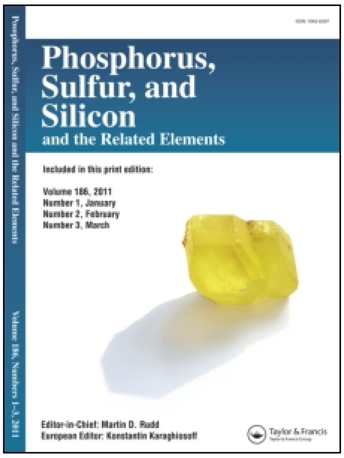

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Pietrusiewicz, K. M. , Zabłocka, M. and Wisniewski, W.(1990) 'Synthesis of Homochiral Phosphorus Compounds: the Chiron Approach', Phosphorus, Sulfur, and Silicon and the Related Elements, 49: 1, 263 — 266
To link to this Article: DOI: 10.1080/10426509008038956
URL: http://dx.doi.org/10.1080/10426509008038956

Phosphorus, Sulfur, and Silicon, 1990, Vols. 49/50, pp. 263-266

SYNTHESIS OF HOMOCHIRAL PHOSPHORUS COMPOUNDS: THE CHIRON APPROACH

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Abstract A large variety of structurally diversified optically active phosphine oxides can be derived from a single readily available homochiral (-)-S-methylphenylvinylphosphine oxide through elaboration of its versatile vinyl functionality.

Optically active compounds possessing stereogenic phosphorus centres find widespread utility as chiral probes in bioorganic and mechanistic studies as well as chiral ligands in asymmetric catalysis. As the Nature fails to supply optically active compounds of this type, their preparation continues to be a challenge to the practitioners in those fields. Most of the existing syntheses of such compounds[1] rely on the individual selection of the chiral auxiliary necessary to obtain effective diastereomeric discrimination in the particular intermediate or target organophosphorus molecule. We wish to demonstrate the efficacy of another approach based on the use of a single suitably substituted homochiral organophosphorus precursor which, by virtue of its non-phosphorus functionalities, could be transformed into a variety of novel structures containing its P-homochiral unit intact.

(-)-S-Methylphenylvinylphosphine oxide 1,[2] which is readily available in multigram quantities, has been chosen as the key substrate for our synthetic explorations. As exemplified in Chart I, many structurally diversified optically active phosphine oxides can be derived from 1 in a very straightforward manner. Base catalyzed conjugate additions of alcohols and thiols to 1 provide the corresponding homochiral adducts with great facility.[3] Similarly, noncatalyzed additions of secondary and primary amines to 1 give good yields of valuable homochiral ß-amino phosphine oxides.[4] Simple carbon centered nucleophiles can also be added to 1 in a conjugate fashion either by mediacy of lithium diorganocuprates[2] or, alternatively, by use of simple alkyl halides, zinc-copper couple and sonication.[5] The two procedures are complementary; the former appears to serve better in the additions of primary alkyl groups whereas the latter gives better yields with secondary and tertiary ones.

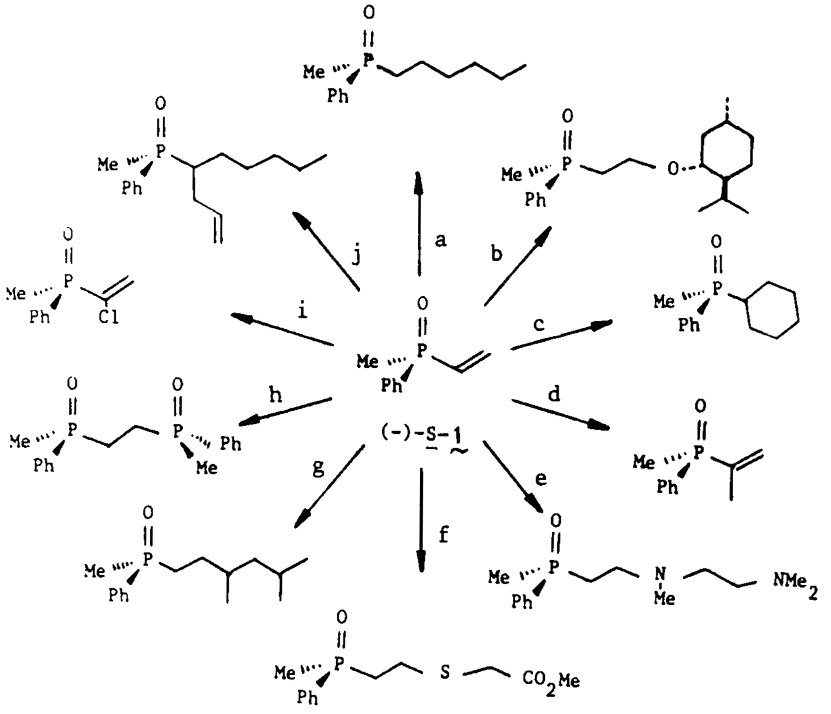


CHART I

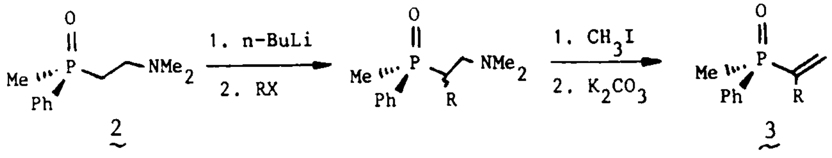
a-Bu$_2$CuLi; 65%. b-L-mentol, NaH cat.; 47%. c-1.CH$_2$=CH-CH=CH$_2$, 160^{o}C. 2.H$_2$, Pd/C; 78%. d-1.Me$_2$NH 2.BuLi 3.CH$_3$I 4.CH$_3$I,K$_2$CO$_3$; 42%. e-Me$_2$NCH$_2$-CH$_2$NHMe; 91%. f-HSCH$_2$CO$_2$Me, KOH cat.; 72%. g-Me$_2$CHCH$_2$CHIMe, Zn(Cu), 71%. h-MePhPHO; 78%. i-1.Cl$_2$ 2.Et$_3$N; 90%. j-1.Bu$_2$CuLi 2.CH$_2$=CHCH$_2$Br; 53%.

Additions of secondary phosphine oxides to **1** offer in turn a ready access to important P-chiral 1,2-diphosphinylethanes and they are best effected thermally.[6] In the additions involving nonsymmetrical secondary phosphine oxides the produced chiral di(tertiary phosphine) oxides constitute the interesting self-resolving systems in which one homochiral phosphorus centre enables resolution of the other.[6] Assignment of the absolute configuration of the newly resolved P-centres in such compounds has been ascertained in one case by the single-crystal X-ray diffraction measurement and can now be done in the others by the comparative spectral and chromatographic analysis.[7]

The use of **1** as a dipolarophile in cycloaddition reactions with nitrones or nitrile oxides[8] or, in the Diels-Alder reaction with dienes,[2] leads to the formation of the optically active phosphine oxides bearing heterocyclic or carbocyclic substituents. Interestingly, in its reaction with cyclopentadiene,[10] 1 shows only little discrimination between an exo and an endo approach. Cycloaddition of 1 to 3,4-dihydro-2,2-dimethyl-2*H*-pyrrole 1-oxide favors however a single mode, which has been determined to be exo.[9]

In addition, electrophilic additions of chlorine or bromine to 1 combined with the subsequent elimination of HCl or HBr from the corresponding adducts have been shown to serve as a convenient route to novel optically active α-halogenovinylphosphine oxides.[11]

Apart from being important target molecules by themselves, some of the prepared homochiral phosphine oxides have also been predestined for further synthetic applications. Amino phosphine oxide 2 for example, can act as a synthetic equivalent of 1 in some metalation reactions requiring the use of a strong base.[12] As typified below, a novel nitrogen-directed metalation of 2 combined with the subsequent alkylation and elimination reactions provides satisfactory yields of alkenylmethylphenylphosphine oxides 3, demonstrating the feasibility of formal α-monoalkylation of 1. Bromovinylphosphine oxide 4 in turn, is not only the apparent precursor of the highly valuable (though elusive)[10] acetylenic phosphine oxide 5 but, it also constitutes a convenient



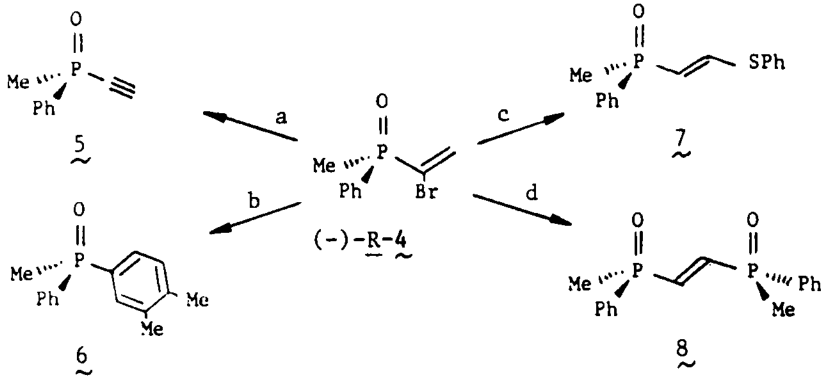


CHART II

a-n-BuLi, -78°C; low yield. b-2,3-Dimethylbutadiene, 180°C, 6h; 23%. c-PhSH, pyridine, reflux, 45h; 33%. d-1.MePhPHO, 110°C 2.Et_3N; 49%.

synthetic equivalent of **5** *per se* (Chart II). For example, the use of **4** in the Diels-Alder reaction with dienes leads directly to diaryl(methyl)-phosphine oxides (e.g., **6**) albeit in low yields.[10] Reaction of thiophenol with bromo oxide **4** in refluxing pyridine furnishes directly optically active *trans*-methylphenyl(2-phenylthiovinyl)phosphine oxide **7**,[11] formally securing also an access to the corresponding sulfinyl and sulfonyl derivatives, which can be obtained from **7** via simple adjustment of the oxidation level of sulfur. Furthermore, reactions of **4** with nonsymmetrical secondary phosphine oxides carried out in the presence of amine result in the formation of the optically active *trans*-1,2-diphosphinylethenes possessing two, either equivalent or non-equivalent, homochiral phosphorus centres.[11]

In conclusion, it is interesting to note that in the presented syntheses the starting oxide **1** acts as a typical chiron (P_1). In all the synthesized compounds the entire structural entity of **1** is indeed incorporated with the original chirality at phosphorus fully preserved. By the same token, unsaturated dioxide **8** should be equally useful as a P_2-chiron and studies along this line are in progress.

Acknowledgement We wish to thank Prof. Jan Michalski for his kind interest in this project (CPBP-01.13).

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