Amido-Phosphane Ligands as \(P,O\)-Chelates in Palladium-Catalyzed Enantioselective Allylic Alkylations

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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. The \(P,O\)-chelation mode was supported by the X-ray crystal structure of the \(P,O\)-chelated palladium complex (\(PF_6^-\) counterion). Also, a moderate enantioselectivity was obtained with the ligand, which suggested that other aminophosphane ligands, depicted as a general structure, 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 have been developed for the catalytic reactions, neutral \(PO\)-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; however, use of \(P,O\)-chelates based on carboxamide oxygens for the catalytic reactions appeared very recently. Chiral \(PO\)-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. Our study demonstrates that simple amido-phosphanes constitute a potentially useful ligand system for the palladium-catalyzed allylic alkylations.

Synthesis of the ligands 5-7. As a class of chiral ligands categorized by the general structure, we devised benzene-based amido-phosphanes 5-7. The new \(PO\)-chelates are readily prepared by coupling of (2-diphenylphosphino)benzoic acid 8 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 (\(1H\), \(13C\), and \(31P\)), 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, but failed to get the coupling products, possibly owing to increased steric hindrance.

Evaluation of the ligands 5-7 as \(PO\)-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-
lytic reaction with the new chiral ligands. Depending on the reaction conditions (NaH/THF, BSA/KOAc/CH₂Cl₂, BSA/LiOAc/CH₂Cl₂, and Cs₂CO₃/CH₂Cl₂), dramatic changes in the reactivity and enantioselectivity result. Generally, higher yields were obtained under the conditions of BSA/KOAc/CH₂Cl₂ and BSA/LiOAc/CH₂Cl₂. With Cs₂CO₃ 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 PO-chelates 5-7 show lower reactivity than those of PN-chelates, resulting in slower conversion. Carboxamide oxygens are expected to be weaker ligands than amine and phosphate 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/CH₂Cl₂ 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 PN-chelates.8-11

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 PO-chelate 7 exists as two rotamers, its catalytic system shows very high enantioselectivity. Energy minimization at PM3 level for its PdCl₂ complexes of different conformers readily converged to single conformer (Fig. 1). In the energy-minimized structure, 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(η¹-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).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 (Ctrans-O), which is in contrast with the case of PN-chelated complexes, in which the nucleophile attacks at the allylic carbon trans to the PdP bond (Ctrans-P). However, the attack at Ctrans-O is an unlikely situation because Ctrans-P is more electron-deficient than Ctrans-O. Judging from the ¹³C NMR spectrum of the intermediate: All the allylic carbons appeared as two sets, owing to the rotational barrier of the amide bond, and Ctrans-O appeared at upfield from Ctrans-P. Therefore, formation of the major (S)-product can be explained by the nucleophilic attack at Ctrans-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 co-workers, 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.² It is further mechanistic study is necessary to elucidate the enantioselection pathway.

We briefly examined the ligand ability of the PO-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 1](image1.png)

**Figure 1.** The PM3-minimized structure of a 7-PdCl₂ complex.

![Figure 2](image2.png)

**Figure 2.** The PM3-minimized structures of [(7)Pd(η¹-PhCHCHCHPh)]⁺ complexes.
propene. Under the condition of BSA/KOAc/CH\textsubscript{2}Cl\textsubscript{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 PO-chelates in the palladium catalyzed allylic alkylations. The catalytic reaction proceeded with high enantioselectivity 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 F\textsubscript{254} pre-coated silica gel plate. Specific rotations (\(\left[\alpha\right]_D\)) 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\textsubscript{2}Cl\textsubscript{2} and hexane were dried with CaH\textsubscript{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\textsubscript{2}Cl\textsubscript{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)-(−)-\(\alpha\)-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\textsubscript{2}Cl\textsubscript{2} and H\textsubscript{2}O. The organic phase was separated, washed with brine, and dried over MgSO\textsubscript{4}. Concentration of the resultant solution and purification of the residue by column chromatography (Hexane : E\textsubscript{t}OAc : 8 : 2, by volume) afforded compound 5 in 87% (0.87 mmol, 356 mg) yield as a white solid: mp 148 °C. [\(\left[\alpha\right]_D\)]\textsubscript{D} = 12.9 (c 1.0, CHCl\textsubscript{3}). \textsuperscript{1}H NMR (300 MHz, CD\textsubscript{3}CN): \(\delta\) 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). \textsuperscript{13}C NMR (75 MHz, CD\textsubscript{3}CN): \(\delta\) 168.6, 142.4, 142.0, 138.6, 134.8, 134.7, 134.6, 134.5, 134.3, 131.7, 130.8, 129.5, 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. \textsuperscript{31}P NMR (121 MHz, COCD\textsubscript{3}): \(\delta\) -8.06; MS (EI) m/z 406.15 [M\textsuperscript{+}]; elemental analysis calculated (%) for C\textsubscript{31}H\textsubscript{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]benzo[y]pyrrolidine-2(\textsuperscript{R})-carboxylate (7).** Amido-phosphate 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. [\(\left[\alpha\right]_D\)]\textsubscript{D} = 27.8 (c 1.0, CHCl\textsubscript{3}). As noted previously, two rotamers of amide 7 resulted in complicated NMR spectra, particularly in the \textsuperscript{13}C NMR spectrum, and in this case the relevant peaks are grouped in parentheses. \textsuperscript{1}H NMR (300 MHz, CD\textsubscript{3}CN): \(\delta\) 7.22-7.45 (m, 13H), 7.06-7.14 (m, 1H); 4.55 and 4.02 (m, 2H); 3.43-3.48, 3.29-3.37, and 3.10-3.16 (m, 3H); 2.15-2.22, 1.81-2.00 and 1.59-1.68 (m, 4H). \textsuperscript{13}C NMR (75 MHz, CD\textsubscript{3}CN): \(\delta\) (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). \textsuperscript{31}P NMR (121 MHz, CD\textsubscript{3}CN): \(\delta\) -11.78, -12.23; MS (EI) m/z 415.18 [M\textsuperscript{+}]; elemental analysis calculated (%) for C\textsubscript{26}H\textsubscript{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 [(\textsuperscript{R}-allyl)PdCl\textsubscript{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\textsuperscript{P}]; 25 cm × 0.46 cm; hexane: i-PrOH = 98:2; flow rate = 0.5 mL/min; \(t_0 = 19.60\) (R-isomer), 20.64 (S-isomer) min. In the case of methyl 2-methoxy-carbonyl-3-methyl-4-hexenoate and 1-acetoxy-2-cyclohexene, the enantioselectivity was determined by \textsuperscript{1}H NMR analysis in the presence of a chiral shift reagent, Eu(hpc).

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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 ($\pi$-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).

8. In the course of our study, related P,O-chelates have been used for the palladium-catalyzed allylic alkylations, and up to 84% ee was obtained: Mino, T.; Kashiwara, K.; Yamashita, M. Tetrahedron: Asymmetry 2001, 12, 287-291.