ORGANIC LETTERS

2001
Vol. 3, No. 21
3329−3331

# Chiral Phosphine-Free Pd-Mediated Asymmetric Allylation of Prochiral Enolate with a Chiral Phase-Transfer Catalyst

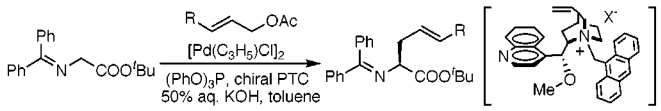
**Masayoshi Nakoji, Takatoshi Kanayama, Tomotaka Okino, and Yoshiji Takemoto***

*Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan*

*takemoto@pharm.kyoto-u.ac.jp*

**Received August 13, 2001**

## ABSTRACT




**A chiral phase-transfer catalyst has been applied to the asymmetric allylation of the *tert*-butyl glycinate-benzophenone Schiff base with various allylic acetates for the first time to give the allylated products in good yields and with comparable to higher enantioselectivity than for asymmetric alkylation at the same temperature (91–96% ee) without any chiral ligands for coordinating to the palladium.**

Chiral α-alkyl and α,α-dialkyl α-amino acids are an important class of nonproteogenic amino acids and have attracted considerable attention in biological and pharmacological studies because introduction of these amino acids to peptides induces conformational constraints and enhances metabolic stability.[1] As a result, thus far, a number of diastereoselective synthetic methods of α-alkylated amino acids using various chiral auxiliaries has been reported.[2] Recently, the catalytic asymmetric synthesis has been intensively studied, and some efficient methods have been developed other than the asymmetric hydrogenation of dehydroamino acids.[3−6] The asymmetric alkylation of glycine iminoesters by a chiral phase-transfer catalyst (PTC) would be a versatile method in terms of operational simplicity and high enantioselectivity.[3] However, the PTC-mediated reaction only produces a single chiral center in α-alkylated amino acids. On the other hand, the asymmetric allylation of the glycine iminoester through a chiral $\pi$-allyl palladium(II) complex can construct two stereogenic centers on both the

(1) Fenteany, G.; Standaert, R. F.; Lane, W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L. *Science* **1995**, *268*, 726−731. Krohn, K.; Kirst, H. A.; Maag, H. *Antibiotics and Antiviral Compounds*, VCH: Weinheim, 1993. Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244−1267. Jung, G.; Beck-Sickinger, A. G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 367−383.

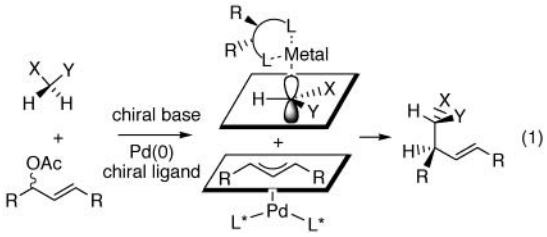
(2) Guillena, G.; Nájera, C. *J. Org. Chem.* **2000**, *65*, 7310−7322. Calmes, M.; Daunis, J. *Amino Acids* **1999**, *16*, 214−250. Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225−227. Ohfune, Y.; Moon, S.-H.; Horikawa, M. *Pure Appl. Chem.* **1996**, *68*, 645−648. Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708−2748. Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995. Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383−389. Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238−264. Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989.

(3) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3−15. Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Larionov, O. V.; Harutyunyan, S. R.; Vyskocil, S.; North, M.; Kagan, H. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1948−1951. Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92−138. Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2000**, *11*, 3277−3281. Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228−5229. Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000−13001. Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671−8674.

(4) Kazmaier, U.; Maier, S.; Zumpe, F. L. *Synlett* **2000**, 1523−1535. You, S.-L.; Hou, X.-L.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1933−1934. Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727−10737. Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1468−1470. Hiroi, K.; Hidaka, A.; Sezaki, R.; Imamura, Y. *Chem. Pharm. Bull.* **1997**, *45*, 769−777. Baldwin, I. C.; Williams, J. M. J.; Beckett, R. P. *Tetrahedron: Asymmetry* **1995**, *6*, 1515−1518. Genet, J.-P.; Juge, S.; Achi, S.; Mallart, S.; Montes, J. R.; Levif, G. *Tetrahedron*, **1988**, *44*, 5263−5275. Very recently a similar reaction has been reported by the Chinese groups: Chen, G.; Deng, Y.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1567−1571.

10.1021/ol016567h CCC: $20.00 
**Published on Web 09/15/2001**

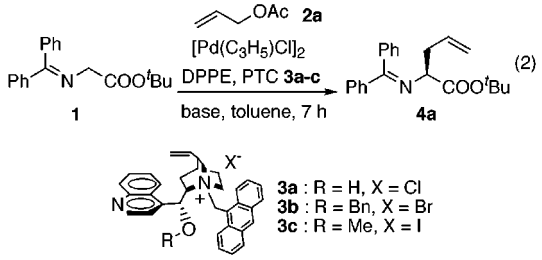
allylic substrate and the prochiral nucleophile, albeit stereoselectivity of the latter chiral center might be low.[4] In general, the enantioselective nucleophilic attack of a prochiral nucleophile to a $\pi$-allyl complex is not easily controlled by a chiral ligand on the palladium atom located at the opposite side of the $\pi$-allyl carbon structure from the approching nucleophile.[7] To overcome the problems incurred in this reaction, several ingenious ligands for constructing an effective chiral environment around the $\pi$-allyl palladium(II) complex have been developed.[8] With the aim of establishing a different methodology, we examined the possibility of using a chiral ligand for constructing an effective chiral environment around a prochiral nucleophile (eq 1). Herein, we wish to report a highly enantioselective




allylation (up to 96% ee) of diphenylimino glycinate **1** with several allylic aceates **2a**−**g**, catalyzed by the achiral metal complex [Pd($\pi$-allyl)Cl]$_2$/(PhO)$_3$P in the presence of the chiral *O*-methyl chinconidinium salt **3c**.

The first attempt for asymmetric Pd-mediated allylation of **1** with allyl acetate **2a** was carried out in toluene at room temperature in the presence of the chinchonidium salts **3a**−**c** and various achiral phosphine or phosphite ligands. These representative results are shown in Table 1 (eq 2). The reaction of **1** in the presence of **3a** and 1,2-bis(diphenylphosphino)ethane (DPPE) was completed in 6 h to give the corresponding allylation product **4a** in good yields but with low enantioselectivity (3% ee, entry 1). Similar reactions with O-alkylated PTCs **3b** and **3c** afforded the same product **4a**

**Table 1.** Asymmetric Allylation of **1** under PTC Conditions[a]




| entry | PTC | ligand, mol % | base | yield, %[b] | ee, %[c] |
|---|---|---|---|---|---|
| 1 | **3a** | DPPE (8) | KOH | 83 | 3 |
| 2 | **3b** | DPPE (8) | KOH | 91 | 9 |
| 3 | **3c** | DPPE (8) | KOH | 74 | 24 |
| 4 | **3c** | *n*-Bu$_3$P (16) | KOH | 69 | 4 |
| 5 | **3c** | Ph$_3$P (16) | KOH | 32 | 59 |
| 6 | **3c** | (PhO)$_3$P (16) | KOH | 19 | 82 |
| 7[d] | **3c** | (PhO)$_3$P (16) | 50% KOH | 82 | 94 |

[a] All reactions were carried out in toluene at room temperature. The ratio of **1**:**2**:base:[Pd($\pi$-allyl)Cl]$_2$:PTC was 100:200:150:3.5:10 unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC analysis with Daicel Chiral Pack OD-H column. [d] The reaction was carried out at 0 °C. The ratio of **1**:**2**:base:[Pd($\pi$-allyl)Cl]$_2$:(PhO)$_3$P:PTC was 100:200:300:8.7:40:10.

with slightly improved enantioselectivity (entries 2 and 3). We next examined the effect of Pd ligands other than DPPE on the enantionselectivity. Whereas the addition of *n*-Bu$_3$P in place of DPPE decreased the enantioselectivity, Ph$_3$P and (PhO)$_3$P gave the desired product **4a** in 59% and 82% ee's at the expense of the chemical yield, respectively (entries 4−6). Furthermore, it was revealed that the best result (82% yield, 94% ee) was obtained when the reaction was performed with 3 equiv of a 50% aqueous KOH solution in place of solid KOH at 0 °C (entry 7).

Having established higher levels of enantioselectivity, the allylation of **1** with some allylic substrates **2b**−**g** was examined using a combination of (PhO)$_3$P and **3c**, and the representative results are summarized in Table 2 (eq 3). Various optically active allylation products **4b**−**g** were obtained with 91−96% ee in moderate to good yields. The allylation of **1** with $\gamma$-substituted allylic substrate **2b**−**g** provided selectively the corresponding products **4b**−**g** without accompanying regio- and (*Z*)-geometrical isomers. Noteworthy is that the enantioselectivity of **4b**−**g** was not affected by the *p*-substituent of the aromatic ring of **2b**−**g**, while the reaction rate decreased with increasing electron-donating ability of the substituent. In addition, the allylation of **1** with the racemic acetate **5** afforded the same product (*S*)-**4b** with nearly identical enantioselectivity (47% yield, 93% ee) (eq 4).[9] The result suggests that the nucleophilic attack of the enolate of **1** may be slow as compared with any possible $\pi-\sigma-\pi$ isomerization of the $\pi$-allyl-palladium complex initially generated. Furthermore, from the fact that

(5) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2000**, *39*, 4114−4116. Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J*. **2000**, *6*, 2435−2448. Yamada, K.; Harwood: S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed*. **1999**, *38*, 3504−3506. Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem*. **1999**, *64*, 2168−2169. Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc*. **1999**, *121*, 5450−5458. Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem*. **1999**, *64*, 2614−2615. Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed*. **1998**, *37*, 979−981; Drury, W. J., III; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc*. **1998**, *120*, 11006−11007.

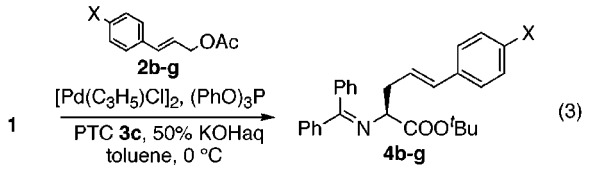
(6) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

(7) Malleron, J. L.; Fiaud, J. C.; Legros, J. Y. *Handbook of Palladium-Catalyzed Organic Reactions*; Academic Press: San Diego, 1997. Trost, B. M.; Van Vranken, D. L. *Chem. Rev*. **1996**, *96*, 395−422. Trost, B. M. *Acc. Chem. Res*. **1996**, *29*, 355−364. Williams, J. M. J. *Synlett* **1996**, 705−710. Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995.

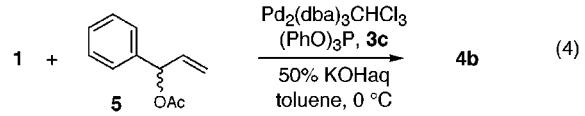
(8) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. *Org. Lett*. **2001**, *3*, 149−151. Braun, M.; Laicher, F.; Meier, T. *Angew. Chem., Int. Ed*. **2000**, *39*, 3494−3497. Trost, B. M.; Surivet, J.-P. *J. Am. Chem. Soc*. **2000**, *122*, 6291−6292. Kuwano, R.; Ito, Y. *J. Am. Chem. Soc*. **1999**, *121*, 3236−3237. Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc*. **1999**, *121*, 6759−6760. Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc*. **1997**, *119*, 7879−7880. Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc*. **1996**, *118*, 3309−3310. Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc*. **1992**, *114*, 2586−2592.

(9) Fuji, K. Ohnishi, H.; Moriyama, S.; Tanaka, K.; Kawabata, T.; Tsubaki, K. *Synlett* **2000**, 351−352; Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc*. **1998**, *120*, 1681−1687; Prétot, R.; Pfaltz, A. *Angew. Chem., Int. Ed*. **1998**, *37*, 323−325; Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc*. **1996**, *118*, 235−236.

**Table 2.** Allylation of **1** with Other Allylic Acetates **2b**−**g**[a]




(**b**: X = H, **c**: X = Cl, **d**: X = F, **e**: X = $NO_2$, **f**: X = Me, **g**: X = OMe)



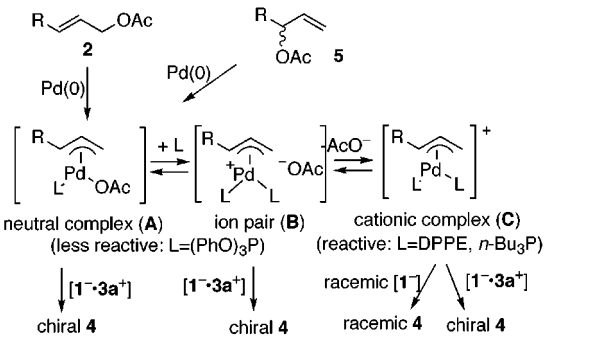

| entry | acetate (X) | time, h | yield, %[b] | ee, %[c] |
|---|---|---|---|---|
| 1 | **2b** (X = H) | 3 | 89 | 96 |
| 2 | **2c** (X = Cl) | 7 | 85 | 93 |
| 3 | **2d** (X = F) | 6 | 83 | 93 |
| 4 | **2e** (X = $NO_2$) | 5 | 47 | 91 |
| 5 | **2f** (X = Me) | 9 | 67[d] | 91 |
| 6 | **2g** (X = OMe) | 23 | 39[d] | 96 |

[a] All reactions were carried out in toluene at 0 °C. The ratio of **1**:**2b**−**g**:50% aq KOH:[Pd($\pi$-allyl)Cl]$_2$:(PhO)$_3$P:PTC was 100:200:300:8.7:40:10. [b] Isolated yield. [c] Determined by HPLC analysis with Daicel Chiral Pack OD-H column. [d] The starting material **1** was not consumed completely.

the reaction did not proceed without the palladium catalyst and the same product (*S*)-**4a**−**g** was obtained similarly to the asymmetric alkylation of **1** with **3a**−**c**, the chiral ion pair of the enolate of **1** and **3c**, which seems to be the most reactive nucleophile,[3] would react with the $\pi$-allyl complex (**A** or **B**), giving the chiral product **4a**−**g** with high enantioselectivity (Scheme 1). It is known that the cationic complex **C** is more reactive than the neutral and ion pair complexes **A** and **B** for the following nucleophilic substitution.[10] Therefore, if the more $\sigma$-donating ligands such as DPPE and *n*-$Bu_3$P are used, the active cationic complex **C** might be formed predominantly. Any achiral enolates as well as the chiral ion pair of the enolate of **1** and **3c** can react

(10) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089−1122.

**Scheme 1**




with **C**, resulting in poor enantioselectivity. In contrast, when the more $\pi$-accepting ligand such as $(PhO)_3P$ is used, the less reactive complexes **A** and **B** might be formed exclusively, and complete suppression of the racemic reactions with achiral enolates leads to the highly enantiomeric pure product.[11]

In conclusion, while the reasons for the high dependence of the enantioselectivity on the Pd ligands employed have not been made clear, we have succeeded in the first highly enantioselective allylation of the prochiral enolate of **1** by using the chiral PTC **3c** but not a chiral Pd ligand. By this method, various optically active α-allylic amino acids **4a**−**g** could be prepared with comparable to higher enantioselectivity than that of the asymmetric alkylation of **1** with **3a** or **3b** at 0 °C to room temperature.

**Acknowledgment.** This work was supported by the Mitsubishi Chemical Corporation Fund and the Takeda Science Foundation.

**Supporting Information Available:** Experimental details and characterization of **3c**, **4a**, **4b**, **4c**, and **4g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Kuhn, O.; Mayr, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 343−34.