Catalytic Asymmetric Allylation of Prochiral Nucleophiles, α-Acetamido-*β*-ketoesters

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Catalytic asymmetric allylation through a chiral *π*-allylpalladium(II) complex has been intensively studied.[1] Most of the successful examples introduce a chiral center on an allylic substrate.[2] The enantioselective electrophilic attack of a *π*-allylpalladium(II) to a stabilized prochiral nucleophile is not facile to be controlled by a chiral ligand on the palladium atom,[3,4] which is at the opposite side of the *π*-allyl carbon structure from the approaching nucleophile (Figure 1).[5] Some devices have led to

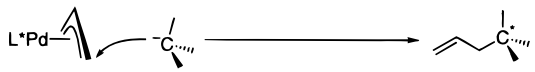


Figure 1.

the high enantioselective allylation of carbon nucleophiles, for example, (i) by the use of a bimetallic catalyst system for allylation with chiral rhodium(I) enolate of α-cyanopropionates,[6] (ii) by the use of a chiral bidentate ligand with wide bite angle for asymmetric allylation of cyclic *β*-ketoesters,[7] which may induce effective transmission of the ligand chirality.

Herein, we wish to report a highly enantioselective allylation (up to 95% ee) of prochiral nucleophiles, α-acetamido-*β*-ketoesters **1**, catalyzed by the chiral BINAP−palladium complex. The α-acetamido-*β*-ketoesters are new carbon nucleophiles, which undergo palladium-catalyzed allylations to furnish α-allyl-α-acetamido-*β*-ketoesters **3** having a quaternary stereogenic center at the α-carbon.[8]

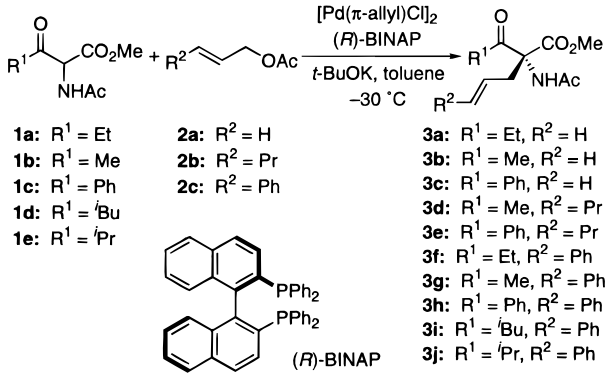
Table 1. Asymmetric Allylation of α-Acetamido-*β*-ketoesters **1**[a]

entry	R^1 (**1**)	R^2 (**2**)	time, h	product	yield, %[b]	ee, %[c]
1	Me (**1b**)	H (**2a**)	24	**3b**	84	76
2	Ph (**1c**)	H (**2a**)	24	**3c**	92	80
3	Me (**1b**)	Pr (**2b**)	24	**3d**	96	87
4	Ph (**1c**)	Pr (**2b**)	48	**3e**	40	89
5	Et (**1a**)	Ph (**2c**)	4	**3f**	87	91
6	Me (**1b**)	Ph (**2c**)	2	**3g**	87	94
7	Ph (**1c**)	Ph (**2c**)	48	**3h**	71	95
8	*i*-Bu (**1d**)	Ph (**2c**)	2	**3i**	86	92
9	*i*-Pr (**1e**)	Ph (**2c**)	4	**3j**	85	91

[a] All reactions were carried out in toluene (0.2 M) at −30 °C. The ratio of **1**:**2**:*t*-BuOK:[Pd(*π*-allyl)Cl]$_2$:(*R*)-BINAP was 100:150:120:1:1.05 unless otherwise noted. [b] Isolated yield by PTLC. [c] Determined by HPLC analysis with chiral stationary-phase column.

The first attempt for asymmetric allylation of methyl 2-(*N*-acetylamino)-3-oxopentanoate (**1a**) with allyl methyl carbonate was carried out in THF at 0 °C in the presence of the palladium catalyst generated from $Pd_2(dba)_3$·$CHCl_3$ and (*R*)-BINAP.[9] The reaction was completed in 5 h to give the corresponding allylation product (**3a**) with 45% ee in 97% yield.[10,11] The enantioselectivity was improved up to 72% ee by the use of allyl acetate and *t*-BuOK in toluene at −30 °C for 30 h in the presence of the palladium complex catalyst generated from [Pd(*π*-allyl)Cl]$_2$ and (*R*)-BINAP, giving **3a** in 76% yield (Scheme 1).

Scheme 1



The allylations of α-acetamido-*β*-ketoesters **1** with some allylic substrates **2** in toluene at −30 °C were examined, as summarized in Table 1. Various optically active allylation products **3b**−**j** were obtained with 77−95% ee in high yields by the use of the (*R*)-BINAP−palladium catalyst. Noteworthy is that the allylation of **1** with *γ*-substituted allylic substrates **2b** and **2c** provided selectively the corresponding **3d**−**j** without being accompanied by the regio- and (*Z*)-geometrical isomers. The enantioselectivities depended significantly upon substituent at the *γ*-carbon of **2**,

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(8) For catalytic asymmetric syntheses of α-alkylated α-amino acids with high enantiomeric excess, see: (a) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron* **1988**, *44*, 5253−5262. (b) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532−11533 and ref 4b.

(9) (*R*)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl: Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932−7934.

(10) Representative results with other chiral ligands in THF were as follows: (+)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane (DIOP: 2% ee), (2*S*,3*S*)-2,3-bis(diphenylphosphino)butane (CHIRAPHOS: 1% ee), (*R*)-*N*,*N*-dimethyl-1-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]-ethylamine (BPPFA: 13% ee), (*R*,*R*)-2,2″-bis[(*S*)-1-(diphenylphosphino)ethyl]-1,1″-biferrocene (PhTRAP: 21% ee), (1*R*,2*R*)-bis[*N*-(2′-diphenylphosphino)-benzoylamino]cyclohexane (no reaction), (*S*)-2-[2-(diphenylphosphino)phenyl]-4-(phenyl)oxazoline (1% ee).

(11) Toluene was superior to THF, giving 56% ee of **3a**. The enantioselectivities of **3a** in some other solvents were as follows: Et_2O (47% ee), CH_2Cl_2 (31% ee), *i*-PrOH (40% ee).

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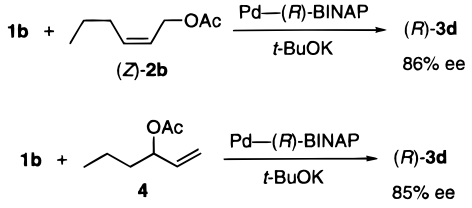
giving higher enantioselectivities with increasing steric bulkiness of the γ-substituents. In general, the allylation of **1** with cinnamyl acetate (**2c**) proceeded well at −30 °C to afford the corresponding **3f**−**j** with 91−95% ee (entries 5−9). On the other hand, the acyl substituent R^1 of **1** affected the enantioselectivities of the allylation reaction slightly.

The allylation of **1b** with either (*Z*)-**2b** or **4** afforded (*R*)-**3d** with nearly identical enantioselectivity (85−86% ee) without the formation of its regio- and geometrical isomers, suggesting that the nucleophilic attack of an enolate of **1** may be slow as compared with any possible $\pi-\sigma-\pi$ isomerization of the π-allylpalladium complex initially generated (Scheme 2).[12]

Scheme 2



Although the mechanism for the enantioface-selection of the enolate of **1** has not been made clear yet, the phenyl groups of BINAP ligand may be crucially important for the control of stereoselectivity. As seen from the X-ray crystal structure of [Pd(π-allyl){(*R*)-BINAP}]ClO_4 (Figure 2),[13] two equatorial[14] phenyls on the phosphorus stretch out over the π-allyl ligand on the palladium atom. Consequently, the phenyl groups of BINAP may interact with the prochiral nucleophile approaching the π-allyl carbon structure from the opposite face.

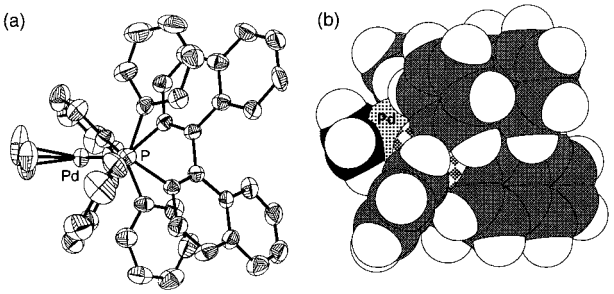
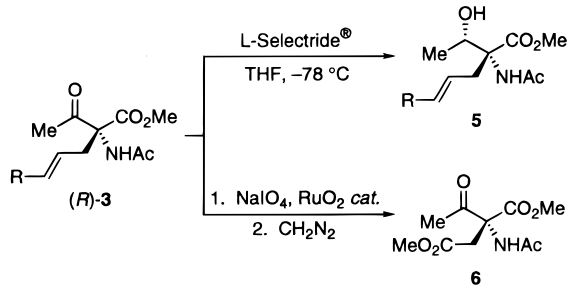


Figure 2. X-ray crystal structure of [Pd(π-allyl){(*R*)-BINAP}]ClO_4·(CH_3COCH_3). (a) ORTEP drawing (50% probability level). Hydrogen atoms, perchlorate anion, and acetone are omitted for clarity. (b) Space filling model. Black atoms indicate the carbon atoms of the π-allyl ligand.

Optically active (*R*)-2-(*N*-acetylamino)-3-oxocarboxylates **3** thus obtained were readily converted into various α-alkylated α-amino acid derivatives (Scheme 3). Reductions of **3** with

Scheme 3



L-Selectride[15] gave the corresponding (2*R*,3*S*)-α-alkyl-β-hydroxy-α-amino acid derivatives **5** with high diastereoselectivities (>96% de).[16] The absolute configurations of **3** were assigned to be *R* by NMR studies of the MTPA esters of **5**.[17] Oxidative cleavage of the olefin of **3g** with $NaIO_4$ and a catalytic amount of RuO_2 (2 mol %) followed by treatment with diazomethane gave a protected α-acetylaspartic acid **6** in 82% yield without the loss of the enantiopurity.[18]

We succeeded in highly enantioselective allylation of prochiral nucleophile **1** by a BINAP−palladium catalyst, providing optically active α-allyl-α-acetamido-β-ketoesters **3**, which are versatile precursors for the synthesis of β-hydroxy-α-alkyl-α-amino acids. Further mechanistic studies are in progress.

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Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystal structure data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For crystal structures of BINAP−palladium complexes with a di- or trisubstituted π-allyl ligand, see: (a) Pregosin, P. S.; Rüegger, H.; Salzmann, R.; Albinati, A.; Lianza, F.; Kunz, R. W. *Organometallics* **1994**, *13*, 83−90. (b) Pregosin, P. S.; Rüegger, H.; Salzmann, R.; Albinati, A.; Lianza, F.; Kunz, R. W. *Organometallics* **1994**, *13*, 5040−5048. (c) Drommi, D.; Nesper, R.; Pregosin, P. S.; Trabesinger, G.; Zürcher, F. *Organometallics* **1997**, *16*, 4268−4275. (d) Yamaguchi, M.; Yabuki, M.; Yamagishi, T.; Sakai, K.; Tsubomura, T. *Chem. Lett.* **1996**, 241−242.

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