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Organocatalytic C-H Functionalization of Simple Alkanes

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Abstract: The direct functionalization of inert C(sp^3)-H bonds to form carbon-carbon and carbon-heteroatom bonds offers vast potential for chemical synthesis and therefore receives intense attention. At present, most successes come from strategies using metal catalysts/reagents or photo/electrochemical processes. The use of organocatalysis for this purpose remains very limited or even unexplored especially when dealing with challenging C-H bonds such as those from simple alkanes. Here we disclose the first organocatalytic direct functionalization/acylation of inert C(sp^3)-H bonds of completely unfunctionalized alkanes. Our approach involves N-heterocyclic carbene catalyst-mediated carbonyl radical intermediate generation and coupling with simple alkanes (through the corresponding alkyl radical intermediates generated via a hydrogen atom transfer process). Unreactive C-H bonds are widely present in fossil fuel feedstocks, commercially important organic polymers, and complex molecules such as natural products. Our present study shall inspire a new avenue for quick functionalization of these molecules under the light- and metal-free catalytic conditions.

Direct functionalization of inert C(sp^3)-H bonds to form carbon-carbon and carbon-heteroatom bonds represents a significant area of research in chemistry.[1] Currently, these transformations can be achieved with the assistance of metal catalysts/reagents[2] or combinations of metals with photo/electrochemical processes (Figure 1A).[3] In addition to forming new chemical bonds, challenges in stereo-control have also been well addressed with chiral ligands and transition metals, as pioneered by Yu and others.[4] In contrast, the use of organocatalysis for direct reactions of inert C(sp^3)-H bonds is much less developed. While there have been some impressive successes,[5] they are primarily limited to C(sp^3)-H bonds that are attached to aryl/alkene units (such as benzylic sp^3-C-H bonds)[6] or heteroatoms (such as amines[7] and ethers[8]) (Figure 1B, left). Another elegant approach involves β-sp^3-carbons of saturated carbonyl compounds via the corresponding (formal) enol intermediate or its equivalents.[9] This type of organocatalytic β-carbon transformations of carbonyl compounds may also be considered as functionalization of sp^3-C-H bonds that are adjacent to carbon-carbon double bonds. Up to now, it remains difficult to directly couple simple alkane sp^3-carbon atoms in organocatalytic

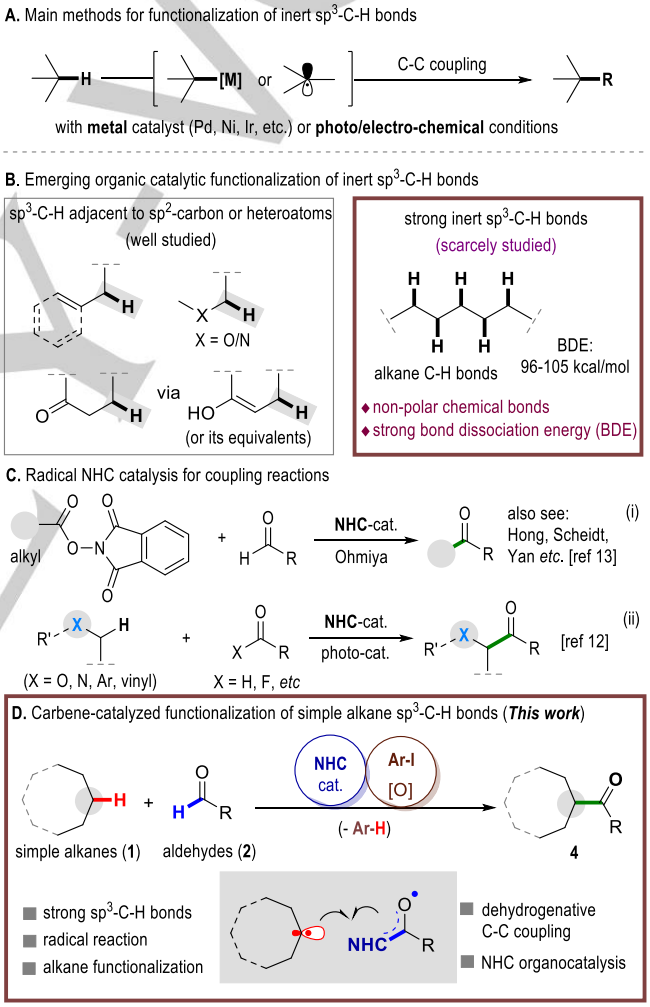

Figure 1. Functionalization of inert C-H bonds via C-C bond formations

reactions.[10] Such C-H bonds from simple non-functionalized alkanes are barely polarized and possess high bond dissociation energy (96-105 kcal/mol) (Figure 1B, right). Therefore, in most cases, prefunctionalization of the inert hydrocarbons are generally required by increasing their reactivity to forge C-C or C-heteroatom bond formations. N-heterocyclic carbene (NHC) organocatalysts can promote single-electron-transfer radical reactions,[11] and thus may offer unique opportunities for functionalization of inert chemical bonds.[12] Ohmiya, Scheidt, Hong and others have demonstrated that when simple alkanes

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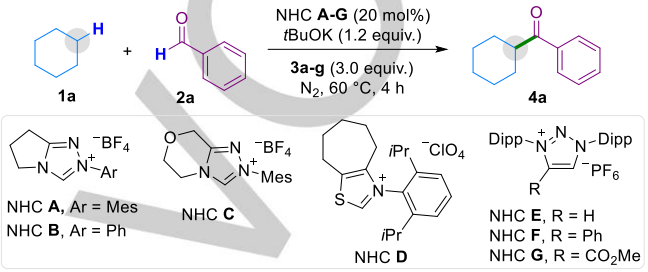
are prefunctionalized (e.g., in the forms of alkane halides or redox-active esters), the resulting alkane radical intermediates can couple with NHC catalyst-bound carbonyl intermediates to afford the corresponding ketone products (Figure 1C-i).[13] Intriguingly, direct functionalization of sp^3-C-H bonds has recently emerged as an attractive approach to couple with carbonyl derivatives by NHC catalysis. In this context, focuses were mostly directed to C-C bond formations involving substrates bearing C-H bonds that are "activated" by hyperconjugation effect (e.g., α-heteroatom, benzylic, and allylic C-H bonds), as reported by Studer, Ohmiya, Scheidt, and others (Figure 1C-ii).[12] To the best of our knowledge, there are no reports of NHC-catalyzed coupling reactions involving simple non-functionalized alkane substrates.

Built upon our ongoing program on NHC-catalyzed radical transformations,[14] we devote our efforts to address the long-standing challenge of unactivated alkane functionalization, aiming to enable modular C-C forming acylative transformations. Here we demonstrate a direct intermolecular coupling reaction of unexplored aliphatic hydrocarbons with aldehydes under NHC organocatalysis, resulting in the synthesis of a diverse array of ketone products in high efficiency (Figure 1D). Briefly, the key activation of aliphatic C-H bonds involves a hydrogen atom transfer (HAT) process, facilitated by the in situ generated aryl radical from single electron reduction of aromatic iodides. This process leads to subsequent radical-radical coupling to form the desired ketone products in high yields. Notably, this study represents the first success to realize direct coupling of carbonyl compounds with unreacted alkanes by means of organocatalytic approach. Furthermore, our carbene catalytic method offers high efficiency under mild conditions without the need of typical light or metal catalysts,[15] which shall provide a valuable strategy for rapid functionalization of alkanes and late-stage functionalization of intriguing complex molecules.

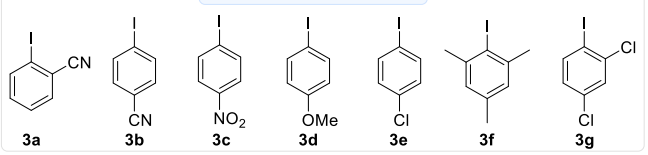
Based on our hypothesis, we commenced the study to investigate the dehydrogenative coupling reaction between cyclohexane (**1a**) and benzaldehyde (**2a**). Triazolium NHC catalyst **A** was first chose to test our hypothesis. Whereas most of the conditions employed failed to give the desired product (see Table S1, Supporting Information for details), the reaction performed in pure cyclohexane shows a trace amount of coupling product **4a** (Table 1, entry 1). Encouraged by this observation, we turned our effort to examine other NHCs to tackle a more efficient catalytic system for the alkane C-H acylations. In comparison to the commonly used NHC catalysts (entries 2-4),[11] we were pleased to find that NHC **E**, featuring a mesoionic scaffold,[16] provided the desired product **4a** in a significantly improved yield (27%, entry 5). We anticipated that the structure of oxidant **3** would be pivotal to the key SET oxidation and HAT process. With this in mind, we achieved a better yield (70%) by switching **3a** to the *para*-cyano substituted iodobenzene **3b** (entry 6). A range of aromatic iodides **3c**-**g** were thereby carefully explored in the catalytic C-H functionalizations (Table 1, entries 7-11). Gratifyingly, iodide **3e** was identified to be superior in the dehydrogenative coupling (entry 9). Subsequently, by evaluating the effects of other catalysts, base and temperature (entries 12-16), we were pleased to achieve an optimal yield of **4a** (85%) when the reaction was performed with NHC **E** in the presence of *t*BuOK and 2.0 equivalents of aryl iodide **3e** at 30 °C for 0.5 h (entry 16).

With the optimal conditions established, we set out to study the generality of the NHC-catalyzed alkane coupling reactions (Table 2). Aldehyde substrates possessing various alkyl moieties on the *para* sites, such as methyl, ethyl, isopropyl or *t*-butyl group as well as OMe group were initially examined, furnishing corresponding ketone products **4b-f** in good yields (42-83%). Substrates containing halogen units were also readily converted, leading to **4g** and **4h** in 76% and 45% yield respectively. Moreover, a diverse set of ketone products **4i-l** with various substituents at *meta* site of the aromatic ring were obtained under the optimal conditions. Furthermore, 2-naphthyl aldehyde and typical heteroaromatic aldehyde bearing 2-/3-thienyl group or pyridine unit underwent the intermolecular HAT pathway smoothly to give

Table 1. Optimization of the dehydrogenative coupling reaction[a]



Entry	NHC	Ar-I (**3**)	Base	Yield (%)[b]
1	**A**	**3a**	*t*BuOK	trace
2	**B**	**3a**	*t*BuOK	-
3	**C**	**3a**	*t*BuOK	trace
4	**D**	**3a**	*t*BuOK	-
5	**E**	**3a**	*t*BuOK	27
6	**E**	**3b**	*t*BuOK	70
7	**E**	**3c**	*t*BuOK	-
8	**E**	**3d**	*t*BuOK	72
9	**E**	**3e**	*t*BuOK	83
10	**E**	**3f**	*t*BuOK	63
11	**E**	**3g**	*t*BuOK	59
12	**F**	**3e**	*t*BuOK	70
13	**G**	**3e**	*t*BuOK	63
14	**E**	**3e**	*t*BuONa	-
15	**E**	**3e**	Cs_2CO_3	-
16[c]	**E**	**3e**	*t*BuOK	85 (85)



[a] The reactions were performed with **2a** (0.05 mmol, 1.0 equiv.), **1a** (1.0 mL), NHC (20 mol%), **3a**-**g** (0.15 mmol, 3.0 equiv.), and base (0.06 mmol, 1.2 equiv.) under N_2 atmosphere at 60 °C for 4 h; [b] Yields of **4a** were determined via ^1H NMR analysis with 1,3,5-trimethoxy-benzene as an internal standard; Isolated yield in the parenthesis; [c] Reaction was performed with **3e** (0.10 mmol, 2.0 equiv.) at 30 °C for 0.5 h; Mes = 2,4,6-trimethylphenyl, Dipp = 2,6-diisopropylphenyl.

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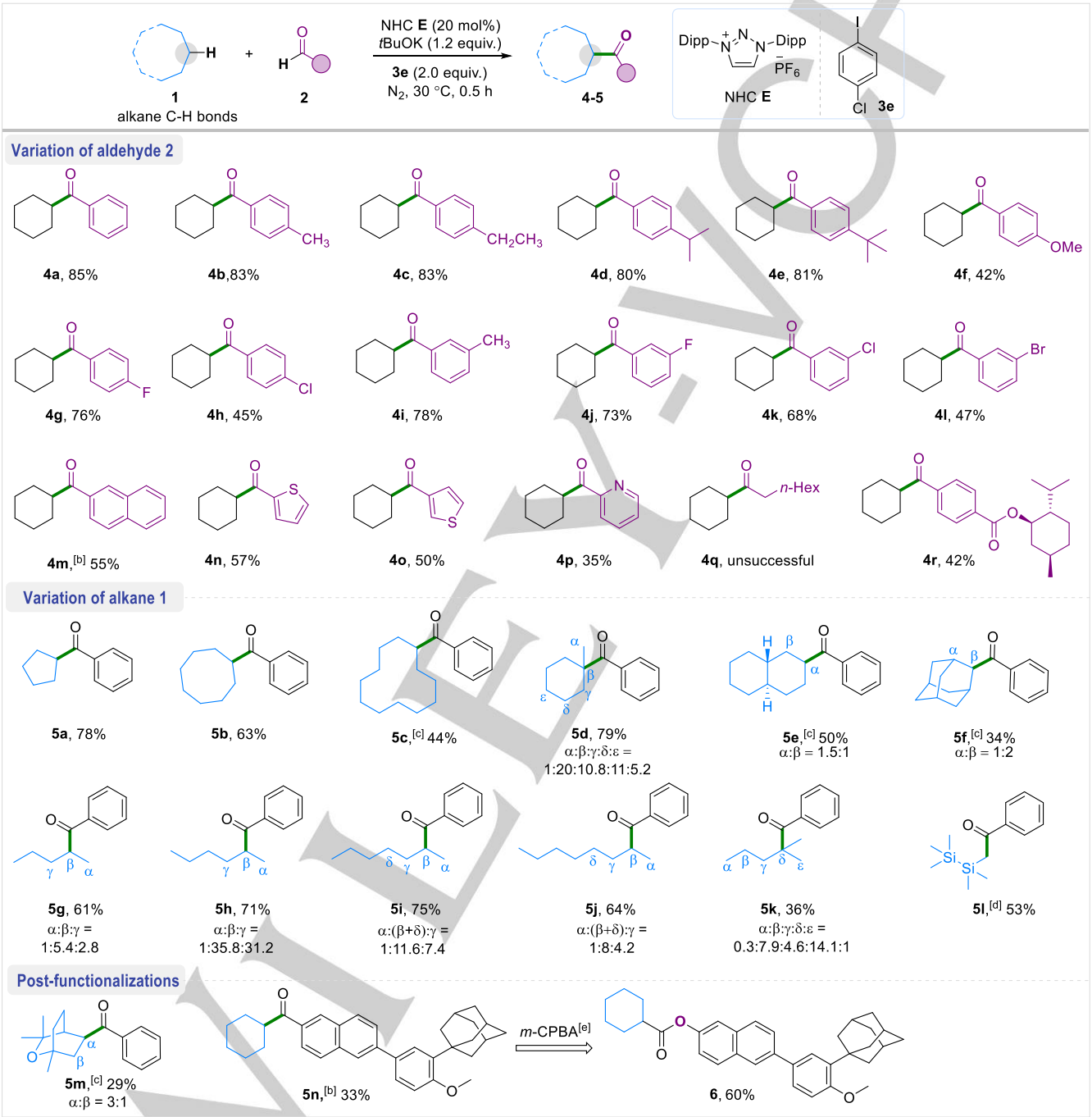
the corresponding acylation coupling products **4m**-**p**, albeit in modest yields (35-57%). Unfortunately, aliphatic aldehydes did not react successfully under these conditions, as observed with octanal, where product **4q** was not detected. Notably, aldehyde derived from menthol was also compatible with the reaction, affording the ketone product **4r** in 42% yield.

Variation of the alkanes was further explored with benzaldehyde (**2a**) used as the standard coupling partner. Various cycloalkanes with 5, 8 or even up to 12 membered rings were successfully functionalized through dehydrogenative coupling with aldehyde **2a**, resulting in products **5a**-**c** with yields ranging from 44-78%. Reactions with methyl cyclohexane and bicyclic *trans*-decahydronaphthalene also gave the corresponding products **5d** (79%, α:β:γ:δ:ε 1:20:10.8:11:5.2) and **5e** (50%, α:β 1.5:1), respectively. Cage adamantane delivered to the corresponding product **5f** in 34% yield and with a selectivity of

Table 2. Substrate scope of the dehydrogenative couplings[a]



[a] The reactions were conducted with **2** (0.1 mmol, 1.0 equiv.), NHC **E** (20 mol%), **3e** (0.2 mmol, 2.0 equiv.) and *t*BuOK (0.12 mmol, 1.2 equiv.) in **1** (2.0 mL) under N_2 atmosphere at 30 ºC for 0.5 h; Isolated yields; [b] Reactions at 80 ºC for 4 h; [c] Reactions were performed with **2a** (0.1 mmol, 1.0 equiv.), alkane **1** (5.0 equiv.), NHC **E** (20 mol%), **3f** (0.3 mmol, 3.0 equiv.) and *t*BuOK (0.12 mmol, 1.2 equiv.) in PhF (0.5 mL) under N_2 atmosphere at 80 ºC for 6 h; [d] Yield reported after postdesilylation; [e] The reactions were performed with **5n** (0.02 mmol, 1.0 equiv.), *m*-CPBA (0.08 mmol, 4.0 equiv.), trifluoroacetic acid (0.04 mmol, 2.0 equiv.) in CH_2Cl_2(1.0 mL) under air at 30 ºC for 24 h.

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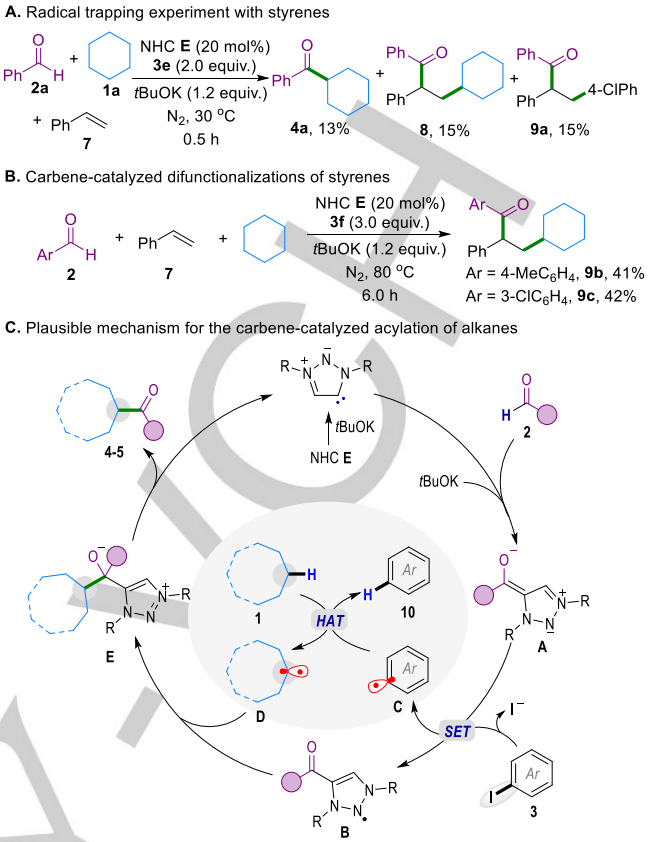
1:2 (α:β). Notably, bicyclic alkane (**5e**) and adamantane (**5f**) showed a preference of site selectivity at the internal secondary positions, as the bridgehead radical generated at tertiary position is not a planar structure which could be destabilized compared to acyclic tertiary radicals. Next, we turned to examine the C-H functionalization with acyclic alkanes. Not surprisingly, various linear alkanes, including *n*-pentane, *n*-hexane, *n*-heptane, *n*-octane and 2-methylpentane were found to afford the corresponding acylation products **5g**-**k** in modest yields (36-75%). It's worth noting that in these cases (**5d** and **5g**-**k**), alkanes were generally preferentially functionalized at internal tertiary and secondary positions, presumably owing to the difference in BDE among the 3°, 2° and 1° sp^3-C-H bonds that influences the rate of C-H abstraction (typical BDE of alkane C-H bonds: 3°<2°<1°). Moreover, the C-H bond of silane was readily functionalized, providing the product **5l** in 53% yield.

Application of the carbene-catalyzed alkane functionalization to complex molecule of Eucalyptol was carried out to give product **5m** that further expands the reaction scope and synthetic utility of this method. Additionally, our protocol provided a synthetic platform for drug modifications. For instance, when substrate derived from adapalene was subjected to the acylation reaction, the desired coupling functionalized product **5n** was readily prepared, which could be further transformed to product **6** through a Baeyer-Villiger oxidation.

A radical trapping experiment with styrenes was performed to gain insights into the possible C-H functionalization mechanism. As illustrated in Scheme 1A, 2.0 equiv. of alkene **7** were added to the model reaction under standard conditions. Along with the isolation of coupling product **4a** in 13% yield, alkene 1,2-difunctionalization product **8** and **9a** through radical relay were successfully obtained, demonstrating the formation of NHC-bound radical (**B**), 4-chlorophenyl (**C**) and cyclohexyl (**D**) radicals (Scheme 1C) in the catalytic reaction. Furthermore, by switching **3e** with a sterically bulky oxidant **3f** to inhibit the aryl radical addition pathway, straightforward alkene 1,2-difunctionalization products **9b** and **9c** via the three-component reaction were thereby achieved in modest yields (Scheme 1B).

Built upon the radical trapping experiment (Scheme 1A) and previous reports,[12b,14c,16a,b] a plausible mechanism is proposed for this carbene-catalyzed alkane C-H functionalization (Scheme 1C, see Supporting Information for more details). Initially, single-electron oxidation of the deprotonated Breslow intermediate **A** by aryl iodide **3** would give the NHC-bound radical **B** and an aryl radical **C**. Subsequent hydrogen atom transfer between radical species **C** and alkane **1** gives rise to aromatic **10** and alkyl radical **D** that enables further radical-radical coupling with radical species **B** to eventually give the desired ketone products **4**-**5** and regenerate the carbene catalyst for the next catalytic cycle.



Scheme 1. Radical trapping experiment

In summary, we have developed an organocatalytic approach for direct functionalization of strong alkane sp^3-C-H bonds through a carbene-catalyzed acylation with aldehydes. A broad range of simple alkanes were readily directly converted to diverse functionalized ketone products under mild conditions. The inert aliphatic C-H bonds are efficiently cleaved through intermolecular hydrogen atom transfer facilitated by the catalytically generated aryl radical species. Our approach provides an alternative organocatalyst-mediated approach for inert alkane C-H functionalization, complementing the existing transition metal based or photochemical/electrochemical catalytic methods. New avenues for synthetic implementation from hydrocarbon feedstocks to high value-added functional molecules by the light- and metal-free approach could be anticipated and development of catalyst-controlled strategy to precisely control the site- and stereoselectivity of C-H functionalization is ongoing in our lab.

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Keywords: C-H Functionalization • Organocatalysis • N-Heterocyclic Carbene • Aryl Radical • Hydrogen Atom Transfer

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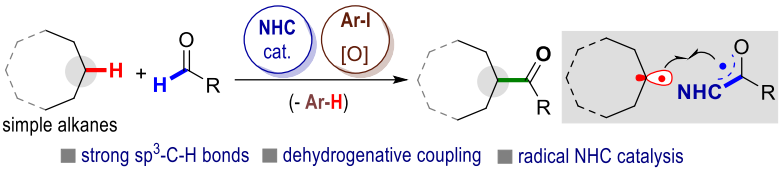

An organocatalytic direct functionalization/acylation of strong aliphatic C(sp^3)-H bonds is disclosed via an *N*-heterocyclic carbene (NHC)-catalyzed dehydrogenative coupling of aldehydes with simple alkanes. The inert aliphatic C-H bonds are efficiently cleaved through intermolecular hydrogen atom transfer, providing an alternative organocatalytic approach for inert alkane C-H functionalization under transition metal- and light free conditions.