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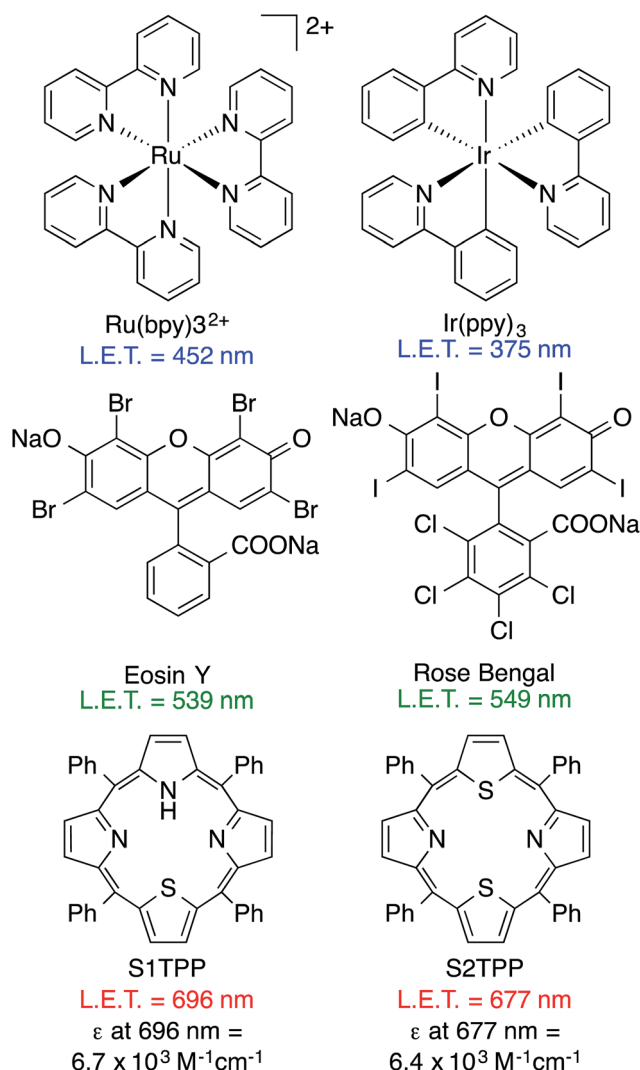
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Thiaporphyrin-mediated photocatalysis using red light†

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Penetration of light through biological tissue improves in the near-IR windows beyond 650 nm. In an effort to explore the chemical reactivity accessible using this low-energy radiation, this study reveals catalysts and reactions that are experimentally viable with red light. Thiophene-containing porphyrin compounds are capable of catalytic, photo-reductive dehalogenation on an array of α -halo ketone model substrates with low catalyst loadings (0.1 mol%), in the presence of low energy, red light (>645 nm).

Photo-mediated reactions have reemerged in synthetic chemistry as powerful tools to form and break chemical bonds.¹ With major advances in the field, most light-mediated synthetic chemistry utilizes high energy blue or green light (375–570 nm). Recent developments in proximity-directed chemistry and photochemical release or activation of bioactive molecules, have validated the approach of using light to probe and interact with biological systems.^{2,3} The most commonly used photocatalysts in the field are ruthenium and iridium based polypyridyl complexes which absorb photons in the blue region of the visible spectrum (Fig. 1).^{4–6} Organic dyes such as eosin Y⁷ and rose bengal, which absorb in the green region, have also been reported in literature to be used as photocatalysts and show significant promise for synthetic applications.^{8,9} After identification of the synthetically tunable, thiophene-containing porphyrin scaffold, we decided to explore the photoreductive properties of *meso*-5,10,15,20-tetraphenyl-21-monothiaporphyrin (S1TPP), and 5,10,15,20-tetraphenyl-21,23-dithiaporphyrin (S2TPP) due to their absorbance properties at wavelengths beyond 650 nm and moderate excited state reduction potentials (−0.586 to −0.741 eV).^{10–13} Recent reports have also shown that S2TPP-related compounds, together with oxygen, have potential as light-activatable drug delivery systems

Fig. 1 Absorption properties of commonly used photocatalysts.⁸

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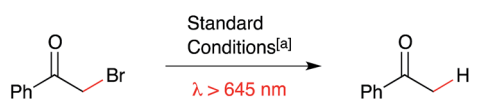
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using 'photo-unclick' chemistry.¹⁴ Based on our interest in exploring low-energy light reactivity within biological microenvironments, it was necessary to complete a model study on the reductive, bond-cleaving reactions that can occur using thiophene-containing porphyrins.

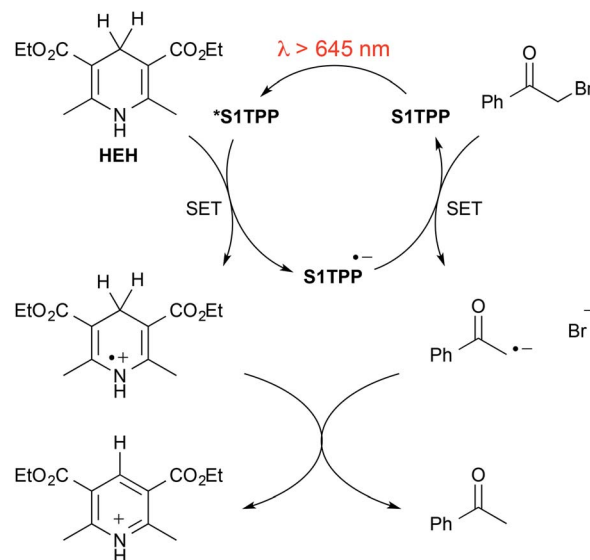
We selected dehalogenation as a model system for exploring the use of red light for metal-free, photoreductive catalysis (Table 1). It was observed that alone, Ru(bpy)₃Cl₂ had very low reactivity under long wavelength light (entry 1). Combining Hantzsch ester (HEH) and Ru(bpy)₃Cl₂ provided a modest increase in yield (entry 2) above the reactivity of HEH without catalyst (entry 3).¹⁵ The addition of *N,N*-diisopropylethylamine (DIPEA) ensured consistent pH levels in the optimization reactions. Omission of catalyst and HEH resulted in a very low level of background dehalogenation (entry 4). In the absence of catalyst and base, the background reactivity of HEH was observed (entry 5). We immediately observed improved dehalogenation reactivity for S1TPP and S2TPP beyond reactions using Ru(bpy)₃Cl₂ at 0.1 mol% loading (entry 6,7). DIPEA plays a role in effective photocatalysis as reactions with only catalyst and HEH resulted in a decrease in yield (entry 8, 9). In combination with HEH, and base, yields of thiophene-mediated red light dehalogenation improved dramatically (entry 10, 11). Alternative bases triethyl- and tributyl amine were less effective than DIPEA (entry 12, 13) while the biomimetic NADH analog, 1-benzyl-1,4-dihydronicotinamide (BNAH), was the only alternate hydrogen atom source that provided effective reactivity – formic acid was ineffective in the reaction conditions (entry 14,15). To explore the possibility of a radical chain reaction-type mechanism, the reaction yield for bromoacetophenone under standard conditions was determined after 5 minutes of red-light

irradiation (25% yield) that remained unchanged after an additional 17 hours in the dark (data not shown). Using the same model system, the addition of 5 eq. of TEMPO resulted in consumption of the Hantzsch ester and complete recovery of bromoacetophenone after 1 h. These results are not consistent with a radical chain reaction but instead support a typical photo-catalytic mechanism mediated by a hydrogen atom transfer agent^{1e} (Scheme 1). Note that the dehalogenation model reaction of bromoacetophenone is complete within 1 h (73%) under the standard reaction conditions and is unaffected by the addition of 1 equivalent of water (74%). With the intent of reaching a balance between practicality and product yield, we selected a standard reaction time of 18 h to ensure low levels of substrate reactivity were not overlooked. Building on these preliminary results, we investigated the substrate scope on an array of α -functionalized carbonyl-containing compounds (Table 2). The influence of steric hindrance on dehalogenation efficiency for the thiophene-containing catalysts was evident based on decreasing isolated yields due to lower conversion and reduced reaction rates (entries 1–6). This analysis also revealed a trend that when S2TPP was used as the catalyst, isolated yields were consistently lower than S1TPP (40–60% vs. 75–90% respectively). These differences in reactivity are attributed to the stronger reduction potential,¹⁰ and marginally better solubility properties, of S1TPP. With reliably better yields, S1TPP was selected for further evaluation. Other halogens were also evaluated for reactivity under the optimized red-light conditions (entry 7, 8). Although chloroacetophenone showed some reactivity in the red-light optimized conditions, the rate of reaction and corresponding conversion are considerably lower than for bromoacetophenone. Similarly, the more labile iodoacetophenone reacted quantitatively, clearly demonstrating the effect of substrate bond-strength on the catalytic reactivity. No reactivity was observed on analogous ester or amide-derived substrates (entry 9, 10). Notably, under the standard reaction conditions,

Table 1 Catalyst and reaction optimization

				
Entry	Catalyst	Base	H-Atom source	Yield [%] ^b
1	Ru(bpy) ₃ Cl ₂	DIPEA	None	3
2	Ru(bpy) ₃ Cl ₂ ^a	DIPEA	HEH	18
3	No catalyst	DIPEA	HEH	13
4	No catalyst	DIPEA	None	3
5	No catalyst	None	HEH	21
6	S1TPP	DIPEA	None	26
7	S2TPP	DIPEA	None	25
8	S1TPP	None	HEH	13
9	S2TPP	None	HEH	10
10	S1TPP ^a	DIPEA	HEH	75
11	S2TPP ^a	DIPEA	HEH	72
12	S1TPP	Et ₃ N	HEH	45
13	S1TPP	Bu ₃ N	HEH	45
14	S1TPP	DIPEA	HCO ₂ H	2
15	S1TPP	DIPEA	BNAH	58

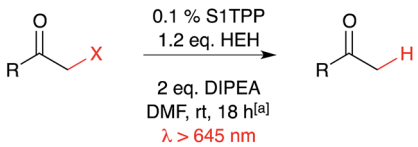
^a Standard conditions: 0.1 mol% catalyst, 1.1 eq. Hantzsch ester (HEH), 2 eq. DIPEA, DMF, 18 h, rt. ^b Yield determined through analysis with GC-MS.



Scheme 1 Proposed mechanism adapted from MacMillan and coworkers.^{1e} HEH = Hantzsch ester, SET = single electron transfer.



Table 2 Study of reaction scope for isolated yields on 1 mmol scale



Entry	Substrate	Product	% yield	Entry	Substrate	Product	% yield	Entry	Substrate	Product	% yield
1			90	7			12	13			86
2			78	8			Quant	14			85
3			75	9			NR	15			76
4 ^b			60	10			NR	16			80
5 ^b			60	11			16 ^c	17			92
6 ^b			40	12			40	18			98

^a Yield of purified product on 1 mmol scale. ^b S2TPP used as catalyst. ^c Yield determined through GC-MS analysis due to volatility of product. NR = no reaction, adam = adamantyl, biphenyl = 1-(1,1'-biphenyl)-4-yl.

alkyl halo-ketones (entry 11, 12), also displayed modest conversion to the corresponding methyl ketones. There appears to be no inherent correlation between electronic effects of substituents as the overall yield is comparable for electron donating or withdrawing substituents (entry 13, 14). Aryl-bromides and nitriles remain compatible with the reaction conditions (entry 15, 16). The position of aryl functional groups and the effect of extended conjugation on reactivity were also explored (entry 17, 18). No by-products were detected during the course of our investigations, highlighting the advantage of using low energy photons for chemoselective bond cleavage. We have shown that thiophene-containing porphyrin catalysts are capable of directly catalyzing a modest scope of photo-reductive dehalogenation reactions using low energy red light above 645 nm. In contrast to many other photocatalytic dehalogenation reactions, this method does not require expensive transition metal catalysts for these dehalogenations to occur. Given the success of red-light mediated methods emerging in the recent literature, the further exploration of thiophene-based porphyrins for chemoselective light-mediated reactivity is warranted. We have optimized a reaction methodology that is capable of

photochemically altering chemical bonds using light beyond 645 nm, deep into the red wavelengths of light. Further investigations toward expanding the substrate scope, and exploring chemoselectivity of the modified thiophene-containing porphyrins are currently underway.

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- 15 M. Neumann, S. Földner, B. König and K. Zietler, *Angew. Chem., Int. Ed.*, 2011, **50**, 951.
- 16 To a solution of α -haloketone (1 mmol) in DMF (5 mL), HEH (279 mg, 1.1 equiv.), DIPEA (0.35 mL, 2 equiv.), and S1TPP, S2TPP, or Ru(bpy)₃Cl₂ (0.1 mol%) were added under stirring. The reaction vessel was kept in the dark until irradiation with red light. After 18 h of irradiation, the reaction mixture was diluted with water (8 mL) and extracted with Et₂O (3 \times 8 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to give pure product. All reactions reported at rt remained at a temperature of 22 $^{\circ}$ C \pm 2 $^{\circ}$ C over the course of the reaction.

