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Chiral *N*-phosphonyl imine chemistry: new reagents and their applications for asymmetric reactions

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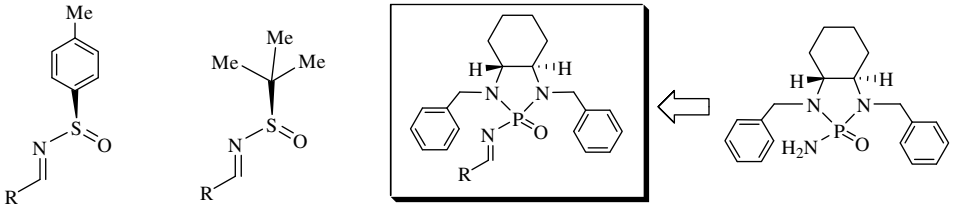
Abstract

Novel chiral *N*-phosphonyl imines **2** have been designed and synthesized using chiral *N*-phosphoramide **1**. These *N*-phosphonyl imines have been successfully utilized for asymmetric aza-Darzens reaction and asymmetric aza-Henry reaction. The C_2-symmetric chiral auxiliary tolerates oxidation, is not sensitive to racemization and can be recycled for large scale synthesis.

Keywords: Phosphoramide; *N*-Phosphonyl imines; Aziridine; aza-Darzens reaction; aza-Henry reaction; C_2-Symmetric diamine

The chiral imine chemistry has been one of the most active topics in asymmetric synthesis because the drug development and discovery heavily depend on the amine functionality.[1–3] In the past several decades, this field has been represented by *N*-sulfinyl imine (or sulfinimine) chemistry, which was pioneered by Davis,[1,4] Ellman,[2,5] and several others[6,7] (Fig. 1, **A** and **B**). Very recently, it has been addressed that asymmetric nucleophilic additions of organometallic reagents to C=N bonds of chiral sulfinimines represent 'the most direct and reliable method for the asymmetric construction of diverse amine derivatives having a nitrogen attached to a stereogenic center'.[1b] In our recent effort on the development of new chiral nitrogen sources to render asymmetric aminohalogenation and diamination reactions,[8,9] we found that one of these nitrogen sources, the free NH_2 group-attached phosphoramide (Fig. 1, **1**), can be readily converted into chiral *N*-phosphonyl imines (Fig. 1, **C**) to serve as electrophiles for asymmetric nucleophilic additions by organometallic reagents.

Even though a great progress has been made on *N*-sulfinyl imine chemistry, there still exist some limitations during the use of *N*-sulfinyl imines for asymmetric synthesis. In addition to the shortcomings described in the literature,[2] the *N*-sulfinyl functionality is sensitive to oxidative



A **B** **C** **1**

Fig. 1. Chiral *N*-sulfinyl and *N*-phosphonyl imines.

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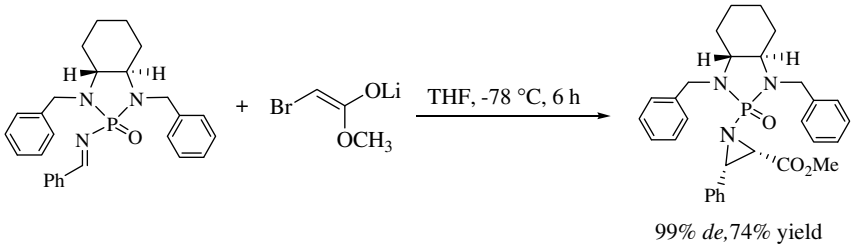
conditions, which makes some further transformations inconvenient. The deprotection of *N*-sulfinyl group is performed by treating with Brønsted-Lowry acids, which destroys the chiral functionality and makes the recovery of chiral auxiliary impossible; or, possible racemization can occur on sulfur center if other methods are used. In addition, this functionality cannot well tolerate strong Lewis acids (e.g., $TiCl_4$).[10] Therefore, it is necessary to develop new chiral imines to overcome shortcomings of *N*-sulfinyl imines. In this Letter, we would like to report our preliminary results on the design and the synthesis of new chiral *N*-phosphonyl imines and the study of asymmetric aza-Darzens reaction[11,12] by using these new chiral imines as represented by Scheme 1 and the results are summarized in Tables 1 and 2. Also, the initial study on asymmetric aza-Henry reaction[13] by using chiral *N*-phosphonyl imines is disclosed.

We initially chose chiral hydrobenzoin and (1*R*,2*R*)-1,2-diphenylethylenediamine for the design and the synthesis of chiral phosphonyl imine derivatives, but the unwanted opening of the five-membered ring and soluble problems caused us to put off this project for a while until recently when we came up with the idea of using (1*R*,2*R*)-diaminocyclohexane to replace (1*R*,2*R*)-1,2-diphenylethylenediamine. When this modification was made, the resulting new chiral *N*-phosphonyl imines can be dissolved in most organic solvents even at low temperature; this led to the present success.

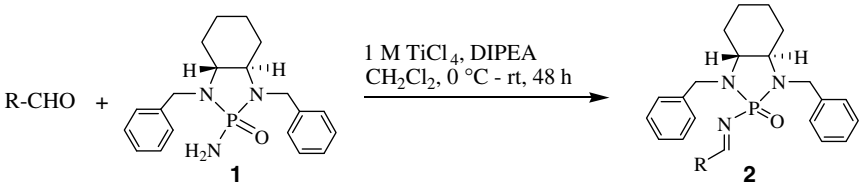
The C_2-symmetry is the most common structural characteristic in asymmetric chemistry, and it exists in common chiral reagents.[14,15] The present new chiral *N*-phosphonyl imines containing this structural unit are certainly very attractive to asymmetric field. Although the C_2-symmetric diaminocyclohexane-based phosphoramides have been widely utilized as Lewis base ligands for asymmetric catalysis,[15] surprisingly, the free NH_2 group-attached chiral phosphoramides have not been introduced to asymmetric synthesis yet. This situation is probably due to the fact that the reactivity, selectivity, stability, and solubility of these phosphoramides are unknown. Certainly, it has not been known if the chiral phosphoramide-derived imines can undergo the asymmetric aza-Darzens reaction or not.

Phosphoramide **1** was prepared starting from (1*R*,2*R*)-1,2-diaminocyclohexane according to the procedure for the synthesis of *N*-alkyl phosphoramides without the use of chromatography.[15] The synthesis of phosphoramide **1** has been carried out on a 40.0 g-scale to give consistent chemical yields of >90%. This white solid product has been stored at rt without inert gas protection for several months; there was no sign of decomposition as revealed by TLC, ^1H



Scheme 1. Asymmetric aza-Darzens reaction using *N*-phosphonimine.

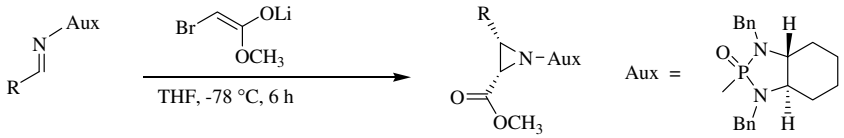
Table 1
Results of the synthesis of chiral *N*-phosphonyl imines



Entry	R	Product	Yield[a] (%)
1	Phenyl	**2a**	65
2	4-MeO-phenyl	**2b**	66
3	4-BnO-phenyl	**2c**	65
4	4-Me-phenyl	**2d**	68
5	2-Me-phenyl	**2e**	64
6	4-F-phenyl	**2f**	74
7	4-Cl-phenyl	**2g**	69
8	2-Cl-phenyl	**2h**	66
9	4-Br-phenyl	**2i**	67
10	2-Thienyl	**2j**	63

[a] Isolated yields after flash column chromatography.

Table 2
Results of asymmetric aza-Darzens reaction[18]



2a - 2j **3a - 3j**

Entry	R	Product	de[a] (%)	Yield[b] (%)
1	Phenyl	**3a**	>99	74[c]
2	4-MeO-phenyl	**3b**	92	81
3	4-BnO-phenyl	**3c**	94	72
4	4-Me-phenyl	**3d**	88	78
5	2-Me-phenyl	**3e**	92	76
6	4-F-phenyl	**3f**	88	64
7	4-Cl-phenyl	**3g**	86	66
8	2-Cl-phenyl	**3h**	88	59
9	4-Br-phenyl	**3i**	86	68
10	2-Thienyl	**3j**	80	82

[a] Determined by the crude ^{1}H NMR or ^{31}P NMR analysis.
[b] Combined yields of the two diastereomers.
[c] Isolated yield of a single diastereomer.

NMR, and ^{31}P NMR analysis. The X-ray crystal structure of this compound has been obtained and shown in Figure 2.[16] In the crystalline state, the C_2-symmetry can be clearly identified and two benzyl groups are arranged asymmetrically so as to participate in the asymmetric induction.

The synthesis of chiral *N*-phosphonyl imines was first conducted by reacting chiral phosphoramide **1** with benzaldehyde in CH_2Cl_2 in the presence of milder Lewis acids such as $Ti(OiPr)_4$ and $Ti(OEt)_4$, which follows the procedure of *N*-sulfinimine synthesis.[5] However, the reaction did not give any product at rt and even under refluxing condition. After the stronger Lewis acid, $TiCl_4$, was employed in the presence of *N*,*N*-diisopropyl ethylamine (DIPEA), a low yield (35%) of product was obtained at 0 °C after 48 h. The yield was improved to 65% when the temperature was raised to rt. Increased amounts of $TiCl_4$ and adding 4 Å molecular sieves did not show any beneficial effect on this reaction. The optimized condition is described below: Chiral phosphoramide **1** and aldehydes (1:1 mol ratio) were dissolved in dichloromethane. The resulting mixture was cooled down to 0 °C under nitrogen protection. *N*,*N*-diisopropylethylamine was added prior to dropwise additions of $TiCl_4$ solution in CH_2Cl_2 (1.0 M, 0.5 equiv). The reaction was stirred at 0 °C for 30 min and then at rt for 48 h. The results for the synthesis of ten chiral *N*-phosphonyl imines (**2**) were summarized in Table 1.

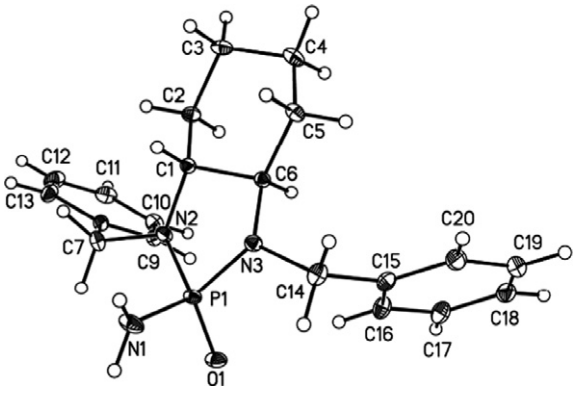


Fig. 2. X-ray structure of chiral phosphoramide **1**.

The asymmetric aza-Darzens reaction was next studied by using the above chiral *N*-phosphonyl imines as the electrophiles. This reaction is among the most suitable model reactions to examine chiral imine chemistry because it consists of two steps in a one-pot operation; and the resulting chiral aziridine-2-carboxylic esters are invaluable building blocks for many biologically important compounds,[1] such as α- and β-amino acids, β-substituted α-amino acids, β-hydroxy α-amino acids, α-amino aldehydes, and ketones. Although chiral *N*-*p*-toluenesulfinyl imines have been proven to be suitable for aza-Darzens reaction,[11a] a successful aza-Darzens example by the use of chiral *tert*-butanesulfinyl imines has not been reported yet.[11d,e] The procedure of this *N*-phosphonyl imines asymmetric reaction is similar to that of *N*-*p*-toluenesulfinyl imine-based system in which *N*-phosphonyl imines (**2**, 1.0 equiv) were added into preformed lithium enolate of methyl 2-bromoacetate (2.0 equiv) in THF solution and stirred at −78 °C for 6 h. Modest to good chemical yields (59–82%) and good to excellent diastereoselectivity (80–99% de) were obtained (Table 2). As compared with the previous *N*-*p*-toluenesulfinyl imine-based aziridination in which 2.5 h are needed, the present process required a longer period of 6 h. This prolonged period indicates *N*,*N*-dibenzylphosphonyl imines **2** have lower electrophilicity than *N*-*p*-toluenesulfinyl imines. Importantly, the electrophilicity of our new chiral *N*-phosphonyl imines can be controlled by introducing a variety of

electron-donating or electron-withdrawing groups onto nitrogen to replace the benzyl group. This controlling strategy cannot be realized in *N*-sulfinyl imine chemistry. In addition, these new imines have been proven to be more stable than *N*-sulfinyl imines.

The diastereoselectivity was determined by the crude ^{1}H NMR or ^{31}P NMR analysis of aziridine products. The phosphorus decoupled ^{1}H NMR analysis revealed that the methyl aziridine-2-carboxylate products were controlled in *cis*-geometry ($J = 6.5$ Hz for coupling of C-2 and C-3 protons). Interestingly, unlike the *N*-*p*-toluenesulfinyl imine-based aziridination, there were no trans isomers detected for all the cases we examined by the crude NMR analysis.

The absolute structure was determined by converting an aziridine product into an authentic sample, β-hydroxyl α-amino acid methyl ester.[11a] The ring opening hydrolysis was performed by treating *N*-phosphonyl aziridine-2-carboxylic ester with trifluoroacetic acid in acetone and water at rt. Two diastereoisomers were obtained in a ratio of 4:1. Under this condition, the *N*-phosphonyl protection group can be cleaved simultaneously, which enables the recovery of diamine auxiliary.

Based on resulting chirality on the carbonyl addition, a cyclic six-membered transition state is proposed as shown in Figure 3. Attacking of *E*-configured lithium enolate of methyl 2-bromoacetate onto *N*-phosphonimine should be directed onto its *Re*-face. Very interestingly, unlike *N*-*p*-toluenesulfinyl imine-based aza-Darzens reaction, the coordination of phosphonyl oxygen with lithium cation to form an additional four-membered ring is inhibited during the present reaction process. The bulky moiety of chiral auxiliary is pushed away by the sterically hindered side of the six-membered transition state. The asymmetric arrangement of the C_2-symmetric benzyl groups on two nitrogens is resulted from the X-ray structural analysis of chiral phosphoramide **1** shown in Figure 1. As revealed in Figure 3, there are two smaller steric moieties, hydrogen and a lone pair of electrons existing along the enolate attacking pathway within a widely open space of *N*-phosphonimine template. This asymmetric environment ensures the resulting *S*-chirality on the carbonyl addition center as well as the chirality of the α-position of *N*-phosphonyl aziridine-2-carboxylic esters.

Finally, the new chiral *N*-phosphonyl imines also showed promising results for the aza-Henry reaction. The chiral *N*-phosphonyl imine **2a** reacted with the nitromethane-derived lithium anion to give β-nitro amine **4** in 72% yield and 92% de (Scheme 2).[17] Our ongoing research indicated that these results can be improved simply by using different lithium bases.

In summary, the free NH_2 group-attached chiral phosphoramide **1** and novel chiral *N*-phosphonyl imines **2** have been designed and synthesized. The reactivity and stability of these *N*-phosphonyl imines proved to be suitable for asymmetric aza-Darzens reaction and asymmetric aza-Henry reaction. New conditions for the synthesis of chiral *N*-phosphonyl imines, the improvements on yields and diastereoselectivity for these two asymmetric reactions and the applications of chiral *N*-phosphonyl imines to a series of other asymmetric C–C bond formations will be investigated. The larger scale synthesis for recycling chiral auxiliary will also be studied in our laboratories. We believe the chiral *N*-phosphonimine results described in this Letter can open a new door for chiral imine chemistry, and will attract a widespread attention among organic community.

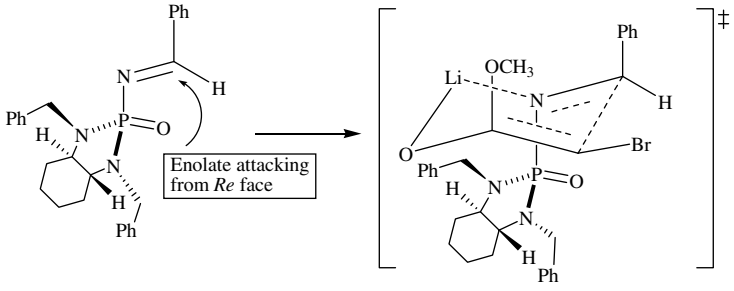
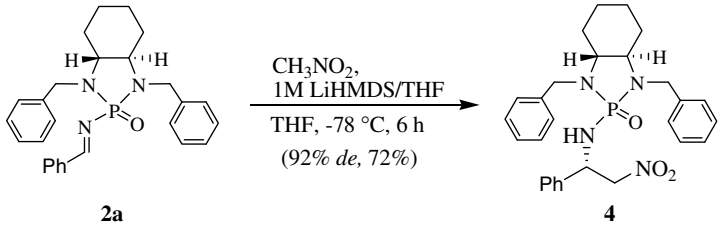


Fig. 3. Proposed transition state model for aza-Darzens reaction.



Scheme 2. Asymmetric aza-Henry reaction using *N*-phosphonimine.

Acknowledgments

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16. CCDC 647795 contains the supplementary crystallographic data for this Letter. The data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
17. The asymmetric induction is assumed to be the same as that of aza-Darzens reaction. For ^{1}H NMR spectrum for this product, see supporting materials.
18. *Typical procedure for the aza-Darzens reaction*: Into an oven dried and N_2 flushed vial were loaded with methyl 2-bromoacetate (0.8 mmol) and THF (4.0 mL). Reaction was cooled to −78 °C and lithium bis(trimethylsilylamide) (1 M solution in THF, 0.8 mmol) was added slowly. After the resulting mixture was stirred for 30 min at −78 °C, a precooled solution of *N*-phosphonyl imine (**2**, 0.4 mmol) was added dropwise via a cannula at the same temperature. Stirring was continued at −78 °C for 6 h and then quenched with water (1.0 mL). The crude product was obtained after standard work-up and purified via flash column chromatography (hexane/EtOAc = 7:3) to give the product as an oil.