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Development of Chiral Phosphine Ligands Bearing a Carboxyl Group and Their Application to Catalytic Asymmetric Reaction

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Abstract: A new chiral phosphine ligand bearing a carboxyl group, 3-(diphenylphosphino)butanoic acid, was developed and used for palladium catalyzed asymmetric allylic alkylation of cyclic *cis*-allylic acetates such as 2-cyclopentenyl, 2cyclohexenyl, and 2-cycloheptenyl acetate. These acetates reacted with tricthyl sodiophosphonoacetate in the presence of the palladium catalyst with the ligand to give the corresponding alkylation products in good enantiomeric excesses.

Asymmetric carbon-carbon bond formation utilizing a chiral catalyst is one of the most important and attractive subjects in synthetic organic chemistry.¹ Recently, palladium catalyzed asymmetric allylic alkylation has been fairly extensively investigated and a wide variety of chiral phosphine ligands have been developed.²⁻⁴ While high enantioselectivities (> 80%) were achieved in certain cases, such high asymmetric inductions were mostly observed using *trans*-allylic substrates.² In contrast, relatively little work has been done using cyclic *cis*-allylic substrates such as 3-cyclohexenyl acetate,^{3,4} and there appears to be only one example of the asymmetric allylic alkylations in excellent enantiomeric excess.⁴ Thus, hitherto known palladium catalyzed asymmetric allylic alkylations still have a limitation in terms of allylic substrates. We have recently reported the synthesis of a new type of chiral cycloalkylphosphines bearing a carboxyl group and have shown that the carboxyl group plays an important role in the asymmetric induction.⁵ We also found that these chiral phosphine ligands were effective to the asymmetric allylic alkylations using cyclic *cis*-allylic substrates (30–78%ee). On the basis of these results, the development of more effective chiral phosphine ligands was envisaged. We describe here the convenient synthesis of a chiral alkylphosphinocarboxylic acid ligand and its application to asymmetric alkylations.

Results and Discussion

Synthesis of Chiral Phosphinocarboxylic Acids. The synthesis of 3-(diphenylphosphino)butanoic acid is outlined in eq 1. 1,4-Addition of lithium diphenylphosphide to *tert*-butyl crotonate (1a) in tetrahydrofuran (THF) containing hexamethylphosphoric triamide (HMPA) at -78 °C for 0.5 h gave *tert*-butyl 3-(diphenylphosphino)-butanoate 2a in a quantitative yield. The subsequent treatment of 2a with *p*-toluenesulfonic acid in benzene under reflux for 3 h led to racemic 3-(diphenylphosphino)butanoic acid (\pm)-3a quantitatively. Furthermore, this synthetic method was successively applied to the synthesis of a cycloalkyl homologue. For example, *tert*-butyl 2-(diphenylphosphino)cyclopentanecarboxylate 2b was prepared from *tert*-butyl 2-cyclopentenecarboxylate 1b. Treatment of 2b with acid gave 2-(diphenylphosphino)cyclopentanecarboxylic acid 3b in a similar manner to that described above (overall yield 95 %). This new synthetic method, which includes 1,4-addition of

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diphenylphosphine to α,β -unsaturated esters, is convenient for the preparation of these phosphinocarboxylic acids compared with the method reported previously.⁵

$$Me \xrightarrow{1a} O^{t}Bu + Ph_{2}PH \xrightarrow{n} HMPA-THF Me \xrightarrow{t} O^{t}Bu \xrightarrow{t} O^{t}$$

Racemic **3a** was treated with (+)- α -methylbenzylamine (PEA) in acetone to give white diastereomeric ammonium salts. After filtration, recrystallization of these diastereomeric salts from acetone three times gave the pure salt, $[\alpha]_D{}^{30}$ 33.0 (c 0.87, CHCl₃). Treatment of a chloroform solution of this salt with dilute hydrochloric acid gave enantiomerically pure (+)-**3a**, $[\alpha]_D{}^{34}$ 29.8 (c 0.97, CHCl₃), of which absolute configuration is not yet determined. Enantiomerically pure (-)-**3a**, $[\alpha]_D{}^{34}$ -29.3 (c 0.84, CHCl₃), was obtained similarly using (-)-PEA.

(+)- and (-)-3a resolved as described above were confirmed to be enantiomerically pure by HPLC analysis of their diastereomeric amides 4a, derived from each of 3a and (-)-PEA(eq 2).⁶



Asymmetric Allylic Alkylation. The reaction of triethyl sodiophosphonoacetate 5 with cyclic *cis*-allylic acetates **6a-c** was carried out in the presence of the chiral palladium catalyst prepared from the chiral phosphine (–)-**3a** and palladium acetate in THF at room temperature to give optically active allylic alkylation products **7a-c** (Scheme 1), (Table 1). These results indicate that enantiomeric excesses somewhat increased with increasing ring sizes of the substrates. Alkylated products **7a-c** were successively transformed, after the treatment with sodium hydride and paraformaldehide, into the Wittig-Horner reaction products **8a-c**. The specific rotations of **8b** and **8c** are as follows: **8b**, $[\alpha]_D^{29}$ 80.7 (c 0.80, CH₂Cl₂); **8c**, $[\alpha]_D^{28}$ 33.0 (c 0.47, CH₂Cl₂).



(-)-3-(Dipnenyipnosprino)outanoic acid (-)-3a-Panadium Com								
entry	allylic substrate	product	yield(%) ^b	%eec				
1	6a	(+)-7 a	71	59				
2 ^d	6b	(+)- 7b	77	86				
3	6с	(+)-7c	50	88				

Table 1. Asymmetric Allylic Alkylation of Cyclic *cis*-Allylic Acetate Catalyzed by (-)-3-(Diphenylphosphino)butanoic acid (-)-3a-Palladium Complex^a

^aReactions were run with 0.01–0.02 equiv of Pd(OAc)₂ and 0.04–0.08 equiv of (–)-3a in THF. ^bIsolated yield based on acetate **6a-c.** ^cEnantiomeric excesses were determined by the method described previously.⁵ ^dThe reaction was carried out under reflux.

On the other hand, the use of (-)-trans-2-(diphenylphosphino)cyclopentanecarboxylic acid (-)-3b resulted in a drop of enantiomeric excess (eq 3).⁵ This result was unexpected in the view of the fact that 3a has a high degree of conformational freedom compared to 3b.



Furthermore, in order to investigate the influence of the structures of allylic substrates on enantioselectivity, the reaction of 3-acetoxy-1,3-diphenyl-1-propene 9 with 5 was examined in the presence of the phosphine (-)-3a-palladium complex. The allyl substituted product (-)-10 was obtained in 91 % yield with a remarkably decreased enantiomeric excess (33 %ee), while the same reaction using the phosphine (--)-3b-palladium complex as a catalyst afforded 10 in 74 % yield (77 %ee).⁵



Table 2.	Asymmetric Allylic Alkylation of 1-Acetoxy-1,3-diphenyl-1-propene 9 Catalyzed
	by Chiral Phosphinocarboxylic Acid-Palladium Complexes ^a

entry	chiral ligand	reaction conditions		yield(%)b	%eec
		temp	time(h)	_ •	
1	(-)- 3a	60 ℃	4	91	33
2 ^d	(-)- 3b	reflux	2	74	77

^aReactions were run with 0.01-0.02 equiv of Pd(OAc)₂ and 0.04-0.08 equiv of (-)-3a or 3b in THF. ^bIsolated yield based on acetate 9. ^cEnantiomeric excesses were determined by the method described previously.⁵ ^dThis result was already published.⁵

These findings (eq 3, Table 1, and 2) are consistent with the following interpretation: *Flexible* ligands such as **3a** are effective for asymmetric allylic alkylations of *rigid* substrates. On the other hand, *rigid* ligands such as **3b** are suited for the alkylations of *flexible* substrates. This is consistent with the result that the combination of a

flexible ligand and a flexible substrate led lower enantioselectivity (entry 1 in Table 2).

In conclusion, the following points are pertinent: (1) a new chiral alkylphosphine ligand bearing a carboxyl group, 3-(diphenylphosphino)butanoic acid **3a**, has been developed; (2) **3a**-palladium catalyst has proven to be a highly enantioselective catalyst for the allylic alkylation of cyclic *cis*-allylic substrates.

Experimental Section

General Procedures. A melting point was determined with a Büchi 530 melting point apparatus and was not corrected. ¹H and ¹³C NMR, and ³¹P NMR spectra were obtained on a JEOL JNM-A500 spectrometer in CDCl₃ operating at 500 and 125, and 202MHz respectively, with Me4Si and with H₃PO₄ as internal standard. IR spectra were recorded with a JEOL JIR-5500 spectrometer. High-resolution mass spectra (HRMS) were recorded on a JEOL DX-300 mass spectrometer. Analytical high performance liquid chromatography (HPLC) was carried out with a Shimadzu HPLC system equipped with a stationary phase column, Nomura Chemical Co. Ltd., DEVELOSIL Packed Column (4.6 mm X 250 mm), and hexane/ethyl acetate (3/1) as eluting solvent. Optical rotations were measured with a JASCO DIP-1000 polarimeter. All reactions were carried out using degassed solvents under an argon atmosphere.

Materials. 2-Cyclopentenyl acetate, 2-cyclohexenyl acetate, 2-cycloheptenyl acetate and diphenylphosphine were prepared according to the reported procedures.^{7,8} *tert*-Butyl 1-cyclopentenecarboxylate **1b** was prepared in 84 % yield from the reaction of 1-cyclopentenecarboxylic acid with 2-methylpropene in the presence of catalytic amount of conc. H₂SO₄ in dichloromethane.

tert-Butyl 3-(diphenylphosphino)butanoate 2a. To a cooled solution of diphenylphosphine (3.48 g, 18.7 mmol) in dry THF (35 mL) at -78 °C was added dropwise *n*-BuLi (1.64 M in hexane, 10.5 mL, 17.3 mmol). After the mixture was stirred at -78 °C for 0.5 h, a solution of *tert*-butyl crotonate (2.05 g, 14.4 mmol) in THF (10 mL) was added dropwise, followed by addition of HMPA (3 mL), to the mixture, and the reaction mixture was stirred at this temperature for 2 h. The reaction was quenched by the addition of saturated aqueous NH4Cl (50 mL), and extracted with ether, and the extract was washed with brine, dried over Na₂SO₄, and evaporated *in vacuo*. The residue was chromatographed on silica gel [elution with Et₂O/hexane (1/4)] to give 2a in quantitative yield (4.73 g, 100 %). The phosphine 2a is susceptible to air oxidation.

2a: IR (neat) 1726, 1435, 1367, 1146, 742, 698 cm⁻¹; ¹H NMR (CDCl₃) δ 1.08 (dd, *J*=15.0, 7.0 Hz, 3H, Me), 1.43 (s, 9H, C(CH₃)₃), 2.05 (ddd, *J*=15.3, 11.0, 5.5 Hz, 1H, one of CH₂), 2.38 (ddd, *J*=15.3, 8.2, 3.1 Hz, 1H, one of CH₂), 2.79-2.87 (m, 1H, PCH), 7.29-7.35 (m, 6H, phenyl *H*), 7.45-7.55 (m, 4H, phenyl *H*); ¹³C-NMR (CDCl₃) δ 16.5 (d, ²*J*_{CP}=16.6 Hz, CHCH₃), 27.2 (d, ¹*J*_{CP}=10.3 Hz, Ph₂PCH), 28.7 (s, C(CH₃)₃), 39.5 (d, ²*J*_{CP}=18.6 Hz, CH₂), 80.5 (s, C(CH₃)₃), 128.3 (d, ³*J*_{CP}=7.3 Hz, *meta* C), 128.4 (d, ³*J*_{CP}=7.2 Hz, *meta* C), 128.8 (s, *para* C), 128.9 (s, *para* C), 133.5 (d, ²*J*_{CP}=19.7 Hz, *ortho* C), 136.3 (d, ¹*J*_{CP}=14.5 Hz, *ipso* C), 136.4 (d, ¹*J*_{CP}=14.5 Hz, *ipso* C), 172.0 (d, ³*J*_{CP}=15.5 Hz, C=O); ³¹P-NMR (CDCl₃) δ -0.29; HRMS calcd for C₂₀H₂₅O₂P 328.15940, found 328.16080.

3-(Diphenylphosphino)butanoic acid 3a. A solution of **2a** (4.73 g, 14.4 mmol) in benzene (80 mL) containing *p*-toluenesulfonic acid (6.20 g, 32.6 mmol) was heated at reflux for 3 h. After water (100 mL) was added to the reaction mixture, the mixture was extracted with CHCl₃ (3 x 100 mL), dried over Na₂SO₄, and evaporated *in vacuo*. The residue was chromatographed on silica gel [elution with CHCl₃/MeOH(10/1)] to give (\pm)-**3a** in essentially quantitative yield (3.88 g, 99 %).

(±)-3a: IR (neat) 3500-2400, 1703, 1435, 1377, 742, 696 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.11 (dd, J=15.0, 7.0

Hz, 3H, Me), 2.20 (ddd, J=15.7, 11.0, 5.7 Hz, 1H, one of CH₂), 2.51 (ddd, J=15.7, 8.2, 3.2 Hz, 1H, one of CH₂), 2.82-2.91 (m, 1H, PCH), 7.32-7.36 (m, 6H, phenyl H), 7.45-7.55(m, 4H, phenyl H); ¹³C-NMR (CDCl₃) δ 16.7 (d, ²J_{CP}=16.6 Hz, CHCH₃), 26.8 (d, ¹J_{CP}=10.3 Hz, Ph₂PCH), 38.1 (d, ²J_{CP}=18.6 Hz, CH₂), 128.5 (d, ³J_{CP}=7.2 Hz, meta C), 128.6 (d, ³J_{CP}=7.2 Hz, meta C), 129.0 (s, para C), 129.1 (s, para C), 133.5 (d, ²J_{CP}=20.0 Hz, ortho C), 133.6 (d, ²J_{CP}=18.6 Hz, ortho C), 135.9 (d, ¹J_{CP}=14.5 Hz, ipso C), 136.0 (d, ¹J_{CP}=13.5 Hz, ipso C), 178.6 (d, ³J_{CP}=15.5 Hz, C=O); ³¹P-NMR (CDCl₃) δ -0.61; MS m/e 272 (M⁺); HRMS calcd for C₁₂H₁₇O₂P 272.0967, found 272.0989.

Resolution of 3a. A solution of **3a** (2.0 g, 7.4 mmol) and D-(+)- α -methylbenzylamine (PEA)(0.533 g, 4.4 mmol) in acetone (5 mL) was heated under reflux for 0.5 h and was then cooled to -78 °C to induce to crystallize, followed by standing at 0 °C for 3 h. After the precipitating diastereomeric salt (+)-**3a**•(+)-PEA was filtered under a nitrogen atmosphere, washed with cold acetone, and dried, the crude salt was recrystallized three times from acetone to give the pure salt, [α]_D³⁰ 33.0 (c 0.87, CHCl₃). A chloroform solution of the salt was washed with dil. HCl, dried (Na₂SO₄), and evaporated *in vacuo*. The residue was passed through a short silica gel column with CHCl₃-MeOH (10/1) to give optically pure (+)-**3a** (0.62 g), [α]_D³⁴ 29.8 (c 0.97, CHCl₃). Optically pure (-)-**3a**, [α]_D³⁴ -29.3 (c 0.84, CHCl₃), was obtained similarly by the use of (-)-PEA.

The enantiomeric purities of (+)- and (-)-3a were determined by HPLC analysis of diastereomeric amides (+)- and (-)-4a. General procedure for the synthesis of (+)- and (-)-4a is as follows: To a suspension of (+)- of (-)-3a (0.13 mmol) and 2-chloro-1-methylpyrimidine iodide (48 mg, 0.19 mmol) in dry CH₂Cl₂ (3 mL) was added a solution of triethylamine (40 mg, 0.40 mmol) and (-)-PEA in CH₂Cl₂ (2 mL). The reaction mixture was stirred for 10 h at room temperature, quenched with 2N HCl, washed with water, and dried over Na₂SO₄. After evaporation of the solvent *in vacuo*, crude (+)- or (-)-4a was obtained and analyzed by HPLC.

tert-Butyl trans-2-(diphenylphosphino)cyclopentanecarboxylate 2b. This compound was prepared from tert-butyl cyclopentenecarboxylate and diphenylphosphine following the same procedure as that given above for the preparation of tert-butyl 3-(diphenylphosphino)butanoate 2a.

2b: mp(ⁱPrOH) 93-96 °C; IR (KBr) 1721, 1371, 1155, 742, 698 cm⁻¹; ¹H NMR (CDCl₃) δ 1.33 (s, 9H, C(CH₃)₃), 1.52-2.07 (m, 6H, CH₂), 2.72-2.80 (m, 1H, COCH), 2.92-2.98 (m, 1H, PCH), 7.27-7.36 (m, 6H, phenyl H), 7.43-7.48 (m, 2H, phenyl H), 7.52-7.56 (m, 2H, phenyl H); ¹³C-NMR (CDCl₃) δ 26.38 (d, ³J_{CP}=5.2 Hz, CH₂), 27.9 (s, C(CH₃)₃), 31.3 (d, ²J_{CP}=18.6 Hz, CH₂), 32.6 (d, ³J_{CP}=4.1 Hz, CH₂), 37.6 (d, ¹J_{CP}=8.3 Hz, Ph₂PCH), 48.9 (d, ²J_{CP}=21.7 Hz, CHCO), 79.9 (s, C(CH₃)₃), 128.3 (d, ³J_{CP}=3.1 Hz, meta C), 128.3 (d, ³J_{CP}=2.1 Hz, meta C), 128.7 (s, para C), 128.8 (s, para C), 133.4 (d, ²J_{CP}=18.6 Hz, ortho C), 133.8 (d, ²J_{CP}=19.7 Hz, ortho C), 137.7 (d, ¹J_{CP}=13.5 Hz, ipso C), 138.0 (d, ¹J_{CP}=13.5 Hz, ipso C), 175.3 (d, ³J_{CP}=6.2 Hz, C=O); ³¹P-NMR (CDCl₃) δ -2.6; HRMS calcd for C₂₂H₂₇O₂P 354.1750, found 354.1744.

trans-2-(Diphenylphosphino)cyclopentanecarboxylic acid 3b. This compound was prepared from *tert-Butyl trans-2-(diphenylphosphino)cyclopentanecarboxylate 2b* following the same procedure as that given above for the preparation of 3-(diphenylphosphino)butanoic acid 3a by the procedure described above using 1b (2.55 g, 15.2 mmol) and diphenylphosphine (3.39 g, 18.2 mmol) in 4.30 g (14.4 mmol, 95 %) overall yield. Physical data of this compound are consistent with those of previously prepared 2-(diphenylphosphino)-cyclopentanecarboxylic acid.⁵

Asymmetric Allylic Alkylation of 6a-c or 9 with 5. General Procedure. A chiral ligand (0.04–0.08 mmol) and palladium acetate (2.2–4.5 mg, 0.01–0.02 mmol) were placed in a two-necked flask equipped with magnetic stirring bar, a serum cap and three-way stopcock. The flask was filled with nitrogen

after evacuation and to it was added dry THF (3 mL). The mixture was stirred for 0.5 h at room temperature, and a THF solution (2 mL) of **6a-c** or **9** (1 mmol) was added. The mixture was stirred for 0.5 h at room temperature, and a solution of **5**, generated from triethyl phosphonoacetate (1.6 mmol) and sodium hydride (60% dispersion in mineral oil, 60 mg, 1.5 mmol) in dry THF (5 mL) was added. The reaction mixture was kept stirring at given temperatures for 2–87h. After the reaction mixture was quenched with pH 7 phosphate buffer, the mixture was extracted with ethyl acetate, washed with water and brine, dried (Na₂SO₄), and evaporated. The residue was purified over preparative TLC on silica gel to give the product **7a-c** or **10**. The enantiomeric purities of **7a-c** and **10** were determined by HPLC analysis as described previously.⁵

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