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Asymmetric synthesis of α -alkenyl homoallylic primary amines via 1,2-addition of Grignard reagent to α,β -unsaturated phosphonyl imines

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Abstract

A series of chiral *N*-phosphonyl protected α -alkenyl homoallylic primary amines were synthesized by asymmetric addition of allylmagnesium bromide Grignard reagent towards chiral α,β -unsaturated imines. Only 1,2-adduct was obtained for all the imines with good yields and excellent diastereoselectivities. The chiral auxiliary could be easily removed under simple conditions, giving free multiple functionalized primary amines.

1. Introduction

Homoallylic amines are key building blocks for the synthesis of biologically active compounds and are often found in the structures of natural products and pharmaceuticals.^{1,2} Among them, α -alkenyl homoallylic amines are extremely important in medicinal chemistry, because they are very useful precursors to derivate into heterocycles, such as piperidine³, pyrrolidine⁴, indole⁵ and pyrans.⁶ Furthermore, these compounds were found to play a crucial role in multiple drug resistance reversing activity and cancer treatment.^{7–9} Given the importance of such compounds, there have been several versatile approaches were reported for their preparations, such as allylic reagents addition to imines,¹⁰ amination of allylic compounds,¹¹ aminoalkylation of aromatic compounds,¹² ring-closing reactions¹³ and other relate reactions.¹⁴ However, these methods are prone to focus on synthesis of simple homoallylic amines. Furthermore, metal catalysts or metal reagents were usually needed in these methods.¹⁴ To our knowledge, few reports about the synthesis of α -alkenyl homoallylic primary amines were documented due to difficult regulation of multiple functional groups.¹⁵ Since their present and potential usage resulting from multiple reactive sites, systematic investigations of synthesis for them are urgently needed, especially on their asymmetric manner.

In recent years, our groups have developed several novel chiral phosphonyl auxiliaries, which are proven to induce good chemical yields and excellent diastereoselectivities in diverse types of imine addition reactions. Up to now, successful examples have been

achieved in aza-Henry reaction¹⁶, aza-Mannich reaction¹⁷, Grignard reaction¹⁸, Strecker reaction¹⁹ and so on. Owing to their advantages in wide versatility and high efficiency, we tried to utilize this chiral auxiliary in more asymmetric addition reactions. In this paper, we reported for the first time the asymmetric addition of allylmagnesium bromide to chiral α,β -unsaturated imines in the absence of any additives with excellent yields.

2. Results and discussion

Preparation of chiral α,β -unsaturated imines was the initial task. In our previous works,¹⁶ we found that the auxiliaries with isopropyl moiety usually have a strong steric hinderance, which means few choices for nucleophilic attack, thus bringing higher stereoselectivities during addition processes. We chose phosphoramidate **1** reacting with cinnamaldehyde for the synthesis of imine, and the condensation conditions were carefully investigated (Table 1). As shown in Table 1, only the titanium chloride was the suitable condensation reagent among several classical methods (entries 1–6).²⁰ The highest yield was found the reaction was carried out in the presence of triethylamine with dichloromethane as solvent at room temperature for 48 h (entry 12).

Under the optimized reaction conditions, eleven chiral *N*-phosphonyl α,β -unsaturated imines containing the isopropyl group were synthesized from cinnamaldehydes. The results were shown in Table 2. Modest to good chemical yields (69–83%) were achieved for this synthesis. Besides, these α,β -unsaturated imines are stable enough to be stored in the refrigerator for six months with no more than 5 mol % decomposed by ¹H NMR detection.

The asymmetric addition reactions were initially optimized with allylmagnesium bromide and chiral imine **3a** (Table 3). As is shown in table 3, THF was the best solvent for the reactions, giving 80% yield and 98:2 diastereoselectivity (entries 1–4). Temperature has a dramatic influence on the reaction, and no desired product was obtained at all when the reaction was done at 0 °C (entries 5 and 6). The yield could be further increased to 85% when 2.5 equiv of Grignard reagent was used (entry 7). Further increasing the loading amount of Grignard reagent did not give any improvement (entry 8). Also, the reaction could complete within 24 h, and prolonged the reaction to 36 h seemed not necessary (entry 9). Sometimes, Lewis acids can activate imine by affecting nitrogen atom.²¹ So we tried some additives in our system, but none of them can make any improvement (entries 10–13).

Then the scope of imine substrates was examined under the optimal reaction conditions. As shown in Table 4, the asymmetric reaction of allylmagnesium bromide with the α,β -unsaturated imines provided α,β -alkenyl homoallylic primary amines in good chemical yields (66–85%). The reaction was found to be suitable for both electron-withdrawing (entries 2 and 3), and electron-donating group-substituted (entries 4–8) aromatic phosphonyl imines. Notably, substrates with heterocyclic groups **3j** and **3k** were also well tolerated in this reaction along with good chemical yields (entries 10 and 11). Variation of the position of substituents on the aromatic rings did not show any obvious effect on efficiencies. Excellent diastereoselectivities ranging from 87:13 to 99:1 were obtained for all examples that were examined. Fortunately, only 1,2-adduct is confirmed to form in our system for all cases.

The chiral auxiliary on compound **5a** could be easily removed to give free amine **6**. In this conversion, **5a** was subjected to deprotection with 36% HCl aqueous solution stirring at room temperature in methanol for 4 days. Since **6** has a good solubility in water, washing aqueous phase with DCM several times can get rid of the rest compounds. Pure hydrochloride of amine is obtained through direct concentration of aqueous phase with 53% isolated yield. Optical rotation of this product was confirmed to be consistent with that of the known sample with *S* configuration.²²

3. Conclusions

In summary, this work describes a facile asymmetric addition of allylmagnesium bromide Grignard reaction to α,β -unsaturated imines. The reaction was found to tolerate a wide scope of imine substrates with good chemical yield and excellent diastereoselectivities. This methodology provides an easy access to chiral α,β -alkenyl homoallylic primary amines for the first time. The phosphonyl moiety can be cleaved easily in simple conditions, bearing hydrochloride of free amines. The use of this α,β -unsaturated imines for other addition reaction are current underway in our group.

4. Experimental section

General information

All the reactions were carried out in oven-dried glasswares under an atmosphere of dry argon, unless otherwise stated. All commercially available reagents were used without further purification. Ether, toluene, THF, 2-MeTHF used for the reaction were distilled using benzophenone-sodium under nitrogen prior to use. DCM was dried over calcium hydride and then distilled under an atmosphere of nitrogen prior to use. ^1H NMR, ^{13}C NMR, ^{31}P NMR spectra (TMS used as internal standard) were recorded at 400 MHz, 100 MHz, 162 MHz respectively in CDCl_3 with JMT-400/54/55. High resolution mass spectra for all the new compounds were done by the Bruker APEX IV instruments. Optical rotation values were taken using AUTOPOL IV automatic polarimeter. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm precoated silica gel plates and the compounds were visualized with UV light ($\lambda = 254$ nm). Compounds were purified using flash column chromatography (forced flow) on silica gel (SiO_2) 60 Å (32–63 μm) particle size.

General procedure for synthesis of α,β -unsaturated imines

An oven dried and argon flushed reaction vial was charged in succession with cinnamaldehyde (1.5 mmol), phosphoramidate (1.0 mmol), triethylamine (2.0 mmol) in DCM (8.0 mL). The mixture was cooled in an ice bath, then titanium chloride (0.5 mmol in a 1 mol/L DCM solution) was added dropwise during 30 min. After addition, the ice bath was removed and the whole solution was kept at rt. 48 h later, the mixture was poured into a pad of celite, washing the pad with 100 mL DCM. After concentrated under reduced pressure, the residue was purified via column chromatography with ethyl acetate and petroleum ether (from 1:10 to 1:2 v/v) as eluent to give the product **3**.

3a. pale yellow solid: mp 70–71 °C, $[\alpha]_{\text{D}}^{25} = -26.0$ ($c = 1.08$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 9.01 (dd, $J = 33.2, 8.8$ Hz, 1H), 7.60 (dd, $J = 7.6, 1.2$ Hz, 2H), 7.44–7.25 (m, 14 H), 7.13 (ddd, $J = 11.2, 8.8, 2.0$ Hz, 1H), 4.25 (qd, $J = 6.0, 3.6$ Hz, 2H), 3.25–3.06 (m, 2H), 1.22 (dd, $J = 8.8, 7.2$ Hz, 6H), 1.07 (d, $J = 6.4$ Hz, 3H), 0.89 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 174.7 (d, $J = 7.2$ Hz), 148.9, 141.9 (d, $J = 5.3$ Hz), 140.7 (d, $J = 6.4$ Hz), 135.2 (d, $J = 1.3$ Hz), 130.4, 129.4, 129.1, 128.6, 128.5, 128.2, 128.0, 127.8, 127.6, 67.7 (d, $J = 11.1$ Hz), 67.1 (d, $J = 11.4$ Hz), 46.7 (d, $J = 4.9$ Hz), 45.9 (d, $J = 4.5$ Hz), 21.2 (d, $J = 1.6$ Hz), 21.1 (d, $J = 1.2$ Hz), 20.9 (d, $J = 1.8$ Hz); ^{31}P NMR (162 MHz, CDCl_3) 24.0; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{35}\text{N}_3\text{OP}$, 472.2518; found, 472.2510.

3b. pale yellow solid: mp 74–76 °C, $[\alpha]_{\text{D}}^{25} = -53.1$ ($c = 0.89$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 8.99 (dd, $J = 33.2, 8.8$ Hz, 1H), 7.54 (dt, $J = 8.8, 1.6$ Hz, 2H), 7.46–7.44 (m, 2H), 7.31–7.24 (m, 11H), 7.10 (ddd, $J = 11.2, 8.8, 2.4$ Hz, 1H), 4.25 (qd, $J = 6.4, 4.0$ Hz, 2H), 3.22–3.06 (m, 2H), 1.21 (dd, $J = 8.4, 7.2$ Hz, 6H), 1.06 (d, $J = 6.4$ Hz, 3H), 0.88 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 174.2 (d, $J = 7.2$ Hz), 147.2, 141.9 (d, $J = 5.1$ Hz),

140.7 (d, $J = 6.2$ Hz), 134.1 (d, $J = 1.2$ Hz), 132.3, 130.0, 129.6, 129.5, 128.6, 128.5, 128.0, 127.8, 127.7, 127.6, 124.6, 67.7 (d, $J = 11.1$ Hz), 67.1 (d, $J = 11.3$ Hz), 46.8 (d, $J = 4.9$ Hz), 45.9 (d, $J = 4.5$ Hz), 21.2, 21.1 (d, $J = 1.2$ Hz), 20.9 (d, $J = 1.8$ Hz); ^{31}P NMR (162 MHz, CDCl_3) 23.8; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{34}\text{BrN}_3\text{OP}$, 550.1623; found, 550.1612.

3c. pale yellow solid: mp 57–59 °C, $[\alpha]_{\text{D}}^{25} = -45.6$ (c = 1.21, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 8.91 (d, $J = 31.6$ Hz, 1H), 7.96–7.94 (m, 2H), 7.48–7.25 (m, 14H), 4.29–4.24 (m, 2H), 3.29–3.10 (m, 2H), 1.21 (dd, $J = 11.6, 6.8$ Hz, 6H), 1.04 (d, $J = 6.4$ Hz, 3H), 0.89 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 169.7 (d, $J = 4.8$ Hz), 142.5 (d, $J = 4.1$ Hz), 142.4, 141.5 (d, $J = 6.0$ Hz), 133.5 (d, $J = 1.3$ Hz), 132.4, 132.1, 130.9, 130.6, 128.8, 128.7, 128.6, 128.0, 127.8, 127.7, 127.5, 67.7 (d, $J = 12.0$ Hz), 66.6 (d, $J = 11.9$ Hz), 46.6 (d, $J = 5.4$ Hz), 46.0 (d, $J = 4.6$ Hz), 21.7 (d, $J = 1.9$ Hz), 21.2 (d, $J = 2.2$ Hz), 21.1 (d, $J = 1.6$ Hz); ^{31}P NMR (162 MHz, CDCl_3) 23.0; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{34}\text{ClN}_3\text{OP}$, 506.2128; found, 506.2144.

3d. pale yellow solid: mp 66–67 °C, $[\alpha]_{\text{D}}^{25} = -38.5$ (c = 0.68, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 9.04 (dd, $J = 33.2, 8.8$ Hz, 1H), 7.69–7.63 (m, 2H), 7.33–7.18 (m, 13H), 7.07 (ddd, $J = 11.2, 8.8, 2.0$ Hz, 1H), 4.26 (qd, $J = 6.0, 3.6$ Hz, 2H), 3.24–3.05 (m, 2H), 2.44 (s, 3H), 1.21 (dd, $J = 6.4$ Hz, 6H), 1.07 (d, $J = 6.8$ Hz, 3H), 0.89 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 174.9 (d, $J = 7.2$ Hz), 145.4, 142.0 (d, $J = 5.1$ Hz), 140.8 (d, $J = 6.2$ Hz), 133.9, 132.1 (d, $J = 1.4$ Hz), 131.6, 131.3 (d, $J = 2.2$ Hz), 130.9, 129.0, 128.6, 128.5, 128.0, 127.8 (d, $J = 4.5$ Hz), 127.7, 127.2, 126.4, 125.6, 125.2, 123.1, 67.7 (d, $J = 11.2$ Hz), 67.1 (d, $J = 11.3$ Hz), 46.8 (d, $J = 5.1$ Hz), 45.9 (d, $J = 4.5$ Hz), 21.2, 21.0 (d, $J = 1.7$ Hz); ^{31}P NMR (162 MHz, CDCl_3) 24.1; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{37}\text{N}_3\text{OP}$, 486.2674; found, 486.2672.

3e. white solid: mp 64–65 °C, $[\alpha]_{\text{D}}^{25} = -42.0$ (c = 0.60, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 9.00 (dd, $J = 33.2, 9.2$ Hz, 1H), 7.48 (d, $J = 8.4$ Hz, 2H), 7.34–7.20 (m, 13H), 7.08 (ddd, $J = 16.0, 9.2, 2.4$ Hz, 1H), 4.25 (qd, $J = 6.0, 3.6$ Hz, 2H), 3.22–3.07 (m, 2H), 2.37 (s, 3H), 1.21 (dd, $J = 8.8, 7.2$ Hz, 6H), 1.07 (d, $J = 6.8$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 174.9 (d, $J = 7.1$ Hz), 149.0, 141.9 (d, $J = 5.3$ Hz), 140.8 (d, $J = 6.4$ Hz), 132.5 (d, $J = 1.1$ Hz), 129.8, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8 (d, $J = 0.8$ Hz), 127.6, 67.7 (d, $J = 11.1$ Hz), 67.1 (d, $J = 11.4$ Hz), 46.7 (d, $J = 4.9$ Hz), 45.9 (d, $J = 4.5$ Hz), 21.6, 21.2 (d, $J = 1.9$ Hz), 21.1 (d, $J = 1.2$ Hz), 20.9 (d, $J = 1.6$ Hz); ^{31}P NMR (162 MHz, CDCl_3) 24.1; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{37}\text{N}_3\text{OP}$, 486.2674; found, 486.2669.

3f. pale yellow solid: mp 61–62 °C, $[\alpha]_{\text{D}}^{25} = -12.2$ (c = 0.97, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 9.01 (dd, $J = 33.6, 9.2$ Hz, 1H), 7.75 (d, $J = 16.0$ Hz, 1H), 7.62 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.37–7.24 (m, 11H), 7.18 (ddd, $J = 11.2, 9.2, 2.4$ Hz, 1H), 6.98 (t, $J = 7.6$ Hz, 1H), 6.93 (d, $J = 8.4$ Hz, 1H), 4.25 (qd, $J = 6.4, 2.4$ Hz, 2H), 3.90 (s, 3H), 3.22–3.06 (m, 2H), 1.22 (dd, $J = 7.2, 8.4$ Hz, 6H), 1.07 (d, $J = 6.4$ Hz, 3H), 0.89 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 175.7 (d, $J = 7.2$ Hz), 158.1, 144.4, 141.8 (d, $J = 5.6$ Hz), 140.7 (d, $J = 7$ Hz), 131.8, 129.6, 129.3, 128.6, 128.5, 128.4, 128.0, 127.8, 127.7, 124.1 (d, $J = 1.4$ Hz), 120.9, 111.3, 67.7 (d, $J = 11.1$ Hz), 67.1 (d, $J = 11.2$ Hz), 55.7, 46.7 (d, $J = 4.8$ Hz), 45.9 (d, $J = 4.5$ Hz), 21.2 (d, $J = 1.9$ Hz), 21.1 (d, $J = 1.3$ Hz), 20.9 (d, $J = 1.6$ Hz); ^{31}P NMR (162 MHz, CDCl_3) 24.2; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{37}\text{N}_3\text{O}_2\text{P}$, 502.2623; found, 502.2611.

3g. yellow solid: mp 63–65 °C, $[\alpha]_{\text{D}}^{25} = -10.4$ (c = 0.47, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 8.97 (dd, $J = 33.2, 9.2$ Hz, 1H), 7.56–7.54 (m, 2H), 7.33–7.27 (m, 11H), 6.99 (ddd, $J = 11.2, 9.2, 2.4$ Hz, 1H), 6.96–6.92 (m, 2H), 4.25 (qd, $J = 6.0, 3.2$ Hz, 2H), 3.85 (s, 3H),

3.22-3.06 (m, 2H), 1.21 (dd, $J = 7.2$ Hz, 6H), 1.07 (d, $J = 6.4$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 175.2 (d, $J = 7.1$ Hz), 161.6, 149.1, 141.7 (d, $J = 5.5$ Hz), 140.7 (d, $J = 6.4$ Hz), 129.9, 128.6, 128.5, 128.0, 127.8, 127.7, 127.1, 126.8, 114.5, 67.7 (d, $J = 11.1$ Hz), 67.1 (d, $J = 11.2$ Hz), 55.5, 46.7 (d, $J = 4.6$ Hz), 45.9 (d, $J = 4.3$ Hz), 21.2, 21.1, 20.9; ^{31}P NMR (162 MHz, CDCl_3) 24.3; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{37}\text{N}_3\text{O}_2\text{P}$, 502.2623; found, 502.2629.

3h. red solid: mp 67–68 °C, $[\alpha]_{\text{D}}^{25} = -33.4$ ($c = 1.15$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 8.94 (dd, $J = 33.6$, 9.2 Hz, 1H), 7.44 (d, $J = 8.8$ Hz, 2H), 7.31-7.21 (m, 11H), 6.94 (ddd, $J = 15.6$, 9.2, 2.0 Hz, 1H), 6.64 (d, $J = 8.8$ Hz, 2H), 4.23 (qd, $J = 6.4$, 3.6 Hz, 2H), 3.20-3.06 (m, 2H), 2.98 (s, 6H), 1.21 (dd, $J = 7.2$ Hz, 6H), 1.05 (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 175.4 (d, $J = 6.9$ Hz), 151.9, 150.2, 141.8 (d, $J = 5.6$ Hz), 140.8 (d, $J = 6.4$ Hz), 130.0, 128.5, 128.4, 127.9, 127.8, 127.7 (d, $J = 0.9$ Hz), 124.4, 124.0, 123.0 (d, $J = 1.2$ Hz), 111.9, 67.7 (d, $J = 11.0$ Hz), 67.2 (d, $J = 11.0$ Hz), 46.7 (d, $J = 4.8$ Hz), 45.9 (d, $J = 4.4$ Hz), 40.2, 21.2 (d, $J = 1.8$ Hz), 21.1 (d, $J = 1.2$ Hz), 21.0 (d, $J = 2.8$ Hz), 20.8 (d, $J = 1.6$ Hz); ^{31}P NMR (162 MHz, CDCl_3) 24.7; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{40}\text{N}_4\text{OP}$, 515.2940; found, 515.2934.

3i. pale yellow solid: mp 74–75 °C, $[\alpha]_{\text{D}}^{25} = -45.3$ ($c = 1.65$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 9.07 (dd, $J = 33.6$, 9.2 Hz, 1H), 7.98 (s, 1H), 7.89-7.83 (m, 3H), 7.77 (dd, $J = 8.8$, 1.6 Hz, 1H), 7.54-7.50 (m, 3H), 7.34-7.24 (m, 11H), 4.27 (qd, $J = 6.0$, 3.6 Hz, 2H), 3.25-3.09 (m, 2H), 1.24 (dd, $J = 8.8$, 6.8 Hz, 6H), 1.09 (d, $J = 6.4$ Hz, 3H), 0.91 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 174.7 (d, $J = 7.2$ Hz), 148.9, 141.9 (d, $J = 5.3$ Hz), 140.8 (d, $J = 6.3$ Hz), 134.3, 133.5, 132.7 (d, $J = 1.4$ Hz), 129.9, 129.6, 129.3, 128.9, 128.7, 128.6, 128.5, 128.0, 127.9, 127.8 (d, $J = 1.5$ Hz), 127.7, 127.4, 126.9, 123.7, 67.7 (d, $J = 11.2$ Hz), 67.1 (d, $J = 11.3$ Hz), 46.8 (d, $J = 5.0$ Hz), 45.9 (d, $J = 4.5$ Hz), 21.2 (d, $J = 1.8$ Hz), 21.1 (d, $J = 1.3$ Hz), 20.9 (d, $J = 1.7$ Hz); ^{31}P NMR (162 MHz, CDCl_3) 24.0; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{37}\text{N}_3\text{OP}$, 522.2674; found, 522.2683.

3j. brown solid: mp 64–65 °C, $[\alpha]_{\text{D}}^{25} = -52.6$ ($c = 1.40$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 8.91 (dd, $J = 33.2$, 9.2 Hz, 1H), 7.51 (d, $J = 1.6$ Hz, 1H), 7.31-7.22 (m, 10H), 7.11 (d, $J = 15.6$ Hz, 1H), 6.98 (ddd, $J = 11.2$, 8.8, 2.0 Hz, 1H), 6.65 (d, $J = 3.2$ Hz, 1H), 6.47 (dd, $J = 3.2$, 1.6 Hz, 1H), 4.22 (qd, $J = 6.0$, 4.0 Hz, 2H), 3.20-3.04 (m, 2H), 1.19 (dd, $J = 8.8$, 7.2 Hz, 6H), 1.04 (d, $J = 6.4$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 152.6, 144.0 (d, $J = 5.4$ Hz), 143.0 (d, $J = 2.8$ Hz), 141.9, 134.1, 131.4 (d, $J = 3.8$ Hz), 128.6 (d, $J = 4.6$ Hz), 127.7, 127.6, 127.5, 126.7, 118.6, 118.4, 111.3, 107.7, 66.3 (d, $J = 15.1$ Hz), 65.1 (d, $J = 12.8$ Hz), 53.3, 46.1 (d, $J = 4.7$ Hz), 45.1 (d, $J = 5.6$ Hz), 22.9 (d, $J = 1.6$ Hz), 22.3 (d, $J = 5.2$ Hz), 20.8, 20.6 (d, $J = 3.1$ Hz); ^{31}P NMR (162 MHz, CDCl_3) 24.0; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_2\text{P}$, 462.2310; found, 462.2207.

3k. pale yellow solid: mp 67–69 °C, $[\alpha]_{\text{D}}^{25} = -26.8$ ($c = 0.64$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 8.94 (dd, $J = 33.6$, 9.2 Hz, 1H), 7.70 (s, 1H), 7.47-7.46 (m, 1H), 7.31-7.24 (m, 12H), 6.83 (ddd, $J = 11.2$, 8.8, 2.0 Hz, 1H), 6.69 (d, $J = 1.6$ Hz, 1H), 4.24 (qd, $J = 6.4$, 3.6 Hz, 2H), 3.23-3.04 (m, 2H), 1.21 (dd, $J = 8.8$, 7.2 Hz, 6H), 1.06 (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 174.6 (d, $J = 7.2$ Hz), 144.7, 144.4, 141.8 (d, $J = 5.4$ Hz), 140.7 (d, $J = 6.4$ Hz), 138.5, 129.4, 129.1, 128.6, 128.5, 128.0, 127.8 (d, $J = 1.1$ Hz), 127.6, 123.7 (d, $J = 1.4$ Hz), 107.6, 67.7 (d, $J = 11.1$ Hz), 67.1 (d, $J = 11.4$ Hz), 46.7 (d, $J = 5.0$ Hz), 45.9 (d, $J = 4.6$ Hz), 21.2 (d, $J = 1.9$ Hz), 21.1 (d, $J = 2.1$ Hz), 20.9 (d, $J = 1.8$ Hz); ^{31}P NMR (162 MHz, CDCl_3) 24.1; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_2\text{P}$, 462.2310; found, 462.2318

General procedure for nucleophilic addition of α,β -unsaturated imines

Into a reaction vial under argon, allylmagnesium bromide (0.5 mmol) was taken followed by THF (4.0 mL). Reaction mixture was then cooled to $-78\text{ }^{\circ}\text{C}$ using dry ice-acetone bath for 5 min. At the same time, α,β -unsaturated imines (0.2 mmol, dissolved in 4.0 mL of THF) properly sealed with a rubber septum in dry argon atmosphere, was cooled to $-78\text{ }^{\circ}\text{C}$ in the same dry ice-acetone bath for 5 min. Then the imines were added dropwise *via* a cannula at $-78\text{ }^{\circ}\text{C}$ and stirring was continued for 36 h at the same temperature. After confirming the consumption of imine, the reaction mixture was quenched with saturated Ammonium chloride (4.0 mL) and the organic layer was extracted with ethyl acetate. The organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was purified using flash column chromatography on silica gel using EtOAc/Hexanes (1:2, v/v) as the eluent to afford adduct **5**.

5a. colorless oil: $[\alpha]_{\text{D}}^{25} = -16.2$ ($c = 1.89$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 7.44-7.18 (m, 15H), 6.70 (d, $J = 16.0$ Hz, 1H), 6.32 (dd, $J = 16.0$, 6.4 Hz, 1H), 5.96-5.86 (m, 1H), 5.21-5.16 (m, 2H), 4.31-4.13 (m, 3H), 3.56-3.45 (m, 2H), 2.69-2.49 (m, 3H), 1.21 (d, $J = 6.4$ Hz, 3H), 1.10 (d, $J = 6.4$ Hz, 3H), 0.84 (dd, $J = 6.4$, 2.0 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) 143.9 (d, $J = 5.5$ Hz), 143.0 (d, $J = 2.9$ Hz), 137.0, 134.2, 132.7 (d, $J = 3.7$ Hz), 129.8, 128.7, 128.6, 127.7 (d, $J = 6.6$ Hz), 127.6, 126.8, 126.4, 118.6, 66.3 (d, $J = 15.0$ Hz), 65.2 (d, $J = 12.8$ Hz), 53.6, 46.2 (d, $J = 4.7$ Hz), 45.1 (d, $J = 5.6$ Hz), 42.3 (d, $J = 5.6$ Hz), 23.0 (d, $J = 1.4$ Hz), 22.4 (d, $J = 5.0$ Hz), 20.8, 20.7 (d, $J = 3.1$ Hz); ^{31}P NMR (162 MHz, CDCl_3) 23.0; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{32}\text{H}_{41}\text{N}_3\text{OP}$, 514.2987; found, 514.2998

5b. colorless oil: $[\alpha]_{\text{D}}^{25} = -11.4$ ($c = 0.88$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 7.43-7.20 (m, 14H), 6.61 (d, $J = 15.6$ Hz, 1H), 6.30 (dd, $J = 15.6$, 6.4 Hz, 1H), 5.93-5.82 (m, 1H), 5.20-5.16 (m, 2H), 4.29-4.10 (m, 3H), 3.52-3.45 (m, 2H), 2.62-2.47 (m, 3H), 1.17 (d, $J = 6.4$ Hz, 3H), 1.07 (d, $J = 6.8$ Hz, 3H), 0.81 (dd, $J = 8.8$, 6.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) 144.0 (d, $J = 5.3$ Hz), 143.0 (d, $J = 2.6$ Hz), 135.9, 134.1, 133.6 (d, $J = 3.5$ Hz), 131.8, 128.6 (d, $J = 4.0$ Hz), 127.9, 127.8, 127.7, 127.5, 126.7, 121.2, 118.7, 66.3 (d, $J = 15.0$ Hz), 65.1 (d, $J = 12.8$ Hz), 53.6, 46.1 (d, $J = 4.7$ Hz), 45.1 (d, $J = 5.7$ Hz), 42.1 (d, $J = 5.8$ Hz), 22.9 (d, $J = 1.5$ Hz), 22.4 (d, $J = 5.0$ Hz), 20.8, 20.7 (d, $J = 3.1$ Hz); ^{31}P NMR (162 MHz, CDCl_3) 22.8; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{32}\text{H}_{40}\text{BrN}_3\text{OP}$, 592.2092; found, 592.2084.

5c. colorless oil: $[\alpha]_{\text{D}}^{25} = -5.9$ ($c = 0.88$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 7.61 (d, $J = 7.2$ Hz, 2H), 7.51 (d, $J = 7.2$ Hz, 2H), 7.36-7.25 (m, 11H), 6.83 (s, 1H), 5.89-5.78 (m, 1H), 5.21-5.10 (m, 2H), 4.50-4.42 (m, 1H), 4.16-4.09 (m, 2H), 3.53-3.44 (m, 2H), 2.83 (t, $J = 9.2$ Hz, 1H), 2.64-2.55 (m, 2H), 1.06 (dd, $J = 6.8$, 2.8 Hz, 6H), 0.83 (d, $J = 6.8$ Hz, 3H), 0.72 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) 144.4, 143.4, 136.6, 134.5, 134.1, 129.3, 128.6, 128.3, 128.0, 127.7, 127.5, 127.2, 126.4, 125.9, 118.2, 66.3 (d, $J = 15.8$ Hz), 64.7 (d, $J = 13.3$ Hz), 59.7, 46.0, 45.3 (d, $J = 5.4$ Hz), 40.0 (d, $J = 8.0$ Hz), 22.8, 22.6 (d, $J = 4.8$ Hz), 20.9; ^{31}P NMR (162 MHz, CDCl_3) 21.3; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{32}\text{H}_{40}\text{ClN}_3\text{OP}$, 548.2598; found, 548.2611.

5d. colorless oil: $[\alpha]_{\text{D}}^{25} = -4.7$ ($c = 1.10$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 7.44 (d, $J = 7.2$ Hz, 2H), 7.33-7.23 (m, 12H), 7.19 (t, $J = 7.2$ Hz, 2H), 6.60 (s, 1H), 5.87-5.77 (m, 1H), 5.18-5.11 (m, 2H), 4.19-4.12 (m, 3H), 3.57-3.47 (m, 2H), 2.78 (t, $J = 10.0$ Hz, 1H), 2.66-2.45 (m, 2H), 1.94 (s, 3H), 1.21 (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 6.8$ Hz, 3H), 0.83 (dd, $J = 12.4$, 6.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) 144.1 (d, $J = 5.3$ Hz), 143.1 (d, $J = 2.7$ Hz), 139.3 (d, $J = 2.7$ Hz), 137.9, 134.5, 129.0, 128.6 (d, $J = 4.1$ Hz), 128.2, 127.7, 127.6, 127.5, 126.7, 126.4 (d, $J = 5.3$ Hz), 117.9, 66.3 (d, $J = 15.1$ Hz), 65.1 (d, $J = 12.8$ Hz), 59.1, 46.1 (d, $J = 4.7$ Hz), 45.1 (d, $J = 5.7$ Hz), 40.2 (d, $J = 6.2$ Hz), 23.0 (d, $J = 1.3$ Hz), 22.6 (d, $J = 4.8$ Hz).

=5.3 Hz), 20.8, 20.6 (d, J = 3.3 Hz), 14.8; ^{31}P NMR (162 MHz, CDCl_3) 23.0; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{43}\text{N}_3\text{OP}$, 528.3144; found, 528.3153.

5e. colorless oil: $[\alpha]_{\text{D}}^{25} = -4.3$ (c = 1.12, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 7.41 (s, 2H), 7.33-7.25 (m, 10H), 7.11 (dd, J = 7.6, 2.4 Hz, 2H), 6.65 (dd, J = 16.0, 2.4 Hz, 1H), 6.25 (dq, J = 6.0, 3.2 Hz, 1H), 5.94-5.84 (m, 1H), 5.20-5.15 (m, 2H), 4.24-4.11 (m, 3H), 3.53-3.48 (m, 2H), 2.64-2.51 (m, 3H), 2.31 (d, J = 3.2 Hz, 3H), 1.20 (dd, J = 6.4, 3.2 Hz, 3H), 1.08 (dd, J = 6.4, 3.2 Hz, 3H), 0.83 (dd, J = 6.8, 3.2 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) 143.9 (d, J = 5.7 Hz), 143.0 (d, J = 2.7 Hz), 137.3, 134.3 (d, J = 8.4 Hz), 131.6 (d, J = 3.8 Hz), 129.6, 129.4, 128.6 (d, J = 5.1 Hz), 127.7 (d, J = 7.4 Hz), 127.6, 126.8, 126.3, 118.5, 66.3 (d, J = 14.9 Hz), 65.2 (d, J = 12.9 Hz), 53.6, 46.2 (d, J = 4.6 Hz), 45.1 (d, J = 5.7 Hz), 42.4 (d, J = 5.6 Hz), 23.0, 22.4 (d, J = 5.1 Hz), 21.3, 20.8, 20.6 (d, J = 3.0 Hz); ^{31}P NMR (162 MHz, CDCl_3) 23.1; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{43}\text{N}_3\text{OP}$, 528.3144; found, 528.3148.

5f. colorless oil: $[\alpha]_{\text{D}}^{25} = -15.2$ (c = 0.98, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 7.43 (dd, J = 7.6, 5.2 Hz, 2H), 7.33-7.17 (m, 9H), 7.04 (d, J = 16.0 Hz, 2H), 6.90 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.31 (dd, J = 16.0, 6.0 Hz, 1H), 5.97-5.86 (m, 1H), 5.20-5.15 (m, 2H), 4.31-4.24 (m, 1H), 4.19 (t, J = 4.8 Hz, 1H), 4.15 (dd, J = 10.0, 4.8 Hz, 1H), 3.78 (s, 3H), 3.57-3.46 (m, 2H), 2.68-2.48 (m, 3H), 1.22 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 0.84 (dd, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) 156.7, 143.9 (d, J = 5.7 Hz), 143.1 (d, J = 3.1 Hz), 134.4, 133.2 (d, J = 4.0 Hz), 128.6, 128.5, 127.7, 127.6, 126.9, 126.7, 126.1, 124.4, 120.7, 118.4, 110.8, 66.3 (d, J = 15.0 Hz), 65.3 (d, J = 12.8 Hz), 55.4, 53.8, 46.2 (d, J = 4.6 Hz), 45.1 (d, J = 5.7 Hz), 42.5 (d, J = 5.3 Hz), 23.1 (d, J = 1.4 Hz), 22.2 (d, J = 5.3 Hz), 20.8, 20.6 (d, J = 3.2 Hz); ^{31}P NMR (162 MHz, CDCl_3) 23.2; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{43}\text{N}_3\text{O}_2\text{P}$, 544.3093; found, 544.3090.

5g. colorless oil: $[\alpha]_{\text{D}}^{25} = -13.8$ (c = 1.33, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 7.41 (d, J = 6.8 Hz, 2H), 7.33-7.25 (m, 11H), 6.85-6.82 (m, 2H), 6.61 (d, J = 16.0 Hz, 1H), 6.16 (dd, J = 15.6, 6.4 Hz, 1H), 5.93-5.84 (m, 1H), 5.20-5.15 (m, 2H), 4.23-4.10 (m, 3H), 3.78 (s, 3H), 3.53-3.47 (m, 2H), 2.63-2.46 (m, 3H), 1.20 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H), 0.82 (dd, J = 6.8, 2.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) 159.2, 143.9 (d, J = 5.7 Hz), 143.0 (d, J = 2.7 Hz), 134.4, 130.5 (d, J = 3.6 Hz), 129.8, 129.2, 128.6 (d, J = 4.6 Hz), 127.7, 127.6, 127.5, 126.8, 118.4, 114.1, 66.3 (d, J = 14.9 Hz), 65.2 (d, J = 12.8 Hz), 55.4, 53.6, 46.1 (d, J = 4.4 Hz), 45.1 (d, J = 5.6 Hz), 42.4 (d, J = 5.5 Hz), 23.0, 22.4 (d, J = 5.1 Hz), 20.8, 20.6 (d, J = 3.0 Hz); ^{31}P NMR (162 MHz, CDCl_3) 23.1; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{43}\text{N}_3\text{O}_2\text{P}$, 544.3093; found, 544.3071.

5h. pale yellow oil: $[\alpha]_{\text{D}}^{25} = -29.0$ (c = 0.92, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 7.41 (d, J = 6.8 Hz, 2H), 7.34-7.25 (m, 10H), 6.67-6.65 (m, 2H), 6.58 (d, J = 16.0 Hz, 1H), 6.09 (dd, J = 15.6, 6.4 Hz, 1H), 5.96-5.85 (m, 1H), 5.19-5.13 (m, 2H), 4.24-4.10 (m, 3H), 3.55-3.46 (m, 2H), 2.93 (s, 6H), 2.64-2.48 (m, 3H), 1.22 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H), 0.84 (dd, J = 6.8, 2.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) 150.1, 143.9 (d, J = 5.8 Hz), 143.1 (d, J = 3.2 Hz), 134.6, 129.6, 128.6, 128.5, 128.2 (d, J = 4.0 Hz), 127.7, 127.6, 127.3, 126.9, 125.5, 118.2, 112.5, 66.3 (d, J = 14.8 Hz), 65.3 (d, J = 12.7 Hz), 53.7, 46.2 (d, J = 5.4 Hz), 45.1 (d, J = 5.7 Hz), 40.6, 23.0 (d, J = 1.4 Hz), 22.4 (d, J = 5.2 Hz), 20.8, 20.6 (d, J = 3.2 Hz); ^{31}P NMR (162 MHz, CDCl_3) 23.2; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{43}\text{N}_3\text{O}_2\text{P}$, 557.3409; found, 557.3403.

5i. colorless oil: $[\alpha]_{\text{D}}^{25} = -29.0$ (c = 0.92, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 7.78 (dd, J = 7.6, 2.0 Hz, 3H), 7.72 (s, 1H), 7.60 (dd, J = 8.4, 1.6 Hz, 1H), 7.46-7.24 (m, 12H), 6.86 (d, J = 16.0 Hz, 1H), 6.45 (dd, J = 16.0, 6.4 Hz, 1H), 6.00-5.89 (m, 1H), 5.24-5.19 (m, 2H), 4.37-4.14 (m, 3H), 3.59-3.46 (m, 2H), 2.71-2.53 (m, 3H), 1.21 (d, J = 6.8 Hz, 3H), 1.11 (d, J

= 6.8 Hz, 3H), 0.85 (dd, J = 6.4, 3.2 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) 144.0 (d, J = 5.5 Hz), 143.0 (d, J = 2.9 Hz), 134.4, 134.3, 133.7, 133.1 (d, J = 3.7 Hz), 133.0, 129.9, 128.6 (d, J = 6.3 Hz), 128.3, 128.0, 127.8, 127.7, 127.6, 126.8, 126.4, 126.3, 125.9, 123.6, 118.6, 66.3 (d, J = 15.0 Hz), 65.2 (d, J = 12.7 Hz), 53.7, 46.2 (d, J = 4.7 Hz), 45.2 (d, J = 5.7 Hz), 42.3 (d, J = 5.9 Hz), 23.0 (d, J = 1.4 Hz), 22.4 (d, J = 5.2 Hz), 20.8, 20.7 (d, J = 3.1 Hz); ^{31}P NMR (162 MHz, CDCl_3) 23.0; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{36}\text{H}_{43}\text{N}_3\text{OP}$, 564.3144; found, 564.3145.

5j. pale yellow oil: $[\alpha]_{\text{D}}^{25} = -4.0$ (c = 1.24, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 7.42 (d, J = 7.2 Hz, 1H), 7.34-7.23 (m, 9H), 6.50 (dd, J = 16.0, 1.6 Hz, 1H), 6.33 (dd, J = 3.2, 1.6 Hz, 1H), 6.26 (dd, J = 16.0, 6.4 Hz, 1H), 6.18 (d, J = 3.2 Hz, 1H), 5.93-5.83 (m, 1H), 5.19-5.15 (m, 2H), 4.24-4.09 (m, 3H), 3.54-3.44 (m, 2H), 2.63-2.45 (m, 3H), 1.17 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.81 (dd, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) 152.6, 144.0 (d, J = 5.4 Hz), 143.0 (d, J = 2.8 Hz), 141.9, 134.1, 131.4 (d, J = 3.8 Hz), 128.6 (d, J = 4.6 Hz), 127.7, 127.6, 127.5, 126.7, 118.6, 118.4, 111.3, 107.7, 66.3 (d, J = 15.1 Hz), 65.1 (d, J = 12.8 Hz), 53.3, 46.1 (d, J = 4.7 Hz), 45.1 (d, J = 5.6 Hz), 42.1 (d, J = 4.7 Hz), 22.9 (d, J = 1.6 Hz), 22.3 (d, J = 5.2 Hz), 20.8, 20.6 (d, J = 3.1 Hz); ^{31}P NMR (162 MHz, CDCl_3) 23.0; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{36}\text{H}_{43}\text{N}_3\text{OP}$, 504.2780; found, 504.2782.

5k. pale yellow oil: $[\alpha]_{\text{D}}^{25} = -4.4$ (c = 1.06, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 7.42-7.23 (m, 12H), 6.55-6.50 (m, 2H), 6.02 (dd, J = 13.6, 6.4 Hz, 1H), 5.93-5.82 (m, 1H), 5.19-5.15 (m, 2H), 4.20-4.09 (m, 3H), 3.53-3.44 (m, 2H), 2.53-2.44 (m, 3H), 1.18 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H), 0.82 (dd, J = 6.8, 4.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) 144.0 (d, J = 5.6 Hz), 143.6, 143.0 (d, J = 2.9 Hz), 140.4, 134.3, 132.3 (d, J = 3.6 Hz), 128.6 (d, J = 2.7 Hz), 127.7, 127.6, 127.5, 126.7, 123.8, 119.5, 118.5, 107.6, 66.3 (d, J = 15.0 Hz), 65.1 (d, J = 12.7 Hz), 53.5, 46.1 (d, J = 4.8 Hz), 45.1 (d, J = 5.7 Hz), 42.2 (d, J = 5.9 Hz), 22.9 (d, J = 1.5 Hz), 22.4 (d, J = 5.2 Hz), 20.7, 20.6 (d, J = 3.0 Hz); ^{31}P NMR (162 MHz, CDCl_3) 23.1; HRMS-(ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{39}\text{N}_3\text{O}_2\text{P}$, 504.2780; found, 504.2777.

General procedure for cleavage of auxiliary

Compound **5a** (0.5 ml) was dissolved in methanol (4.0 mL), concentrated hydrochloric acid (4.0 mL) was added dropwise during 5min by syringe. When the auxiliary was confirmed to be completely cleaved by crude ^{31}P NMR (normally 4 days was needed), solvent was removed under vacuum. The residue was dissolved in DCM/water (10.0 mL/10.0 mL), The aqueous phase was washed by DCM (4×20.0 mL), and then evaporated under vacuum to give free amine as a white solid **6** with 53% isolated yield.

(S,E)-1-phenylhexa-1,5-ammonium chloride (6) White solid: mp 184–186 °C ^1H NMR (400 MHz, DMSO) 8.55 (bs, 3H), 7.22-7.40 (m, 5H), 6.70 (d, J = 15.6 Hz, 1H), 6.22 (q, J = 15.6 Hz, 1H), 5.75-5.78 (m, 1H), 5.08-5.17 (m, 2H), 3.88 (dd, J = 12.4, 8.0 Hz, 1H), 2.60-2.63 (m, 1H), 2.47-2.50 (m, 1H); ^{13}C NMR (100 MHz, DMSO) 135.7, 133.4, 133.0, 128.8, 128.2, 126.2, 125.6, 118.8, 52.3, 37.2

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Cleavage of chiral auxiliary

Table 1

1

2a

3a

condensation

Entry	Condensation reagent ^a	T (°C)	solvent	Time (h)	Yield (%) ^b
1	4ÅM.S./MgSO ₄	rt	DCM	24	NR
2	4ÅM.S./MgSO ₄	120	toluene	24	NR
3	PPTS	rt	DCM	24	NR
4	CuSO ₄	rt	DCM	24	NR
5	Dean-Stark Apparatus	120	toluene	24	NR
6	TiCl ₄ /DIPEA	rt	DCM	24	59
7	TiCl ₄ /Et ₃ N	45	DCM	24	27
8	Ti(OEt) ₄ /Et ₃ N	rt	DCM	24	trace
9	Ti(O ^{<i>i</i>} Pr) ₄ /Et ₃ N	rt	DCM	24	trace
10	TiCl ₄ /Et ₃ N	rt	DCM	12	42
11	TiCl ₄ /Et ₃ N	rt	DCM	24	63
12	TiCl ₄ /Et ₃ N	rt	DCM	48	79
13	TiCl ₄ /Et ₃ N	rt	DCM	72	78
14	TiCl ₄ /Et ₃ N	rt	Et ₂ O	48	69
15	TiCl ₄ /Et ₃ N	rt	THF	48	74
16	TiCl ₄ /Et ₃ N	rt	toluene	48	51

^aReaction conditions: Phosphoramidite **1** (0.4 mmol), cinnamaldehyde **2a** (0.6 mmol), in solvent 3 mL.

^bIsolated yields.

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Table 2Synthesis of novel α,β -unsaturated imines ^a

Entry	Ar	Imine	Yield (%) ^b
1	C ₆ H ₅	3a	79
2	4-BrC ₆ H ₄	3b	77
3	2-ClC ₆ H ₄	3c	85
4	2-CH ₃ C ₆ H ₄	3d	76
5	4-CH ₃ C ₆ H ₄	3e	77
6	2-CH ₃ OC ₆ H ₄	3f	71
7	4-CH ₃ OC ₆ H ₄	3g	69
8	4-(CH ₃) ₂ NC ₆ H ₄	3h	78
9	2-Naphthyl	3i	83
10	2-Furyl	3j	82
11	3-Furyl	3k	80

^a Reaction conditions: Cinnamaldehyde **2** (1.5 mmol), phosphoramidate **1** (1.0 mmol), triethylamine (2.0 mmol), titanium chloride (0.5 mmol, 1M in DCM), in DCM (8.0 mL) at rt for 48 h.

^b Isolated yields.

Table 3

Optimization of asymmetric addition of Grignard reagent to α,β -unsaturated imines ^a

Entry	Solvent	T (°C)	Ratio of 4:3a	Time (h)	Yield (%) ^b	dr ^c
1	ether	-78	2:1	24	28	83:17
2	toluene	-78	2:1	24	15	67:33
3	THF	-78	2:1	24	80	98:2
4	2-MeTHF	-78	2:1	24	79	96:4
5	THF	0	2:1	24	NR	—
6	THF	-45	2:1	24	70	89:11
7	THF	-78	2.5:1	24	85	98:2
8	THF	-78	3:1	24	85	98:2
9	THF	-78	2.5:1	36	85	98:2
10	THF	-78	2.5:1	36	Trace	— ^d
11	THF	-78	2.5:1	36	Trace	— ^e
12	THF	-78	2.5:1	36	Trace	— ^f
13	THF	-78	2.5:1	36	NR	— ^g

^aReaction conditions: Imine **3** (0.2 mmol), solvent (4 mL).

^bIsolated yields.

^cDetermined by ³¹P NMR.

Table 4

Scope of **3**, -unsaturated imines ^a

Entry	Ar	Product	Time (h)	Yield (%) ^b	dr ^c
1	C ₆ H ₅	5a	24	85	98:2
2	4-BrC ₆ H ₄	5b	24	85	98:2
3	2-ClC ₆ H ₄	5c	24	66	87:13
4	2-CH ₃ C ₆ H ₄	5d	24	79	99:1
5	4-CH ₃ C ₆ H ₄	5e	24	83	98:2
6	2-CH ₃ OC ₆ H ₄	5f	36	80	98:2
7	4-CH ₃ OC ₆ H ₄	5g	36	77	98:2
8	4-(CH ₃) ₂ NC ₆ H ₄	5h	36	75	96:4
9	2-Naphthyl	5i	24	87	99:1
10	2-Furyl	5j	24	82	99:1
11	3-Furyl	5k	24	83	98:2

^aReaction conditions: Allylmagnesium bromide (0.5 mmol), imine **3** (0.2 mmol), THF (4 mL), at -78 °C.

^bIsolated yields.

^cDetermined by ³¹P NMR.