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Visible-light-driven Oxidation of 1,3-Dicarbonyl Compounds via Catalytic Disproportionation of TEMPO by Photoredox Catalysis

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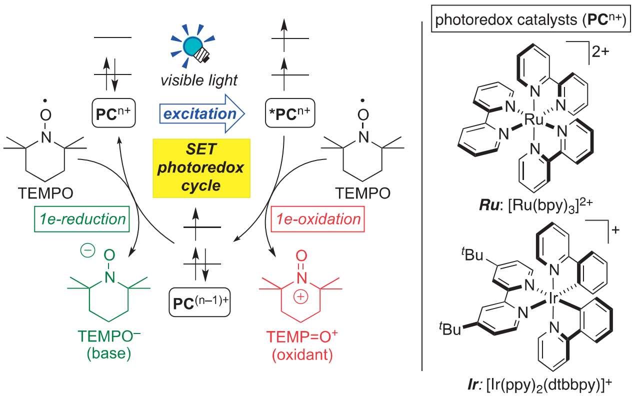
Visible light irradiation of a mixture of 1,3-dicarbonyls and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) in the presence of photoredox catalysts, $[Ru(bpy)_3]^{2+}$ and $[Ir(ppy)_2(dtbbpy)]^+$ (bpy: 2,2′-bipyridine, ppy: 2-phenylpyridine, dtbbpy: 4,4′-di-*tert*-butyl-2,2′-bipyridine), afforded two types of oxidized products, i.e., α-oxyaminated products from acyclic 1,3-dicarbonyls and oxidatively dimerized products from cyclic 1,3-dicarbonyls. The Ir catalyst turned out to be more active than the Ru catalyst. This is a new photocatalytic oxidation of 1,3-dicarbonyls based on a single-electron-transfer process mediated by excited photoredox catalysts.

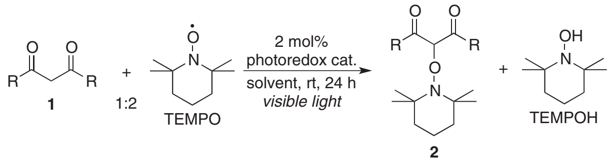
Recently, photoredox catalysts ($\mathbf{PC}^{n+}$) such as $[Ru(bpy)_3]^{2+}$ (abbreviated as ***Ru***; bpy: 2,2′-bipyridine) and $[Ir(ppy)_2(dtbbpy)]^+$ (abbreviated as ***Ir***; ppy: 2-phenylpyridine, dtbbpy: 4,4′-di-*tert*-butyl-2,2′-bipyridine) have received considerable attention from the viewpoint of efficient use of solar energy (visible light) for organic synthesis.[1–3] We also previously reported ***Ru***-mediated reactions of enamines with TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) and silyl enol ethers, leading to α-oxyaminated carbonyl products[4] and γ-diketones, respectively.[5] The photoredox catalysis is attributed to the excited triplet species ($^*\mathbf{PC}^{n+}$) generated under the irradiation with visible light ($h\nu$: $\lambda > 400$ nm), which are able to serve either as a single electron oxidant or as a reductant and return to the initial ground state ($\mathbf{PC}^{n+}$) through a successive *single-electron-transfer (SET) process*. On the basis of the fact that TEMPO is a redox-active organic compound, we expected that it serves as the counterpart of the above-mentioned bimodal SET process to be transformed into *N*-oxoammonium species ($TEMP{=}O^+$; an oxidant) and aminoalkoxide ($TEMPO^-$; a base) via photocatalytic disproportionation as shown in Scheme 1.[6] Herein we describe α-oxyamination of acyclic 1,3-dicarbonyls and oxidative dimerization of cyclic 1,3-dicarbonyls by the action of photoredox catalysts under visible light irradiation. In general, α-oxyamination of carbonyl compounds requires activation of substrates in situ or pretreatment, that is, generation of enamine, enolate, and *N*-oxoammonium species, $TEMP{=}O^+$.[7] Our photocatalytic protocol based on the bimodal reactivity of TEMPO allows us to carry out direct and efficient α-oxyamination of 1,3-dicarbonyls with TEMPO without pretreatment or any additives. Recently, Tan and co-workers reported the related α-oxyamination of acyclic 1,3-dicarbonyls catalyzed by organic dyes.[8] Interestingly, they proposed a reaction mechanism involving the first electron transfer event from the photoexcited dyes to 1,3-dicarbonyls, which is different from our photoredox system.



Scheme 1. Concept for photocatalytic disproportionation of TEMPO.

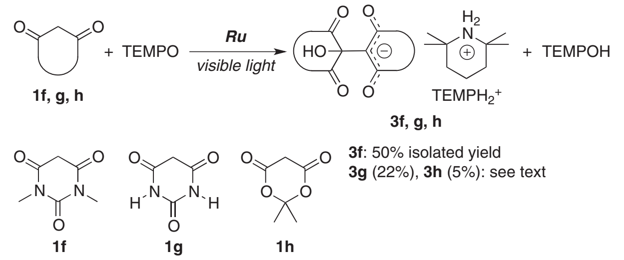
Photoredox catalysts $[Ru(bpy)_3](PF_6)_2$ (***Ru***$(PF_6)_2$) and $[Ir(ppy)_2(dtbbpy)](PF_6)$ (***Ir***(PF_6)) have proven to catalyze oxidative coupling of acetylacetone **1a** with TEMPO at room temperature under irradiation with visible light (a Xe lamp: $\lambda > 420$ nm), giving the α-oxyaminated 1,3-dicarbonyl compound **2a**[7c] as shown in Table 1. Monitoring the reaction of a CD_3CN solution of **1a**, TEMPO, and ***Ru***$(PF_6)_2$ (2 mol %) by ^{1}H NMR spectroscopy showed that the α-oxyamination proceeded but turned out to be very sluggish (Entry 1 in Table 1). In contrast, it was found that the photoreaction in CD_2Cl_2 catalyzed by ***Ir***(PF_6) afforded **2a** almost quantitatively in 22 h under visible light (Entry 2). This transformation did not proceed either in the dark or in the absence of the Ir catalyst (Entries 3 and 4), suggesting

Table 1. α-Oxyamination of 1,3-dicarbonyls



Entry	Photoredox cat.[a]	Light source	R	Solvent	Yield /%
1	***Ru***$(PF_6)_2$	Xe	CH_3(**a**)	CD_3CN	34[b], 32 h
2	***Ir***(PF_6)	Xe	CH_3(**a**)	CD_2Cl_2	95[b], 22 h
3	***Ir***(PF_6)	—	CH_3(**a**)	CD_2Cl_2	0[b], 22 h
4	—	Xe	CH_3(**a**)	CD_2Cl_2	0[b], 22 h
5	***Ir***(PF_6)	LED	CH_3(**a**)	CH_2Cl_2	97[c]
6	***Ir***(PF_6)	LED	Ph(**b**)	CH_2Cl_2	71[c]
7	***Ir***(PF_6)	LED	CH_3, OEt(**c**)	CH_2Cl_2	99[c]
8	***Ir***(PF_6)	LED	Ph, OEt(**d**)	CH_2Cl_2	98[c]
9	***Ir***(PF_6)	Xe	OCH_3(**e**)	CD_2Cl_2	6[b], 48 h

[a] ***Ru***: $[Ru(bpy)_3]^{2+}$, ***Ir***: $[Ir(ppy)_2(dtbbpy)]^+$. [b] Determined by ^{1}H NMR. [c] Isolated yield.



Scheme 2. Oxidative dimerization of **1f**, **1g**, and **1h**.

that the excited species of the Ir photoredox catalyst is involved in this reaction. Notably, the amount of TEMPO is crucial for the conversion. That is, 1 equivalent of TEMPO to **1a** was not enough to complete the reaction and left half of **1a** unreacted. In addition, the progressive formation of TEMPOH was observed by ^{1}H NMR.[9]

A Xe lamp is often used as a pseudosunlight source because it covers the broad range from ultraviolet to visible region. Now, small LED lamps are readily available and can irradiate light of 400 nm, which is essential to excite the photoredox catalysts.[10] Because irradiation by a Xe lamp with a cutoff filter ($\lambda >$ 420 nm) and an LED lamp ($\lambda = 425$ nm) gave similar results (Entries 2 and 5), we mainly used a Xe lamp for NMR-scale experiments to determine the reaction conditions and an LED lamp for larger-scale preparative experiments.[11]

Under the same conditions, 1,3-diketones and β-ketoesters were also transformed to the corresponding coupling products **2b**–**2d** in excellent yields (Entries 6–8), although the reaction of dimethyl malonate (**1e**) was very slow (Entry 9). The X-ray crystallographic analysis of products **2a** and **2b** (See Supporting Information[12]) confirmed that the C1–O1 bonds (1.412(3) Å for **2a** and 1.430(4) Å for **2b**) are single bonds, which are comparable to those in the previously reported oxyaminated compounds.[13]

On the other hand, reaction of cyclic 1,3-dicarbonyl compounds **1f**–**1h** did not give the corresponding α-oxyaminated product but oxidatively dimerized compounds **3f**–**3h** as shown in Scheme 2. For example, the reaction of 1,3-dimethylbarbituric acid (**1f**) with TEMPO using the ***Ru*** catalyst under visible light irradiation gave **3f**.[14] The X-ray crystallographic analysis of **3f** revealed the dimeric structure with (i) the C–C single bond between the two active methylene carbon atoms, (ii) the OH group attached to one of the active methylene carbon atoms, and (iii) the planar C7 atom (the sum of the bond angles: 360.0°) (Figure 1). These structural features lead to the assignment to the delocalized anionic β-ketoenolate structure, which is supported by (i) the C–C and C–O bond lengths of the delocalized moiety falling between those of the single and double C–C/O bond lengths, (ii) the presence of the 2,2,6,6-tetramethylpiperidinium cation in the unit cell, and (iii) the broad ^{1}H NMR signal for the NH$_2$ moiety (δ 6.4 (2H)).

Time-conversion curves on the basis of NMR data are shown in Supporting Information (Figure S7-1[12]). These results confirm that (i) the ***Ir*** catalyst is more effective, (ii) product **3f** is produced quantitatively, and (iii) the amount of TEMPO is important for this oxidative dimerization as well. The amount of TEMPO can be reduced to an equimolar amount with respect to 1,3-dimethylbarbituric acid (**1f**), which is distinct from the α-oxyamination mentioned above. The same oxidative transformation of barbituric acid (**1g**) and meldrum's acid (**1h**) proceeded under similar reaction conditions as revealed by X-ray crystallography of the products **3g** and **3h**,[15] although the poor solubility of **3g** and **3h** hindered isolation of analytically pure samples of them.

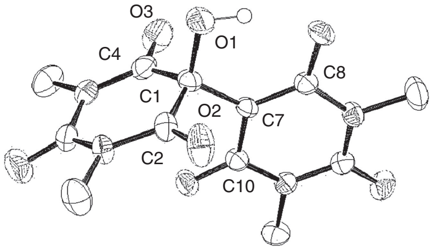


Figure 1. Structure of the anionic part of **3f**.[15]

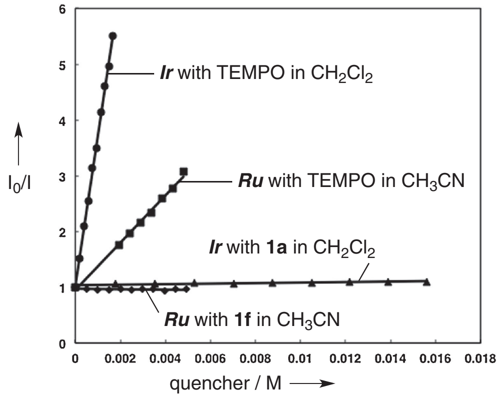
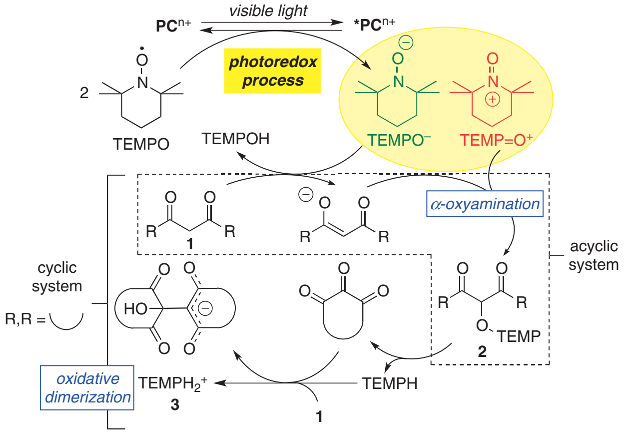


Figure 2. Luminescence quenching of ***Ru*** and ***Ir*** by **1a**, **1f**, and TEMPO.

To gain insight into the reaction mechanism, luminescence quenching studies were conducted (Figure 2). As a result, emission from the excited species of both of ***Ru*** and ***Ir*** was not quenched by 1,3-dicarbonyls **1a** and **1f** but by TEMPO. It is shown that the photoactivated photoredox catalysts (***PC**$^{n+}$) react with TEMPO first. Furthermore it was found that ***Ir*** in CH$_2$Cl$_2$ was quenched more efficiently by TEMPO than ***Ru*** in CH$_3$CN. Thus the higher catalytic activity of ***Ir*** may be ascribed to efficient electron transfer.[16]

Based on the experimental data, a possible reaction mechanism is presented in Scheme 3. First, visible-light irradiation of photoredox catalysts (**PC**$^{n+}$) causes excitation to ***PC**$^{n+}$, which relaxes to the ground state accompanying electron-transfer processes from and into TEMPO to generate TEMP=O$^+$ (an oxidant) and TEMPO$^-$ (a base), respectively. Deprotonation of 1,3-dicarbonyls **1** by TEMPO$^-$ followed by nucleophilic attack of the resultant ketoenolate at TEMP=O$^+$ gives the α-oxyaminated product **2**. This α-oxyamination process requires 2 equivalents of TEMPO with respect to **1**. In the reaction of cyclic dicarbonyls, it appears that the corresponding α-oxyaminated product **2** with a highly acidic methine proton can be susceptible to 1,2-dehydroamination to form 1,2,3-triketone, which undergoes aldol condensation with the ketoenolate generated by interaction with the eliminated amine (TEMPH) and **1**. Final C–to–O H$^+$-migration furnishes the



Scheme 3. A proposed mechanism.

oxidatively dimerized product **3**. In this oxidatively dimerized process, an equimolar amount of TEMPO to **1** is enough to transform **1** into **3**.

In summary, we have found that highly efficient α-oxyamination of acyclic 1,3-dicarbonyls using TEMPO without any pretreatment is achieved by the photoredox catalyst under visible light irradiation. Furthermore, it is revealed that the reaction of cyclic 1,3-dicarbonyls gives oxidatively dimerized products. In these oxidative transformations, $[Ir(ppy)_2(dtbbpy)]^+$ turns out to be a catalyst more efficient than $[Ru(bpy)_3]^{2+}$. The key steps involved in these reactions are *SET processes* between the photoredox catalyst and TEMPO, leading to photocatalytic disproportionation of TEMPO, i.e., production of TEMP=O$^+$ (an oxidant) and TEMPO$^-$ (a base) in situ.

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16 Redox potentials of photoexcited species and substrates are one of the important factors to induce photoredox reactions. We should also consider photophysical properties such as quantum yields and lifetimes for photoexcited species. Emission quantum yield of the ***Ir*** cat. is almost 4 times as high as that of the ***Ru*** cat. This might affect on rection efficiency. For photophysical data of the ***Ir*** cat. and the ***Ru*** cat., see: J. D. Slinker, A. A. Gorodetsky, M. S. Lowry, J. Wang, S. Parker, R. Rohl, S. Bernhard, G. G. Malliaras, *J. Am. Chem. Soc.* **2004**, *126*, 2763.