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Advanced Synthesis & Catalysis

Synthesis of Linear Enamides and Enecarbamates *via* Photoredox Acceptorless Dehydrogenation

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Abstract: In recent years, several methods for the direct desaturation of aliphatic compounds have been developed, facilitated by the unique combination of photoredox and transition-metal catalysis. Hereby, alkenes with high functionalization potential can be prepared in a straightforward fashion. We adapted a previously reported system involving tetrabutylammonium decatungstate (TBADT) as hydrogen atom transfer (HAT) agent and a cobaloxime co-catalyst for dihydrogen evolution for the dehydrogenative preparation of linear enamides and enecarbamates from saturated precursors. The substrate scope includes several natural products and drug derivatives. The reaction does not require noble metal catalysts, exhibits short reaction times compared to previous methods and is suitable for the late-stage functionalization of drug derivatives.

Keywords: Photocatalysis; Dehydrogenation; HAT Catalysis; β-hydride elimination; Enamide

The direct dehydrogenation of aliphatic compounds to olefins carried out by enzymes is an essential transformation in living systems, and is involved in several biosynthetic pathways such as the desaturation of fatty acids or carotenoids.[1] The emulation of these reactions by chemists has remained unmet, since the activation of two relatively inert C(sp^3)–H bonds in a single process is kinetically and thermodynamically disfavoured.[2] As a result, direct desaturations often require harsh reaction conditions involving the combination of transition metal catalysts with external oxidants/H-acceptors,[3] or in situ generation of intramolecular radicals as H-acceptors, often at high temperatures.[4] In view of this, the development of alternatives with better atom- and energy efficiency for the conversion of alkanes to alkenes is highly desirable.[5] Over the last decade, photochemistry has emerged as a technique by which transformations under milder reaction conditions can be achieved. Heat is replaced by light for generating radicals,[4a,c,d,e,6] and the use of oxidizing agents/H-acceptors can be precluded by the design of acceptorless catalytic systems which release dihydrogen instead.[7–9] Preoxidized or prefunctionalized starting materials[10] can be avoided. Acceptorless cooperative HAT-based protocols for instance, have been applied for the desaturation of aliphatic substrates including even unactivated cycloalkanes[7a] to alkenes[7] and aromatics.[7c,8,9] Even though some of these methodologies involve organocatalysts as additional HAT-mediators,[9] most systems rely on a dual catalytic approach by combining a photoexcitable HAT-catalyst, which upon irradiation is capable of generating a C-centered radical, and a transition-metal complex that is required for subse-

quent β-hydride elimination and dihydrogen evolution.[7,8] In the context of alkene synthesis, cobaloxime complexes have proven their efficiency as co-catalysts in combination with photoexcitable hydrogen atom abstractors, such as 2-chloroanthraquinone,[7c] or tetra-*N*-butylammonium decatungstate (TBADT).[7a]

Enamide and enamine scaffolds are valuable synthetic building blocks, which are ubiquitous among agrochemicals, natural products, pharmaceuticals, and as monomers for the preparation of polymeric materials.[11] The synthetic strategies for their access commonly employ heating, activated substrates or expensive catalysts and ligands.[3d,12] This has partly been circumvented with the development of novel photochemical methodologies relying on dehydrogenation processes. In this regard, the Tunge group published a protocol for the elimination of *N*-acyl amino acids via a dual catalytic approach involving an acridinium-based photocatalyst and a cobalt complex.[7b] In the same year, the Gevorgyan group reported a site-selective protocol for the desaturation of amines, wherein the position of the double bond is controlled by the effect of a directing group attached to the substrate. The photoexcitation of a palladium catalyst leads to an intramolecular 1,n-HAT process and a subsequent desaturation (Figure 1a).[4e] More recently, the El-Sepelgy group published an alternative methodology based on the same principle for the desaturation of a variety of amines and amides, using a tin-cobaloxime complex instead (Figure 1b).[13] Although both protocols give access to a wide array of synthons in good yields, the incorporation of the directing group requires an additional step which limits their application in late-stage functionalization or even for the desaturation of biologically relevant molecules. As an alternative to these approaches, the Huang group reported a versatile protocol for the desaturation of a wide array of aliphatics. However, the system requires a particularly high-catalyst loading, long reaction times and is limited in terms of enamide and enecarbamate scope (Figure 1c).[7c]

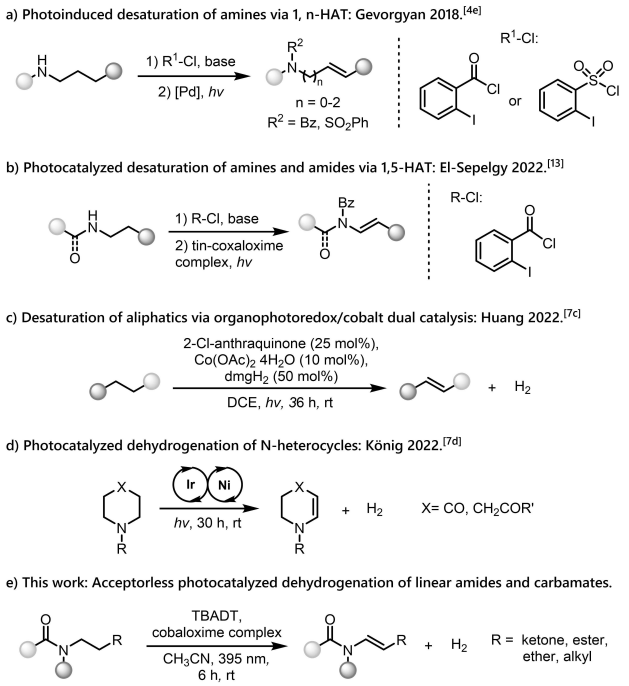


Figure 1. Photochemical preparation of enamides and enecarbamates via HAT-mediated desaturations.

In this context, our group recently reported the dehydrogenation of aliphatic *N*-heterocycles such as cyclic enamides and enecarbamates via a novel cooperative catalytic approach between an iridium photocatalyst and a nickel complex (Figure 1d).[7d] This reaction proceeds regioselectively under mild conditions, and with perfect atom economy.

Building on the above-mentioned methodologies developed by the Huang and the König group,[7c,d] we decided to further expand the scope of these protocols. For this purpose, we adapted the synergistic system reported by Sorensen,[7a] for the preparation of challenging linear enamides and enecarbamates (Figure 1e).

We began our study with *N*-methyl-*N*-(3-oxobutyl) benzamide (**1 a**) as the model substrate by subjecting it to the dehydrogenation reaction conditions recently published by our group.[7d] Unfortunately, only trace amounts of the desired product **1 b** were observed. Inspired by a recent report from the Sorensen group,[7a] we hypothesized that photoexcitable TBADT could act as a HAT agent to form radical intermediate **II**. The resulting reduced form of TBADT is oxidized by a Co(II) complex, thus closing the catalytic cycle. We found that with 2 mol% of TBADT as the photocatalyst, and 5 mol% of $Co(dmgH)_2(pyr)Cl$ (COPC) as the co-catalyst in acetonitrile (50 mM) under 395 nm blue LED, the desired dehydrogenated product **1 b** was formed in 9% yield after 24 h at 25 °C. Encouraged by this result, we decided to further optimize the reaction conditions.

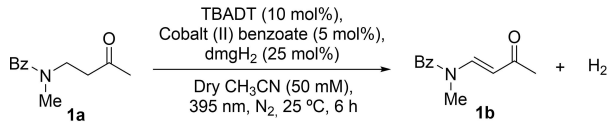
Different photocatalysts were screened and only decatungstate based photocatalysts were active (Table S1, supporting information). The reaction time was optimized, and 6 h was found to be ideal since extending the reaction time did not further increase the product yield (Table S2, supporting information). Next, the light source, solvent, co-catalyst, and catalyst loading were tested (Table S3–S7, supporting information). A high loading of TBADT was essential for achieving a high product yield in short reaction times. Reducing the catalyst loading leads to a notable increase in reaction time. As the olefinic products slowly degrades when irradiated for longer periods of time (as seen by the decrease in yield after 6 h in

Table S2) it is important to complete the reaction in a short time. Gratifyingly, after these optimizations, the yield of the desired dehydrogenated product **1b** increased to 71% yield in presence of 10 mol% TBADT, 5 mol% cobalt benzoate and 25 mol% of dimethylglyoxime ($dmgH_2$) in acetonitrile (50 mM) under 395 nm blue LED for 6 h at 25 °C (Table 1, entry 1). No reaction occurred in the dark either at room temperature or at 50 °C (Table 1, entries 2–3) confirming a visible light mediated transformation. Similarly, no product was observed in the absence of the photo- or cobalt-catalyst (Table 1, entries 4–5). Only trace amounts of the product were obtained when the reaction was carried out without adding $dmgH_2$ (Table 1, entry 6), suggesting the critical role of the $dmgH_2$ ligand framework in the hydrogen evolution process.[14] Furthermore, a higher catalyst loading of 15 mol% of TBADT (Table 1, entry 7) did slightly decrease the product yield.

Inspired by our recently published desaturation protocol for *N*-heterocycles,[7d] several linear structural analogues were prepared for attaining equivalent transformations (Scheme 1). Accordingly, the optimized catalytic system was initially tested with tertiary *N*-substituted scaffolds featuring an electron-withdrawing carbonyl group at the desaturation site.

Hereby, the presented methodology delivered enamide **1b** and *N*-protected enamines (**2b**–**8b**) as the corresponding desaturation products in moderate to good yields (30–71%). In addition, the structure of **7b** in the crystal was determined by X-ray analysis.[15] Notably, enamide **1b** afforded the best result (71% yield), presumably due to the high electron-withdrawing ability of its aromatic moiety which can stabilize

Table 1. Reaction conditions and control experiments.[a]



Entry	Deviation from conditions	Yield of **1b** (%)[b]
1	–	71
2	in dark	n.d.
3	50 °C instead of irradiation	n.d.
4	no photocatalyst	n.d.
5	no cobalt catalyst	n.d.
6	no $dmgH_2$	n.d.
7[c]	–	65

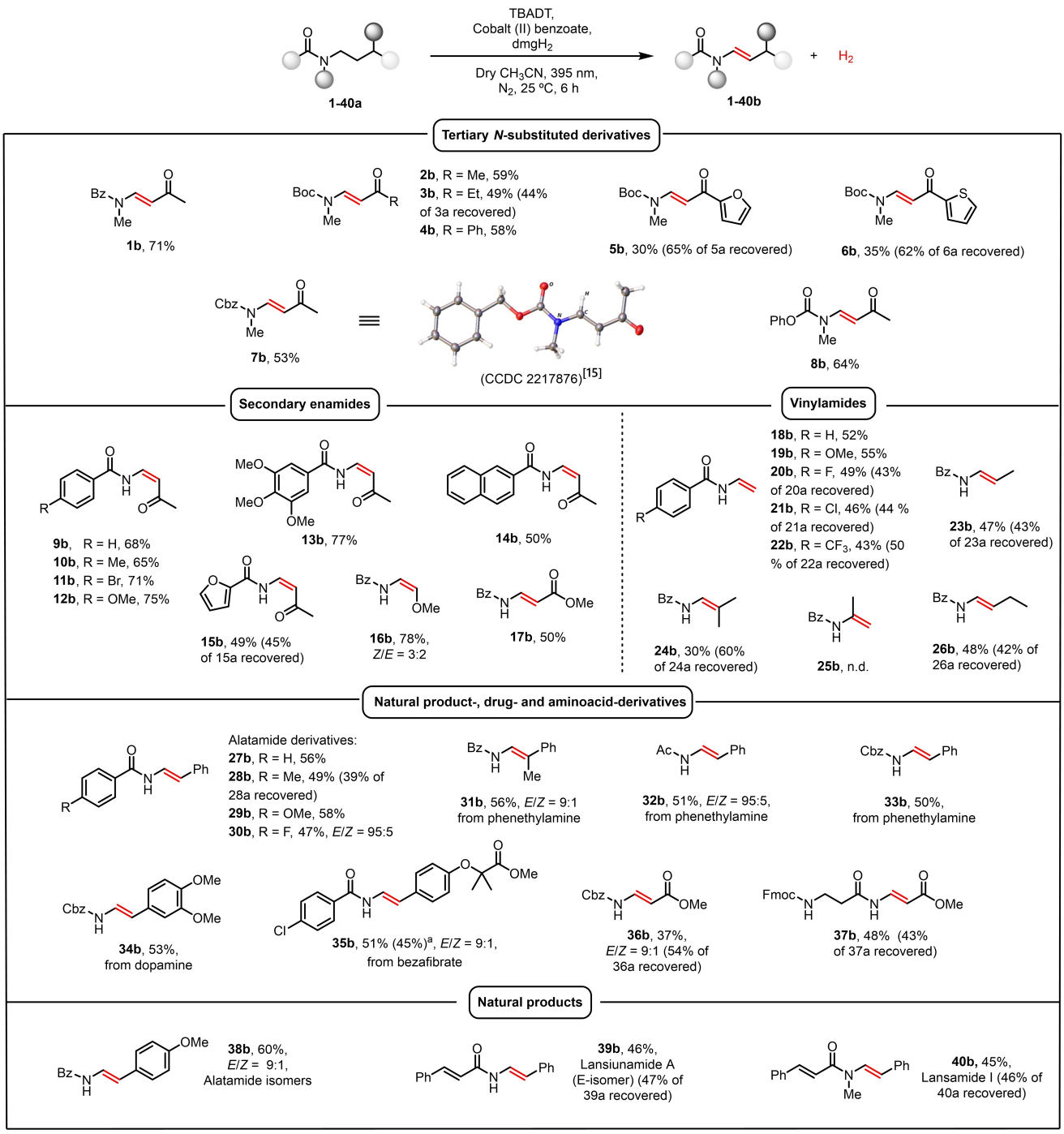
[a] Reaction conditions: **1a** (0.1 mmol), TBADT (10 mol%), cobalt benzoate (5 mol%), $dmgH_2$ (25 mol%), CH_3CN (2 mL), 395 nm LED (2.1 W), 25 °C, N_2.
[b] Yields were determined by GC-FID analysis against benzonitrile as internal standard.
[c] 0.015 mmol of TBADT instead of 0.01 mmol. n.d.: product not detected.

the C-centered radical formed at α-position to the nitrogen atom.[16] Although the aromatic carbamate moiety in **8b** seemed to have a similar effect on the reaction yield (64%), no clear correlation between reactivity and structural or electronic properties could be identified.

With these preliminary results in hand, the methodology was applied to secondary amides, furnishing several to date unreported enamides (**9b**–**17b**) in satisfactory yields (49–77%). A possible electronic effect on the aromatic amide moiety was investigated. For this, various *para*-substituted aromatic amides were prepared displaying different EDGs (**9a**–**12a**). However, no clear trend was observed, as the reaction yield did not show a direct correlation with the variation in the electronic properties of the tested substituents (**9b**–**12b**). The ether group in compound **16b**, and the *β*-alanine ester substructure featured by **17b** were well tolerated. Interestingly, while for the previously discussed tertiary *N*-substituted derivatives the *E*-isomer was exclusively obtained, secondary moieties besides **16b** and **17b**[17] afforded solely the corresponding *Z* isomer. Even though the *E*-configuration of these olefinic products is thermodynamically favoured,[18] the predominance of the *Z*-configuration among secondary enamides suggests that *Z*-isomer formation might be favoured due to intramolecular hydrogen bonding between the nitrogen and the carbonyl group. The same argument might be valid for explaining the predominant formation of the *Z*-isomer of **16b**, as it features a methoxy group which can act as a hydrogen bond acceptor.

Aromatic alkylamides proved suitable too, giving the corresponding vinylamides (**18b**–**25b**) in moderate yields (30–55%). Herein unreported desaturations of relatively simple molecules could be carried out in a mild and straightforward fashion. These results suggest that apart from nitrogen, an additional EWG attached to the aliphatic desaturation site is not essential for promoting the dehydrogenation process. No electronic effect of the aromatic amide moiety was observed (**18b**–**22b**). However, a certain steric effect was identified, as the reaction yield dropped notably with increasing substitution on the aliphatic C-end of the substrate (**23b** and **24b**). In addition, further investigations revealed that α-substituted amides such as **25a** did not render the expected products (**25b** in this case). This is presumably due to the increased steric hindrance, as cobaloxime complexes involving tertiary carbon centers are not common. Contrary to the substitution degree of the carbon atoms attached to the desaturation site, the chain length, as observed for products **18b**, **23b** and **26b** has no relevant impact on the reaction yield. Also, for **26a** only the monodesaturation product **26b** was observed.

The reaction scope for the synthesis of biologically relevant scaffolds was also examined. Alatamide,



Scheme 1. Substrate scope. Reaction conditions: Substrate (0.1 mmol), TBADT (0.01 mmol), cobalt benzoate (0.005 mmol), $dmgH_2$ (0.025 mmol), CH_3CN (2 ml), 395 nm LED, 6 h, 25 °C, N_2. Given yields are Isolated. [a] Reaction at 500 mg scale.

phenethylamine, and dopamine derivatives (**27a**–**34a**) seemed particularly attractive targets as they have many synthetic and pharmacological applications.[19] The desaturation of several substrates bearing these motifs was carried out, giving access to products with potential biological activity (**27b**–**34b**) in moderate yields (47–58%) and exclusively (**27b**–**29b**, **34b**, **33b**) or predominantly (**30b**, **31b**, **32b**) in *E*-configuration. Likewise, the desaturation of the methyl ester of the commercial drug bezafibrate, a potent hypolipidemic agent,[20] gave a novel derivative of this drug (**35b**), predominantly in its *E*-configuration. Furthermore, the scalability of our methodology was demonstrated by carrying out the desaturation of **35a** on a 0.5-gram scale, giving the product **35b** (45%), in

slightly lower yield than the small-scale reaction (51%).

Based on the successful desaturation of **17 a** to **17 b**, two *β*-alanine derivatives were prepared. Herein, the dehydrogenation of an aminoacid ester (**36 a**) and a dipeptide (**37 a**) was accomplished. Regarding the dipeptide, the desaturation proceeded chemoselectively as a single desaturation product was isolated (**37 b**) while the corresponding two-fold desaturation product was only observed in trace amount by GC-MS.

Lastly, three natural products were successfully prepared by the dehydrogenation of their saturated precursors. Alatamide (**38 b**) for instance, an amide derived from *β*-phenylethylamine[18,20] could be prepared through a facile two-step approach in moderate yield as a diastereoisomeric mixture (*E*/*Z* = 9:1). Similarly, Lansiunamide A (**39 b**) and Lansamide I (**40 b**), two naturally occurring cinnamamides,[21b,22] were prepared following a two-step synthetic scheme, hereby circumventing tedious total synthesis protocols.[21b,23]

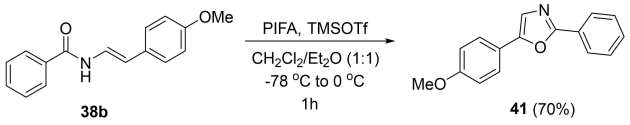
Although our method is highly efficient for the desaturation of secondary aliphatic carbon centers, tertiary C-centers at *α*- or *β*-position to the nitrogen (except for **24 b** and **31 b**) react less efficient, as sterics seem to prohibit the reaction (Scheme S7). In addition, as observed for failed substrates 4-(*N*-benzyl-*N*-methylamino)-2-butanone **SM-A** and 1-(*N*-benzyl-*N*-methylamino)-3-pentanone **SM-C** (for details, please see Supporting Information) that did not deliver the corresponding desaturated products, the protocol is only suitable for substrates displaying electron-withdrawing *N*-protecting groups such as amides and carbamates with generally high oxidation potentials. Free amines do not yield the desired products as the excited decatungstate anion with an oxidation potential of around +2.44 V vs SCE acts as an oxidant via SET. As a result, if a free amine was subjected to the given system, most likely, a *N*-centered radical cation is generated instead of a HAT event taking place.[24c]

To demonstrate the synthetic utility of the products, a post functionalization reaction was carried out. Herein, the *E*-isomer of natural product **38 b** was used for the preparation of oxazole **41** (70%) via an hypervalent-iodine mediated oxidative cyclization (Scheme 2).

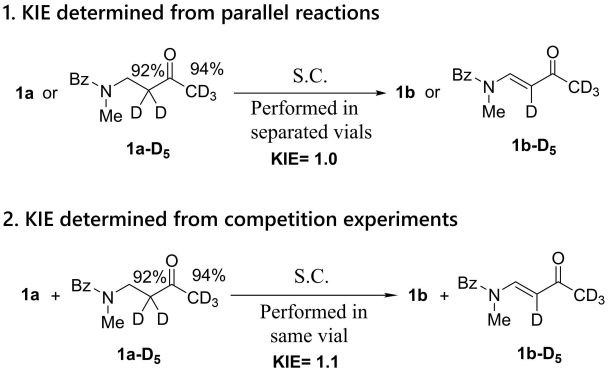
Spectroscopic studies, control experiments, and kinetic isotope effect (KIE) studies were performed to investigate the reaction mechanism. An UV-Vis kinetic study was chosen to gain insight into the combined catalyst system. A solution of substrate **1 a** and TBADT in acetonitrile was irradiated (Figure S3). After 2 minutes of irradiation, an immediate growth of a broad band (absorbance maximum at 450 nm, 630 nm, and 780 nm), characteristic for the reduced form of TBADT was observed. Further, no significant change was observed when a solution of **1 a** and cobalt complex in acetonitrile, and a solution of cobalt complex and TBADT in acetonitrile was irradiated (Figure S4–S5). Additionally, when we irradiated **1 a**, TBADT, and the cobalt complex (Figure S6), a peak at 430 nm was observed which indicated the reduction of Co (III) to Co (II). The results suggested that the oxidation of the reduced photocatalyst takes place by single electron transfer to Co(III). The peak at 780 nm indicated the presence of reduced TBADT in the reaction solution. The hydrogen gas was evolved quantitatively as determined by GC analysis of the crude product mixture (Fig. S7–S8). Light "on-off" experiments suggested that continuous light irradiation is required for the reaction to proceed (Fig. S11).

Kinetic isotope effects (KIE) were calculated by estimating the parallel rates of the reaction for substrates **1 a** and **1 a-D$_5$** (Scheme 3, (**1**)), as well as from competition experiments between **1 a** and **1 a-D$_5$** (Scheme 3, (**2**)). Small KIE values of the order 1–1.1 units were observed in both cases. These results exclude the *β*-hydride elimination step as the rate determining step of the reaction.

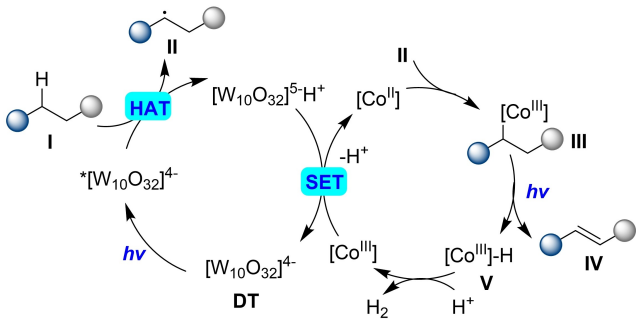
Based on the mechanistic routes reported in the literature,[7c,14,24–27] we propose a rational mechanism for the photocatalytic dehydrogenation of aliphatic *N*-hetero acyclic systems as shown in Scheme 4. Photoexcitation of decatungstate anion $[W_{10}O_{32}]^{4-}$ produces a triplet excited state $*[W_{10}O_{32}]^{4-}$, which abstracts a hydrogen atom from substrate **I**, producing alkyl radical **II** and the protonated reduced decatungstate $[W_{10}O_{32}]^{5-}H^{+}$.[24] Alkyl radical **II** is subsequently trapped by the Co(II) complex, yielding an alkyl



Scheme 2. Synthetic application of Alatamide (*E*-isomer) for the preparation of an oxazole.



Scheme 3. KIE meassurements.



Scheme 4. Proposed plausible reaction mechanism.

Co(III) intermediate **III**.[24] Photo-irradiation of **III** delivers the alkene product **IV** along with a Co (III)-H intermediate via a formal β hydrogen elimination process.[7c,25a,c,26] The intermediate **V** engages with another proton to evolve hydrogen gas and releases a Co(III) complex.[14,27]

Lastly, the oxidation of the protonated reduced photocatalyst $[W_{10}O_{32}]^{5-}H^+$ takes place by single electron transfer (SET) from the Co(III) intermediate ($E_{1/2}$ $Co^{III}/Co^{II} = -0.68$ V vs Ag/Ag^+ in MeCN, $E_{1/2}$ $[W_{10}O_{32}]^{4-}/[W_{10}O_{32}]^{5-} = -0.96$ V vs Ag/Ag^+ in MeCN), regenerating both catalysts in their ground states.[28]

In conclusion, we report a light-driven acceptorless cooperative HAT method for the dehydrogenation of aliphatic carbamates and amides to the corresponding enecarbamates and enamides. TBADT and a cobaloxime complex have been used as H-abstractor and β-hydride elimination agent respectively. The method features short reaction times and exhibits broad functional group tolerance, making it suitable for late-stage functionalization of drug derivatives.

Experimental Section

For full Experimental Details see supporting information.

General Synthetic Procedure for Photocatalyzed Dehydrogenations

A 5 mL crimp-cap vial equipped with a stirring bar, was loaded with the corresponding aliphatic substrate (100 µmol, 1.00 eq.), TBADT (33.3 mg, 10 µmol, 10 mol%), cobalt (II) benzoate (1.5 mg, 5 µmol, 5 mol%) and $dmgH_2$ (3.0 mg, 25 µmol, 25 mol%). The vial was sealed, evacuated, and back filled with N_2 (3x) before adding dry CH_3CN (2 mL). The reaction mixture was subsequently purged with N_2 for 15 min and stirred under irradiation using a 2.2 W 395 nm (±15 nm) LED set-up for 6 h at 25 °C (temperature controlled by a thermostat). Reaction progress was monitored by TLC or GC analysis. Afterwards, the solvent was evaporated under reduced pressure and the crude product was purified via flash column chromatography (FCC).

Acknowledgements

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