

TEMPO/ NaIO_4 – SiO_2 : A Catalytic Oxidative Rearrangement of Tertiary Allylic Alcohols to β -Substituted α,β -Unsaturated Ketones

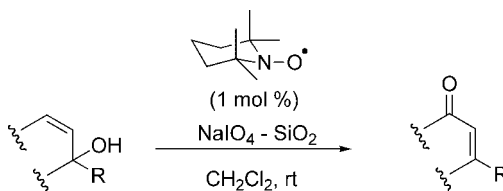
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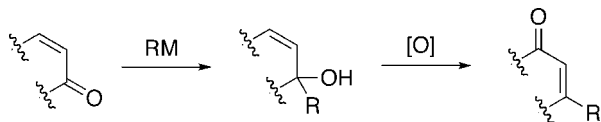
ABSTRACT



The novel catalytic method for the oxidative rearrangement of tertiary allylic alcohols to β -substituted α,β -unsaturated ketones is described. $\text{TEMPO}/\text{NaIO}_4$ – SiO_2 causes facile and efficient oxidative rearrangement of various acyclic substrates as well as medium-sized and macrocyclic substrates.

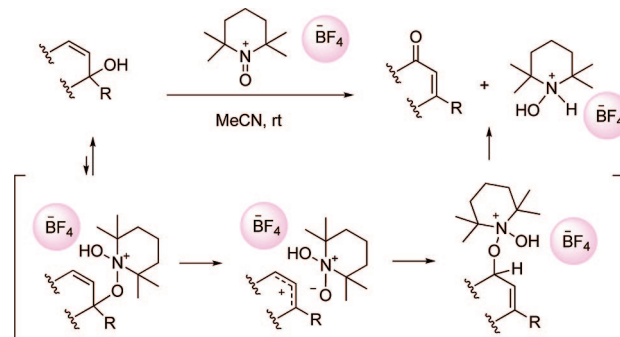
An α,β -unsaturated ketone is an exceptional motif that offers versatility in organic synthesis. The alkylative carbonyl transposition of α,β -unsaturated ketones, which entails the 1,2-addition of organometallic reagents and the oxidative rearrangement of the resulting tertiary allylic alcohols to furnish β -substituted α,β -unsaturated ketones, is a tactic that further extends the synthetic latitude of this functionality (Scheme 1). Unfortunately, the scope of this method is

Scheme 1. Alkylative Carbonyl Transposition of α,β -Unsaturated Ketones



limited due to the lack of scalable, green methods that enable the second step: the oxidative rearrangement of tertiary allylic

Scheme 2. $[\text{TEMPO}^+][\text{BF}_4^-]$ -Mediated Oxidative Rearrangement of Tertiary Allylic Alcohols



alcohols. Thus, until recently, only methods using stoichiometric amounts of toxic oxochromium (VI)-based reagents had been known.^{1–3} To address this problem, we have explored methods enabling the oxidative 1,3-rearrangement of tertiary allylic alcohols to β -substituted α,β -unsaturated

Table 1. Evaluation of Catalytic Conditions

entry	catalyst (equiv)	additive (equiv)	oxidant (equiv)	solvent	time (h)	yield (%)
1	[TEMPO ⁺][BF ₄ ⁻] (1.1)			MeCN	0.1	94
2	TEMPO (0.05)		PhI(OAc) ₂ (1.5)	MeCN	24	5
3	TEMPO (0.05)	LiBF ₄ (1.5)	PhI(OAc) ₂ (1.5)	MeCN	1	27
4	[TEMPO ⁺][BF ₄ ⁻] (0.05)		PhI(OAc) ₂ (1.5)	MeCN	0.1	64
5	[TEMPO ⁺][BF ₄ ⁻] (0.05)	H ₂ O (3.0)	PhI(OAc) ₂ (1.5)	MeCN	2	80
6	[TEMPO ⁺][BF ₄ ⁻] (0.05)	H ₂ O (10.0)	PhI(OAc) ₂ (1.5)	MeCN	7	60
7	[TEMPO ⁺][BF ₄ ⁻] (0.05)		PhI(TFA) ₂ (1.5)	MeCN	1	42
8	[TEMPO ⁺][BF ₄ ⁻] (0.05)		NaIO ₄ (1.5)	CH ₂ Cl ₂ -H ₂ O	2	85
9	[TEMPO ⁺][BF ₄ ⁻] (0.05)		NaIO ₄ -SiO ₂ (2.0)	CH ₂ Cl ₂	0.5	90
10	TEMPO (0.01)		NaIO ₄ -SiO ₂ (2.0)	CH ₂ Cl ₂	2	92

ketones and have reported two environmentally friendly alternatives using IBX⁴ and oxoammonium salts.^{5–9}

In discovering the markedly productive method using oxoammonium salts, such as [TEMPO⁺][BF₄⁻] and [TEMPO⁺][SbF₆⁻], we identified that bulky, less nucleophilic counteranions such as BF₄⁻ and SbF₆⁻ play indispensable roles in this particular transformation (Scheme 2).⁵ With this insight, we have begun investigations to find agents that make oxoammonium ions work catalytically.¹⁰ We disclose herein the novel catalytic oxidative 1,3-rearrangement of tertiary allylic alcohols to β -substituted α,β -unsaturated ketones.

We started screening reagents capable of converting **1a** to **1b**, where PhI(OAc)₂¹¹ was employed as the bulk oxidant,

in light of the satisfactory precedents¹² in the catalytic oxidation of alkenyl substrates using nitroxyl radical/oxoammonium ion as catalyst (Table 1).^{13,14}

Typical catalytic conditions with TEMPO/PhI(OAc)₂ only gave rise to a sluggish reaction, producing **1b** in 5% after 24 h, along with recovered **1a** (entry 2). Simple addition of 1.5 equiv of LiBF₄ to this reaction slightly improved the situation to give **1b** in 27% yield (entry 3). Notably, [TEMPO⁺][BF₄⁻] resulted in the better turnover with PhI(OAc)₂ to convert **1a** to **1b** in 64% yield within 10 min, supporting the important role of BF₄⁻ anion, although it was accompanied by 20% yield of 1-acetoxy-3-butylcyclohex-2-ene (**1c**) (entry 4). Addition of 3 equiv of H₂O effectively improved the catalytic performance of TEMPO⁺, yielding **1b** in 85% yield, by suppressing production of **1c**, while addition of 10 equiv of H₂O attenuated the yield to 60% (entries 5 and 6). The use of PhI(TFA)₂ as bulk oxidant induced decomposition (entry 7). We next examined an inorganic version of a hypervalent iodine reagent, NaIO₄, to determine its effect (entry 8).¹⁸ Use of NaIO₄ on SiO₂ brought about further improvement in the catalytic efficiency (entry 9).¹⁹ Ultimately, it was found that NaIO₄-SiO₂ allowed us to use TEMPO, indicating that IO₄⁻ exerts a profound effect on TEMPO⁺, similar to that of BF₄⁻ and

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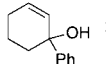
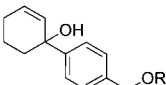
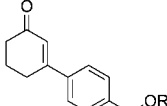
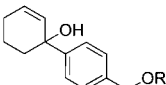
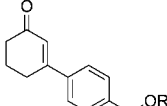
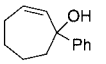
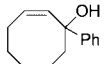
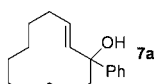
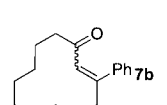
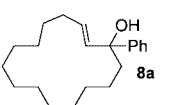
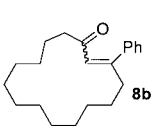
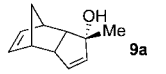
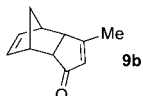
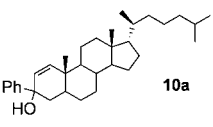
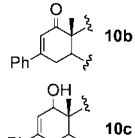
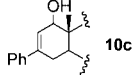
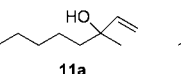
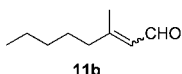
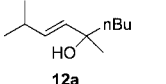
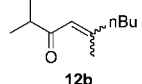
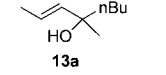
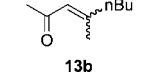
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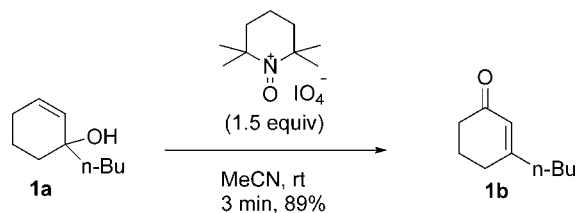
Table 2. Scope and Limitations of Catalytic Oxidative Rearrangement

entry	substrate	product	time (h)	yield (%) ^a
1			2	92
2			2	83
3			2	96
4			8	94
5			14	92
6			24	89 ^{b,c}
7			24	92 ^{b,c}
8			12	81 ^c
9		 	4	9(78) ^c
10			24	0 ^c
11			20	76 ^{b,c}
12			15	84 ^{c,d}

^a Standard reaction conditions employed 1 mol % of TEMPO and 2 equiv of NaIO₄ on silica gel in CH₂Cl₂ at rt. ^b E:Z = 2:1. ^c The reaction was performed with 10 mol % of TEMPO and 4 equiv of NaIO₄ on silica gel. ^d E:Z = 3.6:1.

SbF₆⁻. Use of NaIO₄ as a terminal oxidant in TEMPO-catalyzed alcohol oxidation was recently reported, in which

Scheme 3



the addition of 10 mol % of NaBr was essential for efficient reaction.¹⁸ Therefore, it should be stressed that the catalytic oxidative 1,3-transposition can be conducted without the aid of NaBr.

The scope and limitations of this new catalytic system are demonstrated in Table 2. Six-, seven-, and eight-membered substrates readily responded to the oxidative rearrangement to give the expected β -substituted α,β -ketones in high yield (entries 1–5). Protecting groups such as TBS as well as TBDPS tolerated the reaction conditions (entries 2 and 3). Macrocyclic substrates²⁰ and tricyclic substrate also furnished the expected products in good yields, although 10 mol % of TEMPO was needed. The steroid **10a** afforded the secondary allylic alcohol **10c**, which resisted further oxidation due to steric problems. Unfortunately, TEMPO/NaIO₄–SiO₂ could not effect the oxidative rearrangement of terminal olefinic substrates (entry 10),²¹ although internal olefinic substrates afforded the desired products in good yield (entries 11 and 12).

We prepared [TEMPO⁺][IO₄⁻] and examined the oxidative rearrangement of 1-butylcyclohexanol (**1a**) to confirm its high reactivity: the reaction was over within 3 min to furnish **1b** in 89% yield,²² indicating that SiO₂ is not essential for the promotion of the 1,3-allylic rearrangement (Scheme 3).

(12) Selected examples of successful uses of cat. TEMPO/PhI(OAc)₂ oxidation in complex natural product synthesis, see: (a) Mandal, M.; Yun, H.; Dudley, G. B.; Lin, D.; Tan, D. S.; Danishefsky, S. J. *J. Org. Chem.* **2005**, *70*, 10619–10637. (b) Nicolaou, K. C.; Kofitis, T. V.; Vyskocil, S.; Petrovic, G.; Tang, W.; Frederick, M. O.; Chen, D. Y.-K.; Li, Y.; Ling, T.; Yamada, Y. M. A. *J. Am. Chem. Soc.* **2006**, *128*, 2859–2872. (c) Paterson, I.; Ashton, K.; Britton, R.; Cecere, G.; Chouraqui, G.; Florence, G. J.; Stafford, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6167–6171.

(13) In our previous work leading to the discovery of oxoammonium salt-mediated oxidative rearrangement,⁵ we conducted a screening of several well-established terminal oxidants, including NaOCl,¹⁵ Oxone,¹⁶ and PhI(OAc)₂, where only PhI(OAc)₂ gave the clean spot of the desired product although the reaction was sluggish. See the Supporting Information.

(14) According to the comment by one of the reviewers of this manuscript, we examined the feasibility of cat. TEMPO/I₂ conditions¹⁷ for the oxidative rearrangement of **1a** in 10% aq NaHCO₃–CH₂Cl₂ and obtained **1b** in 24% yield from multiple spots of the reaction products. See the Supporting Information for details.

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In summary, we have developed the novel catalytic method for efficient oxidative rearrangement by employing 1 mol % of TEMPO and NaIO₄ on silica gel. The broad substrate applicability extends the synthetic scope of the alkylative carbonyl transposition of α,β -unsaturated ketones.

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(21) When we used stoichiometric amounts of oxoammonium salts, it was observed that the addition of H₂O prolonged the reaction time. Thus it was possible that water contained in silica gel would retard the reaction.

form Japan Society for the Promotion of Science and Encouragement of Young Scientists (B) (No. 17790005) from Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: The experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(22) [TEMPO⁺][IO₄⁻] could have been active species, although [TEMPO⁺][IO₃⁻] is also possible. We failed to prepare [TEMPO⁺][IO₃⁻].