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Linking BINOL: C_2-Symmetric Ligands for Investigations on Asymmetric Catalysis

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Abstract

The synthesis of new C_2-symmetric chiral ligands consisting of two binaphthol units linked by a short bridge is described. These ligands can be used for investigating catalytic asymmetric reactions which utilize BINOL or related ligands as was demonstrated for the ring opening reaction of cyclohexene oxide with 4-methoxyphenol.

Keywords: C_2-symmetric ligands; Asymmetric catalysis; Catalytic asymmetric ring opening; Ga-complexs

Among the most commonly applied chiral ligands in recent asymmetric catalytic synthesis, C_2-symmetric 1,1-bi-2-naphthols play a major role, with a wide range of center metals being used as Lewis acids [1]. In many instances the catalytically active species of these reactions is thought to contain several equivalents of ligand per metal center. For example remarkable non-linear effects have been observed for titanium complexes used in glyoxylate-ene reactions [2]. Similarly, investigations on heterobimetallic lanthanoid catalysts [3] by NMR spectroscopy [4] and X-ray crystallography [5] suggested, that in many cases the catalytically important species has three BINOL ligands coordinated to the lanthanoid center. An even more complicated picture has been drawn for a chiral BINOL aluminium complex, a catalyst for the 1,4-addition of Horner-Wadsworth-Emmons reagents to α,β-unsaturated carbonyl compounds. In the presence of base three different complexes with aluminium to BINOL ratios of 1:1, 1:2 and 1:3 have been shown to be in equilibrium [6].

Trying to investigate such cases of varying stoichiometry it seemed desirable to link two BINOL units in a defined way together thereby ensuring their spatial proximity which would disfavour dissociation after complexation. The linker should allow a limited amount of flexibility for the BINOL units as details of the geometry might be crucial to enantioselection. Therefore the introduction of an ethylene bridge (see ligand **1**) or a methylene bridge (see

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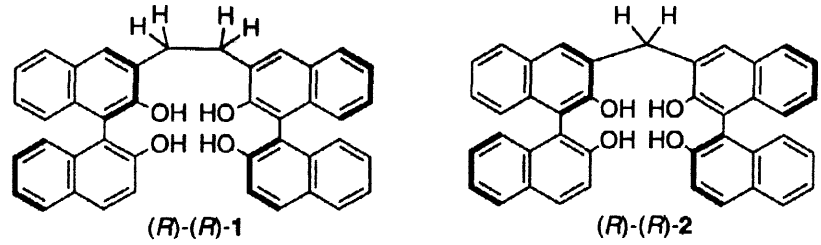
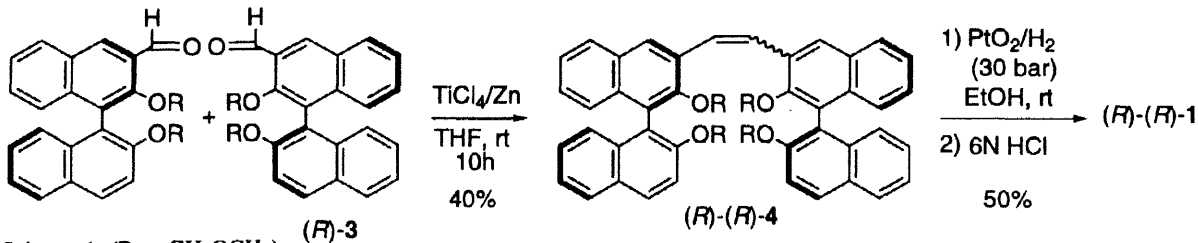
ligand **2**) in the 3-position of BINOL seemed best suited for our purpose.



(*R*)-(*R*)-**1** (*R*)-(*R*)-**2**

To our surprise we found that even though the concept is simple, no such ligands have been reported to date. Related work includes the incorporation of chiral BINOL units into crown ethers by Cram et al. [7] and, more recently, the synthesis of BINOL-based oligomers by Chow and Ng with BINOL being connected by an acetylenic bridge in the 4-position [8]. Similarly, a BINOL-based polymer has been applied recently after treatment with diethylaluminium chloride as a catalyst for the Mukaiyama aldol condensation with the BINOL-units being linked to each other at the 6- and 6'-positions [9].

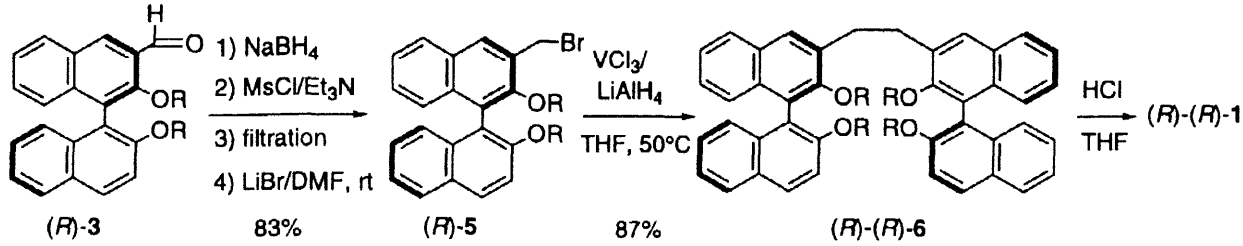
Our synthetic approach to **1** (ethylene-bridged-bis-BINOL, ebb-Binol) started from MOM-protected 3-formyl-(*R*)-BINOL **3** (Scheme 1, MOM = CH_3OCH_2-) [10], which was subjected to McMurry conditions [11], but the temperature was kept below 30 °C to avoid racemization. The coupling product **4** was obtained in up to 40% yield with partial deprotection taking place during work up [12]. The new chiral intermediate **4** may itself be a useful ligand for stabilizing mono- or dinuclear metal fragments. After unsuccessfully applying several other methods, the hydrogenation of **4** to yield the targeted ligand **1** could be achieved using PtO_2 / H_2 (30 bar) in ethanol (50% yield) [13]. Starting from 13.1 g of (*R*)-BINOL we have been able to obtain 1.0 g of the C_2-symmetric ebb-BINOL (*R*)-(*R*)-**1** [14] utilizing the synthetic route outlined above (8% overall yield from BINOL).



(*R*)-**3** (*R*)-(*R*)-**4**

Scheme 1. (R = -CH_2OCH_3)

To improve the yield of the reaction sequence, we also developed a different route using a VCl_3/$LiAlH_4$ promoted coupling as the key step [15] (Scheme 2). Reduction of **3** with $NaBH_4$ in MeOH/THF at 0 °C yielded 3-hydroxymethyl-BINOL, which after mesylation with



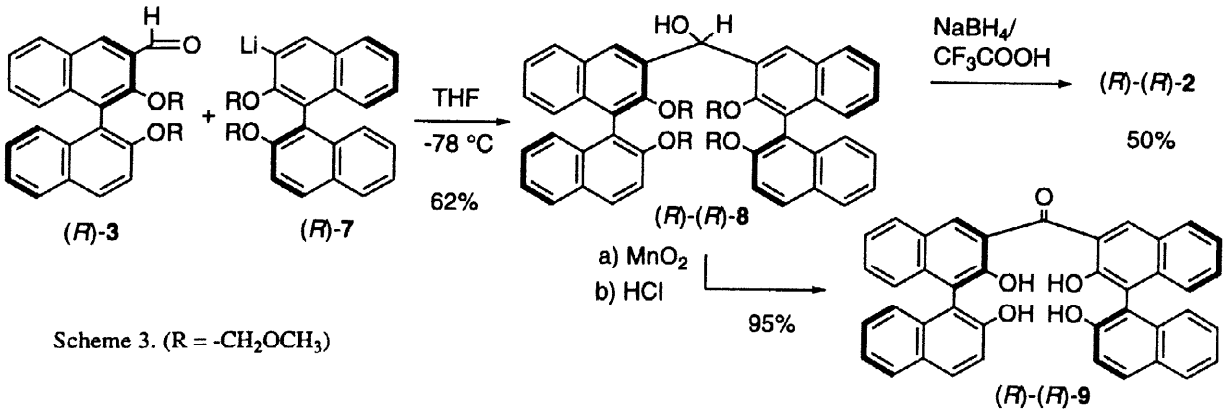
(*R*)-**3** 83% (*R*)-**5** 87% (*R*)-(*R*)-**6**

Scheme 2.

MsCl/Et_3N in toluene at 0 °C, filtration of Et_3N•HCl and treatment with LiBr in DMF gave **5** in about 83% yield from (*R*)-**3** [16]. Reductive coupling of **5** in THF at 50 °C for 60 min

afforded **6** in 87% yield. After deprotection, ebb-BINOL (*R*)-(*R*)-**1** was obtained in an increased overall yield of 53% starting from MOM-BINOL. The new ligands (*R*)-(*R*)-**1** and (*S*)-(*S*)-**1** can therefore conveniently be prepared on a useful scale [17].

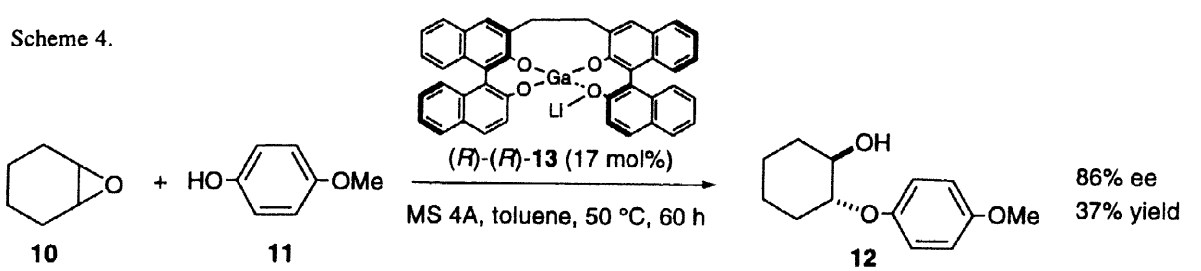
To synthesize (*R*)-(*R*)-**2** (methylene-bridged-bis-BINOL, mbb-BINOL), the 3-lithiated MOM-protected BINOL (*R*)-**7** [10] was reacted with the aldehyde **3** at -78 °C (Scheme 3). After warming to rt and work up, the new alcohol (*R*)-(*R*)-**8** was obtained in 62% yield. (*R*)-(*R*)-**8** has been easily tranformed to the new C_2-symmetric chiral ketone **9** (MnO_2, rt, $CHCl_3$, yellow crystalline solid) and may also be attached to solid support.



Scheme 3. (R = $-CH_2OCH_3$)

By treatment with sodium borohydride in trifluoroacetic acid [18] the methylene bridged C_2-symmetric ligand (*R*)-(*R*)-**2** was obtained in 50% yield (pale yellow crystals) [19]. We believe that the new chiral ligands **1** and **2** can be applied for numerous metal catalyzed reactions as the C_2-axis can serve the important function of reducing the number of possible competing diastereomeric transition states [20]. In addition **1** and **2** can be applied for mechanistic investigations as a dissociation of derived metal complexes is very unlikely.

Scheme 4.



To prove that utility, the (*R*)-(*R*)-**1**-Ga/Li-complex **13** (whose predicted structure is shown above) was used for the asymmetric ring opening reaction of cyclohexene oxide (**10**) with 4-methoxyphenol (**11**) [21] (Scheme 4). The catalyst was prepared in a similar manner to GaLibis(binaphthoxide) [21a]. Thus (*R*)-(*R*)-**1** was treated with 4 mol eq of *n*-BuLi at 0 °C in THF, followed by the addition of 1 mol eq of $GaCl_3$. A small amount of solid precipitated after 1 h, but the supernatant solution contained predominantly one Ga-species as could be shown by ^{13}C-NMR [22]. The ring opened product **12** could be obtained in 86% ee and 37% yield using 17 mol% of **13** after 60 h, a result which is similar to what was obtained using (*R*)-BINOL as a ligand (20 mol% cat., 72 h, 48% yield, 93% ee) [21b]. As dissociation of the (*R*)-(*R*)-**1** complex is extremely unlikely, we therefore believe that the complex **13** is the active catalyst. Further investigations are in progress.

Acknowledgments

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[12] The major coupling product **4** (about 80%) was assigned to be the *trans*-isomer according to its ^{1}H-NMR spectrum, see: Tirado-Rives J, Gandour RD, Fronczek FR, Tetrahedron Lett. 1982; 23: 1639-1642. For the following hydrogenation reaction the mixture of isomers can be used, however.

[13] Bosch A, Brown RK, Can. J. Chem. 1968; 46: 715-728. To complete the deprotection, **1** was treated with 6 M HCl in THF prior to purification by flash chromatography.

[14] **1**: colorless glass; MS: m/z 598 $[M]^+$ (62%), 299 (100%); IR ($CHCl_3$): cm^{-1} 3528 (OH), 3019, 1214, 779, 741; ^{1}H-NMR ($CDCl_3$; 500 MHz; rt): δ 7.95, d, J = 8.9 Hz, 2H; 7.87, d, J = 8.3 Hz, 2H; 7.81, m, 4H; 7.37 - 7.32, m, 6H; 7.25, ddd, J^1 = 8.5 Hz, J^2 = 7.0 Hz, J^3 = 1.3 Hz, 2H; 7.13, ddd, J^1 = 8.6 Hz, J^2 = 7.1 Hz, J^3 = 1.2 Hz, 2H; 7.08, d, J = 8.0 Hz, 2H; 7.01, d, J = 8.2 Hz, 2H; 5.39, s, 2H, OH; 4.93, br, 2H, OH; 3.38, s, 4H, CH_2; ^{13}C-NMR ($CDCl_3$; 125 MHz; rt): δ 152.6, s, C-O; 151.7, s, C-O; 133.4, s; 132.3, s; 131.2, d; 130.4/130.4, s; 130.2, s; 129.4, d; 128.3, d; 127.8, d; 127.3, d; 126.6, d; 124.1/124.1, d; 124.0, d; 123.9, d; 117.7, d; 111.3, s; 110.9, s; 31.5, t, CH_2.

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[16] **5** contains small amounts of the chloride substituted compound. Without filtration of $Et_3N{\cdot}HCl$, the chloride substituted compound was obtained predominantly.

[17] The optical purity of (*R*)-(*R*)-**1** was determined by chiral HPLC analysis using a DAICEL CHIRALPAK AD column, hex/*i*-PrOH = 1/1, flow rate 1.0 ml/min, (*R*)-(*R*)-**1** 10.5 min, (*S*)-(*S*)-**1** 40 min, >99% ee.

[18] Gribble GW, Leese RM, Synthesis 1977: 172-176.

[19] **2**: yellow crystals; MS: m/z 584 $[M]^+$ (100%); ^{1}H-NMR ($CDCl_3$; 500 MHz; rt): δ 7.94, d, J = 8.9 Hz, 2H; 7.88, s, 2H; 7.86, d, J = 8.6 Hz, 2H; 7.80, d, J = 8.0 Hz, 2H, 7.37 - 7.23, m, 10H; 7.17, d, J = 8.6 Hz, 2H; 7.12, d, J = 8.3 Hz, 2H; 5.42, s, OH; 5.1, broad, OH; 4.48, s, 2H, CH_2; ^{13}C-NMR ($CDCl_3$; 125 MHz; rt): δ 152.7, s; 151.5, s; 133.4, s; 132.5, s; 131.3, d; 131.1, d; 129.5, s; 129.5, s; 128.9, s; 128.4, d; 128.0, d; 127.5, d; 126.9, d; 124.2, d; 124.1, d; 124.1, d; 124.0, d; 117.8, d; 111.3, s; 111.2, s; 31.6, t, CH_2. While preparing this communication we obtained a single crystal X-ray structure of (*R*)-(*R*)-**2**.

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[22] The concentration of the supernatant was 15% less than expected for a homogeneous solution. ^{13}C-NMR (THF, D_2O capillary, 125 MHz, rt) δ 158.2, 156.3, 139.7, 135.6, 134.3, 130.7, 129.9, 128.8, 128.7, 128.3, 128.0, 127.4, 127.1, 125.5, 124.9, 124.9, 123.1, 123.0, 122.8, 122.6.