# A Concise and First Synthesis of α-Aminophosphinates with Two Stereogenic Atoms Leading to Optically Pure α-Amino-*H*-phosphinic Acids

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As phosphorus analogues of natural α-aminocarboxylic acids, synthetic study of α-aminophosphonic acids is of great interest to organic, bioorganic, and medicinal chemists.[1] Very recently, our group has reported a convenient method for the preparation of optically active α-aminophosphonic acids based on a nucleophilic addition of dialkylphosphite to sp²-carbon atom under mild reaction conditions using *N-tert*-butanesulfinyl imines as chiral auxiliaries.[2] However, direct comparison of α-aminophosphonic acids with α-aminocarboxylic acids is not reasonable, since the former belong to dibasic acids while the latter are monobasic acids in nature. From this structural point of view, α-amino-*H*-phosphinic acids are much closer to natural α-aminocarboxylic acids (Scheme 1). It is well documented that optically active α-aminocarboxylic acids play an irreplaceable role in the biological metabolism.[3] Consequently, it is reasonable to assume that optically active α-amino-*H*-phosphinic acids might demonstrate greater biological activity than the well-
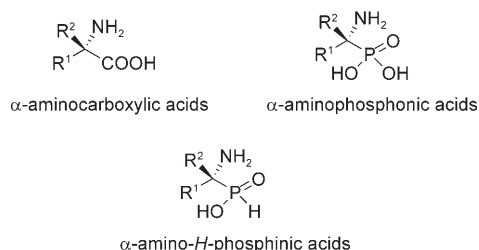
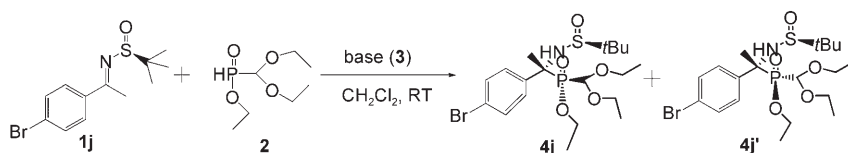Scheme 1. Natural α-aminocarboxylic acids and their phosphorus analogues.

studied α-aminophosphonic acids as it could act as a more effective surrogate of α-aminocarboxylic acids and block the reproduction of DNA. Unfortunately, probably due to the unique structure, it was more difficult to synthesize optically pure α-amino-*H*-phosphinic acids[4] and most of the synthetic methods available only lead to racemates.[5] For these reasons, further chemical and biological studies on this kind of compounds have run aground for decades.

Adol reaction has been always an effective way to introduce hydroxyl or amino group into target molecules, and with this strategy both α-hydroxyl phosphonates and α-hydroxylphosphinates have been obtained successfully.[6,7] Our group has also realized the convenient synthesis of α-aminophosphonates initiated by this concept.[2] To the best of our knowledge, however, owing to the lack of effective chiral-inducing reagents, syntheses of optically active α-aminophosphinates have not yet been reported by a nucleophilic adol reactions. As part of our efforts, we wish to disclose a novel and facile and highly stereoselective synthesis of α-aminophosphinates by nucleophilic attack of ethyl diethoxymethylphosphinate to Ellman's *N-(tert-*butanesulfinyl)ketimines[8] in CH_2Cl_2 using Rb_2CO_3 as a base at room temperature; subsequently these compounds can be readily converted to optically pure α-amino-*H*-phosphinic acids. During this process, for the first time, a pair of diastereoisomers, which have different configurations at the phosphorus atom, was obtained.

In the first set of experiments, we chose (*S*)-(*tert*-butanesulfinyl)methyl (*p*-bromo)phenylketimine (**1j**) as the model compound to study its reaction with ethyl diethoxymethylphosphinate (**2**; Scheme 2).[9] The reaction conditions were chosen based on our previous work: K_2CO_3 as base and CH_2Cl_2 as solvent were initially an ideal conditions for the reaction, because they gave excellent results in the reactions of dimethyl phosphonate with various Ellman's *N-(tert-*butanesulfinyl)ketimines. However, probably due to the subtle differences between the chemical characteristics of ethyl diethoxymethylphosphinate and dimethyl phosphonate, these conditions proved not to be so effective, in that few products were detected even after five days. The change of

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Scheme 2. The screening of reaction conditions.

Compound (S_S,R_C,R_P)-**4** or (S_S,R_C,S_P)-**4′** can be readily converted to its corresponding optically active α-amino-*H*-phosphinic acids by refluxing in 4 N HCl (Scheme 3).

CH_2Cl_2 to benzene gave better results, but the reaction still needed more than five days to complete. Considering that the steric hindrance of ethyl diethoxymethylphosphinate is much larger than that of dimethyl phosphonate, we assumed that the basicity of K_2CO_3 is too weak to initiate the reaction. This assumption was supported by the fact that other weak bases such as $CaCO_3$, $BaCO_3$, and KF were also ineffective in this reaction. On the basis of this assumption, we chose Cs_2CO_3, which is a much stronger base, to study this reaction. To our delight, the reactants did disappear in much shorter time (one day); however, we still got very few products. We surmised that the reactants, both **1j** and **2**, may be unstable under too basic conditions. Finally, we decided to choose Rb_2CO_3, which has moderate basicity compared with K_2CO_3 and Cs_2CO_3. It is interesting that we obtained two isomers (**4j** and **4j′**), which can be separated completely by silica gel chromatography. Through the ^1H NMR analysis, we found that they have minor differences with shifts at 3.5 and 4.2 ppm, respectively, which can be assigned to the diethoxymethyl and the ethoxyl groups of the products. What's more surprising is that the ^{31}P NMR spectra indicated that each of the two isomers had single structure—they both gave single peak in the ^{31}P NMR spectrum! To clarify the enantioselectivity of this reaction, we subsequently hydrolyzed the two isomers to their corresponding α-amino-*H*-phosphinic acids and measured their optical values and found that they had similar values, which indicated that this reaction may afford high enantioselectivity on α-C, and it may, at the same time, split the two P isomers. Further investigation into the reaction was then carried out and the results were summarized in Table 1.

We are fortunately enough to obtain the single crystals of **4q** and **4n′**,[10] and we confirmed their structures and absolute configurations by single-crystal X-ray analysis. (Figure 1)

As shown in ORTEP drawings, it can be easily found that the configuration of α-C of **4q** and **4n′** are both *R*, which indicated that the high enantioselectivity of α-C was achieved in combination with the ^{31}P NMR analysis ($>95\%$ diastereomeric excess (*de*)). What is more interesting is that, according to ORTEP drawings, the two isomers of phosphorus atom were also obtained! (for **4q**, the configuration of phosphorus atom is *R*; while for **4n′**, the configuration of phosphorus atom is *S*). That is to say, in this novel reaction, high enantioselectivity of both α-C and P were realized simultaneously, and we can call this "one stone, two birds". Actually this is the first direct experimental evidence supporting the stereogenic nature of phosphorus atom of α-aminophosphinates.

Table 1. The synthesis of (S_S,R_C,R_P)-**4** and (S_S,R_C,S_P)-**4′**.

	R^1	Yield [%][a,b] **4**	Yield [%][a,b] **4′**
1a	Ph	46 (35.23)	50 (35.72)[b]
1b	p-$CH_3C_6H_4$	37 (35.29)	48 (35.78)
1c	p-$CH_3OC_6H_4$	48 (34.57)	50 (35.00)
1d	p-$CH_3SC_6H_4$	37 (34.97)	34 (35.72)
1e	p-morpholino-C_6H_4	29 (35.37)	36 (35.87)
1f	3,4-methylenedioxy-C_6H_4	49 (35.07)	49 (35.37)
1g	o-FC_6H_4	37 (35.35)	36 (35.98)
1h	p-FC_6H_4	43 (34.82)	50 (35.14)
1i	p-ClC_6H_4	46 (34.64)	48 (34.95)
1j	p-BrC_6H_4	41 (33.84)	35 (34.13)
1k	1-furanyl	35 (34.49)	49 (34.93)
1l	1-thiophenyl	45 (33.90)	47 (34.06)
1m	3-pyridinyl	50 (34.54)	35 (34.56)
1n	2-naphthyl	43 (35.33)	49 (36.03)
1o	4-biphenyl	49 (35.20)	49 (35.66)
1p	4-cyanoC_6H_4	41 (34.13)	48 (34.26)
1q	4-nitroC_6H_4	32 (34.02)	38 (34.07)
1r	hexyl	45 (40.73)	30 (40.27)

[a] Isolated yield. [b] The values in the brackets are the ^{31}P NMR chemical shift values in ppm, each product give single peak in its ^{31}P NMR, indicating its *de*% is more than 95% (except for **4g** and **4h**, for which 91% *ee* were obtained).

To further determine the accurate enantiomeric excess (*ee*) values of the products, we oxidized (S_S,R_C,R_P)-**4q** and (S_S,R_C,S_P)-**4q′** into their corresponding sulfonylamide derivatives (R_C,R_P)-**6q** and (R_C,S_P)-**6q′** (see Scheme 4).[11,12] The high optical purity of (R_C,R_P)-**6q** and (R_C,S_P)-**6q′** are determined by HPLC ($>99\%$ *ee*), indicating that this synthetic method promises to be a general and convenient approach for the preparation of enantiomerically pure α-amino-*H*-phosphinic acids.

In conclusion, the unprecedented nucleophilic attack of ethyl diethoxymethylphosphinate to Ellman's *N-(tert*-butanesulfinyl)ketimines by using Rb_2CO_3 as base, followed by heating under reflux with 4 N HCl has shown to be a highly stereoselective and convenient synthesis of α-amino-*H*-phosphinic acids. In view of the mild conditions of this novel reaction, the optically pure α-amino-*H*-phosphinic acids are now more accessible and their potential application in biological systems is therefore feasible and encouraging. The mechanism of this subtle reaction and the application of the present synthetic methodology in the synthesis of optically
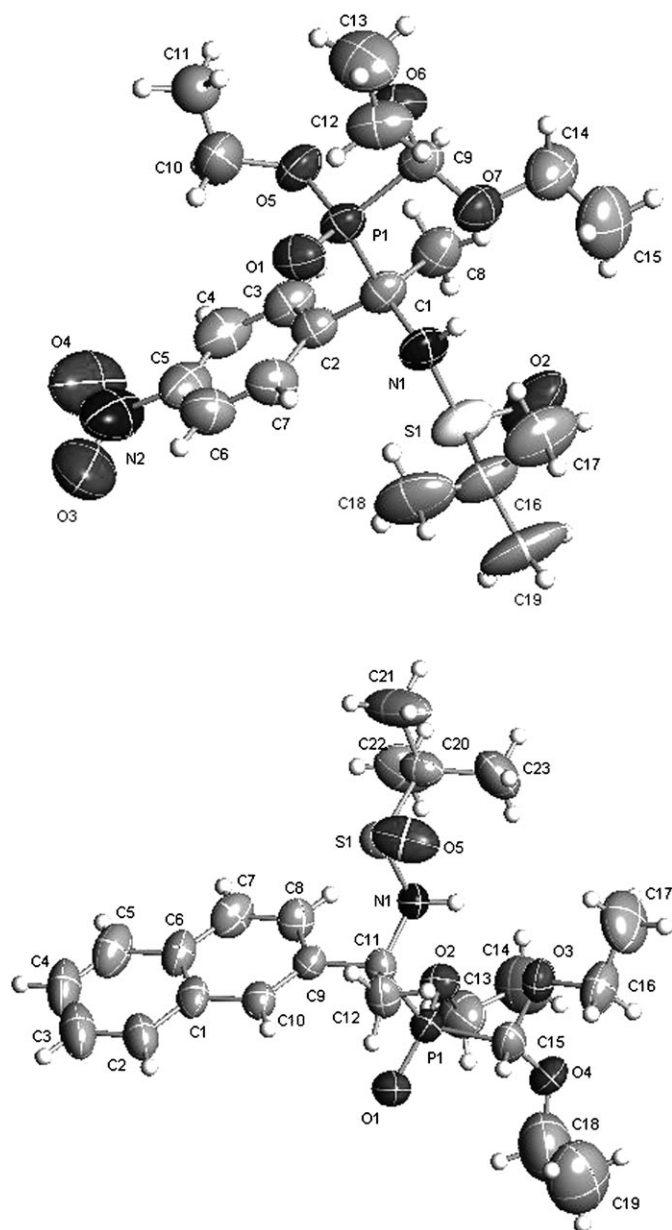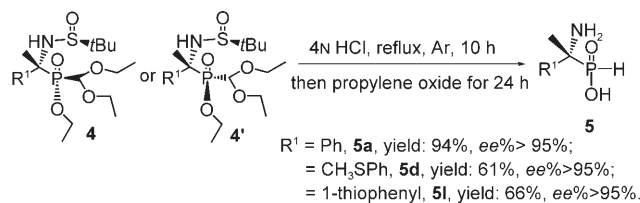
R^1 = Ph, **5a**, yield: 94%, *ee*%> 95%;
= CH$_3$SPh, **5d**, yield: 61%, *ee*%>95%;
= 1-thiophenyl, **5l**, yield: 66%, *ee*%>95%.

Scheme 3. Synthesis of optically active α-amino-*H*-phosphinic acids.

R^1 = *p*-NO$_2$Ph

R^1 = *p*-NO$_2$Ph
[α]^{24} +64.3 (*c*=1.00, CHCl$_3$)
ee: >99%

R^1 = *p*-NO$_2$Ph

R^1 = *p*-NO$_2$Ph
[α]^{24} +40.2 (*c*=1.00, CHCl$_3$)
ee: >99%

Scheme 4. Transformation of (S_S,R_C,R_P)-**4q** and (S_S,R_C,S_P)-**4q′** into their corresponding sulfonyl-amide derivatives (R_C,R_P)-**6q** and (R_C,S_P)-**6q′**.

Figure 1. ORTEP drawing for ($S_S R_C$,R_P)-**4q** (top) and (S_S,R_C,S_P) **4n′** (bottom).
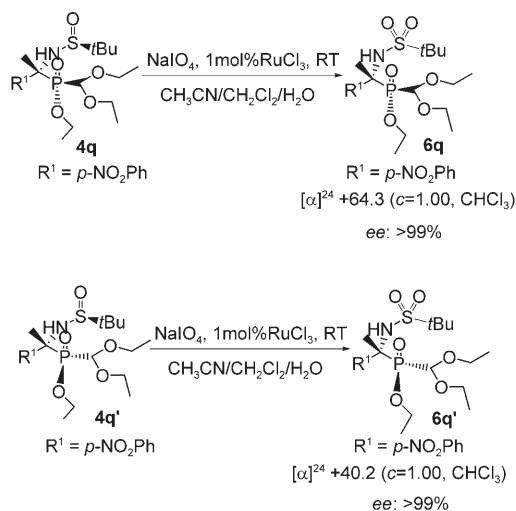
pure β-amino-*H*-phosphinic acids and γ-amino-*H*-phosphinic acids are currently under investigation in our laboratory.

Experimental Section

General procedure for the stereoselective synthesis of ethyl 1′,1′-diethoxy-ethyl-(S_S,R_C,R_p)-(+)-1-(*tert*-butanesulfinylamino)-1-aryl-1-methylphosphinate (4) and ethyl 1′,1′-diethoxyethyl-(S_S,R_C,S_P)-(+)-1-(*tert*-butanesulfinylamino)-1-arylmethylphosphinate (4′): Ethyl diethoxymethylphosphinate (**2**; 392 mg, 2 mmol) and Rb$_2$CO$_3$ (577 mg, 2.5 mmol) in CH$_2$Cl$_2$ (5 mL) were placed in a 20 mL Schlenk flask and (*S*)-*N*-*tert*-butanesulfinylketimines **1** (0.5 mmol) were then added at room temperature. The mixture was then stirred for 3–4 d, while being carefully monitored by TLC. After the reaction came to the completion, water (5 mL) was

added to quench it. Then the organic layer was separated and the aqueous layer was washed with Et$_2$O (3×10 mL). The organic layers were again washed with brine and dried over anhydrous Na$_2$SO$_4$ overnight. The solvent was removed under reduced pressure and the residue was subjected to silica gel chromatography (300–400 mesh, EtOAc/petroleum 3:1 to 6:1 for compound **4** and acetone/EtOAc 1:1 for compound **4′**) to afford pure **4** and **4′**.

General procedure for the synthesis of (*R*)-(+)-α-methyl-α-amino-*H*-phosphinic acid (5): A 20 mL Schlenk flask was flushed with Ar. Then **4** or **4′** (0.2 mmol) was added under Ar atmosphere followed by infusing with 4 N HCl (4 mL). The mixture was heated to reflux with stirring for 10 h before it was cooled to room temperature. The aqueous solution was then washed with CH$_2$Cl$_2$ (5×5 mL), after which EtOH (30 mL) was added to the aqueous layer and the resulting mixture was treated to reduced pressure to remove the solvent (water as well as EtOH) to near dryness. The residue was again dissolved in a minimum amount of EtOH followed by the addition of excess propylene oxide, in the process of which a large amount of a white precipitate formed. The mixture was stirred for 24 h and then filtered. The solid was collected while the filtrate was then evaporated to near dryness (a little amount of EtOH was usually required) and treated with EtOAc. The resulting white precipitate was again filtrated and the solid collected in combination with that previously obtained was then washed with propylene oxide or petroleum to afford pure **5**.

The identity and purity of the known products were confirmed by sufficient spectroscopic analysis, and the new products were fully characterized (see the Supporting Information).

Acknowledgements

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[10] a) For the correlation of the single-crystal structures of **4q** and **4n'** with the ^{1}H NMR data, please see the Supporting Information; b) CCDC 675307 (**4q**) and 675308 (**4n'**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[12] It should be emphasized that difficulties were encountered during the synthesis of the racemic **6q** and **6q'** with *S* configuration on the sulfur atom. The racemates, which consist of four isomers prepared from racemic *N*-*tert*-butanesulfinylketimines, have different chiralities on the sulfur atom, so it is necessary for us to eliminate the chirality at the sulfur atom to obtain two pairs of isomers with two chiral atoms (C and P). Only with the above treatment, HPLC analyses became possible.