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ARTICLE

Overriding the Radical Polarity Matching Principle: Selective Chlorohydroxylation of Electron-Deficient Alkenes Enabled by Ce Photocatalysis

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Luchuan Ou[a†], Yihang Bai[a†], Shanshuo Liu[c†], Zongling Kan[c], Yu Lan[a,b,d*], Jiali Zhu[a], Shihan Liu[e], Zhigang Ren[c*], Shi-Jun Li[a,b*], and Linbin Niu[a,b*]

Abstract: Radical addition to alkenes generally follows the polarity matching principle; for instance, the electrophilic chlorine radical favors electron-rich double bonds over electron-deficient ones in alkenes. Herein, we achieve a one-step selective aerobic chlorohydroxylation of alkenes via Ce-LMCT-generated chlorine radicals. The protocol exhibits a broad substrate scope, notably extending to electron-deficient, amide-containing alkenes—a class of substrates historically challenging for the addition of electrophilic radicals due to the polarity matching principle. Theoretical calculations reveal that the radical adduct generated from the chlorine radical and amide-containing alkene is stabilized by the amide group, which helps the system to override the radical polarity matching principle.

Introduction

Radical addition to alkenes is a fundamental transformation in radical-mediated organic synthesis. Generally, a nucleophilic radical prefers to add to an electron-deficient alkene rather than an electron-rich one. Conversely, an electrophilic radical favors addition to electron-rich alkenes (Figure 1A).[1] This polarity matching rule governing radical addition to unsaturated bonds is important for designing highly selective radical relay reactions.[2] However, the scope of these radical reactions may be limited by their reliance on the addition step. To circumvent the polarity matching rule, methods that allow, for example, the effective addition of electrophilic radicals to electron-deficient alkenes are highly desirable, as they would provide access to novel synthetic pathways.[3]

C(sp^3)–Cl bonds not only are extensively present in natural products, pharmaceuticals, agrochemicals, and functional materials,[4] but also serve as an indispensable synthon in modern organic synthesis (Figure 1B). Numerous catalytic strategies have been developed to construct C(sp^3)–Cl bonds,[5] among which chlorine radical-mediated approaches show intriguing reactivity and selectivity.[6] The electrophilic chlorine radical (electrophilicity index: 3.90) exhibits a strong preference for electron-rich alkenes, which enables the elegant, anti-Markovnikov selective synthesis of various C(sp^3)–Cl-containing chemicals.[7] For instance, the Lin group achieved the dichlorination of electron-rich alkenes to vicinal dichlorides via electrocatalysis;[8] the West group recently reported anti-Markovnikov hydrochlorination of electron-rich alkenes for the production of alkyl chlorides using iron photocatalysis.[9] Nevertheless, the selective chlorohydroxylation of electron-deficient alkenes via chlorine radical addition remains under-explored.

Visible light-induced organic transformations have been rapidly developed and are highly attractive in organic synthesis due to their safety and environmental friendliness.[10] As one of the prevalent electron transfer mechanisms under visible light, LMCT has garnered widespread attention from organic synthetic chemists. This process typically involves using specific wavelengths of light to excite the electrons from ligands to vacant metal orbitals, thereby generating ligand-derived radicals that can be utilized to facilitate various types of chemical reactions, such as addition to unsaturated bonds or activation of inert chemical bonds.[11] To date, a wide range of metals have demonstrated the capability to mediate LMCT reactions.[12] Among them, cerium, the most abundant lanthanide element in the earth's crust, possesses a unique electronic configuration [Xe] 4f^{1}5d^{1}6s^2.[13] Cerium photocatalysis via the LMCT mechanism has flourished over the past decade.[14] The Zuo group presented a highly representative paradigm: the cerium-alcohol complex generated in-situ from cerium salts and alcohols undergoes homolysis to produce electrophilic alkoxy radicals under visible light irradiation. Alkoxy radical can abstract the hydrogen atom of C(sp^3)–H bonds to generate

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[a] College of Chemistry, State Key Laboratory of Antiviral Drugs and Pingyuan Laboratory, Zhengzhou University, Zhengzhou, Henan 450001, P. R. China.
[b] State Key Laboratory of Antiviral Drugs, Henan Normal University, Xinxiang, Henan 453007, P. R. China.
[c] Department of Infectious Diseases, State Key Laboratory of Antiviral Drugs, Pingyuan Laboratory, the First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, P. R. China.
[d] School of Chemistry and Chemical Engineering, Chongqing Key Laboratory of Chemical Theory and Mechanism, Chongqing University, Chongqing 401331, P. R. China.
[e] College of Chemistry and Molecular Sciences, Henan University, Kaifeng 475004, P. R. China.
[*] Corresponding Authors: lanyu@cqu.edu.cn (Y. L.); fccrenzg@zzu.edu.cn (Z. R.); lishijunzong@zzu.edu.cn (S. L.); nlb@zzu.edu.cn (L. N.).

[†] These authors contributed equally to this work.

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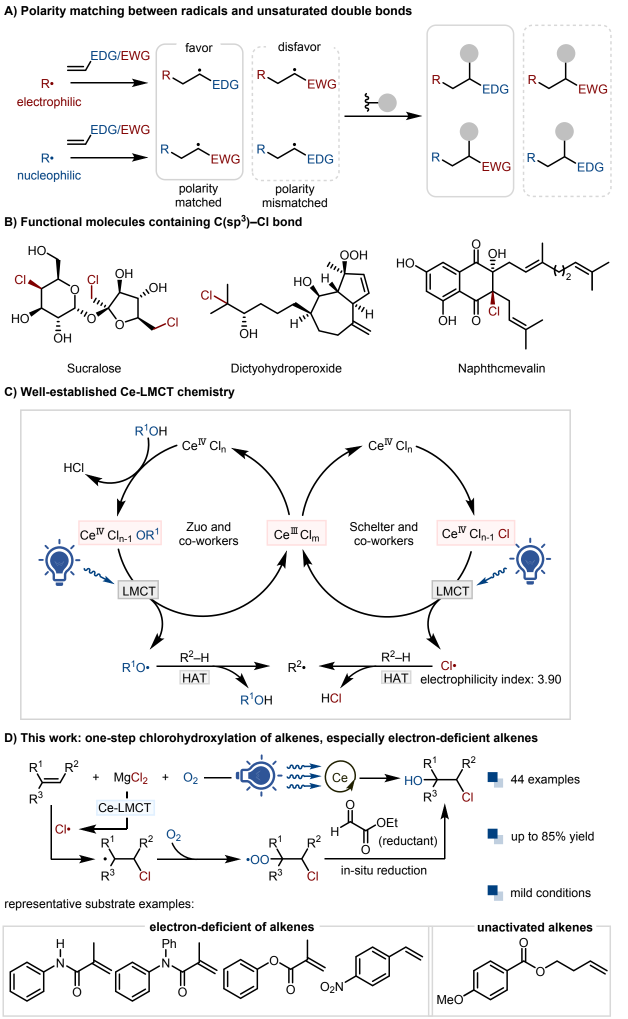


Figure 1. One-step chlorohydroxylation of electron-deficient alkenes through chlorine radical addition.

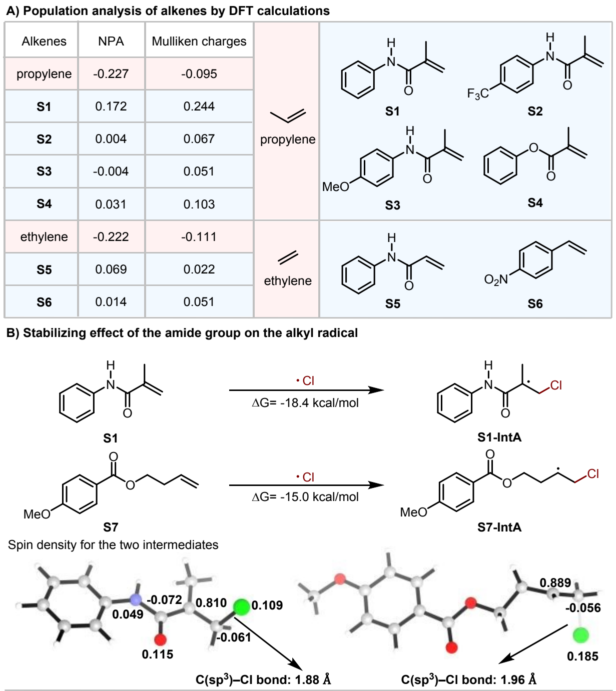
nucleophilic alkyl radicals, which tend to react with electron-deficient unsaturated bonds, thereby fulfilling C(sp^3)–H functionalization (Figure 1C).[15] In contrast, Walsh, Schelter, and their colleagues found that visible light-induced homolysis of cerium-chloride complexes generates chlorine radicals, which subsequently abstract hydrogen atoms from alkanes to form alkyl radicals (Figure 1C).[16] Notably, reports in which Ce-LMCT-generated chlorine radicals add to electron-deficient alkenes to form C(sp^3)–Cl bonds are scarce.[17]

Thus, we sought to study the reaction of chlorine radicals with electron-deficient alkenes under the conditions of Ce-LMCT, aiming to unlock the selective chlorohydroxylation of electron-deficient alkenes. O_2 was expected to intercept the radical adduct from the thermodynamically unfavorable addition of chlorine radical to electron-deficient alkenes.[18] Theoretically, this step is also reversible, indicating that overcoming this reversibility to ensure the success of the desired one-step aerobic chlorohydroxylation may rely on a suitable reducing reagent to promptly and irreversibly convert the O–O intermediate into the alcohol.[19] Herein, by combining ethyl glyoxylate as a unique reducing reagent and aerobic Ce-LMCT photocatalysis, we successfully unlock the selective chlorohydroxylation of electron-deficient alkenes in a single step. Moreover, using this system, unactivated alkyl alkenes can also be well tolerated.

Results and Discussion

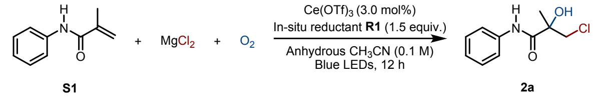
Given the ubiquitous presence of amide groups in natural products and pharmaceutical molecules,[20] incorporating amide functionalities into the unsaturated C=C double bonds of alkenes could further improve the potential value of the corresponding chlorohydrin products. Additionally, the electron-withdrawing character of the carbonyl in the amide group renders this kind of alkene electron-poor.[21] Then, we evaluated the electronic properties of the alkenes containing amide groups using DFT calculations (Figure 2A). Both the Mulliken and natural population analysis charge calculations of amide-containing alkenes exhibited more positive charges compared to those of propylene and ethylene. In addition to amide-containing alkenes, phenyl methacrylate and 4-nitrostyrene also show similar charge characteristics to the amide-containing alkenes. Furthermore, the spin density analysis also revealed that the amide group can effectively stabilize the alkyl radical **S1-IntA** generated from the addition of chlorine radical to *N*-phenylmethacrylamide (**S1**), which helps to override the radical polarity matching principle.

Subsequently, **S1** was selected as the model substrate to investigate the conditions of the aerobic chlorohydroxylation. The target product, 3-chloro-2-hydroxy-2-methyl-*N*-phenylpropanamide **2a**, was obtained in 78% isolated yield when employing $MgCl_2$ as the chlorine source and ethyl glyoxylate (**R1**) as an in-situ reductant (Scheme 1, Entry 1). A series of control experiments revealed that blue light irradiation, **R1**, Ce catalyst, and O_2 are indispensable for the generation of **2a** (Entries 2-6). The reaction under an air atmosphere gave a

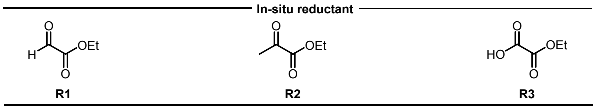


Alkenes	NPA	Mulliken charges
propylene	-0.227	-0.095
S1	0.172	0.244
S2	0.004	0.067
S3	-0.004	0.051
S4	0.031	0.103
ethylene	-0.222	-0.111
S5	0.069	0.022
S6	0.014	0.051

Figure 2. Theoretical calculations on the alkenes and the key radical intermediates.



Entry	Variation from above conditions	Yield of **2a** (%)
1	none	78
2	darkness	0
3	60 °C, darkness	0
4	w/o **R1**	0
5	w/o $Ce(OTf)_3$	trace
6	N_2 instead of O_2	0
7	air instead of O_2	60
8	add 20.0 mg 4Å MS	54
9	add 2.0 equiv. H_2O	72
10	add 2.0 equiv. H_2O, w/o **R1**	0
11	**R2** instead of **R1**	0
12	**R3** instead of **R1**	50[a]



Scheme 1. Optimization of the reaction conditions. Unless otherwise identified, products were purified by silica gel chromatography to afford the isolated yields. Reaction conditions: *N*-phenylmethacrylamide (0.2 mmol, 1.0 equiv.), $Ce(OTf)_3$ (0.006 mmol, 3.0 mol%), in-situ reductant **R1** (0.3 mmol, 1.5 equiv.), $MgCl_2$ (0.3 mmol, 1.5 equiv.), and anhydrous CH_3CN (2.0 mL) were stirred under O_2 atmosphere and irradiated by blue LEDs (24 W) at room temperature for 12 h. [a]GC yield.

decreased yield of 60% (Entry 7). We further observed that the addition of 4Å molecular sieves (4Å MS, 20.0 mg) to the system resulted in a lower isolated yield of 54% (Entry 8); adding two equivalents of H_2O did not inhibit the formation of product (Entry 9), and H_2O could not replace **R1** in this reaction (Entry 10). These results suggested that the hydrogen in the hydroxyl group is derived from **R1**. It was worth noting that ethyl pyruvate **R2** failed to afford the chlorohydrin (Entry 11), whereas oxalic acid 1-ethyl ester **R3** succeeded (Entry 12).

With the optimal conditions in hand, the reaction scope of the terminal alkenes containing amide scaffolds was systematically examined (Figure 3). Under our standard conditions, a series of *N*-phenylmethacrylamides more electron-deficient than **S1** were converted to the corresponding chlorohydrins in moderate to good yields (**2b**-**2q**), successfully accommodating not only strong electron-withdrawing groups (e.g., $-CF_3$, −CN, $-NO_2$; **2b-2d**) but also medicinally relevant motifs (e.g., fluoro, trifluoromethoxy, phosphoryl; **2e**, **2k**, **2l**). Most notably, even alkenes bearing multiple electron-withdrawing substituents (**2m-2q**) proved to be competent substrates. These results collectively indicated that our protocol effectively overcomes the reactivity constraints imposed by the classic polarity matching principle for radical additions. In addition, a range of alkenes with different electron-donating groups, such as −Me, −OMe, −OPh, −NHCOMe, −Ph, and −*t*-Bu, smoothly underwent this protocol to afford diverse chlorohydrin products (**2r-2w**). Given that the introduction of heterocycles is an effective strategy for developing lead compounds and drug candidates in medicinal chemistry, we evaluated relevant heterocyclic scaffolds, such as phthalide and quinoline, and successfully afforded the desired products **2x** and **2y**. The compatibility of the fluorene scaffold, which is of high interest in materials science, was also demonstrated, giving chlorohydrins **2z** and **2aa**. This result further highlights the excellent functional group tolerance of this method. The one-step chlorohydroxylation was also successful on substrates where the methyl group of **S1** was replaced by benzyl or removed, delivering **2ab** and **2ac**, respectively. This method also efficiently enabled the selective transformation of the alkenes derived from commercial drug Benzocaine and from the key intermediate for Amisulpride into the desired chlorohydrins **2ad** and **2ae** in good yields, further underscoring its robustness.

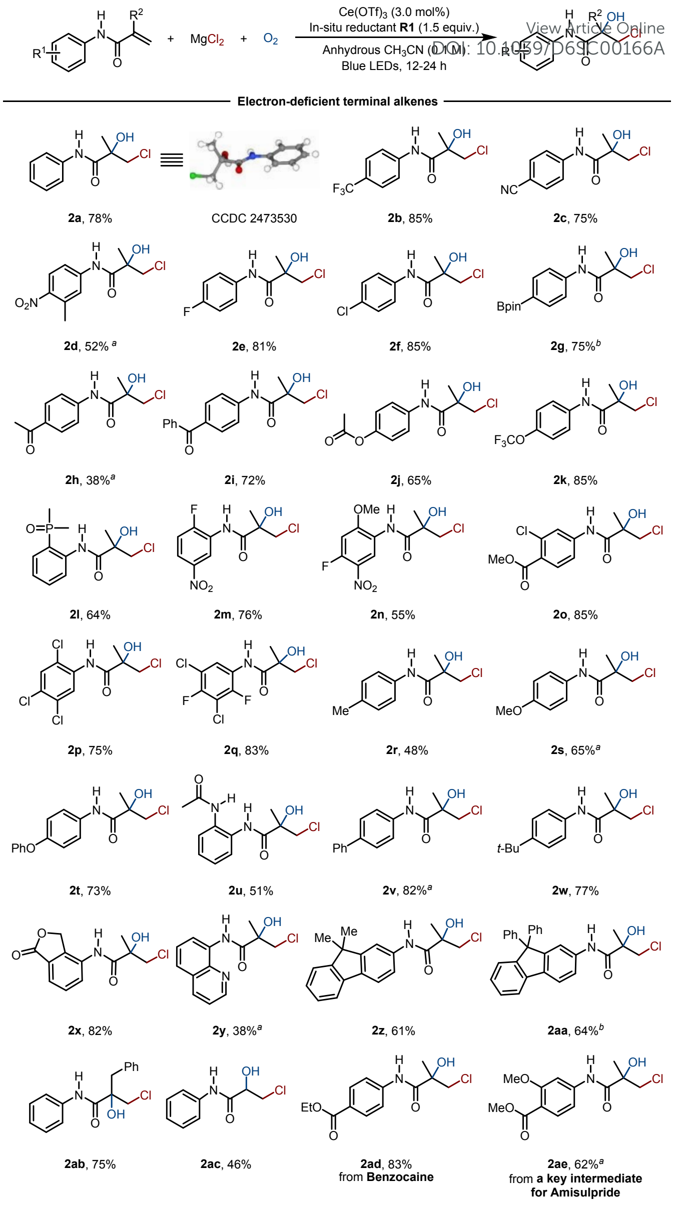


Figure 3. The scope of electron-deficient terminal alkenes. Unless otherwise identified, products were purified by silica gel chromatography to afford the isolated yields. Reaction conditions: alkene (0.2 mmol, 1.0 equiv.), $Ce(OTf)_3$ (0.006 mmol, 3.0 mol%), in-situ reductant **R1** (0.3 mmol, 1.5 equiv.), $MgCl_2$ (0.3 mmol, 1.5 equiv.), and anhydrous CH_3CN (2.0 mL) were stirred under O_2 atmosphere and irradiated by blue LEDs (24 W) at room temperature for 12 h. [a]Irradiated by blue LEDs (40 W) for 24 h. [b]Reaction conditions: alkene (0.1 mmol, 1.0 equiv.), $Ce(OTf)_3$ (0.006 mmol, 6.0 mol%), $MgCl_2$ (0.3 mmol, 3.0 equiv.), in-situ reductant **R1** (0.3 mmol, 3.0 equiv.), and anhydrous CH_3CN (2.0 mL) were stirred under O_2 atmosphere and irradiated by blue LEDs (24 W) at room temperature for 12 h.

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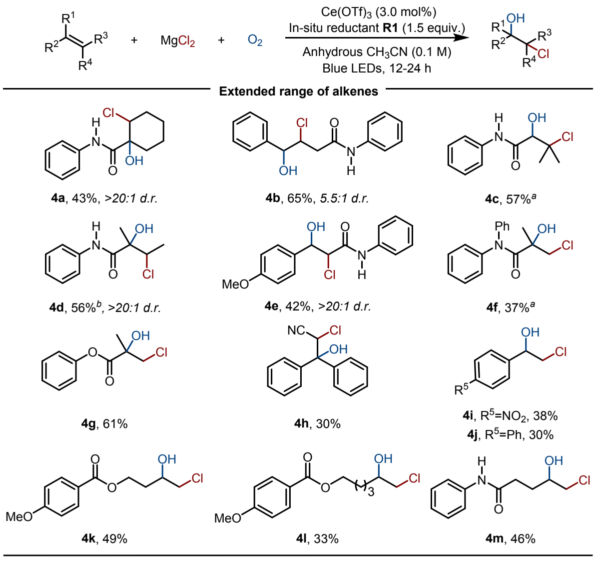

Figure 4. Extended range of alkenes. Unless otherwise identified, products were purified by silica gel chromatography to afford the isolated yields. Reaction conditions: alkene (0.2 mmol, 1.0 equiv.), Ce(OTf)$_3$ (0.006 mmol, 3.0 mol%), in-situ reductant **R1** (0.3 mmol, 1.5 equiv.), MgCl$_2$ (0.3 mmol, 1.5 equiv.), and anhydrous CH$_3$CN (2.0 mL) were stirred under O$_2$ atmosphere and irradiated by blue LEDs (24 W) at room temperature for 12 h. [a]Irradiated by blue LEDs (40 W) for 24 h. [b]The regio-isomer **4d'** (3-chloro-2-hydroxy-2-methyl-*N*-phenylbutanamide) was obtained in 23% isolated yield and with *>20:1 d.r.* All *d.r.* values were determined by ^{1}H NMR analysis.

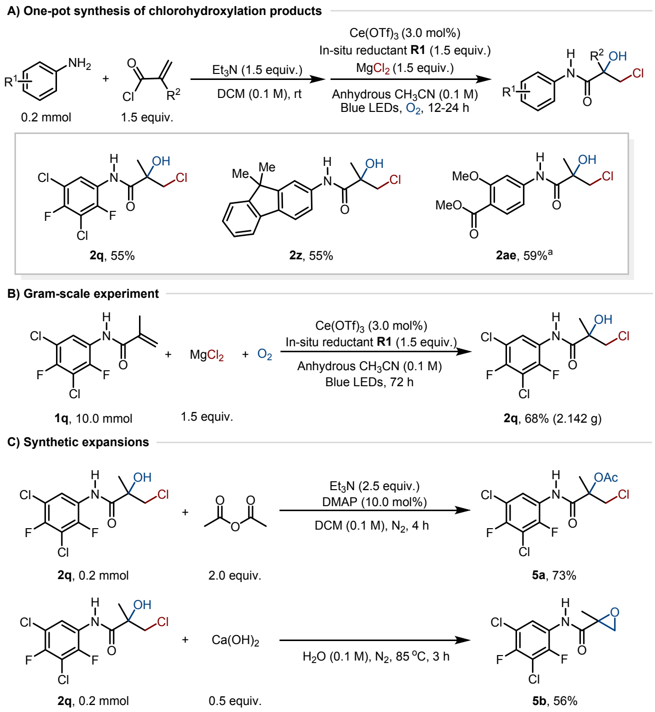

Figure 5. Demonstration of synthetic utility. Unless otherwise identified, products were purified by silica gel chromatography to afford the isolated yields. [a]Irradiated by blue LEDs (40 W) for 24 h.

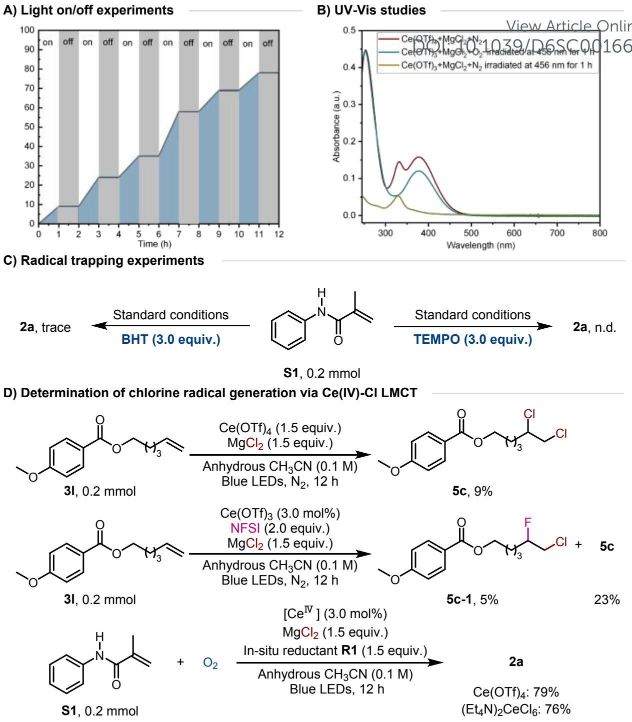

Figure 6. Mechanistic studies.

Besides the terminal amide-based alkenes, the substrate scope was also found to cover diverse internal alkenes, such as those derived from 1-cyclohexene-1-carboxylic acid (**4a**), *trans*-styrylacetic acid (**4b**), 3,3-dimethylacrylic acid (**4c**), tiglic acid (**4d**), and *trans*-4-methoxycinnamic acid (**4e**), all of which afforded the corresponding chlorohydrins in moderate to good yields. Notably, the replacement of the N−H moiety in **S1** with an N−Ph group was tolerated, furnishing product **4f** in 37% yield. Inspired by this result, the amide was replaced with an ester group, which provided product **4g** in 61% yield, indicating that the amide scaffold is not essential for the reaction. Furthermore, the broad substrate scope was underscored by the successful conversion of diverse alkene types, including electron-deficient styrenes (**4h** and **4i**), conjugated aryl alkenes (**4j**) and unactivated alkyl alkenes (**4k-4m**).

Encouraged by the positive experimental results discussed above, we further demonstrated the synthetic utility of this methodology. A one-pot procedure was developed, wherein anilines bearing different functional groups were condensed with methacryloyl chloride to generate the amide-containing alkene substrates in situ, and then directly subjected to chlorohydroxylation without purification (Figure 5A; 55-59% yields for **2q**, **2z**, and **2ae**). This process effectively simplifies the synthetic workflow by eliminating the need for column chromatography isolation of the intermediate alkene. Furthermore, a gram-scale reaction was conducted smoothly under the standard conditions, delivering the product **2q** in 68% yield (Figure 5B). The product from this gram-scale experiment was then used in subsequent transformations. It was successfully converted to the ester **5a** in 73% yield and epoxide product **5b** in 56% yield, respectively (Figure 5C).

To gain insight into the mechanism, several mechanistic experiments were conducted. Light on/off experiments confirmed that continuous blue light irradiation is essential for the reaction to proceed (Figure 6A). UV-Vis spectroscopy was also employed to gain insight into the in-situ generation of the Ce-based light-absorbing system (Figure 6B). It was interesting that irradiation of a Ce(OTf)$_3$ and MgCl$_2$ mixture with blue light under O$_2$ for 1 hour produced a Ce(IV)-based absorption peak in the blue light region, whereas no such peak was observed under N$_2$ atmosphere. Consequently, O$_2$ can be identified as promoting the in-situ generation of the Ce(IV)-based light-absorbing system from Ce(III) under blue light irradiation.[15a,16a] Furthermore, ^{18}O-labelling experiments also demonstrated that the oxygen atom incorporated into the product is indeed derived from O_2 (Figure S10). The inhibition of the chlorohydroxylation of alkenes by both 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-tert-butyl-4-methylphenol (BHT) suggested that the reaction proceeds via a radical pathway (Figure 6C). Notably, dichlorination of alkenes was observed when using stoichiometric $Ce(OTf)_4$ and $MgCl_2$ under blue LEDs irradiation (Figure 6D). *N*-Fluorobenzenesulfonimide (NFSI) was further found to be able to complete the catalytic cycle of Ce. These results indicated that chlorine radicals are crucial intermediates generated by the Ce photocatalysis.[16a,22] Last but not least, the direct use of $Ce(OTf)_4$ or $(Et_4N)_2CeCl_6$ as catalysts also afforded the desired chlorohydroxylation in good yields.

Conclusion

In conclusion, we have developed a one-step aerobic selective chlorohydroxylation protocol that overcomes the limitations imposed by the polarity matching principle for the chlorine radical addition to electron-deficient alkenes. The practical utility and broad application value of this protocol are evidenced by its excellent functional group tolerance, successful late-stage functionalization of commercial drug derivatives, gram-scale synthesis, and one-pot procedure. Further efforts toward developing novel chlorine radical transformation platforms are ongoing in our laboratory.

Author contributions

Conceptualization: L.O., Y.B., S.L., Z.K., Y.L., J.Z., Z.R., S.L., L.N.; Methodology: L.O., Y.B., Y.L., J.Z., S.L., L.N.; Investigation: L.O., Y.B., S.L., Z.K., Y.L., J.Z., Z.R., S.L., L.N.; Supervision: Y.L., Z.R., S.L., L.N.; Writing—original draft: L.O., Y.B., Y.L., S.L., L.N.; Writing—review & editing: L.O., Y.B., S.L., Z.K., Y.L., J.Z., Z.R., S.L., L.N.

Conflicts of interest

The authors declare that they have no conflict of interest.

Data availability

Experimental details and characterization of the products are available in the supplementary information.

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