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Asymmetric Synthesis of α-Hydroxy- Phosphonamides, Phosphonates and Phosphonic Acids

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Abstract: The addition of the anion of the bicyclic chiral phosphorous acid diamide **1a** to aldehydes in THF solution gave α-hydroxy phosphonamides in good yield and good diastereoselectivity (54-93% de). The phosphonamides were hydrolyzed with aqueous HCl in dioxane to give α-hydroxy phosphonic acids. Methylation of the resulting phosphonic acids with diazomethane gave α-hydroxy dimethyl phosphonates without loss of stereochemical integrety.

α-Hydroxy phosphoryl compounds (phosphonates and phosphonic acids) are biologically active and have been shown to inhibit enzymes such as renin,[1] EPSP synthase,[2] and HIV protease.[3] In addition, α-hydroxy phosphonates are useful intermediates in the synthesis of other α-substituted phosphonates and phosphonic acids.[4] The absolute configuration at the α-position in substituted phosphonic acids has been shown to be important for biological activity.[5] Allylic α-hydroxy phosphonates can also serve as precursors, via 1,3 interchange of functionality, for biologically active γ-substituted phosphonates and phosphonic acids.[6] In contrast to the more extensively studied α-amino phosphoryl compounds,[7] chiral, non-racemic hydroxy phosphoryl compounds have only recently begun to receive attention.[8]

Encouraged by the earlier success of Hanessian and coworkers in applying the α-carbanions of chiral bicyclic phosphonamides to asymmetric olefinations[9] and the synthesis of α-substituted phosphonic acids,[10] we began an study of chiral phosphorous acid diamides as potential asymmetric phosphonylating agents. We recently reported the preparation and alkylation[11] of chiral phosphorous acid diamides **1**. These stable and generally crystalline compounds were easily prepared by the addition of N,N'-disubstituted C_2 diamines to PCl_3, followed by addition of water to the resulting chlorophosphine diamide [11a] Treatment of the phosphorous acid diamides **1** in THF solution with strong base resulted in the formation of the acid anion. The lithium salts were prepared using *n*-BuLi, LDA or $LiN(SiMe_3)_2$ as base. However, varying amounts of an impurity are formed with *n*-BuLi, probably resulting from addition of butyl to the phosphoryl group. Once formed at −70 °C the anions were stable in solution up to room temperature. The diastereoselective addition of the anions to aldehydes was examined [12] The neopentyl substituted diamide **1a** was found to react with several aldehydes to give 1-hydroxy phosphonamides **2** (Scheme 1) in good yields, and with moderate to high diastereoselectivity (Table 1) The diastereoisomeric pair **2** were easily distinguished from each other by ^{31}P

NMR spectroscopy thereby providing a suitable method for the determination of isomeric ratios Aromatic (entries 2,4 and 5), aliphatic (entries 6 and 7) and unsaturated aldehydes (entries 1 and 3) are tolerated under the reaction conditions. It appears that the larger, sterically bulkier aldehydes result in better stereoselectivity.

Scheme 1

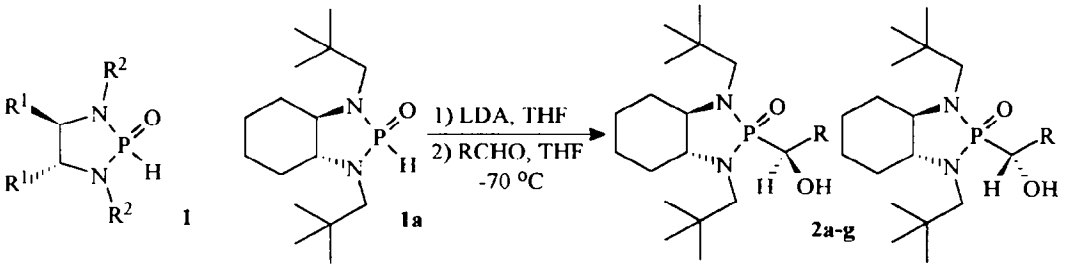


TABLE 1. REACTION OF CHIRAL PHOSPHOROUS ACID DIAMIDE 1a WITH ALDEHYDES

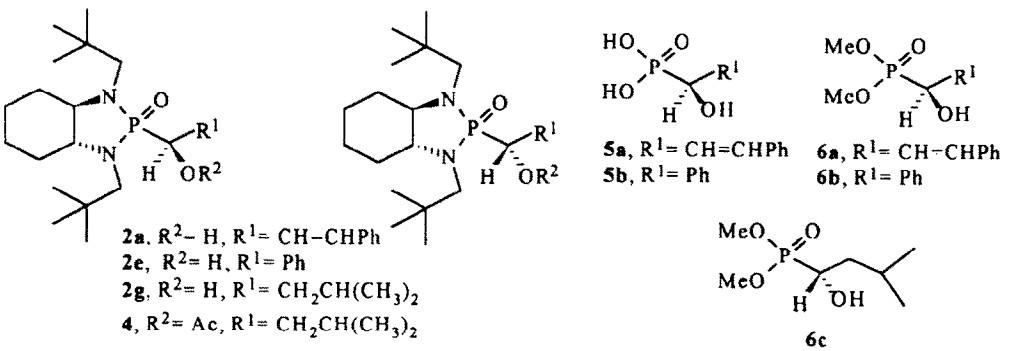
ENTRY	ALDEHYDE	PRODUCT	YIELD[a] (%)	ISOMERIC[b] RATIO (% de)	MELTING POINT (°C)	^{31}P, δ, ppm[c] major/minor
1	**Cinnamaldehyde**	**2a**	**68**	**7.9 : 1 (77)[d]**	**182 - 183**	**39.7 / 39.1**
2	**β-Naphthaldehyde**	**2b**	**58**	**14 : 1 (87)[d]**	**162 - 163**	**39.2 / 38.1**
3	**Crotonaldehyde**	**2c**	**91**	**6.9 : 1 (75)[d]**	**153.5 - 157**	**40.4 / 39.5**
4	**α-Naphthaldehyde**	**2d**	**91**	**29 : 1 (93)[d]**	**168.5 - 170**	**37.8 / 37.3**
5	**Benzaldehyde**	**2e**	**49**	**25 : 1 (92)[d]**	**186.5 - 187.5**	**39.0 / 38.1**
6	**Heptaldehyde**	**2f**	**80**	**4 : 1 (60)[d]**	**127.0 - 129.5**	**42.4 / 41.8**
7	**Isovaleraldehyde**	**2g**	**82**	**3.4 : 1 (54)**	**190 - 191.5**	**42.6 / 42.3**

The reactions were performed on a 1 2 mmol scale in THF with *n*-BuLi, LiHMDS or LDA as base. a) Yields are given after purification[13] by recrystallization (1x) or column chromatography. b) The diastereoisomeric ratios were determined by integration of the ^{31}P NMR spectra of the crude products The results were compared to the ratios determined by integration of suitable signals in the ^{1}H NMR spectra of the crude products. c) NMR spectra were recorded in $CDCl_3$. d) crystallized to a single diastereoisomer by one or more recrystallizations. e) Reaction entries 3,4 and 5 were performed at −75°C, all other entries at 60°C

The hydrolysis of structurally similar α-amino phosphonamides to amino phosphonic acids with aq. HCl has been reported.[10] Conversion of the hydroxy phosphonamides to phosphonic acid and phosphonates was studied with three representative compounds containing, alkenyl **2a**, aryl **2e**, and alkyl **2g**, hydroxymethyl substituted phosphonamides. The reaction of **1a** with cinnamaldehyde gave an 8 1 mixture of diastereoisomeric phosphonamides **2a**. Recrystallization from EtOAc/hexanes gave only the major isomer [13] An X-ray structure determination[14] allowed assignment of the new (C-1) chiral center as S resulting from the R,R diamide. The hydroxyalkyl phosphonamide diastereoisomers **2g** could not be separated by recrystallization or chromatography on silica gel. However, acetylation gave the acetates **4** which were separated by chromatography on silica gel. An X-ray structure determination on the more polar, major acetate diastereoisomer **4b** again allowed assignment of the new chiral center as S resulting from the R,R diamide [15] The α-hydroxy phosphonamides appeared to be sensitive to treatment with aq acids at elevated temperature, but were successfully hydrolyzed at room temperature (scheme 2). Phosphonamides **2a** (major isomer) and **2e**

(14:1 mixture) hydrolyzed cleanly at room temperature within 24 hours to give the phosphonic acids **5a** and **5b**, respectively.[16] The phosphonic acids were isolated by ion exchange chromatography (Amberlite IR120+) and characterized as the cyclohexylammonium salts (**5a**, 35% and **5b**, 60%, recrystallized yields). In separate experiments the phosphonic acids were dissolved in ethanol and methylated with etheral diazomethane to give the dimethyl phosphonates **6a** (79% isolated) and **6b** (62% isolated), respectively.[16] The ee of the phosphonates **6a** and **6b** were determined by HPLC[17] as >99% and 86% respectively, thus the stereochemical integrety remains intact. Phosphonate **6b** showed an $[\alpha]_D$ of −23, and thus by comparison with the reported[8e] value indicated that the predominant enantiomer had the S configuration (again resulting from the R,R diamide) Treatment of the minor acetate diastereoisomer (R,R,R configuration) **4a** with aq. HCl in dioxane at room temperature gave a mixture of hydroxy and acetoxy phosphonic acids The acetate was cleaved with 1M aq.KOH in ethanol to give the hydroxy phosphonic acid potassium salt, which was neutralized (methanolic HCl), and methylated (CH_2N_2 in Et_2O) to give the phosphonate **6c** in 58% isolated yield and >99% ee (HPLC analysis).

Scheme 2



Direct methanolysis of the phosphonamides with methanolic HCl was unsuccessful. The initial, rapidly formed, product was the result of 5 membered ring cleavage and the addition of methanol to the phosphorus atom. Attempts to force the reaction to completion at elevated temperatures resulted in either decomposition or isolation of the mono methyl ester of hydroxy phosphonic acid. The major diastereoisomer in each of the phosphonamides examined had the S configuration at C-1, resulting from a *si* face addition of the R,R phosphorous acid diamide **1a** on the aldehyde

In conclusion, we have shown that chiral phosphorous acid diamides are useful reagents for the stereoselective preparation of α-hydroxy- phosphonamides, phosphonates and phosphonic acids. A detailed study of this reaction and further reactions of phosphorous acid diamides is currently underway in our laboratories and will be reported in due course

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12. Several phosphorous acid diamides were examined but the neopentyl substituted diamide **1a** consistently gave the highest selectivities A full account of this work will be published in due course.

13 The diastereoisomeric ratio were generally improved by recrystallization, however the diastereoisomers could not be separated by chromatography on silica gel

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16 Satisfactory spectroscopic data and elemental analysis was obtained for all new compounds. The phosphonic acids **5a-c** gave NMR spectra identical to the racemic acids; Sekine, M ; Yamamoto, I. Hashizume, A.; Hata, T. *Chem. Lett.*, **1977**, 485. The hydroxy phosphonates **6a-c** gave NMR spectra identical to racemic standards, Texier-Boullet, F , Foucaud, A *Synthesis*, **1982**, 165.

17. Direct analysis on a ChiralPak AS column, EtOH-hexanes, (9:1 or 2:8), 1 ml/min, detection at 254nm for phosphonates **6a** and **6b**, and using a differential refractometer for phosphonate **6c**. The order of elution was the R enantiomer followed by the S enantiomer in all 3 examples

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