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Photoelectrochemical cross-dehydrogenative coupling of benzothiazoles with strong aliphatic C–H bonds⁺

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A photoelectrochemical strategy for the cross-dehydrogenative coupling of unactivated aliphatic hydrogen donors (e.g. alkanes) with benzothiazoles is reported. We used tetrabutylammonium decatungstate as the photocatalyst to activate strong $C(sp^3)$ -H bonds in the chosen substrates, while electrochemistry scavenged the extra electrons.

A successful combination of photocatalysis¹ and electrochemistry^{2,3} has recently opened new avenues in synthesis,^{4–7} offering unparalleled mild operative conditions and contributing to addressing the urgent need of developing sustainable synthetic protocols.⁸

A seminal example dealt with the photoelectrochemical (PEC) alkylation of (hetero)arenes by a variety of alkyltrifluoroborates (Scheme 1a).⁹ In this process, a mesitylacridinium (Mes-Acr⁺) photocatalyst activated $R-BF_3^-$ substrates (potassium salts) *via* an oxidative single electron transfer (SET), delivering a C-centered radical (R[•]). On the other hand, electrochemistry took care of photocatalyst recovery¹⁰ and of adjusting the redox state of the involved intermediates, enabling this net-oxidative transformation in the absence of any chemical redox agent. More recently, the PEC trifluoromethylation¹¹ and carbamoylation¹² of (hetero)-arenes have been likewise described.

A much more convenient and straightforward approach would require starting from substrates containing a C–H bond, in an overall cross-dehydrogenative coupling (CDC) process.^{6c,13,14} In one instance, a trisaminocyclopropenium (TAC⁺) catalyst has been used to activate the targeted C–H bond in ethers. In particular, electrochemical oxidation of TAC⁺ afforded TAC^{•2+}, which functioned as the actual photocatalyst.¹⁵

In another instance, a different strategy for the CDC of heteroarenes with aliphatic C-H bonds was developed. In such a case, Cl_2 was electrogenerated *in situ* (from excess HCl) and



We hereby report our results on the development of a PEC strategy enabling the CDC of benzothiazoles with strong aliphatic $C(sp^3)$ –H bonds in the presence of tetrabutylammonium decatungstate (TBADT, $(Bu_4N)_4[W_{10}O_{32}]$; Scheme 1c).^{17,18} Our approach exploits the excited state of TBADT to trigger a mild and selective C–H bond activation *via* a hydrogen-atom transfer (HAT) step.¹⁹ The obtained products contain the benzothiazole ring, an important structural motif in several bioactive compounds.²⁰ In particular, 2-alkyl substituted benzothiazoles, among the other applications, have been adopted as anticancer, antimicrobial, antitubercular, antidiabetic and antidepressant agents.^{20a}

Building upon our previous studies on the TBADT-photocatalyzed Minisci-type CDC of H-donors with heteroarenes, which took place in the presence of potassium persulfate ($K_2S_2O_8$, 2 equiv.) as the terminal oxidant,²¹ we started off by investigating the oxidative coupling of cyclohexane (**1a**) and benzothiazole (**2a**) to



Scheme 1 Selected strategies for the functionalization of benzothiazoles encompassing the combination of electrochemistry and light.

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[†] Electronic supplementary information (ESI) available: Experimental details about the used materials, sample preparation, electrochemical measurements, laser flash photolysis, kinetic analysis and copy of NMR spectra. See DOI: 10.1039/ d1cc01012c

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^{*a*} Reactions performed on a 0.75 mmol scale. Anolyte: **1a** (0.25 M, 5 equiv.), **2a** (0.05 M), TBADT (4 mol%), LiNTf₂ (0.05 M) in MeCN/H₂O 10:1 (15 mL). Catholyte: LiNTf₂ (0.05 M) in H₂O (15 mL). ^{*b*} NMR yield, CH₂Br₂ used as an external standard. ^{*c*} TBAClO₄ was poorly soluble. ^{*d*} Complex mixture. ^{*e*} 2 mA applied to transfer 2 F mol⁻¹ within 20 h. The formation of a thick deposit on the electrode surface was observed. ^{*f*} The experiment was stopped after 30 min since a very low current was observed (~1 µA). ^{*g*} The redox-neutral adduct 2-cyclohexylbenzothiazoline (3') was also formed in 9% yield. GC: glassy carbon; Pt:Pt gauze, BDD: boron-doped diamond (see ESI for further information).

give adduct **3** (Table 1). The reaction setup consisted of a conventional H-type electrochemical cell (separator: Nafion[®] N-117 polymeric membrane) equipped with a three-electrode system, while irradiation was performed with an LED lamp ($\lambda_{em} = 390$ nm; 40 W) under rigorous oxygen-free conditions (see the ESI† for details). The anolyte was composed of a LiNTf₂ (0.05 M) MeCN/H₂O 10:1 solution (15 mL) containing **2a** (0.05 M), **1a** (5 equiv.) and TBADT (4 mol%), while a LiNTf₂ (0.05 M) water solution (15 mL) was used for the catholyte.

Gratifyingly, when the cell was operated in a potentiostatic mode by setting a fixed potential between the working (WE) and the reference (RE) electrode ($\Delta E_{WE-RE} = +150$ mV; reference electrode: Ag/AgCl, Sat'd NaCl; anode: glassy carbon; cathode: Pt gauze), we found that product 3 was formed in 80% NMR yield (at >90% starting materials conversion; total charge: 1.9 F mol⁻¹; entry 1). The reaction was rather sensitive to the nature of the electrolyte used, with yields failing to reach 55% when using TBAClO₄ or different Li-based salts (entries 2-4). Similarly, different photocatalyst loadings were found to be detrimental (entries 5 and 6). Next, we considered the influence of different electrochemical parameters on the reaction outcome and modified the applied potential $\Delta E_{\text{WE-RE}}$, as well as adopted an amperostatic operation mode (2 mA for 20 h), however a lower yield of 3 was observed in all cases (entries 7-9). Next, we screened alternative materials for the WE, including carbon cloth, boron-doped diamond (BDD) and Ptgauze electrodes, finding that 3 could be formed in 80% yield when using the noble metal electrode (entries 10-12). We also attempted to run the model reaction in a round bottom flask (undivided cell conditions), however a very poor performance was obtained (entry 13). Control experiments proved the essential role of light, photocatalyst and electricity (entries 14-16). Notably, under purely photocatalytic conditions, a small amount (9% yield) of the redox-neutral adduct 2-cyclohexylbenzothiazoline (3') was observed besides traces of product 3 (entry 16). Finally, we replaced the potentiostat with two 1.5 V batteries (AAA-type; ~ 3 V applied) in a 2-electrode setup, observing the formation of product 3 in 65% yield (entry 17; see the ESI[†] for further details).

With the optimized conditions in hand (Table 1, entries 1 and 12), we next evaluated the scope of the reaction by reacting parent 2a with a library of selected H-donors (Table 2, upper part). We consistently adopted Pt gauze as the anode for its robustness and ease of cleaning, while selected entries were run with a GC electrode (see Table S1 in the ESI⁺). Thus, the model reaction allowed the isolation of product 3 in 78% yield; no improvement was observed if the excess of 1a was increased to 10 equiv. (75% isolated yield). On the other hand, with cyclopentane (1b) a higher excess of H-donor (up to 20 equiv.) was required to push the reaction to full conversion with adduct 4 isolated in 73% yield. Cycloheptane (1c; 5 equiv. used) was scarcely soluble under our conditions, however the expected arylated adduct 5 and the dimerization product 5A were formed in 42 and 21% isolated yield, respectively. Similarly, norbornane (1d) was smoothly functionalized to give the expected product 6 in 61% isolated yield (77% brsm) as an exo/ endo 8:1 mixture, along with a minor amount of 2-(cyclopentylmethyl)benzothiazole (6A; 8% yield).§²² Finally, the selective functionalization^{17a} of isocapronitrile (1e; at the methine position) and cyclopentanone (1f; at the β -position) occurred in high isolated yields (>80%) to give products 7 and 8 when using 10 equiv. of the H-donors, respectively.

Next, we turned our attention to the scope in terms of benzothiazoles (Table 2, lower part) and selected **1a** as the model H-donor (10 equiv. used). Halogenated derivatives in the 6-position offered different reactivity profiles depending on the substituent nature, leading to products **9–11** in modest to excellent isolated yields (26–80%). Strong electron-withdrawing or donating substituents offered similar results, as testified by adducts **12** and **13**, that were both isolated in 50% yield (the former with a better mass balance). The biologically-relevant trifluoromethoxy group²³ was tolerated as well,



 a A minor amount (8% yield) of 2-(cyclopentylmethyl) benzothiazole (6A) was also formed.

product **14** being obtained in 75% yield. Finally, we varied the number and position of the substituents on the starting benzothiazole, and products **15** and **16** were formed in 67% (87% brsm) and 47% yields, respectively.

To have insights into the mechanism, we monitored over time the reaction between **1a** and **2a** and found that the redoxneutral adduct 2-cyclohexylbenzothiazoline (3') was formed at short reaction times, along with the desired product **3** (see kinetic analysis in Section 1.2 in the ESI†). When we subjected adduct 3' to optimized PEC conditions, we discovered that it could be easily converted to the final product **3** in 60% NMR yield. In contrast, the conversion of 3' to **3** did not occur under purely electrochemical conditions (irradiation omitted; see Section 1.3 in the ESI† for further information).

Scheme 2 depicts the proposed reaction mechanism, based on the data reported above, as well as the laser flash photolysis (LFP; Section 1.4) and electrochemical experiments (Section 1.5) reported in the ESI.† Thus, upon light absorption the reactive excited state of TBADT (**wO**) is generated,^{17*d*,24} which is responsible for aliphatic C(sp³)–H bond activation (*e.g.* in 1a) to afford organoradical I[•]. The latter then adds onto the 2-position of benzothiazole (*e.g.* 2a) to afford radical adduct **II**[•]. At this stage, **II**[•] may follow two different pathways to be ultimately converted to product 3. One possibility is that **II**[•] undergoes a back-HAT (*b*-HAT) from the reduced form of



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Scheme 2 Proposed reaction mechanism.

decatungstate $H^+[W_{10}O_{32}]^{5-}$ (W_{red} (H^+)) to give the redoxneutral benzothiazoline derivative 3', also restoring the original form of the photocatalyst (path *a*). Eventually, as mentioned before, 3' is converted to 3 *via* a photoelectrochemical sequence, wherein **wO** triggers an oxidative SET event to deliver intermediate **III**[•] upon deprotonation (see Section 1.4 in the ESI[†]).

Alternatively, the formation of the final product 3 from II• can occur via path b: we suggest that II[•] undergoes a spincenter shift (SCS),^{25,26} possibly mediated by the protic medium,²⁷ to give III[•]. Notably, the intermediacy of this species is corroborated by the formation of 5A in the reaction between cycloheptane 1c and benzothiazole 2a via the dimerization of the corresponding III° species. To evaluate the feasibility of the conversion of III[•] to 3, following a previously reported approach⁹ we estimated its oxidation potential by measuring the reduction potential of the protonated product 3-H⁺; a value of $E_{p/2}^{red}(3-H^+/III^{\bullet}) = -0.68 \text{ V} \nu s$. SCE has been found (see Section 1.5 in the ESI[†] for additional details). Indeed, due to the transient nature of III[•], we consider its direct oxidation by the anode unlikely and postulate that the decatungstate anion might serve as an electrocatalyst to promote this step. This possibility is fully supported by cyclic voltammetry experiments, indicating a reduction event at $E_{p/2}^{red}(W/W_{red}) = -0.52 \text{ V} \text{ vs. SCE in}$ our conditions, ¶²⁸ confirming the above mentioned hypothesis. The electrochemical reaction in the anolyte was balanced by the cathodic reduction of protons to molecular hydrogen.

The hereby reported PEC protocol, wherein electricity functions as the terminal oxidant, compares favourably with our previous work based on the use of a chemical oxidant (excess $K_2S_2O_8$).²¹ In particular, compound **3** was prepared in 60% isolated yield adopting the latter method, while photoelectrochemistry allowed the improvement of this value (up to 78%) with the adoption of a lower H-donor excess (5 equiv. *vs.* 20 equiv.).

Overall, the present work unlocks the use of aliphatic substrates featuring strong $C(sp^3)$ -H bonds in photoelectrochemical manifolds and enables their arylation with benzothiazoles in a cross-dehydrogenative coupling protocol. Notably, the decatungstate anion shows a chameleonic attitude in the reported transformation and plays a three-fold role: HAT photocatalyst, photoredox catalyst and electrocatalyst. The process occurs under extremely mild conditions and with a very low applied potential, resulting in a perfect matching with the reactivity profile offered by TBADT, that is turned over after each catalytic cycle with an excellent faradaic efficiency.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

§ We attribute the formation of **6A** to an over-oxidation pathway. See ref. 22.

¶ The analysis of the redox behavior of TBADT through cyclic voltammetry has been previously reported, indicating a reduction event at -0.97 V *vs.* SCE in MeCN. The original potential was expressed against the Ag/0.01 M AgNO₃ and was here converted against SCE by adding +298 mV. See ref. 28.

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