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Synthesis of C_2-Symmetry 2,2'-Bipyridine and 1,10-Phenanthroline Chiral Ligands bearing the 6,6-Dimethylnorpinan-2-yl Group

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Abstract: 6-{(1S,2S)-6,6-dimethylbicyclo[3.1.1.]hept-2-yl})-2-{6-{(1S,2S)-6,6-dimethylbicyclo [3.1.1.]hept-2-yl}-pyridin-2-yl}-pyridine (**5**), 2,9-bis{(1S,2S)-6,6-dimethylbicyclo[3.1.1.]hept-2-yl}-5,6-dihydro-1,10-phenanthroline (**11**) and 2,9-bis{(1S,2S)-6,6-dimethylbicyclo[3.1.1.]hept-2-yl}-1,10-phenanthroline (**12**), three new chiral nitrogen ligands of C_2 symmetry have been prepared.

Chiral 2,2'-bipyridines and 1,10-phenanthrolines have been showed to be effective bidentate ligands in asymmetric catalysis.[1-4] In this context, the best results in enantioselective processes, employing catalysts having alkyl 2,2'-bipyridines and 1,10-phenanthrolines as ligands, have been obtained using the 6,6-dimethylnorpinan-2-yl group as chiral substituent of the organic moiety.[3] In connection also with our recent studies on catalytic asymmetric reactions,[5] we have now devoted our attention to prepare the corresponding C_2-symmetry substituted ligands, taking into account that a chiral 2,2'-bipyridine ligand having a C_2-symmetry axis has been found to be a very efficient catalyst in the enantioselective addition of diethylzinc to benzaldehyde.[2]

In this paper, we report therefore the synthesis of three new chiral nitrogen ligands of C_2-symmetry, 6-{(1S,2S)-6,6-dimethylbicyclo[3.1.1.]hept-2-yl})-2-{6-{(1S,2S)-6,6-dimethylbicyclo[3.1.1.]hept-2-yl}-pyridin-2-yl}pyridine (**5**), 2,9-bis{(1S,2S)-6,6-dimethylbicyclo[3.1.1.]hept-2-yl}-5,6-dihydro-1,10-phenanthroline (**11**) and 2,9-bis {(1S,2S)-6,6-dimethylbicyclo[3.1.1.]hept-2-yl}-1,10-phenanthroline (**12**).

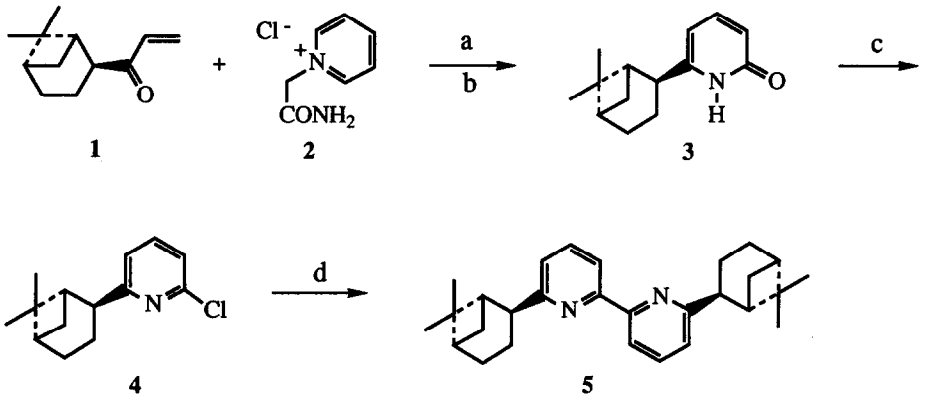
The synthesis of bipyridine **5** was achieved following the sequences reported in Scheme 1. The key intermediate pyridinone **3** was obtained, in 35 % yield, by heating a mixture of {(1S,2S)-6,6-dimethylbicyclo[3.1.1.]hept-2-yl}-2-propen-1-one[4] (**1**) and N-(carbamylmethyl)pyridinium chloride (**2**), followed by thermal decomposition at about 200 °C of the primary reaction adduct.[6]

It is noteworthy that, in spite of the proximity of the asymmetric center to the heterocyclic ring, no epimerization occurs under the drastic conditions of cyclization. Compound **3** was converted into the corresponding chloropyridine **4** by reaction with phosphorous oxychloride in dimethylformamide (71 %). The final bipyridine **5** was achieved by homo-coupling of the chloropyridine **4** by a nickel (0)/triphenylphosphine-mediated reaction[7] (60 %).

The reaction sequence leading to the phenanthroline **12** is shown in Scheme 2. Starting from the ketone **1**, the tetrahydroquinoline **7** was obtained in 51 % yield, by reaction with 1-(1-cyclohexenyl)pyrrolidine (**6**), fol-

lowed by treatment with hydroxylammine hydrochloride of the primary reaction adduct. The crucial intermediate 8-quinolinone **9** was prepared by a two step route, involving treatment of **5** with benzaldehyde in acetic anhydride which leads to the formation of the 8-benzylidene derivative **8** (82 % yield), which was ozonolized in a CH_2Cl_2/MeOH mixture at -35 °C; subsequent reduction of the ozonide with methyl sulfide gave **9** (74%).

Scheme 1



1 2 3 4 5

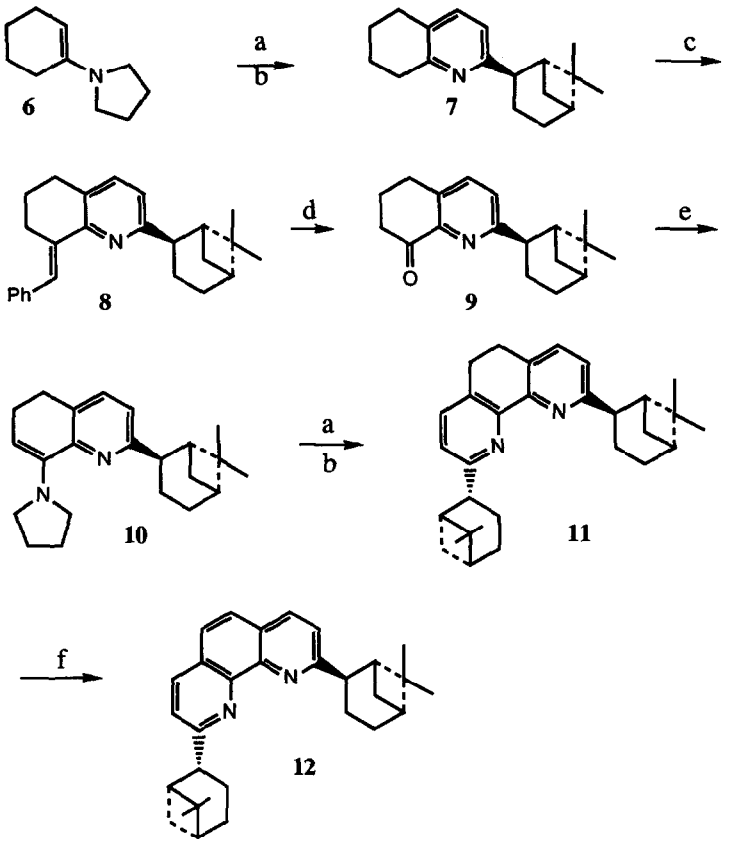
a: MeOH, reflux, 12 h; b: neat, 200 °C, 10 min., 35 %; c: $POCl_3$, DMF, 110 °C, 1.5 h, 70 %; d: $NiCl_2 \cdot 6H_2O$, PPh_3, Zn, NaI, DMF, 70 °C, 3 h, 30 %.

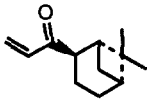
For the construction of the second pyridine ring the same heteroannelation reaction employed for **7** has been followed. In this fashion, the dihydrophenanthroline **9** has been prepared by reaction of the pyrrolidino enamine of **9** with the ketone **1**, followed by treatment with hydroxylammonium chloride of the primary reaction adduct. Finally, **11** was converted into the phenanthroline **12** by dehydrogenation in refluxing xylene in the presence of catalytic amount of palladium on charcoal.

In summary, in this paper we report the syntheses of three new related chiral nitrogen ligands of C_2 symmetry, which might show different coordinating properties In fact, on passing from the 2,2'-bipyridine **5**, in which the free rotation about the 2,2'-bond is still possible, to the 1,10-phenanthroline **12**, in which the nitrogen lone pair orbitals are coplanar, it is possible to find an increasing difference of the type of cooperative chemistry which the two nitrogens might undergo, thus influencing the kind of complexation which can occur.[8] An intermediate situation it is possible to find in the dihydrophenanthroline **11**, in which the 3,3'-bridge can control the relative orientation of the two rings, thus influencing the shape of the chelating "bite" as well as their cooperativity.[8]

Current work will cover the use of these ligands in enantioselective reactions.

Scheme 2



a:  , benzene, reflux, 3h; b: EtOH/H_2O, NH_2OH HCl, reflux, 5 h; c: PhCHO, Ac_2O, 170 °C; d: O_3, MeOH/CH_2Cl_2, -35 °C, then Me_2S; e: pyrrolidine, toluene; f: Pd/C, xylene, reflux.

Experimental Section

Boiling point are uncorrected. Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. The ^1H NMR (300 MHz) and ^{13}C NMR (75.4 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 analyzer. {(1S,2S)-6,6-Dimethylbicyclo[3.1.1.]hept-2-yl}-2-

propen-1-one (**1**) was prepared according to a reported procedure.[4] N-(carbamylmethyl)pyridinium chloride (**2**) was prepared according to Cook *et al.*.[9]

6-{(1S,2S)-6,6-Dimethylbicyclo[3.1.1.]hept-2-yl}-2(1H)-pyridinone, 3. A solution of **1** (10.28 g, 0.06 mol), N-(carbamylmethyl)pyridinium chloride (10,4 g, 0.06 mol) and triethylamine (8,4 ml, 0,06 mol) in MeOH (200 ml) was heated under reflux for 10 h. The solvent was evaporated and the residue heated at 200 °C for 15 minutes. Extraction with boiling benzene and evaporation of the solvent gave a oily residue which was chromatographed on silica gel (eluent : benzene/acetone, 8/2) to give pure **3** as a sticky solid (4.56 g, 35 %); ^{1}H NMR ($CDCl_3$) δ 9.5 (m broad, 1H), 7.35 (dd, 1H), 6.38 (d, 1H), 6.04 (d, 1H), 3.20 (t, 1H), 3.24-1.65 (m, 8H), 1.25 (s, 3H), 0.96 (s, 3H); *Elem. anal.*, found % (calcd. for $C_{14}H_{19}NO$): C, 77.37 (77.15); H, 8.82 (8.90); N, 6.45 (6.30).

2-Chloro-6-{(1S,2S)-6,6-dimethylbicyclo[3.1.1.]hept-2-yl}pyridine, 4. A solution of **3** (4.12 g, 0.019 mol) and phosphoroxychlorid (10.4 ml, 0.114 mol) in DMF (4 ml) was heated at 110 °C for 1.5 h. The residue taken up with H_2O and extracted with Et_2O. The ethereal phase was washed with 10% aqueous NaOH and then with H_2O, dried (Na_2SO_4) and the solvent evaporated to give pure **4** (3.17 g, 71%); bp 130 °C (0.1 mm); $[\alpha]^{25}_D$ -2.66 (*c* 2.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32 (t, 1H), 7.10 (d, 1H), 7.07 (d, 1H), 3.37 (t, 1H), 2.23-1.81 (m, 7H), 1.72 (d, 1H), 1.13 (s, 3H),,0.95 (s, 3H); *Elem. anal.*, found % (calcd. for $C_{14}H_{18}NCl$): C, 71.46 (71.20); H, 7.72 (7.50); N, 5.96 (6.12).

6-{(1S,2S)-6,6-Dimethylbicyclo[3.1.1.]hept-2-yl})-2-{6-{(1S,2S)-6,6-dimethylbicyclo [3.1.1.]hept-2-yl}-pyridin-2-yl}-pyridine, 5. Zinc powered (0.32 g, 5 mmol) was added at 60 °C to a stirred mixture of nickel(II) chloride hexahydrate (11.18 g, 5 mmol) and triphenylphosphine in DMF (25 ml). After 1 h, **4** (1.17 g, 5 mmol) was added. The mixture was stirred at 70 °C for 7 h, and then poured into dilute ammonia solution (100 ml), extracted with CH_2Cl_2. After drying over Na_2SO_4, the solvent was evaporated and the residue chromatographed on silica gel (eluent: benzene/hexane, 9/3) to give pure **5**; 0.6 g (60%); mp 117 °C; $[\alpha]^{25}_D$ + 18.55 (*c* 0.64 , $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.26 (d, 2H), 7,68 (t, 2H),7.10 (d, 2H), 3.42 (t, 2H), 2.31-1.86 (m, 20H), 1.26 (s, 6H), 1.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 165.7, 155.7, 136.9, 121.2, 118.2, 46.5, 43.0, 39.9, 39.9, 26.8, 24.7, 23.9, 21.17, 20.3; *Elem. anal.*, found % (calcd. for $C_{28}H_{36}N_2$): C, 83.94 (84.12); H, 9.06 (9.12); N, 7.00 (6.85).

2-{(1S,2S)-6,6-Dimethylbicyclo[3.1.1.]hept-2-yl}-5,6,7,8-tetrahydroquinoline, 7. A solution of 1-(1-cyclohexenyl)pyrrolidine (9.82 g, 65 mmol) and **1** (11.56 g, 65 mmol) in benzene was heated under reflux for 3 h. The solvent was evaporated under vacuo and the residue taken up with hydroxylammonium chloride (13.5 g, 0.195 mol), H_2O (15 ml) and EtOH (15 ml). After 5 h of heating under reflux, the solution was poured into H_2O and extracted with ether. The aqueous phase was treated with a 10 % solution of sodium hydroxide and extracted with ether. The organic phase was dried over Na_2SO_4, evaporated of the solvent and the residue purified by distillation to give pure **7**; 8.5 g (51%); bp 150 °C (0.5 mm); $[\alpha]^{25}_D$ + 0.809 (*c* 3.12 , $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.24 (d,1H), 6.95 (d, 1H), 3.26 (m, 1H), 2.86 (t, 2H), 2.68 (t, 2H), 2.24-1.65 (m, 12H), 1.21 (s, 3H), 0.95 (s, 3H); *Elem. anal.*, found % (calcd. for $C_{18}H_{25}N$): C, 84.64 (84.63); H, 9.87 (9.70); N, 5.49 (5.60).

2-{(1S,2S)-6,6-Dimethylbicyclo[3.1.1.]hept-2-yl}-8-benzylidene-5,6-dihydro-(7H)-quinoline, 8. A mixture of **7** (6.4 g, 25 mmol) and benzaldehyde (4 g, 38 mmol) in acetic anhydride was heated at 170 °C under nitrogen for 17 h. The solution was poured into a 10 % solution of sodium hydroxyde and extracted with ether. The organic phase was dried over Na_2SO_4, the solvent evaporated and the residue chromatographed on silica gel (eluent: hexane/acetone, 10/2) to give pure **8**; 7.0 g (82%); ^{1}H NMR ($CDCl_3$) δ 8.08 (s, 1H), 7.48-7.22 (m, 6H), 6.95 (d, 1H), 3.29 (t, 1H), 2.89 (t, 2H), 2.80 (t, 2H), 2.32-1.76 (m, 10H), 1.28 (s, 3H), 1.00 (s, 3H); *Elem. anal.*, found % (calcd. for $C_{25}H_{29}N$): C, 87.40 (87.50); H, 8.52 (8.60); N, 4.08 (3.90).

2-{(1S,2S)-6,6-Dimethylbicyclo[3.1.1.]hept-2-yl}-5,6-dihydro-8-(7H)-quinoline, 9. A solution of **8** (6.86 g, 20 mmol) in CH_2Cl_2 (100 ml) and MeOH (100 ml) was treated with a mixture of ozone and oxygen at -35 °C until the solution became blue. The dissolved ozone was purged by bubbling nitrogen through the solution and then methyl sulfide (3 ml) was added at -35 °C. After 0.5 h the solution was allowed to reach room temperature and stirred overnight. The solvent and most part of benzaldehyde was evaporated under vacuo and the residue chromatographed on silica gel (eluent: hexane/acetone, 3/2) to give pure **9**, 4.0 g (74%); mp. 61-2 °C; $[\alpha]^{25}_D$ + 1.46 (*c* 2.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$), 7.52 (d, 1H), 7.30 (d, 1H), 3.52 (m, 1H), 2.93 (t, 2H), 2.73 (t, 2H), 2.25-1.68 (m, 10H), 1.21 (s, 3H), 0.92 (s, 3H); *Elem. anal.*, found % (calcd. for $C_{18}H_{23}NO$): C, 80.24 (80.30); H, 8.61 (8.50); N, 5.20 (5.33).

2,9-Bis{(1S,2S)-6,6-dimethylbicyclo[3.1.1.]hept-2-yl}-5,6-dihydro-1,10-phenanthroline, 11. A solution of **9** (4.03 g, 15 mmol) and pyrrolidine (5.32 g, 75 mmol) in anhydrous benzene (50 ml) was heated under reflux in a Kumagawa apparatus containing 4A molecular sieves (10 g). After 24 h the solvent and the unreacted pyrrolidine was distilled off under reduced pressure. The residue was taken up with anhydrous benzene (20 ml) and **1** (2.67 g, 15 mmol) was added. The resulting solution was heated under reflux for 12 h. Then most of the solvent was removed under reduced pressure and the residue taken up with EtOH (20 ml), H_2O (20 ml). Hydroxylamine hydrochloride (3 g) was added and the resulting mixture heated under reflux for 5 h . Then the solution was poured into 10% aqueous NaOH (100 ml) and extracted with CH_2Cl_2. The organic phase was separed, dried (Na_2SO_4), the solvent evaporated and the residue taken up with xylene (50 ml) and the resulting solution heated under reflux for 4 h. The solvent was evaporated and the residue chromatographed on aluminium oxide (eluent: petroleum ether/ethyl acetate, 8/2) to give pure **11**, 1.34 g (21 %); mp.123-4 °C; $[\alpha]^{25}_D$ -10.39 (*c*. 2.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$), 7.41 (d, 2H), 7.10 (d, 2H), 3.55 (t, 2H), 2.87 (s, 4H), 2.28-1.88 (m, 16H), 1.27 (s, 6H), 1.02 (s, 6H); ^{13}C NMR ($CDCl_3$), 165.8, 151.1, 135.9, 131.1, 120.5, 27.4, 26.8, 24.8, 24.1, 21./8, 20.3; *Elem. anal.*, found % (calcd. for $C_{30}H_{38}N_2$): C, 84.66 (84.46); H, 8.61 (8.98); N, 5.20 (6.33).

2,9-Bis{(1S,2S)-6,6-dimethylbicyclo[3.1.1.]hept-2-yl}-1,10-phenanthroline, 12. A suspension of 10 % palladium on charcoal (0.1 g) in xylene (10 ml) containing **11** (0.426 g, 1 mmol) was heated under reflux for 3 h. After cooling the suspension was filtered and the solvent was removed. The residue was filtered on silica gel (eluent:petroleum ether/ethyl acetate, 8:2) to give pure **12**, 0.36 g (85 %); 58-60 °C; $[\alpha]^{25}_D$ + 23.13 (*c* 2.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$), 8.09 (d, 2H), 7.65 (s, 2H), 7.51 (d, 2H), 3.79 (t, 2H), 2.25-

1.96 (m, H), 1.31 (s, 6H), 1.08 (s, 6H); ^{13}C NMR ($CDCl_3$), 166.7, 145.6, 136.2, 127.1, 125.2, 121.1, 46.2, 43.7, 39.8, 26.7, 24.7, 24.1, 21.6, 20.3; *Elem. anal.*, found % (calcd. for $C_{30}H_{36}N_2$): C, 80.64 (80.86); H, 8.61 (8.56); N, 6.30 (6.60).

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