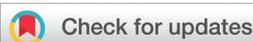


RESEARCH ARTICLE

View Article Online
View Journal | View IssueCite this: *Org. Chem. Front.*, 2025, 12, 4970**Beyond HAT: harnessing TBADT for photocatalyzed Giese-type C(sp³)-C(sp³) bond formation through reductive decarboxylation†**Matteo Leone, ^{a,b} Dalila Arnaldi^a and Maurizio Fagnoni ^{*a}

The decatungstate anion as a tetrabutylammonium salt (TBADT) facilitates a variety of chemical transformations under mild conditions, primarily through hydrogen atom transfer (HAT) and marginally through single electron transfer (SET) mechanisms. This study explores the dual ability of TBADT to cleave C-H bonds and initiate SET processes, leading to efficient C(sp³)-C(sp³) coupling reactions. We address the main limitations of direct HAT by leveraging the doubly-reduced form of TBADT [W₁₀O₃₂]⁶⁻ to activate redox-active esters (RAEs), enabling the formation of alkyl radicals for Giese-type additions. An extensive screening of various hydrogen donors showed their pivotal role in the selective generation of the reduced form of TBADT and in suppressing any undesired C-H activation. Our optimized conditions, using γ -terpinene as the hydrogen donor, gave high yields in alkylations of various olefins, demonstrating the versatility and robustness of the proposed strategy. This methodology extends the application of TBADT in sustainable organic synthesis and in late-stage functionalization of complex molecules for the synthesis of pharmaceutical building blocks.

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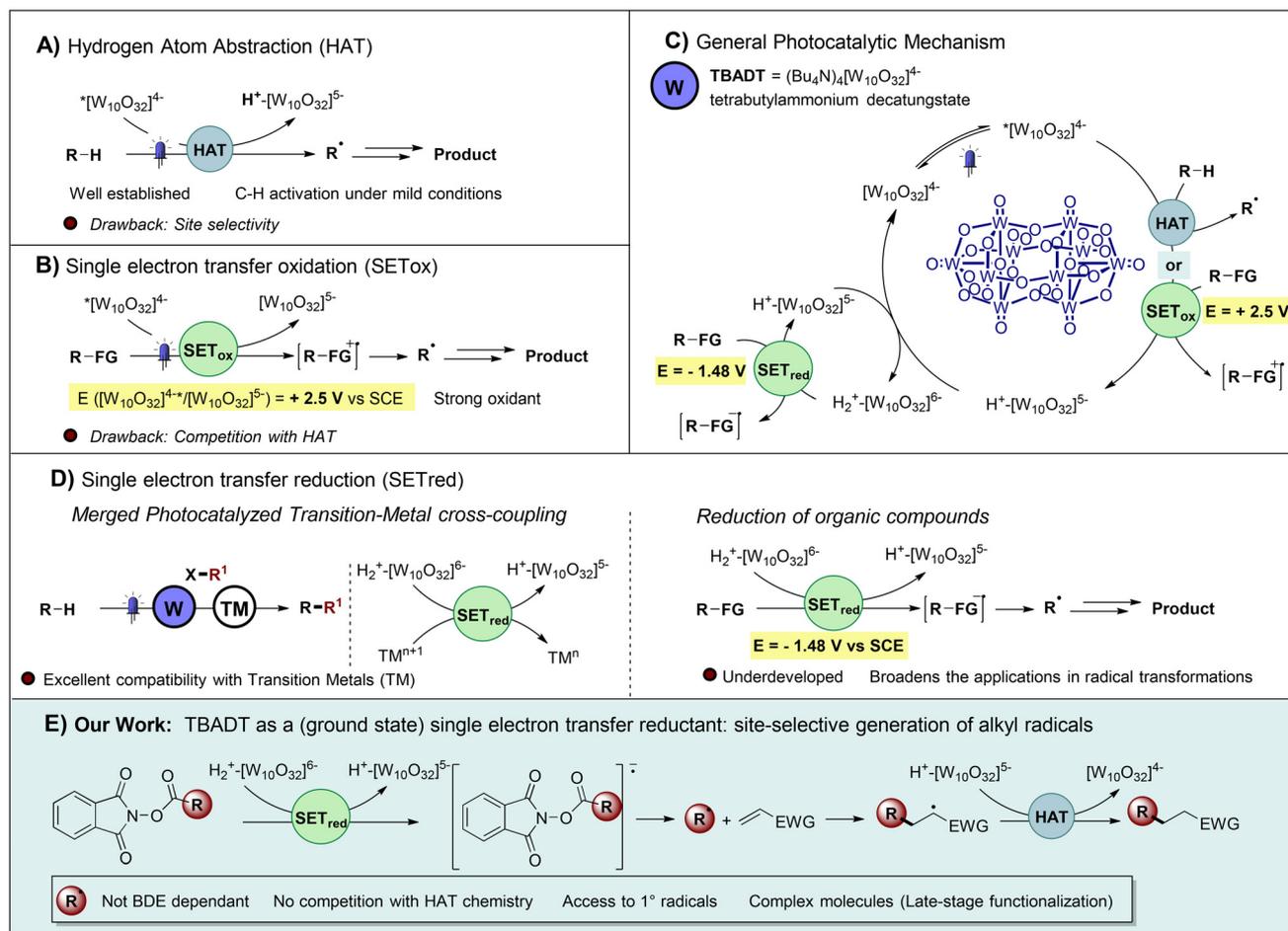
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Introduction

In recent years, photocatalysis has emerged as a powerful and sustainable approach for developing novel and efficient synthetic routes.¹ Among various photocatalysts, the decatungstate anion [W₁₀O₃₂]⁴⁻ (mainly as a tetrabutylammonium salt, TBADT) has garnered significant attention due to its exceptional photochemical activity, particularly its ability to facilitate a wide range of chemical reactions under mild conditions.² Since the earliest reports,^{3,4} TBADT has entered its golden age in photocatalytic organic transformations thanks to its peculiar properties. Mechanistic studies have shown that in its excited state, TBADT undergoes a ligand-to-metal charge transfer (LMCT) mechanism, imparting partial radical character to the monocoordinated oxygen centers. This enables it to homolytically cleave C(sp³)-H and formyl C(sp²)-H bonds in various aliphatic derivatives through a hydrogen atom transfer (HAT) mechanism (Scheme 1A).⁵ For many years, this feature has been exploited for the direct activation of C-H bonds

under mild conditions, facilitating effective C-C couplings,⁶ C-N couplings,⁷ fluorinations,⁸ oxygenations,⁹ and dehydrogenations.¹⁰ Additional studies evidenced that in the presence of TBADT, synergistic control by polar and steric effects allows, to some extent, selective C-H functionalization at competitive sites.¹¹ The ability of TBADT to homolytically cleave unactivated C-H bonds with high bond dissociation energies (BDEs) has (in part) restricted its use in the functionalization of complex molecules, where the presence of multiple active sites can lead to competing reactions.¹² Nevertheless, the application of TBADT is thus mostly confined to HAT processes hiding its propensity toward photoredox catalyzed processes. In fact, TBADT has a remarkably high redox potential in the excited state ($E([W_{10}O_{32}]^{4-*}/[W_{10}O_{32}]^{5-}) \approx +2.5$ V vs. SCE),¹³ comparable to the most commonly used strong photo-oxidants,¹⁴ making it ideal for activating a vast array of substrates *via* oxidative single-electron transfer (SETox, Scheme 1B).¹⁵ To this end, TBADT has been applied to photoredox promoted desilylation of alkyl^{16a} and acyl^{16b} silanes, decarboxylative benzylations^{17a} and ring opening of cyclopropanols.^{17b} However, one of the major limitations of this approach is the potential competition between HAT and SET processes deriving from the same excited state, which could lead to unpredictable reactivity.¹⁸ On the other hand, the final catalytic step of TBADT reveals intriguing characteristics for SET processes that circumvent this limitation, a feature that was largely overlooked until recent years. In fact, the reduced form of the decatung-

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Scheme 1 A) Application of TBADT in HAT transformations. (B) TBADT mediated photo-oxidations. (C) General mechanism for the photocatalytic pathways of TBADT. (D) TBADT mediated photo-reductions. (E) Development of a novel approach for TBADT photocatalyzed Giese type additions.

state anion $[W_{10}O_{32}]^{5-}$ can disproportionate, regenerating the ground state photocatalyst $[W_{10}O_{32}]^{4-}$ and forming doubly-reduced decatungstate $[W_{10}O_{32}]^{6-}$, a good reductant ($E_{1/2}^{red}$ ($[W_{10}O_{32}]^{5-}/[W_{10}O_{32}]^{6-}$) = -1.48 V vs. SCE)¹⁹ (Scheme 1C). The reducing potential of TBADT was useful when merging a photocatalyst with a transition-metal (TM) catalyst in dual catalyzed cross-couplings.²⁰ The authors proposed that $[W_{10}O_{32}]^{6-}$ undergoes SET with TM^{n+1} to restore the active TM^n . Inspired by this, numerous novel transformations have been developed, merging TBADT with transition-metal catalysis (Scheme 1D, left part).²¹ We were, however, surprised by the limited applications of TBADT as a versatile direct reductant of organic compounds²² even though this approach could overcome the inherent limitations of direct HAT.²³ As a matter of fact, this strategy could (i) eliminate dependence on bond dissociation energy (BDE), (ii) reduce the need for excess precious hydrogen donors, (iii) give access to the more elusive 1° radicals and (iv) enable late-stage functionalization (LSF) without site competition in complex molecules (Scheme 1D, right part). Additionally, the redox potential of the doubly-reduced form of TBADT is suitable for most SOMophiles, since these are

mostly difficult to reduce compared to the most commonly used redox active functional groups, preventing unwanted side-reduction processes.²⁴ On this basis, we envisioned the forging of new $C(sp^3)-C(sp^3)$ bonds starting from ubiquitous alkyl carboxylic acids, ideal starting materials present in natural products and pharmaceuticals.²⁵

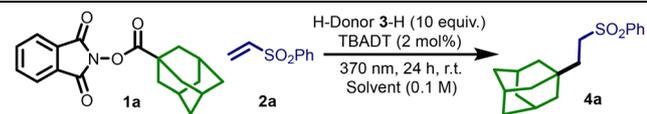
We hypothesized that in the presence of a suitable hydrogen donor (D-H), $[W_{10}O_{32}]^{6-}$ could accumulate in solution and may reduce various redox-active esters (RAEs) *via* SETred (Scheme 1E).²⁶ Hydroxyphthalimide (NHPI) esters are well-suited for the reaction thanks to their reduction potential ($E_{1/2}^{red}$ ≈ -1.3 V vs. SCE).²⁷ The resulting alkyl radicals, derived from the mesolytic cleavage of the N-O bond followed by CO_2 loss, could then undergo Giese-type additions with a wide range of SOMophiles, potentially yielding the target molecules of pharmaceutical interest. Photocatalyzed reductive decarboxylation is a well-established and extensively studied method for generating carbon-centered radicals, widely applied in Giese-type additions.²⁸ Therefore, we envisioned this transformation as an excellent platform to investigate the reactivity of TBADT as a photoreductant.



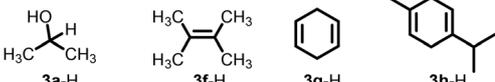
Results and discussion

Building on previous studies and our expertise²⁹ it is apparent that the choice of the sacrificial D-H would be critical in the reaction mechanism for effectively generating the desired product.³⁰ An efficient initial hydrogen atom abstraction is the key step to accumulate the blue colored species ($[W_{10}O_{32}]^{6-}$) in the reaction medium, thus promoting the entire process. Therefore, we aimed to select an ideal D-H that should have very labile C–H bonds, facilitating the initial HAT step.³⁰ The donor (a commercially available and cost-effective compound) should be easily separable from the reaction medium and the resulting radical (D^{\cdot}) should not interfere with the reaction course. Saying so, we began our study with a model reaction using NHPI ester **1a** as the radical precursor, **2a** as the radical acceptor, and TBADT as the photocatalyst (Table 1). In our initial attempts, we screened various alcohols (e.g. **3a-H**, BDE(C–H) *ca.* 94 kcal mol⁻¹)^{31a} as H-donors³² (Table S1 ESI†), but these mostly resulted in competitive radical addition onto **2a**, leading to low yields of the desired product **4a**. Consequently, we shifted our focus to more stabilized allylic radical precursors,³³ hypothesizing that the stability of the resulting radical may hamper the interaction with the SOMOphiles. With tetramethylethylene **3f-H** (BDE(C–H) *ca.* 85 kcal mol⁻¹)^{31b} and cyclohexadiene **3g-H** (BDE(C–H) = 75 kcal mol⁻¹),^{31a} we observed a clean reaction, free from competitive addition to **2a**, yielding **4a** in promising amounts (entries 2 and 3). However, due to the high cost and volatility of these alkenes, which could result in partial evaporation, we turned our attention to low volatility γ -terpinene **3h-H**. γ -Terpinene, a natural product found in medicinal and aromatic plants,³⁴ is commercially available (0.53€ per g)³⁵ and possesses all the required

Table 1 Conditions optimization



Entry	H-donor	Solvent (0.1 M)	Yield ^a (%)	Deviations
1	3a-H	ACN	20%	
2	3f-H	ACN	41%	
3	3g-H	ACN/DCM 9/1	84%	
4	3h-H	ACN/DCM 9/1	92%	
5	3h-H	Acetone	95%	
6	3h-H	ACN/DCM 9/1	53%	390 nm
7	3h-H	ACN/DCM 9/1	—	No photocatalyst
8	3h-H	ACN/DCM 9/1	—	No light
9	—	ACN/DCM 9/1	—	No H-donor

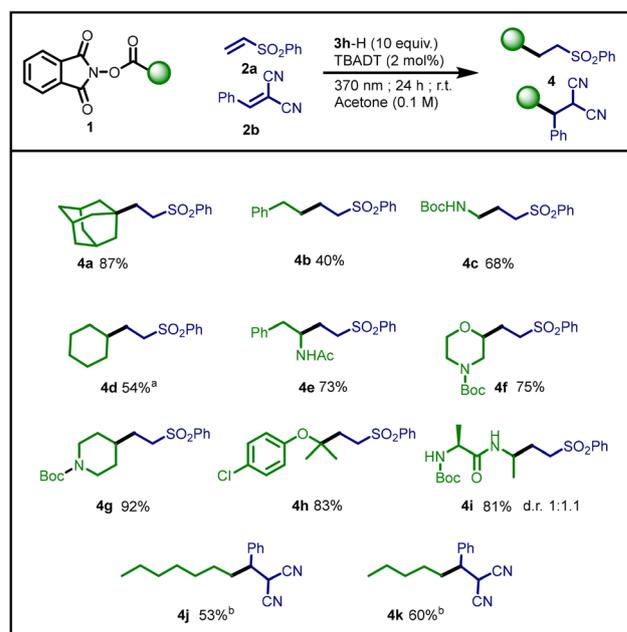


Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), 3-H (1.0 mmol) and TBADT (2 mol%) in 1.0 mL of solvent under N₂. Reactions were irradiated with a 40 W Kessil lamp (370 nm) for 24 h. ^a ¹H NMR yield of **4a** was determined by using CH₂Br₂ as an internal standard.

features for our target reaction (calculated BDE(C–H) is *ca.* 70 kcal mol⁻¹).^{33b} Accordingly, the reaction carried out in an acetonitrile/dichloromethane (ACN/DCM) 9 : 1 mixture gave **4a** in 92% yield (entry 4). When shifting to a greener solvent, such as acetone,³⁶ the yield slightly increased (95%, entry 5). Conducting the reaction under 390 nm Kessil lamp irradiation for 24 h resulted in incomplete conversion of **1**, although no significant side products were observed, indicating that the reaction proceeds at a slower rate (entry 6). Further variation by adjusting the catalyst loading or the equivalents of **2a** or **3h-H** led to lower yields (see Table S2, ESI†). Control experiments confirmed that the reaction was completely inhibited in the absence of light, the photocatalyst, or the D-H (entries 7–9).

Encouraged by these results, we proceeded to explore the addition of radicals derived from NHPI esters onto phenyl vinylsulfone **2a** or benzylidenemalononitrile **2b** (Scheme 2). We began by screening the reactivity of primary (1°) radicals, which are challenging to generate and capture through direct HAT.³⁷

We successfully isolated products **4b** and **4c** in moderate to good yields. In the latter case, the formation of **4c** benefits from substantial stabilization of the radical from the adjacent nitrogen group. Notably, switching to the more reactive radical trap **2b**³⁸ enabled the incorporation of additional primary radicals, affording products **4j** and **4k** in good yields. Interestingly, the use of **2b**, a more easily reducible SOMOphile [*E*_{1/2} = -1.35 V vs. SCE],³⁹ led to the formation of benzylmalononitrile as a byproduct in approximately 10%



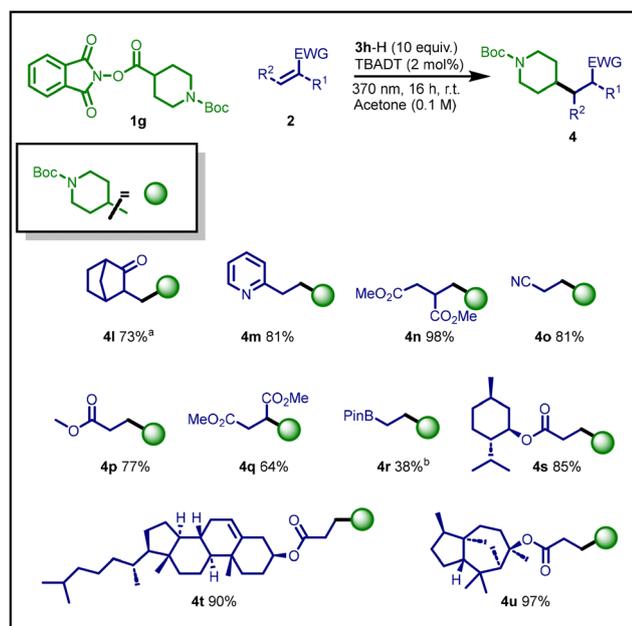
Scheme 2 Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), **3h-H** (2.0 mmol) and TBADT (2 mol%) in 2.0 mL of acetone under N₂. Reactions were irradiated with a 40 W Kessil lamp (370 nm) for 24 h; isolated yields. ^a Reaction performed in ACN/DCM 9/1 (0.1 M). ^b 2-Benzylmalononitrile was isolated in *ca.* 10% yield.



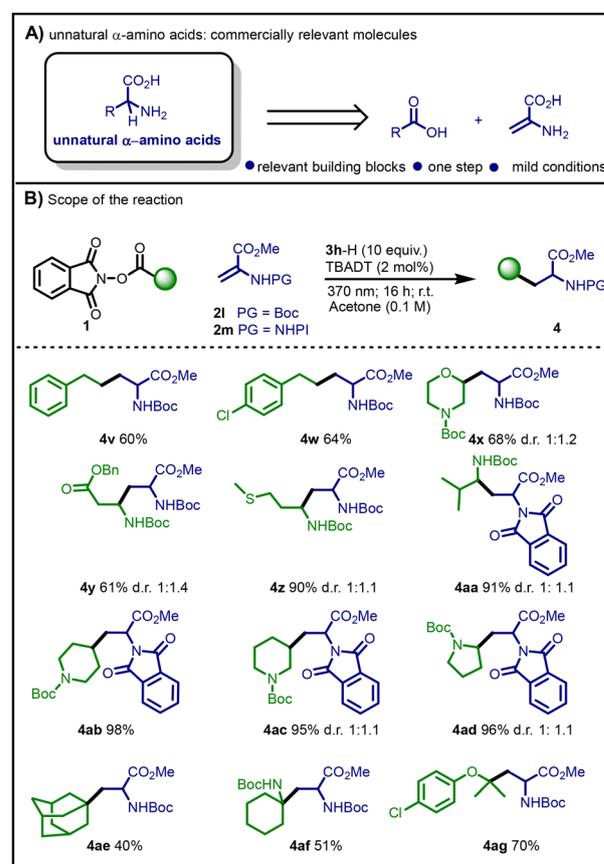
yield. This observation suggests a possible SET event between the doubly reduced form of TBADT and the radical trap.

Next, we were particularly interested in applying our strategy to compounds where TBADT might activate multiple C–H sites, potentially leading to several side products. Accordingly, we screened a diverse range of secondary (2°) radicals, achieving good to excellent yields of products **4d–4g**. Satisfactorily, we observed no competitive formation of undesired α -amido radicals *via* direct HAT, due to the efficient role of γ -terpinene as a H-donor which completely quenched the catalytic activity of TBADT as a hydrogen atom abstractor. We were then able to synthesize the desired products **4f** and **4g**, which are difficult to obtain through direct HAT when omitting the NHPI moiety. Building on these promising outcomes with various carboxylic acid derived radical precursors, we further investigated the functionalization of potential bioactive compounds, such as clofibrac acid⁴⁰ and a dipeptide (Boc-Ala-Ala-OH).⁴¹ In both cases, we successfully isolated the desired products **4h** and **4i** in more than 80% yield. We then investigated the feasibility of our strategy for the alkylation of various α,β -unsaturated ketones, esters, nitriles *etc.* (Scheme 3). Notably, the Giese adducts (**4l–4q**) were formed in a shorter reaction time (16 h) mostly in >70% yield, with product **4n** being obtained in nearly quantitative yield. Lower yields were observed for **4r**, attributed to the lower electrophilicity of the olefin, which led to partial reduction of **1g** to *N*-Boc piperidine. Remarkably, the reaction could also be applied to more complex molecules having stereogenic centers, such as menthol **4s**, cholesterol **4t**, and cedrol **4u** derivatives. These desired products were isolated with exceptional yields, without unwanted C–H activations (or

racemization) catalyzed by TBADT of starting **1g** and **2**. These findings underscore the potential of this strategy for late-stage functionalization of complex molecules by maintaining their structural features. We then extended our methodology to the synthesis of promising commercially relevant molecules. Considering the growing global demand for unnatural α -amino acids, and their potential as valuable building blocks in bioactive compounds,⁴² we explored the possibility of applying our approach for their preparation in one step and under mild conditions by adopting suitable radical acceptors (Scheme 4A). To this end, we screened various NHPI esters in the presence of **2l** and **2m**, as α -amino acid precursors (Scheme 4B). In positive case, this methodology may lead to the formation of racemic products but may represent the starting point for future synthesis of enantiopure α -amino acids by adopting an enantioselective variant.⁴³ We evaluated the behaviour of primary (1°), secondary (2°), and tertiary (3°) radicals. To our delight, we successfully incorporated 1° radicals (compounds **4v** and **4w**). Subsequently, screening different 2° radicals yielded excellent results for **4x–4ad**. In particular, carboxylic acids with multiple functional groups exhibited high reactivity, producing good yields for **4x–4z** and showing excel-



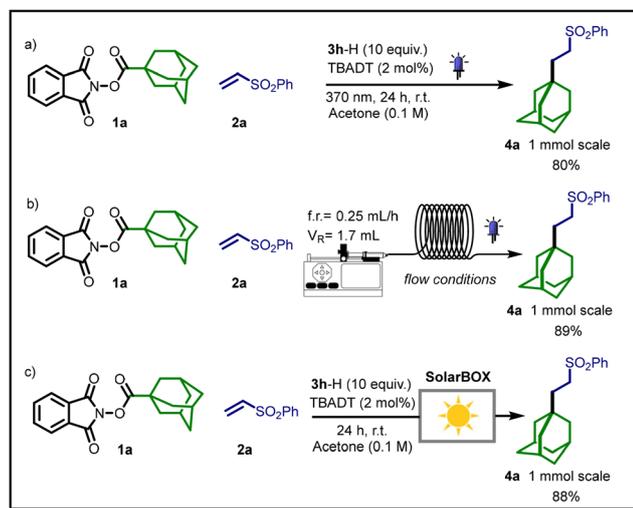
Scheme 3 Reaction conditions: **1g** (0.2 mmol), **2** (0.24 mmol), **3h-H** (2.0 mmol) and **TBADT** (2 mol%) in 2.0 mL of acetone under N₂. Reactions were irradiated with a 40 W Kessil lamp (370 nm) for 16 h; isolated yields. ^a Endo configuration ^b *N*-Boc piperidine as a byproduct.



Scheme 4 Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), **3h-H** (2.0 mmol) and **TBADT** (2 mol%) in 2.0 mL of acetone under N₂. Reactions were irradiated with a 40 W Kessil lamp (370 nm) for 16 h; isolated yields.



lent compatibility with our methodology. Finally, 3° radicals (**4ae–4ag**) gave the desired products in up to 70% yields. As for compounds **4aa–4ad** it was possible to obtain derivatives showing orthogonality of the protecting groups of the nitrogen atoms.⁴⁴ To further demonstrate the practicality of this protocol, we scaled-up the synthesis of **4a** up to a 1 mmol scale using different setups (see Fig. S2 and S3 ESI†). The reaction performed well under both batch and flow conditions (>80% yield), thereby confirming the robustness of the methodology (Scheme 5).

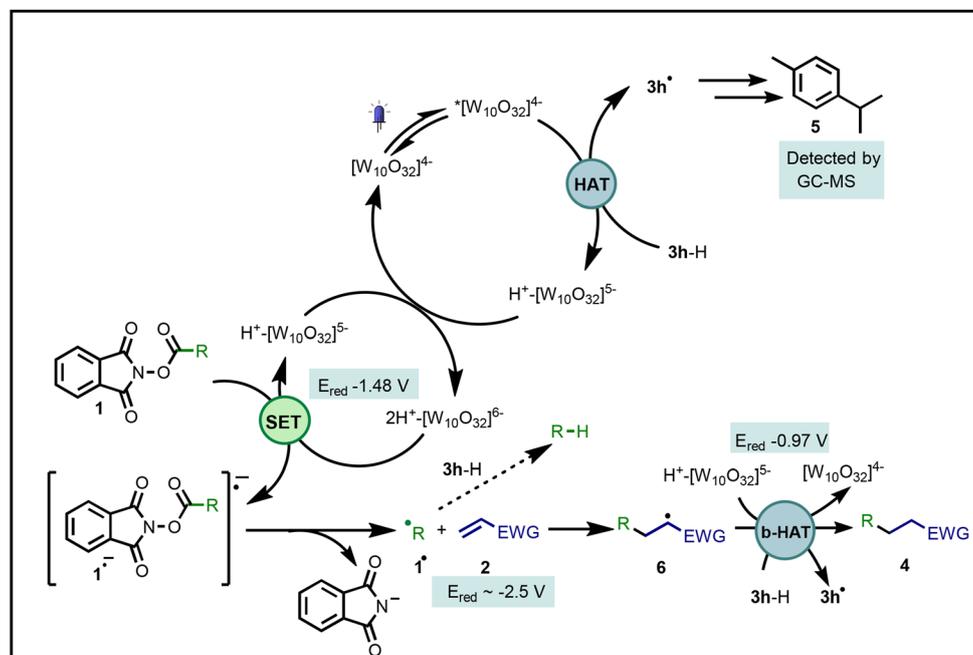


Scheme 5 Synthesis of **4a** on a 1 mmol scale under (a) batch, (b) flow, and (c) solar simulated conditions. Isolated yields of **4a**.

We also tested the reaction under solar simulated light and achieved a good yield of **4a** (88% yield) (see Fig. S4 ESI†). This suggests that diverse building blocks can be efficiently accessed using sunlight as a green energy source.^{2a,45}

Additionally, a reaction performed with TEMPO (5 equiv.) as a radical scavenger was completely inhibited, indicating that a radical step is involved in the reaction pathway. Finally, a light ON–OFF experiment provided no evidence of a radical chain propagation mechanism (see Fig. S5–S8 ESI†).

On the basis of the experiments performed and literature precedents, we propose the mechanistic scenario detailed in Scheme 6.⁴⁶ Previous reports point to a smooth hydrogen abstraction of allylic hydrogens in tetramethylethylene and cyclohexene by excited TBADT.⁴⁷ In addition, cyclohexadiene derivatives are known to be excellent H-donors in photocatalyzed HAT reactions. In fact, the rate constant for abstraction of the C–H bond in 1,4-cyclohexadiene (CHD) by excited TBADT is very high ($3 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$).⁴⁸ Moreover, the rate constant for H-atom abstraction by OH• radicals is 1.7 times higher for γ -terpinene than for CHD.⁴⁹ This opens the way for the use of γ -terpinene as an elective H-donor in photocatalyzed reactions.⁵⁰ Thus, the TBADT excited state cleaves exclusively the weak allylic C–H bond in γ -terpinene, producing $[\text{W}_{10}\text{O}_{32}]^{5-}$ and radical **3h•**. Selective HAT from the allylic C–H bonds of **3h-H** is due to its high H-donor capability along with its high concentration in solution causing no competitive cleavage of other C–H bonds present in other reaction partners. The so formed **3h•** is a pro-aromatic radical⁵¹ that easily undergoes aromatization to *p*-cymene **5** (a well-documented process)^{48,49,52} which was confirmed by GC-MS analysis (see Fig. S9 ESI†). At this stage, direct reduction of NHPI esters



Scheme 6 Proposed mechanism. All the redox potentials are referred to the SCE.



seems unlikely due to the insufficient redox potential of the reduced TBADT $[W_{10}O_{32}]^{4-}/[W_{10}O_{32}]^{5-}$ ($E = -0.97$ V vs. SCE).^{19a} Accordingly, the disproportionation of $[W_{10}O_{32}]^{5-}$ to regenerate $[W_{10}O_{32}]^{4-}$ along with $2H^+[W_{10}O_{32}]^{6-}$ can be envisaged. In its doubly-reduced form, $[W_{10}O_{32}]^{5-}/[W_{10}O_{32}]^{6-}$ ($E = -1.48$ V vs. SCE),¹⁹ TBADT can undergo an exergonic SET with NHPI **1** [$E^{\text{red}} \approx -1.3$ V vs. SCE]²⁷ (Scheme 6), while direct reduction of the SOMOphiles was safely excluded due to their higher redox potentials [$E^{\text{red}} \approx -2.5$ V vs. SCE]²⁴ except for the case of **2b**.³⁹ The resulting alkyl radical **1**[•] undergoes a Giese-type addition to the electron-poor olefin **2**, forming the radical adduct **6**. The presence of an excess of **3h**-H did not cause, however, the conversion of **1** to R-H (the rate constant of H-abstraction of alkyl radicals on CHD is *ca.* $4-5 \times 10^5$ M⁻¹ s⁻¹).⁵³ Two pathways may be hypothesized at this stage for the release of the final product **4**. First, the interaction of **6** with $H^+[W_{10}O_{32}]^{5-}$ by back-HAT or reduction followed by protonation seems more plausible. The occurrence of the latter pathway is witnessed because the redox potential [$E^{\text{red}} = -0.97$ V vs. SCE] of $H^+[W_{10}O_{32}]^{5-}$ is enough to reduce **6** ($E^{\text{red}} [\approx -0.6$ vs. SCE]^{16b}) to the corresponding anion. An alternative pathway leveraging hydrogen abstraction from **3h**-H by **6**, however, may not be safely excluded.⁵⁴

Conclusions

In summary, we have developed a practical and sustainable alkylation method based on SET processes with TBADT serving as an efficient reductant. γ -Terpinene is the elective hydrogen donor for the full exploitation of our methodology to synthesize key building blocks (*e.g.* unnatural α -amino acids) under robust and mild conditions. The reaction could be carried out in a 1 mmol scale (under batch or flow conditions or under solar simulated sunlight). We extended the application of TBADT beyond its conventional role in C-H activation, demonstrating that this photocatalyst has yet to reveal its full potential.

Author contributions

This work was conceptualized by Prof. M. F. and experimentation was performed by M. L. and D. A. The first draft of the manuscript was prepared by M. L. and the final version was edited and revised by M. L. and Prof. M. F.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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