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Biocatalytic preparation of optically active 4-(*N*,*N*-dimethylamino)pyridines for application in chemical asymmetric catalysis

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Abstract—4-Chloro-2-(1-hydroxybenzyl)pyridine and 4-chloro-2-(1-hydroxyalkyl)pyridines were obtained with moderate to excellent enantiomeric excesses and high isolated yields by bioreduction with Baker's yeast of the corresponding ketones. The resulting optically active alcohols were transformed into adequate DMAP derivatives, which have been applied in asymmetric catalytic processes as nucleophilic catalysts in the stereoselective chemical alkoxycarbonylation of 1-phenylethanol or as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde.

1. Introduction

4-(*N*,*N*-Dimethylamino)pyridine (DMAP) has become one of the most popular catalysts for different processes such as acylations, alkylations, silylations, Baylis–Hillman reaction and nucleophilic substitutions of alcohols and amines.[1] The development of chiral DMAP derivatives has received considerable attention, since they have been successfully employed as chiral nucleophilic catalysts in a wide range of asymmetric synthetic processes.[1b,2] There are many different strategies for the preparation of DMAP analogues, for instance Ruble and Fu introduced the concept of 'planar chirality',[3] and a few examples of ferrocene-fused DMAP complexes have been described in the literature, which have been used in stereoselective processes.[4] The synthesis of atropoisomeric biaryl complexes,[5] 2-,[6] 3-,[7] and 4-substituted DMAP derivatives[8] have also been described, some of which have been applied to different asymmetric processes showing different degrees of reactivity and stereoselectivity.

Enzymes are recognized as valuable tools for the synthesis of optically active compounds. The use of oxidoreductases, in particular Baker's yeast (*Saccharomyces cerevisiae*), has attracted significant attention because it provides very efficient access to important optically enriched products. Fermentation processes of heteroaryl-alkyl and heteroaryl-aryl ketones like α,β,γ-acetylpyridines, α-acetylfuran,[9] benzoylpyridine *N*-oxides,[10] and benzoylpyridines[10b] with Baker's yeast were studied by Takeshita et al. achieving, in some cases, the corresponding alcohols with high enantiopreferences. Successful enantioselective reductions of 2,6-diacetylpyridine[11] and other diacetylaromatics[12] have also been described. Other biocatalysts have been employed in recent years in the bioreduction of pyridine ketone derivatives such as immobilized cells of *Daucus carota*,[13] *Geotrichum candidum*,[14] *Camellia sinensis*,[15] *Rhizopus arrhizus*,[16] *Pseudomonas putida*,[17] *Rhodococcus species*[18] or *Candida viswanathii*,[19] while some recombinant strains have shown activity toward these substrates.[20]

Herein, we report the development of a new chemoenzymatic route for the synthesis of chiral 2-substituted DMAP derivatives where the key step for the introduction of chirality is the bioreduction of ketones catalyzed by different oxidoreductases. The preparation and application of adequate chiral DMAP analogues in asymmetric catalytic processes have also been studied.

2. Results and discussion

Recently, we described the chemoenzymatic synthesis of enantiomerically pure 4-(*N*,*N*-dimethylamino)-2-(1-hydroxyalkyl)pyridines, where *Pseudomonas cepacia* lipase

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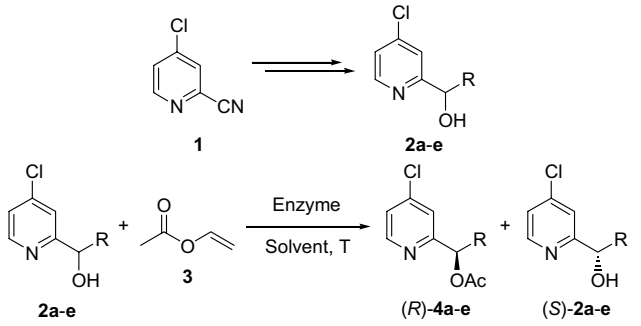
(PSL-C) played a fundamental role in the introduction of chirality, which was possible through transesterification reactions of 4-chloro-2-(1-hydroxyalkyl)pyridines **2a–d** using 3 equiv of vinyl acetate as the acyl donor and THF as the solvent (Scheme 1).[21]



Scheme 1. Synthesis and lipase-catalyzed resolution of 4-chloro-2-(substituted)pyridines.

In all cases, PSL-C showed excellent stereoselectivities in the acylation of these 4-chloro derivatives ($E > 200$). Our next goal was the extension of these results to the enzymatic resolution of 4-chloro-2-(1-hydroxybenzyl)pyridine **2e**, which was synthesized from 4-chloro-2-cyanopyridine **1** in 75% yield. Initially we carried out the enzymatic transesterification of **2e** under the same conditions than the ones used in the kinetic resolution of **2a–d**, however no reaction was observed and neither at 60 °C. Other enzymes such as *Candida antarctica* lipase A (CAL-A) and *C. antarctica* lipase B (CAL-B) were also tested but the final product could not be detected. Finally, we decided to carry out the process using vinyl acetate as solvent and acyl donor at 60 °C and after 166 h, 42% conversion was reached affording enantiomerically enriched product (82% ee) and substrate (59% ee).

Previously we have described the resolution of substrates **2a–d**, which led to the formation of the corresponding acetates (*R*)-**4a–d**, whose stereochemistries follow the ones expected for Kazlauskas' rule.[22] To determine the configuration of substrate **2e** and product **4e** from the enzymatic transesterification of racemic **2e**, we applied Kelly's empirical method,[23] which is described below.

2.1. Bioreduction of 2-alkanoyl-4-chloropyridines and 2-benzoyl-4-chloropyridine using Baker's yeast

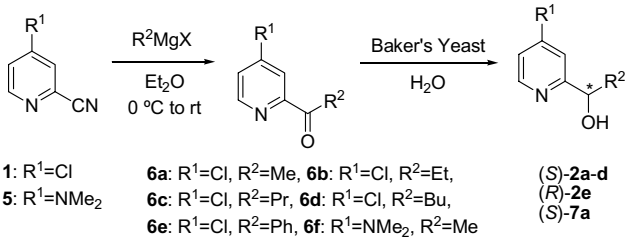
Due to the low enantioselectivity obtained in the enzymatic transesterification of **2e** ($E = 18$), we started to investigate new enzymatic routes for the synthesis of enantiomerically pure 4-chloro-2-(1-hydroxysubstituted)pyridines. By taking into account the excellent selectivities achieved in the bioreduction of pyridine ketone derivatives using Baker's yeast,[9–12] we turned our attention to this type of processes.

The synthesis of 2-alkanoyl-4-chloropyridines is not an easy task because they present serious problems of volatility; for that reason we reacted 4-chloro-2-cyanopyridine **1** with different organomagnesium derivatives (Table 1 and Scheme 2) and the isolation steps after flash chromatography were carried out taking as many precautions as possible. For example, by assuring that the bath temperature of the rotary evaporator was always below 25 °C, avoiding later use of the vacuum pump, and storing the products at cold temperature. In this manner ketones **6a–e** were obtained with good yields (75–87%).

Table 1. Synthesis of ketones **6a–e**

Entry	R^2	X	Yield[a] (%)
1	Me	I	87
2	Et	Br	81
3	Pr	Br	79
4	Bu	Cl	85
5	Ph	Br	75

[a] Isolated yield by flash chromatography.



Scheme 2. Synthesis of ketones **6a–f** and bioreduction using Baker's yeast as biocatalyst.

For the formation of 2-acetyl-4-(*N*,*N*-dimethylamino)pyridine **6f** we first tried to react **1** with a 40% aqueous solution of dimethylamine at 100 °C, isolating 2-cyano-4-(*N*,*N*-dimethylamino)pyridine **5** in 71% yield, however, this substrate was not soluble in the diethyl ether solution of the organomagnesium derivative, so we decided to prepare **6f** from **6a** instead of **1** by simple substitution of the chlorine atom by the dimethylamino group which occurred with moderate yield (53%) as reaction by-products appeared during the process.

Bioreduction of ketones **6a–f** was carried out in an aqueous solution of glucose, shaking the corresponding mixtures at 30 °C (Table 2). All conversions were up to 75% after 60 h except for the case of **6f** due to solubility problems. Comparing the alkanoyl substrates **6a–d**, a decrease in the conversion occurred when the size of the alkyl chain length was increased from the methyl substitution **6a** to bulkier groups

Table 2. Bioreduction of ketones **6a–f** using Baker's yeast as a biocatalyst

Entry	R^1	R^2	t (h)	c[a] (%)	ee[b] (%)
1	Cl	Me	60	100 (76)	98
2	Cl	Et	60	90 (71)	91
3	Cl	Pr	60	79 (73)	81
4	Cl	Bu	60	84 (72)	80
5	Cl	Ph	60	88 (84)	97
6	NMe_2	Me	168	58 (40)	98

[a] Calculated by ^{1}H NMR of the reaction crude. Isolated yields in brackets.
[b] Calculated by HPLC.

such as ethyl, propyl or butyl **6b–d**. Nevertheless, the isolated yields of all reactions reached similar values. Better yields were obtained for **6e** (entry 5) as the phenyl substituent made the molecule more hydrophobic and could be easily extracted in the purification step. In the case of **6f** longer reaction times were needed in order to afford significant conversions to **7a** (entry 6).

Importantly, alcohols **2a–e** and **7a** were obtained with moderate to excellent ee (80–98%), up to 95% with $R^2 = Me$ or Ph and decreasing when the alkyl chain was elongated. Enzymatic reduction of the ketones afforded the (*S*)-alcohols, except in the case of the phenyl derivative, which gave (*R*)-**2e**. Synthesis, using yeast of enantiomerically enriched alcohol **2e** ($R^2 = Ph$) represents a great advantage in comparison, with lipase-catalyzed transesterification which occurs with low enantioselectivity. Moreover, isolated yields can exceed 50%, which is generally the main limitation of a kinetic resolution.

The absolute stereochemistries of alcohols **2a–d** and **7a–d** were assigned by comparing the values of the specific rotation with those previously described.[21] To determine the stereochemistry of the products obtained in the lipase-catalyzed transesterification reaction, the optically enriched acetate (*R*)-**4e** was converted in the alcohol (*R*)-**2e** using sodium hydroxide in MeOH, and later to the Mosher's ester observing clearly a major signal, which corresponds to the (*R*,*R*)-diastereoisomer ($\delta = 8.50$ ppm, Fig. 1).

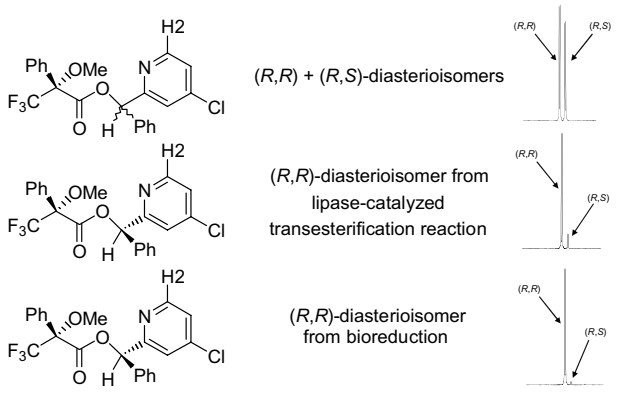


Figure 1. Structure of (*R*)-MTPA esters derivatives of **2e**.

The reason for these spectra is that the hydrogen atom at the 2-position of the pyridine ring is not shielded by the phenyl group of the Mosher's reagent. The same stereochemistry was assigned for the alcohol obtained in the bioreduction, as the same order of peaks was observed in the ^{1}H NMR spectrum.

In spite of the good results obtained in the bioreduction of pyridine ketones using Baker's yeast, we explored the use of other oxidoreductases such as alcohol dehydrogenases from *Thermoanaerobacter species* (T-ADH) or from *Lactobacillus brevis* (LB-ADH) that present complementary enantiopreferences; T-ADH catalyses the enantioselective reduction of prochiral ketones to (*S*)-alcohols meanwhile LB-ADH allow the production of (*R*)-alcohols. Although they require the inconvenient use of the NADPH cofactor, there is advantage of affording alcohol derivatives with opposite stereochemistry than the ones obtained from the reduction with Baker's yeast. Bioreduction processes were carried out in a TRIS/HCl buffer solution of pH 7 and the results are summarized in Table 3.

Table 3. Reduction of ketones **6a–e** using T-ADH and LB-ADH

Entry	6	ADH	*t* (h)	*c*[a] (%)	ee[b] (%)	Conf.
1	**a**	T	38	100 (89)	>99	*S*
2	**a**	LB	38	100 (87)	>99	*R*
3	**b**	T	47	100 (94)	>99	*S*
4	**b**	LB	47	100 (91)	>99	*R*
5	**c**	T	168	—	—	—
6	**c**	LB	168	—	—	—
7	**d**	T	168	—	—	—
8	**d**	LB	168	—	—	—
9	**e**	T	168	—	—	—
10	**e**	LB	168	—	—	—

[a] Calculated by ^{1}H NMR of the reaction crude. Isolated yields in brackets.
[b] Calculated by HPLC.

Both enzymes were only active with the less hindered ketones **6a–b**, and no reaction was observed with bulkier substrates. Fortunately, these two alcohol dehydrogenases were completely enantioselective, showing opposite stereoselections. In this manner, T-ADH produced (*S*)-alcohols similar to Baker's yeast; meanwhile LB-ADH allowed the formation of enantiomerically pure (*R*)-alcohols. Isolated yields were higher than the ones obtained with Baker's yeast as the reaction work-ups for the isolation of the final product were easier (see Section 4).

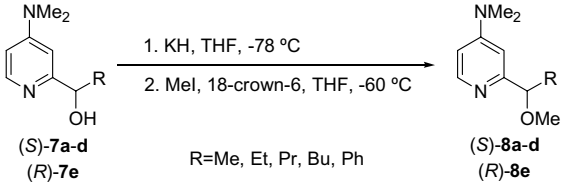
2.2. Synthesis of a chiral catalyst and application in asymmetric catalysis

Once the reduction processes of the ketones were successfully achieved, the chloro derivatives (*S*)-**2a–d** and (*R*)-**2e** were converted into the corresponding 4-*N*,*N*-dimethylamino products, using the same procedure for the transformation of **1** into **5**.

For the benzyl derivative, we used the product obtained in the bioreduction process as previously described, because this reaction led to the formation of the product (*R*)-**2e** in 97% ee. However, as not all the enzymatic reductions of the alkyl derivatives occurred with complete selectivity, and in order to compare the selectivity factor(s) in the application of these catalysts to chemical asymmetric processes,[24] we decided to use those obtained through the lipase-catalyzed transesterification of the corresponding alcohols, that were previously isolated enantiomerically pure.[21] It is also noteworthy that the alkyl catalysts **8a–d** have an (*S*)-configuration and the benzyl derivative **8e** has (*R*)-configuration, which explains the opposite configuration of substrates and products obtained in the chemical alkoxycarbonylation depending upon the catalyst used in the reaction.

To apply these synthons to catalytic asymmetric processes, protection of the oxygen of the hydroxyl group was

required in order to avoid the formation of reaction by-products during the development of the asymmetric processes. For this process, potassium hydride was used as a base and methyl iodide as the electrophilic agent (Scheme 3), obtaining the *O*-methylated compounds (*S*)-**8a–d** and (*R*)-**8e** in good yields (70–76%). No racemization occurred in these nucleophilic substitution steps as (*R*)-**7e** and (*R*)-**8e** were injected in an HPLC and compared with the corresponding racemates.



Scheme 3. Synthesis of *O*-methylated derivatives (**8a–e**).

Vedejs et al. developed the chemical synthesis of a chiral DMAP substituted at the 2-position of the pyridine ring with a structure similar to that of compounds **8a–e** having a *tert*-butyl substituent instead of an alkyl or phenyl substitutions.[6a] They tested the selectivity of the catalyst in the alkoxycarbonylation of 1-phenylethanol using 2,2,2-trichloro-1,1-dimethylethyl chloroformate **10** as an alkoxycarbonylating reagent. At this point, we decided to use our catalysts in this model reaction with NEt_3 as base and $ZnCl_2$ as a Lewis acid (Scheme 4).

Carboxyl transfer occurred with moderate selectivities (Table 4, $s = 4.2$–10.1) which increased when the alkyl chain became longer (entries 1–4). However, the use of **8e**, where the phenyl substitution is present, gave the lowest selectivity factors (entry 5).

Additionally, the synthesis and later application of the *O*-butyl derivative (*S*)-**9** was performed using 1-iodobutane in order to compare the influence of the substituent on the oxygen atom of the catalyst. Interestingly slightly better results were observed for the bulkier substrate in comparison with the *O*-methylated compound (entries 1 and 6).

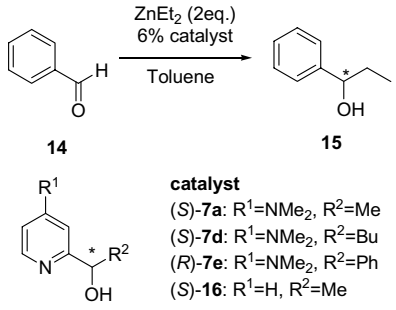
One advantage of these catalysts is that although it is necessary to use them in stoichiometric amounts, they can be recovered at the end of the process and reused as many times as it would be necessary. On the other hand, it is noteworthy that the production of enantiomerically pure 1-phenylethanol is more likely through other chemical or enzymatic procedures, however, these results are encouraging for the application of these novel catalysts in other asymmetric catalytic processes.

Table 4. Nonenzymatic kinetic resolution of 1-phenylethanol at room temperature during 60 h

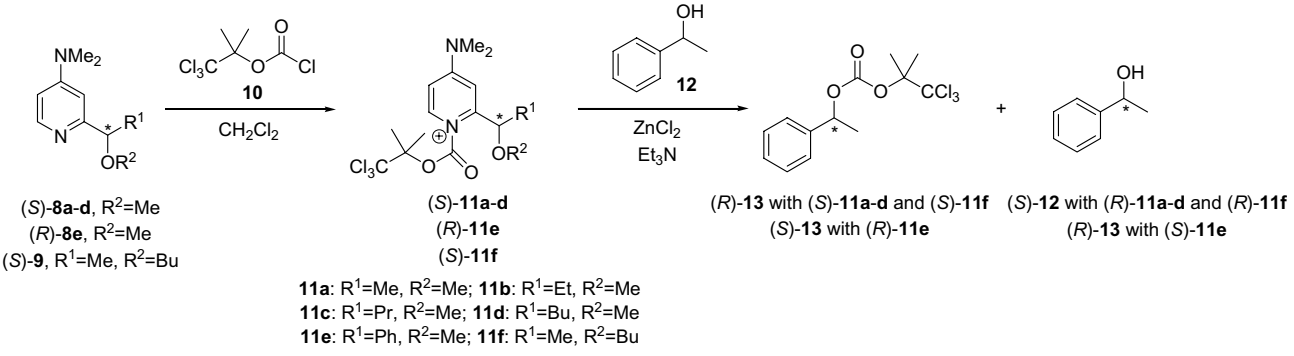
Entry	R^1	R^2	c[a] (%)	ee_s[b] (%)	ee_p[b] (%)	s[c]
1	Me	Me	32	28	60	5.5
2	Et	Me	34	34	65	6.5
3	Pr	Me	37	43	73	9.6
4	Bu	Me	34	38	75	10.1
5	Ph	Me	50	46	46	4.2
6	Me	Bu	36	36	65	6.7

[a] $c = ee_s/(ee_s + ee_p)$.
[b] Calculated by chiral HPLC.
[c] $s = \ln[(1 - c) \times (1 - ee_p)]/\ln[(1 - c) \times (1 + ee_p)]$.

Once the potential of chiral DMAP derivatives as nucleophilic catalysts had been demonstrated, we studied their role as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde, one of the most effective methods for the production of chiral secondary alcohols.[25] Traditionally, amino alcohols are considered as excellent ligands for the enantioselective addition of organometallic reagents to aldehydes.[26] For that reason, we decided to examine the behavior of (*S*)-**7a**, (*S*)-**7d**, and (*R*)-**7e** (Scheme 5).



Scheme 5. Enantioselective addition of $ZnEt_2$ to benzaldehyde promoted by chiral DMAP ligands.



Scheme 4. Stereoselective carboxylation of 1-phenylethanol catalyzed by chiral DMAP analogues.

Reactions were performed using 2 equiv of $ZnEt_2$ and toluene as solvent isolating 1-phenylpropan-1-ol in 100% conversion and with moderate ee (Table 5), which overcome the ee observed when no substitution was present at the 4-position of the pyridine ring (entry 4) in comparison with (*S*)-**7a** (33%).[27]

Table 5. Use of chiral DMAP derivatives in the enantioselective addition of $ZnEt_2$ to benzaldehyde

Entry	Chiral ligand	Yield (%)	ee[a] (%)	Conf. (**15**)
1	(*S*)-**7a**	80	33	*S*
2	(*S*)-**7d**	79	31	*S*
3	(*R*)-**7e**	83	35	*R*
4	(*S*)-**16**	75	27	*S*

[a] Calculated by chiral HPLC.

3. Conclusions

In conclusion, a new family of chiral catalysts derived from DMAP has been obtained through a straightforward chemoenzymatic synthesis where the stereoselective reduction of a broad range of ketones has been achieved with high enantiomeric excesses using Baker's yeast as the biocatalyst. Moreover, the corresponding analogues have shown some degree of enantiopreference as nucleophilic catalysts in the nonenzymatic kinetic resolution of 1-phenylethanol, while their use as chiral ligands in the addition of diethylzinc to benzaldehyde has also been demonstrated.

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. Baker's yeast (type II from *S. cerevisiae*) was purchased from Sigma. Alcohol dehydrogenases *T. species* (T-ADH, 378 U/mL) and *L. brevis* (LB-ADH, 1300 U/mL) were obtained from Jülich Fine Chemicals. Chemical reagents were commercialized by Aldrich, Fluka or Lancaster. Solvents were distilled over an appropriate 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 using NaCl plates or KBr pellets in a Perkin–Elmer 1720-X F7. ^1H, ^{13}C NMR, DEPT, ^1H–^1H homonuclear experiments, and ^1H–^{13}C heteronuclear experiments were obtained using AC-200 (^1H, 200.13 MHz and ^{13}C, 50.3 MHz), AC-300 (^1H, 300.13 MHz and ^{13}C, 75.5 MHz), DPX 300 (^1H, 300.13 MHz and ^{13}C, 75.5 MHz), AV-400 (^1H, 400.13 MHz and ^{13}C, 100.6 MHz) or AV-600 (^1H, 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 a HP1100 chromatograph mass detector, or EI^+ with a Finigan MAT 95 spectrometer 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.

4.1.1. 4-Chloro-2-cyanopyridine 1. The preparation of **1** was carried out according to the procedure reported before from 4-chloropyridine *N*-oxide in 85% yield.[21]

4.1.2. 4-Chloro-[2-(1-hydroxybenzyl)]pyridine] 2e. To a phenylmagnesium bromide 3.0 M solution in Et_2O (4.81 mL, 14.43 mmol) at 0 °C and under a nitrogen atmosphere, a solution of 4-chloro-2-cyanopyridine (500 mg, 3.61 mmol) in dry Et_2O (13 mL) was added. Once the addition was complete, the mixture was stirred at room temperature for 4 h, after which the solution was added to a saturated ammonium chloride solution at 0 °C (20 mL), adding HCl concd until pH = 1. The resulting mixture was stirred at room temperature for an additional 14 h. The solution was neutralized with NH_3 aq and extracted with Et_2O (3 × 50 mL). The solvent was evaporated by distillation under reduced pressure obtaining 2-benzoyl-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 $NaBH_4$ (683 mg, 18.04 mmol) was added in small portions. The clear solution was stirred for 2 h at room temperature, after which MeOH was evaporated and the resulting white solid dissolved in water and extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined, dried over Na_2SO_4 and evaporated at reduced pressure. The crude of the reaction mixture was purified by flash chromatography (30–40% EtOAc/hexane) yielding 597 mg of a white solid (75%). R_f (40% EtOAc/hexane): 0.32; IR (KBr): ν 3204, 3063, 2894, 1654, 1637, 1579, 1556, 1456, 1437, 1388, 1311, 1216, 1095, 1056, 898, 824, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 4.97 (d, $^3J_{HH} = 4.0$ Hz, 1H, OH), 5.73 (d, $^3J_{HH} = 4.0$ Hz, 1H, H_7), 7.22–7.37 (m, 7H, H_3+H_5+2H_9+2H_{10}+H_{11}), 8.44 (d, $^3J_{HH} = 5.4$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 75.1 (C_7), 121.6 (C_3), 123.0 (C_5), 127.0 (2C_9), 128.2 (C_{11}), 128.8 (2C_{10}), 142.4 (C_8), 145.0 (C_4), 148.9 (C_6), 163.0 (C_2); MS (EI^+, *m*/*z*): 221 [$(M^{37}Cl)^+$, 33%], 220 [$(M^{37}Cl–H)^+$, 18%], 219 [$(M^{35}Cl)^+$, 100%] 218 [$(M^{35}Cl–H)^+$, 53%], 184 [$(M–Cl)^+$, 7%], 144 [$(M^{37}Cl–Ph)^+$, 20%], 142 [$(M^{35}Cl–Ph)^+$, 67%]. Anal. Calcd (%) for $C_{12}H_{10}NOCl$: C, 65.61; H, 4.59; N, 6.38. Found: C, 65.6; H, 4.5; N, 6.4.

4.1.3. Enzymatic resolution of 4-chloro-[2-(1-hydroxybenzyl)]pyridine] 2e. A suspension of compound **2e** (55 mg, 0.25 mmol) and PSL-C (40 mg) in vinyl acetate (2.5 mL, 27.1 mmol) under a nitrogen atmosphere was shaken at 250 rpm and 60 °C taking regularly aliquots that were analyzed by HPLC. Reaction was stopped when the reaction reached 42% conversion, the enzyme was filtered and washed with CH_2Cl_2 (3 × 10 mL). Solvent was evaporated

under reduced pressure obtaining a crude that was purified by flash chromatography (5–20% EtOAc/CH_2Cl_2) affording (*S*)-(+)-**2e** [91% isolated yield and 59% ee, $[\alpha]_D^{20} = +22.3$ (*c* 2, $CHCl_3$)], and (*R*)-(−)-**4e** {94% isolated yield and 82% ee, $[\alpha]_D^{20} = -60.3$ (*c* 2, $CHCl_3$)}. (*R*)-(−)-*1-(4-Chloro-2-pyridinyl)benzyl acetate* **4e**. White solid; R_f (15% EtOAc/hexane): 0.26. Mp: 56–58 °C; IR (KBr): *v* 2969, 2364, 2344, 1752, 1577, 1558, 1392, 1373, 1220, 1028, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 2.21 (s, 3H, H_{13}), 6.80 (s, 1H, H_7), 7.19 (dd, $^3J_{HH} = 5.1$, $^4J_{HH} = 2.0$ Hz, 1H, H_5), 7.30–7.44 (m, 6H, H_3+$2H_9$+$2H_{10}$+H_{11}), 8.47 (d, $^3J_{HH} = 5.1$ Hz 1H, H_6); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 21.2 (C_{13}), 77.4 (C_7), 121.2 (C_3), 123.0 (C_5), 127.4 ($2C_9$), 128.5 (C_{11}), 128.7 ($2C_{10}$), 138.4 (C_8), 144.9 (C_4), 150.4 (C_6), 161.0 (C_2), 170.0 (C_{12}); MS (ESI^+, *m*/*z*): 286 [$(M^{37}Cl+Na)^+$, 32%], 284 [$(M^{35}Cl+Na)^+$, 100%], 262 [$(M^{35}Cl+H)^+$, 13%]. Anal. Calcd (%) for $C_{14}H_{12}NO_2Cl$: C, 68.44; H, 4.92; N, 5.70. Found: C, 68.6; H, 4.7; N, 5.9.

4.1.4. 2-Cyano-4-(*N*,*N*-dimethylamino)pyridine 5. A mixture of **1** (200 mg, 1.44 mmol) and a 40% aqueous solution of Me_2NH (1.78 mL) were stirred in a sealed tube at 100 °C until complete consumption of the starting material (20 h). The solvent was evaporated by distillation at reduced pressure and the resulting crude purified by flash chromatography (10% MeOH/EtOAc) yielding 150 mg of a white solid (71%). R_f (10% MeOH/EtOAc): 0.23. Mp: 190 °C (decomposition); IR (KBr) *v* 1700, 1664, 1609, 1541, 1508, 1463, 1383, 1225, 1066, 1000, 870, 814, 789 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 3.03 (s, 6H, H_7), 6.54 (dd, $^3J_{HH} = 5.7$, $^4J_{HH} = 2.8$ Hz, 1H, H_5), 7.44 (d, $^4J_{HH} = 2.8$ Hz, 1H, H_3), 8.14 (d, $^3J_{HH} = 5.7$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 39.1 ($2C_7$), 105.2 (C_3), 108.2 (C_5), 148.3 (C_6), 149.6 (C_2), 155.1 (C_4), 167.9 (CN); MS (ESI^+, *m*/*z*): [$(M+H_2O+H)^+$, 100%]. Anal. Calcd (%) for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.3; H, 6.2; N, 28.6.

4.1.5. 2-Acetyl-4-chloropyridine 6a. Over a methylmagnesium iodide 3.0 M solution in Et_2O (9.64 mL, 28.94 mmol) at 0 °C and under a nitrogen atmosphere, a solution of **1** (1.00 g, 7.24 mmol) in dry Et_2O (20 mL) was added. Once the addition was complete, 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 an additional 14 h. The solution was neutralized with NH_3 aq and extracted with Et_2O (3 × 100 mL). The organic phases were dried over Na_2SO_4 and the solvent evaporated by distillation at reduced pressure and the resulting crude purified by flash chromatography (20% EtOAc/hexane) yielding 987 mg of a colorless oil (87%). R_f (20% EtOAc/hexane): 0.36; IR (NaCl): *v* 3445, 1701, 1570, 1554, 1398, 1353, 1281, 1258, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 2.71 (s, 3H, H_8), 7.47 (dd, $^3J_{HH} = 5.2$, $^4J_{HH} = 2.1$ Hz, 1H, H_5), 8.03 (d, $^4J_{HH} = 2.1$ Hz, 1H, H_3), 8.58 (d, $^3J_{HH} = 5.2$, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 25.6 (C_8), 122.1 (C_3), 127.1 (C_5), 145.4 (C_4), 149.9 (C_6), 154.7 (C_2), 198.8 (C_7); MS (ESI^+, *m*/*z*): 180 [$(M^{37}Cl+Na)^+$, 20%], 178 [$(M^{35}Cl+Na)^+$, 70%], 156 [$(M^{35}Cl+H)^+$, 38%]. Anal. Calcd (%) for C_7H_6NOCl: C, 54.04; H, 3.89; N, 9.00. Found: 54.0; H, 3.9; N, 8.9.

4.1.6. 4-Chloro-2-propanoylpyridine 6b. Same procedure as that used for **6a**, using ethylmagnesium bromide instead of methylmagnesium iodide. Colorless oil (81% isolated yield). R_f (10% EtOAc/hexane): 0.31; IR (NaCl): *v* 2979, 2361, 1704, 1571, 1555, 1581, 1461, 1400, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 1.22 (t, $^3J_{HH} = 7.2$ Hz, 3H, H_9), 3.22 (q, $^3J_{HH} = 7.2$ Hz, 2H, H_8), 7.47 (dd, $^3J_{HH} = 5.2$, $^4J_{HH} = 2.0$ Hz, 1H, H_5), 8.03 (d, $^4J_{HH} = 2.0$ Hz, 1H, H_3), 8.57 (d, $^3J_{HH} = 5.2$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 7.8 (C_9), 31.4 (C_8), 122.2 (C_3), 127.0 (C_5), 145.4 (C_4), 150.0 (C_6), 154.6 (C_2), 201.3 (C_7); MS (ESI^+, *m*/*z*): 194 [$(M^{37}Cl+Na)^+$, 25%], 192 [$(M^{35}Cl+Na)^+$, 95%], 172 [$(M^{37}Cl+H)^+$ 30%], 170 [$(M^{35}Cl+H)^+$ 100%]. Anal. Calcd (%) for C_8H_8NOCl: C, 56.65; H, 4.75; N, 8.26. Found: C, 56.7; H, 4.7; N, 8.2.

4.1.7. 2-Butanoyl-4-chloropyridine 6c. Same procedure as that used for **6a**, using propylmagnesium bromide instead of methylmagnesium iodide. Colorless oil (79% isolated yield). R_f (10% EtOAc/hexane): 0.33; IR (NaCl): *v* 2963, 2935, 2361, 1701, 1570, 1555, 1340, 1217 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 0.95 (t, $^3J_{HH} = 7.4$ Hz, 3H, H_{10}), 1.71–1.96 (m, 2H, H_9), 3.12 (t, $^3J_{HH} = 7.4$ Hz, 2H, H_8), 7.41 (dd, $^3J_{HH} = 5.1$, $^4J_{HH} = 2.0$ Hz, 1H, H_5), 7.96 (d, $^4J_{HH} = 2.0$ Hz, 1H, H_3), 8.52 (d, 1H, $^3J_{HH} = 5.1$, 1H, H_6); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 13.7 (C_{10}), 17.2 (C_9), 39.6 (C_8), 122.1 (C_3), 126.9 (C_5), 145.3 (C_4), 149.7 (C_6), 154.6 (C_2), 200.7 (C_7); MS (ESI^+, *m*/*z*): 186 [$(M^{37}Cl+H)^+$, 32%], 184 [$(M^{35}Cl+H)^+$, 100%]. Anal. Calcd (%) for $C_9H_{10}NOCl$: C, 58.87; H, 5.49 N, 7.63. Found: C, 58.7; H, 5.5; N, 7.6.

4.1.8. 4-Chloro-2-pentanoylpyridine 6d. Same procedure as that used for **6a**, using butylmagnesium chloride instead of methylmagnesium iodide. Colorless oil (85% isolated yield). R_f (10% EtOAc/hexane): 0.34; IR (NaCl): *v* 3318, 2957, 2932, 2881, 1581, 1557, 1467, 1557, 1392, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): 0.95 (t, $^3J_{HH} = 7.1$ Hz, 3H, H_{11}), 1.24–1.31 (m, 2H, H_{10}), 1.54–1.59 (m, 2H, H_9) 3.05 (t, $^3J_{HH} = 7.1$ Hz, 2H, H_8), 7.33 (dd, $^3J_{HH} = 5.4$, $^4J_{HH} = 2.0$ Hz, 1H, H_5), 7.85 (d, $^4J_{HH} = 2.0$ Hz, 1H, H_3), 8.44 (d, 1H, $^3J_{HH} = 5.4$, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.5 (C_{11}), 22.0 (C_{10}), 25.5 (C_9), 37.0 (C_8), 121.5 (C_3), 126.4 (C_5), 144.8 (C_4), 149.4 (C_6), 154.2 (C_2), 200.0 (C_7); MS (ESI^+, *m*/*z*): 222 [$(M^{37}Cl+Na)^+$, 11%], 220 [$(M^{35}Cl+Na)^+$, 60%], 200 [$(M^{37}Cl+H)^+$, 35%], 198 [$(M^{35}Cl+H)^+$, 100%]. Anal. Calcd (%) for $C_{10}H_{12}NOCl$: C, 60.76; H, 6.12; N, 7.09. Found: C, 60.9; H, 6.3; N, 7.2.

4.1.9. 2-Benzoyl-4-chloropyridine 6e. Same procedure as that used for **6a**, using phenylmagnesium bromide instead of methylmagnesium iodide. White solid (75% isolated yield). R_f (10% Et_2O/hexane): 0.28. Mp: 82–84 °C; IR (KBr): *v* 1654, 1596, 1570, 1553, 1452, 1394, 1322, 1283, 1162, 1216, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 7.42–7.68 (m, 4H, $2H_{10}$+H_{11}+H_5), 8.05–8.10 (m, 3H, H_3+$2H_9$), 8.63 (d, $^3J_{HH} = 5.0$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 125.1 (C_3), 126.3 (C_5), 128.3 (C_{10}), 131.0 (C_9), 133.3 (C_{11}), 135.8 (C_8), 145.5 (C_4),

149.5 (C_6), 156.3 (C_2), 192.5 (C_7); MS (ESI$^+$, m/z): 242 [($M^{37}Cl$+Na)$^+$, 33%], 240 [($M^{35}Cl$+Na)$^+$, 100%], 218 [($M^{35}Cl$+H)$^+$, 20%]. Anal. Calcd (%) for $C_{12}H_8NOCl$: C, 66.22; H, 3.70; N, 6.44. Found: C, 66.2; H, 3.8; N, 6.4.

4.1.10. 2-Acetyl-4-(*N*,*N*-dimethylamino)pyridine 6f. A mixture of **6a** (100 mg, 0.64 mmol) and a 40% aqueous solution of Me_2NH (700 μL) were stirred in a sealed tube at 100 °C until complete consumption of the starting material (24 h). The solvent was evaporated by distillation at reduced pressure and the resulting crude purified by flash chromatography (20–40% MeOH/EtOAc) yielding 60 mg of a colorless oil (53%). R_f (20% MeOH/EtOAc): 0.30; IR (NaCl): ν 1700, 1570, 1558, 1458, 1400, 1304, 1217 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 2.70 (s, 3H, H_8), 3.06 (s, 6H, H_9), 6.63 (dd, $^3J_{HH} = 6.3$, $^4J_{HH} = 3.1$ Hz, 1H, H_5), 7.30 (d, $^4J_{HH} = 3.1$ Hz, 1H, H_3), 8.30 (d, $^3J_{HH} = 6.3$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 25.9 (C_8), 39.0 ($2C_9$), 104.3 (C_3), 109.0 (C_5), 148.9 (C_6), 153.6 (C_4), 154.6 (C_2), 201.0 (C_7); MS (ESI$^+$, m/z): 165 [(M+H)$^+$, 100%]. Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.8; H, 7.4; N, 17.0.

4.1.11. (*S*)-(−)-4-Chloro-2-(1-hydroxyethyl)pyridine 2a. A suspension of **6a** (500 mg, 3.21 mmol) and Baker's yeast (25 g) in 210 mL of an aqueous solution of glucose (25 mg/mL) was shaken at 30 °C and 250 rpm. Aliquots were regularly analyzed by TLC, until complete consumption of the starting material (60 h). After that time, the mixture was centrifuged to separate the yeast, and the solution extracted with CH_2Cl_2 (3 × 100 mL). The organic phases were combined and dried over Na_2SO_4 and the solvent distilled under a reduced pressure to obtain a crude mixture, which was purified by flash chromatography (60–80% EtOAc/hexane) to yield 383 mg of (*S*)-**2a** (76%) with 98% ee as a white solid. Spectroscopic data are in accordance with the ones previously described in the literature.[21]

4.1.12. (*S*)-(−)-4-Chloro-2-(1-hydroxypropyl)pyridine 2b. Same procedure as that of (*S*)-**2a**, using **6b** as starting material instead of **6a** (see Table 2). Colorless oil (71% isolated yield and 91% ee). Spectroscopic data are in accordance with the ones previously described in the literature.[21]

4.1.13. (*S*)-(−)-4-Chloro-2-(1-hydroxybutyl)pyridine 2c. Same procedure as that of (*S*)-**2a**, using **6c** as starting material instead of **6a** (see Table 2). Colorless oil (73% isolated yield and 81% ee). Spectroscopic data are in accordance with the ones previously described in the literature.[21]

4.1.14. (*S*)-(−)-4-Chloro-2-(1-hydroxypentyl)pyridine 2d. Same procedure as that of (*S*)-**2a**, using **6d** as starting material instead of **6a** (see Table 2). Colorless oil (72% isolated yield and 80% ee). Spectroscopic data are in accordance with the ones previously described in the literature.[21]

4.1.15. (*R*)-(−)-4-Chloro-2-(1-hydroxybenzyl)pyridine 2e. Same procedure as that of (*S*)-**2a**, using **6e** as starting material instead of **6a** (see Table 2). White solid (84% isolated yield and 97% ee). R_f (5% EtOAc/CH_2Cl_2): 0.19; $[\alpha]_D^{20} = -43.4$ (c 2, $CHCl_3$).

4.1.16. (*S*)-(−)-4-(*N*,*N*-Dimethylamino)-2-(1-hydroxyethyl)-pyridine 7a by bioreduction with Baker's yeast. Same procedure as that of (*S*)-**2a**, using **6f** as starting material instead of **6a** (see Table 2). White solid (40% isolated yield and 98% ee). Spectroscopic data are in accordance with the ones previously described in the literature.[21]

4.1.17. Typical procedure for the bioreduction of ketones using alcohol dehydrogenases. The corresponding ketone **6a–e** (0.32 mmol) was dissolved in 2-propanol (0.54 mL) and a TRIS/HCl buffer solution of pH 7 (2.56 mL) was added. Finally NADP (0.56 mg, 6.4×10^{-4} mmol) and T-ADH (16 U, 44 μL) or LB-ADH (16 U, 12 μL) were added. The resulting mixture was shaken at 30 °C for the required time. The reaction was extracted with CH_2Cl_2 (3 × 15 mL) and the organic phases combined. The solvent was then distilled under reduced pressure. The reaction crude was purified by flash chromatography (20–80% EtOAc/hexane) yielding alcohols **2a–b** or ketones **6c–e** (see Table 3).

4.1.18. (*S*)-(−)-4-(*N*,*N*-Dimethylamino)-2-(1-hydroxyethyl)-pyridine 7a by chloro substitution. The preparation of **7a** was carried out according to the procedure reported before, from (*S*)-(−)-4-chloro-2-(1-hydroxyethyl)pyridine.[21]

4.1.19. (*S*)-(−)-4-(*N*,*N*-Dimethylamino)-2-(1-hydroxypropyl)-pyridine 7b. The preparation of **7b** was carried out according to the procedure reported before from (*S*)-(−)-4-chloro-2-(1-hydroxypropyl)pyridine.[21]

4.1.20. (*S*)-(−)-4-(*N*,*N*-Dimethylamino)-2-(1-hydroxybutyl)-pyridine 7c. The preparation of **7c** was carried out according to the procedure reported before from (*S*)-(−)-4-chloro-2-(1-hydroxybutyl)pyridine.[21]

4.1.21. (*S*)-(−)-4-(*N*,*N*-Dimethylamino)-2-(1-hydroxypentyl)-pyridine 7d. The preparation of **7d** was carried out according to the procedure reported before from (*S*)-(−)-4-chloro-2-(1-hydroxypentyl)pyridine.[21]

4.1.22. (*R*)-(−)-4-(*N*,*N*-Dimethylamino)-2-(1-hydroxybenzyl)-pyridine 7e. Same procedure as that of (−)-**7a**, using (−)-**2e** as starting material (24 h). Colorless oil (91% isolated yield). R_f (100% MeOH): 0.28; IR (NaCl): ν 3343, 2927, 1602, 1543, 1513, 1436, 1378, 1255, 966, 909, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 2.93 (s, 6H, H_{12}), 5.34 (br s, 1H, OH), 5.66 (s, 1H, H_7), 6.34–6.43 (m, 2H, H_3+H_5), 7.29–7.45 (m, 5H, $2H_9$+$2H_{10}$+H_{11}), and 8.15 (d, $^3J_{HH} = 5.5$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 39.0 ($2C_{12}$), 74.8 (C_7), 103.2 (C_3), 105.7 (C_5), 126.8 (C_{10}), 127.3 (C_{11}), 128.2 (C_9), 143.7 (C_8), 147.3 (C_6), 154.8 (C_4), and 160.9 (C_2); MS (ESI$^+$, m/z): 229 [(M+H)$^+$, 100%]. Anal. Calcd (%) for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.6; H, 7.1; N; 12.3.

4.1.23. (*S*)-(−)-4-(*N*,*N*-Dimethylamino)-2-[(1-methoxyethyl)-pyridine] 8a. To a solution under a nitrogen atmosphere of (*S*)-**7a** (100 mg, 0.60 mmol) in dry THF (10 mL) at −78 °C was added a 30% dispersion of KH in mineral oil (100 mg, 0.75 mmol). The resulting suspension was stirred at −60 °C for 2 h, after which time the mixture was cooled

to −78 °C, adding successively 18–6 crown ether (155 mg, 0.59 mmol) and MeI (47 μL, 0.75 mmol). The mixture was stirred at −60 °C for 3 h. The reaction was stopped by adding 4 mL of H_2O and 1 mL of a NaOH (4 M) solution and extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined and dried over Na_2SO_4, and the solvent evaporated under reduced pressure affording a crude mixture, which was purified by flash chromatography (100% hexane–20% MeOH/EtOAc) affording 81 mg of a colorless oil (75%). R_f (80% EtOAc/MeOH): 0.19; $[\alpha]_D^{20} = -100.2$ (*c* 2.1, $CHCl_3$); IR (NaCl): *v* 2931, 2630, 2342, 1605, 1545, 1378, 1225, 994 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.46 (d, $^3J_{HH} = 6.7$ Hz, 3H, H_8), 3.03 (s, 6H, H_{10}), 3.34 (s, 3H, H_9), 4.33 (q, $^3J_{HH} = 6.7$ Hz, 1H, H_7), 6.41 (dd, $^3J_{HH} = 5.9$, $^4J_{HH} = 2.0$ Hz, 1H, H_5), 6.61 (d, $^4J_{HH} = 2.0$ Hz, 1H, H_3), 8.18 (d, $^3J_{HH} = 5.9$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 22.4 (C_8), 39.1 ($2C_{10}$), 56.8 (C_9), 80.9 (C_7), 101.8 (C_3), 105.4 (C_5), 148.8 (C_6), 155.1 (C_4), 162.9 (C_2); MS (ESI^+, *m*/*z*): 181 $[(M+H)^+$, 100%]. Anal. Calcd (%) for $C_{10}H_{16}N_2O$: C, 66.64; H, 8.95; N, 15.55. Found: C, 66.7; H, 9.0; N, 15.7.

4.1.24. (*S*)-(−)-4-(*N*,*N*-Dimethylamino)-2-[(1-methoxypropyl)-pyridine] 8b. Same procedure as that of (−)-**8a**, using (−)-**7b** as starting material. Colorless oil (79%). R_f (20% MeOH/EtOAc): 0.21; $[\alpha]_D^{20} = -80.6$ (*c* 1.1, $CHCl_3$); IR (NaCl) *v* 2996, 2932, 2361, 1603, 1545, 1509, 1376, 1223, 1127, 1092, 998 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 0.91 (t, $^3J_{HH} = 7.0$ Hz, 3H, H_9), 1.69–1.83 (m, 2H, H_8), 3.00 (s, 6H, H_{11}), 3.30 (s, 3H, H_{10}), 4.07 (t, $^3J_{HH} = 7.0$ Hz, 1H, H^7), 6.38 (dd, $^3J_{HH} = 5.9$, $^4J_{HH} = 2.7$ Hz, 1H, H_5), 6.58 (d, $^4J_{HH} = 2.7$ Hz, 1H, H_3), 8.15 (d, $^3J_{HH} = 5.9$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 10.0 (C_9), 29.7 (C_8), 39.0 ($2C_{11}$), 57.0 (C_{10}), 86.5 (C_7), 102.5 (C_3), 105.4 (C_5), 148.9 (C_6), 154.9 (C_4), 161.9 (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, 68.0; H, 9.2; N, 14.5.

4.1.25. (*S*)-(−)-4-(*N*,*N*-Dimethylamino)-2-[(1-methoxybutyl)-pyridine] 8c. Same procedure as that of (−)-**8a**, using (−)-**7c** as starting material. Colorless oil (72%). R_f (20% MeOH/EtOAc): 0.25; $[\alpha]_D^{20} = -73.9$ (*c* 1.1, $CHCl_3$); IR (NaCl) *v* 2958, 2931, 2360, 1605, 1544, 1508, 1377, 1223, 1091, 996 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 0.84 (t, $^3J_{HH} = 7.5$ Hz, 3H, H_{10}), 1.17–1.70 (m, 4H, H_9+H_8), 2.93 (s, 6H, H_{12}), 3.60 (s, 3H, H_{11}), 4.09 (t, $^3J_{HH} = 6.5$ Hz, 1H, H_7), 6.33 (dd, $^3J_{HH} = 6.2$, $^4J_{HH} = 2.7$ Hz, 1H, H_5), 6.53 (d, $^4J_{HH} = 2.7$ Hz, 1H, H_3), 8.09 (d, $^3J_{HH} = 6.2$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.8 (C_{10}), 18.8 (C_9), 39.0 (C_8), 39.0 ($2C_{12}$), 57.0 (C_{11}), 85.0 (C_7), 102.2 (C_3), 105.3 (C_5), 148.8 (C_6), 154.9 (C_4), 162.1 (C_2); MS (ESI^+, *m*/*z*): 209 $[(M+H)^+$, 100%]. Anal. Calcd (%) for $C_{12}H_{20}N_2O$: C, 69.18; H, 9.68; N, 13.45. Found: C, 69.0; H, 9.7; N, 13.5.

4.1.26. (*S*)-(−)-4-(*N*,*N*-Dimethylamino)-2-[(1-methoxypentyl)-pyridine] 8d. Same procedure as that of (−)-**8a**, using (−)-**7d** as starting material. Colorless oil (76%). R_f (20% MeOH/EtOAc): 0.28; $[\alpha]_D^{20} = -77.5$ (*c* 1.0, $CHCl_3$); IR (NaCl): *v* 2931, 2871, 2360, 1602, 1545, 1507, 1376, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 0.86 (t, $^3J_{HH} = 7.1$ Hz, 3H, H_{11}), 1.27–1.35 (m, 4H, H_9+H_{10}), 1.71–1.74 (m, 2H, H_8), 3.00 (s, 6H, H_{13}), 3.30 (s, 3H, H_{12}), 4.14 (t, $^3J_{HH} = 6.5$ Hz, 1H, H_7), 6.39 (dd, $^3J_{HH} = 6.0$, $^4J_{HH} = 2.5$ Hz, 1H, H_5), 6.58 (d, $^4J_{HH} = 2.5$ Hz, 1H, H_3), 8.15 (d, $^3J_{HH} = 6.0$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.8 (C_{11}), 22.5 (C_{10}), 27.8 (C_9), 36.7 (C_8), 39.0 ($2C_{13}$), 57.0 (C_{12}), 85.2 (C_7), 102.2 (C_3), 105.3 (C_5), 148.8 (C_6), 154.9 (C_4), 162.2 (C_2); MS (ESI^+, *m*/*z*): 223 $[(M+H)^+$, 100%]. Anal. Calcd (%) for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 69.9; H, 9.9; N, 12.5.

4.1.27. (*R*)-(−)-4-(*N*,*N*-Dimethylamino)-2-[(1-methoxybenzyl)pyridine] 8e. Same procedure as that of (−)-**8a**, using (−)-**7e** as starting material. Colorless oil (73%). R_f (20% MeOH/EtOAc): 0.34; $[\alpha]_D^{20} = -62.9$ (*c* 1.5, $CHCl_3$); IR (NaCl) *v* 2932, 1604, 1542, 1513, 1452, 1378, 1094, 1007 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 2.98 (s, 6H, H_{13}), 3.43 (s, 3H, H_{12}), 5.27 (s, 1H, H_7), 6.36 (dd, $^3J_{HH} = 6.0$, $^4J_{HH} = 2.3$ Hz, 1H, H_5), 6.72 (d, $^4J_{HH} = 2.3$ Hz, 1H, H_3), 7.22–7.45 (m, 5H, $2H_9$+$2H_{10}$+H_{11}), 8.14 (d, $^3J_{HH} = 6.0$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 39.0 ($2C_{13}$), 57.1 (C_{12}), 86.6 (C_7), 102.7 (C_3), 105.4 (C_5), 126.8 ($2C_{10}$), 127.4 (C_{11}), 128.2 ($2C_9$) 141.2 (C_8), 149.0 (C_6), 155.0 (C_4), 161.2 (C_2); MS (ESI^+, *m*/*z*): 265 $[(M+Na)^+$, 3%], 243 $[(M+H)^+$, 100%]. Anal. Calcd (%) for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.3; H, 7.5; N; 11.5.

4.1.28. (*S*)-(−)-4-(*N*,*N*-Dimethylamino)-2-[(1-butoxyethyl)-pyridine] 9. Same procedure as that of (−)-**9a**, using 1-iodobutane instead of methyl iodide. Colorless oil (68%). R_f (80% MeOH/EtOAc): 0.18; $[\alpha]_D^{20} = -107.3$ (*c*, 2.5, $CHCl_3$); IR (NaCl): *v* 3376, 2958, 2871, 1602, 1543, 1509, 1375, 1224, 1224, 1102, 993 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 0.89 (m, 3H, H_{12}), 1.33–1.67 (m, 4H, H_{10}+H_{11}), 1.44 (d, $^3J_{HH} = 6.5$ Hz, 1H, H_8), 3.00 (s, 6H, H_{13}), 3.40 (m, 3H, H_9), 4.40 (q, $^3J_{HH} = 6.5$ Hz, 1H, H_7), 6.38 (dd, $^3J_{HH} = 6.0$, $^4J_{HH} = 2.9$ Hz, 1H, H_5), 6.66 (d, $^4J_{HH} = 2.9$ Hz, 1H, H_3), 8.15 (d, $^3J_{HH} = 6.0$ Hz, 1H, H_6); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.9 (C_{12}), 19.4 (C_8), 22.8 (C_{11}), 32.0 (C_{10}), 39.1 (C_{13}), 68.9 (C_9), 79.3 (C_7), 101.7 (C_3), 105.3 (C_5), 148.9 (C_6), 155.0 (C_4), 163.9 (C_2); MS (ESI^+, *m*/*z*): 223 $[(M+H)^+$, 100%]. Anal. Calcd (%) for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.1; H, 9.9; N, 12.6.

4.1.29. Catalytic resolution of 1-phenylethanol 12. To a solution of the corresponding catalyst **8a**–**e** or **9** (0.15 mmol) in dry CH_2Cl_2 (1.5 mL) at 0 °C was added $ZnCl_2$ of a 1.0 M solution in Et_2O (300 μL, 0.30 mmol), and the mixture stirred for 10 min at room temperature. Finally **12** (37 mg, 0.30 mmol) and NEt_3 (63 μL, 0.45 mmol) were added successively. The resulting mixture was stirred for an additional 60 h, after which CH_2Cl_2 was distilled out under reduced pressure and the residue was purified by flash chromatography (5–20% EtOAc/hexane) yielding 27 mg of **12** and **13** with different yields and ee (see Table 4). Catalyst **8** or **9** was quantitatively recovered by flushing with 20% MeOH/EtOAc.

4.1.30. 1,1,1-Trichloro-2-methylpropan-2-yl-1-phenylethyl carbonate 13. R_f (5% EtOAc/hexane): 0.21. Mp: 72–74 °C; IR (KBr): *v* 1744, 1458, 1388, 1371, 1338, 1274,

1212, 1163, 1055, 824, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 200.13 MHz): δ 1.64 (d, $^3J_{HH} = 6.7$ Hz, 3H, H_6), 1.90 (s, 3H, H_9), 1.98 (s, 3H, H_6), 5.75 (*c*, $^3J_{HH} = 6.7$ Hz, 1H, H5), 7.30–7.45 (m, 5H, $H_1+2H_2+2H_3$); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.1 (C_9), 22.5 (C_6), 77.4 (C_5), 89.6 (C_8), 105.5 (C_{10}), 125.7 (C_3), 128.5 (C_1), 128.5 (C_2), 141.0 (C_4), 151.8 (C_7); MS (ESI^+, *m*/*z*): 325 [$(M+H)^+$, 100%]. Anal. Calcd (%) for $C_{13}H_{15}O_3Cl_3$: C, 47.95; H, 4.64; Found: C, 47.9; H, 4.6.

4.1.31. Typical experimental procedure for the enantioselective addition of $ZnEt_2$ to benzaldehyde in the presence of chiral catalysts (*S*)-7a, (*S*)-7d, (*R*)-7e or (*S*)-16. A solution of catalyst (0.06 mmol) in toluene (1 mL) was cooled at 0 °C and stirred for 5 min under nitrogen atmosphere. After this time, a 1 M $ZnEt_2$ solution in hexane (2.1 mL, 2.1 mmol) was slowly added over 5 min and the resulting mixture stirred at room temperature during 30 min. This solution was cooled at 0 °C and benzaldehyde (106 μL, 1.1 mmol) was added. The reaction mixture was stirred at room temperature for an additional 20 h. At this time, the reaction was quenched with HCl 1 N (4 mL) and extracted with EtOAc (3 × 15 mL). The organic phases were combined and the solvent distillated under reduced pressure. The crude was purified by flash chromatography (20% EtOAc/hexane) to yield optically active **15** (see Table 5).

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