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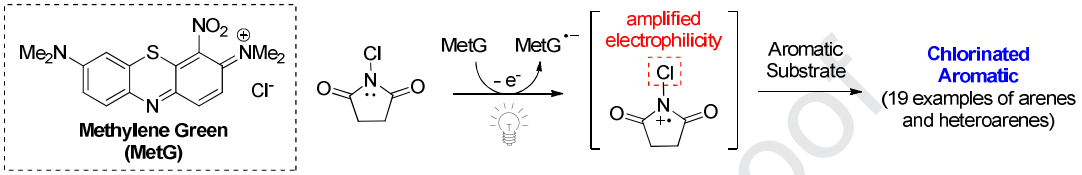

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Visible-light photocatalytic activation of N-chlorosuccinimide by organic dyes for the chlorination of arenes and heteroarenes

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ABSTRACT

A variety of arenes and heteroarenes are chlorinated in moderate to excellent yields using N-chlorosuccinimide (NCS) under visible-light activated conditions. A screening of known organic dye photocatalysts resulted in the identification of methylene green as the most efficient catalyst to use with NCS. According to mechanistic studies described within, the reaction is speculated to proceed via a single electron oxidation of NCS utilizing methylene green under visible-light photoredox pathway. The photo-oxidation of NCS amplifies the electrophilicity of the chlorine atom of the NCS, thus leading to enhanced reactivity as a chlorinating reagent with aromatic substrates.

1. Introduction

Chlorinated arenes and heteroarenes are prevalent as end-products and intermediates in a wide range of synthetic applications including the production of pharmaceuticals, polymeric materials, and agrochemicals.[1-2] Numerous methods for arene chlorination are available to the synthetic community, however, there are a range of limitations in systems currently available. For example, some readily available chlorinating agents are highly reactive but hazardous (Cl_2, SO_2Cl_2, ^tBuOCl).[3] N-Chloro reagents such as N-chlorosuccinimide (NCS),[4] 1,3-dichloro-5,5-dimethylhydantoin (DCDMH),[5] chloro-bis(methyoxycarbonyl)guanidine (CBMG or "Palau'chlor"),[6] trichloroisocyanuric acid (TCCA),[7] N-chloro-N-fluorobenzenesulfonylamine (CFBSA)[8] and N-chlorosaccharin[9] are relatively stable, but frequently require activation by redox active metals, Bronsted or Lewis acids, or radical initiators. In addition, some of these reagents either require synthesis (CFBSA) or are costly when commercially available (CBMG, N-chlorosaccharin).

The balance between reactivity, selectivity, functional group tolerance, economy, and safety are necessary considerations when selecting an appropriate chlorinating reagent. Within the domain of drug discovery and development, the installation of a chlorine atom to an aromatic/heterocyclic scaffold can provide synthetic intermediates for further functionalization or end-products with altered electronic and physical properties.[2, 10] The synthesis and transformation of complex molecules requires the balance of chlorinating agent characteristics to favor selectivity, economy, and functional group tolerance above others. With regard to selectivity and economy, the use of stable, inexpensive chlorinating reagents that operate through direct C(sp^2)-H "Friedel-Crafts" electrophilic aromatic substitution (S_EAr)[11] mechanistic pathways are attractive. Functional group tolerance, however, remains a concern due to the necessary activation (typically using acidic conditions) of the stable chlorinating reagent. Thus, further exploration toward the development of an inexpensive, mild, and selective chlorination reaction of arenes and heteroarenes that are relevant to drug discovery and development remains a valuable pursuit.

In terms of reagent stability, availability, and practicality, NCS is an attractive source of electrophilic chlorine. Traditionally, activation of NCS by a Bronsted or Lewis acid is required in order to increase the electrophilicity of the Cl atom.[12] Recently, Hering and Konig demonstrated that the polarization of the N-Cl bond in NCS could be enhanced by a one-electron oxidation using a Ru(II) visible-light photoredox catalyst (Scheme 1, Method A).[13] In their pioneering study, oxidized NCS was used to chlorinate aromatic compounds in modest yields, though the substrate scope was limited to electron rich arenes, and heteroarene substrates were unexplored. Inspired by this initial report, our research group has previously reported an organic dye catalyzed amplification of N-bromosuccinimide (NBS) in which the electrophilic bromine atom is activated by erythrosine B under visible-light-promoted conditions (Scheme 1, Method B).[14]

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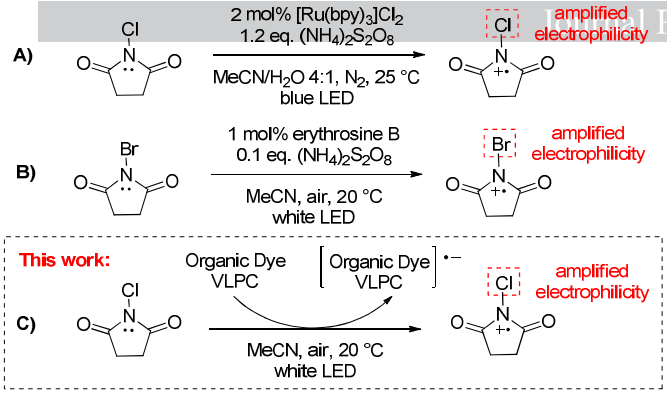


Scheme 1. Visible-light photoredox catalytic (VLPC) methods for amplification of N-halosuccinimide electrophilicity.

The bromination of arenes via oxidative activation of NBS by catalytic erythrosine B has joined a growing number of systems within the recent explosion of visible-light photoredox catalysis (VLPC) transformations in which inexpensive organic dyes can have comparable, or even superior, activity when compared to their expensive Ru(II) and Ir(III) transition-metal counterparts.[15] Even though organic dyes (Figure 1) have the potential to be superior catalysts, they are largely overlooked during the screening of catalysts in favor of the well-understood Ru(II) and Ir(III) VLPCs.[16] Herein, we describe a photoredox catalysis approach that employs VLPC organic dyes to amplify the electrophilicity of NCS for chlorination of arenes and heteroarenes. This strategy offers a cost-effective, practical alternative for the production of valuable chlorinated compounds under non-acidic conditions.

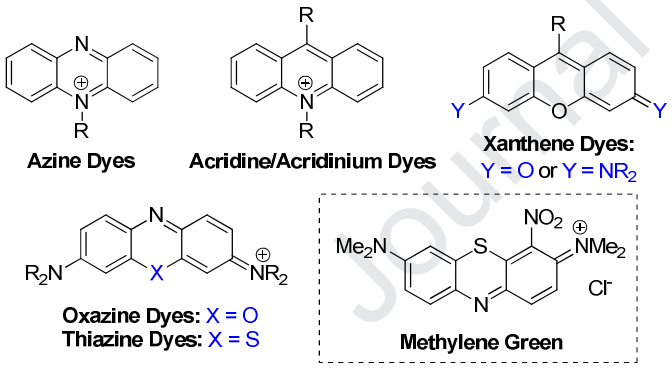
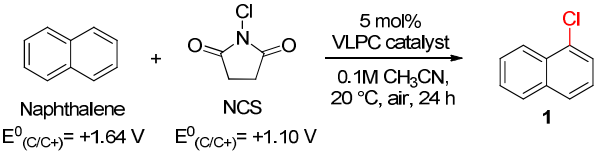


Figure 1. Structural classification of the VLPC organic dyes used in this investigation.

2. Results and Discussion

To begin our investigation, known VLPC organic dyes were selected to screen for activity in the chlorination of naphthalene using NCS (all dye structures are shown in supporting information, Figure S1). We hypothesized that a VLPC catalyst with an excited state one-electron reduction potential that lies between the oxidation potential of NCS (+1.10V vs SCE)[13] and that of naphthalene (+1.64V vs SCE)[17] could serve as a catalyst strong enough to oxidize NCS, but not too strong to oxidize naphthalene and lead to unwanted by-products. The initial reaction conditions shown in Table 1 were chosen to screen for a highly practical system (open to air, ambient temperature) under white LED irradiation as well as in the absence of light. To our delight, several catalysts performed more efficiently than uncatalyzed (Table 1, entry 1) reaction. The most effective VLPC catalysts (Table 1, entries 10-13) have excited state reduction potentials between +1.10 and +1.64, and the formation of **1** was halted in light-free conditions, providing strong evidence of a photocatalytic mechanism.



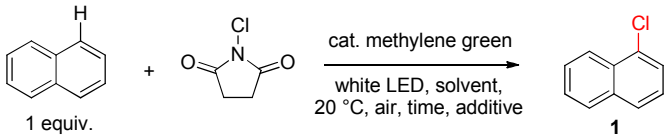
Entry	Catalyst	Structural Classification	E^*_{red} (V vs SCE)	% Yld **1**[a] (white LED)	% Yld **1**[a] (Dark)
1	NONE	-	-	3	2
2	Acridine Orange	Acridine	+0.60[b]	7	1
3	Fluorescein	Xanthene	+0.77[b]	8	1
4	Rose Bengal	Xanthene	+0.81[b]	0	0
5	Eosin Y	Xanthene	+0.83[b]	8	0
6	$[Ru(bpy)_3]Cl_2$	-	+0.84[c]	5	2
7	Nile Blue	Oxazine	+0.87[c]	21	27
8	Methylene Blue	Thiazine	+0.97[c]	22	26
9	Safranin O	Azine	+1.07[c]	9	30
10	Erythrosine B	Xanthene	+1.14[d]	23	0
11	Methylene Violet 3RAX	Azine	+1.17[c]	20	3
12	Methylene Green	Thiazine	+1.28[c]	42	3
13	Thionin	Thiazine	+1.35[c]	29	0
14	Pyronin Y	Xanthene	+1.47[c]	15	5
15	Rhodamine 6G	Xanthene	+1.48[c]	5	1
16	Rhodamine B	Xanthene	+1.62[c]	10	1
17	9-Mesityl Acridinium	Acridinium	+2.08[c]	0	17

a) Gas chromatography (GC) yields calculated using adamantane as the internal standard. Conditions: 0.25 mmol naphthalene, 0.25 mmol NCS, 0.0125 mmol catalyst, 2.5 mL MeCN, air, 20 °C. b) Reported in reference 15f. c) Reported in reference 15e. d) Reported in reference 14.

Table 1. Screening of organic dye VLPCs for chlorination of naphthalene using NCS.

A variety of structurally different catalysts were screened, however, there appeared to be no correlation to the efficiency of 1-chloronaphthalene **1** formation and the structural classification of the organic dyes. Compared to their Ru(II) and Ir(III) counterparts, the use of organic dyes to activate NCS for chlorination of arenes is complicated by the structural constitution of the organic dye. For example, chlorination of the aromatic region of the dye instead of the arene substrate is a distinct possibility. In addition, transfer of the electrophilic chlorine from NCS to a nitrogen atom of a dye is also plausible, which may account for some of the dyes serving as catalysts for chlorination in the absence of light (Table 1, entries 7-9). In contrast, a comparison of the known excited state one-electron reduction potentials of the organic dye VLPCs with the formation of **1** resulted in an observable trend.

Following the screening of organic dyes, methylene green was selected as the best performing photoredox catalyst. Methylene green (MetG) is a commercially available member of the thiazine family of VLPCs that has been used as a catalyst in a variety of light-promoted systems.[15d, 18] Using naphthalene as a test substrate with NCS and catalytic MetG, an optimization of stoichiometry and reaction conditions was performed (Table 2). The best conversion to 1-chloronaphthalene 1 (72%, entry 15) was obtained using 1 equiv. naphthalene, 1.1 equiv. NCS, 0.05 equiv. MetG, 0.1 equiv. ammonium peroxodisulfate in acetonitrile (0.2M relative to naphthalene) open to air in a white LED photochamber for 24 hours at ambient (20 °C) temperature.

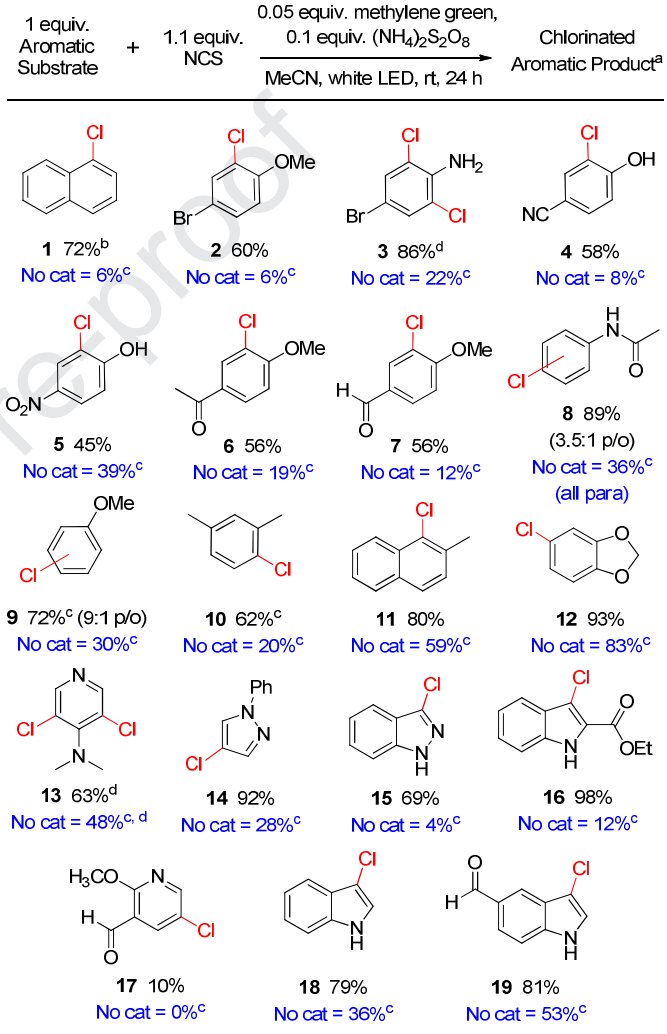


Entry	NCS (equiv.)	solvent (0.1 M)	catalyst (mol %)	time (hours)	additive (equiv.)	Yield **1** (%)[a]
1	1.1	MeCN	5	24	-	42
2	1.1	MeCN	2	24	-	20
3	3	MeCN	2	24	-	33
4	1.1	MeCN	1	24	-	20
5	1.1	MeCN	0	24	-	3
6	1.1	MeOH	5	24	-	9
7	1.1	DCM	5	24	-	1
8	1.1	4:1 MeCN/H_2O	5	24	-	3
9	1.1	MeCN (0.2M)	5	24	-	52
10	1.1	MeCN (0.05M)	5	24	-	7
11	1.1	MeCN	5	24	$(NH_4)_2S_2O_8$ (1)	44
12	1.1	MeCN	5	6	$(NH_4)_2S_2O_8$ (1)	21
13	1.1	MeCN	5	24	$(NH_4)_2S_2O_8$ (0.1)	63
14	1.1	MeCN	0	24	$(NH_4)_2S_2O_8$ (0.1)	3
15	1.1	MeCN (0.2M)	5	24	$(NH_4)_2S_2O_8$ (0.1)	72

a) Gas chromatography (GC) yields calculated using adamantane as the internal standard.

Table 2. Optimization of reaction conditions for chlorination of naphthalene by NCS.

With optimized reaction conditions in hand, the substrate scope of the reaction was investigated (Table 3). Disubstituted benzene derivatives that contain an activating (electron-donating) and deactivating (electron-withdrawing) group were tested, and good to excellent product yields (**2-7**) were obtained with high regioselectivity, indicative of a S_EAr mechanism. A mixture of mono- and dichlorinated product was formed when using standard conditions (1.1 equiv. of NCS) with 4-bromoaniline, so the reaction was performed with 2.2 equivalents NCS in order to cleanly produce the dichlorinated product **3** without observation of oxidation of the amine functionality. It is also noteworthy that chlorination was not observed α to the carbonyl using 4-methoxyacetophenone **6**, and the aldehyde functionality was not oxidized under the reaction conditions (product **7**). Acetanilide was chlorinated (89% total) at both the para (69%) and ortho (20%) positions (Table 3, product **8**), which is a departure from the uncatalyzed reaction that only produces the para isomer (36%). A number of additional substituted arenes with electron-donating groups were chlorinated using catalytic MetG with improvement over background reaction (products **9-12**). 2-Methylnaphthalene and *m*-xylene were both chlorinated under photocatalytic conditions without chlorination of the benzylic C-H position (**10** and **11**). A number of *N*-heteroarenes were also tested using the standard reaction conditions. Pyridine, pyrrole, indazole, and indole heteroarenes were all tested, and chlorinated products **13-19** were formed with significant improvement over uncatalyzed background reaction. In general, a number of functionalities are tolerated by the reaction conditions including aryl halide, ether, phenol, nitro, nitrile, ketone, aldehyde, ester, amide, benzylic and α to carbonyl C(sp^3)-H's, and 1° and 3° amine. Catalysis using the organic dye, methylene green, offers notable advantages over the Ru(II) catalyst including catalyst cost (MetG = \$1.41/g – MP Biomedicals; $Ru(bpy)_3Cl_2$ = \$65.20/g – Sigma-Aldrich), increased product yield with comparable substrates, and ability to chlorinate arenes with deactivating groups and heteroarenes. These results validate the inclusion of NCS/MetG as a viable option for cost-effective and practical chlorination of arenes and heteroarenes.

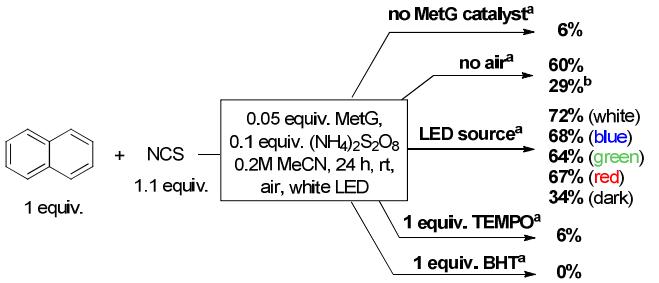


a) Yields are isolated. Conditions: 0.5 mmol aromatic substrate, 0.55 mmol NCS, 0.05 mmol $(NH_4)_2S_2O_8$, 0.025 mmol methylene green, 2.5 mL MeCN, white LED, air, 20 °C, 24 h. b) GC yield was calculated using adamantane as internal standard. c) ^1H NMR yield was determined using $PhNO_2$ as internal standard. d) 2 equiv. NCS (1.10 mmol) used.

Table 3. Substrate scope of arene and heteroarene chlorination.

In order to verify that a photoredox mechanism was responsible for chlorination of (hetero)arene substrates, a series of control and mechanistic experiments were conducted (Scheme 2). The absence of catalyst resulted in a significant reduction in product formation from 72% (catalyzed) to 6% yield. In addition, air plays a key role in the reaction as observed by the decreased efficiency of the reaction under anaerobic conditions, with or without external oxidant $(NH_4)_2S_2O_8$. The elimination of light from the standard reaction conditions produced **1** in a similar

yield to the catalyst-free reaction, implicating both light and catalyst as integral components of the reaction. Variation of the LED light source (red, green, and blue LED) was also investigated, and the most efficient production of **1** resulted when using white LEDs. Finally, known radical inhibitors such as TEMPO and BHT were separately added to a standard reaction, and suppression of naphthalene chlorination was observed.

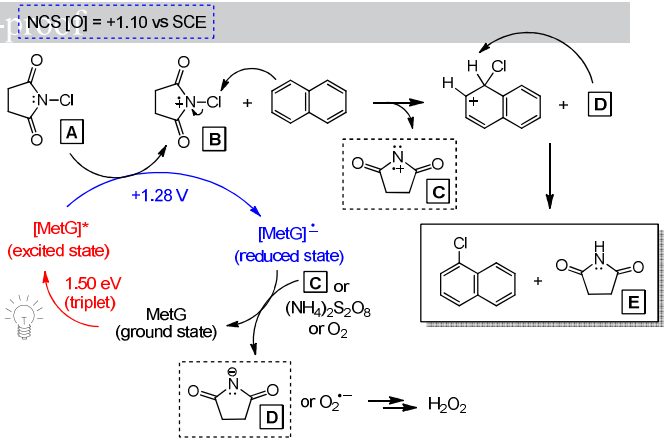


a) Yields of product **1** were quantified via ^{1}H NMR integration using nitrobenzene as internal standard. All reactions were run in triplicate, and the yield is an average of three trials. b) Anaerobic reaction was performed without $(NH_4)_2S_2O_8$ present.

Scheme 2. Control and mechanistic experiments.

The iodide test (NaI in glacial acetic acid) was performed to attempt to observe the presence of H_2O_2 following completion of the reaction. The presence of hydrogen peroxide would indicate the formation of superoxide anion under the photocatalyzed conditions. Ammonium peroxodisulfate was intentionally excluded from the standard reaction mixture in order to prevent a false positive test that would result from the oxidation of iodide by $(NH_4)_2S_2O_8$. The reaction was performed for 24 hours, and the formation of hydrogen peroxide was observed, albeit in low concentration, as a yellowish-orange appearance of iodine (see Supporting Information Figure S3). This indicates that oxygen does play a small role, but another species is primarily responsible for oxidation of the reduced catalyst back to its ground state.

Based upon the observed mechanistic experimental results and literature reports of related systems,[13-14, 19] a plausible reaction mechanism is proposed in Scheme 3. The photo-excited state of methylene green induces a single-electron oxidation of NCS **A** to cationic radical species **B**, thus amplifying the positive polarization on the chlorine atom. The arene substrate then undergoes electrophilic aromatic chlorination, and methylene green is returned to its ground state primarily by either an external oxidant (such as ammonium peroxodisulfate) or by the resulting charged succinimide species **C** which could oxidize the reduced state of the catalytic methylene green to form the succinimide anion **D**.



Scheme 3. Plausible mechanism.

3. Conclusions

Methylene green has been developed as an organic dye, visible-light photoredox catalyst to chlorinate arenes and heteroarenes by operating through an amplification of the electrophilic chlorine of *N*-chlorosuccinimide via a one-electron oxidation of NCS. The methylene green catalyzed reaction operates under mild, practical conditions and produces chlorinated arenes in high regioselectivity and with dramatic enhancement relative to the analogous uncatalyzed reaction. A variety of aromatic and heteroaromatic substrates were chlorinated in good to excellent yields and many functionalities are tolerated. According to mechanistic studies, the reaction is speculated to operate via a single electron oxidation of NCS by methylene green, which is in turn oxidized back to its ground state. The reaction provides a useful chlorinating method by activating NCS without the use of traditional (acidic) conditions. The employment of a VLPC strategy to activate additional reagents containing N-X bonds for electrophilic transformations are currently underway in our laboratory and will be reported in due course.

4. Experimental

4.1. Materials and Instrumentation

All reagents and solvents were purchased from commercial sources and used without further purification. Methylene Green (Basic Green 5) was purchased from MP Biomedicals (CAS # 284533; FW = 364.86). A description of the construction of our light bath (LED) photochamber is provided in the supporting information. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400/100 (400 MHz) spectrometer in deuterated chloroform ($CDCl_3$), dimethyl sulfoxide (DMSO), or methanol (CD_3OD) with the solvent residual peak as internal reference unless otherwise stated ($CDCl_3$: ^{1}H = 7.26 ppm, ^{13}C = 77.02 ppm; DMSO: ^{1}H = 2.50 ppm, ^{13}C = 39.52 ppm; CD_3OD: ^{1}H = 3.31 ppm, ^{13}C = 49.00 ppm). Data are reported in the following order: Chemical shifts (δ) are reported in ppm, and spin-spin coupling constants (*J*) are reported in Hz, while multiplicities are abbreviated by s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), dt (double of triplets), td (triplet of doublets), m (multiplet), q (quartet). Infrared spectra were recorded on a Nicolet iS50 FT-IR spectrometer, and peaks are reported in reciprocal centimeters (cm^{-1}). Melting points (m.p.) were recorded on a Mel-Temp II (Laboratory Devices, USA) and were uncorrected. Nominal MS (EI) were obtained using a Shimadzu GC-2010 Plus with GCMS-QP2010. Relative intensity

(in percentage) is shown in parentheses following the fragment peak where appropriate.

4.2. General procedure for the chlorination of arenes and heteroarenes

To an oven-dried flask was added a magnetic stir bar, methylene green (9.1 mg, 0.05 equiv, 0.025 mmol), ammonium peroxodisulfate (11.4 mg, 0.1 equiv, 0.05 mmol), arene/heteroarene (1 equiv, 0.5 mmol), acetonitrile (2.5 mL), and then *N*-chlorosuccinimide (73.4 mg, 1.1 equiv, 0.55 mmol). The reaction mixture was stirred open to air at room temperature (20 °C) in a white LED chamber for 24 hours. For substrates that produced a mixture of mono- and di-brominated products upon full conversion, 2.2 equivalents (1.1 mmol) of *N*-chlorosuccinimide was employed. Upon completion of the reaction, the crude mixture was evaporated under pressure and the chlorinated product was isolated via column chromatography on silica gel.

4.3. Procedure for light-dependent chlorination of naphthalene

Using visible-light photochambers assembled in our laboratory (see supporting information, Figure S2), the yield of product **1** was calculated using ^{1}H NMR integration with nitrobenzene as internal standard according to the following procedure: to an oven-dried reaction vessel was added naphthalene (64 mg, 0.5 mmol), ammonium peroxodisulfate (11.4 mg, 0.05 mmol), NCS (73.4 mg, 0.55 mmol), methylene green (9.1 mg, 0.025 mmol), and nitrobenzene as internal standard (1 equiv., 10.3 μL, 0.1 mmol), in CH_3CN (2.5 mL) at ambient temperature in a visible-light photochamber that has been protected from any external background light (inside a light-proof chamber constructed in our laboratory) for 24 h. The crude was analyzed directly by ^{1}H NMR and a yield was calculated in comparison to internal standard signals. Reactions were run in triplicate and the three trials for each LED photochamber were averaged. For the dark reaction, the reaction flask was wrapped in aluminum foil and the reaction was shielded from light in a darkened laboratory with a light-proof chamber constructed in our laboratory.

4.4. Iodide Test

Test solution preparation: 0.100g KI dissolved in 10 mL glacial acetic acid.

Control test: Three drops of 3% H_2O_2 solution were added by pipette to the KI/AcOH test solution in a 4 dram vial. The vial was capped and shaken, resulting in an opaque red-brown color (see supporting information, Figure S3, for photos of all experiments pertaining to the iodide test).

0-minute test: A reaction vessel was loaded with methylene green (9.1 mg, 0.025 mmol), naphthalene (0.062 g, 0.50 mmol), 2.5 mL CH_3CN, and *N*-chlorosuccinimide (0.097 g, 0.55 mmol). After addition of all reagents, the reaction vessel was lightly shaken to mix contents. Three drops of the crude reaction mixture was immediately transferred via pipette to a freshly prepared KI/AcOH test solution in a 4-dram vial. The vial was capped and shaken, giving a green color resembling the color of the reaction mixture.

24-hour test: A reaction vessel was loaded with methylene green (9.1 mg, 0.025 mmol), naphthalene (0.062 g, 0.50 mmol), 2.5 mL CH_3CN, and *N*-chlorosuccinimide (0.097 g, 0.55 mmol). After addition of all reagents, the reaction vessel was equipped with a stir bar and allowed to react open to air in a white LED photochamber for 24 hours. Upon completion of the reaction, three, nine, and fifteen drops of the crude reaction mixture were immediately transferred via pipette to three separate, freshly prepared KI/AcOH test solutions in three 4-dram vials. The vials were capped and shaken, giving an opaque yellow color resembling the color of a diluted control test, indicating that a small amount of hydrogen peroxide was forming.

4.5. Compound characterization

All chloroarenes were isolated according to general procedure unless otherwise noted and display the characterizational data shown below (spectra available in electronic supporting information). Known compounds were verified by comparison to literature reports.

4.5.1. 1-Chloronaphthalene (**1**) The title compound was prepared according to the general procedure and quantified using gas chromatography with adamantane as an internal standard. A standard curve of 1-chloronaphthalene (Supporting Information, Figure S4) was prepared in 6 separate reaction vessels by adding varying amounts of 1-chloronaphthalene (between 0 and 0.25 mmol) to 3 mL of acetonitrile. To each of the 3 mL acetonitrile solutions was added 8 mL of hexanes and 0.156 mmol (20 mg) of adamantane. The acetonitrile solution was extracted with the hexanes, and 1 mL of the hexanes portion was removed for gas chromatography injection. Gas chromatography was performed using a Shimadzu GC-2010 Plus with GCMS-QP2010 with a Restek Rtx-5MS capillary column (30m; 0.25 mmID; 0.25 μm df; Crossbond – 5% diphenyl/95% dimethyl pilosiloxane). The GC method was as follows: 40 °C for 5 minutes, then increase at 10 °C/minute for 16 minutes (up to 200 °C). 200 °C is maintained for 10 additional minutes. As seen in Supporting Information Figure S5, 1-chloronaphthalene is observed at 16.8 minutes, and confirmed by MS (EI): *m/z* 164(M+2, 31), 162(M+, 100), 127(43), 126(20), 81(18), 77(10), 75(14), 74(11), 68(10), 63(33), 51(44), 50(23).

4.5.2. 4-Bromo-2-chloro-1-methoxybenzene (**2**)[19] The title compound was prepared according to the general procedure. Orange solid. 60% yield (66.5 mg); purification (hexanes:EtOAc = 9:1). R_f = 0.66. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 (d, J = 2.4 Hz, 1H), 7.25 (dd, J_1 = 8.6 Hz, J_2 = 2.4 Hz, 1H), 6.71 (d, J = 8.6 Hz, 1H), 3.81 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.0, 132.3, 130.3, 123.2, 113.0, 112.1, 56.0 ppm. MS (EI): *m/z* 222(M+2, 10), 220(M+, 10), 207(11), 205(11), 63(13), 44(100), 43(23), 40(30).

4.5.3. 4-Bromo-2,6-dichloroaniline (**3**)[19] The title compound was prepared according to the general procedure. Red solid; m.p. 78-82 °C. 86% yield (103.8 mg); purification (hexanes:EtOAc = 80:20). R_f = 0.75. ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.31 (s, 2H), 4.45 (bs, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.4, 130.2, 120.0, 107.9 ppm. MS (EI): *m/z* 243(M+4, 44), 241(M+2, 100), 239(M+, 58), 162(20), 160(32), 124(36), 63(51), 61(54), 52(25).

4.5.4. 3-Chloro-4-hydroxybenzonitrile (**4**)[20] The title compound was prepared according to the general procedure. Pale yellow solid. 55% yield (42.6 mg); purification (hexanes:DCM = 1:2). R_f = 0.05. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (d, J = 2.0 Hz, 1H), 7.50 (dd, J_1 = 8.6 Hz, J_2 = 2.0 Hz, 1H), 7.10 (d, J = 8.2 Hz, 1H), 6.71 (bs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.3, 133.0, 132.8, 120.8, 117.7, 117.2, 105.0 ppm. MS (EI): *m/z* 155(M+2, 33), 153(M+, 100), 89(39), 63(31), 62(47), 53(13), 44(12), 39(12), 38(24), 37(18).

4.5.5. 2-Chloro-4-nitrophenol (**5**)[21] The title compound was prepared according to the general procedure. Red solid; m.p. 108-110 °C. 45% yield (38.9 mg); purification (DCM = 100%). R_f = 0.14. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 2.3 Hz , 1H), 8.13 (dd, J_1 = 9.0 Hz, J_2 = 2.3 Hz, 1H), 7.14 (d, *J* = 9.0 Hz, 1H), 6.19 (bs, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.8, 141.6, 125.3, 124.6, 120.3, 116.3 ppm. MS (EI): *m/z* 175(M+2, 18), 173(M+, 54), 143(45), 107(30), 99(59), 91(35), 79(27), 73(44), 63(100), 62(46), 53(66), 51(41), 39(33), 38(26), 37(22).

4.5.6. 1-(3-Chloro-4-methoxyphenyl)ethan-1-one (**6**)[22] The title compound was prepared according to the general procedure. Pink solid; m.p. 72-74 °C. 56% yield (51.3 mg); purification (hexanes:EtOAc = 1:1). R_f = 0.15. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 (d, *J* = 2.0 Hz, 1H), 7.86 (dd, J_1 = 8.6 Hz, J_2 = 2.0 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 3.96 (s, 3H), 2.55 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 195.7, 158.7, 130.7, 130.6, 128.8, 122.8, 111.2, 56.4, 26.3 ppm. MS (EI): *m/z* 186(M+2, 8), 184(M+, 25), 171(22), 169(100), 141(12), 77(27), 75(11), 63(34), 62(12), 43(41).

4.5.7. 3-Chloro-4-methoxybenzaldehyde (**7**)[21] The title compound was prepared according to the general procedure. Red solid. 56% yield (48.3 mg); purification (hexanes:DCM = 3:1). R_f = 0.51. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.85 (s, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 7.78 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 3.99 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.7, 159.8, 131.2, 130.6, 130.3, 123.7, 111.7, 56.5 ppm. MS (EI): *m/z* 172(M+2, 20), 170(M+, 59), 169(100), 99(24), 75(23), 73(17), 50(19), 63(48), 62(18), 51(15).

4.5.8. 4'-Chloroacetanilide and 2'-chloroacetanilide (**8**)[19, 23] The title compounds were prepared according to the general procedure. *4'-Chloroacetanilide:* Red solid; m.p. 175-178 °C. 69% yield (57.7 mg); purification (hexanes:EtOAc = 80:20). R_f = 0.09. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 2.17 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.3, 136.4, 129.3, 129.0, 121.0, 24.6 ppm. MS (EI): *m/z* 171(M+2, 3), 169(M+, 19), 129(29), 127(96), 65(17), 63(17), 43(100), 39(12). *2'-chloroacetanilide:* Red solid. 20% yield (16.7 mg); purification (hexanes:EtOAc = 80:20). R_f = 0.34. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.36 (d, *J* = 8.2 Hz, 1H), 7.62 (bs, 1H), 7.36 (dd, J_1= 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.27 (m, 1H), 7.04 (t, J_1=J_2= 7.8, 1H), 2.24 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.3, 134.6, 129.0, 127.7, 124.6, 122.5, 121.6, 24.9 ppm. MS (EI): *m/z* 171(M+2, 2), 169(M+, 10), 134(35), 129(27), 127(94), 99(10), 92(15), 65(17), 64(12), 63(19), 43(100), 39(17).

4.5.9. 4-Chloroanisole and 2-chloroanisole (**9**)[24] The title compounds were prepared according to the general procedure in 9:1 para/ortho ratio, according to ^{1}H NMR, and signals were in agreement with reported values. Yield was calculated by ^{1}H NMR integration with nitrobenzene (52 mL, 0.5 mmol, 1 equiv. relative to anisole) added at the beginning of the reaction as internal standard. MS (EI) of *4-chloroanisole*: *m/z* 144(M+2, 33), 142(M+, 100), 127(70), 99(86).

4.5.10. 1-Chloro-2,4-dimethylbenzene (**10**)[25] The title compound was prepared according to the general procedure, and ^{1}H NMR signals were in agreement with reported values. Yield was calculated by ^{1}H NMR integration with nitrobenzene (52 mL, 0.5 mmol, 1 equiv. relative to *m*-xylene) added at the beginning of the reaction as internal standard. MS (EI): *m/z* 142(M+2, 15), 140(M+, 27), 105(100), 79(16), 77(18), 51(36), 39(16).

4.5.11. 1-Chloro-2-methylnaphthalene (**11**)[26] The title compound was prepared according to the general procedure. Pink oil. 80% yield (69.7 mg); purification (100% hexanes). R_f = 0.57. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.59 (m, 1H), 7.49 (m, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 2.60 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 133.4, 133.0, 131.1, 130.6, 128.7, 128.0, 127.0, 126.4, 125.6, 124.1, 20.8 ppm. MS (EI): *m/z* 178(M+2, 16), 176(M+, 50), 141(100), 139(34), 115(25), 70(70).

4.5.12. 5-Chloro-1,3-benzodioxole (**12**)[27] The title compound was prepared according to the general procedure. Clear oil. 93% yield (72.7 mg); purification (hexanes:EtOAc = 90:10). R_f = 0.56. ^{1}H NMR (400 MHz, $CDCl_3$) δ =6.80 (m, 2H), 6.72 (d, *J* = 7.8 Hz, 1H), 5.97 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.3, 146.4, 126.2, 121.3, 109.6, 108.9, 101.7 ppm. MS (EI): *m/z* 157(37), 156(M+, 76), 155(100), 63(99), 62(36), 65(22).

4.5.13. 3,5-Dichloro-4-(N,N-dimethylamino)pyridine (**13**)[28] The title compound was prepared according to the general procedure using 2.2 equiv. of NCS. Yellow oil. 63% yield (50.0 mg); purification (hexanes:EtOAc = 70:30). R_f = 0.62. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (s, 2H), 3.01 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 149.11, 149.08, 128.2, 42.6 ppm. MS (EI): *m/z* 194(M+4, 7), 193(M+3, 12), 192(M+2, 31), 191(M+1, 64), 190(M+, 52), 189(100), 112(21), 59(17), 51(20), 44(19), 42(61).

4.5.14. 4-Chloro-1-phenylpyrazole (**14**)[28] The title compound was prepared according to the general procedure. White solid; m.p. 75-76 °C. 92% yield (82.3 mg); purification (hexanes:EtOAc = 85:15). R_f = 0.53. ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.90 (s, 1H), 7.63 (m, 3H), 7.45 (m, 2H), 7.31 (tt, J_1 = 7.2 Hz, J_2 = 1.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 129.51, 129.49, 127.0, 124.8, 118.9, 112.3 ppm. MS (EI): *m/z* 180(M+2, 29), 178(M+, 91), 152(21), 143(19), 116(27), 115(20), 90(14), 89(32), 77(90), 63(20), 51(100).

4.5.15. 3-Chloro-1H-indazole (**15**)[4b] The title compound was prepared according to the general procedure. Pale yellow solid; m.p. 133-138 °C. 69% yield (26.0 mg); purification (hexanes:EtOAc = 80:20). R_f = 0.36. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.88 (bs, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.46 (m, 1H), 7.25 (m, 1H) ppm. ^{1}H NMR (400 MHz, DMSO) δ = 12.34 (bs, 1H), 6.70 (dt, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 1H), 6.61 (dt, J_1 = 8.2 Hz, J_2 = 1.0, 1H), 6.49 (m, 1H), 6.27 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.4, 135.1, 128.1, 121.7, 120.5, 119.6, 110.4 ppm. ^{13}C NMR (100 MHz, DMSO) δ = 141.2, 132.3, 127.7, 121.6, 119.5, 118.7, 111.1 ppm. MS (EI): *m/z* 154(M+2, 27), 152(M+, 100), 117(40), 90(57), 64(25), 63(42), 62(27), 39(31), 38(24), 37(17).

4.5.16. Ethyl 3-chloro-1H-indole-2-carboxylate (**16**)[28] The title compound was prepared according to the general procedure. Pale yellow solid; m.p. 150-152 °C. 98% yield (110.0 mg); purification (hexanes:EtOAc = 80:20). R_f = 0.47. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 (bs, 1H), 7.72 (dt, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 1H), 7.38 (m, 2H), 7.22 (ddd, J_1 = 8.2 Hz, J_2 = 6.3 Hz, J_3 = 2.0 Hz, 1H), 4.49 (q, *J* = 7.3 Hz, 2H), 1.47 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 134.8, 126.5, 126.2, 122.3, 121.2, 120.2, 112.2, 112.1, 61.5, 14.4 ppm. MS (EI): *m/z* 225(M+2, 10), 223(M+, 29), 179(32), 178(18), 177(100), 149(27), 123(17), 114(26).

4.5.17. 5-Chloro-2-methoxy-3-pyridinecarboxaldehyde (**17**)[19] The title compound was prepared according to the general procedure. Pale yellow solid; m.p. 87-90 °C. 10% yield (8.5 mg); purification (hexanes:EtOAc = 90:10). R_f = 0.54. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.29 (s, 1H), 8.30 (d, *J* = 2.9 Hz, 1H), 8.03 (d, *J* = 2.9 Hz, 1H), 4.05 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 188.0, 162.7, 151.0, 136.8, 125.1, 119.0, 54.4 ppm. MS (EI): *m/z* 173(M+2, 21), 171(M+, 37), 144(34), 143(28), 142(95), 140(17), 127(14), 116(13), 115(21), 114(52), 113(65), 112(30), 111(14), 78(100), 76(46), 73(33), 64(49), 50(53).

4.5.18. 3-Chloro-1H-indole (**18**)[28] The title compound was prepared according to the general procedure. Pale yellow solid; m.p. 87-89 °C. 79% yield (58.9 mg); purification (hexanes:EtOAc = 70:30). R_f = 0.42. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (bs, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.22 (m, 2H), 7.12 (d, *J* = 2.7 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 134.9, 125.3, 123.1, 120.8, 120.5, 118.2, 111.5, 106.5 ppm. MS (EI): *m/z* 153(M+2, 32), 151(M+, 100), 116(23), 89(57), 63(28), 62(22), 58(21), 76(21).

4.5.19. 3-Chloro-1H-indole-5-carboxaldehyde (**19**)[19] The title compound was prepared according to the general procedure. Pale yellow solid; m.p. 134-136 °C. 81% yield (35.8 mg); purification (hexanes:EtOAc = 50:50). R_f = 0.51. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.08 (s, 1H), 8.63 (bs, 1H), 8.18 (d, *J* = 0.8 Hz, 1H), 7.83 (dd, J_1 = 8.6 Hz, J_2 = 2.3 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 7.30 (d, *J* = 2.3 Hz, 1H) ppm. ^{1}H NMR (400 MHz, CD_3OD) δ = 9.97 (s, 1H), 8.11 (dd, J_1 = 1.6 Hz, J_2 = 0.8 Hz, 1H), 7.74 (dd, J_1 = 8.6 Hz, J_2 = 1.6 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.40 (s, 1H) ppm. ^{13}C NMR (100 MHz, CD_3OD) δ = 194.2, 140.2, 131.0, 126.5, 125.0, 124.4, 123.2, 113.7, 108.0 ppm. MS (EI): *m/z* 181(M+2, 28), 180(M+1, 39), 179(M+, 89), 178(100), 152(30), 150(84), 114(28), 89(40), 87(21), 75(22), 63(35), 62(31), 60(21), 57(37).

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6. Supplementary data

The supporting information (^{1}H and ^{13}C NMR spectra) is available free of charge on the Elsevier Tetrahedron website at X.

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Highlights

- The first example of non-metal photo-oxidative activation of N-chlorosuccinimide (NCS) by a visible-light photoredox catalyst.
- The reaction utilizes methylene green, an inexpensive and conspicuously overlooked visible-light photoredox catalyst in the thiazine family of organic dyes.
- Good to excellent yields of chlorinated arenes and heteroarenes using mild reaction conditions (ambient temperature, open to air).
- Wide range of functional group tolerance – a feature important for fine chemical chlorination of complex molecules.