Palladium-Catalyzed Allylic Alkylation Using Chiral Hydrazones as Ligands

Takashi Mino,*,† Masashi Shiotsuki,‡ Nozomi Yamamoto,† Tomoe Suenaga,† Masami Sakamoto,† Tsutomu Fujita,† and Masakazu Yamashita*,‡

Department of Materials Technology, Faculty of Engineering, Chiba University, Inage-ku, Chiba 263-8522, Japan, and Department of Molecular Science and Technology, Faculty of Engineering, Doshisha University, Kyotanabe, Kyoto 610-0394, Japan

tmino@planet.tc.chiba-u.ac.jp

Received October 26, 2000

Palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**4**) with a dimethyl malonate−BSA−LiOAc system and its derivatives has been successfully carried out in the presence of a new chiral hydrazone ligands such as 2-(diphenylphosphino)benzaldehyde SAMP hydrazone (DPPBA-SAMP) (**3a**) in high yields with high enantioselectives.

Introduction

Palladium-catalyzed allylic alkylation is a widely used process in organic synthesis,[1] and the development of efficient enantioselective catalysis for this reaction is awaited.[2] Since chiral phosphine ligands can induce a high enantiomeric excesses in palladium-catalyzed reactions of racemic and achiral allylic substrates with nucleophiles, P,P-chelate chiral ligands such as BINAP,[3] chiraphos,[4] and Trost's ligand[5] play an important role in catalytic asymmetric synthesis. Recently, the catalytic asymmetric synthesis using P,N-chelate chiral ligands such as chiral 2-(2-phosphinophenyl)dihydrooxazoles[6] has been reported.[7]

On the other hand, Enders has reported the asymmetric alkylation of various carbonyl compounds using chiral hydrazones which were prepared from (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) as a chiral auxiliary.[8] Åkermark has reported that (η^3-allyl)palladium(II) was coordinated with 2-(diphenylphosphino)benzaldehyde dimethylhydrazone.[9] Thus we prepared novel chiral hydrazone ligands for application to asymmetric catalysis. Here, we report the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**4**) in the presence of chiral hydrazone such as 2-(diphenylphosphino)benzaldehyde SAMP hydrazone (DPPBA−SAMP) (**3a**).[10]

Results and Discussion

Preparation of Chiral Hydrazone Ligands. Chiral hydrazones **3a**,**b** as ligands were easily prepared from 2-(diphenylphosphino)benzaldehyde **2** and chiral hydrazine **1** such as (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP), (*S*)-1-amino-2-(1′-methoxy-1′-methylethyl)pyrrolidine (SADP), and (*S*)-1-amino-2-(1′-methoxy-1′-ethylpropyl)pyrrolidine (SAEP) in good yields (Scheme 1).

Palladium-Catalyzed Asymmetric Allylic Alkylation. First, asymmetric allylic alkylation of racemic 1,3-diphenyl-2-propenyl acetate (**4**)[11] was examined using chiral hydrazones **3**. These results are summarized in Table 1.

The reaction with dimethyl malonate (**5a**) under standard conditions[12] (2 mol % of [Pd(η^3-C_3H_5)Cl]$_2$, 6 mol % of chiral hydrazone **3a**, and a mixture of *N*,*O*-bis(trimethylsilyl)acetamide (BSA)[13] and a catalytic amount of KOAc in CH_2Cl_2) proceeded smoothly to give good enantioselectivity (87% ee) (entry 1). By use of LiOAc instead of KOAc, the enantioselectivity of **6a** was increased to 90% ee (entry 2). However, by use of NaOAc instead of KOAc, the enantioselectivity of **6a** was decreased to 72% ee (entry 3). So the reaction using lithium as alkali metal gave the best result in the various metal acetates. In each case the product **6a** was formed with the (*R*)-(+)-enantiomer predominating, as determined from the sign of the optical rotation.[14] 2-(diphenylphosphino)benzaldehyde RAMP hydrazone (*ent*-**3a**), which was an enantiomer of **3a**, was used as a ligand (entry 4),

* To whom correspondence should be addressed. T. Mino: Phone: +81 43 290 3385. Fax: +81 43 290 3401.
† Chiba University.
‡ Doshisha University.

(1) (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (b) Trost, B. M.; Verhoeven, T. R. in *Comprehensive Organometallic Chemistry;* Wilkinson, G.; Stone, F. G. A.; Abel, E. W. Eds.; Pergamon: Oxford, 1982; Vol. 8, p 799. (c) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.
(2) (a) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: New York, 1999; Chapter 24. (b) Trost, B. M.; Van Vranken, D L. *Chem. Rev.* **1996**, *96*, 395. (c) Williams, J. M. J. *Synlett* **1996**, 705. (d) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (e) Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; p 325. (f) Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257.
(3) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493.
(4) Yamaguchi, M.; Shima, T.; Yamagishi, T.; Hida, M. *Tetrahedron: Asymmetry* **1991**, *2*, 663.
(5) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089.
(6) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203.
(7) For example, see Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159.
(8) Enders, D. in *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p 275.
(9) Åkermark, B.; Krakenberger, B.; Hansson, S. *Organometallics* **1987**, *6*, 620.
(10) Mino, T.; Imiya, W.; Yamashita, M. *Synlett* **1997**, 583.
(11) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033.
(12) Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143.
(13) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.
(14) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191.

10.1021/jo0057001 CCC: $20.00
Published on Web 02/10/2001

Scheme 1

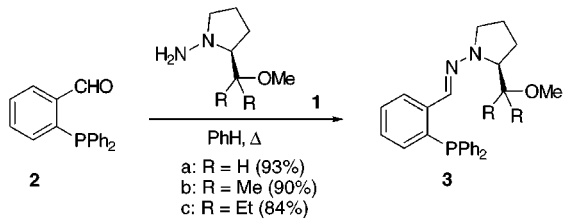
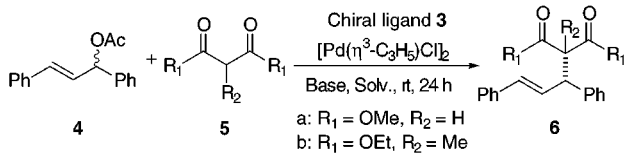


Table 1. Asymmetric Allylic Alkylation Catalyzed by Palladium Complexes with Chiral Hydrazone Ligands 3



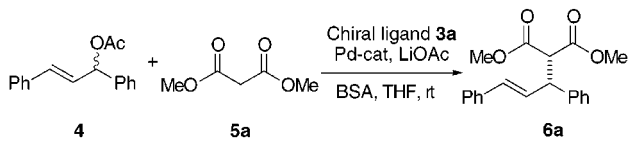
entry	ligand	5	base	solvent	yield (%)[a]	ee (%)[b]
1	**3a**	**5a**	KOAc−BSA	CH_2Cl_2	96	87
2	**3a**	**5a**	LiOAc−BSA	CH_2Cl_2	98	90
3	**3a**	**5a**	NaOAc−BSA	CH_2Cl_2	98	72
4	*ent*-**3a**[c]	**5a**	LiOAc−BSA	CH_2Cl_2	99	92
5	**3a**	**5b**	LiOAc−BSA	CH_2Cl_2	85	80[d]
6	**3a**	**5a**	LiOAc−BSA	THF	96	92
7	**3a**	**5a**	LiOAc−BSA	MeCN	100	78
8	**3a**	**5a**	LiOAc−BSA	PhMe	98	73
9	**3a**	**5a**	Li_2CO_3−BSA	THF	61	97
10[e]	**3a**	**5a**	LiOAc−BSA	THF	94	89
11[f]	**3a**	**5a**	LiOAc−BSA	THF	98	95
12[g]	**3a**	**5a**	LiOAc−BSA	THF	26	>98
13	**3b**	**5a**	LiOAc−BSA	THF	95	71
14	**3c**	**5a**	KOAc−BSA	THF	84	72

[a] Isolated yields. [b] Determing by HPLC analysis using a chiral column (Chiralcel OD (hexane:*i*-PrOH = 99:1)). [c] RAMP was used instead of SAMP as a hydrazine. [d] Determing by HPLC analysis using a chiral column (Chiralcel OD (hexane:*i*-PrOH = 199:1)). [e] The reaction was carried out at 50 °C for 3 h. [f] The reaction was carried out at 4 °C for 48 h. [g] The reaction was carried out at −20 °C for 7 d.

(*S*)-(−)-**6a** was obtained in good enantioselectivity (92% ee). The reaction with diethyl methylmalonate in place of dimethyl malonate gave the corresponding product **6b** in good yield (85%) with 80% ee (entry 5). When the reaction was carried out in THF, the enantioselectivity was obtained higher than CH_2Cl_2, MeCN, and PhMe (entry 6 vs entries 1, 7, and 8). By use of Li_2CO_3 instead of LiOAc, the enantioselectivity of **6a** was increased to 97% ee, but the reaction was proceeded slowly (entry 2). The enantioselectivity and yield were slightly dependent on the reaction temperature (entries 6 and 10−12), the highest enantioselectivity (>98% ee) was obtained at −20 °C (entry 12). The chiral hydrazones **3b** and **3c** as ligands, which were prepared from SADP or SAEP, proceed slowly to product in moderate enantioselectivity (entries 13 and 14). We investigated the effect of palladium precursor on this reaction (Table 2). The reaction using $(dba)_3Pd_2{\cdot}CHCl_3$ as a palladium precursor provided good chemical yield of **6a**, but the enantioselectivity was obtained only 66% ee (entry 2). On the other hand, the reaction using $PdCl_2(PhCN)_2$ proceeded slowly with 77% ee (entry 4).

X-ray Structure of Palladium Complex of 3a. Ligand **3a** was treated with $PdCl_2(PhCN)_2$ followed by addition of KPF_6 to give the palladium complex **7**. Suitable crystals of **7** were obtained from CH_2Cl_2−hexane (Scheme 2). When the other palladium precursors such as $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ were used, the corresponding suitable

Table 2. Effect of Palladium Precursor on the Asymmetric Allylic Alkylation



entry	Pd-cat	reaction time (d)	yield (%)[a]	ee (%)[b]
1	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	1	96	92
2	$(dba)_3Pd_2{\cdot}CHCl_3$	1	88	66
3	$(dba)_3Pd_2$	2	67	62
4	$PdCl_2(PhCN)_2$	7	42	77
5	$PdCl_2$	7	12	73

[a] Isolated yields. [b] Determing by HPLC analysis using a chiral column (Chiralcel OD (hexane:*i*-PrOH = 99:1)).

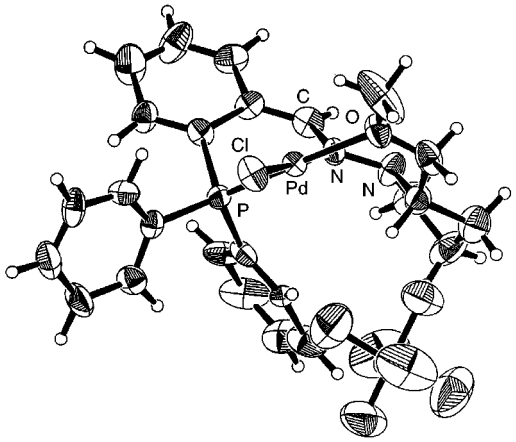
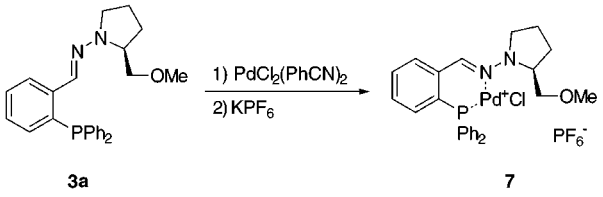
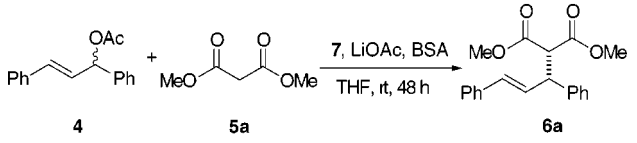


Figure 1. ORTEP diagram of **7**.

Scheme 2



Scheme 3

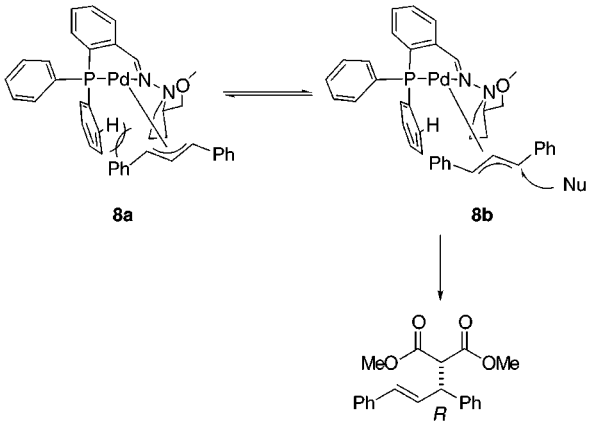


crystals were not obtained. X-ray analysis of **7** was carried out (Figure 1).

The four coordination sites are occupied by the P, N, O, Cl atoms. The ligand **3a** has two nitrogen atoms at the hydrazone moiety, but Pd atom was coordinated only with the nitrogen atom at imino group. Unexpectedly, the Pd atom was coordinated the oxygen atom of methoxymethyl moiety. Asymmetric allylic alkylation of racemic acetate **4** with a dimethyl malonate−BSA−LiOAc system was examined using this palladium complex **7** in THF. This reaction gave the product **6a** in moderate yield (44%) with 88% ee for 48 h (Scheme 3).

According to the analysis of X-ray structure of **7**, the reaction probably proceeds though a W-type **8b** rather than an M-type **8a** intermediate (Scheme 4). The nucleophilic attack occurs predominantly at the allyl terminus

Scheme 4



from trans to the better π-acceptor (P > N).[15] So (*R*)-products were obtained in this reaction using the chiral hydrazone **3a** as a ligand.

Conclusion

We have prepared new phosphine−hydrazone ligands from 2-(diphenylphosphino)benzaldehyde and chiral hydrazines such as SAMP. These ligands such as **3a** can be used as a chiral ligand in palladium-catalyzed asymmetric allylic alkylation with high enantiomeric excesses.

Experimental Section

NMR spectra were recorded on a JEOL A-400 system or LA-400 system or a Bruker DPX-300 system with TMS as an internal standard. IR spectra were recorded on a Hitachi 260-10 spectrometer or a JASCO FT/IR-230 spectrometer. Mass spectra were recorded on a JEOL JMS-HX110 or a JMS-700 or a Shimadzu GCMS-QP2000A or a Hitachi M-80B. Optical rotations were measured on a JASCO DIP-370 or a HORIBA SEPA-200.

Typical Procedure for the Preparation of 3. A mixture of chiral hydrazine **1** (0.46 mmol), 2-(diphenylphosphino)-benzaldehyde **2** (0.110 g, 0.38 mmol), catalytic amount of trifluoroacetic acid, and benzene (5 mL) was added to a flask under an argon atmosphere. The mixture was heated under reflux for 24 h and then cooled to room temperature. The reaction mixture was diluted with ether and water. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated with a rotary evaporator, and the residue was purified by column chromatography.

2-(Diphenylphosphino)benzaldehyde SAMP hydrazone (3a): 93%; $[\alpha]^{23}_D = -57.3°$ (*c* 1.02, EtOH) (*ent*-**3a**: $[\alpha]^{23}_D = +58.4°$ (*c* 1.01, EtOH)); ^{1}H NMR (400 Mz, $CDCl_3$) δ 1.80−1.96 (m, 4H), 2.83 (dd, 7.6 and 16.8 Hz, 1H), 3.26−3.34 (m, 2H), 3.32 (s, 3H), 3.47 (dd, 3.7 and 9.5 Hz, 1H), 3.52−3.58 (m, 1H), 6.76−6.82 (m, 1H), 7.06 (t, 7.5 Hz, 1H), 7.25−7.33 (m, 11H), 7.66 (d, 4.3 Hz, 1H), 7.85 (t, 4.0 Hz, 1H); ^{31}P NMR (166 Mz, $CDCl_3$) δ −12.67; FAB-MS *m*/*z* 403 (M^+ + H, 7); Anal. Calcd for $C_{25}H_{27}N_2OP$: C, 74.61; H, 6.76; N, 6.96. Found: C, 74.55; H, 6.79; N, 6.82.

2-(Diphenylphosphino)benzaldehyde SADP hydrazone (3b): 90%; $[\alpha]^{23}_D = +16.8°$ (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 Mz, $CDCl_3$) δ 1.12 (s, 3H), 1.24 (s, 3H), 1.72−2.02 (m, 4H), 2.65−2.76 (m, 1H), 3.23 (s, 3H), 3.29−3.39 (m,1H), 3.52−3.61 (m, 1H), 6.75−6.82 (m, 1H), 7.06 (t, 7.0 Hz, 1H), 7.18−7.39 (m, 11H), 7.71 (d, 4.6 Hz, 1H), 7.86−7.94 (m, 1H); ^{31}P NMR (166 Mz, $CDCl_3$) δ −13.00; ^{13}C NMR (75 Mz, $CDCl_3$) δ 21.05, 23.25, 23.51, 24.48, 49.59, 50.38, 70.85, 77.62, 124.29−140.96 (m, Ar); FAB-MS *m*/*z* 431 (M^+ + H, 100); HRMS (FAB) calcd for $C_{27}H_{32}N_2OP$ $(M + H)^+$ 431.2252, found 431.2241; Anal. Calcd for $C_{27}H_{31}N_2OP$: C, 75.33; H, 7.26; N, 6.51. Found: C, 74.95; H, 7.14; N, 6.40.

2-(Diphenylphosphino)benzaldehyde SAEP hydrazone (3c): 84%; $[\alpha]^{23}_D = +64.70°$ (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 Mz, $CDCl_3$) δ 0.87 (t, 7.6 Hz, 3H), 0.89 (t, 7.3 Hz, 3H), 1.48−2.05 (m, 8H), 2.68 (d, 8.7 and 17.9 Hz, 1H), 3.19 (s, 3H), 3.22−3.31 (m,1H), 3.66−3.76 (m, 1H), 6.74−6.82 (m, 1H), 7.06 (t, 7.0 Hz, 1H), 7.24−7.37 (m, 11H), 7.64 (d, 4.9 Hz, 1H), 7.86−7.95 (m, 1H); ^{31}P NMR (166 Mz, $CDCl_3$) δ −13.13; ^{13}C NMR (75 Mz, $CDCl_3$) δ 7.84, 8.60, 23.00, 23.75, 26.35, 50.05, 50.48, 68.17, 68.27, 80.41, 123.96−141.00 (m, Ar); FAB-MS *m*/*z* 459 (M^+ + H, 38); HRMS (FAB) calcd for $C_{29}H_{36}N_2OP$ $(M + H)^+$ 459.2565, found 459.2559; Anal. Calcd for $C_{29}H_{35}N_2OP$: C, 75.96; H, 7.69; N, 6.11. Found: C, 75.31; H, 7.64; N, 6.17.

General Procedure for the Palladium-Catalyzed Allylic Alkylation. To mixture of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.01 mmol, 0.004 g), chiral hydrazone **3** (0.03 mmol), and metal acetate (0.01 mmol) in a solvent (1 mL) were added BSA (1.5 mmol, 0.37 mL), racemic 1,3-diphenyl-2-propenyl acetate (**5a**) (0.5 mmol, 0.126 g), and 1,3-dicarbonyl compounds **4** (1.5 mmol) at room temperature under an argon atmosphere. After being stirred for 24 h, the reaction mixture was diluted with ether and water. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated with a rotary evaporator, and the residue was purified by column chromatography.

6a. (Table 1, entry 2) 98% yield; 90% ee; $[\alpha]^{25}_D = 17.7°$ (*c* 1.02, EtOH) [(*S*)-**6a**: $[\alpha]^{23}_D = -18.4°$ (*c* 1.1, EtOH),[4] $[\alpha]^{25}_D = -22.4°$ (*c* 1.8, $CHCl_3$)[16]]; ^{1}H NMR (400 Mz, $CDCl_3$) δ 3.51 (s, 3H), 3.70 (s, 3H), 3.95 (d, 11.0 Hz, 1H), 4.27 (dd, 8.5 and 11.0 Hz, 1H), 6.44 (dd, 8.5 and 15.8 Hz, 1H), 6.71 (d, 15.8 Hz, 1H), 7.19−7.33 (m, 10H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 49.20, 52.45, 52.63, 57.66, 126.40, 127.18, 127.58, 127.86, 128.48, 128.73, 129.12, 131.85, 136.83, 140.18, 167.79, 168.21; MS (EI) *m*/*z* 324 (M^+, 30). **6b**. (Table 1, entry 5) 85% yield; 80% ee; $[\alpha]^{25}_D = 25.5°$ (*c* 1.04, EtOH); ^{1}H NMR (400 Mz, $CDCl_3$) δ 1.13−1.28 (m, 6H), 1.47 (s, 3H), 4.04−4.18 (m, 2H), 4.14−4.20 (m, 2H), 4.29 (d, 8.9 Hz, 1H), 6.44 (d, 15.8 Hz, 1H), 6.71 (dd, 8.9 and 15.8 Hz, 1H), 7.18−7.34 (m, 10H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 13.94, 14.03, 18.81, 46.19, 53.72, 58.89, 61.34, 126.33, 127.10, 127.31, 128.20, 128.43, 128.86, 129.61, 132.58, 170.92, 171.19; MS (EI) *m*/*z* 366 (M^+, 3).

Preparation of Palladium Complex 7. To a solution of $PdCl_2(PhCN)_2$ (0.078 mmol, 0.0298 g) in a CH_2Cl_2 (1 mL) was added 2-(diphenylphosphino)benzaldehyde SAMP hydrazone **3a** (0.078 mmol, 0.0315 g) at room temperature under an argon atmosphere. After 80 min, KPF_6 (0.078 mmol, 0.0143 g) was added and stirring was continued for 30 min. The reaction mixture was filtered, evaporated under reduced pressure, and purified by recrystallization from a CH_2Cl_2−hexane mixture.

61%; ^{1}H NMR (300 Mz, $CDCl_3$) δ 1.25−1.68 (m, 1H), 1.76−1.82 (m, 1H), 1.84−2.01 (m, 2H), 3.28 (br, 2H), 3.96−4.02 (m, 1H), 4.51 (br, 1H), 6.81−6.96 (m, 1H), 7.41−7.76 (m, 14H); ^{31}P NMR (121 Mz, $CDCl_3$) δ 36.53, −143.86 (sept, 710 Hz); FAB-MS *m*/*z* 545 ($M^+ - PF_6 + 1$, 34).

X-ray Structural Analysis: $C_{25}H_{27}N_2OP_2PdF_6Cl$, $M = 689.29$ g mol^{-1}, orthorhobic sace group $P2_12_12_1$ (no. 19), $a = 21.028(10)$, $b = 7.968(6)$, $c = 16.843(7)$ Å, $V = 2822(2)$ Å^3, $Z = 4$, $d_{calcd} = 1.62$ g cm^{-3}, μ(Mo Kα) 9.28 cm^{-1}, $F(000) = 1384$.

Acknowledgment. We thank the Ogura group (Chiba University) for generously sharing their Bruker DPX-300 system.

Supporting Information Available: Crystallographic data for X-ray structural analysis of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0057001

(15) Åkermark, B.; Hansson, S.; Krakenberger, B.; Vitagliano, A.; Zetterberg, K. *Organometallics* **1984**, *3*, 679.

(16) Sprinz, J.; Helmchem, G. *Tetrahedron Lett.* **1993**, *34*, 1769.