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Oxidative Rearrangement of Tertiary Allylic Alcohols Employing Oxoammonium Salts

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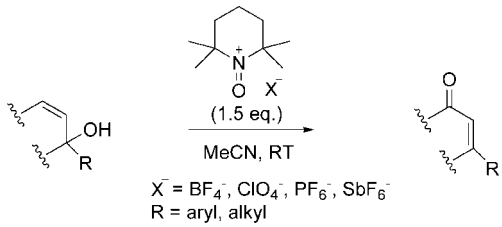
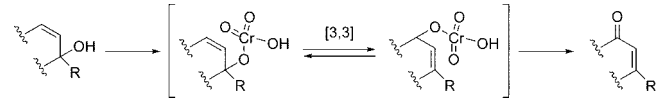


Practical and highly efficient methods for oxidative rearrangement of tertiary allylic alcohols to β-substituted α,β-unsaturated carbonyl compounds employing oxoammonium salts are described. The methods developed are applicable to acyclic substrates as well as medium membered ring substrates and macrocyclic substrates. The counteranion of the oxoammonium salt plays crucial roles on this oxidative rearrangement.

The oxidative rearrangement of tertiary allylic alcohols to β-substituted α,β-unsaturated carbonyl compounds is one of the useful transformations in synthetic chemistry.[1] Since the report in the mid-70s that PCC, PDC, and Collins reagent exert the one-pot allylic transposition-oxidation of a variety of tertiary allylic alcohols, oxochromium(VI)-based reagents have been the first-choice reagents and have played indispensable roles in organic synthesis (Scheme 1).[1–3] However, the ever-growing demand for the development of green sustainable methodologies has urged us to alternatives to hazardous oxochromium(VI)-based reagents.[4] On the basis of the speculation that the Cr═O motif plays a role in the rearrangement step, we took interest in the potential use of organic oxoammonium ions ($R_1R_2N^+$═O),[5] which are active species for the nitroxyl-radical {e.g., TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy)[6] and AZADOs (2-azaadamantane *N*-oxyl)[7] }-catalyzed oxidation of alcohols in promoting this particular oxidative transformation. We now report a novel oxoammonium-salt-based method that

SCHEME 1. Cr(VI)-Mediated Oxidative Rearrangement of Tertiary Allylic Alcohols



enables the facile and efficient oxidative rearrangement of a variety of tertiary allylic alcohols.

An exploratory experiment was started by screening the reactivity of readily available TEMPO-derived oxoammonium salts with 1-phenylcyclohex-2-en-1-ol (**1a**) as the substrate (Table 1).[5i,8] It was found that $TEMPO^+$ species carrying bulky, poor nucleophilic anions, such as BF_4^- **2a** or SbF_6^- **2b**, exhibit excellent reactivity to furnish 3-phenylcyclohex-2-en-1-one (**1b**) in 95% yield within 3 min at room temperature (entries 1 and 2). On the other hand, $TEMPO^+Br_3^-$ (**2c**) and $TEMPO^+Cl^-$ (**2d**) are completely ineffective for the same reaction (entries 3 and 4). It is important to point out that typical TEMPO oxidation conditions with NaOCl, $PhI(OAc)_2$, or Oxone as the co-oxidant

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(2) For a recent review on an oxochromium(VI)-based oxidant, see: (a) Luzzio, F. A. *Org. React.* **1998**, *53*, 1–221. (b) Wietzerbin, K.; Bernadou, J.; Meunier, B. *Eur. J. Inorg. Chem.* **2000**, 1391–1406.

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

(5) (a) Kagiya, T.; Kumuro, C.; Sakano, K.; Nishimoto, S. *Chem. Lett.* **1983**, 365–368. (b) Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. *J. Org. Chem.* **1985**, *50*, 1332–1334. (c) Bobbitt, J. M.; Flores, M. C. L. *Heterocycles* **1988**, *27*, 509–533. (d) Liu, Y.-C.; Liu, Z.-L.; Wu, L.-M.; Chen, P. *Tetrahedron Lett.* **1985**, *26*, 4201–4202. (e) Miyazawa, T.; Endo, T. *J. Org. Chem.* **1985**, *50*, 3930–3931. (f) Bobbitt, J. M.; Guttermuth, M. C. F.; Ma, Z.; Tang, H. *Heterocycles* **1990**, *30*, 1131–1140. (g) Ma, Z.; Bobbitt, J. M. *J. Org. Chem.* **1991**, *56*, 6110–6114. (h) Ren, T.; Liu, Y.-C.; Guo, Q.-X. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2935–2941. (i) Bobbitt, J. M. *J. Org. Chem.* **1998**, *63*, 9367–9374. (j) Takata, T.; Tsujino, Y.; Nakanishi, S.; Nakamura, K.; Yoshida, E.; Endo, T. *Chem. Lett.* **1999**, 937–938. (k) Kernag, C. A.; Bobbitt, J. M.; McGrath, D. V. *Tetrahedron Lett.* **1999**, *40*, 1635–1636. (l) Merbouh, N.; Bobbitt, J. M.; Brückner, C. *J. Org. Chem.* **2004**, *69*, 5116–5119. (m) Zakrzewski, J.; Grodner, J.; Bobbitt, J. M.; Karpińska, M. *Synthesis* **2007**, 2491–2494.

(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.

(7) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412–8413.

(8) (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, E. 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. Se.r* **1970**, *19*, 188–190.

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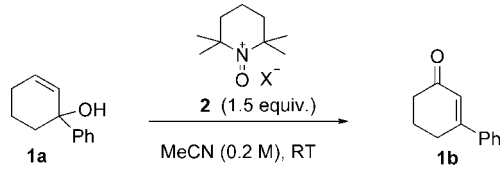
TABLE 1. Reaction Properties of Oxoammonium Salts of TEMPO



entry	X	time (min)	yield (%)
1	BF_4 (**2a**)	3	95
2	SbF_6 (**2b**)	3	97
3[a]	Br_3 (**2c**)	30	0[b]
4	Cl (**2d**)	240	0

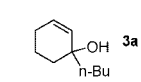
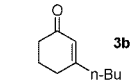
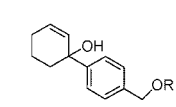
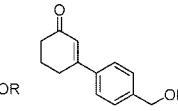
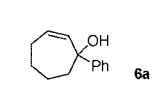
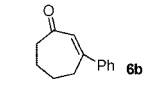
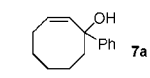
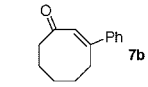
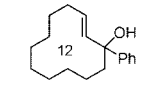
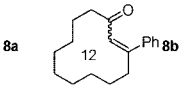
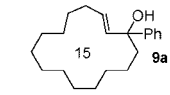
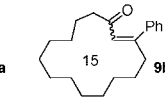
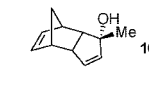
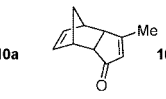
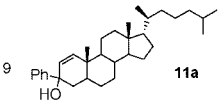
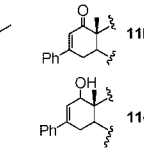
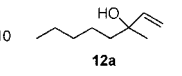
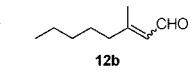
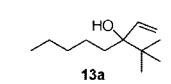
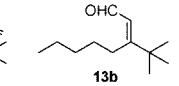
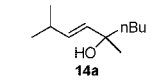
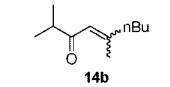
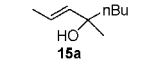
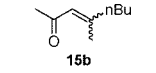
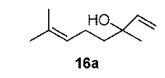
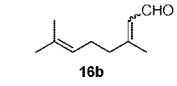
[a] CH_2Cl_2 was used as the solvent. [b] 2,3-Dibromo-1-phenylcyclohexanol was produced quantitatively.

did not afford the product, although they are competent to generate oxoammonium species.[6,9,10]

Experiments for probing the range of tertiary allylic alcohols that undergo oxidative transformation are summarized in Table 2. The aryl- and alkyl-substituted six-membered substrates **3a**−**5a** were smoothly converted to the corresponding transposed products in high yields (entries 1−3). For medium to macrocyclic substrates,[11] the reactions suffered from generation of several byproduct including dimeric ethers. We found that H_2O addition in some cases greatly improves the productivity to allow the spot-to-spot conversion in high yields (entries 4−7). We conjecture that H_2O aids the reactions in part to proceed in the S_N2' pathway (vide infra). The tricyclic substrate **10a** also effectively yielded the desired product **10b** (entry 8). The steroid **11a** afforded the secondary allylic alcohol **11c** in moderate yield, due to considerable steric hindrance. Acyclic substrates also smoothly underwent oxidative rearrangement in high yield, although endo olefinic substrates need the addition of H_2O (entries 12 and 13).[4] Unfortunately, the substrate **16a** did not yield the desired product **16b**, instead an ene-like adduct was obtained in moderate yield as a major product (entry 14).[12] The reaction of **13a** to **13b** with $TEMPO^+SbF_6^-$ was markedly accelerated by warming the reaction mixture to 70 °C (entry 11). In these experiments, the $TEMPO^+SbF_6^-$ salt **2b** as well as $TEMPO^+ClO_4^-$ and $TEMPO^+PF_6^-$ tended to afford better results than $TEMPO^+BF_4^-$.[13] $TEMPO^+TfO^-$ and $TEMPO^+Tf_2N^-$ showed similar reactivity to $TEMPO^+BF_4^-$.[13]

Plausible reaction pathways are depicted in Scheme 2. Considering the steric and electronic effect of the anion, it would be reasonable to expect that the oxoammonium salt carrying a bulkier counteranion, such as BF_4^- and SbF_6^-, should be more electrophilic, due to the enhanced electrostatic potential, to allow formation of the crucial adduct **i** under equilibrium. Once formed, **i** could facilely proceed to give a rearranged product **iii** via either allylic cation formation (path A) or concerted intramolecular rearrangement (path B), which has been proposed for PCC or IBX.[1b,4] In the case that H_2O addition plays productive roles, we believe that mechanism C where H_2O attacks intermediate **i** in the S_N2' mode operates in part.

TABLE 2. Scope of Oxoammonium-Mediated Oxidative Rearrangement[a]

entry	substrate	product	X	time (h)	yield (%)[b]
1			BF_4 (**2a**)	0.1	94
2					
		4a, **4b** : R = TBS	BF_4 (**2a**)	0.1	83
3		**5a**, **5b** : R = TBDPS	BF_4 (**2a**)	0.1	93
4			BF_4 (**2a**)	0.2 0.2	88 97[c]
5			BF_4 (**2a**) SbF_6 (**2b**)	0.2 0.2	93 95[c]
6			BF_4 (**2a**) SbF_6 (**2b**)	6 0.1 1.5	78[c,d] multi spots 99[c,d]
7			BF_4 (**2a**) SbF_6 (**2b**)	10 4	80[c,d] 98[c,d]
8			BF_4 (**2a**)	0.3 0.2	80 98[c]
9			BF_4 (**2a**) SbF_6 (**2b**)	7 1	17 (33[e]) 14 (60[e])
10			BF_4 (**2a**) SbF_6 (**2b**)	6 4	75[f] 80[f]
11			BF_4 (**2a**) SbF_6 (**2b**) SbF_6 (**2b**)	4 6 0.7	76[h] 84[i] 86[j]
12			BF_4 (**2a**) BF_4 (**2a**) SbF_6 (**2b**)	6 5 4	58[d] 78[c,d] 83[c,d]
13			BF_4 (**2a**) SbF_6 (**2b**)	1 1	73[c,k] 85[c,k]
14			BF_4 (**2a**)	6 0.3	trace[l] 21[g]

[a] Standard reaction conditions employed 1.5 equiv of oxoamonium salts in MeCN at RT. [b] Isolated yield. [c] MeCN and H_2O (1:1) solution was used as the solvent. [d] *E*:*Z* = 2:1. [e] Yield of allylic alcohol **11c**. [f] *E*:*Z* = 2.4:1. [g] *E*:*Z* ratio was not determined. [h] Reaction performed at 50 °C. [i] Reaction performed at 40 °C. [j] Reaction performed at 70 °C. [k] *E*:*Z* = 3.5:1. [l] Ene-like adduct (67%) was obtained.

(9) (a) Anelli, P. L.; Banfi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970–2972. (b) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977. (c) Bolm, C.; Magnus, A. S.; Hidebrand, J. P. *Org. Lett.* **2000**, *2*, 1173–1175.

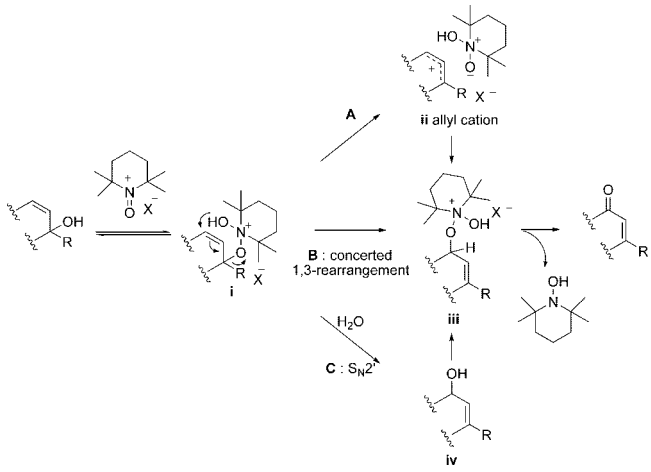
(10) Under the condition using NaClO or $PhI(OAc)_2$, unreacted starting material was recovered. Under the condition using Oxone, 1-phenylcyclohexa-1,3-diene was produced as the major product with an accompanying small amount (~20%) of **1b**.

(11) Tello-Aburto, R.; Ochoa-Teran, A.; Olivo, H. F. *Tetrahedron Lett.* **2006**, *47*, 5915–5917.

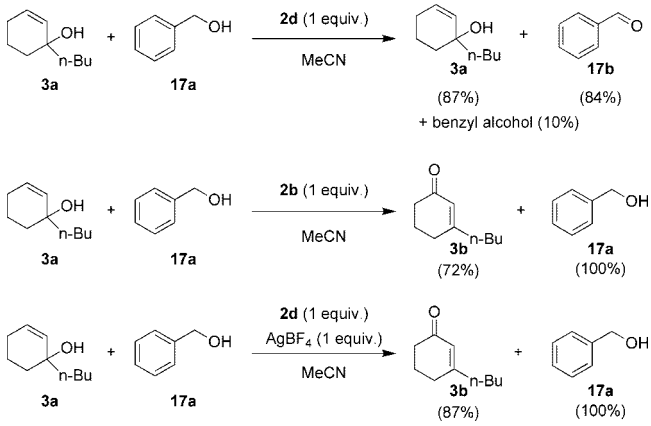
(12) Pradhan, P. P.; Bobbitt, J. M.; Bailey, W. F. *Org. Lett.* **2006**, *8*, 5485–5487.

(13) See the Supporting Information.

SCHEME 2. Plausible Reaction Mechanism



SCHEME 3. Intermolecular Competitive Reactions

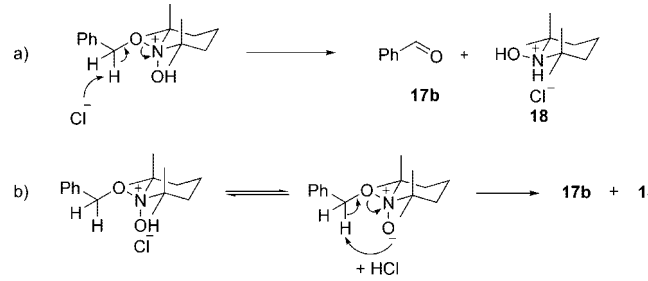


To probe the reactive nature of oxoammonium salts, we conducted intermolecular competition experiments with the tertiary allylic alcohol **3a** and benzyl alcohol (**17a**) (Scheme 3). On treatment with $TEMPO^+Cl^-$ (**2d**), benzaldehyde (**17b**) was rapidly produced and **3a** was recovered. On the other hand, treatment with $TEMPO^+SbF_6^-$ (**2b**) converted **3a** into **3b** selectively. The treatment of **3a** with **2d** in the presence of an equimolar amount of $AgBF_4$ afforded almost the same result as the reaction with **2b**.[14,15]

The observed chemoselectivity would be rationalized by considering the basicity of the counteranions (Scheme 4).[16] Thus, in the case of $TEMPO^+Cl^-$ (**2d**), the chloride anion can act as a base that abstracts a proton from either the benzylic (path a) or the OH proton (path b) giving an ammonium oxide to bring about generation of **17b** and **18**. On the other hand, less basic BF_4^- refrains for abstracting a proton, and thus slows the oxidation.[17,18]

In summary, we disclosed a novel one-pot oxidative rearrangement of tertiary allylic alcohols to β-substituted α,β-unsaturated carbonyl compounds employing oxoammonium salts, which are alternatives to toxic oxochromium(VI)-based reagents in organic chemistry. We found that counteranions are important for the reactivity of the oxoammonium salts. Studies toward the development of a catalytic version of this process are under way.

SCHEME 4. Proposed Pathways for the Oxidation of Benzyl Alcohol by $TEMPO^+Cl^-$



Experimental Section

Synthesis of $TEMPO^+BF_4^-$ (2a). TEMPO (10 g, 64 mmol) was slurried with H_2O (32 mL, 2 M) and 42% HBF_4 (13.4 mL, 64 mmol) was slowly added dropwise over 1 h at room temperature. After the solution turned to amber color, NaOCl (23 mL, 32 mmol) was added over 1 h at 0 °C and stirred for an additional 1 h at 0 °C. The reaction mixture was filtered and the yellow crystalline precipitate was washed with ice-cold 5% $NaHCO_3$ (20 mL), water (40 mL), and ice-cold Et_2O (400 mL). The solid was dried over 24 h at 50 °C in vacuo to yield $TEMPO^+BF_4^-$ (**2a**) (12.1 g, 49.9 mmol, 78%) as the bright yellow solid, mp 162−163 °C (recrystallized from H_2O). Anal. Calcd for $C_9H_{18}BF_4NO$: C, 44.47; H, 7.46; N, 5.76. Found: C, 44.33; H, 7.12; N, 5.78.

Synthesis of $TEMPO^+SbF_6^-$ (2b). The same procedure with 65% $HSbF_6$ instead of 42% HBF_4 provided $TEMPO^+$ SbF_6 (**2b**). Anal. Calcd for $C_9H_{18}F_6NOSb$: C, 27.58; H, 4.63; N, 3.57. Found: C,27.36; H, 4.60; N, 3.50.

General Procedure for the Oxidative Allylic Rearrangement Reaction with TEMPO-Derived Oxoammonium Salts. To a solution of 1-*n*-butyl-2-cyclohexenol **3a** (200 mg, 1.3 mmol) in MeCN (6.5 mL, 0.2 M) was added $TEMPO^+BF_4^-$ (474 mg, 1.95 mmol) at room temperature. The reaction mixture was stirred for 3 min and then diluted with Et_2O. The organic layer was washed sequentially with water and brine and then dried over $MgSO_4$. The solution was concentrated in vacuo and the residue was purified by flash column chromatography (SiO_2, 1:6 Et_2O:hexane) to give 3-*n*-butyl-cyclohexenone **3b** (185 mg, 1.22 mmol, 94%) as a colorless oil.

3-Butylcyclohex-2-en-1-one (3b). ^1H NMR (400 MHz, $CDCl_3$) δ 5.87 (t, 1H, J = 1.4 Hz), 2.35 (ddd, 2H, J = 7.5, 6.7, 2.2 Hz), 2.29 (t, 2H, J = 6.1 Hz), 2.21 (t, 2H, J = 7.5 Hz), 2.05−1.95 (m, 2H), 1.53−1.45 (m, 2H), 1.39−1.29 (m, 2H), 0.92 (td, 3H, J = 7.3, 2.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 166.5, 125.4, 37.7, 37.3, 29.6, 29.0, 22.7, 22.3, 13.8. IR (neat, cm^{-1}) 1670. MS *m*/*z* 152 (M^+), 82 (100%). HRMS calcd for $C_{10}H_{16}O$ 152.1201, found 152.1180.

Acknowledgment. We thank Prof. Emeritus Kunio Ogasawara of Tohoku University for his encouragement and helpful discussion. This work was supported by JSPS and MEXT, Japan.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800634R

(14) It was assumed that $TEMPO^+BF_4^-$ was generated in situ.

(15) Gorin, D. J.; Toste, F. D. *Nature* **2007**, 446–396.

(16) (a) Olah, G. A.; Prakash, G. K. S. *Superacids*; John Wiley and Sons: New York, 1973. (b) Olah, G. A. *J. Org. Chem.* **2005**, *70*, 2413–2429.

(17) Bailey, W. F.; Bobbitt, J. M.; Wiberg, K. B. *J. Org. Chem.* **2007**, *72*, 4504–4509.

(18) If the substrate possesses protons acidic enough (cf. allylic methine proton in cyclohexenol), the proton would be abstracted by a solvent to afford oxidized products.