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Enantioselective catalysis. Part 119:[1] New chiral 2-(2-pyridinyl)oxazoline ligands containing an additional optically active substituent in the pyridine system

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Abstract

The synthesis of novel chiral nitrogen ligands and their precursors is described. They consist of an optically active oxazoline bound to pyridine in the 2-position. In addition, another optically active substituent is attached to the pyridine ring. The effect of the two independent stereogenic units in one ligand was studied in the Rh(I)-catalysed enantioselective hydrosilylation of acetophenone with diphenylsilane.

1. Introduction

Nitrogen-containing chiral ligands proved to be efficient in the Rh(I)-catalysed enantioselective hydrosilylation.[2,3] These ligands usually carry one optically active substituent (which of course can have more than one stereogenic centre).[2–4] In addition, there are C_2-symmetrical ligands (e.g. 2,6-bis(2-oxazolinyl)pyridines) which possess two identical chiral substituents.[5–9] In the present approach we tried to combine two different optically active substituents on both sides of the pyridine system (Scheme 1). As chiral oxazolines tend to induce high enantiomeric excess[2–9] and are in addition easily accessible by condensation of enantiopure amino alcohols with suitable precursors,[10] the oxazoline system was maintained as one of the chiral substituents, whereas the other chiral substituent was varied (Scheme 1). By this substitution pattern diastereomeric ligands are produced allowing a kind of internal double stereoselection. The new ligands were tested in the Rh(I)-catalysed enantioselective hydrosilylation and the results were compared with those obtained using ligands containing single chiral substituents.

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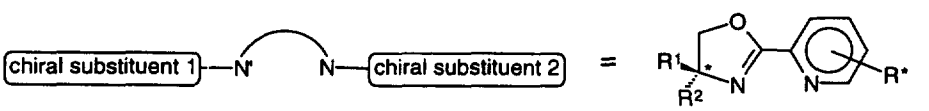
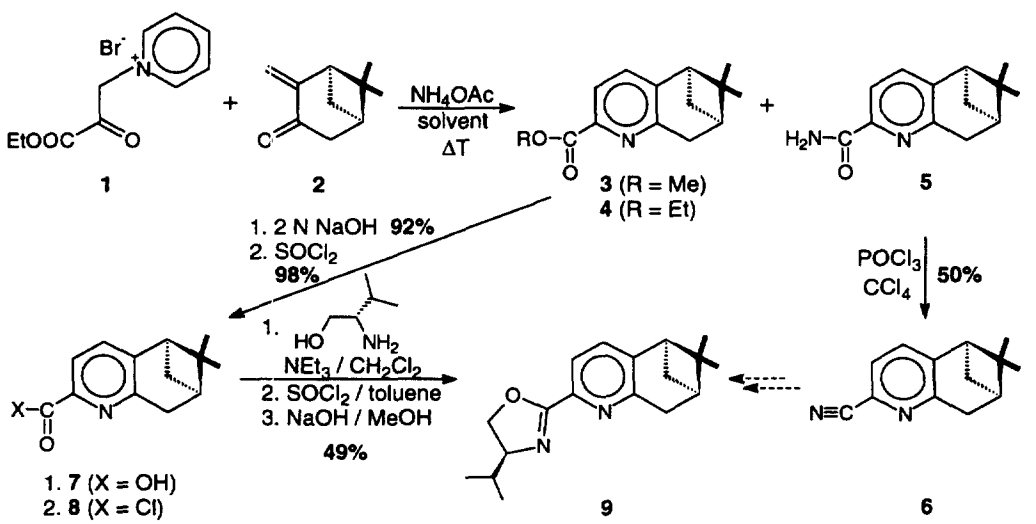


Scheme 1.

2. Synthesis and characterisation of the ligands

Chiral pyridines can be prepared by attaching an optically active frame to the pyridine system via Kröhnke condensation[11] between optically active pinane derivatives and suitable Michael synthons.[12] Our system should have a substituent in the 2-position which can be the transformed to an oxazoline ring. Thus, the previously unknown compounds **3–5** were prepared by Kröhnke reaction of (+)-pinocarvone **2** with the pyruvate **1** (Scheme 2). Although different conditions were used following literature procedures,[13–15] only moderate yields of the condensation products **3–5** were obtained (max. 23%). The undesired carboxamide **5** was always present in yields of 7–10%. Hence, the separation of the products was difficult. The reaction in refluxing methanol following the method of Hünig et al.[13] gave the methylate **3** (15%) besides the ethylate **4** (<1%) and the amide **5** (7%). Compound **5** was converted into the nitrile **6**, another possible oxazoline-precursor (Scheme 2).[10] The esters **3** and **4** were saponified yielding the acid **7** which subsequently was converted into the acid chloride **8**. (*S*)-Valinol and **8** gave the oxazoline **9** via a three-step reaction in 49% yield (Scheme 2).



Scheme 2.

Recrystallised **9** was diastereomerically pure by ^{1}H NMR spectroscopy.[16] Compound **9** and all its precursors were extensively characterised by NMR spectroscopy. 2-D NMR experiments allowed complete assignment of all hydrogen and carbon signals. The protons of the pinane system exhibited an interesting coupling pattern due to the long range coupling between H-5 and H-7 (Fig. 1). Since $^4J_{5,7}$ has exactly the same value as $^3J_{5,6exo}$ and $^3J_{6exo,7}$, pseudo-triplets appear. H-6_{endo} only couples with the geminal H-6_{exo}, because it is orthogonally orientated to H-5 as well as H-7 and hence does not give rise to any coupling.

Hentges and Sharpless had used 2-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]pyridine [(−)-2-L-menthylpyridine][17] as a chiral base for asymmetric oxidations, but its synthesis has never been published.[18] We chose (−)-2-L-menthylpyridine, because by α-cyanation of the pyridine ring a

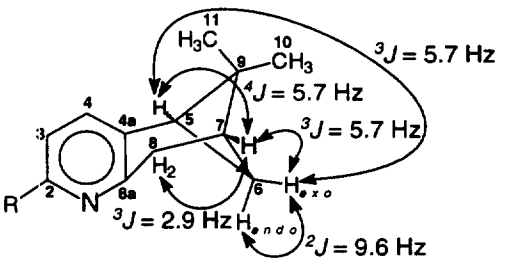
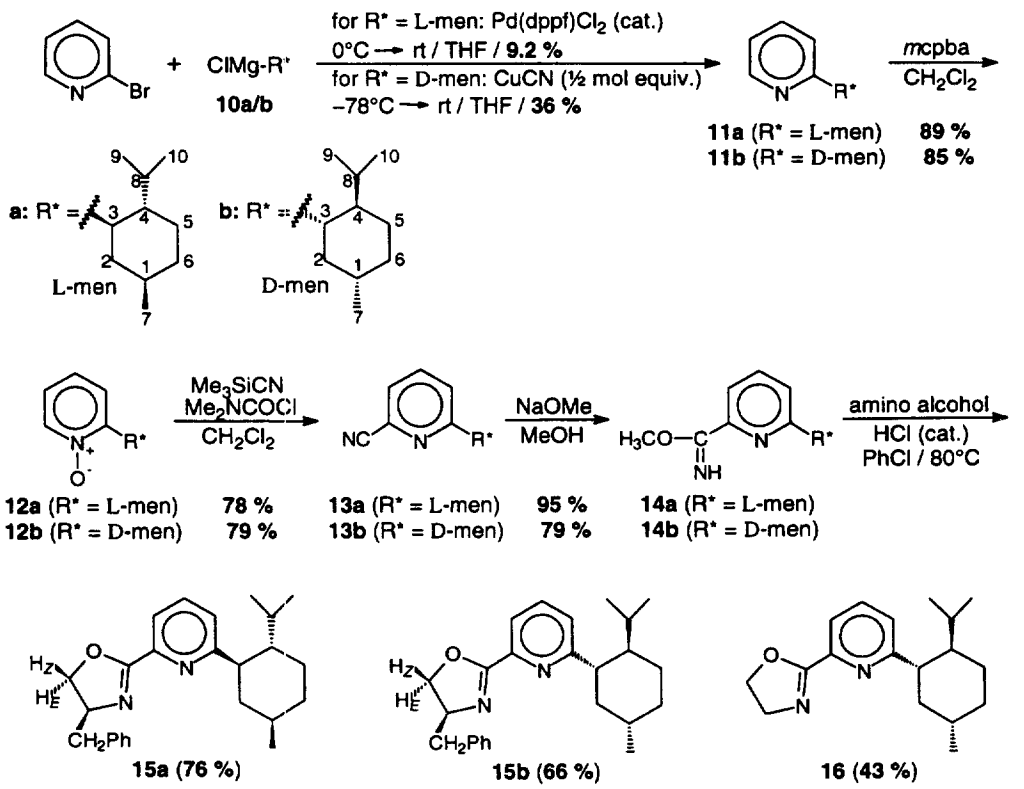


Fig. 1. ^{1}H–^{1}H-Coupling constants in the pinane system, values taken from **3** (R=COOMe)

suitable oxazoline-precursor could be synthesised. Moberg and Macedo had prepared similar 6-(2-oxazolinyl)pyridine-2-carbinols using this reaction sequence.[19] We synthesised (−)-2-L-menthylpyridine **11a** following Hentges' Grignard cross coupling of menthyl Grignard **10a** (derived from (−)-L-menthylchloride) with 2-bromopyridine (Scheme 3), but could not reproduce the reported 18% yield.[20] With Pd(dppf)Cl_2 as a catalyst (recommended for the coupling of secondary alkyl Grignards)[21] the highest yield of **11a** was 9.2%. All hydrogen and carbon signals of **11a** were completely assigned by analysis of ^{13}C/^{1}H and ^{1}H/^{1}H NMR correlation spectra, proving **11a** to be diastereomerically pure, because no signals of a possible diastereomer were evident.



Scheme 3.

Although menthyl Grignards are easily prepared[22] and tend to couple smoothly with halides yielding usually only one main product,[22,23] there were problems in the cross coupling reaction with 2-bromopyridine. Besides uncharacterised menthyl derivatives, we always isolated 2,2′-bipyridine originating from a homo-coupling of 2-bromopyridine. Thus, for the synthesis of (+)-2-D-menthylpyridine **11b**

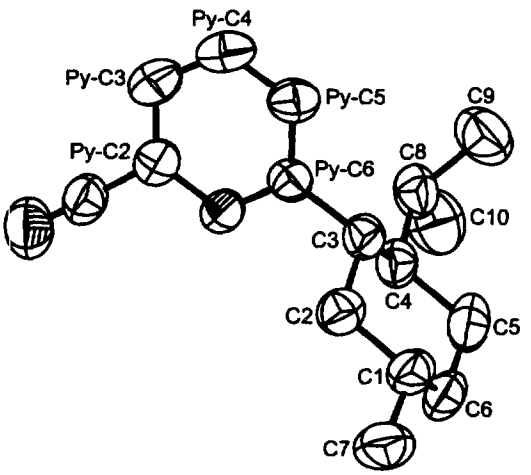


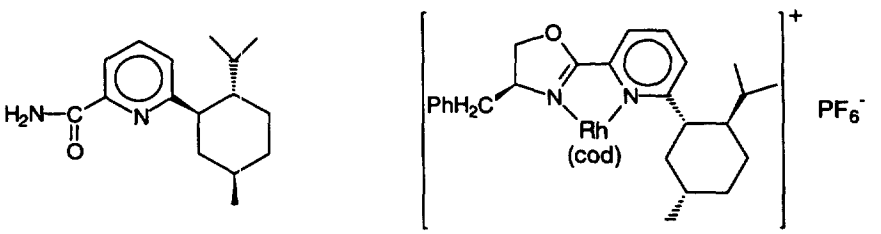
Fig. 2. Molecular structure of **13b** (Ortep plot)

we turned to the method of Bell et al., who prepared alkylated heterocycles using 2:1 alkyl Grignard:Cu(I) mixtures.[24] However, to obtain good yields they had to use an eightfold excess of alkyl Grignard relative to the halide.[24] We succeeded in synthesising (+)-2-D-menthylpyridine **11b** in 36% yield from 2-bromopyridine and menthyl Grignard **10b** (derived from (+)-D-menthylchloride) using a ratio of 1:1 (Scheme 3).

The subsequent synthesis was straightforward. 2-D-Menthylpyridine **11** was oxidised with *m*-cpba yielding the *N*-oxide **12**, which was converted into the nitrile **13** using trimethylsilylcyanide and dimethylcarbamoylchloride in CH_2Cl_2 (Scheme 3).[25] An X-ray structure analysis of **13b** proved the expected equatorial orientation of the menthyl substituents (Fig. 2). Thus, the Cu(I)-mediated reaction of menthyl Grignard **10b** with 2-bromopyridine proceeded diastereoselectively with retention of configuration at C-3 of the menthyl system. The nitrile **13b** exhibited the same specific rotation as its counterpart **13a**, but with opposite sign. The same situation was found for the two *N*-oxides **12a** and **12b**. Hence, also the Pd(II)-catalysed Grignard cross coupling was highly diastereoselective. The methyl carboximidate **14** was prepared by stirring the nitrile **13** in methanol with catalytic amounts of methanolate.[26] The following reaction with the amino alcohol required acid catalysis. However, already three drops of conc. HCl led to hydrolysis of the iminoether **14a** yielding the carboxamide **17** (Scheme 4). With only tiny amounts of conc. HCl **14a/b** reacted smoothly with (*S*)-phenylalaninol in chlorobenzene at 80°C to give the oxazolines **15a/b** (Scheme 3). The resinous diastereomers **15a** and **15b** did not crystallise and they showed almost identical spectroscopic behaviour. Ligand **16**, having an achiral oxazoline ring, was analogously prepared from ethanolamine and **14b** (Scheme 3). With this ligand the asymmetric induction of the menthyl part of the ligand should be tested in catalysis. By reaction of **15b** with $[Rh(cod)Cl]_2$ (1/2 mol equivalent) in methylene chloride and subsequent anion exchange with NH_4PF_6 the Rh(I)-complex **18** was prepared in 64% yield (Scheme 4).

3. Catalytic results

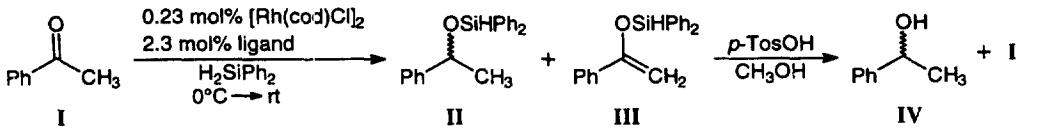
All the new ligands were tested in the enantioselective hydrosilylation of acetophenone with diphenylsilane (Scheme 5).[1] The amount of silylenol ether [**III/(II+III)**], the degree of hydrosilylation (i.e. the conversion of acetophenone) [**(II+III)/(I+II+III)**] and the chemical yield of silylalkyl ether



17 18

Scheme 4.

[II/(I+II+III)] were calculated from ^{1}H NMR spectra recorded after each catalytic run.[1] The enantiomeric excess was determined after hydrolysis by GC (see experimental).



I II III IV

Scheme 5.

The only comparable ligands with two different chiral substituents, having been tested in the Rh(I)-catalysed asymmetric hydrosilylation, are the 6-(2-oxazolinyl)pyridine-2-carbinols and their methyl ethers.[19] Although these ligands gave good optical yields in other asymmetric catalyses,[19,27] in the hydrosilylation reactions only racemic products were obtained.[19]

Entries 1–3 of Table 1 show the catalytic results obtained with oxazoline **9** and the ligands containing either optically active pinane or oxazoline substituents (**19** and **20**, Scheme 6). The values for **20** were taken from the literature,[28] those for **19**[29] were established in this study.[30] Ligand **9** proved to be the best ligand. Surprisingly, **9** and **19** induced the opposite configuration in the product compared to **20**. Inversion of the product configuration has been reported,[31,32] if 2-(2-pyridinyl)oxazolines, unsubstituted in the pyridine ring, are replaced by the corresponding picoline- or quinoline-oxazolines, containing substituents in the 5- and/or 6-position of the pyridine ring as cocatalysts.

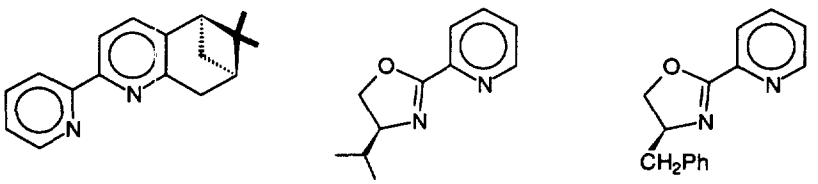
The results of the menthyl-substituted ligands and the corresponding 2-(2-pyridinyl)oxazoline **21**[28]

Table 1

Hydrosilylation of acetophenone with diphenylsilane (CCl_4 as solvent); reaction time: 18 h; catalyst: 0.24 mol% $[Rh(cod)Cl]_2$ (0.48 mol% Rh); 2.35 mol% ligand, substrate/Rh: 210:1

Entry	Ligand	Runs	Amount of silyl-enol ether [%][a]	Conversion [%][a, b]	Chemical Yield [%][a]	ee (*configuration*) [%][c]
1	**9**	2	0, 4	87, 94	87, 90	76.4, 79.6 *(S)*
2	**19**	2	0, 3	90, 87	90, 84	33.8, 33.7 *(S)*
3	**20**	2	12, 14	99, 97	87, 83	62.8, 61.6 *(R)*
4	**15a**	2	24, 22	76, 71	58, 55	*racemate*
5	**15a**[d]	3	14, 11, 7	67, 78, 78	58, 70, 58	26.8, 11.4, 6.0 *(S)*
6	**15b**	2	39, 37	83, 87	51, 54	0.7, 0.6 *(R)*
7	**18**[e]	2	28, 29	84, 89	61, 63	*racemate*
8	**16**	2	8, 6	88, 86	81, 81	9.0, 8.9 *(R)*
9	**21**	2	3, 3	99, 97	96, 94	62.8, 62.0 *(R)*

[a] determined by ^{1}H NMR spectroscpopy (80 MHz, $CDCl_3$)
[b] complete conversion of diphenylsilane
[c] determined by chiral GC
[d] excess of $AgBF_4$ added
[e] 0.48 mol% complex, no additional ligand



19 20 21

Scheme 6.

are displayed in entries 4–9. Only **16**, the ligand with the achiral oxazoline, tends to induce asymmetry (entry 8). The diastereomers **15a** and **15b** did not lead to significant enantioselectivities, contrary to the good enantiomeric excesses of ligand **21** (entry 9) having the same oxazoline ring as **15a** and **15b**. However, while preparing the in situ Rh(I)-catalyst, it was noticed that the solution did not turn red as usually observed during the catalyst preparation. Due to steric hindrance the complexation of **15** may be unfavourable as already proposed for other bulky oxazoline ligands.[19] Hence, in three catalytic runs with **15a** (entry 5) excess of $AgBF_4$[33] was added to remove the chloride from $[Rh(cod)Cl]_2$ and to assist in the formation of Rh(**15a**)-complexes. The yellow solutions of ligand and $[Rh(cod)Cl]_2$ did in fact change their colour to orange after $AgBF_4$ had been added. The solutions turned immediately black after the addition of diphenylsilane. Enantioselectivities up to 26.8% ee were obtained, depending on the amount of $AgBF_4$ added. The synthesised Rh(I)-complex **18** (entry 7) gave better chemical yields than the corresponding in situ system with **15b** (entry 6), but no stereoselectivity was found.

4. Experimental section

Chromatography: Merck silica gel 60 (63–200 mesh). Melting points (not corrected): Büchi SMP 20 (open capillaries). Elemental analyses: Microanalytical Laboratory, University of Regensburg. ^1H NMR: Bruker AW-80 (80 MHz, 31°C), AC-250 (250 MHz, 24°C) and ARX-400 (400 MHz, 21°C), ^{13}C NMR: Bruker AC-250 (62.9 MHz, 24°C), TMS or the solvent itself as internal standard. For optimal resolution some spectra were processed after recording using Bruker WIN NMR 5.0/5.1 software. The abbreviations *qC* in the ^{13}C NMR data represent quaternary carbon atoms. MS: Finnigan MAT 311 A (EI, 70 eV) and MAT 95 (FD). High-resolution mass spectra were recorded on a Joel JMS-SX102A (EI, 70 eV) at the *Max–Planck–Institut für medizinische Forschung in Heidelberg*. IR: Beckman IR 4240 (solids as KBr pellets, liquids as films between NaCl plates), only characteristic bands are listed. Optical rotation: Perkin–Elmer polarimeter 241 (0.1 dm cuvettes). Commercially available reagents were used without further purification if not stated otherwise. All anhydrous solvents were stored under nitrogen. Abbreviations: cod=η^4-1,5-cyclooctadiene, dppf=1,1′-bis(diphenylphosphanyl)ferrocene, *m*-cpba=*m*-chloroperbenzoic acid, men=menthyl, Ox=oxazoline, EA=ethyl acetate, PE=petroleum ether (b.p. 40–60°C).

4.1. 1-(2-Ethoxycarbonyl-2-oxoethyl)pyridinium-bromide 1

Following the method of Hünig et al.[13] dry pyridine (2.0 ml, 24.8 mmol) in dry ether (15 ml) was added at 0°C to a stirred solution of 5.1 g (≥23.5 mmol) of ethyl bromopyruvate (>90%, Fluka) in dry ether (15 ml) under nitrogen. Stirring in the ice bath (which was warming up) continued for 2 h. The yellow precipitate was filtered off, carefully avoiding any contact with air. After washing with dry ether (2×7 ml) the product was dried in vacuo. The light yellow salt (5.21 g, 19.0 mmol, 81% [lit.[13]: 89%])

was extremely hygroscopic and immediately became an orange oil if exposed to air. Even under argon it can only be stored for a short while. ^{1}H NMR (250 MHz, CD_3OD); δ=1.34 (t, ^3J=7.2 Hz, 3H, CH_2CH_3), 4.34 (q, ^3J=7.2 Hz, 2H, CH_2CH_3), 4.73 (d, J=11.6 Hz), 4.91 (d, J=13.3 Hz), 5.02 (d, J=13.3 Hz), 5.14 (d, J=11.6 Hz, together 2H, $COCH_2$), 8.14 ('dd', ^3J=7.9 Hz, ^3J=6.8 Hz, 2H, *H-3*, *H-5*), 8.68 ('tt', ^3J=7.9 Hz, ^4J=1.4 Hz, 1H, *H-4*), 8.94 ('dd', ^3J=6.8 Hz, ^4J=1.4 Hz, 2H, *H-2*, *H-6*). ^{13}C NMR (62.9 MHz, CD_3OD); δ=14.5 (CH_3), 64.0 (CH_2CH_3), 66.8 ($COCH_2$), 128.5 (*C-3*, *C-5*), 147.8 (*C-4*), 148.1 (*C-2*, *C-6*), 169.0 (*C*OOEt). IR (film): ν (cm^{-1})=3140/3095 s, 2995 m (*C–H*), 1750 vs (*C=O*), 1270/1150/1105 s (*C–O*).

Kröhnke condensation of 1-(2-ethoxycarbonyl-2-oxoethyl)pyridinium-bromide **1** and (+)-pinocarvone **2**: 5.27 g (max. 19.3 mmol) of **1**, 8.9 g (115.4 mmol) of anhydrous ammonium acetate and 1.66 g (11.0 mmol) of (+)-pinocarvone **2**[30,34] were refluxed in dry methanol (17 ml) under nitrogen for 16 h. The solvent was evaporated and the brown residue was treated with water (30 ml). The solution was extracted with CH_2Cl_2 (2×20 ml) and $CHCl_3$ (2×20 ml). The combined organic layers were washed with brine (20 ml), dried over $MgSO_4$ and evaporated. The remaining oil was flash chromatographed (SiO_2, 11×3 cm, PE:EA 4:1): unidentified pinane derivatives were eluted first, followed by a mixture of 5,6,7,8-tetrahydroquinoline compounds (yield: 23%). By a second flash chromatography (SiO_2, 12×3 cm, PE:EA 5:1 → 3:2) this mixture was then separated into the following three products (in order of elution):

4.2. Product: (−)-methyl (5R,7R)-5,6,7,8-tetrahydro-5,7-(9,9-dimethylmethano)quinoline-2-carboxylate **3**[35]

Light yellow liquid (383 mg, 1.7 mmol, 15%), R_f=0.52 (EA). ^{1}H NMR (250 MHz, CD_2Cl_2); δ=0.63 (s, 3H, *H-11*), 1.26 (d, ^2J=9.6 Hz, 1H, *H-6$_{endo}$*), 1.41 (s, 3H, *H-10*), 2.39 ('tt', $^3J_{7,6exo}$=$^4J_{7,5}$≈5.7 Hz, $^3J_{7,8}$=2.9 Hz, 1H, *H-7*), 2.72 (dt, ^2J=9.6 Hz, $^3J_{6exo,5}$=$^3J_{6exo,7}$≈5.7 Hz, 1H, H-6$_{exo}$), 2.85 (t, $^3J_{5,6exo}$=$^4J_{5,7}$≈5.7 Hz, 1H, H-5), 3.15 (d, $^3J_{8,7}$=2.9 Hz, 2H, H-8), 3.92 (s, 3H, $COOCH_3$), 7.33 (d, ^3J=7.7 Hz, 1H, H-4), 7.81 (d, ^3J=7.7 Hz, 1H, *H-3*). ^{13}C NMR (62.9 MHz, CD_2Cl_2); δ=21.3 (*C-11*), 26.1 (*C-10*), 31.9 (*C-6*), 36.9 (*C-8*), 39.7 (*C-9*), 40.6 (*C-5*), 47.2 (*C-7*), 52.5 ($COOCH_3$), 122.7 (*C-3*), 133.7 (*C-4*), 145.7 (*C-4a*), 146.6 (*C-2*), 157.8 (*C-8a*), 166.4 (*C*=O). MS (EI): *m/z* (%)=231 (71) [M^+], 230 (27), 216 (27) [M^+-CH_3], 189 (27), 188 (79) [$M^+-C_3H_7$], 172 (26), 171 (34), 170 (40), 158 (21), 157 (39), 156 (46), 144 (43), 130 (28), 129 (63), 128 (100), 43 (30) [$C_3H_7^+$]. IR (film): ν (cm^{-1})=2960/2940/2920 s, 2885 m (*C–H*), 1740/1720 s (*C=O*). Specific rotation (c=1.1, $CHCl_3$); $[\alpha]_D^{22}$=−56, $[\alpha]_{578}^{22}$=−58, $[\alpha]_{546}^{22}$=−66, $[\alpha]_{436}^{22}$=−119.

4.3. Product: (−)-ethyl (5R,7R)-5,6,7,8-tetrahydro-5,7-(9,9-dimethylmethano)quinoline-2-carboxylate **4**[35]

Yellow liquid (22 mg, 0.1 mmol, 0.8%), R_f=0.49 (EA). ^{1}H NMR (250 MHz, CD_2Cl_2); δ=0.63 (s, 3H, *H-11*), 1.26 (d, ^2J=9.6 Hz, 1H, *H-6$_{endo}$*), 1.40 (t, ^3J=7.1 Hz, 3H, CH_2CH_3), 1.41 (s, 3H, *H-10*), 2.39 ('tt', $^3J_{7,6exo}$=$^4J_{7,5}$≈5.7 Hz, $^3J_{7,8}$=2.9 Hz, 1H, *H-7*), 2.72 (dt, ^2J=9.6 Hz, $^3J_{6exo,5}$=$^3J_{6exo,7}$≈5.7 Hz, 1H, H-6$_{exo}$), 2.85 (t, $^3J_{5,6exo}$=$^4J_{5,7}$≈5.7 Hz, 1H, *H-5*), 3.16 (d, $^3J_{8,7}$=2.9 Hz, 2H, *H-8*), 4.39 (q, 3H, ^3J=7.1 Hz, 2H, CH_2CH_3), 7.33 (d, ^3J=7.7 Hz, 1H, *H-4*), 7.81 (d, ^3J=7.7 Hz, 1H, *H-3*). ^{13}C NMR (62.9 MHz, CD_2Cl_2); δ=14.5 (CH_2CH_3), 21.3 (*C-11*), 26.1 (*C-10*), 31.9 (*C-6*), 37.0 (*C-8*), 39.7 (*C-9*), 40.6 (*C-5*), 47.2 (*C-7*), 61.6 ($COOCH_2$), 122.7 (*C-3*), 133.6 (*C-4*), 146.0 (*C-4a*), 146.5 (*C-2*), 157.8 (*C-8a*), 165.9 (*C*=O). MS (EI); *m/z* (%)=245 (65) [M^+], 203 (25), 202 (80) [$M^+-C_3H_7$], 173 (33), 171 (44), 170 (41), 158 (24), 157 (37), 156 (54), 130 (38), 129 (55), 128 (100), 43 (30) [$C_3H_7^+$], 41 (21). IR (film); ν (cm^{-1})=2985/2930

s, 2875 m (*C–H*), 1745/1720 s (*C=O*). Specific rotation (c=1.1, $CHCl_3$); $[\alpha]_D^{22}=-44$, $[\alpha]_{578}^{22}=-48$, $[\alpha]_{546}^{22}=-54$, $[\alpha]_{436}^{22}=-103$.

4.4. *Product: (−)-(5R,7R)-5,6,7,8-tetrahydro-5,7-(9,9-dimethylmethano)quinoline-2-carboxamide* 5[35]

Yellow solid (160 mg, 0.7 mmol, 6.7%), R_f=0.43 (EA), m.p. 141–144°C. ^{1}H NMR (250 MHz, $CDCl_3$); δ=0.64 (s, 3H, *H-11*), 1.27 (d, ^2J=9.6 Hz, 1H, *H-6$_{endo}$*), 1.42 (s, 3H, *H-10*), 2.39 ('tt', $^3J_{7,6exo}=^4J_{7,5}\approx5.7$ Hz, $^3J_{7,8}$=2.9 Hz, 1H, *H-7*), 2.71 (dt, ^2J=9.6 Hz, $^3J_{6exo,5}=^3J_{6exo,7}\approx5.7$ Hz, 1H, *H-6$_{exo}$*), 2.84 (t, $^3J_{5,6exo}=^4J_{5,7}\approx5.7$ Hz, 1H, *H-5*), 3.10 (d, $^3J_{8,7}$=2.9 Hz, 2H, *H-8*), 6.16 (br s, 1H, N*H*H′), 7.34 (d, ^3J=7.7 Hz, 1H, *H-4*), 7.87 (br s, 1H, NH*H*′), 7.91 (d, ^3J=7.7 Hz, 1H, *H-3*). ^{13}C NMR (62.9 MHz, $CDCl_3$); δ=21.2 (*C-11*), 26.0 (*C-10*), 31.7 (*C-6*), 36.4 (*C-8*), 39.4 (*C-9*), 40.1 (*C-5*), 46.7 (*C-7*), 119.6 (*C-3*), 133.7 (*C-4*), 145.5 (*C-4a*), 147.0 (*C-2*), 155.9 (*C-8a*), 167.5 (*C*=O). MS (EI); *m/z* (%)=216 (74) [M^+], 174 (24), 173 (67) [$M^+-C_3H_7$], 172 (32), 171 (25), 170 (35), 156 (45), 130 (26), 129 (55), 128 (100). IR (KBr): ν (cm^{-1})=3445 s, 3265 m, 3150 s (*N–H*), 2995/2980/2970 m, 2940/2930 s, 2910/2870 m (*C–H*), 1690 vs (*C=O*). Specific rotation (c=1.1, $CHCl_3$); $[\alpha]_D^{23}=-61$, $[\alpha]_{578}^{23}=-63$, $[\alpha]_{546}^{23}=-72$.

4.5. *(−)-2-Cyano-(5R,7R)-5,6,7,8-tetrahydro-5,7-(9,9-dimethylmethano)quinoline* 6[35]

155 mg (0.7 mmol) of **5** and $POCl_3$ (0.2 ml, 2.2 mmol) in CCl_4 (4 ml) were refluxed for 18 h. After cooling and evaporation the residue was treated with $CHCl_3$ (20 ml) and half-saturated aqueous $NaHCO_3$ (20 ml). The organic layer was washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$ and evaporated. Flash chromatography (SiO_2, 7×2.5 cm, CH_2Cl_2) and recrystallisation from PE led to 70 mg (0.35 mmol, 50%) of **6**. Colourless crystals, R_f=0.26 (CH_2Cl_2), m.p. 60–62°C. ^{1}H NMR (250 MHz, CD_2Cl_2); δ=0.63 (s, 3H, *H-11*), 1.25 (d, ^2J=9.8 Hz, 1H, *H-6$_{endo}$*), 1.42 (s, 3H, *H-10*), 2.39 ('tt', $^3J_{7,6exo}=^4J_{7,5}\approx5.7$ Hz, $^3J_{7,8}$=2.9 Hz, 1H, *H-7*), 2.74 (dt, ^2J=9.8 Hz, $^3J_{6exo,5}=^3J_{6exo,7}\approx5.7$ Hz, 1H, *H-6$_{exo}$*), 2.86 (t, $^3J_{5,6exo}=^4J_{5,7}\approx5.7$ Hz, 1H, *H-5*), 3.12 (d, $^3J_{8,7}$=2.9 Hz, 2H, *H-8*), 7.32 (d, ^3J=7.7 Hz, 1H, *H-4*), 7.42 (d, ^3J=7.7 Hz, 1H, *H-3*). ^{13}C NMR (62.9 MHz, CD_2Cl_2); δ=21.3 (*C-11*), 26.0 (*C-10*), 31.7 (*C-6*), 36.8 (*C-8*), 39.7 (*C-9*), 40.3 (*C-5*), 47.3 (*C-7*), 118.3 (*C*≡N), 126.1 (*C-3*), 130.8 (*C-4a*), 133.6 (*C-4*), 147.1 (*C-2*), 159.9 (*C-8a*). MS (EI); *m/z* (%)=198 (32) [M^+], 197 (25), 183 (44), 157 (15), 156 (41), 155 (100) [$M^+-C_3H_7$], 154 (34), 143 (11), 142 (15), 128 (13), 41 (11). IR (KBr); ν (cm^{-1})=2975/2945 s, 2875 m (*C–H*), 2230 m (*C*≡*N*). Specific rotation (c=1.1, $CHCl_3$); $[\alpha]_D^{24}=-69$, $[\alpha]_{578}^{24}=-73$, $[\alpha]_{546}^{24}=-83$, $[\alpha]_{436}^{24}=-147$, $[\alpha]_{365}^{24}=-237$.

4.6. *(−)-(5R,7R)-5,6,7,8-Tetrahydro-5,7-(9,9-dimethylmethano)quinoline-2-carboxylic acid* 7[35]

3 (100 mg, 0.4 mmol) was refluxed in 2 N NaOH (10 ml) for 1 h. The cooled solution was acidified with conc. HCl and extracted with $CHCl_3$ (3×10 ml). The combined organic layers were washed with brine (10 ml), dried over $MgSO_4$ and evaporated. Recrystallisation from PE:ether (1:1) gave 80 mg (0.37 mmol, 92%) of **7**. Yellow solid, m.p. 158–162°C. ^{1}H NMR (250 MHz, CD_2Cl_2): δ=0.63 (s, 3H, *H-11*), 1.27 (d, ^2J=9.8 Hz, 1H, *H-6$_{endo}$*), 1.43 (s, 3H, *H-10*), 2.41 ('tt', $^3J_{7,6exo}=^4J_{7,5}\approx5.6$ Hz, $^3J_{7,8}$=2.8 Hz, 1H, *H-7*), 2.76 (dt, ^2J=9.8 Hz, $^3J_{6exo,5}=^3J_{6exo,7}\approx5.6$ Hz, 1H, *H-6$_{exo}$*), 2.85 (t, $^3J_{5,6exo}=^4J_{5,7}\approx5.6$ Hz, 1H, *H-5*), 3.14 (d, $^3J_{8,7}$=2.8 Hz, 2H, *H-8*), 7.46 (d, ^3J=7.7 Hz, 1H, *H-4*), 7.89 (d, ^3J=7.7 Hz, 1H, *H-3*), 9.28 (br s, 1H, COO*H*). ^{13}C NMR (62.9 MHz, CD_2Cl_2); δ=21.3 (*C-11*), 26.0 (*C-10*), 31.9 (*C-6*), 36.4 (*C-8*), 39.8 (*C-9*), 40.4 (*C-5*), 47.2 (*C-7*), 121.1 (*C-3*), 135.2 (*C-4*), 143.8 (*C-4a*), 148.1 (*C-2*), 156.8 (*C-8a*), 164.8 (*C*=O). MS (EI); *m/z* (%)=217 (39) [M^+], 216 (27), 175 (27), 174 (66) [$M^+-C_3H_7$], 173 (32), 171 (25), 170 (35), 156 (40), 130 (37), 129 (59), 128 (100). IR (KBr): ν (cm^{-1})=2990 m, 2960/2930 s, 2870

m (*C–H*), 1740 s (*C=O*). Specific rotation (c=1.1, $CHCl_3$); $[\alpha]_D^{24}=-57$, $[\alpha]_{578}^{24}=-60$, $[\alpha]_{546}^{24}=-69$, $[\alpha]_{436}^{24}=-121$.

4.7. (−)-(5R,7R)-5,6,7,8-Tetrahydro-5,7-(9,9-dimethylmethano)quinoline-2-carboxylic acid chloride **8**[35]

240 mg (1.1 mmol) of **7** and thionylchloride (2.0 ml) were refluxed for 30 min. Excess thionylchloride was removed and the light brown residue (254 mg, 1.1 mmol, 98%) was dried in vacuo. It was directly used in the next reaction.

4.8. (−)-(4S)-Isopropyl-2-[(5R,7R)-5,6,7,8-tetrahydro-5,7-(9,9-dimethylmethano)quinolin-2-yl]oxazoline **9**[35]

To a stirred solution of (*S*)-valinol (110 mg, 1.1 mmol) and triethylamine (130 mg, 1.3 mmol) in dry CH_2Cl_2 (3 ml) was added 254 mg (1.08 mmol) of **8** in CH_2Cl_2 (5 ml) at 0°C under nitrogen. After stirring for 16 h in an ice-bath which was warming up the solvent was removed and the residue treated with dry toluene (4 ml) and thionylchloride (0.25 ml, 3.4 mmol) at 0°C. The temperature was stepwise increased to 100°C and stirring continued for 30 min. After evaporation of the solvent the residue was refluxed in dry methanol (4 ml) and 245 mg (6.2 mmol) of NaOH for 4 h. To the cooled solution ether (25 ml), brine (5 ml) and the necessary amount of water to dissolve everything was added. The organic layer was washed with brine (5 ml) and dried over $MgSO_4$. Purification was performed by flash chromatography (SiO_2, 11×3 cm, PE:EA 4:1 → 3:1). 151 mg (0.5 mmol, 49%) of **9** crystallised slowly from PE/ether at −20°C. White solid, R_f=0.48 (EA), m.p. 75–76°C. ^{1}H NMR (250 MHz, $CDCl_3$); δ=0.64 (s, 3H, *H-11*), 0.94 (d, ^3J=6.7 Hz, 3H, C*H*$_3$), 1.06 (d, ^3J=7.3 Hz, 3H, C*H*$_3$′), 1.26 (d, ^2J=9.6 Hz, 1H, *H-6*$_{endo}$), 1.41 (s, 3H, *H-10*), 1.92 ('sept', $^3J\approx$6.7 Hz, 1H, C*H*Me$_2$), 2.38 ('tt', $^3J_{7,6exo}=^4J_{7,5}$=5.9 Hz, $^3J_{7,8}$=2.9 Hz, 1H, *H-7*), 2.69 (dt, ^2J=9.6 Hz, $^3J_{6exo,5}=^3J_{6exo,7}\approx$5.9 Hz, 1H, *H-6*$_{exo}$), 2.81 (t, $^3J_{5,6exo}=^4J_{5,7}\approx$5.9 Hz, 1H, *H-5*), 3.21 (d, $^3J_{8,7}$=2.9 Hz, 2H, *H-8*), 4.10–4.24 (m, 2H, Ox–C*H*$_Z$H$_E$ and Ox–C*H*?), 4.50 (m, 1H, Ox–CH$_Z$*H*$_E$?), 7.27 (d, ^3J=7.7 Hz, 1H, *H-4*), 7.72 (d, ^3J=7.7 Hz, 1H, *H-3*). ^{13}C NMR (62.9 MHz, $CDCl_3$); δ=18.1 (*C*H$_3$), 19.2 (*C*H$_3$′), 21.2 (*C-11*), 26.0 (*C-10*), 31.7 (*C-6*), 32.7 (*C*HMe$_2$), 36.7 (*C-8*), 39.4 (*C-9*), 40.2 (*C-5*), 46.8 (*C-7*), 70.9 (Ox–*C*H$_2$), 73.2 (Ox–*C*H), 121.1 (*C-3*), 133.2 (*C-4*), 144.2/144.5/157.2 (*qC*), 162.9 (*C*=N). MS (EI); *m/z* (%)=284 (32) [M$^+$], 243 (48) [M$^+$−C$_3$H$_5$], 242 (29), 241 (100) [M$^+$−C$_3$H$_7$], 213 (36), 157 (25), 155 (21). IR (film); ν (cm^{-1})=2950/2930 s, 2865 m (*C–H*), 1640 s (*C=N*). Specific rotation (c=1.1, $CHCl_3$); $[\alpha]_D^{22}=-137$, $[\alpha]_{578}^{22}=-144$, $[\alpha]_{546}^{22}=-165$, $[\alpha]_{436}^{22}=-315$, $[\alpha]_{365}^{22}=-583$. $C_{18}H_{24}N_2O$ (284.40): calcd C 76.02; H 8.51; N 9.85, found C 75.45; H 8.38; N 9.69%.

*4.9. (−)-2-*L*-Menthylpyridine* ***11a***

1.48 g (60.9 mmol) of magnesium turnings in dry THF (20 ml) were activated by stirring with a few drops of 1,2-dibromoethane under nitrogen. After 5 min, 10 ml of a solution of freshly distilled (−)-L-menthylchloride[36] (10.0 ml, 53.8 mmol) in THF (60 ml) was added. Warming to ca. 50°C started the reaction. Over a 45 min period the remaining (−)-L-menthylchloride solution was added dropwise and stirring at 50°C continued for 16 h. After cooling unreacted magnesium was filtered off under nitrogen, rinsed with THF (2×5 ml) and dried. By weighing the magnesium the theoretical amount of menthyl Grignard **10a** was estimated to be 47.7 mmol (89%). It was then added over 1 h to a stirred solution of 2-bromopyridine (4.6 ml, 47.5 mmol) and 350 mg (0.48 mmol) of Pd(dppf)Cl_2[21] in THF (20 ml) at 0°C under nitrogen. After 48 h stirring in an ice-bath, which was allowed to warm up, the solution was

quenched with saturated aqueous NH_4Cl (230 ml) and diluted with enough water to dissolve precipitated magnesium salts. The aqueous layer was extracted with ether (2×50 ml). The combined organic layers were washed with brine (40 ml), dried over $MgSO_4$ and the solvents evaporated. The remaining brown oil was flash chromatographed (SiO_2, 13×5 cm, CH_2Cl_2). Sequence of elution: uncharacterised menthyl derivatives, unreacted 2-bromopyridine (R_f=0.4) and the crude product (R_f=0.27). By adding EA to the eluent 2,2′-bipyridine was isolated as the last fraction. Analytically pure **11a** (950 mg, 4.4 mmol, 9.2%) was obtained by kugelrohr distillation at 120–130°C/ca. 1 torr. ^{1}H NMR (400 MHz, $CDCl_3$); δ=0.70 (d, ^3J=6.9 Hz, 3H, *H-9* or *H-10*), 0.81 (d, ^3J=6.9 Hz, 3H, *H-10* or *H-9*), 0.90 (d, ^3J=6.4 Hz, 3H, *H-7*), 1.07 (m, 1H, *H-6*), 1.19 (m, 1H, *H-5*), 1.30 (m, 1H, *H-8*), 1.32 (m, 1H, *H-2*), 1.50 (m, 1H, *H-1*), 1.71 (m, 1H, *H-4*), 1.76 (m, 1H, *H-5′*), 1.79 (m, 1H, *H-2′*), 1.81 (m, 1H, *H-6′*), 2.65 (dt, ^3J=11.5 Hz, ^3J=3.4 Hz, 1H, *H-3*), 7.07 (ddd, ^3J=7.7 Hz, ^3J=4.9 Hz, ^4J=1.2 Hz, 1H, Py–*H-5*), 7.10 ('dt', ^3J=7.7 Hz, ^4J=^5J≈1.1 Hz, 1H, Py–*H-3*), 7.57 (dt, ^3J=7.7 Hz, ^4J=1.9 Hz, 1H, Py-*H-4*), 8.54 (ddd, ^3J=4.9 Hz, ^4J=1.9 Hz, ^5J=1.0 Hz, 1H, Py-*H-6*). ^{13}C NMR (62.9 MHz, $CDCl_3$); δ=15.7/21.3 (*C-9* and *C-10*), 22.4 (*C-7*), 24.6 (*C-5*), 27.9 (*C-8*), 33.0 (*C-1*), 35.1 (*C-6*), 43.5 (*C-2*), 46.5 (*C-4*), 49.9 (*C-3*), 120.8 (Py–*C-5*), 122.3 (Py–*C-3*), 136.0 (Py–*C-4*), 149.6 (Py–*C-6*), 165.8 (Py–*C-2*). MS (EI); *m/z* (%)=217 (33) [M^+], 202 (10) [M^+-CH_3], 174 (29) [$M^+-C_3H_7$], 106 (100) [(Py–C_2H_4)$^+$], 93 (37) [$C_6H_7N^+$]. IR (film); ν (cm^{-1})=2955/2920 vs, 2870 s (*C–H*). Specific rotation (c=3.25, EtOH); $[\alpha]_D^{23}$=−36 (lit.[18] $[\alpha]_D^{21}$=−43.82), $[\alpha]_{578}^{23}$=−38, $[\alpha]_{546}^{23}$=−43, $[\alpha]_{436}^{23}$=−72, $[\alpha]_{365}^{23}$=−109. $C_{15}H_{23}N$ (217.35): calcd. C 82.89; H 10.67; N 6.44, found C 82.76; H 10.48; N 6.26%.

4.10. (−)-2-L-Menthylpyridine-N-oxide **12a**

250 mg (1.15 mmol) of **11a** and 300 mg (≥1.39 mmol) of 80–90% *m*-cpba were stirred in CH_2Cl_2 (5 ml) at rt for 3 days. The solution was diluted with $CHCl_3$ (10 ml) and extracted with 2 N NaOH (2×10 ml) and 10% aqueous K_2CO_3 (10 ml). The remaining organic layer was then washed with brine (10 ml), dried over $MgSO_4$ and evaporated. Purification by flash chromatography (SiO_2, 10×3 cm, acetone) gave 240 mg of **12a** (1.0 mmol, 89%), R_f=0.2 (acetone), b.p. 180–200°C/ca. 1 torr. ^{1}H NMR (250 MHz, C_6D_6); δ=0.65 (q, ^3J=11.9 Hz, 1H, men–*H*), 0.80 ('d', ^3J=6.7 Hz, 6H, *H-9* and *H-10*), 0.89 (d, ^3J=6.9 Hz, 3H, *H-7*), 1.03–1.75 (m, 7H, men–*H*), 1.95 (dd, *J*=12.4 Hz, *J*=2.0 Hz, 1H, men–*H*), 4.21 (dt, ^3J=11.5 Hz, ^3J=3.3 Hz, 1H, *H-3*), 6.17 (ddd, ^3J=7.9 Hz, ^3J=6.4 Hz, ^4J=2.0 Hz, 1H, Py-*H-5*), 6.38 (dt, ^3J=7.9 Hz, ^4J=0.8 Hz, 1H, Py–*H-4*), 6.60 (dd, ^3J=7.9 Hz, ^4J=2.0 Hz, 1H, Py–*H-3*), 8.02 (dd, ^3J=6.4 Hz, ^4J=0.8 Hz, 1H, Py-*H-6*). ^{13}C NMR (62.9 MHz, CD_2Cl_2); δ=16.5/21.6 (*C-9* and *C-10*), 22.4 (*C-7*), 25.0 (*C-5*), 28.8 (*C-8*), 33.2 (*C-1*), 35.4 (*C-6*), 38.8 (*C-3*), 42.2 (*C-2*), 46.7 (*C-4*), 123.0 (Py–*C-5*?), 124.3 (Py–*C-4*?), 125.5 (Py–*C-3*?), 139.9 (Py–*C-6*), 156.5 (Py–*C-2*). MS (EI); *m/z* (%)=233 (18) [M^+], 216 (100) [M^+−OH], 190 (67) [$M^+-C_3H_7$], 122 (54), 109 (51), 106 (40) [(Py-C_2H_4)$^+$], 93 (27) [$C_6H_7N^+$]. IR (film): ν (cm^{-1})=2950/2920/2870 s (*C–H*), 1275 m, 1230 s (*N–O*). Specific rotation (c=1.1, $CHCl_3$); $[\alpha]_D^{21}$=−70, $[\alpha]_{578}^{21}$=−75, $[\alpha]_{546}^{21}$=−84, $[\alpha]_{436}^{21}$=−147, $[\alpha]_{365}^{21}$=−223.

4.11. (−)-2-Cyano-6-L-menthylpyridine **13a**

235 mg (1.0 mmol) of **12a** and trimethylsilylcyanide (0.2 ml, 1.6 mmol) in dry CH_2Cl_2 (2.5 ml) were stirred for 5 min under nitrogen. Then dimethylcarbamoylchloride (0.1 ml, 1.1 mmol) was added and allowed to react for 3 days. After dilution with CH_2Cl_2 (8 ml) a solution of 10% aqueous K_2CO_3 (10 ml) was added and stirring continued for 10 min., the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×5 ml). The combined organic layers were washed with brine (5 ml), dried over $MgSO_4$ and evaporated. The residue crystallised at −20°C from PE (1 ml) to give 190 mg (0.8 mmol,

78%) of **13a**. Colourless crystals, m.p. 78–79°C. ^{1}H NMR (250 MHz, CD_2Cl_2); δ=0.69 (d, ^3J=6.9 Hz, 3H, *H-9* or *H-10*), 0.81 (d, ^3J=6.9 Hz, 3H, *H-10* or *H-9*), 0.91 (d, ^3J=6.5 Hz, 3H, *H-7*), 0.97–1.34 (m, 4H, *H-6*, *H-5*, *H-8*, *H-2*), 1.49 (m, 1H, *H-1*), 1.65–1.87 (m, 4H, *H-4*, *H-5'*, *H-2'*, *H-6'*), 2.74 (dt, ^3J=11.5 Hz, ^3J=3.5 Hz, 1H, *H-3*), 7.36 (dd, ^3J=7.8 Hz, ^4J=1.0 Hz, 1H, Py–*H-5*), 7.51 (dd, ^3J=7.8 Hz, ^4J=1.0 Hz, 1H, Py–*H-3*), 7.73 (t, ^3J=7.8 Hz, 1H, Py–*H-4*). ^{13}C NMR (62.9 MHz, CD_2Cl_2); δ=15.9/21.5 (*C-9* and *C-10*), 22.6 (*C-7*), 24.9 (*C-5*), 28.6 (*C-8*), 33.3 (*C-1*), 35.4 (*C-6*), 43.6 (*C-2*), 46.9 (*C-4*), 50.2 (*C-3*), 118.2 (*C*N), 126.2/126.4 (Py–*C-3* and *C-5*), 133.8 (Py–*C-2*), 137.5 (Py–*C-4*), 168.6 (Py–*C-6*). MS (EI); *m/z* (%)=242 (27) [M$^+$], 200 (12), 199 (38) [M$^+$−C_3H_7], 146 (17), 145 (14), 132 (14), 131 (100), 118 (57), 41 (13). IR (KBr); ν (cm^{-1})=2960/2950/2940/2890/2870/2850 s (*C–H*), 2230 m (*C≡N*). Specific rotation (c=1.1, $CHCl_3$); $[\alpha]_D^{24}$=−44, $[\alpha]_{578}^{24}$=−46, $[\alpha]_{546}^{24}$=−52, $[\alpha]_{436}^{24}$=−90, $[\alpha]_{365}^{24}$=−138. $C_{16}H_{22}N_2$ (242.36): calcd C 79.29; H 9.15; N 11.56, found C 79.08; H 8.92; N 11.45%.

4.12. (−)-Methyl 6-L-menthylpyridine-2-carboximidate **14a**

10 mg (0.4 mmol) of sodium were dissolved in dry methanol (7 ml) under nitrogen. 250 mg (1.0 mmol) of **13a** was added and stirring was continued at rt for 3 days. After adding acetic acid (2 drops) the solvent was removed in vacuo and the residue treated with warm ether (100 ml). Insoluble inorganic salts were removed by filtration. Evaporation of the ether yielded 270 mg (0.98 mmol, 98%) of an oily residue, which was used directly in the next reactions. IR (film); ν (cm^{-1})=3290 w (*N–H*), 2970/2915 s, 2870/2845 m (*C–H*), 1655 s (*C=N*).

4.13. (−)-6-L-Menthylpyridine-2-carboxamide **17**

260 mg (0.95 mmol) of **14a** and conc. HCl (3–4 drops) in dry chlorobenzene (20 ml) were heated at 80°C for 64 h with a gentle stream of nitrogen bubbling through. Direct flash chromatography (SiO_2, 5.5×3 cm, CH_2Cl_2) yielded a small amount of an uncharacterised side-product. With ether, the main product was eluted (R_f=0.25) and recrystallised from PE (15 ml) to give 100 mg (0.4 mmol, 40%) of **17**. Colourless crystals, m.p. 142–143°C. ^{1}H NMR (250 MHz, $CDCl_3$); δ=0.70 (d, ^3J=6.9 Hz, 3H, *H-9* or *H-10*), 0.80 (d, ^3J=6.9 Hz, 3H, *H-10* or *H-9*), 0.92 (d, ^3J=6.5 Hz, 3H, *H-7*), 1.00–1.35 (m, 4H, *H-6*, *H-5*, *H-8*, *H-2*), 1.50 (m, 1H, *H-1*), 1.62–1.88 (m, 4H, *H-4*, *H-5'*, *H-2'*, *H-6'*), 2.71 (dt, ^3J=11.4 Hz, ^3J=3.3 Hz, 1H, *H-3*), 6.14 (br s, 1H, N*H*H'), 7.26 (dd, ^3J=7.5 Hz, ^4J=1.2 Hz, 1H, Py–*H-5*), 7.75 (t, ^3J=7.5 Hz, 1H, Py–*H-4*), 7.99 (br s, 1H, NH*H'*), 8.01 (dd, ^3J=7.5 Hz, ^4J=1.2 Hz, 1H, Py–*H-3*). ^{13}C NMR (62.9 MHz, $CDCl_3$); δ=15.7/21.3 (*C-9* and *C-10*), 22.4 (*C-7*), 24.6 (*C-5*), 28.0 (*C-8*), 33.0 (*C-1*), 35.1 (*C-6*), 43.4 (*C-2*), 46.8 (*C-4*), 49.6 (*C-3*), 119.6 (Py–*C-3*), 125.2 (Py–*C-5*), 137.4 (Py–*C-4*), 149.0 (Py–*C-2*), 164.7 (*C*=O), 167.3 (Py–*C-6*). MS (EI); *m/z* (%)=260 (39) [M$^+$], 245 (10) [M$^+$−CH_3], 217 (48) [M$^+$−C_3H_7], 172 (13), 164 (19), 163 (14), 150 (11), 149 (100), 136 (39), 132 (15), 104 (21). IR (KBr); ν (cm^{-1})=3435 m, 3275/3195 w (*N–H*), 2950/2920 m, 2870 w (*C–H*), 1700 s (*C=O*). Specific rotation (c=1.1, $CHCl_3$); $[\alpha]_D^{22}$=−39, $[\alpha]_{578}^{22}$=−41, $[\alpha]_{546}^{22}$=−45, $[\alpha]_{436}^{22}$=−75, $[\alpha]_{365}^{22}$=−111. $C_{16}H_{24}N_2O$ (260.38): calcd C 73.81; H 9.29; N 10.76, found C 73.82; H 9.29; N 10.74%.

4.14. (−)-(4S)-Benzyl-2-(6-L-menthylpyridin-2-yl)oxazoline **15a**

500 mg (1.8 mmol) of **14a**, 280 mg (1.85 mmol) of (*S*)-phenylalaninol and conc. HCl (1 drop) were dissolved in dry chlorobenzene (12 ml) and stirred at 80°C for 88 h with a gentle stream of nitrogen bubbling through. The cooled solution was purified by flash chromatography (SiO_2, 6.5×2.5 cm) with CH_2Cl_2 as an eluent (R_f=0.07). Kugelrohr distillation at 250°C/ca. 1 torr gave 520 mg (1.4 mmol, 76%)

of the oxazoline **15a** as a light yellow resin, which could not be crystallised. ^{1}H NMR (250 MHz, $CDCl_3$); δ=0.71 (d, ^3J=6.8 Hz, 3H, *H-9* or *H-10*), 0.83 (d, ^3J=6.9 Hz, 3H, *H-10* or *H-9*), 0.88 (d, ^3J=6.5 Hz, 3H, *H-7*), 1.00–1.43 (m, 4H, *H-6*, *H-2*, *H-5*, *H-8*), 1.50 (m, 1H, *H-1*), 1.58–1.95 (m, 4H, *H-4*, *H-5'*, *H-6'*, *H-2'*), 2.74 (dd, ^2J=13.7 Hz, ^3J=9.2 Hz, 1H, CH_AH_BPh), 2.87 (dt, ^3J=11.6 Hz, ^3J=3.3 Hz, 1H, *H-3*), 3.31 (dd, ^2J=13.7 Hz, ^3J=4.8 Hz, 1H, CH_AH_BPh), 4.23 (dd, ^2J=8.6 Hz, ^3J=7.5 Hz, 1H, Ox–CH_ZH_E), 4.42 (dd, ^2J=8.6 Hz, ^3J=9.4 Hz, 1H, Ox–CH_ZH_E), 4.63 (dddd, ^3J=9.4 Hz, ^3J=9.2 Hz, ^3J=7.5 Hz, ^3J=4.8 Hz, 1H, Ox–C*H*), 7.19–7.36 (m, 6H, Ph–*H* and Py–*H-5*), 7.67 (t, ^3J=7.5 Hz, 1H, Py–*H-4*), 7.88 (dd, ^3J=7.5 Hz, ^4J=1.2 Hz, 1H, Py–*H-3*). ^{13}C NMR (62.9 MHz, $CDCl_3$); δ=15.7/21.5 (*C-9* and *C-10*), 22.4 (*C-7*), 24.7 (*C-5*), 28.1 (*C-8*), 32.9 (*C-1*), 35.1 (*C-6*), 41.8 (CH_2Ph), 43.9 (*C-2*), 46.6 (*C-4*), 50.1 (*C-3*), 68.0 (Ox–*C*H), 72.5 (Ox–CH_2), 121.6 (Py–*C-3*), 123.4 (Py–*C-5*), 126.5 (*p*-Ph–*C*), 128.6/129.3 (*o*- and *m*-Ph–*C*), 136.5 (Py–*C-4*), 138.1 (*qC* of Ph), 146.4 (Py–*C-2*), 163.8 (*C*=N), 166.3 (Py–*C-6*). MS (EI); *m/z* (%)=376 (18) [M$^+$], calcd for $C_{25}H_{32}N_2O$: 376.2515, found 376.2520, diff. +0.5 mmu/1.3 ppm, 286 (20), 285 (100) [M$^+$−$PhCH_2$], 259 (14), 257 (20), 91 (14) [$PhCH_2^+$]. IR (film); ν (cm^{-1})=3065/3030 w, 2960/2925/2875 s (*C–H*), 1645 m (*C=N*). Specific rotation (c=1.1, $CHCl_3$); $[\alpha]_D^{16}$=−43, $[\alpha]_{578}^{16}$=−48, $[\alpha]_{546}^{16}$=−51, $[\alpha]_{436}^{16}$=−91, $[\alpha]_{365}^{16}$=−169.

4.15. (+)-2-D-*Menthylpyridine* **11b**

From 1.4 g (57.6 mmol) of magnesium turnings and freshly distilled (+)-D-menthylchloride[36] (10.0 ml, 53.8 mmol) the Grignard **10b** was prepared as described in the synthesis of **11a**. According to the theoretical amount of menthyl Grignard **10b** (45.7 mmol, 85%) CuCN (2.05 g, 22.9 mmol) was suspended in dry THF (50 ml) and at −78°C the menthyl Grignard solution was added dropwise. Stirring was continued at −78°C for 20 min, then 2-bromopyridine (4.4 ml, 45.4 mmol) was added via a cannula. After 2 h stirring was continued at rt for 17 h. A solution of 32% aqueous NH_3 (50 ml) was added, the pH was adjusted to 10 with 2 N NaOH and insoluble material was removed by filtration, followed by rinsing with ether. The organic layer was separated and the aqueous layer was extracted with ether (2×20 ml). The combined organic layers were washed with brine (20 ml), dried over $MgSO_4$ and evaporated. By a first flash chromatography (SiO_2, 15×5 cm, CH_2Cl_2) the residue was separated into uncharacterised menthyl derivatives and a 2-bromopyridine/product mixture. Separation of this mixture by a second flash chromatography (SiO_2, 20×5 cm) with PE:EA 9:1 as an eluent gave crude **11b** (R_f=0.26), which was finally purified by kugelrohr distillation at 120–130°C/ca. 1 torr yielding 3.59 g (16.5 mmol, 36%) of **11b** with spectroscopic properties identical with enantiomer **11a**. Specific rotation (c=3.25, EtOH); $[\alpha]_D^{21}$=+29, $[\alpha]_{578}^{21}$=+30, $[\alpha]_{546}^{21}$=+35, $[\alpha]_{436}^{21}$=+59, $[\alpha]_{365}^{21}$=+93.

4.16. (+)-2-D-*Menthylpyridine*-N-*oxide* **12b**

3.23 g (14.8 mmol) of **11b** and 3.83 g (≥17.7 mmol) of 80–90% *m*-cpba in CH_2Cl_2 (60 ml) were stirred at rt for 6 days. The precipitation of *m*-chlorobenzoic acid was completed at −20°C for 4 h. The filtered solution was treated as described for **12a** yielding 2.95 g (12.6 mmol, 85%) of **12b** as a colourless oil. Specific rotation (c=1.1, $CHCl_3$); $[\alpha]_D^{21}$=+70, $[\alpha]_{578}^{21}$=+71, $[\alpha]_{546}^{21}$=+89, $[\alpha]_{436}^{21}$=+144, $[\alpha]_{365}^{21}$=+220.

4.17. (+)-2-Cyano-6-D-*menthylpyridine* **13b**

Synthesised from 2.95 g (12.5 mmol) of **12b**, trimethylsilylcyanide (1.8 ml, 14.4 mmol) and dimethylcarbamoylchloride (1.15 ml, 12.5 mmol) in dry CH_2Cl_2 (25 ml) and reacted for 6 days as decribed

Table 2
Atomic coordinates and equivalent isotropic displacement coefficients

Py-N	8676(3)	5002(3)	1547(2)	54(1)
Cyano-N	12313(4)	4550(4)	1811(2)	90(2)
Cyano-C	11089(5)	4370(4)	1869(2)	66(2)
Py-C2	7240(4)	4815(4)	1585(2)	51(1)
Py-C3	6635(4)	3744(4)	2022(2)	63(1)
Py-C4	7534(5)	2846(4)	2423(2)	72(2)
Py-C5	9024(4)	3007(4)	2378(2)	68(2)
Py-C6	9538(4)	4110(4)	1935(2)	55(1)
C1	5698(4)	8338(4)	922(3)	69(2)
C2	6586(4)	7286(3)	1386(2)	62(1)
C3	6301(3)	5803(3)	1111(2)	55(1)
C4	6570(4)	5665(3)	200(2)	58(1)
C5	5635(4)	6715(4)	-257(2)	75(2)
C6	5931(4)	8167(4)	31(3)	76(2)
C7	6065(4)	9804(4)	1204(3)	94(2)
C8	6402(4)	4184(4)	-117(2)	69(2)
C9	4869(4)	3588(4)	-32(3)	99(2)
C10	6919(5)	4069(4)	-992(3)	103(2)

for **13a**. After 40 and 64 h trimethylsilylcyanide (2×0.2 ml, 1.6 mmol) and dimethylcarbamoylchloride (2×0.1 ml, 1.1 mmol) were replenished. Yield: 2.39 g (9.9 mmol, 79%) of **13b** as colourless crystals. Specific rotation (c=1.1, $CHCl_3$); $[\alpha]_D^{21}$=+43, $[\alpha]_{578}^{21}$=+46, $[\alpha]_{546}^{21}$=+53, $[\alpha]_{436}^{21}$=+90, $[\alpha]_{365}^{21}$=+138.

4.18. X-Ray structure analysis of 13b

$C_{16}H_{22}N_2$ (242.36); crystal dimensions 0.25×0.35×0.60 mm^3; crystal system rhombic; space group D2/4, P212121, (19); unit cell dimensions: a=9.119(3), b=9.725(3), c=16.599(5) Å, α=β=γ=90°, V=1472(1) $Å^3$, Z=4; density d_{calcd}=1.09 g/cm^3, μ(Mo–K_α)=0.06 mm^{-1}, 9.0°<2θ<27.0°; total no. of reflections 2622, unique reflections 2395; F(000)=528; diffractometer Syntex R3. The structure was solved by direct methods using the SHELXTL PLUS version 4.2/800 program system. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, e-mail: teched@chemcrys.carn.ac.uk. (Table 2).

4.19. (+)-Methyl 6-D-menthylpyridine-2-carboximidate 14b

From **13b** (2.38 g, 9.8 mmol) and sodium (23 mg, 1.0 mmol) in dry methanol (10 ml) as described for **14a**. Purification by flash chromatography (SiO_2, 10×3 cm, CH_2Cl_2) gave 2.11 g (7.7 mmol, 79%) of **14b** (R_f=0.1), which was used directly in the next reactions.

4.20. (+)-(4S)-Benzyl-2-(6-D-menthylpyridin-2-yl)oxazoline 15b

1.1 g (4.0 mmol) of **14b**, 610 mg (4.0 mmol) of (*S*)-phenylalaninol and conc. HCl (1 drop) in dry chlorobenzene (20 ml) were stirred at 80°C for 67 h with a gentle stream of nitrogen bubbling through. Purification by flash chromatography (SiO_2, 8×3 cm, CH_2Cl_2) followed by kugelrohr distillation at 250°C/ca. 1 torr yielded 990 mg (2.6 mmol, 66%) of **15b** (R_f=0.07), as a light yellow resin, which could not be crystallised. ^1H NMR (250 MHz, $CDCl_3$); δ=0.72 (d, ^3J=6.9 Hz, 3H, *H-9* or *H-10*), 0.82

(d, ^3J=6.9 Hz, 3H, *H-10* or *H-9*), 0.89 (d, ^3J=6.5 Hz, 3H, *H-7*), 1.05 (m, 1H, *H-6*), 1.18 (m, 1H, *H-2*), 1.22 (m, 1H, *H-5*), 1.33 (m, 1H, *H-8*), 1.51 (m, 1H, *H-1*), 1.63 (m, 1H, *H-4*), 1.74 (m, 1H, *H-5'*), 1.81 (m, 1H, *H-6'*), 1.87 (m, 1H, *H-2'*), 2.76 (dd, ^2J=13.9 Hz, ^3J=9.1 Hz, 1H, CH_AH$_B$Ph), 2.88 (dt, ^3J=11.5 Hz, ^3J=3.2 Hz, 1H, *H-3*), 3.28 (dd, ^2J=13.9 Hz, ^3J=5.2 Hz, 1H, CH$_A$$H_B$Ph), 4.23 (dd, ^2J=8.3 Hz, ^3J=7.5 Hz, 1H, Ox–CH_ZH$_E$), 4.42 (dd, ^2J=8.3 Hz, ^3J=9.1 Hz, 1H, Ox–CH$_Z$$H_E$), 4.63 (dddd, ^3J=9.1 Hz, ^3J=9.1 Hz, ^3J=7.5 Hz, ^3J=5.2 Hz, 1H, Ox–C*H*), 7.19–7.33 (m, 5H, Ph–*H*), 7.23 (m, 1H, Py–*H-5*), 7.66 (t, ^3J=7.5 Hz, 1H, Py–*H-4*), 7.88 (dd, ^3J=7.5 Hz, ^4J=1.2 Hz, 1H, Py–*H-3*). ^{13}C NMR (62.9 MHz, $CDCl_3$); δ=15.8/21.4 (*C-9* and *C-10*), 22.4 (*C-7*), 24.6 (*C-5*), 28.1 (*C-8*), 32.9 (*C-1*), 35.1 (*C-6*), 41.7 (*C*H$_2$Ph), 43.7 (*C-2*), 46.7 (*C-4*), 50.1 (*C-3*), 68.0 (Ox–*C*H), 72.4 (Ox–*C*H$_2$), 121.5 (Py–*C-3*), 123.3 (Py–*C-5*), 126.5 (*p*-Ph–*C*), 128.5/129.3 (*o*- and *m*-Ph–*C*), 136.5 (Py–*C-4*), 138.0 (*qC* of Ph), 146.4 (Py–*C-2*), 163.7 (*C*=N), 166.3 (Py–*C-6*). MS (EI); *m/z* (%)=376 (4) [M$^+$], 285 (37) [M$^+$−PhCH$_2$], 275 (31), 260 (18), 233 (11), 232 (66), 179 (18), 178 (22), 172 (14), 165 (14), 164 (100), 151 (48), 132 (18), 130 (13), 105 (11), 104 (26), 91 (13) [PhCH$_2^+$], 41 (11). IR (film); ν (cm^{-1})=3060/3025 w, 2950/2920 s, 2870/2850 m (*C–H*), 1645 m (*C=N*). Specific rotation (c=1.1, $CHCl_3$); [α]$_D^{22}$=+51, [α]$_{578}^{22}$=+54, [α]$_{546}^{22}$=+62, [α]$_{436}^{22}$=+116, [α]$_{365}^{22}$=+217. $C_{25}H_{32}N_2O$ (376.54): calcd. C 79.75; H 8.57; N 7.44, found C 78.82; H 8.37; N 7.17%.

*4.21. (+)-2-(6-*D*-Menthylpyridin-2-yl)oxazoline* **16**

1.0 g (3.6 mmol) of **14b**, 225 mg (3.6 mmol) of ethanolamine (dried over 4 Å molsieve) and conc. HCl (1 drop) in dry chlorobenzene (20 ml) were stirred at 80°C for 70 h with a gentle stream of nitrogen bubbling through. Purification by flash chromatography (SiO_2, 6.5×3 cm, CH_2Cl_2) followed by kugelrohr distillation at 250°C/1 torr yielded the oxazoline which solidified upon cooling. After recrystallisation from PE (3 ml) 440 mg (43%) of **16** was obtained. White solid, R_f=0.05 (CH_2Cl_2), m.p. 97–100°C. ^{1}H NMR (250 MHz, $CDCl_3$); δ=0.71 (d, ^3J=6.9 Hz, 3H, *H-9* or *H-10*), 0.81 (d, ^3J=6.9 Hz, 3H, *H-10* or *H-9*), 0.88 (d, ^3J=6.5 Hz, 3H, *H-7*), 0.95–1.40 (m, 4H, *H-6*, *H-2*, *H-5*, *H-8*), 1.50 (m, 1H, *H-1*), 1.59–1.94 (m, 4H, *H-4*, *H-5'*, *H-6'*, *H-2'*), 2.86 (dt, ^3J=11.5 Hz, ^3J=3.4 Hz, 1H, *H-3*), 4.11 (t, ^3J=9.5 Hz, 2H, N–C*H*$_2$), 4.51 (t, ^3J=9.5 Hz, 2H, O–C*H*$_2$), 7.23 (dd, ^3J=7.9 Hz, ^4J=1.2 Hz, 1H, Py–*H-5*), 7.67 (t, ^3J=7.9 Hz, 1H, Py–*H-4*), 7.84 (dd, ^3J=7.9 Hz, ^4J=1.2 Hz, 1H, Py–*H-3*). ^{13}C NMR (62.9 MHz, $CDCl_3$); δ=15.8/21.4 (*C-9* and *C-10*), 22.4 (*C-7*), 24.6 (*C-5*), 28.1 (*C-8*), 32.9 (*C-1*), 35.0 (*C-6*), 43.7 (*C-2*), 46.5 (*C-4*), 50.1 (*C-3*), 55.1 (Ox–N*C*H$_2$), 68.1 (Ox–O*C*H$_2$), 121.3 (Py–*C-3*), 123.3 (Py–*C-5*), 136.4 (Py–*C-4*), 146.3 (Py–*C-2*), 164.3 (*C*=N), 166.3 (Py–*C-6*). MS (EI); *m/z* (%)=286 (23) [M$^+$], 271 (21) [M$^+$−CH$_3$], 243 (80) [M$^+$−C$_3$H$_7$], 229 (69), 217 (21), 175 (100), 164 (24), 162 (29), 149 (43), 136 (24), 104 (27). IR (KBr); ν (cm^{-1})=2950/2915 s, 2865/2840 m (*C–H*), 1645 s (*C=N*). Optical rotation (c=1.1, $CHCl_3$); [α]$_D^{22}$=+52, [α]$_{578}^{22}$=+56, [α]$_{546}^{22}$=+65, [α]$_{436}^{22}$=+117, [α]$_{365}^{22}$=+215. $C_{18}H_{26}N_2O$ (286.42): calcd C 75.48; H 9.15; N 9.78, found C 75.04; H 8.96; N 9.60%.

*4.22. (+)-(η^4-1,5-Cyclooctadiene)[(4*S*)-benzyl-2-(6-*D*-menthylpyridin-2-yl)oxazoline-*N,N′*]rhodium(I)-hexafluorophosphate* **18**

To a stirred solution of **15b** (325 mg, 0.86 mmol) in dry CH_2Cl_2 (5 ml) were added 212 mg (0.43 mmol) of [Rh(cod)Cl]$_2$ in CH_2Cl_2 (5 ml) under nitrogen. The resulting yellow solution was stirred for 1.5 h, then solid NH_4PF_6 (210 mg, 1.3 mmol) was added. After stirring for another 1.5 h, the inorganic salts were filtered off and rinsed with CH_2Cl_2 (3×2 ml). The orange filtrate was evaporated and the residue dissolved in benzene/PE. After cooling to −20°C for 24 h 400 mg (0.55 mmol, 64%) of **18** were collected. Orange solid, m.p. >120°C (dec.). ^{1}H NMR (250 MHz, $CDCl_3$); δ=0.65–2.50 (m, 26H, men–*H* and cod–C*H*$_2$),

2.83 (dd, ^2J=13.7 Hz, ^3J=7.0 Hz, 1H, CH_AH$_B$Ph), 2.90–2.95 (m, 1H, *H-3*?), 2.99 (dd, ^2J=13.7 Hz, ^3J=4.8 Hz, 1H, CH$_A$$H_B$Ph), 3.85–4.15 (m, 2H, cod–C*H*), 4.48–4.80 (m, 1H, Ox–C*H*?), 4.67 (dd, ^2J=9.3 Hz, ^3J=3.6 Hz, 1H, Ox–CH_ZH$_E$?), 4.81 ('t', ^2J=^3J≈9.3 Hz, 1H, Ox–CH$_Z$$H_E$?), 7.18–7.35 (m, 5H, Ph–*H*), 7.64 (dd, ^3J=8.0 Hz, ^4J=1.4 Hz, 1H, Py–*H-3* or *H-5*), 7.72 (dd, ^3J=7.6 Hz, ^4J=1.4 Hz, 1H, Py–*H-5* or *H-3*), 8.07 (dd, ^3J=8.0 Hz, ^3J=7.6 Hz, 1H, Py-*H-4*). ^{13}C NMR (62.9 MHz, $CDCl_3$); δ=16.1/21.2 (*C-9* and *C-10*), 22.2 (*C-7*), 24.9 (*C-5*), 28.3 (*C-8*), 29.5/31.4 (cod–CH_2), 31.9 (*C-1*), 34.6 (*C-6*), 41.4 (CH_2Ph), 42.8 (*C-2*), 48.6 (*C-4*), 49.3 (*C-3*), 61.9 (Ox–CH), 76.0 (Ox–CH_2), 79.2–81.0/83.4–84.4 (br, cod–CH), 124.1 (Py–*C*), 127.5 (*p*-Ph–*C*?), 127.8 (Py–*C*?), 128.7/130.1 (*o*- and *m*-Ph–*C*), 135.1 (*qC* of Ph), 141.0 (Py–*C*), 143.7 (Py–*C-2*), 169.5 (Py–*C-6*), 171.1 (*C*=N). MS (FD, CH_2Cl_2); *m/z*=587 [Rh(cod)**15b**$^+$]. IR (KBr): ν (cm^{-1})=2945/2915 s, 2860 m (CH), 1645 w (C=N), 890 vs, 555 s (PF). Specific rotation (c=1.1, $CHCl_3$); $[\alpha]_D^{22}$=+93, $[\alpha]_{578}^{22}$=+101, $[\alpha]_{546}^{22}$=+123. $C_{33}H_{44}F_6N_2OPRh \cdot H_2O$ (750.61): calcd. C 52.81; H 6.18; N 3.73, found C 52.94; H 6.30; N 3.58%.

4.23. *Asymmetric hydrosilylation of acetophenone*

10 mg (0.02 mmol) of $[Rh(cod)Cl]_2$ (0.04 mmol Rh) and ligand (0.2 mmol, if not otherwise stated) were dissolved in acetophenone (1.0 ml, 8.5 mmol) under argon. 2.0 ml of CCl_4 were added and the solution was stirred at rt for 30 min (if $AgBF_4$ was added, stirring was continued for another 30 min). After cooling to 0°C for 30 min diphenylsilane (1.6 ml, 8.6 mmol) was added and stirring in the ice bath which was warming up was continued for the period quoted.

To determine the amount of silylenol ether [**III/(II+III)**], the conversion of acetophenone (i.e. the degree of hydrosilylation) [**(II+III)/(I+II+III)**] and the chemical yield of silylalkyl ether [**II/(I+II+III)**], a sample was taken and a ^{1}H NMR spectrum ($CDCl_3$, 80 MHz) was recorded. The following integrals were used for analysis: δ=5.70 ppm (s, Si–*H*, silylenol ether=I_E), δ=5.40 (s, Si–*H*, silylalkyl ether=I_A), and δ=2.50 (s, C*H*$_3$, acetophenone=I_{AP}).

Calculations:

$$\mathrm{III}/(\mathrm{II}+\mathrm{III})[\%] = \frac{\mathrm{IE}}{\mathrm{IA}+\mathrm{IE}}100$$

$$(\mathrm{II}+\mathrm{III})/(\mathrm{I}+\mathrm{II}+\mathrm{III})[\%] = \frac{3\mathrm{IE}+3\mathrm{IA}}{3\mathrm{IA}+3\mathrm{IE}+\mathrm{IAP}}100$$

$$\mathrm{II}/(\mathrm{I}+\mathrm{II}+\mathrm{III})[\%] = \frac{3\mathrm{Ia}}{3\mathrm{Ia}+3\mathrm{Ie}+\mathrm{Iap}}100 \text{ (reproducibility } \pm 5\%)$$

Hydrolysis was performed by adding methanol (10 ml) and a few crystals of *p*-TosOH. After stirring at rt for 30 min the solvents were evaporated and the residue was distilled in a kugelrohr apparatus at 100–120°C/ca. 1 torr. The enantiomeric excess was determined by injecting 0.4 μl of the diluted distillate (3–4 drops in 1 ml of CH_2Cl_2) into a Fisons 8130 gas chromatograph (reproducibility ±0.5%). Column: Chrompack Chirasil-DEX CB (l=25 m, ∅=0.25 mm), integrator: Varian 4290, retention times (118°C): 7.3–7.7 min [(*R*)-1-phenylethanol] and 8.0–8.3 min [(*S*)-1-phenylethanol].

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16. Since (+)-pinocarvone was prepared from (−)-α-pinene (ca. 80% *ee*) 10% of the other enantiomer was present. Hence, after synthesis of the chiral oxazoline **9** there might be a mixture of diastereomers.
17. In this paper L-menthyl- represents [(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]- and D-menthyl- represents [(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl]-.
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