

# Enantioselective Construction of Quaternary $\alpha$ -Carbon Centers on $\alpha$ -Amino Phosphonates via Catalytic Asymmetric Allylation

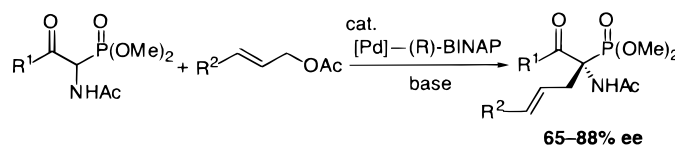
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## ABSTRACT



Asymmetric allylation of  $\alpha$ -acetamido  $\beta$ -keto phosphonates was promoted, in the presence of potassium *tert*-butoxide as a base, by a palladium catalyst prepared from  $[Pd(\pi\text{-allyl})(cod)]BF_4$  and (*R*)-BINAP and gave the corresponding  $\alpha$ -alkyl  $\alpha$ -amino phosphonic acid derivatives with 65–88% ee. Diastereoselective reduction of the carbonyl group in the product was accomplished by  $NaBH_4$  or  $Bu_4NBH_4$ . The diastereoselection in the reduction was reversed by choice of solvent.

Optically active  $\alpha$ -amino phosphonic acids have received much attention due to their potential biological activity<sup>1</sup> as well as being haptens of catalytic antibodies.<sup>2</sup> The efficient synthesis of optically active  $\alpha$ -amino phosphonic acids is one of the important topics in organic synthetic chemistry. Although various chiral  $\alpha$ -amino phosphonic acids have been prepared with high enantiomeric excess by stoichiometric<sup>3</sup>

or catalytic<sup>4</sup> asymmetric reaction,<sup>5</sup> only one example of stereoselective synthesis of  $\alpha$ -amino phosphonic acids, bearing a quaternary chiral  $\alpha$ -carbon atom, has been, to the best of our knowledge, reported.<sup>6,7</sup>

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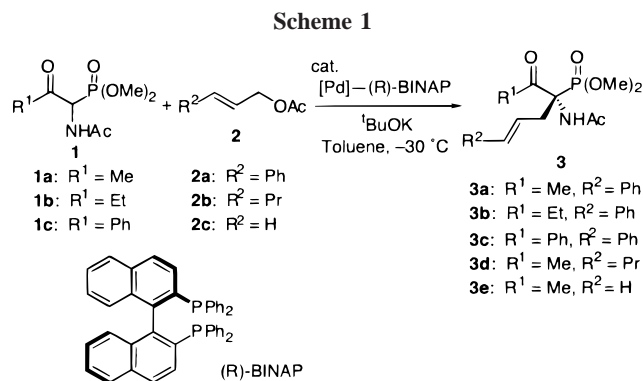
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A chiral carbon center is considerably difficult to construct on prochiral nucleophiles with palladium-catalyzed asymmetric allylation;<sup>8,9</sup> however, a few catalyst systems have been devised for highly enantioselective allylation.<sup>7b,10</sup> Recently, we reported an asymmetric allylation of prochiral nucleophiles,  $\alpha$ -acetamido  $\beta$ -keto esters, introducing a chiral carbon center to the substrate in high enantioselectivity.<sup>11</sup> Herein, we describe an asymmetric allylation of  $\alpha$ -acetamido  $\beta$ -keto phosphonates **1**<sup>4c</sup> catalyzed by an optically active BINAP<sup>12</sup>–palladium complex, which provided chiral  $\alpha$ -allylated  $\alpha$ -amino  $\beta$ -keto phosphonates **3** with up to 88% ee (Scheme 1). The reaction is the first catalytic enantioselective



synthesis of  $\alpha$ -amino phosphonates with a quaternary chiral carbon center.

The asymmetric allylation of **1** with **2** was carried out in toluene at  $-30\text{ }^{\circ}\text{C}$  with potassium *tert*-butoxide and 1 mol % of the chiral catalyst prepared in situ by mixing (*R*)-BINAP and [Pd( $\pi$ -allyl)(cod)]BF<sub>4</sub>.<sup>13</sup> The results are summarized in Table 1. The BINAP–palladium catalyst was

**Table 1.** Catalytic Asymmetric Allylation of  $\alpha$ -Acetamido  $\beta$ -Keto Phosphonates **1**<sup>a</sup>

entry	R <sup>1</sup> ( <b>1</b> )	R <sup>2</sup> ( <b>2</b> )	time (h)	product	yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	Me ( <b>1a</b> )	Ph ( <b>2a</b> )	20	<b>3a</b>	87	87
2	Et ( <b>1b</b> )	Ph ( <b>2a</b> )	48	<b>3b</b>	72	78
3	Ph ( <b>1c</b> )	Ph ( <b>2a</b> )	48	<b>3c</b>	78	88
4	Me ( <b>1a</b> )	Pr ( <b>2b</b> )	48	<b>3d</b>	27	79
5	Me ( <b>1a</b> )	H ( <b>2c</b> )	48	<b>3e</b>	80	65

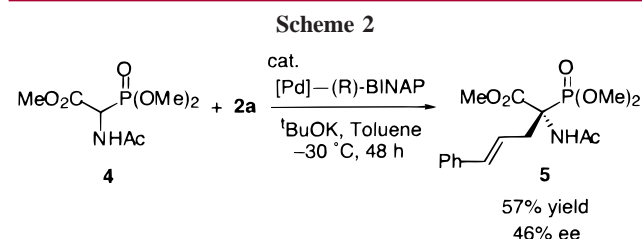
<sup>a</sup> All reactions were carried out in toluene (0.2 M) at  $-30\text{ }^{\circ}\text{C}$ . The ratio of **1**/**2**/*t*BuOK/[Pd( $\pi$ -allyl)(cod)]BF<sub>4</sub>/(*R*)-BINAP was 110:100:120:1:1.1. <sup>b</sup> Isolated yield based on **2**. <sup>c</sup> Determined by HPLC analysis with a chiral stationary phase column.

effective for the asymmetric allylation of **1a** with cinnamyl acetate (**2a**), giving (*S*)-**3a** with 87% ee in 87% isolated yield on the basis of **2a** (entry 1).<sup>14</sup> The allylation of **1a**, which was less reactive than the corresponding  $\alpha$ -acetamido  $\beta$ -keto ester,<sup>11</sup> was carried out by use of an excess amount (1.1 equiv) of **1a** over **2a**.<sup>15</sup> The *O*-substituents on the phosphonyl group affected both the reactivity and the stereoselectivity.

The bulkier isopropyl group brought about a higher degree of enantioface selection of the enolate of **1** (89% ee), but in lower yield (34% yield for 48 h).

Other  $\alpha$ -acetamido  $\beta$ -keto phosphonates **1b** and **1c** also reacted with **2a**, giving **3b** and **3c** with high stereoselectivities, respectively (entries 2 and 3). On the other hand, the reactions of **1a** with allyl acetates **2b** and **2c** proceeded with 79% and 65% ee, respectively (entries 4 and 5). The  $\gamma$ -substituent R<sup>2</sup> of **2** seemed to influence enantioselectivity more than R<sup>1</sup>.

Next, trimethyl 1-(*N*-acetylamino)phosphonoacetate (**4**),<sup>16</sup> in which a phosphonyl group replaced the ketone moiety of  $\alpha$ -acetamido  $\beta$ -keto ester, was subjected to the present asymmetric allylation with **2a** (Scheme 2). The reaction



proceeded slowly with lower enantioselectivity as compared with those of **1**. In comparison with the asymmetric allylation of  $\alpha$ -acetamido  $\beta$ -keto esters reported previously, the ketone moiety may play a more important role in the stereocontrol than the alkoxy carbonyl group.

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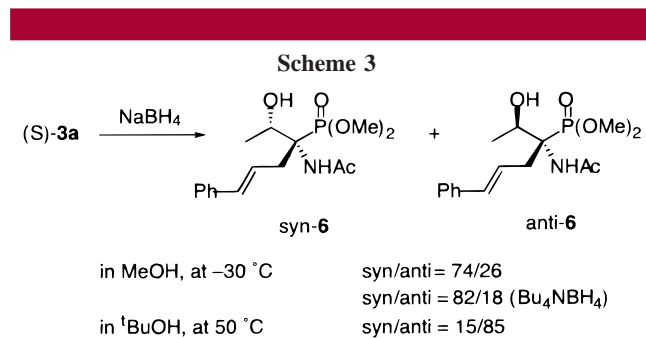
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(13) **General Procedure for the Asymmetric Allylation of  $\alpha$ -Acetamido  $\beta$ -Keto Phosphonates.** A mixture of [Pd( $\pi$ -allyl)(cod)]BF<sub>4</sub> (1.7 mg, 5.0  $\mu$ mol) and (*R*)-BINAP (3.3 mg, 5.3  $\mu$ mol) in toluene (0.5 mL) was stirred for 10 min at room temperature. Allyl ester **2** (0.50 mmol) was added to the solution. After 10 min, the solution was added to a suspension of  $\alpha$ -acetamido  $\beta$ -keto phosphonate **1** (0.55 mmol) and *t*BuOK (67.3 mg, 0.60 mmol) in toluene (2.0 mL) at  $-30\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred for 20 h. The reaction was quenched by 1 N HCl aqueous (3.0 mL). The mixture was extracted three times with EtOAc. The organic layer was washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure. The residue was purified by preparative TLC (EtOAc/MeOH = 10/1), giving **3**.

Optically active **3a** can be readily converted to an  $\alpha$ -alkyl  $\beta$ -hydroxy  $\alpha$ -amino phosphonic acid derivative **6** (Scheme 3). Diastereoselective reduction of (*S*)-**3a** was accomplished



by  $\text{NaBH}_4$  in MeOH to give **6** a 74:26 *syn/anti* ratio of isomers in 74% yield.<sup>17</sup> The *syn*-selectivity was improved to 82:18 (89% yield) by the use of  $\text{Bu}_4\text{NBH}_4$ , which does not contain any metal cation. The improvement of the selectivity suggests that the reduction of the ketone in MeOH may proceed through a nonchelation transition state.<sup>18</sup> The stereoselectivity was significantly dependent upon reaction solvent. The use of  $t\text{BuOH}$  as a reaction solvent led to a reverse in the diastereoselectivity, giving preferentially *anti*-(*2S,3R*)-**6** (*anti/syn* = 85:15) in 78% yield.<sup>19</sup>

In conclusion, asymmetric allylation of  $\alpha$ -acetamido  $\beta$ -keto phosphonates **1** proceeded in good enantioselectivity by

(14) The palladium catalyst prepared in situ from  $[\text{Pd}(\pi\text{-allyl})\text{Cl}]_2$  was also effective for the asymmetric reaction to give 86% ee of **3a**. However, the reaction rate was somewhat slow.

(15) The allylation of **1a** with 1.5 equiv of **2a** proceeded much slower (78% yield for 48 h), and the enantiomeric excess of the product was 84%.

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BINAP–palladium catalyst, giving  $\alpha$ -amino phosphonic acid derivatives **3** bearing a quaternary chiral carbon center at the  $\alpha$ -position. We also succeeded in diastereoselective reduction of **3**, providing either diastereomer of the  $\beta$ -hydroxy  $\alpha$ -amino phosphonates **6** by the appropriate choice of solvent.

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**Supporting Information Available:** Full characterization and  $^{13}\text{C}$  NMR spectra for compounds **3**, **5**, and **6**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) **General Procedure for the Chemoselective Reduction of 3.** To a solution of **3** (0.25 mmol) in MeOH or  $t\text{BuOH}$  (2.5 mL) was added  $\text{NaBH}_4$  or  $\text{Bu}_4\text{NBH}_4$  (0.35 mmol) at the reaction temperature. After **3** disappeared completely, saturated  $\text{NH}_4\text{Cl}$  aqueous (1.0 mL) was added to the mixture, and stirred for 5 min. The mixture was passed through a short column of  $\text{Na}_2\text{SO}_4$  (EtOAc), and the eluent was evaporated under reduced pressure. The residue was purified by medium-pressure liquid chromatography after passing through a short column of silica gel, giving **6**.

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(19) The relative and absolute configuration in **6** was assigned as follows: Each diastereomer of **6** was converted into the corresponding cyclic carbamate with bis(trichloromethyl)carbonate and diisopropylethylamine. The relative configuration of **6** was assigned by NOE experiments of the cyclic carbamates. The absolute configurations of **6** was determined by  $^1\text{H}$  NMR analysis of the *O*-methylmandelate derivative of *syn*-**6** according to Trost's procedure (see ref 20). Further details are described in the Supporting Information.

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