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Chiral pentacyclic phosphines as a new ligand class†‡

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A new sterically encumbered monophosphine has been prepared stereoselectively from (1*R*)-camphor and some aspects of its coordination chemistry with palladium examined.

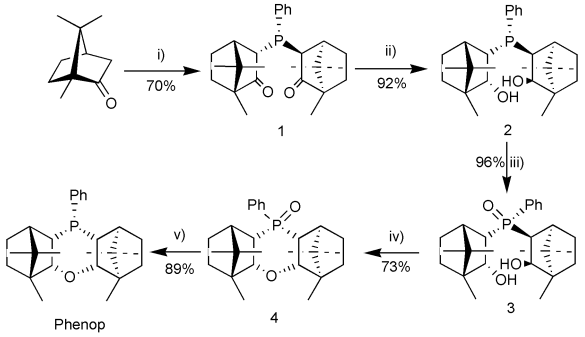
Metal complexes of electron-rich, bulky monodentate phosphines and, in particular, related cyclometallated (*P*,*C*) derivatives have proved valuable catalysts for a number of synthetically appealing C–C and C-heteroatom bond forming reactions.[1] Palladium remains the metal of choice for Heck and Suzuki type coupling, although phosphaplatinacycles have recently been shown to be highly efficient Suzuki catalysts.[2] Whilst considerable interest has focused on these systems, the development of chiral derivatives for the asymmetric synthesis of, for example biaryls, has been slow to take off. Buchwald[3] and Cammidge[4] have employed optically pure binaphthyl- and ferrocenyl-derived phosphines for the production of various chiral biaryls with modest to good enantioselectivities. Others have used similar type ligands[5] but have observed little to no asymmetric induction in Heck couplings, although sulfur donating metallocycles[6] have produced modest enantioselectivities. Thus, the search for new ligands that may prove effective in this type of reaction and others remains a focal point for chemists within this field.

We are interested in developing inherently chiral monophosphines with unusual, rigid, multicyclic structures that contain alkyl substituents predisposed for cyclometallation with a view to employing them as ligands in catalysis. To this end we have synthesised the new ligand (1*S*,4*R*,4a*S*,5a*R*,6*R*,9*S*,9a*S*,10a*R*)-4,6,11,11,12,12-hexamethyl-10-phenyldodecahydro-1,4:6,9-dimethanophenoxaphosphinine (**phenop**) from readily available (1*R*)-camphor (Scheme 1).

The reaction of the enolate of camphor with dichlorophenylphosphine gave the diketophosphine **1** in high yield. Recrystallisation of **1** from ethanol gave a single isomer determined from NMR data to be *endo*,*endo*-**1**. Lithium aluminium hydride reduction of the carbonyl functions was performed in THF at rt to give the phosphinodiol **2** as the all *endo* isomer. Attempts to cyclise this diol directly to **phenop** have thus far been unsuccessful. However, conversion of the phosphinodiol to the oxide **3** is readily achieved without compromising the chiral integrity of the compound and reacting **3** with two mol equivalents of toluene-*p*-sulfonyl chloride in toluene at reflux gave **phenop** as the oxide (**4**) in 73% yield. Compound **4** was reduced with excess trichlorosilane in refluxing toluene over 24 h to give **phenop** in 40% overall yield (based on camphor).

The isolation of the *endo*,*endo* isomer of **1** accords with the observations of Shaw *et al.* on the related bicyclic diphenylphosphine system; these workers showed that this was the thermodynamically favoured isomer.[7] The subsequent stereoselective $LiAlH_4$ reduction of **1** to the *endo*,*endo*-alcohol **2** also accords with previous observations on the bicyclic system.[8] The stereochemical outcome of the ring forming reaction (**3** → **4**) was less predictable, as no precedent for such a conversion was evident in the literature, and it came as some surprise that only a single isomer was observed and isolated in good yield. Thus, starting from camphor with a predefined stereochemistry (in our case the 1*R* enantiomer), a further four chiral centres are created in a controlled manner during the synthesis of **4**. Assignment of the absolute configuration of these newly generated centres was made possible through determination of the crystal structure of **4** (Fig. 1).§

The compound is an unusual pentacyclic phosphine which has eight stereogenic centres and two sets of fused 5- and 6-membered rings (from the camphor) flanking a central 6-membered oxaphosphinane (oxide) ring. The peripheral 6-membered rings are necessarily boat as dictated by the [2.2.1] bicyclic structure of camphor, but surprisingly the central heterocyclic ring also adopts a boat conformation. The phenyl substituent on the phosphorus projects equatorially and the oxide is axial. The phosphorus centre may be defined as being pseudochiral as, although it possesses two structurally equivalent groups, the stereogenic carbon atoms directly bound to the



Scheme 1 *Reagents*: (i) n-BuLi, 0.5 $PhPCl_2$; (ii) $LiAlH_4$; (iii) H_2O_2; (iv) TsCl, toluene, reflux; (v) $HSiCl_3$.

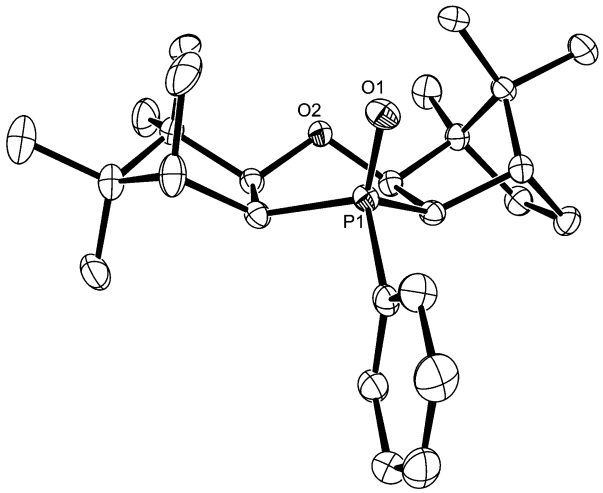


Fig. 1 ORTEP representation of **4**.

† Electronic supplementary information (ESI) available: characterisation data for the new compounds. See http://www.rsc.org/suppdata/cc/b2/b207937b/

‡ Dedicated to the memory of Sam M. Liddiard, a true friend and colleague.

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phosphorus have the opposite configuration (one is *S*, the other *R*). The phosphorus and oxygen atoms in the ring are disposed *endo*- with respect to one of the [2.2.1] bicyclic units and *exo*- with regard to the other, *i.e.* two carbon centres, one adjacent to oxygen, one to phosphorus, have inverted on conversion of **3** to **4**. This suggests that an elimination (dehydration) occurs prior to cyclisation to give a vinyl phosphine oxide that adds the remaining alcohol in a Michael-type fashion to yield the pentacycle **4**. Reduction of the phosphine oxide to the phosphine occurs with retention of stereochemistry at all centres, *i.e.* the oxide function has simply been removed. The resultant **phenop** can be crystallised from ethanol and is air-stable in the solid state indefinitely; the half-life for oxidation in solution is about one week (^{31}P NMR in dichloromethane).

Addition of 1 mole equivalent of **phenop** per palladium to $Pd_3(OAc)_6$ in toluene gives, after 48 h stirring at rt and removal of solvent, a colourless air-stable solid in high yield (84%). The compound was crystallised from toluene in air and an X-ray structure revealed it to be a bis(cyclometallated ligand)bis(μ-acetato) dimer, *cis*-[Pd_2(μ-κ^1-OAc)(μ-κ^2-OAc)(κ*P*,κC-**phenop**)$_2$], **6** (Fig. 2).§

Several features of the structure are worthy of comment. Firstly, the **phenop** ligands have cyclometallated at the 9-methyl position of one of the [2.2.1]-bicycloheptane units of each ligand and are thus bound as *P*,*C* bidentates: such phosphapalladacycles are well established for other bulky phosphines notably tri-*tert*-butylphosphine[9] and tri-*ortho*-tolylphosphine.[1*f*] The resulting chelates are fused 6- (pseudo-boat) and 7-membered (pseudo-chair) rings for each ligand. The Pd–P bond lengths are relatively short at 2.197 Å (av.) compared to non-cyclometallated phosphine complexes (2.24–2.35 Å), and the phosphorus donors are orientated *cis* with respect to the Pd–Pd axis. Cyclometallation at the C(9) methyl of each ligand generates a further chiral centre at the C(7) carbon of the original camphor units. These stereogenic centres have the absolute configuration *S* as dictated by the structure of the oxaphosphine ligands; the pro-*R* methyls being disposed away from the metal centres. Furthermore, the phosphorus atoms themselves become stereogenic centres on coordination with the absolute configuration *S*. Thus, coordination in this mode generates two further chiral centres (one carbon, one phosphorus) in each ligand with absolute stereospecificity. The bridging acetates have an unusual arrangement with one adopting the familiar μ-κ^2 mode through coordination of one oxygen to Pd(1) and the second oxygen to Pd(2) whereas the other acetate binds in a μ-κ^1 fashion using a single oxygen to coordinate both palladium atoms. This produces a central Pd_2O_3C 6-membered ring that is hitherto unknown for complexes of this type. The ring has an envelope conformation with the κ^2-acetate and two Pd atoms being close to coplanar and the remaining oxygen of the κ^1 acetate at the vertex of the flap of the envelope. The two distinct acetates are readily distinguished in the infrared spectrum of **6** where the κ^2 type is identified by ν_s at 1403 cm^{-1} and ν_{as} at 1557 cm^{-1} and the κ^1 form by stretches at 1285 (ν_s) and 1656 (ν_{as}) cm^{-1}.

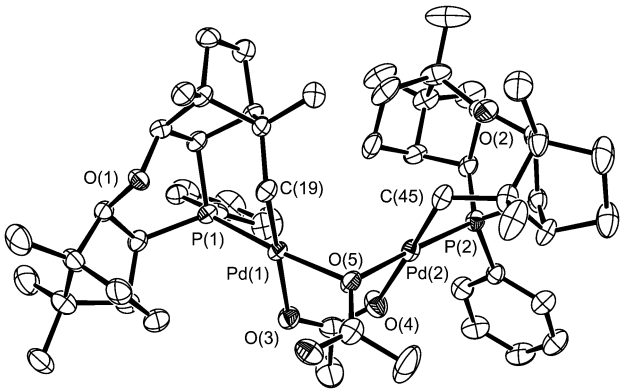

Fig. 2 ORTEP representation of *cis*-[Pd_2(μ-κ^1-OAc)(μ-κ^2-OAc)(κ*P*,κC-phenop)$_2$], **6**. Selected bond lengths (Å) and angles (°): Pd(1)–P(1) 2.195(2), Pd(2)–P(2) 2.201(2), Pd(1)–C(19) 2.036(5), Pd(2)–C(45) 2.029(6), Pd(1)–O(3) 2.166(4), Pd(1)–O(5) 2.130(4), Pd(2)–O(4) 2.163(4), Pd(2)–O(5) 2.136(4); P(1)–Pd(1)–C(19) 86.89(16), P(2)–Pd(2)–C(45) 86.59(18), O(3)–Pd(1)–O(5) 86.35(15), O(4)–Pd(2)–O(5) 88.14(16), P(1)–Pd(1)–O(3) 97.16(12), P(2)–Pd(2)–O(4) 95.83(12), C(19)–Pd(1)–O(5) 89.84(19), C(45)–Pd(2)–O(5) 89.5(2).

The ^{31}P{^{1}H} NMR spectrum of **6** in d_8-toluene is a broad singlet at δ 17 ppm which sharpens on heating to 70 °C. On cooling to low temperature, the singlet broadens further before splitting into two separate resonances in a 1:1 ratio at −70 °C. This behaviour is mirrored in the ^{1}H NMR where the five distinct methyl resonances split into ten singlets at low temperature. Broad NMR spectra are typical of these types of phosphapalladacycle dimers, and have been interpreted as resulting from an equilibrium between the dimer and a monomeric species. We do not believe that this is the case here, rather the central 6-membered dipalladium diacetate ring in **6** is fluxional, with a particular conformation, such as that in Fig. 2, being frozen out at low temperature. In this conformation, the phosphorus donors become inequivalent as do the remaining ligand fragments in the formally C_1 complex and the two phosphorus nuclei and all proton groups appear as separate resonances in the respective NMR spectra. Further features of the coordination chemistry of these new ligands and the application of the resulting complexes in catalysis will appear in the near future.

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Notes and references

§ *Crystal data* for **4**: $C_{26}H_{37}O_2P$, M = 412.53, orthorhombic, $P2_12_12_1$, a = 11.656(2), b = 12.060(2), c = 16.579(3) Å, V = 2330.5(7) Å^3, Z = 4, D_c = 1.176 g cm^{-3}, μ(Mo-Kα) = 0.71073 Å, T = 293 K, 16833 reflections collected, 5310 independent reflections [R(int) = 0.0465], F^2 refinement, R_1 = 0.0365, wR_2 = 0.0831, 268 parameters. The absolute structure was correctly indicated by the Flack parameter being zero within experimental error [−0.07(7)] based on the comparison of 2298 Freidel pairs (*hkl* and $\bar{h}\bar{k}\bar{l}$). For **6**·0.25C_7H_8: $C_{57.75}H_{80}O_6P_2Pd_2$, M = 1144.96, orthorhombic, $P2_12_12_1$, a = 12.7814(2), b = 18.9991(3), c = 23.0978(5) Å, V = 5608.96(17) Å^3, Z = 4, D_c = 1.356 g cm^{-3}, μ(Mo-Kα) = 0.71073 Å, T = 150 K, 36501 reflections collected, 10215 independent reflections [R(int) = 0.0758], F^2 refinement, R_1 = 0.0456, wR_2 = 0.0944, 621 parameters. The absolute structure was correctly indicated by the Flack parameter being zero within experimental error [0.01(3)] based on the comparison of 4534 Freidel pairs (*hkl* and $\bar{h}\bar{k}\bar{l}$). CCDC 191755 and 191756. See http://www.rsc.org/suppdata/cc/b2/b207937b/ for crystallographic data in CIF or other electronic format.

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