ORGANIC LETTERS

2013
Vol. 15, No. 3
624–627

Oxidative C−C Bond Cleavage of Aldehydes via Visible-Light Photoredox Catalysis

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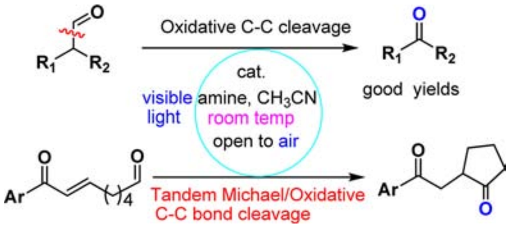
Received December 16, 2012

ABSTRACT



The visible-light mediated oxidative C−C bond cleavage of aldehydes has been achieved in good yields at ambient temperature and open to air using Ru(bpy)$_3$Cl$_2$ (bpy = 2,2′-bipyridine) as the photoredox catalyst. Moreover, we further demonstrated the application in a tandem Michael/oxidative C−C bond cleavage reaction.

Efficient and rapid C−C bond cleavage has been a clear goal of synthetic organic and medicinal chemistry, and accordingly, many research efforts have been focused on developing new methodologies. In the case of cleaving the C−C bond of aldehydes, however, very few procedures with mild reaction conditions are available. One of the most powerful methods is the oxidation of the enamines in the presence of strong metal oxidants (Scheme 1, eq 1).[1] However, these methods suffer from the drawbacks of harsh reaction conditions, various byproducts and limitation to the substrates. Recently, an elegant example from Chi's group reported the metal-free oxidative C−C bond cleavage of aldehydes in the presence of 4-methoxyaniline using molecular O_2 as the oxidant, in which heating and high pressure, for example, 10 atm of O_2, were required to achieve the corresponding chiral ketones (Scheme 1, eq 2).[2] Nowadays, the field of organic photochemical reactions experiences a veritable revival of activity in both academics and industry. The contribution from Turro's work on the photooxidation of enecarbamates with singlet oxygen has successfully demonstrated the efficiency of the organic photochemical reaction in organic synthesis (Scheme 1, eq 3). However, the generation of high-intensity UV light requires specialized photoreactors, which limits their scalability, and for photochemical reactions, selectivity remains to be a challenging task in targeted synthesis. Hence, the discovery of new processes to achieve C−C bond cleavage of aldehydes through milder reaction conditions and more environmentally friendly chemical synthesis is still appealing.

In recent years, research efforts have been focused on harnessing visible light as a promoter in organic transformations owing to its natural abundance, renewability, and ease of use. Due to the inability of many organic molecules

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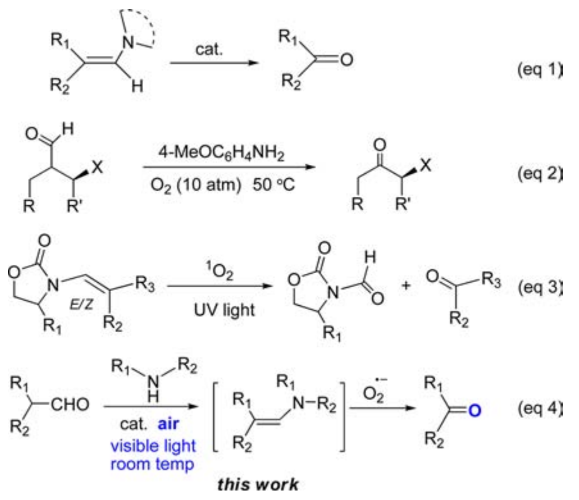
10.1021/ol303437m

Scheme 1. Oxidative C−C Bond Cleavage Reactions



to absorb visible light, Photocatalysts such as $Ru(bpy)_3Cl_2$[3] were employed through electron-transfer processes to sensitize organic molecules to carry out required photochemical reactions. Since the pioneering work from the groups of MacMillan,[4] Stephenson,[5] Yoon[6] and others[7] demonstrated the utility of $Ru(bpy)_3Cl_2$ and its application to various visible light induced synthetic transformations, the application of visible light photoredox catalysis has emerged as a growing field in organic chemistry and successfully applied in a variety of reactions.[8] Among these advances, air was usually employed as an oxidant to regenerate Ru^{2+} from Ru^{+} in the reductive quenching cycle and result in the formation of $[O_2]^{\bullet -}$. With our continuous investigations on photochemical reactions,[9] we envisioned that the resulted $[O_2]^{\bullet -}$ could act as an oxidant to selectively cleave C−C bond of the enamines formed *in situ* from aldehydes and secondary amines enabled by photoredox catalysts (Scheme 1, eq 3). Herein we report what we have achieved on the realization of the strategy for the direct oxidative cleavage of C−C bond to ketones using visible-light irradiation and air as the source of the oxidant. This new photocatalytic approach is particularly attractive because mild reaction conditions, such as visible light, open to air, and ambient temperature are involved.

Our initial investigation was carried out on the reaction of **1a** with 1 equiv piperidine in the presence of 5 mol % $Ru(bpy)_3Cl_2$ in CH_3CN under irradiation with a 15 W fluorescent light bulb. To our delight, the desired C−C cleavage product **2a** was obtained in 29% yield after irradiation for 2 h (Table 1, entry 1). Such a result, to the best of our knowledge, presents the first example of oxidative decarbonylation using a visible-light photocatalytic strategy and encourages us to explore the optimal reaction conditions. Therefore 3 equiv piperidine and same reaction time were employed which led to the yield increased to 86% (Table 1, entry 2). If the reaction time was prolonged to 5 h, excellent yield of 95% was obtained (Table 1, entry 6). Further studies indicated that second amine had a significant effect on the reaction efficiency (Table 1, entries 5−11). Among all tested amines, piperidine showed the best transformation to product **2a**.

The reaction proceeded equally well in DMF, CH_3CN and CH_3OH (Table 1, entries 3, 4, 6 and 7) producing the

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(3) Oxidative quenching of $Ru(bpy)_3^{2+*}$ provides $Ru(bpy)_3^{3+}$, a strong oxidant (1.29 V vs SCE, in CH_3CN), while reductive quenching provides $Ru(bpy)_3^{+}$, a strong reducing agent (−1.33 V vs SCE in CH_3CN).

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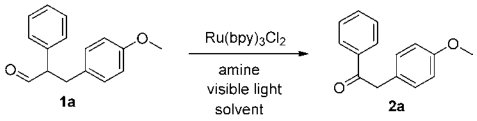
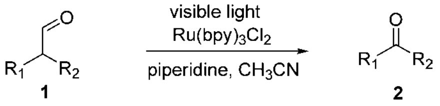
Table 1. Optimization of the Photocatalytic Oxidative Cleavage Conditions for Aldehyde **1a**[a]

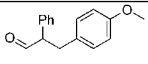
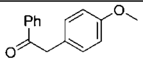
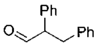
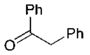
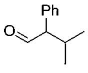
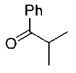
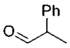
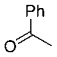
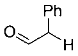
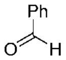
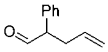
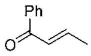
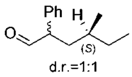
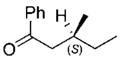
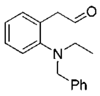
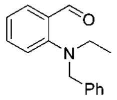
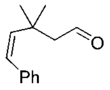
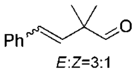
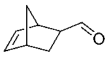
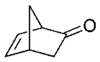
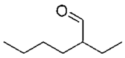
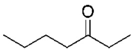


entry	amine	solvent	time (h)	yield (%)[b]
1[c]	piperidine	CH_3CN	2	29
2	piperidine	CH_3CN	2	86
3	piperidine	CH_3OH	5	89
4	piperidine	DMF	5	94
5	diisopropylamine	CH_3CN	5	33
6	**piperidine**	**CH_3CN**	**5**	**95**
7	pyrrolidine	CH_3CN	5	93
8	morpholine	CH_3CN	5	60
9	N-methylaniline	CH_3CN	5	35
10	4-methoxy-N-methylaniline	CH_3CN	5	79
11	dibenzylamine	CH_3CN	5	65

[a] Reaction conditions: **1a** (0.1 mmol, 0.1 M in solvent), amine (0.3 mmol), $Ru(bpy)_3Cl_2$ (0.005 mmol), irradiation with a 15 W fluorescent light bulb under air at 25 °C. [b] Determined by GC. [c] Piperidine (1 equiv) was used in the reaction.

Table 2. Scope of the Photocatalytic Oxidative Cleavage Conditions.[a]



entry	substrate	product	time (h)	yield[b] (%)
1	 **1a**	 **2a**	6	94(80[c])
2	 **1b**	 **2b**	7	94(78[c])
3	 **1c**	 **2c**	12	96(71[c])
4	 **1d**	 **2d**	12	87(75[c])
5	 **1e**	 **2e**	12	72
6	 **1f**	 **2f**	12	85(70[c])
7	 **1g**	 **2g**	12	90(76[c])
8	 **1h**	 **2h**	8	(60[c])
9	 **1i**	 **2i**	12	(77[c])
10	 **1j**	 **2j**	24	83[d]
11	 **1k**	 **2k**	24	70[d]

[a] Reaction conditions: **1**(0.1 mmol, 0.1 M in CH_3CN), piperidine (0.3 mmol), $Ru(bpy)_3Cl_2$ (0.005 mmol), irradiation with a 15 W fluorescent light bulb under air at 25 °C. [b] Determined by GC unless otherwise noted. [c] Isolated yield in parentheses. [d] ${}^{i}Pr_2NH$ used instead of piperidine.

product in excellent yields. In addition, the reaction degassed with N_2 resulted in a a trace amount of product, indicating that the oxygen plays an important role in the reaction. Notably, exclusion of any of the reaction components, including photocatalyst, the light source and amine, did not afford the desired product **2a**.

The scope of the reaction was examined by employing a variety of aldehydes to the optimal reaction conditions. As summarized in Table 2, the aldehydes were smoothly oxidized to the corresponding ketones in good to excellent yields. Among them the α-aryl aldehydes were effectively converted to phenyl ketones (Table 2, entries 1−7). Interestingly, more thermodynamically stable α,β-unsaturated ketone was obtained from the reaction of γ,δ-unsaturated aldehyde after decarbonylation and sequential C−C double bond shifting (Table 2, entry 6). Moreover, the optically pure ketone could be obtained from the diastereomers without apparent erosion on the chiral center of the ketone product under irradiation (Table 2, entry 7). Notably, the substrate with an amino group also afforded the corresponding product in acceptable yield (Table 2, entry 8). The phenyl substituted olefin was isomerized to afford the mixture of (*E*) and (*Z*)-olefins when subjected to the reaction conditions. No further reaction was observed albeit irradiation was for a longer time, which indicates that the α-hydrogen of the aldehyde plays a crucial role in the reaction (Table 2, entry 9). In addition, cyclic or alkyl aldehydes were also tolerated under the reaction conditions and as high as 83% yield was obtained (Table 2, entries 10 and 11).

Accordingly, a tentative mechanism for this novel catalytic cycle was proposed in Scheme 2. The enamine **A** formed *in situ* from aldehyde **1** and secondary amine was oxidized to cation radical **B** through the reductive quenching process. Ru^+ was oxidized by the oxygen of air to regenerate Ru^{2+} and form $[O_2]^{\bullet -}$ which was reacted with **B** to yield the final product.

To add more credence to the existence of intermediate **B**, a control experiment was conducted by addition of 0.5 equiv 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) to a mixture of **1i**, 3 equiv piperidine and 5 mol % $Ru(bpy)_3Cl_2$ to capture the radical generated in the reaction.[10] The above mixture was then irradiated with a 15 W fluorescent light bulb in CH_3CN (Scheme 3). Indeed, the α-oxyaminated aldehyde product **4i** was isolated and characterized by NMR spectra, along with which formamide **3i** and

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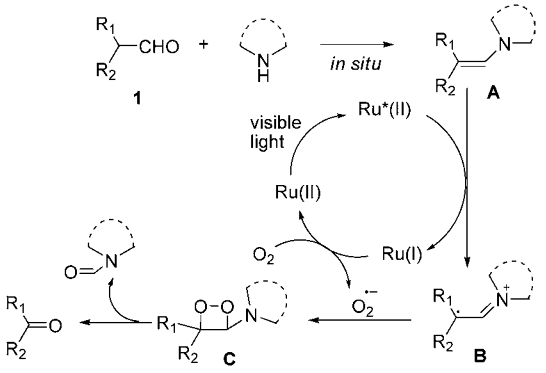
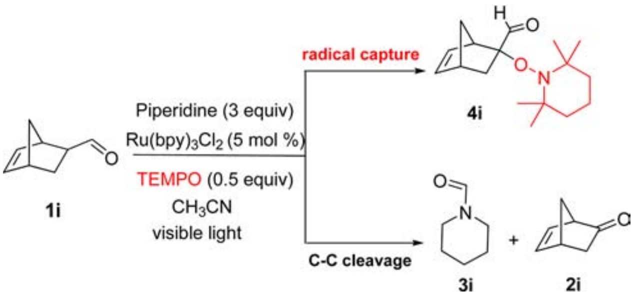
(10) Koike, T.; Akita, M. *Chem. Lett.* **2009**, *38*, 166.

product **2i** were also detected by GC-MS due to that only 0.5 equiv TEMPO was applied.

Scheme 2. Proposed Mechanism

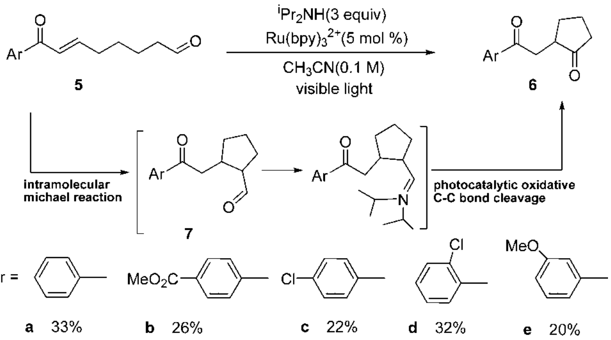


Scheme 3. Control Experiment with TEMPO



To further investigate the applicability of this protocol in organic synthesis, the formyl enone **5a** prepared from 1,6-hexanediol[11] was treated with 3 equiv ^{i}Pr$_2$NH and 5 mol % Ru(bpy)$_3$Cl$_2$ under irradiation with a 15 W fluorescent light bulb. We envisioned that the secondary amine could act both as the catalyst and reductive quencher to realize a tandem reaction in which the cyclopentyl aldehyde **7** could be generated from ^{i}Pr$_2$NH catalyzed intramolecular Michael reaction, which was sequentially transformed to the cylclopentanone **6a** through an oxidative C–C bond cleavage reaction. As expected, product **6a** was obtained directly from the starting material **5a** in 33% isolated yield. The scope of the reaction was examined by subjecting the compounds substituted with electron donating and/or withdrawing groups at the different positions on the phenyl groups to the reaction condtions, and the corresponding products were obtained in 20–33% yield (Scheme 4a–e). To the best of our knowledge, the result represents the first example of such a Michael/Oxidative C–C bond cleavage tandem reaction and provides a novel access to the synthesis of cyclopentanone derivatives.

Scheme 4. Tandem Michael/Oxidative C–C Bond Cleavage Reaction



In conclusion, we have developed a visible-light induced photocatalytic reaction for oxidative C–C bond cleavage of aldehydes using air as the oxidant. Compared with the previous procedures, this reaction was conducted in the milder conditions, such as room temperature, open air, and compatible with a wider range of substrates. More importantly, the photocatalytic reaction was first applied in a tandem Michael/oxidative C–C bond cleavage process through the use of amine as both the catalyst and reactant.

Acknowledgment. We are grateful for the financial supports from China NSFC (Nos. 21272047, 21002018 and 21072038) and ZJNSF (No. LY12B02009).

Supporting Information Available. Supplementary details. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.