Published in final edited form as:

Synthesis (Stuttg). 2013 February 1; 45(4): 463–470. doi:10.1055/s-0032-1317984.

Synthesis of Cyclic α -Aminophosphonates through Copper Catalyzed Enamine Activation

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Abstract

A copper-catalyzed tandem cyclization triggered addition strategy that relies on electrophilic enamine activation has been used to synthesize various cyclic α -aminophosphonates derivatives in good to excellent yields. Both five and six membered rings can be generated under mild conditions with high regioselectivity. A mechanism based on copper catalyzed enamine activation is proposed.

Keywords

cyclic α -aminophosphonates; enamine; copper; hydroamination; cyclization

Medicinal chemists are continuously seeking better methods to prepare N-heterocycles of different ring sizes and various substitution patterns because of their important biological properties.¹ A case in point is the synthesis of cyclic α -aminophosphonates. α -Aminophosphonates and their corresponding α -aminophosphonic acids have received much attention in organic and medicinal chemistry because they are structural analogues of the corresponding α -amino acids and transition state mimics of peptide hydrolysis.² Moreover, α -aminophosphonates have broad applications due to their biological activity^{2d, 3} such as antibacterial,⁴ anti-cancer,⁵ antiviral, and as enzyme inhibitors.⁶ In this communication, we report the synthesis of cyclic α -aminophosphonates *via* a one-pot tandem hydroamination/phosphorylation strategy. The central tenet of our strategy is the electrophilic enamine activation shown in Scheme 1: a cyclic enamine is formed first through a well-established transition metal-catalyzed intramolecular hydroamination of alkynes,⁷ then the same transition metal interacts with the *in situ*-generated enamine, activating it as an electrophile in a reaction with an incoming nucleophile. We have successfully used this strategy for tandem amination/alkynylation, amination/cyanation, and amination/trifluoromethylation.⁸ An added advantage of our approach is that all of these processes take place in one pot and one batch, without protection/deprotection steps.

Despite their importance, most literature syntheses of cyclic α -aminophosphonates have significant limitations. For example, the most common method to make α -aminophosphonates—the Kabachnik-Fields reaction (the three-component coupling of a carbonyl, an amine and a hydrophosphoryl compound)⁹—is effective to construct acyclic (linear) products, but much less so in the generation of ring systems, because of the

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Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synthesis>.

difficulty in preparing the corresponding starting material without extensive protection and de-protection steps (Scheme 2a).¹⁰ Another method to make α -aminophosphonates is the oxidative addition of a dialkyl phosphite to a cyclic amine. In 2009, Li's group reported such synthesis using oxygen as oxidant (Scheme 2b),¹¹ but this method suffers from a narrow substrate scope (a benzylic proton must be present). The third method is the decarboxylative-coupling of natural α -amino acids and phosphites (Scheme 2c).¹² However, because this method relies on natural cyclic amino acids as starting materials, and the pool of natural cyclic amino acids (e.g. L-proline) is shallow. This problem is magnified when cyclic amino acids with ring sizes that natural amino acids lack--such as a six-membered--are needed. Consequently, their syntheses require more steps. Similar to our strategy, Doye's group reported synthesis of α -aminophosphonates through early transition metal titanium catalyzed hydroamination, followed by addition of dialkylphosphite.¹³ Because Doye's method only works for primary amines, and our methodology mainly uses secondary amines, we believe our method is a good complement to Doye's approach.

The keystone of our strategy--transforming an enamine into a good electrophile--runs contrary to the ingrained teachings on enamine nucleophilicity. Although a handful of reports on the reaction of enamine with nucleophiles exist,¹⁴ they pale in comparison to the overwhelming number of reports on enamine used as nucleophiles. Not only the use of enamines as electrophiles is uncommon in organic synthesis, even the mechanism of enamine activation is poorly understood; for example, unlikely interactions in the Cu-catalyzed reaction of enamines have been proposed previously (Scheme 3a).^{14a, b, 15} While enamines are known to be good nucleophiles they can also be made to act as a good electrophile. It is instructive to consider the oxygen analog as a model of comparison: enol ethers are normally good nucleophiles, but if they are activated by, say a Brønsted acid, then they become good electrophiles. One notable example of this transformation is the tetrahydropyranyl (THP) protection of alcohols (Scheme 3b). In theory, an enamine can also be protonated to generate an iminium intermediate (Scheme 3c). Most mechanistic studies have shown preferential attack at N by proton followed by rearrangement to the more stable C-protonated iminium form,¹⁶ which can then act as electrophile. As it happens, in the case of electron rich enamines (e.g. R = alkyl), both, the starting material and the product, are rather basic (i.e., alkyl amines), and therefore, they combine to neutralize the acidity of the acid catalyst, so this method often does not work except for enamines with electron-withdrawing groups.

One solution to this problem consists in using a late transition metal Lewis acid, which normally has a relative higher affinity for the electron-rich double bond. The electrophilic activation of this double bond facilitates nucleophilic attack (Scheme 3d). DFT calculations¹⁷ predict the η^2 -bound Cu:enamine σ -complex to be more stable (by 2.2 kcal/mol) than the corresponding σ -complex, while Cu:enamine coordination is also stronger than to an alkynyl group (Scheme 4). Unsymmetrical coordination of Cu(I) to the enamine π -bond leads to shortening of the C-N bond and increased positive charge at the α -carbon: calculated Mulliken charges show the enamine transfers 0.32 units of charge to CuBr with a build up at C α by 0.13. We posit that in the presence of a suitable catalyst, even an electron rich enamine can act as an electrophile. Specifically, our strategy could deliver N-heterocycles through a transition metal-activated enamine that acts as electrophile. The same metal catalyzes both, the generation of the enamine *in situ*--by intramolecular amination of an alkyne--and its reaction with a nucleophile.

It should be noted that cyclic enamines (where the nitrogen is part of the ring) are not trivial to prepare. Whereas acyclic enamines can be easily made by the reaction of an aldehyde or ketone with a secondary amine, the equivalent approach to synthesize a cyclic enamine (e.g., I in Scheme 1) would require placing an amino group and an aldehyde (or ketone) in the

same molecule, a task that would add extra protection/deprotection steps.¹⁸ An additional experimental difficulty of working with enamines, especially electron-rich enamines (e.g. N,N-dialkyl/arylenamines), is that they are sensitive to moisture and hydrolyze with relative ease.¹⁹ This trait makes them difficult to isolate and purify. But our tandem chemistry overcomes this problem by using an in situ generated enamine, which reacts with another nucleophile simultaneously. Our method involves a tandem addition of two different nucleophiles to an alkyne. Literature reports on tandem addition of two different nucleophiles to an alkyne in one pot are not common.²⁰

In a preliminary attempt, reaction of aminoalkyne **1a** and diethyl phosphite **2a** in the presence of 5 mol % CuBr in 1, 4-dioxane at room temperature for 6 hours gave the desired product **3a** in 76% yield (Table 1, entry 1). In addition, pyrrolidine **4a** was isolated in 20% yield (Table 1, entry 1). Water strongly affected the ratio of the **3a** and **4a**. Two equivalents of water in dioxane depressed the formation of **3a** (58% yield) and increased the yield of **4a** (Table 1, entry 2). Most of starting material was converted to pyrrolidine **4a** in the presence of 20 mol % formic acid. The best choice of solvent was toluene, which provided **3a** in better yield (Table 1, entry 4). Further optimization revealed that the yield of **3a** could be improved to 92% yield by adding 3A molecular sieves (Table 1, entry 5). Higher temperature led to faster reaction, but the yield was reduced slightly (Table 1, entry 6). And this reaction can't be catalyzed by strong Brønsted acid (Table 1, entry 7). With optimized conditions in hand, we examined the scope of this reaction (Table 2).

Various aminoalkynes were used in the reaction. Both, benzyl amines and aromatic amines, were tolerated in this reaction. The aromatic amine **1i** with a methoxy group in the *para* position produced **3i** in good yield (Table 2, entry 9). The reaction of substrate **1j** with an electron-withdrawing chloro substituent on the aromatic ring did not take place, and most of the starting material was recovered (Table 2, entry 10). Complete regioselectivity was observed in all cases. The regioselectivity obeyed Baldwin's rules.²¹ That is, cyclization of 3-yn-amine **1a** and 4-yn-amine **1c** gave five-membered ring products through 5-endo-dig and 5-exo-dig mechanisms whereas the reaction of 5-yn-amine (e.g., **1f**) produced a six-membered ring through a 6-exo-dig pathway. When chiral aminoalkyne **1k** was used, a moderate chiral induction was observed (dr= 1:1.1, Table 2, entry 11). Dimethyl and dibenzyl phosphites could also be employed using our reaction conditions (Table 2, entries 12–13). Both of them gave excellent yields of products.

The proposed mechanism of enamine activation is shown in Scheme 5. The aminoalkyne **1** is first activated by coordination to the Lewis acidic copper center. Nucleophilic attack of the lone electron pair of nitrogen atom generates the enamine **5** through intermediate **4**. This enamine intermediate **5** can form a complex **6** with CuBr. Then the nucleophile (diethyl phosphite in our case)--activated by base (amine starting material or product)--reacts with the activated enamine intermediate to give the final product. Alternatively, the enamine intermediate **5** can react with CuBr and the nucleophile first to generate an iminium intermediate and a **Nu-Cu** species. Addition of **Nu-Cu** to the iminium intermediate furnishes final product. This mechanism is based in the classic role of iminium species (Scheme 5A). At this time, it is difficult to verify which of the two possible mechanisms prevail. The iminium mechanism (mechanism A) involves generation of two relative energetic species: a **Nu-Cu** species and an iminium species (Scheme 5), so we prefer the more concerted mechanism B.

In summary, a one-pot cyclization triggered addition strategy has been successfully used to synthesize cyclic α -aminophosphonates in good to excellent yields. Both five and six membered ring can be generated under mild conditions. Further studies on the asymmetrical version are now underway.

^1H , ^{13}C and ^{31}P NMR spectra were recorded at 400, 100 and 162 MHz respectively, using CDCl_3 as a solvent. The chemical shifts are reported in δ (ppm) values relative to CHCl_3 (δ 7.26 ppm for ^1H NMR and δ 77.0 ppm for ^{13}C NMR) and ^{31}P NMR, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants, J , are reported in Hertz. Coupling constants are reported in hertz (Hz). All air and/or moisture sensitive reactions were carried out under argon atmosphere. Solvents (tetrahydrofuran, ether, dichloromethane and DMF) were chemically dried using a commercial solvent purification system. All other reagents and solvents were employed without further purification. The products were purified using a commercial flash chromatography system or a regular glass column. TLC was developed on Merck silica gel 60 F254 aluminum sheets. HRMS obtained at the CREAM Mass Spectrometry Facility, University of Louisville, The microwave reactor (CEM, model Discovery) was used in microwave condition.

Diethyl (2-butyl-1-phenylpyrrolidin-2-yl)phosphonate (3a)

Typical Procedure

N-(oct-3-yn-1-yl) aniline **1a** (30 mg, 0.15 mmol), diethyl phosphite (41 mg, 0.3 mmol), toluene (1 mL) were charged into a small vial, and CuBr (1.1 mg, 5% equiv) was added to the mixture under stirring. Then the reaction mixture was stirred at room temperature for 6h. The resulting reaction mixture was directly concentrated in a rotary evaporator and purified by silica gel flash chromatography (3:1 hexane: ethyl acetate) to give a yellow liquid **3a** (48 mg, 92%).

^1H NMR (400 MHz, CDCl_3): δ = 0.73 (t, 3H, J = 7.6 Hz), 0.83–0.96(m, 1H), 1.12–1.34 (m, 9H), 1.76–1.93 (m, 2H), 1.98–2.15 (m, 2H), 2.23–2.37 (m, 1H), 2.51–2.62, 3.31–3.42 (m, 2H), 3.88–4.09 (m, 4H), 6.63–6.76 (m, 1H), 7.16–7.22 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ = 13.8, 16.5(d, J = 3.9 Hz), 16.5 (d, J = 3.1 Hz), 22.7 (d, J = 1.6 Hz), 22.7, 24.4 (d, J = 10.1 Hz), 32.0 (d, J = 10.9 Hz), 35.7, 51.8 (d, J = 3.1 Hz), 61.4 (d, J = 7.8 Hz), 62.7(d, J = 7 Hz), 66.2 (d, J = 154 Hz), 155.5, 117.4, 128.4, 146.4.

^{31}P NMR (162 MHz, CDCl_3) δ = 28.77.

ESI-HRMS (ESI+): m/z calcd. for $\text{C}_{18}\text{H}_{30}\text{NO}_3\text{P}$ ($\text{M}^+ + \text{H}$) 340.2042, found 340.2047.

Diethyl (1-benzyl-2-butylpyrrolidin-2-yl)phosphonate (3b)

Yield: 50 mg (94%); yellow oil.

^1H NMR (700 MHz, CDCl_3): δ = 0.91 (t, J = 7 Hz, 3H), 1.21–1.37 (m, 10H), 1.40–1.48 (m, 2H), 1.62–1.69 (m, 1H), 1.61–1.72 (m, 1H), 1.73–1.82 (m, 3H), 1.83–1.94 (m, 1H), 2.22–2.28 (m, 1H), 2.65–2.74 (m, 2H), 3.94 (d, J = 1.4 Hz, 2H), 4.06–4.17 (m, 4H), 7.14–7.31 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ = 14.2, 16.7 (t, J = 8.9 Hz, 2C), 22.7 (d, J = 3 Hz), 23.4, 25.7 (d, J = 8.9 Hz), 31.9, 32.6 (d, J = 11.9 Hz), 51.5 (d, J = 3.7 Hz), 53.4, 61.1 (d, J = 7.4 Hz), 62.1 (d, J = 8.2 Hz), 65.2 (d, J = 143.7 Hz).

^{31}P NMR (162 MHz, CDCl_3): δ = 30.51.

ESI-HRMS (ESI+): m/z calcd. for $\text{C}_{19}\text{H}_{32}\text{NO}_3\text{P}$ ($\text{M}^+ + \text{H}$) 354.2193, found 354.2197.

Diethyl (2-methyl-1-phenylpyrrolidin-2-yl)phosphonate (3c)

Yield: 41 mg (93%); Yellow oil.

^1H NMR (400 MHz, CDCl_3): δ = 1.23 (t, J = 7.2 Hz, 1H), 1.30 (t, J = 7.2 Hz, 1H), 1.56 (d, 14.4Hz, 1H), 1.78–1.96 (m, 2H), 2.09–2.21 (m, 1H), 2.66–2.76 (m, 1H), 3.34–3.41 (m, 1H), 3.43–3.49 (m, 1H), 3.95–4.13 (m, 4H), 6.72–6.78 (m, 1H), 7.20–7.23 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ = 16.5, 16.5, 21.5 (d, J = 10.9 Hz), 22.6 (d, J = 1.6 Hz), 40.4, 51.0 (d, J = 11.0 Hz), 63.6 (d, J = 7.8 Hz), 62.8 (d, J = 6.9Hz), 62.9 (d, J = 158.8 Hz), 116.1 (d, J = 1.6 Hz), 117.6, 128.4, 146.0 (d, J = 1.5 Hz).

^{31}P NMR (162 MHz, CDCl_3) δ = 28.41.

ESI-HRMS (ESI+): m/z calcd. for $\text{C}_{15}\text{H}_{24}\text{NO}_3\text{P}$ ($\text{M}^+ + \text{H}$) 298.1567, found 298.1572.

Diethyl (1-benzyl-2-methylpyrrolidin-2-yl)phosphonate (3d)

Yield: 41 mg (88%); yellow oil.

^1H NMR (400 MHz, CDCl_3): δ = 1.26 (td, J = 7.2, 3.2 Hz, 6H), 1.32 (d, J = 15.2 Hz, 3H), 1.52–1.73 (m, 4H), 2.31–2.48 (m, 2H), 2.72–2.79 (m, 1H), 3.55 (d, J = 13.2 Hz, 1H), 4.03–4.19 (m, 4H), 7.18–7.29 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ = 16.6(d, J = 5.4 Hz), 16.7 (d, J = 5.4 Hz), 18.8 (d, J = 10.9 Hz), 22.6 (d, J = 4.7 Hz), 36.7, 51.5 (d, J = 10.1 Hz), 54.2, 61.3 (d, J = 7.8 Hz), 62.7 (d, J = 7.7 Hz), 64.1 (d, J = 143.2 Hz), 126.6, 128.1, 128.5, 140.8.

^{31}P NMR (162 MHz, CDCl_3) δ = 28.77.

ESI-HRMS (ESI+): m/z calcd. for $\text{C}_{16}\text{H}_{26}\text{NO}_3\text{P}$ ($\text{M}^+ + \text{H}$) 312.1723, found 312.1724.

Diethyl (1-benzylpyrrolidin-2-yl)phosphonate (3e)

Yield: 30 mg (67%); yellow Oil.

^1H NMR (400 MHz, CDCl_3): δ = 1.27 (td, J = 7.0, 3.5 Hz, 6H), 1.52–1.74 (m, 2H), 1.85–1.78(m, 1H), 2.12–2.19 (m, 1H), 2.83–2.89 (m, 1H), 2.92 (dd, J = 10, 6Hz, 1H), 3.34 (d, J = 13.2 Hz, 1H), 4.07–4.20 (m, 4H), 4.36 (d, 13.2 Hz, 1H), 7.11–7.30 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ = 16.6 (d, J = 5.4 Hz), 16.6 (d, J = 5.4 Hz), 24.4 (d, J = 5.4 Hz), 27.0 (d, 9.2 Hz), 54.3 (d, J = 15.5Hz), 58.6, 60.2 (d, J = 2.3Hz), 61.3, 61.8 (d, J = 7.7 Hz), 62.6 (d, J = 7Hz), 126.8, 128.0, 128.8, 139.4;

^{31}P NMR (162 MHz, CDCl_3) δ = 27.13.

ESI-HRMS (ESI+): m/z calcd. for $\text{C}_{15}\text{H}_{24}\text{NO}_3\text{P}$ ($\text{M}^+ + \text{H}$) 298.1567, found 298.1572.

Diethyl (1-benzyl-2-methylpiperidin-2-yl)phosphonate (3f)**Typical Procedure**

Yield: 41 mg (83%); yellow Oil.

^1H NMR (400 MHz, CDCl_3): δ = 1.33 (t, J = 7.2 Hz, 6H), 1.39 (d, J = 14.4 Hz, 3H), 1.76–1.54 (m, 2H), 1.68–1.71 (m, 1H), 2.05–2.13 (m, 1H), 2.39–2.45 (m, 1H), 2.77–2.89 (m, 1H),

3.73 (dd, $J = 14.4, 2.8$ Hz, 1H), 4.02 (d, $J = 14.8$ Hz, 1H), 4.09–4.20 (m, 1H), 7.04–7.04 (m, 1H), 7.21 (m, $J = 7.6$ Hz, 2H), 7.22–7.31 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 16.7$ (t, $J = 6.1$ Hz, 2C), 21.0 (d, $J = 3.8$ Hz), 21.8 (d, $J = 6.6$ Hz), 26.0, 35.7 (d, $J = 3$ Hz), 46.9 (d, $J = 3.8$ Hz), 55.6, 58.2 (d, $J = 130.6$ Hz), 60.9 (d, $J = 8.3$ Hz), 61.6 (d, $J = 7.6$ Hz), 126.4, 128.0, 128.0, 141.2.

^{31}P NMR (162 MHz, CDCl_3): $\delta = 31.77$.

ESI-HRMS (ESI+): m/z calcd. for $\text{C}_{17}\text{H}_{28}\text{NO}_3\text{P}$ ($\text{M}^+ + \text{H}$) 326.1880, found 326.1886.

Diethyl (1-benzyl-2-pentylpiperidin-2-yl)phosphonate (3g)

Yield: 49 mg (86%); yellow oil.

^1H NMR (400 MHz, CDCl_3): $\delta = 0.83$ (t, $J = 6$ Hz, 3H), 1.12–1.33 (m, 14H), 1.52–2.08 (m, 3H), 2.16–2.28 (m, 1H), 2.58–2.72 (m, 2H), 3.89 (s, 2H), 3.92–4.18 (m, 4H), 7.18–7.28 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 14.1, 16.6$ (t, $J = 5.2$ Hz, 2C), 22.5, 22.7 (d, $J = 3.8$ Hz), 23.5 (d, $J = 9.7$ Hz), 30.0, 31.9, 32.9 (d, $J = 11.9$ Hz), 51.5 (d, $J = 3.7$ Hz), 53.4, 61.1 (d, $J = 8.2$ Hz), 62.1 (d, $J = 7.4$ Hz), 65.2 (d, $J = 143.6$ Hz), 126.5, 128.1, 128.3, 140.9.

^{31}P NMR (162 MHz, CDCl_3): $\delta = 28.80$.

ESI-HRMS (ESI+): m/z calcd. for $\text{C}_{21}\text{H}_{36}\text{NO}_3\text{P}$ ($\text{M}^+ + \text{H}$) 382.2506.

Diethyl (2-pentyl-1-phenylpiperidin-2-yl)phosphonate (3h)

Yield: 49 mg (89%); yellow oil.

^1H NMR (400 MHz, CDCl_3): $\delta = 0.72$ (t, $J = 6.8$ Hz, 3H), 0.77–0.92 (m, 1H), 0.96–1.22 (m, 7H), 1.14 (t, $J = 6.8$ Hz, 3H), 1.22 (t, $J = 7.2$ Hz, 3H), 1.72–1.88 (m, 2H), 1.92–2.11 (m, 2H), 2.18–2.30 (m, 1H), 2.46–2.58 (m, 1H), 3.27–3.39 (m, 2H), 3.80–4.05 (m, 4H), 6.58–6.69 (m, 1H), 7.06–7.16 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 13.9, 16.5$ (t, $J = 3.8$ Hz, 2C), 22.2 (d, $J = 9.8$ Hz), 22.4, 22.7, 29.3, 31.5, 32.3 (d, $J = 10.6$ Hz), 35.6, 51.8, 61.5 (d, $J = 7.6$ Hz), 62.8, 6.8 Hz), 66.2 (d, $J = 154.1$ Hz).

^{31}P NMR (162 MHz, CDCl_3): $\delta = 28.80$.

ESI-HRMS (ESI+): m/z calcd. for $\text{C}_{20}\text{H}_{34}\text{NO}_3\text{P}$ ($\text{M}^+ + \text{H}$) 368.2349, found 368.2346.

Diethyl (1-(4-methoxyphenyl)-2-pentylpiperidin-2-yl)phosphonate (3i)

Yield: 54 mg (91%); yellow oil.

^1H NMR (400 MHz, CDCl_3): $\delta = 0.77$ (t, $J = 7.2$ Hz, 3H), 0.87–1.01 (m, 1H), 1.03–1.22 (m, 7H), 1.19 (t, $J = 7.2$ Hz, 3H), 1.26 (t, $J = 7.2$ Hz, 3H), 1.68–1.89 (m, 2H), 1.95–2.01 (m, 2H), 2.01–2.13 (m, 1H), 2.46–2.57 (m, 1H), 3.28–3.36 (m, 2H), 3.73 (s, 3H), 3.88–4.09 (m, 4H), 6.78 (d, $J = 8.8$ Hz, 2H), 7.17 (d, $J = 9.2$ Hz, 2H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 13.9, 16.5$ (t, $J = 5.3$ Hz, 2C), 22.2 (d, $J = 10.6$ Hz), 22.4, 22.9, 29.3, 31.5, 32.4 (d, $J = 10.7$ Hz), 35.2, 52.1 (d, $J = 3$ Hz), 55.6, 61.3 (d, $J = 7.6$ Hz),

62.7 (d, $J = 7.6$ Hz), 66.1 (d, $J = 154.8$ Hz), 113.9, 117.4, 140.6, 152.2. ^{31}P NMR (162 MHz, CDCl_3) $\delta = 28.98$.

ESI-HRMS (ESI+): m/z calcd. for $\text{C}_{21}\text{H}_{36}\text{NO}_4\text{P}$ ($\text{M}^+ + \text{H}$) 398.2455, found 398.2458.

Diethyl (2-methyl-1-((R)-1-phenylethyl)pyrrolidin-2-yl)phosphonate (3k)

Yield: 43 mg (88%); yellow oil.

The spectrum contains mixture of diastereoisomers. The ratio is 48:52, which is based on ^{31}P NMR.

^{31}P NMR (162 MHz, CDCl_3) $\delta = 28.40, 30.72$.

ESI-HRMS (ESI+): m/z calcd. for $\text{C}_{17}\text{H}_{28}\text{NO}_3\text{P}$ ($\text{M}^+ + \text{H}$) 326.1880, found 326.1882.

Dimethyl (1-benzyl-2-methylpyrrolidin-2-yl)phosphonate (3l)

Yield: 39 mg (91%); Yellow oil.

^1H NMR (400 MHz, CDCl_3): $\delta = 1.38$ (d, $J = 16$ Hz, 1H), 1.67–1.75 (m, 3H), 2.40–2.56 (m, 2H), 2.77–2.85 (m, 1H), 3.58 (d, $J = 12.8$ Hz, 1H), 3.78 (d, $J = 10$ Hz, 1H), 3.85 (d, $J = 9.6$ Hz, 1H), 4.21 (d, $J = 12.8$ Hz, 1H), 7.18–7.39 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 18.6$ (d, $J = 10.9$ Hz), 22.6 (d, $J = 5.4$ Hz), 36.8, 51.5 (d, $J = 10$ Hz), 53.2 (d, $J = 7.7$ Hz), 54.0 (d, $J = 7.7$ Hz), 54.2, 62.1 (d, $J = 161.1$ Hz), 126.6, 128.1, 128.5, 140.5.

^{31}P NMR (162 MHz, CDCl_3) $\delta = 31.24$.

ESI-HRMS (ESI+): m/z calcd. for $\text{C}_{14}\text{H}_{22}\text{NO}_3\text{P}$ ($\text{M}^+ + \text{H}$) 284.1410, found 284.1412.

Dibenzyl (1-benzyl-2-methylpyrrolidin-2-yl)phosphonate (3m)

Yield: 61 mg (91%); Yellow oil. (The spectrum contaminated with dibenzyl phosphite)

^1H NMR (400 MHz, CDCl_3): $\delta = 1.42$ (d, $J = 15.6$ Hz), 1.58–1.79 (m, 3H), 2.42–2.58 (m, 2H), 2.78–2.86 (m, 1H), 3.63 (d, $J = 12.8$ Hz, 1H), 4.25 (d, $J = 13.2$ Hz, 1H), 4.86–5.15 (m, 4H), 7.16–7.38 (m, 15H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 18.6$ (d, $J = 11.6$ Hz), 22.6 (d, $J = 4.7$ Hz), 36.8, 51.6 (d, $J = 9.3$ Hz), 54.3, 62.2 (d, $J = 159.5$ Hz), 66.8 (d, $J = 7.7$ Hz), 68.4 (d, 7.7 Hz), 126.6, 127.8, 127.8, 127.9, 128.0, 128.1, 128.1, 128.4, 128.5, 128.5, 128.6, 132.7, 133.5, 140.5.

^{31}P NMR (162 MHz, CDCl_3) $\delta = 31.24$.

ESI-HRMS (ESI+): m/z calcd. for $\text{C}_{26}\text{H}_{30}\text{NO}_3\text{P}$ ($\text{M}^+ + \text{H}$) 436.2036, found 436.2037.

2-butyl-1-phenylpyrrolidine (4a)

Yellow oil;

^1H NMR (400 MHz, CDCl_3): $\delta = 0.85$ (t, $J = 7.2$ Hz, 1H), 1.24–1.37 (m, 5H), 1.62–1.68 (m, 1H), 1.73–1.78 (m, 1H), 1.83–1.99 (m, 3H), 3.06 (dd, $J = 16$ Hz, 9.2 Hz, 1H), 3.33 (t, $J = 6.8$ Hz, 1H), 3.55 (t, $J = 6$ Hz, 1H), 6.48 (d, $J = 8.4$ Hz, 2H), 6.56 (t, $J = 6.8$ Hz, 1H), 7.11–7.18 (m, 2H);

^{13}C NMR (100 MHz, CDCl_3): δ = 14.2, 22.8, 23.5, 28.9, 30.3, 32.8, 48.2, 58.6, 111.7, 115.1, 129.1, 147.3;

ESI-HRMS (ESI⁺): m/z calcd. for $\text{C}_{14}\text{H}_{21}\text{N}$ ($\text{M}^+ + \text{H}$) 204.1747, found 204.1750.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the National Institutes of Health for financial support (NIGMS-1R15GM101604-01). We thank Professor Dr. Bernhard Straub (Heidelberg University) for his insights on the reaction mechanism. We acknowledge the support provided by the CREAM Mass Spectrometry Facility (University of Louisville) funded by NSF/EPSCoR grant # EPS-0447479.

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Scheme 1.

Tandem protocol for the construction of rings through enamine activation.

Scheme 2.

Literature synthesis of cyclic α -amino phosphonates derivatives.

Scheme 3.
Activation of enamine – converting enamine to an electrophile.

Scheme 4.

CuBr coordination to enamine and alkyne (B3LYP-D3/6-311+G(d,p) with LANL2DZ ECPs for Cu/Br. Relative free energy at 298K in kcal/mol).

Scheme 5.
Proposed mechanisms (Nu-H =dialkyl phosphite).

Table 1

Optimization of the reaction condition for **3a**^a

entry	catalyst	additive	solvent	temp/time	yield ^b 3a(4a)%
1	CuBr	none	dioxane	rt, 6h	76(21)
2	CuBr	H ₂ O (2 equiv)	dioxane	rt, 6h	58(37)
3	CuBr	HCOOH	dioxane	rt, 6h	12(63)
4	CuBr	none	toluene	rt, 6h	86
5	CuBr	3A MS	toluene	rt, 6h	92
6	CuBr	3A MS	toluene	microwave, 100°C, 0.5h	88

^aReaction condition: amino alkyne **1a** (0.15 mmol), diethyl phosphite **2a** (0.3 mmol) with 5 mol % CuBr in 1mL solvent.

^bIsolated yields.

Table 2

Scope of the tandem amination/phosphorylation.

1	+	$\text{HP}(\text{OR})_2$ 2	$\xrightarrow[\text{toluene, rt, 6h}]{5 \text{ mol } \% \text{ CuBr, 3A MS}}$	3
entry	1	2	3, yield	
1			3a, 92%	
2			3b, 94%	
3			3c, 93%	
4			3d, 88%	
5			3e, 67%	

1	+	O $\text{HP}(\text{OR})_2$ 2	$\xrightarrow[\text{toluene, rt, 6h}]{5 \text{ mol \% CuBr, 3A MS}}$		3
entry	1	2	3, yield		
6					
7					
8					
9					
10					

1 + 2		$\xrightarrow[\text{toluene, rt, 6h}]{5 \text{ mol } \% \text{ CuBr, 3A MS}}$	3
entry	1	2	3, yield
11		2a	3k , 88% dr= 1:1.1
12		2b	3l , 91%
13		2c	3m , 94%

^aCondition: 5mol% CuBr, **1** (0.15 mmol), **2** (0.3 mmol), 3A MS, toluene, rt, 6h.

^bIsolated yield.

^cThe isolated product was contaminated with a small amount of dibenzylphosphite.