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Visible-Light Photoredox Catalysis: Dehalogenation of Vicinal Dibromo-, α-Halo-, and α,α-Dibromocarbonyl Compounds

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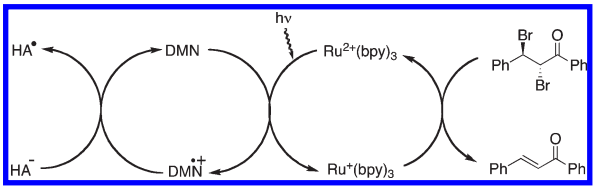

vic-Dibromo-, α-halo-, or α,α-dibromocarbonyl compounds can be efficiently dehalogenated using catalytic tris(2,2′-bipyridyl)ruthenium dichloride ($Ru(bpy)_3Cl_2$) in combination with 1,5-dimethoxynaphthalene (DMN) and ascorbate as sacrificial electron donor. For this process, a visible light promoted photocatalytic cycle is proposed that involves the reduction of carbon halogen bonds via free radical intermediates.

Bromination−debromination sequences are widely used in organic synthesis for the protection−deprotection of olefins. Although functionalization of olefins by simple bromination generally proceeds smoothly and stereospecifically in high yields, reversing the process to the parent olefin via a debromination step is more challenging. There are a number of reagents known for this transformation;[1] however, the necessity to employ stoichiometric amounts of strongly reducing agents might cause problems of selectivity and functional group compatibility. Moreover, the toxicity of some reagents such as the widely used organotin compounds makes the development of more sustainable alternatives desirable.

In recent years, there has been increasing interest in the use of visible light to drive organic reactions because of its infinite availability, ease of handling, and promising application in industry.[2] However, the use of visible light in organic reactions is limited due to the inability of many organic molecules to absorb in the range between 400 to 800 nm. Utilizing photosensitizers and photocatalysts[3] solved this long-standing problem.

In accord with our interest to develop new chemical transformations going through radical intermediates,[4] we wanted to utilize alkyl and vinyl bromides as radical precursors being liberated by photoredox catalysis. Recent reports from the groups of MacMillan[5] and Stephenson[6] have focused on the use of photoredox catalyst $Ru(bpy)_3Cl_2$ to promote enantioselective alkylations of aldehydes or reductive dehalogenations, respectively, starting from acyl bromides or tertiary benzyl halides. In all of these cases, photoexcited $*Ru^{2+}$ receives an electron from a sacrificial electron donor such as a tertiary amine, which in turn transfers that electron to a substrate. When we applied those conditions to a variety of primary acyl bromides, we noticed, however, their undesired direct reaction with the tertiary amine by a nucleophilic substitution, thus greatly reducing the yield of the desired radical processes.

In the search for an alternative photocatalytic system we came across the combination of 1,5-dimethoxynaphthalene (DMN) as a primary and ascorbic acid as a sacrificial electron donor,[7] as applied by Pandey et al.[8] for the cyclization of aldehydes and ketones onto tethered α,*β*-unsaturated esters. We report here that these reagents in combination with $Ru(bpy)_3Cl_2$ form an excellent photocatalytic system allowing the visible light mediated reductive debromination of vicinal dibromides as well as α-halocarbonyl compounds in high yields.

Irradiation of vicinal dibromocarbonyl compounds **1** by a blue LED (455 ± 10 nm) with $Ru(bpy)_3Cl_2$ in the presence of DMN and ascorbic acid smoothly gave rise to the corresponding α,*β*-unsaturated carbonyl compounds **2** (Scheme 1 and Table 1), with quantum yields ranging between 0.01 and 0.02. Optimization of the reaction conditions revealed that a methanol−water mixture (10:1) is the best choice of solvent for the process,[9] employing 2 mol % of ruthenium catalyst and 50 mol % of DMN. Reducing the amount of the latter was possible but resulted in slower conversion of the substrates (cf. entries 1 and 2). However, DMN could be

(1) (a) Ranu, B. C.; Guchhait, S. K.; Sarkar, A. *Chem. Commun.* **1998**, 2113–2114. (b) Schmidt, A.; Snovydovych, B.; Gjikaj, M. *Synthesis* **2008**, 2798–2804. (c) Ranu, B. C.; Jana, R. *J. Org. Chem.* **2005**, *70*, 8621–8624. (d) Butcher, T. S.; Detty, M. R. *J. Org. Chem.* **1998**, *63*, 177–180. (e) Li, W.; Li, J.; Lin, M.; Wacharasindhu, S.; Tabei, K.; Mansour, T. S. *J. Org. Chem.* **2007**, *72*, 6016–6021.

(2) Sala, X.; Romero, I.; Rodríguez, M.; Escriche, L.; Llobet, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2842–2852.

(3) (a) Kuczkowski, R. L. *J. Am. Chem. Soc.* **1963**, *85*, 3047–3048. (b) Baldwin, J. E.; Greeley, R. H. *J. Am. Chem. Soc.* **1965**, *87*, 4514–4516. (c) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1974**, *96*, 1137–1144. (d) Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785–9789. (e) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2010**, 39.

(4) (a) Prediger, I.; Weiss, T.; Reiser, O. *Synthesis* **2008**, 14. (b) Gheorghe, A.; Schulte, M.; Reiser, O. *J. Org. Chem.* **2006**, *71*, 2173–2176. (c) Lin, H.; Schall, A.; Reiser, O. *Synlett* **2005**, 2603–2606. (d) Jezek, E.; Schall, A.; Kreitmeier, P.; Reiser, O. *Synlett* **2005**, 915–918.

(5) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77–80.

(6) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756–8757.

(7) Hamada, T.; Nishida, A.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 140–145.

(8) (a) Pandey, G.; Hajra, S.; Ghorai, M. K.; Kumar, K. R. *J. Org. Chem.* **1997**, *62*, 5966–5973. (b) Pandey, G.; Hajra, S.; Ghorai, M. K.; Kumar, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 8777–8787.

(9) Solvent combinations had to be employed in which the ruthenium catalyst and DMN are soluble. The reaction proceeded well in acetonitrile or methanol, although with considerably longer reaction times (24 h instead of 5 h for full conversion), while DMF resulted in an unclean reaction with the formation of a number of unidentified side products.

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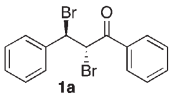
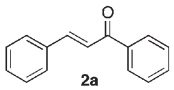
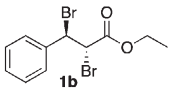
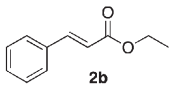
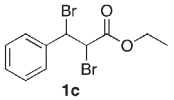
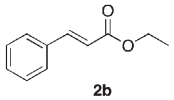
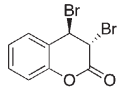
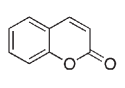
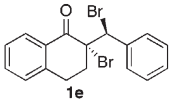
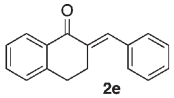
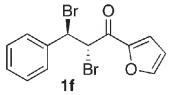
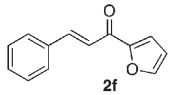
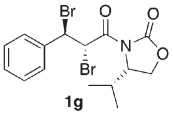
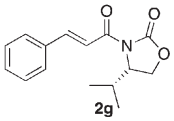
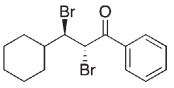
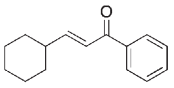
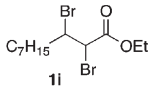
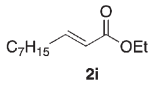
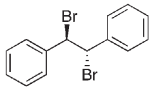
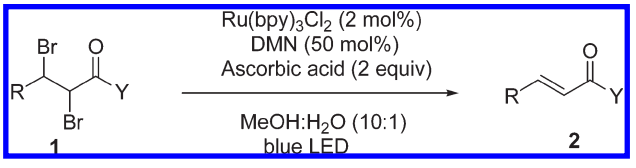
TABLE 1. Reductive Debromination of Vicinal Dibromocarbonyl Compounds Leading to Disubstituted Alkenes[a]

Entry	Substrate	Product	Time (h)	Isolated yield[b] (%)
1	 **1a**	 **2a**	8 36	92 83[c]
2	 **1b**	 **2b**	8 36	88 74[c]
3[d]	 **1c**	 **2b**	12	73
4	 **1d**	 **2d**	5	92
5	 **1e**	 **2e**	8	75
6	 **1f**	 **2f**	24	26[e]
7	 **1g**	 **2g**	5	89
8	 **1h**	 **2h**	36	28[e]
9	 **1i**	 **2i**	24	26[e]
10	 **1j**	-----	24	NR[f]

[a]Reaction conditions: *vic*-dibromo compound (1.0 equiv), $Ru(bpy)_3Cl_2$ (2 mol %), DMN (50 mol %), ascorbic acid (2 equiv), MeOH/H_2O = 10:1, blue LED. [b]Isolated yield after purification by chromatography on SiO_2. [c]Reaction performed with 25 mol % of DMN keeping other conditions unaltered. [d]Erythro/threo = 43:57. [e]$Ru(bpy)_3Cl_2$ (4 mol %). [f]No reaction.

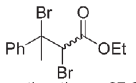
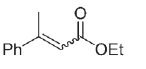
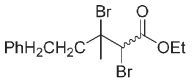
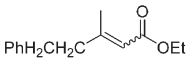
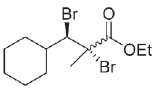
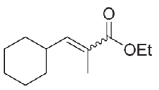
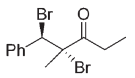
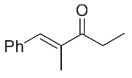
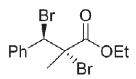
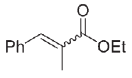
SCHEME 1. Photocatalyzed Reductive Debromination of Vicinal Dibromocarbonyl Compounds



recovered at the end of the reaction and reused, making the employment of higher amounts more practical but nevertheless economically acceptable.

A representative range of *vic*-dibromides **1** underwent debromination by this procedure to provide the corresponding alkenes (Table 1). A carbonyl substituent, e.g., a ketone, ester, lactone, or oxazolidinone, adjacent to the bromide is required for the debromination to take place (entries 1−9), e.g., no reaction took place with 1,2-dibromo-1,2-diphenylethane (entry 10). Moreover, alkyl-substituted dibromides react sluggishly in most cases (Table 1, entries 8 and 9; Table 2, entries 2 and 3). Only (*E*)-configured disubstituted alkenes were obtained from acyclic precursors in all cases, even when a 43:57 mixture of erythro and threo *vic*-dibromide **1c** (Table 1, entry 3) was subjected to the above conditions. The cyclic dibromide **1d** also underwent debromination smoothly (Table 1, entry 4), giving rise to enone **2d** predetermined by the ring size of the cycle.

TABLE 2. Reductive Debromination of Vicinal Dibromocarbonyl Compounds

Entry	Substrate	Product	Time (h)	Isolated Yield (%)
1	 **1k**: erythro:threo=67:33	 **2k**: E:Z=95:5	12	70
2	 **1l**: erythro:threo=80:20	 **2l**: E:Z=84:16	24	65[a]
3	 **1m**: erythro:threo=52:48	 **2m**: E:Z=95:5	24	27[a]
4	 **1n**: erythro:threo=100:0	 **2n**: E:Z=100:0	24	75[a]
5	 **1o**: erythro:threo=100:0	 **2o**: E:Z=75:25	24	65[a]

[a]4 mol % of $Ru(bpy)_3Cl_2$ was employed.

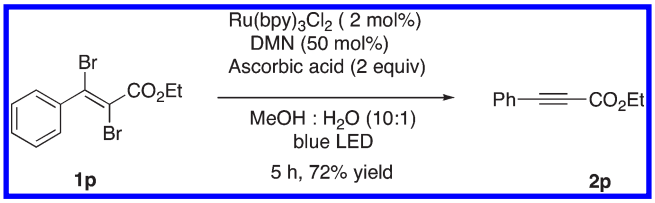
The *E*/*Z*-selectivity in debrominations of compounds that give rise to trisubstituted alkenes (Table 2) seems to be governed by the relative stability of the products, allowing in some cases the conversion of stereomixtures of dibromides to one geometrically pure alkene (Table 2, entries 1 and 3) but might also lead to *E*/*Z*-mixtures of alkenes despite starting from diastereomerically pure dibromide (Table 2, entry 5).

These observations confirm that the mechanism does not proceed by a stereospecific E2-type *anti*-elimination but rather involves a relatively stable radical or anion intermediate which breaks down to the alkenes according to their thermodynamic stability.

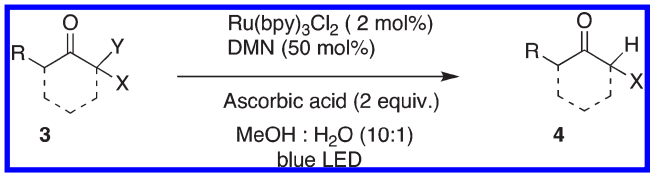
The synthesis of an alkyne from the corresponding *vic*-dibromoalkene was also achieved successfully utilizing the same reaction conditions as previously applied for the debromination of the *vic*-dibromoalkanes (Scheme 2).

Using **1a** (Table 1, entry 1) as a representative substrate, a series of control experiments were performed. Exclusion of any one of the reaction components ($(Ru(bpy)_3Cl_2)$, DMN, or ascorbic acid) yielded only a negligible amount of the product, even after 48 h.

SCHEME 2. Photocatalytic Reductive Debromination of a *vic*-Dibromoalkene



SCHEME 3. Photocatalytic Reductive Dehalogenations of α-Halocarbonyl Compounds



The conditions described here for the debromination of *vic*-dibromoalkanes and *vic*-dibromoalkenes were also successfully employed in the dehalogenation of a variety of α-halocarbonyl compounds (Scheme 3, Table 3).

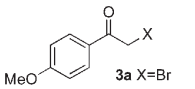
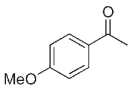
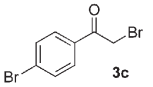
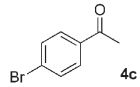
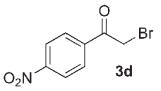
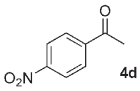
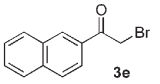
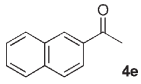
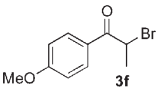
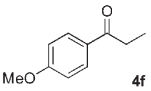
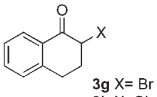
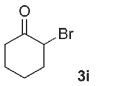
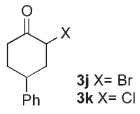
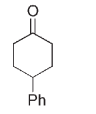
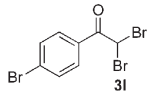
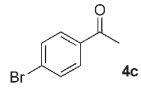
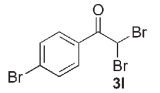
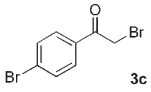
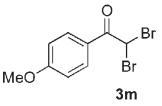
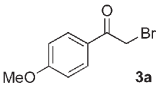
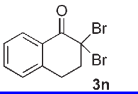
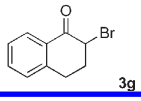
Irradiating **3a** (Table 3, entry 1) with blue LED light gave rise to **4a** within 5 h in excellent yield (93%). No side product was observed, whereas DMN could be reisolated almost quantitatively during purification of the product on silica. A control experiment excluding $Ru(bpy)_3Cl_2$ gave a very negligible amount of **4a**, whereas decreasing the amount of DMN (10 mol %) requires 40 h to complete the reaction. Both primary and secondary α-bromocarbonyl compounds can be reduced in high yield (Table 3, entries 1−8) under the reaction conditions. This protocol is also amenable to the corresponding α-chlorocarbonyl compounds; however, longer reaction times are necessary to achieve good conversion (Table 3, entries 1, 6, and 8). Good functional group tolerance, notably for those that could in principle also undergo reduction such as aromatic nitro or bromo moieties (Table 3, entries 3, 9, and 10), was observed.

The protocol described here is also useful for the selective debromination of α,α-dibromo to their corresponding monobromo ketones (Table 3, entries 10−12), a transformation that is difficult to achieve with conventional reducing reagents.[10] By simple control of the reaction time, the selective photocatalytic reduction of α,α-dibromoketones to either monobromo ketones or to the doubly debrominated parent ketones (Table 3, entries 9−12) becomes possible.

Mechanistically, we propose that the dehalogenation involves the activation of the substrate to form a radical intermediate by transferring an electron from Ru(I) (Scheme 4) following literature precendent.[6] It is well established[11] that Ru(II) readily accepts a photon from a variety of light sources (here from a blue LED) to populate the activated *Ru(II) metal-to-ligand charge transfer excited state. DMN acting as the primary donor transfers an electron to initiate the catalytic cycle by generating a Ru(I) complex. As Ru(I) is a potent reductant, it is able to transfer a single electron to the α-halocarbonyl substrate, thus furnishing a radical anion that rapidly eliminates a halide. The resulting α-acyl radical then could be further reduction by the photocatalyst to give an enolate that is ultimately undergoes protonation or halide elimination to the products observed.

In conclusion, we have developed a conceptually new photocatalytic system with visible light to drive sequential electron transfer processes for reductive debromination of vicinal dibromo compounds to the corresponding (*E*)-alkenes and alkynes, *gem*-dibromides to monobromides,

TABLE 3. Photocatalyzed Reductive Dehalogenation of α-Haloketones[a]

Entry	Substrate	Product	Time (h)	Isolated yield[b] (%)
1	 **3a** X=Br	 **4a**	5 40	93 90[c]
	3b X=Cl		15	81
2	 **3c**	 **4c**	5	89
3	 **3d**	 **4d**	24	72
4	 **3e**	 **4e**	12	84
5	 **3f**	 **4f**	24	54
6	 **3g** X= Br **3h** X=Cl	 **4g**	24 36	71 82
7	 **3i**	 **4i**	24	50
8	 **3j** X= Br **3k** X= Cl	 **4j**	18 24	75 63
9	 **3l**	 **4c**	9	71
10	 **3l**	 **3c**	0.5	88
11	 **3m**	 **3a**	2	70
12	 **3n**	 **3g**	0.5	54

[a]Reaction conditions: organohalide (1.0 equiv), $Ru(bpy)_3Cl_2$ (2 mol %), DMN (50 mol %), ascorbic acid (2 equiv), $MeOH/H_2O$ = 10:1, blue LED. [b]Isolated yield after purification by chromatography on SiO_2. [c]10 mol % DMN was employed. [d]The reaction was stopped (TLC monitoring) when 2-fold debrominated product just started to form.

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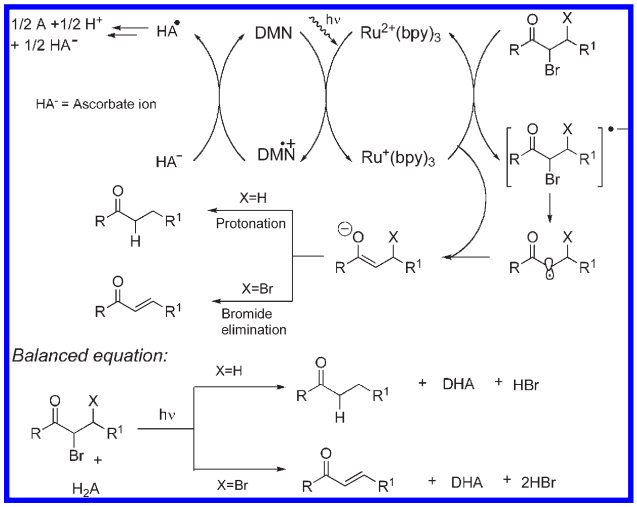
(11) (a) Juris, A.; Balzani, V.; Barigelletti, F.; Campagna, S.; Belser, P.; von Zelewsky, A. *Coord. Chem. Rev.* **1988**, *84*, 85–277. (b) Inagaki, I.; Akita, M. *Coord. Chem. Rev.* **2010**, *254*, 1220–1239.

SCHEME 4. Mechanistic Proposal for the Photocatalyzed Debromination Processes



and monobromides or chlorides to their dehalogenated counterparts. As a key structural feature, a carbonyl group positioned alpha to one halogen atom is required for the success of these transformation. The photosystem is also highlighted by its chemoselectivity, resulting in reduced products in high yields under mild reaction conditions.

Experimental Section

General Procedure for the Photoredox-Catalyzed Transformation of Organohalides. An oven-dried 10 mL vial equipped with a plastic septum and magnetic stir bar was charged with tris-(2,2′-bipyridyl)ruthenium(II) chloride hexahydrate (2.5 mg, 2 mol %), the corresponding halide (0.17 mmol, 1.0 equiv), 1,5-dimethoxynaphthalene (16 mg, 0.09 mmol, 0.5 equiv), and ascorbic acid (61 mg, 0.35 mmol, 2 equiv). The flask was purged with a stream of nitrogen and 1 mL of solvent (MeOH/H_2O = 10:1) was added. The resultant mixture was degassed for 10 min by nitrogen sparging and placed at a distance of ~0.5−1.0 cm away from a blue LED lamp. After the reaction was completed (as judged by TLC analysis), the mixture was diluted with 3 mL of methanol and concentrated in vacuo. The residue was purified by chromatography on silica gel, using hexanes/ethylacetate 9:1 as the eluent. 1,5-Dimethoxynaphthalene (13 mg, 82%) was reisolated during the column purification (R_f 0.63).

In a typical experiment (2*S**,3*R**)-dibromo-1,3-diphenylpropan-1-one (64 mg, 0.17 mmol, 1.0 equiv) (**1a**) was converted to (*E*)-1,3-diphenylprop-2-en-1-one (**2a**, 33 mg, 92%, R_f (EtOAc/hexanes 1:9) 0.41) along with reisolation of DMN (13 mg, 82%, R_f 0.63). **2a**:[12] ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.36−7.70 (m, 9H), 7.84 (d, J = 15.6 Hz, 1H), 7.98−8.10 (m, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 122.1, 128.5 (relative intensity 2), 128.6, 128.9, 130.5, 132.8, 134.9, 138.2, 144.8, 190.6.

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Supporting Information Available: Experimental procedures, detailed studies, and spectral characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Mahesh, M.; Murphy, J. A.; Wessel, H. P. *J. Org. Chem.* **2005**, *70*, 4118–4123.