Synthesis of a Novel Optically Active C_2-Symmetric 2,2′-Bipyridine

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Received August 12, 1991

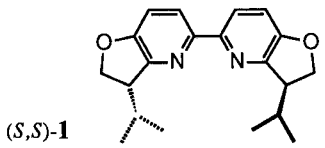
Key Words: 2,2′-Bipyridine / Chiral ligand / Palladium complexes / Copper complexes / Cobalt complexes

Optically active 2,2′-bipyridine (*S,S*)-**1** was synthesized by radical cyclization and a nickel(0)-mediated coupling of enantiomerically pure bromopyridine (*S*)-**8**. Palladium, copper, and cobalt complexes of **1** were prepared. The solid-state structures of *meso*-**1** and **11** were determined by X-ray crystal structure analysis.

Successful asymmetric catalysis by metal complexes relies mainly on the use of appropriate optically active ligands. They must create a favorable chiral environment at the metal center together with suitable kinetics to effect enantioselective catalysis[1].

Optically active 2,2′-bipyridines have been used in several enantioselective chemical transformations including alkylation of aldehydes[2], conjugate addition to enones[3], and reduction of ketones by hydrogen transfer or hydrosilylation[4]. 2,2′-Bipyridines bearing a chelating side chain have been synthesized with the intention of reducing conformational flexibility by additional intramolecular interaction between the ligand and the complexed metal. The presence of a twofold axis of symmetry is expected to reduce the number of possible diastereomeric conformations in the stereo-determining step[5].

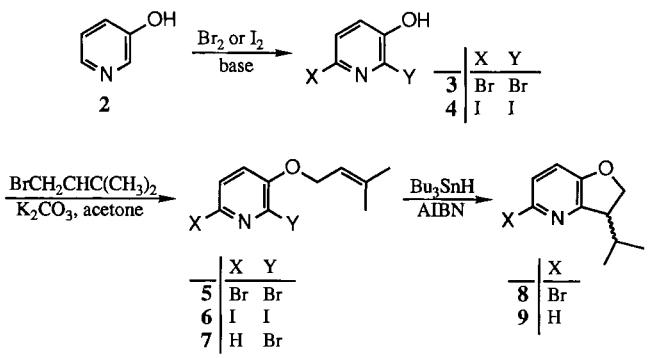
In this paper the synthesis of enantiomerically pure 2,2′-bipyridine (*S,S*)-**1** is described. The major features of this compound are its C_2 axis and its high rigidity caused by the steric constraints of the annulated dihydrofuran rings.



(*S,S*)-**1**

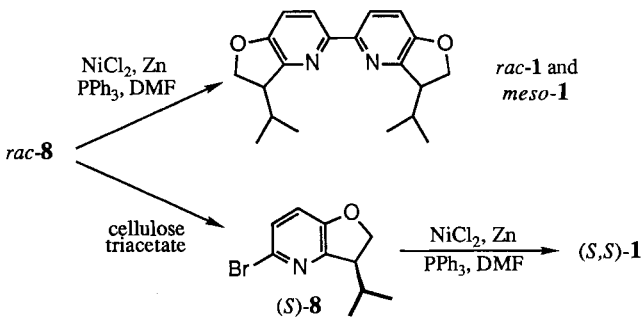
2,6-Dibromo-3-hydroxypyridine (**3**) was obtained by the reaction of 3-hydroxypyridine (**2**) with bromine in aqueous NaOH[6]. Allylation of **3** with 3-methyl-2-butenyl bromide under basic conditions in acetone afforded **5** in 92% yield. Radical cyclization using one equivalent of Bu_3SnH and AIBN as initiator gave a product mixture in which **8** was identified as the major compound (29% of unreacted **5**; product ratio **7**:**8**:**9** = 14:76:10)[7]. *rac*-**8** was isolated by column chromatography followed by kugelrohr distillation in 42% yield. Slow addition of Bu_3SnH and AIBN by a syringe pump or by use of tris(trimethylsilyl)silane[8] instead of Bu_3SnH gave lower conversions of **5** (^{1}H-NMR analysis of the crude mixture). Using two equivalents of Bu_3SnH, we obtained **9** as the major product. 2,6-Diiodopyridine **6** was synthesized by treatment of **2** with I_2 under basic conditions (Na_2CO_3 in water) to give **4**[6], followed by allylation with 3-methyl-2-butenyl bromide in acetone. Radical cyclization of **6** did not lead to a major improvement in the formation of the corresponding cyclized product.

Scheme 1



Nickel(0)-mediated coupling[9] of *rac*-**8** gave the two diastereomers *rac*-**1** and *meso*-**1**, which could be separated by column chromatography. The ^{1}H- (400 MHz) and ^{13}C-NMR spectra (75 MHz) of *rac*-**1** and *meso*-**1** were identical. The structure of *meso*-**1** was ultimately assigned by X-ray analysis (Figure 1)[10].

Scheme 2



  0009–2940/92/0202–453 $ 3.50+.25/0

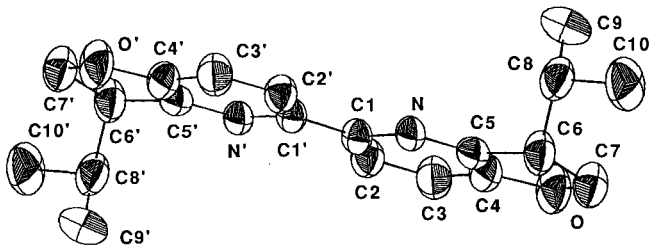
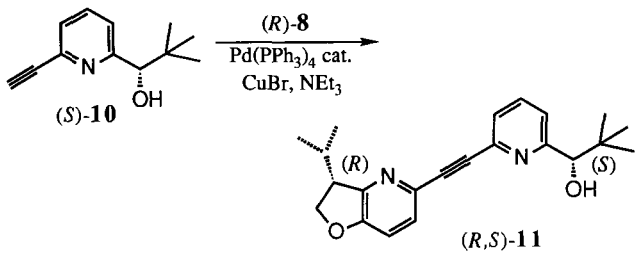


Figure 1. Molecular structure of *meso*-**1** (ORTEP, 50% probability ellipsoids, with atomic numbering; H atoms omitted for clarity)[10]

In order to synthesize enantiomerically pure **1**, the enantiomers of **8** were separated by column chromatography (or MPLC) by using cellulose triacetate as the stationary phase[11]. The resolution of **8** was almost complete; only a few small fractions of scalemic mixtures were obtained. The enantiomeric excess during the separation process was determined by HPLC on a stationary chiral phase (Chiralcel OD, DAICEL).

In order to determine the absolute configuration of **8**, (*S*)-**10**[12] was coupled by palladium(0) catalysis with the second enantiomer of **8** eluted during the cellulose triacetate resolution to afford **11** in 75% yield. Bispyridine **11** was then analyzed by X-ray diffraction (Figure 2)[10]. According to this analysis, (*R*)-**8** was the slower eluting enantiomer.

Scheme 3



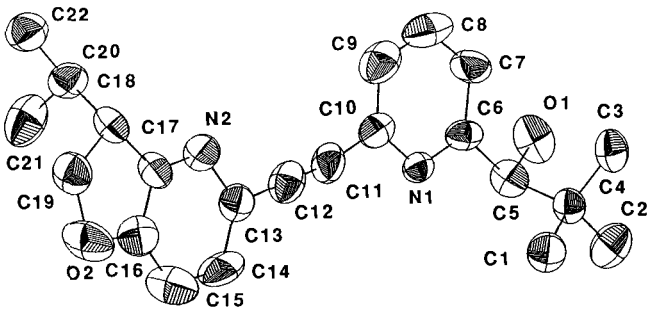


Figure 2. Molecular structure of compound (*R*,*S*)-**11** (ORTEP, 50% probability ellipsoids, with atomic numbering; H atoms omitted for clarity)[10]

Optically pure (*S*,*S*)-(−)-**1** was obtained by nickel(0)-mediated coupling of enantiomerically pure (*S*)-**8** in 63% yield (Scheme 2). From the characteristic downfield shift of the NMR signals of the protons at C3/3′ (**1**: $\delta H_{3/3'} = 8.12$), a transoid orientation of the pyridine nitrogens must be assumed in solution[13]. This arrangement was also found for *meso*-**1** and **11** in the solid state.

To test the complexation behavior of this sterically crowded bipyridine[14], (*S*,*S*)-**1** was treated with $PdCl_2 \cdot (CH_3CN)_2$ in acetonitrile. Upon standing, brown crystals of **1** · $PdCl_2$ were formed which could be recrystallized from ethyl acetate. The upfield shift in the proton spectrum of the resulting complex for the protons at C3/3′ indicate that both pyridine nitrogen atoms coordinate to the palladium ion (**1** · $PdCl_2$: $\delta H_{3/3'} = 7.56$). A fragment of composition **1** · $PdCl^+$ was observed by FAB mass spectrometry. The use of $CoCl_2$ also led to the formation of a 1:1 complex which was identified by elemental analysis and FAB/MS. Addition of copper(I) triflate or $CuBF_4 \cdot (CH_3CN)_4$ resulted in a red solution; however, only broadening but no shift differences were observed in the ^{1}H-NMR spectra recorded in either $CDCl_3$ or CD_3CN at room temperature. Evaporation of the solvent gave a red solid, which showed a signal for $\mathbf{1}_2 \cdot Cu^+$ in FAB/MS. The further coordination behavior of 2,2′-bipyridine **1** and its use in asymmetric catalysis is currently under investigation.

This research was generously supported by the *Volkswagen-Stiftung* and the *Ciba-Stiftung*. C. B. is grateful to the *Fonds der Chemischen Industrie* for a Liebig fellowship and the *Freiwilligen Akademischen Gesellschaft* for a Treubel Fonds stipend. We acknowledge the help of *D. Glasmacher*.

Experimental

^{1}H- and ^{13}C-NMR: Varian Gemini 300, Varian VXR 400; solvent $CDCl_3$, unless noted otherwise. Chemical shifts given in values relative to TMS for protons; $CDCl_3$ (δ = 77) for carbon atoms. – Melting points: Kofler melting point apparatus (corrected values). – IR: Perkin-Elmer 781. – MS: VG 70–250. – All reactions were carried out in flame-dried glassware under argon using anhydrous solvents. Products were isolated by CC or flash chromatography on SiO_2 (35–70 micron) and detected by UV or phosphomolybdic acid (PMA). – For the separation of enantiomers: cellulose triacetate, 25–40 micron. – HPLC: Kontron Instruments (pump: Kontron 420, detector: Kontron 432); column: Chiralcel OD (Daicel), 25 cm × 0.46 cm I.D. – X-ray: Enraf-Nonius CAD4.

Preparation of Compounds: 2,6-Dibromo-3-hydroxypyridine (**3**)[6], 2,6-diiodo-3-hydroxypyridine (**4**)[6b], 2-bromo-3-pyridinyl 3-methyl-2-butenyl ether (**7**)[7], *rac*-2,3-dihydro-3-isopropylfuro[3,2-*b*]pyridine (**9**)[7], and (*S*)-1-(6-ethinyl-2-pyridinyl)-2,2-dimethyl-1-propanol (**10**)[12] were prepared according to known procedures.

2,6-Dibromo-3-pyridinyl 3-Methyl-2-butenyl Ether (**5**): A suspension of 2.53 g (10 mmol) of **3**, 1.79 g (12 mmol) of 3-methyl-2-butenyl bromide, and 3.32 g (24 mmol) of K_2CO_3 in 25 ml of acetone was refluxed for 1.5 h. After cooling to room temp. the solvent was removed under reduced pressure, and 100 ml of diethyl ether followed by 20 ml of water was added. The organic layer was separated and dried with Na_2SO_4. The solvent was removed to give 3.17 g of a yellow solid which was recrystallized from hexane (20 ml): 2.96 g (92%) of **5**. TLC: **3**: R_f = 0.15 (silica gel, hexane/ethyl acetate, 3:1), **5**: R_f = 0.39 (same solvent system). M.p. 76–77°C. – IR (KBr): $\tilde{\nu}$ = 1938 cm^{-1} (m), 1548 (m), 1422 (s), 1373 (s), 1270 (s), 1230 (s), 1055 (s), 970 (s), 822 (s), 699 (m), 627 (m). – ^{1}H NMR: δ = 1.75 (s, 3H, CH_3), 1.79 (d, J = 0.7 Hz, 3H, CH_3), 4.61 (d, J = 6.6 Hz, 2H, CH_2), 5.41–5.61 (m, 1H, CH), 7.02 (d, J = 8.5 Hz, 1H, aromatic H), 7.35 (d, J = 8.5 Hz, 1H, aromatic H). – ^{13}C NMR: δ = 16.3 (CH_3), 25.6 (CH_3), 66.7 (CH_2), 116.1 (CH), 122.7 (CH),

127.3 (CH), 131.6 (C), 139.8 (C), 152.1 (C). – MS (EI, 70 eV): *m/z* (%) = 324 (2) [M + 1$^+$], 323 (1) [M$^+$], 322 (2) [M + 1$^+$], 321 (2) [M$^+$], 319 (1) [M$^+$], 256 (18), 255 (48), 254 (31), 253 (100), 252 (22), 251 (50), 226 (39), 224 (87), 222 (41).

$C_{10}H_{11}Br_2NO$ (321.0)
Calcd. C 37.41 H 3.46 N 4.36
Found C 37.55 H 3.34 N 4.37

2,6-Diiodo-3-pyridinyl 3-Methyl-2-butenyl Ether (**6**): A suspension of 10.41 g (30 mmol) of **4**, 5.37 g (36 mmol) of 3-methyl-2-butenyl bromide, and 9.95 g (72 mmol) of K_2CO_3 in 75 ml of acetone was refluxed for 1 h. After cooling to room temp. the solvent was removed under reduced pressure, and 150 ml of diethyl ether followed by 60 ml of water was added. The aqueous layer was extracted three times with 60 ml each of diethyl ether, and the combined organic layers were washed with 150 ml of brine and dried with Na_2SO_4. The solvent was removed under reduced pressure to give a yellow solid which was recrystallized from hexane (40 ml): 5.28 g (42%) of **6**. M.p. 58°C (hexane). – IR (KBr): $\tilde{\nu}$ = 2930 cm^{-1} (m), 1550 (m), 1419 (s), 1381 (m), 1342 (s), 1288 (s), 1279 (s), 1229 (m), 1048 (s), 975 (m), 823 (s). – ^{1}H NMR: δ = 1.75 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 4.59 (d, *J* = 6.6 Hz, 2H, CH_2), 5.42–5.46 (m, 1H, CH), 6.69 (d, *J* = 8.3 Hz, 1H, aromatic H), 7.53 (d, *J* = 8.5 Hz, 1H, aromatic H). – ^{13}C NMR: δ = 18.3 (CH_3), 25.6 (CH_3), 66.6 (CH_2), 103.4 (C), 111.5 (C), 118.3 (CH), 120.6 (CH), 134.2 (CH), 139.8 (C), 155.5 (C). – MS (EI, 70 eV): *m/z* (%) = 347 (45), 220 (8), 165 (6), 69 (100), 64 (12), 41 (55). – MS (CI, NH_3): *m/z* (%) = 416 (60) [M + 1$^+$], 348 (100), 290 (16), 222 (50), 96 (68).

$C_{10}H_{11}I_2NO$ (415.0)
Calcd. C 28.94 H 2.68 N 3.38
Found C 29.21 H 2.69 N 3.62

2-Bromo-3-pyridinyl 3-Methyl-2-butenyl Ether (**7**)[7]: ^{1}H NMR: δ = 1.76 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 4.64 (d, *J* = 7 Hz, 2H, CH_2), 5.48 (t, *J* = 7 Hz, 1H, CH), 7.12–7.24 (m, 2H, aromatic H), 7.98 (m, 1H, aromatic H).

rac-6-Bromo-2,3-dihydro-3-isopropylfuro[3,2-b]pyridine (*rac*-**8**): A solution of 321 mg (1.0 mmol) of **5**, 291 mg (1.0 mmol) of Bu_3SnH and 60 mg (0.37 mmol) of AIBN in 25 ml of toluene was heated to 95°C (oil bath) for 20 h. The solvent was removed under reduced pressure, and 20 ml of diethyl ether followed by 10 ml of a satd. solution of KF was added to the residue. Upon stirring, a white precipitate formed. After stirring at room temp. for 4 h the aqueous layer was separated and extracted three times with diethyl ether. The combined organic layers were washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure to give 420 mg of a yellow oil (^{1}H-NMR analysis of the crude mixture: **5**:**7**:**8**:**9** = 29:10:54:7; corresponding to a product ratio of **7**:**8**:**9** = 14:76:10). **8** was purified by kugelrohr distillation (50–125°C/3.5 mbar) to give 128 mg of a product mixture, followed by chromatography (CC: 40 g of silica gel, petroleum ether/ethyl acetate, 10:1): 103 mg (42%) of **8**.

6.5 g (20.25 mmol) of **5**, 5.9 g (20.25 mmol) of Bu_3SnH, and 1.4 g (8.53 mmol) of AIBN in 500 ml of toluene gave 1.4 g (29%) of **8**. The work up was modified as follows: The white precipitate which formed after the addition of a satd. aqueous KF solution was separated by filtration and the solvent of the organic layer was removed under reduced pressure. The residue was dissolved in 150 ml of acetonitrile and the resulting solution was extracted three times with 120 ml each of petroleum ether. The combined petroleum ether layers were extracted twice with 30 ml each of acetonitrile. All combined acetonitrile layers were dried with Na_2SO_4, and **8** was isolated and purified as described above (kugelrohr distillation and CC [80 g of silica gel, petroleum ether/ethyl acetate, 10:1]); white solid, m.p. 48–49°C. – ^{1}H NMR: δ = 0.85 (d, *J* = 6.9 Hz, 3H, CH_3), 1.01 (d, *J* = 6.9 Hz, 3H, CH_3), 2.16–2.27 [m, 1H, C*H*(CH_3)$_2$], 3.34–3.41 (m, 1H, C*H*CH_2), 4.49 (dd, *J* = 9.4, 5.8 Hz, 1H, CHC*H*$_2$), 4.64 (dd, *J* = 9.5, 9.5 Hz, 1H, CHC*H*$_2$), 6.91 (d, *J* = 8.4 Hz, 1H, aromatic H), 7.17 (dd, *J* = 8.5, 0.6 Hz, 1H, aromatic H). – ^{13}C NMR: δ = 17.6 (CH_3), 20.0 (CH_3), 30.7 (CH), 47.8 (CH), 73.6 (CH_2), 116.3 (CH), 126.1 (CH), 134.4 (C), 153.8 (C), 154.0 (C). – MS (EI, 70 eV): *m/z* (%) = 243 (17) [M$^+$], 241 (16) [M$^+$], 201 (78), 200 (100), 199 (83), 198 (92), 124 (60), 123 (60), 91 (61), 90 (45), 64 (45), 41 (68), 32 (58).

$C_{10}H_{12}BrNO$ (242.1)
Calcd. C 49.60 H 5.01 N 5.79
Found C 49.32 H 4.95 N 5.84

Resolution of **8** *by Using Cellulose Triacetate (CTA) as Stationary Phase:* A stirred suspension of 250 g of CTA in 700 ml of 95% EtOH was refluxed for 30 min. After cooling to room temp. the slurry was sonicated in an ultrasonic bath for 3 min and transferred to the chromatography column (diameter: 9 cm, packing height: 15 cm). The column was then loaded with *rac*-**8** (1 g), dissolved in 4 ml of 95% EtOH (warming). After 700 ml of the solvent had been eluted, samples with a volume of approximately 20 ml were collected. The solvent of each sample was removed and the residue analyzed by HPLC using a chiral stationary phase [HPLC analysis: Chiralcel OD (DAICEL), 0.2% 2-propanol in hexane; flow rate 1.0 ml/min, UV detector (254 nm); retention times: (*R*)-**8**: 7.2 min, (*S*)-**8**: 8.5 min. The elution order was the reverse to that on cellulose triacetate.] Combination of appropriate samples gave 4 fractions (A–D). A: 471 mg of (*S*)-**8**; B: 40 mg of (*S*)-**8**:(*R*)-**8** = 96:4; C: 99 mg of (*S*)-**8**:(*R*)-**8** = 13:87 and D: 391 mg of (*R*)-**8**. Attempts to recrystallize the fractions from petroleum ether/ethyl acetate failed. Fractions A and D were dissolved in hexane and filtered. Slow evaporation of the solvent from the filtrate gave two slightly yellowish solids. Fraction A: m.p. 34°C; fraction D: m.p. 37–38°C. Recrystallization of fraction D (80 mg from 5 ml of hexane and slow evaporation of the solvent) gave white needles, m.p. 56.5–58.5°C. [α]$_D$ +41.4 (*c* = 0.37, EtOH). The relative configuration of derivative **11** was determined by X-ray diffraction analysis. According to this analysis, the slower eluting enantiomer (fraction D) had (*R*)-configuration.

rac-2,3-Dihydro-3-isopropylfuro[3,2-b]pyridine (**9**)[7]: ^{1}H NMR: δ = 0.87 (d, *J* = 6.8 Hz, 3H, CH_3), 1.03 (d, *J* = 6.9 Hz, 3H, CH_3), 2.17–2.26 [m, 1H, C*H*(CH_3)$_2$], 3.36–3.43 (m, 1H, C*H*CH_2), 4.47 (dd, *J* = 9.4, 5.8 Hz, 1H, CH_2), 4.63 (dd, *J* = 9.5, 9.4 Hz, 1H, CH_2), 7.01 (d, *J* = 3.6 Hz, 2H, aromatic H), 8.07–8.09 (m, 1H, aromatic H).

(3S,3'S)-2,2',3,3'-Tetrahydro-3,3'-diisopropyl-5,5'-bi(furo[3,2-b]pyridine) [(*S,S*)-**1**]: A solution of 0.428 g (1.80 mmol) of nickel dichloride hexahydrate in 9 ml of carefully degassed DMF was heated to 72°C (oil bath temp.), and 1.900 g (7.2 mmol) of triphenylphosphane was added. The green solution turned blue. After the addition of zinc powder (0.127 g, 1.94 mmol) the resulting brown mixture was stirred at 70°C for 1 h. A solution of 0.359 g (1.48 mmol) of (*S*)-**8** in 2 ml of carefully degassed DMF was added, and stirring was continued at 70°C for 2 h. The brown mixture was cooled to room temp. (30 min) and quenched with 15 ml of 5% ammonia. The mixture was extracted three times with 50 ml each of CH_2Cl_2/diethyl ether (2:1), and the combined organic layers were concentrated under reduced pressure. The residue was dissolved in 30 ml of CH_2Cl_2 and extracted four times with 10 ml each of water. The organic layer was washed with 20 ml of brine and dried with Na_2SO_4. The solvent was removed under reduced pressure to give 2.77 g of a red-brown oil that solidified upon standing. (*S,S*)-**1** was

isolated by chromatography (CC: 80 g of silica gel, petroleum ether/ethyl acetate, 10:1): 0.152 g (63%) of (*S,S*)-**1**; white crystals, m.p. 105–106.5°C (hexane). TLC: R_f = 0.17 (silica gel, petroleum ether/ethyl acetate, 10:1), $[\alpha]_D$ = −51 (*c* = 0.3 $CHCl_3$). – ^{1}H NMR: δ = 0.95 (d, *J* = 6.7 Hz, 6H, CH_3), 1.09 (d, *J* = 6.7 Hz, 6H, CH_3), 2.17–2.26 [m, 2H, $CH(CH_3)_2$], 3.37–3.44 (m, 2H, CHCH), 4.49 (dd, *J* = 9.4, 6.0 Hz, 2H, CH_2), 4.69 (dd, *J* = 9.4, 9.4 Hz, 2H, CH_2), 7.09 (d, *J* = 8.6 Hz, 2H, aromatic H), 8.12 (d, *J* = 8.6 Hz, 2H, aromatic H). – ^{1}H NMR (CD_3CN/TMS): δ = 0.94 (d, *J* = 6.8 Hz, 6H, CH_3), 1.06 (d, *J* = 6.9 Hz, 6H, CH_3), 2.10–2.19 [m, 2H, $CH(CH_3)_2$], 3.36–3.43 (m, 2H, CHCH), 4.49 (dd, *J* = 9.5, 6.2 Hz, 2H, CH_2), 4.70 (dd, *J* = 9.5, 9.5 Hz, 2H, CH_2), 7.10 (d, *J* = 8.3 Hz, 2H, aromatic H), 8.08 (d, *J* = 8.5 Hz, 2H, aromatic H). – ^{13}C NMR: δ = 18.4 (CH_3), 19.9 (CH_3), 31.1 (CH), 47.9 (CH), 73.8 (CH_2), 116.0 (CH), 119.3 (CH), 149.4 (C), 152.4 (C); 153.7 (C). – MS (EI, 70 eV): *m/z* (%) = 325 (10) [M + 1$^+$], 324 (43) [M$^+$], 282 (62), 281 (100), 238 (8), 237 (21), 200 (9).

$C_{20}H_{24}N_2O_2$ (324.5)
Calcd. C 74.03 H 7.47 N 8.64
Found C 73.85 H 7.28 N 8.50

(3S,3'R)-2,2',3,3'-Tetrahydro-3,3'-diisopropyl-5,5'-bi(furo[3,2-b]pyridine) (*meso*-**1**): Nickel(0)-mediated homocoupling of *rac*-**8** gave a mixture of approximately 1:1 of *rac*-**1** and *meso*-**1**: TLC: R_f = 0.26 (silica gel, petroleum ether/ethyl acetate, 10:1), m.p. 177–178°C. – IR (KBr): $\tilde{\nu}$ = 2955 cm^{-1} (s), 1578 (m), 1475 (m), 1425 (s), 1237 (s), 1159 (s), 1105 (s), 942 (s), 833 (s). – The ^{1}H- and ^{13}C-NMR data were identical with those of (*S,S*)-**1**. – MS (EI, 70 eV): *m/z* (%) = 325 (10) [M + 1$^+$], 324 (41) [M$^+$], 283 (15), 282 (94), 281 (100), 237 (30).

$C_{20}H_{24}N_2O_2$ (324.5)
Calcd. C 74.03 H 7.47 N 8.64
Found C 74.06 H 7.38 N 8.73

(3S,3'S)-2,2',3,3'-Tetrahydro-3,3'-diisopropyl-5,5'-bi(furo[3,2-b]pyridine) Cobalt(II) Complex (*S,S*)-**1** · $CoCl_2$: A solution of 12.5 mg (0.053 mmol) of $CoCl_2 \cdot 6\ H_2O$ in 1 ml of MeOH was added to a stirred solution of 17 mg (0.052 mmol) of (*S,S*)-**1** in 3 ml of acetonitrile. A brown solution resulted which was refluxed for 30 min. The solvent was slowly evaporated to leave a brown solid that was recrystallized from 3 ml of toluene. Black-brown crystals were obtained. Recrystallization from 2 ml of ethyl acetate gave brown microcrystals. – IR (KBr): $\tilde{\nu}$ = 2960 cm^{-1} (m), 1590 (m), 1479 (m), 1435 (s), 1240 (s), 942 (m), 832 (m). – MS (FAB, NBA): *m/z* (%) = 420 (34) [**1** + CoCl$^+$], 419 (25) [**1** + CoCl$^+$], 418 (25) [**1** + CoCl$^+$], 417 (11), 381 (20), 374 (10), 325 (13) [M + 1$^+$].

$C_{20}H_{24}Cl_2CoN_2O_2$ (454.3)
Calcd. C 52.87 H 5.34 N 6.17
Found C 52.45 H 5.73 N 5.93

(3S,3'S)-2,2',3,3'-Tetrahydro-3,3'-diisopropyl-5,5'-bi(furo[3,2-b]pyridine) Palladium Complex (*S,S*)-**1** · $PdCl_2$: A solution of 26 mg (0.100 mmol) of $PdCl_2 \cdot (CH_3CN)_2$ in 5 ml of acetonitrile was added to a solution of 26 mg (0.080 mmol) of (*S,S*)-**1** in 5 ml of acetonitrile. No color change was observed. The clear solution was refluxed for 15 min and filtered. Slow cooling and evaporation of the solvent resulted in the formation of a golden solid (46 mg). Recrystallization from ethyl acetate (31 mg in 30 ml of solvent) and slow evaporation of the solvent at room temp. gave golden-brown crystals, m.p. 235°C (dec.). – IR (KBr): $\tilde{\nu}$ = 2970 cm^{-1} (m), 1424 (s), 1245 (s), 1223 (s), 954 (m), 838 (m). – ^{1}H NMR: δ = 0.61 (d, *J* = 7.0 Hz, 6H, CH_3), 1.05 (d, *J* = 6.9 Hz, 6H, CH_3), 2.86–2.91 [m, 2H, $CH(CH_3)_2$)], 4.52–4.63 (m, 4H, CHCH, CH_2), 5.18–5.23 (m, 2H, CH_2), 7.27 (d, *J* = 8.6 Hz, 2H, aromatic H), 7.56 (d, *J* = 8.7 Hz, 2H, aromatic H). – MS (FAB, NBA): *m/z* (%) = for [**1** + PdCl$^+$]: 469 (1), 467 (3), 466 (2), 465 (4), 464 (2), 463 (1); for [**1** + Pd$^+$]: 435 (2), 434 (14), 433 (25), 432 (36), 431 (52), 430 (5), 429 (82), 428 (66).

$C_{20}H_{24}Cl_2N_2O_2Pd$ (501.8)
Calcd. C 47.87 H 4.83 N 5.58
Found C 49.19 H 5.57 N 5.52

No correct elemental analysis could be obtained.

(3S,3'S)-2,2',3,3'-Tetrahydro-3,3'-diisopropyl-5,5'-bi(furo[3,2-b]pyridine) Copper(I) Complex (*S,S*)-**1** · $CuBF_4$: A solution of 7 mg (0.022 mmol) of (*S,S*)-**1** in 2 ml of acetonitrile was heated to 60°C (oil bath) and treated with a warm (60°C) solution of 13 mg (0.041 mmol) of $CuBF_4 \cdot (CH_3CN)_4$ in 2 ml of acetonitrile. A red color appeared immediately. [^{1}H NMR (CD_3CN/TMS): Extensive line broadening after the addition of $CuBF_4 \cdot (CH_3CN)_4$.] The solution was kept at 62°C (oil bath temp.) for 15 min, and the solvent was slowly evaporated at room temp. to give a red solid. – MS (FAB, NBA): *m/z* (%) = 714 (28), 713 (56) [**1**$_2$ + Cu$^+$], 712 (48) [**1**$_2$ + Cu$^+$], 711 (100) [**1**$_2$ + Cu$^+$], 389 (36) [**1** + Cu$^+$], 388 (21) [**1** + Cu$^+$], 387 (80) [**1** + Cu$^+$], 326 (21), 325 (88) [M + 1$^+$], 324 (52) [M$^+$], 323 (12), 282 (13), 281 (24).

(S)-1-{6-[(R)-2,3-Dihydro-3-isopropylfuro[3,2-b]pyridine-5-yl-ethynyl]-2-pyridinyl}-2,2-dimethyl-1-propanol (**11**): A stirred solution of 78 mg (0.413 mmol) of (*R*)-**8** (second enantiomer eluted during the cellulose triacetate separation), 11.4 mg (0.010 mmol) of tetrakis(triphenylphosphane)palladium(0), and 3.6 mg (0.025 mmol) of copper(I) bromide in 1.7 ml of dry triethylamine was treated with 100 mg (0.413 mmol) of (*S*)-**10** [(*S*)-**10**:(*R*)-**10** = 96:4]. After 5 h at 50°C (oil bath temp.) the brown mixture was cooled to room temp., and 30 ml of diethyl ether was added. The solution was washed twice with 7 ml each of a satd. aqueous NH_4Cl solution. After drying of the organic phase with Na_2SO_4, the solvent was removed under reduced pressure to give 157 mg of a brown oil which was purified by chromatography (CC: 11 g of silica gel, petroleum ether/ethyl acetate, 2:1): 119 mg (82%) of **11**; yellowish oil, which crystallized after the addition of ethyl acetate (0.2 ml). TLC: R_f = 0.56 (silica gel, petroleum ether/ethyl acetate, 1:2). ^{1}H-NMR spectroscopy indicated the presence of two diastereomers (identified by a comparison with a ^{1}H-NMR spectrum of a diastereomeric mixture of **11** which was obtained by coupling of *rac*-**8** with *rac*-**10**). Recrystallization of 48 mg of **11** (3 ml of ethyl acetate) gave crystals which consisted of the major diastereomer only. The relative configuration was determined by X-ray structure analysis[10]. – Major diastereomer of **11** [from (*S*)-**10** and (*R*)-**8**]: $[\alpha]_D$ = +58.6 (*c* = 0.58 EtOH). – ^{1}H NMR: δ = 0.85 (d, *J* = 6.1 Hz, 3H, CH_3), 0.93 [s, 9H, $C(CH_3)_3$], 1.03 (d, *J* = 6.1 Hz, 3H, CH_3), 2.28–2.34 [m, 1H, $CH(CH_3)_2$], 3.40–3.47 (m, 1H, $CHCH_2$), 4.27 (d, D_2O exchange, *J* = 7.4 Hz, 1H, OH), 4.38 (d, *J* = 7.1 Hz, 1H, CHOH), 4.55 (dd, *J* = 9.4, 5.4 Hz, 1H, CH_2), 4.89 (dd, *J* = 10.4, 9.3 Hz, 1H, CH_2), 6.99–7.02 (m, 1H, aromatic H), 7.17 (d, *J* = 5.8 Hz, 1H, aromatic H), 7.42 (d, *J* = 8.2 Hz, 1H, aromatic H), 7.49 (d, *J* = 7.7 Hz, 1H, aromatic H), 7.83 (dd, *J* = 7.2, 7.2 Hz, 1H, aromatic H). – Minor diastereomer of **11** [from (*R*)-**10** and (*R*)-**8**]: ^{1}H NMR: δ = 0.85 (d, *J* = 6.1 Hz, 3H, CH_3), 0.93 [s, 9H, $C(CH_3)_3$], 1.03 (d, *J* = 6.1 Hz, 3H, CH_3), 2.28–2.34 [m, 1H, $CH(CH_3)_2$], 3.40–3.47 [m, 1H, $CH(CH_3)_2$], 4.25 (d, D_2O exchange, *J* = 7.3 Hz, 1H, OH), 4.38 (d, *J* = 7.1 Hz, 1H, CHOH), 4.55 (dd, *J* = 9.4, 5.4 Hz, 1H, CH_2), 4.89 (dd, *J* = 10.4, 9.3 Hz, 1H, CH_2), 6.99–7.02 (m, 1H, aromatic H), 7.17 (d, *J* = 5.8 Hz, 1H, aromatic H), 7.42 (d, *J* = 8.2 Hz, 1H, aromatic H), 7.49 (d, *J* = 7.7 Hz, 1H, aromatic H), 7.83 (dd, *J* = 7.2, 7.2 Hz, 1H, aromatic H). – For a mixture of diastereomers of **11** (obtained by coupling of *rac*-**10** with *rac*-**8**): IR (KBr): $\tilde{\nu}$ = 3390 cm^{-1} (m), 2950 (s), 2883 (w), 2208 (w), 1580 (s), 1565 (s), 1450 (s),

Table 1. Crystal structure determination data for the compound *meso*-**1**

Formula $C_{20}H_{24}N_2O_2$, M_r = 324.46; a = 23.926(8), b = 6.759(3), c = 22.897(7) Å; β = 103.29(2)°, V = 3603.87 Å^3, Z = 8, monoclinic system, space group $C2/c$ (No. 15), μ(Mo-K_α) = 0.44 cm^{-1}, graphite monochromator, T = 22°C, $(\sin\Theta/\lambda)_{max}$ = 28, $+/-h$, $+k$, $+l$ range, scan width = 0.65 + 0.4 · tan(Θ), scan speed 1.5–5.0°/min, ω/2Θ mode.
2474 independent reflections, 1360 reflections with $F > 2\sigma(F)$, 229 refined parameters, R = 0.085; R_w = 0.061; $w = 3.7015/(\sigma^2(F) + 0.000039\,F^2)$

Table 2. Crystal structure determination data for the compound **11**

Formula $C_{22}H_{26}N_2O_2$, M_r = 350.50; a = 9.500(2), b = 6.893(2), c = 15.189(3) Å; β = 93.01(1)°, V = 993.26 Å^3, Z = 2, monoclinic system, space group $P2_1$ (No. 4), μ(Mo-K_α) = 0.42 cm^{-1}, graphite monochromator, T = 22°C, $(\sin\Theta/\lambda)_{max}$ = 25, $+/-k$, $+k$, $+l$ range, scan width = 0.65 + 0.4 · tan(Θ), scan speed 1.5–5.0°/min, ω/2Θ mode.
1509 independent reflections, 1221 reflections with $F > 2\sigma(F)$, 252 refined parameters, R = 0.105*, R_w = 0.075; $w = 1.7500/(\sigma^2(F) + 0.001132\,F^2)$.
* R value due to bad crystal

Table 3. Fractional atomic coordinates for compound *meso*-**1**

Atom	x/a	y/b	z/c	B_{eq}[a]
Molecule A:				
C1	0.2732 (2)	0.3048 (10)	0.5206 (3)	3.59
C2	0.2650 (3)	0.4918 (9)	0.5415 (3)	4.63
C3	0.3087 (3)	0.5911 (10)	0.5801 (3)	5.53
C4	0.3602 (3)	0.4959 (10)	0.5959 (3)	4.14
C5	0.3665 (2)	0.3084 (10)	0.5728 (3)	3.40
C6	0.4270 (2)	0.2393 (8)	0.5975 (3)	3.54
C7	0.4538 (2)	0.4208 (9)	0.6345 (3)	4.29
C8	0.4300 (2)	0.0454 (9)	0.6331 (3)	4.25
C9	0.3987 (3)	0.0601 (10)	0.6835 (3)	6.49
C10	0.4924 (2)	-0.0220 (10)	0.6558 (3)	5.54
N1	0.3250 (2)	0.2115 (7)	0.5359 (2)	3.58
O1	0.4086 (2)	0.5631 (6)	0.6342 (2)	5.45
Molecule B:				
C11	0.0292 (2)	-0.0369 (10)	0.5145 (2)	3.32
C12	0.0450 (3)	-0.2323 (9)	0.5072 (3)	4.32
C13	0.0998 (3)	-0.2993 (10)	0.5349 (3)	5.00
C14	0.1353 (3)	-0.1624 (11)	0.5686 (3)	4.38
C15	0.1167 (3)	0.0299 (10)	0.5741 (3)	3.79
C16	0.1644 (2)	0.1454 (9)	0.6144 (3)	4.06
C17	0.2133 (2)	-0.0078 (10)	0.6248 (3)	4.93
C18	0.1474 (3)	0.2195 (11)	0.6712 (3)	5.56
C19	0.1959 (3)	0.3477 (11)	0.7084 (3)	7.84
C20	0.1312 (3)	0.0543 (12)	0.7089 (3)	8.12
N2	0.0650 (2)	0.0965 (7)	0.5483 (2)	3.78
O2	0.1903 (2)	-0.1956 (7)	0.6004 (2)	5.58

[a] $B_{eq} = 8\pi^2(U_{11} + U_{22} + U_{33})/3$.

1433 (s), 1225 (s), 1065 (m), 940 (m), 835 (m), 815 (m), 760 (m). – ^{13}C NMR: δ = 17.2 (CH_3), 20.2 (CH_3), 25.9 (CH_3), 30.7 (CH), 36.2 (C), 47.7 (CH), 73.3 (CH_2), 80.3 (CH), 86.3 (C), 88.5 (C), 115.4 (CH), 122.0 (CH), 127.6 (CH), 128.1 (CH), 133.9 (C), 135.5 (CH), 141.3 (C), 154.1 (C), 154.2 (C), 160.4 (C). – MS (EI, 70 eV): m/z (%) = 294 (36), 293 (100), 251 (16), 249 (18). – MS (CI, NH_3): m/z (%) = 352 (26) [M + 1$^+$], 351 (100) [M + 1$^+$].

$C_{22}H_{26}N_2O_2$ (350.5)
Calcd. C 75.38 H 7.49 N 7.99
Found C 75.27 H 7.27 N 7.89

Table 4. Fractional atomic coordinates for compound **11**

Atom	x/a	y/b	z/c	B_{eq}[a]
C1	1.2249 (9)	0.1811 (16)	0.5906 (6)	5.27
C2	1.3518 (10)	0.3465 (19)	0.4732 (5)	6.40
C3	1.3714 (8)	0.4709 (17)	0.6268 (5)	4.89
C4	1.2721 (8)	0.3782 (14)	0.5567 (5)	3.77
C5	1.1445 (8)	0.5074 (15)	0.5323 (5)	4.34
C6	1.0565 (8)	0.5564 (15)	0.6101 (5)	3.83
C7	1.0796 (10)	0.7271 (16)	0.6576 (6)	5.13
C8	0.9942 (12)	0.7650 (20)	0.7272 (6)	6.52
C9	0.8935 (10)	0.6366 (19)	0.7463 (6)	6.06
C10	0.8773 (8)	0.4677 (16)	0.6987 (5)	4.18
C11	0.7726 (9)	0.3323 (19)	0.7233 (5)	5.00
C12	0.6857 (10)	0.2335 (17)	0.7540 (5)	5.22
C13	0.5815 (8)	0.1173 (16)	0.7935 (6)	4.58
C14	0.5435 (11)	-0.0686 (18)	0.7652 (5)	5.92
C15	0.4437 (11)	-0.1713 (19)	0.8057 (6)	6.68
C16	0.3814 (9)	-0.0868 (19)	0.8744 (5)	5.13
C17	0.4228 (8)	0.0980 (18)	0.9010 (5)	4.23
C19	0.2548 (9)	-0.0198 (16)	0.9925 (6)	5.56
C18	0.3396 (8)	0.1608 (15)	0.9751 (5)	3.93
C20	0.2496 (9)	0.3425 (16)	0.9523 (5)	4.93
C21	0.1500 (11)	0.3128 (21)	0.8725 (6)	7.26
C22	0.1706 (9)	0.4097 (17)	1.0313 (6)	6.01
N1	0.9576 (6)	0.4260 (13)	0.6309 (4)	3.49
O1	1.1964 (6)	0.6825 (0)	0.4967 (4)	5.61
N2	0.5184 (7)	0.2029 (14)	0.8615 (4)	4.45
O2	0.2792 (7)	-0.1603 (14)	0.9223 (4)	6.95

[a] $B_{eq} = 8\pi^2(U_{11} + U_{22} + U_{33})/3$.

Crystal structure data and structure refinement parameters are given in Tables 1 and 2. Tables 3 and 4 contain the fractional atomic coordinates for compounds *meso*-**1** and **11**[10]. The analysis of quality and intensity distribution of the diffraction data of both structures shows a very small percentage of strong reflections, due to crystal size (one dimension <0.1 mm) and crystal quality; *meso*-**1** has only 29% (1009) of intensities being larger than 3σ(I), **11** has even less. Since both structures were only used to determine the stereochemical outcome, we accepted the poor quality of the material.

CAS Registry Numbers

rac-**1**: 137624-62-5 / *meso*-**1**: 137624-61-4 / (*S,S*)-**1**: 137569-53-0 / (*S,S*)-**1** · $CoCl_2$: 137593-91-0 / (*S,S*)-**1** · $PdCl_2$: 137593-92-1 / (*S,S*)-**1**$_2$ · $CuBF_4$: 137569-61-0 / **3**: 6602-33-1 / **4**: 14764-90-0 / **5**: 137569-54-1 / **6**: 137569-55-2 / **7**: 104886-37-5 / *rac*-**8**: 137569-56-3 / (*S*)-**8**: 137624-59-0 / (*R*)-**8**: 137624-60-3 / *rac*-**9**: 137569-57-4 / *rac*-**10**: 137624-63-6 / (*R*)-**10**: 137569-62-1 / (*S*)-**10**: 137569-58-5 / (*R,S*)-**11**: 137569-59-6 / (*R,R*)-**11**: 137569-63-2 / $BrCH_2CH{=}C(CH_3)_2$: 870-63-3

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