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Group-Assisted Purification (GAP) chemistry for Asymmetric Mannich-type reaction of chiral *N*-phosphonyl imines with azlactones leading to syntheses of *α*-quaternary *α*, *β*-diamino acid derivatives†

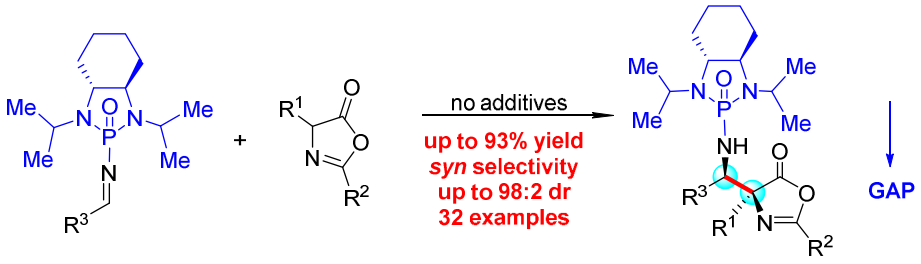
Haowei Zhang‡, Zhen Yang‡, Brian Nlong Zhao‡,$ and Guigen Li*‡,#

‡Institute of Chemistry and BioMedical Sciences, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, 210093, China

#Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, USA

*E-mail: guigen.li@ttu.edu.

† We would like to dedicate this work to Professor Albert Padwa on occasion of his 80th birthday.



ABSTRACT: Asymmetric Mannich-type reaction between chiral *N*-phosphonyl imines and azlactones (oxazol-5(4*H*)-ones) has been established under convenient conditions at room temperature. The reaction was performed without using any bases, additives or catalysts to achieve up to excellent chemical yields and diastereoselectivity for 32 examples. The *α*-quaternary *syn*-*α*, *β*-diamino acid products were purified simply by washing the crude mixtures with co-solvents, following the group-assisted purification (GAP) chemistry/technology, without involving traditional chromatography or recrystallization methods. The auxiliary can be readily removed and recycled for re-use. The absolute configuration was unambiguously assigned by X-ray structural analysis.

KEY WORDS: *N*-phosphonyl imine, azlactone, oxazolones, *α*, *β*-diamino acid, quaternary chiral center.

INTRODUCTION

α, *β*-Diamino acids are important common structural building blocks found in natural products, peptides, peptidomimetics, antibiotics and many other medicinally valuable compounds.[1-2] These diamino acids containing two vicinal nitrogen-bearing and *α*-quaternary chiral centers have represented a challenging task for synthetic organic community, especially when their enantiopure

forms need to be controlled efficiently. As so, a variety of methodologies have been devised for their preparation in enantiomeric selective manners.[1, 3] One of the most straightforward approaches to chiral *α, β*-diamino acids is to perform direct Mannich reaction between *α*-amino acid equivalents and imines, in which C-C bonds and two stereogenic centers are created in a single synthetic operation.[4-6] To approach asymmetric synthesis of *α, β*-diamino acid derivatives, several chiral enolates[4] and chiral sulfinyl imines[3a, 5] were ultilized in these Mannich reactions. However, these reactions often suffered from strong bases (such as LDA or Li-HMDS) and low temperature (often lowered to -78 ^{o}C).

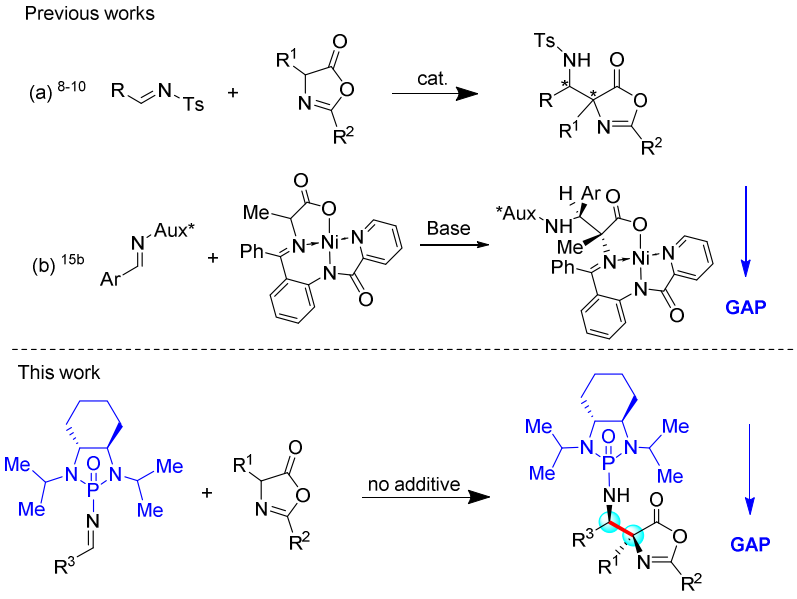
Among different nucleophilic *α*-amino acid equivalents, azlactones (also known as oxazolones or oxazol-5(4*H*)-ones) have been well-known alternatives, since their scaffold basically consists of "masked" amino acids, which can be used in the synthesis of natural and biomedical molecules, and in the construction of quaternary *α*-amino acids.[7] Several studies have been conducted in regards to the efficient syntheses of *α*, *β*-diamino acid equivalents *via* asymmetric Mannich-type reaction between sulfonyl-imines and azlactones.[7-8] TMS quinine[8b], gold complexes[8c], chiral ion-pair catalysts[9], phosphoric acid derivatives[8f] and chiral thioureas[10] were also utilized in these reactions to obtain good to excellent yields and stereoselectivities. However, quite complex catalysts or high catalyst loadings are usually required, and in some cases, the stereoselectivities were poorly controlled. Sometimes, their substrate scope also limits their applications on large scales. As far as we are concerned, except for sulfonyl-imines, chiral sufinyl imines and *N*-phosphonyl imines have not been applied into the Mannich reaction with azlactones so far.

Over the past few years, we have made many efforts on designing new chiral *N*-phosphonyl imines for asymmetric reactions. Many asymmetric reactions have been successfully conducted, including aza-MBH reaction[12], borylation[13], the umpolung reaction[14] and several others.[15] In addition to well-controlling stereoselectivities, these auxiliaries have extra bonus effects on simplifying the purification progress. With *N*-phosphonyl containing groups are attached, the resulting products can often be obtained simply by washing the crude mixture with common solvents without recourse to chromatography or recrystallization,[12-16] leading to a new concept called group-assisted purification (GAP) chemistry/technology. GAP chemistry is generally defined as the chemistry for organic synthesis and chemical production that can avoid classical purification processes, such as chromatography and recrystallization, by purposely introducing well-functionalized groups in starting materials, followed by being transferred into final products. This strategy can amazingly convert liquid products into corresponding solid ones, for further enabling their purification simply by washing with common solvents. Indeed, GAP chemistry is the first such a concept in chemical sciences that combines all four aspects of reagent, reaction, separation and purification. Due to its hybrid characteristics, GAP chemistry has to meet the requirements of chemical and physical aspects, such as chemical reactivity and stability of GAP starting materials, adequate solubility of GAP products for washing and for further reactions, asymmetric control by chiral GAP groups for both asymmetric synthesis and asymmetric catalysis, extensive substrate scopes, and deprotection of GAP auxiliaries for recycle and re-use.

During our continuing research on this topic, we are eager to expand GAP chemistry scope by developing more diversities of asymmetric reactions by involving *N*-phosphonyl imines as GAP starting materials. Following the previous studies in our laboratory,[15b, 17] here we would like to report that the asymmetric Mannich-type reactions between *N*-phosphonyl imines and azlactones leads to the efficient formation of *α*-quaternary *syn*-*α*, *β*-diamino acid analogs, without the use of

any bases, additives and catalysts (Scheme 1). Azlactones derived from several natural and unnatural α-amino acids were successfully apllied in this reaction with good to high yields and excellent diastereoselectivities. This reaction follows the GAP chemistry process in which pure products can be obtained simply by washing crude mixtures with co-solvents of DCM and hexane.

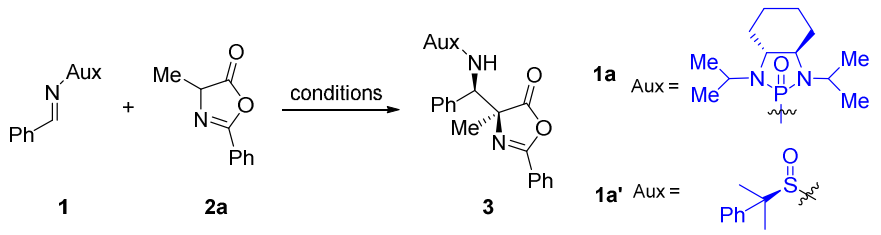
Scheme 1 Asymmetric synthesis of α-quaternary α,β-diamino acid derivatives



RESULTS AND DISCCUTION

Initially, we conducted the Mannich-type reaction between *N*-phosphonyl imine **1a** and 4-methyl-2-phenyl-oxazol-5(4*H*)-one **2a**. The reaction conditions were carefully optimized, and the results were summarized in Table 1. Considering the acidity of the α-hydrogen of the azlactone (pKa≈9), some organic and inorganic bases were utilized to form nucleophilic enolates (entries 1-4). However, except DABCO gave a modest yield (55%), other stronger bases gave only trace amounts of products, because the azlactones can be decomposed to amino esters. Giving the fact that imines can be activated by the Bronsted-Lowry acids, we then added several acids into the reaction mixture (entries 5-8). Surprisingly, when imine and azlactone were reacted in DCM with no additives (entry 5), we got excellent conversion rate (92%) and diastereoselectivities (only *syn* isomers were observed, dr of *syn* 12:1). Notably, after concentration, precipitating with hexane and washing the crude mixture with co-solvents of DCM and hexane, the major product can be obtained in 83% yield and >20:1 dr, following the GAP chemistry work-up procedure. Acetic acid or benzoic acid (10% mol) can accelerate the reaction, allowing the completion within 8 hours (entries 6, 7), as well as increasing the diastereoselectivity slightly. However, stronger acid TFA can cause the decomposition of the imine, thus lower the yield. Then, decreasing the temperature to 0 ^{o}C led to >20:1 dr but an inferior conversion rate (entry 9). Finally, the optimization of solvents revealed that all five solvents THF, toluene, ether, acetonitrile and acetone deliver lower yields and diastereoselectivity than DCM (entries 10-14). In order to compare the reactivity with the N-phosphonyl imine, we introduced the chiral sulfinyl imine **1a'** into the reaction (entries 15, 16), which led to no product but the recovery of the starting materials.

Table 1. Screening of reaction conditions



1 **2a** **3**

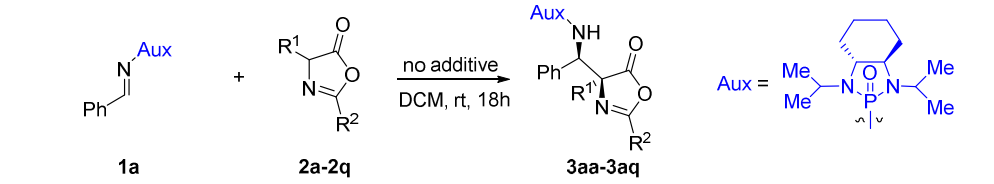
entry[a]	imine	additive	solvent	yield	*syn*:*anti*[e]	dr of *syn*[e]
1[b]	**1a**	DABCO	DCM	55%	>20:1	8.8:1
2	**1a**	KOH	DCM	19%	>20:1	1:3.2
3	**1a**	K_2CO_3	DMF	<5%	/	/
4	**1a**	LDA	DCM	trace	/	/
5	**1a**	**/**	**DCM**	**92% (83%[e])**	>20:1	**12:1 (>20:1[e])**
6[c]	**1a**	AcOH (10% mol)	DCM	89%	>20:1	17:1
7[c]	**1a**	PhCOOH (10% mol)	DCM	93%	>20:1	16:1
8	**1a**	TFA (10% mol)	DCM	29%	>20:1	2.6:1
9[d]	**1a**	/	DCM	82%[d]	>20:1	>20:1
10	**1a**	/	THF	54%	>20:1	6.8:1
11	**1a**	/	Et_2O	84%	>20:1	11:1
12	**1a**	/	toluene	81%	>20:1	9.1:1
13	**1a**	/	MeCN	83%	>20:1	8.8:1
14	**1a**	/	acetone	63%	>20:1	10:1
15	**1a'**	DABCO	DCM	0%[f]	/	/
16	**1a'**		DCM	0%[f]	/	/

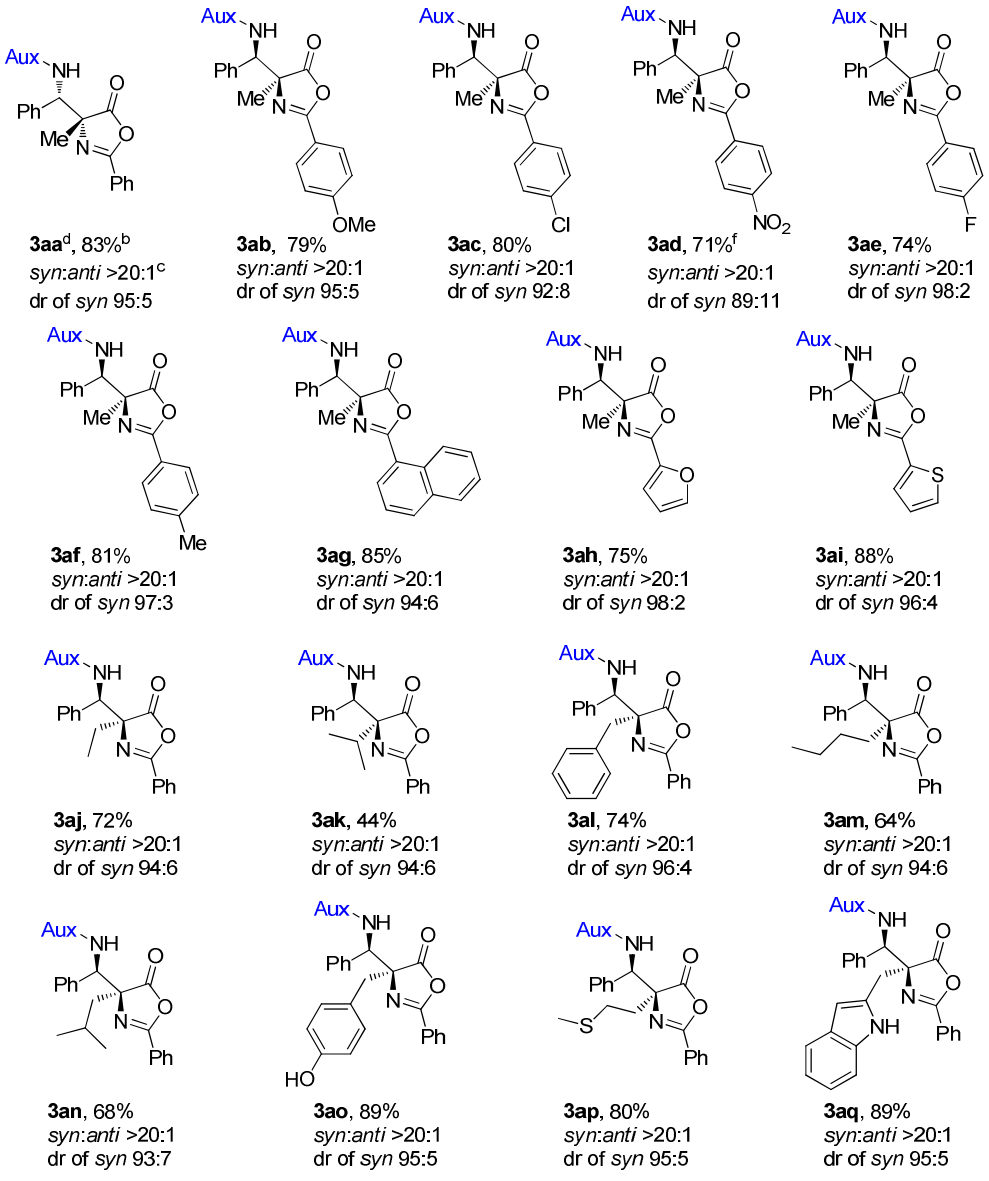
[a]Reactions were performed with imine (0.4 mmol), azlactone (0.48 mmol) in 10 mL solvent under N_2 at room temperature for 18h. [b]Reaction time 48h.[c]Reaction time 8h. [d]Temperature decreased to 10 °C. [e]isolated yield by GAP washing. Other conversion rates were determined by ^{31}P NMR analysis of the crude mixture. [e]The diastereoisomer ratio were determined by crude ^{31}P NMR. *syn*:*anti*>20:1 means only syn isomers were observed. dr represents the ratio of two *syn* isomers. [f]The starting materials were maintained.

With the optimized reaction conditions established, the substrate scope of azlactones **2** was evaluated, and the results were summarized in Scheme 2. We got good to high yields, as well as complete *syn* selectivity and good diastereoselectivity in all the cases. The substituent on the aromatic ring (R^2 group) did not have significant effect on asymmetric induction (**3aa-3ai**), but 4-nitro substituent (**3ad**) showed that the electron-withdrawing group has a negative effect on the diastereoselectivity. The hetero-aryl groups were also bearable in the reactions (**3ah**, **3ai**). Then,

azlactones derived from several natural α-amino acids (including Ala, Val, Phe, Leu, Met, Tyr and Trp) and some unnatural cases were conducted into the reactions (**3aj**-**3aq**). The isopropyl group seriously diminished the yield (**3ak**, 44%) maybe due to the steric hindrance. The hetero atom-containing groups on the side chain were also tolerable (**3ao**-**3aq**), leading to high yields (80%-89%) and dr (95:5).

Scheme 2. Substrate scope of the azlactones[a]



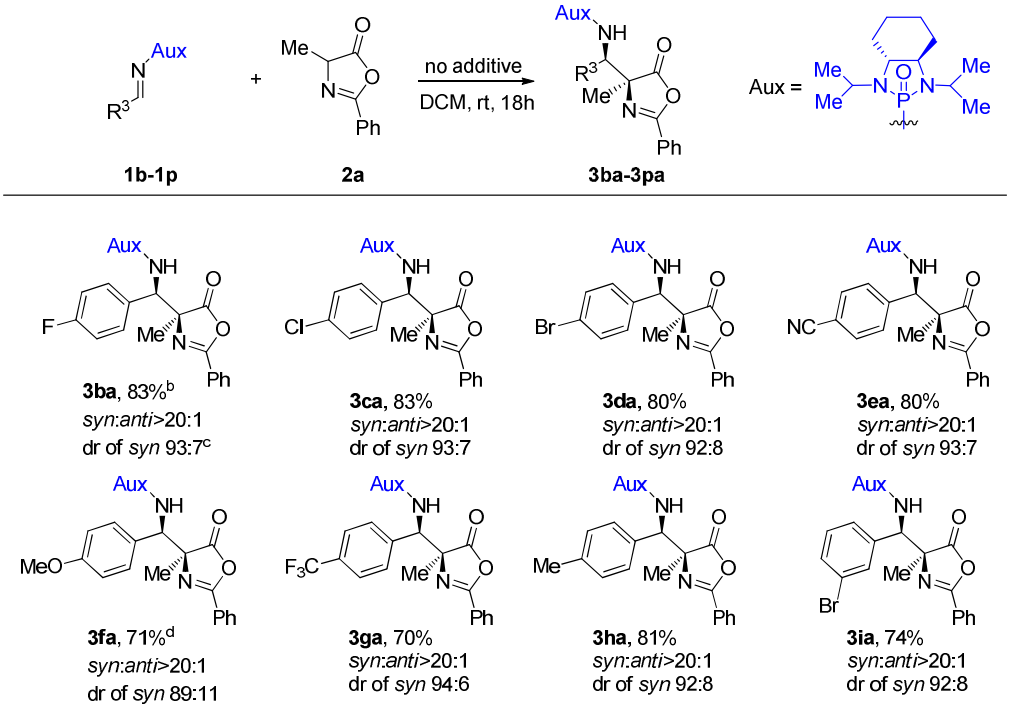


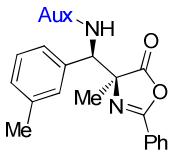
[a]Reactions were performed with imine (0.4 mmol), azlactone (0.48 mmol) in dry DCM at room temperature for 18h. [b]Isolated yields after GAP washing. [c]the *syn*:*anti* ration and dr were determined from ^{31}P NMR of crude

reaction mixture, see Support Information for details. [d]The reaction was conducted on 2g scale. [e]The absolute stereochemistries of **3ah** were determined by X-ray crystallography, and those of the other products were assigned by analogy. [f]Further recrystallization was conducted after GAP washing to afford the single isomer.

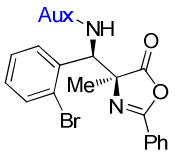
Subsequently, the substrate scope of *N*-phosphonyl imines **1** was evaluated, and the results were listed in Scheme 3. Various aromatic imines containing either electron-withdrawing or electron-donating groups could be used in the reaction. Good yields and excellent diastereoselectivities were obtained in most cases, except the 4-methyloxyl, 2-bromo, 2-furyl, 2-thienyl cases (**3fa**, **3ka**, **3pa**, **3oa**), in which the dr were lower than 90:10. In most of the cases , the pure products were obtained simply by washing the crude mixture with hexane/DCM once or twice without the use of chromatography. However, due to the low dr value, further recrystallization was needed in cases **3fa**, **3ka** and **3oa** to afford the single isomer. Besides the aromatic *N*-phosphonyl imines (R^3=aryl), the aliphatic imines (R^3= cyclohexyl, *i*-Pr, Et, etc.) were unstable and inseparable, which failed to participate in these reactions.

Scheme 3. Substrate scope of the *N*-phosphonyl imines[a]

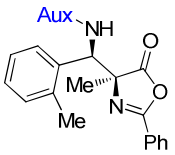




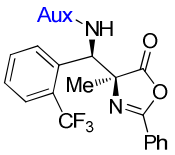
3ja, 79%
syn:*anti*>20:1
dr of *syn* 96:4



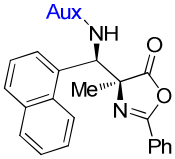
3ka, 63%[d]
syn:*anti*>20:1
dr of *syn* 85:15



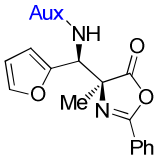
3la, 76%
syn:*anti*>20:1
dr of *syn* 96:4



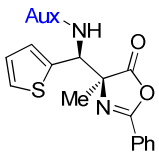
3ma, 78%
syn:*anti*>20:1
dr of *syn* 95:5



3na, 85%
syn:*anti*>20:1
dr of *syn* 93:7



3oa, 61%[d]
syn:*anti*>20:1
dr of *syn* 85:15



3pa, 77%
syn:*anti*>20:1
dr of *syn* 89:11

[a]Reactions were performed with imine (0.4 mmol), azlactone (0.48 mmol) in dry DCM at room temperature for 18h. [b]Isolated yields after GAP washing. [c]the *syn*:*anti* ration and dr were determined from ^{31}P NMR of crude mixture. [d]Further recrystallization was conducted after GAP washing to afford the single isomer.

The absolute configuration of **3h** was determined by X-ray structural analysis (see Supporting Information), revealing the two vicinal chiral centers retaining a (2*S*, 3*R*) configuration, which is in contrast with our previous work[18]. According to the literature report[19], this reaction seems to follow an aza-ene reaction. The transition state shown in Figure 1 revealed that the P-O bond of the *N*-phosphonyl imine activated the enol intermediate of the azlactone through a hydrogen bond[8e, 8f, 19c], followed by an aza-ene type reaction to form the observed stereochemistry, which was controlled by the chiral auxiliary.

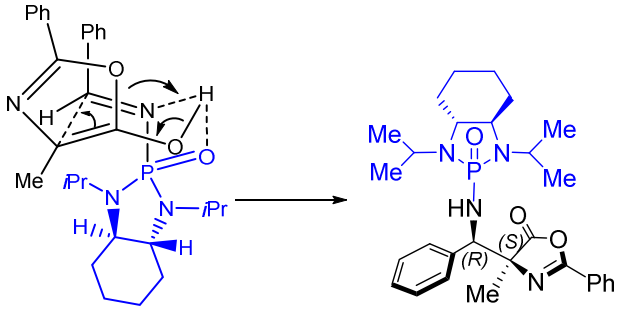
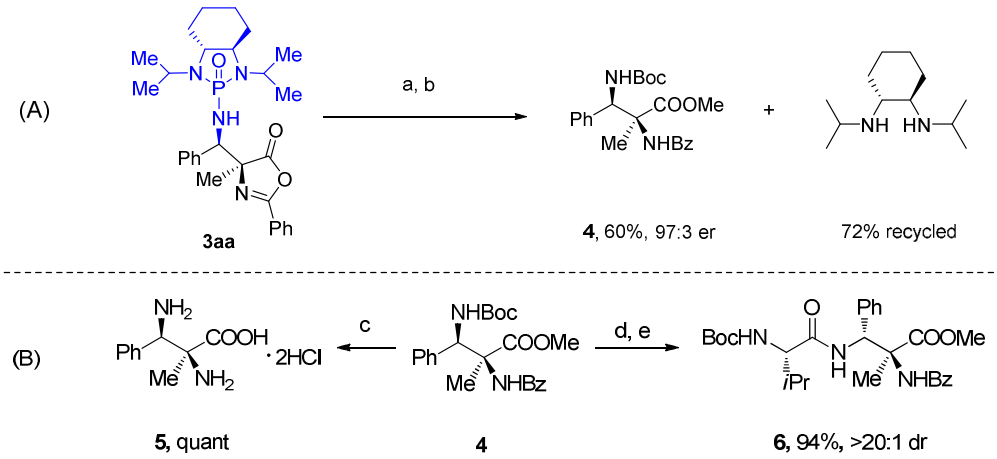


Figure 1 Plausible activation mode for the stereoselective reaction between chiral *N*-phosphonyl imines and azlactones

To expand the synthetic utility of the present system, the chiral auxiliary was cleaved (Scheme 4A). The Mannich product **3aa** was dissolved in MeOH and treated with 48% aqueous HBr, followed by Boc protection, to form quaternary *syn*-*α*, *β*-diamino ester **4** in 60% overall yield, with 72% of the chiral amine recycled. Adduct **4** was subsequently converted to other derivatives, including fully deprotected *α*, *β*-diamino acid **5** and dipeptide **6** in one or two operations (Scheme 4B). These compounds are crucial fragments of some bioactive peptides and medicinally valuable compounds.

Scheme 4 Derivatization of the Mannich product 3aa[a]



[a]Conditions: (a) 10 eq. HBr, MeOH, rt; (b) $(Boc)_2O$, TEA, DCM, rt; (c) PhOH, AcOH, 6M HCl, reflux; (d) TFA, DCM, rt; (e) Boc-Val-OH, EDC, HOBt, TEA, DCM, 0 °C to rt.

In summary, asymmetric Mannich-type reaction between chiral *N*-phosphonyl imines and azlactones has been presented. Without the use of any additives, bases or catalysts, the reaction went smoothly to form *α*-quaternary *syn*-*α*, *β*-diamino acid derivatives in good to excellent chemical yields and diastereoselectivity. The pure products can be obtained simply by GAP work-up procedure, and can be further transformed into valuable Boc-protected *α*, *β*-diamino esters, fully deprotected *α*, *β*-diamino acids and dipeptides. The absolute stereochemistry was determined by X-ray analysis, which was in contrast with our previous work. Our further studies will be focused on new asymmetric reactions of *N*-phosphonyl imines, enamines and hemiaminals.

EXPERIMENTAL SECTION

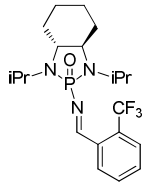
General Method

All commercially available chemicals were used as received without further purification. Solvents were delivered from Innovation Technology solvent system. All reactions were carried out in flame dried flask under nitrogen atmosphere. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 400 MHz instrument with TMS as internal standard. Chemical shifts (δ) were reported in ppm with respect to TMS. Data are represented as follows: chemical shift, mutiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (J, Hz) and integration. HRMS analyses were carried out using a TOF-MS instrument with an ESI source.

Synthesis and Characterization of *N*-Phosphonyl Imines 1a-1p

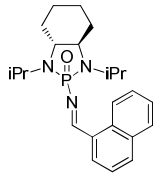
These compounds were synthesized according to our published procedures.[20] Into a dried and nitrogen flushed round-bottomed flask, chiral phosphoramide (259 mg, 1.00 mmol), aldehyde (1.50 mmol) and DCM (5 mL) were loaded. The resulting mixture was protected by nitrogen and was cooled to 0 °C prior to the addition of DIEA (0.50 mL, 3 mmol). Into the above mixture, a solution of $TiCl_4$ in DCM (1 M, 0,60 mmol) was added in drops. The reaction was stirred at 0 °C for 30 min and at room temperature for 24 h. The clear solution of the crude reaction mixture was directly transferred to silica gel (200–300 mesh) packed in a column for chromatography and eluted by mixed solvents of PE/EA (v/v,7:3 to 1:1) to give imine products. The ^1H , ^{13}C and ^{31}P

NMR data for these compounds agree with the published data.[20] Some newly synthesized imines were characterized as follows.



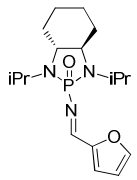
(3aR,7aR)-1,3-diisopropyl-2-((E)-(2-(trifluoromethyl)benzylidene)amino)octahydro-1H-benzo[d][1,3-,2]diazaphosphole 2-oxide(**1m**):

Yellow solid, 305 mg, 74% yield; $[\alpha]_D^{20}$ = +41.8 (c = 0.78, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.28 (dd, *J* = 31.9, 2.0 Hz, 1H), 8.38 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.69-7.59 (m, 2H), 3.61-3.39 (m, 2H), 3.12-3.01 (m, 1H), 2.55 (td, *J* = 10.8, 2.9 Hz, 1H), 2.16-1.98 (m, 2H), 1.82 (d, *J* = 11.4 Hz, 2H), 1.40-1.23 (m, 13H), 1.07 (d, *J* = 6.6 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 134.0 (d, *J* = 28.1 Hz), 132.3, 131.9, 130.8 (q, *J* = 31.3 Hz), 129.1, 125.9 (d, *J* = 5.5 Hz), 124.2 (q, *J* = 274.3 Hz), 59.9 (d, *J* = 7.8 Hz), 58.9 (d, *J* = 10.4 Hz), 45.4 (d, *J* = 2.5 Hz), 44.8 (d, *J* = 2.5 Hz), 30.0 (d, *J* = 9.2 Hz), 29.5 (d, *J* = 10.2 Hz), 24.4, 24.3, 21.9 (d, *J* = 2.8 Hz), 21.5 (d, *J* = 4.1 Hz), 20.8, 20.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.92; HRMS (ESI-TOF) m/z $[C_{20}H_{29}F_3N_3OP+Na]^+$ calcd for 438.1893, found 438.1896.



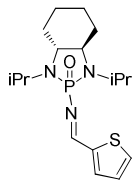
(3aR,7aR)-1,3-diisopropyl-2-((E)-(naphthalen-1-ylmethylene)amino)octahydro-1H-benzo[d][1,3,2]diazaphosphole 2-oxide(**1n**):

White solid, 317 mg, 80% yield; $[\alpha]_D^{20}$ = +4.1 (c = 0.73, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, *J* = 33.8 Hz, 1H), 9.09 (d, *J* = 8.5 Hz, 1H), 8.21 (d, *J* = 6.0 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.67-7.62 (m, 1H), 7.61-7.54 (m, 2H), 3.56-3.40 (m, 2H), 3.20-3.08 (m, 1H), 2.93 (s, 1H), 2.12 (d, *J* = 11.4 Hz, 2H), 1.84 (d, *J* = 4.6 Hz, 2H), 1.44-1.28 (m, 13H), 1.14 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0 (d, *J* = 6.9 Hz), 134.0, 133.7, 132.2, 131.7, 128.9, 128.0, 126.5, 125.4, 124.1, 60.1 (d, *J* = 8.3 Hz), 59.6 (d, *J* = 9.1 Hz), 45.4 (d, *J* = 2.8 Hz), 44.8 (d, *J* = 3.1 Hz), 29.9 (d, *J* = 9.8 Hz), 29.8 (d, *J* = 9.0 Hz), 24.53, 24.49, 22.2 (d, *J* = 3.3 Hz), 21.4 (d, *J* = 3.2 Hz), 20.9, 20.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.21; HRMS (ESI-TOF) m/z $[C_{20}H_{29}F_3N_3OP+Na]^+$ calcd for 438.1893, found 438.1896.



(3aR,7aR)-1,3-diisopropyl-2-((E)-(furan-2-ylmethylene)amino)octahydro-1H-benzo[d][1,3,2]diazaphosphole 2-oxide(**1o**):

White solid, 182 mg, 52% yield; $[\alpha]_D^{20}$ = -52.7 (c = 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 33.7 Hz, 1H), 7.67 (s, 1H), 7.12 (s, 1H), 6.63-6.55 (m, 1H), 3.46-3.28 (m, 2H), 3.13-3.04 (m, 1H), 2.99 (s, 1H), 2.14-1.98 (m, 2H), 1.81 (d, *J* = 5.8 Hz, 2H), 1.38-1.21 (m, 13H), 1.14 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (d, *J* = 5.7 Hz), 152.6 (d, *J* = 31.7 Hz), 147.3, 119.7, 112.7, 59.98 (d, *J* = 8.6 Hz), 59.57 (d, *J* = 8.8 Hz), 45.17 (d, *J* = 3.0 Hz), 44.62 (d, *J* = 3.3 Hz), 29.86 (d, *J* = 9.8 Hz), 29.30 (d, *J* = 9.4 Hz), 24.5, 24.4, 22.0 (d, *J* = 3.5 Hz), 21.0 (d, *J* = 2.8 Hz), 20.8, 20.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.58; HRMS (ESI-TOF) m/z $[C_{17}H_{28}N_3O_2P+Na]^+$ calcd for 360.1811, found 360.1813.



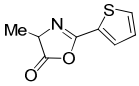
(3aR,7aR)-1,3-diisopropyl-2-((E)-(thiophen-2-ylmethylene)amino)octahydro-1H-benzo[d][1,3,2]diazaphosphole 2-oxide(**1p**):

Yellow solid, 157 mg, 44%; $[\alpha]_D^{20}$ = +36.9 (c = 0.51, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.08 (dd, *J* = 31.5, 0.6 Hz, 1H), 7.63 (d, *J* = 4.0 Hz, 2H), 7.17 (t, *J*

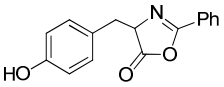
= 4.3 Hz, 1H), 3.48-3.31 (m, 2H), 3.12-3.03 (m, 1H), 2.89 (s, 1H), 2.07 (d, *J* = 5.7 Hz, 2H), 1.81 (s, 2H), 1.39-1.24 (m, 13H), 1.13 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 134.9, 133.0, 128.3, 59.9 (d, *J* = 8.3 Hz), 59.5 (d, *J* = 8.8 Hz), 45.2 (s), 44.7 (d, *J* = 3.0 Hz), 29.8 (d, *J* = 10.0 Hz), 29.5 (d, *J* = 9.5 Hz), 24.5, 24.4, 22.0 (d, *J* = 3.0 Hz), 21.1 (d, *J* = 2.8 Hz), 20.9, 20.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.20; HRMS (ESI-TOF) m/z $[C_{17}H_{28}N_3OPS+Na]^+$ calcd for 376.1583, found 376.1586.

Synthesis and Characterization of Azlactones 2a-2q

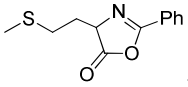
The azlactones **2a-2q** were prepared according to the literature method.[21] To a suspension of *N*-aroyl amino acid (1 equiv) in dry DCM (0.1 M based on substrate) under N_2 at 0 ^{o}C was added EDCI (1.1 equiv). The materials were stirred at 0 ^{o}C for 1 hour. The reaction mixture was diluted with an equal volume of DCM, and washed successively with saturated aqueous $NaHCO_3$, water and brine (each 1/2 the volume of the organic phase), then dried over Na_2SO_4 and concentrated under reduced pressure. In all cases products were obtained in a form suitable for use without further purification. The NMR data agree with the literature report.[21] Some newly synthesized azlactones were characterized as follows.



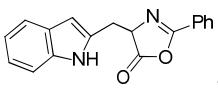
4-methyl-2-(thiophen-2-yl)oxazol-5(4H)-one (**2i**): white solid, 2.33g, 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 3.7 Hz, 1H), 7.60 (d, *J* = 5.0 Hz, 1H), 7.15 (dd, *J* = 5.0, 3.8 Hz, 1H), 4.43 (q, *J* = 7.5 Hz, 1H), 1.58 (d, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 157.5, 132.0, 131.8, 128.5, 128.1, 60.9, 17.0; HRMS (ESI-TOF) m/z $[C_8H_7NO_2S+Na]^+$ calcd for 204.0090, found 204.0089.



4-(4-hydroxybenzyl)-2-phenyloxazol-5(4H)-one (**2o**): white solid, 875mg, 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.0 Hz, 2H), 7.56 (t, J = 7.1 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.68 (d, *J* = 8.2 Hz, 2H), 4.67 (t, *J* = 5.4 Hz, 1H), 3.32 (dd, *J* = 14.1, 4.4 Hz, 1H), 3.13 (dd, *J* = 14.1, 6.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 162.3, 155.0, 133.1, 131.0, 129.0, 128.1, 127.1, 125.6, 115.5, 66.7, 36.6; HRMS (ESI-TOF) m/z $[C_{16}H_{13}NO_3+Na]^+$ calcd for 290.0788, found 204.0791.



4-(2-(methylthio)ethyl)-2-phenyloxazol-5(4H)-one (**2p**): colorless oil, 1.12g, 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 6.9 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 4.60 (t, *J* = 6.3 Hz, 1H), 2.74 (t, *J* = 6.9 Hz, 2H), 2.36-2.25 (m, 1H), 2.21-2.13 (m, 1H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 162.2, 132.9, 128.9, 128.0, 125.9, 63.8, 30.6, 30.2, 15.2; HRMS (ESI-TOF) m/z $[C_{12}H_{13}NO_2S+Na]^+$ calcd for 258.0559, found 258.0561.



4-((1H-indol-2-yl)methyl)-2-phenyloxazol-5(4H)-one (**2q**): yellow solid, 1.18g, 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.72 (d, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.1 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.18-7.07 (m, 3H), 4.76 (s, 1H), 3.59-3.48 (m, 1H), 3.41 (dd, *J* = 14.7, 5.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.0, 162.1, 136.1, 132.8, 128.8, 128.1, 127.5, 125.9, 123.5, 122.2, 119.7, 119.3, 111.1, 109.8,

66.6, 27.4; HRMS (ESI-TOF) m/z $[C_{18}H_{14}N_2O_2+Na]^+$ calcd for 313.0947, found 313.0948.

Typical Procedure for the Asymmetric Synthesis of Mannich Products 3aa-3pa through GAP Progress

In an oven dried and nitrogen charged 50 mL round-bottom vial, a solution of 0.4 mmol *N*-phosphonyl imine **1** in 5 mL DCM was stirred at room temperature. Then a solution of 0.48 mmol azlactone **2** in 5mL DCM was added. The reaction mixture was stirred for 8~18 hours until TLC analysis indicated complete consumption of the imine. After that, the solution was concentrated before adding hexane to form precipitation. After filtration, the crude solid was washed once or twice with hexane/DCM (v/v, 10/1) to afford the pure product. In some cases, further recrystallization was conducted to obtain the single isomer for characterization.

Data for Pure Products 3aa-3pa

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(phenyl)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3aa**): 2.0 g imine **1** (5.76 mmol) was applied in this reaction, obtaining a white solid, 2.50 g, 83% yield; m.p. 171.4-174.2 ^oC; $[\alpha]_D^{20}$ = -53.5 (c = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.7 Hz, 2H), 7.59 (t, J = 7.3 Hz, 1H), 7.54-7.46 (m, 4H), 7.32 (t, J = 7.3 Hz, 2H), 7.25 (t, J = 7.2 Hz, 1H), 4.93-4.85 (m, 1H), 3.63-3.48 (m, 1H), 2.96-2.75 (m, 3H), 2.68 (t, J = 8.0 Hz, 1H), 1.95 (m, 2H), 1.67 (d, J = 10.1 Hz, 2H), 1.36 (s, 3H), 1.30-1.16 (m, 7H), 0.98 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H), 0.65 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.2, 161.2, 140.5, 133.0, 128.9, 128.6, 128.5, 128.2, 128.0, 126.1, 74.1 (d, J = 10.3 Hz), 62.1, 59.4 (d, J = 11.6 Hz), 58.8 (d, J = 9.5 Hz), 44.1 (d, J = 3.9 Hz), 44.0 (d, J = 3.4 Hz), 32.0 (d, J = 12.2 Hz), 31.1 (d, J = 10.1 Hz), 24.4 (d, J = 3.6 Hz), 24.3 (d, J = 9.1 Hz), 23.5 (d, J = 4.3 Hz), 22.4, 19.7, 19.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.84; HRMS (ESI-TOF) m/z $[C_{29}H_{39}N_4O_3P+Na]^+$ calcd for 545.2652, found 545.2650.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(phenyl)methyl)-2-(4-methoxyphenyl)-4-methyloxazol-5(4H)-one (**3ab**): white solid, 174 mg, 79% yield; m.p. 96.1-98.0 ^oC; $[\alpha]_D^{20}$ = -44.3 (c = 0.84, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.9 Hz, 2H), 7.50 (d, J = 7.2 Hz, 2H), 7.31 (t, J = 7.3 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 6.98 (d, J = 8.9 Hz, 2H), 4.84 (dd, J = 11.3, 9.5 Hz, 1H), 3.88 (s, 3H), 3.60-3.45 (m, 1H), 3.00-2.78 (m, 3H), 2.75-2.64 (m, 1H), 1.95 (t, J = 12.1 Hz, 2H), 1.67 (d, J = 11.1 Hz, 2H), 1.33 (s, 3H), 1.29-1.18 (m, 7H), 0.95 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.3, 163.4, 160.9, 140.2, 130.1, 128.7, 128.4, 128.0, 118.3, 114.3, 74.1 (d, J = 7.3 Hz), 61.5, 59.5 (d, J = 11.4 Hz), 59.1 (d, J = 10.6 Hz), 55.7, 44.1 (d, J = 3.1 Hz), 43.5 (d, J = 4.8 Hz), 31.9 (d, J = 12.0 Hz), 31.3 (d, J = 10.3 Hz), 24.7 (d, J = 8.5 Hz), 24.4, 23.7 (d, J = 5.0 Hz), 22.4, 19.6, 19.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.02; HRMS (ESI-TOF) m/z $[C_{30}H_{41}N_4O_4P+Na]^+$ calcd for 575.2758, found 575.2759.

(S)-2-(4-chlorophenyl)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(phenyl)methyl)-4-methyloxazol-5(4H)-one (**3ac**): white solid, 178 mg, 80% yield; m.p. 110.5-111.8 ^oC; $[\alpha]_D^{20}$ = -41.4 (c = 0.78, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.3 Hz, 4H), 7.31 (t, J = 7.2 Hz, 2H), 7.25 (t, J = 7.3 Hz, 1H), 4.88 (t, J = 10.5 Hz, 1H), 3.60-3.48 (m, 1H), 2.94-2.73 (m, 3H), 2.72-2.60 (m, 1H), 2.00-1.89 (m, 2H), 1.68 (d, J = 10.5 Hz, 2H), 1.37 (s, 3H), 1.31-1.15 (m, 7H), 0.97 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H), 0.64 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.8, 160.3, 139.9, 139.3, 129.5, 129.3, 128.5, 128.4, 128.1, 124.4, 74.4 (d, J = 7.2 Hz), 61.5, 59.4 (d, J = 11.1 Hz), 59.1 (d, J = 10.6 Hz), 44.2 (d, J = 4.9 Hz), 43.6 (d, J = 4.7 Hz), 31.8 (d, J = 13.2 Hz),

31.2 (d, J = 10.0 Hz), 24.7 (d, J = 8.4 Hz), 24.4, 23.6 (d, J = 4.9 Hz), 22.3, 19.6, 19.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.78; HRMS (ESI-TOF) m/z $[C_{29}H_{38}ClN_4O_3P+Na]^+$ calcd for 579.2262, found 579.2266.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2 (3H)-yl)amino)(phenyl)methyl)-4-methyl-2-(4-nitrophenyl)oxazol-5(4H)-one (**3ad**): After GAP washing procedure, the single isomer was recrystallized as a pale yellow solid, 160 mg, 71% yield; m.p. 125.4-126.6 ^{o}C; $[\alpha]_D^{20}$ = -26.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 8.6 Hz, 2H), 8.17 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 7.0 Hz, 2H), 7.31 (t, J = 7.2 Hz, 2H), 7.26-7.23 (m, 1H), 4.94 (t, J = 10.6 Hz, 1H), 3.64-3.49 (m, 1H), 3.01-2.78 (m, 3H), 2.77-2.61 (m, 1H), 2.03-1.89 (m, 2H), 1.69 (d, J = 10.4 Hz, 2H), 1.45 (s, 3H), 1.31-1.15 (m, 7H), 1.00 (d, J = 5.0 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H), 0.65 (d, J = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.1, 159.4, 150.3, 139.4, 131.4, 129.1, 128.4, 128.2, 128.1, 123.9, 74.7 (d, J = 6.9 Hz), 61.5, 59.3 (d, J = 9.5 Hz), 59.0 (d, J = 10.8 Hz), 44.2 (d, J = 8.3 Hz), 43.5 (d, J = 4.6 Hz), 31.7 (d, J = 10.0 Hz), 31.1 (d, J = 10.2 Hz), 24.5 (d, J = 8.1 Hz), 24.3, 23.4 (d, J = 4.5 Hz), 22.1, 19.4, 19.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.72; HRMS (ESI-TOF) m/z $[C_{29}H_{38}N_5O_5P+Na]^+$ calcd for 590.2503, found 590.2505.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2 (3H)-yl)amino)(phenyl)methyl)-2-(4-fluorophenyl)-4-methyloxazol-5(4H)-one (**3ae**): white solid, 160 mg, 74% yield; m.p. 151.3-153.2 ^{o}C; $[\alpha]_D^{20}$ = -37.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 8.7, 5.4 Hz, 2H), 7.47 (d, J = 7.2 Hz, 2H), 7.31 (t, J = 7.3 Hz, 2H), 7.25 (t, J = 7.3 Hz, 1H), 7.17 (t, J = 8.6 Hz, 2H), 4.88 (dd, J = 11.2, 9.7 Hz, 1H), 3.62-3.48 (m, 1H), 2.96-2.78 (m, 3H), 2.75-2.62 (m, 1H), 2.01-1.89 (m, 2H), 1.68 (d, J = 10.4 Hz, 2H), 1.37 (s, 3H), 1.31-1.17 (m, 7H), 0.97 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.8, 165.5 (d, J = 254.5 Hz), 160.1, 139.8, 130.5 (d, J = 9.1 Hz), 128.4, 128.3, 128.0, 122.1 (d, J = 3.2 Hz), 116.1 (d, J = 22.2 Hz), 74.2 (d, J = 7.1 Hz), 61.4, 59.3 (d, J = 11.4 Hz), 59.0 (d, J = 10.6 Hz), 43.4 (d, J = 4.7 Hz), 31.7 (d, J = 12.1 Hz), 31.1 (d, J = 10.3 Hz), 24.5 (d, J = 8.3 Hz), 24.3, 23.5 (d, J = 4.9 Hz), 22.2, 19.5, 19.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.76; HRMS (ESI-TOF) m/z $[C_{29}H_{38}FN_4O_3P+Na]^+$ calcd for 563.2558, found 563.2563.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2 (3H)-yl)amino)(phenyl)methyl)-4-methyl-2-(p-tolyl)oxazol-5(4H)-one (**3af**): white solid, 174 mg, 81% yield; m.p. 104.8-105.0 ^{o}C; $[\alpha]_D^{20}$ = -37.6 (c = 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.34-7.28 (m, 4H), 7.26-7.22 (m, 1H), 4.87 (dd, J = 11.4, 9.4 Hz, 1H), 3.59-3.46 (m, 1H), 2.93-2.73 (m, 3H), 2.63 (t, J = 9.3 Hz, 1H), 2.44 (s, 3H), 2.00-1.88 (m, 2H), 1.67 (d, J = 13.3 Hz, 2H), 1.35 (s, 3H), 1.31-1.17 (m, 7H), 0.96 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.63 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.3, 161.2, 143.7, 140.1, 129.6, 128.6, 128.4, 128.2, 128.0, 123.2, 74.2 (d, J = 7.2 Hz), 61.5, 59.5 (d, J = 11.4 Hz), 59.1 (d, J = 10.6 Hz), 44.1 (d, J = 3.4 Hz), 43.5 (d, J = 4.8 Hz), 31.9 (d, J = 12.2 Hz), 31.3 (d, J = 10.2 Hz), 24.7 (d, J = 8.5 Hz), 24.4, 23.7 (d, J = 5.0 Hz), 22.3, 21.9, 19.6, 19.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.88; HRMS (ESI-TOF) m/z $[C_{30}H_{41}N_4O_3P+Na]^+$ calcd for 559.2808, found 559.2813.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2 (3H)-yl)amino)(phenyl)methyl)-4-methyl-2-(naphthalen-1-yl)oxazol-5(4H)-one (**3ag**): Pale yellow solid, 194 mg, 85% yield; m.p. 149.5-150.7 ^{o}C; $[\alpha]_D^{20}$ = -45.4 (c = 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.11 (dd, J = 8.6, 1.6 Hz, 1H), 7.98-7.88 (m, 3H), 7.65-7.50 (m, 4H),

7.33 (t, *J* = 7.4 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 4.93 (dd, *J* = 11.5, 9.5 Hz, 1H), 3.64-3.50 (m, 1H), 2.88 (dt, *J* = 9.7, 6.8 Hz, 3H), 2.64 (t, *J* = 8.2 Hz, 1H), 2.02-1.87 (m, 2H), 1.69-1.60 (m, 2H), 1.41 (s, 3H), 1.31-1.18 (m, 7H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.65 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1, 161.3, 140.1, 135.5, 132.7, 129.7, 129.3, 128.8, 128.6, 128.5, 128.4, 128.1, 128.0, 127.2, 123.8, 123.2, 74.4 (d, *J* = 7.3 Hz), 61.6, 59.5 (d, *J* = 12.0 Hz), 59.1 (d, *J* = 10.5 Hz), 44.3 (d, *J* = 7.4 Hz), 43.6 (d, *J* = 5.0 Hz), 31.3 (d, *J* = 10.0 Hz), 31.1, 24.6 (d, *J* = 7.3 Hz), 24.4, 23.70 (d, *J* = 5.0 Hz), 22.4, 19.6, 19.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.92; HRMS (ESI-TOF) m/z $[C_{33}H_{41}N_4O_3P+Na]^+$ calcd for 595.2808, found 595.2813.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2 (3H)-yl)amino)(phenyl)methyl)-2-(furan-2-yl)-4-methyloxazol-5(4H)-one (**3ah**): white solid, 153 mg, 75% yield; m.p. 162.9-165.0 ^{o}C; $[\alpha]_D^{20}$ = -55.8 (c = 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 0.8 Hz, 1H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.29-7.24 (m, 1H), 7.10 (d, *J* = 3.4 Hz, 1H), 6.59 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.87 (dd, *J* = 11.4, 9.5 Hz, 1H), 3.57-3.44 (m, 1H), 2.93-2.80 (m, 2H), 2.76 (t, *J* = 10.3 Hz, 1H), 2.68-2.60 (m, 1H), 2.02-1.88 (m, 2H), 1.68 (d, *J* = 11.4 Hz, 2H), 1.33 (s, 3H), 1.29-1.16 (m, 7H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.62 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 153.4, 146.9, 140.8, 139.6, 128.4, 128.0, 117.4, 112.2, 73.8 (d, *J* = 7.1 Hz), 61.4, 59.4 (d, *J* = 11.5 Hz), 58.9 (d, *J* = 10.7 Hz), 43.9 (d, *J* = 3.0 Hz), 43.4 (d, *J* = 4.6 Hz), 31.8 (d, *J* = 12.1 Hz), 31.2 (d, *J* = 10.3 Hz), 24.5 (d, *J* = 8.6 Hz), 24.3, 23.6 (d, *J* = 5.0 Hz), 22.2, 19.5, 18.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.67; HRMS (ESI-TOF) m/z $[C_{27}H_{37}N_4O_4P+Na]^+$ calcd for 535.2445, found 535.2448.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2 (3H)-yl)amino)(phenyl)methyl)-4-methyl-2-(thiophen-2-yl)oxazol-5(4H)-one (**3ai**): white solid, 184 mg, 88% yield; m.p. 158.7-160.7 ^{o}C; $[\alpha]_D^{20}$ = -28.0 (c = 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.61 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.26-7.22 (m, 1H), 7.16 (dd, *J* = 4.9, 3.8 Hz, 1H), 4.86 (dd, *J* = 11.5, 9.5 Hz, 1H), 3.58-3.44 (m, 1H), 2.94-2.74 (m, 3H), 2.66 (t, *J* = 8.5 Hz, 1H), 2.01-1.88 (m, 2H), 1.68 (d, *J* = 10.7 Hz, 2H), 1.35 (s, 3H), 1.29-1.16 (m, 7H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.64 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 157.1, 139.9, 132.2, 131.9, 128.7, 128.6, 128.5, 128.2, 128.1, 74.3 (d, *J* = 7.1 Hz), 61.6, 59.5 (d, *J* = 11.4 Hz), 59.1 (d, *J* = 10.5 Hz), 44.2 (d, *J* = 2.6 Hz), 43.6 (d, *J* = 4.7 Hz), 31.9 (d, *J* = 12.4 Hz), 31.3 (d, *J* = 10.3 Hz), 24.6 (d, *J* = 8.6 Hz), 24.4, 23.7 (d, *J* = 5.0 Hz), 22.3, 19.6, 19.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.78; HRMS (ESI-TOF) m/z $[C_{27}H_{37}N_4O_3PS+Na]^+$ calcd for 551.2216, found 551.2220.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2 (3H)-yl)amino)(phenyl)methyl)-4-ethyl-2-phenyloxazol-5(4H)-one (**3aj**): white solid, 154 mg, 72% yield; m.p. 157.0-159.0 ^{o}C; $[\alpha]_D^{20}$ = -65.9 (c = 0.81, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.0 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 6.7 Hz, 4H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.26-7.22 (m, 1H), 4.90 (dd, *J* = 11.4, 9.4 Hz, 1H), 3.65-3.48 (m, 1H), 2.98-2.59 (m, 4H), 2.01-1.87 (m, 3H), 1.67 (d, *J* = 9.8 Hz, 2H), 1.61-1.51 (m, 1H), 1.32-1.13 (m, 7H), 1.00 (s, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.74 (t, *J* = 7.4 Hz, 3H), 0.63 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 161.5, 140.5, 132.9, 128.9, 128.7, 128.4, 128.3, 128.0, 125.9, 79.3 (d, *J* = 7.1 Hz), 61.2, 59.4 (d, *J* = 11.4 Hz), 59.1 (d, *J* = 10.5 Hz), 44.1, 43.5 (d, *J* = 4.7 Hz), 31.9 (d, *J* = 12.1 Hz), 31.3 (d, *J* = 10.1 Hz), 28.9, 24.7 (d, *J* = 8.7 Hz), 24.4, 23.7 (d, *J* = 5.0 Hz), 19.6, 19.1, 8.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.84; HRMS (ESI-TOF) m/z $[C_{30}H_{41}N_4O_3P+Na]^+$ calcd for 559.2808, found 559.2811.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(phenyl)methyl)-4-isopropyl-2-phenyloxazol-5(4H)-one (**3ak**): white solid, 97 mg, 44% yield; m.p. 144.5-145.6 °C; $[\alpha]_D^{20}$ = -38.4 (c = 0.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 2H), 7.57 (d, *J* = 6.8 Hz, 3H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.31-7.27 (m, 2H), 7.25-7.19 (m, 1H), 5.09 (dd, *J* = 11.1, 9.4 Hz, 1H), 3.66-3.51 (m, 1H), 2.89 (t, *J* = 9.6 Hz, 1H), 2.82-2.60 (m, 3H), 2.10 (dt, *J* = 13.6, 6.8 Hz, 1H), 1.98 (d, *J* = 10.3 Hz, 1H), 1.90 (d, *J* = 9.7 Hz, 1H), 1.67 (d, *J* = 9.2 Hz, 2H), 1.32-1.18 (m, 7H), 1.06 (t, *J* = 7.5 Hz, 6H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.56 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.2, 161.1, 140.6, 132.8, 128.8, 128.3, 128.2, 127.9, 125.9, 81.4 (d, *J* = 7.1 Hz), 59.3 (d, *J* = 11.1 Hz), 59.1, 59.0, 44.2 (d, *J* = 9.8 Hz), 43.4 (d, *J* = 4.4 Hz), 32.6, 31.9 (d, *J* = 12.1 Hz), 31.5 (d, *J* = 10.4 Hz), 24.8 (d, *J* = 8.9 Hz), 24.4, 24.0 (d, *J* = 5.4 Hz), 19.6, 19.0, 17.5, 16.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.96; HRMS (ESI-TOF) m/z $[C_{31}H_{43}N_4O_3P+Na]^+$ calcd for 573.2965, found 573.2968.

(S)-4-benzyl-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(phenyl)methyl)-2-phenyloxazol-5(4H)-one (**3al**): white solid, 177 mg, 74% yield; m.p. 128.3-130.1 °C; $[\alpha]_D^{20}$ = -123.9 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.7 Hz, 2H), 7.55 (d, *J* = 7.4 Hz, 2H), 7.50 (d, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.28-7.23 (m, 1H), 7.11-7.01 (m, 5H), 5.13-5.05 (m, 1H), 3.66-3.54 (m, 1H), 3.27 (d, *J* = 13.3 Hz, 1H), 2.95-2.77 (m, 4H), 2.66 (t, *J* = 8.6 Hz, 1H), 1.98 (d, *J* = 11.4 Hz, 1H), 1.92 (d, *J* = 10.6 Hz, 1H), 1.68 (d, *J* = 11.9 Hz, 2H), 1.33-1.16 (m, 7H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.65 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9, 161.1, 140.3, 134.4, 132.7, 130.3, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.1, 125.8, 79.8 (d, *J* = 6.9 Hz), 61.5, 59.5 (d, *J* = 11.4 Hz), 59.1 (d, *J* = 10.7 Hz), 44.1 (d, *J* = 3.1 Hz), 43.6 (d, *J* = 4.7 Hz), 41.9, 32.0 (d, *J* = 12.1 Hz), 31.3 (d, *J* = 10.4 Hz), 24.8 (d, *J* = 8.4 Hz), 24.4, 23.6 (d, *J* = 5.1 Hz), 19.6, 19.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.86; HRMS (ESI-TOF) m/z $[C_{35}H_{43}N_4O_3P+Na]^+$ calcd for 621.2965, found 621.2970.

(S)-4-butyl-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(phenyl)methyl)-2-phenyloxazol-5(4H)-one (**3am**): white solid, 144 mg, 64% yield; m.p. 85.2-89.1 °C; $[\alpha]_D^{20}$ = -40.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.53-7.44 (m, 4H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.26-7.21 (m, 1H), 4.93-4.86 (m, 1H), 3.64-3.50 (m, 1H), 2.94-2.73 (m, 3H), 2.70-2.61 (m, 1H), 2.01-1.87 (m, 3H), 1.67 (d, *J* = 10.4 Hz, 2H), 1.55 (td, *J* = 12.9, 4.0 Hz, 1H), 1.31-1.06 (m, 11H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.76 (t, *J* = 7.0 Hz, 3H), 0.63 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7, 161.2, 140.4, 132.9, 128.9, 128.6, 128.4, 128.2, 127.9, 125.9, 78.6 (d, *J* = 7.1 Hz), 61.3, 59.4 (d, *J* = 11.5 Hz), 59.0 (d, *J* = 10.6 Hz), 44.1, 43.5 (d, *J* = 4.8 Hz), 35.4, 31.9 (d, *J* = 12.1 Hz), 31.3 (d, *J* = 10.3 Hz), 26.1, 24.8 (d, *J* = 8.6 Hz), 24.4, 23.8 (d, *J* = 5.0 Hz), 22.6, 19.6, 19.1, 13.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.87; HRMS (ESI-TOF) m/z $[C_{32}H_{45}N_4O_3P+Na]^+$ calcd for 587.3121, found 587.3128.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(phenyl)methyl)-4-isobutyl-2-phenyloxazol-5(4H)-one (**3an**): white solid, 153 mg, 68% yield; m.p. 109.0-111.9 °C; $[\alpha]_D^{20}$ = -41.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.29-7.24 (m, 2H), 7.23-7.17 (m, 1H), 4.92-4.84 (m, 1H), 3.70-3.57 (m, 1H), 2.95-2.72 (m, 3H), 2.66 (s, 1H), 2.03-1.94 (m, 2H), 1.92 (d, *J* = 9.7 Hz, 1H), 1.76-1.63 (m, 3H), 1.52-1.40 (m, 1H), 1.30-1.16 (m, 7H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H),

0.76 (d, J = 6.6 Hz, 3H), 0.62 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.5, 160.7, 140.3, 132.8, 128.9, 128.6, 128.3, 128.2, 127.9, 126.0, 78.0 (d, J = 6.8 Hz), 62.3, 59.3 (d, J = 10.3 Hz), 59.1 (d, J = 10.6 Hz), 44.3, 43.5 (d, J = 4.8 Hz), 31.9 (d, J = 11.4 Hz), 31.3 (d, J = 10.2 Hz), 25.1, 24.8 (d, J = 7.6 Hz), 24.4 (d, J = 3.0 Hz), 24.0, 23.7 (d, J = 5.1 Hz), 23.5, 19.5, 19.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.98; HRMS (ESI-TOF) m/z $[C_{32}H_{45}N_4O_3P+Na]^+$ calcd for 587.3121, found 587.3128.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(phenyl)methyl)-4-(4-hydroxybenzyl)-2-phenyloxazol-5(4H)-one (**3ao**): white solid, 219 mg, 89% yield; m.p. 176.5-179.4 °C; $[\alpha]_D^{20}$ = -122.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.3 Hz, 2H), 7.52-7.43 (m, 3H), 7.37 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.2 Hz, 2H), 7.26-7.21 (m, 1H), 6.87 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 8.5 Hz, 2H), 4.99 (dd, J = 11.2, 9.6 Hz, 1H), 3.63-3.50 (m, 1H), 3.11 (d, J = 13.5 Hz, 1H), 2.97-2.62 (m, 5H), 1.98-1.84 (m, 2H), 1.66 (d, J = 10.2 Hz, 2H), 1.31-1.18 (m, 4H), 1.13 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H), 0.59 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9, 161.0, 156.3, 140.1, 132.5, 131.1, 128.6, 128.5, 128.4, 127.95, 127.92, 125.7, 124.7, 79.8 (d, J = 6.9 Hz), 61.2, 59.3 (d, J = 11.2 Hz), 59.0 (d, J = 10.4 Hz), 44.1, 43.4 (d, J = 4.4 Hz), 41.0, 31.6 (d, J = 11.3 Hz), 31.2 (d, J = 10.8 Hz), 24.5 (d, J = 8.4 Hz), 24.2, 23.4 (d, J = 5.1 Hz), 19.3, 19.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.06; HRMS (ESI-TOF) m/z $[C_{35}H_{43}N_4O_4P+Na]^+$ calcd for 637.2914, found 637.2921.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(phenyl)methyl)-4-(2-(methylthio)ethyl)-2-phenyloxazol-5(4H)-one (**3ap**): white solid, 186 mg, 80% yield; m.p. 117.0-118.7 °C; $[\alpha]_D^{20}$ = -52.2 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.5 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.50 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 9.1 Hz, 2H), 7.29 (t, J = 7.3 Hz, 2H), 7.23 (t, J = 7.2 Hz, 1H), 4.94 (dd, J = 11.5, 9.7 Hz, 1H), 3.68-3.57 (m, 1H), 2.95-2.63 (m, 4H), 2.44-2.36 (m, 1H), 2.34-2.24 (m, 2H), 2.05-1.98 (m, 2H), 1.97 (s, 3H), 1.91 (d, J = 10.3 Hz, 1H), 1.68 (d, J = 9.1 Hz, 2H), 1.30-1.19 (m, 7H), 1.07 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 0.60 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6, 161.8, 139.9, 133.0, 128.9, 128.6, 128.5, 128.3, 128.2, 125.8, 77.4, 61.5, 59.3 (d, J = 11.2 Hz), 59.1 (d, J = 10.6 Hz), 44.4, 43.6 (d, J = 5.0 Hz), 34.6, 31.8 (d, J = 15.0 Hz), 31.3 (d, J = 10.2 Hz), 28.8, 24.8 (d, J = 9.2 Hz), 24.4 (d, J = 5.7 Hz), 23.6 (d, J = 5.1 Hz), 19.5, 19.1, 15.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.86; HRMS (ESI-TOF) m/z $[C_{31}H_{43}N_4O_3PS+Na]^+$ calcd for 605.2686, found 605.2689.

(S)-4-((1H-indol-2-yl)methyl)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(phenyl)methyl)-2-phenyloxazol-5(4H)-one (**3aq**): white solid, 227 mg, 89% yield; m.p. 145.1-147.8 °C; $[\alpha]_D^{20}$ = -135.8 (c = 0.82, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48-8.27 (m, 1H), 7.73 (d, J = 7.3 Hz, 2H), 7.59 (d, J = 7.3 Hz, 2H), 7.53 (d, J = 7.5 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H), 7.38-7.27 (m, 5H), 7.18 (d, J = 7.1 Hz, 1H), 7.02-6.95 (m, 2H), 6.93 (d, J = 2.3 Hz, 1H), 5.13 (dd, J = 11.3, 9.4 Hz, 1H), 3.66-3.54 (m, 1H), 3.40 (d, J = 14.2 Hz, 1H), 3.02-2.78 (m, 4H), 2.74-2.64 (m, 1H), 2.00-1.89 (m, 2H), 1.67 (d, J = 12.2 Hz, 2H), 1.33-1.14 (m, 7H), 1.00 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6, 161.3, 140.5, 135.9, 132.4, 128.8, 128.5, 128.1, 128.0, 127.7, 125.9, 123.9, 121.6, 119.7, 119.2, 111.0, 108.5, 80.4 (d, J = 7.0 Hz), 61.2, 59.4 (d, J = 11.1 Hz), 59.1 (d, J = 10.5 Hz), 44.3, 43.6 (d, J = 4.9 Hz), 31.8, 31.7, 31.3 (d, J = 10.2 Hz), 24.6 (d, J = 10.5 Hz), 24.4, 23.6 (d, J = 5.1 Hz), 19.5, 19.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.09; HRMS

(ESI-TOF) m/z $[C_{37}H_{44}N_5O_3P+Na]^+$ calcd for 660.3074, found 660.3077.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(4-fluorophenyl)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3ba**): white solid, 179 mg, 83% yield; m.p. 108.2-110.0 °C; $[\alpha]_D^{20}$ = -61.0 (c = 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.4 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.53-7.45 (m, 4H), 7.01 (t, J = 8.6 Hz, 2H), 4.91 (t, J = 10.4 Hz, 1H), 3.60-3.47 (m, 1H), 2.93-2.59 (m, 4H), 2.00-1.88 (m, 2H), 1.67 (d, J = 11.6 Hz, 2H), 1.35 (s, 3H), 1.29-1.14 (m, 7H), 0.99 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.67 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9, 162.5 (d, J = 246.7 Hz), 161.3, 136.2 (d, J = 3.2 Hz), 133.0, 130.3 (d, J = 8.4 Hz), 128.9, 128.2, 125.9, 115.2 (d, J = 21.3 Hz), 74.2 (d, J = 7.3 Hz), 60.8, 59.4 (d, J = 11.1 Hz), 59.1 (d, J = 10.7 Hz), 44.2, 43.5 (d, J = 4.8 Hz), 31.8 (d, J = 11.9 Hz), 31.3 (d, J = 10.2 Hz), 24.7 (d, J = 8.6 Hz), 24.4, 23.6 (d, J = 4.8 Hz), 22.3, 19.6, 19.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.62; HRMS (ESI-TOF) m/z $[C_{29}H_{38}FN_4O_3P+Na]^+$ calcd for 563.2558, found 563.2561.

(S)-4-((R)-(4-chlorophenyl)(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3ca**): white solid, 182 mg, 83% yield; m.p. 116.8-118.2 °C; $[\alpha]_D^{20}$ = -68.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.3 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 4.90 (dd, J = 11.3, 9.4 Hz, 1H), 3.59-3.48 (m, 1H), 2.95-2.74 (m, 3H), 2.71-2.64 (m, 1H), 2.00-1.89 (m, 2H), 1.68 (d, J = 12.7 Hz, 2H), 1.35 (s, 3H), 1.28-1.16 (m, 7H), 1.00 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.69 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.8, 161.4, 138.7, 133.9, 133.1, 130.1, 129.0, 128.5, 128.3, 125.8, 74.1 (d, J = 7.1 Hz), 60.8, 59.4 (d, J = 11.5 Hz), 59.1 (d, J = 10.5 Hz), 44.2, 43.6 (d, J = 4.7 Hz), 31.8 (d, J = 12.0 Hz), 31.3 (d, J = 10.2 Hz), 24.6 (d, J = 8.6 Hz), 24.4, 23.7 (d, J = 4.9 Hz), 22.4, 19.6, 19.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.64; HRMS (ESI-TOF) m/z $[C_{29}H_{38}ClN_4O_3P+Na]^+$ calcd for 579.2262, found 579.2260.

(S)-4-((R)-(4-bromophenyl)(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3da**): white solid, 190 mg, 80% yield; m.p. 138.6-139.8 °C; $[\alpha]_D^{20}$ = -65.0 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.54-7.45 (m, 4H), 7.40 (d, J = 8.1 Hz, 2H), 4.93-4.83 (m, 1H), 3.61-3.48 (m, 1H), 3.01-2.67 (m, 4H), 2.00-1.91 (m, 2H), 1.68 (d, J = 10.5 Hz, 2H), 1.34 (s, 3H), 1.29-1.19 (m, 7H), 1.01 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.7 Hz, 3H), 0.70 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.8, 161.4, 139.2, 133.1, 131.5, 130.4, 128.9, 128.2, 125.8, 122.0, 74.0 (d, J = 7.0 Hz), 60.8, 59.4 (d, J = 11.4 Hz), 59.0 (d, J = 10.6 Hz), 44.1, 43.5 (d, J = 4.5 Hz), 31.8 (d, J = 12.0 Hz), 31.2 (d, J = 10.1 Hz), 24.6 (d, J = 8.4 Hz), 24.4, 23.7 (d, J = 4.9 Hz), 22.3, 19.6, 19.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.59; HRMS (ESI-TOF) m/z $[C_{29}H_{38}BrN_4O_3P+Na]^+$ calcd for 623.1757, found 623.1755.

(S)-4-((R)-(4-nitrilephenyl)(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3ea**): white solid, 181 mg, 80% yield; m.p. 141.5-143.1 °C; $[\alpha]_D^{20}$ = -61.5 (c = 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-7.99 (m, 2H), 7.70-7.64 (m, 4H), 7.64-7.59 (m, 1H), 7.51 (t, J = 7.6 Hz, 2H), 4.97 (dd, J = 11.2, 9.3 Hz, 1H), 3.56-3.44 (m, 1H), 3.10-2.98 (m, 1H), 2.94-2.77 (m, 2H), 2.70 (t, J = 8.8 Hz, 1H), 2.00-1.92 (m, 2H), 1.74-1.65 (m, 2H), 1.35 (s, 3H), 1.29-1.16 (m, 7H), 0.96 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.71 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 161.8, 145.4, 133.3, 132.2, 132.0, 130.5, 129.6, 129.0, 128.3, 125.6, 118.7, 112.0, 73.7 (d, J

= 7.0 Hz), 61.1, 59.6 (d, *J* = 11.7 Hz), 59.2 (d, *J* = 10.5 Hz), 44.3 (d, *J* = 4.3 Hz), 43.6 (d, *J* = 4.7 Hz), 31.8 (d, *J* = 10.6 Hz), 31.3 (d, *J* = 10.1 Hz), 24.5 (d, *J* = 8.6 Hz), 24.4, 23.7 (d, *J* = 4.7 Hz), 22.4, 19.53, 19.47; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.73; HRMS (ESI-TOF) m/z $[C_{30}H_{38}N_5O_3P+Na]^+$ calcd for 570.2604, found 570.2601.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(4-methoxyphenyl)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3fa**): After GAP washing procedure, the single isomer was recrystallized as a white solid, 156 mg, 71% yield; m.p. 110.1-112.0 °C; $[\alpha]_D^{20}$ = -52.3 (c = 0.88, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-7.98 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.86 (dd, *J* = 11.4, 9.5 Hz, 1H), 3.79 (s, 3H), 3.61-3.47 (m, 1H), 2.94-2.81 (m, 2H), 2.76-2.59 (m, 2H), 2.01-1.87 (m, 2H), 1.67 (d, *J* = 12.6 Hz, 2H), 1.35 (s, 3H), 1.30-1.15 (m, 7H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.67 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1, 161.1, 159.3, 132.9, 132.4, 129.7, 128.8, 128.2, 126.0, 113.7, 74.5 (d, *J* = 7.3 Hz), 60.9, 59.4 (d, *J* = 11.4 Hz), 59.0 (d, *J* = 10.6 Hz), 55.4, 44.1, 43.5 (d, *J* = 4.6 Hz), 31.8 (d, *J* = 12.1 Hz), 31.2 (d, *J* = 10.2 Hz), 24.7 (d, *J* = 8.5 Hz), 24.4, 23.6 (d, *J* = 5.1 Hz), 22.3, 19.6, 19.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.86; HRMS (ESI-TOF) m/z $[C_{30}H_{41}N_4O_4P+Na]^+$ calcd for 575.2758, found 575.2756.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(4-(trifluoromethyl)phenyl)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3ga**): white solid, 165 mg, 70% yield; m.p. 134.7-135.5 °C; $[\alpha]_D^{20}$ = -61.2 (c = 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 3H), 7.52 (t, *J* = 7.6 Hz, 2H), 4.98 (dd, *J* = 11.1, 9.4 Hz, 1H), 3.53 (dd, *J* = 11.3, 6.7 Hz, 1H), 2.97-2.63 (m, 4H), 2.00-1.90 (m, 2H), 1.68 (d, *J* = 12.1 Hz, 2H), 1.34 (s, 3H), 1.28-1.20 (m, 7H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.64 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7, 161.7, 144.3, 133.3, 130.4 (q, *J* = 32.8 Hz), 129.2, 129.0, 128.3, 125.8, 125.4 (q, *J* = 3.8 Hz), 73.9 (d, *J* = 7.1 Hz), 61.1, 59.5 (d, *J* = 11.9 Hz), 59.2 (d, *J* = 10.6 Hz), 44.2, 43.6 (d, *J* = 4.8 Hz), 31.8 (d, *J* = 12.9 Hz), 31.3 (d, *J* = 10.1 Hz), 24.6 (d, *J* = 8.4 Hz), 24.4, 23.7 (d, *J* = 4.8 Hz), 22.3, 19.6, 19.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.58; HRMS (ESI-TOF) m/z $[C_{30}H_{38}F_3N_4O_3P+Na]^+$ calcd for 613.2526, found 613.2524.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(p-tolyl)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3ha**): white solid, 183 mg, 81% yield; m.p. 160.3-161.8 °C; $[\alpha]_D^{20}$ = -66.7 (c = 0.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.8 Hz, 2H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 7.6 Hz, 2H), 4.85 (t, *J* = 10.4 Hz, 1H), 3.60-3.44 (m, 1H), 2.95-2.79 (m, 2H), 2.72 (t, *J* = 10.3 Hz, 1H), 2.63 (t, *J* = 8.8 Hz, 1H), 2.31 (s, 3H), 2.00-1.87 (m, 2H), 1.67 (d, *J* = 11.0 Hz, 2H), 1.34 (s, 3H), 1.28-1.13 (m, 7H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.65 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1, 161.1, 137.6, 137.0, 132.8, 128.9, 128.8, 128.5, 128.2, 126.0, 74.4 (d, *J* = 7.3 Hz), 61.2, 59.4 (d, *J* = 11.4 Hz), 59.0 (d, *J* = 10.6 Hz), 44.1 (d, *J* = 3.0 Hz), 43.5 (d, *J* = 4.7 Hz), 31.8 (d, *J* = 12.2 Hz), 31.3 (d, *J* = 10.3 Hz), 24.6 (d, *J* = 8.5 Hz), 24.4, 23.7 (d, *J* = 5.0 Hz), 22.3, 21.2, 19.6, 19.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.93; HRMS (ESI-TOF) m/z $[C_{30}H_{41}N_4O_3P+Na]^+$ calcd for 559.2808, found 559.2809.

(S)-4-((R)-(3-bromophenyl)(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3ia**): white solid, 178 mg, 74% yield; m.p. 95.2-96.7 °C; $[\alpha]_D^{20}$ = -63.2 (c = 0.78, $CHCl_3$); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.04 (d, J = 7.4 Hz, 2H), 7.70 (s, 1H), 7.61 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.46-7.39 (m, 2H), 7.20 (t, J = 7.8 Hz, 1H), 4.88 (dd, J = 11.3, 9.3 Hz, 1H), 3.60-3.45 (m, 1H), 2.95-2.65 (m, 4H), 2.00-1.90 (m, 2H), 1.68 (d, J = 11.0 Hz, 2H), 1.36 (s, 3H), 1.31-1.17 (m, 7H), 0.99 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7, 161.5, 142.5, 133.1, 131.6, 131.2, 129.9, 129.0, 128.3, 127.6, 125.8, 122.5, 74.0 (d, J = 7.2 Hz), 61.0, 59.4 (d, J = 11.6 Hz), 59.1 (d, J = 10.5 Hz), 44.3, 43.6 (d, J = 4.8 Hz), 31.7 (d, J = 12.0 Hz), 31.4 (d, J = 10.2 Hz), 24.6 (d, J = 8.4 Hz), 24.4, 23.4 (d, J = 5.0 Hz), 22.4, 19.6, 19.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.64; HRMS (ESI-TOF) m/z $[C_{29}H_{38}BrN_4O_3P+Na]^+$ calcd for 623.1757, found 623.1759.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2 (3H)-yl)amino)(m-tolyl)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3ja**): white solid, 169 mg, 79% yield; m.p. 132.5-134.1 °C; $[\alpha]_D^{20}$ = -42.7 (c = 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.31-7.27 (m, 2H), 7.19 (t, J = 7.7 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 4.85 (dd, J = 11.5, 9.4 Hz, 1H), 3.60-3.48 (m, 1H), 2.92-2.72 (m, 3H), 2.66 (t, J = 8.5 Hz, 1H), 2.33 (s, 3H), 2.00-1.89 (m, 2H), 1.67 (d, J = 12.3 Hz, 2H), 1.37 (s, 3H), 1.30-1.16 (m, 7H), 0.97 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.2, 161.1, 139.9, 137.9, 132.9, 129.4, 128.9, 128.7, 128.3, 128.2, 126.1, 125.7, 74.3 (d, J = 7.3 Hz), 61.5, 59.4 (d, J = 11.3 Hz), 59.1 (d, J = 10.5 Hz), 44.2, 43.5 (d, J = 4.8 Hz), 31.8 (d, J = 12.2 Hz), 31.4 (d, J = 10.4 Hz), 24.6 (d, J = 8.4 Hz), 24.4, 23.8 (d, J = 5.0 Hz), 22.4, 21.6, 19.6, 19.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.94; HRMS (ESI-TOF) m/z $[C_{30}H_{41}N_4O_3P+Na]^+$ calcd for 559.2808, found 559.2809.

(S)-4-((R)-(2-bromophenyl)(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2] diazaphosphol-2(3H)-yl)amino)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3ka**): After GAP washing procedure, the single isomer was recrystallized as a white solid, 151 mg, 63% yield; m.p. 101.5-102.5 °C; $[\alpha]_D^{20}$ = -37.5 (c = 0.88, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.4 Hz, 2H), 7.65 (d, J = 7.8 Hz, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.55-7.46 (m, 3H), 7.36 (t, J = 7.5 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 5.32 (dd, J = 11.3, 8.6 Hz, 1H), 3.37-3.10 (m, 3H), 3.00 (t, J = 8.3 Hz, 1H), 2.89 (t, J = 9.9 Hz, 1H), 2.10 (d, J = 9.5 Hz, 1H), 1.89 (d, J = 11.1 Hz, 1H), 1.74-1.64 (m, 2H), 1.37 (s, 3H), 1.33-1.19 (m, 4H), 1.14-1.05 (m, 9H), 0.42 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6, 161.7, 139.7, 133.2, 132.6, 129.5, 128.9, 128.4, 128.0, 125.6, 125.3, 74.1 (d, J = 8.9 Hz), 59.8 (d, J = 12.4 Hz), 59.2 (d, J = 10.2 Hz), 58.3, 44.5, 43.8 (d, J = 4.9 Hz), 31.8 (d, J = 8.7 Hz), 31.7 (d, J = 10.6 Hz), 24.6 (d, J = 3.1 Hz), 24.5 (d, J = 7.6 Hz), 23.6 (d, J = 10.2 Hz), 21.5, 20.3 (d, J = 2.8 Hz), 19.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.44; HRMS (ESI-TOF) m/z $[C_{29}H_{38}BrN_4O_3P+Na]^+$ calcd for 623.1757, found 623.1753.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2 (3H)-yl)amino)(o-tolyl)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3la**): white solid, 156 mg, 76% yield; m.p. 123.2-125.5 °C; $[\alpha]_D^{20}$ = -31.0 (c = 0.86, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.5 Hz, 2H), 7.60-7.52 (m, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.21-7.14 (m, 1H), 7.13-7.07 (m, 2H), 5.34-5.22 (m, 1H), 3.62-3.49 (m, 1H), 2.96-2.83 (m, 2H), 2.80-2.64 (m, 2H), 2.57 (s, 3H), 1.98 (d, J = 11.7 Hz, 1H), 1.92 (d, J = 9.0 Hz, 1H), 1.68 (d, J = 9.8 Hz, 2H), 1.43 (s, 3H), 1.32-1.17 (m, 7H), 0.99 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.65 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.7, 160.9, 139.0, 136.8, 132.9, 130.3, 128.9, 128.2, 127.7, 127.2, 126.4, 126.0, 74.7 (d, J = 7.5 Hz), 59.4 (d, J = 11.5 Hz), 59.0 (d, J = 10.5 Hz), 56.2, 44.4, 43.5 (d, J = 4.8 Hz), 31.8 (d, J = 13.0 Hz), 31.3 (d, J = 9.9 Hz), 24.4 (d, J = 3.6 Hz), 23.6 (d, J = 4.9 Hz),

22.8, 21.7, 20.4, 19.5, 19.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.44; HRMS (ESI-TOF) m/z $[C_{30}H_{41}N_4O_3P+Na]^+$ calcd for 559.2808, found 559.2803.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2 (3H)-yl)amino)(2-(trifluoromethyl)phenyl)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3ma**): white solid, 176 mg, 78% yield; m.p. 124.3-126.6 ^{o}C; $[\alpha]_D^{20}$ = -60.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.4 Hz, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.63-7.57 (m, 2H), 7.50 (t, J = 7.6 Hz, 2H), 7.40 (t, J = 7.6 Hz, 1H), 5.26 (dd, J = 10.9, 8.6 Hz, 1H), 3.34-3.04 (m, 3H), 2.93-2.75 (m, 2H), 2.06-1.99 (m, 1H), 1.90 (d, J = 11.9 Hz, 1H), 1.72-1.61 (m, 2H), 1.30 (s, 3H), 1.35-1.19 (m, 4H), 1.14 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H), 0.51 (d, J = 5.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 161.5, 139.1, 133.1, 132.1, 129.5, 128.79 (q, J = 29.8 Hz), 128.77, 128.2, 128.0, 125.9 (q, J = 5.9 Hz), 125.5, 124.7(q, J = 251.7 Hz), 73.9 (d, J = 8.0 Hz), 59.0 (d, J = 10.3 Hz), 58.9 (d, J = 10.2 Hz), 55.0, 44.4, 43.4 (d, J = 5.2 Hz), 31.8 (d, J = 9.1 Hz), 31.4 (d, J = 14.0 Hz), 24.5 (d, J = 4.0 Hz), 24.3 (d, J = 10.4 Hz), 23.7 (d, J = 9.8 Hz), 22.1, 19.3 (d, J = 2.3 Hz), 19.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.11; HRMS (ESI-TOF) m/z $[C_{30}H_{38}F_3N_4O_3P+Na]^+$ calcd for 613.2526, found 613.2523.

(S)-4-((R)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2 (3H)-yl)amino)(naphthalen-1-yl)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3na**): white solid, 194 mg, 85% yield; m.p. 158.1-159.3 ^{o}C; $[\alpha]_D^{20}$ = -62.6 (c = 0.87, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 8.7 Hz, 1H), 7.96-7.90 (m, 3H), 7.81 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.51-7.43 (m, 4H), 6.00-5.91 (m, 1H), 3.64-3.48 (m, 1H), 3.00 (s, 1H), 2.90-2.81 (m, 1H), 2.63 (dd, J = 13.5, 6.6 Hz, 2H), 1.95-1.82 (m, 2H), 1.70-1.58 (m, 2H), 1.37 (s, 3H), 1.30-1.10 (m, 7H), 0.90 (d, J = 6.9 Hz, 3H), 0.65 (d, J = 6.8 Hz, 3H), 0.42 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.4, 161.1, 137.2, 133.6, 132.9, 132.1, 128.8, 128.6, 128.5, 128.2, 126.7, 125.9, 125.8, 125.32, 125.30, 124.1, 75.1 (d, J = 7.2 Hz), 59.4 (d, J = 11.5 Hz), 59.1 (d, J = 10.5 Hz), 54.7, 44.2 (d, J = 2.9 Hz), 43.3 (d, J = 4.7 Hz), 31.8 (d, J = 12.3 Hz), 31.3 (d, J = 10.2 Hz), 24.6 (d, J = 8.7 Hz), 24.4, 23.6 (d, J = 5.0 Hz), 22.0, 19.6, 18.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.09; HRMS (ESI-TOF) m/z $[C_{33}H_{41}N_4O_3P+Na]^+$ calcd for 595.2808, found 595.2810.

(S)-4-((S)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2 (3H)-yl)amino)(furan-2-yl)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3oa**): After GAP washing procedure, the single isomer was recrystallized as a white solid, 124 mg, 61% yield; m.p. 147.7-148.3 ^{o}C; $[\alpha]_D^{20}$ = -47.5 (c = 0.93, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.3 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.30 (d, J = 1.0 Hz, 1H), 6.33 (d, J = 3.2 Hz, 1H), 6.25 (dd, J = 3.0, 1.9 Hz, 1H), 5.04 (dd, J = 11.3, 9.8 Hz, 1H), 3.68-3.55 (m, 1H), 3.07-2.88 (m, 3H), 2.67 (t, J = 8.5 Hz, 1H), 2.01 (d, J = 11.5 Hz, 1H), 1.95 (d, J = 10.2 Hz, 1H), 1.70 (d, J = 9.9 Hz, 2H), 1.53 (s, 3H), 1.35-1.19 (m, 7H), 1.10 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.8, 161.2, 152.7, 142.0, 132.9, 128.8, 128.2, 125.9, 110.3, 108.7, 72.9 (d, J = 6.7 Hz), 59.4 (d, J = 11.1 Hz), 59.1 (d, J = 10.7 Hz), 55.5, 44.1 (d, J = 3.1 Hz), 43.9 (d, J = 4.4 Hz), 31.9 (d, J = 11.8 Hz), 31.0 (d, J = 10.5 Hz), 24.7 (d, J = 7.8 Hz), 24.4, 23.3 (d, J = 5.4 Hz), 22.0, 19.8, 19.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.55; HRMS (ESI-TOF) m/z $[C_{27}H_{37}N_4O_4P+Na]^+$ calcd for 535.2445, found 535.2442.

(S)-4-((S)-(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2 (3H)-yl)amino)(thiophen-2-yl)methyl)-4-methyl-2-phenyloxazol-5(4H)-one (**3pa**): white solid, 165

mg, 77% yield; m.p. 155.0-157.1 °C; $[\alpha]_D^{20}$ = -46.3 (c = 0.82, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.3 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.25 (d, J = 5.1 Hz, 1H), 7.19 (d, J = 3.3 Hz, 1H), 6.95 (dd, J = 5.0, 3.6 Hz, 1H), 5.28 (dd, J = 11.0, 9.6 Hz, 1H), 3.62-3.48 (m, 1H), 3.00-2.84 (m, 2H), 2.63 (t, J = 8.7 Hz, 1H), 2.47 (t, J = 9.9 Hz, 1H), 2.00-1.87 (m, 2H), 1.66 (d, J = 13.3 Hz, 2H), 1.40 (s, 3H), 1.32-1.14 (m, 7H), 1.02 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.69 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.3, 161.7, 143.0, 133.1, 128.9, 128.4, 127.7, 126.3, 126.0, 125.9, 74.4 (d, J = 7.0 Hz), 59.3 (d, J = 11.4 Hz), 59.1 (d, J = 10.8 Hz), 57.3, 44.1 (d, J = 2.7 Hz), 43.8 (d, J = 4.8 Hz), 31.8 (d, J = 12.0 Hz), 31.3 (d, J = 10.3 Hz), 24.8 (d, J = 8.4 Hz), 24.4, 23.8 (d, J = 5.3 Hz), 22.1, 19.6, 18.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.48; HRMS (ESI-TOF) m/z $[C_{27}H_{37}N_4O_3PS+Na]^+$ calcd for 551.2216, found 551.2218.

Synthesis of Protected *α*-Quaternary-*syn*-*α*, *β*-Diamino Ester 4

The Mannich product **3aa** (5.0 mmol, 2.61g) was dissolved in 20 mL MeOH, followed by addition of 3.10 mL 48% aq. HBr (50 mmol, 10 equiv.). The reaction mixture was stirred at room temperature for 24 hours. After complete conversion of **3aa**, volatiles were evaporated under vacuum at 50 °C and dried for 3 hours under high vacuum to obtain a crude solid. The solid was dissolved in 20 mL of dichloromethane, and then the suspension was cooled to 0 °C. At this temperature, triethylamine (2.08 mL, 15.0 mmol) and di-tert-butyl dicarbonate (2.30 mL, 10.0 mmol) were added to the resulting mixture, and the reaction mixture was stirred overnight. The reaction mixture was concentrated, and pure product **4** was obtained in 60% overall yield through column chromatography on silica gel using PE/EA (v/v, 4/1) as eluent.

(2S,3R)-methyl 2-benzamido-3-((tert-butoxycarbonyl)amino)-2-methyl-3-phenylpropanoate (**4**): white solid, 988 mg, 60% yield; $[\alpha]_D^{20}$ = -20.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.84 (t, J = 11.8 Hz, 2H), 7.50 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.4 Hz, 2H), 7.35-7.29 (m, 3H), 7.22 (d, J = 5.9 Hz, 2H), 5.92 (d, J = 7.1 Hz, 1H), 5.31 (d, J = 7.9 Hz, 1H), 3.58 (s, 3H), 1.71 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 166.9, 157.2, 136.5, 134.1, 131.7, 128.7, 128.6, 128.5, 127.8, 127.4, 81.1, 65.8, 60.8, 52.5, 28.5, 17.5; HRMS (ESI-TOF) m/z $[C_{23}H_{28}N_2O_5+Na]^+$ calcd for 435.1890, found 435.1889. Chiral HPLC (CHIRALPAK IC column; hexane/i-PrOH, v/v = 80:20; 1.0 mL/min, 254nm), *syn*-major t_r = 24.97 min, *syn*-minor t_r = 22.95 min, 94% ee.

Synthesis of Fully Deprotected *α*, *β*-Diamino Acid 5

Into an ordinary 50 mL round-bottom vial equipped with a magnetic stirring bar, diamino ester **4** (1.0 mmol, 412mg), phenol (3.0 mmol, 282 mg), acetic acid (3.0 mmol, 0.17mL) and 10mL 6M HCl were added subsequently. The reaction mixture were set to reflux and stirred for 12 hours. After cooling to room temperature, the orange solution was washed with EA (3×30 mL), and the aqueous phase was concentrated at 50 °C under vacuum to yield **5** as a crystalline solid.

(2S,3R)-2,3-diamino-2-methyl-3-phenylpropanoic acid hydrochloride (**5**):

Colorless crystalline solid, 270 mg, quantitative yield, slightly contaminated by impurities. $[\alpha]_D^{20}$ = -10.5 (c = 0.44, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 7.56 (s, 5H), 4.86-4.83 (m, 1H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 169.5, 130.7, 130.4, 129.7, 128.2, 60.6, 58.5, 20.5. These NMR data match those found in the literature.[22]

Synthesis of dipeptide 6

Trifluoroacetic acid was added to a solution of **4** (0.10 mmol, 31 mg) in DCM (5 mL). The

reaction solution was stirred for 10 hours at room temperature. The reaction was quenched with saturated aqueous Na_2CO_3 (10 mL) and was then extracted with EA (3×10 mL), dried with anhydrous sodium sulfate and concentrated i*n vacuo* to yield crude white solid. This material was carried forward without any further purification.

Triethylamine (0.25 mmol, 35 μL), HOBt (0.12 mmol, 16 mg) and EDCI (0.12 mmol, 23 mg) were added to a solution of the crude material obtained above and Boc-L-Val-OH (0.12 mmol, 26 mg) in DCM (5 mL). The reaction solution was stirred for 12 hours before washed with saturated aqueous Na_2CO_3, water and brine. The organic phase was dried with anhydrous sodium sulfate and concentrated i*n vacuo* to yield a white solid, which was characterized without further purification.

(2S,3R)-methyl-2-benzamido-3-((S)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)-2-methyl-3-phenylpropanoate (**6**):

White solid, 51 mg, 94% yield, >20:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 6.0 Hz, 1H), 7.82 (d, J = 7.3 Hz, 2H), 7.74 (s, 1H), 7.51 (t, J = 7.3 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.31 (d, J = 6.5 Hz, 3H), 7.26 – 7.21 (m, 2H), 5.56 (d, J = 7.9 Hz, 1H), 5.06 (s, 1H), 3.99 – 3.89 (m, 1H), 3.62 (s, 3H), 2.25 (td, J = 13.4, 6.7 Hz, 1H), 1.66 (s, 3H), 1.37 (s, 9H), 0.92 (t, J = 7.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 171.7, 167.5, 136.4, 133.9, 131.9, 128.7, 128.6, 128.0, 127.4, 65.4, 60.8, 59.5, 52.7, 29.8, 28.3, 19.6, 19.3, 18.0. HRMS (ESI-TOF) m/z $[C_{28}H_{37}N_3O_6+Na]^+$ calcd for 534.2575, found 534.2568.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

X-ray crystal data for **3ah**.

^{31}P NMR analysis of the crude reaction mixtures.

^{1}H and ^{13}C NMR spectra for all pure products.

HPLC data of compound **4**

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REFERENCES

[$]Summer High School Participant: Shanghai High School International Division No. 989, Baise Road, Shanghai, China 200231.

(1) Selected review articles of α, β-diamino acids: (a) Viso, A.; Pradilla, R.; Garcia, A.; Flores, A. *Chem. Rev.* **2011**, *111*, 3167. (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580.

(2) (a) Luo, Y.; Blaskovich, M. A.; Lajoie, G. A. *J. Org. Chem.* **1999**, *64*, 6106. (b) Wang, M.; Gould, S. J. *J. Org. Chem.* **1993**, *58*, 5176. (c) Rane, D. F.; Girijavallabhan, V. M.; Ganguly, A. K.; Pike, R. E.;Saksena, A. K.; McPhail, A. T. *Tetrahedron Lett.* **1993**, *34*, 3201. (d) Li, G.; Kim, S. H.; Wei, H. X. *Tetrahedron Lett*, **2000**, *42*, 8699. (e) Chen, D. J.; Timmons, C.; Chao, C.; Li, G. *Eur. J. Org. Chem*. **2004**, *14*, 3097.

(3) (a) Davis, F. A.; Deng, J. *Org. Lett.* **2004**, *6*, 2789. (b) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P.; Meervelt, L. V.; Mischenko, N. *Tetrahedron Lett*. **1997**, *38*, 4671. (c) Kiss, L.; Mangelinckx, S.; Sillanpaa, R.; Fülöp, F.; De Kimpe, N. *J. Org. Chem.* **2007**, *72*, 7199. (d) Kiss, L.; Mangelinckx, S.; Fülöp, F.; De Kimpe, N. *Org. Lett.* **2007**, *9*, 4399. (e) Callebaut, G.; Mangelinckx, S.; Van der Veken, P.; Törnroos, K. W.; Augustyns, K.; De Kimpe, N. *Beilstein J. Org. Chem.* **2012,** *8,* 2124. (f) Callebaut，G.; Meiresonne，T.; De Kimpe, N.; Mangelinckx, S. *Chem. Rev.*, **2014**, *114*, 7954.

(4) (a)Wang, J.; Shi, T.; Deng, G.; Jiang, H.; Liu, H. *J. Org. Chem.* **2008**, *73*, 8563. (b) Wang, J.; Lin, D.; Shi, J.; Ding, X.; Zhang, L.; Jiang, H.; Liu, H. *Synthesis* **2010**, 1205. (c)Zhang, H.; Hu, X.; Wang, X.; Luo, Y.; Xu, P. *J. Org. Chem.* **2008**, *73*, 3634. (d) Ghorai, M. K.; Ghosh, K.; Yadav, A. K. *Tetrahedron Lett.* **2009**, *50*, 476.

(5) (a) Callebaut, G.; Mangelinckx, S.; Kiss, L.; Sillanpaa, R.; Fülöp, F.; De Kimpe, N. *Org. Biomol. Chem.* **2012**, *10*, 2326. (b) Viso, A.; Pradilla, R. F.; Lopez-Rodriguez, M. L.; Garcia, A.; Flores, A.; Alonso, M. *J. Org. Chem.* **2004**, *69*, 1542. (c) Viso, A.; Pradilla, R. F.; Garcia, A.; Guerrero-Strachan, C.; Alonso, M.; Tortosa, M.; Flores, A.; Martinez-Ripoll, M.; Fonseca, I.; Andre, I.; Rodriguez, A. *Chem. Eur. J.* **2003**, *9*, 2867.

(6) Selected examples of catalytic Mannich reactions: (a) Hernandez-Toribio, J.; Go´mez Arraya´s, R.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 16150. (b) Hernandez-Toribio, J.; Gomez Arrayas, R.; Carretero, J. C. *Chem. Eur. J.* **2010**, *16*, 1153. (c) Shang, D.; Liu, Y.; Zhou, X.; Liu, X.; Feng, X. *Chem. Eur. J.* **2009**, *15*, 3678. (d) Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociok-Kohn, G.; Willis, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 10632. (e) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.;Yamaguchi, K.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4564. (f) Li, L.; Ganesh, M.; Seidel,D. *J. Am. Chem. Soc.* **2009**, *131*, 11648. (g) Zhang,H.; Syed, S.; Barbas III, C. F. *Org. Lett.* **2010**, *12*, 708.

(7) Selected review articles of azlactones: (a) Castro, P. P.; Carpanez A. G.; Amarante, G. W. *Chem. Eur. J.* **2016**, *22*, 10294. (b) Alba, A. R.; Rios, R. *Chem. Asian J.* **2011**, *6*, 720 (c) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432–1440.

(8) Selected examples of enantioselective Mannich-type reaction between imines and azlactones: (a) Uraguchi, D.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 14088. (b) Liu, X.; Deng, L.; Jiang, X.; Yan, W.; Liu, C.; Wang, R. *Org. Lett.* **2010**, *12*, 876. (c) Melhado, A. D.; Amarante, G. W.; Wang, Z. J.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 3517. (d) Zhang, W.-Q.; Cheng, L.-F.; Yu, J.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 4085. (e) Shi, S.-H.; Huang, F.-P.; Zhu, P.; Dong, Z.-W.; Hui, X.-P. *Org. Lett.* **2012**, *14*, 2010. (f) Ávila, E. P.; Justo, R. M. S.; Gonçalves, V. P.; Pereira, A. A.; Diniz, R.; Amarante, G. W. *J. Org. Chem.* **2015**, *80*, 590.

(9) Uraguchi, D.; Yoshioka, K.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2012**, *134*, 19370.

(10) Zabka, M.; Malastova, A.; Sebesta, R. *RSC Adv.* **2015**, *5*, 12890.

(11) A review article of N-phosphonyl imines and GAP chemistry: An, G.; Seifert C.; Li, G. *Org. Biomol. Chem.* **2015**, *13*, 1600.

(12) (a) Yang, B.; Shen, M.; Ji, X.; Sun, H.; Jiang, B.; Li, G. *J. Org. Chem.* **2016**, *81*, 2488.

(13) (a) Xie, J.; Luo, J.; Winn, T. R.; Cordes, D. B.; Li, G. *Beilstein J. Org. Chem.* **2014**, *10*, 746.

(14) Kattamuri, P. V.; Ai, T.; Pindi, S.; Sun, Y.; Gu, P.; Shi, M.; Li, G. *J. Org. Chem.* **2011**, *76*, 2792.

(15) Seifert, C. W.; Pindi, S.; Li, G. *J. Org. Chem*. **2015**, *80*, 447.

(16) Seifert, C. W.; Paniagua, A.; White, G. A.; Cai, L.; Li, G. *Eur. J. Org. Chem.* **2016**, *9*, 1714.

(17) In recent work, we have reported the asymmetric addition between Ni(II)-complexed alanine Schiff base and *N*-phosphonyl imines which provided the asymmetric synthesis of α-methyl-α,β-diamino acid derivatives with good to high yields (61%-93%) and complete diastereoselectivity (>99:1 dr). However, aside from glycine and alanine, the Ni(II) complexes derived from other α-amino acids were not suitable for the Mannich reactions with *N*-phosphonyl imines.

(18) The Mannich-type reaction between Ni(II)-complexed alanine Schiff base and *N*-phosphonyl imines led to (2*R*, 3*S*) configuration using the same auxiliary. See: Zhang, H.; Yang, B.; Yang, Z.; Lu, H.; Li, G. *J. Org. Chem.*, **2016**, *81,* 7654.

(19) (a) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem.* **2006**, *118*, 2312. (b) Fisk, J. S.; Tepe, J. J. *J. Am. Chem. Soc.* **2007**, *129*, 3058. (c) Terada, M.; Moriya, K.; Kanomata, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 12586

(20) Kattuboina, A.; Kaur, P.; Ai, T.; Li, G. *Chem. Biol. Drug Des.* **2008**, *71*, 216.

(21) Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638.

(22) Guerrini, A.; Varchi, G.; Samori, C.; Battaglia, A. *Eur. J. Org. Chem.* **2008**, 3834.