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A Novel Type of Chiral Diphosphine Ligand, trans-2,3-Bis(diphenylphosphino)-1-methyl-1-cyclopropanecarboxylic Acid and Asymmetric Allylic Alkylation by the Use of Its Palladium Complex

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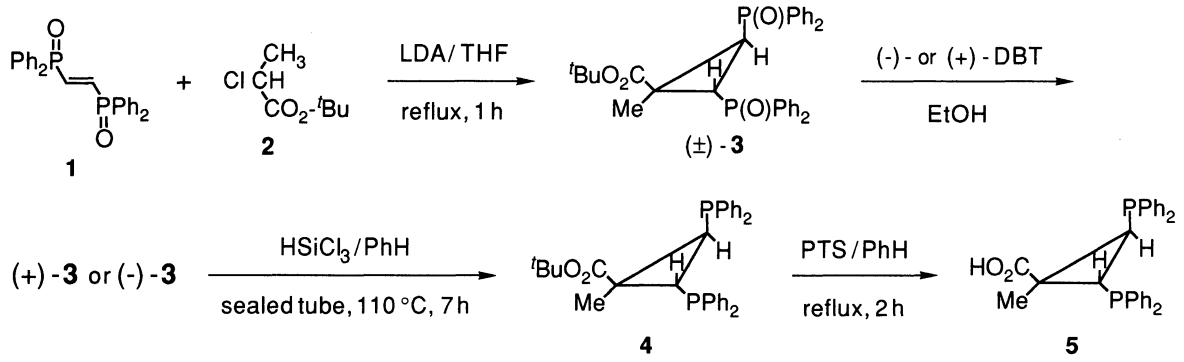
Optically active trans-2,3-bis(diphenylphosphino)-1-methyl-1-cyclopropanecarboxylic acid was synthesized from trans-1,2-bis(diphenylphosphinyl)ethene *via* resolution of the racemic diphosphine oxide. Asymmetric allylic alkylation of 2-cyclohexenyl acetate with *l*-menthyl sodiodiethylphosphonoacetate was achieved in good optical yields by the use of its palladium complex.

A variety of chiral diphosphines has been recently synthesized as chelating agents for homogeneous metal catalysts.[1, 2] We have previously reported a simple method for the synthesis of optically active cycloalkylphosphines bearing a carboxyl group at the β-position and its important role in inducing high stereoselectivity for the asymmetric allylic alkylation catalyzed by phosphine-palladium complexes.[3, 4] We report here the synthesis of a novel type of chiral diphosphine bearing a carboxyl group and its application to asymmetric alkylation.

The synthesis of trans-2,3-bis(diphenylphosphino)-1-methyl-1-cyclopropanecarboxylic acid (**5**) was accomplished as follows (Scheme 1). To a solution of LDA (2.0 mmol) in THF (15 ml) was added *t*-butyl α-chloropropionate (**2**) (2.0 mmol) at -70 °C. After stirring for 30 min, trans-1,2-bis(diphenylphosphinyl)ethene (**1**) (1.0 mmol) was added to the solution. The mixture was stirred overnight at room temperature and refluxed for an additional 1 h. The reaction mixture was quenched with dil. HCl aqueous solution and extracted with $CHCl_3$. The extracts were washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Column chromatography of the residue on silica gel with $CHCl_3$-ethyl acetate (1:1) gave *t*-butyl trans-2,3-bis(diphenylphosphinyl)-1-methyl-1-cyclopropanecarboxylate (**3**) in 81% yield.[5]

Similar to the resolution of (±)-DPCB oxide,[2] treatment of the racemic mixture of **3** with a stoichiometric quantity of D-(+)-dibenzoyltartaric acid (DBT) in ethanol resulted in the formation of the precipitate, in which diastereoisomer (-)-**3**•(+)-DBT was enriched. After filtration, recrystallization of the precipitate from ethanol gave

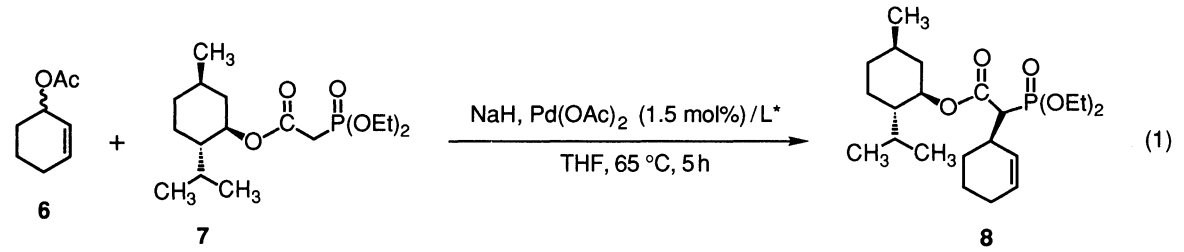
pure (-)-**3**•(+)-DBT, mp 123-126 °C. Treatment of (-)-**3**•(+)-DBT with aqueous NaOH led to optically pure (-)-**3**.[6] Optically pure (+)-**3**[6] was obtained by a similar resolution of (±)-**3** with (-)-DBT.



Scheme 1.

Reduction of optically pure (-)-**3** (2.0 mmol) was carried out with trichlorosilane (20 mmol) in benzene (10 ml) at 110 °C for 5 h in a sealed tube to give the *t*-butyl diphosphinocarboxylate (-)-**4**[7] in 97% yield. Subsequent treatment of (-)-**4** with *p*-toluenesulfonic acid in benzene at reflux for 2 h gave optically active (-)-trans-2,3-bis(diphenylphosphino)-1-methyl-1-cyclopropanecarboxylic acid [(-)-**5**][8] in 71% yield, $[\alpha]_D^{24}$ -55.39° (c 6.60, CH_2Cl_2). The optical purities of both (-)- and (+)-**5** were over 99% ee, which was determined by HPLC analysis of their diastereomeric amides.[9]

The reaction of 2-cyclohexenyl acetate (**6**) (1.0 mmol) with *l*-menthyl sodiodi-



(1)

ethylphosphonoacetate (1.5 mmol) generated from *l*-menthyl diethylphosphonoacetate (**7**)[10] (1.7 mmol) and sodium hydride (60% dispersion in mineral oil, 1.5 mmol) was carried out at 65 °C for 5 h, in the presence of the palladium complex (1.5 mol%) prepared *in situ* by mixing the chiral ligand **5** with palladium acetate (0.15 mmol) in THF (10 ml), which gave the optically active allylic alkylation product **8**. The enantiomeric purity of **8** was similarly determined by HPLC analysis of its conversion into the corresponding diastereomeric amide.[9] The results are summarized in Table 1.

The reaction of **6** with **7** using the (-)-**5**-palladium complex as a catalyst led to **8** in 58% ee, while the use of (+)-**5** instead of (-)-**5** as a ligand decreased the optical yield of **8**

Table 1. Asymmetric Allylic Alkylation of 2-Cyclohexenyl Acetate (**6**) with *l*-Menthyl Diethylphosphonoacetate (**7**) Catalyzed by Chiral Phosphine-Palladium Complexes[a)]

Entry	Ligand	$Pd(OAc)_2$ / L*	Product (% yield)[b)]	%ee[c)]
1	(-) - **5**	1 / 0.8	(+) - **8** (100)	61
2	(-) - **5**	1 / 1.1	(+) - **8** (86)	58
3	(-) - **5**	1 / 1.8	(+) - **8** (88)	48
4	(-) - **5**	1 / 2.2	(+) - **8** (94)	36
5	(+) - **5**	1 / 1.1	(-) - **8** (79)	26
6	(-) - **4**[d)]	1 / 1.0	(+) - **8** (94)	48
7	(-) - DPCBC[e)]	1 / 2.6	(+) - **8** (100)	32
8	(+) - DPCBC[e)]	1 / 2.2	(-) - **8** (100)	40
9	PPh_3	1 / 2.4	(+) - **8** (92)	31
10	(+) - DIOP	1 / 1.2	(-) - **8** (85)	7
11	(-) - DIOP	1 / 0.8	(+) - **8** (100)	19

a) Reaction of 1 mmol of **6** with 1.5 mmol of **7** in 10 ml of THF was carried out in the presence of 0.015 mmol of $Pd(OAc)_2$ at 65 °C for 5 h. b) Isolated yield based on the acetate **6**. c) The enantiomeric purity of **8** was determined by HPLC analysis of diastereomeric amide prepared from **9**[11)] and (-)-PEA, with a stationary phase column (Nomura Chemical Co., Develosil). d) $[\alpha]_D^{22}$ -33.11° (c 3.66, CH_2Cl_2). e) DPCBC = (2-Diphenylphosphino)cyclobutanecarboxylic acid.[3)]

to 26% ee (entries 2 and 5). These results indicate that the ligand (-)-**5** matched but the ligand (+)-**5** ill-matched with the nucleophile **7** in this catalytic allylic alkylation. The highest optical yield was obtained by the use of the palladium complex prepared from (-)-**5** and $Pd(OAc)_2$ in the ratio of *ca* 1:1 (entries 1-4). The replacement of the carboxyl substituent of (-)-**5** with ester remarkably decreased optical yield (entry 6). In contrast, the use of the monophosphine-carboxylic acid (-)- or (+)-DPCBC as a ligand resulted in decreasing optical yields (entries 2, 7, and 8) and exhibited a slight double stereodifferentiation. Furthermore, the use of PPh_3 or DIOP in this alkylation afforded **8** with low enantioselectivity (7-31% ee) (entries 9-11). On the basis of these results, it is evident that the diphosphine bearing the carboxyl group plays an important role in determining enantioselectivity.

Thus, trans-2,3-bis(diphenylphosphino)-1-methyl-1-cyclopropanecarboxylic acid **5** was easily prepared from trans-1,2-bis(diphenylphosphinyl)ethene in optically pure form and this new type of chiral diphosphine is applicable to asymmetric allylic alkylation as an effective ligand for palladium catalyst.

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5) **3**: Mp 192-197 °C; IR (KBr) 1720, 1435, 1190, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 9H, t-Bu), 1.71 (s, 3H, CH_3), 2.10-3.10 (m, 2H, CH), 7.00-8.20 (m, 20H, phenyl H); Anal. Found: C, 70.91; H, 6.19%. Calcd for $C_{33}H_{34}O_4P_2$: C, 71.21; H, 6.16%.

6) (-)-**3**: $[\alpha]_D^{23}$ -55.86° (c 1.13, CH_2Cl_2). (+)-**3**: $[\alpha]_D^{23}$ +54.32° (c 1.04, CH_2Cl_2).

7) **4**: Mp 119-121 °C; IR (KBr) 1710,1430, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 9H, t-Bu), 1.65 (s, 3H, CH_3), 1.72-2.08 (m, 1H, CH), 2.32-2.82 (m, 1H, CH), 6.90-7.64 (m, 20H, phenyl H); Anal. Found: C, 75.40; H, 6.58%. Calcd for $C_{33}H_{34}O_2P_2$: C, 75.56; H, 6.53%.

8) **5**: Mp 174-179 °C; IR (KBr) 1690, 1430, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (s, 3H, CH_3), 1.76-2.15 (m, 1H, CH), 2.49-2.90 (m, 1H, CH), 6.80-7.60 (m, 20H, phenyl H), 9.59 (br s, 1H, COOH); Anal. Found: C, 74.09; H, 5.67%. Calcd for $C_{29}H_{26}O_2P_2$: C, 74.35; H, 5.59%.

9) The enantiomeric purities of (-)-**5**, (+)-**5**, and **8** were determined by HPLC analysis of the corresponding diastereomeric amides prepared from the carboxylic acids (-)-**5**, (+)-**5**, and **9**[11] and (-)-α-methylbenzylamine (PEA) by the use of 2-chloro-pyridinium iodide and triethylamine as condensing agents.

10) *l*-Menthyl diethylphosphonoacetate **7** was prepared from *l*-menthol and diethylphosphonoacetic acid by using 2-chloropyridinium iodide and triethylamine, bp 125-130 °C/0.4 mmHg, $[\alpha]_D^{24}$ -44.29° (c 1.00, $CHCl_3$); IR (neat) 2940, 1730, 1270, 1025, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (d, J=6.89 Hz, 3H, CH_3), 0.90 (d, J=6.74 Hz, 6H, CH_3), 1.34 (t, J=7.18 Hz, 6H, CH_3), 0.70-2.24 (m, 9H, CH_2 and CH), 2.95 (d, J=21.68 Hz, CH_2), 3.90-4.42 (m, 4H, CH_2), 4.44-4.96 (br m, 1H, CH).

11) The Wittig reaction of **8** with paraformaldehyde in the presence of NaH in THF, followed by hydrolysis with sodium hydroxide in aqueous ethanol gave α-(2-cyclohexenyl)acrylic acid (**9**) in good yield.

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