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Synthesis and Resolution of 1,1-Bi-8-methylisoquinoline: Formation of an Optically Active Complex with High Chiral Recognition

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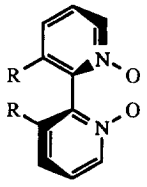
Abstract: The synthesis and resolution of 1,1-bi-8-methylisoquinoline (±)-5 is reported. An optically active palladium complex with high chiral recognition was formed during the complexation between a chiral palladium complex and the two enantiomers of (±)-**5**. The free energy barrier $\Delta G^{\neq}$ for interconversion of enantiomers was estimated to be 97,2 KJ/mol at 40 °C.

Chiral 2,2'-bipyridines are gaining an important role in homogeneous catalytic asymmetric reactions.[1] Moreover, much recent asymmetric synthesis has been based on atropoisomerically chiral ligands.[2] Also the 2,2'-bipyridine skeleton if properly stabilized could generate an atropoisomeric feature. Pyridine derivatives possessing similar geometric features are, for example, the bipyridine **1**[3] where all four positions (3,3' and 1,1') adjacent to the central connecting bond are substituted and the diazabiaryl **2**[4] where the chirality is imparted to the 2,2'-bipyridine by fusion to a cyclooctatetraene nucleus.
A further example is provided by the 1,1'-bi-isoquinoline **3**, but attempts to achieve its resolution failed.[5] The obstruction to the free rotation in about the interannular bond must be very slight since the transition state for rotation in one planar position has only two close N---H interactions (2:8' and 2':8). The introduction on the two nitrogen atoms of **3** of two substituents makes this compound resolvable. In fact, 1,1'-bi-isoquinoline-N,N'-dioxide **4** has been prepared and the corresponding enantiomers separated using high performance liquid chromatography (HPLC) with a chiral column.[6]



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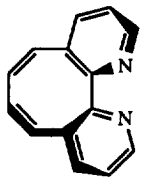

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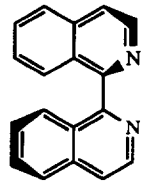

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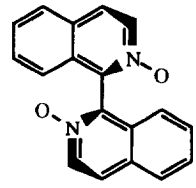

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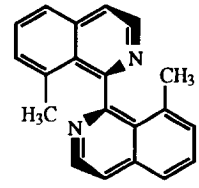

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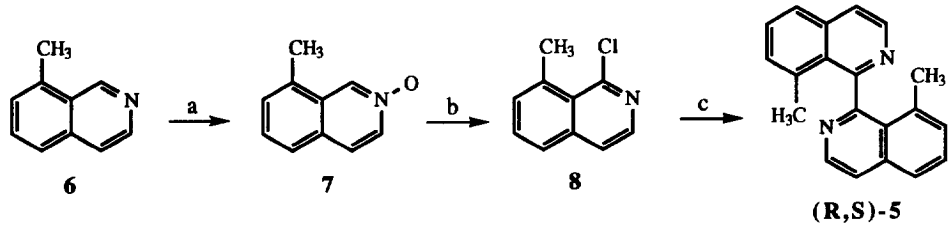
It is reasonable to expect that the substitution of the hydrogen atoms on the 8 and 8' positions of the 1,1'-bi-isoquinoline with a bulkier substituent could make up for the lack of the steric requirement of the nitrogen lone-pairs and thus give an axially chiral 2,2'-bi-isoquinoline.
Here we wish to report the synthesis and resolution of 1,1'-bi-8-methylisoquinoline **5**.

According to Scheme 1, 8-methylisoquinoline **6**, prepared by minor modifications of older procedures,[7] was converted to the corresponding N-oxide **7** by oxidation with 3-chloroperbenzoic acid. Treatment of **7** with phosphoryl chloride afforded the 1-chloroisoquinoline **8** (41 %), which by homocoupling catalyzed with $NiCl_2$-PPh_3-Zn[8] gave 1,1'-bi-8-methylisoquinoline **5** in 56 % yield.

Scheme 1



6 **7** **8** **(R,S)-5**

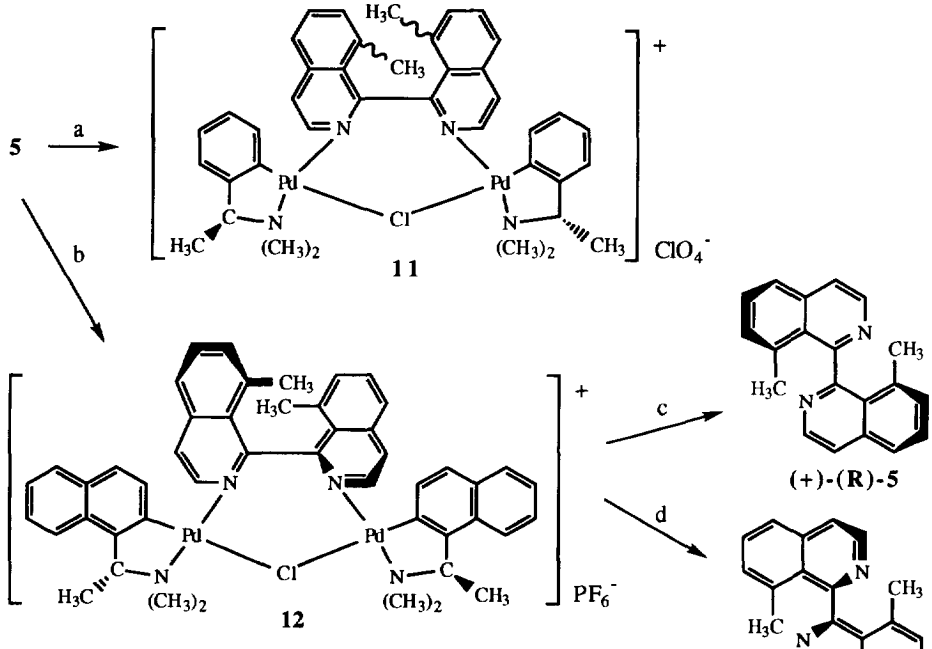
a: H_2O_2, AcOH, 16h, 95 %; b:$POCl_3$, $CHCl_3$, 2h, reflux, 41 %;
c: $NiCl_2$, PPh_3, Zn, DMF, 50 °C, 5h, 56%.

For the resolution of racemic **5** a standard method for the enantiomeric separation of chelating ligands was followed.[9] The reaction of **5** and (-)-di-μ-chlorobis[(S)-dimethyl(1-(1-phenylethyl)aminato-C^2,N]dipalladium(II) **(S)-9** (in an acetone or methanol solution and in the presence of $NaClO_4$ or KPF_6) produced the pair of diastereomeric complexes **(S9,R5)-11** and **(S9,S5)-11** in equal amounts, as shown in the ^1H NMR spectrum by the two doublets at δ 1.03 and 0.39 ppm for the benzylic methyls of the two diastereomers. The diastereomers **11** are binuclear Pd complexes (determined from both the integration of the ^1H NMR spectrum and elemental analysis) as previously observed for the analogue complexes obtained by reaction of **(S)-** or **(R)-9** with 1,1'-bi-isoquinoline **(R,S)-3**. In that case chiral recognition between the complexing partners occurred and only the single diastereomeric complexes **(S9,S3)** and **(R9,R3)** were obtained.[10] The ^1H NMR spectra of these enantiomeric complexes showed a doublet at δ 0.44 ppm for the benzylic methyl group. On this basis, it is reasonable to attribute in the ^1H NMR spectrum of **11** the two doublets at δ 1.03 and 0.39 ppm to the complexes **(S9,R5)-11** and **(S9,S5)-11**, respectively. In order to obtain a different ratio of these two diastereomers some experiments were carried out. When the preparation of the palladium complexes was accomplished by adding slowly the component **9** to **5** in 1:4 molar ratio in acetone, diastereomers **11** were formed in 1:1 molar ratio. Furthermore, by heating **11** in several solvents up to 110 °C, no change in the diastereomeric ratio was observed. Attempted separations of these diastereomers by crystallisation was unsuccessful and only by chromatography was a mixture of **(S9,R5)-11** and **(S9,S5)-11** in an enriched ratio of 66:34 obtained. The ^1H NMR spectrum of this mixture allowed the related signals to be assigned unambiguously to **(S9,R5)-11** and **(S9,S5)-11**.

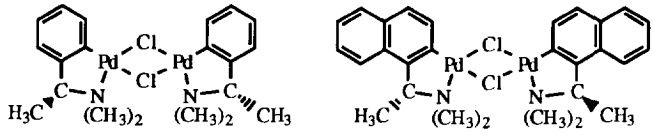
We then turned to the use of the naphthyl analogue of **9**.[11] Mixing (+)-di-μ-chlorobis[(R)-dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]dipalladium(II) **(R)-10** and ligand **5** in 1:1 molar ratio in MeOH at room temperature for 16 hours in the presence of KPF_6, a white powder was collected by filtration. The ^1H NMR spectrum of this solid showed it consisted of a single diastereomeric binuclear Pd complex **12**. Concentration of the mother liquors left a solid from which compound **5** was separated by chromatography on a short neutral alumimium oxide column. This compound showed a negative specific rotation of $[\alpha]_D^{22}$ -71.6 (c 0.81, $CHCl_3$). During the complexation of **(R)-10** with racemic **5**, therefore chiral recognition occurred between the partners and only **12** resulted by reaction of **(R)-10** with **(±)-5**.[12]

Despite a great deal of effort, we were unable to obtain good quality single crystals of the complex **12** for X-ray structural elucidation. However, in the light of the aforementioned points and its ^1H NMR spectrum, which showed a doublet at δ 0.41 for the benzylic methyl group, it is reasonable to assign to **12** the absolute (**R**10,**R**5) configuration. The free ligand (**R**)-**5**, generated from the palladium complex (**R**10,**R**5)-**12** by treatment with 1,2-bis(diphenylphosphino)ethane in $CHCl_3$, showed a positive specific rotation of $[\alpha]_D^{22}$ +72.2 (*c* 1.05, $CHCl_3$) but unexpectedly, it was enantiomerically unstable in solution.[13] The kinetics of its racemization were therefore followed in $CHCl_3$ in the temperature range 20-60 °C. For the interconversion of the enantiomers of (±)-**5**, the free energy barrier $\Delta G^{\neq}$ amounted to 97,2 KJ/mol at 40 °C.

Scheme 2



a: (**S**)-**9**, Me_2CO, $NaClO_4$, rt, 16h; b:(**R**)-**10**, MeOH, KPF_6, rt, 16h ; c: 1,2-bis(diphenylphosphino)ethane, $CHCl_3$, 15 min.; d: from the mother liquors



(**S**)-**9** (**R**)-**10**

In conclusion, the synthesis of a new chiral ligand was achieved and the free energy barrier to ring inversion found. Further structural constraints are required to raise the rotational barrier before asymmetric catalysis can be performed.

Experimental section

Boiling points are uncorrected. Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. The ^1H NMR (300 MHz) spectra were obtained with a Varian VXR-300 spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in a 1 dm tube. Elemental analyses were performed on a Perkin-Elmer 240 B analyser. (-)-Di-μ-chlorobis[(S)-dimethyl(1-(1-phenylethyl)aminato-C^2,N] dipalladium(II) **(R)-9**,[14] (+)-di-μ-chlorobis[(R)-dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]dipalladium (II) **(S)-10**[15] were prepared according to literature procedures.

8-Methylisoquinoline, 6. A solution of *o*-methylbenzylideneaminoethanaldietoxyacetal[7] (2.07 g, 10 mmol) in MeOH (5 ml) under a nitrogen atmosphere was slowly added to concentrated H_2SO_4 (50 ml) heated at 160 °C. The reaction mixture was stirred at 160 °C for 2 h, allowed to cool to room temperature and then cautiously poured on crushed ice. The resulting mixture was basified with a 50 % NaOH solution and the product was removed from the resulting black solution by steam distillation. The distillate was extracted with ether, the organic phase separated, dried on anhydrous Na_2SO_4 and the solvent evaporated. The residue was purified by kugelrohr distillation to give pure **6**: 0.36 g (25 %); bp 95 °C (0.1 mm). ^1H NMR ($CDCl_3$) δ 9.37 (s, 1H), 8.49 (d, 1H), 7.54-7.40 (m, 3H), 7.25 (d, 1H), 2.64 (s, 3H). *Elem. Anal.*, found % (calcd. for $C_{10}H_9N$) C, 83.99 (83.88); H, 6.32 (6.34); N, 9.75 (9.78).

8-Methylisoquinoline-N-oxide, 7. 3-Chloroperbenzoic acid (3.94 g, 50 %, 23.1 mmol) was added slowly to a solution of **6** (3 g, 21 mmol) in $CHCl_3$ (250 ml). The reaction mixture was stirred for 5 h before extra 3-chloroperbenzoic acid (1.79 g, 10.5 mmol) was added. The resulting solution was stirred for an additional 16 h. A saturated aqueous solution of $NaHCO_3$ (250 ml) was added and stirring continued for 0.5 h. The organic phase was separated and the aqueous solution extracted exhaustively with $CHCl_3$. The combined organic fractions were dried (Na_2SO_4) and the solvent evaporated to give **7**: 3.17 g (95%); mp 137 °C; ^1H NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.16 (d, 1H), 7.66 (m, 2H), 7.47 (m, 2H), 2.61 (s, 3H). *Elem. Anal.*, found % (calcd. for $C_{10}H_9NO$) C, 75.55 (75.45); H, 5.62 (5.70); N, 8.77 (8.80).

1-Chloro-8-methylisoquinoline, 8. Phosphorus oxychloride (11.2 ml, 12 mmol) was slowly added to a solution of **7** (1.91 g, 12 mmol) in $CHCl_3$ (100 ml). The resulting solution was heated under reflux for 2 h. After cooling to room temperature the solution was poured on crushed ice and alkalinised with concentrated NH_4OH. The organic phase was separated and the aqueous phase extracted exhaustively with $CHCl_3$. The combined organic fractions were dried (Na_2SO_4) and the solvent evaporated . The residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 7/3) to give pure **8**: 0.87 g (41 %); mp 78 °C; ^1H NMR ($CDCl_3$) δ 8.19 (d, 1H), 7.65 (d, 1H), 7.51 (m, 2H), 7.42 (d,1H), 3.05 (s, 3H). *Elem. Anal.*, found % (calcd. for $C_{10}H_8ClN$) C, 67.60 (67.62); H, 4.62 (4.54); N, 7.87 (7.89).

1,1'-Bi-8-methylisoquinoline, 5. Powered zinc (1.03 g, 15.7 mmol) was added at 60 °C under an argon atmosphere to a stirred mixture of nickel (II) chloride hexahydrate (3.45 g, 14.5 mmol) and triphenylphosphine (15.24 g, 58.1 mmol) in carefully degassed DMF (100 ml). After 1 h a solution of **8** (2.14 g, 12.1 mmol) in carefully degassed DMF (3 ml) was added. After 5 h at 50 °C the mixture was allowed to cool to room temperature and 5 % aqueous NH_3 (120 ml) was added. The mixture was extracted three times with $CHCl_3$ (3x150 ml). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated. The residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 7/3) to give pure **5**: 0.96 g (56 %); mp 207-210 °C dec. ^1H NMR ($CDCl_3$) δ 8.56 (d, 1H), 7.76 (m, 2H), 7.56 (t, 1H), 7.31 (d, 1H), 1.84 (s, 3H). *Elem. Anal.*, found % (calcd. for $C_{20}H_{16}N_2$) C, 84.50 (84.48); H, 5.62 (5.67); N, 9.77 (9.85).

Resolution of (R,S)-5: Formation of diastereomers (S9,R5)-11 and (S9,S5)-11. A solution of (S)-**9** (1.06 g, 1.83 mmol) and (0.52 g, 1.83 mmol) in anhydrous acetone (50 ml) was stirred for 5 h, then $NaClO_4$ (1.12 g, 9.15 mmol) was added and stirring continued for 11 h. The solvent was evaporated and the residue taken up with CH_2Cl_2. The unsoluble compounds were removed by filtration and the CH_2Cl_2 solution concentrated. Petroleum ether was added and the solid collected by filtration to give a 1:1 mixture of (S9,R5)-**11** and (S9,S5)-**11**: 1.56 g (92 %). In an attempt to separate these diastereomers, the mixture was chromatographed on silica gel eluting with petroleum ether/ethyl acetate=7/3 and then dichloromethane to give a fraction containing a mixture of (S9,R5)-**11** and (S9,S5)-**11** in an enriched ratio of 66:34: (S9,R5)-**11**: ^{1}H-NMR ($CDCl_3$) δ 8.98 (d, 1H), 8.54 (d, 1H), 8.15 (d, 1H), 6.56 (d, 1H), 6.96-6.45 (m, 4H), 6.41 (d, 1H), 2.98 (m, 1H), 2.39 (s, 3H), 2.22 (s, 3H), 1.67 (s, 3H), 1.03 (d, 3H). (S9,S5)-**11**: ^{1}H NMR ($CDCl_3$) δ 9.10 (d, 1H), 8.44 (d, 1H), 8.08 (d, 1H), 7.65 (d, 1H), 7.12 (d, 1H), 6.96-6.45 (m, 4H), 3.10 (m, 1H), 2.62 (s, 3H), 2.22 (s, 3H), 1.64 (s, 3H), 0.39 (d, 3H). *Elem. Anal.*, found % (calcd. for $C_{40}H_{44}Cl_2N_4O_4Pd_2$) C, 51.60 (51.74); H, 4.62 (4.78); N, 6.07 (6.03).

When the above reaction was carried out using methanol as solvent in the presence of KPF_6 the collected solid showed the usual diastereomeric composition. Its ^{1}H NMR (DMSO) spectrum showed two doublets at δ 0.97 and 0.27 ppm for the benzylic methyls of the two diastereomers.

Resolution of (R,S)-5: Formation of (R10,R5)-12. A solution of (**R**)-**10** (0.635 g, 1 mmol) and **5** (0.284 g, 1 mmol) in MeOH (220 ml) was stirred for 5 h, then KPF_6 (0.184 g, 1 mmol) was added and stirring continued for 11 h. The formed solid was collected by filtration to give (R10,R5)-**12**: 0.483 g (45 %); mp 255 °C; ^{1}H-NMR (DMSO) δ 9.38 (d, 1H), 8.65 (d, 1H), 8.21 (d, 1H), 7.80-7.24 (m, 5H), 7.63 (t, 1H), 7.10 (d, 1H), 6.93 (d, 1H), 4.08 (m, 1H), 2.62 (s, 3H), 2.28 (s, 3H), 1.60 (s, 3H), 4.01 (d, 3H). *Elem. Anal.*, found % (calcd. for $C_{48}H_{48}ClF_6N_4PPd_2$) C, 53.60 (53.67); H, 4.52 (4.50); N, 5.27 (5.22).

In a repeated experiment a solution of (**R**)-**10** and **5** in $CHCl_3$ containing KPF_6 was stirred at room temperature for 12 days. After the usual work-up (R10,R5)-**12** was obtained in 89 % yield.

(-)-1,1'-Bi-8-methylisoquinoline, (-)-(S)-5. The mother liquors recovered after filtration of (R10,R5)-**12** in the above preparation, were quickly concentrated *in vacuo* (0.1 mm) at 0 °C and the residue purified by filtration on a short neutral aluminium oxide column (20x2 cm) eluting with petroleum ether/ethyl acetate=7/3 (the eluting fractions must be quickly concentrated *in vacuo* (0.1 mm) at 0 °C) to give pure **5**: 0.088 g (31 %); $[\alpha]_D^{22}$ -71.6 (*c* 0.81, $CHCl_3$).

(+)-1,1'-Bi-8-methylisoquinoline, (+)-(R)-5. 1,2-Bis(diphenylphosphino)ethane (0.319 g, 0.8 mmol) was added to a solution of (R10,R5)-**12** (0.43 g, 0.4 mmol) in $CHCl_3$ and stirring continued for 15 minutes. The solvent was quickly removed *in vacuo* (0.1 mm) at 0 °C and the residue purified by filtration on a short neutral aluminium oxide column (20x2 cm) eluting with petroleum ether/ethyl acetate=7/3 (the eluting fractions must be quickly concentrated *in vacuo* (0.1 mm) at 0 °C) to give pure **5**: 0.1 g (89 %); $[\alpha]_D^{22}$ +72.2 (*c* 1.05, $CHCl_3$).

Racemization of optically active (+)-5. A solution of (+)-**5** (50 mg) in $CHCl_3$ (5 ml) was heated at a given temperature in a thermostated 1 dm polarimeter cell and optical rotation was measured at appropriate intervals. The racemization first-order rate constants k were obtained from plots of ln α vs time. The obtained racemization rates k were $5.63\ 10^{-5}$ s^{-1} at 20 °C, $3.17\ 10^{-4}$ s^{-1} at 40 °C, $2.39\ 10^{-3}$ s^{-1} at 60 °C.

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12. After the determination of the enantiomeric unstability of optically active **5**, the reaction for formation of **12** was carried out in $CHCl_3$ at room temperature for 12 days. Also in this case, by rapid mutarotation of **5** and complete chiral recognition between the partners, only ($\mathbf{R}_{10}$,$\mathbf{R}_5$)-**12** was obtained in 89 % yield.
13. The kinetic resolution during the complexation of (**R**)-**10** with racemic **5** apparently could be in contrast with the instability of the **S**-enantiomer towards racemisation ($t_{1/2}$ = 3.42 h at 20°C) and, on the basis of the measured rate constants, the biquinolyl (**S**)-**5** should not be recovered enantiomerically pure. Moreover, the yield of the complex **12** should be greater than 50% if the newly formed **R**-enantiomer is intercepted. A plausible explanation can be provided by the following considerations. If the reaction of (**R**)-**5** with (**R**)-**10** is fast compared with the racemisation process of the **S**-enantiomer, the (**R**)-**10** excess completely intercepts the newly formed **R**-enantiomer. The remaining (**S**)-**5** can therefore be recovered enantiomerically pure. The yield of complex **12** (45 %) refers only to the solid collected by filtration from the reaction mixture. Since the **S**-enantiomer was recovered in 31% yield from the mother liquors after filtration of **12**, it is possible to foresee for **12** a total yield higher than 45% (up to 69 %). For a higher yield of complex **12** (up to 89 %) see Ref. 12.
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