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Chemoenzymatic synthesis of chiral 4-(*N*,*N*-dimethylamino)pyridine derivatives

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Abstract—Chiral 4-(*N*,*N*-dimethylamino)pyridine derivatives have been prepared through a chemoenzymatic synthesis where the enzymatic kinetic resolution of a family of 4-chloro-2-(1-hydroxyalkyl)pyridines is the key step for the formation of potentially important chiral catalysts. *Pseudomonas cepacia* lipase (PSL) showed excellent enantioselectivity in the acylation of the (*R*)-enantiomers ($E > 200$) using vinyl acetate as acylating agent and THF as solvent, obtaining products and substrates enantiomerically pure and with excellent yields.

1. Introduction

4-(*N*,*N*-Dimethylamino)pyridine DMAP, **1** is one of the most versatile reagents, as it is known for its use in different processes such as acylation or silylation of alcohols and amines, for the formation of amides from α-substituted carboxylic acids and isocyanates, transesterification of esters, and others.[1] DMAP also has the advantage of working under mild reaction conditions thus avoiding, for example, racemization problems and enhances the rate of reaction in several orders in comparison with the process in the absence of catalyst; moreover, only a catalytic amount of catalyst is usually required and can be recovered at the end of the process.

Different examples of chiral 4-(*N*,*N*-disubstituted amino)pyridine derivatives have been described over the years allowing the development of enantioselective processes (Chart 1). For example, Fu et al. introduced the concept of 'planar-chiral' DMAP derivatives based on the π-complexation of a heterocycle to a transition metal, using these analogues in the enantioselective acylation of secondary alcohols and cyanosilylation of aldehydes.[2] In addition, Vedejs et al. explored the possibility of introducing the chirality in the DMAP-nucleus generating a 2-substituted DMAP derivative **3**. The resulting catalyst was successfully used in the enantioselective alkoxycarbonylation of secondary alcohols using chloroformates.[3] Employing two chiral DMAP derivatives of opposite stereochemistry, Vedejs and Chen introduced the concept of a parallel kinetic resolution in order to maximize the ee as well as the percent of conversion in the resolution of racemic mixtures.[4] The introduction of chirality in the C-3 and C-4 position was also studied years later achieving the formation of more reactive catalysts than those substituted at the C-2 position.[5]

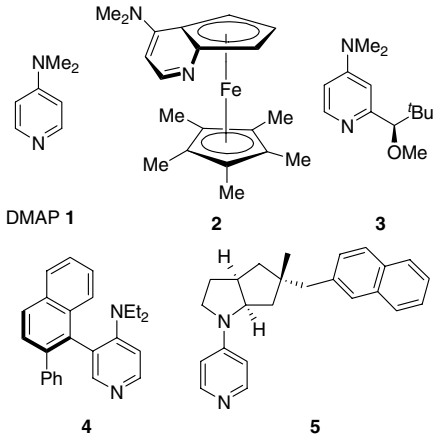

Chart 1. DMAP and other derivatives used as catalysts.

Biocatalysis is recognized as a powerful tool for the enantioselective modification of very different chiral building blocks under mild reaction conditions. Enzymes,

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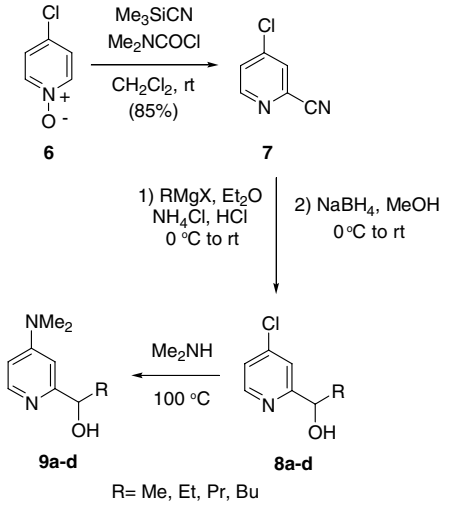
in particular lipases (E.C.3.1.1.3) have shown remarkable chemoselectivity, regioselectivity, and enantioselectivity toward a broad range of substrates over the last few decades. In fact, the resolution of pyridyl-ethanols was firstly achieved in 1992 by Schneider et al. by enzymatic hydrolysis or esterification of the corresponding substrates using the lipase SAM II from *Pseudomonas* sp.[6]

The use of other acylating agents, exploration of the complementary enzymatic hydrolysis reaction or the use of other biocatalysts, has allowed an optimization in the resolution of these interesting compounds and other bipyridylethanols for their application in the synthesis of enantiomerically pure oligopyridines.[7] Also in aqueous media, the reduction of acetylpyridines[8] and benzoylpyridines[9] by asymmetric microbial reduction using Baker's yeast, obtaining the corresponding enantiomerically enriched alcohols was possible. Less studied are the amine derivatives, which have also been successfully resolved using enzymatic methodologies.[10] We report herein the chemoenzymatic synthesis of a new family of chiral catalysts based on the kinetic resolution of 4-chloro-2-(1-hydroxyalkyl)pyridines as a key step in the development of the analogues as that is the process responsible of the introduction of chirality. The kinetic resolution of these derivatives allows us to obtain catalysts with potential application and with opposite stereochemistry, which gives us the possibility to perform complementary stereoselective processes.

2. Results and discussion

4-Chloropyridine *N*-oxide **6** has been used for the preparation of 4-chloro-2-cyanopyridine **7** as described by Bisagni et al. by reaction with trimethylsilyl cyanide and dimethylcarbamyl chloride affording **7** in 85% isolated yield (Scheme 1).[11]



Scheme 1. Chemical synthesis of DMAP derivatives.

The introduction of the cyano functionality allowed us to synthesize different ketones at the 2-position of the pyridine ring by reaction with the corresponding organomagnesium derivative. However, there were several difficulties in the isolation of the alkyl ketones due to their volatility, so we decided to perform the reduction step over the crude of the reaction using $NaBH_4$ in MeOH without further purification of the ketones. Thus, alcohols were obtained in high isolated yields after both steps (see Table 1).

Table 1. Transformation of **7** in different alcohols **8a–d**

Entry	Product	R	X	Yield (%)[a]
1	**8a**	Me	I	77
2	**8b**	Et	Br	76
3	**8c**	Pr	Br	76
4	**8d**	Bu	Cl	74

[a] Isolated yield by flash chromatography.

Substitution of the chlorine atom for the dimethylamino group at the 4-position of the pyridine ring was performed by heating the corresponding substrate **8a–d** with a 40% aqueous solution of dimethylamine, thus isolating the racemic potential catalysts in quantitative yields.

Once that the synthesis of the racemic compounds was achieved, we decided to obtain the potential catalyst in the enantiopure form. For that reason, **9a** was selected as a model substrate and its kinetic resolution attempted using PSL-C as biocatalyst, which has been described in the literature as an ideal enzyme for the resolution of pyridine derivatives.[6,9] The data are summarized in Table 2 (Scheme 2).

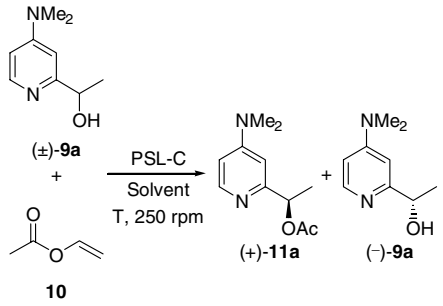
Table 2. Enzymatic acetylation of **9a** using 3 equiv of **10** and PSL-C

Entry	Solvent	T (°C)	t (h)	ee_P (%)[a]	ee_S (%)[a]	c (%)[b]	E[c]
1	THF	30	14.5	>99	52	34	>200
2	THF	30	24	>99	69	41	>200
3	THF	30	38	>99	76	43	>200
4	THF	30	65	>99	71	42	>200
5	MeCN	30	14.5	>99	42	30	>200
6	MeCN	30	24	>99	46	31	>200
7	MeCN	30	38	>99	59	37	>200
8	MeCN	30	65	95	62	39	73
9	MeCN	45	70	81	49	38	15

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

PSL-C showed an excellent selectivity toward the formation of acetate (+)-**11a** in 99% ee when the reaction was carried out with 3 equiv of vinyl acetate at 30 °C on THF. This process was monitored by HPLC observing 34% conversion after 14.5 h (entry 1). Longer reaction times gave higher yields without reached half conversion in the first 65 h of the process, when a drop in the ee of **9a** was observed. However (+)-**11a** was always detected enantiomerically pure (entries 2–4).

Using a more polar solvent as acetonitrile, low reactivity was observed in comparison with THF but also with



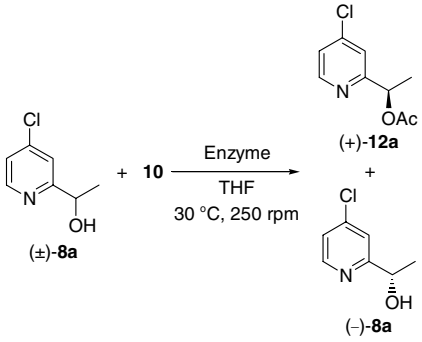
Scheme 2. Enzymatic transesterification of **9a** using vinyl acetate as acyl donor and PSL-C as catalyst.

excellent stereoselectivities, until 65 h when it started to show a decrease in the enantioselectivity (entries 5–8). More drastic conditions, for example, higher temperatures, gave lower values of selectivity as it commonly happens in biocatalysis (entry 9).

At this point, and before undertaking a further study of all the parameters that influence the enzymatic catalysis, we decided to turn our attention to the enzymatic resolution of the synthon **8a**, as **9a** can easily be obtained from those in quantitative yield. In addition, chlorinated derivatives are also advantageous because of their great versatility in organic synthesis. In this manner, we focused our efforts trying to reach conversions close to 50% and 99% ee for substrate and product. Thus, isolated yields could be higher and potential catalyst obtained in enantiopure form in both stereochemistries.

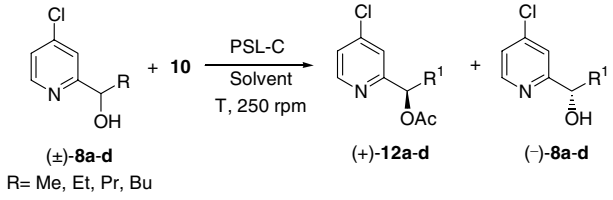
The more significant results are shown in Table 3; both *Candida antarctica* lipase type A (CAL-A) and the protease subtilisin (entries 1 and 2) did not show any activity toward **8a**. However, different forms of *C. antarctica* lipase type B (CAL-B), immobilized (Novozyme 435) or supported (Chirazyme) stereoselectively acetylated **8a** (entries 3–5). Novozyme 435 showed a higher activity but there was a loss of stereoselectivity after reaction times longer than 2 days as a hydrolysis effect was observed causing a decrease in the enantioselectivity of the process before 50% conversion was reached (entry 4). The best conditions were achieved using immobilized *Pseudomonas cepacia lipase* (PSL-C, entry 6) as after 14 h the reaction reached 50% conversion giving product and starting material in 99% ee, isolating both with high yields. This result overcomes the problems, which appeared in the enzymatic resolution of **9a**.

Different biocatalysts were used in the enzymatic transesterification using vinyl acetate as the acyl donor and THF as the solvent (Scheme 3).



Scheme 3. Enzymatic transesterification of **8a** using vinyl acetate as the acyl donor and THF as solvent.

Once that PSL-C was selected as the optimal biocatalyst for the transesterification of **8a**, this study was extended to alcohols **8b–d** in order to extend the family of catalyst depending of the alkyl chain length (Scheme 4). The results are summarized in Table 4.



Scheme 4. Kinetic resolution of **8a–d** with **10** catalyzed by PSL-C.

In all cases where values of E higher than 200 were achieved, those processes were slower when the alkyl group of the 4-chloro-[2-(1-hydroxyalkyl)]pyridine derivative was longer. In this manner, **8b** showed the same activity as previously observed with **8a** (entry 2), and after 14.5 h, 50% conversion was reached affording product and substrate enantiomerically pure and with high yields. PSL-C showed a decrease in the activity

Table 3. Enzymatic acylation of **8a** using 3 equiv of **10** in dry THF at 30 °C, where values presented in brackets show the isolated yields

Entry	Enzyme	t (h)	ee_P (%)[a]	ee_S (%)[a]	c (%)[b]	E[c]
1	CAL-A	38	—	—	—	—
2	Subtilisin	71	—	—	—	—
3	CAL-B (Novozyme)	48	>99	82	42	>200
4	CAL-B (Novozyme)	71	96	81	45	149
5	CAL-B (Chirazyme)	70	>99	70	41	>200
6	PSL-C	14.5	>99 (85)	>99 (88)	50	>200

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

Table 4. Enzymatic transesterification of **8a–d** using **10** as acyl donor and PSL-C as biocatalyst, isolated yields in brackets

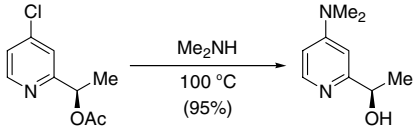
Entry	Substrate	Solvent	T (°C)	t (h)	ee_P (%)[a]	ee_S (%)[a]	c (%)[b]	E[c]
1	**8a**	THF	30	14.5	>99 (85)	>99 (88)	50	>200
2	**8b**	THF	30	14.5	>99 (82)	>99 (88)	50	>200
3	**8c**	THF	30	14.5	>99	88	47	>200
4	**8c**	THF	30	38	99 (97)	>99 (89)	50	>200
5	**8d**	THF	30	14.5	>99	49	33	>200
6	**8d**	THF	30	60	>99 (88)	>99 (89)	50	>200

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

for the reaction with the propyl rest **8c** but maintained the enantiopreference, requiring 38 h to reach 50% conversion (entries 3 and 4). The decrease in reactivity of precursor **8d** was observed in terms of reaction times but 50% conversion was reached after 60 h with excellent ee and isolated yields (entries 5 and 6). Biocatalysis represents a very effective tool to selectively modify one of the enantiomer of the racemic pyridine derivatives and PSL-C shows a great versatility to accommodate different substituted pyridines in its active site.

Substitution of the chlorine atom for the dimethylamino group at the 4-position of the pyridine ring was achieved heating the corresponding substrate (−)-**8a–d** with a 40% aqueous solution of dimethylamine, thus isolating the potential catalyst (−)-**9a–d** in quantitative yields. In all cases it was confirmed by HPLC that no racemization occurred during the reaction.

One of the main advantages of this chemoenzymatic synthesis is that potential catalysts of opposite stereochemistry can be obtained. We have demonstrated the access to (−)-**9a–d** but we also developed a one-step route, which would lead to the corresponding enantiomers (+)-**9a–d**. The formation of (+)-**9a** was achieved by refluxing (+)-**12a** in an aqueous solution of Me_2NH, the substitution of the chlorine atom for the dimethylamino group at the same time showed that the acetate was deprotected, thus forming the corresponding alcohol in 95% isolated yield (Scheme 5).



(+)-**12a** (+)-**9a**

Scheme 5. Synthesis of (+)-**9a** from (+)-**12a** by reaction with Me_2NH.

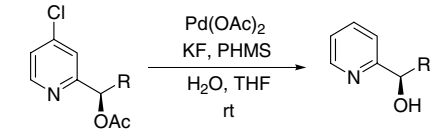
To confirm the configuration of the stereogenic centers, the dechlorination of (−)-**8a** was attempted following the procedure described by Maleczka Jr. et al. for chloroarenes in order to obtain (−)-**13a** of known stereochemistry.[12] However when using polymethylhydrosiloxane (PMHS) under palladium catalysis in the presence of KF, no reaction was observed for alcohol (−)-**8a** after 24 h (Table 5, entry 1).

Table 5. Dechlorination processes to obtain **14a–d**

Entry	Substrate	Yield (%)[a]
1	(−)-**8a**	—
2	(+)-**12a**	56
3	(+)-**12b**	50
4	(+)-**12c**	39
5	(+)-**12d**	62

[a] Isolated yield by flash chromatography.

We then decided to use acetyl derivative (+)-**12a** (Scheme 6), and after 4 h, (+)-**13a** was obtained with 43% yield (entry 2). Determination of the specific rotation confirmed the (*R*)-configuration.[13] Using the same approach, the (*R*)-configuration of (+)-**12b–d** was also assigned as (+)-**13b–d** and obtained in moderate yields. The specific rotation of (+)-**12b** was in accordance with previously published data (see also experimental part),[14] meanwhile (+)-**12c** and (+)-**12d** were not described before in the literature but the symbols of the optical rotation were the same as the ones for (+)-**12a** and (+)-**12b**, and the elution orders in the HPLC were the same for all four compounds. Thus, all the cases are in accordance with Kazlauskas' rule.[15]



(+)-**12a-d**
R= Me, Et, Pr, Bu

(+)-**13a-d**

Scheme 6. Dechlorination of 4-chloropyridines to confirm their stereochemistry.

3. Conclusions

In conclusion, we have synthesized a new family of chiral catalysts derived from 4-(*N*,*N*-dimethylamino)-pyridine using a chemoenzymatic approach. In this manner, *P. cepacia* lipase has shown excellent stereoselectivity in the transesterification reaction of 4-chloro-2-(1-hydroxyalkyl)pyridine derivatives. The kinetic resolution using lipases as biocatalysts is an ideal tool to obtain chiral synthons, which moreover we can synthesize in both stereochemistries as alcohol and acetate form. This easy methodology allows the preparation of new chiral catalyst for use in asymmetric synthesis.

4. Experimental

4.1. General

C. antarctica lipase type B (CAL-B, Novozyme 435, 7300 PLU/g) was a gift from Novo Nordisk Co. *C. antarctica* lipase type A (CAL-A, Chirazyme L-5, c-f, lyophilized, 1000 U/g using tributyrin) was acquired from Roche. *P. cepacia* lipase (PSL-C, 783 U/g) was obtained from Amano Pharmaceutical Co. All other reagents were purchased from Aldrich and used without further purification. Solvents were distilled over an adequate desiccant under nitrogen. Flash chromatographies were performed using silica gel 60 (230–240 mesh). High performance liquid chromatography (HPLC) analyses were carried out in a Hewlett Packard 1100 chromatograph 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 on using NaCl plates or KBr pellets in a Perkin–Elmer 1720-X F7. ^{1}H, ^{13}C NMR, DEPT, and ^{1}H–^{13}C heteronuclear experiments were obtained using 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), DPX-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) or AV-400 (^{1}H, 400.13 MHz and ^{13}C, 100.6 MHz) spectrometers. The chemical shifts are given in delta (δ) values and the coupling constants (J) in hertz (Hz). ESI^{+} using a HP1100 chromatograph mass detector, or EI with a Finigan MAT 95 spectrophotometer were used to record mass spectra (MS). Microanalyses were performed on a Perkin–Elmer model 2400 instrument. Measurement of the optical rotations were done in a Perkin–Elmer 241 polarimeter.

4.1.1. 4-Chloro-2-cyanopyridine 7. To a solution of 4-chloropyridine *N*-oxide (5.00 g, 38.6 mmol) in dry CH_2Cl_2 (70 mL) were successively added trimethylsilyl cyanide (4.92 mL, 39.3 mmol) and *N*,*N*-dimethylcarbamyl chloride in small portions. The resulting solution was stirred at room temperature for 9 days, after which time the solvent was evaporated at reduced pressure. The crude of the reaction was purified by flash chromatography (20% EtOAc/hexane) yielding 4.54 g as a white solid (85%). R_f (20% EtOAc/hexane): 0.38. Mp: 83–85 °C; IR (KBr): ν 3456, 3087, 2240, 1570, 1547, 1462, 1382, 1288, 1214, 1108, 990, 886, and 847 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 7.54 (dd, $^{3}J_{HH} = 5.1$, $^{4}J_{HH} = 1.7$ Hz, 1H, H_5), 7.71 (d, $^{4}J_{HH} = 1.7$ Hz, 1H, H_3), and 8.63 (d, $^{3}J_{HH} = 5.1$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 116.1 (CN), 127.4 (C_5), 128.8 (C_3), 135.0 (C_4), 145.3 (C_2), and 151.9 (C_6); MS (EI, *m*/*z*): 140 [$(M^{37}Cl)^{+}$, 32%], 138 [$(M^{35}Cl)^{+}$, 100%], and 103 [$(M\text{-}Cl)^{+}$, 61%]. Anal. Calcd (%) for $C_6H_3N_2Cl$: C, 52.01; H, 2.18 N, 20.22. Found: C, 52.0 H, 2.2 N, 20.2.

4.1.2. (±)-4-Chloro-2-(1-hydroxyethyl)pyridine 8a. Over a 3.0 M solution of methylmagnesium iodide in Et_2O (9.64 mL, 28.94 mmol) at 0 °C under a nitrogen atmosphere, a solution of 4-chloro-2-cyanopyridine (1.00 g, 7.24 mmol) in dry Et_2O (25 mL) was added. Once the addition was completed, the mixture was stirred at room temperature for 4 h, after which time the solution was poured onto a saturated ammonium chloride solution at 0 °C (23.9 mL) adding HCl concd until pH = 1. The resulting mixture was stirred at room temperature for additional 14 h. The solution was neutralized with NH_3 aq and extracted with Et_2O (3 × 15 mL). The solvent was evaporated by distillation under reduced pressure to obtain 2-acetyl-4-chloropyridine, which was used for the next step without further purification. This resulting crude was dissolved in MeOH (60 mL) and cooled at 0 °C, moment when $NaBH_4$ (1.36 g, 36.10 mmol) was added in small portions. The clear solution was stirred for 2 h at room temperature, then MeOH was evaporated, and the resulting white solid was dissolved in water and extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4, and evaporated at reduced pressure. The crude of reaction was purified by flash chromatography (80% EtOAc/hexane) yielding 880 mg as a white solid (77%). R_f (80% EtOAc/hexane): 0.40. Mp: 73–75 °C; IR (KBr): ν 3195, 1582, 1555, 1390, 1132, 1082, 1020, 918, and 846 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.49 (d, $^{3}J_{HH} = 6.7$ Hz, 3H, H_8), 4.50 (s, 1H, OH), 4.88 (q, $^{3}J_{HH} = 6.7$ Hz, 1H, H_7), 7.21 (dd, $^{3}J_{HH} = 5.4$, $^{4}J_{HH} = 2.0$ Hz, 1H, H_5), 7.34 (d, $^{4}J_{HH} = 2.0$ Hz, 1H, H_3), and 8.45 (d, $^{3}J_{HH} = 5.4$, 1H, H_6); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 23.9 (C_8), 69.0 (C_7), 120.1 (C_3), 122.5 (C_5), 144.8 (C_4), 149.0 (C_6), and 165.1 (C_2); MS (ESI^{+}, *m*/*z*): 180 [$(M^{35}Cl+Na)^{+}$, 23%], 160 [$(M^{37}Cl+H)^{+}$, 33%], and 158 [$(M^{35}Cl+H)^{+}$, 100%]. Anal. Calcd (%) for C_7H_8NOCl: C, 53.35; H, 5.12; N, 8.89. Found: C, 53.4; H, 5.1; N, 8.9.

4.1.3. (±)-4-Chloro-2-(1-hydroxypropyl)pyridine 8b. Same procedure as **8a**, using ethylmagnesium bromide instead of methylmagnesium iodide. Colorless oil (76% isolated yield). R_f (80% EtOAc/hexane): 0.42; $[\alpha]_D^{20} = -29.4$ (*c* 2, $CHCl_3$); IR (NaCl): ν 3356, 2967, 2935, 2877, 2342, 1581, 1557, 1463, 1393, 1217, 1127, 1099, 984, 826, and 807 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 0.95 (t, $^{3}J_{HH} = 7.5$ Hz, 3H, H_9), 1.67–1.94 (m, 2H, H_8), 3.99 (s, 1H, OH), 4.68 (t, $^{3}J_{HH} = 7.5$ Hz, 1H, H_7), 7.21 (dd, $^{3}J_{HH} = 5.4$, $^{4}J_{HH} = 1.6$ Hz, 1H, H_5), 7.33 (d, $^{4}J_{HH} = 1.6$ Hz, 1H, H_3), and 8.43 (d, $^{3}J_{HH} = 5.4$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 9.4 (C_9), 31.1 (C_8), 73.9 (C_7), 120.8 (C_3), 122.7 (C_5), 144.7 (C_4), 149.2 (C_6), and 164.2 (C_2); MS (ESI^{+}, *m*/*z*): 174 [$(M^{37}Cl+H)^{+}$, 33%] and 172 [$(M^{35}Cl+H)^{+}$, 100%]. Anal. Calcd (%) for $C_8H_{10}NOCl$: C, 55.99; H, 5.87; N, 8.16. Found: C, 55.9; H, 5.9; N, 8.1.

4.1.4. (±)-4-Chloro-2-(1-hydroxybutyl)pyridine 8c. Same procedure as **8a**, using propylmagnesium bromide instead of methylmagnesium iodide. Colorless oil (76% isolated yield). R_f (20% EtOAc/hexane): 0.16; IR (NaCl): ν 3332, 2959, 2933, 2872, 2360, 2341, 1581, 1556, 1466, 1392, 825, and 706 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 0.96 (t, $^{3}J_{HH} = 7.4$ Hz, 3H, H_{10}), 1.40–1.51 (m, 2H, H_9), 1.63–1.85 (m, 2H, H_8), 3.89 (d, $^{3}J_{HH} = 4.8$ Hz, 1H, OH), 4.73 (td, $^{3}J_{HH} = 7.4$, $^{3}J_{HH} = 4.8$ Hz, 1H, H_7), 7.21 (dd, $^{3}J_{HH} = 5.4$, $^{4}J_{HH} = 1.9$ Hz, 1H, H_5), 7.33 (d, $^{4}J_{HH} = 1.9$ Hz, 1H, H_3), and 8.44 (d, $^{3}J_{HH} = 5.4$ Hz, 1H, H_6); ^{13}C NMR

($CDCl_3$, 100.61 MHz): δ 14.0 (C_{10}), 18.5 (C_9), 40.5 (C_8), 72.7 (C_7), 120.7 (C_3), 122.6 (C_5), 144.7 (C_4), 149.2 (C_6), and 164.5 (C_2); MS (ESI^+, m/z): 188 [$(M^{37}Cl+H)^+$, 32%] and 186 [$(M^{35}Cl+H)^+$, 100%]. Anal. Calcd (%) for $C_9H_{12}NOCl$: C, 58.23; H, 6.51; N, 7.54. Found: C, 58.3; H, 6.6; N, 7.6.

4.1.5. (±)-4-Chloro-2-(1-hydroxypentyl)pyridine 8d. Same procedure as **8a**, using butylmagnesium chloride instead of methylmagnesium iodide. Colorless oil (74% isolated yield). R_f (20% EtOAc/hexane): 0.22; IR (NaCl): ν 3318, 2957, 2932, 2881, 1581, 1557, 1467, 1557, 1392, and 826 cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 0.91 (t, $^3J_{HH} = 7.2$ Hz, 3H, H_{10}), 1.30–1.45 (m, 4H, $2H_9+2H_{10}$), 1.65–1.88 (m, 2H, H_8), 3.95 (d, $^3J_{HH} = 5.5$ Hz, 1H, OH), 4.70–4.75 (m, 1H, H_7), 7.22 (dd, $^3J_{HH} = 5.3$, $^4J_{HH} = 1.9$ Hz, 1H, H_5), 7.33 (d, $^4J_{HH} = 1.9$ Hz, 1H, H_3), and 8.44 (d, $^3J_{HH} = 5.3$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 14.0 (C_{11}), 22.6 (C_{10}), 27.4 (C_9), 38.1 (C_8), 72.9 (C_7), 120.7 (C_3), 122.7 (C_5), 144.7 (C_4), 149.2 (C_6), and 164.5 (C_2); MS (ESI^+, m/z): 224 [$(M^{37}Cl+Na)^+$, 32%], 222 [$(M^{35}Cl+Na)^+$, 100%], and [$(M^{35}Cl+H)^+$, 8%]. Anal. Calcd (%) for $C_{10}H_{14}NO_2Cl$: C, 60.15; H, 7.07; N, 7.01. Found: C, 60.2; H, 6.9; N, 7.2.

4.1.6. Kinetic resolution of (±)-8a. To a suspension of **8a** (500 mg, 3.12 mmol) and PSL-C (500 mg) in dry THF (31 mL) under a nitrogen atmosphere, vinyl acetate (859 μL, 9.38 mmol) was added and the reaction shaken at 30 °C and 250 rpm. Aliquots were regularly analyzed by HPLC until 50% conversion was reached, then the reaction was stopped, and the enzyme filtered with CH_2Cl_2 (3 × 10 mL). The solvent was evaporated and the crude of the reaction purified by flash chromatography (20–60% EtOAc/hexane) affording (*S*)-(−)-**8a** {88% isolated yield and >99% ee, $[\alpha]_D^{20} = -36.1$ (*c* 2, $CHCl_3$)} and (*R*)-(+)-**12a** {85% isolated yield and >99% ee, $[\alpha]_D^{20} = +90.6$ (*c* 2, $CHCl_3$)}.

4.1.7. (*R*)-(+)-1-(4-Chloro-2-pyridinyl)ethyl acetate 12a. Colorless oil; R_f (20% EtOAc/hexane): 0.24; IR (NaCl): ν 3449, 1736, 1579, 1558, 1469, 1371, 1239, 1100, 1071, 1031, 949, and 828 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.57 (d, $^3J_{HH} = 6.7$ Hz, 3H, H_8), 2.14 (s, 3H, H_{10}), 5.86 (q, $^3J_{HH} = 6.7$ Hz, 1H, H_7), 7.18 (dd, $^3J_{HH} = 5.4$, $^4J_{HH} = 1.8$ Hz, 1H, H_5), 7.34 (d, $^4J_{HH} = 1.8$ Hz, 1H, H_3), and 8.46 (d, $^3J_{HH} = 5.4$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 20.6 (C_8), 21.1 (C_{10}), 72.4 (C_7), 120.6 (C_3), 122.9 (C_5), 145.2 (C_4), 150.1 (C_6), 162.0 (C_2), and 170.0 (C_9); MS (ESI^+, m/z): 222 [$(M^{35}Cl+Na)^+$, 7%], 202 [$(M^{37}Cl+H)^+$, 32%], and 200 [$(M^{35}Cl+H)^+$, 100%]. Anal. Calcd (%) for $C_9H_{10}NO_2Cl$: C, 54.15; H, 5.05; N, 7.02. Found: C, 54.2; H, 5.0; N, 7.0.

4.1.8. Kinetic resolution of (±)-8b. To a suspension of **8b** (500 mg, 2.91 mmol) and PSL-C (466 mg) in dry THF (29 mL) under a nitrogen atmosphere, vinyl acetate (800 μL, 8.74 mmol) was added and the reaction shaken at 30 °C and 250 rpm. Aliquots were regularly analyzed by HPLC until 50% conversion was reached. The reaction was then stopped and the enzyme filtered with CH_2Cl_2 (3 × 10 mL). The solvent was evaporated and the crude of reaction purified by flash chromatography (15–60% EtOAc/hexane) affording (*S*)-(−)-**8b** {88% isolated yield and >99% ee, $[\alpha]_D^{20} = -29.4$ (*c* 2, $CHCl_3$)} and (*R*)-(+)-**12b** {82% isolated yield and >99% ee, $[\alpha]_D^{20} = +82.5$ (*c* 2, $CHCl_3$)}.

4.1.9. (*R*)-(+)-1-(4-Chloro-2-pyridinyl)propyl acetate 12b. Colorless oil; R_f (20% EtOAc/hexane): 0.30; IR (NaCl): ν 2973, 2938, 1738, 1578, 1558, 1465, 1394, 1372, 1234, 1022, 972, 829, and 709 cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 0.91 (t, $^3J_{HH} = 7.4$ Hz, 3H, H_9), 1.85–2.04 (m, 2H, H_8), 2.15 (s, 3H, H_{11}), 5.69 (t, $^3J_{HH} = 6.7$ Hz, 1H, H_7), 7.21 (dd, $^3J_{HH} = 5.4$, $^4J_{HH} = 1.6$ Hz, 1H, H_5), 7.31 (d, $^4J_{HH} = 1.6$ Hz, 1H, H_3), and 8.47 (d, $^3J_{HH} = 5.4$, 1H, H_6); ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 9.6 (C_9), 21.1 (C_{11}), 27.9 (C_8), 76.7 (C_7), 121.3 (C_3), 122.7 (C_5), 144.7 (C_4), 150.2 (C_6), 161.4 (C_2), and 170.4 (C_{10}); MS (ESI^+, m/z): 238 [$(M^{37}Cl+Na)^+$, 33%], 236 [$(M^{35}Cl+Na)^+$, 100%], and 214 [$(M^{35}Cl+H)^+$, 5%]. Anal. Calcd (%) for $C_{10}H_{12}NO_2Cl$: C, 56.21; H, 5.66; N, 6.55. Found: C, 56.2; H, 5.6; N, 6.6.

4.1.10. Kinetic resolution of (±)-8c. To a suspension of **8c** (500 mg, 2.69 mmol) and PSL-C (431 mg) in dry THF (27 mL) under a nitrogen atmosphere, vinyl acetate (740 μL, 8.08 mmol) was added, and the reaction shaken at 30 °C and 250 rpm. Aliquots were regularly analyzed by HPLC until 50% conversion was reached. The reaction was then stopped and the enzyme filtered with CH_2Cl_2 (3 × 10 mL). The solvent was evaporated and the crude of reaction purified by flash chromatography (15–60% EtOAc/hexane) affording (*S*)-(−)-**8c** {89% isolated yield and >99% ee, $[\alpha]_D^{20} = -41.7$ (*c* 2, $CHCl_3$)} and (*R*)-(+)-**12c** {97% isolated yield and >99% ee, $[\alpha]_D^{20} = +74.9$ (*c* 2, $CHCl_3$)}.

4.1.11. (*R*)-(+)-1-(4-Chloro-2-pyridinyl)butyl acetate 12c. Colorless oil; R_f (20% EtOAc/hexane): 0.37; IR (NaCl): ν 2961, 2935, 2874, 1739, 1578, 1557, 1372, 1232, 1030, 828, and 709 cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz) δ 0.91 (t, $^3J_{HH} = 7.3$ Hz, 3H, H_{10}), 1.23–1.43 (m, 2H, H_9), 1.83–1.91 (m, 2H, H_8), 2.12 (s, 3H, H_{12}), 5.75 (t, $^3J_{HH} = 7.0$ Hz, 1H, H_7), 7.17 (dd, $^3J_{HH} = 5.3$, $^4J_{HH} = 1.8$ Hz, 1H, H_5), 7.28 (d, $^4J_{HH} = 1.8$ Hz, 1H, H_3), and 8.45 (d, $^3J_{HH} = 5.3$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 100.61 MHz): δ 13.7 (C_{10}), 18.5 (C_9), 21.0 (C_{12}), 36.8 (C_8), 75.9 (C_7) 121.1 (C_3), 122.9 (C_5), 144.6 (C_4), 150.2 (C_6), 161.6 (C_2), and 170.2 (C_{11}); MS (ESI^+, m/z): 252 [$(M^{37}Cl+Na)^+$, 33%], 250 [$(M^{35}Cl+Na)^+$, 100%], and 228 [$(M^{35}Cl+H)^+$, 4%]. Anal. Calcd (%) for $C_{11}H_{14}NO_2Cl$: C, 58.02; H, 6.20; N, 6.15. Found: C, 58.0; H, 6.1; N, 6.1.

4.1.12. Kinetic resolution of (±)-8d. To a suspension of **8d** (500 mg, 2.50 mmol) and PSL-C (402 mg) in dry THF (25 mL) under a nitrogen atmosphere, vinyl acetate (690 μL, 7.50 mmol) was added and the reaction shaken at 30 °C and 250 rpm. Aliquots were regularly analyzed by HPLC until 50% conversion was reached, then the reaction was stopped, and the enzyme filtered with CH_2Cl_2 (3 × 10 mL). The solvent was evaporated

and the crude of reaction purified by *flash* chromatography (15–55% EtOAc/hexane) affording (*S*)-(−)-**8d** {89% isolated yield and >99% ee, $[\alpha]_D^{20} = -45.8$ (*c* 2, $CHCl_3$)} and (*R*)-(+)-**12d** {88% isolated yield and >99% ee, $[\alpha]_D^{20} = +70.8$ (*c* 2, $CHCl_3$)}.

4.1.13. (*R*)-(+)-1-(4-Chloro-2-pyridinyl)pentyl acetate 12d. Colorless oil; R_f (20% EtOAc/hexane): 0.47; IR (NaCl): *v* 2958, 2932, 2863, 1742, 1578, 1557, 1372, 1233, and 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 0.89 (t, $^3J_{HH} = 6.9$ Hz, 3H, H_{13}), 1.26–1.38 (m, 4H, $2H_9$+$2H_{10}$), 1.79–1.95 (m, 2H, H_8), 2.15 (s, 3H, H_{13}), 5.76 (t, $^3J_{HH} = 6.7$ Hz, 1H, H_7), 7.21 (dd, $^3J_{HH} = 5.3$, $^4J_{HH} = 1.9$ Hz, 1H, H_5), 7.31 (d, $^4J_{HH} = 1.9$ Hz, 1H, H_3), and 8.48 (d, $^3J_{HH} = 5.3$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 13.9 (C_{11}), 21.1 (C_{13}), 22.4 (C_{10}), 27.4 (C_9), 34.5 (C_8), 76.2 (C_7), 121.2 (C_3), 122.9 (C_5), 144.7 (C_4), 150.2 (C_6), 161.7 (C_2), and 170.3 (C_{12}); MS (ESI^+, *m*/*z*): 264 [$(M^{35}Cl+Na)^+$, 7%], 244 [$(M^{37}Cl+H)^+$, 33%], and 242 [$(M^{35}Cl+H)^+$, 100%]. Anal. Calcd (%) for $C_{12}H_{16}NO_2Cl$: C, 59.63; H, 6.67; N, 5.79. Found: C, 59.9; H, 6.8; N, 5.6.

4.1.14. Kinetic resolution of (±)-9a. To a suspension of **9a** (33.2 mg, 0.20 mmol) and PSL-C (32 mg) in dry solvent (2 mL) under a nitrogen atmosphere, vinyl acetate (55 μL, 0.60 mmol) was added and the reaction shaken at 250 rpm. Aliquots were regularly analyzed by HPLC, then the reaction was stopped and the enzyme filtered with CH_2Cl_2 (3 × 2 mL). The solvent was evaporated and the crude of reaction purified by flash chromatography (15–100% MeOH/EtOAc) affording (*R*)-(+)-**11a** and (*S*)-(−)-**9a** (see Table 2).

4.1.15. (*R*)-(+)-1-[4-(*N*,*N*-Dimethylamino)-2-pyridinyl]-ethyl acetate 11a. $[\alpha]_D^{20} = +36.6$ (*c* 0.8, $CHCl_3$). Colorless oil; R_f (100% MeOH): 0.51; IR (NaCl): *v* 3423, 2947, 1736, 1607, 1544, 1375, 1424, and 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz) δ 1.58 (d, $^3J_{HH} = 6.6$ Hz 3H, H_8), 2.12 (s, 3H, H_{10}), 3.02 (s, 6H, H_{11}), 5.80 (q, $^3J_{HH} = 6.6$ Hz, 1H, H_7), 6.42 (dd, $^3J_{HH} = 5.9$, $^4J_{HH} = 2.7$ Hz, 1H, H_5), 6.52 (d, $^4J_{HH} = 2.7$ Hz, 1H, H_5), and 8.23 (d, $^3J_{HH} = 5.9$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 20.6 (C_8), 21.2 (C_{10}), 39.1 (C_{11}), 73.1 (C_7), 103.0 (C_3), 105.6 (C_5), 148.7 (C_6), 155.0 (C_4), 159.6 (C_2), and 170.2 (C_9); MS (ESI^+, *m*/*z*): 209 [$(M+H)^+$, 100%]. Anal. Calcd (%) for $C_{11}H_{16}N_2O_2$: C, 63.42; H, 7.75; N, 13.46. Found: C, 63.4; H, 7.8; N; 13.5.

4.1.16. (*S*)-(−)-4-(*N*,*N*-Dimethylamino)-2-(1-hydroxyethyl)pyridine 9a. A mixture of (−)-**8a** (150 mg, 0.95 mmol) and a 40% aqueous solution of Me_2NH (4 mL) was stirred in a sealed tube at 100 °C until complete consumption of the starting material (32 h). The solvent was evaporated by distillation at a reduced pressure and the resulting crude purified by flash chromatography (80–100% MeOH/EtOAc) yielding 159 mg as a white solid (99%). $[\alpha]_D^{20} = -31.5$ (*c* 1, EtOH); R_f (100% MeOH): 0.10. Mp: 120–122 °C; IR (KBr): *v* 3384, 2973, 2928, 1608, 1544, 1514, 1379, 1226, and 1000 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.48 (d, $^3J_{HH} = 6.3$ Hz, 3H, H_8), 3.01 (s, 6H, H_{10}), 4.11 (br s, 1H, OH), 4.77 (q, $^3J_{HH} = 6.3$ Hz, 1H, H_7), 6.41–6.44 (m, 2H, H_3+H_5), and 8.14 (d, $^3J_{HH} = 5.7$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 24.4 (C_8), 39.1 (C_{10}), 68.9 (C_7), 101.3 (C_3), 105.5 (C_5), 147.9 (C_6), 154.9 (C_4), and 163.2 (C_2); MS (ESI^+, *m*/*z*): 167 [$(M+H)^+$, 100%]. Anal. Calcd (%) for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 65.1; H, 8.5; N; 16.9.

4.1.17. (*R*)-(+)-4-(*N*,*N*-Dimethylamino)-2-(1-hydroxyethyl)pyridine 9a. Same procedure as (−)-**9a** affording (+)-**9a** from (+)-**12a**, as a colorless oil after 22 h (95%). $[\alpha]_D^{20} = +34.1$ (*c* 1, EtOH).

4.1.18. (*S*)-(−)-4-(*N*,*N*-Dimethylamino)-2-(1-hydroxypropyl)pyridine 9b. Same procedure as (−)-**9a** affording (−)-**9b** from (−)-**8b**, as a colorless oil after 24 h (100%). $[\alpha]_D^{20} = -19.9$ (*c* 1, EtOH); R_f (100% MeOH): 0.12; IR (NaCl): *v* 3344, 2959, 2361, 1643, 1558, 1514, 1443, 1401, 1228, and 1008 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 0.95 (t, $^3J_{HH} = 7.4$ Hz, 3H, H_9), 1.66–1.89 (m, 2H, H_8), 3.01 (s, 6H, H_{10}), 4.51–4.57 (m, 1H, H_7), 5.83 (br s, 1H, OH), 6.39–6.44 (m, 2H, H_3+H_5), and 8.10 (d, $^3J_{HH} = 5.9$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.64 (C_9), 31.0 (C_8), 39.1 (C_{10}), 74.0 (C_7), 102.5 (C_3), 105.3 (C_5), 146.8 (C_6), 155.0 (C_4), and 161.6 (C_2); MS (ESI^+, *m*/*z*): 182 [$(M+H)^+$, 100%]. Anal. Calcd (%) for $C_{10}H_{16}N_2O$: C, 66.64; H, 8.95; N, 15.54 Found: C, 66.7; H, 9.0; N; 15.5.

4.1.19. (*S*)-(−)-4-(*N*,*N*-Dimethylamino)-2-(1-hydroxybutyl)pyridine 9c. Same procedure as (−)-**9a** affording (−)-**9c** from (−)-**8c**, as a colorless oil after 24 h (100%). $[\alpha]_D^{20} = -26.7$ (*c* 1, EtOH); R_f (100% MeOH): 0.15; IR (NaCl): *v* 3473, 3215, 3103, 2968, 2361, 2343, 1645, 1602, 1597, 1004, and 984 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz) δ 0.90 (t, $^3J_{HH} = 7.4$ Hz, 3H, H_{10}), 1.37–1.47 (m, 2H, H_9), 1.72–1.76 (m, 2H, H_8), 3.01 (s, 6H, H_{11}), 4.68–4.70 (m, 1H, H_7), 6.45–6.52 (m, 2H, H_3+H_5), 6.89 (br s, 1H, OH), and 8.08 (d, $^3J_{HH} = 6.0$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.8 (C_{10}), 18.6 (C_8), 39.4 (C_{11}), 39.9 (C_8), 71.8 (C_7), 102.7 (C_3), 105.3 (C_5), 144.0 (C_6), 155.8 (C_4), and 160.6 (C_2); MS (ESI^+, *m*/*z*): 195 [$(M+H)^+$, 100%]. Anal. Calcd (%) for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.42. Found: C, 67.9; H, 9.3; N; 14.4.

4.1.20. (*S*)-(−)-4-(*N*,*N*-Dimethylamino)-2-(1-hydroxypentyl)pyridine 9d. Same procedure as (−)-**9a** affording (−)-**9d** from (−)-**8d**, as a colorless oil after 48 h (100%). $[\alpha]_D^{20} = -21.8$ (*c* 1, EtOH); R_f (100% MeOH): 0.22; IR (NaCl): *v* 3408, 2957, 1644, 1564, 1466, 1403, 1231, and 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz) δ 0.90 (t, $^3J_{HH} = 7.0$ Hz, 3H, H_{11}), 1.26–1.46 (m, 4H, $2H_9$+$2H_{10}$), 1.65–1.83 (m, 2H, H_8), 3.00 (s, 6H, H_{11}), 4.56–4.63 (m, 1H, H_7), 6.40–6.43 (m, 2H, H_3+H_5), and 8.15 (d, $^3J_{HH} = 6.7$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.0 (C_{11}), 22.7 (C_{10}), 27.5 (C_9), 38.4 (C_8), 39.1 (C_{12}), 73.0 (C_7), 102.3 (C_3), 105.5 (C_5), 148.0 (C_6), 154.8 (C_4), and 162.5 (C_2); MS (ESI^+, *m*/*z*): 209 [$(M+H)^+$, 100%]. Anal. Calcd (%) for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found: C, 69.2; H, 9.7; N; 13.4.

4.1.21. (*R*)-(+)-2-(1-Hydroxyethyl)pyridine 13a. To a suspension of (+)-**12a** (64 mg, 0.32 mmol) and palladium acetate (II) (0.016 mmol, 3.6 mg) in dry THF and under a nitrogen atmosphere were added successively potassium fluoride solution (0.64 mmol, 37 mg) in degassed water (640 μL) and polyhydroxymethylsiloxane (77 mg, 1.28 mmol). The mixture was stirred for 4 h at room temperature until complete disappearance of the starting material. Excess of PMHS was destroyed by adding 3 M NaOH solution (15 mL) and stirring the mixture for 5 h. Then the solution was extracted with Et_2O (3×10 mL), the organic phases combined, dried over Na_2SO_4, and finally the solvent distilled under reduced pressure to obtain a crude of reaction, which was purified by flash chromatography (70% Et_2O/hexane) isolating 22 mg as a colorless oil (43%). R_f (70% Et_2O/hexane): 0.11; $[\alpha]_D^{20} = +18.4$ (*c* 1.0, EtOH), literature $[\alpha]_D^{20} = +14.7$ (*c* 4.4, EtOH);[13] ^1H NMR ($CDCl_3$, 200 MHz): δ 1.51 (d, $^3J_{HH} = 6.7$ Hz, 3H, H_8), 4.51 (br s, 1H, OH), 4.90 (q, $^3J_{HH} = 6.7$ Hz, 1H, H_7), 7.17–7.31 (m, 2H, H_3+H_5), 7.65–7.74 (m, 1H, H_4), and 8.54 (dd, $^3J_{HH} = 4.9$, $^4J_{HH} = 0.8$ Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 24.2 (C_8), 68.7 (C_7), 119.7 (C_3), 122.1 (C_5), 136.7 (C_4), 148.0 (C_6), and 162.9 (C_2).

4.1.22. (*R*)-(+)-2-(1-Hydroxypropyl)pyridine 13b. Same procedure as (+)-**13a** affording (+)-**13b** from (+)-**12b**, as a colorless oil (50%). R_f (70% Et_2O/hexane): 0.13; $[\alpha]_D^{20} = +11.7$ (*c* 1.1, $CHCl_3$), literature $[\alpha]_D^{20} = +38.0$ (*c* 1.68, EtOH);[14] ^1H NMR ($CDCl_3$, 200 MHz): δ 0.96 (t, $^3J_{HH} = 7.4$ Hz, 3H, H_9), 1.62–2.00 (m, 2H, H_8), 4.25 (br s, 1H, OH), 4.71 (t, $^3J_{HH} = 5.3$ Hz, 1H, H_7), 7.18–7.28 (m, 2H, H_3+H_5), 7.66–7.74 (m, 1H, H_4), and 8.56 (d, $^3J_{HH} = 5.1$ Hz 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 9.3 (C_9), 31.3 (C_8), 73.6 (C_7), 120.3 (C_3), 122.1 (C_5), 136.5 (C_4), 148.1 (C_6), and 161.9 (C_2).

4.1.23. (*R*)-(+)-2-(1-Hydroxybutyl)pyridine 13c. Same procedure as (+)-**13a** affording (+)-**13c** from (+)-**12c**, as a colorless oil (39%). R_f (70% Et_2O/hexane): 0.17; $[\alpha]_D^{20} = +29.8$ (*c* 0.5, $CHCl_3$); IR (NaCl): *v* 3363, 1728, 1596, 1573, 1477, 1437, 1255, 1120, 1084, and 1019 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.97 (t, $^3J_{HH} = 7.2$ Hz, 3H, H_{10}), 1.29–1.50 (m, 2H, H_9) 1.52–1.98 (m, 2H, H_8), 4.58 (br s, 1H, OH), 4.73 (t, $^3J_{HH} = 7.0$ Hz, 1H, H_7), 7.09–7.30 (m, 2H, H_3+H_5), 7.61–7.71 (m, 1H, H_4), and 8.49 (d, $^3J_{HH} = 4.7$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 14.0 (C_{10}), 18.4 (C_9), 40.7 (C_8), 72.5 (C_7), 120.3 (C_3), 122.1 (C_5), 136.5 (C_4), 148.1 (C_6), and 162.2 (C_2); MS (ESI^+, *m*/*z*): 174 [$(M+Na)^+$, 100%], and 152 [$(M+H)^+$, 87%]. Anal. Calcd (%) for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.6; H, 8.5; N; 9.3.

4.1.24. (*R*)-(+)-2-(1-Hydroxypentyl)pyridine 13d. Same procedure as (+)-**13a** affording (+)-**13d** from (+)-**12d**, as a colorless oil (62%). R_f (70% Et_2O/hexane): 0.18; $[\alpha]_D^{20} = +20.7$ (*c* 1.5, $CHCl_3$); IR (NaCl): *v* 3385, 1643, 1596, 1478, 1437, 1255, 1121, 1084, 1018, and 905 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 0.88 (t, $^3J_{HH} = 7.1$ Hz, 3H, H_{11}), 1.28–1.44 (m, 2H, H_{10}), 1.62–1.85 (m, 2H, H_9), 1.62–1.84 (m, 2H, H_8), 4.23 (br s, 1H, OH), 4.72 (t, $^3J_{HH} = 4.5$ Hz, 1H, H_7), 7.16–7.26 (m, 2H, H_3+H_5), 7.64–7.69 (m, 1H, H_4), and 8.52 (d, $^3J_{HH} = 4.5$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ ($CDCl_3$, 75.5 MHz): δ 13.9 (C_{11}), 22.6 (C_{10}), 27.3 (C_9), 38.2 (C_8), 72.7 (C_7), 120.2 (C_3), 122.1 (C_5), 136.5 (C_4), 148.1 (C_6), and 162.4 (C_2); MS (ESI^+, *m*/*z*): 188 [$(M+Na)^+$, 100%], and 166 [$(M+H)^+$, 85%]. Anal. Calcd (%) for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.7; H, 9.1; N; 8.5.

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