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## INVESTIGATION ON AMINO-HECK CYCLIZATION OF 1-(2-VINYLCYCLOHEXYL)KETONE DIETHYL PHOSPHINYLOXIMES

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**Abstract** – Upon the treatment with Pd(PPh<sub>3</sub>)<sub>4</sub> and Et<sub>3</sub>N in DMF at 80 °C, a range of *trans*-1-(2-vinylcyclohexyl)-substituted ketone diethylphosphinyloximes underwent the cyclization in a 6-*endo* pathway to afford 1-substituted tetrahydroisoquinolines in varying yields. Among which, the reactions of the substrates bearing the saturated alkyl groups were severely competed by hydrolysis and/or Beckmann rearrangement, while these undesired side reactions could be suppressed by introducing a β-aryl moiety possibly due to the stabilizing π-π stacking interactions between the phosphoryl and/or vinyl group and the aryl rings.

### INTRODUCTION

The palladium-catalyzed intramolecular cyclization of unsaturated acyloxime derivatives (amino-Heck reaction) has emerged as a powerful means for preparing aza-heterocyclic compounds.<sup>1,2</sup> The well-accepted mechanism for this process involves the oxidative insertion of Pd(0) to N-O bond, followed by the reaction of the resulting aminopalladium(II) complex with an internal olefin to form a cyclic product. To ensure an efficient annulation, the selection of the leaving groups on the oxime nitrogen has proven to be an important issue. First, this group should possess enough stability to minimize the competitive side reactions, mostly as Beckmann rearrangement and hydrolysis. On the other hand, it should also be sufficiently reactive towards the initial oxidative addition by Pd(0) catalyst. In term of achieving a subtle balance between the two demands, pioneering work by Narasaka and co-workers has established that *O*-pentafluorobenzoyl oximes are more useful in practice than many other types of oximes,<sup>2a</sup> and from which, the preparation of a large range of valuable heterocycles such as pyrroles,<sup>4</sup> pyridines,<sup>6</sup> imidazoles<sup>7</sup> and pyrrolines<sup>8</sup> have been realized.

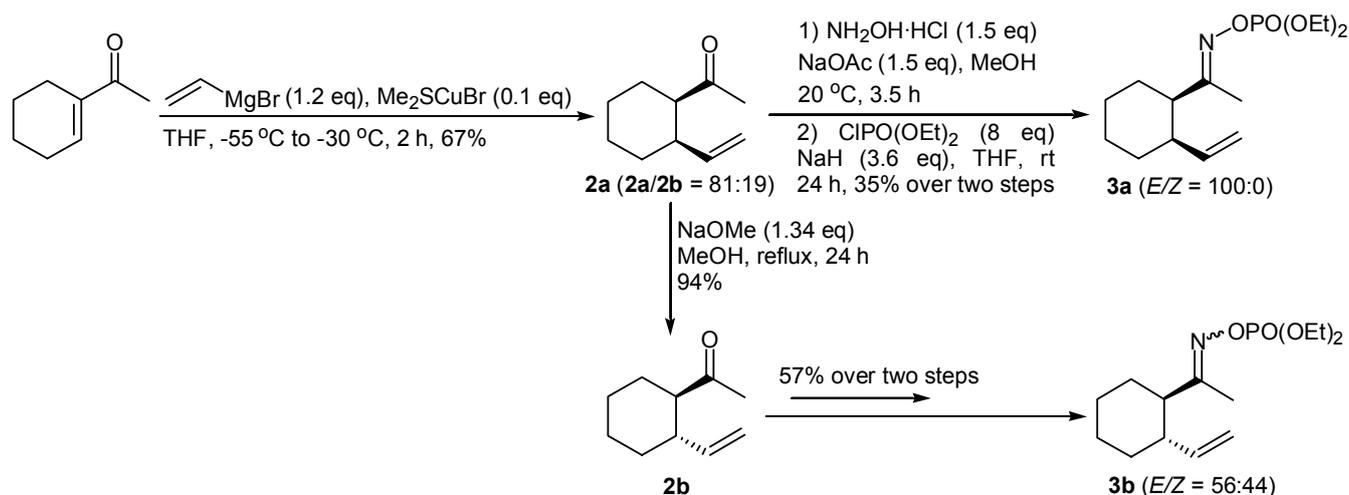
Recently we reported the application of *O*-diethylphosphinyloximes as the new precursors into amino-Heck reaction.<sup>10</sup> Under the catalysis of Pd(PPh<sub>3</sub>)<sub>4</sub>, the cyclization of a range of acyclic  $\gamma,\delta$ -, or  $\delta,\varepsilon$ -unsaturated phosphinyloximes occurred smoothly to provide the substituted pyrroles or pyridines in moderate to excellent yields. More interestingly, it was observed that the regioselectivity of the cyclization (*5-exo* versus *6-endo*) of the  $\gamma,\delta$ -unsaturated substrates could be controlled by the adjustment of catalytic conditions, to thus allow the selective generation of pyrroles<sup>10a</sup> or pyridines<sup>10b</sup> with the same precursors. Following this investigation, we have further extended the reaction to the 2-vinylcyclohexyl-substituted phosphinyloxime derivatives. To our knowledge, it is the first time that the amino-Heck reaction has been applied to the oximes bearing such structural motif. In addition to documenting the utility of the protocol in the construction of azabicyclic molecules, our research program is also aimed at investigating the substituting and steric factors playing on the cyclization. Herein we wish to disclose our preliminary experimental results.

## RESULTS AND DISCUSSION

To access the 2-vinylcyclohexyl-substituted precursors, we first carried out the 1,4-addition reaction of 1-acetylcyclohexene with vinylmagnesium bromide in the established protocol<sup>11</sup> to produce the known ketone **2a**<sup>11</sup> along with its *trans*-isomer **2b** (**2a/2b** = 81:19) (Scheme 1). The mixture was then allowed to react with hydroxylamine hydrochloride (NH<sub>2</sub>OH·HCl) in the presence of sodium acetate (NaOAc)<sup>10a</sup> to yield four oxime intermediates (*cis-E/cis-Z/trans-E/trans-Z* = 72:8.7:13.8:5.5). After chromatographic separation, the major *cis-E*-isomer<sup>12</sup> was treated with diethyl chlorophosphate [(EtO)<sub>2</sub>POCl] and sodium hydride (NaH) in THF to give the *cis*-substrate **3a** (*E/Z* = 100:0) (Scheme 1). Moreover, compound **2a** was further transformed into **2b** through the base-promoted isomerization,<sup>13</sup> which was similarly converted into the *trans*-substrate **3b** as a mixture of two isomers (*E/Z* = 56:44).<sup>14</sup>

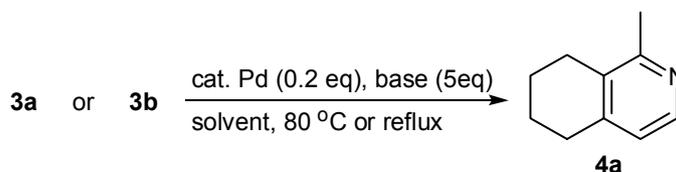
With **3a** and **3b** in hand, we submitted them to the amino-Heck reaction. We first examined the cyclization of **3a** under the catalysis of Pd(PPh<sub>3</sub>)<sub>4</sub> (0.2 equiv) in *N,N*-dimethylformamide (DMF) with the different bases<sup>10</sup> including triethylamine, 1,8-diazabicycloundec-7-ene (DBU), *N,N*-diisopropylethylamine (DIPEA), and K<sub>2</sub>CO<sub>3</sub> (Table 1). At 80 °C,<sup>15</sup> the cyclization reactions with triethylamine, DBU, and DIPEA all proceeded in a *6-endo* pathway and were followed by the in situ oxidative dehydrogenation mediated by palladium species<sup>10b</sup> to provide 1-methyl-5,6,7,8-tetrahydroisoquinoline (**4a**)<sup>16</sup> in 12-38% yields, and the best conversion was obtained with triethylamine (entry 3). Besides, large amounts of recovered **2a** (10-40%) were isolated from these reactions (Table 1, entries 1-3). On the other hand, the use of K<sub>2</sub>CO<sub>3</sub> did not afford any cyclization product but rather gave **2a** solely (entry 4). By using triethylamine as a base, we further screened the catalytic conditions of Pd(OAc)<sub>2</sub>/PPh<sub>3</sub>/DMF/80 °C and Pd(PPh<sub>3</sub>)<sub>4</sub>/CH<sub>3</sub>CN/reflux, but did not receive any

improvement on the yield (entries 5 and 6). The application of the catalytic conditions in entry 3 to **3b** led to the formation of **4a** in a slightly higher yield (40%, entry 7). Moreover, the time for the cyclization of **3b** (30 min) was found to be much shorter than that of **3a** (3 h), suggesting that *trans*-oxime precursors should be more suited for the cyclization than the *cis*-isomers due to the favorable proximity of the equatorial-equatorial steric relationship (Figure 1). As such, we utilized the *trans*-oximes throughout the following investigations.



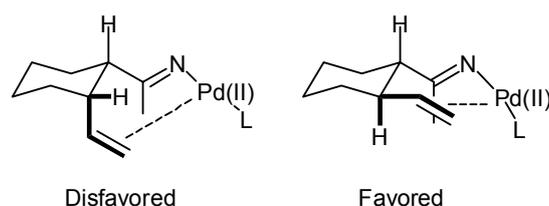
**Scheme 1.** Preparation of **3a** and **3b**

**Table 1.** Optimization of reaction conditions for Pd(PPh<sub>3</sub>)<sub>4</sub>-catalyzed cyclization of **3a** and **3b**



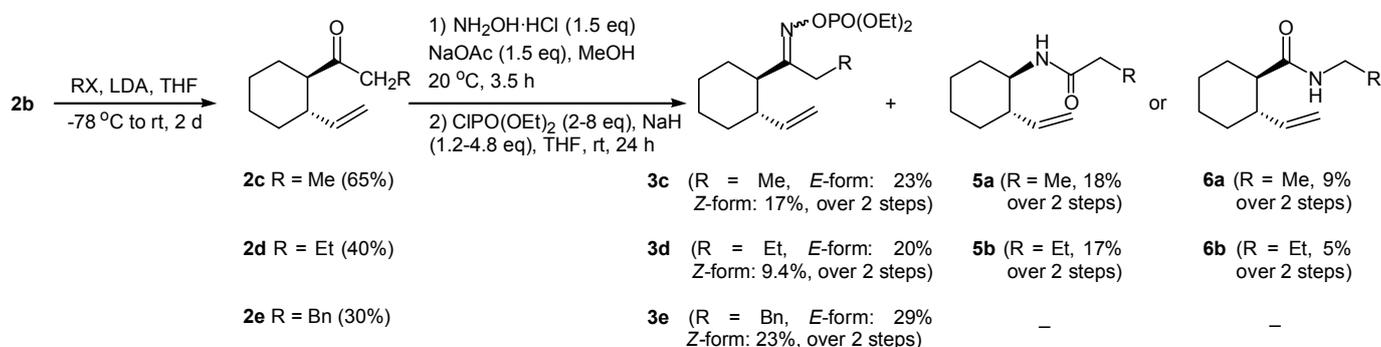
entry <sup>a</sup>	substrate	catalytic conditions	time (h)	yield (%) <sup>b</sup>
1	<b>3a</b>	Pd(PPh <sub>3</sub> ) <sub>4</sub> /DBU/DMF/80 °C	3	12
2	<b>3a</b>	Pd(PPh <sub>3</sub> ) <sub>4</sub> /DIPEA/DMF/80 °C	21	15
3	<b>3a</b>	Pd(PPh <sub>3</sub> ) <sub>4</sub> /Et <sub>3</sub> N/DMF/80 °C	3	38
4	<b>3a</b>	Pd(PPh <sub>3</sub> ) <sub>4</sub> /K <sub>2</sub> CO <sub>3</sub> /DMF/80 °C	3	-
5	<b>3a</b>	Pd(OAc) <sub>2</sub> /PPh <sub>3</sub> (0.4 eq)/Et <sub>3</sub> N/DMF/80 °C	23	21
6	<b>3a</b>	Pd(PPh <sub>3</sub> ) <sub>4</sub> /Et <sub>3</sub> N/MeCN/reflux	3	18
7	<b>3b</b>	Pd(PPh <sub>3</sub> ) <sub>4</sub> /Et <sub>3</sub> N/DMF/80 °C	0.5	40

a) All reactions were performed using 0.02 M of substrates. b) Isolated yields.

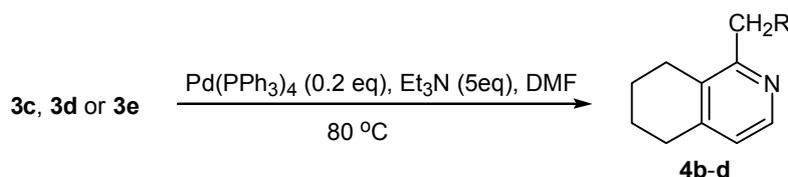


**Figure 1.** Effect of *cis*- and *trans*-steric relationships on cyclization

After the optimization of the catalytic conditions, we subsequently carried out the alkylation on **2b** with iodomethane, iodoethane and benzyl bromide, respectively, to prepare ketones **2c-e** (Scheme 2).<sup>17</sup> Their oximation afforded the hydroxyloxime intermediates uniformly as the separable *E*- and *Z*-isomers. During the phosphinylation, it was observed that partial phosphinyloximes derived from **2c** and **2d** (**3c** and **3d**) underwent the in situ rearrangement to yield amides **5a/5b** (from *E*-isomers) and **6a/6b** (from *Z*-isomers), which could be attributed to the increased steric hindrance as compared with **3b**. Interestingly, no rearrangement was seen for the phosphinylation of **3e**<sup>18</sup> bearing an even larger 2-phenylethyl group. The Pd(PPh<sub>3</sub>)<sub>4</sub>-catalyzed cyclization of **3c** and **3d** afforded isoquinolines **4b** and **4c** only in 14-34% yields (Table 2, entries 1-4), and the reactions were all severely competed by the rearrangement or the hydrolysis to give the corresponding amides or ketone. Markedly different from this, the cyclization of **3e** in *E*-form took place efficiently to furnish **4d** in 70% yield without giving any detectable by-products (entry 5). Besides, a synthetically useful yield of **4d** (53%) was also obtained from the *Z*-isomer (entry 6). For **3c-e**, it was noticed that the *E*-oximes (entries 1, 3 and 5) are more favored for the cyclization than the corresponding *Z*-isomers (entries 2, 4 and 6). Furthermore, we envision that the relatively high yields of **4d** should be due to a stabilizing  $\pi$ - $\pi$  interaction between the vinyl and the  $\beta$ -phenyl groups of **3e** to suppress the competitive side reactions. In addition, the reaction of the *E*-isomer may further benefit from an additional orbital interaction between the P=O bond and the benzene ring (Figure 2).

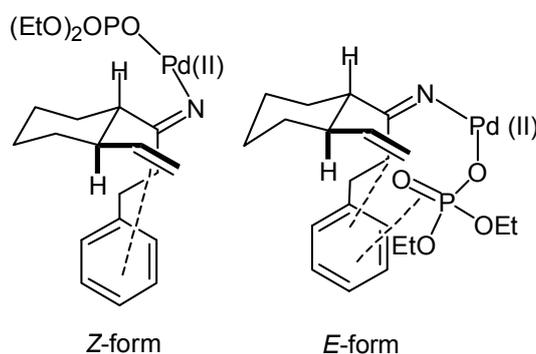


**Scheme 2.** Preparation of **3c-e**

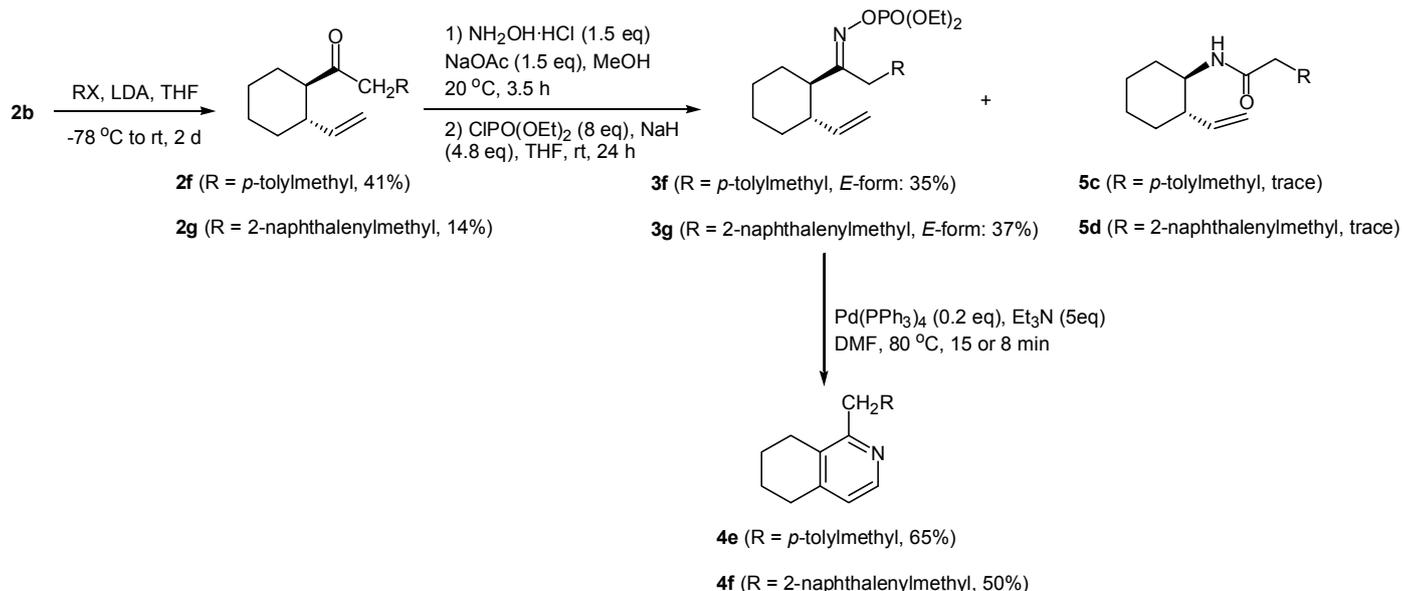
**Table 2.** Pd(PPh<sub>3</sub>)<sub>4</sub>-catalyzed cyclization of **3c-e**

entry <sup>a</sup>	substrate	time (min)	product(s) & yield (%) <sup>b</sup>
1	<b>3c</b> ( <i>E</i> -form)	11	<b>4b</b> (R = Me, 34%); <b>2c</b> (15%)
2	<b>3c</b> ( <i>Z</i> -form)	12	<b>4b</b> (R = Me, 17%); <b>2c</b> (30%)
3	<b>3d</b> ( <i>E</i> -form)	12	<b>4c</b> (R = Et, 22%); <b>5b</b> (20%)
4	<b>3d</b> ( <i>Z</i> -form)	13	<b>4c</b> (R = Et, 14%); <b>6b</b> (25%)
5	<b>3e</b> ( <i>E</i> -form)	15	<b>4d</b> (R = Bn, 70%)
6	<b>3e</b> ( <i>Z</i> -form)	15	<b>4d</b> (R = Bn, 53%)

a) All reactions were performed using 0.02 M of substrates. b) Isolated yields.

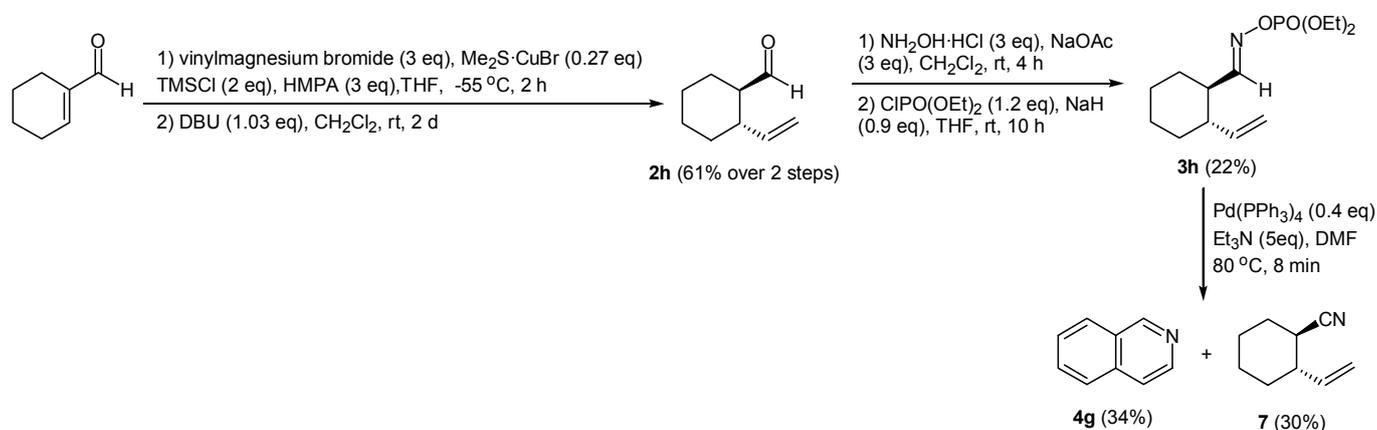
**Figure 2.** Possible stabilizing  $\pi$ - $\pi$  interactions of aminopalladium(II) intermediates of **3e**

To verify the effect of the  $\pi$ - $\pi$  interactions, we further synthesized the aromatic precursors **3f** and **3g** through the alkylation of **2b** with  $\alpha$ -bromo-*p*-xylene and 2-(bromomethyl)naphthalene, followed by the oximation and phosphinylation (Scheme 3, **2b**  $\rightarrow$  **2f/2g**  $\rightarrow$  **3f/3g**). In the sequence, the formation of trace amounts of amides **5c** and **5d** were also observed. Under the standard catalytic conditions, the cyclization of both substrates proceeded smoothly to provide **4e** and **4f** in good to acceptable yields without accompanying by hydrolysis and rearrangement, thus again confirming the positive role that the aryl moieties played on the cyclization.



**Scheme 3.** Preparation and Pd(PPh<sub>3</sub>)<sub>4</sub>-catalyzed cyclization of **3f** and **3g**

In addition to the ketone oximes, we also attempted the protocol on a phosphinylaldehyde. As outlined in Scheme 4, the synthesis of the precursor began with the 1,4-addition of 1-cyclohexene-1-carboxaldehyde followed by the isomerization<sup>19</sup> to afford aldehyde **2h**, which was subsequently transformed into **3h** as the sole *E*-isomer.<sup>20</sup> Herein, we used CH<sub>2</sub>Cl<sub>2</sub> as the solvent instead of previously employed CH<sub>3</sub>OH in the oximation step to avoid the formation of the acetal. Based on the previous experience,<sup>21</sup> we predicted that the cyclization of **3h** would be inevitably competed by the cyanation under the basic reaction conditions, and consequently utilized a duplicated catalytic loading (0.4 equiv) to minimize this. Under the catalysis, the reaction afforded 34% of isoquinoline (**4g**)<sup>10b,22</sup> together with 30% of cyanide **7** as the side product. Therefore the utility of the strategy has been further underscored by the generation of **4g** possessing the significant biological<sup>23</sup> and synthetic values.



**Scheme 4.** Preparation and Pd(PPh<sub>3</sub>)<sub>4</sub>-catalyzed cyclization of **3h**

In summary, we have disclosed that a range of 2-vinylcyclohexyl *O*-diethylphosphinyloximes underwent a 6-*endo* cyclization under the catalysis of Pd(PPh<sub>3</sub>)<sub>4</sub> to furnish tetrahydroisoquinoline derivatives in varying yields. As we know, it is the first time that this type of compounds has been prepared through the amino-Heck approach.<sup>24</sup> More importantly, we discovered that the undesired side reactions competing with the cyclization could be suppressed by introducing a β-aryl moiety, and the π-π stacking interactions between the phosphoryl and/or vinyl group and aryl ring are proposed to account for this. Therefore, this method should be of particular use for preparing the tetrahydroisoquinolines bearing an 2-arylethyl appendage.

## EXPERIMENTAL

All of starting materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran was distilled from sodium and benzophenone, *N,N*-dimethylformamide, triethylamine, diisopropylamine and dichloromethane were distilled from calcium hydride before use. TLC analysis and preparation were carried out on Merck 25 DC-Alufolien Kieselgel 60F254 glass-backed plates visualised by using UV light, or by means of ethanolic solution of vanillin (5%) with sulphuric acid (5%), iodine or aqueous KMnO<sub>4</sub> solution (10%). The flash chromatographic purifications were performed on Merck Art.9385 Kieselgel 60 silica gel (230–400 mesh) or Brockmann I basic aluminum oxide (~150 mesh). NMR spectra (<sup>1</sup>H, <sup>13</sup>C-NMR, DEPT, 2D-NOESY) were recorded on a Bruker 400 or Varian 600 MHz spectrometer using deuteriochloroform (CDCl<sub>3</sub>) as solvent. Chemical shifts measurements are reported in delta (δ) units. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Coupling constants (*J*) are reported in Hertz (Hz). Infrared (IR) spectra were recorded on an IR-FT JASCO 410 spectrophotometer (neat) and resonances are reported in wave numbers (cm<sup>-1</sup>). High resolution mass spectra (HRMS) were determined by a Finnigan/Thermo Quest MAT 95XL spectrometer in electron impact (EI) or electrospray ionization (ESI) modes.

**Typical Procedure for the Preparation of *o*-Diethylphosphinyloximes from Ketones; *cis*-(*E*)-Diethyl 1-(2-vinylcyclohexyl)ethylideneaminoxyphosphonate (3a):** To a stirred solution of 1-(2-vinylcyclohexyl)ethanone (**2a**) (*cis/trans* = 81:19, 354 mg, 2.33 mmol) in MeOH (6.4 mL), sodium acetate (289 mg, 3.50 mmol) and NH<sub>2</sub>OH·HCl (253 mg, 3.50 mmol) were successively added. The resulting suspension was stirred at 20 °C for 3.5 h, then diluted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and washed with water (40 mL x 2) and brine (40 mL). After concentration, the crude residue was purified by flash chromatography on silica gel (hexane-EtOAc 30:1, 5:1) to give the *cis*-*E*-oxime (213 mg) as the major isomer followed by the mixture of *cis*-*Z*- and the *trans*-*E*, *Z*-oximes (82.6 mg, *cis*-*Z*/*trans*-*E*/*trans*-*Z* = 31:49:20). *cis*-*E*-oxime: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.10 (broad s, 1H), 5.97 (m, 1H), 5.03 (dm, *J* = 10.8 Hz, 1H), 5.02 (dm, *J* = 16.3 Hz, 1H), 2.67 (ddd, *J* = 8.2, 7.8, 3.3 Hz, 1H), 2.34 (ddd, *J* = 11.3, 3.9,

3.9 Hz, 1H), 1.85–1.77 (m, 2H), 1.83 (s, 3H), 1.73–1.55 (m, 3H), 1.51–1.43 (m, 2H), 1.33–1.23 (m, 1H). *cis-Z*-oxime:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.12 (ddd,  $J = 17.2, 10.2, 9.5$  Hz, 1H), 5.08–4.86 (m, 2H), 3.30 (ddd,  $J = 12.8, 3.9, 3.8$  Hz, 1H), 2.87 (ddd,  $J = 9.1, 8.2, 3.4$  Hz, 1H), 1.74 (s, 3H), 1.72–1.67 (m, 2H), 1.52 (m, 4H), 1.42–1.26 (m, 2H). Under a nitrogen atmosphere, NaH (60%, 183 mg, 4.58 mmol) and diethyl chlorophosphate (95%, 1.55 mL, 10.2 mmol) were successively added to a stirred solution of *cis-E*-oxime (213 mg, 1.27 mmol) in dry THF (7.7 mL) pre-cooled at 0 °C. The reaction mixture was continued to stir for 24 h at room temperature, then cooled at 0 °C and carefully quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution (20 mL). The resulting mixture was diluted with EtOAc (100 mL), washed with water (20 mL x 2) and brine (20 mL), and concentrated under vacuo. The crude mixture was subjected to chromatographic purification on silica gel (hexane-EtOAc 15:1, 5:1, 3:1, 1:1) to afford **3a** as a pale yellow oil (248 mg, 35% over two steps).

IR (neat) 3050, 2982, 2932, 1637, 1448, 1276, 1033, 978, 916  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.95 (ddd,  $J = 17.0, 9.2, 8.8$  Hz, 1H), 4.98 (br d,  $J = 17.6$  Hz, 1H), 4.97 (br d,  $J = 9.2$  Hz, 1H), 4.23–4.10 (m, 4H), 2.61 (ddd,  $J = 8.4, 8.2, 3.8$  Hz, 1H), 2.47–2.43 (m, 1H), 1.86 (s, 3H), 1.81–1.71 (m, 2H), 1.70–1.57 (m, 3H), 1.48–1.41 (m, 2H), 1.31 (t,  $J = 7.0$ , 3H), 1.30 (t,  $J = 7.1$ , 3H), 1.27–1.19 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  168.9 (d,  $J = 12.4$  Hz), 137.7, 115.8, 64.4 (d,  $J = 5.9$  Hz), 64.2 (d,  $J = 5.8$  Hz), 47.4, 41.5, 32.1, 25.4, 24.1, 21.3, 16.2 (d,  $J = 6.5$  Hz), 14.8; HRMS-EI:  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{14}\text{H}_{26}\text{NO}_4\text{P}$ : 303.1599; found: 303.1594.

**trans-(E,Z)-Diethyl 1-(2-vinylcyclohexyl)ethylideneaminooxyphosphonate (3b)**: The typical procedure for the preparation of **3a** was followed; **2b** (211 mg, 1.39 mmol) was used as the starting material. Flash chromatography on silica gel (hexane-EtOAc 8:1, 5:1, 3:1, 2:1) gave **3b** as a mixture of two isomers ( $E/Z = 56:44$ ) in 57% (236 mg) yield over two steps.

The *E*- and *Z*-oxime intermediates were isolated as a inseperable mixture (hexane-EtOAc 30:1, 5:1):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) *E*-isomer:  $\delta$  8.19 (br s, 1H), 5.61 (ddd,  $J = 17.2, 10.2, 7.8$  Hz, 1H), 4.95 (dd,  $J = 17.3, 1.8$  Hz, 1H), 4.90 (dd,  $J = 10.3, 1.8$  Hz, 1H), 2.11–2.06 (m, 2H), 1.82–1.73 (m, 3H), 1.78 (s, 3H), 1.70 (m, 1H), 1.42–1.15 (m, 4H); *Z*-isomer:  $\delta$  8.36 (br s, 1H), 5.70–5.56 (m, 1H), 5.03–4.88 (m, 2H), 2.14–2.02 (m, 2H), 1.82–1.73 (m, 3H), 1.77 (s, 3H), 1.70 (m, 1H), 1.42–1.15 (m, 4H).

**3b**: IR (neat) 3050, 2982, 2928, 1639, 1278, 1033, 973, 916  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): *E*-isomer  $\delta$  5.64–5.52 (m, 1H), 5.00–4.84 (m, 2H), 4.25–4.10 (m, 4H), 2.29 (ddd,  $J = 11.3, 11.3, 3.2$  Hz, 1H), 2.12–1.98 (m, 1H), 1.85 (s, 3H), 1.82–1.67 (m, 5H), 1.37–1.27 (m, 8H), 1.24–1.15 (m, 1H); *Z*-isomer:  $\delta$  5.64–5.52 (m, 1H), 5.00–4.84 (m, 2H), 4.25–4.10 (m, 4H), 3.18 (m, 1H), 2.12–1.98 (m, 1H), 1.86 (s, 3H), 1.82–1.67 (m, 5H), 1.37–1.27 (m, 8H), 1.24–1.15 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ): *E*-isomer  $\delta$  169.8 (d,  $J = 12.3$  Hz), 141.5, 114.3, 64.3 (d,  $J = 5.8$  Hz), 64.1 (d,  $J = 5.5$  Hz), 48.4, 44.5, 32.7, 29.8, 25.5, 25.3, 16.1 (d,  $J = 6.4$  Hz), 11.9; *Z*-isomer:  $\delta$  169.9 (d,  $J = 13.2$  Hz), 141.2, 114.3, 64.3 (d,  $J = 5.2$  Hz),

64.2 (d,  $J = 6.6$  Hz), 43.7, 32.6, 28.6, 25.6, 25.2, 16.1 (d,  $J = 6.4$  Hz); HRMS-EI  $m/z$   $[M]^+$  cacl. for  $C_{14}H_{26}NPO_4$  303.1599; found 303.1608.

**Typical Procedure for Amino-Heck Cyclization of *trans*-2-Vinylcyclohexyl-substituted Phosphyloximes; 1-Methyl-5,6,7,8-tetrahydroisoquinoline (4a):** To a solution of **3b** (186 mg, 0.61 mmol) in dry DMF (30.7 mL, 0.02 M) was added  $Pd(PPh_3)_4$  (143 mg, 0.12 mmol) under  $N_2$ . The mixture was stirred at room temperature for 5 min before the addition of  $Et_3N$  (0.43 mL, 3.07 mmol). The reaction mixture was heated at 80 °C for 30 min, cooled to rt and diluted with water (30 mL). The solution was extracted with  $Et_2O$  (100 mL x 2). The combined organic layers were washed with water (40 mL x 2) and brine (40 mL). After concentration, the crude residue was subjected to chromatographic purification on aluminum oxide (hexane-EtOAc 50:1, 20:1, 10:1) to afford recovered **2b** (9.3 mg, 10%) followed by the known **4a**<sup>16</sup> (36 mg, 40%).

**4a:** IR (neat) 3051, 2929, 1643, 1567, 1589, 835, 808  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.15 (d,  $J = 5.0$  Hz, 1H), 6.82 (d,  $J = 5.0$  Hz, 1H), 2.71 (t,  $J = 6.2$  Hz, 2H), 2.61 (d,  $J = 6.2$  Hz, 2H), 2.42 (s, 3H), 1.88–1.80 (m, 2H), 1.79–1.72 (m, 2H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  156.9, 146.0, 145.1, 130.9, 122.1, 29.4, 25.9, 23.0, 22.1; HRMS-EI  $m/z$   $[M]^+$  cacl. for  $C_{10}H_{13}N$  147.1048; found 147.1042.

**Typical Procedure for Alkylation of 2b; *trans*-1-(2-vinylcyclohexyl)propan-1-one (2c):** Under a  $N_2$  atmosphere, a solution of *n*-BuLi (2.25 mL, 1.6 M in hexane, 3.60 mmol) was slowly added to a stirred solution of diisopropylamine (0.5 mL, 3.60 mmol) in dry THF (4.7 mL) pre-cooled to 0 °C via a syringe in 5 min. The resulting pale-yellow solution was then cooled at -78 °C and stirred for 30 min. After this, a solution of **2b** (498 mg, 3.27 mmol) in dry THF (3.7 mL) was added dropwise to the mixture via a syringe within 18 min, and stirring was continued for an additional 30 min at -78 °C before the quick addition of iodomethane (0.19 mL, 2.94 mmol). The mixture was allowed to stir at room temperature for 42 h, then diluted with saturated aqueous  $NH_4Cl$  solution (15 mL) and extracted with  $Et_2O$  (100 mL). The organic layer was separated and washed with water (40 mL x 2) and brine (40 mL). The combined aqueous layers were re-extracted with another portion of  $Et_2O$  (100 mL) and the organic layer was washed with water and brine. The combined organic layers were concentrated under reduced pressure, and the crude residue was purified by flash chromatography on silica gel (hexane-EtOAc 300:1, 150:1) to give **2c** in 65% yield (355.4 mg,) along with recovered **2b** (54 mg).

**2c:** IR (neat) 3078, 2974, 2931, 1711, 1640, 917, 622  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  5.65 (ddd,  $J = 17.2, 10.2, 7.6$  Hz, 1H), 4.94 (dm,  $J = 17.1$  Hz, 1H), 4.89 (dd,  $J = 10.3, 1.8$  Hz, 1H), 2.51–2.26 (m, 4H), 1.80–1.71 (m, 4H), 1.38–1.15 (m, 4H), 0.99 (t,  $J = 7.2$  Hz, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  214.6, 141.6, 114.4, 55.8, 43.7, 35.9, 31.9, 29.1, 25.4, 25.4, 7.4; HRMS-EI:  $m/z$   $[M]^+$  calcd. for  $C_{11}H_{18}O$ : 166.1358; found: 166.1365.

**trans-1-(2-Vinylcyclohexyl)butan-1-one (2d):** **2d** was similarly prepared as **2c** from **2b** (200 mg, 1.31 mmol) by using 1.5 equiv of iodoethane (0.16 mL, 1.97 mmol) and 1.16 equiv of LDA (*n*-BuLi: 1.6 M in hexane, 1.15 mL, 1.84 mmol; diisopropylamine: 0.21 mL, 1.52 mmol). After chromatographic purification on silica gel (hexane-EtOAc 400:1, 300:1, 200:1, 100:1), 73.5 mg of **2d** was obtained (40% yield based on recovered **2b**).

IR (neat) 3077, 2955, 1727, 1601, 1462, 1122, 723, 700  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.61 (ddd,  $J = 17.3, 10.2, 7.5$  Hz, 1H), 4.95 (dm,  $J = 17.0$  Hz, 1H), 4.89 (dd,  $J = 10.3, 1.6$  Hz, 1H), 2.44–2.24 (m, 4H), 1.82–1.71 (m, 4H), 1.59–1.49 (m, 2H), 1.38–1.10 (m, 4H), 0.88 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  214.0, 141.6, 114.4, 55.9, 44.6, 43.5, 31.9, 29.1, 25.4, 25.4, 16.7, 13.8; HRMS-EI:  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{12}\text{H}_{20}\text{O}$ : 180.1514; found: 180.1506.

**trans-3-Phenyl-1-(2-vinylcyclohexyl)propan-1-one (2e):** **2e** was similarly prepared as **2c** from **2b** (278.3 mg, 1.83 mmol) by using 2 equiv of benzyl bromide (0.45 mL, 3.66 mmol) and 1.16 equiv of LDA (*n*-BuLi: 1.6 M in hexane, 1.6 mL, 2.56 mmol; diisopropylamine: 0.30 mL, 2.12 mmol). After chromatographic purification on silica gel (hexane-EtOAc 100:0, 200:1), 98.7 mg of **2e** was obtained (30% yield based on recovered **2b**).

IR (neat) 3097, 3064, 2928, 2855, 1710, 1639, 1604, 916, 748, 700  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31–7.24 (m, 2H), 7.21–7.15 (m, 3H), 5.59 (ddd,  $J = 17.2, 10.2, 7.5$  Hz, 1H), 4.94 (dm,  $J = 17.5$  Hz, 1H), 4.89 (dm,  $J = 10.3$  Hz, 1H), 2.85 (t,  $J = 7.2$  Hz, 2H), 2.77–2.61 (m, 2H), 2.34–2.21 (m, 2H), 1.80 (m, 4H), 1.34–1.27 (m, 2H), 1.23–1.09 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  213.0, 141.5, 141.4, 128.4, 128.3, 126.0, 114.5, 56.1, 44.3, 43.7, 31.9, 29.3, 28.9, 25.3; HRMS-EI  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{17}\text{H}_{22}\text{O}$  242.1671; found 242.1664.

**trans-3-*p*-Tolyl-1-(2-vinylcyclohexyl)propan-1-one (2f):** **2f** was similarly prepared as **2c** from **2b** (493.3 mg, 3.24 mmol) by using 0.9 equiv of  $\alpha$ -bromo-*p*-xylene (551 mg, 2.92 mmol, dissolved in 2.0 mL of THF before the addition) and 1.1 equiv of LDA (*n*-BuLi: 1.6 M in hexane, 2.2 mL, 3.56 mmol; diisopropylamine: 0.5 mL, 3.56 mmol). After chromatographic purification on silica gel (hexane-EtOAc 100:0, 200:1), 211.8 mg of **2f** was obtained (41% yield based on recovered **2b**).

IR (neat) 3088, 3030, 2927, 1711, 1639, 1516, 992, 809  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.08 (d,  $J = 8.3$  Hz, 2H), 7.05 (d,  $J = 8.3$  Hz, 2H), 5.59 (ddd,  $J = 17.2, 10.2, 7.4$  Hz, 1H), 4.94 (dm,  $J = 17.0$  Hz, 1H), 4.89 (dm,  $J = 10.3$  Hz, 1H), 2.81 (br d,  $J = 7.0$  Hz, 2H), 2.77 (dd,  $J = 9.4, 4.2$  Hz, 1H), 2.74–2.58 (m, 2H), 2.34–2.24 (m, 2H), 2.31 (s, 3H), 1.80–1.70 (m, 4H), 1.37–1.29 (m, 2H), 1.23–1.12 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  213.0, 141.5, 138.3, 135.4, 129.1, 128.2, 114.5, 56.1, 44.4, 43.7, 31.9, 28.9, 28.8, 25.4, 21.0; HRMS-EI  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{18}\text{H}_{24}\text{O}$  256.1827; found 256.1823.

**trans-3-Naphthalen-2-yl-1-(2-vinylcyclohexyl)propan-1-one (2g):** **2g** was similarly prepared as **2c** from **2b** (502.9 mg, 3.30 mmol) by using 0.9 equiv of 2-(bromomethyl)naphthalene (685 mg, 2.97 mmol,

dissolved in 2.0 mL of THF before the addition) and 1.2 equiv of LDA (*n*-BuLi: 1.6 M in hexane, 2.48 mL, 3.96 mmol; diisopropylamine: 0.56 mL, 3.96 mmol). After chromatographic purification on silica gel (hexane-EtOAc 400:1, 200:1, 100:1, 60:1), 138.5 mg of **2g** (14%) was obtained mixed with the dialkylated byproduct.

IR (neat) 3054, 2927, 2855, 1707, 1640, 1509, 917, 854, 817  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86–7.70 (m, 3H), 7.61 (s, 1H), 7.50–7.38 (m, 3H), 5.61 (ddd,  $J = 17.1, 10.2, 7.6$  Hz, 1H), 4.95 (dm,  $J = 17.1$  Hz, 1H), 4.89 (dm,  $J = 10.4$ , 1H), 3.02 (t,  $J = 7.9$  Hz, 2H), 2.90–2.64 (m, 2H), 2.37–2.23 (m, 2H), 1.81–1.71 (m, 4H), 1.40–1.07 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  212.8, 141.5, 138.9, 133.6, 132.0, 128.0, 127.6, 127.4, 127.2, 126.4, 126.0, 125.2, 114.5, 56.2, 44.2, 43.7, 32.0, 29.4, 29.0, 25.4; HRMS-EI:  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{21}\text{H}_{24}\text{O}$ : 292.1827; found: 292.1835.

**trans-(E)- and (Z)-Diethyl 1-(2-vinylcyclohexyl)propylideneaminoxyphosphonate (3c), trans-N-(2-vinylcyclohexyl)propionamide (5a) and trans-N-ethyl-2-vinylcyclohexanecarboxamide (6a)**: **3c** was similarly prepared as **3a** by using **2c** as the starting material. Oximation of **2c** (328.4 mg, 1.98 mmol) with  $\text{NH}_2\text{OH}\cdot\text{HCl}$  and NaOAc gave 181 mg of *E*-oxime and 98 mg of *Z*-oxime after the chromatographic purification on silica gel (hexane-EtOAc 80:1, 40: 1 and 10:1). *E*-oxime:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.84 (broad s, 1H), 5.64 (ddd,  $J = 17.2, 10.1, 7.6$  Hz, 1H), 4.94 (dm,  $J = 17.2$  Hz, 1H), 4.90 (dm,  $J = 10.0$  Hz, 1H), 2.37 (dq,  $J = 15.0, 7.6$  Hz, 1H), 2.14 (dq,  $J = 15.0, 7.6$  Hz, 1H), 2.20–2.11 (m, 1H), 2.05 (ddd,  $J = 11.3, 11.1, 3.0$  Hz, 1H), 1.82–1.72 (m, 4H), 1.44–1.14 (m, 4H), 1.11 (t,  $J = 7.5$  Hz, 3H); *Z*-oxime:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.66 (br s, 1H), 5.64 (ddd,  $J = 17.2, 10.2, 7.8$  Hz, 1H), 4.96 (dm,  $J = 17.2$  Hz, 1H), 4.89 (dm,  $J = 10.5$  Hz, 1H), 3.10 (m, 1H), 2.20 (q,  $J = 7.3$  Hz, 2H), 2.16–2.03 (m, 1H), 1.81–1.66 (m, 4H), 1.43–1.13 (m, 4H), 1.06 (t,  $J = 7.3$  Hz, 3H).

The phosphinylation of *E*-oxime (61.4 mg, 0.34 mmol) was carried out with  $(\text{EtO})_2\text{POCl}$  (95%, 0.10 mL, 0.68 mmol) and NaH (60%, 16 mg, 0.41 mmol) in THF. Chromatographic purification on silica gel (hexane-EtOAc 10:1, 5:1, 3:1, 1:1) gave **3c** (*E*-form, 49.7 mg, 23% over two steps) and **5a** (22.3 mg, 18%, over two steps) as an inseparable mixture.

**3c** (*E*-form):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.73–5.54 (m, 1H), 5.03–4.84 (m, 2H), 4.27–4.12 (m, 4H), 2.42 (dq,  $J = 12.7, 7.6$  Hz, 1H), 2.25 (ddd,  $J = 11.4, 11.3, 2.6$  Hz, 1H), 2.20–2.12 (m, 2H), 1.86–1.66 (m, 4H), 1.47–1.14 (m, 4H), 1.34 (td,  $J = 7.1, 0.9$  Hz, 6H), 1.11 (t,  $J = 7.6$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) major:  $\delta$  173.5 ( $J = 12.2$  Hz), 141.8, 114.3, 64.2 ( $J = 5.6$  Hz), 64.1 ( $J = 5.6$  Hz), 48.6, 44.4, 32.7, 30.4, 25.5, 25.4, 21.1, 16.1 (d,  $J = 6.7$  Hz).

**5a**: IR (neat) 3307, 3074, 2975, 2933, 1642, 1543, 994, 912  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.66 (ddd,  $J = 17.1, 10.1, 8.6$  Hz, 1H), 5.23 (br s, 1H), 4.99 (dm,  $J = 17.2$  Hz, 1H), 4.95 (dm,  $J = 10.3$  Hz, 1H), 3.60 (dtd,  $J = 15.0, 6.8, 4.0$ , 1H), 2.14 (q,  $J = 7.6$  Hz, 2H), 2.05 (dm,  $J = 12.6$  Hz, 1H), 1.85–1.65 (m, 4H), 1.42–1.28 (m, 2H), 1.27–1.18 (m, 2H), 1.11 (t,  $J = 7.6$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.1,

141.3, 115.0, 51.5, 49.4, 33.2, 32.5, 30.0, 25.3, 25.1, 10.0; HRMS-EI  $m/z$   $[M]^+$  cacl. for  $C_{11}H_{19}NO$  181.1467; found 181.1459.

The phosphinylation of *Z*-oxime (85.3 mg, 0.47 mmol) was carried out with  $(EtO)_2POCl$  (95%, 0.29 mL, 1.88 mmol) and NaH (60%, 45 mg, 1.13 mmol) in THF. Chromatographic purification on silica gel (hexane-EtOAc 10:1, 5:1, 2:1) gave **3c** (*Z*-form, 94.0 mg, 17% over two steps) and **6a** (28 mg, 9%, over two steps) as an inseparable mixture.

**3c** (*Z*-form):  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  5.69–5.52 (m, 1H), 5.04–4.85 (m, 2H), 4.26–4.10 (m, 4H), 3.14–2.91 (m, 1H), 2.25 (q,  $J = 7.2$  Hz, 2H), 2.18–2.05 (m, 1H), 1.84–1.71 (m, 4H), 1.33 (t,  $J = 7.0$  Hz, 6H), 1.30–1.11 (m, 4H), 1.07 (t,  $J = 7.1$  Hz, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  172.2 ( $J = 12.1$  Hz), 141.5, 114.2, 64.4 ( $J = 5.9$  Hz), 64.3 ( $J = 6.0$  Hz), 43.6, 32.8, 28.8, 25.6, 25.4, 16.2 ( $J = 6.4$  Hz), 10.3.

**6a**: IR (neat) 3295, 3081, 2975, 1639, 1556, 995, 911  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  5.64 (ddd,  $J = 17.2, 10.2, 7.7$  Hz, 1H), 5.52 (br s, 1H), 5.00 (dm,  $J = 17.2$  Hz, 1H), 4.90 (dm,  $J = 10.2$  Hz, 1H), 3.32–3.15 (m, 2H), 2.29–2.18 (m, 1H), 1.84–1.68 (m, 5H), 1.53 (ddm,  $J = 19.4, 12.9$  Hz, 1H), 1.34–1.10 (m, 3H), 1.08 (t,  $J = 7.2$  Hz, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  174.9, 141.5, 114.2, 51.6, 43.8, 34.4, 31.8, 29.8, 25.4, 25.4, 14.9; HRMS-EI:  $m/z$   $[M]^+$  cacl. for  $C_{11}H_{19}NO$ : 181.1467; found: 181.1470.

**trans-(E) and (Z)- Diethyl 1-(2-vinylcyclohexyl)butylideneaminooxyphosphonate (3d), trans-N-(2-vinylcyclohexyl)butyramide (5b) and trans-N-propyl-2-vinylcyclohexanecarboxamide (6b)**: **3d** was similarly prepared as **3a** by using **2d** as the starting material. Oximation of **2d** (164.6 mg, 0.91 mmol) with  $NH_2OH \cdot HCl$  and NaOAc gave 99 mg of *E*-oxime and 41.6 mg of *Z*-oxime after the chromatographic purification on silica gel (hexane-EtOAc 60:1, 40:1, 10:1). *E*-oxime:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.42 (br s, 1H), 5.64 (ddd,  $J = 17.2, 10.2, 7.8$  Hz, 1H), 4.94 (dm,  $J = 17.3$  Hz, 1H), 4.90 (dm,  $J = 10.4$  Hz, 1H), 2.30 (ddd,  $J = 12.5, 11.0, 5.5$  Hz, 1H), 2.18–1.98 (m, 3H), 1.82–1.72 (m, 4H), 1.68–1.57 (m, 1H), 1.54–1.43 (m, 1H), 1.39–1.16 (m, 4H), 0.96 (t,  $J = 7.4$  Hz, 3H); *Z*-oxime:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  9.23 (br s, 1H), 5.65 (ddd,  $J = 17.3, 10.2, 7.8$  Hz, 1H), 4.96 (dm,  $J = 17.2$  Hz, 1H), 4.90 (dm,  $J = 10.5$  Hz, 1H), 3.10 (m, 1H), 2.11 (td,  $J = 7.8, 2.7$  Hz, 2H), 2.13–2.09 (m, 1H), 1.81–1.66 (m, 4H), 1.61–1.46 (m, 2H), 1.45–1.12 (m, 4H), 0.92 (t,  $J = 7.3$  Hz, 3H).

The phosphinylation of *E*-oxime (98 mg, 0.50 mmol) was carried out with  $(EtO)_2POCl$  (95%, 0.31 mL, 2.00 mmol) and NaH (60%, 48 mg, 1.20 mmol) in THF. Chromatographic purification on silica gel (hexane-EtOAc 10:1, 5:1, 2:1) gave **3d** (*E*-form, 60 mg, 20% over two steps) mixed with **5b** (31.4 mg, 17.8%, over two steps).

**3d** (*E*-form):  $^1H$  NMR (400 MHz,  $CDCl_3$ ) major:  $\delta$  5.73–5.56 (m, 1H), 5.04–4.86 (m, 2H), 4.27–4.09 (m, 4H), 2.35 (ddd,  $J = 12.2, 11.1, 5.5$  Hz, 1H), 2.26–2.14 (m, 2H), 2.14–2.03 (m, 1H), 1.86–1.67 (m, 4H), 1.55–1.43 (m, 2H), 1.43–1.14 (m, 4H), 1.34 (t,  $J = 7.0$  Hz, 6H), 0.91 (t,  $J = 7.2$  Hz, 3H);  $^{13}C$  NMR (100

MHz, CDCl<sub>3</sub>) major:  $\delta$  172.3 (d,  $J$  = 12.1 Hz), 141.7, 114.2, 64.2 (d,  $J$  = 5.8 Hz), 64.1 (d,  $J$  = 5.8 Hz), 48.6, 44.5, 32.7, 30.6, 30.2, 25.5, 25.4, 19.6, 16.1 (d,  $J$  = 6.4 Hz), 14.6.

**5b**: IR (neat) 3289, 3075, 2959, 1640, 1550, 989, 909 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.66 (ddd,  $J$  = 17.3, 10.0, 8.6 Hz, 1H), 5.23 (br s, 1H), 4.99 (dm,  $J$  = 17.3 Hz, 1H), 4.95 (dm,  $J$  = 10.0 Hz, 1H), 3.61 (dtd,  $J$  = 13.1, 8.7, 4.3 Hz, 1H), 2.15–2.02 (m, 3H), 1.85–1.70 (m, 4H), 1.61 (tq,  $J$  = 7.4, 7.4 Hz, 2H), 1.42–1.14 (m, 3H), 1.12–1.01 (m, 1H), 0.91 (t,  $J$  = 7.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.3, 141.3, 115.0, 51.6, 49.3, 39.0, 33.3, 32.5, 25.3, 25.1, 19.3, 13.8; HRMS-EI:  $m/z$  [M]<sup>+</sup> calcd. for C<sub>12</sub>H<sub>21</sub>NO: 195.1623; found: 195.1615.

The phosphinylation of *Z*-oxime (23.3 mg, 0.12 mmol) was carried out with (EtO)<sub>2</sub>POCl (95%, 0.07 mL, 0.48 mmol) and NaH (60%, 11 mg, 0.29 mmol) in THF. Chromatographic purification on silica gel eluting with hexane and EtOAc (15:1, 6:1, 3:1) gave **6b** (5.1 mg, 5% over two steps) followed by **3d** (*Z*-form, 15.9 mg, 9.4% over two steps).

**3d** (*Z*-form): IR (neat) 3083, 2964, 1640, 1448, 1276, 1035, 967, 914 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.59 (ddd,  $J$  = 17.2, 10.0, 8.0 Hz, 1H), 4.95 (br d,  $J$  = 17.2 Hz, 1H), 4.89 (dm,  $J$  = 9.9 Hz, 1H), 4.26–4.12 (m, 4H), 3.22–2.92 (m, 1H), 2.23–2.07 (m, 3H), 1.81–1.71 (m, 3H), 1.67 (br d,  $J$  = 13.1 Hz, 1H), 1.63–1.53 (m, 2H), 1.37–1.11 (m, 4H), 1.34 (t,  $J$  = 7.0 Hz, 3H), 1.33 (t,  $J$  = 7.1 Hz, 3H), 0.91 (t,  $J$  = 7.3 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  171.1 (d,  $J$  = 12.6 Hz), 141.5, 114.2, 64.3 (d,  $J$  = 5.9 Hz), 64.2 (d,  $J$  = 5.8 Hz), 46.5, 32.8, 28.7, 25.6, 25.4, 19.1, 16.2 (d,  $J$  = 6.5 Hz), 14.0; HRMS-EI:  $m/z$  [M]<sup>+</sup> calcd. for C<sub>16</sub>H<sub>30</sub>NO<sub>4</sub>P: 331.1912; found: 331.1903.

**6b**: IR (neat) 3300, 3081, 2960, 1638, 1556, 995, 911 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.66 (ddd,  $J$  = 17.3, 10.2, 7.7 Hz, 1H), 5.37 (br s, 1H), 5.02 (dm,  $J$  = 17.2 Hz, 1H), 4.93 (dm, 10.3 Hz, 1H), 3.27–3.09 (m, 2H), 2.30–2.20 (m, 1H), 1.87–1.69 (m, 5H), 1.62–1.52 (m, 1H), 1.48 (qt,  $J$  = 7.3, 7.3 Hz, 2H), 1.39–1.09 (m, 3H), 0.90 (t,  $J$  = 7.4 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  175.0, 114.5, 114.3, 51.8, 43.8, 40.9, 31.8, 29.9, 25.4, 25.3, 22.9, 11.4; HRMS-EI:  $m/z$  [M]<sup>+</sup> calcd. for C<sub>12</sub>H<sub>21</sub>NO: 195.1623; found: 195.1616.

**trans-(E) and (Z)-Diethyl 3-phenyl-1-(2-vinylcyclohexyl)propylideneaminoxyphosphonate (3e)**: **3e** was similarly prepared as **3a** by using **2e** as the starting material. Oximation of **2e** (98.7 mg, 0.43 mmol) with NH<sub>2</sub>OH·HCl and NaOAc gave 53.4 mg of *E*-oxime and 35.4 mg of *Z*-oxime after the chromatographic purification on silica gel (hexane-EtOAc 50:1, 20:1, 10:1).

The phosphinylation of *E*-oxime (53.4 mg, 0.21 mmol) was carried out with (EtO)<sub>2</sub>POCl (95%, 0.25 mL, 1.66 mmol) and NaH (60%, 40 mg, 1.00 mmol) in THF. Chromatographic purification on silica gel (hexane-EtOAc 10:1, 5:1, 2:1) gave **3e** (*E*-form,<sup>18</sup> 50 mg, 29% over two steps).

IR (neat) 3027, 2982, 1640, 1604, 1276, 1033, 979, 924 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.32–7.28 (m, 2H), 7.21 (m, 1H), 7.22 (br d,  $J$  = 7.2 Hz, 2H), 5.61 (ddd,  $J$  = 17.1, 10.2, 8.2 Hz, 1H), 4.94 (dm,  $J$  =

17.1 Hz, 1H), 4.90 (dm,  $J = 10.2$  Hz, 1H), 4.27–4.14 (m, 4H), 2.93 (ddd,  $J = 11.8, 11.6, 5.0$  Hz, 1H), 2.75 (ddd,  $J = 11.6, 11.6, 4.5$  Hz, 1H), 2.66 (ddd,  $J = 11.6, 11.6, 4.5$  Hz, 1H), 2.41 (ddd,  $J = 11.8, 11.5, 5.1$  Hz, 1H), 2.27 (ddd,  $J = 11.3, 11.3, 3.1$  Hz, 1H), 2.20–2.11 (m, 1H), 1.81–1.72 (m, 4H), 1.46–1.18 (m, 4H), 1.36 (t,  $J = 7.0$  Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.7 (d,  $J = 12.3$  Hz), 141.8, 141.1, 128.6, 128.2, 126.4, 114.5, 64.4 (d,  $J = 5.9$  Hz), 64.2 (d,  $J = 5.7$  Hz), 48.8, 44.7, 32.8, 32.0, 30.3, 30.2, 25.5, 25.4, 16.2 (d,  $J = 6.5$  Hz); HRMS-EI  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{21}\text{H}_{32}\text{NPO}_4$  393.2069; found 393.2075.

The phosphinylation of *Z*-oxime (34 mg, 0.13 mmol) was carried out with  $(\text{EtO})_2\text{POCl}$  (95%, 0.08 mL, 0.53 mmol) and NaH (60%, 13 mg, 0.32 mmol) in THF. Chromatographic purification on silica gel (hexane-EtOAc 8:1, 2:1) gave **3e** (*Z*-form, 37 mg, 23% over two steps).

IR (neat) 3055, 2921, 1639, 1452, 1266, 1034, 965, 916  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34–7.26 (m, 2H), 7.23–7.16 (m, 3H), 5.60 (ddd,  $J = 17.2, 10.3, 8.1$  Hz, 1H), 4.95 (dm,  $J = 17.2$  Hz, 1H), 4.90 (dm,  $J = 10.3$  Hz, 1H), 4.28–4.14 (m, 4H), 3.32–3.03 (m, 1H), 2.93–2.83 (m, 2H), 2.60–2.49 (m, 2H), 2.19–2.06 (m, 1H), 1.86–1.63 (m, 4H), 1.36 (t,  $J = 7.1$  Hz, 6H), 1.33–1.13 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.7 (d,  $J = 12.4$  Hz), 141.5, 141.4, 128.4, 128.4, 126.1, 114.4, 64.4 (d,  $J = 6.0$  Hz), 64.3 (d,  $J = 5.9$  Hz), 43.7, 32.7, 31.5, 28.7, 25.6, 25.3, 16.2 (d,  $J = 6.4$  Hz); HRMS-EI  $m/z$   $[\text{M}]^+$  calcd.  $\text{C}_{21}\text{H}_{32}\text{NPO}_4$  393.2069; found 393.2078.

**1-Ethyl-5,6,7,8-tetrahydroisoquinoline (4b)**: The typical procedure for the preparation of **4a** was followed; **3c** (*E*-form) (49.3 mg, 0.16 mmol, mixed with 22.1 mg of **5a**) was used as the starting material. The reaction time was 11 min. Flash chromatography on silica gel (hexane-EtOAc 30:1, 5:1, 2:1) gave **4b** (8.4 mg, 34%) plus non-reacted **5a** (20 mg) and **2c** (3.9 mg, 15%). **4b** was also prepared from the *Z*-form of **3c** (73.3 mg, 0.23 mmol, mixed with 21.6 mg of **6a**). Chromatographic purification on silica gel (hexane-EtOAc 30:1, 8:1, 1:1) gave **4b** (6.6 mg, 17.7%) plus non-reacted **6a** (19 mg) and **2c** (11.5 mg, 30%).

**4b**: IR (neat) 3066, 2925, 1773, 1674, 1591, 1578, 1457, 841, 736  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.22 (d,  $J = 5.1$  Hz, 1H), 6.82 (d,  $J = 5.1$  Hz, 1H), 2.79–2.66 (m, 6H), 1.87–1.81 (m, 2H), 1.81–1.73 (m, 2H), 1.26 (t,  $J = 7.5$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  161.3, 146.1, 145.4, 130.2, 122.0, 29.5, 27.9, 25.3, 23.0, 22.1, 12.7; HRMS-EI:  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{11}\text{H}_{15}\text{N}$ : 161.1204; found: 161.1197.

**1-Propyl-5,6,7,8-tetrahydroisoquinoline (4c)**: The typical procedure for the preparation of **4a** was followed; **3d** (*E*-form) (59.6 mg, 0.18 mmol, mixed with 31.1 mg of **5b**) was used as the starting material. The reaction time was 12 min. Flash chromatography on silica gel (hexane-EtOAc 20:1, 10:1, 2:1) gave **4c** (6.8 mg, 22%) plus **5b** (38.1 mg, 20% based on the total amount). **4c** was also prepared from the *Z*-form of **3d** (14.7 mg, 0.044 mmol). Chromatographic purification on silica gel (hexane-EtOAc 20:1, 8:1, 2:1) gave **4c** (1.1 mg, 14%) plus **6b** (2.2 mg, 25%).

IR (neat) 3049, 2926, 1650, 1587, 1564, 1460, 836, 812  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20 (d,  $J = 5.0$  Hz, 1H), 6.82 (d,  $J = 4.9$  Hz, 1H), 2.75–2.67 (m, 6H), 1.88–1.65 (m, 6H), 1.00 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  160.4, 146.2, 145.3, 130.4, 122.0, 36.9, 29.7, 25.4, 23.1, 22.1, 22.0, 14.3; HRMS-EI:  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{12}\text{H}_{17}\text{N}$ : 175.1361; found: 175.1366.

**1-Phenethyl-5,6,7,8-tetrahydroisoquinoline (4d)**: The typical procedure for the preparation of **4a** was followed; **3e** (*E*-form) (39.6 mg, 0.10 mmol) was used as the starting material. The reaction time was 15 min. Flash chromatography on silica gel (hexane-EtOAc 30:1, 8:1, 4:1) provided **4d** (17 mg, 70%). **4d** was also prepared from the *Z*-form of **3e** (35.9 mg, 0.09 mmol). Chromatographic purification on silica gel (hexane-EtOAc 30:1, 8:1) gave **4d** (11.5 mg, 53%).

IR (neat) 3057, 3026, 2928, 1643, 1588, 1563, 840, 812  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.26 (d,  $J = 5.0$  Hz, 1H), 7.31–7.26 (m, 2H), 7.25–7.17 (m, 3H), 6.86 (d,  $J = 5.0$  Hz, 1H), 3.01 (s, 4H), 2.74 (dd,  $J = 6.2, 6.2$  Hz, 2H), 2.62 (dd,  $J = 5.9, 5.9$  Hz, 2H), 1.84–1.71 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.4, 146.3, 145.5, 142.2, 130.6, 128.5, 128.4, 125.9, 122.3, 36.9, 35.0, 29.5, 25.4, 23.0, 22.0; HRMS-EI  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{17}\text{H}_{19}\text{N}$  237.1517; found 237.1510.

**trans-(E)-Diethyl 3-*p*-tolyl-1-(2-vinylcyclohexyl)propylideneaminoxyphosphonate (3f) and trans-3-*p*-tolyl-*N*-(2-vinylcyclohexyl)propionamide (5c)**: **3f** was similarly prepared as **3a** by using **2f** as the starting material. Oximation of **2f** (176.2 mg, 0.69 mmol) with  $\text{NH}_2\text{OH}\cdot\text{HCl}$  and NaOAc gave 113 mg of *E*-oxime, which was then subjected to phosphinylation with  $(\text{EtO})_2\text{POCl}$  (0.51 mL, 3.32 mmol) and NaH (60%, 80 mg, 1.99 mmol) in THF. Flash chromatography on silica gel (hexane-EtOAc 8:1, 2:1) gave 97 mg of **3f** (35%, over 2 steps) as a viscous oil and a trace amount of **5c**.

**3f**: IR (neat) 3080, 1638, 1516, 1100, 1066, 980, 922  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.11 (br s, 4H), 5.61 (ddd,  $J = 17.2, 10.3, 8.2$  Hz, 1H), 4.94 (dm,  $J = 17.2$  Hz, 1H), 4.89 (dm,  $J = 10.3$  Hz, 1H), 4.27–4.14 (m, 4H), 2.89 (ddd,  $J = 12.2, 11.0, 4.8$  Hz, 1H), 2.70 (ddd,  $J = 12.3, 11.6, 4.8$  Hz, 1H), 2.63 (ddd,  $J = 11.8, 11.6, 4.8$  Hz, 1H), 2.39 (ddd,  $J = 11.6, 10.9, 4.8$  Hz, 1H), 2.32 (s, 3H), 2.27 (ddd,  $J = 11.2, 11.4, 3.1$  Hz, 1H), 2.21–2.11 (m, 1H), 1.82–1.73 (m, 4H), 1.36 (t,  $J = 7.0$  Hz, 6H), 1.31–1.22 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.7 (d,  $J = 12.3$  Hz), 141.8, 138.0, 135.9, 129.2, 128.1, 114.4, 64.3 (d,  $J = 5.8$  Hz), 64.2 (d,  $J = 5.8$  Hz), 48.8, 44.7, 32.8, 31.6, 30.5, 30.3, 25.5, 25.4, 21.0, 16.2 (d,  $J = 6.6$  Hz); HRMS-EI:  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{22}\text{H}_{34}\text{NPO}_4$ : 407.2225; found: 407.2229.

**5c**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.08 (s, 4H), 5.60 (ddd,  $J = 17.1, 10.1, 8.3$  Hz, 1H), 5.10 (br s, 1H), 4.94 (dm,  $J = 17.2$  Hz, 1H), 4.91 (dm,  $J = 10.1$  Hz, 1H), 3.58 (dtd,  $J = 13.4, 8.4, 4.3$  Hz, 1H), 2.89 (t,  $J = 7.6$  Hz, 2H), 2.44–2.36 (m, 2H), 2.31 (s, 3H), 2.03 (dm,  $J = 12.8$  Hz, 1H), 1.80–1.66 (m, 4H), 1.41–1.16 (m, 3H), 1.06–0.94 (m, 1H); HRMS-EI:  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{18}\text{H}_{25}\text{NO}$ : 271.1936; found: 271.1927.

**trans-(E)-Diethyl 3-(naphthalen-2-yl)-1-(2-vinylcyclohexyl)propylideneaminoxyphosphonate (3g) and 3-naphthalen-2-yl-*N*-(2-vinylcyclohexyl)propionamide (5d)**: **3g** was similarly prepared as **3a** by

using **2g** as the starting material. Oximation of **2g** (117.7 mg, 0.40 mmol) with  $\text{NH}_2\text{OH}\cdot\text{HCl}$  and  $\text{NaOAc}$  gave 91.4 mg of *E*-oxime, which was then subjected to phosphinylation with  $(\text{EtO})_2\text{POCl}$  (0.35 mL, 2.32 mmol) and  $\text{NaH}$  (60%, 56 mg, 1.39 mmol) in THF. Flash chromatography on silica gel (hexane-EtOAc 5:1, 2:1) afforded 64mg of **3g** (37%, over 2 steps) and a trace amount of **5d**.

**3g**: IR (neat) 3056, 1636, 1508, 1281, 1034, 973, 920  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86–7.76 (m, 3H), 7.65 (s, 1H), 7.45 (m, 2H), 7.37 (dd,  $J = 8.4, 1.5$  Hz, 1H), 5.63 (ddd,  $J = 17.2, 10.2, 8.1$  Hz, 1H), 4.96 (dm,  $J = 17.2$  Hz, 1H), 4.91 (dm,  $J = 10.3$  Hz, 1H), 4.29–4.15 (m, 4H), 3.09 (ddd,  $J = 12.1, 13.5, 5.3$  Hz, 1H), 2.92 (ddd,  $J = 12.6, 11.0, 5.3$  Hz, 1H), 2.76 (ddd,  $J = 12.0, 12.4, 5.3$  Hz, 1H), 2.51 (ddd,  $J = 12.0, 12.0, 5.2$  Hz, 1H), 2.30 (ddd,  $J = 11.2, 11.4, 2.7$  Hz, 1H), 2.26–2.14 (m, 1H), 1.85–1.74 (m, 4H), 1.51–1.42 (m, 1H), 1.37 (t,  $J = 7.0$  Hz, 3H), 1.36 (t,  $J = 7.0$  Hz, 3H), 1.32–1.17 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.6 (d,  $J = 11.8$  Hz), 141.8, 138.5, 133.6, 132.2, 128.2, 127.6, 127.4, 126.9, 126.4, 126.1, 125.4, 114.5, 64.4 (d,  $J = 6.0$  Hz), 64.2 (d,  $J = 5.7$  Hz), 48.9, 44.7, 32.8, 32.2, 30.4, 30.3, 25.5, 25.4, 16.2 (d,  $J = 6.5$  Hz); HRMS-EI:  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{25}\text{H}_{34}\text{NO}_4\text{P}$ : 443.2225; found: 443.2216.

**5d**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.83–7.72 (m, 3H), 7.62 (s, 1H), 7.42–7.39 (m, 2H), 7.32 (dd,  $J = 8.5, 1.3$  Hz, 1H), 5.53 (ddd,  $J = 17.1, 10.0, 8.4$  Hz, 1H), 5.22 (br s, 1H), 4.89 (dm,  $J = 17.1$  Hz, 1H), 4.77 (dm,  $J = 10.2, 1.6$  Hz, 1H), 3.58 (dtd,  $J = 14.0, 8.1, 3.9$  Hz, 1H), 3.10 (t,  $J = 7.6$  Hz, 2H), 2.50 (t,  $J = 7.9$  Hz, 2H), 2.01 (dm,  $J = 12.6$  Hz, 1H), 1.79–1.62 (m, 4H), 1.40–1.23 (m, 2H), 1.20–1.10 (m, 1H), 1.03–0.90 (m, 1H); HRMS-EI:  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{21}\text{H}_{25}\text{NO}$ : 307.1936; found: 307.1945.

**1-(2-*p*-Tolyl-ethyl)-5,6,7,8-tetrahydroisoquinoline (4e)**: The typical procedure for the preparation of **4a** was followed; **3f** (54 mg, 0.13 mmol) was used as the starting material. The reaction time was 15 min. Flash chromatography on silica gel (hexane-EtOAc 30:1, 15:1, 4:1) provided **4e** (22 mg, 65%) as a brown oil.

IR (neat) 3046, 3008, 1645, 1586, 1514, 839, 809  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.25 (d,  $J = 5.0$  Hz, 1H), 7.14 (d,  $J = 8.0$  Hz, 2H), 7.10 (d,  $J = 8.0$  Hz, 2H), 6.85 (d,  $J = 5.0$  Hz, 1H), 2.98 (s, 4H), 2.74 (t,  $J = 6.3$  Hz, 2H), 2.64 (t,  $J = 6.4$  Hz, 2H), 2.33 (s, 3H), 1.85–1.73 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  159.5, 146.2, 145.5, 139.2, 135.3, 130.6, 129.0, 128.3, 122.2, 37.0, 34.5, 29.5, 25.4, 23.0, 22.1, 21.0; HRMS-EI:  $m/z$   $[\text{M}]^+$  calcd. for  $\text{C}_{18}\text{H}_{21}\text{N}$ : 251.1674; found: 251.1680.

**1-(2-Naphthalen-2-yl-ethyl)-5,6,7,8-tetrahydroisoquinoline (4f)**: The typical procedure for the preparation of **4a** was followed; **3g** (31.4 mg, 0.071 mmol) was used as the starting material. The reaction time was 8 min. Flash chromatography on silica gel (hexane-EtOAc 10:1) provided **4f** (10.3 mg, 50%) as a brown oil.

IR (neat) 3050, 1635, 1589, 1508, 959, 890, 853, 816, 746  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.28 (d,  $J = 5.0$  Hz, 1H), 7.86–7.74 (m, 3H), 7.66 (s, 1H), 7.47–7.37 (m, 3H), 6.87 (d,  $J = 5.0$  Hz, 1H), 3.22–3.15 (m, 2H), 3.15–3.06 (m, 2H), 2.74 (t,  $J = 6.0$  Hz, 2H), 2.65 (t,  $J = 6.0$  Hz, 2H), 1.81–1.72 (m, 4H);  $^{13}\text{C}$  NMR

(100 MHz, CDCl<sub>3</sub>)  $\delta$  159.3, 146.3, 145.5, 139.8, 133.7, 132.0, 130.6, 127.9, 127.6, 127.5, 127.4, 126.4, 125.9, 125.1, 122.3, 36.7, 35.1, 29.5, 25.5, 23.0, 22.0; HRMS-EI:  $m/z$  [M]<sup>+</sup> calcd. for C<sub>21</sub>H<sub>21</sub>N: 287.1674; found: 287.1678.

**trans-(E)-Diethyl (2-vinylcyclohexyl)methyleneaminooxyphosphonate (3h)**: Vinylmagnesium bromide (0.7 M in THF, 57.4 mL, 40.17 mmol) and hexamethylphosphoramide (7.06 mL, 40.17 mmol) were successively added to a solution of Me<sub>2</sub>S·CuBr (762 mg, 3.67 mmol) in THF (20 mL) pre-cooled to -55 °C. The resulting dark orange solution was continued to stir for 30 min and added dropwise with a mixture of 1-cyclohexene-1-carboxaldehyde (1.56 mL, 13.39 mmol) and chlorotrimethylsilane (3.4 mL, 26.78 mmol) in dry THF (10 mL) via a syringe. At -55 °C, the reaction mixture was stirred for an additional 2 hours, then diluted with Et<sub>2</sub>O (350 mL), and successively washed with aqueous 10% HCl solution (70 mL), water (70 mL x 2) and brine (70 mL). After concentration, the crude residue was subjected to chromatographic purification on silica gel (hexane-EtOAc 200:1) to afford 1.07 g of vinyl-aldehyde as a mixture of two isomers (*cis*: *trans* = 60:40). The freshly prepared vinylaldehyde (1.07 g) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (36 mL) and added with 1,8-diazabicyclo[5.4.0]undec-7-ene (1.22 mL, 7.98 mmol). The mixture was stirred at room temperature for 2 days and concentrated under reduced pressure. Chromatography on silica gel (hexane-EtOAc 200:1) gave *trans*-2-vinylcyclohexanecarbaldehyde (**2h**) (870 mg, 61%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.56 (d, *J* = 3.2 Hz, 1H), 5.72 (ddd, *J* = 17.2, 10.1, 7.8 Hz, 1H), 5.02 (dm, *J* = 17.2 Hz, 1H), 5.00 (dm, *J* = 10.0 Hz, 1H), 2.31–2.20 (m, 1H), 2.18–2.08 (m, 1H), 1.87–1.72 (m, 4H), 1.68–1.54 (m, 1H), 1.40–1.14 (m, 3H). To a stirred solution of **2h** (411.6 mg, 2.98 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL), NaOAc (737 mg, 8.93 mmol) and NH<sub>2</sub>OH·HCl (647 mg, 8.93 mmol) were successively added. The resulting suspension was stirred at room temperature for 4 h, then diluted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and washed with water (50 mL x 2) and brine (30 mL). After concentration, the crude residue was purified by flash chromatography on silica gel (hexane-EtOAc 20:1, 10:1) to give the oxime intermediate as a single isomer (398 mg). Under a nitrogen atmosphere, NaH (60%, 25 mg, 0.63 mmol) and diethyl chlorophosphate (95%, 0.13 mL, 0.84 mmol) were successively added to a stirred solution of the oxime (107 mg, 0.70 mmol) in dry THF (3 mL) pre-cooled at 0 °C. The reaction mixture was continued to stir for 24 h at room temperature, then cooled at 0 °C and carefully quenched with saturated aqueous NH<sub>4</sub>Cl solution (2 mL). The resulting mixture was diluted with EtOAc (20 mL), washed with water (5 mL x 2) and brine (5 mL), and concentrated under vacuo. The crude mixture was subjected to chromatographic purification on silica gel (hexane-EtOAc 12:1, 1:1) to afford **3h**<sup>20</sup> as a yellow oil (43.2 mg, 22% over two steps, base on the recovered starting oxime) plus 16.7 mg of recovered oxime.

IR (neat) 3057, 1737, 1642, 1037, 982, 910, 738 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.47 (d, *J* = 7.8 Hz, 1H), 5.61 (ddd, *J* = 17.2, 10.0, 8.4 Hz, 1H), 5.04–4.92 (m, 2H), 4.25–4.14 (m, 4H), 2.28–2.18 (m, 1H),

2.02–1.92 (m, 1H), 1.88–1.73 (m, 4H), 1.33 (t,  $J = 7.1$  Hz, 6H), 1.31–1.22 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  163.6 ( $J = 13.9$  Hz), 141.4, 115.1, 64.4 ( $J = 5.9$  Hz), 64.3 ( $J = 5.6$  Hz), 45.4, 42.9, 32.4, 29.8, 25.2, 24.9, 16.1 (d,  $J = 6.6$  Hz); HRMS-ESI  $m/z$  [ $\text{M}$ ] $^+$  cacl. for  $\text{C}_{13}\text{H}_{24}\text{O}_4\text{NP}$ : 289.1443; found: 289.1043.

**Isoquinoline (4g) and trans-2-vinylcyclohexanecarbonitrile (7):** To a solution of **3h** (41.2 mg, 0.14 mmol) in dry DMF (7.1 mL, 0.02 M) was added  $\text{Pd}(\text{PPh}_3)_4$  (66 mg, 0.057 mmol) under  $\text{N}_2$ . The mixture was stirred at room temperature for 5 minutes before the addition of  $\text{Et}_3\text{N}$  (0.1 mL, 0.71 mmol). The reaction mixture was heated at 80 °C for 8 min, cooled to rt and diluted with water (7 mL). The solution was extracted with  $\text{Et}_2\text{O}$  (70 mL x 2). The combined organic layers were washed with water (20 mL x 2) and brine (20 mL). After concentration, the crude residue was subjected to TLC preparation (eluting solvent: hexane-EtOAc 2:1) to afford **4g**<sup>22</sup> (6.3 mg, 34%) and **7** (5.8 mg, 30%).

**4g:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.26 (s, 1H), 8.53 (d,  $J = 5.8$  Hz, 1H), 7.98 (d,  $J = 8.2$  Hz, 1H), 7.83 (d,  $J = 8.2$  Hz, 1H), 7.7 (td,  $J = 6.9, 0.8$  Hz, 1H), 7.66 (d,  $J = 5.8$  Hz, 1H), 7.61 (td,  $J = 7.5, 0.8$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  152.6, 143.0, 135.8, 130.3, 128.7, 127.6, 127.3, 126.5, 120.5.

**7:** IR (neat) 3081, 2936, 2238, 1642, 995, 922  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.76 (ddd,  $J = 17.2, 10.3, 7.2$  Hz, 1H), 5.19 (dm,  $J = 17.2$  Hz, 1H), 5.15 (dm,  $J = 10.3$  Hz, 1H), 2.25 (ddd,  $J = 11.0, 10.9, 3.6$  Hz, 1H), 2.21–2.10 (m, 2H), 1.90–1.84 (m, 1H), 1.83–1.73 (m, 2H), 1.65–1.56 (m, 1H), 1.38–1.12 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  139.4, 121.8, 116.3, 44.3, 34.3, 31.2, 29.7, 24.7, 24.6.

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