Amido-Phosphane Ligands as *P,O*-Chelates in Palladium-Catalyzed Enantioselective Allylic Alkylations

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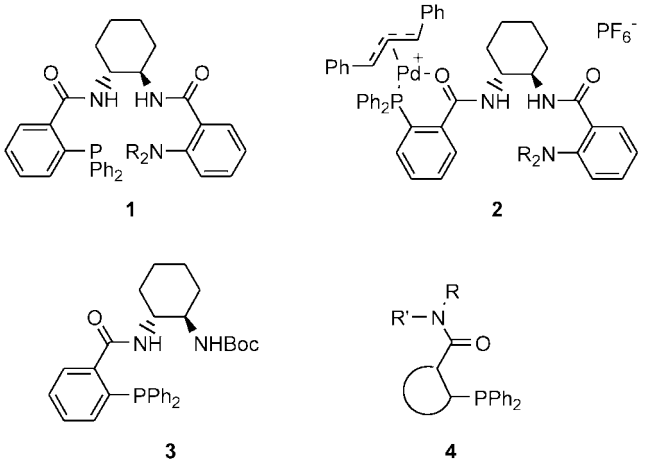
Received October 15, 2002

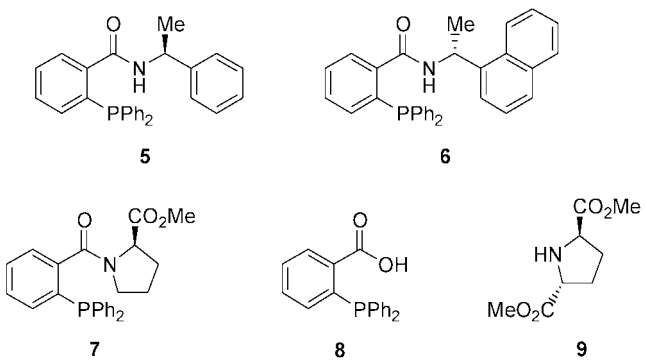
Key Words : Chiral ligand, *P,O*-Chelate, Palladium catalyst, Enantioselective allylic alkylation

In the course of our study to develop didentate ligands that might provide wide bite angles in the metal chelation, we observed that a *P,O*-chelation mode could intervene with expected *P,N*-chelation in the palladium catalyzed allylic alkylations with aminophosphane ligands **1**.[1] The *P,O*-chelation mode was supported by the X-ray crystal structure of the *P,O*-chelated palladium complex **2** (PF_6^- counterion).[2] Also, a moderate enantioselectivity was obtained with the ligand **3**, which suggested that other aminophosphane ligands, depicted as a general structure **4**, might be developed as efficient ligands for the catalytic reactions. While a number of hetero-chelates such as *P,N*-, *P,O*- and *P,S*-chelates[3,4] have been developed for the catalytic reactions, neutral *P,O*-chelates based on carboxamide functionality have been rarely studied for that purposes: Intervention of the *P,O*-chelation mode in the catalytic reactions from amido-phosphane moiety have been observed earlier;[5,6] however, use of *P,O*-chelates based on carboxamide oxygens for the catalytic reactions appeared very recently.[7] Chiral *P,O*-chelates of amido-phosphane derivatives can be readily synthesized from various known chiral amines and carboxyphosphanes. We synthesized amido-phosphanes from simple chiral amines and evaluated their ligand ability in the catalytic reaction.[8] Our study demonstrates that simple amido-phosphanes constitute a potentially useful ligand system for the palladium-catalyzed allylic alkylations.



<chemical structures of *P,N* and *P,O* chelates **1-4**>

Synthesis of the ligands 5-7. As a class of chiral ligands categorized by the general structure **4**, we devised benzene-based amido-phosphanes **5-7**. The new *P,O*-chelates are readily prepared by coupling of (2-diphenylphosphino)benzoic acid **8**[1] with corresponding chiral amines. The coupling reactions were carried out using a standard amide formation method (EDC-HOBt-NMM) and the desired amido-phosphanes were obtained in 84-90% isolated yields. In the cases of ligands **5** and **6**, a carboxamide anion, instead of the neutral carboxamide oxygen, may intervene as the ligand group under basic reaction conditions. The ligand **7** was synthesized to exclude this possibility. The ligand **7** consists of two rotamers in a ratio of 3 : 1, judged from its NMR spectra (^1H, ^{13}C, and ^{31}P), which is probably due to the hindered rotation of the amide bond. To get an analog of single conformer, we attempted to couple acid **8** with a symmetrical secondary amine such as **9** under several coupling conditions [EDC-HOBt-NMM, Et_3N-ClCOOEt, and cat. DMF-$(COCl)_2$] but failed to get the coupling products, possibly owing to increased steric hindrance.



<chemical structures of *P,O* chelates **5-9**>

Evaluation of the ligands 5-7 as *P,O*-chelates in the Pd-catalyzed allylic alkylations. The palladium-catalyzed asymmetric allylic alkylations were carried out between a typical allylic substrate, 2-acetoxy-1,3-diphenyl-2-propene and dimethyl malonate under several established procedures. Table 1 summarizes the enantioselectivities observed in the cata-

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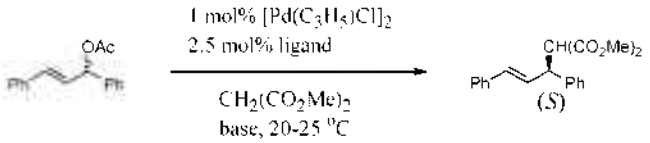
lytic reaction with the new chiral ligands. Depending on the reaction conditions (NaH/THF, BSA/KOAc/CH_2Cl_2, BSA/LiOAc/CH_2Cl_2, and Cs_2CO_3/CH_2Cl_2), dramatic changes in the reactivity and enantioselectivity result. Generally, higher yields were obtained under the conditions of BSA/KOAc/CH_2Cl_2 and BSA/LiOAc/CH_2Cl_2. With Cs_2CO_3 as the base, lower reactivity was observed. The highest enantioselectivity resulted when proline-based ligand **7** was used under the condition of NaH in THF, giving 94% ee with 76% yield, which indicates that the amido-phosphane ligands also constitute an efficient ligand system for the catalytic reaction. The catalytic systems with *P,O*-chelates **5-7** show lower reactivity than those of *P,N*-chelates, resulting in slower conversion. Carboxamide oxygens are expected to be weaker ligands than amine and phosphane donors in the palladium complexes. However, it is difficult to correlate the reactivity of the catalysts with their ligand affinity. In the case of ligand **7**, the catalytic reaction under the condition of BSA/KOAc/CH_2Cl_2 was completed within 3 h at room temperature, albeit the enantioselectivity was moderate. The higher reactivity observed in the case of ligand **7** is comparable to that of the typical *P,N*-chelates.[9-11]

The absolute stereochemistry of the product is dependent on that of the ligands. Thus, the catalytic system with (*S*)-ligand **5** gives the substitution product with (*S*)-stereochemistry and that of (*R*)-ligand **6** gives the opposite enantiomer.

In the case of ligand **7**, (*S*)-product is obtained, which may be explained if we assume that the carbomethoxy group of the pyrrolidine ring is equivalent to the methyl group in ligands **5** and **6**.

Of particular note is that even though *P,O*-chelate **7** exists as two rotamers, its catalytic system shows very high enantioselectivity. Energy minimization at PM3 level[†] for its $PdCl_2$ complexes of different conformers readily converged to single conformer (Fig. 1). In the energy-minimized structure,

Table 1. Palladium Catalyzed Enantioselective Allylic Alkylations Using Ligands **5-7**



entry	ligand	base[a]	time, h	solvent	yield, %[b]	% ee[c]
1	**5**	NaH	30	THF	26	52(*S*)
2	**5**	BSA, KOAc	22	CH_2Cl_2	63	84(*S*)
3	**5**	$CsCO_3$	35	CH_2Cl_2	<5	86(*S*)
4	**6**	NaH	20	THF	23	11(*R*)
5	**6**	BSA, KOAc	19	CH_2Cl_2	90	30(*R*)
6	**6**	$CsCO_3$	28	CH_2Cl_2	*d*	–
7	**7**	NaH	16	THF	76	94(*S*)
8	**7**	BSA, KOAc	3	CH_2Cl_2	99	69(*S*)
9	**7**	$CsCO_3$	19	CH_2Cl_2	70	45(*S*)
10	**7**	BSA, LiOAc	6	Et_2O	80	49(*S*)
11	**7**	BSA, LiOAc	6	CH_2Cl_2	84	53(*S*)

[a]BSA: *N,O*-bis(trimethylsilyl)acetamide. [b]Isolated yields. [c]Determined by HPLC using Chiralcel OD column. [d]No reaction.

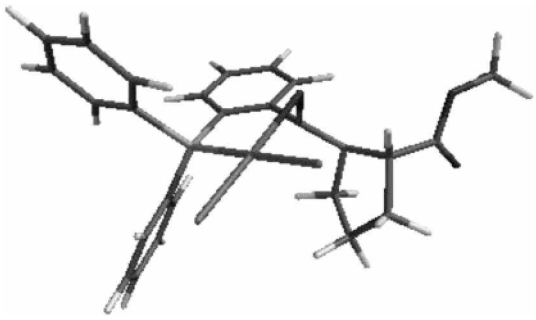


Figure 1. The PM3-minimized structure of a **7**-$PdCl_2$ complex.

the dihedral angle between the N-C4 bond of the pyrrolidine ring and the C(C=O)-C(Ph) bond is 71.6 degree, and the carbomethoxy group is away from the palladium center.

To get an idea on the enantioselection mechanism, similar energy minimizations are performed for two plausible [(**7**)Pd(η^3-PhCHCHCHPh)]$^+$ complexes (**I** and **II**), reactive intermediates in the catalytic reaction. The calculations indicate that the intermediate **I** is more stable than the intermediate **II** (Fig. 2).[‡]

For the formation of the major (*S*)-enantiomer *via* more stable intermediate **I**, the nucleophile should attack at the allylic carbon *trans* to the PdO bond ($C_{trans\text{-}O}$), which is in contrast with the case of *P,N*-chelated complexes, in which the nucleophile attacks at the allylic carbon *trans* to the PdP bond ($C_{trans\text{-}P}$). However, the attack at $C_{trans\text{-}O}$ is an unlikely situation because $C_{trans\text{-}P}$ is more electron-deficient than $C_{trans\text{-}O}$, judging from the ^{13}C NMR spectrum of the intermediate: All the allylic carbons appeared as two sets, owing to the rotational barrier of the amide bond, and $C_{trans\text{-}O}$ appeared at upfield from $C_{trans\text{-}P}$: $C_{trans\text{-}P}$, δ 95.5 and 91.6 ppm; $C_{trans\text{-}O}$, δ 76.4 and 74.4 ppm; C (central), δ 110.1 and 109.3 ppm.[¶] Therefore, formation of the major (*S*)-product can be explained by the nucleophilic attack at $C_{trans\text{-}P}$ in the less stable intermediate **II**, which is thus assumed to be more reactive species. This explanation corresponds to the "steric strain-reactivity argument" proposed by von Matt and coworkers, which suggests that a sterically more encumbered (π-allyl)Pd complex would undergo nucleophilic substitution more readily to relieve its steric strain than does a sterically less hindered one.[12,13] A further mechanistic study is necessary to elucidate the enantioselection pathway.

We briefly examined the ligand ability of the *P,O*-chelate **7** in the catalytic reactions of two other substrates, 2-acetoxy-3-pentene and 1-acetoxy-2-cyclohexane, which are known to behave very differently from 2-acetoxy-1,3-diphenyl-2-

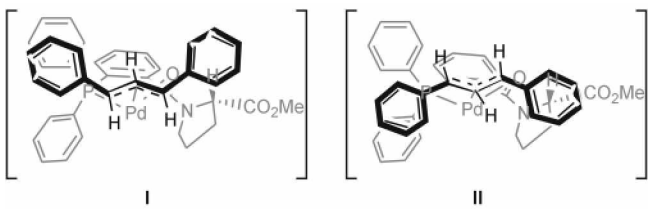


Figure 2. The PM3-minimized structures of [(**7**)Pd(π^3-PhCHCHCHPh)]$^+$ complexes.

propene.[3] Under the condition of BSA/KOAc/CH_2Cl_2, the catalytic reactions proceeded slowly for the former substrate (39% yield after 38 h) and well for the latter substrate (99% yield after 2 h), and little (5% ee) and low (27% ee) enantioselectivities were observed, respectively. The poor results are likely owing to reduced steric influence at the reaction site from the chiral center of the ligand in the case of such sterically less demanding substrates. A search for new ligand system for the poor substrates may be feasible, considering that various chiral amine sources are available.

We have demonstrated that amido-phosphanes can act as efficient *P,O*-chelates in the palladium catalyzed allylic alkylations. The catalytic reaction proceeded with high enantioselection and a reasonable rate in the case of a proline-derived ligand. Various other amido-phosphanes can be conceivable as tunable ligands for catalytic allylic alkylation reactions, which are substrate-dependent catalytic reactions. Further studies on other hetero-chelates and on the enantioselection mechanism are under investigation.

Experimental Section

General. Column Chromatography was carried out on Merck silica gel 60, 230-400 mesh ASTM. All reactions were monitored by TLC Merck 60 F_{254} pre-coated silica gel plate. Specific rotations ($[\alpha]_D$) are reported in degrees per decimeter at room temperature, and the concentration (c) is given in grams per 10 mL in the specific solvent. Solvents such as CH_2Cl_2 and hexane were dried with CaH_2 and distilled before use.

Preparation of (*S*)-2-diphenylphosphanyl-*N*-(1-phenylethyl)benzamide (5). To a stirred solution of 2-diphenylbenzoic acid (**8**) (306 mg, 1 mmol) in CH_2Cl_2 were added 1-hydroxybenzotriazole (HOBT, 184 mg, 1.2 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 230 mg, 1.2 mmol), *N*-methylmorpholine (NMM, 0.12 mL, 1.1 mmol), and (*S*)-(-)-α-methylbenzylamine (0.13 mL, 1 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature over 3 h, and it was diluted with CH_2Cl_2 and H_2O. The organic phase was separated, washed with brine, and dried over $MgSO_4$. Concentration of the solvent and purification of the residue by column chromatography (Hexane : EtOAc: 8 : 2, by volume) afforded compound **5** in 87% (0.87 mmol, 356 mg) yield as a white solid: mp 148 °C. $[\alpha]_D^{25}$ 12.9 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (d, J = 6.9 Hz, 3H), 5.16 (m, 1H), 6.23 (d, J = 6.5 Hz, 1H), 6.91-6.94 (m, 1H), 7.15-7.37 (m, 17H), 7.58 7.61 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 134.7, 134.6, 134.5, 134.3, 130.8, 129.6, 129.5, 129.46, 129.3, 129.2, 128.9, 127.9, 126.9, 50.2, 22.2. ^{31}P NMR (121 MHz, $CDCl_3$): δ -10.64; MS (EI) m/z 410.25 $[M]^+$. Elemental analysis: calcd (%) for $C_{27}H_{24}NOP$: C 79.20, H 5.91, N 3.42; found C 78.63, H 5.82, N 3.45.

Preparations of (*R*)-2-diphenylphosphanyl-*N*-[(1-naphthalen-1-yl)ethyl]benzamide (6). Amido-phosphane **6** was synthesized similarly as above by EDC-mediated coupling of (*R*)-(+)-1-(1-naphthyl)ethylamine (0.16 mL, 1mmol) with 2-(diphenylphosphanyl)benzoic acid (306 mg, 1mmol) in 89% yield (516 mg) as a white solid: mp 120 °C. $[\alpha]_D^{25}$ 39.3 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (d, J = 6.7 Hz), 6.00 (m, 1H), 6.20 (s, 1H), 6.90 (m, 1H), 7.24-7.56 (m, 17H), 7.58-7.61 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 142.4, 142.0, 138.6, 134.8, 134.7, 134.6, 134.5, 134.4, 134.3, 131.7, 130.8, 129.5, 129.44, 129.4, 129.3, 129.2, 128.9, 128.7, 128.6, 127.2, 126.5, 125.8, 124.4, 123.3, 45.9, 21.1. ^{31}P NMR (121 MHz, $CDCl_3$): δ -8.06; MS (EI) m/z 460.15 $[M]^+$; elemental analysis calcd (%) for $C_{31}H_{26}NOP$: C 81.03, H 5.70, N 3.05; found C 81.04, H 5.68, N 3.11.

Preparations of methyl 1-[2-diphenylphosphanyl]benzoyl]pyrrolidine-2(*R*)-carboxlate (7). Amido-phosphane **7** was synthesized similarly as above by EDC-mediated coupling of L-proline methyl ester hydrochloride (166 mg, 1 mmol) with 2-(diphenylphosphanyl)benzoic acid (306 mg, 1 mmol) in 86% yield (359 mg) as a white solid: mp 49 °C. $[\alpha]_D^{25}$ 27.8 (c 1.0, $CHCl_3$). As noted previously, two rotamers of amide **7** resulted in complicated NMR spectra, particularly in the ^{13}C NMR spectrum, and in this case the relevant peaks are grouped in parentheses. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22-7.45 (m, 13H), 7.0.6-7.14 (m, 1H); 4.55 and 4.02 (m, 1H); 3.74 and 3.56 (s, 3H); 3.65-3.78, 3.29-3.37 and 3.10-3.16 (m, 2H); 2.15-2.22, 1.81-2.00 and 1.59-1.68 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (172.3, 172.2), (167.0, 168.7), (142.7, 142.2), (136.3, 136.2), (135.8, 135.7), (134.2, 134.0), (133.7, 133.6, 133.5, 133.3, 133.2, 133.0, 132.9), (128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.96, 127.9), (126.2, 126.2) (60.5, 57.8, 51.1, 48.5, 45.5, 31.1, 30.4, 28.9, 24.4, 22.2). ^{31}P NMR (121 MHz, $CDCl_3$): δ -11.78, -12.23; MS (EI) m/z 418.15 $[M]^+$; elemental analysis, calcd (%) for $C_{25}H_{24}NOP$: C 71.93, H 5.80, N 3.36; found C 71.78, H 5.98, N 3.37.

A representative procedure for the Pd-catalyzed allylic alkylations. A mixture of $[(\pi\text{-allyl})PdCl]_2$ (3.7 mg, 0.01 mmol) and ligand **7** (10 mg, 0.025 mmol) in THF (1.7 mL) was stirred at room temperature for 30 min. To this Pd-catalyst was added 2-acetoxy-1,3-diphenyl-2-propene (252 mg, 1 mmol) in THF (1.7 mL), followed by a THF (1 mL) solution of dimethyl malonate (0.23 mL, 2.0 mmol) and NaH (60% in mineral oil, 60 mg, 1.5 mmol) at room temperature. An extractive work-up and purification are followed as described above.

Determination of the enantioselectivity. In the case of methyl 2-methoxycarbonyl-3,5-diphenyl-4-pentenoate, the enantioselectivity was determined by HPLC analysis using a chiral column [Chiralcel OD®; 25 cm × 0.46 cm; hexane: *i*-PrOH = 98:2; flow rate = 0.5 mL/min; t_R = 19.60 (*R*-isomer), 20.64 (*S*-isomer) min]. In the case of methyl 2-methoxycarbonyl-3-methyl-4-hexenoate and 1-acetoxy-2-cyclohexane, the enantioselectivity was determined by ^{1}H NMR analysis in the presence of a chiral shift reagent, Eu(hpc)$_3$.

Acknowledgment. This work was financially supported by the Korea Research Foundation Grant (KRF-2001-015-DP0332).

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†The PM3 semi-empirical calculation was carried out using PC Spartan Pro. Wavefunction, Inc.

‡The calculation gave a large difference in the relative energy between I and II (8.0 kcal·mol^{-1}); however, such a difference seemed to be unrealistic comparing their molecular structures.

¶ ^{31}P NMR spectra of the (π-allyl)Pd complex show major two peaks at 31.5 and 28.7 ppm, supposed to be the amide bond rotamers, and minor peaks at 32.2, 31.4, 29.3 ppm (5-10% relative to the major peaks), which probably come from the isomerism of the allylic complex (Fig. 2).

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