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Novel chiral phosphines derived from limonene: the synthesis and structure of 4,8-dimethyl-2-phosphabicyclo[3.3.1]nonane

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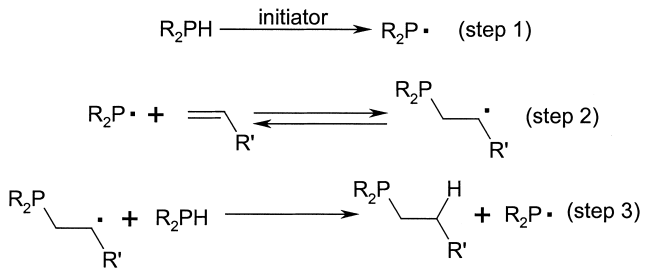
Abstract—The radical addition of PH_3 to limonene results in the formation of 4,8-dimethyl-2-phosphabicyclo[3.3.1]nonane, which has been characterized by X-ray crystallographic analyses of its oxidation products, 2-(4-methylcyclohexyl)propylphosphonic acid and 4,8-dimethyl-2-phosphabicyclo[3.3.1]nonan-2-ol-oxide.

Chiral phosphine ligands have played a central role in the development of catalytic enantioselective processes over the last 25 years, particularly in the area of homogenous asymmetric hydrogenation.[1] New phosphine ligands continue to be developed as do their applications to synthetically valuable asymmetric carbon–carbon bond forming reactions.[2–4] Many of the ligands employed (including such bisphosphines as CHIRAPHOS,[5] BINAP[6] and those based on TADDOL derivatives[7]) are actually derivatives of a small number of chiral precursors such as tartaric acid, mannitol or axially chiral biaryl skeletons and, hence, an overall issue is the narrow molecular diversity within the ligands set. Recent efforts in our laboratories have focused on the development of new chiral platforms in order to expand the available molecular diversity.[8] Herein, we report on the preparation of structurally novel phosphine derivatives generated by the free radical addition of phosphine (PH_3) to the chiral pool terpene limonene. This represents a specific example of a general methodology to structurally diverse phosphines.

The addition of phosphinyl radicals to olefins has been reported as a means by which to generate various alkylphosphines.[9] Amenable to the industrial scale production of a variety of mono-, di- and trialkyl phosphines, the reaction is illustrated in Scheme 1. Generally, the phosphine and alkene are charged into a suitable reactor and, after heating the contents to the desired reaction temperature (typically 75–100°C), a solution of an initiator (in a suitable solvent such as toluene, octane or even the olefin) is added over 2–4 hours. A phosphinyl radical is generated (step 1) and addition across the alkene occurs (which is reversible)[10] to begin the radical propagation (step 2). Abstraction of a H atom generates another phosphinyl radical (step 3) which then continues the propagation by adding to another alkene.

Application of this method as a means of obtaining structurally diverse chiral phosphines prompted us to consider the reaction employing readily-available, chiral-pool alkenes. The monoterpene limonene was chosen as the basis for our initial model studies. These indicated that, provided the correct experimental conditions are chosen and polymerization of the alkene is minimized, an interesting, sterically-demanding,



Scheme 1.

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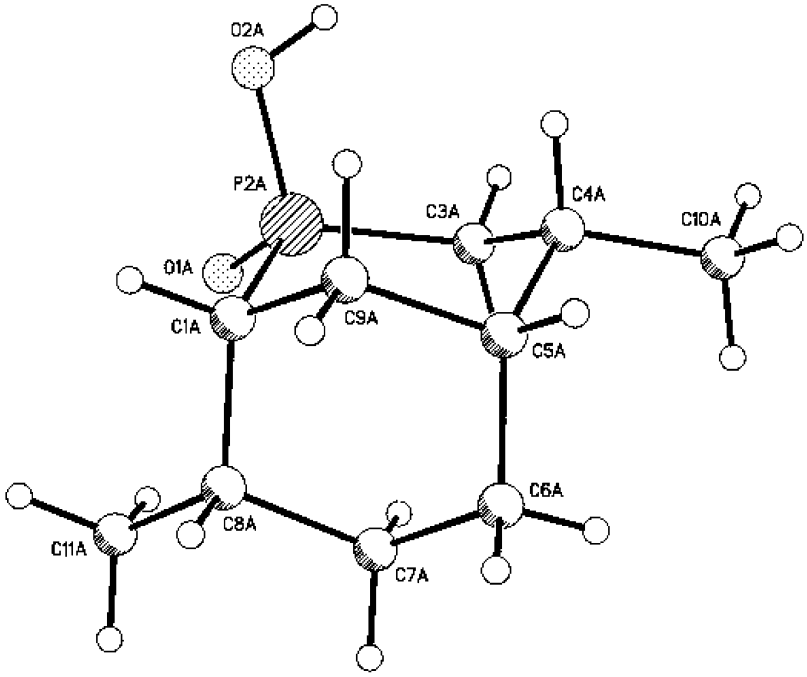
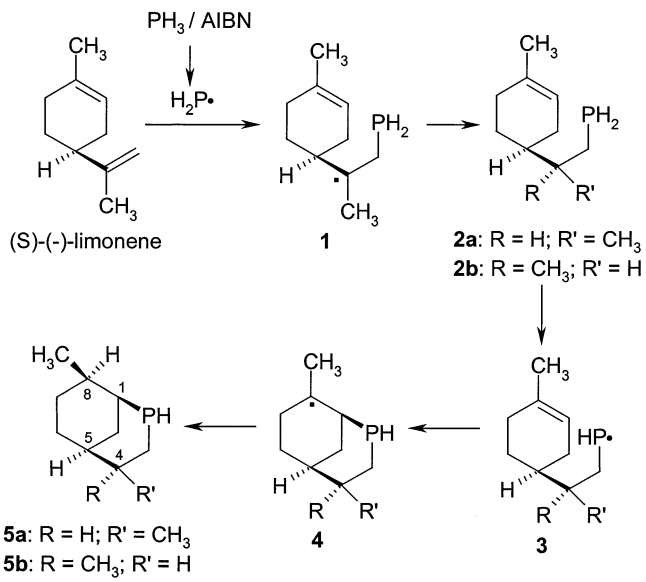


Figure 1. ORTEP of the 4,8-dimethyl-2-phosphabicyclo[3.3.1]nonan-2-ol-oxide (major component) (**6**).

bicyclic, secondary phosphine, 4,8-dimethyl-2-phosphabicyclo[3.3.1]nonane, could be generated. The initial addition of the phosphinyl radical would be expected to occur across the sterically less demanding exocyclic double bond leading to radical **1** (Scheme 2) which would be trapped as diastereomeric phosphines **2a** and **2b** via an indiscriminate H abstraction from PH_3. Subsequent generation of phosphinyl radical **3** from **2a** and **2b** would be followed by intramolecular cyclization onto the endocyclic double bond producing radical **4**, trapped as **5a** and **5b**. Conformational analyses of **3** and **4** led us to believe that the second, intramolecular phosphinyl radical addition and the terminal H abstraction should both occur in a highly disatereoselective manner producing only the two diastereomers shown.

We have investigated this reaction in detail and can now report that under controlled conditions, PH_3 adds to limonene in good yields providing bicyclic phosphines with predictable stereochemistry. A toluene solution of AIBN is slowly added to limonene and PH_3 in toluene at 75°C and the reaction is continued for a further 4 hours. The products were readily isolated by distillation (yield >85%). ^{31}P NMR and GC–MS analysis[11] of the viscous oily product showed that only two compounds were produced in a ratio of 1:0.8. Structural assignment of these two compounds, which we tentatively assigned as **5a** and **5b** (vide infra), was carried out by X-ray analyses of their oxides. A sample of the phosphinic acid, 4,8-dimethyl-2-phosphabicyclo[3.3.1]nonan-2-ol 2-oxide (**6**), could be prepared by treating a mixture of the two diastereomeric phosphines (generated from (*R*)-(+)-limonene) with hydrogen peroxide under acidic catalysis.[12] Recrystallization from water gave material suitable for X-ray crystallographic analysis.[13] The major component (shown in Fig. 1) confirms the mechanism postulated in Scheme 2 with each of the substituents at C1, C5 and C8 on the same face of the cyclohexyl ring. Furthermore, the X-ray structure revealed that each of the three molecules in the asymmetric cell packs into the crystal lattice with its C4 epimer[14] (the position of the first H-addition in Scheme 2). In other words, both of the original diastereomeric phosphines could be oxidized, crystallized and incorporated in the same crystal lattice (Fig. 2).

Interestingly, it was noted that when the mixture of diastereomeric phosphines **5a** and **5b** were exposed to air, rapid oxidation occurred and a solid could be



Scheme 2.

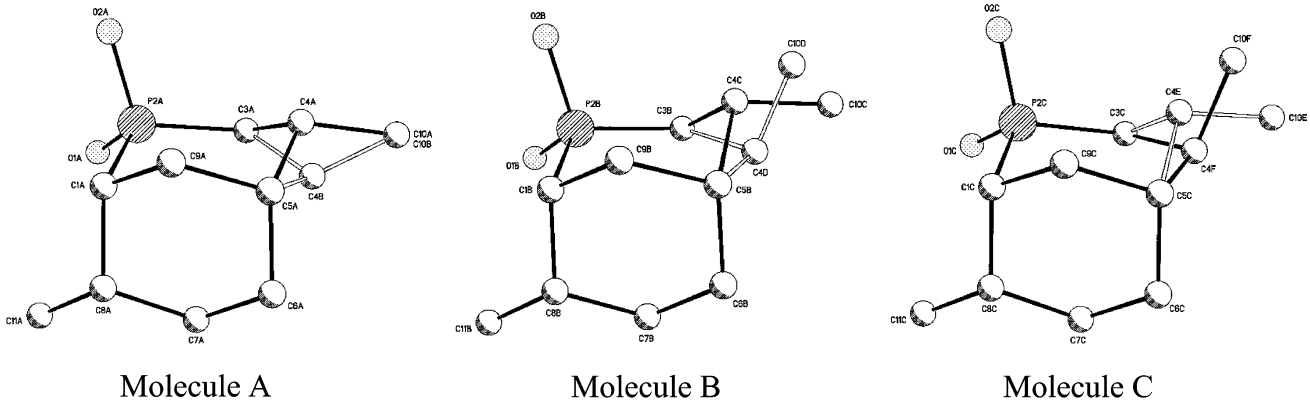


Figure 2. Diastereomeric pairs of 4,8-dimethyl-2-phosphabicyclo[3.3.1]nonan-2-ol 2-oxide (**6**).

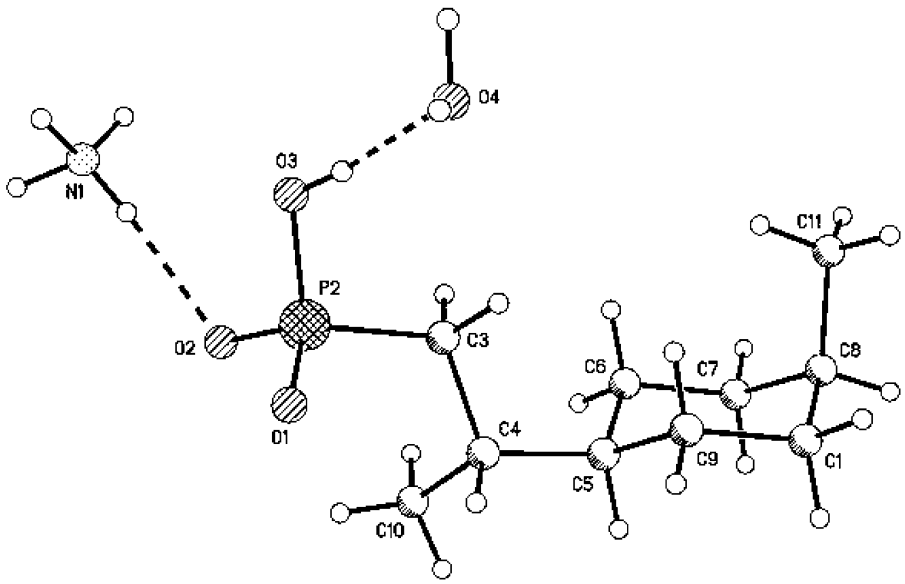
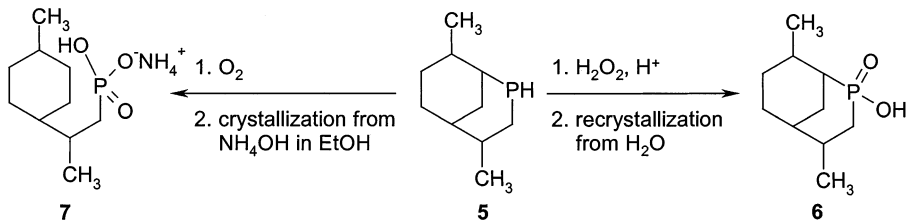


Figure 3. ORTEP of the ammonium salt of 2-(4-methylcyclohexyl)propylphosphonic acid (**7**).



Scheme 3.

precipitated. The oxide was collected and recrystallized from a solution of aqueous ammonium hydroxide in ethanol. Much to our surprise, the compound isolated was not the phosphinic acid nor the secondary phosphine oxide, but rather a single diastereomer of the ammonium salt of 2-(4-methylcyclohexyl)propylphosphonic acid (**7**) as evidenced by X-ray crystallographic analysis (Fig. 3).[15] The dichotomous oxidation of the phosphine mixture (Scheme 3) raises a number of intriguing mechanistic considerations. The aerial oxidation of secondary phosphines has been studied[16] and proceeds via a radical mechanism to the phosphine oxide which can often be isolated. In the present example (and to our knowledge, the only example), the phosphine is oxidized to the level of a phosphonate with a concomitant cleavage of a P–C bond. Additional work needs to be carried out in order to fully elucidate this mechanism.

In conclusion, we have shown that the free radical addition of phosphine to limonene proceeds in a predictable manner providing high yields of alkylphosphines under the conditions described. The chemistry outlined provides rapid access to chiral phosphines and paves the way for the application of the phosphinyl radical addition methodology to other terpenes as well

as looking at the employment of various mono- and dialkyl substituted phosphines (currently under investigation).

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11. Column: DB-5; 30 m×0.25 mm; 0.1 μm film; oven temperature ramped from 50 to 300°C at 10°C/min; He flow: 1 ml/min. The diastereomeric phosphines had retention times of 11.54 and 11.65 minutes.
12. The corresponding phosphinic acids were prepared by adding a 10–15% molar excess of 25% H_2O_2 to a stirred mixture of the bicyclic secondary phosphine adducts in water at 90–95°C. H_2SO_4 (2–3 mol%) was added as a catalyst. On cooling, the organic layer solidifies and **6** were recrystallized from water (72% yield, mp 125°C).
13. *Crystal data* for **6**: $C_{10}H_{19}O_2P_1$, $M=202.22$, orthorhombic, $a=6.6012(6)$, $b=20.6673(18)$, $c=23.980(2)$ Å, $U=3271.6(5)$ Å^3, $T=123$ K, space group $P2_12_12_1$ (no. 19), $Z=12$, $D_{calcd}=1.232$ g cm^{-1}, μ(Mo-Kα)$=0.221$ mm^{-1}. Data collected on a Bruker AXS SMART CCD diffractometer, 26116 reflections measured, data truncated to 0.80 Å ($\theta_{max}=26.37°$, 99.9% complete), 6668 reflections unique ($R_{int}=0.0420$). Final agreement factors for 405 parameters and 0 restraints gave $R_1=0.0516$, $wR^2=0.1275$ and GOF$=1.004$ based on 5520 reflections with $I\geq 2\sigma(I)$. Final difference map +0.45 and −0.36 e Å^{-3}. Absolute structure parameter$=0.04(10)$, (Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876). Programs used: Bruker AXS SMART and SAINT control and integration software, SHELXTL structure solution and refinement (Sheldrick, G. M. SHELXTL; University of Göttingen: Germany). Further details of the structural investigations of **6**, including supplementary data, are available on request from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (Depository number CCDC 152980).
14. Diastereomeric ratios for each molecule in the asymmetric cell are as follows: molecule A, 87:13; molecule B, 46:54; and molecule C, 54:46.
15. *Crystal data* for **7**: $C_{10}H_{26}N_1O_4P_1$, $M=255.29$, monoclinic, $a=41.4282(4)$, $b=6.4194(2)$, $c=10.6629(3)$ Å, $\beta=93.209(2)°$, $U=2831.29(12)$ Å^3, $T=123$ K, space group $C2/c$ (no. 15), $Z=8$, $D_{calcd}=1.198$ g cm^{-1}, μ(Mo-Kα)$=0.195$ mm^{-1}. Data collected on a Bruker AXS SMART CCD diffractometer, 11495 reflections measured, data truncated to 0.80 Å ($\theta_{max}=26.37°$, 99.9% complete), 2883 reflections unique ($R_{int}=0.1095$). Final agreement factors for 175 parameters and 0 restraints gave $R_1=0.0633$, $wR^2=0.0903$ and GOF$=1.010$ based on 1826 reflections with $I\geq 2\sigma(I)$. Final difference map +1.34 and −0.29 e Å^{-3}. Programs used: Bruker AXS SMART and SAINT control and integration software, SHELXTL structure solution and refinement (Sheldrick, G. M. SHELXTL; University of Göttingen: Germany). Depository Number CCDC 152981.
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