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Chiral *N*-Phosphonyl Imines for an Aza-Morita–Baylis–Hillman Reaction via Group-Assisted Purification (GAP) Chemistry

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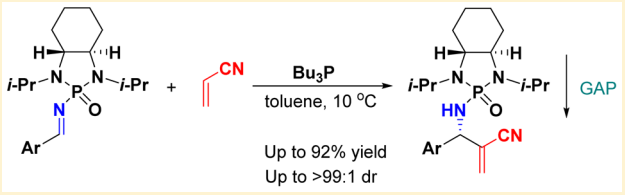
Supporting Information

ABSTRACT: Seventeen examples of aza-Morita–Baylis–Hillman (aza-MBH) adducts have been synthesized by reacting chiral *N*-phosphonyl imines with acrylonitrile in good to excellent yields (up to 96%) and high diastereoselectivity (up to 99:1 dr). The synthesis of these adducts followed the method of group-assisted purification (GAP) chemistry, in which the pure aza-MBH products were readily obtained by washing the crude products with cosolvents of hexane and ethyl acetate.



INTRODUCTION

Chiral and achiral imines represent a highly valuable class of compounds and widely serve as "privileged synthons" in asymmetric reactions for the construction of chiral amino products, including natural and medicinal targets.[1−7] In this context, our effort was devoted to exploring the use of chiral *N*-phosphonyl imines for aza-Morita–Baylis–Hillman (aza-MBH)[8] reactions under concise systems and through group-assisted purification (GAP) chemistry.[3] In fact, the development of greener and more practical chiral N-protected imines with high efficiency for asymmetric transformations is highly desirable and important. Over the past several years, our group has made great progress on the design of chiral N-protected imines using different phosphorus-containing auxiliaries. For instance, *N*-phosphonyl-, *N*-phosphoryl-, and *N*-phosphinyl-attached imines have been successfully utilized for the synthesis of various amide derivatives,[3] including amino acids, α-amino esters, and peptides, and applied in many named and unnamed reactions, such as the Strecker reaction,[4] aza-Henry reaction,[5] and umpolung reaction.[6] The products resulting from these studies could be easily purified simply by washing the crude mixture with the common solvents without the use of the traditional purification methods of chromatography and recrystallization. This method resulted in a concept called group-assisted purification (GAP) chemistry. Taking advantage of GAP chemistry not only reduces the use of materials such as silica gels, eluents, and energy but also creates a simple and convenient workup process.[7]

Over the past few decades, the Morita–Baylis–Hillman (MBH) reaction has become a significant tool for the collection of functional olefins,[8] which can further serve as building blocks in organic synthesis[9] and pharmaceutical research.[10] For instance, chiral β-amino nitriles can be converted into the corresponding chiral β-amino carboxylic acids[11] and 1,3-diamines[12] under suitable conditions. Therefore, much attention has been paid to the development of new MBH approaches to multiple functional olefin products, especially for asymmetric MBH processes.[13] Several research groups[9a,14] have independently reported a series of enantioselective aza-MBH reactions of N-tosylated imines with acrylonitrile using different chiral catalysts, affording the corresponding β-amino nitriles. In addition, chiral auxiliary-controlled aza-MBH reactions have attracted attention due to the potential for large-scale synthesis and application. Aggarawal et al. reported the asymmetric aza-MBH reaction of enantiomerically pure *N*-*p*-toluenesulfinimines and *N*-*tert*-butanesulfinimines with methyl acrylate, albeit low diastereoselectivity was reported.[15] Zhou and co-workers developed an enantioselective aza-MBH reaction using *N*-thiophosphoryl imines bearing an (*S*)-binaphthalene moiety with useful diastereoselectivity.[16] The continuous exploration of a new auxiliary-assisted aza-MBH reaction with high diastereoselectivity, particularly combined with the GAP chemistry, for the formation of chiral functionalized olefins in a simple purification manner remains highly attractive and practical. As a continuation of our project on aza-MBH reaction[8,17] and GAP chemistry,[3−6] we became interested in taking the above combinational advantage by using a chiral *N*-phosphonyl auxiliary. Herein, we report a practical aza-MBH synthesis using acrylonitrile and chiral *N*-phosphonyl auxiliary imines in the presence of Bu_3P as a catalyst that affords a versatile protocol for the formation of a wide range of functionalized β-amino nitriles with excellent yields (up to 96% yield) and diastereoselectivity (up to >99:1 dr) (Scheme 1). Use of GAP chemistry results in a convenient and simple purification process where pure chiral products can be obtained simply by washing the resulting crude mixture with hexane or other common solvents. Meanwhile, the *N*-phosphonyl auxiliary can

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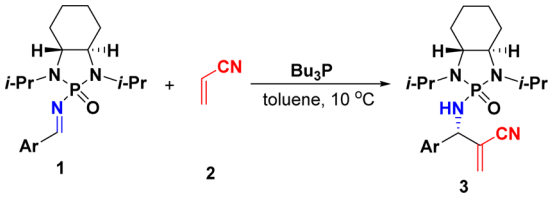
Scheme 1. Asymmetric GAP Synthesis of Aza-MBH Adducts



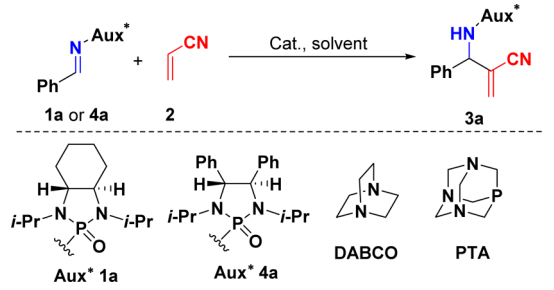
be easily removed in an acidic alcohol solution and recovered after workup, thereby enabling the reuse of auxiliaries to reduce expenses and waste generation.

RESULTS AND DISCUSSION

Initially, various catalysts and solvents for the aza-MBH reaction of *N*-phosphonyl imines with acrylonitrile were systematically examined. Reaction of *N*-phosphonyl imine **1a** with acrylonitrile was conducted in toluene at room temperature under N_2 conditions, and the results are summarized in Table 1. Among the Lewis bases that were examined (Table 1, entries 1−5), Bu_3P showed the highest catalytic reactivity, giving the desired product **2a** in 91% conversion with 95:5 dr (entry 5). Afterward, optimizing examination of the solvents revealed that both *N*,*N*-dimethylformamide (DMF) and dichloromethane (DCM) led to yields and diastereoselectivity lower than those of toluene (entry 5 vs entries 6 and 7), whereas the reactions in THF and Et_2O delivered higher diastereoselectivity but lower yields when compared to those of toluene (entry 5 vs entries 8 and 9). Because of the high yield obtained in toluene, we thus employed toluene as the reaction media and varied other parameters to improve the diastereoselectivity of this reaction, including the loading of Bu_3P, substrate ratio, reaction temperature, and chiral auxiliary (entries 10−13). Increasing the loading of Bu_3P showed a negative impact on the yield of **2a** (entry 10). After careful optimization, we found that adjusting the substrate ratio (**1a**:**2**) to 1:3 and decreasing the reaction temperature to 10 °C resulted in the best outcomes (90% yield and 99:1 dr) (entry 11). Exchanging auxiliary **1a** for **4a** led to inferior results (entries 12 and 13).

With the optimized reaction conditions in hand, the scope of the aza-MBH reaction was evaluated. As shown in Scheme 2, a wide range of highly functionalized *β*-amino nitriles **3a**−**q** were

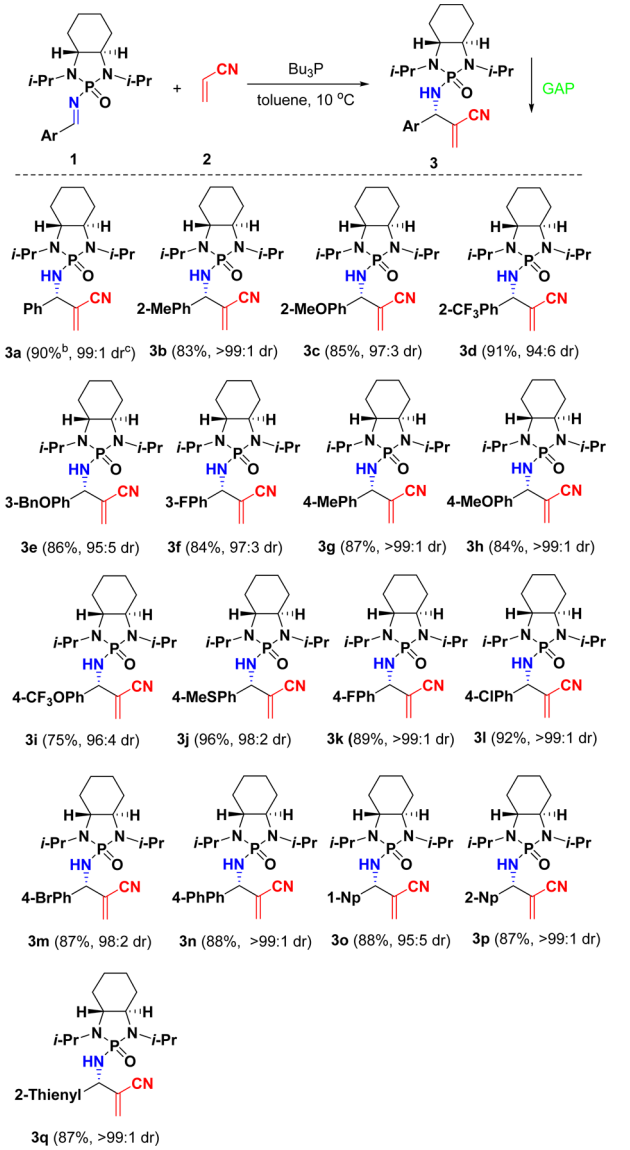
Table 1. Screening of the Reaction Conditions



entry[a]	imine	cat. (mol %)	solvent	time (h)	yield (%)	dr[b]
1	**1a**	Ph_2PMe (20)	toluene	72	no reaction	
2	**1a**	Ph_3P (20)	toluene	72	no reaction	
3	**1a**	DABCO (20)	toluene	72	no reaction	
4	**1a**	PTA (20)	toluene	72	no reaction	
5	**1a**	Bu_3P (20)	toluene	72	91[c]	95:5
6	**1a**	Bu_3P (20)	DCM	72	63[c]	79:21
7	**1a**	Bu_3P (20)	DMF	72	79[c]	81:19
8	**1a**	Bu_3P (20)	THF	72	76[c]	93:7
9	**1a**	Bu_3P (20)	Et_2O	192	85	98:2
10	**1a**	Bu_3P (30)	toluene	72	81	96:4
11	**1a**	Bu_3P (20)	toluene	144	90[d]	99:1
12	**3**	Bu_3P (20)	toluene	72	9[c]	
13	**3**	Bu_3P (20)	Et_2O	72	20[c]	

[a]Reactions were performed with imine **1a** (1.0 mmol), acrylonitrile (2.0 mmol), and a catalyst at room temperature under N_2. [b]Based on analysis of ^1H and ^{31}P NMR data of the reaction mixture. [c]Results were conversion rates determined by ^{31}P NMR, in which the reactions were not accomplished. Others were isolated yields achieved by GAP washing. [d]Reactions were performed with imine **1a** (1.0 mmol), acrylonitrile (3.0 mmol), and a catalyst at 10 °C.

Scheme 2. Scope of the Aza-MBH Reaction[a]



[a]Reactions were performed with imine (1.0 mmol), acrylonitrile (3.0 mmol), and Bu_3P (0.20 mmol) at 10 °C in dry toulene under N_2. [b]Total yield of the isomers. [c]Based on analysis of ^1H and ^{31}P NMR data of the reaction mixture.

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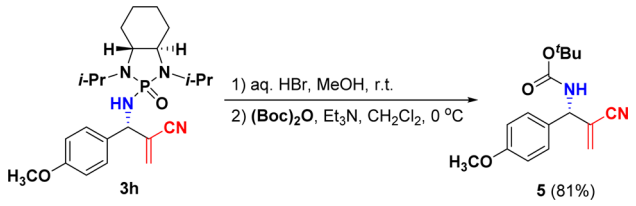
obtained in a highly diastereoselective and functional-group compatible manner. Substrates **1** with both electron-donating and electron-withdrawing groups at different positions on the aromatic rings can be efficiently transformed into the corresponding β-amino nitriles **3** in good to excellent yields and high diastereoselectivity. More sterically demanding 2-methyl (**1b**), 2-methoxy (**1c**), and 2-trifluoromethyl (**1d**) substituents were engaged in these aza-MBH reactions, affording the corresponding products **3b–d** in good yields (83%–91%) and high diastereoselectivity (up to >99:1 dr). Similarly, 1- and 2-naphthalenyl (1- and 2-Np) counterparts were adaptable substrates in these transformations, allowing the aza-MBH reaction to afford the corresponding β-amino nitriles **3o** and **3p** in 88% and 87% yields, respectively. In addition, 2-thienyl-substituted imines can work well in this aza-MBH reaction, which proves the high efficiency of the present method using *N*-phosphonyl heteroaryl-functionalized imines. In all cases, the pure aza-MBH adducts were obtained simply by washing the crude products with hexane/ethyl acetate (v/v, 10/1) without the use of chromatography and recrystallization.[3c,d]

To expand the synthetic utility of this methodology, the cleavage reaction of the resulting adduct **3h** was performed in a HBr solution, followed by Boc protection, to afford β-amino acrylonitriles **5** (81% yield, >99% ee) (Scheme 3) with an easy recycling of the chiral diamines. This convenient deprotection enables the present method to be a protocol synthesis of free chiral β-amino acrylonitriles.

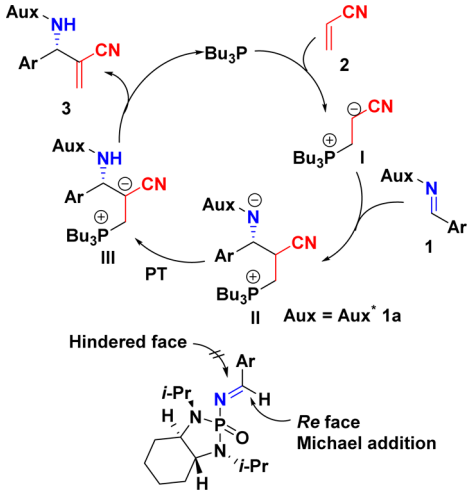
Scheme 3. Cleavage of the Auxiliary of the Aza-MBH Adducts



Absolute configuration was determined by X-ray analysis of **3a**, revealing the formed stereocenter to be an (*S*)-configuration (CCDC no. 1051852). On the basis of the assignment of the absolute configuration of adducts and pertinent literature discussions,[18] a straightforward mechanism and asymmetric induction model are shown in Scheme 4. At the first step of this process, the Michael addition of Bu_3P onto acrylonitriles **2** occurs to yield zwitterionic adduct **I**, followed by a carbonyl addition reaction with *N*-phosphonyl imines **1**. At this step, the asymmetric induction is explained by the fact that nucleophilic attacking occurs from the *re* face of the *N*-phosphonyl imine substrate to give the second zwitterionic-type intermediate **II**. Subsequent proton transfer (in either an intramolecular or intermolecular manner) and elimination of Bu_3P results in the final aza-MBH adducts **3**. The regenerated Bu_3P continues driving catalytic circles until the reaction is complete.

In conclusion, chiral *N*-phosphonyl imines have been proven to be effective substrates for highly diastereoselective aza-MBH reactions. The good to excellent diastereoselectivity and chemical yields have been achieved through convenient operations and mild systems. The chiral auxiliary can be readily removed and recycled. This research provides a nice addition to the practical GAP *N*-phosphonyl imine chemistry.

Scheme 4. Proposed Mechanism of the Aza-MBH Reaction



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 were delivered from the Innovation Technology solvent system. All reactions were carried out in flame-dried flasks under a nitrogen atmosphere. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 400 MHz instrument with TMS as the internal standard. Chemical shifts (δ) were reported in ppm with respect to TMS. Data are represented as follows: chemical shift, multiplicity (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.

Synthesis of Compounds 1a–q. Compounds **1a–q** were synthesized according to the procedures found in the literature.[19] ^{1}H and ^{31}P NMR data obtained were consistent with the literature data.

Typical Procedure for the Asymmetric GAP Synthesis of Aza-MBH Adducts 3a–q Using Chiral *N*-Phosphonyl Imines 1a–q. The chiral *N*-phosphonyl imines (1.0 mmol) predissolved in 10 mL of toluene were placed in a 25 mL oven-dried, round-bottomed reaction vial under inert gas protection. Bu_3P (0.20 mmol) was added to the mixture, and the reaction mixture was stirred in an ice bath. Acrylonitrile (3.0 mmol) was added to the resulting solution, and the reaction mixture was stirred at 10 °C. After the completion of the reaction by TLC had been confirmed, the solvent was evaporated, and the residue was dissolved in 20–30 mL of hexane/ethyl acetate (v/v, 10/1). The crude solid product precipitated and was filtered. Next, the cake was washed with hexane (2–5 mL) to afford the pure product. In some cases, ultrasonic vibration can contribute to the GAP washing.

Data for Pure Compounds 3a–q. *2-((S)-(((3aR,7aR)-1,3-Diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino) (phenyl)methyl)acrylonitrile (**3a**).* White solid, 0.360 g, 90% yield; mp 169–171 °C; $[\alpha]_D^{20} = -53.7$ (*c* = 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, 3H, *J* = 6.4 Hz), 1.12 (d, 3H, *J* = 6.8 Hz), 1.17 (t, 6H, *J* = 6.0 Hz), 1.22–1.33 (m, 4H), 1.77 (d, 2H, *J* = 6.8 Hz), 2.05 (d, 2H, *J* = 8.4 Hz), 2.83–2.84 (m, 1H), 2.94–2.98 (m, 1H), 3.11 (s, 1H), 3.28–3.46 (m, 2H), 5.17 (t, 1H, *J* = 10.0 Hz), 5.95 (s, 1H), 6.04 (s, 1H), 7.30 (q, 1H, *J* = 4.0 Hz), 7.36 (d, 4H, *J* = 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0 (d, *J* = 6.0 Hz), 23.2, 23.3, 24.4 (d, *J* = 4.0 Hz), 30.9 (d, *J* = 9.0 Hz), 31.2 (d, *J* = 11.0 Hz), 44.1 (d, *J* = 3.0 Hz), 44.5, 59.1, 59.3 (d, *J* = 9.0 Hz), 60.1 (d, *J* = 11.0 Hz), 117.6, 126.5, 127.6 (d, *J* = 4.0 Hz), 128.3, 129.1, 129.7, 140.1 (d, *J* = 2.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.99; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{34}N_4OP$ 401.2465, found 401.2465; $[M + Na]^+$ calcd for $C_{22}H_{33}N_4OPNa$ 423.2284, found 423.2284.

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*2-((S)-(((3aR,7aR)-1,3-Diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(o-tolyl)methyl)acrylonitrile (**3b**).* White solid, 0.344 g, 83% yield; mp 184−186 °C; $[\alpha]_D^{20}$ = −26.0 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, 3H, *J* = 6.4 Hz), 1.09−1.14 (m, 9H), 1.22−1.33 (m, 4H), 1.77 (d, 2H, *J* = 7.2 Hz), 2.05 (s, 2H), 2.39 (s, 3H), 2.83 (s, 1H), 2.92−2.97 (m, 1H), 3.15−3.24 (m, 1H), 3.37−3.46 (m, 1H), 3.28−3.46 (m, 2H), 5.39 (t, 1H, *J* = 10.0 Hz), 5.91 (d, 2H, *J* = 6.8 Hz), 7.14−7.27 (m, 3H), 7.34 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8 (d, *J* = 5.0 Hz), 23.2 (d, *J* = 3.0 Hz), 24.4 (d, *J* = 3.0 Hz), 30.9 (d, *J* = 9.0 Hz), 31.1 (d, *J* = 10.0 Hz), 44.1 (d, *J* = 3.0 Hz), 44.5, 55.0, 59.4 (d, *J* = 9.0 Hz), 60.0 (d, *J* = 11.0 Hz), 117.7, 126.0, 126.9, 128.2, 129.6, 131.0, 135.1, 138.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.00; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{36}N_4OP$ 415.2621, found 415.2620; $[M + Na]^+$ calcd for $C_{23}H_{35}N_4OPNa$ 437.2441, found 437.2443.

*2-((R)-(((3aR,7aR)-1,3-Diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(2-methoxyphenyl)methyl)acrylonitrile (**3c**).* White solid, 0.366 g, 85% yield; mp 163−165 °C; $[\alpha]_D^{20}$ = −23.9 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (dd, 6H, *J* = 11.6, 6.8 Hz), 1.10 (d, 3H, *J* = 6.8 Hz), 1.15 (d, 3H, *J* = 6.8 Hz), 1.24−1.33 (m, 4H), 1.77 (d, 2H, *J* = 5.2 Hz), 2.04 (d, 2H, *J* = 3.2 Hz), 2.84−2.97 (m, 2H), 3.21−3.41 (m, 2H), 3.65−3.67 (m, 1H), 3.83 (s, 3H), 5.19 (t, 1H, *J* = 10.8 Hz), 5.91 (s, 1H), 6.01 (s, 1H), 6.88 (d, 1H, *J* = 8.4 Hz), 6.96 (t, 1H, *J* = 7.6 Hz), 7.27 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 20.1 (d, *J* = 2.0 Hz), 23.0 (d, *J* = 3.0 Hz), 23.5 (d, *J* = 7.0 Hz), 24.5 (d, *J* = 1.0 Hz), 24.5, 30.8 (d, *J* = 9.0 Hz), 31.3 (d, *J* = 11.0 Hz), 44.1 (d, *J* = 4.0 Hz), 44.4, 55.4, 55.9, 59.3 (d, *J* = 10.0 Hz), 60.3 (d, *J* = 11.0 Hz), 111.3, 118.0, 121.1, 126.9 (d, *J* = 7.0 Hz), 128.2 (d, *J* = 2.0 Hz), 128.7, 129.2, 129.6, 156.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.18; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{36}N_4O_2P$ 431.2570, found 431.2570; $[M + Na]^+$ calcd for $C_{23}H_{35}N_4O_2PNa$ 453.2390, found 453.2391.

*2-((S)-(((3aR,7aR)-1,3-Diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(2-(trifluoromethyl)phenyl)methyl)acrylonitrile (**3d**).* White solid, 0.426 g, 91% yield; mp 180−182 °C; $[\alpha]_D^{25}$ = −44.2 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, 3H, *J* = 6.8 Hz), 0.87 (d, 3H, *J* = 6.4 Hz), 1.17 (d, 3H, *J* = 6.8 Hz), 1.22 (d, 3H, *J* = 7.2 Hz), 1.25−1.32 (m, 4H), 1.72−1.76 (m, 2H), 1.95−2.08 (m, 2H), 2.73−2.78 (m, 1H), 2.94−2.99 (m, 1H), 3.19−3.33 (m, 1H), 3.48−3.62 (m, 1H), 4.50 (t, 1H, *J* = 9.6 Hz), 5.51 (t, 1H, *J* = 10.4 Hz), 5.87 (s, 1H), 5.96 (d, 1H, *J* = 0.4 Hz), 7.42 (t, 1H, *J* = 7.6 Hz), 7.63 (t, 2H, *J* = 8.0 Hz), 7.85 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6 (d, *J* = 3.0 Hz), 19.8, 23.4 (d, *J* = 4.0 Hz), 23.7 (d, *J* = 8.0 Hz), 24.4 (d, *J* = 1.0 Hz), 24.5, 31.0 (d, *J* = 8.0 Hz), 31.1 (d, *J* = 10.0 Hz), 43.9 (d, *J* = 4.0 Hz), 44.5 (d, *J* = 3.0 Hz), 54.2 (d, *J* = 2.0 Hz), 59.5, 59.6, 117.4, 126.4 (q, *J* = 6.0 Hz), 126.4 (d, *J* = 7.0 Hz), 128.4, 129.1, 131.8, 132.9, 139.4 (m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.47; ^{19}F NMR (376.38 MHz, $CDCl_3$) δ −57.21; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{33}F_3N_4OP$ 469.2339, found 469.2341; $[M + Na]^+$ calcd for $C_{23}H_{32}F_3N_4OPNa$ 491.2158, found 491.2159.

*2-((S)-(3-(Benzyloxy)phenyl)(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)methyl)acrylonitrile (**3e**).* White solid, 0.436 g, 86% yield; mp 67−69 °C; $[\alpha]_D^{25}$ = −46.5 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, 3H, *J* = 6.8 Hz), 1.12 (d, 3H, *J* = 6.8 Hz), 1.18 (dd, 6H, *J* = 7.2, 9.2 Hz), 1.25−1.33 (m, 4H), 1.77 (d, 2H, *J* = 6.8 Hz), 2.05 (d, 2H, *J* = 7.6 Hz), 2.80−2.83 (m, 1H), 2.92−2.98 (m, 1H), 3.01−3.22 (m, 1H), 3.28−3.48 (m, 2H), 5.07 (s, 2H), 5.14 (t, 1H, *J* = 10.4 Hz), 5.94 (s, 1H), 6.02 (s, 1H), 6.91 (dd, 1H, *J* = 2.4, 8.4 Hz), 6.95−7.00 (m, 2H), 7.26−7.28 (m, 1H), 7.30−7.34 (m, 1H), 7.36−7.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 20.0 (d, *J* = 2.0 Hz), 23.2 (d, *J* = 2.0 Hz), 23.3, 24.4 (d, *J* = 3.0 Hz), 30.9 (d, *J* = 10.0 Hz), 31.1 (d, *J* = 11.0 Hz), 44.1 (d, *J* = 4.0 Hz), 44.6, 59.1 (d, *J* = 1.0 Hz), 59.4 (d, *J* = 10.0 Hz), 60.1 (d, *J* = 12.0 Hz), 70.2, 113.4, 114.5, 117.6, 119.0, 127.6, 128.2, 128.7, 129.7, 130.2, 136.9, 141.7 (d, *J* = 4.0 Hz), 159.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.98; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{40}N_4O_2P$ 507.2883, found 507.2881; $[M + Na]^+$ calcd for $C_{29}H_{39}N_4O_2PNa$ 529.2703, found 529.2705.

*2-((S)-(((3aR,7aR)-1,3-Diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(3-fluorophenyl)methyl)acrylonitrile (**3f**).* White solid, 0.352 g, 84% yield; mp 152−154 °C; $[\alpha]_D^{25}$ = −47.3 (*c* = 0.91, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, 3H, *J* = 6.8 Hz), 1.14 (d, 3H, *J* = 6.4 Hz), 1.18 (d, 6H, *J* = 6.8 Hz), 1.29−1.36 (m, 3H), 1.77−1.94 (m, 3H), 2.06 (d, 2H, *J* = 8.4 Hz), 2.77−2.89 (m, 1H), 2.93−2.99 (m, 1H), 3.04−3.15 (m, 1H), 3.26−3.48 (m, 2H), 5.21 (t, 1H, *J* = 10.4 Hz), 5.98 (s, 1H), 6.07 (s, 1H), 6.98−7.03 (m, 1H), 7.09 (t, 1H, *J* = 9.6 Hz), 7.16 (d, 1H, *J* = 7.6 Hz), 7.32−7.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 20.1 (d, *J* = 1.0 Hz), 23.2 (d, *J* = 4.0 Hz), 23.3 (d, *J* = 7.0 Hz), 24.4, 30.9 (d, *J* = 10.0 Hz), 31.2 (d, *J* = 12.0 Hz), 44.2 (d, *J* = 4.0 Hz), 44.5 (d, *J* = 2.0 Hz), 58.8, 59.4 (d, *J* = 10.0 Hz), 60.1 (d, *J* = 12.0 Hz), 113.6 (d, *J* = 22.0 Hz), 115.3 (d, *J* = 21.0 Hz), 117.3, 122.2 (d, *J* = 3.0 Hz), 127.0 (d, *J* = 5.0 Hz), 130.2, 130.7 (d, *J* = 8.0 Hz), 162.0, 164.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.91; ^{19}F NMR (376.38 MHz, $CDCl_3$) δ −111.68; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{33}FN_4OP$ 419.2371, found 419.2375; $[M + Na]^+$ calcd for $C_{22}H_{32}FN_4OPNa$ 441.2190, found 441.2193.

*2-((S)-(((3aR,7aR)-1,3-Diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(p-tolyl)methyl)acrylonitrile (**3g**).* Colorless crystal, 0.361 g 87% yield; mp 148−150 °C; $[\alpha]_D^{20}$ = −38.0 (*c* = 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, 3H, *J* = 6.8 Hz), 1.12 (d, 3H, *J* = 6.8 Hz), 1.18 (t, 6H, *J* = 6.4 Hz), 1.22−1.33 (m, 4H), 1.77 (d, 2H, *J* = 7.2 Hz), 2.06 (s, 2H), 2.33 (s, 3H), 2.83−2.85 (m, 1H), 2.93−2.98 (m, 1H), 3.29−3.46 (m, 2H), 5.12 (t, 1H, *J* = 10.0 Hz), 5.92 (s, 1H), 6.02 (s, 1H), 7.16 (d, 2H, *J* = 8.0 Hz), 7.23 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0 (d, *J* = 6.0 Hz), 21.2, 23.2, 23.3 (d, *J* = 4.0 Hz), 24.4 (d, *J* = 4.0 Hz), 30.9 (d, *J* = 9.0 Hz), 31.1 (d, *J* = 12.0 Hz), 44.1 (d, *J* = 4.0 Hz), 44.6 (d, *J* = 1.0 Hz), 58.9, 59.3 (d, *J* = 9.0 Hz), 60.1 (d, *J* = 11.0 Hz), 117.6, 126.3, 127.8 (d, *J* = 5.0 Hz), 129.4, 129.7, 137.0 (d, *J* = 4.0 Hz), 138.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.05; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{36}N_4OP$ 415.2621, found 415.2618; $[M + Na]^+$ calcd for $C_{23}H_{35}N_4OPNa$ 437.2441, found 437.2443.

*2-((S)-(((3aR,7aR)-1,3-Diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(4-methoxyphenyl)methyl)acrylonitrile (**3h**).* Colorless crystal, 0.362 g, 84% yield; mp 181−182 °C; $[\alpha]_D^{20}$ = −58.1 (*c* = 0.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, 3H, *J* = 6.8 Hz), 1.12 (d, 3H, *J* = 6.4 Hz), 1.18 (t, 6H, *J* = 5.6 Hz), 1.25−1.35 (m, 4H), 1.77 (d, 2H, *J* = 6.8 Hz), 2.05 (d, 2H, *J* = 6.8 Hz), 2.82−2.83 (m, 1H), 2.93−2.98 (m, 1H), 3.27−3.48 (m, 2H), 3.80 (s, 3H), 5.12 (t, 1H, *J* = 10.0 Hz), 5.92 (s, 1H), 6.01 (s, 1H), 6.88 (d, 2H, *J* = 8.4 Hz), 7.27 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 20.1 (d, *J* = 1.0 Hz), 23.3 (d, *J* = 4.0 Hz), 24.4 (d, *J* = 4.0 Hz), 30.9 (d, *J* = 10.0 Hz), 31.1 (d, *J* = 1.0 Hz), 31.2 (d, *J* = 1.0 Hz), 44.1 (d, *J* = 3.0 Hz), 44.5 (d, *J* = 3.0 Hz), 55.4, 58.6, 59.3 (d, *J* = 9.0 Hz), 60.1 (d, *J* = 11.0 Hz), 114.4, 117.7, 127.7, 127.8 (d, *J* = 5.0 Hz), 129.2, 132.2 (d, *J* = 3.0 Hz), 159.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.09; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{36}N_4O_2P$ 431.2570, found 431.2569; $[M + Na]^+$ calcd for $C_{23}H_{35}N_4O_2PNa$ 453.2390, found 453.2389.

*2-((S)-(((3aR,7aR)-1,3-Diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(4-(trifluoromethoxy)phenyl)methyl)acrylonitrile (**3i**).* White solid, 0.363 g, 75% yield; mp 69−71 °C; $[\alpha]_D^{25}$ = −46.7 (*c* = 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06−1.18 (m, 12H), 1.24−1.37 (m, 4H), 1.77 (d, 2H, *J* = 8.4 Hz), 2.05 (d, 2H, *J* = 10.4 Hz), 2.80−2.82 (m, 1H), 2.93−2.98 (m, 1H), 3.16−3.49 (m, 3H), 5.20 (t, 1H, *J* = 10.4 Hz), 5.98 (s, 1H), 6.09 (s, 1H), 7.21 (d, 2H, *J* = 8.0 Hz), 7.42 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.0 (d, *J* = 1.0 Hz), 23.1 (d, *J* = 3.0 Hz), 23.4 (d, *J* = 7.0 Hz), 24.4 (d, *J* = 2.0 Hz), 30.8 (d, *J* = 10.0 Hz), 31.2 (d, *J* = 12.0 Hz), 44.1 (d, *J* = 4.0 Hz), 44.5 (d, *J* = 2.0 Hz), 58.5 (d, *J* = 1.0 Hz), 59.3 (d, *J* = 10.0 Hz), 60.1 (d, *J* = 11.0 Hz), 117.5, 121.5, 126.9 (d, *J* = 5.0 Hz), 128.2, 130.2, 139.1 (d, *J* = 4.0 Hz), 149.0 (d, *J* = 1.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.93; ^{19}F NMR (376.38 MHz, $CDCl_3$) δ −57.91; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{33}F_3N_4O_2P$ 485.2288, found 485.2290; $[M + Na]^+$ calcd for $C_{23}H_{32}F_3N_4O_2PNa$ 507.2107, found 507.2110.

2-((S)-(((3aR,7aR)-1,3-Diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(4-(methylthio)phenyl)-

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*methyl)acrylonitrile (**3j**).* White solid, 0.429 g, 96% yield; mp 175−177 °C; $[\alpha]_D^{25}$ = −31.7 (*c* = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, 3H, *J* = 6.8 Hz), 1.12 (d, 3H, *J* = 6.4 Hz), 1.17 (t, 6H, *J* = 7.2 Hz), 1.29−1.35 (m, 3H), 1.76 (d, 2H, *J* = 8.4 Hz), 2.04 (d, 3H, *J* = 9.2 Hz), 2.46 (s, 3H), 2.78−2.82 (m, 1H), 2.92−2.98 (m, 1H), 3.09 (t, 1H, *J* = 9.6 Hz), 3.28−3.45 (m, 2H), 5.12 (t, 1H, *J* = 10.4 Hz), 5.93 (s, 1H), 6.04 (s, 1H), 7.21−7.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 20.0, 20.0 (d, *J* = 2.0 Hz), 23.2 (d, *J* = 4.0 Hz), 23.3, 24.4, 30.9 (d, *J* = 9.0 Hz), 31.2 (d, *J* = 11.0 Hz), 44.1 (d, *J* = 4.0 Hz), 44.5 (d, *J* = 3.0 Hz), 58.7 (d, *J* = 1.0 Hz), 59.3 (d, *J* = 10.0 Hz), 60.1 (d, *J* = 11.0 Hz), 117.6, 127.0, 127.5 (d, *J* = 5.0 Hz), 129.6, 136.8 (d, *J* = 4.0 Hz), 138.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.95; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{36}N_4OSP$ 447.2342, found 447.2342; $[M + Na]^+$ calcd for $C_{23}H_{35}N_4OSPNa$ 469.2161, found 469.2167.

*2-((S)-(((3aR,7aR)-1,3-Diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(4-fluorophenyl)methyl)acrylonitrile (**3k**).* Colorless crystal, 0.372 g, 89% yield; mp 146−148 °C; $[\alpha]_D^{20}$ = −55.0 (*c* = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, 3H, *J* = 6.4 Hz), 1.13 (d, 3H, *J* = 6.4 Hz), 1.18 (d, 6H, *J* = 6.8 Hz), 1.25−1.33 (m, 4H), 1.78 (d, 2H, *J* = 5.6 Hz), 2.06 (s, 2H), 2.85−2.87 (m, 1H), 2.97 (t, 1H, *J* = 9.2 Hz), 3.25−3.35 (m, 1H), 3.37−3.47 (m, 1H), 5.19 (t, 1H, *J* = 10.4 Hz), 5.97 (s, 1H), 6.04 (s, 1H), 7.06 (t, 2H, *J* = 8.0 Hz), 7.36 (t, 2H, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.1 (d, *J* = 1.0 Hz), 23.2 (d, *J* = 4.0 Hz), 24.4 (d, *J* = 7.0 Hz), 30.8 (d, *J* = 10.0 Hz), 31.0 (d, *J* = 12.0 Hz), 44.2 (d, *J* = 4.0 Hz), 44.8, 58.6, 59.4 (d, *J* = 10.0 Hz), 59.9 (d, *J* = 10.0 Hz), 115.9, 116.1, 117.5, 127.3 (d, *J* = 6.0 Hz), 128.4 (d, *J* = 8.0 Hz), 136.0, 161.4, 163.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.93; ^{19}F NMR (376.38 MHz, $CDCl_3$) δ −113.86; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{33}FN_4OP$ 419.2371, found 419.2371; $[M + Na]^+$ calcd for $C_{22}H_{32}FN_4OPNa$ 441.2190, found 441.2189.

*2-((S)-(4-Chlorophenyl)(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)methyl)acrylonitrile (**3l**).* White solid, 0.400 g, 92% yield; mp 172−174 °C; $[\alpha]_D^{20}$ = −35.0 (*c* = 1.30, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, 3H, *J* = 6.4 Hz), 1.17−1.19 (m, 6H), 1.23 (d, 3H, *J* = 6.4 Hz), 1.34 (d, 4H, *J* = 4.8 Hz), 1.79−1.80 (m, 4H), 2.04−2.10 (m, 2H), 2.98−2.99 (m, 1H), 3.20−3.32 (m, 1H), 3.41−3.51 (m, 1H), 5.21 (t, 1H, *J* = 10.0 Hz), 6.00 (d, 2H, *J* = 8.8 Hz), 7.36 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 20.1 (d, *J* = 2.0 Hz), 23.2 (d, *J* = 4.0 Hz), 23.3 (d, *J* = 7.0 Hz), 24.4 (d, *J* = 4.0 Hz), 30.8 (d, *J* = 10.0 Hz), 31.1 (d, *J* = 3.0 Hz), 31.2, 44.1 (d, *J* = 5.0 Hz), 44.6 (d, *J* = 1.0 Hz), 58.6 (d, *J* = 1.0 Hz), 59.3 (d, *J* = 9.0 Hz), 60.1 (d, *J* = 11.0 Hz), 117.4, 127.1 (d, *J* = 5.0 Hz), 128.0, 129.2, 130.0, 134.2, 138.8 (d, *J* = 4.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.79; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{33}ClN_4OP$ 435.2075, found 435.2070; $[M + Na]^+$ calcd for $C_{22}H_{32}ClN_4OPNa$ 457.1894, found 457.1895.

*2-((S)-(4-Bromophenyl)(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)methyl)acrylonitrile (**3m**).* White solid, 0.416 g, 87% yield; mp 149−151 °C; $[\alpha]_D^{20}$ = −51.1 (*c* = 0.82, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, 3H, *J* = 6.8 Hz), 1.12 (d, 3H, *J* = 6.8 Hz), 1.16−1.18 (m, 6H), 1.25−1.33 (m, 4H), 1.78 (d, 2H, *J* = 6.0 Hz), 2.06 (s, 2H), 2.81−2.88 (m, 1H), 2.94−2.99 (m, 1H), 3.25−3.45 (m, 2H), 5.15 (t, 1H, *J* = 10.4 Hz), 5.97 (s, 1H), 6.07 (s, 1H), 7.27 (d, 2H, *J* = 9.2 Hz), 7.50 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 20.1, 23.2 (d, *J* = 3.0 Hz), 23.3, 24.4 (d, *J* = 3.0 Hz), 30.8 (d, *J* = 9.0 Hz), 31.1 (d, *J* = 3.0 Hz), 31.2 (d, *J* = 1.0 Hz), 44.2 (d, *J* = 4.0 Hz), 44.6 (d, *J* = 2.0 Hz), 58.7, 59.4 (d, *J* = 9.0 Hz), 60.0 (d, *J* = 11.0 Hz), 117.3, 122.2, 127.0 (d, *J* = 5.0 Hz), 128.2, 130.1, 132.2, 139.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.91; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{33}BrN_4OP$ 479.1570, found 479.1549; $[M + Na]^+$ calcd for $C_{22}H_{32}BrN_4OPNa$ 501.1389, found 501.1389.

*2-((S)-[1,1′-Biphenyl]-4-yl(((3aR,7aR)-1,3-diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)methyl)acrylonitrile (**3n**).* White solid, 0.419 g, 88% yield; mp 196−198 °C; $[\alpha]_D^{25}$ = −50.5 (*c* = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, 3H, *J* = 6.4 Hz), 1.16−1.22 (m, 9H), 1.29−1.44 (m, 4H), 1.78 (d, 2H, *J* = 5.2 Hz), 2.06 (d, 2H, *J* = 9.6 Hz), 2.89−3.51 (m, 5H), 5.25 (t, 1H, *J* = 10.4 Hz), 5.99 (s, 1H), 6.07 (s, 1H), 7.36 (t, 1H, *J* = 7.2 Hz), 7.43−7.46 (m, 4H), 7.59 (t, 4H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0 (d, *J* = 9.0 Hz), 23.2 (d, *J* = 3.0 Hz), 23.3, 24.4 (d, *J* = 4.0 Hz), 30.9 (d, *J* = 9.0 Hz), 31.1, 31.2 (d, *J* = 2.0 Hz), 44.2 (d, *J* = 3.0 Hz), 44.6, 58.9, 59.3 (d, *J* = 9.0 Hz), 60.0 (d, *J* = 11.0 Hz), 117.6, 127.0, 127.2, 127.5 (d, *J* = 4.0 Hz), 127.6, 127.8, 128.9, 129.8, 139.1 (d, *J* = 2.0 Hz), 140.5, 141.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.03; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{38}N_4OP$ 477.2778, found 477.2778; $[M + Na]^+$ calcd for $C_{28}H_{37}N_4OPNa$ 499.2597, found 499.2603.

*2-((S)-(((3aR,7aR)-1,3-Diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(naphthalen-1-yl)methyl)acrylonitrile (**3o**).* White solid, 0.396 g, 88% yield; mp 224−226 °C; $[\alpha]_D^{20}$ = −34.6 (*c* = 0.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, 3H, *J* = 6.8 Hz), 1.04 (t, 6H, *J* = 6.4 Hz), 1.10 (d, 3H, *J* = 6.8 Hz), 1.22−1.32 (m, 4H), 1.74 (d, 2H, *J* = 6.8 Hz), 2.10 (t, 2H, *J* = 9.6 Hz), 2.78 (t, 1H, *J* = 8.8 Hz), 2.94 (t, 1H, *J* = 9.6 Hz), 3.18−3.29 (m, 1H), 3.29−3.47 (m, 2H), 5.94−6.00 (m, 2H), 6.04 (s, 1H), 7.48−7.57 (m, 3H), 7.63 (d, 1H, *J* = 6.8 Hz), 7.82 (d, 1H, *J* = 8.0 Hz), 7.87 (d, 1H, *J* = 8.0 Hz), 8.08 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 19.9 (d, *J* = 2.0 Hz), 23.2, 23.2 (d, *J* = 3.0 Hz), 24.4, 29.8, 30.9 (d, *J* = 10.0 Hz), 31.2 (d, *J* = 11.0 Hz), 44.0 (d, *J* = 4.0 Hz), 44.3 (d, *J* = 3.0 Hz), 54.8, 59.3 (d, *J* = 10.0 Hz), 60.0 (d, *J* = 12.0 Hz), 117.7, 123.0, 124.6, 125.5, 126.1, 126.7, 127.2 (d, *J* = 7.0 Hz), 129.1, 129.2, 130.1 (d, *J* = 4.0 Hz), 134.1, 136.3 (d, *J* = 3.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.03; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{36}N_4OP$ 451.2621, found 451.2621; $[M + Na]^+$ calcd for $C_{26}H_{35}N_4OPNa$ 473.2441, found 473.2441.

*2-((S)-(((3aR,7aR)-1,3-Diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(naphthalen-2-yl)methyl)acrylonitrile (**3p**).* White solid, 0.392 g, 87% yield; mp 202−203 °C; $[\alpha]_D^{25}$ = −41.9 (*c* = 1.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, 3H, *J* = 6.8 Hz), 1.15−1.22 (m, 9H), 1.26−1.41 (m, 4H), 1.78 (d, 2H, *J* = 6.8 Hz), 2.04−2.07 (m, 2H), 2.82−3.20 (m, 3H), 3.29−3.53 (m, 2H), 5.38 (t, 1H, *J* = 10.0 Hz), 6.00 (s, 1H), 6.09 (s, 1H), 7.42−7.44 (m, 1H), 7.47−7.52 (m, 2H), 7.82−7.86 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 20.1, 23.3 (d, *J* = 3.0 Hz), 23.4 (d, *J* = 7.0 Hz), 24.5 (d, *J* = 4.0 Hz), 30.9 (d, *J* = 9.0 Hz), 31.2 (d, *J* = 12.0 Hz), 44.2 (d, *J* = 3.0 Hz), 44.6 (d, *J* = 1.0 Hz), 59.3, 59.4, 60.1 (d, *J* = 11.0 Hz), 117.6, 124.3, 125.3, 126.5, 126.7, 127.5 (d, *J* = 4.0 Hz), 127.8, 128.2, 129.1, 130.0, 133.1, 133.4, 137.4 (d, *J* = 3.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.01; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{36}N_4OP$ 451.2621, found 451.2622; $[M + Na]^+$ calcd for $C_{26}H_{35}N_4OPNa$ 473.2441, found 473.2441.

*2-((R)-(((3aR,7aR)-1,3-Diisopropyl-2-oxidohexahydro-1H-benzo[d][1,3,2]diazaphosphol-2(3H)-yl)amino)(thiophen-2-yl)methyl)acrylonitrile (**3q**).* Colorless crystal, 0.354 g, 87% yield; mp 144−146 °C; $[\alpha]_D^{20}$ = −33.9 (*c* = 0.95, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, 6H, *J* = 6.4 Hz), 1.24−1.26 (m, 7H), 1.32−1.40 (m, 3H), 1.77 (d, 2H, *J* = 7.6 Hz), 2.07 (d, 2H, *J* = 6.4 Hz), 2.85−2.87 (m, 1H), 2.98 (t, 1H, *J* = 9.2 Hz), 3.39−3.56 (m, 2H), 5.45 (t, 1H, *J* = 9.6 Hz), 6.01 (s, 1H), 6.06 (s, 1H), 6.98−7.10 (m, 2H), 7.26−7.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0 (d, *J* = 9.0 Hz), 23.4 (d, *J* = 3.0 Hz), 23.5 (d, *J* = 6.0 Hz), 24.4 (d, *J* = 6.0 Hz), 31.0 (d, *J* = 9.0 Hz), 31.3 (d, *J* = 1.0 Hz), 44.2, 44.7, 55.8, 59.3 (d, *J* = 9.0 Hz), 59.9 (d, *J* = 10.0 Hz), 117.2, 125.1, 125.6, 126.9, 127.4, 130.3, 144.2 (d, *J* = 3.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.46; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{32}N_4OPS$ 407.2029, found 407.2028; $[M + Na]^+$ calcd for $C_{20}H_{31}N_4OPSNa$ 429.1848, found 429.1848.

Removal of *N*-Phosphonyl Group Followed by in Situ *t*-Boc Protection. In a 25 mL round-bottom flask, 0.215 g (0.5 mmol) of aza-MBH adduct **3g** was dissolved in 7.5 mL of methanol. To this solution was added 0.84 mL of 48% aq HBr (10.0 equiv), and the reaction mixture was stirred overnight at room temperature. After complete conversion of **3g** was observed by TLC, volatiles were evaporated under vacuum at 60 °C and dried overnight under high vacuum to obtain a crude solid. The solid was dissolved in 10.0 mL of dichloromethane, and then the suspension was cooled to 0 °C. At this temperature, triethylamine (0.42 mL, 3.0 mmol) and di-*tert*-butyl dicarbonate (0.436 g, 2.0 mmol) were added to the resulting mixture, and the reaction mixture was stirred overnight. The reaction mixture

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was concentrated, and the pure product **5** (0.117 g, 81%) was obtained as a colorless solid in accordance with the former literature.[3,19] Mp 82−84 °C; $[\alpha]_D^{20}$ = −49.8 (*c* = 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 3.80 (s, 3H), 5.04−5.05 (m, 1H), 5.33 (d, 1H, *J* = 4.0 Hz), 5.98 (d, 1H, *J* = 1.2 Hz), 6.05 (d, 1H, *J* = 0.8 Hz), 6.88−6.92 (m, 2H), 7.23 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 55.4, 57.0, 80.7, 114.6, 117.3, 124.8, 128.3, 129.3, 130.5 (d, *J* = 1.0 Hz), 154.6, 159.9. These NMR data match those found in the literature.[20] Chiral HPLC (CHIRALPAK ID column; hexane/*i*-PrOH, v/v = 80/20; 1.0 mL/min, 236 ± 4 nm), t_R(minor) = 10.6 min, t_R(major) = 12.3 min, 99.1% ee. In this process, 90% of the GAP auxiliary (0.089 g) can be recovered for reuse.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00049.

^{1}H and ^{13}C NMR spectra for all pure products (PDF)

X-ray crystal data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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