Synthesis of a New Optically Active Triphosphine with a Neopentane Backbone

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Triphosphine, Chiral Malonic Ester

The resolution of the racemate \((\text{BzlOCH}_2)(\text{MeC}(\text{COOH})(\text{COOEt}) (\pm)1\) is the entry point for the enantioselective synthesis of the key compound \(7\) \((\text{MeC}(\text{CH}_2\text{Br})(\text{CH}_2\text{OTf}))\). Successive phosphination of \(7\) furnishes the triphosphine \(10\) \((\text{MeC}(\text{CH}_3\text{PPh}_2)(\text{CH}_2\text{DBP})(\text{CH}_2\text{P}(3,5-\text{Me}_2\text{C}_6\text{H}_3))\) in both enantiomeric forms \((\text{DBP} = \text{di-benzophospholyl})\). The structures of the precursors \((+)^8\text{S}\) \((\text{MeC}(\text{CH}_3\text{PPh}_2)(\text{CH}_2\text{DBP})(\text{CH}_2\text{Cl}))\) and \((\pm)^9\) \((\text{MeC}(\text{CH}_2\text{Br})(\text{CH}_2\text{Cl})(\text{CH}_2\text{DBP}))\) have been confirmed by X-ray analysis.

The synthetic potential of terdentate ligands e.g. \(\text{MeC}(\text{CH}_2\text{PPh}_2)_3\) \((\text{triphos})\) in coordination chemistry has been amply worked out by the groups of L. Sacconi [1] and C. Bianchini [2]. Catalytic properties of triphos-metal-templates have recently become a topic [3–6]. Some chiral derivatives of triphos \((X(\text{CH}_2\text{P}R'R')_3, X = \text{MeSi, BuSn, HC})\) have been described [7–9]. One of these \(C_3\)-symmetric ligands has been successfully tested in asymmetric transition metal catalysis [10].

In the tripod ligands presented here the symmetry is reduced from \(C_3\) to \(C_1\), by fixing three different \(R_2\text{P}\)-donor groups \(P\) \((P_S(\text{small}), P_M(\text{medium})\) and \(P_L(\text{large}))\) at the neopentane backbone (Fig. 1). In the case of facial coordination to a metal center the tripod ligand completely shields one side of the metal center. An appropriate choice of the donor groups \(P_S, P_M\) and \(P_L\) should allow the specific shaping of a free coordination site for a substrate in such a complex. Considering the well established potential of chiral diphosphines in enantioselective catalysis, the synthesis of an optically active tripod ligand e.g. \(\text{MeC}(\text{CH}_2P_S)(\text{CH}_2P_M)(\text{CH}_2P_L)\) presents itself as an especially rewarding goal. We report here on the EPC-synthesis [11] of such a tripod ligand with three differently sized phosphino groups in both enantiomeric forms and on the X-ray structural analyses of the enantiomerically pure precursor \((+)^8\text{S}\) and racemic \((\pm)^9\) [12].

**Results**

The synthesis of racemic tripod ligands of this type has shown that the key for an EPC synthesis is an enantioselective approach to the neopentane compound \(7\) bearing a bromo, chloro and triflato group [12]. Very recently we have reported an chemo-enzymatic synthesis of \(7R\), selectively leading to one enantiomer in a purity of 72% ee [13].

As an alternative the following route has been developed. The resolution of the easily accessible racemic malonic monoester \((\pm)1\) [14, 15] furnished both enantiomers. Recrystallization of the ammonium salt with \(S-(\text{S}-1-\text{phenylethylamine})\) [16] leads to the \(R\)-enantiomer \((1R)\) in 19% yield. Recovery of \((\pm)1\) from the remaining filtrates and recrystallization with \(R-(\text{S})-1-\text{phenylethylamine}\) yields 30% of \((\pm)1\). The yields may be improved by repeating the isolation and recrystallization procedure. The chiral amine may be recovered and the process as a whole could in principle be automated. This process is a more effective source for enantiomerically pure \(1\) than the enzymatic procedure [13].

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Using the procedures already established [13], the functionalization of 1 to 7 results in slightly better yields than reported for the methylester analogue of 1 (Scheme 1) [13]. The configuration of the compounds 1 and 2 can be related to the known absolute configuration of (-)3S [13, 14].

The selective stepwise substitution of the three different leaving groups, chloride, bromide and triflate by three differently sized phosphines occurs under the same conditions as described for racemic 7 [12].

Treating 7 with 1.2 eq. of lithium dibenzophospholide (LiDBP) in THF at −20 °C yields the monophosphine 8 which reacts with 1.2 eq. of lithium diphenylphosphide in THF at 0 °C to give the diphosphine 9. The remaining chloride at the neopentyl backbone needs the potassium di(3,5-dimethylphenyl)phosphide in DMSO at 130 °C for an effective substitution to produce the target molecule 10. The tripod ligand 10 contains three differently sized phosphino groups: dibenzophospholyl (DBP), PPh2 and P(3,5-Me2C6H3)2.

Slow cooling of a hot saturated solution of the monophosphine (+)-8S in ethanol yields single crystals suitable for an X-ray structural analysis [17] to prove the constitution, conformation and absolute configuration (Table I, II, Fig. 2). There are two independent molecules in the chiral unit cell (space group P21). Anomalous dispersion unambiguously shows that both molecules have the absolute configuration S as expected. On the basis of the experimental data (Table II) the agreement factor is \(R_1 = 6.4\%\) for the S-configuration (Flacks X-Parameter [20]: 0.0298 (esd = 0.0211)), while for the wrong R-enantiomer it augments to 6.9\% (Flacks X-Parameter [20]: 0.1236 (esd = 0.0200)). The weighted agreement factors evaluated on the basis of \(F^2\) differ correspondingly in \(R_w = 20.5\%\) for S and \(R_w = 21.5\%\) for the wrong enantiomeric form. From the two independent molecules (+)-8S within the unit cell only one is completely unaffected by disorder phenomena. Fig. 2 and Table I refer to the data of that molecule. About 80\% of the disordered molecules adopt a conformation derived from the conformation of the undisordered methylphenyl)phosphide in DMSO at 130 °C for an effective substitution to produce the target molecule 10. The tripod ligand 10 contains three differently sized phosphino groups: dibenzophospholyl (DBP), PPh2 and P(3,5-Me2C6H3)2.
molecule (Fig. 2) by a +45° rotation of C3–C5 around C3–P1 and a +120° rotation of the C(CH2Br)(CH2Cl)(CH3) moiety around C3–C5. The configuration of this molecule is also definitely S. The remaining 20% of the molecules in this position show an conformation almost identi-
cal to the one observed for the undisordered molecules, so their configuration is S as well.

The pure enantiomers of 9 crystallize only in thin needles by slow cooling of a hot saturated ethanolic solution. These were not suitable for an X-ray structural analysis, but the racemate [12] furnishes suitable single crystals (Table I, II, Fig. 3) [17]. In the molecule (±)9 the bond lengths and angles at the DBP-phosphorus atom (P1) correspond to the relevant bond lengths and angles of the tripodal ligand MeC(CH$_2$DBP)$_3$ [18]. The geometry around the diphenylphosphino phosphorus atom (P2) agrees with the corresponding bond lengths and angles of MeC(CH$_2$PPh$_2$)$_3$ [19] (Table I).

**Resume**

The overall yield for this 9 step process 1 → 10 is 13%. The synthesis has been performed starting from both enantiomers 1. All the chiral compounds have been fully characterized and are optically active. All of the enantiomeric pairs show the same absolute value of optical rotation in the opposite directions. This should exclude a racemization along the pathway 1 → 10. This is an important finding in so far as the enantiomerically pure intermediate 7 is easily prepared and as it shows that the phosphide substitution processes leading from 7 to 10 do not destroy the chiral information. A wide range of enantiomerically enriched tripod ligands should thus be accessible.

**Experimental**

Generally see [12, 13]. For all structurally new compounds satisfactory microanalyses have been obtained: C ± 0.3, H ± 0.3, Cl ± 0.3. The compounds (±)1 [14, 15] and 4–10 [12, 13] have been synthesized following published procedures. The spectroscopic data were fully consistent with those reported [12, 13].

**Resolution of (±)-2-benzylxoxymethyl-2-methylmalonicacidmonoethylester ((±)-1) into its enantiomers (−)-1S and (+)-1R [13, 16]**

(−)-S-1-phenylethylamine (32 ml, 0.252 mol) was added to a solution of (±)-1 (67.0 g, 0.252 mol) in diisopropyl ether (270 ml) and ethanol (90 ml) at 50 °C. The solution was slowly cooled to 20 °C by removing the heater. As soon as crystallization started the suspension was cooled in an ice bath and vigorously stirred for 2.5 h. The voluminous solid was filtered off and washed with diethyl ether (2×60 ml). Drying of the solid at 50 °C in vacuo yielded 12.4 g (26%, 62% ee) of the ammonium salt of (+)-1R as a colourless microcrystalline solid. A second crystallization (s.a.) from diisopropyl ether (240 ml) and ethanol (70 ml) furnished the ammonium salt of (±)-1R; yield: 9.4 g (19%, >95% ee); m.p. 107–108 °C. Extraction of the acidified filtrate (pH 2) with diethyl ether (4×200 ml) and evaporation of the solvent in vacuo at 50 °C yielded (±)-1 (53.3 g, 0.2 mol). Alcalization of the aqueous layer with NaOH and extraction with ether (3×100 ml) yielded after distillation S-(−)-1-phenylethylamine (16.4 ml, 0.13 mol). Three crystallizations (s.a.) of the reisolated (±)-1 with (+)-R-1-phenylethylamine (1 equiv.) yielded the ammonium salt of (−)-1S; yield: 14.6 g (30%, >95% ee). The % de value of the ammonium salts were controlled by 1H NMR analysis [13]. Suspending the ammonium salt of (+)-1R or (−)-1S, respectively, (20.5 g, 0.053 mol) in diated HCl (2 M, 200 ml), extraction with ether (4×150 ml) yielded after evaporating the solvent in vacuo at 50 °C furnished (+)-1R and (−)-1S, respectively, as colourless syrup; yield: 13.3 g (94%); (+)-1R: [α]$_D$ +10.63° (c = 2.05, MeOH); (−)-1S: [α]$_D$ -10.76° (c = 3.00, MeOH). − 1H NMR (200 MHz; CDCl$_3$): δ = 1.26 (t, 3J$_{HH}$ = 7.1 Hz, 6 H.
CO₂CH₂CH₃), 1.55 (s, 3H, CqCH₃), 3.82 (s, 2H, CO₂CH₂CH₃), 4.57 (s, 2H, PhCH₂O), 7.39–7.24 (m, 5H, Ph). – ¹³C NMR (50 MHz; CDCl₃): δ = 14.0 (CO₂CH₂CH₃), 18.5 (CqCH₃), 54.8 (CqCH₃), 62.0 (CO₂CH₂CH₃), 72.7 (CH₂OBzl), 73.6 (PhCH₄O), 128.5, 127.8, 127.6 (C₀, C₂, C₆), 137.7 (C₇), 171.0 (CO₂CH₂CH₃), 175.8 (CO₂H). – MS (EI): m/z = 266 (M⁺, 8%), 160 (18), 142 (38), 114 (35), 107 (C₇H₇O⁺, 28), 106 (C₇H₆O⁺, 56), 91 (C₇H₅⁺, 100).

(-)-R-2-Benzoyloxymethyl-3-hydroxy-2-methyl-propionic acid ethyl ester ((-)2R) and (+)-2S, respectively

Reaction and workup according to lit. [13]. Yield: 69%, colourless oil; (+)-2S: [α]D = 5.98° (c = 1.99, CHCl₃); (-)-2R: [α]D = -5.80° (c = 4.37, CHCl₃). – ¹H NMR (200 MHz; CDCl₃): δ = 1.19 (s, 3H, CqCH₃), 1.27 (t, 3H, JHH = 7.0 Hz, COOCH₂CH₃), 2.59 (bs, 1H, CH₂OH), 3.74, 3.50 (2d, JHH = 9.0 Hz, 2H, OCH₂CH₃), 3.87, 3.68 (2d, JHH = 11.0 Hz, 2H, BzlOCH₂), 4.19 (q, JHH = 7.1 Hz, 2H, COOCH₂CH₃), 4.54 (s, 2H, PhCF₃O), 7.38–7.27 (m, 5H, Ph). – ¹³C NMR (50 MHz, CDCl₃): (δ = 14.2 (COOCH₂CH₃), 17.8 (CqCH₃), 48.8 (CqCH₃), 60.9 (COOCH₂CH₃), 66.5 (CH₂O), 73.5 (BzlOCH₂), 73.6 (PhCH₄O), 128.5, 127.7, 127.5 (C₀, C₂, C₆), 138.1 (C₇), 173.5 (COOCH₂CH₃). – GC/MS: tret = 13.72 min. – MS (EI): m/z = 252 (M⁺ + 2, 0.3%), 247 (M⁺, 1); 128 (26), 107 (C₇H₅O⁺, 24), 92 (C₇H₅⁺, 12), 91 (C₇H₄⁺, 100).

(+)-R-2-Benzoyloxymethyl-3-chloro-2-methyl-propionic acid ethyl ester ((+)-4S) and (-)-4R, respectively

Reaction and workup according to lit. [13]. (+)-4S: [α]D = 5.25° (c = 1.60, CHCl₃); (-)-4R: [α]D = -5.40° (c = 2.02, CHCl₃) (Lit. [13]: [α]D = -4.00° (c = 2.50, CHCl₃) for 72% ee).

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[17] Further crystallographic data have been deposited at the Fachinformationszentrum Karlsruhe GmbH. D-76344 Eggenstein-Leopoldshafen. They are available on request by quoting the registration numbers CSD 401008 and CSD 401009, respectively, the authors and the reference.