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PAPER

Enzymatic enantiomeric resolution of phenylethylamines structurally related to amphetamine†

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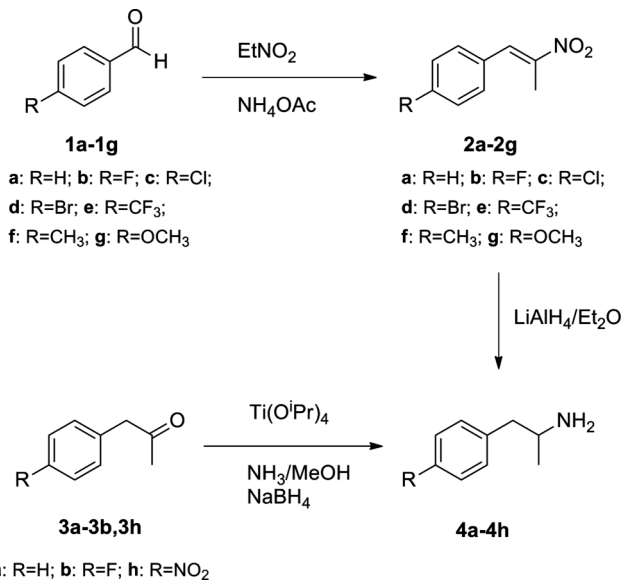
Both enantiomers of several phenylethylamines, structurally related to amphetamine, have been prepared in good yields and excellent enantiomeric purity by enzymatic kinetic resolution using CAL-B and ethyl methoxyacetate as the acyl donor. In the case of the 4-hydroxyderivative of amphetamine (compound **4i**), the *S* enantiomer racemized possibly in a dynamic kinetic resolution (DKR) under the enzymatic conditions used.

Introduction

Optically pure amines are frequently used in the pharmaceutical and agrochemical fields because of their broad range of applications.[1] They are used as resolving agents, chiral auxiliaries and chiral synthons for the synthesis of many bioactive compounds. The most established methods for the enantioselective preparation of chiral amines are asymmetric hydrogenation of acetamides and imines[2] and the asymmetric addition of carbanions to aldimines.[3] However, when the two separate enantiomers are required, the best strategy is the resolution of the racemates by distillation or fractional crystallization of the diastereomeric salts,[4] or chromatographic separation of diastereomeric amides.[5] In this context, enzymatic synthesis has emerged in recent decades as a powerful and recognized tool for the development of chemo-, regio-, and stereoselective processes.[6] Lipases have become one of the most common catalysts because of their easy availability, reasonable price, high stability, and versatility of action.[7]

It is well known that phenylethylamines are powerful stimulants of the central nervous system. They interfere with the peripheral nervous system and are able to induce the release of noradrenaline, acting therefore as potent vasoconstrictors.[8] In addition, they are intermediates for the synthesis of compounds of physiological interest, such as alkaloids and amino acids. In this paper we present a successful, enantioselective synthesis of both enantiomers of amphetamine and amphetamine-related amines by enzymatic kinetic resolution using CAL-B and ethyl methoxyacetate as the acyl donor in excellent *ee*. The availability of both enantiomers is particularly relevant because very often the pharmacological activity of these amines is related to the configuration of the stereogenic center. Thus, for instance, the (*S*)-(+)-enantiomer of amphetamine (**4a**, Scheme 1) displays *ca.* 5× greater psychostimulant activity than the (*R*)-(−)-form.[9]



Scheme 1 Approaches used for the synthesis of racemic amines **4a–4h**.

Results and discussion

Synthesis of phenylethylamines can be performed in a number of ways. One of the most usual strategies is based on the nitroaldolic condensation (Henry reaction) of a nitroalkane with an aromatic aldehyde[10] followed by LAH reduction of the corresponding nitroalkene. Alternatively, they can be obtained by reductive amination of the corresponding aldehydes or ketones through the intermediate formation of an imine, an iminium salt or an enamine.[11] The main advantage of the reductive amination *vs.* the Henry reaction is that the former can be performed in a

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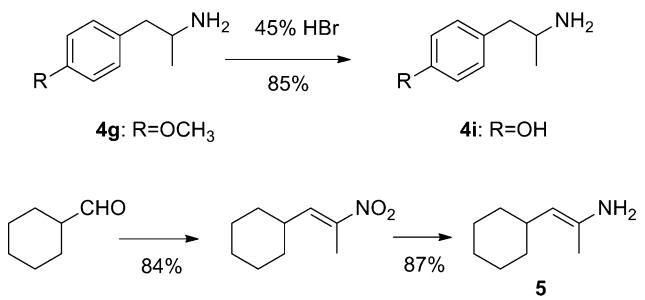
Table 1 Synthesis of racemic amines **4** and **5**[a]

Entry	Starting material	Nitrostyrene, yield (%)	Amine, yield (%)
1	**1a**	**2a**, 83	**4a**, 77
2	**3a**	—	**4a**, 75[b]
3	**1b**	**2b**, 74	**4b**, 77
4	**3b**	—	**4b**, 70[b]
5	**1c**	**2c**, 92	**4c**, 82
6	**1d**	**2d**, 71	**4d**, 80
7	**1e**	**2e**, 85	**4e**, 73
8	**1f**	**2f**, 79	**4f**, 71
9	**1g**	**2g**, 94	**4g**, 86
10	**3h**	—	**4h**, 89[b]
11	**4g**	—	**4i**, 85[c]
12	**Cyclohexanecarbaldehyde**	84	**5**, 87

[a] By reduction of nitroalkenes **2** unless noted otherwise. [b] By reductive amination. [c] By cleavage of the methoxy amine **4g**.

one-pot reaction. Following these two strategies, a series of different phenylethylamines **4a–4h** was prepared for subsequent enzymatic resolution (Scheme 1).

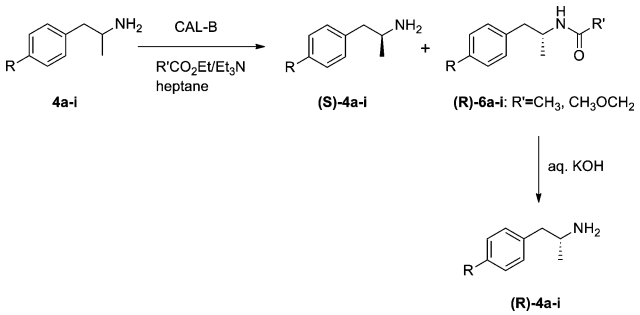
As shown in Table 1, amines **4** were obtained in good isolated yields, the reductive amination process affording clearly better overall yields when the starting ketone **3** was commercially available (compare entries 1–2 and 3–4). Preparation of 1-(4′-hydroxy)phenyl-2-propanamine (**4i**) was performed by cleavage of methoxy derivative **4g** in refluxing HBr (Scheme 2).[12] In this case, we had to overcome serious problems in the extraction process because **4i** was obtained as a salt at several pHs considered. Successful recovery of the product was achieved by adjusting the crude to pH 9, and the aqueous layer subjected to a continuous liquid–liquid extraction with AcOEt. Amine **4i** was thus obtained in 85% yield (entry 11). 1-Cyclohexyl-2-propanamide (**5**) was obtained from the corresponding cyclohexanecarbaldehyde in 73% overall yield (entry 12).



Scheme 2 Synthesis of amines **4i** and **5**.

When the racemic amines were available, two possibilities emerged for their enantiomeric resolution: the classical resolution by crystallization of the diastereomeric salts and the enzymatic resolution. We initially tested formation of the corresponding diastereomeric salts using (*L*)-(+)-tartaric acid as the resolving agent.[13] However, after several trials for the resolution of amine **4g**, only a 45% yield and 30% *ee* of the *R* enantiomer was obtained using a 1 : 2 amine : tartaric acid molar ratio. Consequently, the enzymatic resolution appeared to be an alternative and attractive choice.

A wide range of chiral amines has been successfully resolved using *Candida antarctica* lipase type B (CAL-B), a highly enantioselective and reliable biocatalyst for this purpose,[14] and, therefore, our first candidate for the enzymatic resolution of amines **4a–i** (Scheme 3). It is well known that selection of the appropriate acyl donor is crucial for the kinetic resolution of amines.[15] In this context, ethyl acetate is probably the most commonly used acylating agent because of its low cost, easy handling, and suitability as organic solvent for the biotransformation. Thus, Gonzalez-Sabin *et al.*[11b] successfully resolved *o*-, *m*-, and *p*-methoxyamphetamines using CAL-B and ethyl acetate in good yields and excellent enantioselectivities. However, in our case preliminary trials using ethyl acetate afforded only moderate enantioselectivities of amines **4g** and **4d** (entries 1, 5; Table 2). Therefore, we chose the more activated ethyl methoxyacetate as an acyl donor. The methoxy substituent increases the carbonyl activity so that the initial acylation rate also increases. In addition, it does not favor other non-enzymatic side reactions as other highly activated acyl donors do, such as trichloroacetic acid esters.[16] In all experiments triethylamine was used as non-nucleophilic base to enhance the reaction rate and the enantioselectivity of the process.[17]



Scheme 3 Enzymatic resolution of racemic amines **4a–i**.

To find the optimal experimental conditions for the resolution of the model amine **4g**, we considered the relative amount of enzyme *vs.* substrate, temperature of the biotransformation and the presence or not of solvent (heptane) (Table 2). The highest enantiomeric purity of the (*R*)-amide (99%) and the corresponding (*R*)-amine (93%) was achieved by using a mixture of ethyl methoxyacetate, heptane and triethylamine (0.1/10/0.02 ml mmol^{-1} substrate) at 35 °C (entry 2). When these conditions were applied at 50 °C, the less reactive (*S*)-amine was obtained in an excellent 97% *ee* but the *ee* of the desired (*R*)-amine dropped to 87% (entry 3). Therefore, since the *ee* of the (*S*)-amine could be improved by a sequential second resolution, we selected the conditions of entry 2 for the resolution of the remaining amines. As cited, the more reactive enantiomer had the *R* configuration, in agreement with a model originally developed to predict the preferentially acylated enantiomer of secondary alcohols.[18]

When these conditions (entry 2, Table 2) were applied to amine **4d**, the reaction rate was too high to stop the conversion at 50% in a reproducible manner (not shown). Therefore, the relative amount of the enzyme was reduced from 200 to 40 mg mmol^{-1} of substrate. Under these conditions, (*R*)-**4d** was obtained in 95% *ee* and an enantioselectivity ratio $E = 88$ (entry 7, Table 2). Removal of Et_3N or lowering the temperature to 25 °C resulted in similar yields but lower enantioselectivities of the more reactive amine (entries 8–9, Table 2). The *ee* of the (*R*)-amides **6d–6g** was determined by

Table 2 Optimization of conditions for the resolution of amines **4g** and **4d**

		Conditions					(*S*)-Amine (%)		(*R*)-Amide (%)		(*R*)-Amine (%)		
Entry	Amine	acyl donor/solvent/cat. ml mmol^{-1} substrate	mg enzyme/ mmol substrate	*T*/°C	Conversion (%)[a]	*t* (h)	Yield	*ee*[b]	Yield	*ee*[c]	Yield[d]	*ee*[b]	*E*[e]
1	**4g**	CH_3CO_2Et/Et_3N 3/0.02	50	35	—[f]	5	48	43	37	89[g]	72	85	19
2	**4g**	$CH_3OCH_2CO_2Et$/heptane/Et_3N 0.1/10/0.02	200	35	49	1.5	36	62	38	99	70	93	52
3	**4g**	$CH_3OCH_2CO_2Et$/heptane/Et_3N 0.1/10/0.02	200	50	51	25	40	97	49	90	70	87	59
4	**4g**	$CH_3OCH_2CO_2Et$/heptane/Et_3N 0.1/10/0.02	200	80	51	5	21	79	60	80	53	79	20
5	**4d**	CH_3CO_2Et/Et_3N 3/0.02	50	35	41	7	47	53	43	ND	38	71	10
6	**4d**	$CH_3OCH_2CO_2Et/Et_3N$ 3/0.02	40	35	47	0.8	51	76	51	ND	68	77	17
7	**4d**	$CH_3OCH_2CO_2Et$/heptane/Et_3N 0.1/10/0.02	40	35	48	2.7	50	75	45	95	73	95	88
8	**4d**	$CH_3OCH_2CO_2Et$/heptane 0.1/10	40	35	40	4	33	76	38	ND	66	81	21
9	**4d**	$CH_3OCH_2CO_2Et$/heptane/Et_3N 0.1/10/0.02	40	25	45	6.25	48	65	43	92	74	90	37

[a] Calculated by direct integration of the amide/amine peaks in GC. [b] Calculated by ^{19}F NMR after derivatization with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride.[19] [c] Determined by chiral HPLC on a CHIRALPACK IA column, except for amine **4g** in entry 1. [d] Yield of hydrolysis of the corresponding (*R*)-amide. [e] Enantiomeric ratio (*E*) values were determined from the *ee*'s of the residual and reacted amines.[26] [f] Controlled by TLC. [g] Calculated by comparison with the specific rotation found in literature.[27]

chiral HPLC by comparison of their chromatographic behavior with that of the racemic amides. However, since hydrolysis of these chiral amides to the corresponding (*R*)-amines occurred with equal or less than 6% racemization, it was considered unnecessary to analyze the chiral purity of the remaining amides by HPLC. Therefore, we hydrolysed all amides with base and determined the ee values of the resulting (*R*)-amines by conversion to their Mosher amides followed by ^{19}F NMR.[19]

When the optimized conditions (entry 7, Table 2) were applied for the resolution of the remaining amines, compounds **4a**, **4f** and **5** gave the corresponding (*R*)-amines in good yields and enantioselectivities (see below) but the amines with electron-withdrawing groups (**4e**: R = CF_3; **4b**: R = F; **4c**: R = Cl; **4h**: R = NO_2) remained unreactive. Therefore, new optimization studies were performed for these types of substrates taking amine **4e** as representative example (Table 3). Using ethyl methoxyacetate as a cosolvent (entry 1), the conversion rate of amine **4e** was enhanced to 43% in 4 h reaction but the *ee* of the *R* amine was only moderate (80%). Removal of heptane in the solvent mixture markedly improved the *ee* of (*R*)-**4e** to 93% and the enantioselectivity ratio to *E* = 64 (entry 2). Lower or higher temperatures did not substantially modify this result (entries 3–5; Table 3).

As cited above, compounds **4a**, **4f** and **5** were subjected to the conditions of entry 7, Table 2 to give the (*R*)-amines in excellent enantioselectivity (92–99% *ee*, *E* = 50–382) (entries 1, 7, 11; Table 4). Amines **4b**, **4c**, **4e** with moderate electron-withdrawing groups were successfully resolved using the conditions stated in entry 2, Table 3 in 90–93% *ee* (entries 3, 4, 6; Table 4), whereas amine **4h** with the strongest deactivating nitro group, was absolutely inert under these conditions (not shown). The moderate enantioselectivity towards the residual substrate (amines (*S*)-**4a**–**4g**, and (*S*)-**5**) could be the result of some racemization under the enzymatic conditions used. Particularly interesting was resolution of amine **4i** because the (*S*)-amine resulted completely racemic (entry 9, Table 4), inconsistent with the degree of conversion (50%) and the high enantioselectivity for the *R* enantiomer (96% *ee*). To confirm this unexpected result, a new resolution with an increased conversion (71%) was performed. This would result in an increase of the enantioselectivity towards the (*S*)-amine and a decrease of the (*R*)-amine *ee*. However, again, the *S* enantiomer was obtained in practically racemic form and the *R* was of high enantiomeric purity (95% *ee*) (entry 10, Table 4). At first sight, this process could be explained in terms of a dynamic kinetic resolution (DKR), which allows a theoretical 100% yield of the more reactive enantiomer by racemization of the slow-reacting enantiomer.[20] However, the classical DKR implies an *in situ* racemization of the substrate prior to the enzymatic reaction, but racemization of unfunctionalized amines is difficult and requires harsh conditions. This is the reason why very few examples of DKR of amines have been described so far. DKR of racemic phenylethylamine has been reported to occur by CAL-B after 8 days reaction in the presence of Pd/C,[21] and other primary amines by the same enzyme in the presence of a ruthenium catalyst in toluene at 90 °C[22] or a palladium nanocatalyst at 100 °C.[23] Very recently, a radical racemization with trifluoroethanethiol followed by an enzymatic resolution mediated by alkaline protease has been reported.[24] Remarkably, in our case *racemization occurs without need of any metal catalyst* and under very mild conditions.

Table 3 Optimization of conditions for the resolution of (trifluoromethyl)amine **4e**

	Conditions					(*S*)-Amine (%)		(*R*)-Amide (%)		(*R*)-Amine (%)		
Entry	acyl donor/solvent/cat. ml mmol^{-1} substrate	mg enzyme/ mmol substrate	*T*/°C	Conversion (%)[a]	*t* (h)	Yield	*ee*[b]	Yield	*ee*[c]	Yield[d]	*ee*[b]	*E*[e]
1	$CH_3OCH_2CO_2Et$/heptane/Et_3N 4/6/0.02	40	35	43	4	42	30	40	84	60	80	12
2	$CH_3OCH_2CO_2Et$/Et_3N 4/0.02	40	35	45	1.5	51	77	41	ND	72	93	64
3	$CH_3OCH_2CO_2Et$/Et_3N 4/0.02	40	15	38	36	45	20	35	ND	68	80	11
4	$CH_3OCH_2CO_2Et$/Et_3N 4/0.02	40	25	43	1.5	53	75	38	ND	66	93	62
5	$CH_3OCH_2CO_2Et$/Et_3N 4/0.02	40	50	41	0.5	52	41	38	ND	68	86	20

[a] Calculated by direct integration of the amide/amine peaks in GC. [b] Calculated by ^{19}F NMR after derivatization with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride.[19] [c] Determined by chiral HPLC on a CHIRALPACK IA column. [d] Yield of hydrolysis of the corresponding (*R*)-amide. [e] Enantiomeric ratio (*E*) values were determined from the *ee*'s of the residual and reacted amines.[26]

Table 4 Summary for the kinetic resolutions of amines **4a–g**, **4i** and **5**

					(*S*)-Amine (%)		(*R*)-Amide (%)		(*R*)-Amine (%)		
Entry	Amine	Conditions	Conversion (%)[a]	*t* (h)	Yield	*ee*[b]	Yield	*ee*[c]	Yield[d]	*ee*[b]	*E*[e]
1	**4a**	entry 7; Table 2	42	2.6	40	70	49	ND	59	92	50
2	**4a**[f]	entry 7; Table 2	45	2.6	41	73	47	ND	68	91	46
3	**4b**	entry 2; Table 3	40	5.5	55	48	35	ND	72	90	31
4	**4c**	entry 2; Table 3	40	5.5	50	45	38	ND	79	92	37
5	**4d**	entry 7; Table 2	48	2.7	50	75	45	94	73	95	88
6	**4e**	entry 2; Table 3	45	1.5	51	77	41	ND	72	93	64
7	**4f**	entry 7; Table 2	48	2.5	50	71	42	97	65	96	104
8	**4g**	entry 2; Table 2	49	1.5	36	62	38	99	70	93	52
9	**4i**	entry 2; Table 3	50	24	36	0	47	ND	53	96	49
10	**4i**	entry 2; Table 3	71	96	20	5	67	ND	50	95	41
11	**5**	entry 7; Table 2	42	2	45	63	38	ND	75	99	382

[a] Calculated by direct integration of the amide/amine peaks in GC. [b] Calculated by ^{19}F NMR after derivatization with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride.[19] [c] Determined by chiral HPLC on a CHIRALPACK IA column. [d] Yield of hydrolysis of the corresponding (*R*)-amide. [e] Enantiomeric ratio (*E*) values were determined from the *ee*'s of the residual and reacted amines.[26] [f] Kinetic resolution of amine **4a** at a 10 g scale.

Further experiments were conducted to establish how the racemization of (*S*)-**4i** was taking place. Thus, two enantioenriched samples of (*R*)-**4i** (*S*)-**4i** with different enantiomeric ratios (*R* : *S* = 96 : 4 and 26 : 74, respectively) were prepared, the former by enzymatic resolution and the latter by diastereomeric salt formation and crystallization.[25] These substrates were subjected to different resolution experiments in which either the acyl donor, catalyst or the enzyme were suppressed. In no case was there conversion of the amine into the corresponding amide and, thus, the ee of the unreacted amines remained unaltered in all reactions. Therefore, all reagents were necessary for the resolution and none of them responsible for the racemization of amine (*S*)-**4i**. Additional studies are necessary to shed some light on the mechanism of this particular racemization, which could be related to the ionization state of this amphiprotic substrate affecting its solubility in the reaction medium.

To test the possible scalability of the enzymatic resolution, amine **4a** (10 g, 74 mmol) was subjected to the conditions of entry 7, Table 2. The results (entry 2, Table 4) in terms of the *ee*'s of both chiral amines and the enantioselectivity (*E*) of the process were similar to previously obtained in small scale, proving that the enzymatic procedure can be scaled up without loss of yield and enantioselectivity.

To obtain the (*S*)-amines in almost enantiomerically pure state, a second sequential kinetic resolution of the (*S*)-enantioenriched amines **4a–f** and **5** was undertaken. The process occurred as expected under the conditions specified in Table 5 in moderate to good yields and excellent enantioselectivities (90–99% ee).

Conclusions

Several primary amines, structurally related to amphetamine analogues, have been synthesized and subjected, some of them for the first time, to enzymatic kinetic resolution using CAL-B and ethyl methoxyacetate as the acyl donor. Although successful resolution has not been attained under identical conditions for all amines, both enantiomers have been obtained in good yields and excellent *ee*. Particularly interesting is the case of amine **4i** (R = OH), whose *S* enantiomer racemizes possibly in a DKR

Table 5 Sequential kinetic resolution of (*S*)-enantioenriched amines **4a–f** and **5**

Entry	Amine	Initial *S* : *R* ratio	Conditions	Conversion (%)[a]		(*S*)-Amine (%) Yield	(*S*)-Amine (%) *ee*[b]
1	**4a**	85 : 15	entry 6; Table 2	15	1.3	63	96
2	**4b**	74 : 26	entry 2; Table 3	36	5	62	92
3	**4c**	60 : 40	entry 2; Table 3	48	4	49	92
4	**4d**	75 : 25	entry 6; Table 2	24	1	52	98
5	**4e**	69 : 31	entry 2; Table 3	32	1.5	59	90
6	**4f**	85 : 15	entry 6; Table 2	22	1.7	70	96
7	**5**	82 : 18	entry 6; Table 2	17	1	78	99

[a] Calculated by direct integration of the amide/amine peaks in GC. [b] Calculated by ^{19}F NMR after derivatization with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride.[19]

process under the enzymatic conditions in absence of a metal catalyst.

Experimental

General

All solvents were dried and distilled according to standard procedures. IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. Kinetic resolutions were monitored by GC on a HP-5 (25 m × 0.20 mm × 0.33 μm) fused silica capillary column. NMR spectra were recorded at 300, 400, or 500 MHz for ^{1}H, 75 or 100 MHz for ^{13}C, and 282 MHz for ^{19}F on a Varian Unity 300, Varian Mercury 400, or Varian Inova 500 spectrometer. Mass spectra (MS) were obtained on a Fisons MD 800 spectrometer. HRMS were run on a UPLC Acquity (Waters, USA) coupled to a mass spectrometer LCT Premier XE (Waters, USA).

Optical rotations were measured on a Perkin Elmer 341 polarimeter. The enantiomeric excess of chiral amines was determined by ^{19}F NMR after derivatization with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (2 equiv.), DMAP and triethylamine.[19] The enantiomeric purity of chiral amides was determined by chiral HPLC using a CHIRALPACK IA column (25 × 0.46 cm) at 0.5 ml min^{-1} of isopropanol : hexane 10 : 90 (isocratic conditions).

Nitrostyrenes **2a**,[28] **2b**,[29] **2c**,[30] **2d**,[31] **2e**,[32] **2f**,[33] **2g**,[33] and the precursor[34] of amine **5** were prepared from the corresponding aldehydes with nitroethane under reflux in 71–94% isolated yields after recrystallization in EtOH/hexane.

Preparation of amines 4a–g and 5 by reduction of the corresponding nitrostyrenes. A solution of the precursor nitro compound (2.61 mmol) in 20 ml of anh. Et_2O was slowly added with continuous stirring to a solution of $LiAlH_4$ (0.40 g, 10.45 mmol) in 20 ml of anh. Et_2O under Ar. After the addition, the solution was refluxed for 3 h. The reaction was allowed to cool to 0 °C and quenched by slow addition of 0.4 ml of H_2O, 0.4 ml of 15% NaOH aq. soln. and 1.2 ml of H_2O. The lithium and aluminum salts were filtered off and washed with Et_2O. The crude amine was distilled under reduced pressure in a Kugelrohr apparatus.

1-Phenyl-2-propanamine (**4a**),[35] 77% yield.
1-(4′-Fluoro)phenyl-2-propanamine (**4b**),[11a] 77% yield.
1-(4′-Chloro)phenyl-2-propanamine (**4c**),[36] 82% yield.
1-(4′-Bromo)phenyl-2-propanamine (**4d**),[31] 80% yield.
1-(4′-Trifluoromethyl)phenyl-2-propanamine (**4e**),[37] 73% yield.
1-(4′-Methyl)phenyl-2-propanamine (**4f**),[38] 71% yield.
1-(4′-Methoxy)phenyl-2-propanamine (**4g**),[11b] 86% yield.
1-Cyclohexyl-2-propanamine (**5**),[39] 87% yield.

Preparation of 1-(4′-hydroxy)phenyl-2-propanamine (4i) by cleavage of 4g. A mixture of amine **4g** (2.5 g, 15.15 mmol) in 21 ml of 45% HBr was heated at reflux for 3 h. The neutral materials were separated by extraction with AcOEt, the pH was adjusted to 9 by adding solid KOH and the aqueous solution was subjected to continuous liquid–liquid extraction with AcOEt for 24 h. The organic layer was dried with anh. $MgSO_4$ and concentrated to yield amine **4i**[40] as a yellow waxy solid (1.9 g, 85%).

Preparation of amines 4a–b and 4h by reductive amination of ketones 3a–b and 3h. A mixture of the corresponding ketone **3a–b** and **3h** (10 mmol), titanium(IV) isopropoxide (6.0 ml, 20 mmol) and a 7 N NH_3 soln. in methanol (25 ml, 50 mmol) was stirred under Ar at room temperature for 6 h. Solid sodium borohydride (0.56 g, 15 mmol) was then added and the resulting mixture was stirred at room temperature for an additional 3 h. The reaction was then quenched by pouring into 25% NH_4OH soln. (25 ml), the resulting inorganic precipitate was filtered off and washed with AcOEt. The combined aqueous and organic layers were acidified with 1 M HCl and extracted with AcOEt to separate the neutral materials. The aqueous extract was treated with solid KOH to pH 10 and repeatedly extracted with AcOEt. The combined extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under vacuum to afford the corresponding amine.

1-Phenyl-2-propanamine (**4a**),[35] 75% yield. The spectroscopic data were identical to those of the compound obtained by reduction of nitrostyrene **2a**.
1-(4′-Fluoro)phenyl-2-propanamine (**4b**),[11a] 70% yield. The spectroscopic data were identical to those of the compound obtained by reduction of nitrostyrene **2b**.
1-(4′-Nitro)phenyl-2-propanamine (**4h**),[41] 89% yield.

Enzymatic kinetic resolution of amines 4a–g, 4i and 5. General procedure

A solution of amine (1.00 mmol), *C. antarctica* lipase B (CAL-B, Novozym 435) (40–200 mg) and a mixture of anh. $CH_3OCH_2CO_2Et$/heptane/Et_3N in the required ratio was placed under N_2 in a thermostated bath at 35 °C and shaken at 80 U min^{-1}.

The reaction was monitored by GC and when the transformation was *ca.* 50% the mixture was filtered off, and the enzyme washed with ethyl acetate, CH_2Cl_2 and MeOH. The solvent was stripped off and the resulting crude dissolved in CH_2Cl_2, acidified with 6 N HCl and repeatedly extracted with CH_2Cl_2 to afford the (*R*)-amide. The aqueous layer was then adjusted to pH 10 with solid KOH and extracted with CH_2Cl_2, dried with anh. $MgSO_4$ and concentrated to yield the (*S*)-amine.

To obtain the (*R*)-amine, the (*R*)-amide (1.00 mmol) was subjected to hydrolysis with 3 M KOH (30 ml, 89 mmol) at reflux overnight.[17] The reaction mixture was acidified to pH 1 with 6 N HCl and extracted with CH_2Cl_2 to remove the neutral material. The aqueous layer was treated again with solid KOH to pH 10, extracted with CH_2Cl_2, dried over anh. $MgSO_4$ and concentrated under reduced pressure to yield the (*R*)-amine. The spectroscopic data were identical to those described for the racemic amines.

The enantioenriched (*S*)-amines resulting from the enzymatic resolution were subjected to a second kinetic resolution under the conditions stated in Table 5 to yield the expected amines in 52–78% isolated yields and 90–99% *ee*. The spectroscopic data were identical to those described for the racemic amines.

The resolution procedure was scaled up to 10 g (74 mmol) of amine **4a** with similar conversion (45%) and ee of the resulting chiral amines ((*S*)-**4a**, 41% yield, 73% ee; (*R*)-**4a**, 68% yield after hydrolysis of the amide, 91% ee).

(*R*)-(−)-*1-Phenyl-2-propanamine* [(*R*)-**4a**],[42] 29% overall yield, 92% ee, $[\alpha]_D^{20}$ −26.8 (*c* 1.1, $CHCl_3$).

(*S*)-(+)-*1-Phenyl-2-propanamine* [(*S*)-**4a**],[43] 63% yield, 96% ee, $[\alpha]_D^{20}$ = +27.5 (c 1.2, $CHCl_3$).

(*R*)-(−)-*1-(4′-Fluoro)phenyl-2-propanamine* [(*R*)-**4b**],[44] 25% overall yield, 90% ee, $[\alpha]_D^{20}$ −23.2 (*c* 1.1, $CHCl_3$).

(*S*)-(+)-*1-(4′-Fluoro)phenyl-2-propanamine* [(*S*)-**4b**],[44] 62% yield, 92% ee, $[\alpha]_D^{20}$ = +25.2 (c 1.4, $CHCl_3$).

(*R*)-(−)-*1-(4′-Chloro)phenyl-2-propanamine* [(*R*)-**4c**],[45] 30% overall yield, 92% ee, $[\alpha]_D^{20}$ −26.1 (*c* 0.9, $CHCl_3$).

(*S*)-(+)-*1-(4′-Chloro)phenyl-2-propanamine* [(*S*)-**4c**],[45] 49% yield, 92% ee, $[\alpha]_D^{20}$ = +25.0 (c 1.1, $CHCl_3$).

(*R*)-(−)-*1-(4′-Bromo)phenyl-2-propanamine* [(*R*)-**4d**],[46] 33% overall yield, 95% ee, $[\alpha]_D^{20}$ −28.5 (*c* 1.2, $CHCl_3$).

(*S*)-(+)-*1-(4′-Bromo)phenyl-2-propanamine* [(*S*)-**4d**],[46] 52% yield, 98% ee, $[\alpha]_D^{20}$ = +27.0 (c 1.2, $CHCl_3$).

(*R*)-(−)-*1-(4′-Trifluoromethyl)phenyl-2-propanamine* [(*R*)-**4e**],[47] 30% overall yield, 93% ee, $[\alpha]_D^{20}$ −23.5 (*c* 1.2, $CHCl_3$).

(*S*)-(+)-*1-(4′-Trifluoromethyl)phenyl-2-propanamine* [(*S*)-**4e**] 59% yield, 90% ee, $[\alpha]_D^{20}$ = +22.2 (c 1.1, $CHCl_3$).

(*R*)-(−)-*1-(4′-Methyl)phenyl-2-propanamine* [(*R*)-**4f**], 27% overall yield, 96% ee, $[\alpha]_D^{20}$ −33.9 (*c* 1.1, $CHCl_3$).

(*S*)-(+)-*1-(4′-Methyl)phenyl-2-propanamine* [(*S*)-**4f**] 70% yield, 96% ee, $[\alpha]_D^{20}$ = +35.0 (c 1.6, $CHCl_3$).

(*R*)-(−)-*1-(4′-Methoxy)phenyl-2-propanamine* [(*R*)-**4g**],[48] 27% overall yield, 93% ee, $[\alpha]_D^{20}$ −27.8 (*c* 0.7, MeOH); lit.[27] = −29.5 (*c* 1.0, MeOH).

(*S*)-(+)-*1-(4′-Methoxy)phenyl-2-propanamine* [(*S*)-**4g**],[48] 40% yield, 97% ee, $[\alpha]_D^{20}$ = +29.1 (*c* 1.0, MeOH); lit.[27] = +29.5 (*c* 1.0, MeOH).

(*R*)-(−)-*1-(4′-Hydroxy)phenyl-2-propanamine* [(*R*)-**4i**], 33% overall yield, 95% ee, $[\alpha]_D^{20}$ −45.9 (*c* 0.5, EtOH); lit.[49] = −52.0 (*c* 0.8, EtOH).

(*R*)-(−)-*1-Cyclohexyl-2-propanamine* [(*R*)-**5**],[50] 29% overall yield, 99% ee, $[\alpha]_D^{20}$ −7.0 (*c* 1.2, $CHCl_3$).

(*S*)-(+)-*1-Cyclohexyl-2-propanamine* [(*S*)-**5**],[51] 78% yield, 99% ee, $[\alpha]_D^{20}$ = +7.1 (c 0.8, $CHCl_3$).

Synthesis of amides 6d–g

To a solution of amine **6d–g** (0.61 mmol) in dry THF (1.5 ml) was added Et_3N (0.61 mmol) under N_2. The resulting solution was cooled to 0 °C, and methoxyacetyl chloride (0.91 mmol) was carefully added.[52] The mixture was allowed to warm to room temperature and stirred overnight until no starting material was detected by TLC. The organic solvent was evaporated under reduced pressure and the reaction crude was purified by flash chromatography (hexane : AcOEt 1 : 1) to yield the corresponding amide.

N-[2-(4′-Bromophenyl)-1-methylethyl]-2-methoxyacetamide (**6d**), 82% yield. ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.41 (d, J = 8.4 Hz, 2H); 7.06 (d, J = 8.1 Hz, 2H); 6.34 (d, J = 7.2 Hz, 1H); 4.27 (m, 1H); 3.83 (d, J = 3.0 Hz, 2H); 3.36 (s, 3H); 2.83 (dd, J_1 = 13.5 Hz, J_2 = 6.0 Hz, 1H); 2.67 (dd, J_1 = 13.8 Hz, J_2 = 7.2 Hz, 1H); 1.14 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8 (C); 136.7 (C); 131.4 (2CH); 131.1 (2CH); 120.3 (C); 71.9 (CH_2); 59.0 (CH_3); 45.3 (CH); 41.8 (CH_2); 19.9 (CH_3) ppm. IR (film) ν: 3407, 3298, 2972, 2930, 2343, 1667, 1531, 1489, 1198, 1115, 1071, 1012, 798 cm^{-1}. MS (EI) m/z (%): 287 [(M + 2)$^+$, 1)]; 285 [(M)$^+$, 1]; 196 (25); 169 (24); 116 (100); 90 (34); 56 (63); 45 (78). HRMS Calcd for $C_{12}H_{17}NO_2Br$ (M$^+$): 286.0443; Found: 286.0447.

N-[2-(4′-Trifluoromethylphenyl)-1-methylethyl]-2-methoxyacetamide (**6e**), 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 8.1 Hz, 2H); 7.30 (d, J = 8.1 Hz, 2H); 6.37 (d, J = 7.5 Hz, 1H); 4.34 (m, 1H); 3.83 (d, J = 3.3 Hz, 2H); 3.36 (s, 3H); 2.94 (dd, J_1 = 13.5 Hz, J_2 = 6.3 Hz, 1H); 2.78 (dd, J_1 = 13.5 Hz, J_2 = 7.2 Hz, 1H); 1.13 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7 (C); 141.9 (C); 129.6 (2CH); 128.8 (q, J = 32.5 Hz, CCF_3); 125.3 (q, J = 3.7 Hz, 2CH); 124.2 (q, J = 270.4 Hz, CF_3); 72.0 (CH_2); 59.0 (CH_3); 45.3 (CH); 42.4 (CH_2); 19.9 (CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.86 (s) ppm. IR (film) ν: 3306, 2934, 2359, 1665, 1533, 1325, 1151, 1067, 1019, 817 cm^{-1}. MS (EI) m/z (%): 275 (M$^+$, 1); 186 (7); 159 (57); 116 (98); 56 (73); 45 (100). HRMS Calcd for $C_{13}H_{17}NO_2F_3$ (M$^+$): 276.1211; Found: 276.1216.

N-[2-(4′-Methylphenyl)-1-methylethyl]-2-methoxyacetamide (**6f**), 91% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (m, 4H); 6.40 (d, J = 6.9 Hz, 1H); 4.25 (m, 1H); 3.83 (d, J = 4.8 Hz, 2H); 3.35 (s, 3H); 2.77 (dd, J_1 = 13.5 Hz, J_2 = 6 Hz, 1H); 2.67 (dd, J_1 = 13.5 Hz, J_2 = 7.2 Hz, 1H); 2.32 (s, 3H); 1.14 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7 (C); 136.1 (C); 134.7 (C); 129.4 (2CH); 129.2 (2CH); 72.1 (CH_2); 59.2 (CH_3); 45.7 (CH); 42.2 (CH_2); 21.1 (CH_3); 20.1 (CH_3) ppm. IR (film) ν: 3412, 3305, 2925, 2362, 1671, 1528, 1452, 1197, 1115, 984, 804 cm^{-1}. MS (EI) m/z (%): 221 (M$^+$, 1); 132 (67); 116 (74); 105 (53); 45 (100). HRMS Calcd for $C_{13}H_{20}NO_2$ (M$^+$): 222.1494; Found: 222.1490.

N-[2-(4′-Methoxyphenyl)-1-methylethyl]-2-methoxyacetamide (**6g**), 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (d, J = 8.4 Hz, 2H); 6.82 (d, J = 8.7 Hz, 2H); 6.36 (d, J = 7.5 Hz, 1H); 4.25 (m, 1H); 3.83 (d, J = 4.8 Hz, 2H); 3.78 (s, 3H); 3.35 (s, 3H); 2.79 (dd, J_1 = 13.5 Hz, J_2 = 6.0 Hz, 1H); 2.66 (dd, J_1 = 13.8 Hz, J_2 = 7.2 Hz, 1H); 1.12 (d, J = 6.6 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7 (C); 158.2 (C); 130.3 (2CH); 129.9 (C); 113.7 (2CH); 71.9

(CH_2); 59.1 (CH_3); 55.2 (CH_3); 45.6 (CH); 41.7 (CH_2); 19.9 (CH_3) ppm. IR (film) ν: 3307, 2931, 1661, 1612, 1583, 1512, 1246, 1033 cm^{-1}. MS (EI) m/z (%): 237 (M^+, 1); 148 (69); 121 (45); 116 (32); 91 (13); 78 (18); 56 (59); 45 (100). HRMS Calcd for $C_{13}H_{20}NO_3$ (M^+): 238.1443; Found: 238.1435.

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