*Tetrahedron: Asymmetry* Vol. 2, No. 7, pp. 667-682, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

# Synthesis of a Novel Type of Chiral Phosphinocarboxylic Acids. The Phosphine-Palladium Complexes Catalyzed Asymmetric Allylic Alkylation

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(*Received* 1 *May* 1991)

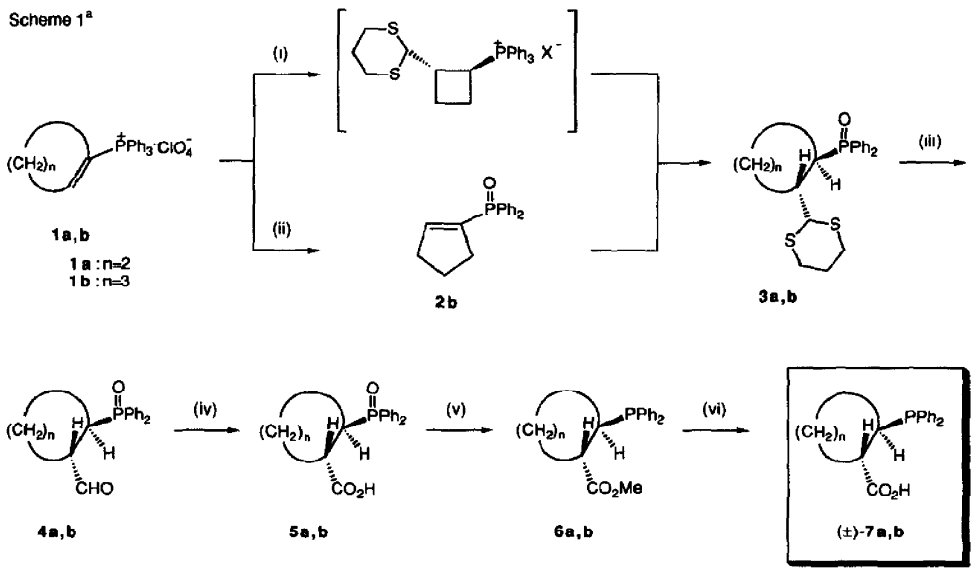
**Abstract:** A novel type of chiral cycloalkylphosphines bearing the carboxy group at the β-position were developed, and used for palladium catalyzed asymmetric allylic alkylation of allylic substrates such as 2-cyclohexenylacetate and 1,3-disubstituted-propenyl acetates ($R^1CH=CHCH(OAc)R^2$: $R^1=R^2=Ph$; $R^1=Ph$, $R^2=(CH_2)_4OAc$; $R^1=Ph$, $R^2=(CH_2)_6OAc$; $R^1=Ph$, $R^2=(CH_2)_{10}OAc$). Reaction of the propenyl acetates with soft carbon nucleophiles such as triethyl sodiophosphonoacetate and sodiomalonic acid esters in the presence of a palladium catalyst prepared in situ from $Pd(OAc)_2$ and chiral (2-diphenylphosphino)cycloalkanecarboxylic acids (**7a,b**) gave high yields of alkylation products ($PhCH=CHCH(X)Ph$: >77 %ee for $X=CH(CO_2Et)P(O)(OEt)_2$ and >72 %ee for $X=CH(CO_2Me)_2$). The alkylation products **15** and **28a-c** were converted into optically active α-methylene-γ-lactone and α-methylene macrolide derivatives. The high stereoselectivity demonstrated by the chiral phosphinocarboxylic acid-palladium catalyzed allylic alkylation suggested to be caused by an electronic repulsion between the carboxy group on the ligand and the incoming soft carbon nucleophile, which directs the nucleophilic attack on one of the π-allyl carbons.

One of the most advantageous and attractive methods for obtaining optically active compounds in synthetic organic chemistry is catalytic asymmetric synthesis by means of a chiral catalyst.[1] From this point of view, a variety of optically active diphosphines as chelating agents for chiral homogeneous catalysts has been recently developed. However, one needs to develop more effective ligands and to study on their application to asymmetric synthesis, since hitherto known diphosphine ligands still have the limitation in the effect and are generally difficult to prepare. As one of instances using chiral diphosphines in asymmetric synthesis, chiral diphosphine-palladium complexes catalyzed asymmetric allylic substitution reactions has been fairly investigated.[2] These reactions are characteristic for that racemic allylic substrates can be converted into optically active products via a π-allylpalladium intermediate where the original chirality of the substrate is lost. We have preliminarily reported[3] asymmetric allylic alkylation which proceeds via a π-allylpalladium intermediate containing a meso type π-allyl group.[4] That is, both enantiomer of racemic allylic acetate bearing the same substituents at 1- and 3-positions form, by oxidative addition to palladium (0), the meso type π-allylpalladium intermediate. The asymmetric induction arises from a preferential attack by the nucleophile on either of the two diastereotopic π-allyl carbon atoms in the π-allylpalladium intermediate. We report here the synthesis of a novel type of chiral cycloalkylphosphines bearing the carboxy group and the phosphine-palladium complexes catalyzed asymmetric allylic alkylation in detail.

## Results and Discussion

Synthesis of Chiral Phosphinocarboxylic Acids. The syntheses of trans-(2-diphenylphosphino)cycloalkanecarboxylic acids **7a,b** and trans-[2-(diphenylphosphino)cycloalkyl]acetic acids **10a,b** were outlined in scheme 1 and scheme 2, respectively. As shown in scheme 1, the addition of 2-lithio-1,3-dithiane to a cyclobutenylphosphonium salt **1a**[5b] in tetrahydrofuran (THF) at -40 °C~-20 °C for 3 h gave [2-(1',3'-dithian-2'-yl)cyclobutyl]phosphonium salt, followed by alkaline hydrolysis to produce [2-(1',3'-dithian-2'-yl)cyclobutyl]diphenylphosphine oxide (**3a**) (89% yield). Treatment of **3a** with ceric ammonium nitrate (CAN) in aqueous acetone led to (2-formylcyclobutyl)diphenylphosphine oxide (**4a**) (78% yield). Subsequent oxidation of **4a** with potassium permanganate ($KMnO_4$) in aqueous acetone provided (2-diphenylphosphinyl)cyclobutanecarboxylic acid (**5a**)

Scheme 1[a]

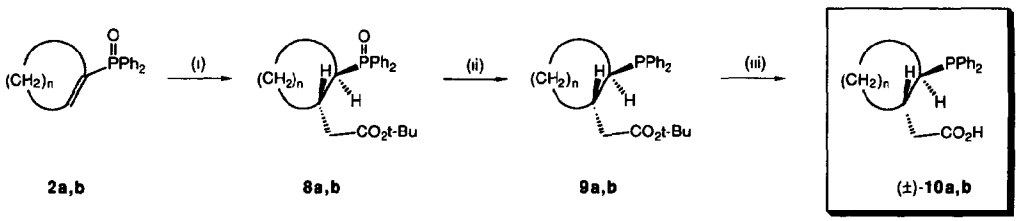



[a]Reagents . (I) 1,3-dithiane, n-BuLi, THF, -40~-20 °C, 3 h. (ii) NaOH, MeOH/$H_2O$, reflux, 7 h. (iii) CAN, $Me_2CO/H_2O$, r.t., overnight. (iv) $KMnO_4$, $Me_2CO/H_2O$, r.t., overnight. (v) conc. $H_2SO_4$, MeOH, reflux, 7 h, then $HSiCl_3$, benzene, 110 °C, 8 h, in a sealed tube. (vi) NaOH, THF/$H_2O$,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

(82% yield). Attempts to resolve a racemic mixture of (+)-**5a** and (-)-**5a** with various resolving agents such as α-methylbenzylamine (PEA), brucine dihydrate, and cinchonidine were unsuccessful, possibly because the strong intramolecular hydrogen bonding between the phosphinyl group and the carboxy group is present. Then, conversion of **5a** to its methyl ester, followed by reduction with trichlorosilane ($HSiCl_3$), produced methyl (2-diphenylphosphino)cyclobutanecarboxylate (**6a**) in good yield. Hydrolysis of **6a** in aqueous THF containing sodium hydroxide (NaOH) afforded racemic (2-diphenylphosphino)cyclobutanecarboxylic acid (**7a**) (86%). Treatment of a solution of a racemic mixture of (±)-**7a** in acetone with 0.6 molar equiv of (-)-PEA in acetone resulted in the formation of the white precipitate[6], in which the diastereomeric salt (+)-**7a**•(-)-PEA is enriched. After filtration, recrystallization of the diastereomeric salt (+)-**7a**•(-)-PEA from acetone three times gave the pure salt, mp 158.5~160 °C. Treatment of a chloroform solution of this salt with dilute hydrochloric acid (HCl) led to

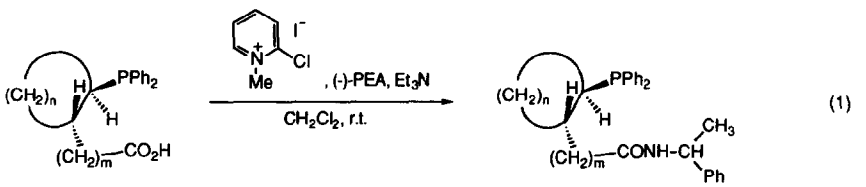
optically pure (+)-trans-(2-diphenylphosphino)cyclobutanecarboxylic acid [(+)-**7a**], $[\alpha]^{24}_D$=86.5 (c 2.2, $CH_2Cl_2$). The acid (-)-**7a** was obtained by the similar resolution of (±)-**7a** with (+)-PEA. In contrast, optically active (+)- and (-)-(2-diphenylphosphino)cyclopentanecarboxylic acid [(+)-**7b**] and [(-)-**7b**] were similarly resolved by the use of (+)-PEA and (-)-PEA, respectively.

Scheme 2[a]




**2a,b** **8a,b** **9a,b** (±)-**10a,b**

[a]Reagents : (i) $CH_3CO_2$t-Bu, LDA, THF,-50~-30 °C, 0.5 h.
(ii)$HSiCl_3$, benzene, 110 °C, 8 h, in a sealed tube.
(iii) PTS, benzene, reflux, 3 h.




(1)

**7a,b, 10a,b** **11a-d**

**7a**, **11a** : n=2, m=0
**7b**, **11b** : n=3, m=0
**10a**, **11c** : n=2, m=1
**10b**, **11d** : n=3, m=1

Table 1. Optical Purities of Chiral Phosphinocarboxylic Acid Ligands

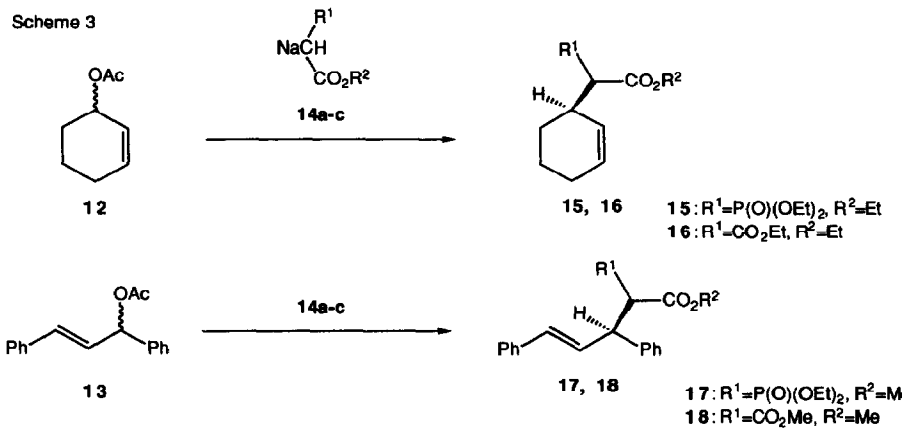
| entry | phosphine | specific rotation $[\alpha]_D$ (c, $CH_2Cl_2$) | optical purity[a] (%ee) |
|---|---|---|---|
| 1 | (+)-**7a** | 86.5 (2.2) | 92 |
| 2 | (-)-**7a** | -90.1 (6.3) | 96 |
| 3 | (+)-**7b** | 31.4 (1.0) | 95 |
| 4 | (-)-**7b** | -29.6 (1.8) | 83 |
| 5 | (+)-**10a** | 24.1 (1.6) | >99 |
| 6 | (+)-**10b** | 6.79 (1.0) | 97 |
| 7 | (-)-**10b** | -2.69 (1.0) | 94 |

[a]Determined by HPLC analysis of diastereomeric amides **11a-d** derived from the optically active phosphines **7a,b** and **10a,b**, and (-)-PEA, with stationary phase column (Nomura Chemical Co., Develosil).

The synthesis and the resolution of the chiral [2-(diphenylphosphino)cycloalkyl]acetic acids **10a,b** are, in turn, achieved as follows. The addition of the t-butyl acetate carbanion, generated from t-butyl acetate and lithium diisopropylamide (LDA), to the cycloalkenylphosphine oxides **2a,b**[5] in THF at -50~-30 °C for 3 h gave t-butyl [2-(diphenylphosphinyl)cycloalkyl]acetates (**8a,b**). Similar reduction of **8a,b** with $HSiCl_3$ produced t-butyl [2-(diphenylphosphino)cycloalkyl]acetates (**9a,b**). Treatment of **9a,b** with p-toluenesulfonic acid (PTS) afforded racemic [2-(diphenylphosphino)cycloalkyl]acetic acids (**10a,b**). Optically active (+)-[2-(diphenylphosphino)cyclobutyl]acetic acid [(+)-**10a**], and (+)- and (-)-[2-(diphenylphosphino)cyclopentyl]acetic acid [(+)-**10b**] and [(-)-**10b**] were similarly resolved by the use of (-)-PEA, and (-)-PEA and (+)-PEA, respectively. The respective enantiomeric purities of the obtained chiral phosphines (+)-**7a**, (-)-**7a**, (+)-**7b**, (-)-**7b**, (+)-**10a**, (+)-**10b**, and (-)-**10b** were determined by HPLC analysis of their diastereomeric amides **11a-d**,[7] derived from each of the optically active phosphines and (-)-PEA (eq 1), with a stationary phase column (Nomura Chemical Co., Develosil). The results were summarized in Table 1.

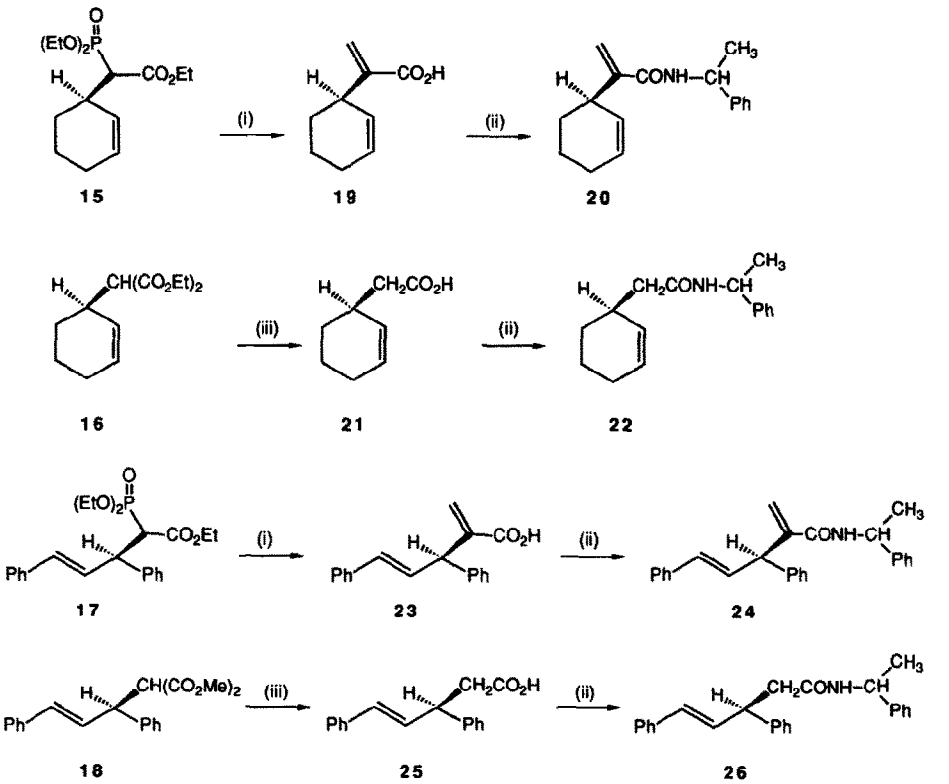
Aymmetric Allylic Alkylation. The reactions of triethyl sodiophosphonoacetate (**14a**), diethyl sodiomalonate (**14b**), or dimethyl sodiomalonate (**14c**) with 2-cyclohexenyl acetate (**12**) or 3-acetoxy-1,3-diphenyl-1-propene (**13**) in the presence of an in-situ prepared palladium complex (1.0~1.5 mol%) by mixing a chiral ligand with palladium acetate ($Pd(OAC)_2$) (P/Pd=2/1) in THF were carried out under various conditions to give optically

Scheme 3




active allylic alkylation products **15**, **16**, **17**, or **18** (Scheme 3). The reaction conditions and results are summarized in Table 2 and 3. The enantiomeric purities of **15**, **16**, **17**, and **18** were similarly obtained by the conversion into the corresponding diastereomeric N-[(-)-α-methylbenzyl]amides **20**, **22**, **24**, and **26**.[7] The reaction of **12** or **13** using the phosphine **7a**-palladium complex as a catalyst at room temperature led to **15** in 94% (31~44 %ee) yields, **16** in 96~98% (49~51 %ee) yields, **17** in 78~91% (79 %ee) yields, and **18** in 75~79% (74~77 %ee) yields (entries 1, 2, 13, 14, 23, 24, 34, and 35), while use of (-)-**7b** instead of **7a** as a ligand under similar conditions produced the products (+)-**15**, (+)-**16**, (-)-**17**, and (-)-**18** in 61% (55 %ee), 42% (78 %ee), 39% (82 %ee), and 22% (72 %ee) yields, respectively (entries 3, 15, 25, and 36). These results indicated that, in catalytic allylic alkylation, optical yields somewhat increased and chemical yields significantly decreased with increasing ring sizes of the ligands from **7a** to **7b**. As seen in entries 3 and 4, 15 and 16, 25 and 26, and 36 and 37, the rise of the reaction temperature caused remarkable improvement of chemical yields, but

Scheme 4[a]




[a]Reagents: (i) NaH, $(HCHO)_n$, THF, r.t., 1 h, then NaOH, EtOH / $H_2O$, reflux, 1 h.
(ii) 2-chloro-1-methylpyridinium iodide, $Et_3N$, (-)-PEA, $CH_2Cl_2$, r.t., 10 h.
(iii) NaOH, EtOH / $H_2O$, reflux, 2 h, then PTS, $H_2O$, 150 °C, 3 h, in a sealed tube.

slightly influenced optical yields.[8] The asymmetric reaction of the allylic acetate **13** with the phosphonoacetate **14a** and the malonates **14b** and **14c** afforded optical yields 22~48% and 25~39%, respectively, higher than the corresponding reaction using the allylic acetate **12**.

On the other hand, the phosphinocyclobutylacetic acid ligand **10a**, in which one carbon chain between the carboxy group and the cyclobutane ring is elongated, resulted in the formation of very low %ee of the alkylation products (entries 6, 18, 28, and 40). In the reaction of **13** with nucleophiles, use of the phosphine ligand **7b** afforded optical yields 46~58 %ee and 59 %ee higher than the use of the ligand **10b**, although, in the reaction of 12, both ligands 7b and 10b gave comparable optical yield (entries 3~5 and 7~10, 15~17 and 19~20, 25~27 and 29~32, and 36~38 and 41~42). These results indicated that optical yields significantly decreased with introducing carbon chain between the carboxy group and the cycloalkylphosphine group.

In order to investigate the carboxy substituent role in determining stereoselectivity in the phosphine-palladium complexes catalyzed asymmetric allylic alkylation, the replacement of the carboxy substituent of (+)-

**7a** with ester and diphenylphosphino substituents remarkably decreased the optical yields (entries 11, 21, 33, 39, and 43). Furthermore, the use of DIOP, as well as DPCB,[9] as a chiral ligand in the similar asymmetric alkylation resulted in the alkylation products with low chemical yields and very low enantioselectivity (4~5 %ee) (entries 12 and 22). On the basis of these results, it is evident that the carboxy group locating at an appropriate distance from the reaction site on the π-allylpalladium intermediate plays an important role in determining

Table 2. Asymmetric Allylic Alkylation of 2-Cyclohexenyl Acetate (**12**) Catalyzed by Chiral Phosphinocarboxylic Acid-Palladium Complexes[a]

| entry | nucleophile | chiral ligand | reaction conditions | | product (% yield)[b] | %ee[c] |
|---|---|---|---|---|---|---|
| | | | temp | time, h | | |
| 1 | **14a** | (-)-**7a**[d] | r.t. | 39 | (+)-**15** (94) | 44[e] |
| 2 | **14a** | (+)-**7a**[d] | r.t. | 48 | (-)-**15** (94) | 31 |
| 3 | **14a** | (-)-**7b** | r.t. | 42 | (+)-**15** (61) | 55 |
| 4 | **14a** | (-)-**7b** | reflux | 2 | (+)-**15** (100) | 55 |
| 5 | **14a** | (+)-**7b** | reflux | 2 | (-)-**15** (95) | 56 |
| 6 | **14a** | (+)-**10a** | reflux | 2 | (-)-**15** (46) | 2 |
| 7 | **14a** | (-)-**10b** | r.t. | 40 | (+)-**15** (33) | 64 |
| 8 | **14a** | (-)-**10b** | reflux | 2 | (+)-**15** (76) | 45 |
| 9 | **14a** | (+)-**10b** | r.t. | 40 | (-)-**15** (30) | 59 |
| 10 | **14a** | (+)-**10b** | reflux | 2 | (-)-**15** (77) | 46 |
| 11 | **14a** | (+)-DPCB[f] | reflux | 5 | (-)-**15** (59) | 3 |
| 12 | **14a** | (+)-DIOP[f] | r.t. | 48 | (-)-**15** (36) | 5 |
| 13 | **14b** | (-)-**7a**[d] | r.t. | 39 | (+)-**16** (96) | 49[g] |
| 14 | **14b** | (+)-**7a**[d] | r.t. | 40 | (-)-**16** (98) | 51 |
| 15 | **14b** | (-)-**7b** | r.t. | 44 | (+)-**16** (42) | 78 |
| 16 | **14b** | (-)-**7b** | reflux | 2 | (+)-**16** (99) | 46 |
| 17 | **14b** | (+)-**7b** | reflux | 2 | (-)-**16** (100) | 68 |
| 18 | **14b** | (+)-**10a** | r.t. | 40 | (-)-**16** (29) | 2 |
| 19 | **14b** | (-)-**10b** | r.t. | 40 | (+)-**16** (81) | 56 |
| 20 | **14b** | (+)-**10b** | r.t. | 40 | (-)-**16** (83) | 56 |
| 21 | **14b** | (+)-DPCB | reflux | 5 | (-)-**16** (42) | 5 |
| 22 | **14b** | (+)-DIOP | r.t. | 48 | (-)-**16** (19) | 4 |

[a]Reaction of 1 mmol of **12** with 1.5 mmol of **14a,b** 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 **12**. [c]The enantiomeric purities of alkylation products **15** and **16** were determined by HPLC analysis of diastereomeric amides prepared from **19** and **21** 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]$[\alpha]^{21}_D$=12.03 (c 1.92, $CH_2Cl_2$). [f]Chiral bisphosphine / $Pd(OAc)_2$=1 / 1. DPCB=trans-bis-1,2-(diphenylphosphino)cyclobutane. DIOP= 2,3-Isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane. [g]$[\alpha]_D$=22.27 (c 4.94, $CH_2Cl_2$).

Table 3. Asymmetric Allylic Alkylation of 3-Acetoxy-1,3-diphenyl-1-propene (**13**) Catalyzed by Chiral Phosphinocarboxylic Acid-Palladium Complexes[a]

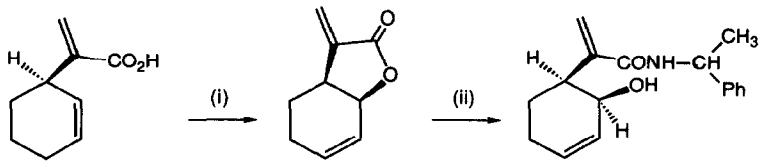
| entry | nucleophile | chiral ligand | reaction conditions | | product (% yield)[b] | %ee[c] |
|---|---|---|---|---|---|---|
| | | | temp | time, h | | |
| 23 | **14a** | (-)-**7a**[d] | r.t. | 45 | (-)-**17** (91) | 79[e] |
| 24 | **14a** | (+)-**7a**[d] | r.t. | 42 | (+)-**17** (78) | 79 |
| 25 | **14a** | (-)-**7b** | r.t. | 48 | (-)-**17** (39) | 82 |
| 26 | **14a** | (-)-**7b** | reflux | 2 | (-)-**17** (74) | 77 |
| 27 | **14a** | (+)-**7b** | reflux | 2 | (+)-**17** (74) | 83 |
| 28 | **14a** | (+)-**10a** | reflux | 2 | (+)-**17** (46) | 2 |
| 29 | **14a** | (-)-**10b** | r.t. | 40 | (-)-**17** (26) | 36 |
| 30 | **14a** | (-)-**10b** | reflux | 2 | (-)-**17** (77) | 22 |
| 31 | **14a** | (+)-**10b** | r.t. | 40 | (+)-**17** (26) | 48 |
| 32 | **14a** | (+)-**10b** | reflux | 2 | (+)-**17** (72) | 25 |
| 33 | **14a** | (+)-DPCB[f] | reflux | 5 | (+)-**17** (66) | 4 |
| 34 | **14c** | (-)-**7a**[d] | r.t. | 40 | (-)-**18** (75) | 74[g] |
| 35 | **14c** | (+)-**7a**[d] | r.t. | 39 | (+)-**18** (79) | 77 |
| 36 | **14c** | (-)-**7b** | r.t. | 42 | (-)-**18** (22) | 72 |
| 37 | **14c** | (-)-**7b** | reflux | 2 | (-)-**18** (74) | 69 |
| 38 | **14c** | (+)-**7b** | reflux | 2 | (+)-**18** (68) | 85 |
| 39 | **14c** | (+)-**6a**[h] | r.t. | 5 | (+)-**18** (84) | 37 |
| 40 | **14c** | (+)-**10a** | r.t. | 40 | (+)-**18** (58) | 2 |
| 41 | **14c** | (-)-**10b** | r.t. | 40 | (-)-**18** (93) | 13 |
| 42 | **14c** | (+)-**10b** | r.t. | 40 | (+)-**18** (93) | 7 |
| 43 | **14c** | (+)-DPCB[f] | reflux | 5 | (+)-**18** (23) | 2 |

[a]Reaction of 1 mmol of **13** with 1.5 mmol of **14a,c** 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 **13**. [c]The enantiomeric purities of alkylation products **17** and **18** were determined by HPLC analysis of diastereomeric amides prepared from **23** and **25** 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]$[\alpha]^{21}_D$=-9.75 (c 1.38, $CH_2Cl_2$). [f]Chiral bisphosphine / $Pd(OAc)_2$= 1 / 1. DPCB=trans-bis-1,2-(diphenylphosphino)cyclobutane. [g]$[\alpha]_D$=-12.81 (c 1.72, $CH_2Cl_2$). [h]Prepared from (+)-**7a** (87 %ee) and methanol. $[\alpha]_D$=51.45 (c 0.93, $CH_2Cl_2$).

enantioselectivity. That is, the carboxy group would direct the nucleophilic attack on one of the two diastereotopic π-allyl carbon atoms in the π-allylpalladium intermediate by electronic repulsion between the negatively charged carboxy group and the incoming nucleophiles, since the positively charged π-allyl carbon atoms would be expected to attract the carboxy group.[10]

In order to extend the synthetic utility of an optically active alkylation product **15**, the Wittig-Horner reaction of **15** (44 %ee) with paraformaldehyde followed by alkaline hydrolysis afforded optically active α-(2-

Scheme 5[a]



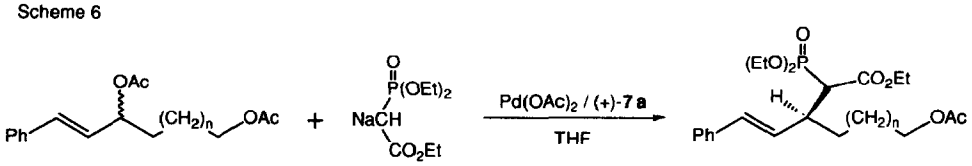

19 27 28

[a]Reagents: (i) $NaHCO_3$, KI, $I_2$, $H_2O$, r.t., overnight, then DBU, benzene, reflux, 1.5 h. (ii) (-)-PEA, n-BuLi, THF, -40 °C, 3 h.

cyclohexenyl)acrylic acid (**19**), which underwent iodolactonization and subsequent dehydroiodination with DBU to lead to an optically active ring fused α-methylene-γ-lactone **27**[11] in 69% (43 %ee) yield (Scheme 5).

For the synthesis of optically active α-methylene macrolides, similar asymmetric reaction of allylic acetates **29a-c** with **14a** using the (+)-**7a**-palladium complex led to regiospecific alkylation products (+)-**30a-c** in 49~57% (9~45 %ee) yields (Scheme 6, Table 4). Of the allylic acetates **29a-c** used, 3,9-diacetoxy-1-phenyl-non-1-ene (**29b**) was found to produce the alkylation product **30b** with the best enantioselectivity (45 %ee), although the selectivity is not necessarily satisfactory (entry 2 in Table 4). The enantiomeric purities of (+)-**30a-**

Scheme 6




**29a-c**
**29a** : n=2
**29b** : n=4
**29c** : n=8

**14a**

**30a-c**
**30a** : n=2
**30b** : n=4
**30c** : n=8

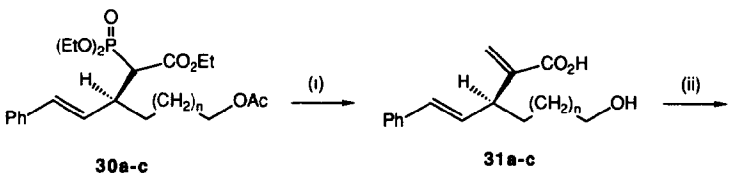
Table 4. Asymmetric Allylic Alkylation of (**29a-c**) Catalyzed by Chiral Phosphinocarboxylic Acid-Palladium Complexes[a]

| entry | n | reaction conditions | | product (% yield)[b] | %ee[c] |
|---|---|---|---|---|---|
| | | temp | time, h | | |
| 1 | 2 | r.t. | 38 | (+)-**30a** (57) | 9 |
| 2 | 4 | r.t. | 60 | (+)-**30b** (49) | 45 |
| 3 | 8 | r.t. | 87 | (+)-**30c** (52) | 23 |

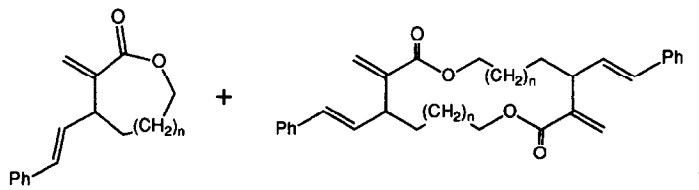
[a]Reaction of 1 mmol of **29a-c** with 1.5 mmol of **14a** in 10 ml of dry THF in the presence of 0.015 mmol of $Pd(OAc)_2$ and 0.03 mmol of (+)-**7a**. [b]Isolated yield. [c]The enantiomeric purities of alkylation products **30a-c** were determined by HPLC analysis of diastereomeric amides prepared from **32a-c** and (-)-PEA, with a stationary phase column (Nomura Chemical Co., Develosil).

c were similarly determined by HPLC analysis of diastereomeric N-[(-)-α-methylbenzyl]amides **33a-c**.[7] The cyclization reaction of **31a,c** in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine[12] gave the expected intramolecular lactonization products **34a,c** (23~42% yields) together with the intermolecular products **35a,c** (12% yields) (Scheme 7).

Scheme 7[a]




**30a-c** **31a-c**

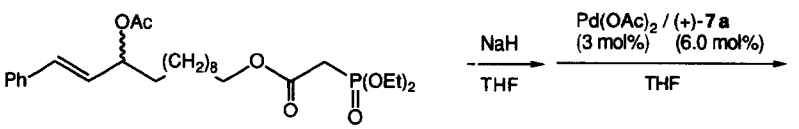



**34a,c** **35a,c**

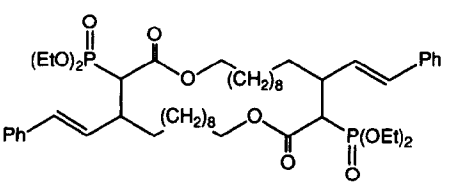
| n | product (yield %) | |
|---|---|---|
| | **34** | **35** |
| 2 | **34a** (42) | **35a** (12) |
| 8 | **34c** (23) | **35c** (12) |

[a]Reagents: (i) NaH, $(HCHO)_n$, THF, r.t., then NaOH, EtOH-$H_2O$, reflux. (ii) $PPh_3$, DEAD, benzene, r.t.

For the purpose of investigating the intramolecular asymmetric alkylation,[13] similar reaction of the allylic acetate **36** in the presence of the (+)-**7a**-palladium complex at 50 °C for 5 h did not provide the desired intramolecular alkylation product, but only an intermolecular alkylation product **37**[14] was obtained in low yield (11 %) as an isolable product (eq 2).




**36**




(2)

**37**

In conclusion, the following points from this investigation are pertinent: (1) a novel type of chiral cycloalkylphosphine ligands bearing carboxy group, 2-(diphenylphosphino)cycloalkanecarboxylic acids and [2-

(diphenylphosphino)cycloalkyl]acetic acids were developed; (2) the carboxy group locating at an appropriate distance from reaction site on the π-allylpalladium intermediate plays an important role in inducing high stereoselectivity in the asymmetric allylic alkylation; (3) a new route for the synthesis of optically active α-methylene-γ-lactone and α-methylene macrolide derivatives by using allylic acetates and triethyl phosphonoacetate was provided.

## Experimental Section

General Procedures. $^1H$ NMR and $^{13}C$ NMR spectra were obtained on a JEOL JNM-FX-60 spectrometer in $CDCl_3$ operating at 60 and 15.04 MHz with $Me_4Si$ as an internal standard. IR spectra were recorded with a Shimadzu IR-408 instrument. 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 Horiba SEPA-200 polarimeter. Melting points were measured in open capillary tubes and are uncorrected.

Materials. (1-Cyclobutenyl)triphenylphosphonium perchlorate **1a**[5b], (1-cyclopentenyl)triphenylphosphonium perchlorate **1b**[5a], 2-cyclohexenylacetate **12**, 3-acetoxy-1,3-diphenyl-1-propene **13**[2f], 3,7-diacetoxy-1-phenyl-1-heptene **29a**, 3,9-diacetoxy-1-phenyl-1-nonene **29b**, 3,13-diacetoxy-1-phenyl-1-tridecene **29c** and 3-acetoxy-1-phenyl-1-tridecenyl diethylphosphonoacetate **36** were prepared according to the established procedures.

Synthesis of [2-(1',3'-Dithian-2'-yl)cyclobutyl]diphenylphosphine Oxide (**3a**). To a solution of the 2-lithio-1,3-dithiane (21 mmol), generated in situ from 1,3-dithiane (3.60 g, 30 mmol) and n-BuLi (1.5 M in hexane, 14 mL, 21 mmol) in 50 mL of dry THF at -40 °C for 0.5 h, was added (1-cyclobutenyl)triphenylphosphonium salt (**1a**) (6.22 g, 15 mmol) at this temperature. The mixture was stirred for 3 h at -40~-20 °C. After the reaction mixture was neutralized with 2 N HCl, the mixture was extracted with dichloromethane ($CH_2Cl_2$), washed with water, dried over anhydrous sodium sulfate ($Na_2SO_4$), and evaporated under reduced pressure. To a solution of the residue in 70 mL of methanol was added a solution of NaOH (6.00 g, 150 mmol) in 50 mL of water. After the mixture was heated under reflux for 7 h, the reaction mixture was neutralized with 2 N HCl, extracted with $CH_2Cl_2$, washed with water, dried ($Na_2SO_4$), and evaporated. Column chromatography of the residue on silica gel with $CHCl_3$-ethyl acetate (1:1) gave [2-(1',3'-dithian-2'-yl)cyclobutyl]diphenylphosphine oxide (**3a**) (5.00 g, 89%).

**3a**: mp 167~169 °C; IR (KBr) 1435, 1180, 1120, 720, 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.40-3.00 (m, 10H, $CH_2$), 3.00-3.80 (m, 3H, CH), 7.00-8.10 (m, 10H, phenyl H). Anal. Calcd for $C_{20}H_{23}OPS_2$: C, 64.14; H, 6.19. Found: C, 63.99; H, 6.30.

Synthesis of [2-(1',3'-Dithian-2'yl)cyclopentyl]diphenylphosphine Oxide (**3b**). To a solution of 2-lithio-1,3-dithiane (12 mmol) was added N, N, N', N'-tetramethylethylenediamine (TMEDA) (1.39 g, 12 mmol) at -40 °C. After the mixture was stirred for 1 h at this temperature, (1-cyclopentenyl)diphenylphosphine oxide (2.68 g, 10 mmol) was added to the mixture. The reaction mixture was stirred for 3 h at -40~-20 °C. After similar workup, the residue was chromatographed on silica gel column with $CHCl_3$ to give [2-(1',3'-dithian-2'-yl)cyclopentyl]diphenylphosphine oxide (**3b**) (3.07 g, 79%).

**3b**: mp 148.5~149.5 °C; IR (KBr) 1435, 1175, 1110, 720, 690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.40-3.40 (m, 15H,

CH and $CH_2$), 7.20-8.00 (m, 10H, phenyl H). Anal. Calcd for $C_{21}H_{25}OPS_2$: C, 64.92; H, 6.49. Found: C, 65.22; H, 6.60.

General Procedure for the Synthesis of (2-Formylcycloalkyl)diphenylphosphine Oxides **4a,b**. To a suspension of **3a,b** (13 mmol) in 100 mL of acetone was added dropwise a solution of CAN (14.23 g, 26 mmol) in 40 mL of water with stirring at room temperature. After being stirred overnight at this temperature, the reaction mixture was extracted with $CH_2Cl_2$, washed with water, dried ($Na_2SO_4$), and evaporated. Column chromatography of the residue on silica gel with $CHCl_3$-ethyl acetate (1:1) gave samples **4a,b**.

(2-Formylcyclobutyl)diphenylphosphine oxide (**4a**): yield 78%; IR (neat) 1720, 1180, 1120, 720, 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.40-3.00 (m, 4H, $CH_2$), 3.00-3.90 (m, 2H, CH), 7.00-8.00 (m, 10H, phenyl H), 9.47 (s, 1H, CHO); HRMS calcd for $C_{17}H_{17}O_2P$ m/e 284.0966, found 284.0990.

(2-Formylcyclopentyl)diphenylphosphine oxide (**4b**): yield 99%; IR (neat) 1710, 1190, 1115, 720, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.00-2.50 (m, 6H, $CH_2$), 2.70-3.70 (m, 2H, CH), 7.20-8.10 (m, 10H, phenyl H), 9.43 (s, 1H, CHO); HRMS calcd for $C_{18}H_{19}O_2P$ m/e 298.1122, found 298.1106.

General Procedure for the Synthesis of (2-Diphenylphosphinyl)cycloalkanecarboxylic Acids **5a,b**. To a stirred solution of **4a,b** (15 mmol) in 50 mL of acetone was added dropwise a solution of $KMnO_4$ (2.37 g, 15 mmol) in 25 mL of water at room temperature. After being stirred overnight, conc. HCl was added to the reaction mixture until a clear solution was obtained. The mixture was extracted with $CH_2Cl_2$, washed with water, dried ($Na_2SO_4$), and concentrated. Column chromatography of the residue on silica gel with $CHCl_3$-methanol (15:1) gave samples **5a,b**.

(2-Diphenylphosphinyl)cyclobutanecarboxylic acid (**5a**): yield 82%; mp 178~178.5 °C; IR (KBr) 2900, 2500, 1715, 1140, 1115, 720, 690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.50-2.80 (br, 4H, $CH_2$), 3.00-4.00 (m, 2H, CH), 6.90-8.20 (m, 10H, phenyl H), 10.50 (br s, 1H, COOH); Anal. Calcd for $C_{17}H_{17}O_3P$: C, 68.00; H, 5.71. Found: C, 68.21; H, 5.70.

(2-Diphenylphosphinyl)cyclopentanecarboxylic acid (**5b**): yield 66%; IR (neat) 2950, 1710, 1150, 720, 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.00-2.40 (m, 6H, $CH_2$), 2.70-3.50 (m, 2H, CH), 7.00-8.40 (m, 11H, phenyl H and COOH); HRMS calcd for $C_{18}H_{19}O_3P$ m/e 314.1072, found 314.1072.

General Procedure for the Synthesis of Methyl (2-Diphenylphosphino)cycloalkanecarboxylate **6a,b**. A solution of **5a,b** (10 mmol) in 60 mL of methanol containing conc. $H_2SO_4$ (0.5 mL) was heated under reflux for 7 h. After similar workup, the residue was chromatographed on silica gel column with $CHCl_3$-ethyl acetate (1:1) to give the pure methyl esters of **5a,b** in quantitative yields. A solution of these methyl ester derivatives (15 mmol) and trichlorosilane (7.5 mL, 75 mmol) in 50 mL of dry benzene was heated at 110 °C for 8 h in a sealed tube. The mixture was concentrated under reduced pressure, diluted with $CHCl_3$, quenched with water, and filtered through the celite pad. The organic layer was separated from the filtrate and aqueous layer was extracted three times with $CHCl_3$. The combined extracts were washed with water, dried ($Na_2SO_4$), and concentrated. The residue was passed through a short silica gel column with $CHCl_3$ to give samples **6a,b**.

Methyl (2-diphenylphosphino)cyclobutanecarboxylate (**6a**): yield 72%; IR (neat) 1725, 1435, 1200, 1120, 720, 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.70-2.50 (m, 4H, $CH_2$), 2.60-3.70 (m, 2H, CH), 3.46 (s, 3H, $CH_3$), 7.00-7.60 (m, 10H, phenyl H); HRMS calcd for $C_{18}H_{19}O_2P$ m/e 298.1123, found 298.1133.

Methyl (2-diphenylphosphino)cyclopentanecarboxylate (**6b**): yield 77%; IR (neat) 1725, 1430, 1190, 1110, 720, 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.40-2.20 (m, 6H, $CH_2$), 2.40-3.20 (m, 2H, CH), 3.28 (s, 3H, $CH_3$), 7.00-7.60 (m, 10H, phenyl H); HRMS calcd for $C_{19}H_{21}O_2P$ m/e 312.1280, found 312.1296.

Hydrolysis of **6a,b**. To a solution of **6a,b** (15 mmol) in 50 mL of THF was added a solution of NaOH (3.00 g, 75 mmol) in 50 mL of water. The mixture was stirred overnight at room temperature or heated at reflux for 8 h. After the mixture was neutralized with 2 N HCl, the mixture was extracted with $CH_2Cl_2$, washed with water, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was passed through a short silica gel column with $CHCl_3$-ethyl acetate (1:1) to give (2-diphenylphosphino)cycloalkanecarboxylic acids **7a,b**.
(2-Diphenylphosphino)cyclobutanecarboxylic acid (**7a**): yield 86%; IR (neat) 1700, 1430, 740, 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.50-2.60 (br m, 4H, $CH_2$), 2.60-3.90 (br m, 2H, CH), 7.00-7.40 (m, 10H, phenyl H), 10.82 (s, 1H, COOH). Anal. Calcd for $C_{17}H_{17}O_2P$: C, 71.82; H, 6.03. Found: C, 71.55; H, 5.99.
(2-Diphenylphosphino)cyclopentanecarboxylic acid (**7b**): yield 78%; mp 114~115 °C; IR (KBr) 1700, 1430, 740, 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.30-2.20 (m, 6H, $CH_2$), 2.40-3.20 (m, 2H, CH), 7.00-7.60 (m, 10H, phenyl H), 9.26 (s, 1H, COOH); HRMS calcd for $C_{18}H_{19}O_2P$ m/e 298.1122, found 298.1160.

General Procedure for the Synthesis of t-Butyl (2-Diphenylphosphinyl)cycloalkylacetates **8a,b**. To a solution of lithium diisopropylamide, generated in situ from diisopropylamine (4.2 mL, 30 mmol) and n-BuLi (19.2 mL, 30 mmol) in 50 mL of dry THF at -78 °C for 0.5 h, was added t-Butyl acetate (16.7 mL, 125 mmol) at this temperature. After the solution was stirred at -50 °C for 0.5 h, (1-cycloalkenyl)diphenylphosphine oxide **2a,b** (23 mmol) was added to the solution. After the reaction mixture was stirred at -50 °C for 3 h, the mixture was quenched with 2 N HCl at this temperature with stirring. The reaction mixture was extracted with $CH_2Cl_2$, washed with water, dried ($Na_2SO_4$), and evaporated. Column chromatography of the residue on silica gel with $CHCl_3$-ethyl acetate (1:1) gave pure **8a,b**.
t-Butyl (2-diphenylphosphinyl)cyclobutylacetate (**8a**): yield 84%; mp 118~120 °C; IR (KBr) 1720, 1435, 1180, 1140, 1110, 720, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.39 (s, 9H, t-Bu), 1.80-2.60 (br m, 6H, CH and $CH_2$), 2.80-3.30 (br, 2H, $CH_2$), 7.20-7.90 (m, 10H, phenyl H); Anal. Calcd for $C_{22}H_{27}O_3P$: C,71.33; H, 7.35. Found: C, 71.50; H, 7.40.
t-Butyl (2-diphenylphosphinyl)cyclopentylacetate (**8b**): yield 72%; mp 131~132 °C; IR (KBr) 1720, 1435, 1180, 1135, 1110, 720, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.39 (s, 9H, t-Bu), 1.20-2.30 (m, 7H, CH and $CH_2$), 2.30-3.20 (m, 3H, CH and $CH_2$), 7.30-8.00 (m, 10H, phenyl H); Anal. Calcd for $C_{23}H_{29}O_3P$: C, 71.86; H, 7.60. Found: C, 71.78; H, 7.66.

General Procedure for the Synthesis of t-Butyl (2-Diphenylphosphino)cycloalkylacetates **9a,b**. A solution of **8a,b** (10 mmol) and trichlorosilane (5 mL, 50 mmol) in 50 mL of dry benzene was heated at 110 °C for 8 h in a sealed tube. The mixture was concentrated under reduced pressure, diluted with $CHCl_3$, quenched with water, and filtered through the celite pad. The organic layer was separated from the filtrate and aqueous layer was extracted three times with $CHCl_3$. The combined extracts were washed with water, dried ($Na_2SO_4$), and concentrated. The residue was passed through a short silica gel column with $CHCl_3$ to give samples **9a,b**.
t-Butyl (2-diphenylphosphino)cylobutylacetate (**9a**): yield 76%; IR (neat) 1720, 1430, 1145, 735, 690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.39 (s, 9H, t-Bu), 1.50-3.00 (br m, 8H, CH and $CH_2$), 7.10-7.50 (m, 10H, phenyl H); Anal. Calcd for $C_{22}H_{27}O_2P$: C, 74.55; H, 7.68. Found: C, 74.43; H, 7.70.
t-Butyl (2-diphenylphosphino)cyclopentylacetate (**9b**): yield 97%; IR (neat) 1720, 1430, 740, 690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.39 (s, 9H, t-Bu), 1.10-2.60 (br, 10H, CH and $CH_2$), 7.10-7.62 (m, 10H, phenyl H); Anal. Calcd for $C_{23}H_{29}O_2P$: C, 74.98; H, 7.93. Found: C,74.35; H, 8.02.

General Procedure for the Synthesis of (2-Diphenylphosphino)cycloalkylacetic Acids **10a,b**. A solution of **9a,b** (10 mmol) and p-toluenesulfonic acid monohydrate (7.61 g, 40 mmol) in 80 mL of benzene was heated

under reflux for 3 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure, diluted with $CH_2Cl_2$, washed with water, and dried ($Na_2SO_4$). After the solvent was evaporated in vacuo, the residue was passed through a short silica gel column with $CHCl_3$-ethyl acetate (1:1) to give samples **10a,b**. (2-Diphenylphosphino)cyclobutylacetic acid (**10a**): yield 96%; mp 57~58 °C; IR (KBr) 1700, 1430, 1260 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.20-2.30 (br, 6H, CH and $CH_2$), 2.30-3.10 (br, 2H, $CH_2$), 7.20-7.50 (m, 10H, phenyl H); Anal. Calcd for $C_{18}H_{19}O_2P$: C, 72.47; H, 6.42. Found: C, 72.43; H, 6.53. (2-Diphenylphosphino)cyclopentylacetic acid (**10b**): yield 84%; mp 137~138 °C; IR (KBr) 1690, 1430, 690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.10-3.00 (m, 10H, CH and $CH_2$), 6.82 (br s, 1H, COOH), 7.00-8.00 (m, 10H, phenyl H); Anal. Calcd for $C_{19}H_{21}O_2P$: C, 73.06; H, 6.78. Found: C, 72.76; H, 6.78.

Optical Resolution of **7a,b** and **10a,b**. General Procedure. A solution of **7a,b** or **10a,b** (8 mmol) and L-(-)- or D-(+)-α-methylbenzylamine (PEA) (0.58 g, 4.8 mmol) in 50 mL of acetone degassed with nitrogen was heated under reflux for 1 h under nitrogen and was then cooled to 0 °C. The diastereomeric salts (+)-**7a**•(-)-PEA, (-)-**7a**•(+)-PEA, (-)-**7b**•(-)-PEA, (+)-**7b**•(+)-PEA, (+)-**10a**•(-)-PEA, (+)-**10b**•(-)-PEA, or (-)-**10b**•(+)-PEA were formed as white pricipitates. After the salts were filtered, washed with cold acetone, and dried, the crude salts were recrystallized three times from acetone to give pure salts. A chloroform solution of the salts was washed with dil. HCl, dried ($Na_2SO_4$), and evaporated in vacuo. The residue was passed through a short silica gel column with $CHCl_3$-ethyl acetate (1:1) to give optically pure phosphinocarboxylic acids (+)- and (-)-**7a,b**, and (+)- and (-)-**10a,b**. The enantiomeric purities of (+)- and (-)-**7a,b**, and (+)- and (-)-**10a,b** were determined by HPLC analysis of diastereomeric amides **11a-d**. General procedure for the synthesis of **11a-d** is as follows. To a suspension of (-)- or (+)-**7a,b**, or (+)- or (-)-**10a,b** (0.13 mmol) and 2-chloro-1-methylpyridinium iodide (48 mg, 0.19 mmol) in 3 mL of dry $CH_2Cl_2$ was added a solution of triethylamine (40 mg, 0.40 mmol) and (-)-PEA (30 mg, 0.25 mmol) in 2 mL of dry $CH_2Cl_2$. The reaction mixture was stirred at room temperature for 10 h, quenched with 2 N HCl, washed with water, and dried ($Na_2SO_4$). After evaporation of the solvent in vacuo, the residue was chromatographed on preparative TLC (silica gel, Wakogel B-5F, $CHCl_3$) to give diastereomeric amides **11a-d**. The results were summarized in Table 1.

Asymmetric Allylic Alkylation of **12**, **13**, or **29a-c** with **14a-c**. General Procedure. A chiral ligand **7a,b** or **10a,b** (0.02-0.03 mmol) and palladium acetate (2-3 mg, 0.01-0.015 mmol) were placed in a two-necked flask equipped with a magnetic stirring bar, a serum cap, and three-way stopcock. The flask was filled with nitrogen after evacuation and to it was added 3 mL of dry THF. The mixture was stirred for 0.5 h at room temperature, and then a solution of **12**, **13**, or **29a-c** (1 mmol) in 2 mL of dry THF were added. The mixture was stirred for 0.5 h at room temperature, and then a solution of **14a-c**, generated from triethyl phosphonoacetate, dimethyl malonate, or diethyl malonate (1.5 mmol) and sodium hydride (60% dispersion in mineral oil, 60 mg, 1.5 mmol) in 5 mL of dry THF was added. The reaction mixture was kept stirring at given temperatures for 2-87 h. After the reaction mixture was quenched with 2 N HCl, the mixture was extracted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$), and evaporated. The residue was chromatographed on preparative TLC on silica gel (ether, benzene-hexane (1:1), or benzene) to give samples **15**, **16**, **17**, **18**, or **30a-c**. The reaction conditions and results are summarized in Table 2, 3, and 4. The enantiomeric purities of **15**, **16**, **17**, **18**, and **30a-c** were determined by HPLC analysis of their N-[(-)-α-methylbenzyl]amide derivatives **20**, **22**, **24**, **26** and **33a-c**.

General Procedure for the Synthesis of **20** and **24**. To a solution of **15** or **17** (1 mmol) in 5 mL of dry THF was added sodium hydride (60% dispersion in mineral oil, 44 mg, 1.1 mmol). After the mixture was

stirred for 1 h, paraformaldehyde (60 mg, 2 mmol) was added to the mixture at room temperature. The reaction mixture was stirred at this temperature for 1 h, and then quenched with 2 N HCl. After similar workup, the residue was chromatographed on preparative TLC (benzene-hexane 1:1) to give Wittig-Horner reaction products. A solution of this products (0.5 mmol) in 5 mL of 50% aqueous ethanol containing NaOH (0.10 g, 2.5 mmol) was heated under reflux for 1 h, and then neutralized with 2 N HCl, followed by similar workup, to give acid **19** or **23**. The reaction of **19** or **23** with (-)-PEA was carried out as described above to give samples **20** or **24**.

General Procedure for the Synthesis of **22** and **26**. A solution of **16** or **18** (1 mmol) in 10 mL of 50% aqueous ethanol containing NaOH (0.4 g, 10 mmol) was heated under reflux for 2 h, and then neutralized with 2 N HCl. The mixture was extracted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$), and evaporated. The mixture of the residue and small amount of PTS in 3 mL of water was heated at 150 °C for 3 h in a sealed tube, followed by similar workup, to give monocarboxylic acids **21** or **25**. The reaction of **21** or **25** with (-)-PEA was carried out as described above to give samples **22** or **26**.

The synthesis of optically active α-methylene-γ-lactone **27**. To a solution of (-)-**19** (0.46 g, 3.0 mmol), and sodium bicarbonate (0.38 g, 4.5 mmol) in 10 mL of water, was added a solution of potassium iodide (1.49 g, 9.0 mmol), and iodine (1.52 g, 6 mmol) in 10 mL of water at room temperature. After stirring overnight, the mixture was extracted with ethyl acetate, washed with aqueous sodium hydrogen sulfite, water, and brine, and dried ($Na_2SO_4$). After evaporation of the solvent in vacuo, the residue was chromatographed on preparative TLC on silica gel (benzene-hexane (1:1)) to give a iodolactonization product (0.61 g, 73% yield). A solution of this product and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.67 g, 4.4 mmol) in 10 mL of benzene was heated under reflux for 1.5 h. The mixture was washed with water and concentrated. The residue was chromatographed on preparative TLC on silica gel (benzene-hexane (1:1)) to give **27** (0.31 g, 94% yield), $[\alpha]_D$=-6.46 (c 1.78, $CH_2Cl_2$). The optical purity of **27** was determined by HPLC analysis of the converted N-[(-)-α-methylbenzyl]amide derivative **28** as following. To a solution of (-)-PEA (0.18 g, 1.5 mmol) in 3 mL of THF was added n-BuLi (0.7 mL, 1.1 mmol) at -78 °C. After stirring for 0.5 h at this temperature, **27** (0.16 g, 1.1 mmol) was added to the reaction mixture. Additionally stirring for 10 h, the mixture was quenched with 2 N HCl. After similar workup, the residue was chromatographed on preparative TLC on silica gel ($CHCl_3$) to give N-[(-)-α-methylbenzyl]-(2-hydroxy-3-cyclohexenyl)acrylamide **28** (0.14 g, 48%).

**28**: IR (neat) 3250, 1650, 1610, 1520, 695 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.46 (d, J=6.9 Hz, 3H, $CH_3$), 1.40-2.30 (m, 4H, $CH_2$), 2.50-3.10 (br m, 2H, CH and OH), 4.08 (br s, 1H, CH), 4.80-5.60 (m, 1H, CH), 5.22 (s, 1H, vinylic H), 5.54 (s, 1H, vinylic H), 5.70-5.90 (m, 2H, olefinic H), 6.93 (br d, J=7.8 Hz, 1H, NH), 7.28 (s, 5H, phenyl H); HRMS calcd for $C_{17}H_{21}NO_2$ 271.1572, found 271.1572.

General Procedure for the Synthesis of **33a-c**. To a solution of **30a-c** (1 mmol) in 5 mL of dry THF was added sodium hydride (60% dispersion in mineral oil, 44 mg, 1.1 mmol). After the mixture was stirred for 1 h, paraformaldehyde (60 mg, 2 mmol) was added to the mixture at room temperature. The reaction mixture was stirred at this temperature for 1 h, and then quenched with 2 N HCl. After similar workup, the residue was chromatographed on preparative TLC (benzene) to give Wittig-Horner reaction products. A solution of this products (0.5 mmol) in 5 mL of 50% aqueous ethanol containing NaOH (0.10 g, 2.5 mmol) was heated under reflux for 1 h, and then neutralized 2 N HCl, followed by similar workup, to give acid **31a-c**. A solution of **31a-c**, catalytic amount of DMAP, and acetic anhydride in pyridine was stirred at room temperature overnight. The mixture was extracted with ethyl acetate, washed with aqueous potassium hydrogen sulfate, aqueous

sodium bicarbonate, and brine, and dried ($Na_2SO_4$). After evaporation of the solvent in vacuo, the residue was chromatographed on preparative TLC on silica gel ($CHCl_3$-ether (1:1)) to give ω-acetylation products **32a-c**. The reaction of **32a-c** with (-)-PEA was carried out as discribed above to give samples **33a-c**.

The Cyclization Reaction of **31a,c**. To a solution of **31a,c** (0.3 mmol) and triphenylphosphine (0.13 g, 0.5 mmol) in 7 mL of dry benzene, was added a solution of DEAD (0.12 g, 0.7 mmol) in 3 mL of dry benzene at room temperature with stirring. After being stirred overnight at this temperature, the reaction mixture was concentrated. The residue was chromatographed on preparative TLC on silica gel (benzene-hexane (1:1)) to give samples **34a,c** and **35a,c**.

3-Methylene-1-oxa-4-(trans-phenylethenyl)cyclooctan-2-one (**34a**): yield 42%; IR (neat) 1710, 1620 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.60-1.90 (br, 6H, $CH_2$), 3.20-3.70 (m, 1H, CH), 4.23 (t, J=4.0 Hz, 2H, $CH_2$), 5.54 (d, J=1.2 Hz, 1H, vinylic H), 6.23 (d, J=1.2 Hz, 1H, vinylic H), 6.24 (dd, J=15.8 and 4.0 Hz, 1H, olefinic H), 6.51 (d, J=14.5 Hz, 1H, olefinic H), 7.3 (s, 5H, phenyl H); HRMS calcd for $C_{16}H_{18}O_2$ m/e 242.1307, found 242.1277.

3-Methylene-1-oxa-4-(trans-phenylethenyl)cyclooctadecan-2-one (**34c**): yield 23 mg (23%); IR (neat) 2900, 1710, 1620 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.00-2.00 (br, 18H, $CH_2$), 3.00-3.80 (m, 1H, CH), 4.00-4.60 (br, 2H, CH), 5.50 (d, J=1.2 Hz, 1H, vinylic H), 6.16 (d, J=1.3 Hz, 1H, vinylic H), 6.20 (dd, J=16.0 and 4.3 Hz, 1H, olefinic H), 6.51 (d, J=14.2 Hz, 1H, olefinic H), 7.30 (s, 5H, phenyl H); HRMS calcd for $C_{22}H_{30}O_2$ m/e 326.2246, found 326.2256.

3,11-Dimethylene-1,9-dioxa-4,12-di(trans-phenylethenyl)cyclohexadecane-2,10-dione (**35a**): IR 1710, 1620 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.20-2.00 (br, 12H, $CH_2$), 3.20-3.60 (m, 2H, CH), 4.23 (br t, J=5.1 Hz, 4H, $CH_2$), 5.57 (br s, 2H, vinylic H), 6.17 (d, J=15.7 Hz, 2H, olefinic H), 6.24 (d, J=1.2 Hz, 2H, vinylic H), 6.52 (d, J=14.6 Hz, 2H, olefinic H), 7.10-7.50 (m, 10H, phenyl H); HRMS calcd for $C_{32}H_{36}O_4$ m/e 484.2614, found 484.2620.

3,17-Dimethylene-1,15-dioxa-4,18-di(trans-phenylethenyl)cyclooctacosane-2,16-dione (**35c**);yield 12 mg (12%); IR (neat) 2900, 1710, 1620 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.00-2.00 (br, 36H, $CH_2$), 3.10-3.60 (m, 2H, CH), 4.19 (t, J=5.6 Hz, 4H, $CH_2$), 5.54 (br s, 2H, vinylic H), 6.21 (d, J=1.2 Hz, 2H, vinylic H), 6.21 (d, J=15.2, 2H, olefinic H), 6.47 (d, J=16.0 Hz, 2H, olefinic H), 7.00-7.40 (m, 10H, phenyl H); HRMS calcd for $C_{44}H_{60}O_4$ m/e 652.4491, found 652.4514.

Acknowledgement. We are grateful for financial support of this work by a Grant-in Aid for Developmental Scientific Research (62850150) and for Scientific Research on Priority Areas from the Japan Ministry of Education, Science and Culture.

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