## Enantioselective Palladium Catalyzed Allylic Alkylation with C2-symmetric Chiral Diamine Ligands

Hideki Kubota,<sup>a</sup> Makoto Nakajima,<sup>b</sup> and Kenji Koga<sup>b</sup>\*

\*Tokyo R&D Center, Daiichi Pharmaceutical Co., Ltd., Edogawa-ku, Tokyo 134, Japan

<sup>b</sup>Paculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract: A C2-symmetric chiral diamine ligand 1 was found to be effective for palladium catalyzed asymmetric allylic substitution of racemic 1,3-diphenyl-2-propenyl acetate 5 with dimethyl malonate. The X-ray analysis and NMR study of the palladium complex 7 with chiral diamine 1 have revealed the mechanism of high enantioselection.

Palladium catalyzed allylic substitution is one of the most significant carbon-carbon bond forming reactions in organic synthesis and its enantioselective control has been a challenge in recent asymmetric synthesis.<sup>1</sup>

During the last years, it has been shown that a number of chiral phosphine complexes catalyze the conversion of racemic allylic substrates to optically active substitution products.<sup>2</sup> Recently, several groups have reported that promising enantioselectivity is achieved with chiral ligands containing nitrogen, 3.4.5 which have been received considerable attention because of greater advantage of design versatility over phosphine ligands. Although chiral oxazoline ligands were systematically studied by Pfaltz,<sup>3</sup> there is only one example reported about the use of aliphatic tertiary amine with  $\sigma$ -donor character by Togni.<sup>4</sup>

Optically active C<sub>2</sub>-symmetric pyrrolidines, on the other hand, have been utilized as chiral auxiliaries for asymmetric synthesis.<sup>6</sup> We have reported that bidentate diamine ligands constructed by chiral pyrrolidines are effective for asymmetric 1,2-addition and asymmetric dihydroxylation.<sup>7</sup> Here, we wish to describe the development of a simple diamine ligand 1 for palladium catalyzed asymmetric alkylation of racemic 1,3-diphenyl-2-propenyl acetate 5 and the investigation of the mechanism of asymmetric induction.



A mixture of 6 mol% of one of the chiral diamine ligands  $1-4^8$  and 2.5 mol% of allylic palladium chloride dimer in an appropriate solvent was treated with one equivalent of allylic acetate 5 and 3 equivalents of dimethyl malonate in the presence of 3 equivalents of N,O-bis(trimethylsilyl)acetamide and a catalytic amount of potassium acetate, according to procedures described by Trost or Pfaltz.<sup>2a,3b</sup>

Some representative results are shown in Table 1. The most effective ligand was 2,5-dimethylpyrrolidine derivative 1, which gave the product (-)-6 in high yields with high enantiomeric excesses. Little solvent effect on enantioselectivity was observed in the allylic substitution with the palladium complex with 1. In diethyl ether, THF, benzene or 1,2-dichloroethane, the enantioselectivity was almost unchanged (87-88%e.e.). Interestingly, in polar solvents such as acetonitrile or DMF, the reaction proceeded smoothly without diminishing enantioselectivity (entries 2-4). The reaction in acetonitrile at 4 °C afforded the most promising result (91%e.e.) (entry 3). The use of sodium dimethyl malonate as a nucleophile in THF lowered enantiomeric excess (78%e.e.).

The chiral diamine ligands 2,3 containing larger substituents at 2,5-position of the pyrrolidine rings showed lower reactivities, probably for steric reason (entries 5 and 6). The 3,4-diphenyl pyrrolidine derivative 4 proved to be less effective (entry 7).



	~	$\begin{array}{c} \textbf{OAc} \\ \textbf{S} \\ \textbf{S} \\ \textbf{S} \\ \textbf{S} \end{array} \stackrel{\textbf{2.5 mol \%}}{=} [Pd (\eta^3 - C_3H_5) CI]_2 \\ \textbf{6 mol \% Chiral Diamine} \\ \textbf{S} \\ S$			CH(COOMe)2	
P	<sup>r</sup> h 5	∕~Ph	CH <sub>2</sub> (COOMe) <sub>2</sub> Ph BSA , AcOK, r.t.		Ph 6	
Entry	Ligand	Solvent	Time (h)	Yield (%)	% e.e. <sup>#</sup>	(Abs. config.) <sup>b</sup>
1	1	CH <sub>2</sub> Cl <sub>2</sub>	36	84	89	(S)
2	1	MeCN	6	97	89	(S)
3°	1	MeCN	24	<b>, 98</b>	91 <sup>d</sup>	(S)
4	1	DMF	24	87	89	(S)
5	2	CH <sub>2</sub> Cl <sub>2</sub>	72	80	64	(R)
6	3	CH <sub>2</sub> Cl <sub>2</sub>		no reaction		
7	4	CH <sub>2</sub> Cl <sub>2</sub>	38	89	48	(R)

a) The e.e. values were determined by HPLC with chiral columns (Daicel Chiralpack AD, hexane/ iPrOH= 20/1).

b) The absolute configuration was determined by comparison of the optical rotation with literature values.<sup>2,3</sup>

c) The reaction was carried out at 4 °C. d)  $\alpha \vec{b}$  -18.3° (c 1.74, EtOH).

In the case of asymmetric substitution to the 1,3-diphenyl allyl complex with palladium(II), the enantioselection should be dependent on the regioselection of nucleophilic attack to one of the two allylic termini. Although a number of chiral phosphine ligands are claimed to control the nucleophilic regioselection by the interaction between ligands and nucleophiles,<sup>2a,c</sup> our chiral diamine 1 is so compact that 1 should not be considered to interact with the nucleophile. We have assumed that the



interaction between the chiral ligand and the substrate brings about the asymmetric induction. As a consequence of the steric repulsion between the allylic phenyl group and the methyl group of a chiral ligand 1, one of the allylic termini should be distinguished from the other. Very recently, Pfaltz made a similar explanation in their catalytic system.<sup>3c</sup>

In order to investigate the mechanism of enantioselection, we prepared the (1,3-diphenylallyl)palladium complex with a C<sub>2</sub>-symmetric chiral diamine 1 which is considered to be an intermediate in the catalytic reaction. The palladium complex 7 ([(1)(1,3-diphenylallyl)Pd] PF6) was obtained as an air stable crystalline material.<sup>9</sup> The crystals were grown from dichloromethane solution and the crystal structure was determined by a X-ray diffraction study (Figure 2).<sup>10</sup> The complex 7 was found to have a little distorted square-planar coordination geometry of palladium(II) and different bond lengths between the palladium and the two allylic termini (Figure 3). The repulsive interaction between the chiral diamine ligand and the substrate apparently discriminates the two allylic termini of the substrate.

This discrimination was clearly observed in  $^{13}$ C NMR spectroscopy of the palladium complex  $7^{11,12}$  in dichloromethane-d<sub>2</sub>. Two allylic terminal carbons have different chemical shifts and CX-CY shift difference is 13 ppm, which suggests that the CX carbon should have more cationic character and should be attacked preferentially by a nucleophile.

In summary we have shown that the palladium complex with a simple C2-symmetric diamine ligand 1 catalyzes asymmetric allylic substitution with a high level of enantioselectivity. As a result of the analysis of the intermediate 7, we have found that the asymmetric induction is caused by the repulsive interaction between the chiral ligand and the substrate, which affects the electronic character of the two allylic termini.



Figure 2. Stereoview of 7

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- The diamine 1 was prepared from (2*R*,5*R*)-2,5-dimethylpyrrolidine by the treatment with oxallyl chloride followed by lithium aluminum hydride reduction. 1: [α]<sup>β</sup> -183° (c 3.05, CHCl<sub>3</sub>); <sup>1</sup>H NMR(270MHz, CDCl<sub>3</sub>):δ 1.00 (d, 12H, *J*=6.3 Hz), 1.40 (m, 4H), 2.00 (m, 4H), 2.66 (m, 4H), 3.06 (m, 4H); <sup>13</sup>C NMR(67MHz, CDCl<sub>3</sub>):δ 17.0, 30.9, 47.0, 55.8.

The diamine 2 was prepared from *N*-benzyl-(2*R*,5*R*)-2,5-bis(hydroxymethyl)pyrrolidine<sup>6a</sup> in 5 steps ((1) thionyl chloride, (2) Me<sub>2</sub>CuLi, (3) Pd(OH)<sub>2</sub>, H<sub>2</sub>, (4) oxallyl chloride, (5) lithium aluminum hydride). 2:  $[\alpha_{D}^{\infty} + 169^{\circ}$  (c 1.3, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR(270MHz, CDCl<sub>3</sub>): $\delta$  0.85 (t, 12H, *J*=7.3Hz), 1.12 (m, 4H), 1.48 (m, 4H), 1.65 (m, 4H), 1.88 (m, 4H), 2.68 (s, 4H), 2.70 (m, 4H); <sup>13</sup>C NMR(67MHz, CDCl<sub>3</sub>): $\delta$  11.0, 23.0, 27.5, 46.0, 62.8. The diamines 3,4 were prepared according to the procedure. <sup>7</sup>c

- The comlex 7 was prepared by the treatment of the mixture of [(1,3-diphenylallyl)PdCl]<sub>2</sub> and 1 with AgPF<sub>6</sub>, according to the literature.<sup>2b</sup> 7: mp 216-8 °C (dec.); [α]<sup>2</sup>/<sub>0</sub> +101° (c 0.76, CH<sub>2</sub>Cl<sub>2</sub>).
- Crystal data for 7: C<sub>29</sub>H<sub>41</sub>F<sub>6</sub>N<sub>2</sub>PPd, M=669.0, Orthorhombic, space group P<sub>212121</sub>; a=16.620(6), b=21.083(7)
   c=8.579(4)Å, V=3006(2)Å<sup>3</sup>, F (000)=1376, Z=4, D<sub>c</sub>=1.48 g/cm<sup>3</sup>, Cu-Kα radiation, λ=1.54178Å, μ(Cu-Kα)=57.60cm<sup>-1</sup>. Intensites were measured on a Mac Science MXC18 diffractometer at room temperature. 2807 reflections with F 3.0σ(F) were used in the structure refinement. The final R values was 0.062 (R<sub>W</sub>=0.079).
- 11. We have assigned key aspect of the complex 7 by C-H COSY and NOESY 2D <sup>1</sup>H-NMR methods.
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