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Oxidative Conversion of Silyl Enol Ethers to α,β-Unsaturated Ketones Employing Oxoammonium Salts

Masaki Hayashi,[‡] Masatoshi Shibuya,[†] and Yoshiharu Iwabuchi*,[†]

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aobayama, Sendai 980-8578, Japan, and Process Technology Research Laboratories, Daiichi Sankyo Co., Ltd., 1-12-1 Shinomiya, Hiratsuka, Kanagawa 254-0014, Japan

iwabuchi@mail.pharm.tohoku.ac.jp

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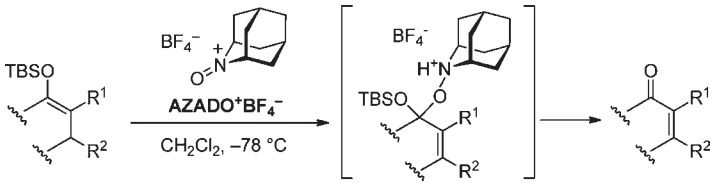
ABSTRACT



The oxidative conversion of silyl enol ethers to α,β-unsaturated ketones using a less-hindered class of oxoammonium salts (AZADO$^+$BF$_4^-$) is described. The reaction proceeds via the ene-like addition of oxoammonium salts to silyl enol ethers.

Oxoammonium salts are attractive oxidants whose use continuously expands in contemporary organic chemistry.[1] They enable efficient alcohol oxidation either catalytically or stoichiometrically[2] and effect particular oxidative transformations such as the α-aminooxylation of ketone and enol ethers,[3] the ene-like addition to alkenes to form allylic alkoxyl amines,[4] the oxidative rearrangement of tertiary allylic alcohols,[5] and others.[6−9]

We have recently disclosed that a less-hindered class of oxoammonium salts, generated from the corresponding nitroxyl radicals, namely, 2-azaadamantane *N*-oxyls (AZADO and 1-Me-AZADO),[10a,f] 9-azabicyclo-[3.3.1]nonane *N*-oxyl (ABNO),[10b] and 9-aza-noradamantane *N*-oxyl (Nor-AZADO),[10g] exhibit superior catalytic activity to that derived from 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and the related derivatives in alcohol oxidation[10,11] (Figure 1). During our continuous investigation of the chemistry of oxoammonium salts/nitroxyl radicals, we encountered an unprecedented reaction of oxoammonium salts with silyl enol ethers.

[‡] Daiichi Sankyo Co., Ltd.
[†] Tohoku University.

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(2) For reviews on alcohol oxidation, see: (a) Bobbitt, J. M.; Flores, M. C. L. *Heterocycles* **1988**, *27*, 509–533. (b) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153–1174. (c) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661–3688. (d) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051–1071. (e) Merbouh, N.; Bobbitt, J. M.; Brückner, C. *Org. Prep. Proced. Int.* **2004**, *36*, 1–31. (f) Caron, S.; Dugger, R. W.; Ruggeri, S. G.; Ragan, J. A.; Ripin, D. H. B. *Chem. Rev.* **2006**, *106*, 2943–2989. (g) Vogler, T.; Studer, A. *Synthesis* **2008**, 1979–1993. (h) Ciriminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2010**, *14*, 245–251.

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Herein, we report a facile and metal-free oxidative conversion of silyl enol ethers to α,β-unsaturated ketones employing oxoammonium salts, which can be a useful alternative to current methods,[12–16] such as the Pd(II)-based Saegusa–Ito reaction,[12] selenylation–selenoxide elimination method,[13] Mukaiyama reaction,[14] and a hypervalent-iodine-based method.[15]

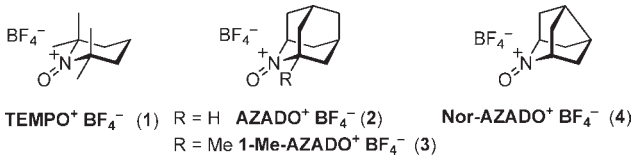
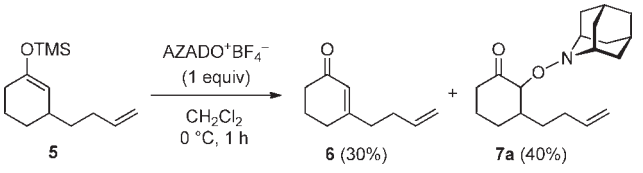


Figure 1. Structures of oxoammonium salts.

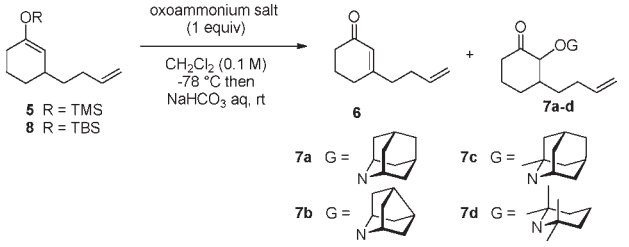
Oxoammonium salts derived from TEMPO react with enol ethers to give α-aminooxy ketones.[3] Thus, we examined an α-aminooxylation reaction of silyl enol ether **5** employing the azaadamantane-derived oxoammonium salts **2**–**4**[10] and surprisingly confirmed that α,β-unsaturated ketone **6** was generated along with the anticipated α-aminooxy ketone **7a** (Scheme 1).

Scheme 1. Formation of α,β-Unsaturated Ketone through Treatment of Silyl Enol Ether with Oxoammonium Salt



Prompted by the promising use of the side reaction, we sought optimal conditions to enhance the yield of the α,β-unsaturated ketone **6** (Table 1). It was found that the yield and chemoselectivity were improved by carrying out the reaction at low temperatures (entries 1, 2). The chemoselectivity for the α,β-unsaturated ketone was further improved by switching the TMS group to the TBS group (entries 2, 3).[17] We next screened a panel of oxoammonium salts and found that the chemoselectivity is sensitive to the structure of the oxoammonium salt (entries 3–6), for which the best result was obtained in the case of AZADO$^+$BF$_4^-$ (entry 3). It is interesting to point out that TEMPO$^+$BF$_4^-$ (**1**) gave the α-aminooxy ketone **7d** as the major product, showing an interesting contrast to less-hindered oxoammonium salts (entry 6).

Table 1. Optimization of Reaction Conditions for α,β-Unsaturated Ketone **6**



entry	R	oxoammonium salts	temp	time	yield
1	TMS	AZADO$^+$BF$_4^-$	0 °C	1 h	**6** (30%) **7a** (40%)
2	TMS	AZADO$^+$BF$_4^-$	–78 °C	1 h	**6** (65%) **7a** (28%)
3	TBS	AZADO$^+$BF$_4^-$	–78 °C	1 h	**6** (80%) **7a** (6%)
4	TBS	Nor-AZADO$^+$BF$_4^-$	–78 °C	1 h	**6** (59%) **7b** (11%)
5	TBS	Me-AZADO$^+$BF$_4^-$	–78 °C	1 h	**6** (45%) **7c**(16%)
6	TBS	TEMPO$^+$BF$_4^-$	–78 °C	3 h	**6** (19%) **7d** (53%)

To explore the effect of counteranion of oxoammonium salts, we screened the various salts (Table 2). Although there were no significant differences in the reactivity, apparent differences were observed in the chemoselectivity

(5) (a) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *J. Org. Chem.* **2008**, *73*, 4750–4752. (b) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *Org. Lett.* **2008**, *73*, 4715–4718. (c) Vatèle, J.-M. *Synlett* **2008**, 1785–1788. (d) Vatèle, J.-M. *Synlett* **2009**, 2143–2145. (e) Vatèle, J.-M. *Tetrahedron* **2010**, *66*, 904–912.

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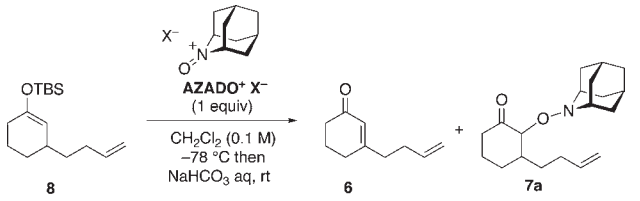
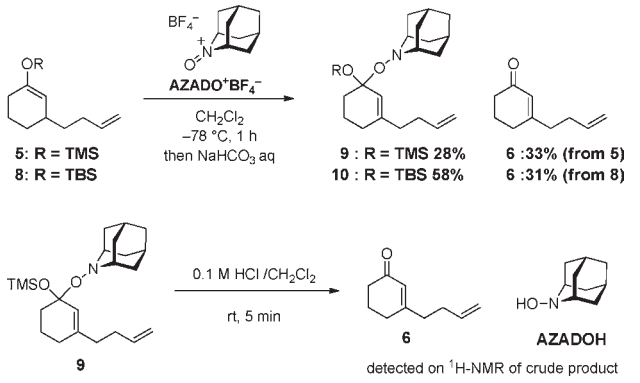
Table 2. Optimization of Reaction Conditions: Effect of Counteranion of Oxoammonium Salts



entry	X^-	time	product ratio* 6 / 7a
1	BF_4^-	1 h	94 / 6
2	PF_6^-	1 h	91 / 9
3	ClO_4^-	1 h	90 / 10
4	SbF_6^-	1 h	88 / 12
5	Cl^-	1 h	84 / 16
6	NO_3^-	1 h	76 / 24

[a] Product ratio was determined by ^{1}H NMR of the crude product.

Scheme 2. Isolation of Mixed Acetal Intermediates and Their Conversion to α,β-Unsaturated Ketone



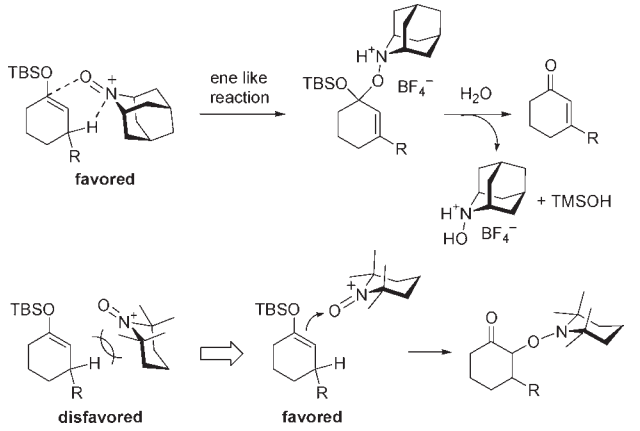
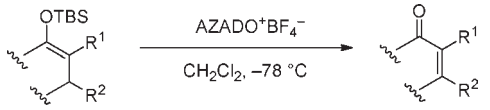
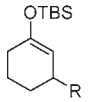
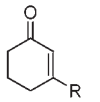
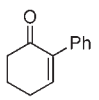
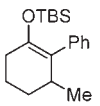
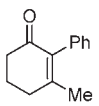
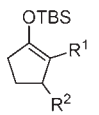
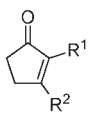
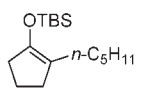
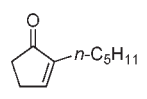
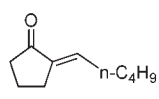
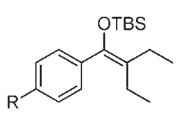
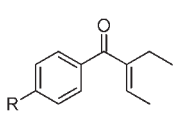
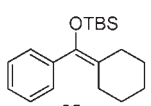
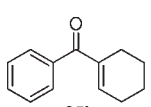
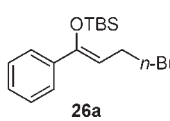
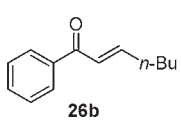


Figure 2. Plausible reaction pathway.

Table 3. Scope of the Reaction[a]



entry	substrates	products	yield
1 2 3	 **11a-13a**	 **11b-13b**	**11**: R = Ph, 88% **12**: R = *n*-Bu, 88% **13**: R = vinyl, 80%
4	 **14a**	 **14b**	83%
5	 **15a**	 **15b**	88%
6 7 8 9 10	 **16a-20a**	 **16b-20b**	**16**:R^1 = H, R^2 = Ph, 85% **17**:R^1 = Ph, R^2 = H, 71% **18**:R^1 = Ph, R^2 = *n*-Bu, 77% **19**:R^1 = Ph, R^2 = Me, 82% **20**:R^1 = *n*-C_5H_{11}, R^2 = Me, 76%
11	 **21a**	 **21b**	 **21c** 73% **21b**:**21c**=7:3
12 13 14	 **22a-24a**	 **22b-24b**	**22**:R = H 56% **23**:R = OMe 58% **24**:R = CF_3 19%
15	 **25a**	 **25b**	87%
16[b]	 **26a**	 **26b**	6%

[a] All reactions were carried out using 1 equiv of $AZADO^+BF_4^-$ in CH_2Cl_2 at −78 °C for 1 h, followed by treatment with sat. aqueous $NaHCO_3$ at rt. [b] The corresponding α-aminooxylated ketone was obtained in 80% yield.

depending on the type of counteranion, in which the best result was obtained in the case of BF_4 salt (entry 1).

During the experiments, we observed a transient intermediate on analytical TLC, which was ultimately isolated upon careful quench/workup of the reaction and determined to be the mixed acetal **9** or **10** (Scheme 2) (see Supporting Information, SI). The treatment of **9** with 0.1 M HCl in CH_2Cl_2 afforded the α,β-unsaturated ketone **6** and AZADOH.

The plausible reaction pathway of this novel transformation is shown in Figure 2. The mixed acetal intermediate (**9**, **10**) may be formed through the ene-like addition[4c] of the oxoammonium salt onto the carbon−carbon π-bond of the silyl enol ether, the hydrolysis of which in the workup leads to the α,β-unsaturated ketone **6**. The difference in steric hindrance between TEMPO and AZADO provides a reasonable rationale for the selectivity of these radicals: the N═O double bond of less-hindered $AZADO^+$ can approach and attack the C═C—C—H moiety of the silyl enol ether, which induces an ene-like reaction. On the other hand, a similar approach by $TEMPO^+$ is disfavored owing to the steric hindrance of four bulky methyl groups. As a result, TEMPO-derived oxoammonium ion attacks the π-electrons of silyl enol ether to give an α-aminooxy ketone.[3]

The scope and limitations of this reaction are demonstrated in Table 3.[18] Six- and five-membered ring substrates, which have aryl, alkyl, and alkenyl substituents, were smoothly converted to the corresponding products in high yield (entries 1−11). Unfortunately, a seven-membered substrate, namely, 3-phenylcyclohept-1-enyl *tert*-butyldimethylsilyl ether, only gave the α-aminooxylated ketone (see SI). The reaction of tetrasubstituted acyclic silyl enol ethers proceeded in moderate to high yield except **24a** having an electron-withdrawing group on the aromatic ring (entries 12−15), which were converted to α,β-unsaturated ketones stereoselectively. E isomers were obtained as a single isomer (entries 12−14). Meanwhile, the trisubstituted acyclic substrate (**26a**) resulted in low yields because of predominant α-aminooxylation (entry 16). It should be stressed that AZADOH is facilely recovered after conventional workup and simple recrystallization and used to regenerate $AZADO^+BF_4^-$ (see SI).

In summary, we disclose a oxidative conversion of silyl enol ethers to α,β-unsaturated ketones by employing a less-hindered class of oxoammonium salts, the operational simplicity of which offers a useful option for the synthesis of α,β-unsaturated ketones from ketones. This study highlights the critical difference in chemoselectivity between less-hindered oxoammonium ions and TEMPO-derived ones, which should inspire the development of useful chemistry based on oxoammonium salts.

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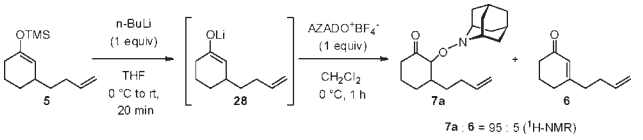
Supporting Information Available. Experimental procedures, characterization data, and copy of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) For other reported methods for the synthesis of α,β-unsaturated ketones from silyl enol ethers, see: (a) Evans, P. A.; Longmire, J. M.; Modi, D. P. *Tetrahedron Lett.* **1995**, *36*, 3985–3988. (b) Friedrich, E.; Lutz, W. *Angew. Chem., Int. Ed.* **1977**, *16*, 413–415. (c) Jung, M. E.; Pan, Y.-G.; Rathke, M. W.; Sullivan, D. F.; Woodbury, R. P. *J. Org. Chem.* **1977**, *42*, 3961–3963. (d) Ryu, I.; Murai, S.; Hatayama, Y.; Sonoda, N. *Tetrahedron Lett.* **1978**, *19*, 3455–3458. (e) Magnus, P.; Lacour, J.; Evans, P. A.; Rigollier, P.; Tobler, H. *J. Am. Chem. Soc.* **1998**, *120*, 12486–12499.

(17) We also attempted a reaction of lithium enolate, **28**, which is prepared in situ from **5**, although a trace amount of α,β-unsaturated ketone **6** was observed because of predominant α-aminooxylation.



(18) The silyl enol ether substrates (**11a**−**13a** and **15a**−**21a**) were prepared by conjugate cuprate addition or conjugate reduction of α,β-unsaturated ketones followed by quenching with TBSCl. The substrates (**14a** and **22a**−**26a**) were prepared by silyl enolization of ketones (see SI).