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Synthesis of novel chiral lipophilic pyridyl-containing β-amino alcohol ligands and enantioselective hydrolysis of α-amino acid esters by chiral metallomicelles

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Abstract

Seven novel chiral lipophilic pyridyl-containing β-amino alcohol ligands have been synthesized by coupling of 6-alkoxymethyl-2-chloromethylpyridine **3** with the corresponding chiral β-amino alcohols or L-cysteine. Their metal ion complexes have been investigated as catalysts for the enantioselective hydrolysis of *N*-protected α-amino acid esters in aqueous comicellar solution. The results indicate that the hydrophobic interactions between substrate and metallocatalyst, the rigidity of the ligand, the hydroxyl group of the ligand acting as a nucleophile for the transacylation process, and the micellar microenvironment are important factors for the activity and enantioselectivity. Large rate accelerations (up to three orders of magnitude) and moderate enantioselectivities (up to 7.81 (k_R/k_S)) employing **4a**–Cu^{2+} have been observed.

1. Introduction

Metallomicelles are currently receiving considerable interest as new catalytic systems.[1–7] These supramolecular systems are made up of ligand surfactants (or lipophilic ligands) chelating metal ions. Of particular interest are the micellar models of hydrolytic metalloenzymes that are able to promote the cleavage of phosphoric and carboxylic esters or amides. Most of them are focused on the ligands containing imidazole, pyridine or 1,10-phenanthroline as the basic chelating subunit and as the molecular junction for the paraffinic chain. Despite such progress, there are only a few examples dealing with the enantioselective hydrolysis by chiral homo and mixed metallomicelles as models for hydrolytic metalloenzymes.[8] We have recently reported the first example of chiral macrocyclic metallomicelles and their effect on the enantioselective cleavage of *N*-dodecanoylamino acid *p*-nitrophenyl esters.[9] In this paper, we report our work on the synthesis of new chiral lipophilic pyridyl-containing β-amino alcohol

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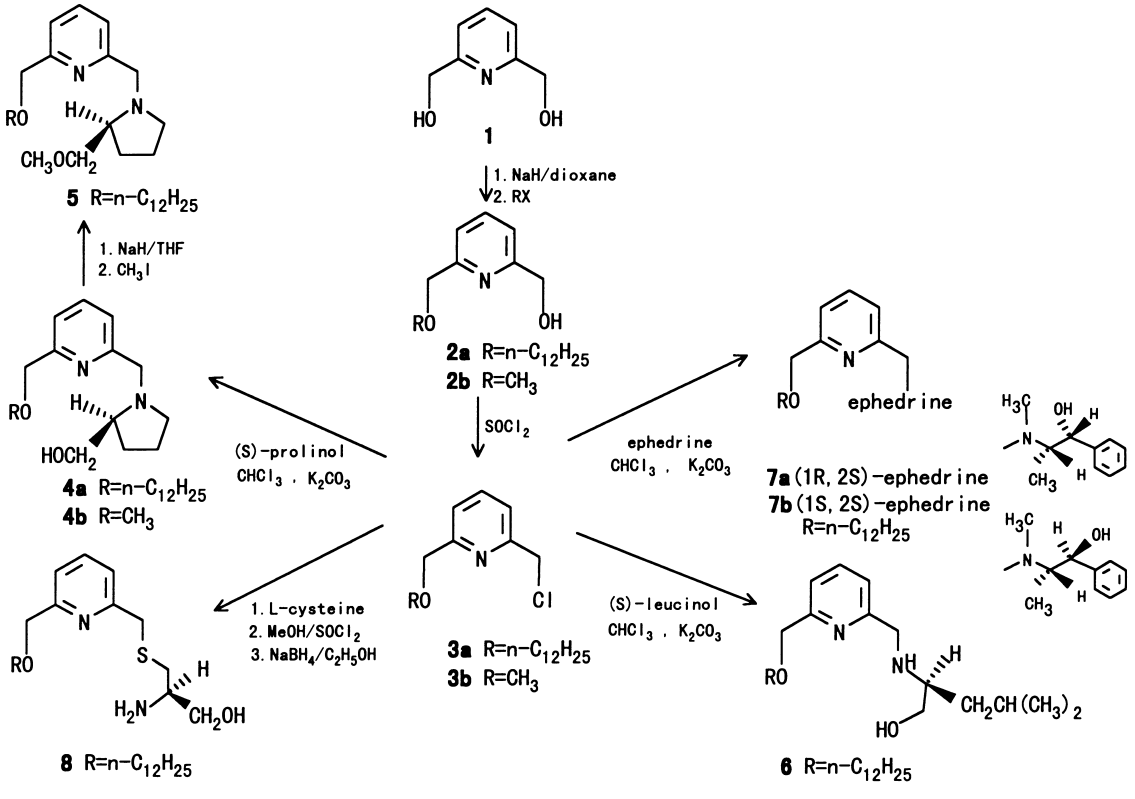
ligands, **4**–**8**, and the enantioselective hydrolysis of α-amino acid esters by their metal ion complexes in chiral metallomicelles. Ligands **4**, **6** and **8** contain the rigid prolinol group, the flexible leucinol group and the flexible cysteinol group with one stereogenic center, respectively, and ligand **7** contains the ephedrine group with two stereogenic centers. Ligand **5**, the *O*-methylated analogue of **4a**, lacks the hydroxymethyl group with the aim of defining the role of the hydroxy function in the complexes with ligands **4**, **6**, **7** and **8**. The water soluble ligand **4b**, which does not contain a hydrophobic long chain, has also been investigated so that the catalytic activity of this compound can be used for comparison.

2. Results and discussion

2.1. Ligands and substrates

Ligands **4**–**8** were synthesized according to the procedures outlined in Scheme 1 using 2,6-bis(hydroxymethyl)pyridine **1** as a starting material, which was selectively partially *O*-alkylated to 6-alkoxymethyl-2-hydroxymethylpyridine **2**, in the presence of a slight excess of NaH in dry dioxane in good yield. It is necessary to point out that the halide should be added dropwise; otherwise bis-alkylation mainly occurred. Compound **2** was then converted to 6-alkoxymethyl-2-chloromethylpyridine **3** by addition of $SOCl_2$.



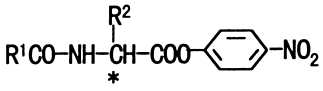
Scheme 1.

Ligands **4a**, **4b**, **6**, **7a** and **7b** were obtained by coupling of **3** with the desired chiral β-amino alcohols. In the case of ligand **8**, **3a** selectively reacted with the mercapto instead of the amino in the presence of NaOH and NaI, and the adduct was converted to the ester derivative and subsequently reduced to ligand

8 with $NaBH_4$.[9,10] Ligand **5** was obtained by the reaction of ligand **4a** with CH_3I. Their structures are confirmed by elemental analysis, MS and ^1H NMR.

Lipophilic ligands **5**, **6** and **7** are barely soluble in neutral water. Their clear solutions, free or as transition metal ion complexes, can be obtained only in the presence of micelles of inert surfactants such as Brij35 as a matrix of comicellar aggregates. The kinetic experiments were carried out using mixed micelles, composed of a metal ion complex and a cosurfactant. Compounds **4a** and **8** are soluble in water and form micellar aggregates: the critical micellar concentrations (cmc) are 2.0×10^{-4} M and 2.8×10^{-4} M in MES buffer (0.05 M, pH 6.30), respectively.[8c]

Scheme 2 shows the substrates investigated: they are all chiral, nonmetallophilic substrates, i.e., the *N*-protected *p*-nitrophenyl esters of *R*(*S*)-phenylalanine, *R*(*S*)-leucine and *R*(*S*)-alanine.



Substrate	R^1	R^2
R(S)-C_{12}-Phe-PNP	n-$C_{11}H_{23}$	CH_2Ph
R(S)-C_{12}-Leu-PNP	n-$C_{11}H_{23}$	$CH_2CH(CH_3)_2$
R(S)-C_{12}-Ala-PNP	n-$C_{11}H_{23}$	CH_3
R(S)-C_2-Ala-PNP	CH_3	CH_3

Scheme 2.

2.2. Kinetics

The rate of hydrolysis was followed by observing the release of *p*-nitrophenol spectrophotometrically under pseudo-first-order conditions. The pseudo-first-order constants (k_R and k_S) for the cleavage of *R*(*S*)-C_{12}-Phe-PNP catalyzed by metal ion complexes comicellized with Brij35 are summarized in Table 1. The enantioselectivity of each system is indicated by the ratio k_R/k_S. The results show that large rate enhancements and enantioselectivities are observed only in the presence of both the ligand and metal ion. The catalytic activity is the result of synergistic cooperation of the ligand and metal ion. More strikingly, the enantioselectivity of **4a**–M^{2+} shows a distinct dependence on the nature of the transition metal ion, and has the order of $Cu^{2+}>Zn^{2+}>Mn^{2+}>Co^{2+}>Ni^{2+}$. For ligands with one stereogenic center (except ligand **5**) they react faster with the enantiomeric substrate of opposite absolute configuration. For the diastereomeric **7a** and **7b** an inversion of stereoselectivity is observed.

Normal micelles have a loose and mobile structure that is not very effective at inducing stereoselectivity. However, in the present system good enantioselectivity is obtained. We believe that this is caused by a highly oriented substrate–metallocatalyst ternary complex. In this ternary complex, the motional freedom of both the hydroxyl group of the ligand and the substrate is restricted by the template effect of the metal ion.

Although for both **4a** and **6** the OH group is located at the δ-position in the side group of the pyridine residue, ligand **6** exhibits less activity and stereoselectivity compared to ligand **4a**. According to CPK models, by binding of the metal ion to the nitrogen atom of the rigid (*S*)-prolinol group of ligand **4**, the structure of the (*S*)-prolinol group is frozen, and the OH group is in close proximity to metal ion. For ligand **6**, binding the metal ion to the nitrogen atom of the flexible (*S*)-leucinol group does not induce complete fixation of the side group, and rotation around the C1–C2 axis of the (*S*)-leucinol group is still possible. This indicates that the rigid structure of the ligand is more efficient, as expected from the reduction in the degrees of freedom of the system. The lower activity and enantioselectivity of **7** and **8** are also probably attributed to the higher structural flexibility of the ephedrine moiety and the cysteinol

Table 1
Pseudo-first-order constants (k_R and k_S, s^{-1}) and enantioselectivities (k_R/k_S) for the cleavage of *R*(*S*)-C_{12}-Phe-PNP by ligands **4**–**8** and M^{2+} comicellized with Brij35

Entry	Ligand	M^{2+}	Cosurfactant	$k_S/10^{-5}$	$k_R/10^{-5}$	k_R/k_S
1	none	none	Brij35	2.17	2.09	0.96
2	none	Cu^{2+}	Brij35	3.01	3.05	1.01
3	**4b**	Cu^{2+}	Brij35	76.7	138	1.80
4	**4a**	none	Brij35	6.25	6.25	1.00
5	**4a**	Cu^{2+}	none	547	2190	4.00
6	**4a**	Cu^{2+}	Brij35	210	1640	7.81
7	**4a**	Zn^{2+}	Brij35	95.0	381	4.01
8	**4a**	Co^{2+}	Brij35	55.3	84.6	1.53
9	**4a**	Ni^{2+}	Brij35	103	121	1.17
10	**4a**	Mn^{2+}	Brij35	69.0	135	1.96
11	**5**	Cu^{2+}	Brij35	196	145	0.74
12	**6**	Cu^{2+}	Brij35	106	287	2.71
13	**7a**	Cu^{2+}	Brij35	309	139	0.45
14	**7b**	Cu^{2+}	Brij35	115	311	2.70
15	**8**	Cu^{2+}	Brij35	111	53.6	0.48

Conditions: 25 ± 0.1 ℃, pH 6.30 [0.05 M MES buffer], [ligand]=5.0×10^{-4} M, [substrate]=5.0×10^{-5} M, [M^{2+}]=5.0×10^{-4} M, [Brij35]=4.0×10^{-3} M.

group, and the lower nucleophilicity of the more sterically hindered secondary OH in ligand **7**. Taking the analogous ligands **4a** and **5** as an exemplary case (compare entries 6 and 11), methylation of the hydroxy group leads to a dramatic decrease in rate and enantioselectivity, and an inversion of enantioselectivity is observed. This suggests that the free hydroxy group of a ligand is mandatory in the transacylation process as a nucleophile, as reported previously.[9] From the data in Table 1, we notice that the water-soluble **4b**–Cu^{2+} lacking a long chain is also less reactive and enantioselective in comparison with the lipophilic **4a**–Cu^{2+}, indicating that the hydrophobic interactions between substrate and metallocatalyst are favorable for both high rate acceleration and good enantioselectivity. A lipophilic long chain can introduce an extra orientation requirement in the supramolecular assembly between the metal ion complex and the lipophilic substrate coexisting in the micelle by the hydrophobic interactions.

Table 2 shows the kinetic data observed for the cleavage of *R*(*S*)-C_{12}-Phe-PNP in the absence and presence of anionic *n*-dodecyl sodium sulfate (SDS), cationic *n*-hexadecyltrimethylammonium bromide (CTABr), nonionic polyethylene glycol dodecyl ether (Brij35) or chiral *n*-dodecylquininium bromide (DQB) as the matrix of comicellar aggregates. In the Brij35 micelle the enantioselectivity induced by **4a**–Cu^{2+} is higher than in CTABr and SDS. It is clearly seen that the chiral DQB has no significant effect on the observed rate and enantioselectivity. Its blank reaction in the absence of metallocatalyst also displays an insignificant enantioselectivity (k_R/k_S=0.86). These observations indicate that chiral DQB hardly recognizes the chirality of metallocatalyst and substrate. In summary the micellar microenvironment is of importance for the activity and the enantioselectivity.

The structural effect of substrates on the hydrolysis catalyzed by mixed micelles composed of **4a**–Cu^{2+}

Table 2
Pseudo-first-order constants (k_R and k_S, s^{-1}) and enantioselectivities (k_R/k_S) for the cleavage of *R*(*S*)-C_{12}-Phe-PNP by **4a** and Cu^{2+} comicellized with different cosurfactants

Entry	Ligand	Cu^{2+}	Cosurfactant	$k_S/10^{-5}$	$k_R/10^{-5}$	k_R/k_S
1	none	none	DQB	39.9	34.5	0.86
2	**4a**	Cu^{2+}	DQB	265	735	2.77
3	**4a**	Cu^{2+}	none	547	2190	4.00
4	**4a**	Cu^{2+}	Brij35	210	1640	7.81
5	**4a**	Cu^{2+}	CTABr	811	2380	2.93
6	**4a**	Cu^{2+}	SDS	276	774	2.80

Conditions : [cosurfactant]=4.0×10^{-3} M. See Table 1 for other conditions.

Table 3
Structural effect of substrates on pseudo-first-order constants (k_R and k_S, s^{-1}) and enantioselectivities (k_R/k_S) catalyzed by a mixed micellar system composed of **4a**–Cu^{2+} and Brij35

Entry	Substrate	$k_S/10^{-5}$	$k_R/10^{-5}$	k_R/k_S
1	R(S)-C_{12}-Phe-PNP	210	1640	7.81
2	R(S)-C_{12}-Leu-PNP	197	1390	7.06
3	R(S)-C_{12}-Ala-PNP	161	410	2.55
4	R(S)-C_2-Ala-PNP	30.0	41.2	1.37

Conditions: [substrate]=5.0×10^{-5} M. See Table 1 for other conditions.

and Brij35 is depicted in Table 3. The increase in the size of the amino acid side chain of residue R^2 from alanine up to phenylalanine is accompanied by an increase in the selectivity from k_R/k_S=2.55 up to 7.81. The enhancement of selectivity is almost exclusively due to the increasing rate of the (*R*)-substrate whereas the rate of the (*S*)-substrate is hardly affected. The hydrophobicity of the amino acid side chain increases from the methyl moiety in the alanyl residue up to the benzyl moiety in the phenylalanyl residue. Quite likely, the increase in the rate of the (*R*)-substrate is due to an increased hydrophobically driven interaction between metallocatalyst and (*R*)-substrate. Such an interaction is absent with the (*S*)-substrate. In the deacylation of *R*(*S*)-C_2-Ala-PNP, the extent of the enantioselectivity increase is negligibily small (k_R/k_S=1.37). As discussed above, this indicates that such ester substrates as *R*(*S*)-C_2-Ala-PNP lacking the hydrophobic long chain are likely to be adsorbed onto the water–micelle interface and are hardly incorporated into the micellar phase, leading to insufficient substrate–metallocatalyst approximation.

2.3. Stoichiometry of the reactive complexes

In order to determine the stoichiometry of the kinetically reactive complexes, the kinetic version of Job plots was examined by plotting k_R and k_S as a function of molar fraction of ligand (γ), keeping the total concentrations of the ligand and metal ion constant. The results shown in Fig. 1 indicate that in the case of Cu^{2+} and ligand **4a** the rate maxima are observed at γ=0.5, which correspond to a stoichiometry

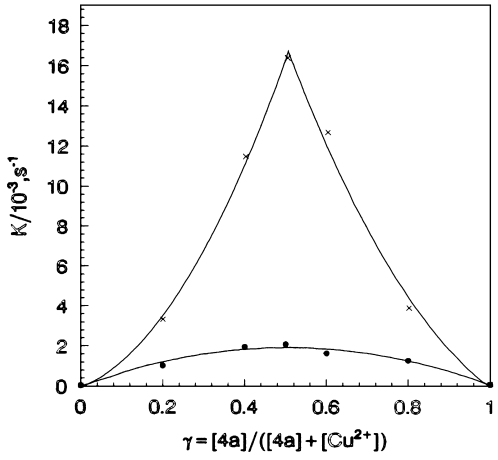


Figure 1. Kinetic Job plots for the cleavage of (*R*)-Phe-PNP (×) and (*S*)-Phe-PNP (•) by ligand **4a** and Cu^{2+} in MES buffer, pH 6.30, 25±0.1°C. [**4a**]+[Cu^{2+}]=1.0×10^{-3} M. See Table 1 for other conditions

of ligand:Cu^{2+}=1:1. Ligand **4a** forms stable complexes with Cu^{2+} as indicated by the sharp maxima in the Job plots.

2.4. pH-Rate profile

As discussed above, from the analysis of Table 1, a free hydroxyl in the ligand structure is of importance for high rate acceleration and good enantioselectivity in micelles. The pH-rate constant profiles were determined for reactions of (*R*)-C_{12}-Phe-PNP with catalyst **4a**–Cu^{2+} and (*S*)-C_{12}-Phe-PNP with **8**–Cu^{2+}. The pH value was checked before and after any kinetic run and proved to be constant to within ±0.05 pH unit. The inflections in the pH-rate profiles are diagnostic of an operative pK_a value of ca. 6.7 and 7.0, respectively (Fig. 2). They are taken as the systematic pK_a of the hydroxyl bound to Cu^{2+} under our micellar reaction conditions. A pK_a=7.2 for a Cu^{2+} coordinated primary hydroxyl has been recently reported by our laboratory.[9] It would be very interesting to know the pK_a of the Cu^{2+}-bound secondary alcohol. Regrettably, solutions of the complex **7a**–Cu^{2+} were unstable at pH>7.6. Up to that pH we did not observe any break in the log k versus pH profile.

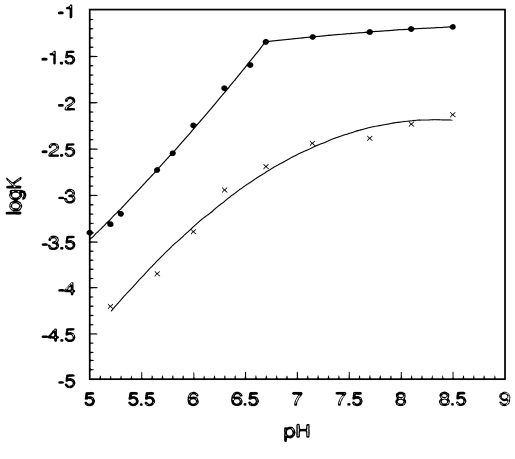
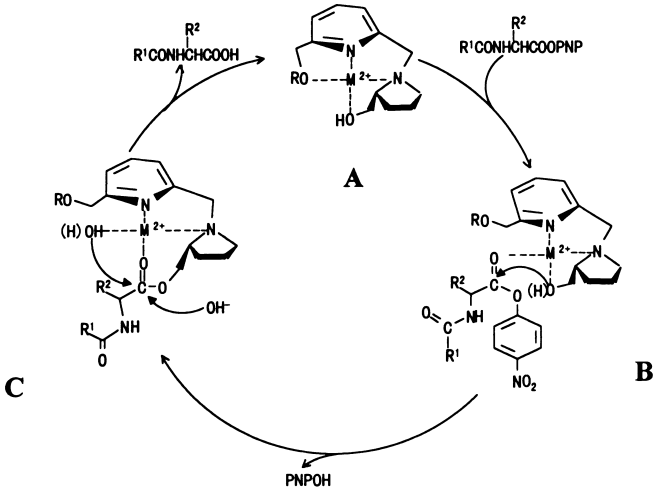


Figure 2. Log k versus pH for the hydrolysis of (*R*)-C_{12}-Phe-PNP by **4a**–Cu^{2+} (•) and (*S*)-C_{12}-Phe-PNP by **8**–Cu^{2+} (×). See Table 1 for other conditions

2.5. Mechanism

The above kinetic behavior of **4a**–M^{2+}-catalyzed hydrolysis of *N*-protected α-amino acid esters is outlined in Scheme 3 on the basis of previous reports.[3c,4b,8c] The possible mechanism is based on an octahedral geometry of the metal ion complex although for Ni^{2+}, Cu^{2+}, Zn^{2+}, Co^{2+} and Mn^{2+} alternative forms are possible.[11] The mechanism involves:

(i) The formation of the metal complex **A**: M^{2+} coordinates up to six donors in an octahedral geometry. The metal complex may be represented as **A** where the two nitrogen atoms and two oxygen atoms of ligand **4a** occupy the strongest position in a planar configuration.



Scheme 3. A possible mechanism of the cleavage of α-amino acid esters by chiral metallomicelles

(ii) The formation of the ternary complex **B**: this is the key step of the hydrolysis. The oxygen atom of the $CH_3(CH_2)_nOCH_2$ group of the ligand is not a strong donor. For the formation of the ternary complex, it should be displaced by the carbonyl group of the substrate.[3b,12] Therefore the function of this group will primarily incorporate the ligand into the micellar phase. The hydroxyl group of ligand is activated by the metal ion, and its pK_a value is reduced to provide the effective nucleophile at near neutral pH.

(iii) The formation of the transacylation intermediate **C**: in the above mentioned ternary complex, a pseudo-intramolecular nucleophilic attack of the activated ligand hydroxyl on the carbonyl function of the substrate results in the expulsion of *p*-nitrophenol and the formation of an acylated intermediate **C**.

(iv) The cleavage of the intermediate: this intermediate is hydrolyzed to release the amino acid and regenerate the catalytic species by attack of the free or metal-ion-bound hydroxide ion to the coordinated ester group, thus defining the catalytic cycle.

3. Experimental

3.1. General methods and materials

Melting points were taken on a micro-melting apparatus and are uncorrected. ^1H NMR spectra were recorded at 90 MHz and 299.95 MHz, and chemical shifts in ppm are reported relative

to internal Me_4Si. Mass spectra data were recorded on a Finnigan MAT 4510 spectrometer. Elemental analyses were performed with a Carlo Erba 1106 instrument. Optical rotations were taken on a WZZ-1 polarimeter. Kinetic runs were conducted on a Shimadzu UV-265FW spectrophotometer equipped with a thermostated cell compartment. $Zn(NO_3)_2 \cdot 6H_2O$, $Cu(NO_3)_2 \cdot 6H_2O$, $Co(NO_3)_2$, $Ni(NO_3)_2$, $MnCl_2$, *n*-dodecyl sodium sulfate (SDS), *n*-hexadecyltrimethylammonium bromide (CTABr) and polyethylene glycol dodecyl ether (Brij35) were purchased from commercial sources and used without further purification. The buffers were 2-morpholinoethanesulfonic acid (MES) (pH=5.0–6.8), 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) (pH=6.8–7.8) and 4-(2-hydroxyethyl)-1-piperazinepropanesulfonic acid (EPPS) (pH=7.7–8.5). The following compounds were prepared according to literature procedures: 2,6-bis(hydroxymethyl)pyridine,[13] the *p*-nitrophenyl esters of the *N*-protected α-amino acids,[14] and (*S*)-amino alcohols.[15] Chloroform, tetrahydrofuran and dioxane were purified according to the standard methods. All other chemicals and reagents were obtained commercially and used without further purification.

*3.2. General procedure for the synthesis of **2***

To a solution of 2,6-bis(hydroxymethyl)pyridine **1** (4.5 g, 32.4 mmol) in 50 mL of dry dioxane was added NaH (1.17 g of 80% dispersion in mineral oil) under a nitrogen atmosphere. After the mixture was kept for 2 h, the halide (1-bromododecane for **2a** or iodomethane for **2b**) (32.4 mmol) in 25 mL of dioxane was added dropwise. The mixture was stirred at room temperature overnight. The slurry was filtered, the organic solvent was evaporated, and the crude material purified by column chromatography (SiO_2, $CHCl_3$:CH_3OH, 100:5) to give a pale yellow oil.

*3.2.1. 6-(*n*-Dodecyloxymethyl)-2-(hydroxymethyl)pyridine **2a***

The resulting oil was recrystallized from petroleum (b.p. 30–60°C) to give white needles (yield 81.0%); m.p. 44–45°C. δ_H (90 MHz, $CDCl_3$): 0.88 (t, J=6.4 Hz, 3H, CH_3), 1.26 (s, 18H, $(CH_2)_9CH_3$), 1.56 (m, 2H, $OCH_2CH_2(CH_2)_9$), 3.55 (t, J=6.7 Hz, 2H, $OCH_2(CH_2)_{10}CH_3$), 4.63 (s, 2H, $PyCH_2OC_{12}H_{25}$), 4.74 (s, 2H, $PyCH_2OH$), 7.09 and 7.31 (2d, J=7.6 Hz, 2H, *Py*H5 and *Py*H3), 7.71 (t, J=7.6 Hz, 1H, *Py*H4). MS (m/z): 308 (M^++1, 20).

*3.2.2. 6-(Methyloxymethyl)-2-(hydroxymethyl)pyridine **2b***

Pale yellow oil (yield 88.5%). δ_H (90 MHz, $CDCl_3$): 3.50 (s, 3H, CH_3), 4.58 (s, 2H, $PyCH_2OCH_3$), 4.71 (s, 2H, $PyCH_2OH$), 7.20 and 7.34 (2d, J=7.5 Hz, 2H, *Py*H5 and *Py*H3), 7.65 (t, J=7.5 Hz, 1H, *Py*H4). MS (m/z): 154 (M^++1, 80).

*3.3. General procedure for the synthesis of **3***

To 15 mL of $SOCl_2$ was added compound **2** (4.1 mmol) at 0°C. The reaction mixture was stirred for 20 h at room temperature, and then concentrated in vacuo. The residue was dissolved in 100 mL of $CHCl_3$ and washed with a saturated solution of $NaHCO_3$ until the pH was 8.5. The organic phase was separated, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was chromatographed on silica gel (ethyl acetate:methanol, 100:5).

*3.3.1. 6-(*n*-Dodecyloxymethyl)-2-(chloromethyl)pyridine **3a***

White solid (yield 89.1%); m.p. 35–36°C. δ_H (90 MHz, $CDCl_3$): 0.88 (t, J=6.2 Hz, 3H, CH_3), 1.26 (s, 18H, $(CH_2)_9CH_3$), 1.65 (m, 2H, $OCH_2CH_2(CH_2)_9$), 3.56 (t, 2H, J=6.5 Hz, $OCH_2(CH_2)_{10}CH_3$), 4.61 (s,

2H, PyCH_2 Cl), 4.65 (s, 2H, Py$CH_2OC_{12}H_{25}$), 7.27 and 7.40 (2d, J=7.6 Hz, 2H, *Py*H3 and *Py*H5), 7.73 (t, J=7.6 Hz, 1H, *Py*H4). MS (m/z): 326 (M^+, 30).

3.3.2. 6-(Methyloxymethyl)-2-(chloromethyl)pyridine ***3b***

Pale yellow oil (yield 95.4%). δ_H (90 MHz, $CDCl_3$): 3.56 (s, 3H, CH_3), 4.63 (s, 2H, PyCH_2Cl), 4.70 (s, 2H, PyCH_2OCH_3), 7.21 and 7.39 (2d, J=7.5 Hz, 2H, *Py*H3 and *Py*H5), 7.71 (t, J=7.5 Hz, 1H, *Py*H4). MS (m/z): 172 (M^+, 70).

3.4. General procedure for the synthesis of ligands ***4****,* ***6*** *and* ***7***

To a stirred mixture of K_2CO_3 (1.0 g) and the appropriate amino alcohol (3.1 mmol of (*S*)-prolinol for **4**, 3.1 mmol of ephedrine for **7**, or 6.2 mmol of (*S*)-leucinol for ligand **6**) in 20 mL of freshly distilled $CHCl_3$ was added, dropwise, 3.1 mmol of the appropriate 6-alkoxymethy-2-chloromethylpyridine (compound **3a** for ligands **4a**, **6** and **7**, or compound **3b** for ligand **4b**) dissolved in 15 mL of $CHCl_3$ at reflux under a nitrogen atmosphere. After the addition was complete, the mixture was kept at this temperature for 4 h. Water (15 mL) was then added. The organic layer was separated, dried over Na_2SO_4, evaporated under reduced pressure, and the raw product purified by column chromatography (SiO_2, $CHCl_3$:CH_3OH, 100:3).

*3.4.1. (*S*)-*N*-[6-(*n*-Dodecyloxymethyl)pyridine-2-yl]methylprolinol* ***4a***

Pale yellow oil (yield 83.6%); $[\alpha]_D^{25}=-10.8$ (c=1.0, $CHCl_3$). δ_H (299.95 MHz, $CDCl_3$): 0.88 (t, J=6.9 Hz, 3H, CH_3), 1.26 (s, 18H, $(CH_2)_9CH_3$), 1.37 (m, 2H, $OCH_2CH_2(CH_2)_9$), 1.65 (m, 4H, $(CH_2)_2CHCH_2OH$), 1.92 (m, 1H, $CH_{2a}(CH_2)_2CHCH_2OH$), 2.51 (m, 1H, $CH_{2b}(CH_2)_2CHCH_2OH$), 2.87 (m, 1H, $CHCH_2OH$), 3.11 (br s, 1H, OH), 3.43 (dd, J=3.3, 4.2 Hz, 1H, $CH_{2a}OH$), 3.48 (dd, J=3.3, 4.5 Hz, 1H, $CH_{2b}OH$), 3.55 (t, J=6.6 Hz, 2H, $OCH_2(CH_2)_{10}$), 3.71 (d, J=14.4 Hz, 1H, PyCH_{2a}N), 4.04 (d, J=14.4 Hz, 1H, PyCH_{2b}N), 4.62 (s, 2H, PyCH_2O), 7.20 and 7.34 (2d, J=7.5 Hz, 2H, *Py*H3 and *Py*H5), 7.67 (t, J=7.5 Hz, 1H, *Py*H4). Anal. calcd for $C_{24}H_{42}N_2O_2$: C, 73.79, H, 10.84, N, 7.17; found: C, 73.46, H, 11.02, N, 6.95. MS (m/z): 391 (M^++1, 90).

*3.4.2. (*S*)-*N*-[6-(Methyloxymethyl)pyridine-2-yl]methylprolinol* ***4b***

Pale yellow oil (yield 80.7%); $[\alpha]_D^{25}=-31.2$ (c=1.0, $CHCl_3$). δ_H (299.95 MHz, $CDCl_3$): 1.86 (m, 4H, $(CH_2)_2CHCH_2OH$), 2.10 (m, 1H, $CH_{2a}(CH_2)_2CHCH_2OH$), 2.52 (m, 1H, $CH_{2b}(CH_2)_2CHCH_2OH$), 2.65 (m, 1H, $CHCH_2OH$), 3.03 (br s, 1H, OH), 3.46 (dd, J=3.2, 4.2 Hz, 1H, $CH_{2a}OH$), 3.51 (dd, J=3.2, 4.5 Hz, 1H, $CH_{2b}OH$), 3.58 (s, 3H, OCH_3), 3.82 (d, J=14.5 Hz, 1H, PyCH_{2a}N), 4.05 (d, J=14.5 Hz, 1H, Py CH_{2b}N), 4.62 (s, 2H, PyCH_2O), 7.20 and 7.33 (2d, J=7.5 Hz, 2H, *Py*H3 and *Py*H5), 7.70 (t, J=7.5 Hz, 3H, *Py*H4). Anal. calcd for $C_{13}H_{20}N_2O_2$: C, 66.07, H, 8.53, N, 11.86; found: C, 65.79, H, 8.70, N, 11.57. MS (m/z): 237 (M^++1, 90).

*3.4.3. (*S*)-*N*-[6-(n-Dodecyloxymethyl)pyridine-2-yl]methylleucinol* ***6***

Pale yellow oil (yield 75.8%); $[\alpha]_D^{25}=+10.0$ (c=1.0, $CHCl_3$). δ_H (299.95 MHz, $CDCl_3$): 0.89 (m, 9H, CH_3), 1.26 (m, 18H, $CH_2(CH_2)_9$), 1.38 (m, 2H, OCH_2 $CH_2(CH_2)_9$), 1.65 (m, 3H, $CH_2CH(CH_3)_2$), 2.78 (m, 1H, $CHCH_2OH$), 3.01 (br s, 2H, NH, OH), 3.34 (dd, J=3.6, 6.3 Hz, 1H, $CH_{2a}OH$), 3.37 (dd, J=3.6, 6.3 Hz, 1H, $CH_{2b}OH$), 3.55 (t, J=6.6 Hz, 2H, $OCH_2(CH_2)_9$), 3.89 (d, J=15.0 Hz, 1H, PyCH_{2a}N), 3.99 (d, J=14.7 Hz, 1H, PyCH_{2b}N), 4.61 (s, 2H, PyCH_2O), 7.14 and 7.33 (2d, J=7.5 Hz, 2H, *Py*H3 and *Py*H5), 7.66 (t, J=7.5 Hz, 1H, *Py*H4). Anal. calcd for $C_{25}H_{46}N_2O_2$: C, 73.84, H, 11.40, N, 6.89; found: C, 73.49, H, 11.10, N, 6.65. MS (m/z): 407 (M^++1, 100).

*3.4.4. (1*R,*2*S*)*-N-[6-(*n-Dodecyloxymethyl)pyridine-2-yl]methylephedrine **7a***

The crude was purified by column chromatography (SiO_2, $CHCl_3$:CH_3OH, 100:1) and then by treatment with charcoal from absolute methanol under a nitrogen atmosphere to give a pale yellow oil (yield 54.0%); $[\alpha]_D^{25}$=−15.9 (c=1.9, $CHCl_3$). δ_H (299.95 MHz, $CDCl_3$): 0.88 (t, J=6.0 Hz, 3H, $(CH_2)_{11}CH_3$), 1.04 (d, J=7.1 Hz, 3H, $CHCH_3$), 1.19 (m, 18H, $(CH_2)_9CH_3$), 1.57 (m, 2H, $OCH_2CH_2(CH_2)_9$), 2.30 (s, 3H, NCH_3), 2.99 (m, 1H, $CHCH_3$), 3.54 (t, J=6.5 Hz, 2H, $OCH_2(CH_2)_{10}$), 3.62 (d, J=14.4 Hz, 1H, PyCH_{2a}N), 3.79 (d, J=14.4 Hz, 1H, Py CH_{2b}N), 4.09 (br s, 1H, OH), 4.60 (s, 2H, PyCH_2O), 4.89 (d, J=4.1 Hz, 1H, *CH*OH), 7.05–7.72 (m, 8H, HPh and HPy). Anal. calcd for $C_{29}H_{46}N_2O_2$: C, 76.60, H, 10.20, N, 6.16; found: C, 76.05, H, 9.98, N, 5.80. MS (m/z): 456 (M^++1, 70).

*3.4.5. (1*S,*2*S*)*-N-[6-(*n-Dodecyloxymethyl)pyridine-2-yl]methylephedrine **7b***

The crude was purified by column chromatography (SiO_2, $CHCl_3$:CH_3OH, 100:1) and then by treatment with charcoal from absolute methanol under a nitrogen atmosphere to give a pale yellow oil (yield 61.0%); $[\alpha]_D^{25}$=+5.1 (c=1.9, $CHCl_3$). δ_H (299.95 MHz, $CDCl_3$): 0.87 (t, 3H, J=6.4 Hz, $(CH_2)_{11}CH_3$), 0.96 (d, J=7.2 Hz, 3H, $CHCH_3$), 1.21 (m, 18H, $(CH_2)_9CH_3$), 1.59 (m, 2H, $OCH_2CH_2(CH_2)_9$), 2.30 (s, 3H, NCH_3), 2.90 (m, 1H, $CHCH_3$), 3.01 (br s, 1H, OH), 3.56 (t, J=6.6 Hz, 2H, $OCH_2(CH_2)_{10}$), 3.70 (d, J=14.0 Hz, 1H, PyCH_{2a}N), 3.89 (d, J=14.0 Hz, 1H, PyCH_{2b}N), 4.31 (d, J=7.2 Hz, 1H, *CH*OH), 4.60 (s, 2H, PyCH_2O), 7.05–7.79 (m, 8H, HPh and HPy). Anal. calcd for $C_{29}H_{46}N_2O_2$: C, 76.60, H, 10.20, N, 6.16; found: C, 76.18, H, 10.34, N, 6.06. MS (m/z): 456 (M^++1, 50).

*3.5. (*S*)*-N-[6-(*n-Dodecyloxymethyl)pyridine-2-yl]methylprolinol methyl ether **5***

To a solution of ligand **4a** (0.63 g, 1.61 mmol) in 30 mL of dry THF was added NaH (0.1 g of 80% dispersion in mineral oil) in an ice bath under a nitrogen atmosphere. After the mixture had been stirred at this temperature for 1.5 h, CH_3I (0.23 g, 1.61 mmol) in 10 mL of THF was added dropwise. Water (20 mL) was added, and the solvent evaporated. The residue was extracted with $CHCl_3$ and evaporated under reduced pressure. The raw product was chromatographed on silica gel ($CHCl_3$:CH_3OH, 100:3) to give a pale yellow oil (yield 58.4%); $[\alpha]_D^{25}$=−34.8 (c=1.0, $CHCl_3$). δ_H (299.95 MHz, $CDCl_3$): 0.93 (t, J=6.9 Hz, 3H, CH_3), 1.31 (s, 18H, $(CH_2)_9CH_3$), 1.38 (m, 2H, $OCH_2CH_2(CH_2)_9$), 1.68 (m, 4H, $(CH_2)_2CHCH_2OCH_3$), 2.01 (m, 1H, $CH_{2a}(CH_2)_2CH\ CH_2OCH_3$), 2.35 (m, 1H, $CH_{2b}(CH_2)_2CHCH_2OCH_3$), 2.91 (m, 1H, $CHCH_2OCH_3$), 3.33 (s, 3H, OCH_3), 3.46 (d, J=4.5 Hz, 2H, $CHCH_2OCH_3$), 3.56 (t, J=6.6 Hz, 2H, $OCH_2(CH_2)_{10}$), 3.76 (d, J=14.5 Hz, 1H, PyCH_{2a}N), 4.10 (d, J=14.5 Hz, 1H, PyCH_{2b}N), 4.61 (s, 2H, PyCH_2O), 7.21 and 7.34 (2d, J=7.5 Hz, 2H, *Py*H3 and *Py*H5), 7.65 (t, J=7.5 Hz, 1H, *Py*H4). Anal. calcd for $C_{25}H_{44}N_2O_2$: C, 74.21, H, 10.96, N, 6.92; found: C, 74.00, H, 11.23, N, 6.70. MS (m/z): 405 (M^++1, 70).

*3.6. (*R*)*-S-[6-(*n-Dodecyloxymethyl)pyridine-2-yl]methylcysteinol **8***

L-Cysteine hydrochloride (0.48 g, 3.06 mmol) and NaI (0.1 g) were dissolved in a solution of 3.06 mL of water and 20 mL of ethanol, and NaOH (6.12 mmol) was added slowly with stirring in an ice bath. After compound **3a** (1.0 g, 3.06 mmol) in 10 mL of ethanol was added, the mixture was kept for 4 h at 60°C. The precipitate was filtered off and sequentially washed with water and ethanol, and dried to give a white solid (yield 71.5%).

The above amino acid (0.9 g, 2.2 mmol) was suspended in 25 mL of methanol and cooled to 0°C in an ice bath. $SOCl_2$ (0.7 mL) was added dropwise with stirring and the mixture was stirred at the same

temperature for 24 h and then at 60°C for another 1 h. The solvent was evaporated under vacuum to give the ester of amino acid hydrochloride (yield 81.1%).

The above ester (0.9 g, 1.81 mmol) was dissolved in 60 mL of EtOH containing $NaBH_4$ (0.5 g, 13.2 mmol). After it was stirred at room temperature for 1 h, the mixture was refluxed for 5 h. The solvent was evaporated and the residue was treated with water and extracted with $CHCl_3$ (4×30 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, $CHCl_3$:CH_3OH, 5:1) to give a white solid (yield 51.0%); m.p. 51–52°C; $[\alpha]_D^{25}=-10.0$ (c=1.0, $CHCl_3$). δ_H (299.95 MHz, $CDCl_3$): 0.88 (t, J=6.6 Hz, 3H, CH_3), 1.26 (s, 18H, $CH_2(CH_2)_9$), 1.35 (m, 2H, $OCH_2CH_2(CH_2)_9$), 1.64 (m, 2H, SCH_2CHNH_2), 2.67 (m, 2H, NH_2), 3.24 (s, 1H, OH), 3.54 (t, 2H, J=6.6 Hz, $OCH_2(CH_2)_9CH_3$), 3.60 (m, 2H, CH_2OH), 3.84 (s, 2H, PyCH_2S), 4.60 (s, 2H, PyCH_2 O), 7.23 and 7.32 (2d, J=7.8 Hz, 2H, *Py*H3 and *Py*H5), 7.65 (t, J=7.8 Hz, 1H, *Py*H4). Anal. calcd for $C_{22}H_{40}N_2O_2S$: C, 66.62, H, 10.17, N, 7.06; found: C, 66.34, H, 10.32, N, 6.89. MS (m/z): 397 (M^+, 100).

3.7. Kinetic studies

Solutions of the ligands, metal ions and cosurfactants were prepared in the appropriate buffer (0.05 M). The reaction temperature was maintained at 25±1°C. Kinetics were typically started by injecting an acetonitrile solution (0.01 M) of substrate ester, into a 1 cm cuvette containing 2.5 mL of buffered micellar solution and the desired concentration of metal ion and ligand. Pseudo-first-order rate constants (k_R and k_S) for the hydrolysis of substrate ester were determined by monitoring the release of *p*-nitrophenol at 320 nm (pH 5.0–6.3) or 400 nm (pH 6.3–8.5) for at least five half-lives, and obtained by linear plots of $\ln(A_\infty - A_t)$ versus time. The rate constants for each reaction were determined three times from three separate runs with an uncertainty of less than 5%.

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