Electrophotocatalytic hydroxymethylation of azaarenes with methanol

Beatriz Quevedo-Flores, Irene Bosque,* Jose C. Gonzalez-Gomez*

Instituto de Síntesis Orgánica (ISO) and Departamento de Química Orgánica, Universidad de Alicante, 03080, Spain.

Supporting Information Placeholder

- ✓ Redox-selectivity
- ✓ readily available catalysts
- ✓ Chemical oxidant-free
- ✓ Mild & sustainable reaction conditions
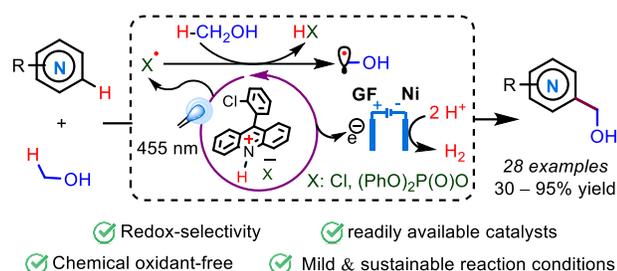
ABSTRACT: The merge of electrochemistry and photocatalysis allowed the required selectivity for the hydroxymethylation of functionalized azaarenes with methanol, including bioactive substrates. The two electrophotocatalytic protocols developed in this work address this transformation, using non-toxic and readily available reagents under mild reaction conditions with electricity as the only "sacrificial oxidant."

Installing a hydroxymethyl group on bioactive nitrogenated heterocycles can profoundly affect their physical properties, such as solubility (log P) and their interaction with pharmacophores through hydrogen bonds. This moiety is not only found in pharmaceuticals like pirbuterol, renierol, and losartan, but it also offers the potential for the easy transformation of this group into other functionalities, thereby expanding the scope of drug design and synthesis.[1, 2]

Hundreds of millions of tons of methanol are produced annually from different sources, including the catalytic reduction of CO_2 (contributing to carbon neutrality). Therefore, using methanol as a C_1 source for the direct hydroxymethylation of azaarenes is an inexpensive and sustainable approach.[3] This transformation exemplifies a cross-dehydrogenative coupling (CDC) with the potential for late-stage functionalization of bioactive azaarenes.[4] The weakness of C-H bonds in methanol makes their selective activation *vs.* the O-H bonds feasible, likely involving hydrogen atom transfer (HAT) processes. The rapid reaction of this radical with protonated azaarenes was comprehensively studied by F. Minisci in 1985.[5] However, years later, the same authors developed an indirect approach using ethylene glycol as the hydroxymethyl radical source to improve the selectivity of the desired transformation.[6] Among the challenges presented in the direct hydroxymethylation are (a) the possible unproductive charge transfer between the highly nucleophilic hydroxymethyl radical and the protonated azaarene, (b) the reversibility of the radical addition due to the increased stability of the radical (Scheme 1).

Scheme 1. Some challenges in the direct hydroxymethylation of azaarenes with MeOH.
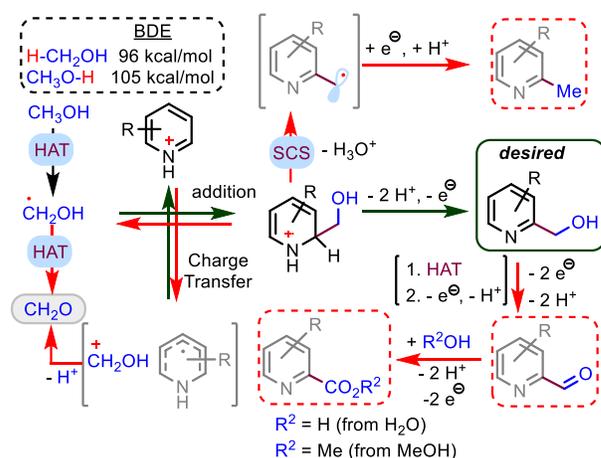
Deprotonation of the hydroxymethyl cation or β-scission from hydroxymethyl radical should furnish formaldehyde in competition with the desired transformation. An excess of methanol might compensate for its partial oxidation. However, the resulting hydroxymethyl derivatives are prone to suffer further oxidation due to their benzylic structure, which commonly occurs, giving rise to aldehydes or carboxylic acid derivatives by overoxidation. In addition, the most favorable process under redox-neutral conditions is the spin-center shift, obtaining the

corresponding methylated products.[7, 8] Moreover, poly-hydroxymethylation is often observed when more than one C(sp^2)-H bond is available due to the high nucleophilicity of the radical, which has been addressed with indirect methods such as the alkylation of *N*-methoxypyridinium derivatives.[9]

Given the mild conditions employed in photoredox catalysis to generate alkyl radicals from C-H bonds,[10] photoinduced Minisci-like reactions have experienced significant growth in recent years.[11-13] However, maybe due to the abovementioned complications, only a few general protocols have been reported for the photoinduced hydroxymethylation of azaarenes with methanol.[14-18] To our knowledge, a general approach to this transformation without chemical sacrificial oxidants remains unexplored. Under the reaction conditions previously reported by our group for the photoinduced alkylation of azaarenes,[19] we observed that MeOH gave mainly the corresponding methyl derivative for various substrates (unreported results). We hypothesize that maintaining mild oxidant conditions during the reaction would minimize the spin-center shift pathway and the abovementioned overoxidation to aldehydes and carboxylic acid derivatives. Recent reports show that readily available 9-(2-chlorophenyl)acridine (**A**) becomes photoactive with blue light (455 nm) upon protonation with HCl.[20] Since the photoexcited acridinium is oxidant enough (+2.2 V *vs.* SCE) for the single-electron oxidation of chloride anion (+1.21 V *vs.* SCE), we decided to test this *in situ* generation of chlorine radicals to promote the formation of hydroxymethyl radicals *via* HAT from methanol. With this in mind, we designed an electrophotocatalytic approach for the hydroxymethylation of azaarenes,[21, 22] using acridine **A** pre-photocatalyst and inexpensive chlorohydric acid (HCl(aq.)) at a low constant current or voltage. Moreover, our reaction design includes chloride salts as supporting electrolytes (SE) and a source of chlorine radicals. Importantly, these salts are innocuous, abundant in diverse forms, and much more inexpensive than other SE commonly used in electrocatalysis.

To test our hypothesis, we first examined the hydroxymethylation of 2-phenylquinoline using LiCl with aqueous HCl in MeOH and acridine **A** as the photocatalyst. The reaction was conducted in an undivided cell at a constant current (2 mA), irradiating with blue LEDs at room temperature. The screening of different electrodes (Table S1, entries 1-3) exposed that graphite as anode and Ni-plate as cathode gave optimal results after 24 h (entries 1 vs. 4). These electrodes are rather inexpensive and deliver superior results. We examined other acids instead of HCl, which gave poorer results or no reaction (entry 5). We also found that other chloride salts can promote the reaction with good yields but less efficiently than LiCl (entry 6). Furthermore, the reaction works much better without excluding air (entry 7 vs. 1), despite the possible overoxidation of the hydroxymethyl functionality, making this protocol more user-friendly. Notably, our results contrast the recently reported formylation of quinolines with methanol under HAT-mediated electrocatalytic conditions.[23] In addition, control experiments revealed that the acid, the acridine **A**, the light, and the electricity were essential for the progress of the reaction (entries 8, 9). It is worth noting that dehydrogenative coupling requires 2 F•mol^{-1}, but we have observed that the reaction is generally complete after 6 F•mol^{-1}. This has also been observed in previous works and could be associated with the cathodic reduction of chlorine radicals and other unproductive radical processes consuming the charge.[24]

Subsequently, the substrate scope was investigated under the optimal electrophotocatalytic conditions for a range of azaarenes (Figure 1). 2-Alkyl quinolines, containing different halides or ester groups at C6/C7, provided the corresponding 4-hydroxymethyl products (**2**-**6**) in good yields (60% − 89%). Additionally, 4-substituted quinolines afforded 2-hydroxymethyl products in moderate-to-excellent yields (**7-12**, 40%−95%), with tolerance to halide−, alkyl−, aryl−, and alkyne−substituents. Notably, 3-methylquinoline and quinoline 8-sulfonic acid afforded the corresponding 2,4-dihydroxymethyl products in good yields (**13** in 74%, **14** in 50%). In the former case, it could be a result of a similar steric hindrance at C2/C4, while in the latter case, it must be due to the high electron-withdrawing effect of the sulfonic acid, which increases the reactivity of the azaarene with the nucleophilic hydroxymethyl radical. Interestingly, selective monosubstitution was achieved with 2,2`biquinoline (**15**, 47%), and the protocol was successfully applied to a quinoline-menthol hybrid molecule (**16**, 45%).
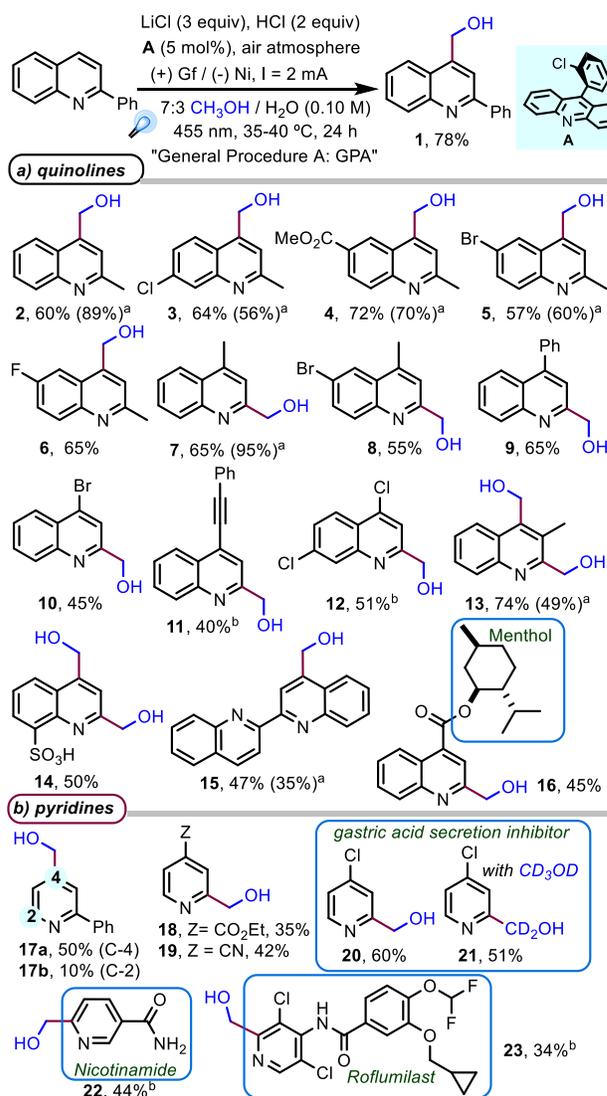
Figure 1. Substrate scope with LiCl/HCl. Yields for isolated pure products are given. [a] Current at 4 mA. [b] Cell voltage at 1.5 V.

2-Phenylpyridine gave monoalkylation, being the 4-hydroxymethyl product the major one, which is in line with the

preferential attack of a nucleophilic radical at C4 of a pyridinium ion, the atom with the largest coefficient in the LUMO (C4).[25] Monoalkylation was also observed for C-4 substituted pyridines, obtaining compounds **18**-**21** in moderate to good yields. We found this quite interesting because, under classical (and harsher) Minisci conditions, mixtures of mono- and dialkylated products are commonly obtained, which are difficult to separate.[26] In particular, we obtained compound **20** in 60% yield, while 20−30% yield is reported using $(NH_4)_2S_2O_8$ as sacrificial oxidant and thermal activation.[(9)] This product is an inhibitor of gastric secretion, and we could prepare its deuterated analog from CD_3OD in satisfactory yield (**21**, 53%). Remarkably, vitamin B3 gave 6-(hydroxymethyl)nicotinamide **22** with excellent regio- and chemo-selectivity. Furthermore, Roflumilast, an inhibitor of phosphodiesterase-4 used as medication in severe chronic obstructive pulmonary disease, afforded the corresponding monoalkylated product **23** in synthetically useful yield, exhibiting a good tolerance to various functionalities. Notably, quinaldine and lepidine gave the products in better yields with higher current intensity (products **2** and **7**). Still, we have checked for other five products (**3**, **4**, **5**, **13**, **15**), but similar or better results were obtained at 2 mA. Moreover, other more sensitive substrates gave the best results under potentiostatic conditions, with the cell voltage at 1.5 V (products **11**, **12**, **22** and **23**). A list of substrates that failed to give the desired product in more than 25% yield is given in Table S3. For isoquinoline, we observed the incorporation of a chlorine radical under the reaction conditions shown in Figure 1. Therefore, after screening new reaction conditions in the absence of chlorides (Table S2), Bu_4NBF_4 was the optimal supporting electrolyte when diphenyl hydrogen phosphate was used instead of HCl to generate the HAT catalyst.[27] Under these conditions, five isoquinolines were selectively hydroxymethylated at C1, including the acetyl derivative of Fasudil, a potent Rho-kinase inhibitor and vasodilator (Figure 2, products **24**− **28**). In addition, the phenanthridine has shown a singular reactivity. When the substrate was submitted to the reaction conditions of GPA (chlorine mediated), the methyl derivative **29** was obtained in good yield. Instead, the reaction conditions of **GPB**, but fixing the cell voltage at 1.5 V, afforded the corresponding formyl derivative **30** in good yield. We suspected the aerobic O_2 could facilitate the overoxidation, but similar results were obtained under Ar-atmosphere. Moreover, using CD_3OH, we obtained the deuterated formyl derivative **31** with a very good yield. The dichotomy found in the reactivity of phenanthridine reveals that fine-tuning the reaction conditions is necessary to obtain the desired hydroxymethylation (redox selectivity) without further reduction (methylation) or further oxidation (formylation).

In preliminary mechanistic investigations, we have observed that radical inhibitors such as TEMPO and 1,1-diphenylethene completely shut down the reaction, and we were able to detect by LC-MS the adducts **Ad1 / Ad2** with the hydroxymethyl radical (Scheme 2A, see details in the SI). Moreover, $CuCl_2$, a single-electron scavenger, also efficiently inhibited the reaction. In an attempt to trap the chlorine radical, we submitted the 1,1-diphenylethene to the reaction conditions of GPA (Scheme 2B), observing the formation of **Ad3** by LC-MS and ^{1}H-NMR. Considering our mechanistic observations (including control experiments and reactivity of substrates) and literature precedents, we propose a plausible mechanism (Scheme 2C). Photoinduced electron transfer (PET) between the activated acridinium catalyst and chloride anion should form chlorine radicals that might

participate in hydrogen atom transfer (HAT) with methanol, considering the corresponding bond dissociation energies.[28]
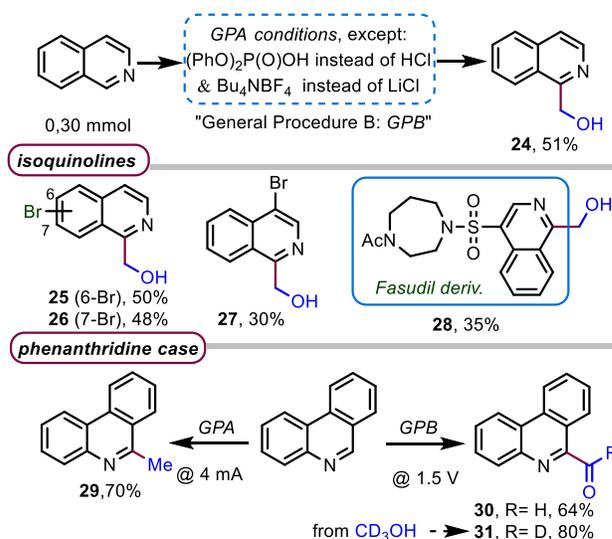
Figure 2. Substrate scope in the absence of chlorides. Yields for isolated pure products are given.

Scheme 2. Mechanistic Investigations and Proposal
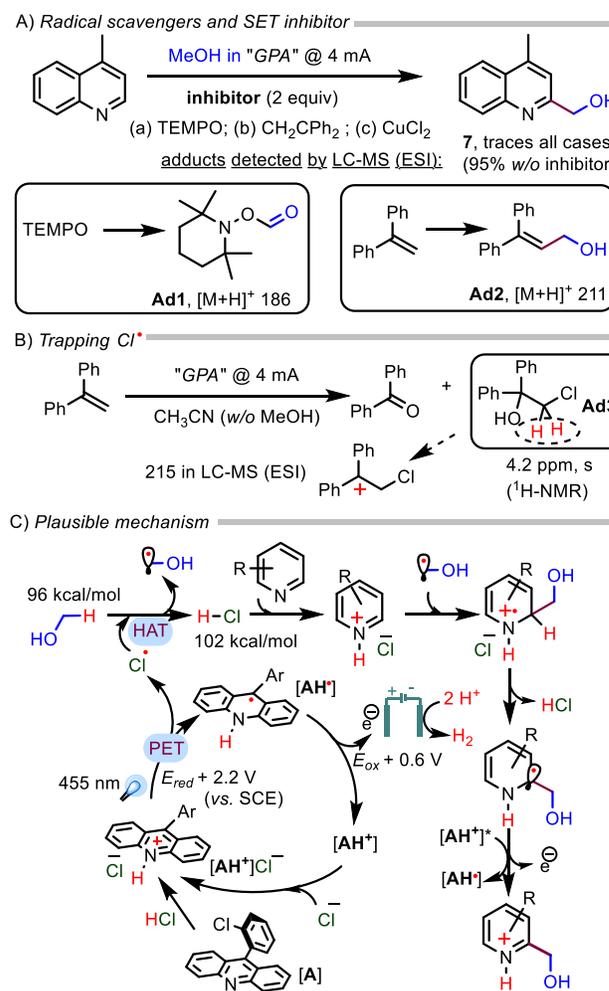
The addition of the hydroxymethyl radical generated to the protonated azaarene must be followed by deprotonation and single-electron oxidation, likely in solution by [AH⁺]*, but anodic oxidation is also possible. A crucial element of our reaction design is the anodic oxidation of the AH⁺ at a low oxidation potential (+0.6 V *vs.* SCE), revitalizing the photocatalyst under mild oxidation conditions.

As commented above, we have observed the methylation of azaarenes with methanol under photocatalytic conditions,[19] illustrated for product **32** in Scheme 3A, while formylation has recently been reported under electrocatalytic conditions.[23] We have also verified that hydroxymethyl compound **1** can be electrochemically oxidized to **33**, and its reduction to **32** has been reported under photocatalytic conditions.[15] Therefore, *combining electrochemical and photochemical activation modes provides a different redox selectivity than that obtained with each activation mode.* To make the protocol more user-friendly, we demonstrated that the hydroxymethylation of **s4** can be executed in good yields using an inexpensive 1.5 V battery, even under solar irradiation without stirring (Scheme 3B). Moreover, four parallel hydroxymethylations of **S4** were conducted using a carrousel (see details in the SI) to obtain 1.34 mmol of product **4**, which precipitated from EtOAc after the workup and was obtained pure after filtration (Scheme 3C). It is worth noting that we obtained a yield for isolated pure product **4** similar to the one obtained at 0.30 mmol scale (67% *vs.* 72%).

Scheme 3. Selectivity and applicability
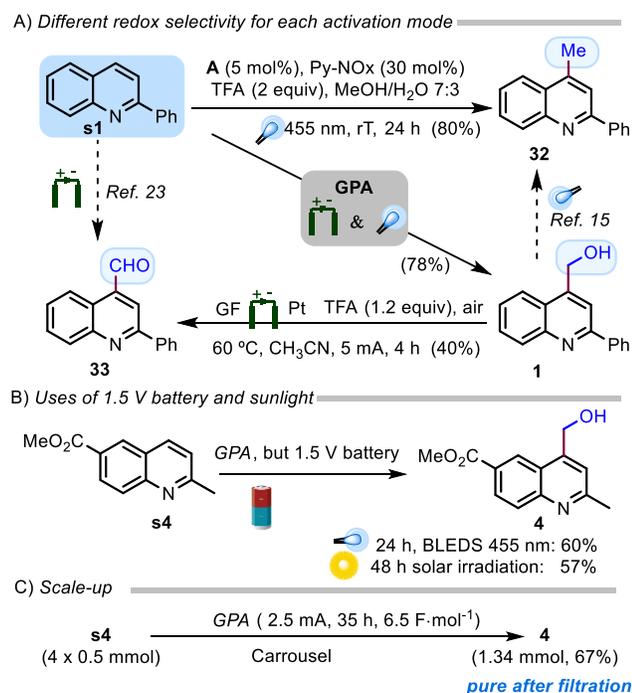
In conclusion, we developed an electrophotocatalytic protocol for the hydroxymethylation of azaarenes with methanol. We demonstrated that merging photochemistry and electrochemistry provides a selectivity different from the one obtained with each activation mode. This approach relies on readily available acridine **A** as organophotocatalyst and LiCl/HCl (aq.) to generate chlorine atoms for one protocol (GPA) or diphenyl hydrogen phosphate for isoquinolines (GPB) as HAT reagents.

ASSOCIATED CONTENT

AUTHOR INFORMATION

Corresponding Author

* Irene Bosque
Instituto de Síntesis Orgánica (ISO) and Departamento de Química Orgánica Universidad de Alicante, 03080 Alicante (Spain); orcid.org/0000-0003-0321-2167; Email: irene.bosque@ua.es
* Jose C. Gonzalez-Gomez
Instituto de Síntesis Orgánica (ISO) and Departamento de Química Orgánica Universidad de Alicante, 03080 Alicante (Spain); orcid.org/0000-0001-5334-7938; E-mail: josecarlos.gonzalez@ua.

REFERENCES

(1)   Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W., The medicinal chemist's toolbox for late stage functionalization of drug-like molecules. *Chem. Soc. Rev.* **2016,** *45* (3), 546-576.
(2)   Boström, J.; Brown, D. G.; Young, R. J.; Keserü, G. M., Expanding the medicinal chemistry synthetic toolbox. *Nat. Rev. Drug Discov.* **2018,** *17* (10), 709-727.
(3)   Li, H.; Li, C.; Liu, W.; Yao, Y.; Li, Y.; Zhang, B.; Qiu, C., Photo-Induced C1 Substitution Using Methanol as a C1 Source. ChemSusChem 2023, 16 (17), e202300377.
(4)   Tian, T.; Li, Z.; Li, C.-J., Cross-dehydrogenative coupling: a sustainable reaction for C–C bond formations. *Green Chem.* **2021,** *23* (18), 6789-6862.
(5)   Minisci, F.; Citterio, A.; Vismara, E.; Giordano, C., Polar effects in free-radical reactions. New synthetic developments in the functionalization of heteroaromatic bases by nucleophilic radicals. *Tetrahedron* **1985,** *41* (19), 4157-4170.
(6)   Minisci, F.; Porta, O.; Recupero, F.; Punta, C.; Gambarotti, C.; Pruna, B.; Pierini, M.; Fontana, F., A New, Convenient, Highly Selective Free-Radical Hydroxymethylation of Heteroaromatic Bases by Persulfate Oxidation of Ethylene Glycol and Glycerol, Catalysed by AgNO₃. *Synlett* **2004,** *2004* (05), 0874-0876.
(7)   Jin, J.; MacMillan, D. W. C., Alcohols as alkylating agents in heteroarene C–H functionalization. *Nature* **2015,** *525* (7567), 87-90.
(8)   Liu, W.; Yang, X.; Zhou, Z.-Z.; Li, C.-J., Simple and Clean Photo-induced Methylation of Heteroarenes with MeOH. *Chem* **2017,** *2* (5), 688-702.
(9)   Katz, R. B.; Mistry, J.; Mitchell, M. B., An Improved Method for the Mono-Hydroxymethylation of Pyridines. A Modification of the Minisci Procedure. *Synthetic Communications* **1989,** *19* (1-2), 317-325.

(10) Holmberg-Douglas, N.; Nicewicz, D. A., Photoredox-Catalyzed C–H Functionalization Reactions. *Chem. Rev.* **2022,** *122* (2), 1925-2016.

(11) Douglas, J. J.; Sevrin, M. J.; Stephenson, C. R. J., Visible Light Photocatalysis: Applications and New Disconnections in the Synthesis of Pharmaceutical Agents. *Org. Process Res. Dev.* **2016,** *20* (7), 1134-1147.

(12) Proctor, R. S. J.; Phipps, R. J., Recent Advances in Minisci-Type Reactions. *Angew. Chem. Int. Ed.* **2019,** *58* (39), 13666-13699.

(13) Zhang, X.; Li, S.; Qiu, F.; Ang, H. T.; Wu, J.; Jia, P., Photocatalyzed Minisci-type reactions for late-stage functionalization of pharmaceutically relevant compounds. *Green Chem.* **2024,** *26* (7), 3595-3626.

(14) Huff, C. A.; Cohen, R. D.; Dykstra, K. D.; Streckfuss, E.; DiRocco, D. A.; Krska, S. W., Photoredox-Catalyzed Hydroxymethylation of Heteroaromatic Bases. *J. Org. Chem.* **2016,** *81* (16), 6980-6987.

(15) Niu, L.; Liu, J.; Liang, X.-A.; Wang, S.; Lei, A., Visible light-induced direct α C–H functionalization of alcohols. *Nat Commun* **2019**, *10* (1), 467.

(16) Rammal, F.; Gao, D.; Boujnah, S.; Hussein, A. A.; Lalevée, J.; Gaumont, A.-C.; Morlet-Savary, F.; Lakhdar, S., Photochemical C–H Silylation and Hydroxymethylation of Pyridines and Related Structures: Synthetic Scope and Mechanisms. *ACS Catalysis* **2020,** *10* (22), 13710-13717.

(17) Zhang, Y.; Yue, X.; Zhu, J.; Peng, J.; Zhou, C.; Wu, J.; Zhang, P., Visible light-induced hydroxymethylation and formylation of (iso)quinolines with alcohols. *Molecular Catalysis* **2022,** *530*, 112594.

(18) Yin, C.; Hu, P., Visible-Light-Induced Cross-Dehydrogenative Coupling of Heteroarenes with Aliphatic Alcohols Mediated by Iodobenzene Dichloride. *Eur. J. Org. Chem.* **2023,** *26* (11), e202300015.

(19) Laze, L.; Quevedo-Flores, B.; Bosque, I.; Gonzalez-Gomez, J. C., Alkanes in Minisci-Type Reaction under Photocatalytic Conditions with Hydrogen Evolution. *Org. Lett.* **2023,** *25* (48), 8541-8546.

(20) Kim, J.; Sun, X.; van der Worp, B. A.; Ritter, T., Anti-Markovnikov hydrochlorination and hydronitrooxylation of α-olefins via visible-light photocatalysis. *Nat. Catal.* **2023,** *6* (2), 196-203.

(21) Huang, H.; Steiniger, K. A.; Lambert, T. H., Electrophotocatalysis: Combining Light and Electricity to Catalyze Reactions. *J. Am. Chem. Soc.* **2022,** *144* (28), 12567-12583.

(22) Wu, S.; Kaur, J.; Karl, T. A.; Tian, X.; Barham, J. P., Synthetic Molecular Photoelectrochemistry: New Frontiers in Synthetic Applications, Mechanistic Insights and Scalability. *Angew. Chem. Int. Ed.* **2022,** *61* (12), e202107811.

(23) Liao, Y.; Jiang, C.; Qiang, C.; Liu, P.; Sun, P., HAT-Mediated Electrochemical C(sp2)–H Acylation of Quinolines with Alcohols. *Org. Lett.* **2023,** *25* (40), 7327-7331.

(24) Xu, P.; Chen, P.-Y.; Xu, H.-C., Scalable Photoelectrochemical Dehydrogenative Cross-Coupling of Heteroarenes with Aliphatic C−H Bonds. *Angew. Chem. Int. Ed.* **2020,** *59* (34), 14275-14280.

(25) Tauber, J.; Imbri, D.; Opatz, T. Radical Addition to Iminium Ions and Cationic Heterocycles. *Molecules*, **2014**, 19, 16190-16222.

(26) Duncton, M. A. J., Minisci reactions: Versatile CH-functionalizations for medicinal chemists. *Med. Chem. Commun.* **2011,** *2* (12), 1135-1161.

(27) Li, D.-S.; Liu, T.; Hong, Y.; Cao, C.-L.; Wu, J.; Deng, H.-P., Stop-Flow Microtubing Reactor-Assisted Visible Light-Induced Hydrogen-Evolution Cross Coupling of Heteroarenes with C(sp3)–H Bonds. *ACS Catal.* **2022,** *12* (8), 4473-4480.

(28) Capaldo, L.; Ravelli, D.; Fagnoni, M., Direct Photocatalyzed Hydrogen Atom Transfer (HAT) for Aliphatic C–H Bonds Elaboration. *Chem. Rev.* **2022**, *122* (2), 1875-1924.