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Utilization of Natural Sunlight and Air in the Aerobic Oxidation of Benzyl Halides

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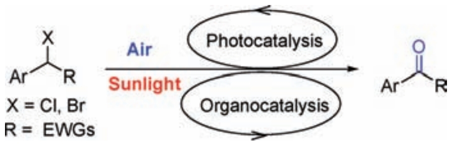
ABSTRACT



A novel, efficient oxidation of α-aryl halogen derivatives to the corresponding α-aryl carbonyl compounds at room temperature has been disclosed. Natural sunlight and air are successfully utilized in this approach through the combination of photocatalysis and organocatalysis. A plausible mechanism was proposed on the basis of the mechanistic studies.

The utilization of natural solar energy,[1] as well as molecular oxygen as the ideal oxidant,[2] are arguably two of the most important scientific and technical challenges due to their secure, clean, green, and sustainable characters. Although employing visible light absorbing photocatalysts such as Ru(II)polypyridine complexes in the photochemical synthesis for those substrates which cannot absorb visible light has recently attracted great attention,[3–5] visible light absorbing photocatalysts inducing aerobic oxidative transformation with sunlight excitation are still limited and pose a challenging task.[6,7] Recently, Zen and co-workers[6a] made a significant contribution toward the visible light photocatalytic oxidation of sulfides to sulfoxides employing Ru(bpy)$_3^{2+}$ as a photoredox catalyst, while the group of Ma and Zhao[7] developed the visible light induced aerobic oxidation of alcohols in a dye-sensitized TiO$_2$ and TEMPO system. On the other hand, MacMillan and co-workers pioneered the merger of the photoredox catalysis and their enamine catalysis on the enantioselective α-alkylation and α-fluoroalkylation of aldehydes.[4b,c] With the booming of organocatalysis in the past decades,[8] it is

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evident that the combination of photocatalysis and organocatalysis can substantially broaden the field of visible light photochemistry. We describe herein a Ru(bpy)$_3^{2+}$- and pyridine-cocatalyzed utilization of natural sunlight and air in the aerobic oxidation of benzyl halides, in which a radical is generated by the cooperation of the photocatalyst and organocatalyst (Figure 1). Although pyridine derivatives as bases or zwitterions have been used in organic catalysis,[9] as far as we know, this is not only a cooperation of photocatalyst and organocatalyst but also a novel pyridine derivative catalyzed radical reaction.

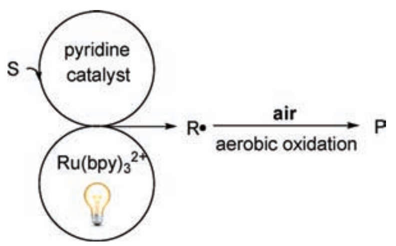


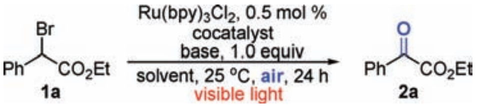
Figure 1. Combining photocatalysis and organocatalysis.

Recently, we developed a Cu-catalyzed aerobic oxidative amidation–diketonization of terminal alkynes,[10a] in which O_2 was employed as a radical trap to introduce oxygen into organic molecules. On the basis of these results, our continued efforts in the application of dioxygen in organic synthesis[10] prompted us to explore the possibility of aerobic oxidation of α-aryl halogen derivatives through a Ru(bpy)$_3$Cl$_2$-catalyzed single-electron-transfer process induced by visible light at room temperature.

Initially, Ru(bpy)$_3$Cl$_2$ (0.5 mol %)-catalyzed aerobic oxidation of **1a** was investigated in CH_3CN under air with visible light irradiation. However, no desired oxidation product was determined (entry 1, Table 1). Gratifyingly, 55% yield was achieved when catalytic amounts of pyridine (20 mol %) were used in this transformation (entry 2). This condition, based on what we know, is an interesting pyridine-catalyzed oxidation reaction of α-aryl halogen derivatives using air as oxidant in homocatalysis.[11]

When 4-methoxypyridine was used instead of pyridine, the yield of **2a** increased to 80% (entry 4). The yield increased slightly to 82% (isolated yield: 75%) when the reaction was carried out in DMA (entry 5). Other solvents, such as DCE or DMF, showed low efficiencies (see the Supporting Information). In addition, the case employing 1.2 equiv of pyridine as base and catalyst gave low yield (entry 3). Although the stronger base was in favor of quenching the produced acid, when a different base such as Na_2CO_3 was used, the yield was low (35%, entry 6). We envisioned that **1a** could decompose in the presence of a relatively stronger base. It is noteworthy that both Ru(bpy)$_3$Cl$_2$ and visible light are essential for this aerobic oxidation (entries 7 and 8, Table 1).

Table 1. Screening on Different Parameters.[a]



entry	base	cocatalyst (mol %)	solvent	yield[b] (%)
1	Li_2CO_3	none	CH_3CN	0
2	Li_2CO_3	pyridine (20)	CH_3CN	55
3	none	pyridine (120)	CH_3CN	42
4	Li_2CO_3	4-methoxypyridine (20)	CH_3CN	80
5	$\mathbf{Li_2CO_3}$	**4-methoxypyridine (20)**	**DMA**	**82 (75)**
6	Na_2CO_3	4-methoxypyridine (20)	CH_3CN	35
7[c]	Li_2CO_3	4-methoxypyridine (20)	CH_3CN	0
8[d]	Li_2CO_3	4-methoxypyridine (20)	CH_3CN	trace

[a] Reaction conditions: **1a** (0.2 mmol), Ru(bpy)$_3$Cl$_2$ (0.001 mmol), base (0.2 mmol), and cocatalyst were added in solvent (1 mL) under air at 25 °C. Irradiation time using a 24 W compact fluorescent bulb at 20 cm was 24 h. [b] Determined by GC; the number in parentheses is the isolated yield. [c] In the absence of Ru(bpy)$_3$Cl$_2$. [d] The reaction was carried out in the dark.

Importantly, when the aerobic oxidation was executed under ambient sunlight (Figure 2), the reaction of **1a** proceeded very well giving **2a** in 78% yield. Therefore, the utilization of natural sunlight and air in this organic transformation is a practical strategy.

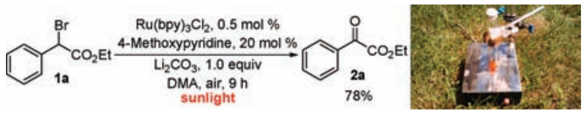


Figure 2. Utilization of natural sunlight and air.

With the optimal reaction conditions in hand, we then probed the reaction scope using various benzyl halides (Table 2). These reactions of α-haloarylacetic acid esters proceeded smoothly producing the corresponding products in good yields (entries 1–6, Table 2). Both chloride and bromide as a leaving group are tolerated in this transformation. Additionally, the selectivity for the oxidative dehalogenation is very high with the retention of the chloro atom on the aryl ring (entry 4). Besides the

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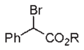
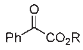
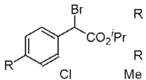
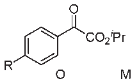
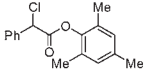
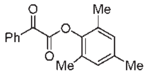
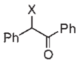
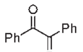
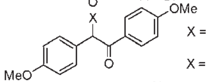
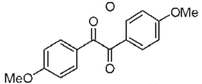
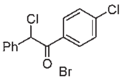
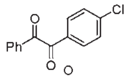
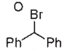
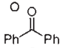
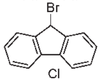
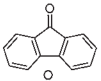
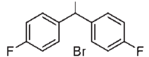
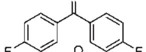
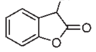
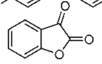
(10) For some of our recent results using O_2 as the oxidant, see: (a) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (b) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572. (c) Shi, Z.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7895. (d) Shi, Z.; Zhang, B.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 4036. (e) Zhang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 6174.

(11) (a) For the oxidation of benzyl halids using dioxygen as the oxidant in heterocatalysis, see: Itoh, A.; Kodama, T.; Inagaki, S.; Masaki, Y. *Org. Lett.* **2000**, *2*, 2455. (b) For examples using other oxidants, see: Li, C.; Zheng, P.; Li, J; Zhang, H.; Cui, Y.; Shao, Q.; Ji, X.; Zhang, J.; Zhao, P.; Xu, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 5063.

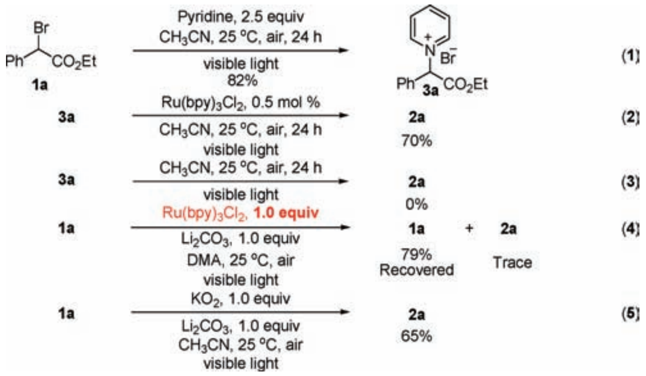
electronic property of the substitution at the aryl ring, the expansion of α-aryl carbonyl compounds formation chemistry to 2-halo-1, 2-diarylethanones provided moderate to good yields (entries 7−11). Although the oxidation of benzhydryl halides was not effective under these optimized conditions, the desired products, benzophenone (**2j**), 9-fluorenone (**2k**), and 4,4′-difluorobenzophenone (**2l**), were obtained in 40%, 56%, and 39% yield, respectively, when 2.5 equiv of pyridine was employed in the presence of Cs_2CO_3 (entries 12−14). However, the reaction of **1o** did not generate the desired product **2m** (entry 15, Table 2), which is consistent with the previous study on this kind of benzyl radical.[12]

The pyridinium salt **3a** was isolated (82%) from the reaction of **1a** with 2.5 equiv of pyridine in the absence of the $Ru(bpy)_3Cl_2$ catalyst without the observation of **2a** (eq 1). Interestingly, **3a** could undergo the oxidation smoothly to form the desired product **2a** in 70% yield under these conditions (eq 2), which indicates that the pyridinium salts could be the key intermediates during this catalytic cycle. In addition, **2a** was not observed in the similar reaction of **3a** in the absence of the photocatalyst $Ru(bpy)_3Cl_2$ (eq 3). Hence, the cooperation of the catalysts ($Ru(bpy)_3Cl_2$ and pyridine) is essential for this aerobic oxidation.

Table 2. Synthesis of α-Aryl Carbonyl Compounds **2** from **1**[a]

entry	1			product (2)			yield(%)[b]
1		R = Et	**1a**		R = Et	**2a**	75
2		R = Me	**1b**		R = Me	**2b**	75
3		R = ${}^{i}Pr$	**1c**		R = ${}^{i}Pr$	**2c**	83
4		R = Cl	**1d**		R = Cl	**2d**	85
5		R =OMe	**1e**		R =OMe	**2e**	85
6[c,d]			**1f**			**2f**	64
7		X = Cl	**1g**			**2g**	81
8		X = Br	**1h**				81
9[d,e]		X = Cl	**1i**			**2h**	60
10		X = Br	**1j**				72
11			**1k**			**2i**	82
12[f,g]			**1l**			**2j**	40
13[f,g]			**1m**			**2k**	56
14[f,g]			**1n**			**2l**	39
15			**1o**			**2m**	0

[a] Reaction conditions: see entry 5 in Table 1. [b] Isolated yield. [c] 4-Methoxypyridine (0.08 mmol) was used. [d] The irradiation time is 48 h. [e] Na_2CO_3 was used instead of Li_2CO_3. [f] 2.5 equiv of pyridine was used. [g] Cs_2CO_3 was used instead of Li_2CO_3.



Although it has been known that the oxidative quenching of $Ru(bpy)_3{}^{2+*}$ to $Ru(bpy)_3{}^{3+}$ by O_2 can generate the superoxide radical ($O_2{}^{-}$),[13] the reactions in the absence of pyridine did not work (entry 1, Table 1), even when 1.0 equiv of $Ru(bpy)_3Cl_2$ was employed (eq 4). On the contrary, the oxidation of α-aryl halogen derivatives employing KO_2 as the oxidant in the similar conditions produced the desired product **2a** in 65% yield (eq 5). Therefore, although the excited state $Ru(bpy)_3{}^{2+*}$ can be easily oxidized ($Ru(bpy)_3{}^{3+}$) or reduced ($Ru(bpy)_3{}^{+}$),[3b,13c] the photoredox catalysis between $Ru(bpy)_3{}^{2+*}$and $Ru(bpy)_3{}^{+}$ is preferred in this novel transformation.

To further understand this transformation, some luminescence quenching experiments were conducted.[4b,14] For the formation of the benzyl radical, either $Ru(bpy)_3{}^{+}$ or $Ru(bpy)_3{}^{2+*}$ was needed to act as a reductant in our catalytic system. Since a decrease in $Ru(bpy)_3{}^{2+*}$ luminescence was not observed in the presence of α-bromophenylacetic acid ethyl ester or its pyridinium salt (see the Supporting Information), the possibility that $Ru(bpy)_3{}^{+}$ is participating as a reductant to form the benzyl radical was supported. The $Ru(bpy)_3{}^{2+*}$ excited state should behave as an oxidant to close the photoredox catalytic cycle.

Significantly, when the reaction of **3a** in the absence Ru catalyst under O_2 was recorded by EPR (monitored with the addition of the radical trap 5-,5-dimethyl-1-pyrroline

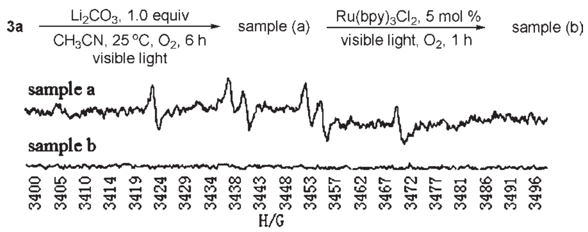


Figure 3. EPR studies: electroparamagnetic resonance (EPR) spectra (X band, 9.7 GHz, rt). Sample a: reaction mixture without $Ru(bpy)_3Cl_2$ in the presence of the radical trap DMPO (2.5×10^{-2} M). Sample b: reaction of sample (a) with the addition of $Ru(bpy)_3Cl_2$ catalyst in the presence of the radical trap DMPO (2.5×10^{-2} M).

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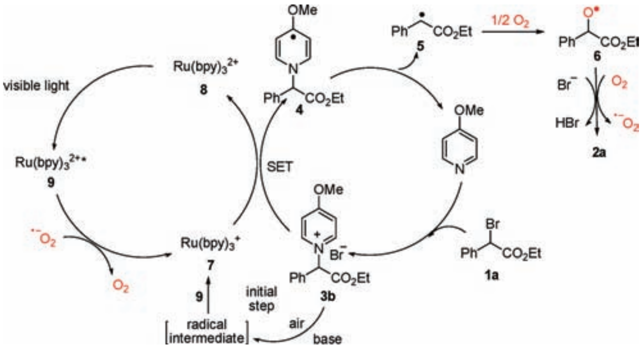
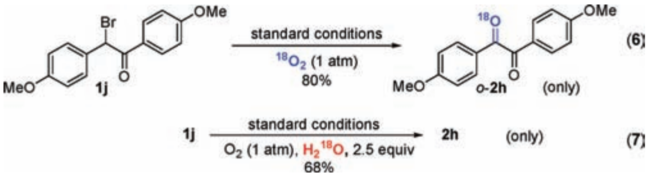
N-oxide (DMPO)), several signals of a radical intermediate can be obviously observed (sample a, Figure 3). However, these reactions without the addition of Ru catalyst did not afford the expected product (see eq 3 and eq S6 (Supporting Information)). In contrast, no signals were detected in the absence of O_2 (see Figure S5, Supporting Information). It is noteworthy that with the addition of $\mathrm{Ru(bpy)_3Cl_2}$ into the above reaction mixture, the signals of the radical intermediate disappeared completely (sample b, Figure 3). Although the structure of the radical intermediate detected by EPR is difficult to identify, we believe that this phenomenon maybe arise from a redox reaction between the formed radical intermediate in situ and the Ru catalyst **9** leading to the initial generation of Ru(I) species **7** (Scheme 1).

Scheme 1. Proposed Mechanism for the Transformation



On the basis of the above results, the catalytic cycle of this transformation was proposed in Scheme 1. As we have mentioned, 4-methoxypyridine can react with **1a** to afford the corresponding pyridinium salt **3b**.[15] A radical intermediate generated under O_2 from sacrificial **3b** is considered to serve as the reductive quencher to reduce the catalyst **9** into Ru(I) species **7** in the initial step of this transformation (Scheme 1). The other formed **3b** could accept a single electron from Ru(I) species **7** to form the dihydropyridyl radical **4**.[16] The benzyl radical **5** and 4-methoxypyridine were then provided via the homolysis of the C−N bond of **4**.[17] The aerobic oxidation of benzyl radicals in the presence of O_2 was widely reported.[18] In this case, **2a** is efficiently produced from **5** with the formation of the superoxide radical anions[18b] via the alkoxyl radical intermediates **6** (Scheme S1, Supporting Information).[18d] Because of the formation of acid, inorganic base is required to protect 4-methoxypyridine from generating the corresponding pyridinium salt. In the photoredox catalytic cycle, $[\mathrm{Ru(bpy)_3}]^{2+}$ (**8**) could readily accept a photon from visible light to populate the excited state $[\mathrm{Ru(bpy)_3}]^{2+*}$ (**9**) via metal-to-ligand charge transfer (MLCT). Subsequently, the O_2^- radicals, which could be oxidized,[19] donate a electron to the $[\mathrm{Ru(bpy)_3}]^{2+*}$ excited state (**9**) to regenerate the active reductant $[\mathrm{Ru(bpy)_3}]^{+}$ (**7**) to close this catalytic cycle. In addition, a decrease of the $\mathrm{Ru(bpy)_3}^{2+*}$ emission intensity at low concentration of KO_2 was observed (see the Supporting Information, Figure S4), which supports the proposed pathway that the generated O_2^- radicals in the right circle could be as a reductant in the left circle to reduce **9** into **7**.



Two ^{18}O labeling experiments were carried out (eq 6 and 7, determined by HRMS; see the Supporting Information). It was found that the oxygen of the new formed carbonyl group was wholly from molecular oxygen rather than from H_2O. These results support that benzyl radical intermediate is involved in this transformation.

In summary, we have disclosed a novel, efficient oxidation of α-aryl halogen derivatives to the corresponding α-aryl carbonyl compounds at room temperature. Natural sunlight and air are successfully utilized in this approach through the combination of photocatalysis and organocatalysis. To the best of our knowledge, this is not only a cooperation of photocatalyst and organocatalyst but also a novel pyridine derivative catalyzed radical reaction. For a clearer understanding of the reaction mechanism and the synthetic applications, further studies are ongoing in our laboratory.

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

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