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Atropo-enantioselective synthesis of a C_3-symmetric tripodal ligand with three axially chiral biaryl subunits☆

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Dedicated to Professor Dr. W. Malisch on the occasion of his 60th birthday

Abstract—In contrast to the numerous successful applications of C_2-symmetric biaryls as powerful tools for asymmetric synthesis, there have so far been only few reports on combinations of C_3-symmetry with axial chirality. We present here the first enantioselective synthesis of a novel family of tripodal ligands containing three axially chiral biaryl subunits in an (*M*,*M*,*M*)- or, optionally, (*P*,*P*,*P*)-configured form. The incorporation of a PCl_2- and a TiCl-fragment into the central cavity was achieved.

1. Introduction

In view of the great success achieved with C_2-symmetric ligands in asymmetric synthesis,[1] interest has focused more recently on the preparation of homochiral auxiliaries possessing three rotationally hindered axes.[2] Their application as chiral ligands in octahedral complexes permits a reduction in the number of possible diastereomorphous transition states, as for C_2-symmetric systems in tetrahedral or square-planar environments.[2,3] For the oxophilic transition metals of the 4th and 5th sub-groups, in particular centrochiral trialkanolamines such as **1**[4–6] are well suited for this purpose (Fig. 1), because they form stable, mostly discrete so-called metallatranes.[6–8] As an example, Zr-complexes of **1** have been successfully used as chiral catalysts in the stereoselective ring opening of *meso*-epoxides with azidosilanes.[9,10] In contrast, practically nothing is known about the potentially promising combination of C_3-symmetry with *axial* chirality.[11] Herein we report on the atropo-enantioselective synthesis of the axially chiral tripodal ligand **2**, belonging to a novel type of

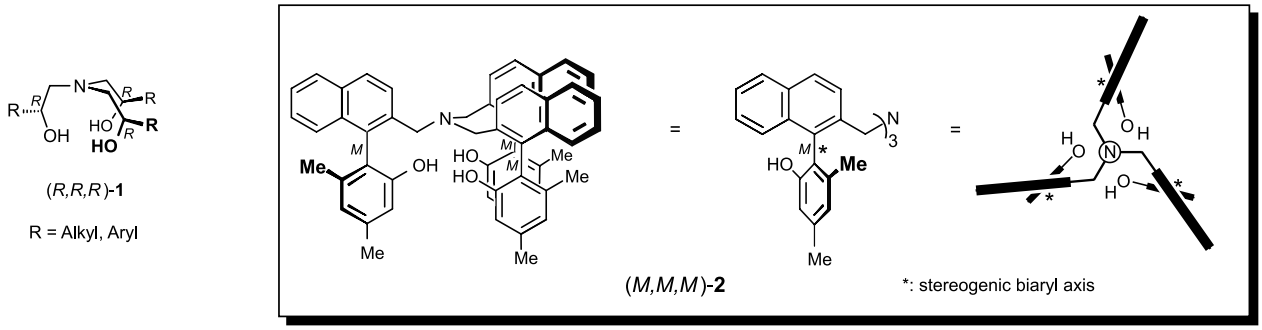

Figure 1. Known C_3-symmetric trialkanolamines of type **1** and the novel threefold axially chiral tripodal ligand (*M*,*M*,*M*)-**2**.

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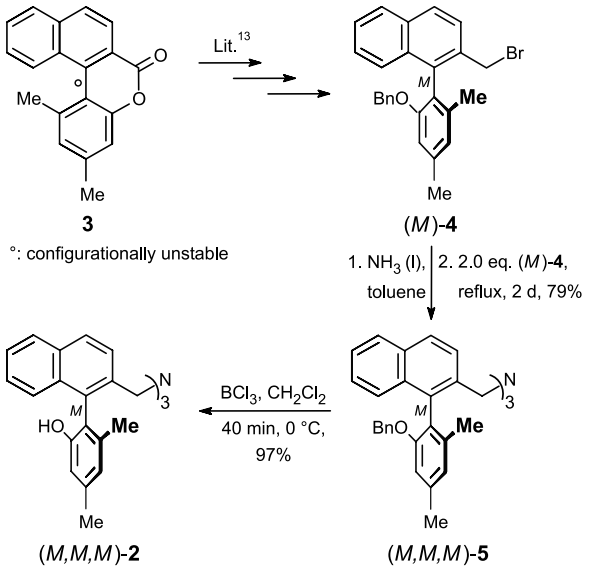
tris(oxybiarylmethylene)amines, equipped with three homochiral biaryl subunits, optionally in an (*M*,*M*,*M*)- or (*P*,*P*,*P*)-configured form. Furthermore, we describe the transformation of **2** into C_3-symmetric complexes containing a PCl_2- or a TiCl-unit in the central cavity.

2. Results and discussion

2.1. Synthesis of the tripodal ligand (*M*,*M*,*M*)-2

The synthesis of the tris(oxybiarylmethylene)amine (*M*,*M*,*M*)-**2** started from the homochiral phenylnaphthalene (*M*)-**4**[12,13] (Scheme 1), which is easily accessible from the configurationally labile, since lactone-bridged biaryl **3** (Scheme 1), with the efficient atropo-enantioselective ring opening of **3** (e.g. by CBS[15]-reduction) as the stereochemically deciding step.[14]

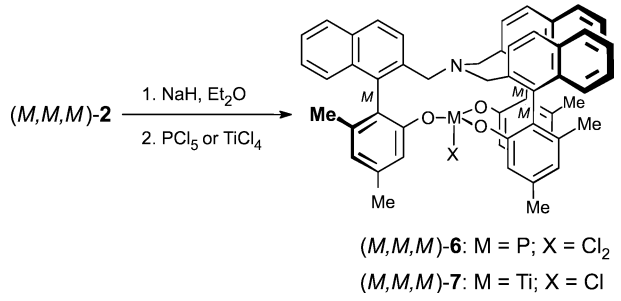


Scheme 1. Enantioselective synthesis of the C_3-symmetric axially chiral tris(oxybiarylmethylene)amine (*M*,*M*,*M*)-**2**.

Treatment of (*M*)-**4** with liquid ammonia in toluene led to the corresponding primary amine as the initial product. This was further alkylated in situ with an additional 2 equiv. of (*M*)-**4** to give the tertiary amine (*M*,*M*,*M*)-**5** in 79% yield. Deprotection of the oxygen functional groups furnished the desired axially chiral tripodal ligand (*M*,*M*,*M*)-**2** in nearly quantitative yield. By the same reaction sequence, lactone **3** can also be converted into the enantiomeric tripodal ligand, (*P*,*P*,*P*)-**2**, just by the use of the other enantiomer of the ring-opening reagent.[16]

2.2. Incorporation of heteroatoms

The rigid biaryl portions of (*M*,*M*,*M*)-**2** potentially form a cage that might be capable of incorporating heteroatoms or metals in its interior. As an example of a main-group element, a phosphorus fragment was introduced by triple deprotonation of (*M*,*M*,*M*)-**2** with NaH and subsequent treatment with PCl_5. According to ^{31}P, ^{1}H, and ^{13}C NMR spectra, the desired C_3-symmetric product (*M*,*M*,*M*)-**6** was formed quantitatively (Scheme 2). By-products possessing either reduced or no symmetry, e.g. structures involving intermolecular bridges, were not detected in significant quantities. The central nitrogen atom of **6** does not act as a donor ligand for the phosphorus atom, which is evident from the shift in the ^{31}P NMR spectrum ($\delta = -22.06$ ppm).[17] The isolation or further purification of (*M*,*M*,*M*)-**6**, e.g. by column chromatography, proved to be difficult due to its moisture sensitivity and low stability.[18]



Scheme 2. Synthesis of the compounds (*M*,*M*,*M*)-**6** and (*M*,*M*,*M*)-**7**.

As an example of a transition metal, Ti^{IV} was incorporated by treatment of (*M*,*M*,*M*)-**2** with NaH and then with $TiCl_4$, providing the C_3-symmetric complex (*M*,*M*,*M*)-**7**. Despite its high moisture sensitivity, it was possible to characterize (*M*,*M*,*M*)-**7** by NMR-, MS-, and IR-investigations. All attempts to replace the remaining chlorine ligand in (*M*,*M*,*M*)-**7** by other nucleophiles, failed. As an example, reaction of (*M*,*M*,*M*)-**7** with 1 equiv. of MeOH delivered, besides unchanged (*M*,*M*,*M*)-**7**, only the free ligand (*M*,*M*,*M*)-**2** and $Ti(OMe)_4$ according to ^{1}H NMR. The ease of this Ti-extrusion, the low stability and the high moisture sensitivity of (*M*,*M*,*M*)-**6** and (*M*,*M*,*M*)-**7** indicate that the internal cavity of (*M*,*M*,*M*)-**2** is very narrow and, even though an incorporation of PCl_2- and TiCl-fragments is possible, it does not provide an optimal environment for delivering stable complexes.

3. Conclusion

In summary, we have developed an easy and short route for the enantioselective construction of threefold axially chiral tripodal ligands, starting from a configurationally labile lactone-bridged biaryl precursor. Using the options provided by the 'lactone method',[14] it should be also possible to adapt this synthetic pathway to the synthesis of electronically (e.g. OMe instead of Me in the phenolic part) or sterically (e.g. *t*Bu instead of Me) modified analogs of (*M*,*M*,*M*)-**2**. Of particular interest is the preparation of related systems possessing a larger cavity. The synthesis of such spatially extended C_3-symmetric, axially chiral tripodal ligands and their application in enantioselective catalysis is currently in progress.

4. Experimental

4.1. General remarks

Melting points were determined with a Kofler melting point apparatus and are uncorrected. The optical rotations were measured with a Perkin–Elmer polarimeter. The IR spectra were scanned from KBr pellets or neat using a Perkin–Elmer spectrophotometer model 1420. The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 250 (250 MHz) or a Bruker Avance 400 (400 MHz) instrument using the deuterated solvent as an internal reference; J values are given in hertz. The ^{31}P NMR spectrum of (*M*,*M*,*M*)-**6** was recorded at 163 MHz. The chemical shift δ refers to the signal of 85% H_3PO_4 ($\delta = 0$). Elemental analyses were performed in the Institute of Inorganic Chemistry of the University of Würzburg. Mass spectra were measured on a Finnigan MAT 2000 mass spectrometer at 70 eV. All reactions with moisture and/or air sensitive materials were carried out with flame-dried glassware using the Schlenk tube technique under inert argon atmosphere.

4.2. Tris-{(*M*)-2-[1-(2′-benzyloxy-4′,6′-dimethylphenyl)]-naphthylmethyl}amine (*M*,*M*,*M*)-5

In a three-necked flask equipped with a dry ice condenser, (*M*)-**4** (500 mg, 1.16 mmol) and NH_4Cl (120 mg, 2.24 mmol) were added to a mixture of toluene (22 mL) and liquid ammonia (250 mL). The resulting suspension was stirred for 12 h without further cooling of the reaction flask. After evaporation of the solvents, the residue was suspended in toluene (40 mL) and (*M*)-**4** (1.00 g, 2.32 mmol) was added. The mixture was refluxed for 2 d. After removal of the solvent, the crude product was purified by column chromatography (deactivated silica gel, petroleum ether/diethyl ether 50:1→10:1) to yield (*M*,*M*,*M*)-**5** as a pale yellow oil, which was precipitated from dichloromethane/petroleum ether to afford a white solid (980 mg, 918 μmol, 79%): mp 183°C; $[\alpha]_D^{20} = 69.1$ (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.24 (d, $J = 8.4$ Hz, 3H), 7.85 (d, $J = 8.4$ Hz, 6H), 7.40 (tm, $J = 7.1$ Hz, 3H), 7.19–7.32 (m_c, 6H), 6.88–7.02 (m, 9H), 6.66 (m_c, 9H), 6.54 (s, 3H), 4.50, 4.62 (d, d, $J = 13.0$ Hz each, 3H each), 3.21, 3.58 (d, d, $J = 14.7$ Hz each, 3H each, CH_2N), 2.37 (s, 9H), 1.54 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 156.3, 138.0, 137.8, 137.4, 136.4, 133.5, 132.7, 132.5, 127.9, 127.3, 126.8, 126.3, 126.0, 125.5, 125.4, 124.7, 124.5, 123.4, 123.3. 110.9, 69.3, 56.2, 21.7, 19.5 ppm. IR (KBr): ν 3010, 1590, 1565, 1495, 1485, 1310, 1230 cm^{-1}. MS: m/z 1067 (M^+, 22), 976 (6), 716 (73), 608 (24), 366 (14), 352 (25), 259 (100), 91 (48). Anal calcd for $C_{78}H_{69}NO_3$: C, 87.69; H, 6.51; N, 1.31; found C, 87.63; H, 6.37; N, 1.47.

4.3. Tris-{(*M*)-2-[1-(2′-hydroxy-4′,6′-dimethylphenyl)]-naphthylmethyl}amine (*M*,*M*,*M*)-2

To a solution of (*M*,*M*,*M*)-**5** (980 mg, 918 μmol) in dichloromethane (10 mL), BCl_3 (1.0 M in *n*-hexane, 3.7 mL, 3.7 mmol) was added at 0°C. The resulting solution was stirred for 1 h and quenched with aqueous K_2CO_3 (1N, 15 mL). The reaction mixture was extracted three times with diethyl ether and the combined organic layers were dried over $MgSO_4$. Purification by column chromatography afforded crude (*M*,*M*,*M*)-**2** as a yellow oil, which was precipitated from dichloromethane/petroleum ether to give a white powder (710 mg, 891 μmol, 97%): mp 161°C; $[\alpha]_D^{20} = -12.7$ (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.88 (s, 6H), 7.85 (d, $J = 8.1$ Hz, 3H), 7.44 (tm, $J = 7.2$ Hz, 3H), 7.23–7.37 (m, 6H), 6.56, 6.64 (s, s, 3H each), 3.08, 3.57 (d, d, $J = 13.6$ Hz each, 3H each), 2.32 (s, 9H), 1.60 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 153.2, 138.7, 137.7, 136.2, 133.1, 132.6, 131.7, 128.7, 128.1, 127.1, 126.6, 125.9, 125.6, 123.1, 121.1, 113.9, 56.2, 21.3, 19.6 ppm. IR (film): ν 3550–2500, 3040, 1610, 1555, 1440, 1290, 1250, 1170, 1150, 1040, 820, 745 cm^{-1}. MS: m/z 797 (M^+, 10), 536 (42), 262 (29), 261 (66), 260 (46), 259 (100), 246 (39), 231 (34), 202 (36). Anal. calcd for $C_{57}H_{51}NO_3$: C, 85.79; H, 6.44; N, 1.76; found C, 85.50; H, 6.59; N, 1.71.

4.4. General procedure for the synthesis of (*M*,*M*,*M*)-6 and (*M*,*M*,*M*)-7

To a suspension of NaH (12.4 μmol, 2.97 mg) in diethyl ether (1 mL) was added (*M*,*M*,*M*)-**2** (30 mg, 3.76 μmol) at 0°C and the reaction mixture was stirred for 30 min. PCl_5 (7.75 mg, 3.76 μmol) or $TiCl_4$ (1.0 mM in *n*-pentane, 3.76 mL, 3.76 μmol) was added at 0°C and the reaction mixture was allowed to warm to room temperature. After 6 h of stirring, the solvent was removed in vacuo and the residue was dried carefully. Due to the high moisture sensitivity of (*M*,*M*,*M*)-**6** and (*M*,*M*,*M*)-**7** and their low solubility, all spectroscopic investigations were performed without further purification. According to the NMR spectra, both compounds were analytically pure, with yields >95%.

(*M*,*M*,*M*)-**6**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.62–7.76 (m, 6H), 7.34–7.40 (m, 6H), 7.19–7.21 (m, 6H), 6.30, 6.6.0 (s, s, 3H each), 4.43 (d, br., $J = 10.9$ Hz, 3H), 3.78, (s, br., 3H), 1.77 (s, 9H), 1.30 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 153.4, 139.2, 138.2, 137.0, 133.9, 132.4, 128.6, 127.8, 127.0, 126.8, 126.7, 124.3, 122.5, 119.3, 114.8, 57.7, 20.7, 19.4 ppm. ^{31}P NMR ($CDCl_3$, 162 MHz) δ −22.06. IR (film): ν 3052, 2967, 1618, 1578, 1448, 1044, 804 cm^{-1}.

(*M*,*M*,*M*)-**7**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.88 (s, 6H), 7.63–7.70 (m, 3H), 7.51 (s, br., 3H), 7.40–7.43 (m_c, 3H), 7.19–7.25 (m, 6H), 6.29, 6.67 (s, s, 3H each), 3.81, 4.50 (s, s, br., 3H each), 1.74 (s, 9H), 1.32 (s, 9 H, 6′-CH_3). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 171.5, 154.7, 153.5, 139.2, 134.0, 132.6, 132.4, 128.1, 128.0, 127.1, 126.8, 126.7, 122.5, 121.3, 114.8, 57.9, 20.7, 19.3 ppm. IR (KBr): ν 3052, 2921, 1648, 1618, 1448, 1069, 820 cm^{-1}. MS: m/z 842 (M^+, 9), 262 (100), 260 (46), 259 (43), 247 (45).

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