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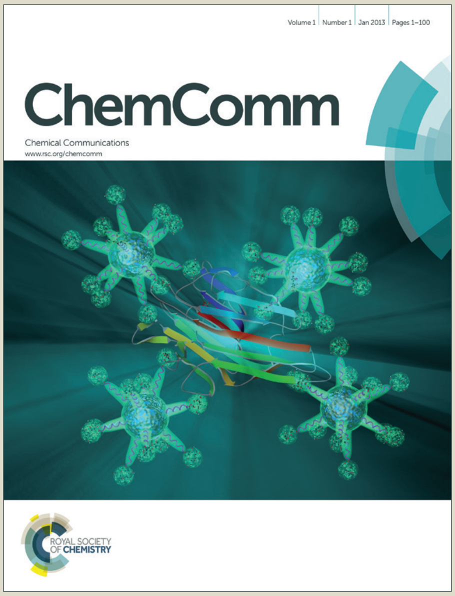

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A Highly Reducing Metal-free Photoredox Catalyst: Design and Application in Radical Dehalogenations

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Here we report the use of 10-phenylphenothiazine (PTH) as an inexpensive, highly reducing metal-free photocatalyst for the reduction of carbon-halogen bonds via the trapping of carbon-centered radical intermediates with a mild hydrogen atom donor. Dehalogenations were carried out on various substrates with excellent yields at room temperature in the presence of air.

In recent years, photoredox chemistry has enabled the development of a wide variety of synthetic transformations.[1] These methods are based on photocatalysts which, upon absorption of light, enter either a highly reducing or oxidizing excited state capable of facilitating redox-based transformations. In particular, the reduction of activated carbon-halide (C–X) bonds has generated wide interest, largely because of the broad synthetic utility of resulting carbon-centered radical intermediates.[1-10] One example includes subsequent trapping of these intermediates with a mild H-atom source to achieve radical dehalogenations.[3,5,6,9] In this case, the power of using a photoredox approach is that it offers a more efficient and safer alternative to traditional dehalogenation protocols involving metal-halogen exchange,[11,12] stoichiometric tin hydride,[13] and various other highly toxic reagents.[14-16] However, despite the notable advantages of photoredox catalysis,[1] a number of major challenges still exist. This includes the use of catalysts based on rare-earth transition metals such as Ru and Ir, which have inherent limitations due to the cost of the catalyst itself (~$1/mg for Ir(ppy)$_3$),[17] as well as the expense associated with the removal of trace metals from the desired products - critical for applications from pharmaceuticals to micro-electronics. In addition, although an assortment of activated carbon-halogen bonds have been accessed using these catalysts,[1] higher energy unactivated halides are a significantly more challenging task, with only unactivated iodides being explored to date.[10] To this end, a more affordable gold-based photocatalyst has been developed,[10] and although offering broader substrate scope, the disadvantages of metal-based systems remain. In addressing this, the use of an organic perylene diimide (PDI)-based photocatalyst was recently reported, and while providing a metal-free alternative, it requires elevated temperatures and has a scope limited to activated aryl-halides.[8] In this context, we envisioned the development of a highly reducing, inexpensive, metal-free photocatalyst that could offer access to a wide range of carbon-halogen substrates under markedly mild conditions (Figure 1).

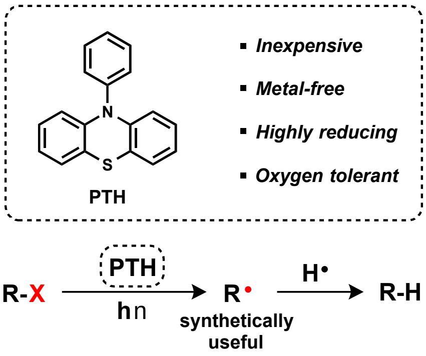

Fig. 1 Properties and application of 10-phenylphenothiazine (PTH)

Our group previously employed 10-phenylphenothiazine (PTH) as a metal-free catalyst for photomediated atom transfer radical polymerizations (ATRP).[19] In this system, PTH acts as a photoreductant in a similar manner to Ir(ppy)$_3$ with a reduction potential ($E^*_{1/2}$ = - 2.1 V vs. SCE) significantly higher than Ir(ppy)$_3$ ($E^*_{1/2}$ = -1.7 V vs. SCE). Based on our interest in metal-free ATRP, we envisioned that the same radical based processes enabled by PTH could also be used to access a variety of carbon-centered radical intermediates that could be used for subsequent synthetic transformations, such as the reduction of carbon-halogen bonds. Highlighted by the use of mild reagents and a readily accessible light source, coupled with its high degree of oxygen tolerance, we believe this no

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x metal-free system will serve as a platform for expanding the synthetic utility of photoredox chemistry.

The initial test system chosen for investigation was the reduction of iodobenzene, employing PTH as the photocatalyst. After optimization (Tables S1-3), quantitative reduction of iodobenzene (**1**) to benzene (98 % yield) could be achieved in 1 h under 380 nm LED irradiation (Table 1) in the presence of 5 mol % PTH and 5 equivalents each of tributylamine and formic acid. It is worth noting that although we utilize higher catalyst loadings than traditional metal-based photoredox systems such as Ir(ppy)$_3$, calculations based on a cost per reaction basis illustrate that 5 mol% PTH is still over an order of magnitude cheaper than using 0.01 mol% of rare-earth derived Ir(ppy)$_3$ (see SI). Significantly, the reaction was compatible with a range of solvents as well as amine sources leading to similar yields and reaction rates. Notably, quantitative reduction could also be achieved with catalyst loadings as low as 0.5 mol %, albeit at a slower reaction rate. Full conversion of iodobenzene was also observed using visible light sources, such as 25 W CFLs and blue LEDs (Table S1 and S3). This demonstrates the inherent flexibility of PTH as a photoredox catalyst platform, which was further enhanced by the use of a commercially available N-Me phenothiazine derivative for the successful reduction of iodobenzene (see SI).

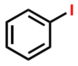
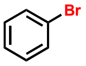
To validate PTH as an organic photoredox catalyst, a series of control experiments in the absence of light, catalyst, or amine were conducted. In each case, no reaction was observed (Table S2). We next sought to compare the performance of PTH with widely used photoredox systems such as Ir(ppy)$_3$, as well as the metal-free PDI based system, and in both cases we observed higher reactivity.[20] For example, only 23 % yield was obtained after 1 h for the reduction of iodobenzene using Ir(ppy)$_3$ when compared to the quantitative reduction observed for PTH (Table 1). [21] It is worth noting that the 380 nm LED light source matches the excitation maximum of Ir(ppy)$_3$ (378 nm),[1] while the absorption spectrum of PTH has only a small shoulder at this wavelength (Figure S2). However, this does not appear to hinder reactivity. Similarly, comparison of the perylene diimide-based photocatalyst also showed no reduction of iodobenzene after 1 h.

This increased performance encouraged the examination of PTH as a photocatalyst for the reduction of more challenging unactivated brominated substrates, which to date has not been accessible using a metal-free photoredox system. Significantly, bromobenzene was successfully reduced in 85 % yield after 72 h (by comparison, no reaction was observed after 72 h using Ir(ppy)$_3$ or PDI). These results nicely demonstrate that the higher-energy excited state reduction potential of PTH is necessary to activate more challenging C-Br bonds (E^{red} = -2.05 to -2.57).[22,23]

With a general protocol in place, we next set out to demonstrate the broad applicability of PTH as a photoredox catalyst for a library of aryl iodides and bromides including unactivated, or even deactivated derivatives (Table 2). Excellent activity was observed with compounds containing electron-rich substituents such as **3**, **4**, and **5** being dehalogenated in high yields. Additionally, achieving high fidelity reduction of substrates **4**, **6**, and **7** exemplifies the mildness of our protocol and its tolerance across many different functional groups including acids, phenolic alcohols and amines. A range of more challenging aryl bromides (**8**–18) were then examined, with near quantitative conversion to the dehalogenated product being observed for substrates **8–11**. Extension to more synthetically interesting heterocyclic aryl bromides was also observed with excellent yields being obtained for brominated pyridine (**13**), benzothiazole (**14**), and thiophene systems (**15–16**). Particularly noteworthy was the application of PTH for the reduction of primary alkyl bromides (**17–18**), and even electron-rich aryl bromides like 4-bromophenol (**12**) could be reduced in good yield. The use of one set of conditions for the reduction of both unactivated alkyl and aryl bromides further demonstrates the synthetic versatility of PTH-based organic photoredox catalysts.

Table 1 Comparison of reduction capabilities of Ir(ppy)$_3$, PDI with PTH for the reduction of iodo- and bromobenzene.[a]

$$\textbf{Ph-X} \xrightarrow[h\nu\textbf{, conditions}]{\textbf{Photocatalyst}} \textbf{Ph-H}$$

Substrate	Time	Photocatalyst	Yield
 **1**	1 h	PTH	98 %
		Ir(ppy)$_3$	23 %
		PDI	0 %
 **2**	72 h	PTH	85 %
		Ir(ppy)$_3$	0 %
		PDI	0 %

[a] Reaction conditions using PTH and Ir(ppy)$_3$: Iodo- or bromobenzene (1 equiv.), PTH (5 mol %) or Ir(ppy)$_3$ (1 mol %),[20] formic acid (5 equiv.) and tributylamine (5 equiv.), acetonitrile (0.02 M of substrate) at RT with irradiation by 380 nm LEDs (1.8 μW/cm^2). ^{1}H NMR yield determined using 1,3,5-trimethoxybenzene or 1,2,4,5-tetramethylbenzene as internal standard. Reaction conditions using PDI: Iodo- or bromobenzene (1 equiv.), PDI (5 mol %), triethylamine (8 equiv), dimethylformamide (0.02 M of substrate) at 40 °C with irradiation from 465 nm LEDs (5 μW/cm^2). ^{1}H NMR yield determined using 1,2,4,5-tetramethylbenzene as internal standard.

Encouraged by the successful reduction of a wide range of C–Br bonds, we next explored the reduction of activated aryl chlorides. After 24 h of irradiation time in the presence of PTH, benzyl 4-chlorobenzoate was successfully reduced, with the desired product being isolated in 83% yield. A variety of other activated aryl chlorides were subsequently examined with methyl benzoate, benzonitrile, and benzoic acid derivatives undergoing dechlorination in good yields (**20–22**).

With a broad substrate scope and the potential of this metal-free photoredox system established, the physical aspects of PTH were studied in more detail, in particular the high excited state reduction potential, given by:

$$E^*_{1/2} = E_{1/2}^{ox} - hc / \lambda_{max}$$

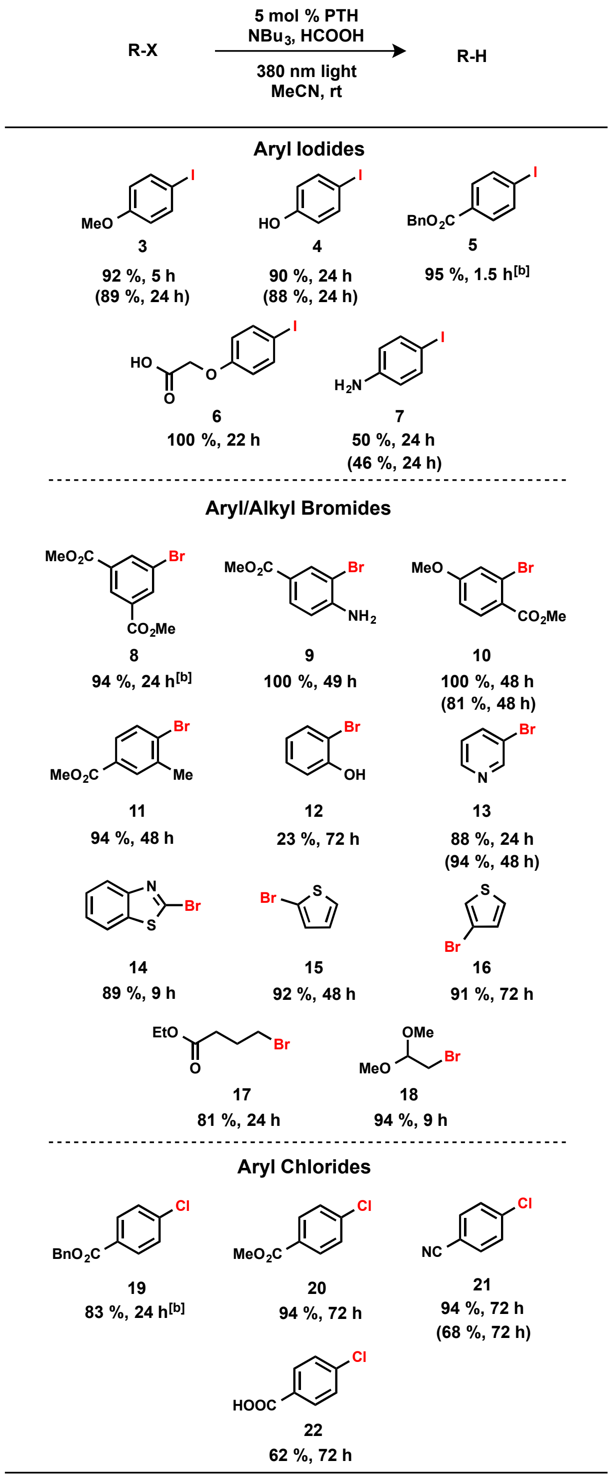
where $E^*_{1/2}$ is the excited state reduction potential, $E_{1/2}^{ox}$ is the ground state oxidation potential, *h* is Planck's constant, *c* is the speed of light and λ_{max} is the photoluminescence maximum.[24] While the ground state oxidation potential of PTH ($E_{1/2}^{ox}$ = 0.68 vs. SCE)[19] is only slightly lower than that of $Ir(ppy)_3$ ($E_{1/2}^{ox}$ = 0.77 V vs. SCE), the photoluminescence maximum of PTH (λ_{max} = 445 nm, Figure S3) is significantly lower ($Ir(ppy)_3$ λ_{max} = 500 nm).[1] In contrast to the triplet emission of $Ir(ppy)_3$, the higher-energy emission from PTH is the result of fluorescence from the singlet state, with an observed lifetime of < 3 ns (see SI). To confirm, we measured the energy of the triplet excited state of PTH at 77 K, and under these conditions it more closely resembled the energy of $Ir(ppy)_3$ (λ_{max} = 510 nm). This implies that the increased excited state energy of the singlet is the primary origin of PTH's ability to access higher energy bonds.

To probe whether the singlet excited state of PTH could be responsible for the catalysis in this system, the reduction of iodobenzene was performed open to air, with oxygen acting as a potent triplet quencher.[7] Under these conditions, where triplet pathways should be inhibited, a 57 % yield was observed after 2 h, suggesting that the singlet state may be the primary mode of catalysis. Further, the reaction proceeded to 90 % yield within 15 h with only a moderate decrease in reaction rate being observed. Encouraged by these results, we further examined the oxygen tolerance of PTH with a range of substrates from each aryl halide class. Significantly, a variety of aryl iodides (**3-4**, **7**), bromides (**10**, **13**), and chlorides (**21**) could be successfully dehalogenated in moderate to good yields (Table 2), confirming the oxygen tolerance of PTH with yields being similar in all cases to those obtained for carefully deoxygenated solutions, suggesting new opportunities previously unavailable with traditional photocatalysis.

After observing reactivity in the presence of air, this phenomenon was further probed by the use of a PTH-based catalyst functionalized with a triplet-sensitizing moiety (Figure S3). In this case, conjugation with benzophenone, a well-known triplet sensitizer, was expected to greatly increase the rate of intersystem crossing leading to an exclusive, triplet state excited catalyst, PTH-BP. Photoluminescence spectra were obtained both at room temperature and 77 K with luminescence observed only at 77 K, indicating that fluorescence from the singlet state had been completely deactivated (Figures S6-7). Moreover, the use of PTH-BP for the reduction of iodobenzene under our optimized conditions resulted in no reaction, suggesting that the singlet state is necessary for catalysis.[25]

To illustrate the scalability and practical nature of PTH as an organic photoredox catalyst, we then conducted a multigram-scale reaction in the presence of air (Scheme 2). We envisioned a very rudimentary experimental set-up with no precautions taken to ensure an air or moisture-free environment. Using a 125-mL Erlenmeyer flask, we scaled up our general conditions by 7000 % using benzyl 4-iodobenzoate as our substrate, and observed 98 % conversion by ^1H NMR after 20 h. The reaction was purified by column chromatography to yield the desired product in 87 % yield

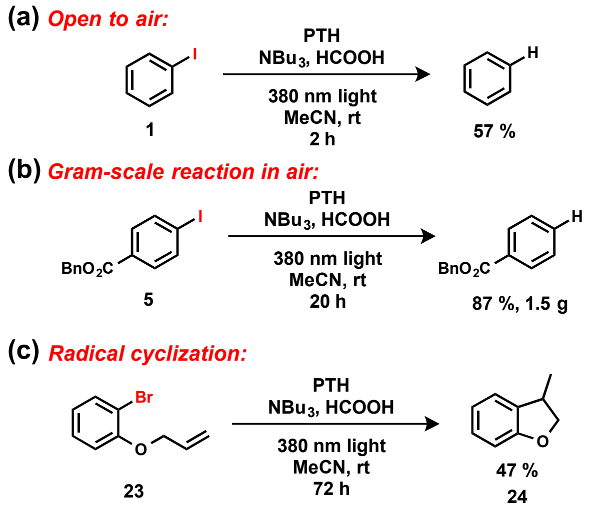
Table 2 Substrate scope of reductive dehalogenations of iodides, bromides, and chlorides using PTH.[a]



[a] Reaction conditions: substrate (1 equiv.), PTH (5 mol %), formi acid (5 equiv.), tributylamine (5 equiv.), acetonitrile (0.08 M substrate) at RT with irradiation by 380 nm LEDs. ^1H NMR yield determined using 1,3,5-trimethoxybenzene or 1,2,4,-tetramethylbenzene as internal standard. Yields and times in parentheses were run in the presence of air. [b] isolated yields ru on 0.2 mmol scale.

(1.5 g), demonstrating both the scalability and robustness of our protocol. Further, during the course of purification, we were also able to isolate the PTH catalyst used in the reaction. This catalyst sample was then re-used in the reduction of **5**, and quantitative conversion to the desired product was observed after 1.5 h, again highlighting the simplicity and inherent robustness of PTH.

Scheme 1 a) Reaction in the presence of air (triplet quencher) proceeds b) Preparative scale reaction conducted without degassing demonstrates modularity and scalability c) Cyclization suggests radical mechanism.



Additional, mechanistic experiments were conducted providing strong evidence of an oxidative-quenching cycle with deuterium studies supporting the primary source of hydrogen atoms being the tributylamine (For in-depth discussion see SI and Scheme S1). Furthermore, evidence of a radical-based mechanism was obtained via a successful radical cyclization of substrate **23** (Scheme 1b). The desired product **24** was obtained in 47 % yield, providing strong support for the reaction proceeding via a radical process, as well as preliminary evidence illustrating that generated radical intermediates can be used for carbon–carbon bond forming reactions.

In conclusion, we have developed a highly reducing, organic photocatalytic platform with broad applicability for the generation of carbon-centered radical intermediates on route to efficient dehalogenations of aryl and alkyl iodides, bromide and chlorides. In addition to offering an inexpensive, metal-free alternative to current halide reductions, this approach is highlighted by a robust and facile nature with high yields being obtained even in the presence of air. Moreover, in contrast to classic photoredox systems, preliminary evidence suggests that PTH is primarily operating through the singlet state. Further investigations regarding the mechanism, the tunability of the catalyst, and its potential to open doors for new organic bond forming transformations are currently in progress.

Acknowledgements

We thank the MRSEC program of the National Science Foundation (DMR 1121053, C.J.H., J.R.A.) and The Dow Chemical Company through the Dow Materials Institute at UCSB (N.J.T., E.H.D., K.M.. , S.O.P., Y.L., C.J.H., J.R.A.) for financial support. N.J.T., E.H.D., an K.M.M. thank the NSF Graduate Research Fellowship for fundin and Z.M.H. acknowledges the California NanoSystems Institute for an Elings Prize Fellowship in Experimental Science.

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