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

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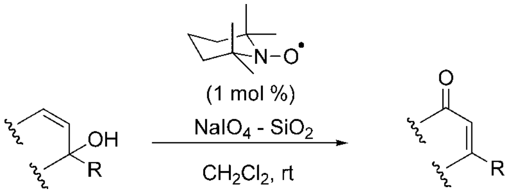
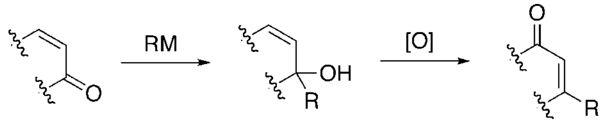
ABSTRACT

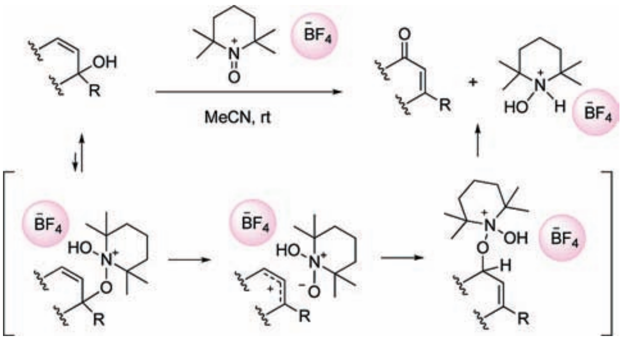


The novel catalytic method for the oxidative rearrangement of tertiary allylic alcohols to β-substituted α,β-unsaturated ketones is described. TEMPO/$NaIO_4$−SiO_2 causes facile and efficient oxidative rearrangement of various acyclic substrates as well as medium-sized and macrocyclic substrates.

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



Scheme 2. [$TEMPO^+$][BF_4^-]-Mediated Oxidative Rearrangement of Tertiary Allylic Alcohols



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

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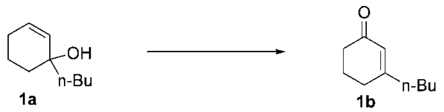
Table 1. Evaluation of Catalytic Conditions



entry	catalyst (equiv)	additive (equiv)	oxidant (equiv)	solvent	time (h)	yield (%)
1	$[\mathrm{TEMPO^+}][\mathrm{BF_4^-}]$ (1.1)			MeCN	0.1	94
2	TEMPO (0.05)		$\mathrm{Phl(OAc)_2}$ (1.5)	MeCN	24	5
3	TEMPO (0.05)	$\mathrm{LiBF_4}$ (1.5)	$\mathrm{Phl(OAc)_2}$ (1.5)	MeCN	1	27
4	$[\mathrm{TEMPO^+}][\mathrm{BF_4^-}]$ (0.05)		$\mathrm{Phl(OAc)_2}$ (1.5)	MeCN	0.1	64
5	$[\mathrm{TEMPO^+}][\mathrm{BF_4^-}]$ (0.05)	$\mathrm{H_2O}$ (3.0)	$\mathrm{Phl(OAc)_2}$ (1.5)	MeCN	2	80
6	$[\mathrm{TEMPO^+}][\mathrm{BF_4^-}]$ (0.05)	$\mathrm{H_2O}$ (10.0)	$\mathrm{Phl(OAc)_2}$ (1.5)	MeCN	7	60
7	$[\mathrm{TEMPO^+}][\mathrm{BF_4^-}]$ (0.05)		$\mathrm{Phl(TFA)_2}$ (1.5)	MeCN	1	42
8	$[\mathrm{TEMPO^+}][\mathrm{BF_4^-}]$ (0.05)		$\mathrm{NalO_4}$ (1.5)	$\mathrm{CH_2Cl_2{-}H_2O}$	2	85
9	$[\mathrm{TEMPO^+}][\mathrm{BF_4^-}]$ (0.05)		$\mathrm{NalO_4{-}SiO_2}$ (2.0)	$\mathrm{CH_2Cl_2}$	0.5	90
10	TEMPO (0.01)		$\mathrm{NalO_4{-}SiO_2}$ (2.0)	$\mathrm{CH_2Cl_2}$	2	92

ketones and have reported two environmentally friendly alternatives using IBX[4] and oxoammonium salts.[5−9]

In discovering the markedly productive method using oxoammonium salts, such as $[\mathrm{TEMPO^+}][\mathrm{BF_4^-}]$ and $[\mathrm{TEMPO^+}][\mathrm{SbF_6^-}]$, we identified that bulky, less nucleophilic counteranions such as $\mathrm{BF_4^-}$ and $\mathrm{SbF_6^-}$ 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 $\mathrm{PhI(OAc)_2}$[11] was employed as the bulk oxidant, in light of the satisfactory precedents[12] in the catalytic oxidation of alkenyl substrates using nitroxyl radical/oxoammonium ion as catalyst (Table 1).[13,14]

Typical catalytic conditions with $\mathrm{TEMPO/PhI(OAc)_2}$ 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 $\mathrm{LiBF_4}$ to this reaction slightly improved the situation to give **1b** in 27% yield (entry 3). Notably, $[\mathrm{TEMPO^+}][\mathrm{BF_4^-}]$ resulted in the better turnover with $\mathrm{PhI(OAc)_2}$ to convert **1a** to **1b** in 64% yield within 10 min, supporting the important role of $\mathrm{BF_4^-}$ anion, although it was accompanied by 20% yield of 1-acetoxy-3-butylcyclohex-2-ene (**1c**) (entry 4). Addition of 3 equiv of $\mathrm{H_2O}$ effectively improved the catalytic performance of $\mathrm{TEMPO^+}$, yielding **1b** in 85% yield, by suppressing production of **1c**, while addition of 10 equiv of $\mathrm{H_2O}$ attenuated the yield to 60% (entries 5 and 6). The use of $\mathrm{PhI(TFA)_2}$ as bulk oxidant induced decomposition (entry 7). We next examined an inorganic version of a hypervalent iodine reagent, $\mathrm{NaIO_4}$, to determine its effect (entry 8).[18] Use of $\mathrm{NaIO_4}$ on $\mathrm{SiO_2}$ brought about further improvement in the catalytic efficiency (entry 9).[19] Ultimately, it was found that $\mathrm{NaIO_4{-}SiO_2}$ allowed us to use TEMPO, indicating that $\mathrm{IO_4^-}$ exerts a profound effect on $\mathrm{TEMPO^+}$, similar to that of $\mathrm{BF_4^-}$ and

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(1) (a) Babler, J. H.; Coghlan, M. J. *Synth. Commun.* **1976**, *6*, 469–474. (b) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682–685. (c) Sundararaman, P.; Hertz, W. L. *J. Org. Chem.* **1977**, *42*, 813–819.

(2) For a recent review on an oxochromium(VI)-based oxidant, see: Luzzio, F. A. *Org. React.* **1998**, *53*, 1–221.

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(4) Shibuya, M.; Ito, S.; Takahashi, M.; Iwabuchi, Y. *Org. Lett.* **2004**, *6*, 4303–4306.

(5) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *J. Org. Chem.* **2008**, *73*, 4750–4752.

(6) (a) de Nooy, A. E.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153–1174. (b) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051–1071.

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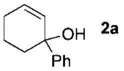
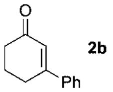
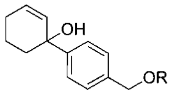
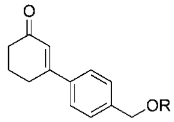
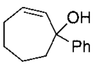
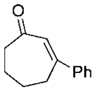
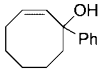
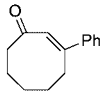
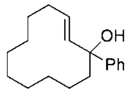
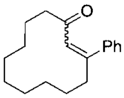
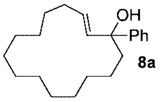
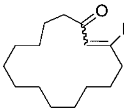
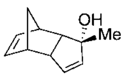
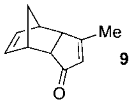
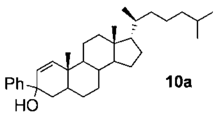
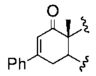
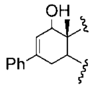
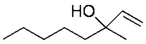
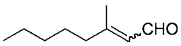
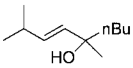
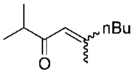
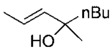
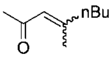
(9) (a) Golubev, V. A.; Rozantsev, E. G.; Neiman, M. B. *Bull. Acad. Sci. U.S.S.R., Chem. Sci.* **1965**, *11*, 1898–1904. (b) Zhdanov, R. I.; Golubev, V. A.; Rozantsev, É. G. *Bull. Acad. Sci. U.S.S.R., Chem. Ser.* **1970**, *19*, 186–187. (c) Golubev, V. A.; Zhdanov, R. I.; Rozantsev, É. G. *Bull. Acad. Sci. U.S.S.R., Chem. Ser.* **1970**, *19*, 188–190.

(10) During the preparation of our manuscript for publication, the catalytic oxidative rearrangement of tertiary allylic alcohols by the Lewis acid/TEMPO/PhIO system was reported: Vatéle, J. M. *Synlett* **2008**, 1785–1788.

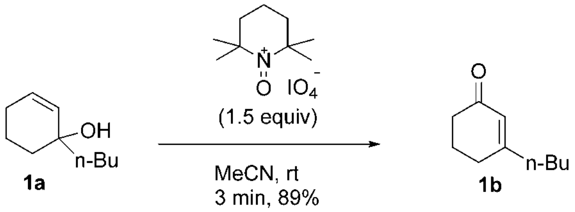
(11) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977.

Table 2. Scope and Limitations of Catalytic Oxidative Rearrangement

entry	substrate	product	time (h)	yield (%)[a]
1	 **2a**	 **2b**	2	92
2		 **3a**, **3b** : R = TBS	2	83
3		**4a**, **4b** : R = TBDPS	2	96
4	 **5a**	 **5b**	8	94
5	 **6a**	 **6b**	14	92
6	 **7a**	 **7b**	24	89[b,c]
7	 **8a**	 **8b**	24	92[b,c]
8	 **9a**	 **9b**	12	81[c]
9	 **10a**	 **10b**  **10c**	4	9(78)[c]
10	 **11a**	 **11b**	24	0[c]
11	 **12a**	 **12b**	20	76[b,c]
12	 **13a**	 **13b**	15	84[c,d]

[a] Standard reaction conditions employed 1 mol % of TEMPO and 2 equiv of $NaIO_4$ on silica gel in CH_2Cl_2 at rt. [b] E:Z = 2:1. [c] The reaction was performed with 10 mol % of TEMPO and 4 equiv of $NaIO_4$ on silica gel. [d] E:Z = 3.6:1.

Scheme 3



SbF_6^-. Use of $NaIO_4$ as a terminal oxidant in TEMPO-catalyzed alcohol oxidation was recently reported, in which 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 substrates[20] 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/$NaIO_4$−SiO_2 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 $[TEMPO^+][IO_4^-]$ and examined the oxidative rearrangement of 1-butylcyclohexenol (**1a**) to confirm its high reactivity: the reaction was over within 3 min to furnish **1b** in 89% yield,[22] indicating that SiO_2 is not essential for the promotion of the 1,3-allylic rearrangement (Scheme 3).

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(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-establishd 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/I_2 conditions[17] for the oxidative rearrangement of **1a** in 10% aq $NaHCO_3$−CH_2Cl_2 and obtained **1b** in 24% yield from multiple spots of the reaction pruducts. 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 $NaIO_4$ on silica gel. The broad substrate applicability extends the synthetic scope of the alkylative carbonyl transposition of α,β-unsaturated ketones.

Acknowledgment. We thank Prof. Emeritus Kunio Ogasawara of Tohoku University for his encouragement and useful discussions. This work was partly supported by a Grant-in-Aid for Scientific Research (B) (No. 17390002) form Japan Society for the Promotion of Science and Encouragement of Young Scientists (B) (No. 17790005) from Ministry of Education, Culure, 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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(21) When we used stoichiometric amounts of oxoammonium salts, it was observed that the addition of H_2O prolonged the reaction time. Thus it was possible that water contained in silica gel would retard the reaction.

(22) $[TEMPO^+][IO_4^-]$ could have been active species, although $[TEMPO^+][IO_3^-]$ is also possible. We failed to prepare $[TEMPO^+]$-$[IO_3^-]$.