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Photoinduced cerium-catalyzed C–H acylation of unactivated alkanes†

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Ketones are ubiquitous motifs in the realm of pharmaceuticals and natural products. Traditional approaches to accessing these species involve the addition of metal reagents to carboxyl compounds under harsh conditions. Herein, we report a cerium-catalyzed acylation of unactivated C(sp³)–H bonds using bench-stable acyl azolium reagents under mild and operationally-friendly conditions. This reaction exhibits excellent generality, accommodating a wide range of feedstock chemicals such as cycloalkanes and acyclic compounds as well as facilitating the late-stage functionalization of pharmaceuticals. We demonstrate further applications of our strategy with a three-component radical relay reaction and an enantioselective N-heterocyclic carbene (NHC) and cerium dual-catalyzed reaction.

Introduction

Simple alkanes represent one of the most abundant materials on earth,¹ but reactions involving these unactivated substrates typically require prefunctionalization to selectively activate desired C(sp³)–H bonds over others with similar reactivities.² The resurgence of photoredox reactions has inspired a series of innovative strategies, expanding the boundaries of chemical reactivity beyond traditional two-electron processes.³ Intermolecular hydrogen atom transfer (HAT) is one such strategy which has enabled the direct utilization of simple alkanes as substrates in radical transformations. This process efficiently cleaves normally inert C(sp³)–H bonds under mild conditions, yielding highly reactive radical species.⁴ One of the pivotal determinants of HAT processes is the bond dissociation energy (BDE); increasing the bond strength (Fig. 1A) leads to a higher activation energy barrier, consequently decelerating the HAT rate.⁵ This heightened barrier makes it challenging to access unactivated hydrocarbons, which have some of the highest C(sp³)–H BDEs.⁶ Over the past decade, substantial research endeavors have been directed towards the discovery of novel HAT methodologies for the functionalization of unactivated C(sp³)–H bonds.⁷ The first asymmetric ketone synthesis *via* direct HAT process was reported by the Ryu and Fagnoni in 2011, allowing the three-component reaction of simple alkane, carbon monoxide and electron-deficient alkenes.⁸ In 2018, the MacMillan group reported a direct HAT reaction using a decatungstate photocatalyst, successfully coupling aryl bromides and alkanes with unactivated C(sp³)–H bonds (Fig. 1A).⁹

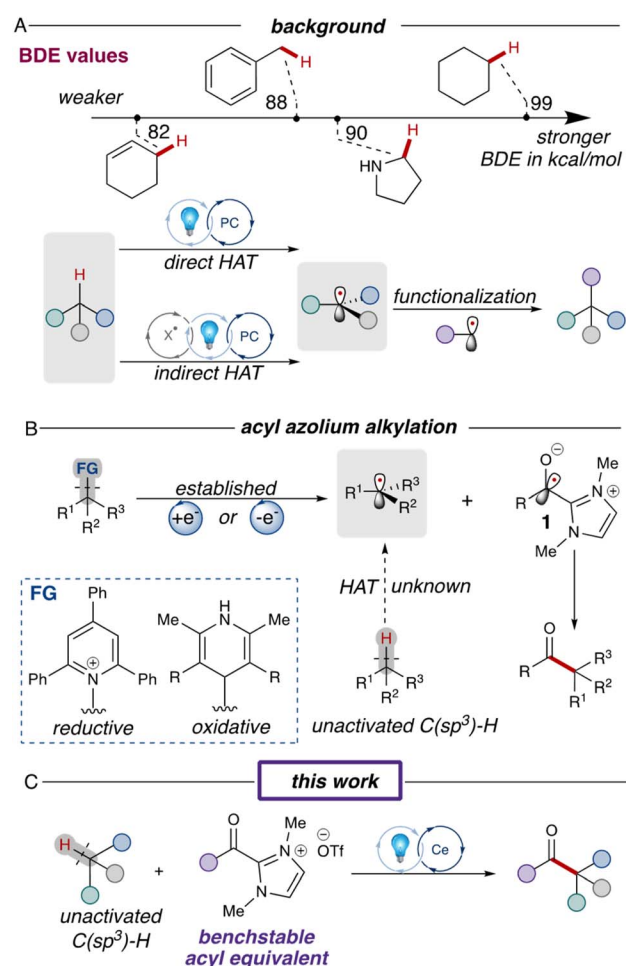


Fig. 1 (A) Background for HAT processes and BDE parameters.¹⁰ (B) Established photoredox acylations *via* NHC intermediates and their challenges. (C) This work's strategy utilizing a LMCT process.

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Indirect HAT reactions, on the other hand, introduce HAT agents which can be oxidized under photoredox conditions to generate an electrophilic radical that serves as the hydrogen atom abstractor.¹¹ In 2018, the Zuo group reported the use of a ligand-to-metal charge transfer (LMCT) process to generate high energy alkoxy radicals capable of cleaving various unactivated C(sp³)-H bonds.¹² More recently, the Hong group combined the photoredox and nickel dual catalysis protocols for the synthesis of unsymmetric ketones using alkane substrates.¹³

Recently, studies merging N-heterocyclic carbene (NHC) catalysis with photoredox catalysis have garnered significant attention from the scientific community.¹⁴ One of the key discoveries was the generation of ketyl radical **1** either through single-electron reduction of the acyl azolium or oxidation of the Breslow intermediate, enabling the synthesis of ketones through ketyl radical cross-coupling (Fig. 1B).¹⁵ However, this reaction has been limited to prefunctionalized redox-active substrates like Hantzsch esters,¹⁶ Katritzky salts,¹⁷ and NHPI esters.¹⁸ Earlier this year, our group reported an acylation reaction involving unfunctionalized structures, such as proline derivatives.¹⁹ However, in this process, the acyl azolium proved unreactive with unactivated C(sp³)-H bonds due to the high energy barrier for HAT. To address this limitation, we sought a more potent HAT agent capable of activating inert C(sp³)-H bonds. In this work,²⁰ we report the cerium-catalyzed acylation reactions of unactivated alkanes, employing *in situ* LMCT-generated chlorine radicals as the HAT agents (Fig. 1C).

Results and discussion

Our initial studies commenced with an examination of the acylation reaction between benzoyl dimethylimidazolium triflate (**2a**) and cyclohexane (**3a**, 5 equiv.). Following a series of screenings, we identified optimal conditions using cerium trichloride (0.2 equiv.), sodium chloride (1.0 equiv.), and sodium phosphate (3.0 equiv.). With these conditions, the desired ketone product **4a** was isolated with 65% yield after 3 hours of 390 nm LED irradiation in 0.1 M acetonitrile (Table 1, entry 1). Switching cerium trichloride to cerium triflate significantly dropped the yield to 16% (Table 1, entry 2), but changing the cation for the chloride dopant to potassium led to a less dramatic loss in yield (Table 1, entry 3). Using a weaker base like sodium acetate dropped the yield to 35% (Table 1, entry 4), while organic base DBU failed to yield any of the desired product **4a** (Table 1, entry 5). This reaction also showed sensitivity to the solvent environment, as seen when using ethyl acetate (48%, Table 1, entry 6) or dimethylformamide (0%, Table 1, entry 7). Tuning the reaction concentration, comparatively, had less of an impact on the yield of ketone **4a** (43% and 45%, Table 1, entries 8–9). Control experiments showed no product formation in the absence of light or base (Table 1, entries 14 and 15). Interestingly, the reaction also provided the desired product **4a** with 12% yield in the absence of cerium trichloride (Table 1, entry 12). This suggested that photoexcited acyl azolium **2a** could serve as a less effective HAT agent in generating the cyclohexyl radical compared to the LMCT

Table 1 Optimization of reaction conditions

Entry	Deviation from standard	Yield ^a (%)
1	None	62 (56 ^b)
2	Ce(OTf) ₃ instead of CeCl ₃	16
3	KCl instead of NaCl	42
4	NaOAc instead of Na ₃ PO ₄	35
5	DBU instead of Cs ₂ CO ₃	0
6	EtOAc instead of CH ₃ CN	48
7	DMF instead of CH ₃ CN	0
8	0.05 M instead of 0.1 M	43
9	0.2 M instead of 0.1 M	45
10	365 nm instead of 390 nm	11
11	427 nm instead of 390 nm	0
12	No CeCl ₃	12
13	No NaCl	30
14	No Na ₃ PO ₄	0
15	No irradiation	0

^a Yields were determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard. ^b Yield was based on isolation after chromatography. See ESI for reaction details.

process. Finally, switching the light wavelength to 365 nm or 427 nm provided unsatisfying results (Table 1, entries 10 and 11).

With the optimized conditions established, the reaction scope was explored starting with different ring sizes of the cycloalkanes, which all provided the corresponding ketones in good yields (Table 2, 56% to 64%, **4b** to **4e**). Cyclohexene **3j** selectively reacted at the weak allylic C-H bond, leading to the formation of ketone **4j** with 61% yield. Acyclic alkanes like *n*-pentane **3f** coupled with acyl azolium **2f** to generate a mixture of regioisomers (60%, 1:5:2 rr), whereas cyclopentanone **3g** exclusively provided the 1,4-dicarbonyl **4g** in 48% yield. Due to the stabilization effect by adjacent heteroatoms, substrates **3h**, **3l**, **3k** and **3g** all preferentially furnished the α -acylated products with moderate to good yields. When employing benzylic alkanes as substrates, the conditions exhibited exceptional versatility, accommodating primary, secondary and tertiary radical precursors with consistently good yields. Various functional groups, such as esters (**4q** and **4r**), trimethoxysilane (**4s**), and pinacolborane (**4u**), were all found to be well-tolerated under these conditions.

We subsequently proceeded to examine different acyl azolium partners. When modifying the substituents on the *para* position of the phenyl ring, both electron-poor substituents (**3y**, **3z**) and electron-rich ones (**3v**, **3w**) resulted in the formation of ketones with satisfactory yields. However, for more hindered cases, such as *ortho*-ethoxy benzoyl azolium **3aa**, the yield of the product **4aa** decreased to 40%. Different halogenated acyl azoliums (**3ac**, **3ad**, **3ae**) were well tolerated under the conditions as



Table 2 Substrate scope of the cerium-catalyzed reaction between acyl azoliums and alkanes^a

		alkane scope
4a , 60% 5 mmol, 48%	4b , 56%	4c , 64%
4d , 60%	4e , 62%	4f , 60% a:b:c = 1:5:2 rr
4g , 48%	4h , 42%	4i , 52%
4j , 61%	4k , 46%	4l , 77%
4m , R = H, 81% 4n , R = Me, 80% 4o , R = Et, 75%		
4p , 84%	4q , 36% a:b = 1:8 rr	4r , 60%
4s , 54%	4t , 51%	4u , 44%
		azolium scope
4v , 60%	4w , 64%	4x , 36%
4y , 68%	4z , 53%	4aa , 40%
4ab , 39%	4ac , 63%	4ad , 60%
4ae , 58%	4af , 51%	
		late-stage functionalization
from flurbiprofen 4ag , 34%, 1:1 dr ^b	from nabumetone 4ah , 48% ^b	from telmisartan 4ai , 30% ^b a:b = 3:1 rr

^a Yields were based on isolation after chromatography. ^b Reaction was performed with 1.0 equiv. of the coupling partner. See ESI for reaction details.

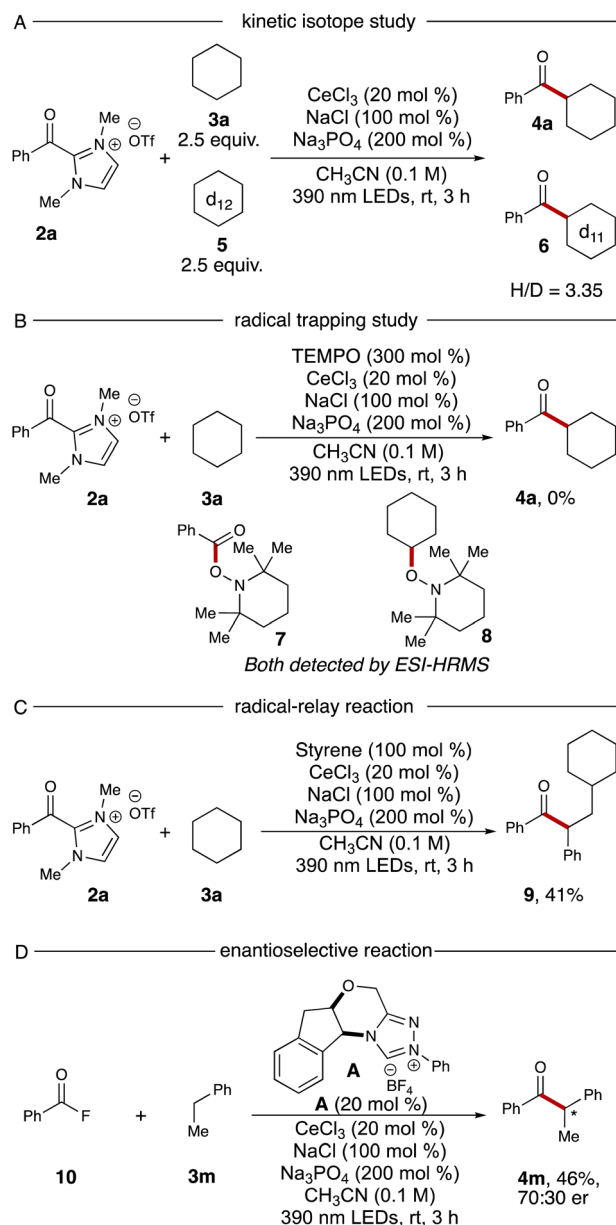
well. These conditions could also be extended to the late stage functionalizations of pharmaceuticals. Both nabumetone **3ah** and telmisartan derivative **3ai** provided the acylated products **4ah** and **4ai** with moderate yields while only employing 1.0 equivalent of the drug substrate. Flurbiprofen derivative **3ag** also provided the corresponding ketone **4ag** in 34% yield and 1 : 1 dr.

To probe the mechanism of this reaction, we conducted two experiments. A kinetic isotope effect study was performed *via* using equal amounts of cyclohexane **3a** and cyclohexane- d_{12} **5** in a single reaction vial, resulting in products **4a** and **6** in a 3.35 : 1

ratio (Scheme 1A). The high ratio is indicative of a primary kinetic isotope effect, implying the HAT process is the rate-determining step. Next, a TEMPO trapping experiment was performed with the standard reaction. After addition of 3.0 equivalents of TEMPO to the standard conditions, no ketone **4a** could be detected. Additionally, TEMPO adducts with the intermediary cyclohexyl radical and the azolium radical intermediate were both observed *via* ESI-HRMS (TEMPO adducts **7** and **8**, Scheme 1B).

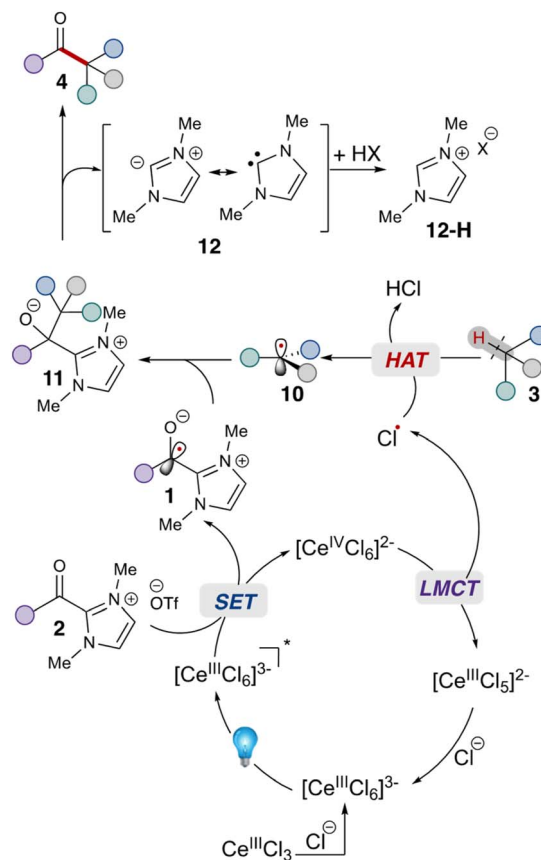
The radical-relay reaction of alkenes offers powerful methods for rapidly assembling molecular complexity using





Scheme 1 (A) Competition KIE experiment with cyclohexane and cyclohexane- d_{12} . (B) TEMPO trapping experiment. (C) Three-component radical relay reaction. (D) Enantioselective NHC and cerium trichloride dual catalyzed reaction.

readily available materials. Recent work by our group,²¹ Studer,²² Ohmiya,²³ Chi,^{15e} and Wang²⁴ have extended the reactivity pattern of acyl azoliums into three-component radical reactions. When adding 1.0 equivalent of styrene into our standard reaction conditions, the desired relay product **9** was furnished with 41% yield without further optimization (Scheme 1C). Finally, we examined the enantioselective NHC-catalyzed acylation using benzoyl fluoride **10** as the acyl azolium precursor. After screening a series of chiral NHC catalysts, we identified that catalyst **A** provided the chiral ketone **4m** in 46% yield and 70:30 er (Scheme 1D, details for other chiral NHC screening see ESI†).



Scheme 2 Proposed mechanism for the acylation of alkane **3** with acyl azolium **2**.

Given these studies,²⁵ we propose the following reaction mechanism (Scheme 2). Initially, the catalytically-active metal complex $[Ce^{III}Cl_6]^{3-}$ is generated from cerium chloride. This species, when photoexcited, serves as a single electron reductant ($E_{1/2}^*(Ce^{IV}/Ce^{III}) = -3.05$ V vs. SCE),²⁶ which can reduce the acyl azolium (benzoyl azolium **2a**, $E_{1/2} = -1.29$ V vs. SCE).¹⁶ to provide the persistent azolium radical intermediate **1** and $[Ce^{IV}Cl_6]^{2-}$.²⁷ Following this is the LMCT process, wherein $[Ce^{IV}Cl_6]^{2-}$, after excitation to a short-lived excited state, undergoes homolytic cleavage, yielding the reduced $[Ce^{III}Cl_5]^{2-}$ complex and a chloride radical.²⁸ The chloride radical then abstracts a hydrogen atom from alkane **3**, resulting in alkyl radical **10**. Subsequent radical-radical coupling leads to the formation of the tertiary azolium intermediate **11**. Under basic conditions, this intermediate ejects the carbene **12**, ultimately yielding the ketone **4**.

Conclusions

In summary, we have successfully established a cerium-catalyzed acylation capable of functionalizing unactivated $C(sp^3)-H$ bonds using bench-stable acyl azolium reagents. This reaction demonstrates remarkable versatility, accommodating various types of $C-H$ bonds with moderate to good yields. We have further demonstrated the application of these conditions

to a three-component reaction without further optimization, thus underscoring their potential applicability in a wide range of acylating transformations. Additionally, the enantioselective NHC and cerium dual-catalyzed reaction serves as a preliminary demonstration of asymmetric ketone synthesis from unactivated alkanes. The development of new catalytic applications for cerium, a cheap and earth-abundant lanthanide, has opened up new avenues for sustainable synthesis.²⁹ By integrating cerium catalysis in conjunction with acyl azoliums and NHC catalysis, we are able to achieve the acylation of unactivated C(sp³)-H bonds in simple alkanes. Future studies around developing the highly enantioselective acylation of simple alkanes is ongoing in our group.

Data availability

All experimental data, and detailed experimental procedures are available in the published article and ESI.†

Author contributions

The work was conceptualized by K. A. S. The experiments were performed by J. C. and J. L. Z. The manuscript was written through contributions of all authors. K. A. S. secured funding and supervised the entire work.

Conflicts of interest

There are no conflicts to declare.

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