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THE FIRST SYNTHESIS OF CHIRAL PHOSPHINOCARBOXYLIC ACID LIGANDS, TRANS-2-(DIPHENYLPHOSPHINO)CYCLOALKANECARBOXYLIC ACIDS. THE PHOSPHINE-PALLADIUM COMPLEXES CATALYZED ASYMMETRIC ALLYLIC ALKYLATION

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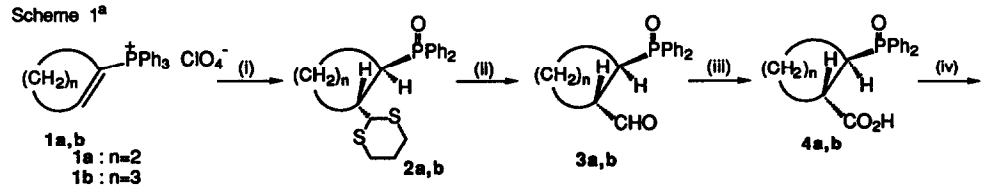
Summary: The first synthesized chiral phosphinocarboxylic acids were effective as ligand for the palladium-catalyzed asymmetric allylic alkylation of 3-acetoxy-1,3-diphenyl-1-propene and 2-cyclohexenyl acetate with soft carbanion from dimethyl malonate or triethyl phosphonoacetate and sodium hydride to give the alkylation products of up to 83% ee.

In recent years, there has been an increasing amount of research devoted to asymmetric synthesis catalyzed by chiral diphosphine-transition metal complexes.[1] One of the most important and challenging problems in research on the catalytic asymmetric synthesis is development of the optically active ligands which give rise to good optical yields.

We report here the first synthesis and resolution of a novel type of chiral phosphinocarboxylic acids ligands,[2] trans-2-(diphenylphosphino)cycloalkanecarboxylic acids and asymmetric allylic alkylation catalyzed with the phosphine-palladium complexes.[3]

The synthesis of trans-2-(diphenylphosphino)cycloalkanecarboxylic acids **6a,b** was outlined in scheme 1. The addition of 2-lithio-1,3-dithiane (21 mmol), generated from 1,3-dithiane (30 mmol) and n-BuLi (21 mmol) to a cyclobutenylphosphonium salt **1a**[4a] (15 mmol) and subsequent hydrolysis of the adduct with NaOH (150 mmol) gave phosphine oxide **2a** (89%), mp 167-169 °C. Treatment of **2a** (15 mmol) with ceric ammonium nitrate (CAN) (26 mmol) led to (2-formylcyclobutyl)phosphine oxide **3a** (78%). Subsequent oxidation of **3a** (10 mmol) with $KMnO_4$ (10 mmol) provided carboxylic acid **4a** (82%), mp 178-178.5 °C. Conversion of **4a** (8 mmol) to its methyl ester followed by reduction with trichlorosilane (40 mmol) produced methyl phosphinocarboxylate **5a** (72%). Hydrolysis of **5a** (5 mmol) with NaOH (25 mmol) afforded racemic 2-(diphenylphosphino)cyclobutanecarboxylic acid (**6a**)[5] (86%). Treatment of a solution of (+)-**6a** in acetone with (R)-(+)-α-

Scheme 1[a]



[a]Reagents : (i) n=2; 1,3-dithiane, n-BuLi, THF, -40~-20 °C, 3 h, then NaOH, MeOH/H_2O, reflux, 7 h. n=3; NaOH, MeOH/H_2O, reflux, 7 h, then 1,3-dithiane, n-BuLi, TMEDA, THF, -40~-20 °C, 3 h. (ii) CAN, Me_2CO/H_2O, r.t., overnight. (iii) $KMnO_4$, Me_2CO/H_2O, r.t., overnight. (iv) conc. H_2SO_4, MeOH, reflux, 7 h, then $HSiCl_3$, benzene, 110 °C, 8 h, in a sealed tube. (v) NaOH, THF/H_2O, r.t., overnight or reflux, 8 h.

methylbenzylamine [(+)-PEA] gave diastereomeric salt (-)-**6a** (+)-PEA, mp 158.5-160 °C. Treatment of this salt with dilute hydrochloric acid gave an optically pure acid (-)-**6a**, $[\alpha]^{24}_D$=-90.1 (c 6.3, CH_2Cl_2). An optically active (-)-**6b** were similarly resolved with (-)-PEA. The enantiomeric purities of the chiral phosphines (-)-**6a** and (-)-**6b** were 96 and 83% ee.[6]

The usefulness of a new type of chiral ligands **6a,b** was examined in the reaction of racemic allylic acetates **7** or **8** with triethyl sodiophosphonoacetate (**9**) or dimethyl sodiomalonate (**10**) (Scheme 2) (Table 1). The reaction of **7** with **9** or **10** using (-)-**6a** at room temperature gave (-)-**11** (91%, 79% ee) or (-)-**12** (75%, 74% ee) (entries 1 and 5), while use of (-)-**6b** under similar conditions produced the (-)-**11** (39%, 82% ee) or (-)-**12** (22%, 72% ee) (entries 2 and 6). These results

Scheme 2

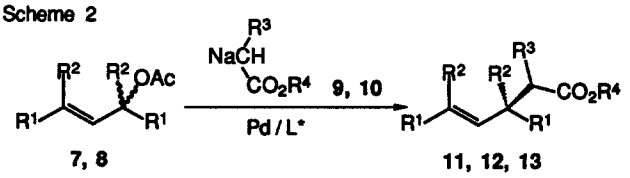
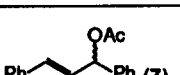
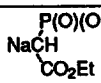
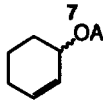


Table 1. Asymmetric Allylic Alkylation of 1-Acetoxy-1,3-diphenyl-1-propene (**7**) or 2-Cyclohexenyl Acetate (**8**) Catalyzed by Chiral Phosphinocarboxylic Acid-Palladium Complexes[a]

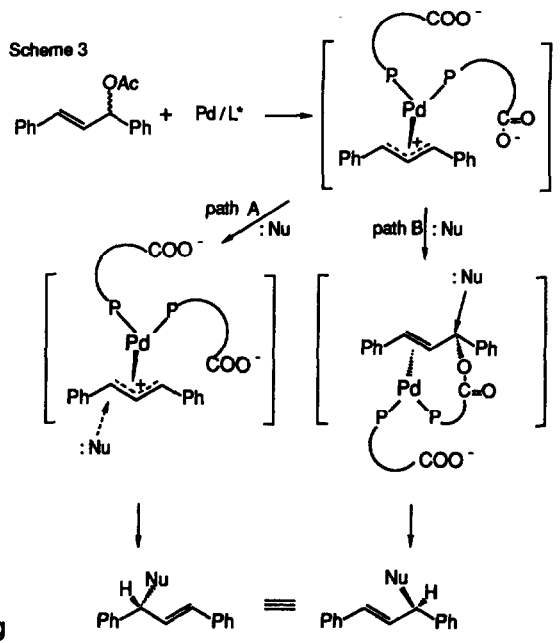
entry	allylic acetate	nucleophile	chiral ligand	reaction conditions temp	time, h	product (% yield)[b]	%ee[c]
1	 (**7**)	 (**9**)	(-)-**6a**[d]	r.t.	45	(-)-**11** (91)	79[e]
2	**7**	**9**	(-)-**6b**	r.t.	48	(-)-**11** (39)	82
3	**7**	**9**	(-)-**6b**	reflux	2	(-)-**11** (74)	77
4	**7**	**9**	(+)-DPCB[f]	reflux	5	(+)-**11** (26)	5
5	**7**	$NaCH(CO_2Me)_2$ (**10**)	(-)-**6a**[d]	r.t.	40	(-)-**12** (75)	74[g]
6	**7**	**10**	(-)-**6b**	r.t.	42	(-)-**12** (22)	72
7	**7**	**10**	(-)-**6b**	reflux	2	(-)-**12** (74)	72
8	**7**	**10**	(+)-**5a**[h]	r.t.	5	(+)-**12** (84)	37
9	 (**8**)	**9**	(-)-**6a**[d]	r.t.	39	(+)-**13** (94)	44[i]
10	**8**	**9**	(-)-**6b**	reflux	2	(+)-**13** (100)	55

[a]Reaction of 1 mmol of **7** or **8** with 1.5 mmol of **9** or **10** in 10 ml of dry THF in the presence of 0.01 mmol of $Pd(OAc)_2$ and 0.02 mmol of a chiral ligand unless otherwise noted. [b]Isolated yield and based on the acetate **7** or **8**. [c]The enantiomeric purities of alkylation products **11**, **12**, and **13** were determined by HPLC analysis of diastereomeric amides prepared from **14**, **15**, and **16** and (-)-PEA, with a stationary phase column (Nomura Chemical Co., Develosil). [d]Reaction in the presence of 0.015 mmol of $Pd(OAc)_2$ and 0.03 mmol of a chiral ligand. [e]$[\alpha]^{21}_D$=-9.8 (c 1.4, CH_2Cl_2). [f]Bisphosphine/$Pd(OAc)_2$=1/1. DPCB=trans-Bis-1,2-(diphenylphosphino)cyclobutane. [g]$[\alpha]^{21}_D$=-12.8 (c 1.7, CH_2Cl_2). [h]Prepared from (+)-**6a** (87% ee) and methanol. $[\alpha]^{24}_D$=51.5 (c 0.9, CH_2Cl_2). [i]$[\alpha]^{21}_D$=12.0 (c 1.9, CH_2Cl_2).

indicated that chemical yields significantly decreased with increasing ring sizes of the ligands. The rise of the reaction temperature caused remarkable improvement of chemical yields, but optical yields showed a slight temperature dependence (entries 2 and 3 and 6 and 7).

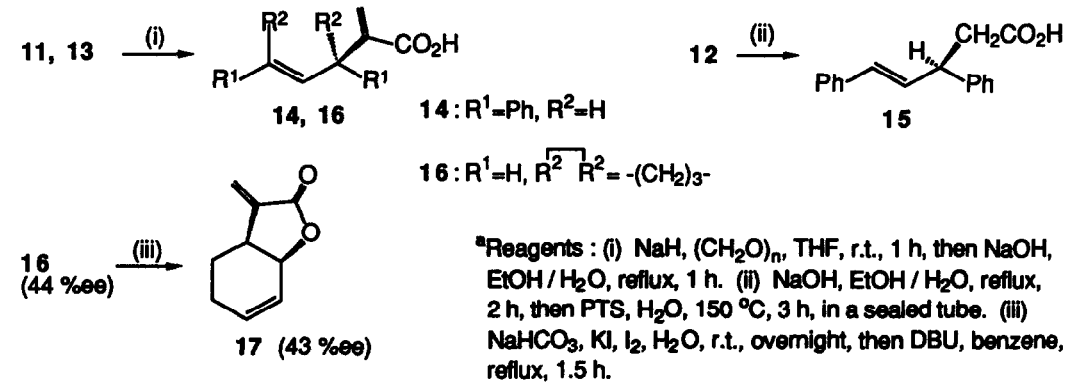
Similar reaction of **7** with **10** using (+)-**5a** (87% ee)[7] gave (+)-**12** of low enantiomeric purity (37% ee) (entry 8). (+)-Trans-bis-1,2-(diphenylphosphino)cyclobutane (DPCB)[8]-palladium complex exerted little catalytic effect (5% ee) (entry 4). These results suggest that the carboxy group of the ligands **6a,b** *in the π-allylpalladium intermediates coordinated with the chiral phosphinocarboxylic* acids plays an important role for causing an asymmetric induction, which may be explained by one of two possible mechanisms: (1) the carboxy group may direct the nucleophilic attack on one of the two diastereotopic π-allyl carbon atoms in the π-allylpalladium intermediate by an electronic repulsion between the negatively charged carboxy group and nucleophiles, since the positively charged π-allyl carbon atoms would be expected to attract the carboxy group[9] (path A). (2) prior to the attack of nucleophiles, the π-allyl complex may undergo the intra-molecular attack of the carboxylate anion of the ligands to convert to chiral allylcarboxylate intermediates bearing the diphenylphosphino group, followed by the predominant attack of nucleophiles on the carbon atom where the leaving group is attached[10] (path B) (Scheme 3).

Scheme 3



The Wittig reaction of **13** with paraformaldehyde afforded optically active α-(2-cyclohexenyl)-acrylic acid (**16**), which underwent iodolactonization and subsequent dehydroiodination with DBU to

Scheme 4[a]



[a]Reagents : (i) NaH, $(CH_2O)_n$, THF, r.t., 1 h, then NaOH, EtOH / H_2O, reflux, 1 h. (ii) NaOH, EtOH / H_2O, reflux, 2 h, then PTS, H_2O, 150 °C, 3 h, in a sealed tube. (iii) $NaHCO_3$, KI, I_2, H_2O, r.t., overnight, then DBU, benzene, reflux, 1.5 h.

lead to an optically active ring-fused α-methylene-γ-lactone **17**[11,12] in 69% (43% ee) yield, $[\alpha]^{25}_{D}$=-6.5 (c 1.8, CH_2Cl_2) (Scheme 4).

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A preliminary account of these results has been reported at 16th Symposium on Organic Sulfur and Phosphorus Chemistry of the Chemical Society of Japan, Morioka, January, 1989; abstract p. 131.

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5 **6a**: IR (neat) 1700 cm^{-1}. Anal. Calcd for $C_{17}H_{17}O_2P$: C, 71.82; H, 6.03. Found: C, 71.55; H, 5.99.

6 The enantiomeric purities of **6a,b**, **11**, **12**, and **13** were determined by HPLC analysis of the corresponding diastereomeric amides prepared from the carboxylic acids **6a,b**, **14**, **15**, and **16** and (-)-PEA in the presence of 2-chloro-1-methylpyridinium iodide and triethylamine.

7 The compound (+)-**5a** was prepared by the reaction of (+)-**6a** (87 %ee) with methanol in dry benzene containing catalytic amount of conc. H_2SO_4. (+)-**5a**: $[\alpha]^{24}_{D}$=51.5 (c 0.9, CH_2Cl_2).

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12 The enantiomeric purity of **17** was determined by HPLC analysis of its diastereomeric 6-[(-)-(α-methylbenzylamido)-vinyl]cyclohex-2-en-1-ol (48%, 43% ee) which was obtained by the reaction of **17** with lithium (-)-α-methylbenzylamide, generated in situ from (-)-PEA with n-BuLi in dry THF.

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