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Enantioselective Construction of Quaternary α-Carbon Centers on α-Amino Phosphonates via Catalytic Asymmetric Allylation

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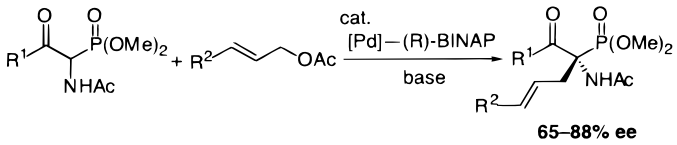
ABSTRACT



Asymmetric allylation of α-acetamido *β*-keto phosphonates was promoted, in the presence of potassium *tert*-butoxide as a base, by a palladium catalyst prepared from [Pd(*π*-allyl)(cod)]BF_4 and (*R*)-BINAP and gave the corresponding α-alkyl α-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 α-amino phosphonic acids have received much attention due to their potential biological activity[1] as well as being haptens of catalytic antibodies.[2] The efficient synthesis of optically active α-amino phosphonic acids is one of the important topics in organic synthetic chemistry. Although various chiral α-amino phosphonic acids have been prepared with high enantiomeric excess by stoichiometric[3] or catalytic[4] asymmetric reaction,[5] only one example of stereoselective synthesis of α-amino phosphonic acids, bearing a quaternary chiral α-carbon atom, has been, to the best of our knowledge, reported.[6,7]

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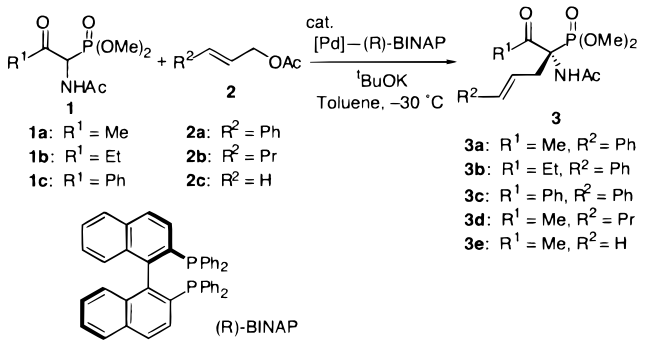
A chiral carbon center is considerably difficult to construct on prochiral nucleophiles with palladium-catalyzed asymmetric allylation;[8,9] however, a few catalyst systems have been devised for highly enantioselective allylation.[7b,10] Recently, we reported an asymmetric allylation of prochiral nucleophiles,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

Scheme 1



synthesis of α-amino phosphonates with a quaternary chiral carbon center.

The asymmetric allylation of **1** with **2** was carried out in toluene at −30 °C with potassium *tert*-butoxide and 1 mol % of the chiral catalyst prepared in situ by mixing (*R*)-BINAP and [Pd(π-allyl)(cod)]BF_4.[13] The results are summarized in Table 1. The BINAP−palladium catalyst was

Table 1. Catalytic Asymmetric Allylation of α-Acetamido β-Keto Phosphonates **1**[a]

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

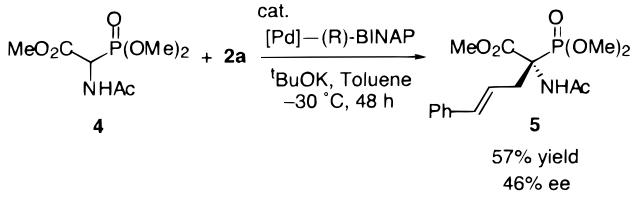
[a] All reactions were carried out in toluene (0.2 M) at −30 °C. The ratio of **1**/**2**/^{t}BuOK/[Pd(π-allyl)(cod)]BF_4/(*R*)-BINAP was 110:100:120:1:1.1. [b] Isolated yield based on **2**. [c] Determined by HPLC analysis with a chiral stationary phase column.

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).[14] The allylation of **1a**, which was less reactive than the corresponding α-acetamido β-keto ester,[11] was carried out by use of an excess amount (1.1 equiv) of **1a** over **2a**.[15] 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 α-acetamido β-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 γ-substituent R^2 of **2** seemed to influence enantioselectivity more than R^1.

Next, trimethyl 1-(*N*-acetylamino)phosphonoacetate (**4**),[16] in which a phosphonyl group replaced the ketone moiety of α-acetamido β-keto ester, was subjected to the present asymmetric allylation with **2a** (Scheme 2). The reaction

Scheme 2



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

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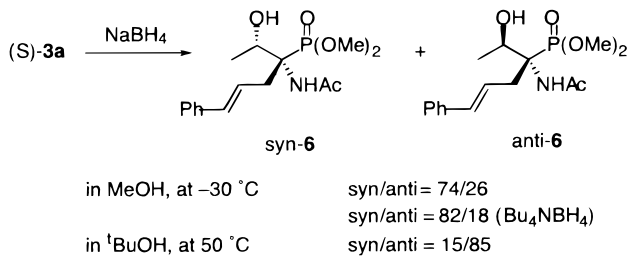
(13) **General Procedure for the Asymmetric Allylation of α-Acetamido β-Keto Phosphonates.** A mixture of [Pd(π-allyl)(cod)]BF_4 (1.7 mg, 5.0 μmol) and (*R*)-BINAP (3.3 mg, 5.3 μmol) in toluene (0.5 mL) was stirred for 10 min at room temperature. Allyl ester **2** (0.50 mmol) was added to the solution. After 10 min, the solution was added to a suspension of α-acetamido β-keto phosphonate **1** (0.55 mmol) and ^{t}BuOK (67.3 mg, 0.60 mmol) in toluene (2.0 mL) at −30 °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_2SO_4, 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 α-alkyl *β*-hydroxy α-amino phosphonic acid derivative **6** (Scheme 3). Diastereoselective reduction of (*S*)-**3a** was accomplished

Scheme 3



by $NaBH_4$ in MeOH to give **6** a 74:26 *syn*/*anti* ratio of isomers in 74% yield.[17] The *syn*-selectivity was improved to 82:18 (89% yield) by the use of Bu_4NBH_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.[18] The stereoselectivity was significantly dependent upon reaction solvent. The use of ^{t}BuOH as a reaction solvent led to a reverse in the diastereoselectivity, giving preferentially *anti*-(2*S*,3*R*)-**6** (*anti*/*syn* = 85:15) in 78% yield.[19]

In conclusion, asymmetric allylation of α-acetamido *β*-keto phosphonates **1** proceeded in good enantioselectivity by BINAP−palladium catalyst, giving α-amino phosphonic acid derivatives **3** bearing a quaternary chiral carbon center at the α-position. We also succeeded in diastereoselective reduction of **3**, providing either diastereomer of the *β*-hydroxy α-amino phosphonates **6** by the appropriate choice of solvent.

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Supporting Information Available: Full characterization and ^{13}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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(14) The palladium catalyst prepared in situ from [Pd(*π*-allyl)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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(17) **General Procedure for the Chemoselective Reduction of 3.** To a solution of **3** (0.25 mmol) in MeOH or ^{t}BuOH (2.5 mL) was added $NaBH_4$ or Bu_4NBH_4 (0.35 mmol) at the reaction temperature. After **3** disappeared completely, saturated NH_4Cl aqueous (1.0 mL) was added to the mixture, and stirred for 5 min. The mixture was passed through a short column of Na_2SO_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}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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