

REVIEW

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Cite this: *Org. Chem. Front.*, 2025, **12**, 6631Recent advances in C(sp³)-H functionalization via molecular electrocatalysisXiao-Li Lai,^a Ying-Kai Lai,^a Peng Xiong^{*b} and Hai-Chao Xu^{id} ^{*b}

Selective functionalization of inert C(sp³)-H bonds remains a central challenge in modern organic synthesis. Molecular electrocatalysis provides a sustainable platform for C(sp³)-H activation by enabling catalyst-controlled electron transfer or atom transfer under mild conditions. This review highlights recent advances in molecular electrocatalytic systems, including both transition metal-based and metal-free catalysts, for efficient C(sp³)-H functionalization. Mechanistic insights into outer- and inner-sphere electron transfer pathways are discussed, along with their applications in enhancing regio- and enantioselectivity in asymmetric radical transformations. Special emphasis is placed on emerging photoelectrocatalytic approaches that integrate electrochemical redox control with photochemical excitation. Through critical evaluation of representative systems, this review illustrates the growing potential of molecular electrocatalysis for achieving selective and sustainable C(sp³)-H functionalization.

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10th anniversary statement

It is a great pleasure to contribute to the 10th anniversary of *Organic Chemistry Frontiers*. Our group has been privileged to publish in this journal, beginning in 2018 with the development of an electrochemical cascade radical cyclization for the construction of seven-membered carbocycles (*Org. Chem. Front.*, 2018, **5**, 3129), and more recently in 2025 with diverse C(sp³)-H functionalizations enabled by electrochemical benzylic oxygenation (*Org. Chem. Front.*, 2025, **12**, 1850). These studies underscore the journal's role as a premier platform for disseminating innovative and impactful research in organic chemistry. Over the past decade, *Organic Chemistry Frontiers* has evolved into a truly international journal, fostering scientific exchange and highlighting important advances from China, Asia, and across the world. I look forward to its continued success in shaping the future of organic chemistry and in promoting sustainable methodologies for synthetic science.

^aCollege of Chemistry and Materials Science, Fujian Normal University, Fuzhou 350117, China. E-mail: xiaoli.lai@fjnu.edu.cn^bKey Laboratory of Chemical Biology of Fujian Province, State Key Laboratory of Physical Chemistry of Solid Surfaces, and College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China. E-mail: pengxiong@xmu.edu.cn, haichao.xu@xmu.edu.cn

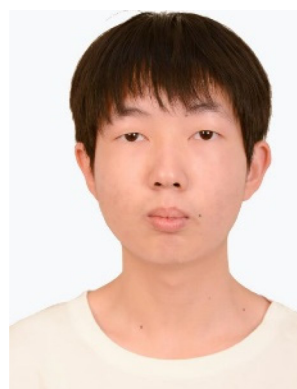
1 Introduction

C(sp³)-H bonds are among the most abundant structural motifs in organic molecules. Their direct functionalization represents a powerful transformation in synthetic chemistry, eliminating the need for prefunctionalized substrates and



Xiao-Li Lai

Xiao-Li Lai received her BS degree in 2018 and PhD in 2023 from Xiamen University under the supervision of Professor Hai-Chao Xu. In 2023, she joined Fujian Normal University as a faculty member to begin her academic career. Her current research focuses on green organic synthesis.



Ying-Kai Lai

Ying-Kai Lai obtained his BS degree in 2024 from Quanzhou Normal University. He is currently pursuing his MS degree under the supervision of Assoc. Prof. Xiao-Li Lai at Fujian Normal University. His research focuses on functional covalent organic frameworks for photoelectrocatalysis.

enhancing step and atom economy.¹ Such strategies have found broad applications across the pharmaceutical, agrochemical, and materials science sectors, underscoring the demand for efficient and general C(sp³)-H activation.² Nevertheless, this area continues to face several key challenges: (i) the high bond dissociation energy (BDE, typically 95–105 kcal mol⁻¹) and high redox potential of C(sp³)-H bonds,³ (ii) difficulties in achieving site-selectivity among multiple similar C-H sites,⁴ and (iii) the need for mild and sustainable methods that avoid stoichiometric oxidants or reductants.⁵

To address these challenges, a wide range of C(sp³)-H functionalization strategies have been developed, including thermochemical, enzymatic, and transition metal-catalyzed approaches.⁶ Among these, radical-based methods have emerged as particularly promising due to their ability to distinguish C-H bonds based on subtle electronic and steric differences.⁷ These approaches often obviate the need for directing groups and offer distinct advantages in achieving selective C(sp³)-H functionalization.^{1b,8} Traditional radical generation methods, however, typically require large amounts of stoichiometric oxidants, reductants, or radical initiators, which can lead to undesired byproducts, safety concerns, and increased waste generation.⁹

In recent years, photochemical and electrochemical techniques for radical generation have attracted considerable interest owing to their inherent sustainability. Photocatalytic methods have primarily focused on redox-neutral transformations, but those applied to multi-electron or net oxidative or reductive reactions often require stoichiometric sacrificial redox agents that generate undesired byproducts and increase reaction complexity.¹⁰ In contrast, electrochemical methods employ electric current as a clean and tunable redox input, eliminating the need for stoichiometric oxidants or reductants, and thereby minimizing waste generation and improving functional group tolerance.¹¹ Moreover,

electrochemical setups offer fine control over redox potentials, enabling selective activation of inert C(sp³)-H bonds under mild conditions.

Despite these advantages, conventional direct electrolysis remains limited by the inherent challenges of heterogeneous electron transfer at the electrode interface.^{11h,12} Localized generation of reactive intermediates at the electrode surface often leads to undesired side processes, such as overoxidation, overreduction and electrode passivation. Moreover, competitive oxidation among multiple electroactive species can significantly impair selectivity.

Molecular electrocatalysis offers a powerful solution to the challenges associated with direct electrolysis by enabling controlled, homogeneous electron transfer between the electrode and the substrate.¹³ This approach lowers the energetic threshold for substrate activation and spatially decouples electron transfer from the electrode surface, thereby enhancing both reactivity and selectivity.

Mechanistically, electron transfer in molecular electrocatalysis can occur *via* outer-sphere or inner-sphere pathways, depending on the nature of the catalyst-substrate interaction (Scheme 1a). In outer-sphere mechanisms, electron transfer occurs without direct bonding between the catalyst and substrate and can tolerate moderate mismatches in redox potential. In contrast, inner-sphere pathways involve transient coordination or bond formation, enabling efficient activation even when substantial redox potential differences exist.

To date, a variety of molecular electrocatalysts have been developed that enable diverse C(sp³)-H functionalization reactions under synthetically practical conditions, as illustrated in Scheme 1b. These cost-effective and readily accessible catalysts provide a sustainable alternative to precious metal complexes such as Rh, Ir, and Ru, which are frequently employed in photocatalytic C(sp³)-H functionalization.

Although recent reviews have examined electrochemical strategies for C-H bond transformation,¹⁴ systematic analyses



Peng Xiong

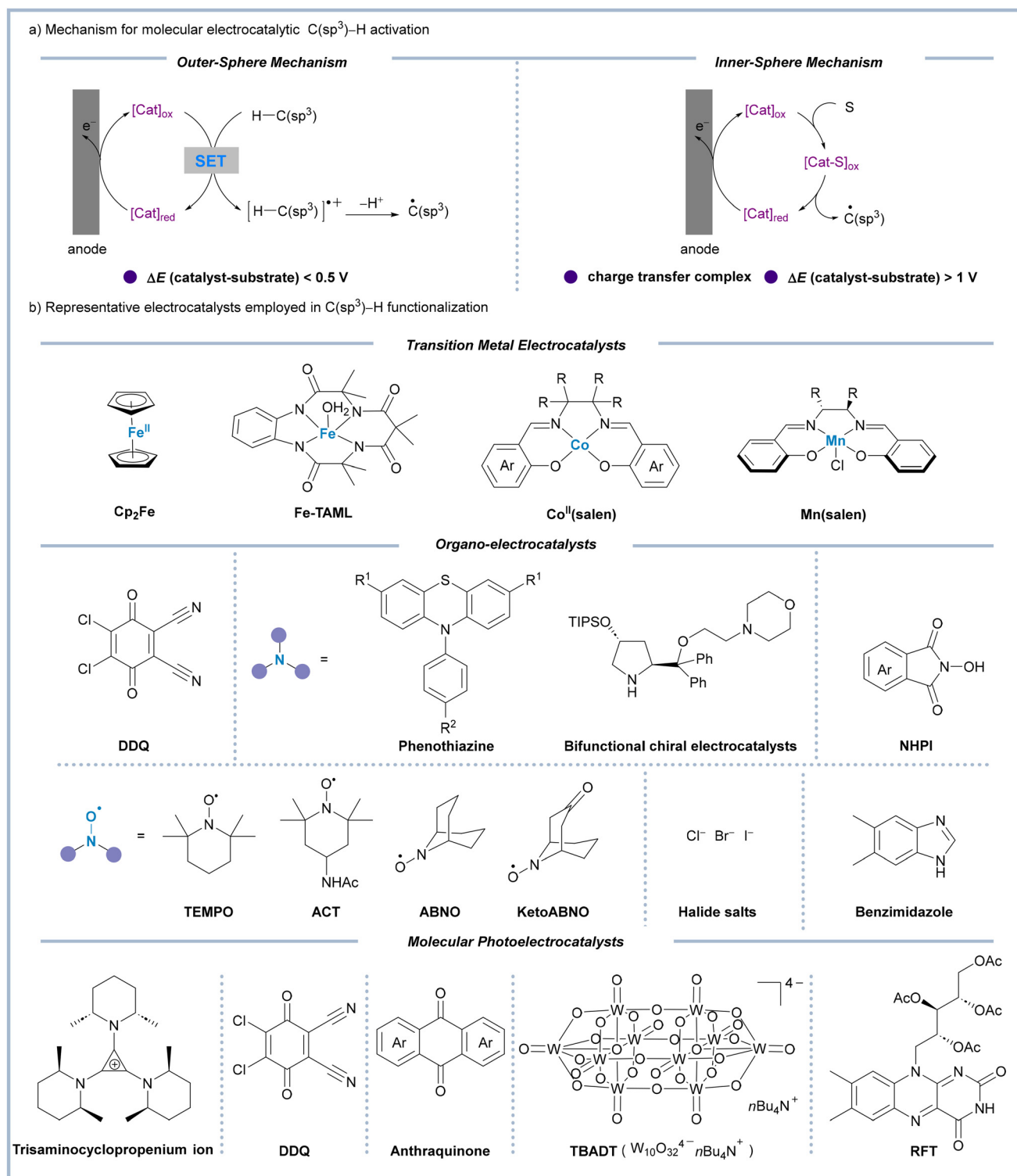
Peng Xiong received his BS degree in 2014 from Nanchang University and PhD degree in 2020 from Xiamen University under the supervision of Hai-Chao Xu. After postdoctoral work with Prof. Eric Meggers at the University of Marburg (Germany) from 2021 to 2023, he joined Korea Institute of Basic Science & Korea Advanced Institute of Science and Technology for his second postdoctoral fellowship with Prof.

Sukbok Chang. In 2024, he joined Xiamen University to begin his independent career. His research focuses on organic electrosynthesis.



Hai-Chao Xu

Hai-Chao Xu obtained his BS degree in 2006 from Xiamen University and PhD degree in 2010 from Washington University in St Louis (USA) under the supervision of Prof. Kevin D. Moeller. After postdoctoral research with Prof. Jonathan A. Ellman at Yale University (USA) from 2011 to 2013, he joined the faculty at Xiamen University to start his independent career. His research interest focuses on synthetic electrochemistry.



Scheme 1 Mechanism for molecular electrocatalytic C(sp³)-H activation and representative electrocatalysts employed in C(sp³)-H functionalization.

focusing specifically on molecular electrocatalysis for C(sp³)-H activation remain scarce.^{13b,c,15} In this review, we provide a critical survey of recent advances in this emerging area. We discuss representative examples involving both transition

metal-based and metal-free catalytic systems, examine mechanistic principles that govern selectivity and efficiency, and highlight current limitations as well as promising directions for future development.

2 Molecular electrocatalysis

2.1 Transition metal electrocatalysts

Transition metal complexes have emerged as highly versatile electrocatalysts owing to their tunable redox properties, which can be modulated through ligand design, and their capacity to mediate both outer-sphere and inner-sphere electron transfer processes.^{13b,16} Among them, first-row Earth-abundant metals such as iron, cobalt, and manganese are of particular interest due to their cost efficiency and distinctive catalytic reactivity.

2.1.1 Fe-based electrocatalysts

Ferrocene. Ferrocene (Cp_2Fe), a seminal compound in organometallic chemistry, features a stable sandwich structure and displays well-defined electrochemical behavior, making it an ideal internal standard and reference redox couple in cyclic voltammetry and electrochemical analysis.¹⁷ The Fe(II)/Fe(III) redox couple undergoes a reversible one-electron oxidation at approximately 0.35 V–0.56 V vs. SCE in typical organic solvents.¹⁸ A notable breakthrough of ferrocene in electrochemical synthesis was reported by Xu and co-workers, who demonstrated that ferrocene effectively mediates the generation of amidyl radicals from *N*-arylamides.¹⁹ These nitrogen-centered radicals undergo addition to unsaturated bonds, enabling the efficient construction of diverse nitrogen heterocycles.²⁰

This ferrocene-catalyzed radical platform has been further extended to $\text{C(sp}^3\text{)-H}$ functionalization of carbonyl compounds bearing activated α -positions (Scheme 2). Two mechanistically distinct pathways have been identified, both initiated by anodic oxidation of ferrocene (Cp_2Fe) to ferrocenium (Cp_2Fe^+). For substrates (**2-2**) containing two electron-withdrawing groups (EWGs), base-mediated deprotonation yields a carboanion (**2-3**), which undergoes single electron transfer with ferrocenium, generating a carbon-centered radical and regenerating ferrocene. Alternatively, in the case of less acidic ketones (**2-4**), the addition of a Lewis acid facilitates enolization, producing an enol intermediate (**2-5**) that is subsequently oxidized by ferrocenium to afford an α -carbonyl

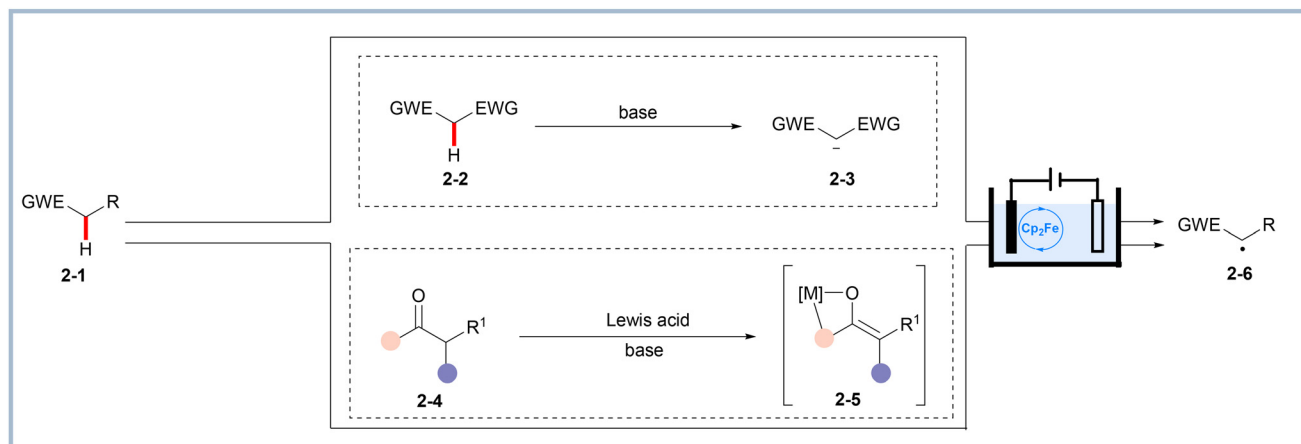
radical (**2-6**). Importantly, in contrast to conventional oxidant-based protocols,²¹ this electrochemical strategy obviates the need for stoichiometric oxidants and noble metal catalysts. Furthermore, *in situ* base generation *via* cathodic reduction obviates the need for strong bases, thereby ensuring compatibility with base-sensitive substrates.

In 2017, Xu and co-workers reported a ferrocene-catalyzed intramolecular $\text{C(sp}^3\text{)-H}$ arylation of 1,3-dicarbonyl compounds (**3-1** to **3-2**, Scheme 3a).²² In this transformation, fluorinated carbon-centered radicals (**3-5**) were generated under mild conditions to access 3-fluorooxindoles (**3-7**). The methodology was later extended to α -alkyl-substituted 1,3-dicarbonyl compounds (**3-11**, Scheme 3b),²³ enabling the construction of polyfunctionalized tetrahydroisoquinolones (**3-12**) *via* intramolecular radical cyclization.

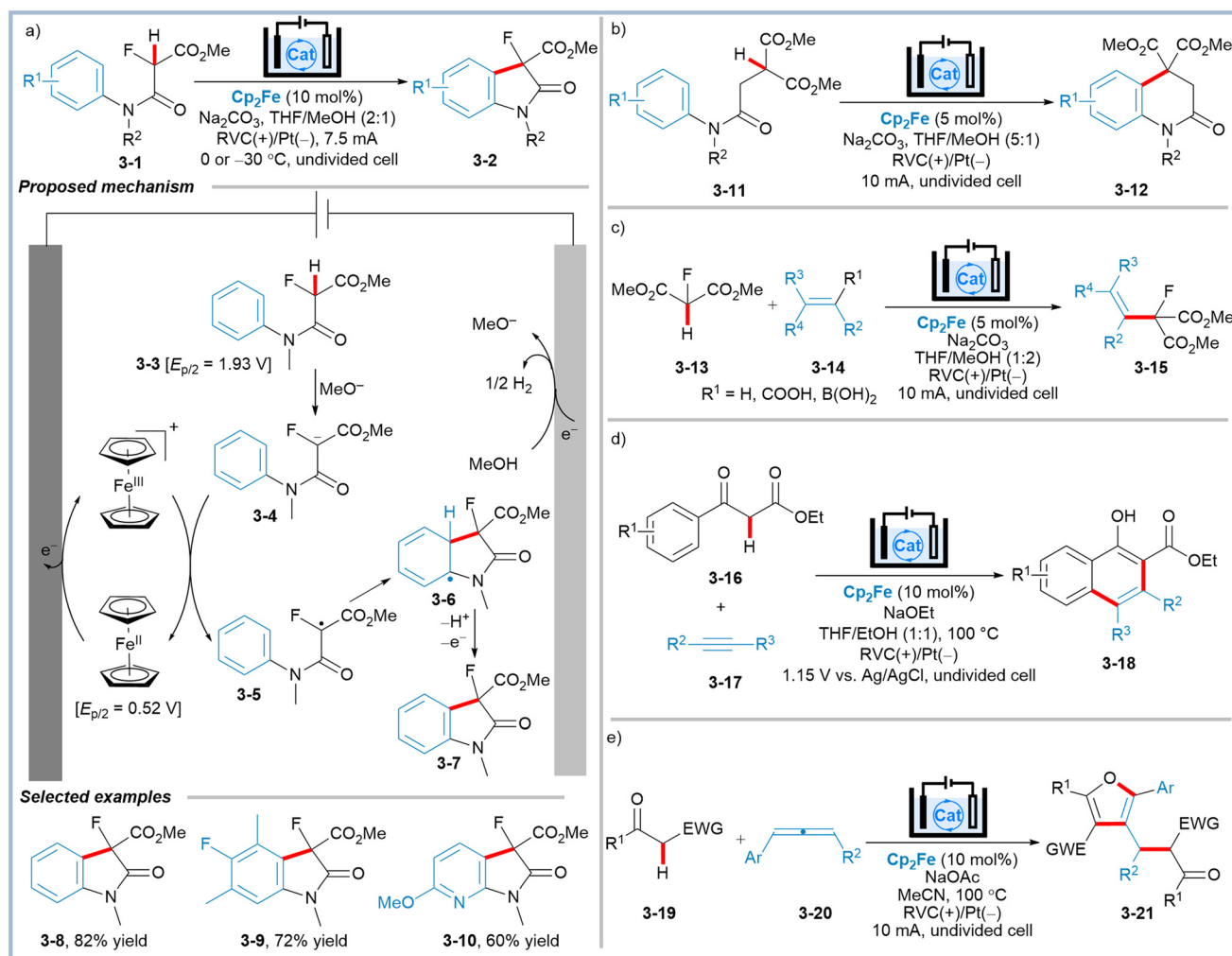
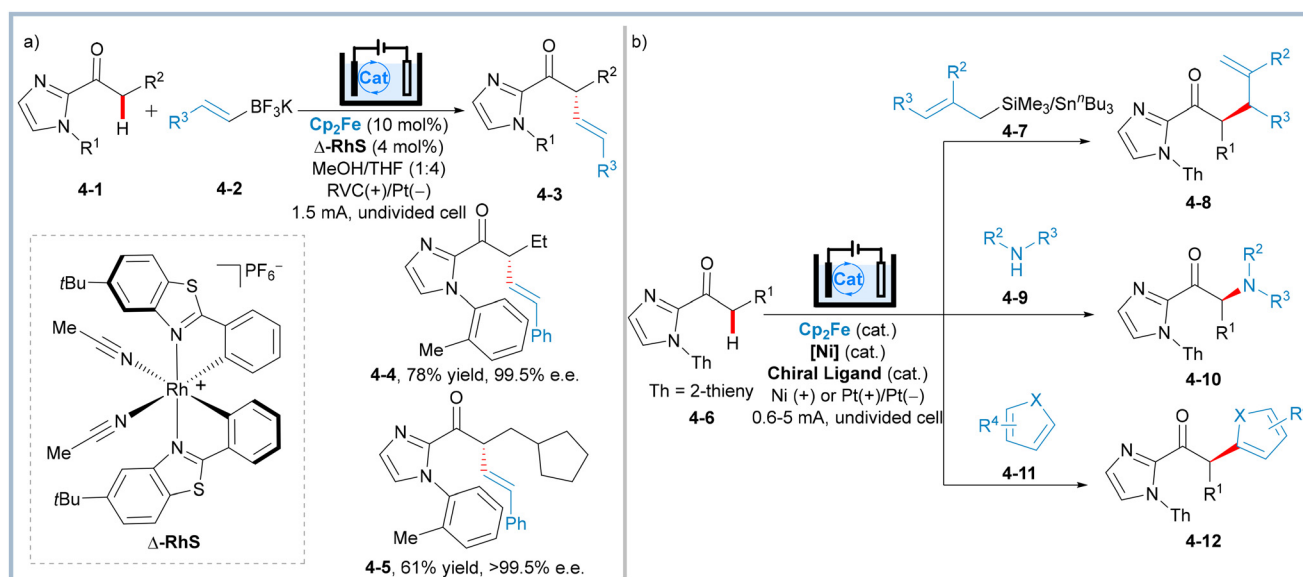
This ferrocene-mediated strategy was later applied to the intermolecular alkenylation of fluorinated 1,3-dicarbonyl substrates (**3-13**) with styrenes, cinnamic acid, and vinyl boronic acid by Wang,²⁴ Ackermann,²⁵ and co-workers (**3-15**, Scheme 3c). In a similar fashion, non-fluorinated substrates bearing electron-withdrawing substituents also participated in cyclization with alkynes and aryl allenes under similar conditions, affording 1-naphthols (**3-18**, Scheme 3d) and substituted furans (**3-21**, Scheme 3e).²⁶

The application of ferrocene-mediated electrocatalysis was further expanded to asymmetric $\text{C(sp}^3\text{)-H}$ functionalization. Meggers and co-workers developed a dual catalytic system combining ferrocene redox catalysis with asymmetric Lewis acid catalysis to achieve highly enantioselective α - $\text{C(sp}^3\text{)-H}$ alkenylation of 2-acylimidazoles (**4-1/4-2** to **4-3**, Scheme 4a).²⁷ A chiral rhodium complex acted as a Lewis acid, forming an enolate with the imidazolone substrate to reduce its oxidation potential and impart stereocontrol. This strategy enabled excellent enantioselectivities, as exemplified by products **4-4** and **4-5** (99.5% ee and >99.5% ee, respectively).

Meanwhile, Guo and co-workers developed a ferrocene-mediated enantioselective electrochemical protocol for the α - $\text{C(sp}^3\text{)-H}$ functionalization of 2-acylimidazoles (**4-6**), encompass-



Scheme 2 Ferrocene-catalyzed generation of carbon-centered radicals. EWG = electron-withdrawing group.

Scheme 3 Ferrocene-catalyzed C(sp³)-H functionalization of 1,3-dielectron-deficient substrates.Scheme 4 Ferrocene-catalyzed enantioselective electrochemical C(sp³)-H functionalization.

ing allylation (4-8),²⁸ amination (4-10),²⁹ and heteroarylation (4-12) reactions (Scheme 4b).³⁰ In these systems, ferrocene serves as the redox mediator, while a combination of cheap nickel catalysts and chiral diamine ligands enables asymmetric induction. The chiral nickel complex functions as a Lewis acid, coordinating to the imidazolone core and facilitating enolate formation, thereby lowering the oxidation potential and imparting stereocontrol. These dual catalytic strategies highlight the synergy between redox and chiral catalysis and underscore the broad potential of ferrocene-mediated enantioselective C(sp³)-H functionalization.³¹

Fe-TAML. Fe-TAML (tetraamido macrocyclic ligand) complexes constitute a distinct class of iron-based catalysts that operate *via* high-valent iron-oxo intermediates.³² These complexes mimic the oxidative reactivity of metalloenzymes such as peroxidases and cytochrome P450.³³ A defining feature of Fe-TAML catalysis is the generation of the Fe(v)-oxo species, which are competent in activating strong C-H bonds *via* hydrogen atom abstraction.³⁴

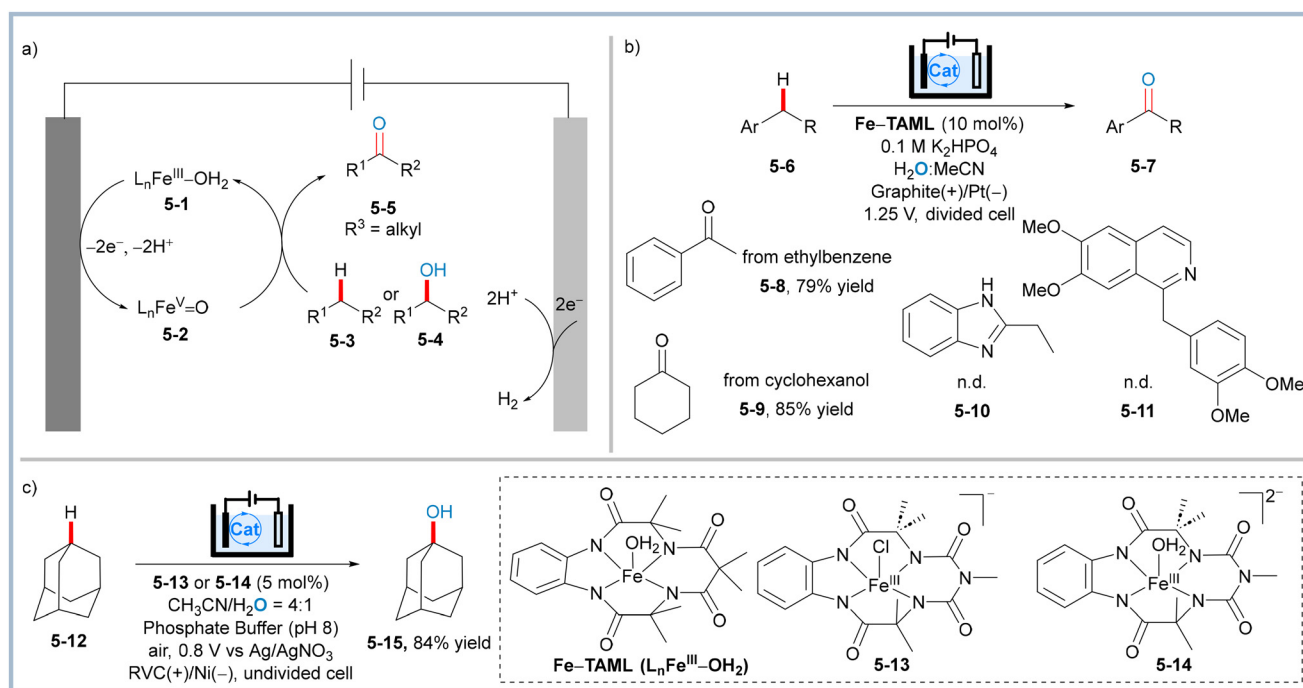
In 2019, Stahl and co-workers reported an electrochemical protocol for C(sp³)-H oxygenation using Fe-TAML complexes.³⁵ In this method, the (TAML)Fe^V=O (5-2) species is generated *via* proton-coupled electrochemical oxidation of the corresponding (TAML)Fe^{III}-OH₂ complex (5-1). Such electrochemical oxidation of Fe-OH₂ complexes couples with proton reduction to generate H₂ as the sole byproduct, eliminating the need for stoichiometric chemical oxidants and offering a sustainable, environmentally friendly pathway.³⁶ The resulting high-valent Fe(v)=O intermediate undergoes oxygen atom transfer with benzylic C(sp³)-H bonds (5-3) to afford the corresponding alco-

hols, which can undergo further oxidation to ketones (5-5) (Scheme 5a). Alternatively, alcohol substrates (5-4) can be directly oxidized to ketones by the high-valent iron species. However, this method proved ineffective for substrates bearing heteroaromatic or electron-rich aromatic groups, as exemplified by substrates 5-10 and 5-11, which did not undergo the desired oxidation under the reported conditions (Scheme 5b).

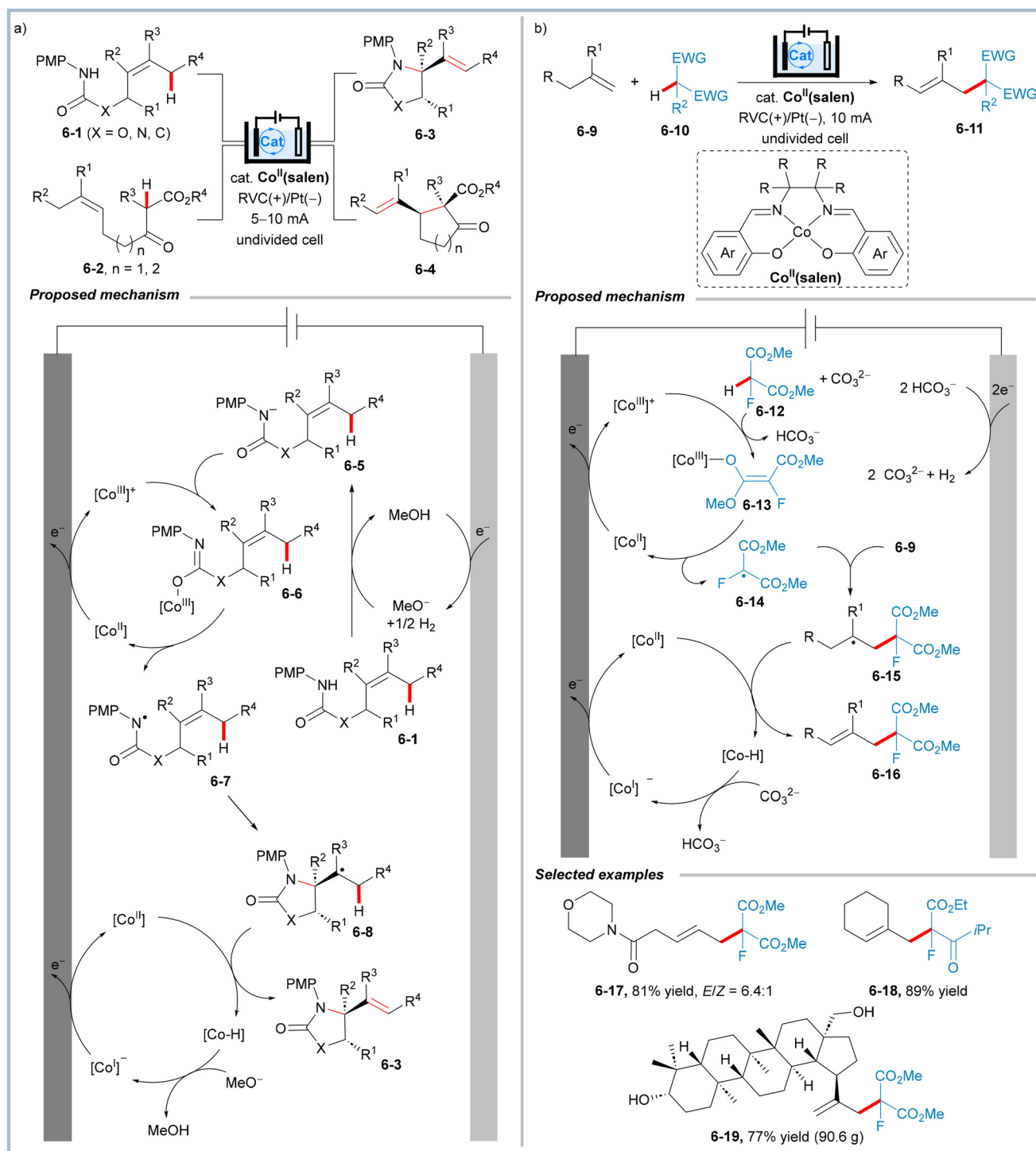
Building on this strategy, Gupta and co-workers reported the electrochemical hydroxylation of unactivated alkanes using other Fe-TAML catalysts (5-12 to 5-15, Scheme 5c),³⁷ further extending the scope of Fe-TAML catalysis to the functionalization of inert C(sp³)-H bonds in simple hydrocarbon frameworks.

2.1.2 Co-based electrocatalysts. Cobalt complexes have gained considerable attention as sustainable and cost-effective alternatives to noble metals in C-H functionalization. Electrochemical protocols using simple cobalt salts such as Co(OAc)₂·4H₂O were independently reported by Ackermann, Lei, and others, paving the way for cobalt-based electrocatalytic C(sp²)-H functionalization.³⁸ Lin and co-workers introduced an enantioselective electrocatalytic hydrocyanation of alkenes *via* a cooperative Co(salen)/Cu system.³⁹

Subsequently, Xu and colleagues developed a Co(salen)-catalyzed intramolecular allylic C-H amination (6-1 to 6-3) and allylic C-H alkylation (6-2 to 6-4) of 1,3-dicarbonyl compounds under electrochemical conditions (Scheme 6a).⁴⁰ Cyclic voltammetry experiments revealed that direct electron transfer between the substrate and the Co(salen) complex is thermodynamically unfavorable, as the oxidation potential of the Co(salen) catalyst is significantly lower than that of the substrate (by more than 1 V). Further electrochemical analysis showed



Scheme 5 Electrochemical C(sp³)-H oxygenation employing Fe-TAML as catalysts. n.d. = not detected.



Scheme 6 Allylic C(sp³)-H functionalization with cobalt catalysts. PMP = *p*-methoxyphenyl.

that the Co^{III}/Co^{II} redox couple remained unchanged in the presence of Na₂CO₃, a weak base, whereas in the presence of NaOMe, the reduction wave disappeared and no catalytic current was observed. These findings suggest that cathodically generated MeO⁻ acts as a base to deprotonate the amide substrate **6-1**, forming the conjugate compound **6-5**, which then undergoes inner-sphere electron transfer with Co^{III} to generate

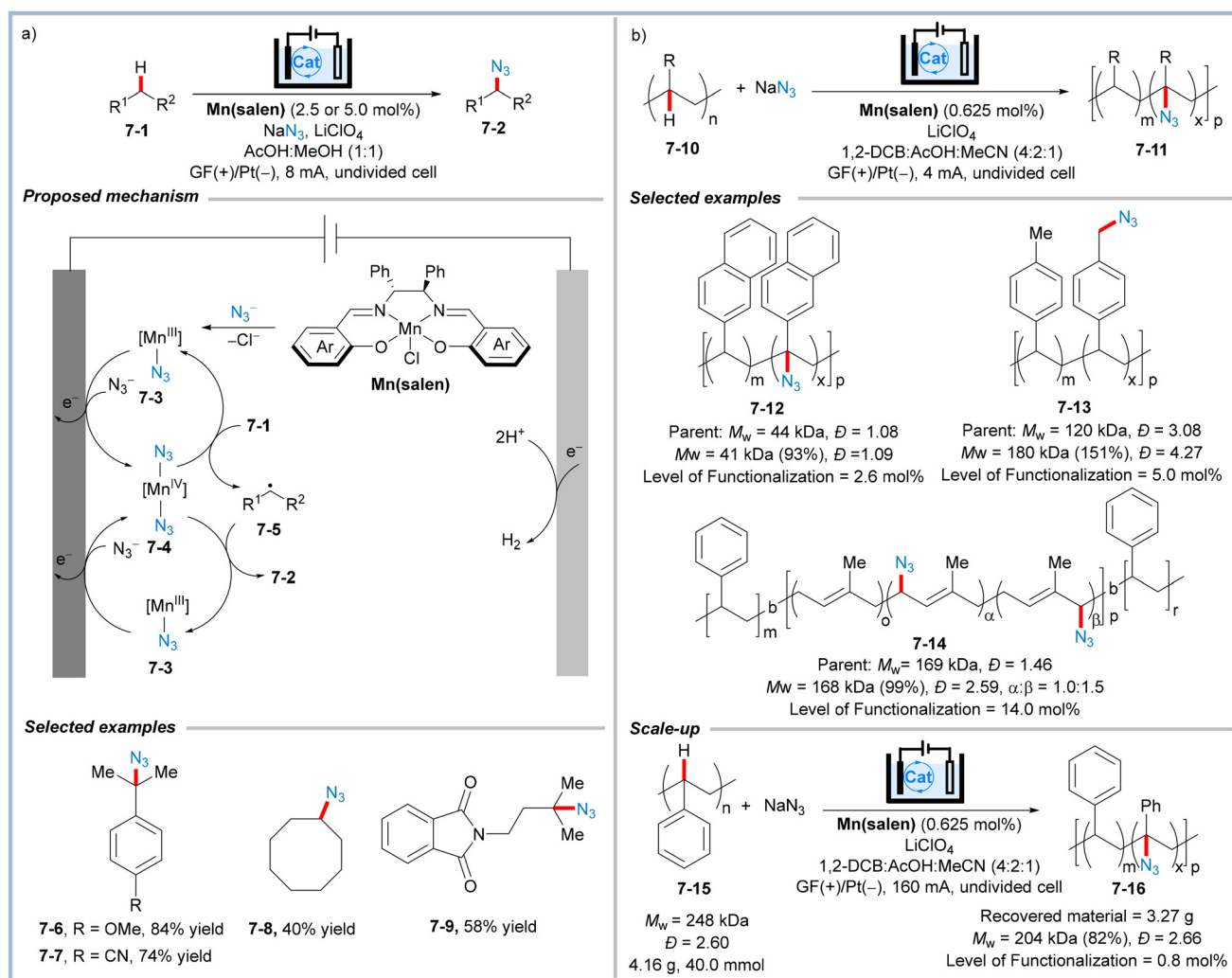
the amidyl radical intermediate **6-7**. The resulting radical cyclizes to give the carbon-centered radical **6-8**, which can be oxidized by [Co^{II}] *via* hydrogen abstraction or β-hydrogen elimination, resulting in the amination product **6-3** and [Co^I(H⁺)]. The catalytic cycle is completed by cathodic deprotonation and anodic reoxidation of [Co^I] to regenerate the active Co^{II} catalyst.

This catalytic system was further extended to intermolecular allylic C–H alkylation using the Co(salen) catalyst (Scheme 6b).⁴¹ The reaction proceeds through a similar charge-transfer complex (6-13), followed by radical addition and termination. Notably, Co(salen) simultaneously serves as both the redox mediator and radical trapping catalyst. Selected examples include successful reactions with linear olefins such as 6-17 (81% yield, *E/Z* = 6.4 : 1), branched nucleophiles such as 6-18 (89% yield), and even complex steroidal substrates like 6-19 (77% yield). This method demonstrates excellent functional group compatibility and tolerance toward a wide array of carbophilic nucleophiles, as well as unactivated olefins. Additionally, the reaction can be easily scaled up to nearly a hectogram (6-19).

Compared with oxidant-based or direct electrolysis methods,⁴² Co(salen)-catalyzed protocols demonstrate excellent functional group tolerance and broad applicability across diverse alkene substitution patterns, ranging from di-substituted to tetrasubstituted alkenes.

2.1.3 Mn-based electrocatalysts. Manganese complexes are particularly attractive as redox-active reagents due to their low cost, Earth abundance, and minimal toxicity. While significant progress has been made in olefin difunctionalization using manganese electrocatalysis, as demonstrated by the Lin,⁴³ Mo,⁴⁴ and Lei groups,⁴⁵ manganese-catalyzed electrochemical C(sp³)-H functionalization remains relatively underexplored.

Recognizing the significance of azide functional groups,⁴⁶ the Ackermann group developed a manganese-catalyzed, electrochemically inert C(sp³)-H azidation method in 2021 (Scheme 7a).⁴⁷ The reaction utilizes sodium azide (NaN₃) as the nitrogen source and Mn(salen) as the redox mediator. The reaction begins with ligand exchange between Mn(salen) and NaN₃, forming the active Mn^{III}-N₃ complex 7-3, which is subsequently oxidized at the anode to generate the diazo-manganese(IV) complex 7-4. This high-valent manganese complex (7-4) then abstracts hydrogen atoms from substrate 7-1, generating the carbon-centered radical 7-5. Simultaneously, the high-valent manganese is reduced back to Mn^{III}-N₃, completing the



Scheme 7 Mn-catalyzed electrochemical C(sp³)-H azidation. 1,2-DCB = 1,2-dichlorobenzene. GF = graphite felt.

manganese catalytic cycle. The carbon radical **7-5** undergoes an azide radical transfer with the manganese(IV) diazide complex **7-4** to yield the C(sp³)-H azidation product **7-2**. This reaction exhibits good functional group compatibility and is suitable for both electron-rich substrates, such as compound **7-6**, and electron-deficient substrates, such as compound **7-7**. Moreover, the system facilitates the C(sp³)-H azidation of simple alkanes (**7-8** and **7-9**).

Building on this strategy, the Ackermann group further demonstrated that Mn(salen)-catalyzed electrocatalysis could be extended to the late-stage C(sp³)-H azidation of commodity polymers (**7-10** to **7-11**, Scheme 7b).⁴⁸ This protocol proved effective across a wide range of homopolymers and copolymers, including polystyrene (**7-12** and **7-13**) and polyolefins (**7-14**), affording azide-functionalized materials with high degrees of azide incorporation and minimal loss in molecular weight. Notably, the reaction is scalable to the gram level, underscoring its practicality and potential utility in polymer post-functionalization.

Notably, these two electrochemical C(sp³)-H azidation reactions employ anodic oxidation in place of hypervalent iodine reagents, thereby enhancing both the safety and chemoselectivity of the reaction.⁴⁹

2.2 Organo-electrocatalysts

Organo-electrocatalysts have attracted growing interest due to their ready availability, structural tunability, and simplified post-reaction handling.^{11h,m,15b} Their metal-free nature eliminates concerns about residual contamination, making them particularly appealing for pharmaceutical applications. In recent years, several classes of organic mediators have demonstrated high efficacy in promoting C(sp³)-H functionalization under electrochemical conditions.⁵⁰

2.2.1 DDQ. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has emerged as a versatile oxidant in organic synthesis, notable for its high reduction potential and well-defined redox behavior.⁵¹ DDQ exists in three accessible oxidation states: quinone, semiquinone, and hydroquinone (DDQH₂). The reduced form, DDQH₂, generated during oxidation processes, can be catalytically regenerated to DDQ through a sequential electron-proton transfer mechanism (Scheme 8a).⁵²

In 2003, Rozenberg and colleagues demonstrated the oxidative functionalization of benzylic C(sp³)-H bonds under DDQ electrocatalytic conditions in aqueous acetic acid (Scheme 8b).⁵² They proposed a mechanism involving the initial formation of the charge-transfer complex **8-3** between the aromatic substrate **8-1** and DDQ, followed by intramolecular proton transfer to generate the benzyl radical **8-4**. Subsequent electron transfer produces the benzyl cation **8-5**, which undergoes divergent reactivity depending on the solvent conditions: nucleophilic addition in protic media, yielding **8-8**, or coupling with **8-6** to form **8-7** in aprotic solvents. Further DDQ-mediated oxidation of **8-8** affords the target product **8-2**.

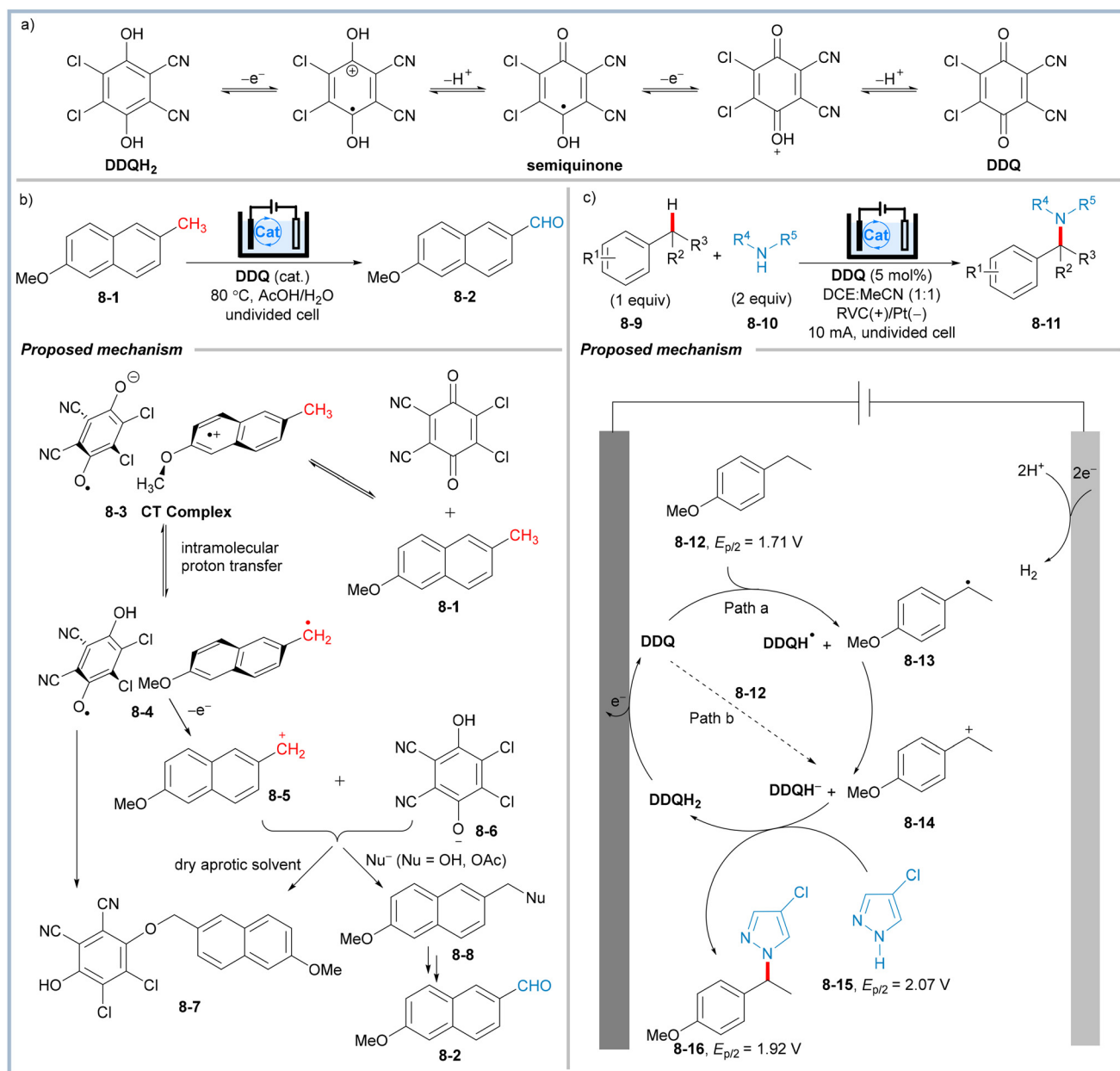
In 2021, Hou, Wang and coworkers reported the benzylic C(sp³)-H amination of electron-rich alkylarenes *via* DDQ redox electrocatalysis (Scheme 8c).⁵³ The transformation proceeds

through two possible pathways: (a) hydrogen atom transfer between alkylarenes and DDQ, generating the benzyl radical **8-13**, followed by oxidation to the benzyl cation **8-14** or (b) direct hydride transfer, leading to the formation of the benzyl cation **8-14**. The resultant benzyl cation then undergoes nucleophilic addition with pyrazoles, yielding the C(sp³)-H amination products.

2.2.2 Phenothiazine. Phenothiazine is an organic aromatic compound consisting of a sulfur atom and a nitrogen atom attached to two benzene rings.⁵⁴ These compounds exhibit strong absorption in the ultraviolet region that extends into the visible light spectrum. As a result, *N*-phenylphenothiazine derivatives are commonly employed as photoredox catalysts in organic synthesis.^{10,55}

Xu and colleagues pioneered the application of *N*-arylphenothiazines as electrocatalysts for the synthesis of nitrogen heterocycles through dehydrogenative annulation between *N*-allyl amides (**9-1**) and 1,3-dicarbonyl compounds (**9-2**) (Scheme 9).⁵⁶ Mechanistically, the process begins with anodic oxidation of the catalyst **PT-1** to its corresponding radical cation, coupled with the cathodic reduction of water to generate hydrogen and hydroxide ions. The hydroxide-mediated deprotonation of the 1,3-dicarbonyl compound **9-2** forms an electron-rich anion, which undergoes single-electron oxidation with the phenothiazine radical cation to generate the radical intermediate **9-5**. This intermediate then adds to *N*-allylamide **9-6**, forming the tertiary carbon radical **9-7**. Subsequent electrochemical oxidation generates a carbocation intermediate, which undergoes intramolecular nucleophilic attack by the adjacent carbonyl oxygen to form the cyclized oxonium intermediate **9-8**. This intermediate is then attacked by hydroxide to open the ring, affording the phenylamine intermediate **9-10**. When R⁴ is a methyl group, **9-10** undergoes base-promoted intramolecular dehydration to yield the tetrahydropyridine derivative **9-11**. In contrast, when R⁴ is a strongly electron-donating methoxy group, **9-10** is further oxidized to form the pyrrole product **9-12**. This substrate-dependent divergence enables selective access to structurally distinct nitrogen-containing scaffolds, including pyrroles (**9-13** to **9-15**) and tetrahydropyridines (**9-16** and **9-17**).

In 2022, Xu and colleagues further expanded the synthetic utility of phenothiazine (PT) catalysts by developing an electrochemical cyclopropanation strategy (**10-1** to **10-2**, Scheme 10).⁵⁷ This transformation employs a modified phenothiazine derivative, **PT-2**, as the redox mediator. Mechanistic studies revealed that the substrate-catalyst adduct **10-4**, detected by high-resolution mass spectrometry during electrolysis, serves as a key intermediate. These findings suggest that phenothiazine catalysts not only function as electron mediators but also directly participate in bond-forming processes through radical-radical coupling. In this dual role, **PT-2** facilitates the formation of the carbon radical **10-6** *via* electron transfer; **10-6** subsequently undergoes intramolecular cyclization to form the alkyl radical intermediate **10-7**, which undergoes radical-radical coupling with the phenothiazine radical cation to furnish the sulfur ylide intermediate **10-8**. Finally,



Scheme 8 DDQ-catalyzed electrochemical C(sp³)-H functionalization.

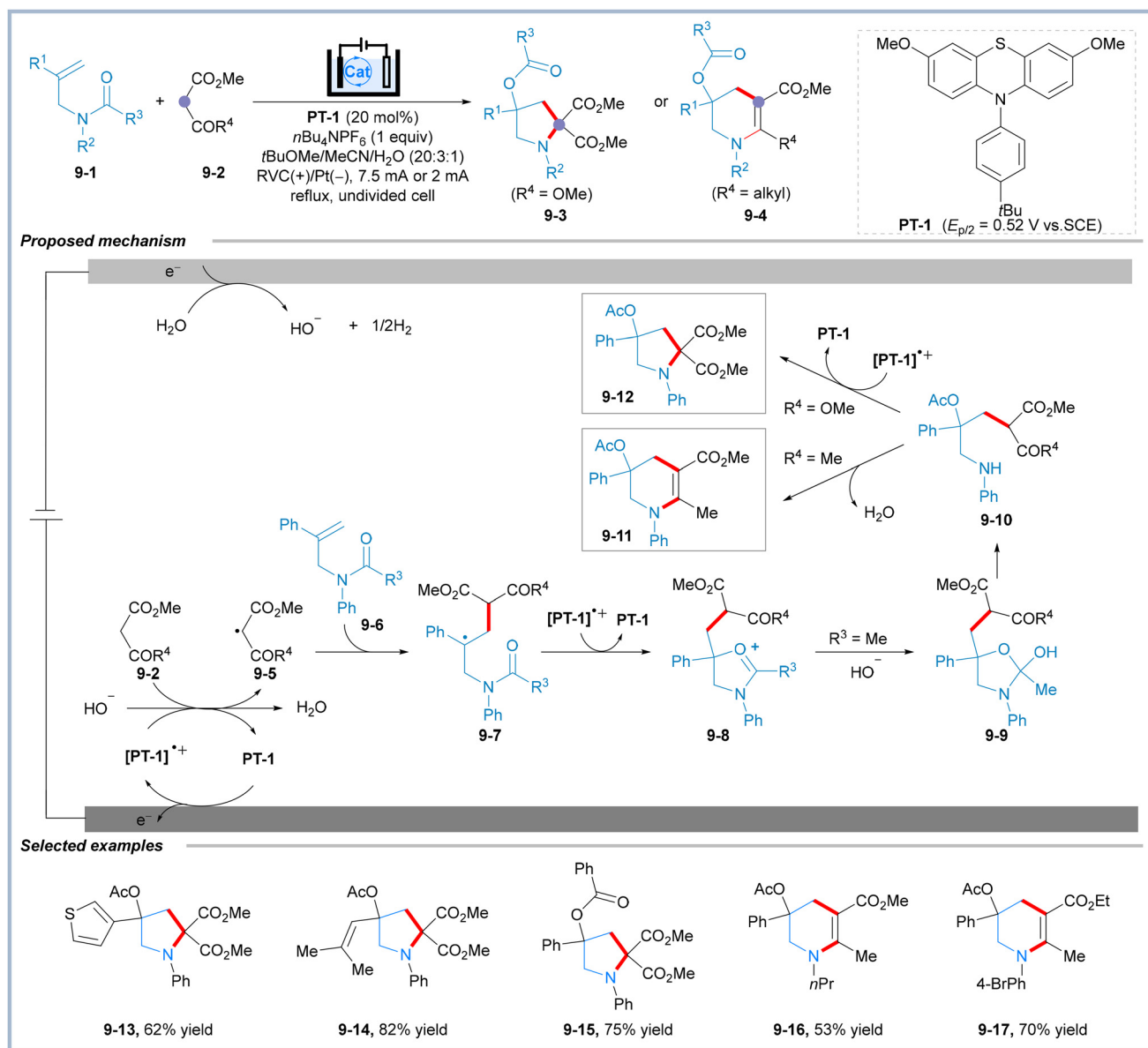
base-promoted nucleophilic attack by CF₃CH₂O⁻ triggers the extrusion of **PT-2**, delivering the target product **10-9** and regenerating the redox catalyst to complete the catalytic cycle. This methodology demonstrates remarkable substrate scope, accommodating various alkene substitution patterns, including mono-, di-, and tri-substituted systems (**10-10**, **10-11**, and **10-12**). The protocol tolerates heterocyclic substrates, such as unprotected amines (**10-11**), pyridines (**10-12**), and various cyclic frameworks, including lactams (**10-13**), lactones (**10-14**), and cyclohexanones (**10-15**).

2.2.3 N-Oxyl compounds. N-Oxyl compounds represent an important class of radical precursors, distinguished by their exceptional stability and well-defined reactivity, making them

highly effective for the selective oxidation of organic substrates.^{50,58} Representative reagents include *N*-hydroxyphthalimide (NHPI), (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO).

NHPI. *N*-Hydroxyphthalimide (NHPI) is a stable and easily accessible precursor to phthalimide *N*-oxyl (PINO). Under electrochemical conditions, NHPI undergoes deprotonation, followed by anodic single-electron oxidation to generate the catalytically active PINO radical (Scheme 11a).⁵⁹ This radical engages in hydrogen atom transfer (HAT) to activate C(sp³)-H bonds, enabling selective oxidative transformations.

The Stahl group developed an electrochemical protocol for benzylic C(sp³)-H iodination using NHPI as a redox mediator



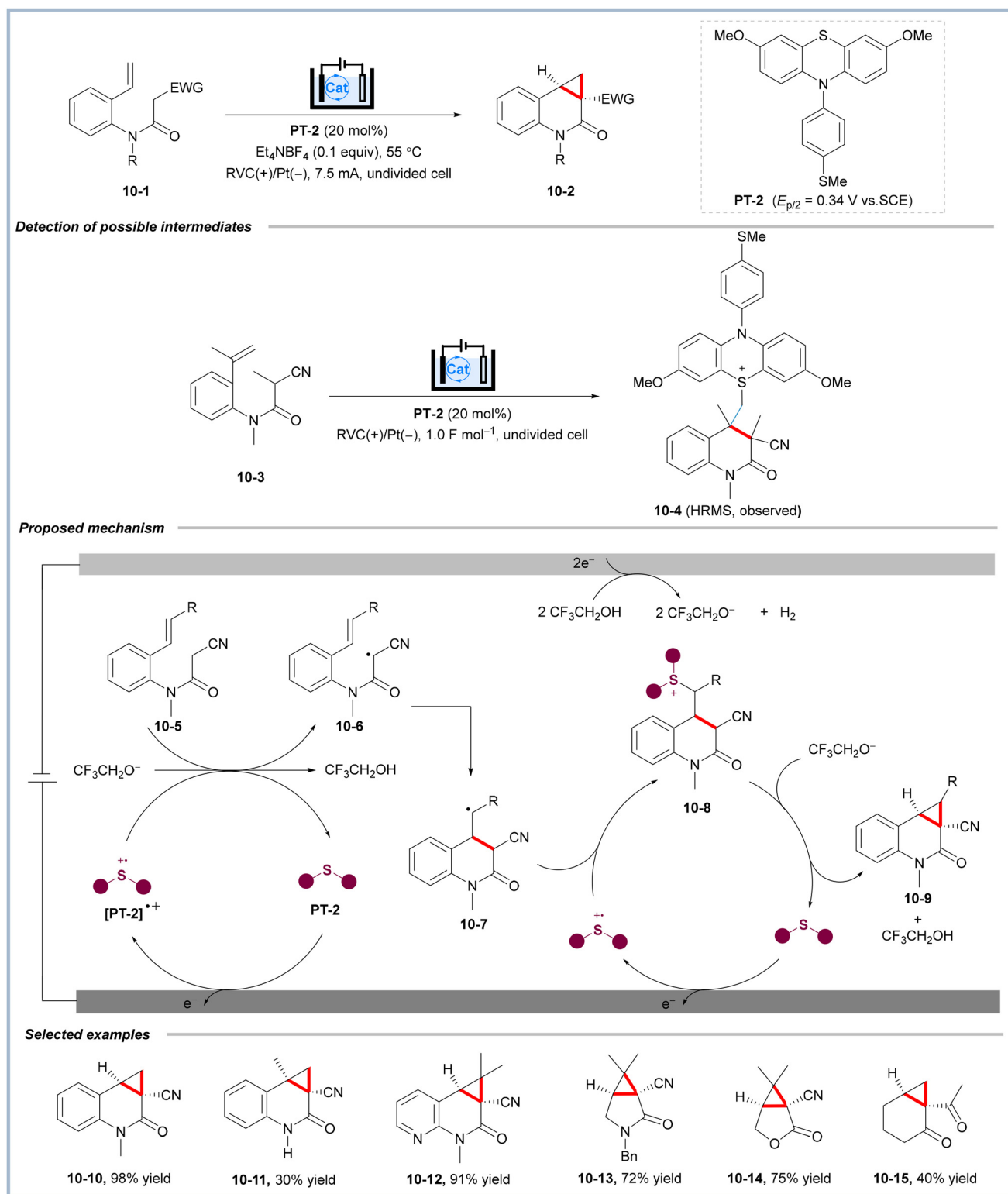
Scheme 9 Phenothiazine-catalyzed electrochemical dehydrogenative annulation of *N*-allyl amides with 1,3-dicarbonyl compounds.

(Scheme 11b).⁶⁰ Electrochemical oxidation of NHPI generates the phthalimide *N*-oxyl (PINO) radical, which abstracts a hydrogen atom from the benzylic substrate to form the benzyl radical **11-4**. This radical is trapped by molecular iodine to yield benzyl iodide **11-2**, which can undergo *in situ* nucleophilic substitution with pyridine to form the corresponding pyridinium salt **11-3**. Notably, PINO exhibits dual reactivity. As shown in Scheme 11c, stoichiometric NHPI in the presence of pyridine and PyHBF_4 enables direct trapping of benzyl radicals to afford benzyl PINOylation products (**11-5**).⁶¹ Structural modification of NHPI can further tune its redox properties. For instance, the Baran group demonstrated that the tetrachlorinated derivative Cl_4NHPI , which exhibits a higher oxidation potential than NHPI, enables efficient oxygenation of

allylic $\text{C}(\text{sp}^3)\text{-H}$ bonds in the presence of *t*BuOOH (Scheme 11d).⁶²

TEMPO. TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl is a prototypical *N*-oxyl radical, renowned for its exceptional redox reversibility.^{50,63} Under electrochemical conditions, TEMPO undergoes anodic oxidation to generate the corresponding oxoammonium species (**12-1**), which facilitates the transformation of amine substrates into iminium intermediates (**12-4**) *via* a sequence of single-electron oxidation, deprotonation, and further oxidation. This overall process closely resembles hydride abstraction (Scheme 12a).⁶⁴

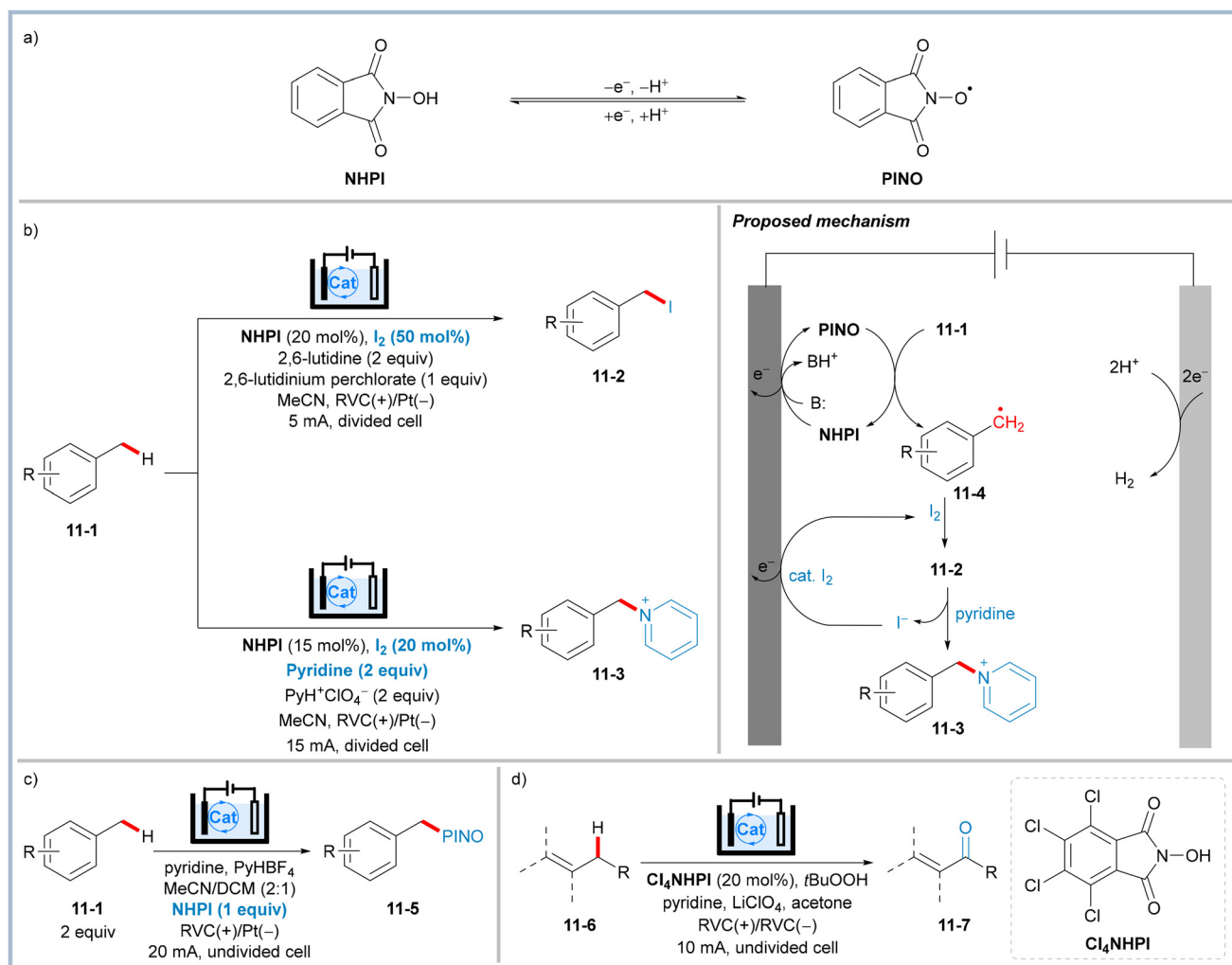
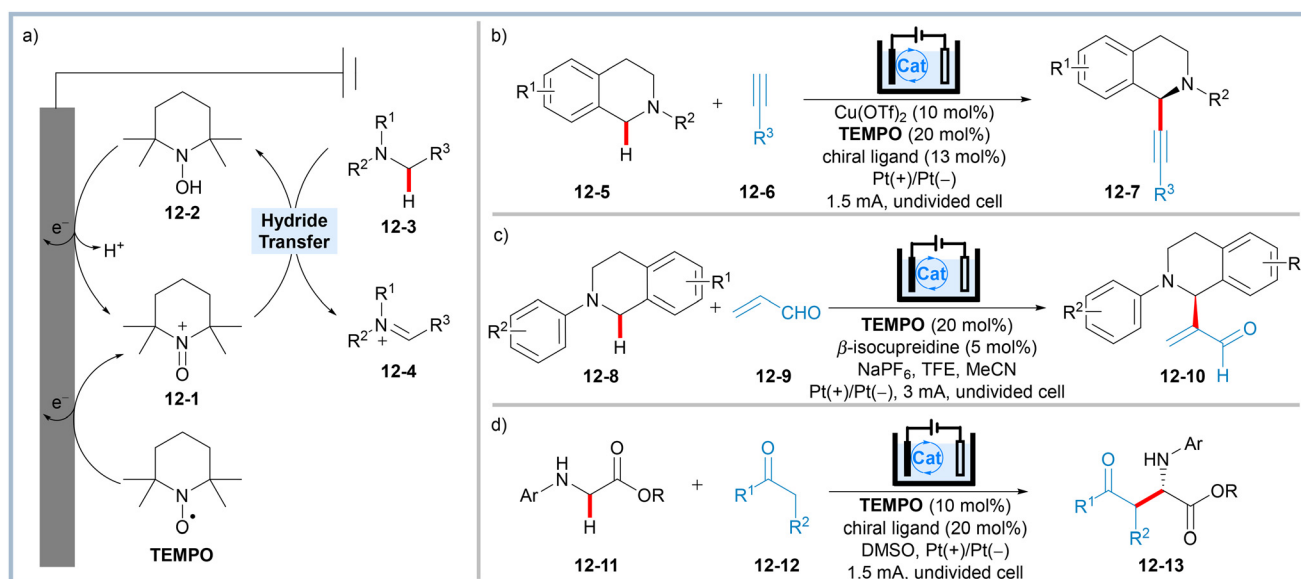
In 2020, Mei and co-workers developed an enantioselective $\alpha\text{-C}(\text{sp}^3)\text{-H}$ alkylation of cyclic tertiary amines using a dual catalytic system comprising TEMPO as a redox mediator and a



Scheme 10 Phenthiazine-catalyzed electrochemical cyclopropanation.

copper/chiral bisoxazoline complex for stereocontrol (Scheme 12b).⁶⁵ This electrocatalytic transformation proceeds efficiently in an undivided cell and enables the direct dehydrogenative coupling of tetrahydroisoquinolines (**12-5**) with term-

inal alkynes (**12-6**). Subsequently, Guo and colleagues extended this strategy to enantioselective alkenylation reactions of tetrahydroisoquinolines using chiral organic amines as catalysts (**12-8/12-9** to **12-10**, Scheme 12c).⁶⁶ Mei further expanded the

Scheme 11 NHPI/Cl₄NHPI-mediated electrochemical C(sp³)-H functionalization.Scheme 12 TEMPO-enabled electrochemical α-C(sp³)-H functionalization of amines.

substrate scope to include acyclic amines, enabling the asymmetric synthesis of α -amino acid derivatives under electrochemical conditions without the use of transition metals (12-11/12-12 to 12-13, Scheme 12d).⁶⁷ Collectively, these advances highlight the versatility of TEMPO-mediated electrochemical protocols in sustainable, enantioselective α -C(sp³)-H functionalization of amines.

ABNO. 9-Azabicyclo[3.3.1]nonane *N*-oxyl (ABNO) is a structurally distinct aminoxyl radical, whose exceptional stability arises from the rigid bicyclic framework that constrains the *N*-oxyl-adjacent carbon atoms in bridgehead positions (Scheme 13a).⁶⁸ In 2018, Stahl and co-workers developed an electrochemical protocol utilizing ABNO as a redox mediator for the selective α -C(sp³)-H cyanation of unprotected piperidines (13-1 to 13-2, Scheme 13b).⁶⁹ This transformation is particularly notable for its tolerance of free amines under electrochemical conditions. Mechanistically, ABNO is oxidized to oxoammonium species (13-3) at the anode, which facilitates

the generation of an iminium ion intermediate (13-5). Subsequent nucleophilic trapping with TMSCN affords the α -cyanated product 13-2.

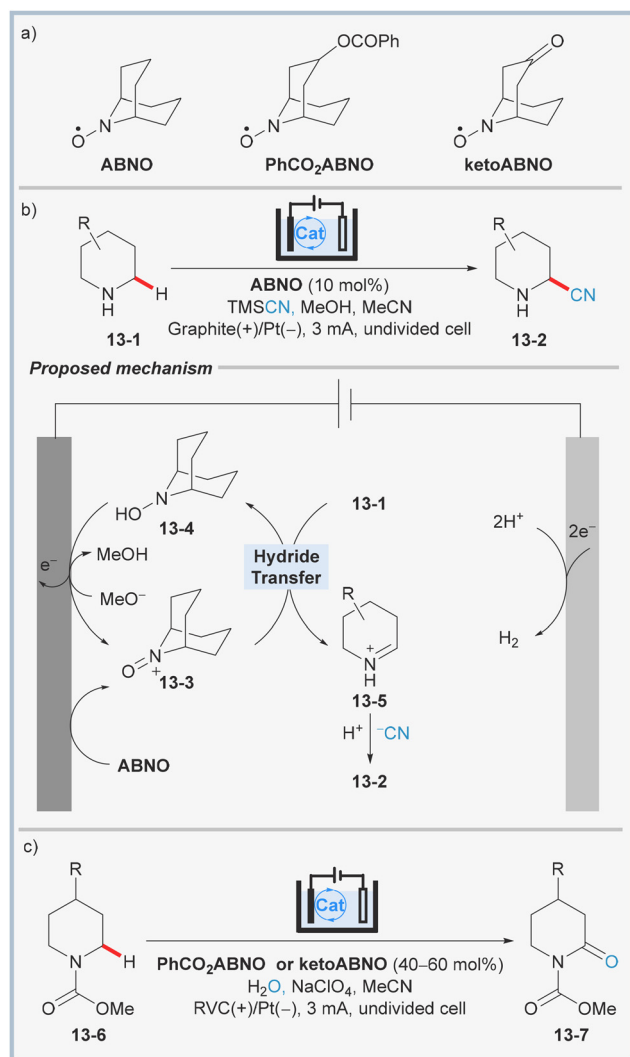
Furthermore, modified ABNO derivatives such as PhCO₂ABNO and ketoABNO have been applied as electrocatalysts for the oxidation of cyclic secondary amines (13-6) to lactams (13-7), using water as the terminal oxygen atom source, thereby broadening the scope of ABNO-mediated C(sp³)-H functionalization (Scheme 13c).⁷⁰

2.2.4 Halide salts. Halide ions are among the most fundamental and widely used classes of redox mediators. Their anodic oxidation furnishes electrophilic halogen species (e.g., Br₂ and I₂),⁷¹ which are instrumental in enabling diverse oxidative C(sp³)-H functionalization reactions through halogenation, substitution, or elimination pathways.⁷²

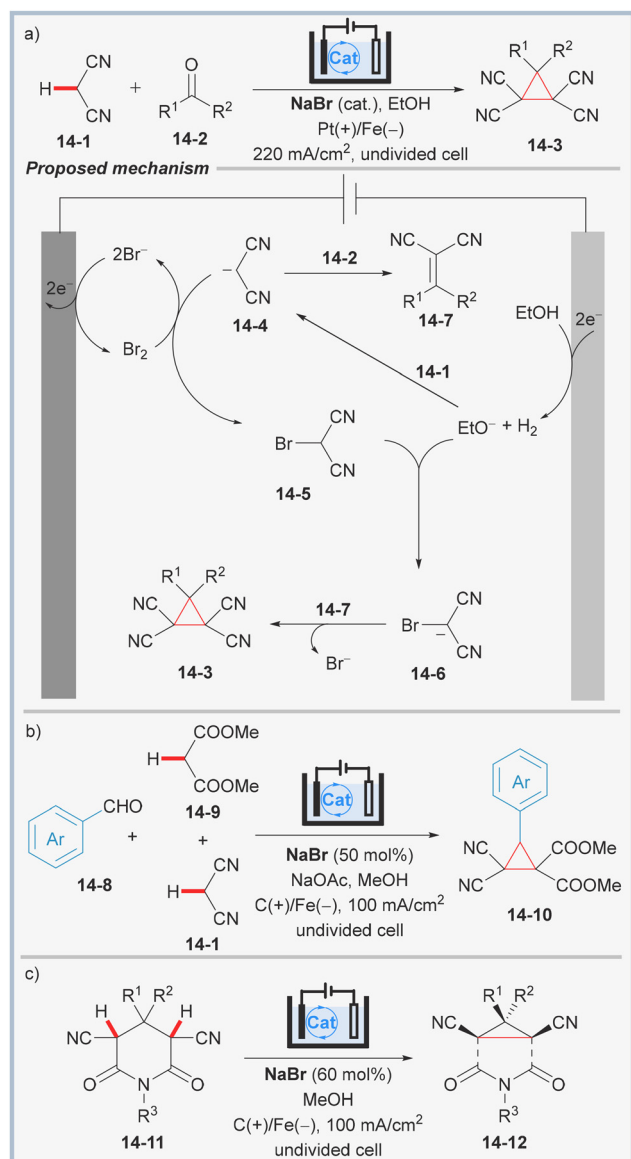
Bromide. Nikishin and colleagues demonstrated the electrocatalytic activity of bromide ions in facilitating the stereoselective synthesis of functionalized cyclopropanes from malononitrile and carbonyl substrates (14-1/14-2 to 14-3, Scheme 14a).⁷³ The mechanism begins with the anodic oxidation of bromide to generate molecular bromine, concurrent with the cathodic reduction of ethanol to ethoxide, accompanied by hydrogen evolution. The acidic malononitrile undergoes base-mediated deprotonation to form the corresponding carbanion 14-4. This nucleophile then undergoes electrophilic bromination to produce intermediate 14-5, which is further deprotonated to yield carbanion 14-6. Simultaneously, nucleophilic addition of carbanion 14-4 to the carbonyl electrophile generates the activated olefin 14-7. The reaction cascade concludes with an intramolecular cyclization between intermediates 14-7 and 14-6, forming the 1,1,2,2-tetracyanocyclopropane product 14-3. This strategy was extended to a three-component protocol involving aldehydes (14-8), malononitrile (14-1), and malonates (14-9) (Scheme 14b),⁷⁴ and further adapted to an intramolecular cyclization variant, enabling single-step cyclopropane construction (14-11 to 14-12, Scheme 14c).⁷⁵

Iodide. The Ren group developed a novel method for the electrochemically promoted α -C(sp³)-H amination of ketones, enabling the efficient and environmentally friendly synthesis of diverse α -amino ketones (15-1/15-2 to 15-3, Scheme 15a).⁷⁶ The reaction employed NH₄I as the redox catalyst. Mechanistic studies indicated that anodic oxidation of I⁻ generated I₂, which subsequently reacted with ketone 15-1 to form the key intermediate, α -iodo ketone 15-4. This intermediate then underwent nucleophilic substitution with amine 15-2 to yield the α -amino ketone product 15-3, along with the release of HI. Building on this strategy, Ren's group further extended the methodology to α -C(sp³)-H thiocyanation and sulfenylation of ketones.⁷⁷

In a mechanistically distinct approach, the Zeng group reported a cross-dehydrogenative coupling of arylglycine esters with C-H nucleophiles (electron-rich arenes and 1,3-dicarbonyl compounds) using tetrabutylammonium iodide as an electrocatalyst (15-5 to 15-6, Scheme 15b).⁷⁸ The reaction proceeds *via* the formation of an iodide intermediate (15-7), which



Scheme 13 ABNO-catalyzed electrochemical C(sp³)-H functionalization of cyclic amines.



Scheme 14 Bromide-catalyzed electrochemical $\text{C}(\text{sp}^3)\text{-H}$ functionalization.

undergoes intramolecular elimination with the loss of a molecule of HI to generate the intermediate **15-8**. Subsequent activation of the imine by acetic acid leads to the formation of an intermediate iminium (**15-9**), which then undergoes nucleophilic addition with C-H nucleophiles to furnish the C-C coupled product **15-6**.

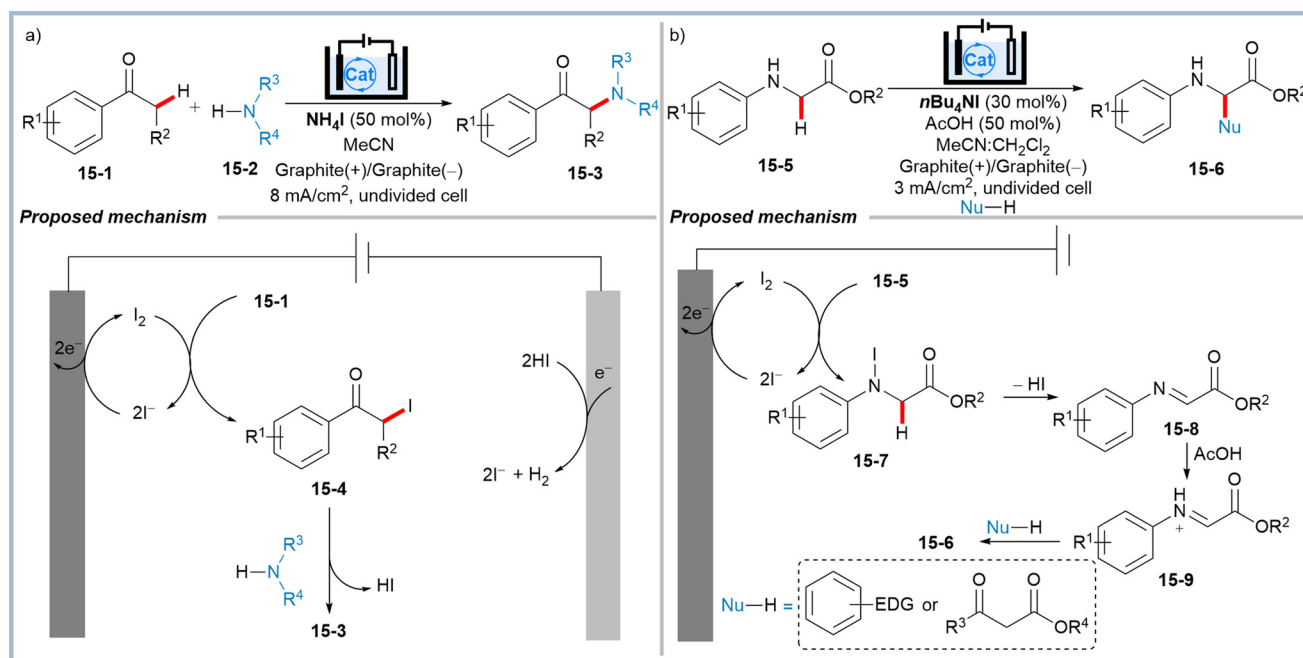
2.2.5 Benzimidazole. Benzimidazole derivatives, with a broad range of oxidation potentials (0.9–1.72 V vs. Ag/Ag^+) and high bond dissociation energies (92–116 kcal mol⁻¹), are attractive hydrogen atom transfer (HAT) mediators for electrochemical $\text{C}(\text{sp}^3)\text{-H}$ functionalization. Inspired by the work of the Lei group on N-centered radical-mediated electrochemical $\text{C}(\text{sp}^3)\text{-H}$ arylation,⁷⁹ Li, Zhang, and co-workers developed an electrochemical $\text{C}(\text{sp}^3)\text{-H}$ amination strategy employing benzimidazole derivatives as precursors to N-centered radicals (**16-1**

to **16-3**, Scheme 16).⁸⁰ In this reaction, benzimidazole **16-2** undergoes anodic oxidation *via* a proton-coupled electron transfer (PCET) process, assisted by a cathodically generated hexafluoroisopropanol anion, to form the key N-centered radical **16-5**. This radical abstracts a hydrogen atom from the substrate, generating a carbon-centered radical (**16-6**) and regenerating benzimidazole **16-4**. The carbon radical **16-6** is then oxidized at the anode to the carbocation **16-7**, which undergoes a Ritter-type reaction with acetonitrile to afford the amination intermediate **16-7**. Subsequent nucleophilic addition of **16-7** with benzimidazole furnishes the key intermediate **16-9**, which undergoes hydrolysis under acidic conditions to afford the aminated product **16-3**. This method exhibits a broad substrate scope, accommodating both electron-deficient (**16-10**) and electron-rich (**16-11**) ethylbenzenes. It is also compatible with other nitrile (**16-12**) and diverse $\text{C}(\text{sp}^3)\text{-H}$ (**16-13** and **16-14**) substrates, and has been successfully scaled up to gram quantities (**16-14**). However, the method is less effective for highly electron-rich substrates (**16-15**, **16-16**), which primarily yield trace amounts of azolation or oxidation products.

3 Molecular photoelectrocatalysis

Over the past decade, photocatalysis and electrocatalysis have emerged as powerful tools for sustainable redox transformations.^{10,11,81} However, each approach faces intrinsic limitations: photocatalysis often relies on stoichiometric oxidants or reductants to facilitate multi-electron processes, raising concerns regarding waste generation and sustainability, while electrocatalysis may suffer from overoxidation, poor chemoselectivity, or electrode passivation due to the uncontrolled accumulation of reactive radical intermediates at the electrode interface. To address these challenges, molecular photoelectrocatalysis has emerged as a promising strategy, merging photocatalysis and electrocatalysis into a synergistic platform that harnesses the complementary strengths of both methodologies.^{11k,82} In this dual activation mode, substrate activation is facilitated by the excited-state photocatalyst, while anodic oxidation facilitates photocatalyst regeneration. Concurrently, the cathodic half-reaction typically evolves molecular hydrogen as an environmentally benign byproduct. This integrated approach broadens the accessible redox window, obviates the need for sacrificial chemical oxidants or reductants, and enables highly selective $\text{C}(\text{sp}^3)\text{-H}$ functionalization under mild and sustainable conditions.

Despite these compelling advantages, the field received limited attention until 2019, when Xu,⁸³ Lambert⁸⁴ and Stahl⁸⁵ independently reported its application in radical transformations under photoelectrocatalytic conditions, representing the first modern examples. Since then, molecular photoelectrocatalysis has rapidly gained recognition as a powerful platform for achieving otherwise inaccessible oxidative and reductive transformations, particularly those involving inert $\text{C}(\text{sp}^3)\text{-H}$ bonds.^{15a,82,86}



Scheme 15 Electrochemical C(sp³)-H functionalization with an iodide catalyst. EDG = electron-donating group.

Mechanistically, C(sp³)-H activation *via* molecular photoelectrocatalysis proceeds through three principal pathways: single-electron transfer (SET), hydrogen atom transfer (HAT), and ligand-to-metal charge transfer (LMCT).^{82f} In the SET pathway, photoexcited catalysts oxidize substrates to generate radical intermediates that subsequently undergo functionalization. HAT pathways, mediated by either photoexcited species or electrochemically generated intermediates, enable direct abstraction of hydrogen atoms from unactivated C(sp³)-H bonds. LMCT pathways, which are characteristic of certain photoexcited transition metal complexes, involve ligand-to-metal charge transfer upon photoirradiation, generating transient metal-centered excited states and ligand-based radicals. These reactive species can enable selective C-H activation through pathways such as hydrogen atom transfer (HAT) or homolytic bond cleavage. Each mechanism offers distinct reactivity profiles and substrate compatibilities.

3.1 Photoelectrocatalytic C(sp³)-H functionalization *via* SET

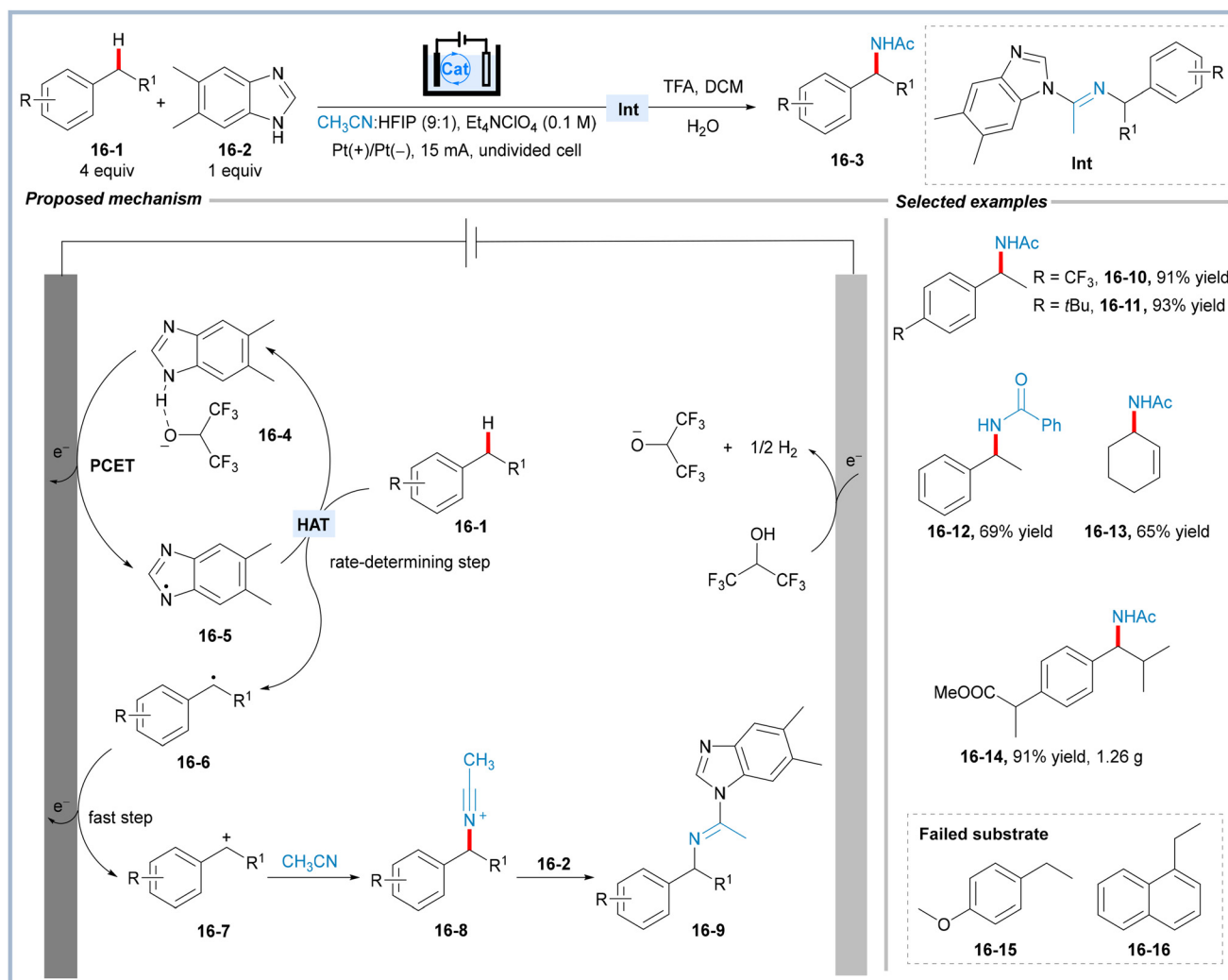
The single-electron transfer (SET) pathway typically exhibits high site-selectivity by preferentially targeting electron-rich C-H bonds. However, the activation of inert aliphatic C(sp³)-H bonds remains challenging due to the scarcity of photocatalysts with sufficiently high oxidative potentials. To address this, the Lambert group developed trisaminocyclopropenium ion (TAC⁺) as a potent photoelectrocatalyst (Scheme 17a).⁸⁴ TAC⁺ is a bench-stable white solid that undergoes electrochemical oxidation to generate the radical dication TAC^{•2+}. Upon photoexcitation, TAC^{•2+} forms an excited-state species, [TAC^{•2+}]*, possessing an exceptional excited-state reduction

potential of +3.33 V *vs.* SCE, which is capable of oxidizing otherwise inert C(sp³)-H bonds *via* SET.

Using this platform, the Lambert group reported a photoelectrocatalytic diamination of unactivated aliphatic C(sp³)-H bonds (17-1 to 17-2/17-3, Scheme 17b).⁸⁷ The transformation proceeds through carbocationic intermediates derived from sequential oxidation of adjacent C-H sites. The reaction outcome is governed by the choice of electrolyte: using tetraethylammonium tetrafluoroborate (Et₄NBF₄) provides 3,4-dihydroimidazoles (*e.g.*, 17-2), whereas using lithium perchlorate (LiClO₄) leads to 2-oxazolines (*e.g.*, 17-3). The protocol demonstrates broad functional group compatibility and has been successfully applied to the late-stage functionalization of complex bioactive molecules, such as 17-4 and 17-5. In the case of 4-methylisopropylbenzene, the reaction afforded the desired diamination product (17-6) in 51% yield, accompanied by a minor Ritter-type byproduct (11%).

Building on this foundation, the same group subsequently developed a Ritter-type benzylic C(sp³)-H amination protocol under TAC⁺-catalyzed photoelectrocatalytic conditions, converting 17-7 to 17-8 (Scheme 17c).⁸⁸

More recently, the Lambert group extended the utility of this platform to enable multiple, site-selective oxygenations of adjacent C(sp³)-H bonds (17-12/17-13, Scheme 17d).⁸⁹ The transformation involves stepwise oxidation to form carbocation intermediates, followed by olefin elimination and nucleophilic trapping. The use of specific acid additives and nucleophiles enables precise control over the sequential oxygenation of multiple adjacent C(sp³)-H bonds (17-16 to 17-21). This process tolerates diverse functional groups including heterocycles (17-22 and 17-23) and amides (17-24). Notably, the



Scheme 16 Benzimidazole as a hydrogen atom transfer mediator in electrochemical C(sp³)-H amination.

method enables eight- to twelve-electron oxidations in a single operation, affording tetrafunctionalized (**17-25**), pentafunctionalized (**17-26**), and even hexafunctionalized (**17-27**) products. Such high-order oxidative transformations remain an exceptional synthetic challenge and, to date, have otherwise only been realized in biosynthetic pathways.⁹⁰

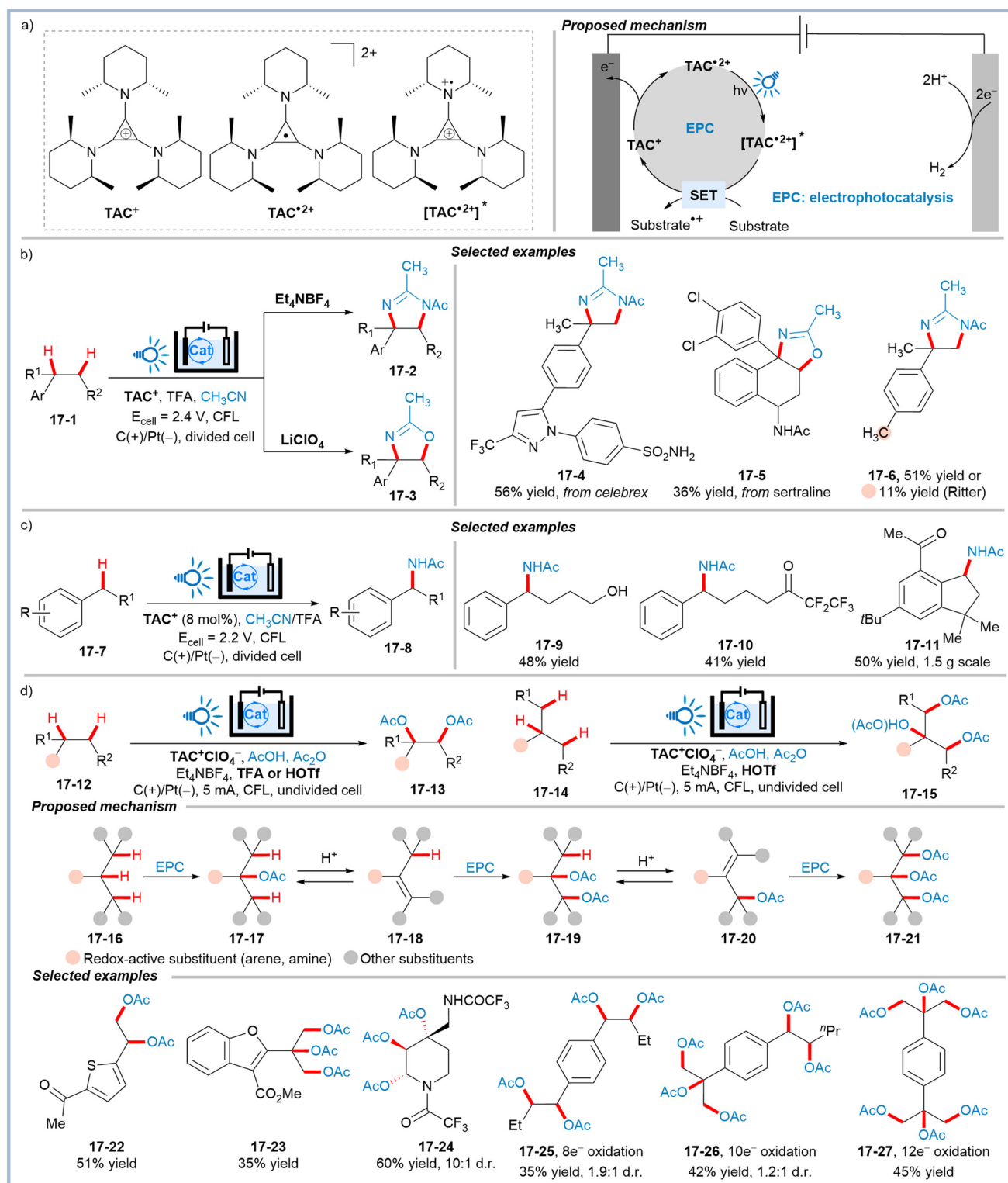
3.2 Photoelectrocatalytic C(sp³)-H functionalization via HAT

Hydrogen atom transfer (HAT) is a powerful strategy for generating relatively stable alkyl radicals from aliphatic C(sp³)-H bonds. Within the context of photoelectrocatalysis, HAT processes can be induced either through electrochemically generated halogen species or *via* photoexcited-state catalysts, offering distinct mechanistic avenues for radical generation and C-H functionalization.

3.2.1. HAT via halogen-mediated processes. In 2019, Stahl and co-workers reported a photoelectrocatalytic Hofmann-Löffler-Freytag-type (HLF-type) reaction for intramolecular C(sp³)-H amination of sulfonamide (**18-1**) and imidate (**18-3**),

using tetrabutylammonium iodide (TBAI) as a halide mediator under mild conditions (Scheme 18a).⁸⁵ Mechanistically, electrochemical oxidation of iodide at a low potential (0.5–0.7 V vs. Fc⁺/Fc) generates I₂, which subsequently forms an N-I intermediate (**18-6**) with the *N*-alkyl sulfonamide substrate **18-5**. Upon photoirradiation, homolysis of the N-I bond affords an amidyl radical, which undergoes intramolecular 1,5-HAT to selectively generate an alkyl radical. This carbon-centered radical is subsequently trapped by I₂ to form an alkyl iodide intermediate (**18-7**), which undergoes base-promoted nucleophilic substitution with nitrogen nucleophile, releasing iodide (I⁻) and completing the catalytic cycle.

In 2020, the Xu group reported a photoelectrocatalytic C(sp³)-H heteroarylation protocol, leveraging chloride as a halogen mediator (**18-9/18-10** to **18-11**, Scheme 18b).^{72c} Mechanistically, electrochemical oxidation of Cl⁻ produces Cl₂ *in situ*, which is homolyzed under 392 nm LED irradiation to form Cl[•] radicals. These highly reactive species abstract hydrogen atoms from a broad range of C(sp³)-H substrates to yield

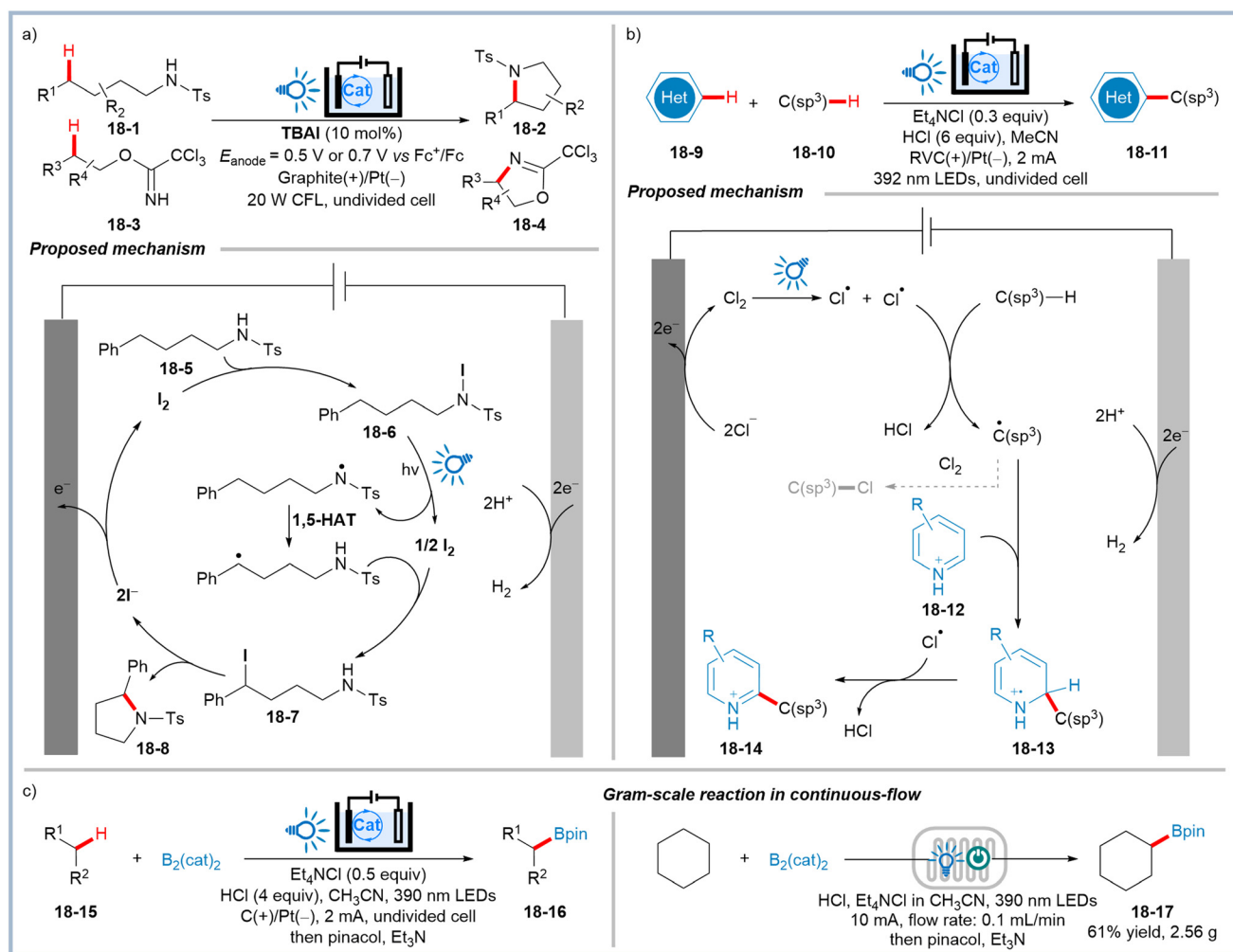


Scheme 17 Photoelectrocatalyzed C(sp³)-H functionalization via TAC⁺-mediated SET processes.

alkyl radicals, which subsequently undergo radical substitution with heteroarenes to furnish heteroarylated products (18-14). Importantly, the continuous photoelectrochemical generation of low concentrations of Cl₂ circumvents the use of

hazardous gaseous chlorine and minimizes the formation of undesired alkyl chloride byproducts.

In 2023, Xia and co-workers extended this photoelectrocatalytic chlorine-radical-mediated HAT strategy to achieve C(sp³)-



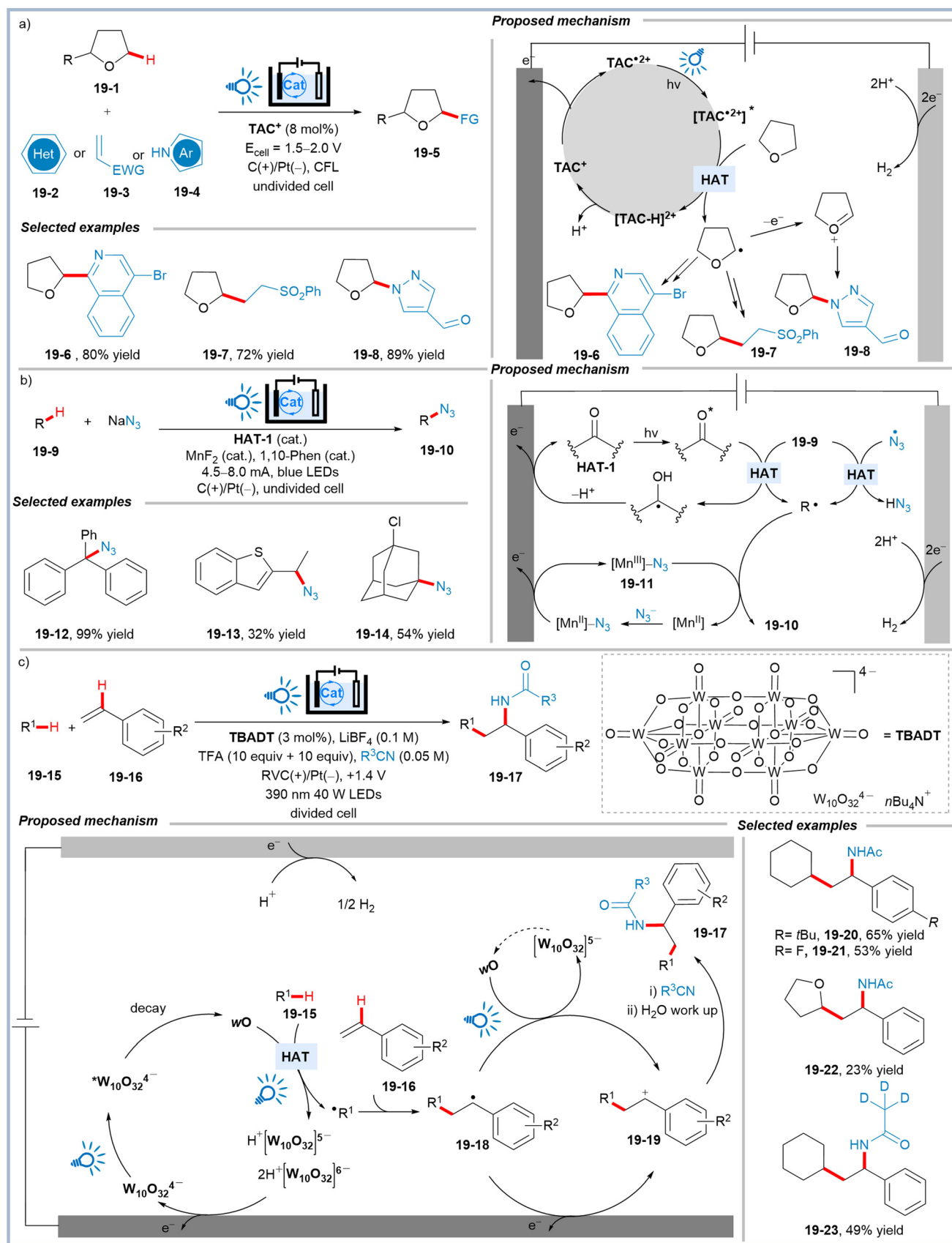
Scheme 18 Photoelectrocatalyzed $C(sp^3)$ -H functionalization via halogen-mediated HAT processes.

H borylation (18-15 to 18-16, Scheme 18c).⁹¹ The system employs $B_2(cat)_2$ as the boron source and leverages photoelectrochemically generated chlorine radicals to abstract hydrogen atoms from aliphatic C-H bonds, forming carbon-centered radicals that undergo C-B bond formation with $B_2(cat)_2$. The protocol was successfully implemented in a continuous-flow photoelectrochemical reactor, enabling gram-scale synthesis of borylated products (18-17).

3.2.2. HAT via excited-state photocatalysis. TAC^+ can serve not only as a single-electron transfer (SET) oxidant but also as an efficient hydrogen atom transfer (HAT) catalyst under photoelectrocatalytic conditions. In 2020, the Lambert group demonstrated that the photoexcited radical dication $[TAC^{*2+}]^*$ acts as a powerful HAT acceptor, enabling regioselective $C(sp^3)$ -H functionalization of ethers (Scheme 19a).⁹² In these reactions, $[TAC^{*2+}]^*$ selectively abstracts hydrogen atoms from the α -position of ethers (18-1) to generate carbon-centered radicals, which can undergo diverse downstream transformations. These include Minisci-type additions to isoquinolines (18-2), conjugate additions to electron-deficient olefins (18-3), and oxidative couplings with azoles (18-4). This strategy enables multiple $C(sp^3)$ -H

functionalization pathways, highlighting the versatility and synthetic utility of TAC^+ -based photoelectrocatalysis.

In the same year, Lei and co-workers reported a photoelectrocatalytic $C(sp^3)$ -H azidation protocol using aryl ketones or 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) as a photoelectrocatalyst (18-9 to 18-10, Scheme 19b).⁹³ Upon irradiation, **HAT-1** is excited to a photoactive state capable of abstracting hydrogen atoms from aliphatic $C(sp^3)$ -H bonds, thereby generating carbon-centered radicals. The **HAT-1** catalyst is subsequently regenerated through anodic oxidation, completing a redox-neutral cycle. Concurrently, anodic oxidation of sodium azide (NaN_3) produces azide radicals (N_3^{\cdot}), which can engage in HAT from $C(sp^3)$ -H bonds. Meanwhile, azide anions (N_3^-) can coordinate with $Mn(II)/L$ complexes (where L denotes ligands such as 1,10-phenanthroline or acetate), which are subsequently anodically oxidized to furnish electrophilic $Mn(III)/L-N_3$ species (18-11). These $Mn(III)$ -azide complexes act as key azide transfer agents that efficiently trap carbon-centered radicals to deliver the desired azidated products (18-10). An alternative pathway involves the interception of N_3^{\cdot} by $Mn(II)/L$ species to form the same $Mn(III)/L-N_3$ intermediate. Notably,

Scheme 19 Photoelectrocatalyzed C(sp³)-H functionalization via excited-state photocatalyst-mediated HAT processes.

this method effectively functionalizes oxidation-sensitive tertiary benzylic (e.g., **19-12**) and aliphatic (e.g., **19-14**) C(sp³)-H bonds.

In 2024, Barham, Tian, and co-workers reported a carboxamidation of styrenes by merging tetrabutylammonium decatungstate (TBADT) photocatalysis with electrochemical oxidation (**19-15/19-16** to **19-17**, Scheme 19c).⁹⁴ Mechanistically, inert alkanes are activated *via* TBADT-mediated hydrogen atom transfer (HAT), with the photocatalyst electrochemically regenerated from its reduced form through anodic oxidation. Notably, the unique radical-polar crossover reactivity accessible under photoelectrochemical conditions enables radical intermediates to undergo further oxidation (**19-18** to **19-19**), thereby addressing a key limitation of previous TBADT-based photocatalytic systems, which were largely restricted to monofunctionalization.⁹⁵ This strategy effectively activated a broad range of hydrocarbons (e.g., **19-20** and **19-22**), whose carbon-centered radicals added to diverse alkene partners (e.g., **19-20** and **19-21**).

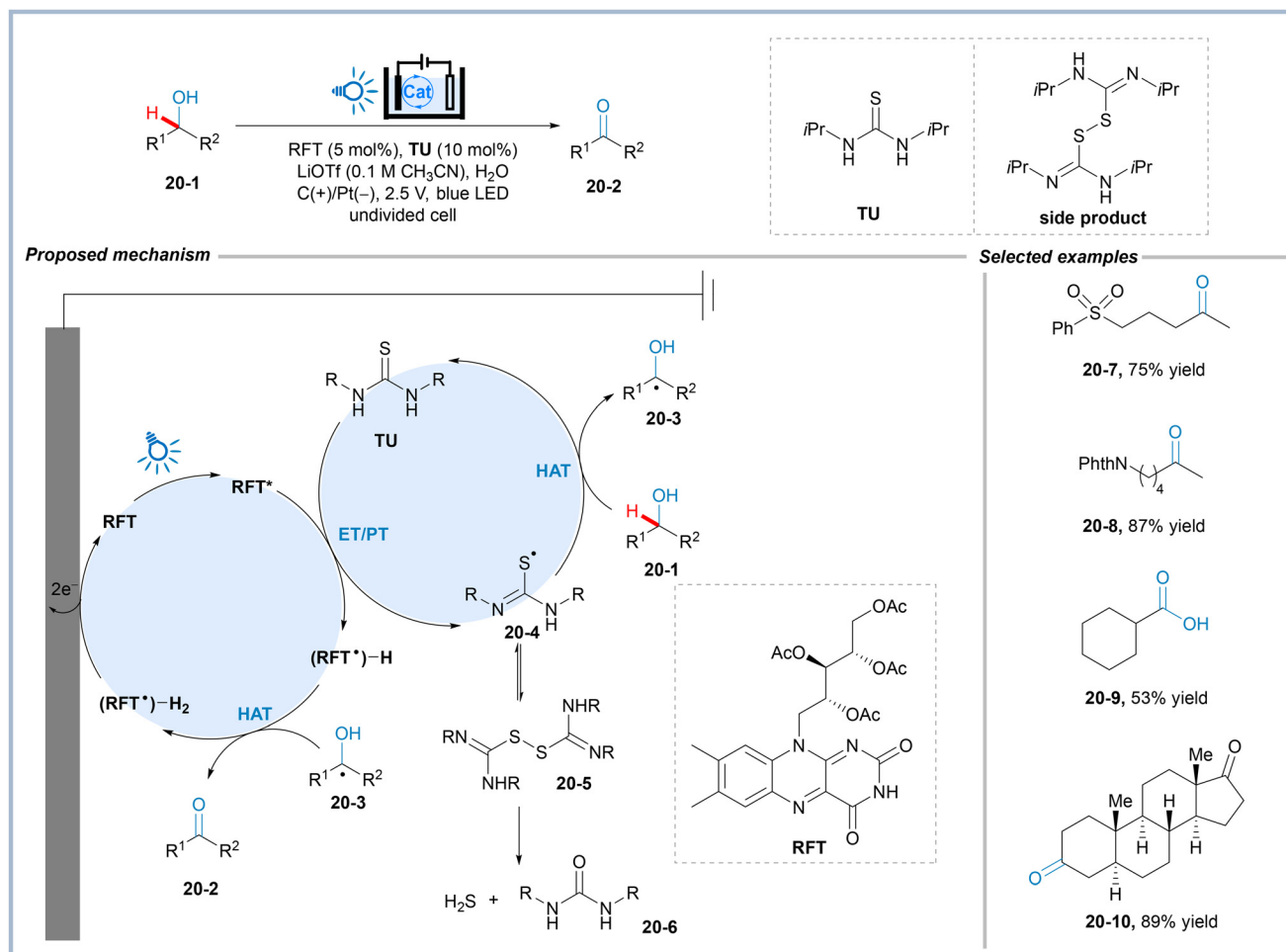
3.2.3. HAT *via* dual catalysis: RFT/thiourea synergistic system. Riboflavin tetraacetate (RFT) is a readily accessible photocatalyst with an excited-state oxidation potential of +1.67 V *vs.* SCE under photoirradiation. Owing to this redox prop-

erty, RFT and its derivatives have been widely employed in photocatalytic aerobic oxidation reactions.⁹⁶

In 2020, Lin and co-workers developed a photoelectrochemical oxidation protocol that expanded the application of flavin photocatalysis to the oxidation of unactivated aliphatic alcohols (**20-1** to **20-2**, Scheme 20).⁹⁷ This strategy proceeds without the need for oxygen or external oxidants and avoids the generation of H₂O₂ byproducts. These advancements not only broaden the substrate scope (e.g., **20-7**, **20-8**, **20-9**, and **20-10**) but also unveil new mechanistic insights.⁹⁸ In this thiourea-assisted system, the photoexcited RFT (RFT*) oxidizes thiourea (TU) through an electron-proton transfer sequence to form a thiyl radical (**20-4**), along with the reduced flavin (RFT*)-H. The thiyl radical abstracts a hydrogen atom from the alcohol **20-1** to generate the α -hydroxyalkyl radical **20-3** and regenerate TU.

3.3 Photoelectrocatalytic C(sp³)-H functionalization *via* LMCT

Photoelectrocatalytic ligand-to-metal charge transfer (LMCT) leverages inner-sphere electron transfer, which is inherently compatible with ultrashort excited-state lifetimes.⁹⁹ This feature allows for highly efficient and rapid substrate acti-



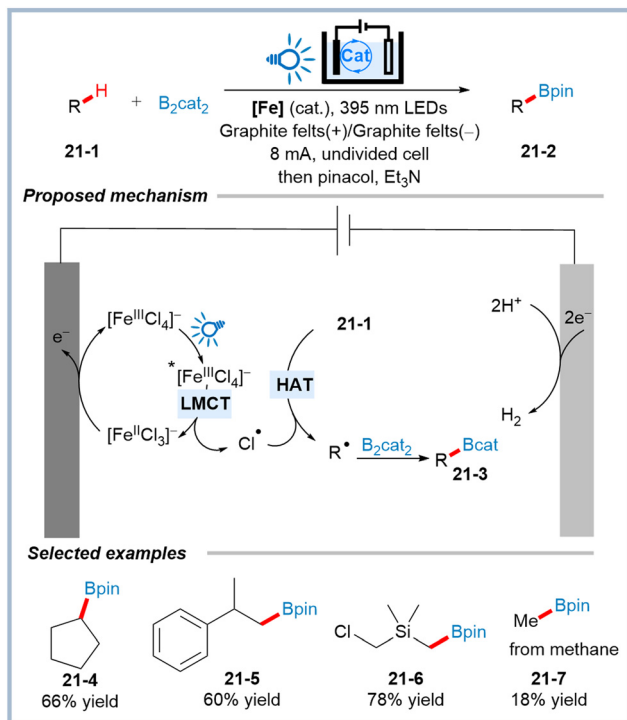
Scheme 20 Thiourea-mediated photoelectrocatalytic oxidation of unactivated aliphatic alcohols.

vation, positioning LMCT as a powerful and increasingly studied strategy in photocatalysis. Recent studies have demonstrated that photoelectrocatalytic LMCT can enable the selective activation of abundant functional groups under mild, oxidant-free conditions.¹⁰⁰ For instance, Xu¹⁰¹ and Fu¹⁰² applied cerium-based LMCT catalysis to promote decarboxyla-

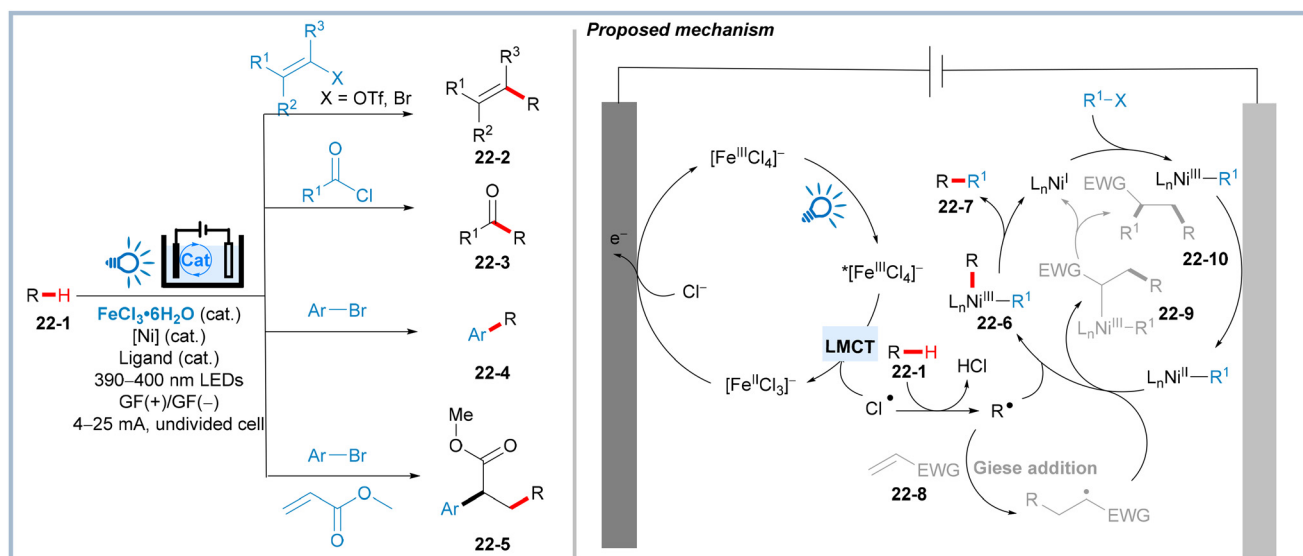
tive alkylation reactions. Zeng extended this strategy to the activation of Si-H bonds,¹⁰³ while Lei developed a Ce-LMCT system for the activation of alcohols.¹⁰⁴

In the context of C(sp³)-H activation, a representative example of LMCT-enabled C(sp³)-H functionalization is the iron-catalyzed photoelectrocatalytic borylation of unactivated alkanes reported by Lu and co-workers (Scheme 21).¹⁰⁵ In this system, electrochemical oxidation of [Fe^{II}Cl₃]⁻ generates the [Fe^{III}Cl₄]⁻ complex, which undergoes ligand-to-metal charge transfer (LMCT) under the irradiation of blue LEDs, resulting in homolytic cleavage of the Fe-Cl bond to produce a chlorine radical (Cl[•]). The Cl[•] species initiates a hydrogen atom transfer (HAT) process with the C(sp³)-H substrate (21-1), generating a carbon-centered radical that is subsequently intercepted by B₂cat₂ to afford the borylated product (21-3).

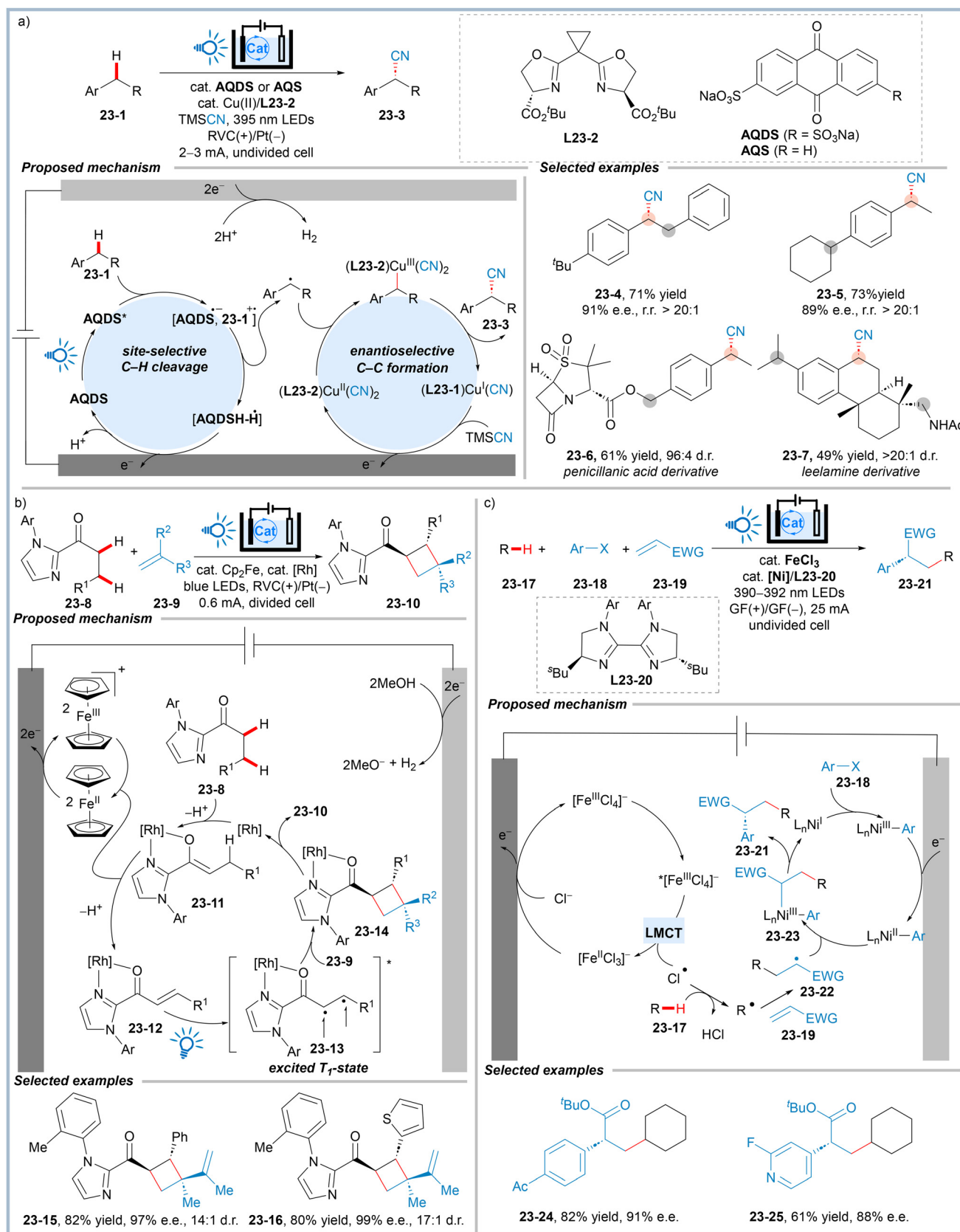
Building on the iron-catalyzed LMCT strategy for chlorine radical-mediated C(sp³)-H activation, Lu and co-workers developed a unified photoelectrocatalytic platform that merges LMCT with nickel cross-coupling catalysis to enable diverse C(sp³)-H functionalization reactions (Scheme 22).¹⁰⁶ In these transformations, anodic photoelectrocatalysis initiates C(sp³)-H activation *via* LMCT-mediated HAT from aliphatic C-H bonds (22-1), generating alkyl radicals. These radicals are intercepted by a variety of electrophilic nickel intermediates generated at the cathode, including L_nNi^{III}-R¹ species derived from aryl, alkenyl, or acyl halides. The resulting cross-coupling furnishes C(sp³)-C(sp²) bonds in products such as alkylated olefins (22-2), ketones (22-3), and arylated products (22-4). Additionally, the alkyl radicals can undergo Giese-type addition to electron-deficient alkenes, followed by nickel-catalyzed cross-coupling to furnish three-component products (22-5). This paired electrocatalysis design exploits the distinct redox properties of Fe and Ni: anodic oxidation mediates the Fe^{II}/Fe^{III} cycle, while cathodic reduction activates Ni^I/Ni^{III} intermediates.



Scheme 21 Photoelectrocatalyzed C(sp³)-H borylation *via* Fe-mediated LMCT processes.



Scheme 22 Photoelectrocatalyzed C(sp³)-H functionalization *via* Fe/Ni catalysis under paired electrolysis conditions.



Scheme 23 Photoelectrochemical asymmetric catalysis.

These systems thus enable efficient redox-neutral cross-coupling under mild, oxidant-free conditions, offering a versatile and sustainable platform for C(sp³)-H functionalization.

3.4 Photoelectrochemical asymmetric catalysis

The merger of molecular photoelectrocatalysis with asymmetric catalysis has given rise to a new paradigm in stereoselective synthesis—photoelectrochemical asymmetric catalysis (PEAC).^{11J} This strategy harnesses the controlled generation of radical intermediates *via* photoexcitation while leveraging electrochemical redox control to sustain catalytic turnover without stoichiometric oxidants or reductants. Importantly, the incorporation of chiral catalysts within the photoelectrocatalytic platform enables precise spatial and stereochemical control, facilitating highly enantioselective transformations under mild and sustainable conditions.

In 2022, Xu and co-workers reported a pioneering example of PEAC for enantioselective benzylic C(sp³)-H cyanation (23-1 to 23-3, Scheme 23a).¹⁰⁷ The reaction utilizes AQS or AQDS as a photoelectrocatalyst, in combination with a copper catalyst bearing the chiral ligand L23-2. This transformation relies on two key catalytic cycles: (1) a photoelectrocatalytic C(sp³)-H activation cycle mediated by AQDS: the photoexcited AQDS* undergoes electron transfer with the alkylbenzene substrate 23-1, generating an ion-radical pair [AQDS^{•-}, 23-1^{•+}]. This is followed by a proton transfer step to produce the benzylic radical; and (2) an enantioselective C-C bond-forming cycle catalyzed by copper: the benzylic radical then reacts with the chiral copper(II) complex [(L23-2)Cu^{II}(CN)₂] to generate a copper(III) intermediate, which undergoes enantio-determining reductive elimination to form the chiral benzylic nitrile product 23-3.

Notably, the electron-withdrawing sulfonate groups on AQDS increase its reduction potential, favoring a sequential electron-proton transfer pathway over direct hydrogen atom transfer. This mechanistic feature imparts high site-selectivity, enabling preferential activation of the most electron-rich and sterically accessible benzylic C-H bonds. As a result, this strategy achieves highly site-selective asymmetric cyanation in complex molecular scaffolds. For instance, both penicillanic acid (23-6) and leelamine derivatives (23-7), which contain multiple benzylic C-H sites, undergo regio- and enantioselective C-H cyanation at the most electronically and sterically favorable position under PEAC conditions.

Independently, Liu, Wang, and co-workers developed a similar PEAC protocol for benzylic C(sp³)-H cyanation,¹⁰⁸ which eliminated the need for stoichiometric N-F reagents and significantly broadened the substrate scope compared to their earlier oxidant-based strategy.¹⁰⁹

In 2023, Meggers and co-workers disclosed a photoelectrochemical asymmetric dehydrogenative [2 + 2] cycloaddition of alkyl ketones (23-8) and alkenes (23-9) (Scheme 23b).¹¹⁰ This transformation was enabled by cooperative catalysis between ferrocene (Cp₂Fe) and a chiral-at-metal Rh(III) complex.

The reaction begins with coordination and deprotonation of the ketone to generate a Rh-bound enolate intermediate (23-

11), which undergoes electrochemical oxidation by ferrocenium (Cp₂Fe⁺) to form a Rh-coordinated enone species (23-12). Upon photoexcitation, this enone intermediate accesses a triplet excited state that engages in an enantioselective [2 + 2] cycloaddition with olefin (23-9), furnishing the chiral cyclobutane product 23-10. Remarkably, this method enables the direct synthesis of enantioenriched cyclobutanes bearing up to four contiguous stereocenters from simple ketone precursors.

Most recently, Lu and co-workers developed a photoelectrochemical enantioselective three-component alkylarylation of olefins (Scheme 23c),¹¹¹ employing an iron/nickel dual catalytic system. The reaction is initiated by light-induced ligand-to-metal charge transfer (LMCT) from an [Fe^{III}Cl₄]⁻ complex to generate a chlorine radical, which abstracts a hydrogen atom from the C(sp³)-H precursor 23-17 to form an alkyl radical. This radical undergoes Giese-type addition to an electron-deficient alkene (23-19), followed by nickel-catalyzed asymmetric cross-coupling with an aryl halide (23-18) to yield the alkylarylation product 23-21 with high yield and enantioselectivity. The use of a chiral bisoxazoline ligand (L23-20) enables stereocontrol in the nickel-catalyzed C-C bond-forming step. This work showcases the power of merging LMCT-driven HAT with nickel-catalyzed enantioselective cross-coupling under paired electrolysis, providing a general and sustainable strategy for multicomponent enantioselective C(sp³)-H functionalization. In contrast, photochemical methods can also accomplish related transformations using TBADT or diaryl ketone photocatalysts in combination with nickel-catalyzed radical relay processes.¹¹² However, photochemical approaches typically require lower temperatures (5 °C) and higher equivalents of olefins.

4 Conclusions

Molecular electrocatalysis has become a powerful and sustainable strategy for C(sp³)-H bond functionalization by enabling precise control over redox events without the need for stoichiometric oxidants or reductants. Recent advances in both transition metal-based and metal-free catalysts have facilitated a broad range of electrochemical C(sp³)-H transformations, such as oxidation, amination, alkylation, and borylation, under mild and environmentally benign conditions. The merger of electrocatalysis with photocatalysis has further broadened the synthetic scope and improved selectivity by enabling new modes of radical generation and accessing reactivity profiles not achievable by either method alone.

Despite these advances, current methodologies remain largely limited to the functionalization of benzylic, allylic, α -heteroatom, or α -carbonyl C(sp³)-H bonds, which are inherently more reactive. The selective activation of simple and unactivated C(sp³)-H bonds remains a major challenge, particularly when high levels of regioselectivity and enantioselectivity are required. Furthermore, many protocols depend on high catalyst loadings and employ catalysts or mediators that are difficult to recover, recycle, or scale. Overcoming these

challenges will require the development of recyclable heterogeneous electrocatalysts, surface-modified electrode materials, and tunable redox mediators with improved efficiency. Additionally, integrating electrochemistry with biocatalysis *via* electroenzymatic approaches offers a promising route to achieve regio- and enantioselective functionalization of inert C(sp³)-H bonds through active-site engineering and mediator tuning.¹¹³ Future efforts can focus on engineered enzymes or artificial metalloenzymes coupled with tailored redox mediators to improve selectivity in complex transformations. A deeper mechanistic understanding will also be essential to guide rational catalyst design and enable predictive control over selectivity. In addition, innovations in electrochemical reactor engineering that support scalable and continuous operation will be critical for translating these methodologies into practical applications in complex molecule synthesis and industrial production.

Conflicts of interest

There are no conflicts to declare.

Data availability

This is a review article with no new data. All the compounds have been reported previously.

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