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Chiral *N*-Phosphonyl Imine Chemistry: Asymmetric Additions of Ester Enolates for the Synthesis of β -Amino Acids

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Abstract

Chiral phosphonyl imines attached by 1-naphthyl protection group were found to react with lithium ester enolates smoothly and give chiral β -amino esters in good yields (70–88%) and up to excellent diastereoselectivity (>99:1 dr). Triisopropoxytitanium (IV) chloride was found to enhance diastereoselectivity when used as the Lewis acid promoter. The chiral auxiliary can be readily removed by treating with HBr to give free amino esters. The absolute structure has been unambiguously determined by converting one of the products into an authentic sample. This reaction provides an easy access to β -amino acid derivatives.

Keywords

chiral phosphoramidate; chiral *N*-phosphonyl imines; β -amino acid; lithium enolate; triisopropoxytitanium(IV) chloride

1. Introduction

There has been a continuing interest in the development of new methods for asymmetric synthesis β -amino acids and their derivatives in organic and medicinal chemistry, because β -amino acids belong to extremely important building blocks for studying natural products, pharmaceuticals and peptide and peptidomimetics (1-9). In addition, they are also precursors to chiral amino alcohols which are important chemical and biological molecules (10-11).

In recent years, many methods have been developed for the asymmetric synthesis of β -amino acids (12-27). Among these methods the reaction of chiral imines with ester enolates has become one of the most powerful and practical tool for this synthesis including the use of chiral *N*-sulfinyl imines (27-35).

Very recently, we have established novel chiral *N*-phosphonyl imine chemistry, and successfully utilized this chemistry for asymmetric aza-Darzens reaction (36), asymmetric aza-Henry reaction (37) and asymmetric Mannich reaction (38). As a continuing effort on this important new chemistry, we would like to report the addition of lithium ester enolates onto chiral phosphonyl imines in the presence of triisopropoxytitanium (IV) chloride for the asymmetric synthesis of chiral β -amino esters (Scheme 1). Initially, we utilized *N*-phosphonyl imines for this reaction that were substituted with either benzyl or iso-propyl groups. Unfortunately, the reaction of lithium ester enolates with these imines afforded either low diastereoselectivity or modest chemical yields. Next, we modified the structure of phosphonyl imine by using different groups on the two nitrogen atoms of the auxiliary.

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Pleasantly, we found that the replacement of the original protection groups with a 1-naphthyl counterpart can enhance diastereoselectivity and provide a good chemical yield of 81% (entry 1, Table 1). Obviously, the bulky 1-naphthyl groups showed a larger steric effect on asymmetric induction during this addition process.

Imine **1b** was then chosen as the model substrate for further optimizing reaction conditions by changing bases for enolate generation (Table 2). Among the various bases listed in Table 2, LDA was found to be the best candidate. Other bases such as *n*-BuLi, LiHMDS and (Me₃Si)₂NK gave either poor diastereoselectivity or low yields. Even though LiHMDS gave almost the same yield as LDA did under the same condition, diastereoselectivity was decreased to 79:21 (entry 3, Table 2). Interestingly, the potassium enolate generated by using (Me₃Si)₂NK as the base afforded a much lower yield of 45% (entry 4, Table 2), which could be attributed to the fact that potassium cation cannot act as a good Lewis acid for phosphonyl imine activation.

The solvent effect was also examined for this reaction. Among the three common solvents including THF, Et₂O and CH₂Cl₂, THF was found to be the best choice regarding both chemical yield and diastereoselectivity. For the cases of Et₂O and CH₂Cl₂, very poor yields (25% and 35%, respectively) and diastereoselectivity (55:45 and 70:30, respectively) were obtained (entries 5 and 6, Table 2). Similar to the sulfinyl imine-based systems, triisopropoxytitanium(IV) chloride was proven to be beneficial to diastereoselectivity by acting as a Lewis acid promoter (entry 7, Table 2) (31-32,36).

Based on the above optimal condition, we then examined the scope of substrates. As shown in Table 3, a variety of phosphoryl imines derived from benzaldehyde (entries 4 and 5, Table 3), 1-naphthaldehyde (entry 13 Table 3), aldehyde containing electron withdrawing groups on aromatic rings (entries 6–8, 11–12, Table 3) and electron donating groups on aromatic rings (entries 1–3, 9–10, Table 3) are all suitable for this reaction to give good chemical yields (70–88%). Good to excellent diastereoselectivities, ranging from 77:23 to >99:1, were obtained in all cases that were examined. Slightly better diastereoselectivities were obtained in cases of 2-substituted benzaldehyde-derived imines. Besides benzyl acetate, methyl acetate and *t*-butyl acetate were also proven to be suitable substrates for generating lithium enolates to give good to excellent yields and diastereoselectivities. To determine absolute structure, the product **5ba** was subjected to deprotection reaction with HBr/MeOH at room temperature (37) followed by protection using (Boc)₂O in the presence of triethylamine. The *in situ* procedure resulted in methyl (*R*)-*N*-*t*-BOC-3-phenyl-β-alanineate **6** which is a known compound. An overall yield of 82% was obtained under these conditions, which enables the present method to be an efficient approach to 3-aryl-β-alanines and their ester derivatives (Scheme 2) (27,39-40).

In summary, a new method has been developed for the asymmetric synthesis of chiral β-amino esters in good to excellent diastereoselectivity (up to >99:1 dr) and good yields (up to 88%). Triisopropoxytitanium (IV) chloride was found to be an efficient Lewis acid promoter for the asymmetric addition of lithium ester enolates to chiral phosphonyl imines. Various aromatic phosphonyl imines with both electron withdrawing and electron donating groups on their rings are suitable substrates for this reaction.

Experimental Section

General Methods

All solvents used for the reactions were purified and dried by passing through an alumina column immediately prior to use. THF was distilled freshly from sodium/benzophenone ketyl. Chiral phosphonyl imines were prepared according to the reported methods (36-38).

The addition reactions were performed in oven-dried vials under protection of nitrogen gas. Flash column chromatography was performed using silica gel (Merck 60, 230–400 mesh). NMR spectra were recorded at 500/300, 125, 202 MHz for ^1H , ^{13}C and ^{31}P respectively. Internal TMS ($\delta = 0.0$ ppm) was used as the reference for ^1H NMR and ^{13}C NMR. ^{31}P NMR spectra were referenced to external H_3PO_4 . Melting points were measured in open capillaries. 2 M LDA solution in THF, 1 M TiCl_4 solution in dichloromethane and $\text{TiCl}(\text{O}i\text{Pr})_3$ were obtained from Aldrich. These and other chemicals were used as obtained from commercial sources without further purifications.

Enolate addition to chiral N-phosphonyl imines

Into an oven dried reaction vial flushed with N_2 were loaded ester (0.6 mmol) and 3.0 mL of dry THF. The reaction vial was cooled to -78°C and 0.33 mL of 2 M LDA solution in THF was added dropwise with stirring over 10 minutes and the solution was stirred for another 30 min at -78°C . To this solution, $\text{TiCl}(\text{O}i\text{Pr})_3$ (0.72 mmol) in 0.5 mL THF was added dropwise. The solution was stirred for another 1 h. Into the resulting mixture was added dropwise 3.0 mL of THF off phosphonyl imine **1** (0.3 mmol). The reaction was stirred at -78°C for 6 h and was quenched with 1.0 mL of saturated NH_4Cl solution followed by 5.0 mL water at room temperature. The mixture was transferred into a separation funnel, and the aqueous layer was extracted with 2×20 mL of ethyl acetate. Combined organic layers were dried on anhydrous sodium sulfate. Sodium sulfate was filtered off and evaporated the organic solvent. Purification by column obtained adducts **5**.

5aa—White solid. Mp $60\text{--}62^\circ\text{C}$. $[\alpha]_D^{25} = +2.2^\circ$ ($c = 0.46$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 8.13 (d, $J = 8.4$ Hz, 1H), 7.92 (d, $J = 7.2$ Hz, 1H), 7.85–7.88 (m, 1H), 7.76–7.80 (m, 3H), 7.64 (d, $J = 8.1$ Hz, 1H), 7.44–7.58 (m, 3H), 7.30–7.43 (m, 6H), 6.98–7.03 (m, 1H), 6.86 (d, $J = 8.1$ Hz, 1H), 4.87 (dd, $J = 11.7, 16.2$ Hz, 1H), 4.61–4.74 (m, 1H), 4.47 (dd, $J = 12.0, 16.2$ Hz, 1H), 4.10 (dd, $J = 12.0, 17.4$ Hz, 1H), 3.98 (t, $J = 11.7$ Hz, 1H), 3.80 (s, 3H), 3.51 (dd, $J = 8.4, 17.7$ Hz, 1H), 3.49 (s, 3H), 3.07–3.24 (m, 2H), 2.50 (dd, $J = 9.3, 15.9$ Hz, 1H), 1.99–2.08 (m, 1H), 1.93–1.97 (m, 1H), 1.73–1.77 (m, 1H), 1.49–1.58 (m, 2H), 1.41–1.49 (m, 1H), 1.08–1.35 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 171.2 (d, $J = 1.0$ Hz), 156.9, 135.4, 135.4, 134.4, 134.3, 133.5, 133.2, 135.4, 135.4, 134.4, 134.3, 133.5, 133.2, 131.2, 130.4, 130.3, 130.3, 129.6, 128.7, 128.6, 128.5, 127.4, 126.8, 126.0, 125.6, 125.5, 125.4, 125.3, 125.1, 124.4, 123.0, 122.4, 120.5, 110.9, 65.3 (d, $J = 10.1$ Hz), 64.0 (d, $J = 8.3$ Hz), 55.1, 51.2, 50.4, 44.8, 44.8, 44.3, 44.3, 40.7, 40.6, 30.3, 30.2, 29.8, 29.7, 24.3, 24.2, 24.2; ^{31}P NMR (202 MHz, CDCl_3): δ 28.5.

5ab—Liquid. $[\alpha]_D^{25} = +8.0^\circ$ ($c = 0.43$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 8.13 (d, $J = 8.4$ Hz, 1H), 7.97 (d, $J = 6.9$ Hz, 1H), 7.85–7.88 (m, 1H), 7.57–7.75 (m, 3H), 7.63 (d, $J = 8.1$ Hz, 1H), 7.46–7.58 (m, 3H), 7.32–7.43 (m, 6H), 6.99–7.04 (m, 1H), 6.88 (d, $J = 8.4$ Hz, 1H), 4.96 (dd, $J = 11.7, 16.2$ Hz, 1H), 4.64 (ddd, $J = 4.5, 11.4, 21.6$ Hz, 1H), 4.47 (dd, $J = 9.9, 16.2$ Hz, 1H), 4.11 (dd, $J = 11.7, 17.4$ Hz, 1H), 4.00 (t, $J = 11.4$ Hz, 1H), 3.76 (s, 3H), 3.49 (dd, $J = 8.4, 17.4$ Hz, 1H), 3.07–3.20 (m, 2H), 2.44 (dd, $J = 9.9, 14.7$ Hz, 1H), 2.05 (dd, $J = 4.5, 14.7$ Hz, 1H), 1.82–1.88 (m, 1H), 1.65–1.67 (m, 1H), 1.38–1.51 (m, 3H), 1.25 (s, 9H), 1.04–1.24 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 169.9 (d, $J = 1.4$ Hz), 157.1, 135.4, 135.4, 134.5, 134.5, 133.4, 133.1, 131.1, 130.4, 130.2, 129.8, 128.6, 128.5, 128.4, 127.3, 126.7, 125.9, 125.4, 125.4, 125.3, 125.2, 125.1, 125.0, 124.2, 122.8, 122.3, 120.2, 110.9, 80.1, 65.3 (d, $J = 9.8$ Hz), 64.2 (d, $J = 8.9$ Hz), 55.1, 50.9, 44.8, 44.8, 44.3, 44.3, 42.3, 42.3, 30.2, 30.1, 29.9, 29.8, 27.8, 24.3, 24.2; ^{31}P NMR (202 MHz, CDCl_3): δ 28.7.

5ac—White solid. Mp $82\text{--}84^\circ\text{C}$. $[\alpha]_D^{25} = +3.4^\circ$ ($c = 0.32$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 8.11 (d, $J = 8.1$ Hz, 1H), 7.91 (d, $J = 6.9$ Hz, 1H), 7.64–7.85 (m, 5H), 7.28–7.55

(m, 12H), 7.16–7.20 (m, 2H), 6.90–7.01 (m, 1H), 6.86 (d, $J = 8.4$ Hz, 1H), 4.89 (d, $J = 9.0$ Hz, 2H), 4.85–4.99 (m, 1H), 4.67 (ddd, $J = 4.2, 9.9, 21.6$ Hz, 1H), 4.45 (dd, $J = 11.1, 15.9$ Hz, 1H), 4.08 (dd, $J = 12.0, 17.7$ Hz, 1H), 3.95 (t, $J = 11.7$ Hz, 1H), 3.74 (s, 3H), 3.46 (dd, $J = 8.7, 17.7$ Hz, 1H), 3.05–3.19 (m, 2H), 2.55 (dd, $J = 11.1, 15.3$ Hz, 1H), 2.01 (dd, $J = 4.2, 15.6$ Hz, 1H), 1.89–1.96 (m, 1H), 1.70–1.71 (m, 1H), 1.39–1.52 (m, 3H), 1.04–1.25 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.6 (d, $J = 1.0$ Hz), 157.1, 135.7, 135.4, 135.4, 134.4, 134.4, 133.5, 133.2, 131.2, 130.4, 130.2, 129.8, 128.8, 128.6, 128.5, 128.4, 128.1, 127.4, 126.8, 126.0, 125.5, 125.5, 125.3, 125.3, 125.1, 124.4, 122.9, 122.4, 120.5, 111.0, 66.0, 65.3 (d, $J = 10.3$ Hz), 64.2 (d, $J = 8.9$ Hz), 55.2, 50.7, 44.9, 44.9, 44.4, 44.3, 41.0, 40.9, 30.3, 30.2, 29.9, 29.8, 24.4, 24.2; ^{31}P NMR (202 MHz, CDCl_3): δ 28.5.

5ba—White solid. Mp 174–176 °C. $[\alpha]_D^{25} = -45.7^\circ$ ($c = 0.11$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 8.17 (d, $J = 8.1$ Hz, 1H), 7.82–7.98 (m, 3H), 7.71–7.80 (m, 3H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.46–7.59 (m, 3H), 7.36–7.43 (m, 3H), 7.27–7.32 (m, 4H), 7.15–7.20 (m, 1H), 4.77 (dd, $J = 10.8, 15.0$ Hz, 1H), 4.49 (t, $J = 14.7$ Hz, 1H), 4.31–4.44 (m, 1H), 4.14 (dd, $J = 11.7, 17.4$ Hz, 1H), 3.41 (s, 3H), 3.31–3.46 (m, 1H), 2.90–3.17 (m, 2H), 2.05–2.09 (m, 1H), 1.95 (dd, $J = 8.1, 15.6$ Hz, 1H), 1.81 (dd, $J = 4.5, 15.3$ Hz, 1H), 1.71–1.76 (m, 1H), 1.46–1.57 (m, 2H), 0.90–1.38 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.5, 143.5, 143.6, 135.3, 135.3, 134.0, 134.0, 133.6, 133.2, 131.5, 130.4, 128.7, 128.6, 128.5, 128.4, 127.7, 127.4, 126.9, 126.8, 126.6, 126.3, 126.1, 125.5, 125.5, 125.4, 125.4, 125.2, 124.4, 123.2, 122.4, 64.9 (d, $J = 10.3$ Hz), 64.0 (d, $J = 8.9$ Hz), 51.9, 51.3, 44.9, 44.1, 44.0, 42.6, 42.5, 30.1, 30.0, 29.6, 29.5, 24.3, 24.2; ^{31}P NMR (202 MHz, CDCl_3): δ 27.4.

5bb—White solid. Mp 74–76 °C. $[\alpha]_D^{25} = -24.5^\circ$ ($c = 0.44$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 8.15 (d, $J = 8.4$ Hz, 1H), 7.89 (d, $J = 6.9$ Hz, 1H), 7.64–7.84 (m, 5H), 7.45–7.55 (m, 2H), 7.34–7.44 (m, 4H), 7.27–7.34 (m, 8H), 7.07–7.20 (m, 3H), 4.77–4.90 (m, 3H), 4.36–4.57 (m, 2H), 4.10 (dd, $J = 10.8, 16.5$ Hz, 1H), 3.48 (t, $J = 9.9$ Hz, 1H), 3.29 (dd, $J = 8.4, 17.4$ Hz, 1H), 2.90–3.17 (m, 2H), 2.02–2.13 (m, 2H), 1.86 (dd, $J = 4.5, 15.3$ Hz, 1H), 1.72–1.76 (m, 1H), 1.43–1.61 (m, 2H), 0.88–1.37 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.8, 169.9, 169.9, 143.5, 143.4, 135.4, 135.3, 135.3, 134.0, 134.0, 133.5, 133.2, 131.4, 130.4, 128.6, 128.6, 128.5, 128.4, 128.1, 128.1, 127.7, 127.4, 126.9, 126.9, 126.5, 126.1, 125.5, 125.5, 125.4, 125.4, 125.1, 124.4, 123.1, 122.3, 66.0, 64.9 (d, $J = 10.3$ Hz), 64.0 (d, $J = 8.4$ Hz), 52.0, 45.0, 45.0, 44.0, 44.0, 42.8, 42.7, 30.1, 30.0, 29.6, 29.5, 24.3, 24.2; ^{31}P NMR (202 MHz, CDCl_3): δ 27.5.

5c—White solid. Mp 78–80 °C. $[\alpha]_D^{25} = -19.0^\circ$ ($c = 0.43$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 8.12 (d, $J = 8.4$ Hz, 1H), 7.87 (d, $J = 6.9$ Hz, 1H), 7.78–7.82 (m, 2H), 7.65–7.76 (m, 3H), 7.50–7.55 (m, 1H), 7.42–7.46 (m, 2H), 7.35–7.40 (m, 4H), 7.27–7.30 (m, 3H), 7.26–7.29 (m, 2H), 7.13–7.20 (m, 2H), 6.98–7.09 (m, 2H), 4.73–4.97 (m, 4H), 3.98 (t, $J = 15.3$ Hz, 1H), 4.87 (dd, $J = 11.7, 17.4$ Hz, 1H), 3.91 (t, $J = 10.8$ Hz, 1H), 3.51 (dd, $J = 8.4, 17.4$ Hz, 1H), 3.02–3.23 (m, 2H), 2.27 (dd, $J = 8.7, 15.9$ Hz, 1H), 1.97–2.09 (m, 2H), 1.71–1.78 (m, 1H), 1.49–1.58 (m, 2H), 1.34–1.44 (m, 1H), 1.06–1.34 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 169.9, 161.1, 159.1, 135.4, 135.1, 135.1, 134.0, 133.9, 133.5, 133.2, 131.1, 130.4, 129.4, 129.4, 129.1, 129.0, 128.6, 128.6, 128.4, 128.2, 127.7, 127.0, 126.3, 126.1, 125.5, 125.5, 125.4, 125.4, 125.2, 124.5, 124.3, 124.2, 123.0, 122.2, 115.8, 155.6, 66.1, 65.0 (d, $J = 10.4$ Hz), 64.1 (d, $J = 8.5$ Hz), 47.1, 44.9, 44.9, 44.0, 44.0, 41.0, 40.9, 30.1, 30.1, 29.6, 29.5, 24.3, 24.2; ^{31}P NMR (202 MHz, CDCl_3): δ 27.8.

5d—White solid. Mp 78–80 °C. $[\alpha]_D^{25} = -14.2^\circ$ ($c = 0.35$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 8.17 (d, $J = 8.4$ Hz, 1H), 7.92 (d, $J = 6.9$ Hz, 1H), 7.78–7.82 (m, 2H), 7.65–7.75 (m, 3H), 7.53–7.58 (m, 1H), 7.39–7.49 (m, 5H), 7.35–7.37 (m, 3H), 7.24–7.33 (m, 4H),

7.11–7.18 (m, 3H), 4.83 (d, $J = 2.1$ Hz, 2H), 4.80–4.93 (m, 1H), 4.49 (t, $J = 15.3$ Hz, 1H), 4.18 (dd, $J = 12.0, 17.4$ Hz, 1H), 4.01 (t, $J = 11.1$ Hz, 1H), 3.33 (dd, $J = 8.1, 17.4$ Hz, 1H), 2.92–3.17 (m, 2H), 2.08 (dd, $J = 4.2, 15.6$ Hz, 1H), 2.04–2.06 (m, 1H), 1.72–1.84 (m, 2H), 1.51–1.61 (m, 2H), 0.94–1.39 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.1, 140.1, 135.3, 135.2, 135.1, 133.9, 133.9, 133.6, 133.2, 131.8, 131.4, 130.4, 129.7, 129.7, 128.7, 128.6, 128.5, 128.4, 128.2, 128.2, 127.7, 127.0, 126.9, 126.6, 126.1, 125.6, 125.5, 125.5, 125.4, 125.1, 124.5, 123.2, 122.2, 66.1, 64.9 (d, $J = 10.4$ Hz), 64.0 (d, $J = 8.9$ Hz), 48.8, 44.9, 44.1, 44.1, 39.5, 39.5, 30.2, 30.1, 29.6, 29.5, 24.3, 24.2; ^{31}P NMR (202 MHz, CDCl_3): δ 27.9.

5e—White solid. Mp 64–66 °C. $[\alpha]_D^{25} = -7.0^\circ$ ($c = 0.37$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 8.19 (d, $J = 8.1$ Hz, 1H), 7.93 (d, $J = 6.9$ Hz, 1H), 7.78–7.82 (m, 2H), 7.65–7.74 (m, 3H), 7.54–7.59 (m, 2H), 7.40–7.50 (m, 4H), 7.35–7.40 (m, 3H), 7.25–7.29 (m, 3H), 7.19–7.21 (m, 2H), 7.11–7.15 (m, 2H), 4.78–4.91 (m, 3H), 4.50 (t, $J = 15.3$ Hz, 1H), 4.15–4.27 (m, 2H), 3.27 (dd, $J = 8.1, 17.4$ Hz, 1H), 2.96–3.16 (m, 2H), 2.07–2.19 (m, 2H), 1.61–1.73 (m, 2H), 1.51–1.54 (m, 2H), 0.96–1.42 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.1, 141.7, 135.3, 135.2, 135.2, 133.9, 133.8, 133.6, 133.2, 132.9, 131.4, 130.4, 129.9, 128.9, 128.7, 128.6, 128.4, 128.3, 128.2, 127.7, 127.7, 126.9, 126.6, 126.1, 125.6, 125.5, 125.5, 125.4, 125.1, 124.5, 123.2, 122.2, 122.1, 66.1, 64.9 (d, $J = 10.3$ Hz), 64.0 (d, $J = 8.4$ Hz), 50.9, 44.9, 44.9, 44.2, 39.2, 39.2, 30.2, 30.1, 29.6, 29.5, 24.3, 24.2; ^{31}P NMR (202 MHz, CDCl_3): δ 27.4.

5f—White solid. Mp 66–68 °C. $[\alpha]_D^{25} = -28.6^\circ$ ($c = 0.22$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 8.19 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 7.2$ Hz, 1H), 7.78–7.83 (m, 2H), 7.72–7.73 (m, 2H), 7.65 (d, $J = 8.1$ Hz, 1H), 7.52–7.57 (m, 1H), 7.36–7.50 (m, 7H), 7.25–7.28 (m, 3H), 7.13–7.21 (m, 2H), 7.06–7.10 (m, 3H), 4.81 (s, 2H), 4.61–4.78 (m, 2H), 4.48 (t, $J = 15.3$ Hz, 1H), 4.21 (dd, $J = 11.7, 17.4$ Hz, 1H), 3.55 (t, $J = 9.9$ Hz, 1H), 3.28 (dd, $J = 8.1, 17.4$ Hz, 1H), 2.77–3.16 (m, 2H), 2.38 (s, 3H), 2.04–2.09 (m, 1H), 1.80–1.97 (m, 1H), 1.70–1.78 (m, 1H), 1.39–1.54 (m, 2H), 0.96–1.31 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.1, 141.1, 135.4, 135.3, 133.9, 133.9, 133.8, 133.6, 133.2, 131.5, 130.6, 130.5, 128.7, 128.5, 128.4, 128.1, 127.7, 127.2, 127.1, 126.9, 126.7, 126.3, 126.0, 125.6, 125.5, 125.5, 125.4, 125.2, 124.5, 123.2, 122.5, 66.0, 65.0 (d, $J = 10.4$ Hz), 63.7 (d, $J = 8.5$ Hz), 48.2, 44.8, 44.8, 44.2, 44.1, 41.1, 41.1, 30.1, 30.1, 29.6, 29.5, 24.3, 24.3, 19.3; ^{31}P NMR (202 MHz, CDCl_3): δ 27.8.

5g—White solid. Mp 76–78 °C. $[\alpha]_D^{25} = -24.4^\circ$ ($c = 0.22$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 8.17 (d, $J = 8.7$ Hz, 1H), 7.91 (d, $J = 6.9$ Hz, 1H), 7.77–7.83 (m, 2H), 7.73–7.74 (m, 2H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.51–7.57 (m, 3H), 7.36–7.50 (m, 4H), 7.26–7.29 (m, 3H), 7.05–7.14 (m, 3H), 6.96–7.03 (m, 2H), 4.87–5.01 (m, 1H), 4.76 (d, $J = 2.1$ Hz, 2H), 4.69–4.74 (m, 1H), 4.48 (t, $J = 15.3$ Hz, 1H), 4.12 (dd, $J = 11.4, 17.4$ Hz, 1H), 3.20 (dd, $J = 8.7, 17.4$ Hz, 1H), 3.08–3.16 (m, 1H), 2.79–2.87 (m, 2H), 2.52 (s, 3H), 2.42 (dd, $J = 9.3, 14.4$ Hz, 1H), 2.35 (s, 3H), 2.02–2.05 (m, 1H), 1.83 (dd, $J = 6.6, 14.7$ Hz, 1H), 1.69–1.73 (m, 1H), 1.37–1.53 (m, 2H), 0.85–1.27 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3): δ 169.7 (d, $J = 1$ Hz), 138.1, 136.4, 135.9, 135.4, 135.4, 135.4, 133.7, 133.6, 133.6, 133.3, 131.5, 130.7, 130.5, 129.0, 128.6, 128.6, 128.4, 128.1, 128.0, 127.7, 127.3, 126.9, 126.9, 126.1, 125.6, 125.5, 125.5, 125.2, 124.7, 123.2, 122.5, 66.1, 64.4 (d, $J = 10.9$ Hz), 63.7 (d, $J = 8.4$ Hz), 48.0, 44.9, 44.9, 43.4, 43.4, 40.3, 40.2, 30.3, 30.2, 29.4, 29.3, 24.3, 24.3, 21.2, 21.1; ^{31}P NMR (202 MHz, CDCl_3): δ 27.7.

5h—White solid. Mp 178–180 °C. $[\alpha]_D^{25} = -43.3^\circ$ ($c = 0.32$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 7.97 (d, $J = 7.8$ Hz, 1H), 7.89 (d, $J = 7.8$ Hz, 1H), 7.83–7.86 (m, 2H), 7.77 (d, $J =$

7.2 Hz, 1H), 7.71–7.74 (m, 2H), 7.62 (d, $J = 6.6$ Hz, 1H), 7.44–7.54 (m, 5H), 7.35–7.41 (m, 1H), 7.04–7.11 (m, 4H), 4.52–4.62 (m, 3H), 4.31 (dd, $J = 11.7, 15.9$ Hz, 1H), 4.21 (dd, $J = 7.5, 17.1$ Hz, 1H), 3.69 (t, $J = 11.7$ Hz, 1H), 3.09–3.12 (m, 2H), 2.32 (dd, $J = 5.1, 15.3$ Hz, 1H), 2.10 (dd, $J = 6.6, 15.3$ Hz, 1H), 1.70–1.72 (m, 1H), 1.55–1.63 (m, 3H), 1.23 (s, 9H), 1.14–1.30 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.2, 141.9, 141.9, 135.1, 135.1, 133.6, 133.6, 133.5, 133.4, 132.7, 131.2, 130.7, 128.7, 128.6, 128.3, 127.9, 127.3, 127.2, 126.0, 125.9, 125.7, 125.4, 125.4, 125.3, 124.6, 122.8, 122.7, 81.0, 64.9 (d, $J = 9.7$ Hz), 63.6 (d, $J = 9.4$ Hz), 51.8, 44.5, 44.4, 44.2, 43.7, 43.6, 29.6, 29.5, 29.3, 29.2, 27.8, 24.2, 24.2; ^{31}P NMR (202 MHz, CDCl_3): δ 27.3.

5i—White solid. Mp 193–195 °C. $[\alpha]_D^{25} = -31.5^\circ$ ($c = 0.39$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 7.97 (d, $J = 8.1$ Hz, 1H), 7.89 (d, $J = 8.1$ Hz, 1H), 7.84–7.86 (m, 2H), 7.77 (d, $J = 6.9$ Hz, 1H), 7.71–7.74 (m, 2H), 7.61 (d, $J = 7.2$ Hz, 1H), 7.44–7.55 (m, 5H), 7.35–7.42 (m, 2H), 7.20–7.25 (m, 1H), 7.02–7.05 (m, 2H), 4.49–4.64 (m, 3H), 4.30 (dd, $J = 11.7, 15.9$ Hz, 1H), 4.21 (dd, $J = 7.8, 17.1$ Hz, 1H), 3.69 (t, $J = 10.8$ Hz, 1H), 3.06–3.15 (m, 2H), 2.32 (dd, $J = 5.1, 15.3$ Hz, 1H), 2.10 (dd, $J = 6.6, 15.3$ Hz, 1H), 1.70–1.74 (m, 1H), 1.56–1.59 (m, 3H), 1.23 (s, 9H), 1.15–1.28 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3): δ 170.4, 142.7, 135.4, 135.3, 133.8, 133.8, 133.7, 133.6, 131.5, 131.5, 130.9, 128.9, 128.8, 128.5, 127.6, 127.4, 126.2, 126.2, 126.0, 125.7, 125.6, 124.9, 123.0, 122.9, 121.1, 81.3, 65.2 (d, $J = 8.0$ Hz), 63.7 (d, $J = 9.2$ Hz), 52.1, 44.7, 44.7, 44.4, 44.4, 43.9, 43.9, 29.9, 29.8, 29.6, 29.4, 28.1, 24.4; ^{31}P NMR (202 MHz, CDCl_3): δ 26.7.

5j—White solid. Mp 74–76 °C. $[\alpha]_D^{25} = -7.9^\circ$ ($c = 0.29$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 8.22 (d, $J = 8.4$ Hz, 1H), 8.06 (d, $J = 8.4$ Hz, 1H), 7.95 (d, $J = 7.2$ Hz, 1H), 7.89–7.93 (m, 1H), 7.73–7.84 (m, 4H), 7.59–7.66 (m, 2H), 7.53–7.56 (m, 1H), 7.43–7.51 (m, 5H), 7.30–7.36 (m, 4H), 7.18–7.25 (m, 3H), 6.99–7.07 (m, 3H), 5.19–5.28 (m, 1H), 4.79–4.88 (m, 1H), 4.81 (s, 2H), 4.49 (t, $J = 15.0$ Hz, 1H), 4.04 (dd, $J = 11.7, 17.4$ Hz, 1H), 3.68 (t, $J = 9.9$ Hz, 1H), 2.97–3.13 (m, 2H), 2.65–2.72 (m, 1H), 2.15–2.16 (m, 1H), 2.06–2.09 (m, 1H), 1.38–1.71 (m, 4H), 0.84–1.36 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3): δ 170.1, 139.0, 135.3, 135.2, 135.2, 133.9, 133.8, 133.6, 133.1, 131.5, 130.3, 130.0, 129.1, 128.7, 128.5, 128.3, 128.1, 128.1, 127.8, 126.8, 126.8, 126.3, 126.1, 125.7, 125.6, 125.5, 125.4, 125.4, 125.3, 125.1, 124.3, 123.2, 122.7, 122.2, 66.0, 64.3 (d, $J = 10.4$ Hz), 63.7 (d, $J = 8.5$ Hz), 44.8, 44.8, 43.8, 43.8, 41.8, 41.8, 29.9, 29.8, 29.5, 29.4, 24.3, 24.1; ^{31}P NMR (202 MHz, CDCl_3): δ 27.4.

Removal of N-phosphonyl group of 5ba and synthesis of N-Boc protected β -amino ester 6

Into a 50 mL round flask were loaded 309 mg of **5ba** (0.5 mmol) and 15.0 mL of methanol. To this solution was added 48% aq. HBr (5 mL), and the reaction was stirred at r.t. for 8 h. The cleavage was monitored by TLC. Volatiles were removed to obtain yellow oil, to which was added 15.0 mL of methylenechloride and 0.70 mL of triethyl amine (5.0 mmol) at room temperature. The resulting mixture was added 0.654 g of di-*tert*-butyl dicarbonate (3.0 mmol) and stirred at room temperature overnight. The crude reaction mixture obtained after standard aqueous work-up was purified by using silica gel column chromatography (230–400 mesh) with 15% ethyl acetate in hexanes as the eluent. *N*-Boc β -amino ester **6** was obtained as a white solid in 82% yield (114 mg). $[\alpha]_D^{25} = +14.7^\circ$ ($c = 1.02$, CHCl_3); ^1H NMR (300 MHz, CDCl_3): δ 7.22–7.36 (m, 5H), 5.44 (s, br, 1H), 5.10 (s, br, 1H), 3.61 (s, 3H), 2.77–2.92 (m, 2H), 1.42 (s, 9H).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Addition of lithium ester enolates to *N*-phosonyl imines.

Scheme 2.
Removal of chiral phosphonyl auxiliary of **5ba**

Table 1Optimization of chiral phosphonyl auxiliary.^a

entry	imine	R	yield (%) ^b	dr ^c
1	1b	1-naphthyl	81	82:18
2	2	Ph	82	77:23
3	3	2-MeO-Ph	80	72:28
4	4	<i>i</i> Pr	60	76:24

^a Reaction condition: 0.1 mmol imine, 0.2 mmol ester, 0.22 mmol base, 2 equiv TiCl(O*i*Pr)₃, 2 mL solvent.^b Isolated yield.^c Determined by ³¹P NMR.

Table 2Solvent effect on the asymmetric reaction of phosphonyl imines with lithium ester enolates^a

entry	base	solvent	temp (°C)	yield (%)	dr ^b
1	LDA	THF	-78	81	82:18
2	n-BuLi	THF	-78	50	70:30
3	LiHMDS	THF	-78	83	79:21
4	(Me ₃ Si) ₂ NK	THF	-78	45	72:28
5	LDA	Et ₂ O	-78	25	55:45
6	LDA	CH ₂ Cl ₂	-78	35	70:30
7	LDA	THF	-78	80	69:31 ^c

^aReaction condition: 0.1 mmol imine, 0.2 mmol ester, 0.22 mmol base, 2 equiv TiCl(OiPr)₃, 2 mL solvent.^bDetermined by ³¹P NMR.^cNo TiCl(OiPr)₃ was added.

Table 3

Examination of the scope of reaction substrates^a

entry	imine	Ar	R	product	yield (%) ^b	dr ^c
1	1a	2-MeO-Ph	Me	5aa	84	96:4
2	1a	2-MeO-Ph	<i>t</i> -Bu	5ab	75	98:2
3	1a	2-MeO-Ph	Bn	5ac	83	>99:1
4	1b	Ph	Me	5ba	88	77:23
5	1b	Ph	Bn	5bb	81	82:18
6	1c	2-F-Ph	Bn	5c	79	94:6
7	1d	2-Cl-Ph	Bn	5d	73	93:7
8	1e	2-Br-Ph	Bn	5e	83	93:7
9	1f	2-Me-Ph	Bn	5f	80	>99:1
10	1g	2,6-di-Me-Ph	Bn	5g	70	>99:1
11	1h	4-Cl-Ph	<i>t</i> -Bu	5h	77	97:3 ^d
12	1i	4-Br-Ph	<i>t</i> -Bu	5i	80	94:6 ^d
13	1j	1-Naphthyl	Bn	5j	88	85:15

^a All the reactions were run in 0.05 M solution of THF.^b Isolated yields after column.^c Diastereoselectivities were determined by ³¹P NMR spectra of crude samples.^d Ti(OiPr)₄ was used.