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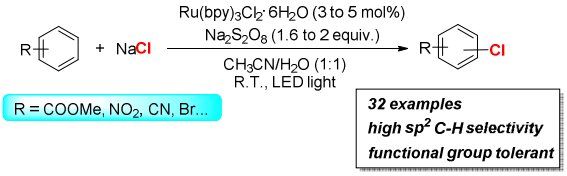

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Room temperature C(sp^2)-H oxidative chlorination via photoredox catalysis

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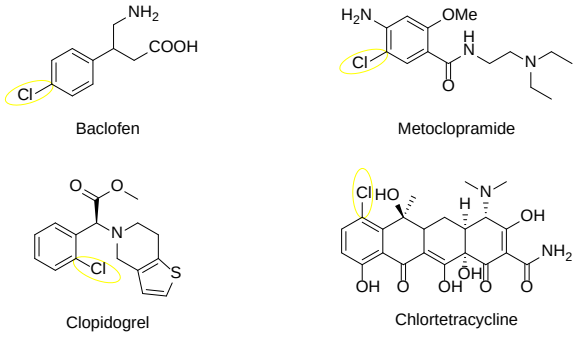
Photoredox catalysis has been developed to achieve oxidative C-H chlorination of aromatic compounds using NaCl as the chlorine source and $Na_2S_2O_8$ as the oxidant. The reactions occur at room temperature and exhibit exclusive selectivity for C(sp^2)-H bonds over C(sp^3)-H bonds. The method has been used for the chlorination of a diverse set of substrates, including the expedite synthesis of key intermediates to bioactive compounds and a drug.

Chlorinated aromatic compounds exist extensively as natural products, synthetic pharmaceuticals, pesticides, and materials (Scheme 1).[1] Moreover, they are versatile start materials and synthetic intermediates in organic synthesis, for example, through transition-metal-catalysed cross-coupling reactions. Thus, efficient methods to synthesize chlorinated aromatic compounds are of significant interest. Direct C(sp^2)-H electrophilic chlorination is an appealing strategy for aryl chlorination, because no directing or leaving group needs to be pre-installed on the substrates, leading to wider substrate availability, lower cost, and better step-economy. However, traditional electrophilic chlorination methods employ either toxic, hazardous, and corrosive chlorine gas, or organic electrophilic chlorination reagents, such as N-Chlorosuccinimide (NCS) and *t*BuOCl,[2-6] which are prepared from Cl_2 and generate significant amounts of organic wastes.



Scheme 1: Selected examples of pharmaceuticals and natural products containing an aryl-Cl moiety

In Nature, halogenases have been evolved to carry out C-H chlorination using the benign chloride anion in an oxidative manner.[7] Inspired by Nature, synthetic systems for oxidative chlorination have been developed,[8-9] but their scope and selectivity remain to be improved. Additionally, the majority of these systems employ H_2O_2 as the oxidant and operate under acidic conditions,[10] which pose a constraint in functional group compatibility. Konig, Wolf, and co-workers[11] recently reported an elegant photoredox approach for oxidative chlorination using dioxygen as the oxidant. Photoexcitation of the organic dye, riboflavin tetraacetate (RFT), followed by quenching with O_2, generated H_2O_2 in situ, which oxidized acetic acid to peracetic acid. The latter in turn oxidized Cl^- to OCl^-, which was the active species for electrophilic chlorination of a number of aromatic substrates. Notwithstanding the novelty of this approach, at this early stage of its development, 6-10 equivalents of acetic acids, HCl, and *p*-methoxy benzyl alcohol (to regenerate the dye) were necessary and the scope were limited to simple arenes containing a methoxy, amino or amide group. Zhang and co-workers[12] used potassium persulfate, a convenient inorganic oxidant for oxidative chlorination. However, a high temperature (95~100 °C) was needed and a sulphonamide group was essential to improve efficiency through formation of a proposed N-Cl intermediate. In several cases C(sp^3)-H chlorination was preferred over C(sp^2)-H chlorination.

A key challenge in electrophilic C(sp^2)-H chlorination is to achieve selectivity over competing C(sp^3)-H chlorination. However, literature data show the opposite selectivity for substrates containing weak benzylic and α-carbonyl C(sp^3)-H bonds. For example, acetophenone was exclusively chlorinated at the α-C(sp^3) position under oxidative chlorination conditions using either H_2O_2 or O_2 as oxidant [Eq. (1)].[11] Likewise, methyl 4-(chloromethyl)benzoate was only chlorinated at the benzylic C(sp^3) position using $K_2S_2O_8$ as oxidant at 100°C [Eq. (2)].[12] To further illustrate this issue, toluene, which contains both C(sp^2)-H bonds and benzylic C(sp^3)-H bonds, was subjected to oxidative chlorination conditions at 100 °C using $K_2S_2O_8$ as oxidant [Eq. (3)]. The C(sp^3)-H chlorination product, chloromethybenzene, was obtained in 45% yield while the C(sp^2)-H chlorination product was not formed. This undesired selectivity probably originates from the frequent formation of

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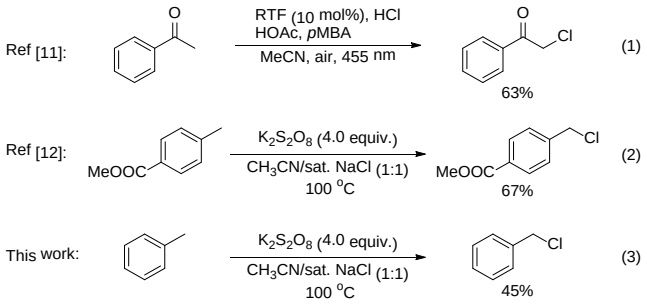
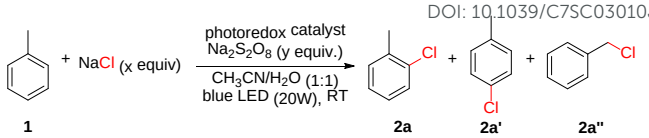
Cl radical under electrophilic chlorination conditions, which reacts faster with weaker C(sp^3)-H bonds than with the stronger C(sp^2)-H bonds. For the broad applicability of oxidative C(sp^2)-H chlorination, this selectivity problem has to be resolved. Another challenge is to develop methods that operate under mild conditions, which are essential to achieve high functional group compatibility. Here we describe a room-temperature oxidative chlorination method to selectively chlorinate aryl C-H bonds in the presence of benzylic and α-carbonyl C(sp^3)-H bonds. Key to achieve this selectivity is the use of photoredox catalysis,[13-16] which is able to generate efficiently the electrophilic chlorination reagent in situ while supressing the detrimental Cl radical. The scope, application, and preliminary mechanistic study are described.



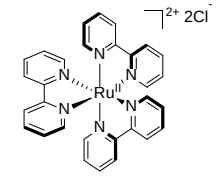
We commenced our study using toluene as the model substrate (Table 1). The selective chlorination of toluene is relatively challenging compared to other election-rich aromatic compounds. The methyl group is not a strong election-donating group and several side products such as benzaldehyde and chloromethylbenzene might form. We aimed for an "open-flask" method, so the optimizations were conducted under air (for details, see table S1, SI). To our delight, selective C(sp^2-H) chlorination could be obtained at room temperature using $Ru(bpy)_3Cl_2{\cdot}6H_2O$ **3** (3 mol%) as photocatalyst, $Na_2S_2O_8$ (1.6 equiv.) as oxidant, NaCl (3.0 equiv.) as the chlorine source, CH_3CN/H_2O (1:1) as solvent, yielding 56% of 1-chloro-2-methyl-benzene **2a** and 34% of 1-chloro-4-methyl-benzene **2a'** (entry 1). The use of other commonly used photocatalysts such as $Ir[dFppy]_2(dtbbpy)PF_6$ **4** (entry 2), Eosin Y **5** (entry 3) and 9,10-anthracenedicarbonitrile **6** (entry 4) led to no yield of chlorination. Control experiments showed that under identical conditions but in the absence of light (entry 5), $Ru(bpy)Cl_2{\cdot}6H_2O$ (entry 6), or $Na_2S_2O_8$ (entry 7), no chlorination was obtained. It should be noted that no chlorination of benzylic C-H bond was observed.

Table 1: Optimization of reaction conditions[a]

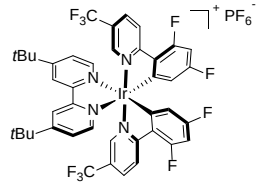


1 2a 2a' 2a''

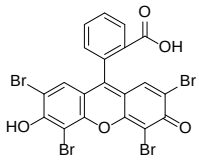
Entry	photo catalyst	NaCl (x equiv.)	$Na_2S_2O_8$ (y equiv.)	Yield (%) 2a	2a'	2a''
1	**3** (3 mol%)	3.0	1.6	56%	34%	0%
2	**4** (3 mol%)	3.0	1.6	0%	0%	0%
3	**5** (10 mol%)	3.0	1.6	0%	0%	0%
4	**6** (10 mol%)	3.0	1.6	0%	0%	0%
5[b]	**3** (3 mol%)	3.0	1.6	0%	0%	0%
6	0	3.0	1.6	0%	0%	0%
7	**3** (3 mol%)	3.0	0	0%	0%	0%



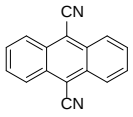
$Ru(bpy)_3Cl_2$, **3**



$Ir[dFppy]_2(dtbbpy)PF_6$, **4**



Eosin Y, **5**



9,10-anthracenedicarbonitrile **6**

[a] Reaction conditions: Toluene (0.25 mmol) in CH_3CN/H_2O (1 mL) at 25 °C. Yields were obtained from the crude reaction mixture by GC relative to mesitylene internal standard. [b] Without light.

With the optimized conditions in hand, we studied the scope and limitation of this C-H chlorination method (Table 2). We first explored monosubstituted aromatic compounds. The substrates with an electron-donating group (isopropyl, **2b**; methoxy, **2c**) on the phenyl ring were chlorinated in good yields, and both *para*- or *ortho*- chlorinated products were formed. Substrates bearing functional groups such as –CN (**2d**), ester (**2e**), and halogen (**2f** and **2g**) were all chlorinated in good yields as well. 1-(3-bromopropyl)-4-chlorobenzene (**2g**) is an important building block for the synthesis of Parogrelil hydrochloride, a medication for the treatment of intermittent claudication. Previously[17] it took four steps to prepare this compound, whereas using our method 1-(3-bromopropyl)-4-chlorobenzene (**2g**, 39%) and its isomer 1-(3-bromopropyl)-4-chlorobenzene (**2g'**, 33%) were prepared in one step. The two isomers were easily separated by column chromatography. In addition, aromatic compounds containing unprotected tertiary alcohol (**2h**) and amide groups (**2i**, **2j**) were suitable substrates. In agreement with the limiation of electrophilic chlorination, substrates containing only an election-withdrawing group such as nitrobenzene (**2k**) and (trifluoromethoxy)benzene (**2l**) could not be chlorinated by this method.

However, substrates with election-withdrawing group(s) could be used if they also contain an election-donating group on the

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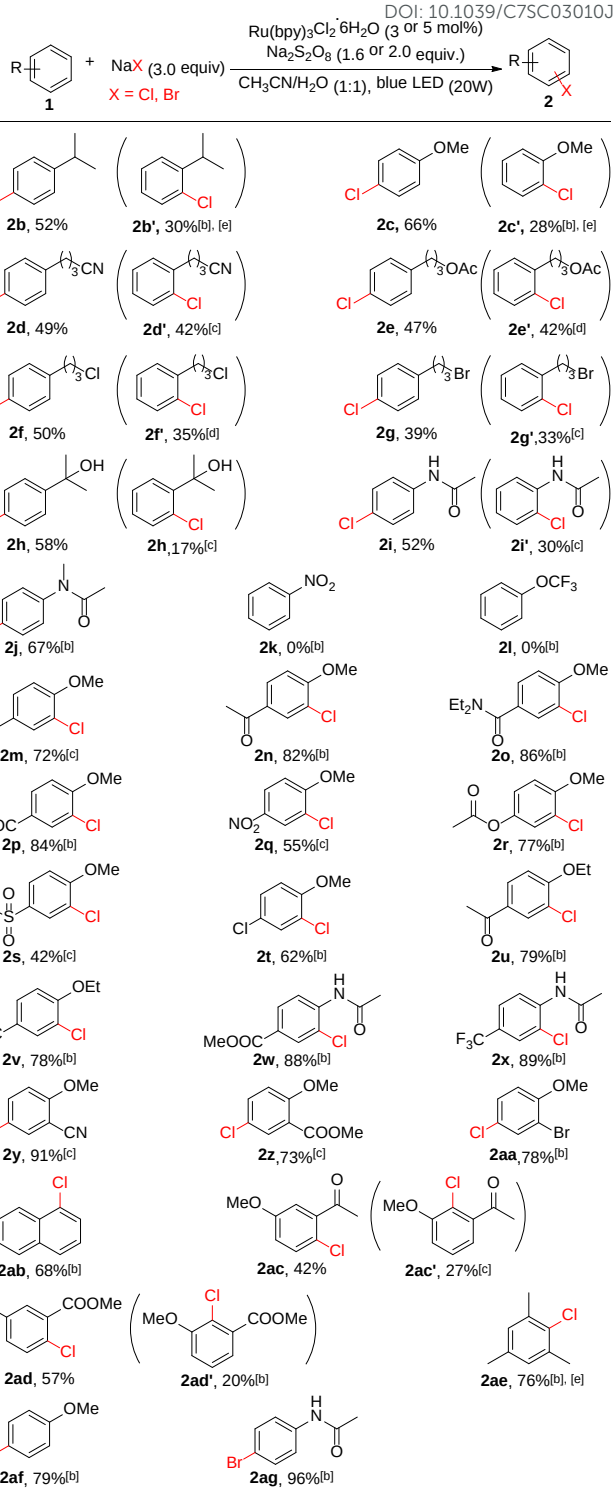
aryl ring, for example, an alkoxy group (**2m-2v, 2y, 2z, 2aa, 2ac, 2ad**). Thus, electron-withdrawing functional groups such as ester (**2p**, **2r**), trifluoromethyl (**2x**), amide (**2o**), halogen (**2t**, **2aa**), and sulfonate (**2s**) were all comptaible. Even strong election-withdrawing groups such as cyano (**2m**) and nitro (**2q**) groups were tolerated. Although mono-substituted substrates are chlorinated at both ortho and para positions due to the inate reactivity of Cl^+ (see below), complate site selectivity could be achieved for disubstitued substrates bearing functional groups at either 1,4 and 1,2 positions. In these cases the chlorination occured exclusively ortho to the electron-donating group. It is noted that exlusive C(sp^2)-H chlorination occurred also for substates containing an acyl group (**2n**, **2u**, **2ac**). Previous electrophilic chlorination methods normally leads to α-carbonyl C(sp^3)-H chlorination for acetophenone substrates.[11-12] In addition to alkoxy groups, the amide group (**2w** and **2x**) could be used to promote the chlorination of electron-poor substrates. Chlorination of mesitylene gave the monochlorinated product in 76% yield (**2ae**). The photocatalytic oxidative halogenation strategy was also applicable to bromination. For example, bromination of anisole and N-phenylacetamide gave 1-bromo-4-methoxybenzene (**2ag**, 79%) and N-(4-bromophenyl)acetamide (**2ag**, 96%), respectively. However, iodination of anisole was not successful, possibly due to over-oxidation of iodine.

Table 2. Scope of C(sp^2)-H chlorination[a]



[a] Reaction conditions: Substrate (0.5 mmol) in CH_3CN/H_2O (2 mL) at 25 °C. Unless otherwise specified, yields shown are isolated yields. Reaction time: 24 h.; [b] 3 mol% of $Ru(bpy)_3Cl_2.6H_2O$, 1.6 equiv of $Na_2S_2O_8$; [c] 5 mol% of $Ru(bpy)_3Cl_2.6H_2O$, 2.0 equiv of $Na_2S_2O_8$; [d] 5 mol% of $Ru(bpy)_3Cl_2.6H_2O$, 1.6 equiv of $Na_2S_2O_8$. [e] Substrate (0.25 mmol) in CD_3CN/H_2O (1 mL). Yields were determined by ^1H NMR relative to mesitylene internal standard. Reaction time: 15 h.

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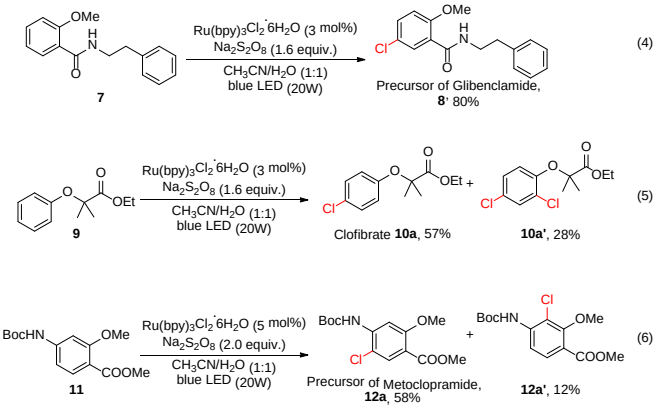
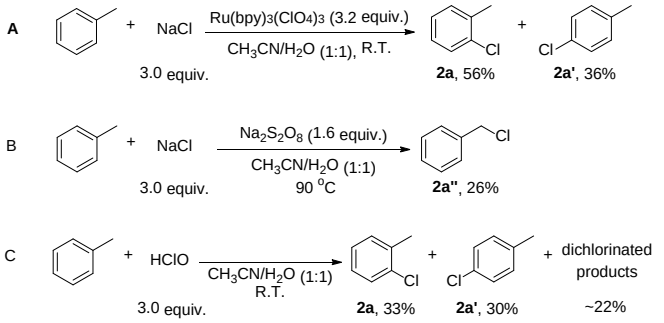
To demonstrate the potential utility of this oxidative chlorination method, it was applied for the expedite synthesis of some drugs and their key precursors. **8** is the precursor of Glibenclamide, a medication used to treat type 2 diabetes. This compound could be obtained directly from **7** in 80% yield [Eq. (4)]. Clofibrate (**10a**) is a lipid-lowering agent used for controlling the high cholesterol and triacylglyceride level in the blood. This compound could be obtained in one-step using our C-H chlorination method from its precursor **9** in 57% yield, together with 28% of the dichlorination product [Eq. (5)]. Chorination of Boc-protected aminobenzene **11** gave **12a** (58%) and **12a'** (12%) [Eq. (6)]. The major product **12a** is a precursor for synthesis of several gastroprokinetic agents including Metoclopramide, Renzapride, and Cisapride. Metoclopramide is one of the most widely used medicines for treating and preventing nausea and vomiting, and it is listed on the World Health Organization's List of Essential Medicines.



The mechanism of the reactions was then probed. It is well established that under light illumination, the excited $*Ru(bpy)_3^{2+}$ reacts with $S_2O_8^{2-}$ to give $Ru(bpy)_3^{3+}$ and $SO_4^{\cdot-}$, which further reacts with $Ru(bpy)_3^{2+}$ to give $Ru(bpy)_3^{3+}$ and SO_4^{2-}.[18] Thus, either $Ru(bpy)_3^{3+}$ or $SO_4^{\cdot-}$ or both might be the actual oxidant in this system. To probe these possibilities, $Ru(bpy)_3^{3+}$ was prepared chemically.[19] With $Ru(bpy)_3^{3+}$ (3.2 equiv.; in accord with the loading of $Na_2S_2O_8$ in the catalytic system (1.6 equiv.)) as the sole oxidant, the reaction of toluene (1.0 equiv.) with NaCl (3.0 equiv.) gave 1-chloro-2-methyl-benzene (**2a**, 56%) and 1-chloro-4-methyl-benzene (**2a'**, 36%) in 30 min at room temperature (Scheme 2, A). The faster rate of this reaction compared to catalysis reflects the higher loading of $Ru(bpy)_3^{3+}$ in the former. Thus, $Ru(bpy)_3^{3+}$ is a competent oxidant for the chlorination. Heating a solution of $Na_2S_2O_8$ at 90 °C is known to generate $SO_4^{\cdot-}$.[12] The reaction of toluene (1.0 equiv.) with NaCl (3.0 equiv.) was then conducted in the presence of 1.6 equiv. of $Na_2S_2O_8$ at 90 °C (Scheme 2, B). However, no C(sp^2)-H chlorination occurred; instead, a small amount of chloromethylbenzene (**2a''**, 26%), the C(sp^3-H) chlorination product, was formed (Scheme 2, B). This result suggests that $SO_4^{\cdot-}$ is not the major oxidant to react with the substrates in our system. To probe whether the chlorination reaction operates via a chain reaction mechanism after activation of $S_2O_8^{2-}$ under the photocatalytic conditions, the chlorination of toluene was conducted under illuminated for 40 minutes, and then the light was removed while allowing the reaction for 15 further hours. Only 11% of 1-chloro-2-methyl-benzene **2a** and 7% of 1-chloro-4-methyl-benzene **2a'** were formed. The yields were much lower than the reaction conducted under illunination for the whole duration. This result indicates that a chain reaction based on activation peroxodisulfate is unlikely.



Scheme 2. Experiments to probe the actual oxidant and chlorinating species in the current system

Oxidative chlorination is proposed to occur via two major pathways.[12, 20-21] The first pathway (See supporting information, Scheme S1, Path A) involves oxidation of chloride anion (Cl^-) to chloride cation or its equivalent ("Cl^+")[22], which reacted with aromatic compounds to give the chlorination products. The second pathway (Scheme S1, Path B) involves oxidation of aromatic compounds to aromatic radicals, which then react with chloride anion to give the chlorination products. According to its oxidative potential, $Ru(bpy)_3^{3+}$ ($E_{1/2}^{III/II}$ = +1.29 V vs SCE) is not able to oxidize toluene (+2.28 V vs SCE). To confirm this, the reaction of $Ru(bpy)_3^{3+}$ with toluene was monitored by UV-Vis spectroscopy. In CH_3CN/H_2O (1:1), $Ru(bpy)_3^{3+}$ alone slowly decays into $Ru(bpy)_3^{2+}$ (Figure S1, SI). When toluene (20 equiv.) was added to the solution containing $Ru(bpy)_3^{3+}$, the reduction rate remained constant (Figure S2, SI). When NaCl (60 equiv.) was added to the solution, the reduction rate of $Ru(bpy)_3^{3+}$ became much faster (Figure S3, SI). These results suggest that $Ru(bpy)_3^{3+}$ oxidizes Cl^- rather than the aromatic substrates in the catalysis. Due to the presence of water, the "Cl^+" species might exist in the form of HClO, which worked as the actual chlorinating species. To test this hypothesis, HClO was used as the chlorinating reagent for the chlorination of toluene. 1-chloro-2-methyl-benzene (**2a**, 33%), 1-chloro-4-methyl-benzene (**2a'**, 30%) and some dichlorinated products (~22%) were detected after 15 h (Scheme 2, C). The product distribution is similar, although not exactly the same, as that of the photocatalytic reaction. The dichlorinated products might originate from a high concentration of HClO in the stoichiometric reaction. Overall, the result in Scheme 2 suggests HClO as a probable chlorinating species in the photocatalytic reaction.

According to the above results, a tentative catalytic cycle is proposed in Figure 1. Upon photoirradiation of $Ru(bpy)_3^{2+}$, $*Ru(bpy)_3^{2+}$ was formed [23]. Reaction of $*Ru(bpy)_3^{2+}$ with $Na_2S_2O_8$ gives $Ru(bpy)_3^{3+}$ and $SO_4^{\cdot-}$. The latter oxidizes $Ru(bpy)_3^{2+}$ to give a further equivalent of $Ru(bpy)_3^{3+}$. $Ru(bpy)_3^{3+}$ then oxidize Cl^- to Cl^+ or its equivalent (HClO), probably via a Cl radical intermediate. When the chlorination of toluene was

conducted in the presence of (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO, 3 equiv), the chlorination was completely inhibited, supporting the involvement of Cl radical. The further oxidation of Cl radical must be very fast as no C(sp^3-H) chlorination was observed. Finally, the chlorinating species reacts with an aromatic compound to effect the C(sp^2-H) chlorination. This step likely occurs via an electrophilic addition process rather than an aromatic substitution process. To verify this, a 1:1 mixture of toluene and cyclohexene was subjected to the chlorination. After 1 h, 2-chlorocyclohexan-1-ol (~20%) and 1,2-dichlorocyclohexane (2%) were generated while no chlorination of toluene was observed. This result supports the electrophilic addition pathway.

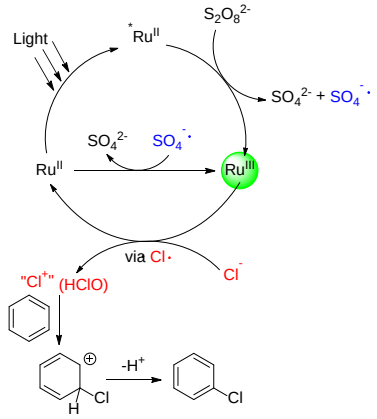


Figure 1. Proposed mechanism of the photocatalytic oxidative chlorination reaction

Conclusions

In conclusion, we have developed a photoredox catalytic method for C(sp^2)-H oxidative chlorination at room temperature. Our method employs abundant and non-toxic NaCl as the chlorine source and inexpensive $Na_2S_2O_8$ as the oxidant, which offer a practical and convenient alternative to existing electrophilic chlorination methods. The mild conditions lead to broad scope and high functional group compatibility. The synthetic utility of this method is demonstrated in the chlorination of a diverse set of substrates, including the expedite synthesis of key intermediates to bioactive compounds and a drug.

Acknowledgements

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