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Regioselective synthesis of optically active (pyrazolyl)pyridines with adjacent quaternary carbon stereocenter: chiral *N,N*-donating ligands

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Abstract—Novel optically active 2-(pyrazol-1-yl)pyridines have been prepared using resolved the *O*-methyl ether of atrolactic acid as a source of the adjacent quaternary carbon stereocenter. Different regioisomers were formed selectively in the reaction of 2-hydrazinopyridines with the chiral 1,3-diketone and in the nucleophilic substitution of 2-chloropyridines with the potassium salt of the chiral pyrazole. The second route gave 2-(pyrazol-1-yl)pyridines with the stereogenic center neighboring the coordinating nitrogen in the pyrazole ring. Also, new C_2-symmetric chiral ligands based on 2,6-bis(pyrazolyl)pyridine and 6,6′-bis(pirazolyl)-2,2′-bipyridine structures were obtained.

1. Introduction

Chiral chelating ligands are considered as important for transition-metal catalyzed enantioselective reactions.[1] Usually, the most successful are C_2 symmetric catalysts.[2] However, in some prominent cases, lack of C_2 symmetry leads to additional stereoelectronic effects that improve enantioselectivity.[2] This effect can be attained using heterodonatig ligands, for example, N, S-[3] or ligands with donating atoms of the same element but differing in electronic character. A plethora of chiral *N,N*-donating ligands have already been described,[4] but only a few of them combine pyrazole (π-excessive, weaker basicity) and pyridine (π-deficient, higher basicity) systems.[5] The most prepared chiral pyrazoles are those derived from the natural monoterpenes. On the other hand, achiral ligands of this type are well known and their complexes were studied.[6] As well as the complexing property, another feature essential for enantioselectivity in catalysis is a stereocontrolling element. In order to gain high chiral discrimination it is usually located closely to the catalytically active metal center. For all these reasons, we decided to develop the synthesis of 2-(pyrazol-1-yl)pyridines bearing a chiral quaternary carbon center derived from enantiomeric the *O*-methyl ether of atrolactic acid. This nonracemizing acid is an analogue of the *O*-methyl ether of mandelic acid, well known for its high stereodiscriminating properties.[7] In spite of that fact, its synthetic use has not been explored up to now.

2. Results and discussion

A multi-gram synthesis of racemic *O*-methyl ether of atrolactic acid (**2**) was carried out in three steps from inexpensive *rac*-mandelic acid. The racemic product was resolved by the crystallization of its brucine salt[8a] and subsequently both enantiomeric acids were esterified. The methyl ester **1** (90% e.e., ^{1}H NMR spectroscopy with Eu(hfc)$_3$) and acetone underwent the Claisen condensation using sodium hydride to give the corresponding chiral 1,3-diketone **3** in good yield (Scheme 1).

Both enantiomeric diketones were submitted to the reaction with hydrazine to give the respective chiral pyrazole **4**. 2-Hydrazinopyridine and 2-chloro-6-hydrazinopyridine were treated with the diketone **3** analogously and the optically active 2-(pyrazol-1-yl)pyridines **5a** and **5b** resulted in each case as a single product, respectively (Scheme 2).

When the potassium salt of chiral pyrazole **4** was used in a nucleophilic substitution with 2,6-dichloropyridine, depending upon the ratio of reagents, the other (pyrazolyl)pyridine **6** or **7** was formed (Scheme 3).

Keywords: Cyclization; Pirazolylpyridines; Quaternary carbon stereocenter; Nitrogen chiral ligands.
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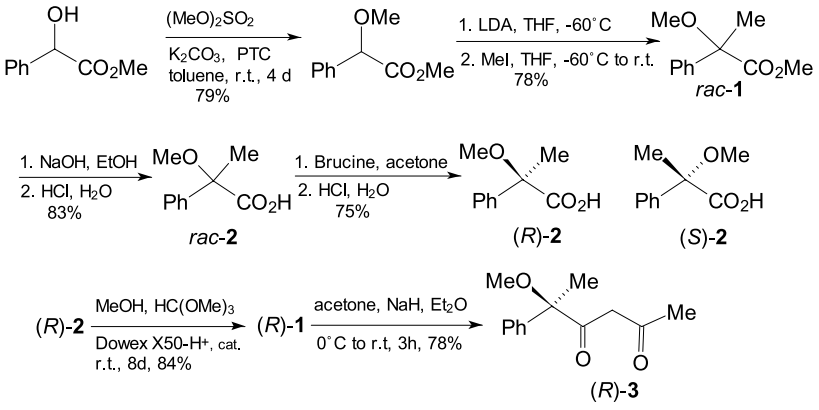
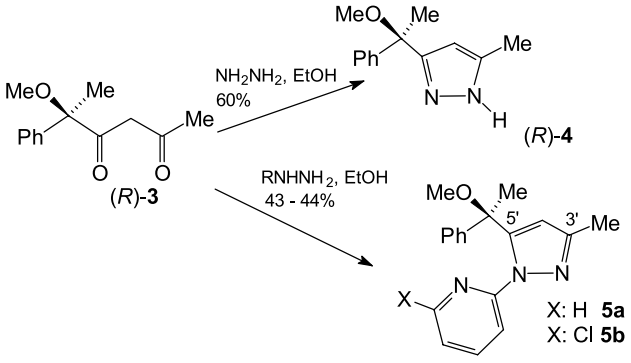
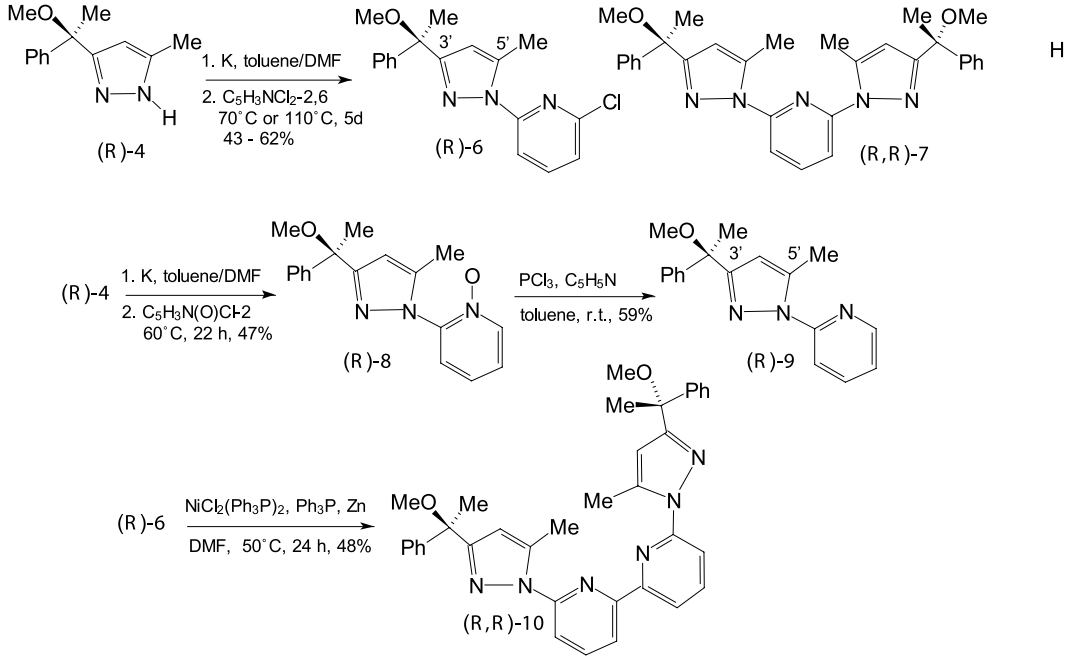


Scheme 1.



Scheme 2.

The products **5b** and **6** are regioisomers and both types of compounds have already been reported. Generally, the reaction of arylhydrazines with unsymmetrical 1,3-diketones leads to mixtures of both regioisomers.[9] On the other hand, the pyrazoles bearing bulky substituents give main products of N-arylation at the nitrogen furthest from the bulky group.[10] Here, both reactions were regioselective and the structures of the products were unambiguously established by ^{1}H NMR spectroscopy. Thus, the cyclization products **5** showed the presence of a 3′-methyl group $\delta=$ 2.2–2.3 ppm, while the substitution products **6** and **9** showed the 5′-methyl deshielded by the pyridine moiety to $\delta=2.5$–2.7 ppm. This interpretation has already been proposed for similar compounds.[11] Moreover, 2,6-bis(pyrazol-1-yl)pyridine derivative **7** formed in the substitution of 2,6-dichloropyridine with four equivalents of the potassium salt of chiral pyrazole was a regio- and diastereomerically pure product of C_2-symmetry with both pyrazole 5′-methyl groups appearing as a single resonance at $\delta=2.55$ ppm. Additionally, inspection of a molecular model for the prevailing *trans*,*trans*-conformation of 5′-methyl derivative **7** suggests that the *O*-methyl group should be deshielded by the pyrazole nitrogen lone pair (observed $\delta=3.26$ ppm). A similar chemical shift was found for **9** ($\delta=3.27$ ppm). This effect is not expected for **5a** (observed $\delta=3.06$ ppm). This explanation is in accord with nuclear Overhauser effects that



Scheme 3.

we observed in the respective NOESY spectra, namely for **5a**: OMe gave a strong cross-peak with 3-H and for **7**: no such NOE enhancement was detected between OMe and 3-H.

An attempted direct nucleophilic substitution with 2-chloropyridine failed, so we activated this derivative by its oxidation to the respective *N*-oxide. In this case we obtained the corresponding 2-(pyrazol-1-yl)pyridine-1-oxide **8** as a single product. Finally, the deoxygenation of **8** with phosphorus trichloride in the presence of excess pyridine gave the required *N*,*N*-complexing ligand **9** (Scheme 3).

An interesting C_2-symmetric tetradentate ligand **10** was obtained by the reductive homocoupling of the 2-chloro-6-(pyrazol-1-yl)pyridine **6** with $Ni(Ph_3P)_2Cl_2/Zn/Ph_3P$.[12] Even though the starting material was of 90% e.e., both C_2-symetric derivatives, **7** and **10** were obtained as enantiopure products and no *meso*-diastereomers could be detected.

It is noteworthy that the nucleophilic substitution products **7**, **9** and **10** with 5′-methyl groups contain a potentially highly stereodiscriminating center at 3′-positions, in close proximity to the complexed metal. This makes them very promising chiral ligands. However, preliminarily examination of their catalytic use in the Pd-catalyzed allylic alkylation of dimethyl malonate with *rac*-1,3-diphenyl-2-propenyl acetate[3b] gave ca 30% e.e. as the best result. Further work on the catalytic use of the new ligands with other transition metals is currently underway in our laboratory.

3. Experimental

3.1. General

Melting points were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker CPX (^{1}H, 300 MHz) or a Bruker Avance (^{1}H, 500 MHz) spectrometer using TMS as an internal standard. Observed rotations at 589 nm were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. GC/MS analyses were determined on a Hewlett-Packard 5890 II gas chromatograph (25 m capillary column) with a Hewlett Packard mass spectrometer 5971 A operating on the electron impact mode (70 eV). High resolution mass spectra were recorded on a Finnigan MAT 95 spectrometer operating on the same mode (EI, 70 eV). Separations of products by chromatography were performed on silica gel 60 (230–400 mesh) purchased from Merck. Thin layer chromatography analyses were performed using silica gel 60 precoated plates (Merck).

3.2. α-Methoxy-α-phenylacetic acid methyl ester

To the mechanically stirred mixture of methyl mandelate (61 g, 0.37 mol), K_2CO_3 (300 g, 2.2 mol) and Adogen® (6.9 g) in toluene (230 mL), at room temperature was added dropwise for 2 h $(CH_3O)_2SO_2$ (52 mL, 0.55 mol). The mixture was left for 2 days and after this time another portion of $(CH_3O)_2SO_2$ (7 mL) was added and the stirred mixture was heated at 90 °C for 12 h. After cooling the mixture was treated slowly with water until the layers were separated. The aqueous phase was saturated with NaCl and extracted with toluene (100 mL). The combined organic phase was washed with brine (50 mL), dried (Na_2SO_4). Concentration by distilling off toluene afforded 73 g of the crude product (71.5% by GC/MS, 79% yield), that was directly submitted to the next reaction.

3.2.1. 2-Methoxy-2-phenylpropionic acid (2). To a solution of LDA in THF (4.55 M, 75 mL, 0.34 mol) stirred under argon atmosphere at −60 °C was added for 1 h, by a syringe, a solution of crude α-methoxy-α-phenylacetic acid methyl ester (52.2 g, 0.29 mol) in dry THF (100 mL). The mixture was allowed to warm to 0 °C and it was further stirred for 60 min. After cooling again to −60 °C, a solution of methyl iodide (23 mL, 0.37 mol) in THF (25 mL) was added for 45 min, the mixture was left for 30 min at this temperature and allowed to warm to 20 °C. After 18 h, the reaction mixture was quenched by the addition of HCl (100 mL, 10% aq) and ether (100 mL). The separated organic layer was washed with HCl (100 mL, 1 M, aq), water (100 mL), $NaHCO_3$ (50 mL, sat. aq), brine (50 mL) and dried (Na_2SO_4). Concentration in vacuo gave brown oil (45.5 g), which was treated with solution of NaOH pallets (12.06 g, 0.30 mol) in the mixture of C_2H_5OH–H_2O (150 mL, 11:4, v/v) and allowed to crystallize for 2 days at rt. The filtered crystals were washed with cold C_2H_5OH, recrystallized from C_2H_5OH–H_2O (11:2, v/v) giving pure sodium salt of *O*-methyl atrolactic acid (45.6 g, 96%) as a white solid.

To the solution of sodium salt of **2** (40.2 g, 225 mmol) in water (100 mL) was added in 5 portions HCl (23 mL, 12 M, aq). The resulted emulsion was extracted successively with toluene (10×20 mL). The combined organic extract was washed with water (60 mL) and filtered through a paper filter to give a clear and colorless liquid which was evaporated leaving of *title compound rac*-**2** (28.7 g, 87% yield) as a light yellow oil.

Resolution of the diastereomeric salts of *rac*-**2** (24.7 g) with brucine was carried out according to the literature procedure[8a] and gave 11.37 g (46%) of *R*-(−)-2-methoxy-2-phenyl-propionic acid, *R*-(−)-**2**: $[\alpha]_D=-25.5$ (*c* 1, MeOH), lit[8a]: −26 (*c* 1, MeOH) and free *S*-(+)-**2**: 7.22 g (29%), $[\alpha]_D=+24$ (*c* 1.2, MeOH), lit[8a]: +25 (*c* 1, MeOH), lit[8b]: +37.6 (*c* 8.8, MeOH) for 97% e.e.; *m*/*z* (EI, 70 eV) 180 (0.02, M^+), 135 (100), 105 (11), 77 (17), 43 (38%). IR and ^{1}H NMR spectroscopic data identical to that reported in the literature.[13]

3.2.2. *R*-(−)-2-Methoxy-2-phenylpropionic acid methyl ester (*R*-(−)-1). A solution of *R*-(−)-**2** (9.70 g, 53.8 mmol) in methanol (100 mL) with DOWEX 50Wx4 resin, H^+-form (2.7 g) was left for 4 days. Then, after the addition of methyl orthoformate (6 mL), the mixture was refluxed for 10 h. After evaporation the crude product was dissolved in CH_2Cl_2 (100 mL) and left overnight over anhd. K_2CO_3. Solvent evaporation gave pure (GC) *title product R*-(+)-**1** (8.8 g, 84%) as a yellowish oil; $[\alpha]_D=-12.9$ (*c* 0.92, MeOH); Lit.[8a] $[\alpha]_D=-12$, (*c* 1, MeOH). The enantiomeric excess of 90% was determined by ^{1}H NMR in CCl_4 in the

presence of 10 mol% of Eu(hfc)$_3$; $\Delta\delta=0.055$ ppm for the ester methyl singlet was observed with the signal for the major levoratory enantiomer shifted downfield. *S*-(+)-**1**, (90% yield); $[\alpha]_D=+11.9$ (*c* 0.9, MeOH); lit.[8c] for 44% e.e. $[\alpha]_D=+6.4$ (MeOH); *m/z* (EI, 70 eV) 194 (0.2, M^+), 135 (100), 105 (12), 77 (17), 43 (23%). IR and ^{1}H NMR spectroscopic data identical to that reported in the literature.[13]

3.2.3. *R*-5-Methoxy-5-phenyl-hexane-2,4-dione (*R*-(+)-3). To a sodium hydride (1.56 g, 32.5 mmol, 50% dispersion in oil) at 25 °C were added a solutions of *R*-(+)-**1** (2.99 g, 15.4 mmol) in dry ether (8 mL) and, under inert atmosphere by a syringe for 1.5 h, acetone (1.82 g, 31.4 mmol) in dry ether (8 mL). After 45 min the reaction flask was placed on a sonic bath and the addition was continued for the next 40 min. Then the mixture was poured into ether (20 mL), quenched by the addition of water and acidified to pH=2.5 with HCl (1 M). The layers were separated and the aqueous layer was extracted with ether (6×8 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4) and the solvent evaporated in vacuo giving 3.40 g of oiled mixture containing 78% (GC/MS) of the *title compound* (2.65 g, 78% yield). This crude product was submitted to the following step without purification. An analytical sample of *R*-(+)-**3** was isolated using column chromatography on silica gel (10% ethyl acetate/*n*-hexane) as a yellow oil; R_f 0.45 (10% ethyl acetate/*n*-hexane); $[\alpha]_D=+91$ (*c* 0.4, MeOH); ν_{max} (liquid film) 3089, 3060, 3026, 2987, 2937, 2831, 1729, 1712, 1599, 1447, 1246, 1173, 1134, 1072, 1047 cm^{-1}; δ_H (300 MHz, $CDCl_3$), for the main (81%) tautomer 15.05 (1H, bs, –O*H*), 7.28–7.46 (5H, m, Ph), 5.96 (1H, s, –C*H*=), 3.25 (3H, s, O–*Me*), 2.07 (3H, s, *Me*), 1.70 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 202.1, 187.5, 141.5, 128.2, 127.7, 126.2, 96.3, 86.2, 51.8, 23.8, 20.3; *m/z* (EI, 70 eV) 220 (0.14, M^+), 135 (100), 105 (7.5), 77 (10), 43 (22%); HRMS (EI): M^+ found 220.1104. $C_{13}H_{16}O_3$ requires 220.1099.

S-(−)-**3** $[\alpha]_D=-96$ (*c* 0.45, MeOH), 79% of the main tautomer by NMR.

3.2.4. *R*-3(5)-(1-Methoxy-1-phenyl-ethyl)-5(3)-methyl-1*H*-pyrazole (*R*-(+)-4). A solution of the crude diketone *R*-(+)-**3** (2.99 g, 12 mmol) and hydrazine monohydrate (2 mL, 41.2 mmol) in absolute ethanol (5 mL) was refluxed for 0.5 h and left overnight at room temperature. Ethanol was evaporated and the residue was partitioned between water (10 mL) and Et_2O (10 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), and the solvent evaporated in vacuo. Purification of the crude product by column chromatography (silica gel, $CHCl_3$/ethyl acetate/EtOH 2:1:0.05, v/v/v) gave the *title compound R*-(+)-**4** (1.55 g, 60% yield) as a yellow oil; R_f 0.34 ($CHCl_3$/ethyl acetate/EtOH 2:1:0.05); $[\alpha]_D=+36$ (*c* 0.86, MeOH); ν_{max} (liquid film) 3396, 3190, 3104, 2936, 2871, 1582, 1493, 1464, 1367, 1185, 1104 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24–7.41 (5H, m, Ph), 5.99–6.12 (1H, bs, N*H*), 5.86 (1H, s, H-4, pyrazole), 3.19 (3H, s, O*Me*), 2.27 (3H, s, *Me*), 1.85 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 151.9, 145.3, 144.5, 128.1, 126.1, 112.6, 103.9, 77.7, 51.0, 25.2, 12.4; *m/z* (EI, 70 eV) 216 (16, M^+), 201 (100), 185 (51), 139 (16), 105 (30), 77 (27%); HRMS (EI): M^+ found 216.1261. $C_{13}H_{16}ON_2$ requires 216.1263.

S-(−)-**4**; $[\alpha]_D=-35.7$ (*c* 0.98, MeOH).

3.2.5. *R*-2-[5-(1-Methoxy-1-phenylethyl)-3-methylpyrazol-1-yl]pyridine (*R*-5a). A solution of *R*-(+)-**3** (100 mg, 0.46 mmol), 2-hydrazinopyridine (50 mg, 0.46 mmol) and TsOH (catalytic amount) in ethanol (1.5 mL) was refluxed for 5 h and then left at room temperature for 2 days. Solvent was removed in vacuo and the residue was treated with water (10 mL) and extracted with CH_2Cl_2 (5×10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and evaporated in vacuo. Purification of the crude product by column chromatography on silica gel ($CHCl_3$/ethyl acetate/EtOH 2:1:0.025, v/v/v) gave the *title compound* (58 mg, 43% yield) as a brown oil; R_f 0.34 ($CHCl_3$/ethyl acetate/EtOH 2:1:0.025); $[\alpha]_D=+28$ (*c* 0.84, MeOH); ν_{max} (liquid film) 3086, 3058, 3025, 2983, 2935, 2827, 1590, 1575, 1477, 1446, 1364, 1103, 1066 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.24 (1H, dd, $J=4.8$, 1.5 Hz), 7.33 (1H, dt, $J=7.9$, 1.5 Hz), 6.97–7.11 (6H, m), 6.72 (1H, d, $J=7.9$ Hz), 6.29 (1H, s), 3.06 (3H, s), 2.30 (3H, s), 1.76 (3H, s); δ_C (75 MHz, $CDCl_3$) 152.8, 148.8, 148.1, 147.2, 145.2, 136.9, 127.7, 126.9, 125.8, 122.7, 121.0, 108.9, 77.5, 51.0, 26.8, 13.7; *m/z* (EI, 70 eV) 293 (6.7, M^+), 278 (100), 78 (21), 77 (12%); HRMS (EI): M^+ found 293.1533. $C_{18}H_{19}ON_3$ requires 293.1528.

3.2.6. *R*-2-Chloro-6-[5-(1-methoxy-1-phenylethyl)-3-methylpyrazol-1-yl] pyridine (*R*-5b). A solution of *R*-(+)-**3** (129 mg, 0.58 mmol) and 2-chloro-6-hydrazinopyridine (84 mg, 0.58 mmol) in ethanol (6 mL) was refluxed for 3 h, then stirred at room temperature for 17 h and finally concentrated in vacuo. Purification of the residue by column chromatography (silica gel, 10% ethyl acetate/*n*-hexane) gave the *title compound* (84 mg, 44%) as a red oil; R_f 0.33 (10% ethyl acetate/*n*-hexane); $[\alpha]_D=+32$ (*c* 0.74, MeOH); ν_{max} (liquid film) 3087, 3060, 3027, 2983, 2935, 2826, 1581, 1550, 1455, 1411, 1364, 1133, 1100, 1068 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35 (1H, t, $J=7.8$ Hz), 7.13–7.04 (5H, m), 7.01 (1H, dd, $J=7.8$, 0.7 Hz), 6.80 (1H, dd, $J=7.8$, 0.7 Hz), 6.31 (1H, s), 3.06 (3H, s), 2.28 (3H, s), 1.86 (3H, s); δ_C (75 MHz, $CDCl_3$) 152.3, 149.3, 148.9, 148.3, 139.4, 127.7, 127.5, 127.0, 126.1, 122.9, 118.7, 109.3, 76.7, 50.6, 26.1, 13.7; *m/z* (EI, 70 eV) 329 (2, M^+ +2), 327 (7, M^+), 312 (100), 297 (32), 210 (14), 105 (13), 77 (13%); HRMS (EI): M^+ found 327.1145. $C_{18}H_{18}O^{35}ClN_3$ requires 327.1138.

3.2.7. *R*-2-Chloro-6-[3-(1-methoxy-1-phenyl-ethyl)-5-methylpyrazol-1-yl]pyridine (*R*-6). To a solution of *R*-(+)-**4** (380 mg, 1.76 mmol) in toluene (15 mL) pieces of potassium (70 mg, 1.79 mmol) were added followed by the addition of two drops of abs. EtOH. The mixture was stirred at 90 °C until the metal was dissolved. Most of toluene was removed under the reduced pressure and the remaining suspension was treated with a solution of 2,6-dichloropyridine (260 mg, 1.76 mmol) in DMF (5 mL) and kept for 5 days at 67 °C. The mixture was concentrated in vacuo, treated with water (10 mL) and extracted with CH_2Cl_2 (5× 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. Purification of the crude product by column chromatography on silica gel (10% ethyl acetate/*n*-hexane) gave the *title compound* (352 mg, 62%) as a colourless oil; R_f 0.50 (10% ethyl acetate/*n*-hexane); $[\alpha]_D=+76$ (*c* 0.5, MeOH); ν_{max} (liquid film) 3088, 3059,

3026, 2985, 2934, 2826, 1577, 1557, 1472, 1434, 1375, 1131, 1120 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.84 (1H, d, J= 8.0 Hz), 7.65 (1H, dd, J=8.0, 7.8 Hz), 7.41 (2H, d, J= 7.9 Hz), 7.25 (2H, dd, J=7.9, 7.0 Hz), 7.17 (1H, t, J=7.0 Hz), 7.09 (1H, d, J=7.8 Hz), 5.97 (1H, s), 3.20 (3H, s), 2.57 (3H, s), 1.86 (3H, s); δ_C (75 MHz, $CDCl_3$) 157.5, 153.3, 148.7, 145.9, 142.3, 140.5, 128.0, 126.9, 126.0, 120.6, 113.8, 108.5, 78.5, 51.2, 24.6, 14.9; *m/z* (EI, 70 eV) 329 (0.2, M^+ +2), 327 (0.8, M^+), 312 (81), 297 (100), 112 (50), 103 (30), 77 (56), 51 (20%); HRMS (EI): M^+ found 327.1139. $C_{18}H_{18}O^{35}ClN_3$ requires 327.1138.

3.2.8. *R,R*-2,6-Bis[3-(1-methoxy-1-phenylethyl)-5-methylpyrazol-1-yl]pyridine (*R,R*-7). To a solution of *R*-(+)-**4** (746 mg, 3.45 mmol) in toluene (15 mL) was added potassium (144 mg, 3.68 mmol) and the reaction mixture was heated to 90 °C under neutral atmosphere until whole metal was dissolved. The mixture was concentrated in vacuo, treated with DMF (6 mL) and 2,6-dichloropyridine (127 mg, 0.86 mmol) and heated for 5 days in 110 °C. Cooled mixture was concentrated, poured into water (10 mL) and extracted with ether (5×8 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4) and evaporated in vacuo. Purification of the crude product by column chromatography on silica gel (*n*-hexane/$CHCl_3$/ethyl acetate, 6:1:1, v/v/v) gave the *title compound* (*R,R*)-**7** (186 mg, 43%) as a colourless oil; R_f 0.42 (*n*-hexane/$CHCl_3$/ethyl acetate, 6:1:1); $[\alpha]_D^{20}$ +88 (*c* 2.48, MeOH); ν_{max} (liquid film) 3088, 3058, 3026, 2984, 2935, 2826, 1598, 1584, 1471, 1435, 1359, 1145, 1123, 1075 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.87 (1H, t, J=8.1 Hz), 7.76 (2H, d, J=8.1 Hz), 7.66 (4H, d, J=7.9 Hz), 7.27–7.32 (4H, m), 7.20–7.23 (2H, m), 5.98 (2H, s), 3.26 (6H, s), 2.55 (6H, s), 1.92 (6H, s); δ_C (125 MHz, $CDCl_3$) 157.7, 152.0, 146.3, 141.6, 140.8, 128.4, 127.3, 126.5, 114.7, 108.2, 78.9, 51.6, 24.9, 14.8; *m/z* (EI, 70 eV) 507 (1.2, M^+), 445 (13), 43 (100), 39 (13%); HRMS (EI): M^+ found 507.2632. $C_{31}H_{33}O_2N_5$ requires 507.2634.

3.2.9. *R*-2-[3-(1-Methoxy-1-phenylethyl)-5-methyl-pyrazol-1-yl]pyridine-1-oxide (*R*-8). To the stirred solution of *R*-(+)-**4** (220 mg, 1.0 mmol) in toluene (3 mL) pieces of potassium were added (46 mg, 1.1 mmol) and the resulted suspension was heated in 80 °C under argon until whole metal was dissolved. After cooling, a solution of 2-chloropyridine N-oxide (200 mg, 1.5 mmol) in DMF (3 mL) was added dropwise from syringe for 35 min, stirred at this temperature for the next 30 min, and then at 60 °C for 22 h. Most of the solvents were evaporated and remaining DMF was removed in a desiccator. Purification of the crude product by column chromatography (gradient chloroform/chloroform–ethanol 2:0.07, v/v) gave 70 mg of recovered **4** (32%) and the *title compound R*-**8** (149 mg, 47%) as a colourless solid, mp 203–205 °C (EtOH); $[\alpha]_D$ = +80 (*c* 0.22, MeOH); ν_{max} (KBr) 3128, 3100, 3046, 2980, 1557, 1511, 1431, 1370, 1257, 1118, 1030 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.30–8.32 (1H, m), 7.53–7.57 (1H, m), 7.48 (2H, d, J=7.3 Hz), 7.20–7.34 (5H, m), 6.05 (1H, s), 3.27 (3H, s), 2.26 (3H, s), 1.88 (3H, s); δ_C (75 MHz, $CDCl_3$) 159.2, 145.8, 145.5, 144.1, 140.3, 128.0, 126.9, 126.4, 126.1, 125.45, 125.40, 106.1, 78.4, 51.2, 24.7, 11.6; *m/z* (EI, 70 eV) 277 (12), 260 (100), 249 (18), 78 (54), 51 (22%).

3.2.10. *R*-2-[3-(1-Methoxy-1-phenylethyl)-5-methyl-pyrazol-1-yl]pyridine (*R*-9). To a vigorously stirred suspension of *R*-**8** (87 mg, 0.3 mmol) in toluene (1.2 mL) and pyridine (0.8 mL) at 0 °C was added dropwise, by a syringe, phosphorus trichloride (0.1 mL, 1.2 mmol). The mixture was warmed to room temperature for 25 min and sonicated for further 30 min. Then, it was quenched with ice in $NaHCO_3$ (sat. aq), made alkaline (pH≅9), and extracted with ether (5×5 mL). The combined organic layers were washed with brine (5 mL), dried (K_2CO_3), evaporated in vacuo and dried overnight in a vacuum desiccator over H_2SO_4 giving the *title compound R*-**9** (50 mg, 59%, >97% pure, GC/MS) as a colourless oil; R_f 0.59 (3.5% EtOH/$CHCl_3$); $[\alpha]_D$ = +90 (*c* 0.96, MeOH); ν_{max} (liquid film) 3086, 3060, 2984, 2934, 2826, 1591, 1579, 1557, 1475, 1429, 1370, 1144, 1089 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.41–8.42 (1H, m), 7.93 (1H, d, J=8.1 Hz), 7.78 (1H, dt, J=8.1, 1.5 Hz), 7.49 (2H, d, J=7.4 Hz), 7.21–7.34 (3H, m), 7.15 (1H, dd, J=6.8, 1.5 Hz), 6.02 (1H, s), 3.27 (3H, s), 2.63 (3H, s), 1.93 (3H, s); δ_C (75 MHz, $CDCl_3$) 156.8, 153.9, 147.4, 146.2, 141.6, 138.2, 128.1, 126.8, 126.1, 120.9, 116.3, 107.9, 78.5, 51.2, 25.0, 14.6; *m/z* (EI, 70 ev) 293 (1.5, M^+), 278 (69), 263 (100), 216 (10), 105 (17), 78 (38), 77 (21), 51 (13%); HRMS (EI): M^+ found 293.1527. $C_{18}H_{19}ON_3$ requires 293.1528.

3.2.11. *R,R*-6,6′-Bis[3-(1-methoxy-1-phenylethyl)-5-methylpyrazol-1-yl]-[2,2′]bipyridine (*R,R*-10). A suspension of [$NiCl_2(PPh_3)_2$] (441 mg, 0.67 mmol), PPh_3 (353 mg, 1.34 mmol), and zinc dust (48 mg, 0.73 mmol), in DMF (3 mL) was vigorously stirred in argon atmosphere at 50 °C changing color from dark blue to brown-deep red. Then, a solution of *R*-**6** (221 mg, 0.67 mmol) and slight amount of NaI in DMF (2 mL) was added, by a syringe, and the whole mixture was stirred at 50 °C for 24 h. Cooled mixture was quenched by addition of NH_3 (10 mL, 25% aq) and brine (5 mL) and extracted with CH_2Cl_2 (5×8 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried (Na_2SO_4) and evaporated in vacuo. The crude product, dried from DMF in a desiccator over sulfuric acid, was purified by column chromatography (silica gel, 2.5% EtOH/$CHCl_3$) and gave the *title compound* (*R,R*)-**10** (95 mg, 48%) as a white solid, mp 116–118 °C; $[\alpha]_D$ = +137, (*c* 0.7, CH_2Cl_2); ν_{max} (KBr) 3109, 3085, 3058, 2985, 2931, 2824, 1589, 1569, 1466, 1430, 1370, 1090 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.15 (2H, d, J=7.7 Hz), 7.97 (2H, d, J=8.0 Hz), 7.85 (2H, dd, J=8.0, 7.7 Hz), 7.44 (4H, d, J=7.1 Hz), 7.26 (4H, dd, J=7.7, 7.1 Hz), 7.15–7.19 (2H, m), 6.01 (2H, s), 3.27 (6H, s), 2.75 (6H, s), 1.88 (6H, s); δ_C (75 MHz, $CDCl_3$) 157.0, 153.7, 153.3, 146.1, 141.4, 139.3, 128.0, 126.8, 126.1, 117.9, 116.2, 108.2, 78.6, 51.2, 24.7, 15.5; *m/z* (EI, 70 eV) 584 (12, M^+), 569 (37), 552 (79), 522 (100), 277 (14), 269 (13), 105 (11%); HRMS (EI): M^+ found 584,2922. $C_{36}H_{36}O_2N_6$ requires 584.2900.

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