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Synthesis of Diastereoenriched *α*-Aminomethyl Enaminones *via* A Brønsted Acid-Catalyzed Asymmetric *aza*-Baylis-Hillman Reaction of Chiral *N*-Phosphonyl Imines

Yangxue Liu,[a] Sultan Ahmed,[a] Xiao-Yan Qin,[c] Hossein Rouh,[a] Guanzhao Wu,[a,b] Guigen Li,*[a,b] Bo Jiang*[c]

Dedication ((optional))

Abstract: An effective chiral GAP methodology for preparing *α*-aminomethyl enaminones through a (*R*)-CSA-catalyzed asymmetric *aza*-Baylis-Hillman reaction is reported. Excellent yields and high diastereoselectivity could be obtained under mild conditions and convenient GAP techniques. The confirmations of the absolute configuration of *N*-phosphonyl imine and chiral enaminone by X-ray diffraction provides an explicit explanation of the chirality mechanism for GAP chemistry.

Introduction

Enaminone framework widely exists in biologically active substances (Figure 1) such as the anticonvulsant (type I),[1a] natural products such as the glucose-lowering (-)-multiflorine (type II),[1b] and synthetic pharmaceutical agents such as the antibacterial ciprofloxacin (type III).[1c] They are also served as highly important synthons for the synthesis of heterocycles[2] and pharmaceutical compounds[3] (anticonvulsants,[3a] antibacterials[3b]). Besides, they also behaved as ligands for transition metal-catalyzed transformations.[4] With these significant contributions, the development of efficient pathways for the synthesis of functionalized enaminones and their derivatives from readily available starting materials has attracted considerable attention.[5] Although enaminones could be synthesized through traditional condensation reactions of 1,3-dicarbonyl compounds with amines,[6] the enantioselectivity of the chiral derivates was difficult to control.[7] Recently, Shi and co-workers reported the enantioselective synthesis of enaminone-containing 3-amino-2-oxindoles via a chiral phosphoric acid-catalyzed asymmetric addition of enaminones to isatin-derived *N*-Boc ketimines. However, the demand for strong electron-deficient ketimines limited its application.[8] Therefore, the continuous exploration of enantioselective synthesis of functionalized enaminones under mild conditions is still highly desirable for their application in pharmaceutical chemistry.

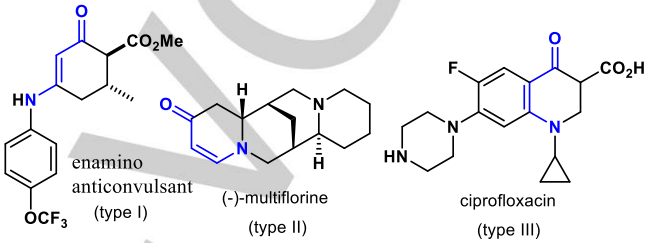
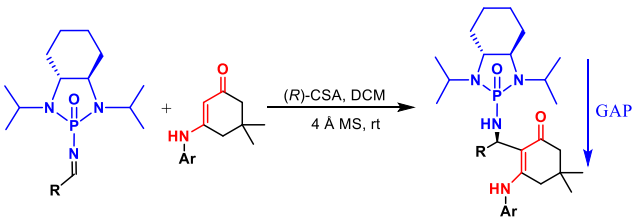
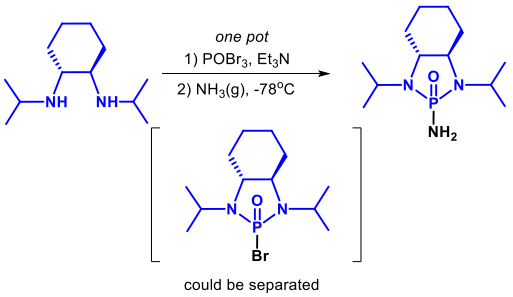


Figure 1. Biologically Active Enaminones.

Over the past several years, our efforts have made great progress on the design of chiral *N*-phosphonyl auxiliaries and used their derived imines to develop many effective methods for the synthesis of chiral functional molecules including amides, amino acids, *α*-amino esters and peptides.[9] It was interesting to note that these auxiliaries could simplify the purification progress because the products would often be obtained simply by washing the crude mixture with common solvents without traditional chromatography or recrystallization, which was defined as group-assisted purification (GAP) chemistry.[10] To continue this project, we found that the catalytic asymmetric *aza*-Baylis-Hillman reaction[11-13] of chiral *N*-phosphonyl imines with



Scheme 1. Asymmetric GAP Reaction of *N*-phosphonyl Imine.



Scheme 2. New one pot strategy of GAP Phosphonylamide

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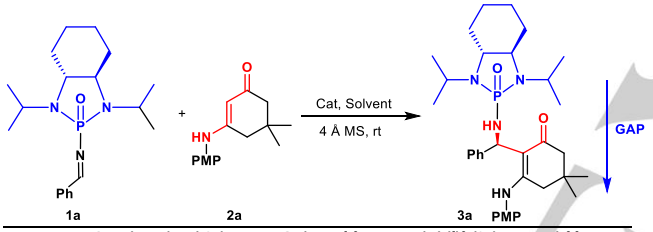
cyclic enaminones in the presence of (1*R*)-(-)-10-camphorsulfonic acid (CSA) as a Brønsted acid catalyst worked smoothly, affording a wide range of functionalized *α*-aminomethyl enaminones in high yields (up to 94% yield) and diastereoselectivity (up to >99:1 dr) (Scheme 1). Compared with our previous strong base-promoted transformations, this reaction could be well-tolerated with Brønsted acid catalytic system, making the reaction condition milder. The synthesis also followed the GAP chemistry/technology, in which the pure *α*-aminomethyl enaminones were obtained by washing the crude products with hexane solvent. In the meanwhile, we optimized the procedure of synthesizing GAP amine to avoid the employ of NaN_3, which replaced phosphoryl chloride with phosphoryl bromide followed by ammonia (Scheme 2). The overall yield of phosphamide reached up to 95% with this strategy.

Results and Discussion

In the initial experiments, we investigated an asymmetric *aza*-Baylis-Hillman reaction between chiral *N*-phosphonyl imine **1a**

Table 1. Optimization of the Reaction Conditions.

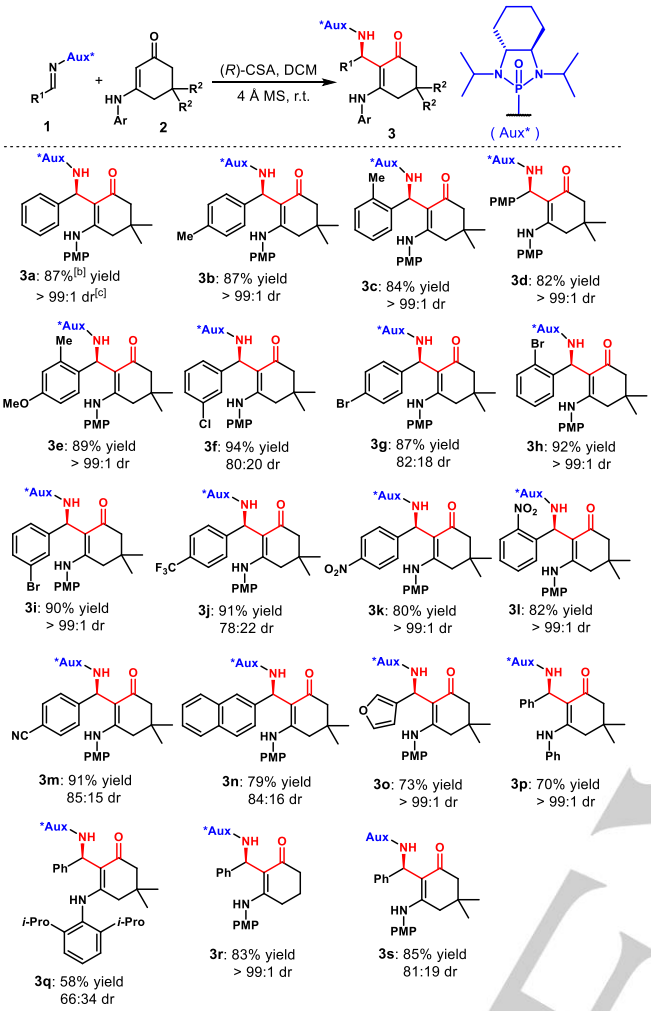


Entry	Catalyst (mol %)	Solvent[a]	yield[b] (%)	dr[c]
1	-	DCM	trace	-
2	$BiNPO_4H$ (10)	DCM	98	73:27
3	$BiNPO_4H$ (10)	toluene	80	60:40
4	$BiNPO_4H$ (10)	EA	80	65:35
5	$BiNPO_4H$ (10)	THF	95	71:29
6	$BiNPO_4H$ (10)	MeOH	trace	-
7	$BiNPO_4H$ (10)	DMF	26	50:50
8	$BiNPO_4H$ (10)	1,4-Dioxane	75	76:24
9	$BiNPO_4H$ (10)	MeCN	57	81:19
10	$PhCO_2H$	DCM	78	79:21
11	AcOH	DCM	50	75:25
12	*p*-Nitrobenzoic acid	DCM	95	85:15
13	(*R*)-CSA	DCM	91(87[d])	>99:1
14	TsOH	DCM	decomposed	-
15	H_3PO_4	DCM	decomposed	-

[a] Reactions were performed on a 0.2 mmol scale in 3 mL solvent at 23 °C with 4 Å activated molecular sieves (20 mg) for 16 h unless otherwise mentioned. [b] The conversions were determined by ^{31}P-NMR, in which the reactions were not accomplished. [c] Based on analysis of ^{1}H and ^{31}P-NMR. [d] Yield after GAP purification.

and cyclic enaminone (*p*-methoxyphenyl = PMP) **2a** to search the optimal conditions (Table 1). The reaction did not almost proceed in the presence of 4 Å molecular sieves (MS) in dichloromethane (DCM) at room temperature without any catalyst (entry 1). The presence of racemic 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate ($BiNPO_4H$) could drive the conversion into product **3a** in 98% yield, but with poor diastereoselectivity (73:27 dr, entry 2). The following examination on solvents revealed that the use of either toluene, ethyl acetate (EA), tetrahydrofuran (THF), MeOH, or *N*,*N*-dimethylformamide (DMF) as the reaction media led to lower yields and diastereoselectivities than that in DCM (entries 3-7 vs. entry 2), whereas the reaction in 1,4-dioxane or MeCN delivered higher diastereoselectivity but lower yields as compared with DCM (entries 8-9). In view of these results, we employed DCM as the solvent and varied Lewis acid catalysts. Exchanging $BiNPO_4H$ (10 mol %) for $PhCO_2H$ or HOAc gave a slightly high diastereoselectivity but with a remarkably reduced yield (entries 10-11). *p*-Nitrobenzoic acid was beneficial for this transformation, furnishing 95% yield and 85:15 dr (entry 12). To our delight, an employment of the use of (1*R*)-(-)-10-camphorsulfonic acid (CSA) as a Brønsted acid catalyst gave 91% conversion and >99:1 dr analyzed by ^{31}P-NMR. After simply washing by hexane, the pure product **3a** could be obtained in 87% yield and >99:1 dr (entry 13). When both TsOH and H_3PO_4 was used Brønsted acid catalysts, the reaction did not provide the desired product **3a** as both acids could decompose *N*-phosphonyl imine **1a** (entries 14-15).

With the optimized reaction conditions established, we then sought to study the generality of this *aza*-Baylis-Hillman reaction by examining a variety of chiral *N*-phosphonyl imines **1** and cyclic enaminones. As shown in Scheme 3, cyclic enaminone **2a** was first chosen to probe the influence of the position and electronic properties of the substituents in the phenyl of imines **1**. Various substituents did not hamper the reaction process, delivering the corresponding *α*-aminomethyl enaminones **3b–3m** with 80-94% yields and 78:22 to >99:1 dr. Both electron-donating (methyl **1b-1c** and methoxy **1d, 1e**) and electron-withdrawing (chloro **1f**, bromo **1g–1i**, trifluoromethyl **1j**, nitro **1k–1l**, and cyano **1m**) groups residing in different positions of the phenyl ring could tolerate this catalytic system well. Of these groups, the sterically crowded *o*-methyl-, *o*-bromo-, and *o*-nitrophenyl counterparts could completely orient the diastereoselectivity to generate the corresponding products with good yields. Alternatively, 2-naphthyl analogue **1n** still showed highly reactivity, furnishing the desired products **3n** in 79% yield and 84:16 dr. Notably, substrate **1o** having a 3-furanyl group was also proven to be suitable, providing product **3o** with 73% yield and >99:1 dr. Without methoxy group on the *N*-phenyl ring, cyclic enaminone **2b** led to a slightly decreased yield (70%) of **3p** but retained excellent diastereoselectivity (>99:1 dr). When two bulky isopropyl groups were installed into C2 and C6 positions of the *N*-phenyl ring, respectively, the reaction seemed reluctant to undergo this catalytic process, as product **3q** was generated in a low yield of 58%, alone with poor diastereoselectivity. 1,3-Cyclohexanedione-derived enaminone **2d** was successfully engaged in this metal-free *aza*-Baylis-



[a] Reactions were performed with imine (0.2 mmol, 1 equiv), enaminone (1.2 equiv), (*R*)-CSA (10 mol %) in 3 mL DCM at r.t. with 4 Å activated molecular sieves (20mg) for 16 h. [b] Total yield of the isomers. [c] Based on analysis of ^{1}H and ^{31}P-NMR of reaction mixture.

Scheme 3. Substrate Scope of the Asymmetric *aza*-Baylis-Hillman Reaction[a].

Hillman reaction, rendering a highly diastereoselective protocol toward the expected *α*-aminomethyl enaminone **3r** in 83% yield and >99:1 dr. As expected, achiral imine reacted with **2a** just afforded 81:19 dr (**3s**), which proved GAP chiral auxiliary is indispensable in this asymmetric *aza*-Baylis-Hillman Reaction. The structures of these products were identified by their NMR and HRMS spectra. In the case of **3a**, the stereo-structure was unequivocally determined by X-ray analysis (See Supporting Information).[14]

Based on the X-ray configurations of compounds **1a** & **3a**, as well as the previous literatures, a reasonable mechanism is proposed in Scheme 4. As the configuration of imine is fixed by the groups (*i*Pr) on the *N*-atoms which are controlled by the top chiral group, the (*R*)-CSA forms H-bonding with imines from the less hindered direction. Then nucleophilic attack of enaminones **2** to imines **1** yields the intermediate **Int** which followed by tautomerization to generate the final products **3**.

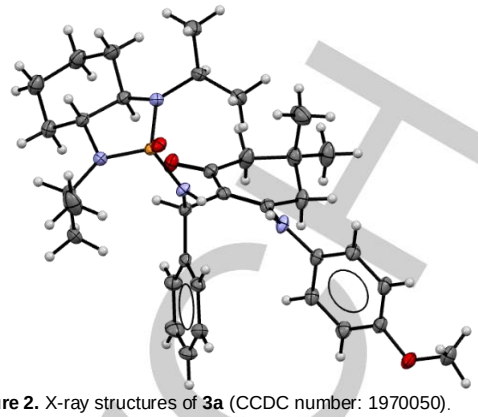
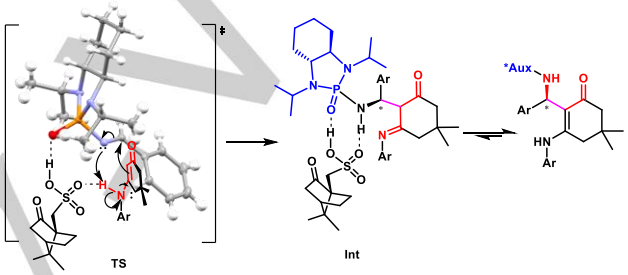


Figure 2. X-ray structures of **3a** (CCDC number: 1970050).



Scheme 4. Proposed Mechanism of the Asymmetric *aza*-Baylis-Hillman Reaction.

Conclusion

In summary, we have developed an effective chiral GAP methodology for preparing *α*-aminomethyl enaminones through a (*R*)-CSA-catalyzed asymmetric *aza*-Baylis-Hillman reaction. Excellent yields and high diastereoselectivity could be obtained under mild conditions and convenient GAP techniques. The confirmation of the absolute configuration of *N*-phosphonyl imine and chiral enaminone by X-ray diffraction provides an explicit explanation of the chirality mechanism for GAP chemistry.

Experimental Section

Synthetic Procedures.

One pot synthesis of chiral/achiral phosphoryl bromide intermediate and *N*-Phosphonylamide. Dissolve diamine (1.1g, 5.55 mmol) into 50 mL anhydrate DCM, followed by Et_3N (1.68g, 16.64 mmol) dropwise in ice bath. $POBr_3$ (2.23g, 7.76 mmol) was added portion wise with stirring at 0 °C and stirred the solution mixture at r.t. for overnight. After reaction completed, cooled reaction mixture to -78 °C, ammonia gas condensed directly into reaction. Monitored crude reaction solution by ^{31}P NMR. After reaction completed, concentrated reaction mixture and extracted with water/ DCM. Collected organic layer and dried with $MgSO_4$. Pure product was obtained as a pale solid. ^{1}H and ^{31}P NMR data of *N*-Phosphonylamide obtained were consistent with the literature data.

(3aR,7aR)-2-bromo-1,3-diisopropyloctahydrobenzo[d][1,3,2]diazaphosphole 2-oxide: light yellow oil, 440mg, 99% yield, $[\alpha]_D^{25}$ = -33.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 3.63 – 3.36 (m, 2H), 3.02 (td, *J* = 10.3, 3.0 Hz, 1H), 2.87 – 2.67 (m, 1H), 2.05 – 1.87 (m, 2H), 1.71 (t, *J* = 16.5 Hz, 2H), 1.29 (d, *J* = 6.9 Hz, 3H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 61.14, 61.04, 58.60, 58.49, 45.51, 45.47, 45.25, 45.21, 29.84, 29.70, 29.62, 24.23, 24.22, 24.07, 24.05, 21.90, 21.87, 21.73, 21.66, 20.28, 20.26, 18.95, 18.93. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 15.18. HRMS (ESI- TOF) *m/z* $[C_{12}H_{24}BrN_2OP + H]^+$ calcd for 323.0888, found 323.0864.

General Synthesis of *N*-Phosphonyl Imine with the GAP Technique. In a 100 mL oven-dried flask, phosphonylamide (1.0g, 3.86mmol) was dissolved in 5.0 mL of toluene under an argon atmosphere. Then aldehyde (1.1 equiv, 4.246 mmol) and $Ti(OiPr)_4$ (1.0 equiv, 1.2 mL, 3.86 mmol) were added subsequently. The solution mixture was stirred at 90 °C for 12h. The reaction was monitored by ^{31}P NMR of the crude reaction mixture. After reaction completed, the clear solution was concentrated by vacuum; then, 50 mL of dry hexane was added, and the resulting solution was stirred for 2h until precipitate formed (GAP). After filtration and washes with dry hexane, *N*-Phosphonyl imine was isolated as a pale yellow solid.

General Procedure for the Synthesis of Products. Dissolved *N*-Phosphonyl imine (0.5 mmol, 1 equiv) and cyclic enaminone (1.2 equiv) with freshly distilled DCM (5 mL) in a 10 mL oven-dried flask. At room temperature, 4 Å activated molecular sieves (50 mg) was added to the solution and stirred for 30 min, followed by adding (1*R*)-(-)-10-Camphorsulfonic acid (0.1 equiv). Completion of the starting material was monitored by both thin layer chromatography and ^{31}P NMR of the reaction mixture (reaction could be completed in 24h). The solvent was evaporated under vacuum after the filtration of 4 Å activated molecular sieves with celite; concentrate was transferred to silica column for chromatography and eluted by mixed solvents of hexane/ ethyl acetate (v/v, 5:1) to give pure product.

*2-((R)-(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(phenyl)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one (**3a**)*: white solid, 220 mg, 87% yield; mp 85-86 °C; $[\alpha]_D^{25}$ = -215.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 9.74 (s, 1H), 7.28 – 7.24 (m, 2H), 7.05 (dt, *J* = 4.8, 2.8 Hz, 4H), 6.87 – 6.82 (m, 2H), 5.54 (t, *J* = 10.8 Hz, 1H), 3.79 (s, 3H), 3.43 – 3.29 (m, 2H), 3.01 – 2.92 (m, 1H), 2.79 (dd, *J* = 13.3, 6.0 Hz, 1H), 2.67 (d, *J* = 16.8 Hz, 1H), 2.27 (s, 3H), 2.01 (ddd, *J* = 34.9, 30.0, 16.4 Hz, 6H), 1.75 (d, *J* = 6.7 Hz, 2H), 1.32 (d, *J* = 7.9 Hz, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.23 (d, *J* = 6.8 Hz, 3H), 1.15 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 195.07, 158.34, 156.93, 141.43, 141.34, 134.87, 133.06, 128.33, 125.77, 125.73, 116.45, 114.39, 59.89, 58.88, 55.59, 51.86, 50.89, 43.99, 40.20, 32.11, 31.39, 30.68, 29.04, 27.88, 24.46, 23.79, 23.72, 22.68, 22.64, 21.14, 19.83. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.53. HRMS (ESI- TOF) *m/z* $[C_{34}H_{49}N_4O_3P + H]^+$ calcd for 593.3621, found 593.3606.

*2-((R)-(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(p-tolyl)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one (**3b**)*: white solid, 320 mg, 87% yield; mp 108-110 °C; $[\alpha]_D^{25}$ = -332.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 9.71 (s, 1H), 7.30 – 7.23 (m, 2H), 7.10 – 7.01 (m, 4H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.66 – 5.42 (m, 1H), 3.79 (s, 3H), 3.36 (dtt, *J* = 20.6, 13.6, 6.8 Hz, 2H), 3.01 – 2.92 (m, 1H), 2.79 (dd, *J* = 13.0, 5.9 Hz, 1H), 2.66 (d, *J* = 16.8 Hz, 1H), 2.27 (s, 3H), 2.15 – 1.91 (m, 6H), 1.74 (d, *J* = 6.8 Hz, 2H), 1.31 (d, *J* = 7.9 Hz, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.03 (s, 3H), 0.94 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 195.10, 158.38, 156.95, 141.35, 134.88, 133.02, 128.34, 125.73, 116.38, 114.39, 59.78, 58.88, 55.59, 51.85, 50.89, 44.11, 44.03, 40.21, 32.12, 31.37, 30.69, 29.02, 27.89, 24.47, 24.33, 23.77, 23.70, 22.69, 22.64, 21.14, 19.89, 19.84. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.45. HRMS (ESI- TOF) *m/z* $[C_{35}H_{51}N_4O_3P + H]^+$ calcd for 607.3777, found 607.3771.

*2-((R)-(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(o-tolyl)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one (**3c**)*: white solid, 289 mg, 84% yield; mp 156-157 °C; $[\alpha]_D^{25}$ = -315.9 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 9.03 (s, 1H), 7.16 (d, *J* = 6.1 Hz, 1H), 6.73 (t, *J* = 5.7 Hz, 1H), 6.61 (dd, *J* = 12.2, 6.0 Hz, 4H), 6.47 (d, *J* = 6.8 Hz, 2H), 5.36 (t, *J* = 9.0 Hz, 1H), 4.19 (dd, *J* = 18.0, 8.8 Hz, 1H), 4.02 (s, 3H), 3.71 (dt, *J* = 16.7, 5.5 Hz, 1H), 3.53 (ddd, *J* = 16.2, 10.7, 5.3 Hz, 1H), 3.37 (t, *J* = 6.9 Hz, 1H), 3.20 (t, *J* = 6.7 Hz, 1H), 3.09 (d, *J* = 13.4 Hz, 1H), 2.78 (s, 3H), 2.68 – 2.56 (m, 4H), 2.51 (d, *J* = 12.9 Hz, 1H), 2.39 (s, 2H), 2.03 (d, *J* = 5.2 Hz, 6H), 1.89 (d, *J* = 5.3 Hz, 3H), 1.85 (d, *J* = 5.4 Hz, 3H), 1.82 (d, *J* = 5.2 Hz, 3H), 1.73 (d, *J* = 10.5 Hz, 6H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 195.03, 158.12, 156.93, 141.29, 141.21, 134.38, 133.13, 129.65, 127.86, 125.80, 125.56, 124.60, 114.42, 114.05, 59.73, 58.79, 55.57, 50.93, 50.43, 44.11, 40.23, 34.74, 32.17, 31.25, 30.46, 28.59, 28.25, 25.35, 24.46, 24.30, 23.58, 22.00, 19.95, 19.66, 19.42. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.33. HRMS (ESI- TOF) *m/z* $[C_{35}H_{51}N_4O_3P + H]^+$ calcd for 607.3777, found 607.3771.

*2-((R)-(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(4-methoxyphenyl)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one (**3d**)*: white solid, 342 mg, 82% yield; mp 111-112 °C; $[\alpha]_D^{25}$ = -268.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 9.74 (d, *J* = 44.9 Hz, 1H), 7.28 (t, *J* = 8.1 Hz, 1H), 7.03 (t, *J* = 9.0 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.54 (dd, *J* = 25.5, 14.6 Hz, 1H), 3.80 (d, *J* = 6.7 Hz, 2H), 3.75 (s, 2H), 3.35 (qt, *J* = 13.4, 6.8 Hz, 1H), 3.05 – 2.90 (m, 1H), 2.78 (t, *J* = 9.6 Hz, 1H), 2.65 (d, *J* = 16.9 Hz, 1H), 2.21 – 1.82 (m, 3H), 1.73 (t, *J* = 11.5 Hz, 1H), 1.66 (s, 1H), 1.31 (d, *J* = 7.8 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 2H), 1.21 (d, *J* = 6.8 Hz, 2H), 1.14 (d, *J* = 6.7 Hz, 2H), 1.08 (d, *J* = 6.9 Hz, 2H), 1.03 (s, 2H), 0.92 (d, *J* = 13.2 Hz, 1H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 194.97, 158.14, 157.37, 156.81, 132.87, 126.77, 125.62, 116.15, 114.25, 112.81, 59.73, 59.63, 58.74, 58.65, 55.42, 55.03, 51.47, 50.78, 43.93, 43.89, 40.06, 31.99, 31.20, 30.49, 28.83, 27.78, 24.32, 24.18, 23.59, 23.53, 22.45, 22.41, 19.75, 19.70. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.42. HRMS (ESI- TOF) *m/z* $[C_{35}H_{51}N_4O_4P + H]^+$ calcd for 623.3726, found 623.3721.

*2-((R)-(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(4-methoxy-2-methylphenyl)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one (**3e**)*: white solid, 260 mg, 89% yield; mp 112-113 °C; $[\alpha]_D^{25}$ = -409.8 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 10.00 (s, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.03 (dd, *J* = 7.0, 5.1 Hz, 2H), 6.87 – 6.82 (m, 2H), 6.72 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.57 (t, *J* = 7.9 Hz, 1H), 5.40 (t, *J* = 11.5 Hz, 1H), 3.97 (dd, *J* = 14.0, 9.4 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.43 – 3.32 (m, 1H), 3.24 – 3.11 (m, 1H), 2.99 – 2.90 (m, 1H), 2.75 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.61 (d, *J* = 16.8 Hz, 1H), 2.20 (s, 3H), 2.11 – 2.04 (m, 1H), 1.99 (d, *J* = 16.6 Hz, 3H), 1.89 (d, *J* = 16.2 Hz, 1H), 1.72 (d, *J* = 11.3 Hz, 2H), 1.32 – 1.24 (m, 6H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.02 (s, 2H), 0.94 (t, *J* = 3.2 Hz, 3H), 0.90 (s, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 195.23, 157.92, 157.39, 156.90, 135.64, 133.69, 133.15, 128.91, 125.55, 115.17, 114.42, 114.34, 109.66, 59.82, 58.78, 55.59, 55.05, 50.97, 49.94, 44.11, 40.21, 34.73, 32.18, 31.21, 30.42, 28.60, 28.21, 26.98, 25.35, 24.31, 23.60, 21.97, 19.94, 19.69, 19.58. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.34. HRMS (ESI- TOF) *m/z* $[C_{36}H_{53}BrN_4O_4P + H]^+$ calcd for 637.3882, found 637.3877.

*2-((R)-(3-chlorophenyl)(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one (**3f**)*: light yellow solid, 310 mg, 94% yield; mp 114-115 °C; $[\alpha]_D^{25}$ = -219.8 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 9.82 (s, 1H), 7.42 (s, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.10 – 7.02 (m, 3H), 6.88 – 6.81 (m, 2H), 5.60 (t, *J* = 10.9 Hz, 1H), 5.52 (t, *J* = 10.9 Hz, 1H), 3.78 (s, 3H), 3.46 – 3.30 (m, 2H), 3.00 – 2.92 (m, 1H), 2.80 (t, *J* = 8.2 Hz, 1H), 2.60 (dd, *J* = 60.5, 16.9 Hz, 1H), 2.15 – 1.91 (m, 5H), 1.79 – 1.69 (m, 2H), 1.34 – 1.30 (m, 2H), 1.28 – 1.21 (m, 7H), 1.19 – 1.14 (m, 4H), 1.08 (d, *J* = 6.8 Hz, 2H), 1.05 (d, *J* = 4.5 Hz, 3H), 0.94 (dd, *J* = 6.1, 2.1 Hz, 3H). ^{13}C

NMR (101 MHz, CHLOROFORM-D) δ = 194.92, 159.04, 157.07, 133.63, 132.76, 128.79, 126.13, 125.81, 124.01, 115.50, 114.44, 114.42, 59.78, 58.92, 55.58, 51.86, 50.77, 44.15, 44.05, 40.26, 32.34, 32.22, 31.28, 30.77, 28.89, 28.04, 24.45, 24.31, 23.83, 22.91, 19.92, 19.84. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.47, 25.88. HRMS (ESI- TOF) *m/z* [$C_{34}H_{48}ClN_4O_3P$ + H] $^+$ calcd for 627.3231, found 627.3225.

2-((R)-(4-bromophenyl)(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one ***(3g)****:* pale yellow solid, 330 mg, 87% yield; mp 119-120 °C; [α]$_D^{25}$ = -219.2 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 9.78 (s, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.02 (dd, *J* = 8.8, 5.5 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.58 (t, *J* = 10.9 Hz, 1H), 5.49 (t, *J* = 10.9 Hz, 1H), 3.77 (s, 3H), 3.43 – 3.24 (m, 2H), 2.95 (dd, *J* = 14.5, 5.7 Hz, 1H), 2.76 (t, *J* = 7.9 Hz, 1H), 2.59 (t, *J* = 31.1 Hz, 1H), 2.11 – 1.90 (m, 5H), 1.72 (t, *J* = 9.5 Hz, 2H), 1.35 – 1.28 (m, 3H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.13 (dd, *J* = 6.7, 3.2 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.1 Hz, 3H), 0.95 – 0.90 (m, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 194.98, 158.90, 157.64, 157.10, 143.74, 132.74, 130.72, 130.55, 127.78, 127.40, 127.05, 125.87, 119.39, 115.55, 114.42, 59.78, 58.82, 55.60, 55.57, 55.56, 44.06, 40.24, 34.73, 32.14, 31.30, 30.61, 28.93, 27.91, 25.35, 24.44, 24.29, 23.66, 22.58, 19.93, 19.86. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.32, 25.71. HRMS (ESI- TOF) *m/z* [$C_{34}H_{48}BrN_4O_3P$ + H] $^+$ calcd for 671.2725, found 671.2720.

2-((S)-(2-bromophenyl)(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one ***(3h)****:* light yellow solid, 305 mg, 92% yield; mp 95-96 °C; [α]$_D^{25}$ = -261.4 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 10.07 (s, 1H), 7.83 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.40 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.09 – 7.04 (m, 2H), 6.99 (td, *J* = 7.8, 1.4 Hz, 1H), 6.86 – 6.82 (m, 2H), 5.49 (t, *J* = 11.5 Hz, 1H), 4.02 (t, *J* = 11.4 Hz, 1H), 3.78 (s, 3H), 3.46 – 3.33 (m, 1H), 3.23 – 3.10 (m, 1H), 2.99 – 2.90 (m, 1H), 2.74 (dd, *J* = 13.6, 6.1 Hz, 1H), 2.63 (d, *J* = 16.7 Hz, 1H), 2.16 – 1.85 (m, 6H), 1.72 (d, *J* = 11.0 Hz, 2H), 1.29 (d, *J* = 6.8 Hz, 4H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.97 (s, 3H), 0.93 (t, *J* = 5.5 Hz, 1H), 0.90 (s, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 194.87, 159.93, 157.06, 142.44, 132.93, 132.16, 130.48, 127.50, 125.88, 125.85, 122.58, 114.39, 112.64, 59.82, 58.98, 55.58, 52.96, 50.83, 44.23, 44.05, 40.20, 34.74, 32.08, 31.09, 30.37, 28.82, 28.05, 26.98, 25.35, 24.44, 24.30, 23.45, 21.97, 19.98, 19.73. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 26.88. HRMS (ESI- TOF) *m/z* [$C_{34}H_{48}BrN_4O_3P$ + H] $^+$ calcd for 671.2725, found 671.2720.

2-((R)-(3-bromophenyl)(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one ***(3i)****:* white solid, 120 mg, 90% yield; mp 110-111 °C; [α]$_D^{25}$ = -219.2 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 9.89 (d, *J* = 40.3 Hz, 1H), 7.59 (s, 1H), 7.29 – 7.22 (m, 2H), 7.13 – 7.04 (m, 3H), 6.88 – 6.83 (m, 2H), 5.56 (dt, *J* = 33.5, 10.9 Hz, 1H), 3.78 (d, *J* = 4.9 Hz, 3H), 3.43 – 3.31 (m, 2H), 3.01 – 2.93 (m, 1H), 2.81 (dd, *J* = 13.2, 6.1 Hz, 1H), 2.69 (d, *J* = 16.9 Hz, 1H), 2.53 (q, *J* = 7.2 Hz, 2H), 2.16 – 1.91 (m, 5H), 1.75 (d, *J* = 6.7 Hz, 2H), 1.32 (d, *J* = 7.0 Hz, 2H), 1.29 – 1.22 (m, 8H), 1.17 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.06 (s, 3H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 5.8 Hz, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 194.90, 159.03, 157.06, 147.10, 132.78, 129.12, 129.01, 128.69, 126.87, 125.78, 124.46, 122.04, 115.51, 114.43, 59.89, 58.92, 55.59, 51.82, 50.77, 46.31, 44.13, 44.02, 40.25, 32.23, 31.30, 30.79, 29.79, 28.90, 28.03, 24.46, 24.30, 23.78, 22.93, 19.93, 19.84, 11.59. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.52. HRMS (ESI- TOF) *m/z* [$C_{34}H_{48}BrN_4O_3P$ + H] $^+$ calcd for 671.2725, found 671.2720.

2-((R)-(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(4-(trifluoromethyl)phenyl)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one ***(3j)****:* pale yellow solid, 264 mg, 91% yield; mp 121-122 °C; [α]$_D^{25}$ = -212.2 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 9.87 (s, 1H), 7.49 (s, 4H), 7.05 (t, *J* = 6.9 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.68 (t, *J* = 10.8 Hz, 1H), 5.59 (t, *J* = 10.7 Hz, 1H), 3.79 (s, 3H), 3.45 – 3.26 (m, 2H), 2.98 (dd, *J* = 14.3, 5.6 Hz, 1H), 2.79 (d, *J* = 9.1 Hz, 1H), 2.60 (dd, *J* = 62.2, 16.9 Hz, 1H), 2.11 – 1.91 (m, 5H), 1.75 (d, *J* = 6.0 Hz, 2H), 1.32 (d, *J* = 7.3 Hz, 2H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.20 – 1.13 (m, 5H), 1.09 (d, *J* = 6.8 Hz, 2H), 1.03 (d, *J* = 4.1 Hz, 3H), 0.95 (d, *J* = 5.7 Hz, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 194.91, 159.22, 157.17, 132.67, 127.62, 127.06, 126.14, 125.91, 125.90, 125.76, 124.53, 115.49, 114.46, 59.81, 58.84, 55.58, 52.16, 50.71, 44.11, 44.03, 40.25, 32.27, 32.12, 31.26, 30.64, 29.00, 27.85, 24.44, 24.29, 23.83, 22.64, 19.93, 19.83. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.47, 25.82. HRMS (ESI- TOF) *m/z* [$C_{35}H_{48}F_3N_4O_3P$ + H] $^+$ calcd for 661.3494, found 661.3475.

2-((R)-(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(4-nitrophenyl)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one ***(3k)****:* yellow solid, 270 mg, 80% yield; mp 107-108 °C; [α]$_D^{25}$ = -148.3 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 9.98 (s, 1H), 8.16 – 8.06 (m, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.12 – 7.00 (m, 2H), 6.91 – 6.83 (m, 2H), 5.61 (t, *J* = 10.9 Hz, 1H), 3.80 (s, 3H), 3.45 – 3.26 (m, 2H), 3.02 – 2.93 (m, 1H), 2.81 (dd, *J* = 13.3, 6.0 Hz, 1H), 2.69 (d, *J* = 17.0 Hz, 1H), 2.06 (dd, *J* = 16.6, 6.9 Hz, 4H), 1.95 (d, *J* = 16.4 Hz, 1H), 1.82 – 1.74 (m, 2H), 1.33 (dd, *J* = 8.8, 4.2 Hz, 2H), 1.29 (d, *J* = 6.9 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 4H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 3H), 0.96 – 0.93 (m, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 194.79, 159.62, 157.29, 152.83, 146.08, 132.46, 126.63, 125.88, 122.97, 115.06, 114.51, 59.85, 58.98, 55.59, 52.39, 50.61, 44.12, 40.29, 32.18, 31.65, 31.25, 30.49, 28.88, 27.92, 24.41, 24.28, 23.84, 22.66, 20.00, 19.86, 14.19. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.39. HRMS (ESI- TOF) *m/z* [$C_{35}H_{48}N_5O_5P$ + H] $^+$ calcd for 638.3471, found 638.3466.

2-((R)-(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(2-nitrophenyl)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one ***(3l)****:* brown solid, 213 mg, 82% yield; mp 114-115 °C; [α]$_D^{25}$ = -532.4 (*c* = 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 10.18 (s, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.57 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.25 (dd, *J* = 8.8, 5.8 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.86 (dd, *J* = 7.0, 5.0 Hz, 2H), 6.07 (t, *J* = 11.2 Hz, 1H), 3.78 (s, 3H), 3.46 – 3.26 (m, 2H), 3.03 – 2.94 (m, 1H), 2.79 (t, *J* = 8.1 Hz, 1H), 2.51 (d, *J* = 16.3 Hz, 1H), 2.08 – 1.96 (m, 5H), 1.84 (d, *J* = 16.1 Hz, 1H), 1.74 (t, *J* = 9.8 Hz, 2H), 1.32 (d, *J* = 6.6 Hz, 2H), 1.28 (d, *J* = 6.9 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 4H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 3H), 0.85 (d, *J* = 3.1 Hz, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 194.63, 160.80, 157.36, 148.28, 139.13, 132.50, 130.95, 129.17, 126.70, 126.31, 123.91, 114.38, 113.06, 59.98, 58.98, 55.57, 50.56, 49.28, 44.08, 40.14, 34.73, 32.43, 31.66, 31.40, 30.64, 28.95, 27.74, 25.34, 24.44, 23.88, 22.79, 20.02, 19.88. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.08. HRMS (ESI- TOF) *m/z* [$C_{34}H_{48}N_5O_5P$ + H] $^+$ calcd for 638.3471, found 638.3466.

4-((R)-(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(2-((4-methoxyphenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl)benzonitrile ***(3m)****:* pale yellow solid, 355 mg, 91% yield; mp 128-129 °C; [α]$_D^{25}$ = -195.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 10.15 – 9.59 (m, 1H), 7.51 (dd, *J* = 18.7, 8.4 Hz, 2H), 7.26 – 7.21 (m, 1H), 7.02 (t, *J* = 16.4 Hz, 1H), 6.95 – 6.72 (m, 1H), 5.68 – 5.61 (m, 1H), 5.56 (t, *J* = 11.1 Hz, 1H), 3.78 (dd, *J* = 10.1, 6.6 Hz, 2H), 3.45 – 3.21 (m, 1H), 2.97 (t, *J* = 9.9 Hz, 1H), 2.78 (s, 1H), 2.67 (d, *J* = 16.9 Hz, 1H), 2.06 (dd, *J* = 27.0, 11.4 Hz, 2H), 1.93 (d, *J* = 16.5 Hz, 1H), 1.75 (s, 1H), 1.66 (s, 1H), 1.32 (d, *J* = 6.5 Hz, 1H), 1.27 (d, *J* = 6.8 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 2H), 1.14 (d, *J* = 6.6 Hz, 2H), 1.09 (d, *J* = 6.8 Hz, 1H), 1.02 (s, 1H), 0.94 (d, *J* = 5.3 Hz, 2H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 194.72, 159.56, 157.26, 132.43, 131.36, 119.37, 114.41, 109.27, 59.73, 58.91, 55.49, 53.55, 52.25, 50.60, 44.04, 40.29, 34.67, 34.52, 32.23, 32.09, 31.59, 31.22, 30.58, 29.06, 28.79, 27.87, 25.29, 24.37, 23.65, 22.66, 20.73, 19.92, 19.81, 14.16, 11.46. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.40, 25.96. HRMS (ESI- TOF) *m/z* [$C_{35}H_{48}N_5O_3P$ + H] $^+$ calcd for 618.3573, found 618.3557.

2-((R)-(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(naphthalen-2-yl)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one ***(3n)****:* light yellow solid, 212 mg, 79% yield; mp 123-124 °C; [α]$_D^{25}$ = -170.1 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 9.81 (s, 1H), 7.94 (s, 1H), 7.80 – 7.68 (m, 3H), 7.45 – 7.34 (m, 3H), 7.08 (t, *J* =

9.7 Hz, 2H), 6.89 – 6.84 (m, 2H), 5.82 (t, *J* = 10.9 Hz, 1H), 5.74 (t, *J* = 10.9 Hz, 1H), 3.97 (dt, *J* = 13.6, 11.3 Hz, 1H), 3.80 (s, 3H), 3.49 – 3.31 (m, 2H), 3.04 – 2.95 (m, 1H), 2.86 (dd, *J* = 13.2, 5.9 Hz, 1H), 2.63 (dd, *J* = 64.7, 16.9 Hz, 1H), 2.03 (ddd, *J* = 37.4, 18.5, 12.4 Hz, 6H), 1.77 (d, *J* = 7.1 Hz, 2H), 1.34 (d, *J* = 7.4 Hz, 2H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.10 (t, *J* = 8.6 Hz, 3H), 1.05 (d, *J* = 3.7 Hz, 3H), 0.97 – 0.94 (m, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 195.07, 158.74, 157.02, 142.04, 133.29, 132.95, 132.13, 127.93, 127.60, 127.12, 125.84, 125.63, 125.19, 125.00, 123.91, 115.83, 114.43, 59.95, 58.85, 55.61, 52.29, 50.87, 44.11, 40.30, 32.22, 31.26, 30.72, 28.91, 28.01, 26.99, 25.36, 24.49, 24.36, 23.69, 22.72, 19.97, 19.90. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.44, 25.82. HRMS (ESI- TOF) *m/z* [$C_{38}H_{51}N_4O_3P$ + H] $^+$ calcd for 643.3776, found 643.3771.

2-((R)-(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(furan-3-yl)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one (***3o***)*:* light yellow solid, 177 mg, 73% yield; mp 94-95 °C; $[\alpha]_D^{25}$ = -317.7 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 9.59 (s, 1H), 7.34 (s, 1H), 7.26 (dd, *J* = 5.7, 4.0 Hz, 1H), 7.03 – 6.97 (m, 2H), 6.84 – 6.80 (m, 2H), 6.34 – 6.28 (m, 1H), 5.50 – 5.35 (m, 1H), 3.77 (s, 3H), 3.44 – 3.26 (m, 2H), 2.93 (td, *J* = 11.0, 3.1 Hz, 1H), 2.73 (dd, *J* = 13.1, 6.1 Hz, 1H), 2.59 (d, *J* = 16.9 Hz, 1H), 2.17 (t, *J* = 11.8 Hz, 1H), 2.03 – 1.96 (m, 4H), 1.71 (t, *J* = 12.6 Hz, 2H), 1.31 – 1.27 (m, 2H), 1.24 (d, *J* = 3.4 Hz, 3H), 1.23 (d, *J* = 3.3 Hz, 3H), 1.14 (d, *J* = 6.7 Hz, 3H), 1.08 – 1.03 (m, 6H), 0.95 – 0.92 (m, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 195.20, 158.51, 157.01, 142.28, 138.77, 132.81, 129.54, 129.44, 125.84, 114.47, 114.37, 110.36, 59.69, 58.71, 55.56, 51.06, 45.90, 44.17, 44.01, 40.27, 32.15, 31.13, 30.54, 28.80, 28.03, 24.43, 24.29, 23.59, 22.35, 19.88, 19.84. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 26.77. HRMS (ESI- TOF) *m/z* [$C_{32}H_{47}N_4O_4P$ + H] $^+$ calcd for 583.3413, found 583.3408.

2-((R)-(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(phenyl)methyl)-5,5-dimethyl-3-(phenylamino)cyclohex-2-en-1-one (***3p***)*:* grey yellow solid, 230 mg, 70% yield; mp 103-104 °C; $[\alpha]_D^{25}$ = +67.4 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 10.04 (s, 1H), 7.38 (d, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.24 (dd, *J* = 9.1, 6.1 Hz, 2H), 7.11 (t, *J* = 6.8 Hz, 3H), 5.72 – 5.49 (m, 1H), 3.85 (t, *J* = 10.8 Hz, 1H), 3.36 (qt, *J* = 13.6, 6.8 Hz, 2H), 3.03 – 2.93 (m, 1H), 2.81 (dd, *J* = 21.8, 14.0 Hz, 2H), 2.12 (dd, *J* = 16.5, 7.5 Hz, 2H), 1.99 (dd, *J* = 24.6, 12.5 Hz, 4H), 1.75 (d, *J* = 6.5 Hz, 2H), 1.32 (d, *J* = 7.7 Hz, 2H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 8.7 Hz, 6H), 0.95 (s, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 195.52, 157.59, 144.10, 140.33, 129.19, 127.57, 125.87, 125.72, 124.03, 123.48, 117.69, 59.91, 59.81, 58.79, 52.18, 51.09, 44.15, 44.05, 40.17, 32.50, 31.28, 30.59, 28.59, 28.22, 24.46, 24.32, 23.75, 22.53, 19.95, 19.82. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.50. HRMS (ESI- TOF) *m/z* [$C_{33}H_{47}N_4O_2P$ + H] $^+$ calcd for 563.3515, found 563.3509.

2-((R)-(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(phenyl)methyl)-3-((2,6-diisopropylphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one (***3q***)*:* white solid, 176 mg, 58% yield; mp 85-86 °C; $[\alpha]_D^{25}$ = -1055 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 8.50 – 8.02 (m, 1H), 7.51 (dd, *J* = 12.1, 7.7 Hz, 2H), 7.26 (ddd, *J* = 9.7, 5.9, 3.6 Hz, 3H), 7.16 (ddd, *J* = 12.1, 9.0, 5.5 Hz, 3H), 5.74 (t, *J* = 11.0 Hz, 1H), 5.67 (t, *J* = 10.8 Hz, 1H), 3.47 – 3.03 (m, 4H), 2.99 – 2.89 (m, 1H), 2.80 (dd, *J* = 15.8, 6.3 Hz, 1H), 2.45 (s, 1H), 2.02 (dd, *J* = 27.1, 21.3 Hz, 5H), 1.72 (d, *J* = 11.0 Hz, 2H), 1.31 – 1.23 (m, 9H), 1.22 – 1.18 (m, 6H), 1.18 – 1.13 (m, 8H), 1.10 (t, *J* = 6.6 Hz, 6H), 0.95 (d, *J* = 1.4 Hz, 1H), 0.90 (d, *J* = 10.2 Hz, 5H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 195.17, 159.85, 147.20, 147.06, 146.61, 144.94, 133.69, 128.63, 128.20, 127.87, 127.71, 126.16, 125.93, 125.89, 123.99, 123.91, 123.55, 123.37, 114.19, 59.69, 59.01, 51.08, 50.83, 44.32, 43.99, 40.36, 34.74, 32.06, 31.57, 30.85, 28.47, 28.15, 25.36, 24.95, 24.87, 24.48, 23.97, 23.38, 22.96, 22.45, 22.32, 20.10, 19.82, 19.71. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 25.75, 24.41. HRMS (ESI- TOF) *m/z* [$C_{39}H_{59}BrN_4O_2P$ + H] $^+$ calcd for 647.4454, found 647.4448.

2-((R)-(((3aS,7aS)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(phenyl)methyl)-3-((4-methoxyphenyl)amino)cyclohex-2-en-1-one (***3r***)*:* white solid, 184 mg, 83% yield; mp 93-94 °C; $[\alpha]_D^{25}$ = -209.6 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 9.76 (s, 1H), 7.40 (d, *J* = 7.6 Hz, 2H), 7.24 (dd, *J* = 8.7, 6.6 Hz, 2H), 7.15 – 7.04 (m, 3H), 6.86 – 6.81 (m, 2H), 5.54 (t, *J* = 10.6 Hz, 1H), 3.90 (dd, *J* = 24.8, 13.9 Hz, 1H), 3.78 (s, 3H), 3.46 – 3.31 (m, 2H), 3.00 – 2.91 (m, 1H), 2.82 (ddd, *J* = 24.2, 12.2, 7.3 Hz, 2H), 2.25 (dt, *J* = 16.5, 5.1 Hz, 1H), 2.18 – 1.72 (m, 9H), 1.32 (d, *J* = 7.7 Hz, 2H), 1.26 (d, *J* = 6.9 Hz, 6H), 1.17 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 195.46, 160.63, 157.08, 144.48, 132.97, 127.59, 125.95, 125.79, 125.67, 117.49, 114.35, 59.80, 58.93, 55.59, 52.17, 44.13, 43.93, 37.32, 34.74, 31.67, 31.27, 30.68, 26.96, 24.46, 24.33, 23.57, 22.70, 22.65, 21.31, 19.90, 19.84. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.73. HRMS (ESI- TOF) *m/z* [$C_{32}H_{45}N_4O_3P$ + H] $^+$ calcd for 565.3307, found 565.3302.

2-((1R)-((1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)amino)(phenyl)methyl)-3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-en-1-one (***3s***)*:* light yellow solid, 142 mg, 85% yield; mp 81-83 °C; $[\alpha]_D^{25}$ = -13.6 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 9.74 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.27 – 7.22 (m, 3H), 7.12 (t, *J* = 7.3 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.88 – 6.81 (m, 2H), 5.65 (t, *J* = 10.8 Hz, 1H), 5.57 (t, *J* = 10.9 Hz, 1H), 3.80 (d, *J* = 4.2 Hz, 3H), 3.46 – 3.29 (m, 2H), 3.02 – 2.92 (m, 1H), 2.85 – 2.74 (m, 1H), 2.59 (dd, *J* = 64.6, 16.8 Hz, 1H), 2.15 – 1.91 (m, 5H), 1.81 – 1.67 (m, 3H), 1.32 (d, *J* = 8.1 Hz, 2H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.23 (t, *J* = 4.2 Hz, 3H), 1.15 (dd, *J* = 6.7, 2.8 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 2H), 1.04 (d, *J* = 3.8 Hz, 3H), 0.95 (d, *J* = 5.4 Hz, 3H). ^{13}C NMR (101 MHz, CHLOROFORM-D) δ = 195.00, 158.49, 156.95, 144.46, 144.36, 133.02, 127.56, 125.87, 125.78, 125.66, 116.30, 114.40, 59.90, 58.79, 55.60, 52.10, 50.86, 44.09, 43.99, 40.21, 32.13, 31.29, 30.58, 29.04, 27.90, 24.46, 24.33, 23.75, 22.71, 22.67, 19.88, 19.84. ^{31}P NMR (162 MHz, CHLOROFORM-D) δ = 27.52, 25.96. HRMS (ESI- TOF) *m/z* [$C_{34}H_{49}N_4O_3P$ + H] $^+$ calcd for 593.3621, found 593.3602.

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[14] CCDC 1970049 (**1a**) and 1970050 (**3a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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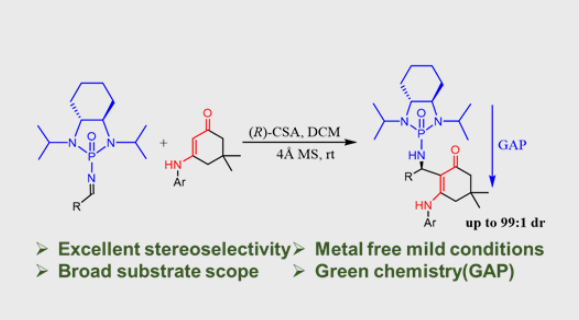

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