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Enzymatic Preparation of Novel Aminoalkylpyridines using Lipases in Organic Solvents

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Abstract: A wide range of novel, enantiomerically pure 4-chloro(amino)pyridine derivatives has been synthesised through a chemoenzymatic approach, *Candida antarctica* lipase B (CAL-B) and *Pseudomonas cepacia* lipase (PSL) being found to be excellent biocatalysts for the preparation of new and interesting amines and amides in enantiomerically pure form through enzymatic aminolysis reactions. A study of the enzymatic reactivity of CAL-B and PSL has been done in the resolution of a library of amine structures in an attempt to rationalise the experimental results obtained in their enzymatic kinetic resolution mediated by lipases.

Keywords: amines; enzymatic aminolysis; kinetic resolution; lipases; pyridine

Introduction

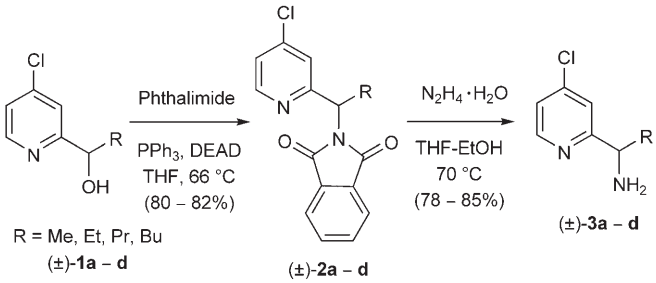
Enantiomerically pure amines constitute a valuable group of organic compounds because of their interesting possibilities in the preparation of products with remarkable biological properties and industrial applications.[1] On the other hand, the pyridine core has attracted much attention since it is present in a variety of compounds with outstanding biological activities.[2] Many different chemical methods are currently accepted as adequate strategies for the preparation of these chiral building blocks, for example, asymmetric hydrogenation of imines[3] or the hydroamination of alkenes,[4] but nowadays biocatalysis offers clean and ecological routes to achieve the production of amines in optically active form and with high yields, such as lipase-catalysed resolution reactions,[5] reductive amination processes using transaminases,[6] deracemisation of primary, secondary or recently tertiary amines combining evolved amino oxidases and convenient chemical reducing agents,[7] and other methods that have attracted great attention for the industrial sector.[8]

Among these methods, enzymatic kinetic resolutions of racemates still have a remarkable importance because they proceed under environmentally friendly conditions with high stereoselectivities, at the same time that the easy handling of the reactions and the simple isolation of the final products represent some of its advantages.[9] In this manner only a few examples have appeared in the literature about the lipase-catalysed resolution of aminopyridine derivatives using *Candida antarctica* lipase B (CAL-B) as biocatalyst in the enantioselective enzymatic acetylation of the corresponding racemic amines affording amides and amines in optically active form.[10] This biocatalyst is so far one of the most effective catalysts in the preparation of enantiomerically pure nitrogenated compounds.[11]

Recently in our research group we have studied the enzymatic resolution of 4-chloro-2-(1-hydroxyalkyl)-pyridines and 4-chloro-3-(1-hydroxyalkyl)pyridines through transesterification processes, where *Pseudomonas cepacia* lipase (PSL) has shown excellent stereoselectivities towards the C-2 substituted derivatives,[12] meanwhile CAL-B has been found to be the best lipase for the C-3 substituted derivatives.[13] Herein, we report the development of a new chemoenzymatic route for the synthesis of 2-(1-aminoalkyl)-4-chloropyridines and 3-(1-aminoalkyl)-4-chloropyridines testing different lipases and enzymatic reaction conditions in order to compare the behaviour of the alcohol and amine derivatives, and finally to achieve interesting optically active compounds that present the advantage of possessing a chloro functionality, which is easy to modify allowing the preparation of 4-dimethylamino derivatives that could be used for asymmetric catalytic processes or resin supported reagents to use in solid phase processes and others.

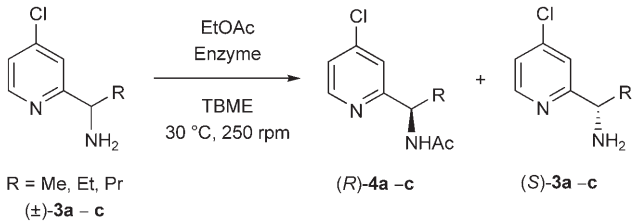
Results and Discussion

Alcohols **1a–d** have been used as starting materials for the synthesis of racemic amines **3a–d** through a two-step route that involves the Mitsunobu inversion reactions with phthalimide and later deprotection processes of the corresponding amide **2a–d** using hydrazine, obtaining the corresponding 2-(1-aminoalkyl)-4-chloropyridines with good overall yields in short reaction times (Scheme 1).



Scheme 1. Chemoenzymatic synthesis of racemic **3a–d**.

Initially 2-(1-aminoethyl)-4-chloropyridine (**3a**) was considered as the model substrate and its enzymatic resolution was attempted with 5 equivalents of ethyl acetate (EtOAc) as acyl donor using different lipases such as *Candida antarctica* lipase A (CAL-A), CAL-B and PSL that were tested at 30 °C (Scheme 2 and Table 1). Compound **3a** showed a slow reaction rate and a poor enantioselectivity in the enzymatic reaction employing CAL-A (entry 1), however both CAL-B and PSL afforded the enantiomerically pure (*R*)-amide **4a** and (*S*)-amine **3a**, observing shorter reaction times for CAL-B (entry 2) than for the corresponding process with PSL as biocatalyst (entry 3). In both cases the optically active amine and amide were recovered with high isolated yields.



Scheme 2. Kinetic resolution of **3a–c** by lipase-catalysed aminolysis reactions using EtOAc.

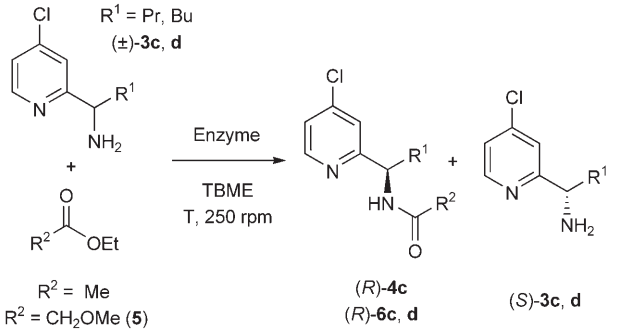
With the best results on hand we extended the enzymatic study to the racemates **3b** and **3c** using CAL-B and PSL, in this manner 2-(1-aminopropyl)-4-chloropyridine (**3b**) was enantioselectively acetylated by both lipases (entries 4 and 5), observing longer reaction times in comparison with **3a** that possesses a less hindered substitution in the C-2 position of the pyridine ring. The increase of the substituent size led to a dramatic decrease of the selectivity of the process (entries 6 and 7), and inclusively an enzyme such as CAL-A that has shown interesting activities towards substrates with highly hindered positions did not shown improvements in the kinetic resolution of **3c** (entry 8).[14]

At this point we decided to turn our attention to other non-activated esters such as ethyl methoxyacetate (**5**) that has recently allowed the achievement of high enantioselectivities in the resolution of primary amino groups of bulky substrates (Scheme 3).[16] Using PSL and 5 equivalents of **5** at 30 °C the *E* value increased up to 114, isolating after common work-up substrate and product with more than 90% *ee* (entry 1, Table 2). Trying to decrease the reaction time, the process was carried out at higher temperatures or using a larger excess of **5** (entries 2 and 3), finding the best reaction conditions when 10 equivalents of ethyl methoxyacetate were used. These conditions allowed the recovery of the (*R*)-amide and the

Table 1. Kinetic resolution of amines **3a–c** through lipase-catalysed acylation using 5 equivalents of EtOAc in TBME at 30 °C. Isolated yields in brackets.

Entry	Amine	Enzyme	*t* [h]	ee_S [%][a]	ee_P [%][b]	c [%][c]	E[d]
1	**3a**	CAL-A	168	1	5	17	1
2	**3a**	CAL-B	4	>99 (81)	>99 (99)	50	>200
3	**3a**	PSL	32	>99 (88)	>99 (98)	50	>200
4	**3b**	CAL-B	31.5	>99 (89)	>99 (90)	50	>200
5	**3b**	PSL	48	95	>99	49	>200
6	**3c**	CAL-B	72	10	74	12	7
7	**3c**	PSL	72	29	96	23	68
8	**3c**	CAL-A	72	2	58	3	4

[a] Determined by GC.
[b] Determined by GC or HPLC.
[c] $c = ee_S/(ee_S + ee_P)$.
[d] $E = \ln[(1-c)\times(1-ee_S)]/\ln[(1-c)\times(1+ee_S)]$.[15]

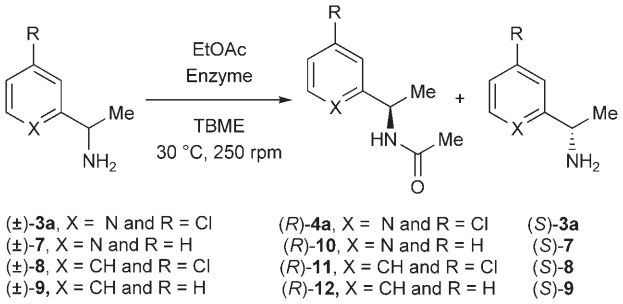


Scheme 3. Kinetic resolution of **3c–d** by lipase-catalysed aminolysis using different esters in TBME.

(*S*)-substrate in very high optical purities and isolated yields just after 1 day of reaction at 30 °C.

Similar results were observed with compound **3d** in the enzymatic reactions with PSL (entries 4 and 5), which led to enantiomerically enriched amine and amide, achieving an $E=102$ using 10 equivalents of **5** at 30 °C and isolating the optically active products in high yields. In this manner the enzymatic resolutions of a wide set of 2-(1-aminoalkyl)-4-chloropyridines has been satisfactorily achieved obtaining in all cases the (*R*)-amides and the (*S*)-amines with enantioselectivities depending on the type and amount of acyl donor and also the temperature of the processes. The stereochemistries of amines **3a–d** were assigned converting them in the corresponding amides using the (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride, demonstrating the (*S*)-configuration of the amines and obviously then the (*R*)-configuration of the amides **4a**, **4b** and **6c**, **6d**,[17] which is in good agreement with Kazlauskas' rule.[18]

Once that the enzymatic resolution of 2-(1-aminoalkyl)-4-chloropyridine derivatives was successfully developed we decided to study the behaviour of the lipases for which better results have been shown in the kinetic resolution of these aminopyridines (PSL and CAL-B) towards a panel of amines that differ from the initial ones in some structural features such as the presence of a benzene or a pyridine ring, or bearing a chloro or hydrogen atom in the 4-position of the cyclic fragment. In this manner we have shown the success of the approach for the resolution of the mentioned substrates (Scheme 4).



Scheme 4. Enzymatic kinetic resolution of racemic **3a**, **7**, **8** and **9** using CAL-B and PSL.

On the basis of the excellent results previously obtained for the 2-(1-aminoethyl)-4-chloropyridine (**3a**), the selected reaction conditions were 5 equivalents of EtOAc in TBME at 30 °C, and the processes were carefully followed by GC analysis, summarising the experimental results in Table 3. In all cases the amides were recovered in enantiomerically pure form demonstrating for both lipases an excellent stereoselectivity. Heterocyclic compounds **3a** and **7** (entries 1–4) showed faster reaction rates compared with the substrates that possess a benzene ring (**8** and **9**, entries 5–8), moreover CAL-B acted with a significantly higher activity than that showed by PSL, the enzyme that presented a poor reactivity in the enzymatic resolution of benzene derivatives. Also remarkable is the fact that *m*-chloro-α-methylbenzylamine (**8**) is so far the least reactive substrate of all of this panel of compounds.

Last of all, we decided to prepare and enzymatically resolve 3-(1-aminoethyl)-4-chloropyridine (**15**), a compound bearing the amino functionality in the C-3-position of the pyridine ring. The synthetic approach

Table 2. Kinetic resolution of amines **3c-d** through PSL-catalysed aminolysis using ethyl methoxyacetate (**5**) in TBME. Isolated yields in brackets.

Entry	Amine	**5** [equivs.]	T [°C]	t [h]	ee_S [%][a]	ee_P [%][b]	c [%][c]	E[d]
1	**3c**	5	30	48	97	93	51	114
2	**3c**	5	45	43	>99	72	58	31
3	**3c**	10	30	24	98 (83)	93 (91)	51	129
4	**3d**	5	30	48	87	92	49	70
5	**3d**	10	30	25.5	95 (84)	93 (81)	51	102

[a] Determined by GC.
[b] Determined by GC or HPLC.
[c] $c=ee_S/(ee_S+ee_P)$.
[d] $E=\ln[(1-c)\times(1-ee_S)]/\ln[(1-c)\times(1+ee_S)]$.[15]

Table 3. Kinetic resolution of amines **3a** and **7–9** through lipase-mediated resolution using EtOAc in TBME at 30 °C.

Entry	Amine	Enzyme	t [h]	ee_S [%][a]	ee_P [%][a]	c [%][b]	E[c]
1	**3a**	CAL-B	4	>99	>99	50	>200
2	**3a**	PSL	32	>99	>99	50	>200
3	**7**	CAL-B	6	>99	>99	50	>200
4	**7**	PSL	32	91	>99	48	>200
5	**8**	CAL-B	72	98	>99	50	>200
6	**8**	PSL	32	3	>99	3	>200
7	**9**	CAL-B	32	>99	>99	50	>200
8	**9**	PSL	32	10	>99	10	>200

[a] Determined by GC.
[b] $c = ee_S/(ee_S+ee_p)$.
[c] $E = \ln[(1-c)\times(1-ee_S)]/\ln[(1-c)\times(1+ee_S)]$.[15]

was based on the method previously described by us, using 4-chloro-3-(1-hydroxyethyl)pyridine as starting material[13] which, by a Mitsunobu inversion reaction with phthalimide and consequent deprotection using hydrazine monohydrate in a refluxing mixture of THF and EtOH, allowed the isolation of **15** in good overall yield (Scheme 5).

Attempts for the enzymatic resolution of racemic amine **15** were initially done by varying the type of biocatalysts (Table 4). PSL did not shown any activity

Table 4. Kinetic resolution of **15** through lipase-catalysed acylation in TBME at 30 °C.

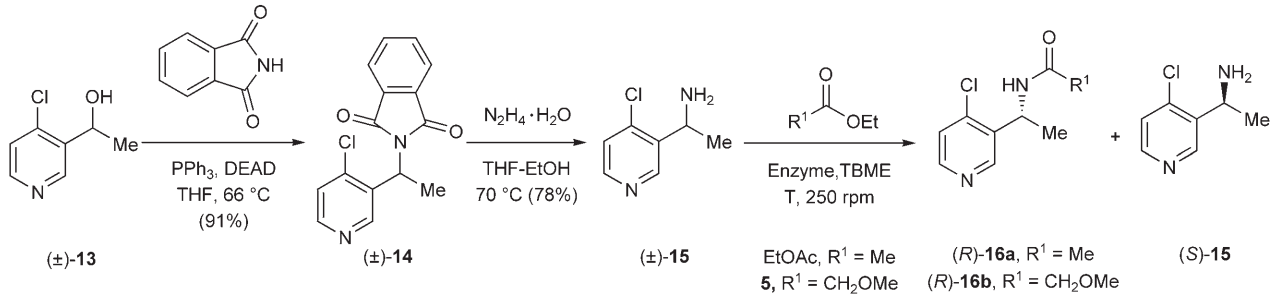
Entry	Acyl donor [equivs.]	Enzyme	t [h]	ee_S [%][a]	ee_P [%][a]	c [%][b]	E[c]
1	EtOAc	PSL	133	–	–	–	–
2	EtOAc	CAL-B	87.5	92	>99	48	>200
3	**5**	CAL-B	13.5	>99	>99	50	>200

[a] Determined by HPLC.
[b] $c = ee_S/(ee_S+ee_p)$.
[c] $E = \ln[(1-c)\times(1-ee_S)]/\ln[(1-c)\times(1+ee_S)]$.[15]

(entry 1), meanwhile CAL-B reacted with a complete stereopreference in the acetylation of the (*R*)-enantiomer with EtOAc at 30 °C in TBME (entry 2). In order to reduce the reaction time and develop a more efficient process, ethyl methoxyacetate was used as acyl donor obtaining the product (*R*)-**16** and substrate (*S*)-**15** both enantiomerically pure after just 13.5 h (entry 3). The stereochemical preferences were assigned by comparing the optical rotation of the amine **15** obtained by the enzymatic resolution of the racemic mixture and the one obtained by chemical methods starting from the (*S*)-alcohol obtained by lipase-mediated resolution of the corresponding racemate **13**,[13] which was subjected to Mitsunobu inversion using DEAD, PPh_3 and phthalimide and later deprotection with hydrazine. The opposite sign of the optical rotation for both compounds indicated the (*S*)-configuration of the remaining amine obtained by the enzymatic kinetic resolution of the amine **15**.

Conclusions

In summary, we have developed an efficient methodology for the chemical synthesis and enzymatic resolution of 2- or 3-(1-aminoalkyl)-4-chloropyridines, CAL-B and PSL being found to be excellent biocatalysts depending on the amine's structure. Additional examples of enzymatic kinetic resolutions mediated by lipases have been shown, trying to find explanations for the different behaviour of lipases towards



Scheme 5. Chemical synthesis and enzymatic kinetic resolution of compound **15**.

these substrates, observing the outstanding effect of the nitrogen atom in pyridine structures with respect to similar cyclic rings. Use of computational methods should allow an understanding of mechanistic aspects related to the different enzymatic processes and give some insight about the favoured reaction pathways.

Experimental Section

General Remarks

Candida antarctica lipase type B (CAL-B, Novozyme 435, 7300 PLU/g) was a gift from Novo Nordisk Co. *Candida antarctica* lipase type A (CAL-A, Chirazyme L-5, c-f, lyophilized, 1000 U/g using tributyrin) was acquired from Roche. *Pseudomonas cepacia* lipase (PSL-C, 783 U/g) was obtained from Amano Pharmaceutical Co. Chemical reagents were commercial products from Aldrich, Fluka or Acros. Solvents were distilled over an appropriate desiccant under nitrogen. Flash chromatographies were performed using silica gel 60 (230–240 mesh). Gas chromatography (GC) was carried out with flame ionisation detection (FID) using nitrogen as carrier gas and an RT-β-Dexe capillary column (30 m × 0.25 mm × 0.25 μm) or a Chiralsil-Dex-CB (25 m × 0.25 mm × 0.25 μm). High performance liquid chromatography (HPLC) analyses were carried out in a Hewlett Packard 1100 chromatograph with UV detector at 210 nm using a Daicel CHIRALCEL OD or OB-H column (25 cm × 4.6 mm I.D.), varying the conditions depending on the specific substrate. Melting points were taken on samples in open capillary tubes and are uncorrected. IR spectra were recorded using NaCl plates or KBr pellets in a Perkin–Elmer 1720-X F7. ^{1}H, ^{13}C NMR, DEPT, ^{1}H-^{1}H homonuclear experiments, and ^{1}H-^{13}C heteronuclear experiments were obtained using AC-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz), DPX 300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) or AV-600 (^{1}H, 600.15 MHz and ^{13}C, 150.9 MHz) spectrometers. The chemical shifts are given in delta (δ) values and the coupling constants (*J*) in Hertz (Hz). ESI$^+$ using an HP 1100 chromatograph mass detector were used to record mass spectra (MS). Microanalyses were performed on a Perkin–Elmer model 2400 instrument. Measurement of the optical rotation was done in a Perkin–Elmer 241 polarimeter.

General Procedure for the Mitsunobu Reaction of Alcohols of 1a–d and 13

To a solution of the corresponding alcohol[19] (4.32 mmol) in dry THF (22 mL) were successively added PPh_3 (1.36 g, 5.18 mmol) and phthalimide (635 mg, 4.32 mmol) under a nitrogen atmosphere. The resulting solution was cooled to 0 °C and DEAD (0.82 mL, 5.18 mmol) dissolved in dry THF (6.8 mL) was added. The mixture was left to warm to room temperature and stirred for 2 h, not detecting after this time starting material by TLC analysis. The organic solvent was evaporated under reduced pressure and the crude mateiral obtained purified by flash chromatography (25% EtOAc/hexane for **2a–d** or gradient eluent 40–60% EtOAc/hexane for **14**) isolating the corresponding compounds as white solids; yield: 80–91%.

***N*-[1-(4-Chloropyridin-2-yl)ethyl]phthalimide (2a):** Yield: 1.00 g (81%); R_f (25% EtOAc/hexane): 0.28; mp 118–120 °C; IR (KBr): ν = 3425, 2361, 2315, 1710, 1578, 1467, 1383, 879, 714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 1.96 (d, 3H, H-8, $^3J_{H,H}$ = 7.34 Hz), 5.64 (q, 1H, H-7, $^3J_{H,H}$ = 7.34 Hz), 7.20–7.23 (m, 1H, H-5), 7.45–7.46 (m, 1H, H-3), 7.74–7.77 (m, 2H, H-12), 7.86–7.89 (m, 2H, H-13), 8.45 (d, 1H, H-6, $^3J_{H,H}$ = 5.25 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 16.6 (C-8), 50.1 (C-7), 121.3 (C-3), 122.6 (C-5), 123.3 (2C, C-12), 131.2 (2C, C-11), 133.9 (2C, C-13), 144.6 (C-4), 150.0 (C-6), 160.5 (2C, C-10), 167.9 (C-2); MS (ESI$^+$): *m*/*z* = 289 [(M^{37}Cl + H)$^+$, 35%], 287 [(M^{35}Cl + H)$^+$, 100%]; anal. calcd. (%) for $C_{15}H_{11}ClN_2O_2$: C 62.84, H 3.87, N 9.77; found: C 62.5, H 3.9, N 9.7.

***N*-[1-(4-Chloropyridin-2-yl)propyl]phthalimide (2b):** Yield: 1.07 g (82%); R_f (25% EtOAc/hexane): 0.28; mp 91–93 °C; IR (KBr): ν = 3463, 2971, 1772, 1716, 1576, 1558, 1466, 1386, 721 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 1.03 (t, 3H, H-9, $^3J_{H,H}$ = 7.35 Hz), 2.37–2.61 (m, 2H, H-8), 5.39 (dd, 1H, H-7, $^3J_{H,H}$ = 5.84 Hz, $^3J_{H,H}$ = 10.55 Hz), 7.18–7.21 (m, 1H, H-5), 7.46–7.47 (m, 1H, H-3), 7.73–7.76 (m, 2H, H-13), 7.85–7.88 (m, 2H, H-14), 8.44 (d, 1H, H-6, $^3J_{H,H}$ = 5.28 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 11.2 (C-9), 23.4 (C-8), 57.1 (C-7), 121.9 (C-3), 122.8 (C-5), 123.5 (2C, C-13), 131.7 (2C, C-12), 134.0 (2C, C-14), 144.6 (C-4), 149.9 (C-6), 160.2 (2C, C-11), 168.3 (C-2); MS (ESI$^+$): *m*/*z* = 303 [(M^{37}Cl + H)$^+$, 36%], 301 [(M^{35}Cl + H)$^+$, 100%]; anal. calcd. (%) for $C_{16}H_{13}ClN_2O_2$: C 63.90, H 4.36, N 9.31; found: C 63.9, H 4.3, N 9.3.

***N*-[1-(4-Chloropyridin-2-yl)butyl]phthalimide (2c):** Yield: 1.09 g (80%); R_f (25% EtOAc/hexane): 0.32; mp 119–120 °C; IR (KBr): ν = 3467, 2962, 1771, 1714, 1576, 1558, 1467, 1385, 1074, 918, 722 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 0.99 (t, 3H, H-10, $^3J_{H,H}$ = 7.32 Hz), 1.35–1.47 (m, 2H, H-9), 2.21–2.34 (m, 1H, H-8), 2.49–2.62 (m, 1H, H-8), 5.47 (dd, 1H, H-7, $^3J_{H,H}$ = 5.39 Hz, $^3J_{H,H}$ = 10.79 Hz), 7.17 (dd, 1H, H-5, $^3J_{H,H}$ = 5.39 Hz, $^4J_{H,H}$ = 1.92 Hz), 7.44–7.45 (m, 1H, H-3), 7.70–7.73 (m, 2H, H-14), 7.74–7.81 (m, 2H, H-15), 8.42 (d, 1H, H-6, $^3J_{H,H}$ = 5.39 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.5 (C-10), 19.8 (C-9), 32.1 (C-8), 55.2 (C-7), 121.9 (C-3), 122.7 (C-5), 123.3 (2C, C-14), 131.8 (2C, C-13), 134.0 (2C, C-15), 144.5 (C-4), 150.0 (C-6), 160.4 (2C, C-12), 168.2 (C-2); MS (ESI$^+$): *m*/*z* = 317 [(M^{37}Cl + H)$^+$, 37%], 315 [(M^{35}Cl + H)$^+$, 100%]; anal. calcd. (%) for $C_{17}H_{15}ClN_2O_2$: C 64.87, H 4.80, N 8.90; found: C 64.8, H 4.9, N 8.9.

***N*-[1-(4-Chloropyridin-2-yl)pentyl]phthalimide (2d):** Yield: 1.15 g (81%); R_f (25% EtOAc/hexane): 0.31; mp 101–103 °C; IR (KBr): ν = 3461, 2961, 2932, 2862, 1715, 1576, 1558, 1464, 1386, 1067, 722 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 0.89 (t, 3H, H-11, $^3J_{H,H}$ = 6.93 Hz), 1.33–1.43 (m, 4H, H-10, H-9), 2.26–2.37 (m, 1H, H-8), 2.49–2.62 (m, 1H, H-8), 5.45 (dd, 1H, H-7, $^3J_{H,H}$ = 5.39 Hz, $^3J_{H,H}$ = 10.79 Hz), 7.16–7.18 (m, 1H, H-5), 7.44 (d, 1H, H-3, $^4J_{H,H}$ = 1.92 Hz), 7.70–7.73 (m, 2H, H-15), 7.83–7.86 (m, 2H, H-16), 8.42 (d, 1H, H-6, $^3J_{H,H}$ = 5.19 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.9 (C-11), 22.2 (C-10), 28.8 (C-9), 29.8 (C-8), 55.6 (C-7), 121.9 (C-3), 122.7 (C-5), 123.3 (2C, C-15), 131.8 (2C, C-14), 134.0 (2C, C-16), 144.5 (C-4), 150.0 (C-6), 160.4 (2C, C-13), 168.2 (C-2); MS (ESI$^+$): *m*/*z* = 331 [(M^{37}Cl + H)$^+$, 34%], 329 [(M^{35}Cl + H)$^+$, 100%]; anal. calcd.

(%) for $C_{18}H_{17}ClN_2O_2$: C 65.75, H 5.21, N 8.52; found: C 65.8, H 5.2, N 8.5.

***N*-[1-(4-Chloropyridin-3-yl)ethyl]phthalimide (14):** Yield: 1.12 g (91%); R_f (60% EtOAc/hexane): 0.28; mp 143–144 °C; IR (KBr): $\nu = 3374, 2942, 2356, 1713, 1660, 1552, 1385, 1222, 1083\ cm^{-1}$; ^1H NMR ($CDCl_3$, 300.13 MHz): $\delta =$ 1.83 (d, 3H, H-8, $^3J_{H,H} = 7.20$ Hz), 5.74 (q, 1H, H-7, $^3J_{H,H} =$ 7.20 Hz), 7.17–7.19 (m, 1H, H-5), 7.60–7.63 (m, 2H, H-12), 7.70–7.73 (m, 2H, H-13$_3$), 8.34 (d, 1H, H-6, $^3J_{H,H} = 5.22$ Hz), 8.89 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 17.2$ (C-8), 45.0 (C-7), 123.2 (2C, C-12), 124.3 (C-5), 131.6 (2C, C-11), 132.7 (C-3), 134.1 (2C, C-13), 143.2 (C-4), 149.6 (C-2), 150.9 (C-6), 167.5 (2C, C-10); MS (ESI$^+$): $m/z = 289$ [$(M^{37}Cl+H)^+$, 34%], 287 [$(M^{35}Cl+H)^+$, 100%]; anal. calcd. (%) for $C_{15}H_{11}ClN_2O_2$: C 62.84, H 3.87, N 9.77; found: C 62.9, H 3.9 N, 9.8.

General Procedure for the Deprotection of Compounds 2a–d and 14

To a solution of **2a–d** or **14** (3.34 mmol) in THF (48 mL) and EtOH (7.6 mL), hydrazine monohydrate (1.2 mL, 25.1 mmol) was added and the mixture stirred at 70 °C for 2 h. The white suspension formed after this time was filtered and washed with THF, the organic solvent evaporated under reduced pressure obtaining a crude that was purified by flash chromatography (100% MeOH for **3a–d** or 50–60% MeOH/EtOAc for **15**), isolating the corresponding amines as oils; yield: 78–85%.

4-Chloro-2-(1-aminoethyl)pyridine (3a): Yield: 382 mg (73%); R_f (100% MeOH): 0.20; IR (NaCl): $\nu = 3361, 3284, 2964, 2928, 2330, 1575, 1553, 1453, 1392, 1096, 827\ cm^{-1}$; ^1H NMR ($CDCl_3$, 300.13 MHz): $\delta = 1.30$ (d, 3H, H-8, $^3J_{H,H} =$ 6.63 Hz), 1.79 (br s, 2H, NH_2), 4.02 (q, 1H, H-7, $^3J_{H,H} =$ 6.63 Hz), 7.04 (dd, 1H, H-5, $^3J_{H,H} = 5.22$, $^4J_{H,H} = 1.91$ Hz), 7.24 (d, 1H, H-3, $^4J_{H,H} = 1.91$ Hz), 8.32 (d, 1H, H-6, $^3J_{H,H} =$ 5.22 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 24.2$ (C-8), 52.3 (C-7), 120.5 (C-3), 122.1 (C-5), 144.5 (C-4), 150.0 (C-6), 167.5 (C-2); MS (ESI$^+$): $m/z = 159$ [$(M^{37}Cl+H)^+$, 34%], 157 [$(M^{35}Cl+H)^+$, 100%]; anal. calcd. (%) for $C_7H_9ClN_2$: C 56.68, H 5.79, N 17.89; found: C 56.7, H 5.8, N 17.9; $[\alpha]_D^{20}$: −20.4° (*c* 0.5, $CHCl_3$) for the (*S*)-enantiomer with >99% *ee* after lipase-kinetic resolution.

4-Chloro-2-(1-aminopropyl)pyridine (3b): Yield: 443 mg (78%); R_f (100% MeOH): 0.28; IR (NaCl): $\nu = 3364, 2964, 2932, 1654, 1576, 1558, 1458, 1394, 1101, 826, 704\ cm^{-1}$; ^1H NMR ($CDCl_3$, 300.13 MHz): $\delta = 0.94$ (t, 3H, H-9, $^3J_{H,H} =$ 7.46 Hz), 1.73–1.89 (m, 2H, H-8), 2.54 (br s, 2H, NH_2), 3.95 (t, 1H, H-7, $^3J_{H,H} = 6.74$ Hz), 7.04 (dd, 1H, H-5, $^3J_{H,H} = 5.25$, $^4J_{H,H} = 1.80$ Hz), 7.37 (d, 1H, H-3, $^4J_{H,H} = 1.80$ Hz), 8.49 (d, 1H, H-6, $^3J_{H,H} = 5.25$ Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta =$ 10.9 (C-9), 31.7 (C-8), 58.8 (C-7), 121.8 (C-3), 122.6 (C-5), 144.7 (C-4), 150.4 (C-6), 167.1 (C-2); MS (ESI$^+$): $m/z = 173$ [$(M^{37}Cl+H)^+$, 31%], 171 [$(M^{35}Cl+H)^+$, 100%]; anal. calcd. (%) for $C_8H_{11}ClN_2$: C 56.31, H 6,50, N 16.42; found: C 56.2, H 6.3, N 16.3; $[\alpha]_D^{20}$: −5.1° (*c* 0.6, $CHCl_3$) for the (*S*)-enantiomer with >99% *ee* after lipase-kinetic resolution.

4-Chloro-2-(1-aminobutyl)pyridine (3c): Yield: 524 mg (85%); R_f (100% MeOH): 0.38; IR (NaCl): $\nu = 3443, 2955, 2909, 1653, 1559, 1338, 1110\ cm^{-1}$; ^1H NMR ($CDCl_3$, 300.13 MHz): $\delta = 0.88$ (t, 3H, H-10, $^3J_{H,H} = 7.32$ Hz), 1.22–139 (m, 2H, H-9), 1.56–1.74 (m, 2H, H-8), 2.10 (br s, 2H, NH_2), 3.91 (t, 1H, H-7, $^3J_{H,H} = 6.65$ Hz), 7.12 (dd, 1H, H-5, $^3J_{H,H} = 5.19$, $^4J_{H,H} = 1.92$ Hz), 7.28 (d, 1H, H-3, $^4J_{H,H} =$ 1.92 Hz), 8.40 (d, 1H, H-6, $^3J_{H,H} = 5.19$ Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 13.8$ (C-10), 19.3 (C-9), 40.5 (C-8), 56.7 (C-7), 121.3 (C-3), 122.1 (C-5), 144.3 (C-4), 150.0 (C-6), 166.8 (C-2); MS (ESI$^+$): $m/z = 187$ [$(M^{37}Cl+H)^+$, 33%], 185 [$(M^{35}Cl+H)^+$, 100%]; anal. calcd. (%) for $C_9H_{13}ClN_2$: C 58.54, H 7.10, N 15.17; found: C 58.5, H 7.2, N 15.2; $[\alpha]_D^{20}$: −9.1° (*c* 0.4, $CHCl_3$) for the (*S*)-enantiomer with 98% *ee* after lipase-kinetic resolution.

4-Chloro-2-(1-aminopentyl)pyridine (3d): Yield 564 mg (85%); R_f (100% MeOH): 0.32; IR (NaCl): $\nu = 3364, 2930, 2858, 1654, 1576, 1558, 1458, 1394, 1100, 825, 704\ cm^{-1}$; ^1H NMR ($CDCl_3$, 300.13 MHz): $\delta = 0.91$ (t, 3H, H-11, $^3J_{H,H} = 6.8$ Hz), 1.32–1.38 (m, 4H, H-10+H-9), 1.67–1.84 (m, 2H, H-8), 2.03 (br s, 2H, NH_2), 3.96 (t, 1H, H-7, $^3J_{H,H} =$ 6.68 Hz), 7.19 (dd, 1H, H-5, $^3J_{H,H} = 5.28$, $^4J_{H,H} = 0.89$ Hz), 7.35 (s, 1H, H-3), 8.48 (d, 1H, H-6, $^3J_{H,H} = 5.28$ Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 13.8$ (C-11), 22.5 (C-10), 28.3 (C-9), 38.1 (C-8), 57.0 (C-7), 121.2 (C-3), 122.0 (C-5), 144.3 (C-4), 150.0 (C-6), 166.9 (C-2); MS (ESI$^+$): $m/z = 201$ [$(M^{37}Cl+H)^+$, 33%], 199 [$(M^{35}Cl+H)^+$, 100%]; anal. calcd. (%) for $C_{10}H_{15}ClN_2$: C 60.45, H 7.61, N 14.10; found: C 60.5, H 7.6, N 14.1; $[\alpha]_D^{20}$: −7.9° (*c* 0.5, $CHCl_3$) for the (*S*)-enantiomer with 95% *ee* after lipase-kinetic resolution.

4-Chloro-3-(1-aminoethyl)pyridine (15): Yield: 408 mg (78%); R_f (50% MeOH/EtOAc): 0.23; IR (NaCl): $\nu = 3358, 2971, 1576, 1556, 1468, 1408, 1076, 825, 701\ cm^{-1}$; ^1H NMR ($CDCl_3$, 300.13 MHz): $\delta = 1.37$ (d, 1H, H-8, $^3J_{H,H} = 6.57$ Hz), 2.30 (br s, 2H, NH_2), 4.46 (q, 1H, H-7, $^3J_{H,H} = 6.57$ Hz), 7.18 (d, 1H, H-5, $^3J_{H,H} = 5.28$ Hz), 8.28 (d, 1H, H-6, $^3J_{H,H} =$ 5.28 Hz), 8.68 (s, 1H, H-2$_2$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 23.1$ (C-8), 46.3 (C-7), 124.2 (C-5), 139.5 (C-3), 142.2 (C-4), 148.4 (C-6), 148.4 (C-2); MS (ESI$^+$): $m/z = 159$ [$(M^{37}Cl+H)^+$, 33%], 157 [$(M^{35}Cl+H)^+$, 100%]; anal. calcd. (%) for $C_7H_9ClN_2$: C 53.68, H 5.79, N 17.89; found: C 53.6, H 5.8, N 17.9. $[\alpha]_D^{20}$: −36.3° (*c* 0.5, $CHCl_3$) for the (*S*)-enantiomer with >99% *ee* after lipase-kinetic resolution.

General Procedure for the Kinetic Resolution of Amines 3a–d and 15

To a suspension of the corresponding amine (1.28 mmol) and the enzyme (ratio 1:1 by weight with respect to the amine) in dry TBME (12.8 mL) under a nitrogen atmosphere, ethyl acetate or ethyl methoxyacetate was added (5–10 equivalents with respect to the amine), and the mixture shaken for the required time to achieve a conversion close to 50%. Then the enzyme was filtered, washed with CH_2Cl_2 and the organic solvent was evaporated, obtaining a crude material that was purified by flash chromatography (gradient eluent 10% MeOH/EtOAc to 100% MeOH), isolating the optically active (*R*)-amides and (*S*)-amines (see Table 1, Table 2 and Table 4).

***N*-[1-(4-Chloropyridin-2-yl)ethyl]acetamide (4a):** R_f (100% EtOAc): 0.12; mp 84–85 °C; IR (KBr): $\nu = 3417, 3293, 2360, 1650, 1580, 1555, 1469, 1374\ cm^{-1}$; ^1H NMR ($CDCl_3$, 300.13 MHz): $\delta = 1.49$ (d, 3H, H-8, $^3J_{H,H} = 6.81$ Hz), 2.06 (s, 3H, H-11), 5.09–5.19 (m, 1H, H-7), 6.86 (br s, 1H, NH), 7.24 (dd, 1H, H-5, $^3J_{H,H} = 5.32$, $^4J_{H,H} = 1.97$ Hz), 7.30–7.31 (s, 1H, H-3), 8.46 (d, 1H, H-6, $^3J_{H,H} = 5.32$ Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 22.3$ (C-8), 23.3 (C-11),

49.6 (C-7), 121.8 (C-3), 122.7 (C-5), 144.7 (C-4), 149.8 (C-6), 162.7 (C-10), 167.5 (C-2); MS (ESI$^+$): m/z = 201 [($M^{37}Cl$+H)$^+$, 33%], 199 [($M^{35}Cl$+H)$^+$, 100%]: anal. calcd. (%) for $C_9H_{11}ClN_2O$: C 54.42, H 5.58, N 14.10; found: C 54.4, H 5.6, N 14.2. $[\alpha]_D^{20}$: +62.7° (*c* 0.5, $CHCl_3$) for the (*R*)-enantiomer with >99% *ee* after lipase-kinetic resolution.

***N*-[1-(4-Chloropyridin-2-yl)propyl]acetamide (4b):** R_f (100% EtOAc): 0.15; mp 86–88 °C; IR (KBr): ν = 3305, 2961, 1646, 1539, 1457, 1374, 1289, 1154, 846, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 0.86 (t, 3H, H-9, $^3J_{H,H}$ = 7.44 Hz), 1.77–1.95 (m, 2H, H-8), 2.05 (s, 3H, H-12), 4.99 (dd, 1H, H-7, $^3J_{H,H}$ = 14.78 Hz, $^3J_{H,H}$ = 6.80 Hz), 6.75 (d, 1H, NH, $^3J_{H,H}$ = 6.75 Hz), 7.23 (dd, 1H, H-5, $^3J_{H,H}$ = 5.25, $^4J_{H,H}$ = 1.83 Hz), 7.28 (d, 1H, H-3, $^4J_{H,H}$ = 1.83 Hz), 8.47 (d, 1H, H-6, $^3J_{H,H}$ = 5.25 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 9.8 (C-9), 23.3 (C-12), 29.1 (C-8), 54.9 (C-7), 122.6, 122.7 (2C, C-3+C-5), 144.4 (C-4), 149.9 (C-6), 161.7 (C-11), 169.4 (C-2); MS (ESI$^+$): m/z = 213 [($M^{35}Cl$+H)$^+$, 38%], 215 [($M^{37}Cl$+H)$^+$, 13%], 235 [($M^{35}Cl$+Na)$^+$, 21%], 448 [(2$M^{35}Cl$+H+Na)$^{2+}$, 100%], 450 [($M^{35}Cl$+$M^{37}Cl$+H+Na)$^{2+}$, 68%], 452 [(2$M^{37}Cl$+H+Na)$^{2+}$, 12%]; anal. calcd. (%) for $C_{10}H_{13}ClN_2O$: C 56.47, H 6.16, N 13.17; found: C 56.4, H 6.2, N 13.2; $[\alpha]_D^{20}$: +55.5° (*c* 0.7, $CHCl_3$) for the (*R*)-enantiomer with >99% *ee* after lipase-kinetic resolution.

***N*-[1-(4-Chloropyridin-2-yl)butyl]acetamide (4c):** R_f (100% EtOAc): 0.15; mp 94–96 °C; IR (KBr): ν = 3422, 1653, 1577, 1558, 1540, 1458, 1103 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 0.94 (t, 3H, H-10, $^3J_{H,H}$ = 7.28 Hz), 1.27–134 (m, 2H, H-9), 1.72–1.85 (m, 2H, H-8), 2.06 (s, 3H, H-13), 5.07 (dd, 1H, H-7, $^3J_{H,H}$ = 14.79 Hz, $^3J_{H,H}$ = 6.65 Hz), 6.59 (br s, 1H, NH), 7.23–7.25 (m, 1H, H-5), 7.28–7.31 (m, 1H, H-3), 8.48 (d, 1H, H-6, $^3J_{H,H}$ = 5.25 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.7 (C-10), 18.8 (C-9), 23.4 (C-13), 38.4 (C-8), 53.6 (C-7), 122.5, 122.7 (2C, C-3+C-5), 144.5 (C-4), 150.1 (C-6), 162.4 (C-12), 169.3 (C-2); MS (ESI$^+$): m/z = 229 [($M^{37}Cl$+H)$^+$, 34%], 227 [($M^{35}Cl$+H)$^+$, 100%]; anal. calcd. (%) for $C_{11}H_{15}ClN_2O$: C 58.28, H 6.67, N 12.36; found: C 58.2, H 6.7, N 12.3.

***N*-[1-(4-Chloropyridin-2-yl)butyl]-2-methoxyacetamide (6c):** R_f (100% EtOAc): 0.33; mp 81–83 °C; IR (KBr): ν = 3408, 2959, 2932, 1670, 1577, 1558, 1521, 1466, 1198, 1116, 988, 829, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 0.89 (t, 3H, H-10, $^3J_{H,H}$ = 7.32 Hz), 1.18–1.35 (m, 2H, H-9), 1.66–1.89 (m, 2H, H-8), 3.42 (s, 3H, H-15), AB spin system (δ_A 3.87 δ_B 3.92, d, 2H, H-13, $|^2J_{AB}|$ = 24.66 Hz), 5.06 (dd, 1H, H-7, $^3J_{H,H}$ = 15.51 Hz, $^3J_{H,H}$ = 7.02 Hz), 7.17–7.19 (m, 1H, H-5), 7.23–7.26 (m, 1H, H-3), 7.39 (d, 1H, NH, $^3J_{H,H}$ = 8.07 Hz), 8.48 (d, 1H, H-6, $^3J_{H,H}$ = 5.37 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.7 (C-10), 18.9 (C-9), 38.1 (C-8), 53.0 (C-7), 59.1 (C-15), 71.9 (C-13), 122.3, 122.7 (2C, C-3+C-5), 144.4 (C-4), 150.2 (C-6), 162.0 (C-12), 168.9 (C-2); MS (ESI$^+$): m/z = 257 [($M^{35}Cl$+H)$^+$, 100%], 259 [($M^{37}Cl$+H)$^+$, 33%], 279 [($M^{35}Cl$+Na)$^+$, 75%], 281 [($M^{37}Cl$+Na)$^+$, 24%]; anal. calcd. (%) for $C_{12}H_{17}ClN_2O_2$: C 56.14, H 6.67, N 10.91; found: C 56.2, H 5.1, N 6.8; $[\alpha]_D^{20}$: +33.2° (*c* 1.1, $CHCl_3$) for the (*R*)-enantiomer with 93% *ee* after lipase-kinetic resolution.

***N*-[1-(4-Chloropyridin-2-yl)pentyl]-2-methoxyacetamide (6d):** R_f (100% EtOAc): 0.31; mp 52–53 °C; IR (KBr): ν = 3408, 2932, 1684, 1654, 1577, 1558, 1521, 1457, 1198, 1116, 828 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 0.72 (t, 3H, H-11, $^3J_{H,H}$ = 6.92 Hz), 1.05–1.22 (m, 4H, H-10+H-9), 1.54–1.78 (m, 2H, H-8), 3.30 (s, 3H, H-16), AB spin system (δ_A 3.75 δ_B 3.80, d, 2H, H-14_{14}, $|^2J_{AB}|$ = 25.85 Hz), 4.92 (dd, 1H, H-7, $^3J_{H,H}$ = 15.53 Hz, $^3J_{H,H}$ = 7.07 Hz), 7.06 (dd, 1H, H-5, $^3J_{H,H}$ = 5.37 Hz, $^4J_{H,H}$ = 1.98 Hz), 7.12 (d, 1H, H-3, $^3J_{H,H}$ = 1.98 Hz), 7.28 (d, 1H, NH, $^3J_{HH}$ = 8.34 Hz), 8.33 (d, 1H, H-6, $^3J_{H,H}$ = 5.37 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 13.8 (C-11), 22.3 (C-10), 27.7 (C-9), 35.7 (C-8), 53.2 (C-7) 59.1 (C-16), 71.9 (C-14), 122.3, 122.7 (2C, C-3+C-5), 144.4 (C-4), 150.2 (C-6), 162.0 (C-13), 168.9 (C-2); MS (ESI$^+$): m/z = 271 [($M^{35}Cl$+H)$^+$, 100%], 273 [($M^{37}Cl$+H)$^+$, 30%], 293 [($M^{35}Cl$+Na)$^+$, 51%], 295 [($M^{37}Cl$+Na)$^+$, 15%]; anal. calcd. (%) for $C_{13}H_{19}ClN_2O_2$: C 57.67, H 7.07, N 10.35; found: C 57.8, H 7.1, N 10.5; $[\alpha]_D^{20}$: +25.8° (*c* 0.8, $CHCl_3$) for the (*R*)-enantiomer with 93% *ee* after lipase-kinetic resolution.

***N*-[1-(4-Chloropyridin-3-yl)ethyl]acetamide (16a):** R_f (20% MeOH/EtOAc): 0.55; IR (NaCl): ν = 3415, 3296, 2358, 1653, 1584, 1557, 1468, 1372 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 1.50 (d, 3H, H-8, $^3J_{H,H}$ = 67.23 Hz), 2.0 (s, 3H, H-11), 5.34–5.43 (m, 1H, H-7), 6.55 (d, 1H, NH, $^3J_{H,H}$ = 6.57 Hz), 7.33 (d, 1H, H-5, $^3J_{H,H}$ = 5.04 Hz), 8.39 (br s, 1H, H-6), 8.61 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): d = 20.6 (C-8), 23.0 (C-11), 45.4 (C-7), 125.0 (C-5), 134.4 (C-3), 143.2 (C-4), 148.2, 148.4 (2C, C-6+C-2), 169.3 (C-10); MS (ESI$^+$): m/z = 199 [($M^{35}Cl$+H)$^+$, 100%], 201 [($M^{37}Cl$+H)$^+$, 29%], 397 [(2$M^{35}Cl$+H)$^+$, 23%]; anal. calcd. (%) for $C_9H_{11}ClN_2O$: C 54.42, H 5.58, N 14.10; found: C 54.2, H 5.1, N 6.9; $[\alpha]_D^{20}$: +34.3° (*c* 0.9, $CHCl_3$) for the (*R*)-enantiomer with >99% *ee* after lipase-kinetic resolution.

***N*-[1-(4-Chloropyridin-3-yl)ethyl]-2-methoxyacetamide (16b):** R_f (10% MeOH/EtOAc): 0.36; IR (NaCl): ν = 3409, 2962, 1675, 1580, 1557, 1466, 1198, 986, 835, 738 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ = 1.59 (d, 3H, H-8, $^3J_{H,H}$ = 7.02 Hz), 3.47 (s, 3H, H-13), AB spin system (δ_A 3.90 δ_B, 3.95, d, 2H, H-11, $|^2J_{AB}|$ = 20.93 Hz), 5.42–5.51 (m, 1H, H-7), 7.05 (d, 1H, NH, $^3J_{HH}$ = 6.93), 7.34 (d, 1H, H-5, $^3J_{H,H}$ = 5.25 Hz), 8.44 (br s, 1H, H-6) 8.59 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 20.6 (C-8), 44.7 (C-7), 59.1 (C-13), 71.7 (C-11), 125.4 (C-5), 133.9 (C-3), 142.7 (C-4), 148.5, 149.1 (2C, C-6+C-2), 168.7 (C-10); MS (ESI$^+$): m/z = 257 [($M^{35}Cl$+H)$^+$, 100%], 259 [($M^{37}Cl$+H)$^+$, 33%], 279 [($M^{35}Cl$+Na)$^+$, 75%], 281 [($M^{37}Cl$+Na)$^+$, 24%]; anal. calcd. (%) for $C_{10}H_{13}ClN_2O_2$: C 52.52, H 5.73, N 12.25; found: C 52.6, H 5.7, N 12.1; $[\alpha]_D^{20}$: +31.0° (*c* 0.3, $CHCl_3$) for the (*R*)-enantiomer with >99% *ee* after lipase-kinetic resolution.

General Procedure for the Kinetic Resolution of Amines 3a, 7, 8 and 9

To a suspension of the corresponding amine (0.26 mmol) and the enzyme (ratio 1:1 by weight with respect to the amine) in dry TBME (2.6 mL) under a nitrogen atmosphere, ethyl acetate was added (1.28 mmol, 125 μL), and the mixture shaken for the required time (see Table 3). Then the enzyme was filtered, washed with CH_2Cl_2 and the organic solvent was evaporated, obtaining a crude material that was purified by flash chromatography (gradient eluent 10% MeOH/EtOAc to 100% MeOH), isolating the optically active (*R*)-acetamides and (*S*)-amines.

***m*-Chloro-α-methylbenzylamine (8):** R_f (100% MeOH): 0.20; IR (NaCl): ν = 3364, 2966, 1597, 1474, 1436, 1374, 1111,

880, 786, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): $\delta = 1.41$ (d, 3H, H-8, $^3J_{H,H} = 6.54$ Hz), 1.69 (s, 2H, NH_2), 4.02 (q, 1H, H-1, $^3J_{H,H} = 6.54$ Hz), 7.22–7.32 (m, 4H, H-3 + H-5 + H-6 + H-7); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 25.5$ (C-8), 50.9 (C-1), 123.9, 125.9, 126.8, 129.7 (4C, C-3 + C-5 + C-6 + C-7), 134.2 (C-2), 149.7 (C-4); MS (ESI^+): $m/z = 158$ [$(M^{37}Cl + H)^+$, 31%], 156 [$(M^{35}Cl + H)^+$, 100%]; anal. calcd. (%) for $C_8H_{10}ClN$: C 61.74, H 6.48, N 9.00; found: C 61.9, H 6.5, N 8.9.

***N*-[1-(*m*-Chlorophenyl)ethyl]acetamide (11):** R_f (100% EtOAc): 0.28; mp 54–55 °C; IR (KBr): $\nu = 3282$, 3066, 2977, 2932, 1652, 1558, 1374, 1210, 1140, 1180, 785, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): $\delta = 1.46$ (d, 3H, H-8, $^3J_{H,H} = 6.90$ Hz), 1.99 (s, 3H, H-11), 5.04–5.13 (m, 1H, H-1), 6.25 (br s, 1H, NH), 7.17–7.31 (m, 4H, H-3 + H-5 + H-6 + H-7); ^{13}C NMR ($CDCl_3$, 75.5 MHz): d = 21.6 (C-8), 23.1 (C-11), 48.2 (C-1), 124.4, 126.1, 127.2, 129.7 (4C, C-3 + C-5 + C-6 + C-7), 134.3 (C-2), 145.4 (C-4), 169.2 (C-10); MS (ESI^+): $m/z = 198$ [$(M^{35}Cl + H)^+$, 63%], 200 [$(M^{37}Cl + H)^+$, 22%], 395 [$(2M^{35}Cl + H)^+$, 100%], 397 [$(M^{35}Cl + M^{37}Cl + H)^+$, 73%], 399 [$(2M^{37}Cl + H)^+$, 11%]; anal. calcd. (%) for $C_{10}H_{12}ClNO$: C 60.76, H 6.12, N 7.09; found: C 60.7, H 6.1, N 7.1.

Compounds (*S*)-**7** and (*R*)-**10** have been previously described from the enzymatic resolution of the racemic amine under similar conditions,[10a,b] meanwhile (*S*)-**9** and (*R*)-**12** are commercially available compounds.

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[19] Alcohols **1a–d** were obtained following the protocols described in ref.[12a] and alcohol **13** was obtained following the protocol described in ref.[13]

