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A new strategy for asymmetric synthesis of aminophosphonic acid derivatives: the first enantioselective catalytic reduction of C-phosphorylated imines

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ABSTRACT

The first highly enantioselective catalytic reduction of 1-imino-2,2,2-trifluoroethylphosphonates and the synthesis of enantiomerically enriched biorelevant phosphonotrifluoroalanine is reported.

α-Aminophosphonic acids are phosphorus analogues of α-amino acids in which the carboxylic group is replaced by a phosphonic acid moiety. This class of compounds has attracted considerable interest because of their wide spectrum of biological activity[1,2] Due to the tetrahedral configuration at phosphorus, aminophosphonic acids serve as stable analogues of the unstable tetrahedral carbon intermediates formed in enzymatic processes and therefore act as enzyme inhibitors. Many phosphonic analogues of protein and nonprotein amino acids, which have been synthesized in the past two decades, exhibit antibacterial, anticancer, and antiviral properties as well as pesticidal, insecticidal, and herbicidal activities. A few have found commercial applications in agriculture and medicine. Of particular interest in modern drug discovery are non-racemic fluorine-containing aminophosphonic acids. They are expected to be resistant to metabolic degradation due to the strong C–F bond. Moreover, the presence of fluorine in the structure of aminophosphonic acids could improve their lipophilicity and pharmacokinetic properties.[3] However, in contrast to the widely investigated α-aminophosphonic acids, synthetic approaches to enantiomeric fluorine-containing analogues are few in number and of limited applicability.[4] For this reason, the development of new synthetic methodologies for preparing enantiomerically enriched compounds of this type is still a challenging task.

Most of the reported methods for the asymmetric synthesis of α-aminophosphonic acids **1** involve asymmetric addition of phosphites to non-phosphorylated imines **2** as the key step (Scheme 1, path a).[1,5] The best illustration of this approach is the highly diastereoselective addition of dialkyl or diamidophosphites to enantiopure sulfinimines leading, after separation of the diastereomeric adducts and deprotection of the amino and phosphonate functions, to enantiopure α-aminophosphonic acids.[6]

Here, we disclose an alternative general approach to α-aminophosphonic acids based on the use of C-phosphorylated imines **3** as starting materials. These compounds have been synthesized in our laboratory including C-phosphorylated N–H imines **4**.[7] It is interesting to point out that the starting imine **3** contains the phosphoryl group which is able to coordinate the reagent/catalyst and additionally activate the C=N bond allowing addition of even weakly nucleophilic reagents so structurally diverse aminophosphonates **1** can be accessed readily (Scheme 1, path b).

With regard to the synthesis of fluorine-containing α-aminophosphonates, it is worth mentioning that in contrast to **3**, fluoromethylated imines **2** ($R = CF_3$, RCF_2) are unstable and difficult to access.[4] Although the preparation of the corresponding non-racemic aminophosphonic acids **1** ($R = CF_3$, Y = H, R^1 = H, Alk) from enantiomerically pure *N*-(α-phenylethyl)trifluoroacetimidoyl

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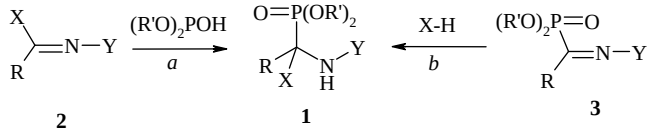
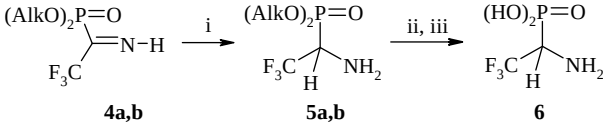


Scheme 1.

chloride has been accomplished by us[8] and later by a Chinese group,[9] the procedure involved a multi-stage laborious synthesis.

In the first stage of our effort to apply C-phosphorylated N–H imines **4** in the asymmetric synthesis of α-aminophosphonic acid derivatives, we focused on their catalytic reduction (Scheme 2). Commercially available methyl oxazaborolidines (OAB), successfully used for enantioselective reduction of simple N–H imines[10] or trihalomethyl ketones,[11] were chosen as chiral catalysts. We found initially, that reduction of **4a** with $BH_3{\cdot}Me_2S$ catalyzed by (*R*)-(+)-OAB (5 mol %) proceeds in a non-enantioselective manner (Table 1, entry 1) although the corresponding racemic aminophosphonate **5a** is formed in quantitative yield. However, as we continued to screen other reducing agents, we discovered that the use of catecholborane (catBH) resulted in the enantioselective reduction of **4a**. The enantioselectivity of this reaction was found to be dependent on the chiral catalyst content. Thus, ee values of 17% and 70% were observed with 5 and 100 mol % catalyst, respectively (Table 1, entries 2 and 3). These results suggested that due to the high reactivity of imines **4**, caused by the electron-withdrawing effect of the phosphoryl and trifluoromethyl groups, a non-catalytic reduction pathway dominates at low catalyst content.

Taking into account the fact that adducts of alcohols with imines such as **7** (Scheme 3) exist in solution in equilibrium with the respective starting compounds,[7f] it was reasonable to assume that the effective concentration of the reacting imine can be decreased by using their alcohol adducts **7** for asymmetric reduction. In this way, the enantioselectivity of the asymmetric reaction under discussion was expected to be enhanced. We were pleased to find that the reduction of adducts **7** with catecholborane led to aminophosphonates **5** in high yields and with moderate to high enantioselectivity even with 5 mol % of catalyst (Scheme 3, Table

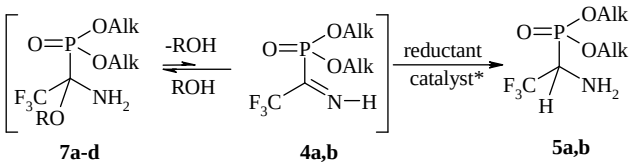


4a, 5a Alk = Et
4b, 5b Alk = n-Pr

Scheme 2. Reagents and conditions: (i) reducing agent, chiral catalyst (Table 1), THF, −78 °C; (ii) 6 N aq HCl, 100 °C, 6 h; (iii) propylene oxide.

Table 1
Catalytic enantioselective reduction of imines **4** and their alcohol adducts **7**

Entry	Substrate	Reductant	Catalyst (mol %)	**5**, yield (%)	ee (%)
1	**4a**	$Me_2S\ BH_3$	*R*-(+)-OAB (5)	(±)-**5a**, 100	0
2	**4a**	catBH	*R*-(+)-OAB (5)	(−)-**5a**, 97	17
3	**4a**	catBH	*S*-(−)-OAB (100)	(+)-**5a**, 98	70
4	**4b**	catBH	*R*-(+)-OAB (100)	(−)-**5b**, 95	72
5	**7a**	catBH	*R*-(+)-OAB (5)	(−)-**5a**, 97	50
6	**7a**	catBH	*S*-(−)-OAB (5)	(+)-**5a**, 98	53
7	**7b**	catBH	*R*-(+)-OAB (5)	(−)-**5a**, 98	72
8	**7b**	catBH	*S*-(−)-OAB (5)	(+)-**5a**, 98	72
9	**7c**	catBH	*R*-(+)-OAB (5)	(−)-**5a**, 65	30
10	**7d**	catBH	*S*-(−)-OAB (5)	(+)-**5b**, 98	72



7a Alk = Et, R = Me
7b Alk = Et, R = Et
7c Alk = Et, R = 2-$PyCH_2$
7d Alk = n-Pr, R = Et

Scheme 3.

1, entries 5–10). In view of the above results, it seems that the dissociation of **7**→**4** is a major factor that limits the concentration of the reacting imine and therefore the beneficial catalyst/imine ratio is maintained during the course of reduction. Hence, adducts **7** serve as masked sources of the corresponding imines **4**.

An inspection of the results of this set of experiments (Table 1, entries 5–10) reveals that the enantioselectivity of the reduction is only slightly dependent on substituents bonded to phosphorus but it increases with the increasing stability of **7** in the following order: **7b**, **7d** > **7a** > **7c**. Thus, of those investigated, the ethanol adducts **7b** and **7d** turned out to be the best for asymmetric reduction.

The enantiomeric ratio of aminophosphonates **5** prepared here was determined by NMR techniques using the commercially available chiral shift reagent (ESR), europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate. It was found that at a 1:1 ratio of ESR and **5**, the resonance signals of the diastereomeric complexes formed were nicely separated in both ^{19}F and ^{31}P NMR spectra ($\Delta\delta \sim 0.3$ and 3.8 ppm, respectively) thus allowing the precise determination of enantiomeric excesses (δ_F −66.71 ppm, J_{FP} 6.6 Hz, δ_P 9.3 ppm for the (+)-**5**/ESR complex; δ_F −66.97 ppm, J_{FP} 6.6 Hz, δ_P 5.47 ppm for the (−)-**5**/ESR complex). Moreover, the ee values of optically active **5** obtained from both ^{31}P and ^{19}F NMR spectra were in good agreement.

Having in hand both enantiomerically enriched (+)- and (−)-α-aminophosphonates **5a**, we were able to realize our main goal, that is, the synthesis of fluorine-containing α-aminophosphonic acids. Thus, (+)-**5a**, $[\alpha]_D$ +2.27 (*c* 2.0, $CHCl_3$), was hydrolyzed under acidic conditions[8b] to give (+)-α-aminotrifluoroethylphosphonic acid **6**, 72% ee, $[\alpha]_D$ +2.31 (*c* 1.5, H_2O), in 90% yield (Scheme 2). In a similar way (−)-**6**, $[\alpha]_D$ −2.31 (*c* 1.5, H_2O), was obtained from (−)-**5a**, $[\alpha]_D$ −2.26 (*c* 2.0, $CHCl_3$). The spectroscopic properties of the isolated acids **6** were identical with those reported for the racemic compound.[8b]

In summary, we have developed the first method for the catalytic enantioselective reduction of C-phosphorylated N–H imines affording enantiomerically enriched α-aminotrifluoroethylphosphonates, which were transformed into the respective biorelevant aminophosphonic acids. Future work will include the application of new methodology in other types of asymmetric functionalization of C-phosphorylated imines.

Typical procedure for catalytic reduction: A solution of (*R*)-1-methyl-3,3-diphenylpyrrolidinooxazaborolidine (0.045 mL, 1 M solution in toluene, 0.045 mmol) was dissolved in THF (2 mL), cooled to −15 °C, and catecholborane (1.35 mL, 1 M solution in THF, 1.35 mmol) was added. A solution of α-aminophosphonate **7b** (0.25 g, 0.9 mmol) in THF (3 mL) was added dropwise over a period of 3 h. After addition was complete, the reaction mixture was stirred at −15 °C for 2 h. The reaction was quenched with aqueous 1 N HCl (3 mL) and allowed to warm to room temperature. The mixture was extracted with diethyl ether (3 × 5 mL), and the layers were separated. The aqueous layer was basified with saturated aqueous $NaHCO_3$ (2 mL) and was extracted with ethyl

acetate (3 × 10 mL). The combined extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure to leave a colorless oil, which was purified on silica gel using diethyl ether as eluent to give analytically pure aminophosphonate (−)-**5a** (0.205 g, 98%, 72% ee) as a colorless oil, $[\alpha]_D^{25}$ −2.26 (*c* 2.0, $CHCl_3$). Physico-chemical constants of compound **5a** were in agreement with literature data.[12]

Enantioselective reduction with (*S*)-1-methyl-3,3-diphenylpyrrolidinooxazaborolidine as catalyst gave aminophosphonate (+)-**5a** in 98% yield and 72% ee, $[\alpha]_D^{25}$ +2.27 (*c* 2.0, $CHCl_3$).

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References and notes

1. *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley & Sons: New York, 2000.
2. Kafarski, P.; Lejczak, B. *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *63*, 193.
3. *Organic Compounds in Medicinal Chemistry and Biomedicinal Applications*; Filler, R., Kobayshi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993.
4. Romanenko, V. D.; Kukhar, V. P. *Chem. Rev.* **2006**, *106*, 3868.
5. Cherkasov, R. A.; Galkin, V. I. *Russ. Chem. Rev.* **1998**, *67*, 857.
6. (a) Mikołajczyk, M.; Łyżwa, P.; Drabowicz, J. *Tetrahedron: Asymmetry* **1997**, *8*, 3991; (b) Lefebvre, I. M.; Evans, S. A., Jr. *J. Org. Chem.* **1997**, *62*, 7532; (c) Mikołajczyk, M.; Łyżwa, P.; Drabowicz, J. *Tetrahedron: Asymmetry* **2002**, *13*, 2571; (d) Mikołajczyk, M. *J. Organomet. Chem.* **2005**, *690*, 2488.
7. (a) Sinitsa, O.A.; Kolotilo, N.V.; Onys'ko, P.P. *Ukr. Khim. Zhurn.* **1998**, 64, 5, 47. [*Ukr. Chem. J.* **1998**, *64*, 5, 43 (Engl. Trans.)]; (b) Rassukana, Yu. V.; Onys'ko, P. P.; Davydova, K. O.; Sinitsa, A. D. *Eur. J. Org. Chem.* **2004**, 3643; (c) Rassukana, Yu. V.; Sinitsa, O. A.; Onys'ko, P. P. *Russ. Chem. Bull.* **2005**, *54*, 2648; (d) Rassukana, Yu. V.; Sinitsa, O. A.; Onys'ko, P. P. *Russ. Chem. Bull.* **2005**, *54*, 2652; (e) Kolotilo, N. V.; Sinitsa, O. A.; Rassukana, Yu. V.; Onys'ko, P. P. *Russ. J. Gen. Chem.* **2006**, *76*, 1210; (f) Rassukana, Yu. V.; Kolotylo, M. V.; Sinitsa, O. A.; Pirozhenko, V. V.; Onys'ko, P. P. *Synthesis* **2007**, *17*, 2627.
8. (a) Onys'ko, P. P.; Kim, T. V.; Kiseleva, E. I.; Sinitsa, A. D.; Kornilov, M. Y. *Russ. J. Gen. Chem.* **1990**, *60*, 1165; (b) Onys'ko, P. P.; Kim, T. V.; Kiseleva, E. I.; Sinitsa, A. D. *Russ. J. Gen. Chem.* **2004**, *74*, 1868.
9. Xiao, J.; Zhang, X.; Yuan, C. *Heteroat. Chem.* **2000**, *11*, 536.
10. Gosselin, F.; O'Shea, P. D.; Roy, S.; Reamer, R. A.; Cheng-yi Chen; Volante, R. P. *Org. Lett.* **2005**, *7*, 355.
11. Corey, E. J.; Link, J. O.; Bakshi, R. K. *Tetrahedron Lett.* **1992**, *33*, 7107.
12. Onys'ko, P.P.; Kim, T.V.; Kiseleva, E.I.; Pirozhenko, V.V.; Sinitsa, A.D. Ukr. Khim. Zh. 2002, 68, 11, 16.