Chiral *N*-phosphonyl imine chemistry: Asymmetric synthesis of α,β-diamino esters by reacting phosphonyl imines with glycine enolates

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ARTICLE INFO

ABSTRACT

Chiral phosphonyl imines attached with *N*-isopropyl protection group were found to react with lithium glycine enolates under convenient conditions to give α,β-diamino esters. Thirteen examples have been examined in good to excellent chemical yields (85–97%) diastereoselectivity (up to 99% de). By treating with HBr at room temperature, the chiral auxiliary can be readily removed and recycled. The absolute structure has been unambiguously determined by converting a product to a known sample.

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Vicinal diamino functionality is an important structural unit existing in many biologically active compounds.[1,2] For example, chiral α,β-diamino acid derivatives bearing vicinal diamino frameworks are widely found in number of antibiotics and natural products.[3] Several methods have been developed for the synthesis of α,β-diamino acids and their derivatives including asymmetric Mannich reaction,[4] asymmetric aza-Henry reaction,[5] aziridine ring openings,[6,7] imino-aldol reaction,[8,9] etc. Among these known methods, a direct diastereoseletive addition reaction between a glycine equivalent and an imine is particularly attractive since 'two stereogenic centers could be created in a single operation'.[10]

Very recently, we have established novel *N*-phosphoramide and *N*-phosphonyl imine chemistry, and successfully utilized this chemistry in many nucleopholic addition reactions, such as asymmetric aza-Darzens reaction,[11] asymmetric aza-Henry reaction,[12] asymmetric Mannich reaction,[13] asymmetric additions of allymagnesium bromides,[14] asymmetric additions of Weinreb amide- and malonate-derived enolates.[15] In continuation of our studies on this important chemistry, we would like to report the additions of lithium glycine enolates onto chiral phosphonyl imines for the asymmetric synthesis of chiral α,β-diamino esters (Scheme 1).

In our previous work,[13] the *N*-protection group on imine auxiliary was found to be important in controlling diastereoselectivity of addition reactions. Therefore, we first examined the reaction between 2.0 equiv of lithium glycine enolate and phosphonyl imines bearing different *N*-protection groups (Table 1). The formation of four diastereoisomers was clearly indicated by ^{31}P NMR of the crude reaction mixtures (Table 1, entries 1–5). Among the five protection groups, isopropyl group showed highest diastereoselectivity to give *anti* stereoisomer as major product (Table 1, entry 1).

To further optimize this reaction, several conditions were examined by using different bases for enolate generation and imine **1a** as the electrophilic substrate (Table 2). Among the four bases listed in Table 2, n-BuLi was found to be the best for the generation of metal enolates (Table 2, entry 7). Interestingly, the potassium enolate generated by (Me$_3$Si)$_2$NK failed to react with imine **1a** (Table 2, entry 6). This observation could be attributed to the poor activation of phosphonyl imine by potassium cation.

5.0 Equiv of lithium enolate was found to be necessary to achieve higher diastereoselectivity and chemical yields (Table 2,
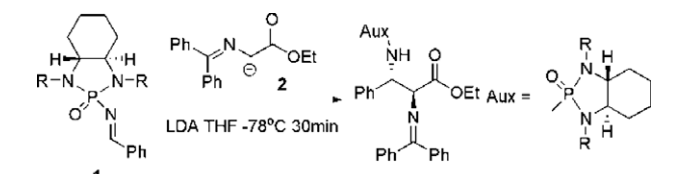
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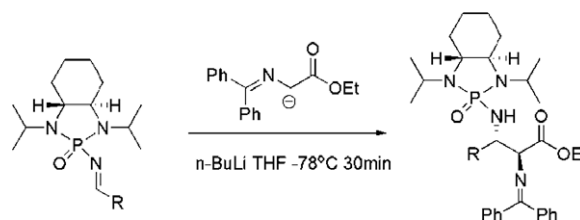
Scheme 1. Additions of glycine enolate to *N*-phosphonyl imines.

Table 1
Effects of protection groups on chiral auxiliary[a]
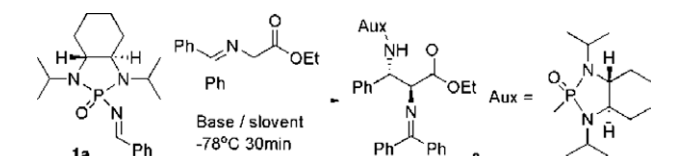
Entry	R	Imine	Ratio[b]	Yield[c] (%)
1	H$_3$C / H$_3$C (isopropyl)	**1a**	100:1:1:15	85
2	H$_3$C / H$_3$C (isobutyl)	**1b**	100:0:0:23	60
3	cyclohexyl	**1c**	100:0:1:25	75
4	benzyl	**1d**	100:3:25:61	80
5	naphthylmethyl	**1f**	100:3:5:30	78

[a] Reaction condition: 0.10 mmol of imine, 0.20 mmol of glycine ethyl ester, 0.22 mmol of base.
[b] Determined by ^{31}P NMR.
[c] Conversion yield, isomers not separated.
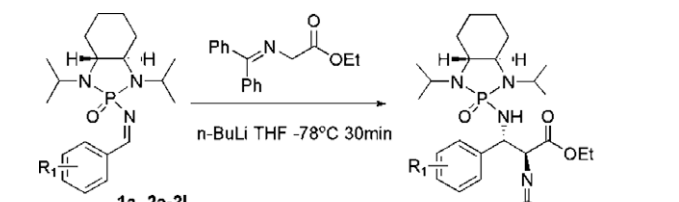
Table 2
Optimization of reaction conditions

Entry	Base	Equiv	Solvent	Isomer ratio[a]	Yield[b] (%)
1	LDA	1.1	THF	100:1:2:14	80
2	LDA	2.0	THF	100:1:1:15	85
3	LDA	3.0	THF	100:2:1:14	92
4	LDA	5.0	THF	100:3:1:9	93
5	LiHMDS	5.0	THF	100:3:1:8	90
6	KHMDS	5.0	THF	—	<10
7	n-BuLi	5.0	THF	100:1:0:5	93
8	n-BuLi	2.0	THF	100:3:1:7	90
9	n-BuLi	5.0	Et2O	100:3:4:5	92
10	n-BuLi	5.0	CH$_2$Cl$_2$	100:2:5:28	88
11	n-BuLi	5.0	PhCH$_3$	100:0:18:16	85

[a] Determined by ^{31}P NMR.
[b] Conversion yield, isomers not separated.

Table 3
Asymmetric additions of phosphonyl imines[a]

Entry	R$_1$	Ratio[b]	Yield[c] (%)
1	Ph (**1a**)	100:1:0:5	93 (**3**)
2	4-CH3 (**2a**)	100:0:0:7	88 (**3a**)
3	4-OCH3 (**2b**)	100:5:0:11	85 (**3b**)
4	4-OBn (**2c**)	100:5:0:8	97 (**3c**)
5	2-Br (**2d**)	100:0:3:5	89 (**3d**)
6	4-Br (**2e**)	100:0:0:12	94 (**3e**)
7	2-Cl (**2f**)	100:0:4:5	87 (**3f**)
8	4-Cl (**2g**)	100:6:0:11	92 (**3g**)
9	4-F (**2h**)	100:1:0:10	90 (**3h**)
10	4-CN (**2i**)	100:7:4:11	92 (**3i**)
11	4-NO$_2$ (**2j**)	100:0:0:12	97 (**3j**)
12	Naphth-1-yl (**2k**)	100:0:0:17	85 (**3k**)
13	Naphth-2-yl (**2l**)	100:4:0:10	88 (**3l**)

[a] Reaction condition: 0.1 mmol imine, 0.5 mmol glycine ethyl ester, 0.55 mmol n-BuLi.
[b] Determined by ^{31}P NMR.
[c] Conversion yield, isomers not separated.

entries 1–4, 7 and 8). The excess amount of glycine ethyl ester can be easily recovered via column purification.

The solvent effect was also examined for this reaction. Tetrahydrofuran (THF) was proven to be the best solvent regarding both chemical yields and diastereoselectivity. When Et$_2$O was employed as solvent, the reaction proceeded smoothly to give a similar yield of 92%, but afforded a slightly lower diastereoselectivity (Table 2, entry 7 and 9). For the cases of CH$_2$Cl$_2$ and toluene as solvents, the diastereoselectivity and chemical yields were decreased (Table 2, entries 10 and 11).

Based on the above optimized condition, we next examined the scope of substrates by using several phosphonyl imines (**2a–2l**). All thirteen cases were performed smoothly with good to excellent chemical yields (85–97%). Both electron-donating (Table 3, entries 2–4) and electron-withdrawing (Table 3, entries 5–11) group-attached phosphonyl imines were found to be suitable for this reaction. When imines bearing ortho groups on their aromatic rings were also used as substrates, slightly higher diastereoselectivites were obtained (Table 3, entries 5–8).

The absolute configuration of product **3** was determined by chemical conversions as shown in Scheme 2. Treatment of **3** with aqueous HBr in methanol at room temperature for 12 hours followed by neutralization with NaHCO$_3$ gave (2S, 3S)-**4** in 90% yield. Further converting **4** to **5** was performed using carbonyl diimidazole and H-4, H-5 coupling constant of 9.6 Hz is consistent with cis
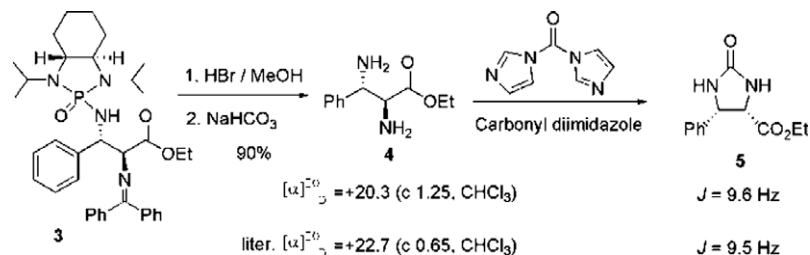
Scheme 2. Determination of the absolute configurations of **3**.

configuration.[10a,16] The optical rotation of **4** and coupling constant of **5** reveals the absolute configuration of diamino product **3** is shown as (2*S*, 3*S*).

In summary, a new method has been developed for the asymmetric synthesis of biologically important chiral α-β diamino esters in good yields and excellent diastereoselectivity. By changing different *N*-protecting groups, the chiral *N*-phosphonyl imines can be optimized to give better results for this reaction. The use of excess amounts of enolates was found to be crucial to the success of this synthesis.

Acknowledgment

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.001.

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