Catalytic Oxidation of Silyl Enol Ethers to 1,2-Diketones Employing Nitroxyl Radicals

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Abstract: A novel and efficient method for the preparation of 1,2-diketones is reported. A series of α-diketones were readily prepared by the nitroxyl-radical-catalyzed oxidation of silyl enol ethers using magnesium monoperoxyphthalate hexahydrate (MMPP·6H_2O) as the co-oxidant.

Key words: oxidation, catalysis, enols, diketones, nitroxyl radical

1,2-Diketones are an important class of compounds frequently found in substructures of natural products and biologically active compounds.[1] Moreover, they constitute important intermediates in organic and medicinal chemistry as precursors of various biologically active heterocyclic compounds, such as imidazoles, triazoles, pyrazines, and quinoxalines.[2]

The direct oxidation of α-methylene ketones or their derivatives is an important transformation for the synthesis of 1,2-diketones. The conventional methods for this transformation, which are based on the use of stoichiometric amounts of toxic metal oxidants such as selenium oxide,[3] pyridinium chlorochromate,[4] and potassium permanganate,[5] have limited applications owing to the expanding demand for environmental conservation.

Several metal-free methods of synthesizing diketones, including the DMSO-mediated oxidation of α-methylene ketones or α-bromo ketones,[6] the photooxygenation of enamino ketones,[7] and the microwave-promoted oxidation of α-nosyloxy ketones by pyridine *N*-oxide,[8] have been developed. However they have disadvantages for practical use, such as strongly acidic conditions, cryogenic conditions, photooxidative conditions, and microwave irradiation conditions.

Recently, Jiang et al. have reported an excellent DABCO-catalyzed procedure.[9] Various benzil derivatives can be obtained from α-methylene ketones in high yield, although the process requires high reaction temperatures.

Hunter and Barton reported an alternative process for synthesizing 1,2-diketones using an oxoammonium ion derived from 2,2,6,6-tetramethylpipedine 1-oxyl [TEMPO (**1**); Figure 1].[10] They demonstrated that α-aminooxy ketones, prepared by the addition of ketones to an oxoammonium ion, are converted into 1,2-diketones by thermolysis. However, this method has rarely been used for synthesizing 1,2-diketones owing to the need for a stoichiometric amount of TEMPO. In addition, the TEMPO moiety is converted into its corresponding amine after the thermolysis of the N–O bond of an α-aminooxy ketone, which impedes the construction of a redox catalyst system. To address these issues, we have developed a redox catalytic cycle, in which the oxidation of an α-aminooxy ketone intermediate to *N*-oxide regenerates oxoammonium ions,[11] thereby completing the catalytic cycle. We envisaged that a less hindered class of nitroxyl radicals, such as AZADO (2-azaadamantane *N*-oxyl; Figure 1) (**2**) and Nor-AZADO (9-azanoradamantane *N*-oxyl) (**3**)[12] will accommodate productive interactions between an intermediate and an oxidant.

Herein, we report a practical method for the synthesis of diketones catalyzed by nitroxyl radicals using MMPP·6H_2O as the co-oxidant.

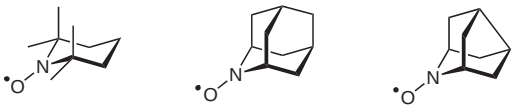

Figure 1 Structures of TEMPO, AZADO, and Nor-AZADO

We first examined the stoichiometric reaction of deoxybenzoine **4** and AZADO$^+BF_4^-$ (**5**),[13] the oxoammonium salt derived from AZADO, in which the expected addition reaction proceeded to give **6** in high yield at room temperature, although the reaction required a rather long time (Scheme 1, 91% after 24 h).

We then changed the substrate to a more reactive silyl enol ether **7a**, in which the addition reaction proceeded rapidly and the desired alkoxyl amine **6** was generated quantitatively. It was found that clean oxidation to benzil **8a** was realized by the one-pot oxidation of **6** using MMPP·6H_2O as the oxidant (Scheme 1).

We next explored the catalytic conditions (Table 1). The treatment of **7a** in the presence of 1.5 equivalents of MMPP·6H_2O and 20 mol% AZADO$^+BF_4^-$ (**5**) at room temperature for 24 hours afforded **7a** in 68% yield (Table 1, entry 1), along with α-hydroxylated by-products **9** and **10**, which were generated through the direct Rubottom oxidation[14] of **7a**. The reaction time was prolonged when

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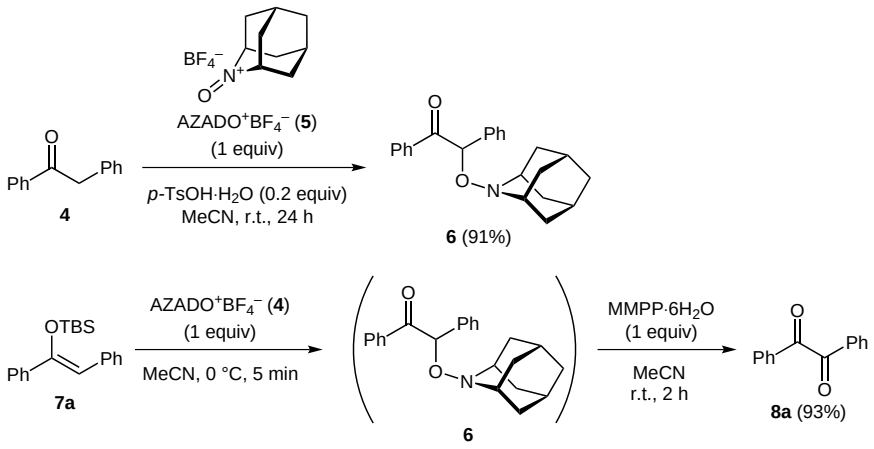


Scheme 1 Stoichiometric reaction of oxoammonium ion

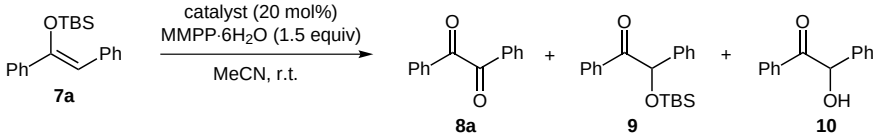
a nitroxyl radical was used as the catalyst instead of oxoammonium salt (Table 1, entry 2). The reaction was sensitive to the structure of the nitroxyl radical (Table 1, entries 2–4). Hindered TEMPO did not work as a catalyst under the conditions (1%, Table 1, entry 3). Meanwhile, the yield of **8a** was highest when least-hindered Nor-AZADO[12f] was used, even though the reaction was not completed even after 30 hours (60%, Table 1, entry 4).

Upon obtaining the results of the above experiments, we investigated additives for accelerating the reaction. We examined the reaction in the presence of $LiBF_4$ with a view to generate Nor-AZADO$^+BF_4^-$ (**11**) in situ,[15] in which the reaction was completed within two hours (Table 1, entry 5). However the yield remained at 61% because the direct Rubottom oxidation of **7a** was also accelerated by $LiBF_4$. A significant improvement in the yield was achieved by changing the procedure to the reverse addition of **7a** (Method B, Table 1, entry 6), in which the direct Rubottom oxidation of **7a** was suppressed and the yield increased to 86%. We also confirmed that no **8a** was formed in the absence of a catalyst (Table 1, entry 7).

We attempted the reaction of deoxybenzoine **4** instead of silyl enol ether **7a** under the optimized catalytic conditions (Table 1, entry 6), in which no **8a** was formed.

The scope and limitations of this catalytic system are shown in Table 2. Most of the reactions to form benzil derivatives proceeded in moderate to high yield (55–85%, Table 2, entries 1–9). An electron-withdrawing group at the aromatic ring lowered the yield (55%, Table 2, entry 5). Heterocyclic substrates such as indole and benzooxazole derivatives were converted into their corresponding diketones in high yield (81–89%, Table 2, entries 10 and

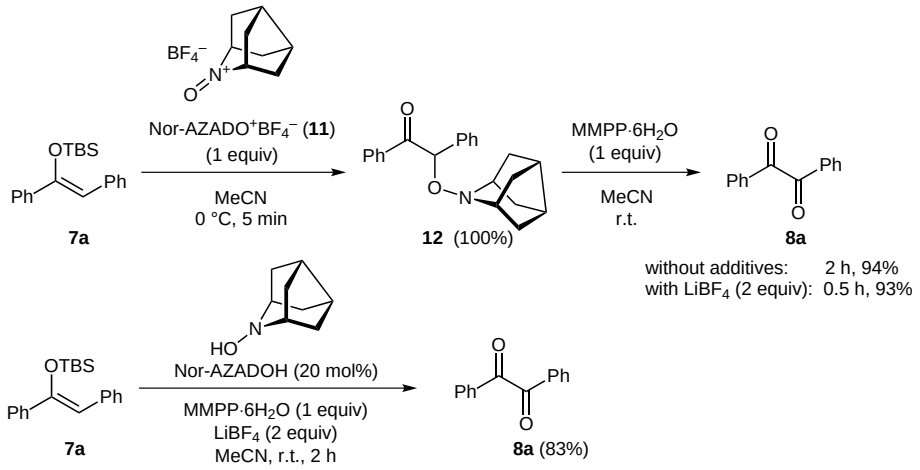
Table 1 Experimental Conditions and Results for the Catalytic Oxidation of **7a** to **8a**



Entry	Method[a]	Catalyst (20 mol%)	Additive (2 equiv)	Time (h)	Production ratio[b] **7a**/**8a**/**9**/**10**	Yield
1	A	AZADO$^+BF_4^-$		24	N.D./75/22/N.D.	68%
2	A	AZADO		30	38/42/12/3	48%
3	A	TEMPO		30	8/1/76/4	1%
4	A	Nor-AZADO		30	29/55/8/2	60%
5	A	Nor-AZADO	$LiBF_4$	2	N.D./64/25/7	61%
6	B	Nor-AZADO	$LiBF_4$	2	N.D./92/3/4	86%
7	B			2	N.D./N.D./62/19	–

[a] Method A: MMPP·$6H_2O$ (1.5 equiv) was added to the mixture of **7a** (0.5 mmol), catalyst (20 mol%) and additive (2 equiv) in MeCN (5 mL). Method B: A solution of **7a** (0.5 mmol) in MeCN (5 mL) was added to the mixture of MMPP·$6H_2O$ (1.5 equiv), catalyst (20 mol%) and additive (2 equiv) in MeCN (5 mL).

[b] The ratio of HPLC peak area; N.D. = not detected.

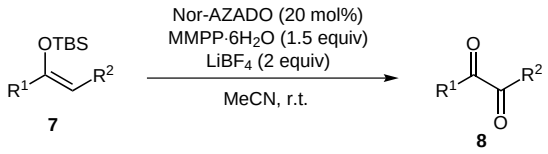


Scheme 2 Isolation and oxidation of intermediate **12**

11). Silyl enol ethers that have an alkyl substituent resulted in moderate yield (37–68%, Table 2, entries 12–14).

To study the reaction pathway, we isolated the α-aminooxy ketone intermediate **12**, which was readily prepared by the addition reaction of **7a** with Nor-AZADO$^+$BF$_4^-$ (**11**)[13] (Scheme 2). It was also confirmed that **12** was oxidized to **8a** in high yield with MMPP·6H$_2$O, and the reaction was accelerated by the addition of LiBF$_4$, which indicate an effect of LiBF$_4$ as Lewis acid. We also demonstrated that Nor-AZADOH, which is supposed to be formed after oxidation of **12,** catalyze the reaction, proving that the reaction involves redox catalyst system.

Table 2 Scope and Limitation



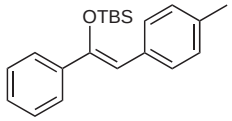
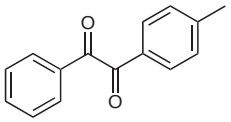
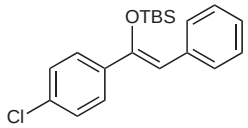
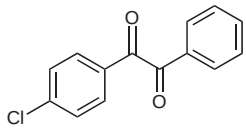
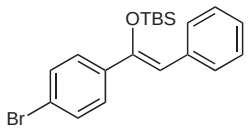
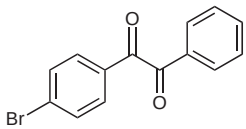
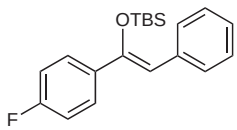
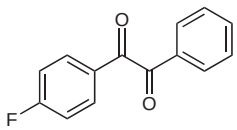
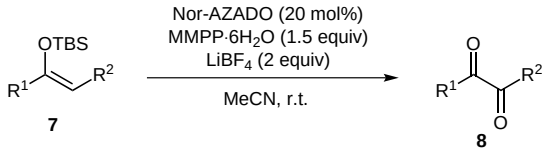
Entry[a]	Substrate	Product	Time (h)	Yield (%)
1	 **7b**	 **8b**	2	85
2	 **7c**	 **8c**	3	81
3	 **7d**	 **8d**	3	81
4	 **7e**	 **8e**	2	83

Table 2 Scope and Limitation (continued)



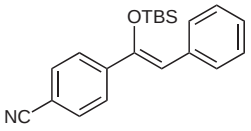
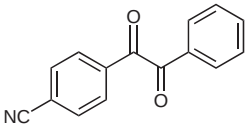
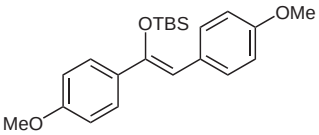
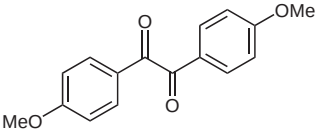
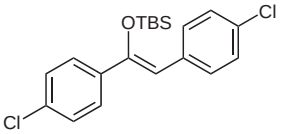
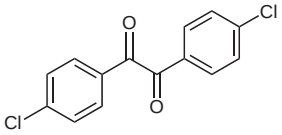
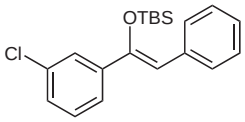
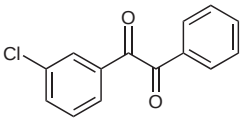
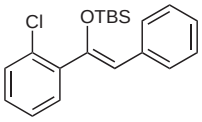
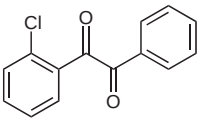
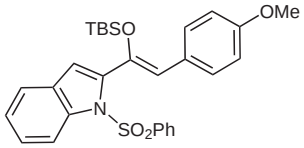
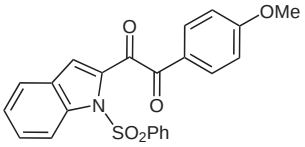
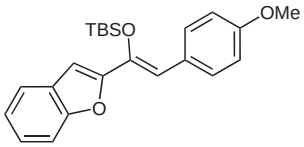
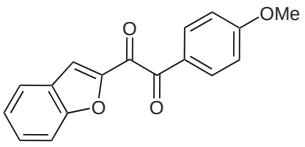
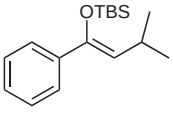
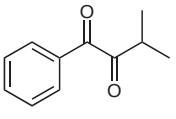
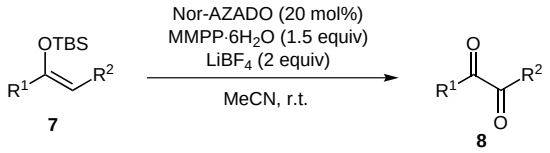
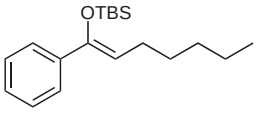
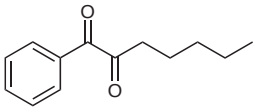
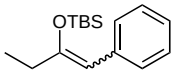
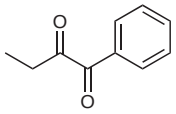
Entry[a]	Substrate	Product	Time (h)	Yield (%)
5	 **7f**	 **8f**	26	55
6	 **7g**	 **8g**	1	84
7	 **7h**	 **8h**	3	68
8	 **7i**	 **8i**	20	76
9	 **7j**	 **8j**	21	63
10	 **7k**	 **8k**	3	89
11	 **7l**	 **8l**	2	81
12	 **7m**	 **8m**	1	68

Table 2 Scope and Limitation (continued)

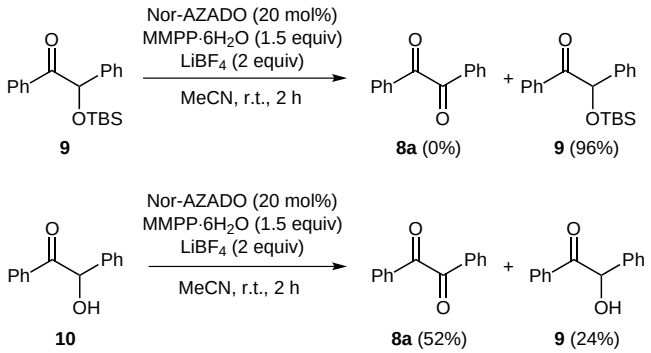


7 8

Entry[a]	Substrate	Product	Time (h)	Yield (%)
13	 **7n**	 **8n**	1	44
14	 major/minor = 83:17 **7o**	 **8o**	3	37

[a] Reaction procedure: A solution of **7** (0.5 mmol) in MeCN (5 mL) was added to the mixture of MMPP·6H_2O (1.5 equiv), catalyst (20 mol%) and additive (2 equiv) in MeCN (5 mL).

To exclude another plausible route involving an initial Rubottom oxidation followed by the oxidation of α-hydroxy ketone **9**, we treated the α-hydroxylated by-products **9** and **10** with Nor-AZADO, MMPP·6H_2O, and $LiBF_4$ under the reaction conditions (Scheme 3), in which no reaction was observed in the case of **9**, and the oxidation of **10** resulted in moderate yield.



Scheme 3 Oxidation of **9** and **10**

On the basis of the above results, we propose a plausible pathway for the catalytic oxidation of silyl enol ethers to 1,2-diketones (Scheme 4). The reaction involves the initial formation of the α-aminooxy ketone **12** with the addition of **7a** to Nor-AZADO$^+X^-$, which is generated in situ through the oxidation of Nor-AZADO. Then, **8a** and Nor-AZADOH are produced through the oxidation of **12** by MMPP·6H_2O. Nor-AZADOH is oxidized to Nor-AZADO$^+X^-$ by MMPP·6H_2O to complete the catalytic cycle.

In summary, we have demonstrated a novel method for the synthesis of 1,2-diketones through the nitroxyl-radical-catalyzed oxidation of silyl enol ethers using MMPP·6H_2O as the oxidant at room temperature.[16] The simple operation and mild room temperature and metal-free conditions are advantages for the practical synthesis of 1,2-diketones.

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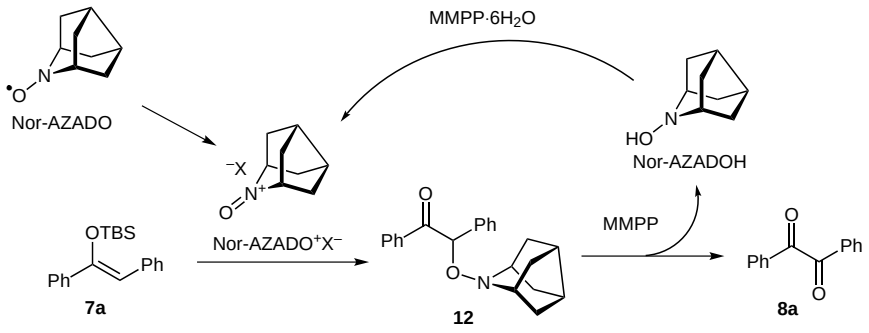

Scheme 4 Plausible reaction pathway

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References and Notes

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(16) **General Procedure for the Catalytic Oxidation of Silyl Enol Ether to 1,2-Diketone**: To a solution of MMPP·$6H_2O$ (565 mg, 0.994 mmol), Nor-AZADO (18 mg, 0.133 mmol) and $LiBF_4$ (124 mg, 1.33 mmol) in MeCN (6.6 mL) was added dropwise a solution of **7a** (206 mg, 0.663 mmol) in MeCN (6.6 mL) over 4 h and stirred for 2 h at r.t. Solutions of 5% aq $NaHCO_3$ (5 mL) and 20% aq $Na_2S_2O_3$ (5 mL) were added and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **8a** (120 mg, 0.571 mmol, 86%).

