Direct Synthesis of Enantiopure Tripod Ligands from C_2-Symmetric Precursors

Ina Hegelmann[a] and Nicolai Burzlaff*[a]

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A new enantiopure chiral tripod ligand is obtained from C_2-symmetric bis(camphorpyrazol-1-yl)methane by introducing a carboxylate group at the bridging carbon atom. A prochiral centre is formed rather than an additional stereocentre. Therefore, a homochiral tripod ligand is achieved without separation of the stereoisomers.

Chiral facially coordinating tripod ligands play an important role in stereoselective synthesis.[1] Recently we reported a racemic example of a bis(pyrazol-1-yl)acetato tripod ligand, namely (3,5-di-*tert*-butylpyrazol-1-yl)(3′,5′-dimethylpyrazol-1-yl)acetate (bpa$^{t\mathrm{Bu2,Me2}}$; Figure 1a).[2] Usually, the chirality of these ligands originates from three different donor groups that are bound to a bridging atom with a noncoordinating group, atom or lone pair.

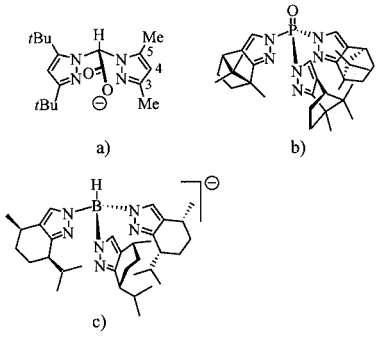


Figure 1. Chiral tripod ligands

For asymmetric induction two problems have to be solved: (a) enantiomeric purity, and (b) a stable configuration of the stereogenic centres. Separation of the enantiomers is often an elaborate, low-yield process and demands a measurement of the enantiomeric purity. If one of the donor groups is chiral and enantiopure, or derived from the chiral pool, the problem is converted into one of separation of the diastereomers. This can be avoided if C_3-symmetric ligands with three identical, chiral donor groups are applied.[3] Chiral pool derived ligands such as [OP(pz$^{\mathrm{cam}}$)$_3$] or [BH(pz$^{\mathrm{menth}}$)$_3$]$^-$ (Figure 1b, c) are often cited as examples.[4] Due to the steric hindrance of the three chiral donor groups, however, the application of these ligands is limited, especially in octahedral complexes. We now report on a general concept to obtain new enantiopure facially binding tripod ligands from C_2-symmetric precursors.

C_2 symmetry is a common feature in chiral bidentate ligands.[5] If two identical enantiopure donor groups Y* are connected by a tetrahedral bridging atom, any additional group Z at this atom will form a prochiral centre rather than an additional stereocentre (Figure 2a).[6] Trihydroxyglutaric acid, either *S*,*S* or *R*,*R*, is a textbook example of this.[6] Inversion of configuration at C3 in (*S*,*S*)-trihydroxyglutaric acid (Figure 2b) yields the identical compound.

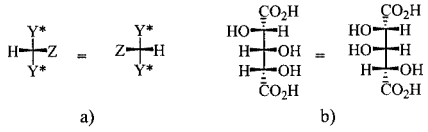


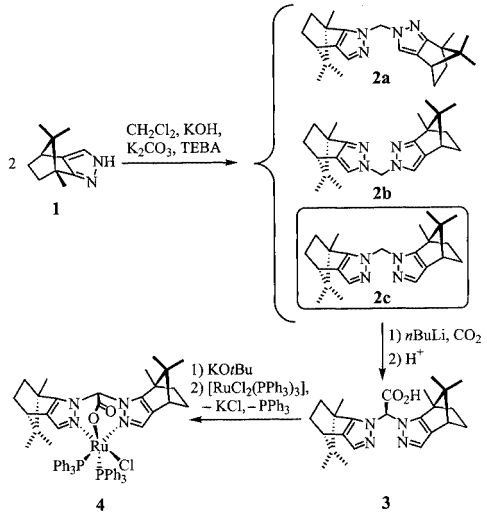
Figure 2. Prochiral centre of (*S*,*S*)-trihydroxyglutaric acid[6]

Therefore, a homochiral tripod ligand can be obtained from a C_2-symmetric precursor without additional separation of enantiomers or diastereomers. As an example of this concept we chose bis(camphorpyrazol-1-yl)methane, an enantiopure but C_2-symmetric bidentate ligand which is obtained in three steps from (+)-camphor (Scheme 1).

As reported by Steel et al., three structural isomers of bis(camphorpyrazol-1-yl)methane (**2a**, **2b** and **2c**) are formed by coupling of camphorpyrazole **1** with CH_2Cl_2 in a two-phase system.[7] Reaction with CH_2Cl_2 as both reactant and solvent reduces the reaction time to 8 hours compared to the 10 days reported previously. Compound **2c** can be separated from the other two structural isomers in two crystallisation steps from pentane and acetone, respectively, to give colourless crystals. A single-crystal X-ray diffraction experiment proved the desired constitution of **2c**.[8] According to Steel et al. isomer **2b** can also be isolated.[7]

By analogy with the synthesis of bis(3,5-dialkylpyrazol-1-yl)acetic acids,[2,9] deprotonation at the bridging carbon

[a] Fachbereich Chemie der Universität Konstanz,
Universitätsstraße 10, Fach M728, 78457 Konstanz, Germany
Fax: (internat.) + 49-(0)7531/88-3136
E-mail: nicolai@chemie.uni-konstanz.de



Scheme 1. Synthesis and coordination of bis(camphorpyrazol-1-yl) acetic acid

atom and subsequent reaction with carbon dioxide introduces a carboxylate group at this position. Due to missing substituents at the pyrazolyl carbon C5, **2b** is also deprotonated at C5. A similar deprotonation at C5 has been published recently by Otero et al. for an achiral bis(pyrazol-1-yl)methane.[10] Therefore, only the minor isomer **2c** out of the two C_2-symmetric isomers **2b** and **2c** is suitable for this reaction sequence. Acidic workup yields the enantiopure bis(camphorpyrazol-1-yl)acetic acid bpa^{cam2}H (**3**; Scheme 1).[11] Two sets of signals are found for the camphorpyrazolyl groups in the ^{1}H and ^{13}C NMR spectra. A strong IR band at $\tilde{\nu}$ = 1712 cm^{-1} and a ^{1}H NMR signal at δ = 11.59 ppm confirm the presence of the carboxylate group. Crystals of **3** suitable for X-ray structure determination were obtained from CH_2Cl_2 (Figure 3).[8] The bond lengths and bond angles in **3** are in good agreement with those reported earlier for other achiral bis(3,5-dialkylpyrazol-1-yl)acetic acids.[9,12]

Reaction of the potassium salt of bpa^{cam2}H (**3**) with [$RuCl_2(PPh_3)_3$] yields [Ru(bpa^{cam2})Cl(PPh_3)$_2$] (**4**; Scheme 1). Recently we reported the formation of the ruthenium complexes [Ru(bpza)Cl(PPh_3)$_2$] and [Ru(bdmpza)Cl(PPh_3)$_2$] [bpza = bis(pyrazol-1-yl)acetate; bdmpza = bis(3,5-dimethylpyrazol-1-yl)acetate] in a similar reaction.[13] An asymmetric carboxylate signal ($\tilde{\nu}_{as}$ = 1656 cm^{-1}) in the IR spectrum and the molecular ion peak (MH$^+$ = 1069) in the FAB mass spectrum indicate the coordination of the ligand. As in **3** two sets of signals are observed in the ^{1}H and ^{13}C NMR spectra for the camphorpyrazolyl groups. Two sets of signals in these spectra and two doublets in the ^{31}P NMR spectrum at δ = 39.2 and 42.7 ppm ($^2J_{P,P}$ = 35.6 Hz and 32.4 Hz) are expected for two PPh_3 ligands in a chiral environment. According to the cross coupling observed in the COSY spectrum, two singlets in the ^{1}H NMR spectrum are assigned to the bridging CH group (^{1}H NMR: δ = 6.30 ppm; ^{13}C NMR: δ = 72.9 ppm) and one of the two pyrazole C3 protons (^{1}H NMR: δ = 5.99 ppm; ^{13}C NMR: δ = 138.5 ppm). The second pyrazole C3 proton signal is probably hidden underneath the PPh_3 signals. A rather similar downfield shift of such a C3 proton signal was observed for the asymmetrical isomer of the related ruthenium complex [Ru(bpza)Cl(PPh_3)$_2$], in which one PPh_3 ligand is *trans* to the carboxylate group.[13] Therefore, a geometry with one of the PPh_3 ligands *trans* to the carboxylate group and the other *trans* to the camphorpyrazolyl group is assumed for complex **4**.

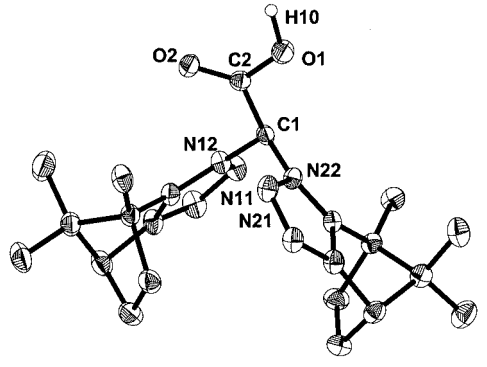


Figure 3. Molecular structure of bpa^{cam2}H (**3**); thermal ellipsoids at 50% probability level; selected bond lengths (Å) and angles (°): C1–C2 1.534(5), C2–O1 1.320(4), C2–O2 1.198(4), C1–N12 1.457(4), C1–N22 1.446(4); O1–C2–O2 126.0(3), C2–C1–N12 111.4(3), C2–C1–N22 112.9(3), N12–C1–N22 111.2(3)[8]

Our results show that new enantiopure facially binding tripod ligands can be obtained from C_2-symmetric precursors. In this concept an additional donor group is introduced at the bridging atom, forming a prochiral centre rather than an additional stereocentre. Therefore, a homochiral ligand is obtained by a simple separation of structural isomers without any separation of enantiomers or diastereomers. Future work to extend this concept will focus on the conversion of other C_2-symmetric ligands into enantiopure tripod ligands.

Experimental Section

bpa^{cam2}H (3): A solution of bpm^{cam2} (**2c**) (288 mg, 0.790 mmol) in THF (20 mL) was treated with *n*BuLi (1.6 M in *n*-hexane, 0.500 mL, 0.800 mmol) at −70 °C. The solution was allowed to warm to −45 °C over a period of 2 h and finally flushed with a flow of CO_2 for 10 min. The solvent was removed in vacuo at ambient temperature and the residue dissolved in water (50 mL). The aqueous solution was acidified with HCl (6 M) to pH 1 and extracted with Et_2O (4 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Recrystallisation from acetone yielded the acid bpa^{cam2}H (**3**) as a colourless crystalline powder. Yield 247 mg (77%); m.p. 175 °C (dec.). $[\alpha]_D^{23}$ = +55.3 (*c* = 0.01, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.68 (m, 1 H, CH_2), 0.77 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3), 0.88 (s, 3 H, CH_3), 0.92 (s, 3 H, CH_3), 0.97 (m, 2 H, CH_2), 1.30 (m, 1 H, CH_2), 1.33 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 1.59 (m, 1 H, CH_2), 1.75 (m, 1 H, CH_2), 1.98 (m, 2 H, CH_2), 2.76 (d, $^3J_{H,H}$ = 3.7 Hz, 1 H, CH), 2.82 (d, $^3J_{H,H}$ = 3.7 Hz, 1 H, CH), 6.78 (s, 1 H, H_{pz}), 7.17 (s, 1 H, H_{pz}), 7.37 (s, 1 H, CH), 11.59 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 11.2, 11.4, 19.3, 19.5, 20.3, 20.4 (6 × CH_3), 27.2, 27.3, 32.1, 33.0 (4 × CH_2), 47.4, 47.5 (2 × CH), 53.2, 53.8, 62.8, 63.1 (4 × C_q), 69.7 (CH), 130.5, 130.6 (2 × C_{pz}), 131.2, 133.0 (2 × CH_{pz}),

154.1, 155.9 (2 × C_{pz}), 165.6 (CO_2H) ppm. FAB MS (NBOH): *m/z* (%) = 409 (10) [MH^+], 189 (100) [$(C_{11}H_{15}N_2)CH_2$]. IR (CH_2Cl_2): $\tilde{\nu}$ = 1712 (CO_2H) cm^{-1}. $C_{24}H_{32}N_4O_2$ (408.54): calcd. C 70.56, H 7.89, N 13.71; found C 70.43, H 7.80, N 13.65.

[Ru(bpa^{cam2})Cl(PPh$_3$)$_2$] (4): A solution of bpa^{cam2}H (585 mg, 1.43 mmol) and KO*t*Bu (137 mg, 1.22 mmol) in THF (40 mL) was stirred at ambient temperature for 1 h. [$RuCl_2(PPh_3)_3$] (1.06 g, 1.11 mmol) was then added and the solvent was removed in vacuo after 1 h. The residue was dissolved in Et_2O (5 mL), precipitated by addition of pentane (50 mL) and filtered off. It was washed with H_2O (2 × 10 mL) and pentane (40 mL) and dried in vacuo to afford [Ru(bpa^{cam2})Cl(PPh_3)$_2$] (**4**) as an amber crystalline powder. Yield 604 mg (51%); m.p. 162 °C (dec.). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.46 (m, 3 H, CH_3), 0.54 (m, 1 H, CH_2), 0.67 (s, 3 H, CH_3), 0.80 (s, 3 H, CH_3), 0.85 (s, 3 H, CH_3), 0.88 (m, 1 H, CH_2), 1.03 (m, 2 H, CH_2), 1.44 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.71 (m, 1 H, CH_2), 1.78 (m, 2 H, CH_2), 1.86 (m, 1 H, CH_2), 2.43 (d, $^3J_{H,H}$ = 3.4 Hz, 1 H, CH), 2.49 (d, $^3J_{H,H}$ = 3.4 Hz, 1 H, CH), 5.99 (s, 1 H, H_{pz}), 6.30 (s, 1 H, CH), 7.00−7.42 (m, 31 H, H_{pz} and 2 PPh_3) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 11.1, 12.1, 19.1, 19.4, 20.4, 20.5 (6 × CH_3), 26.7, 26.9, 32.7, 34.4 (4 × CH_2), 47.1, 47.2 (2 × CH), 53.2, 54.0, 61.9, 65.0 (4 × C_q), 72.6 (CH), 126.9 (d, $^2J_{C,P}$ = 8.8 Hz, *o*-PPh_3), 127.1 (d, $^2J_{C,P}$ = 8.8 Hz, *o*-PPh_3), 128.5 (s, *p*-PPh_3), 128.6 (s, *p*-PPh_3), 129.3, 129.6 (2 × C_{pz}), 131.9 (CH_{pz}), 134.7 (d, $^3J_{C,P}$ = 9.1 Hz, *m*-PPh_3), 135.0 (d, $^1J_{C,P}$ = 39.2 Hz, *i*-PPh_3), 135.4 (d, $^3J_{C,P}$ = 9.2 Hz, *m*-PPh_3), 136.1 (d, $^1J_{C,P}$ = 38.3 Hz, *i*-PPh_3), 138.6 (CH_{pz}), 155.3, 156.0 (2 × C_{pz}), 166.3 (CO_2^-) ppm. ^{31}P NMR (161.8 MHz, $CDCl_3$): δ = 39.2 (d, $^2J_{P,P}$ = 35.6 Hz), 42.7 (d, $^2J_{P,P}$ = 32.4 Hz). FAB MS (NBOH): *m/z* (%) = 1069 (39) [MH^+], 1034 (53) [M^+ − Cl], 807 (100) [MH^+ − PPh_3], 772 (43) [MH^+ − PPh_3 − Cl]. IR (CH_2Cl_2): $\tilde{\nu}$ = 1656 s (*as*-CO_2^-), 1482 (C=C) cm^{-1}. $C_{60}H_{61}ClN_4O_2P_2Ru$ (1068.64): calcd. C 67.44, H 5.75, N 5.24; found C 67.41, H 6.10, N 4.85.

Acknowledgments

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[8] [8a] **Crystal data for 2c**: $C_{23}H_{32}N_4$, M_r = 364.53, orthorhombic space group $P2_12_12_1$, *a* = 11.0364(18), *b* = 11.975(3), *c* = 15.597(2) Å, *V* = 2061.3(6) Å^3, *Z* = 4, $\rho_{calcd.}$ = 1.175 g cm^{-3}. Final *R* indices: R_1 = 0.0382, wR_2 = 0.0960 {for 2363 reflections considered observed [$I > 2\sigma(I)$]}; R_1 = 0.0412, wR_2 = 0.0983 (all data) for the 245 parameters. **Crystal data for 3**: $C_{24}H_{32}N_4O_2{\cdot}CH_2Cl_2$, M_r = 493.46, orthorhombic space group $P2_12_12_1$, *a* = 8.4259(17), *b* = 14.990(3), *c* = 20.490(4) Å, *V* = 2588.1(9) Å^3, *Z* = 4, $\rho_{calcd.}$ = 1.266 g cm^{-3}. Final *R* indices: R_1 = 0.0656, wR_2 = 0.1572 {for 4139 reflections considered observed [$I > 2\sigma(I)$]}; R_1 = 0.0950, wR_2 = 0.1754 (all data) for the 302 parameters. CCDC-195681 (bpm^{cam2}; **2c**) and CCDC-195682 (bpa^{cam2}H; **3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]. [8b] G. M. Sheldrick, SHELX-97, Programs for Crystal Structure Analysis, University of Göttingen, Göttingen (Germany), **1997**.

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[11] To avoid extraordinarily long abbreviations for **3** and **2c**, the abbreviation system for Tp ligands introduced by S. Trofimenko was used. This resulted in the abbreviations bpm^{cam2} (**2c**), bpa^{cam2}H (**3**) and bpa^{cam2} for the anion of **3**. For further details see: S. Trofimenko, *Scorpionates − The Coordination Chemistry of Polypyrazolylborate Ligands*, Imperial College Press, London, **1999**, pp. 5−9.

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