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Asymmetric [3 + 2] Cycloaddition of Chiral *N*-Phosphonyl Imines with Methyl Isocyanoacetate for Accessing 2-Imidazolines with Switchable Stereoselectivity

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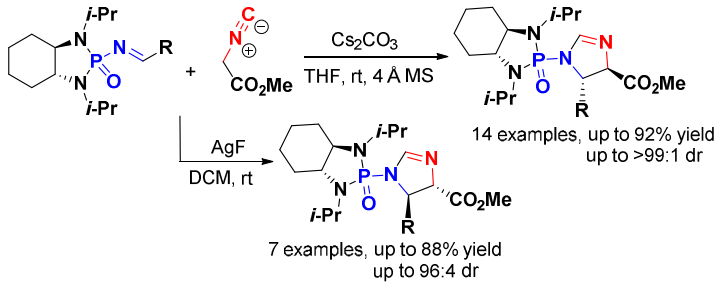


ABSTRACT. Asymmetric [3 + 2] cycloaddition of chiral *N*-phosphonyl imines with methyl isocyanoacetate have been established, enabling controllable/switchable stereoselectivity accessing to 21 examples of cycloadducts with good to excellent chemical yields (up to 92%) and high diastereoselectivity (up to 99:1 dr). The cycloaddition reaction promoted by Cs_2CO_3 resulted in diastereoenriched (4*R*,5*S*)-products, with dr >99:1. However, it showed the reverse stereoselectivity as diastereoenriched (4*S*,5*R*)-products when AgF was employed as the catalyst. The synthesis followed the group-assisted purification (GAP) chemistry/technology, in which the pure 2-imidazoline products were readily provided by washing the crude products with co-solvents of hexane and ethyl acetate.

Introduction

2-Imidazolines represent a highly valuable class of five-membered heterocycles and can often serve as ‘‘privileged motifs’’ in medical and pharmaceutical chemistry owing to their significant biological activities such as analgesic and anti-inflammatory activity,[1] cardiovascular activity,[2] anti-neoplastic activity,[3] anti-fungal activity[4], etc. Besides, the stereochemistry of this privileged scaffold has been found to display diverse biological characteristics, represented by NF-κB inhibitory skeleton I[5] and p53 activator framework II (Figure 1).[6] Specifically, stereospecific 2-imidazolines are also extensively utilized as chiral auxiliaries,[7] chiral catalysts,[8] and ligands for asymmetric catalysis.[9] Therefore, many efforts have been made to develop various methodologies for the stereoselective synthesis of 2-imidazolines, which made them more powerful and applicable. The great majority of these approaches involved multi-step cyclization of chiral 1,2-diamines[10a] or *β*-hydroxy amides,[10b] transannulation of chiral aziridines,[11] metal-catalyzed asymmetric [3 + 2] cycloaddition of isocyanoacetates with N-sulfonylimines (Scheme 1a)[12] and Tf_2O/Ph_3PO-mediated intramolecular cyclization of chiral *N*-acyl diamines.[13] However, these methods suffered from multi-steps, the use of noble metal catalysts like Au, and limited substrate scopes as well as inferior enantioselective control when the transformation were enlarged, thereby limiting their potential industrial applications. Therefore, many chemists focused these efforts on the development of chiral auxiliary-controlled asymmetric reactions due to its potential application of large-scale transformations. An extensive survey revealed that chiral auxiliaries mainly involve include *N*-tosyl,[14] *N*-*tert*-butylsulfonyl[15] and *N*-thiophosphoryl,[16] but frequently give poor diastereoselectivity. Over the years, we have designed new chiral *N*-phosphonyl auxiliary imines, enabling their asymmetric additions with nucleophiles to synthesize diverse chiral amines with high stereoselectivity (Scheme 1b).[17] During this project, we conceived that under suitable reaction conditions, asymmetric [3 + 2] cycloaddition of isocyanoacetates with *N*-phosphonyl auxiliary imines could proceed readily, efficiently affording 2-imidazolines with high diastereoselectivity.

Herein, we would like to report this special *N*-phosphonyl 2-imidazoline synthesis by using readily available isocyanoacetates and the preformed chiral *N*-phosphonyl auxiliary imines **1** (Schemes 1c and 1d). Interestingly, switchable stereoselectivity was realized in this transformation when bases and Ag-catalyst were employed, respectively. By using Cs_2CO_3 as a base promoter, the reaction resulted in diastereoenriched (4*R*,5*S*)-products **3**, often with final dr >99:1 (Scheme 1c) whereas the reverse stereoselectivity was observed in Ag-catalysis as diastereoenriched (4*S*,5*R*)-products **4** were provided (Scheme 1d). Notably, *N*-phosphonyl 2-imidazolines **3** and **4** could be obtained simply by washing the crude mixture with common hexane and ether, thereby simplifying the purification process while avoiding the use of traditional purification methods (column chromatography, recrystallization, etc.). This convenient workup for obtaining pure products directly by introducing well-functionalized groups in starting materials or newly generated functionalities in target molecules belongs to a concept called group-assisted purification (GAP) chemistry/technology. Besides, *N*-phosphonyl auxiliary can be easily recovered and recycled though the cleavage of P-N bond of *N*-phosphorylated products under the mild conditions, which makes this strategy highly attractive.

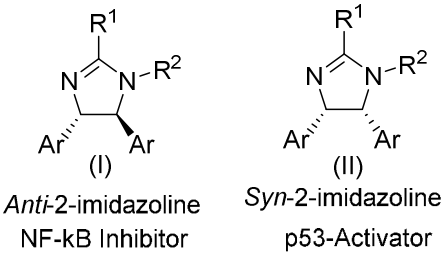
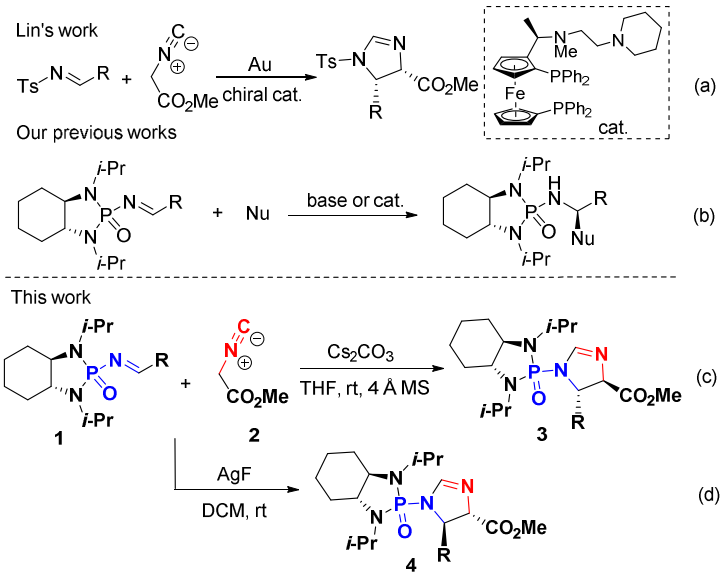


Figure 1. *Anti* and *syn*-2-imidazolines

Scheme 1. Asymmetric Synthesis of 2-Imidazolines

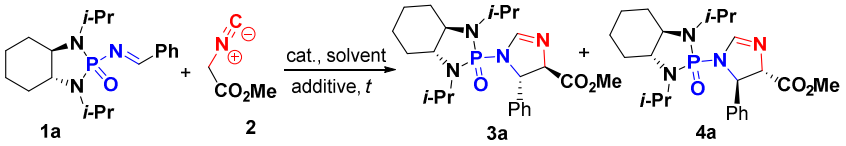


Results and discussion

Our initial investigation began with the asymmetric [3 + 2] cycloaddition of the preformed phosphonyl imine (**1a**) with methyl isocyanoacetate (**2**). The reaction in tetrahydrofuran (THF) was carried out at room temperature using LiOH as a base promoter, giving access to 95% yield of product **3a**, but with moderate diastereoselectivity (dr = 73:27, Table 1, entry 1). Exchanging THF for MeOH lowered the conversion (66%) and diastereoselectivity (dr = 57:43, entry 2). Using NaOH as a base promoter, a very lower yield (25%) and poor diastereoselectivity (dr = 51:49) were observed (entry 3). Organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO) completely suppressed the reaction process (entries 4-5). The use of Cs_2CO_3 resulted in high diastereoselectivity (dr = 96:4) albeit with a moderate yield (49%, entry 6). Lowering temperature is adverse to the reaction process and led to a complex mixture (entry 7). To our delight, 4Å molecular sieves as additive facilitated the transformation, affording the expected product **3a** with 99% yield (an isolated 92% yield) and high stereoselectivity (96:4 dr, entry 8). Since silver catalyst has generally showed a highly catalytic activity in [3 + 2] cycloaddition of isocyanoacetates,[18] we decided to utilize silver catalyst to investigate this transformation. Surprisingly, Ag_2O as a catalyst drive the reaction to the opposite diastereoselectivity, and the (4*S*,5*R*)-product **4a** was obtained with 91% yield and 78:22 dr (entry 9). The investigation of solvent

revealed that dichloromethane (DCM) exhibited the best performance, affording the desired product **3a** with 97% yield and 84:16 dr (entry S10) whereas both THF and toluene gave inferior diastereoselectivity compared with dichloromethane (entries 9 and 11). Afterward, we attempted to employ other silver catalysts such as AgOTf and AgF to improve the reaction efficiency (entries 12-13). AgF was proven to be the most efficient, delivering 99% yield (an isolated 87% yield) and 88:12 dr (entry 12). In particular, the reverse diastereoselectivity was observed and diastereoenriched product **3a** with 91:9 dr was detected when LiCl as additives was added in this Ag-catalysis (entry 13). These results suggested that the base-promoted asymmetric [3 + 2] cycloaddition underwent a different mechanism pathways compared with Ag-catalyzed version.

Table 1. Screening of the Reaction Conditions



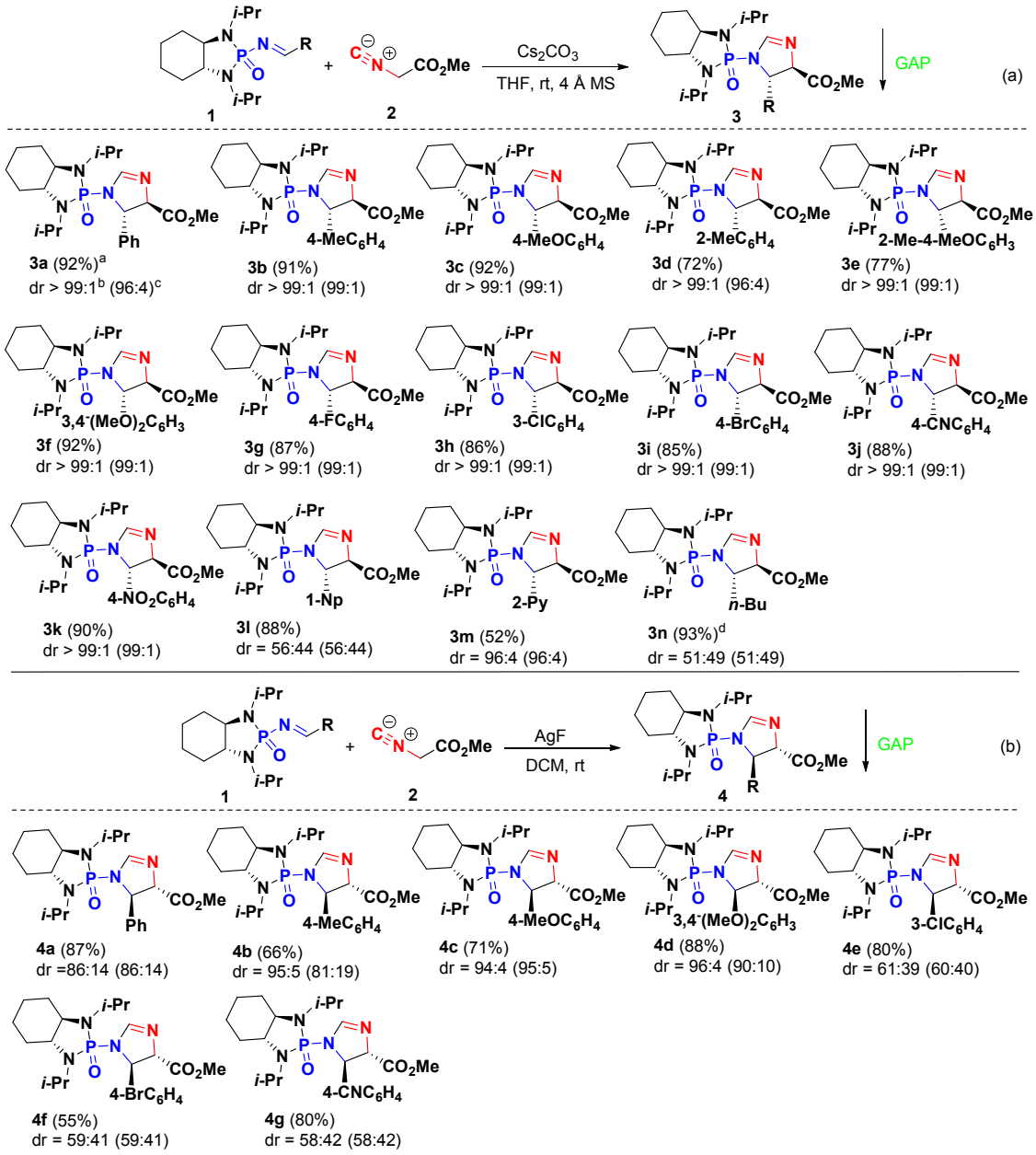
entry	base (or cat.)	solvent	conversion[a]	**3a**/**4a** (dr)[b]
1	LiOH	THF	95%	73:27
2	LiOH	MeOH	66%	57:43
3	NaOH	THF	25%	51:49
4	DBU	THF	trace	-
5	DABCO	THF	trace	-
6	Cs_2CO_3	THF	49%	96:4
7[c]	Cs_2CO_3	THF	47%	messy
8[d]	Cs_2CO_3	THF	99% (92%)[e]	96:4
9	Ag_2O	THF	91%	22:78
10	Ag_2O	DCM	97%	16:84
11	Ag_2O	toluene	99%	42:58

12	AgOTf	DCM	trace	-
13	AgF	DCM	99% (87%)[e]	12:88
14[f]	AgF	DCM	88%	91:9

[a] The conversions were determined by ^{31}P NMR after 16 hours at room temperature. [b] The diastereoisomer ratio were determined by ^{31}P NMR. [c] Reaction at -41 ^{o}C; [d] Use of activated 4Å MS (50 mg); [e] Isolated yield based on **1a**; [f] LiCl as additive.

With the optimized reaction conditions for selectively forming products **3a** (Table 1, entry 8) and **4a** (entry 12) in hand, we then set out to investigate the scope of asymmetric [3 + 2] cycloaddition toward *N*-phosphonyl 2-imidazolines **3** and **4** by examining chiral *N*-phosphonyl auxiliary imines **1** with methyl isocyanoacetate (**2**). First, a wide range of chiral *N*-phosphonyl imines **1** were subjected to the reaction with methyl isocyanoacetate (**2**) under Cs_2CO_3-promoted conditions, and the corresponding densely functionalized 2-imidazolines **3a-3n** with generally excellent yields and high diastereoselectivity (Scheme 2a). Chiral *N*-phosphonyl imines **1** possessing both electron-donating and electron-withdrawing groups directly bounded phenyl ring did not hamper the reaction process. A large variety of diverse functional groups, including methyl, methoxy, fluoro, chloro, bromo, cyano, and nitro, were well tolerated under this system. Among them, the sterically encumbered *o*-methylphenyl, counterparts (**1d** and **1e**) were appropriate imine partners, enabling their asymmetric [3 + 2] cycloaddition to access the desired products **3d** and **3e** with 72% and 77% yields and >99:1 dr, respectively. Alternatively, 1-naphthyl (1-Np, **1l**) and *n*-butyl (**1n**) analogues proved to be effective, giving access to the corresponding products **3l** and **3n** in 88% and 93% yield, respectively, albeit with poor diastereoselectivity whereas 2-pyridinyl counterpart (**1m**) seemed very reluctant to undergo the reaction, in which **3m** was generated in a relatively low 52% yield, but with high 96:4 dr. Next, we turned our attention to evaluating the scope of AgF-catalyzed asymmetric [3 + 2] cycloaddition toward diastereoenriched products **4** under the standard conditions (Table 1, entry

Scheme 2. The Scope of Asymmetric [3 + 2] Cycloaddition

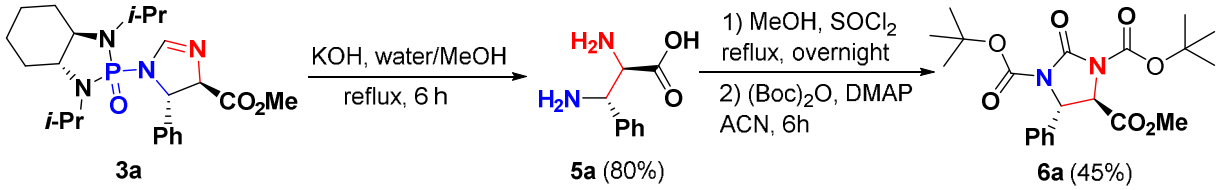


(i) Reactions condition A: *N*-phosphonyl imines, (0.5 mmol, 1 equiv) 4Å activated molecular sieves (50 mg), methyl isocyanide (3.0 equiv) and Cs_2CO_3 (2.2 equiv) was reacted in THF (5 mL) at room temperature for 16 h; (ii) Reactions condition B: *N*-phosphonyl imine (0.5 mmol, 1 equiv), methyl isocyanide (1.2 equiv) and AgF (5 mol %) in DCM (5 mL), at room temperature for 16 h. [a] Yield based on GAP technology. [b] The diastereoisomer ratio was determined by ^{31}P NMR of the reaction mixture. [c] The diastereoisomer ratio in brackets before GAP procedure. [d] Isolated yield by chromatography as product **3n** is oil.

12). As shown in Scheme 2b, this protocol can tolerate structurally diverse chiral *N*-phosphonyl imines **1** carrying either electronically neutral, rich, or poor groups attached by phenyl moiety, paving the way of the collection of richly decorated *N*-phosphonyl 2-imidazolines **4a-4g** in 55%-88% yields. The presence of electron-donating functionality on the phenyl ring gave high diastereoselectivity (**4b-4d**) whereas the poor diastereoselectivity was observed with use of

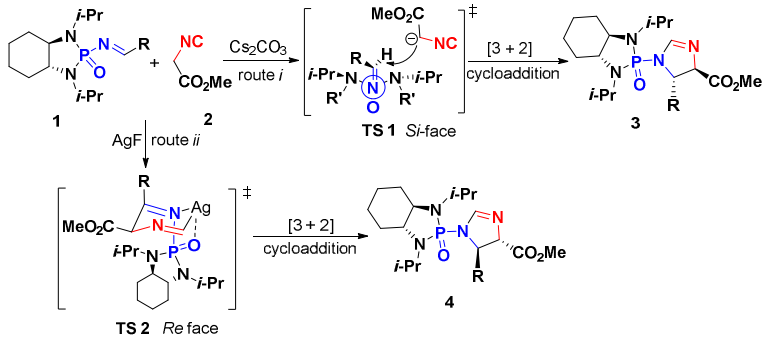
electron-withdrawing substituents (**4e-4g**). In all cases, the pure cycloadducts **3** and **4** with generally high diasyereoselectivity were obtained simply by washing the crude products with hexane/ether without use of traditional chromatography and recrystallization.[17] Note that this is the first reported procedure for the synthesis of these new *N*-phosphonyl 2-imidazolines with switchable diastereoselectivity through base-promoted or Ag-catalyzed asymmetric [3 + 2] cycloaddition of chiral *N*-phosphonyl auxiliary imines with methyl isocyanoacetate. The structures of these products were confirmed by their NMR and HRMS spectra. In the cases of **3a** and **4a**, the stereo-structures were unequivocally determined by X-ray analysis (See Supporting Information).[19]

Scheme 3. Cleavage of auxiliary of Cycloadducts



To investigate the synthetic utility of the resulting 2-imidazolines, the cleavage reaction of resulting cycloadduct **3a** was conducted in the presence of KOH in mixed solvent of water and MeOH, affording 2,3-diamino acid **5a** in 80% yield.[20] 2,3-Diamino acid **5a** was converted into imidazolidine-1,3,4-tricarboxylates **6a** in 45% yield through Boc protection (Scheme 3). This method could be used for the synthesis of various substituted 2,3-diamino acids or diamino alcohols which are crucial fragment of biologically active peptides and other industrially useful molecules.

Scheme 4. Proposed Mechanism of [3 + 2] Cycloaddition Reaction



Based on above observation and analysis, the mechanisms for selectively forming products **3** and **4**

may involve two different transition states in [3 + 2] cycloaddition reactions with chiral *N*-phosphonyl imines, which are depicted in Scheme 4. Under basic conditions (Scheme 2a), similar to our previous reports,[20] the diastereoselectivity could be explained by Newman project transition state 1 (TS1, route *i*); it is controlled well by the attack of deprotonated isocyanoacetates as a nucleophile on the favorable *si*-face of the auxiliary group, giving a nearly diastereopure intermediates followed by intramolecular nucleophilic addition to products **3**. Importantly, the less selectivity of using aliphatic substrate **1n** as an electrophile could be explained by equal *E/Z* configuration of *N*-phosphonyl imines derived from hemiaminal under basic condition, and this observation is consistent with the proposed transition state.[21] On the other hand, a tentative transition state 2 (TS2) accounts for the opposite selectivity can be proposed: during Ag catalysis (Scheme 2b), the stereo-oriented carbon-carbon forming step is supposed to be consistent with cyclization through a six-member ring consisting of the nitrogen atom on the imine substrate, the carbon atom of isocyanide group, and the coordinated silver ion which is stabilized by oxygen on the phosphonyl group. The remarkable decrease of diastereoselectivity of the electron-withdrawing substrates might be ascribed to their relatively less stability of such a transition state.

In summary, we have established base-promoted or Ag-catalyzed asymmetric [3 + 2] cycloaddition reactions with chiral *N*-phosphonyl imines and methyl isocyanoacetate, allowing facile and efficient synthesis of *N*-phosphonyl 2-imidazolines with switchable stereoselectivity. During the reaction process, the use of Cs_2CO_3 as a base promoter led to diastereoenriched (4*R*,5*S*)-products, often with final dr >99:1 whereas (4*S*,5*R*)-products with reverse stereoselectivity were provided in Ag-catalysis. These products of this reaction can be further transformed into other valuable and highly functionalized entities. Our further studies will focus on the discovery of new asymmetric reactions of *N*-phosphonyl functionality with other nucleophiles.

Experimental Section

General Information

All commercially available chemicals were used as received without further purification. Solvents were obtained as follows: Ether, dichloromethane, tetrahydrofuran and toluene are delivered from Innovation Technology solvent system. All reactions were carried out in flame dried flask under nitrogen atmosphere. The ^{1}H 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. ^{31}P NMR spectra were referenced to external H_3PO_4 (0.00 ppm). Shifts in ^{19}F NMR spectra were reported based on an external hexafluorobenzene reference. HRMS analyses were carried out using a TOF-MS instrument with an ESI source.

General synthesis of *N*-phosphonyl imine with GAP technique

To a 100 mL oven dried flask with a Teflon-coated magnetic stir bar was added (S, S)-phosphonylamide (1.0 g, 3.86 mmol). 5.0 mL of toluene was added under argon atmosphere. Aldehyde (2 equiv, 7.72 mmol) and $Ti(OiPr)_4$ (1.0 equiv, 1.2 mL, 3.86 mmol) were added subsequently. The suspension was stirred at 80 °C for 24 hours. The reaction was monitored by $^{31}PNMR$ of the reaction mixture. When complete, the clear solution was concentrated under vacuum, and 50 mL of dry hexane was added and the result solution was slurry for 6 h until a precipitation formed (GAP). After filtration, the *N*-phosphonyl imine was isolated as a pale yellow solid.

General Procedure for the Synthesis of Products **3**

A 10 mL flame-dried round-bottomed flask was charged under argon with N-phosphonylimine (0.5 mmol, 1 equiv) and freshly distilled THF (5.0 mL). At room temperature, 4 Å activated molecular sieves (50 mg) and Cs_2CO_3 (2.2 equiv) were added to this solution in one portion followed by the addition of methyl isocyanide (3.0 equiv) dropwise through a syringe. Completion of the starting

material was monitored by thin layer chromatography and ^{31}PNMR of the reaction mixture (The reaction could be completed in 16 hours). At this stage, 10 mL of water was added to the reaction mixture and extracted with 2 × 5 mL of ethyl acetate. The combined organic layers were washed with water (1 × 5 mL) and brine solution (1 × 10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated after filtration, and the crude mixture was co-concentrated with hexanes. The products were dried under high vacuum. The solid products were dissolved with ether and treated dry hexane to afford a pure product without column chromatography (GAP). In the case of compound **3n**, it was purified with column chromatography which is soluble in hexane.

Data for pure compounds 3a-3n:

Methyl (4R,5S)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl) -5-phenyl-4,5-dihydro-1H-imidazole-4-carboxylate (3a)

White solid, 205 mg, 92% yield; mp 148−151 °C; $[\alpha]^{25}{}_1$D =-119 (c = 3.8, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.38 (s, 1H), 7.30-7.20 (m, 5H), 5.08-5.06 (m, 1H), 4.75-4.71 (m, 1H), 3.71 (s, 3H), 3.18-3.13 (m, 1H), 2.88-2.86 (m, 2H), 2.80-2.79 (m, 1H), 2.02-2.00 (m, 1H), 1.98 (m, 1H), 1.78-1.75 (m, 2H), 1.56-0.88 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.6, 155.1, 128.8, 128.9, 128.3, 128.2, 127.6, 127.3, 78.7, 63.9, 60.2, 52.6, 44.9, 43.5, 30.8, 29.9, 29.8, 24.3, 24.2, 22.4, 21.5, 20.3, 20.1; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 14.4; HRMS (TOF ES+) m/z calcd for $C_{23}H_{36}N_4O_3P$ [(M + H)$^+$], 447.2520; found, 447.2538.

Methyl (4R,5S)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl) -5-(p-tolyl)-4,5-dihydro-1H-imidazole-4-carboxylate (3b)

White solid, 209 mg, 91%; mp 49−51 °C; $[\alpha]^{25}{}_1$D =-132 (c = 2.2, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.43 (s, 1H), 7.22-7.09 (m, 4H), 5.08-5.05 (m, 1H), 4.67-4.62 (m, 1H), 3.73 (s, 3H), 3.21-3.19 (m, 2H), 2.91-2.88 (m, 1H), 2.46-2.44 (m, 1H), 2.30-2.25 (m, 3H), 2.05-2.01 (m, 1H), 1.88-1.82 (m, 1H), 1.73-1.69 (m ,2H), 1.55-0.88 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.6,

155.3, 139.8, 138.1, 129.5, 129.3, 127.8, 127.2,79.4, 64.1, 64.0,60.1, 59.9, 52.6, 44.4, 31.0, 30.2, 24.4, 24.3, 22.9, 22.8, 22.7, 21.2, 19.8; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 14.5; HRMS (TOF ES+) m/z calcd for $C_{24}H_{38}N_4O_3P$ [$(M + H)^+$], 461.2676; found, 461.2662.

Methyl (4R,5S)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl) -5-(4-methoxyphenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (3c)

White solid; 219 mg, 92%, mp 112−114 °C; $[\alpha]^{25}{}_1D$ =-144 (c = 2.9, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.39 (s, 1H), 7.18-7.15 (m, 2H), 6.84-6.82 (m, 2H), 5.06-5.02 (m, 1H), 4.66-4.62 (m, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.23-3.21 (m, 2H), 2.90-2.88 (m, 1H), 2.48-2.45 (m, 1H), 2.02-2.00 (m, 1H), 1.98-1.97 (m, 1H), 1.77-1.74 (m, 2H), 1.44-0.98 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.6, 159.6, 155.1, 134.9, 128.5, 128.4, 114.1, 114.0,79.2, 63.8, 60.1, 60.0, 55.4, 52.5, 44.4, 30.7, 30.1, 24.4, 24.2, 22.7, 21.7, 21.2, 19.7; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 13.7; HRMS (TOF ES+) m/z calcd for $C_{24}H_{38}N_4O_4P$ [$(M + H)^+$], 477.2625; found, 477.2627.

Methyl (4R,5S)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl) -5-(o-tolyl)-4,5-dihydro-1H-imidazole-4-carboxylate (3d)

White solid; 165 mg, 72%; mp 108−109 °C; $[\alpha]^{25}{}_1D$ =-89 (c = 2.8, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.55 (s, 1H), 7.14-6.94 (m, 4H), 5.48 (s, 1H), 4.59 (s, 1H), 3.75 (s, 3H), 3.28-3.26 (m, 2H), 2.91-2.89 (m, 1H), 2.45-2.41 (m, 4H), 2.06-2.02 (m, 1H), 1.98-1.90 (m, 1H) 1.66-1.59 (m, 2H), 1.26-0.97(m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.7, 155.2, 141.3, 135.1, 130.5, 127.7, 126.6, 125.8, 79.2, 59.9, 59.8, 59.4, 52.5, 44.3, 30.9, 30.7, 30.3, 30.2,24.4, 24.3, 22.9, 20.9, 19.7, 19.5; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 14.6; HRMS (TOF ES+) m/z calcd for $C_{24}H_{38}N_4O_3P$ [$(M + H)^+$], 461.2676; found, 461.2668.

Methyl (4R,5S)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl) -5-(4-methoxy-2-methylphenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (3e)

White solid; 188mg, 77%; mp 83−84 °C; $[\alpha]^{25}{}_1D$ =-73 (c = 3.6, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz)

δ = 7.44 (s, 1H), 7.11 (m, 1H), 6.66-6.56 (m, 2H), 5.47 (s, 1H), 4.54-4.42 (m, 1H), 3.79 (s, 3H), 3.26-3.33 (m, 2H), 2.88 (t, *J* = 2.5 Hz, 1H), 2.48 (t, *J* = 3 Hz, 1H), 2.39 (s, 3H), 2.06-2.02 (m, 1H), 1.98-1.96 (m, 1H), 1.69-1.67 (m, 2H), 1.23-0.97 (m, 17H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.9, 158.9, 155.2, 136.5, 133.8, 127.2, 115.3, 112.5,79.7, 60.2, 59.9, 59.1, 55.3, 52.6, 44.3, 30.9, 30.8, 30.3, 30.2, 24.4, 24.3, 22.9,21.0, 20.2, 19.8; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 14.5; HRMS (TOF ES+) m/z calcd for $C_{25}H_{40}N_4O_4P$ [$(M + H)^+$], 491.2782; found, 491.2776.

Methyl (4R,5S)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl) -5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (3f)

White solid; 233 mg ,92%; mp 97−98 °C; $[\alpha]^{25}{}_1$D =-161 (c = 1.8, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.34 (s, 1H), 6.81-6.73 (m, 3H), 5.05-5.02 (m, 1H), 4.67-4.62 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.69-3.66 (m, 3H), 3.22-3.20 (m, 2H), 2.88-2.85 (m, 1H), 2.50-2.47 (m, 1H), 1.97-1.95 (m, 1H), 1.85-1.82 (m, 1H), 1.70-1.66 (m, 2H), 1.35-0.99 (m, 15H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.5, 155.0, 149.3, 149.0, 135.2, 135.1, 119.7, 111.0, 109.8, 79.1, 64.1, 60.1, 60.0, 56.1, 55.9, 52.5, 44.4, 30.7, 30.3,24.4, 24.2, 22.9, 22.7,21.2, 19.7; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 15.4; HRMS (TOF ES+) m/z calcd for $C_{25}H_{40}N_4O_5P$ [$(M + H)^+$], 507.2731; found, 507.2725.

Methyl (4R,5S)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl) -5-(4-fluorophenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (3g)

White solid; 202 mg, 87%; mp 138−139 °C; $[\alpha]^{25}{}_1$D =-155 (c = 1.1, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.35 (s, 1H), 7.23-6.95 (m, 4H), 5.11 (s, 1H), 4.64 (s, 1H), 3.72 (s, 3H), 3.27-3.25 (m, 1H), 3.07-3.03 (m, 1H), 2.89-2.87 (m, 1H), 2.55 (t, *J* = 10 Hz, 1H), 2.03-2.00 (m, 2H), 1.74-1.72 (m, 2H), 1.45-0.98 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.3, 163.8, 161.3, 154.7, 138.7, 128.9, 115.7, 79.1, 63.6, 60.2, 59.8, 52.6,44.4, 44.2, 30.8, 30.1,24.3, 24.2, 23.8, 22.7, 22.6, 21.1, 19.7; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 14.2; HRMS (TOF ES+) m/z calcd for $C_{23}H_{35}FN_4O_3P$ [$(M + H)^+$], 465.2425; found, 465.2428.

Methyl (4R,5S)-5-(3-chlorophenyl)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2] diazaphosphol-2-yl)-4,5-dihydro-1H-imidazole-4-carboxylate (3h)

White solid; 208 mg, 86%; mp 64−65 °C; $[\alpha]^{25}{}_{1}D$ =-107 (c = 1.5, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.41 (s, 1H), 7.27-7.19 (m, 4H), 5.12 (s, 1H), 4.65 (s, 1H), 3.76 (s, 3H), 3.28-3.26 (m, 2H), 2.93-2.90 (m, 1H), 2.55 (t, *J* = 8 Hz, 1H), 2.07-2.04 (m, 1H), 1.92-1.89 (m, 1H), 1.78 (s, 2H), 1.43-1.06 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.2, 154.9, 144.7, 134.7, 130.2, 128.4, 127.1, 125.3, 78.9, 63.8, 60.2, 60.1,52.7,44.4, 43.8, 30.9,24.4, 24.2, 22.9, 22.8, 22.7, 21.2, 19.7; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 13.7; HRMS (TOF ES+) m/z calcd for $C_{23}H_{35}ClN_4O_3P$ $[(M + H)^+]$, 481.2130; found, 481.2140.

Methyl (4R,5S)-5-(4-bromophenyl)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2] diazaphosphol-2-yl)-4,5-dihydro-1H-imidazole-4-carboxylate (3i)

White solid; 223 mg, 85%; mp 48−50 °C; $[\alpha]^{25}{}_{1}D$ =-127 (c = 1.5, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.49-7.46 (m, 2H), 7.37 (s, 1H), 7.18-7.12 (m, 2H), 5.13 (s, 1H), 4.63 (s, 1H), 3.74 (s, 3H), 3.33-3.30 (m, 1H), 3.20-3.17 (m, 1H), 2.93-2.90 (m, 1H), 2.62 (t, *J* = 8 Hz, 1H), 2.18-2.14 (m, 2H), 1.72-1.68 (m, 2H), 1.55-1.08 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.3, 154.7, 141.8, 131.9, 131.8, 128.8, 128.7, 122.2, 78.9, 63.7, 60.3, 60.2, 52.7,44.4, 31.2, 30.1,24.3, 24.2, 23.8, 22.9, 22.8, 21.1, 19.8; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 13.3; HRMS (TOF ES+) m/z calcd for $C_{23}H_{35}BrN_4O_3P$ $[(M + H)^+]$, 525.1625; found, 525.1633.

Methyl (4R,5S)-5-(4-cyanophenyl)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]d iazaphosphol-2-yl)-4,5-dihydro-1H-imidazole-4-carboxylate (3j)

White solid; 207 mg, 88%; mp 158−160 °C; $[\alpha]^{25}{}_{1}D$ =-152 (c = 1.1, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.62-7.41 (d, 4H), 7.34 (s, 1H), 5.27-5.22 (m, 1H), 4.63-4.59 (m, 1H), 3.76 (s, 3H), 3.35-3.28 (m, 1H), 3.05-3.01 (m, 1H), 2.92-2.88 (m, 1H), 2.68 (t, *J* = 9.6Hz, 1H), 2.07-2.00 (m, 2H), 1.79-1.71 (m, 2H), 1.45-1.01 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 170.9, 154.2, 147.8, 132.6,

127.8, 118.6, 112.1, 78.5, 63.9, 60.2, 59.6, 52.8, 44.3, 44.2, 31.2, 30.8,24.3, 24.2, 23.1, 23.0, 22.8,22.7, 20.8, 19.8; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 14.1; HRMS (TOF ES+) m/z calcd for $C_{24}H_{35}N_5O_3P$ [$(M + H)^+$], 472.2472; found, 472.2466.

Methyl (4R,5S)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl) -5-(4-nitrophenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (3k)

White solid; 221 mg, 90%; mp57−58 °C; $[\alpha]^{25}{}_1D$ =-236 (c = 0.8, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.91 (d, *J* = 14 Hz, 1H), 7.51-7.42 (m, 4H), 5.87 (s, 1H), 4.62 (s, 1H), 3.81 (s, 3H), 3.32-3.31 (m, 1H), 3.30-3.25 (m, 1H), 2.95-2.88 (m, 1H), 2.67-2.59 (m, 1H), 2.02-1.91 (m, 2H), 1.78-1.71 (m, 2H), 1.43-1.07 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 170.7, 154.8, 147.9, 133.4, 128.7, 124.8, 124.7, 79.2, 60.1,59.7, 59.6, 52.7,44.4, 44.2, 30.3, 30.2,24.3, 24.2, 23.6, 23.2, 23.1, 20.7, 19.6; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 14.7; HRMS (TOF ES+) m/z calcd for $C_{23}H_{35}N_5O_5P$ [$(M + H)^+$], 492.2370; found, 492.2472.

Methyl (4R,5S)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl) -5-(naphthalen-1-yl)-4,5-dihydro-1H-imidazole-4-carboxylate (3l)

White solid; 218 mg, 88%; mp 78−79 °C; $[\alpha]^{25}{}_1D$ =-89 (c = 1.3, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 8.31 (d,*J* =8 Hz, 1H), 7.83-7.30 (m, 7H), 6.20-5.13 (m, 1H), 5.03-4.64 (m, 1H), 3.73-3.63 (m, 3H), 3.33-3.23 (m, 2H), 2.90-2.85 (m, 1H), 2.66-2.59 (m, 1H), 2.02-1.89 (m, 2H), 1.77-1.70 (m, 2H), 1.47-0.88 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 172.7, 157.7, 139.2, 133.2, 129.5, 128.9, 128.7, 128.2, 126.8, 126.1, 125.6, 124.7, 123.4,80.4, 66.1, 60.1, 58.4, 52.7,44.6, 44.5, 30.4,30.2, 24.3, 24.2, 24.1, 23.2, 21.5, 19.8; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 15.8, 14.8; HRMS (TOF ES+) m/z calcd for $C_{27}H_{38}N_4O_3P$ [$(M + H)^+$], 497.2676; found, 497.2660.

Methyl (4R,5R)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl) -5-(pyridin-2-yl)-4,5-dihydro-1H-imidazole-4-carboxylate (3m)

White solid; 116 mg, 52%; mp88−90 °C; $[\alpha]^{25}{}_1D$ =-48 (c = 1.9, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz)

δ = 8.58 (d, 1H, *J*= 4.8 Hz), 7.64-7.25 (m, 4H), 5.29-5.19 (m, 1H), 4.97-4.88 (m, 1H), 3.75 (s, 3H), 3.31-3.23 (m, 1H), 3.09-3.02 (m, 1H), 2.92-2.87 (m, 1H), 2.59-2.44 (m, 1H), 2.02-1.95 (m, 2H), 1.74-1.66 (m, 2H), 1.12-0.98 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 160.2, 154.3, 154.2, 149.9, 136.5, 123.4, 123.1, 65.1, 60.3, 60.2, 59.9, 52.6, 44.4, 30.7, 30.1, 24.4, 24.3, 22.8, 22.6, 22.5, 21.2, 19.8; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 14.1; HRMS (TOF ES+) m/z calcd for $C_{22}H_{35}N_5O_3P$ [$(M + H)^+$], 448.2472; found, 448.2477.

Methyl (4R,5S)-5-butyl-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosph ol-2-yl)-4,5-dihydro-1H-imidazole-4-carboxylate (3n)

clear liquid; 196 mg, 92%; $[\alpha]^{25}{}_1$D =-32 (c = 2.6, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.13 (s, 1H), 4.38-4.32 (m, 1H), 4.12-4.05 (m, 1H), 3.67 (s, 3H), 3.38-3.26 (m, 2H), 2.97-2.92 (m, 1H), 2.74-2.69 (m, 1H), 2.02-1.88 (m, 3H), 1.76-1.62 (m, 2H), 1.45-0.88 (m, 24H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.3, 154.7, 141.8, 131.9, 131.8, 128.8, 128.7, 122.2, 78.9, 63.7, 60.3, 60.2, 52.7,44.4, 31.2, 30.1,24.3, 24.2, 23.8, 22.9, 22.8, 22.8, 21.1, 19.8; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 14.2, 14.1; HRMS (TOF ES+) m/z calcd for $C_{21}H_{40}N_4O_3P$ [$(M + H)^+$], 427.2833; found, 427.2867.

General Procedure for the Synthesis of Products 4

At room temperature, AgF (5% mol) was added to a solution of *N*-phosphonylimine (0.5 mmol, 1 equiv.) in dry DCM (5 mL), followed by the addition of methyl isocyanide (1.2 equiv.) dropwise through a syringe. Completion of the starting material was monitored by thin layer chromatography and ^{31}PNMR of the reaction mixture (The reaction could be completed in 16 h). At this stage, 10 mL of water was added to the reaction mixture and extracted with 2 × 5 mL of dichloromethane. The combined organic layers were washed with water (1 × 5 mL) and brine solution (1 × 10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated after filtration, and the crude mixture was co-concentrated with hexanes. The products were dried under high vacuum. The solid products were dissolved with ether and treated dry hexane to afford a pure product without column chromatography

(GAP).

Methyl (4S,5R)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl) -5-phenyl-4,5-dihydro-1H-imidazole-4-carboxylate (4a)

White solid; 194 mg, 87%; mp 48−49 °C; $[\alpha]^{25}{}_{1}D$ =31 (c = 3.6, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.41 (s, 1H), 7.27-7.22 (m, 5H), 5.04 (s, 1H), 4.72-4.66 (m, 1H), 3.69 (s, 3H), 3.18-3.05 (m, 1H), 2.91-2.83 (m, 2H), 2.82-2.71 (m, 1H), 2.01-1.95 (m, 1H), 1.89-1.82 (m, 1H), 1.71-1.69 (m, 2H), 1.56-0.88 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.5, 155.2, 142.6, 128.8, 128.5, 128.3, 127.8, 127.3, 77.5, 63.9, 60.3, 59.9, 52.5, 44.9, 43.4, 30.8, 29.8, 24.3, 24.2, 23.9, 23.2, 21.9, 20.1; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 14.9; HRMS (TOF ES+) m/z calcd for $C_{23}H_{36}N_4O_3P$ $[(M + H)^+]$, 447.2520; found, 447.2530.

Methyl (4S,5R)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl) -5-(p-tolyl)-4,5-dihydro-1H-imidazole-4-carboxylate (4b)

White solid; 152 mg, 66%; mp 60−61 °C; $[\alpha]^{25}{}_{1}D$ =39 (c = 2.2, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.44 (s, 1H), 7.37-7.03 (m, 4H), 5.14-5.07 (m, 1H), 4.72-4.66 (m, 1H), 3.67 (s, 3H), 3.20-3.15 (m, 1H), 2.91-2.88 (m, 3H), 2.30-2.25 (m, 3H), 2.01-1.95 (m, 1H), 1.82-1.76 (m, 1H), 1.74-1.65 (m ,2H), 1.55-0.88 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.6, 155.1, 139.6, 138.0, 129.4, 129.3, 127.8, 127.1, 78.6, 68.1, 63.7, 60.2, 59.9, 52.5, 44.9, 43.5, 31.1, 30.8, 25.6, 24.3, 24.2, 21.2, 21.1, 20.1; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 15.1; HRMS (TOF ES+) m/z calcd for $C_{24}H_{38}N_4O_3P$ $[(M + H)^+]$, 461.2676; found, 461.2688.

Methyl (4S,5R)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl) -5-(4-methoxyphenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (4c)

White solid; 169 mg, 71%; mp55−58 °C; $[\alpha]^{25}{}_{1}D$ =9.6 (c = 2.0, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.33 (s, 1H), 7.20-7.12 (m, 2H), 6.81-6.65 (m, 2H), 5.04-4.98 (m, 1H), 4.71-4.66 (m, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.23-3.28 (m, 1H), 2.90-2.81 (m, 2H), 2.87-2.79 (m, 1H), 2.01-1.91 (m, 1H),

1.89-1.82 (m, 1H) 1.73-1.69 (m, 2H), 1.43-0.79 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.6, 159.5, 154.8, 134.8, 128.9, 128.8, 114.1, 113.9, 78.4, 63.5, 60.1, 59.9, 55.4, 52.5, 43.5, 43.3, 30.8,29.7, 24.4, 24.3, 24.2, 23.4, 23.3, 21.4, 21.3, 21.2, 19.7; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 15.3HRMS (TOF ES+) m/z calcd for $C_{24}H_{38}N_4O_4P$ [$(M + H)^+$], 477.2625; found, 477.2619.

Methyl (4S,5R)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl) -5-(2,4-dimethoxyphenyl)-4,5-dihydro-1H-imidazole-4-carboxylate (4d)

White solid; 222 mg, 88%; mp 58−59 °C; $[\alpha]^{25}{}_1$D =117 (c = 2.3, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.28 (s, 1H), 6.81-6.70 (m, 3H), 5.01-4.88 (m, 1H), 4.69-4.63 (m, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 3.69 (s, 3H), 3.21-3.18 (m, 1H), 2.86-2.81 (m, 2H), 2.69-2.62 (m, 1H), 1.95-1.91 (m, 2H), 1.68-1.59 (m, 1H), 1.39-0.88 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.4, 154.7, 149.1, 149.0, 135.1, 120.1, 111.0, 110.5, 78.1, 63.8, 59.9, 59.8, 56.1, 52.5, 44.8, 43.4, 30.8, 29.9,24.2, 24.1, 23.3, 23.2, 21.3,21.2, 20.1, 19.7; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 15.4; HRMS (TOF ES+) m/z calcd for $C_{25}H_{40}N_4O_5P$ [$(M + H)^+$], 507.2731; found, 507.2760.

Methyl (4S,5R)-5-(3-chlorophenyl)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2] diazaphosphol-2-yl)-4,5-dihydro-1H-imidazole-4-carboxylate (4e)

White solid; 192 mg, 80%; mp 77−78 °C; $[\alpha]^{25}{}_1$D =-23 (c = 1.8, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.38 (d, *J* = 8 Hz, 1H), 7.36-7.21 (m, 4H), 5.10 (s, 1H), 4.68 (s, 1H), 3.74 (s, 3H), 3.24-3.19 (m, 1H), 2.89-2.22 (m, 2H), 2.03-1.95 (m, 1H), 1.90-1.88 (m, 1H), 1.73 (s, 2H), 1.55-0.73 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.2, 154.9, 144.7, 134.7, 130.1, 128.4, 127.5, 125.9, 78.9, 63.5, 60.2, 60.1,52.6,44.9, 43.5, 30.1,24.2, 24.1, 23.3, 23.1, 20.1, 19.8; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 15.2, 14.2; HRMS (TOF ES+) m/z calcd for $C_{23}H_{35}ClN_4O_3P$ [$(M + H)^+$], 481.2130; found, 481.2131.

Methyl (4S,5R)-5-(4-bromophenyl)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2] diazaphosphol-2-yl)-4,5-dihydro-1H-imidazole-4-carboxylate (4f)

White solid; 145 mg, 55%; mp 66−67 °C; $[\alpha]^{25}{}_1$D =-39 (c = 2.5, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz)

δ = 7.45-7.38 (m, 2H), 7.34 (d, *J* = 10 Hz, 1H), 7.15-7.03 (m, 2H), 5.11 (s, 1H), 4.68 (s, 1H), 3.74 (s, 3H), 3.25-3.22 (m, 1H), 2.89-2.82 (m, 2H), 2.58-2.52 (m, 1H), 2.03-1.95 (m, 2H), 1.88-1.82 (m, 2H), 1.47-0.81 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 171.3, 154.9, 141.8, 131.9, 131.8, 129.3, 128.9, 122.2, 78.9, 63.5, 60.2, 59.9, 52.6,44.9, 43.5, 30.9, 29.9,24.3, 24.2, 23.2, 23.1, 20.2,19.8; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 15.4, 14.3; HRMS (TOF ES+) m/z calcd for $C_{23}H_{35}BrN_4O_3P$ [$(M + H)^+$], 525.1625; found, 525.1623.

Methyl (4S,5R)-5-(4-cyanophenyl)-1-((3aR,7aR)-1,3-diisopropyl-2-oxidooctahydrobenzo[d][1,3,2]diazaphosphol-2-yl)-4,5-dihydro-1H-imidazole-4-carboxylate (4g)

White solid; 188 mg, 80%; mp147−148 °C; $[\alpha]^{25}{}_1D$ =-59 (c = 1.7, $CHCl_3$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.63-7.44 (m, 4H), 7.23 (s, 1H), 5.23-5.20 (m, 1H), 4.67-4.61 (m, 1H), 3.75-3.70 (m, 3H), 3.25-3.18 (m, 1H), 2.91-2.87 (m, 2H), 2.66-2.59 (m, 1H), 2.05-2.01 (m, 2H), 1.77-1.72 (m, 2H), 1.57-0.88 (m, 16H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 170.9, 154.7, 147.8, 132.6, 132.5,128.4, 127.8, 118.6, 112.2, 78.5, 63.8, 60.4, 60.3, 52.8,45.0, 44.3, 43.6, 30.7,29.9, 24.3, 24.2, 23.1, 22.2, 21.9, 20.1; ^{31}P NMR ($CDCl_3$ 162 MHz): δ 15.3, 14.1; HRMS (TOF ES+) m/z calcd for $C_{24}H_{35}N_5O_3P$ [$(M + H)^+$], 472.2472; found, 472.2482.

1,3-Di-tert-butyl 4-methyl (4R,5S)-2-oxo-5-phenylimidazolidine-1,3,4-tricarboxylate (6a)[10c]

The resulting imidazoline **3a** (60 mg, 0.134 mmol) was dissolved in a 50% KOH solution in water (2 mL), and the solution was refluxed for 10 hours. Then, the reaction was cooled to 0 ºC and neutralized with a 1.0 M HCl solution (until pH 6.7). The solvents were removed in vacuo and the remaining residue was loaded onto a Amberlite H^+ ion exchange resin. The column was flushed with water, dioxane, more water and eluted with 2.0 M aqueous ammonia. The ammoniacal fraction was reduced in vacuo to afford the crude diaminoacid **5a** as a white solid in 80% yield (20 mg). The diamino acid **5a** (20 mg, 0.111 mmol) was dissolved in methanol (0.5 mL), and the solution was cooled to 0 ºC, then $SOCl_2$ (0.2 mL) was added dropwise and the reaction mixture was stirred under

reflux for 12 hours. After evaporation of solvents under vacuum, the crude diaminoester was dissolved in dry acetonitrile (5 mL), followed by addition of DMAP and $(Boc)_2O$ at 0 ºC. The reaction mixture was stirred at room temperature for 12 hours. Evaporation of acetonitrile under vacuum gave a solid, which was purified by column chromatography on silica gel, affording the compound **6a** as a pale yellow liquid in 47% yield (21 mg).

^{1}HNMR ($CDCl_3$, 400 MHz) δ = 7.80-7.77 (m, 1H), 7.78 (d, *J* = 6.8 Hz, 1H), 7.54-7.47 (m, 3H), 4.26 (s, 1H), 3.90 (s, 3H), 3.74 (s, 1H), 1.47-1.30 (m, 18H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ = 166.1, 164.7, 148.9, 141.6, 135.3, 132.4, 128.2, 125.6, 124.5, 120.2, 114.9, 84.7, 82.2, 71.8, 59.1, 28.1; HRMS (TOF ES+) m/z calcd for $C_{21}H_{29}N_2O_7$ [$(M + H)^+$], 421.1969; found, 421.1948.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all pure products, and X-ray crystal data (CIF) for **3a** and **4a**. This material is available free of charge via the Internet at http//pubs.acs.org.

Notes

The authors declare no competing financial interest.

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