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A Reagent-Controlled Phospha-Michael Addition Reaction of Nitroalkenes with Bifunctional N-Heterocyclic Phosphine (NHP)-Thioureas

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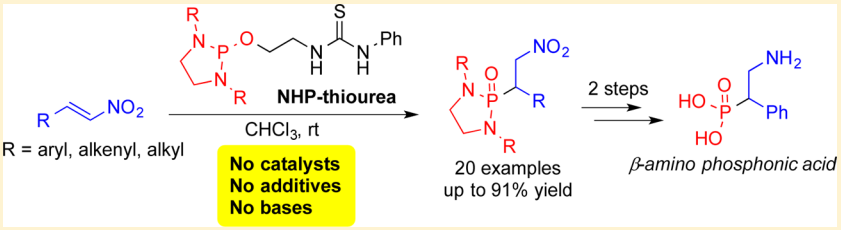
Supporting Information



ABSTRACT: Bifunctional N-heterocyclic phosphine (NHP)-thioureas have been successfully applied for phospha-Michael addition reaction of nitroalkenes to afford diversely substituted β-nitrodiazaphosphonates. This transformation takes place at room temperature under catalyst-free conditions and exhibits broad functional group tolerance. The key to success in catalyst, additive-free reaction conditions is the suitable hydrogen-bond activation of the nitro group by a Brønsted acid (thiourea), which artfully combined with the highly nucleophilic NHP motif for a synergetic effect. Importantly, this transformation enables a two-step synthesis of pharmaceutically, biologically significant β-amino phosphonic acids.

INTRODUCTION

β-Aminophosphonates and their phosphonic acid derivatives have received significant attention in recent years because of their unique biological properties and broad pharmaceutical applications (Figure 1).[1] They are widely used in medicine and drug applications as *N*-methyl-D-aspartate (NMDA) receptor antagonists (**a**, **b**, **c**).[2] In addition, they exhibit a wide range of enzyme inhibitions such as imidazole glycerol phosphate dehydratase inhibitors (**d**)[3] and norstatine renin inhibitors (**e**).[4] Therefore, the development of mild and efficient methods for the synthesis of β-aminophosphonate derivatives is necessitated and currently attracting growing interest.[5]

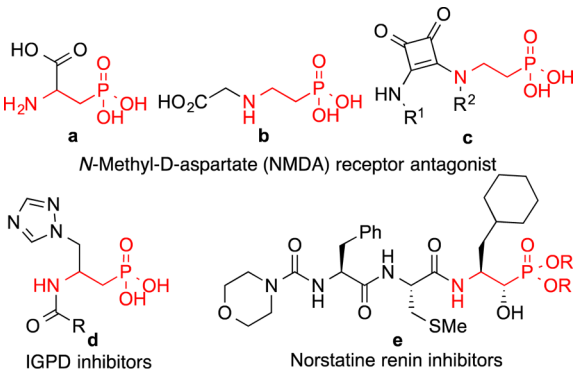


Figure 1. Biologically active and pharmaceutically important β-aminophosphonates and their derivatives.

Among the various synthetic methods for β-aminophosphonates,[1a] the phospha-Michael reaction of nitroalkenes with dialkyl phosphonates or trialkyl phosphites[6] provides a practical and straightforward route to the β-aminophosphonates, which can be readily transformed from the corresponding Michael adduct of the β-nitrophosphonates, after a simple reduction of the nitro group.[7] In addition, this method allows the construction of many different products available with various substitution patterns, relying on both the diverse Michael acceptors and donors.

For a successful development of this transformation, three main hurdles should be addressed jointly, with efforts to promote more efficient, mild reaction conditions: (i) activation of the nitroalkene Michael acceptor, (ii) facilitation of the equilibrium between reactive phosphite and unreactive phosphonate form in favor of the former, (iii) nucleophile additives for the transformation of P(III) to P(V). Since the pioneering early investigation by Pudovik in 1979, various reaction conditions of the phospha-Michael reaction of nitroalkenes have been developed over the past decades.

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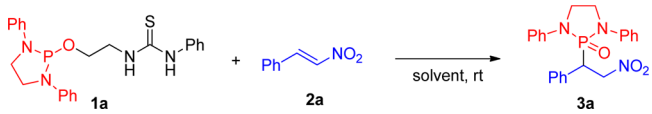
Terada[7c] and Zhao[8] groups independently reported a Brønsted acid-catalyzed phospha-Michael reaction of nitroalkenes with diphenylphosphites in which a hydrogen-bond activation of the nitroalkene Michael acceptor was established by thiourea or guanidine groups, and additionally molecular sieves were added to achieve the equilibrium in favor of the phosphite form in situ. On the other hand, the desired equilibrium toward a reactive phosphite form was accomplished through a hydrogen-bond activation of the unreactive phosphonate form by a tertiary amine group tethered to a Brønsted acid, reported by Rawal,[9] Wang,[7b] Herrera,[10] Nagasaw,[11] and Zlotin,[12] separately. This strategy using the bifunctional amino Brønsted acids does not require the use of molecular sieves for the favored equilibrium, providing simpler reaction conditions. Similarly, Lewis acid-catalyzed phospha-Michael reaction reported by Namboothiri demonstrated molecular sieve-free reaction conditions.[13] Other methods to achieve this phospha-Michael reaction of nitroalkenes use amines as bases,[14] auxiliaries requiring extra synthetic steps,[15] LiI as external nucleophiles,[16] or elevated reaction temperatures for inducing the reactive phosphite nucleophiles.[17] Despite great efforts devoted to the synthesis of pharmaceutically, biologically significant β-nitrophosphonate derivatives, there are limitations such as harsh reaction conditions (strong bases, high reaction temperatures) and requirements of external nucleophiles, additives, or catalysts. In addition, to the best of our knowledge, there is no efficient method available for the synthesis of β-nitrophosphonates under catalyst, additive free-reaction conditions at mild room temperature.[7b,9−12,16] With our recently developed N-heterocyclic phosphine (NHP)-thioureas as novel bifunctional phosphonylation reagents,[18] we envisioned that this phospha-Michael reaction of nitroalkenes would precede without additives or catalysts under mild reaction conditions. Herein, we report a NHP-thiourea-promoted phospha-Michael/intramolecular nucleophilic substitution reaction of nitroalkenes for the synthesis of β-nitrophosphonates as a simple and mild route.

RESULTS AND DISCUSSION

To test our hypothesis, NHP-thiourea **1a** and (*E*)-(2-nitrovinyl)benzene **2a** were used as model substrates to screen for optimal reaction conditions described in Table 1. The initial solvent studies revealed that the halogenated solvent ($CHCl_3$) proved to be superior to the nonhalogenated solvents and polar solvents (entry 2 vs entries 6−7), providing 64% yield of the desired products without additives or catalysts. A slight increment of the ratio of Michael acceptor **2a** helped to improve the product yield (entry 8, 75%). The reaction under reflux conditions provided 71% yield (entry 9). A significant improvement in reactivity for this phospha-Michael reaction was observed in higher solvent concentration conditions, which also reduced the reaction time drastically (entry 10, 91%, 4 h).

Next, we investigated the effect of a Brønsted acid motif on the intramolecular nucleophilic substitution reaction process of this phospha-Michael reaction (Table 2). The parent NHP-thiourea **1a** generated the phospha-Michael adduct **3a** in 91% yield (entry 1). Further optimization studies of the bifunctional NHPs disclosed that the tether length between the NHP motif and a Brønsted acid has a direct influence on the effective hydrogen-bond activation of the nitro group. NHPs with a lengthy tether reduced the efficiency of this transformation, resulting in the lower product yields (entry 1 vs entries 2−3). For instance, a drastic decrement of the product yield was

Table 1. Optimization of Reaction Conditions[a]



entry	ratio (**1a**:**2a**)	solvent	time (h)	yield (%)[b]
1	1:1	DCM	18	54
2	1:1	$CHCl_3$	18	64
3	1:1	DCE	18	49
4	1:1	Et_2O	18	55
5	1:1	toluene	18	50
6	1:1	THF	18	23
7	1:1	CH_3CN	18	43
8	1:1.2	$CHCl_3$	18	75
9[c]	1:1.2	$CHCl_3$	18	71
10[d]	1:1.2	$CHCl_3$	4	91

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.1−0.12 mmol), and solvent (0.5 mL) for 4−18 h. [b]Isolated yield (%). [c]Under reflux conditions. [d]0.3 mL solvent was used.

observed with the NHP-thiourea having a four-carbon length tether (entry 3). In addition, the electronic effects of the thiourea motif on this substitution reaction were also investigated. NHPs with a strongly electron-donating group (4-methoxyphenyl thiourea, **1d**) and an electron-withdrawing group (3,5-bis(trifluoromethyl)phenyl, **1e**) on the thiourea moiety were subjected to the standard reaction conditions, yet both of them showed inferior results than that of the parent NHP-thiourea **1a** (entry 1 vs entries 4−5). These outcomes clearly showed an important relationship between a suitable hydrogen-bond activation of the nitroalkenes by a Brønsted acid and the nucleophilicity of an in situ-generated anionic thiourea intermediate for the intramolecular nucleophilic substitution reaction. Having a methyl substituent on the nitrogen atom of the Brønsted acid motif such as *N*-methyl thiourea **1f** and *N*-methyl amide **1g**, the reaction efficiency was significantly reduced (entries 6−7), seemingly owing to the obstructing of intramolecular nucleophilic substitution reaction course. Finally, it should be noted that the replacement of a thiourea group with a sulfonic acid amide totally reduced the reaction efficiency, which reveals the critical role of thiourea group in this Michael addition reaction (entry 8).

Having the optimized reaction conditions, we studied the scope of this reaction by treating NHP-thioureas with nitroalkenes (Table 3). First, it is worth mentioning that this reaction can be easily scaled up (2.0 mmol) with an excellent yield of the target product (**3a**, 95%). Next, the study of electronic and steric effects of the NHP motif on this transformation was performed under the standard reaction conditions. While the electronics have a negligible influence (**3b**, **3c**), the steric effects of the *ortho*-substituents on the NHP motif **1k** suppressed the reaction completely (**3d**). Gratifyingly, this phospha-Michael addition reaction tolerated a wide range of functional groups on the nitroalkenes including electron-donating groups (**3e**−**3g**) and electron-withdrawing groups (**3h**−**3k**) and provided good to high yields. Nitroalkenes with disubstituted phenyl groups were also viable substrates for this phospha-Michael reaction and afforded the corresponding β-nitrodiazaphosphonates in high yields (**3n**, **3o**). Heteroaromatic nitroalkenes also succeeded in producing the desired adduct in 56−57% yields (**3p**, **3q**). Aliphatic nitroalkenes such as (*E*)-(2-nitrovinyl)cyclohexane **2r**, (*E*)-1-nitropent-1-ene **2s**,

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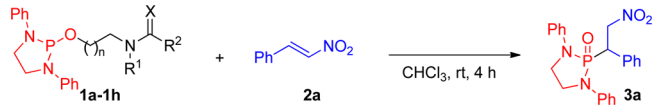
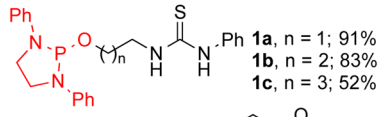
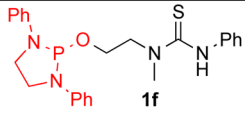
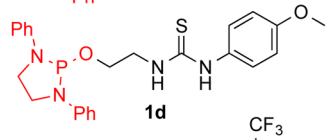
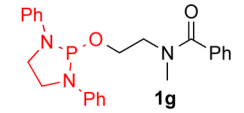
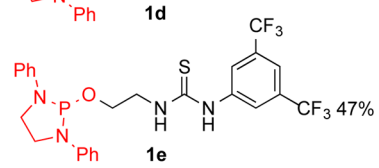
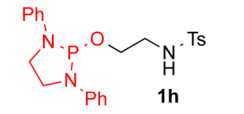
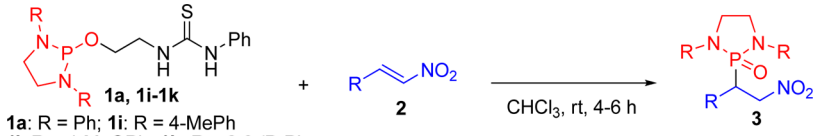
Table 2. Scope of NHP-Thioureas[a]



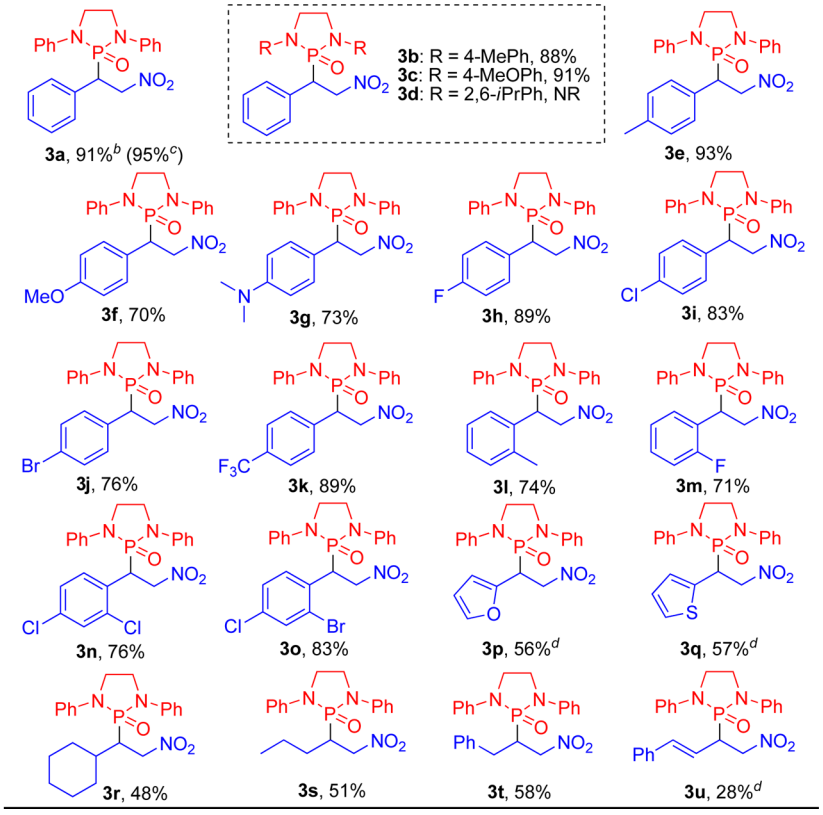
entry	NHP	3a yield (%)[b]	entry	NHP	3a yield (%)[b]
1		**1a**, n = 1; 91%	6		40%
2		**1b**, n = 2; 83%		**1f**	
3		**1c**, n = 3; 52%			
4	 **1d**	58%	7	 **1g**	0%
5	 **1e**	47%	8	 **1h**	trace

[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.12 mmol), and $CHCl_3$ (0.3 mL) at rt for 4 h. [b]Isolated yield (%).

Table 3. Scope of Nitroalkenes and NHP-Thioureas for Phospha-Michael Reaction[a]



1a: R = Ph; **1i**: R = 4-MePh
1j: R = 4-MeOPh; **1k**: R = 2,6-*i*PrPh



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), and $CHCl_3$ (0.3 mL) at rt for 4 h. [b]Isolated yield (%). [c]Scale-up experiment with 2.0 mmol of **1a**. [d]Reaction run for 6 h.

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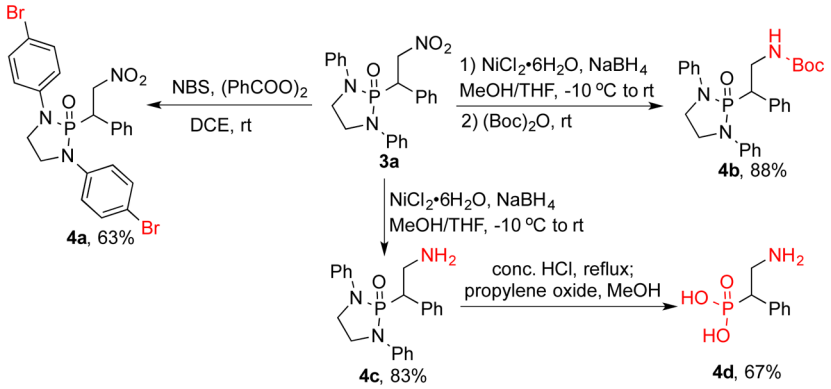
Scheme 1. Synthetic Manipulations of Phospha-Michael Adduct 3a

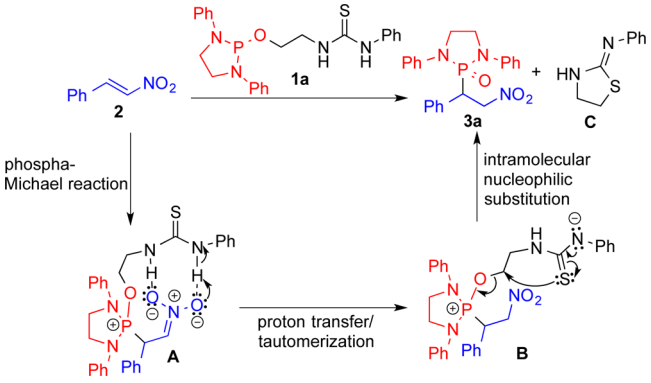


and (*E*)-(3-nitroallyl)benzene **2t** also proved to be useful substrates under the standard reaction conditions (**3r**–**3t**). Finally, highly conjugated nitroalkenes, ((1*E*,3*E*)-4-nitrobuta-1,3-dien-1-yl)benzene **2u**, furnished an allylphosphonate compound **3u** in an acceptable yield (28%).

We next explored the synthetic utilities of the phospha-Michael adducts (Scheme 1). The regioselective bromination of electron-rich aromatic ring **3a** was performed using NBS and benzoyl peroxide in which only the *N*-aryl-brominated product **4a** was obtained in 63% yield. The reduction of a nitro group to an amine was achieved under the modified nickel boride conditions, and this method afforded a *N*-Boc-protected *β*-amino diazaphosphonate **4b** in 88% yield and a primary *β*-amino diazaphosphonate **4c** in 83% yield.[10] Gratifyingly, hydrolysis of **4c** furnished a *β*-amino phosphonic acid **4d** in 67% yield under conc. HCl conditions.[19]

On the basis of experimental observations and our previous works,[18] a rational mechanism for the formation of **3** is depicted in Scheme 2. The Michael addition of NHP-thiourea

Scheme 2. A Proposed Mechanism



1a to nitroalkene **2** activated through a hydrogen bonding with a thiourea motif generates a diazaphosphonium intermediate **A**. Following the sequential proton transfer/tautomerization process furnishes an anionic thiourea intermediate **B**. The anionic thiourea-initiated intramolecular nucleophilic substitution reaction responses to the formation of *β*-nitrodiazaphosphonate **3a** and thiazolidine byproduct **C**.

CONCLUSIONS

In summary, bifunctional NHP-thioureas recently developed in our laboratory have been successfully applied in phospha-Michael reaction of nitroalkenes to afford a variety of substituted *β*-nitrodiazaphosphonates. This work is the first example of phospha-Michael reaction of nitroalkenes with bifunctional NHP-thiourea by combining a phosphonylation reagent with Brønsted acid motif, which demonstrated a synergetic effect to achieve mild reaction conditions (catalyst-, nucleophile additive-, and base-free reaction conditions at room temperature). In addition, synthetic manipulations of the Michael adduct demonstrated an easy access to a *para*-selective aryl bromination product **4a** and reductive amination compounds **4b**, **4c**. Importantly, a three-step synthesis of a pharmaceutically valuable *β*-amino phosphonic acid **4d** was achieved using this method. Further studies on the efficient enantioselective phospha-Michael reaction of nitroalkenes with chiral bifunctional NHP-thioureas are underway and will be reported in due course.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under atmospheric conditions in oven-dried glassware with magnetic stirring bar. Dry solvents (THF, toluene, and DCM) were obtained by solvent purification system under argon. All commercially available reagents were used as received without further purification. Purification of reaction products was carried out by flash column chromatography using silica gel 60 (230–400 mesh). Analytical thin-layer chromatography was performed on 0.25 mm aluminum-backed silica gel 60-F plates. Visualization was accompanied by UV light and $KMnO_4$ solution. Concentration under reduced pressure refers to the removal of volatiles using a rotary evaporator attached to a dry diaphragm pump (10–15 mmHg), followed by pumping to a constant weight with an oil pump (<300 mTorr). Infrared (IR) spectra were recorded on an IR spectrometer with KBr wafers or a film on KBr plate. High-resolution mass spectra (HRMS) were recorded on LCMS-IT-TOF mass spectrometer using electrospray ionization (ESI). ^{1}H NMR spectra were recorded in $CDCl_3$ on 400 MHz NMR spectrometer. The ^{1}H chemical shifts are referenced to residual solvent signals at δ 7.26 ($CHCl_3$) or δ 0.00 (TMS). ^{1}H NMR coupling constants (*J*) are reported in Hertz (Hz), and multiplicities are indicated as follows: s (singlet), bs (broad singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), and ddd (doublet of doublet of doublets). ^{13}C NMR spectra were proton decoupled and recorded in $CDCl_3$ on 100.5 MHz NMR spectrometer. The ^{13}C chemical shifts are referenced to solvent signals at δ 77.16 ($CDCl_3$). ^{31}P NMR spectra were proton decoupled and recorded in $CDCl_3$ on 162 MHz NMR spectrometer. ^{31}P chemical shifts are reported relative to 85% H_3PO_4 (0.00 ppm) as an external standard.

General Procedure for the Synthesis of NHP-Thioureas 1. NHP-Thioureas **1** were synthesized and characterized according to our previously reported methodology.[18a] To a solution of 2-chloro-1,3-diphenyl-1,3,2-diazaphospholidine[20] (1.00 g, 3.62 mmol) in DCM (25

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mL) were added 1-(2-hydroxyethyl)-3-phenylthiourea[21] (0.711 g, 3.62 mmol) and triethylamine (0.438 g, 4.34 mmol) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 2 h. After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (gradient eluent of Hexanes:EtOAc: 7/1 to 5/1) to give colorless crystalline solid **1a**.

General Procedure for the Phospha-Michael Reaction of Nitroalkenes with NHP-Thioureas. NHP-thioureas **1** (0.1 mmol) and nitroalkenes **2** (0.12 mmol) were dissolved in $CHCl_3$ (0.3 mL) in a 2 dram vial. The resulting mixture was stirred for 4 h at room temperature. After stirring for 4 h, the volatiles were removed under reduced pressure. The residue was subjected to column chromatography on silica gel to give corresponding products **3**.

*2-(2-Nitro-1-phenylethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3a**).* 37.0 mg, 91% yield; white solid; mp 150 °C (decomp.); R_f 0.20 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3061, 2958, 2858, 1599, 1554, 1498, 1375, 1269, 1230, 1124, 958; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.37 (m, 4 H), 7.34−7.29 (m, 4 H), 7.28−7.12 (m, 5 H), 6.75−6.70 (m, 2 H), 5.28 (ddd, J = 4.0, 7.6, 12.0 Hz, 1 H), 4.90 (ddd, J = 4.4, 11.8, 15.0 Hz, 1 H), 4.78 (ddd, J = 4.0, 14.8, 21.6 Hz, 1 H), 3.53−3.37 (m, 2 H), 2.93−2.85 (m, 1 H), 2.80−2.72 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 141.2 (dd, J = 74.4, 8.2 Hz), 132.0 (d, J = 7.4 Hz), 129.8 (d, J = 5.2 Hz), 128.6 (d, J = 3.7 Hz), 128.3 (d, J = 3.7 Hz), 128.2 (d, J = 5.2 Hz), 123.0 (d, J = 44.6 Hz), 117.1 (dd, J = 63.3, 4.5 Hz), 74.6 (d, J = 5.9 Hz), 45.8 (d, J = 102.7 Hz), 43.7 (d, J = 8.2 Hz), 42.6 (d, J = 8.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.7 ppm; HRMS (ESI^+): m/z calcd for $C_{22}H_{22}N_3O_3P$ $[M + Na]^+$: 430.1291; Found: 430.1293.

*2-(2-Nitro-1-phenylethyl)-1,3-di-p-tolyl-1,3,2-diazaphospholidine 2-Oxide (**3b**).* 38.2 mg, 88% yield; white solid; mp 155 °C (decomp.); R_f 0.20 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3032, 2960, 2918, 2877, 1618, 1554, 1514, 1473, 1375, 1363, 1269, 1234, 964; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.17 (m, 11 H), 6.77−6.72 (m, 2 H), 5.24 (ddd, J = 3.6, 7.4, 12.2 Hz, 1 H), 4.88 (ddd, J = 4.4, 11.8, 15.0 Hz, 1 H), 4.55 (ddd, J = 3.6, 14.6, 21.4 Hz, 1 H), 3.49−3.33 (m, 2 H), 2.89−2.81 (m, 1 H), 2.80−2.72 (m, 1 H), 2.37 (s, 6 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 138.7 (dd, J = 69.9, 8.1 Hz), 132.5 (d, J = 48.3 Hz), 132.2 (d, J = 6.7 Hz), 130.3 (d, J = 3.0 Hz), 128.5 (d, J = 3.0 Hz), 128.3 (d, J = 5.2 Hz), 128.2 (d, J = 3.7 Hz), 117.4 (dd, J = 63.3, 3.8 Hz), 74.7 (d, J = 5.9 Hz), 45.7 (d, J = 102.7 Hz), 44.0 (d, J = 8.2 Hz), 42.9 (d, J = 9.0 Hz), 20.7 (d, J = 2.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.1 ppm; HRMS (ESI^+): m/z calcd for $C_{24}H_{26}N_3O_3P$ $[M + Na]^+$: 458.1604; Found: 458.1605.

*1,3-Bis(4-methoxyphenyl)-2-(2-nitro-1-phenylethyl)-1,3,2-diazaphospholidine 2-Oxide (**3c**).* 42.4 mg, 91% yield; white solid; mp 185 °C (decomp.); R_f 0.16 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (1/1/4) for column; IR ν (KBr, cm^{-1}) 3007, 2960, 2910, 2839, 1556, 1510, 1458, 1375, 1273, 1244, 1188, 1031, 962; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.19 (m, 7 H), 6.95 (tt, J = 9.2, 2.4 Hz, 4 H), 6.81−6.77 (m, 2 H), 5.17 (ddd, J = 4.0, 7.6, 12.4 Hz, 1 H), 4.81 (ddd, J = 4.4, 11.8, 15.0, Hz, 1 H), 4.46 (ddd, J = 3.6, 14.2, 21.4 Hz, 1 H), 3.85 (d, J = 1.2 Hz, 6 H), 3.46−3.33 (m, 2 H), 2.90−2.80 (m, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 155.8 (d, J = 21.6 Hz), 134.3 (dd, J = 61.0, 8.2 Hz), 132.3 (d, J = 6.7 Hz), 128.5 (d, J = 3.0 Hz), 128.4 (d, J = 5.2 Hz), 128.2 (d, J = 3.7 Hz), 119.6 (dd, J = 69.2, 3.8 Hz), 115.0 (d, J = 8.2 Hz), 74.7 (d, J = 5.3 Hz), 55.5 (d, J = 3.7 Hz), 45.7 (d, J = 103.4 Hz), 44.9 (d, J = 8.2 Hz), 43.8 (d, J = 8.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.9 ppm; HRMS (ESI^+): m/z calcd for $C_{24}H_{26}N_3O_5P$ $[M + Na]^+$: 490.1502; Found: 490.1511.

*2-(2-Nitro-1-(p-tolyl)ethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3e**).* 39.1 mg, 93% yield; white solid; mp 168 °C (decomp.); R_f 0.20 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3061, 2916, 2893, 1599, 1554, 1498, 1371, 1269, 1236, 1120, 958; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.37 (m, 4 H), 7.34−7.29 (m, 4 H), 7.15−7.11 (m, 2 H), 7.00 (d, J = 8.4 Hz, 2 H), 6.60 (dd, J = 8.0, 2.4 Hz, 2 H), 5.26 (ddd, J = 3.6, 7.4, 12.2 Hz, 1 H), 4.87 (ddd, J = 4.4, 11.8, 15.0 Hz, 1 H), 4.56 (ddd, J = 3.6, 14.6, 21.4 Hz, 1 H), 3.53−3.37 (m, 2 H), 2.95−2.87 (m, 1 H), 2.84−2.78 (m, 1 H), 2.29 (d, J = 2.4 Hz, 3 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 141.3 (dd, J = 75.9, 8.9 Hz), 138.2 (d, J = 3.7 Hz), 129.8 (d, J = 4.5 Hz), 129.3 (d, J = 2.9 Hz), 128.8 (d, J = 6.7 Hz), 128.1 (d, J = 5.9 Hz), 122.9 (d, J = 43.2 Hz), 117.1 (dd, J = 61.0, 4.4 Hz), 74.8 (d, J = 6.0 Hz), 44.4 (d, J = 103.4 Hz), 43.7 (d, J = 8.2 Hz), 42.6 (d, J = 8.2 Hz), 21.1; ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.8 ppm; HRMS (ESI^+): m/z calcd for $C_{23}H_{24}N_3O_3P$ $[M + Na]^+$: 444.1447; Found: 444.1441.

*2-(1-(4-Methoxyphenyl)-2-nitroethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3f**).* 30.8 mg, 70% yield; white solid; mp 174 °C (decomp.); R_f 0.20 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3061, 2957, 2891,1600, 1554, 1512, 1373, 1273, 1255, 1226, 1180, 1035, 958; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.37 (m, 4 H), 7.32 (t, J = 8.4 Hz, 4 H), 7.17−7.11 (m, 2 H), 6.75−6.70 (m, 2 H), 6.66−6.61 (m, 2 H), 5.26 (ddd, J = 3.6, 7.4, 11.8 Hz, 1 H), 4.83 (ddd, J = 4.4, 11.8, 15.0 Hz, 1 H), 4.53 (ddd, J = 3.6, 14.6, 21.0 Hz, 1 H), 3.76 (s, 6 H), 3.54−3.39 (m, 2 H), 3.06−2.95 (m, 1 H), 2.98−2.82 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 159.5 (d, J = 2.9 Hz), 141.3 (dd, J = 76.6, 8.9 Hz), 129.8 (d, J = 3.0 Hz), 129.4 (d, J = 5.2 Hz), 123.7 (d, J = 6.7 Hz), 122.9 (d, J = 42.4 Hz), 117.1 (dd, J = 58.8, 4.5 Hz), 114.0 (d, J = 3.0 Hz), 74.9 (d, J = 7.4 Hz), 55.2, 45.0 (d, J = 104.9 Hz), 43.7 (d, J = 8.2 Hz), 42.6 (d, J = 8.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.1 ppm; HRMS (ESI^+): m/z calcd for $C_{23}H_{24}N_3O_4P$ $[M + Na]^+$: 460.1397; Found: 460.1389.

*2-(1-(4-(Dimethylamino)phenyl)-2-nitroethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3g**).* 32.9 mg, 73% yield; white solid; mp 146 °C (decomp.); R_f 0.14 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (3/1/1) for column; IR ν (KBr, cm^{-1}) 3059, 2951, 2891, 1618, 1599, 1552, 1527, 1375, 1269, 1230, 1122, 956; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.37 (m, 4 H), 7.36−7.29 (m, 4 H), 7.15−7.10 (m, 2 H), 6.59−6.48 (m, 4 H), 5.24 (ddd, J = 3.6, 7.4, 11.8 Hz, 1 H), 4.82 (ddd, J = 4.4, 11.0, 15.0 Hz, 1 H), 4.48 (ddd, J = 3.6, 14.2, 21.0 Hz, 1 H), 3.52−3.38 (m, 2 H), 3.00−2.86 (m, 2 H), 2.91 (s, 6 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 150.2 (d, J = 2.2 Hz), 141.5 (dd, J = 76.7, 8.9 Hz), 129.7 (d, J = 2.2 Hz), 129.0 (d, J = 5.2 Hz), 122.7 (d, J = 41.0 Hz), 118.7 (d, J = 7.5 Hz), 117.0 (dd, J = 55.8, 4.8 Hz), 112.1 (d, J = 2.2 Hz), 75.0 (d, J = 7.4 Hz), 45.0 (d, J = 104.2 Hz), 43.6 (d, J = 7.5 Hz), 42.5 (d, J = 8.2 Hz), 40.3; ^{31}P NMR (162 MHz, $CDCl_3$): δ 26.1 ppm; HRMS (ESI^+): m/z calcd for $C_{24}H_{27}N_4O_3P$ $[M + Na]^+$: 473.1713; Found: 473.1710.

*2-(1-(4-Fluorophenyl)-2-nitroethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3h**).* 37.8 mg, 89% yield; white solid; mp 162 °C (decomp.); R_f 0.20 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3066, 2951, 2893, 1599, 1554, 1500, 1477, 1373, 1267, 1232, 1161, 1124, 1105, 956; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.38 (m, 4 H), 7.35−7.29 (m, 4 H), 7.19−7.13 (m, 2 H), 6.91 (t, J = 8.4 Hz, 2 H), 6.73−6.67 (m, 2 H), 5.28 (ddd, J = 2.8, 4.6, 7.8 Hz, 1 H), 4.84 (ddd, J = 4.4, 12.2, 15.0 Hz, 1 H), 4.57 (ddd, J = 3.6, 14.6, 21.4 Hz, 1 H), 3.58−3.43 (m, 2 H), 3.02−2.93 (m, 1 H), 2.92−2.84 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 162.4 (dd, J = 247.0, 3.7 Hz), 141.1 (dd, J = 75.9, 8.9 Hz), 130.0, 129.9 (d, J = 3.7 Hz), 127.9 (dd, J = 4.6, 2.3 Hz), 123.2 (d, J = 42.5 Hz), 117.2 (dd, J = 59.5, 4.4 Hz), 115.2 (dd, J = 21.6, 3.0 Hz), 74.8 (d, J = 6.7 Hz), 45.0 (d, J = 104.2 Hz), 43.9 (d, J = 8.2 Hz), 42.8 (d, J = 8.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.3 ppm; HRMS (ESI^+): m/z calcd for $C_{22}H_{21}FN_3O_3P$ $[M + Na]^+$: 448.1197; Found: 448.1200.

*2-(1-(4-Chlorophenyl)-2-nitroethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3i**).* 36.7 mg, 83% yield; white solid; mp 172 °C (decomp.); R_f 0.22 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3063, 2947, 2895, 1599, 1554, 1491, 1475, 1369, 1267, 1232, 1124, 956; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.38 (m, 4 H), 7.35−7.28 (m, 4 H), 7.22−7.13 (m, 4 H), 6.69−6.63 (m, 2 H), 5.26 (ddd, J = 3.6, 7.4, 12.2 Hz, 1 H), 4.83 (ddd, J = 4.4, 11.8, 14.6 Hz, 1 H), 4.56 (ddd, J = 3.6, 14.6, 21.4 Hz, 1 H), 3.58−3.42 (m, 2 H), 3.04−2.95 (m, 1 H), 2.93−2.85 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 141.0 (dd, J = 75.2, 8.2 Hz), 134.3 (d, J = 4.4 Hz), 130.7 (d, J = 6.7 Hz), 129.9 (d, J = 3.8 Hz), 129.6 (d, J = 5.2 Hz), 128.9 (d, J = 2.9 Hz), 123.2 (d, J = 43.2 Hz), 117.2 (dd, J = 60.2, 4.4 Hz), 74.6 (d, J = 6.0 Hz), 45.2 (d, J = 103.4 Hz), 44.0 (d, J = 8.2 Hz), 42.8 (d, J = 8.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.6 ppm; HRMS (ESI^+): m/z calcd for $C_{22}H_{21}ClN_3O_3P$ $[M + Na]^+$: 464.0901; Found: 464.0911.

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*2-(1-(4-Bromophenyl)-2-nitroethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3j**).* 36.9 mg, 76% yield; white solid; mp 167 °C (decomp.); R_f 0.22 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3059, 2918, 2893, 159, 1554, 1500, 1477, 1371, 1265, 1228, 1120, 956; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.38 (m, 4 H), 7.36−7.28 (m, 6 H), 7.18−7.13 (m, 2 H), 6.62−6.57 (m, 2 H), 5.26 (ddd, J = 3.6, 7.4, 12.6 Hz, 1 H), 4.83 (ddd, J = 4.4, 11.8, 15.0 Hz, 1 H), 4.55 (ddd, J = 4.0, 14.4, 21.2 Hz, 1 H), 3.58−3.42 (m, 2 H), 3.04−2.95 (m, 1 H), 2.93−2.85 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 141.0 (dd, J = 75.2, 8.2 Hz), 131.8 (d, J = 3.0 Hz), 131.2 (d, J = 6.7 Hz), 129.9 (d, J = 3.8 Hz), 129.8 (d, J = 59 Hz), 123.2 (d, J = 43.2 Hz), 122.4 (d, J = 4.4 Hz), 117.2 (dd, J = 59.6, 4.5 Hz), 74.5 (d, J = 5.2 Hz), 45.3 (d, J = 103.5 Hz), 44.0 (d, J = 8.1 Hz), 42.8 (d, J = 8.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.3 ppm; HRMS (ESI^+): m/z calcd for $C_{22}H_{21}BrN_3O_3P$ $[M + Na]^+$: 508.0396; Found: 508.0418.

*2-(2-Nitro-1-(4-(trifluoromethyl)phenyl)ethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3k**).* 42.3 mg, 89% yield; white solid; mp 200 °C (decomp.); R_f 0.26 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3061, 2920, 2885, 1599, 1558, 1500, 1327, 1263, 1234, 1118, 1070, 960; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.39 (m, 6 H), 7.34−7.29 (m, 4 H), 7.17 (t, J = 7.2 Hz, 2 H), 6.87 (dd, J = 8.0, 2.0 Hz, 2 H), 5.29 (ddd, J = 3.6, 7.4, 12.6 Hz, 1 H), 4.90 (ddd, J = 4.0, 12.0, 14.8 Hz, 1 H), 4.65 (ddd, J = 3.2, 14.4, 21.2 Hz, 1 H), 3.60−3.43 (m, 2 H), 3.04−2.95 (m, 1 H), 2.90−2.81 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 140.9 (dd, J = 72.2, 8.2 Hz), 136.4 (d, J = 6.0 Hz), 130.0 (d, J = 5.3 Hz), 128.7 (d, J = 5.2 Hz), 125.6 (m), 123.7 (d, J = 270.9 Hz), 123.4 (d, J = 41.7 Hz), 117.4 (dd, J = 56.6, 3.7 Hz), 74.5 (d, J = 5.2 Hz), 45.7 (d, J = 102.8 Hz), 44.1 (d, J = 8.2 Hz), 42.9 (d, J = 8.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.7 ppm; HRMS (ESI^+): m/z calcd for $C_{23}H_{21}F_3N_3O_3P$ $[M + Na]^+$: 498.1165; Found: 498.1167.

*2-(2-Nitro-1-(o-tolyl)ethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3l**).* 31.2 mg, 74% yield; white solid; mp 176−177 °C; R_f 0.20 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3092, 3018, 2951, 1599, 1550, 1500, 1371, 1269, 1232, 1116, 960; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.35 (m, 6 H), 7.28 (d, J = 8.0 Hz, 2 H), 7.17−7.01 (m, 5 H), 6.82 (d, J = 8.0 Hz, 1 H), 5.35−5.29 (m, 1 H), 4.95−4.81 (m, 2 H), 3.53−3.43 (m, 2 H), 3.06−2.95 (m, 1 H), 2.91−2.82 (m, 1 H), 1.73 (s, 3 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 141.5 (dd, J = 61.1, 9.0 Hz), 138.3 (d, J = 6.7 Hz), 131.1 (d, J = 3.0 Hz), 130.5 (d, J = 6.7 Hz), 129.8 (d, J = 5.2 Hz), 128.0 (d, J = 3.0 Hz), 127.1 (d, J = 4.5 Hz), 125.9 (d, J = 3.7 Hz), 122.8 (d, J = 49.9 Hz), 116.8 (dd, J = 63.3, 4.5 Hz), 76.2 (d, J = 6.7 Hz), 43.6 (d, J = 8.2 Hz), 42.2 (d, J = 8.2 Hz), 41.7 (d, J = 104.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 25.4 ppm; HRMS (ESI^+): m/z calcd for $C_{23}H_{24}N_3O_3P$ $[M + Na]^+$: 444.1447; Found: 444.1455.

*2-(1-(2-Fluorophenyl)-2-nitroethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3m**).* 30.2 mg, 71% yield; white solid; mp 158 °C (decomp.); R_f 0.14 (v_{Hexane}/v_{EA} = 3:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3076, 3043, 2960, 2879, 1599, 1554, 1492, 1473, 1267, 1234, 1128, 1107, 958; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.28 (m, 8 H), 7.24−7.17 (m, 1 H), 7.15−7.09 (m, 2 H), 6.98−6.89 (m, 2 H), 6.76 (tt, J = 7.6, 2.0 Hz, 1 H), 5.28−5.21 (m, 1 H), 5.00−4.84 (m, 2 H), 3.61−3.46 (m, 2 H), 3.17−3.09 (m, 1 H), 3.05−2.97 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ160.8 (dd, J = 248.6, 6.0 Hz), 141.2 (dd, J = 78.2, 8.2 Hz), 130.0 (dd, J = 8.2, 3.7 Hz), 129.7, 129.2, 124.2 (t, J = 3.0 Hz), 123.0 (d, J = 20.8 Hz), 119.5 (dd, J = 14.2, 6.7 Hz), 117.3 (dd, J = 24.5, 3.7 Hz), 115.9 (dd, J = 22.3, 3.0 Hz), 74.3 (dd, J = 5.9, 2.3 Hz), 43.8 (d, J = 9.0 Hz), 42.8 (d, J = 9.0 Hz), 39.4 (d, J = 106.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.1 (d, J = 3.6 Hz) ppm; HRMS (ESI^+): m/z calcd for $C_{22}H_{21}FN_3O_3P$ $[M + Na]^+$: 448.1197; Found: 448.1188.

*2-(1-(2,4-Dichlorophenyl)-2-nitroethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3n**).* 35.9 mg, 76% yield; white solid; mp 188 °C (decomp.); R_f 0.28 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (5/1/1) for column; IR ν (KBr, cm^{-1}) 3028, 2939, 2856, 1599, 1560, 1552, 1500, 1477, 1373, 1269, 1116, 960; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.27 (m, 6 H), 7.23 (d, J = 8.0 Hz, 2 H), 7.19 (dd, J = 2.4, 0.8 Hz, 1 H), 7.14−7.01 (m, 3 H), 6.87 (dd, J = 8.8, 2.4 Hz, 1 H), 5.17−5.01 (m, 2 H), 4.93−4.83 (m, 1 H), 3.69−3.52 (m, 2 H), 3.48−3.39 (m, 1 H), 3.25−3.17 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 141.2 (dd, J = 31.3, 8.2 Hz), 135.9 (d, J = 6.7 Hz), 134.5 (d, J = 3.7 Hz), 129.8 (d, J = 2.9 Hz), 129.6 (d, J = 13.4 Hz), 129.5, 128.9 (d, J = 6.7 Hz), 127.1 (d, J = 3.8 Hz), 123.2 (d, J = 8.9 Hz), 117.4 (d, J = 5.2 Hz), 75.2 (d, J = 6.0 Hz), 43.8 (d, J = 9.7 Hz), 42.7 (d, J = 9.7 Hz), 41.9 (d, J = 104.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.0 ppm; HRMS (ESI^+): m/z calcd for $C_{22}H_{20}Cl_2N_3O_3P$ $[M + Na]^+$: 498.0512; Found: 498.0518.

*2-(1-(2-Bromo-4-chlorophenyl)-2-nitroethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3o**).* 43.0 mg, 83% yield; white solid; mp 160 °C (decomp.); R_f 0.30 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3085, 2958, 2926, 1600, 1554, 1498, 1473, 1375, 1273, 1232, 1126, 958; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.34 (m, 5 H), 7.30−7.25 (m, 2 H), 7.21 (d, J = 8.0 Hz, 2 H), 7.14−7.04 (m, 3 H), 6.90 (dd, J = 8.8, 2.84 Hz, 1 H), 5.13−5.00 (m, 2 H), 4.91−4.82 (m, 1 H), 3.70−3.54 (m, 2 H), 3.54−3.45 (m, 1 H), 3.31−3.23 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 141.2 (dd, J = 17.8, 7.4 Hz), 134.6 (d, J = 3.7 Hz), 133.1 (d, J = 2.2 Hz), 130.7 (d, J = 6.7 Hz), 129.6 (d, J = 23.1 Hz), 127.6 (d, J = 3.0 Hz), 126.3, 123.2 (d, J = 3.0 Hz), 117.5 (dd, J = 5.9, 4.4 Hz), 75.5 (d, J = 5.3 Hz), 44.7 (d, J = 105.0 Hz), 43.8 (d, J = 8.9 Hz), 42.6 (d, J = 9.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.9 ppm; HRMS (ESI^+): m/z calcd for $C_{22}H_{20}BrClN_3O_3P$ $[M + Na]^+$: 542.0006; Found: 542.0024.

*2-(1-(Furan-2-yl)-2-nitroethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3p**).* 22.2 mg, 56% yield; white solid; mp 120 °C (decomp.); R_f 0.20 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3007, 2957, 2852, 1600, 1554, 1498, 1473, 1307, 1267, 1236, 1155, 1126; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.28 (m, 9 H), 7.17−7.11 (m, 2 H), 6.29 (dd, J = 2.8, 2.0 Hz, 1 H), 5.87 (t, J = 3.6 Hz, 1 H), 5.11 (ddd, J = 3.2, 7.6, 12.4 Hz, 1 H), 4.77−4.59 (m, 2 H), 3.69−3.60 (m, 1 H), 3.53 (dq, J = 8.8, 3.6 Hz, 1 H), 3.35 (dq, J = 8.8, 4.0 Hz, 1 H), 3.13−3.05 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 146.6 (d, J = 10.4 Hz), 142.4 (d, J = 3.8 Hz), 140.8 (dd, J = 50.6, 8.2 Hz), 129.7 (d, J = 20.8 Hz), 123.3 (d, J = 64.0 Hz), 117.9 (dd, J = 119.8, 3.7 Hz), 110.9 (d, J = 3.7 Hz), 108.9 (d, J = 8.2 Hz), 73.0 (d, J = 5.9 Hz), 43.5 (d, J = 8.9 Hz), 43.0 (d, J = 8.2 Hz), 39.5 (d, J = 105.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.0 ppm; HRMS (ESI^+): m/z calcd for $C_{20}H_{20}N_3O_4P$ $[M + Na]^+$: 420.1084; Found: 420.1093.

*2-(2-Nitro-1-(thiophen-2-yl)ethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3q**).* 23 mg, 57% yield; white solid; mp 122 °C (decomp.); R_f 0.20 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3014, 2957, 2881, 1599, 1558, 1498, 1471, 1267, 1228, 1126, 960; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.30 (m, 8 H), 7.19−7.12 (m, 3 H), 6.87 (ddd, J = 0.4, 3.8, 4.6 Hz, 1 H), 6.44−6.41 (m, 1 H), 5.26 (ddd, J = 2.0, 6.6, 11.4 Hz, 1 H), 4.85 (ddd, J = 3.6, 14.2, 21.0 Hz, 1 H), 4.71 (ddd, J = 3.6, 11.8, 14.2 Hz, 1 H), 3.61−3.47 (m, 2 H), 3.19−3.06 (m, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 140.9 (dd, J = 67.7, 8.1 Hz), 134.4 (d, J = 8.2 Hz), 129.8 (d, J = 8.2 Hz), 127.0 (d, J = 3.8 Hz), 126.7 (d, J = 7.5 Hz), 125.5 (d, J = 4.0 Hz), 123.2 (d, J = 50.6 Hz), 117.6 (dd, J = 91.6, 4.5 Hz), 75.9 (d, J = 6.7 Hz), 44.2 (d, J = 8.2 Hz), 43.1 (d, J = 8.2 Hz), 41.1 (d, J = 107.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.1 ppm; HRMS (ESI^+): m/z calcd for $C_{20}H_{20}N_3O_3PS$ $[M + Na]^+$: 436.0855; Found: 436.0861.

*2-(1-Cyclohexyl-2-nitroethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3r**).* 19.9 mg, 48% yield; white solid; mp 168−169 °C; R_f 0.17 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 2924, 2887, 2850, 1599, 1552, 1502, 1491, 1375, 1273, 1215, 1122, 962; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.30 (m, 8 H), 7.14−7.07 (m, 2 H), 4.77 (ddd, J = 5.2, 11.4, 15.4 Hz, 1 H), 4.40 (ddd, J = 8.4, 9.4, 17.0 Hz, 1 H), 3.96−3.76 (m, 4 H), 3.30−3.19 (m, 1 H), 1.80−1.67 (m, 1 H), 1.65−1.50 (m, 3 H), 1.39 (d, J = 13.2 Hz, 1H), 1.30 (d, J = 13.2 Hz, 1 H), 1.16−0.89 (m, 4 H), 0.85−0.74 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 141.4 (dd, J = 43.2, 8.2 Hz), 129.7 (d, J = 2.3 Hz), 123.3 (d, J = 46.2 Hz), 118.5 (dd, J = 117.6, 4.5 Hz), 72.9 (d, J = 3.0 Hz), 45.1 (d, J = 8.1 Hz), 44.6 (d, J = 3.7 Hz), 44.0 (d, J = 96.0 Hz), 37.0, 33.0 (d, J = 11.2 Hz), 28.7 (d, J = 3.0 Hz), 26.8, 26.4, 25.6; ^{31}P NMR (162 MHz, $CDCl_3$): δ 29.2 ppm; HRMS (ESI^+): m/z calcd for $C_{22}H_{28}N_3O_3P$ $[M + Na]^+$: 436.1760; Found: 436.1764.

*2-(1-Nitropentan-2-yl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3s**).* 19.1 mg, 51% yield; white solid; mp 128−130 °C; R_f 0.17

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(v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3061, 2964, 2931, 2895, 1600, 1560, 1500, 1481, 1267, 1220, 1126, 956; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.31 (m, 8 H), 7.14−7.08 (m, 2 H), 4.83 (ddd, J = 4.8, 11.2, 14.4 Hz, 1 H), 4.21 (ddd, J = 9.2, 9.4, 15.0 Hz, 1 H), 3.97−3.76 (m, 4 H), 3.38−3.26 (m, 1 H), 1.74−1.61 (m, 1 H), 1.31−1.14 (m, 3 H), 0.74 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 141.2 (dd, J = 11.9, 7.4 Hz), 129.7 (d, J = 3.0 Hz), 123.3 (d, J = 27.5 Hz), 118.1 (dd, J = 22.3, 4.4 Hz), 75.8 (d, J = 2.3 Hz), 44.9 (d, J = 8.1 Hz), 44.4 (d, J = 8.9 Hz), 38.2 (d, J = 111.6 Hz), 30.1 (d, J = 3.0 Hz), 20.5 (d, J = 9.6 Hz), 13.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.9 ppm; HRMS (ESI^+): m/z calcd for $C_{19}H_{24}N_3O_3P$ $[M + Na]^+$: 396.1447; Found: 396.1451.

*2-(1-Nitro-3-phenylpropan-2-yl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3t**).* 24.4 mg, 58% yield; white solid; mp 138−139 °C; R_f 0.17 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3056, 3022, 2957, 2924, 1599, 1558, 1492, 1377, 1271, 1220, 1118, 972; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.33 (m, 6 H), 7.25−7.09 (m, 7 H), 6.92−6.87 (m, 2 H), 4.90 (ddd, J = 5.6, 11.6, 14.8 Hz, 1 H), 4.29 (ddd, J = 8.0, 10.0, 16.4 Hz, 1 H), 3.80−3.64 (m, 3 H), 3.62−3.54 (m, 1 H), 3.30−3.20 (m, 1 H), 3.00 (ddd, J = 7.2, 10.8, 14.0 Hz, 1 H), 2.58 (ddd, J = 8.4, 15.4, 19.0 Hz, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 141.1 (dd, J = 41.7, 7.4 Hz), 136.9 (d, J = 9.6 Hz), 129.8 (d, J = 23.8 Hz), 128.7, 128.4, 127.1, 123.2 (d, J = 30.6 Hz), 117.8 (dd, J = 16.3, 5.2 Hz), 75.5 (d, J = 3.0 Hz), 44.3 (d, J = 8.9 Hz), 43.5 (d, J = 9.0 Hz), 39.1 (d, J = 111.7 Hz), 34.0 (d, J = 2.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 27.6 ppm; HRMS (ESI^+): m/z calcd for $C_{23}H_{24}N_3O_3P$ $[M + Na]^+$: 444.1447; Found: 444.1460.

*(E)-2-(1-Nitro-4-phenylbut-3-en-2-yl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**3u**).* 12.1 mg, 28% yield; white solid; mp 142 °C (decomp.); R_f 0.17 (v_{Hexane}/v_{EA} = 2:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3024, 2914, 2881, 1599, 1554, 1500, 1491, 1265, 1226, 1122, 960; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.37 (m, 6 H), 7.36−7.26 (m, 5 H), 7.19−7.15 (m, 4 H), 6.17 (dd, J = 16.0, 5.6 Hz, 1 H), 5.72 (ddd, J = 5.6, 12.0, 13.2 Hz, 1 H), 5.05 (ddd, J = 3.6, 8.2, 11.4 Hz, 1 H), 4.43 (ddd, J = 4.0, 11.2, 14.0 Hz, 1 H), 4.19−4.06 (m, 1 H), 3.82−3.69 (m, 4 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 140.9 (dd, J = 47.6, 8.9 Hz), 136.2 (d, J = 12.7 Hz), 135.4 (d, J = 6.3 Hz), 129.9 (d, J = 10.4 Hz), 128.8, 128.5 (d, J = 1.5 Hz), 126.3 (d, J = 1.5 Hz), 123.4 (d, J = 71.4 Hz), 119.5 (d, J = 10.4 Hz), 117.8 (dd, J = 91.6, 4.5 Hz), 75.6 (d, J = 4.5 Hz), 44.7 (d, J = 12.7 Hz), 43.8 (d, J = 7.4 Hz), 43.6; ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.6 ppm; HRMS (ESI^+): m/z calcd for $C_{24}H_{24}N_3O_3P$ $[M + Na]^+$: 456.1447; Found: 456.1448.

General Procedure for the Large-Scale Reaction. To a solution of NHP-thiourea **1a** (0.86 g, 2.0 mmol) in $CHCl_3$ (6 mL) was added (*E*)-(2-nitrovinyl)benzene **2a** (0.35 g, 0.46 mmol). The reaction mixture was stirred at room temperature for 6 h. After stirring for 6 h, the reaction mixture was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (Hexane/EA/DCM = 8:2:1 and Hexane/EA = 1:2) to give corresponding product **3a** (788 mg, 95%) and byproduct **C** (303 mg, 85%).

Synthetic Manipulation of Phospha-Michael Adduct 3a. 1,3-Bis(4-bromophenyl)-2-(2-nitro-1-phenylethyl)-1,3,2-diazaphospholidine 2-oxide (**4a**): To a solution of **3a** (40.8 mg, 0.1 mmol) in 1,2-dichloroethane (1.0 mL) were added benzoyl peroxide (4.7 mg, 0.012 mmol) and *N*-bromosuccinimide (44.3 mg, 0.25 mmol) at room temperature. After stirring for 3 h, volatiles were removed under reduced pressure. The residue was subjected to column chromatography (Hexanes/DCM = 1/1) on silica gel to give pale-yellow solid **4a** (35.6 mg, 63%); mp 178 °C (decomp.); R_f 0.31 (v_{Hexane}/v_{DCM}= 1:1); IR ν (KBr, cm^{-1}) 3028, 2957, 2875, 1591, 1556, 1491, 1473, 1363, 1309, 1267, 1234, 960; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.48 (m, 4 H), 7.30−7.15 (m, 7 H), 6.75−6.70 (m, 2 H), 5.23 (ddd, J = 4.0, 8.0, 12.0 Hz, 1 H), 4.86 (ddd, J = 5.6, 11.2, 14.8 Hz, 1 H), 4.54 (ddd, J = 4.0, 14.4, 20.8 Hz, 1 H), 3.49−3.32 (m, 2 H), 2.87−2.79 (m, 1 H), 2.75−2.66 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 140.2 (dd, J = 78.1, 8.9 Hz), 132.8 (d, J = 3.0 Hz), 131.6 (d, J = 6.7 Hz), 128.9 (d, J = 3.0 Hz), 128.6 (d, J = 3.7 Hz), 128.1 (d, J = 5.2 Hz), 118.7 (dd, J = 63.3, 4.5 Hz), 116.0 (d, J = 42.5 Hz), 74.3 (d, J = 5.2 Hz), 45.7 (d, J = 104.2 Hz), 43.7 (d, J = 7.4 Hz), 42.6 (d, J = 8.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.6 ppm; HRMS (ESI^+): m/z calcd for $C_{22}H_{20}Br_2N_3O_3P$ $[M + Na]^+$: 585.9501; Found: 585.9494.

*Tert-butyl(2-(2-oxido-1,3-diphenyl-1,3,2-diazaphospholidin-2-yl)-2-phenylethyl)carbamate (**4b**).* To a solution of **3a** (40.6 mg, 0.1 mmol) in MeOH/THF (3:1, 2.0 mL) were added $NiCl_2{\cdot}6H_2O$ (59.6 mg, 0.25 mmol) and $NaBH_4$ (38.1 mg, 1 mmol) at −10 °C. After stirring for 2 h at −10 °C, the reaction mixture was warmed up to room temperature, and then di-*tert*-butyl dicarbonate (68.3 mg, 0.3 mmol) was added to the mixture, which was kept stirring for another 2.5 h. The reaction was quenched with 1 N aq. $NaHCO_3$, and the volatiles were removed under reduced pressure. The aqueous phase was extracted with DCM. The organic phase was dried over anhydrous Na_2SO_4, and Na_2SO_4 was filtered off. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography to afford **4b** (41.6 mg, 88%); white solid; mp 180−181 °C; R_f 0.41 (v_{Hexane}/v_{EA} = 1:1), $v_{Hexane}/v_{EA}/v_{DCM}$ (8/2/1) for column; IR ν (KBr, cm^{-1}) 3448, 3057, 2976, 2889, 1710, 1599, 1500, 1365, 1271, 1170, 1126, 954; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.32 (m, 6 H), 7.27 (dd, J = 8.0, 0.8 Hz, 2 H), 7.24−7.13 (m, 3 H), 7.10−7.05 (m, 2 H), 6.67 (dd, J = 7.2, 1.6 Hz, 2 H), 5.67 (b, 1 H), 3.90−3.70 (m, 3 H), 3.50−3.41 (m, 1 H), 3.41−3.33 (m, 1 H), 2.86 (b, 1 H), 2.70 (b, 1 H), 1.41 (s, 9 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 155.7, 141.9 (dd, J = 90.8, 8.2 Hz), 134.9, 129.6 (d, J = 13.4 Hz), 128.7 (d, J = 5.2 Hz), 128.3 (d, J = 3.0 Hz), 127.6, 122.3 (d, J = 59.5 Hz), 116.9 (dd, J = 98.2, 4.4 Hz), 79.3, 47.5 (d, J = 102.7 Hz), 43.8 (d, J = 7.4 Hz), 42.4 (d, J = 7.5 Hz), 40.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ 29.1 ppm; HRMS (ESI^+): m/z calcd for $C_{27}H_{32}N_3O_3P$ $[M + Na]^+$: 500.2073; Found: 500.2076.

*2-(2-Amino-1-phenylethyl)-1,3-diphenyl-1,3,2-diazaphospholidine 2-Oxide (**4c**).* To a solution of **3a** (145.7 mg, 0.36 mmol) in MeOH/THF (2.5:1, 7.0 mL) were added $NiCl_2{\cdot}6H_2O$ (211.9 mg, 0.90 mmol) and $NaBH_4$ (136.4 mg, 3.6 mmol) at −10 °C. After stirring for 2 h at −10 °C, the reaction mixture was warmed up to room temperature and quenched with 1 N aq. $NaHCO_3$, and the volatiles were removed under reduced pressure. The aqueous phase was extracted with DCM. The organic phase was dried over anhydrous Na_2SO_4, and Na_2SO_4 was filtered off. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography to afford **4c** (112.3 mg, 83%); white solid; mp 130−131 °C; R_f 0.05 (v_{EA}/v_{MeOH} = 9:1), v_{EA}/v_{MeOH} (9/1) for column; IR ν (KBr, cm^{-1}) 3436, 3368, 3059, 2943, 2880, 1598, 1493, 1472, 1270, 1229, 1125, 997, 957; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.34 (m, 6 H), 7.27 (dd, J = 7.6, 0.8 Hz, 2 H), 7.24−7.16 (m, 3 H), 7.10−7.04 (m, 2 H), 6.73−6.69 (m, 2 H), 3.77 (ddd, J = 6.4, 12.4, 17.2 Hz, 1 H), 3.66 (ddd, J = 6.4, 10.0, 10.0 Hz, 1 H), 3.50−3.34 (m, 2 H), 3.21 (ddd, J = 9.2, 9.4, 17.4 Hz, 1 H), 2.84−2.72 (m, 2 H), 1.91 (b, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 142.0 (dd, J = 88.6, 8.2 Hz), 134.9 (d, J = 6.0 Hz), 129.5 (d, J = 16.4 Hz), 128.9 (d, J = 6.0 Hz), 128.4 (d, J = 3.8 Hz), 127.5 (d, J = 3.7 Hz), 122.2 (d, J = 49.9 Hz), 116.9 (dd, J = 101.3, 4.5 Hz), 51.2 (d, J = 102.0 Hz), 43.8 (d, J = 7.4 Hz), 42.4 (d, J = 7.4 Hz), 42.1; ^{31}P NMR (162 MHz, $CDCl_3$): δ 29.4 ppm; HRMS (ESI^+): m/z calcd for $C_{22}H_{24}N_3OP$ $[M + H]^+$: 378.1730; Found: 378.1735.

*(2-Amino-1-phenylethyl)phosphonic Acid (**4d**).* A mixture of **4c** (29.4 mg, 0.078 mmol) in 36% aq. HCl (0.3 mL) was refluxed for 20 h. The mixture was allowed to cool down and co-evaporated two times with water. The crude residue was dissolved in water (2.0 mL), and the solution was stirred for 30 min after addition of Na_2CO_3 (4.0 equiv). After stirring for 30 min, the water was evaporated under reduced pressure. The resulting solid was dissolved in MeOH (2.0 mL) and filtered to remove the undissolved solid. Propylene oxide (100 μL) was added to the filtrate, and the solution was stirred for 30 min at 0 °C. After stirring for 30 min, a white precipitate formed. The solid was filtered and dried to give **4d**:[19] (10.5 mg, 67%); white solid; ^{1}H NMR (400 MHz, D_2O) δ 7.43−7.30 (m, 5 H), 3.63−3.55 (m, 1 H), 3.53−3.43 (m, 1 H), 3.28 (ddd, J = 5.2, 13.4, 19.4 Hz, 1 H); ^{13}C NMR (100.5 MHz, D_2O) δ 134.4 (d, J = 7.4 Hz), 129.2 (d, J = 2.3 Hz), 129.0 (d, J = 5.9 Hz), 128.0 (d, J = 2.2 Hz), 44.6 (d, J = 128.0 Hz), 40.6 (d, J = 3.0 Hz); ^{31}P NMR (162 MHz, D_2O): δ 15.6 ppm.

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■ ASSOCIATED CONTENT

Supporting Information

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^{1}H and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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