

Decatungstate as Direct Hydrogen Atom Transfer Photocatalyst for SOMOphilic Alkynylation

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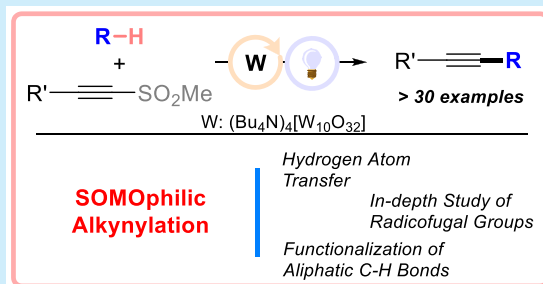


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ABSTRACT: A versatile approach for the alkynylation of a variety of aliphatic hydrogen donors, including alkanes, is reported. We used tetrabutylammonium decatungstate as photocatalyst to generate organoradicals from C–H/Si–H bonds via hydrogen atom transfer. The latter intermediates underwent SOMOphilic alkynylation by methanesulfonyl alkynes to afford internal alkynes upon loss of a sulfonyl radical. The effect of different radicofugal groups on the reaction outcome was evaluated and rationalized via a combined experimental and computational approach.



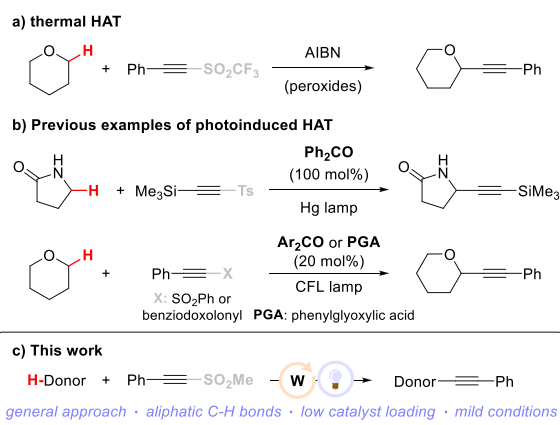
The C≡C triple bond is a privileged functional group in different fields, spanning from medicinal chemistry to polymer science. In fact, both internal and terminal alkynes are frequently used in drugs due to their capability to modulate the activity of several proteins,¹ as well as for the late-stage manipulation of organic molecules through click chemistry,^{2a–d} nowadays routinely used for bioconjugation. What is more, alkynes are precious building blocks that offer direct access to a plethora of functionalities, including alkenes, alkanes, halides, and carbonyl compounds, among the others.^{3–5} Finally, the C≡C triple bond plays a key role in materials science as well, where the use of Mo- and W-based complexes has been reported to catalyze alkyne metathesis polymerization.⁶

Accordingly, it comes as no surprise that diverse synthetic strategies have been devised for the alkynylation of organic molecules. Even though most reports deal with classical nucleophilic and electrophilic alkynylation manifolds, a conceptually different approach is offered by SOMOphilic alkynylation.⁷ In this process, an organoradical generated during the reaction is trapped by a suitable alkynylation reagent and, after loss of a radicofugal group (e.g., a sulfonyl or benziodoxolonyl radical), the hoped-for alkyne is obtained.⁷

The most direct and atom-economical way to form the needed C-centered radical is through the homolytic cleavage of a C–H bond via hydrogen atom transfer (HAT). In one instance, AIBN (azobis(isobutyronitrile), Scheme 1a) was exploited to trigger a thermal HAT, while the triflyl radical was used as the radicofugal group. The fragmentation of the latter intermediate generated an electrophilic trifluoromethyl radical that sustained a radical chain process. The reaction could be performed also in the absence of AIBN, due to the probable presence of peroxides in the substrate, used as the solvent.⁸

A more controlled activation manifold is offered by photocatalyzed HAT, which has secured its place as one of

Scheme 1. SOMOphilic Alkynylation via Hydrogen-Atom Transfer (HAT)

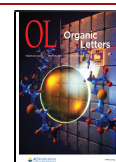


Alkynylation reactions via direct C–H functionalization: thermal HAT (a), previous examples of photoinduced HAT (b) and this work (c). AIBN: azobis(isobutyronitrile). W: tetrabutylammonium decatungstate, (Bu₄N)₄[W₁₀O₃₂]. CFL: Compact Fluorescent Lamp. Ts: tosyl.

the most convenient and sustainable ways for the generation of C-centered radicals.⁹ Thus, the excited state of the photocatalyst (PC) generated upon light absorption can be exploited

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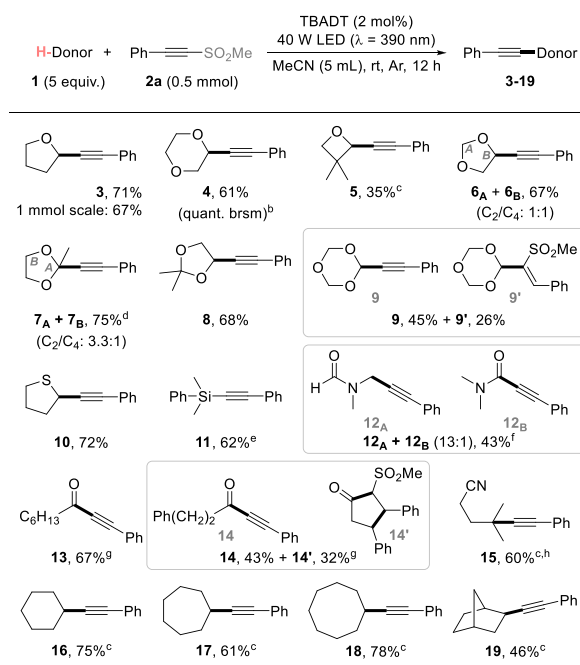


for the desired homolytic C–H bond cleavage to afford the needed intermediate.¹⁰ Only a few precedents of direct photoinduced C–H to C–C(sp) bond conversion are available in the literature, employing benzophenone or 4,4'-dichlorobenzophenone (Scheme 1b).^{11–14} Often, high loading of these aromatic ketones is required to obtain reasonable yields of the desired products and the reported protocols are mainly restricted to the activation of rather labile α -to-O and α -to-N C(sp³)–H bonds, H-donors being used in large excess or even as the reaction medium. Very recently, phenylglyoxylic acid (PGA) has been used as well to catalyze the alkylation of α -to-O C–H bonds under visible light irradiation (Scheme 1b). Interestingly, when S-heterocycles (e.g., tetrahydrothiophene, THT) were employed, a concomitant oxidative ring-opening occurred.¹⁵

However, a general platform for the alkylation of strong aliphatic C(sp³)–H bonds remains an unmet goal. Building upon our expertise in the use of TBADT (tetrabutylammonium decatungstate, (Bu₄N)₄[W₁₀O₃₂]) as photocatalyst for the functionalization of organic substrates via HAT,^{16,17} we evaluated the use of this polyoxometalate to promote the alkylation of a variety of aliphatic H-donors, including ethers, acetals, aldehydes, amides, a silane and even hydrocarbons.

We identified the alkylation of tetrahydrofuran (**1a**) by ((methylsulfonyl)ethynyl)benzene (**2a**) as our model reaction. After a routine survey of reaction conditions (Table S1 in the Supporting Information) in terms of solvent, photocatalyst loading and light source, we found that the irradiation of an acetonitrile solution containing **2a** (0.1 M), **1a** (5 equiv) and TBADT (2 mol %) with a 40 W LED ($\lambda = 390$ nm) yielded 2-(phenylethynyl)tetrahydrofuran **3** in 74% GC yield after 12 h (Scheme S1a and Figure S1). The reaction proved to be exceptionally robust, since it could be run under visible light irradiation as well ($\lambda = 405$ nm, 18 W) or with a catalyst loading as low as 0.5 mol %, with minimal changes in terms of **3** formation (GC yields consistently >60%), albeit 24 h irradiation was required in the last case. Control experiments showed that both light and the photocatalyst were needed to trigger the observed reactivity, while quantum yield measurements safely excluded a chain propagation mechanism ($\Phi = 0.07$; see the Supporting Information). By reacting an equimolar mixture of **1a** and **1a-d₈** with **2a**, a kinetic isotope effect (KIE) of 1.5 was observed, indicating the H-atom transfer as the rate-determining step of the reaction (Scheme S2 and Figure S2).

Gratifyingly, the model reaction proceeded smoothly on a preparative scale (0.5 mmol) and allowed to isolate product **3** in 71% yield (67% when doubling the scale to 1 mmol). We then screened several oxygenated heterocycles and obtained products **4–9** in good yields, except for oxetane derivative **5** (Scheme 2). Thus, when 1,3-dioxolane (**1d**) was employed as the H-donor, the reaction proceeded to deliver a 1:1 mixture of isomers **6_A** and **6_B** (67% overall yield), resulting from the functionalization at the acetalic and ethereal positions, respectively. Differently, the selectivity diverted to the methine C(sp³)–H in the case of 2-methyl-1,3-dioxolane (**1e**), affording products **7_A** and **7_B** in 75% overall yield with a 3.3:1 ratio. This selectivity pattern has been previously reported and can be rationalized based on the stability of the involved radical intermediates.^{16b,18} When trioxane (**1g**) was used in the role of H-Donor, in addition to the expected alkyne

Scheme 2. Substrate Scope: H-donors^a

^aReaction conditions: an Ar-bubbled MeCN solution (5 mL) containing **1** (5 equiv), **2a** (0.5 mmol, 0.1 M), and TBADT (2 mol %) was irradiated with an LED lamp (for further details, see the Supporting Information). ^bbased on 61% consumption of **2a**. ^c5 mol % TBADT was used. ^dReaction performed in the presence of 1 equiv of NaHCO₃. ^e2 equiv of the silane was used. ^f4 equiv of DMF was used. ^g1 equiv of the aldehyde was used. ^h10 equiv of the nitrile was used. Brsm: based on remaining starting material.

9 (45% yield), the hydroalkylation adduct **9'** was isolated as well in 26% yield.

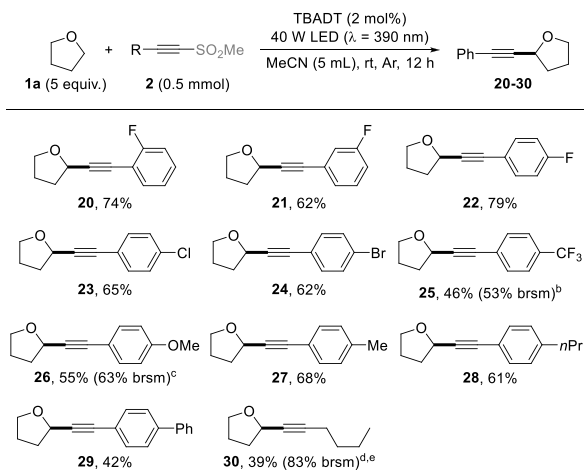
We also achieved the functionalization of the α -to-S C(sp³)–H bond of tetrahydrothiophene to give product **10** in 72% isolated yield, while no ring-opening of the sulfur-heterocycle was observed.¹⁵ Silane **1i** (see Chart S1 in the Supporting Information) was likewise a competent substrate in the reaction, as demonstrated by the isolation of **11** in 62% yield. When dimethylformamide was subjected to our conditions, a mixture of products was obtained in 43% overall yield, with a significant preference for the functionalization of the C(sp³)–H (**12_A**) over the formyl C(sp²)–H bond (**12_B**). To study into greater detail the functionalization of formyl C(sp²)–H bonds, we subjected heptaldehyde (**1k**) and 3-phenylpropionaldehyde (**1l**) to our reaction conditions: while product **13** was smoothly obtained in 67% yield from **1k**, the presence of weak benzylic C–H bonds in **1l** enabled an additional reaction path. Indeed, a mixture of **14** (43% yield) and **14'** (32% yield) was obtained: while **14** derives from the usual reactivity, we propose that **14'** is formed upon an addition/1,5-HAT/ring-closure sequence (for further details, see Scheme S4).

Finally, we extended the present synthetic protocol to nitriles and cycloalkanes, to eventually achieve the alkylation of strong, unactivated, aliphatic C–H bonds. Upon increasing the amount of TBADT to 5 mol %, the corresponding unsaturated hydrocarbons were obtained in very good yields (products **15–19** in Scheme 2, see also Scheme S1 and Figure

S1). Interestingly, product **19** was obtained as a single regioisomer.

We next turned our attention to the scope of the alkynylating reagent (Scheme 3) and reacted **1a** with a series

Scheme 3. Substrate Scope: Methanesulfonyl Alkynes^a

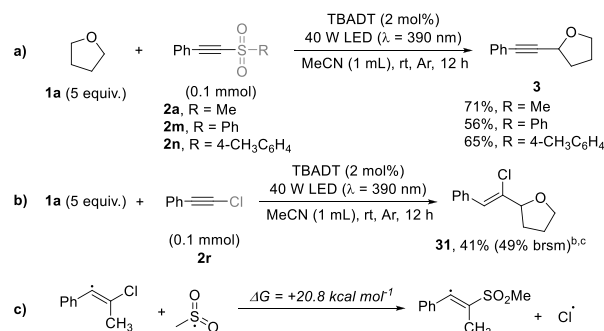


^aReaction conditions: an Ar-bubbled MeCN solution (5 mL) containing **1a** (5 equiv), **2** (0.5 mmol, 0.1 M), and TBADT (2 mol %) was irradiated with an LED lamp (for further details, see the Supporting Information). ^bBased on 86% consumption of **2g**. ^cBased on 88% consumption of **2h**. ^dNMR yield, based on 46% consumption of **2l**. ^eIrradiation time: 36 h.

of methanesulfonyl alkynes (**2b–l**). The substitution pattern of the aromatic ring was investigated by testing traps **2b–d** at first: the expected alkynes **20–22** were obtained in good yields (62–79%), the *para*-derivative **2d** offering the highest yield. Different halogens were then tested and the corresponding products **23** and **24** were isolated in 65% and 62% yield, respectively. Interestingly, the electronic nature of the substituent had a remarkable effect on the reaction: when either a strongly electron-withdrawing (CF_3 in **2g**) or electron-donating (OMe in **2h**) group was present on the aromatic ring, incomplete conversion of the starting sulfones was observed (products **25** and **26**). On the contrary, methanesulfonyl alkynes containing milder electron-donating alkyl substituents on the 4-position (**2i,j**) proved to be more efficient, and products **27** and **28** were obtained in good yield (68% in both cases). Biphenyl alkynyl sulfone **2k** was a competent substrate as well, allowing us to isolate product **29**, albeit in a modest yield (42%). Finally, we attempted the alkynylation of **1a** with an aliphatic derivative (**2l**), however, the yield of **30** did not exceed 39% (by NMR, compound not isolated; 83% brsm) upon prolonged irradiation (36 h).

At the time of writing, Hashmi and co-workers reported the visible light-photocatalyzed hydroalkylation of chloroalkynes.¹⁹ Thus, we started wondering about the role of the radicofugal group in the present methodology and reacted compounds **2m–r** (see Chart S1) with **1a** under optimized conditions. We found that only sulfonyl alkynes gave product **3** in good yields (Scheme 4a; reactivity order: **2a** > **2n** > **2m**), while the well-known benziodoxolone-based alkynylating reagent (**2o**, see Chart S1) proved to be photochemically unstable under our conditions and **3** was formed only in a poor yield (17%, data not shown). Turning to halogenated derivatives, while (iodoethynyl)benzene (**2p**) and (bromoethynyl)benzene

Scheme 4. Survey of Different Radicofugal Groups^a

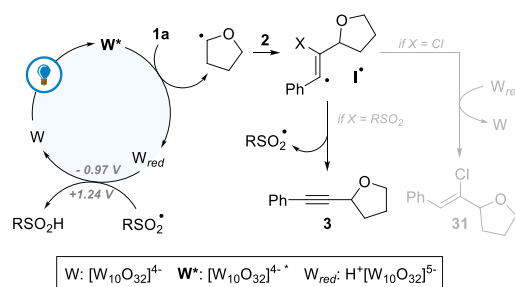


^aReaction conditions in (a) and (b) as indicated in Table S1 (GC yields reported). Level of theory in (c): U ω B97xD/def2tzvp in the gas phase. ^bConsumption of **2r**: 83%. ^c**31** was isolated running an experiment on a 0.5 mmol scale: 41% (49% brsm) isolated yield.

(**2q**) were recovered unreacted, chloroalkyne **2r** led to the formation of product **31** only (41% isolated yield, *Z* isomer; Scheme 4b), in accordance with the report by Hashmi.¹⁹ Intrigued by this marked difference in reactivity, we undertook a computational analysis based on density functional theory (DFT; U ω B97xD/def2tzvp level of theory in the gas phase) and compared the aptitude of the different RSO_2^\bullet moieties vs Cl^\bullet in the role of radicofugal groups (Table S2). In particular, the equation reported in Scheme 4c compares the tendency of MeSO_2 and Cl to stabilize the vinyl radical adduct with respect to their intrinsic stability as free radicals. The largely positive ΔG value is indicative of a more pronounced aptitude of MeSO_2 to act as a radicofugal group.

On the basis of the above, we propose the mechanism shown in Scheme 5. The excited state of TBADT (W^*) is

Scheme 5. Proposed Mechanism



populated upon UV (or visible) light irradiation, triggering the cleavage of a C–H bond in the H-donor (e.g., **1a**). The thus-formed organoradical is readily trapped by the alkynylating reagent (**2**) to deliver I^\bullet . From this point, two scenarios can be envisaged. On one hand, the loss of a good radicofugal group (e.g., RSO_2^\bullet) affords the expected alkyne. Thus, the recovery of the spent photocatalyst ($E[\text{W}/\text{W}_{\text{red}}] = -0.97$ V vs SCE)²⁰ is entrusted to the highly oxidizing sulfonyl radical (e.g., $E[\text{MeSO}_2^\bullet/\text{MeSO}_2^-] = +1.24$ V vs SCE),²¹ albeit a back-HAT step from W_{red} to RSO_2^\bullet may be likewise operative. On the other hand, when **2r** is used as alkynylating reagent, the elimination of the chlorine atom is disfavored (Scheme 4c) and the hydroalkylation product **31** is formed via back-HAT or sequential electron transfer/proton transfer (see Schemes S3).¹⁹ This scenario is corroborated by deuterium labeling experiments reported in Scheme S3.

In conclusion, a robust protocol for the radical alkynylation of Si–H, formyl C(sp²)–H, and strong C(sp³)–H bonds via photocatalyzed HAT triggered by the decatungstate anion has been reported. Methanesulfonyl alkynes, most of which have been synthesized here for the first time, have proved to be a convenient and more atom-economical alternative to common agents for SOMOphilic alkynylations. The relative stability of the radical group has proved crucial to obtain the expected alkynylated products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.1c00381>.

Experimental details about the used materials and reaction conditions, GC/MS, sample preparation, product characterization, kinetic analysis, computational details, DFT optimized geometries, and NMR spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Talele, T. T. Acetylene Group, Friend or Foe in Medicinal Chemistry. *J. Med. Chem.* **2020**, *63* (11), 5625–5663.
(2) (a) Hu, X.; Zhao, X.; He, B.; Zhao, Z.; Zheng, Z.; Zhang, P.; Shi, X.; Kwok, R. T. K.; Lam, J. W. Y.; Qin, A.; et al. A Simple Approach to Bioconjugation at Diverse Levels: Metal-Free Click Reactions of Activated Alkynes with Native Groups of Biotargets without Prefunctionalization. *Research* **2018**, *2018*, 1–12. (b) Presolski, S.

I.; Hong, V. P.; Finn, M. G. Copper-Catalyzed Azide–Alkyne Click Chemistry for Bioconjugation. *Curr. Protoc. Chem. Biol.* **2011**, *3* (4), 153–162. (c) Meldal, M.; Diness, F. Recent Fascinating Aspects of the CuAAC Click Reaction. *Trends Chem.* **2020**, *2* (6), 569–584. (d) Porte, K.; Riomet, M.; Figliola, C.; Audisio, D.; Taran, F. Click and Bio-Orthogonal Reactions with Mesoionic Compounds. *Chem. Rev.* **2020**, DOI: [10.1021/acs.chemrev.0c00806](https://doi.org/10.1021/acs.chemrev.0c00806).

(3) Heravi, M. M.; Dehghani, M.; Zadsirjan, V.; Ghanbarian, M. Alkynes as Privileged Synthons in Selected Organic Name Reactions. *Curr. Org. Synth.* **2019**, *16* (2), 205–243.

(4) Alabugin, I.; Gonzalez-Rodriguez, E.; Kawade, R.; Stepanov, A.; Vasilevsky, S. Alkynes as Synthetic Equivalents of Ketones and Aldehydes: A Hidden Entry into Carbonyl Chemistry. *Molecules* **2019**, *24* (6), 1036.

(5) Munslow, I. J. Alkyne Reductions. In *Modern Reduction Methods*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2008; pp 363–385.

(6) Yang, H.; Jin, Y.; Du, Y.; Zhang, W. Application of Alkyne Metathesis in Polymer Synthesis. *J. Mater. Chem. A* **2014**, *2* (17), 5986.

(7) Le Vaillant, F.; Waser, J. Alkynylation of Radicals: Spotlight on the “Third Way” to Transfer Triple Bonds. *Chem. Sci.* **2019**, *10* (39), 8909–8923. and references therein.

(8) Gong, J.; Fuchs, P. L. Alkynylation of C–H Bonds via Reaction with Acetylenic Triflones. *J. Am. Chem. Soc.* **1996**, *118* (18), 4486–4487.

(9) Capaldo, L.; Ravelli, D. Hydrogen Atom Transfer (HAT): A Versatile Strategy for Substrate Activation in Photocatalyzed Organic Synthesis. *Eur. J. Org. Chem.* **2017**, *2017* (15), 2056–2071.

(10) Capaldo, L.; Quadri, L. L.; Ravelli, D. Photocatalytic Hydrogen Atom Transfer: The Philosopher’s Stone for Late-Stage Functionalization? *Green Chem.* **2020**, *22* (11), 3376–3396.

(11) Hoshikawa, T.; Kamijo, S.; Inoue, M. Photochemically Induced Radical Alkynylation of C(sp³)–H Bonds. *Org. Biomol. Chem.* **2013**, *11* (1), 164–169.

(12) Nagatomo, M.; Yoshioka, S.; Inoue, M. Enantioselective Radical Alkynylation of C(sp³)–H Bonds Using Sulfoximine as a Traceless Chiral Auxiliary. *Chem.: Asian J.* **2015**, *10* (1), 120–123.

(13) Paul, S.; Guin, J. Radical C(sp³)–H Alkenylation, Alkynylation and Allylation of Ethers and Amides Enabled by Photocatalysis. *Green Chem.* **2017**, *19* (11), 2530–2534.

(14) Matsumoto, K.; Nakajima, M.; Nemoto, T. Visible Light-Induced Direct S₀ → T_n Transition of Benzophenone Promotes C(sp³)–H Alkynylation of Ethers and Amides. *J. Org. Chem.* **2020**, *85* (18), 11802–11811.

(15) Voutyritsa, E.; Garreau, M.; Kokotou, M. G.; Triandafillidi, I.; Waser, J.; Kokotos, C. G. Photochemical Functionalization of Heterocycles with EBX Reagents: C–H Alkynylation versus Deconstructive Ring Cleavage. *Chem. - Eur. J.* **2020**, *26*, 14453–14460.

(16) For reviews on tetrabutylammonium decatungstate, see: (a) Ravelli, D.; Protti, S.; Fagnoni, M. Decatungstate Anion for Photocatalyzed “Window Ledge” Reactions. *Acc. Chem. Res.* **2016**, *49* (10), 2232–2242. (b) Ravelli, D.; Fagnoni, M.; Fukuyama, T.; Nishikawa, T.; Ryu, I. Site-Selective C–H Functionalization by Decatungstate Anion Photocatalysis: Synergistic Control by Polar and Steric Effects Expands the Reaction Scope. *ACS Catal.* **2018**, *8* (1), 701–713.

(17) For representative works on tetrabutylammonium decatungstate, see: (a) Laudadio, G.; Deng, Y.; van der Wal, K.; Ravelli, D.; Nuño, M.; Fagnoni, M.; Guthrie, D.; Sun, Y.; Noël, T. C(sp³)–H Functionalizations of Light Hydrocarbons Using Decatungstate Photocatalysis in Flow. *Science* **2020**, *369* (6499), 92–96. (b) Quattrini, M. C.; Fujii, S.; Yamada, K.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Ryu, I. Versatile Cross-Dehydrogenative Coupling of Heteroaromatics and Hydrogen Donors via Decatungstate Photocatalysis. *Chem. Commun.* **2017**, *53* (15), 2335–2338. (c) Capaldo, L.; Quadri, L. L.; Merli, D.; Ravelli, D. Photoelectrocatalytic Cross-Dehydrogenative Coupling of Unactivated Aliphatic Hydrogen

Donors with Benzothiazoles: Synthetic Applications and Mechanistic Insights. *ChemRxiv* **2020**, DOI: [10.26434/chemrxiv.13281182.v1](https://doi.org/10.26434/chemrxiv.13281182.v1).

(d) Bonassi, F.; Ravelli, D.; Protti, S.; Fagnoni, M. Decatungstate Photocatalyzed Acylations and Alkylations in Flow via Hydrogen Atom Transfer. *Adv. Synth. Catal.* **2015**, *357* (16–17), 3687–3695.

(e) Laudadio, G.; Govaerts, S.; Wang, Y.; Ravelli, D.; Koolman, H. F.; Fagnoni, M.; Djuric, S. W.; Noël, T. Selective C(sp³)-H Aerobic Oxidation Enabled by Decatungstate Photocatalysis in Flow. *Angew. Chem., Int. Ed.* **2018**, *57* (15), 4078–4082.

(18) Raviola, C.; Ravelli, D. Efficiency and Selectivity Aspects in the C-H Functionalization of Aliphatic Oxygen Heterocycles by Photocatalytic Hydrogen Atom Transfer. *Synlett* **2019**, *30* (7), 803–808.

(19) Adak, T.; Hoffmann, M.; Witzel, S.; Rudolph, M.; Dreuw, A.; Hashmi, A. S. K. Visible Light-Enabled sp³-C-H Functionalization with Chloro- and Bromoalkynes: Chemoselective Route to Vinylchlorides or Alkynes. *Chem. - Eur. J.* **2020**, *26* (67), 15573–15580.

(20) Renneke, R. F.; Pasquali, M.; Hill, C. L. Polyoxometalate Systems for the Catalytic Selective Production of Nonthermodynamic Alkenes from Alkanes. Nature of Excited-State Deactivation Processes and Control of Subsequent Thermal Processes in Polyoxometalate Photoredox Chemistry. *J. Am. Chem. Soc.* **1990**, *112* (18), 6585–6594.

(21) The original potential was expressed against the Ag/AgCl in saturated LiCl/EtOH reference electrode and was here converted against SCE by subtracting 45 mV. See: Nikl, J.; Lips, S.; Schollmeyer, D.; Franke, R.; Waldvogel, S. R. Direct Metal- and Reagent-Free Sulfonylation of Phenols with Sodium Sulfinates by Electrosynthesis. *Chem. - Eur. J.* **2019**, *25* (28), 6891–6895.