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Synthesis of an Optically Active Al(salalen) Complex and Its Application to Catalytic Hydrophosphonylation of Aldehydes and Aldimines

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Abstract: Optically active aluminum(salalen) complex **2** was newly synthesized in a modular synthetic manner, and it was found to serve as an efficient catalyst for hydrophosphonylation of aldehydes and aldimines, giving the corresponding α-hydroxy and α-amino phosphonates with high enantioselectivity, respectively. The scope of the hydrophosphonylation was wide, and both aliphatic and aromatic aldehydes and aldimines were successfully used as substrates for the reaction. The potent catalysis of the complex is attributed to its unique structure: it adopts a distorted trigonal bipyramidal configuration which allows the salalen ligand to take a *cis*-β-like structure wherein the chiral amino group is located close to the metal center.

1. Introduction

Optically active α-hydroxy and α-amino phosphonic acids and their derivatives are biologically active compounds which are widely used in pharmaceutical applications, and much effort has been directed toward the development of asymmetric hydrophosphonylation of carbonyl and imine compounds.[1−5] To our knowledge, heterobimetallic complexes (LLB and ALB) reported by Shibasaki et al. are the most efficient catalysts for asymmetric hydrophosphonylation of carbonyl compounds (Pudovik reaction): LLB and ALB have been complementarily used as catalysts for the reaction of various aldehydes.[2d,f] Recently, Kee et al. reported that chiral Al(salen) complexes served as the catalyst for asymmetric hydrophosphonylation; however, the enantioselectivities obtained were modest (up to 49% ee).[6] Shibasaki et al. also reported a competent catalytic enantioselective hydrophosphonylation of aliphatic and cyclic imines by using various heterobimetallic complexes suitably as catalysts.[7,8] Use of dimethyl phosphite of small molecular weight is another advantage of this procedure. In 2004, Jacobsen et al. reported a unique approach to α-amino phosphonates using chiral thioureas as organocatalysts and for the first time achieved high to excellent enantioselectivity in hydrophosphonylation of both aromatic and branched aliphatic imines.[9] Still, introduction of a novel catalyst that can show wide applicability for

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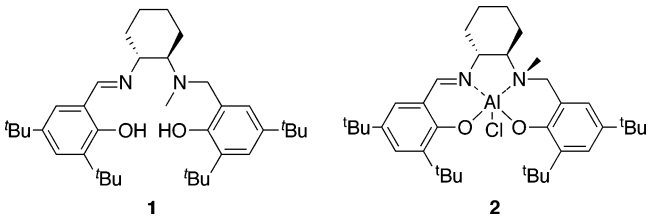
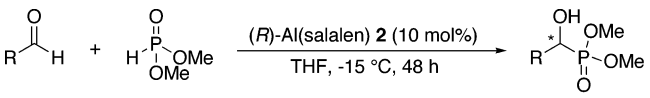


1 **2**

Figure 1. The structure of salalen ligand **1** and its aluminum complex **2**.

Scheme 1



R= C_6H_5: 90% ee, 87% (*S*)
R= *p*-$O_2NC_6H_4$: 94% ee, 95% (*S*) R= *p*-ClC_6H_4: 88% ee, 88% (*S*)
R= *p*-$MeOC_6H_4$: 81% ee, 87% (*S*) R= *o*-ClC_6H_4: 91% ee, 96%
R= (*E*)-PhCH=CH: 83% ee, 77% (*S*) R= $PhCH_2CH_2$: 91% ee, 94%
R= $(CH_3)_2CH$: 89% ee, 89% R= CH_3CH_2: 89% ee, 61% (*S*)

hydrophosphonylation of various aldehydes and aldimines has been strongly required.

Some of these previous studies[7] have disclosed that a function which holds two different substrates [aldehyde (or aldimine) and phosphite] simultaneously in a highly asymmetric atmosphere is very important for constructing a new catalyst for asymmetric hydrophosphonylation. For the past two decades, chiral salen ligands have received a great deal of attention due to their high asymmetry-inducing ability and ready availability. To date, they have been successfully applied to a wide range of enantioselective reactions including epoxidation, aziridination, sulfoxidation, Michael reaction, epoxide-opening reaction, etc.[10] These salen complexes adopt a mostly octahedral configuration in which two ancillary ligands are *trans*-oriented. However, recent studies have disclosed that *cis*-β isomers that provide two vicinal coordination sites show unique catalysis.[10c] For example, a di-μ-oxo Ti(salen) complex that bears chiral *cis*-β salen ligands catalyzes asymmetric cyanation with high enantioselectivity.[11] Furthermore, a di-μ-oxo Ti(salen) complex has been found to be an excellent precatalyst for asymmetric sulfoxidation, in which a monomeric *cis*-β peroxo complex has been proven to be the active species.[12] Despite the potentiality of *cis*-β isomers for asymmetric catalysis, metallosalen complexes intrinsically adopt the *trans* conformer in preference to the *cis*-β isomer. On the other hand, Kol et al. quite recently reported that treatment of an achiral hybrid salan/salen tetradentate [ONN(Me)O]-type ligand (hereafter referred to as salalen ligand) with titanium and zirconium tetraethoxides yielded the corresponding octahedral Ti- and Zr(salalen)$(OEt)_2$ complexes, respectively, in which the two diastereotopic ethoxy groups are *cis*-oriented and the coordinated amino-nitrogen atom that is closer to the metal ion by one C−C bond than the ethylene carbon is chiral.[13] Thus, we were intrigued by the catalysis of the salalen complexes for hydrophosphonation. However, it was considered that the presence of two diastereomeric alkoxides that might be substituted equally easily with substrates would lead to formation of a mixture of diastereomeric intermediates, and therefore, the salalen complexes would not be very suitable for the hydrophosphonylation. To take an advantage of the salalen ligand, we synthesized the corresponding optically active Al(salalen) complex instead and examined asymmetric hydrophosphonylation of aldehydes and aldimines to give optically active α-hydroxy and α-amino phosphonates. In this paper, we describe the synthesis of a chiral aluminum salalen complex and the full scope of asymmetric hydrophosphonylation using the complex as catalyst.[14]

2. Results and Discussion

2.1. Preparation of Optically Active Aluminum(salalen) Complex 2. A new optically active salalen ligand **1** was prepared from cyclohexane-1,2-diamine in a stepwise manner and converted into the desired aluminum complex **2** by its treatment with Et_2AlCl.[14] The X-ray analysis demonstrated that complex **2** possessed a distorted trigonal bipyramidal configuration, and the absolute configuration of the coordinated tertiary amine was determined to be *S* (Figure 1). The *N*-methyl group was oriented *syn* to the chloro ligand that should be replaced by a substrate, when the complex is used as a Lewis acid catalyst.[15]

2.2. Asymmetric Hydrophosphonylation of Aldehydes. With complex **2** in hand, we examined asymmetric hydrophosphonylation of benzaldehyde and found that the best result was obtained when the reaction was carried out in tetrahydrofuran (THF) at −15 °C with dimethyl phosphite (Scheme 1). Use of bulky dialkyl or diaryl phosphite such as diphenyl phosphite diminished enantioselectivity. Under the optimized conditions, we examined the hydrophosphonylation of both aromatic and aliphatic aldehyde. Fortunately, high enantioselectivity was observed in both of the reactions. To our knowledge, this is the first example that a molecular catalyst can be applied to the reactions of both aromatic and aliphatic aldehydes with enantioselectivities greater than 80% ee.[14]

2.3. Asymmetric Hydrophosphonylation of Aldimines. In Lewis acid promoted aldehyde reactions, the Lewis acid is generally coordinated to the lone pair electrons *trans* to the carbonyl substituent. In contrast, the imino nitrogen atom carries an *N*-substituent, and its coordination requires a wider reaction space than that of an aldehyde carbonyl group. Due to the following unique structural features,[15] however, we expected that complex **2** could also be applied to hydrophosphonylation of imines: (i) the *cis*-β-like ligand structure provides a wide reaction site allowing coordination of imines, since the coordination should occur from the open convex side of the salalen ligand; (ii) nonetheless, the stereochemistry of the reaction there should be efficiently controlled by the substituent on the chiral nitrogen atom next to the metal ion.

Since the *N*-protecting group of aldimines was considered to affect the stereochemistry and rate of the hydrophosphonylation, the reaction of dimethyl phosphite with aldimines derived from

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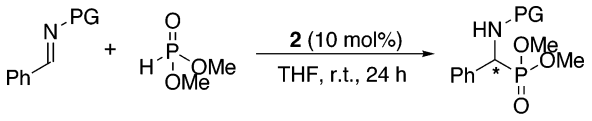
(15) For the X-ray structure of **2**, see the Supporting Information.

Table 1. Asymmetric Hydrophosphonylation of Various Benzaldimine Derivatives[a]



3a-h **4a-h**

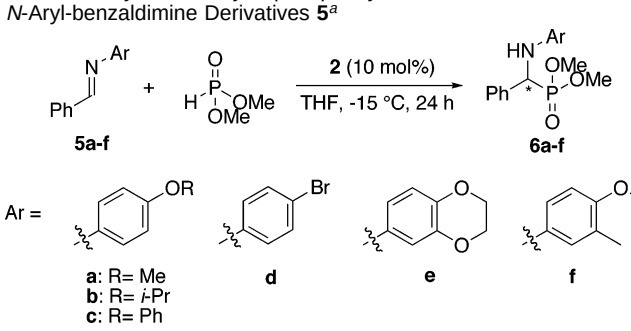
entry	PG		yield/%[b]	% ee
1	MeO−	**a**	N.D.[c]	
2	Me_2N−	**b**	N.D.[c]	
3	^{t}BuO(O)C−	**c**	<10	42[d]
4	Ts	**d**	35	17[e]
5	Bn	**e**	80	60[f]
6	*p*-$MeOC_6H_4CH_2$−	**f**	80	56[f]
7	Ph_2CH−	**g**	<10	16[f]
8	Ph	**h**	91	60[f]
9[g]	Ph	**h**	96	75[f]

[a] Reactions were carried out with imine (0.1 mmol) and dimethyl phosphite (0.15 mmol) in the presence of **2** (10 mol %). [b] Isolated yield. [c] Not determined. [d] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AS-H; hexane/*i*-PrOH = 24:1). [e] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak IA; hexane/AcOEt = 3:2). [f] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AS-H; hexane/*i*-PrOH = 4:1). [g] The reaction was carried out at −15 °C.

benzaldehyde and various amines was initially examined at room temperature in THF by using complex **2** as catalyst (Table 1). *N*-Methoxy- and *N*-(dimethylamino)-aldimines (**3a** and **3b**) did not show any reactivity (entries 1 and 2). *N*-*tert*-Butoxycarbonyl- and *N*-*p*-toluenesufonyl-aldimines (**3c** and **3d**) were poorly reactive, and the enantioselectivities of their reactions were modest (entries 3 and 4). Thus, we next examined the reactions of the aldimines (**3e** and **3f**) bearing a simple and noncoordinating group such as benzyl and *p*-methoxybenzyl groups and found that their reactions proceeded with good chemical yields and moderate enantioselectivities (entries 5 and 6). Introduction of a more bulky diphenylmethyl group badly diminished the reaction rate and enantioselectivity (entry 7). Finally, a phenyl group gave a promising result: the reaction of the *N*-phenylaldimine **3h** gave the best chemical yield with the same enantioselectivity as that of the reaction of *N*-benzylaldimine **3e** (entry 8), and it proceeded almost quantitatively even at −15 °C with a better enantioselectivity of 75% ee.

Encouraged by these results, we next examined the reactions of benzaldimines bearing a substituted phenyl group as the *N*-protecting group (Table 2).[16] Introduction of a *p*-methoxy substituent improved enantioselectivity to 78% ee (entry 1), while that of a *p*-bromo substituent largely reduced enantioselectivity (entry 4). We also examined the effect of some other substituted phenyl groups and found that the reaction of *N*-(3,4-ethylenedioxyphenyl)imine **5e** showed good enantioselectivity of 82% ee together with good chemical yield (entry 5). Since it had been reported that a 4-methoxyphenyl group can be cleaved by treatment with cerium ammonium nitrate (CAN),[5a,17,18] we expected that a 3,4-ethylenedioxyphenyl group could also be deprotected by the same procedure but it gave messy products.

Table 2. Asymmetric Hydrophosphonylation of *N*-Aryl-benzaldimine Derivatives **5**[a]



5a-f **6a-f**

Ar =

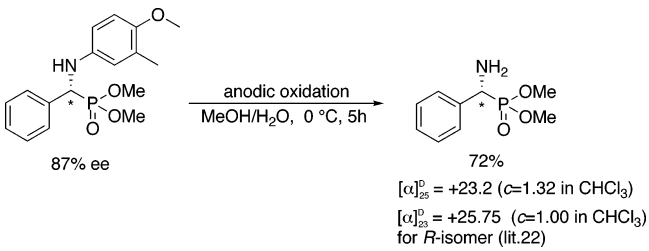
a: R= Me
b: R= *i*-Pr
c: R= Ph

d **e** **f**

entry	Ar	yield/%[b]	% ee
1	**a**	91	78 (*R*)[c,d]
2	**b**	91	80[e]
3	**c**	89	69[f]
4	**d**	95	31[c]
5	**e**	93	82[c]
6[g]	**f**	90	87 (*R*)[d,f]

[a] Reactions were carried out with imine (0.1 mmol) and dimethyl phosphite (0.15 mmol) in the presence of **2** (10 mol %). [b] Isolated yields. [c] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AS-H; hexane/*i*-PrOH = 4:1). [d] Absolute configuration was determined by chiroptical comparison of the amino phosphonate obtained by deprotection of the product (ref 22). [e] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak IA; hexane/*i*-PrOH = 9:1). [f] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AD-H; hexane/*i*-PrOH = 9:1). [g] The reaction was carried out with imine (0.5 mmol) and dimethyl phosphite (0.75 mmol) in the presence of **2** (10 mol %).

Scheme 2



87% ee 72%

$[\alpha]^D_{25}$ = +23.2 (*c*=1.32 in $CHCl_3$)

$[\alpha]^D_{23}$ = +25.75 (*c*=1.00 in $CHCl_3$) for *R*-isomer (lit.22)

With the thought that an *m*-alkoxy group may exert not an electronic but a steric effect on enantioselectivity, we further examined the reaction of *N*-(4-methoxy-3-methylphenyl)aldimine **5f** instead and attained the best enantioselectivity of 87% ee (entry 6). Fortunately, use of **5f** as aldimine gave another advantage: anodic oxidation[19,20] successfully deprotected the 4-methoxy-3-methylphenyl group to give the corresponding amine in a good yield of 72% without loss of enantiopurity (Scheme 2), though its deprotection with CAN gave the amine in a moderate yield (<40%). It is noteworthy to mention that asymmetric induction observed in this reaction is opposite to that observed in the hydrophsphonylation of benzaldehyde (cf. Scheme 1 and Table 2). This might suggest that **5f** was coordinated in its stable (*E*)-form to complex **2**.[21]

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(17) For examples, see: (a) Kronenthal, D. R.; Han, V. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765−2768. (b) Hasegawa, M.; Taniyama, D.; Tomioka, K. *Tetrahedron* **2000**, *56*, 10153−10158. (c) Saito, S.; Hatanaka, K.; Yamamoto, H. *Tetrahedron* **2001**, *57*, 875−887. (d) Haak, E.; Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2002**, 457−463.

(18) It has been reported that a 4-methoxyphenyl group can be deprotected by means of CAN to give the corresponding α-aminophosphonate in moderate yields; see: refs 5a, 17d.

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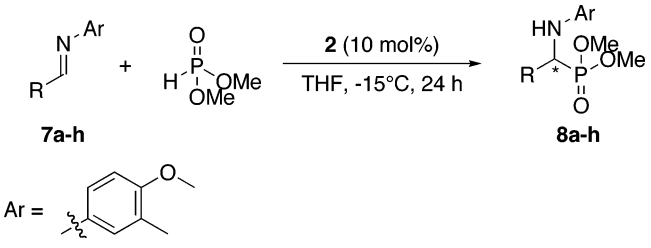
(20) The deprotection was carried out according to the reported procedure in ref 19 with a slight modification.

Table 3. Asymmetric Hydrophosphonylation of Various Aromatic Aldimines[a]



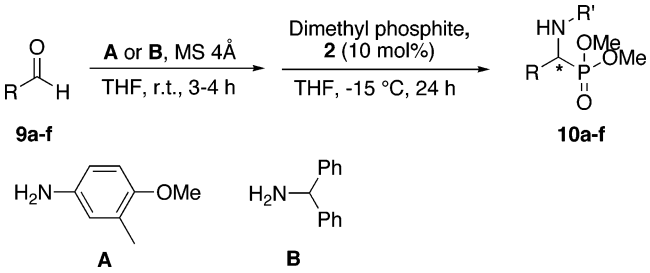
entry	R		yield/%[b]	% ee
1	*p*-BrC_6H_4	**a**	>99	95[c]
2	*p*-ClC_6H_4	**b**	95	95[c]
3	*p*-$MeOC_6H_4$	**c**	92	85[c]
4	*p*-$CH_3C_6H_4$	**d**	95	90[c]
5	*o*-$CH_3C_6H_4$	**e**	93	87[c]
6	2-C_4H_3S	**f**	91	84[c]
7	2-C_4H_3O	**g**	>99 (94)[d]	63 (69)[d,e]
8[d]	2-[5-PhC_4H_2O]	**h**	92	79[e]

[a] Reactions were carried out with imine (0.2 mmol) and dimethyl phosphite (0.3 mmol) in the presence of **2** (10 mol %). [b] Isolated yields. [c] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AD-H; hexane/*i*-PrOH = 7:3). [d] The reaction was carried out in tetrahydropyran. [e] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AD-H; hexane/*i*-PrOH = 17:3).

Under the optimized conditions, we examined asymmetric hydrophosphonylation of aromatic aldimines bearing a 4-methoxy-3-methylphenyl group as an *N*-protecting group (Table 3). All the reactions proceeded with good enantioselectivity. When the substrate carried an electron-withdrawing *p*-substituent, enantioselectivity was improved up to 95% ee (entries 1 and 2); however, the presence of an electron-donating *p*-substituent somewhat decreased enantioselectivity to 85% ee (entry 3). The presence of a methyl substituent at the *o*- or *p*-position had little effect on enantioselectivity (entries 4 and 5). We also examined the reactions of heteroaromatic aldimines. The reaction of 2-thienyl aldimine proceeded with high enantioselectivity of 84% ee (entry 6). However, that of 2-furyl aldimine was moderately enantioselective (63% ee, entry 7). Although the reason for this diminished enantioselectivity was not completely clear, the presence of a hard base, furan ring, seemed to be responsible. Thus, the reaction was examined in tetrahydropyran, a more polar solvent, and a slight enantioselectivity enhancement was observed.[23] Thus, we further examined the reaction of 2-(5-phenylfuryl) aldimine with the expectation that the phenyl group would reduce the coordinating ability of the furan ring. Indeed, the reaction in tetrahydropyran showed a significantly improved enantioselectivity of 79% ee (entry 8).

We also examined the reaction of aliphatic aldimines (Table 4). Different from aromatic *N*-aryl aldimines that are mostly crystalline, most aliphatic *N*-aryl aldimines are not crystalline and are difficult to be purified chromatographically due to their poor stability. Therefore, we examined the condensation of an aliphatic aldehyde with an amine and subsequent hydrophosphonylation in one pot. To our delight, the reactions of branched

Table 4. One-Pot Hydrophosphonylation of Various Aldimine Derivatives[a]



entry	R		amine	yield/%[b]	% ee
1	*t*-Bu	**a**	**A**	28	88[c]
2	cyclohexyl	**b**	**A**	84	94[c]
3	$(CH_3)_2CHCH_2$	**c**	**B**	80	91[d]
4	octyl	**d**	**B**	83	84[d]
5	PhC≡C	**e**	**B**	92	86[c]
6	(*E*)-PhCH═CH	**f**	**B**	51	15[d]

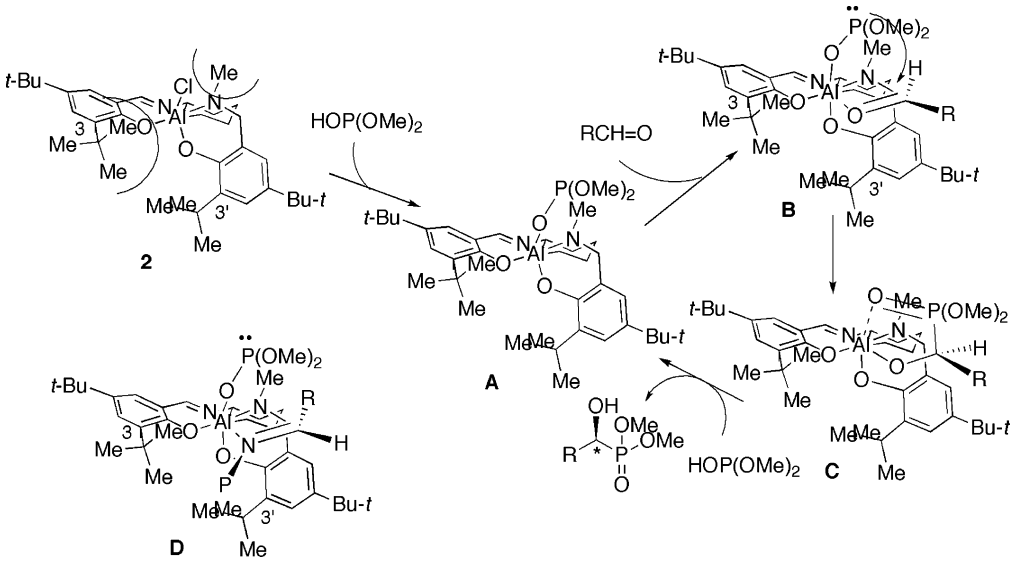
[a] Reactions were carried out with aldehyde (0.2 mmol), amine (0.2 mmol), and dimethyl phosphite (0.3 mmol) in the presence of **2** (10 mol %) and MS 4 Å (ca. 100 mg). [b] Isolated yields. [c] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AD-H; hexane/*i*-PrOH = 17:3). [d] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AD-H; hexane/*i*-PrOH = 9:1).

aliphatic aldimines also proceeded with high enantioselectivity (entries 1 and 2), although the reaction of pivalaldimine was slow. On the other hand, condensation of nonbranched aliphatic aldehyde and 4-methoxy-3-methylphenylaniline gave not the desired aldimine but unidentified polymeric materials.[24] To avoid this problem, we used bulky diphenylmethylamine[7] instead of 4-methoxy-3-methylphenylaniline. Fortunately, in situ hydrophosphonylation of the aldimines prepared from nonbranched aliphatic aldehydes proceeded with high enantioselectivities together with good chemical yields (entries 3 and 4).[25] In situ hydrophosphonylation of aldimines prepared from branched aliphatic aldehydes and diphenylmethylamine was slow. It has been reported that a diphenylmethyl group can be cleaved under mild conditions.[7,25] We also examined the reactions of alkynyl and alkenyl aldimines in one pot. The reaction of the aldimine prepared from phenylpropargyl aldehyde and diphenylmethylamine also proceeded with high enantioselectivity (entry 5). However, the reactions of cinnamaldimines prepared from diphenylmethylamine or 4-methoxy-3-methylphenylaniline were low enantioselectively and slow, though the reason is unclear (entry 6).

2.4. Mechanistic Consideration. In order to shed light on the mechanism of the present reactions, we examined the relation between the enantiomeric excesses (ee's) of the product and the catalyst in the hydrophosphonylation of benzaldehyde and found that the ee's correlated linearly to each other.[26] This suggested that dimeric aluminum species do not participate in this reaction and all the events occur in a monomeric *cis*-β aluminum species. From this consideration and the X-ray structure of **2**, we propose a possible mechanism for this reaction (Scheme 3). When complex **2** is exposed to a mixture of aldehyde and dimethyl phosphite, the chloro ligand is replaced

(21) We cannot completely rule out the possibility that stable (*E*)-**5f** is isomerized to (*Z*)-**5f** in the presence of complex **2**, but it is unlikely because no formation of a minor isomer was detected under the conditions.
(22) Tongcharoensirikul, P.; Suarez, A. I.; Voelker, T.; Thompson, C. M. *J. Org. Chem.* **2004**, *69*, 2322−2326.
(23) The enantioselectivity of the reaction of benzaldimine that bears no hard base unit did not depend on the solvent. The reactions both in THF and in tetrahydropyran showed the identical enantioselectivity.
(24) Layer, R. W. *Chem. Rev.* **1963**, *63*, 489−510.
(25) It has been reported that compound **10c** can be converted to optically active phospholeucine which is a potent inhibitor of leucine aminopeptidase: Shibasaki, M.; Sasai, H.; Tahara, Y. *PCT Int. Appl*. 1997, WO 9711954 A1 19970403.
(26) For the data, see Supporting Information.

Scheme 3



by the phosphite to give species **A**, to which the aldehyde directing its carbonyl substituent (R) outward is coordinated. The resultant species **B** undergoes intramolecular addition to give an (*S*)-α-hydroxy phosphonate that is replaced by dimethyl phosphite and completes the catalytic cycle. On the other hand, when the substrate is an aldimine, it is coordinated to the species **A** with the R group *cis* to the ion and the resultant **D** undergoes the subsequent intramolecular addition to give an (*R*)-α-amino phosphonate. This proposal agrees with the observed stereochemistry.

In conclusion, we were able to synthesize chiral trigonal bipyramidal aluminum(salalen) complex **2** providing a unique asymmetric reaction site, in which the nitrogen atom is bound to the metal ion and the *N*-methyl group on the resulting chiral nitrogen atom is *cis* to the chloro ligand. Moreover, complex **2** was demonstrated to be an efficient catalyst for enantioselective hydrophosphonylation of various aldehydes and aldimines with dimethyl phosphite. The present study will open a new entry to a general method for preparing optically active α-hydroxy and α-amino phosphonic acids.

3. Experimental Section

3.1. General. All reagents and solvents were used as supplied commercially, except for THF that was distilled from Na/Ph_2CO, before use. ^1H and ^{13}C NMR spectra were measured on a JEOL GX-400 spectrometer at 400 and 100 MHz, respectively. All chemical shifts were recorded in δ (ppm) relative to tetramethylsilane (TMS). Melting points were measured with a BÜCHI Melting Point B-545 apparatus and uncorrected. Infrared spectra were measured as a KBr disc or as a thin film using a NaCl plate on a SHIMADZU FTIR-8600 spectrophotometer, and only diagnostic absorptions are listed below. Optical rotation was measured with a JASCO P-1020 polarimeter. High-resolution FAB mass spectra were obtained from a JEOL JMX-SX/SX 102A spectrometer. Enantiomeric excesses were determined by HPLC analysis using a SHIMADZU LC-10AT-VP equipped with an appropriate optically active column, as described in the footnotes to the corresponding tables. TLC analysis was performed on Silica gel 60 F_{254}-coated glass plates (Merck). Visualization was accomplished with irradiation of 254 nm UV light or a spray of a 12-molybdo(VI)-phosphoric acid ethanol solution as the developing agent. Preparations of catalysts and all the reactions were carried out under inert atmosphere, unless otherwise specified.

3.2. Synthesis of Salalen Ligand 1 and Its Aluminum Complex 2. 3.2.1. Synthesis of Salalen Ligand 1. To a solution of (1*R*,2*R*)-1,2-cyclohexanediamine monohydrochloride (3.40 g, 22.56 mmol) in dry methanol (ca. 100 mL) was added 3,5-di-*tert*-butyl salicylaldehyde (5.03 g, 21.48 mmol), and the resulting mixture was stirred for 3 h at room temperature. After cooling to 0 °C, sodium borohydride (2.03 g, 53.7 mmol) was added to the solution and stirred for another 2 h at room temperature. The reaction was quenched with H_2O, and the mixture was extracted with Et_2O three times. The combined organic phases were washed with brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated in vacuo and redissolved in dry ethanol (100 mL). To the solution was added di-*tert*-butyl dicarbonate (5.45 mL, 23.6 mmol) at room temperature and stirred for 1.5 h. The mixture was concentrated under reduced pressure and chromatographed on silica gel (hexane/ethyl acetate = 9/1−4/1) to give *N*-(*tert*-butoxycarbonyl)-*N*′-(3,5-di-*tert*-butyl-2-hydroxyphenylmethyl)cyclohexanediamine (6.24 g, 67%).[27]

Colorless solid (hygroscopic). $[\alpha]_D^{22}$ +8.85 (*c* 1.33, $CHCl_3$); IR (KBr): 3317, 2955, 2862, 1701, 1510, 1481, 1454, 1391, 1363, 1236, 1171, 1107, 1016, 872 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.21 (d, J = 2.4 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 4.42 (br d, J = 10.3 Hz, 1H), 4.08 (d, J = 13.43 Hz, 1H), 3.87 (d, J = 13.43 Hz, 1H), 3.40 (m, 1H), 2.32−2.23 (m, 2H), 2.00 (m, 1H), 1.76−1.69 (m, 2H), 1.46 (s, 9H), 1.42 (s, 9H), 1.28 (s, 9H), 1.40−1.12 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 155.7, 154.5, 140.1, 135.7, 123.0, 122.7, 122.1, 79.5, 60.4, 54.1, 50.4, 35.0, 34.2, 33.5, 31.8, 31.4, 29.8, 28.5, 25.1, 24.7; HRFABMS. Calcd for $[C_{26}H_{44}N_2O_3]^+$: m/z = 432.3352. Found: m/z = 432.3349.

To a methanolic solution (ca. 80 mL) of the cyclohexanediamine derivative (5.63 g, 13.01 mmol) in a 300 mL round-bottomed flask were added aq. CH_2O (ca. 37%, 1.21 mL, 16.27 mmol) and 10% Pd/C (1.03 g) at room temperature. The flask was purged with H_2 and installed with a rubber balloon filled with H_2. After stirring for about 5 h at room temperature, the mixture was filtered through a pad of Celite that was subsequently washed with MeOH. The filtrate was concentrated in vacuo and redissolved in MeOH (30 mL). To the solution was added 3 M HCl (30 mL), and the whole mixture was stirred for 36 h at room temperature. The reaction was quenched with 3 M NaOH (35 mL), and the resulting mixture was extracted with Et_2O three times. The combined organic phases were washed with brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated in vacuo and redissolved in methanol (ca. 100 mL). To the solution was added 3,5-di-*tert*-butylsalicylaldehyde (3.04 g, 13.0 mmol) and stirred for 3.5

(27) Campbell, E. J.; Nguyen, S. T. *Tetrahedron Lett.* **2001**, *42*, 1221−1225.

h at room temperature. The precipitate was filtered off and washed with methanol to give the ligand **1** (5.54 g, 76%).

Yellow solid. $[\alpha]_D^{22}$ −100.4 (*c* 1.00, $CHCl_3$); IR (KBr): 2955, 2864, 1628, 1601, 1477, 1447, 1393, 1362, 1244, 1204, 1171, 1030, 876, 826 cm^{-1}; ^1H NMR ($CDCl_3$): δ 13.56 (s, 1H), 10.58 (br s, 1H), 8.37 (s, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 6.79 (d, J = 2.4 Hz, 1H), 3.79 (br ABq, 2H), 3.29 (m, 1H), 2.96 (m, 1H), 2.22 (s, 3H), 2.00−1.63 (m, 5H), 1.43−1.29 (m, 3H), 1.47 (s, 9H), 1.29 (s, 9H), 1.25 (s, 9H), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 165.5, 157.9, 154.5, 139.6, 139.6, 136.4, 135.2, 126.7, 125.6, 123.1, 122.3, 120.8, 117.9, 70.2, 66.6, 35.3, 35.1, 34.8, 34.2, 31.8, 31.6, 29.7, 29.5, 25.3, 24.8; Anal. Calcd for $C_{37}H_{58}N_2O_2$: C, 78.95; H, 10.39; N, 4.98%. Found: C, 78.94; H, 10.40; N, 4.92%.

3.2.2. Synthesis of Aluminum Salalen Complex 2. To a solution of salalen ligand **1** (453 mg, 0.806 mmol) in dry toluene (10 mL) was added diethylaluminum chloride (0.92 M in hexane, 876 μL) at 0 °C, and the solution was stirred overnight at room temperature. The yellow suspension was concentrated in vacuo and resuspended in hexane. The yellow precipitate was filtered off and washed with hexane to give complex **2** (468 mg, 93%).

Yellow solid. IR (KBr): 2951, 2909, 2864, 1620, 1543, 1483, 1441, 1420, 1389, 1360, 1304, 1256, 1204, 1177, 1130, 1011, 962, 851, 761, 635, 600, 577 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.44 (s, 1H), 7.57 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.82 (d, J = 2.4 Hz, 1H), 4.57 (d, J = 13.2 Hz, 1H), 3.40 (m, 1H), 3.37 (d, J = 13.2 Hz, 1H), 2.54 (m, 1H), 2.45 (s, 3H), 2.36−2.27 (m, 1H), 1.77−1.84 (m, 3H), 1.52 (s, 9H), 1.38 (s, 9H), 1.29 (s, 9H), 1.27 (s, 9H), 1.57−1.12 (m, 3H), 1.00−0.94 (m, 1H); Anal. Calcd for $C_{37}H_{56}N_2O_2AlCl$: C, 71.30; H, 9.06; N, 4.49%. Found: C, 71.35; H, 9.03; N, 4.53%.

3.3. Asymmetric Hydrophosphonylation of Aldehydes. 3.3.1. General Procedure for Asymmetric Hydrophosphonylation of Aldehydes with Dimethyl Phosphite. Complex **2** (12.5 mg, 0.02 mol) and dimethyl phosphite (10.1 μL, 0.21 mmol) were dissolved in THF (1.0 mL) under a nitrogen atmosphere and stirred for 10 min at 0 °C. After cooling to −15 °C, aldehyde (0.20 mmol) was added to the solution and stirred for 48 h. The reaction mixture was quenched with 1 M HCl and extracted with AcOEt (ca. 1 mL × 3). The combined organic phases were passed through a pad of Celite and Na_2SO_4. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (hexane/acetone = 7:3−3:7) to give the corresponding α-hydroxy phosphonate. The ee values were determined by HPLC on a chiral stationary phase under the conditions described in ref 14.

(*S*)-Dimethyl Phenyl(hydroxy)methylphosphonate. Colorless solid. Yield 87% (90% ee); Mp 95.4−95.9 °C; $[\alpha]_D^{25}$ −44.7 (*c* 1.50, $CHCl_3$), [lit. (*S*)-isomer (85% ee); (*c* 1.0, $CHCl_3$)];[2d] IR (KBr): 3242, 3011, 2957, 2851, 1601, 1493, 1458, 1337, 1205, 1028, 862, 839, 779, 700, 673, 554 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.50−7.48 (m, 2H), 7.39−7.30 (m, 3H), 5.05 (dd, J = 5.4, 11.0 Hz, 1H), 4.24 (br s, 1H), 3.70 (d, J = 10.4 Hz, 3H), 3.67 (d, J = 10.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 136.2, 128.2 (d, J = 2.5 Hz), 128.1(d, J = 3.3 Hz), 126.9 (d, J = 5.8 Hz), 70.6 (d, J = 158.4 Hz), 54.0 (d, J = 6.7 Hz), 53.7 (d, J = 7.5 Hz); Anal. Calcd for $C_9H_{13}O_4P$: C, 50.01; H, 6.06%. Found: C, 49.91; H, 6.06%.

(*S*)-Dimethyl Hydroxy(4-nitrophenyl)methylphosphonate. Colorless solid. Yield 95% (94% ee); Mp 132.8−133.3 °C; $[\alpha]_D^{24}$ −57.4 (*c* 1.20, $CHCl_3$), [lit. (*S*)-isomer (71% ee); (*c* 1.0, $CHCl_3$)];[2d] IR (KBr): 3220, 2959, 2856, 1605, 1524, 1416, 1354, 1227, 1186, 1065, 1020, 866, 826, 779, 731, 696, 563 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.24 (d, J = 8.5 Hz, 2H), 7.68 (dd, J = 2.1, 8.5 Hz, 2H), 5.21 (d, J = 5.1, 12.2 Hz, 1H), 4.46 (br s, 1H), 3.78 (d, J = 9.9 Hz, 3H), 3.67 (d, J = 9.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 147.5, 143.5, 127.4 (d, J = 5.0 Hz), 123.4, 70.0 (d, J = 157.6 Hz), 54.4 (d, J = 6.7 Hz), 53.8 (d, J = 7.5 Hz); Anal. Calcd for $C_9H_{12}NO_6P$: C, 41.39; H, 4.63; N, 5.36%. Found: C, 41.37; H, 4.58; N, 5.25%.

(*S*)-Dimethyl Hydroxy(4-chlorophenyl)methylphosphonate. Colorless solid. Yield 88% (88% ee); Mp 70.1−70.7 °C; $[\alpha]_D^{22}$ −50.4 (*c* 1.64, $CHCl_3$), [lit. (*S*)-isomer (83% ee); (*c* 1.0, $CHCl_3$)];[2d] IR (KBr): 3256, 2959, 2855, 1489, 1447, 1402, 1259, 1213, 1177, 1063, 1022, 880, 835, 799, 723, 561 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.43 (dd, J = 2.2, 8.3 Hz, 2H), 7.36 (d, J = 8.6 Hz 2H), 5.04 (dd, J = 4.8, 10.9 Hz, 1H), 3.72 (d, J = 10.5 Hz, 3H), 3.71 (d, J = 10.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 134.7, 133.9 (d, J = 3.3 Hz), 128.4 (d, J = 2.5 Hz), 128.2 (d, J = 5.8 Hz), 70.0 (d, J = 159.3 Hz), 54.1 (d, J = 6.8 Hz), 53.7 (d, J = 7.5 Hz); Anal. Calcd for $C_9H_{12}ClO_4P$: C, 43.13; H, 4.83%. Found: C, 43.02; H, 4.71%.

(*S*)-Dimethyl Hydroxy(4-methoxyphenyl)methylphosphonate. Colorless solid. Yield 87% (81% ee); Mp 71.2−71.3 °C; $[\alpha]_D^{24}$ −39.6 (*c* 1.59, $CHCl_3$), [lit. (*S*)-isomer (78% ee); (*c* 1.0, $CHCl_3$)];[2d] IR (KBr): 3225, 2955, 2851, 1612, 1512, 1464, 1250, 1205, 1063, 1032, 843, 800, 762, 685, 554 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.42 (dd, J = 2.2, 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz 2H), 4.99 (dd, J = 4.9, 10.0 Hz, 1H), 3.73 (d, J = 10.5 Hz, 3H), 3.67 (d, J = 10.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 159.4 (d, J = 3.3 Hz), 128.3 (d, J = 5.4 Hz), 128.1 (d, J = 1.7 Hz), 113.7, 69.8 (d, J = 160.9 Hz), 55.4, 54.0 (d, J = 7.5 Hz), 53.7 (d, J = 6.7 Hz); Anal. Calcd for $C_{10}H_{15}O_5P$: C, 48.78; H, 6.14%. Found: C, 48.72; H, 6.11%.

Dimethyl Hydroxy(2-chlorophenyl)methylphosphonate. Colorless solid. Yield 96% (91% ee); Mp 112.9−113.2 °C; $[\alpha]_D^{23}$ −65.7 (*c* 2.26, $CHCl_3$); IR (KBr): 3288, 3066, 3015, 2959, 1572, 1472, 1443, 1188, 1045, 839, 781, 754, 698, 626, 571, 536 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.72 (m, 1H), 7.39−7.26 (m, 4H), 5.58 (dd, J = 5.7, 11.8 Hz, 1H), 3.82 (d, J = 10.6 Hz, 3H), 3.65 (d, J = 10.6 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 134.5, 132.7 (d, J = 7.5 Hz), 129.22, (d, J = 3.3 Hz) 129.16 (d, J = 2.5 Hz), 129.0 (d, J = 4.2 Hz), 126.9 (d, J = 2.5 Hz), 66.9 (d, J = 160.9 Hz), 54.1 (d, J = 7.5 Hz), 53.8 (d, J = 7.5 Hz); Anal. Calcd for $C_9H_{12}ClO_4P$: C, 43.13; H, 4.83%. Found: C, 43.22; H, 4.85%.

(*S*)-Dimethyl 1-Hydroxy-3-phenyl-2-propenylphosphonate. Colorless solid. Yield 77% (83% ee); Mp 82.6−83.3 °C; $[\alpha]_D^{24}$ −22.1 (*c* 1.45, $CHCl_3$), [lit. (*S*)-isomer (82% ee); (*c* 1.0, $CHCl_3$)];[2d] IR (KBr): 3238, 3020, 2957, 2831, 1442, 1221, 1200, 1097, 1051, 976, 843, 795, 764, 694, 569 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.41−7.23 (m, 5H), 6.80 (dt, J = 5.7, 15.9 Hz, 1H), 6.34 (dd, J = 4.7, 15.9 Hz, 1H), 4.73 (ddd, J = 1.5, 6.4, 15.9 Hz, 1H), 3.84 (d, J = 10.4 Hz, 3H), 3.82 (d, J = 10.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 136.0 (d, J = 2.5 Hz), 132.5 (d, J = 3.3 Hz), 128.4, 127.8, 126.5 (d, J = 1.7 Hz), 123.3 (d, J = 4.2 Hz), 69.3 (d, J = 161.8 Hz), 54.0 (d, J = 6.7 Hz), 53.7 (d, J = 7.5 Hz); Anal. Calcd for $C_{11}H_{15}O_4P$: C, 54.55; H, 6.24%. Found: C, 54.70; H, 6.11%.

Dimethyl 1-Hydroxy-3-phenyl-2-propylphosphonate. Colorless oil. Yield 94% (91% ee); $[\alpha]_D^{25}$ +19.4 (*c* 0.74, $CHCl_3$); IR (neat): 3302, 3024, 2953, 2855, 1736, 1603, 1495, 1452, 1234, 1033, 930, 829, 795, 843, 748, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.31−7.18 (m, 5H), 3.90 (m, 1H), 3.82 (d, J = 3.7 Hz, 3H), 3.79 (d, J = 3.7 Hz, 3H), 2.98−2.91 (m, 1H), 2.78−2.71 (m, 1H), 2.10−2.00 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 140.9, 128.4, 128.3, 125.9, 66.8 (d, J = 160.1 Hz), 53.4 (d, J = 7.5 Hz), 53.3 (d, J = 7.5 Hz), 33.0, 31.7(d, J = 13.4 Hz); Anal. Calcd for $C_{11}H_{17}O_4P$: C, 54.10; H, 7.02%. Found: C, 53.97; H, 6.98%.

Dimethyl 1-Hydroxy-2-methylpropylphosphonate. Colorless oil. Yield 89% (89% ee); $[\alpha]_D^{24}$ +4.29 (*c* 0.80, $CHCl_3$); IR (neat): 3312, 2959, 1466, 2855, 1387, 1219, 1130, 1040, 829, 787 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.83 (d, J = 4.4 Hz, 3H), 3.80 (d, J = 4.4 Hz, 3H), 3.70 (dd, J = 6.8, 12.5 Hz, 1H), 2.57 (br s, 1H), 2.15−2.05 (m, 1H), 1.08 (d, J = 10.5 Hz, 3H), 1.06 (d, J = 10.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 72.9 (d, J = 155.1 Hz), 53.2 (d, J = 6.8 Hz), 53.0 (d, J = 6.8 Hz), 30.2 (d, J = 2.5 Hz), 19.9 (d, J = 9.0 Hz), 17.8 (d, J = 7.5 Hz); Anal. Calcd for $C_6H_{15}O_4P$: C, 39.56; H, 8.30%. Found: C, 39.42; H, 8.28%.

(*S*)-Dimethyl 1-Hydroxypropylphosphonate. Colorless oil. Yield 61% (89% ee); $[\alpha]_D^{23}$ +12.0 (*c* 0.94, $CHCl_3$), [lit. (*S*)-isomer (50.8%

ee); $[\alpha]_D^{25}$ −4.3 (*c* 0.5, $CHCl_3$)];[28] IR (neat): 3314, 2961, 2856, 1460, 2855, 1217, 1119, 1034, 980, 837, 779 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.81 (pseudo d, J = 10.5 Hz, 6H), 3.35 (br s, 1H), 1.79 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 69.2 (d, J = 159.3 Hz), 53.3 (d, J = 5.0 Hz), 53.2 (d, J = 5.0 Hz), 24.8, 10.4 (d, J = 13.3 Hz); Anal. Calcd for $C_5H_{13}O_4P$: C, 35.72; H, 7.79%. Found: C, 35.64; H, 7.81%.

3.4. Asymmetric Hydrophosphonylation of Imines. 3.4.1. General Procedure for Asymmetric Hydrophosphonylation of Aromatic *N*-(4-Methoxy-3-methylphenyl)aldimine Derivatives with Dimethyl Phosphite (Tables 2 and 3). Complex **2** (12.5 mg, 0.020 mmol) and aromatic *N*-(4-methoxy-3-methylphenyl)aldimine (0.20 mmol) were dissolved in THF (1 mL) at −15 °C under nitrogen. To the solution was added dimethyl phosphite (0.30 mmol, 27.5 μL), and the mixture was stirred for 24 h. The reaction was quenched with H_2O, the mixture was extracted with AcOEt (3× ca. 1 mL), and the combined organic phases were passed through a pad of Celite and Na_2SO_4. After concentrating the filtrate under reduced pressure, the residue was chromatographed on silica gel (hexane/AcOEt = 7:3−3:7) to give the corresponding α-aminophosphonate. The ee values were determined by HPLC on a chiral stationary phase under the conditions described in the footnotes to Tables 2 and 3.

(*R*)-Dimethyl [*N*-(4-Methoxy-3-methylphenyl)amino]phenylmethylphosphonate (6f, Table 2, Entry 6). Viscous yellowish oil. Yield 90% (87% ee); $[\alpha]_D^{24}$ +29.0 (*c* 1.89, $CHCl_3$); IR (neat): 3310, 2999, 2952, 2851, 1616, 1504, 1458, 1234, 1184, 1034, 835, 756, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.47−7.45 (m, 2H), 7.34 (m, 2H), 7.29−7.25 (m, 1H), 6.64 (d, J = 8.6 Hz, 1H), 6.49 (d, J = 2.7 Hz, 1H), 6.35 (dd, J = 2.7, 8.6 Hz, 2H), 4.73 (d, 24.2 Hz, 1H), 3.76 (d, J = 10.7 Hz, 1H), 3.49 (s, 3H), 3.48 (d, J = 10.5 Hz, 3H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 150.9, 139.5 (d, J = 15.8 Hz), 135.7, 128.5, 127.8, 127.6, 127.5, 117.6, 111.4, 111.2, 55.6 (d, J = 150.9 Hz), 55.9, 53.9 (d, J = 6.8 Hz), 53.7 (d, J = 6.8 Hz), 16.5; Anal. Calcd for $C_{17}H_{22}NO_4P$: C, 60.89; H, 6.61; N, 4.18. Found: C, 60.81; H, 6.63; N, 4.16.

Dimethyl [*N*-(4-Methoxy-3-methylphenyl)amino](4-bromophenyl)methylphosphonate (8a, Table 3, Entry 1). Viscous yellowish oil. Yield quant. (95% ee); $[\alpha]_D^{25}$ +48.0 (*c* 1.43, $CHCl_3$); IR (neat): 3306, 2995, 2951, 1616, 1591, 1506, 1462, 1234, 1184, 1032, 839, 754 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46 (d, J = 8.3 Hz, 2H), 7.34 (dd, J = 2.4, 8.5 Hz, 2H), 6.64 (d, J = 8.6 Hz, 1H), 6.59 (d, J = 8.4 Hz, 1H), 6.31 (dd, J = 2.9, 8.4 Hz, 2H), 4.68 (d, 24.4 Hz, 1H), 3.76 (d, J = 10.7 Hz, 3H), 3.70 (s, 3H), 3.55 (d, J = 10.8 Hz, 3H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 151.1, 139.1 (d, J = 15.8 Hz), 135.0, 131.7 (d, J = 2.5 Hz), 129.3 (d, J = 5.8 Hz), 127.6, 121.8 (d, J = 4.2 Hz), 117.6, 111.4, 111.1, 56.1 (d, J = 150.9 Hz), 55.9, 54.1 (d, J = 6.7 Hz), 53.8 (d, J = 7.5 Hz), 16.5; HRFABMS. Calcd for $[C_{17}H_{21}NO_4PBr]^+$: m/z = 413.0392. Found: m/z = 413.0392.

Dimethyl [*N*-(4-Methoxy-3-methylphenyl)amino](4-chlorophenyl)methylphosphonate (8b, Table 3, Entry 2). Viscous yellowish oil. Yield 95% (95% ee); $[\alpha]_D^{24}$ +44.5 (*c* 1.47, $CHCl_3$); IR (neat): 3306, 2995, 2953, 2849, 1734, 1616, 1504, 1462, 1410, 1234, 1184, 1038, 839, 777, 754 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.40 (dd, J = 2.3, 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 6.59 (d, J = 8.6 Hz, 1H), 6.46 (d, J = 2.9 Hz, 1H), 6.31 (dd, J = 2.9, 8.6 Hz, 2H), 4.70 (d, 24.2 Hz, 1H), 3.70 (s, 3H), 3.68 (d, J = 10.7 Hz, 3H), 3.55 (d, J = 10.5 Hz, 3H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 151.1, 139.2 (d, J = 15.0 Hz), 134.4 (d, J = 2.5 Hz), 133.6 (d, J = 4.2 Hz), 128.9 (d, J = 5.0 Hz), 128.8 (d, J = 3.3 Hz), 127.6, 117.6, 111.4, 111.1, 56.1 (d, J = 150.9 Hz), 55.9, 54.1 (d, J = 7.5 Hz), 53.8 (d, J = 6.8 Hz), 16.5; HRFABMS. Calcd for $[C_{17}H_{21}NO_4PCl]^+$: m/z = 369.0897. Found: m/z = 369.0904.

Dimethyl [*N*-(4-Methoxy-3-methylphenyl)amino](4-methoxyphenyl)methylphosphonate (8c, Table 3, Entry 3). Viscous yellowish oil. Yield 92% (85% ee); $[\alpha]_D^{26}$ +43.3 (*c* 0.98, $CHCl_3$); IR (neat): 3308, 2997, 2951, 2835, 1611, 1508, 1462, 1302, 1236, 1180, 1032, 835, 791, 754 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.37 (dd, J = 2.4, 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.59 (d, J = 8.5 Hz, 1H), 6.49 (d, J = 2.9 Hz, 1H), 6.35 (dd, J = 2.9, 8.5 Hz, 2H), 4.67 (d, 23.7 Hz, 1H), 3.78 (s, 3H), 3.76 (d, J = 11.0 Hz, 3H), 3.70 (s, 3H), 3.50 (d, J = 10.5 Hz, 3H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.4, 151.3, 139.9 (d, J = 15.8 Hz), 129.1 (d, J = 5.8 Hz), 127.86, 118.0, 114.4 (d, J = 2.5 Hz), 111.8, 111.5, 56.3 (d, J = 153.4 Hz), 56.28, 55.6, 54.2 (d, J = 6.7 Hz), 54.1 (d, J = 6.7 Hz), 16.9; HRFABMS. Calcd for $[C_{18}H_{24}NO_5P]^+$: m/z = 365.1392. Found: m/z = 365.1394.

Dimethyl [*N*-(4-Methoxy-3-methylphenyl)amino](4-methylphenyl)methylphosphonate (8d, Table 3, Entry 4). Viscous yellowish oil. Yield 95% (90% ee); $[\alpha]_D^{24}$ +44.2 (*c* 1.03, $CHCl_3$); IR (neat): 3310, 2951, 2853, 1616, 1506, 1462, 1414, 1298, 1234, 1184, 1120, 1032, 835, 791, 756 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.33 (dd, J = 2.1, 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.59 (d, J = 8.6 Hz, 1H), 6.49 (d, J = 2.9 Hz, 1H), 6.35 (dd, J = 2.9, 8.6 Hz, 1H), 4.69 (dd, J = 8.1, 23.8 Hz, 1H), 4.41 (m, 1H), 3.76 (d, J = 10.6 Hz, 3H), 3.69 (s, 3H), 3.49 (d, J = 10.6 Hz, 3H), 2.31 (s, 3H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 150.9, 139.6 (d, J = 15.0 Hz), 137.5 (d, J = 3.3 Hz), 132.6, 129.3 (d, J = 2.5 Hz), 127.56, 127.47 (d, J = 3.3 Hz), 117.6, 111.4, 111.2, 56.3 (d, J = 151.8 Hz), 55.9, 53.9 (d, J = 6.7 Hz), 53.7 (d, J = 6.7 Hz), 21.3, 16.5; HRFABMS. Calcd for $[C_{18}H_{24}NO_4P]^+$: m/z = 349.1443. Found: m/z = 349.1409.

Dimethyl [*N*-(4-Methoxy-3-methylphenyl)amino](2-methylphenyl)methylphosphonate (8e, Table 3, Entry 5). Viscous yellowish oil. Yield 93% (87% ee); $[\alpha]_D^{25}$ +22.7 (*c* 1.73, $CHCl_3$); IR (neat): 3312, 2951, 2831, 1616, 1506, 1443, 1234, 1182, 1124, 1032, 833, 793, 756 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.52−7.50 (m, 1H), 7.20−7.15 (m, 3H), 6.58 (d, J = 8.5 Hz, 1H), 6.45 (d, J = 2.8 Hz, 1H), 6.28 (dd, J = 2.8, 8.5 Hz, 1H), 3.78 (d, J = 10.7 Hz, 3H), 3.68 (s, 3H), 3.49 (d, J = 10.5 Hz, 3H), 2.49 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 150.8, 139.5 (d, J = 15.0 Hz), 136.1 (d, J = 6.7 Hz), 134.0 (d, J = 1.7 Hz), 130.4 (d, J = 1.7 Hz), 127.6 (d, J = 3.3 Hz), 127.5, 126.9 (d, J = 4.2 Hz), 126.4 (d, J = 3.3 Hz), 117.4, 112.2, 111.0, 55.9, 53.8 (d, J = 7.5 Hz), 53.7 (d, J = 6.8 Hz), 52.6 (d, J = 152.6 Hz), 19.8, 16.5; HRFABMS. Calcd for $[C_{18}H_{24}NO_4P]^+$: m/z = 349.1443. Found: m/z = 349.1416.

Dimethyl [*N*-(4-Methoxy-3-methylphenyl)amino](2-thienyl)methylphosphonate (8f, Table 3, Entry 6). Viscous yellowish oil. Yield 91% (84% ee); $[\alpha]_D^{26}$ +43.7 (*c* 1.08, $CHCl_3$); IR (neat): 3312, 2951, 2853, 1616, 1501, 1464, 1296, 1242, 1188, 1119, 1022, 826, 795, 754, 702 cm^{-1}; ^1H NMR ($CDCl_3$): 7.23 (d, J = 4.4 Hz, 1H), 7.15 (m, 1H), 6.97 (t, J = 4.3, 4.3 Hz, 1H), 6.64 (d, 8.3 Hz, 1H), 6.55 (d, J = 2.7 Hz, 1H), 6.46 (dd, J = 2.7, 8.8 Hz, 1H), 4.99 (dd, 7.3, 23.6 Hz, 1H), 4.26 (m, 1H), 3.79 (d, J = 10.3 Hz, 3H), 4.26 (s, 3H), 3.63 (d, J = 10.5 Hz, 3H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 151.3, 139.7, 139.3 (d, J = 13.3 Hz), 127.5, 127.0 (d J = 2.5 Hz), 126.0 (d, J = 7.5 Hz), 125.2 (d, J = 4.2 Hz), 117.8, 111.7, 111.1, 55.8, 54.2 (d, J = 6.7 Hz), 53.8 (d, J = 7.5 Hz), 52.8 (d, J = 159.3 Hz), 16.5; Anal. Calcd for $C_{15}H_{20}NO_4PS$: C, 52.78; H, 5.91; N, 4.10. Found: C, 53.06; H, 5.96; N, 3.97.

Dimethyl [*N*-(4-Methoxy-3-methylphenyl)amino](2-furyl)methylphosphonate (8g, Table 3, Entry 7). Viscous yellowish oil. Yield 94% (69% ee); $[\alpha]_D^{26}$ +72.2 (*c* 1.21, $CHCl_3$); IR (neat): 3305, 2976, 2851, 1738, 1616, 1502, 1445, 1296, 1234, 1115, 1024, 833, 793, 746 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.39 (s, 1H), 6.65 (d, J = 8.5 Hz, 1H), 6.54 (d, J = 2.7 Hz, 1H), 6.46 (dd, J = 2.8, 8.7 Hz, 1H), 6.37 (t, J = 3.2, 3.2 Hz, 1H), 6.33 (m, 1H), 4.83 (dd, J = 8.4, 23.8 Hz, 1H), 4.19 (br s, 1H), 3.82 (d, J = 10.5 Hz, 3H), 3.73 (s, 3H), 3.64 (d, J = 10.7 Hz, 3H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 151.3, 149.1 (d, J = 1.7

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Hz), 142.3 (d, $J = 3.3$ Hz), 139.2 (d, $J = 14.2$ Hz), 127.5, 117.9, 111.8, 111.1, 110.7 (d, $J = 2.5$ Hz), 108.7 (d, $J = 7.5$ Hz), 55.8, 54.1 (d, $J = 6.7$ Hz), 53.6 (d, $J = 6.7$ Hz), 51.0 (d, $J = 160.1$ Hz), 16.5; Anal. Calcd for $C_{15}H_{20}NO_5P$: C, 55.38; H, 6.20; N, 4.31. Found: C, 55.14; H, 6.22; N, 4.21.

Dimethyl [*N*-(4-Methoxy-3-methylphenyl)amino][2-(5-phenylfuryl)]methylphosphonate (8h, Table 3, Entry 8). Viscous yellowish oil. Yield 95% (79% ee); $[\alpha]_D^{26}$ +74.7 (*c* 1.38, $CHCl_3$); IR (neat): 3306, 2976, 2853, 1614, 1504, 1445, 1296, 1234, 1184, 1109, 1020, 835, 793, 748 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.65 (d, $J = 7.3$ Hz, 2H), 7.37 (t, $J = 7.7$, 7.7 Hz, 2H), 7.26 (m, 1H), 6.65 (d, $J = 8.5$ Hz, 1H), 6.58 (d, $J = 3.2$ Hz, 2H), 6.50 (dd, $J = 2.9$, 8.5 Hz, 1H), 6.45 (t, $J = 3.3$, 3.3 Hz, 1H), 4.89 (dd, $J = 6.3$, 24.1 Hz, 1H), 4.23 (br s, 1H), 3.85 (d, $J = 10.7$ Hz, 3H), 3.72 (s, 3H), 3.66 (d, $J = 10.7$ Hz, 3H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 153.7 (d, $J = 3.3$ Hz), 151.4, 148.8 (d, $J = 1.7$ Hz), 139.2 (d, $J = 14.2$ Hz), 130.4, 128.5, 127.5, 127.3, 123.5, 117.9, 111.9, 111.1, 110.8 (d, 7.5 Hz), 106.1 (d, 2.5 Hz), 55.9, 54.2 (d, $J = 6.7$ Hz), 53.8 (d, $J = 6.7$ Hz), 51.3 (d, $J = 160.9$ Hz), 16.5; HRFABMS. Calcd for $[C_{21}H_{24}NO_5P]^+$: $m/z = 401.1392$. Found: $m/z = 401.1390$.

3.4.2. General Procedure for in Situ Asymmetric Hydrophosphonylation of *N*-(4-Methoxy-3-methylphenyl)aldimine and *N*-Diphenylmethylimine Derivatives with Dimethyl Phosphite (Table 4). To a suspension of activated MS4 Å (ca. 100 mg) in THF (1 mL) were added aldehyde (0.20 mmol) and amine (0.20 mmol), and the suspension was stirred for 3−4 h at room temperature under a nitrogen atmosphere. To the suspension were added complex **2** (12.5 mg, 20 μmol) and dimethyl phosphite (0.30 mmol, 27.5 μL) at −15 °C, and the mixture was stirred for 24 h at −15 °C. The reaction was quenched with H_2O, the mixture was extracted with AcOEt (3 × ca. 1 mL), and the combined organic phases were passed through a pad of Celite and Na_2SO_4. After concentrating the filtrate under reduced pressure, the residue was chromatographed on silica gel (hexane/AcOEt = 7:3−3:7 or CH_2Cl_2/AcOEt = 19:1−9:1) to give the corresponding α-aminophosphonate. The ee values were determined by HPLC on a chiral stationary phase under the conditions described in the footnotes to Table 4.

Dimethyl 1-[*N*-(4-Methoxy-3-methylphenyl)amino]-2,2-dimethylpropylphosphonate (10a, Table 4, Entry 1). Colorless solid. Yield 28% (88% ee); Mp 54.0−54.1 °C; $[\alpha]_D^{23}$ −60.5 (*c* 0.53, $CHCl_3$); IR (KBr): 3342, 2951, 1616, 1514, 1306, 1225, 1182, 1063, 1022, 826, 754 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.68 (d, $J = 8.5$ Hz, 1H), 6.48 (d, $J = 2.9$ Hz, 1H), 6.44 (dd, $J = 2.9$, 8.5 Hz, 1H), 3.75 (s, 3H), 3.68 (d, $J = 10.7$ Hz, 3H), 3.66 (d, $J = 10.0$ Hz, 3H), 2.17 (s, 3H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 150.3, 141.4 (d, $J = 4.2$ Hz), 127.5, 116.4, 111.4, 111.4, 61.1 (d, $J = 147.6$ Hz), 56.0, 53.5 (d, $J = 7.5$ Hz), 52.1 (d, $J = 7.5$ Hz), 35.7 (d, $J = 7.5$ Hz), 27.7 (d, $J = 6.8$ Hz), 16.6; Anal. Calcd for $C_{15}H_{26}NO_4P$: C, 57.13; H, 8.31; N, 4.44. Found: C, 57.13; H, 8.16; N, 4.36.

Dimethyl [*N*-(4-Methoxy-3-methylphenyl)amino]cyclohexylmethylphosphonate (10b, Table 4, Entry 2). Colorless oil. Yield 84% (94% ee); $[\alpha]_D^{23}$ −14.1 (*c* 0.85, $CHCl_3$); IR (neat): 3319, 2926, 2853, 1616, 1506, 1448, 1414, 1232, 1184, 1124, 1032, 826, 752 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.68 (d, $J = 8.6$ Hz, 1H), 6.49 (d, $J = 2.9$ Hz, 1H), 6.45 (dd, $J = 2.9$, 8.6 Hz, 1H), 3.75 (s, 3H), 3.72 (d, $J = 10.5$ Hz, 3H), 3.68 (d, $J = 10.0$ Hz, 3H), 3.54 (m, 2H) 1.96−1.62 (m, 6H), 1.36−1.06 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 150.4, 141.2 (d, $J = 5.8$ Hz), 127.6, 116.7, 111.4, 110.7, 57.2 (d, $J = 150.1$ Hz), 56.0, 53.4 (d, $J = 6.8$ Hz), 52.4 (d, $J = 7.5$ Hz), 40.0 (d, $J = 5.0$ Hz), 31.0 (d, $J = 11.7$ Hz), 28.5 (d, $J = 5.0$ Hz), 26.4, 26.3, 26.1, 16.6; Anal. Calcd for $C_{17}H_{28}NO_4P$: C, 59.81; H, 8.27; N, 4.10. Found: C, 59.81; H, 8.27; N, 4.08%.

Dimethyl 1-[*N*-(Diphenylmethyl)amino]-3-methylbutylphosphonate (10c, Table 4, Entry 3). Viscous colorless oil. Yield 80% (91% ee); $[\alpha]_D^{24}$ −73.1 (*c* 1.96, $CHCl_3$); IR (neat): 3302, 3059, 3026, 2953, 2866, 1597, 1491, 1456, 1242, 1182, 1055, 1028, 812, 742, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.44−7.41 (m, 4H), 7.31−7.26 (m, 4H), 7.23−7.17 (m, 2H), 5.28 (d, $J = 2.7$ Hz, 1H), 3.78 (d, $J = 10.5$ Hz, 3H), 3.75 (d, $J = 10.5$ Hz, 3H), 2.86 (m, 1H), 1.96 (septet, $J = 6.6$ Hz, 1H), 1.80 (br s, 1H), 1.56−1.45 (m, 2H), 0.87 (d, $J = 6.6$ Hz, 3H), 0.63 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 143.8, 142.8, 128.3, 127.8, 127.12, 127.07, 126.9, 64.7 (d, $J = 3.3$ Hz), 52.7 (d, $J = 7.5$ Hz), 52.7 (d, $J = 7.5$ Hz), 49.7 (d, $J = 143.4$ Hz), 24.4 (d, $J = 10.8$ Hz), 23.5, 21.6; HRFABMS. Calcd for $[C_{20}H_{29}NO_3P]^+$: $m/z = 362.1885$. Found: $m/z = 362.1886$.

Dimethyl 1-[*N*-(Diphenylmethyl)amino]octylphosphonate (10d, Table 4, Entry 4). Viscous colorless oil. Yield 83% (84% ee); $[\alpha]_D^{24}$ −23.1 (*c* 1.81, $CHCl_3$); IR (neat): 3472, 3308, 3061, 3026, 2926, 2853, 1599, 1491, 1456, 1244, 1182, 1055, 1028, 818, 746, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.44−7.41 (m, 4H), 7.29 (m, 4H), 7.23−7.18 (m, 2H), 5.22 (d, $J = 1.7$ Hz, 1H), 3.79 (d, $J = 10.5$ Hz, 3H), 3.74 (d, $J = 10.5$ Hz, 3H), 2.85 (m, 1H), 1.83−1.72 (m, 2H), 1.63−1.50 (m, 2H), 1.37−1.17 (m, 9H), 0.88 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 143.5, 143.0, 128.32, 128.29, 127.6, 127.2, 127.1, 127.0, 64.7 (d, $J = 5.8$ Hz), 52.8 (d, $J = 6.7$ Hz), 52.7 (d, $J = 6.7$ Hz), 51.5 (d, $J = 145.1$ Hz), 31.9, 30.3 (d, $J = 2.5$ Hz), 29.6, 29.2, 26.0 (d, $J = 10.0$ Hz), 22.8, 14.3; HRFABMS. Calcd for $[C_{23}H_{35}NO_3P]^+$: $m/z = 404.2355$ Found: $m/z = 404.2328$.

Dimethyl 1-[*N*-(Diphenylmethyl)amino]-3-phenylpropargylphosphonate (10e, Table 4, Entry 5). Viscous colorless oil. Yield 92% (86% ee); $[\alpha]_D^{26}$ −133.5 (*c* 1.36, $CHCl_3$); IR (neat): 3306, 3059, 3026, 2974, 2847, 1599, 1491, 1448, 1261, 1184, 1115, 1022, 837, 812, 747, 696 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.48 (d, $J = 7.8$ Hz, 4H), 7.42 (d, $J = 7.8$ Hz, 2H), 7.35−7.19 (m, 9H), 5.30 (s, 1H), 3.96 (d, $J = 10.7$ Hz, 3H), 3.93 (br s, 1H), 3.88 (d, $J = 10.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 143.2, 141.3, 131.8 (d, $J = 2.5$ Hz), 128.6, 128.4, 128.2, 127.6, 127.4, 127.2, 127.1, 122.3 (d, $J = 3.3$ Hz), 86.1, 83.2 (d, $J = 4.2$ Hz), 64.9 (d, $J = 16.7$ Hz), 54.6 (d, $J = 7.5$ Hz), 54.4 (d, $J = 7.5$ Hz), 46.9; HRFABMS. Calcd for $[C_{24}H_{25}NO_3P]^+$: $m/z = 406.1572$. Found: $m/z = 406.1563$.

Dimethyl 1-[*N*-(Diphenylmethyl)amino]-3-phenyl-2-propenylphosphonate (10f, Table 4, Entry 6). Colorless solid. Yield 51% (15% ee); Mp 97.9−98.0 °C; $[\alpha]_D^{26}$ +12.0 (*c* 0.00, $CHCl_3$); IR (KBr): 3275, 3059, 3026, 2951, 2847, 1597, 1489, 1450, 1240, 1180, 1074, 1034, 804, 766, 746, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.45−7.16 (m, 15H), 6.50 (dd, $J = 4.3$, 16.0 Hz, 1H), 6.15 (ddd, $J = 5.6$, 8.5, 15.9 Hz, 1H), 5.03 (s, 1H), 3.89 (d, $J = 10.5$ Hz, 3H), 3.76 (d, $J = 10.5$ Hz, 3H), 3.64 (dd, $J = 8.8$, 21.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 143.4, 142.0, 136.1 (d, $J = 2.5$ Hz), 134.6 (d, $J = 13.3$ Hz), 128.6, 128.5, 128.3, 127.9, 127.5, 127.2, 127.1, 127.0, 126.9 (d, $J = 4.2$ Hz), 126.4 (d, $J = 2.5$ Hz), 123.5 (d, $J = 5.0$ Hz), 63.9 (d, $J = 15.8$ Hz), 56.0 (d, $J = 157.6$ Hz), 53.9 (d, $J = 7.5$ Hz), 53.2 (d, $J = 7.5$ Hz); Anal. Calcd for $C_{24}H_{26}NO_3P$: C, 70.75; H, 6.43; N, 3.44. Found: C, 70.65; H, 6.35; N, 3.37.

3.4.3. Deprotection of *N*-Protecting 4-Methoxy-3-methylphenyl Group through Anodic Oxidation (Scheme 2). The deprotection was carried out according to the reported procedure[19] with a slight modification; the reaction was carried out without a reference electrode.

N-Protected α-amino phosphonate **6f** (144.3 mg, 0.430 mmol) was dissolved in a mixture of CH_3CN (18 mL) and H_2O (2 mL), which contained $NaClO_4$ (1 mmol) and $HClO_4$ (0.859 mmol). The electrolysis was conducted at 0 °C in a divided glass cell equipped with two platinum electrodes. The reaction was monitored by TLC analysis at intervals of ca. 15 min until the starting material was consumed (ca. 5 h). The voltage gradually ramped up by rotating a voltage knob and was maintained at a constant voltage after the formation of the product was detected. After 5 h, $NaHCO_3$ and anhydrous Na_2SO_4 were added to the solution, and the mixture was stirred and evaporated carefully under reduced pressure. The concentrate was diluted with AcOEt and filtrated through a pad of Celite and anhydrous Na_2SO_4. After the filtrate was concentrated under reduced pressure, the residue was chromatographed on silica gel (CH_2Cl_2/MeOH = 49/1−19/1) to give the

corresponding α-amino phosphonate (66.5 mg, 72%). Its spectroscopic data were identical to those of the reported product.[22]

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Supporting Information Available: Experimental data and X-ray crystallographic data files in CIF format for complex **2**. These materials are available free of charge via the Internet at http://pubs.acs.org.

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