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Dehydroxymethylation of Alcohols Enabled by Cerium Photocatalysis

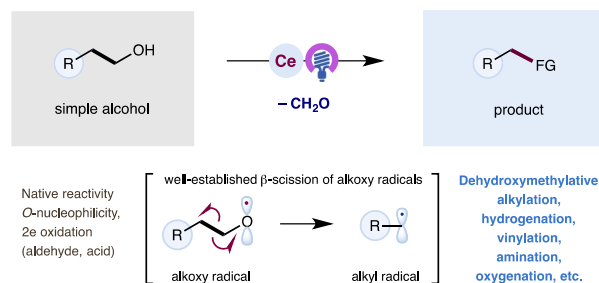
Kaining Zhang[†], Liang Chang[†], Qing An, Xin Wang and Zhiwei Zuo[★]

School of Physical Science and Technology, ShanghaiTech University, Shanghai 201210, China

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

Supporting Information Placeholder

ABSTRACT: Dehydroxymethylation, the direct conversion of alcohol feedstocks as alkyl synthons containing one less carbon atom, is an unconventional and underexplored strategy to exploit the ubiquity and robustness of alcohol materials. Under mild and redox-neutral reaction conditions, utilizing inexpensive cerium catalyst, a photocatalytic dehydroxymethylation platform has been furnished. Enabled by ligand-to-metal charge transfer catalysis, alcohol functionality has been reliably transferred into nucleophilic radicals with the loss of one molecule of formaldehyde. Intriguingly, we found that the dehydroxymethylation process can be significantly promoted by the cerium catalyst and stabilization effect of the fragmented radicals also plays a significant role. This operationally simple protocol has enabled the direct utilization of primary alcohols as unconventional alkyl nucleophiles for radical-mediated 1,4-conjugate additions with Michael acceptors. A broad range of alcohols, from simple ethanol to complex nucleosides and steroids, have been successfully applied to this fragment coupling transformation. Furthermore, the modularity of this catalytic system has been demonstrated in diversified radical-mediated transformations including hydrogenation, amination, alkenylation and oxidation.



INTRODUCTION

Cerium compounds, commonly utilized as Lewis acids in organic synthesis, have recently been explored as effective photocatalysts for a variety of practical transformations.¹⁻² The Earth abundance of Ce (relative abundance, $\sim 10^{1.5}$ atoms per 10^6 atoms of Si) and the ubiquity of simple cerium salts in synthetic labs have greatly facilitated the development of sustainable photochemistry. Upon irradiation, cerium compounds in different oxidation states (Ce(III) vs. Ce(IV)) adopt distinct mechanisms of electronic transitions, revealing orthogonal photoactivities and providing intriguing opportunities to access diversified activation modes in photoredox catalysis.³⁻¹¹ Prominently, the Schelter group exploited photoinduced metal-centered charge transfer process of Ce(III) compounds, rendering excited Ce(III) species as photoreductants, leading to the development of dehalogenation, arylation, and borylation reactions of aromatic halides.¹²⁻¹⁵ Concurrently, in our pursuit of sustainable photocatalysts, we recently became interested in the photoinduced ligand-to-metal charge transfer (LMCT) excitation mode of Ce(IV) complexes, which provides facile and efficient access to versatile alkoxy radicals via an excitation-homolysis sequence, enabling the development of a selective remote C-H amination of primary alkanols and ring-opening transformations of cycloalkanols.¹⁶⁻¹⁷ Through the synergistic utilization of hydrogen atom transfer (HAT) catalysis and LMCT catalysis, we subsequently accomplished C(*sp*³)-H aminations of methane and other gaseous alkanes under ambient reaction conditions, in the presence of low catalytic loadings of inexpensive Ce(IV) salts.¹⁸ Notably, this robust LMCT strategy has recently been

embraced by the König group for the photocatalytic decarboxylation of a variety of aliphatic carboxylic acids¹⁹.

As easily accessible and robust nucleophiles, alcohol compounds have been widely employed for numerous C-O bond constructions in organic synthesis. Nevertheless, diverse modes of activation have been developed to exploit the ubiquity and robustness of alcohols as valuable synthetic precursors.²⁰⁻²⁸ Dehydroxymethylation, an unconventional mode to utilize inexpensive alcohols as carbon synthons containing one less carbon atom, is an intriguing and underutilized strategy to transfer abundant alcohol feedstocks into value-added products.²⁹⁻³⁵ Due to the inertness of the β -hydroxy C-C bond, a tandem catalytic process, alcohol dehydrogenation followed by aldehyde decarbonylation, is commonly employed and enabled by noble transition metal catalysts (Figure 1A). Nonetheless, stoichiometric amounts of oxidants or acceptors are normally needed in the dehydrogenation step and the inhibitory effect of carbon monoxide on the transition metal catalysts has been hampering the development of dehydroxymethylation transformations. Moreover, established transformations typically lead to alkane products.³¹⁻³² Remarkably, the Dong group recently reported a Rh-catalyzed oxidative dehydroxymethylation which could convert alcohols into synthetically valuable alkenes with high efficiency (Figure 1B).³⁵ Employing an electron-deficient olefin as the efficient acceptor for transfer hydrogenation, excellent efficiencies and selectivities were achieved for a broad range of alcohols. Despite these powerful approaches to alcohol diversification, a general dehydroxymethylation manifold that allows the facile installation of diversified functionalities has yet to be realized.

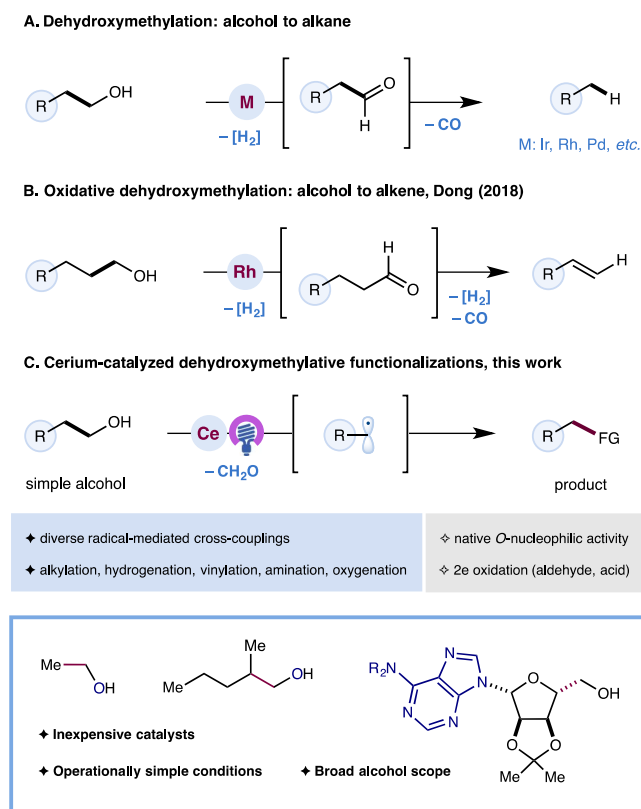


Figure 1. Utilizing simple and robust alcohols as alkyl synthons via cerium-catalyzed dehydroxymethylation.

The recent advancement of photoredox catalysis has enabled the activation of alcohols into nucleophilic carbon-centered radical fragments, providing diverse cross-coupling transformations otherwise unattainable.³⁶⁻⁴⁰ Notably, via easily prepared derivatives such as *N*-phthalimidoyl oxalates or oxalate salts, alcohols have been successfully activated into nucleophilic alkyl radicals through photocatalytic oxalate decarboxylations by the Overman and MacMillan groups, leading to the development of a series of synthetically valuable transformations including alkylation and arylation. Eminently, this strategy has been applied in elegant natural product syntheses.⁴¹ Inspired by those synthetically valuable transformations, herein, we demonstrate a photocatalytic dehydroxymethylative platform, where abundant alcohols from simple ethanol to complex nucleosides and steroids, could be directly converted to value-added products with the extrusion of formaldehyde. Utilizing inexpensive cerium catalysts, this straightforward protocol has enabled the development of various radical-mediated cross-couplings including alkylation, hydrogenation, amination, alkenylation, and oxidation under operationally simple conditions. (Figure 1C).

RESULTS AND DISCUSSION

Initial studies were focused on dehydroxymethylative alkylation, the fragment coupling of free alcohols with electron deficient alkenes. We questioned whether the β -scission of primary alkoxy radicals which generates an alkyl radical with the extrusion of formaldehyde could be a straightforward and general pathway to achieve dehydroxymethylation of free

Table 1. Reaction Optimization.

Entry	Catalysts	Light	Yield (%) ^a	O-addition(%) ^a
1	CeCl ₃ , (<i>n</i> -Bu) ₄ NCl	400 nm	2	6
2	CeCl ₃ , (<i>n</i> -Bu) ₄ NCl	365 nm	39	10
3	CeBr ₃ , (<i>n</i> -Bu) ₄ NBr	400 nm	15	12
4	CeBr ₃ , (<i>n</i> -Bu) ₄ NBr	365 nm	85	trace
5	CeBr ₃	365 nm	trace	9
6	Ce(OTf) ₃	365 nm	trace	34
7	Ce(OTf) ₃ , 30 mol% (<i>n</i> -Bu) ₄ NBr	365 nm	79	trace
8	(<i>n</i> -Bu) ₄ NBr	365 nm	0	0
9	CeBr ₃ , (<i>n</i> -Bu) ₄ NBr	dark	0	27
10	entry 1, 2 mol% DPA	400 nm	51	trace
11	entry 1, 5 mol% DPA	400 nm	81	trace

^aYields were determined by GC analysis of the crude reaction mixtures.

alcohols. We realized that several factors could impede the development of radical-mediated dehydroxymethylative couplings. While β -scission strategy has previously been applied in C–C bond cleavage,⁴²⁻⁵⁴ tertiary or strained cyclic alkoxy radicals are often employed; meanwhile, primary alkoxy radicals have been comparatively underexploited in this reactivity mode, owing to their relatively small tendency to undergo homolytic C–C cleavage over competitive intramolecular hydrogen atom abstraction.⁵⁵⁻⁶³ In order to successfully extend this transformation to complex alcohols containing multiple δ - or ϵ -hydrogen atoms, excellent selectivity has to be achieved for β -scission over 1,5-HAT. Furthermore, free primary alcohols are good O-nucleophiles and prone to 2e oxidations to generate aldehydes or carboxylic acids under oxidative conditions. Different from indirect approaches which employ redox-active alcohol derivatives or intermediates for alkoxy radical generation thusly masking the innate reactivity,^{44, 48-50} the direct utilization of free alcohols in this protocol would require the development of a faster radical-mediated pathway to outcompete the innate 2-electron addition or oxidation pathways.

The evaluation of cerium-catalyzed dehydroxymethylative system began with the coupling of electron deficient alkene **2** and cyclohexanemethanol, a primary alcohol conformationally disfavored for intramolecular HAT. To suppress the innate Michael addition, only neutral conditions were considered. Under the irradiation of 400 nm LED (photon flux, 10.0 μ Einstein), with cerium trichloride and tetrabutylammonium chloride, we only observed little amount of desired product together with hetero-Michael addition side-product after 12 h (Table 1, entry 1). Interestingly, while optimizing other parameters such as catalyst loadings, solvents and reaction temperatures failed to accelerate the desired radical-mediated addition pathway, switching the light source to 365 nm LED (photon flux, 7.6 μ Einstein) led to a significant increase of the dehydroxymethylation efficiency (entry 2). Furthermore, swapping the counterion of the employed cerium salt from

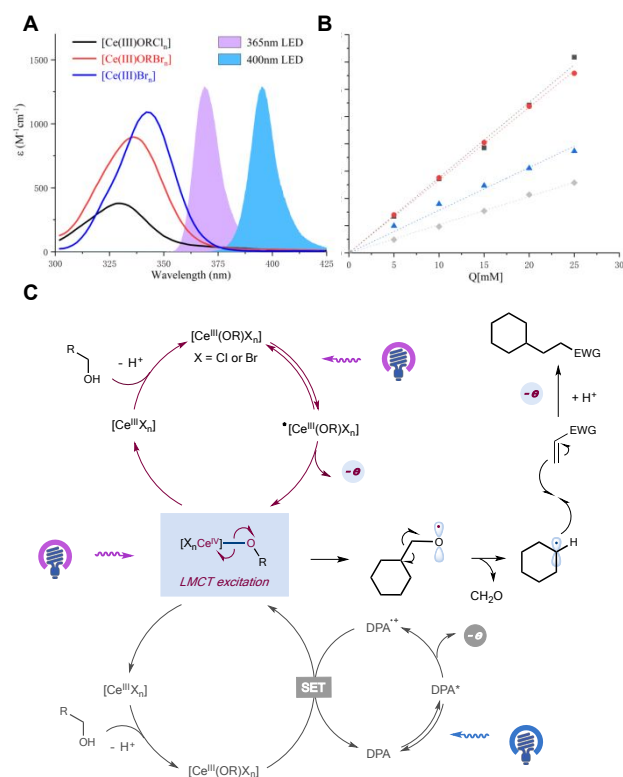
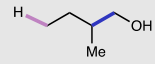
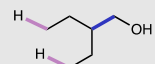
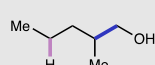
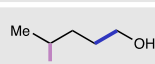
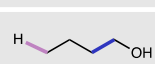
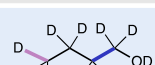
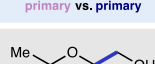
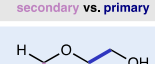

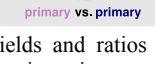
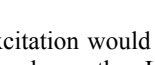
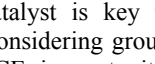
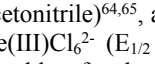
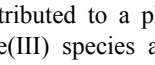
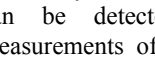




Figure 2. Mechanistic investigations. A. UV-vis absorption spectra of *in situ* formed $[\text{Ce(III)ORCl}_n]$, $[\text{Ce(III)ORBr}_n]$, and $[\text{Ce(III)Br}_n]$. ROH, cyclohexanemethanol. B. Stern-Volmer quenching experiments by electron-deficient alkene of cerium complexes, $[\text{Ce(III)ORBr}_n]$ (black), $[\text{Ce(III)ORCl}_n]$ (red), $[\text{Ce(III)Br}_n]$ (blue) and DPA (gray). C. Proposed mechanism.

chloride to bromide was found to be beneficial under both 400 nm and 365 nm LED irradiation (entries 3 and 4). The optimal yield was obtained using 5 mol% cerium(III) bromide and 15 mol% tetrabutylammonium bromide under ambient temperature; under these conditions, the hetero-Michael addition was negligible. To probe the acceleration effect of bromide counterion, control experiments were carried out (entries 5 and 6). In the absence of exogenous bromide, the cerium(III) bromide catalyst lost catalytic efficiency completely. Nevertheless, cerium(III) triflate, a strong Lewis acid that is soluble in acetonitrile, only led to large amount of presumably Lewis acid-catalyzed *O*-addition side-product. Intriguingly, the dehydroxymethylation pathway was instantly turned on and became predominant upon the addition of tetrabutylammonium bromide, unambiguously suggesting that the coordination of bromide with the cerium center is crucial to the desired photoactivity (entries 6 and 7). Moreover, cerium salts and light were proven to be essential for this transformation (entries 8 and 9). Interestingly, our previously-utilized dual-photocatalyst conditions employing CeCl_3 and 9,10-diphenylanthracene (DPA) could also deliver the desired transformation, with 5 mol% loading of DPA, optimal yield could be obtained (entry 11).

To elucidate the acceleration effect of the combination of 365 nm LED irradiation and the bromide additive, a number of spectroscopy experiments were performed. Based on our previous studies, the LMCT excitation of Ce(IV)-alkoxide species, the key event for the generation of alkoxy radicals, can be photoinduced either by 400 nm and 365 nm LED lights (the

Table 2. Selectivity Assessment.

Alcohols	Conditions	Dehydroxymethylation Vs. HAT
 4 primary vs. secondary	entry 4, table 1	88% : 0% (> 20:1 ratio)
 5 primary vs. secondary	entry 11, table 1	72% : 0% (> 20:1 ratio)
 6 secondary vs. secondary	entry 4, table 1	90% : 0% (> 20:1 ratio)
 7 secondary vs. primary	entry 11, table 1	62% : 0% (> 20:1 ratio)
 8 primary vs. primary	entry 4, table 1	89% : 0% (> 20:1 ratio)
 9 secondary vs. primary	entry 2, table 1	7% : 25% (1:3.6 ratio)
 10 secondary vs. primary	entry 4, table 1	20% : 17% (1.2:1 ratio)
 11 primary vs. primary	entry 2, table 1	11% : 6% (1.8:1 ratio)
 12 primary vs. primary	entry 4, table 1	30% : 6% (5:1 ratio)
 13 primary vs. primary	entry 2, table 1	15% : 0% (> 20:1 ratio)
 14 primary vs. primary	entry 4, table 1	52% : 0% (> 20:1 ratio)
 15 secondary vs. primary	entry 4, table 1	66% : 4% (16.5:1 ratio)
 16 secondary vs. primary	entry 11, table 1	83% : 6% (15.2:1 ratio)
 17 primary vs. primary	entry 4, table 1	81% : 0% (> 20:1 ratio)
 18 primary vs. primary	entry 11, table 1	70% : 0% (> 20:1 ratio)
 19 primary vs. primary	entry 4, table 1	80% : 0% (> 20:1 ratio)
 20 primary vs. primary	entry 11, table 1	70% : 0% (> 20:1 ratio)

Yields and ratios were determined by GC analysis of the crude reaction mixtures.

excitation would be slightly more efficient under 365 nm light based on the LMCT absorption intensity). Owing to the oxidizing nature of Ce(III) species, the turnover of the cerium catalyst is key to the improvement of catalytic efficiency. Considering ground state Ce(III) species ($E_{1/2} = 0.40$ V versus SCE in acetonitrile) are not reducing enough for the SET reduction of α -acyl radicals ($E_{1/2} = -0.60$ V versus SCE in acetonitrile)^{64,65}, and the Schelter group's discovery that excited Ce(III)Cl_6^{2-} ($E_{1/2} = -3.07$ V versus SCE in acetonitrile) was capable of reducing challenging aryl chlorides, we postulated that the acceleration rendered by the 365 nm LED could be attributed to a photoinduced electron transfer (PET) between Ce(III) species and α -acyl radicals. Indeed, *in situ* formed Ce(III) alkoxide complexes with CeCl_3 or CeBr_3 can be effectively excited at 365 nm and strong fluorescence emission can be detected. Furthermore, time-resolved emission measurements of these complexes revealed a short life time around 10 ns (the reported lifetime for Ce(III)Cl_6^{2-} , 22 ns. See

Supporting Information for details). The subtle difference in the absorption spectra of different cerium bromide complexes (formed in the presence and absence of cyclohexanemethanol) make it somewhat challenging to probe the complex responsible for the PET activity; nevertheless, we went on to carry out Stern-Volmer quenching experiments of different excited species at the same concentration to probe their rate differences. As demonstrated in Figure 2B, Stern-Volmer quenching experiments suggest that the heteroleptic Ce(III) bromide complex formed in the presence of alcohol, exhibits a much faster quenching rate compared to Ce(III) bromide complex⁶⁶, and thus would be a more effective reducing PET catalyst. Although Ce(III) alkoxide complex formed with CeCl₃ demonstrated comparable quenching efficiency, UV-vis absorption spectra revealed that the corresponding complex formed with CeBr₃ exhibited a more intense absorption in the 360 - 380 nm region, suggesting CeBr₃ catalyst could harness photons much more efficiently under the irradiation of 365 nm LED for PET reduction, accounting for the improved catalytic performance.

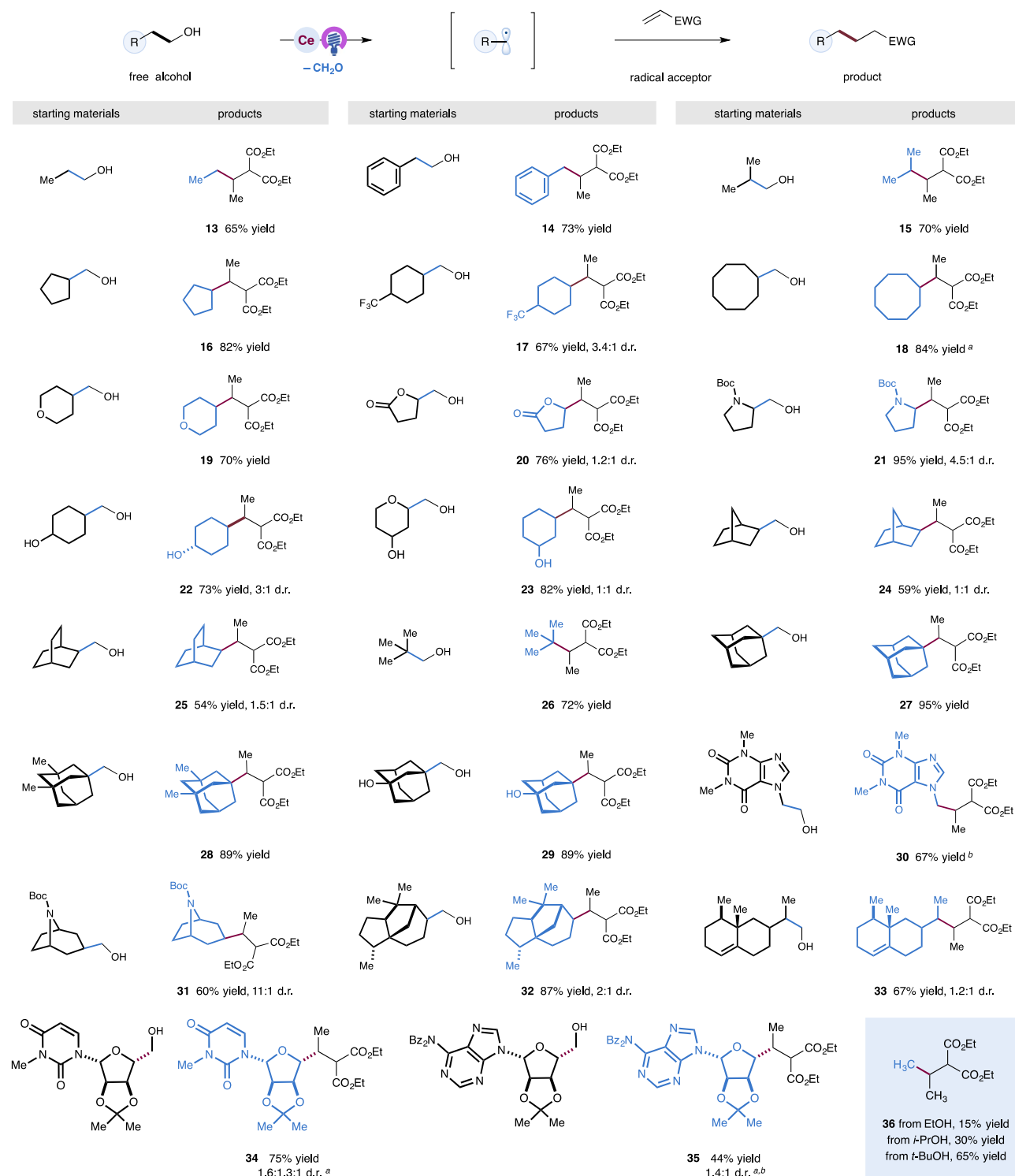
In light of these experiments, a double excitation mechanism is proposed for this straightforward dehydroxymethylative alkylation (Fig. 2C). Under irradiation of 365 nm LED or 400 nm LED, the *in situ* formed Ce(IV) alkoxide species was excited to the transient LMCT excited state, subsequently underwent the bond homolysis to generate the corresponding primary alkoxy radicals. The β -scission of the resulting alkoxy radical would lead to the generation of a nucleophilic alkyl radical and one molecule of formaldehyde. A radical-mediated conjugate addition of the resulting alkyl radical to the electron-deficient alkene would form the desired C-C bond and the α -acyl radical, an electrophilic radical that needs further SET reduction to generate the desired product. If the reaction was irradiated with 365 nm LED, Ce(III) alkoxide complex could be promoted to its excited form, which is a superior reductant capable of engaging in SET reduction with α -acyl radical to generate the desired product and Ce(IV) alkoxide. Nevertheless, in the case of 400 nm photons, which were energetically insufficient to promote the metal centered charge transfer of Ce(III) alkoxide complex (the spectrum of 400 nm LED barely overlaps with the absorption spectral of Ce(III) species), photoexcited DPA was required to promote the SET reduction of the α -acyl radical to generate the desired product. Meanwhile, the resultant radical cation of DPA could engage in SET oxidation with Ce(III) complex to complete the dual catalytic cycle concurrently.

With optimized conditions in hand, we sought to evaluate the propensity of our protocol to enable the desired β -scission process of alkoxy radical over the 1,5-HAT process. Extensive studies of primary alkoxy radicals have shown that the 1,5-HAT process (rate constant, $2.7 \times 10^7 \text{ s}^{-1}$)⁶⁷ is several orders of magnitude faster than β -scission (rate constant for *t*-butoxyl radical which is understood to be more prone to fragmentation than primary alkoxy radicals, $1.8 \times 10^4 \text{ s}^{-1}$)⁶⁸. Moreover, several research groups recently have demonstrated that primary alkoxy radicals derived from linear alcohols could render selective functionalizations at the δ -carbon without any interruption from C-C bond cleavage.^{65, 69-72} Consequently, alcohols with easily accessible δ -hydrogen atoms become extreme challenging substrates for radical-mediated dehydroxymethylations. Intriguingly, we found that dehydroxymethylation can be significantly promoted by the cerium catalyst, possibly due to

the weak interaction of the alkoxy radicals with the surrounding cerium salts which are Lewis acids by nature, and stabilization effect of the fragmented radicals also plays a significant role. As demonstrated in alcohols 4-6, the intramolecular HAT pathways were found to be suppressed completely, dehydroxymethylative alkylation products were generated in good yields and excellent selectivity via the intermediacy of a secondary alkyl radical, rendering β -branched alcohols as reliably effective substrates in this platform. However, the reaction with *n*-pentanol was found sluggish, as the generation of a less-stabilized primary radical via dehydroxymethylation is seemingly disadvantageous, competing with the HAT pathway that resulted in a secondary radical. Nonetheless, in the case of *n*-butanol, where two competitive pathways both led to the generation of primary radicals, we were able to obtain the dehydroxymethylative product as the leading product, albeit in low yield possibly due to the relatively less reactive nature of primary alkyl radicals. Accordingly, we recognized that the displacement of C-H bonds with stronger C-D bonds at the δ -position would further discourage the 1,5-HAT to facilitate dehydroxymethylation. As evident in *d*₁₀-butanol (9), the HAT pathway was deactivated and the desired product was obtained exclusively. More importantly, we found that the CeBr₃ catalyst in fact promoted the desired β -scission pathway, as we observed an increase in both selectivity and efficiency for the dehydroxymethylation products (5:1 ratio, 30% yield). As such, although the lone pair of the oxygen atom can provide conjugative stabilization for both the radicals generated via HAT or homolytic scission in the case of 2-ethoxyethanol (10), we found that the stabilization effect was more beneficial to dehydroxymethylation and synthetically useful selectivity was obtained (16.5:1 ratio). Moreover, switching the ethoxy group to the methoxy group, a rather delicate adverse change for the 1,5-HAT pathway resulted in an exclusive formation of the dehydroxymethylation product (> 20:1 ratio). Further, we observed that 2-pentanol (12), forming a secondary alkoxy radical that easily fragments,⁵⁵ yield the desired selectivity (> 20:1 ratio).

We then turned our attention to evaluating the scope of alcohols using this operationally simple protocol. As shown in Table 2, we were delighted to find that a variety of alcohols can be applied in this fragment coupling transformation to construct C-C bonds through the extrusion of one molecule of formaldehyde, demonstrating a practical strategy utilizing abundant alcohol feedstocks directly as robust surrogates for organometallic reagents in 1,4-additions. This transformation displayed good functionality tolerance, with a variety of commonly encountered functionalities, such as ether (19), ester (20), amide (21, 31), heterocycle (30, 34-35), alkene (33) and ketal (34, 35) being left unscathed in this reaction. Different substitution patterns at the β -position of the hydroxyl group, which would affect the nucleophilicity of the carbon-centered radicals, could be accommodated, regardless of linear or cyclic, irrespective of primary, second or tertiary. Vitaly, primary hydroxyls embedded in complex molecules proved to be efficient and reliable functional handles, as several complex alcohols reacted well to deliver the corresponding dehydroxymethylation products (31-33). Notably, protected nucleosides such as acetonydes of uridine and adenosine were amenable to the reaction, producing the expected fragment-coupled products (34 and 35). We were delighted to find that this catalytic system exhibits good selectivity towards primary hydroxyl groups, as demonstrated in products 22, 23 and 29,

Table 3. Alcohol scope.

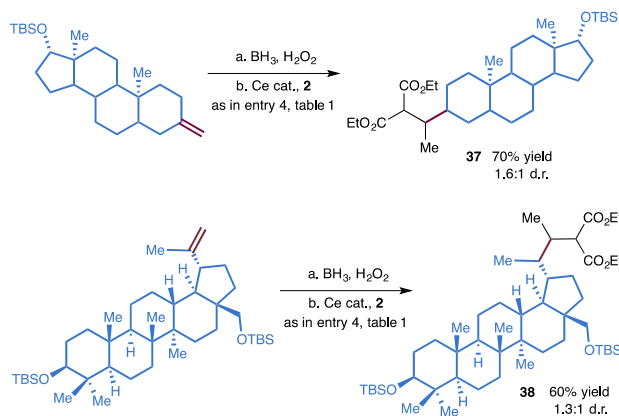


General reaction conditions: alcohol substrate (0.4 mmol), alkene substrate (3 equiv.), CeBr₃ (0.05 equiv.), (*n*-Bu)₄NBr (0.15 equiv.), acetonitrile (0.8M), 365nm LEDs. All yields are isolated yields. Diastereoselectivity was determined by ¹H NMR analysis or HPLC analysis.^a 0.1 equiv. CeBr₃ and 0.3 equiv. (*n*-Bu)₄NBr were used. ^b benzonitrile was used as solvent. See Supporting Information for experimental details.

only primary hydroxyl groups were selectively harnessed for the dehydroxymethylation while secondary and tertiary hydroxyl groups on the carbon cycles remained intact. Further studies revealed that proximal diols, including vicinal, 1,2- and 1,3-diols, that could potentially form a chelate complex with

cerium shut down the photoactivity completely, only led to *O*-addition byproducts. Whereas 1,5-pentanediol and 1,6-hexanediol were less

v



Scheme 1. Sequential hydroboration-oxidation and dehydroxymethylation. See Supporting Information for details.

inhibitory for cerium photocatalysis, the desired dehydroxymethylation product can be obtained (See Supporting Information for details). One of the most challenging, yet economical substrates for dehydroxymethylation is ethanol. It is well-known that radical methylation is amongst the most challenging transformations due to the high energy nature of the methyl radical. We were pleased to find that this photocatalytic platform could utilize ethanol as a methylation reagent, giving the desired product **36** in 15% yield under the standard reaction condition. Additionally, synthetically useful yield of the same product can be obtained utilizing *tert*-butanol, obviously facilitated by a faster β -scission of *tert*-alkoxy radicals. Notably, merging this cerium catalyzed dehydroxymethylation alkylation with hydroboration-oxidation of alkenes, a frequently utilized straightforward protocol to introduce hydroxyl groups, we could achieve a formal C=C double bond cleavage and alkylation. As shown in Scheme 1, alkenes embedded in complex steroid frameworks can be successfully employed in this two-step sequence, affording alkylation products with satisfactory yields.

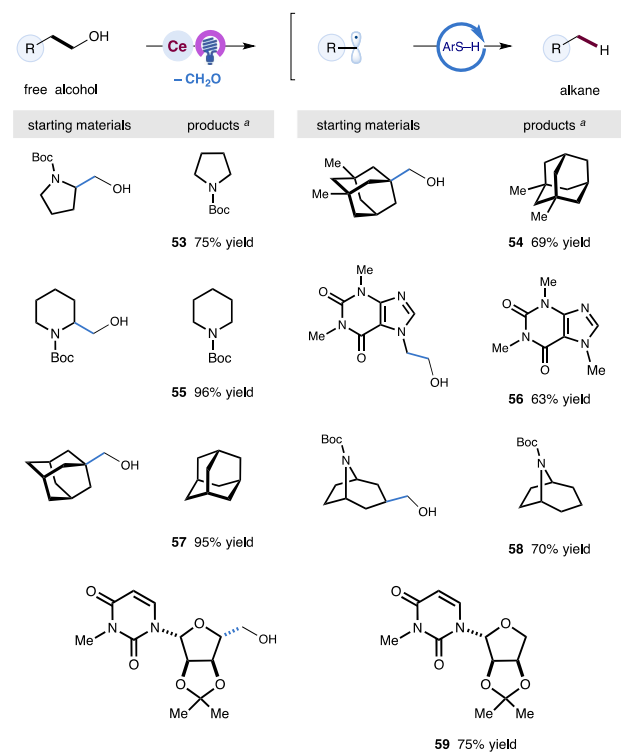
Next, we explored the scope of Michael acceptors in this protocol with 1-adamantanemethanol to probe the generality of this platform in the construction of quaternary carbon centers. As shown in Table 3, a range of electron-deficient alkenes proved suitable coupling partners in this photocatalytic process, delivering the corresponding alkylated product in moderate to good yields. Importantly, only dehydroxymethylation products were obtained in all cases. For some Michael acceptors with sufficiently low-lying LUMOs (products **47-52**), the reaction efficiency was compromised by undesired alkene reduction and dimerization, yet we found that synthetically useful yields could be obtained if more equivalents of alcohols were employed. Highly reactive methylenemalonate also underwent the desired transformation, albeit with slightly lower efficiency due to the propensity of oligomerization (product **50**). A number of α , or β -substituents on the alkene, including aryl chloride (**42**) and fluoride (**43**), trifluoromethyl (**46**), cyano groups (**51**) were well-tolerated. For substituted acrylates and atopates substrates, interestingly, the cerium/DPA dual-photocatalytic system was found to be more efficient, affording the desired alkylation products with higher yields (products **39-41**, **43-46**).

Table 4. Alkene Scope.

alkenes	products	alkenes	products
	39 84% yield ^a		40 69% yield ^a
	41 78% yield ^a		42 65% yield ^b
	43 53% yield ^a		44 62% yield ^a
	45 58% yield ^a		46 66% yield ^a
	47 42% yield ^b		48 85% yield ^b
	49 68% yield ^b		50 65% yield ^b
	51 69% yield ^b		52 75% yield ^b

^a alcohol substrate (0.2 mmol), alkene substrate (3 equiv.), DPA (0.05 equiv.), CeCl₃ (0.05 equiv.), (*n*-Bu)₄NCl (0.15 equiv.), acetonitrile (0.05M), 400nm LEDs. ^balcohol substrate (3 equiv.), alkene substrate (1 equiv.), CeBr₃ (0.05 equiv.), (*n*-Bu)₄NBr (0.15 equiv.), acetonitrile, 365nm LEDs.

The feasibility and generality of converting abundant alcohols into synthetically versatile alkyl radicals through this operationally simple cerium catalyzed system encouraged us to further explore the synthetic utility of photocatalytic dehydroxymethylative transformations. Reductive dehydroxymethylation, the conversion of free alcohols into alkane products, would address the need of removing polar hydroxyl groups in late stage functional group manipulations and provide a platform for selective conversions of biomass materials into chemical feedstocks, thusly has drawn a lot of research attention. Previously, this reaction has been achieved via a dehydrogenation and decarbonylation sequence, we posited that this cerium catalyzed system could provide a more straightforward approach by expelling one molecule of formaldehyde from alcohols directly. As depicted in Table 5, we found that the photocatalytic reductive dehydroxymethylation of alcohols can be readily achieved by employing thiols as the hydrogen transfer catalyst. Utilizing

Table 5. Dehydroxymethylative functionalizations.

^a alcohol substrate (0.4 mmol), DPA (0.05 equiv.), CeCl₃ (0.1 equiv.), (*n*-Bu)₄NCl (0.3 equiv.), TRIP₂S₂ (0.2 equiv.), acetonitrile (0.1M), 400nm LEDs. All yields are isolated yields. See Supporting Information for details.

inexpensive CeCl₃ as the catalyst, a number of primary alcohols, including those derived from complex molecules, could be selectively converted to the corresponding alkanes with one less carbon atoms with moderate to excellent efficiency under mild conditions. We believe that this photoinduced radical-mediated protocol would be complementary to, in the aspects of mechanism and synthetic applications, transition-metal-catalyzed dehydroxymethylation processes.

This operationally simple platform enables us to harness the nucleophilicity of alkyl radicals to modularly install valuable functionalities under a single catalytic system. Under the standard condition with CeBr₃ as the photocatalyst, the resulting alkyl radical generated from 1-adamantanemethanol

could be efficiently trapped by di-*tert*-butyl azodiformate to afford the amine product **60** in 78% yield (Scheme 2). Moreover, diphenyl-substituted vinyl sulfone, which is prone to radical addition and subsequent single-electron elimination, turned out to be a capable radical trapper in this photocatalytic system, delivering the corresponding alkenylation product in synthetic useful yield under the standard conditions. Notably, this cerium protocol is compatible with aerobic oxidation. Irradiation of the reaction solution of 1-adamantanemethanol and Ce-catalyst under O₂ atmosphere furnished 1-adamantol, although the efficiency was partially compromised by the α -C-H oxidation. These results further demonstrated the modularity of our cerium catalyzed LMCT system.

In summary, we have developed a general and practical photocatalytic protocol for dehydroxymethylative functionalization of alkanols via the intermediacy of versatile alkyl radicals, enabling alkylation, hydrogenation, amination, alkenylation, and oxidation transformations. Utilizing light energy and inexpensive cerium catalysts, a broad range of alcohols, from simple ethanol to complex nucleosides, can be employed in this fragment-coupling transformation. This operationally simple platform enables the direct utilization of ubiquitous hydroxyl groups as functional handles for the generation of alkyl radicals, offering intriguing opportunities for rapid molecular complexity construction.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the website at DOI.

Experimental procedures and compound characterization data (PDF)

AUTHOR INFORMATION

Corresponding Author

*zuozhw@shanghaitech.edu.cn

Author Contributions

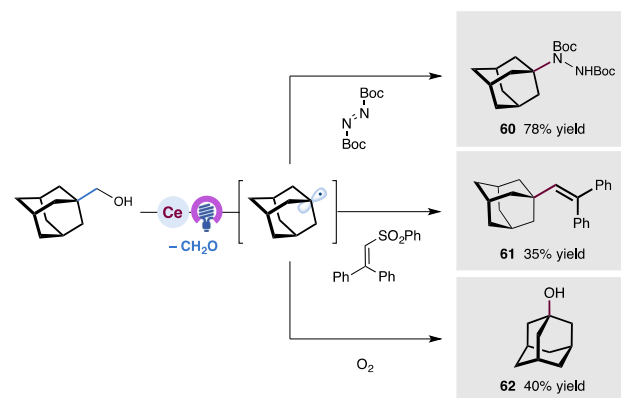
*K.Z. and L. C. contributed equally to this work.

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Scheme 2. Modular installation of functionalities via cerium catalyzed dehydroxymethylation. See Supporting Information for details.

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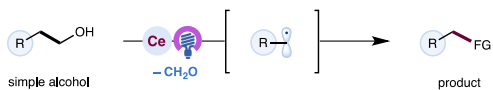
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◆ diverse radical-mediated cross-couplings
◆ native O-nucleophilic activity
◆ alkylation, hydrogenation, vinylation, amination, oxygenation
◆ 2e oxidation (aldehyde, acid)

