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Highly stereoselective, thermodynamically controlled and reversible formation of a new *P*-chiral phosphine

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The highly stereoselective formation of a chiral α-hydroxyphospholane under very mild condition is reported, taking place on a camphor skeleton by an intramolecular thermodynamically controlled and reversible addition of an epimeric secondary phosphine group to a carbonyl group.

The stereoselective generation of enantiomerically pure *P*-chiral (scalemic) phosphines[1] attracts great interest from the mechanistic point of view as well as for the synthesis of chiral ligands for transition metal catalysts.[2] *P*-Chiral phosphines can be prepared either by kinetic resolution *e.g.* of racemic phosphine oxides, sulfides or borane adducts[3] or *via* diastereoselective synthesis in the presence of a chiral auxiliary.[1,4] For the latter approach the use of diastereomerically pure aminophosphonites derived from ephedrine[5] or menthyl phosphinites is particularly promising.[6] However, these methods require performing several subsequent reactions in order to obtain the scalemic phosphine.

Herein we report on a new and highly stereoselective formation of a phospholane with a chiral phosphorus atom, bearing a hydroxy group at the neighbouring stereogenic carbon atom. Our starting material is enantiomerically pure bromide **1**, which can be easily derived from (*R*)-camphor.[7] The bromide was reacted with LiPHPh to give phosphine **2** (Scheme 1).

The $^{31}P\{^{1}H\}$-NMR spectrum of **2** depicted in Fig. 1 shows that under the conditions chosen the reaction proceeds non-selectively (THF, reflux, 12 h): two diastereomers are formed in a ratio of *ca.* 1 : 1 (δ −65.1, −65.0).

In the next step the keto group was liberated by acidic hydrolysis of the 1,3-dioxolane. The subsequent nucleophilic addition of the secondary phosphine to the carbonyl group afforded α-hydroxyphospholane **3** with >99.5% de.† Noteworthy, the cyclization proceeds quantitatively in the presence of a base in a protic solvent like methanol at room temp. The $^{31}P\{^{1}H\}$-NMR spectrum of the crude product in CD_3OD showed a single resonance at δ −2.2 (Fig. 1b) and gives proof that only one diastereomer was formed in this reaction. The other signal in this area (δ −2.1) which could be assigned to the other diastereomer of **3** has an integral intensity <1% of the main signal. Crystals suitable for X-ray structural analysis could be obtained by crystallization from methanol. The molecular structure of **3** is depicted in Fig. 2.‡

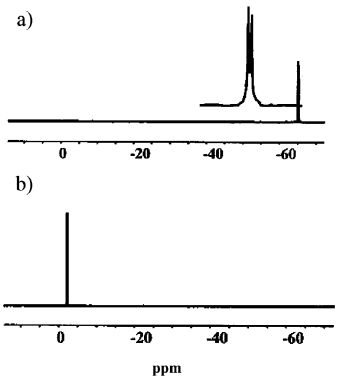


Fig. 1 $^{31}P\{^{1}H\}$-NMR spectra of **2** (a) and **3** (b) in CD_3OD (δ in ppm).

The crystal structure suggests a plausible explanation of the high diastereoselectivity. The phenyl ring and the methyl group at C3 of the camphor skeleton are in *trans*-positions minimizing the steric repulsion, so the diastereomer formed (under thermodynamically controlled conditions) is the least sterically hindered.

Obviously, prior to the formation of the phospholane, deprotonation of the secondary phosphine group should take place. Without the anion generation the formation of a diastereomerically pure product starting from a mixture of epimers **2** can hardly be explained. The formation of the intermediate anion can also be observed spectroscopically (Scheme 2). Thus, by addition of BuLi to a THF solution of keto

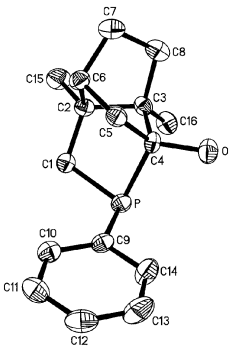
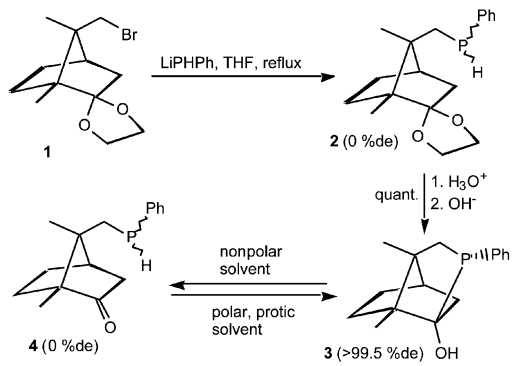
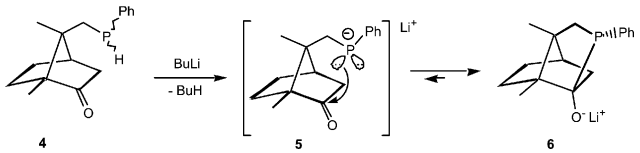


Fig. 2 Crystal structure of **3**; thermal ellipsoids are shown at 30% probability; selected bond lengths [Å] and angles [°]: P–C1: 1.855(3), P–C4: 1.865(3), P–C9: 1.827(3), C4–O:1.424(4); P–C4–O: 111.1(2); hydrogen atoms are omitted for clarity.



Scheme 1 Highly stereoselective synthesis of *P*-chiral α-hydroxyphospholane **3** and subsequent reversible ring cleavage.



Scheme 2 Base catalyzed addition of the phosphide group at the carbonyl group.

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phosphine **4** a resonance at δ −66.8 can be observed in the $^{31}P\{^{1}H\}$-NMR spectrum characterizing phosphide **5**. This signal disappears slowly within 5 h and a new signal arises at δ −9.5 which is assigned to lithium alcoholate **6**.

Related stereoselective ring closure reactions have been known for more than a century in carbohydrate chemistry affording important hemiacetals (*e.g.* furanoses) by intramolecular addition of hydroxy groups on diastereotopic carbonyl groups. In contrast to this chemistry in the example discussed herein two stereogenic centers are formed simultaneously from an epimeric centre with extremely high diastereoselectivity.

The formation of the heterocycle was found to be reversible and the equilibrium depends on the solvent polarity. The phospholane ring opens in benzene yielding phosphinyl ketone **4**. The first step of this reaction, the C–P bond cleavage, results in the formation of the corresponding phosphide. The latter is stabilized by protonation to give secondary phosphine **4**. The addition of the proton proceeds entirely nonselective affording a mixture of two diastereomeric secondary phosphines in a ratio of 1 : 1 as indicated in the $^{31}P\{^{1}H\}$-NMR spectrum ((C_6D_6) δ −66.5; −66.1). When this secondary phosphine was dissolved in a polar solvent (*e.g.* methanol) the diastereo- and enantiomerically pure hydroxy phosphine **3** could be reconstructed. Thus, the criterion for a reversible, highly stereoselective formation of a *P*-chiral phosphine is fullfilled. To the best of our knowledge hitherto such a process is without precedence in phosphorus chemistry.[8]

The possibility of highly stereoselective synthesis of other *P*-heterocycles of varying ring size[9] and bearing other substituents is currently under study in our laboratory.

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Notes and references

† Preparation of (1*R*,2*R*,3a*R*,4*R*,6a*R*)-3a,6a-dimethyl-2-phenylhexahydro-1,4-methanocyclopenta[*c*]phosphol-1(2*H*)-ol: A THF solution of $PhPHLi$ was prepared by mixing $PhPH_2$ (0.78 ml, 7.08 mmol) and BuLi (3.54 ml of a 2 M solution in pentane, 7.08 mmol) in an ice bath. The yellow reaction mixture obtained was stirred at r.t. for 2 h and then added to a solution of bromo ketal **1** (1.3 g, 4.72 mmol)[10] in THF. The solution was heated at reflux for 12 h. Then water (20 ml) was added and the product extracted with ether. The combined ether extracts were washed with water (2 × 10 ml). The solvent was removed and the residue dissolved in THF. Water (5 ml) and conc. HCl (2 ml) were added and the solution heated at reflux for 5 h. NaOH plates were added to adjust the pH to approximately 10. The product was extracted with ether. The combined extracts were washed with water and the ether removed. The optically pure phosphine **3** was purified by flash chromatography (silica gel Merck 60, dichloromethane as eluent). White crystals, 1.02 g, 83% yield. ^{1}H-NMR (400.13 MHz, CD_3OD) δ: 7.40–7.70 (m, 5H, arom.); 2.21 (dd, J = 6.9, 14.0 Hz, 1H), 1.93 (dd, J = 14.0, 20.7 Hz, 1H, P–CH_2); 2.10 (m, 1H), 1.01 (dd, J = 3.4, 12.0 Hz, 1H, 7-CH_2); 2.10 (m, 1H), 1.47 (m, 1H); 1.89 (m, 1H), 1.27 (d, J = 17.0 Hz, 1H, 5- and 6-CH_2); 1.77 (m, 1H, 4-CH); 1.15 (s, 3H, CH_3); 1.34 (s, 3H, CH_3). ^{13}C-NMR (100.63 MHz, CD_3OD) δ: 140.2 (d, J = 30 Hz, C_{ipso}); 131.0 (d, J = 14.3 Hz), 128.1 (s), 127.5 (s, arom. CH); 86.8 (d, J = 4.8 Hz, 1-C); 55.2 (d, J = 21.9 Hz, 3a-C); 50.5 (d, J = 1.9 Hz, 6a-C); 47.9 (s, 4-CH); 38.5 (d, J = 3.81 Hz, 7-CH_2); 32.0 (s, CH_2); 29.9 (d, J = 3.8 Hz, CH_2); 26.3 (d, J = 11.5 Hz, P–CH_2); 18.6 (d, J = 2.9 Hz, CH_3); 12.5 (d, J = 23.8 Hz, CH_3). $^{31}P\{^{1}H\}$-NMR (161.98 MHz, CD_3OD) δ: −2.2.

‡ Crystal structural analysis of **3**: STOE-IPDS diffractometer, graphite monochromated Mo-K_α-radiation, λ = 0.71069 Å. Structure solved with direct methods and refined by full-matrix least-squares against F^2.[11] XP (Bruker AXS) was used for structure representation. Crystal and refinement data: crystal size 0.4 × 0.3 × 0.1 mm, colourless prisms, space group $P2_12_12_1$, orthorhombic, a = 6.759(1), b = 9.998(2), c = 21.043(4) Å, V = 1422.0(4) Å^3, Z = 4, $\rho_{calcd.}$ = 1.216 g cm^{-3}, 5231 reflections collected, 1494 symmetry independent reflections, 1230 observed reflections ($I > 2\sigma(I)$), $R1$ = 0.034, wR^2 (all data) = 0.079, 168 parameters. The absolute structure of **3** (x = −0.15(19)) corresponds to the known chirality of the starting material **1**. CCDC 202862. See http://www.rsc.org/suppdata/cc/b3/b306153a/ for crystallographic data in CIF or other electronic format.

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