Photoinduced Oxyamination of Enamines and Aldehydes with TEMPO Catalyzed by $[Ru(bpy)_3]^{2+}$

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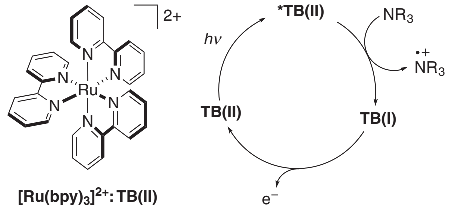
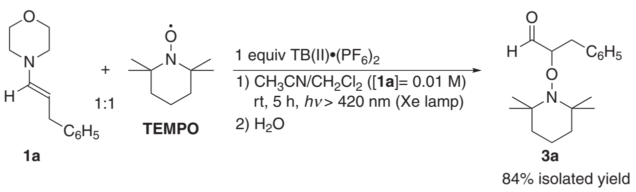
Tris(bipyridyl)ruthenium(II) ($[Ru(bpy)_3]^{2+}$: TB(II)) catalyzes oxidative coupling of enamines and aldehydes with 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) under irradiation of visible light to afford α-oxyaminated carbonyl compounds. The visible light irradiation is essential to generate the triplet excited state of *TB(II) which acts as an oxidizing agent. This is a new procedure for radical coupling based on single electron transfer mediated by photoactivated TB.

Homogeneous photocatalytic systems with unique light-driven redox properties have been studied extensively from the viewpoint of artificial photosynthesis, but only a limited number of examples of its application to organic synthesis have appeared.[1] Tris(bipyridyl)ruthenium(II) complex ($[Ru(bpy)_3]^{2+}$: TB(II)) is one of the most investigated photocatalysts due to its outstanding photo- and electrochemical properties originating from metal-to-ligand charge transfer (MLCT).[2] Its photosensitization effect related to catalysis is shown in Scheme 1.[3] Visible light irradiation of TB(II) forms the *TB(II) species, which in the presence of a sacrificial electron donor such as $N(CH_2CH_2OH)_3$ and $N(CH_2CH_3)_3$, is further converted to the reduced species ($[Ru(bpy)_3]^+$: TB(I)) via single electron transfer. Thus the photoexcited *TB(II) is capable of 1e-oxidation of tertiary amines including enamines.

We have developed some organometal-catalyzed reactions using TB(II) and its derivatives as an energy-transfer reagent.[4] However, the photocatalysis based on the above-mentioned single electron oxidation of amines has been investigated to a lesser extent, mainly because of the instability of the generated amine radicals. We extended the photochemical oxidation to enamines and found that photocatalytic reaction of enamines with 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) leading to α-oxyamination of carbonyl compounds. Oxyamination products are not only useful as initiators of radical polymerization[5] but also convertible to diols through reductive transformation.[6] Although the oxidative transformation of enamines using excess oxidant such as CAN and $FeCl_3$ in the presence of cooxidants has been reported,[7] a catalytic oxidation process would be more attractive from economic and environmental points of view. Recently, Nicewicz and MacMillan have reported independently that TB(II) catalyzed the oxidation of enamines leading to asymmetric C–C bond formation.[8] They developed organocatalysts to be combined with the photoredox catalyst. In contrast, we have intensively investigated the catalysis and energy transfer of TB(II).[4] Herein, we report C–O bond formation based on the catalytic oxidation of enamines by the photoactivated TB(II).



Scheme 1. Photosensitization process of TB(II).

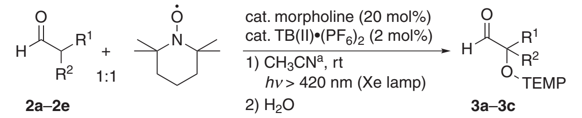


Scheme 2. Reaction of enamine with TEMPO in the presence of *TB(II).

TB(II) has proven to effect oxidative coupling of 4-(3-phenyl-1-propenyl)morpholine (**1a**) with TEMPO at room temperature under irradiation with visible light ($h\nu > 420\,\mathrm{nm}$), giving α-oxyaminated aldehyde **3a** in 84% isolated yield (Scheme 2). Notably, the reaction did not proceed at all without visible light irradiation, suggesting that the excited *TB(II) species is involved in this oxidative transformation.

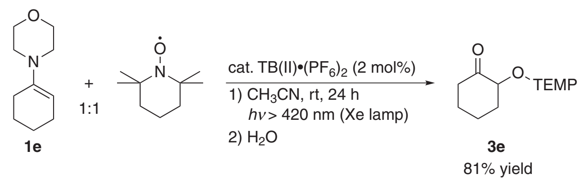
It is remarkable to note that (1) the amount of TB(II) can be reduced to a catalytic amount (2 mol %) and (2) 3-phenylpropionaldehyde (**2a**) can be directly transformed into the oxyaminated product **3a** in 56% isolated yield without prior conversion to enamine **1a**, when the reaction is carried out in the presence of a catalytic amount of morpholine (20 mol %) (Table 1, Entry 1).[9] Morpholine was essential to form the enamine intermediate in situ (Entry 2). Addition of a small excess amount of amine accelerated the conversion of aldehydes, while increasing the amounts of unidentified by-products (Entry 3). This reaction

Table 1. Catalytic oxyamination of aldehydes with TEMPO



Entry	R¹	R²	Time/h	Isolated yield/%
1	**2a**: H	$CH_2C_6H_5$	24	**3a**: 56
2[b]			15	no reaction
3[c]			15	**3a**: 45
4[c,d]			15	**3a**: 40
5	**2b**: H	$(CH_2)_6CH_3$	24	**3b**: 68 (83[e])
6	**2c**: H	$(CH_2)_3CH{=}CH(C_2H_5)$	24	**3c**: 54
7	**2d**: $-(CH_2)_5-$		24	no reaction
8	**2e**: cyclohexanone		24	no reaction

[a] [carbonyl compound] = 0.1 M. [b] No additive morpholine. [c] 1.2 equiv of morpholine was used. [d] In DMF. [e] Determined by ^1H NMR.

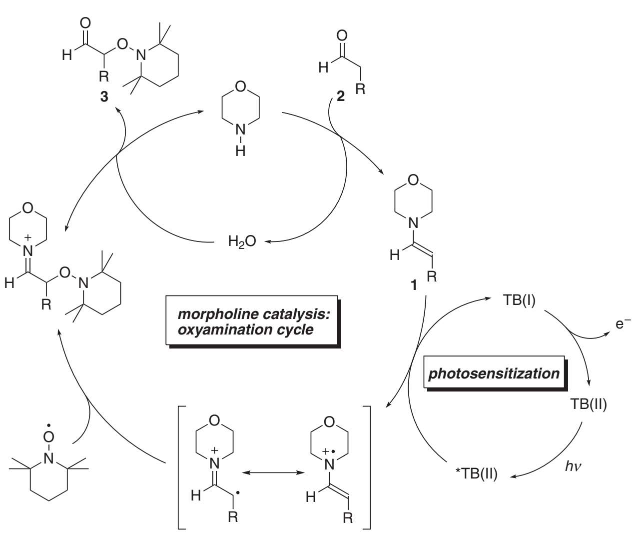


Scheme 3. Oxyamination of enamine derived from ketone.

proceeded equally well in CH_3CN and DMF (Entries 3 and 4). Other aldehydes **2b** and **2c** could be transformed under the same reaction conditions to the corresponding coupling products **3b** and **3c** (Entries 5 and 6). The (*Z*)-6-nonenal (**2c**) did not afford cyclic compounds resulting from radical cyclization but linear product **3c**. On the other hand, the cyclohexanecarboxaldehyde (**2d**) and cyclohexanone (**2e**) gave no α-oxyamination product (Entries 7 and 8), suggesting that efficient formation of enamine from secondary amine and carbonyl compounds seems to be crucial for the progress of this oxidative reaction. In fact, the reaction of 4-(1-cyclohexen-1-yl)morpholine (**1e**) gave the α-oxyaminated cyclohexanone (**3e**) in 81% yield (Scheme 3).[10]

Monitoring a CD_3CN solution of nonanal (**2b**), TEMPO, TB(II) (2 mol %), and morpholine (20 mol %) at room temperature by ^{1}H NMR spectroscopy showed a rapid appearance of two signals assigned to olefinic protons in the enamine at 5.8 ppm ($^3J_{HH} = 13$ Hz, doublet) and 4.4 ppm (broad multiplet), respectively. This result suggested a single isomer of the enamine was efficiently formed under these conditions. As visible light was irradiated to the reaction mixture, an increase of the COC*H*OTEMP signal at 4.0 ppm was observed with the smooth conversion of **2b** to **3b**. On the contrary, **3b** was not observed at all in the dark (see Supporting Information[11]), indicating that irradiation of visible light promotes this oxidation.

Although the reaction mechanism has not been clarified in detail yet,[12] photo- and electrochemical data supported the oxidation of enamines by the photoactivated TB. Emission data for TB(II) with **1e** or TEMPO exhibited a decrease in emission intensity of *TB(II). Cyclic voltammetry data for **1e** and TEMPO showed an irreversible oxidation wave at +0.55 V and a reversible redox wave at +0.62 V, respectively (see Supporting Information[11]). These data suggests photoactivated TB can easily oxidize **1e** rather than TEMPO. Based on these results, a possible catalytic cycle was proposed as summarized in Scheme 4. First of all, morpholine reacts with aldehyde **2** to give enamine **1**. Then, **1** is 1e-oxidized by the photoactivated TB(II), leading to the radical cation. Finally, radical coupling with TEMPO gives the product **3**, regenerating the morpholine by hydrolysis afterward.



Scheme 4. Possible reaction mechanism.

In summary, we found α-oxyamination of aldehydes with TEMPO using photoredox-active TB and morpholine as catalysts. The present photoinduced oxidative transformation with TB is a clean process that proceeds under mild conditions with minimal metal waste. Further efforts to apply to asymmetric oxidative transformation and to expand further the scope are now underway.

References and Notes

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9 Typical experimental procedure is as follows: A 20-mL Schlenk tube was charged with TEMPO (0.50 mmol), $TB(II){\cdot}(PF_6)_2$ (0.010 mmol), and CH_3CN (5 mL) under N_2. After **2** (0.50 mmol) had been introduced, morpholine (0.10 mmol) was added to the reaction solution. Then, the tube was degassed. The reactions were carried out at room temperature under irradiation of visible light ($h\nu > 420$ nm, Xe lamp at distance of 7 cm) for 24 h. The reaction was quenched with exposure to air and NH_4Cl (aq). The mixture was extracted with CH_2Cl_2 and organic layer was dried over anhydrous $MgSO_4$ and evaporated. The crude product was purified by preparative TLC to give **3**.
10 The reaction of 4-(cyclohexylidenemethyl)morpholine (**1d**) gave some products which were also obtained from the reaction without TEMPO. Characterization of products is now underway.
11 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.
12 Especially, electron acceptor in the photosensitization process is unclear for now. We will report on the detailed mechanism in a forward full paper.

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