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Asymmetric Synthesis and Absolute Configuration of (+)- and (–)-Perhexiline

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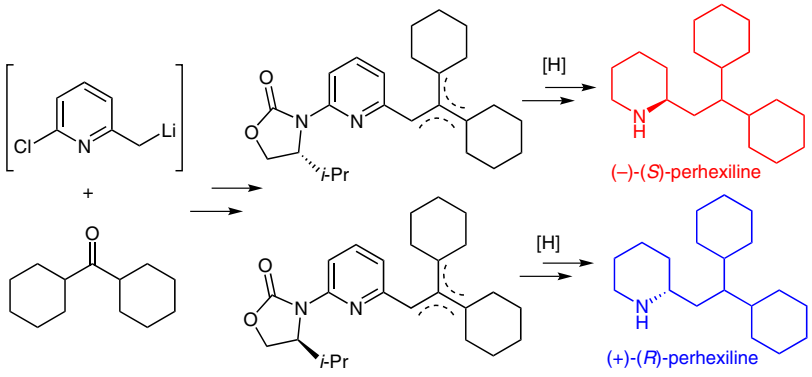
This work is dedicated to Professor Iwao Ojima on the occasion of his 70th birthday.



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Abstract Racemic perhexiline has been used (or is currently undergoing clinical trials) for the treatment of a variety of cardiovascular disorders. Increasing evidence suggests that the (–)-enantiomer should be used, as opposed to the racemic mixture. Here, we report the first asymmetric synthesis of both enantiomers of perhexiline in high enantiomeric excess and the assignment of their (–)-*S*/(+)-*R* absolute stereochemistry by X-ray crystallography.

Key words perhexiline, asymmetric synthesis, stereochemistry, medicinal chemistry, crystal structure

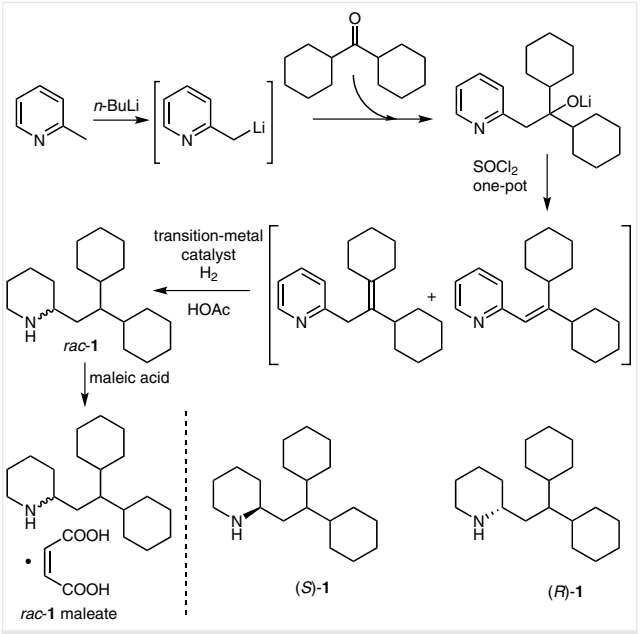
Cardiovascular diseases are the leading cause of death in the developed world and they are now also one of the leading causes of death in the developing world. Among cases of heart failure (HF), systolic HF can be treated pharmacologically by a number of therapeutic agents, such as loop diuretics, β-blockers, and inhibitors of angiotensin-converting enzyme. In contrast, diastolic HF currently has no effective treatments, and its prognosis is comparable to that of systolic HF.[1a] Clinical trials of perhexiline in systolic HF[1b] and hypertrophic cardiomyopathy[1c] have shown excellent efficacy, and perhexiline is currently in Phase II clinical trials for the treatment of diastolic HF (NCT00839228).

Perhexiline was originally designed as an antianginal drug, and was launched on the UK market in 1975 under the trade name Pexid, as a racemic mixture of the maleate salt; however, it was withdrawn in 1985, owing to serious side-effects, including neuro- and hepatotoxicity. Currently, racemic perhexiline maleate is still used as an antianginal drug in Australia and New Zealand, where it is administered under strict medical surveillance. The drug is highly efficacious in many cardiac contexts in which alternative treatments have failed.[2] However, the primary route of metabolism for perhexiline is via CYP2D6,[3a] a member of the cytochrome P450 oxidase system for which many polymorphisms exist. The rate of perhexiline clearance can vary 100-fold between patients; consequently, it is unlikely that racemic perhexiline could ever be reintroduced for clinical use outside a controlled and carefully monitored patient population. Perhexiline is believed to be an inhibitor of carnitine palmitoyltransferase-1 (CPT-1), and probably also of carnitine palmitoyltransferase-2 (CPT-2).[4] These enzymes are responsible for the transport of free mid- and long-chain fatty acids across mitochondrial cell membranes. Recent research has revealed the ability of perhexiline to alter myocardial metabolism from fatty acid to carbohydrate consumption, which improves substrate-utilization efficiency.[3a] As an effective CPT-1 inhibitor, perhexiline might also represent a potential candidate for use as an anticancer drug.[5–7]

It has long been known that the pharmacokinetic properties of the two enantiomers of perhexiline differ, and that (–)-perhexiline is more rapidly metabolized than (+)-perhexiline.[3] In addition, the two enantiomers have different metabolic fates and produce different metabolites.[8] It has recently been shown that (+)- and (–)-perhexiline also have different pharmacodynamic profiles, and it has been suggested that the (–)-enantiomer is primarily responsible for the therapeutic effects, whereas the (+)-enantiomer is primarily responsible for the toxic effects.[3] It has been proposed that the use of (–)-perhexiline, as opposed to the racemic mixture, might represent an important therapeutic strategy for the treatment of a number of cardiovascular conditions, which would not be restricted to limited patient populations or to use in clinical environments, thereby benefitting a wider patient population for a range of cardiovascular diseases (e.g., HF).

To the best of our knowledge, however, the absolute configuration of the (+)- and (–)-perhexiline enantiomers is unknown and no stereoselective synthesis of perhexiline has yet been reported.

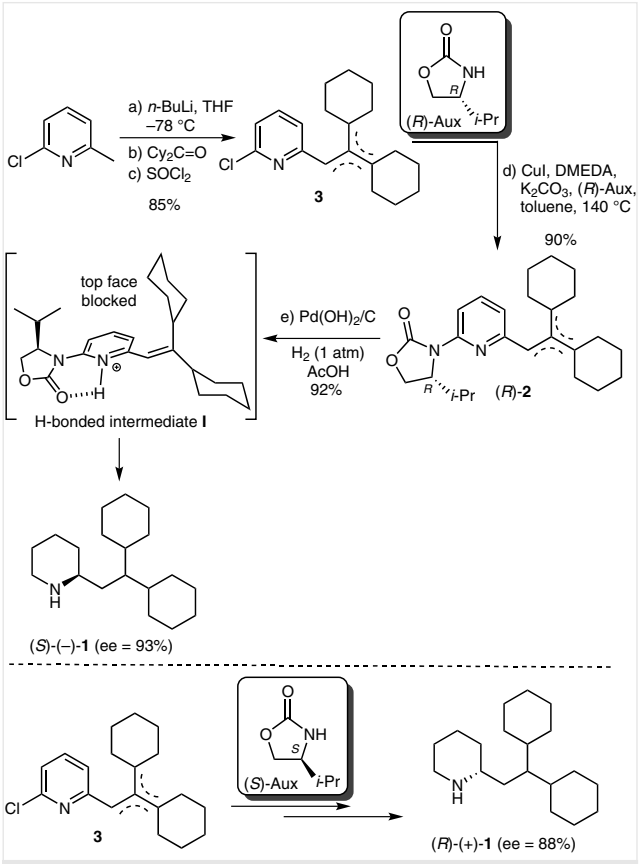
In terms of its structure, perhexiline consists of a piperidine framework with a 2,2-dicyclohexylethyl substituent at the 2-position (Scheme 1). The known synthesis of racemic perhexiline (*rac*-**1**) is based on nucleophilic addition of lithiated 2-picoline to dicyclohexyl ketone to give the corresponding tertiary lithium alkoxide, which undergoes thionyl chloride mediated elimination and subsequent full reduction catalyzed by a transition metal in an acidic reaction medium under a hydrogen atmosphere.[9]



Scheme 1 Previous synthesis of *rac*-perhexiline maleate salt (*rac*-**1** maleate), and the structures of the two enantiomers of perhexiline [(*S*)-**1** and (*R*)-**1**]

Optically enriched perhexiline has been hitherto obtained by resolution of the 1,1′-binaphthyl-2,2′-diyl(hydrogen)phosphate (BNPA) diastereomeric salts of perhexiline by a series of fractional crystallization processes.[8] (*S*)-(–)-Perhexiline [(*S*)-**1**] can be obtained by treatment of *rac*-perhexiline (*rac*-**1**) with (*S*)-(+)-BNPA, followed by crystallization from a methanol–acetone mixture, whereas the (+)-enantiomer (*R*)-**1** is prepared by resolution with (*R*)-(–)-BNPA. Although the two enantiomers are obtained with high optical purity by chiral resolution of *rac*-perhexiline, this process requires tedious iterative crystallization operations from the diastereomeric salts, which limits the availability of both enantiomers.

Here, we report an efficient and scalable synthesis of both enantiomers of perhexiline in high enantiomeric excess through a stereoselective catalytic hydrogenation of the 2-(oxazolidin-2-one)-substituted-pyridine **2** (Scheme 2) as a key precursor;[10–13] we also report the elucidation of the absolute configurations of the two enantiomers of perhexiline.



Scheme 2 Synthesis of (*S*)-(–)- and (*R*)-(+)-perhexilines [(*S*)-**1** and (*R*)-**1**, respectively] by asymmetric hydrogenation guided by an Evans chiral auxiliary

By addition of lithiated 6-chloro-2-picoline to dicyclohexylmethanone, followed by a one-pot elimination using thionyl chloride, we obtained the intermediate **3** (Scheme 2) as a 2:1 mixture of noninterconverting double-bond regioisomers, not separable by silica gel chromatography. In the sequence leading to (*S*)-perhexiline [(*S*)-**1**], the (*R*)-oxazolidinone was employed for Ullmann–Goldberg coupling[14,15] to afford the chiral pyridines (*R*)-**2** as a 2:1 ratio of regioisomers. Full reduction of the pyridine–oxazolidinone adducts (*R*)-**2** in acetic acid with one atmosphere of hydrogen in the presence of Pearlman's catalyst [$Pd(OH)_2$] gave the desired hydrogenation product **1**. We hypothesize that the stereocontrol stems from a rigid six-membered-ring intermediate **I** (Scheme 2), in which the orientation of the chiral auxiliary is rigidly defined by hydrogen bonding between its carbonyl group and the adjacent pyridinium nitrogen, leading to efficient shielding of one π-face. As a result, hydrogen atoms absorbed onto heterogeneous catalysts can be predominantly delivered from the face of the

isopropyl group opposite to the aromatic system. Based on a conformational analysis of the intermediate **I**, the (*R*)-auxiliary should result in a piperidine skeleton with an (*S*)-configuration. Polarimetric analysis showed *levo*-rotation indicating that the stereochemical assignment of this product is (*S*)-(–)-perhexiline [(*S*)-**1**] (70% overall yield, 93% ee.).[16] (*R*)-(+)-perhexiline [(*R*)-**1**] (68% overall yield, 88% ee) was then synthesized by using the corresponding (*S*)-chiral auxiliary, following the same protocol (Scheme 2).

A range of heterogeneous catalysts was evaluated for asymmetric hydrogenation of (*R*)-**2** as a model system to give enantiomerically enriched (*S*)-(–)-perhexiline **1** [(*S*)-**1**] (Table 1). Conventional palladium-, platinum- and rhodium-based heterogeneous catalysts were screened, and the progress of the hydrogenation was monitored by electrospray ionization mass spectrometry. Palladium and platinum catalysts were found to be effective, affording (*S*)-(–)-perhexiline [(*S*)-**1**] in good to excellent enantiomeric excess (Table 1, entries 1–4). Conversely, the rhodium/alumina-catalyzed hydrogenation (entry 5) was sluggish (>168 hours), and showed no improvement at a higher temperature. Note that (*R*)-**2** was reduced to the intermediate aminal **4** after 24 hours under one atmosphere of hydrogen at 23 °C in acetic acid, but the dissociation of the auxiliary from aminal **4** to give the iminium ion **5** and the subsequent hydrogenation of the C=N bond to give the desired product and the oxazolidinone required longer reaction times under these conditions.

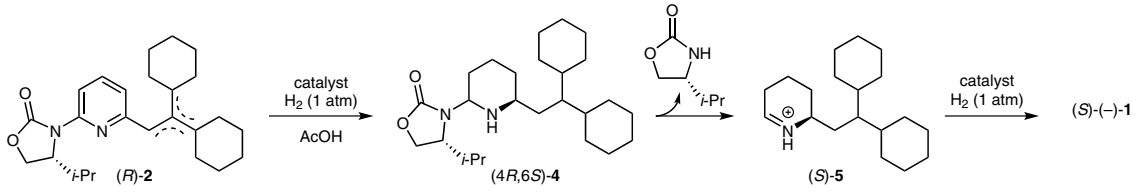
Palladium(II) hydroxide/carbon was found to be the optimal catalytic system for hydrogenation of the regioisomeric pyridine–oxazolidinone adducts **2**, giving perhexiline with high optical purity and yield. Treatment of (*R*)-**2** with palladium(II) hydroxide/carbon under one atmosphere of hydrogen in acetic acid at 23 °C for 24 h, followed by increasing the temperature to 65 °C, facilitated the formation of (*S*)-(–)-perhexiline [(*S*)-**1**] with no loss of stereoselectivity (Table 1, entry 4).

Having established the asymmetric hydrogenation profiles of the pyridine–oxazolidinone adducts **2**, we turned our attention to the synthesis of enantiomerically pure (*R*)-(+)-perhexiline [(*R*)-**1**] on a preparative scale by using adduct (*S*)-**2** (2.16 mmol) under the optimal conditions, namely 20 mol% palladium(II) hydroxide in acetic acid at 23 °C. Upon completion of the hydrogenation, hydrochloric acid was added to form the perhexiline hydrochloride, salt which was purified to afford (+)-perhexiline hydrochloride [(+)-**6**; 91% yield, 88% ee], with 85% recovery of the chiral auxiliary. Further crystallization of (+)-**6** from 1:1 dichloromethane–ethyl acetate gave 420 mg of (+)-perhexiline hydrochloride [(+)-**6**] (68% yield, 98% ee) as crystals suitable for X-ray structural analysis, which confirmed the (*R*)-absolute configuration of the (+)-enantiomer (Figure 1).[17]

The six-membered rings in the $C_{19}H_{36}N^+$ cation adopt chair conformations, with the linking bond in an equatorial orientation in each case. The C5–C6–C7–C8 link has an *anti*-orientation [torsion angle = 165.8 (3)°], whereas the C5–C6–C7–C14 link is *gauche* [–67.0 (3)°]. The C8–C13 ring is disordered over two orientations in a 0.814(5):0.186(5) ratio. In the extended structure, the chloride ions bridge the cations into [010] chains through N–H···Cl hydrogen bonds.

In conclusion, we have developed a practical and scalable asymmetric synthesis of both enantiomers perhexiline with excellent optical purities. The method involves a late-stage asymmetric hydrogenation of the 2-oxazolidinone-

Table 1 Screening of Heterogeneous Catalysts for Stereoselective Hydrogenation



Entry	Catalyst[a]	Time (h)	Yield[b] (%)	ee[c] (%)
1	$Pd(OH)_2/C$	96	92	93
2	PtO_2	72	85	87
3	Pd/C	60	62	90
4[d]	$Pd(OH)_2/C$	48	88	92
5[e]	Rh/Al_2O_3	>168	–	–

[a] Reaction conditions: catalyst loading: 2% metal-to-substrate ratio, AcOH, 23 °C, H_2 (1 atm).
[b] Isolated yield.
[e] Determined by chiral HPLC analysis of the *N*-benzoyl derivative **7**; HPLC conditions: ChiralPak IA, 4.6 × 250 mm, 5 µm, mobile phase: 2-propanol–hexane (3:97); flow rate: 0.6 mL/min; UV/vis detection: 220 nm.
[d] Reaction carried out at 23 °C for 24 h and then at 65 °C.
[c] Reaction carried out at 23 °C for 24 h and then at 80 °C.

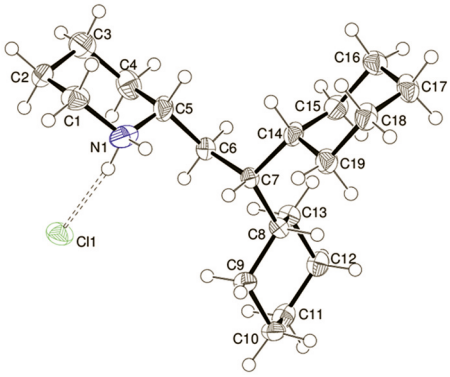


Figure 1 Molecular structure of (*R*)-(+)-perhexiline·HCl [(+)-**6**], showing 50% displacement ellipsoids. Only the major disorder component of the C8–C13 ring is shown.

substituted pyridines **2** catalyzed by active charcoal-supported palladium(II) hydroxide in acetic acid under one atmosphere of hydrogen, and traceless cleavage of the chiral auxiliary, which can be recycled. Furthermore, the (–)-(*S*) and (+)-(*R*) absolute configurations of the perhexiline enantiomers have been unambiguously assigned by X-ray crystallography.

All reactions were carried out under N_2 or argon in dry solvents under anhydrous conditions, unless otherwise mentioned. Solvents and reagents: Anhyd THF, Et_2O, CH_2Cl_2, and toluene were purchased from commercial suppliers. Reagents were purchased at the highest commercial quality, used without further purification, and handled in accordance with the COSHH health and safety regulations. Chromatography: Flash chromatography was carried out on silica gel (Merck silica gel Si 60, 40–63 µm), according to the method described by Still.[18] TLC was carried out on glass-based 0.25 mm Merck Millipore silica gel plates (60F-254) with development by UV irradiation (254 or 365 nm), aq $KMnO_4$ and ethanolic ammonium molybdate, or heat. ^{1}H NMR spectra: These were recorded at 400 MHz on a Bruker AVANCE III 400 instrument. Chemical shifts are given in ppm, referenced to the appropriate residual solvent peak. ^{13}C NMR spectra: These were recorded at 100.6 MHz on a Bruker AVANCE III 400 instrument. Chemical shifts are given in ppm, referenced to $CHCl_3$. HPLC: Analyses were carried out by using an Agilent Technologies 1200 Series HPLC system equipped with a DAD and a 6120 MS detector consisting of an ESI ionization source and a single quadrupole mass-selective detector [Column: analytic normal-phase ChiralPak IA (4.6 × 250 mm, 5 µm) chiral column (Daicel Chemical Industries Ltd); mobile phase: *i*-PrOH–hexane (3:97); flow rate: 0.6 mL/min; UV/vis detection: 220 nm]. Optical rotations: These were measured on an AA-65 Angular Scale automatic polarimeter (Optical Activity Ltd.) with a 1 dm cell at the sodium D line. IR spectra: These were recorded on a PerkinElmer Spectrum Two FT-IR spectrometer with a diamond ATR accessory. HRMS: Analyses were performed by using an LTQ Orbitrap XL MS spectrometer.

2-Chloro-6-(2,2-dicyclohexylvinyl)pyridine and 2-Chloro-6-(2-cyclohexyl-2-cyclohexylideneethyl)pyridine (3)

A 2.5 M solution of BuLi in hexanes (11 mmol, 4.4 mL) was added dropwise to a stirred solution of 2-chloro-6-methylpyridine (1.40 g, 11 mmol, 1.2 mL) in THF (15 mL) at –78 °C. The resulting red solution was stirred at –78 °C for 10 min then warmed to –10 °C for 20 min. The mixture was then cooled to –78 °C, and a solution of Cy_2CO (2.56 g, 13.2 mmol, 2.6 mL) in THF (2 mL) was added. The mixture was stirred at –78 °C for 30 min, then $SOCl_2$ (2.12 g, 17.8 mmol, 1.3 mL) was added. The milky mixture was warmed to 0 °C for 30 min and then the reaction was quenched with sat. aq NH_4Cl (10 mL). The mixture was diluted with EtOAc (20 mL), and the layers were separated. The organic layer was washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography [silica gel, hexanes–EtOAc (5:1)] gave a mixture of pyridines **3** as a white amorphous solid; yield: 2.87 g (85%, ~2:1 mixture of regioisomers by ^{1}H NMR).

IR (film): 2926, 2851, 1632, 1578, 1436, 1134, 188 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.43 (m, 1 H), 7.15–6.88 (m, 2 H), 6.21 (s, 0.6 H), 3.58 (s, 0.6 H), 3.17 (tt, *J* = 11.7, 3.1 Hz, 0.6 H), 2.68–2.55 (m, 0.3 H), 2.52–2.39 (m, 0.1 H), 2.35–2.23 (m, 0.6 H), 2.16–2.05 (m, 0.6 H), 2.05–1.99 (m, 0.6 H), 1.88–1.51 (m, 9 H), 1.50–0.99 (m, 10 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 163.4, 160.2, 158.4, 150.3, 150.2, 138.5, 138.2, 136.6, 129.9, 121.9, 121.6, 120.9, 120.5, 120.2, 49.1, 40.8, 40.7, 40.3, 36.4, 34.8, 31.7, 31.6, 30.5, 30.1, 28.6, 28.5, 28.0, 27.0, 26.9, 26.6, 26.24, 26.21, 26.1, 26.0, 25.8, 25.7.

MS (ESI): *m/z* = 304 [M(^{35}Cl) + H]$^+$.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{19}H_{27}{}^{35}ClN^+$: 304.1827; found: 304.1825 (Δ –0.5 ppm).

(*R*)-3-[6-(2,2-Dicyclohexylvinyl)pyridin-2-yl]-4-isopropyl-1,3-oxazolidin-2-one and (*R*)-3-[6-(2-Cyclohexyl-2-cyclohexylideneethyl)pyridin-2-yl]-4-isopropyl-1,3-oxazolidin-2-one [(*R*)-2]

These regioisomers were prepared by a modification of the method reported by Buchwald.[14] A flame-dried tube was charged with the mixture of pyridines **3** (751 mg, 2.47 mmol) in toluene (10 mL). (*R*)-(+)-4-isopropyl-2-oxazolidinone (2.96 mmol, 382.5 mg, 99% ee), CuI (141 mg, 0.74 mmol), *N*,*N*′-dimethylethane-1,2-diamine (99 mg, 1.13 mmol, 121 µL), and K_2CO_3 (683 mg, 4.95 mmol) were added to the stirred solution at 23 °C, and the tube was sealed. The resulting mixture was stirred and heated at 140 °C for 60 h, then cooled to 23 °C. The reaction was quenched with sat. aq NH_4Cl (10 mL), and the mixture was diluted with EtOAc (10 mL). The layers were separated and the organic layer was washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography [silica gel, hexanes–EtOAc (2:1)] gave the regioisomeric adducts (*R*)-**2** as a white amorphous solid; yield: 878 mg (90%, ~2:1 mixture of regioisomers by ^{1}H NMR).

IR (film): 2923, 2850, 1758, 1578, 1448, 1437, 1392, 1207, 1156, 796 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.78 (m, 1 H), 7.70–7.58 (m, 0.66 H), 7.58–7.53 (m, 0.35 H), 6.95–6.77 (m, 1 H), 6.15 (s, 0.66 H), 5.01–4.84 (m, 1 H), 4.45–4.31 (m, 1 H), 4.31–4.20 (m, 1 H), 3.55–3.39 (m, 1.33 H), 2.63–2.38 (m, 1.4 H), 2.28 (s, 0.66 H), 2.15–2.04 (m, 1.34 H), 1.85–1.51 (m, 9 H), 1.48–1.08 (m, 9.6 H), 0.97–0.86 (m, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.6, 158.8, 156.0, 155.6, 155.5, 149.5, 137.82, 137.77, 135.8, 130.8, 122.0, 119.8, 117.8, 111.6, 111.0, 62.9, 58.8, 58.7, 40.9, 40.3, 40.1, 36.5, 35.12, 35.09, 31.93, 31.87, 31.8, 30.22, 30.19, 28.6, 28.1, 27.67, 27.65, 27.1, 27.0, 26.74, 26.72, 26.67, 26.23, 26.21, 26.15, 26.0, 17.9, 17.8, 14.5, 14.4.

MS (ESI): *m/z* = 397 $[M + H]^+$.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{37}N_2O_2^+$: 397.2850; found: 397.2843 (Δ –1.6 ppm).

(*S*)-3-[6-(2,2-Dicyclohexylvinyl)pyridin-2-yl]-4-isopropyl-1,3-oxazolidin-2-one and (*S*)-3-[6-(2-Cyclohexyl-2-cyclohexylideneethyl)pyridin-2-yl]-4-isopropyl-1,3-oxazolidin-2-one [(*S*)-2]

Prepared by the same procedure as above by using 2-pyridines **3** (110 mg, 0.362 mmol), (*S*)-(–)-4-isopropyl-2-oxazolidinone (56.1 mg, 0.434 mmol, 98% ee), CuI (20 mg, 0.105 mmol), *N*,*N*′-dimethylethane-1,2-diamine (14 mg, 0.16 mmol, 17 μL), and K_2CO_3 (100 mg, 0.725 mmol) to give regioisomeric adducts (*S*)-**2** as a white amorphous solid; yield: 129 mg (90%, ~2:1 mixture of regioisomers by ^{1}H NMR). The analytical and spectroscopic data were identical to those of (*R*)-**2**.

(2*S*)-(–)-2-(2,2-Dicyclohexylethyl)piperidine [(*S*)-(–)-Perhexiline] [(*S*)-1]; Hydrogenation Procedure (Table 1, Entry 1)

This procedure is a modified version of the method reported by Glorius.[10] To a stirred solution of the pyridine–oxazolidinone adducts (*R*)-**2** (72 mg, 0.182 mmol) in AcOH (10 mL) was added 20% $Pd(OH)_2$/active charcoal (15 mg, ~50% H_2O; 2% catalyst-to-substrate by weight). The reaction vessel was charged with H_2 (1 atm), evacuated, and backfilled with H_2, and the mixture was stirred at 23 °C under an atmosphere of H_2. When the hydrogenation was complete (ESI-MS analysis), the mixture was filtered through a plug of Celite and flushed with MeOH (5 mL) and EtOAc (10 mL). The combined filtrates were neutralized with sat. aq $NaHCO_3$ until effervescence ceased. The layers were separated and the organic layer was washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography [silica gel, MeOH–CH_2Cl_2 (0:100 to 10:90)] gave a pale-yellow oil; yield: 46.4 mg (92%, 93% ee); $[\alpha]_D^{20}$ –6.1 (*c* 3.3, CH_2Cl_2). The ee value was determined by HPLC analysis of the corresponding benzamide derivative **7** (see below).

IR (film): 3258 (br), 2922, 2851, 1447, 1403, 1260, 1014, 894, 734, 704 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.00 (d, *J* = 10.9 Hz, 1 H), 2.54 (td, *J* = 11.7, 2.2 Hz, 1 H), 2.33 (dt, *J* = 10.3, 6.7 Hz, 1 H), 1.82–0.74 (m, 32 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 56.9, 47.4, 45.4, 40.0, 39.9, 36.6, 33.3, 31.8, 31.8, 29.9, 29.8, 27.03, 26.98, 26.8 (2 C), 26.70, 26.6, 26.6, 25.0.

MS (ESI): *m/z* = 278 $[M + H]^+$.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{36}N^+$: 278.2842; found: 278.2838 (Δ –1.4 ppm).

Table 1, Entry 2

(*R*)-**2** (60 mg, 0.151 mmol) and PtO_2 (1.2 mg, 2% w/w) were employed, following the procedure of entry 1 above, to give (*S*)-**1**; yield: 35.6 mg (85%, 87% ee).

Table 1, Entry 3

(*R*)-**2** (62 mg, 0.156 mmol) and dry 10% Pd/active charcoal (12 mg) were employed, following the procedure of entry 1 above, to give (*S*)-**1**; yield: 26.8 mg (62%, 90% ee).

Table 1, Entry 4

(*R*)-**2** (85 mg, 0.214 mmol) and wet 20% $Pd(OH)_2$/active charcoal (18 mg) were employed, following the procedure of entry 1, modified as follows. The suspended solution was stirred at 23 °C for 24 h under an atmosphere of H_2 before it was heated to 65 °C for 24 h. Purification by flash column chromatography [silica gel, MeOH–CH_2Cl_2 (0:100 to 10:90)] gave (*S*)-**1**; yield: 52.3 mg (88%, 92% ee).

Table 1, Entry 5

(*R*)-**2** (60 mg, 0.151 mmol) and 5% Rh/Al_2O_3 (24 mg) were employed, following the procedure of entry 1, modified as follows. The suspension was stirred at 23 °C for 24 h under an atmosphere of H_2 then heated to 80 °C (ESI-MS monitoring). The majority of products were found to be partially hydrogenated, and no further progress was made after stirring at 80 °C for over 144 h.

(*R*)-(+)-Perhexiline [(*R*)-1]

This was prepared by the same method as described above for preparing (*S*)-**1**, but using (*S*)-**2** (55 mg, 0.139 mmol) and wet 20% $Pd(OH)_2$ on active charcoal (11 mg). Purification by flash column chromatography [silica gel, MeOH–CH_2Cl_2 (0:100 to 10:90)] gave a pale-yellow oil; yield: 34.6 mg (90%, 88% ee); $[\alpha]_D^{20}$ +5.3 (*c* 3.4, CH_2Cl_2). The analytical and spectroscopic data were identical to those for (*S*)-**1**.

(2*R*)-(+)-2-(2,2-Dicyclohexylethyl)piperidine hydrochloride [(*R*)-(+)-Perhexiline Hydrochloride] (6)[8]

This was prepared by the same method as that described previously for preparing (*S*)-**1**, using (*S*)-**2** (857 mg, 2.16 mmol) and wet 20% $Pd(OH)_2$ on active charcoal (172 mg) in AcOH (25 mL). The reaction was monitored by ESI-MS analysis until hydrogenation was complete. The mixture was filtered through a plug of Celite and flushed with MeOH (3 × 10 mL). The collected filtrates were combined, mixed with 12 N aq HCl (0.36 mL), and concentrated in vacuo until no AcOH remained. Flash column chromatography [silica gel, hexanes–EtOAc (50:50 to 0:100)] gave (*S*)-(–)-4-isopropyl-2-oxazolidinone (237 mg, 85%) as a white solid. Further elution with EtOH–CH_2Cl_2 (10:90 to 20:80) gave **6** as a pale-yellow solid; yield: 617 mg (91%, 88% ee). This was crystallized from 1:1 CH_2Cl_2–EtOAc to give white needle crystals; yield: 420 mg (68%, 98% ee); mp 233–235 °C; $[\alpha]_D^{20}$ +17.6 (*c* 2.4, EtOH) {Lit.[8] $[\alpha]_D^{24}$ +18.2 (*c* 2.78, EtOH)}.

IR (film): 3391 (br), 2922, 2850, 2709, 2499, 1447, 1268, 732, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (br s, 1 H, NH), 9.13 (br s, 1 H, NH), 3.76–3.06 (m, 1 H), 3.04–2.55 (m, 2 H), 2.17–0.77 (m, 31 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 57.4, 44.9, 44.8, 40.0, 39.1, 32.3, 31.9, 31.4, 30.0, 29.5, 28.4, 27.0, 26.9, 26.7, 26.7, 26.49, 26.47, 22.5, 22.3.

Crystal structure:[17] $C_{19}H_{36}ClN$, M_r = 313.94, orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 6.19730(10) Å, *b* = 10.8191(2) Å, *c* = 27.3890(6) Å, *V* = 1836.41(6) Å^3, *Z* = 4, *T* = 100 K; absolute structure parameter = 0.13(8); 3411 reflections, 216 parameters, *R*(*F*) = 0.048, *wR*(F^2) = 0.127.

(±)-1-Benzoyl-2-(2,2-dicyclohexylethyl)piperidine (*rac*-7)

BzCl (23 mg, 0.164 mmol, 19 μL), DMAP (1 mg, 0.01 mmol), and Et_3N (36 mg, 0.359 mmol, 50 μL) were added to a stirred solution of *rac*-perhexiline (30 mg, 0.108 mmol) in CH_2Cl_2 (2 mL) at 0 °C, and the mixture was stirred at 0 °C for 16 h. The reaction was then quenched with sat. aq NH_4Cl (5 mL), and the mixture was diluted with EtOAc (10 mL). The layers were separated and the organic layer was washed

with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography [silica gel, hexanes–EtOAc (3:1)] gave a colorless oil; yield: 39 mg (95%).

IR (film): 2921, 2850, 1627, 1578, 1445, 1423, 1272, 1011, 784, 732, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.27 (m, 5 H), 4.97 (br s, 0.5 H), 4.58 (br s, 0.5 H), 3.89 (br s, 0.5 H), 3.50 (br s, 0.5 H), 3.14 (br s, 0.5 H), 2.90 (br s, 0.5 H), 1.86–0.66 (m, 31 H); rotamers were present at 298 K.

MS (ESI): *m/z* (%) = 382 $[M + H]^+$.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{40}NO^+$: 382.3104; found: 382.3106 (Δ +0.4 ppm).

(2*S*)-(–)-1-Benzoyl-2-(2,2-dicyclohexylethyl)piperidine [(*S*)-(–)-7]

This was prepared by the same method as described above for preparing *rac*-**7**, using (*S*)-perhexiline (42 mg, 0.151 mmol), BzCl (32 mg, 0.23 mmol, 27 µL), DMAP (1 mg, 0.01 mmol), and Et_3N (51 mg, 0.504 mmol, 70 µL) to give a colorless oil; yield: 55 mg (95%); $[\alpha]_D^{23}$ –34.7 (*c* 2.6, CH_2Cl_2). Spectroscopic data were identical to those for *rac*-**7**.

(2*R*)-(+)-1-Benzoyl-2-(2,2-dicyclohexylethyl)piperidine [(*R*)-(+)-7]

This was prepared by the same method as described above for preparing *rac*-**7**, using (*R*)-perhexiline (30 mg, 0.108 mmol), BzCl (23 mg, 0.164 mmol, 19 µL), DMAP (1 mg, 0.01 mmol), and Et_3N (36 mg, 0.359 mmol, 50 µL) to give a colorless oil; yield: 38 mg (92%); $[\alpha]_D^{23}$ +31.3 (*c* 1.5, CH_2Cl_2). Spectroscopic data were identical to those for *rac*-**7**.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560708.

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(16) Because perhexiline **1** is not UV-detectable, the enantiomeric excesses of perhexiline samples were determined by chiral HPLC analysis of the corresponding UV-detectable benzamide derivatives **7**. See the experimental section for details on the preparation of **7** from perhexiline.

(17) Crystallographic data for compound **6** have been deposited with the accession number CCDC 1057017, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.

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