How to cite: *Angew. Chem. Int. Ed.* **2024**, *63*, e202405775
doi.org/10.1002/anie.202405775

Photoredox Catalysis

Biomimetic Photoexcited Cobaloxime Catalysis in Organic Synthesis

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Angewandte International Edition Chemie

Abstract: Drawing inspiration from nature has long been a cornerstone of chemical innovation, with natural systems offering a wealth of untapped potential for discovery. In this minireview, we delve into the burgeoning field of cobaloxime catalysis in organic synthesis, which mimics the catalytic activity of the natural organometallic alkylcobalamine enzymes. Our focus lies on elucidating the latest advancements in this area, as well as delineating the primary mechanistic pathways at play. By describing, and comparing these mechanisms, we provide a comprehensive overview of the current state-of-the-art, while also shedding light on the key unresolved challenges that await further exploration.

1. Introduction

Biomimetic catalysis, which emulates the highly efficient biological transformations, offers a potent approach for the deliberate design of artificial small molecule catalysts.[1] Methylcobalamin (MeCbl or MeB_{12}) and Adenosylcobalamin (AdoCbl), two forms of Vitamin B_{12}, serve as rare examples of natural organometallic compounds that contains metal-alkyl bonds (Scheme 1).[2] The formation and cleavage of the Co–C bond within these molecules is pivotal in their enzymatic functions.[3] For example, methylcobalamin acts as a reversible free radical carrier that effectively stabilizes highly reactive methyl radicals via the formation of weak carbon–cobalt bonds.[4] These weak Co–C bond (bond dissociation energy (BDE) ≈ 14–42 kcal/mol) can undergo facile cleavage via thermolysis or photolysis.[5]

Simple cobaloxime complexes have been initially synthesized to mimic the structure of natural alkylcobalamines and to study the mechanism of its enzymatic function.[6] These octahedral cobalt(III) complexes are featuring dioximate ligands interconnected via hydrogen bonding or BF_2 bridges. Typically, the two axial ligands are nitrogen-containing ligands like pyridine and halogens (Scheme 1). Cobaloximes are well-known as proton reduction catalysis for water splitting processes.[7] However, the extensive use of these complexes in organic synthesis has only gained attention recently. Several excellent reviews have already sparked excitement; however, they predominantly concentrate on the merger of photoredox and cobalt catalysis, rather than delving deeply into the concepts of cobaloxime catalysis.[8] This minireview comprehensively summarizes, critically discusses, and reclassifies the chemistry of cobaloxime catalysis in organic synthesis.

The seminal stoichiometric reactivity of cobaloxime in organic synthesis was reported in the 1980s by the groups of Tada, Pattenden, Branchaud, and Giese.[9] Additionally, several groups have reported the catalytic turnover of cobaloxime under reductive conditions, such as electrochemistry or stoichiometric amounts of reductants like Zn, sodium borohydride, or Grignard reagents.[10] An important milestone in the cobaloxime catalysis is from the group of Carriera in 2011. The authors have outlined the possibility of cobaloxime turnover using simple organic base base.[11] Another milestone is the merger of cobaloxime catalysis with photoredox catalysis in 2015.[12] To aid comprehension for readers unacquainted with this chemistry, we furnished a concise summary in this section elucidating the principal catalytic concepts of cobaloxime complexes.

The catalytic activity of cobaloxime catalysis can be categorized into two general types: inner-sphere and outer-sphere reactivities, which may occur in either the excited or ground state (Scheme 1). Inner-sphere reactivity or ligand-to-metal charge transfer (LMCT)[13] involves the direct association of the catalyst and the reactant, resembling enzymatic processes closely. In this scenario, [Co^{III}]-alkyl complexes can be formed through S_N2-type reactions of highly nucleophilic [Co^{I}] species with alkyl electrophiles (polar path), or by capturing organic radicals with persistent [Co^{II}] radicals (radical path). The Co–C bond within this complex can be reversibly homolyzed into a radical pair under thermal conditions or irradiation. This radical pair could undergo radical-type β-hydrogen elimination, resulting in the formation of [Co^{III}]–H via hydrogen atom transfer (HAT) and an olefin or aromatic compound. Alternatively, the organic radical may escape from the radical pair and engage in free radical transformations, primarily radical addition to olefin or arene, leading to the formation of a new radical intermediate. This intermediate could then be trapped again by the metalloradical [Co^{II}] species, yielding [Co^{III}]–H and a new olefin or functionalized aromatic compound.

On the other hand, outer-sphere reactivity is also proposed in cobaloxime catalysis (Scheme 1). For instance, ground-state [Co^{II}] metalloradicals could induce outer-sphere single electron transfer (SET) oxidation of organic radicals, resulting in the formation of carbocations and [Co^{I}] species. These intermediates could further undergo a proton transfer (PT) process to produce [Co^{III}]–H and unsaturated compounds. Given the low reductive potential of [Co^{II}] species ($E_{p/2}(Co^{II}/Co^{I}) = -1.13$ V *vs* SCE), this approach is likely suitable for radical intermediates that can be readily oxidized, such as benzylic and dibenzylic radicals, to form stable carbocations ($E_{ox} < 0$ V vs SCE).[14] Another outer-sphere reactivity of cobalt complexes involves photoinduced SET (photoredox activity). In this respect, excited-state [Co^{III}] complexes function as photoredox catalyst for the

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oxidation of H-phosphines, leading to the formation of P-radical and [Co^{II}] species.

The turnover of [Co^{III}]–H can be facilitated by a one-step polar pathway through simple deprotonation with an organic base such as iPr_2NEt to produce the Co(I) species (Scheme 1). Alternatively, two-steps radical pathway can occur, [Co^{III}]–H can react with another proton to release H_2 and form [Co^{III}] species, a process that could be accelerated in the presence of proton shuttle such as pyridine or protic acid such as acetic acid. The [Co^{III}] species could also form upon the reaction of the [Co^{III}]–H with an imine salt intermediate. The electron-deficient [Co^{III}] species could be readily reduced to [Co^{II}] species directly by a substrate such as H-phosphine or by a co-catalyst ($E_{p/2}(Co^{III}/Co^{II}) = -0.68$ V *vs* SCE).

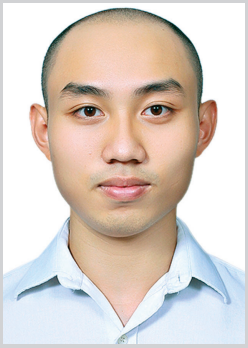
2. Alkyl Heck-Type Reaction

Palladium catalyzed Mizoroki-Heck reaction represents one of the most versatile synthetic methods to form C–C bonds. However, the reaction generally cannot be performed on alkyl halide substrates due to the slow oxidative addition and the facile competing β-hydrogen elimination.[15]

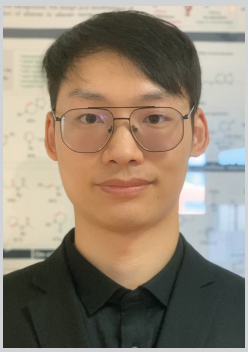
2.1. Polar Alkyl Heck-Type Reaction

In 2011, Carreira and co-workers reported the use of the simple **Co-1** complex together with under visible light conditions for the intramolecular *exo*-selective Heck reaction of primary alkyl iodides (Scheme 2).[11] The key to success is the formal reduction of [Co^{III}]–H to an anionic Co(I) species via deprotonation using a simple organic base (iPr_2NEt). The authors have proposed the formation of the alkylcobalt intermediates via nucleophilic substitution with the catalytically active Co(I) species. It is worth noting that, secondary alkyl iodide (only one example) remained unreactive under these conditions with **Co-1** catalyst but showed reactivity when using stannyl cobaloxime complex (**Co-2**). In 2023, El-Sepelgy group have outlined that the bifunctional Co–Sn complex (**Co-2**) operates via a different radical pathway, elucidating the disparate reactivity of **Co-1** and **Co-2** catalysts in the seminal work of Carreira.[16] Recently, El-Sepelgy and co-workers have reported intramolecular *endo*-selective Heck reaction of iodo- and bromomethylsilyl ethers of phenols and alkenols using the **Co-1** catalyst (Scheme 2).[17] The method could be used for the formal hydroxymethylation of allylic alcohols and *o*-hydroxystyrenes, eliminating the need for the use of palladium salts and expensive phosphine ligand.[18] In 2016, the Morandi group demonstrated the use of epoxides and aziridines as electrophiles and intramolecular coupling with alkenes catalyzed by **Co-1**.[19]

The cobalt-catalyzed polar alkyl Heck-type reaction starts with the visible light homolysis of the **Co-1** complex to produce [Co^{III}]–H and propene. After deprotonation with a base such as iPr_2NEt or methoxide, the super nucleophile [Co^{I}] species is in situ generated. A key mechanistic step involves the S_N2-type reaction between the [Co^{I}] species and the primary alkyl electrophiles (**2.1**) to give the corresponding alkyl-[Co^{III}] intermediate (**2.2**). This Co–C bond is cleaved under irradiation to produce [Co^{II}] species and an alkyl radical intermediate (**2.3**). DFT calculated location of a



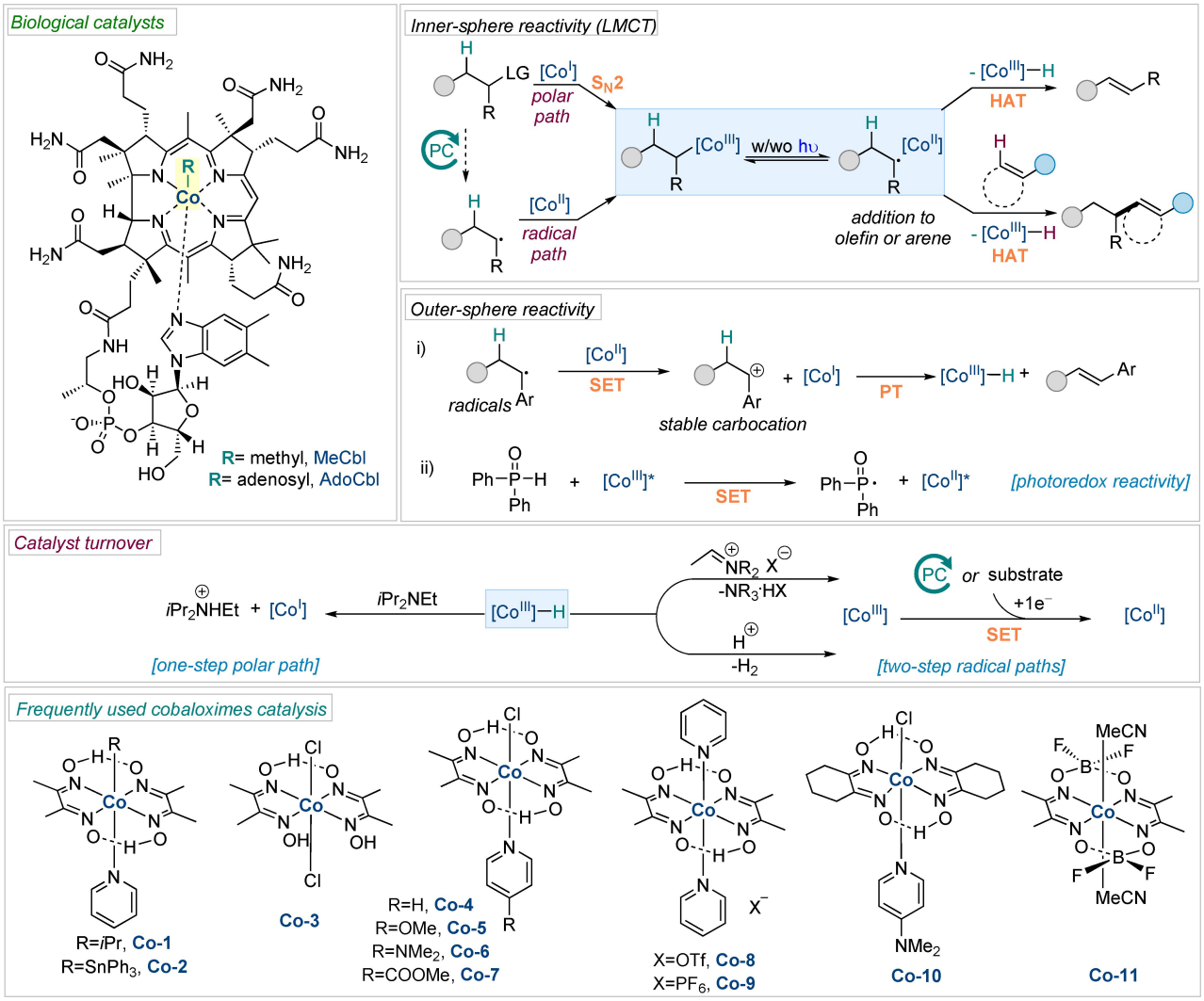
Phong Dam earned his B.Sc. from Hanoi University of Science and Technology (HUST). Afterwards, he pursued M.Sc. studies under the guidance of Prof. Thanh Huyen Pham at HUST, Hanoi, and Prof. Angelika Brückner at LIKAT Rostock. He is currently pursuing his doctoral studies in the group of Dr. Osama El-Sepelgy at LIKAT Rostock. His research interests revolve around photoexcited cobalt catalysis and operando spectroscopic mechanistic studies.



Kaiming Zuo was born in Sichuan, China. He studied chemical engeneering at Hainan University (master thesis in material science with Prof. Yanan Gao). Currently he is a Ph.D student at the Leibniz Institute for Catalysis (LIKAT Rostock) under the guidance of Dr. Osama El-Sepelgy. His research focouses on photoexcied base-metal catalyzed C-H functionalization transformations.

Luis Miguel Azofra received his M.Sc. and Ph.D. degrees from Universidad Autónoma de Madrid. Following this, he pursued postdoctoral studies at Monash University and King Abdullah University of Science and Technology. Later, he moved to Universidad de Las Palmas de Gran Canaria. Since 2023, he has served as a Ramón y Cajal research leader and lecturer at the same institution. His primary research focus revolves around utilizing quantum mechanics to model catalytic processes.

Osama El-Sepelgy completed his Ph.D. studies with Prof. Jacek Mlynarski at Jagiellonian University in Krakow and Prof. Christoph Schneider at the University of Leipzig in 2014. Then, he pursued two years of postdoctoral studies at RWTH Aachen University with Prof. Magnus Rueping. Subsequently, he led a sub-group at the same institution. In July 2021, Osama started his independent career at the Leibniz Institute of Catalysis (LIKAT Rostock). His group focuses on dicovery of new sustainable catalytic methods employing base metal catalysis and harnessing visible light.



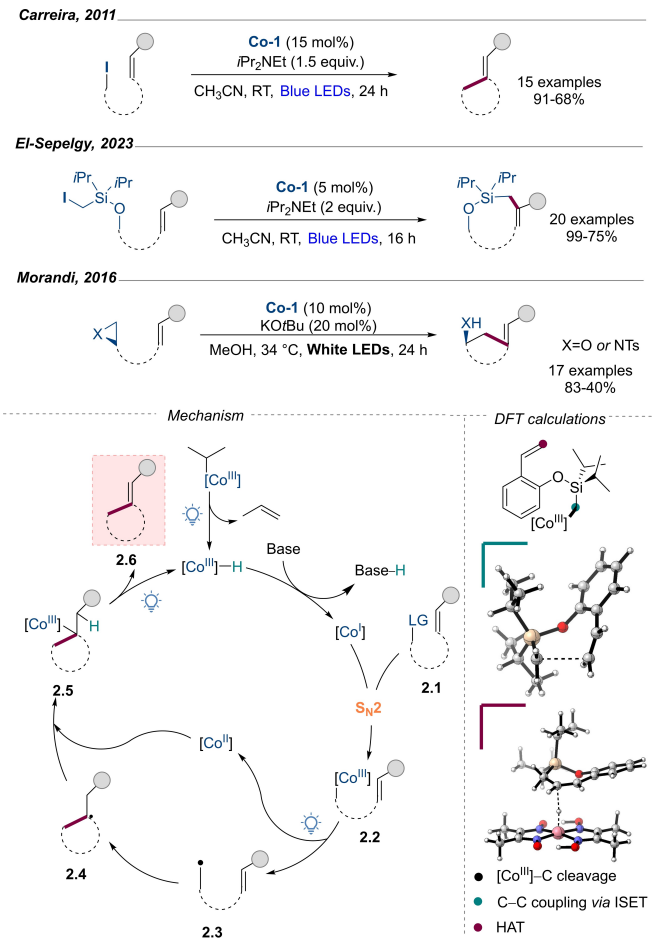
Scheme 1. Conceptualization of cobaloxime catalysis: from biological catalysis to small-molecule catalytic concepts.

transition state (TS) confirms the carbon–carbon coupling in the radical substrate via an intramolecular SET (Scheme 2, green). Intramolecular *endo*- or *exo*-radical addition furnishes a radical intermediate (**2.4**), which can recombine with [Co^{II}] to form another alkyl-[Co^{III}] intermediate (**2.5**). The cobalt species (**2.5**) under visible light irradiation results in the formation of the desired cyclic alkene (**2.6**) and a [Co^{III}]-hydride complex (Scheme 2, purple).

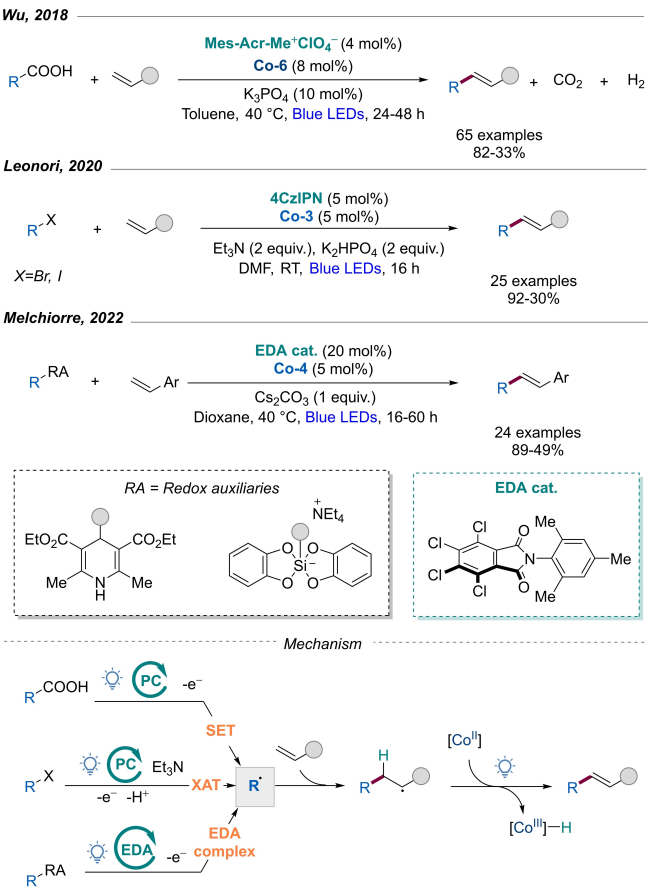
2.2. Radical Alkyl-Heck Reaction

The previously mentioned polar-based Heck reactions are mostly limited to intramolecular transformations of primary alkyl iodides. To overcome these limitations, efforts were directed towards the generation of alkyl radicals under visible light conditions using a co-catalyst followed by addition of the radicals to olefins, while a suitable cobaloxime enables the regeneration of the double bond and the formation of alkene products (Scheme 3). In this regards, Wu and co-workers have first reported decarboxylative alkyl Heck reaction using a dual photoredox/cobaloxime dual catalysis.[20] Carboxylic acids were used as precursors of a broad range of primary, secondary and tertiary alkyl radicals under oxidative photoredox conditions. Two years later, Leonori and co-workers disclosed alkyl Heck reaction of alkyl iodides and bromides.[21] The radical generation was enabled by halogen atom transfer (XAT) strategy. This XAT approach is proposed to be achieved via aminoalkyl radical reagent, which could be in situ generated using Et_3N and photocatalyst (4CzIPN). More recently, Melchiorre and co-workers outlined the merger of the alkyl radical generation using electron donating acceptor complex (EDA) photoactivation with cobalt catalyzed dehydrogenation.[22] The authors have used electron-rich radical precursors bearing redox auxiliaries such as 1,4-dihydropyridines, silicates and trifluoroborates together with tetrachlorophthalimides as EDA acceptor catalyst.

In all cases, the subsequent addition of the alkyl radical to olefin followed by the β-hydrogen eliminations using



Scheme 2. Cobaloxime catalysed polar alkyl-Heck reaction.



Scheme 3. Radical-type alkyl Heck reaction.

cobaloxime catalysis leads to the formation of the desired Heck product and [Co^{III}]–H intermediate. To enable the catalytic turnover, [Co^{III}]–H is initially converted to [Co^{III}] by reaction with another proton or iminium salt intermediate. Afterwards the electron poor [Co^{III}] undergoes SET reduction, leading to the regeneration of [Co^{II}] species and the photocatalyst or the EDA catalyst.

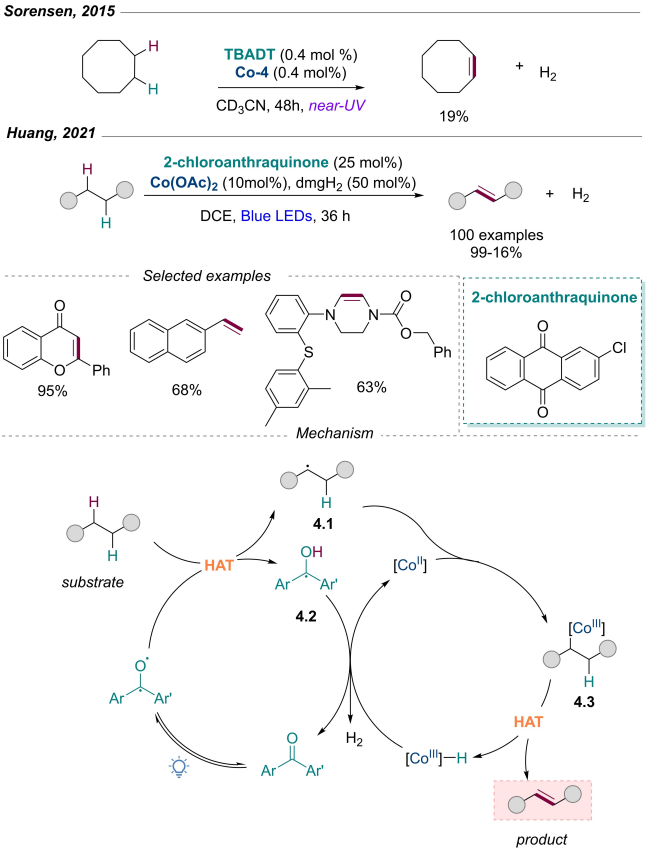
3. Desaturation of Aliphatic Compounds

The transformation of alkanes into alkenes stands as a fundamental pursuit in synthetic chemistry, offering pathways to valuable unsaturated compounds crucial in various industrial applications.[23] In this section, we summarize the recent achievements on the use of cobaloxime catalysis for the oxidant free desaturation of aliphatic compounds under visible light conditions at room temperature.

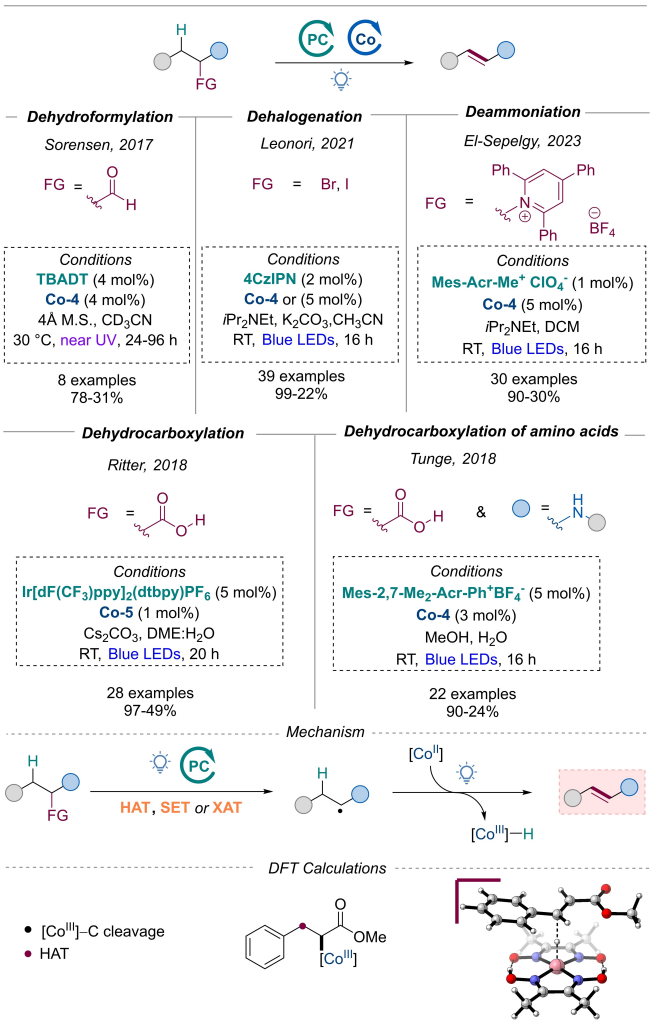
3.1. Nondirected Desaturation

In 2015, Sorensen and colleagues reported a pioneering example of radical and oxidant free desaturation of non-functionalized alkanes such as cyclooctane to the cyclooctene in low yield.[12b] This approach utilized tetrabutylammonium decatungstate catalyst (TBADT) as HAT catalyst for a hard hydrogen atom abstraction to generate a carbon-centered radical, followed by cobaloxime catalyzed desaturation under near UV light irradiation.[24] More recently, Huang and Xu further enhanced this nondirected desaturation of functionalized alkanes by using a dual 2-chloroanthraquinone photocatalyst and in situ generated cobaloxime catalysis (Scheme 4).[25]

The reaction selectivity is governed by the strength and electronic properties of sp^3 C–H bonds. For example, the catalytic system shows a very good reactivity and selectivity for the conversion of alkyl (hetero)arenes such as ethylbenzene to the corresponding styrenes. The detailed reaction mechanism is described in Scheme 4. The reaction was initiated though a HAT process with excited anthraquinone, resulting in ketyl radical (**4.2**) and alkyl radical (**4.1**). This intermediate (**4.1**) can be captured by [Co^{II}] to generate [Co^{III}]-alkyl species (**4.3**), which under irradiation leads to the formation of the desired olefin and [Co^{III}]–H species. The SET and PT from the ketyl radical (**4.2**) to [Co^{III}]–H result in the regeneration of the [Co^{II}] species and the HAT photocatalyst (Scheme 4).



Scheme 4. Synthesis of olefins via nondirected desaturation of alkanes.



Scheme 5. Dehydrofunctionalization enabled by photoredox/cobaloxime dual catalysis.

3.2. Dehydrofunctionalisation

Defunctionalization chemistry facilitates the transition from fossil-based to bio-based chemicals, promoting sustainability. By selectively removing functional groups and substituting them with alkenes, it streamlines the synthesis of bio-derived compounds from renewable feedstocks. This reduces reliance on finite fossil resources and minimizes environmental impact. Through tailored catalysts and reaction conditions, defunctionalization enables the conversion of biomass into value-added chemicals while adhering to green chemistry principles.[26]

In comparison with the non-directed desaturation, the use of functional group as a radical precursor enables excellent regioselectivity of the produced alkene. In this regard, Sorensen and co-workers have reported a mild method for the dehydroformylation of α-quaternary aliphatic aldehydes using a dual HAT and cobaloxime catalysis (Scheme 5).[27] The dehydroformylation cycle begins with HAT of the aldehyde hydrogen excited-state tungsten photocatalyst resulting in the formation of acyl radicals, which undergo decarbonylation to extrude CO and generate alkyl radicals. The radical intermediate undergoes cobaloxime desaturation to produce the corresponding olefin and [Co^{III}]–H. Next, the groups of Ritter and Tunge have independently developed the dehydrodecarboxlation of a wide range of carboxylic acids[28] and amino acids[14b] using a combined photoredox and cobaloxime system. The photocatalyst enables the oxidation of the carboxylic acid to its corresponding alkyl radical while the cobaloxime catalyst act as H-abstractor and *β*-hydrogen elimination agent. Shortly thereafter, Larionov showcased the viability of a similar cobaloxime/photoredox system for upgrading biomass-derived carboxylic acids.[29] Building on these findings, Summerlin and Seidel have recently established elegant methods for the degradation of carboxylate-containing polymers under visible light irradiation.[30]

In 2021, Leonori et al. reported a photochemical dehalogenative olefination of alkyl halides by using photoredox/cobaloxime system.[31] The radical generation from the alkyl halides is enable by XAT using α-amino radical that could be in situ generated using photocatalyst and simple organic base such as *i*Pr$_2$NEt. Notably, the authors have shown that the regioselectivity of products can be controlled by modulating suitable steric and electric properties of the cobalt catalysts. Very recently, El-Sepelgy et al. have developed a biomimetic method for the dehydroammoniation of primary amines.[32] Pyridinium salts were used as

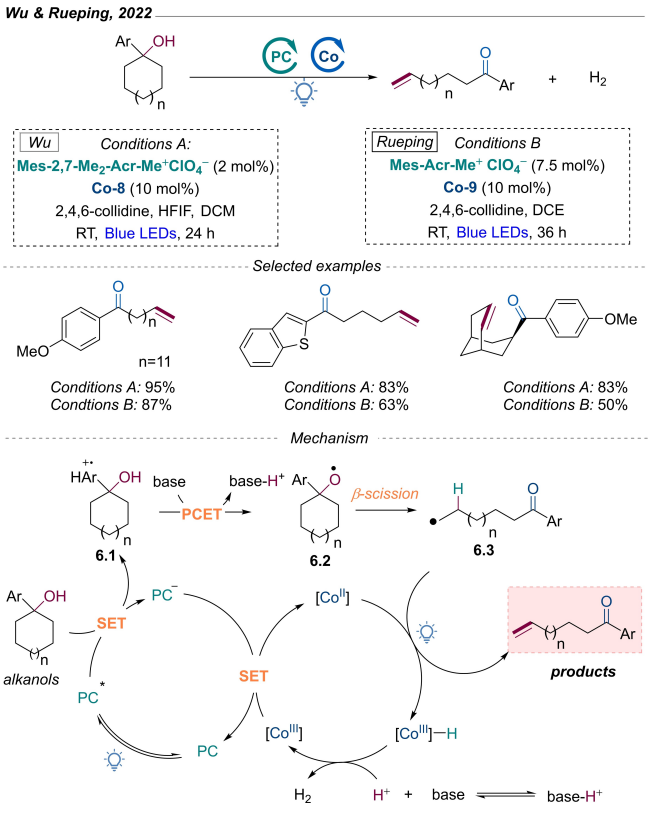
redox-active amines, together with acridinium photocatalyst and cobaloxime, providing the first mild alternative to the classical Hoffmann[33] and Cope elimination.[34] The methodology allows the dehydroamination of wide range of primary amines including amino acids, pharmaceuticals, and natural products. DFT calculations suggests that the homolysis of [Co^{III}]-alkyl bonds is taking place by the action of visible light in the excited (triplet) state. An example of transition state of β-hydrogen elimination is shown in the bottom of Scheme 5.

A related dehydrofunctionalization approach was also reported independently by Rueping and Wu.[35] Dual photoredox/cobaloxime catalytic system was used for the dehydrogenative conversion of electron-rich tertiary alcohols to form remotely dehydrogenated ketones (Scheme 6). The mechanism initiates with a SET from aryl substituents of alcohols to the excited state of the photoredox catalyst, generating cation radical species (**6.1**). These intermediates undergo intramolecular PCET in the presence of base to yield alkoxyl radical species (**6.2**), which can cleave into alkyl radicals and carbonyl moiety (**6.3**) via β-scission of the neighbouring C–C bond. The formed alkyl radical subsequently undergoes the desaturation process via cobaloxime catalysis, resulting in the formation of remotely dehydrogenated ketones.

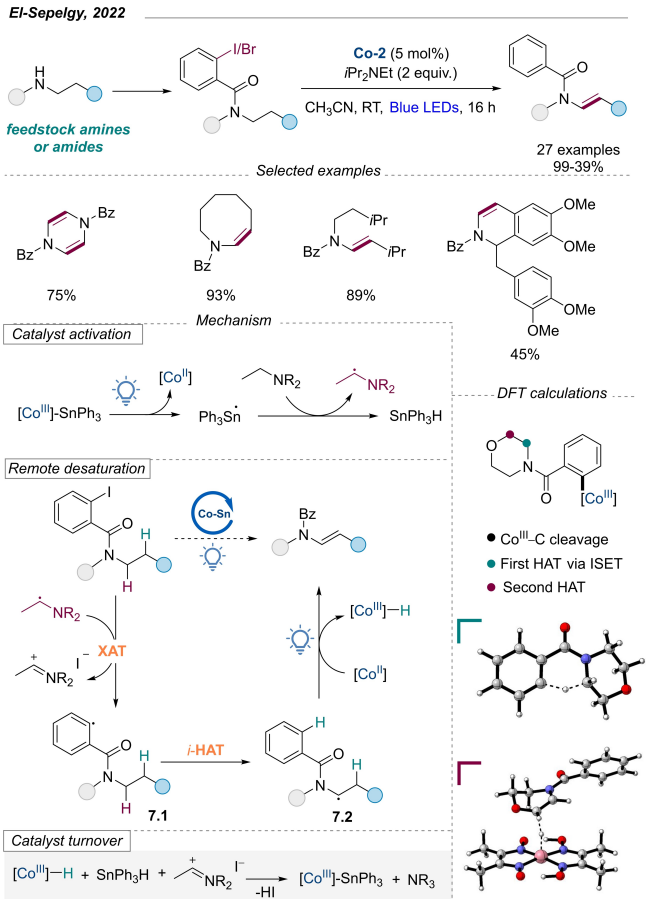
3.3. Remote Desaturation of Aliphatic Compounds

Motivated by the groundbreaking advancements in dehydrofunctionalization chemistry catalysed by dual photoredox/cobaloxime systems, the group of El-Sepelgy decided to integrate this approach with intramolecular hydrogen atom transfer to achieve remote C–H desaturation.[16] It's noteworthy that a similar strategy was concurrently reported by Xu's group.[36] To validate the concept, the authors focused on exploring the desaturation of aliphatic amines and amides tethered with *o*-iodo-benzoyl tethers.[37] Initial trials employing combined photoredox/cobaloxime catalysis failed to yield any desaturated products, primarily due to challenges in activating the aryl iodide.

Nevertheless, employing cobaloxime-triphenyltin complex (**Co-2**) enabled the efficient conversion of a broad scope of amides and imides into the corresponding enamides and enimides at room temperature without the need for additional photocatalyst. Drawing from both experimental observations and theoretical investigations, the authors proposed a mechanistic pathway illustrated in Scheme 7. Upon visible light irradiation, homolytic cleavage of Co–$SnPh_3$ complex generates a metalloradical Co(II) species alongside a triphenyltin radical. The latter is believed to promote the formation of an α-amino radical from iPr_2NEt, serving as an XAT reagent to abstract iodo or bromo atoms



Scheme 6. Synthesis of distally unsaturated ketones via dehydrogenated alcohols.



Scheme 7. Remote desaturation of aliphatic amines and amides.

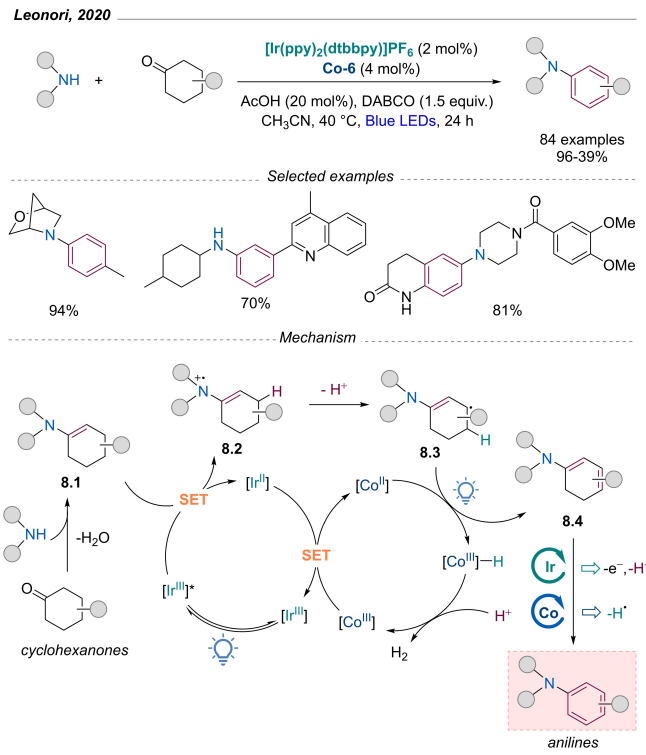
from the substrate to generate aryl radical (**7.1**). Subsequently, this radical undergoes 1,5-HAT, leading to radical formation at an unactivated site of the alkyl chain (**7.2**). The alkyl radical (**7.2**) then undergoes desaturation utilizing the Co(II) species to furnish the unsaturated product along with [Co^{III}]–H. This hydride species facilitates the catalyst turnover by the reaction between $SnPh_3H$ and an iminium salt to regenerate the cobalt-tin catalyst. DFT investigations suggest that the excitation strategy of the cobaloxime-substrate complex plays a pivotal role in two key stages of the process. Initially, homolytic cleavage of the [Co^{III}]–C bond enables 1,5-HAT via intramolecular single electron transfer (SET) in the radical species (Scheme 7, green). Also, the desaturation of the alkyl intermediate (**7.2**) takes place in the excited state under visible light irradiation (Scheme 7, purple).

4. Desaturative Synthesis of Aromatics

Recently, Leonori group has developed several methodologies for converting aliphatic substrates into high-value aromatic products.[38] These transformations involve multiple acceptorless dehydrogenation steps utilizing dual catalytic systems including cobaloxime catalysis.

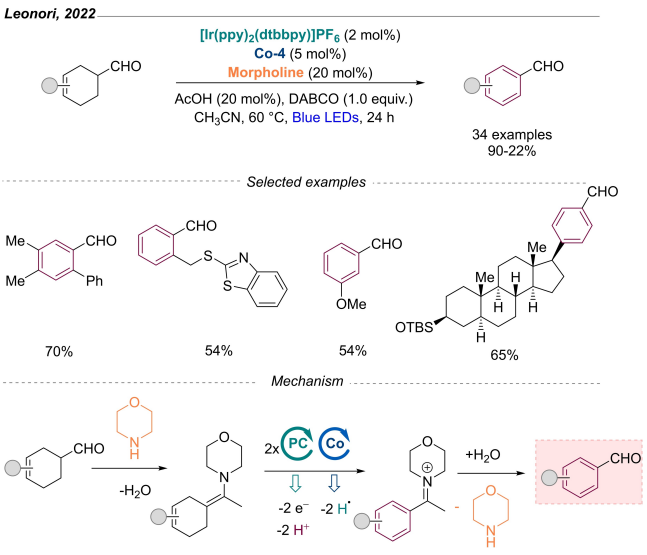
In 2020, Leonori group introduced a general and site-selective approach for synthesizing anilines from corresponding cyclohexanes and ammonia, primary, or secondary amines.[38a] The reaction commences with a straightforward condensation between the amine or ammonia and the cyclohexane derivative to form the corresponding enamine (**8.1**) (Scheme 8). The enamine intermediate undergoes single-electron oxidation with an iridium photocatalyst, generating an enaminium radical (**8.2**) which then deprotonates to yield the β-enamine radical (**8.3**). This radical subsequently reacts with a [Co^{II}] metalloradical via HAT, leading to the formation of the di-enamine (**8.4**) along with a [Co^{III}]–H species. This di-enamine is proposed to undergo a second oxidation-dehydrogenation process with the cobaloxime/photocatalyst system, resulting in the complete aromatization of the aniline derivatives. The reaction demonstrates excellent tolerance for various functional groups in the *ortho*-, *meta*-, and *para*- positions of the cyclohexanone. This method has been showcased to simplify the preparation of a wide range of pharmaceuticals. During the review of this manuscript, the same group has extended this methodology to the synthesis of aminated heteroaromatics from the corresponding amines and cyclic ketones.[39]

In 2021, Leonori and co-workers outlined a method for synthesizing a wide range of substituted aromatic aldehydes from the corresponding cyclohexanecarbaldehydes.[38b] This new approach involves a triple catalytic system comprising an amine catalyst, a photocatalyst, and cobaloxime, resulting in the production of aromatic aldehydes and hydrogen gas as the sole side-product. In this method, the morpholine catalyst reacts with the aldehyde, leading to the formation of the corresponding enamine. Similar to the dehydrogenative synthesis of anilines, the enamine intermediate undergoes two cycles of oxidation-deprotonation using an iridium photocatalyst, followed by desaturation with cobaloxime (Scheme 9). Finally, hydrolysis leads to the formation of the desired aldehydes.

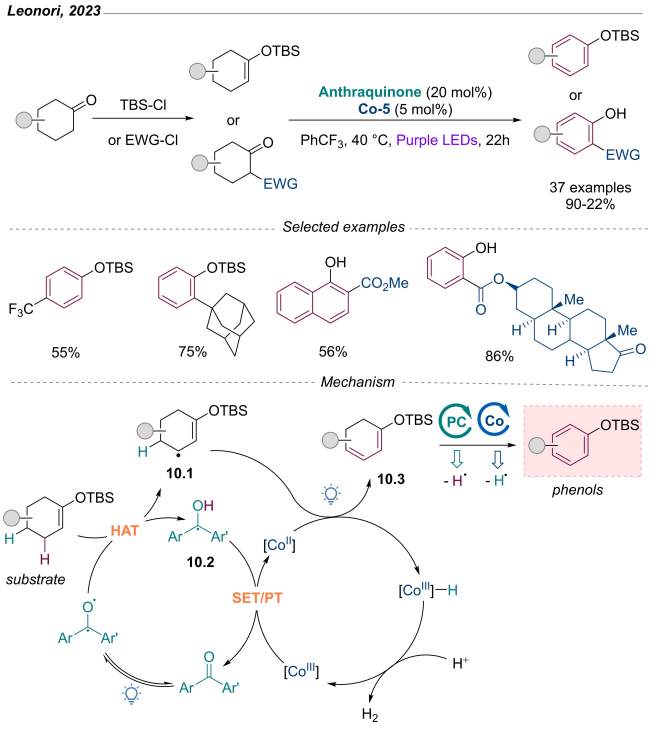


Scheme 8. Synthesis of anilines from amines and cyclohexanones.

More recently, Leonori et al. have introduced a new method for the complete aromatization of cyclohexanones to phenols (Scheme 10).[38c] This innovative strategy exploits the synergistic interplay of photocatalytic HAT and cobalt catalysis, alternating between each other, to sequentially remove four hydrogen atoms from the saturated precursors.



Scheme 9. Dehydrogenative synthesis of aldehydes.



Scheme 10. Synthesis of phenols via desaturation of cyclohexanones.

To facilitate a facile HAT process, the authors initially convert the cyclohexenes to the corresponding enol ether or introduce an electron-withdrawing group (e.g., acetyl, ester) at the α-position to favour the enol tautomer over the ketone form. The catalysis starts with HAT process, hydrogen is transferred from the substrate to the triplet excited state of the HAT catalyst the allylic radical (**10.1**) and a ketyl radical (**10.2**). Subsequently, radical (**10.1**) undergoes desaturation with [Co^{II}] species, producing a diene (**10.3**). This diene then undergoes a second round of HAT and desaturation catalysis, resulting in the formation of phenol derivatives.

5. Cross Dehydrogenative Coupling (CDC)

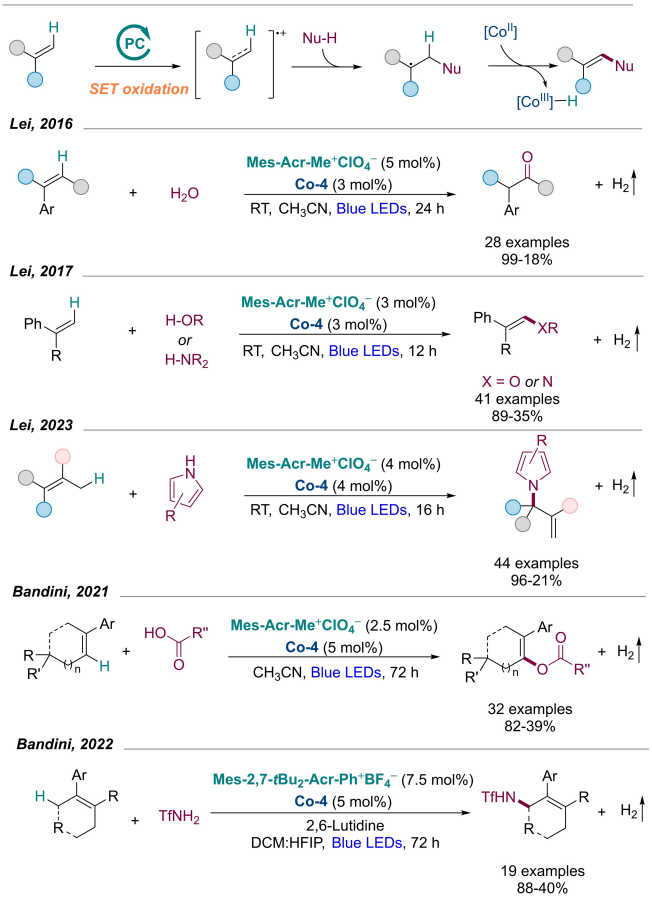
Cross dehydrogenative coupling (CDC) is a powerful synthetic method in organic chemistry used to form new carbon–carbon or carbon–heteroatom bonds by coupling two different C–H bonds from two different molecules without requiring prefunctionalization. This process allows for the direct transformation of readily available and relatively inert C–H bonds into more complex structures, facilitating the synthesis of diverse organic compounds. In this section, we summarize the application of the cobaloxime catalysis in CDC reactions of olefins and arenes. However, the CDC reactions that involves iminium and oxonium cation intermediates[12a,40] and formal cycloaddition reactions[41] are already summarized elsewhere.[8a]

5.1 CDC of Olefins

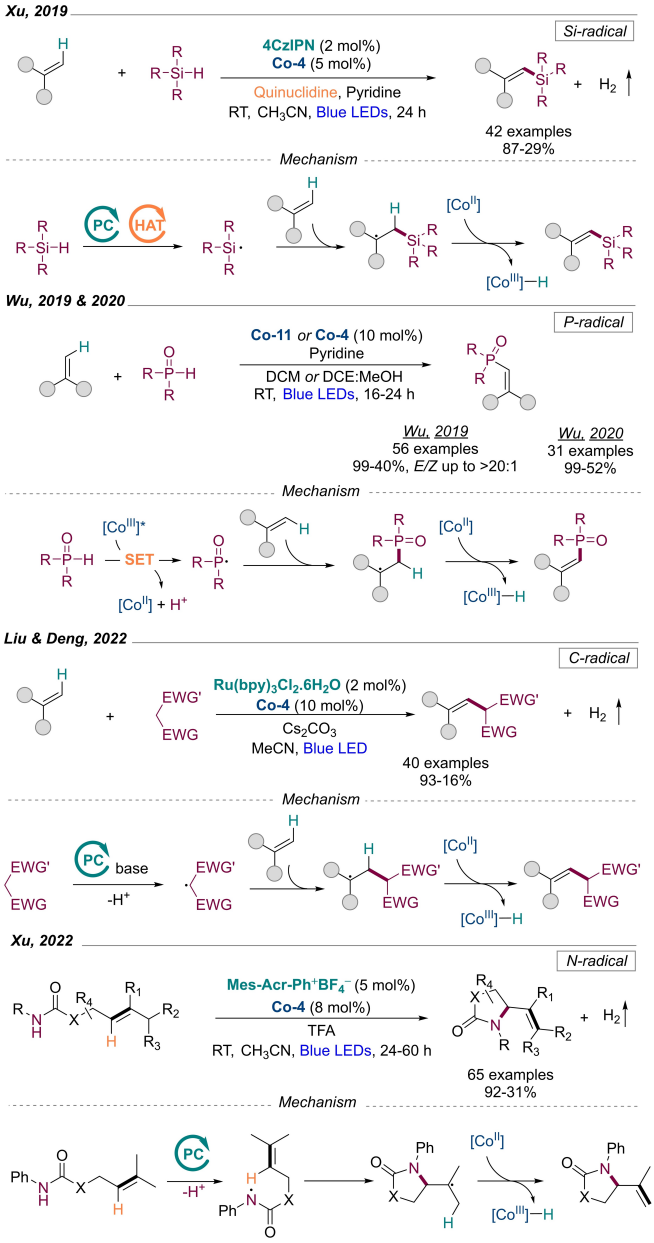
The dehydrogenative functionalization of alkenes presents a promising avenue for sustainable synthesis by streamlining chemical transformations and minimizing waste generation. Leveraging the inherent reactivity of alkenes and strategically employing transition metal catalysts, this methodology facilitates the direct conversion of abundant, renewable feedstocks into valuable chemical products. Cobaloxime catalysis has emerged as a notable approach, either as a single catalyst or in conjunction with co-catalysts, for acceptorless dehydrogenation functionalization of olefins.

In general, these transformations can be initiated through two mechanistic scenarios: on one hand, SET oxidation of alkenes into their corresponding radical cations followed by reaction with neutral nucleophiles (Scheme 11); on the other hand, addition of an in situ radical to a neutral olefin (Scheme 12). In both pathways, the newly generated carbon-centered radical intermediates undergo desaturation catalyzed by cobaloxime to yield the desired olefin and [Co^{III}]–H. The interception between the radical generation cycle and the dehydrogenation cycles enables the catalysis turnover.

In line with the first scenario, Lei et al. have reported the anti-Markovnikov oxidation of β-alkyl styrenes using



Scheme 11. Dehydrogenative functionalization of olefins via olefin SET oxidation.



Scheme 12. Dehydrogenative functionalization via radical addition to olefins.

water as ideal oxidant.[42] Shortly after, the same group explored the dehydrogenative cross-coupling of alkenes with alcohols and azoles utilizing Acr–Mes–$Me^+ClO_4^-$ as a strongly oxidizing photocatalyst in conjunction with cobaloxime.[43] This reaction facilitates the formation of new $C(sp^2)$–O and $C(sp^2)$–N bonds. Furthermore, the same research group recently demonstrated the application of this catalytic system for coupling methyl-substituted alkenes with amines to produce allylazoles.[44] Additionally, Bandini et al. disclosed a similar acridinium/cobaloxime catalytic system for the dehydrogenative functionalization of styrenes with carboxylic acids and triflamides.[45]

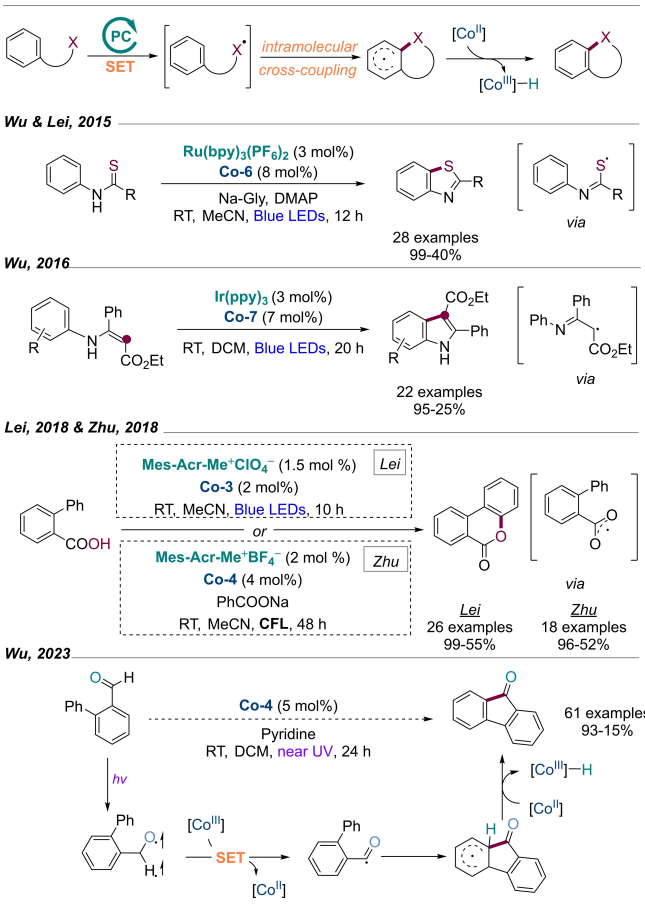
In the second scenario, Xu et al. have demonstrated the in situ generation of silyl radicals from tris(trimethylsilyl)silane (TTMSS) through a combined photoredox and HAT catalysis.[46] Subsequent addition of the silyl radical to the olefin yields a carbon-centered radical intermediate, which undergoes desaturation catalysed by cobalt, resulting in the formation of allylsilane and [Co^{III}]–H. In 2019, Wu et al. reported the synthesis of alkenylphosphine oxides from corresponding alkenes and H-phosphines using cobaloxime catalysis, without the need for additional photocatalyst.[47] The authors highlighted the unique dual functionality of the cobaloxime catalyst, serving as both a photoredox catalyst and an inner-sphere desaturation catalyst. The [Co^{III}] complex acts as an outer-sphere photocatalyst for the activation of H-phosphine oxides, leading to the formation of phosphinoyl-centered radicals and [Co^{II}] species. The resulting phosphorus radical intermediate subsequently reacts with an olefin or enamine,[48] yielding an organic radical intermediate. This intermediate can then be trapped by [Co^{II}] species to produce the alkenylphosphine oxide product and [Co^{III}]–H. Very recently, the same group reported the addition of the P-radical to isocyanides and the subsequent synthesis of phosphorylated heteroaromatics.[49]

More recently, Liu and Deng developed dehydrogenative allylic $C(sp^3)$–H alkylation via triple Brønsted base/cobaloxime/photoredox catalysis.[50] The Brønsted base/photoredox catalysis facilitates the conversion of active methylene compounds to the corresponding radical followed by addition to methyl substituted olefins to produce carbon-centered radicals which can undergo cobaloxime dehydrogenation to deliver the desired allylic $C(sp^3)$–H allylation products.

Furthermore, Xu et al. also reported on the intramolecular dehydrogenative amination of alkenes through synergistic photoredox and cobaloxime catalysis, resulting in the formation of a diverse array of five-membered *N*-heterocycles.[51] Photoredox catalysis facilitates the formation of nitrogen radicals, which undergo 5-*exo*-trig cyclization to form a radical intermediate. This intermediate is subsequently captured by [Co^{II}] to generate [Co^{III}]–H and the dehydrogenative amination product.

5.2 CDC of Arenes

Similarly to the previously summarized dehydrogenative functionalization of olefins, few examples of intramolecular cross-dehydrogenative coupling of arenes catalyzed by cobaloxime catalysis have been reported in recent years (Scheme 13). An early example was presented by Wu and Lei in 2015, demonstrating aromatic C–H thiolation and the construction of $C(sp^2)$–S bonds.[12c] The photoredox catalyst is suggested to convert *N*-phenylthioamides to the corresponding S-radicals in the presence of a base, which then undergoes 5-*exo*-trig cyclization followed by rearomatization facilitated by cobaloxime catalysis. Similarly, utilizing dual photoredox/cobaloxime catalysis, *N*-arylenamines could be transformed into the corresponding indoles via the generation of C-radicals[52] and lactonization of 2-arylbenzoic acidthrough carboxylate radicals formation.[53] Recently, Wu's group reported a sustainable method for converting 2-

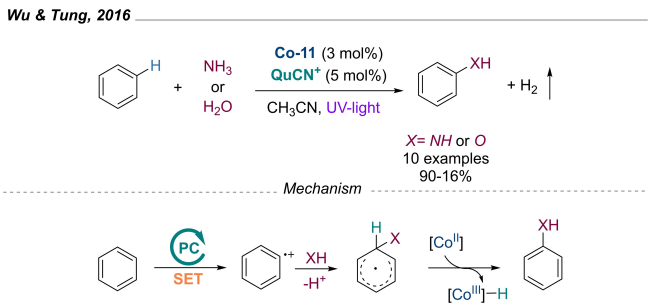


Scheme 13. Intramolecular dehydrogenative functionalization of arenes.

phenylbenzaldehydes into the corresponding fluorenones using cobaloxime catalysis without the need for a photoredox catalyst.[54] The authors proposed that under near UV light irradiation, the aromatic aldehydes enter a highly reactive triplet excited state, which is intercepted by cobaloxime in its ground state, leading to the formation of acyl radicals and [Co^{II}] species. Subsequent radical cyclization followed by rearomatization and fluorenone formation is enabled by the [Co^{II}] species.

It is worth noting that, a related intremolecular dehydrogenative Minisci alkylation between heteroarene and numerous carbon radical precursors has been reported. The C–C cross-coupling was realized by a photoredox/cobaloxime dual photocatalytic system, producing hydrogen gas as side product.[55]

The alternative approach for the arene dehydrogenative substitution involves the oxidation of the arene moiety with highly oxidizing photocatalyst (Scheme 14). In 2016 and 2017, Wu and Tung have reported the use of the highly oxidizing quinolinium ion QuCN$^+$ catalysts ($E^*_{red} = 2.72$ V) under UV light irradiation for the amination, hydroxylation and etherification of benzene in the presence of the cobaloxime catalysis for the rearomatization of the benzene.[56] The SET from the QuCN radical to the [Co^{III}] intermediate enables the catalysts regeneration. Simultaneously, Lei and co-workers demonstrated the possibility of



Scheme 14. Direct functionalization of arenes.

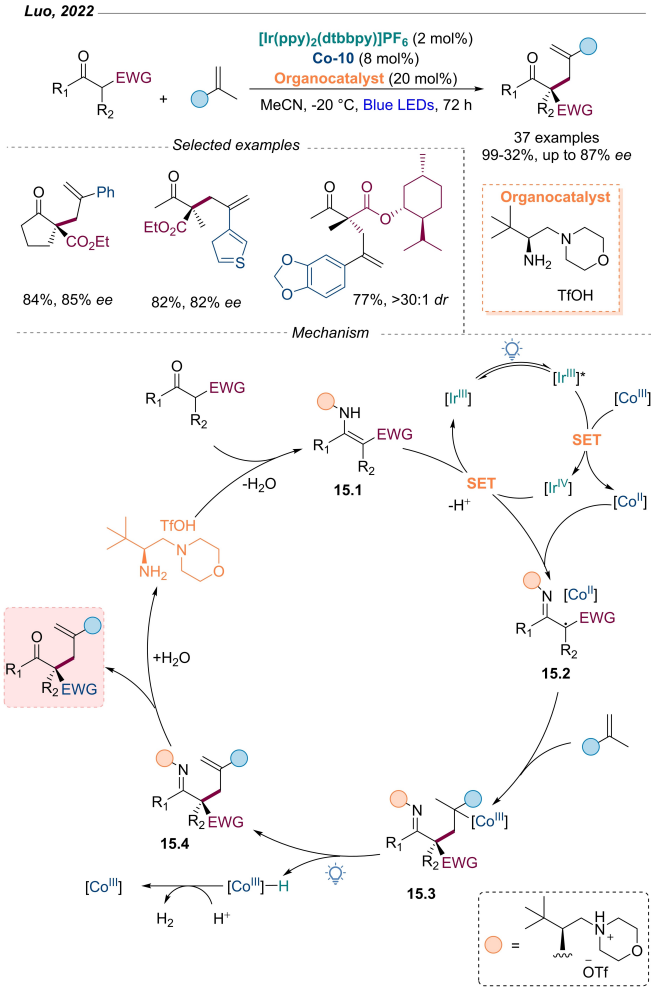
using acridinium visible light catalysis for the oxidation of arene and subsequent amination, however, the scope is limited to the electron rich arenes.[57]

6. Asymmetric Catalysis

The first application of cobaloxime in asymmetric synthesis was demonstrated by Luo and Wu in 2017.[58] A triple enamine/photoredox/cobaloxime catalysis was used for the asymmetric CDC of tetrahydroisoquinolines with carbonyl compounds. Recently Luo and co-workers have demonstrated the application of a related triple catalytic system for dehydrogenative allylic alkylation of 2-arylpropenes with β-ketocarbonyls (Scheme 15).[59] The reaction between the chiral primary amine organocatalyst and the β-ketocarbonyl compound yielded the enamines (**15.1**). These enamines undergo SET oxidation to generate α-iminoradicals, which readily react with the in situ generated [Co^{II}] species to form the organocobalt intermediate (**15.2**). Subsequent radical addition to the 2-arylpropenes, followed by dehydrogenation, leads to the formation of (**15.4**) via the cobalt intermediate (**15.3**). The hydrolysis of the imine (**15.4**) yields the desired product along with the regenerated organocatalyst (Scheme 15).

7. Conclusion and Outlook

In recent years, significant strides have been taken toward developing sustainable desaturative transformations, notably catalyzed by cost-effective cobaloxime catalysts. Cobaloxime catalysts have found diverse applications, including catalyzing challenging transformations such as alkyl-Heck reactions in both polar and radical fashion, desaturation of functionalized and unfunctionalized alkanes, remote desaturation of aliphatic compounds, and dehydrodefunctionalization of various functional groups including aldehydes, carboxylic acids, amines, alkyl halides, and tertiary alcohols. Recent contributions have showcased innovative dehydrogenative methods for synthesizing anilines, heteroarylamines, phenols, and aromatic aldehydes under cobaloxime catalysis. Additionally, significant progress has been achieved in cross-dehydrogenative coupling reactions facilitated by cobaloxime catalysis. These developments underscore the



Scheme 15. Cobaloxime in asymmetric catalysis.

versatility and efficacy of cobaloxime catalysis in advancing sustainable synthetic methodologies, paving the way for further exploration and application in the field of organic synthesis. Despite the significant progress made, the application of cobaloxime catalysis is still in its infancy, and further academic and industrial research is anticipated, including progress in the practical applications of dehydrodefunctionalization of aliphatic compounds for upgrading biomass-derived compounds and upcycling of plastics, the expansion of remote and selective desaturation of aliphatic compounds,[60] exploration of Leonori's desaturative synthesis of aromatic compounds beyond enamine intermediates, the potential of merging cobaloxime with chiral catalysis for enhancing enantioselectivity, and the exploration of heterogenization of cobaloxime to facilitate catalyst recovery and reuse, thus improving the sustainability of cobaloxime catalysis. In addition to exploring new catalytic concepts and applications, cobaloxime catalysis lacks detailed theoretical and experimental studies, with several mechanistic steps currently under debate awaiting further investigations. For instance, there is discrepancy regarding the stepwise versus concerted hydrogen transfer, as well as the differentiation between homolytic cleavage of C–Co bonds in ground and excited states.

Acknowledgements

This work has been financially supported by the Deutsche Forschungsgemeinschaft (DFG, grant number EL 1041/3-1) and by the Leibniz Institute for Catalysis e.V. K.Z thanks Chinese Scholarship Council (CSC) for the predoctoral fellowship. L.M.A. is a Ramón y Cajal fellow (ref RYC2021-030994-I) and thanks MCIN/AEI and NextGenerationEU/PRTR for support. O.E.-S thanks Prof. Dr. Matthias Beller for his continued generous support. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: Cobaloxime · photoredox catalysis · biomimetic chemistry · cobalt

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Manuscript received: March 26, 2024
Accepted manuscript online: May 22, 2024
Version of record online: July 15, 2024