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Direct coupling of inert C–H bonds in NHC organocatalysis

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Direct coupling of inert C–H bonds by N-heterocyclic carbenes (NHCs) represents a fascinating area of research in organocatalysis. Recently, several notable studies have disclosed the potential of NHCs to directly functionalize latent C–H bonds of diverse simple molecules (*e.g.*, ethers, amines, and arenes). These methodologies offer straightforward and efficient routes for C–C bond-forming transformations by diminishing the need for prefunctionalization manipulations of inert C–H bonds, allowing for the synthesis of a broad range of high value-added functional ketone molecules. Consequently, this highlight aims to present the latest advancements in NHC organocatalysis, specifically focusing on direct coupling functionalization of inert C–H bonds involving the electron or proton transfer process (ET/PT pathways) and hydrogen atom transfer pathway (HAT pathway).

Introduction

The development of catalytic strategies for the direct functionalization of robust C–H bonds represents one of the most formidable challenges in synthetic chemistry.[1] The conversion of these resilient chemical compounds into high-value-added functional molecules is considered the ultimate goal of organic synthesis. To date, most of the protocols for forming C–C or C–heteroatom bonds with non-reactive C(sp^3) atoms have relied on the prefunctionalization of hydrocarbons into polarized C–X bonds, such as C–Cl, Br, O, N, *etc.*, by increasing their reactivity in C–C bond formation. However, despite its wide application in organic synthesis, this approach suffers from limitations in terms of atom and step economy due to the requirement of pre-installed functional groups.

In contrast, the strategy of direct coupling of inert C–H bonds has emerged as an attractive approach, offering significant advantages in the sustainable construction of C–C bonds. This method bypasses the need for additional prefunctionalization manipulations of the substrates, thereby streamlining the synthesis process. Moreover, it presents a unique opportunity for late-stage transformations of otherwise unreactive C–H bonds and holds great promise for the efficient synthesis of complex organic molecules.

Within the wide range of C–H functionalization methods for constructing C–C and C–heteroatom bonds, acylative cross-coupling of C–H bonds continues to be a significant objective in synthetic chemistry. Various efforts have been dedicated to achieving such functionalization reactions, particularly using a light-driven cooperative photoredox/Ni catalytic strategy.[2] Interestingly, a recent alternative organocatalytic approach utilizing N-heterocyclic carbenes (NHCs) has emerged to achieve direct acylative functionalizations of inert C(sp^3)–H bonds through persistent NHC-bound ketyl radical intermediates.[3] The potential of carbene organocatalysis in inert C–H bond functionalization had been overlooked for a long time, as the focus of NHCs was mainly directed towards reacting with other reactive partners, such as electron-deficient double bonds in sp^2-carbon atoms.[4] However, the facile activation of C–H bonds through radical formation is crucial in NHC-catalyzed direct C–H acylations. Generally, there are two distinct strategies to cleave the unreactive C–H bonds: (1) single-electron oxidation of electron-rich moieties to form radical cation species that would enable facile deprotonation to give carbon radicals (electron or proton transfer pathway, ET/PT pathways) and (2) radical-mediated direct abstraction of hydrogen atoms through the hydrogen atom transfer (HAT) process.

C–H functionalization *via* single-electron-oxidation of electron-rich arenes or amines (ET/PT pathways)

In radical NHC catalysis, NHC-bound acyl azoliums constitute one of the most intensively explored strategies owing to their

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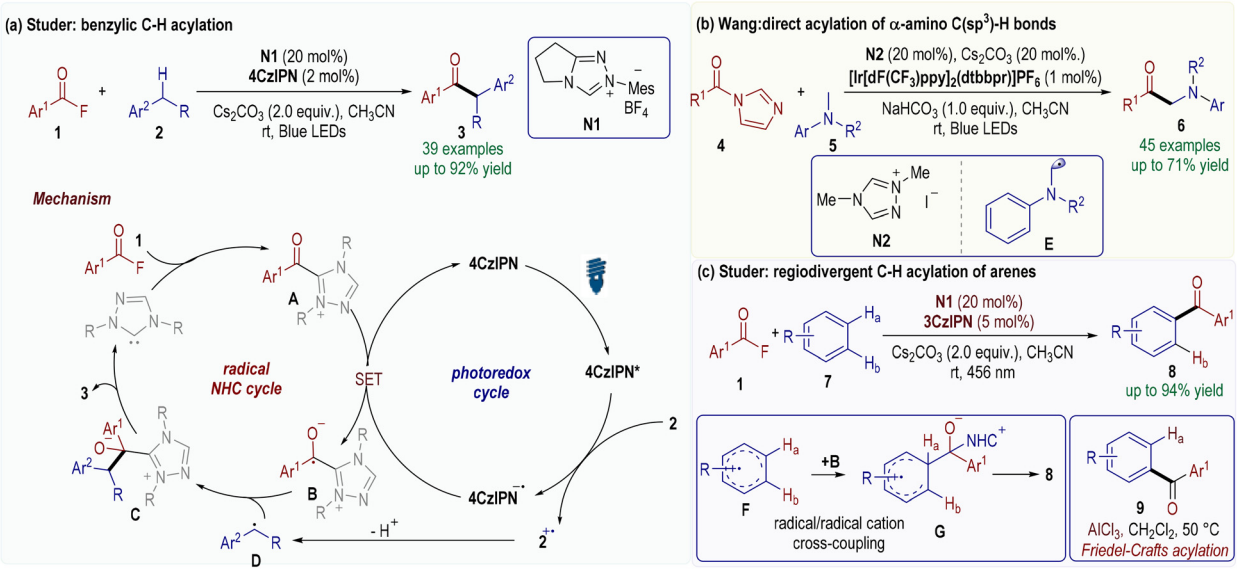

Fig. 1 Direct radical acylation involving photoredox and NHC catalysis.

unique single-electron-reduction potential that shows particular synthetic significance by the accomplishment of the catalytic cycle in a dual photocatalytic system.

In 2021, the Studer group reported an intriguing benzylic C–H acylative coupling between acyl fluorides (**1**) and electron-rich arenes (**2**) using the triazolium catalyst **N1** in the presence of blue LEDs to provide ketone coupling products **3** with up to 92% yield (Fig. 1a).[5] In this cooperative NHC and photoredox catalysis, the key benzyl radical **D** was generated through single-electron oxidation of arenes and subsequent facile deprotonation, providing an intriguing approach for benzylic C–H activation. On the other hand, the persistent azolium radical anion **B** was formed through single-electron reduction by the reduced photocatalyst species to complete the photocatalytic cycle. Radical–radical coupling and elaboration of the NHC would eventually lead to the cross coupling of ketone products **3** (see Fig. 1 for a detailed mechanism). Additionally, aryl amines are other electron-rich moieties that are capable of single-electron oxidation and subsequent deprotonation to access α-amino radicals **E**. Wang and co-workers accomplished a straightforward coupling reaction between α-amino C(sp^3)–H bonds of *N*,*N*-dimethylaniline (**5**) and acyl imidazole derivatives (**4**) using catalyst **N2** under irradiation with blue LEDs.[6] The methodology enabled the synthesis of a broad range of biologically relevant α-amino ketone products through radical–radical cross couplings (Fig. 1b).

Very recently, the Studer group realized a direct C–H acylation of electron-rich arenes **7** with acyl fluorides **1** in the presence of a dual system of a carbene (**N1**) and a photocatalyst (3CzCIIPN).[7] Interestingly, the direct coupling reactions follow distinct pathways compared to conventional Friedel–Crafts acylations, resulting in the formation of exclusive regioisomeric products **8** (Fig. 1c). The catalytic strategy involves a radical NHC mechanism, wherein the key arene radical cation intermediate **F** is first generated under photoredox conditions. Subsequently, C–H functionalization occurs through radical–radical coupling between the NHC-bound ketyl radical and the transient arene radical cation intermediate.

C–H activation through the hydrogen atom transfer (HAT) pathway

The direct abstraction of hydrogen atoms through hydrogen atom transfer (HAT) represents a complementary strategy for activating inert C–H bonds.[8] The trapping of the generated synthetically valuable radical intermediates utilizing NHC-bound ketyl radicals provides efficient C–C bond-forming transformations that allow for rapid acylations with a broad range of simple C–H abundant starting materials.

In 2021, Ohmiya's research group disclosed an efficient coupling reaction of aldehydes **10** with α-C–H of secondary amines **11** using a thiazolium salt precursor (**N3**), leading to a diverse array of amino ketones in modest to excellent yields (up to 96% yield).[9] Interestingly, an aryl radical **J** formed from single-electron-reduction by deprotonated Breslow intermediate **I** paved the way for intramolecular hydrogen atom abstraction. The resulting α-amino radical **K** was subsequently coupled with NHC-derived ketyl radical **M** and thus delivered the direct coupling products **12** with high efficiency (Fig. 2a).

In their work, Li *et al.* employed the 1,5-hydrogen atom transfer approach to develop a thiazolium NHC (**N3**)-catalyzed remote C(sp^3)–H acylation of alkyl carbamates **13** bearing an *N*-OBs^{Cl} moiety, affording functionalized ketone products **14** with impressive isolated yields (up to 87%).[10] The HAT was realized through an N-radical **L** that was generated from single-electron oxidation of the deprotonated Breslow intermediate by a sulfonyl functionalized carbamate. This C–H activation

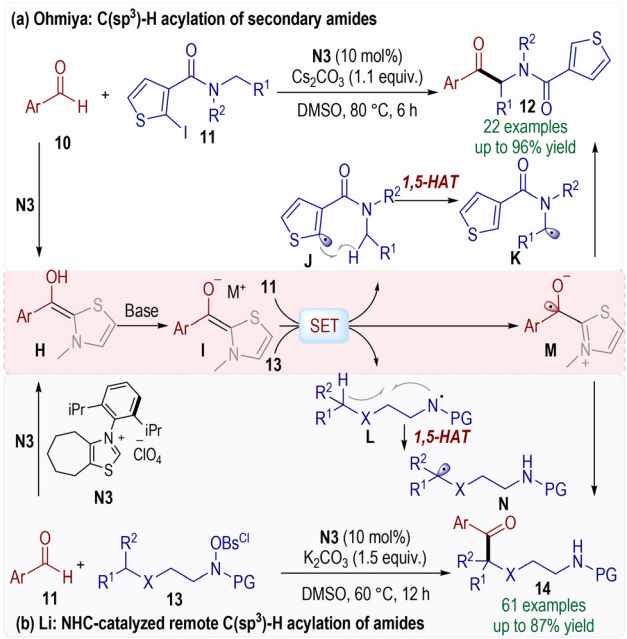

Fig. 2 NHC-catalyzed remote C(sp^3–H) functionalization using an intramolecular 1,5-HAT strategy.

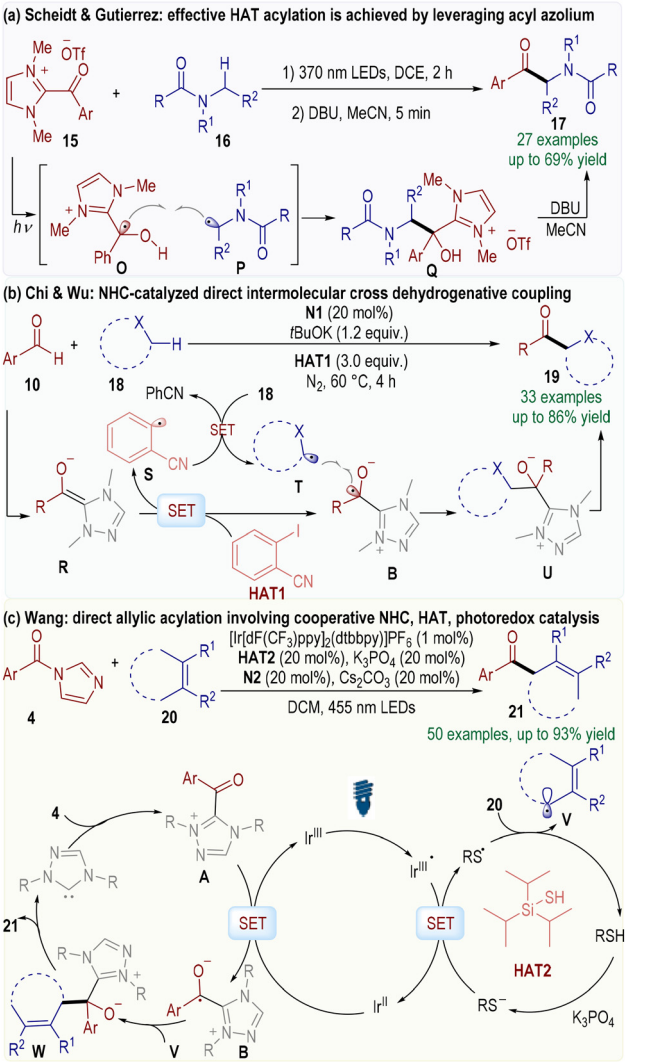

Fig. 3 C–H functionalization through intermolecular hydrogen atom transfer.

step resulted in the formation of radical species, enabling direct coupling reactions and leading to the synthesis of a diverse array of functionalized δ-amino ketones **14** (Fig. 2b).

In 2023, Scheidt and Gutierrez reported a notable advancement in the field, introducing a stable, isolable acyl azolium **15** that was used for direct acylation of inert C–H bonds of **16** through an intermolecular hydrogen atom transfer (HAT) process upon irradiation with a 370 nm LED.[11] Further studies by experiment and computation reveal the formation of a key triplet diradical intermediate upon photoexcitation of the azolium species and the subsequent intersystem cross-coupling process (Fig. 3a). Notably, a diverse range of substrates including amines, ethers, and benzylic and allylic C–H bonds can engage in the HAT pathway, leading to the formation of various ketones through radical–radical coupling reactions.

In a complementary approach, Chi/Wu and co-workers disclosed a straightforward dehydrogenative coupling of aldehydes **10** with C(sp^3)–H bonds of ethers/amines **18**, affording a diverse set of ketones **19** with high efficiency.[12] Simple *ortho*-cyanoiodobenzene (**HAT2**) was found to be essential for activation of the two distinct C–H bonds involved in the reaction. Mechanistically, oxidation of the Breslow intermediate would give the NHC-derived ketyl radical **B** and generate an aryl radical **S**, which was pivotal to providing the aliphatic carbon radical **T** through intermolecular hydrogen atom transfer (HAT) with inert C(sp^3)–H bonds (Fig. 3b). Various ether, amine or aromatic benzylic positions were readily functionalized to provide a wide range of ketone products under metal- and light-free conditions.

Almost at the same time, the group of Wang reported a triple carbene/photoredox/HAT-catalytic system to access β,γ-unsaturated ketones **21** from acyl imidazole derivative **4** with olefins **20**.[13] In this system, an *in situ* formed thiyl radical behaved as an effective HAT catalyst, facilitating the activation of the allylic C–H bond and leading to the formation of a transient radical species **V** (Fig. 3c). The radical–radical coupling with the NHC-bound ketyl radical **B**, formed through the single-electron reduction of the azolium intermediate by the Ir (II) species, results in the desired β,γ-unsaturated ketone products.

Very recently, Ye and colleagues described the coupling of aldehydes **10** with unactivated alkyl C–H bonds (**22**) to effectively prepare ketones **23** with 21–94% yields through photoredox cooperative NHC/Pd catalysis (Fig. 4).[14] This intricate process encompasses palladium-initiated 1,*n*-hydrogen atom transfer (HAT) mediated by primary carbon-centred radicals to activate distal C(sp^3)–H bonds, followed by the coupling of the resultant radicals. Notably, this reaction is characterized by its

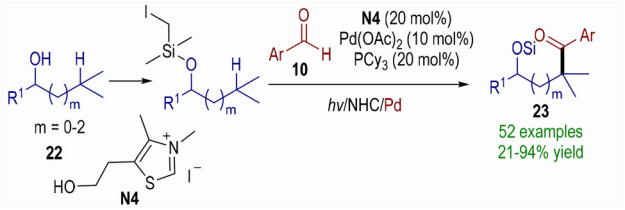

Fig. 4 Ketone synthesis *via* photoredox NHC/Pd-catalyzed acylation of alkyl C(sp^3)–H bonds.

mild reaction conditions and wide tolerance of diverse functional groups.

Conclusions

Through the exploration of radical N-heterocyclic carbene (NHC) organocatalysis, highly efficient direct acylations of a broad range of simple molecules, including ethers, amines, arenes, and functionalized hydrocarbons, have been successfully achieved. Two catalytic strategies have been developed to enable the key C–H bond cleavage for subsequent functionalizations: the electron or proton transfer pathway (ET/PT pathways) and the hydrogen atom transfer pathway (HAT pathway). These strategies provide an efficient approach for C–C bond-forming transformations by diminishing the need for prefunctionalization manipulations of inert C–H bonds. This advancement allows for streamlined and direct functionalization of a wide range of substrates, significantly expanding the scope of C–H functionalization in organic synthesis.

Despite notable achievements, the development of enantioselective acylative transformations to access optically pure ketone products still faces significant challenges. These difficulties stem from the high reactivity of multiple radical intermediates, leading to rapid coupling reactions and posing challenges for catalyst stereocontrol. Catalyst design with novel chiral scaffolds or future developments of the dual enantioselective catalytic systems, such as in assistance with contact ion-pairing interactions, might help to accomplish the acylation transformations in a highly stereoselective manner. Additionally, there is great anticipation that radical NHC catalysis will continue to drive the advancement of organocatalytic C–H functionalization strategies for a diverse range of biologically intriguing molecular frameworks.

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgements

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References

1 (*a*) H. W. L. Davies, J. Du Bois and J.-Q. Yu, C-H Functionalization in organic synthesis, *Chem. Soc. Rev.*, 2011, **40**, 1855–1856; (*b*) B. Liu, A. M. Romine, C. Z. Rubel, K. M. Engle and B.-F. Shi, Transition-metal-catalyzed, coordination-assisted functionalization of nonactivated C(sp^3)-H Bonds, *Chem. Rev.*, 2021, **121**, 14957–15074; (*c*) S. Rej, Y. Ano and N. Chatani, Bidentate directing groups: an efficient tool in C-H bond functionalization chemistry for the expedient construction of C-C bonds, *Chem. Rev.*, 2020, **120**, 1788–1887; (*d*) Ł. Woźniak, J.-F. Tan, Q.-H. Nguyen, A. Madron du Vigné, V. Smal, Y.-X. Cao and N. Cramer, Catalytic enantioselective functionalizations of C-H bonds by chiral iridium complexes, *Chem. Rev.*, 2020, **120**, 10516–10543; (*e*) For a definition of "inert", "unreactive" or "robust" CH bonds, please see: Y. Qin, L. Zhu and S. Luo, Organocatalysis in Inert C-H Bond Functionalization, *Chem. Rev.*, 2017, **117**, 9433.

2 (*a*) C. L. Joe and A. G. Doyle, Direct acylation of C(sp^3)–H bonds enabled by nickel and photoredox catalysis, *Angew. Chem., Int. Ed.*, 2016, **55**, 4040–4043; (*b*) Z. Sun, N. Kumagai and M. Shibasaki, Photocatalytic α-acylation of ethers, *Org. Lett.*, 2017, **19**, 3727–3730; (*c*) G. S. Lee, J. Won, S. Choi, M. H. Baik and S. H. Hong, Synergistic activation of amides and hydrocarbons for direct C(sp^3)-H acylation enabled by metallaphotoredox catalysis, *Angew. Chem., Int. Ed.*, 2020, **59**, 16933–16942.

3 (*a*) S. W. Ragsdale, Pyruvate ferredoxin oxidoreductase and its radical intermediate, *Chem. Rev.*, 2003, **103**, 2333–2346; (*b*) T. Ishii, K. Nagao and H. Ohmiya, Recent advances in *N*-heterocyclic carbene-based radical catalysis, *Chem. Sci.*, 2020, **11**, 5630–5636; (*c*) L. Dai and S. Ye, Recent advances in *N*-heterocyclic carbene-catalyzed radical reactions, *Chin. Chem. Lett.*, 2021, **32**, 660–667; (*d*) Q.-Z. Li, R. Zeng, B. Han and J.-L. Li, Single-electron transfer reactions enabled by *N*-heterocyclic carbene organocatalysis, *Chem. – Eur. J.*, 2021, **27**, 3238–3250; (*e*) A. V. Bay and K. A. Scheidt, Single-electron carbene catalysis in redox processes, *Trends Chem.*, 2022, **4**, 277–290; (*f*) K. Liu, M. Schwenzer and A. Studer, Radical NHC catalysis, *ACS Catal.*, 2022, **12**, 11984–11999;

(*g*) Q.-Z. Li, X.-X. Li, T. Qi and J.-L. Li, Merging *N*-heterocyclic carbene organocatalysis with hydrogen atom transfer strategy, *ChemCatChem*, 2023, **15**, e202201320.

4 (*a*) D. M. Flanigan, F. Romanov-Michailidis, N. A. White and T. Rovis, Organocatalytic reactions enabled by *N*-heterocyclic carbenes, *Chem. Rev.*, 2015, **115**, 9307–9387; (*b*) C. Zhang, J. F. Hooper and D. W. Lupton, *N*-Heterocyclic, carbene catalysis via the α,β-unsaturated acyl azolium, *ACS Catal.*, 2017, **7**, 2583–2596; (*c*) K. J. R. Murauski, A. A. Jaworski and K. A. Scheidt, A continuing challenge: *N*-heterocyclic carbene-catalyzed syntheses of γ-butyrolactones, *Chem. Soc. Rev.*, 2018, **47**, 1773–1782; (*d*) S. Mondal, S. R. Yetra, S. Mukherjee and A. T. Biju, NHC-catalyzed generation of α,β-unsaturated acylazoliums for the enantioselective synthesis of heterocycles and carbocycles, *Acc. Chem. Res.*, 2019, **52**, 425–436; (*e*) X.-Y. Chen, Z. Gao and S. Ye, Bifunctional *N*-heterocyclic carbenes derived from L-pyroglutamic acid and their applications in enantioselective organocatalysis, *Acc. Chem. Res.*, 2020, **53**, 690–702.

5 Q.-Y. Meng, L. Lezius and A. Studer, Benzylic C-H acylation by cooperative NHC and photoredox catalysis, *Nat. Commun.*, 2021, **12**, 2068.

6 X. Wang, B. Zhu, Y. Liu and Q. Wang, Combined photoredox and carbene catalysis for the synthesis of α-amino ketones from carboxylic acids, *ACS Catal.*, 2022, **12**, 2522–2531.

7 J. Reimler, X.-Y. Yu, N. Spreckelmeyer, C. G. Daniliuc and A. Studer, Regiodivergent C–H Acylation of Arenes by Switching from Ionic- to Radical-type chemistry using NHC catalysis, *Angew. Chem., Int. Ed.*, 2023, e202303222.

8 (*a*) S. K. Kariofillis and A. G. Doyle, Synthetic and mechanistic implications of chlorine photoelimination in nickel/photoredox C(sp^3)-H cross-coupling, *Acc. Chem. Res.*, 2021, **54**, 988–1000; (*b*) H. Cao, X. Tang, H. Tang, Y. Yuan and J. Wu, Photoinduced intermolecular hydrogen atom transfer reactions in organic synthesis, *Chem. Catal.*, 2021, **1**, 523–598; (*c*) L. Capaldo, D. Ravelli and M. Fagnoni, Direct photocatalyzed hydrogen atom transfer (HAT) for aliphatic C-H bonds elaboration, *Chem. Rev.*, 2022, **122**, 1875–1924.

9 Y. Matsuki, N. Ohnishi, Y. Kakeno, S. Takemoto, T. Ishii, K. Nagao and H. Ohmiya, Aryl radical-mediated *N*-heterocyclic carbene catalysis, *Nat. Commun.*, 2021, **12**, 3848.

10 (*a*) Q.-Z. Li, R. Zeng, Y. Fan, Y.-Q. Liu, T. Qi, X. Zhang and J.-L. Li, Remote C(sp^3)-H acylation of amides and cascade cyclization via *N*-heterocyclic carbene organocatalysis, *Angew. Chem., Int. Ed.*, 2022, **61**, e202116629; (*b*) Y. Man, S. Liu, B. Xu and X. Zeng, *N*-Heterocyclic-carbene-catalyzed, C-H acylation via radical relay, *Org. Lett.*, 2022, **24**, 944–948.

11 J. L. Zhu, C. R. Schull, A. T. Tam, Á. Rentería-Gómez, A. R. Gogoi, O. Gutierrez and K. A. Scheidt, Photoinduced acylations via azolium-promoted intermolecular hydrogen atom transfer, *J. Am. Chem. Soc.*, 2023, **145**, 1535–1541.

12 F. Su, J. Zou, X. Lv, F. Lu, Y. Long, K. Tang, B. Li, H. Chai, X. Wu and Y. R. Chi, Carbene-catalyzed intermolecular dehydrogenative coupling of aldehydes with C(sp^3)-H bonds, *Angew. Chem., Int. Ed.*, 2023, **62**, e202303388.

13 X. Wang, R. Yang, B. Zhu, Y. Liu, H. Song, J. Dong and Q. Wang, Direct allylic acylation via cross-coupling involving cooperative *N*-heterocyclic carbene, hydrogen atom transfer, and photoredox catalysis, *Nat. Commun.*, 2023, **14**, 2951.

14 H.-Y. Wang, X.-Y. Wang, B.-A. Zhou, C.-L. Zhang and S. Ye, Ketones from aldehydes via alkyl C(sp^3)-H functionalization under photoredox cooperative NHC/palladium catalysis, *Nat. Commun.*, 2023, **14**, 4044.