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Introduction

Heteroarenes are ubiquitous skeletons for pharmaceutical and agricultural uses, as well as small molecule studies. Therefore, functionalization of these molecules especially during the late stage to create diversity is a long-lasting topic.¹ Minisci alkylation is a powerful reaction to construct a C(sp³)-C(sp³) bond between electron-deficient heteroarenes and electron-rich alkyl radicals, and is complementary to 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 alkyl radical generation in more efficient and greener ways. Although alkyl radicals could be generated through carbon-heteroatom bond cleavage of alkyl iodides,² boronic acids³ and others,⁴ or carbon-carbon bond cleavage of aldehydes,⁵ acid derivatives,⁶ and oxime esters,⁷ pre-synthesis of alkyl radical precursors is required. Alternatively, direct alkyl radical generation *via* hydrogen atom abstraction from alkanes is the most desirable because alkyl structures are naturally abundant, and formal removal of H₂ through cross-dehydrogenative coupling (CDC) between alkanes and arenes gives the greatest atom and step economy (Fig. 1).⁸

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Diacetyl as a “traceless” visible light photosensitizer in metal-free cross-dehydrogenative coupling reactions†

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Minisci alkylation is of prime importance for its applicability in functionalizing diverse heteroarenes, which are core structures in many bioactive compounds. In alkyl radical generation processes, precious metal catalysts, high temperatures and excessive oxidants are generally involved, which lead to sustainability and safety concerns. Herein we report a new strategy using diacetyl (2,3-butanedione) as an abundant, visible light-sensitive and “traceless” hydrogen atom abstractor to achieve metal-free cross-dehydrogenative Minisci alkylation under mild conditions. Mechanistic studies supported hydrogen atom transfer (HAT) between an activated C(sp³)-H substrate and diacetyl. Moreover, with the assistance of di-*tert*-butyl peroxide (DTBP), the scope of the reaction 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.

The key to cross-dehydrogenative alkylation is the activation of inert C(sp³)-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 for the reaction design. Most of the strategies used oxygen-centered radicals, routinely generated from peroxides or persulfates, to perform hydrogen atom abstraction from alkanes. Traditional methods relied on thermo-cleavage of O-O bonds; however, demands of high reaction temperatures might deteriorate the reaction selectivity and functional group tolerance. Also, heating explosive peroxides could cause safety concerns and limit the reaction scale.¹⁰ To solve these issues, visible light-mediated CDC with an iridium photocatalyst [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ at room temperature was introduced by MacMillan.¹¹ Alternatively, Ryu's group employed solar light to activate a decatungstate

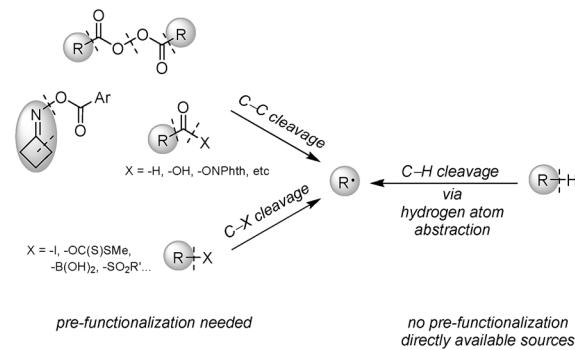


Fig. 1 Alkyl radical generation through C-C, C-X and C-H bond cleavage.



photocatalyst (TBADT) as a hydrogen atom abstractor, with persulfate salt being added to regenerate the catalyst.¹² Other than oxy radical-based oxidants, hydrogen atom abstractors such as nitrogen-centered radical cations from *N*-hydroxysuccinimide (NHS) and Selectfluor,¹³ thiyl radicals from thiols,¹⁴ iodine/azide-centered radicals from phenyliodine bis-(trifluoroacetate) (PIFA)/sodium azide,¹⁵ and chlorine radicals 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 ketones 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 peroxides.^{4b,c} Later, our group reported light-induced C(sp²)–H trifluoromethylation with NaSO₂CF₃ enabled by excited acetone or diacetyl (2,3-butandione) as transient single-electron oxidants (Fig. 2a).¹⁷ Inspired by persulfate-based bimolecular homolytic substitution (S_{H2}) reactions 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 (Fig. 2b).¹⁹ Based on these studies, 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 reactions.

As a stoichiometric amount of the oxidant is required for the dehydrogenation process, the removal of excessive oxidant and its byproducts needs tedious and costly laboratory processes. Diacetyl is the smallest visible light sensitive ketone (380–460 nm), which can be a traceless photosensitizer due to its high volatility and solubility in water (200 g L⁻¹ at 20 °C). The reduced product of diacetyl, acetoin, is miscible with water (1 kg L⁻¹ at 20 °C). Considering this, 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 for the cross-dehydrogenative system.

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 in the excited state (Fig. 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.

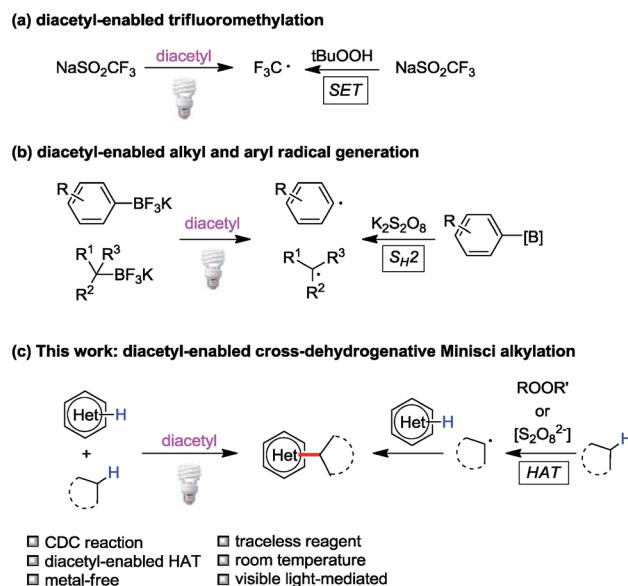
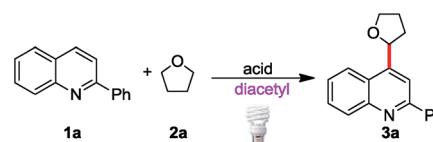


Fig. 2 Diacetyl as a peroxide/persulfate surrogate.

Results and discussion

In the preliminary studies, 2-phenylquinoline (**1a**) was selected as the radical acceptor due to 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

Table 1 Optimization of 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** and **2a**, and 2 equiv of acid and diacetyl, and a 40 W CFL at room temperature under argon for 20 h. ^b The yield was determined by ¹H NMR using mesitylene as the internal standard. Isolated yield in parentheses. ^c The reaction was run for 36 h. ^d In air. ^e The reaction was irradiated using a blue LED. ^f The reaction was heated to 70 °C in the dark.

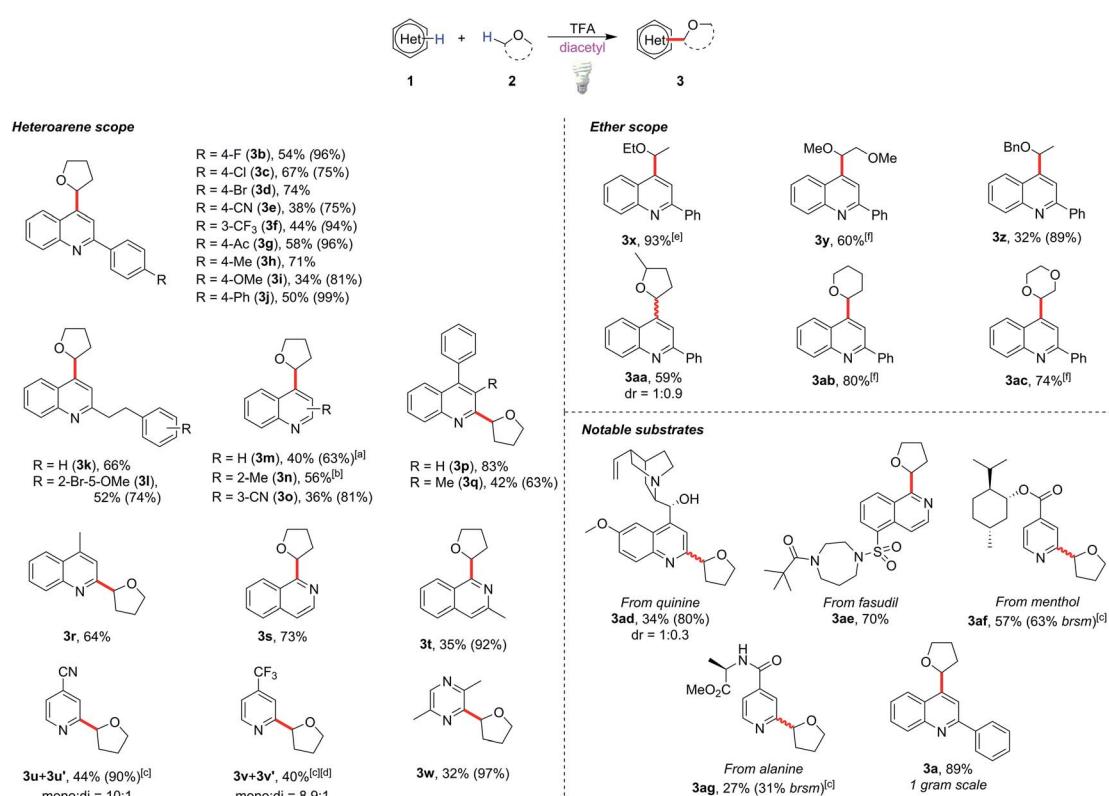


visible light irradiation using a 40 W compact fluorescent lamp (CFL) as the light source (see ESI Table S1†). Then we chose THF (2a) as the model substrate to perform our optimization as it produced the highest yield along with its ease of use in spectral analysis. As given in Table 1, trifluoroacetic acid (TFA) was essential for the transformation while acetic (AcOH) or triflic acids (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 completed by prolonging the reaction time to 36 h (entry 7). In this reaction, a blue LED gave inferior yield (entry 9). Finally, the control experiments showed that the light, diacetyl and an inert 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 chromatographic purification (see ESI Fig. 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, and 3m and 3r) was observed. Substrates with a steric effect (3o) or a strong

electron-donating group (3i), which might obstruct 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 ESI 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) could be functionalized 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 the ESI†).

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). A prominent primary isotope effect was



Scheme 1 Scope of Minisci alkylation with ethers. All reactions were conducted under optimized conditions for 48 h unless otherwise specified, and the yields were isolated ones. Yields in 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 ^1H 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.



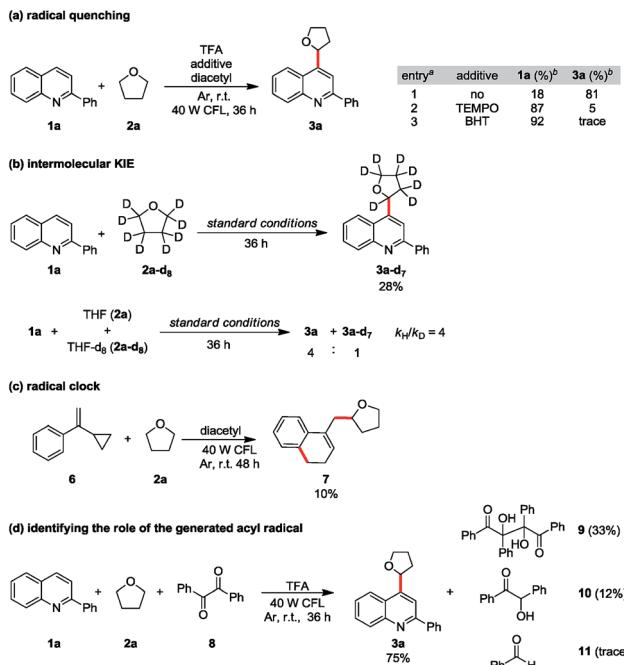
observed in the KIE experiments ($k_H/k_D = 4$), indicating that the α -C–H homocleavage of THF is the rate-determining step in this reaction.²¹ Furthermore, hydrogen atom abstraction is quite selective as no proton/deuterium exchange was observed from the reaction with THF-d₈ (Scheme 2b and ESI Fig. S4†). When cyclopropyl phenyl ethylene (6) was tested, we were able to isolate an 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% 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 from the reaction as byproducts, indicating direct HAT from THF to the excited benzil (Scheme 2d). Although we could not completely exclude the possibility that an acyl radical took part in HAT, these results strongly suggested that diketones do play an indispensable role in hydrogen atom abstraction to generate alkyl radicals.

For the coupling of 2-phenylquinoline with other ether derivatives (Scheme 1), diethyl ether gave an excellent yield of the alkylated product 3x. Reaction with 2-methyl tetrahydrofuran also gave moderate yield of the desired product 3aa where the reaction occurred selectively on the less hindered α -carbon. Surprisingly, some ethers such as 1,2-dimethoxyethane (DME), tetrahydropyran (THP) and dioxane yielded only 10 to 20% of the corresponding products. According to the literature,²³ the bond dissociation energy of these ethers is slightly higher, roughly 2 to 4 kcal mol⁻¹, than that of 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 a 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 transfer agents to facilitate alkene isomerization,²⁴ cycloaddition,²⁵ metallic reductive elimination²⁶ and homolytic bond cleavage.²⁷ Theoretically, the triplet state energy of diacetyl, about 55 to 57 kcal mol⁻¹,²⁸ would be enough to induce the cleavage of weak peroxide O–O bonds (BDE is generally lower than 50 kcal mol⁻¹).²⁹ Considering that di-*tert*-butyl peroxide (DTBP) has a low O–O bond-dissociation energy (38 kcal mol⁻¹) 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 at room temperature and reached completion after 20 h to give good yields of the products 3y, 3ab and 3ac.

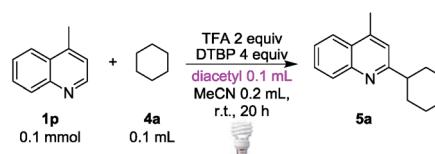
When diacetyl was used to cleave the strong C(sp³)–H bond of cyclohexane (4a), it was not surprising that only a trace amount of the cyclohexyl adduct 5a was observed (Table 2, entry 2). Further optimizations of the protocol were performed by adding DTBP as the oxidant, and 84% of 5a could be obtained with MeCN as the cosolvent (for detailed optimizations see ESI Table S2†). In order to eliminate the possibility of thermal cleavage of peroxides 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). In contrast, no reaction took place in the absence of light, even when the reaction was heated to 70 °C (entry 4). These control experiments supported energy transfer-induced peroxide cleavage rather than thermal-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 ESI 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 2 Mechanistic studies: (a) radical quenching, (b) intermolecular KIE studies, (c) radical clock, and (d) identifying the role of the generated acyl radical.

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



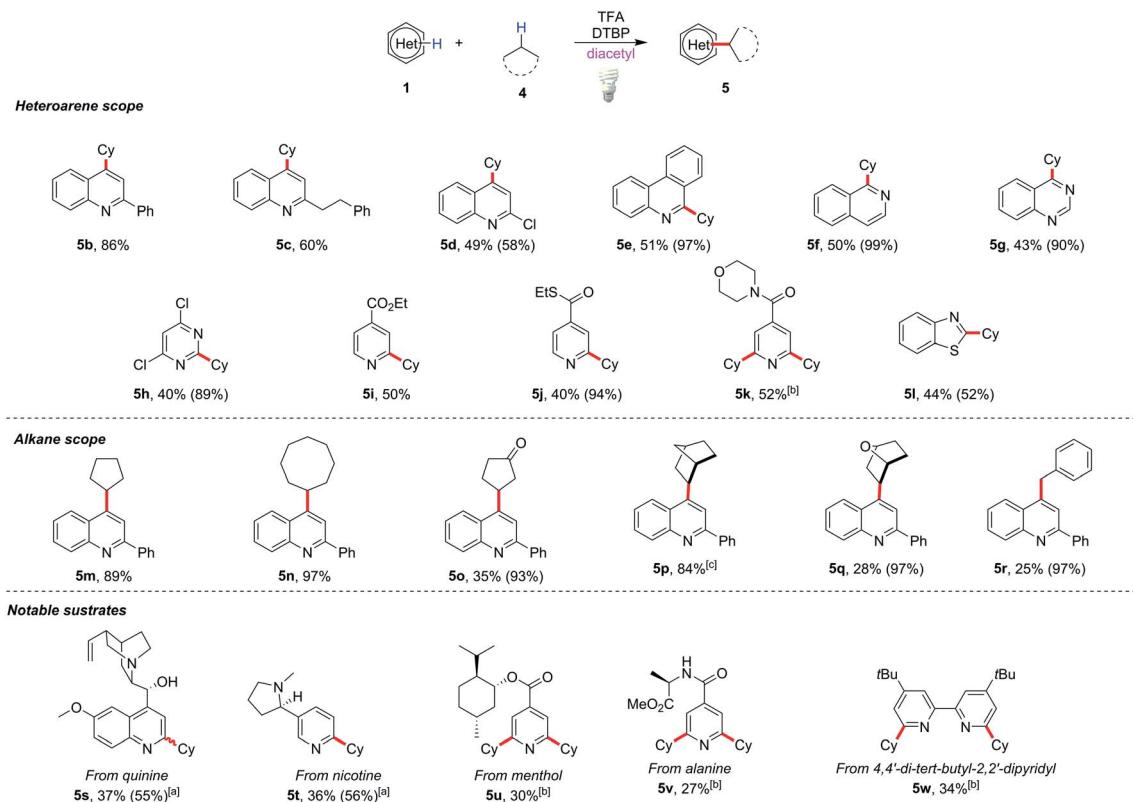
Entry	Deviations from the standard conditions	1p (%) ^a	5a (%) ^a
1	No	—	87 (84)
2	Conditions in Table 1, entry 7	83	6
3	Reacted at 4 °C for 24 h	—	86
4	Reacted at 70 °C, and no light	>99	—

^a The yield was determined by ¹H NMR using mesitylene as the internal standard. Isolated yield in parentheses.

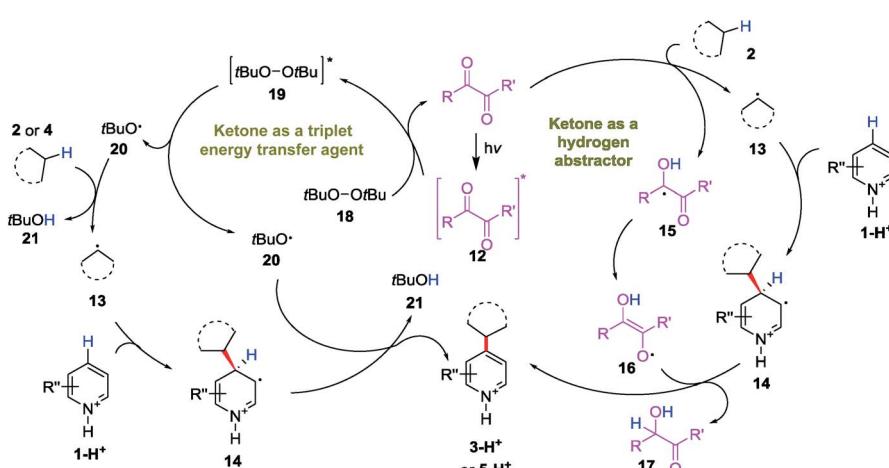
(Scheme 3). Valuable substrates, for example, quinine (**5s**), nicotine (**5t**), and menthol or L-alanine derivatives (**5u** and **5v**), could be functionalized albeit with lower yields (27–37%). The method is also useful to modify heterocyclic ligands such as 4,4'-di-*tert*-butyl-2,2'-dipyridyl, yielding 34% dialkylated product **5w**. Diverse alkylated products could be obtained by replacing cyclohexane with other alkyl substrates such as cyclopentane and cyclooctane in excellent yields (89–97%) of heterocycle derivatives (**5m** and

5n). Reactions with bridged hydrocarbon norbornane gave 84% alkylated product **5p**, while those with 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 literature 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



Scheme 3 Scope of Minisci alkylation with unactivated $C(sp^3)-H$ species. All reactions were conducted under optimized conditions unless otherwise specified, and the yields were isolated ones. Yields in 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.

alkyl radical **13** to couple with protonated heteroarene **1-H⁺** (Scheme 4, right). The protonated ketyl radical **15** might undergo tautomerization to form an enol radical **16** and perform a second hydrogen atom abstraction to rearomatize the alkyl adduct **14**, which gives the product **3-H⁺**. When a peroxide (DTBP) was added to enhance the HAT, the role of the triplet ketone is switched to that as the energy transfer agent (Scheme 4, left). By energy transfer from the excited ketone **12** to a peroxide **18**, the excited peroxide **19** cleaves into 2 equiv of the oxy radical **20** to abstract a hydrogen atom from the alkane **2/4** and the 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 triplet diacetyl as either a hydrogen atom abstractor or an energy transfer agent 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.

Experimental section

Detailed experimental procedures are provided in the ESI.†

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) J. Wu, Y. Liu, C. Lu and Q. Shen, *Chem. Sci.*, 2016, **7**, 3757–3762; (b) R. S. J. Proctor, H. J. Davis and R. J. Phipps, *Science*, 2018, **360**, 419–422.
- F. Fontana, F. Minisci and E. Vismara, *Tetrahedron Lett.*, 1988, **29**, 1975–1978.
- (a) G.-X. Li, C. A. Morales-Rivera, Y. Wang, F. Gao, G. He, P. Liu and G. Chen, *Chem. Sci.*, 2016, **7**, 6407–6412; (b) L. Zhang and Z.-Q. Liu, *Org. Lett.*, 2017, **19**, 6594–6597.
- (a) F. Coppa, F. Fontana, F. Minisci, G. Pianese, P. Tortoreto and L. Zhao, *Tetrahedron Lett.*, 1992, **5**, 687–690; (b) Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond and P. S. Baran, *Proc. Natl. Acad. Sci. U.S.A.*, 2011, **108**, 14411–14415; (c) Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond and P. S. Baran, *J. Am. Chem. Soc.*, 2012, **134**, 1494–1497; (d) P. Liu, W. Liu and C.-J. Li, *J. Am. Chem. Soc.*, 2017, **139**, 14315–14321.
- R.-J. Tang, L. Kang and L. Yang, *Adv. Synth. Catal.*, 2015, **357**, 2055–2060.
- (a) F. Minisci, R. Bernardi, F. Bertini, R. Galli and M. Perchinummo, *Tetrahedron*, 1971, **27**, 3575–3579; (b) R. Xia, M.-S. Xie, H.-Y. Niu, G.-R. Qu and H.-M. Guo, *Org. Lett.*, 2014, **16**, 444–447; (c) R. A. Garza-Sanchez, A. Tlahuext-Aca, G. Tavakoli and F. Glorius, *ACS Catal.*, 2017, **7**, 4057–4061; (d) W.-M. Cheng, R. Shang, M.-C. Fu and Y. Fu, *Chem.-Eur. J.*, 2017, **23**, 2537–2541.
- (a) B. Zhao and Z. Shi, *Angew. Chem., Int. Ed.*, 2017, **56**, 12727–12731; (b) X.-Y. Yu, J.-R. Chen, P.-Z. Wang, M.-N. Yang, D. Liang and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2018, **57**, 738–743; (c) L. Yang, P. Gao, X.-H. Duan, Y.-R. Gu and L.-N. Guo, *Org. Lett.*, 2018, **20**, 1034–1037.
- (a) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335–344; (b) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74–100; (c) H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh and A. Lei, *Chem. Rev.*, 2017, **117**, 9016–9085.
- For selected oxidative C–H activations, see (a) D. Liu, C. Liu, H. Li and A. Lei, *Angew. Chem., Int. Ed.*, 2013, **52**, 4453–4456; (b) D. Liu, C. Liu, H. Li and A. Lei, *Chem. Commun.*, 2014, **50**, 3623–3626; (c) A. Studer and D. P. Curran, *Angew. Chem., Int. Ed.*, 2016, **55**, 58–102; (d) L. Zhang, H. Yi, J. Wang and A. Lei, *J. Org. Chem.*, 2017, **82**, 10704–10709; (e) X. Hu, G. Zhang, F. Bu, L. Nie and A. Lei, *ACS Catal.*, 2018, **8**, 9370–9375; Y. Zhang and C.-J. Li, *Eur. J. Org. Chem.*, 2007, **2007**, 4654–4657; G. Deng, L. Zhao and C.-J. Li, *Angew. Chem., Int. Ed.*, 2008, **47**, 6278–6282; G. Deng, K. Ueda, S. Yanagisawa, K. Itami and C.-J. Li, *Chem.-Eur. J.*, 2009, **15**, 333–337; X. Guo and C.-J. Li, *Org. Lett.*, 2011, **13**, 4977–4979.
- (a) C. Giordano, F. Minisci, E. Vismara and S. Levi, *J. Org. Chem.*, 1986, **51**, 536–537; (b) G. Deng and C.-J. Li, *Org. Lett.*, 2009, **11**, 1171–1174; (c) Z. Xie, Y. Cai, H. Hu, C. Lin, J. Jiang, Z. Chen, L. Wang and Y. Pan, *Org. Lett.*, 2013, **15**, 4600–4603; (d) X. Li, H.-Y. Wang and Z.-J. Shi, *New J. Chem.*, 2013, **37**, 1704–1706; (e) N. Okugawa, K. Moriyama and H. Togo, *Eur. J. Org. Chem.*, 2015, **2015**, 4973–4981; (f) A. Correa, B. Fiser and E. Gómez-Bengoa, *Chem. Commun.*, 2015, **51**, 13365–13368; (g) B. A. Mir, A. Banerjee, S. K. Santra, S. Rajamanickam and B. K. Patel, *Adv. Synth. Catal.*, 2016, **358**, 3471–3476; (h) J. Yuan, J. Fu, J. Yin, Z. Dong, Y. Xiao, P. Mao and L. Qu, *Org. Chem. Front.*, 2018, **5**, 2820–2828.
- (a) J. Jin and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2015, **54**, 1565–1569; for another iridium photocatalyst-based CDC, see ; (b) J. Dong, Q. Xia, X. Lv, C. Yan, H. Song, Y. Liu and Q. Wang, *Org. Lett.*, 2018, **20**, 5661–5665.



12 M. C. Quattrini, S. Fujii, K. Yamada, T. Fukuyama, D. Ravelli, M. Fagnoni and I. Ryu, *Chem. Commun.*, 2017, **53**, 2335–2338.

13 (a) S. Liu, A. Liu, Y. Zhang and W. Wang, *Chem. Sci.*, 2017, **8**, 4044–4050. During the preparation of our manuscript, a related study was published; (b) L. Niu, J. Liu, X.-A. Liang, S. Wang and A. Lei, *Nat. Commun.*, 2019, DOI: 10.1038/s41467-019-08413-9.

14 J. Jin and D. W. C. MacMillan, *Nature*, 2015, **525**, 87–90.

15 A. P. Antonchick and L. Burgmann, *Angew. Chem., Int. Ed.*, 2013, **52**, 3267–3271.

16 W. Liu, X. Yang, Z.-Z. Zhou and C.-J. Li, *Chem*, 2017, **2**, 688–702.

17 L. Li, X. Mu, W. Liu, Y. Wang, Z. Mi and C.-J. Li, *J. Am. Chem. Soc.*, 2016, **138**, 5809–5812.

18 (a) I. B. Sieple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel and P. S. Baran, *J. Am. Chem. Soc.*, 2010, **132**, 13194–13196; (b) J. W. Lockner, D. D. Dixon, R. Risgaard and P. S. Baran, *Org. Lett.*, 2011, **13**, 5628–5631.

19 (a) P. J. Krusic and J. K. Kochi, *J. Am. Chem. Soc.*, 1969, **91**, 3942–3944; (b) A. G. Davies and B. P. Roberts, *Nature*, 1971, **229**, 221–223; (c) A. G. Davies and B. P. Roberts, *Acc. Chem. Res.*, 1972, **5**, 387–392; (d) C. Carra and J. C. Scaiano, *Eur. J. Org. Chem.*, 2008, **2008**, 4454–4459; (e) W. Liu, P. Liu, L. Lv and C.-J. Li, *Angew. Chem., Int. Ed.*, 2018, **57**, 13499–13503.

20 (a) C. Walling and M. J. Gibian, *J. Am. Chem. Soc.*, 1965, **87**, 3361–3364; (b) H. A. J. Carless and S. Mwesigye-Kibende, *J. Chem. Soc. Chem. Commun.*, 1987, 1673–1674; (c) K.-i. Wada, M. Yamamoto and J.-i. Setsune, *Tetrahedron Lett.*, 1999, **40**, 2773–2776; (d) A. M. Cardarelli, M. Fagnoni, M. Mella and A. Albini, *J. Org. Chem.*, 2001, **66**, 7320–7327; (e) S. Kamijo, T. Hoshikawa and M. Inoue, *Org. Lett.*, 2011, **13**, 5928–5931; (f) J.-B. Xia, C. Zhu and C. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 17494–17500; (g) T. Hoshikawa, S. Kamijo and M. Inoue, *Org. Biomol. Chem.*, 2013, **11**, 164–169; (h) A. Lipp, G. Lahm and T. Opatz, *J. Org. Chem.*, 2016, **81**, 4890–4897; (i) S. Kamijo, G. Takao, K. Kamijo, T. Tsuno, K. Ishiguro and T. Murafuji, *Org. Lett.*, 2016, **18**, 4912–4915.

21 Y. Zhu and Y. Wei, *Chem. Sci.*, 2014, **5**, 2379–2382.

22 L. Zhang, X. Si, Y. Yang, M. Zimmer, S. Witzel, K. Sekine, M. Rudolph and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2019, **58**, 1823–1827.

23 (a) E. T. Denisov, I. B. Afanas'ev, *Oxidation and Antioxidants in Organic Chemistry and Biology*, Taylor & Francis Group, 2005, pp. 281–298; (b) H. Matsubara, S. Suzuki and S. Hirano, *Org. Biomol. Chem.*, 2015, **13**, 4686–4692.

24 (a) K. Singh, S. J. Staig and J. D. Weaver, *J. Am. Chem. Soc.*, 2014, **136**, 5275–5278; (b) J. B. Metternich and R. Gilmour, *Synlett*, 2016, **27**, 2541–2552.

25 (a) P. Sharma, B. Lygo, W. Lewis and J. E. Moses, *J. Am. Chem. Soc.*, 2009, **131**, 5966–5972; (b) Z. Lu and T. P. Yoon, *Angew. Chem., Int. Ed.*, 2012, **51**, 10329–10332; (c) J. Zhao, J. L. Brosmer, Q. Tang, Z. Yang, K. N. Houk, P. L. Diaconescu and O. Kwon, *J. Am. Chem. Soc.*, 2017, **139**, 9807–9810; (d) N. Münster, N. A. Parker, L. van Dijk, R. S. Paton and M. D. Smith, *Angew. Chem., Int. Ed.*, 2017, **56**, 9468–9472.

26 (a) D. R. Heitz, J. C. Tellis and G. A. Molander, *J. Am. Chem. Soc.*, 2016, **138**, 12715–12718; (b) E. R. Welin, C. Le, D. M. Arias-Rotondo, J. K. McCusker and D. W. C. MacMillan, *Science*, 2017, **355**, 380–385; (c) Y. Shen, Y. Gu and R. Martin, *J. Am. Chem. Soc.*, 2018, **140**, 12200–12209.

27 (a) E. P. Farney and T. P. Yoon, *Angew. Chem., Int. Ed.*, 2014, **53**, 793–797; (b) E. Arceo, E. Montroni and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2014, **53**, 12064–12068; (c) M. Teders, C. Henkel, L. Anhäuser, F. Strieth-Kalthoff, A. Gómez-Suárez, R. Kleinmans, A. Kahnt, A. Rentmeister, D. Guldi and F. Glorius, *Nat. Chem.*, 2018, **10**, 981–988.

28 (a) M. W. Schmidt and E. K. C. Lee, *J. Am. Chem. Soc.*, 1970, **92**, 3579–3586; (b) A. W. Jackson and A. J. Yarwood, *Can. J. Chem.*, 1972, **50**, 1331–1337.

29 (a) S. L. Khursan, D. A. Mikhailov, A. A. Gusmanov and I. M. Borisov, *Russ. J. Phys. Chem. A*, 2001, **75**, 724–732; (b) F. Agapito, B. J. C. Cabral and J. A. M. Simões, *J. Mol. Struct. THEOCHEM*, 2005, **729**, 223–227.

