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Preparation of Optically Pure 1,2,5-Triphenylphospholane. Use as Ligand for Enantioselective Transition-Metal Catalysis.

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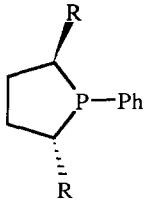
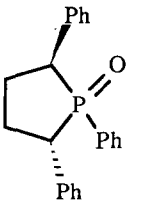
Abstract: *Base-catalyzed isomerization of achiral (E,E)-1,2,5-triphenylphospholane oxide leads to the racemic (E,Z)-isomer. Resolution by Supercritical Fluid Chromatography (SFC) followed by reduction gives the two enantiomers. The activity of this new ligand is tested in palladium-catalyzed coupling of cyclohex-2-enyl acetate with nucleophiles.*

Monophosphine ligands have been less useful than chelating biphosphines in enantioselective transition-metal catalysis.[1] In palladium-catalyzed coupling of allyl acetates and phenylzinc chloride however, monophosphines showed higher reactivity and enantioselectivity than chelating diphosphines.[2] Optically active monophosphines have been shown to be efficient chiral inductors (up to 80%ee) in Ziegler-Natta type nickel complexes for the hydrovinylation reaction (codimerization between ethylene and cycloocta-1,3-diene or norbornene).[3] Basic phosphines such as dialkylarylphosphines or trialkylphosphines have been reported to display better catalytic activity than alkyldiarylphosphines or triarylphosphines in rhodium-catalyzed hydrogenation of simple, non-functionalized ketones.[4] Moreover optically active monophosphines (such as menthyldimethylphosphine) have been used for the resolution of cyclododecatrienylnickel(0) complex.[5]



1a: R = Ph
1b: R = Me
1c: R = Et
1d: R = iPr

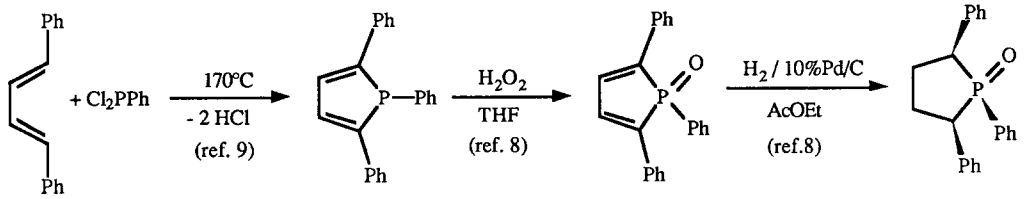


2

Recent reports on the preparation and use of 1-phenyl-2,5-dialkylphospholanes **1** (**1b-d**, R=Me,[6,7] Et, iPr[7]) prompted us to disclose our work dealing with the preparation of racemic (*E,Z*)-1,2,5-

triphenylphospholane oxide **2**, its resolution and the reduction of each enantiomer to give optically pure **1a** (R = Ph). Some preliminary results concerning the use of **1a** as ligand for transition-metal complexes in enantioselective catalytic organic reactions are also reported.

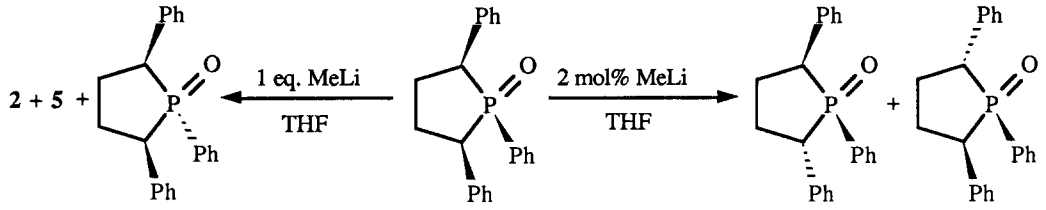
The synthesis of racemic 1,2,5-triphenylphospholane oxide **5** (Scheme 1) has already been reported by Ezzell and Freedman, but with no indication about the stereochemistry of the product.[8] 1,2,5-triphenylphosphole **3** was readily prepared according to a reported procedure,[9] oxidized (H_2O_2, THF) and quantitatively hydrogenated (10%Pd/C, AcOEt)[8] to give a stereochemically homogeneous compound **5**. ^{13}C NMR data indicate a symmetry plane in the molecule and hence a *cis* relationship between the two phenyl substituents in 2 and 5 positions.[10] The stereochemistry at phosphorus was tentatively assigned as (*E,E*), assuming a coordination of the substrate **4** by its less hindered face on the heterogeneous hydrogenation catalyst.



3 **4** **5**

Scheme 1: Synthesis of (*E,E*)-1,2,5-Triphenylphospholane oxide **5**

Isomerization of this compound with one equivalent of methyl lithium in THF at room temperature gave a mixture of the starting material and two new diastereoisomers, the other achiral (*Z,Z*)-**6** [^{31}P NMR ($CDCl_3$): δ = 42.5 ppm relative to 85% H_3PO_4] and the expected chiral (*E,Z*)-**2** (Scheme 2). Equilibration in the presence of catalytic amounts of methyl lithium (2 mol%) as a base afforded **2** as the sole product. On proper concentration conditions (0.5 M), **2** crystallized out and could be readily recovered from the THF solution by filtration. ^{13}C NMR data indicate no symmetry plane in the molecule, in agreement with a *trans* relationship between the two phenyl substituents in 2 and 5 positions.[11]



6 **5** **2** (racemic)

Scheme 2: Isomerizations of (*E,E*)-**5**

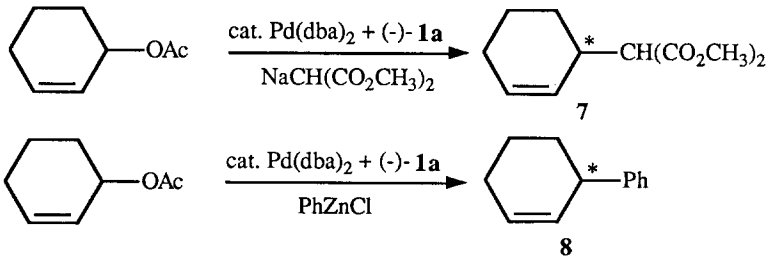
Calculations of the relative energies of **2**, **5** and **6** by a molecular modeling program (PCmodel, MMX program) indicated that, among the three isomers, (*E,Z*)-**2** was favored over (*E,E*)-**5** by 11.4 KJ.mol^{-1}, and over (*Z,Z*)-**6** by 13.2 KJ.mol^{-1}.

Analytical enantiomer separation of **2** was carried out by liquid chromatography (LC) using the previously described [12] chiral stationary phase (S)-thio-DNB-Tyr-E . However, due to the low (α = 1.1) separation factor value, preparative separation was performed by chiral SFC (Supercritical Fluid

Chromatography) [carbon dioxide with a polar modificator as eluent].[13] Each enantiomer could be obtained enantiomerically pure (>99%ee)[14] by a single recrystallization (EtOH: H_2O 60:40) from an elution fraction showing 84% ee.

Since the phosphorus atom is not a stereogenic center in (*E,Z*)-**2**, one has not to pay attention to the stereochemistry of reduction of **2**. However one should avoid epimerization at benzylic carbon atoms C2 or C5 which would either produce the (*Z,Z*)-**6** or (*E,E*)-**5** diastereomer or lead to enantiomerization of **2**. From this point of view, both phenylsilane and $LiAlH_4$ gave satisfactory results. The phospholane **1a** obtained by reduction of (-)-**2** with these reagents was enantiomerically pure (as shown by chiral HPLC analysis of the reoxidation product from **1a**).

Activity and enantioselectivity of phospholane (-)-**1a** [^{31}P NMR ($CDCl_3$): δ = 21.2 ppm relative to 85% H_3PO_4] as ligand were evaluated in the following palladium-catalyzed allylic coupling reactions of cyclohex-2-enyl acetate with sodium dimethylmalonate and phenylzinc chloride:



The catalyst was prepared *in situ* by stirring a THF solution of bis(dibenzylideneacetone)palladium(0) and crude (-)-**1a** (1:2 ratio) resulting from $PhSiH_3$ reduction of enantiomerically pure (-)-**2**. The catalytic activity was very high, the reaction led rapidly to allylated dimethylmalonate **7** (74% isolated yield) and 3-phenylcyclohexene **8** (60% isolated yield) respectively, as a single product in each case. Unfortunately, the enantioselectivities were low (10% ee in each case), but comparable to reported results [6% ee for **7** using (+)-DIOP[15] as chiral ligand and 9.4% ee for **8** with (+)-NMDPP].[16]

Work is currently in progress in our laboratory to find out appropriate reactions using this new chiral phosphine ligand.

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10. Selected data for compound **5** (in $CDCl_3$):
^1H NMR (δ, ppm): 2.5-2.8 (4H, m), 4.0 (2H, dt, J 24 and 9 Hz), 7.0-7.3 (15 H, m).
^{13}C NMR (non aromatic carbons) (δ, ppm): 26.6 (d, C3 and C4, $^2J_{^{31}P-^{13}C}$ 11 Hz), 47.4 (d, C2 and C5, $^1J_{^{31}P-^{13}C}$ 60 Hz): carbons 2 and 5 (as 3 and 4) are magnetically equivalent.
^{31}P NMR: δ = 61.7 ppm relative to 85% H_3PO_4.
11. Selected data for compound **2** (in $CDCl_3$):
^1H NMR (δ, ppm): 2.1-2.4 (1H, m), 2.4-2.9 (3H, m), 3.6 (1H, dt, J 12 and 8 Hz), 3.9 (1H, ddd, J 25, 12 and 7 Hz), 7.0-7.3 (15 H, m).
^{13}C NMR (non aromatic carbons) (δ, ppm): 27.9 (d, C3 or C4, $^2J_{^{31}P-^{13}C}$ 8 Hz), 31.6 (d, C3 or C4, $^2J_{^{31}P-^{13}C}$ 7 Hz), 46.8 (d, C2 or C5, $^1J_{^{31}P-^{13}C}$ 62 Hz), 51.0 (d, C2 or C5, $^1J_{^{31}P-^{13}C}$ 62 Hz): carbons 2 and 5 (as 3 and 4) are not magnetically equivalent.
^{31}P NMR: δ = 53.6 ppm relative to 85% H_3PO_4.
Elemental Analysis: found C, 79.25; H, 6.44; P, 9.15. $C_{22}H_{21}OP$ calc.: C, 79.26; H, 6.35; P, 9.29.
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