Novel Chiral Pyridine *N*-Oxide Ligands and Their Application in the Enantioselective Catalytic Reduction of Ketones and the Addition of Diethylzinc to Aldehydes

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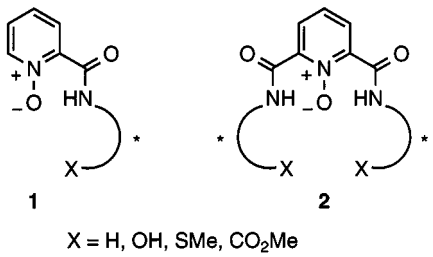
Starting from picolinic acids **3** and **4**, the amino acid-derived 2-aminoacylpyridine *N*-oxides **1a**,**c**–**e** and 2,6-bis(aminoacyl)pyridine *N*-oxides **2b**–**e** can be prepared in two steps by the coupling of picolinic acid *N*-oxides **5** and **6** under Appel conditions with the corresponding L-amino acid ester or (1*R*,2*S*)-norephedrine. Compounds **1** and **2** were used as chiral ligands in two different asymmetric catalyses. In the catalytic addition of diethylzinc to benzaldehyde **11**, low enantioselectivities (2–29% *ee*) were obtained regardless of the amino acid moiety. However, the corresponding 2,6-bis(aminoacyl)pyridines **7** and **8** led to increased *ee* values (55% *ee*). In the catalytic reduction of ketones **9a**–**c** to alcohols **10a**–**c** low enantioselectivities were observed for alanine-, valine-, and leucine-derived *N*-oxides **1a**,**c** and **2b**,**c**. An increase of selectivity was observed for bis-methionine ligand **2d** (32–38% *ee*) relative to that of mono-methionine ligand **1d** (7–16% *ee*). However, mono-norephedrine ligand **1e** (≤ 64% *ee*) and the corresponding bis-norephedrine ligand **2e** (≤ 51% *ee*) displayed the highest selectivities. The influence of the *N*-oxide moiety on the enantioselectivity was demonstrated by the observation that 2,6-bis(aminoacyl)pyridines **7** and **8** gave much lower selectivities than the corresponding pyridine *N*-oxides **2d** and **e**.

Chiral pyridines and especially 2,6-diacylpyridines have been used extensively as ligands in asymmetric catalysis.[1][2] It was also found that metallomicelles containing diacylpyridine moieties show a prominent catalytic ability to mimic hydrolytic metallo enzymes.[3] In contrast, pyridine *N*-oxides have been used mainly in achiral form for rate enhancement of transition metal catalyzed processes.[4] They were employed only in few cases as ligands,[5] e.g. for the thione−thiol rearrangement[6] or as chiral NMR solvating agents.[7] This is surprising for several reasons. First, the amine *N*-oxide acts as a strong electron donor, which provides a suitable electronic environment for a central metal ion.[8] Second, attachment of chiral substituents to the pyridine *N*-oxide is easily achieved with a 2,6-diacylpyridine precursor and a chiral amine. Because of the wide variety of chiral amines derived from natural products, it should therefore be possible to tune the stereochemical environment of the ligand as desired. In particular, 2,6-bis(aminoacyl)pyridine *N*-oxides might even be used for asymmetric transformations as chiral ligands in the absence of any metal ion, because of their marked ability to form hydrogen bonds.[9] Therefore we decided to prepare mono- and disubstituted pyridine *N*-oxides **1**and **2** (Scheme 1). For evaluation of the enantioselectivity of the ligands **1** and **2** two different asymmetric catalyses were chosen, viz. the catalytic reduction of ketones with $BH_3 \bullet SMe_2$[10] and the addition of diethylzinc to aldehydes.[11] In order to enhance the chelating abilities and hopefully the enantioselectivity, chiral amines derived from amino acids bearing additional donor groups X were employed, because previous work by O′Neil et al. has shown that amine *N*-oxides derived from tertiary amines could be successfully used for the enantioselective reduction of ketones.[12] The authors reported increased selectivities for those amine *N*-oxides bearing donor groups such as hydroxy or pyridine. The following manuscript describes the synthesis of the novel ligands **1** and **2** and their application in asymmetric catalysis.



Scheme 1

Two different synthetic approaches towards pyridine *N*-oxides **1** and **2** are conceivable. Starting from picolinic acids **3** and **4**, either the amides may be formed first followed by subsequent oxidation, or alternatively **3** and **4** are oxidized to the corresponding *N*-oxides **5** and **6** and then coupled with chiral amines to give **1** and **2** (Scheme 2). Preliminary

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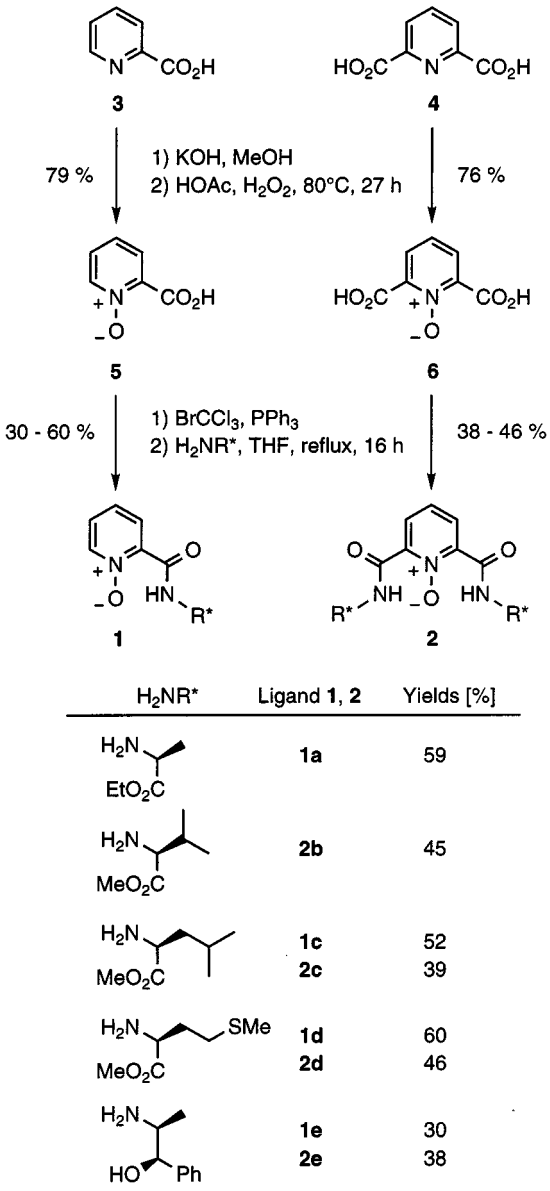
experiments showed that oxidation of aminoacylpyridines proceeded rather sluggishly even under forcing conditions. This was particularly true for the disubstituted derivative, presumably as a result of the steric hindrance of the carbonyl oxygens around the pyridine nitrogen. A similar observation was recently reported by Sharpless when he attempted to prepare methyl picolinate *N*-oxide with bis(trimethylsilyl)peroxide in the presence of catalytic amounts of perrhenic acid.[13]

We therefore turned our attention to the second strategy. Following a procedure by Profft and Steinke,[14] 2-picolinic acid **3** was converted into the corresponding potassium carboxylate, which was further oxidized with hydrogen peroxide in HOAc to give *N*-oxide **5** in 79% yield. Analogous reaction of 2,6-dipicolinic acid **4** gave *N*-oxide **6** in 76% yield.[15] Unfortunately, facile racemization of the amino acids prevented the use of acid chlorides for amide formation. In addition, application of milder coupling agents such as *N,N'*-dicyclohexylcarbodiimide[16] gave only low conversions to **1** and **2**. Next, we tried a method of Hruby[17] employing bromotrichloromethane/triphenylphosphane for activation of the carboxylic acids **5** and **6**, which gave the desired amides **1** and **2** upon addition of a chiral amine in moderate yields. The following amines were used: *L*-alanine ethyl ester, L-valine methyl ester, L-leucine methyl ester, L-methionine methyl ester, and (1*R*,2*S*)-norephedrine.

In case of the bis-methionine pyridine *N*-oxide **2d**, an X-ray crystal structure could be obtained, which is shown in Figure 1.[18] In the solid state compound **2d** displays exact C_2 symmetry, whereby the amino acid moieties are oriented in such a way that the *N*-oxide is stabilized via two intramolecular hydrogen bonds. The absolute configuration was confirmed on the basis of anomalous scattering by sulfur.

For comparison, the corresponding 2,6-bis(aminoacyl)-pyridines **7** and **8** were prepared by converting **4** to the 2,6-diacyl chloride and subsequent treatment with methionine methyl ester or norephedrine,[2b] respectively (Scheme 3).

Chiral pyridine *N*-oxides **1** and **2** and pyridines **7** and **8** were used as ligands in the catalytic reduction of ketones **9a**–**c** with $BH_3 \cdot SMe_2$ (Scheme 5).[19] In a typical experiment 5 mol-% of ligand **1**, **2**, **7**, or **8** were sufficient to achieve complete conversion of **9** within 5 min.[20] After workup the corresponding alcohols **10** were obtained in 97–99% yield. Concerning the reduction of acetophenone **9a** and propiophenone **9b**, the results in Table 1 show that both mono- and disubstituted pyridine *N*-oxides **1a**,**c** and **2b**,**c** derived from alkyl-substituted amino acids such as alanine, leucine or valine gave only low enantioselectivities (7–17% *ee*). This outcome is in good agreement with previous results by Grundon et al.[21]. The authors observed 17–20% *ee* for the reduction of **9a** with amino acid ester borane complexes derived from leucine, phenylalanine, or valine. In contrast, ligands derived from methionine or norephedrine displayed a different behavior. Whereas the monosubstituted ligands **1d**,**e** again resulted in low *ee* values (7–21% *ee*), a significant increase of the enantioselectivity was observed for the corresponding disubstituted ligands **2d**,**e** (31–38% *ee*). When methionine- and norephedrine-derived diacylpyridines **7** and **8** were used for the reduction of acetophenone **9a** instead of the corresponding *N*-oxides **2d**,**e** the enantioselectivity dropped to 4 and 14% *ee*, respectively. This clearly demonstrates the influence of the *N*-oxide moiety. Using 2-chloroacetophenone **9c** gave slightly increased enantioselectivities over those of the other ketones **9a**,**b**. Again bis-methionine ligand **2d** produced a much higher enantiomeric excess (37% *ee*) than monomethionine ligand **1d** (16% *ee*). The only exceptions to the general trend were the norephedrine-derived ligands **1e**, **2e**. Contrary to the previously mentioned cases, mono-norephedrine ligand **1e** gave alcohol **10c** in 64% *ee*, compared to 51% *ee* for the disubstituted ligand **2e**. As shown in Scheme 4, the major enantiomers of the product alcohols **10a**–**c** have the same absolute configuration. It should be noted however that, because of the priority rules of the CIP system, alcohols **10a**,**b** are (*R*) configured, whereas alcohol



H_2NR^*	Ligand **1**, **2**	Yields [%]
H_2N, EtO_2C	**1a**	59
H_2N, MeO_2C	**2b**	45
H_2N, MeO_2C	**1c**	52
	2c	39
H_2N, SMe, MeO_2C	**1d**	60
	2d	46
H_2N, HO, Ph	**1e**	30
	2e	38

Scheme 2

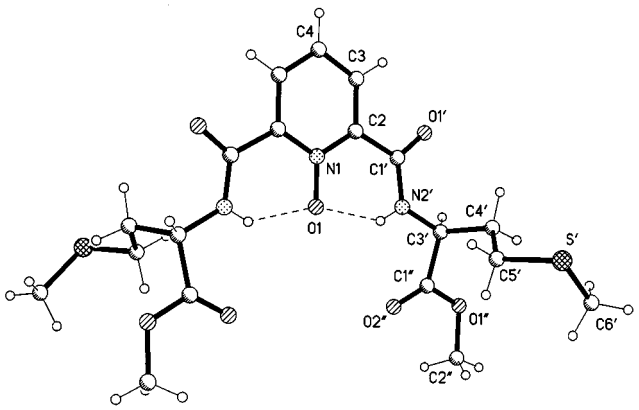
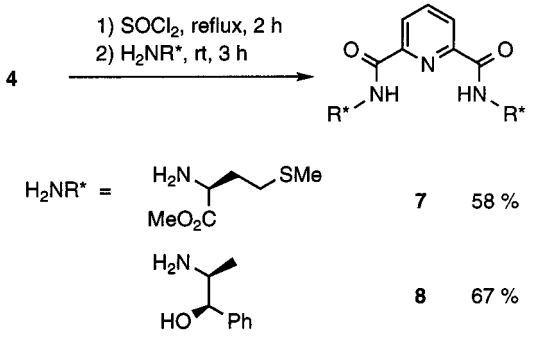
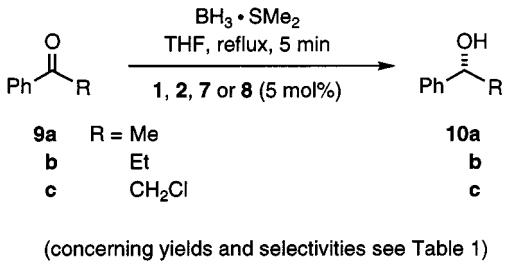


Figure 1. X-ray crystal structure of bis-methionine ligand **2d**. Selected bond lengths [pm] and angles [°]: O(1)−N(1) 131.3(3), N(1)−C(2) 137.0(2), C(1′)−C(2) 151.6(3), N(2′)−C(1′) 133.6(3), O(1′)−C(1′) 122.8(2), N(2′)−C(3′) 144.7(2), N(2′)−H 75(2), H−O(1) 199(2), N(2′)−O(1) 259.9(2), O(1)−N(1)−C(2) 99.83(10), N(1)−C(2)−C(1′) 123.19(18), N(2′)−C(1′)−C(2) 118.66(18), C(1′)−N(2′)−C(3′) 120.29(18), N(2′)−H−O(1) 139(2).



Scheme 3

10c is (*S*) configured. O′Neil reported 68 and 96% *ee* for alcohols (*R*)-**10a** and (*S*)-**10c**, respectively, when using chiral prolinol *N*-oxides.[12] In his ligands the presence of a tertiary alcohol and a pyridyl moiety seemed to be essential for achieving high enantioselectivities.



Scheme 4

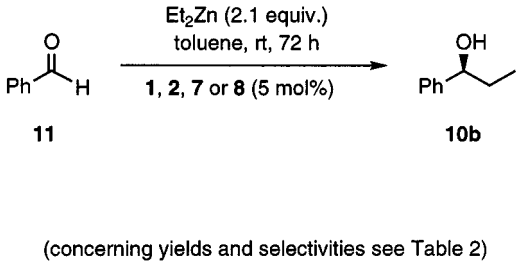
Next, pyridine *N*-oxides **1** and **2** were tested in the asymmetric addition of diethylzinc to aldehydes (Scheme 5). According to a procedure by Chelucci[22] *N*-oxides **1** and **2** were treated with diethylzinc at 0° C, followed by addition of benzaldehyde **11**. After 72 h at room temperature the mixture was worked up to give 1-phenylpropanol **10b** in moderate to high yields depending on the ligand (Table 2). Higher yields were generally observed with disubstituted ligands **2b**−**e**. Both mono- and disubstituted ligands **1a**,**c** and

Table 1. Yields and enantiomeric excesses of alcohols **10** via reduction of ketones **9** with $BH_3 \cdot SMe_2$ in the presence of chiral ligands **1**, **2**, **7**, or **8**[a,b]

Ligand	**10a** (R = Me) Yield [%]	% *ee*	Alcohols**10b** (R = Et) Yield [%]	% *ee*	**10c** (R = CH_2Cl) Yield [%]	% *ee*
1a	99	7	98	8	99	20
1c	99	11	99	17	97	21
1d	99	7	99	12	99	16
1e	99	20	98	21	99	64
2b	97	9	98	9	99	21
2c	99	10	99	16	99	33
2d	99	32	99	38	99	37
2e	99	31	99	33	98	51
10	99	4	---	---	---	---
11	99	14	---	---	---	---

[a] Reaction conditions: **9** (1 equiv.), $BH_3 \cdot SMe_2$ (1 equiv.), ligand **1**, **2**, **7**, or **8** (0.05 equiv.), THF, reflux, 5 min. Yields refer to isolated product. − [b] Enantiomeric excesses were determined by capillary GC of the crude products using a chiral stationary phase. Depending on the substituent R, the major enantiomer of **10** has the following absolute configuration: (*R*)-**10a** (R = Me), (*R*)-**10b** (R = Et), (*S*)-**10c** (R = CH_2Cl). For details see Experimental Section.

2b,**c** derived from alanine, valine, or leucine gave only low enantioselectivities (7−16% *ee*). An increase of selectivity and yield was discovered for bis-methionine ligand **2d** (92%, 29% *ee*) relative to that of mono-methionine ligand **1d** (37%, 2% *ee*). Surprisingly low selectivities were obtained for the norephedrine ligands (**1e**: 9% *ee*, **2e**: 8% *ee*). However, much higher enantioselectivities of **10b** could be accomplished by using 2,6-bis(aminoacyl)pyridines **7** and **8** (55 and 56% *ee*, respectively). Except for the reaction catalyzed by *N*-oxide **2e**, the absolute configuration of the major enantiomer of **10b** was assigned (*S*).



Scheme 5

From these results several conclusions can be drawn. It seems reasonable to assume that concerning the enantioselective reduction of ketones **9** proceeds by in situ complexation of boron by the oxygen atom of the *N*-oxide.[23] This stabilization is enhanced by the presence of additional donor groups such as thiomethyl (**1d**, **2d**) or hydroxy (**1e**, **2e**).[24] Thus a boronate species with a stereochemically defined environment is formed, which coordinates the prochiral ketone, so that attack of the hydride occurs preferentially from the *Si*-face (for **12a**,**b**) or *Re*-face (for **12c**). In particular, bis-methionine *N*-oxide **2d** and norephedrine *N*-oxides **1e** and **2e** are superior to the corresponding 2,6-bis(aminoacyl)pyridines **7** and **8** and seem to be good candidates for designing further novel ligands for the catalytic

Table 2. Yields and enantiomeric excesses of 1-phenylpropanol **10b** (R = Et) via addition of diethylzinc to benzaldehyde **11** in the presence of chiral ligands **1**, **2**, **7**, or **8**[a,b]

Ligand	**10b** Yield [%]	% *ee*	Configuration
1a	52	16	(*S*)
1c	37	12	(*S*)
1d	37	2	(*S*)
1e	71	9	(*S*)
2b	71	11	(*S*)
2c	88	7	(*S*)
2d	92	29	(*S*)
2e	88	8	(*R*)
10	66	55	(*S*)
11	56	56	(*S*)

[a] Reaction conditions: 1) Et_2Zn (2.2 equiv.), ligand **1**, **2**, **7**, or **8** (0.05 equiv.), THF, 0°C to room temp., 20 min; 2) **11** (1.0 equiv.), rt, 72 h . Yields refer to isolated product. − [b] Enantiomeric excesses were determined by capillary GC of the crude products using a chiral stationary phase. For details see Experimental Section.

asymmetric reduction of ketones. Work towards this end is currently in progress. In contrast, 2,6-bis(aminoacyl)pyridine ligands **7** and **8** are much better suited to the diethylzinc addition than the corresponding pyridine *N*-oxides **1** and **2**. This reaction is probably highly dependent on the presence of a β-amino alcohol function in the catalytic species in order to achieve high enantioselectivities

Experimental Section

General: All reactions were carried out under nitrogen with standard Schlenk techniques. Solvents were dried and deoxygenated by standard procedures. − Analytical TLC was performed on precoated Merck Si 254 F plates (0.25 mm thickness) and the products were visualized by UV detection. Flash chromatography[25] was carried out with Merck silica gel 60 (230−400 mesh). − NMR spectra: Bruker AC 200 P (^{1}H: 200 MHz, ^{13}C: 50 MHz), Bruker AM 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz). Multiplets in ^{13}C-NMR spectra were assigned with the aid of DEPT experiments. − Optical rotations (1-dm cells, 1-mL capacity, room temp.): Perkin−Elmer Model 241 polarimeter. − Melting points: Rheometric Scientific DSC SP, heating and cooling rate: 10 K min^{-1}. − IR: Nicolet 5DXC FT-IR spectrometer. − MS: Finnigan Model MAT 8430 (EI). − For determination of enantiomeric excesses of **10a**,**b** a Carlo Erba Instruments GC (column 1) coupled with a Carlo Erba Instruments GC (column 2) was used. Column 1: Macherey−Nagel DD-wax capillary column (ID 0.25 mm, length 30 m), column 2: Macherey−Nagel Hydrodex β-3P capillary column (ID 0.25 mm, length 25 m). For determination of enantiomeric excesses of **10c** a GC with heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrine as chiral stationary phase (50% in polysiloxane OV 1701, w/w, column length 10 m)[26] was used. − (1′*R*,2′*S*)-2,6-Bis[2-(1-hydroxy-1-phenyl)propylaminocarbonyl]-pyridine (**8**) was prepared according to ref.[2b] The absolute configuration was determined by comparison with authentic samples.

Picolinic Acid *N*-Oxide (5): To an ice-cooled solution of picolinic acid **3** (25.0 g, 0.20 mol) in MeOH (140 mL) was added KOH (11.4 g, 0.20 mol). The solvent was removed in vacuo and the remaining solid was dissolved in HOAc (120 mL). Then H_2O_2 (24 mL, 30% aqueous solution) was added and the mixture was heated at 80°C for 3 h. Additional H_2O_2 (20 mL, 30% aqueous solution) was added and the mixture was stirred at 90°C for 24 h. After removal of the solvent in vacuo, the residue was dissolved in H_2O (10 mL) and the pH adjusted to 1 by addition of conc. HCl. The precipitate was filtered and washed with ice-cold H_2O (100 mL) to give 21.9 g (0.16 mol, 79%) of a colorless solid: mp. 162°C. − ^{1}H NMR (200 MHz, NaOD): δ = 7.45 (d, *J* = 6.1 Hz, 1 H, 6-H), 6.93 (dd, *J* = 7.0/8.2 Hz, 1 H, 5-H), 6.69−6.65 (m, 2 H, 4-H, 3-H). − ^{13}C NMR (50 MHz, NaOD): δ = 168.1 (CO), 147.6 (C-2), 139.6 (C-6), 132.4, 126.5, 124.4 (C-3, C-4, C-5). − MS (EI) *m*/*z* (%): 139 (42) [M$^+$], 95 (67), 78 (100), 63 (8), 51 (23). $C_6H_5NO_3$ (139.11): calcd. C 51.80, H 3.62, N 10.07; found C 51.68, H 3.76, N 10.08.

Dipicolinic Acid *N*-Oxide (6): Following the procedure described for **5** but using dipicolinic acid **4** (16.7 g, 0.10 mol) 13.9 g (76.0 mmol, 76%) of a colorless solid were obtained: mp. 171°C. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.67−14.59 (br, 2 H, COOH), 8.74 (d, *J* = 8.0 Hz, 2 H, 3-H), 7.99 (t, *J* = 8.0 Hz, 1 H, 4-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3 (COOH), 138.2 (C-2), 133.7 (C-3), 132.5 (C-4). − MS (EI) *m*/*z* (%): 183 (22) [M$^+$], 139 (100), 122 (78), 106 (18), 94 (30), 78 (41), 63 (8), 51 (34). − $C_7H_5NO_5$ (183.02): calcd. C 45.91, H 2.75, N 7.65; found C 46.02, H 2.94, N 7.53.

General Procedure for the Preparation of Pyridine *N*-Oxides (1, 2): To a solution of triphenylphosphane (1.05 g, 4.00 mmol), picolinic acid *N*-oxides **5** or **6** (4.00 mmol), and bromotrichloromethane (0.79 g, 4.00 mmol) in THF (20 mL) was added amine (8.00 mmol in case of **5** or 16.0 mmol in case of **6**), and the resulting mixture was refluxed for 16 h. After cooling to room temperature, the precipitate was removed by filtration. The solvent was removed in vacuo and the crude product was purified by flash chromatography.

(2′*S*)-2-[(1-Ethoxycarbonyl)ethylaminocarbonyl]pyridine *N*-Oxide (1a): Flash chromatography on SiO_2 (hexanes/$CHCl_3$/2-propanol, 8:3:1) gave 560 mg (2.35 mmol, 59%) of a yellow oil; $[\alpha]_D^{22}$ = 0.3 (*c* = 1.00, $CHCl_3$). − IR (KBr): ṽ = 1740 cm^{-1}, 1669, 1530. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.71 (d, *J* = 5.4 Hz, 1 H, NH), 8.40 (dd, *J* = 2.5/7.9 Hz, 1 H, 3-H), 8.27 (dd, *J* = 1.0/6.4 Hz, 1 H, 6-H), 7.46 (ddd, *J* = 1.0/6.4/7.4 Hz, 1 H, 4-H), 7.42 (ddd, *J* = 2.5/7.9/7.4 Hz, 1 H, 5-H), 4.77 (dd, *J* = 5.4/7.2 Hz, 1 H, 2′-H), 4.25 (q, *J* = 7.3 Hz, 2 H, OCH_2CH_3), 1.55 (d, *J* = 7.2 Hz, 3 H, 3′-H), 1.30 (t, *J* = 7.3 Hz, 3 H, OCH_2CH_3). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0 (COO), 159.2 (CONH), 140.5 (C-6), 140.3 (C-2), 128.8 (C-3), 127.4 (C-5), 126.9 (C-4), 61.4 (OCH_2CH_3), 48.8 (C-2′), 18.0 (OCH_2CH_3), 14.0 (C-3′). − MS (EI) *m*/*z* (%): 239 (100) [M$^+$ + 1], 223 (11), 165 (32), 160 (5), 141 (6), 122 (6). − $C_{11}H_{14}N_2O_4$ (238.24): calcd. C 55.46, H 5.92, N 11.76; found C 54.90, H 6.03, N 11.52.

(2′*S*)-2-[(1-Methoxycarbonyl-3-methyl)butylaminocarbonyl]pyridine *N*-Oxide (1c): Flash chromatography on SiO_2 (hexanes/$CHCl_3$/2-propanol, 8:3:1) gave 550 mg (2.07 mmol, 52%) of a yellow oil; $[\alpha]_D^{22}$ = 4.3 (*c* = 1.00, $CHCl_3$). − IR (KBr): ṽ = 1747 cm^{-1}, 1673, 1538. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.65 (d, *J* = 7.7 Hz, 1 H, NH), 8.41 (dd, *J* = 2.4/7.7 Hz, 1 H, 3-H), 8.27 (dd, *J* = 1.5/6.4 Hz, 1 H, 6-H), 7.48 (ddd, *J* = 1.5/7.7/7.4 Hz, 1 H, 4-H), 7.42 (ddd, *J* = 2.4/6.4/7.4 Hz, 1 H, 5-H), 4.79−4.76 (m, 1 H, 2′-H), 3.75 (s, 3 H, OCH_3), 1.82−1.76 (m, 3 H, 3′-H, 4′-H), 0.99 (d, *J* = 2.9 Hz, 3 H), 0.97 (d, *J* = 3.0 Hz, 3 H, 5′-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (COO), 159.5 (CONH), 140.5 (C-6), 140.3 (C-2), 128.9 (C-3), 127.4 (C-5), 127.0 (C-4), 52.3 (OCH_3), 51.5 (C-1′), 40.9 (C-2′), 25.0 (C-3′), 22.8, 21.7 (C-4′, C-5′). − MS (CI) *m*/*z* (%): 267 (100) [M$^+$ + 1], 259 (24), 234 (38), 207 (8), 146

(12), 86 (4). − $C_{11}H_{14}N_2O_4$ (266.30): calcd. C 58.64, H 6.81, N 10.52; found C 58.62, H 7.18, N 10.39.

(2′*S*)-2-[(1-Methoxycarbonyl-3-thiomethyl)propylaminocarbonyl]pyridine *N*-Oxide (1d): Flash chromatography on SiO_2 ($CHCl_3$/hexanes/2-propanol, 3:8:1) gave 550 mg (2.07 mmol, 52%) of a yellow solid; mp. 78°C; $[\alpha]_D^{22}$ = 8.6 (*c* = 1.00, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 1741 cm^{-1}, 1663, 1527. − ^1H NMR (400 MHz, $CDCl_3$): δ = 11.81 (d, *J* = 6.9 Hz, 1 H, NH), 8.42 (dd, *J* = 2.3/6.9 Hz, 1 H, 3-H), 8.29 (dd, *J* = 1.3/6.3 Hz, 1 H, 6-H), 7.49 (ddd, *J* = 1.3/6.9/7.7 Hz, 1 H, 4-H), 7.42 (ddd, *J* = 2.3/6.3/7.7 Hz, 1 H, 5-H), 4.92 (ddd, *J* = 6.9/7.7/7.8 Hz, 1 H, 2′-H), 3.77 (s, 3 H, OCH_3), 2.63 (t, *J* = 7.4 Hz, 2 H, 4′-H), 2.30−2.12 (m, 2 H, 3′-H), 2.11 (s, 3 H, SCH_3). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5 (COO), 159.6 (CONH), 140.5 (C-6), 140.1 (C-2), 128.9 (C-3), 127.5 (C-5), 127.0 (C-4), 52.5 (OCH_3), 52.0 (C-2′), 31.5, 30.1 (C-3′, C-4′), 15.4 (SCH_3). − MS (CI) *m/z* (%):285 (100) [M^+ + 1], 269 (4). − $C_{12}H_{16}N_2O_4S$ (284.33): calcd. C 50.69, H 5.67, N 9.85, S 11.28; found C 50.20, H 5.67, N 9.62, S 11.42.

(1′*R*,2′*S*)-2-[2-(1-Hydroxy-1-phenyl)propylaminocarbonyl]pyridine *N*-Oxide (1e): Flash chromatography on SiO_2 ($CHCl_3$/hexanes/MeOH, 9:3:1) gave 332 mg (1.22 mmol, 30%) of a yellow oil; $[\alpha]_D^{22}$= −10.1 (*c* = 1.00, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 1664 cm^{-1}, 1655, 1534. − ^1H NMR (400 MHz, $CDCl_3$): δ = 11.45 (d, *J* = 7.4 Hz, 1 H, NH), 8.44 (dd, *J* = 2.2/8.0 Hz, 1 H, 3-H), 8.22 (dd, *J* = 0.9/6.4 Hz, 1 H, 6-H), 7.69 (ddd, *J* = 0.9/8.0/8.4 Hz, 1 H, 4-H), 7.57 (ddd, *J* = 2.2/6.4/8.4 Hz, 1 H, 5-H), 7.48−7.25 (m, 5 H, 2′′-H, 3′′-H, 4′′-H, 5′′-H, 6′′-H), 5.01 (d, *J* = 3.3 Hz, 1 H, 1′-H), 4.51 (m, 1 H, 2′-H), 4.13−4.09 (br, 1 H, OH), 1.17 (d, *J* = 6.9 Hz, 3 H, 3′-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4 (CO), 141.2 (C-2), 140.5 (C-6), 132.1, 131.9 (C-1′, C-4′), 128.8 (C-3), 128.5, 128.3 (C-2′, C-3′, C-5′, C-6′), 128.1 (C-5), 127.2 (C-4), 75.7 (C-1′), 51.7 (C-2′), 14.0 (C-3′). − MS (CI) *m/z* (%): 273 (100) [M^+ + 1], 257 (58), 239 (4), 195 (2), 149 (6). − $C_{15}H_{16}N_2O_3$ (272.30): calcd. C 66.16, H 5.92, N 10.29; found C 66.20, H 5.91, N 10.49.

(2′*S*)-2,6-Bis[(1-methoxycarbonyl-2-methyl)propylaminocarbonyl]pyridine *N*-Oxide (2b): Flash chromatography on SiO_2 (hexanes/$CHCl_3$/2-propanol, 10:1:1) gave 368 mg (0.90 mmol, 45%) of a colorless oil; $[\alpha]_D^{22}$ = 53.9 (*c* = 1.00, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 1744 cm^{-1}, 1680, 1522. − ^1H NMR (400 MHz, $CDCl_3$): δ = 11.15 (d, *J* = 7.8 Hz, 2 H, NH), 8.57 (d, *J* = 7.9 Hz, 2 H, 3-H), 7.63 (t, *J* = 7.9 Hz, 1 H, 4-H), 4.71 (dd, *J* = 7.8/5.0 Hz, 2 H, 2′-H), 3.79 (s, 6 H, OCH_3), 2.39 (dd, *J* = 5.0/2.1 Hz, 2 H, 3′-H), 1.08 (d, *J* = 2.1 Hz, 6 H), 1.06 (d, *J* = 2.1 Hz, 6 H, 4′-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6 (COO), 159.3 (CONH), 141.1 (C-2), 131.4 (C-3), 127.7 (C-4), 58.4 (OCH_3), 52.1 (C-2′), 30.9 (C-3′), 19.2, 18.0 (C-4′). − MS (CI) *m/z* (%): 409 (2) [M^+], 392 (92), 391 (100) [$M^+ - H_2O$]. − $C_{19}H_{28}N_3O_7$ [M^+ + H]: calcd. 410.1927, found 410.1912 (MS).

(2′*S*)-2,6-Bis[(1-methoxycarbonyl-3-methyl)butylaminocarbonyl]pyridine *N*-Oxide (2c): Flash chromatography on SiO_2 (hexanes/$CHCl_3$/2-propanol, 8:3:1) gave 340 mg (0.78 mmol, 39%) of a yellow oil; $[\alpha]_D^{22}$ = 5.2 (*c* = 1.00, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 1747 cm^{-1}, 1677, 1522. − ^1H NMR (400 MHz, $CDCl_3$): δ = 10.97 (d, *J* = 7.9 Hz, 2 H, NH), 8.57 (d, *J* = 8.0 Hz, 2 H, 3-H), 7.60 (t, *J* = 8.0 Hz, 1 H, 4-H), 4.84−4.79 (m, 2 H, 2′-H), 3.77 (s, 6 H, OCH_3), 1.80−1.76 (m, 6 H, 3′-H, 4′-H), 1.01−0.99 (m, 12 H, 5′-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7 (COO), 159.2 (CONH), 141.1 (C-2), 131.5 (C-3), 127.6 (C-4), 52.4 (OCH_3), 51.6 (C-2′), 41.1 (C-3′), 25.0 (C-4′), 22.8, 21.8 (5′-H). − MS (CI) *m/z* (%): 455 (21) [M^+ + NH_4], 438 (100) [M^+ + 1], 420 (18), 378 (34), 318 (4), 279 (16). − $C_{21}H_{31}N_3O_7$ (437.49): calcd. C 57.65, H 7.14, N 9.60; found C 57.94, H 7.19, N 8.99.

(2′*S*)-2,6-Bis[(1-methoxycarbonyl-3-thiomethyl)propylaminocarbonyl]pyridine *N*-Oxide (2d): Flash chromatography on SiO_2 (hexanes/acetone, 3:2) gave 431 mg (0.91 mmol, 46%) of a yellow solid; mp. 49°C; $[\alpha]_D^{22}$ = −5.0 (*c* = 1.00, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 1744 cm^{-1}, 1676, 1524. − ^1H NMR (400 MHz, $CDCl_3$): δ = 11.11 (d, *J* = 7.5 Hz, 2 H, NH), 8.58 (d, *J* = 8.0 Hz, 2 H, 3-H), 7.62 (t, *J* = 8.0 Hz, 1 H, 4-H), 4.98 (ddd, *J* = 7.5/7.7/7.8 Hz, 2 H, 2′-H), 3.81 (s, 6 H, OCH_3), 2.65 (t, *J* = 7.5 Hz, 4 H, 4′-H), 2.36−2.28 (m, 2 H, 3′-H_a), 2.23−2.09 (m, 2 H, 3′-H_b), 2.14 (s, 6 H, SCH_3). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7 (COO), 159.2 (CONH), 141.1 (C-2), 131.6 (C-3), 127.8 (C-4), 52.7 (OCH_3), 52.2 (C-2′), 31.5, 30.2 (C-3′, C-4′), 15.5 (SCH_3). − MS (CI) *m/z* (%): 491 (38) [M^+ + NH_4], 474 (100) [M^+ + 1], 458 (40). − $C_{19}H_{27}N_3O_7S_2$ (473.56): calcd. C 48.19, H 5.75, N 8.87, S 13.54; found C 48.14, H 5.75, N 8.70, S 13.63. − X-Ray structure analysis of **2d**: $C_{19}H_{27}N_3O_7S_2$, M_r = 473.56, crystal size 0.90 × 0.42 × 0.16 mm, monoclinic, space group *C*2, *a* = 2388.9(5) pm, *b* = 925.7(2) pm, *c* = 520.27(10) pm, β = 98.720(15)°, *V* = 1.1372(4) nm^3, $\rho_{calcd.}$ = 1.383 Mg m^{-3}, *T* = 173(2) K, *Z* = 2, λ = 71.073 pm. Siemens P4 diffractometer, 2883 reflections collected to 2θ 55°, 2603 independent reflections, 148 refined parameters, *R*1 = 0.0338, *wR*2 = 0.0771. The absolute configuration was confirmed crystallographically: χ = 0.15(8). Programs used: SHELXL-93. See ref.[18]

(1′*R*,2′*S*)-2,6-Bis[2-(1-hydroxy-1-phenyl)propylaminocarbonyl]pyridine *N*-Oxide (2e): Flash chromatography on SiO_2 ($CHCl_3$/hexanes/MeOH, 9:6:1) gave 341 mg (0.76 mmol, 38%) of a colorless solid; mp. 53°C; $[\alpha]_D^{22}$ = 11.5 (*c* = 1.00, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 1668 cm^{-1}, 1514. − ^1H NMR (400 MHz, $CDCl_3$): δ = 10.81 (d, *J* = 7.9 Hz, 2 H, NH), 8.51 (d, *J* = 7.9 Hz, 2 H, 3-H), 7.56 (t, *J* = 7.9 Hz, 1 H, 4-H), 7.42 (d, *J* = 6.9 Hz, 4 H, 2′′-H), 7.36 (dd, *J* = 6.9/5.9 Hz, 4 H, 3′′-H), 7.29 (t, *J* = 5.9 Hz, 2 H, 4′′-H), 5.04 (s, 2 H, OH), 4.51 (ddd, *J* = 2.9/7.9/6.9 Hz, 2 H, 2′-H), 3.25 (d, *J* = 2.9 Hz, 2 H, 1′-H), 1.17 (d, *J* = 6.9 Hz, 6 H, 3′-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (CONH), 141.3 (C-2), 140.7 (C-1′′), 131.1 (C-3), 128.2, 127.7, 127.6 (C-4), 126.2 (C-2′′, C-3′′, C-4′′, C-5′′, C-6′′), 75.7 (C-1′), 51.9 (C-2′), 14.1 (C-3′). − MS (CI) *m/z* (%): 450 (100) [M^+ + 1], 432 (28), 425 (54), 343 (26), 279 (60), 195 (50). − $C_{25}H_{27}N_3O_5$ (449.51): calcd. C 66.80, H 6.05, N 9.35; found C 66.39, H 6.33, N 9.58.

(2′*S*)-2,6-Bis[(1-methoxycarbonyl-3-thiomethyl)propylaminocarbonyl]pyridine (8): A mixture of dipicolinic acid **4** (140 mg, 0.75 mmol) and thionyl chloride (8.15 g, 5 mL, 70.0 mmol) was refluxed for 2 h. After removal of the remaining thionyl chloride in vacuo, the residue was dissolved in CH_2Cl_2 (5 mL) and added dropwise to an ice-cooled solution of L-methionine methyl ester (262 mg, 1.60 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 h at room temperature and then hydrolyzed with 1 N NaOH (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2× 20 mL). After drying the combined organic layers with $MgSO_4$ and evaporating the solvent in vacuo, the crude product was purified by flash chromatography on SiO_2 (ether) to give 230 mg (0.50 mmol, 67%) of a yellow oil; $[\alpha]_D^{22}$ = −8.0 (*c* = 1.00, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1744 cm^{-1},1679, 1526. − ^1H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 7.9 Hz, 2 H, NH), 8.36 (d, *J* = 7.9 Hz, 2 H, 3-H), 8.06 (t, *J* = 7.9 Hz, 1 H, 4-H), 4.97 (ddd, *J* = 7.9/7.4/5.4 Hz, 1 H, 2′-H), 3.80 (s, 6 H, OCH_3), 2.67 (t, *J* = 7.4 Hz, 2 H, 4′-H), 2.34−2.29 (m, 1 H, 3′-H_a), 2.25−2.18 (m, 1 H, 3′-H_b), 2.14 (s, 6 H, SCH_3). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0 (COO), 163.2 (CONH), 148.2 (C-2), 139.0 (C-4), 125.3 (C-3), 52.6 (OCH_3), 51.9 (C-2′), 31.1, 30.2

(C-3′, C-4′), 15.4 (SCH_3). − MS (EI) *m/z* (%): 457 (26) [M^+], 398 (20), 383 (100), 351 (24), 328 (21), 268 (45), 252 (12), 220 (13), 194 (25), 162 (26), 134 (10), 124 (11), 106 (17), 78 (13), 61 (31). − $C_{19}H_{27}N_3O_6S_2$: calcd. 457.1341, found 457.1335 (MS).

General Procedure for the Reduction of Ketones (9a−c) to Alcohols (10a−c): To a solution of pyridine *N*-oxide **1**, **2** or pyridine **7**, **8** (0.05 mmol) in THF (5 mL) was added $BH_3 \bullet SMe_2$ (0.5 mL, 0.10 mmol of a 2 M solution in THF) and the resulting mixture was refluxed for 5 min. Then ketone **9** (1.00 mmol) in THF (1.0 mL) was added dropwise and the mixture was refluxed for 5 min.[20] After cooling to room temperature the mixture was hydrolyzed by addition of H_2O (3 mL) and the aqueous layer was extracted with CH_2Cl_2 (3× 30 mL). The combined organic layers were dried with $MgSO_4$, evaporated in vacuo and the crude products **10a**,**b** and **10c** were analyzed by capillary GC-GC and capillary GC respectively, using chiral stationary phases.

1-Phenylethanol (10a): Temperature program: 170°C isothermal for 3 min, then with 5°C min^{-1} up to 200°C (column 1), 100°C isothermal for 20 min, then with 1°C min^{-1} up to 160°C (column 2). *(R)-Isomer:* R_t = 15.25 min. *(S)-Isomer:* R_t = 15.88 min.

1-Phenylpropanol (10b): Temperature program: 170°C isothermal for 3 min, then with 5°C min^{-1} up to 200°C (column 1), 100°C isothermal for 5 min, then with 1°C min^{-1} up to 160°C (column 2). *(R)-Isomer:* R_t = 24.55 min. *(S)-Isomer:* R_t = 25.19 min.

2-Chloro-1-phenylethanol (10c): Temperature: 100°C isothermal. *(S)-Isomer:* R_t = 9.18 min. *(R)-Isomer:* R_t = 11.25 min.

General Procedure for the Addition of Diethylzinc to Benzaldehyde (11): Diethylzinc (2.2 mL, 2.20 mmol of a 1 M solution in hexane) was added dropwise over 5 min at 0°C to a solution of pyridine *N*-oxide **1** or **2** (0.05 mmol) and the resulting mixture was stirred for 20 min at room temperature and then cooled to 0°C. Then benzaldehyde **11** (106 mg, 1.00 mmol) was added dropwise and the mixture was stirred for 72 h at room temperature. After hydrolysis with H_2SO_4 (5 mL, 10% aqueous solution), the mixture was extracted with Et_2O (3× 30 mL), washed with sat. $NaHCO_3$ (30 mL), and dried with $MgSO_4$. After removal of the solvent in vacuo the crude product **10b** was analyzed by capillary GC using chiral stationary phases as described above.

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