ACS Catalysis

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Stop-Flow Microtubing Reactor-Assisted Visible Light-Induced Hydrogen-Evolution Cross Coupling of Heteroarenes with C(sp^3)−H Bonds

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Cite This: *ACS Catal.* 2022, 12, 4473−4480 Read Online

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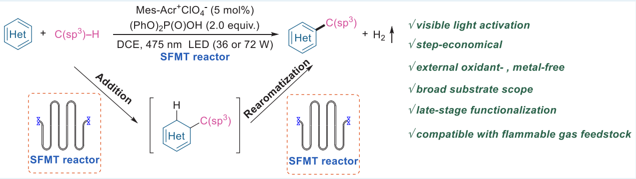


ABSTRACT: The synthesis of valuable alkyl-substituted heteroarenes from abundant and inexpensive feedstocks under mild conditions is attractive and highly desirable in pharmaceutical and natural product synthesis. Minisci-type cross dehydrogenative coupling between heteroarenes and C(sp^3)−H bonds offers direct access to these important scaffolds in a step-economic manner. Herein, assisted by stop-flow microtubing reactors, an operationally simple protocol for the visible light-induced hydrogen-evolution cross coupling of heteroarenes with unactivated C(sp^3)−H bonds was developed in a metal- and external oxidant-free manner. A wide range of alkylated heteroarenes was generated with common feedstock chemicals, including ethane. Mechanistic studies indicated that photoredox-induced hydrogen atom transfer processes followed by dehydrogenative rearomatization delivered the desired coupling products. The merits of this strategy were further demonstrated by the late-stage functionalization of various complex bioactive molecules.

KEYWORDS: *hydrogen-evolution cross coupling, hydrogen atom transfer, stop-flow microtubing reactor, heteroarenes, C(sp^3)−H feedstock, metal- and oxidant-free*

Cross dehydrogenative coupling (CDC) of C(sp^3)−H bonds has been recognized as one of the most step-economical approaches to C−C bond formation[1−5] and has found widespread application in the pharmaceutical, agrochemical, and materials science fields. However, stoichiometric oxidants are generally required, which results in a diminished atom economy of the overall process with unwanted waste generation and poor functional group compatibility. Over the past decade, a greener approach involving CDC reactions with hydrogen evolution in the absence of any external oxidants has been achieved through transition metal catalysis,[6,7] photoredox/cobalt dual catalysis,[8−11] quantum dot photocatalysis,[12−17] and electrocatalysis.[10,18,19] Although the strategy of hydrogen-evolution cross coupling of C(sp^3)−H bonds has gained significant momentum, such approaches have several limitations, including a reliance on transition metal catalysts or specialized electrochemical equipment. Therefore, the development of new strategies of hydrogen-evolution cross coupling with readily available C(sp^3)−H feedstocks in a metal-free and operationally simple manner is highly desirable.

Organic compounds that contain alkyl-functionalized heteroarene motifs are ubiquitous in pharmaceuticals, agrochemicals, and natural products (Figure 1A).[20] A further incentive arises from the rapid access to diverse alkyl-functionalized heteroarenes, which is important for the late-stage functionalization of pharmaceutical compounds.[21,22] The Minisci reaction is a classical method to achieve alkyl-functionalized heteroarenes with nucleophilic alkyl radicals.[23−27] However, previous methods involving Minisci reactions were limited by the employment of prefunctionalized alkyl radical precursors, such as carboxylic acids or derivatives,[28−31] alcohols,[32−34] aldehydes,[35,36] alkenes,[37] and boronic acids,[38−40] or involved C(sp^3)−H substrates that required sacrificial oxidants.[23−27] In recent years, considerable efforts have been devoted to the development of different activation pathways of C(sp^3)−H bonds for Minisci alkylation under mild conditions via photocatalysis or electrocatalysis.[24] In 2020, Xu and co-workers described a photoelectrochemical hydrogen-evolution cross coupling of heteroarenes with C(sp^3)−H substrates,[41] wherein electricity was applied to replace sacrificial chemical oxidants (Figure 1B). Likewise, a photoelectrochemical hydrogen-evolution cross coupling of benzothiazoles with C(sp^3)−H bonds was reported by Ravelli et al.[42] with the use of tetrabutylammonium decatungstate as a hydrogen atom transfer (HAT) photocatalyst. Shortly thereafter, Wu and co-workers[43] developed an elegant approach involving the allylic C(sp^3)−H functionalization of heteroarenes by quantum dot photocatalysis with hydrogen released

Received: March 3, 2022
Revised: March 29, 2022

https://doi.org/10.1021/acscatal.2c01087

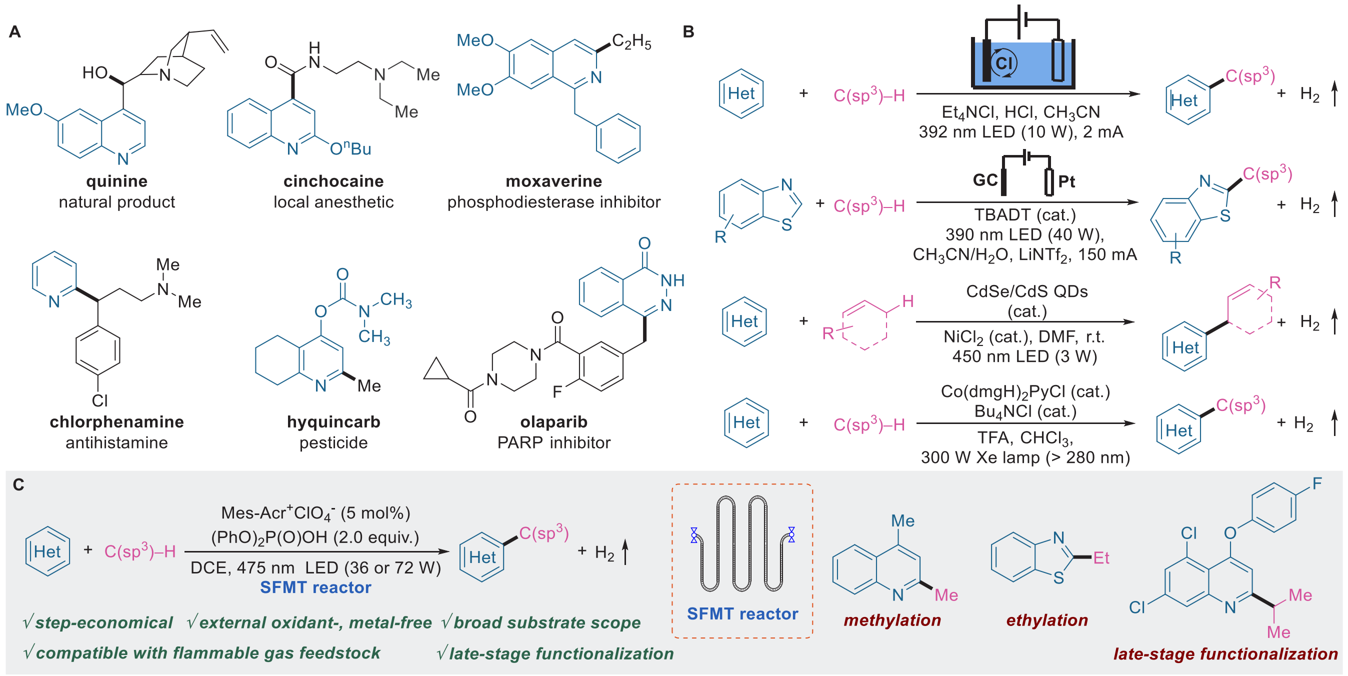


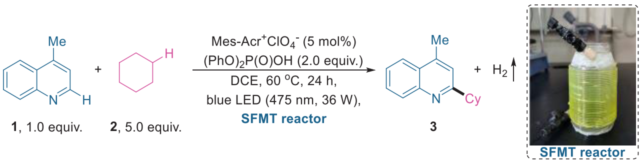
Figure 1. Strategies for CDC reactions of heteroarenes with $C(sp^3)$−H feedstocks. (A) Selective examples of alkyl-functionalized heteroarene motifs in pharmaceuticals, agrochemicals, and natural products. (B) State-of-the-art hydrogen-evolution cross coupling of heteroarenes with $C(sp^3)$−H feedstocks.[41−44] (C) This work: stop-flow microtubing reactor-assisted visible light-induced hydrogen-evolution cross coupling of heteroarenes with $C(sp^3)$−H bonds.

as the coupled product (Figure 1B). Recently, Li et al.[44] established an effective UV light-promoted cobalt-catalyzed hydrogen-evolution cross coupling of heteroarenes with $C(sp^3)$−H bonds. However, oxidant- and metal-free coupling that accommodates a wide range of $C(sp^3)$−H partners with diverse heteroarenes without the usage of specialized electrochemical equipment or harmful UV light is still unknown and highly desirable.

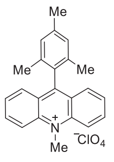
In line with our ongoing interests[45−50] in visible light-induced HAT catalysis,[51] herein, assisted by stop-flow microtubing reactors, we develop an operationally simple protocol for the hydrogen-evolution cross coupling of heteroarenes with a variety of $C(sp^3)$−H partners via visible light-induced HAT catalysis. This approach provides a simple and effective way to construct alkyl-functionalized heteroarenes with a wide range of $C(sp^3)$−H substrates in a metal- and oxidant-free manner. The synthetic utilities of this methodology were demonstrated in the late-stage functionalization of complex bioactive molecules (Figure 1C).

Minisci-type reactions normally require acids as additives to activate heteroarenes. We envisioned that the acid can play a dual role in activating heteroarene substrates and in promoting the HAT process triggered by photoredox catalysis.[45,52] The synergistic merger of photoredox catalysis with cobalt cocatalysis pioneered by Wu[9] and Lei[10] offered enormous opportunities for hydrogen-evolution cross coupling under oxidant-free conditions.[48,53−58] Moreover, we have developed a stop-flow microtubing (SFMT) reactor that has several advantages in visible light-mediated transformations over conventional batch reactors, including enhanced light penetration and maintenance of volatile and gaseous reagents and intermediates at elevated temperatures.[45,49,59−61] In this context, we initiated the study of the proposed hydrogen-evolution cross coupling reaction using lepidine **1** and cyclohexane **2** as the model substrates in an SFMT reactor. Our investigation of the conditions indicated that a catalytic amount of mesityl-10-methylacridinium perchlorate (Mes-$Acr^+ClO_4^-$) and Co(dmgh)$_2$PyCl in the presence of two equivalents of diphenyl phosphate in acetonitrile at 60 °C under blue LED light (475 nm, 36 W) irradiation for 24 h gave desired coupling product **3** in 87% yield (Table 1, entry 1). Unexpectedly, an improved product yield (95%) was obtained using 1,2-dichloroethane (DCE) as the solvent even in the absence of cobalt catalyst, which was essential in the existing reported hydrogen evolution dehydrogenative couplings[8−11,44] (entry 2). Hydrogen gas was detected as the coupled product (Figure S4). This result indicated that our transformation underwent an alternative dehydrogenative pathway without the need for cobaloxime catalysts. In comparison, the use of Ir(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$ or 2,4,5,6-tetra(9H-carbazol-9-yl)-isophthalonitrile (4CzIPN) as the photocatalyst resulted in slightly lower yields (entries 3 and 4). Further screening of different acid additives illustrated that diphenyl phosphate was the optimal activator of the heteroarene substrate and the HAT agent (entries 5 and 6). When using acetone as the solvent, the desired product was generated in moderate yield (entry 7); however, other solvents, such as acetonitrile, ethyl acetate or dibromomethane, afforded only sluggish reactivities (entry 8). Decreasing the reaction temperature to 40 °C led to a lower yield of **3** (83%) (entry 9). Lowering the amount of **2** to two equivalents delivered the desired product in a significantly lower yield (entry 10). The reaction proceeded much more efficiently in the SFMT reactor than in conventional batch reactors such as a sealed-tube (entry 11), probably due to its high surface/volume ratio and excellent photon efficiency[62] (Table S6 and S7). Control experiments indicated that photocatalyst, diphenyl phosphate, and light were all crucial for this transformation (entry 12). To further demonstrate the

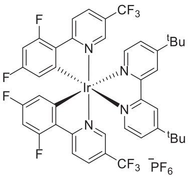
Table 1. Evaluation of Reaction Conditions for Hydrogen-Evolution Cross Coupling between Lepidine and Cyclohexane



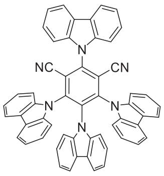
entry	variation to standard conditions	yield of 3 (%)[a]
1	with Co(dmgh)$_2$PyCl (10 mol%), CH_3CN instead of DCE	87
2	none	95 (90)[b]
3	Ir(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$ instead of Mes-Acr$^+$ClO$_4^-$	79
4	4CzIPN instead of Mes-Acr$^+$ClO$_4^-$	91
5	HCl or HBr instead of (PhO)$_2$P(O)OH	~10
6	CF_3SO_3H or $PhCO_2H$ instead of (PhO)$_2$P(O)OH	0
7	acetone instead of DCE	55
8	CH_3CN, EtOAc or CH_2Br_2 instead of DCE	<10
9	40 °C instead of 60 °C	83
10	2.0 equiv. of **2** instead of 5.0 equiv.	55
11	sealed-tube instead of SFMT reactor	34
12	without Mes-Acr$^+$ClO$_4^-$, (PhO)$_2$P(O)OH, or light	0
13[c]	a 56.0 mL SFMT reactor instead of a 3.0 mL SFMT reactor, 0.2 M concentration based on **1** instead of 0.05 M	75[b] (1.89 g)



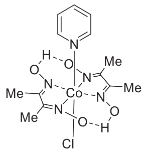
Mes-Acr$^+$ClO$_4^-$



Ir(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$



4CzIPN



Co(dmgH)$_2$PyCl

[a] The yield of **3** was determined by analysis of the crude ^{1}H NMR spectrum using CH_2Br_2 as an internal standard. [b] Isolated yield. DCE, 1,2-dichloroethane; EtOAc, ethyl acetate. [c] Gram-scale synthesis.

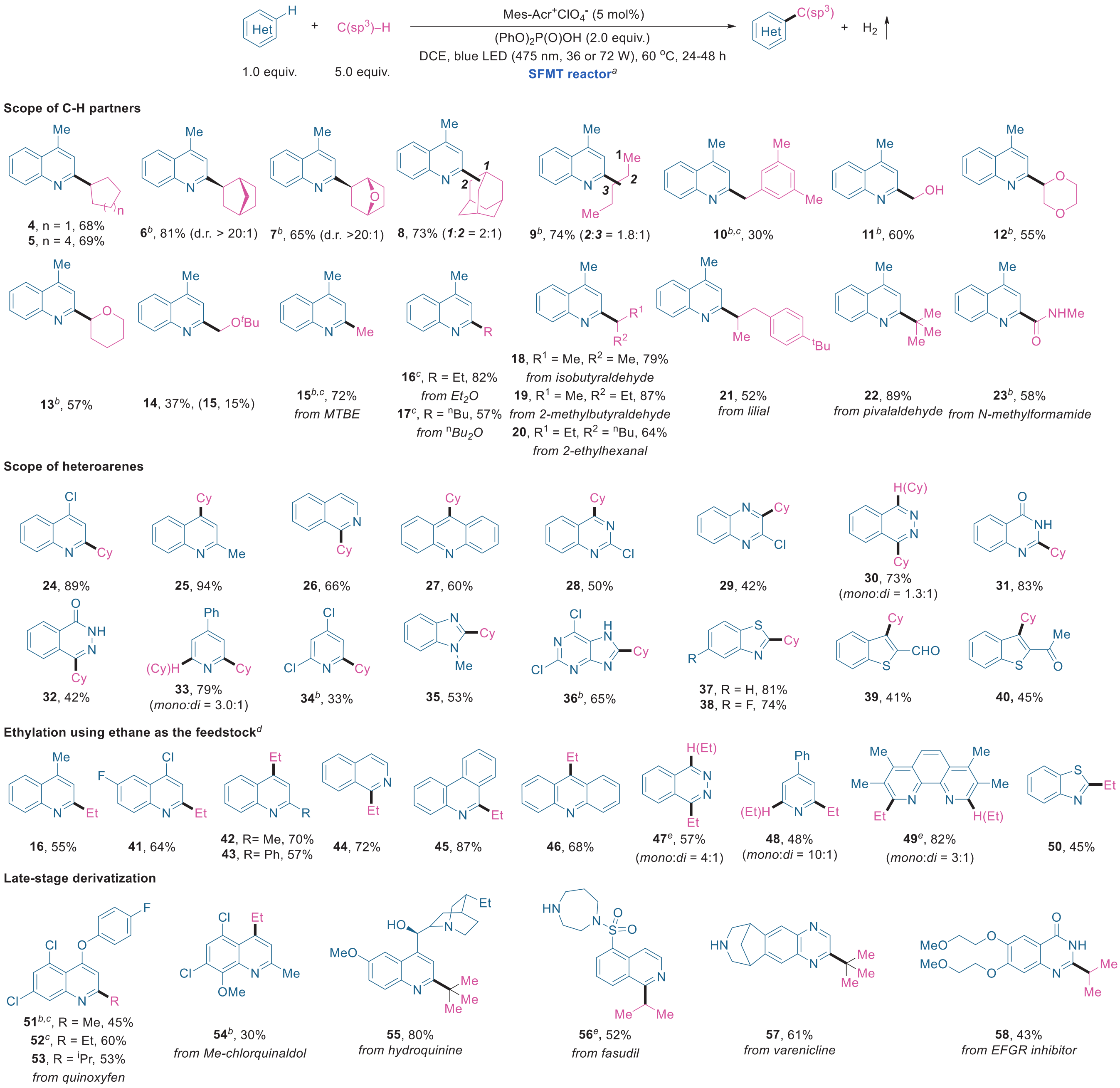
synthetic utility of this methodology, hydrogen-evolution cross coupling was demonstrated to be amenable to scale up to the gram scale (75%, 1.89 g) using a 56 mL SFMT reactor (entry 13).

With the optimal conditions, the generality of C(sp^3)−H partners was evaluated. As shown in Table 2, cycloalkanes including cyclopentane (**4**) and cyclooctane (**5**) gave the corresponding products in moderate yields. Because of the rigid structure, bridged cyclic hydrocarbons such as norbornane (**6**) and 1,4-epoxycyclohexane (**7**) were functionalized at only the position of secondary C(sp^3)−H bonds, generating exo isomers exclusively. Alkanes bearing multiple reactive sites, such as adamantane (**8**) and pentane (**9**), resulted in good reactivity but poor regioselectivity. The reaction of benzylic C(sp^3)−H bonds was less efficient, delivering the corresponding product (**10**) in 30% yield when 4CzIPN was used as a photocatalyst. Alcohols participated in the present transformation effectively to afford the coupling product (**11**) in 60% yield, with the reaction occurring exclusively at the α position of the hydroxy group. Cyclic ethers (**12** and **13**) are feasible substrates to deliver α-heteroatom C−H functionalized ethereal products. Linear ether-like methyl tertial butyl ether (MTBE) as the C(sp^3)−H partner was used to obtain the ethereal coupling product (**14**), accompanied by a small amount of the methylation byproduct (**15**). However, when 4CzIPN was used as the photocatalyst, the methylation product was achieved exclusively. Introducing a methyl group to bioactive compounds reduces the free energy of desolvation or increases the potency, which would be beneficial to drug development based on the "magic methyl effect"[63,64] in the pharmaceutical industry. Similar to photoinduced methylation of heteroarenes using methanol as the methyl precursor developed by MacMillan[32] and Li,[33] our protocol provided an alternative strategy to achieve methylation of heteroarenes. Moreover, C−O cleavage could be achieved using diethyl ether or dibutyl ether as the alkylation precursor, delivering the corresponding ethylation or butylation products (**16** and **17**) in good yields. Secondary and tertiary aldehydes acted as alkyl precursors under our reaction conditions to afford decarbonylative coupling products (**18**−**22**) exclusively in moderate to good yields (52−89%). However, this protocol was not suitable for primary aldehydes, which resulted in complex mixtures of unidentified compounds. Importantly, the formamide generated a carbamoyl radical via C(sp^2)−H functionalization, providing a direct and easy pathway to install a carbamoyl group on heteroarenes (**23**).

Next, the scope of heteroarenes was evaluated. Quinolines substituted at the C4 or C2 positions reacted smoothly to afford C2 or C4 coupling products (**24** and **25**) in excellent yields, respectively. Other heteroarenes, such as isoquinoline (**26**), acridine (**27**), and C2-chlorinated quinazoline and quinoxaline (**28** and **29**), were feasible substrates to give coupling products with cyclohexane in moderate to good yields. Phthalazine (**30**) reacted smoothly to produce both mono- and disubstituted coupling products. 4-Hydroxyquinazoline (**31**) and phthalazone (**32**) were also compatible with this protocol and were essential motifs in drugs such as raltiterxed[65] and azelastine.[66] Monocyclic heteroarenes such as 4-phenylpyridine (**33**) and 2,4-dichloropyridine (**34**) were exploited to afford the corresponding cyclohexyl-coupled pyridine derivatives in moderate to good yields. Furthermore, 5-membered heteroarenes, including benzimidazole (**35**), purine (**36**), and benzothiazole (**37** and **38**), all afforded the desired products in good yields. Remarkably, non-nitrogen-incorporated heterocycles such as benzothiophenes bearing a carbonyl group at the C2 position (**39**-**40**) were proven to be suitable substrates, generating C3 coupling products in useful yields.

Methane and ethane are abundant, low-cost hydrocarbon feedstocks for organic synthesis.[67] However, because of their high bond dissociation energies (BDEs, methane, BDE = 104 kcal/mol; ethane, BDE = 101.5 kcal/mol), C(sp^3)−H functionalization of methane or ethane under mild conditions has been a fundamental challenge.[45,68−70] Moreover, the flammable nature of methane and ethane increases the risk of explosion in the presence of oxidants, which could be a problem for conventional CDC transformations with attractive feedstocks, especially at a large scale. Our previous studies have demonstrated the use of SFMT reactors as an excellent platform for gas-involved photoinduced transformations.[45,59−61] Delightfully, ethane proved to be an efficient substrate to couple with lepidine **1** assisted by the SFMT reactor under these external oxidant-free conditions, delivering the corresponding ethylation product **16** in 55% yield. However, methane failed to give the methylation product. Notably, control experiments showed that product **16** was not generated when using conventional batch reactors (Scheme S2). Ethylation was effective for a wide variety of heteroarenes, including substituted quinoline (**41**−**43**), isoquinoline (**44**), phenanthridine (**45**), and acridine (**46**), giving the ethylation products in moderate to good yields (57−87%). Using

Table 2. Substrate Scope of Hydrogen-Evolution Cross Coupling



[a] A mixture of heteroarenes (0.15 mmol), C−H partner (0.75 mmol), Mes-Acr$^+$ClO$_4^-$ (0.0075 mmol), diphenyl phosphate (0.3 mmol) in 1,2-dichloroethane (3.0 mL) in an SFMT reactor (3.0 mL) was irradiated at 60 °C under 36 W blue LED for 24−48 h. The yields were isolated combined yields of all the isomers, and the ratio was determined by analysis of the crude ^{1}H NMR spectrum, unless otherwise noted. [b] 10.0 equiv. C−H partner was employed. [c] 4CzIPN was used as the photocatalyst. [d] Reactions were conducted with ethane gas (∼10 equiv) at 20 atm, and the reaction mixture was irradiated under 72 W blue LEDs for 48 h. [e] 3.0 equiv of diphenyl phosphate was used.

heteroarenes with multiple reactive sites (**47**−**49**), mono-ethylation products were generated with moderate to good selectivity. Benzothiazole (**50**) was a suitable candidate, affording the desired product in 45% yield.

The synthetic utility of this mild hydrogen-evolution cross coupling protocol was demonstrated by the late-stage functionalization of several complex pharmaceutical compounds. For example, quinoxyfen, a fungicide used mainly to control powdery mildew in cereals, reacted smoothly to deliver methylation, ethylation, and isopropylation products (**51**−**53**) in moderate yields. In addition, derivatives of readily available drugs such as chlorquinaldol, quinine, fasudil, and varenicline also afforded the corresponding alkylation products in moderate to good yields (**54**−**57**). Moreover, the EFGR inhibitor[71] (**58**) was effective in alkylation with this simple protocol.

A series of control experiments were performed to elucidate the reaction mechanisms. As indicated by fluorescence quenching experiments, lepidine and diphenyl phosphate anions were able to quench the excited state of acridinium, whereas cyclohexane and diphenyl phosphate could not (Figure 2A). The quenching rate constants of different

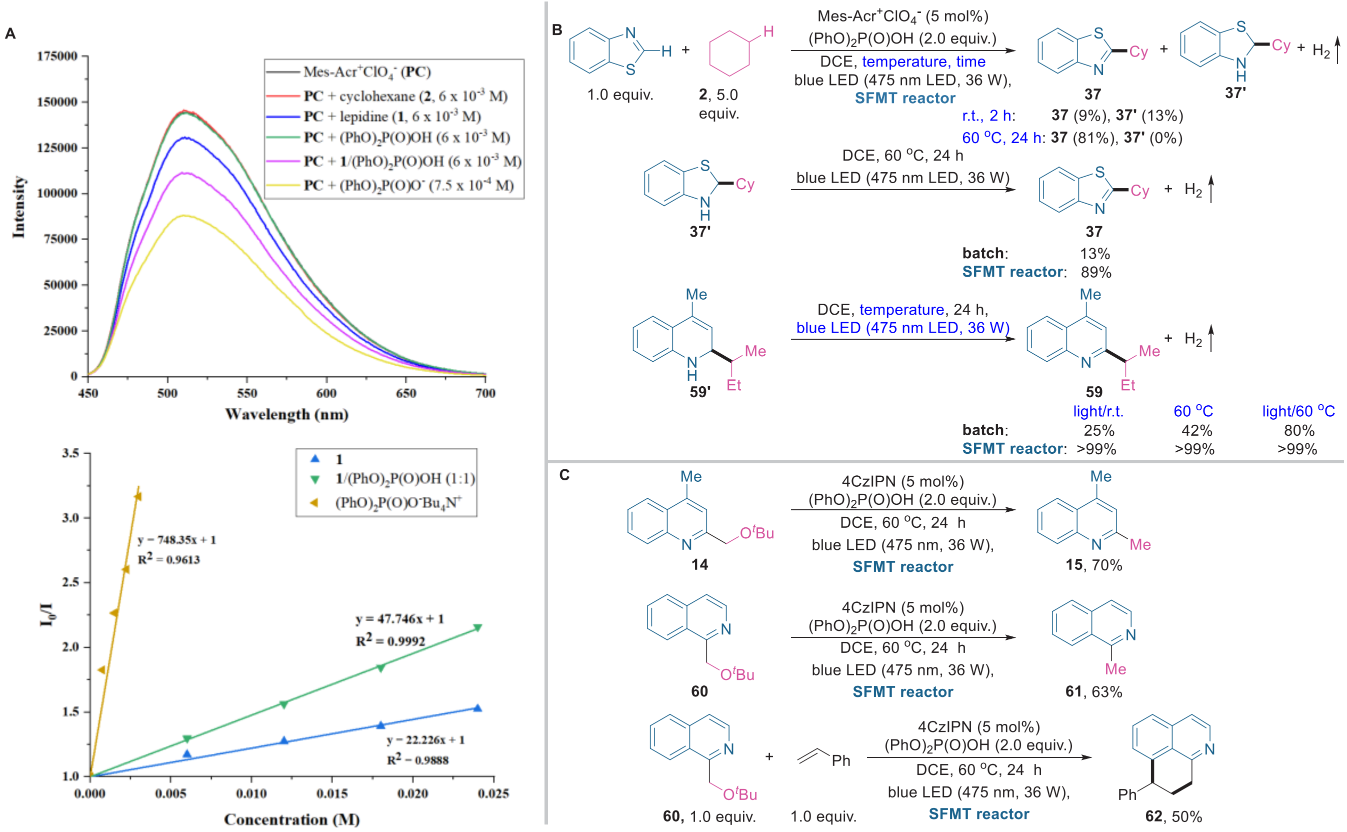


Figure 2. Control experiments for mechanistic study. (A) Stern−Volmer fluorescence quenching study. (B) Control experiments to elucidate the mechanisms involved in the dehydrogenation. (C) Control experiments to probe the C−O cleavage.

quenchers were determined by Stern−Volmer quenching experiments, indicating that the excited state of acridinium was quenched by the diphenyl phosphate anion most efficiently (Figure 2A). The resulting active phosphate radical (BDE(O−H) = 102.4 kcal mol^{-1}) could abstract the hydrogen atom from a C(sp^3)−H bond (BDE(C−H) = 89.4−101.5 kcal mol^{-1}) to form the corresponding transient carbon radical,[72,73] which could be captured by (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (commonly known as TEMPO) as the radical scavenger (Scheme S4). The kinetic isotope effects (KIEs) were determined from two parallel reactions and a competition experiment (Scheme S5), giving k_H/k_D = 1.05 and 1.36, respectively. These results suggested that C(sp^3)−H activation might not be involved in the rate-determining step. The light on/off experiments suggested that continuous light irradiation was necessary for the transformation (Figure S5). Both light on/off experiments and the calculated quantum yield (Φ = 0.0015) suggested a nonchain pathway for hydrogen-evolution cross coupling.

Further control experiments were conducted to probe the plausible dehydrogenation pathway. We monitored the reaction of benzothiazole with cyclohexane by ^{1}H NMR spectroscopy and found that desired CDC product **37** was generated even at room temperature within 2 h of reaction, along with the adduct 2-cyclohexylbenzothiazoline (**37′**) (Figure 2B). Adduct **37′** could be converted into aromatic product **37** in 89% yield with hydrogen gas as the coupled product, where light and the SFMT reactor were essential to achieve efficient dehydrogenation (Table S3). Adducts dihydroquinoline intermediates were detected by high resolution mass spectrometry (Figures S15−18). The control experiment indicated that dehydrogenative rearomatization of dihydroquinoline **59′**[74] could be triggered either by blue light-irradiation or heating conditions (Figure 2B), which proceeded more efficiently in the SFMT reactor than in the conventional batch reactor (Table S4). These results suggested that the dehydrogenative process was initiated by rearomatization of the radical addition adduct under our reaction conditions.[75] The driving force for such a dehydrogenative process is the gain in aromaticity for the CDC products.

Finally, we tried to probe the C−O cleavage observed with acyclic ether substrates. When noncleaved ethereal compounds **14** and **60** were treated under standard CDC conditions, the detert-butoxylated products **15** and **61** were generated in good yields (Figure 2C). When styrene was used as a radical trapping reagent, coupling product **62** was generated in 50% yield (Figure 2C), suggesting that C−O cleavage occurred with the coupling product through a spin center shift (SCS) process.[32,33]

On the basis of the aforementioned results, a plausible mechanism was proposed, as depicted in Figure 3. Visible light irradiation of the acridinium photocatalyst to its excited state delivers a strong oxidant ($E_{1/2}^{\text{red}}$ = +2.06 V vs SCE), which readily oxidizes the diphenyl phosphate anion ($E_{\text{p}/2}^{\text{ox}}$ = +1.59 V vs SCE, Figure S13) to diphenyl phosphate radical **I**. A subsequent hydrogen atom abstraction from C(sp^3)−H bonds by **I** produces carbon radical **II**, which undergoes nucleophilic addition to protonated electrophilic heteroarenes **1**+H$^+$ to achieve radical cation intermediate **III**. Radical cation **III** is capable of oxidizing the reduced form of acridinium to regenerate the photocatalyst and produce coupling adduct **IV**. Assisted by the SFMT reactor, under light irradiation with

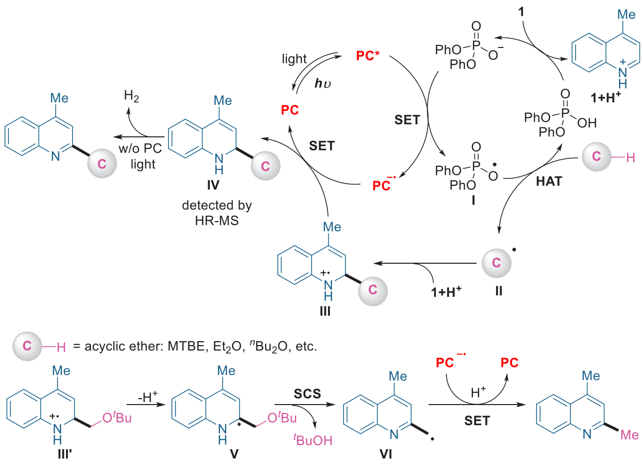


Figure 3. Proposed plausible mechanisms.

heating, adduct **IV** undergoes rearomatization to afford the desired coupling product, along with hydrogen release (Figure S19). When acyclic ethers are used as the C(sp^3)−H substrates, the radical cation adduct intermediate **III′** deprotonates to form the α-amino radical **V**. The subsequent SCS elimination of an alcohol delivers the radical intermediate **VI**, which undergoes single-electron reduction and protonation to achieve the alkylation product.

In conclusion, we have developed a protocol for visible light-induced hydrogen-evolution cross coupling of heteroarenes with unactivated C(sp^3)−H bonds in an operationally simple, metal- and oxidant-free manner. By the synergistic merger of photoredox catalysis with HAT catalysis, a broad range of readily available C(sp^3)−H feedstocks, including ethane gas, were coupled efficiently with diverse heteroarenes. The merit of this strategy has been demonstrated by successful applications to late-stage functionalization of complex bioactive compounds. Mechanistic studies revealed that the reaction proceeded via an unprecedented photomediated dehydrogenative process, where the acid additives played a dual role, to activate the heteroarenes and serve as the HAT agent. The key factor to our success lies in the use of the SFMT reactor. Expansion of this catalytic strategy to other types of transformations is currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c01087.

> General experimental procedures, tables of reaction optimizations, mechanistic study, characterization data including ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Author Contributions

⊥D.-S.L. and T.L. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support provided by the National Natural Science Foundation of China (Grant No. 21901121 to H.D., 21871205 and 22071170 to J.W.), the Natural Science Foundation of Jiangsu Province, China (BK20190502 to H.D.), the Fundamental Research Funds for the Central Universities (KJQN202054 to H.D.), the Ministry of Education of Singapore (MOET2EP10120-0014 to J.W.), National University of Singapore (R-143-000-B60-114 to J.W.), the National University of Singapore Flagship Green Energy Program (R-279-000-553-646 and R-279-000-553-731 to J.W.), and the NUS Suzhou Research Institute.

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