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**Invited paper**

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# A blueprint for green chemists: lessons from nature for sustainable synthesis

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**Abstract:** The design of new chemical reactions that are convenient, sustainable, and innovative is a preeminent concern for modern synthetic chemistry. While the use of earth abundant element catalysts remains underdeveloped by chemists, nature has developed a cornucopia of powerful transformation using only base metals, demonstrating their viability for sustainable method development. Here we show how study of nature's approach to disparate chemical problems, from alkene desaturation to photodetection in bacteria, can inspire and enable new approaches to difficult synthetic chemistry problems past, present, and future.

**Keywords:** 2019 IUPAC-Zhejiang NHU International Award; bio-inspired; catalysis; earth abundant elements; Green Chemistry; photocatalysis; sustainability.

## Introduction

How can we make sustainably? With an escalating climate crisis, diminishing petrochemical resources, and ever-increasing energy and material demands, the manner by which we produce the molecules of modern life, from commodity chemical feedstocks to pharmaceuticals, becomes increasingly important. The field of Green Chemistry has sought to enumerate the means by which the sustainability of chemical synthesis might be improved, with entries on both the UN Sustainable Development Goals [1] and 12 Principles of Green Chemistry developed by Anastas and Warner [2] providing great introductions to the overall characteristics needed in sustainable chemical processes, including earth abundant and safe reagents and waste streams, minimized energetic inputs, and improved atom and step economy [3] of syntheses.

The original "green" chemist, nature has devised a dizzying array of enzymatic transformations that already embody these sustainably-minded synthetic approaches. An example of this unparalleled craft is found in photosynthesis, where water and carbon dioxide are converted to carbohydrates and dioxygen gas with solar irradiation as the sole energetic input [4]. While the net reaction is awe-inspiring, each one of the component steps is capable of teaching chemists a dizzying amount. A particular standout in this regard is photosystem II (PSII), a photoactive enzyme that not only passes electrons through the light-escalated *Z*-scheme [5] of photosynthesis but, also, contains the oxygen evolving complex (OEC), the site of one of the most startling reactions in nature: the oxidation of water to form dioxygen gas [6, 7].

How is something so endergonic as water oxidation performed at ambient temperature using only earth abundant elements? Careful study of the OEC has revealed several clever tricks that evolution has leveraged in this process (Fig. 1) [6, 8]. First, this four electron oxidation is divided over many atoms, delocalizing this accumulation of charge over four redox active manganese sites, avoiding the energetic penalty of quadruply-

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**Article note:** A collection of peer-reviewed articles by the winners of the 2019 IUPAC-Zhejiang NHU International Award for Advancements in Green Chemistry.

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oxidizing a single atomic site. Second, these electrons are not removed all at once: oxidation is performed one electron at a time via the so-called Kok cycle [9], progressing from the fully reduced $S_0$ state to the fully oxidized $S_4$ state which spontaneously evolves $O_2$ in the presence of water. This stepwise oxidation of the OEC allows for the generation of the highly-reactive and fully-oxidized $S_4$ state to be delayed until the final electron transfer, with the first three electron removals proceeding via less-reactive, metastable states. Finally, the highly-endergonic single-electron oxidations of the Kok cycle are made tenable via photoinduced electron transfer, where the vast and sustainable energy of solar irradiation permits single-electron charge separation that would be nigh-impossible otherwise. These three innovations in concert help permit the oxidation of one of the most electronegative elements to occur sustainably and at enormous scale and in collaboration with the many other enzymes of photosynthesis [4], providing invaluable lessons for synthetic chemists.

Recently, chemists have begun to capture some of these same design principles in the development of molecular catalysts. A shining example of this approach is shown in tetra-n-butylammonium decatungstate (TBADT, Fig. 2), an earth-abundant element polyoxometalate readily synthesized from commodity chemical precursors [10]. A first feature of this polyoxoanion is its ability to delocalize charge over the large $W_{10}O_{32}$ framework, an ability reflected by the deep-blue coloration of its reduced states (an appearance akin to that of solvated electrons) [11, 12]. Second, this species can reversibly cycle between three redox states, $W_{10}O_{32}^{4-}$, the singly-reduced $W_{10}O_{32}^{5-}$, and the doubly-reduced $W_{10}O_{32}^{6-}$, providing a means of stepwise oxidation/reduction as strategically employed by the OEC in PSII. Finally, upon near UV (323 nm) irradiation, this compound accesses an excited state, *wO*, akin to the triplet state of aryl ketones capable of both electron transfer and hydrogen atom transfer (HAT) [11, 13]. This suite of properties has allowed for many inspiring reactions to be realized [14, 15], from C–H alkylation [16–19], hydrazination [20], and fluorination [21] to recent examples of arylation [22] and trifluoromethylation [23]. HAT is also a key elementary step in many enzymatic processes [24–26], leading us to wonder if we might leverage this photo-HAT reactivity to mimic some of nature's most impressive chemical feats.

## Dehydrogenation via cooperative catalysis

The catalytic desaturation of alkyl functional groups is an essential reaction in many living systems, including our own [27, 28]. Performed by *desaturase* enzymes, the removal of vicinal hydrogen atoms from alkyl

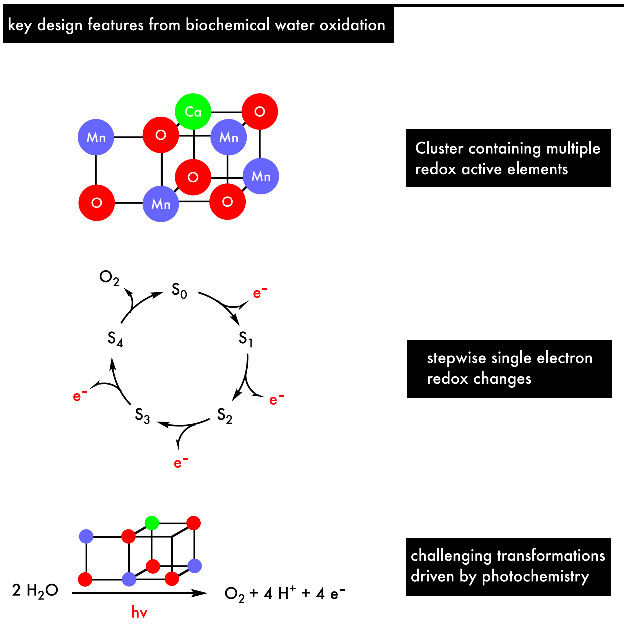
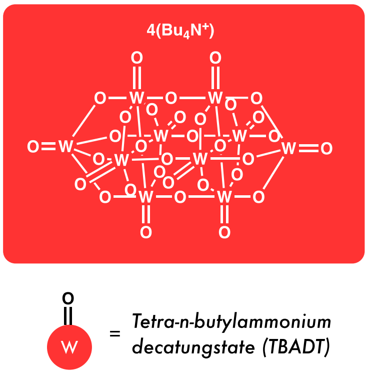


**Fig. 1:** Photosystem II has many key design features for achieving sustainable catalytic approaches to difficult chemical transformations.



KEY DESIGN ASPECTS

- cluster of redox-active elements
- capable of reversible single electron transfers
- performs difficult chemical reactions (hydrogen atom abstraction) photochemically

**Fig. 2:** Tetra-*n*-butyldecatungstate (TBADT) is a molecular photocatalyst that leverages several of the key characteristics of PSII, making it a prime candidate for the design of sustainable catalytic reactions.

fragments is thought to be achieved via stepwise hydrogen atom transfer to a high-valent non-heme iron oxo active site, resulting in twofold reduction of the cofactor (Fig. 3) [29–31]. This reaction proceeds readily at physiological temperature using earth abundant elements; however, it requires a stoichiometric oxidant to turn over.

The power of this stepwise, radical approach whereby each hydrogen atom is transferred in turn was noted by Breslow and coworkers, who sought to replicate it using photoexcited aryl ketones as the stoichiometric hydrogen acceptor (Fig. 3) [32–34]. While successful in the desaturation of various alkyl fragments at ambient temperatures, including an inspiring example of site-selective desaturation of a steroidal scaffold using a tethered benzophenone subunit, this chemistry is firmly stoichiometric in arylketone, making catalytic reaction non-obvious to achieve [33].

Noting the advantages of the Breslow system, ambient temperature and non-enzymatic operation, the early part of my graduate career asked a simple question: might we make this chemistry catalytic by employing more lessons from nature? TBADT appeared to be an ideal candidate for performing the initial HAT needed for desaturation for the reasons mentioned above: it is able to generate a delocalized, reduced state that can perform single electron reductions following the initial photo-HAT reaction [10, 11, 15]. These bio-inspired properties give the possibility of combining TBADT with a cocatalyst to achieve the net desaturation of simple alkanes and, if judiciously designed, potentially even eliminate the need for stoichiometric hydrogen atom acceptors as required in desaturase enzymes.

If TBADT could perform the initial photo-HAT reaction to generate the alkyl radical intermediate needed for desaturase reactivity, what might accept the second hydrogen atom to form the desired alkene? A potential answer for this question came from the catalytic chain transfer (CCT) polymerization literature pioneered by Dupont Central Research [35], where it was found that cobaloximes, vitamin $B_{12}$ mimic compounds [36], are able to reversibly accept hydrogen atoms adjacent to some carbon-centered radicals at rapid (essentially diffusion-controlled) rates. Subsequent research by Drennan and coworkers revealed that nature had beaten chemists to the punch, with the mechanism of the light-sensing enzyme CarH featuring a key HAT step to a $VB_{12}$ cobalt center from an organic free radical [37, 38], a mechanism likely arising well before humans studied chemistry. This HAT reactivity is incredibly powerful for chemical reaction design [39–41], with many examples beyond simple desaturation (*vide infra*). Thus, it might be possible for the first hydrogen atom to be transferred to photoexcited TBADT while the second is abstracted by cobaloxime.

However, a truly anthropogenic function of $VB_{12}$-like compounds comes in the field of solar fuels, where cobaloximes have been shown to be exceptional electrocatalysts for the hydrogen evolution reaction [42–44]. Indeed, starting from the foundational work of Espenson [45–47], chemists including Gray [48, 49], Peters [50–52], Eisenberg [53], Fontecave and Artero [44, 54] have demonstrated these complexes to be highly effective for electrochemical proton reduction and several of the same intermediates have been implicated as in CCT chemistry [41, 48, 55]. This opened the possibility of the desaturation reaction being turned over by a terminal hydrogen evolution reaction, allowing for stoichiometric hydrogen atom acceptor to be eliminated from our process.

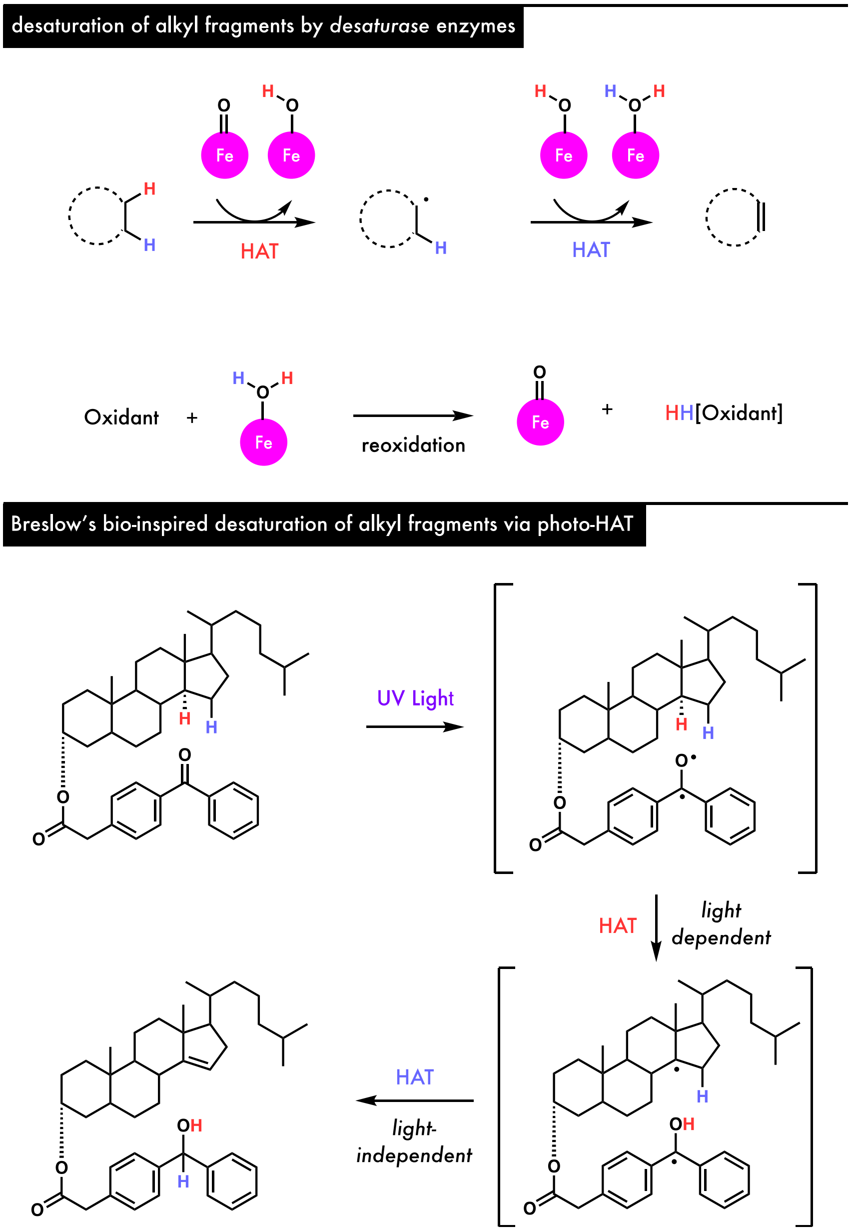


**Fig. 3:** *Desaturase* enzymes install alkene functional groups via stepwise HAT to a high-valent iron oxo cofactor, a mechanism emulated by Breslow's stoichiometric desaturation with arylketones.

Taking these two reactivities of cobaloximes together and combining them with the ability of TBADT to function as both a photo-HAT catalyst and single electron reductant, we wondered whether these two catalysts might function cooperatively to provide a completely catalytic version of Breslow's artificial desaturase system. Gratifyingly, we found this system to work, allowing us to desaturate alkanes and secondary alcohols with hydrogen gas as the sole byproduct (Fig. 4) [56, 57].

Inspired by the enzymatic oxidative demethylation of steroids performed by CYP 51 enzymes, we wondered whether we might be able to effect a similar transformation using our cooperative catalytic system. Indeed, this oxidative dehydroxymethylation is understood to proceed via initial oxidation of the hydroxymethyl alcohol to the aldehyde state followed by oxidative C–C bond cleavage (Fig. 5) [58, 59].

By contrast, we imagined that this initial 'oxidation' could be replaced with a dehydrogenation reaction [57] to generate the aldehyde and an equivalent of hydrogen gas (Fig. 5). This aldehyde C–H bond could then be activated via HAT to the *wO* state, a known reactivity of this species [16], to deliver the reduced $W^R$ state and an

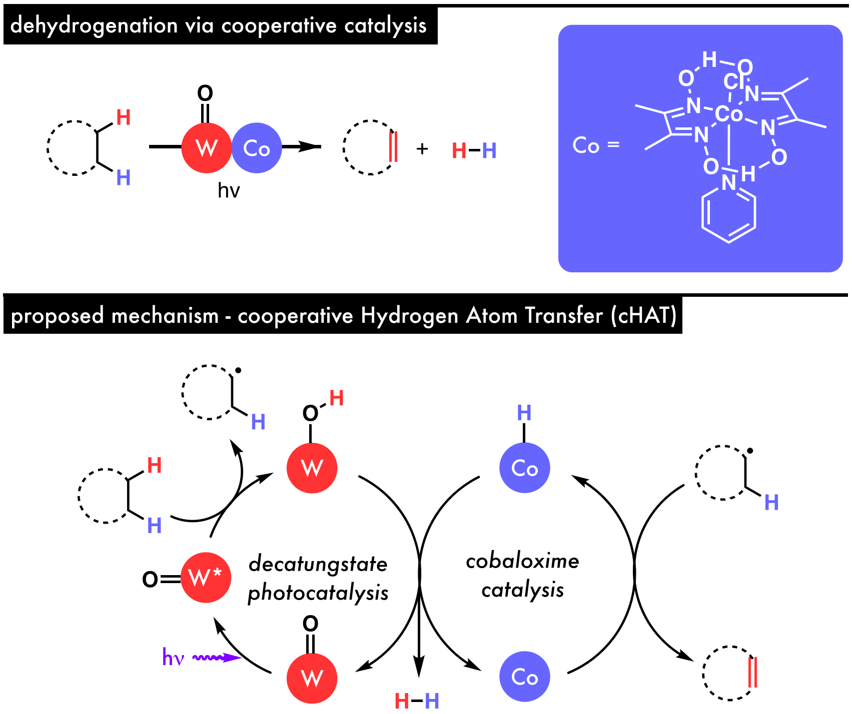


**Fig. 4:** Photodehydrogenation of small molecules via cooperative TBADT/cobaloxime catalysis. This process pursues a stepwise HAT mechanism in analogy to *desaturase* enzymes.

acyl radical. Following radical decarbonylation [60], the resultant alkyl radical could then be intercepted by the cobaloxime cocatalyst to generate an alkene product and, in combination with the $W^R$ equivalent, a second molecule of hydrogen gas, simultaneously closing the cycles of both catalysts as well. This acceptorless dehydroxymethylation would require no stoichiometric reagents, generating hydrogen gas and carbon monoxide as the sole byproducts.

To our delight, when we subjected a primary alcohol to modified dehydrogenation conditions we produced the desired alkene product [61]. GC/TCD analysis of the headspace confirmed the presence of dihydrogen and carbon monoxide, strongly supporting our proposed mechanism. We were also able to react compounds already in the aldehyde oxidation state, performing the net reverse [62, 63] of the industrially-essential hydroformylation reaction [64], producing alkenes, hydrogen, and carbon monoxide in a 1:1:1 stoichiometry. This reactivity demonstrates the generality of this cooperative hydrogen atom transfer reactivity manifold, an approach that is already being extended by others in the community [65].

## On beyond actinium – exploring the photocatalytic capability of uranium

While enabling, the use of TBADT comes with several challenges. First amongst these is the need for UV-light irradiation, a high-energy source of radiation that can lead to side reactions of common organic unsaturated functional groups and is an exposure risk to researchers, at least at high intensities. Second is the lack of fine tunability of the decatungstate framework, which is self-assembled in a pH-dependent fashion from sodium tungstate. While several other polyoxotungstates [12, 66] are known, including Keggin-type phosphotungstate and silicotungstate, these compounds exhibit dramatically different reactivity and/or redox stability compared to decatungstate. Finally, and most importantly, the limited solubility of decatungstate restricts choice of both the solvent and counteraction, necessitating both polar solvents (e.g. acetonitrile, acetone) and relatively non-polar organic countercations (e.g. tetra-n-butylammonium) to achieve homogeneous reaction with organic molecules (especially nonpolar molecules, such as alkanes) and soluble cocatalysts (e.g.

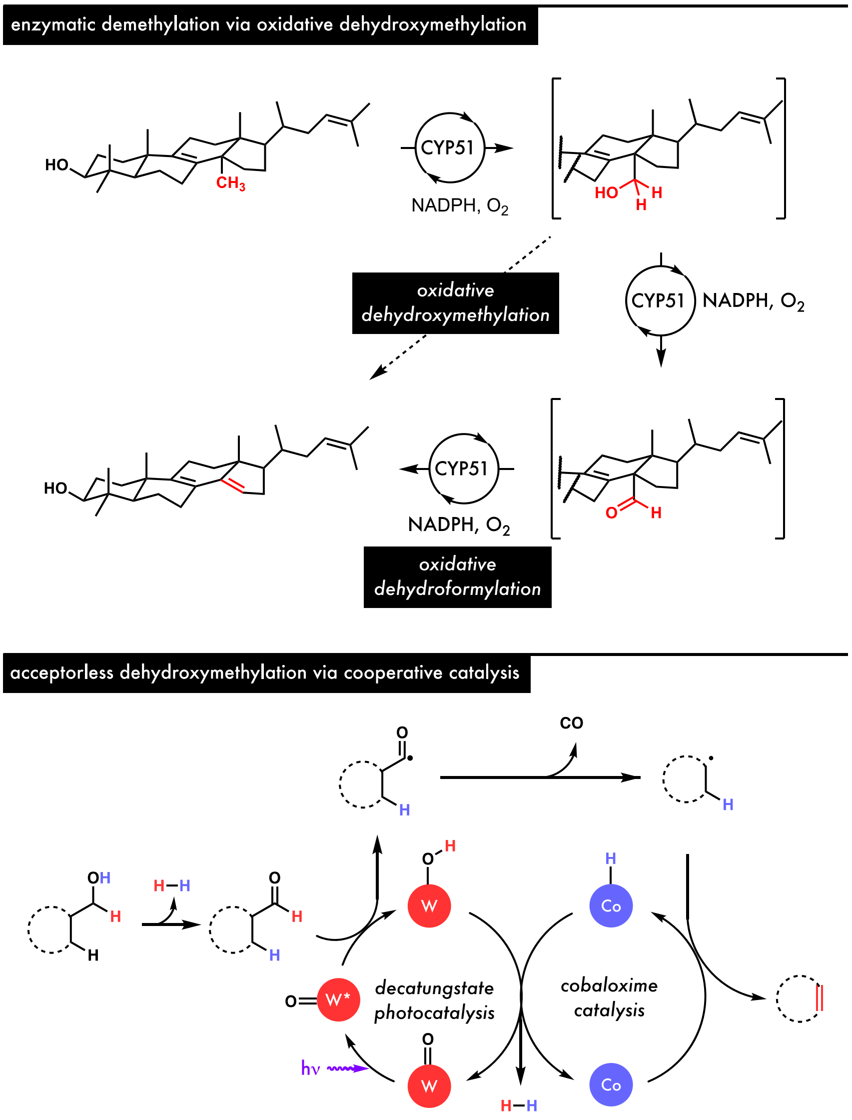
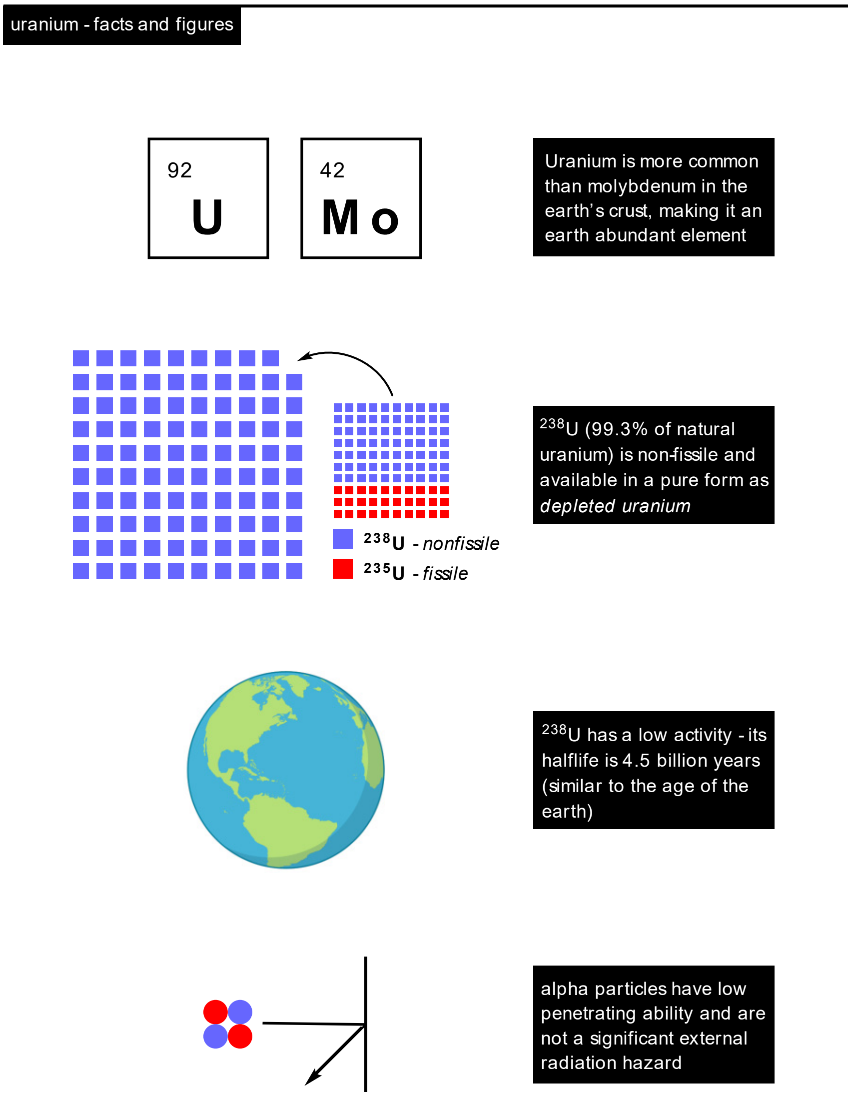


**Fig. 5:** The dehydroxymethylation reactivity of CYP51 can be recapitulated in an acceptorless sense using TBADT/cobaloxime cocatalysis.

cobaloxime). These organic counteractions have long been known to be a liability in TBADT photoreaction, with their competitive destruction via photo-HAT leading to the production of 1-butene, tributylammonium cation, and, as a result of counteraction degradation, insoluble polyoxometalate [67, 68]. This decomposition reaction occurs extensively over the long reaction times of both the dehydrogenation [57] and the dehydroxymethylation/dehydroformylation reactions [61], leading to slowing and ultimate arrest of the reaction.

Toward avoiding these issues, turned back to the periodic table to see if another element might provide solutions to these significant problems. To our collective surprise, an early candidate came in the form of element 92, uranium (Fig. 6). Not only is this element earth abundant (moreso than molybdenum in the earth's crust) [69], but its trans bis-oxo dication, uranyl, exhibits fascinating photophysical properties [70, 71]. Most relevantly, upon blue light irradiation, the uranyl fragment undergoes a transition to generate an incredibly oxidizing (+2.6 V vs NHE) [71] excited state capable of hydrogen atom transfer. This reactivity is characteristic to this molecular triad, again demonstrating the power of involving multiple earth-abundant elements in photocatalytic assemblies. Additionally, solubility of solely inorganic salts of uranyl (e.g. uranyl nitrate, $UO_2(NO_3)_2$) in organic solvents [72] suggested that we might be able to avoid counterion destruction via C–H



Uranium is more common than molybdenum in the earth's crust, making it an earth abundant element

$^{238}$U (99.3% of natural uranium) is non-fissile and available in a pure form as *depleted uranium*

$^{238}$U has a low activity - its halflife is 4.5 billion years (similar to the age of the earth)

alpha particles have low penetrating ability and are not a significant external radiation hazard

**Fig. 6:** Uranium is a surprisingly abundant and safe element to work with as a synthetic chemist.

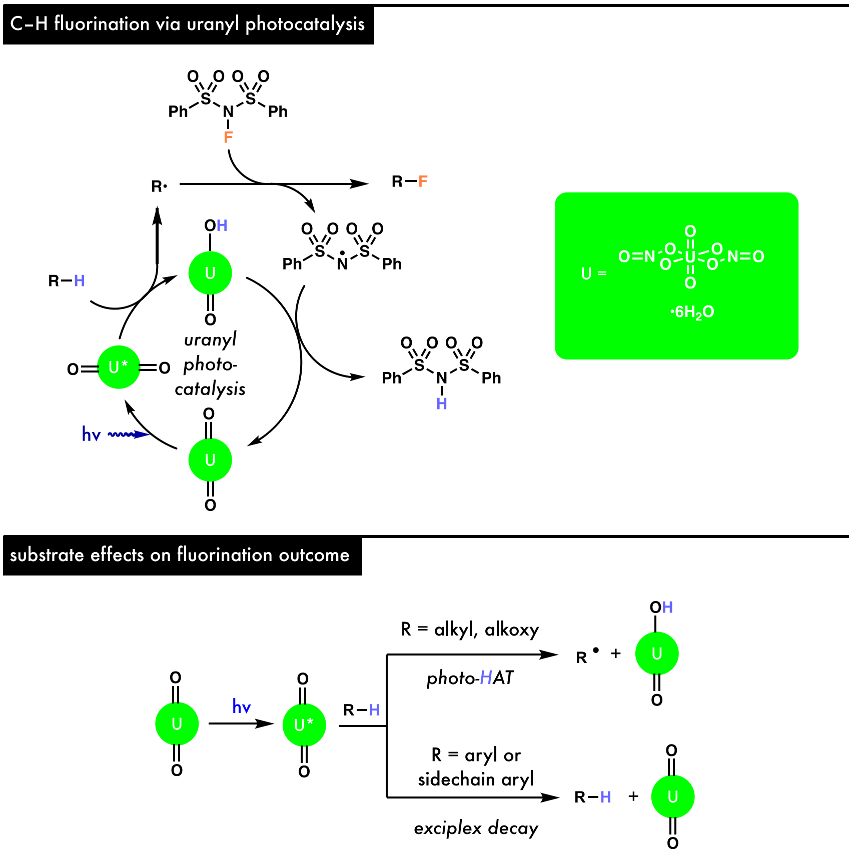
activation as observed in TBADT reactions [67]. Aside from the question of radioactivity, uranyl suddenly became a frontrunner in our search for alternative photo-HAT catalysts.

Our concerns about safety working with an element of such notoriety were allayed upon further reading. First, we learned that it was possible to work with ‘depleted’ uranium. While natural uranium comes as a mixture of two radioactive isotopes, 235U and 238U, only 235U is fissile, meaning that it can undergo the nuclear chain reaction required for power and munitions applications (and responsible for criticality accidents) [73]. Further, 235U makes up only 0.7% of raw ore, with the vast majority (99.3%) being the non-fissile 238U. Finally, through the modern uranium enrichment process, it is able to essentially quantitatively remove 235U from 238U, giving a pure, ‘depleted’ 238U material that is unable to undergo the nuclear chain reaction [74]. Additionally, while 238U is still radioactive, it is an alpha emitter with a long (~4.5 billion years) half-life [69], meaning that its decay particles have low penetrance and are released with very low activity [75]. Thus, the radiation risk of depleted uranium is low and does not require arduous precautions to work with in the laboratory, making it an acceptable candidate for a synthetic chemistry catalyst (Fig. 6) [75].

Indeed, the uranyl cation had previously been demonstrated as an earth-abundant element photocatalyst in the pioneering work of Bakac and coworkers, who showed that aqueous uranyl salts could promote the aerobic oxygenation of hydrocarbons via a photo-HAT mechanism under solar irradiation [76, 77]. Toward addressing the liabilities of TBADT, we became curious whether this photo-HAT reactivity could be general, enabling bond formations other than C–O after C–H bond activation. We quickly settled on C–H fluorination as an attractive proving ground for uranyl photocatalysis. Not only is the transformation useful and desirable, with C–F bonds being key motifs in pharmaceuticals [78–80], agrochemicals [81–83], and advanced materials [84–86], but a powerful [21] and industrially-relevant [87] method using TBADT had already been reported, providing a ready means of comparison and benchmarking of our uranyl catalyst.

Our studies in the lab quickly delivered a working C–H fluorination reaction, with preliminary optimization revealing that just 1 mol% of uranyl allows for production of fluoroalkanes in up to quantitative yield using N-fluorobenzenesulfonimide as the fluorine source and blue light irradiation (Fig. 7) [88]. Interestingly, arenes are uncooperative substrates in this reaction, largely returning unreacted starting material. This is illustrated particularly clearly in a competition experiment between equimolar cyclooctane and toluene, where one would expect toluene ($BDE_{C-H}$ = 88 kcal·mol$^{-1}$) to be fluorinated in strong preference to cyclooctane ($BDE_{C-H}$ = 96 kcal·mol$^{-1}$) under a traditional photo-HAT mechanism, where relative bond strength strongly influences reaction rate. However, under uranyl photocatalysis we observed that cyclooctyl fluoride is the major product, with essentially no benzyl fluoride produced. This unusual selectivity is thought to arise from the extremely oxidizing character of the uranyl excited state (+2.6 V vs NHE) [71], which permits an unproductive exciplex decay back to unreacted ground state molecules in the presence of aromatic substrates [77], a deactivation mode that is not available when encountering alkane substrates (Fig. 7). Similarly, coordination of carbonyls to the uranyl cation allows for excited state relaxation without HAT, potentially explaining the reduced reactivity of carbonyl-containing substrates. Both of these proposals have subsequently been supported by theoretical study [89].

While powerful for C–H oxygenation and fluorination, we were unable to extend the use of uranyl photocatalysis to the acceptorless dehydrogenation [57] and dehydroxymethylation/dehydroformylation [61] reactions above. Our working hypothesis is this incompatibility arises from the highly oxidizing nature of the uranyl excited state and relatively mild reducing potential of its reduced states, where there is not sufficient driving force for reduction of the cobalt cocatalyst required for hydrogen evolution. However, uranyl has


C–H fluorination via uranyl photocatalysis

substrate effects on fluorination outcome

**Fig. 7:** Uranyl nitrate functions as a photocatalyst for C–H fluorination of alkanes. However, this species is unable to efficiently engage arenes or carbonyl-containing compounds in fluorination reactions due to competitive deactivation processes.

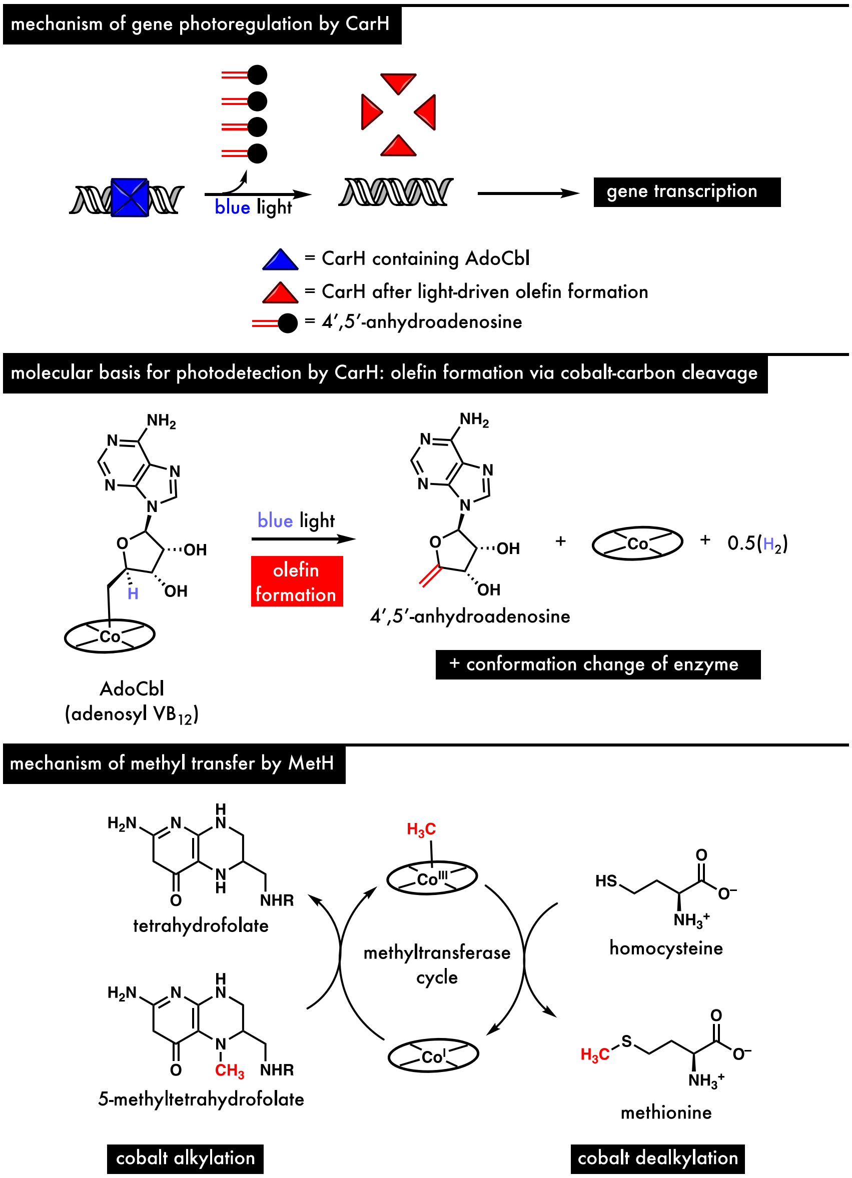


**Fig. 8:** CarH and MetH demonstrate two powerful reactivity modes for vitamin $B_{12}$.

recently been applied for C–H alkylation via a photo-HAT/Giese addition sequence with acrylates, demonstrating that C–C bond formation can be achieved [90]. Thus, while powerful for oxidative reactions, the uranyl cation appears to be a poor candidate for reductive photocatalysis.

## Future opportunities in earth abundant element photocatalysis

Beyond the work recognized by the 2019 IUPAC-Zhejiang NHU Award for Advancements in Green Chemistry, we continue to draw inspiration from nature in the design of sustainable catalytic reactions. A recent example of this continuing mission is found in our development of a mild elimination of alkyl electrophiles to site-selectively form alkenes. This reaction builds upon the photo-HAT reactivity of CarH [37, 38], a fascinating enzyme from *Thermus thermophilus* that uses a $VB_{12}$ cofactor to detect light.

In its pre-irradiated form, CarH exists as a tetramer binding the promoter region of light-activated genes (Fig. 8). Within each copy of this enzyme is an adenosyl cobalamin (AdoCbl) cofactor, containing an apical, organometallic Co–C bond [37, 38]. Upon incident light, this bond is cleaved, leading to transient generation of an adenosyl radical and a Co(II) center (Fig. 8). While the generation of this highly-reactive carbon-centered radical might be expected to promote indiscriminate reactions, nature has found a clever solution to defuse this intermediate: the labilized hydrogen adjacent to the alkyl radical of the adenosyl fragment is rapidly transferred to the Co(II) center to produce an innocuous alkene and a Co(III)–H. This process, analogous to the CCT process catalyzed by synthetic cobalt complexes [35], occurs rapidly under neutral conditions with visible light as the sole energetic input. Additionally, it is relevant to note that this sequence adheres to the design goals discussed in our introduction – a large molecular array ($VB_{12}$) undergoes single electron processes via photoexcitation, again showing the central importance of these considerations in sustainable chemistry.

The nonbasic nature of this biochemical akene formation stood out to our group in comparison to base-mediated elimination (e.g. $E_2$) and traditional olefination reactions (e.g. Wittig), where strong base is required, presenting chemoselectivity [91] and regioselectivity [92, 93] concerns for complex molecules. However, if we were to make use of this homolysis/alkene formation sequence as a synthetic alkene formation, we realized that an efficient means of forming the prerequisite Co–C bond would be needed. Luckily, nature again provides a solution to this puzzle: *methionine synthase* (MetH, Fig. 8) [94], another vitamin $B_{12}$-dependent enzyme. that has been demonstrated to function via two successive nucleophilic substitution reactions, first of Co(I) on the methyl electrophile 5-methyltetrahydrofolate (5-THF) and second of the homocysteine nucleophile attacking the methylcobalamin intermediate to generate methionine and eject a Co(I) leaving group [94–96]. Study of

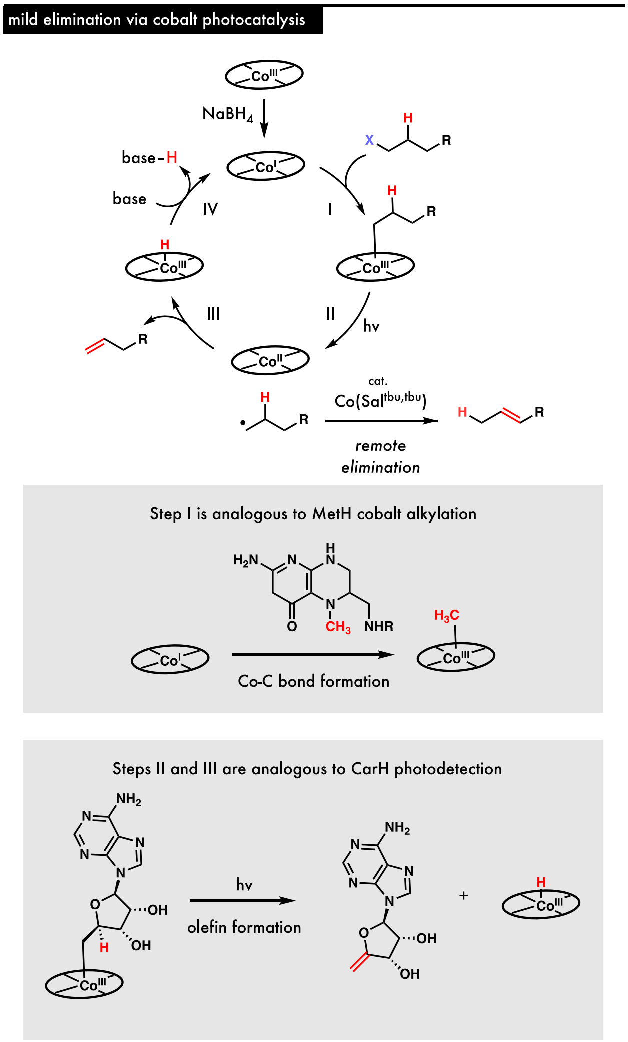


**Fig. 9:** $VB_{12}$ can selectively eliminate alkyl electrophiles to terminal alkenes via visible light photocatalysis using aspects of the mechanisms of both CarH and *methyltransferase*. This reactivity can be combined with the selective olefin isomerization catalyst Co(Salen) to form subterminal alkenes in a single reaction flask.

this Co(I) intermediate has revealed it to be “supernucleophilic” [97], allowing for a wide variety of alkyl electrophiles to be engaged in substitution reactivity, providing access to many different organometallic Co(III) species.

Taking these two ideas together, we envisioned a catalytic means of synthesizing alkenes via $VB_{12}$ photocatalysis (Fig. 9). Starting from a Co(I) supernucleophile (generated via borohydride reduction of an oxidized precursor) [97, 98], an alkyl electrophile substrate can be engaged in a substitution reaction to form a Co(III) organometallic intermediate in analogy to MetH. At this point, instead of participating in a second substitution reaction, we proposed to irradiate this intermediate with visible light, leading to Co–C bond homolysis/HAT as seen in CarH, generating our desired alkene product and a Co(III) hydride species. This cobalt hydride is highly acidic and can then be deprotonated via a mild base, regenerating the Co(I) supernucleophile and closing the catalytic cycle.

Putting this idea into practice, we were excited to find that we are able to form alkenes from alkyl halides and sulfonates using cyanocobalamin as a photocatalyst, blue LEDs as a light source, sodium borohydride as a reductant, and sodium bicarbonate as a terminal proton acceptor (Fig. 9) [99]. This transformation proceeds readily at room temperature and all of these components are needed for successful reaction. Additionally, we found that this alkene formation can be combined with a cobalt salen isomerization catalyst [100] to selectively form subterminal alkyl from terminal alkyl electrophiles, performing a “remote elimination” reaction presumably through a tandem alkene formation/isomerization sequence. These reactions mark the beginning of an exciting new direction in our pursuit of sustainable chemical reactions and efforts to expand tandem alkene formation/functionalization reactivity are ongoing in our laboratory.

## Conclusions

Together, we show how lessons from nature, including the photoactivity of PSII, can inspire the design of sustainable photocatalytic reactions for chemical synthesis. These lessons have been combined with those from other enzymatic systems, including *desaturase,* MetH, and CarH, to deliver bio-inspired catalytic systems to achieve acceptorless dehydrogenation, dehydroxymethylation, and dehydroformylation of small molecules; C–H fluorination of alkanes; and mild elimination of alkyl electrophiles to form terminal or subterminal alkenes. The richness of biochemical processes provides endless inspiration for synthetic chemists and we are excited to see what future sustainable and bio-inspired reactions will be developed.

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