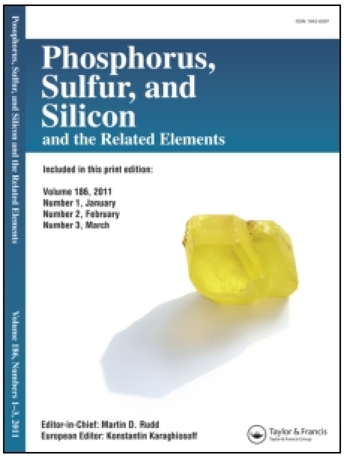

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Reactions of Chiral Phosphorous Acid Diamides

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REACTIONS OF CHIRAL PHOSPHOROUS ACID DIAMIDES

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Abstract: Chiral phosphorous acid diamides were prepared from chiral C_2 diamines *via* the sequential addition of PCl_3 and H_2O. Alternatively, addition of PCl_3 and hydrogen sulfide yielded the analogous thiophosphorous acid diamides. Deprotonation of the phosphorous acids under a variety of conditions gave the anions which reacted smoothly with alkyl halides to give phosphonamides in good yield. Reaction of the anions with aldehydes gave α-hydroxy-phosphonamides in good yield and with modest diastereoselectivity (1:1 - 25:1 ds). Treatment of the phosphorous acids with trialkylsilyl triflates and Hunnig's base gave the product of O-silylation.

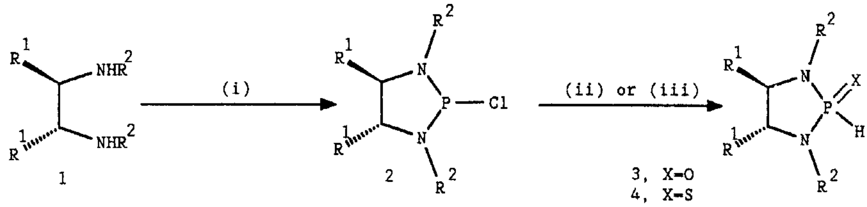
INTRODUCTION

Recently the use of organophosphorus compounds as chiral auxiliaries has attracted the attention of organic chemists.[1-6] In 1984 Hanessian and co-workers[1] used a chiral bicyclic phosphonamide to perform asymmetric olefinations on achiral axially symmetric ketones. In two very recent publications,[2] Hanessian reported further studies of this asymmetric alkylation chemistry. The C_2 symmetry of the bicyclic phosphonamides is particularly attractive and removes the need for isomer separation in the preparation of the starting phosphorus compounds. The application of chiral phosphorus auxiliaries continues to expand[7] with the introduction of new reactions and new classes of phosphorus reagents.

An intriguing possibility is the stereoselective introduction of a chiral center at carbon by the controlled formation of a phosphorus-carbon bond. The addition of chiral phosphites to an imine had been reported,[6] but the diastereoselectivity was low. Amides derived from C_2 diamines appeared to offer a greater chance for success. We began a study of the preparation and reactivity of chiral phosphorous acid diamide derivatives and their applications in stereoselective synthesis.

DISCUSSION

We prepared a series of chiral diamines **1a-i** with C_2 symmetry. These are, in general, readily accessible by the N-substitution of the available parent systems.[8] Condensation of diamines **1a-i** with PCl_3 gives the chlorides **2a-i**. Addition of one equivalent of water to the crude chlorides **2a-i** in toluene solution generates the crystalline chiral phosphorous acid diamides **3a-i**. Alternatively, addition of hydrogen sulfide to **2a** and **2c** under similar conditions yields the thiophosphorous acids **4a** and **4c**. The ^{31}P NMR resonances for the phosphorous acids **3a-i** are found in the range +14.8 to +32.9 ppm, and at +62.5 and 70.6 ppm for the thiophosphorous acids **4a** and **4c**, respectively. The ^1H NMR spectra contain a characteristic doublet for the P-H group in the range 6.5 to 8 ppm for the oxo acids and 7.3 to 9.2 ppm for thioacids. The P-H coupling constants are between 550 and 600 Hz.

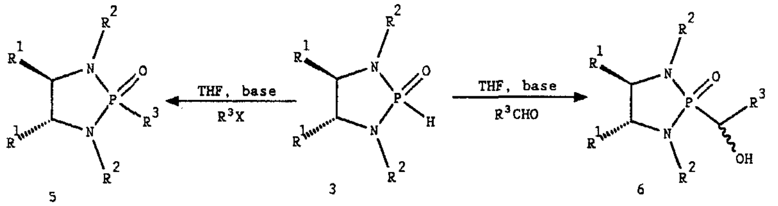


	R^1	R^2
a	1,2-cyclohexyl	$PhCH_2$
b	1,2-cyclohexyl	Me
c	1,2-cyclohexyl	Me_3CCH_2
d	1,2-cyclohexyl	Ph
e	1,2-cyclohexyl	2-Me-$C_6H_4CH_2$
f	1,2-cyclohexyl	2,4,6-Me_3-$C_6H_2CH_2$
g	1,2-cyclohexyl	$(Me)_2CH$
h	Me	$PhCH_2$
i	Ph	$PhCH_2$

Reagents: i) PhMe, Et_3N, PCl_3, -78°C / room temp.; ii) PhMe, Et_3N, H_2O, -78°C / room temp.; iii) PhMe, Et_3N, H_2S, room temp.

The lower homologue phosphorous acid diamides, $(Me_2N)_2P(O)H$ and $(Et_2N)_2P(O)H$, were studied by Nifant'ev[9] and others[10] and were reported to be less reactive than the corresponding dialkyl phosphites, a property attributed, by Nifant'ev, to the low acidity of the P-H bond and the low solubility of the corresponding metal (K, Na, Li) salts. In a very recent study Modro and co-workers[11] observed that these parent acids *could be* alkylated in good yield by treatment with *n*-BuLi and haloalkanes in THF solution.

Our results indicate that the more complex chiral phosphorous acids **3a-i** will undergo deprotonation with ease and that the resulting metal salts react smoothly with electrophiles. The lithium salts are alkylated[12] in THF solution at -78°C to give *a new series of chiral phosphonamides* **5**. The choice of base appears critical for success. Acid **4a** (R^2=$PhCH_2$) gives comparable yields with both *n*-BuLi and LDA, whereas acid **4b** (R^2=Me) gives superior yields and cleaner products with LDA. In comparison, the acid **4c** (R^2=Me_3CCH_2) is deprotonated only with *n*-BuLi. This trend is probably a function of the steric environment of the acidic hydrogen. Addition of the anions to aldehydes occurs with modest selectivity (up to 25 : 1). The diastereoisomeric pair **6** are easily distinguished from each other by ^{31}P NMR spectroscopy, therefore providing a simple method for determination of the isomeric ratios.

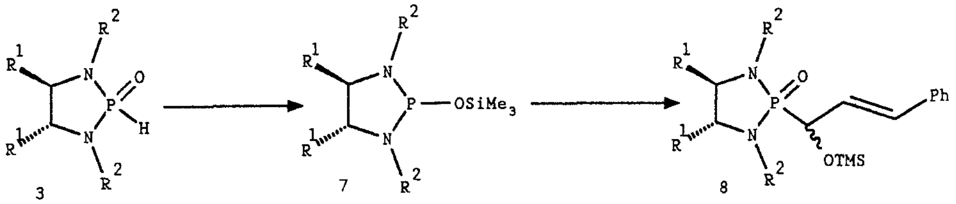


R^3 = $PhCH_2$, $CH_2CH{=}CH_2$, Me, Et

R^3 = Ph, CH=CHPh, 1-Naphth, 2-Naphth, $(CH_2)_4CH_3$, $CH{=}CHCH_3$, $CH{=}CH_2$, $C(CH_3){=}CH_2$.

The phosphorous acid **4c** [R^1= 1,2 cyclohexyl, R^2= Me_3CCH_2] is observed to give the highest diastereoselectivity (7 : 1 to 25 : 1). The isomeric mixture of α-hydroxy-phosphonamides, derived by addition of acid **4c** to cinnamaldehyde, can be crystallized to isomeric purity. An X-ray structure determination of the major isomer arising from the S,S diamine reveals that the relative configuration of the new stereocenter is R.

Treatment of the phosphorous acids with TMSOTf and Hunnig's base in an inert solvent yields the trimethylsilyl phosphorimidite[13] **7** *via* O-silylation. Trimethylsilyl chloride is also an effective reagent, but the reaction is much slower and additional impurities are formed. The phosphorimidite **7** prepared in this way reacts with aldehydes. The reaction appears to be nonselective and is greatly accelerated by excess TMSOTf. The thioacids are unreactive to silylation under similar conditions.



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