Alkyl halides via visible light mediated dehalogenation

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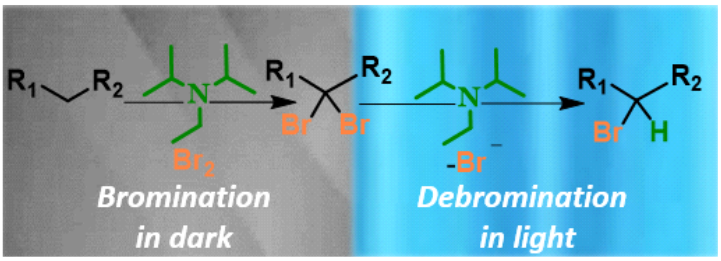
Supporting Information Placeholder

ABSTRACT: Net selective bromination and chlorination of activated C–Hs can be effected in generally high yield via a simple perhalogenation/dehalogenation sequence. The photochemical reductions require no photocatalyst, relying instead on the formation of an electron donor-acceptor complex of the substrate and reductant, or alternatively auto-photocatalysis. Some reactions proceed despite any apparent photon absorption, serving as a cautionary tale for other photochemical reactions involving amines. Mechanistic experiments provide an explanation for this observation.

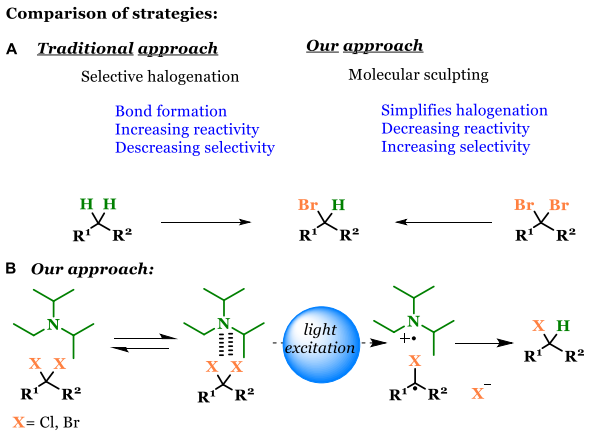


Alkyl bromides and chlorides are found in natural products[1] and play a central role in synthesis.[2] Consequently, efforts have focused on the development of mono-[3] and enantio-[4] selective halogenation. Often the increased reactivity of the products leads to inseparable mixtures un-, mono-, and di-halogenated material. Our group has approached the similar problem of organofluorine synthesis from an alternative direction,[5] sculpting molecules by defluorinating poly- or per-fluorinated molecules to reveal the desired organofluorine. The approach presented herein parallels the work, effectively separating the problems of bond formation and reaction selectivity in the context of organo-bromides and –chlorides (**Scheme 1A**).

The replacement of a halogen by hydrogen is known as hydrodehalogenation, and a number of strategies exist including metal halogen exchange,[6] nucleophilic hydride substitution,[7] atom transfer,[8] or single electron transfer fragmentation.[9] Recently, Stephenson has shown that hydrodehalogenation is possible using a silane via an iridium mediated photocatalysis.[10] While a mild and efficient protocol with broad functional group tolerance, it requires super-stoichiometric amounts of relatively expensive tris(trimethylsilane) in addition to an iridium catalyst which could complicate scaling of the reaction.

Recently, visible light-induced photocatalyst-free organic transformations have received considerable attention.[11] Among these, electron-donor–acceptor (EDA) complex-mediated reactions are particularly intriguing. The diffusion controlled, ground-state association between an electron-rich donor and an electron-poor acceptor, produces an electron donor–acceptor (EDA) complex often characterized by the appearance of a weak absorption band due to charge-transfer from donor to acceptor. In many cases, the energy of this transition lies within the visible range.[12] EDA complexes have been postulated to initiate organic transformations when irradiated by visible light.[13] Though the photophysical properties of EDA complexes have been extensively studied recently,[14] their use in synthetic chemistry has been more limited, though notable examples of their utility exists. They include radical-nucleophilic aromatic substitutions,[15] nitration of substituted benzene compounds,[16] 2-arylation of pyrroles with diaryliodonium salts,[17] intramolecular cyclization α,β-unsaturated lactams, lactones, and cycloalkenones with pendant alkyl iodides,[18] asymmetric α-alkylation of aldehydes with alkyl halides[19] and α-C–H functionalization of tertiary amines.[20]

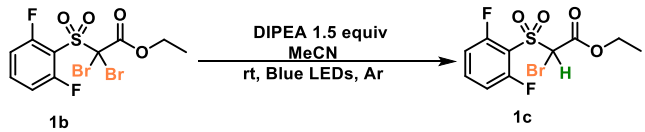
Scheme 1. Conceptual Comparison



Encouraged by the examples of successful reactions mediated by the photochemistry of EDA complexes, we began studying the visible light mediated debromination by *N,N*-diisopropylethylamine (DIPEA) (**Scheme 1B**). We chose α,α-dibromo sulfonyl acetate (**1b**) for optimization of the debromination reaction (**Table 1**). The debromination of **1b** was carried out with 1.5 equiv of DIPEA with blue LED irradiation at room temperature. Initial solvent screening

(entry 2) revealed that dichloromethane, toluene and tetrahydrofuran gave low conversion, while polar solvents (entry 3) facilitated the complete conversion of the reaction with high yield. However, MeCN was found to be the optimal solvent (entry 1) for the debromination. The rate of the reaction did appear to depend on the equivalents of amine (entries 1, 4 and 5) and an increase in the amount of amine led to didebrominated product. Use of 1.5 equiv of amine gave the highest yield for mono-debromination. Exploration of other amines showed diminished reactivity or low yield with triethylamine (entry 6) and DBU (entry 7). As expected, the use of inorganic base, potassium carbonate, did not form any product (entry 8). The reaction did proceed with Hantzsch ester instead of amine, but showed relatively slow conversion (entry 9). Adding water accelerated the reaction (entry 10), but led to undesired didebrominated product. Thus, dry conditions provided higher yields. When the reaction was irradiated with lower energy green light (entry 11) the reaction gave only trace conversion, while higher energy violet light (entry 12) more rapidly gave complete conversion, but also led to didebrominated product, thus we opted to use blue light so as to maintain better control of the product distribution. Control studies demonstrated the necessity of both amine and light (entry 13). The addition of 1.5 equiv TEMPO led to only trace conversion, suggesting the presence of a radical intermediate (entry 14).

Table 1. Optimization of dehalogenation



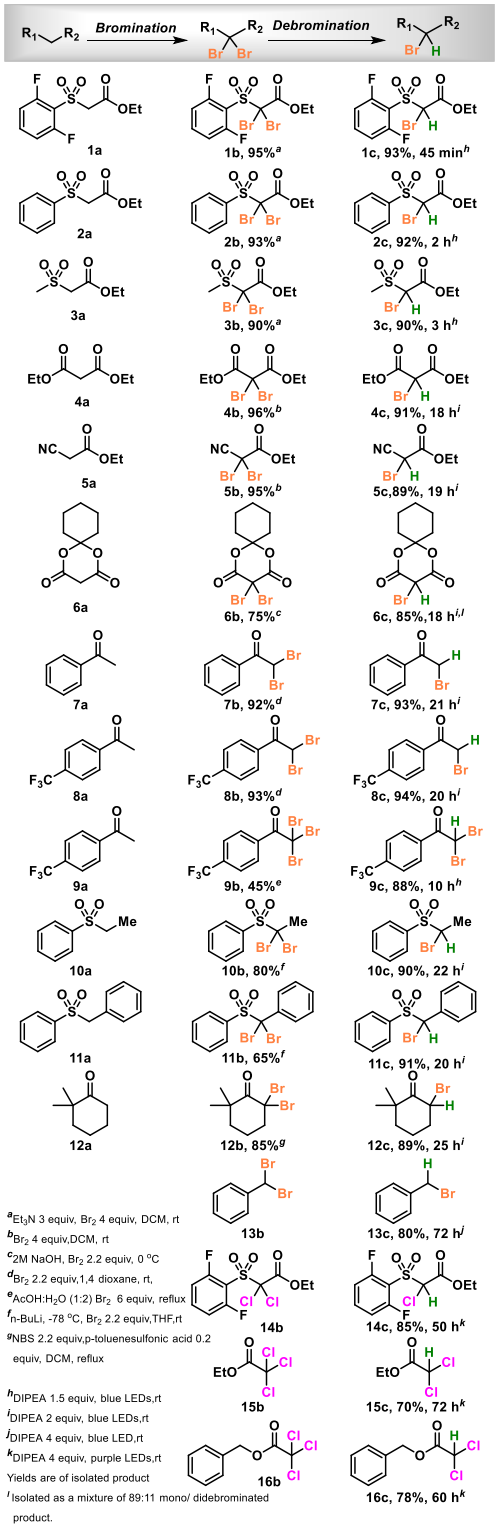
1b 1c

entry	modification	time	conv%[a]	1c%[a]
1	none	45 min	100	96
2	DCM, Tol or THF instead of MeCN	90 min	<39	38-20
3	DMF or DMSO instead of MeCN	60 min	100	85-87[b]
4	1 equiv of DIPEA	73 min	100	90
5	2 equiv of DIPEA	30 min	100	84[b]
6	1.5 equiv of Et_3N instead of DIPEA	90 min	78	75
7	1.5 equiv of DBU instead of DIPEA	90 min	94	75
8	1.5 equiv of K_2CO_3 instead of DIPEA	45 min	0	0
9	1.5 equiv of Hantzsch Ester instead of DIPEA	75 min	63	51
10	3 equiv of water	35 min	100	87[b]
11	Green LEDs instead of Blue LEDs	45 min	5	5
12	Purple LEDs instead of Blue LEDs	30 min	100	89[b]
13	In dark or no DIPEA	45 min	0	0
14	1.5 equiv of TEMPO	45 min	3	3

[a]determined by 19F NMR. [b]formed didebrominated product is 10% or more (see SI).

Having optimized the reaction conditions, we explored the substrate scope (**Scheme 2**). As the first step, we synthesized a series of fully-brominated ketones, esters and sulfones substrates (**1b-12b**). The synthetic utility of our approach hinges on facile perhalogenation, and we show that by using established literature procedures the di- or tri-brominated starting materials can generally be synthesized in high yields.[3h, 21] Next, hydrodebromination was performed. Sulfonyl esters (**1b-3b**) showed complete conversion within a short time period (0.75-2 h) and formed the intended debrominated product (**1c-3c**) in excellent yield. Whereas α-bromo ketones, esters and mono-activated sulfones (**4b-12b**) required longer reaction times and increased DIPEA loading (2 vs. 1.5 equiv) compared to sulfonyl esters, but gave mono-debrominated products in high yield. Furthermore, it is conceivable that enolizable substrate including **7b** & **8b** may undergo debromination via a different mechanism under the reaction condition.[22]

Scheme 2. Molecular sculpting approach to monohalogenation



Dibromotoluene, **13b**, required longer reaction time and higher amine loading, but good conversion was achieved.

Upon further investigation, we found that this protocol was also amenable to the dechlorination of α-chloroketones (**15b**, **16b**) and sulfonyl esters (**14b**). Longer reaction times were found to be necessary to achieve good yields, however. Moreover, the dechlorination reaction took place faster upon switching to higher energy violet LEDs.

During the course of our studies we noticed that a marked yellow color appeared immediately upon mixing ketone **7b** with the DIPEA. We suspected the formation of an EDA complex[23] and that this was responsible for the apparent photochemistry. To gain insight, we performed several UV−Vis spectroscopic experiments. As shown in **Figure 1**, while the UV-Vis spectra of both **7b** and DIPEA in MeCN absorb below 380 nm, the spectrum of a mixture of both components shows a bathochromic shift above 400 nm. The observation of this charge transfer band strongly supports the existence of the EDA complex. The formation of a yellow solution upon mixing of the substrates and DIPEA was generally a good indicator that the reaction would take place via an EDA complex (**7b**, **8b** and **9b**), though for some substrates an EDA complex formed it was not visible (i.e. **13b**). Moreover, following the debromination of **7b** via ^{1}H NMR (**Figure 2, left**) demonstrated the benefit of the additional amine, which gave overall greater formation of the product at a faster rate.

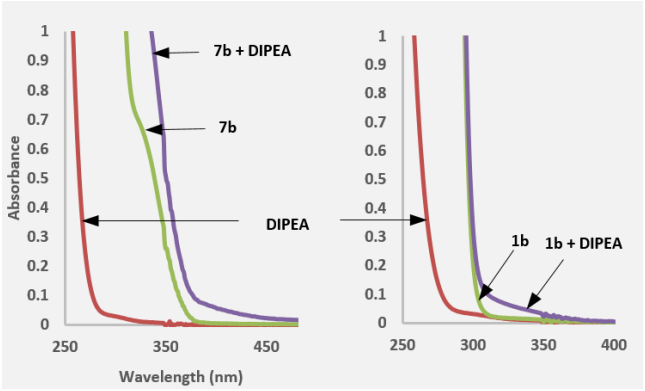


Figure. 1 UV-Vis absorption spectra recorded in MeCN in a 1 cm path quartz cuvettes; [**7b**] = 0.1 M, [DIPEA] = 0.15 M, [**1b**] = 0.1 M.

In stark contrast to ketone **7b**, sulfone **1b** *did not* form any visually detectable EDA complex which was supported by UV-Vis experiments (**Figure 1**, right). Control studies reassured us that this was indeed a photochemical reaction, but by appearances the reaction, in violation of Grotthuss–Draper law, did not absorb a visible photon. As shown in **Figure 1** (right) the absorption of **1b** in MeCN approaches zero near 310 nm but a 1:1.5 mixture of **1b** and DIPEA showed a slight bathochromic displacement but its absorbance too drops off before it reaches the visible region. Following the debromination of **1b** by ^{19}F NMR (**Figure 2**, right) revealed a *sigmoidal* profile. The reaction had a conspicuous lag time in first few minutes. Such a kinetic profile is consistent with autocatalysis.[24]

Furthermore, during the debromination reactions of **1b**, upon irradiation of the reaction mixture with blue light, it was noted that the appearance of the reaction mixture changed from colorless to deep yellow and later to yellowish brown (See inset **Figure 3**). We studied the origin of the prominent color change via UV-Vis spectroscopy.

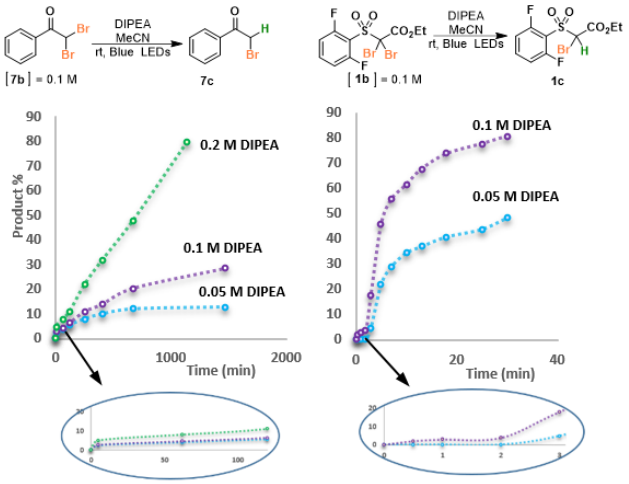


Figure. 2 Photo-reductive debromination of **7b** and **1b** in MeCN solution under blue light with different DIPEA concentrations. Initial concentrations of **7b** = 0.1 M. Percentage of product determined by ^{1}H NMR. Initial concentrations of **1b** = 0.1 M. Percentage of product determined by ^{19}F NMR.

Monitoring the UV-Vis absorption spectra of a reaction mixture taken every 2 min for 32 min during the debromination (**Figure 3,** see SI for details). Initially, only a strong band below 350 nm was noted. But after just 4 minutes had elapsed, new bands started to emerge and became quite prominent after 8 minutes, the solution becoming a deep yellow. Recently, Bach and coworkers[25] noted a similar observation during the intramolecular cyclization of α,β-unsaturated lactams, lactones, and cycloalkenones with pendant alkyl iodides upon irradiation with visible light (λ=419 nm) in the presence of DIPEA. The intensely colored by-products were proposed to be streptocyanine dyes, based on mass spectrometric evidence and comparison with known compounds. Importantly, they were shown to be key to successful reaction.

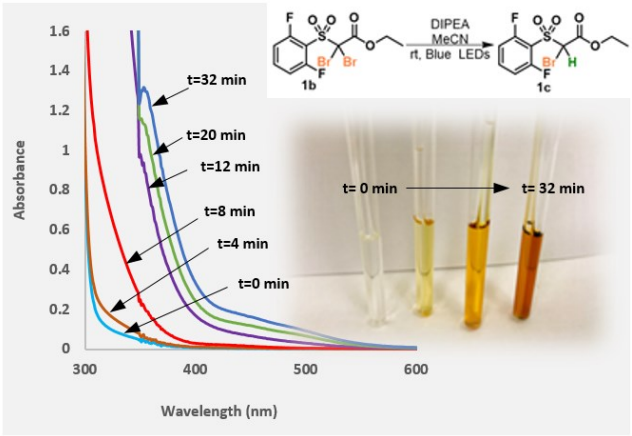


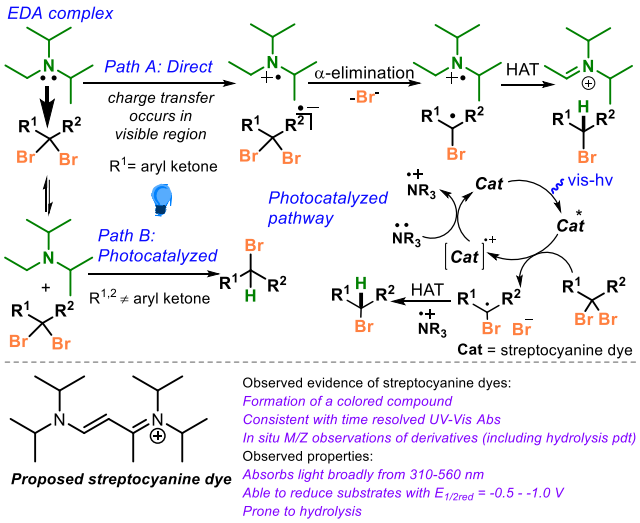
Figure. 3 Time-dependent UV/Vis spectra of debromination reaction of **1b** recorded in MeCN under blue light; [**1b**] = 0.1 M, [DIPEA] = 0.15 M. The reaction was carried out in a 1 cm path quartz cuvette using blue light on a fiber optic cable.

Streptocyanine dyes[26] are part of the family of polymethine dyes.[27] These organic compounds are cationic, contain an odd numbered carbon chain, which terminates in two acyclic nitrogen atoms. When the nitrogen atoms are heterocyclic they are simply called cyanine dyes.[26a, 28] These dyes are potentially formed from the dimerization of amines, conjugating an enamine and an iminium. Depending on the number of conjugated vinyl units, they are

known to absorb photons that can run the energy gamut from the UV to IR region.[25, 29] The cationic nature of the amine makes it ideal for staining cell surfaces for which it is used extensively.[30] Furthermore, they have been used as photocatalysts to excite electrons into the conduction band of titanate complexes.[31] However, to our knowledge they have not been used as catalysts in visible light photocatalysis-at least from the outset of the reaction. The absence of their use in photocatalysis may stem from their tendency to decompose via any number of pathways, including photo,[32] thermal,[32f] and hydrolytic. However, if they can be reliably generated *in situ*, and their reactivity anticipated, they can become another useful tool for the synthetic chemist.

We postulate that a streptocyanine dye of some kind (**Scheme 3**, bottom) is formed under the reaction conditions, and that it is responsible for photoinduced electron transfer to the substrate, generation of a radical anion, subsequent alpha-elimination of the halide and formation of the alkyl radical. The alkyl radical can then undergo hydrogen atom transfer with an amine radical cation. DIPEA reduces the oxidized dye and completes the cycle. Although our attempts to directly characterize the dye failed, we were able to perform several experiments that probed the nature of the active photocatalyst. When the debromination of sulfone **2b** was run to *ca*. 50% conversion, a small aliquot was transferred to a fresh solution involving a different dibromo-substrate (**Scheme 4**, eqn 1). When compared to a control reaction, in which no aliquot from the partially converted reaction had been added, the reaction did not display the aforementioned lag time.

Scheme 3. Proposed mechanism and potential streptocyanine dye

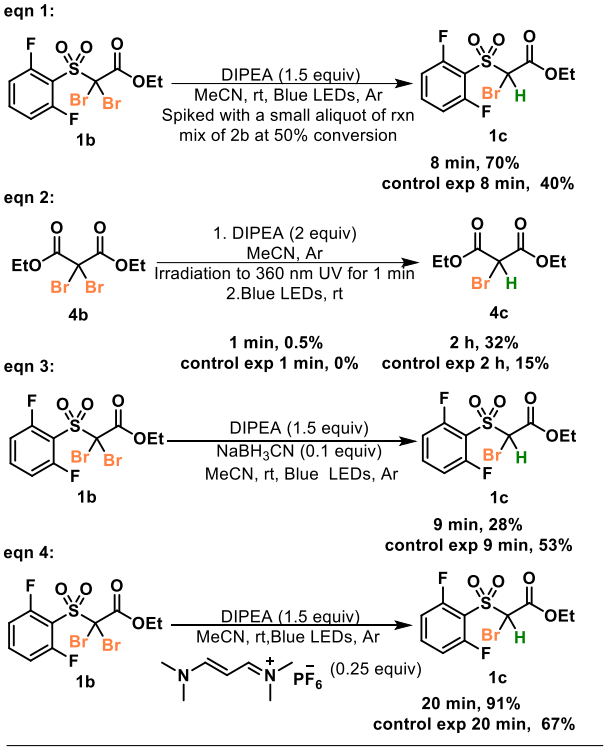


Given that streptocyanine dyes were not present at the beginning of the reaction and therefore could not be the causative agent at the beginning of the reaction, we expected that trace amounts of adventitious UV light might lead to a photoinduced single electron transfer (SET) from the amine to the dibromide substrate and initiate a process that ultimately leads to the formation of a visible light absorbing dye *in situ* that was itself capable of the photoinduced SET and primarily responsible for subsequent visible light mediated hydrodebromination. Consistent with this idea, **Figure 1** (right) displayed an EDA complex, though weak and in the UVA region, between sulfone **1b** and DIPEA. We probed this idea by intentionally subjecting dibromomalonate **4b**, which normally took 18 h to reach completion, to UV-light with a hand-held UV lamp-designed for TLC analysis for just 1 minute and then returned the reaction to the blue LED light bath, we observed that the lag-time could also be avoided (**Scheme 4**, eqn 2).

In another attempt to probe the nature of the active catalyst which we suspected were Streptocyanine dyes, we added 10 mol% sodium cyanoborohydride which we anticipated, and verified, would reduce the iminium but not the sulfone. Indeed, we observed that sodium cyanoborohydride slowed the conversion to the mono-bromide, though it did not stop it completely. (**Scheme 4**, eqn 3). The solution with the sodium cyanoborohydride remained colorless for longer than the control reaction, before eventually coloring. The delayed coloring is consistent with reduction of the conjugated dye.

Using a related commercially available streptocyanine dye, we were able to probe its catalytic ability (**Scheme 4**, eqn 4). Sulfone **2b** was subjected to debromination in the presence of a catalytic amount of the commercial streptocyanine dye, which resulted in a rate enhancement compared with the standard.[33]

Scheme 4. Mechanistic experiments



Conversion determined by ^{19}F NMR of **1c**. Conversion determined by ^{1}H NMR of **4c**.

In conclusion, we have shown that two-step bromination/debromination is a viable approach to bromination, affording valuable building blocks in high yields. We have also shown that the potential for a photochemical reaction should not be assumed based on the presences/absence of an EDA complex, and have provided useable insight into some of the causative agents at work. Given the frequency of the use of tertiary amines in photocatalysis work, care should be taken to ensure that any added photocatalyst is truly the causative agent in respective applications.

ASSOCIATED CONTENT

Supporting Information

Procedures, compound characterization, additional experiments, and spectra (PDF)

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33. For more experiments with streptocyanine dye see SI.