Iron Catalyzed C-C Single Bond Cleavage of Alcohols

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ABSTRACT: An iron-catalyzed deconstruction/hydrogenation reaction of alcohols through C-C bond cleavage is developed under the irradiation of visible light, to produce ketones or aldehydes as the products. Linear alcohols and cycloalkanols with different ring sizes are suitable substrates, containing tertiary, secondary, and primary alcohols bearing a wide range of substitutes. Complex natural alcohols can also perform the transformation selectively. The mechanism investigation reveals an unpresented reaction procedure that involves chlorine radical as a key intermediate, which is generated from [FeCl$_4$]$^-$ through ligand to metal charge transfer (LMCT). The study illustrates new possibilities for iron photocatalysis, especially for various deconstruction/functionalization reactions.

Organic synthesis commonly focuses on C-C or C-heteroatom bond formation, to develop methodologies for the construction of new structures and complex compounds.[1] During the last century, the corresponding methods have been fruitfully created and widely used in both laboratory and industry.[2] Though powerful, the "step by step" synthesis procedures generally start from simple chemicals and sometimes suffer from low efficiency and show limitations for unique molecular structures. Differently, deconstruction through C-C bond scission can provide structurally novel compounds from known chemicals, illustrating another valuable logic for synthesis and showing diverse synthetic possibilities and opportunities.[3] One attracting consideration of this area is "scaffold hopping", resulting in new structures quickly with desired properties from bioactive compounds.[4] The corresponding studies in early times presented many good examples by applying activated molecules, which can enable C-C bond cleavage easier.[5,6] However, selective cleavage of inert C-C bond is always a tough task for chemists due to the large bond dissociation energy (BDE). Recent efforts use transition metal catalysts in a heterolysis manner generally limited to strained ring compounds.[3e-h,7] Besides, homolysis methods involving radical intermediates can lead to the scission of inert C-C bonds and may overcome the strict substrate limitation, suggesting new synthetic directions.[8]

As a kind of core organic chemicals, alcohols are readily accessible radical precursors, which can lead to the consequently C-C bond cleavage through beta-scission. However, the direct formation of alkoxy radical from alcohol is a big challenge, because the high BDE of O-H bond (~ 105 kcal/mol) make the corresponding homolysis cleavage difficult to achieve; and the relative low BDE of sp^3 C-H bonds (92.3- 101 kcal/mol) on the alcohol results in selectivity problems.[9] To handle these issues, pioneer studies usually transform O-H to weaker O-X bonds, such as O-NO;[5a] or use strained alcohols.[8] Illustrated by these discoveries,
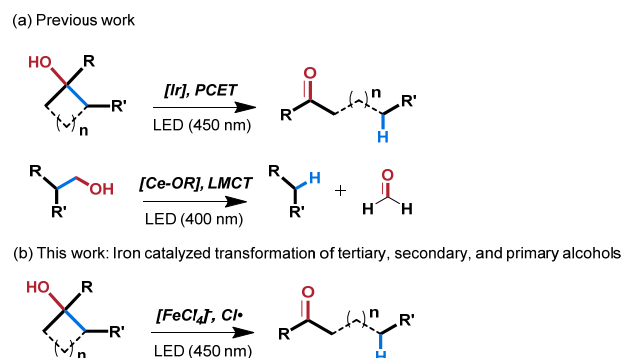

Figure 1. Deconstruction/hydrogenation of alcohols with different photocatalysts

various methods for the defunctionalization of cycloalkanols have been achieved recently, though restricted to strained substrates.[8] In 2016, Knowles and coworkers reported the first C-C scission of unstrained tertiary alcohols through a proton-coupled electron transfer (PCET) pathway by using an Ir photocatalyst.[10a] An improved study was reported by the same group in 2019, which can be applied to secondary alcohols and even some special primary alcohols (Figure 1a).[10b] These two reports show general procedures for the deconstruction/hydrogenation of alcohols to produce the thermodynamically unfavored ketones/aldehydes, which can be applied to transform polycyclic nature products. In addition, limiting to tertiary alcohols, some other deconstructive functionalization, such as allylation[11], halogenation[12], and arylation[13], can also be achieved by applying different photocatalyst systems. Besides, the Zuo group[14] developed a Ce (III) improved photocatalysis system to enable the deconstructive amination and alkylation of both tertiary, secondary and primary alcohols, applying di-tert-butyl azodicarboxylate (DBAD) and electron-deficient olefines as radical acceptors, respectively. The elegant catalyst system is performed through a ligand to metal charge transfer (LMCT) procedure of Ce-O species and shows great potentials for organic synthesis. However, only several examples of deconstruction/hydrogenation reactions were reported, showing dehydroxymethylation products through relatively stable radical intermediates (Figure 1a).[14c] Until now, only the Ir photocatalyst has been discovered for the general deconstruction/hydrogenation reactions of alcohols.[10] Obviously, for the development of various deconstruction/functionalization reactions of alcohols, including deconstruction/hydrogenation reactions, new systems with different catalytic activities and pathways are highly desired.

Table 1. Selected results of optimization study[a]
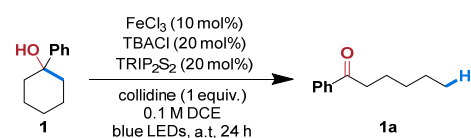
| entry	condition changes	yield %[b]
1	No change	54
2	Without base	14
3	2,6-lutidine as base	43
4	PBu$_4^+$(MeO)$_2$POO$^-$ as base	0
5	PBu$_4^+$(PhO)$_2$POO$^-$ as base	trace
6	TBACl (30 mol%)	51
7	TBACl (10 mol%)	45
8	Without TBACl	26
9	400 nm LED	trace
10	365 nm LED	0
11	Without FeCl$_3$	0
12	Without LED	0
13	48 h	75
14	60 h	88 (81[c])

[a]Reaction conditions: **1** (0.2 mmol), FeCl$_3$ (0.02 mmol, 10 mol %), TBACl (0.04 mmol, 20 mol%), TRIP$_2$S$_2$ (0.04 mmol, 20 mol%), 2,4,6-collidine (0.2 mmol, 1 equiv.), and 1,2-dichloroethane (DCE 2 mL) were irradiated with blue LEDs under N$_2$ for 24 h. [b]Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c]Isolated yield.

Our interests in C-C bond cleavage led us to search for practical catalysts to develop the selective deconstruction/functionalization methods for readily available chemicals. Environmentally friendly and inexpensive iron is one of the most abundant metals on the earth.[15] Early studies show the potentials of iron salts to act as photocatalysts under visible light.[16] In addition, some recent articles published by Jin[17], Jiang[18a], Zeng[18b], and Rovis[19] presented the photocatalytic abilities of iron compounds on oxidative and alkylative transformations. Herein, we report an unpresented redox neutral photocatalysis method to enable the deconstruction/hydrogenation reaction of alcohols through C-C single bond cleavage, applying an iron salt as the photocatalyst (Figure 1b). The simple and inexpensive catalyst system can transform both the tertiary, secondary, and primary alcohols with good functional group tolerance under visible light, illustrating new possibilities for the selective transformation of aliphatic alcohols.

1-Phenyl cyclohexanol is chosen as the substrate for the initial optimization study. Various conditions are tried (See Supporting Information for details) and selected results are listed in Table 1. When the combination of FeCl$_3$, tetrabutylammonium chloride (TBACl), bis(2,4,6-triisopropyl phenyl) disulfide (TRIP$_2$S$_2$), and 2,4,6-collidine are applied, moderate yield of the corresponding C-C bond cleavage product **1a** is observed (entry 1). Base is found to be an essential factor for the performance of the reaction, and the condition in the absence of base leads to low product yield of 14% (entry 2). In addition, 2,6-lutidine results in a lower out-

come as compare to 2,4,6-collidine (entry 3). While tetrabutylphosphonium phosphates, which present the best results for the Ir photocatalysis system[11], give no conversion (entry 4) or trace amount of product (entry 5). The application of a different amount of TBACl changes the mole ratio of Fe and chloride ions and influences the reaction yields. The best combination is 10 mol% of FeCl$_3$ and 20 mol% of TBACl, which equals to a 1: 5 mole ratio of Fe and Cl (entry 1); higher or lower Fe/ Cl ratios lead to inferior outcomes (entries 6-8, see Supporting Information for details). In addition, testing of LEDs with shorter wavelength result in trace or no conversion (entries 9 and 10). Control experiments without FeCl$_3$ or LED result in no product (entries 11 and 12), indicating an iron-catalyzed photocatalysis procedure of the reaction. Longer reaction time is helpful for the performance of the reaction (entry 13), a good isolated yield of **1a** can be obtained after 60 h (entry 14).

With the optimized results, we begin to study the substrate scope (Scheme 1). Tertiary alcohols are tested firstly. Cyclohexanols with different phenyl substitutes on the alfa position show good reactivity, leading to moderate to good isolated yields of the desired products (**1-9**). Interestingly, electron effects on the benzene rings show little influence to the reaction and both electron-donating and withdrawing groups are well tolerated. The alcohols with seven and twelve-membered rings also react successfully, transforming to the ring-opening products in 64% and 53% isolated yields, respectively (**10** and **11**). In addition, the linear alcohol **12** also performs well and a 63% yield of the ketone product is observed. With *para*-methoxyphenyl group (PMP) adjacent to the hydroxyl group, cyclic alcohols with different ring sizes can transform to the corresponding ketone products with moderate to outstanding yields (**13-18**). Electron-rich (**16**) and deficient groups (**17 and 18**) on the rings do not disturb the reaction. However, 1-methylcyclohexanol (**19**) shows inferior reactivity than other substrates and leads to low product yield even after a longer reaction time. Interestingly, 1-benzoylcyclohexanol (**20**) acts as a good substrate, of which the selective C-C bond cleavage results in good yields of cyclohexanone and benzaldehyde, retaining the ring structure. Further substrate investigation involves primary and secondary alcohols. The reaction enables the dehydroxymethylation of primary alcohols through alfa-heteroatom–stabled radical fragments (**21-24**). For secondary alcohols, such as bridged (**25**), 2-substituted (**26-29**), and four-membered ring (**30**) substrates, moderate to excellent yields are observed, showing the generality of the reaction conditions. Even simple cycloalkanol bearing no substitute (**31**) can proceed with the ring opening procedure, though a lower yield is observed. Delightfully, the model compound for the lignin degradation study (**32**) and the similar substrates substituted with different heteroatoms (**33 and 34**) react smoothly under the reaction conditions, generating the corresponding C-C bond cleavage products in good to outstanding yields. Next, we apply the reaction to the nature-originated alcohols, to generate the selective deconstruction/ hydrogenation products that partially reserve the corresponding complex structures. The relatively simple substrates, such as (-)-Nopol (**35**), isoborneol (**36**), and the cyclic glucose derivative (**37**), transform to the target products successfully. Furthermore, complex polycyclic alcohols, including testosterone (**38**), nandrolone (**39**), estradiol benzoate (**40**), 7-methyl testosterone (**41**), and cholesterol (**42**), show good performance for the isomerization transformation,
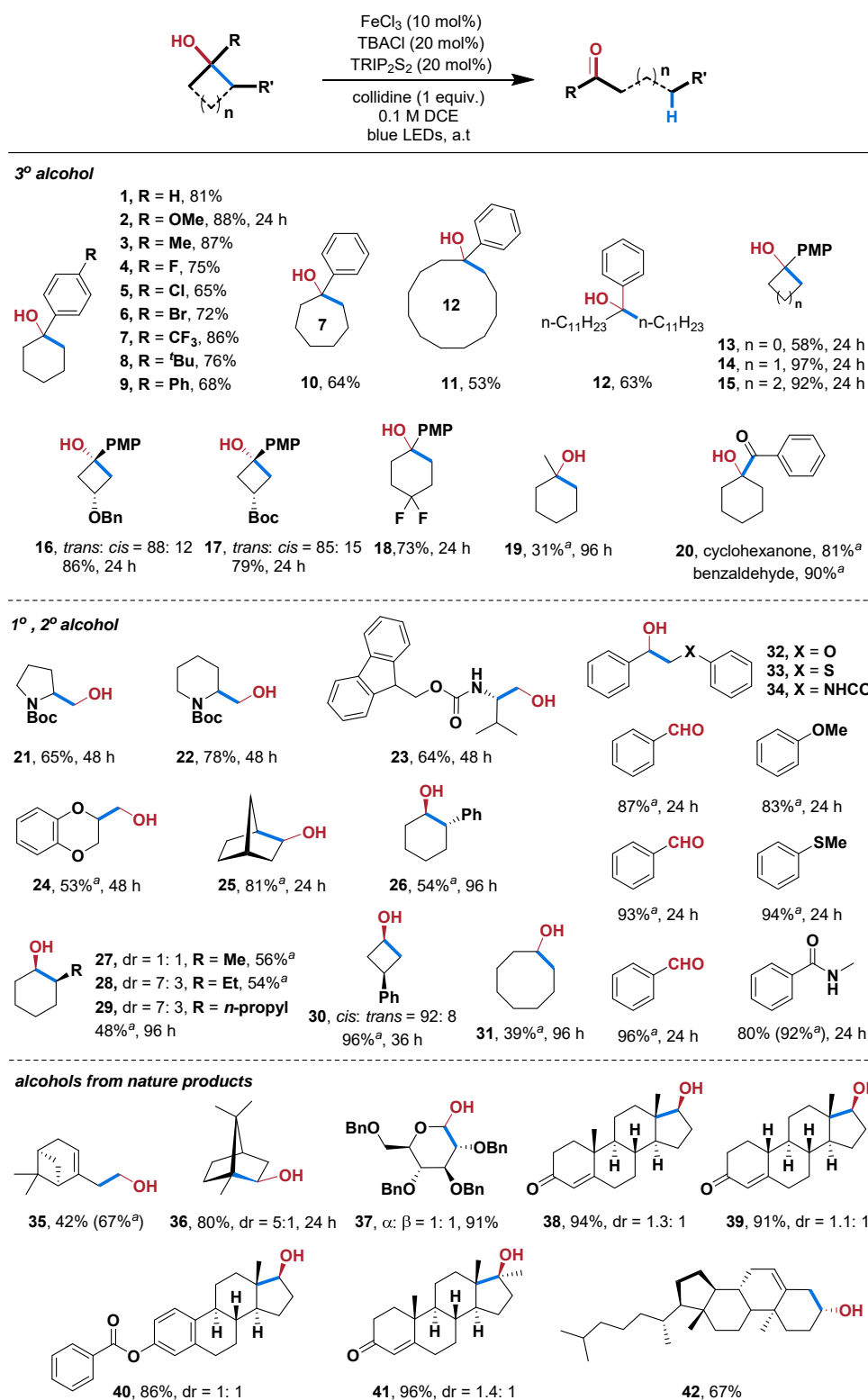
Scheme 1. Substrate Scope. Reaction conditions: alcohol (0.2 mmol), FeCl₃ (0.02 mmol, 10 mol%), TBACl (0.04 mmol, 20 mol%), TRIP₂S₂ (0.04 mmol, 20 mol%), 2,4,6-collidine (0.2 mmol, 1 equiv.), blue LEDs (450 nm), N₂ atmosphere, 60 h. Isolated yields are reported unless otherwise noted. [a]Determined by GC-MS analysis using dodecane as an internal standard due to volatility.

producing the corresponding ring-opening products in moderate to excellent isolated yields. The optimized reaction conditions are efficient enough for various substrates, generally no change is required except the reaction time.

Photocatalysis usually suffers from small reaction scale, because the light intensity will be sharply decreased in the solvent.[20] The large-scale light-promoted reactions often require the application of relatively complex equipment, to perform the reaction in a

flow chemistry way.[21] To test the performance of the large-scale reaction under simple irradiation conditions, we set up a 2 mmol-scale reaction using testosterone (576 mg) as the substrate (Figure 2). Though the conversion speed is relatively slow under the optimized conditions, a satisfactory isolated yield of the desired product (76%, 438 mg) can be obtained, indicating the practical potential of the reaction using simple LED equipment.
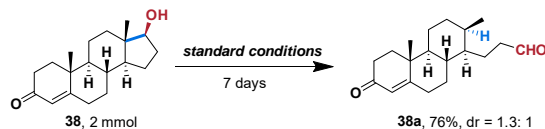

Figure 2. Large scale reaction

During the optimization study, we find the reaction may proceed through a chlorine radical involved mechanism, a different pathway as compared to the reported procedures.[10,14] The condition screening study (see Table 1 and Supporting Information for details) already shows the essential role of chloride anion. To further confirm this, we set some control experiments as shown in Table 2. DCE is changed to the chloro-free MeCN to rule out the influence of the solvent. When the reaction applies Fe(OTf)$_3$ without TBACl, no conversion is observed (entry 1). Alternatively, FeCl$_3$ leads to a 54% yield of the product (entry 2). Addition of 20 mol% of TBACl, which presents a 1: 5 ratio of Fe (III) and Cl anion, increases the outcome to 67% (entry 3). With the same Fe: Cl ratio, changing of FeCl$_3$ to Fe(OTf)$_3$ results in a similar product yield of 73% (entry 4). These results highlight the role of chloride anion as an indispensable part of the catalytic system.

Table 2. Reaction performances with/without chloride

Entry	[Fe]	TBACl (mol%)	Yield (%)[a]
1	Fe(OTf)$_3$	0	0
2	FeCl$_3$	0	54
3	FeCl$_3$	20	67
4	Fe(OTf)$_3$	50	73

Reaction conditions: **1** (0.2 mmol, 1 equiv.), iron salt (10 mol%), TRIP$_2$S$_2$ (20 mol%), 2,4,6-collidine (1 equiv.), and MeCN (2 mL) are irradiated with blue LEDs under N$_2$ for 60 h. [a]Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.
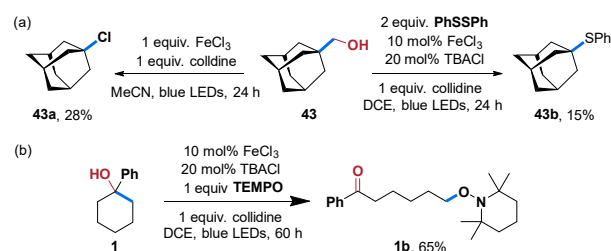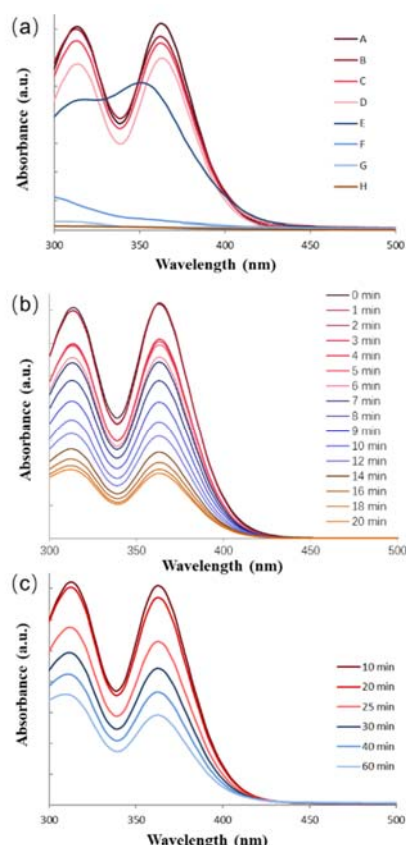

Figure 3. Radical trapping experiments

Figure 4. Investigation of UV-vis absorption of iron salts. Concentration of Fe: 0.1 mmol/L in DCE. (a) UV-vis spectra of different combinations with iron. A: FeCl$_3$ and TBACl (1: 2); B: FeCl$_3$, TBACl and collidine (1: 2: 1); C: FeCl$_3$, TBACl, **1** and collidine (1: 2: 10: 10) ; D: Fe(OTf)$_3$ and TBACl (1: 5); E: FeCl$_3$; F: FeCl$_2$ and TBACl (1: 3); G: FeCl$_2$; H: Fe(OTf)$_3$; (b) UV-vis spectra of mixed solvent of FeCl$_3$ and TBACl (1: 2) after different irradiation time (0-20 min) with blue LED (450 nm); (c) UV-vis spectra of mixed solvent of FeCl$_3$, TBACl, **1** and collidine (1: 2: 10: 10) after different irradiation time (10-60 min) with blue LED (450 nm).

Next, a chlorine radical trapping reaction applying 1-adamantanylmethanol and stoichiometric FeCl$_3$ in the absence of TRIP$_2$S$_2$ is set up, leading to the corresponding product 1-chloroadamantane in 28% yield (Figure 3a, left). PhS• was also trapped using stoichiometric PhSSPh (Figure 3a, right). In addition, TEMPO is applied as a radical trap to stabilize the deconstruction intermediate of 1-phenylcyclohexanol (**1**), presenting the terminal carbon radical-trapped product successfully (Figure 3b). Light on/off experiment is performed, and no reaction is observed without LED, which rules out the chain mechanism (See Supporting Information for details). UV-vis spectra of iron salt with TBACl, collidine and alcohol **1** in different combinations are also detected, as shown in Figure 4a. Interestingly, all the combinations containing TBACl show typical absorption peaks of [FeCl$_4$]$^-$,[22] even in the alcohol and collidine-included case (Figure 4a, C). The time- resolved UV-vis spectra of FeCl$_3$ and TBACl after irradiation with blue light are detected, only absorption peaks of [FeCl$_4$]$^-$ are observed (Figure 4b). Irradiation for a longer time leads to weaker absorption peaks, probably due to the formation of Cl• and [FeCl$_3$]$^-$ from [FeCl$_4$]$^-$ through an LMCT process, which decreases the [FeCl$_4$]$^-$ concentration; since FeCl$_2$ and the

corresponding complex with TBACl show very weak absorption in DCE (Figure 4a, F and G). Further time progression UV-vis spectra of the solution of $FeCl_3$, TBACl, **1** and collidine (1: 2: 10: 10) after irradiation with blue light only show peaks of $[FeCl_4]^-$, no new peak is observed even after a long time of irradiation (Figure 4c). The observation excludes the possibility of the formation of a Fe-alkoxyl species under the reaction conditions,[24a] which can generate the alkoxy radical through an LMCT process.

Table 3. Competition study of benzylic C-H bond activation and C-C bond activation
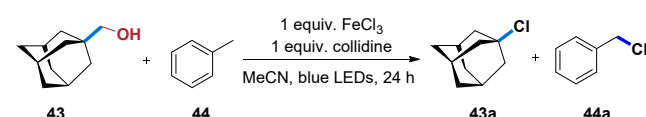
Entry	43 (mmol)	44 (mmol)	43a [%]	yield[a]	44a [%]	yield[a]
1[b]	0	0.2	-		20	
2	0	0.2	-		12	
3[b]	0.2	0.2	0		trace	
4	0.2	0.2	25		trace	
5	0.2	1	19		8	
6	1	0.2	26		0	

Reaction conditions: **43**, **44**, $FeCl_3$ (0.2 mmol, 1 equiv.), 2,4,6-collidine (1 equiv.), and MeCN (2 mL) are irradiated with blue LEDs under N_2 for 24 h. [a]Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [b]Without 2,4,6-collidine

Due to the high energy of Cl•, and the relatively low BDE of C-H bonds as compared to the O-H bond, the unusual selectivity of the reaction is an important issue needs to be studied. To clarify the selectivity problem, competition reactions of different ratios (in mol) of 1-adamantanylmethanol and toluene in the presence of 1 equiv. of $FeCl_3$ were performed, as shown in Table 3. In the absence of 1-adamantanylmethanol and collidine, 20% yield of benzyl chloride was generated (entry 1), which is also a direct evidence of the formation of chlorine radical. However, when the same amount of collidine was applied together with toluene, only 12% of benzyl chloride was observed (entry 2); while 1-adamantanylmethanol showed an even bigger influence to hinder the benzylic C-H chlorination, presenting trace amount of the product (entry 3). The results were clear evidences of the formation of the adduct of Cl• with collidine or the oxygen atom of the alcohol, due to the electrophilic property of chlorine radical.[24] Furthermore, the alcohol showed a bigger tendency to generate the radical adduct than collidine (entry 2 vs. 3). However, no C-C bond cleavage product (**43a**) was observed in the absence of base because of the strong BDE of O-H bond (entry 3), which consisted with the optimization study in Table 1. When collidine, toluene and **43** were used in the same amount, the C-C bond cleavage product 1-chloroadamantane was generated in 25% yield, with trace of benzoyl chloride observed (entry 4). The outcome of benzoyl chloride was still low even under the condition of applying excess of toluene (in 5: 1 mol ratio with **43**); while the yield of **43a** was much higher (entry 5). When excess of **43** was applied, the transformation of toluene was fully restrained (entry 6). The addition of 1-adamantanylmethanol doesn't change the weak BDE of benzylic C-H bond (~ 90 kcal/mol). A reasonable explanation for the surprising result is the quickly formation of the adduct of Cl• and the oxygen atom of the alcohol.[24] Thus, the HAT course

can be restricted on the O-H bond with the assistant of collidine, which can decrease the strength of O-H bond[10] and absorb the subsequently formed HCl.

Based on the above investigation, a mechanism is proposed in Figure 5. $[FeCl_4]^-$ is excited by blue light to form a chlorine radical through an LMCT process.[24] The electrophilic Cl• can easily generate an adduct with the oxygen atom of the alcohol, which then forms the alkoxy radical with the assistant of collidine.[10,24] Further beta-scission of the alkoxy radical leads to the ring-opening radical, which generates the target product and ArS• (Ar = 2,4,6-triisopropyl phenyl or Ph) through HAT with the thiophenol (ArSH).[25] Originally formed from a disulfide (TRIP$_2$S$_2$ or Ph$_2$S$_2$), ArS• can oxidize Fe (II) to Fe (III),[22a,26] regenerating the $[FeCl_4]^-$ species and ArS$^-$. The resulting ArS$^-$ species traps a proton to form the thiophenol (ArSH, Ar = 2,4,6-triisopropyl phenyl, was detected by GC-MS) again.
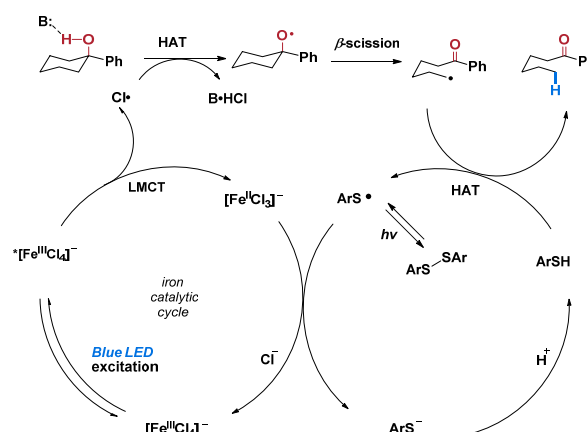

Figure 5. Proposed mechanism

In conclusion, we develop a visible light photocatalysis procedure to enable the redox-neutral deconstruction/hydrogenation of alcohols, forming single C-C bond cleavage products. Applying inexpensive and earth-abundant iron salts as the catalysts, the reaction enjoys a good functional group tolerance and a wide substrate scope. Both tertiary, secondary, and primary alcohols can act as suitable substrates. The tested cycloalkanols with small and large rings all transform to the ring-opening products successfully. Furthermore, the alcohols from natural product sources can smoothly perform the transformation, generating the target compounds selectively, with the resting structure untouched. The mechanism investigation indicates a new reaction pathway, which is promoted by the chlorine radical generated from $[FeCl_4]^-$. The research highlights the potential of simple iron salts as efficient photocatalysts for unique transformations. Further studies of developing iron-catalyzed deconstruction/functionalization reactions through photocatalysis are underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available.

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Notes

The authors declare no competing financial interest.

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Deconstruction/Hydrogenation of Alcohols

Alcohols:
tertiary
secondary
primary

42 examples
up to 96% yield

[Fe]
LMCT, HAT
LED (450 nm)