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Enantiomerically pure 1,2,5-triphenylphospholane through the synthesis and resolution of the chiral *trans*-(2,5)-diphenylphospholanic acid

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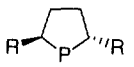
Abstract

The synthesis and resolution of *trans*-(2,5)-diphenylphospholanic acid **7** is described. The phosphinic acid **7** was converted into optically active (1,2,5)-triphenylphospholane **5** which was used as a chiral ligand in Rh-catalyzed hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester to give quantitative yield of methyl N-acetylphenylalaninate with 82 % e.e.

Keywords : Phospholanes, Phosphinic acid and derivatives, enantioselection, asymmetric hydrogenation

Asymmetric hydrogenations, hydrosilylations and C-C bond forming reactions are well developed using homogeneous catalysis with transition metal complexes bearing diphosphines as chiral ligands [1,2]. Among the recently devised chiral diphosphine ligands, a number incorporate the phospholanyl skeleton as a common structural motif [3-11]. Noteably, Burk synthesized [4,5] and developed the use [6] of 1,2-bis(2,5-dialkylphospholanyl)benzene, (DuPHOS) and 1,2-bis(2,5-dialkylphospholanyl)ethane (BPE) which incorporate the *trans*-2,5-disubstituted phospholanyl framework **1** (scheme 1). Since then a number of diphosphines have been described wich have two linked (2,5-dimethylphospholanyl) fragments of the same configuration [10,11].



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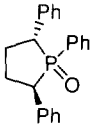

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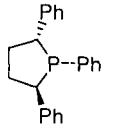

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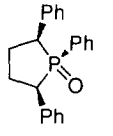

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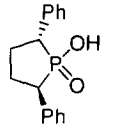

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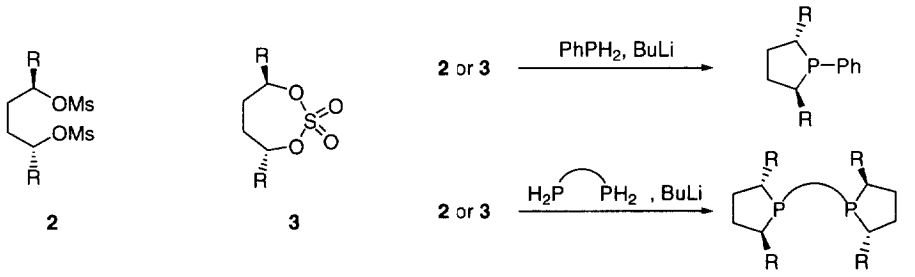
Aiming at the building of the trans-2,5-diphenylphospholanyl framework (**1**, R = Ph), we found that Burk's procedure [4,5] (scheme 1) was not convenient as both the cyclic sulfate **2** (R=Ph) and dimesylate **3** (R=Ph) suffered elimination on treatment with $PhPH_2$ / BuLi to afford the 1,4-diphenylbuta-1,3-diene.



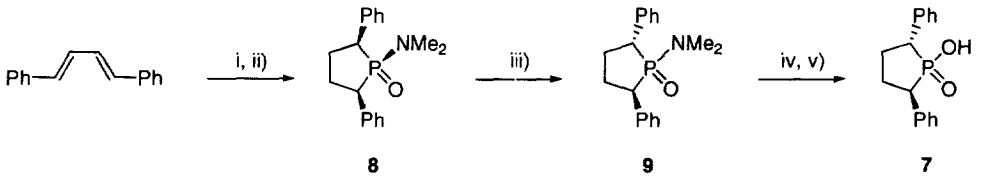
Scheme 1. Synthesis of DuPHOS and BPE according to Burk (R =Me, Et, Pr, *i*-Pr)

We previously reported the synthesis of *trans*-(2*R**,5*R**)-1-oxo-1,2,5-triphenylphospholane **4**, its resolution and subsequent reduction to optically active phospholane **5** by a different synthetic scheme [12]. However, as the resolution procedure (preparative chiral liquid chromatography) of **4** was not practical on a gram scale, we looked for an easier access to enantiomerically enriched **4**. As the asymmetric sparteine-lithium promoted deprotonation / acetic acid protonation sequence of the *meso r*-1-oxo-1,*t*-2,*t*-5-triphenylphospholane **6** could only produce optically active material **5** with a maximum of 45 % e.e. [13], we turned to the synthesis of the corresponding 1-hydroxy-*r*-1-oxo-*c*-2,*t*-5-diphenylphospholane **7** and its resolution through crystallization of diastereomeric salts.

We now report the synthesis and resolution of *trans*-(2,5)-diphenylphospholanic acid **7**, its conversion to optically active (2*R**,5*R**)-(1,2,5)-triphenylphospholane-1-oxide **4** and the reduction of **4** to give the corresponding phosphine **5**.

Reaction of commercially available (*N,N*-diisopropylamino)dichlorophosphine with 1,4-diphenylbuta-1,3-diene afforded 1-(*N,N*-dimethylamino)-*r*-1-oxo-*t*-2,*t*-5-triphenyl-phosphol-3-ene which was hydrogenated to give the corresponding phospholane **8** (scheme 2). Isomerization of **8** to the more stable *trans* isomer **9** was carried out in methanol, with an excess of sodium methoxide. Phospholanic acid **7** was obtained by the acid-promoted hydrolysis of amide **9** and was readily resolved by crystallization of the diastereomeric quinine salts[1].

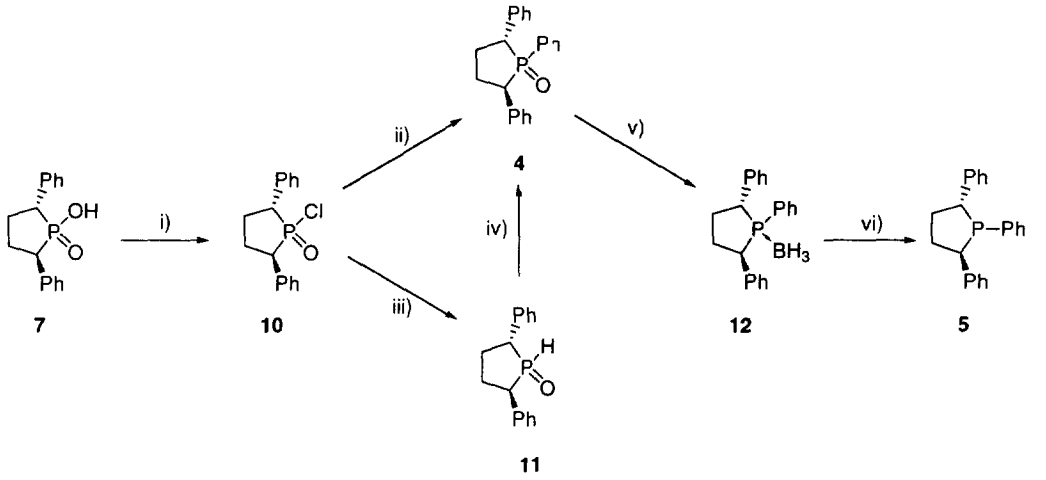
[1] The enantiomeric purity of **7** could be checked as its methyl ester by chiral chromatography (Regis® (*S,S*)-Whelk 01 column with dichloromethane/n-hexane/isopropanol (5/4/1) as eluent). Selected data for (-)-**7** : mp 269-270 °C. $[\alpha]_D^{25}$ = -102.7 (c = 0.6, CH_2Cl_2). ^1H NMR (CD_3OD) : 7.2-7.0 (10H, m) 3.2-3.0 (2H, m) 2.4-1.9 (2H, m). ^{13}C NMR (CD_3OD) : 138.0 (d, J = 5.7 Hz) 129.7 (d, J = 5.5 Hz) 129.5 (d, J = 1.9 Hz) 127.7 (d, J = 2.4 Hz) 47.0 (d, J = 87.0 Hz) 30.2 (d, J = 11.9 Hz). ^{31}P NMR (CD_3OD) : 66.0 Anal. Calcd for $C_{16}H_{17}O_2P$: C, 70.58 ; H, 6.29 ; P, 11.38. Found : C, 70.48 ; H, 6.33 ; P, 11.08.



i) $(CH_3)_2NPCl_2$, $AlCl_3$, CH_2Cl_2, -10°C, then $NaHCO_3$ / EDTA, 0°C ii) 5% Pd / C, H_2 (30-50 atm.), CH_2Cl_2, 16 h, 65%(two steps). iii) MeONa (5 equiv.), MeOH, amb. temp., 16 h, quant. iv) aq. HCl, MeOH; v) quinine, 1 equiv., separation of diastereomeric salts, 40%

Scheme 2. Synthesis of the *trans*-(2,5)-diphenylphospholanic acid.

1-Oxo-1,2,5-triphenylphospholane **4** was obtained by one of two different procedures from chloride **10** (scheme 3), either by coupling with the diphenyl lithiocuprate, or via reduction to the secondary phosphine oxide **11** followed by a palladium-catalyzed coupling with phenyl iodide. The stereochemical integrity (diastereomeric and enantiomeric purity) of **4** could be checked by chiral HPLC analysis[2]. The oxide **4** was converted to the air-stable borane complex **12** of the optically active *trans*-(2,5)-diphenylphospholane **5** through a reduction / complexation sequence. The free phosphine **5** was regenerated from **12** by reaction with half an equivalent of DABCO in toluene.

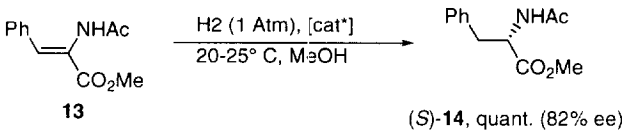


i) $(COCl)_2$, THF, quant.; ii) Ph_2CuLi, - 78°C, THF, 65 %; iii) DiBAl-H, 63% ; iv) PhI, iPr_2NEt, 5 mol% $[Pd(dba)_2]$, 7.5 mol% dppp, 88 %; v) $LiAlH_4$, $CeCl_3$, then BH_3-THF 73 %; vi) DABCO, toluene, quant.

Scheme 3. Synthesis of the optically active (1,2,5)-triphenylphospholane.

The phospholane **5** was examined as a chiral ligand in rhodium-catalyzed hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester **13**. Hydrogenation at atmospheric pressure using 1 mol % of $[RhCl(cod)]_2$ and 2.1 mol % (+)-**5** (*in situ* catalyst) gave (*S*)-**14** in quantitative yield and 82 % e.e., as determined by chiral hplc.

[2] Daicel® Chiralcel OD-H column with *n*-hexane/isopropanol (3/1) as eluent



13 (*S*)-**14**, quant. (82% ee)

[cat*] = $[Rh(COD)Cl]_2$ + 2.1 eq. (+)-**5** / Rh

This result compares favorably with those obtained using P-chiral monophosphines (85 % ee in the Rh-catalyzed hydrogenation of the corresponding acid with o-anisylcyclohexylmethylphosphine as the ligand) [14] and other phospholanes (60% ee in the Rh-catalyzed hydrogenation of **13** with *trans*-(2,5)-dimethyl-1-phenylphospholane **2** (R = Me)) [4].

Work is in progress to apply the synthetic procedures to other monophosphines and diphosphines containing the chiral trans-2,5-diphenylphospholanyl framework and evaluate them as chiral ligands in various enantioselective metal-catalyzed reactions.

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