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3-Imidoallenylphosphonates: *In Situ* Formation and β-Alkoxylation

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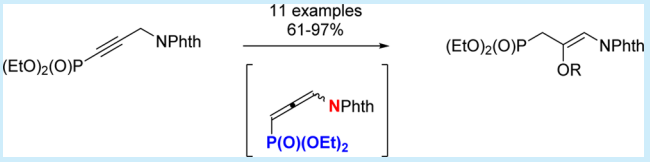
Supporting Information

ABSTRACT: 3-Imidoallenylphosphonates, allenes bearing both an electron-withdrawing and -donating group, were isolated for the first time. An alkoxy substituent was introduced into these unprecedented intermediates in a one-pot approach, yielding β-functionalized aminophosphonates in excellent yields and short reaction times. The mechanistic insights gained are important additions to the domain of allene chemistry. Addition of biologically important molecules, including monoglycerides, amino acids, and nucleosides, proves the general applicability of the developed method.

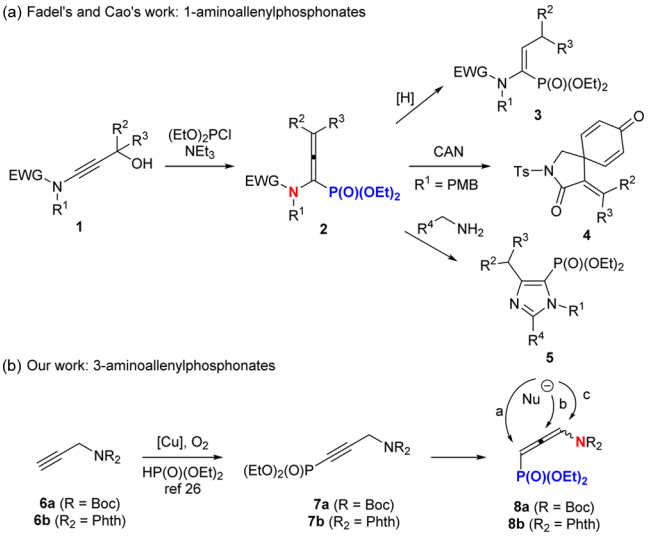


Allenes are highly interesting building blocks, displaying a broad range of reactivities owing to their unique molecular structure of cumulated double bonds.[1,2] Like alkynes,[3,4] they are excellent substrates for transition-metal-catalyzed cycloisomerizations and readily participate in cycloadditions.[5] They are, however, often underused because of their supposedly low stability. Amino-substituted allenes react with alcohols, thiols, and secondary amines to give 1,2-adducts[6] and react in [2 + 2] or [2 + 4] cycloadditions.[7] These electron-rich allenamines, however, are difficult to handle. They tend to polymerize even at low temperatures and are sensitive to moisture.[8] Amidoallenes, being less electron-rich, are more stable and display enamide reactivity. For instance, they are hydroaminated through Lewis acid activation of the proximal double bond[9] or undergo alkoxylation at the α- or γ-position, but usually not at the β-position.[10] On the other hand, nucleophilic addition to acceptor substituted allenes usually takes place at the β-position yielding either the nonconjugated (kinetic control) or the conjugated (thermodynamic control) product. In this work we explored the unique reactivity pattern of allenylphosphonates bearing an imide *N*-substituent. As part of our continuing interest in phosphonylated *N*-containing compounds,[11−15] we investigated the one-pot synthesis and conversion of these previously unreported 3-imidoallenylphosphonates **8** (Scheme 1b). The first synthesis of allenylphosphonates was reported simultaneously by Mark and Boisselle, employing a [2,3]-sigmatropic rearrangement of phosphonylated propargyl alcohols.[16,17] These allenylphosphonates were readily activated by electrophiles to produce oxaphospholenes through intramolecular cyclization.[18] Recently, the Fadel group reported the same sigmatropic rearrangement for ynamido-alcohols, yielding the corresponding 1-sulfonamidoallenylphosphonates **2**.[19] They could be selectively reduced to α-vinylaminophosphonates **3**, but also reacted in a 5-*endo*-*dig* cyclization upon deprotection of the PMB-group with CAN (Scheme 1a).[20] Reaction with primary amines produced phosphonylated imidazoles **5**.[21]

Phosphite addition to propyn iminium salts failed to produce 3-aminoallenylphosphonates, and to the best of our knowledge, there is no further information on the synthesis or reactivity of 3-aminoallenylphosphonates **8**.[22,23] Aside from the mechanistic interest, they are also precursors to γ-aminophosphonates. Aminophosphonates are bioisosteres of amino acids and can act as peptidomimetics in known antibacterial, antifungal, and herbicidal agents.[24] Allenes themselves can also play an important role in the metabolic stability of pharmaceuticals. Enprostil is a marketed prostaglandin analogue that is over 600 times more potent than PGE_2 in inhibiting gastric acid secretion.[25]

Our investigation started from phosphonylated propargylamines **7a−b**, which were easily prepared using an improved literature procedure. Gao reported an elegant phosphonylation

Scheme 1. Approaches for the Synthesis of Aminoallenylphosphonates



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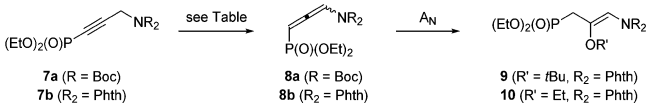
of alkynes under a dry air atmosphere, but only on a 0.5 mmol scale and requiring 16 h.[26] When scaling up the reaction we found that also Glaser coupling occurred, which could be suppressed by bubbling oxygen through the reaction mixture. The phosphonylated alkynes **7a−b** were obtained in high yields on a 10 mmol scale in drastically shortened reaction times (see Supporting Information). In preliminary experiments, phosphonylated *N*,*N*-di-Boc-propargylamine **7a** was used as starting material. At first, stoichiometric isomerization was evaluated with organolithium bases (BuLi, LDA) in aprotic media.[27,28] However, the isomeric allenic products could not be detected (Table 1, entries 1−2).[29]

Table 1. Optimization of Isomerization and Nucleophilic Addition Conditions



7a (R = Boc)
7b (R_2 = Phth)

8a (R = Boc)
8b (R_2 = Phth)

9 (R' = *t*Bu, R_2 = Phth)
10 (R' = Et, R_2 = Phth)

entry	equiv base	base	solvent	time (min)	*t* (°C)	**8** (%)[c]	**9**/**10** (%)[c]
1	1	BuLi	dry Et_2O	60	−78	0	0
2	1	LDA	dry Et_2O	180	0	0	0
3	1	NaH	dry THF	60	rt	32	0
4	0.2	NaH	dry THF	30	Δ	24	0
5	0.2	KO*t*Bu	DMSO	5	rt	0	7
6	1	KO*t*Bu	dry THF	1	rt	19	4
7[a]	0.2	KO*t*Bu	dry THF	2	0	47	0
8	1	KO*t*Bu	*t*-BuOH	5	40	34	25
9	2	KO*t*Bu	*t*-BuOH	1	40	0	100
10[b]	1	K_2CO_3	THF	8 days	rt	0	100
11[b]	1	Cs_2CO_3	THF	40	rt	0	100

[a]1 equiv of *t*-BuOH added. [b]1 equiv of EtOH added. [c]^{31}P NMR conversion.

Accordingly, phthalimidoyl protected alkyne **7b** was then used exclusively, as the Boc-groups of alkyne **7a** were not stable under the previously applied conditions. Next, the isomerization using a milder NaH or KO*t*Bu aprotic system was investigated. Using a stoichiometric amount of NaH, 32% of the starting material was converted into the allene within 1 h,[30] after which degradation quickly occurred (entry 3). Using a catalytic amount of NaH led to a lower conversion, while secondary reactions still occurred (entry 4). When performing the reaction in DMSO with KO*t*Bu as the base,[31] 7% conversion to an addition product **9** was observed (entry 5). Although allene **8b** was not detected, this addition product caught our interest given the position of the double bond.[32] Switching the solvent to THF and employing a stoichiometric amount of base[33] gave the allene intermediate **8b** and the addition product **9** together for the first time (entry 6). Providing a proton source by adding 1 equiv of *t*-BuOH markedly increased the conversion of the starting material, giving ∼50% of the allene in only 2 min at 0 °C (entry 7). Longer reaction times gave complex mixtures. Screening of different solvents in the KO*t*Bu/*t*-BuOH system revealed that conversion to allene **8b** was rapid but a conversion higher than 50% could not be achieved (SI, Table 1), as alkyne **7b** and allene **8b** were most likely in equilibrium. We then decided to scavenge the intermediate allene **8b** to obtain full conversion to the addition product.

Performing the addition in *t*-BuOH instead of adding just 1 equiv of *t*-BuOH as a proton source[34] clearly drives addition of the nucleophile to the allene intermediate (entry 8). Increasing the amount of KO*t*Bu to 2 equiv gave complete reaction in no more than 60 s (entry 9). We next investigated whether other—and eventually nonvolatile—nucleophiles could be added. To that end, a non-nucleophilic base, an aprotic solvent, and the use of a stoichiometric amount of the nucleophile were required (conditions A). Hence, K_2CO_3 and THF were selected, using 1 equiv of EtOH as the nucleophile. The addition product **10** was obtained as the single product, but full conversion required 8 days (entry 10). We reasoned that the limited solubility of the base hampered reaction progress. Thus, replacing K_2CO_3 with Cs_2CO_3 gave a completed reaction in only 40 min (entry 11).[35] NMR disclosed a *Z*-configuration of the olefin based on a 2.5% NOE-enhancement of the vinylic proton when irradiating CH_2P. No NOE-effects were observed between OCH_2 and the vinylic proton.

Next, we prepared a small library of derivatives. The addition of primary, secondary, and tertiary alcohols was first evaluated (Scheme 2, compounds **9−11**). As steric hindrance of the introduced nucleophile increased, the transformation proceeded more slowly, and in the case of *t*-BuOH, a complex mixture was obtained. With *i*-PrOH, the addition product was still the major product, along with some remaining alkyne and allene starting material and a multitude of minor impurities. For volatile nucleophiles, the nucleophile could be applied as the solvent (conditions B). With EtOH, addition was rapid (60 s), and the addition product **10** was isolated in 97% yield. The *i*-PrOH derivative **11** could similarly be obtained in 94% yield. Upon conducting the reaction in *t*-BuOH as a solvent, 82% conversion to **9** was achieved after 3 h at 40 °C. Longer reaction times gave secondary reactions that prevented isolation of **9**. Other primary alcohols such as *n*-BuOH and BnOH smoothly gave the desired compounds **12** and **14** in yields around 90% (conditions A), again without the need for purification. Phenol reacted rapidly to give a mixture of two addition products **13a** and **13b** in a 6:1 ratio and 90% yield. With the sterically demanding (−)-borneol as a nucleophile, the intermediacy of the allene was illustrated once again, but a conversion higher than 20% to the addition product **15** could not be achieved, nor could **15** be isolated. The presence of an electrophilic group in the substrate, such as the aldehyde in 5-HMF (5-hydroxymethylfurfural), did not complicate matters giving full conversion to **16** in 90% crude yield in 1 h. When preparing an analytical sample, the removal of some minor impurities required reversed phase flash chromatography causing partial degradation, which has been previously observed in the isolation of related HMF derivatives.[36] The coupling of two allene moieties with ethylene glycol also proved to be easily achievable as all of the starting material was converted into an easily separable 91/9 mixture of bis-adduct **17a** and monoadduct **17b**. When water was evaluated as a nucleophile, the formation of the corresponding ketone was expected, but we instead observed formation of a complex reaction mixture, probably due to aldol-type reactions.

Finally, the addition of more complex and biologically relevant molecules was investigated. Addition of DL-α-palmitin gave rise to phospholipid-type product **18**. Full conversion was obtained in 30 min, resulting in four addition products (ratio 9:34:50:7 in 96% crude yield), which could not be separately isolated (see SI). Addition of protected amino acids resulted in phosphonopeptides **19** and **20**. Phosphonopeptides often display important biological activities. Bialaphos for instance is an antibacterial metabolite, which also possesses strong herbicidal properties.[24] Adduct **19** was isolated in 63% yield as a 9/1 *Z*/*E* mixture. Partial

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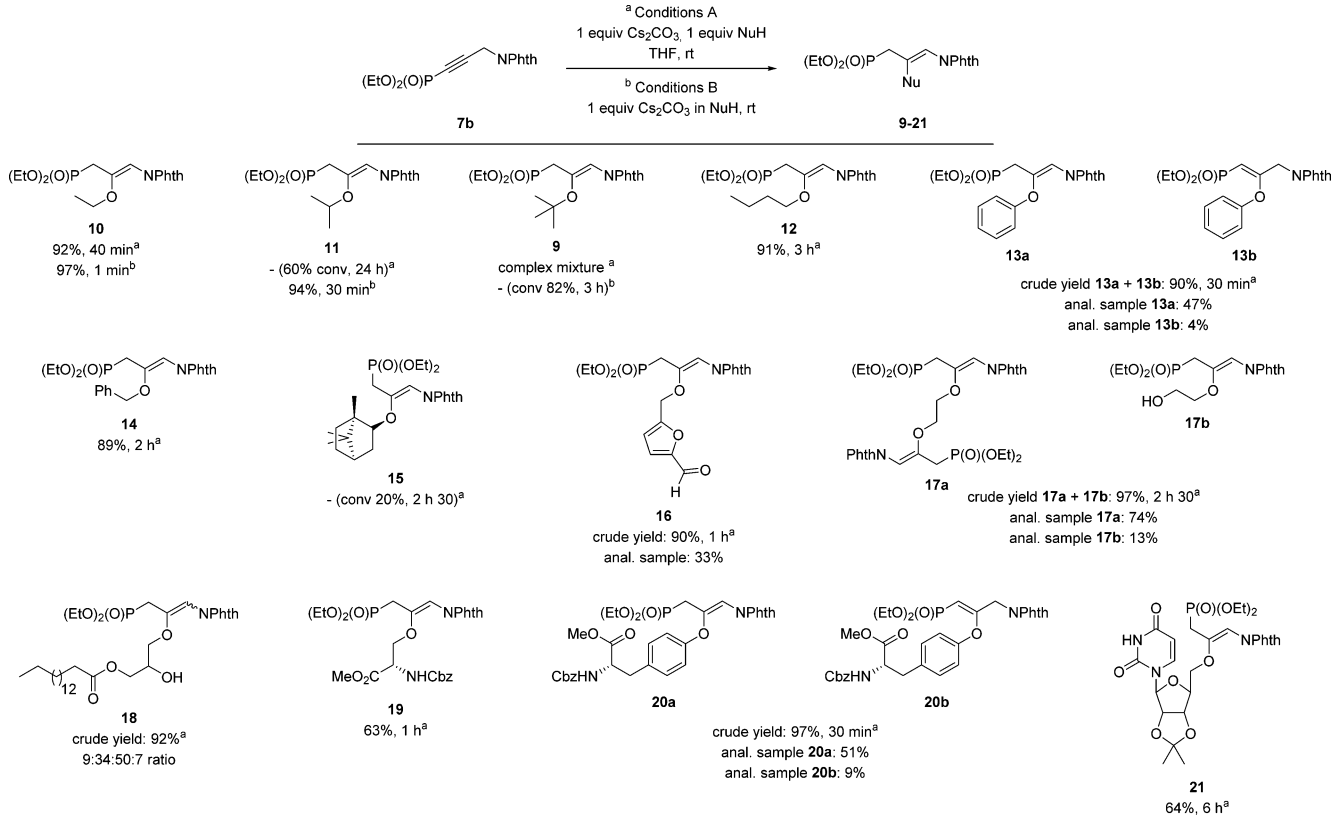
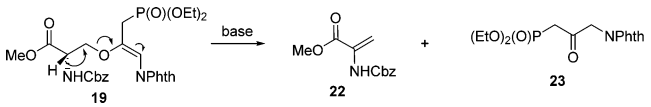
Scheme 2. Substrate Scope of Formation of β-Functionalized Aminophosphonates[a]



[a]Isolated yield and reaction time are indicated.

elimination of the addition product **19**, giving **22** and **23**, was unavoidable, even when running the reaction at 0 °C, and accounts for the slightly lowered yield in comparison to less complex nucleophiles (Scheme 3).

Scheme 3. Elimination of the *N*-*Z*-L-Serine Methyl Ester Addition Product

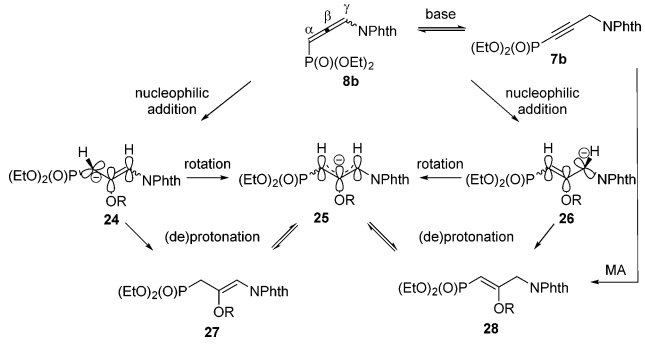


Addition of *N*-*Z*-L-tyrosine methyl ester did not suffer from this elimination reaction, as no acidic proton is present in the tyrosine methyl ester. As was the case with the addition of phenol, allylphosphonate **20a** and vinylphosphonate **20b** were swiftly formed in a 6:1 ratio in 97% crude yield, after which the regioisomers were separated from each other. The conformation of **20b** was confirmed to be *Z*, as a 2% NOE-effect was found on the vinylic proton when irradiating NCH_2. Ultimately, the addition of protected uridine was evaluated, as phosphonucleosides such as tenofovir and adefovir are used in the treatment of HIV. We were pleased to find that the uridine addition product **21** could be isolated in 64% yield. For all of the synthesized derivatives, addition selectively occurs at the central C-atom. This illustrates that 3-imidoallenylphosphonates behave as acceptor substituted allenes.

Finally, we investigated the mechanism of this alkoxylation reaction. Michael addition to alkyne **7b**[37] would initially produce vinylphosphonate **28** which can isomerize to yield the allylphosphonate **27**. Although vinylphosphonate **28** was never detected in NMR experiments, only alkoxylation of isolated allene **8b** can unambiguously rule out Michael addition. To this end, alkyne **7b** was isomerized (Cs_2CO_3/THF; see SI) to the allene **8b** resulting in the first ever isolation of the 3-imidoallenylphosphonate **8b** in 16% yield. First, it was found to be stable for several days, thus countering arguments that these allenes display low stability. Second, allene **8b** was indeed in equilibrium with alkyne **7b**, as 16% isomerization to **7b** was found under the same conditions.

Most importantly, full conversion of allene **8b** to allylphosphonate **27** in the presence of Cs_2CO_3 and EtOH is compelling evidence for the allene being the key intermediate in this one-pot, two-step reaction. However, it is clear that product **28** can also be produced from the addition to allene **8b** (Scheme 4). Regardless of the nucleophile adding across the $C_\alpha-C_\beta$ or the $C_\beta-C_\gamma$ double bond, the formation of a nonconjugated allyl anion, **24** or **26**,

Scheme 4. Proposed Mechanism



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results, owing to the unique orbital structure of allenes. These nonconjugated anions either can be immediately protonated to give **27** or **28** respectively or can rotate around their single bond, forming the conjugated allyl anion **25**. After protonation this can lead again to the formation of either the allylphosphonate **27** or the vinylphosphonate **28**.

During our syntheses we exclusively observed the formation of allylphosphonates **27**, except for phenolic nucleophiles. In the case of phenol addition at rt, a 6:1 **27**/**28** ratio was found. When this addition was repeated at 0 °C we found a 12:1 **27**/**28** ratio. This indicates either that the addition reaction is under kinetic control or that Michael addition to alkyne **7b** occurs (**7b** to **28**) and is suppressed at this lower temperature. Whatever the case, it was shown that the pathway does not primarily pass over **28**. Under the applied conditions (rt, Cs_2CO_3) **28** did not isomerize to **27**. Furthermore, **27** was shown to be the thermodynamically more stable product, as **28** was entirely converted to **27** upon 18 h of reflux. Thus, the formation of **28** is not a part of the major reaction pathway.[38] This is in accordance with literature data, as addition of NaN_3 to 3-phenylpropa-1,2-dienylphosphonate also gives the allylphosphonate, preserving the double bond conjugated to the aromatic group.[39]

In conclusion, the first synthesis of 3-imidoallenylphosphonates was demonstrated. This transformation proceeds via a prototropic rearrangement under very mild conditions, and the imidoallenylphosphonate was isolated and characterized. Moreover, it can be alkoxylated in a one-pot procedure in very short reaction times in excellent chemical yields. The method is applicable to an array of highly functionalized biologically relevant nucleophiles, furnishing these adducts in moderate to good yields. Purification on column was needed only in the case of the more complex nucleophiles (**15**−**21**).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03314.

Experimental details, product characterizations, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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