Asymmetric Catalysis; 140:[1] Tris(2-pyridyl)methane Derivatives with a Chiral Bridging Atom

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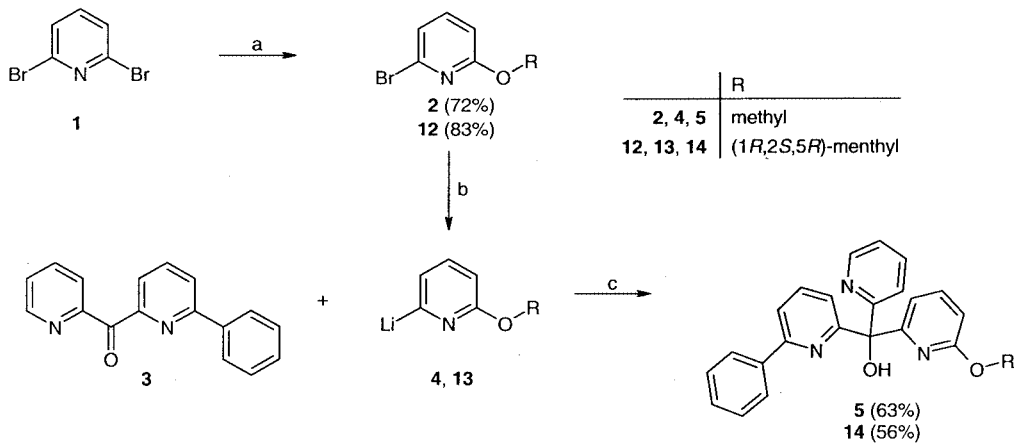
Abstract: Two different series of C_1-symmetric tris(2-pyridyl)methane tripod ligands were synthesized with pyridin-2-yl, 6-phenylpyridin-2-yl and 6-methoxy- or 6-menthyloxypyridin-2-yl substitutents. The menthoxy devivatives were resolved with respect to the bridging carbon atom by chromatography. In reactions with $CuCl_2$ and $RhCl_3$ complexes were obtained which could be analyzed by X-ray crystallography. In the formation of the Rh complex an *ortho*-metallation of the 6-phenyl substituent occurred giving rise to a Δ/Λ-element of chirality. Whereas the chiral tripod ligand conferred a stable configuration to the Rh atom, a fast equilibration of the Δ- and Λ-isomers was observed.

Key words: chiral tripod ligands, tris(2-pyridyl)methane derivatives, Cu-complex, Rh-complex, *ortho*-metallation, absolute configuration

Introduction

There are two different types of tridentate ligands. Either the ligand is flat and coordinates in a *mer*-fashion at an octahedron or the ligand is tripodal and coordinates in a *fac*-fashion at an octahedron. Chiral examples are the pybox ligand introduced by Nishiyama et al.[3] (*mer*-type) and the trisphosphane ligands of Burk et al.[4] and Huttner et al.[5] (*fac*-type). Tris(pyrazolyl)borates are well known trisnitrogen ligands which coordinate facially to transition metals. Their analogues are tris(2-pyridyl) compounds, in which the bridging atom can be carbon, nitrogen, phosphorus or arsenic.[6] There are major differences between tris(pyrazolyl)borate and tris(2-pyridyl)methane tripods. The tris(pyrazolyl)borates are monoanionic, whereas the tris(2-pyridyl)methane ligands are neutral. Furthermore, pyridine is more basic than pyrazole, thus it should be a better σ-donor and it is reported to be a better π-acceptor than pyrazole.[7] Chiral C_3-symmetric tris(pyrazolyl)borates[8] and tris(2-pyridyl)methane derivatives[9] are known, but only few C_1-symmetric tripods are mentioned in the literature[10] and no C_1-symmetric tris(2-pyridyl) derivatives have been reported. Therefore, we synthesized tris(2-pyridyl) derivatives, in which a carbon atom bridges three different pyridine substituents, an unsubstituted 2-pyridine, a 6-methoxy- or 6-menthoxy-substituted 2-pyridine and a 6-phenyl-substituted 2-pyridine.[11] Some of the compounds were resolved with respect to the configuration of the bridging carbon atom.[11] As in a facial coordination, a tripod ligand with a chiral bridging atom confers chirality to the metal centre, this stereochemical aspect was investigated in Cu and Rh complexes.[11] According to a concept recently presented in this journal,[12] chiral C_1-symmetric tris(2-pyridyl) ligands should provide enanti-



Scheme 1 (a) CH_3ONa, CH_3OH, reflux/ (1*R*,2*S*,5*R*)-(–)-menthol, NaH, 90 °C; (b) *n*-BuLi, THF, –60 °C/ *n*-BuLi, THF, –78 °C; (c) 1. CH_3OH, –78 °C → r.t., 2. H_2O, HCl, 3. K_2CO_3.

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oselective catalysts, in which the configuration at the metal atom is held constant throughout the catalysis.

Racemic Tris(2-pyridyl)methane Derivatives

For the preparation of tris(2-pyridyl)methane derivatives with a chiral branching atom the commercially available 2-phenylpyridine was converted into 2-bromo-6-phenylpyridine via 2-amino-6-phenylpyridine.[13] The ketone **3** was accessible by addition of the lithiopyridine derivative obtained from 2-bromo-6-phenylpyridine to pyridine-2-carbonitrile. After a lithium-bromine exchange in 2-bromo-6-methoxypyridine[14] **2** (prepared from 2,6-dibromopyridine **1**) the resulting organometallic compound **4** was added to the ketone **3** to give the racemic tris(2-pyridyl)methanol derivative **5** (Scheme 1).

For the resolution of *rac*-**5** the formation of diastereomeric salts with the chiral acids (1*S*)-(+)-camphorsulfonic acid, (2*R*,3*R*)-(+)-tartaric acid, (2*R*,3*R*)-(–)-dibenzoyltartaric acid, (*R*)-(–)-mandelic acid, (*S*)-(–)-malic acid and (*R*)-(+)-4-(2-chlorophenyl)-2-hydroxy-5,5-dimethyl-1,3,2-dioxophosphorane-2-oxide was attempted without success.[11] Therefore, the chiral auxiliaries were covalently bound to **5** by esterification with (1*R*,2*S*,5*R*)-menthoxy- and (1*S*,2*R*,4*S*)-borneoxyacetic acid, respectively. These acids were prepared and transformed to the acid chlorides according to literature methods[15,16] and reacted with deprotonated **5** (*n*-butyllithium) to give 81% and 54% of the diastereomeric esters **6** and **7**, respectively (Figure 1).

The esters **6** and **7** were obtained as 1:1 mixtures of diastereomers differing in the configuration of the branching carbon atom of the tris(2-pyridyl)methane moiety. They are crystalline substances, which could be recrystallized from petroleum ether and diisopropyl ether. However, repeated recrystallizations did not result in an enrichment of one diastereomer. Therefore, the alcohol functionality was separated from the bridgehead atom by a methylene group. The alcohol **5** was transformed to the bromide **8** by deprotonation with *n*-BuLi and reaction with thionyl bromide. Lithium-bromine exchange and reaction with paraformaldehyde gave the 2,2,2-tris(2-pyridyl)ethanol derivative **9** with 79% yield (Scheme 2).

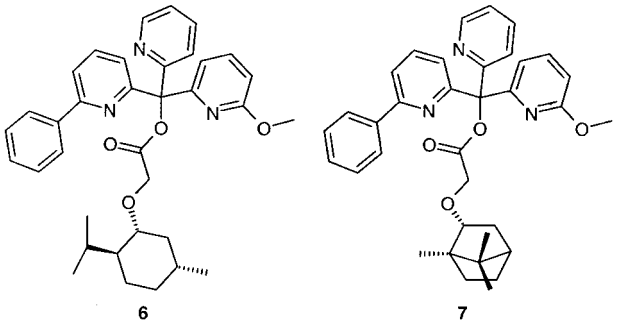
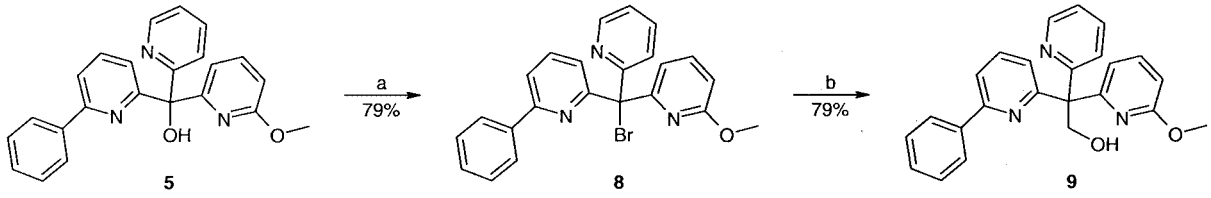
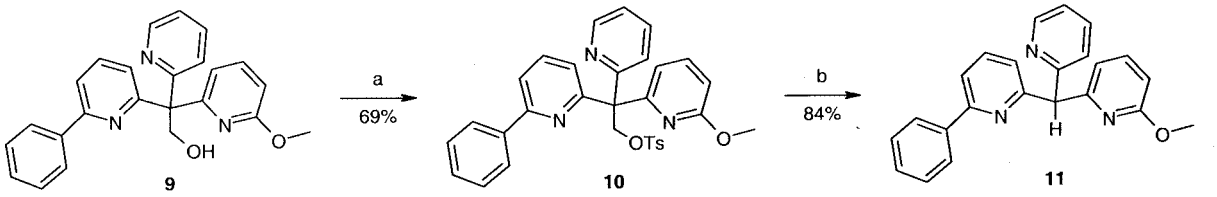


Figure 1

The ethanol derivative **9** could be transformed to the tosylate **10**. Surprisingly, the reaction of **10** with sodium methoxide in methanol did not liberate the alcohol **9** but afforded the methane derivative **11** in 84% yield (Scheme 3). Carboxylates including (1*R*,2*S*,5*R*)-menthoxyacetate and (1*S*,2*R*,4*S*)-borneoxyacetate gave the same product, as did alkoxides (e.g. sodium menthoxide) and sodium hydride in toluene at 70 °C. In the literature such a loss of formaldehyde has been reported for 2,2,2-trisphenylethanol but not for the analogous trispyridinethanol.[17,18] The conversion of the ethyl alcohol **9** to the corresponding ethyl bromide derivative could be performed by refluxing in a solution of thionyl bromide in chloroform.[11]



Scheme 2 (a) 1. *n*-BuLi, THF, r.t., 2. $SOBr_2$, –70 °C → r.t.; (b) 1. *n*-BuLi, Et_2O, –90 °C, 2. paraformaldehyde, –90 °C → r.t., 3. H_2O.



Scheme 3 (a) TsCl, py, r.t., 60 h; (b) CH_3ONa, CH_3OH, reflux, 14 h.

Diastereomeric Tris(2-pyridyl)methane Derivates

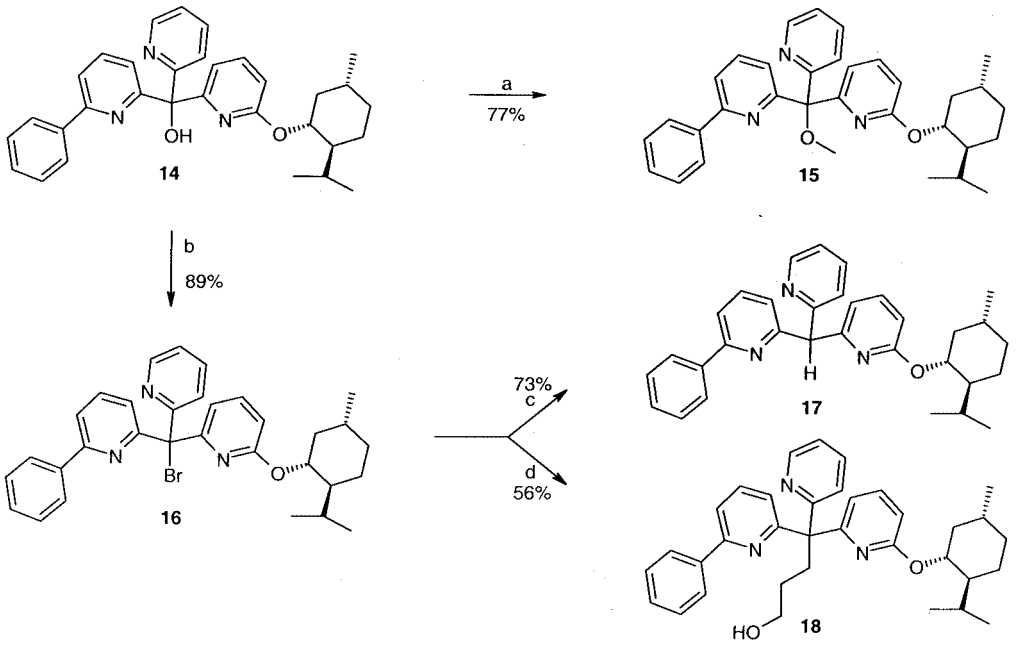
Another possibility for the formation of diastereomeric tris(2-pyridyl)methane derivatives is to introduce one pyridyl group, which is substituted with a chiral substituent. The (1*R*,2*S*,5*R*)-menthyl group was chosen for this purpose. (1*R*,2*S*,5*R*)-Menthol was deprotonated with sodium hydride and reacted with 2,6-dibromopyridine **1** to afford the menthoxy substituted bromopyridine **12** in 83% yield. After lithium-bromine exchange in **12** to give **13**, reaction with the ketone **3** gave the tris(2-pyridyl)methanol derivative **14** (Scheme 1). The diastereomers of **14** are formed as a 1:1 mixture. By repeated chromatography on silica gel it was possible to enrich the faster moving isomer to a ratio of 98:2.

The alcohol **14** is the key intermediate for the subsequent syntheses. Deprotonation of **14** with sodium hydride followed by addition of methyl iodide gave the methyl ether **15**. In this reaction no epimerization took place since the diastereomeric excess of **14** was retained in **15**. The conversion of the alcohol **14** to the bromomethane **16** was performed with thionyl bromide. As the diastereomeric excess of the alcohol **14** was almost completely lost in the reaction to the bromide **16** a S_Ni retention mechanism must be excluded. White and Faller proposed either a S_N2 or a S_N1 mechanism for the halogenation of tris(2-pyridyl)methanol with SOX_2 (X = Br, Cl).[19] The reaction of **16** with *n*-BuLi led to an organometallic intermediate which could either be hydrolyzed with water to give the methane derivative **17** (73%) or treated with oxetane in the presence of an equimolar amount of $BF_3{\cdot}OEt_2$ to provide the 4,4,4-tris(2-pyridyl)butan-1-ol derivative **18** with 56% yield (Scheme 4).

For both alcohols **14** and **18** the diastereomers could be enriched by chromatography, but only the butanol derivative **18** was used subsequently, because it was configurationally stable at the branching carbon atom. Repeated chromatography of **18** on silica gel gave a 95:5 enrichment of the faster moving diastereomer. An X-ray analysis of a rhodium complex of **18** (see below) allowed the assignment of (*S*)-configuration at the bridging atom of the faster moving isomer. The propyl substituent with its terminal OH group at the end in **18** has two major advantages. First, **18** can be modified to adjust the solubility without changing the complexation properties of the tris(2-pyridyl) moiety, and second, the ligand can be heterogenized by covalent binding to a solid phase.

Metal Complexes

From the racemic methane derivative **11** the $CuCl_2$ complex **19** was prepared in methanol in 72% yield. Exclusion of air is important, because the literature reports an example in which a methane derivative was air-oxidized to the corresponding methanol derivative.[20] Diffusion of ether into a methanolic solution of **11** and $CuCl_2$ gave green crystals of **19** suitable for X-ray analysis. In addition to the two chloride ligands the copper(II) centre is chelated by ligand **11** in a bidentate way (Figure 2). Copper(II) complexes in which a tris(2-pyridyl)methane derivative coordinates as a tripod ligand are also known.[20,21] The uncoordinated methoxy-substituted pyridine ring is rotated by 28° relative to the Cu1-C12-C13 plane. The structure can be described as distorted square planar. In the unit cell there are two pairs of enantiomers.



Scheme 4 (a) 1. NaH, DMF, r.t. 2 h, 2. CH_3I, r.t.; (b) 1. *n*-BuLi, Et_2O, –78 °C; 2. $SOBr_2$, –78 °C à r.t., 3. $NaHCO_3$; (c) 1. *n*-BuLi, Et_2O, –90 °C → r.t., 2. H_2O; (d) 1. *n*-BuLi, Et_2O, –90 °C, 2. oxetane, $BF_3{\cdot}OEt_2$, –90 °C → r.t., 3. H_2O, HCl, 4. K_2CO_3.

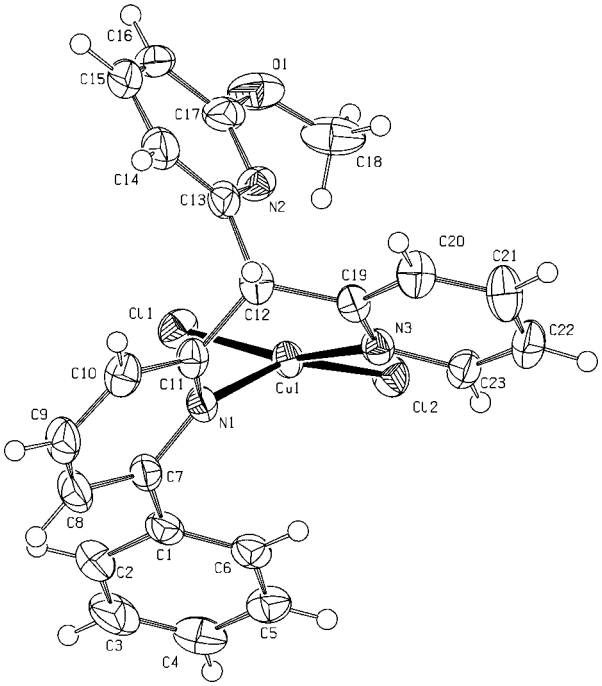


Figure 2 ORTEP representation (50% probability) of **19**. Selected distances [Å] and angles [°]: Cu1-Cl1 2.24, Cu1-Cl2 2.27, Cu1-N1 2.03, Cu1-N3 2.03, Cl1-Cu1-Cl2 94, Cl1-Cu1-N1 93, Cl1-Cu1-N3 161, Cl2-Cu1-N1 155, Cl2-Cu1-N3 95, N1-Cu1-N3 87.

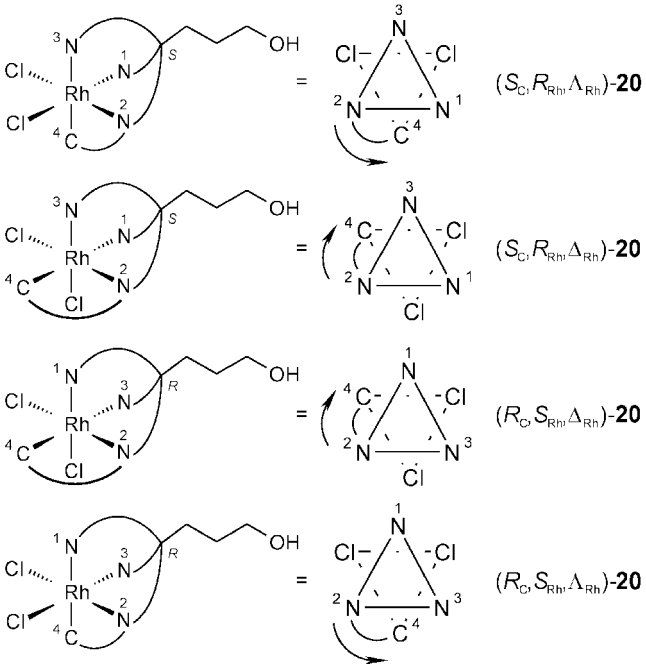


Figure 3 Schematical representation of all possible diastereomers of **20**.

The rhodium complex **20** was synthesized from rhodium(III) chloride trihydrate and the butanol derivative **18** in ethanol. If a 65:35 mixture of the two diastereomers of **18** (the faster moving diastereomer in excess) is used, the ^{1}H NMR spectrum of the complex **20** exhibits four signals with the chemical shifts in DMSO-d_6 of 9.25, 9.32, 9.55 and 9.62 ppm (integration 62:32:2:4) for the downfield proton py-H^6. This means that in solution four diastereomers are present. The X-ray analysis of **20** (see below) shows that in its formation an *ortho*-metallation has taken place. In addition to the two asymmetric centres (bridgehead atom of the ligand and metal atom) the *ortho*-metallation establishes a new element of chirality. The *ortho*-metallation can occur at two different coordination sites, which define a right-handed helix (Δ) and a left-handed helix(Λ), respectively. In Figure 3 the four possible diastereomeric complexes are drawn schematically together with their configurational symbols starting with the asymmetric centre in the ligand. Provided that the specification of the metal chirality is based on the nitrogen atoms of the pyridine ligands in their respective priority, the metal has the opposite configuration compared to the bridgehead carbon atom.

For the separation of the main diastereomer, the 62:32:2:4 mixture of **20** was dissolved in DMSO (gentle warming). Then the solvent was distilled off in vacuo without warming above 50 °C, because at higher temperatures the complex reacts with the solvent,[11] until first crystals appeared. After standing for a few days at r.t. the crystals were filtered off. ^{1}H NMR experiments in DMF-d_7 showed at r.t. a ratio of 96.8:3.2 (only two isomers present). On dissolving the crystals at –25 °C in DMF-d_7 the ^{1}H NMR spectrum indicated a 98.4:1.6 distribution. The ratio shifted to 97.8:2.2 at 0 °C and to 96.8:3.2 at 21 °C. Recooling to –25 °C brought the ratio back to 98.4:1.6. Heating the solution to 50 °C gave an increase of the less abundant diastereomer to 3.6%. Further heating to about 80 °C caused a reversible broadening of the signals. However, at this temperature the ^{1}H NMR spectrum started to show irreversible changes. This temperature-sensitive equilibration is assigned to the interconversion of the Δ/Λ-helicity.

Single crystals suitable for X-ray analysis were obtained from a concentrated solution of **20** in DMSO on standing in an open vessel (anhydrous DMSO is hygroscopic). An ORTEP representation of the complex **20**, which has the configuration (S_C,R_{Rh},Λ_{Rh}), is shown in Figure 4. Three crystals were measured and gave the same result. As a ^{1}H NMR study of the single crystals at r.t. gave an isomer ratio of 97:3, we assign the (S_C,R_{Rh},Λ_{Rh})-configuration to the 97% isomer (chemical shift in DMSO-d_6 9.25 ppm) in the 97:3 mixture (identical with the 62% isomer in the 62:32:2:4 mixture) and we assume its rapid equilibration in solution with the (S_C,R_{Rh},Δ_{Rh})-isomer (9.55 ppm). Then the 32% isomer (9.32 ppm) in the 62:32:2:4 mixture should be the (R_C,S_{Rh},Δ_{Rh})-isomer and the 4% isomer (9.62 ppm) should have (R_C,S_{Rh},Λ_{Rh})-configuration.

20 has a distorted octahedral structure, in which the Rh-Cl and Rh-C bond lengths are in agreement with comparable rhodium complexes.[22] However, the Rh-N bonds differ considerably (1.98, 2.08 and 2.19 Å), whereas in the tris(2-pyridyl)methanol-$RhCl_3$ complex the lengths vary only between 2.03 and 2.05 Å.[22a] This means that the *ortho*-metallation has a significant influence on the Rh-N distances. The bond Rh1-N2 is shortened because of the

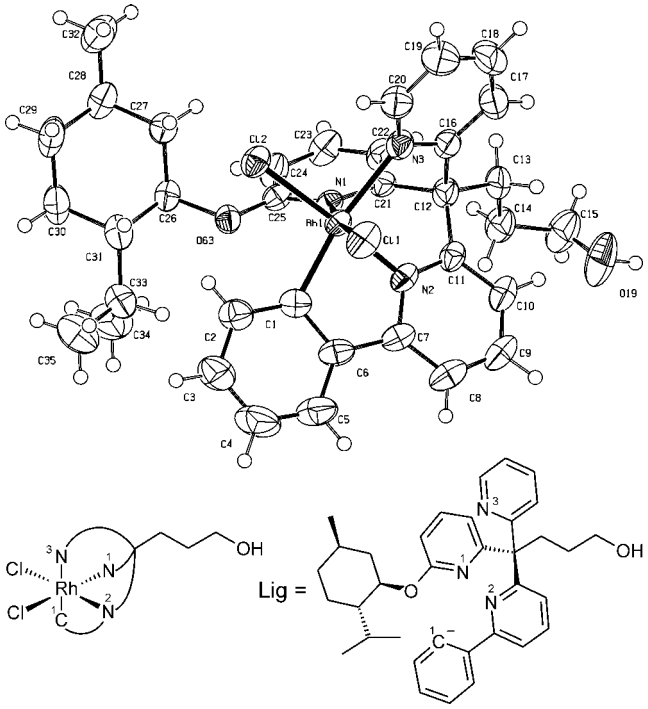


Figure 4 ORTEP representation (50% probability) of (S_C,R_{Rh},Λ_{Rh})-**20**. Selected distances [Å] and angles[°]: Rh1-Cl1 2.35, Rh1-Cl2 2.36, Rh1-C1 2.00, Rh1-N1 2.08, Rh1-N2 1.98, Rh1-N3 2.19, Cl1-Rh1-Cl2 89, Cl1-Rh1-N2 92, Cl1-Rh1-N3 88, Cl1-Rh1-N1 171, Cl1-Rh1-C1 84, Cl2-Rh1-N2 177, Cl2-Rh1-N3 91, Cl2-Rh1-C1 97, N1-Rh1-C1 103, N2-Rh1-N3 92, N2-Rh1-N1 84, N2-Rh1-C1 81, N3-Rh1-N1 85, N3-Rh1-C1 168.

five-membered chelate ring. In contrast, the bond Rh1-N3 is elongated as a result of the strong *trans*-effect of the phenyl substituent. These distortions also affect the Rh1-N1 bond. Surprisingly the bond Rh1-N2 is shorter than Rh1-C1.[22b] In the unit cell there are 6 molecules of the complex. The space group is $P\,6_1$ and the crystal system hexagonal. At the edges of the unit cells along the *c* axis channels are formed, in which solvent molecules reside in a disordered manner. In Figure 5 six molecules of (S_C,R_{Rh},Λ_{Rh})-**20** are shown in their arrangement around the channel along the *c* axis. On the left, the left-handed sense of the helix is obvious from the numbers 1–6. On the right, the side view is represented.

The preparation of air-sensitive compounds was carried out under purified N_2 using standard Schlenk techniques. Solvents were dried and degassed according to standard procedures and stored under N_2. Commercial starting materials were used without further purification. For the chromatographies Merck Geduran® 60 silica gel (63–200 μm) was used. Reaction mixtures and chromatography fractions were analyzed with precoated silica gel 60 F_{254} TLC plates (Merck). Melting points: SMP-20 (Büchi), not corrected. MS: MAT 311A (EI), MAT 95 (DCI) (both Finnigan) and TSQ 7000 (ESI) (ThermoQuest). Optical rotations: Perkin-Elmer 241 polarimeter (1 dm cells). IR spectra: Acculab 3 (Beckman). ^{1}H NMR: AC250 (250 MHz) and ARX400 (400 MHz) (both Bruker), internal standard TMS. ^{13}C NMR: ARX400 (^{1}H decoupled, 101 MHz, Bruker).

The following compounds were synthesized according to the literature: 2-Amino-6-phenylpyridine,[13] 2-bromo-6-phenylpyridine,[13] 2-bromo-6-methoxypyridine (**2**),[14] [(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy]acetic acid,[15] [(1*S*,2*R*,4*S*)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yloxy]acetic acid.[16] *n*-Butyllithium was used as a

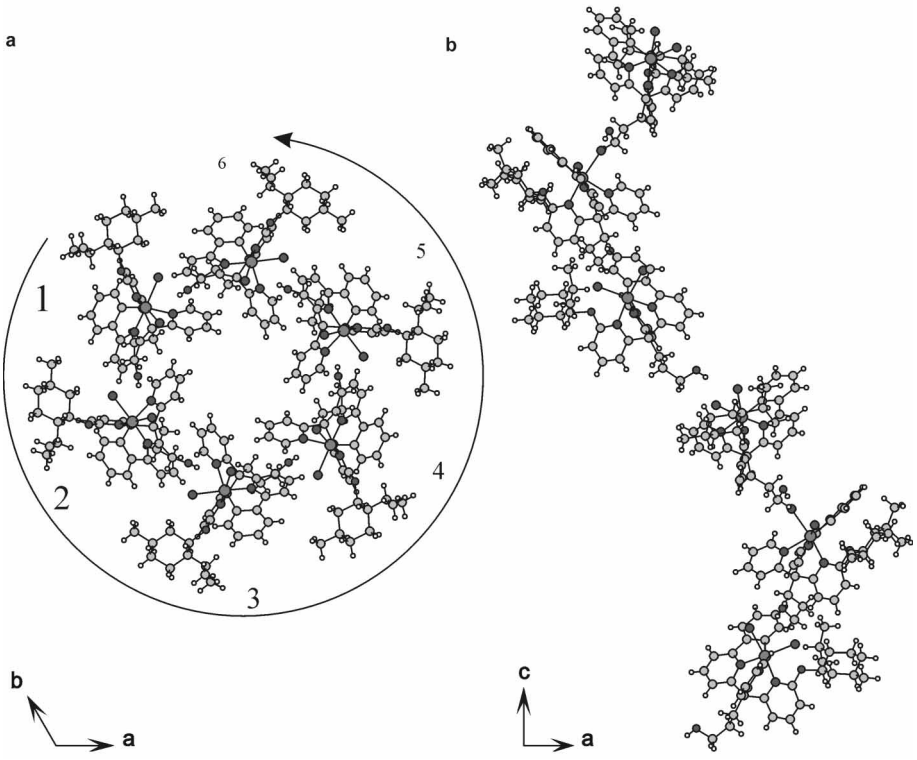


Figure 5 Complex **20**: a top view (along the c axis), b side view (along the b axis)

1.6 M solution in hexane (Merck). The acronym PE for petroleum ether (bp 40–60 °C) will be used. In the ^{1}H NMR data the abbreviation py designates the unsubstituted pyridine ring, py' the methoxy- or menthoxy-substituted ring and py" the phenyl-substituted ring.

(6-Phenylpyridin-2-yl)(pyridin-2-yl)methanone (3)

To a suspension of 2-bromo-6-phenylpyridine (25.2 g, 107 mmol) in anhyd Et_2O (500 mL) was added *n*-BuLi (72 mL, 115 mmol, 1.6 M in hexane) within 1 h at –78 °C. The mixture was allowed to warm to r.t. (clear orange solution). The solution was cooled to –78 °C and a solution of 2-cyanopyridine (11.7 g, 112 mmol) in anhyd Et_2O (150 mL) was added over a period of 45 min. The mixture was allowed to warm to r.t. and poured into ice water (500 mL). HCl (2 M, 150 mL) was added and the solution stirred vigorously. After separation of the phases the organic phase was extracted with HCl (2 M, 3 × 100 mL). The combined aq phases were refluxed for 2 h and carefully neutralized at r.t. with solid K_2CO_3. The resulting suspension was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed through silica gel (6 cm × 6 cm ∅) with CH_2Cl_2–Et_2O (1:1) and recrystallized from PE–acetone (10:1) to give **3** (11.3 g, 41%) as pale pink needles; mp 90–92 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.80 (ddd, 1 H, ^3J = 4.8 Hz, ^4J = 1.8 Hz, ^5J = 0.9 Hz, py-*H*^{6}), 8.17 (ddd, 1 H, ^3J = 7.8 Hz, ^4J = 1.2 Hz, ^5J = 1.0 Hz, py-*H*^{3}), 8.10–7.91 (m, 5 H), 7.89 (ddd, 1 H, ^3J = 7.8 Hz, ^3J = 7.6 Hz, ^4J = 1.8 Hz, py-*H*^{4}), 7.50 (ddd, 1 H, ^3J = 7.6 Hz, ^3J = 4.8 Hz, ^4J = 1.2 Hz, py-*H*^{5}), 7.48–7.37 (m, 3 H, Ph).

IR (KBr): 1660s (C=O) cm^{-1}.

MS (PI-EI, 70 eV): *m/z* (%) = 260 (M, 100), 232 (M–CO, 38), 231 (M–CO–H, 85), 154 (M–pyCO, 36), 127 (M–pyCO–HCN, 34), 78 (C_5H_4N, 41), 51 (C_4H_3, 12).

Anal calcd for $C_{17}H_{12}N_2O$ (260.3): C, 78.44; H, 4.65; N, 10.76. Found: C, 78.39; H, 4.70; N, 10.76.

(6-Methoxypyridin-2-yl)(6-phenylpyridin-2-yl)pyridin-2-ylmethanol (5)

A solution of **2** (8.22 g, 43.0 mmol) in anhyd THF (50 mL) was cooled to –75 °C and *n*-BuLi (29 mL, 46 mmol, 1.6 M in hexane) was added within 30 min. The resulting solution of **4** was cooled to –85 °C and a solution of **3** (10.4 g, 40.0 mmol) in THF (90 mL) was added over a period of 2 h. After stirring for 15 min at –80 °C MeOH (55 mL, 43 g, 1.3 mol) was added. The mixture was allowed to warm to r.t. and acidified with HCl (2 M, 200 mL). The organic solvents were removed and the aq residue was made alkaline with NaOH (6 M). The resulting emulsion was extracted with Et_2O (4 × 50 mL). After washing the combined ethereal solutions with water (2 × 50 mL), the organic solution was dried (Na_2SO_4) and evaporated to give the crude product, which was recrystallized from Et_2O. Colorless crystals of **5** (9.32 g, 63%); mp 92–94 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.55 (ddd, 1 H, ^3J = 4.9 Hz, ^4J = 1.8 Hz, ^5J = 1.0 Hz, py-*H*^{6}), 7.98–7.92 (m, 2 H, Ph), 7.78 (ddd, 1 H, ^3J = 8.0 Hz, ^4J = 1.2 Hz, ^5J = 1.0 Hz, py-*H*^{3}), 7.79–7.62 (m, 3 H, py"), 7.66 (ddd, 1 H, ^3J = 8.0 Hz, ^3J = 7.4 Hz, ^4J = 1.8 Hz, py-*H*^{4}), 7.57 (dd, 1 H, ^3J = 8.2 Hz, ^3J = 7.4 Hz, py'-*H*^{4}), 7.47–7.34 (m, 3 H, Ph), 7.33 (s br, 1 H, O*H*), 7.32 (dd, 1 H, ^3J = 7.4 Hz, ^4J = 0.8 Hz, py'-*H*^{3}), 7.18 (ddd, 1 H, ^3J = 7.4 Hz, ^3J = 4.9 Hz, ^4J = 1.3 Hz, py-*H*^{5}), 6.62 (dd, 1 H, ^3J = 8.2 Hz, ^4J = 0.8 Hz, py'-*H*^{5}), 3.74 (s, 3 H, C*H*$_3$).

MS (PI-EI, 70 eV) *m/z* (%): 369 (M, 71), 291 (M–C_5H_4N, 41), 261 (M–$C_5H_3NOCH_3$, 100), 215 (M–C_5H_3NPh, 59), 154 (C_5H_3NPh, 31), 108 ($C_5H_3NOCH_3$, 12), 78 (C_5H_4N, 35).

Anal calcd for $C_{23}H_{19}N_3O_2$ (369.4): C, 74.78; H, 5.18; N, 11.37. Found: C, 74.66; H, 5.19; N, 11.31.

(6-Methoxypyridin-2-yl)(6-phenylpyidin-2-yl)pyridin-2-ylmethyl [(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy]acetate (6)

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxyacetic acid (5.36 g, 25.0 mmol) was cooled to 0 °C and thionyl chloride (8.7 mL, 14 g, 0.12 mol) was added. The mixture was refluxed for 5 h. After cooling the solution was submitted to a Kugelrohr distillation (bp 100 °C/1 mbar) yielding the acid chloride as a colorless oil, which was kept under N_2 and directly used for the following esterification.

A cooled solution (0 °C) of the alcohol **5** (7.39 g, 20.0 mmol) in THF (40 mL) was deprotonated by addition of *n*-BuLi (12.5 mL, 20.0 mmol, 1.6 M in hexane) over a period of 15 min. After stirring for 15 min a solution of the acid chloride (see above) in THF (25 mL) was added within 20 min. The mixture was warmed to 40 °C and stirred for 24 h. The cooled solution was quenched with H_2O (2 mL) and washed with sat. aq NaCl (3 × 20 mL), dried (Na_2SO_4) and evaporated. The residue was recrystallized from diisopropyl ether to give **6** (9.62 g, 81%) as colorless crystals; mp 65–68 °C. All attempts at enriching one diastereomer by recrystallization failed.

Analytical data for a 1:1 mixture of the two diastereomers:

$[\alpha]_\lambda$ (*c* = 0.5, *n*-hexane, r.t.): –40.1 (589 nm), –41.9 (578 nm), –47.7 (546 nm), –80.0 (436 nm), –125 (365 nm).

^{1}H NMR (250 MHz, $CDCl_3$): The signals were not assigned to the different diastereomers. δ = 8.53 (ddd, 1 H; ^3J = 4.8 Hz, ^4J = 1.8 Hz, ^5J = 0.9 Hz, py-*H*^{6}), 8.53 (ddd, 1 H, ^3J = 4.8 Hz, ^4J = 1.8 Hz, ^5J = 0.9 Hz, py-*H*^{6}), 7.88–7.77 (m, 8 H), 7.72 (dd, 1 H, ^3J = 7.8 Hz, ^3J = 7.7 Hz, py"-*H*^{4}), 7.72 (dd, 1 H, ^3J = 7.8 Hz, ^3J = 7.7 Hz, py"-*H*^{4}), 7.64 (ddd, 1 H, ^3J = 8.1 Hz, ^3J = 7.4 Hz, ^4J = 1.8 Hz, py-*H*^{4}), 7.64 (ddd, 1 H, ^3J = 8.1 Hz, ^3J = 7.4 Hz, ^4J = 1.8 Hz, py-*H*^{4}), 7.60 (dd, 1 H, ^3J = 7.6 Hz, ^4J = 1.2 Hz, py"-*H*$^{3/5}$), 7.60 (dd, 1 H, ^3J = 7.6 Hz, ^4J = 1.2 Hz, py"-*H*$^{3/5}$), 7.55 (dd, 2 H, ^3J = 8.1 Hz, ^3J = 7.5 Hz, py'-*H*^{4}), 7.43–7.30 (m, 8 H), 7.15 (ddd, 2 H, ^3J = 7.4 Hz, ^4J = 4.8 Hz, ^5J = 1.2 Hz, py-*H*^{5}), 6.60 (dd, 2 H, ^3J = 8.1 Hz, ^4J = 0.8 Hz, py'-H^5), 4.51 (AB, 1 H, ^2J = 16.2 Hz, OC*H*^{A}H^B), 4.50 (AB, 1 H, ^2J = 16.2 Hz, OC*H*^{A}H^B), 4.45 (AB, 1 H, ^2J = 16.2 Hz, OCH^A*H*^{B}), 4.45 (AB, 1 H, ^2J = 16.2 Hz, OCH^A*H*^{B}), 3.71 (s, 6 H, OC*H*$_3$), 3.18 (dt, 1 H, ^3J = 10.5 Hz, ^3J = 2.1 Hz, OC*H*), 3.17 (dt, 1 H, ^3J = 10.5 Hz, ^3J = 2.2 Hz, OC*H*), 2.37−2.24 (m, 2 H), 2.15−2.04 (m, 2 H), 1.67−1.55 (m, 4 H), 1.34−1.15 (m, 4 H), 1.03−0.73 (m, 6 H), 0.87 (d, 3 H, ^3J = 6.5 Hz, C*H*$_3$), 0.86 (d, 3 H, ^3J = 6.5 Hz, C*H*$_3$), 0.85 (d, 6 H, ^3J = 7.1 Hz, C*H*$_3$), 0.70 (d, 3 H, ^3J = 6.9 Hz, C*H*$_3$), 0.69 (d, 3 H, ^3J = 6.9 Hz, C*H*$_3$).

IR (KBr): 1775s (C=O) cm^{-1}.

MS (PI-EI 70 eV) *m/z* (%): 565 (M, 0.6), 368 (M–menOCH$_2$CO, 11), 352 (M–menOCH$_2$COO, 100), 337 (M–menOCH$_2$CO–OCH$_3$, 6), 245 (M–menOCH$_2$COO–$C_5H_3NOCH_3$+H, 7)

Anal calcd for $C_{35}H_{39}N_3O_4$ (565.7): C, 74.31; H, 6.95; N, 7.43. Found: C, 74.03; H, 6.96; N, 7.36.

(6-Methoxypyridin-2-yl)(6-phenylpyidin-2-yl)pyridin-2-ylmethyl [(1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yloxy]acetate (7)

This compound was prepared by a method analogous to that used for **6**. Thus, (1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yloxyacetic acid (1.33 g, 6.25 mmol) and **5** (1.26 g, 3.4 mmol) gave the product **7**. Recrystallization from pentane yielded colorless crystals of **7** (1.03 g, 54%); mp 104–109 °C. No enrichment of a diastereomer could be achieved by recrystallization.

Analytical data for a 1:1 mixture of the two diastereomers:

$[\alpha]_\lambda$ (*c* = 0.54, CH_2Cl_2, r.t.): –27.0 (589 nm), –27.0 (578 nm), –32.0 (546 nm), –58.1 (436 nm), –101 (365 nm).

^{1}H NMR (250 MHz, $CDCl_3$): The signals were not assigned to the different diastereomers. δ = 8.53 (ddd, 1 H, ^3J = 4.8 Hz, ^4J = 1.9 Hz, ^5J = 0.9 Hz, py-*H*^{6}), 8.53 (ddd, 1 H, ^3J = 4.8 Hz,

^4J = 1.9 Hz, ^5J = 0.9 Hz, py-H^6), 7.88–7.79 (m, 8 H), 7.72 (dd, 2 H, ^3J = 7.9 Hz, ^3J = 7.6 Hz, py"-H^4), 7.65 (ddd, 2 H, ^3J = 8.1 Hz, ^3J = 7.4 Hz, ^4J = 1.9 Hz, py-H^4), 7.59 (dd, 2 H, ^3J = 7.7 Hz, ^4J = 1.1 Hz, py"-$H^{3/5}$), 7.54 (dd, 2 H; ^3J = 8.1 Hz, ^3J = 7.5 Hz, py'-H^4), 7.43–7.31 (m, 8 H), 7.14 (ddd, 2 H, ^3J = 7.4 Hz, ^3J = 4.8 Hz, ^4J = 1.2 Hz, py-H^5), 6.59 (dd, 2 H, ^3J = 8.1 Hz, ^4J = 0.7 Hz, py'-H^5), 4.43 (AB, 2 H, ^2J = 16.4 Hz, OCH^AH^B), 4.41 (AB, 2 H, ^2J = 16.4 Hz, OCH^AH^B), 3.77–3.68 (m, 2 H), 3.71 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 2.17−2.00 (m, 4 H), 1.74–1.58 (m, 4 H), 1.29–1.06 (m, 6 H), 0.88 (s, 3 H, CH_3), 0.88 (s, 3 H, CH_3), 0.82 (s, 3 H, CH_3), 0.82 (s, 3 H, CH_3), 0.76 (s, 3 H, CH_3), 0.74 (s, 3 H, CH_3).

IR (KBr): 1780s (C=O) cm^{-1}.

MS (PI-EI, 70 eV) *m/z* (%): 563 (M, 0.7), 368 (M–bornOCH$_2$CO, 10), 352 (M–bornOCH$_2$COO, 100), 337 (M–bornOCH$_2$CO–OCH$_3$, 7), 245 (M–bornOCH$_2$COO–C$_5$H$_3$NOCH$_3$+H, 7).

Anal. calcd for $C_{35}H_{37}N_3O_4$ (563.7): C, 74.58; H, 6.62; N, 7.45. Found: C, 74.72 ; H, 6.77; N, 7.17.

Bromo(6-methoxypyridin-2-yl)(6-phenylpyridin-2-yl)pyridin-2-ylmethane (8)

5 (8.05 g, 21.8 mmol) was dissolved at r.t. in THF (50 mL) and deprotonated with *n*-BuLi (15 mL, 24 mmol, 1.6 M in hexane) within 10 min. The resulting solution was cooled to –70 °C and a solution of thionyl bromide (2.0 mL, 5.4 g, 26 mmol) in THF (30 mL) was added within 30 min. The resulting mixture was allowed to warm to r.t. over a period of 3 h. After 12 h of stirring, the mixture was quenched with sat. aq $NaHCO_3$ solution (25 mL). The organic solvent was removed and the aq residue extracted with Et_2O–CH_2Cl_2, 5:1 (3 × 20 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried and evaporated to give a brown oil. The residue was chromatographed through silica gel (8 cm × 5 cm ∅) with Et_2O–CH_2Cl_2 (5:1) to give bromide **8** (7.48 g, 79%) as a yellow highly viscous oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.63 (ddd, 1 H, ^3J = 4.8 Hz, ^4J = 1.9 Hz, ^5J = 0.9 Hz, py-H^6), 7.86–7.80 (m, 2 H, Ph), 7.77–7.62 (m, 2 H, py"), 7.62 (ddd, 1 H, ^3J = 8.1 Hz, ^3J = 7.5 Hz, ^4J = 1.9 Hz, py-H^4), 7.55 (dd, 1 H, ^3J = 8.2 Hz, ^3J = 7.5 Hz, py'-H^4), 7.53 (dd, 1 H, ^3J = 7.7 Hz, ^4J = 1.0 Hz, py"-$H^{3/5}$), 7.41 (ddd, 1 H, ^3J = 8.1 Hz, ^4J = 1.1 Hz, ^5J = 0.9 Hz, py-H^3), 7.39–7.29 (m, 3 H, Ph), 7.18 (ddd, 1 H, ^3J = 7.5 Hz, ^3J = 4.8 Hz, ^4J = 1.1 Hz, py-H^5), 7.13 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 0.7 Hz, py'-H^3), 6.63 (dd, 1 H, ^3J = 8.2 Hz, ^4J = 0.7 Hz, py'-H^5), 3.74 (s, 3 H, CH_3).

2-(6-Methoxypyridin-2-yl)-2-(6-phenylpyridin-2-yl)-2-pyridin-2-ylethanol (9)

To a solution of **8** (8.20 g, 19.0 mmol) in Et_2O (150 mL) was added *n*-BuLi (13 mL, 21 mmol, 1.6 M in hexane) within 20 min at –90 °C. Paraformaldehyde (0.68 g, 23 mmol) was added in one portion and the mixture was allowed to warm to r.t. over 4 h. After stirring for 10 h the mixture was quenched with H_2O (25 mL). The phases were separated and the organic layer was washed with H_2O (4 × 20 mL). After drying (Na_2SO_4) the solvent was evaporated. The residue was chromatographed through silica gel (8 cm × 5 cm ∅) with Et_2O–CH_2Cl_2 (1:1, R_f = 0.56) to give compound **9** (5.79 g, 79%) as a brownish oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.59 (ddd, 1 H, ^3J = 4.8 Hz, ^4J = 1.9 Hz, ^5J = 0.9 Hz, py-H^6), 7.92–7.86 (m, 2 H, Ph), 7.71–7.61 (m, 2 H, py"), 7.60 (ddd, 1 H, ^3J = 8.0 Hz, ^3J = 7.5 Hz, ^4J = 1.9 Hz, py-H^4), 7.50 (dd, 1 H, ^3J = 8.3 Hz, ^3J = 7.4 Hz, py'-H^4), 7.46−7.33 (m, 3 H, Ph), 7.18 (ddd, 1 H, ^3J = 7.5 Hz, ^4J = 4.8 Hz, ^5J = 1.1 Hz, py-H^5), 6.99 (ddd, 1 H, ^3J = 8.0 Hz, ^4J = 1.1 Hz, ^5J = 0.9 Hz, py-H^3), 6.92 (dd, 1 H, ^3J = 6.9 Hz, ^4J = 1.9 Hz, py"-$H^{3/5}$), 6.64 (dd, 1 H, ^3J = 8.3 Hz, ^4J = 0.7 Hz, py'-$H^{3/5}$), 6.58 (dd, 1 H, ^3J = 7.4 Hz, ^4J = 0.7 Hz, py'-$H^{3/5}$), 6.3 (s br, 1H, OH), 4.98 (AB, 1 H, ^2J = 11.2 Hz, CH^AH^{B}OH), 4.96 (AB, 1 H, ^2J = 11.2 Hz, CH^AH^BOH), 3.74 (s, 3 H, CH_3).

2-(6-Methoxypyridin-2-yl)-2-(6-phenylpyridin-2-yl)-2-pyridin-2-ylethyl *p*-toluenesulfonate (10)

To a solution of **9** (2.20 g, 5.80 mmol) in anhyd pyridine (40 mL) was added *p*-TsCl (2.36 g, 12.0 mmol). After stirring the solution at r.t. for 60 h the mixture was quenched with ice water (50 mL). An aq solution of $NaHCO_3$ (1 M, 10 mL) was added and the resulting emulsion extracted with CH_2Cl_2 (4 × 15 mL). The organic layer was washed with $NaHCO_3$ (1 M, 3 × 10 mL), water (2 × 10 mL), dried (Na_2SO_4) and evaporated to dryness. The crude product was suspended in Et_2O, stirred and filtered to give **10** as a slightly brownish powder (2.15 g, 69%); mp 127–129 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.41 (ddd, 1 H, ^3J = 4.8 Hz, ^4J = 1.9 Hz, ^5J = 0.9 Hz, py-H^6), 7.88-7.80 (m, 2 H, Ph), 7.66-7.55 (m, 2 H), 7.56 (ddd, 1 H, ^3J = 8.1 Hz, ^3J = 7.5 Hz, ^4J = 1.9 Hz, pyH^4), 7.49 (dd, 1 H, ^3J = 8.2 Hz, ^3J = 7.5 Hz, py'-H^4), 7.44–7.34 (m, 5 H), 7.27 (ddd, 1 H, ^3J = 8.1 Hz, ^4J = 1.2 Hz, ^5J = 0.9 Hz, py-H^3), 7.17 (dd, 1 H, ^3J = 7.3 Hz, ^4J = 1.4 Hz, py"-$H^{3/5}$), 7.09 (ddd, 1 H, ^3J = 7.5 Hz, ^4J = 4.8 Hz, ^5J = 1.1 Hz, py-H^5), 7.09-7.04 (m, 2 H, Ph'), 6.92 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 0.7 Hz, py'-H^3), 6.57 (dd, 1 H, ^3J = 8.2 Hz, ^4J = 0.7 Hz, py'-H^5), 5.49 (AB, 1 H, ^2J = 9.4 Hz, CH^AH^B), 5.49 (AB, 1 H, ^2J = 9.4 Hz, CH^AH^B), 3.60 (s, 3 H, OCH_3), 2.29 (s, 3 H, CH_3).

IR (KBr): 1180s (SO_2) cm^{-1}.

MS (PI-EI, 70 eV) *m/z* (%): 537 (M, 0.2), 366 (M–TsO, 4), 351 (M–TsO–CH_3, 100), 322 (M–TsO–CH_3–CH_2O, 15).

Anal. calcd for $C_{31}H_{27}N_3O_4S$ (537.6): C, 69.26; H, 5.06; N, 7.82. Found: C, 69.16; H, 5.15; N, 7.76.

(6-Methoxypyridin-2-yl)(6-phenylpyridin-2-yl)pyridin-2-ylmethane (11)

A mixture of **10** (512 mg, 0.95 mmol) and a solution of NaOMe in MeOH (10% w/w, 10 mL) was refluxed for 14 h. The solution was allowed to cool to r.t. and acidified with HCl (10%). After dilution with H_2O (80 mL) it was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was washed with K_2CO_3 (1 M, 2 × 10 mL), water (2 × 10 mL), dried (Na_2SO_4) and evaported. The residue was chromatographed through silica gel (15 cm × 2.5 cm ∅) with Et_2O (R_f = 0.53) to give **11** (281 mg, 84%) as a yellowish, highly viscous oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.57 (ddd, 1 H, ^3J = 4.9 Hz, ^4J = 1.9 Hz, ^5J = 0.9 Hz, py-H^6), 7.99–7.93 (m, 2 H, Ph), 7.71–7.57 (m, 2 H), 7.62 (ddd, 1 H, ^3J = 7.9 Hz, ^3J = 7.4 Hz, ^4J = 1.9 Hz, pyH^4), 7.50 (dd, 1 H, ^3J = 8.2 Hz, ^3J = 7.3 Hz, py'-H^4), 7.49–7.30 (m, 5 H), 7.14 (ddd, 1 H, ^3J = 7.4 Hz, ^3J = 4.9 Hz, ^4J = 1.3 Hz, py-H^5), 6.92 (dd, 1 H, ^3J = 7.3 Hz, ^4J = 0.7 Hz, py'-H^3), 6.59 (dd, 1 H, ^3J = 8.2 Hz, ^4J = 0.8 Hz, py'-H^5), 5.98 (s, 1 H, pypy'py"CH), 3.80 (s, 3 H, CH_3).

MS (PI-EI, 70 eV) *m/z* (%): 353 (M, 100), 352 (M–H, 71), 338 (M–CH_3, 43), 337 (M–H–CH_3, 19), 275 (M–C_5H_4N, 16), 245 (M–$C_5H_3NOCH_3$, 63), 199 (M–C_5H_3Ph, 51).

Anal calcd for $C_{23}H_{19}N_3O$ (353.4): C, 78.17; H, 5.42; N, 11.89. Found: C, 77.34; H, 5.52; N, 11.75

2-Bromo-6-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl-oxy]-pyridine (12)

A mixture of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexan-1-ol (115 g, 730 mmol) and NaH powder (2.96 g, 176 mmol) was slowly heated to 60 °C. After gas evolution ceased the temperature was raised to 90 °C and the mixture was stirred for 2 h. A clear solution resulted, which was allowed to cool to 50 °C. Solid 2,6-dibromopyridine (33.4 g, 141 mmol) was added in portions. The suspension was heated to 90 °C and stirred for 20 h at this temperature. After cooling to r.t. Et_2O (100 mL) was added and the mixture quenched with H_2O (30 mL). The aq layer was extracted with Et_2O (2 × 20 mL) and the organic extracts were concentrated to yield an oil from

which unreacted menthol was distilled off (95 °C/0.2 mbar). The residue was subjected to a fractional distillation to give **12** as a colorless liquid (36.4 g, 83%); bp 86–93 °C/10^{-3} mbar.

$[\alpha]_\lambda$ (c = 2.2, $CHCl_3$, r.t.): –85.1 (589 nm), –89.0 (578 nm), –102 (546 nm), –179 (436 nm), –304 (365 nm).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.36 (dd, 1 H, ^3J = 8.1 Hz, ^3J = 7.5 Hz, py-*H*^{4}), 6.98 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 0.7 Hz, py-*H*^{3}), 6.60 (dd, 1 H, ^2J = 8.1 Hz, ^3J = 0.7 Hz, py-*H*^{5}), 4.97 (dt, 1 H, ^3J = 10.7 Hz, ^3J = 4.4 Hz, OC*H*), 2.20–2.11 (m, 1 H), 1.97 (dsept, 1 H, ^3J = 2.7 Hz, ^3J = 7.0 Hz, C*H*(CH_3)$_2$), 1.76–1.41 (m, 4 H), 1.23–0.72 (m, 3 H), 0.92 (d, 3 H, ^3J = 6.4 Hz, CH_3), 0.89 (d, 3 H, ^3J = 6.9 Hz, CH_3), 0.78 (d, 3 H, ^3J = 6.9 Hz, CH_3).

MS (PI-EI, 70 eV) *m/z* (%): 313/311 (M, 8/9), 176/174 (M–$C_{10}H_{17}$, 97/100), 95 (M–Br–$C_{10}H_{17}$, 71).

Anal calcd for $C_{15}H_{22}BrNO$ (312.3): C, 57.70; H, 7.10; N, 4.49. Found: C, 57.73; H, 7.0; N, 4.59.

{6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]pyridin-2-yl}(6-phenylpyridin-2-yl)pyridin-2-ylmethanol (14)

To a cooled solution (–80 °C) of **12** (8.43 g, 27.0 mmol) in THF (40 mL) was added *n*-BuLi (16 mL, 26 mmol, 1.6 M in hexane) over a period of 30 min. After stirring for 30 min the mixture was cooled to –90 °C and a solution of **3** (6.51 g, 25.0 mmol) in THF (50 mL) was added within 60 min. Further 60 min of stirring was followed by addition of MeOH (25 mL) over a period of 30 min. The solution was allowed to warm to r.t. and H_2O (10 mL) and HCl (2 M, 15 mL) were added. The organic solvent was removed and the remaining aq solution was extracted with CH_2Cl_2 (20 mL). After neutralizing with K_2CO_3 (solid) the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The organic phases were washed with K_2CO_3 (1 M, 2 × 40 mL), H_2O (2 × 20 mL), dried (Na_2SO_4) and evaporated. The residue was stirred with PE (200 mL) and the undissolved ketone was filtered off. The filtrate was concentrated and heated in the Kugelrohr apparatus to 120 °C at a pressure of 10^{-4} mbar to remove the volatiles. The residue was passed through silica gel (11 cm × 6 cm ∅) with PE–Et_2O (3:1, R_f = 0.27) to give **14** (6.93 g, 56%) as a 1:1 mixture of the two diastereomers as a yellowish, highly viscous oil. The faster moving diastereomer could be enriched by chromatography (silica gel, 85 cm × 2.5 cm ∅, PE–Et_2O, 2:1). The first 20% of the product was chromatographed again and this operation was repeated once more. Then the first 20% of the resulting product showed a diastereomeric excess of 96%.

Analytical date for a 1:1 mixture:

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.55 (ddd, 1 H, ^3J = 4.9 Hz, ^4J = 1.9 Hz, ^5J = 1.0 Hz, py-*H*^{6}), 8.54 (ddd, 1 H, ^3J = 4.9 Hz, ^4J = 1.9 Hz, ^5J = 1.0 Hz, py-*H*^{6}), 8.00–7.93 (m, 4 H, Ph), 7.86 (ddd, 1 H, ^3J = 8.1 Hz, ^4J = 1.2 Hz, ^5J = 1.0 Hz, py-*H*^{3}), 7.77–7.60 (m, 9 H), 7.54 (dd, 1 H, ^3J = 8.2 Hz, ^3J = 7.4 Hz, py'-*H*^{4}), 7.54 (dd, 1 H, ^3J = 8.2 Hz, ^3J = 7.4 Hz, py'-*H*^{4}), 7.47–7.33 (m, 6 H, Ph), 7.35 (s br, 2 H, O*H*), 7.30 (dd, 1 H, ^3J = 7.4 Hz, ^4J = 0.8 Hz, py'-*H*^{3}), 7.28 (dd, 1 H, ^3J = 7.4 Hz, ^4J = 0.8 Hz, py'-*H*^{3}), 7.19 (ddd, 1 H, ^3J = 7.4 Hz, ^3J = 4.9 Hz, ^4J = 1.2 Hz, py-*H*^{5}), 7.18 (ddd, 1 H, ^3J = 7.3 Hz, ^3J = 4.9 Hz, ^4J = 1.3 Hz, py-*H*^{5}), 6.53 (dd, 1 H, ^3J = 8.2 Hz, ^4J = 0.8 Hz, py-'*H*^{5}), 6.52 (dd, 1 H, ^3J = 8.2 Hz, ^4J = 0.8 Hz, py'-*H*^{5}), 4.71 (dt, 2 H, ^3J = 10.7 Hz, ^3J = 4.3 Hz, OC*H*), 2.07–1.77 (m, 4 H), 1.67–0.72 (m, 14 H), 0.83 (d, 3 H, ^3J = 7.0 Hz, CH_3), 0.81 (d, 3 H, ^3J = 7.1 Hz, CH_3), 0.80 (d, 3 H, ^3J = 6.5 Hz, CH_3), 0.76 (d, 3 H, ^3J = 6.5 Hz, CH_3), 0.59 (d, 3 H, ^3J = 7.0 Hz, CH_3), 0.53 (d, 3 H, ^3J = 7.0 Hz, CH_3).

MS (PI-DCI) *m/z* (%): 494 (MH, 100).

Anal. calcd for $C_{32}H_{35}N_3O_2$ (493.7): C, 77.86; H, 7.15; N, 8.51. Found: C, 77.57; H, 7.46; N, 8.13.

Analytical date for a 98:2 mixture of the diastereomers:

$[\alpha]_\lambda$ (*c* = 1.7, CH_2Cl_2, r.t.): –85.0 (589 nm), –89.4 (578 nm), –103 (546 nm), –195 (436 nm), –372 (365 nm).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.57 (ddd, 1 H, ^3J = 4.9 Hz, ^4J = 1.8 Hz, ^5J = 1.0 Hz, py-*H*^{6}), 7.98-7.92 (m, 2 H, Ph), 7.90 (ddd, 1 H, ^3J = 8.0 Hz, ^4J = 1.2 Hz, ^5J = 0.9 Hz, py-*H*^{3}), 7.77−7.60 (m, 3 H), 7.68 (ddd, 1 H, ^3J = 8.0 Hz, ^3J = 7.4 Hz, ^4J = 1.8 Hz, py-*H*^{4}), 7.56 (dd, 1 H, ^3J = 8.2 Hz, ^3J = 7.4 Hz, py'-*H*^{4}), 7.45–7.33 (m, 3 H, Ph), 7.35 (s br, 1 H, O*H*), 7.33 (dd, 1 H, ^3J = 7.4 Hz, ^4J = 0.8 Hz, py'-*H*^{3}), 7.21 (ddd, 1 H, ^3J = 7.4 Hz, ^3J = 4.9 Hz, ^4J = 1.2 Hz, py-*H*^{5}), 6.55 (dd, 1 H, ^3J = 8.2 Hz, ^4J = 0.8 Hz, py'-*H*^{5}), 4.75 (dt, 1 H, ^3J = 10.7 Hz, ^3J = 4.3 Hz, OC*H*), 2.07−1.80 (m, 2 H), 1.67−0.72 (m, 7 H), 0.81 (d, 3 H, ^3J = 7.1 Hz, CH_3), 0.80 (d, 3 H, ^3J = 6.5 Hz, CH_3), 0.54 (d, 3 H, ^3J = 7.0 Hz, CH_3).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 162.7 (*C*^{q}), 162.1 (*C*^{q}), 161.9 (*C*^{q}), 161.5 (*C*^{q}), 154.4 (*C*^{q}), 147.2 (*C*H), 139.2 (*C*H), 139.1 (*C*^{q}), 136.8 (*C*H), 135.7 (*C*H), 128.9 (*C*H), 128.6 (2 *C*H), 126.8 (2 *C*H), 123.9 (*C*H), 122.2 (*C*H), 122.0 (*C*H), 118.7 (*C*H), 113.8 (*C*H), 109.5 (*C*H), 81.1 (*C*^{q}), 74.4 (*C*H), 47.1(*C*H), 40.5 (*C*H_2), 34.5 (*C*H_2), 31.4 (*C*H), 26.3 (*C*H), 23.8 (*C*H_2), 22.2 (*C*H_3), 20.6 (*C*H_3), 16.5 (*C*H_3).

{6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]pyridin-2-yl}methoxy(6-phenylpyridin-2-yl)pyridin-2-ylmethanol (15)

To a mixture of **14** (1.48 g, 3.00 mmol) and NaH (suspension 80% in toluene) (105 mg, 3.50 mmol) was added DMF (10 mL). After stirring at r.t. for 2 h a solution resulted. A solution of methyl iodide (0.47 g, 3.3 mmol) in DMF (1 mL) was added and the mixture was stirred for 12 h. After addition of aq NH_3 (2 M, 25 mL) and vigorous stirring the mixture was acidified with HCl (2 M). The combined CH_2Cl_2 extracts (5 × 15 mL) were washed with HCl (2 M, 2 × 10 mL), K_2CO_3 (1 M, 2 × 10 mL) and H_2O (2 × 10 mL) and dried (Na_2SO_4). The residue was chromatographed through silica gel (15 cm × 2 cm ∅) with CH_2Cl_2–Et_2O (15:1, R_f = 0.48) to give **15** (1.18 g, 77%) as a yellowish, highly viscous oil. The diastereomeric excess of the product was equal to the starting material.

Analytical data for a 1:1 mixture of the diastereomers:

$[\alpha]_\lambda$ (c = 1.1, CH_2Cl_2, r.t.): –57.7 (589 nm), –60.0 (578 nm), –68.1 (546 nm), –116 (436 nm), –180 (365 nm).

^{1}H NMR (250 MHz, $CDCl_3$): The signals were not assigned to the different diastereomers. δ = 8.62 (ddd, 1 H, ^3J = 4.8 Hz, ^4J = 1.8 Hz, ^5J = 1.0 Hz, py-*H*^{6}), 8.62 (ddd, 1 H, ^3J = 4.9 Hz, ^4J = 1.8 Hz, ^5J = 0.9 Hz, py-*H*^{6}), 7.96–7.90 (m, 4 H, Ph), 7.76–7.51 (m, 11 H), 7.46 (dd, 1 H, ^3J = 7.3 Hz, ^4J = 1.5 Hz, py''-*H*$^{3/5}$), 7.43–7.31 (m, 6 H, Ph), 7.28 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 0.8 Hz, py'-*H*^{3}), 7.21 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 0.8 Hz, py'-*H*^{3}), 7.16 (ddd, 1 H, ^3J = 7.3 Hz, ^3J = 4.8 Hz, ^4J = 1.3 Hz, py-*H*^{5}), 7.15 (ddd, 1 H, ^3J = 7.3 Hz, ^3J = 4.8 Hz, ^4J = 1.3 Hz, py-*H*^{5}), 6.52 (dd, 1 H, ^3J = 8.2 Hz, ^4J = 0.8 Hz, py'-*H*^{5}), 6.51 (dd, 1 H, ^3J = 8.2 Hz, ^4J = 0.8 Hz, py'-*H*^{5}) 4.65 (dt, 1 H, ^3J = 10.7 Hz, ^3J = 4.3 Hz, OC*H*), 4.63 (dt, 1 H, ^3J = 10.7 Hz, ^3J = 4.3 Hz, OC*H*), 3.41 (s, 3 H, OCH_3), 3.41 (s, 3 H, OCH_3), 2.04–1.69 (m, 4 H), 1.65–1.34 (m, 6 H), 1.27–0.69 (m, 8 H), 0.81 (d, 3 H, ^3J = 7.1 Hz, 3 H, CH_3), 0.80 (d, 3 H, ^3J = 7.1 Hz, CH_3), 0.76 (d, 3 H, ^3J = 6.5 Hz, CH_3), 0.75 (d, 3 H, ^3J = 6.4 Hz, CH_3), 0.53 (d, 3 H, ^3J = 7.0 Hz, CH_3), 0.51 (d, 3 H, ^3J = 7.0 Hz, CH_3).

MS (PI-EI, 70 eV) *m/z* (%): 507 (M, 14), 492 (M–CH_3, 22), 477 (M–CH_2O, 26), 339 (M–OCH_3–$C_{10}H_{17}$, 100).

Bromo{6-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl-oxy]pyridin-2-yl}(6-phenylpyridin-2-yl)pyridin-2-ylmethane (16)

To a solution of **14** (8.75 g, 17.7 mmol) in Et_2O (80 mL) was added *n*-BuLi (11 mL, 18 mmol, 1.6 M in hexane) within 15 min at –78 °C. After 15 min stirring a solution of thionyl bromide (1.62 mL, 4.37 g, 21.0 mmol) in Et_2O (25 mL) was added at –78 °C over a period of 30 min. Within 4 h the mixture was allowed to come to

r.t. and stirred for 12 h. The reaction was quenched by addition of sat. aq $NaHCO_3$ (50 mL). After addition of CH_2Cl_2 (50 mL) the organic layer was separated, washed with sat. aq $NaHCO_3$ (3 × 30 mL), half sat. aq NaCl (3 × 30 mL) and dried (Na_2SO_4). The evaporation of the solvent yielded the crude product, which was purified by chromatography through silica gel (8 cm × 5 cm ∅) with Et_2O (R_f = 0.85) to give **16** (8.79 g, 89%) as a yellow, glassy substance.

Analytical data for a 1:1 mixture of the diastereomers:

$[\alpha]_\lambda$ (*c* = 1.2, CH_2Cl_2, r.t.): –69.6 (589 nm), –72.8 (578 nm), –83.4 (546 nm).

^{1}H NMR (250 MHz, $CDCl_3$): The signals were not assigned to the different diastereomers. δ = 8.66 (ddd, 1 H, ^3J = 4.8 Hz, ^4J = 1.8 Hz, ^5J = 1.0 Hz, py-*H*^{6}), 8.65 (ddd, 1 H, ^3J = 4.8 Hz, ^4J = 1.9 Hz, ^5J = 1.0 Hz, py-*H*^{6}), 7.89–7.82 (m, 4 H, Ph), 7.73–7.61 (m, 4 H), 7.60 (ddd, 2 H, ^3J = 8.1 Hz, ^3J = 7.5 Hz, ^4J = 1.9 Hz, py-*H*^{4}), 7.56 (dd, 1 H, ^3J = 8.2 Hz, ^3J = 7.5 Hz, py'-*H*^{4}), 7.55 (dd, 1 H, ^3J = 8.2 Hz, ^3J = 7.5 Hz, py'-*H*^{4}), 7.46 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 1.2 Hz, py'-*H*^{3}), 7.45 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 1.3 Hz, py'-*H*^{3}), 7.40–7.23 (m, 10 H), 7.19 (ddd, 1 H, ^3J = 7.5 Hz, ^3J = 4.8 Hz, ^4J = 1.1 Hz, py-*H*^{5}), 7.18 (ddd, 1 H, ^3J = 7.5 Hz, ^3J = 4.8 Hz, ^4J = 1.0 Hz, py-*H*^{5}), 6.55 (dd, 2 H, ^3J = 8.2 Hz, ^4J = 0.7 Hz, py'-*H*^{5}), 4.54 (dt, 1 H, ^3J = 10.8 Hz, ^3J = 4.3 Hz, OC*H*), 4.51 (dt, 1 H, ^3J = 10.8 Hz, ^3J = 4.3 Hz, OC*H*), 2.05−1.66 (m, 4 H), 1.60–1.47 (m, 4 H), 1.43–1.20 (m, 4 H), 1.12–0.66 (m, 6 H), 0.80 (d, 3 H, ^3J = 7.0 Hz, C*H*$_3$), 0.79 (d, 3 H, ^3J = 7.0 Hz, C*H*$_3$), 0.73 (d, 3 H, ^3J = 6.5 Hz, C*H*$_3$), 0.69 (d, 3 H, ^3J = 6.5 Hz, C*H*$_3$), 0.51 (d, 3 H, ^3J = 7.0 Hz, C*H*$_3$), 0.51 (d, 3 H, ^3J = 7.0 Hz, C*H*$_3$).

MS (PI-DCI (NH_3) *m/z* (%): 558/556 (MH, 57/54), 478 (MH–Br, 100).

{6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]pyridin-2-yl}(6-phenylpyridin-2-yl)pyridin-2-ylmethane (17)

To a solution of **16** (1.11 g, 2.00 mmol) in Et_2O (40 mL) was added *n*-BuLi (1.50 mL, 2.40 mmol, 1.6 M in hexane) over a period of 30 min at –90 °C. The solution was allowed to warm slowly to r.t. and quenched with water (10 mL). After the addition of HCl (2 M, 2 mL) the phases were separated. The aq layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with sat. aq K_2CO_3 (3 × 10 mL), dried over Na_2SO_4 and evaporated. The crude product was chromatographed through silica gel, (20 cm × 1.5 cm ∅) with CH_2Cl_2–Et_2O, 10:1 (R_f = 0.40) to provide **17** (0.78 g, 73%) as a colorless, highly viscous oil.

Analytical data for a 1:1 mixture of the two diastereomers:

$[\alpha]_\lambda$ (*c* = 2.9, CH_2Cl_2, r.t.): –82.2 (589 nm), –85.6 (578 nm), –97.7 (546 nm), –170 (436 nm).

^{1}H NMR (250 MHz, $CDCl_3$): The signals were not assigned to the different diastereomers. δ = 8.56 (ddd, 1 H, ^3J = 4.9 Hz, ^4J = 1.9 Hz, ^5J = 0.9 Hz, py-*H*^{6}), 8.56 (ddd, 1 H, ^3J = 4.9 Hz, ^4J = 1.8 Hz, ^5J = 0.9 Hz, py-*H*^{6}), 8.00–7.94 (m, 4 H, Ph), 7.70–7.56 (m, 4 H), 7.64 (dd, 2 H, ^3J = 7.6 Hz, ^3J = 7.2 Hz, py''-*H*^{4}), 7.51 (ddd, 1 H, ^3J = 8.0 Hz, ^4J = 1.3 Hz, ^5J = 0.9 Hz, py-*H*^{4}), 7.47 (dd, 2 H, ^3J = 8.2 Hz, ^3J = 7.3 Hz, py'-*H*^{4}), 7.46–7.33 (m, 7 H), 7.31 (dd, 1 H, ^3J = 7.4 Hz, ^4J = 1.2 Hz, py''-*H*$^{3/5}$), 7.30 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 1.2 Hz, py''-*H*$^{3/5}$), 7.13 (ddd, 2 H, ^3J = 7.4 Hz, ^3J = 4.9 Hz, ^4J = 1.3 Hz, py-*H*^{5}), 6.85 (dd, 1 H, ^3J = 7.2 Hz, ^4J = 0.8 Hz, py''-*H*$^{3/5}$), 6.83 (dd, 1 H, ^3J = 7.3 Hz, ^4J = 0.8 Hz, py''-*H*$^{3/5}$), 6.50 (dd, 2 H, ^3J = 8.2 Hz, ^4J = 0.7 Hz, py'-*H*^{5}), 5.94 (s, 2 H, pypy'py''C*H*), 4.85 (dt, 1 H, ^3J = 10.8 Hz, ^3J = 4.3 Hz, OC*H*), 4.84 (dt, 1 H, ^3J = 10.8 Hz, ^3J = 4.3 Hz, OC*H*), 2.06–1.83 (m, 4 H), 1.68–1.57 (m, 4 H), 1.52–1.14 (m, 4 H), 1.06–0.74 (m, 6 H), 0.86 (d, 3 H, ^3J = 6.6 Hz, C*H*$_3$), 0.84 (d, 3 H, ^3J = 7.0 Hz, C*H*$_3$), 0.80 (d, 3 H, ^3J = 6.9 Hz, C*H*$_3$), 0.78 (d, 3 H, ^3J = 6.5 Hz, C*H*$_3$), 0.61 (d, 3 H, ^3J = 6.9 Hz, C*H*$_3$), 0.57 (d, 3 H, ^3J = 6.9 Hz, C*H*$_3$).

MS (PI-EI, 70 eV) *m/z* (%): 477 (M, 34), 434 (M–C_3H_7, 21), 340 (M–$C_{10}H_{17}$, 58), 339 (M–$C_{10}H_{18}$, 100), 338 (M–H–$C_{10}H_{18}$, 78), 246 (M+H–C_5H_3NOmen, 30), 245 (M–$C_5H_3NOC_{10}H_{19}$, 45).

Anal. calcd for $C_{32}H_{35}N_3O$ (477.7): C, 80.46; H, 7.38; N, 8.80. Found: C, 80.24; H, 7.26; N, 8.67.

4-{6-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]pyridin-2-yl}-4-(6-phenylpyridin-2-yl)-4-pyridin-2-ylbutan-1-ol (18)

To a cooled solution (–90 °C) of **16** (4.41 g, 7.90 mmol) in Et_2O (100 mL) was added *n*-BuLi (6.3 mL, 10 mmol, 1.6 M in hexane) within 15 min. After stirring for 30 min oxetane (0.82 mL, 0.73 g, 13 mmol) and $BF_3{\cdot}OEt_2$ (1.6 mL, 1.8 g, 13 mmol) were added at –90 °C. The mixture was allowed to warm to r.t. over a period of 4 h and then stirred for 1 h. After addition of H_2O (20 mL) and HCl (2 M, 10 mL) small portions of CH_2Cl_2 were added until the dark oil dissolved. The resulting mixture was made alkaline with sat. aq K_2CO_3 (20 mL). The separated aq layer was extracted with a 2:1 mixture of Et_2O and CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with sat. aq K_2CO_3 (2 × 20 mL), sat. aq NaCl (2 × 20 mL), dried (Na_2SO_4) and concentrated. The residue was chromatographed through silica gel (10 cm × 6 cm ∅) with CH_2Cl_2 → Et_2O [CH_2Cl_2–Et_2O, 1:0, 10:1, 5:1, 1:1, 0:1; R_f (Et_2O) = 0.41] to give **18** (2.36 g, 56%) as a 1:1 mixture of the two diastereomers as a yellowish, highly viscous oil.

The faster moving diastereomer (*S*)-**18** could be enriched by chromatography (85 cm × 2.5 cm ∅) with CH_2Cl_2–Et_2O, 1.4:1. The first 20% of the product were chromatographed again and this operation was repeated three times. Then the first 20% of the resulting product showed a diastereomeric excess of 90%.

Analytical data for a 1:1 mixture of the two diastereomers:

$[\alpha]_\lambda$ (*c* = 0.4, CH_2Cl_2, r.t.): –66.0 (589 nm), –69.6 (578 nm), –79.5 (546 nm), –143 (436 nm), –251 (365 nm).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (ddd, 1 H, ^3J = 4.9 Hz, ^4J = 1.9 Hz, ^5J = 0.9 Hz, py-*H*^{6}), 8.55 (ddd, 1 H, ^3J = 4.9 Hz, ^4J = 1.9 Hz, ^5J = 0.9 Hz, py-*H*^{6}), 7.96–7.92 (m, 4 H, Ph), 7.65–7.51 (m, 6 H), 7.47 (dd, 2 H, ^3J = 8.2 Hz, ^3J = 7.5 Hz, py'-*H*^{4}), 7.45–7.31 (m, 8 H), 7.23 (dd, 1 H, ^3J = 6.8 Hz, ^4J = 2.0 Hz, py''-*H*$^{3/5}$), 7.21 (dd, 1 H, ^3J = 7.0 Hz, ^4J = 1.8 Hz, py''-*H*$^{3/5}$), 7.11 (ddd, 1 H, ^3J = 7.3 Hz, ^3J = 4.9 Hz, ^4J = 1.1 Hz, py-*H*^{5}), 7.11 (ddd, 1 H, ^3J = 7.3 Hz, ^3J = 4.9 Hz, ^4J = 1.2 Hz, py-*H*^{5}), 6.89 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 0.7 Hz, py'-*H*^{3}), 6.89 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 0.7 Hz, py'-*H*^{3}), 6.49 (dd, 2 H, ^3J = 8.2 Hz, ^4J = 0.6 Hz, py'-*H*^{5}), 4.70 (dt, 1 H, ^3J = 10.8 Hz, ^3J = 4.3 Hz, OC*H*), 4.70 (dt, 1 H, ^3J = 10.7 Hz, ^3J = 4.1 Hz, OC*H*), 3.63 (t, 4 H, ^3J = 6.1 Hz, C*H*$_2$OH), 3.15–2.94 (m, 4 H), 2.10–1.94 (m, 2 H), 1.90–1.80 (m, 2 H), 1.68–0.74 (m, 18 H), 0.84 (d, 6 H, ^3J = 7.0 Hz, C*H*$_3$), 0.80 (d, 6 H, ^3J = 6.5 Hz, C*H*$_3$), 0.60 (d, 6 H, ^3J = 7.0 Hz, C*H*$_3$), O*H* protons at about 3 ppm very broad.

MS (PI-DCI) *m/z* (%): 536 (MH, 100).

Anal. calcd for $C_{35}H_{41}N_3O_2$ (535.7): C, 78.47; H, 7.71; N, 7.84. Found: C, 77.68; H, 7.95; N, 7.30.

Analytical data for (*S*)-**18** in a 95:5 mixture of (*S*)-**18**:(*R*)-**18**:

$[\alpha]_\lambda$ (*c* = 1.2, CH_2Cl_2, r.t.): –46.3 (589 nm), –48.0 (578 nm), –54.4 (546 nm), –90.6 (436 nm), –129 (365 nm).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (ddd, 1 H, ^3J = 4.9 Hz, ^4J = 1.9 Hz, ^5J = 0.9 Hz, py-*H*^{6}), 7.96–7.92 (m, 2 H, Ph), 7.63–7.56 (m, 2 H), 7.54 (ddd, 1 H, ^3J = 8.1 Hz, ^3J = 7.4 Hz, ^4J = 1.9 Hz, py*H*^{4}), 7.47 (dd, 1 H, ^3J = 8.2 Hz, ^3J = 7.5 Hz, py'-*H*^{4}), 7.44–7.33 (m, 4 H), 7.21 (dd, 1 H, ^3J = 7.6 Hz, ^4J = 1.2 Hz, py''-*H*$^{3/5}$), 7.12 (ddd, 1 H, ^3J = 7.4 Hz, ^3J = 4.9 Hz, ^4J = 1.1 Hz, py-*H*^{5}), 6.88 (dd, 1 H, ^3J = 7.5 Hz, ^4J = 0.7 Hz, py'-*H*^{3}), 6.48 (dd, 1 H, ^3J = 8.2 Hz, ^4J = 0.7 Hz, py'-*H*^{5}), 4.67 (dt, 1 H, ^3J = 10.8 Hz, ^3J = 4.2 Hz, OC*H*), 3.62 (t, 2 H, ^3J = 6.1 Hz, C*H*$_2$OH), 3.10–2.97 (m, 2 H), 2.04–1.93

(m, 1 H), 1.86−1.79 (m, 1 H), 1.66–0.76 (m, 9 H), 0.83 (d, 3 H, ^3J = 7.0 Hz, CH_3), 0.78 (d, 3 H, ^3J = 6.5 Hz, CH_3), 0.58 (d, 3 H, ^3J = 7.0 Hz, CH_3), O*H* proton at about 3 ppm very broad.

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 164.6 (*C*^{q}), 164.2 (*C*^{q}), 162.4 (*C*^{q}), 162.1 (*C*^{q}), 155.0 (*C*^{q}), 147.6 (*C*H), 139.4 (*C*^{q}), 138.6 (*C*H), 136.0 (*C*H), 135.1 (*C*H), 128.6 (*C*H), 128.5 (2 *C*H), 126.6 (2 *C*H), 126.0 (*C*H), 123.2 (*C*H), 121.0 (*C*H), 117.2 (*C*H), 115.3 (*C*H), 108.6 (*C*H), 74.1 (*C*H), 63.1 (*C*^{q}), 62.9 (*C*H_2), 47.0 (*C*H), 40.5 (*C*H_2), 34.4 (*C*H_2), 33.6 (*C*H_2), 31.2 (*C*H), 28.7 (*C*H_2), 26.2 (*C*H), 23.7 (*C*H_2), 22.1 (*C*H_3), 20.5 (*C*H_3), 16.4 (*C*H_3).

Dichloro[(6-methoxypyridin-2-yl)(6-phenylpyridin-2-yl-*κN*)-(pyridin-2-yl-*κN*)methane]copper(II) (19)

Anhyd $CuCl_2$ (28.0 mg, 0.21 mmol) was dissolved in a solution of racemic **11** (73.0 mg, 0.21 mmol) in MeOH (2 mL). After diffusion of Et_2O into the methanolic solution **19** (72.0 mg, 72%) was obtained as green, air-stable crystals; mp 185 °C (decomp.). Some of the crystals were suitable for X-ray analysis.

MS (PI-ESI) *m/z* (%): 451 (M–Cl, 43), 415 (M–Cl–HCl, 100), 354 (MH–$CuCl_2$, 25).

Anal. calcd for $C_{23}H_{19}Cl_2CuN_3O$ (478.9): C, 56.62; H, 3.93; N, 8.61. Found: C, 56.28; H, 4.09; N, 8.37.

(R_{Rh},Λ_{Rh})-Dichloro[*(S)*-4-{6-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy]pyridin-2-yl-*κN*}-4-[6-(2-phenyl-*κC*1)pyridin-2-yl-*κN*]-4-(pyridin-2-yl-*κN*)butan-1-ol]rhodium(III) (20)

To a solution of **18** (*S*:*R* = 65:35, 1.50 g, 2.80 mmol) in EtOH (150 mL) was added rhodium(III) chloride trihydrate (645 mg, 2.45 mmol) at ambient temperature. This solution was stirred for 12 h and the resulting yellow solid was filtered off, washed with EtOH (4 × 5 mL), Et_2O (4 × 5 mL) and dried. After addition of Et_2O (30 mL) and PE (20 mL) to the mother liquid the solution was stirred for 12 h to give a second fraction of **20**. Concentration of the mother liquid to a volume of 25 mL gave a third fraction. The yield of the fine crystalline air-stable powder was altogether 1.35 g (78%); mp >250 °C.

For separation of the major diastereomer, a 62:32:2:4 mixture of **20** (300 mg) was dissolved in DMSO (25 mL) at 45 °C. The solution was submitted to a Kugelrohr distillation at 45 °C/10^{-3} mbar to remove the solvent until first crystals appeared. This sat. solution was allowed to stand for several days. Then the product was filtered off to give **20** (90 mg) as fine yellow needles, with a *de* of 94%. X-ray quality yellow prisms were obtained by leaving a concentrated solution of **20** in DMSO undisturbed in an open vessel for about two weeks.

Analytical data for (S_C,R_{Rh},Λ_{Rh})-**20** in a 97:3 mixture of (S_C,R_{Rh},Λ_{Rh})-**20**:(S_C,R_{Rh},Δ_{Rh})-**20**:

$[\alpha]_\lambda$ (*c* = 0.26, DMSO, r.t.): –58.0 (589 nm), –50.2 (578 nm), –17.0 (546 nm).

^{1}H NMR (400 MHz, DMF-d_7): δ = 9.50 (ddd, 1 H, ^3J = 5.4 Hz, ^4J = 1.8 Hz, ^5J = 0.6 Hz, py-*H*^{6}), 8.96 (ddd, 1 H, ^3J = 7.7 Hz, ^4J = 1.3 Hz, ^5J = 0.4 Hz, Ph-*H*^{3}), 8.20 (ddd, 1 H, ^3J = 8.2 Hz, ^4J = 1.3 Hz, ^5J = 0.8 Hz, py-*H*^{3}), 8.15 (ddd, 1 H, ^3J = 8.1 Hz, ^3J = 7.2 Hz, ^4J = 1.8 Hz, py-*H*^{4}), 8.03–7.95 (m, 3 H, py''), 7.89 (dd, 1 H, ^3J = 8.4 Hz, ^3J = 7.9 Hz, py'-*H*^{4}), 7.79 (ddd, 1 H, ^3J = 7.7 Hz, ^4J = 1.3 Hz, ^5J = 0.3 Hz, Ph-*H*^{6}), 7.64 (dd, 1 H, ^3J = 7.9 Hz, ^4J = 1.0 Hz, py'-*H*^{3}), 7.47 (ddd, 1 H, ^3J = 7.2 Hz, ^4J = 5.4 Hz, ^5J = 1.4 Hz, py-*H*^{5}), 7.28 (ddd, 1 H, ^3J = 7.7 Hz, ^3J = 7.2 Hz, ^4J = 1.5 Hz, Ph-*H*$^{4/5}$), 7.25 (dd, 1 H, ^3J = 8.5 Hz, ^4J = 1.0 Hz, py'-*H*^{5}), 7.03 (ddd, 1 H, ^3J = 7.6 Hz, ^3J = 7.3 Hz, ^4J = 1.2 Hz, Ph-*H*$^{4/5}$), 5.05 (s, 1 H, O*H*), 4.44 (dt, 1 H, ^3J = 10.5 Hz, ^3J = 4.7 Hz, OC*H*), 3.92 (m, 2 H, CH_2OH), 3.74–3.64 (m, 1 H, pypy'py"CC*H*^{A}H^B), 3.47–3.37 (m, 1 H, pypy'py"CCH^A*H*^{B}), 2.13–1.97 (m, 3 H, men-C^6*H*H+men-C^2*H*), 1.80–1.64 (m, 4 H, CH_2CH$_2$OH+men-C^5*H*H+men-C^6*H*H), 1.64–1.54 (m, 1 H, men-C^1*H*), 1.25–1.15 (m, 1 H, men-C^8*H*), 1.12-0.98 (m, 2 H, men-C^{5}H*H*+men-C^{6}H*H*), 0.96 (d, 3 H, ^3J = 6.6 Hz, CH_3), 0.60 (d, 3 H, ^3J = 6.9 Hz, CH_3), 0.26 (d, 3 H, ^3J = 7.0 Hz, CH_3).

^{13}C{^{1}H} NMR (101 MHz, DMF-d_7): δ = 171.6 (d, ^1J = 25.7 Hz, *C*^{q}-Rh), 169.4 (*C*^{q}), 168.8 (*C*^{q}), 159.3 (*C*^{q}), 156.7 (*C*^{q}, *J* = 1.0 Hz, py''-*C*^{6}H or Ph-*C*^{2}H), 155.4 (*C*^{q}, *J* = 1.4 Hz, py''-*C*^{6}H or Ph-*C*^{2}H), 155.0 (py-*C*^{6}H), 147.2 (*C*^{q}), 142.0 (py'-*C*^{4}H), 140.7 (Ph-*C*^{3}H), 140.0 (py-*C*^{4}H), 138.8 (py''-*C*^{4}H), 128.6 (Ph-*C*$^{4/5}$H), 123.8 (Ph-*C*^{6}H), 123.5 (py-*C*^{5}H), 122.2 (Ph-*C*$^{4/5}$H), 122.1 (py''-*C*^{3}H), 120.8 (py-*C*^{3}H), 118.5 (py'-*C*^{3}H), 117.7 (py''-*C*^{5}H), 107.5 (py'-*C*^{5}H), 79.9 (men-*C*^{1}H), 63.6 (*C*^{q}, *J* = 2.1 Hz, pypy'py"*C*), 61.7 (*C*H_2OH), 46.1 (men-*C*^{2}H), 39.7 (men-*C*^{6}H$_2$), 34.9 (men-*C*^{4}H$_2$), 31.8 (men-*C*^{5}H), 30.4 (pypy'py"C*C*H$_2$), 29.0 (*C*H$_2$CH$_2$OH), 25.2 (men-*C*^{8}H), 23.0 (men-*C*^{3}H$_2$), 22.4 (men-C^5*C*H$_3$), 21.1 (men-C^{8}H*C*H$_3$), 15.3 (men-C^{8}H*C*H$_3$).

MS (PI-ESI): m/z (%) = 1455 (M_2+K, 4), 1439 (M_2+Na, 19), 746 (M+K, 31), 730 (M+Na, 100), 672 (M – Cl, 27), 536 (M – $RhCl_2$+2 H, 16).

Anal. calcd for $C_{35}H_{40}Cl_2N_3O_2Rh$ (708.5): C 59.33; H, 5.69; N, 5.93. Found: C, 58.90; H, 5.79; N, 5.83.

X-Ray Structure Analysis, General Remarks

The structures were solved by direct methods (SIR-97) and refined by full-matrix anisotropic least squares (SHELXL97) on F^2. The H atoms were calculated geometrically and a riding model was applied during the refinement process. Absorption corrections were not used. For the measurement a diffractometer of the type STOE-IPDS with Mo-K_α radiation and graphite monochromator was used. Further details of the crystal structure investigation may be obtained, free of charge, from the Cambridge Crystallographic Data Centre, where the structures have been deposited.

X-Ray Structure Analysis of (±)-19

$C_{23}H_{19}Cl_2CuN_3O$, MW = 487.86; green prisms; crystal size [mm]: 0.21 × 0.15 × 0.11; space group *P* 2_1/n; monoclinic; *Z* = 4; *a*/*b*/*c* [Å] = 9.3622(8)/14.6885(9)/15.8021(14); β [°] = 105.084(10); *V* = 2098.2(3) Å^3; d_{calcd} = 1.544 g·cm^{-3}; *F*(000) = 996; μ = 1.32 mm^{-1}; *T* = 173(1) K; ω-scan: 2.30 < 2Θ < 26.78°; 27241 reflections collected, 4451 independent, 3067 observed ($I > 2\sigma_I$); R_{int} = 0.0550; *R* ($I > 2\sigma_I$): R_1 = 0.0342; wR_2 = 0.0723; *R* (all data): R_1 = 0.0602; wR_2 = 0.0782; gof = 0.868; CCDC 163405.

X-Ray Structure Analysis of (S_C,R_{Rh},Λ_{Rh})-20

$C_{35}H_{40}Cl_2N_3O_2Rh$, MW = 708.51; yellow prisms; crystal size [mm]: 0.14 × 0.10 × 0.08; space group *P* 6_1; hexagonal; *Z* = 6; *a*/*c* [Å] = 24.5147(11)/9.8658(5); *V* = 5134.7(4) Å^3; d_{calcd} = 1.375 g·cm^{-3}; *F*(000) = 2196; μ = 0.689 mm^{-1}; *T* = 293(2) K; ω-scan: 2.82 < 2Θ < 25.90°; 69461 reflections collected, 6627 independent, 5942 observed ($I > 2\sigma_I$); R_{int} = 0.0380; *R* ($I > 2\sigma_I$): R_1 = 0.0312; wR_2 = 0.0710; *R* (all data): R_1 = 0.0352; wR_2 = 0.0736; gof = 1.035; absolute structure parameter –0.02(2); CCDC 163406. On solving the structure a solvent accessible area containing electron density was detected. The contribution of the disordered solvent to the calculated structure factors was taken into account by back-Fourier transformation with the program SQUEEZE.[23] The void was located at (0, 0, 0), it had a size of 533 Å^3 and contained 29 electrons.

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