Metal- and chlorine-free cross-dehydrogenative coupling of azaarenes with alkanes without sacrificial oxidants.

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Abstract: Minisci-like cross-dehydrogenative coupling of azaarenes with unactivated alkanes offers an appealing approach to bioactive alkyl-substituted heterocycles from abundant feedstocks. Traditionally, this net oxidative C-C bond formation process uses sacrificial chemical oxidants with the consequent waste generation. Here we report a chemical oxidant-free solution for this transformation, promoted by visible light at room temperature in the absence of metals, chlorinated solvents, or chlorine sources. The reaction is run under conventional photochemical conditions and does not require deoxygenation or anhydrous solvents. Remarkably, a readily available 9-arylacridine and the inexpensive pyridine *N*-oxide are used as catalyst precursors. A wide range of azaarenes and C-H partners are compatible with this protocol, which was applied to the late-stage functionalization of bioactive molecules. In addition, the gram-scale synthesis of one API intermediate was accomplished using flow technology. Preliminary mechanistic studies were conducted to support the dual catalytic cycle.

Nitrogen heterocycles are abundant in natural products, agrochemicals, and pharmaceuticals.[1] Most unique small-molecule drugs approved by FDA contain a nitrogen heterocycle.[2] Beyond their intrinsic bioactivities, these heterocycles are also valuable for the fine-tuning of solubility, lipophilicity, polarity, and hydrogen bonding of drugs, resulting in ADME (absorption, distribution, metabolism, and excretion) optimization and reducing toxicity.[3] The straightforward access to alkyl-functionalized nitrogen heterocycles is of pivotal importance in drug discovery,[4] especially if late-stage functionalization of bioactive compounds is possible.[5] In this context, the Minisci reaction has become one of the most helpful approaches by adding nucleophilic alkyl radical (high-lying SOMO) to activated heteroarenes (low-lying LUMO).[6-8] A remarkable strength of the Minisci reaction as a synthetic tool is the regioselectivity observed in the C(sp^2)-H bond activation, which can be controlled by the nitrogen atoms in the heterocycle (innate reactivity) or by π-acceptor substituents (conjugate reactivity).[9] However, functionalized radical precursors are commonly required in this methodology,

usually diminishing its step- and atom-economy while generating waste and compromising the compatibility with different functionalities. Among the most relevant radical precursors used are carboxylic acid derivatives,[10-12] alcohols,[13, 14] aldehydes,[15, 16] alkyl halides,[17] and boronic acids.[18]

Cross dehydrogenative coupling (CDC) is an appealing synthetic approach to C-C bond formation. It is a convergent high atom-economical process that does not require pre-functionalization of the substrates.[19] However, stoichiometric sacrificial oxidants, which also generate waste and decrease the sustainability of the process, are commonly required for this net oxidative process.[20] In recent years, the use of photocatalysis, [21-23] electrocatalysis, [24] and electrophotocatalysis,[25, 26] has opened other access for radical generation from C(sp^3)-H bonds, allowing the Minisci reaction under green and mild CDC conditions.[27] Despite this field's recent advance, new mild and streamlined methodologies must be developed, avoiding expensive transition-metal catalysts, specialized equipment, and operationally complex protocols.

Very recently, the CDC of heteroarenes with alkanes has been accomplished without external chemical oxidants (Fig. 1a) by the *in-situ* generation of chlorine atoms from chloride anions, either using photoelectrochemical[28] or dual photo- cobalt-catalysis[29] for the hydrogen evolution. In addition, photoinduced ligand-to-metal charge transfer (LMCT) is also used to generate chlorine radicals and promote this transformation.[30] These approaches exploit the capacity of chlorine atoms to activate C(sp^3)-H bonds by hydrogen atom transfer (HAT) due to the high bond dissociation energy (BDE) of HCl (Fig. 1b).[31] In addition, diphenyl phosphate has also been successfully used in stoichiometric amounts as a HAT reagent to promote this transformation.[32] Notably, the latter photochemical reaction was accomplished in a chlorinated solvent and using a stop-flow microtubing reactor at 60 ºC to obtain good results. Remarkably, it has been recently demonstrated that common chlorinated solvents such as 1,2-dichloroethane (DCE) can produce chlorine atoms under aerobic photocatalytic conditions and promote the desired transformation.[33] In fact, chlorinated solvents are prominent as reaction media for many organic transformations despite their serious health effects and environmental concerns.[34] More specifically, DCE is nowadays the subject of regulatory controls in the European Union, and there is a pressing need to advance C-H activation methodologies that steer away from chlorinated solvents.[35] Therefore, we proposed herein a user-friendly protocol for the CDC of heteroarenes with alkanes at room temperature, free of stoichiometric chemical oxidants, metals, chlorinated solvents, or other chlorine sources. (Fig. 1c).

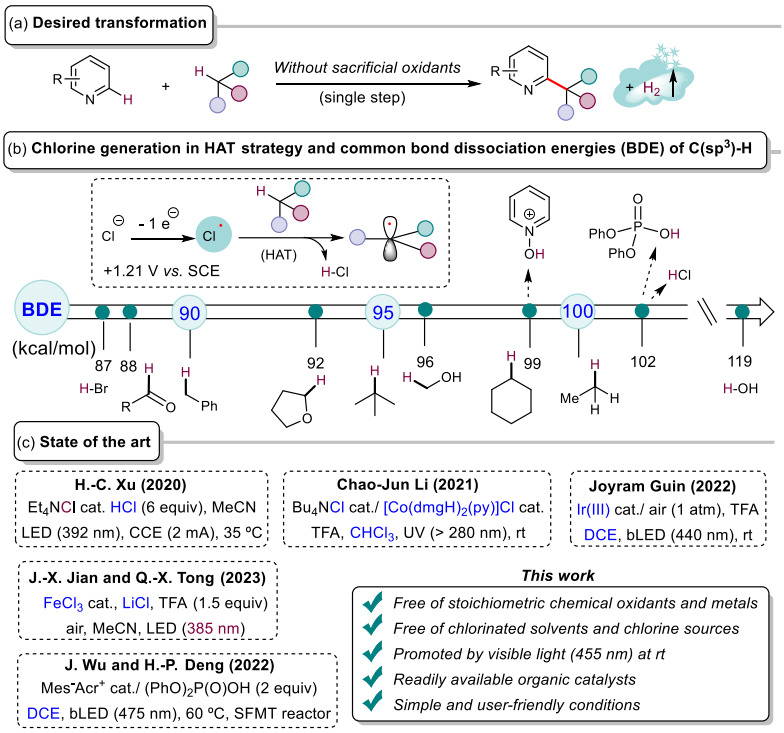


Fig. 1. State of the art on the desired transformation.

Results

Design of the catalytic system

We selected pyridine *N*-oxides (PyOs) as HAT catalysts inspired by the good results obtained by Nicewicz[36] and Deng[37] for the site-selective functionalization of C(sp^3)-H bonds and also due to the high acidity of the resulting PyOH in MeCN. Previously, neutral 9-arylacridines were extensively used to promote photocatalytic decarboxylative functionalization of carboxylic acids through proton-coupled-electron transfer, and it is known that in the presence of trifluoroacetic acid, the corresponding acridinium is formed and become photoactive with visible light.[38-42] We thus hypothesized (Scheme 1) that in the presence of an acid and upon irradiation with blue light (455 nm), the excited state of the resulting acridinium (E_{red} 2.2 V *vs.* SCE for **[A1H]**$^+$)[43] is oxidant enough to remove an electron from **PyO1** (E_{ox} from +1.84 V *vs.* SCE),[36] without redox interference of the trifluoroacetate anion (E_{ox} > +2.25 V *vs.* SCE).[44] The resulting *N*-oxyl radical could abstract hydrogen atoms from C(sp^3)-H bonds (BDE 90–100 kcal/mol)[36] forming **PyOH1** (p*K*a 10)[45] that is significantly more acidic than TFA in MeCN (p*Ka* 12.7)[46] and can be deprotonated by azaarenes to reset the **PyO1**. The choice of the solvent is crucial. For example, in H_2O, TFA is more acidic than **PyOH1** (p*Kas* 0.23 and 0.79, respectively).[46] The resulting protonated azaarene **[I-H]**$^+$ (with a low-lying LUMO) should be more prone

to add a transient nucleophilic radical (**II**). The obtained radical cation **III** would be engaged in a single-electron-transfer (SET) with the acridinyl radical **HA•**, enabling the acridinium photocatalyst's turnover and the dihydroazaarene **IV**'s formation. In principle, dehydrogenation of **IV** to the final product might occur under the reaction conditions without any external oxidant. As indicated previously by Kano and Morofuji,[47] intermediate **IV** could transfer a hydride to radical cation **III**, producing molecular hydrogen together with the protonated product **[P-H]**$^+$ and radical **V**. A final proton transfer should deliver the product **P** and radical cation **III** that might be quenched either by **HA•** or by another molecule of **IV**.

Our approach differs conceptually from using PyOs as stoichiometric oxidants in combination with violet light (405 nm) for the CDC of heteroarenes with alkanes.[48] Furthermore, the photoactivation of 9-arylacridines with HCl has been recently reported with the subsequent generation of chlorine radicals.[43] This is also conceptually different from our work where the trifluoroacetate counterion is not redox active. *Notably, the photocatalyst is activated under the Minisci reaction conditions. Moreover, photoredox and HAT catalysts are readily prepared and fine-tunable organic catalysts for visible light-induced transformations.*

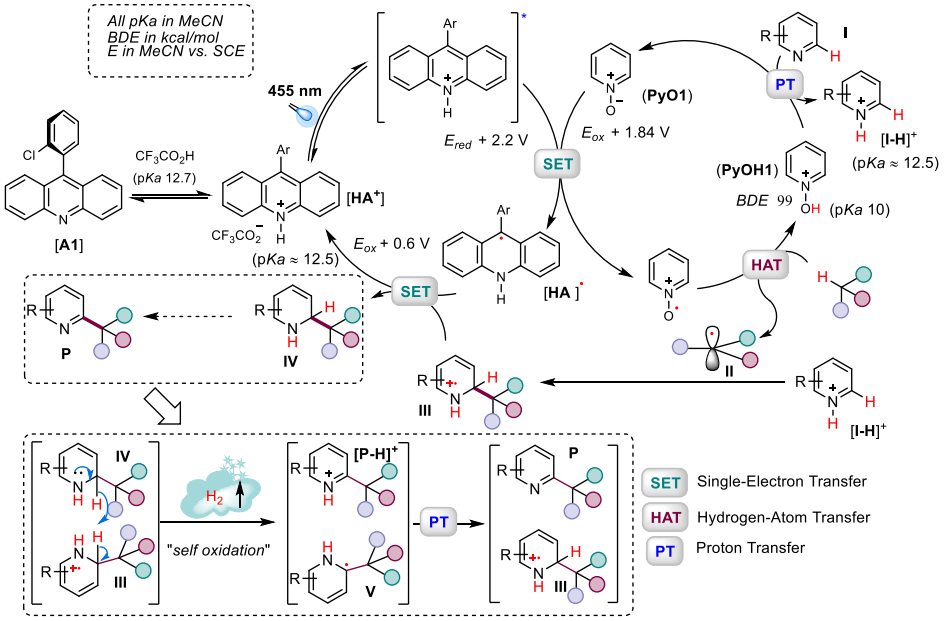


Fig. 2. Reaction design.

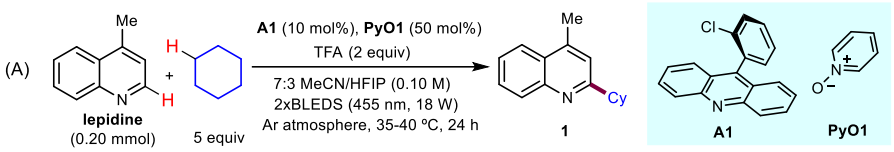
Reaction development. To test our hypothesis, lepidine and cyclohexane (5 equiv) were chosen as substrates in the presence of TFA, using commercial **PyO1** as the HAT catalyst and acridine **A1** (prepared in one step, see Supplementary Information (SI) for details) as

photocatalyst. The reaction was promoted by blue light irradiation (455 nm) under an argon atmosphere at room temperature, which compares favorably with existing methods that require UV activation. To our delight, the expected product was obtained in good yield (**Table 1A**, entry 1). Following this encouraging result, we demonstrated that the reaction requires irradiation to proceed, that the presence of photocatalyst **A1** significantly improves the reaction yield, and that without deoxygenation, the reaction outcome was improved (entry 2). Reexamining our initial hypothesis, aerobic O_2 dissolved in the reaction media is not necessary for the desired transformation, but it might be helpful in the final oxidation steps. The fact that the reaction works under conventional batch conditions in the presence of air, given that $^3O_2$ is a very efficient triplet quencher for acridinium salts,[49] suggests the participation of the singlet-excited state of the photocatalyst.[38] Most importantly, this protocol is more user-friendly than others because inert gases or special equipment (glovebox, stop-flow microtubing reactor, etc.) are not required, and the reaction is promoted at room temperature (30-35 ºC). We thus checked that 200 mol% of TFA was the best choice for the reaction (entries 1 and 3). Significantly, the load of **PyO1** and **A1** could be diminished to 25 mol% and 5 mol%, respectively, without negatively impacting the reaction progress (entry 4). Interestingly, while the reaction yield in MeCN was moderate, no reaction occurred in HFIP. Still, optimal results were obtained in 7:3 MeCN/HFIP (entries 4 *vs.* 5), which was selected as the reaction media because HFIP as a cosolvent might also help to solubilize **PyO1** and other polar substrates without redox interference.[50] For this model reaction, using larger excess of cyclohexane (entry 6) or a higher concentration of reagents (entry 7) did not change the result significantly. Increasing the load of **PyO1** slightly (30 mol%) and running the reaction for a longer time (entry 8) allows the reaction to complete, isolating the desired product in good yield. Importantly, when the reaction was accomplished under these conditions but with the rigorous exclusion of air, the product was obtained in poorer yield (entry 9). However, high enough to probe that air can partially promote the transformation but is not essential.

Given the promising results recently reported with other PyOs as HAT catalysts,[36, 37] we also examined other commercially available PyOs, or readily prepared by one-step oxidation of pyridines, in our model reaction. As shown in Table 1B, six other PyOs were examined, but only **PyO2** y **PyO5** gave similar results to **PyO1**. We thus decided to continue with **PyO1** because it is an inexpensive commercially available chemical that justifies its use as a catalyst, even with relatively high loading (20-30 mol%). Moreover,

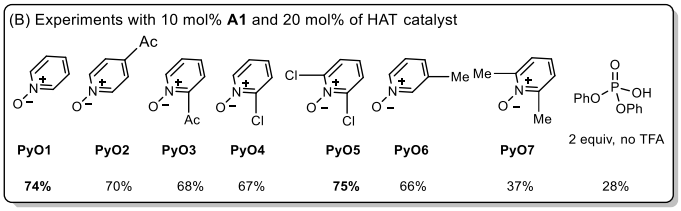
in previous studies, the stability of **PyO1** under our reaction conditions was relatively high.[36] We also examined diphenyl phosphate (2 equivalents and no TFA) as a HAT catalyst, but poorer results than with PyOs were obtained under our conditions. Four other 9-arylacridines were prepared (see details in the SI) and screened as photocatalysts. However, none of them (**A2**-**A5**, **Table 1C**) improved the results obtained with **A1** for our model reaction.

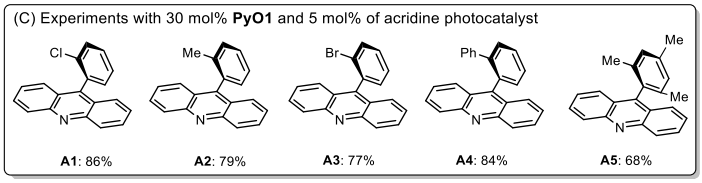
Table 1. Optimization of the model reaction



Entry	Variation from conditions indicated above	Yield of **1** (%)[a]
1	None (The rxm was bubbled with Ar over 5 min)	81
2	**Without Ar**/without **A1**/ without light	**91**/ 25/ 0
3[b]	TFA: 0 mol%/ 20 mol%/ 50 mol%/ 100 mol%/ 300 mol%	0 / 2 / 20 / 44 / 65
4[b]	**PyO1** (25 mol%), **A1** (5 mol%), 22 h *vs.* **32 h**	81 *vs.* **94**
5[b]	**PyO1** (25 mol%), **A1** (5 mol%), **MeCN** *vs.* HFIP	**69** *vs.* 0
6[b]	**PyO1** (25 mol%), **A1** (5 mol%), 10 equiv CyH	82
7[b]	**PyO1** (25 mol%), **A1** (5 mol%), [**lepidine**] = 0.20 M	76
8[b]	**PyO1** (30 mol%), **A1** (5 mol%), **32 h**	100 (76)[c]
9	**PyO1** (30 mol%), **A1** (5 mol%), **48 h**, under rigorous Ar atm.[d]	65

[a] GC yield based on remaining SM without calibration. [b] Closed under air. [c] Isolated pure product. [d] Three cycles of freeze-pump-thaw-Ar backfilled.





Substrate scope. Having found the optimal conditions, we approached the substrate scope by examining different azaarenes in the reaction with cyclohexane as the C(sp^3)-H coupling partner (Fig. 3). Quinolines with substituents placed at C4 or C2 reacted smoothly to obtain C2 or C4 cyclohexyl derivatives (products **1**-**8**) in moderate to excellent yields (41-89%). Besides alkyl- and aryl-groups, functionalities such as halides, methoxy (electron-donating group) and metoxycarbonyl (electron-withdrawing group)

were well tolerated in the quinoline moiety. Notably, the best results were achieved in some cases by adding the **PyO1** in two batches to compensate for its partial decomposition or using larger excess of cyclohexane to speed up the reaction. Unsubstituted quinoline and 6-fluoroquinoline were efficiently transformed into a mixture of products where the C4 alkylated were isolated in the higher yields and inseparable mixture of C2- and di-alkylated products at C2/C4 were also obtained (**9** and **10**). Pyridines substituted at C4 were also suitable substrates. While for *p*-Ph and *p*-CO_2Et substrates, the mono-alkylated pyridines were the main products (**11**, **12**), the dialkylated product was the only one obtained for the more reactive *p*-CN pyridine (**13**). Continuing our interest in quinoxalin-2(1*H*)-ones,[51] we also examined these heterocycles as substrates for the CDC coupling with cyclohexane. Gratifyingly, they were also compatible with this methodology, albeit requiring a larger excess of cyclohexane. *N*-alkylated or free *N*-H quinoxalinones gave the corresponding products (**14**, **15**) in good yields. Remarkably, a nitro group was well tolerated affording product **16** in moderate yield, which nicely illustrates the compatibility of strong electron-withdrawing groups in the heterocycle. Notably, 1,4-diazines, such as quinoxalines and pyrazines, react to selectively afford mono-alkylated products (**17**, **18**) in moderate-to-good yields. Surprisingly, the selectivity obtained for product **17** is much higher than that reported using a stop-flow microtubing photoreactor and a different dual catalytic system,[32] where a 1.3:1 mixture of mono- and di-alkylated products was obtained. We were pleased to observe that phenanthridine gave product **19** in a yield much higher than the one obtained by Gryko`s group (82% *vs.* 21%) through the formation of an EDA complex between the heterocyclic substrate and lutidine oxide in stoichiometric amounts and with more energetic photons (405 nm).[48] It is also worth saying that isoquinoline, a substrate that was successfully turned into the desired product using Gryko`s protocol, failed under our reaction conditions (other azaarenes that were recalcitrant substrates under our conditions are listed in Supplementary Fig. S19). Finally, benzothiazole and benzimidazole substrates gave products **20** and **21** in relatively good yields. Remarkably, the yield obtained from benzothiazole was also significantly better than that obtained with Gryko`s protocol (product **20**: 56% vs. 27%).

Further substrate scope, selectivity, and functional group tolerance were evaluated by coupling lepidine to different C(sp^3)-H starting materials. Other simple cyclic alkanes gave the desired products (**22**, **23**) in good to excellent yields. Notably, lower excess (3 equiv.) of the less volatile cyclododecane was used without compromising the reaction

yield. Using methylcyclopentane revealed that tertiary C-H bonds were more reactive than secondary and much more reactive than primary (substitution at the methyl group was not observed). It is worth noting that the substitution at the tertiary C-H represents 50% of the total isomers formed. The other isomers of **24** resulted from the abstraction of one out of eight secondary hydrogens, which means that considering the number of C-H bonds, the normalized selectivity tertiary *vs.* secondary is 89%. Bridged alkanes also reacted smoothly. Remarkably, norbornane provided exclusively *exo*-**25**, while adamantane reacts preferentially at the tertiary C-H bond to give a 91:9 mixture of C1:C2-**26** (97.6% normalized selectivity). The challenging acyclic alkanes were also suitable substrates (products **27**-**29**), exhibiting excellent site selectivity for tertiary C-H bonds. The functionalization of benzylic C-H bonds was less efficient, furnishing products **30** and **31** with 34% and 30% yields, respectively. Notably, *p*-cymene reacted at the least sterically hindered primary C-H bond. Substrates with a short alkyl chain and electron-withdrawing groups have shown poor reactivity but excellent selectivity at the γ-CH position (valeronitrile→**32**; isoamyl acetate→**33**). Other authors have also observed this site-selectivity using pyridine *N*-oxides as HAT catalysts.[36, 37] Unfortunately, other small cyclic ketones, lactones, and small acyclic esters failed to give the expected product in synthetically valuable yields under our optimal conditions (Supplementary Fig. S19). Given the electrophilic nature of **PyO1** radical cation, we hypothesized that C-H bonds next to heteroatoms would be activated for hydrogen abstraction. However, when different amides were examined, only methyl acetamide and pyrrolidinone gave the products **34** and **35** in low to moderate yields (recalcitrant amides are in Supplementary Fig. S19). For these substrates, Gryko`s protocol provided superior results. Cyclic ethers (dioxane and tetrahydrofuran) and acyclic methyl *tert*-butyl ether reacted selectively to give the corresponding α-heteroatom CDC products **36**-**38**. It is worth noting that C-O bond cleavage *via* Spin-Center Shift (SCS) is the main pathway observed for these ethers when other more reductant photocatalysts are used to reduce a benzylic radical intermediate (*e.g.,* $Ir(ppy)_2(dtbbpy)^{2+}$; 4CzIPN).[14, 32] Notably, methanol reacts smoothly under our reaction conditions, providing the corresponding hydroxymethyl derivative **39** in good yield. This reactivity is complementary to the methylation observed under other photochemical conditions *via* the SCS pathway and can efficiently introduce a deuterated side hydroxymethyl chain into heteroarenes (product **40**).[52] Increasing the steric demand at α-positions of alcohols retarded their reactivity. While ethanol provided product **41** in 36% yield, other branched alcohols failed, and isoamyl alcohol reacted mainly at

γ-position (**42**). The weakness of a C-H bond in a formyl group (BDE 88 kcal/mol) is a result of the activation by the carbonyl lone pair, and we took advantage of this fact to direct the HAT event.[53] However, after site-selective H-atom abstraction, the major pathway depends on the substitution at the adjacent position. On the one hand, primary 3-methylbutanal afforded product **43** in moderate yield *via* the SCS pathway. On the other hand, secondary and tertiary aldehydes provided alkylated heteroarenes **44** and **45** in good yields after decarbonylation and CDC.

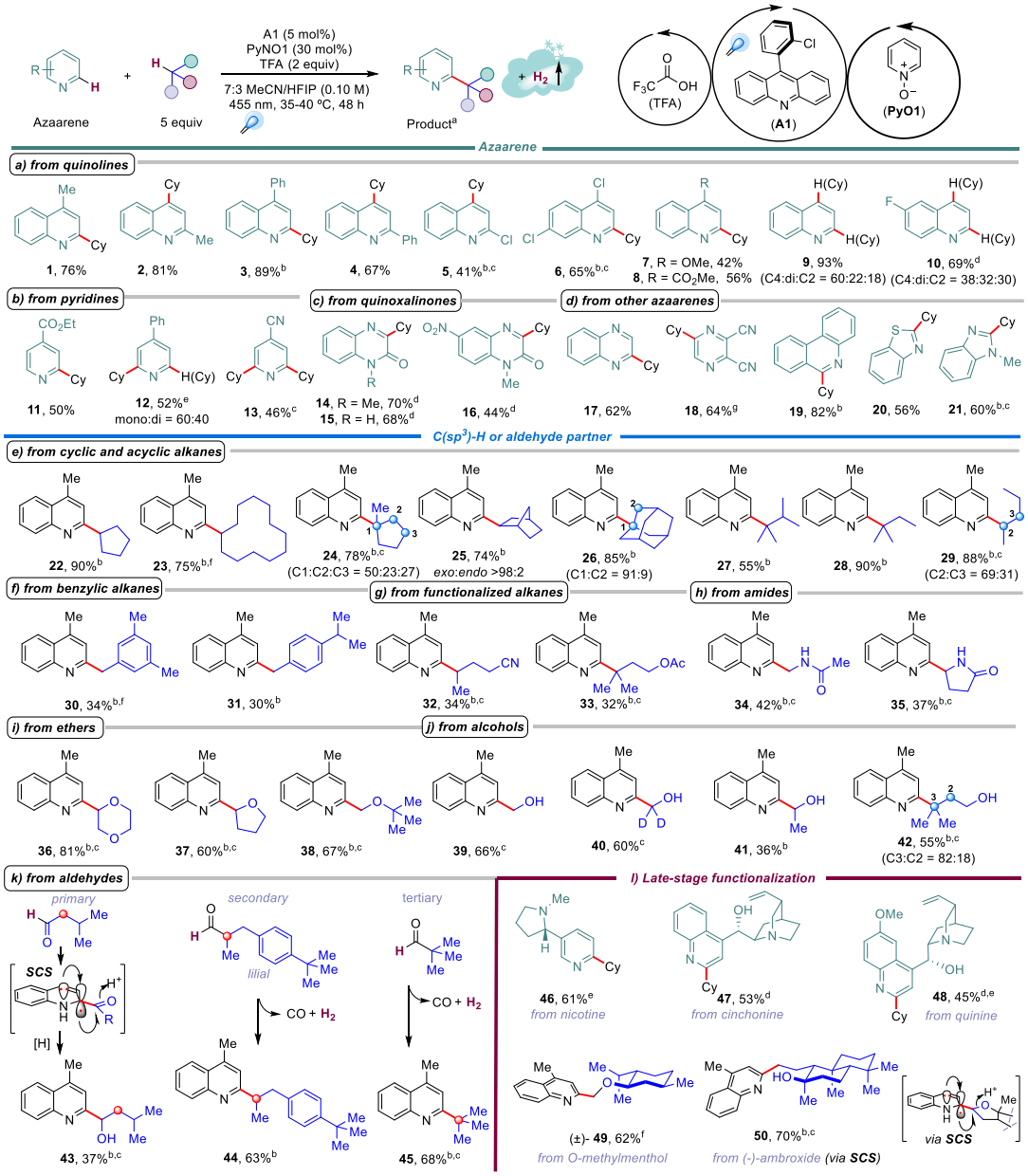


Fig. 3. Substrate scope. Reaction conditions: Azaarene (0.3 mmol), R-H (1.5 mmol), **A1** (0.015 mmol), **PyO1** (0.09 mmol) in 7:3 MeCN: HFIP (3 mL) was irradiated with LEDs (455 nm) at 30-35 ºC for 48 h. [a]Yields for isolated pure products are given. [b]**PyO1** was added in two portions, 20 mol% at the beginning and 10 mol% after 24 h. [c]10 equiv. of R-H (3 mmol). [d]23 equiv. of R-H (6.9 mmol). [e]3 equiv. of TFA (0.9 mmol). [f]3 equiv. of R-H (3 mmol). [g]4 equiv. of TFA (1.2 mmol).

The applicability of our methodology to the late-stage functionalization of different natural bioactive products was examined. The site-selective functionalization of nicotine, cinchonine, and quinine with cyclohexane took place in reasonably good yields (products **46**-**48**). These results illustrate that *m*-substituted pyridines are suitable substrates and that various functional groups, such as tertiary amines, free hydroxyl groups and terminal double bonds, are well tolerated. Examining the functionalization of different natural monoterpenes as C(sp^3)-H partners, we found that menthol and others (Supplementary Fig. S19) failed under our reaction conditions. However, inspired by the good result obtained with *tert*-butyl methyl ether (product **38**), we prepared *O*-methylmenthol in a straightforward step from menthol and demonstrated its site-selective functionalization with lepidine (product **49**). In principle, this strategy could be extended to other natural alcohols. Finally, when ambroxide was examined, selective H-abstraction occurred next to the O-atom, followed by radical addition to protonated lepidine and SCS with C-O bond cleavage, giving product **50** in good yield. Remarkably, the stereogenic centers in the natural products used as starting materials remained intact.

To showcase the synthetic utility of our protocol in preparing synthetic intermediates, we decided to take advantage of the homogeneous reaction mixture and scale up the process using continuous flow conditions for better light harvesting.[54-56] We used a homemade photoreactor and a syringe pump for this purpose (see Supplementary Fig. S2). Our target was 4,7-dichloro-2-cyclohexylquinoline (**6**) because it can be transformed in only three synthetic steps into a DAQ analog, which is a promising antimalarial candidate.[57] In addition, compound **6** can react directly with different amines to obtain 4-aminoquinolines, such as chloroquine and hydroxyquinoline analogs. These molecules have been used as active pharmaceutical ingredients (APIs) for treating many diseases.[58, 59] After carefully optimizing the residence time (t_R), under otherwise identical conditions to the batch protocol, except that the acridine load was decreased to 2.5 mol%, we prepared compound **6** in the gram scale (details are given in the Supplementary section). As shown in Fig. 4a, the productivity was significantly improved compared to the experiment in batch and the use of flow photoreactor of higher volumes would further increase this productivity. Additionally, it is worth saying that product **8** is a precursor of other bioactive molecules, such as TNF-α-converting enzyme (TACE) inhibitors,[60] antitumor-,[61] and antituberculosis agents[62] (Fig. 4b).

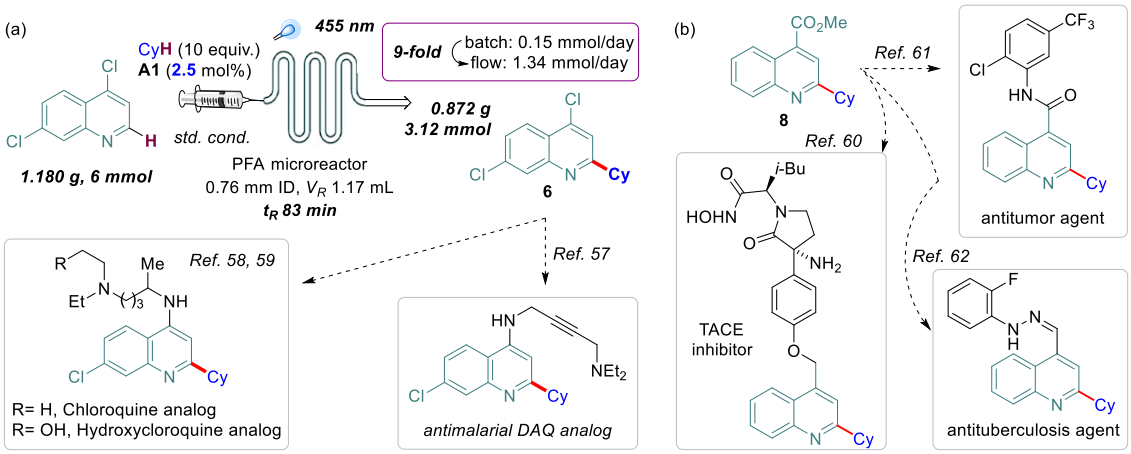


Fig. 4. Scale up in flow and formal syntheses of APIs.

Mechanistic investigation. Preliminary mechanistic studies (Fig. 5) support the proposed catalytic cycles shown in Fig. 2. Radical trapping experiments with TEMPO or 1,1-diphenylethene demonstrated the formation of cyclohexyl radical, likely through HAT from cyclohexane to pyridine-*N*-oxyl radical (Fig. 5a). The quantum yield of the reaction during the first 30 minutes is significantly below 1 (Fig. 5b) to ensure that either the radical chain propagation is inefficient or, more likely, the reaction takes place through a closed photoredox cycle. The reaction profile (Fig. 5g) shows it is much faster in the initial stages (mainly during the first 4 hours). Therefore, the quantum yield should be lower after the initial hours, and a closed photoredox cycle is more plausible. We prepared 2-cyclohexylbenzothiazole (**20**) from the corresponding hydrogenated **20-H₂** under the standard reaction conditions (Fig. 5c), which supports the intermediacy of these compounds and their dehydrogenation. Remarkably, the evolution of H_2 was further confirmed by GC-TCD analysis (Fig. 5d). The analysis of the UV-Vis spectra of all the reaction components confirmed that none of them absorbed light at 455 nm (λ_{max} of irradiation). Still, the addition of TFA to a solution of **A1** caused a significantly increased absorption between 390 and 460 nm (Fig. 5h). Additionally, Stern-Volmer quenching experiments of a solution of **A1** and excess of TFA (Fig. 5g) show that **PyO1** is the best quencher from all reaction components, which is consistent with their redox potentials and the SET between these species proposed in Fig. 2. The rate constants at the initial stages of two parallel reactions, one with cyclohexane and the other one with deuterated cyclohexane (C_6D_{12}), were measured (Fig. 5e). The ratio k_H/k_D obtained was 1.25, indicating that the formation of an alkyl radical *via* HAT from C(sp^3)-H bond is not the turnover-limiting step of the catalytic reaction. However, when the deuterium kinetic

isotope effect (KIE) was determined by a competition experiment (Fig. 5f), a high k_H/k_D value of 6.14 was observed. Thus, similarly, we studied the deuterium KIE to form product **20** from benzothiazole (see the Supplementary section). Once again, we observed a 2º KIE when individual rate constants were measured (k_H/k_D = 1.64) and a 1º KIE for the competition experiment (k_H/k_D = 3). The difference obtained for the KIEs using individual rate constants or intermolecular competition might result from an irreversible C-H bond cleavage occurring after the SET between the excited [**A1H**]$^+$ and **PyO1**, which might be the turnover-limiting step.[63] Therefore, the alkyl radical formation *via* HAT is product-determining but not the rate-determining step.

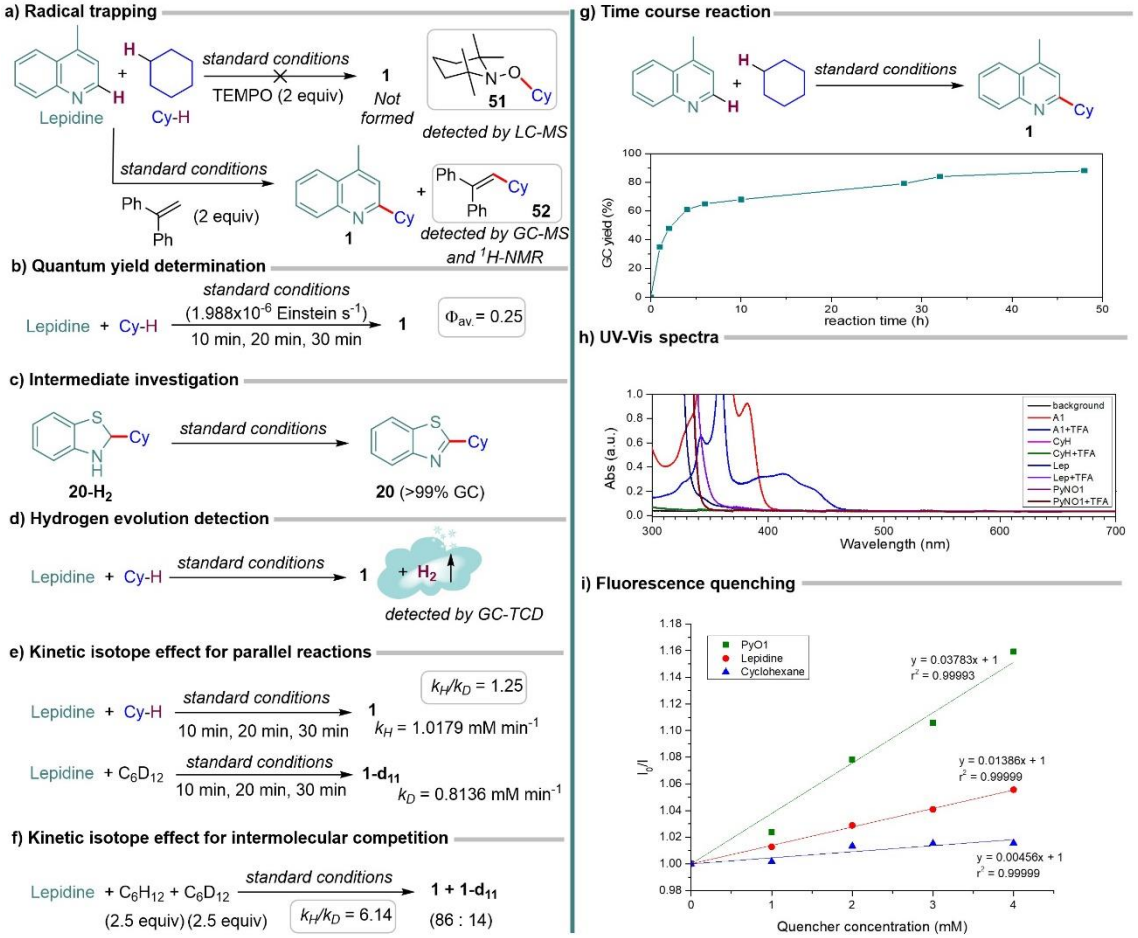


Fig. 5. Mechanistic studies. See Supplementary Information for more detailed descriptions of **a)** Radical trapping, **b)** quantum yield determination, **c)** intermediate investigation, **d)** hydrogen evolution detection, **e)** kinetic isotope effect for parallel reactions, **f)** kinetic isotope effect for intermolecular competition, **g)** time course reaction, **h)** UV-vis spectra, **i)** fluorescence quenching.

Conclusions

The photoinduced Minisci C-H alkylation of azaarenes with unactivated alkanes is now possible without sacrificial oxidants, metals, halide sources or chlorinated solvents. The

reaction is promoted by visible light at room temperature without the interference of air or water traces. A dual catalytic system based on a readily available 9-arylacridine photocatalyst and pyridine *N*-oxide was used for the first time in this transformation. Mechanistic studies support a dual photoredox/HAT catalytic cycle with H_2 evolution. The use of TFA as an additive is crucial to ensure the photoactivation of the acridine and the addition of radicals to azaarenes. Moreover, the high acidity of the *in situ-formed* *N*-hydroxypyridinium in MeCN is critical for regenerating the pyridine *N*-oxide. The developed catalytic system may help in approaching future C-H functionalizations.

Acknowledgments

This work was financially supported by the Generalitat Valenciana (SEJIGENT/2021/005 and IDIFEDER/2021/13) and the University of Alicante (GRE20-03-A granted to I. B.). We thank Dr. Francisco Montilla for giving us access to the spectrofluorometer of his research group at the University of Alicante.

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