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Enantioselective Synthesis of 4-(Dimethylamino)pyridines through a Chemical Oxidation-Enzymatic Reduction Sequence. Application in Asymmetric Catalysis

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Abstract: Enantiomerically pure 4-(dimethylamino)-3-(1-hydroxyalkyl)pyridines and 4-(dimethylamino)-3-[hydroxy(phenyl)methyl]pyridine have been prepared through efficient chemoenzymatic routes. For this purpose different lipases and oxidoreductases have been tested in the preparation of optically active 4-chloro derivatives and baker's yeast was found to be an excellent catalyst for the bioreductions of the corresponding ketones. Their applications as enantioselective nucleophilic catalysts have been studied, important catalytic properties were observed in the stereoselective construction of quaternary centers.

Keywords: asymmetric catalysis; bioreduction; 4-(dimethylamino)pyridine; kinetic resolution; oxidation

Introduction

4-(Dimethylamino)pyridine (DMAP) is the most common nucleophilic catalyst for acyl transfer and similar transformations,[1] and the design of chiral DMAP derivatives is a challenge that has been receiving considerable attention in recent years due to the demonstration of their interesting properties in the development of asymmetric synthetic processes.[2] These compounds have been prepared by different chemical strategies and the introduction of chirality has been possible by different synthetic procedures. Fu and co-workers developed the concept of "planar chirality" for DMAP analogues, obtaining optically active π-complexes of heterocyles with transition metals, which are very versatile catalysts in asymmetric synthesis,[3] and similar complexes have been recently synthesized by other authors.[4] Depending on the substituted position in the pyridine ring, the preparation of chiral DMAP compounds has been reported extensively in the last decade. 4-Pyrrolidinopyridine analogues are the most common derivatives possesing chirality in position 4 of the pyridine structure,[5] but although they are very reactive, the enantiopreferences shown in asymmetric processes are generally moderate. Chemical access to 2-substituted DMAPs is more difficult, but they act with higher selectivities than derivatives with substituents in position 4. However, their reactivity is limited due to the proximity of the catalytic active site, and activation of the DMAP derivative is required in their use as asymmetric catalysts.[6] A number of 3-substituted DMAP derivatives have been described throughout the last decade. Spivey and co-workers described the synthesis and application of atropoisomeric biaryl 4-(dialkylamino)pyridines, in which the chirality stems from restricted rotation about an aryl-aryl bond.[7] Other groups have introduced an element of chirality from adequate precursors through chemically selective modifications of position 3 in the pyridine ring, and encouraging selectivities have been found when they have been employed in different asymmetric processes.[8]

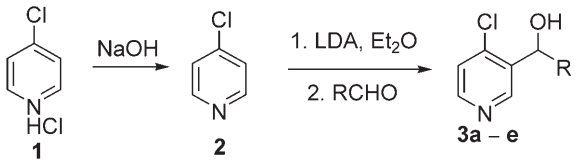
Biocatalysis has made possible the preparation of optically active pyridine derivatives, *via* the asymmetric reductions of ketones[9], through lipase-catalyzed hydrolysis of acetates, or through acylation procedures of alcohols or amines.[10] We have recently described the synthesis of a new family of chiral DMAP catalysts substituted in the C-2 position of the pyridine ring using either *Pseudomonas cepacia* lipase (PSL-C) as biocatalyst,[11] or using different oxidoreductases, especially baker's yeast.[12]

Here we report the development of an efficient chemoenzymatic strategy for the synthesis of chiral 3-substituted DMAP analogues. Different enzymatic

procedures have been explored for the introduction of chirality, such as the lipase-catalyzed transesterification of alcohols, or the bioreduction of ketones mediated by oxidoreductases of different sources. Finally the application of the chiral DMAP analogues in stereoselective processes is studied.

Results and Discussion

For the preparation of 4-chloro-3-(1-hydroxyalkyl)-pyridines (**3a–d**) and 4-chloro-3-[hydroxy-(phenyl)methyl]pyridine (**3e**), we followed a modified procedure of the method described by Quéguiner and co-workers for the preparation of 3,4-disubstituted pyridines (Scheme 1).[13] Commercially available 4-

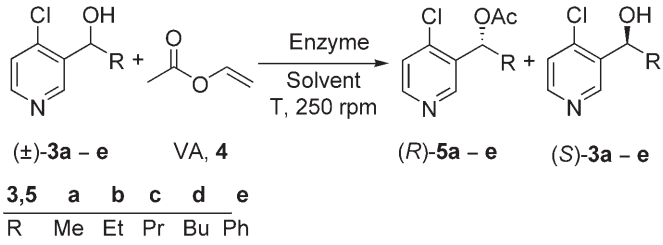


3a: R = Me (68%), **3b**: R = Et (61%), **3c**: R = Pr (63%), **3d**: R = Bu (65%), **3e**: R = Ph (90%)

Scheme 1. Chemical synthesis of (±)-**3a–e**.

chloropyridine hydrochloride salt (**1**) was extracted in basic media to isolate the corresponding pyridine **2**, which was used as starting material. Selective *ortho*-lithiation in dry diethyl ether with 1 equivalent of lithium diisopropylamide (LDA) and later reaction with the corresponding aldehyde, afforded **3a–d** in low yields (40–45%). Reactions were then attempted in the presence of 2 equivalents of LDA, enhancing the conversion values and affording higher isolated yields (61–68%). Use of more equivalents of LDA did not increase the amount of final product; 64% isolated yield, for instance, in the case of **3d**. However, the reaction with benzaldehyde afforded 4-chloro-3-[hydroxy(phenyl)methyl]pyridine (**3e**) in 90% isolated yield with just 1 equivalent of LDA. This is a better yield than those obtained with **3a–d** due to the absence of hydrogen atoms in the α-position to the carbonyl group.

Initially enzymatic resolution of (±)-**3a** was attempted by enzymatic transesterification using vinyl acetate (VA, **4**) as acyl donor, under different reaction conditions and employing *Pseudomonas cepacia* lipase (PSL-C) and *Candida antarctica* lipase B (CAL-B) as biocatalysts since they were the best enzymes in the resolution of 4-chloro-2-(1-hydroxyalkyl)pyridines (Scheme 2, Table 1).[11]



Scheme 2. Kinetic resolution of (±)-**3a–e** by lipase-catalyzed transesterification.

Both PSL-C and CAL-B achieved an excellent enantioselectivity in the reaction with racemic **3a** using 3 equivs. of VA and THF as solvent at 30 °C (entries 1 and 2). CAL-B showed a higher reaction rate, although longer reaction times led to a decrease in the conversion. Reactions at higher temperature or with 10 equivs. of VA led to a slight increase in the conversion values (data not shown). Next, reactions were carried out in VA as solvent and acyl donor (entries 3–5) providing both product and substrate in

Table 1. Enzymatic kinetic resolution of (±)-**3a–e** using vinyl acetate and different lipases.

Entry	**3**	Enzyme	Solvent	VA [equivs.]	T [°C]	t [h]	ee_s [%][a]	ee_p [%][a]	c [%][b]	E[c]
1	**3a**	PSL-C	THF	3	30	62	20	>99	17	>200
2	**3a**	CAL-B	THF	3	30	38	45	>99	31	>200
3	**3a**	PSL-C	VA	–	30	63	86	96	47	137
4	**3a**	CAL-B	VA	–	30	85	>99	>99	50	>200
5	**3a**	CAL-B	VA	–	60	14	>99 (86)	>99 (96)	50	>200
6	**3b**	CAL-B	VA	–	60	38	93 (88)	97 (89)	49	195
7	**3c**	CAL-B	VA	–	60	62	–	–	–	–
8	**3d**	CAL-A	VA	–	60	136	16	>99	14	>200
9	**3c**	CAL-A	VA	–	60	24	12	76	13	8
10	**3e**	CAL-A	VA	–	60	48	55	87	39	25

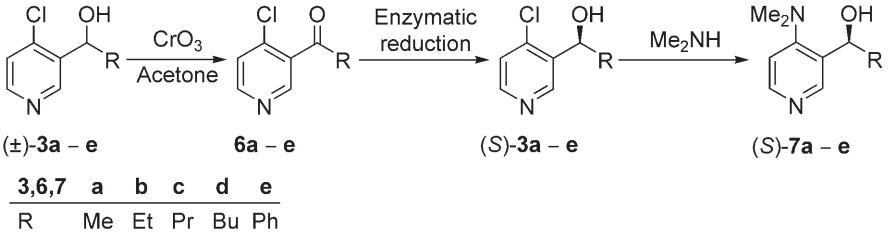
[a] Calculated by HPLC.
[b] $c = ee_S/(ee_S + ee_P)$.
[c] $E = \ln[(1-c)\times(1-ee_S)]/\ln[(1-c)\times(1+ee_S)]$.
[d] Isolated yields in brackets.

high isolated yields and enantiomeric excesses in the case of CAL-B.

With the best reaction conditions in hand, extension of this enzymatic study was done for substrates **3b–d**. CAL-B catalyzed the kinetic resolution of **3b** with high enantioselectivity (entry 6). However, it completely failed with bulkier substrates such as **3c** and **d**, which seem not to fit in the active site of CAL-B.[14] *Candida antarctica* lipase A (CAL-A) has been identified as an ideal enzyme in the resolution of sterically hindered compounds,[15] for which reason we decided to explore the possibilities of this catalyst in the kinetic resolution of **3b–d**. The high enantioselectivity in the case of R = Bu (entry 8) was of note, but this decreased with a smaller substituent (R = Pr, entry 9). Reaction of this biocatalyst with pyridine **3e** was also attempted resulting in a moderate enantiopreference (entry 10).

Traditionally, bioreduction of ketones has appeared as an attractive alternative for the production of enantiomerically pure pyridine alcohols. For instance, baker's yeast has demonstrated its potential in the asymmetric reduction of 2-alkanoyl-4-chloropyridines and 2-benzoyl-4-chloropyridine.[12] Before developing this enzymatic study, it was necessary to synthesize the ketones using the corresponding alcohols as starting materials. Oxidation of alcohol **3a** with MnO_2 in $CHCl_3$ led to ketone **6a** in quantitative yield, although unfortunately it looked very unstable in the presence of air. This process was repeated for **3b–e** but just achieved around 50% conversion, with the stability problems persisting in the case of the compounds with smaller aliphatic substituents. Trying to overcome both problems, we designed a two-step procedure of chemical oxidation and enzymatic enantioselective reduction using the system CrO_3 in acetone for the chemical oxidation. The ketones **6a–e** were obtained, and were rapidly filtered in celite, stabilized with 2-propanol (*i*-PrOH) to avoid dryness and used in the subsequent bioreduction step with different oxidoreductases (Scheme 3).

Three different oxidoreductases were used in the asymmetric reduction of **6a–e**, baker's yeast, alcohol dehydrogenase from *Thermoanaerobacter species* (T-ADH), and alcohol dehydrogenase from *Lactobacillus brevis* (LB-ADH). The oxidation step was carried out at room temperature and the enzymatic reduction was done in an orbital shaker at 30 °C, the results being shown in Table 2. Baker's yeast and TS-ADH showed excellent enantiopreferences in the prepara-



Scheme 3. Preparation of optically active alcohols through a chemical oxidation and enzymatic reduction sequence.

Table 2. Preparation of optically active **3a–e** in a chemical oxidation-enzymatic reduction sequence.

Entry	3	Enzyme	T [°C]	t [h]	c [%][a]	ee_p [%][b]	Configuration[c]
1	**3a**	baker's yeast	30	14	100 (79)	>99	S
2	**3a**	TS-ADH	30	45	100 (89)	>99	*S*
3	**3a**	LB-ADH	30	69	100 (91)	98	*R*
4	**3b**	baker's yeast	30	14	100 (76)	>99	*S*
5	**3b**	TS-ADH	30	88	43	93	*S*
6	**3b**	LB-ADH	30	88	–	–	–
7	**3c**	baker's yeast	30	14	100 (73)	98	*S*
8	**3c**	TS-ADH	30	90	–	–	–
9	**3c**	LB-ADH	30	90	–	–	–
10	**3d**	baker's yeast	30	14	100 (74)	>99	*S*
11	**3e**	baker's yeast	30	115	82	>99	*S*
12	**3e**	baker's yeast	45	24	–	–	–
13	**3e**	baker's yeast[d]	30	43	100 (75)	>99	*S*

[a] Conversions calculated by ^{1}H NMR and isolated yields in brackets.
[b] Calculated by HPLC.
[c] Determined by Mosher's esters.
[d] Use of double amount of enzyme.

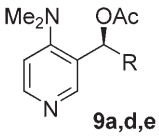
tion of (*S*)-**3a** in line with Prelog's rule (entries 1 and 2), as did LB-ADH. However, the latter showed a complementary selectivity yielding the (*R*)-alcohol (entry 3). Baker's yeast reacted with all the compounds possesing alkyl rests with enantiomerically pure (*S*)-**3b–d** being isolated in high yields (entries 4, 7 and 10). TS-ADH showed a very high enantiopreference in the bioreduction of **6b** but this did not go through to its full extent (entry 5). Meanwhile, no reaction was observed with other more sterically hindered substrates or using LB-ADH as enzyme (entries 6, 8, 9). Finally bioreduction with Baker's yeast of **6e** was successfully achieved at 30 °C using double the amount of enzyme (entry 13) because the same amount of biocatalyst was not enough to reach a complete conversion (entry 11) and an increase in the temperature led to the inactivation of the catalyst (entry 12).

Determination of the stereochemical configuration of the chiral center was done on the basis of Kelly's method,[16] transforming the corresponding alcohols to their ester derivatives (see Experimental Section). Enantiomerically pure (*S*)-4-chloro-3-(1-hydroxyalkyl)pyridines and (*S*)-4-chloro-3-[hydroxy(phenyl)methyl]pyridine were transformed to the corresponding (*S*)-4-(dimethylamino)-3-(1-hydroxyalkyl)pyridines (**7a–d**) and (*S*)-4-(dimethylamino)-3-[hydroxy(phenyl)methyl]pyridine (**7e**) by reaction at 100 °C with an aqueous solution of dimethylamine, the potential nucleophilic catalysts being obtained in nearly quantitative yields.

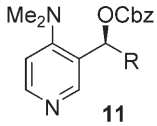
A representative range of chemical catalysts were then selected to evaluate their properties as nucleophilic catalysts. Compounds **7a**, **7d** and **7e** were protected like *O*-acetyl derivatives (**9a**, **9d** and **9e**) to avoid side reactions, and were tested in the enantioselective construction of quaternary centers through the rearrangement of enol carbonates. This application allows the formation of carbon-carbon bonds in a stereoselective fashion, which is considered to be one of the most difficult challenges in asymmetric organic synthesis. For simplicity we chose to examine the Steglich rearrangement of the enol carbonate **8** precursor of the azlactone **10** (Scheme 4).

Reactions were carried out in *tert*-amyl alcohol at different temperatures and all of them were stopped when complete disappearance of the starting material was observed (Table 3). Firstly the reaction was performed at 25 °C using **9a** as catalyst affording **10** in a high isolated yield but low *ee* (entry 1). To improve the enantioselectivity the reaction was carried out at −10 °C, the minimum temperature possible for this solvent due to its melting point of −13 °C. The result was the formation of the final product in 20 % *ee* (entry 2). Under similar reaction conditions the catalysts with the butyl (**9d**) and phenyl substituent (**9e**) were employed. This achieved better *ee* in the formation of **10** (entries 3 and 4), and especially in the case of **9e** which allowed the preparation of the desired product in 70 % *ee*. Finally the effect of varying the acetyl protecting group on oxygen was explored. However, the use of highly hindered derivatives like the *O*-benzyloxycarbonyl derivative **11** led to low enantiopreference (entry 5). These results are in accordance with the levels of enantioselection obtained previously by Vedejs and co-workers,[8b,f] and showed certain advantages like the easy preparation of these novel catalysts by simple chemoenzymatic routes, or the recovery of the catalysts in quantitative yields after flash chromatography once that the reactions are finished, allowing the re-use of the catalyst as often as necessary.

Table 3. Catalytic enantioselective rearrangement of **8** mediated by chiral DMAP analogues.



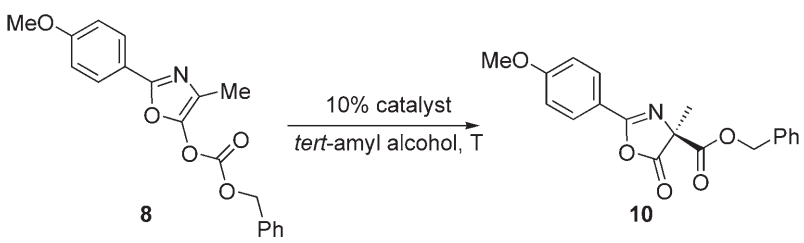
9a,d,e



11

Entry	Catalyst	R	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**9a**	Me	25	5	91	18
2	**9a**	Me	−10	7	94	20
3	**9d**	Bu	−10	8	93	55
4	**9e**	Ph	−10	8	92	70
5	**11**	Bu	−10	8	91	41

[a] Isolated yields after flash chromatography.
[b] Calculated by HPLC.



Scheme 4. Enantioselective rearrangement of **8** catalyzed by DMAP derivatives.

Conclusions

In summary, we have synthesized novel enantiomerically pure 4-(dimethylamino)-3-substituted-pyridines, exploring different chemoenzymatic approaches for the introduction of chirality. In this manner, bioreduction processes using baker's yeast have made possible the preparation of optically active (*S*)-alcohols, which have been easily converted into adequate nucleophilic catalysts in a globally economic sequence. The efficiency of these catalysts in asymmetric synthesis has been positively tested in the rearrangement of enol carbonates. The enantioselective formation of quaternary stereogenic centers has been observed, and the possibility of recovering the catalyst at the end of the process has been demonstrated. Further research exploring the scope of these catalysts is currently under investigation.

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. Recombinant in *E. coli* alcohol dehydrogenases from *Thermoanaerobacter species* (T-ADH, 378 U/mL) and *Lactobacillus brevis* (LB-ADH, 1300 U/mL) were obtained from Jülich Fine Chemicals. Baker's yeast (yeast from *Saccharomyces cerevisae*, type II) was purchased from Sigma. All other reagents were purchased from different commercial sources 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). Detailed characterization of compounds and instrumental techniques used are described in the Supporting Information.

4-Chloropyridine (2)

A solution of 4-chloropyridine hydrochloride (5 g, 33.3 mmol) in H_2O (25 mL) was basified to pH 12 with 4 N NaOH solution (3 mL) and extracted with Et_2O (3 × 50 mL). The organic phases were combined, dried over Na_2SO_4 and the solvent evaporated under reduced pressure at low temperature to afford **2**; yield: 3.55 g (94%).

General Procedure for the Synthesis of 4-Chloro-3-(1-hydroxyalkyl)pyridines (3a–d) and 4-Chloro-3-[hydroxy(phenyl)methyl]pyridine (3e)

To a solution of diisopropylamine (1.28 mL, 8.80 mmol for **3a–d** or 0.64 mL, 4.40 mmol for **3e**) in dry Et_2O (20 mL) at −60 °C was added a 1.6 M BuLi solution in hexane (5.5 mL, 8.80 mmol for **3a–d** or 2.75 mL, 4.40 mmol for **3e**). The mixture was allowed to warm to 0 °C and stirred during 1 h. After this time the solution was cooled to −60 °C and 4-chloropyridine (500 mg, 4.40 mmol) in 4 mL of dry Et_2O was added. The reaction mixture was stirred for additional 4 h, and then the corresponding aldehyde (4.40 mmol) was added and the mixture was stirred and allowed to warm to room temperature during 15 min. Excess of LDA was destroyed with H_2O (25 mL), and the mixture extracted with Et_2O (3 × 25 mL). The organic phases were combined, dried over Na_2SO_4 and the solvent evaporated under reduced pressure obtaining a crude material that was purified by flash chromatography (20–40% EtOAc/hexane) isolating the corresponding alcohol **3a–e**.

Enzymatic Kinetic Resolution of 4-Chloro-3-(1-hydroxyalkyl)pyridines (3a–d) and 4-Chloro-3-[hydroxy(phenyl)methyl]pyridine (3e) by Enzymatic Transesterification

A suspension under nitrogen atmosphere of **3a–e** (0.94 mmol) and CAL-B (150 mg) in vinyl acetate (9.4 mL), was shaken at 60 °C and 250 rpm. Aliquots were regularly analyzed by HPLC and the reaction was stopped by filtering the enzyme with CH_2Cl_2 (3 × 10 mL). The solvent was evaporated and the crude of reaction purified by flash chromatography (20–40% EtOAc/hexane) isolating optically active (*R*)-**5a–e** and (*S*)-**3a–e**.

Chemical Oxidation-Enzymatic Reduction Sequence of 4-Chloro-3-(1-hydroxyalkyl)pyridines (3a–d) and 4-Chloro-3-[hydroxy(phenyl)methyl]pyridine (3e)

A solution of **3a–e** (0.32 mmol) in dry acetone (1 mL) was cooled to 0 °C and CrO_3 (96 mg, 0.96 mmol) was added carefully in small portions. The resulting solution was stirred at room temperature until complete consumption of the starting material (3 h), after this time the reaction was quenched with 2-propanol (160 μL), and the mixture was stirred during 15 min. A saturated solution of $NaHCO_3$ (5 mL) was finally added to precipitate the chromium salts that were filtered over celite and washed with CH_2Cl_2 (6 × 15 mL). The solvent was evaporated under reduced pressure avoiding total dryness to afford the corresponding ketone **6a–e**.

a) Processes with baker's yeast: additional 2-propanol (500 μL), a glucose solution in H_2O (21 mL of 15 mg mL^{-1} concentration) and baker's yeast (2.45 g for **6a–d** or 4.90 g for **6e**) were added, and the resulting solution was shaken during 14 h at 30 °C and 250 rpm until no ketone was detected by TLC analysis. The reaction was centrifuged and the supernatant extracted with CH_2Cl_2 (3 × 50 mL), the organic phases were combined, dried over Na_2SO_4 and the solvent evaporated under reduced pressure obtaining a crude that was purified by flash chromatography (40% EtOAc/hexane) isolating optically active (*S*)-**3a–e** (Table 2).

b) Processes with TS-ADH or LB-ADH: additional 2-propanol (500 μL), TRIS/HCl buffer solution of pH 7 (2.56 mL), 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 and the resulting mixture was shaken at 30 °C for the required time. The reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL), the organic phases were combined and the solvent distilled under reduced pressure, obtaining a crude material that was purified by flash chromatography (40% EtOAc/hexane) isolating optically active **3a–e** (Table 2).

General Procedure for the Synthesis of (*S*)-4-(Dimethylamino)-3-(1-hydroxyalkyl)pyridines (7a–d) and (*S*)-4-(Dimethylamino)-3-[hydroxy(phenyl)methyl]-pyridine (7e)

A solution of (*S*)-4-chloro-3-(1-hydroxyalkyl)pyridines (**3a–d**) or (*S*)-4-chloro-3-[hydroxy(phenyl)methyl]pyridine (**3e**) (1.27 mmol) and a 40% aqueous solution of Me_2NH (3 mL, 24 mmol) was stirred in a sealed tube at 100 °C until complete consumption of the starting material (46 h). Solvent was evaporated by distillation at reduced pressure and the resulting crude material purified by flash chromatography (40% MeOH/EtOAc) yielding (*S*)-**7a–e** in nearly quantitative yields.

General Procedure for the Synthesis of (*S*)-1-[4-(Dimethylamino)-3-pyridinyl]ethyl Acetate (9a), (*S*)-1-[4-(Dimethylamino)-3-pyridinyl]pentyl Acetate (9d) and (*S*)-1-[4-(Dimethylamino)-3-pyridinyl](phenyl)-methyl Acetate (9e)

To a solution of the corresponding (*S*)-4-(dimethylamino)-3-(1-hydroxyalkyl)pyridine (**7a** or **7d**) or (*S*)-4-(dimethylamino)-3-[hydroxy(phenyl)methyl]pyridine (**7e**) (0.18 mmol) in dry CH_2Cl_2 (4.2 mL) under nitrogen atmosphere were successively added NEt_3 (78 μL, 0.54 mmol) and Ac_2O (32 μL, 0.36 mmol). The mixture was stirred during 2 h after which time the solvent was evaporated under reduce pressure obtaining a crude that was purified by flash chromatography (20% MeOH/EtOAc) isolating the corresponding acetates **9a–e**.

Synthesis of Catalyst (*S*)-4-(Dimethylamino)-3-[1-(benzyloxycarbonyloxy)pentyl]pyridine (11)

Catalyst (*S*)-4-(dimethylamino)-3-(1-hydroxypentyl)pyridine [(−)-**7d**] (52 mg, 0.25 mmol) was dissolved in 2 mL of dry CH_2Cl_2 under a nitrogen atmosphere, and the resulting solution was cooled to 0 °C. Pyridine (22 μL, 0.28 mmol) and benzyl chloroformate (40 μL, 0.28 mmol) were carefully added and the mixture was stirred during 6 h at 0 °C. The reaction was stopped evaporating the solvent under reduce pressure obtaining 79 mg of (*S*)-**11** as a colorless oil (92% isolated yield).

Enantioselective Rearrangement of 5-Benzyloxycarbonyloxy-4-methyl-2-(4-methoxyphenyl)-oxazole (8) with Catalysts (*S*)-1-[4-(Dimethylamino)-3-pyridinyl]ethyl Acetate (9a), (*S*)-1-[4-(Dimethylamino)-3-pyridinyl]pentyl Acetate (9d), (*S*)-[4-(Dimethylamino)-3-pyridinyl](phenyl)methyl Acetate (9e) or (*S*)-4-(Dimethylamino)-3-(1-benzyloxycarbonyloxy-pentyl)pyridine (11)

5-Benzyloxycarbonyloxy-4-methyl-2-(4-methoxyphenyl)-oxazole (**8**, 68 mg, 0.20 mmol) was dissolved in *tert*-amyl alcohol (3 mL) and the solution was cooled to −10 °C. The corresponding catalyst (***S***)-**9a, 9d, 9e** or **11** (0.20 mmol) was added in 1 mL of *tert*-amyl alcohol, and the mixture was stirred during 7 h. The solvent was evaporated under reduced pressure and the crude material purified by flash chromatography (10% EtOAc/hexane) isolating optically active 4-methyl-5-oxo-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylic acid benzyl ester **10**,[17] and recovering the initial DMAP catalyst by additional elution of solvents (20% MeOH/EtOAc).

General Procedure for the Synthesis of Mosher's Esters (see Supporting Information for ^{1}H NMR Spectra)

In a typical procedure the alcohol 4-chloro-3-(1-hydroxyalkyl)pyridines (**3a–d**) or 4-chloro-3-[hydroxy(phenyl)-methyl]pyridine (**3e**) (0.10 mmol) was dissolved in 1 mL of dry CH_2Cl_2, then DMAP (0.20 mmol) and (*S*)-(+)-α-methoxy-α-trifluoromethylphenyl acetic acid chloride (0.13 mmol) were successively added. The solution was stirred for 14 h at room temperature until complete consumption of the starting material. The solvent was evaporated under reduced pressure and the crude material purified by flash chromatography (10% EtOAc/hexane) affording the corresponding Mosher's ester.

To determine the absolute stereochemistry of alcohol **3a**, the Mosher's ester of compound (+)-**3a** obtained from the bioreduction of the corresponding ketone **6a** with *Lactobacillus brevis* alcohol dehydrogenase was prepared. In the ^{1}H NMR spectra there are two significant signals: the methoxy group is shield for the pyridine ring so its signal appears at low fields (3.54 ppm) meanwhile the H_2 of the pyridine ring is not shielded for the phenyl group so it appears at high field (8.63 ppm), with this reasoning the configuration of the alcohol is (*R*)-**3a**.

To determine the absolute stereochemistries of alcohols **3b–d**, the Mosher's ester of compounds (−)-**3b–d** obtained from the bioreduction of the corresponding ketone **6b–d** with baker's yeast were prepared. In the ^{1}H NMR spectra there are two significant signals: the methoxy groups are not shielded for the pyridine ring so their signals appear at high field (3.6 ppm) meanwhile the H_2 of the pyridine rings are shielded for the phenyl group so they appear at low field (8.3 ppm), with this reasoning the configuration of the alcohols is (*S*)-**3b–d**.

To determine the absolute stereochemistry of alcohol **3e**, the Mosher's ester of compound (+)-**3e** obtained from the bioreduction of of the corresponding ketone **6e** with baker's yeast was prepared. In the ^{1}H NMR spectra there is one significant signal: the H_2 of the pyridine ring is shielded for the phenyl group so it appears at low field (8.54 ppm), with this reasoning the configuration of the alcohol is (*S*)-**3e**.

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