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ARTICLE

Diacetyl as a "Traceless" Visible Light Photosensitizer in Metal-Free Cross-Dehydrogenative-Coupling Reaction†

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The Minisci alkylation is of prime importance for its applicability to functionalize diverse heteroarenes, which are core structures in many bioactive compounds. During the alkyl radical generation process, precious metal catalysts, high temperatures and excessive oxidants are generally involved, which leads to sustainability and safety concerns. Herein we report a new strategy using diacetyl (2,3-butanedione) as an abundant, visible light-sensitized and "traceless" hydrogen atom abstractor to achieve metal-free cross-dehydrogenative Minisci alkylation under mild conditions. Mechanistic studies supported the hydrogen atom transfer (HAT) between activated C(sp^3)–H substrate and diacetyl. Moreover, with the assistance of di-*tert*-buyl peroxide (DTBP), the reaction scope could be extended to strong aliphatic C–H bonds via diacetyl-mediated energy transfer. The robustness of this strategy was demonstrated by functionalizing complex molecules such as quinine, Fasudil, nicotine, menthol and alanine derivatives.

Introduction

Heteroarenes are ubiquitous skeletons in pharmaceutical and agricultural uses, as well as small molecule studies. Therefore, the functionalization of these molecules especially at the late stage to create diversity is a long-lasting topic.[1] The Minisci alkylation is a powerful reaction to construct a C(sp^2)–C(sp^3) bond between electron-deficient heteroarenes and electron-rich alkyl radical, which is complementary to the Friedel-Crafts alkylation involving electron-rich arenes. Over the past few decades, many efforts have been devoted to the development of novel Minisci alkylations, predominantly focusing on the alkyl radical generation in more efficient and greener ways. Although the alkyl radicals could be generated through carbon–heteroatom bond cleavage of alkyl iodide[2], boronic acid[3] and others[4], or carbon–carbon bond cleavage of aldehyde,[5] acid derivatives,[6] and oxime esters,[7] pre-synthesis of the alkyl radical precursors is required. Alternatively, direct alkyl radical generation via hydrogen atom abstraction of alkanes, is the most desirable because alkyl structures are naturally abundant, and formal removal of H_2 through cross-dehydrogenative-coupling (CDC) between the alkanes and arenes gives the greatest atom and step economy (Figure 1).[8]

The key to cross-dehydrogenative alkylation is the activation of inert C(sp^3)–H bonds, and oxidative C–H activation is a straightforward way to generate carbon radicals via hydrogen atom abstraction;[9] thereby an efficient hydrogen atom abstractor is a requisite in the reaction design. Most of the strategies used oxygen-centered radicals, routinely generated from peroxides or persulfates, to perform the hydrogen atom abstraction from alkanes. Traditional methods relied on thermo-cleavage of the O–O bonds; however, demands of high reaction temperatures might deteriorate the reaction selectivity and functional group tolerance. Also, heating the explosive peroxides could cause safety concerns and limited the reaction scale.[10] To solve these issues, visible light-mediated CDC with iridium photocatalyst [Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6 at room temperature was introduced by MacMillan.[11] Alternatively, Ryu's group employed solar light to activate decatungstate photocatalyst (TBADT) as the hydrogen atom abstractor, with persulfate salt being added to regenerate the catalyst.[12] Other than oxy radical-based oxidant, hydrogen atom abstractors such as nitrogen-centered radical cations from hydroxide succinimide (NHS) and Selectfluor,[13] thiyl radicals from thiols,[14] iodine/azide-centered radicals from phenyliodine bis(trifluoroacetate) (PIFA)/sodium azide,[15] and

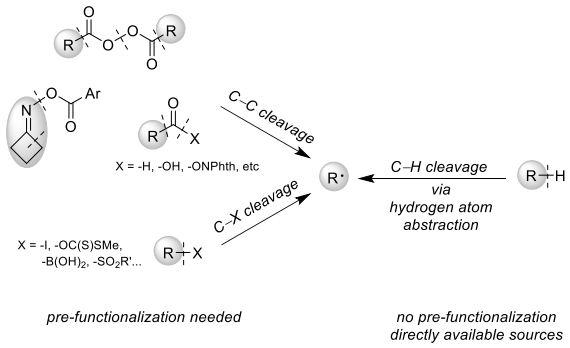

Figure 1. Alkyl radical generations through C–C, C–X and C–H bond cleavage.

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chlorine radical generated from dichloromethane (DCM),[16] were also feasible under mild reaction conditions.

Although numerous facile synthetic strategies have been developed, they are far from being ideal. It would be more desirable to conduct a CDC reaction under milder conditions without using costly photocatalysts and special light sources, while avoiding concomitant production of excess waste salts and harmful byproducts. Herein we wish to report a new approach to cross-dehydrogenative Minisci-type alkylation enabled by visible light using triplet state ketone as the hydrogen atom abstractor.

Research design

Triplet state ketones and peroxides/persulfates display similar redox reactivities to a certain degree. For example, Baran has designed a series of sulfinate salts for C–H functionalization of heteroarenes mediated by peroxide.[4b,4c] Later, our group reported a light-induced C(sp^2)–H trifluoromethylation with $NaSO_2CF_3$ enabled by excited acetone or diacetyl (2,3-butanedione) as the transient single-electron oxidants (Figure 2a).[17] Inspired by persulfate-based bimolecular homolytic substitution (S_H2) reaction of organoboranes,[18] we demonstrated that alkyl/aryl trifluoroborates could be converted to alkyl/aryl radicals through S_H2 by diacetyl under visible light irradiation (Figure 2b).[19] Based on these works, we hypothesized that triplet state ketones could substitute peroxides/persulfates in other carbon-centered radical generation processes, such as hydrogen atom transfer. Indeed, ketones have been used in some hydrogen atom transfer processes[20]; however, they were rarely applied in CDC reaction.

As stoichiometric amount of oxidant is required for the dehydrogenative process, the removal of excessive oxidant and its byproducts needs tedious and costly laboratory endeavor. Diacetyl is the smallest visible light sensitive ketone (380-460 nm), which can be a traceless photosensitizer due to its high volatility and solublity in water (200 g/L at 20 °C). The reduced product of diacetyl, acetoin, is miscible with water (1 kg/L at 20 °C). Considering these, byproducts derived from diacetyl could be removed by aqueous workup and reduced pressure. Furthermore, diacetyl is readily available and non-toxic. These advantages make diacetyl an ideal candidate in the cross-dehydrogenative system.

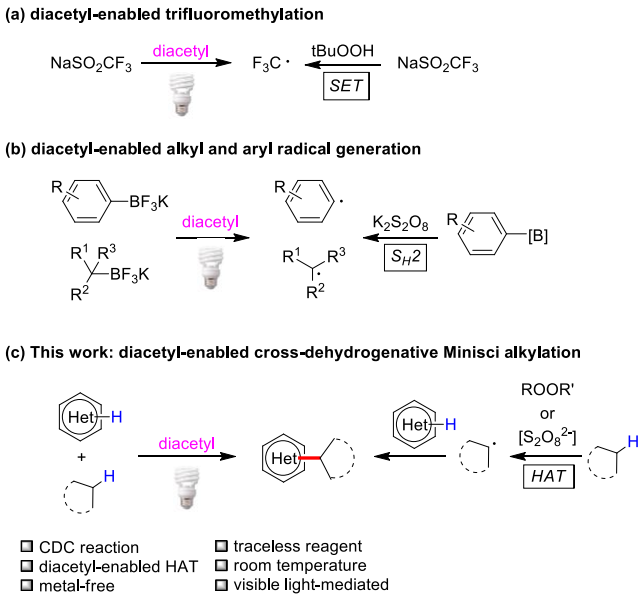


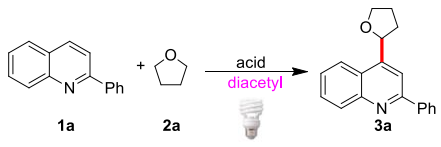
Figure 2. Diacetyl as a peroxide/persulfate surrogate.

Combining the literature reports and our previous experience, we hypothesized that diacetyl could serve as a hydrogen atom abstractor in cross-dehydrogenative Minisci alkylation due to its diradical character at excited state (Figure 2c). We envisioned that the success of this reaction would be a milestone in the exploration of ketone-enabled Minisci reactions and advance the development of greener cross-coupling reactions.

Results and discussion

In the preliminary studies, 2-phenylquinoline (**1a**) was selected as the radical acceptor for its high reactivity. At the beginning, a few representative compounds (tetrahydrofuran (THF), cyclohexane and toluene) were selected as the alkyl radical sources to test our hypothesis. To our delight, all of the corresponding alkylated products were detected by GC-MS under visible light irradiation using 40 W compact fluorescent lamp (CFL) as the light source (see supporting information Table S1). Then we chose THF (**2a**) as the model substrate to perform our optimization as it afforded the highest yield along with the ease of spectral analysis. As given in Table 1, trifluoacetic acid (TFA) was essential for the transformation while acetic (AcOH) or triflic acid (TfOH) were not effective proton sources (Table 1, entries 2 and 3). Different loadings of THF and diacetyl were investigated; the combination of 0.2 mL of THF and 0.2 mL of diacetyl gave the highest yield (entry 4). The reaction was promoted to completion by prolonging the reaction time to 36 h

Table 1. Optimization for the coupling of 2-phenylquinoline and THF.



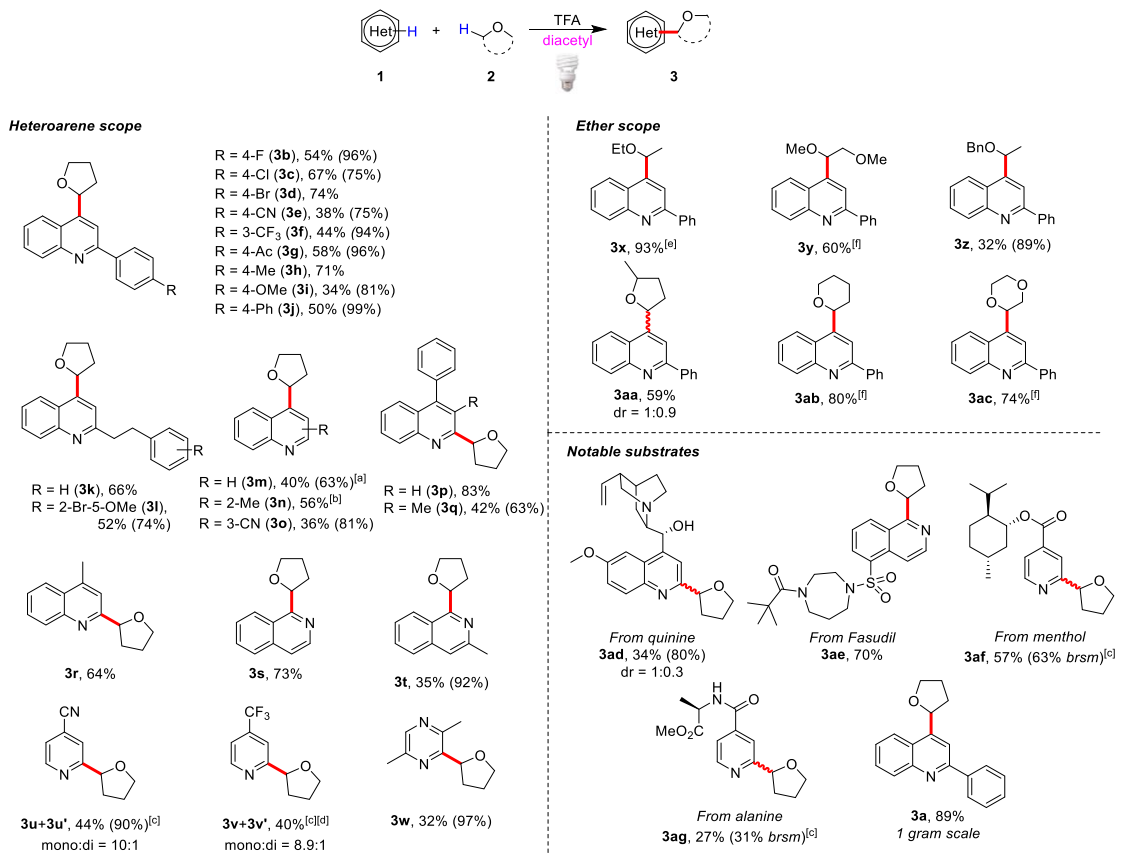
entry[a]	**2a** (mL)	diacetyl (mL)	acid	**1a** (%)[b]	**3a** (%)[b]
1	0.4	0.2	TFA	26	71
2	0.4	0.2	AcOH	>99	-
3	0.4	0.2	TfOH	>99	-
4	0.2	0.2	TFA	10	88
5	0.2	0.1	TFA	43	55
6	0.1	0.1	TFA	40	53
7[c]	0.2	0.2	TFA	-	90 (86)
8[d]	0.2	0.2	TFA	20	64
9[c][e]	0.2	0.2	TFA	-	52
10	0.4	-	TFA	>99	-
11[f]	0.2	0.2	TFA	>99	-

[a] All reactions were conducted with 0.1 mmol of **1a**, **2a**, 2 equiv of acid, diacetyl, and 40 W CFL at room temperature under argon for 20 h. [b] The yield was determined by ^{1}H NMR using mesitylene as the internal standard. Isolated yield in parenthesis. [c] The reaction was run for 36 h. [d] Under air. [e] The reaction was irradiated by Blue LED. [f] The reaction was heated to 70 °C in the dark.

(entry 7). In this reaction, blue LED gave inferior yield (entry 9). Finally, the control experiments showed that the light, diacetyl and innert atmosphere are all important for the reaction (entries 8, 10 and 11). As expected, most of the byproducts of this reaction could be simply removed by aqueous workup and reduced pressure without chromotographic purification (see supporting information Figure S2).

With the optimized conditions in hand, we tested the generality of this method (Scheme 1). The reaction tolerated diverse functional groups such as halides (**3b**-**3d**, **3l**), cyano (**3e**), acetyl (**3g**), methoxy (**3i** and **3l**) and alkyl groups (**3k**-**3m**). Most of the substrates provided moderate to excellent yields of the corresponding products (50-83%), and no significant reactivity bias between C2- and C4-alkylations (**3a** and **3n**, **3m** and **3r**) was observed. Substrates with steric effect (**3o**) or strong electron-donating group (**3i**), which might obstruct the radical addition, could still provide moderate yields (34-42%). It is notable that 3-substituted quinoline selectively gave the C4-alkylated product **3o**, and C4-alkylated quinoline **3m** could be obtained as the major product when unsubstituted quinoline was used. This showed that the C4 position is the more active position in our method. Other heterocycles such as isoquinolines (**3s** and **3t**), pyridines (**3u** and **3v**) and pyrazine (**3w**) could be functionalized smoothly by this protocol, although the reaction failed with heterocycles such as benzothiazole, benzoxazole and quinoxaline and gave poor yields (see supporting information Scheme S1). To our delight, pharmaceutically valuable molecules such as quinine (**3ad**) and Fasudil (**3ae**), or complex menthol and L-alanine derivatives (**3af** and **3ag**) were functionalizable with this method. To show the potential applications in industrial and pharmaceutical uses, we demonstrated a gram-scale reaction with 2-phenylquinoline (**1a**), in which 89% yield of the product (**3a**) could be obtained (for details see supporting information).

To consolidate our hypothesis that diacetyl is a hydrogen atom abstractor, mechanistic studies were conducted. When 2 equiv of radical inhibitor such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the model reaction, the reaction was significantly suppressed, implying that radical formation is involved (Scheme 2a). Prominent primary isotope effect was observed in the KIE experiments (k_H/k_D = 4), indicating that the α-C–H homocleavage of THF is the rate-determining step in this reaction.[21] Furthermore, the hydrogen atom abstraction is quite selective as no proton/deuterium exchange was observed from the reaction with THF-d_8 (Scheme 2b and supporting information Figure S4). When cyclopropyl phenyl ethylene (**6**) was tested, we were able to isolate appreciable amount of the alkylated adduct **7**, confirming the formation of the THF radical (Scheme 2c). To rule out the acyl radical-involved HAT pathway,[22] we replaced diacetyl with benzil (**8**) and 75% of the alkylated quinoline **3a** was obtained from the model substrates **1a** and **2a**, while only a trace amount of benzaldehyde (**11**) was observed from the crude NMR spectra. In contrast, vicinal diol **9** and benzoin (**10**) were isolated



Scheme 1. Scope for the Minisci alkylation with ethers. All reactions were conducted under the optimized conditions for 48 h unless otherwise specified, and the yields were isolated ones. Yields in the parentheses were based on recovered starting materials. [a] 0.1 mL of diacetyl and 0.2 mL of MeCN was added. [b] The reaction was run for 36 h. [c] 20 equiv of TFA was used. [d] Yield is from ^{1}H NMR using mesitylene as the internal standard. [e] 0.3 mL of ether was used. [f] 2 equiv of DTBP was added to the reaction, and the reactions were run for 20 h.

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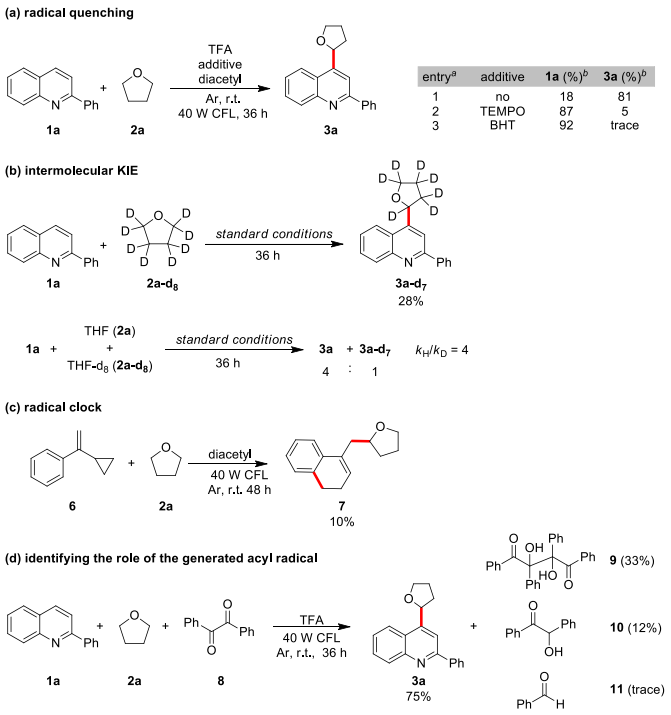


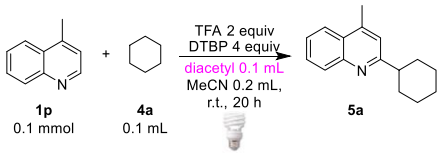
Scheme 2. Mechanistic studies: (a) radical quenching, (b) intermolecular KIE studies, (c) radical clock, and (d) identifying the role of the generate acyl radical.

from the reaction as the byproducts, indicating the direct HAT from THF to the excited benzil (Scheme 2d). Although we could not completely exclude the possibility that acyl radical took part in the HAT, these results strongly suggested that diketone does play an indispensable role in the hydrogen atom abstraction to generate alkyl radicals.

For the coupling of 2-phenylquinoline with other ether derivatives (Scheme 1), diethyl ether gave excellent yield of the alkylated product **3x**. Reaction with 2-methyl tetrahydrofuran also gave moderate yield of the desired products **3aa** in which the reaction occured selectively on the less hindered α-carbon. Surprisingly, some ethers such as 1,2-dimethoxyethane (DME), tetrahydropyrane (THP) and dioxane yielded only 10 to 20% of the corresponding products. According to the literatures,[23] the bond dissociation energy of these ethers are slightly higher, roughly 2 to 4 kcal/mol, than THF. We postulated that unlike traditionally persistent oxyradicals, the transient diketone diradical is a milder and more selective oxidant toward C–H species, which resulted in low efficiency in oxidizing stronger C–H bonds. To overcome this obstacle, a stronger oxidant is necessary. It is known that triplet state photosensitizers can serve as energy transferrers to facilitate alkene isomerization,[24] cycloaddition,[25] metallic reductive elimination[26] and homolytic bond cleavage.[27] Theoretically, the triplet state energy of diacetyl, about 55 to 57 kcal/mol,[28] would be enough to induce the cleavage of weak peroxide O–O bonds (BDE generally lower than 50 kcal/mol[29]). Considering that di-*tert*-buyl peroxide (DTBP) has a low O–O bond-dissociation energy (38 kcal/mol) and the byproduct *tert*-butanol is easily removable, 2 equiv of DTBP was chosen to be added to the reaction system. The reactions proceeded smoothly under room temperature and reached completion after 20 h to give good yields of the products **3y**, **3ab** and **3ac**.

When diacetyl was used to cleave strong C(sp^3)–H bond of cyclohexane (**4a**), it was not surprising that only a trace amount of cyclohexyl adduct **5a** was observed (Table 2, entry 2). Further

Table 2. Optimization for the coupling of 4-methylquinoline and cyclohexane.



entry	deviations from the standard conditions	**1p** (%)[a]	**5a** (%)[a]
1	no	-	87 (84)
2	conditions in Table 1, entry 7	83	6
3	reacted at 4 °C for 24 h.	-	86
4	reacted at 70 °C, and no light.	>99	-

[a] The yield was determined by ^{1}H NMR using mesitylene as the internal standard. Isolated yield in parenthesis.

optimizations of the protocol were performed by adding DTBP as the oxidant, and 84% of **5a** could be obtained with MeCN as the cosolvent (for detailed optimizations see supporting information Table S2). In order to eliminate the possibility of thermo cleavage of peroxide at room temperature, a reaction was conducted at 4 °C, and the same yield could be obtained by prolonging the reaction time to 24 h (entry 3). On the contrary, no reaction took place in the absence of light, even when the reaction was heated to 70 °C (entry 4). These control experiments supported the energy transfer- rather than thermo-induced peroxide cleavage. The efficiency of this energy transfer at low temperature also provided a synthetic option for thermosensitive compounds. Further analysis of the crude components from the reaction also supported the energy transfer rather than radical substitution process between diacetyl and DTBP (see supporting information Schemes S5 and S6).

The scope of this modified protocol was then examined. Various heterocycles including phenanthridine (**5e**), isoquinoline (**5f**), quinazoline (**5g**), pyrimidine (**5h**) and benzothiazole (**5l**) could be functionalized under mild conditions and gave moderate yields (40-50%) of the corresponding products (Scheme 3). Valuable substrates, for example, quinine (**5s**), nicotine (**5t**), menthol or L-alanine derivatives (**5u** and **5v**), could be functionalized albeit with lower yields (27-37%). The method is also useful to modify heterocyclic ligands such as 4,4'-di-*tert*-butyl-2,2'-dipyridyl, yielding 34% of the dialkylated product **5w**. Diverse alkylated products could be obtained by replacing cyclohexane to other alkyl substrates such as cyclopentane and cyclooctane in excellent yields (89-97%) of heterocycle derivatives (**5m** and **5n**). Reactions with bridged hydrocarbon norbonane gave 84% of the alkylated product **5p**, while cyclopentanone, 7-oxabicyclo[2.2.1]heptane and toluene gave only poor to moderate yields of the corresponding products **5o**, **5q** and **5r**.

Based on previous literatures and the mechanistic investigations presented above, a plausible mechanism for the diacetyl-enabled CDC reaction was proposed as follows. The excited ketone **12** acts as a hydrogen atom abstractor to generate the alkyl radical **13** to couple with the protonated heteroarene **1-H$^+$** (Scheme 4, right). The protonated ketyl radical **15** might undergo tautomerization to form an enol radical **16** and perform the second hydrogen atom abstraction to rearomatize the alkyl adduct **14**, which gives the product **3-H$^+$**. When a peroxide (DTBP) was added to dominate the HAT, the role of triplet ketone is switched to the energy transferrer (Scheme 4, left). By energy transfers from the excited ketone **12** to a peroxide **18**, the excited peroxide **19** cleaves into 2 equiv of the oxy radical **20** to abstract hydrogen atom from the alkane **2**/**4** and the

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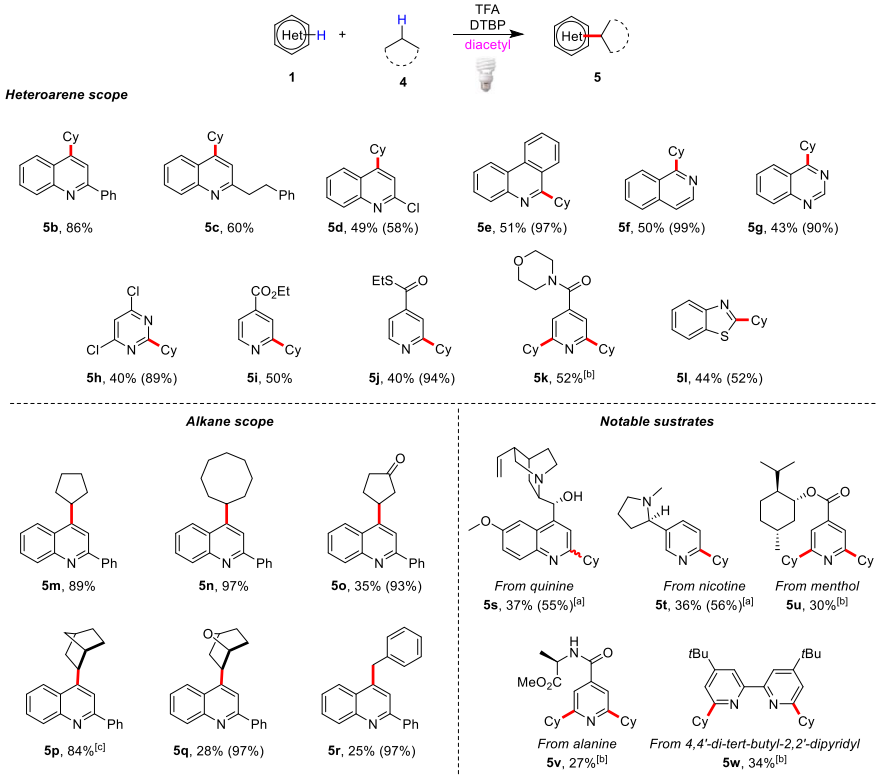
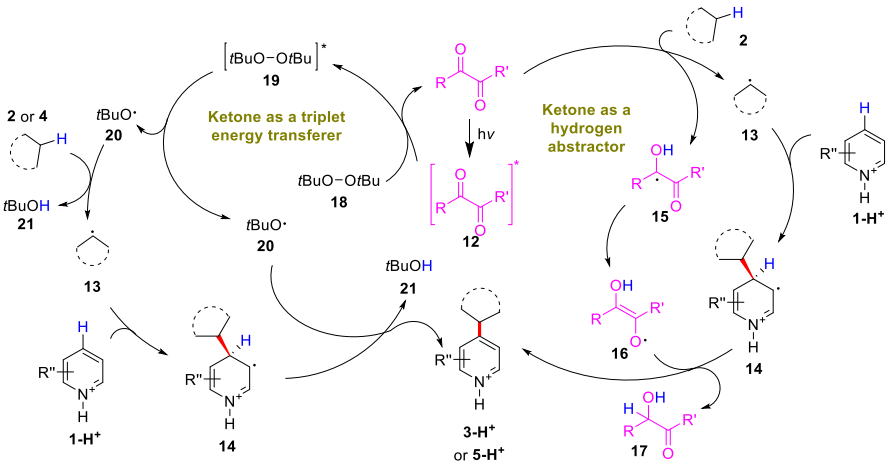
alkyl adduct **14**, respectively, to give a protonated heteroarene **3-H⁺/5-H⁺** as the product.

Conclusions

In summary, the first ketone-enabled cross-dehydrogenative Minisci alkylation using diacetyl as a traceless and sustainable photosensitive reagent, has been developed. This approach utilized the triplet diacetyl as either hydrogen atom abstractor or energy transferrer for the coupling of heterocycles and alkanes under mild conditions. This strategy allowed functionalization of a wide range of substrates bearing copious functional groups. Control experiments and mechanistic studies suggest the involvement of a radical process. Further studies will allow us to understand the hydrogen atom abstraction ability of diacetyl and other potential traceless diketone photosensitizers.



Scheme 3. Scope for the Minisci alkylation with unactivated C(sp^3)–H species. All reactions were conducted under the optimized conditions unless otherwise specified, and the yields were isolated ones. Yields in the parentheses were based on recovered starting materials. [a] 3 equiv of TFA was used. [b] The reactions were conducted with 0.2 mL of alkane, 8 equiv of DTBP, 0.2 mL of diacetyl, and 0.4 mL of MeCN. [c] 5 equiv of alkane was used.



Scheme 4. Proposed ketone-enabled CDC reaction mechanism

Experimental section

Detailed experimental procedures are provided in the Supplemental Information.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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