Photocatalysis

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Visible-Light-Induced Photocatalytic Reductive Transformations of Organohalides**

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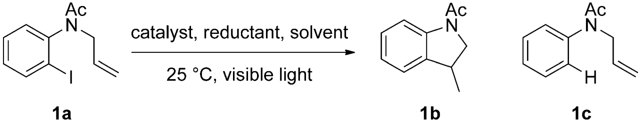
Free-radical generation from organohalides is among the most useful means to access an open-shell reactive intermediate that has found numerous applications in chemical synthesis. The halide abstraction, in particular, has been the mainstay approach in the production of carbon-centered radicals, although there are some problems associated with the method (hazardous reagents and specialized apparatuses).[1] An alternative is the transition-metal-mediated free-radical reaction, in which the odd-electron process starts with the reductive scission of the carbon–halogen bond.[2] This single-electron transfer (SET) strategy has recently been demonstrated to be feasible under visible-light photocatalysis utilizing transition-metal polypyridyl complexes.[3,4] Along with a novel mechanistic modality, the "green chemistry" features inherent to these methods hold great promise for the discovery of new reactions as well as developing practical and environmentally benign processes on industrial scales.[5] However, the visible-light-induced radical reaction has to date been limited only to suitably activated haloalkanes possessing a C(sp^3)−X bond adjacent to a π system (α-carbonyl, benzyl) or heteroatom (halogen, oxygen).[6] Despite the readily conceivable potential, the application to alkenyl, aryl, and unactivated alkyl halides has not been reported. Given the widespread utility of organohalide-based radical processes, it would be of significance to expand the current scope of the visible-light-harnessing catalytic method to include a wide range of substrates. Described herein are the results of our studies on the reductive transformations (cyclization and hydrodehalogenation) of unactivated organohalides by visible-light-induced photocatalysis.

Our initial survey was focused on examining the feasibility of visible-light photoredox catalysis in the cyclization of aryl iodide **1a** (Table 1). The reaction of **1a** under the nickel-catalyzed conditions failed to afford **1b** at 25 °C,[7] but gave **1c** in 79 % yield after a very sluggish reaction at an elevated temperature (4 days, 50 °C, entry 1). The reaction using $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (bpy = 2,2′-bipyridine) and *N*,*N*-diisopropylethylamine (DIPEA) under visible-light irradiation with a 20 W household compact fluorescent lamp (CFL) did induce cyclization to give **1b** albeit in low yield (15 %, entry 2). Changing the catalyst to $[Ir(ppy)_2(dtbbpy)]PF_6$ (ppy = 2-phenyl pyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine),[8] a complex with a higher redox potential (Ir^{III}/Ir^{II} vs Ru^{II}/Ru^{I}), dramatically enhanced the yield to 96 % (entry 3).[9] While the reaction in methanol gave a similar result, other conditions employing dimethylformamide (DMF) or triethylamine (TEA) resulted in a lowered yield or a longer reaction time (entries 4–6).[10] Interestingly, when a 2 W blue light-emitting diode (LED, $\lambda_{max} = 454$ nm) strip was used as the light source instead of a CFL, the reaction was completed in 1.5 h to give **1b** in 98 % yield (entry 7).[11] It was noteworthy that these photocatalytic reactions did not form the simple dehalogenation product **1c** in contrast to the Ni catalysis (entries 1 vs 2–7).

Table 1: Reductive cyclization of aryl halide **1a**.



1a **1b** **1c**

Entry	Catalyst (3 mol %)	Reductant (10 equiv)	Solvent	Time [h]	Yield [%][a]
1[b]	$NiCl_2{\cdot}DME$ + Pybox	Zn	MeOH	48	–
2	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	DIPEA	MeCN	24	15
3	$[Ir(ppy)_2(dtbbpy)]PF_6$	DIPEA	MeCN	5	96
4	$[Ir(ppy)_2(dtbbpy)]PF_6$	DIPEA	MeOH	5	96
5	$[Ir(ppy)_2(dtbbpy)]PF_6$	DIPEA	DMF	12	50
6	$[Ir(ppy)_2(dtbbpy)]PF_6$	TEA	MeCN	12	90
7[c]	$[Ir(ppy)_2(dtbbpy)]PF_6$	DIPEA	MeCN	1.5	98

[a] Reaction conditions: 3 mol % catalyst, 10 equiv reductant, solvent (0.01 M), 25 °C, 20 W CFL. Yields are of isolated product. [b] The reaction was performed with 5 mol % $NiCl_2{\cdot}DME$, 6 mol % Pybox, and 3 equiv of Zn in MeOH (0.2 M) at 25 °C (Ref. [7]). The simple reduction product **1c** was obtained (79 %) from a reaction run at 50 °C for 95 h. [c] A 2 W blue LED strip was used. Ac = acetyl; DME = dimethoxyethane; Pybox = pyridine-2,6-bis(oxazoline).

The visible-light-induced Ir catalysis established in the initial studies was tested for a range of aryl and alkenyl halide reactions (Table 2). Under the standard conditions with either CFL or LED irradiation, aryl (Table 2; entries 1–4) and alkenyl (entries 5–7) halides underwent reductive cyclization to furnish the corresponding carbo- and heterocyclic products in excellent yield. Consistent with the observations made in the initial studies, the use of blue LED led to a significant

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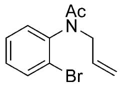
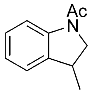
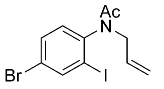
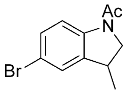
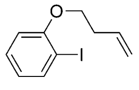
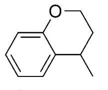
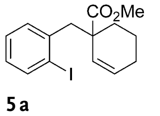
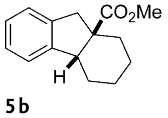
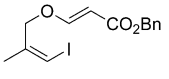
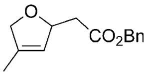
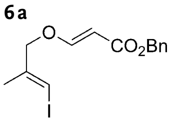
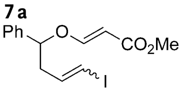
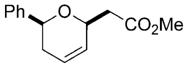
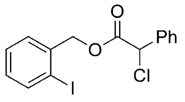
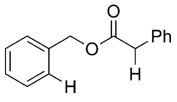
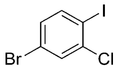
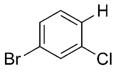
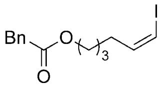
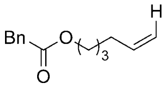
Table 2: Visible-light-induced Ir-catalyzed reductive cyclization and hydrodehalogenation of aryl and alkenyl halides.

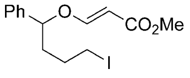
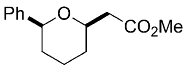
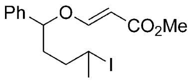
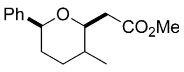
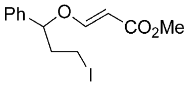
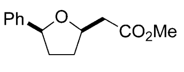
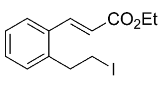
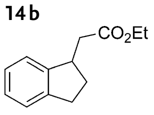
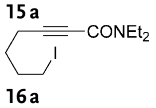
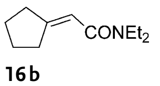
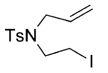
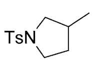
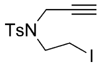
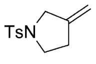
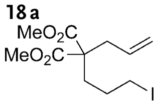
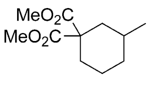
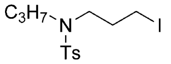
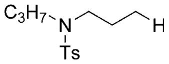
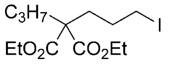
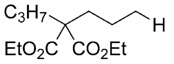
Entry	Reactant	Product	Time [h][a]	Yield [%][a,b]
1	 **2a**	 **1b**	45 (10)	96 (97)
2	 **3a**	 **3b**	4 (1)	90 (93)
3	 **4a**	 **4b**	54 (6)	82 (94)
4	 **5a**	 **5b**	19 (5)	89 (91)
5	 **6a**	 **6b**	19 (6)	92 (93)
6	 **7a**	**6b**	29 (10)	90 (94)
7	 **8a**[c]	 **8b**	52 (12)	88 (93)
8	 **9a**	 **9b**	3 (1)	87 (90)
9	 **10a**	 **10b**	5 (1.5)	90 (92)
10	 **11a**	 **11b**	50 (14)	89 (93)

[a] Reaction conditions: 3 mol% [Ir], 10 equiv DIPEA, substrate (> 0.5 mmol) in MeCN (0.01 M), 25 °C, 20 W CFL or 2 W blue LED strip. The numbers in parentheses refer to the reactions using a blue LED strip. [b] Yield of isolated product. [c] A 3:1 mixture of *E*/*Z* isomers was used.

improvement in both the reaction time and yield. As expected, bromide **2a** was found to be less reactive than iodide **1a**, and the differential reactivity was also manifested in the reaction of **3a** that gave **3b** without reducing the bromo group (entries 1 and 2). The *E* and *Z* isomers of the alkenyl iodides exhibited similar reactivity, both giving rise to the same cyclized products (entries 5–7). The feasibility of cyclization independent of the *E*/*Z* configuration is indicative of a free-radical mechanism for these reactions. This Ir-catalyzed route also proved to be efficient in the hydrodehalogenation of aryl and alkenyl halides, affording the reduction products in high yield (Table 2, entries 8–10). In the reaction of **9a**, containing both alkyl and aryl halides, the reduction of the α-carbonyl chloro and aryl iodo groups proceeded to provide the fully reduced **9b** (entry 8),[12] while the relatively higher reactivity of a C—I bond within an aryl system was noted in the reaction of polyhaloarene **10a** (entry 9).

Having established the applicability of the photochemical reaction to aryl and alkenyl halides, we next probed the potential of this Ir catalysis to effect radical reactions of unactivated alkyl halides. As shown in Table 3, an array of alkyl iodides devoid of an activating group underwent the photocatalytic reaction to give the cyclization (entries 1–8) and hydrodehalogenation (entries 9–10) products. The irradiation with blue LEDs, once again, had beneficial effects on these reactions, resulting in shorter reaction times and higher

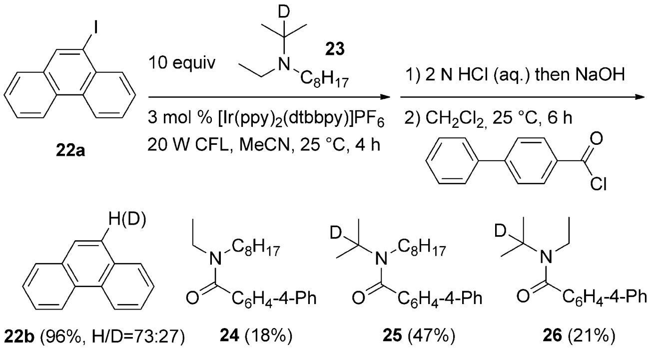
Table 3: Visible-light-induced Ir-catalyzed reductive cyclization and hydrodehalogenation of alkyl iodides.

Entry	Reactant	Product	Time [h][a]	Yield [%][a,b]
1	 **12a**	 **12b**	7 (2)	93 (94)
2	 **13a**	 **13b**[c]	4 (2)	86 (88)
3	 **14a**	 **14b**	9 (3)	94 (94)
4	 **15a**	 **15b**	7 (2)	81 (83)
5	 **16a**	 **16b**	8 (3)	95 (96)
6	 **17a**	 **17b**	9 (3)	89 (90)
7	 **18a**	 **18b**	2 (1)	90 (95)
8	 **19a**	 **19b**	18 (4)	62 (72)
9	 **20a**	 **20b**	11 (4)	90 (93)
10	 **21a**	 **21b**	16 (5)	83 (88)

[a] Reaction conditions: 3 mol% [Ir], 10 equiv DIPEA, substrate (> 0.5 mmol) in MeCN (0.1 M), 25 °C, 20 W CFL or 2 W blue LED strip. The numbers in parentheses refer to the reactions with LEDs. [b] Yield of isolated product. [c] Diastereomeric ratio = 59:41. Ts = *p*-toluenesulfonyl.

yields. Primary as well as secondary iodides with various alkene and alkyne acceptors participated well in the reaction. Moreover, the reaction could be carried out on multigram scales using 1 mol% of the catalyst without decrease in the yield.[13] As observed from the reactions of alkenyl and aryl substrates, no uncyclized reduction product was obtained from the reactions, in contrast to the Ni-catalyzed process where cyclization was typically accompanied by simple hydrodehalogenation (3–5%)[7] and with the organotin-mediated processes requiring slow addition of the reagent for the suppression of the simple reduction.[14]

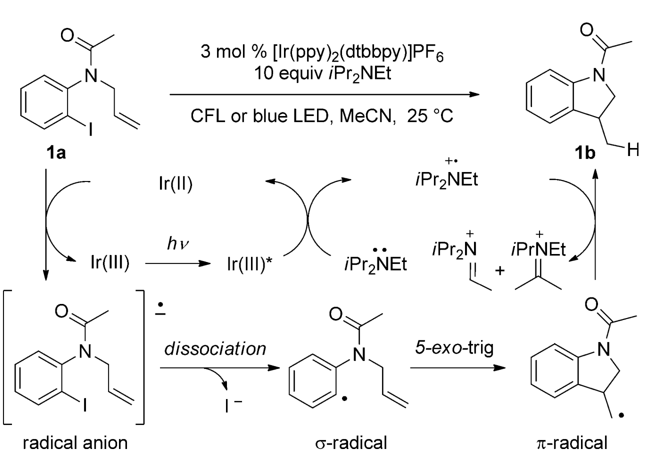
To gain insight into the mechanism of these photoredox processes, a series of deuterium labeling experiments was carried out for the hydrodeiodination of **22a** (Scheme 1).



Scheme 1. Hydrodeiodination of **22a** with deuterated amine **23**.

While a k_H/k_D of 2.1 was estimated from the reaction employing a 1:1 TEA/[D$_{15}$]TEA mixture,[15] the reduction with deuterated amine **23** resulted in 27% deuterium incorporation. From further examination of the product mixture by hydrolysis and acylation with 4-phenylbenzoyl chloride, amides **24**–**26** were obtained (Scheme 1, yield based on **22a**), which arose presumably from their corresponding imminium salts generated by the oxidative degradation of **23**.[16]

A proposed mechanism of the Ir-catalyzed reaction is depicted in Scheme 2, where the iridium complex mediates a free-radical cyclization process through the photoredox catalytic cycle. Crucial to this mechanism is the reductive scission of the C–I bond induced by the single-electron transfer (SET) from the Ir^{II} species (i.e. [Ir^{III}(ppy)$_2$-(dtbbpy$^{\bullet-}$)]). Whereas the SET to alkyl halides is likely to populate the σ*(C–X) orbital directly leading to the dissociation of the halide ion, the reaction of aryl halides may involve a discrete radical anion intermediate, which then undergoes electronic reorganization from the π system to the orthogonal σ*(C–X) orbital for bond breaking.[17] In the case of alkenyl halides, the SET seems less efficient owing to the high-lying π*/σ* orbital, which, together with the high dissociation energy of C(sp^2)–X bonds, may account for the longer reaction times generally observed in these systems (Table 2 entries 5–7 and 10). Finally, the reductive process is completed by a hydrogen-atom abstraction of the carbon-centered radical from the α-amino position of the aminium radical cation, as substantiated by the labeling experiment.[18]



Scheme 2. Proposed mechanism for the visible-light-induced Ir-catalyzed reductive cyclization.

In summary, we have described the iridium-catalyzed reductive cyclization and hydrodehalogenation of organohalides induced by visible light. This work shows that a broad range of alkyl, alkenyl, and aryl halides, not limited to alkyl substrates with an activating group, are competent participants in these photocatalytic free-radical processes and furnish the products in excellent yield. It has also been demonstrated that a simple alteration in reaction conditions, such as changing light sources, can bring about significant rate acceleration. These findings establish the feasibility of using structurally diverse organohalides for various free-radical-mediated reactions through a convenient and environmentally benign catalytic means that makes use of visible light.

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[10] See the Supporting Information for details on the optimization studies (Tables S1 and S2) and control experiments (Table S3).

[11] The rate enhancement by using a blue LED instead of a CFL has been noted, see Ref. [3a,6g,n]. While a detailed understanding requires further studies on the factors affecting the quantum efficiency of this photochemical system, the large rate increase appears to be due to the higher luminance of LED versus CFL, which arises, in part, from the higher directionality of the LED irradiation. The detailed information of the CFL and LED (Figures S5 and S6), and the results of the kinetic studies, including direct rate comparison experiments (Figure S7), are given in the Supporting Information.

[12] When the reaction (CFL irradiation) was examined after 1 h, the reaction mixture contained dechloro-**9a**, **9a** and **9b** in a 8:1:1 ratio. See the Supporting Information. For selective reduction of the chloride using a Ru catalyst, see Ref. [3c,6h].

[13] For example, the reaction of **12a** (2.29 g, 6.37 mmol) with 1 mol% of the Ir catalyst under CFL irradiation gave **12b** in 93% yield after 16 h (cf. Table 3, entry 1). Although an amount of 3 mol% Ir has been used in the present study, the turnover frequencies (TOFs) of the blue-LED-induced reactions are comparable to those of the reactions of activated alkyl halides. See Ref. [6g].

[14] Because the hydrogen donor in this reaction is generated only in a catalytic amount, the reductive quench of carbon-centered radicals under this photocatalysis may occur slowly to emulate the situation of a low tin hydride concentration achieved by slow addition using a syringe pump. Also see Ref. [18].

[15] The reaction with $[D_{15}]$-TEA (98 atom% D) gave a 7:93 (H/D) mixture of **22b** (94% yield). The k_H/k_D values for the reduction of aryl and alkyl halides with Bu_3SnH have been reported to be 1.3–1.6 and 2.7–2.8, respectively. See: a) S. J. Garden, D. V. Avila, A. L. J. Beckwith, V. W. Bowry, K. U. Ingold, J. Lusztyk, *J. Org. Chem.* **1996**, *61*, 805 – 809; b) D. J. Carlsson, K. U. Ingold, *J. Am. Chem. Soc.* **1968**, *90*, 7047 – 7055.

[16] The same sequence employing **22a** and protio-**23** (*N*-ethyl-*N*-isopropyloctan-1-amine) gave **22b** (95%), **24** (26%), protio-**25** (56%), and protio-**26** (9%). See the Supporting Information.

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