Published in final edited form as:

European J Org Chem. 2013 August 1; 2013(22): 4744–4747.

Asymmetric C-C Bond Formation between Chiral *N*-Phosphonyl Imines and Ni(II)-Complex of Glycine Schiff Base Provides a GAP Synthesis of α,β -*syn*-Diamino Acid Derivatives

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Abstract

The GAP asymmetric synthesis of α,β -diamino acid derivatives has been achieved by reacting chiral *N*-phosphonyl imines with Ni(II)-complex of glycine ester-based enolate without the use of traditional purifications of chromatography and recrystallization. The successful control of synstereochemistry of vicinal diamino products complements our previous methods which afforded anti stereoisomers and enables all four individual isomers to be synthesized by simply changing enolate geometry. In contrast to our previous synthesis where required at least 5 equiv of glycine Schiff base enolate for complete conversion, the new synthesis only needs 1.1 equiv of glycine Schiff base enolate to give complete diastereoselectivity (>99% de) and yields (91% – 97%). The absolute stereochemistry has been unambiguously determined by X-ray structural analysis.

Introduction

In green chemical sciences,^{1,2} it has been extremely challenging to design reagents so as to concurrently control the reactivity, stereoselectivity and solubility. Recently, the development of achiral and chiral *N*-phosphonyl and *N*-phosphinyl imines has led to a new concept of the GAP chemistry (Group-Assisted Purification chemistry).^{3–7} This concept enables organic synthesis to be performed without the use of traditional purifications of chromatography, recrystallization, etc. Essentially, the pure products or individual stereoisomers can be obtained simply by washing the crude mixtures with common petroleum solvents or their co-solvents.^{7c–d}

The GAP chemistry requires the auxiliary of starting reagents to show adequate solubility for resulting products that should be soluble in certain solvents, *e.g.*, THF and DCM, for

further transformations; in the meanwhile, these products should not be well dissolved in some others, such as hexane, petroleum ether, their mixtures with EtOAc, etc. so that the washing operation can be conducted for purification. The auxiliaries should enable reactants to show adequate reactivity toward various species; and for chiral auxiliaries, an efficient asymmetric induction under chiral environment is necessary under various systems. In addition, the auxiliaries should have a plenty of flexibilities for structural modifications so that both physical (solubility, thermo stability, etc.) and chemical properties of reagents and resulting products can be readily adjusted.^{6–7} Ideally, the auxiliaries should also be cleavable under convenient conditions and recycled for re-use.⁴

In the past several years, the *N*-phosphonyl and *N*-phosphinyl functional group-based GAP chemistry has been proven to meet the above purposes;^{4–7} this is attributed to the unique polarity of P=O bonds in which negative and positive charges are heavily localized on oxygen and phosphorous atoms.

One of the early *N*-phosphonyl imine reactions was conducted to react with *N*-(diphenylmethylene) glycine ester-derived enolate for the asymmetric synthesis of individual isomers of (2*S*,3*S*) and (2*R*,3*R*) isomers of α,β -*anti*-diamino esters.^{6d,7b} Under that system, (2*R*,3*S*) and/or (2*S*,3*R*)-isomers α,β -*syn*-diamino esters were either formed in tiny amounts or not formed at all. In this communication, we are pleased to present that the asymmetric reaction of chiral *N*-phosphonyl imines with Ni(II) complexed glycine-derived enolate^{8–9} can lead to formation of the latter isomers of α,β -*syn*-diamino ester analogs;^{6d,7b} this synthesis was achieved through the GAP chemistry process without using chromatography and recrystallization to give excellent yields and complete diastereoselectivity as shown in Table 1 and represented by Scheme 1.

Results and discussion

A special attention given to α,β -diamino acid residues is based on the fact that they are versatile building blocks for peptide and protein research for mimicing both α - and β -amino acids acting as hydrogen bonding donors or acceptors.¹⁰ In fact, vicinal α,β -diamino acid structures have been found in a number of antibiotics and natural products.¹¹ So far, a variety of methods for the asymmetric synthesis of vicinal α,β -diamino acid analogs have been developed.^{10b} In 2009, we studied the asymmetric reactions of *N*-(diphenylmethylene) glycine ester-derived enolate with two *N*-phosphonyl imines that are based on vicinal diamino-diphenylethane and diaminocyclohexane, but that method was limited to the synthesis α,β -*anti*-diamino esters as mentioned previously.^{6d,7b} Moreover, that synthesis required at least 5.0 equiv of *N*-(diphenylmethylene) glycine ester enolate for complete conversion, good diastereoselectivity and yields for most substrates. In addition, the formation of minor diastereoisomers and impurities was clearly observed by crude NMR determination. To render the formation of α,β -*syn*-diamino esters, the nickel(II) complexed glycine ester enolate turned out to be the choice because its enolate can be fixed on *Z*-geometry; and it has been widely utilized for many anion-involved reactions.^{8–9}

Among those *N*-phosphonyl imines that we examined, the (1*R*,2*R*)-1,2-diphenylethylene diamine-derived ones protected with *N,N*-di-isopropyl groups^{4–7} was chosen as the

electrophiles because this combination has been proven to be superior to their counterpart of 1,2-diaminocyclohexane-derived ones in our previous synthesis.^{6d,7b} According to the literature that DBU was the suitable base to deprotonate the nickel (II)-complexed glycine ester,^{9c} we thus used DBU as well as several other organic bases of DMAP, TMG and DABCO for the model reaction of **1** and **2** in DCM solution. Surprisingly, there were no products formed by the treatment with DBU, DMAP and TMG even after the reaction was performed for 4 h. However, DABCO did result in the desired product but in a modest yield of 52 %. Also, inorganic bases, such as KOH, MeONa and NaH gave either trace amounts or no products formed at all under the same condition.

Fortunately, other strong bases, such as *n*-BuLi, LDA, *t*-BuONa and *t*-BuOK, generated products all in over 80% chemical yields and complete diastereoselectivity, among them *t*-BuOK and *t*-BuONa gave highest yields of 96 % and 88 %, respectively. In the presence of the latter two bases, the reaction also occurred at faster rates and reached completion within 2 h at -78 °C in DCM. The pure individual isomeric product can be obtained simply by washing the crude products with the co-solvents of hexane and EtOAc (v:v = 2:1) without operating chromatography and recrystallization. Interestingly, when the reaction was performed in THF in the presence of *t*-LDA there was no product observed at all.

Under the above optimized condition, the substrate scope was next examined. As revealed by Table 1, ten substrates attached by both electron-donating and electron-withdrawing groups showed excellent chemical yields (91–97%) and excellent diastereoselectivities (dr > 99:1). Essentially, only single diastereoisomer was detected for each case by using ³¹P-NMR analysis of crude products. All single isomeric products can be obtained *via* GAP chemistry process without using traditional column chromatography and recrystallization. One-time washing of crude products with co-solvents of hexane and EtOAc (v:v = 2:1) was proven to be efficient enough to yield pure isomers.

As compared with our previous synthesis of α,β-diamino esters, the present reaction not only differentiated *anti* and *syn* stereochemistry controlling, but also enhanced the outcomes in regard to both yields and diastereoselectivity for all *N*-phosphonyl imine substrates.^{6–7}

Under the previous system involving *N*-(diphenylmethylene) glycine ester *E*-enolate, only the phenyl substrate (entry 1, Table 1) gave >99% dr and 85% yield. In contrast, the present Ni(II) complexed glycine ester *Z*-enolate not only led to >99% dr but also gave a much high yield of 96%. Two difficult substrates of *p*-NO₂-Ph and *p*-F-Ph imines (entries 8 and 10, Table 1), the *N*-(diphenylmethylene) glycine ester *E*-enolate generated the yield of 75 % and *dr* ratios of 100/11 and 100/7, respectively. However, these two substrates afforded the diastereoselectivity of >99% and yields of 93% and 95%, respectively, under the nickel (II)-complexed glycine ester *Z*-enolate condition.

Obviously, the bulkiness of nickel (II) complexed glycine-derived *Z*-enolate is believed to play a key role during asymmetric generation of the complete diastereoselectivity for all ten substrates. Besides the unique polarity of *N*-phosphonyl functional auxiliary, the polarity of nickel (II) complex should also attribute to the high GAP efficiency in regard to the formation of solid products that are subjected to convenient washing.

It has been proven that all four bases of *n*-BuLi, LDA, *t*-BuONa and *t*-BuOK resulted in the same configuration of (2*R*, 3*S*)- α,β -diamino products, the asymmetric induction is proposed to go through a cyclic six-membered transition state as shown in Figure 2.^{4–7} The aromatic ring on the axial position is arranged nearly parallel to the planar structure of nickel (II) complex to avoid diaxial interaction. The actual asymmetric induction is imposed by vicinal *N,N*-diisopropyl-attached nitrogen centers that are forced to be chiral by the adjacent two phenyl groups on the five-membered ring. As previously suggested in similar transition states,^{4–7} the oxygen of *N*-phosphonyl group doesn't participate in coordination due to the serious diaxial interactions. The nickel (II) complexed glycine-derived *Z*-enolate attacks the *N*-phosphonyl imine from its *Re* face to exclusively generate the *S*-configuration at β -position of diamino acid product. The *syn* stereochemistry of diamino groups can be readily interpreted by the *Z*-geometry of the enolate which is fixed by the Ni(II)-complex cyclic ring.

In summary, the GAP asymmetric synthesis of α,β -diamino acid derivatives has been achieved by reacting chiral *N*-phosphonyl imines with Ni(II)-complex of glycine ester-based enolate without using traditional purifications of chromatography and recrystallization. Complete diastereoselectivity and excellent chemical yields have been obtained for a good scope of substrates. The new synthesis overcame the disadvantage of previous methods that required at least 5 equiv of glycine Schiff base enolate nucleophile. In contrast, the present synthesis can complement the previous methods that can only give *anti*- α,β -diamino acid esters, and enable the all four individual isomeric product to be obtained. The absolute stereochemistry has been unambiguously determined by X-ray structural analysis.

Experimental section

General Method

All commercially available solvents, unless otherwise mentioned, were used without purification. Solvents were dried and distilled prior to use by the usual methods. The starting material **2** was prepared according to reported method.⁹ Melting points were uncorrected. ¹H, ¹³C and ³¹P NMR (TMS used as internal standard) spectra were recorded with Bruker ARX 300, 400, 600 spectrometers. Optical rotations were recorded with Rudolph Autopol IV-T instrument. IR spectra was collected with Nicolet iS5 Ftir spectrometer (KBr pellets). High-resolution mass spectra for all the new compounds were collected on Agilent 1260–6540 Q-TOF LC/MS.

Typical procedure for the reaction

Into a dry vial was added nickel complex **2** (0.44 mmol), *t*-BuOK powders (0.48 mmol), CH₂Cl₂ (5.0 mL) under a nitrogen atmosphere protection. The mixture was cooled down to –78 °C and stirred for 15 min. After that, phosphonyl imine **1** (0.4 mmol in 5 ml DCM) was added dropwise to the reaction mixture within 10 min. The reaction mixture was stirred for another 2 h before it was quenched with saturated aqueous NaHCO₃ solution (1.0 mL). The mixture was dried with anhydrous Na₂SO₄, then filtered and washed with EtOAc. The combined organic layers was concentrated to dryness and added by 6.0 of ml of EtOAc/

hexane (v/v = 1/2), followed by filtration and washing with the same co-solvent afforded pure product **3**.

Compound 3a. Red solid (331 mg, 96% yield); Mp = 220–222 °C; $[\alpha]_D^{20} = -229.2$ (c 1.04, CHCl₃); ¹H NMR (400 MHz, CD₃OD) δ 8.61 (d, *J* = 8.5 Hz, 1H), 8.04–8.01 (m, 1H), 7.72–7.61 (m, 7H), 7.53–7.21 (m, 16H), 6.87–6.83 (m, 1H), 6.75–6.74 (m, 2H), 4.85–4.79 (m, 1H), 4.75–4.70 (m, 1H), 4.51 (d, *J* = 4.8 Hz, 1H), 4.11–4.04 (m, 2H), 2.93–2.84 (m, 1H), 2.74–2.64 (m, 1H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.76 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 6.6 Hz, 3H), 0.60 (d, *J* = 6.7 Hz, 3H) ppm; ¹³C NMR (101 MHz, CD₃OD) δ 179.7, 174.6, 170.8, 154.0, 147.8, 145.3, 144.5, 144.4, 142.0, 141.9, 135.8, 134.9, 134.6, 131.8, 131.2, 130.5, 130.4, 130.0, 129.9, 129.7, 129.4, 129.3, 129.0, 128.9, 128.6, 128.2, 127.8, 125.2, 124.9, 123.0, 77.1 (d, *J* = 9.4 Hz), 67.1 (d, *J* = 15.1 Hz), 66.2 (d, *J* = 13.9 Hz), 59.7, 46.7 (d, *J* = 2.3 Hz), 46.6 (d, *J* = 2.8 Hz), 23.1 (d, *J* = 2.3 Hz), 22.8 (d, *J* = 4.8 Hz), 21.0, 20.9 ppm; ³¹P NMR (162 MHz, DMSO) δ 18.4; IR (KBr): ν = 2967, 1731, 1647, 1589, 1440, 1328, 1229, 1168, 754, 701 cm⁻¹; HRMS (ESI/[M+H]⁺) calcd. for C₄₈H₄₈N₆NiO₄P, 861.2828, found 861.2822.

Compound 3b. Red solid (357 mg, 95% yield); Mp = 214–216 °C; $[\alpha]_D^{20} = -201.5$ (c 3.63, CHCl₃); ¹H NMR (400 MHz, CD₃OD) δ 8.62 (d, *J* = 8.6 Hz, 1H), 8.13–8.10 (m, 1H), 7.76–7.62 (m, 7H), 7.54–7.27 (m, 16H), 6.79–6.76 (m, 2H), 4.82–4.69 (m, 2H), 4.52 (d, *J* = 5.1 Hz, 1H), 4.10–4.06 (m, 2H), 2.96–2.87 (m, 1H), 2.70–2.61 (m, 1H), 0.81 (d, *J* = 6.6 Hz, 6H), 0.71 (d, *J* = 6.6 Hz, 3H), 0.63 (d, *J* = 6.6 Hz, 3H) ppm; ¹³C NMR (75 MHz, CD₃OD) δ 179.4, 174.8, 170.8, 153.6, 147.7, 145.2 (2), 144.4, 142.6, 141.4, 135.8, 134.8, 134.7, 132.6, 132.4, 131.8, 131.2, 130.5, 130.0, 129.9, 129.7, 129.0, 128.7, 128.2, 127.8, 125.5, 125.2, 123.5, 123.0, 76.9 (d, *J* = 9.1 Hz), 67.0 (d, *J* = 15.6 Hz), 66.3 (d, *J* = 13.9 Hz), 59.2, 46.7 (d, *J* = 4.8 Hz), 46.6 (d, *J* = 5.4 Hz), 23.2, 22.8 (d, *J* = 4.5 Hz), 21.1, 20.9 ppm; ³¹P NMR (162 MHz, DMSO) δ 18.4; IR (KBr): ν = 2969, 1739, 1648, 1589, 1441, 1327, 1225, 1167, 754 cm⁻¹; HRMS (ESI/[M+H]⁺) calcd. for C₄₈H₄₇BrN₆NiO₄P, 939.1933, found 939.1922.

Compound 3c. Red solid (328 mg, 92% yield); Mp = 214–216 °C; $[\alpha]_D^{20} = -234.5$ (c 0.96, CHCl₃); ¹H NMR (300 MHz, CDOD) δ 8.56 (d, *J* = 8.6 Hz, 1H), 8.00–7.95 (m, 1H), 7.65–7.55 (m, 7H), 7.40–7.19 (m, 14H), 6.72–6.63 (m, 4H), 4.77–4.73 (m, 1H), 4.49 (d, *J* = 5.0 Hz, 1H), 4.08–4.01 (m, 2H), 3.45 (s, 3H), 2.94–2.81 (m, 1H), 2.73–2.60 (m, 1H), 0.79–0.75 (m, 6H), 0.70 (d, *J* = 6.6 Hz, 3H), 0.60 (d, *J* = 6.7 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDOD) δ 179.8, 174.4, 170.8, 161.3, 153.9, 147.9, 145.3 (2), 144.5, 144.4, 142.1, 135.7, 134.8, 134.6, 133.8, 131.7, 131.6, 131.1, 130.5, 130.0, 129.9, 129.7, 129.0, 128.5, 128.2, 127.8, 125.2, 124.9, 123.0, 114.4, 77.3 (d, *J* = 9.8 Hz), 67.3 (d, *J* = 15.52 Hz), 66.4 (d, *J* = 14.09 Hz), 59.2, 55.4, 46.7 (d, *J* = 4.5 Hz), 46.6 (d, *J* = 5.0 Hz), 23.1, 22.9 (d, *J* = 4.4 Hz), 21.1, 20.9 ppm; ³¹P NMR (162 MHz, DMSO) δ 18.4; IR (KBr): ν = 2965, 1647, 1607, 1440, 1329, 1230, 1177, 754 cm⁻¹; HRMS (ESI/[M+H]⁺) calcd. for C₄₉H₅₀N₆NiO₄P, 891.2934, found 891.2928.

Compound 3d. Red solid (347 mg, 97% yield); Mp = 218–220 °C; $[\alpha]_D^{20} = -223.2$ (c 1.20, CHCl₃); ¹H NMR (400 MHz, CD₃OD) δ 8.59 (d, *J* = 8.5 Hz, 1H), 8.10–8.06 (m, 1H), 7.73–7.62 (m, 7H), 7.52–7.21 (m, 16H), 6.78–6.73 (m, 2H), 4.83–4.78 (m, 1H), 4.72–4.67 (m,

1H), 4.50 (d, $J = 5.0$ Hz, 1H), 4.08-4.03 (m, 2H), 2.94-2.84 (m, 1H), 2.68-2.59 (m, 1H), 0.79 (d, $J = 2.1$ Hz, 3H), 0.77 (d, $J = 2.0$ Hz, 3H), 0.68 (d, $J = 6.6$ Hz, 3H), 0.60 (d, $J = 6.7$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ 179.5, 174.9, 170.8, 153.7, 147.8, 145.2, 144.4(2), 142.5, 141.0, 135.8, 135.5, 134.8, 134.7, 132.1, 131.8, 131.2, 130.6, 130.0, 129.9, 129.7, 129.5, 129.0, 128.9, 128.7, 128.2, 127.8, 125.4, 125.2, 123.0, 76.9 (d, $J = 9.9$ Hz), 67.0 (d, $J = 15.7$ Hz), 66.3 (d, $J = 13.9$ Hz), 59.1, 46.7 (d, $J = 5.1$ Hz), 46.6 (d, $J = 5.6$ Hz), 23.2, 22.8 (d, $J = 4.4$ Hz), 21.1, 20.9 ppm; ^{31}P NMR (162 MHz, DMSO) δ 18.4; IR (KBr): $\nu = 2969$, 1648, 1607, 1441, 1329, 1274, 1226, 1167, 754 cm^{-1} ; HRMS (ESI/[M+H] $^{+}$) calcd. for $\text{C}_{48}\text{H}_{47}\text{ClN}_6\text{NiO}_4\text{P}$, 895.2438, found 895.2423.

Compound 3e. Red solid (353 mg, 94% yield); Mp = 218–220 °C; $[\alpha]_D^{20} = -208.5$ (c 1.03, CHCl_3); ^1H NMR (400 MHz, CD_3CN) δ 8.77 (d, $J = 9.0$ Hz, 1H), 8.02-7.98 (m, 1H), 7.75-7.69 (m, 3H), 7.63-7.57 (m, 3H), 7.51-7.19 (m, 16H), 6.82 (s, 1H), 6.81 (s, 1H), 6.67-6.63 (m, 1H), 5.39-5.33 (m, 1H), 4.53-4.48 (m, 1H), 4.32 (d, $J = 4.6$ Hz, 1H), 4.04-3.99 (m, 2H), 2.79-2.69 (m, 1H), 2.61-2.52 (m, 1H), 0.66-0.64 (m, 6H), 0.60-0.55 (m, 6H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 177.1, 173.9, 168.8, 153.3, 146.6, 144.8, 143.8, 143.7, 140.7, 139.9, 134.7, 133.7, 133.4, 132.7, 130.4, 130.2, 130.0, 129.0, 128.7, 128.5, 128.0, 127.5, 127.4, 127.3, 127.0, 126.8, 126.2, 126.0, 123.6, 123.4, 121.3, 77.0, 65.7 (d, $J = 15.3$ Hz), 64.5 (d, $J = 13.7$ Hz), 57.0, 45.3 (d, $J = 5.5$ Hz), 45.1 (d, $J = 5.7$ Hz), 22.6, 22.2 (d, $J = 4.2$ Hz), 20.6, 20.5 ppm; ^{31}P NMR (162 MHz, CD_3CN) δ 18.5; IR (KBr): $\nu = 2971$, 1729, 1642, 1605, 1441, 1326, 1167, 753, 705 cm^{-1} ; HRMS (ESI/[M+H] $^{+}$) calcd. for $\text{C}_{48}\text{H}_{47}\text{BrN}_6\text{NiO}_4\text{P}$, 939.1933, found 939.1926.

Compound 3f. Red solid (342 mg, 91% yield); Mp = 231–233 °C; $[\alpha]_D^{20} = -211.9$ (c 0.62, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 8.80 (d, $J = 8.4$ Hz, 1H), 7.92-7.89 (m, 2H), 7.78 (d, $J = 7.0$ Hz, 1H), 7.71 (d, $J = 4.1$ Hz, 2H), 7.55-7.51 (m, 3H), 7.41-7.37 (m, 7H), 7.28-7.24 (m, 7H), 7.17-7.14 (t, $J = 15.7$ Hz, 1H), 6.95 (d, $J = 7.4$ Hz, 1H), 6.80 (s, 2H), 4.84-4.77 (m, 1H), 4.53-4.48 (m, 1H), 4.32 (d, $J = 4.2$ Hz, 1H), 3.97-3.95 (m, 2H), 2.96-2.83 (m, 1H), 2.67-2.55 (m, 1H), 0.78-0.71 (m, 6H), 0.69-0.67 (m, 3H), 0.54-0.52 (m, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 177.0, 172.9, 169.3, 152.9, 146.8, 144.6, 143.5(2), 143.4, 140.1, 134.7, 133.8, 133.2, 131.6, 131.0, 130.2, 129.5, 128.9, 128.8, 128.6, 128.5, 128.1, 127.5(2), 126.9, 126.8, 126.2, 123.8, 123.7, 122.9, 121.6, 75.8 (d, $J = 9.8$ Hz), 66.1 (d, $J = 16.2$ Hz), 64.1 (d, $J = 13.9$ Hz), 58.6, 45.2 (d, $J = 5.7$ Hz), 45.1 (d, $J = 5.2$ Hz), 22.6, 22.5, 22.3, 20.6 ppm; ^{31}P NMR (162 MHz, DMSO) δ 18.4; IR (KBr): $\nu = 2969$, 1648, 1440, 1328, 1167, 1071, 752, 700 cm^{-1} ; HRMS (ESI/[M+H] $^{+}$) calcd. for $\text{C}_{48}\text{H}_{47}\text{BrN}_6\text{NiO}_4\text{P}$, 939.1933, found 939.1920.

Compound 3g. Red solid (337 mg, 94% yield); Mp = 201–203 °C; $[\alpha]_D^{20} = -189.5$ (c 1.15, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.82 (d, $J = 8.6$ Hz, 1H), 7.92-7.88 (m, 1H), 7.82-7.77 (m, 2H), 7.70-7.63 (m, 3H), 7.52-7.24 (m, 16H), 7.04 (t, $J = 15.0$ Hz, 1H), 6.84-6.78 (m, 2H), 6.70 (t, $J = 14.3$ Hz, 1H), 5.63-5.57 (m, 1H), 4.53-4.48 (m, 1H), 4.37 (d, $J = 5.1$ Hz, 1H), 3.99-3.96 (m, 2H), 2.88-2.78 (m, 1H), 2.72-2.63 (m, 1H), 0.75-0.71 (m, 6H), 0.68 (d, $J = 6.4$ Hz, 3H), 0.51 (d, $J = 5.9$ Hz, 3H) ppm; ^{13}C NMR (101 MHz, CDCl_3) δ 177.2, 173.9, 168.8, 153.3, 146.6, 149, 143.8, 143.6, 143.4, 139.9, 139.2, 136.0, 134.7, 133.6, 133.4, 130.3, 130.1, 130.0, 129.4, 128.9, 128.7, 128.5, 128.0, 127.4, 126.9, 126.8, 126.4, 126.2, 126.0, 123.6, 123.4, 121.4, 77.2, 65.7 (d, $J = 16.8$ Hz), 64.4 (d, $J = 14.8$ Hz),

54.5 (d, $J = 2.4$ Hz), 45.2 (d, $J = 5.2$ Hz), 45.0 (d, $J = 5.7$ Hz), 22.6 (d, $J = 2.3$ Hz), 22.2 (d, $J = 4.8$ Hz), 20.6, 20.5 ppm; ^{31}P NMR (162 MHz, DMSO) δ 18.0; IR (KBr): $\nu = 2969, 1646, 1545, 1440, 1327, 1236, 1168, 753, 705\text{ cm}^{-1}$; HRMS (ESI/[M+H] $^{+}$) calcd. for $\text{C}_{48}\text{H}_{47}\text{ClN}_6\text{NiO}_4\text{P}$, 895.2438, found 895.2430.

Compound 3h. Red solid (344 mg, 95% yield); Mp = 208–210 °C; $[\alpha]_D^{20} = -248.1$ (c 0.60, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.75 (d, $J = 8.7$ Hz, 1H), 8.10 (d, $J = 8.1$ Hz, 2H), 7.91–7.86 (m, 3H), 7.78–7.73 (m, 2H), 7.57–7.55 (m, 3H), 7.44–7.22 (m, 14H), 6.86–6.82 (m, 2H), 5.02–4.97 (m, 1H), 4.72–4.67 (m, 1H), 4.41 (d, $J = 4.8$ Hz, 1H), 4.02 (d, $J = 9.7$ Hz, 2H), 2.94–2.84 (m, 1H), 2.66–2.57 (m, 1H), 0.78 (d, $J = 6.6$ Hz, 6H), 0.70 (d, $J = 6.5$ Hz, 3H), 0.56 (d, $J = 6.7$ Hz, 3H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 176.7, 173.4, 168.8, 152.8, 148.7, 147.8, 146.3, 144.4, 143.3(2), 140.6, 134.7, 134.1, 133.1, 130.4, 130.3, 130.2, 129.0, 128.8, 128.6, 128.1, 127.6, 127.0, 126.8, 126.7, 126.0, 123.9, 123.1, 121.8, 75.8 (d, $J = 6.5$ Hz), 65.7 (d, $J = 15.8$ Hz), 64.4 (d, $J = 13.8$ Hz), 59.0, 45.3 (d, $J = 4.7$ Hz), 45.0 (d, $J = 5.2$ Hz), 22.6, 22.4 (d, $J = 4.1$ Hz), 20.6 ppm; ^{31}P NMR (162 MHz, DMSO) δ 18.5; IR (KBr): $\nu = 2968, 1648, 1524, 1441, 1345, 1168, 701\text{ cm}^{-1}$; HRMS (ESI/[M+H] $^{+}$) calcd. for $\text{C}_{48}\text{H}_{47}\text{N}_7\text{NiO}_6\text{P}$, 906.2679, found 906.2667.

Compound 3i. Red solid (328 mg, 92% yield); Mp = 227–229 °C; $[\alpha]_D^{20} = -179.5$ (c 0.47, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.83 (d, $J = 8.2$ Hz, 1H), 7.94–7.89 (m, 1H), 7.80–7.68 (m, 2H), 7.58–7.48 (m, 2H), 7.45–7.26 (m, 16H), 7.12 (t, $J = 15.8$ Hz, 1H), 6.86–6.74 (m, 2H), 6.32 (d, $J = 8.4$ Hz, 1H), 4.87–4.84 (m, 1H), 4.53 (t, $J = 21.6$ Hz, 1H), 4.32 (d, $J = 4.8$ Hz, 1H), 3.99–3.96 (m, 2H), 3.55 (s, 3H), 2.98–2.89 (m, 1H), 2.71–2.62 (m, 1H), 0.76 (d, $J = 5.6$ Hz, 6H), 0.71 (d, $J = 7.5$ Hz, 3H), 0.52 (d, $J = 6.5$ Hz, 3H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 177.3, 172.5, 169.1, 159.5, 153.2, 146.5, 144.7, 143.4, 142.1, 139.9, 134.6, 133.7, 133.3, 130.1, 129.1, 128.8, 128.7, 128.5, 128.2, 127.5, 127.4, 126.8, 126.3, 126.2, 123.7, 123.6, 121.5, 121.3, 114.2, 113.7, 76.1 (d, $J = 9.6$ Hz), 65.0 (d, $J = 14.8$ Hz), 64.2 (d, $J = 12.5$ Hz), 59.2, 57.6, 45.2 (d, $J = 4.9$ Hz), 45.0 (d, $J = 5.7$ Hz), 22.4, 22.3 (d, $J = 5.8$ Hz), 20.6, 20.5 ppm; ^{31}P NMR (162 MHz, DMSO) δ 18.4; IR (KBr): $\nu = 2969, 1607, 1440, 1328, 1274, 1168, 701\text{ cm}^{-1}$; HRMS (ESI/[M+H] $^{+}$) calcd. for $\text{C}_{49}\text{H}_{50}\text{N}_6\text{NiO}_4\text{P}$, 891.2934, found 891.2928.

Compound 3j. Red solid (372 mg, 93% yield); Mp = 201–203 °C; $[\alpha]_D^{20} = -251.4$ (c 1.09, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.75 (d, $J = 7.6$ Hz, 1H), 7.90 (t, $J = 15.2$ Hz, 1H), 7.78–7.70 (m, 4H), 7.56–7.50 (m, 3H), 7.41–7.23 (m, 13H), 7.10 (t, $J = 15.1$ Hz, 1H), 6.89–6.80 (m, 4H), 5.42 (m, 1H), 4.56 (t, $J = 22.8$ Hz, 1H), 4.37 (d, $J = 3.5$ Hz, 1H), 3.99–3.96 (m, 2H), 2.95–2.85 (m, 1H), 2.68–2.59 (m, 1H), 0.78–0.75 (m, 6H), 0.69 (d, $J = 7.6$ Hz, 3H), 0.55 (d, $J = 6.8$ Hz, 3H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 177.2, 173.9, 168.9, 162.4, 160.8, 153.3, 146.7, 144.6, 143.4, 143.3, 139.9, 134.6, 133.6, 133.3, 130.3, 130.1, 129.6, 129.2, 128.7, 128.6, 128.5, 128.2, 127.5, 127.4, 126.9, 126.7, 126.2, 123.7, 123.6, 121.4, 115.6, 115.5, 75.4 (d, $J = 9.2$ Hz), 65.9 (d, $J = 15.0$ Hz), 64.4 (d, $J = 14.6$ Hz), 50.8, 45.2 (d, $J = 5.6$ Hz), 45.1 (d, $J = 6.2$ Hz), 22.5, 22.3 (d, $J = 4.0$ Hz), 20.5(2) ppm; ^{31}P NMR (162 MHz, DMSO) δ 18.3; IR (KBr): $\nu = 2968, 1647, 1441, 1329, 1275, 1230, 1168, 754\text{ cm}^{-1}$; HRMS (ESI/[M+H] $^{+}$) calcd. for $\text{C}_{48}\text{H}_{47}\text{FN}_6\text{NiO}_4\text{P}$, 879.2734, found 879.2726.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the financial support from NIH (R21DA031860-01, Li), Robert A. Welch Foundation (D-1361, Li), the National Natural Science Foundation of China (No. 21102071, Pan), the Fundamental Research Funds for the Key Universities (No. 1107020522 and No. 1082020502, Pan) and the Jiangsu 333 program (Pan). We would like to thank Prof Vadim A. Soloshonok for helpful discussions.

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Figure 1.
X-ray crystallography for **3b**.

Figure 2.
Asymmetric induction transition state

Scheme 1.

Table 1

Reaction results of *N*-phosphonyl imines with nickel(II) complexed glycine ester enolate

Entry	Ar	Product	[α] _D ²⁰ (CHCl ₃)	Yield (%) ^b	dr ^c
1	Ph	3a	-229.2 (c 1.04)	96	> 99 : 1
2	4-Br-C ₆ H ₅	3b	-201.5 (c 3.63)	95	> 99 : 1
3	4-MeO-C ₆ H ₅	3c	-234.5 (c 0.96)	92	> 99 : 1
4	4-Cl-C ₆ H ₅	3d	-223.2 (c 1.20)	97	> 99 : 1
5	2-Br-C ₆ H ₅	3e	-208.5 (c 1.03)	94	> 99 : 1
6	3-Br-C ₆ H ₅	3f	-211.9 (c 0.62)	91	> 99 : 1
7	2-Cl-C ₆ H ₅	3g	-189.5 (c 1.15)	94	> 99 : 1
8	4-NO ₂ -C ₆ H ₅	3h	-248.1 (c 0.60)	95	> 99 : 1
9	3-MeO-C ₆ H ₅	3i	-179.5 (c 0.47)	92	> 99 : 1
10	2-F-C ₆ H ₅	3j	-251.4 (c 1.09)	93	> 99 : 1

^[a] Conditions: 1 (0.40 mmol), 2 (0.44 mmol), with *t*-BuOK (0.48 mmol) in DCM (10 ml) at -78 °C for 2 h.

^[b] Diastereomeric ratios were determined by using ³¹P-NMR analysis of crude products.

^[c] Isolated yields.