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# Electron-Transfer Photoredox Catalysis: Development of a Tin-Free Reductive Dehalogenation Reaction

Jagan M. R. Narayanam, Joseph W. Tucker, and Corey R. J. Stephenson*

*Department of Chemistry, Boston University, Boston, Massachusetts 02215*

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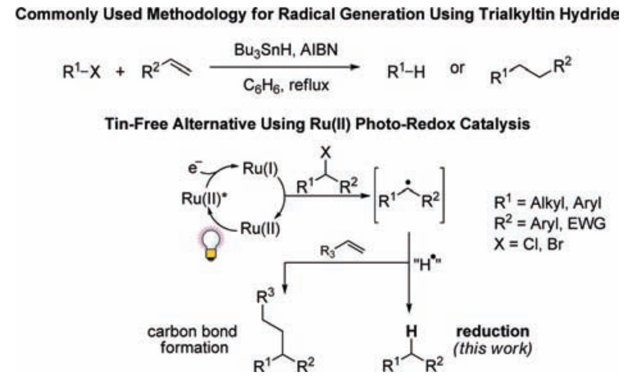
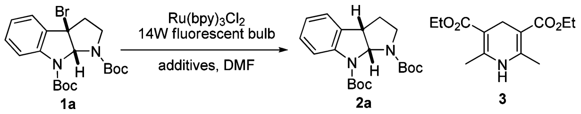
The use of visible light as a promoter in synthesis is appealing because of its natural abundance, ease of use, and potential application on an industrial scale.[1] However, the lack of visible-light absorption by many organic molecules has limited the number of applications documented to date. A solution to this problem involves the use of photosensitive catalysts.[2] Recent efforts from the MacMillan[3a] and Yoon[3b] laboratories have focused on the use of the well-known photoredox catalyst tris(2,2′-bipyridyl)ruthenium(II) chloride, $Ru(bpy)_3Cl_2$,[4] to promote the enantioselective alkylation of aldehydes and [2 + 2] cycloaddition reactions, respectively. In this paper, we describe an environmentally benign,[5] tin-free reductive dehalogenation[6] system that is based on the combination of $Ru(bpy)_3Cl_2$ and an amine as the hydrogen atom source. In addition, this photoredox system gives superior chemoselectivity compared with traditional methodologies based on the chemistry of radicals. Furthermore, photoredox catalysis is presented as a potential means of accessing traditional radical chemistry while avoiding the toxicity and purification problems associated with tin hydrides (Scheme 1).[7−9]

***Scheme 1.*** Photoredox Catalytic Reduction and Potential C−C Bond Formation



Our preliminary studies focused on the reductive debromination of bromopyrroloindoline **1a**.[10,11] Initial success was obtained upon subjecting **1a** to irradiation by a 14 W fluorescent lamp[12] with $Ru(bpy)_3Cl_2$ (5 mol %) as a catalyst in the presence of $^iPr_2NEt$ (2 equiv) in DMF for 24 h.[13] These conditions provided the reduced product in 25% yield (40% conversion). Subsequent optimization revealed two sets of conditions of broad utility for reductive debromination: $Ru(bpy)_3Cl_2$ (2.5 mol %) in DMF with (a) $^iPr_2NEt$ (10 equiv) and formic acid (10 equiv) or (b) $^iPr_2NEt$ (2 equiv) and Hantzsch ester (**3**) (1.1 equiv). In the case of **1a**, both systems cleanly produced the debrominated product in >90% yield. In addition, lower catalyst loading had little effect on the reaction: catalyst loadings as low as 0.05 mol % gave efficient reductive dehalogenation without prolonging the reaction time (Table 1).

***Table 1.*** Optimization of the Reductive Debromination of **1a**

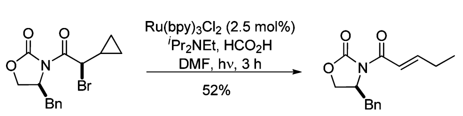


| entry | conditions | yield (%)[a] |
|---|---|---|
| 1 | $^iPr_2NEt$ (2 equiv), HCOOH (2 equiv), $Ru^{2+}$ (5 mol %), 24 h | 25 |
| 2 | $^iPr_2NEt$ (10 equiv), HCOOH (10 equiv), $Ru^{2+}$ (2.5 mol %), 4 h | 90 |
| 3 | $Et_3N$ (10 equiv), HCOOH (10 equiv), $Ru^{2+}$ (5 mol %), 24 h | 20[b] |
| 4 | $^iPr_2NEt$ (2 equiv), **3** (1.1 equiv), $Ru^{2+}$ (2.5 mol %), 4 h | 95 |
| 5 | $^iPr_2NEt$ (10 equiv), HCOOH (10 equiv), $Ru^{2+}$ (1 mol %), 4 h | 90 |
| 6 | $^iPr_2NEt$ (10 equiv), HCOOH (10 equiv), $Ru^{2+}$ (0.05 mol %), 4 h | 75[c] |

[a] Isolated yield after purification by chromatography on $SiO_2$. [b] 25% conversion. [c] Reaction conducted on a 2.0 g (4.6 mmol) scale.

The scope of this process is illustrated by the examples detailed in Table 2. Utilizing our optimized conditions, we were able to successfully reduce both C−Br and C−Cl bonds in the presence of other functional groups such as free hydroxyls (entries 4 and 6), olefins (entry 9), and alkynes (entry 10). Furthermore, we found excellent selectivity for the reductive dehalogenation of alkyl bromides and chlorides α to electron-withdrawing groups over vinyl iodides (entry 9) and aryl bromides and iodides (entries 2, 3, 7, and 8). These conditions were also tolerant of protecting groups, including silyl ethers (entry 5) and carbamates (entries 1−3). In the case of less reactive chlorinated compounds, $S_N2$ substitution by the formate ion was competitive with the dehalogenation reaction. For these substrates, the simple substitution of **3** in place of formic acid as the hydrogen atom source provided a complementary set of reaction conditions for the α-chlorocarbonyl compounds (entries 7−10). Furthermore, reduction of simple alkyl halides was not observed.[14]

Throughout our investigations, we conducted a series of control experiments using **1a** as a representative substrate. Exclusion of any of the reaction components, including visible light, $Ru(bpy)_3Cl_2$, $^iPr_2NEt$, or combinations thereof, afforded only trace amounts of the reduced product **2a** after 48 h. Furthermore, to add credence to the intermediacy of a radical, we utilized an α-bromo-α-cyclopropyl imide substrate as a radical clock (eq 1):[15] The corresponding cyclopropyl ring fragmentation product was obtained in 52% isolated yield. This result strongly suggests that the reaction proceeds via a radical mechanism.

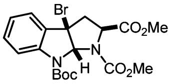
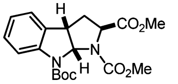
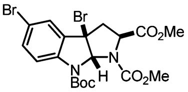
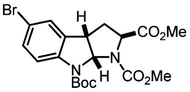
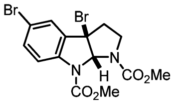
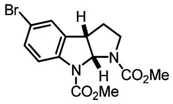
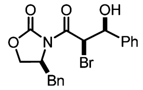
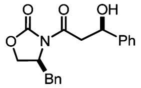
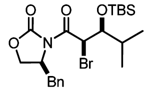
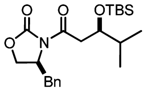
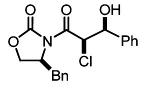
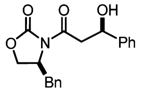
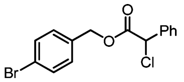
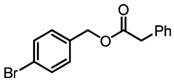
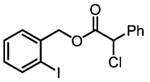
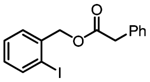
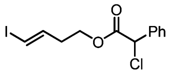
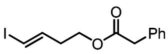
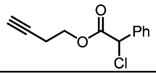
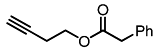


(1)

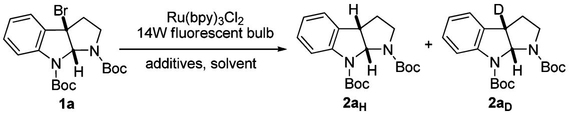
To further support our mechanistic hypothesis, we performed labeling studies using either $DCO_2D$ or $DCO_2H$ (98% D, 10 equiv) with $^iPr_2NEt$ (10 equiv) and $Ru(bpy)_3Cl_2$ (2.5 mol %) in DMF for the reduction of **1a** (eq 2):[16] Both afforded a $\mathbf{2a_H}/\mathbf{2a_D}$ product ratio

10.1021/ja9033582 CCC: $40.75

***Table 2.*** Reductive Dehalogenation Using Photoredox Catalysis

| entry | substrate | product | yield[a] |
|---|---|---|---|
| 1 |  |  | 95[b] |
| 2 |  |  | 92[b] |
| 3 |  |  | 91[b] |
| 4 |  |  | 99[b] |
| 5 |  |  | 79[b] |
| 6 |  |  | 80[b] |
| 7 |  |  | 78[c] |
| 8 |  |  | 88[c] |
| 9 |  |  | 81[c] |
| 10 |  |  | 89[c] |

[a] Isolated yield after purification by chromatography on $SiO_2$. [b] $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (2.5 mol %), $^iPr_2NEt$ (10 equiv), $HCO_2H$ (10 equiv), DMF, *hν*, r.t., 4 h. [c] $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (2.5 mol %), $^iPr_2NEt$ (2 equiv), **3** (1.1 equiv), DMF, *hν*, r.t., 4−24 h.



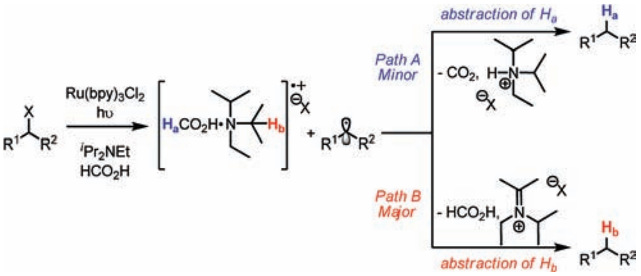
(2)

of ~4:1 ($^1H$ NMR), indicating that $^iPr_2NEt$ likely is the major hydrogen atom source in the reduction. In addition, no deuterium incorporation was observed in **2a** when the reduction reaction was conducted in DMF-$d_7$.

We also performed a reaction using formic acid (10 equiv), $Et_3N$-$d_{15}$ (10 equiv), and $Ru(bpy)_3Cl_2$ (2.5 mol %) in DMF, which led to only 25% conversion of starting material over 24 h and no incorporation of deuterium into the reduced product **2a**. This suggests that in the absence of $^iPr_2NEt$, the formate ion can successfully compete with the triethylammonium radical cation as the major hydrogen atom source (Scheme 2, Path A).

Accordingly, we propose a mechanism wherein single-electron transfer from the ammonium formate complex to the excited Ru(II)* occurs, forming Ru(I) and the radical cation of the complex. Reduction of the carbon−halogen bond by the electron-rich Ru(I) forms the alkyl radical, which can be reduced by abstraction of a hydrogen atom from one of the methine carbons of the radical cation of $^iPr_2NEt$ (Scheme 2, Path B). The proposed hydrogen abstraction from the radical cation of $^iPr_2NEt$ also accounts for the reductive dehalogenation of **1a** by 3° amines alone in the presence of $Ru(bpy)_3Cl_2$.

***Scheme 2.*** Plausible Mechanism for the Reductive Dehalogenation



In conclusion, we have developed a catalytic, tin-free method for reductive dehalogenation utilizing visible-light photocatalysis. The reaction is highlighted by its chemoselectivity, affording the reduced compounds in high yields under mild reaction conditions. Further development and application of photoredox catalysis in the context of radical chemistry and its application to C−C bond-forming reactions are currently underway.

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**Supporting Information Available:** Experimental procedures and $^1H$ and $^{13}C$ NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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