1*R*,2*R*)-**18**(OBz) (200 mg, 78%, 70% de, 80% ee) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, 2H, J=7.6 Hz), 7.56 (t, 1H, J=7.6 Hz), 7.44 (t, 2H, J=7.6 Hz), 5.23–5.33 (m, 1H), 4.99 (td, 1H, J=8.2, 4.3 Hz), 3.49–3.67 (m, 2H), 3.40 (td, 1H, J=8.2, 4.3 Hz), 1.97–2.14 (m, 2H), 2.25–2.45 (m, 2H), 1.15–1.85 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.0, 21.0, 25.3, 27.4, 28.2, 30.5, 39.6, 71.5, 119.9, 128.8, 129.8, 130.7, 133.4, 166.2. $[\alpha]_D^{20}$ +21.5 (*c* 0.5, $CHCl_3$). MS (EI): *m*/*z* 258 (M^++1, 4), 123 (71), 105 (100), 77 (11). HRMS calcd for $C_{16}H_{20}NO_2$: 258.1494, found: 258.1493. HPLC (Chiralpak AD, 2-propanol/hexane 5:95, flow 0.5 mL/min, T=30 °C): t_R=7.1 min (major) and 7.9 min (minor).

4.3. General method for the synthesis of amines (19–21 and 27–28) and benzamides (22–24 and 29–30)

Method ***A***. Diphenyl phosphoryl azide (1.2 equiv) was added to a solution of the alcohol in dry toluene ([alcohol]=0.7–1.2 M) under argon. The reaction mixture was cooled at 0 °C, stirred for 10 min, and DBU (1.2 equiv) was added slowly over 20 min. The mixture was stirred 2 h at 0 °C, then for 20 h at rt, and the solvent was removed in vacuo. The residue was dissolved in a 1:1 EtOAc/hexane mixture, filtered through a short silica pad, concentrated, dissolved in dry THF ([azide]≈0.5 M) and added dropwise to a suspension of $LiAlH_4$ (1.5 equiv) in dry THF. The reaction mixture was stirred for 1 h at rt and heated to reflux for 2 h. After

cooling, the excess $LiAlH_4$ was destroyed by slow addition of 10:1 THF/H_2O, filtered through Celite and concentrated to dryness. Purification by flash chromatography afforded the corresponding amine.

Method ***B***. The synthesis of the azide is as described for method **A**. The crude azide was dissolved in dry THF ([azide] ≈ 0.1 M), and Ph_3P (1.2 equiv) and H_2O (2 equiv) were added. After refluxing overnight, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. Purification by flash chromatography afforded the corresponding amine.

For analytical purposes, the obtained amines were transformed into the corresponding benzamides by conventional benzoylation using benzoyl chloride (1.2 equiv) and Et_3N (1.2 equiv) in dry CH_2Cl_2.

Starting materials, method used for the synthesis, catalyst, eluants, yields, and spectral and analytical data for compounds **19**–**24** and **27**–**30** are as follows:

4.3.1. (1*R*,2*S*)-2,6-Dimethyl-1-aminoindane [(1*R*,2*S*)-19]. From (1*S*,2*S*)-**6** (324 mg, 2 mmol) and following method **B**, the residue was purified by flash chromatography (20:1 CH_2Cl_2/MeOH) to afford (1*R*,2*S*)-**19** (232 mg, 72%, >98% de, 97% ee)[27] as a light yellow solid. Mp 89–91 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (d, 3H, J=6.5 Hz), 1.72 (br s, 2H), 1.98 (m, 1H), 2.34 (s, 3H), 2.42 (dd, 1H, J=15.5 Hz, 9.5 Hz), 2.98 (dd, 1H, J=15.5 Hz, 7.5 Hz), 3.74 (d, 1H, J=8.5 Hz), 6.99 (d, 1H, J=7.5 Hz), 7.05 (d, 1H, J=7.5 Hz), 7.12 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.7, 21.4, 38.2, 47.2, 64.1, 123.9, 124.2, 127.9, 136.1, 139.1, 147.4. $[\alpha]_D^{20}$ +3.5 (*c* 0.9, $CHCl_3$). MS (CI): *m*/*z* 161 (M^+, 17), 160 (51), 145 (100), 144 (72). HRMS *m*/*z* calcd for $C_{11}H_{14}N$: 160.1126, found: 160.1134.

4.3.1.1. *N*-Benzoyl derivative (1*R*,2*S*)-22. From (1*R*,2*S*)-**19** (18 mg, 0.11 mmol), the general procedure afforded (1*R*,2*S*)-**22** (25 mg, 86%, >98% de, 97% ee) as light yellow solid. Mp 157–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (d, 3H, J=6.6 Hz), 2.25–2.40 (m, 4H), 2.55 (dd, 1H, J=15.6 Hz, 9.0 Hz), 3.07 (dd, 1H, J=15.6 Hz, 7.8 Hz), 5.30 (t, 1H, J=8.7 Hz), 6.25 (d, 1H, J=8.7 Hz), 7.02–7.83 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5, 21.5, 38.4, 45.0, 61.6, 124.8, 127.2, 128.9, 129.0, 131.9, 134.8, 136.9, 139.9, 143.7, 167.8. $[\alpha]_D^{20}$ +37.5 (*c* 0.5, $CHCl_3$). MS (EI): *m*/*z* 266 (M^++1, 28), 265 (20), 144 (100), 105 (53). HRMS *m*/*z* calcd for $C_{18}H_{20}NO$: 266.1545, found: 266.1550. HPLC (Chiralpak AD, 2-propanol/hexane 4:96, flow 1.0 mL/min, T=30 °C): t_R=11.15 min (minor) and 14.88 min (major). cis Diastereomers t_R=22.64 min.

4.3.2. (1*R*,2*S*)-2-Methyl-1-aminoindane [(1*R*,2*S*)-20]. From (1*S*,2*S*)-**7** (294 mg, 2 mmol) and following method **B**, purification by flash chromatography (20:1 CH_2Cl_2/MeOH) afforded (1*R*,2*S*)-**20** (216 mg, 74%, 95% de, 97% ee)[27] as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (d, 3H, J=6.6 Hz), 1.60 (br s, 2H), 1.97 (m, 1H), 2.48 (dd, 1H, J=15.6, 9.3 Hz), 3.02 (dd, 1H, J=15.6, 7.8 Hz), 3.78 (d, 1H, J=8.1 Hz), 7.13–7.30 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9, 38.8, 47.3, 64.4, 123.5, 124.7, 126.7, 127.4, 142.4, 147.6. $[\alpha]_D^{20}$ +17.5 (*c* 0.5, $CHCl_3$). MS (CI): *m*/*z* 147 (M^+, 25), 146 (45), 130 (100). HRMS *m*/*z* calcd for $C_{10}H_{13}N$: 147.1048, found: 147.1060.

4.3.2.1. *N*-Benzoyl derivative (1*R*,2*S*)-23. From (1*R*,2*S*)-**20** (16 mg, 0.1 mmol), the general procedure afforded (1*R*,2*S*)-**23** (21 mg, 82%, 95% de, 97% ee) as a light yellow solid. Mp 174–176 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (d, 3H, J=6.6 Hz), 2.35 (m, 1H), 2.60 (dd, 1H, J=15.6, 9.0 Hz), 3.12 (dd, 1H, J=15.6, 7.8 Hz), 5.34 (t, 1H, J=8.4 Hz), 6.28 (d, 1H, J=8.4 Hz), 7.16–7.77 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1, 38.5, 44.5, 61.3, 119.5, 123.0, 123.9, 124.7, 126.8, 126.9, 127.9, 128.6, 131.5, 134.5, 142.7, 143.3, 167.5. $[\alpha]_D^{20}$ +50.9 (*c* 0.6, $CHCl_3$). MS (EI): *m*/*z* 251 (M^+, 25), 130 (100), 122 (30), 105 (55). HRMS *m*/*z* calcd for $C_{17}H_{27}NO$: 251.1310, found: 251.1305. HPLC (Chiralpak AD, 2-propanol/hexane 4:96, flow 1.0 mL/min, T=30 °C): t_R=21.47 min.

4.3.3. (3*R*,4*R*)-3-Methyl-4-aminochromane [(3*R*,4*R*)-21]. From (3*S*,4*S*)-**9** (164 mg, 1 mmol) and following method **B**, flash chromatography (20:1 CH_2Cl_2/MeOH) afforded (3*R*,4*R*)-**21** (110 mg, 84%, 92% de, 95% ee)[27] as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03 (d, 3H, J=6.5 Hz), 1.79–1.87 (m, 1H), 3.57 (d, 1H, J=6.5 Hz), 3.86 (dd, 1H, J=11.0, 7.0 Hz), 4.21 (dd, 1H, J=11.0, 3.0 Hz), 6.78 (d, 1H, J=8.0 Hz), 6.89 (t, 1H, J=8.0 Hz), 7.13 (t, 1H, J=8.0 Hz), 7.35 (d, 1H, J=8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.9, 36.0, 52.3, 68.5, 116.6, 120.6, 126.0, 128.3, 129.0, 154.1. $[\alpha]_D^{20}$ −3.0 (*c* 0.6, $CHCl_3$). MS (CI): *m*/*z* 162 (M^+−1, 5), 147 (56). HRMS calcd for $C_{10}H_{14}NO$: 164.1075, found: 164.1077. HPLC (Chiralpak AD, 2-propanol/hexane 4:96, flow 1.0 mL/min, T=30 °C): t_R=21.47 min.

4.3.3.1. *N*-Benzoyl derivative (3*R*,4*R*)-24. From (3*R*,4*R*)-**21** (29 mg, 0.18 mmol), the general procedure afforded (3*R*,4*R*)-**24** (40 mg, 83%, 92% de, 95% ee) as a white solid. Mp 224–226 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (d, 3H, J=7.2 Hz), 2.16–2.26 (m, 1H), 3.98 (dd, 1H, J=11.2, 7.2 Hz), 4.19 (dd, 1H, J=11.2, 3.2 Hz), 5.06 (t, 1H, J=7.2 Hz), 6.26 (d, 1H, J=8.0 Hz), 6.84 (d, 1H, J=8.0 Hz), 6.90 (t, 1H, J=7.2 Hz), 7.18 (t, 1H, J=8.0 Hz), 7.22 (t, 1H, J=7.2 Hz), 7.43 (t, 2H, J=7.6 Hz), 7.51 (t, 1H, J=7.6 Hz), 7.78 (d, 2H, J=7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 33.8, 50.5, 69.0, 116.9, 121.1, 121.7, 127.0, 128.7, 129.2, 129.5, 131.8, 134.2, 154.8, 167.2. $[\alpha]_D^{20}$ −3.0 (*c* 0.6, $CHCl_3$). MS (CI): *m*/*z* 267 (M^+, 13), 147 (100), 122 (45). HRMS *m*/*z* calcd for $C_{17}H_{18}NO_2$: 268.1338, found: 268.1328. HPLC (Chiralpak AD, 2-propanol/hexane 4:96, flow 1.0 mL/min, T=30 °C): t_R=21.47 min.

4.3.4. (1*R*,2*R*)-2-Fluoro-1-aminoindane [(1*R*,2*R*)-27]. From (1*S*,2*R*)-2-fluoroindan-1-ol [(1*S*,2*R*)-**25**][20] (152 mg, 1 mmol) and following method **B**, flash chromatography (40:1 → 20:1 CH_2Cl_2/MeOH) afforded (1*R*,2*R*)-**27** (106 mg, 70%, >98% de, 95% ee)[27] as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.65 (br s, 2H), 3.04 (m, 1H), 3.32 (m, 1H), 4.43 (dd, 1H, $J_{H,F}$=18.5 Hz, J=5.5 Hz), 4.95 (ddd, 1H, $J_{H,F}$=53.5 Hz, J=11.5, 5.5 Hz), 7.20 (d, 1H, J=5.5 Hz), 7.23–7.27 (m, 2H), 7.33 (d, 1H, J=5.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.6 (d, $J_{C,F}$=22 Hz), 62.0 (d, $J_{C,F}$=23 Hz), 101.7 (d, $J_{C,F}$=184 Hz), 124.0, 125.0, 127.5, 128.3, 138.1, 142.7. ^{19}F NMR (377 MHz,

$CDCl_3$): δ −107.5. $[\alpha]_D^{20}$ +3.5 (*c* 0.9, $CHCl_3$). MS (CI): *m/z* 152 (M^++1, 21), 151 (M^+, 35), 132 (100). HRMS *m/z* calcd for C_9H_9NF: 150.0719, found: 150.0718.

4.3.4.1. *N*-Benzoyl derivative (1*R*,2*R*)-29. From (1*R*,2*R*)-**27** (15 mg, 0.10 mmol), the general procedure afforded (1*R*,2*R*)-**29** (19 mg, 86%, >98% de, 95% ee) as a light yellow solid. Mp 157–159 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.17 (m, 1H), 3.40 (m, 1H), 5.30 (ddt, 1H, $J_{H,F}$=51.5 Hz, *J*=6.0, 3.5 Hz), 5.67 (ddd, 1H, $J_{H,F}$=18.0 Hz, *J*=7.5, 3.5 Hz), 6.27 (br s, 1H), 7.27 (d, 2H, *J*=7.0 Hz), 7.30 (d, 1H, *J*=6.5 Hz), 7.34 (d, 1H, *J*=7.5 Hz), 7.41 (t, 2H, *J*=7.5 Hz), 7.49 (t, 1H, *J*=7.5 Hz), 7.76 (d, 2H, *J*=7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 37.4 (d, $J_{C,F}$=23 Hz), 60.6 (d, $J_{C,F}$=28 Hz), 98.2 (d, $J_{C,F}$=186 Hz), 124.9, 125.3, 127.1, 127.8, 128.6, 129.1, 131.8, 133.9, 139.3, 139.8, 167.5. ^{19}F NMR (377 MHz, $CDCl_3$): δ −103.4. $[\alpha]_D^{20}$ +37.5 (*c* 0.5, $CHCl_3$). MS (EI): *m/z* 257 (M^++2, 11), 256 (M^++1, 64), 235 (75), 105 (100). HRMS *m/z* calcd for $C_{16}H_{15}NOF$: 256.1138, found: 256.1133. HPLC (Chiralpak AD, 2-propanol/hexane 10:90, flow 1.0 mL/min, *T*=30 °C): t_R= 15.22 min (minor) and 18.42 min (major).

4.3.5. (1*R*,2*R*)-2-Fluoro-1-aminotetraline [(1*R*,2*R*)-28]. From (1*S*,2*R*)-2-fluorotetral-1-ol [(1*S*,2*R*)-**26**][20] (166 mg, 1 mmol) and following method **B**, flash chromatography (40:1→20:1 CH_2Cl_2/MeOH) afforded (1*R*,2*R*)-**28** (122 mg, 74%, >98% de, 97% ee)[27] as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.89 (br s, 2H), 2.04 (m, 1H), 2.23 (m, 1H), 2.87 (m, 1H), 2.95 (m, 1H), 4.04 (dd, 1H, $J_{H,F}$=14.0 Hz, *J*=6.0 Hz), 4.57 (dm, 1H, $J_{H,F}$=50.0 Hz), 7.08 (d, 1H, *J*=7.5 Hz), 7.17 (t, 1H, *J*=7.5 Hz), 7.22 (t, 1H, *J*=7.5 Hz), 7.54 (d, 1H, *J*=7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.4, 26.6 (d, $J_{C,F}$=29 Hz), 54.7 (d, $J_{C,F}$=22 Hz), 94.0 (d, $J_{C,F}$=172 Hz), 126.6, 127.2, 127.7, 128.3, 138.2. ^{19}F NMR (377 MHz, $CDCl_3$): δ −110.8. $[\alpha]_D^{20}$ +3.5 (*c* 0.9, $CHCl_3$). HRMS *m/z* calcd for $C_{10}H_{13}NF$: 166.1032, found: 166.1030.

4.3.5.1. *N*-Benzoyl derivative (1*R*,2*R*)-30. From (1*R*,2*R*)-**28** (14 mg, 0.08 mmol), the general procedure afforded (1*R*,2*R*)-**30** (18 mg, 84%, >98% de, 97% ee) as white solid. Mp 157–159 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.13 (m, 1H), 2.21 (m, 1H), 2.85 (dt, 1H, *J*=17.0, 6.0 Hz), 3.03 (dt, 1H, *J*=17.0, 8.0 Hz), 5.00 (ddd, 1H, $J_{H,F}$=53.5 Hz, *J*=7.0, 2.5 Hz), 5.45 (m, 1H), 6.28 (d, 1H, *J*=7.0 Hz), 7.14 (d, 1H, *J*=7.0 Hz), 7.21 (m, 2H), 7.30 (d, 1H, *J*=7.0 Hz), 7.41 (t, 2H, *J*=7.5 Hz), 7.49 (t, 1H, *J*=7.5 Hz), 7.76 (d, 2H, *J*=7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9 (d, $J_{C,F}$=8 Hz), 25.6 (d, $J_{C,F}$=20 Hz), 51.8 (d, $J_{C,F}$=27 Hz), 89.5 (d, $J_{C,F}$=176 Hz), 126.8, 126.9, 127.8, 128.5, 128.6, 129.1, 131.7, 133.4, 133.9, 136.0, 167.0. ^{19}F NMR (377 MHz, $CDCl_3$): δ −108.5. $[\alpha]_D^{20}$ +37.5 (*c* 0.5, $CHCl_3$). MS (CI): *m/z* 270 (M^++1, 82), 250 (100), 249 (61), 105 (81). HRMS *m/z* calcd for $C_{17}H_{17}NOF$: 270.1294, found: 270.1294. HPLC (Chiralpak AD, 2-propanol/hexane 10:90, flow 1.0 mL/min, *T*=30 °C): t_R=15.29 min (minor) and 21.61 min (major).

Acknowledgements

We thank the Spanish 'Ministerio de Ciencia y Tecnología' (grants CTQ2004-00290 and CTQ2004-00241) and the Junta de Andalucía (grant 2005/FQM-658) for financial support. Bayer CropScience is gratefully acknowledged for predoctoral fellowships to A.R. and A.M. and for the donation of chemicals.

References and notes

1. (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069; (b) Brunel, J. M. *Recent Res. Dev. Org. Chem.* **2003**, *7*, 155; (c) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195.
2. (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36; (b) Ratovelomanana-Vidal, V.; Genêt, J.-P. *Can. J. Chem.* **2000**, *78*, 846; (c) Huertas, F. F.; Minidis, A. B. E.; Bäckwall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321; (d) Pellisier, H. *Tetrahedron* **2003**, *59*, 8291.
3. Noyori, R.; Ikeda, T.; Ohkuma, M.; Widhalm, M.; Kitamura, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134.
4. (a) Genêt, J. P.; Mallart, S.; Jugé, S. French Patent, 8911159, 1989; (b) Genêt, J. P.; Pinel, C.; Mallart, S.; Jugé, S.; Thorimbert, S.; Laffite, J. A. *Tetrahedron: Asymmetry* **1991**, *2*, 555.
5. Reviews: (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97; (b) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045; (c) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201; (d) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226.
6. (a) Ohkuma, T.; Ooka, H.; Yamakawa, M.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 4872; (b) Matsumoto, T.; Murayama, T.; Mitsuhashi, T.; Miura, T. *Tetrahedron Lett.* **1999**, *40*, 5043; (c) Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510; (d) Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R. *Org. Lett.* **2004**, *6*, 2681; (e) Ohkuma, T.; Li, J.; Noyori, R. *Synlett* **2004**, 1383.
7. Alcock, N. J.; Mann, I.; Peach, P.; Wills, M. *Tetrahedron: Asymmetry* **2002**, *13*, 2485.
8. Vaccaro, W.; Amore, C.; Berger, J.; Burrier, R.; Clader, J.; Davis, H.; Domalski, M.; Fevig, T.; Salisbury, B.; Sher, R. *J. Med. Chem.* **1996**, *39*, 1704.
9. Shepherd, T. A.; Aikins, J. A.; Bleakman, D.; Cantrell, B. E.; Rearick, J. P.; Simon, R. L.; Smith, E. C. R.; Stephenson, G. A.; Zimmerman, D. M.; Mandelzys, A.; Jarvie, K. R.; Ho, K.; Deverill, M.; Kamboj, R. K. *J. Med. Chem.* **2002**, *45*, 2101.
10. (a) Sterling, J.; Herzig, Y.; Goren, T.; Finkelstein, N.; Lerner, D.; Goldenberg, W.; Miskolczi, I.; Molnar, S.; Rantal, F.; Tamas, T.; Toth, G.; Zagyva, A.; Zekany, A.; Lavian, G.; Gross, A.; Friedman, R.; Razin, M.; Huang, W.; Krais, B.; Chorev, M.; Youdim, M. B.; Weinstock, M. *J. Med. Chem.* **2002**, *45*, 5260; (b) Glezer, S.; Finberg, J. P. M. *Eur. J. Pharmacol.* **2003**, *472*, 173; (c) Am, O. B.; Amit, T.; Youdim, M. B. H. *Neurosci. Lett.* **2004**, *355*, 169; (d) Bonneh-Barkay, D.; Ziv, N.; Finberg, J. P. M. *Neuropharmacology* **2005**, *48*, 406; (e) Abu-Raya, S.; Blaugrund, E.; Trembovler, V.; Lazarovici, P. *Drug Dev. Res.* **2000**, *50*, 285.
11. (a) Hartmann, S.; Ullrich, S.; Hupfer, C.; Frahm, A. W. *Eur. J. Med. Chem.* **2000**, *35*, 377; (b) Grisar, J. M.; Claxton, G. P.; Carr, A. A.; Wiech, N. L. *J. Med. Chem.* **1973**, *16*, 679.
12. Ros, A.; Magriz, A.; Dietrich, H.; Ford, M.; Fernández, R.; Lassaletta, J. M. *Adv. Synth. Catal.* **2005**, *347*, 591.
13. Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *23*, 1977.

14. Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886.
15. (a) Ohkuma, T.; Noyori, R. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, Chapter 6.1; Reviews, see: Ref. 5a,b and (b) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045.
16. Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521.
17. The absolute configuration of (1*S*,2*S*)-**7** was assigned by comparison of its optical rotation with literature data [(1*S*,2*S*)-**7** had $[\alpha]_D^{20}$ +40.5 (*c* 0.5, $CHCl_3$) [lit. (1*R*,2*R*)-**7** (>98% ee): $[\alpha]_D^{25}$ −38.0 (*c* 0.3, $CHCl_3$)]: Bowers, N. I.; Boyd, D. R.; Sharma, N. D.; Goodrich, P. A.; Groocock, M. R.; Blacker, A. J.; Goode, P.; Dalton, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1453. The absolute configuration of (1*S*,2*S*)-**6** was assigned by analogy.
18. For a very recent study of the effect of pH in asymmetric transfer hydrogenation of ketones in aqueous media, see: Wu, X.; Li, X.; King, F.; Xiao, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3407.
19. The absolute configuration of (1*S*,2*S*)-**8** was assigned by comparison of its optical rotation with literature data [(1*S*,2*S*)-**8** had $[\alpha]_D^{20}$ −43.7 (*c* 0.5, C_6H_6); lit.[6d] (1*R*,2*R*)-**8** (97% de, 87% ee): $[\alpha]_D^{20}$ +65.5 (*c* 2.1, C_6H_6)].
20. Ros, A.; Magriz, A.; Dietrich, H.; Fernández, R.; Álvarez, E.; Lassaletta, J. M. *Org. Lett.* **2006**, *8*, 127.
21. The absolute configuration of (1*S*,2*R*)-**12** was assigned by comparison of its optical rotation with literature data [(1*S*,2*R*)-**12** had $[\alpha]_D^{20}$ −46.5 (*c* 0.8, $CHCl_3$); lit. $[\alpha]_D^{25}$ −48.0 ($CHCl_3$): Boyd, D. R.; Sharma, N. D.; Bowers, N. I.; Goodrich, P. A.; Groocock, M. R.; Blacker, A. J.; Clarke, D. A.; Howard, T.; Dalton, H. *Tetrahedron: Asymmetry* **1996**, *6*, 1559].
22. The absolute configuration of (1*R*,2*S*)-**14** was assigned by comparison of its optical rotation with literature data [(1*R*,2*S*)-**14** had $[\alpha]_D^{20}$ −23.8 (*c* 0.96, $CHCl_3$); lit.[21] $[\alpha]_D^{25}$ −38.0 (*c* 0.9, $CHCl_3$, >98% ee)].
23. The absolute configuration of (1*R*,2*R*)-**17** was assigned by comparison of its optical rotation with literature data [(1*R*,2*R*)-**17** had $[\alpha]_D^{20}$ −106.1 (*c* 0.7, MeOH); lit. (1*S*,2*S*)-**17** (de >98%, ee 96%) $[\alpha]_D^{20}$ +106.0 (*c* 0.2, MeOH): Nishiyama, H.; Park, S.-B.; Itoh, K. *Tetrahedron: Asymmetry* **1992**, *3*, 1029].
24. (a) Nishio, M.; Hirota, M. *Tetrahedron* **1989**, *45*, 7201; (b) Peach, P.; Cross, D. J.; Kenny, J. A.; Mann, I.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron* **2006**, *62*, 1864.
25. Haack, K.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 285.
26. Sengupta, S.; Mondal, S. *Tetrahedron Lett.* **1999**, *40*, 3469.
27. De and ee determinations were performed for the corresponding benzamide derivatives.