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Conformationally Constrained α-Boc-Aminophosphonates via Transition Metal-Catalyzed/Curtius Rearrangement Strategies

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A transition metal-catalyzed/Curtius rearrangement sequence toward the development of conformationally constrained α-Boc-aminophosphonates **2**−**6** is described. An approach using the versatile *tert*-butylphosphonoacetate moieties **1a** and **1b** to derive an array of mono- and bicyclic α-Boc-aminophosphonate systems is presented. Conformational constraint is incorporated using either the ring-closing metathesis reaction catalyzed by the first generation Grubbs catalyst or intramolecular cyclopropanation mediated by $Rh_2(OAc)_4$. Using the *tert*-butyl ester functionality in **1a** or **1b** as a potential amino group, the Curtius rearrangement provides an efficient route toward the target α-Boc-aminophosphonates.

Introduction

Aminophosphonic acids and their derivatives have received considerable attention due to their involvement in a variety of biological processes.[1] These entities have been shown to serve as inhibitors of GABA-receptors,[2] inhibitors of various proteolytic enzymes,[3] antitumor agents,[1,4] antihypertensive agents,[5] antibacterial agents,[6] and haptens for the development of catalytic antibodies.[7] They have also served as inhibitors of excitatory transmission,[8] and are of agricultural interest due to their potent fungicidal, herbicidal, and insecticidal activity.[9] Our interest in the synthesis of novel phosphorus compounds via transition metal-catalyzed approaches has drawn us to a series of biologically active cyclic α-aminophosphonates (Figure 1), the phosphonoester surrogates of α-aminophosphonic acids. These compounds have shown promise as peptide-related bioactive agents,[10] as starting units in the total synthesis of natural product analogues,[11] as haptens in catalytic antibody synthesis,[12] and as powerful herbicides.[13]

Although the synthesis of aminophosphorus compounds and their cyclic derivatives has been extensively studied,[1,4,14] the literature contains relatively few examples utilizing transition metal-catalyzed processes to afford either acyclic or cyclic structures.[15] Our interest

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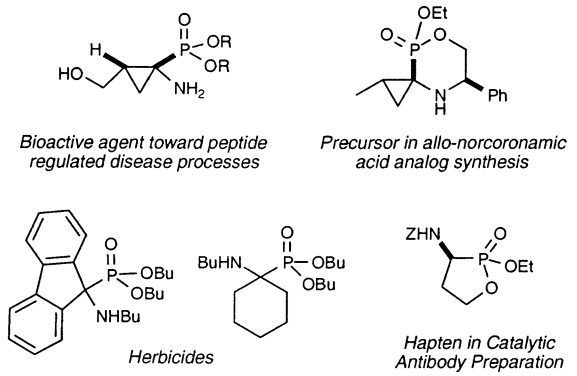

FIGURE 1. Biologically active α-aminophosphonates.

in both ring-closing metathesis (RCM)[16] and intramolecular cyclopropanation (ICP)[17] led us to explore the *tert*-butylphosphonoacetate building block as a potential amino group via a Curtius rearrangement and thus a synthon for the construction of an array of conformationally constrained α-Boc-aminophosphonates (Figure 2). The initial targets we chose have structural similarities of known biologically relevant α-aminophosphonates. The strategy we report utilizes the *tert*-butylphosphonoacetates **1a** and **1b**, in conjunction with an array of transition metal-catalyzed processes, including $Rh_2(OAc)_4$-catalyzed ICP, ruthenium-catalyzed RCM, and $Rh_2(OAc)_4$-catalyzed ylide rearrangements.[18] Subsequent Curtius rearrangement in the presence of ^{t}BuOH[19,20] generates a number of novel mono- and bicyclic α-aminophosphonates **2**−**6** (Figure 2).

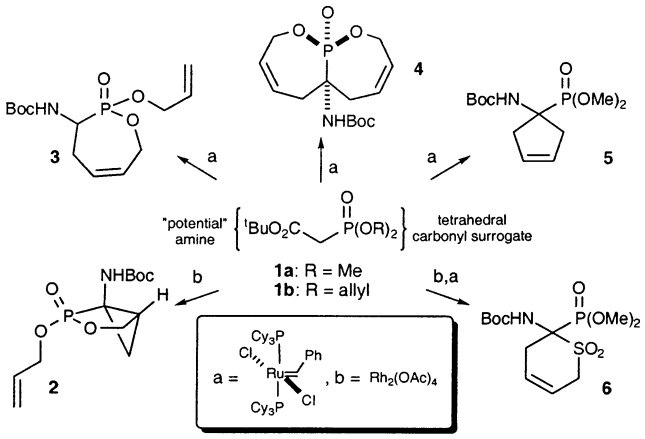

FIGURE 2. Versatile phosphonoacetate precursor.

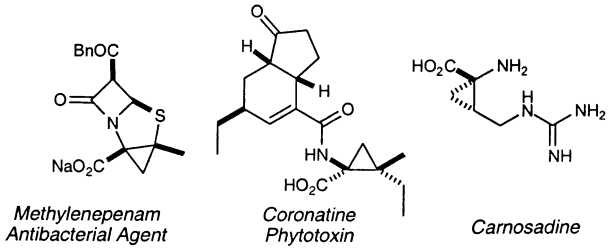

FIGURE 3. Biologically active amino-Cyclopropanes.

Results and Discussion

Our initial focus was directed toward the synthesis of phosphorus surrogates of cyclopropane-containing amino acids. Amino acids incorporating cyclopropane rings have proven to be potent, biologically active compounds (Figure 3). The strategy we devised utilizes $Rh_2(OAc)_4$-catalyzed intramolecular cyclopropanation as outlined in Scheme 1.[17] We believed that this would provide a direct route toward a number of cyclopropane-containing aminophosphonates related to the biologically active systems outlined in Figures 1 and 3. This strategy augments our recent efforts utilizing a double diastereoselective ICP strategy to access bicyclic *P*-chiral phosphonates analogous to **8**.[21]

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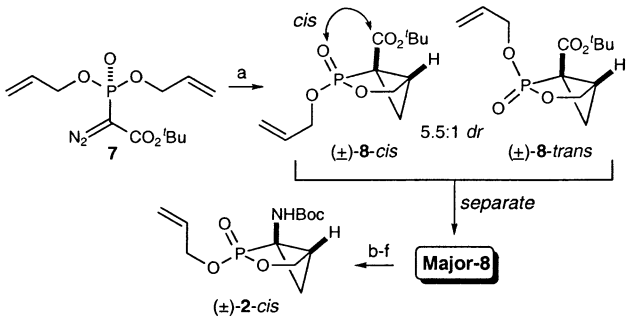
SCHEME 1[a]



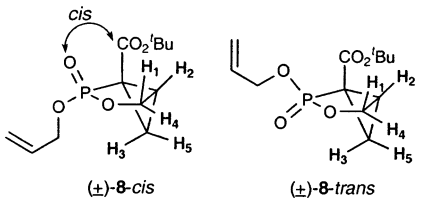
[a] Reagents and conditions: (a) $Rh_2(OAc)_4$, CH_2Cl_2, reflux, 91%; ds 5.5:1; (b) formic acid, neat; (c) $(COCl)_2$, CH_2Cl_2, DMF (cat.), 0 °C to rt; (d) NaN_3, CH_3CN, H_2O quantitative yield; (e) toluene, reflux; (f) ^{t}BuOH, reflux, 50% (five steps).

This series began with diazotization of diallylphosphonoacetate precursor **1b**[22] giving α-diazo phosphonate **7**.[17] Cyclopropanation, facilitated by $Rh_2(OAc)_4$ carbene generation, yielded two diastereomeric, [3.1.0]-bicyclic phosphonoacetates **8** in a 5.5:1.0 ratio. The mixture was separated and the major diastereomer was carried through the optimized Curtius sequence, which entailed formic acid-mediated ester hydrolysis of the *tert*-butyl ester followed by transformation to the acyl chloride. Subsequent azide formation using NaN_3 in CH_3CN/water gave the acyl azide.[23] This product was dissolved in toluene and refluxed over 4 Å molecular sieves to induce the Curtius rearrangement; the reaction progress was monitored by infrared spectroscopy. Once the acyl azide peaks (1740 and 2150 cm^{-1}) vanished and the isocyanate appeared (2240 cm^{-1}), ^{t}BuOH was added, and the reaction mixture was refluxed over 4 Å molecular sieves to yield the solid carbamate **2**. Subsequent recrystallization and X-ray crystallographic analysis (see Supporting Information) enabled us to unambiguously prove the cis relationship between the P═O group and the amino carbamate in the major diastereomer (Scheme 1).

It is worth noting that initially unambiguous identification of the major diastereomer **8**-*cis* was problematic as NOE studies proved to be completely inconclusive. However, it has been shown that in other constrained systems, protons within the "cone" of the P═O of the phosphonate moiety will be shifted downfield relative to those outside the "cone".[24] Therefore, we postulated that the major diastereomer was the cis isomer due to the fact that protons H(1), H(2), and H(4) (Table 1) were all shifted downfield in the major diastereomer in comparison to the same protons in the minor. Similarly, proton H(3) has a downfield shift in the minor isomer.

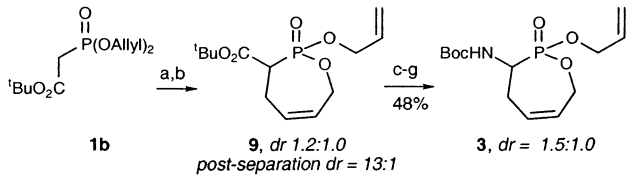
With **2** in hand, we next turned to an RCM strategy toward the synthesis of the seven-membered *P*-heterocyclic α-aminophosphonates **3** (Scheme 2). Monoallylation of diallyl *tert*-butylphosphonoacetate (**1b**) using NaH and allyl bromide in THF at 0 °C followed by RCM utilizing the Grubbs benzylidene catalyst[25] generated a 1.2:1.0 mixture of diastereomeric *P*-heterocycles **9** in excellent yield (Scheme 2). Using the same five-step procedure as before, Boc-protected α-aminophosphonate **3** was generated in 48% overall yield as a 1.5:1 mixture of separable diastereomers.[26] Subsequent allylation of an approximate 1:1 mixture of the aforementioned *P*-heterocyclic diastereomers **9** produced **10** with good yield and with 3:1 diastereoselectivity (Scheme 3). RCM of the major diastereomer gave the [5.5.0]-bicyclic *tert*-butylphosphonoacetate **11** as the cis-fused diastereomer (see Supporting

TABLE 1. ^{1}H NMR Data of Major and Minor Isomers



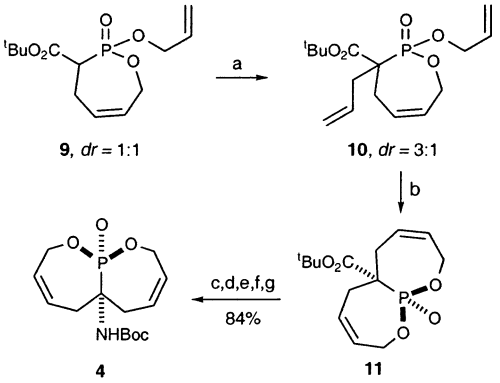
proton	δ major	δ minor
H_1	4.34	4.18
H_2	2.44	2.37
H_3	1.59	1.66
H_4	4.03	4.02
H_5	1.38	1.38

SCHEME 2[a]



[a] Reagents and conditions: (a) NaH, THF, allyl bromide, 0 °C, 85%; (b) Grubbs catalyst (5 mol %), CH_2Cl_2, 94%; (c) formic acid, neat; (d) $(COCl)_2$, CH_2Cl_2, DMF (cat.); 0 °C to rt; (e) NaN_3, CH_3CN, H_2O quantitative (three steps); (f) toluene, reflux; (g) ^{t}BuOH, reflux, 48%.

SCHEME 3[a]



[a] Reagents and conditions: (a) KO^{t}Bu, allyl bromide, CH_2Cl_2, 0 °C to rt, 76%; (b) Grubbs catalyst (5 mol %), CH_2Cl_2, 97%; (c) formic acid, neat; (d) $(COCl)_2$, CH_2Cl_2, DMF (cat.), 0 °C to rt. (e) NaN_3, CH_3CN, H_2O quantitative yield (three steps); (f) toluene, reflux; (g) ^{t}BuOH, reflux 84%.

(22) The *tert*-butyldialkylphosphonoacetates are readily prepared using standard Arbuzov reaction of trimethyl phosphite or triallyl phosphite and *tert*-butyl iodoacetate.

(23) We also attempted the Curtius rearrangement directly from the acid using DPPA; however, the isocyanate peak was never detected by IR.

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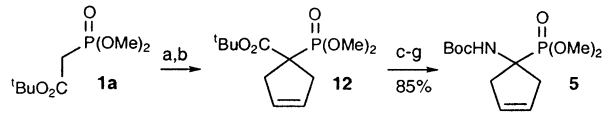
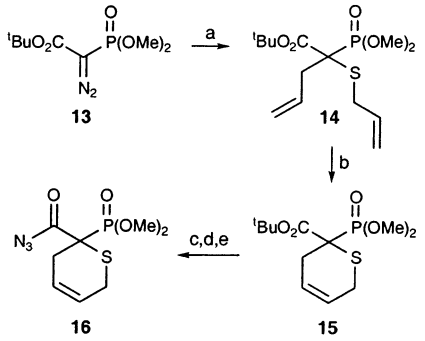
(26) It is interesting to note that conditions incorporated in the Curtius sequence caused complete epimerization at the α-center when starting from a 13:1 mixture of diastereomers (Scheme 1).

SCHEME 4[a]



[a] Reagents and conditions: (a) KO^{t}Bu, allyl bromide, CH_2Cl_2, 0 °C to rt,, 92%; (b) Grubbs catalyst (5 mol %), CH_2Cl_2, 94%; (c) formic acid, neat; (d) $(COCl)_2$, CH_2Cl_2, DMF (cat.), 0 °C to rt. (e) NaN_3, CH_3CN, H_2O quantitative yield (three steps); (f) toluene, reflux; (g) ^{t}BuOH, reflux, 85%.

SCHEME 5[a]



[a] Reagents and conditions: (a) $Rh_2(OAc)_4$, allyl sulfide, CH_2Cl_2, 80%; (b) Grubbs catalyst (5 mol %), CH_2Cl_2, 99%; (c) formic acid, neat; (d) $(COCl)_2$, CH_2Cl_2, DMF (cat.), 0 °C to rt; (e) NaN_3, CH_3CN, H_2O, quantitative yield (three steps).

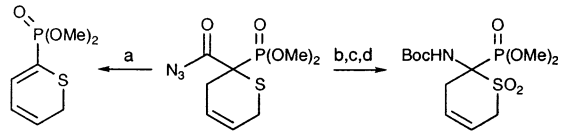
Information) in excellent yield (85−97%). This experiment also proves the selectivity (cis = major) in the allylation process of **9**. Subjection of **10** to Curtius conditions gave the corresponding α-Boc-aminophosphonate **4** in 84% yield (Scheme 3).

As expected, X-ray analysis demonstrates that the Curtuis rearrangement of the bicyclic system proceeds with complete retention of configuration. The cis-ring juncture [P(14) and C(7A) in Supporting Information] generated after the initial methathesis **11** event is maintained in the α-aminophosphonate system **4**. In addition, the carbamate N−H forms an H-bond to the phosphonate P═O.

Similarly, the synthesis of α-aminophosphonate **5** using the dimethyl *tert*-butylphosphonoacetate (**1a**) building block began with bisallylation using KO^{t}Bu and allyl bromide in CH_2Cl_2 at 0 °C. Subsequent RCM produced **12** in excellent yield (Scheme 4). Again, formic acid-mediated ester deprotection gave the corresponding acid quantitatively. Acyl chloride formation followed by azide addition produced the requisite acyl azide. Refluxing in toluene induced the Curtius rearrangement and subsequent addition of ^{t}BuOH afforded the Boc-protected α-aminophosphonate **5** in 85% yield (Scheme 4).

Amending this method to the more elaborate cyclic, α-sulfonyl, α-aminophosphonate **6** (Schemes 5 and 6) allowed us to highlight the full potential of this strategy. Thus, α-diazophosphonoacetate **13**,[27] in the presence of $Rh_2(OAc)_4$ and diallyl sulfide, undergoes ylide formation followed by sigmatropic rearrangement producing the homoallylic α-thio *tert*-butylphosphonoacetate **14**. Subsequent RCM gave the cyclic compound **15**. Ester deprotection, acyl chloride formation, and treatment with NaN_3 gave the cyclic acyl azide **16** in a quantitative, three-step process (Scheme 5).

SCHEME 6[a]



[a] Reagents and conditions: (a) toluene, microwave 45 min, 50%; (b) *m*CPBA, CH_2Cl_2, 82%; (c) toluene, reflux; (d) ^{t}BuOH, reflux, 53% (two steps).

It was found that acyl azide **16** did not undergo a Curtius rearrangement upon refluxing in toluene. Instead, acyl azide elimination was prevalent, most likely arising from direct participation of the adjacent sulfide lone pairs to yield diene **17**. This problem was overcome via oxidation to the corresponding sulfone. Subsequent Curtius protocol produced the α-Boc-aminophosphonate **6**, containing three different heteroatoms on a single carbon atom, in 53% overall yield (Scheme 6).

In conclusion, we have shown that the cyclic α-Boc-aminophosphonates can be synthesized in good yields utilizing the Curtius rearrangement on conformationally constrained phosphorus templates generated from either RCM or $Rh_2(OAc)_4$-catalyzed ICP. This work augments our efforts in the area of producing novel phosphorus systems utilizing transition metal-catalyzed processes; the pursuit of broadening the scope of this project in terms of stereochemical issues and substrate functionalization is ongoing and will be reported in due course.

Experimental Section

General Methods. All reactions were carried out in flame- or oven-dried glassware under an argon atmosphere using standard gastight syringes, cannulaes, and septa. Stirring was accomplished with oven-dried magnetic stir bars. Methylene chloride was purified by distillation over CaH_2 or by passing through a purification system[28] employing activated Al_2O_3. Deuteriochloroform ($CDCl_3$) was stored over molecular sieves (4 Å) and K_2CO_3 at room temperature. NaH was used as a 60% mixture in mineral oil. Mass spectral analysis was performed by the Mass Spectrometry Laboratory at the University of Kansas. Flash column chromatography was performed with silica gel (230−400 mesh). Thin-layer chromatography was performed on silica gel. Visualization of TLC spots was effected using UV and $KMnO_4$ stain.

Representative Procedure for Ring-Closing Metathesis (RCM). A solution of substrate in CH_2Cl_2 was degassed with argon for 10 min. Grubbs catalyst was added, and the solution was brought to reflux and monitored by TLC and GC. The reaction was concentrated under reduced pressure and subjected to flash chromatography to afford the purified cyclic phosphonate products.

Representative Procedure for the Curtius Rearrangement Sequence. The *tert*-butyl ester was dissolved in neat formic acid. Once hydrolysis was complete, excess formic acid was removed under reduced pressure. The crude acid was dissolved in CH_2Cl_2 in a round-bottom flask equipped with drying tube; the solution temperature was taken to 0 °C. Oxalyl chloride was added along with one drop of DMF, which induced CO_2 extrusion. Once CO_2 extrusion subsided, the reaction was concentrated under reduced pressure and dissolved in CH_3CN. A saturated solution of NaN_3 in water was

(27) Prepared from **1a** in our previously reported sequential (2,3)-sigmatropic ylide rearrangement/RCM strategy, see ref 18b.

(28) Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518−1520.

added and reaction was stirred for 5 h. The crude reaction was dissolved in EtOAc, washed with H_2O (2×) and NaCl (2×), dried (Na_2SO_4), and concentrated. The crude acyl azide was dissolved in toluene in a flame-dried pressure tube, 4 Å molecular. sieves were added, and the reaction was refluxed and monitored by infrared spectroscopy. Once the acyl azide peaks vanished and the isocyanate peak was visible, excess ^{t}BuOH was added and the reaction was refluxed until complete as observed by IR analysis. The crude carbamate was purified via flash chromatography (hexanes:EtOAc).

Boc-Protected α-Aminophosphonate 2-*cis* (Major). The major, bicyclic ^{t}butylphosphonoacetate **8** (140 mg, 0.51 mmol) was subjected to the Curtius rearrangement sequence beginning with ester hydrolysis in 3 mL of formic acid. The resulting carboxylic acid (112 mg, 0.51 mmol) was transformed to the acyl chloride using oxalyl chloride (128 mg, 1.0 mmol) in CH_2Cl_2 (1 mL) followed by the addition of 1 drop of DMF (0 °C to rt) in a 5-mL round-bottom flask equipped with a drying tube. The crude acyl chloride (121 mg, 0.51 mmol) was dissolved in CH_3CN (2 mL) and treated with a saturated aqueous solution of NaN_3 (491 mg, 7.6 mmol). The acyl azide (30 mg, 0.12 mmol) was dissolved in toluene (2 mL) and refluxed until formation of the isocyanate was complete (IR), ^{t}BuOH (0.5 mL) was added, and the system was refluxed producing the crude Boc-protected α-aminophosphonate **2**. Flash chromatography (2:1 hexanes:EtOAc), followed by recrystallization from ether/heptane, provided pure aminophosphonate **2** (20 mg, 57%) as a clear, crystalline solid. Mp 105−107 °C; FTIR 1714, 1392, 1365, 1250, 1168 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (dddd, J = 16.3, 10.8, 5.6, 5.6 Hz, 1H), 5.43 (s, 1H), 5.37 (dd, J = 17.1, 1.1 Hz, 1H), 5.24 (d, J = 10.3 Hz, 1H), 4.68−4.65 (m, 2H), 4.54 (ddd, J = 9.2, 3.1, 3.1 Hz, 1H), 4.00 (dd, J = 16.9, 9.3 Hz, 1H), 2.08−2.03 (m, 1H), 1.55−1.49 (m, 1H), 1.45 (s, 10H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 156.01, 132.97 (d, J_{CP} = 6.4 Hz), 118.20, 80.61, 67.96 (d, J_{CP} = 5.2 Hz), 65.14 (d, J_{CP} = 7.2 Hz), 30.28 (d, J_{CP} = 197.9 Hz), 28.21, 25.29 (br), 17.65; ^{31}P NMR (162 MHz, $CDCl_3$) δ 39.52; HRMS calcd for $C_{12}H_{21}O_5NP$ (M + H)$^+$ required 290.1157, found 290.1154.

Boc-Protected α-Aminophosphonate 3. A 13:1 diastereomeric mixture of **9** (400 mg, 1.4 mmol) was subjected to the general Curtius rearrangement sequence beginning with ester deprotection in 5 mL of formic acid. The resulting carboxylic acids (290 mg, 1.3 mmol) were transformed to the acyl chlorides using oxalyl chloride (397 mg, 3.1 mmol) in CH_2Cl_2 (2.5 mL) followed by the addition of 1 drop of DMF. The crude acyl chlorides (315 mg, 1.3 mmol) were dissolved in CH_3CN (2.5 mL) and treated with a saturated aqueous solution of NaN_3 (406 mg, 6.3 mmol). The resulting acyl azides (308 mg, 1.2 mmol) were dissolved in toluene and refluxed until formation of the isocyanates was complete (IR). Once complete, ^{t}BuOH (0.5 mL) was added and the system was refluxed producing the crude Boc-protected α-aminophosphonates **3**. Flash chromatography (1.5:1 hexanes:EtOAc) afforded aminophosphonates **3** (160 mg, 48%) as a 1.5:1 (95 mg Major, 65 mg Minor) mixture of separable diastereomers. **MINOR** (viscous oil): FTIR 1707, 1391, 1366, 1246, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98−5.88 (m, 2H), 5.83−5.78 (m, 1H), 5.36 (dd, J = 17.1, 1.3 Hz, 1H), 5.25 (dd, J = 10.4, 0.7 Hz, 1H), 5.20 (dd, J_{HP} = 9.0 Hz, J_{HH} = 6.0 Hz, 1H), 4.74−4.49 (m, 4H), 4.21−4.10 (m, 1H), 2.71−2.58 (m, 1H), 2.49 (dddd, J_{HH} = 25.6 Hz, J_{HH} = 15.0 Hz, J_{HP} = 7.6 Hz, J_{HH} = 2.9 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.94 (d, J_{CP} = 10.2 Hz), 132.32 (d, J_{CP} = 6.1 Hz), 129.43, 128.36, 118.44, 80.21, 66.83 (d, J_{CP} = 6.7 Hz), 64.03 (d, J_{CP} = 5.0 Hz), 48.15 (d, J_{CP} = 144.8 Hz), 29.34 (d, J_{CP} = 1.4 Hz), 28.24; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.07. **MAJOR** (white solid): mp. 99−101 °C; FTIR 1709, 1392, 1367, 1247, 1166 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01−5.89 (m, 3H), 5.40 (dd, J = 17.1, 1.3 Hz, 1H), 5.26 (d, J = 10.3 Hz, 1H), 4.83−4.69 (m, 2H), 4.64 (dd, J = 7.1, 6.0 Hz, 2H), 4.42 (ddd, J_{HP} = 20.2 Hz, J_{HH} = 14.2 Hz, J_{HH} = 5.0 Hz, 1H), 2.75−2.57 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, CDC_{l3}) (154.71 (d, J_{CP} = 6.3 Hz), 132.39 (d, J_{CP} = 6.3 Hz), 130.54, 129.62, 118.40, 80.20, 66.73 (d, J_{CP} = 5.8 Hz), 62.48 (d, J_{CP} = 3.8 Hz), 47.21 (d, J_{CP} = 144.2 Hz), 28.22, 28.02; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.28; HRMS calcd for $C_{13}H_{23}O_5NP$ (M + H)$^+$ required 304.1314, found 304.1309. Anal. Calcd for $C_{13}H_{22}O_5NP$ (major): C, 51.48; H, 7.31; N, 4.62. Found: C, 51.72; H, 7.22; N, 4.37.

Boc-Protected α-Aminophosphonate 4. Bicyclic *tert*-butylphosphonoacetate **11** (250 mg, 0.83 mmol) was subjected to the general Curtius rearrangement sequence beginning with ester deprotection in 8 mL of formic acid. The resulting carboxylic acid (150 mg, 0.62 mmol) was transformed to the acyl chloride using oxalyl chloride (195 mg, 1.53 mmol) in CH_2Cl_2 (1.8 mL) followed by the addition of 1 drop of DMF. The crude acyl chloride (161 mg, 0.62 mmol) was dissolved in CH_3CN (2 mL) and treated with a saturated aqueous solution of NaN_3 (200 mg, 3.1 mmol). The resulting acyl azide (90 mg, 0.33 mmol) was dissolved in toluene (2 mL) and refluxed until formation of the isocyanate was complete (IR). ^{t}BuOH (0.5 mL) was added and the system was refluxed producing the crude Boc-protected, bicyclic α-aminophosphonate **4**. Flash chromatography (1.5:1 hexanes:EtOAc) generated pure aminophosphonate **4** (88 mg, 84%) as a white solid. Mp 146−148 °C; FTIR 1712, 1392, 1366, 1253, 1165 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85−5.70 (m, 3H), 5.65−5.57 (m, 2H), 4.91−4.82 (m, 2H), 4.81−4.69 (m, 2H), 3.10−2.90 (m, 2H), 2.86−2.77 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.21 (d, J_{CP} = 15.9 Hz), 127.53, 126.99, 79.32, 67.78 (d, J_{CP} = 3.7 Hz), 65.09 (d, J_{CP} = 105.1 Hz), 32.06, 28.30; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.26; HRMS calcd for $C_{14}H_{23}O_5NP$ (M + H)$^+$ required 316.1314, found 316.1300. Anal. Calcd for $C_{14}H_{22}O_5NP$: C, 53.33; H, 7.03; N, 4.44. Found: C, 53.51; H, 7.05; N, 4.42.

Boc-Protected α-Aminophosphonate 5. α-Cyclopentene dimethyl-*tert*-butylphosphonoacetate **12** (100 mg, 0.36 mmol) was subjected to the general Curtius rearrangement sequence beginning with ester deprotection in 3 mL of formic acid. The resulting carboxylic acid (75 mg, 0.34 mmol) was transformed to the acyl chloride using oxalyl chloride (65 mg, 0.51 mmol) in CH_2Cl_2 (1 mL) followed by the addition of 1 drop of DMF. The crude acyl chloride (81 mg, 0.34 mmol) was dissolved in CH_3CN (1 mL) and treated with a saturated aqueous solution of NaN_3 (110 mg, 1.7 mmol). The resulting acyl azide (30 mg, 0.12 mmol) was dissolved in toluene (2 mL) and refluxed until formation of the isocyanate was complete (IR). ^{t}BuOH (0.5 mL) was added and the system was refluxed producing the crude Boc-protected, bicyclic α-aminophosphonate **5**. Flash chromatography (1:1 hexanes:EtOAc) yielded pure aminophosphonate **5** (30.1 mg, 85%) as a white solid. Mp 101−103 °C; FTIR 1716, 1390, 1366, 1242, 1170 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72−5.67 (m, 2H), 4.85 (d, J_{HP} = 4.4 Hz, 1H), 3.83 (d, J_{HP} = 10.4 Hz, 6H), 3.15−2.87 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.28 (d, J_{CP} = 5.3 Hz), 127.67 (d, J_{CP} = 7.5 Hz), 79.69, 58.92 (d, J_{CP} = 159.4 Hz), 53.46 (d, J_{CP} = 6.9 Hz), 41.59, 28.21; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.48; HRMS calcd for $C_{12}H_{23}O_5NP$ (M + H)$^+$ required 292.1314, found 292.1309.

Boc-Protected α-Aminophosphonate 6. α-Acylazido phosphonate **16** (30 mg, 0.11 mmol) was dissolved in CH_2Cl_2 (0.52 mL) and the solution temperature was lowered to 0 °C. *m*CPBA (66 mg, 0.38 mmol) was added, and once oxidation was complete, the crude reaction mixture was subjected to flash chromatography (2:1 then 1:1 hexanes:EtOAc) to afford the corresponding α-sulfonylacylazidophosphonate (27 mg, 0.087 mmol, 82%). The acyl azide (17 mg, 0.055 mmol) was then dissolved in toluene (2 mL) and subjected to the general Curtius conditions in ^{t}BuOH (0.50 mL). Flash chromatography (1:1 hexanes:EtOAc) generated α-aminophosphonate **6** (10 mg, 53%) as a clear oil. FTIR 1720, 1246, 1154 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88−5.86 (m, 1H), 5.61−5.58 (m, 1H), 5.51 (s, 1H), 4.04−3.96 (m, 2H), 3.92 (d, J_{HP} = 2.7 Hz, 3H), 3.90 (d, J_{HP} = 2.6 Hz, 3H), 3.65−3.59 (m, 1H), 3.30−3.26 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.86 (d, J_{CP} = 2.0 Hz), 125.46 (d, J_{CP} = 10.2 Hz), 117.97, 81.46, 73.01 (d, J_{CP} = 155.2 Hz), 54.80 (d, J_{CP} = 2.3 Hz), 54.73 (d, J_{CP} = 2.5 Hz), 49.69,

29.81, 28.11; ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.97; HRMS calcd for $C_{12}H_{23}NO_7PS$ $(M + H)^+$ required 356.0933, found 356.0928.

α-Diazo Diallyl *tert*-Butylphosphonoacetate 7. A solution of phosphonoacetate **8** (550 mg, 2.0 mmol) and CH_2Cl_2 was cooled to 0 °C, then charged with ^{t}BuOK (336 mg, 3.0 mmol) followed by dropwise addition of TsN_3 (591 mg, 3.0 mmol). The reaction was warmed to room temperature and monitored by TLC. Once complete, the reaction was diluted with EtOAc and extracted with H_2O (2×) and brine (1×). The organic portion was dried (Na_2SO_4) then concentrated under reduced pressure and subjected to flash chromatography (3:1 hexanes/EtOAc) to yield 515 mg (85%) as a clear, yellow oil. FTIR 2130, 1702, 1459, 1370, 1298 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (dddd, J = 17.0, 10.7, 5.6, 5.6 Hz, 2H), 5.38 (dddd, J = 17.1, 2.8, 1.2, 1.2 Hz, 2H), 5.24 (dd, J = 10.4, 1.2 Hz, 2H), 4.66−4.58 (m, 4H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.27 (d, J = 12.2 Hz), 132.17 (d, J = 6.9 Hz), 118.33, 83.04, 67.63 (d, J = 5.5 Hz), 28.10; ^{31}P NMR (162 MHz, $CDCl_3$) δ 12.25; HRMS calcd for $C_{12}H_{20}N_2O_5P$ $(M + H)^+$ required 303.1110, found 303.1092.

Cyclopropyl *tert*-Butylphosphonoacetate 8 (Major). α-Diazo diallyl *tert*-butylphosphonoacetate **1** (2.1 g, 6.95 mmol) was dissolved in CH_2Cl_2 (14 mL), $Rh_2(OAc)_4$ (153 mg, 0.35 mmol) was added, and the reaction was stirred at room temperature for 36 h until cyclopropanation was complete (TLC analysis). Flash chromatography (gradient 3:1, 2:1, then 1.8:1 hexanes:EtOAc) afforded 225 mg (12%) of **8** (MAJOR) and 1.52 g (80%) of a diastereomeric mix of **8**, both as colorless oils. FTIR 1729, 1451, 1370, 1270 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (dddd, J = 16.1, 10.6, 5.5, 5.5 Hz, 1H), 5.33 (dd, J = 17.1, 1.4 Hz, 1H), 5.21 (dd, J = 10.4, 0.8 Hz, 1H), 4.68−4.65 (m, 2H), 4.34 (dd, J = 9.3, 3.3 Hz, 1H), 4.00 (dd, J = 21.3, 9.3 Hz, 1H), 2.44−2.39 (m, 1H), 1.59−1.54 (m, 1H), 1.44 (s, 9H), 1.37−1.33 (m, 1H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 166.74 (d, J = 9.4 Hz), 132.69 (d, J = 5.9 Hz), 117.87, 82.66, 67.66 (d, J = 4.9 Hz), 64.41 (d, J = 6.0 Hz), 27.85, 26.34 (d, J = 8.3 Hz), 23.14 (J = 175.6 Hz), 18.01 (d, J = 2.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 36.47; HRMS calcd for $C_{12}H_{21}O_5NP$ $(M + H)^+$ required 275.1048, found 275.1029.

***P*-Heterocyclic, Allyl-*tert*-butylphosphonoacetate 9 (Major).** In a 50-mL round-bottom flask, diallyl-*tert*-buylphosphonoacetate **1b** (1.5 g, 5.4 mmol) was dissolved in THF (15 mL) and the reaction was cooled to 0 °C. NaH (117 mg, 5.9 mmol) was added and the solution was stirred for 5 min, followed by the addition of allyl bromide (590 mg, 4.9 mmol). The progress of the reaction was monitored by GC; once complete, the reaction was diluted with EtOAc and extracted with H_2O (2×) and brine (1×). The organic portion was dried (Na_2SO_4) then concentrated under reduced pressure and subjected to flash chromatography (3:1 hexanes:EtOAc) to afford monoallylated diallyl-*tert*-buylphosphonoacetate (1.5 g, 4.6 mmol, 85%) as a clear oil. Monoallylated diallyl-*tert*-buylphosphonoacetate (530 mg, 1.7 mmol) was subjected to general RCM procedure using Grubbs catalyst (69 mg, 0.08 mmol) and CH_2Cl_2 (34 mL). Flash chromatography (3:1 hexanes:EtOAc) afforded two diastereomeric cyclic phosphonates **9** (0.488 mg, 94%) as a clear oil. Cuts containing a 13:1 mix of major to minor were carried on for further reactions. FTIR 1728, 1393, 1369, 1254, 1148 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95−5.78 (m, 2H), 5.67−5.55 (m, 1H), 5.30 (dd, J = 17.1, 1.4 Hz, 1H), 5.17 (dd, J = 10.4, 1.1 Hz, 1H), 4.68−4.63 (m, 4H), 3.09 (ddd, J_{HP} = 23.1 Hz, J_{HH} = 9.7 Hz, J_{HH} = 3.1 Hz, 1H), 2.75−2.25 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.72 (d, J_{CP} = 5.1 Hz), 132.49 (d, J_{CP} = 6.7 Hz), 129.91, 127.02, 117.83, 82.06, 66.31 (d, J_{CP} = 6.4 Hz), 64.31 (d, J_{CP} = 5.6 Hz), 46.60 (d, J_{CP} = 124.3 Hz), 27.73, 23.57 (d, J_{CP} = 4.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.84; HRMS calcd for $C_{13}H_{22}O_5P$ $(M + H)^+$ required 289.1205, found 289.1190.

Allylated *P*-Heterocyclic, Allyl-*tert*-butylphosphonoacetate 10. In a 15-mL round-bottom flask, a 1:1 mix of diastereomeric **9** (825 mg, 2.9 mmol) was dissolved in CH_2Cl_2 (5 mL) and the reaction was cooled to 0 °C. *t*-BuOK (642 mg, 5.23 mmol) was added, and the solution was stirred 5 min, followed by the addition of allyl bromide (1.0 g, 8.6 mmol). The reaction progress was monitored by GC; once complete, the reaction was diluted with EtOAc and extracted with H_2O (2×) and brine (1×). The organic portion was dried (Na_2SO_4) then concentrated under reduced pressure and subjected to flash chromatography (3:1 hexanes:EtOAc) to afford the allylated adduct **10** (715 mg, 76%) as a clear oil of a 3:1 mix of diastereomers. FTIR 1729, 1393, 1368, 1281, 1251, 1161 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05−5.69 (m, 6H) mix, 5.68−5.55 (m, 2H) mix, 5.38 (ddd, J = 17.1, 2.9, 1.4 Hz, 1H) major, 5.36 (ddd, J = 17.1, 2.9, 1.4 Hz, 1H) minor, 5.24 (dd, J = 10.4, 1.3 Hz, 1H) major, 5.23 (dd, J = 10.4, 1.2 Hz, 1H) minor, 5.17−5.08 (m, 4H) mix, 4.79−4.35 (m, 8H) mix, 3.03−2.66 (m, 4H) mix, 2.65−2.32 (m, 4H) mix, 1.49 (s, 9H) major, 1.46 (s, 9H) minor; ^{13}C NMR (100 MHz, $CDCl_3$) major: δ 168.81 (d, J_{CP} = 4.2 Hz), 132.42 (d, J_{CP} = 15.7 Hz), 132.11 (d, J_{CP} = 14.9 Hz), 131.41, 127.92, 119.07, 117.63, 82.19, 66.67 (d, J_{CP} = 6.4 Hz), 63.04 (d, J_{CP} = 5.0 Hz), 54.72 (d, J_{CP} = 125.3 Hz), 36.45, 27.84, 27.68 (d, J_{CP} = 2.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) minor: δ 168.76 (d, J_{CP} = 4.9 Hz), 132.80 (d, J_{CP} = 6.6 Hz), 132.53 (d, J_{CP} = 5.8 Hz), 128.86, 128.52, 119.12, 118.21, 81.99, 66.61 (d, J_{CP} = 5.5 Hz), 65.33 (d, J_{CP} = 5.8 Hz), 54.96 (d, J_{CP} = 123.7 Hz), 36.50, 28.41 (d, J_{CP} = 3.4 Hz), 27.81; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.00 minor, 27.59 major; HRMS calcd for $C_{16}H_{26}O_5P$ $(M + H)^+$ required 329.1518, found 329.1512.

Bicyclic *tert*-Butylphosphonoacetate 11. A 3:1 mixture of allylated **10** (679 mg, 2.1 mmol) was subjected to general RCM conditions using Grubbs catalyst (85 mg, 0.1 mmol) and CH_2Cl_2 (41 mL). Flash chromatography (2:1 then 1:1 hexanes:EtOAc) afforded the bicyclic *tert*-butylphosphonoacetate **11** (604 mg, 2.0 mmol, 97%) as a white solid. Mp 97−99 °C; FTIR 1723, 1393, 1368, 1279, 1160 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96−5.84 (m, 2H), 5.65 (ddd, J = 11.5, 3.3, 3.3 Hz, 2H), 4.90−4.64 (m, 4H), 2.70 (dddd, J_{HH} = 22.2 Hz, J_{HH} = 14.0 Hz, J_{HP} = 7.5 Hz, J_{HH} = 0.5 Hz, 2H), 2.47 (dddd, J_{HH} = 19.9 Hz, J_{HH} = 14.0 Hz, J_{HP} = 7.2 Hz, J_{HH} = 1.0 Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.29 (d, J_{CP} = 2.8 Hz), 127.88 (d, J_{CP} = 2.1 Hz), 127.45, 82.41, 67.12 (d, J_{CP} = 6.5 Hz), 60.92 (d, J_{CP} = 119.3 Hz), 31.95 (d, J_{CP} = 3.7 Hz), 27.91; ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.49; HRMS calcd for $C_{14}H_{21}O_5P$ $(M + H)^+$ required 301.1205, found 301.1192.

α-Cyclopentene Dimethyl-*tert*-butylphosphonoacetate 12. In a 50-mL round-bottom flask, dimethyl-*tert*-butylphosphonoacetate **1a** (2.4 g, 10.7 mmol) was dissolved in CH_2Cl_2 (20 mL) and the reaction was cooled to 0 °C. ^{t}BuOK (3.6 g, 32.1 mmol) was added, the solution was stirred 5 min, followed by the addition of allyl bromide (4.53 g, 37.5 mmol), and the reaction progress was monitored by GC. Column chromatography (2:1 hexanes:EtOAc) afforded bisallylated dimethyl-*tert*-butylphosphonoacetate (2.0 g, 9.8 mmol, 92%) as clear oil. The bisallylated precursor (1.6 g, 5.3 mmol) was subjected to general metathesis conditions using Grubbs catalyst (216 mg, 0.3 mmol) in CH_2Cl_2 (104 mL). Flash chromatography (1:1 hexanes:EtOAc) afforded cyclic phosphonate **12** (1.4 g, 94%) as a clear oil. FTIR 1724, 1393, 1369, 1255, 1158 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (t, J = 8.1 Hz, 2H), 3.79 (d, J_{HP} = 10.6 Hz, 6H), 3.15−3.04 (m, 2H), 3.03−2.87 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.37 (d, J_{CP} = 2.6 Hz), 127.81 (d, J_{CP} = 8.4 Hz), 81.69, 53.28 (d, J_{CP} = 6.8 Hz), 53.08 (d, J_{CP} = 137.7 Hz), 38.99 (d, J = 2.0 Hz), 27.56; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.89; HRMS calcd for $C_{12}H_{22}O_5P$ $(M + H)^+$ required 277.1205, found 277.1203.

α-Diazo Methyldimethylphosphonoacetate (13). The starting phosphonoacetate (6.0 g, 33 mmol) was subjected to general diazo transfer conditions (see compound **7**), using tosyl azide (7.8 g, 40 mmol) and ^{t}BuOK (4.8 g, 45 mmol) in CH_2Cl_2 (100 mL). Flash chromatography (2:1 hexanes/EtOAc) afforded 6.14 g (89%) of **1a** as a yellow oil. FTIR 2133, 1712, 1437, 1288 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (d, J_{HP} = 16.7 Hz, 6H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.45 (d, J_{CP} = 50 Hz), 53.76 (d, J_{CP} = 22.7 Hz), 52.50; ^{31}P NMR (162 MHz,

$CDCl_3$) δ 14.48; HRMS calcd for $C_5H_{10}N_2O_5P$ $(M + H)^+$ required 209.0327, found 209.0318.

α-Thiohomoallylic Phosphonate 14. In a 16 × 125 mm^2 oven-dried pressure tube was placed the α-diazophosphonoacetate **13** and allyl sulfide in CH_2Cl_2. $Rh_2(OAc)_4$ (0.14 g, 0.32 mmol) was added (color change from green to dark purple) and the pressure tube was flushed with argon, capped, and placed in an oil bath at 85−90 °C. Flash chromatography (5:1 then 1.5:1 hexanes/EtOAc) afforded 0.85 g (80%) of α-thiohomoallylic phosphonate **14** as a clear oil. FTIR 1727, 1637, 1456, 1394, 1369, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87−5.74 (m, 2H), 5.19−5.03 (m, 4H), 3.84 (dd, J_{HP} = 10.7 Hz, J_{HH} = 1.6 Hz, 3H), 3.79 (dd, J_{HP} = 10.7 Hz, J_{HH} = 1.6 Hz, 3H), 3.55−3.43 (m, 2H), 2.86 (dddd, J = 14.5, 7.7, 6.4, 1.2 Hz, 1H), 2.63 (dddd, J = 15.0, 15.0, 7.37, 1.2 Hz, 1H), 1.43 (d, J = 1.5 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.51, 132.55, 132.03 (d, J_{CP} = 9.7 Hz), 118.61, 118.45, 83.20, 55.79 (d, J_{CP} = 143.0 Hz), 54.75 (d, J_{CP} = 7.3 Hz), 54.01 (d, J_{CP} = 7.5 Hz), 37.00 (d, J_{CP} = 8.2 Hz), 33.60, 27.71; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.89; HRMS calcd for $C_{14}H_{26}O_5PS$ $(M + H)^+$ required 337.1239, found 337.1242.

Cyclic α-Thiophosphonoacetate 15. The starting α-thiohomoallylicphosphonoacetate **14** (0.59 g, 1.8 mmol) was subjected to general metathesis conditions utilizing Grubbs catalyst (88 mg, 0.07 mmol) in CH_2Cl_2 (35 mL). Flash chromatography (1.5:1 hexanes/EtOAc) afforded 540 mg (99%) of **15** as a yellow oil. FTIR 1725, 1457, 1391, 1368, 1255 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88−5.79 (m, 2H), 3.88 (d, J_{HP} = 10.7 Hz, 3H), 3.81 (d, J_{HP} = 10.9 Hz, 3H), 3.29−3.19 (m, 2H), 2.88−2.75 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.20 (d, J_{CP} = 3.3 Hz), 125.70 (d, J_{CP} = 8.6 Hz), 123.01, 82.98, 54.91 (d, J_{CP} = 7.0 Hz), 54.03 (d, J_{CP} = 7.2 Hz), 50.89 (d, J_{CP} = 136.8 Hz), 29.69 (d, J_{CP} = 2.1 Hz), 27.62, 25.55 (d, J_{CP} = 4.7 Hz), ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.89; HRMS calcd for $C_{12}H_{22}O_5PS$ $(M + H)^+$ required 309.0926, found 309.0902.

α-Acylazido Phosphonate 16. *tert*-Butylphosphonoacetate **15** (70 mg, 0.23 mmol) was dissolved in HCO_2H (5 mL). Once hydrolysis was complete, the reaction was concentrated under reduced pressure. The crude acid (46 mg, 0.18 mmol) was dissolved in CH_2Cl_2 (1 mL) and the solution was cooled to 0 °C. Oxalyl chloride (46 mg, 0.37 mmol) was added followed by the addition of 1 drop of DMF. Once gas extrusion subsided, the reaction mixture was concentrated under reduced pressure. The resulting red oil was dissolved in CH_3CN (1 mL) and cooled to 0 °C. A saturated aqueous solution of NaN_3 (59 mg, 0.91 mmol) was added. Once complete, the reaction mixture was concentrated under reduced pressure, dissolved in EtOAc (10 mL), washed with H_2O and brine, dried ($NaSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography (1:1 hexanes/EtOAc) afforded acyl azide **15** as pure clear oil (49 mg, 0.17 mmol, 99%). FTIR 2140, 1697, 1461, 1421, 1259 cm^{-1}; ^{1}H NMR (400 Mz, $CDCl_3$) δ 5.90−5.84 (m, 2H), 3.91 (d, J_{HP} = 10.9 Hz, 3H), 3.87 (d, J_{HP} = 11.0 Hz, 3H), 3.40−3.11 (m, 2H), 2.94−2.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.20, 125.80 (d, J_{CP} = 10.3 Hz), 122.95, 55.16 (d, J_{CP} = 7.0 Hz), 54.73 (d, J_{CP} = 7.2 Hz), 52.27 (d, J_{CP} = 136.7 Hz), 29.18 (d, J_{CP} = 3.0 Hz), 25.21 (d, J_{CP} = 5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.08; HRMS calcd for $C_8H_{12}N_3O_4PS$ $(M + H)^+$ required 278.0364, found 278.0347.

Phosphonate Diene Elimination Product 17. α-Acylazido phosphonate **16** (33 mg, 0.12 mmol) was dissolved in 1,2-dichlorobenzene (0.45 mL), and the resulting mixture was exposed to microwave irradiation for 5-, 5-, 7-, 8-, 10-, 15-, and 15-min time periods. The reaction was monitored by GC, then subjected to flash chromatography (hexanes, followed by 1:1 hexanes/EtOAc) to afford diene **17** as a pure yellow oil (11.1 mg, 50%). FTIR 1534, 1250 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (J_{HP} = 18.7 Hz, J_{HH} = 5.7 Hz, 1H), 6.18−6.14 (m, 1H), 5.84−5.78 (m, 1H), 3.79 (d, J = 11.3 Hz, 6H), 3.29 (ddd, J = 5.3, 2.7, 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.02 (d, J_{CP} = 9.3 Hz), 125.91 (d, J_{CP} = 16.2 Hz), 119.94, 119.90, 53.10 (d, J_{CP} = 5.5 Hz), 24.17 (d, J_{CP} = 4.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.94; HRMS calcd for $C_{13}H_{23}O_5PS_2$ $(M + H)^+$ required 207.0245, found 207.0245.

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Supporting Information Available: ^{1}H, ^{13}C, and ^{31}P NMR spectra of new compounds as well as X-ray data for compounds **2**, **4**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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