The First Stereoselective Synthesis of Chiral Halogenophosphines: Optically Active *tert*-Butyl(phenyl)chlorophosphine

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The reaction of optically active *tert*-butyl(phenyl)(methylthio)chlorophosphonium trifluoromethanesulfonate **1** with tris(*N,N*-dimethylamino)phosphine at low temperature was found to give, stereoselectively, optically active *tert*-butyl(phenyl)chlorophosphine; when the salt **1** was treated with triphenylphosphine optically active *tert*-butyl(phenyl)chlorophosphine and methyl *tert*-butyl(phenyl)phosphinothioite were obtained as the result of the respective desulfurization and dehalogenation processes.

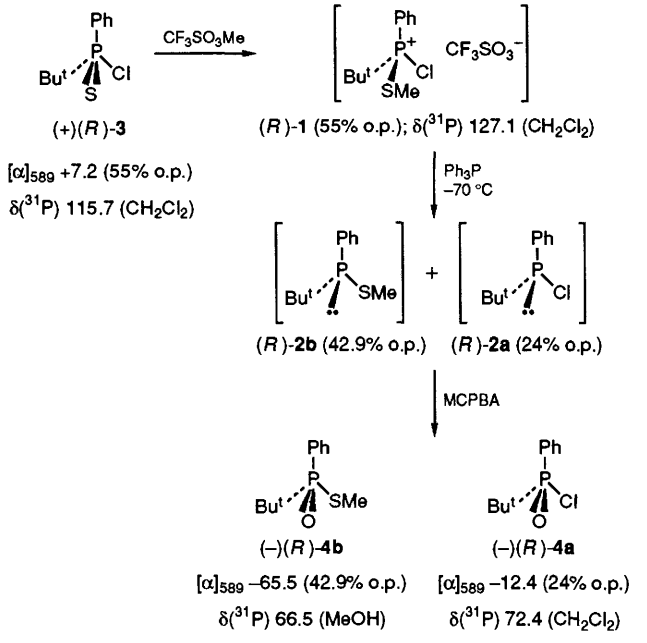
Thirty years ago Horner *et al.*[1] demonstrated for the first time the configurational stability of trigonal pyramidal three-coordinate phosphorus compounds by preparation of the optically active tertiary phosphines. However, other classes of optically active P^{III} derivatives containing P–O, P–S or P–N bonds have been obtained only recently by asymmetric[2] or stereoselective syntheses.[3]

The first attempts to synthesize the optically active chlorophosphines were undertaken by Horner and Jordan[4] who studied the reaction of optically active aminophosphines with hydrogen chloride, phosphorus trichloride and acyl chlorides or fluorides. The formation of racemic halogenophosphines was observed in all these reactions. According to the authors, these reactions were stereoselective by nature but the halogenophosphines racemized as a result of either intra- or inter-molecular displacement reactions at the phosphorus atom.

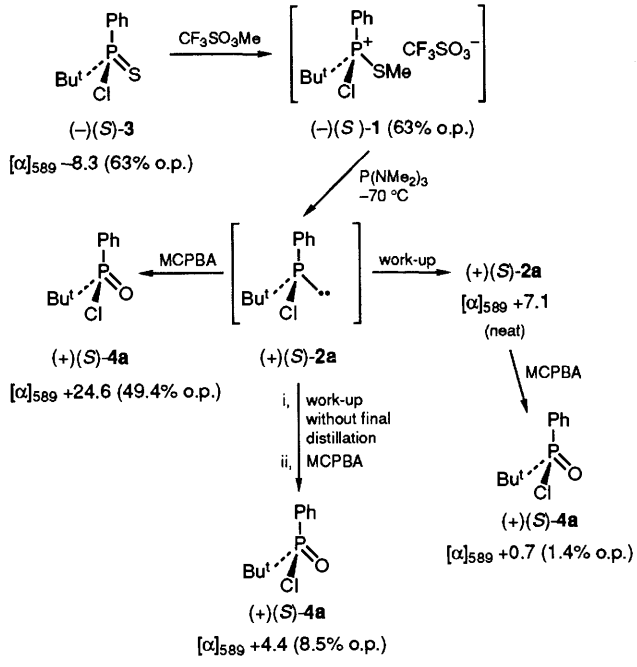
Recently, we reported[5] that the halogenophosphonium salts undergo desulfurization with triphenylphosphine at room temperature or under reflux in a methylene chloride solution giving chiral, racemic alkylaryl- or diaryl-chlorophosphines. Therefore, it was expected that application of this method for the synthesis of optically active chlorophosphines may be more advantageous than Horner's procedure for at least two important reasons: the chloride anion which is responsible for the racemization is absent from the reaction medium, and the reaction can be carried out under very mild conditions at *ca.* −70 °C. Moreover, we decided to use in this study the optically active chlorophosphonium salt **1**, possessing a *tert*-butyl group directly bonded to the phosphorus atom to slow down eventual racemization *via* both intra- or intermolecular displacement reactions.

We found that the reaction of the optically active *tert*-butyl(phenyl)chloro(methylthio)phosphonium triflate **1** with triphenylphosphine at −70 °C yields unexpectedly two products: optically active *tert*-butyl(phenyl)chlorophosphine **2a** and optically active methyl *tert*-butyl(phenyl)phosphinothioite **2b**, both isolated as the stable derivatives **4b** and **4a**, respectively (Scheme 1).

The formation of the optically active derivative **4a** is the first indirect evidence for the existence of the chlorophosphine **2a** in optically active form. Since the oxidation proceeds with retention of the configuration at phosphorus[6] and **4a** and **4b** both have known P-chirality,[7] the chlorophosphine **2a** and *S*-methyl phosphinothioite **2b** should have been formed respectively with retention and inversion of configuration, when compared to the starting salt **1**. The bidirectional course and stereochemistry of the above reaction may be simply explained if a nucleophilic attack by triphenylphosphine on the two electrophilic centres in **1**, phosphorus and sulfur, is



Scheme 1 o.p. = optical purity; ^{31}P NMR reference 85% H_3PO_4



Scheme 2

assumed. As we have earlier demonstrated[3c,d] desulfurization of salts of type **1** involved an attack of the thiophilic nucleophile on the sulfur atom with retention of configuration at the chiral phosphorus centre. On the other hand, the attack of a nucleophile at the phosphorus atom in **1** leads to the phosphinothioite **2b** with inversion of configuration.†

In our earlier work,[3d] we found that tris(*N*,*N*-dimethylamino)phosphine is a very active desulfurization agent and it was thought that its reaction with the salt **1** should give only one product. Indeed, it was gratifying to find that treatment of the optically active salt **1a**, readily available from the optically active compound **3**, with tris(*N*,*N*-dimethylamino)phosphine at −70 °C yielded after standard isolation‡ optically active *tert*-butyl(phenyl)chlorophosphine **2a**, $[\alpha]_{589}$ +7.1 (neat) (Scheme 2).

In order to determine the optical purity of the optically active chlorophosphine **2a** obtained, the distilled product (pure according to ^{31}P NMR spectra) was oxidized with *m*-chloroperbenzoic acid (MCPBA) to give **4a** with known optical purity and chirality at phosphorus.[7]

As can be seen, the first successful synthesis of an optically active chlorophosphine gave the product **2a** of rather low optical purity. In order to find out whether the low optical purity is due to racemization of **2a** during work-up, we oxidized the crude reaction mixture directly after addition of tris(*N*,*N*-dimethylamino)phosphine at −70 °C. In this case, (+)(*S*)-**4a**, isolated by TLC, exhibited much higher optical purity (49.4%) corresponding to a stereoselectivity of 78%. Moreover, it was found that the optical activity of **2a** is lowered during distillation by a factor of six (compare the optical purity of **4a** obtained by oxidation of the distilled **2a** with that prepared from **2a** just before distillation). It is noteworthy that the optically active (+)(*S*)-butyl(phenyl)-chlorophosphine **2a** appeared to be moderately optically stable at room temperature; it slowly racemized in a polarimeter tube, showing after 20 h a complete loss of optical activity.

These observations strongly indicate that in spite of the presence of a bulky group at the phosphorus atom in **2a**, racemization is still a pronounced process, particularly at higher temperature. Intermolecular ligand exchange seems to be the most likely mode of racemization.

In summary, the method described herein for the synthesis of optically active *tert*-butyl(phenyl)chlorophosphine **2a** is general and may be applied for the synthesis of other chiral halogenophosphines.

The author thanks Prof. M. Mikołajczyk for his interest in this work.

Received, 3rd August 1992; Com. 2/04146D

† On the basis of the following sequence: (+)(*R*)-**3**, $[\alpha]_{589}$ + 8.0 (61.1% op. pur.), triflate, → [(+)(*R*)-**1**], −OH, room temp., → (−)(*R*)-**5**, $[\alpha]_{589}$ −88.7 (58.1% op. pur.) we found that hydrolysis of **1** yields exclusively the phosphinothiolate **5** with inversion of configuration and 95% stereoselectivity.

‡ A standard isolation of **2a** consisted in evaporation of dichloromethane *in vacuo*, extraction of the residue with diethyl ether, concentration of the ethereal solution and final distillation. All these operations were carried out in an inert atmosphere and at low temperature (*ca.* 0 to −10 °C).[5]

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