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Hydro/Fluoro-phosphoro(di)thiolation of Allenamides: Toward S_N2-Selective Transition-Metal-Free Formal Hydrocarbonation

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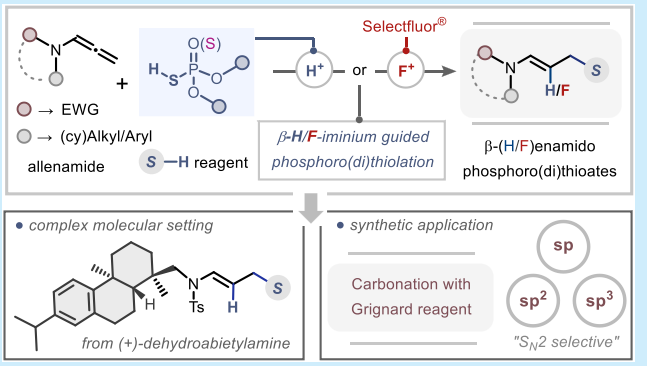
ABSTRACT: Two versatile synthetic strategies for β-H/F-enamide-tagged phosphoro(di)thioates from allenamides are disclosed, relying on electrophilic activation via β-H and F-iminium species. These developed straightforward protocols demonstrate broad applicability in complex molecular contexts with remarkable chemo- and regioselectivity. The synthesized allylphosphoro-thioates (APTs) act as potent electrophiles, enabling S_N2-selective allylic substitution with (hard)C-nucleophiles of all hybridizations to deliver hydrocarbonation products in seamless complement to transition-metal-driven strategies.



Widely valued for its exceptional biological properties, the phosphorothioate group stands as a key structural motif in the agrochemical and pharmaceutical fields.[1,2] In particular, phosphorothioates containing heteroatoms such as nitrogen demonstrate a broad spectrum of biological activities, including pesticidal,[2a] anticholinesterase,[2b] anti-inflammatory,[2c] and cardioprotective properties (top, Scheme 1A).[2d] Furthermore, the concatenation of π-carbogenic units, such as allylic units, is crucial because these motifs can impart vast structural diversity through further synthetic manipulations.[3] In this regard, the diversification of allyl phosphorothioates (APTs), owing to their excellent leaving-group properties derived from C−S bond cleavage, enables a wide range of valuable nucleophilic displacement transformations.[4] A most notable example in this context is the site-specific and stereospecific allylic substitution reaction (ASR) with hard nucleophiles. Wu's group demonstrated that APTs undergo substitution in both S_N2 and S_N2' fashion due to their intrinsic electrophilicity, where Grignard reagents and fluoride anions selectively attack the C−S bond, with regioselectivity in the former case governed by the degree of substitution around the nucleophile (bottom left, Scheme 1A).[4a] Consequently, our endeavor to synthesize enamido-phosphorothioates within the realm of allyl electrophiles, merging the distinctive synthetic virtues of both enamide[5] and phosphorothioate moieties, may unveil noteworthy biological and synthetic significance (bottom right, Scheme 1A).

Central to the synthesis of APTs and their dithio analogues is the use of phosphoro(di)thioic acids under metal-free conditions in which an allylic leaving group or assisting functionality facilitates C−S bond formation (Scheme 1B). A representative example is the photochemical or Lewis acid-mediated strategy reported by Wu's group, which employs allylic alcohols and ethers undergoing S_N2-selective substitution (top, Scheme 1B).[4a,6] Another approach utilizes strained-rings-based allylic substrates, in which strain-release-driven ASR promotes C−S bond formation via the S_N2 or S_N2' pathway (bottom, Scheme 1B).[7] Depending on the substrate architecture and reaction conditions, both substitution patterns can be accessed, although mixtures of *Z* and *E* isomers are sometimes observed. Collectively, these studies highlight the need for site-selective incorporation of a phosphoro(di)thioate group at the allylic position of more diverse π-scaffolds, such as an enamide unit,[5] in an atom-economical and highly selective manner.

In addition, although substantial progress has been made in the phosphorothiolation of alkenes and alkynes, the hydro-phosphorothiolation of allenic π-systems remains largely unexplored despite their ready availability and inherent reactivity. Notably, electron-rich allenamides, well-known for diverse regio- and stereoselective hydrofunctionalization profiles, represent a largely untapped opportunity, as highlighted in recent studies from our group and others.[8,9] Our aim was to develop methods capable of generating conjugated

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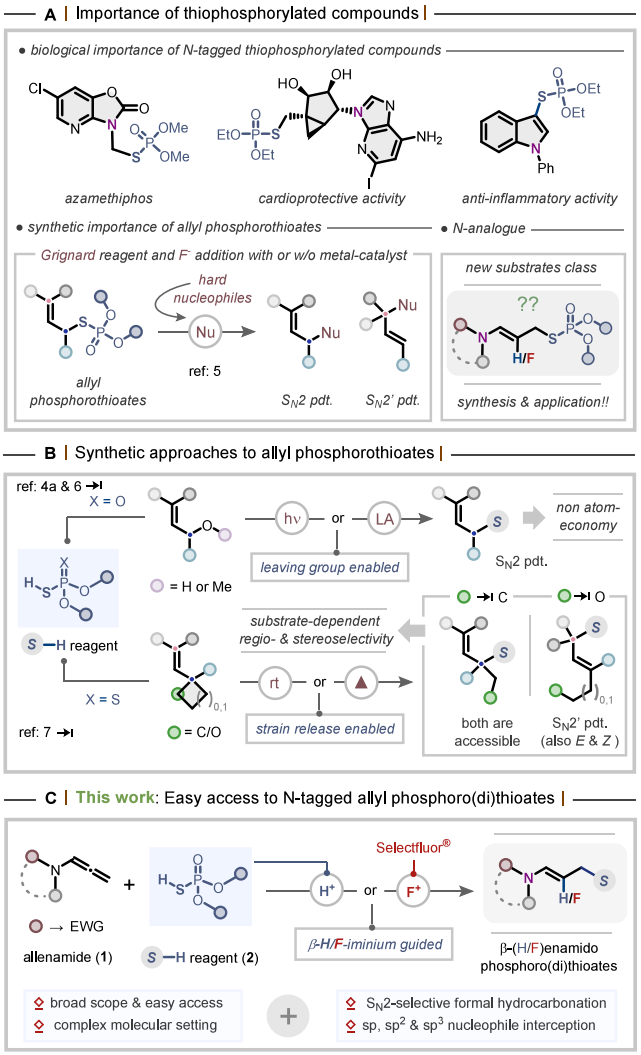
Scheme 1. Inspiration for the Development of Hydro/Fluoro-phosphoro(di)thiolation of Allenamide

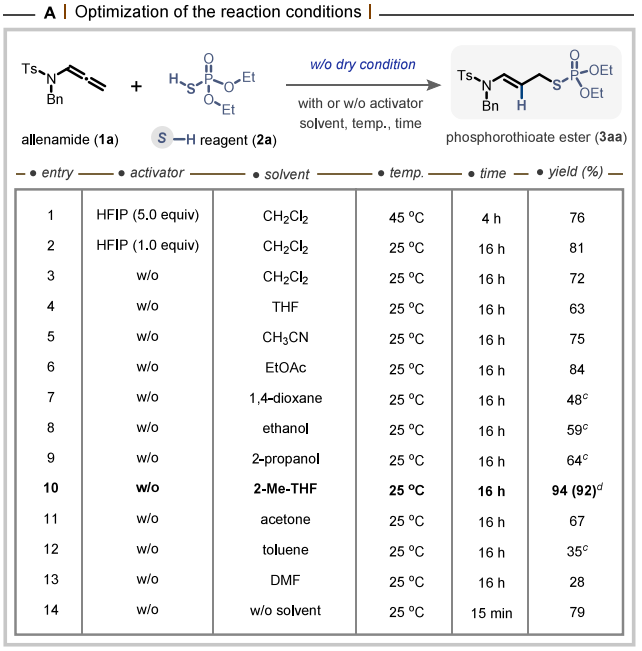


iminium species[10] that retain highly promising reactivity, while being clearly distinguished from conventional π-systems by enabling both regio- and stereoselective transformations. Guided by this concept, the present study was inspired by the use of dialkyl esters of (di)thiophosphoric acids (S−H reagent, **2**; $pK_a \approx 1.5$ in H_2O),[11] which can introduce a (di)thiophosphoryl unit without the need for additional acid promoters.[7,12] In addition, the synthesis of fluorinated analogues, recognized as versatile and multifunctional core scaffolds, offers further synthetic potential.[13] In our recent strategy, β-fluoroaminals were shown to be irreversibly converted into iminium intermediates under Selectfluor activation,[8b] enabling formal fluorocarbonation. We therefore anticipated that engagement of the S-nucleophile (**2**) with the resulting β-F iminium species would forge a C−S bond (Scheme 1c).

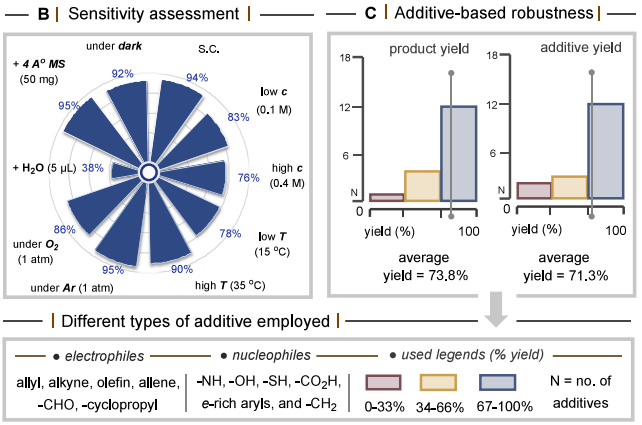
Furthermore, the ASR of substrates bearing an enamido unit, as well as the regioselective interception of hard nucleophiles, has remained largely unexplored. Because APTs can also undergo transition-metal-free ASR (left, Scheme 1A), a strategy that ensures complete site-selective nucleophile interception, typically dictated by steric and nucleophilic parameters, would be highly desirable from a synthetic standpoint. Notably, unlike previous ASR studies involving hard nucleophiles, the transformations reported herein display regioselectivity that is independent of the steric properties of the nucleophiles. Moreover, the resulting compounds constitute new molecular architectures that engage carbon-based nucleophiles of all hybridization types and complement existing transition-metal-catalyzed approaches.[4b,c,14]

We began by examining the reactivity of alleamide (**1a**) and diethylphosphorothioate (**2a**) under various activation conditions (Table 1). Notably, the desired product **3aa** was

Table 1. (A) Optimization Study and Assessment of (B) Sensitivity and (C) Additive-Based Robustness[a,b]



entry	activator	solvent	temp.	time	yield (%)
1	HFIP (5.0 equiv)	CH_2Cl_2	45 °C	4 h	76
2	HFIP (1.0 equiv)	CH_2Cl_2	25 °C	16 h	81
3	w/o	CH_2Cl_2	25 °C	16 h	72
4	w/o	THF	25 °C	16 h	63
5	w/o	CH_3CN	25 °C	16 h	75
6	w/o	EtOAc	25 °C	16 h	84
7	w/o	1,4-dioxane	25 °C	16 h	48[c]
8	w/o	ethanol	25 °C	16 h	59[c]
9	w/o	2-propanol	25 °C	16 h	64[c]
10	**w/o**	**2-Me-THF**	**25 °C**	**16 h**	**94 (92)[d]**
11	w/o	acetone	25 °C	16 h	67
12	w/o	toluene	25 °C	16 h	35[c]
13	w/o	DMF	25 °C	16 h	28
14	w/o	w/o solvent	25 °C	15 min	79



[a]Unless otherwise noted, the reaction of **1a** (0.2 mmol) and **2a** (0.2 mmol) in a solvent (0.2 M) at 25 °C was performed. [b]^{1}H NMR yield of **3aa** using 1,3,5-trimethoxybenzene as an internal standard. [c]No full conversion. [d]Isolated yield of **3aa**.

obtained under multiple conditions even in the absence of a protic activator such as HFIP (entries 1 and 2 vs entries 3−13). The optimized protocol employed equimolar amounts of **1a** and **2a** in 2-methyl tetrahydrofuran (0.2 M) at 25 °C for 16 h without any drying precautions. Remarkably, product **3aa** could also be produced in a synthetically useful 79% yield under solvent-free conditions within just 15 min (entry 14).

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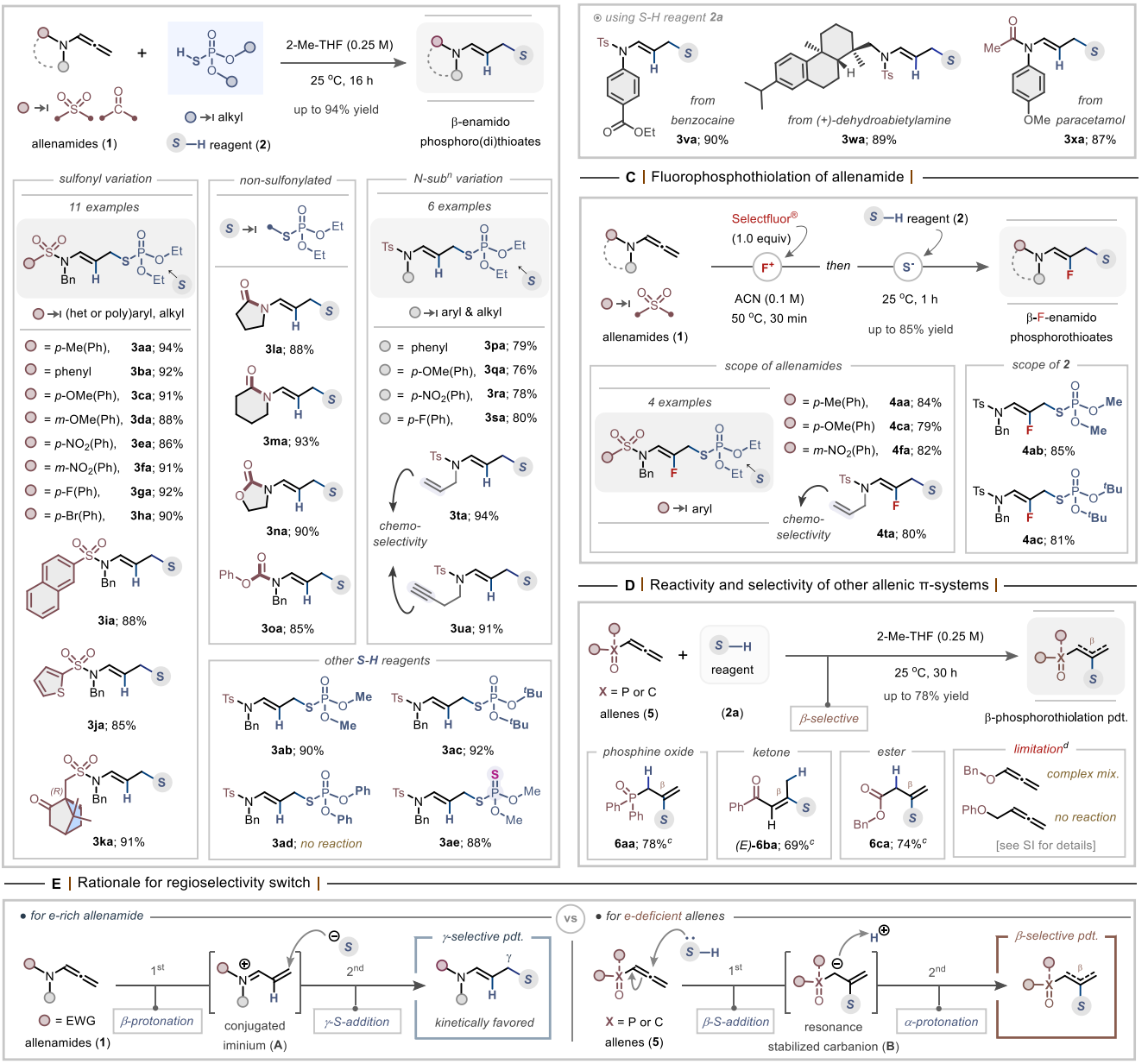
Scheme 2. Generality of the Hydro/Fluoro-phosphoro(di)thiolation Reaction of Allenamides[a,b]



[a]All reactions were carried out using 0.2 mmol of each **1** and **2** under the standard conditions. S.C. = standard condition. EWG = electron-withdrawing group. [b]Isolated yield of **3**. [c]Reaction time of 30 h. [d]For details of the results, see the Supporting Information.

The stereochemistry of **3aa** was confirmed to be *trans*, based on the large vicinal ^{1}H–^{1}H coupling constants ($^3J \geq 14$ Hz) observed for the enamide double bond.

With the optimized conditions established, we evaluated the reaction's robustness using Glorius' condition-based screening.[15] In line with the optimization data, the transformation proved to be largely insensitive to variations in concentration, temperature, light, trace oxygen, and reaction dryness. In contrast, addition of water (5 μL per 0.2 mmol of **1a**) significantly diminished reactivity, likely due to rapid hydrolysis of the iminium intermediate generated from **1a**. To further probe the chemoselectivity, we performed additive-based screening, quantifying both the product yield and additive recovery in the presence of diverse electrophilic and nucleophilic additives. The reaction exhibited broad tolerance toward electrophilic functionalities—including C–C π-systems (internal/terminal alkenes, allylic systems, and alkynes), aldehydes, electron-neutral allenes, and donor–acceptor cyclopropanes—many of which are known to react with thiophosphorates.[16] Electron-rich allenes, however, competitively engaged the electrophile, resulting in product mixtures. In contrast, nucleophilic additives, such as anilines, phenols, thiols, carboxylic acids, and indoles, showed moderate compatibility under the reaction conditions. Full data and analysis are provided in the Supporting Information (Table S3 and Figure S2) and summarized in Table 1C. Overall, the average yields of both the desired product (≈74%) and the additive (≈71%) highlight the chemoselectivity and robust synthetic applicability of the transformation.

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With a reliable synthetic blueprint in hand, we next examined the substrate scope to assess the generality and limitations of the reaction (Scheme 2). A broad array of allenamides (**1**) were smoothly converted into the corresponding enamidophosphorothioates with uniformly excellent regio- and stereoselectivity (Scheme 2A). Sulfonylated allenamides—including derivatives possessing electron-neutral (**3ba**), electron-rich (**3ca** and **3da**), and electron-deficient (**3ea**−**ha**) aryl groups at various substitution sites, along with polyaryl (**3ia**) and heteroaryl (**3ja**) variants—reacted efficiently with S−H reagent **2a** to afford the corresponding products in consistently high yields (85−94%) without notable variation (left, Scheme 2A). Halogen substituents such as bromo (**3ha**) were well tolerated, enabling downstream synthetic diversification. Aliphatic sulfonyl-based allenamides, including a bridged bicyclic system containing an electrophilic carbonyl (**3ka**), also underwent hydrothiophosphorylation in a chemoselective manner. Moreover, among the nonsulfonylated allenamides, both cyclic amides (**3la** and **3ma**) and cyclic (**3na**) and acyclic (**3oa**) carbamates proved to be competent substrates, irrespective of the electronic environment around the nitrogen atom.

Given the versatility of enamide frameworks and the strong influence of N atom electronics on their reactivity, we explored variations of non-electron-withdrawing substituents around the nitrogen atom of the allenamide (top right, Scheme 2A). A variety of aryl rings with distinct electronic profiles delivered the corresponding enamidophosphorothioates (**3pa**−**3sa**) with exclusive distal regioselectivity in good to excellent yields. Interestingly, when olefin- and alkyne-tagged substrates were employed, only the hydrophosphorothiolation products (**3ta** and **3ua**, respectively) arising from the allenic unit were observed. This outcome highlights the pronounced chemoselectivity of the reaction in discriminating between potential iminium-assisted and carbocation-mediated hydrophosphorothiolation pathways. The protocol was also broadly applicable to sterically diverse phosphorothioates (**3ab** and **3ac**) and phosphorodithioates (**3ae**) without additional optimization. In contrast, attempts to prepare phenoxy-based enamidophosphorothioate (**3ad**) were unsuccessful. Owing to its operational simplicity, the synthetic utility of the protocol was further demonstrated in complex molecular settings (Scheme 2B). Allenamides derived from amino ester drugs (benzocaine), complex diterpene amines (dehydroabietylamine), and the nonopioid analgesic and antipyretic agent paracetamol furnished the corresponding enamidophosphorothiolates (**3ua**−**3wa**, respectively) efficiently, underscoring the broad applicability of the method.

Given the versatility and biological relevance of vinyl fluoride frameworks, we next evaluated the applicability of the transformation to fluorinated analogues, drawing inspiration from our recently developed β-fluoroiminium-guided nucleophile interception strategy.[8b] This platform was extended to a fluorophosphorothiolation reaction (Scheme 2C). Using a sequential one-pot protocol analogous to our previous work, treatment of the allenamide with 1.0 equiv of Selectfluor at 50 °C generated the β-fluoro-conjugated iminium electrophile, which was then intercepted by the S−H nucleophile (**2a**). Notably, interception occurred at a faster rate (1 h) relative to the standard conditions, delivering β-fluoro enamidophosphrothioates (**4**) in yields of up to 84%. As expected, extension of the scope to allenamides bearing variations at the sulfonyl group and nitrogen substituents (**4aa**, **4ca**, and **4fa**) revealed no significant electronic preference while maintaining the desired reactivity and selectivity. Furthermore, comparison of β-fluoroiminium-mediated versus carbocation-mediated olefin reactivity allowed for selective hydrophosphorothiolation (see **4ta**). The steric bulk of the S−H reagent had little impact on the efficiency of this formal fluorophosphorothiolation, as demonstrated by products **3ab** and **3ac**.

In contrast, the nature of the allenic substituent proved to be critical for sustaining reactivity and maintaining the required electronic balance within the allenic framework (Scheme 2D). This balance determined whether the standard site selectivity was retained or switched. Unlike *N*-allenamides carrying electron-withdrawing groups (EWGs), electron-deficient C- or P-allenes (e.g., allenic phosphine oxide, ketone, and ester derivatives) efficiently intercepted the S−H nucleophile (**6aa**−**6ca**, respectively) at the central β-carbon, consistent with the electronic effects imparted by these EWGs. These substrates afforded the corresponding products in up to 78% yields, albeit with a longer reaction time (30 h at room temperature).

These results suggest that electron-rich allenamides preferentially undergo initial protonation to generate iminium intermediate **A**, which is kinetically favored over conjugate addition (in the case of **5**). Subsequent sulfur nucleophilic attack proceeds via enolate-like intermediate **B** and is governed predominantly by electronic effects (Scheme 2E). For the allenic ketone, concomitant olefin isomerization furnished more stable *E*-conjugated product **6ba**. The observed regioselectivity switch highlights the potential of this platform for the rapid and modular construction of olefin-functionalized phosphorothioates. The limit of reactivity was reached with comparatively reactive electron-rich allenyl ethers and electron-neutral allenes, both of which proved to be unsuitable for the transformation (bottom right, Scheme 2D). We attribute these limitations to the instability of the electrophilic intermediate in the former, leading to facile hydrolysis, and to the inability of the S−H reagent to protonate the allene in the latter.

In line with prior studies and to further delineate the electrophilic character of the newly synthesized enamido-APTs as a versatile synthetic platform, we examined their reactivity toward hard carbon nucleophiles, derived from Grignard reagents, representing all hybridization types under transition-metal (TM)-free conditions. For substitution studies, enamidophosphorothioate **3aa** was prepared on a 10-fold scale under the optimized conditions, providing 1.34 g of material (Scheme 3A). The ensuing substitution reactions—including (a) alkynylation (**7a**−**7c**), (b) arylation (**7d**), and (c) alkylation (**7e**−**7g**)—all proceeded with complete S_N2 selectivity (top, Scheme 3B). Remarkably, several advantageous features arise from this TM-free protocol. (1) Both the alkynylation and arylation steps constitute formal allenamide hydrocarbonation processes that bypass the need for Pd catalysis and precious phosphine ligands.[14] (2) Nucleophilic substitution reactions with Grignard reagents typically require Cu(I) catalysis,[17] but variants promoted by other transition metals are also known. (3) Unlike prior reports, the substitution selectivity observed here is independent of nucleophile hybridization or steric demand, underscoring the exceptional versatility of γ,δ-enamido ATPs as robust and broadly applicable allylic electrophiles. Unfortunately, interception of fluorinated analogue **4aa** with Grignard nucleophiles of either hybridization was unsuccessful, leading to complex reaction profiles and only 10−20% of the isolable material

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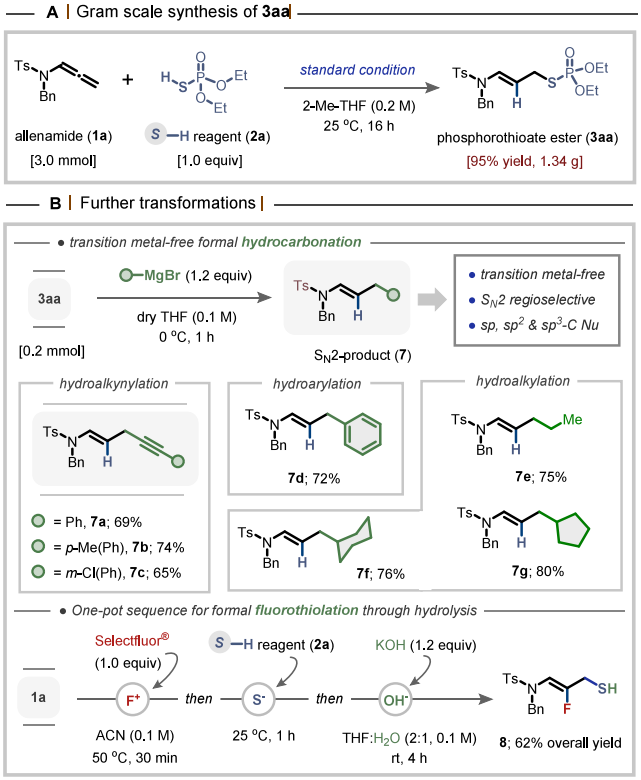
Scheme 3. Synthetic Utility: (A) Scale-up Reaction and (B) Further Diversification through ASR of β-Enamido Phosphorothioate 3aa and Formal Fluorothiolation[a,b]



[a]Experimental details for the scale-up and subsequent transformations are available in the Supporting Information. [b]Isolated yield of products.

corresponding to hydrolysis of the thiophosphorate unit. Motivated by these findings, we developed a one-pot sequential protocol involving the hydrolysis of **4aa**, affecting a formal 2,3-fluorothiolation of the allenamide and affording product **8** in 62% overall yield (bottom, Scheme 3B).

To conclude, we have developed a transition-metal-free and atom-economical strategy for the regioselective synthesis of β-H/F-enamide-tagged phosphoro(di)thiolates, representing the first example of phosphoro(di)thioate nucleophiles intercepting allenic π-systems. The broad generality, functional-group tolerance, and synthetic utility of the approach, demonstrated through modifications in complex molecules, underscore its significance. Furthermore, we have shown that these γ,δ-enamido-APTs serve as highly versatile electrophiles, undergoing complete S_N2-selective alkynylation, arylation, and alkylation with diverse Grignard nucleophiles. The excellent regio- and stereocontrol achieved in this operationally simple protocol establishes it as a valuable complement to existing transition-metal-catalyzed hydrocarbonation strategies.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c05174.

Experimental procedures, compound characterization data, and NMR spectra (PDF)

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Author Contributions

T.R.P. conceived the idea. J.K.P. supervised the project. R.T. and K.S. were involved in the experimental studies. A.B.I. assisted in collecting the analytical data. The manuscript was written through contributions of J.K.P., T.R.P., and P.C.R.B. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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