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THE SYNTHESIS OF (+)- AND (-)-1-(1-ISOQUINOLINYL)-1-(2-PYRIDYL)ETHANOL. A CHIRAL LIGAND WITH USEFUL CHELATING PROPERTIES.

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ABSTRACT: (±)-1-(1-Isoquinolinyl)-1-(2-pyridyl)ethanol has been prepared and the two enantiomers have been resolved by derivatization with a chiral isocyanate followed by a chromatographic separation. The relative configurations of the diastereomers are discussed in relation to their chromatographic behaviour and NMR spectral data. The enantiomeric alcohols obtained after hydrolysis of the diastereomeric carbamates can be alkylated or attached to a Merrifield resin to afford useful chiral chelating ligands for transition metals.

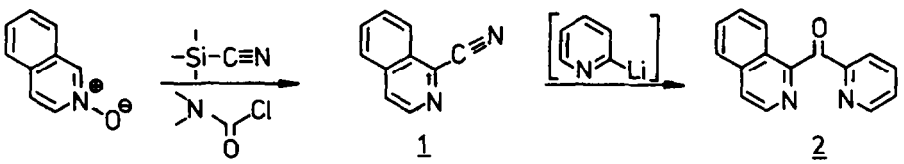
INTRODUCTION

Enantioselective synthesis using asymmetric transition metal complexes is undergoing fast development and many examples of highly selective catalytic reactions have been reported.[1] Rather few studies involving polymer-bound chiral complexes have appeared and polymeric catalysts have in some cases been only moderately successful.[2] The use of such catalysts seem attractive, however, since it allows the recovery and reuse of the often expensive catalyst. The chiral catalysts used for asymmetric synthesis usually contain chelating phosphines and few other chiral ligands capable of transferring chirality to an achiral substrate have been investigated.[3] We have recently prepared 2,2'-dipyridylmethanol and anchored this ligand to chloromethylated and chloroacetylated polystyrene resins and investigated the catalytic activity of transition metal complexes of the polymeric ligand. This paper describes the synthesis and resolution of the chiral analogues (+)- and (-)-1-(1-isoquinolinyl)-1-(2-pyridyl)ethanol. The ligands were prepared, each optically pure, by a five step synthesis involving chromatographic resolution of a pair of diastereomeric carbamates.

RESULTS AND DISCUSSION

The synthesis of (+)- and (-)-1-(1-isoquinolinyl)-1-(2-pyridyl)ethanol was carried out according to schemes 1 and 2.

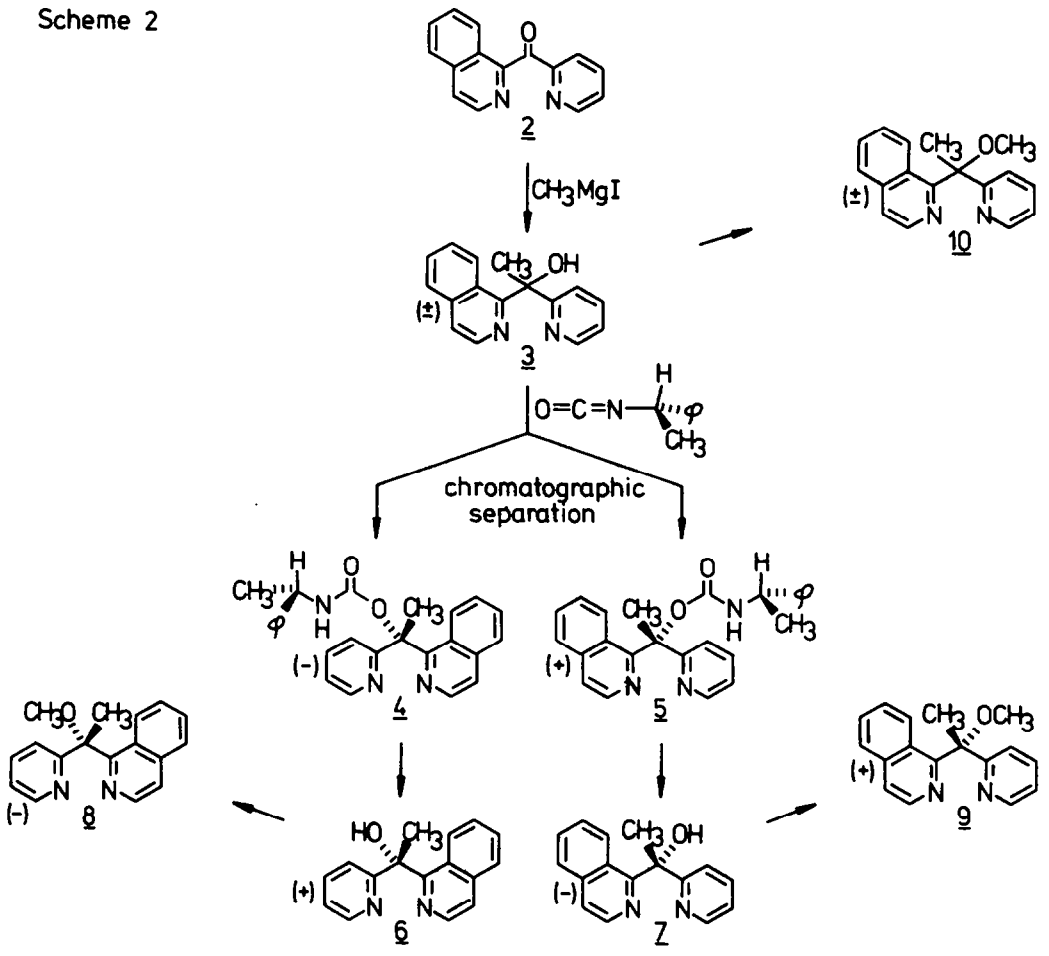
Scheme 1



1 2

1-Cyanoisoquinoline[4] (1) was preared in 97.5% yield by reaction of isoquinoline-N-oxide with trimethylsilyl cyanide and N,N-dimethylcarbamoyl chloride according to a method developed by Fife[5] for the cyanation of pyridine-N-oxides. Holm *et al*[6] described the synthesis of different pyridyl ketones by using pyridyl lithium and different heteroaromatic cyano compounds at low temperatures. Using this method 2 was prepared in good yield (66%). This compound has previously[7] been prepared in two steps starting from 1-cyanoisoquinoline in an overall yield of 19%. The racemic alchol 3 was easily synthesized from 2 and methyl magnesium iodide.

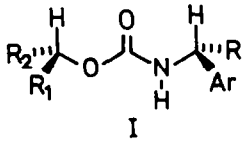
Scheme 2



Many different methods for the resolution of racemic alcohols are known.[8] Recently chromatographic methods for the separation of diastereomeric pairs have been developed[9] and racemic mixtures of alcohols have been separated after derivatization with chiral isocyanates[10] (prepared from easily accessible chiral primary amines).[11] The formation of a chromatographically separable pair of diastereomers seemed attractive since a good separation between the two diastereomers would probably yield optically pure diastereomers without the loss of optically active material. Therefore we decided to prepare the diastereomeric carbamates from the tertiary alcohol[12] and an isocyanate. The tertiary alcohol, (S)-phenylethylisocyanate (prepared from (S)-phenylethylamine and phosgene)[13] and 4-(N,N-dimethylamino)pyridine were reacted to give a good yield of the diastereomeric carbamate mixture. The two carbamates also proved to be separable (ΔR_f=0.06 EtOAc/petroleum ether 7:3) on a silica gel column in gram quantities yielding the optically pure (-) and (+) carbamates, 4 and 5. Considerable amounts of pure (-)-carbamate, could also be obtained after three recrystallizations from ethyl acetate. Thus, separations through recrystallization and chromatography are in this case complementary and by using both methods together the production of optically pure material becomes more efficient.

Pirkle *et al*[14] have studied how the absolute configuration of different pairs of diastereomeric carbamates, obtained from racemic secondary alcohols and an isocyanate with known absolute configuration, can be predicted from the elution order during an ordinary chromatographic procedure. These predictions have also been confirmed[15] by the fact that one

of the carbamates in a diastereomeric pair exhibits NMR line broadening, a phenomenon which can also be used for the assignment of the absolute configuration of carbamates from secondary alcohols. The most stable conformer of the carbamates, due to the rigidity of the carbamate backbone, generated from secondary alcohols can be represented by I (a Z/E ratio of 4:1 for the



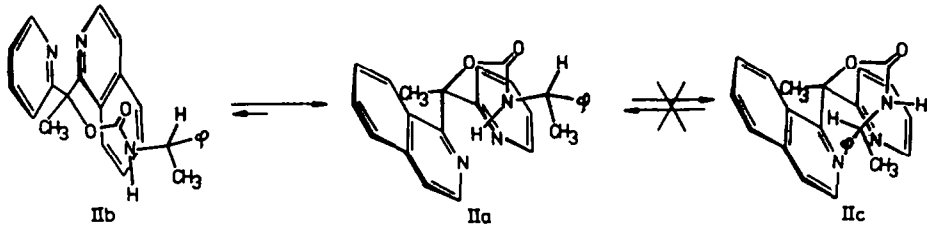
I

two rotamers of the amide part of the carbamate could also be observed.[14]) In our case we felt that, for two reasons, a somewhat different situation was operating:

a) the carbamate was generated from a tertiary alcohol

b) the special chelating properties of the groups corresponding to R_1 and R_2.

Inspection of molecular models strongly suggests that the time averaged conformer of our carbamate is best represented by II a.

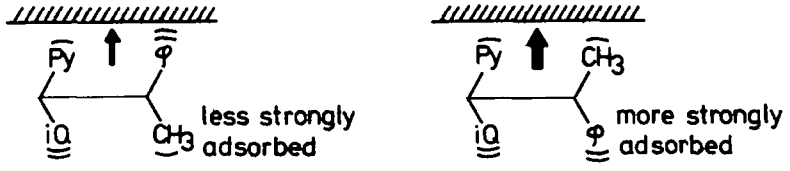


IIb IIa IIc

The contributions from IIb and IIc are probably small. A restricted rotation is imposed on the O-CO bond and the CO-N bond in IIa due to hydrogen bonding between the NH-hydrogen and the two heteroaromatic nitrogens in a chelating fashion. The free rotation is further restricted around the O-CO bond because of the dipolar repulsion between the carbonyl oxygen and the heteroaromatic nitrogens (see IIb) and around the CO-N bond for steric reasons (see IIc). Even though the conformer IIa is different from the conformer I used earlier as a starting point for the prediction of the absolute configuration of carbamates generated from secondary alcohols, the general ideas are still applicable.[17]

The first eluted carbamate i.e. the one less strongly adsorbed, should in our case be the diastereomer having the isoquinolinyl group anti to the phenyl group (Fig. 1). It is therefore assumed, that the (-)-carbamate, which eluted first, has the (S,S) configuration.

Fig. 1



From inspection of molecular models of the (S,S)- and the (R,S)-carbamates certain predictions concerning spectral data differences were made. These predicted spectral data differences were found to be consistent with actual spectral data. Due to the greater shielding effect of the isoquinoline ring compared to the pyridine ring, the chemical shift of the methyl group (in the amine part) situated syn to the isoquinoline (as in the (-)- carbamate) should be at higher

field than that of the same methyl group anti to the isoquinoline (as in the (+)-carbamate). The same rational can also be applied to the phenyl group. We found that δ(methyl(-)-carbamate) = 1.20 ppm versus δ(methyl(+)-carbamate)= 1.42 ppm and δ(phenyl(+)-carbamate)= 7.00 and 6.93 ppm versus δ(phenyl(-)-carbamate)= 7.29 ppm. The methyl group in the alcohol part (of the carbamate) seems to experience little difference, Δδ=0.05, in the magnetic environment between the two diastereomers. A slight peak broadening in the (+)-carbamate can tentatively be explained by a more restricted rotation of the pyridyl group.

The N-H absorbtion frequency difference observed in the IR spectra of the (+)- and (-)-carbamates, 3240 cm^{-1} and 3320 cm^{-1} respectively, may also be a reflection of this rotational difference. The lower absorbtion frequency of the NH-bond in the (+)-carbamate suggests that the NH proton is more strongly hydrogen bonded than in the (-)-carbamate. On the basis of the interrelated consistency of the data, obtained from the suggested time averaged conformer IIa, the relative elution order of the diastereomers and ^1H NMR data, we believe that the (-)-carbamate (4) has the (S,S)- and the (+)-carbamate (5) the (R,S)- absolute configurations.

The optically active (+) and (-) alcohols (6 and 7) were obtained quantitatively after the cleavage of the (-)- and (+)-carbamates, respectively, with potassium hydroxide in ethanol. Attempts to cleave the carbamates using trichlorosilane[18] were unsuccessful. The melting point of the optically pure, (+) or (-), alcohol was 15 degrees above that of the racemic mixture (3). Methylation of the chiral alcohols 6 and 7 with methyl iodide in DME gave the chiral ligands 8 and 9. These optically pure methyl ethers have melting points 31 degrees below that of the racemic mixture 10.

A polymer-supported ligand was also prepared by reaction of the alcohol 3 with a Merrifield resin (chloromethylated polystyrene-2% divinylbenzene) affording a polymer with 0.86 mmol ligand/g resin. The catalytic activity of transition metal complexes of these ligands is presently being investigated.

EXPERIMENTAL SECTION

Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were determined on a Perkin Elmer 241 polarimeter. NMR spectra were recorded in $CDCl_3$ on a Bruker WP 200 spectrometer at 200 MHz; some spectra were recorded using a resolution enhancement technique. IR spectra were recorded on a Perkin-Elmer 421 spectrophotometer. Mass spectra were obtained using an LKB 8000 spectrometer. Diethyl ether and dimethoxyethane (DME) were distilled from benzophenone ketyl under nitrogen. All chromatographic separations were performed on silica (flash) gel (Merck 0.040 - 0.063 mm).

1-Cyanoisoquinonline (1). To isoquinoline-N-oxide (13.5 g, 93 mmol) in 100 ml of CH_2Cl_2 was added with stirring N,N-dimethylcarbamoyl chloride (8.5 ml, 93 mmol) and then trimethylsilyl cyanide (14.0 ml, 111.5 mmol); the addition of trimethylsilyl cyanide was highly exothermic. After 72 h stirring at ambient temperature brine was added leading to evolution of gas. The crude material (15.0 g) obtained from the organic phase was chromatographed with ethyl acetate/petroleum ether (1:1). Evaporation of the solvent and thorough drying gave 14.0 g (97.5%) of 1-cyanoisoquinoline (mp. 85-87 °C).

1-Isoquinolinyl 2-pyridyl ketone (2). 2-Lithiopyridine was prepared by adding butyl lithium (1.25 ml, 1.55 M) to a stirred solution of 2-bromopyridine (0.31 g, 1.95 mmol) in diethyl ether (10 ml) kept at -70 °C under nitrogen. After 30 min 1-cyanoisoquinoline (0.25 g, 1.62 mmol), dissolved in 5 ml of ether, was slowly added keeping the temperature below -65 °C. After 1 h at -65 °C the reaction mixture was allowed to reach room temperature and was then poured into crushed ice. The ether phase was extracted with aqueous 2M HCl. The aqueous phase was then heated at 50 °C for 2h. Neutralization with aqueous Na_2CO_3 followed by extraction with CH_2Cl_2 (3 x 12 ml) yielded, after evaporation of solvent, 0.33 g of crude material. Chromatography (column width 2 cm) with etyl acetate gave 0.25 g (66%) of the desired product. Mp. 92-93 °C. IR (KBr): 1680 (C=O) cm^{-1}. ^1H NMR: δ 7.45-7.97 (6H, m), 8.19-8.24 (2H, m) and 8.67 (1H, d, J=4.6 Hz, 6-pyridyl). MS (70 eV), m/z (rel. int. %): 235(9), 234($M^{+\cdot}$, 60), 233(8), 206(20), 205(100), 128(31), 101(16), 78(22), 51(14), 28(25).

(±)-1-(1-Isoquinolinyl)-1-(2-pyridyl)ethanol (3). To a well stirred suspension of 1-isoquinolinyl 2-pyridyl ketone (3.6 g, 15.4 mmol) in dry diethyl ether (200 ml) was added methyl magnesium iodide (20 ml, 1.0 M in ether) over a period of 15-30 min. The large amount of solvent was convenient since when the Grignard reagent was added the suspension was turned into

a thick greyish slurry. After 5 h reflux the reaction was quenched by the addition of 40 ml of saturated aqueous NH_4Cl. The crude material (obtained after phase separation, drying and evaporation of solvent) was chromatographed on a column with a diameter of 4 cm and with EtOAc/petroleum ether (3:2) as eluent to give 3.12 g (81%) of the desired product as a yellow-brown oil that crystallized on standing and 0.54 g of recovered starting material. The product was further purified by repeated recrystallizations from $EtOH/H_2O$. Mp. 78-79 °C. IR (KBr): 3300 (OH), 3070-3050 (Ar-H), 3000-2980 (CH_3), 1620-1590 (C=C and C=N conjugated) cm^{-1}. ^1H NMR (Res. enhanc.): δ 2.17 (3H, S, CH_3), 7.16 (1H, ddd, J = 1.2, 4.9 and 7.4 Hz, 5-pyridyl), 7.20 (1H, t d, J = 1.1 and 8.0 Hz, 5-isoquinolinyl), 7.36 (1H, ddd, J = 1.4, 6.9 and 8.4 Hz, 7-isoquinolinyl), 7.38 (1H, S, OH), 7.54 (1H, ddd, J = 1.8, 7.4 and 8.2 Hz, 4-pyridyl), 7.57 (1H, ddd, J = 1.2, 6.9 and 8.3 Hz, 6-isoquinolinyl), 7.64 (1H, dd, J = 0.9 and 5.7 Hz, 4-isoquinolinyl), 7.81 (1H, d broad, J = 8.2 Hz, 3-pyridyl), 8.11 (1H, qd, J = 1.0 and 8.7 Hz, 8-isoquinolinyl). 8.51 (1H, d, J = 5.7 Hz, 3-isoquinolinyl) and 8.63 (1H, ddd, J = 1.0, 1.8 and 4.9 Hz, 6-pyridyl).

(-)-(S,S)- and (+)-(R,S)-1-(1-isoquinolinyl)-1-(2-pyridyl) N-(1-phenylethyl)carbamate (4 and 5). (±)-1-(1-Isoquinolinyl)-1-(2-pyridyl)ethanol (1.74 g, 6.95 mmol), 4-(N,N-dimethylamino)pyridine (DMAP) (1.19 g, 9.73 mmol) and (-)-(S)-1-phenylethyl isocyanate (1.43 g, 9.73 mmol) were mixed in a 10 ml reaction flask. The mixture was gently stirred and heated to 135 °C, resulting in a homogeneous melt. The reaction vessel was sealed (to prevent the escape of reactants), and was fully immersed in the oil bath. After 9 h at 135 °C, the mixture was allowed to reach room temperature and was then dissolved in $EtOAc/CH_2Cl_2$. Chromatography on silica (column width 4 cm) with 200 ml of $EtOAc/CH_2Cl_2$ (1:1), followed by 200 ml of $EtOAc/CH_2Cl_2$ (4:1) and then by 800 ml of EtOAc gave a 2.32 g mixture (84%) of the two diastereomers free from by products, unreacted starting materials and DMAP. To obtain optically pure (-)- and (+)-carbamate the diastereomeric mixture was chromatographed, using a MPC (medium pressure chromatography) system, on a silica gel packed column (3 cm x 80 cm). The best separation was accomplished with 1000 ml of $EtOAc/CH_2Cl_2$ (1:1), followed by 700 ml of EtOAc. When 150 ml of the first solvent composition remained, the EtOAc was continously added through a separation funnel into the beaker from which the solvent was pumped, keeping the volume constant at 150 ml. When 870 ml solvent had passed the column the first fractions containing carbamate could be collected. In a typical separation, 1.00 g of the diastereomeric mixture afforded 0.348 g of the (-)-carbamate (which was eluted first), 0.331 g of unseparated mixture and 0.301 g of the (+)-carbamate. By repeating this procedure on the same column gram quantities of the optically pure diastereomers could be obtained within a couple of hours. Optically pure (-)-carbamate could also be obtained after three recrystallizations of the diastereomeric mixture from ethyl acetate. In a typical example, 0.51 g of pure (-)-carbamate was obtained from 2.64 g of the mixture.

(-)-(S,S)-1-(1-Isoquinolinyl)-1-(2-pyridyl) N-(1-phenylethyl)carbamate (4). Mp. 196-198 °C, $[\alpha]_D^{26}$ = -168° (C 0.0109, CH_2Cl_2). IR (KBr): 3320 (NH), 3095-3020 (Ar-H), 3000-2920 (CH_3, CH), 1725 (C=O), 1590 (C=C and C=N conjugated) cm^{-1}. ^1H NMR: δ 1.18-1.22 (3H, m broad, $CHCH_3$), 2.38 (3H, s, -O-C(Py)(IQ)CH_3, 4.60 (1H, m broad, $CHCH_3$), 5.28 (1H, s broad, NH), 7.06-7.65 (11H, m, Ar), 7.76-7.81 (1H, d broad, Ar), 8.09-8.15 (1H, d broad, Ar), 8.48 (1H, s broad, Ar) and 8.61 (1H, d, J = 5.6 Hz, 3-isoquinolinyl). Calc. for $C_{25}H_{23}N_3O_2$: C 75.54 H 5.83 N 10.57%. Found: C 75.2 H 6.0 N 10.6%.

(+)-(R,S)-1-(1-Isoquinolinyl)-1-(2-pyridyl) N-(1-phenylethyl)carbamate (5). Mp. 181-183 °C, $[\alpha]_D^{26}$ = +75 ° (C 0.0092, CH_2Cl_2). IR (KBr): 3240 (NH), 3060-3030 (Ar-H), 3000-2930 (CH and CH_3), 1725 (C=O), 1590 (C=C and C=N conjugated) cm^{-1}. ^1H NMR (Res. enhancem.): δ 1.42 (3 H, d, J = 6.9 Hz, $CHCH_3$), 2.43 (3H, s, -O-C(Py)(IQ)CH_3), 4.60 (1H, m broad, $CHCH_3$), 5.28 (1H, d broad, NH), 6.93 (2H, m broad, 2- and 6-phenyl), 7.10 (3H, m broad, 3-, 4- and 5-phenyl), 7.26 (1H, ddd, J = 1.9, 6.9 and 8.4 Hz, 7-isoquinolinyl), 7.40 (1H, d broad, J = 8.3 Hz), 7.51 (1H, ddd, J = 1.2, 6.9 and 8.2 Hz, 6-isoquinolinyl), 7.57 (1H, dd, J = 0.9 and 5.7 Hz, 4-isoquinolinyl), = 7.5-7.63 (2H, m), 7.76 (1H, d, J = 8.2, 3-pyridyl), 8.06 (1H, d broad, J = 9 Hz, 8-isoquinolinyl), 8.50 (1H, d broad, 6-pyridyl) and 8.59 (1H, d, J = 5.6 Hz, 3-isoquinolinyl).

Cleavage of 4 and 5. The carbamate 4 (0.415 g, 1.04 mmol) was refluxed in 8 ml of ethanol together with potassium hydroxide (0.23 g, 4.17 mmol) for 3 h. The reaction was terminated by the addition of 1 ml of saturated aqueous NH_4Cl. Extraction with 2 x 20 ml of CH_2Cl_2, drying with $MgSO_4$ and evaporation of the solvent yielded 0.38 g of crude product. Chromatography (column width 2 cm) with EtOAc/petroleum ether (1:1) gave, after thorough drying, 0.265 g of (+)-(S)-1-(1-isoquinolinyl)-1-(2-pyridyl)ethanol 6. After recrystallization from $EtOH/H_2O$, 0.194 (75%) of 6 was obtained. Mp. 93-94 °C, $[\alpha]_D^{26}$ = +62 ° (C 0.0119, CH_2Cl_2). Calc. for $C_{16}H_{14}N_2O$: C 76.77 H 5.64 N 11.19 %. Found: C 76.7 H 5.7 N 11.2%.

(-)-(s)-1-(Isoquinolinyl)-1-(2-pyridyl)ethanol (7) was prepared in the same way as described above. Mp. = 93-94 °C, $[\alpha]_D^{26}$ = -62 °(C 0.0119, CH_2Cl_2).

(±)-1-(1-Isoquinolinyl)-1-methoxy-1-(2-pyridyl)ethane (10). To a suspension of sodium hydride (0.02 g, 0.65 mmol) in 3 ml of DME (+)-1-(1-Isoquinolinyl)-1-(2-pyridyl)ethanol (1) (0.136 g, 0.540 mmol) was added under argon at ambient temperature. After the evolution of hydrogen gas had ceased a light yellow transparent solution resulted. Methyl iodide (40.6 µl, 0.65 mmol) was then added using a syringe. After 2h the reaction was terminated by the addition of 0.25 ml of aqueous saturated NH_4Cl. The DME was evaporated and the resulting material was, after the addition of a few ml of water, extracted with CH_2Cl_2. Flash chromatography (column width 2 cm) with EtOAc/petroleum ether (1:1) gave 0.125 g (87%) of 10. Mp. 115-116 °C after recrystallization from petroleum ether. IR (KBr): 3080-3060 (Ar-H), 2990-2830 (CH_2, CH_3), 1620, 1590 (C=C and C=N conjugated) cm^{-1}. ^1H NMR (Res. enhanc.): δ 2.10 (3H, s, CH_3), 3.16 (3H, s, O-CH_3), 7.05 (1H, ddd, J = 1.6, 4.8 and 7.0 Hz, 5-pyridyl), 7.28 (1H, ddd, J = 1.4, 6.8 and 8.5 Hz, 7-isoquinolinyl), 7.52 (1H, ddd, J = 1.2, 6.8 and 8.1 Hz, 6-isoquinolinyl), 7.62 (1H, dd, J

= 0.7 and 5.7 Hz, 4-isoquinolinyl), ≈ 7.62-7.78 (2H, m, 4-pyridyl and 5-isoquinolinyl, 7.77 (1H, d broad, J = 8.2 Hz, 3-pyridyl), 8.26 (1H, qd, J = 1.0 and 8.7 Hz, 8-isoquinolinyl), 8.38 (1H, ddd, J = 1.0, 1.7 and 4.9 Hz, 6-pyridyl) and 8.60 (1H, d, J = 5.7 Hz, 3-isoquinolinyl).

(-)-(s)-1-(1-Isoquinolinyl)-1-methoxy-1-(2-pyridyl)ethane (8). Compound 8 was prepared and purified in the same way as 10 starting from 6. Yield 90%. Mp. 84-85 °C, $[\alpha]_D^{26}$ = -172 ° (C 0.0129, CH_2Cl_2).

(+)-(R)-1(-1-Isoquinolinyl)-1-methoxy-1-(2-pyridyl)ethane (9). Compound 8 was prepared and purified in the same way as 10 starting from 7. Yield 90%. Mp. 84-85 °C, $[\alpha]_D^{26}$ = +172 ° (C 0.0129, CH_2Cl_2).

Polymer-supported (±)-1-(1-isoquinolinyl)-1-(2-pyridyl)ethanol. The racemic alcohol 3 (754 mg, 3 mmol) in DME (10 ml) was added to NaH (140 mg of 80% suspension in oil, 4.5 mmol) in DME (5 ml). After 15 min stirring at ambient temperature this solution was added to a chloromethylated styrene-2% divinylbenzene resin (1 g, 2.6-2.8 mmol chlorine) in DME (10 ml) and the mixture was heated at 80 °C for 23 h. The beads were filtered off, washed thoroughly with DME and methanol and finally dried in a vacuum at 60 °C for 2 h to give 1.21 g of the polymeric ligand. Anal. N: 2.4%.

Acknowledgements

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16. In our case NMR-line broadening was observed for both diastereomers. In the (-)-carbamate the amine part methyl doublet was broadened while not in the (+)-carbamate. In the (+)-carbamate the phenyl group and the other methyl group (singlet) were broadened.
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