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δ-Selective Functionalization of Alkanols Enabled by Visible-Light-Induced Ligand-to-Metal Charge Transfer

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Supporting Information

ABSTRACT: We demonstrate the application of ligand-to-metal charge transfer (LMCT) excitation to the direct catalytic generation of energetically challenging alkoxy radicals from alcohols through a coordination−LMCT−homolysis process with an abundant and inexpensive cerium salt as the catalyst. This catalytic manifold provides a simple and efficient way to utilize the characteristic reactivity and selectivity of transient alkoxy radicals for δ-selective C−H bond functionalization. Under mild redox-neutral conditions without the need for prefunctionalization, this method provides a versatile platform to access molecular complexity from simple and abundant alcohols.

Over the past decade, photoredox catalysis has emerged as a powerful tool for the construction of molecular complexity, most prominently with the generation of high-energy heteroatom-centered radicals as an enabling platform.[1] Typically, these radicals are accessed via single-electron transfer (SET) with a triplet excited state of a metal−polypyridyl photocatalyst generated through visible-light-induced metal-to-ligand charge transfer (MLCT).[2] An alternative excitation manifold, ligand-to-metal charge transfer (LMCT), has comparatively been underexploited in the realm of synthetic organic chemistry, despite holding great promise for the development of novel photoinduced transformations.

Heteroatom-centered radicals have traditionally been utilized as highly versatile synthetic intermediates in transformations such as the Hoffman−Loffler−Freytag and Barton nitrite ester reactions.[3] Nevertheless, the synthetic potential of their well-established reactivity and selectivity in 1,5-hydrogen atom transfer (1,5-HAT) is frequently restrained by the difficulties inherent in the generation of these transient, high-energy radicals, which typically relies upon the utilization of prefunctionalized precursors of alcohols and amines or harsh conditions.[4,5] In contrast, direct homolytic activation of free alcohols and amines represents the most straightforward and demanding strategy;[2d,e,6] however, this has generally proven challenging because of the remarkable stability of the X−H bonds (the O−H bond dissociation energy is ∼105 kcal/mol).[7] Through the concerted transfer of a proton and electron, proton-coupled electron transfer (PCET) catalysis has recently emerged as a novel and efficient strategy for the general activation of N−H bonds, as well as O−H bonds in one catalytic example based on a series of electron-rich arene-substituted tertiary alcohols, to promote various synthetically

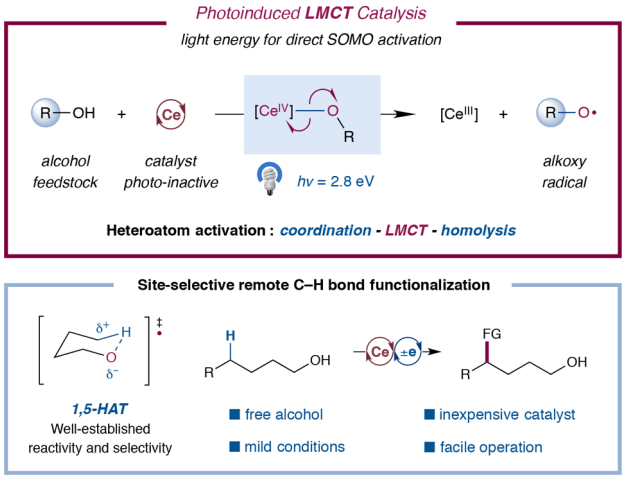

Figure 1. Coordination−LMCT−homolysis activation mode allows general access to alkoxy radicals.

valuable transformations.[8] Thus, a general catalytic platform for the direct generation of alkoxy radicals from alcohols remains in high demand.

LMCT excitation promotes homolysis of a metal−ligand bond to generate ligand-based radical intermediates in a formal reduction of the metal center,[9,10] resulting in oxidation of the ligand directly, presenting an opportunity for facile photocatalytic access to heteroatom-centered radicals. LMCT catalysis, which proceeds through coordination of the substrate to an inorganic salt, photoinduced LMCT, and subsequent homolysis, is a mechanistically distinct photoredox activation mode that promotes substrate oxidation not through SET by an excited or oxidized photocatalyst but in the excitation process itself. This allows for targeted oxidation to occur only at the transiently coordinated functional group while leaving other, easier-to-oxidize functionalities intact. Thus, more challenging oxidations, such as that of alkoxides, can be selectively accomplished by directly exciting the LMCT band of the coordination complex, delivering alkoxy radicals in a simplified and truly general form under mild conditions. This approach would further improve the ease of application, as only a simple, photoinactive inorganic salt would be required, with coordination to the substrate triggering the photocatalytic activity. Interestingly, this strategy has not been thoroughly investigated

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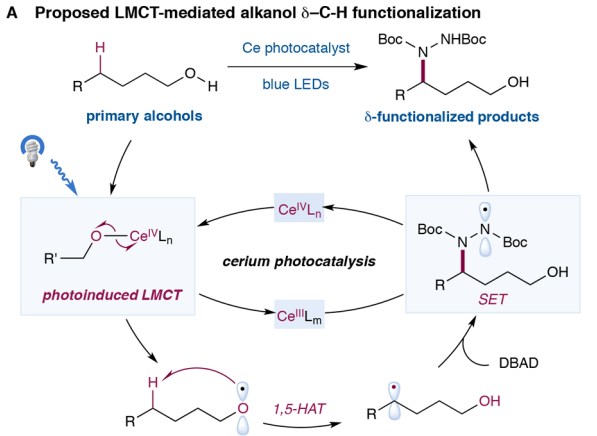
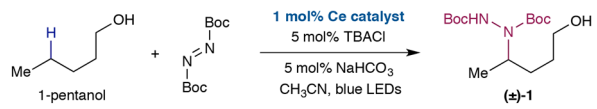
and utilized in the organic synthesis community, likely because of the popularity of coordinatively saturated photocatalysts.[11] Herein we demonstrate the application of LMCT catalysis as a direct and general method for the catalytic generation of alkoxy radicals from alcohols and the successful development of an atom-economical and operationally simple protocol for site-selective remote C−H bond functionalizations of primary alcohols (Figure 1).

Given the ubiquity and importance of amines in pharmaceuticals and natural products, we sought to achieve the site-selective installation of nitrogenous functionality on abundant carbinols. We posited that abundant and inexpensive cerium salts would be ideal catalysts for a sustainable photocatalytic system;[12,13] furthermore, Ce(IV) complexes are well-precedented in the inorganic chemistry literature to participate in redox reactions induced by LMCT excitation, resulting in reduction of the cerium center to Ce(III) and oxidation of the ligand.[14] Intrigued by the ability of alcohols to ligate to the metal center,[15] we envisioned that the coordination complex could be readily photoexcited by visible-light irradiation and subsequently undergo Ce(IV)−OR homolysis to generate the transient alkoxy radical from a simple or complex alkanol, such as butanol or cholesterol (Figure 2A).



B Reaction optimization



Entry	Catalyst	Light	Yield (%)[a]
1	$Ce(OTf)_4$	blue LEDs	43
2	$(n\text{-}Bu_4N)_2[CeCl_6]$	blue LEDs	89
3	-	blue LEDs	0
4	$(n\text{-}Bu_4N)_2[CeCl_6]$ (10%)	OFF (60°C)	0
5[b]	$CeCl_3$	blue LEDs	92

Figure 2. Reaction design and development. [a]Yields were determined by GC analysis of the crude reaction mixtures. [b]The reaction was performed without base.

We anticipated that the δ-C−H bond would then be selectively activated via a thermodynamically favorable 1,5-HAT to generate the highly nucleophilic alkyl radical, which would readily undergo coupling with di-*tert*-butyl azodiformate (DBAD) to forge a new C−N bond with the formation of a nitrogen-centered radical.[16] Single-electron reduction of this radical by the reduced form of the cerium catalyst would regenerate the active Ce(IV) catalyst and deliver the desired product.

With this mechanistic hypothesis in hand, we first examined the proposed C−H bond functionalization using 1-pentanol, DBAD, *tert*-butylammonium chloride (TBACl), cerium catalysts, and blue light-emitting diodes (LEDs) (Figure 2B). Among the commercially available cerium(IV) reagents, we found that the desired product could be isolated in 13% yield when cerium(IV) triflate was employed (see the Supporting Information for further experimental results). With a premade cerium(IV) chloride complex,[17] a light-sensitive yellow compound, excellent efficiency could be achieved, delivering the δ-functionalized alcohol in 89% yield. Control experiments revealed the importance of the cerium catalyst and light, as no desired product was observed in the absence of either the catalyst or blue light. Furthermore, operating the reaction in the dark at elevated temperature led to no observed product formation, even at a higher catalyst loading. To further simplify the reaction conditions and build on our previous success of C−C bond activation of cycloalkanols,[13] commercially available cerium(III) chloride was identified to be a suitable precatalyst, as a 92% yield of the desired product was observed after 8 h under neutral conditions without base.

As a means of elucidating the mechanism of this proposed LMCT-induced transformation, a number of UV−vis experiments were conducted (Figure 3). The absorption spectrum of the Ce(IV)−alkoxide complex formed from a premade $Ce^{IV}Cl_6^{2-}$ complex and pentanol under basic conditions according to the protocol reported by the Anwander group[15d] displayed a band resembling the LMCT band of analogous cerium−alkoxide complexes,[14a,15d] critically, exhibited substantial overlap with the blue LED spectrum, suggesting that the Ce(IV)−alkoxide species could be photoexcited in this reaction (Figure S1). We then probed this possibility by analyzing the absorption spectra of Ce(IV) complexes after irradiation with blue light at different time points. As shown in Figure 3A, the absorption spectrum of a solution containing Ce(IV)−alkoxide complex gradually shifts from λ_{max} = 370 nm to λ_{max}= 330 nm

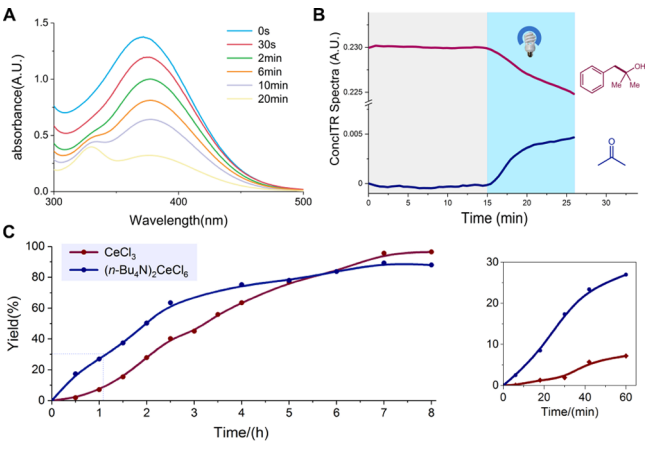


Figure 3. Mechanistic studies. (A) UV−vis spectral changes observed upon photolysis of a solution of $Ce^{IV}(OC_5H_{11})Cl_n$ complex in CH_3CN under blue light (0−20 min). (B) Operando IR experiments with a solution of $(n\text{-}Bu_4N)_2CeCl_6$ and 2-methyl-1-phenyl-2-propanol in the dark (0−15 min) and with blue-light irradiation (15−25 min). (C) Reaction profiles for the δ-C−H amination of 1-pentanol catalyzed by $(n\text{-}Bu_4N)_2CeCl_6$ and $CeCl_3$. See the Supporting Information for experimental details.

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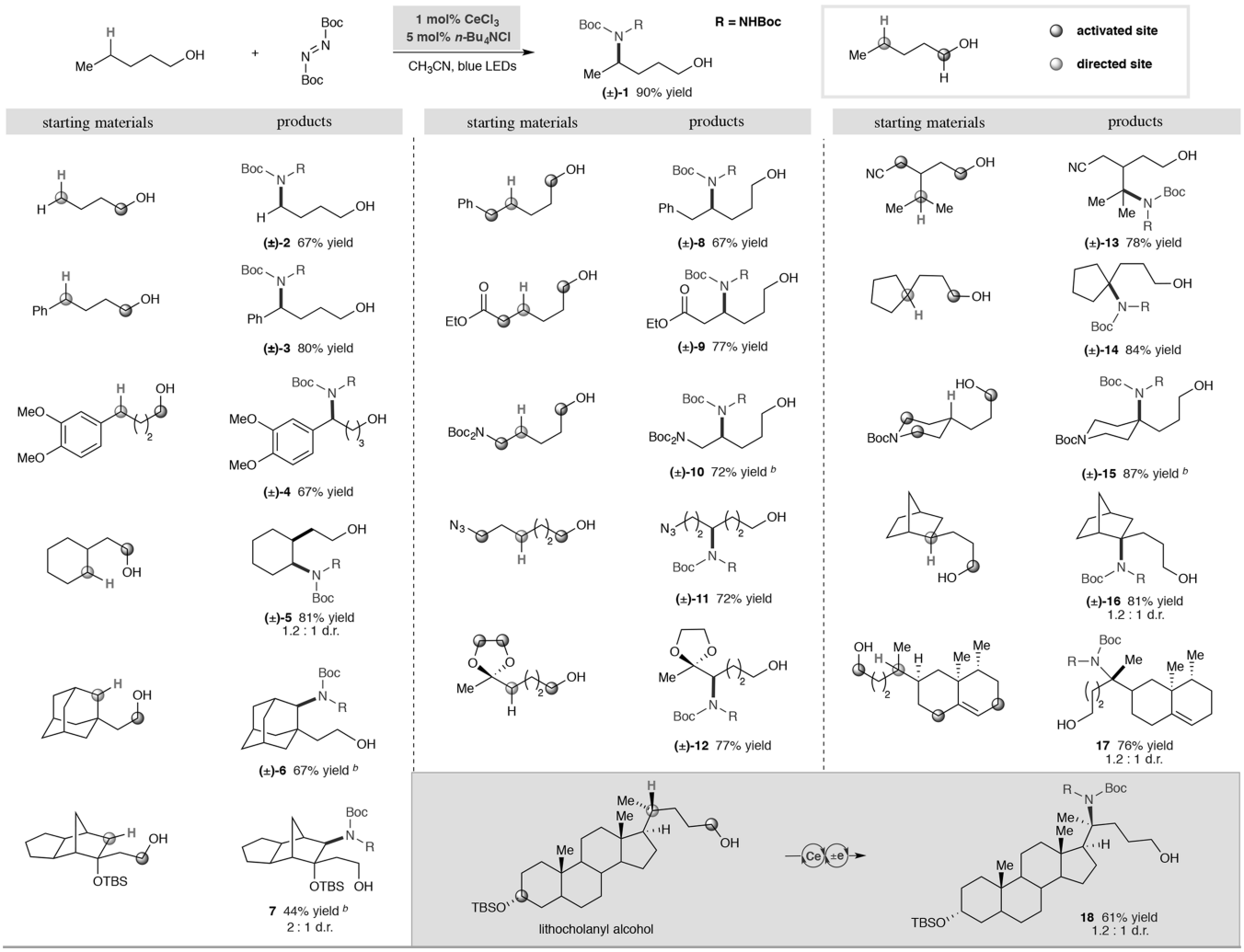

Figure 4. Reaction scope. [a]General reaction conditions: DBAD (0.4 mmol), alcohol substrate (1.2 mmol), $CeCl_3$ (0.004 mmol), TBACl (0.02 mmol), CH_3CN (4 mL), 90 W blue LEDs. All yields are isolated yields. Diastereoselectivity was determined by ^1H NMR or HPLC analysis. See the Supporting Information for full reaction scope and experimental details. [b]The reaction was performed with 2 mol % $CeCl_3$ and 10 mol % TBACl.

upon irradiation, indicative of a photoinduced homolysis event to generate a Ce(III) complex,[14c] while the Ce(IV)−alkoxide complex is completely stable in the dark (Figure S3), indicating that ground-state SET is not operative. To further elucidate the alkoxy radical formation process via LMCT, operando IR experiments with a solution of $(n\text{-}Bu_4N)_2Ce^{IV}Cl_6$ and 2-methyl-1-phenyl-2-propanol was performed. In this case, the oxidation of the tertiary alcohol would lead to a fast β-scission pathway to generate acetone, which is easily quantified by IR spectroscopy, as the C−C bond cleavage product. No acetone formation was detected in the dark (0−15 min), but when the light was turned on (15−25 min), acetone formation (10% yield in 5 min) via photoinduced LMCT generation of the transient *tert*-alkoxy radical was observed (Figure 3B). When the reaction profiles of this remote functionalization transformation with the cerium(IV) chloride complex and cerium(III) chloride are compared, a marked induction period is observed for $CeCl_3$ (Figure 3C). These observations indicate that $CeCl_3$ was functionalized as the precatalyst. We reasoned that Ce(III) species ($E_{1/2}(Ce^{III}/Ce^{IV})$ = 0.41 V vs SCE in CH_3CN) can be activated in situ by a photoinduced single-electron oxidation with DBAD[18] (E^* = 1.66 V vs SCE in CH_3CN; see the Supporting Information). In combination, these studies describe a unique approach to the mild catalytic generation of alkoxy radicals using a simple, commercially available earth-abundant metal salt as a photocatalyst.

We next evaluated the generality of this atom-economical and operationally simple protocol. As partially shown in Figure 4, diverse classes of alcohols could be selectively and predictably functionalized under mild and redox-neutral conditions (see the Supporting Information for expanded reaction scope). Because of the high reactivity of alkoxy radicals, primary (**2**), secondary (**3**−**12**), and tertiary (**13**−**18**) carbon centers could all be functionalized with good efficiency. Critically, for substrates in which weaker, activated C−H bonds were present, only δ-functionalized products were observed in all cases (**8**−**12**, **15**, **17**, and **18**). These results further emphasize the exquisite control that a catalytic 1,5-HAT mechanistic pathway affords for C−H abstraction. Furthermore, the highly electrophilic nature of the alkoxy radical offers additional polarity-based selectivity. Thus, a substrate containing multiple electronically differentiated δ-C−H bonds undergoes selective functionalization at the most electron-rich carbon center, as exemplified by product **13**. As expected, easily oxidized moieties, such as electron-rich arenes (**4**) and alkenes (**17**), were not oxidized in this system because of the

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coordination−LMCT−homolysis pathway for substrate oxidation. Pleasingly, the mild and redox-neutral conditions employed by this reaction technology proved to be tolerant of silyl-protected alcohol-containing substrates (**7** and **18**). Additionally, no degradation was observed for these substrates containing ester (**9**), amino (**10** and **15**), azido (**11**), ketal (**12**), allyl (**17**), and nitrile (**13**) functionality. Complex polycyclic systems, such as monosilylated lithocholanyl alcohol, can also be selectively installed with the nitrogenous functionality, demonstrating the applicability of this manifold to complex molecule synthesis (**18**).

In summary, we have developed a general strategy for catalytic, alkoxy-radical-mediated, site-selective distal functionalization of primary alcohols using an inexpensive cerium photocatalyst. Without the need for prefunctionalization, utilizing mild and redox-neutral conditions, this atom-economical and operationally simple protocol has been applied to a wide array of alcohols. The photoinduced LMCT activation mode is ideal for direct activation of heteroatom-containing functionality and is expected to offer new opportunities for the development of visible-light photoredox transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b13131.

Experimental procedures and additional data (PDF)

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Notes

The authors declare no competing financial interest.

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