Stereochemistry of Nucleophilic Substitution at the Optically Active Trivalent Phosphorus Atom

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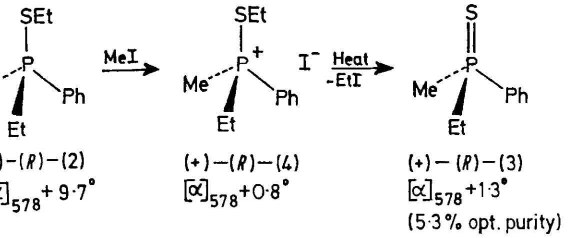
Summary Optically active *O*-methyl ethylphenylphosphinite (**1**) and *S*-ethyl ethylphenylthiophosphinite (**2**) have been shown to react with nucleophilic reagents like methyl-lithium and sodium methoxide with inversion of configuration at the chiral P^{III} centre.

IN contrast to the widely investigated stereochemistry of nucleophilic substitution at the optically active tetracoordinated phosphorus atom[1] studies on the steric course of substitution at the optically active trivalent phosphorus atom are only in the initial stage. The first example of the substitution at the optically active P^{III} centre is that by Kyba[2] who found that the replacement of the benzyl group by n-butyl and t-butyl in optically active tertiary phosphines takes place with almost complete inversion at phosphorus. However, further studies in this field were limited because of the lack of other suitable optically active P^{III} compounds. Our recent successful asymmetric synthesis of the optically active trivalent phosphorus acids esters[3] and their relative optical stability enabled us to perform the nucleophilic reactions at the P^{III} centre and to extend stereochemical studies to other leaving groups and nucleophiles.

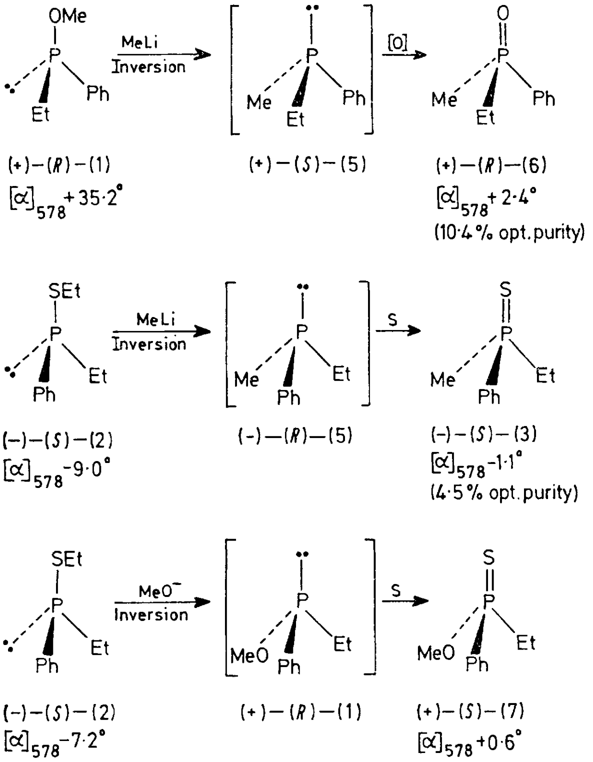
We used in the present study optically active *O*-methyl ethylphenylphosphinite (**1**)[3] and *S*-ethyl ethylphenylthiophosphinite (**2**) as model compounds. The latter has also been obtained by the asymmetric condensation of ethylphenylchlorophosphine with ethanethiol in the presence of (+)- or (−)-*NN*-dimethyl(1-phenylethyl)amine at −70 °C. Its optical purity and absolute configuration has been established by stereospecific conversion into optically active methylethylphenylphosphine sulphide (**3**) (Scheme 1). Thus, (+)-(**2**), $[\alpha]_{578}$ +9·7°,† δ_P −28·7 p.p.m., was treated with an excess of methyl iodide under reflux to give the corresponding phosphonium salt (+)-(**4**), $[\alpha]_{578}$ +0·8°, δ_P −55·8 p.p.m., which was subsequently converted on heating at 120 °C into (+)-phosphine sulphide (**3**), $[\alpha]_{578}$ +1·3° (5·3% opt. purity), having the (*R*) chirality at phosphorus.[4] Since methylation of (+)-(**2**) proceeds with retention of configuration at phosphorus and bonds around phosphorus are not broken on going from (+)-(**4**) to (+)-(**3**), the chirality at phosphorus in (+)-(**2**) is assigned as (*R*).



Scheme 1

When (+)-(*R*)-(**1**), $[\alpha]_{578}$ +35·2°, was treated with 0·8 molar excess of methyl-lithium in ether at −25 °C the crude optically active methylethylphenylphosphine (**5**), δ_P +33·8 p.p.m., was isolated in 37% yield. In order to estimate its optical purity as well as the chirality at phosphorus it was further oxidised by means of *m*-chloroperbenzoic acid to give (+)-(*R*)-methylethylphenylphosphine oxide (**6**), $[\alpha]_{578}$ +2·4° (10·4% optical purity).[5] Similarly, (−)-(*S*)-(**2**), $[\alpha]_{578}$ −9·0°, on treatment with methyl-lithium in ether at −50 °C gave the optically active phosphine (**5**) (72% yield) which was transformed into (−)-(*S*)-methylethylphenylphosphine sulphide (**3**), $[\alpha]_{578}$ −1·1° (4·5% optical purity).[4] Since oxidation of and sulphur addition to (**5**) take place with retention of configuration at phosphorus, it follows that the optically active phosphine (**5**) formed in the first reaction has the (+)-(*S*)-chirality whereas (−)-(*R*)-(**5**) results from the ester (−)-(*S*)-(**2**). Therefore, the displacement of the methoxy or ethylthio group by methyl-lithium occurs with inversion of configuration at the chiral P^{III} atom and with high stereospecificity (>90%).‡

We have also found that the reaction of (−)-(*S*)-(**2**), $[\alpha]_{578}$ −7·2°, with sodium methoxide in methanol for 3 min at −65 °C resulted in the formation of the optically active ester (**1**) as a transesterification product. In order to establish the stereochemistry of this exchange, the reaction mixture containing both P^{III}-esters (**1**) and (**2**) was treated with sulphur and the resulting optically stable (+)-(*S*)-*O*-methyl ethylphenylphosphinothioate (**7**),[6] $[\alpha]_{578}$ +0·6°, and (+)-(*S*)-*S*-ethyl ethylphenylphosphinodithioate, $[\alpha]_{578}$ −2·2°, were isolated by preparative g.l.c. Since addition of sulphur to the optically active ester (**1**) proceeds with retention of configuration at phosphorus, it is reasonable to assume that the chirality of the ester (**1**) formed from (−)-(*S*)-(**2**) is (+)-(*R*). Hence, the displacement of ethylmercapto-ion from the ester (**2**) by methoxide ion occurs with predominant inversion of configuration at phosphorus. All nucleophilic reactions discussed above are summarized in Scheme 2.



Scheme 2

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† The optical rotation measurements were carried out on a Perkin–Elmer Model 241MC polarimeter with a sensitivity of ±0·002°. Rotations refer to methanol solution for (**3**), (**4**), and (**6**), benzene solution for (**7**) and (**8**), and to neat esters for (**1**) and (**2**).

‡ It has been found that the reactions of (−)-(*S*)-(**1**) and (−)-(*S*)-(**2**) with methylmagnesium iodide occur with inversion at phosphorus but with lower stereospecificity. Thus, from (−)-(*S*)-(**1**), $[\alpha]_{578}$ −40·9°, and (−)-(*S*)-(**2**), $[\alpha]_{578}$ −11·4°, *via* (−)-(*R*)-(**5**), the phosphine sulphide (−)-(*S*)-(**3**) has been obtained having optical rotation −0·4° and −0·5°, respectively.

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