Synthesis and Resolution of BICOL, a Carbazole Analogue of BINOL

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The synthesis and resolution of a novel chiral C_2-symmetric bicarbazolediol (BICOL), is reported. The key step in the synthesis is the copper(II)-catalysed oxidative phenol coupling of 3-hydroxycarbazole. Menthyl chloroformate is used as resolving agent for the separation of the two enantiomers of BICOL.

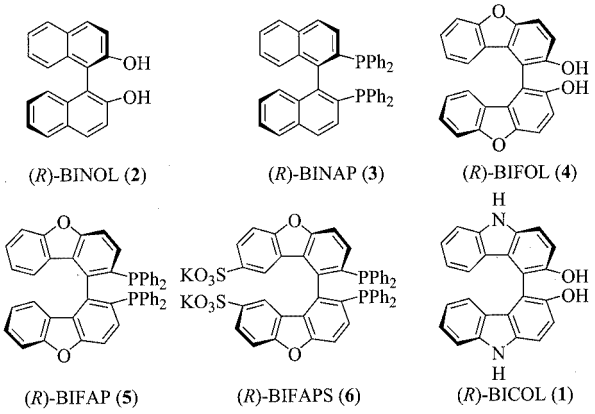
Introduction

Over the last few decades C_2-symmetric bidentate ligands have proven to be very efficient chiral sources in homogeneous asymmetric catalysis.[1] The success of complexes of 2,2′-disubstituted 1,1′-binaphthyls, in particular BINOL **2** and BINAP **3**, in giving high enantioselectivities in numerous catalytic reactions, has encouraged the synthesis of several related ligands.[2] In order to control and optimise the chiral induction, electronic and steric factors were varied widely. In this regard, we recently developed the synthesis of BIFOL **4**, BIFAP **5** and BIFAPS **6**, a family of new bidentate ligands based on the bidibenzofuran backbone and useful for asymmetric catalysis in both organic solvents and in aqueous media.[3] The promising results of these ligands in asymmetric catalysis led to the idea of the synthesis of BICOL **1**, another new chiral bidentate ligand based on the bicarbazole backbone. In addition to the successful bidibenzofuran type ligands **4**–**6**, the carbazole amine allows facile functionalisation. In ongoing studies tailor-made ligands will be made by variations at the carbazole nitrogen in order to fine-tune the electronics and sterics.

In this paper a robust synthesis of BICOL, based on the Fischer indole synthesis[4] and an oxidative phenol coupling reaction, is described. The resolution of BICOL is performed by employing both enantiomers of menthyl chloroformate as the resolving reagents.

Results and Discussion

For the synthesis of 3-hydroxycarbazole **10** we optimised the route developed by Milne and Tomlinson.[5] Tetrahydrocarbazole **7**, smoothly obtained according to the literature procedure[6] from cyclohexanone and 4-methoxyphenylhydrazine hydrochloride, was oxidised to methoxycarbazole **8** using wet palladium on carbon in a high boiling solvent (*p*-cymene, b.p. 176–178 °C). Deactivation of the catalyst by water proved to be essential. Reaction in the absence of water yielded an approximately 1:1 mixture of methoxycarbazole (**8**) and the demethoxylated carbazole **9**, while addition of water shifted this ratio to 99:1 in favour of the desired methoxycarbazole (Scheme 1).



Several oxidative coupling methods were investigated[7] in order to dimerise hydroxycarbazole **10**, obtained from **8** by cleavage of the methyl ether according to the literature procedure.[5] The reaction was carried out successfully using either a stoichiometric amount of oxidant [$Mn(acac)_3$][8] or with the catalysts [CuCl(OH)·TMEDA,[9] $VO(acac)_2$,[10] $CuSO_4/Al_2O_3$ [11]] and molecular oxygen as the oxidant. All reactions yielded the same products in the same ratios; 40–50% symmetric bicarbazolediol **1** (BICOL, m.p. 327–328 °C) and 15–20% asymmetric dimer **11** (m.p. 197–199 °C). After completion of the reaction, as was monitored by TLC, it appeared necessary to remove the oxidants from the reaction mixture, because extensive stirring under oxygen atmosphere led to over-oxidation of the diol, yielding probably quinone-like products. Separation of

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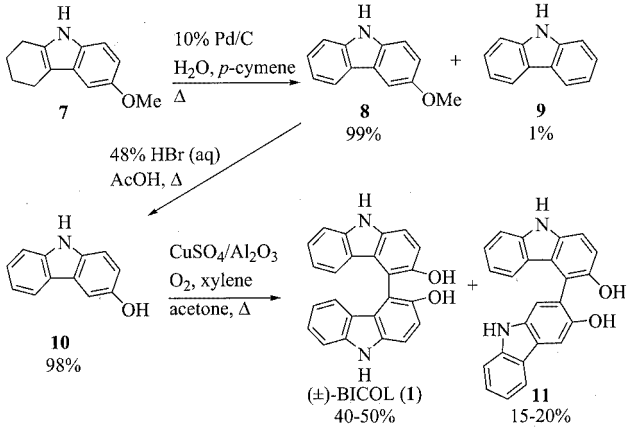
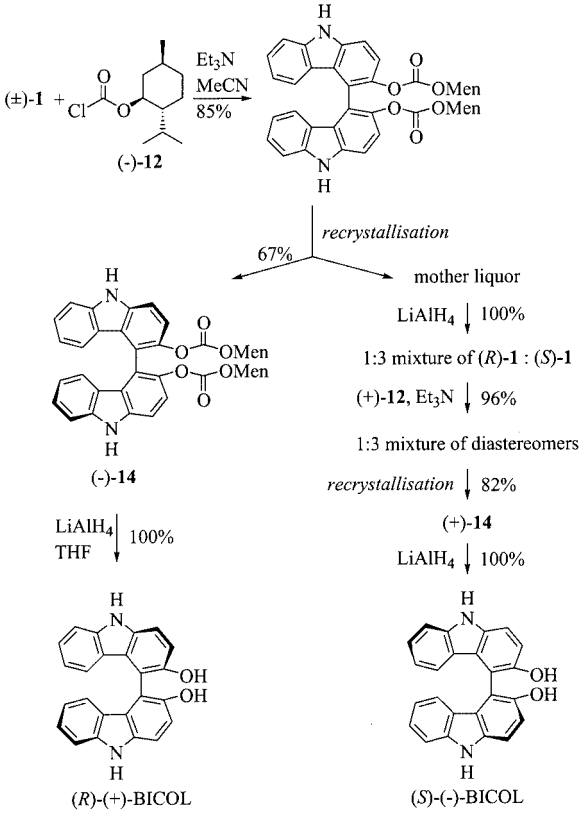


Scheme 1

the product from the metal salts and the by-products could only be accomplished in a practical manner by tedious column chromatography. The finding that the alumina-supported copper(II) sulfate catalyst could be easily removed before column chromatography by filtration made this the method of choice.

In order to use the carbazole-based diol as chiral ligand, the resolution of the enantiomers had to be performed. Of the numerous successful methods for the nonenzymatic resolution of BINOL and its derivatives,[12,13] several were tested. Separation by use of *N*-benzylcinchonidinium chloride (NBC), as described by Reider et al.,[12c] allowed the formation of inclusion crystals. Unfortunately, these crystals consisted of both enantiomers of BICOL together with NBC. The next method we considered was the procedure described by Hu et al.[13b] Reacting (±)-BICOL with $POCl_3$, using a similar procedure as described by Hu et al.,[13b] followed by (*S*)-1-phenylethylamine yielded a 1:1 diastereomeric mixture of phosphoramidates. Regrettably, these products proved to be virtually insoluble in the common solvents, making further purification and/or recrystallisation impossible. More success was obtained with the procedure developed by De Lucchi et al.,[13a] when we used menthyl chloroformate **12** as resolving agent (Scheme 2).



Scheme 2

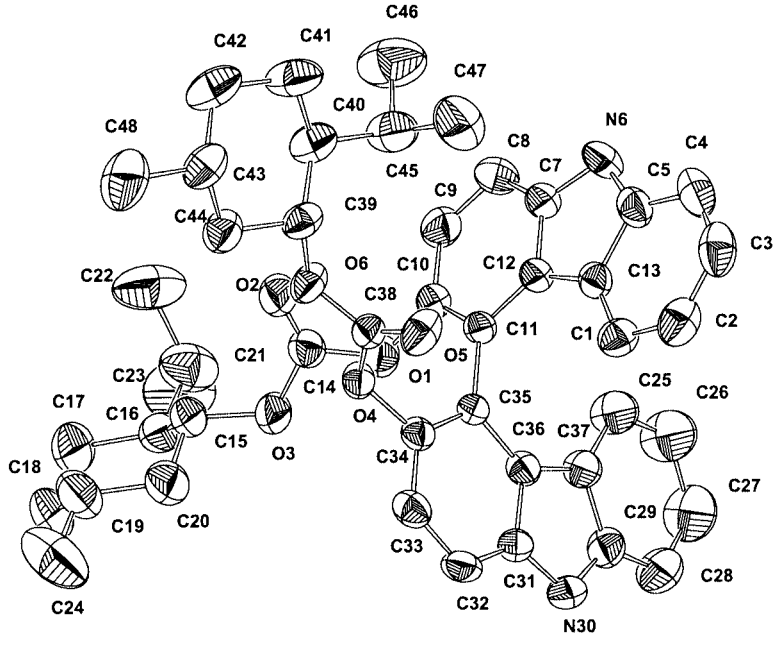


Figure 1. ORTEP view of the crystal structure of compound (−)-**14**.

Reaction of two equivalents of (−)-**12** and (±)-BICOL in the presence of Et_3N in acetonitrile gave a 1:1 mixture of the diastereomers. A single recrystallisation from diisopropyl ether yielded colourless crystals of diastereomerically pure (−)-**14** ($[\alpha]_D^{20} = -242$, m.p. 214 °C) in 67% yield, based on one diastereomer (>98% *de*, checked with HPLC). After removal of the chiral auxiliary employing $LiAlH_4$ as reducing agent, enantiomerically pure (*R*)-(+)-BICOL ($[\alpha]_D^{20} = +105$, m.p. 180−183 °C) was obtained in a quantitative yield. The residue of the recrystallisation was also reduced with $LiAlH_4$, yielding an enriched 3:1 mixture in favour of (*S*)-(−)-BICOL. Upon reaction of this mixture with (+)-menthyl chloroformate (+)-**12**, a 3:1 mixture of the diastereomers was obtained, with (+)-**14** in excess. A single recrystallisation from diisopropyl ether now gave colourless crystals of diastereomerically pure (+)-**14** (>98% *de*, $[\alpha]_D^{20} = +242$, m.p. 214−215 °C) in 82% yield, based on one diastereomer from the 3:1 mixture. In principle, the mother liquor could be subjected to the same reaction sequence, using alternatingly (−)- and (+)-menthyl chloroformate. Removal of the chiral auxiliary using $LiAlH_4$ yielded enantiomerically pure (*S*)-(−)-BICOL ($[\alpha]_D^{20} = -105$, m.p. 180−184 °C). The difference in melting point of ca. 145 °C between racemic and enantiopure BICOL is remarkable. For BINOL this difference is less than 10 °C.

The crystal structure of (−)-**14** was determined by X-ray diffraction (Figure 1).[14] The absolute configuration could not be determined unequivocally. However, because the absolute configuration of the starting reagent [(−)-(1*R*)-menthyl chloroformate] is known, it is concluded that (−)-**14** contains the (*R*)-enantiomer of BICOL. The asymmetric unit contains one molecule of the recrystallisation solvent diisopropyl ether. The structure shows furthermore that the two carbazole moieties are positioned almost perpendicular. The angle between these two planar units is 80.4°.

Conclusions

In conclusion, we have described a straightforward synthesis and resolution of BICOL **1**. A $CuSO_4/Al_2O_3$ catalysed oxidative phenol coupling allowed the formation of the bicarbazole skeleton in one step from 3-hydroxycarbazole **10**. Menthyl chloroformate was successfully used as resolving reagent for the resolution of (±)-BICOL, yielding, after reductive removal of the chiral auxiliary, both enantiomers of BICOL in pure form. Studies towards the application of this new type of BINOL derivatives, by the introduction of substituents at the carbazole nitrogens and further functionalisation of the bicarbazole skeleton (i.e. with phosphane or phosphoramidite groups) towards new classes of ligands will be reported in due course.

Experimental Section

All reactions were carried out under an inert atmosphere of dry argon, unless stated otherwise. Standard syringe techniques were applied for the transfer of air sensitive reagents and dry solvents. Infrared (IR) spectra were obtained from $CHCl_3$ solutions, by using a Bruker IFS 28 FT-spectrophotometer and wavelengths ($\tilde{\nu}$) are reported in cm^{-1}. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were determined in [D_6]acetone with a Bruker ARX 400 (400 MHz and 100 MHz, respectively) unless indicated otherwise. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. HRMS measurements were carried out using a JEOL JMS-SX/SX 102 A Tandem Mass Spectrometer. A HP Series 1050 HPLC was used for HPLC experiments, with an Inertsil ODS-S column (l × *d* = 50 × 4.6 mm, particle size 3μm) with acetonitrile/water, 50:50 → 95:5 (+0.04% formic acid) as the eluent. The detection wavelength was 254 nm. Optical rotations were measured on a Perkin−Elmer 241 polarimeter in a 1-dm cell (2 mL) in the indicated solvent at the indicated concentration, temperature and wavelength. Chromatographic purification refers to flash chromatography[15] by using the indicated solvent (mixture) and Acros silica gel (0.035−0.070 mm). R_f values were obtained by using thin-layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel F_{254}) with PE(60−80)/EtOAc, 1:1 as the eluent unless noted otherwise. Melting points are uncorrected. Dry THF was distilled from sodium benzophenone ketyl prior to use. Dry acetonitrile was distilled from calcium hydride and stored over MS 4 Å under a dry argon atmosphere. Triethylamine was dried and distilled from KOH pellets. All commercially available reagents (Aldrich or Acros) were used as received, unless indicated otherwise.

9*H*-Carbazol-3-ol (10): To a solution of **7**[6] (5.00 g, 24.8 mmol) in *p*-cymene (50 mL) and water (10 mL), 10% Pd on carbon (2.5 g, Aldrich) was added. The resulting suspension was refluxed (170−180 °C) for 48 h, cooled to room temperature and filtered. The residue was flushed with boiling EtOAc. The collected filtrates were concentrated in vacuo to yield a 99:1 mixture of **8** and **9** (4.80 g, 99%). The crude mixture was used for the synthesis of **10**, according to the literature procedure. Spectroscopic data were in accordance with the literature.[16]

(±)-9*H*,9′*H*-[4,4′]Bicarbazole-3,3′-diol (BICOL, 1): To a solution of **8** (3.10 g, 16.9 mmol) in xylene (120 mL) and acetone (22 mL) was added $CuSO_4/Al_2O_3$ (2.3 g). The solution was heated at reflux for 18 h while pure oxygen was bubbled through the suspension. After cooling to room temperature the dark mixture was filtered and the solid material on the filter washed with EtOAc. The combined organic fractions were concentrated in vacuo. Purification by chromatography (PE/EtOAc, 2:1 → 1:1) yielded **1** (1.53 g, 50%) and **11** (0.59 g, 19%) as light brown powders. **1:** R_f = 0.24. M.p. 327−328 °C. ^1H NMR: δ = 6.56 (dt, *J* = 7.2, 0.9 Hz, 2 H), 6.71 (d, *J* = 8.0 Hz, 2 H), 7.12 (m, 4 H), 7.22 (d, *J* = 8.6 Hz, 2 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 7.53 (d, *J* = 8.6 Hz, 2 H), 10.14 (br. s, 2 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 110.1, 110.3, 114.9, 116.6, 117.2, 121.1, 122.0, 123.0, 124.4, 134.1, 140.4, 147.9 ppm. IR: $\tilde{\nu}$ = 3402 (br), 1684. HRMS (FAB+) calcd. for $C_{24}H_{17}O_2N_2$ (MH^+) 365.1290; found 365.1300.

11: R_f = 0.36. M.p. 197−199 °C. ^1H NMR: δ = 6.87 (t, *J* = 7.2, Hz, 1 H), 7.06 (t, *J* = 7.2 Hz, 1 H), 7.12 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.21 (m, 2 H), 7.32 (m, 2 H), 7.43 (m, 3 H), 7.60 (d, *J* = 2.5 Hz, 1 H), 7.81 (m, 2 H), 7.90 (d, *J* = 7.8 Hz, 1 H), 10.17 (br. s, 1 H), 10.23 (br. s, 1 H) ppm. ^{13}C NMR: δ = 104.7, 107.8, 110.7, 111.0, 111.5, 114.1, 116.7, 117.2, 118.0, 118.1, 120.2, 120.7, 122.1, 122.2, 122.8, 125.2, 125.6, 135.0, 135.1, 135.8, 140.2, 140.5, 142.6, 151.5 ppm. IR: $\tilde{\nu}$ = 3406 (br), 1691. HRMS (FAB+) calcd. for $C_{24}H_{17}O_2N_2$ (MH^+) 365.1290; found 365.1292.

Resolution of BICOL: To a stirred solution of racemic BICOL **1** (1.00 g, 2.75 mmol) and Et_3N (1.91 mL, 13.7 mmol) in acetonitrile (27 mL) was added dropwise (−)-(1*R*)-menthyl chloroformate (−)-**12** (1.36 mL, 6.30 mmol). The solution was stirred at room temperature for 1 h. The reaction was quenched by addition of EtOAc (100 mL) and water (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by chromatography (PE/EtOAc, 5:1→2:1) afforded a 1:1 diastereomeric mixture as an off-white solid (1.71 g, 85%). R_f = 0.50 (for both diastereomers). The mixture was dissolved in refluxing diisopropyl ether (8 mL) and set aside at room temperature overnight. The resulting crystals were collected, washed with diisopropyl ether and dried in vacuo, yielding (−)-**14**, as a single diastereomer (0.57 g, 67% yield based on one diastereomer). $[\alpha]_D^{20}$ = −242 (*c* = 1.0, $CHCl_3$). M.p. 214 °C. ^{1}H NMR: δ = 0.24 (d, *J* = 6.9 Hz, 6 H), 0.62 (d, *J* = 7.0 Hz, 6 H), 0.67 (m, 4 H), 0.79 (d, *J* = 6.5 Hz, 6 H), 0.85 (m, 2 H), 1.04 (m, 2 H), 1.27 (m, 4 H), 1.49 (m, 4 H), 1.75 (m, 2 H), 4.14 (dt, *J* = 4.4, 10.9 Hz, 2 H), 6.57 (m, 4 H), 7.13 (dt, *J* = 6.5, 1.7 Hz, 2 H), 7.42 (dd, *J* = 8.7, 8.2 Hz, 4 H), 7.72 (d, *J* = 8.7 Hz, 2 H), 10.57 (s, 2 H) ppm. ^{13}C NMR: δ = 16.3, 20.9, 22.4, 24.1, 26.8, 32.1, 34.9, 41.1, 47.8, 79.1, 111.6, 111.9, 119.4, 121.2, 123.0, 123.2, 123.3, 124.0, 126.5, 139.1, 142.1, 143.2, 154.3. HRMS (FAB+) calcd. for $C_{46}H_{53}N_2O_6$ (MH^+) 729.3904, found 729.3950.

The remaining filtrate was concentrated in vacuo, yielding a yellow solid (1.13 g, 1.55 mmol). After dissolving the mixture in anhydrous THF (31 mL), $LiAlH_4$ (0.58 g, 10.9 mmol) was added in 3 portions over 10 min. The reaction mixture was stirred for 1 h at room temperature. The reaction was carefully quenched by adding water, EtOAc and 1 N aqueous HCl. The layers were separated and the aqueous phase was extracted with EtOAc (3 × 60 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by chromatography (PE/EtOAc, 1:1) afforded a 3:1 mixture of (*S*)-BICOL and (*R*)-BICOL as a white solid (0.41 g, 100% yield).

The 3:1 mixture was reacted with (+)-menthyl chloroformate (+)-**12** according to the procedure described above, yielding a 3:1 mixture of diastereomers (1.08 g, 96%). After recrystallisation from diisopropyl ether (5 mL) the formed cubic crystals were collected, washed with diisopropyl ether and dried in vacuo, yielding (+)-**14**, as a single diastereomer (0.66 g, 82% yield calculated from the 3:1 mixture). $[\alpha]_D^{20}$ = +242 (*c* = 1.0, $CHCl_3$). M.p. 214−215 °C. HRMS (FAB+) calcd. for $C_{46}H_{53}N_2O_6$ (MH^+) 729.3904, found 729.3889. Spectroscopic data are identical to (−)-**14**.

Both diastereomerically pure (−)-**14** and (+)-**14** were treated with $LiAlH_4$ according to the procedure described above, yielding enantiomerically pure (*R*)-(+)-BICOL and (*S*)-(−)-BICOL, respectively, in a quantitative yield after purification by chromatography (EtOAc/PE = 1:1). (*R*)-(+)-BICOL; R_f = 0.24. $[\alpha]_D^{20}$ = +105 (*c* = 1.0, THF). M.p. 180−183 °C. HRMS (FAB+) calcd. for $C_{24}H_{17}N_2O_2$ (MH^+) 365.1290, found 365.1296. $C_{24}H_{16}N_2O_2$·0.6 EtOAc: calcd. C 75.95, H 5.03, N 6.70; found C 76.02, H 4.92, N 6.41. Spectroscopic data are identical to (±)-BICOL and confirmed the presence of EtOAc.

(*S*)-(−)-BICOL: R_f = 0.24. $[\alpha]_D^{20}$ = −105 (*c* = 1.0, THF). M.p. 180−184 °C. HRMS (FAB+) calcd. for $C_{24}H_{17}N_2O_2$ (MH^+) 365.1290, found 365.1284. $C_{24}H_{16}N_2O_2$·0.8 EtOAc: calcd. C 75.15, H 5.19, N 6.45; found C 75.13, H 4.89, N 6.31. Spectroscopic data are identical to (±)-BICOL and confirmed the presence of EtOAc.

Acknowledgments

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