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Enzymatic alkoxycarbonylation reactions on the intermediate in the synthesis of (−)-paroxetine, *trans*-*N*-benzyloxycarbonyl-4-(4′-fluorophenyl)-3-hydroxymethylpiperidine

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Abstract—Several enzymatic alkoxycarbonylation processes are evaluated for the resolution of *trans*-*N*-benzyloxycarbonyl-4-(4′-fluorophenyl)-3-hydroxymethylpiperidine, a chiral intermediate in the synthesis of (−)-paroxetine. *Candida antarctica* lipase B (CAL-B) catalyzes the enzymatic alkoxycarbonylation with diallylcarbonate with high enantioselectivity.

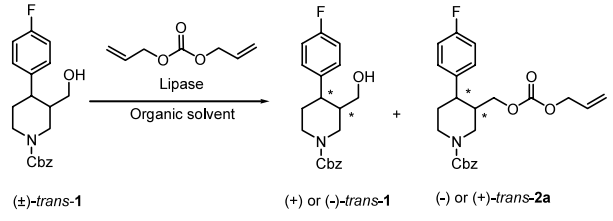
1. Introduction

Biotransformations are nowadays accepted as a methodology for the industrial preparation of enantiomerically pure drugs and fine chemicals.[1] The majority of the enzyme-catalyzed reactions involve the use of hydrolases, specially lipases, in hydrolysis or transesterification reactions.[2] The process of enzymatic alkoxycarbonylation have been less studied. However, lipases have been successfully used for the resolution of racemic alcohols[3a] and amines,[3b,4] as well as for the selective alkoxycarbonylation of natural products.[5] The enzymatic resolution of racemic carbonates has also been achieved.[6] On the other hand, carbonate derivatives are used in the synthesis of compounds with medicinal properties.[7]

As a part of our ongoing program in the enzymatic preparation of optically active drugs by chemoenzymatic methods,[8] we are very interested in the resolution of several intermediates in the synthesis of (−)-paroxetine. The enantiomerically pure (−)-isomer is a selective serotonin (5-HT) reuptake inhibitor that is used in the treatment of depression and other psychological disorders.[9] Several procedures have recently been reported for the preparation of this optically active drug.[10] Biotransformations for the preparation of enantiomerically pure intermediates of (−)-paroxetine have been reported in the last years. In previous reports, we described the resolution of *trans*-4-(4′-fluorophenyl)-3-hydroxymethylpiperidines via a lipase catalyzed acylation with vinyl acetate[11] and with cyclic anhydrides.[12] In addition, other authors have described the preparation of intermediates through enzymatic hydrolysis reactions.[13] These intermediates are suitable precursors for the synthesis of (−)-paroxetine.[14] Herein we describe the application of lipases for the resolution of *trans* - *N* - benzyloxycarbonyl - 4 - (4′ - fluorophenyl) - 3-hydroxymethylpiperidine through enzymatic alkoxycarbonylation processes.

2. Results and discussion

We began the study of the lipase-catalyzed resolution of *trans* - *N* - benzyloxycarbonyl - 4 - (4′ - fluorophenyl) - 3-hydroxymethylpiperidine using diallyl carbonate as the alkoxycarbonylation agent (Scheme 1 and Table 1).



Scheme 1. Enzymatic alkoxycarbonylation of (±)-*trans*-**1** with diallyl carbonate.

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Table 1. Lipase catalyzed alkoxycarbonylation of (±)-*trans*-**1** with diallyl carbonate in organic solvent

Entry	Lipase	Solvent	Equiv. carbonate	T (°C)	Time (h)	c (%)[a]	ee (%)[b] *trans*-**1**	ee (%)[b] *trans*-**2a**	E[c]
1	CAL-A	Toluene	4	30	96	30	14	32	2.2
2	CAL-B	Toluene	4	30	96	15	17	94	38
3	CAL-B	Toluene	10	30	48	23	28	94	42
4	CAL-B	*t*-BuOMe	10	30	30	27	31	84	15
5	CAL-B	Hexane	10	30	6	15	16	90	22
6	CAL-B	1,4-Dioxane	10	30	168	16	18	92	28
7	CAL-B	THF	10	30	168	4	4	92	24
8	CAL-B	Toluene	10	15	96	10	10	95	43
9	CAL-B	Toluene	10	50	24	46	76	88	36
10	CAL-B	Tol./NEt_3[d]	10	30	48	16	18	92	28
11	CAL-B-L2	Toluene	10	30	48	3	5	93	29

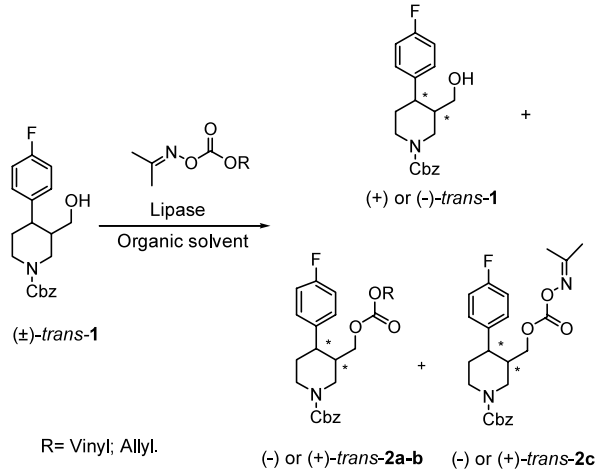
[a] Conversion, $c = ee_S/(ee_S+ee_p)$.
[b] Determined by HPLC.
[c] Enantiomeric ratio, $E = \ln[1-c(1-ee_p)]/\ln[1-c(1-ee_p)]$.
[d] 0.7 equiv. of NEt_3 were added to the reaction media.

Taking into account the best conditions found for the acylation of this derivative in the processes catalyzed by the lipases A and B from *Candida antarctica*,[11] a first set of experiments was carried out in toluene at 30°C using 4 equivalents of diallylcarbonate (entries 1 and 2). As in the case of acylation, these two lipases showed opposite stereochemical preference. CAL-A catalyzed the alkoxycarbonylation of the substrate (3*S*,4*R*), while CAL-B preferred the (3*R*,4*S*) configuration. The lipase CAL-B showed higher enantioselectivity ($E = 38$)[15] under these conditions, even though the reaction rate was low.

In order to improve these results we examined the effect of other parameters in the process catalyzed by CAL-B. First, we increased the amount of diallyl carbonate from 4 to 10 equivalents. Under these conditions, no improvement in E was achieved but, as expected, the reaction rate increased significantly (entry 3). Next, we examined the influence of the organic solvent (entries 4–7). The reactions in *t*-BuOMe or hexane were faster but less enantioselective than in toluene. In the reactions carried out in 1,4-dioxane or tetrahydrofuran, both the rate and the enantioselectivity were lower than in toluene.

As the temperature can have a marked effect on the rate and enantioselectivity, we carried out the reaction catalyzed by CAL-B in toluene at 15 and 50°C (entries 8 and 9). Reaction rates were significantly affected but the effect on the enantioselectivity was negligible. We also studied the effect of a small amount of triethylamine in the reaction media (entry 10), but the enantioselectivity of this process was lower than in the absence of the additive. Finally, the reaction catalyzed by other immobilized form of the lipase CAL-B (CHIRAZYME L-2) was slower and slightly less selective than in the presence of CAL-B, as shown in entry 11.

Taking into account the moderate reaction rate of the reactions carried out with diallyl carbonate we tested the enzymatic alkoxycarbonylation with the more reactive acetone-*O*-[(vinyloxy)carbonyl]oxime[15] (Scheme 2). As expected, all the processes carried out with this alkoxycarbonylation agent showed a higher reaction rate (see Table 2). With both lipases CAL-A and CAL-B at 30°C, after 1 h of reaction a conversion higher than 45% was obtained (entries 1 and 2). Unfortunately, together with the expected allyl carbonate *trans*-**2b**, we observed in the reaction media the oxime derivative *trans*-**2c**. The two reaction products and the remaining substrate obtained in the CAL-B catalyzed process showed moderate enantiomeric excess. At 15°C, similar results were obtained with a slightly lower reaction rate (entry 3). When 1,4-dioxane was used as solvent, formation of the oxime derivative *trans*-**2c** was avoided (entry 4). Nevertheless, the reaction rate and



Scheme 2. Enzymatic alkoxycarbonylation of (±)-*trans*-**1** with acetone-*O*-[(vinyloxy)carbonyl]oxime and acetone-*O*-[(allyloxy)carbonyl]oxime.

Table 2. Lipase catalyzed alkoxycarbonylation of (±)-*trans*-**1** with acetone-*O*-[(vinyloxy)carbonyl]oxime and acetone-*O*-[(allyloxy)carbonyl]oxime in organic solvents[a]

Entry	Lipase	R	Solvent	*T* (°C)	Time (h)	(%)[b] *trans*-**1a**	Ee (%)[c] *trans*-**1**	(%)[b] *trans*-**2a**,**b**	ee (%)[c] *trans*-**2a**,**b**	(%)[b] *trans*-**2c**	ee (%)[c] *trans*-**2c**	*c*[d] (%)	*E*
1	CAL-A	Vinyl	Toluene	30	1	35	1	34	29	31	23	–	–
2	CAL-B	Vinyl	Toluene	30	1	53	75	14	80	33	79	–	–
3	CAL-B	Vinyl	Toluene	15	2	57	71	12	89	31	79	–	–
4	CAL-B	Vinyl	1,4-Dioxane	30	72	–	10	–	81	0	–	11	10
5	CAL-A	Allyl	Toluene	30	2	–	40	–	24	0	–	63	2.3
6	CAL-B	Allyl	Toluene	30	6	39	82	7	83	54	44	–	–
7	CAL-B	Allyl	Toluene	15	7	44	94	10	92	46	67	–	–
8	CAL-B	Allyl	1,4-Dioxane	30	168	–	15	–	84	0	–	15	13
9	CAL-B	Allyl	*t*-BuOMe	30	2	72	23	16	64	12	51	–	–
10	CAL-B	Allyl	THF	30	144	82	20	4	80	14	86	–	–

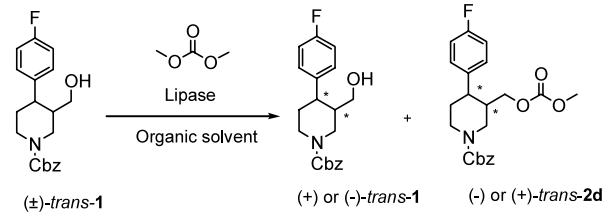
[a] 4 equiv. of carbonate.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC.
[d] Conversion, $c = ee_S/(ee_S+ee_P)$.

the enantioselectivity of the process were too low ($E=10$).

In order to avoid the formation of the undesired product *trans*-**4**, we studied the enzymatic alcoxycarbonylation with the less reactive acetone-*O*-[(allyloxy)carbonyl]oxime (Scheme 2). As shown in Table 2, the formation of the oxime derivative *trans*-**2c** was not detected only in the processes catalyzed by CAL-A in toluene or by CAL-B in 1,4-dioxane (entries 5 and 8). However, the enantioselectivity of these reactions was low. In the reaction catalyzed by CAL-B in toluene at 15°C, the remaining alcohol **1** was obtained with a high enantiomeric excess (94% ee at 56% conversion), although the two reaction products were observed (entry 7). In this reaction, the alcohol **1** has the correct configuration to complete the synthesis of (−)-paroxetine.

The absolute configuration of the oxime derivative *trans*-**2c** was determined by hydrolysis of this product with sodium methoxide in methanol to obtain the corresponding alcohol *trans*-**1**. In all the reactions, the oxime derivative presented the opposite configuration than the remaining alcohol. When CAL-A was used, we obtained (3*S*,4*R*)-*trans*-**2c** and when CAL-B was used, it was formed (3*R*,4*S*)-*trans*-**2c**.

Next, we decided to study the enzymatic process with the symmetric dimethyl carbonate as acylating agent (Scheme 3 and Table 3). Taking into account the low reactivity of this carbonate, 10 equivalents of this reagent were used. In toluene at 30°C, CAL-A showed very low reaction rate and enantioselectivity (entry 1). The process catalysed by CAL-B was also slow but we obtained a better enantioselectivity ($E=16$), as shown in entry 2. We observed an improvement of the CAL-B catalyzed reaction when it was carried out at 50°C or using hexane or *t*-BuOMe as solvent (entries 3–5), but there was no improvement in the enantioselectivities.



Scheme 3. Enzymatic alkoxycarbonylation of (±)-*trans*-**1** with dimethyl carbonate.

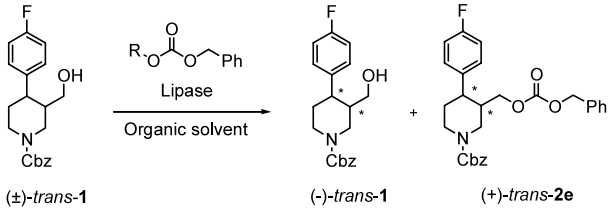
Higher reaction rates and enantioselectivities were obtained when dibenzyl carbonate (Scheme 4, Table 4) was tested in the same conditions as dimethyl carbonate. In toluene at 30°C, neither of the enzymes, CAL-A or CAL-B, catalyzed the process (entries 1 and 2). When the temperature was increased to 50°C, the product (3*R*,4*S*)-**2e** was obtained with 26% conversion and good enantiomeric ratio ($E=33$) in the reaction catalyzed by CAL-B (entry 3). When *t*-BuOMe or hexane were used at 30°C with CAL-B (entries 4 and 5), we observed an increment of the reaction rate, although the enantioselectivities were not enhanced.

In order to improve the reaction rate, we used as acylating agent the more reactive carbonate of benzyl *p*-nitrophenyl carbonate[16] (Scheme 4 and Table 4). Taking into account the presence of a good leaving group in the carbonate, we carried out the enzymatic process with only 4 equivalents of this reagent. Molecular sieves were added in order to prevent the competing enzymatic hydrolysis of the carbonate. As expected, the reaction rate was higher compared to that with the symmetric dibenzyl carbonate. Unfortunately, the enantiomeric ratios were lower. The best results were obtained with CAL-B at 30°C, using toluene ($E=20$) or 1,4-dioxane ($E=24$) as solvents (entries 6 and 8). Reaction in toluene was much faster than in 1,4-dioxane.

Table 3. Lipase catalyzed alkoxycarbonylation of (±)-*trans*-**1** with dimethyl carbonate in organic solvent[a]

Entry	Lipase	Solvent	T (°C)	Time (h)	c (%)[b]	ee (%)[c] *trans*-**1**	ee (%)[c] *trans*-**2d**	E
1	CAL-A	Toluene	30	168	9	3	32	2.0
2	CAL-B	Toluene	30	168	3	3	88	16
3	CAL-B	Toluene	50	72	16	16	86	15
4	CAL-B	*t*-BuOMe	30	168	27	26	69	7.0
5	CAL-B	Hexane	30	72	7	6	86	13

[a] 10 equiv. Dimethyl carbonate.
[b] Conversion, $c = ee_S/(ee_S+ee_p)$.
[c] Determined by HPLC.



Scheme 4. Enzymatic alkoxycarbonylation of (±)-*trans*-**1** with dibenzyl carbonate or with benzyl *p*-nitrophenyl carbonate.

3. Conclusion

The lipase catalyzed resolution of *trans*-*N*-benzyloxycarbonyl-4-(4′-fluorophenyl)-3-hydroxymethylpiperidine has been studied. Both lipases CAL-A and CAL-B catalyze the alkoxycarbonylation of the substrate with several symmetric and asymmetric carbonates, though with lower enantioselectivities than in the acylation reaction.[11] This loss of enantioselectivity is especially pronounced in the case of CAL-A. Nevertheless, good yields and high enantioselectivities can be achieved by an appropriate selection of the reaction parameters when CAL-B is used as a catalyst. The best enantioselectivity was obtained in toluene at 30°C and using the diallyl carbonate as alkoxycarbonylation agent. The reaction rate can also be enhanced by using higher temperatures with no significant loss of enantioselectivity.

Taking into account that the remaining substrate has the correct configuration to complete the synthesis of (−)-paroxetine in the reactions catalyzed by CAL-B, the high enantiomeric excess of the remaining alcohol (3*S*,4*R*)-**1** obtained in the process carried out in presence of acetone-*O*-[(allyloxy)carbonyl]oxime at 15°C is also remarkable.

4. Experimental[17]

4.1. General methods

Candida antarctica lipase B (CAL-B, Novozym 435, 7300 PLU/g) was a gift from Novo Nordisk Co. Lipase B (CAL-B, CHIRAZYME L-2, c-f, C3, ≥400 U/g) and lipase A from *Candida antarctica* (CAL-A, CHIRAZYME L-5, 1 kU/g) were purchased from Roche Molecular Biochemicals. All these commercial lipases were carrier-fixed products. Other chemicals or solvents were of the highest quality grade available.

Optical rotations were measured using a Perkin–Elmer 241 polarimeter and specific rotations are quoted in units of 10^{-1} deg cm^2 g^{-1}. 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 Shimazdu 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).

4.2. Typical procedure for the enzymatic alkoxycarbonylation of (±)-*trans*-*N*-benzyloxycarbonyl-4-(4′-fluorophenyl)-3-hydroxymethylpiperidine (±)-*trans*-2a–e

The lipase (125 mg) and the corresponding carbonate (4 or 10 equiv.) were added to a solution of (±)-*trans*-**1** (100 mg, 1 equiv.) in the corresponding solvent (15 mL). The mixture was shaken at the selected temperature and 250 rpm in a rotatory shaker. The progress of the reaction was monitorized by TLC. Once the reaction was finished, the enzyme was removed by filtration, washed with ethyl acetate and the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to afford the carbonates (+)- or (−)-*trans*-**2a**–**e** and the corresponding enantiomer of the remaining substrate *trans*-**1**.

4.3. Chemical hydrolysis of (3*S*,4*R*)-(±)-*trans*-*N*-benzyloxycarbonyl-4-(4′-fluorophenyl)-3-isopropylidenaminooxycarbonyloxymethylpiperidine *trans*-2c

At 0°C, 8 mL of a sodium methoxide solution 0.2 M in methanol were added to a solution of (3*S*,4*R*)-*trans*-**2c** (100 mg, 0.23 mmol) in methanol (5 mL). The mixture

Table 4. Lipase catalyzed alkoxycarbonylation of (±)-*trans*-**1** with dibenzyl carbonate[a] and benzyl *p*-nitrophenyl carbonate[b] in organic solvent

Entry	Lipase	R	Solvent	*T* (°C)	Time (h)	*c* (%)[c]	ee (%)[d] *trans*-**1**	ee (%)[d] *trans*-**2e**	*E*
1	CAL-A	Benzyl	Toluene	30	168	0	–	–	–
2	CAL-B	Benzyl	Toluene	30	168	0	–	–	–
3	CAL-B	Benzyl	Toluene	50	48	26	33	92	33
4	CAL-B	Benzyl	*t*-BuOMe	30	48	35	48	89	27
5	CAL-B	Benzyl	Hexane	30	48	29	35	87	20
6	CAL-B	*p*-Nitrophenyl	Toluene	30	48	44	64	83	20
7	CAL-B	*p*-Nitrophenyl	*t*-BuOMe	30	24	29	31	75	9.0
8	CAL-B	*p*-Nitrophenyl	1,4-Dioxane	30	168	26	32	89	24

[a] 10 equiv. dibenzyl carbonate.
[b] 4 equiv. benzyl *p*-nitrophenyl carbonate.
[c] Conversion, $c = ee_S/(ee_S+ee_P)$.
[d] Determined by HPLC.

was stirred for 8 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, and the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel with chloroform/diethyl ether (95:5) to afford the compound (3*R*,4*S*)-*trans*-**1** as a white solid (61.5 mg, 78%).

4.3.1. (±)-*trans*-*N*-Benzyloxycarbonyl-4-(4′-fluorophenyl)-3-hydroxymethykpiperidine *trans*-1. 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*)-(−)-1**, HPLC: t_R 19.17 min, $[\alpha]_D^{18}$ −3.51 (*c* 1.12, MeOH), ee 96%; **(3*R*,4*S*)-(+)-1**, HPLC: t_R 23.22 min, $[\alpha]_D^{18}$ +3.47 (*c* 0.90, MeOH), ee 98%.

4.3.2. (±)-*trans*-3-Allyloxycarbonyloxymethyl-*N*-benzyloxycarbonyl-4-(4′-fluorophenyl)piperidine *trans*-2a. Hygroscopic solid. IR (KBr): *v* 3024, 2944, 2862, 1746, 1702, 1651, 1604, 1510, 1478, 1381 and 1227 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.64–1.82 (m, 2H), 1.98–2.11 (m, 1H), 2.57 (td, 1H, $^3J_{HH}$ 4.0, $^3J_{HH}$ 11.7 Hz), 2.76–2.90 (m, 2H), 3.72 (dd, 1H, $^3J_{HH}$ 6.8, $^2J_{HH}$ 11.9 Hz), 3.93 (dd, 1H, $^3J_{HH}$ 3.1, $^2J_{HH}$ 11.9 Hz), 4.24–4.56 (m, 2H), 4.60 (d, 2H, $^3J_{HH}$ 5.7 Hz), 5.17 (s, 2H), 5.25 (dd, 1H, $^3J_{HH}$ 10.5, $^2J_{HH}$ 2.6 Hz), 5.34 (dd, 1H, $^3J_{HH}$ 15.9, $^2J_{HH}$ 2.6 Hz), 5.90 (ddd, 1H, $^3J_{HH}$ 5.7, $^3J_{HH}$ 10.5, $^3J_{HH}$ 15.7 Hz), 6.99 (dd, 2H, $^3J_{HH}$ 8.8, $^3J_{HF}$ 8.8 Hz), 7.12 (dd, 2H, $^3J_{HH}$ 8.8, $^4J_{HF}$ 5.3 Hz) and 7.31–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 33.9 (CH_2), 40.9 (CH), 43.8 (CH), 44.3 (CH_2), 46.8 (CH_2), 67.1 (CH_2), 67.7 (CH_2), 115.6 (d, $^2J_{CF}$ 20.9 Hz, CH), 118.9 (CH_2), 127.8 (CH), 127.9 (CH), 128.4 (CH), 128.5 (d, $^3J_{CF}$ 7.6 Hz, CH), 131.3 (CH), 136.6 (C), 138.2 (C), 154.6 (C=O), 155.1 (C=O) and 161.6 (d, $^1J_{CF}$ 244.9 Hz, C); MS (ESI$^+$, *m*/*z*): 466 [(M+K)$^+$, 100], 450 [(M+Na)$^+$, 90] and 428 [(M+H)$^+$, 7]. Anal. calcd (%) for $C_{24}H_{26}FNO_5$: C, 67.43; H, 6.13; N, 3.28. Found: C, 67.2; H, 5.9; N, 3.5. Determination of the ee by HPLC analysis: 28°C, hexane/*i*-propanol (90;10), 0.8 cm^3 min^{-1}, Rs 2.7. **(3*S*,4*R*)-(−)-2a**, HPLC: t_R 15.57 min, $[\alpha]_D^{18}$ −0.68 (*c* 0.50, MeOH), ee 32%; **(3*R*,4*S*)-(+)-2a**, HPLC: t_R 13.17 min, $[\alpha]_D^{18}$ +3.94 (*c* 0.61, MeOH), ee 94%.

4.3.3. (±)-*trans*-*N*-Benzyloxycarbonyl-4-(4′-fluorophenyl)-3-vinyloxycarbonyloxymethylpiperidine *trans*-2b. Hygroscopic solid. IR (KBr): *v* 3022, 2951, 2847, 1759, 1699, 1628, 1605, 1510, 1474, 1381 and 1218 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.62–1.80 (m, 2H), 2.00–2.10 (m, 1H), 2.59 (td, 1H, $^3J_{HH}$ 4.1, $^3J_{HH}$ 11.3 Hz), 2.71–2.90 (m, 2H), 3.77 (dd, 1H, $^3J_{HH}$ 6.9, $^2J_{HH}$ 11.3 Hz), 3.99 (dd, 1H, $^3J_{HH}$ 3.1, $^2J_{HH}$ 11.3 Hz), 4.26–4.53 (m, 2H), 4.57 (dd, 1H, $^3J_{HH}$ 6.3 Hz, $^2J_{HH}$ 2.3 Hz), 4.91 (dd, 1H, $^3J_{HH}$ 14.0, $^2J_{HH}$ 2.3 Hz), 5.17 (s, 2H), 6.97–7.06 (m, 3H) 7.13 (dd, 2H, $^3J_{HH}$ 8.7, $^4J_{HF}$ 5.3 Hz) and 7.36–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 34.0 (CH_2), 41.0 (CH), 43.9 (CH), 44.4 (CH_2), 46.8 (CH_2), 67.2 (CH_2), 68.3 (CH_2), 97.9 (CH_2), 115.7 (d, $^2J_{CF}$ 21.4 Hz, CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 128.7 (d, $^3J_{CF}$ 7.6 Hz, CH), 136.6 (C), 138.1 (C), 142.5 (CH), 152.4 (C=O), 155.1 (C=O) and 161.7 (d, $^1J_{CF}$ 243.9 Hz, C); MS (ESI$^+$, *m*/*z*): 452 [(M+K)$^+$, 31], 436 [(M+Na)$^+$, 100] and 414 [(M+H)$^+$, 2]. Anal. calcd (%) for $C_{23}H_{24}FNO_5$: C, 66.82; H, 5.85; N, 3.39. Found: C, 67.0; H, 5.8; N, 3.3. Determination of the ee by HPLC analysis: 28°C, hexane/*i*-propanol (90:10), 0.8 cm^3 min^{-1}, Rs 3.4. **(3*S*,4*R*)-(−)-2b**, HPLC: t_R 16.95 min, $[\alpha]_D^{18}$ −0.41 (*c* 0.55, MeOH), ee 23%; **(3*R*,4*S*)-(+)-2b**, HPLC: t_R 13.31 min, $[\alpha]_D^{18}$ +2.66 (*c* 0.64, MeOH), ee 80%.

4.3.4. (±)-*trans*-*N*-Benzyloxycarbonyl-4-(4′-fluorophenyl)-3-isopropylidenaminooxycarbonyloxymethylpiperidine *trans*-2c. Colourless oil. IR (KBr): *v* 3017, 2945, 2854, 1766, 1695, 1664, 1605, 1510, 1471, 1378 and 1228 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.63–1.91 (m, 2H), 2.02–2.10 (m, 7H), 2.56 (td, 1H, $^3J_{HH}$ 4.1, $^3J_{HH}$ 11.5 Hz), 2.76–2.94 (m, 2H), 3.83 (dd, 1H, $^3J_{HH}$ 7.2, $^2J_{HH}$ 11.0 Hz), 4.03 (dd, 1H, $^3J_{HH}$ 3.3, $^2J_{HH}$ 11.0 Hz), 4.28–4.36 (m, 1H), 4.43–4.52 (m, 1H), 5.18 (s, 2H), 7.00 (dd, 2H, $^3J_{HH}$ 8.7, $^3J_{HF}$ 8.7 Hz), 7.14 (dd, 2H, $^3J_{HH}$ 8.7, $^4J_{HF}$ 5.4 Hz) and 7.34–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 16.8 (CH_3), 21.7 (CH_3), 34.0 (CH_2), 40.9 (CH), 44.0 (CH), 44.3 (CH_2), 46.9 (CH_2), 67.2 (CH_2), 68.1 (CH_2) 115.6 (d, $^2J_{CF}$ 20.9 Hz, CH), 127.8 (CH), 127.9 (CH), 128.4 (CH), 128.5 (d, $^3J_{CF}$ 8.1 Hz, CH), 136.6 (C), 138.2 (C), 153.8 (C=O), 155.1 (C=O), 161.5 (d, $^1J_{CF}$ 243.8 Hz, C) and 163.5 (C=N); MS (ESI$^+$, *m*/*z*):

481 [(M+K)$^+$, 28], 465 [(M+Na)$^+$, 100] and 443 [(M+H)$^+$, 5]. Anal. calcd (%) for $C_{24}H_{27}FN_2O_5$: C, 65.15; H, 6.15; N, 6.33. Found: C, 65.4; H, 5.9; N, 6.1. Determination of the ee by HPLC analysis: 28°C, hexane/*i*-propanol (90;10), 0.8 cm^3 min^{-1}, Rs 1.9. **(3*S*,4*R*)-(−)-2c**, HPLC: t_R 35.12 min, $[\alpha]_D^{18}$ −0.39 (*c* 0.56, MeOH), ee 23%; **(3*R*,4*S*)-(+)-2c**, HPLC: t_R 30.79 min, $[\alpha]_D^{18}$ +3.91 (*c* 0.98, MeOH), ee 86%.

4.3.5. (±)-*trans*-*N*-Benzyloxycarbonyl-4-(4′-fluorophenyl)-3-methyloxycarbonyloxymethylpiperidine *trans*-2d. Colourless oil. IR (KBr): *v* 3011, 2955, 2858, 1749, 1703, 1605, 1510, 1474, 1381 and 1221 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.61–1.82 (m, 2H), 2.00–2.09 (m, 1H), 2.56 (td, 1H, $^3J_{HH}$ 4.0, $^3J_{HH}$ 12.0 Hz), 2.75–2.89 (m, 2H), 3.67–3.73 (m, 4H), 3.93 (dd, 1H, $^3J_{HH}$ 2.8, $^2J_{HH}$ 11.1 Hz), 4.25–4.32 (m, 1H), 4.38–4.44 (m, 1H), 5.16 (s, 2H), 6.99 (dd, 2H, $^3J_{HH}$ 8.2, $^3J_{HF}$ 8.2 Hz)m, 3H) 7.11 (dd, 2H, $^3J_{HH}$ 8.2, $^4J_{HF}$ 5.4 Hz) and 7.28–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 33.9 (CH_2), 40.9 (CH), 43.9 (CH), 44.4 (CH_2), 46.8 (CH_2), 54.8 (CH_3), 67.2 (CH_2), 67.8 (CH_2), 115.6 (d, $^2J_{CF}$ 21.5 Hz, CH), 127.8 (CH), 127.9 (CH), 128.4 (CH), 128.5 (d, $^3J_{CF}$ 7.6 Hz, CH), 136.6 (C), 138.2 (C), 155.1 (C=O), 155.4 (C=O) and 161.5 (d, $^1J_{CF}$ 244.1 Hz, C); MS (ESI$^+$, *m*/*z*): 440 [(M+K)$^+$, 32], 424 [(M+Na)$^+$, 100] and 402 [(M+H)$^+$, 8]. Anal. calcd (%) for $C_{22}H_{24}FNO_5$: C, 65.82; H, 6.03; N, 3.49. Found: C, 65.6; H, 6.3; N, 3.7. Determination of the ee by HPLC analysis: 28°C, hexane/*i*-propanol (90:10), 0.8 cm^3 min^{-1}, Rs 3.0. **(3*S*,4*R*)-(−)-2d**, HPLC: t_R 18.24 min, $[\alpha]_D^{18}$ −0.87 (*c* 1.15, MeOH), ee 32%; **(3*R*,4*S*)-(+)-2d**, HPLC: t_R 15.14 min, $[\alpha]_D^{18}$ +3.43 (*c* 0.57, MeOH), ee 88%.

4.3.6. (±)-*trans*-*N*-Benzyloxycarbonyl-3-benzyloxycabonyloxymethyl-4-(4′-fluorophenyl)piperidine *trans*-2e. Hygroscopic solid. IR (KBr): *v* 3065, 3033, 2946, 2858, 1748, 1699, 1604, 1507, 1473, 1394 and 1262 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.60–1.75 (m, 2H), 1.98–2.07 (m, 1H), 2.57 (td, 1H, $^3J_{HH}$ 4.0, $^3J_{HH}$ 12.0 Hz), 2.72–2.84 (m, 2H), 3.73 (dd, 1H, $^3J_{HH}$ 6.5, $^2J_{HH}$ 10.8 Hz), 3.94 (dd, 1H, $^3J_{HH}$ 2.8, $^2J_{HH}$ 10.8 Hz), 4.23–4.31 (m, 1H), 4.37–4.46 (m, 1H), 5.11 (s, 2H), 5.17 (s, 2H), 6.97 (dd, 2H, $^3J_{HH}$ 8.8, $^3J_{HF}$ 8.8 Hz) 7.07 (dd, 2H, $^3J_{HH}$ 8.8, $^4J_{HF}$ 5.4 Hz) and 7.31–7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 33.8 (CH_2), 40.9 (CH), 43.7 (CH), 44.3 (CH_2), 46.8 (CH_2), 67.1 (CH_2), 67.7 (CH_2), 115.7 (d, $^2J_{CF}$ 21.5 Hz, CH), 127.8 (CH), 127.9 (CH), 128.2 (CH), 128.4 (CH), 128.5 (d, $^3J_{CF}$ 7.9 Hz, CH), 134.9 (C), 136.6 (C), 138.2 (C), 154.7 (C=O), 155.0 (C=O) and 161.7 (d, $^1J_{CF}$ 244.3 Hz, C); MS (ESI$^+$, *m*/*z*): 516 [(M+K)$^+$, 63], 500 [(M+Na)$^+$, 100] and 478 [(M+H)$^+$, 2]. Anal. calcd (%) for $C_{28}H_{28}FNO_5$: C, 70.43; H, 5.91; N, 2.93. Found: C, 70.7; H, 5.7; N, 3.1. Determination of the ee by HPLC analysis: 28°C, hexane/*i*-propanol (90;10), 0.8 cm^3 min^{-1}, Rs 4.7. **(3*S*,4*R*)-(−)-2e**, HPLC: t_R 27.41 min, $[\alpha]_D^{18}$ −0.75 (*c* 1.0, MeOH), ee 41%; **(3*R*,4*S*)-(+)-2e**, HPLC: t_R 20.27 min, $[\alpha]_D^{18}$ +2.94 (*c* 0.74, MeOH), ee 92%.

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