Enzymatic Resolution of *trans*-4-(4′-Fluorophenyl)-3-hydroxymethylpiperidines, Key Intermediates in the Synthesis of (−)-Paroxetine

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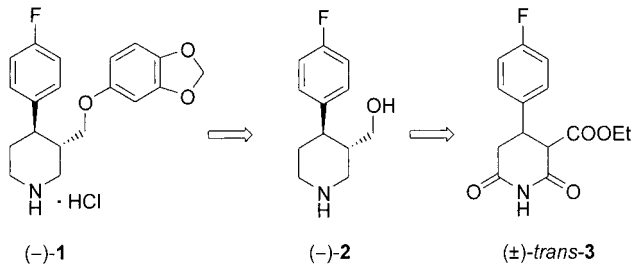
Two *Candida antarctica* lipases catalyze the enantioselective acylation of *N*-substituted *trans*-4-(4′-fluorophenyl)-3-hydroxymethylpiperidines in organic solvents. These two lipases show opposite stereochemical preference in these processes. Both enantiomers can be obtained in their optically pure forms. The (3*S*,4*R*) isomer, is an intermediate for the synthesis of (−)-Paroxetine.

Introduction

(−)-Paroxetine hydrochloride (**1**) is a selective serotonin (5-HT) reuptake inhibitor that is used as an antidepressant.[1] Several synthetic strategies have been developed for the preparation of this compound as a single enantiomer, including the selective recrystallization of diastereomeric salts,[2] chiral auxiliary assisted synthesis,[3] biocatalytic resolutions[4] or the asymmetrization of a prochiral diester intermediate.[5] The increasing interest of the pharmaceutical industry in the preparation of this compound requires the development of new synthetic methods adequate to be carried out at large scale; among them, the use of enzymes as catalysts is very suitable for this purpose.[6]

An inspection of a possible retrosynthetic pathway of (−)-Paroxetine (Scheme 1) reveals that there are two intermediates that can be resolved by an enzymatic process. The enantioselective hydrolysis of the *N*-methyl derivative of imidoester (±)-*trans*-**3**, catalyzed by enzymes[4] and microorganisms,[4c] has been described in previous reports. The resolution of this derivative has the drawback of the cumbersome removal of the methyl group at the nitrogen in a later step of the synthesis. This paper describes the application of lipases for the preparation of both enantiomers of *trans*-**2** and conveniently protected derivatives.[7]

Scheme 1. Retrosynthetic Pathway of (−)-Paroxetine



Results and Discussion

First, we studied the hydrolysis, transesterification, and aminolysis reactions of (±)-*trans*-**3** catalyzed by commercially available lipases, but all our attempts of resolution of this compound failed. Then, we focused our efforts in the resolution of different piperidincarbinol derivatives of (±)-*trans*-**2**. *N*-Protected derivatives (±)-*trans*-**4a**−**d** were used instead of **2** itself in order to prevent the possible competition of the nitrogen with the oxygen in the enzyme-catalyzed reactions. Carbamates were chosen as protective groups for the nitrogen because they are stable enough for our purposes and can be cleaved under mild conditions. We did not know a priori which carbamate would give the best results in the overall process. Therefore, four representative carbamate derivatives (±)-*trans*-**4a**−**d** of varying sizes were selected in order to investigate the scope of the enzymatic reactions. These substrates can be prepared from the ester (±)-*trans*-**3**,[8] according to Scheme 2. As the nitrogen should be protected in any case to complete the synthesis of Paroxetine, the introduction of the carbamate group at this stage does not increase the number of steps.

Our initial experiments were designed to find the most suitable lipase for catalyzing the hydrolysis of the acetyl derivative (±)-*trans*-**5a** (Scheme 3). None of the com-

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(8) For synthesis of (±)-**3** see ref 2b.

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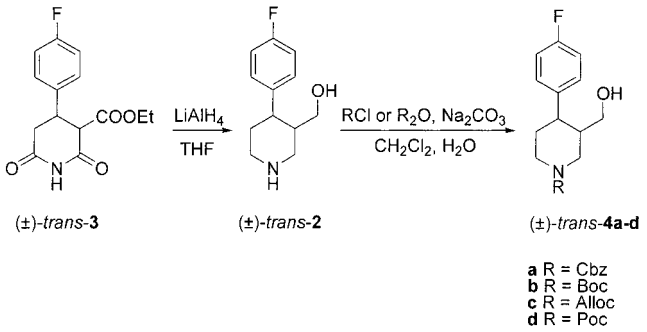
Scheme 2. Synthesis of *N*-Substituted (±)-*trans*-4a−d



mercial enzymes examined catalyzed the hydrolysis of this substrate in aqueous media (phosphate buffer, pH 7), probably because of the low solubility of the substrate under these conditions. The same results were obtained when an organic cosolvent was added.

Then, we examined the process in organic solvents with a small amount of water (10 equiv) as nucleophile (Scheme 3, Table 1). Three of the tested enzymes catalyzed the reaction. Lipase A from *Candida antarctica* (CAL-A) showed the highest enantioselectivity (E = 68 in hexane),[9] but at a low reaction rate. On the other hand, Lipase B from *Candida antarctica* (CAL-B) in isopropyl ether or *tert*-butyl methyl ether gave higher conversions but low enantioselectivity. It is interesting to note the opposite stereochemical preference of these two lipases. CAL-A catalyzed the cleavage of the substrate (3*S*,4*R*), while CAL-B preferred the (3*R*,4*S*) configuration.

The absolute configurations of the product and the remaining substrate were established as follows (Scheme 3). Reduction of (+)-*trans*-**4a** afforded the *N*-unsubstituted piperidine carbinol derivative (+)-*trans*-**2**, whose specific rotation sign was opposite to that reported for the (3*S*,4*R*) configuration, $[\alpha]^{20}_D$ −38.1 (*c* 0.5, EtOH 95).[10] The protection of (+)-*trans*-**2** thus obtained with Boc gave (+)-*trans*-**4b**, whose specific rotation sign was in agreement with that reported for (3*R*,4*S*)-(+)-**4b**, $[\alpha]^{20}_D$ +5.8 (*c* 1.75, MeOH).[3c]

Another common approach for the resolution of racemic alcohols is the enzymatic transesterification reaction. In a first set of experiments, vinyl acetate was chosen as acyl donor for the resolution of piperidincarbinol (±)-*trans*-**4a** in *tert*-butyl methyl ether with several lipases (Scheme 4, Table 2). The best results were obtained with CAL-A and CAL-B. As expected according to the principle of microscopic reversibility, their stereochemical preferences were the same as for the hydrolytic processes: (3*S*,4*R*) enantiomer was preferentially acylated by CAL-A and the (3*R*,4*S*) by CAL-B. Interestingly, CAL-A-catalyzed acylation of (±)-*trans*-**4a** was much faster and much more enantioselective than the corresponding hydrolysis of (±)-*trans*-**5a**, both in *tert*-butyl methyl ether. Thus, a great increase in efficiency has been attained by simply reversing the sense of the transformation in the same solvent. The same does not apply to the CAL-B-catalyzed acylation of (±)-*trans*-**4a,** whose enantioselectivity was similar to that of the hydrolysis of (±)-*trans*-**5a.** Lipases from *Pseudomonas cepacia* (PSL-C and PSL), *Candida rugosa* (CRL), and *Mucor miehei* (MML) also catalyzed the acetylation of the (3*R*,4*S*) enantiomer, but at low rates and enantioselectivities.

In view of these promising results, we decided to study the effect of the reaction parameters on the enantioselectivity of the acylation of alcohol (±)-*trans*-**4a**. First, we studied the influence of the organic solvent. Table 3 summarizes the results of the experiments at 30 °C. The reactions were carried out using 10 equiv of vinyl acetate, except when the vinyl acetate was used itself also as the reaction solvent. Under these conditions, it is apparent that toluene was the best solvent for CAL-A catalysis: after only 6 h, a 49% conversion was achieved, with high enantioselectivity (E = 102). When vinyl acetate or *i*-propyl ether were used as solvents, good reaction rates were also observed, but only with moderate enantioselectivity (E = 17−28). Very low reaction rates were obtained in the other tested solvents.

When the alcohol (±)-*trans*-**4a** was exposed to the CAL-B lipase, the reaction rate was very fast in all the tested solvents. The best enantiomeric ratios were achieved in toluene and vinyl acetate (E = 35 and 32, respectively). Although CAL-B is less enantioselective than CAL-A, the E value of 35 in toluene affords the remaining substrate (3*S*,4*R*)-**4a** in high enantiomeric excess and yield (94% ee at 55% conversion). Other lipases, as PSL-C, gave poorer results.

Taking into account that the temperature can have a marked effect on the enantioselectivity, we lowered it at 15 °C.[11] The enantioselectivity was significantly enhanced in reactions catalyzed by CAL-A or CAL-B in toluene, with only a small decrease of the reaction rate (Table 4). Thus, the enantiomeric ratio increased from E = 102 to 143 for CAL-A and from E = 35 to 76 for CAL-B. The enantioselectivity of CAL-B also increased in *tert*-butyl methyl ether, but did not change in vinyl acetate.

Finally, we examined the influence of the acyl donor in the biocatalytic process (Table 5). Isopropenyl acetate was also a suitable acyl donor for the transesterifications catalyzed by CAL-A and CAL-B, giving similar results to vinyl acetate. For instance, a value of E > 100 was obtained with CAL-A in toluene at 15 °C. More interesting results were obtained when vinyl benzoate was used instead of vinyl acetate. Surprisingly, CAL-A lost its enantioselectivity either in *tert*-butyl methyl ether or in toluene. In contrast, the enantioselectivity of CAL-B was enhanced with vinyl benzoate as acyl donor, both in toluene (E > 100) and in *tert*-butyl methyl ether (E = 35). A very high E value was also observed when vinyl benzoate was used as solvent; however, toluene is preferable as solvent due to the easier workup. Oxime acetate led to lower rates and enantioselectivities in our system, even though it is also an activated ester. The use of ethyl acetate as acyl donor resulted in lower reaction rates compared to vinyl acetate, as expected for its lower reactivity. Nevertheless, the reaction catalyzed by CAL-A showed high enatioselectivity (E = 81).

To establish the scope of this enantiomer separation method, the best biocatalytic conditions found for the

(9) The enantiomeric ratio E is generally accepted as an adequate parameter to quantify the enantioselectivity in biochemical kinetic resolutions. Reactions with high E values afford products in high ee and yield. See Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294−7299.

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Scheme 3. Lipase-Catalyzed Hydrolysis of (±)-*trans*-5a in Organic Solvents

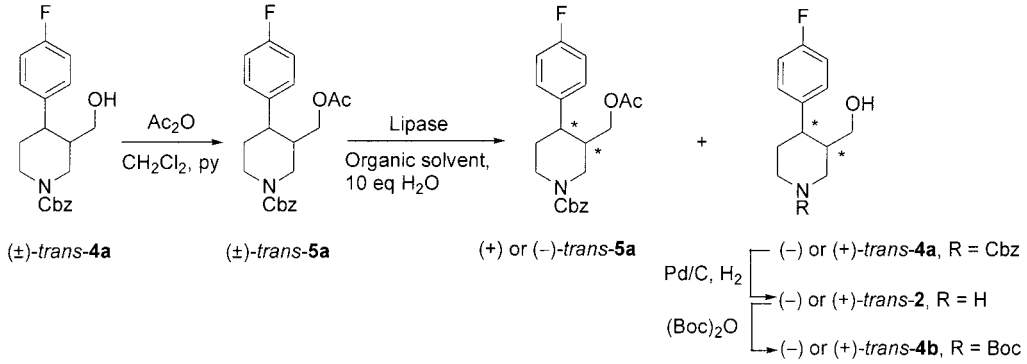

Table 1. Lipase-Catalyzed Hydrolysis of (±)-*trans*-5a in Organic Solvents[a]

				remaining ester *trans*-**5a**		product *trans*-**4a**		
lipase[b]	solvent	time (h)	*c* (%)[c]	conf.	ee$_s$ (%)[d]	conf.	ee$_p$ (%)	*E*[e]
CAL-A	*t*-BuOMe	240	2	(3*R*,4*S*)	2	(3*S*,4*R*)	83	10
CAL-A	hexane	240	4	(3*R*,4*S*)	4	(3*S*,4*R*)	97	68
CAL-B	*t*-BuOMe	72	29	(3*S*,4*R*)	25	(3*R*,4*S*)	66	6
CAL-B	CH_2Cl_2	168	1	(3*S*,4*R*)	1	(3*R*,4*S*)	85	12
CAL-B	toluene	113	2	(3*S*,4*R*)	2	(3*R*,4*S*)	85	12
CAL-B	1,4-dioxane	264	20	(3*S*,4*R*)	19	(3*R*,4*S*)	77	9
CAL-B	THF	168	9	(3*S*,4*R*)	5	(3*R*,4*S*)	50	3
CAL-B	*i*-Pr_2O	168	57	(3*S*,4*R*)	63	(3*R*,4*S*)	47	5
PPL	*t*-BuOMe	240	2	(3*S*,4*R*)	2	(3*R*,4*S*)	53	3

[a] 10 equiv of H_2O, 30 °C. [b] 125 mg. [c] Conversion, $c = ee_s/(ee_s + ee_p)$. [d] Determined by HPLC. [e] Enantiomeric ratio, $E = \ln[(1 - c)(1 + ee_p)]/\ln[(1 - c)(1 - ee_p)]$.[9]

esterification of (±)-*trans*-**4a** were applied to the resolution of other *N*-protected piperidincarbinol derivatives (±)-*trans*-**4b**−**d**. Table 6 summarizes the results of these experiments. In all cases, derivatives (±)-*trans*-**4b**−**d** were resolved by CAL-A-catalyzed acetylations in toluene at 15 °C with excellent reaction rates and enantioselectivities (E = 103−131). In the processes catalyzed by CAL-B, the best enantiomeric ratios were obtained in toluene at 30 °C and using vinyl benzoate as acyl donor (E = 114−142). It is worthy of note the higher reaction rate for the acylation of the allyloxycarbonyl derivative *trans*-**4c** in all the tested conditions, probably due to its smaller size relative to the other derivatives. The lesser steric demand of the Alloc group would allow the molecule to fit more easily in the binding site of the enzyme, thus giving a higher reaction rate. Finally, it is remarkable that, independently of the *N*-protecting group of the derivatives *trans*-**4a**−**d**, the two lipases CAL-A and CAL-B retain their opposite stereochemical preference.

In the CAL-B-catalyzed reaction, the remaining alcohol (3*S*,4*R*)-**4a**−**d** has the correct configuration to complete the synthesis of (−)-Paroxetine. On the other hand, CAL-A catalyzes the acylation of the enantiomer with the correct configuration, thus giving (3*S*,4*R*)-**5a**−**d**. Therefore, it has to be deacylated to (3*S*,4*R*)-**4a**−**d** before continuing the synthesis. This deacylation is easily done in high yield with sodium methoxide in methanol.

The different *N*-protective groups can be easily removed from compounds *trans*-**4a**−**d** to obtain in high yields the corresponding enantiomer of piperidincarbinol *trans*-**2**.

Conclusion

This paper describes the resolution of *N*-substituted *trans*-4-(4′-fluorophenyl)-3-hydroxymethylpiperidines (*trans*-**4a**−**d**) via a lipase-catalyzed acylation. Good yields and high enantioselectivities can be achieved by an appropriate selection of the reaction parameters. In general, the best conditions for CAL-A-catalyzed reactions were the use of vinyl acetate as acyl donor in toluene, at 15 °C. On the other hand, processes catalyzed by CAL-B achieved high enantioselectivities using vinyl benzoate as acyl donor, at 30 °C. It is remarkable the opposite stereochemical preference of the two *Candida antarctica* lipases in these processes. Taking into account the simplicity and easy scale-up of lipase-catalyzed reactions, it is noteworthy the applicability of this method to the industrial preparation of the antidepressant (−)-Paroxetine.[7]

Experimental Section[12]

General Methods. *Candida antarctica* lipase B (CAL-B, 7300 PLU/g) and *Mucor miehei* lipase (MML, LIPOZYME IM 20, 27.9 U/g) were a gift from Novo Nordisk Co. Lipases from *Pseudomonas cepacia* PSL (>10 kilounits/g), *Candida rugosa* (CRL, >250 units/mg), and *Candida antarctica* lipase A (CAL-A, 1 kilounits/g) were commercialized as CHIRAZYME L-1, L-3, and L-5, respectively, by Roche Molecular Biochemicals. *Ps. cepacia* lipase (PSL-C, 1019 units/g) was a product of Amano Co. All these commercial lipases were carrier-fixed products except CHIRAZYME L-3. All other chemicals or solvents were of the highest quality grade available.

Melting points were taken using a Gallenkamp apparatus and were uncorrected. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 1720-X FT Infrared spectrophotometer. ^{1}H and ^{13}C NMR were obtained with TMS (tetramethylsilane) as internal standard, using Bruker AC-200 (^{1}H, 200.13 MHz and ^{13}C, 50.3 MHz), AC-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz), or DPX-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) spectrometers. Mass spectra were recorded on a Hewlett-Packard 1100 Series spectrometer. Microanalyses were performed on a Perkin-Elmer 240B elemental analyzer. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). The ee's were determined by chiral HPLC analysis on a Shimadzu LC liquid chromatograph, using a CHIRALCEL OD column (4.5 × 250 mm). Two well resolved peaks were obtained for all the racemic compounds (1 mg in 4 mL mobile phase; 20 μL sample).

Preparation of (±)-*trans*-4-(4′-Fluorophenyl)-3-hydroxymethylpiperidine [(±)-*trans*-2]. To a suspension of

(12) Compounds **2**,[2b] **3**,[2b] **4a**,[10] and **4b**[3c,10] were previously reported.; ^{1}H and ^{13}C NMR data are given in the Supporting Information. For compounds **4c**, **4d** and **5a**−**h**, full spectral data and copies of ^{1}H and ^{13}C NMR are given in the Supporting Information. The level of purity is indicated by the inclusion of elemental analysis.

Scheme 4. Lipase-Catalyzed Acylation of (±)-*trans*-4 in Organic Solvents

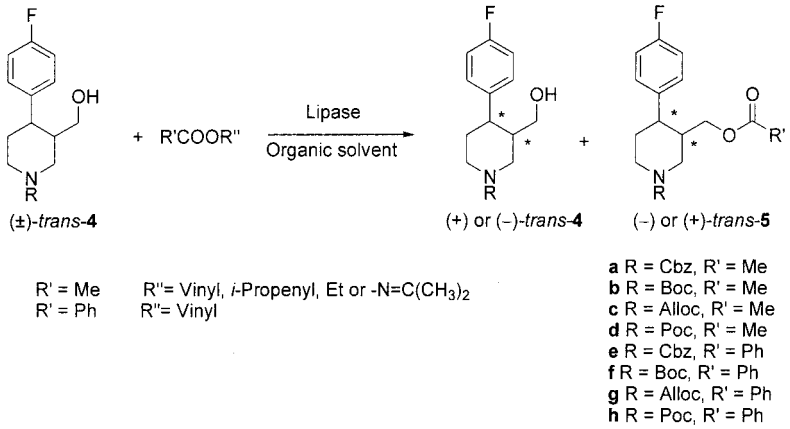

Table 2. Lipase-Catalyzed Acetylation of (±)-*trans*-4a with Vinyl Acetate in *t*-BuOMe[a]

			remaining alcohol *trans*-**4a**		product *trans*-**5a**		
lipase	time (h)	*c* (%)	conf.	ee_s (%)	conf.	ee_p (%)	*E*
CAL-A (125 mg)	2	54	(3*R*,4*S*)	97	(3*S*,4*R*)	81	39
CAL-B (125 mg)	2	57	(3*S*,4*R*)	85	(3*R*,4*S*)	65	12
PSL-C (110 mg)	50	39	(3*S*,4*R*)	45	(3*R*,4*S*)	70	9
PSL (160 mg)	184	16	(3*S*,4*R*)	10	(3*R*,4*S*)	53	4
MML (600 mg)	144	13	(3*S*,4*R*)	13	(3*R*,4*S*)	66	6
CRL (125 mg)	144	40	(3*S*,4*R*)	2	(3*R*,4*S*)	3	1.1

[a] 10 equiv of vinyl acetate, 30 °C.

Table 3. Effect of the Organic Solvent in the Lipase-Catalyzed Acetyzed of (±)-*trans*-4a[a]

				remaining alcohol *trans*-**4a**		product *trans*-**5a**		
lipase	solvent	time (h)	*c* (%)	conf.	ee_s (%)	conf.	ee_p (%)	*E*
CAL-A	toluene	6	49	(3*R*,4*S*)	91	(3*S*,4*R*)	94	102
CAL-A	*i*-Pr_2O	2	64	(3*R*,4*S*)	99	(3*S*,4*R*)	56	17
CAL-A	1,4-dioxane	294	4	(3*R*,4*S*)	3	(3*S*,4*R*)	79	9
CAL-A	acetone	169	5	(3*R*,4*S*)	3	(3*S*,4*R*)	54	3
CAL-A	THF	48	7	(3*R*,4*S*)	7	(3*S*,4*R*)	92	25
CAL-A	CH_2Cl_2	48	5	(3*R*,4*S*)	5	(3*S*,4*R*)	95	40
CAL-A	*t*-BuOH	175	4	(3*R*,4*S*)	2	(3*S*,4*R*)	55	4
CAL-A	vinyl acetate[b]	2	34	(3*R*,4*S*)	53	(3*S*,4*R*)	89	28
CAL-B	toluene	6	55	(3*S*,4*R*)	94	(3*R*,4*S*)	82	35
CAL-B	*i*-Pr_2O	2	60	(3*S*,4*R*)	97	(3*R*,4*S*)	64	18
CAL-B	THF	6	16	(3*S*,4*R*)	15	(3*R*,4*S*)	81	11
CAL-B	hexane	4	71	(3*S*,4*R*)	99	(3*R*,4*S*)	47	12
CAL-B	vinyl acetate[b]	2	40	(3*S*,4*R*)	63	(3*R*,4*S*)	89	32
MML	toluene	173	10	(3*S*,4*R*)	4	(3*R*,4*S*)	56	4
PSL-C	toluene	55	18	(3*S*,4*R*)	18	(3*R*,4*S*)	88	18
PSL-C	vinyl acetate[b]	46	25	(3*S*,4*R*)	23	(3*R*,4*S*)	82	12

[a] 10 equiv of vinyl acetate, 30 °C. [b] Vinyl acetate (10 mL) was used as solvent.

$LiAlH_4$ (6.8 g, 179 mmol) in dry THF (100 mL) was added dropwise a solution of (±)-*trans*-**3** (5.0 g, 17.9 mmol), in 50 mL of dry THF**.** The resulting mixture was refluxed for 6 h and allowed to cool to room temperature. Then, 25 mL of H_2O and 10% NaOH were successively added, and the resulting mixture was stirred for 12 h. After this time, the reaction mixture was filtered through a Celite pad and extracted with ethyl acetate (5 × 100 mL). The combined organic fractions were dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford the crude piperidincarbinol (±)-*trans*-**2** as a white solid (2.59 g, 69%) that can be used without further purification.

Protection of (±)-*trans*-4-(4′-Fluorophenyl)-3-hydroxymethylpiperidine [(±)-*trans*-2]. General Procedure. Distilled H_2O (15 mL) and Na_2CO_3 (2.14 g, 0.2 mol) were added to a stirred solution of compound (±)-*trans*-**2** (1 g, 4.78 mmol) in CH_2Cl_2 (15 mL). The resulting mixture was cooled to 0 °C and the corresponding *tert*-butyl dicarbonate (5.74 mmol) or chloroformate (benzyl or phenyl 9.56 mmol, allyl 5.74 mmol) was added dropwise and stirred for 1 h. Then, the mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic fractions were washed with a 5% aqueous solution of sodium bicarbonate, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel with hexane/ethyl acetate 1:1 to afford the compound (±)-*trans*-**4a**−**d** as a white solid (35−60%).

Table 4. Lipase-Catalyzed Acetylation of (±)-*trans*-4a at 15 °C with Vinyl Acetate

				remaining alcohol *trans*-**4a**		product *trans*-**5a**		
lipase	solvent	time (h)	*c* (%)	conf.	ee_s (%)	conf.	ee_p (%)	*E*
CAL-A	toluene	10	48	(3*R*,4*S*)	88	(3*S*,4*R*)	96	143
CAL-B	toluene	8	47	(3*S*,4*R*)	78	(3*R*,4*S*)	94	76
CAL-B	*t*-BuOMe	12	54	(3*S*,4*R*)	93	(3*R*,4*S*)	83	36
CAL-B	vinyl acetate[a]	5	25	(3*S*,4*R*)	30	(3*R*,4*S*)	92	32
PSL-C	toluene	72	8	(3*S*,4*R*)	6	(3*R*,4*S*)	84	12
PSL-C	*t*-BuOMe	52	9	(3*S*,4*R*)	9	(3*R*,4*S*)	88	17

[a] Vinyl acetate (10 mL) was used as solvent.

Acetylation of (±)-*trans*-*N*-Benzyloxycarbonyl-4-(4′-fluorophenyl)-3-hydroxymethylpiperidine [(±)-*trans*-4a]. Acetic anhydride (0.55 mL, 5.82 mmol) was added dropwise to a 0 °C solution of alcohol (±)-*trans*-**4a** (1 g, 2.91 mmol) in CH_2Cl_2 (90 mL) and pyridine (0.47 ml, 5.82 mmol) and stirred for 8 h. The resulting mixture was washed with 1N HCl. The organic fraction was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel with hexane/ethyl acetate (1:1) to afford the compound (±)-*trans*-**5a** as a white solid (960 mg, 86%).

Enzymatic Hydrolysis of (±)-3-acetyloxymethyl-*trans*-*N*-Benzyloxycarbonyl-4-(4′-fluorophenyl) piperidine [(±)-*trans*-5a]. The reaction mixture contained (±)-*trans*-**5a** (0.1 g), H_2O (10 equiv) and the lipase (amount indicated in Table 2) in the corresponding organic solvent (15 mL). The mixture was shaken at 30 °C and 250 rpm in a rotatory shaker. The progress of the reaction was monitored by TLC using hexane/ethyl acetate 1:1. The enzyme was removed by filtration and washed with ethyl acetate. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 1:1) to afford (+) or (−)-*trans*-**4a** and the corresponding enantiomer of the remaining substrate *trans*-**5a**.

Enzymatic Acylation of *N*-Substituted (±)-*trans*-4-(4′-Fluorophenyl)-3-hydroxymethylpiperidines [(±)-*trans*-

Table 5. Influence of the Acyl Donor in the Lipase-Catalyzed Acylation of (±)-*trans*-4a

							remaining alcohol *trans*-**4a**		product *trans*-**5**		
lipase	R′	R″	solvent	*T* (°C)	time (h)	*c* (%)	conf.	ee$_s$ (%)	conf.	ee$_p$ (%)	E
CAL-A	Me	*i*-propenyl	toluene	30	6	38	(3*R*,4*S*)	58	(3*S*,4*R*)	96	88
CAL-A	Me	*i*-propenyl	toluene	15	24	40	(3*R*,4*S*)	64	(3*S*,4*R*)	97	127
CAL-B	Me	*i*-propenyl	toluene	30	8	58	(3*S*,4*R*)	99	(3*R*,4*S*)	79	43
CAL-B	Me	*i*-propenyl	toluene	15	10	47	(3*S*,4*R*)	79	(3*R*,4*S*)	90	45
PSL-C	Me	*i*-propenyl	toluene	30	55	9	(3*S*,4*R*)	9	(3*R*,4*S*)	88	17
CAL-A	Ph	vinyl	*t*-BuOMe	30	24	46	(3*R*,4*S*)	12	(3*S*,4*R*)	11	1.4
CAL-A	Ph	vinyl	toluene	30	24	55	(3*R*,4*S*)	42	(3*S*,4*R*)	35	3.0
CAL-B	Ph	vinyl	*t*-BuOMe	30	9	57	(3*S*,4*R*)	99	(3*R*,4*S*)	75	35
CAL-B	Ph	vinyl	toluene	30	9	51	(3*S*,4*R*)	98	(3*R*,4*S*)	93	127
CAL-B	Ph	vinyl	*a*	30	9	26	(3*S*,4*R*)	36	(3*R*,4*S*)	98	139
CAL-A	Me	-N=C(Me)$_2$	toluene	30	30	16	(3*R*,4*S*)	18	(3*S*,4*R*)	92	29
CAL-B	Me	-N=C(Me)$_2$	toluene	30	4	53	(3*S*,4*R*)	92	(3*R*,4*S*)	83	34
CAL-A	Me	ethyl	*t*-BuOMe	30	30	11	(3*R*,4*S*)	12	(3*S*,4*R*)	93	31
CAL-A	Me	ethyl	toluene	30	80	16	(3*R*,4*S*)	21	(3*S*,4*R*)	97	81
CAL-A	Me	ethyl	*a*	30	96	18	(3*R*,4*S*)	21	(3*S*,4*R*)	93	35
CAL-B	Me	ethyl	toluene	30	48	38	(3*S*,4*R*)	42	(3*R*,4*S*)	76	10

[a] The acyl donor (10 mL) was used as solvent.

Table 6. Lipase-Catalyzed Acylation of Derivatives (±)-4b−d in Toluene

							remaining alcohol **4**		product **5**		
lipase	R	R′	R″	*T* (°C)	time (h)	*c* (%)	conf.	ee$_s$ (%)	conf.	ee$_p$ (%)	*E*
CAL-A	Boc	Me	vinyl	30	2	38	(3*R*,4*S*)	59	(3*S*,4*R*)	96	89
CAL-A	Boc	Me	vinyl	15	5	22	(3*R*,4*S*)	28	(3*S*,4*R*)	98	130
CAL-A	Boc	Me	*i*-propenyl	30	5	25	(3*R*,4*S*)	36	(3*S*,4*R*)	95	55
CAL-B	Boc	Me	vinyl	30	1	34	(3*S*,4*R*)	48	(3*R*,4*S*)	93	44
CAL-B	Boc	Ph	vinyl	30	7	45	(3*S*,4*R*)	78	(3*R*,4*S*)	96	116
CAL-A	Alloc	Me	vinyl	30	1	45	(3*R*,4*S*)	77	(3*S*,4*R*)	94	75
CAL-A	Alloc	Me	vinyl	15	2	32	(3*R*,4*S*)	46	(3*S*,4*R*)	97	103
CAL-A	Alloc	Me	*i*-propenyl	30	2	27	(3*R*,4*S*)	35	(3*S*,4*R*)	93	38
CAL-B	Alloc	Me	vinyl	30	1	57	(3*S*,4*R*)	91	(3*R*,4*S*)	68	16
CAL-B	Alloc	Ph	vinyl	30	2	45	(3*S*,4*R*)	37	(3*R*,4*S*)	98	142
CAL-A	Poc	Me	vinyl	30	6	51	(3*R*,4*S*)	97	(3*S*,4*R*)	92	101
CAL-A	Poc	Me	vinyl	15	10	47	(3*R*,4*S*)	84	(3*S*,4*R*)	96	131
CAL-A	Poc	Me	*i*-propenyl	30	6	40	(3*R*,4*S*)	64	(3*S*,4*R*)	95	55
CAL-B	Poc	Me	vinyl	30	6	55	(3*S*,4*R*)	99	(3*R*,4*S*)	80	46
CAL-B	Poc	Ph	vinyl	30	9	48	(3*S*,4*R*)	88	(3*R*,4*S*)	95	114

4a−d]. The reaction mixture contained (±)-*trans*-**4a−d** (0.1 g), the corresponding acylating agent (10 equiv), and the lipase (amount indicated in Table 2) in 17 mL of the corresponding organic solvent. The mixture was shaken at 30 °C (unless otherwise stated) and 250 rpm in a rotatory shaker. The progress of the reaction was monitored by TLC using the solvent system hexane/ethyl acetate 1:1. The enzyme was removed by filtration and washed with ethyl acetate. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 1:1 for acetylations, 7:3 for benzoylations) to afford compounds (+) or (−)-*trans*-**5a−h** and the corresponding enantiomer of the remaining substrate *trans*-**4a−d**.

Hydrolysis of the Acetyl Group. To a solution of acetyloxymethylpiperidine *trans*-**5a−d**, (2.6 mmol) in dry methanol (60 mL) were added dropwise 100 mL of a sodium methoxide solution 0.2 M in methanol, at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then allowed to warm to room temperature. After that, Dowex 50 × 4−400 was added until pH 6−7. The Dowex was removed by filtration and washed with methanol. The solution was evaporated under reduced pressure to give the corresponding alcohol *trans*-**4a−d** in 78−88% yield.

Cleavage of the Benzyloxycarbonyl Group. To a solution of *trans*-**4a** (1 g, 2.91 mmol) in ethanol was added Pd/C catalyst (300 mg) under hydrogen atmosphere. The progress of the reaction was monitored by TLC using hexane/ethyl acetate 1:1. After 24 h the resulting mixture was filtered through Celite and the solvent evaporated under reduced pressure to afford the compound *trans*-**2** as a white solid (535 mg, 88%).

Cleavage of the *tert*-Butoxycarbonyl Group. HCl$_{concentrated}$ (1.3 mL) was added to a solution of *trans*-**4b** (1 g, 3.23 mmol) in ethanol (35 mL). The reaction mixture was stirred for 3 h at 50 °C and then allowed to cool to room temperature. The resulting mixture was evaporated under reduced pressure to afford the compound *trans*-**2** hydrochloride as a white solid (526 mg, 78%).

Cleavage of the Allyloxycarbonyl Group. To a solution of *trans*-**4c** (1 g, 3.41 mmol) in 45 mL of ethanol was added Pd/C catalyst (250 mg) under hydrogen atmosphere. The progress of the reaction was monitored by TLC using hexane/ethyl acetate 1:1. After 48 h, the resulting mixture was filtered over Celite, washed with ethanol, and the solvent evaporated under reduced pressure to afford the compound *trans*-**2** as a white solid (570 mg, 80%).

Cleavage of the Phenyloxycarbonyl Group. To a solution of *trans*-**4d** (1 g, 3.04 mmol) in toluene (30 mL) was added KOH (760 mg, 13.68 mmol). The reaction mixture was refluxed for 24 h and then allowed to cool to room temperature. The resulting mixture was washed successively with H_2O (2 × 15 mL) and $NaHCO_3$ (2 × 15 mL), and the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography using MeOH/NH_3(aq) 99:1 to afford the compound *trans*-**2** as a white solid (400 mg, 64%).

***trans*-4-(4′-Fluorophenyl)-3-hydroxymethylpiperidine.** (3*S*,4*R*)-(−)-**2**: $[\alpha]^{25}_D$ −24.3 (*c* = 0.46, MeOH), ee 95%. **(3*R*,4*S*)-(+)-2** $[\alpha]^{25}_D$ +27.8 (*c* = 1.12, MeOH), ee 98%.[10]

***trans*-*N*-Benzyloxycarbonyl-4-(4′-fluorophenyl)-3-hydroxymethylpiperidine (*trans*-4a).** Determination of the ee by HPLC analysis: 28 °C, hexane/*i*-propanol (90:10), 0.8 cm^3 min^{-1}, Rs 2.0. **(3*S*,4*R*)-(−)-4a**: HPLC t_R 19.17 min, $[\alpha]^{25}_D$ −3.51

(c = 1.12, MeOH), ee 96%. **(3*R*,4*S*)-(+)-4a**: HPLC t_R 23.22 min, $[\alpha]^{25}_D$ +3.47 (c = 0.90, MeOH), ee 98%;

***trans*-*N*-*tert*-Butoxycarbonyl-4-(4′-fluorophenyl)-3-hydroxymethylpiperidine (*trans*-4b).** Determination of the ee by HPLC analysis: 28 °C, hexane/*i*-propanol (97:3), 0.5 cm^3 min^{-1}, Rs 2.3. **(3*S*,4*R*)-(−)-4b**: HPLC t_R 39.00 min, $[\alpha]^{25}_D$ −5.16 (c = 0.91, MeOH), ee 98%. **(3*R*,4*S*)-(+)-4b**: HPLC t_R 43.38 min, $[\alpha]^{25}_D$ +5.12 (c = 1.13, MeOH), ee 97%;

***trans*-*N*-Allyloxycarbonyl-4-(4′-fluorophenyl)-3-hydroxymethylpiperidine (*trans*-4c).** ^{1}H NMR ($CDCl_3$-d_1, 200 MHz) δ 1.60−1.85 (m, 4H), 2.56 (td, 1H, $^3J_{HH}$ 4.0, $^3J_{HH}$ 11.0 Hz), 2.72−2.91 (m, 2H), 3.25 (dd, 1H, $^2J_{HH}$ 11.2, $^3J_{HH}$ 6.8 Hz), 3.44 (dd, 1H, $^2J_{HH}$ 11.2, $^3J_{HH}$ 3.3 Hz), 4.24−4.31 (m, 1H), 4.40−4.49 (m, 1H), 4.63 (d, 2H, $^3J_{HH}$ 5.4 Hz), 5.23 (dd, 1H, $^2J_{HH}$ 1.4, $^3J_{HH}$ 10.5 Hz), 5.33 (dd, 1H, $^2J_{HH}$ 1.4, $^3J_{HH}$ 17.5 Hz), 5.97 (ddd, 1H, $^3J_{HH}$ 5.4, $^3J_{HH}$ 10.5 $^3J_{HH}$ 17.5 Hz), 7.00 (dd, 2H, $^3J_{HH}$ 8.7, $^3J_{HF}$ 8.7 Hz) and 7.15 (dd, 2H, $^3J_{HH}$ 8.7, $^4J_{HF}$ 5.3 Hz). MS (ESI$^+$, m/z); 316 [(M + Na)$^+$, 100] and 294 [(M + H)$^+$, 68]. Anal. Calcd for $C_{16}H_{20}FNO_3$: C, 65.51; H, 6.87; N, 4.77. Found: C, 65.40; H, 6.71; N, 4.95. Determination of the ee by HPLC analysis: 28 °C, hexane/*i*-propanol (95:5), 0.8 cm^3 min^{-1}, Rs 3.6. **(3*S*,4*R*)-(−)-4c**, HPLC: t_R 33.49 min, $[\alpha]^{25}_D$ −7.51 (c = 1.14, MeOH), ee 98%. **(3*R*,4*S*)-(+)-4c**: HPLC t_R 42.50 min, $[\alpha]^{25}_D$ +7.63 (c = 1.35, MeOH), ee 98%.

***trans*-4-(4′-Fluorophenyl)-3-hydroxymethyl-*N*-phenyloxycarbonylpiperidine (*trans*-4d).** ^{1}H NMR ($CDCl_3$-d_1, 300 MHz) δ 1.64 (bs, 1H), 1.71−1.96 (m, 3H), 2.56−2.71 (m, 1H), 2.83−3.09 (m, 2H), 3.25 (dd, 1H, $^2J_{HH}$ 11.0, $^3J_{HH}$ 6.5 Hz), 3.43 (dd, 1H, $^2J_{HH}$ 11.0, $^3J_{HH}$ 3.3 Hz), 4.39−4.61 (m, 2H), 7.01 (dd, 2H, $^3J_{HH}$ 8.7, $^3J_{HF}$ 8.7 Hz), 7.13−7.23 (m, 5H) and 7.37 (t, 2H, $^3J_{HH}$ 7.7 Hz). MS (ESI$^+$, m/z) 368 [(M + K)$^+$, 100], 352 [(M + Na)$^+$, 62] and 330 [(M + H)$^+$, 40]. Anal. Calcd for $C_{19}H_{20}FNO_3$: C, 69.29; H, 6.12; N, 4.25. Found: C, 69.58; H, 6.01; N, 4.52. Determination of the ee by HPLC analysis: 28 °C, hexane/*i*-propanol (90:10), 0.8 cm^3 min^{-1}, Rs 5.9. **(3*S*,4*R*)-(−)-4d**: HPLC t_R 44.33 min, $[\alpha]^{25}_D$ −3.49 (c = 0.71, MeOH), ee 96%. **(3*R*,4*S*)-(+)-4d**: HPLC t_R 28.36 min, $[\alpha]^{25}_D$ +3.89 (c = 1.36, MeOH), ee 98%.

***trans*-3-Acetyloxymethyl-*N*-benzyloxycarbonyl-4-(4′-fluorophenyl)piperidine (*trans*-5a).** ^{1}H NMR ($CDCl_3$-d_1, 200 MHz) δ 1.65−1.83 (m, 2H), 2.00−2.10 (m, 4H), 2.51 (td, 1H, $^3J_{HH}$ 4.1, $^3J_{HH}$ 11.5 Hz), 2.62−2.74 (m, 1H), 2.82−2.93 (m, 1H), 3.65 (dd, 1H, $^2J_{HH}$ 11.5, $^3J_{HH}$ 7.7 Hz), 3.85 (dd, 1H, $^2J_{HH}$ 11.5, $^3J_{HH}$ 3.6 Hz), 4.29−4.44 (m, 2H), 5.18 (s, 2H), 7.01 (dd, 2H, $^3J_{HH}$ 8.8, $^3J_{HF}$ 8.8 Hz), 7.13 (dd, 2H, $^3J_{HH}$ 8.8, $^4J_{HF}$ 5.4 Hz) and 7.33−7.41 (m, 5H). MS (ESI$^+$, m/z); 424 [(M + K)$^+$, 40%], 408 [(M + Na)$^+$, 100] and 386 [(M + H)$^+$, 5]. Anal. Calcd for $C_{22}H_{24}FNO_4$: C, 68.56; H, 6.28; N, 3.63. Found: C, 68.82; H, 6.41; N, 3.50. Determination of the ee by HPLC analysis: 28 °C, hexane/*i*-propanol (90:10), 0.8 cm^3 min^{-1}, Rs 2.6. **(3*S*,4*R*)-(−)-5a**: HPLC t_R 17.01 min, $[\alpha]^{25}_D$ −5.12 (c = 0.80, MeOH), ee 98%. **(3*R*,4*S*)-(+)-5a**: HPLC t_R 14.31 min, $[\alpha]^{25}_D$ +5.02 (c = 0.75, MeOH), ee 96%.

***trans*-3-Acetyloxymethyl-*N*-*tert*-butoxycarbonyl-4-(4′-fluorophenyl)piperidine (*trans*-5b).** ^{1}H NMR ($CDCl_3$-d_1, 200 MHz) δ 1.50 (s, 9H), 1.63−1.81 (m, 2H), 2.00−2.09 (m, 4H,), 2.47 (td, 1H, $^3J_{HH}$ 4.3, $^3J_{HH}$ 11.3 Hz), 2.52−2.64 (m, 1H), 2.72−2.85 (m, 1H), 3.64 (dd, 1H, $^2J_{HH}$ 11.3, $^3J_{HH}$ 7.8 Hz), 3.84 (dd, 1H, $^2J_{HH}$ 11.3, $^3J_{HH}$ 3.5 Hz), 4.19−4.24 (m, 2H), 4.33−4.40 (m, 1H), 7.00 (dd, 2H, $^3J_{HH}$ 8.7, $^3J_{HF}$ 8.7 Hz) and 7.13 (dd, 2H, $^3J_{HH}$ 8.7, $^4J_{HF}$ 5.2 Hz). MS (ESI$^+$, m/z) 390 [(M + K)$^+$, 19%], 374 [(M + Na)$^+$, 100] and 352 [(M + H)$^+$, 2]. Anal. Calcd for $C_{19}H_{26}FNO_4$: C, 64.94; H, 7.46; N, 3.99. Found: C, 64.71; H, 7.72; N, 4.15. Determination of the ee by HPLC analysis: 28 °C, hexane/*i*-propanol (97:3), 0.5 cm^3 min^{-1}, Rs 2.4. **(3*S*,4*R*)-(−)-5b**, HPLC: t_R 18.78 min, $[\alpha]^{25}_D$ −7.97 (c = 0.69, MeOH), ee 98%. **(3*R*,4*S*)-(+)-5b**: HPLC t_R 16.29 min, $[\alpha]^{25}_D$ +7.81 (c = 0.78, MeOH), ee 96%.

***trans*-3-Acetyloxymethyl-*N*-allyloxycarbonyl-4-(4′-fluorophenyl)piperidine (*trans*-5c).** ^{1}H NMR ($CDCl_3$-d_1, 200 MHz) δ 1.63−1.84 (m, 2H), 2.00−2.10 (m, 4H), 2.5 (td, 1H, $^3J_{HH}$ 4.1, $^3J_{HH}$ 11.5 Hz), 2.61−2.73 (m, 1H), 2.79−2.93 (m, 1H), 3.64 (dd, 1H, $^2J_{HH}$ 11.5, $^3J_{HH}$ 7.6 Hz), 3.44 (dd, 1H, $^2J_{HH}$ 11.5, $^3J_{HH}$ 3.3 Hz), 4.26−4.33 (m, 1H), 4.35−4.44 (m, 1H), 4.64 (d, 2H, $^3J_{HH}$ 5.5 Hz), 5.23 (dd, 1H, $^2J_{HH}$ 1.4, $^3J_{HH}$ 10.4 Hz), 5.34 (dd, 1H, $^2J_{HH}$ 1.4, $^3J_{HH}$ 17.1 Hz), 5.97 (ddd, 1H, $^3J_{HH}$ 5.5, $^3J_{HH}$ 10.4 $^3J_{HH}$ 17.1 Hz), 7.00 (dd, 2H, $^3J_{HH}$ 8.6, $^3J_{HF}$ 8.6 Hz) and 7.12 (dd, 2H, $^3J_{HH}$ 8.6, $^4J_{HF}$ 5.4 Hz). MS (ESI$^+$, m/z) 374 [(M + K)$^+$, 60%], 358 [(M + Na)$^+$, 100] and 336 [(M + H)$^+$, 30]. Anal. Calcd for $C_{18}H_{22}FNO_4$: C, 64.46; H, 6.61; N, 4.18. Found: C, 64.31; H, 6.87; N, 4.02. Determination of the ee by HPLC analysis: 28 °C, hexane/*i*-propanol (95;5), 0.8 cm^3 min^{-1}, Rs 2.2. **(3*S*,4*R*)-(−)-5c**: HPLC t_R 19.70 min, $[\alpha]^{25}_D$ −9.54 (c = 0.98, MeOH), ee 99%. **(3*R*,4*S*)-(+)-5c**: HPLC t_R 16.48 min, $[\alpha]^{25}_D$ +9.50 (c = 1.00, MeOH), ee 98%.

***trans*-3-Acetyloxymethyl-4-(4′-fluorophenyl)-*N*-phenyloxycarbonylpiperidine (*trans*-5d).** ^{1}H NMR ($CDCl_3$-d_1, 200 MHz) δ 1.62−1.89 (m, 2H), 2.02 (s, 3H), 2.10−2.19 (m, 2H,), 2.58 (td, 1H, $^3J_{HH}$ 4.4, $^3J_{HH}$ 11.3 Hz), 2.70−2.98 (m, 2H), 3.70 (dd, 1H, $^2J_{HH}$ 11.5, $^3J_{HH}$ 7.7 Hz), 3.85−3.92 (m, 1H), 4.42−4.56 (m, 2H), 7.02 (dd, 2H, $^3J_{HH}$ 8.7, $^3J_{HF}$ 8.7 Hz), 7.09−7.23 (m, 5H) and 7.40 (t, 2H, $^3J_{HH}$ 7.6 Hz). MS (ESI$^+$, m/z) 410 [(M + K)$^+$, 100%], 394 [(M + Na)$^+$, 100] and 372 [(M + H)$^+$, 15]. Anal. Calcd for $C_{21}H_{22}FNO_4$: C, 67.91; H, 5.97; N, 3.77. Found: C, 68.12; H, 5.82; N, 3.91. Determination of the ee by HPLC analysis: 28 °C, hexane/*i*-propanol (90:10), 0.8 cm^3 min^{-1}, Rs 5.7. **(3*S*,4*R*)-(−)-5d**: HPLC t_R 23.45 min $[\alpha]^{25}_D$ −5.03 (c = 0.73, MeOH), ee 99%. **(3*R*,4*S*)-(+)-5d**: HPLC t_R 33.34 min $[\alpha]^{25}_D$ +5.01 (c = 0.90, MeOH), ee 98%.

***trans*-3-Benzoyloxymethyl-*N*-benzyloxycarbonyl-4-(4′-fluorophenyl)piperidine (*trans*-5e).** ^{1}H NMR ($CDCl_3$-d_1, 200 MHz) δ 1.67−1.89 (m, 2H), 2.09−2.27 (m, 1H), 2.63 (td, 1H, $^3J_{HH}$ 4.3, $^3J_{HH}$ 11.5 Hz), 2.76−3.00 (m, 2H), 3.91 (dd, 1H, $^2J_{HH}$ 11.3, $^3J_{HH}$ 7.4 Hz), 4.12 (dd, 1H, $^2J_{HH}$ 11.3, $^3J_{HH}$ 3.5 Hz), 4.34−4.42 (m, 1H), 4.53−4.64 (m, 1H), 5.19 (s, 2H), 7.01 (dd, 2H, $^3J_{HH}$ 8.8, $^3J_{HF}$ 8.8 Hz), 7.17 (dd, 2H, $^3J_{HH}$ 8.8, $^4J_{HF}$ 5.4 Hz), 7.40−7.47 (m, 7H), 7.54−7.60 (m, 1H) and 7.97 (d, 2H, $^3J_{HH}$ 7.2 Hz). MS (ESI$^+$, m/z) 486 [(M + K)$^+$, 72%], 470 [(M + Na)$^+$, 100] and 448 [(M + H)$^+$, 6%]. Anal. Calcd for $C_{27}H_{26}FNO_4$: C, 72.47; H, 5.86; N, 3.13. Found: C, 72.74; H, 5.75; N, 3.36. Determination of the ee by HPLC analysis: 30 °C, hexane/*i*-propanol (90:10), 0.6 cm^3 min^{-1}, Rs 5.9. **(3*S*,4*R*)-(+)-5e**, HPLC: t_R 22.42 min $[\alpha]^{25}_D$ +6.21 (c = 0.97, MeOH), ee 98%. **(3*R*,4*S*)-(−)-5e**: HPLC t_R 20.51 min $[\alpha]^{25}_D$ −6.24 (c = 1.03, MeOH), ee 98%.

***trans*-3-Benzoyloxymethyl-*N*-*tert*-butoxycarbonyl-4-(4′-fluorophenyl)piperidine (*trans*-5f).** ^{1}H NMR ($CDCl_3$-d_1, 200 MHz) δ 1.50 (s, 9H), 1.67−1.81 (m, 2H), 2.12−2.24 (m, 1H), 2.57 (td, 1H, $^3J_{HH}$ 4.6, $^3J_{HH}$ 11.5 Hz), 2.66−2.88 (m, 2H,), 3.87 (dd, 1H, $^2J_{HH}$ 11.4, $^3J_{HH}$ 7.6 Hz), 4.12 (dd, 1H, $^2J_{HH}$ 11.4, $^3J_{HH}$ 3.6 Hz), 4.25−4.32 (m, 1H), 4.46−4.53 (m, 1H), 7.02 (dd, 2H, $^3J_{HH}$ 8.8, $^3J_{HF}$ 8.8 Hz), 7.17 (dd, 2H, $^3J_{HH}$ 8.8, $^4J_{HF}$ 5.4 Hz), 7.44 (dd, 2H, $^3J_{HH}$ 7.2 Hz), 7.58 (t, 1H, $^3J_{HH}$ 7.2 Hz) and 7.99 (dd, 2H, $^3J_{HH}$ 7.2 $^4J_{HH}$ 1.5 Hz). MS (ESI$^+$, m/z) 452 [(M + K)$^+$, 40%], 436 [(M + Na)$^+$, 100] and 414 [(M + H)$^+$, 2%]. Anal. Calcd for $C_{24}H_{28}FNO_4$: C, 69.71; H, 6.82; N, 3.39. Found: C, 69.53; H, 7.06; N, 3.21. Determination of the ee by HPLC analysis: 28 °C, hexane/*i*-propanol (99:1), 0.3 cm^3 min^{-1}, Rs 1.7. **(3*S*,4*R*)-(+)-5f**: HPLC t_R 63.00 min $[\alpha]^{25}_D$ +6.41 (c = 1.00, MeOH), ee 98%. **(3*R*,4*S*)-(−)-5f**: HPLC t_R 58.34 min $[\alpha]^{25}_D$ −6.41 (c = 1.17, MeOH), ee 97%.

***trans*-*N*-Allyloxycarbonyl-3-benzoyloxymethyl-4-(4′-fluorophenyl)piperidine (*trans*-5g).** ^{1}H NMR ($CDCl_3$-d_1, 200 MHz) δ 1.70−1.89 (m, 2H), 2.16−2.22 (m, 1H), 2.63 (td, 1H, $^3J_{HH}$ 4.3, $^3J_{HH}$ 11.5 Hz), 2.75−2−93 (m, 2H), 3.91 (dd, 1H, $^2J_{HH}$ 11.4, $^3J_{HH}$ 7.3 Hz), 4.13 (dd, 1H, $^2J_{HH}$ 11.4, $^3J_{HH}$ 3.4 Hz), 4.29−4.36 (m, 1H), 4.51−4.62 (m, 1H), 4.64 (d, 2H, $^3J_{HH}$ 5.4 Hz), 5.23 (dd, 1H, $^2J_{HH}$ 1.5, $^3J_{HH}$ 10.2 Hz), 5.33 (dd, 1H, $^2J_{HH}$ 1.5, $^3J_{HH}$ 17.2 Hz), 5.98 (ddd, 1H, $^3J_{HH}$ 5.4, $^3J_{HH}$ 10.2, $^3J_{HH}$ 17.2 Hz), 7.00 (dd, 2H, $^3J_{HH}$ 8.6, $^3J_{HF}$ 8.6 Hz), 7.17 (dd, 2H, $^3J_{HH}$ 8.6, $^4J_{HF}$ 5.4 Hz), 7.44 (dd, 2H, $^3J_{HH}$ 6.9 Hz), 7.56 (t, 1H, $^3J_{HH}$ 6.9 Hz), 7.99 (dd, 2H, $^3J_{HH}$ 6.9, $^4J_{HH}$ 1.5 Hz). MS (ESI$^+$, m/z); 436 [(M + K)$^+$, 28%], 420 [(M + Na)$^+$, 100] and 398 [(M + H)$^+$, 6]. Anal. Calcd for $C_{23}H_{24}FNO_4$: C, 69.51; H, 6.09; N, 3.52. Found: C, 69.76; H, 6.33; N, 3.69. Determination of the ee by HPLC analysis: 28 °C, hexane/*i*-propanol (95:5), 0.8 cm^3 min^{-1}, Rs 2.3. **(3*S*,4*R*)-(+)-5g**: HPLC t_R 16.45 min $[\alpha]^{25}_D$ +8.71 (c = 1.00, MeOH), ee 97%. **(3*R*,4*S*)-(−)-5g** HPLC t_R 18.74 min $[\alpha]^{25}_D$ −8.98 (c = 0.59, MeOH), ee 99%.

***trans*-3-Benzoyloxymethyl-4-(4′-fluorophenyl)-*N*-phenyloxycarbonylpiperidine (*trans*-5h).** ^{1}H NMR ($CDCl_3$-d_1, 200 MHz) δ 1.82−2.00 (m, 2H), 2.24−2.39 (m, 1H), 2.62−2.78 (m, 1H), 2.86−3.15 (m, 2H), 3.96 (dd, 1H, $^2J_{HH}$ 11.5, $^3J_{HH}$ 7.4 Hz), 4.12 (m, 1H), 4.45−4.51 (m, 1H), 4.63−4.71 (m, 1H), 7.04 (dd, 2H, $^3J_{HH}$ 8.7, $^3J_{HF}$ 8.7 Hz), 7.14−7.23 (m, 5H), 7.36−7.48 (m, 4H), 7.57 (t, 1H, $^3J_{HH}$ 7.2) and 8.00 (dd, 2H, $^3J_{HH}$ 7.2, $^4J_{HH}$ 1.5 Hz); MS (ESI$^+$, *m*/*z*) 456 [(M + Na)$^+$, 100%], 434 [(M + H)$^+$, 22]. Anal. Calcd for $C_{26}H_{24}FNO_4$: C, 72.04; H, 5.58; N, 3.23. Found: C, 71.82; H, 5.84; N, 3.04. Determination of the ee by HPLC analysis: 28 °C, hexane/*i*-propanol (90:10), 0.6 cm^3 min^{-1}, Rs 1.9. **(3*S*,4*R*)-(+)-5h**: HPLC t_R 41.52 min $[\alpha]^{25}_D$ +8.61 (*c* = 1.30, MeOH), ee 98%. **(3*R*,4*S*)-(−)-5h**: HPLC t_R 33.43 $[\alpha]^{25}_D$ −8.59 (*c* = 1.49, MeOH), ee 98%.

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Supporting Information Available: Complete ^{1}H and ^{13}C NMR spectral data in addition to mp, IR, microanalysis, and MS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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