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A concise synthesis of a rigid isomannide-based diphosphine ligand and structural characterisation of an alkoxyphosphonium intermediate†

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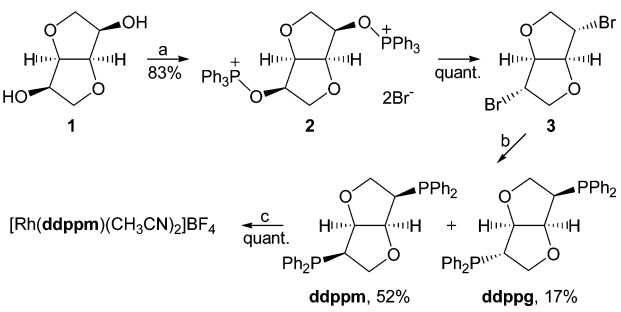
The synthesis of the novel C_2-symmetric diphosphine 1,4:3,6-dianhydro-2,5-bis(diphenylphosphino)-D-mannitol (ddppm) from D-isomannide is reported and its performance in asymmetric hydrogenations discussed.

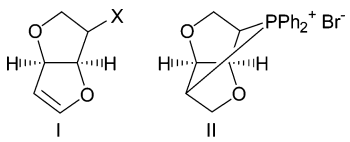
Although D-isomannide (**1**) was first described in 1882 by Fauconnier, reports on its synthetic applications as a commercially available chiral auxiliary have been so far limited.[1] This reflects the synthetic difficulties encountered in forming the hindered *endo* derivatives (the *endo* and *exo* prefixes refer to the cavity formed by the two *cis* fused tetrahydrofuran rings). A report on an *endo*-diimine isomannide derivative, used in catalytic asymmetric Diels–Alder reactions, is the only example to our knowledge of a di-*endo* isomannide-derived ligand.[2] In the case of phosphine isomannide derivatives only the di-*exo*-diphosphine 1,4:3,6-dianhydro-2,5-dideoxy-2,5-bis(diphenyl-phosphino)-L-iditol (**ddppi**) is known. **ddppi** is a non-chelating ligand and has been used as a catalyst in various asymmetric reactions, including hydrogenations.[3] Herein we wish to describe the first reported synthesis of **ddppm**, a di-*endo* phosphine derivative of isomannide. Our interest in developing isomannide phosphine derivatives and their metal complexes stems from their potential uses in catalytic applications. An efficient chirality transfer from **ddppm** was anticipated because of the rigid backbone conformation, its chelating nature and the presence of a C_2 axis. In addition, large bite angles were expected due to the backbone steric requirements that may be a useful feature in catalytic reactions which involve a reductive elimination step.

ddppm was synthesised in just two successive steps from D-isomannide according to the reaction sequence illustrated in Scheme 1. Precursors to **ddppm** with chloride and mesylate leaving groups were also studied but with inferior results to that of dibromide **3**. After several unsuccessful attempts, the key dibromide **3** was prepared using a protocol for the conversion of alkyl alcohols to the corresponding halides.[4] This method constitutes a significant improvement on the reported two step procedure for the preparation of **3** from D-isomannide involving difficult separations from other epimers and low yields.[5] Reaction of D-isomannide with two equivalents each of bromine, triphenyphosphine and imidazole in refluxing acetonitrile afforded **3** in quantitative yields. The same reaction carried out at room temperature affords only the bis-alkoxyphosphonium salt **2** as a stable intermediate. Compound **2** is the first structurally characterised alkoxyphosphonium salt of this type. An ORTEP drawing of **2** shows both – $OPPh_3$ substituents adopting pseudoaxial positions in the solid state (Fig. 1).‡



Scheme 1 (a) 2 eq. Br_2/PPh_3/imidazole, CH_3CN, reflux, 3d; (b) 2 eq. $LiPPh_2$, Et_2O, 3h; (c) $[Rh(COD)_2]BF_4$/**ddppm**, CH_3CN.

The last step in the **ddppm** synthesis involves an S_N2 displacement of the bromide of **3** by diphenyl phosphide as a nucleophile. It is known that the *exo* groups of 1,4:3,6 dianhydrohexitols are reluctant to undergo S_N2 displacements due to steric constraints, in many cases leading to elimination and racemisation by-products.[2,6] Although no elimination by-products were observed in the last step of the **ddppm** synthesis, as was the case for the *endo* diimine isomannide derivative,[2] the epimer 1,4:3,6-dianhydro-2,5-dideoxy-2,5-bis(diphenylphosphino)-D-glucitol (**ddppg**) was also isolated as shown in Scheme 1. The two isomers were separated as colourless, air stable crystals by fractional crystallisation from ethanol. The crystal structure of **ddppm** shows the two phosphine groups occupying pseudoequatorial positions pointing away from the central cavity (Fig. 2).‡ We can speculate that the formation of the minor isomer arises from the hydrophosphination of elimination intermediates such as I (where X = PPh_2) by $HPPh_2$ leading to **ddppg** as the more thermodynamically stable product. Alternatively, **ddppg** may be formed by attack of Ph_2P^- at a bridged phosphonium salt, intermediate II. A secondary amine analogue of II has been reported previously.[6] Ether was the solvent of choice in the formation of **ddppm**. In thf the di-*endo* ligand was not detected and **ddppg** was a minor product. The major products formed were the mono- and di-*exo* phosphines. This preferential formation of *exo* phosphine derivatives favours a competing mechanism *via* phosphide-promoted elimination to yield intermediate I and $HPPh_2$ followed by hydrophosphination.[7]



The chelating ability of **ddppm** is demonstrated with the synthesis of the rhodium complex $[Rh(ddppm)(CH_3CN)_2]BF_4$ (**4**), Scheme 1. The crystal structure of **4** (Fig. 2) shows the two PPh_2 groups of **ddppm** adopting pseudoaxial positions necessary for chelation to the metal.‡ As a result the P–P distance changes from 5.9085(24) Å in the free ligand to 3.4043(1) Å on co-ordination. A distorted tetrahedral arrangement is observed around the phosphorus atoms imposed from the steric requirements of the isommanide backbone, with tetrahedral angles ranging from 98.97° to 127.01°. **ddppm** has a large bite angle of 98.61(3)° accommodated in the square co-ordination plane by the smaller P–Rh–N angles at 85.84(8)° and 87.21(8)° and N–Rh–N angle at 88.39(11)°. For comparison the bidentate angle of BINAP, another seven-membered chelate ligand, in an analogous complex is 91.8(1)°.[8]

In order to assess the efficiency of **ddppm** in asymmetric catalysis we tested **ddppm** in the well established reaction of olefin hydrogenation (Table 1).[9] Using a rhodium catalyst itaconic acid is hydrogenated quantitatively under an atmospheric pressure of H_2 with a good enantioselectivity (run 1). An increase in the hydrogen pressure results in decreased yields and selectivities (run 2). Similar

† Electronic Supplementary Information (ESI) available: characterisation data for **2**, **4**, **ddppm** and **ddppg** (including structural data for **ddppg**), experimental for hydrogenation reactions.

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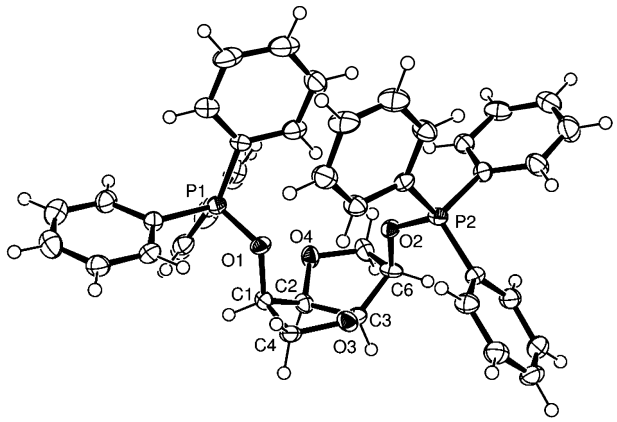


Fig. 1 ORTEP ellipsoid plot at 30% probability of the molecular structure of **2**. The bromide counter ions and solvent molecules have been omitted for clarity. Selected distances (Å): P(1)–O(1) 1.577(4), P(2)–O(2) 1.572(4), O(1)–C(1) 1.460(6), O(2)–C(6) 1.462(6).

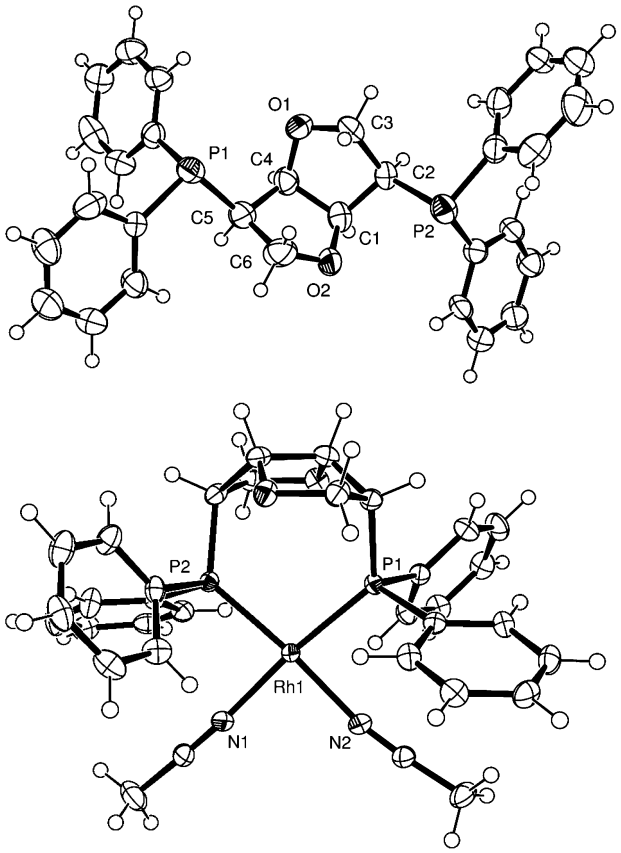
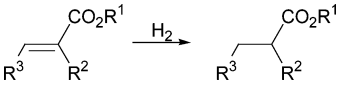


Fig. 2 ORTEP ellipsoid plot at 30% probability of the molecular structure of **ddppm** (top) and **4** (bottom). Solvent molecules and the BF_4 anion in **4** have been omitted for clarity. Selected distances (Å) for **4**: Rh(1)–N(1) 2.068(3), Rh(1)–N(2) 2.069(3), Rh(1)–P(2) 2.2398(9), Rh(1)–P(1) 2.2503(9).

observations have been reported previously by other researchers.[10] The corresponding methyl ester affords methyl succinate quantitatively but with lower enantioselectivity than itaconic acid (compare runs 1 and 3). (*Z*)-*N*-acetamido cinnamic acid is again hydrogenated quantitatively but with moderate enantioselectivity (30%, run 5). For comparison, we also generated *in situ* a ruthenium catalyst from $[Ru(p\text{-cymene})Cl_2]_2$ and **ddppm** (run 7).[10] Here hydrogenation of (*Z*)-*N*-acetamido cinnamic acid gives the best enantioselectivity (73%) observed from this set of experiments. These unoptimised results show that **ddppm** forms active catalysts although currently not with the high enantioselectivities observed with other hydrogenation catalysts.[9]

Table 1 Asymmetric hydrogenation of olefins



Run	R^1	R^2	R^3	H_2 (atm)	Catalyst	% Yield	% ee
1	H	CH_2CO_2H	H	1	A	> 99	64 (*S*)
2	H	CH_2CO_2H	H	3.5	A	89	59 (*S*)
3	Me	CH_2CO_2Me	H	1	A	> 99	41 (*S*)
4	Me	CH_2CO_2Me	H	20	A	15	31 (*S*)
5	H	$NHCOCH_3$	Ph	1	A	> 99	30 (*R*)
6	H	$NHCOCH_3$	Ph	3.5	A	85	36 (*R*)
7	H	$NHCOCH_3$	Ph	3.5	B	50	73 (*R*)

Reaction conditions: 0.01 mmol catalyst, 1 mmol substrate in MeOH (15 mL) at room temperature. Catalyst A = $[Rh(COD)_2]BF_4$/ddppm, B = $[Ru(p\text{-cymene})Cl_2]_2$/ddppm. %ee values were measured by chiral HPLC using a Chiralcel OD column and hexane/IPA as the eluent.

To conclude, we have prepared a new chiral chelating diphosphine ligand with a rigid backbone conformation in two steps from readily available starting materials. Compared to other known chiral diphosphines such as BINAP, ddppm synthesis involves a simpler synthetic methodology that does not require a resolution step.[11] Further work that explores possible catalytic applications of **ddppm** and its derivatives is currently underway.

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Notes and references

‡ *Crystal data* for **ddppm**: $C_{30}H_{28}O_2P_2$, M = 482.46, orthorombic, $P2_12_12_1$, a = 11.5522(9), b = 14.0034(11), c = 15.4518(14) Å^3, V = 2499.6(4) Å^3, Z = 4, D_c = 1.282 g cm^{-3}, μ(Mo–Kα) = 0.71073 Å, T = 150(2) K, 24363 reflections collected, 4278 independent reflections [R(int) = 0.2142], F^2 refinement, R_1 = 0.0731, wR_2 = 0.1400 for [$I > 2\sigma(I)$], 308 parameters. Flack parameter = [0.14(19)]. For **2**·3CH_4O: $C_{45}H_{50}O_7P_2Br_2$, M = 924.61, Monoclinic, $P2_1$, a = 9.3604(2), b = 23.4811(5), c = 9.7168(2) Å^3, β = 95.4883(7)°, V = 2125.89(8) Å^3, Z = 2, D_c = 1.444 g cm^{-3}, μ(Mo–Kα) = 0.71073 Å, T = 150(2) K, 16969 reflections collected, 9299 independent reflections [R(int) = 0.0766], F^2 refinement, R_1 = 0.0609, wR_2 = 0.1466 for [$I > 2\sigma(I)$], 508 parameters. The absolute structure was correctly indicated by the Flack parameter being zero within experimental error [0.020(9)]. For **4**·C_2H_3N: $C_{36}H_{37}BF_4N_3O_2P_2Rh$, M = 795.35, Monoclinic, $P2_1$, a = 10.2793(2), b = 15.1367(4), c = 11.5954(4) Å^3, β = 100.7005(12)°, V = 1772.81(8) Å^3, Z = 2, D_c = 1.490 g cm^{-3}, μ(Mo–Kα) = 0.71073 Å, T = 150(2) K, 16148 reflections collected, 6563 independent reflections [R(int) = 0.0477], F^2 refinement, R_1 = 0.0312, wR_2 = 0.0698 for [$I > 2\sigma(I)$], 445 parameters. The absolute structure was correctly indicated by the Flack parameter being zero within experimental error [−0.04(2)].CCDC 230131–230134. See http://www.rsc.org/suppdata/cc/b4/b401301h/ for crystallographic data in .cif or other electronic format.

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