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Lithium Perchlorate/Diethylether Catalyzed Aminophosphonation of Aldehydes

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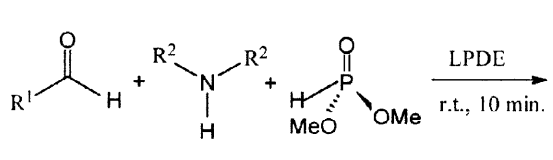
Abstract: A simple and general one-pot method was developed to give α-amino phosphonates from aldehydes + amines + dimethyl phosphite in LPDE. Optically active α-amino phosphonates were synthesized using *(R)*-(+), *(S)*-(-) α-methylbenzylamine, *(R)*-(-), *(S)*-(+) 2-phenylglycinol. *(R)*-(+) α-methylbenzylamine affords predominantly (*S*)-α-amino phosphonates and *(R)*-(-) 2-phenylglycinol leads predominantly to (*R*)-α-amino phosphonates.

α-Amino phosphonic acids and their diesters exhibit a wide range of biological activities. For example many of these compounds are potent antibiotics[1], enzyme inhibitors[2], herbicides[3] and surrogates for α-amino carboxylic acids.[4] A large number of methods have been devised for the preparation of α-amino phosphonates:[5] addition reactions of Schiff bases with di- or trialkyl phosphite derivatives,[6] nucleophilic amination of α-hydroxy phosphonate derivatives (Mitsunobu Reaction conditions),[7] electrophilic amination of α-alkyl phosphonamides,[8] hydrogenation of dehydroaminophosphonate derivatives,[9] aldol reactions of (isocyanomethyl)phosphonates with aldehydes,[10] hydrogenation of aziridinylphosphonate[11] and addition of phosphites to sulfinimines.[12]

We have already reported a general method for one-pot α-aminoalkylation[13] and α-aminocyanation[14] of aldehydes in a solution of lithium perchlorate/diethylether (5.0 M) LPDE.[15] In order to extend this methodology, we examined the reaction using dimethyl phosphite as nucleophile. This report describes a very mild, convenient, simple and fast procedure for the preparation of α-amino phosphonates which provides an alternative to other available methods. Thus, the α-amino phosphonate **4** was prepared by stirring a mixture of aldehyde **1**, amine **2** and dimethyl phosphite **3** in 5*M* LPDE. Aliphatic aldehydes as well as aromatic aldehydes gave α-amino phosphonates in excellent yield.[16]



R¹	Yield 4a %	Yield 4b %
i-Propyl	97	93
n-Propyl	95	97
Benzyl	99	95
Phenyl	90	95
p-MeO-Phenyl	87	90

1 **2a** (R^2 = Ethyl) **2b** (R^2 = Benzyl) **3** **4a** (R^2 = Ethyl) **4b** (R^2 = Benzyl)

To study 1,3-asymmetric induction, we extended this methodology to the preparation of chiral α-amino phosphonates derived from *(R)*-(+) α-methylbenzylamine **5** and aldehydes.

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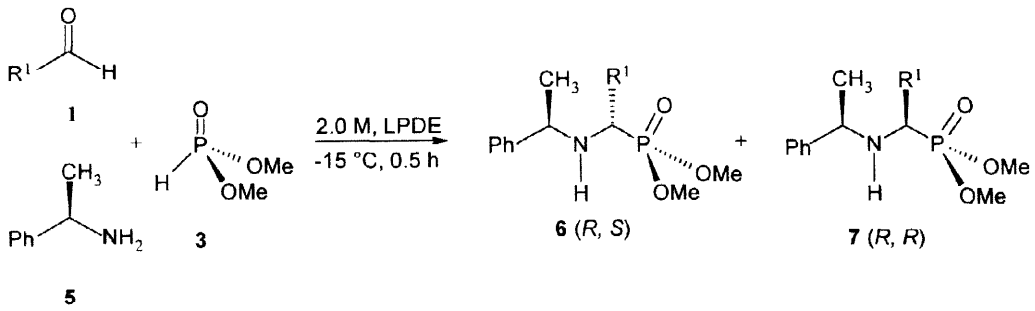
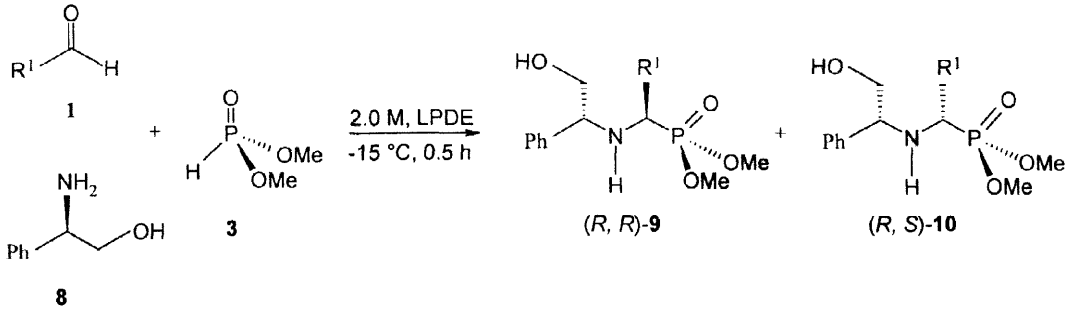


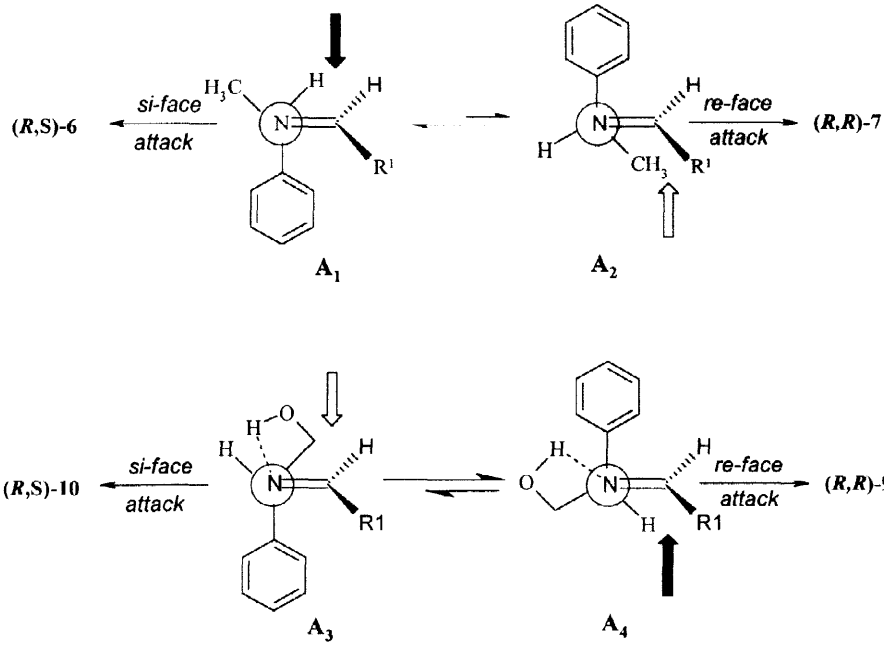
R^1	yield	6:7	6 (*R,S*)		7 (*R,R*)	
	%		δ H-1	*J* P/H-1	δ H-1	*J* P/H-1
iso-Propyl	95	79:21	δ = 2.6	*J* = 12.7 Hz	δ = 2.8	*J* = 19.0 Hz
tert-Butyl	96	82:18	δ = 2.4	*J* = 13.0 Hz	δ = 2.6	*J* = 16.8 Hz
cyclo-Hexyl	92	80:20	δ = 2.5	*J* = 12.7 Hz	δ = 2.6	*J* = 19.5 Hz
Benzyl	90	83:17	δ = 2.6	*J* = 9.2 Hz	δ = 3.1	*J* = 17.5 Hz

The reaction with aliphatic aldehydes in every case afforded mixtures of diastereomers with one diastereomer predominating and purification by HPLC provided **6** and **7** in a useable scale.[16] The configurations of the major and minor diastereomeric products were determined by ^{1}H-NMR spectra using the literature method for similar compounds.[5,17] For example, the ^{1}H-NMR of the crude (**6**+**7**) (R^1 = *cyclo*-hexyl) showed two double/ doublets, one at 2.5 ppm ($J_{P/H}$ = 12.7 Hz) and the other at 2.6 ppm ($J_{P/H}$ = 19.5 Hz) in ratio 79:21. Each double/doublet is derived from the proton attached to the carbon bearing the phosphonate. On the basis of the literature experiment for compound **6** (R^1 = *cyclo*-hexyl)[17] the upfield (major) double/doublet is from the *S* chiral center of the amino phosphonate proton and the downfield (minor) double doublet is from the *R* chiral center. In all cases *R*- **5** and *S*- **5** give similar enantiomeric results. We have been able to apply the new protocol to the synthesis of the (**6**+**7**) [R^1= benzyl, *tert*-butyl] although the phenylacetaldehyde-derived imine apparently isomerizes to the enamine during the reaction with $LiPO(OEt)_2$.[5] In addition, steric congestion inhibited addition of $LiPO(OEt)_2$ to the pivalaldehyde-derived imine which required 72 h at room temperature or 24 h at 67°C.[5] We then explored the generality of the dimethyl phosphite addition with a variety of imines. We turned to (*R*)-(-) 2-phenylglycinol **8** as the chiral amine. The reaction afforded mixtures of diastereomers with one diastereomer predominating and purification by HPLC afforded **9** and **10** in a useable scale.[16] The relative stereochemistry is confirmed by comparison with very similar products described by Smith.[5] In all cases of this reaction, *R*-**8** and *S*-**8** give similar enantiomeric results.



R^1	yield	9:10	9 (*R,R*)		10 (*R,S*)	
	%		δ H-1	*J* P/H-1	δ H-1	*J* P/H-1
iso-Propyl	90	88:12	δ = 2.7	*J* = 12.5 Hz	δ = 2.8	*J* = 19.4 Hz
tert-Butyl	95	91:09	δ = 2.5	*J* = 13.0 Hz	δ = 2.6	*J* = 17.9 Hz
cyclo-Hexyl	94	90:10	δ = 2.7	*J* = 13.0 Hz	δ = 2.8	*J* = 19. 0 Hz

The diastereoselectivity achieved by this method can be explained on the basis of the aza analogue of the Anh-Eisenstein hypothesis.[18] According to this hypothesis, nucleophilic attack on the imine should take place antiperiplanar to the α-phenyl group. There is other work on the attack of nucleophiles on imines with an adjacent stereogenic center, which has also been explained in the same way.[14, 19]



Of the possible transition states $\mathbf{A_1}/\mathbf{A_2}$; $\mathbf{A_3}/\mathbf{A_4}$ where the phenyl group is perpendicular to the imine π-plane, conformers $\mathbf{A_1}/\mathbf{A_4}$, in which the attack takes place from the *si*-face or *re*-face of the imine, give rise to the major (*R, S*)-**6** and (*R, R*)-**9** diastereomers. The transition state $\mathbf{A_4}$ is more favorable not only for steric reasons, the hydroxymethyl group being away from the imine moiety and the incoming nucleophile, but also for extra stabilization through intramolecular 5-membered ring H-bonding.[20] This explains the enhanced diastereoselectivity observed with α-phenylglycinols in comparision with α-methylbenzylamines as the chiral auxiliary where stabilization due to intramolecular H-bonding is not possible.

In summary, we have found that 5*M* LPDE promotes the direct conversion of aldehydes into α-amino phosphonates. The protocol is simple and potentially leads to versatile α-amino phosphonates. This method has a few noteworthy features: 1) excellent yields can be obtained for both aliphatic and aromatic aldehydes 2) great operational simplicity 3) high levels of diastereoselection can be obtained in the synthesis of α-aminophosphonates using (*R*)-, (*S*)-methylbenzylamine and (*R*)-, (*S*)-2-phenylglycinol.

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