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Diastereoselective addition of α-substituted α-amino-*H*-phosphinates to imines using $Yb(OTf)_3$ as an efficient Lewis acid catalyst

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Dedicated to Professor Emeritus Shiroshi Shibuya on the occasion of his 68th birthday

Abstract—Diastereoselective addition of α-substituted α-amino-*H*-phosphinates to imines is described. Among Lewis acids, $Yb(OTf)_3$ was found to be the best catalyst. α,α′-Diaminophosphinic derivatives were obtained with de's ranging from 10 to 95% in the presence of $Yb(OTf)_3$ as an efficient Lewis acid catalyst. The reaction proceeded with retention of configuration at the phosphorus atom.
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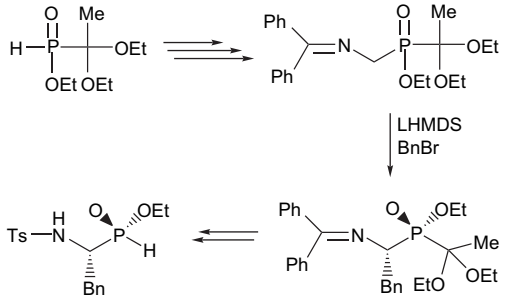
1. Introduction

Phosphorus–carbon bond formation is an active and important research area, as new reactions are continuously being developed for the preparation of organophosphorus compounds such as phosphinates and phosphonates.[1] α-Functionalized phosphinic acids are valuable intermediates for the preparation of medicinal compounds and also useful intermediates in the synthesis of other phosphorus compounds of material interest.[2] Among α-functional phosphinic acids, α-aminophosphinic acids are an important class of compounds that exhibit a variety of interest due to their usefulness both in pharmacologically active substances and in the development of catalytic antibodies.[3,4] In addition, the structure of the phosphinic functional group mimics the transition state of peptide hydrolysis and the symmetric nature of the phosphinic acid derivatives are expected to benefit in their binding to the homodimer of HIV-protease having C_2-axis symmetry.[5] Furthermore, the conjunction of two functionalities in the same molecule such as α-amino-α′-hydroxyphosphinates or α,α′-diaminophosphinates affords powerful inhibitors of HIV-1 protease.[6] In contrast to the widely studied stereoselective synthesis of α-amino or α-hydroxy phosphonic acids derivatives,[7–13,1h] relatively few papers have reported on the stereoselective synthesis of phosphinic acid derivatives.[14,2e] During our studies directed toward stereoselective synthesis and the medicinal application of α-aminophosphinic derivatives, we recently published a novel method for stereoselective synthesis of α-substituted α-amino-*H*-phosphinate. This method involves highly diastereoselective alkylation at α-carbon of the aminomethylphosphinates with 1,1-diethoxyethyl moiety induced by chirality of the phosphorus, and efficient deprotection of 1,1-diethoxyethyl moiety with retention of chirality at the phosphorus atom (Scheme 1).[15]



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Scheme 1.

Due to the stereo-defined feature, compound **1** could be used as a chiral inductor for stereoselective hydrophosphinylation to various electrophiles such as imines and aldehydes. We herein report Lewis acid-catalyzed hydrophosphinylation to imines with **1** to give α,α′-diaminophosphinic acid derivatives in a highly diastereoselective manner.

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Table 1. Reaction of *H*-phosphinate **1** with aldimine **2a** in the presence of Lewis acid catalysts

Entry	Lewis acid	Equivalent of catalyst	Reaction time (h)	Yield[a] (%)	Diastereomeric ratio,[b] **3a/4a**
1	None		48	—	—
2	$BF_3 \cdot OEt_2$	0.1	48	95	54:46
3	$ZnCl_2$	1	48	60	56:44
4	$LiClO_4$	0.1	48	32	70:30
5	$LiClO_4$	1	48	30	70:30
6	LiOTf	0.1	48	41	78:22
7	$Sc(OTf)_3$	0.1	6	95	50:50
8	$Yb(OTf)_3$	0.1	48	96	71:29

[a] Yield refers to ^{31}P NMR yield.
[b] Diastereomeric ratio determined by ^{31}P NMR.

2. Results and discussion

Aldimine **2a** was selected as a model substrate for the screening of Lewis acids as catalysts for hydrophosphinylation with (1*R**,*R**)-ethyl 1-{[(4-methylphenyl)sulfonyl]-amino}-2-phenylethyl phosphinate (**1**) (Table 1). Metal halides, such as $BF_3 \cdot OEt_2$ and $ZnCl_2$, showed good to high yields of products with poor diastereoselectivity (entries 2 and 3). $LiClO_4$ showed good diastereoselection in low yield (entry 4 and 5). It has been reported that imines are effectively activated by rare metal triflates such as ytterbium triflate ($Yb(OTf)_3$) and scandium triflate ($Sc(OTf)_3$).[16] These triflates are stable in water and can be recovered after the reaction is completed and reused. Moreover, they have been used for the activation of nitrogen-containing compounds, which deactivate most Lewis acids.[17] Due to these properties of lanthanide triflates, we planned to use them as catalysts in this reaction. The metal triflates LiOTf, $Sc(OTf)_3$, and $Yb(OTf)_3$ as catalysts showed good results (entries 6–8). Among these, $Yb(OTf)_3$ was found to be the best catalyst. It should be noted that in the absence of the Lewis acid, substrate **2a** did not undergo a hydrophosphinylation reaction with *H*-phosphinate **1** (entry 1). When **2a** (1.5 equiv) was treated with compound **1** (1 equiv) in CH_2Cl_2 in the presence of the $Yb(OTf)_3$ catalyst (10 mol %) at room temperature, within 48 h it gave the desired 1-aminophosphinates **3a** and **4a** in 96% yield and moderate diastereoselectivity (entry 8).

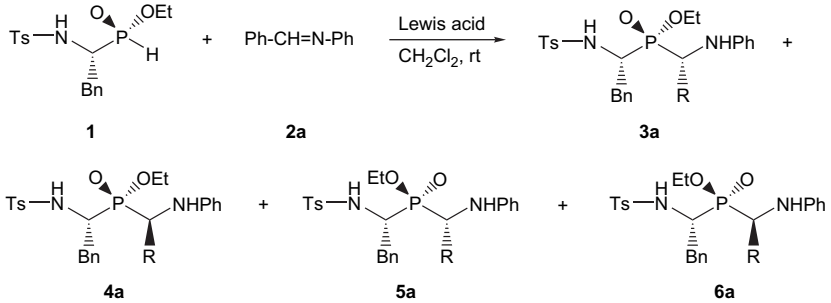
From a stereochemical point of view, four diastereoisomers (**3a**, **4a**, **5a**, and **6a**) could be formed in the addition step, because there are two new stereogenic centers created (one in the phosphorus atom and another in the α' position of product). Our ^{31}P NMR studies of crude mixture showed only two diastereoisomers corresponding to **3a** and **4a** in δ 45.73 and 44.75 ppm with 71 and 29% ratio, respectively (Scheme 2).

The structure of **4a** was determined by monocrystal X-ray analysis. The crystal structure of **4a** is illustrated in Figure 1. The structure shows retention of configuration on the phosphorus atom. Since we could not obtain suitable crystals of **3a** for X-ray analysis, the stereochemistry of **3a** was not determined. However, we deduce that **3a** is also retentive of the configuration at the phosphorus atom on the basis of the following experimental results for other electrophiles (see Scheme 3 and Fig. 2).

This process was successfully applied to other aldimines (**2**) as summarized in Table 2. As shown in Scheme 3 and Table 2, the reaction of *H*-phosphinate **1** with various aldimines (**2b–i**), afforded **3b–i** and **4b–i** in good to high yields. Aliphatic aldimine *N*-(2,2-dimethylpropylidene)aniline (**2b**) reacted with *H*-phosphinate **1** under the same condition to give **3b** and **4b** with good yield and moderate selectivity. However, using the same condition for *N*-(2-methylpropylidene)aniline (**2c**), only very low yields of adduct (<5%) were obtained, even after several days. *N*-(2-Furylmethylene)aniline (**2d**) as a heterocyclic aldimine also gave desired products in 89% yield with a good diastereoselectivity (90/10). The reaction of polynucleic aromatic aldimines, *N*-(1-naphthylmethylene)aniline (**2e**) and *N*-(2-naphthylmethylene)aniline (**2f**), with *H*-phosphinate **1** under the same conditions gave desired products in high yields and moderate to excellent diastereoselectivities (95/5 and 56/44, respectively). Aldimines with aliphatic amines (**2g** and **2h**) gave desired products in high yield and low diastereoselectivity. Using the same conditions for *N*-(2-methylpropylidene)-1-phenylmethanamine (**2i**), only very low yields of adduct (<5%) were obtained, even after several days.

As illustrated in Table 2, the reaction is mild and versatile, proceeds with good to excellent yield and good diastereoselectivity, and has no byproducts. We could obtain suitable crystals for major diastereoisomer **3f** for X-ray analysis. The crystal structure of **3f** is illustrated in Figure 2. It is worthy to note that the structure shows retention of configuration at the phosphorus atom in **3f**, while the addition may be prone to epimerization at the phosphorus atom. All NMR data could be assigned and they were in good agreement with the characteristics of the product.

This good diastereoselectivity is probably due to the result of a more rigid transition state formed by the double



Scheme 2.

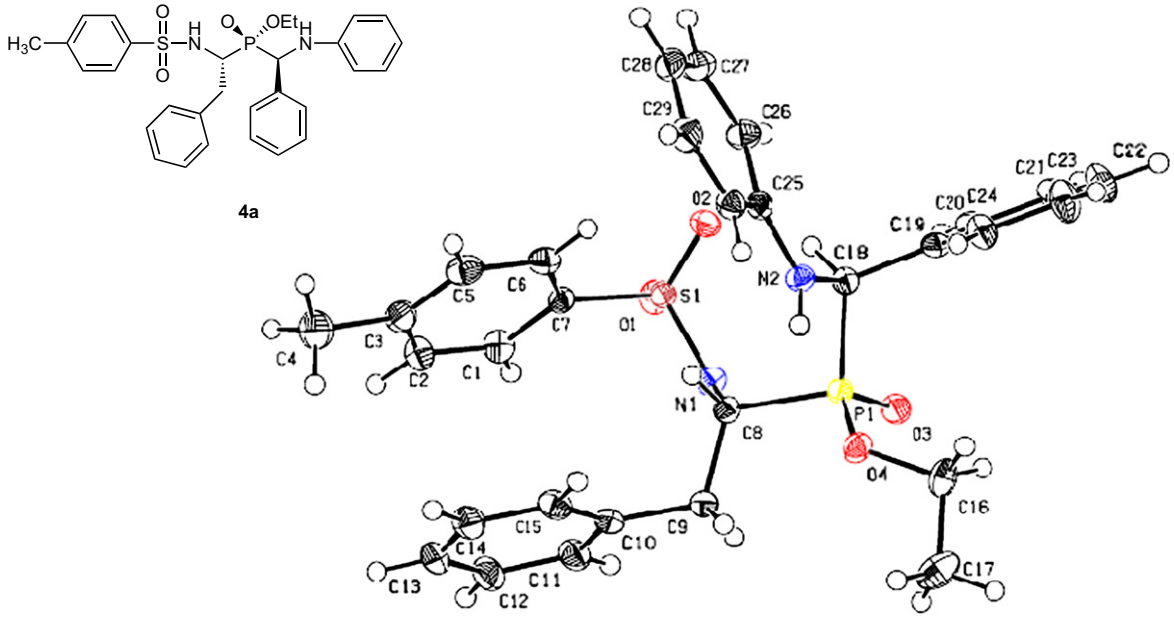


Figure 1. ORTEP drawing of minor diastereoisomer **4a**.

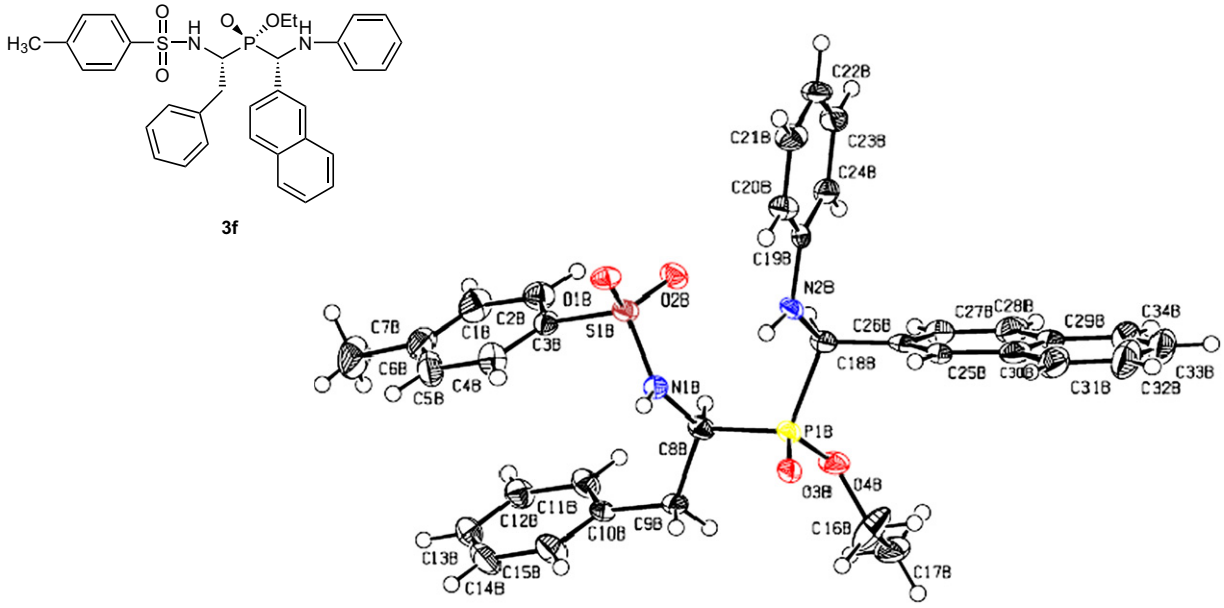
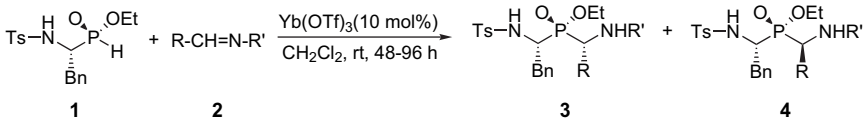


Figure 2. ORTEP drawing of diastereoisomer **3f**.



Scheme 3.

coordination of the catalyst with the nitrogen at the imine and phosphoryl groups.

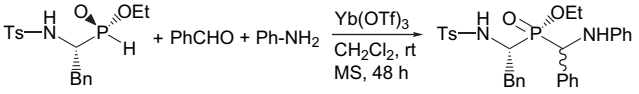
It is desirable from a synthetic point of view that imines, generated in situ from aldehydes and amines, immediately react with *H*-phosphinate to afford 1-aminophosphinate in one-pot way. Then we examined the diastereoselective addition of **1** to a mixture of benzaldehyde and aniline. It was found that the reactions of benzaldehyde, aniline, and *H*-phosphinate **1** took place smoothly within 48 h in the presence of 10 mol % $Yb(OTf)_3$ and 5 Å molecular sieves at room temperature to give the desired 1-aminophosphinates in 62% isolated yield and 40% diastereomeric excess (de) (Scheme 4).

In conclusion, (1*R**,*R*⁄)-ethyl 1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl phosphinate (**1**) was investigated

Table 2. Reaction of *H*-phosphinate **1** with aldimine **2** in the presence of $Yb(OTf)_3$ as an efficient Lewis acid catalyst

2	R	R′	Reaction time (h)	Yield[a] (isolated yield[b]) (%)	Diastereomeric ratio,[a] **3/4** (%)
a	C_6H_5–	C_6H_5–	48	96 (78)	71:29
b	$(CH_3)_3C$–	C_6H_5–	96	78 (56)	67:33
c	$(CH_3)_2CH$–	C_6H_5–	96	ND[c]	ND
d	2-Furyl	C_6H_5–	48	89 (69)	90:10
e	α-Naphthyl	C_6H_5–	48	90 (57)	97:3
f	β-Naphthyl	C_6H_5–	48	95 (53)	78:22
g	C_6H_5–	$C_6H_5CH_2$–	48	93 (13)	55:45
h	2-Furyl	$C_6H_5CH_2$–	72	90 (18)	61:39
i	$(CH_3)_2CH$–	$C_6H_5CH_2$–	96	ND	ND

[a] Determined by ^{31}P NMR spectroscopy.
[b] Yield after purification by column chromatography.
[c] Not Determined (ND). Only very low yields of adducts (<5%) were obtained, even after several days.



1 3a

Scheme 4.

as a chiral substrate for diastereoselective additions to imines. It reacts easily with imines under electrophilic activation, with good diastereomeric excesses affording an effective way for stereoselective α,α′-diaminophosphinic derivatives **3** and **4**. Diastereoselectivity using electrophilic activation for the reaction of imines presents a strong dependence on the Lewis acid effect. Ytterbium triflate afforded the highest de and yield in comparison to the other ones such as scandium triflate or boron trifluoride ethereate. Then, $Yb(OTf)_3$ was found to be an efficient catalyst both in the reaction of imines with *H*-phosphinate and in the one-pot reaction of aldehydes, amines, and *H*-phosphinate to afford 1-aminophosphinate in good to high yields under mild conditions. The structure of minor and major diastereoisomers showed retention of configuration at the phosphorus atom.

3. Experimental

3.1. General

All melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Mass spectra were measured on a LCMASS micromass LCT and Micromass Autospec.

NMR spectra were obtained on Varian Mercury-300BB spectrometer operating at 300 MHz for ^1H and 121 MHz for ^{31}P. ^{13}C NMR spectra were also obtained on Bruker DPX400 NMR instrument operating at 100 MHz. The chemical shift data for each signal on ^1H NMR are given in units of δ relative to $CHCl_3$ (δ=7.26) for $CDCl_3$ solution. For ^{13}C NMR spectra, the chemical shifts in $CDCl_3$ and DMSO-d_6 are recorded relative to the $CDCl_3$ (δ=77.0) and DMSO-d_6 resonances (δ=40.45). The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4 (δ=0) with broad-band ^1H decoupling. Flash column chromatography was performed on 40–100 μm silica gel 60 (KANTO CHEMICAL CO., INC.). Column chromatography was carried out using 63–210 μm silica gel 60 N (KANTO CHEMICAL CO., INC.). Analytical TLC was carried out with precoated silica gel 60 F_{254} plates (Merck).

X-ray crystal data was collected by a Bruker SMART APEX II diffractometer. The structure was solved by a direct method using SHLEXS-97 (Scheldrik, 1997) and refined with a full matrix laser-squares method.

4a: molecular formula=$C_{30}H_{33}N_2O_4PS$, MW=548.61, monoclinic, space group=$P2(1)/n$, a=11.6935(13) Å, b=16.1366(18) Å, c=15.0492(17) Å, V=2837.3(5) Å^3, T=90 K, Z=4, D_x=1.284 Mg/m^3, (Mo Kα)=0.71073 Å, R=0.0374 over independent reflections (6400). Crystallographic data (excluding structure factors) for the X-ray crystal structure analysis reported in this paper have been deposited with the Cambridge Crystallographic Data Center (CCDC) as supplementary publication No. CCDC 641563, copies of these data can be obtained, free of charge, upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

3f: molecular formula=$C_{34}H_{35}N_2O_4PS$, MW=598.67, monoclinic, space group=$P2(1)/n$, a=16.2547(19) Å, b=22.298(3) Å, c=17.123(2) Å, V=6206.0(13) Å^3, T=90 K, Z=4, D_x=1.281 Mg/m^3, (Mo Kα)=0.71073 Å, R=0.0584 over independent reflections (13,751). Crystallographic data (excluding structure factors) for the X-ray crystal structure analysis reported in this paper have been deposited with the Cambridge Crystallographic Data Center (CCDC) as supplementary publication No. CCDC 641564, copies of these data can be obtained, free of charge, upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.2. (1*R**,*R**)-Ethyl 1-{[(4-methylphenyl)sulfonyl]-amino}-2-phenylethyl phosphinate (1)

This compound was obtained according to the method of our previously published work.[15]

3.3. General procedure for addition of (1*R**,*R**)-ethyl 1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl phosphinate (1) to imine 2a catalyzed by Lewis acids

In a 5 mL flask containing 73 mg of *H*-phosphinate **1** (0.2 mmol, 1 equiv) under N_2 was added dry dichloromethane (2 mL) followed by 300 μL portion of a 1 N imine **2a** (0.3 mmol, 1.5 equiv) in dichloromethane. Lewis acid (0.1 or 1 equiv in two experiments) was added while being stirred. After stirring for a known period (Table 1), addition of water and extraction with chloroform were done. Organic layers were dried over $MgSO_4$ and evaporated. Yields and ratio of diastereoisomers were calculated using ^{31}P NMR of the crude mixture.

3.4. General procedure for addition of (1*R**,*R**)-ethyl 1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl phosphinate (1) to imine 2 catalyzed by $Yb(OTf)_3$

In a 5 mL flask containing 73 mg of *H*-phosphinate **1** (0.2 mmol, 1 equiv) under N_2 was added dry dichloromethane (2 mL) followed by 300 μL portion of a 1 N imine **2**

(0.3 mmol, 1.5 equiv) in dichloromethane. A 12–13 mg portion of $Yb(OTf)_3$ (0.1 equiv) was added under stirring. After stirring for known period (Table 2), addition of water and extraction with chloroform were done. Organic layers were dried over $MgSO_4$ and evaporated. Removal of the solvent gave a residue, which was purified by column chromatography (hexane/EtOAc=5:1–1:1) to give a mixture of two diastereoisomers in 13–78% yield. Analytical samples of individual diastereoisomers **4a** and **3f** for X-ray analysis were obtained by several times separation by column chromatography and recrystallization.

3.5. Ethyl anilino(phenyl)methyl((*R**)-1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl)phosphinate (3a and 4a)

White solid (85 mg, two diastereoisomers); yield 78%, de=42%; ^{1}H NMR (300 MHz, $CDCl_3$) major δ 7.66 (d, 2H, J=8.3 Hz), 7.60–7.12 (12H, m), 7.03 (t, 2H, J=7.4 Hz), 6.68 (t, 1H, J=7.3 Hz), 6.28 (2H, d, J=7.7 Hz), 5.90–5.80 (1H, NH), 4.19 (1H, d, J=16.9 Hz), 4.12–3.96 (1H, m), 3.70–3.60 (1H, m), 3.27–3.13 (3H, m), 2.41 (3H, s), 1.40–1.21 (1H, NH), 0.89 (3H, t, J=7.1 Hz); minor δ 7.42 (d, 2H, J=7.3 Hz), 7.40–6.95 (14H, m), 6.74 (t, 1H, J=7.4 Hz), 6.49 (2H, d, J=8.3 Hz), 6.42–6.30 (1H, NH), 4.75 (1H, d, J=16.9 Hz), 4.28–4.10 (1H, m), 4.05–3.84 (2H, m), 3.16 (1H, dt, J=5.6, 14.0 Hz), 2.95–2.85 (1H, m), 2.35 (3H, s), 1.80–1.60 (1H, NH), 1.13 (3H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, DMSO) as a mixture of the two diastereoisomers δ 148.0 (d, J_{PC}=12.8 Hz, minor), 147.7 (d, J_{PC}=14.6 Hz, major), 143.0 (major), 142.9 (minor), 138.4 (d, J_{PC}=10.2 Hz, major), 138.2 (d, J_{PC}=10.1 Hz, major), 137.1 (major), 136.7 (minor), 130.2–126.0 (aromatic), 118.2, 115, 62.9 (d, J_{PC}=7.1 Hz, major), 62.0 (d, J_{PC}=7.1 Hz, minor), 55.4 (d, J_{PC}=92.9 Hz, minor), 55.3 (d, J_{PC}=110.5 Hz, major), 54.9 (d, J_{PC}=109.8 Hz, major), 53.0 (d, J_{PC}=100.8 Hz, minor), 36.7 (major), 35.6 (minor), 21.9, 17.3 (d, J_{PC}=4.8 Hz, minor), 16.7 (d, J_{PC}=5.0 Hz, major); ^{31}P NMR (162 MHz, $CDCl_3$) δ 45.14 and 43.84; MS m/z 549 (MH^+). HRMS calcd for $C_{30}H_{34}N_2O_4PS$ (MH^+): 549.1977. Found: 549.1966.

3.6. Ethyl 1-anilino-2,2-dimethylpropyl(phenyl)-methyl((*R**)-1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl)phosphinate (3b and 4b)

White solid (59 mg); yield 56% as a mixture of two diastereoisomers, de=34%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, 2×2H, J=8.0 Hz), 7.35–6.63 (2×10H, m), 6.60–6.40 (1H, NH), 6.21 (2×2H, d, J=8.0 Hz), 5.55–5.40 (1H, NH), 4.38–3.65 (2×3H, m), 3.40–3.15 (2×1H, m), 3.20–2.65 (2×2H, m), 2.35 (3H, s, major), 2.32 (3H, s, minor), 2.00–1.80 (1H, NH), 1.41 (3H, t, J=7.0 Hz, major), 1.30 (3H, t, J=7.1 Hz, minor), 1.15 (9H, s, minor), 1.03 (9H, s, major), 1.02–0.80 (1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7 (d, J_{PC}=6.2 Hz, minor), 146.5 (d, J_{PC}=8.1 Hz, major), 143.9, 143.1, 142.5, 137.6, 137.2, 136.7, 136.6, 129.7–126.2 (mixed peaks, aromatic), 118.3, 118.0, 113.5, 112.8, 61.9 (d, J_{PC}=6.6 Hz, minor), 61.8 (d, J_{PC}=7.9 Hz, major), 59.1 (d, J_{PC}=91.5 Hz, minor), 58.5 (d, J_{PC}=100.1 Hz, major), 54.0 (d, J_{PC}=90.0 Hz, minor), 53.0 (d, J_{PC}=91.8 Hz, major), 37.5–37.2 (mixed peaks), 35.5, 27.9 (d, J_{PC}=5.0 Hz, major), 27.8 (d, J_{PC}=5.2 Hz, minor), 21.5 (major), 21.4 (minor), 16.5 (d, J_{PC}=5.3 Hz, major), 15.9 (d, J_{PC}=5.3 Hz, minor); ^{31}P NMR (162 MHz, $CDCl_3$) δ 50.91 and 47.77; MS m/z 529 (MH^+). HRMS calcd for $C_{28}H_{38}N_2O_4PS$ (MH^+): 529.2306. Found: 529.2300.

3.7. Ethyl anilino(2-furyl)methyl((*R**)-1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl)phosphinate (3d and 4d)

White solid (74 mg); yield 69% as a mixture of two diastereoisomers, de=80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, 2H, J=8.3 Hz, major), 7.48 (d, 2H, J=8.2 Hz, minor), 7.42–6.90 (2×10H, m), 6.76 (t, 2×1H, J=7.2 Hz), 6.59 (d, 2×1H, J=7.2 Hz), 6.50–6.20 (m, 2×3H+NH, minor), 5.90–5.80 (1H, NH, major), 4.95 (d, 1H, J=16.1 Hz, minor), 4.53 (d, 1H, J=16.7 Hz, major), 4.38–4.30 (m, 1H, minor), 4.15–4.00 (m, 1H, minor), 3.90–3.80 (m, 1H, major), 3.65–3.49 (m, 2×1H), 3.30–2.90 (m, 2×2H+1H, major), 2.38 (3H, s, major), 2.37 (3H, s, minor), 1.40–1.20 (1H, NH, major), 1.05 (3H, t, J=7.1 Hz, major), 0.95–0.85 (1H, NH, minor), 0.81 (3H, t, J=7.2 Hz, minor); ^{13}C NMR (100 MHz, $CDCl_3$) major δ 148.4 (d, J_{PC}=5.4 Hz), 145.4 (d, J_{PC}=13.5 Hz), 143.3, 142.6, 137.1, 136.4 (d, J_{PC}=5.6 Hz), 129.8, 129.0, 128.6, 126.9, 126.4, 125.1, 124.4, 122.1, 118.2, 115.0, 62.7 (d, J_{PC}=7.6 Hz), 53.0 (d, J_{PC}=99.2 Hz), 50.6 (d, J_{PC}=100.8 Hz), 36.6, 21.5, 16.2 (d, J_{PC}=5.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.69 and 42.44; MS m/z 539 (MH^+). HRMS calcd for $C_{28}H_{32}N_2O_5PS$ (MH^+): 539.1770. Found: 539.1726.

3.8. Ethyl anilino(1-naphthyl)methyl((*R**)-1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl)-phosphinate (3e and 4e)

White solid (68 mg, two diastereoisomers); yield 57%, de=95%; ^{1}H NMR (300 MHz, $CDCl_3$) major δ 7.95–7.20 (m, 15H), 7.07 (t, 2H, J=8.4 Hz), 6.70 (t, 1H, J=7.3 Hz), 6.47 (2H, d, J=7.7 Hz), 6.28 (t, 1H, J=6.7 Hz), 5.55 (1H, d, J=15.8 Hz), 5.35–5.10 (1H, NH), 4.18–4.10 (1H, m), 3.40–3.20 (3H, m), 2.60–2.32 (1H, m), 2.47 (3H, s), 2.05–1.80 (1H, NH), 0.33 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) major δ 147.5, 143.2, 139.8, 138.3, 137.8, 136.3, 130.4–126.2 (aromatic), 125.1, 124.4, 122.1, 118.2, 115.4, 115.0, 61.7 (d, J_{PC}=7.1 Hz), 56.6 (d, J_{PC}=100.0 Hz), 52.1 (d, J_{PC}=102.3 Hz), 36.8, 21.9, 15.9 (d, J_{PC}=5.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 45.35 and 44.24; MS m/z 599 (MH^+). HRMS calcd for $C_{34}H_{36}N_2O_4PS$ (MH^+): 599.2133. Found: 599.2109.

3.9. Ethyl anilino(2-naphthyl)methyl((*R**)-1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl)-phosphinate (3f and 4f)

White solid (67 mg, two diastereoisomers); yield 56%, de=53%; ^{1}H NMR (300 MHz, $CDCl_3$) major δ 7.85–7.60 (5H, m), 7.55–7.40 (m, 2H), 7.39–7.12 (m, 9H), 7.01 (t, 2H, J=7.5 Hz), 6.65 (t, 1H, J=7.3 Hz), 6.31 (2H, d, J=7.7 Hz), 5.62–5.55 (1H, NH), 4.33 (1H, d, J=17.2 Hz), 4.15–4.02 (1H, m), 3.65–3.3.55 (1H, m), 3.25–3.10 (3H, m), 2.42 (3H, s), 1.85–1.60 (1H, NH), 0.83 (3H, t, J=7.1 Hz); minor δ 7.85–7.60 (5H, m), 7.55–6.80 (13H, m), 6.72 (t, 1H, J=7.3 Hz), 6.59 (2H, d, J=7.8 Hz), 6.28–6.20 (1H, NH), 5.06 (1H, d, J=17.1 Hz), 4.18–4.08 (1H,

m), 4.05–3.84 (1H, m), 3.25–3.10 (2H, m), 3.01–2.85 (1H, m), 2.31 (3H, s), 1.40–1.20 (1H, NH), 1.13 (3H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) as a mixture of the two diastereoisomers δ 145.3, 145.2, 143.3, 142.8, 137.5, 137.0, 136.6, 136.5, 133.1, 133.0, 132.3, 133.0, 129.7–125.5 (aromatic), 119.3, 118.8, 114.9, 114.5, 114.3, 63.3 (d, J_{PC}=7.5 Hz, major), 62.6 (d, J_{PC}=7.5 Hz, minor), 56.3 (d, J_{PC}=97.6 Hz, minor), 55.7 (d, J_{PC}=95.3 Hz, major), 53.7 (d, J_{PC}=97.5 Hz, minor), 52.2 (d, J_{PC}=97.0 Hz, major), 36.9, 35.7, 21.5 (minor), 21.4 (major), 16.6 (d, J_{PC}=5.4 Hz, major), 16.0 (d, J_{PC}=5.5 Hz, minor); ^{31}P NMR (162 MHz, $CDCl_3$) δ 45.90 and 44.50; MS m/z 599 (MH^+). HRMS calcd for $C_{34}H_{36}N_2O_4PS$ (MH^+): 599.2133. Found: 599.2111. MS m/z 539 (MH^+). HRMS calcd for $C_{28}H_{32}N_2O_5PS$ (MH^+): 539.1770. Found: 539.1726.

3.10. Ethyl (benzylamino)(phenyl)methyl((*R**)-1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl)phosphinate (3g and 4g)

White solid (15 mg); yield 13% as a mixture of two diastereoisomers, de=10%; ^{1}H NMR (300 MHz, $CDCl_3$) 8.50–8.35 (1H, NH, minor), 7.59 (d, 2H, J=8.1 Hz, major), 7.53 (d, 2H, J=8.1 Hz, minor), 7.50–6.90 (m, 2×17H+1H of NH, major), 4.38–2.90 (m, 2×8H), 2.40 (3H, s, major), 2.39 (3H, s, minor), 1.45–1.20 (1H, NH, major), 1.03 (3H, t, J=6.7 Hz, major), 0.95–0.85 (1H, NH, minor), 0.63 (3H, t, J=6.7 Hz, minor); ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.57 and 39.05; MS m/z 563 (MH^+). HRMS calcd for $C_{31}H_{36}N_2O_4PS$ (MH^+): 563.2133. Found: 563.2163.

3.11. Ethyl (benzylamino)(2-furyl)methyl((*R**)-1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl)phosphinate (3h and 4h)

White solid (20 mg); yield 18% as a mixture of two diastereoisomers, de=22%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20–7.95 (1H, NH, minor), 7.59–6.90 (m, 2×15H+1H of NH, major), 6.43–6.28 (m, 2×1H+1H, minor), 6.23 (t, 1H, J=3.0 Hz, major), 4.20–2.73 (m, 2×8H), 2.39 (2×3H, s), 2.20–1.80 (1H, NH, major), 1.40–1.20 (1H, NH, minor), 1.09 (3H, t, J=7.0 Hz, major), 0.86 (3H, t, J=7.1 Hz, minor); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3 (d, J_{PC}=5.0 Hz, major), 147.1 (d, J_{PC}=7.0 Hz, minor), 138.5, 137.8, 136.8 (d, J_{PC}=5.9 Hz, major), 136.6 (d, J_{PC}=7.4 Hz, minor), 130.8–126.5 (aromatic), 110.7, 110.5 (d, J_{PC}=6.4 Hz, major), 110.3 (d, J_{PC}=6.2 Hz, minor), 61.9 (d, J_{PC}=7.3 Hz, minor and major), 55.7–51.2 (mixed peaks), 37.1 (major), 36.4 (minor), 21.5 (major), 21.4 (minor), 16.3 (d, J_{PC}=5.4 Hz, minor), 15.9 (d, J_{PC}=5.6 Hz, minor); ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.04 and 38.26; MS m/z 553 (MH^+). HRMS calcd for $C_{29}H_{34}N_2O_5PS$ (MH^+): 553.1902. Found: 553.1904.

3.12. Procedure for addition of (1*R**,*R**)-ethyl 1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl phosphinate (1) to a mixture of benzaldehyde and aniline catalyzed by Yb(OTf)$_3$

In a 5 mL flask containing 73 mg of *H*-phosphinate **1** (0.2 mmol, 1 equiv) under N_2 was added dry dichloromethane (2 mL) followed by 42 μL of benzaldehyde (0.3 mmol, 1.5 equiv) and 28 μL of aniline (0.3 mmol, 1.5 equiv). Yb(OTf)$_3$ (12–13 mg, 0.1 equiv) was added under stirring in the presence of molecular sieves 5 Å. After stirring for 48 h, addition of water and extraction with chloroform were done. Organic layers were dried over $MgSO_4$ and evaporated. Removal of the solvent gave a residue, which was purified by column chromatography (hexane/EtOAc=5:1–1:1) to give a mixture of two diastereoisomers **3a** and **4a** in 62% yield with 40% diastereomeric excess.

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References and notes

1. (a) Engel, R. *Chem. Rev.* **1977**, *77*, 349–367; (b) Frank, A. W. *Chem. Rev.* **1961**, *61*, 389–424; (c) Kaboudin, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 1749–1751; (d) Montchamp, J.-L. *J. Organomet. Chem.* **2005**, *690*, 2388–2406; (e) Hilderbrand, R. L. *The Role of Phosphonates in Living Systems*; CRC: Boca Raton, FL, 1982; (f) Redmore, D. *Topics in Phosphorus Chemistry*; Griffith, E. J., Grayson, M., Eds.; Wiley: New York, NY, 1976; Vol. 8; (g) Kaboudin, B.; Karimi, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5324–5326; (h) Shibasaki, M.; Arai, T.; Bougauchi, M.; Sasai, H. *J. Org. Chem.* **1996**, *61*, 2926–2927; (i) Afarinkia, K.; Rees, C. W. *Tetrahedron* **1990**, *46*, 7175–7196; (j) Kaboudin, B.; Haghighat, H. *Tetrahedron Lett.* **2005**, *46*, 7955–7957.
2. (a) Martin, M. T.; Angeles, T. S.; Sugasawara, R.; Aman, N. I.; Napper, A. D.; Darsley, M. J.; Sanchez, R. I.; Booth, P.; Titmas, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 6508–6512; (b) Li, T.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2001–2004; (c) Kaboudin, B.; As-habei, N. *Tetrahedron Lett.* **2003**, *44*, 4243–4245; (d) Hiratake, J.; Oda, J. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 211–218 and references cited therein; (e) Yamagishi, T.; Yokomatsu, T.; Suemune, K.; Shibuya, S. *Tetrahedron* **1999**, *55*, 12125–12136; (f) Dingwall, J. G.; Campell, C. D.; Baylis, E. K. U.K. Patent Application, 1,542,938, 1979; *Chem. Abstr.* **1979**, *88*, 105559j; (g) Kafarski, P.; Lejczak, B.; Tyka, R.; Koba, L.; Pliszczak, E.; Wieczorek, P. *J. Plant Growth Regul.* **1995**, *14*, 199–203; (h) Ishiguri, Y.; Yamada, Y.; Kato, T.; Sasaki, M.; Mukai, K. European Patent Application, EP 82-301905, 1982; *Chem. Abstr.* **1983**, *98*, 102686u; (i) Vayron, P.; Renard, P.-Y.; Taran, F.; Creminon, C.; Frobert, Y.; Grassi, J.; Mioskowski, C. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7058–7063; (j) Kaboudin, B.; As-habei, N. *Tetrahedron Lett.* **2004**, *45*, 9099–9101.
3. (a) Kukhar, V. P.; Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; John Wiley and Sons: Chichester, UK, 2000; (b) For a review, see: Collinsová, M.; Jirácek, J. *Curr. Med. Chem.* **2000**, *7*, 629–647; (c) Matziari, M.; Georgiadis, D.; Dive, V.; Yiotakis, A. *Org. Lett.* **2001**, *3*, 659–662; (d) Cristau, H.-J.; Coulombeeau,

A.; Genevois-Borella, A.; Sanchez, F.; Pirat, J.-L. *J. Organomet. Chem.* **2002**, *643–644*, 381–391; (e) Liu, X.; Hu, X. E.; Tian, X.; Mazur, A.; Ebetino, F. H. *J. Organomet. Chem.* **2002**, *646*, 212–222.

4. (a) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Rogers, W. L.; Smith, S. A.; DeForrest, J. M.; Oehl, R. S.; Petrillo, E. W., Jr. *J. Med. Chem.* **1995**, *38*, 4557–4569; (b) Grembecka, J.; Mucha, A.; Cierpicki, T.; Kafarski, P. *J. Med. Chem.* **2003**, *46*, 2641–2655; (c) Lloyd, J.; Schmidt, J. B.; Hunt, J. T.; Barrish, J. C.; Little, D. K.; Tymiak, A. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1323–1326; (d) Makaritis, A.; Georgiadis, D.; Dive, V.; Yiotakis, A. *Chem.—Eur. J.* **2003**, *9*, 2079–2094.
5. Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625–6628.
6. (a) Dreyer, G. B.; Abdel-Meguid, S. S.; Zhao, B.; Murthy, K.; Winborne, E.; Choi, J. W.; DesJarlais, R. L.; Minnich, M. D.; Culp, J. S.; Debouck, C.; Tomaszek, T. A., Jr.; Meek, T. D. *Biochemistry* **1993**, *32*, 7972–7980; (b) World Patent 9200954, January 23, 1992; (c) U.S. Patent 5,707,979, January 13, 1998; (d) Cristau, H.-J.; Herve, A.; Virieux, D. *Tetrahedron* **2004**, *60*, 877–884.
7. (a) Hammerschmidt, F.; Vollenkle, H. *Liebigs Ann. Chem.* **1989**, 577–583; (b) Yokomatsu, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1992**, *3*, 377–378; (c) Baraldi, P. G.; Guarneri, M.; Moroder, F.; Pollini, G. P.; Simoni, D. *Synthesis* **1982**, 653–655; (d) Maier, L. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *76*, 119–122; (e) McClure, C. K.; Mishra, P. K.; Grote, C. W. *J. Org. Chem.* **1997**, *62*, 2437–2441.
8. (a) Kaboudin, B.; Moradi, K. *Tetrahedron Lett.* **2005**, *46*, 2989–2991; (b) Kaboudin, B.; Moradi, K. *Synthesis* **2006**, 2339–2342; (c) Kaboudin, B.; Jafari, E. *Synthesis* **2006**, 3063–3066.
9. (a) Skropeta, D.; Schmidt, R. R. *Tetrahedron: Asymmetry* **2003**, *14*, 265–273; (b) Groaning, M. D.; Rowe, B. J.; Spilling, C. D. *Tetrahedron Lett.* **1998**, *39*, 5485–5488; (c) Rath, N. P.; Spilling, C. D. *Tetrahedron Lett.* **1994**, *35*, 227–230; (d) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1783–1784; (e) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1527–1533; (f) Sasai, H.; Bougauchi, M.; Arai, T.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 2717–2720; (g) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1779–1782; (h) Hammerschmidt, F.; Wuggenig, F. *Tetrahedron: Asymmetry* **1999**, *10*, 1709–1721; (i) Duxbury, J. P.; Cawley, A.; Thorton-Pett, M.; Wantz, L.; Warne, J. N. D.; Greatrex, R.; Brown, D.; Kee, T. P. *Tetrahedron Lett.* **1999**, *40*, 4403; (j) Ward, C. V.; Jiang, M.; Kee, T. P. *Tetrahedron Lett.* **2000**, *41*, 6181–6184.
10. (a) Rowe, B. J.; Spilling, C. D. *Tetrahedron: Asymmetry* **2001**, *12*, 1701–1708; (b) Pamies, O.; Backvall, J.-E. *J. Org. Chem.* **2003**, *68*, 4815–4818; (c) Zhang, Y.; Yuan, C.; Li, Z. *Tetrahedron* **2002**, *58*, 2973–2978; (d) Burk, M. J.; Stammers, T. A.; Straub, J. A. *Org. Lett.* **1999**, *1*, 387–390; (e) Kolodiazhnyi, O. I.; Griskkun, E. V.; Sheiko, S.; Demchuk, O.; Thoennessen, H.; Jones, P. G.; Schmutzler, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1645–1649; (f) Drescher, M.; Hammerschmidt, F. *Tetrahedron* **1997**, *53*, 4627–4636.
11. (a) Dhawan, D.; Redmore, D. *Phosphorus Sulfur* **1987**, *32*, 119–144; (b) Mikolajczyk, M.; Drawbowicz, J.; Kielbasinski, P. *Methods in Organic Chemistry (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21e, Chapter 8; (c) Kukhar, V. P.; Soloshonok, V. A.; Solodenko, V. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, *92*, 239–264.
12. (a) De Risi, C.; Perrone, D.; Dondoni, A.; Pollini, G. P.; Bertolasi, V. *Eur. J. Org. Chem.* **2003**, *10*, 1904–1914; (b) Yager, K. M.; Taylor, C. M.; Smith, A. B., III. *J. Am. Chem. Soc.* **1994**, *116*, 9377–9378; (c) Chung, S.-K.; Kang, D.-H. *Tetrahedron: Asymmetry* **1996**, *7*, 21–24.
13. (a) Blazis, V. J.; Koeller, K. J.; Spilling, C. D. *J. Org. Chem.* **1995**, *60*, 931–940; (b) Blazis, V. J.; De La Cruz, A.; Koeller, K. J.; Spilling, C. D. *Phosphorus Sulfur Silicon* **1993**, *75*, 159–162.
14. (a) Yamagishi, T.; Kusano, T.; Yokomatsu, T.; Shibuya, S. *Synlett* **2002**, 1471–1474; (b) Yokomatsu, T.; Yamagishi, T.; Suemune, K.; Shibuya, S. *Tetrahedron* **2002**, *58*, 2577–2583; (c) Szabo, A.; Jaszay, Z. M.; Hegedus, L.; Toke, L.; Petnehazy, I. *Tetrahedron Lett.* **2003**, *44*, 4603–4606; (d) Lewkowski, J. *J. Organomet. Chem.* **2003**, *681*, 225–227; (e) Grabowski, G.; Lewkowski, J. A.; Nazarski, R. B.; Skowronski, R.; Karolak-Wojciechowska, J. *Pol. J. Chem.* **1999**, *73*, 307–311; (f) Hamilton, R.; Walker, B.; Walker, B. J. *Tetrahedron Lett.* **1995**, *36*, 4451–4454; (g) Szabo, A.; Jaszay, Z. M.; Toke, L.; Penehazy, I. *Tetrahedron Lett.* **2004**, *45*, 1991–1994; (h) Yamagishi, T.; Kusano, T.; Kaboudin, B.; Yokomatsu, T.; Sakuma, C.; Shibuya, S. *Tetrahedron* **2003**, *59*, 767–772; (i) Kaboudin, B.; Haghighat, H.; Yokomatsu, T. *J. Org. Chem.* **2006**, *71*, 6604–6606; (j) Pirat, J.-L.; Monbrun, J.; Virieux, D.; Volle, J.-N.; Tillard, M.; Cristau, H.-J. *J. Org. Chem.* **2005**, *70*, 7035–7041.
15. Yamagishi, T.; Haruki, T.; Yokomatsu, T. *Tetrahedron* **2006**, *62*, 9210–9217.
16. (a) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S. *Chem. Lett.* **1995**, 423–424; (b) Ishitani, H.; Nagayama, S.; Kobayashi, S. *J. Org. Chem.* **1996**, *61*, 1902–1903; (c) Cozzi, P. G.; Simone, B. D.; Ronchi, A. U. *Tetrahedron Lett.* **1996**, *37*, 1691–1694; (d) Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1997**, *62*, 232–233; (e) Qian, C.; Huang, T. *J. Org. Chem.* **1998**, *63*, 4125–4128.
17. (a) Kobayashi, S.; Hachiya, I. *Tetrahedron Lett.* **1992**, *33*, 1625–1628; (b) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233–234; (c) Wang, R.; Lim, C.-M.; Tan, C.-H.; Lim, B.-K.; Sim, K.-Y.; Loh, T.-P. *Tetrahedron: Asymmetry* **1995**, *6*, 1825–1828; (d) Yu, L.; Chen, D.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 2169–2172.