Modular allylation of C(sp^3)−H bonds by combining decatungstate photocatalysis and HWE olefination in flow

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Abstract

The late-stage introduction of allyl groups provides an opportunity to synthetic organic chemists for subsequent diversification, providing rapid access to new chemical space. Here,

we report the development of a modular synthetic sequence for the allylation of strong aliphatic C(sp^3)–H bonds. Our sequence features the merger of two distinct steps to accomplish this goal, including a photocatalytic Hydrogen Atom Transfer and an ensuing Horner-Wadsworth-Emmons reaction. This practical protocol enables the modular and scalable allylation of valuable building blocks and medicinally relevant molecules.

Main article:

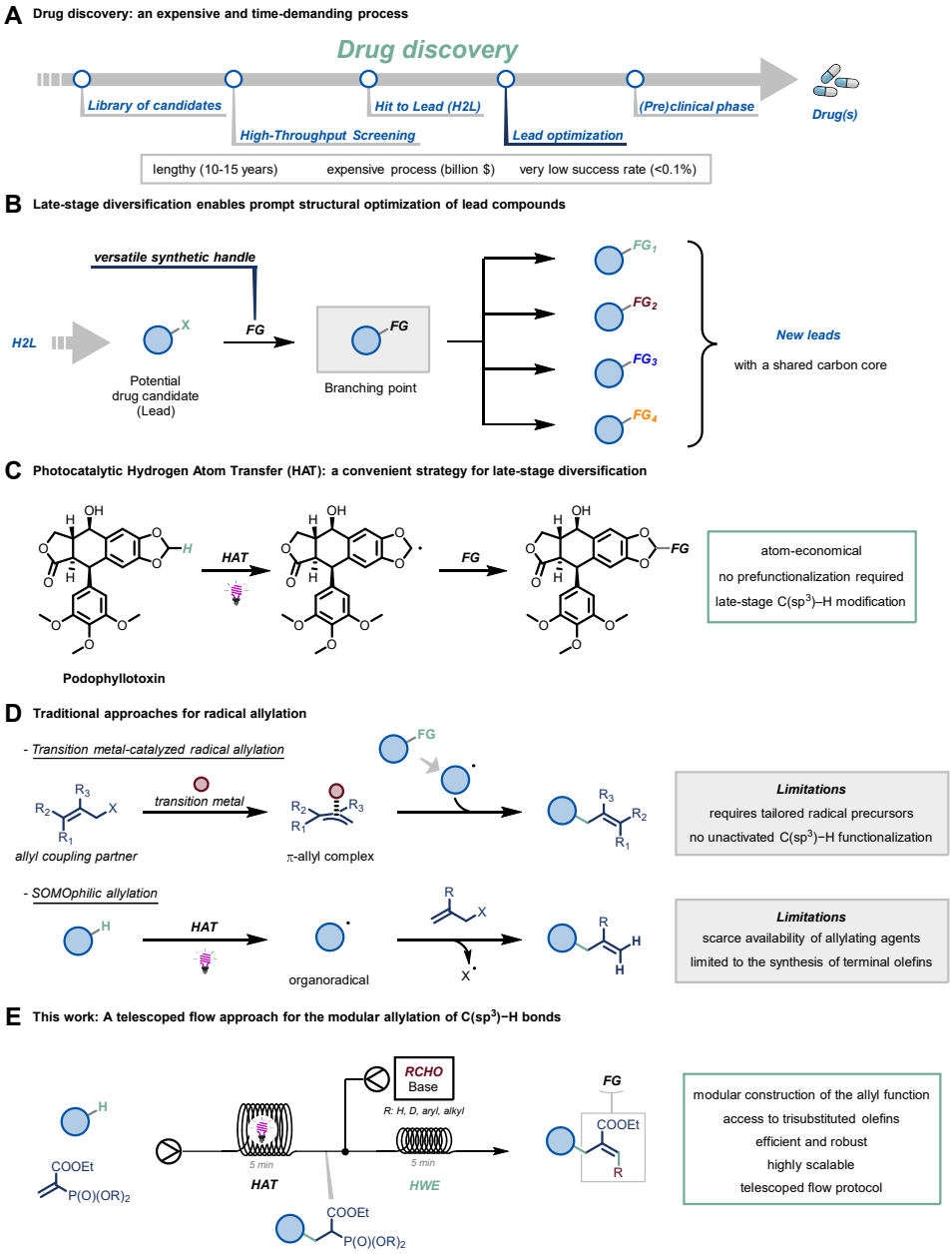
Modern drug discovery programs capitalize increasingly on the application of late-stage functionalization methodologies to accelerate the hit-to-lead (H2L) optimization phase (Scheme 1A).[1,2] Such strategies allow to rapidly and cost-efficiently[3,4] diversify the parent molecule by exploiting native functionalities (e.g., C–H bonds), thus avoiding effectively the need to redesign its entire synthetic route to access new leads.[5–7] More specifically, the late-stage decoration of organic molecules with multipurpose functional groups would provide new points of entry for subsequent diversification (Scheme 1B).[8] Such a strategy could be particularly convenient when it is realized via a chemo- and regioselective functionalization of C–H bonds in the absence of any proximal directing or activating groups.[7] However, while C(sp^2)−H activation has been extensively investigated, the direct functionalization of C(sp^3)−H bonds remains challenging and is often narrow in scope.[9] Recently, photocatalytic hydrogen atom transfer (HAT) has been exploited to enable the late-stage functionalization of C(sp^3)−H bonds, showing remarkable levels of regioselectivity even in complex drug-like molecules (Scheme 1C).[10] In HAT photocatalysis, a catalyst converts light energy into chemical energy for the homolytic cleavage of strong aliphatic C–H bonds. Especially, the decatungstate anion ($[W_{10}O_{32}]^{4-}$) has shown remarkable selectivity for specific C(sp^3)–H bonds, governed by an intricate balance between steric and electronic interactions.[11–13]

We envisioned that the regioselective introduction of an allyl moiety onto hydrocarbon frameworks would be particularly useful as it provides a convenient branching point for further

late-stage synthetic exploitation (Scheme 1B).[14] To install such moieties, radical allylation has manifested itself as a valuable strategy. One approach relies on the use of transition metal complexes to activate a substrate containing an allylic leaving group to afford a π-allyl complex, which is then suited to trap a *C*-centered radical (Scheme 1D).[15] This strategy can engage a diverse set of allyl coupling partners but typically requires purposely designed radical precursors, which prevents the direct allylation of unactivated C(sp^3)−H bonds. SOMOphilic allylation constitutes another tactic and exploits radicofugal groups X (e.g., X = halide, SO_2R, SnR_3) in the allylic position to afford the desired product via a radical addition/fragmentation process (Scheme 1D).[16–29] However, while synthetically useful, the reaction scope is mainly restricted to the synthesis of 1,1-disubstituted olefins.[23,24,30,31]

Seeking to address these challenges, we sought to develop a robust and versatile synthetic platform for the allylation of strong aliphatic C(sp^3)−H bonds. Hereto, a modular synthetic sequence is preferred in which the allyl moiety is assembled in a stepwise fashion, enabling the rapid generation of structurally diverse analogues. Specifically, our sequence features the merger of two distinct synthetic steps to accomplish this goal (Scheme 1 E). First, we planned to activate C(sp^3)−H bonds via decatungstate-catalyzed hydrogen atom transfer[32,33] and subsequently trap the resulting *C*-centered radical with a vinyl phosphonate. The ensuing radical addition product serves as a suitable linchpin for the second step, in which a classical Horner-Wadsworth-Emmons (HWE) olefination[34] is able to deliver the targeted allylated compounds.[1] In order to streamline these two steps, we reasoned that a telescoped flow protocol would be indispensable not only to accelerate access to these valuable building blocks but also to ensure facile scalability.[35–37] Herein, we report the successful realization of such a flow platform enabling both early-stage and late-stage allylation of a wide range of hydrocarbons.

[1] During the writing of this manuscript, Silvi *et al.*[59] reported a one-pot strategy to obtain 1,2-disubstituted olefins via a visible-light driven decarboxylative strategy merged with the Wittig reaction.



Scheme 1. Allylation of C(sp^3)–H bonds. (A) Common steps in the discovery of new drugs. (B) Late-stage functionalization allows rapid diversification of lead compounds. (C) Photocatalytic HAT enables late-stage functionalization of pharmaceutically relevant molecules. (D) Reported approaches for the radical allylation of organic molecules. (E) A telescoped flow platform for the modular allylation of C(sp^3)–H bonds (this work).

Our investigations commenced with the decatungstate-enabled hydroalkylation of ethyl 2-(diethoxyphosphoryl)acrylate (**2**) using cyclohexane as the H-donor (See Supporting Information, Table S1). Following a careful optimization of different reaction parameters, we found that the photocatalytic radical addition performed optimal in continuous-flow using a commercially available Vapourtec UV-150 photochemical reactor (PFA (perfluoroalkoxy) capillary, ID: 0.75 mm; V = 3.06 mL, flow rate = 0.612 mL min^{-1}, τ_r = 5 min) equipped with a 60 W UV-A LED light source, which matches the measured absorption spectrum of decatungstate. A 65% NMR yield (64% after isolation) was obtained for the targeted hydroalkylated compound when a CH_3CN solution of the acrylate (0.1 M), cyclohexane (20 equivalents) and tetrabutylammonium decatungstate (TBADT, $(Bu_4N)_4[W_{10}O_{32}]$) as the photocatalyst (1 mol%) was irradiated for 5 minutes (See Supporting Information, Table S1, Entry 9).[38–46] Other HAT photocatalysts, such as Eosin Y,[47] anthraquinone,[48] 5,7,12,14-pentacenetetrone[30] and fluorenone,[49] were also evaluated, but failed to deliver the targeted product. Interestingly, benzophenone[50,51] showed a comparable activity to the decatungstate anion, although only when used at high catalyst loading (20 mol%, 68% NMR yield). In addition, since benzophenone also dimerizes to give pinacol upon UV-A irradiation, we selected TBADT as the ideal photocatalyst for the targeted hydroalkylation reaction. Notably, this transformation is quite general and a diverse set of alkylphosphonates (**3**) could be readily isolated and characterized (see Supporting Information, Section 6).

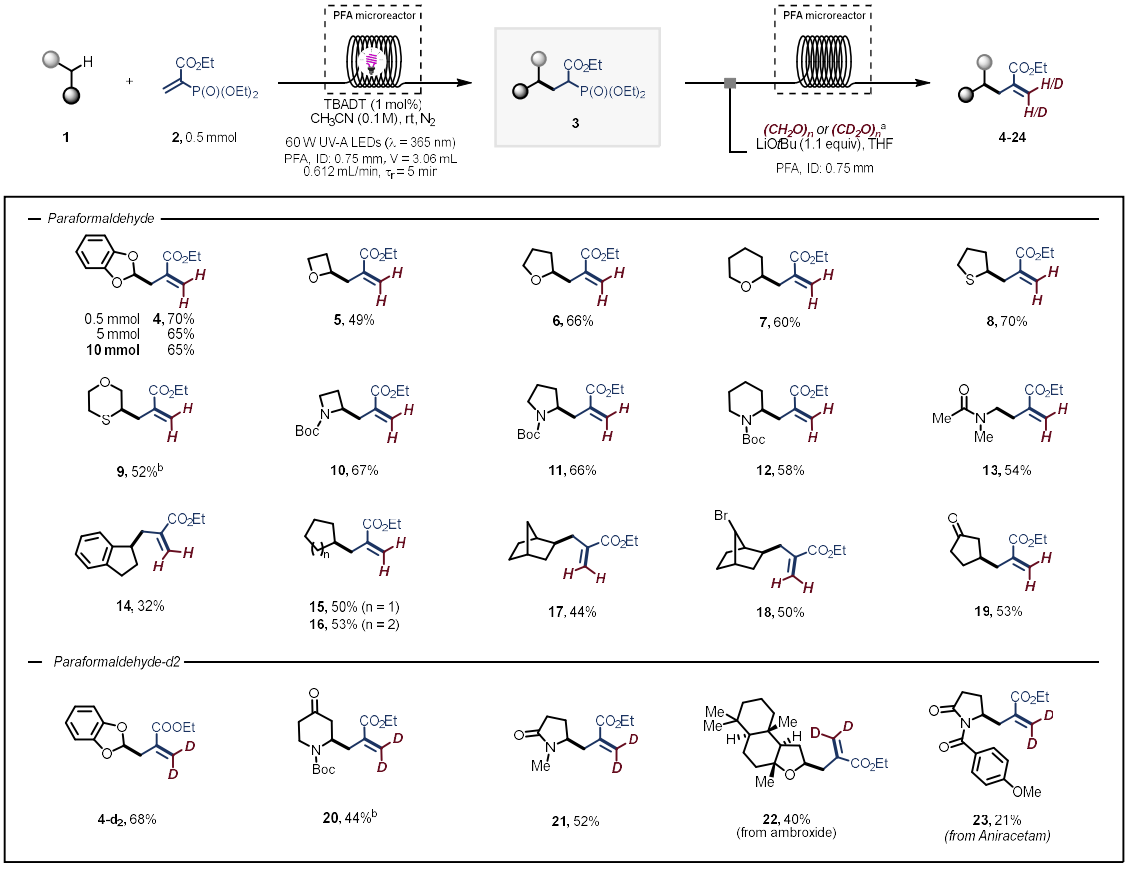
Next, the obtained alkylphosphonates were subjected to the successive HWE olefination (Scheme 2). A telescoped flow approach was developed in which the two individual steps were connected in a single streamlined flow process without intermediate purification. We selected 1,3-benzodioxole (**1a**), a common moiety in many medicinally-relevant molecules, as the H-donor and exposed it to the photocatalytic reaction conditions. Upon exiting the photochemical reactor, the reaction mixture containing the alkylphosphonate is merged with a stream

containing paraformaldehyde (3 equiv.) and lithium *tert*-butoxide (1.1 equiv.) in tetrahydrofuran. The combined reaction mixture is subsequently introduced into a second capillary microreactor (PFA, ID: 0.75 mm; V = 7.1 mL; τ_r = 5 min) and, after only 5 minutes of residence time, the targeted C(sp^3)–H allylated product **4** could be obtained in 80% overall NMR yield (70% isolated yield). Notably, the tactical combination of these two steps in flow results in a very efficient and operationally simple protocol, delivering these coveted scaffolds in only 10 minutes overall reaction time. As another benefit, the flow process could be readily scaled to produce 5-10 mmol of the desired compound (65% isolated yield, Scheme 2) without the need for tedious reoptimization of the reaction conditions, which is typically associated with batch-type scale up procedures.

This telescoped strategy could be subsequently applied to a wide variety of hydrogen donors **1** (Scheme 2). Activated substrates, such as hydrocarbon scaffolds with α-to-O C(sp^3)−H bonds (**5-7**), were regioselectively allylated in yields ranging from 49-66% over two steps. Similarly, substrates containing α-to-S (**8** and **9**) and α-to-N (**10-13**) C(sp^3)−H bonds were functionalized without difficulty (52-70% overall yield). Allyl functional groups could also be appended to activated benzylic positions (**14**, 32%). Finally, even strong, non-activated aliphatic C−H bonds could be readily allylated using our approach (**15-19**, 44-53% yield).

To further demonstrate the potential of this operationally facile approach to introduce allyl functional groups, we wondered whether paraformaldehyde-d_2 could be used in the HWE step. Such a straightforward, regioselective introduction of deuterium atoms in organic molecules would be of tremendous importance for mechanistic,[52,53] spectroscopic and tracer studies.[54] Using our two-step flow protocol, the analogous deutero-allylated compound **4-d²** was isolated in 68% yield, perfectly matching the results obtained for the non-deuterated version **4**. Similarly, *N*-Boc piperidinone was a competent substrate for this protocol affording the deuterated product **20** in 44% yield. Finally, in an effort to demonstrate the applicability of this

method to the late-stage functionalization of some medicinally relevant molecules, we subjected several biologically active molecules to our two-step flow protocol. *N*-methyl-2-pyrrolidone, often used in the formulation of drugs for both oral and transdermal delivery routes,[55] could be regioselectively functionalized at the endocyclic α-to-N position (**21**, 52%). Also the terpenoid ambroxide (**22,** 40% yield) and the nootropic drug aniracetam (**23**, 20% yield) could be efficiently decorated with a deuterated allyl moiety.

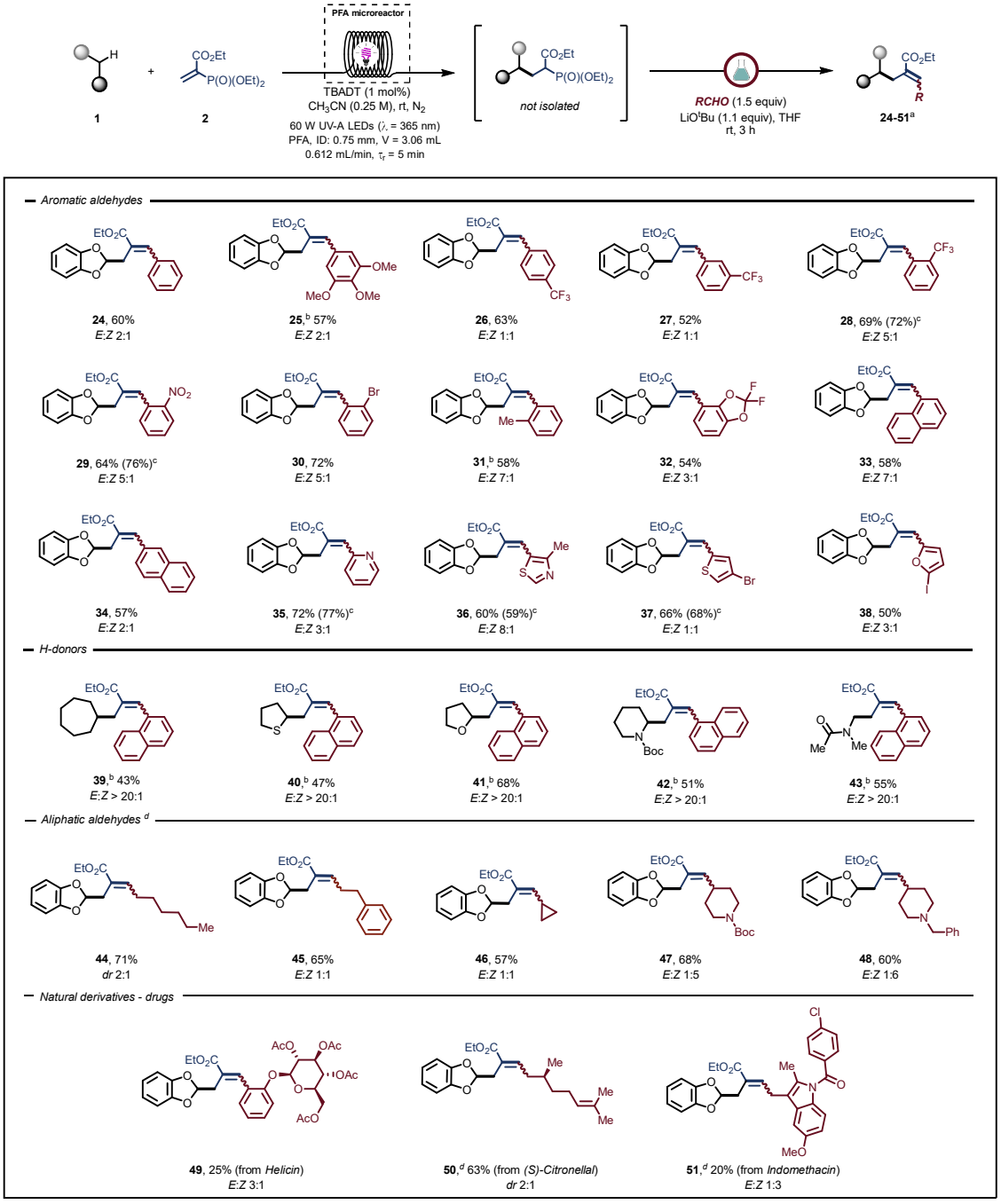


Scheme 2. Scope of the modular allylation of strong aliphatic C−H bonds with (deuterated) paraformaldehyde. [a] For $(CH_2O)_n$: 0.23 M aldehyde and 0.084 M Li*O*t*Bu* solution in tetrahydrofuran; flow rate = 0.802 mL min^{-1}; τ_R = 5 min. For $(CD_2O)_n$: 0.11 M aldehyde and 0.084 M Li*O*t*Bu* solution in tetrahydrofuran; flow rate = 0.802 mL min^{-1}; τ_R = 8 min. [b] TBADT was used 5 mol%.

In a similar vein, we turned our attention to introduce aromatic and aliphatic aldehydes in the second step, yielding trisubstituted allyl moieties, which are particularly challenging to synthesize. By exploiting our modular protocol, a virtually limitless array of substituents can be systematically introduced (Scheme 3). Due to steric hindrance, prolonged reaction times (~ 3 hours) were required to obtain full conversion and thus a fed-batch approach was adopted (Scheme 2). Using this strategy, the expected olefin **24** was obtained in 60% yield (d.r. 2:1) when the reaction stream exiting the photoreactor was added to a stirring solution of benzaldehyde (1.5 equiv) and LiO*t*Bu (1.1 equiv) in tetrahydrofuran. In general, aromatic aldehydes bearing electron-withdrawing substituents required shorter reaction times (e.g., **26-30**) and the presence of *ortho*-substituents resulted in higher *E*-to-*Z* ratios (e.g., **31**, **33** and **36**). This allowed us to utilize our telescoped flow strategy (as shown in Scheme 2) for electron-poor aldehydes and, to our delight, similar results were obtained as with the fed-batch procedure (see e.g., **28**, **29**, **35-37**). Notably, different classes of hydrogen donors, such as hydrocarbons (**39**, 43%), (thio)ethers (**40-41**, 47-68%), protected amines (**42**, 51%) and amides (**43**, 55%), proved all competent reaction partners. In all cases, the reaction performed particularly well, delivering densely functionalized alkenes in high yields and *E*-stereoselectively. It is important to note that it would be extremely challenging to access either of these with the current radical allylation methodologies, which do not allow to synthesize trisubstituted alkenes (Scheme 1D). Unfortunately, all attempts to install fully-substituted olefins, by engaging ketones in the HWE step, failed.

Interestingly, our protocol was also amenable to aliphatic aldehydes containing enolizable positions (**44-48**, 57-71% yield). The use of protected piperidine-4-carboxaldehyde allowed to obtain the corresponding allylated products **47** and **48** in excellent yields (60-68 %) and with good diastereomeric ratios. As a testament to the power of this strategy to rapidly diversify double bonds, medicinal agents and natural products containing carbonyls, such as acetyl-

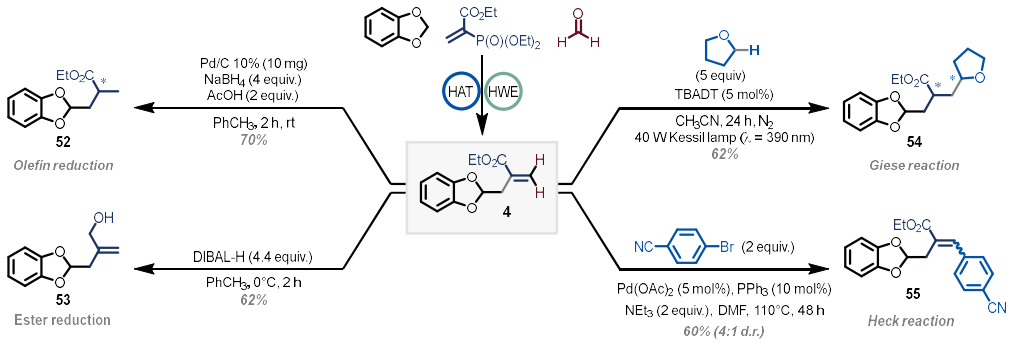
protected helicin, citronellal and indomethacin aldehyde derivatives, were also reactive delivering the targeted value-added olefins in synthetically useful yields (**49-51**, 20-63%).



Scheme 3. Scope of the modular allylation of strong aliphatic C−H bonds with aromatic and aliphatic aldehydes. [a] Reactions were carried out on a 0.5 mmol scale and yields refer to isolated products, *E*:*Z* ratios were measured by NMR or LC-MS. See Section 5 in the Supplementary Information for

experimental details. [b] reaction time 16 h. [c] reaction performed via a fully telescoped approach (see general procedure GP5 in the Supporting Information). [d] reaction performed via a modified version of the fed-batch procedure (see general procedure GP6 in the Supporting Information).

The regioselective and late-stage installation of allyl groups opens up innumerable possibilities for further diversification.[14] As an illustration of this synthetic potential, we explored diverse conditions for the conversion of synthon **4** into functionalized derivatives (Scheme 4). The olefin and the ester functionalities could be orthogonally reduced by exploiting different reduction conditions, yielding compounds **52** (70%) and **53** (62%), respectively.[56,57] Moreover, compound **4** was an ideal substrate for another Giese-type radical addition using decatungstate-photocatalyzed HAT (**54**, 62%). Finally, product **55** could be obtained via a classical Mizoroki-Heck-type coupling (60%).[58]



Scheme 4. Examples of further diversification of compound **4** by exploiting the synthetic options delivered by the olefin synthon, including olefin reduction, ester reduction, Giese-type radical addition and Heck coupling.

In conclusion, we have developed a practical methodology which enables the modular and regioselective allylation of C(sp^3)–H bonds. Our strategy involves a synergistic merger of a photocatalytic Hydrogen Atom Transfer and an ensuing Horner-Wadsworth-Emmons olefination in a scalable and telescoped flow protocol. In its present form, the synthetic

platform offers rapid access to various di- and tri-substituted olefins from abundantly available hydrocarbon feedstocks, including biologically active molecules. The operational simplicity of our flow protocol, requiring no intermediate purification, should facilitate a rapid transition from academic to industrial settings. We anticipate that this practical method will unlock new synthetic opportunities for the rapid and late-stage diversification of building blocks, medicines, natural products and other specialty chemicals.

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