# Engaging unactivated alkyl, alkenyl and aryl iodides in visible-light-mediated free radical reactions

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Radical reactions are a powerful class of chemical transformations. However, the formation of radical species to initiate these reactions has often required the use of stoichiometric amounts of toxic reagents, such as tributyltin hydride. Recently, the use of visible-light-mediated photoredox catalysis to generate radical species has become popular, but the scope of these radical precursors has been limited. Here, we describe the identification of reaction conditions under which photocatalysts such as fac-Ir(ppy)<sub>3</sub> can be utilized to form radicals from unactivated alkyl, alkenyl and aryl iodides. The generated radicals undergo reduction via hydrogen atom abstraction or reductive cyclization. The reaction protocol utilizes only inexpensive reagents, occurs under mild reaction conditions, and shows exceptional functional group tolerance. Reaction efficiency is maintained upon scale-up and decreased catalyst loading, and the reaction time can be significantly shortened when the reaction is performed in a flow reactor.

onventional methods for reducing alkyl, alkenyl and aryl iodide bonds1 consist of metal-halogen exchange, a hydride source or radical reductive dehalogenation. Reductions utilizing metal-halogen exchange<sup>2,3</sup> or a hydride source<sup>4</sup> commonly result in undesired side reactions, and are not functional group tolerant. This has led to the development of alternative methods that can be applied to the reductive dehalogenation of aryl halides and  $\alpha$ -halo carbonyls<sup>5</sup>. Radical reductive dehalogenation is by far the most commonly utilized method for the reduction of carbonhalogen bonds because the reaction conditions are typically mild and pH-neutral; reactions times are short; and product yields are relatively high<sup>1</sup>. These characteristics have allowed radical chemistry to be used effectively for challenging bond constructions, such as those performed in the syntheses of hirsutene<sup>6</sup>, amauromine<sup>7</sup> and (+)-11,11'-dideoxyverticillin A (ref. 8). However, the radical initiator or hydrogen atom donor is typically toxic (for example, organotin)9, potentially explosive (azobisisobutyronitrile (AIBN) and peroxides)<sup>10</sup>, unstable to air (samarium(II) iodide)<sup>11</sup> or pyrophoric (trialkylboranes)<sup>12,13</sup>. In an attempt to avoid the toxicity associated with tributyltin hydride, other hydrogen atom donors have been used, such as 1,4-cyclohexadiene, triethylsilane, tris(trimethylsilyl)silane, triphenylgermane, thiols and diphenylphosphine, but these are less efficient, unstable and/or expensive.

Recent efforts have been made to improve the process of radical reductive dehalogenation through replacement of the radical initiator and the development of new hydrogen atom donors. The ground-state neutral electron donors used by Murphy<sup>14,15</sup> and the alkyland stannyl-cobaloxime catalysts developed by Careirra<sup>16</sup> have successfully generated alkyl radicals from alkyl iodides. In addition, several new hydrogen atom donors have been introduced, such as *N*-heterocyclic carbene boranes<sup>17</sup> and water in the presence of  $Et_3B^{18}$  or Ti(III) salts<sup>19</sup>. Ultimately, the goal is to develop a mild and efficient radical reductive deiodination protocol with broad functional group tolerance that utilizes an easy-to-handle catalyst and an inexpensive and readily accessible hydrogen atom donor. Herein, we report the use of the photocatalyst *fac*-tris[2-phenylpyr-idinato-C<sup>2</sup>,N]iridium(III) (*fac*-Ir(ppy)<sub>3</sub>) and tributylamine in combination with Hantzsch ester or formic acid to perform both reductive deiodination and intramolecular cyclization of alkyl, alkenyl and aryl iodides.

During the last decade, several groups have demonstrated the versatility of metal-based and organic photocatalysts<sup>20</sup> to carry out a variety of transformations<sup>21</sup>, with beneficial applications in total synthesis<sup>22</sup>. A large number of these reactions involve the generation of radical intermediates from activated carbon-halogen bonds, including bromomalonates<sup>23–25</sup>, polyhalomethanes<sup>26–28</sup>, electron-deficient benzyl bromides<sup>29</sup>,  $\alpha$ -halo carbonyls<sup>30,31</sup> and glycosyl bromides<sup>32</sup>. A major advantage of metal-based photocatalysts, such as  $[Ir{dF(CF_3)ppy}_2(dtbbpy)]PF_6$  (1)<sup>33</sup>, Ru(bpy)<sub>3</sub>Cl<sub>2</sub> (2)<sup>34</sup>,  $Ir(dtbbpy)(ppy)_2PF_6$  (3) and fac- $Ir(ppy)_3$  (4)<sup>35,36</sup> is the ease of tuning the complex to achieve desired redox potentials through modification of the ligands or replacement of the metal centre (Fig. 1a)<sup>37</sup>. These photocatalysts are capable of radical reductive cleavage of carbon-halogen bonds by direct reduction from the excited state of the catalyst (oxidative quenching) or via two single electron transfer (SET) processes, where the excited state is reduced by a sacrificial electron donor followed by reduction of the carbon-halogen bond (reductive quenching).

Our work in the field of visible-light-mediated photoredox catalysis has demonstrated the advantages in modifying metalbased photocatalysts to achieve transformations initiated by SETs. In previous studies, we observed the intramolecular cyclization of bromomalonate-tethered  $\pi$ -systems via the reductive quenching of 2 (ref. 38). However,  $\alpha$ -bromoester analogues did not undergo cyclization using 2, although they cyclized efficiently when the catalyst was replaced with 3. In this case, modification of the ligands and replacement of the metal centre result in a more negative reduction potential for 3 (-1.51 V versus saturated calomel electrode (SCE)<sup>35</sup> than 2 (-1.31 V versus SCE)<sup>34</sup>, which enables the radical cyclization of  $\alpha$ -bromoesters onto  $\pi$ -systems. Another example of effective ligand substitution is seen when the 2-phenylpyridyl (ppy) ligands of 3 are replaced with 2-(2,4-difluorophenyl)-5-trifluoromethylpyridyl (dF(CF<sub>3</sub>)ppy) ligands to generate 1, a catalyst that has a more positive reduction potential  $(Ir^{4+} \rightarrow Ir^{3+})$ 

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**Figure 1** | **Visible-light-active photocatalysts and representative examples of compounds capable of undergoing radical reductive cleavage. a**, Visible-light-active photocatalysts commonly used for photoredox catalysis. **b**, Through modification of the metal centre and ligands, transition-metal-based photocatalysts may be tuned appropriately to obtain the desired redox potentials, allowing access to radical reductive cleavage of a variety of carbon-halogen bonds. Although only the most activated carbon-halogen bonds can be reduced by the weakest reductant (1), with an appropriately strongly reducing catalyst, such as 4, electron-deficient benzyl bromides and even unactivated alkyl, alkenyl and aryl iodides can undergo radical reductive cleavage.

Table 1   Reduction of alkyl iodides and aryl iodides.				
f R—I Ha (5a-i)	Procedure A ac-lr(ppy)₃ (1.0 mol%) Bu₃N (2.0 equiv.) antzsch ester* (2.0 equiv.) R—H MeCN, visible light (6a-i)	Ar I (7a-i)	Procedure B fac-Ir(ppy) <sub>3</sub> (1.0 mol%) Bu <sub>3</sub> N (5.0 equiv.) HCO <sub>2</sub> H (5.0 equiv.) MeCN, visible light	Ar—H (8a-i)
Bn0 6a (92%, 20 h) $H \xrightarrow{0}_{HO} \xrightarrow{0}_{O} \xrightarrow{0}_{O}$ 6c (87%, 20 h) $H \xrightarrow{0}_{HO} \xrightarrow{0}_{O} \xrightarrow{0}_{HO}$	TBDPSO <b>6b</b> (84%, 24 h) <b>6b</b> (85%, 16 h) H, $H$ , $H$	NHTs H 8a (94%, 20 h) CO <sub>2</sub> Me	NHBoc H 8b (97%, 28 h)	NHAc H 8c (95%, 44 h)
6e (82%, 18 h) → → → → → → → → → → → → → → → → → → →	6f (90%, 12 h) $F_{17}C_8 \xrightarrow{H} OH$ 6h (95%, 7 h) $F_{17}C_8 \xrightarrow{H} N$ 6i (93%, 6 h)	H 8d (92%, 6 h) $H \rightarrow CO_2 Me$ 8g (98%, 5 h) <sup>†</sup>	CO <sub>2</sub> Me 8e (93%, 8 h) NH <sub>2</sub> CI H 8h (94%, 32 h)	H 8f (95%, 30 h) H () 4 8i (96%, 24 h)

\*Hantzsch ester = Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate; †Allowing the reaction to run for 24 h led to partial reduction of C-Br bond.

than 2 or 3 (ref. 21). Although 1, 2 and 3 are calculated to have similar reductive abilities in their excited states via oxidative quenching, only 1 can efficiently produce atom transfer radical addition of  $CCl_4$  onto olefins<sup>39</sup>. On the other hand, by replacing

the 4,4'-di-tert-butyl-2,2'-dipyridyl (dtbbpy) ligand of **3** with another ppy ligand affording **4**, the reduction potentials of the catalyst become more negative. Specifically, the reduction potential for the  $Ir^{3+} \rightarrow Ir^{2+}$  couple changes from -1.51 V (versus SCE) for

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Table 2 | Reduction of alkenyl iodides and intramolecular reductive cyclizations utilizing Procedure C.

E/Z ratio = 1.3:1; +6.7:1 d.r

3 to  $-2.19~\mathrm{V}$  (versus SCE) for 4 and, likewise, the  $\mathrm{Ir}^{4+} \to \mathrm{Ir}^{3+\star}$ couple becomes more negative (-0.93 V versus SCE for 3 to -1.73 V versus SCE for 4)<sup>35</sup>. The strong reduction potentials of 4 prompted our proposal for a novel reductive dehalogenation protocol for alkyl, alkenyl and aryl iodides. We realized that the reduction of unactivated carbon-iodide bonds would be difficult to achieve with 4 because of the highly negative reduction potentials typical of alkyl, alkenyl and aryl iodides (for example, the reduction potential of s-butyl iodide has been measured to be between -1.61 V and -2.10 V versus SCE<sup>40,41</sup> and the reduction potential of iodobenzene has been measured to be between  $-1.59\;\mathrm{V}$  and  $-2.24\;\mathrm{V}$  versus SCE)<sup>42,43</sup>. However, our investigation was encouraged by the successful utilization of the oxidative quenching of 4 (ref. 44) by MacMillan and co-workers to form benzyl radicals from electrondeficient benzyl bromides (Fig. 1b)<sup>22</sup>, as well as by literature

precedent indicating that 4 may be quenched by compounds with reduction potentials that have been measured to be more negative than -2.00 V (versus SCE)<sup>45</sup>.

#### **Results and discussion**

We began our studies by screening conditions for the reduction of 5-iodopentyl benzyl ether (5a), monitoring the conversion by <sup>1</sup>H NMR. Based on our protocol for the reductive dehalogenation of activated carbon-halogen bonds, we began optimization with N,N-diisopropylethylamine and Hantzsch ester in N,N-dimethylformamide (DMF)<sup>46</sup>. A survey of solvents revealed that acetonitrile gave the best conversion over a 24 h reaction time, although the starting material was not fully consumed, even after increasing the equivalents of N,N-diisopropylethylamine and Hantzsch ester. Replacing N,N-diisopropylethylamine with other

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**Figure 2** | The reduction protocol allows for simultaneous scale-up and lower catalyst loading, and reaction times are shortened when the reaction is run in a flow reactor. **a**, Catalyst loading can be decreased to as low as 0.050 mol% without loss of efficiency for a 4.6 mmol (3 g) reaction with substrate **5h**, demonstrating the scalability of these reaction conditions. **b**, Reaction times are shortened when the reaction is run in a flow reactor, without suffering any loss in yield. A conversion rate of 0.900 mmol  $h^{-1}$  is achieved in the flow reactor, whereas the corresponding batch reaction proceeds at a conversion rate of 0.020 mmol  $h^{-1}$ .



**Figure 3** | **Experimental evidence for proposed mechanistic pathway. a**, In the absence of an electron donor, substrate **9e** forms atom transfer product **11** in 14% yield, indicating the action of the oxidative quenching pathway of *fac*-lr(ppy)<sub>3</sub>. Product **11** arises from short-lived propagation chains initiated by SET from the excited state of *fac*-lr(ppy)<sub>3</sub> to the carbon-iodide bond of **9e**. **b**, Proposed mechanistic pathway of photocatalytic radical reductive cleavage of alkyl, alkenyl and aryl iodides. Through oxidative quenching, visible-light-excited *fac*-lr(ppy)<sub>3</sub> donates an electron to the carbon-iodide bond and is then reduced to its ground state by an electron donor. The carbon radical generated undergoes hydrogen atom abstraction to give the reduced product. Possible electron and hydrogen atom donors are shown, together with their by-products.

reductants, including triethylamine, sodium ascorbate and 1,2-dimethoxybenzene did not improve the conversion. However, tributylamine exhibited a significant increase in conversion, and upon exchanging the method of degassing from freeze-pump-thaw to argon sparging, full consumption of **5a** was achieved in 24 h (Supplementary Table S1).

The tributylamine and Hantzsch ester combination (Procedure A, Methods) was used with several primary and secondary iodides to give reduction products in good to excellent yields (Table 1). This reduction protocol exhibits excellent functional group tolerance without affecting benzyl ethers, silyl ethers, acetals, lactones or free alcohols. In addition, the chemoselective nature of the reaction allows for the reduction of alkyl iodides in the presence of aryl bromides.

Subsequently, we investigated the reactivity of aryl iodides. Reduction of N-(4-iodophenyl)-4-methylbenzenesulfonamide (7a) was successful with Procedure A; however, the reaction requires 52 h for full consumption of 7a. We attempted to improve the reaction efficiency by replacing Hantzsch ester with formic acid, which is inexpensive and can be easily removed during work-up. To our delight, the reduction of 7a was complete in 20 h when 5 equiv. of tributylamine and 5 equiv. of formic acid were used. We tested these new conditions (Procedure B, Methods) on several alkyl iodides, but all attempts led to low yields of the desired reduced compound. We discovered that the use of Procedure B leads to a high level of competitive substitution and elimination reactions with alkyl iodides that are not observed with Procedure A. In particular, secondary iodide 5g provided substantial elimination product with Procedure B, but was cleanly reduced with Procedure A.

Procedure B was applied successfully to a diverse set of aryl iodides (Table 1). The buffered reaction conditions were amenable to both acid and base labile groups, such as carbamates, acetamides and esters. Electron-rich and electron-deficient aryl iodides were all cleanly reduced, although electron-rich aryl iodides required longer reaction times. It is noteworthy that these reaction conditions afford the reduction of challenging electron-rich aryl iodides, making this a general protocol applicable to a wide range of substrates. The reaction conditions also make it possible to reduce aryl iodides in the presence of aryl bromides, aryl chlorides and distal olefins. To achieve the reduction of unactivated alkenyl iodides (Table 2, substrates 9a-9c) in a reasonable timeframe, increasing the amounts of tributylamine and formic acid to 10 equiv. (Procedure C, Methods) was required. Activated alkenyl iodides such as pure Z-9c reduced very efficiently to produce a diastereomeric mixture of 10c with an E/Z ratio of 1:0.75 after 2.5 h (Supplementary Fig. S1). In addition, Procedure C was found to be the most effective for intramolecular cyclizations of alkyl, alkenyl and aryl iodide substrates (Table 2, substrates 9d-9j). Surprisingly, all alkyl iodide substrates cyclized efficiently without any observable substitution or elimination products. These radical reductive cyclizations generated a wide scope of products, including pyrrolidines, tetrahydrofurans, indoles, indolines, dihydrobenzofurans and carbocycles in moderate to high yields.

To demonstrate the efficacy of the reduction protocol on a preparative scale, the reduction of **5h** (3.0 g, 4.6 mmol) was performed with lower catalyst loading and reduced amounts of Hantzsch ester. Gratifyingly, simultaneous scale up of the reaction by 750% and decrease of the catalyst loading by 2,000% did not cause any significant loss of efficiency (Fig. 2a). Furthermore, the reaction time can be significantly shortened when the reductions are performed within a flow reactor<sup>47</sup>. For example, the reduction of 0.60 mmol of **7f** with 1.0 mol% of **4** in a batch reactor required 30 h of light irradiation to afford 95% yield of **8f** (Fig. 2b). However, by utilizing a 1.33 ml flow reactor with a residence time ( $t_R$ ) of 40 min, the same scale reduction, employing only 0.050 mol% of **4**, only requires a 3 h reaction time to afford 93% yield of **8f**, which indicates a turnover number (TON) of at least 1,860.

#### Mechanism

The successful cyclization of substrates **9d–9j**, the more facile reduction of secondary alkyl iodides in comparison to primary alkyl iodides, and control reactions that reveal low conversions of the reduced products in the absence of *fac*-Ir(ppy)<sub>3</sub> and/or visible light irradiation (Supplementary Table S2) strongly suggest a radical-based mechanism. In previous work<sup>46</sup> we demonstrated that formic acid/trialkylamine and Hantzsch ester/trialkylamine combinations are effective electron donor/hydrogen atom donor systems for the reductive dehalogenation of highly activated carbon–halogen bonds. The role of these reagents is probably unchanged for this protocol. However, to ensure that acetonitrile was not acting as an additional hydrogen atom source, the reaction of compound **7a** was performed in deuterated acetonitrile and no deuterium incorporation was observed (Supplementary Fig. S2).

Experimental evidence that the reaction was occurring through the oxidative quenching cycle of **4** was obtained when substrate **9e** and 2.5 mol% of *fac*-Ir(ppy)<sub>3</sub> in acetonitrile were subjected to visible light irradiation for 24 h to produce 14% of atom transfer product **11** together with 75% of recovered starting material (Fig. 3a). In the absence of tributylamine and formic acid, neither reductive quenching of Ir(ppy)<sup>\*</sup><sub>3</sub> nor the formation of **10e** from **9e** are possible, and oxidative quenching of Ir(ppy)<sup>\*</sup><sub>3</sub> leads to an atom transfer product via cyclization and iodine atom abstraction by the vinyl radical. The low yield of **11** probably occurs because fac-Ir(ppy)<sub>3</sub> only acts as an initiator for this reaction—there is no electron donor to effect catalyst turnover and the propagation chains are short-lived. Hence, we propose that the mechanism of the reaction involves the oxidative quenching of Ir(ppy)<sup>\*</sup><sub>3</sub> by the alkyl, alkenyl or aryl iodide. Reductive cleavage generates a carbon-centred radical that is capable of radical cyclization and/or hydrogen atom abstraction from tributylamine, Hantzsch ester or formate. The catalyst *fac*-Ir(ppy)<sub>3</sub> is regenerated from Ir(ppy)<sub>3</sub><sup>+</sup> by oxidation of tributylamine, Hantzsch ester, formate or their oxidized forms (Fig. 3b).

#### Conclusion

We have developed a visible light photoredox-mediated radical reductive deiodination protocol capable of reducing alkyl, alkenyl and aryl iodides. The generated radicals can also undergo intramolecular cyclizations to provide a variety of cyclic scaffolds. The reaction protocol is characterized by mild conditions, low catalyst loading, high yields and the use of inexpensive and accessible electron and hydrogen atom donors. Functional group tolerance towards benzyl ethers, silyl ethers, free alcohols, acetals, lactones, esters, aryl bromides, aryl chlorides, carbamates, distal olefins, sulfonamides, tosylates and acetamides is clearly illustrated. Moreover, the versatility and simplicity of the reduction protocol allows for easy scale-up, low catalyst loading and short reaction times when the reaction is run in a flow reactor. These advances signify the utility of photoredox catalysts in the area of radical chemistry, which previously has been dominated by tin, SmI<sub>2</sub> and trialkylboranes<sup>48</sup>.

#### Methods

Detailed descriptions of experimental and spectroscopic methods and results, as well as characterization data for all new individual compounds and the <sup>1</sup>H and <sup>13</sup>C NMR spectra, are provided in the Supplementary Information.

**Procedure A.** A flame-dried 10 ml round bottom flask with a rubber septum and magnetic stir bar was charged with the corresponding alkyl iodide (0.60 mmol, 1.0 equiv.), MeCN (6.0 ml), Hantzsch ester (1.2 mmol, 2.0 equiv.), tributylamine (1.2 mmol, 2.0 equiv.) and *fac*-Ir(py)<sub>3</sub> (0.0060 mmol, 0.010 equiv.). The heterogeneous mixture was degassed by argon sparging for 30 min and placed in a 250 ml beaker with blue or white light-emitting diodes (LEDs) wrapped inside. The reaction mixture was stirred at 25–30 °C until it was complete (as judged by thin layer chromatography (TLC) analysis or gas chromatography-mass spectrometry (GC-MS)). The solvent was removed from the crude mixture *in vacuo* and the residue was dissolved in EtOAc. The contents were poured into a separatory funnel containing 25 ml of EtOAc and 25 ml of 1 M HCl solution. The layers were separated and the aqueous layer was extracted with EtOAc ( $2 \times 25$  ml). The combined organic layers were washed with sat. NaHCO<sub>3</sub> solution and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to afford the desired product.

**Procedure B.** A flame-dried 10 ml round bottom flask with a rubber septum and magnetic stir bar was charged with the corresponding aryl iodide (0.60 mmol, 1.0 equiv.), MeCN (6.0 ml), tributylamine (3.0 mmol, 5.0 equiv.), formic acid (3.0 mmol, 5.0 equiv.) and *fac*-Ir(ppy)<sub>3</sub> (0.0060 mmol, 0.010 equiv.). The reaction mixture was degassed by argon sparging for 30 min and placed in a 250 ml beaker with blue or white LEDs wrapped inside. The reaction mixture was stirred at 25–30 °C until it was complete (as judged by TLC analysis or GC-MS). The solvent was removed from the crude mixture *in vacuo* and the residue was dissolved in EtOAc. The contents were poured into a separatory funnel containing 25 ml of EtOAc and 25 ml of 2 M HCl solution. The layers were separated and the aqueous layer was extracted with EtOAc ( $2 \times 25$  ml). The combined organic layers were washed with sat. NaHCO<sub>3</sub> solution and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to afford the desired product.

**Procedure C.** A flame-dried 10 ml round bottom flask with a rubber septum and magnetic stir bar was charged with the corresponding alkenyl iodide or cyclization substrate (0.60 mmol, 1.0 equiv.), MeCN (6.0 ml), tributylamine (6.0 mmol, 10 equiv.), formic acid (6.0 mmol, 10 equiv.) and *fac*-Ir(ppy)<sub>3</sub> (0.015 mmol, 0.025 equiv.). The reaction mixture was degassed by argon sparging for 30 min and placed in a 250 ml beaker with blue or white LEDs wrapped inside. The reaction mixture was stirred at 25–30 °C until it was complete (as judged by TLC analysis or GC-MS). The solvent was removed from the crude mixture *in vacuo* and the residue was dissolved in EtOAc. The contents were poured into a separatory funnel containing 25 ml of EtOAc and 25 ml of 2 M HCl solution. The layers were separated and the aqueous layer was extracted with EtOAc ( $2 \times 25$  ml). The combined organic layers were washed with 2 M HCl solution, sat. NaHCO<sub>3</sub> solution

and brine, dried ( $Na_2SO_4$ ) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to afford the desired product.

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#### Author contributions

J.D.N., E.M.D. and J.M.R.N. performed the experiments. All authors conceived and designed the experiments, analysed the data, contributed to discussions and wrote the manuscript.

#### Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to C.R.J.S.

#### **Competing financial interests**

The authors declare no competing financial interests.