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Development of a New Class of Chiral Phosphorus Ligands: P-Chirogenic Diaminophosphine Oxides. A Unique Source of Enantioselection in Pd-Catalyzed Asymmetric Construction of Quaternary Carbons

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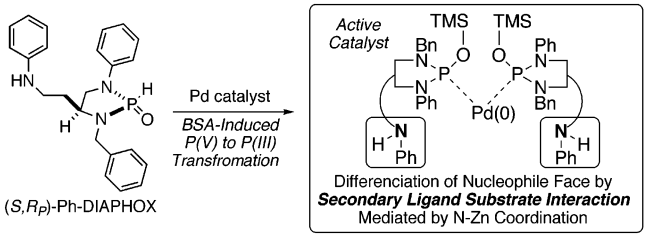

We have recently developed a new class of chiral phosphorus ligands: P-chirogenic diaminophosphine oxides. These pentavalent phosphorus compounds have been successfully applied to Pd-catalyzed asymmetric construction of tertiary and quaternary carbons. The actual ligand structure was the trivalent phosphorus species **17**, which was generated in situ by BSA-induced P(V) to P(III) transformation of **6**, the preligand. Detailed mechanistic studies, including asymmetric amplification and initial rate kinetics, revealed that complex **18** [Pd−**17** (1:2) complex] was the active catalyst. The important function of the nitrogen atom on the sidearm in the ligands was also clarified. The source of enantioselection in the construction of asymmetric quaternary carbons was the secondary ligand substrate interaction mediated by N−Zn coordination.

Introduction

Considerable effort has been devoted to the design and synthesis of various types of chiral ligands for transition metal-mediated asymmetric reactions.[1] From a practical point of view, stable, inexpensive, and easily accessible ligands are highly desirable. The stability of phosphorus atoms toward air oxidation is the simplest but most crucial index for evaluating the practicality of phosphorus ligands. Secondary phosphine oxides and phosphonic acid derivatives are air- and moisture-stable pentavalent phosphorus compounds. These compounds exist in equilibrium between pentavalent forms (RR′P(=O)H) and trivalent tautomeric forms (RR′POH). During equilibrium, stereochemical arrangement around the phosphorus center is retained (Scheme 1).[2] These properties allow for the use of secondary phosphine oxides as air- and moisture-stable ligands in several reactions such as Pt-catalyzed hydroformylation,[3a] Pt-catalyzed hydrolysis[3b] and amidation[3c] of nitriles, Pd-catalyzed aromatic substitution reactions,[4a] and Pd-catalyzed cross-coupling reactions.[4b−h] In those reactions, tautomeric phosphinous acid coordinates to the metal center through a phosphorus atom.

SCHEME 1. Tautomerization of Secondary Phosphine Oxides and Phosphonic Acid Derivatives

Chiral ligands with a stereogenic center on the phosphorus atom are expected to create an effective asym-

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(3) (a) van Leeuen, P. W. N. M.; Roobeek, C. F. In *Homogeneous Transition Metal Catalyzed Reactions*; Advances in Chemistry Series 230; American Chemical Society: Washington, DC, 1992; p 367. (b) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657. (c) Cobley, C. J.; van den Heuvel, M.; Abbadi, A.; de Vries, J. G. *Tetrahedron Lett.* **2000**, *41*, 2467.

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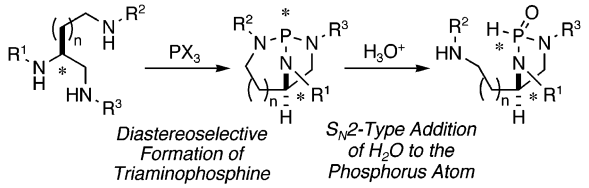
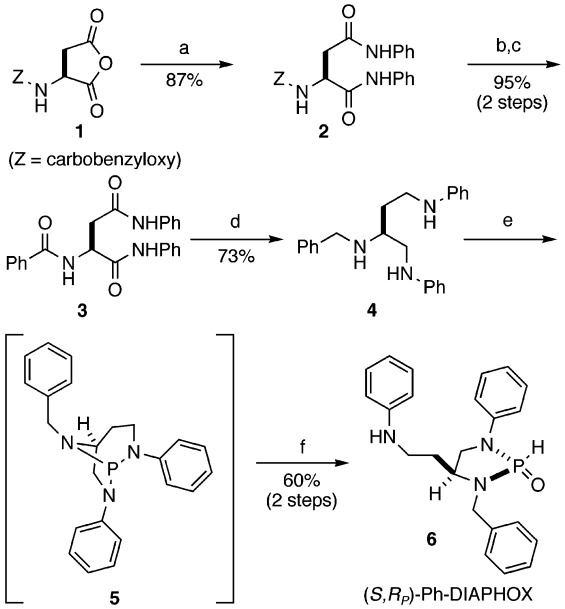
metric environment around the central metal.[5] Although simple P-chirogenic secondary phosphine oxides have been prepared by classical resolution[6a] or phosphanylthioic acid-mediated three-step resolution,[6b] their application to asymmetric catalysis has long been neglected. A recent increase in attention to the potential of secondary phosphine oxides in transition metal catalysis has inspired the creation of a new research field: asymmetric catalysis with P-chirogenic phosphine oxides.[7] The first application of P-chirogenic secondary phosphine oxide to Ir-catalyzed asymmetric hydrogenation was recently reported.[8] In their ligand preparation, however, optical resolution by preparative chiral HPLC is necessary to obtain the chiral secondary phosphine oxides. Thus, the development of an efficient strategy to synthesize various P-chirogenic secondary phosphine oxides or their equivalent in an optically pure form is in high demand. We hypothesized that this preparative drawback could be overcome by designing new ligands based on a chiral diamine framework. We recently reported a new class of chiral phosphorus ligands: aspartic acid-derived P-chirogenic diaminophosphine oxides (DIAPHOXs), which were applied to the catalytic asymmetric synthesis of quaternary carbon centers through Pd-catalyzed asymmetric allylic substitution.[9] While the construction of asymmetric quaternary carbons was successful, the source of enantioselection and the details of the reaction mechanism were obscure. In this article, we report the full details of a Pd-catalyzed asymmetric construction of quaternary carbons using P-chirogenic diaminophosphine oxides. Detailed mechanistic studies of two types of mechanistically different asymmetric allylic substitution reactions clarified the multifunctional properties of the developed ligands in the asymmetric catalysis.

SCHEME 2. Strategy for the Synthesis of P-Chirogenic Diaminophosphine Oxides



SCHEME 3. Synthesis of (S,R_P)-Ph-DIAPHOX 6[a]



[a] Reagents and conditions: (a) aniline, DMF, rt, 1 h, then aniline, WSCI, rt, 24 h. (b) Pd−C (2 mol %), H_2, 2-propanol−DMF, rt, 6 h. (c) Benzoyl chloride, NEt_3, THF, rt, 1 h. (d) $LiAlH_4$, THF, reflux, 13 h. (e) PCl_3, NEt_3, toluene, −78 °C to room temperature, 16 h. (f) SiO_2, H_2O, AcOEt, rt, 18 h.

Results and Discussion

Design, Synthesis, and Application of Aspartic Acid-Derived P-Chirogenic Diaminophosphine Oxides (DIAPHOXs). Cyclic diaminophosphine oxides with a stereogenic center on the phosphorus atom can be prepared from asymmetric diamines. Separation of the diastereomeric mixture, however, is necessary to obtain optically pure P-chirogenic diaminophosphine oxide. Our strategy to introduce chirality into the phosphorus atom is outlined in Scheme 2. Triaminophosphines are reactive to water under acidic conditions via an S_N2-type process, affording the corresponding diaminophosphine oxides through P(III) to P(V) tautomerization.[2] Therefore, we expected that diastereoselective formation of P-chirogenic triaminophosphine starting from optically active branched triamines, followed by the introduction of oxygen functionality on the phosphorus atom, would be an efficient synthetic route.

Our ligand was readily synthesized from the known acid anhydride **1** (Scheme 3). Nucleophilic opening of **1**, followed by condensation with aniline, yielded the corresponding dianilide **2**. Removal of a Z group followed by amide formation with benzoyl chloride afforded triamide **3**. After reduction of all of the amide groups, the obtained triamine **4** was reacted with phosphorus trichloride to afford the corresponding triaminophosphine **5**,

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(5) For recent representative examples of P-chirogenic phosphorus ligands: (a) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635. (b) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988. (c) Tsuruta, H.; Imamoto, T. *Tetrahedron: Asymmetry* **1999**, *10*, 877. (d) Miura, T.; Imamoto, T. *Tetrahedron Lett.* **1999**, *40*, 4833. (e) Ohashi, A.; Imamoto, T. *Org. Lett.* **2001**, *3*, 373. (f) Tsuruta, H.; Imamoto, T. *Synlett* **2001**, 999. (g) Tang, W.; Zhang, X. *Angew Chem., Int. Ed.* **2002**, *41*, 1612. (h) Oohara, N.; Katagiri, K.; Imamoto, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2127. (i) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 3509. (j) Hoge, G. *J. Am. Chem. Soc.* **2003**, *125*, 10219. (k) Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126*, 5966. (l) Hoge, G. *J. Am. Chem. Soc.* **2004**, *126*, 9920. (m) Reetz, M. T.; Ma, J.-A.; Goddard, R. *Angew Chem. Int. Ed.* **2005**, *44*, 412.

(6) (a) Drabowicz, J.; Lyzwa, P.; Omelanczuk, J.; Pietrusiewicz, K. M.; Mikolajajczyk, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2757. (b) Haynes, R. K.; Au-Yeung, Y.-L.; Chen, W.-K.; Lam, W.-L.; Li, Z.-Y.; Yeung, L.-L.; Chen, A. S. C.; Li, P.; Koen, M.; Mitchell, C. R.; Vonwiller, S. C. *Eur. J. Org. Chem.* **2000**, 3205.

(7) Recent progress in transition metal catalysis using chiral and achiral phosphine oxides is highlighted in the following reference; see: Dubrovina, N. V.; Börner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5883.

(8) Jiang, X.; Minnaard, A. J.; Hessen, B.; Feringa, B. L.; Duchateau, A. L. L.; Andrien, J. G. O.; Booger, J. A. F.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 1503.

(9) Nemoto, T.; Matsumoto, T.; Masuda, T.; Hitomi, T.; Hatano, K.; Hamada, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3690.

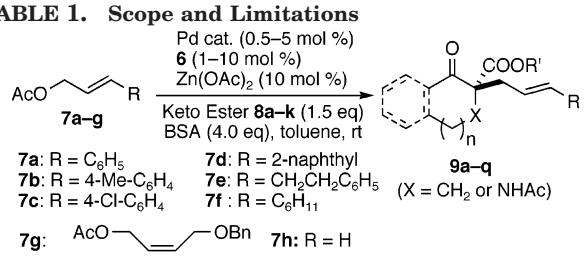
which was converted into diaminophosphine oxide **6** [(S,R_P)-Ph-DIAPHOX] by treatment with silica gel in wet ethyl acetate.[10] Direct purification of the crude triaminophosphine residue with silica gel column chromatography could be utilized as a more convenient alternative method, affording **6** in comparable yield.

The obtained diaminophosphine oxide **6** was applied to catalytic enantioselective construction of a quaternary carbon center.[11] Pd-catalyzed asymmetric allylic substitution using prochiral nucleophiles is one of the most straightforward approaches toward this end. Few successful reactions of this type have been reported since the 1980s.[12−14] When asymmetric allylic substitution of cinnamyl acetate **7a** with ethyl 2-oxocyclohexane carboxylate **8a** was performed using 2.5 mol % (η^3-C_3H_5-PdCl)$_2$ and 10 mol % **6**, no reaction occurred in the presence of typical bases (NaH, LDA, DBU, 1,1,3,3-tetramethylguanidine, and *i*-Pr$_2$NEt). Interestingly, the reaction proceeded in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA)[15] to afford **9a** in 53% ee, even though the yield was only 10%. Encouraged by this result, we investigated the effect of the addition of acetate salt. Detailed screening revealed that Zn(OAc)$_2$ was the best additive for asymmetric induction.[16]

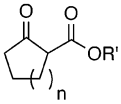
The scope and limitation of different substrates were further examined using these efficient conditions (Table 1). When 0.5−5 mol % of the catalyst was used, asymmetric substitution of allyl acetates **7a**−**h** using prochiral nucleophiles with a six-membered ring (runs 1−5, 10−18) proceeded at room temperature to provide the corresponding products with modest to high enantioselectivity (63−94% ee). This reaction system was also effective for nucleophiles with five-, seven-, and eight-membered rings (runs 6−9) and for acyclic nucleophiles (rus 19−21), resulting in the formation of quaternary carbon centers with modest to good enantioselectivity (72−85% ee).[17]

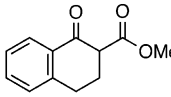
Mechanistic Studies of the Developed Catalytic Asymmetric Reaction: Application to Pd-Catalyzed Asymmetric Allylic Alkylation via an Attack at Enantiotopic Termini of the *meso*-π-Allyl Complex. Enantioselective nucleophilic attack of a stabilized prochiral anion on π-allylpalladium is not easy to control by the chiral ligand on the palladium atom, because the incoming nucleophile resides at the side opposite to the stereogenic center in the transition state. Very interestingly, this difficult process proceeded with high reactivity

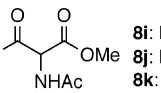
TABLE 1. Scope and Limitations



run	acetates	keto esters	products	time (h)	yield[a] (%)	ee[b] (%)
1[c]	**7a**	**8a** (n = 2, R' = Et)	**9a**	16	99	93(*S*)
2[d]	**7a**	**8a** (n = 2, R' = Et)	**9a**	20	98	92
3[e]	**7a**	**8a** (n = 2, R' = Et)	**9a**	32	85	93
4[c]	**7a**	**8b** (n = 2, R' = Bn)	**9b**	15	99	91(*S*)
5[c]	**7a**	**8c** (n = 2, R' = Me)	**9c**	20	93	94
6[f]	**7a**	**8d** (n = 1, R' = Me)	**9d**	24	75	85(*S*)
7[f]	**7a**	**8e** (n = 1, R' = Bn)	**9e**	24	94	76
8[c,g]	**7a**	**8f** (n = 3, R' = Me)	**9f**	24	85	78
9[c,g]	**7a**	**8g** (n = 4, R' = Me)	**9g**	20	97	72
10[c]	**7a**	**8h**	**9h**	8	99	93(*S*)
11[d]	**7a**	**8h**	**9h**	12	96	93
12[c]	**7b**	**8h**	**9i**	10	98	92
13[c]	**7c**	**8h**	**9j**	7	99	91
14[c]	**7d**	**8h**	**9k**	6	91	91
15[f]	**7e**	**8h**	**9l**	24	74	82
16[f,h]	**7f**	**8h**	**9m**	20	83	80
17[f]	**7g**	**8h**	**9n**[j]	24	80	88
18[f]	**7h**	**8h**	**9o**	48	24	63(*S*)
19[f,i]	**7a**	**8i**	**9p**	48	99	80
20[f,i]	**7a**	**8j**	**9q**	48	99	84
21[f,i]	**7a**	**8k**	**9r**	48	90	78(*R*)

8a–f: 

8h: 

8i: R = *c*Hex
8j: R = *i*-Pr
8k: R = Me


[a] Isolated yield. [b] Determined by HPLC analysis. [c] Performed with 2 mol % of the Pd catalyst. [d] Performed with 1 mol % of the Pd catalyst. [e] Performed with 0.5 mol % of the Pd catalyst. [f] Performed with 5 mol % of the Pd catalyst. [g] Xylenes were used as a solvent. [h] Performed with 12.5 mol % of **6**. [i] Reactions were carried out at 0 °C in the absence of Zn(OAc)$_2$. [j] Product with a *trans*-olefin was obtained exclusively.

and stereoselectivity under unique reaction conditions: (1) BSA is the only base that promoted the reaction; (2) Zn(OAc)$_2$ is the most effective additive for realizing the highly asymmetric induction.

We reasoned that application to a mechanistically different but well-established reaction would be helpful to clarify the reaction mechanism of the developed process. Thus, Pd-catalyzed asymmetric allylic alkylation of **10** with dimethyl malonate was selected for the monitoring reaction, because this asymmetric allylic alkylation is recognized as a benchmark system (Table 2). When the reaction was performed using 1 mol % (η^3-$C_3H_5PdCl)_2$ and 4 mol % **6**, the reaction proceeded smoothly in the presence of Zn(OAc)$_2$, affording the corresponding product **11** in 88% yield and in 96% ee with the (*S*)-configuration. Higher selectivity was obtained

(10) **6** is obtained as an air- and moisture-stable solid. The absolute configuration was unequivocally determined by X-ray crystal structure analysis. For detailed information of the X-ray analysis, see the Supporting Information of ref 9.

(11) For recent reviews, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (c) Douglas, C. J.; Overmann, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101* 5363.

(12) For examples using β-keto esters as the prochiral nucleophile, see: (a) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879. (b) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236. (c) Brunel, J. M.; Tenaglia, A.; Buono, G. *Tetrahedron: Asymmetry* **2000**, *11*, 3585. See also: (d) Sawamura M.; Nakayama, Y.; Tang, W.-M.; Ito, Y. *J. Org. Chem.* **1996**, *61*, 9090. (e) Sawamura, M.; Sudoh, M.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3309.

(13) For examples using 1,3-diketones as the prochiral nucleophile, see: (a) Hayashi, T.; Kanehira, K.; Tsuchiya, H, Kumada, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1162. (b) Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113. (c) Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586. (d) Kuwano, R.; Uchida, K.; Ito, Y. *Org. Lett.* **2003**, *5*, 2177.

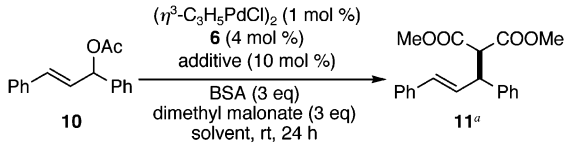
(14) For examples using α-monosubstituted ketones as the prochiral nucleophile, see: (a) Trost, B. M.; Schroeder, G. M. *J. Am. Chem Soc.* **1999**, *121*, 6759. (b) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. *Org. Lett.* **2001**, *3*, 149. (c) Trost, B. M.; Schroeder, G. M.; Kristensen, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3492. (d) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (e) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308. (f) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846.

(15) For review, see: El Gihani, M. T.; Heaney, H. *Synthesis* **1998**, 357.

(16) See Supporting Information for details.

(17) In the case of acyclic nucleophiles, enantioselectivity was not affected by the addition of acetate salt. This result indicates that the source of enantioselection is different from that of cyclic nucleophiles. For detailed data, see Supporting Information.

TABLE 2. Pd-Catalyzed Asymmetric Allylic Alkylation of 10 with Dimethyl Malonate



run	additive	solvent	yield[b]	ee[c]
1	$Zn(OAc)_2$	toluene	88%	96% ee
2	$Zn(OAc)_2$	CH_2Cl_2	98%	98% ee
3	LiOAc	CH_2Cl_2	80%	95% ee
4	NaOAc	CH_2Cl_2	92%	98% ee
5	KOAc	CH_2Cl_2	95%	97% ee
6	CsOAc	CH_2Cl_2	93%	97% ee
7	$Mg(OAc)_2 \cdot 4H_2O$	CH_2Cl_2	86%	97% ee
8	$In(OAc)_3$	CH_2Cl_2	77%	99% ee
9	*n*-Bu_4NOAc	CH_2Cl_2	77%	95% ee
10		CH_2Cl_2	94%	99% ee

[a] Absolute configuration was determined by comparing the measured optical rotation with the reported optical rotation. [b] Isolated yield. [c] Determined by HPLC analysis.

when CH_2Cl_2 was used as the solvent. Further investigations revealed that, in contrast to the case of the quaternary carbon center synthesis, the addition of several acetate salts did not affect the enantioselectivity, and the best result was obtained in the absence of acetate salt (run 10).

BSA-Induced P(V) to P(III) Transformation of Diaminophosphine Oxides. ^{31}P NMR experiments reported in the preceding communication indicated that BSA is related to the generation of a trivalent phosphorus species [chemical shift: 111.0 ppm ($CDCl_3$)] from **6** [chemical shift: 12.5 ppm ($CDCl_3$)].[9] To obtain fundamental information about the mechanism of BSA-induced P(V) to P(III) transformation of diaminophosphine oxides, as well as to determine the actual structure of the trivalent phosphorus species derived from **6**, we first performed NMR experiments using simple diaminophosphine oxide **12**.[16] When **12** (^{31}P NMR chemical shift: 6.7 ppm) was reacted with BSA in $CDCl_3$, the formation of a trivalent phosphorus species (^{31}P NMR chemical shift: 101.0 ppm) was observed similar to the case of **6**. BSA is a powerful reagent for the introduction of trimethylsilyl groups to heteroatoms.[15] No reaction occurred, however, with use of chlorotrimethylsilane instead of BSA, and the predominant peak was observed at the upfield side [^{31}P NMR chemical shift: −12.5 ppm ($CDCl_3$)]. The same transformation was achieved in combination with chlorotrimethylsilane and triethylamine. The fact that no P(V) to P(III) transformation was observed in the presence of only **12** and triethylamine indicates that trimethylsilylation of **12** is essential for the base-induced P(V) to P(III) transformation. These experiments provided useful information to explain the reaction mechanism of BSA-induced P(V) to P(III) transformation (Scheme 4). The reaction is triggered by silylation of diaminophosphine oxide **12**. The resulting cationic product **13** reacts with a BSA-derived anion to provide the trivalent phosphorus species **14**.[18]

Active Catalyst Structure and Reaction Mechanism. Preliminary experiments using **12** were very informative for determining the structure of the diamidophosphite moiety of the trivalent phosphorus species derived from **6**. There is no experimental information,

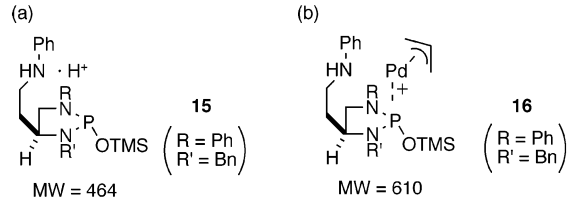
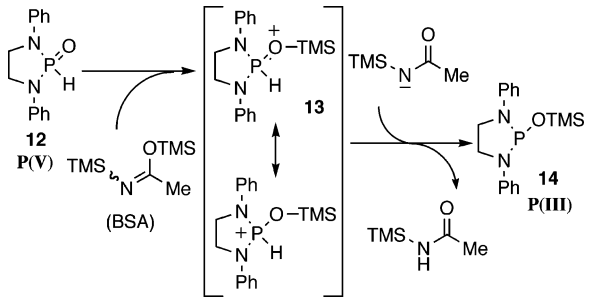


FIGURE 1. Observed species in FAB MS analysis.

SCHEME 4. Reaction Mechanism of BSA-Induced P(V) to P(III) Transformation of 12



however, on the structure of the nitrogen moiety on the sidearm. Thus, we attempted to clarify the actual ligand structure using fast atom bombardment mass spectrometry (FAB MS).[16] FAB MS analysis of the residue obtained from a CH_2Cl_2 solution of **6** and BSA (30 equiv with respect to **6**) exhibited a peak at 464 *m/z*. The detected peak corresponded to the molecular weight of **15** [Figure 1a]. In addition, FAB MS analysis of the residue obtained from a CH_2Cl_2 solution of (η^3-C_3H_5-$PdCl)_2$, **6**, and BSA in a ratio of 1:2:60 (Pd:**6** = 1:1) exhibited a peak at 610 *m/z*. The detected peak corresponded to the molecular weight of the cationic complex **16** [Figure 1b].[19] These data clearly suggested that the nitrogen atom on the sidearm is not silylated, even in the presence of excess BSA.[20] On the basis of these results, we concluded that diaminophosphine oxide **6**, the preligand, reacts with BSA in the reaction mixture, affording the trivalent phosphorus compound **17**, which is proposed to be the actual ligand structure (Scheme 5).[21]

Considering the structure of the actual ligand **17**, as well as the cationic palladium complex **16** detected by FAB MS analysis, it is possible that **17** chelates to the Pd metal in a bidentate manner through both the phosphorus atom and the nitrogen atom. This led us to question whether this Pd−ligand ratio (Pd:**6** = 1:2) was

(18) Structure of **14** was confirmed by comparing the NMR data of an authentic sample, which was prepared according to the reported method using *N*,*N*-diethyltrimethylsilylamine. For reference, see: Plinta, H.-J.; Neda, I.; Fischer, A.; Jones, P. G.; Schmutzler, R. *Chem. Ber.* **1995**, *128*, 695.

(19) ^{31}P NMR analysis of a $CDCl_3$ solution of (η^3-$C_3H_5PdCl)_2$, **6**, and BSA in a ratio of 1:2:60 (Pd:**6** = 1:1) exhibited two singlet signals at 100.0 and 101.7 ppm. Although the corresponding structures have not been clarified, partial information has been obtained from the analytical experiments using **25** instead of **6**. See Supporting Information for details.

(20) No trimethylsilylation of *N*-methylaniline occurred in the presence of excess BSA. This fact strongly supports our conclusion.

(21) For recent examples of P-chirogenic diamidophosphite ligands, see: (a) Brunel, J. M.; Constantieux, T.; Buono, G. *J. Org. Chem.* **1999**, *64*, 8940. (b) Delapierre, G.; Brunel, J. M.; Constantieux, T.; Buono, G. *Tetrahedron: Asymmetry* **2001**, *12*, 1345. (c) Tsarev, V. N.; Lyubimov, S. E.; Shiryaev, A. A.; Zheglov, S. V.; Bondarev, O. G.; Davankov, V. A.; Kabro, A. A.; Moiseev, S. K.; Kalinin, V. N.; Gavrilov, K. N. *Eur. J. Org. Chem.* **2004**, 2214.

SCHEME 5. Actual Ligand Structure

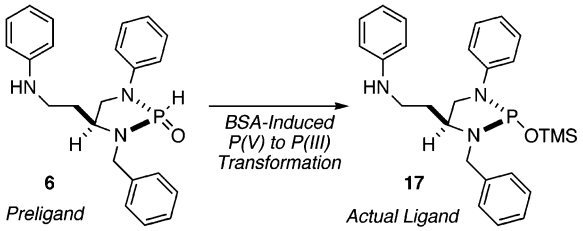
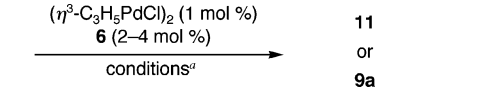


TABLE 3. Effect of Pd−Ligand Ratio



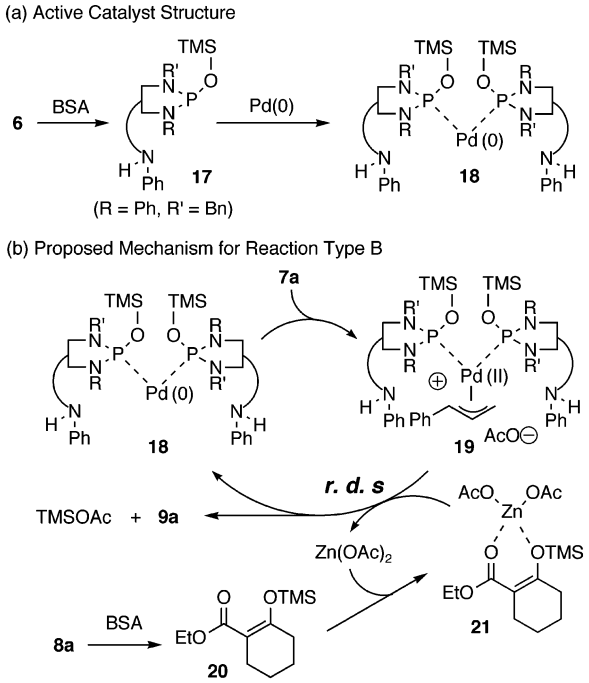
run	substrate	Pd−ligand ratio	time	yield[b]	ee[c]	
1	**10**	1:2	0.5 h	84%	99% ee	type A
2	**10**	1:1.5	0.5 h	57%	98% ee	
3	**10**	1:1	0.5 h	no reaction		
4	**7a**	1:2	2 h	89%	93% ee	type B
5	**7a**	1:1.5	2 h	34%	93% ee	
6	**7a**	1:1	2 h	no reaction		

[a] Reaction conditions. Runs 1−3: dimethyl malonate (3.0 equiv), BSA (3.0 equiv), CH_2Cl_2 (0.2 M), rt. Runs 4−6: **8a** (1.5 equiv), BSA (4.0 equiv), $Zn(OAc)_2$ (10 mol %), toluene (0.15 M), rt. [b] Isolated yield. [c] Determined by HPLC analysis.

optimal. To resolve this issue, we investigated the Pd−ligand ratio using two representative reactions: **10** to **11** (reaction type A) and **7a** to **9a** (reaction type B) (Table 3). When the catalyst was prepared in different Pd−ligand ratios, there was a remarkable decrease in reactivity without any loss of enantioselectivity, as compared to the case of the best ratio. In particular, no reaction occurred using the catalyst prepared from the Pd source and **6** in a ratio of 1:1. In addition, there were positive nonlinear effects[22] in both types of reactions.[16] These results led us to hypothesize that the Pd−**17** (1:2) complex exists in the reaction mixture and might function as the active species.

To elucidate the detailed reaction profiles, we performed kinetic experiments.[16] The reaction rate of allylic alkylation of **10** with dimethyl malonate (reaction type A) had first-order dependence on the Pd catalyst, zero-order dependence on **10**, and first-order dependence on dimethyl malonate. Similarly, the reaction rate of allylic substitution of **7a** with **8a** (reaction type B) had first-order dependence on the Pd catalyst, zero-order dependence on **7a**, first-order dependence on **8a**, and first-order dependence on $Zn(OAc)_2$. These reaction profiles clearly support our expectation that two molecules of the ligand chelate to the Pd metal and result in a positive nonlinear effect. Consequently, we propose the following reaction mechanism. Complexation of the Pd source and **6** first occurred in the presence of BSA, affording the Pd(0) complex **18** (Pd:**17** = 1:2), which is proposed to be the common active species for both types of reactions [Scheme 6a]. Kinetic experiments also indicate that, in the case of reaction type B, the rate-determining nucleophilic attack of enol silyl ether **20**[23] to a cationic π-allylpalladium complex **19** is achieved in cooperation with a single

SCHEME 6. Proposed Reaction Mechanism



molecule of $Zn(OAc)_2$, yielding product **9a** with high enantiomeric excess [Scheme 6b].[24]

Source of Enantioselection in the Asymmetric Catalysis. The sources of enantioselection are quite different between the two types of reactions examined: attack at enantiotopic termini of the *meso*-π-allyl complex (reaction type A) and differentiation of the prochiral nucleophile face (reaction type B).[25] Despite the mechanistic difference, a high level of enantioselection was realized in both cases by the same Pd complex **18**. The fact that the cooperation of $Zn(OAc)_2$ is indispensable to the high stereoselectivity in reaction type B suggested that nitrogen atoms on the sidearms in **19** fix the prochiral nucleophile in the appropriate position through a secondary ligand substrate interaction[13a−c,26] mediated by Zn metal. To examine this possibility, we first investigated the effect of ligand modifications (Table 4). When structurally modified diaminophosphine oxides **22**−**25**[27] were used as the ligand, there were no significant changes in the stereoselectivity in the case of reaction

(22) For review, see: Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2923.

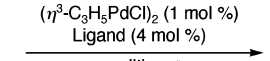
(23) In general, reaction of BSA with β-keto esters proceeds readily to afford the corrsponding trimethylsilyl enol ethers (see ref 15). Enol silyl ether **20** was observed in ^{1}H NMR, when **8a** was treated with 1 equiv of BSA in toluene-d_8. When **20** itself was used as the substrate, however, a remarkable decrease in the reactivity was observed, despite the ee value remaining unchanged [16 h, 13% yield, 93% ee, conditions: Pd catalyst (2 mol %), **6** (4 mol %), $Zn(OAc)_2$ (10 mol %), **20** (1.5 equiv), BSA (2.5 equiv), toluene, rt]. For discussions about this result, see Supporting Information.

(24) In the early 1980s, Negishi and co-workers reported their pioneering work on the Pd-catalyzed allylation of Zn enolates, where enolate nucleophiles attacked the π-allylpalladium species at the side opposite to the Pd metal. [For references, see: (a) Negishi, E.; Matsushita, H.; Chatterjee, S.; John, R. A. *J. Org. Chem.* **1982**, *47*, 3188. (b) Negishi, E.; John, R. A. *J. Org. Chem.* **1983**, *48*, 4098.] The obtained kinetic profiles (first-order dependence on **8a** and first-order dependence on $Zn(OAc)_2$), however, clearly indicate that Zn enolates are not generated in our reaction system.

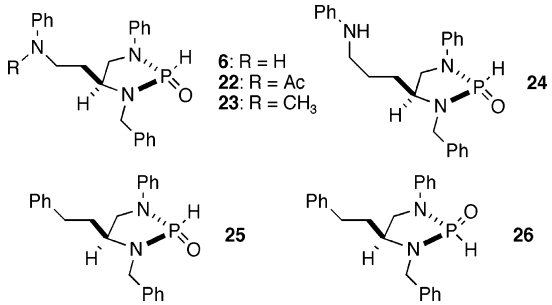
(25) For reviews, see: (a) Trost, B. M. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(26) For reviews, see: (a) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857. (b) Börner, A. *Eur. J. Inorg. Chem.* **2001**, 327.

TABLE 4. Effect of Ligand Modifications



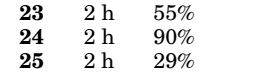
run	substrate	ligand	time	yield[b]	ee[c]	
1	**10**	**6**	0.5 h	84%	99% ee	type A
2	**10**	**22**	0.5 h	98%	98% ee	
3	**10**	**23**	0.5 h	82%	94% ee	
4	**10**	**24**	0.5 h	50%	97% ee	
5	**10**	**25**	0.5 h	85%	97% ee	
6	**10**	**26**	0.5 h	96%	−80% ee[d]	
7	**7a**	**6**	2 h	89%	93% ee	type B
8	**7a**	**22**	2 h	37%	79% ee	
9	**7a**	**23**	2 h	55%	64% ee	
10	**7a**	**24**	2 h	90%	84% ee	
11	**7a**	**25**	2 h	29%	63% ee	
12	**7a**	**26**	2 h	no reaction		



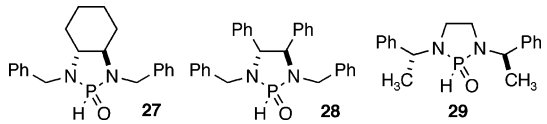
[a]Reaction condition. Runs 1−6: dimethyl malonate (3.0 equiv), BSA (3.0 equiv), CH_2Cl_2 (0.2 M), rt. Runs 7−12: **8a** (1.5 equiv), BSA (4.0 equiv), $Zn(OAc)_2$ (10 mol %), toluene (0.15 M), rt. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Negative value means the opposite enantiomer.

type A (runs 1−5). In contrast, remarkable changes were observed in the case of reaction type B. Electronic and steric changes on the nitrogen atom (runs 8, 9), as well as changes in the sidearm length (run 10), influenced catalytic activity, resulting in decreased reactivity and selectivity. Particularly noteworthy is that there was a significant decrease in the enantioselectivity, when **25**, a ligand without a nitrogen atom on the sidearm, was used (run 11). With the use of **26**,[27] a ligand possessing the (*S*)-configuration on the phosphorus atom, opposite stereoselection was observed in reaction type A (run 6). In addition, no reaction occurred when **26** was used in reaction type B (run 12). These results clearly indicate the importance of chirality on the phosphorus atom. The effect of the ligand structure was also investigated using the known chiral diaminophosphine oxides **27**,[28a] **28**,[28a] and **29**[28b] (Table 5). The structure of the chiral diaminophosphine oxide dramatically affected the catalytic activity, suggesting that ligand structure with a sidearm is important for achieving the asymmetric catalysis. Moreover, the striking difference in the solvent effect indicates that the polarity of the reaction media dramatically affected the transition state structure incorporated with $Zn(OAc)_2$ (Table 6). These experimental findings led us to conclude that the secondary ligand substrate interaction mediated by N−Zn coordination has a crucial role in the enantiofacial recognition of prochiral nucleophiles in reaction type B.[29]

TABLE 5. Effect of Ligand Structure



run	substrate	ligand	time	yield[b]	ee[c]	
1	**10**	**6**	24 h	94%	99% ee	type A
2	**10**	**27**	24 h	27%	87% ee	
3	**10**	**28**	24 h	no reaction		
4	**10**	**29**	24 h	no reaction		
5	**7a**	**6**	16 h	99%	93% ee	type B
6	**7a**	**27**	16 h	no reaction		
7	**7a**	**28**	16 h	no reaction		
8	**7a**	**29**	16 h	no reaction		



[a]Reaction conditions. Runs 1−4: dimethyl malonate (3.0 equiv), BSA (3.0 equiv), CH_2Cl_2 (0.2 M), rt. Runs 5−8: **8a** (1.5 equiv), BSA (4.0 equiv), $Zn(OAc)_2$ (10 mol %), toluene (0.15 M), rt. [b] Isolated yield. [c] Determined by HPLC analysis.

TABLE 6. Solvent Effect

run	substrate	solvent	time	yield[b]	ee[c]	
1	**10**	CH_2Cl_2	24 h	94%	99% ee	type A
2	**10**	THF	24 h	49%	96% ee	
3	**10**	toluene	24 h	67%	96% ee	
4	**10**	CH_3CN	24 h	98%	96% ee	
5	**7a**	CH_2Cl_2	16 h	23%	60% ee	type B
6	**7a**	THF	16 h	41%	78% ee	
7	**7a**	toluene	16 h	99%	93% ee	
8	**7a**	CH_3CN	16 h	no reaction		

[a] Reaction conditions. Runs 1−4: dimethyl malonate (3.0 equiv), BSA (3.0 equiv), CH_2Cl_2 (0.25 M), rt. Runs 5−8: **8a** (1.5 equiv), BSA (4.0 equiv), $Zn(OAc)_2$ (10 mol %), toluene (0.15 M), rt. [b] Isolated yield. [c] Determined by HPLC analysis.

To obtain more detailed structural information for discussion on the sources of enantioselection, we tried crystallizing the catalyst species. Unfortunately, a crystal for X-ray analysis could not be obtained. Although the complete transition state is not clear, the mechanistic findings, as well as the absolute configuration of the products, suggest that the enantiofacial discrimination of prochiral nucleophiles in reaction type B would be explained by the working model shown in Figure 2. The observed absolute configuration of **9a** and other products indicate that the C−C bond formation occurs on the *Si*-face of the enolate nucleophile. The fact that nucleophiles

(27) Diaminophosphine oxide **24** was prepared from (*S*)-glutamic acid; diaminophosphine oxides **25** and **26** were prepared from (*S*)-homophenylalanine. See Supporting Information for details.

(28) (a) Koeller, K. J.; Spilling, C. D. *Tetrahedron Lett.* **1991**, *32*, 6297. (b) Devitt, P. G.; Kee, T. P. *Tetrahedron* **1995**, *51*, 10987. (c) See also, Mareno, G. E.; Quintero, L.; Bernes, S.; de Parrodi, C. A. *Tetrahedron Lett.* **2004**, *45*, 4245.

(29) It is known that coordination affinity of amines for Zn(II) species is dependent on the steric requirement of the amine rather than the amine basicity. In particular, tertiary amines such as triethylamine have extremely low coordination affinity compared with those of primary and secondary amines. [For references, see: (a) Higgins, G. M. C.; Saville, B. *J. Chem. Soc.* **1963**, 2812. (b) Coates, E.; Rigg, B. Saville, B.; Skelton, D. *J. Chem. Soc.* **1965**, 5613.] This information provides us with a reasonable explanation for the observed stereoselectivity in the reaction using **23** (Table 4, run 9), where the sidearm with a tertiary amine would be recognized as one of the steric elements, analogous to that of **25**.

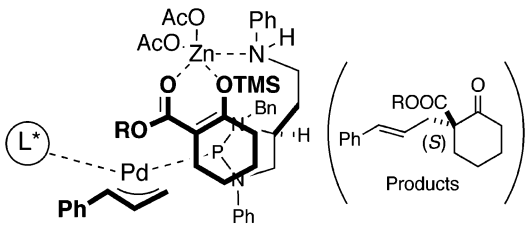


FIGURE 2. Working model. L* = **17**. The trimethylsiloxy group on the phosphorus atom has been omitted for clarity.

with a smaller methyl ester gave higher enantioselectivities suggests that the ester moiety of the nucleophiles is located inside the chiral pocket. This spatial arrangement is stabilized through the Zn-mediated secondary ligand substrate interaction. Effective fixation of the three reactants results in not only an increase in the enantiofacial discrimination of nucleophiles but also an enhancement of the reactivity. The clarified multifunctional properties of the P-chirogenic diaminophosphine oxides will be extended to other catalytic asymmetric reactions.

Experimental Section

Experimental Procedure for the Transformation of Triamine to P-Chirogenic Diaminophosphine Oxides. Synthesis of (S,R_P)-Ph-DIAPHOX (6) from Triamine 4: Method A. To a stirred solution of **4** (1.99 g, 5.77 mmol) and triethylamine (2.90 mL, 20.8 mmol) in toluene (29 mL) at −78 °C was add dropwise phosphorus trichloride (0.553 mL, 6.35 mmol) over 3 min. The reaction temperature was gradually warmed to room temperature, and then the mixture was kept stirring for 12 h. The reaction mixture was diluted with $CHCl_3$, and the organic layer was washed with H_2O, and then dried over Na_2SO_4. After concentration in vacuo, the obtained residue was dissolved into ethyl acetate, and then SiO_2 (50 mg/mmol substrate) and H_2O (0.13 mL, 7.21 mmol) were added. After being stirred for 20 h at room temperature under air, the reaction was diluted with $CHCl_3$ and then filtered through a short pad of silica gel, and the silica residue was washed with $CHCl_3$ and ethyl acetate intensively. After concentration of the organic washings in vacuo, the obtained yellow solid was washed with ethyl acetate and then filtered to afford **6** as a white solid. Additionally, purification of the yellow residue by flash column chromatography (SiO_2, hexane/ethyl acetate 5/1 to 1/1) afforded **6** (total yield: 1.36 g, 60%).

Method B. To a stirred solution of **4** (2.20 g, 6.35 mmol) and triethylamine (3.44 mL, 24.7 mmol) in toluene (42 mL) at −78 °C was add dropwise phosphorus trichloride (0.610 mL, 6.98 mmol) over 5 min. The reaction temperature was gradually warmed to room temperature, and then the mixture was kept stirring for 12 h. After filtration of the generated ammonium salt, the organic phase was concentrated in vacuo. The obtained residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 5/1 to 1/1) to afford **6** (1.26 g, 51%): mp 131−132 °C; IR (KBr) ν 3370, 2927, 1601, 1524, 1502, 1327, 1303, 1219, 1170, 1127, 1034, 950, 751, 730, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67−1.76 (m, 1H), 2.00−2.08 (m, 1H), 3.04−3.18 (m, 2H), 3.31−3.37 (m, 1H), 3.45 (s, 1H), 3.65 (m, 1H), 3.76−3.82 (m, 1H), 4.20 (dd, J = 13.2 Hz (PNC*H*), 15.2 Hz (*HCH*), 1H), 4.44 (dd, J = 10.4 Hz (PNC*H*), 15.2 Hz (*HCH*), 1H), 6.50−6.53 (m, 2H), 6.71−6.75 (m, 1H), 6.99−7.04 (m, 1H), 7.15−7.19 (m, 4H), 7.29−7.47 (m, 7H) 7.70 (d, J = 628 Hz (O=*PH*), 1H); ^{13}C NMR ($CDCl_3$) δ 32.7 (d, J = 3.9 Hz), 39.6, 46.5 (d, J = 6.1 Hz), 48.9 (d, J = 10.4 Hz), 52.1 (d, J = 7.2 Hz), 112.8 (x 2), 115.9 (d, J = 5.3 Hz) (× 2), 117.9, 121.9, 127.8, 128.6 (× 2), 128.7 (× 2), 129.3 (× 2), 129.5 (× 2),136.7, 141.4 (d, J = 7.7 Hz), 147.6; ^{31}P NMR ($CDCl_3$): δ 12.5; EI-LRMS *m/z* 391 (M^+); FAB-LRMS *m/z* 392 (MH^+); $[\alpha]^{18}_D$ −38.6 (*c* 0.5, $CHCl_3$, >99% ee); FAB HRMS calcd for $C_{23}H_{27}N_3OP$: 392.1845 (MH^+), found 392.1854 (MH^+). Anal. Calcd for $C_{23}H_{26}N_3OP$: C, 70.57; H, 6.69; N, 10.73. Found, C, 70.27; H, 6.64; N, 10.66. The enantiomeric excess was determined by HPLC analysis (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 1/1, flow rate 0.4 mL/min, t_R 49.5 min (ligand prepared from D-Asp) and 54.2 min (ligand prepared from L-Asp), detection at 254 nm).

General Procedure for the Pd-Catalyzed Asymmetric Construction of Quaternary Carbons Using (S,R_P)-Ph-DIAPHOX (Table 3, Run 1). To a stirred mixture of cinnamyl acetate (**7a**) (83.3 μL, 0.5 mmol), keto ester (**8a**) (120 μL, 0.75 mmol), (η^3-$C_3H_5PdCl)_2$ (1.8 mg, 0.0025 mmol), **6** (7.8 mg, 0.02 mmol), and $Zn(OAc)_2$ (9.2 mg, 0.05 mmol) in toluene (3.33 mL) was added BSA (0.494 mL, 2.0 mmol) at room temperature. After being stirred for 16 h, the reaction was concentrated under reduced pressure, and the obtained residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 30/1 to 15/1) to give (1*S*)-2-oxo-1-(3-phenyl-allyl)-cyclohexanecarboxylic acid ethyl ester (**9a**) as a colorless oil (143 mg, 99%, 93% ee). $[\alpha]^{18}_D$ −80.9 (*c* 0.85, $CHCl_3$, 93% ee). The enantiomeric excess was determined by HPLC analysis (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 5/95, flow rate 0.4 mL/min, t_R 14.5 min [(*R*)-isomer] and 16.8 min [(*S*)-isomer], detection at 254 nm).

Acknowledgment. This work was supported by a Grant-in Aid for Encouragement of Young Scientists (B) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan, and the Banyu Award in Synthetic Organic Chemistry, Japan.

Supporting Information Available: Experimental procedures, compound characterization, data for the nonlinear effect and the kinetic experiments, and other data and discussions. This material is available free of charge via the Internet at http://pubs.acs.org.

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