Reactivity of TEMPO anion as a nucleophile and its applications for selective transformations of haloalkanes or acyl halides to aldehydes

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Reactivity of TEMPO anion as a nucleophile and its applications for selective transformations of haloalkanes or acyl halides to aldehydes

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Abstract— Sodium 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO$^-$Na$^+$), generated by reduction of TEMPO• with sodium naphthalenide in THF, reacted with alkyl halides or acyl halides to produce *O*-alkylated or acylated TEMPOs, which were in turn oxidized with *m*CPBA or reduced with DIBAL-H to afford the corresponding aldehydes, thus accomplishing a new protocol for the halides-carbonyls conversion.

Keywords: TEMPO and compounds; oxidation; reduction; *m*CPBA; DIBAL-H; aldehyde.

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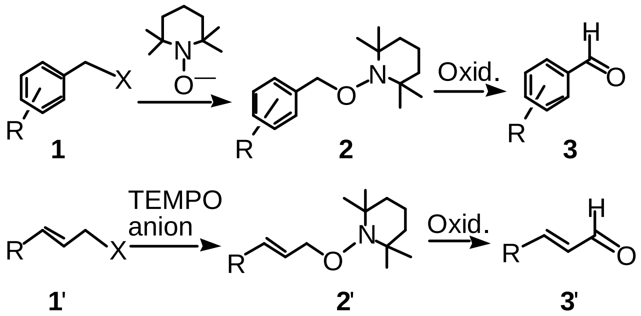
1. Introduction

Selective oxidation of the benzylic and allylic positions of arenes and alkenes to the corresponding carbonyl compounds is an important task especially in the synthesis of bioactive and medicinally significant compounds.[1] Radical halogenation at the benzylic and allylic positions, followed by the oxidation of the resulting halides **1** is one of the most practical methods leading to the desired carbonyl compounds **3**. However, the most conventional method of this conversion,[2] relied on acyloxylation followed by successive hydrolysis and oxidation of the hydroxy group, is a time-consuming procedure.[3] We, therefore, developed an efficient method for the conversion of **1** to **3** by way of the intermediate **2**, by utilizing the 2,2,6,6-tetramethylpiperidine-*N*-oxy (TEMPO)-substituted carbon of **2** as a latent carbonyl function (Scheme 1).[4,5] Furthermore, we found that the reduction of *O*-acylated TEMPOs with DIBAL-H produced primarily the corresponding aldehydes **3**.



Scheme 1. Benzylic and allylic C—X bond oxidation via substitution with the TEMPO anion.

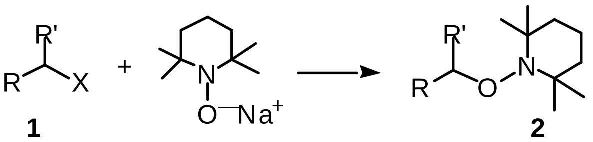
A variety of methods for the preparation of TEMPO-based molecules have thus far been investigated by trapping the carbon centered radical with 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical[6-11] (abbreviated as TEMPO•) and by the reaction of its *N*-oxoammonium salts with ketones and aldehydes.[5a,12,13] On the other hand, 2,2,6,6-tetramethylpiperidine-*N*-oxide (the TEMPO anion), a reduced form of TEMPO•, is also useful species to produce *O*-alkyl TEMPOs. However, the TEMPO anion was usually generated in aqueous media by treatment with sodium or calcium ascrobates followed by deprotonation of the resulting 1-hydroxyTEMP (TEMPOH) with NaH in THF[14,6b] and the reactivity of the TEMPO anion as a nucleophile has not been well explored.[6c] We, therefore, utilized a direct method to generate this anionic species by reduction of TEMPO• with sodium naphthalenide in THF, which is featured by the repeated use of naphthalene, and applied it to the nucleophilic substitution of a variety of alkyl halides **1** including benzylic and allylic halides. Subsequently, oxidation of the resulting *O*-alkylated TEMPOs **2** and **2'** to the corresponding carbonyl compounds **3** and **3'** was examined.

2. Result and discussion

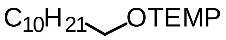
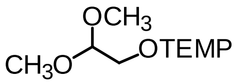
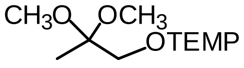
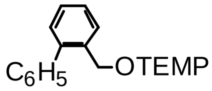
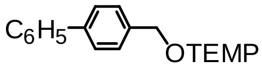
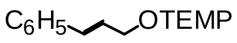
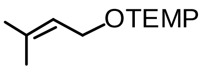
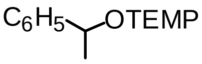
Although reduction of TEMPO• to the TEMPO anion with sodium metal or lithium naphthalenide in DME was reported by Whitesides et al,[6c] we devised a catalytic procedure with respect to naphthalene (2-10 mol%) by stirring with a stoichiometric amount of sodium as a real reducing reagent in THF, during which the red brown color of TEMPO• faded as it was converted to the TEMPO anion. The resulting TEMPO anion-containing solution was used for the S_N2 reactions of a variety of primary and secondary halides **1**, giving the corresponding *O*-alkyl TEMPOs **2**.

As shown in Table 1, primary alkyl halides **1** reacted with the TEMPO anion to give the corresponding alkoxyamines **2** in good to excellent yields (runs 1-7). The lower reactivity of 2-halo acetals **1b**,**c**, presumably due to some steric hindrance, was improved by adding dimethylpropyleneurea (DMPU) or 1,3-dimethyl-2-imidazolidinone (DMI) as a co-solvent (runs 2 and 3). Similar additive effect was also attained with HMPA. *O*-Alkylation with primary benzylic (runs 4 and 5) and allylic halide (runs 6 and 7) proceeded smoothly. On the other hand, secondary halides were less reactive and moderate yield was obtained with benzylic halide (run 8).

Table 1. *O*-Alkylations of 2,2,6,6-tetramethylpiperidine-*N*-oxide anion

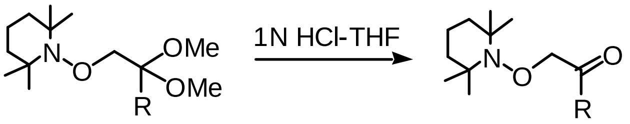


1 **2**

Entry	**1**	Temp/ Time[a]	Product, **2**	Yield/% (method)[b]
1	**a**, X = Br	reflux/ 18 h		92 (A)
2	**b**, X = Br	rt/17 h 70 °C/65 h[c]		43 (B)
3	**c**, X = Br	reflux/ 110 h[d]		67 (B)
4	**d**, X = Br	rt/ 0.5 h[d]		99 (A)
5	**e**, X = Br	rt/ 10 h[d]		99 (A)
6	**f**, X = Cl	reflux/ 20 h		89 (A)
7	**g**, X = Cl	reflux/ 24 h		76 (B)
8	**h**, X = Br	reflux/ 89 h[b]		45 (A)

[a] The reactions were carried out in THF under Ar. [b] Yields are based on isolated products and calculated based on (A) the halides or (B) TEMPO•. [c] Carried out in the presence of DMPU. [d] Carried out in the presence of 1,3-dimethyl-2-imidazolidinone (DMI).

Our attempts at the substitution reaction of 2-halo ketones and esters such as bromoacetophenone and bromoacetate with the TEMPO anion were unsuccessful. However, a synthetically equivalent and/or useful class of aldehyde **4b** and ketone **4c** was obtained in 70-75% yields by hydrolysis of the acetals **2b** and **2c**, prepared by the present method (Scheme 2).

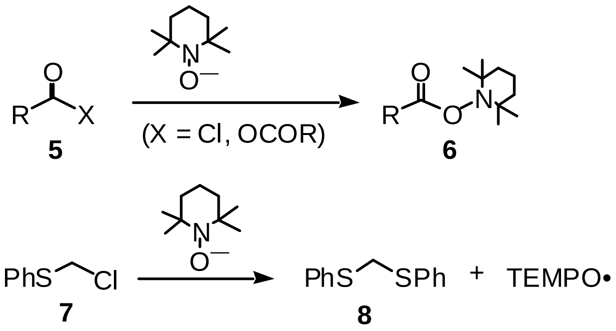


2b, R = H
2c, R = Me

4b, R = H, 70%
4c, R = Me, 75%

Scheme 2. Hydrolysis of α-TEMPO substituted acetals **2**.

The reactivity of the TEMPO anion toward different electrophiles such as acyl halides or acid anhydrides **5** and others was also examined. The *O*-Acyl TEMPOs **6** were easily produced (75-88%) by nucleophilic acyl substitution of **5**.[15] The reaction of the TEMPO anion with phenylthiomethyl chloride **7** led quantitatively to bis(phenylthio)methane **8** instead of the expected *O*-phenylthiomethylTEMPO, which is in sharp contrast to substitution of **7** with sodium alkoxide (Scheme 3).[16]



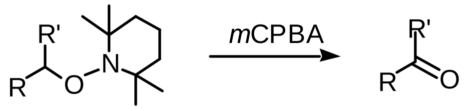
Scheme 3. Reactions of the TEMPO anion with acyl halides or acid anhydrides **5** and $PhSCH_2Cl$ (**7**)

As shown in Table 2, selected *O*-benzyl- and *O*-allyl-TEMPOs **2** were transformed to carbonyl compounds **3**. We examined a variety of oxidizing reagents such as $Mn(OAc)_3$, $Cu(OAc)_2$, *tert*-BuOOH[4b] for this purpose, but it turned out that *m*-chloroperbenzoic acid (*m*CPBA) was highly efficient to complete quickly the reaction at 0-5 °C and the corresponding **3**, conjugated with arenes and C=C double bond, were obtained in excellent yields (runs 1-3).[5a] In the *m*CPBA oxidation, 1-hydroxyTEMP (TEMPOH) along with a small amount of TEMPO• was produced as the one of fragments from **2**.[17]

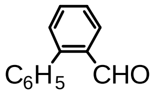
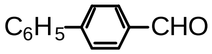
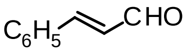
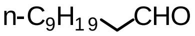
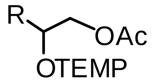
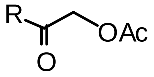
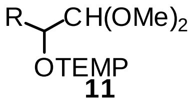
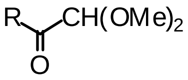
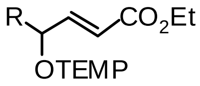
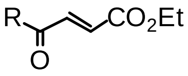
Furthermore, in addition to the case of a simple alkanal **3a** from **2a** (run 4), this reaction was successfully applied to the synthesis of diverse carbonyl compounds[18] including 2-acetoxyketone **10** (run 5), acetal of 1,2-dione **12** (run 6), and 4-oxo-2-

enoate **14**[19] (run 7) from the corresponding precursors **9**, **11**, and **13**, derived from 2-TEMPO-substituted undecanal as a common starting material.[12]

Table 2. Oxidations of (2,2,6,6-tetramethylpiperidinyl-1-oxy)alkanes to aldehydes and ketones[a]



2 **3**

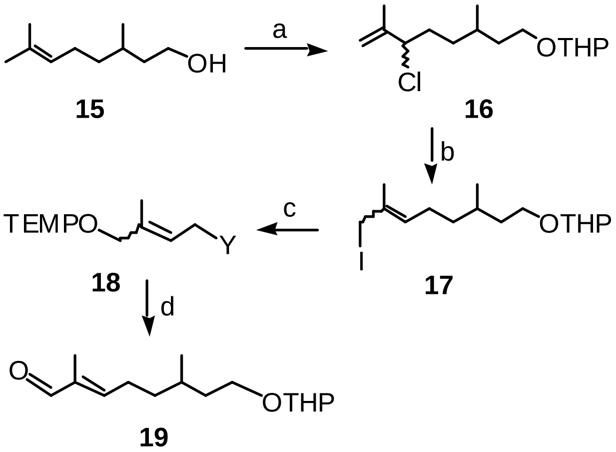
Entry	Substrates	Products	Yield/ %[b]
1	**2d**	 **3d**	99
2	**2e**	 **3e**	86
3	**2f**	 **3f**	86
4	**2a**	 **3a**	88
5[c]	 **9**	 **10**	90
6[c]	 **11**	 **12**	96
7[c]	 **13**	 **14**	89

[a] Carried out by using slightly excess *m*CPBA in CH_2Cl_2 with cooling at 0-5 °C for 30 min.

[b] Yields are based on isolated products.

[c] R = n-C_9H_{19}.

The allylic oxidation of the prenyl derivative **15** was examined by employing the present protocol (Scheme 4). Thus, the electrochemical ene-type chlorination[20] of **15** and the subsequent protection of the hydroxy group as a THP ether, giving **16**, was followed by the Cl/I exchange reaction with NaI to afford the allylic iodide **17** (*E*:*Z* = ca. 2:1). The S_N2 reaction of **17** with the TEMPO anion afforded **18** in 45% yield. The enal **19** was obtained by oxidation with *m*CPBA as a ca. 2:1 *E*/*Z* mixture in 78% yield, which, on standing in $CDCl_3$, converged to *E*-isomer.

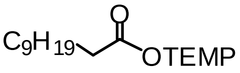
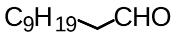
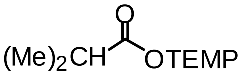
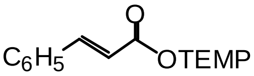
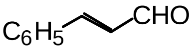
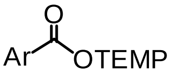
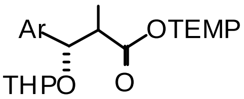
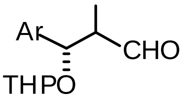


a: (1) electrolysis, -2e, CH_2Cl_2—aq. NaCl/1N HCl (81%), (2) DHP, *p*TsOH, CH_2Cl_2 (81%), **b**: NaI, acetone, heated (74%), **c**: $TEMPO^-Na^+$, THF, reflux, 20 h (45%) (Y =$CH_2CH(Me)CH_2CH_2OTHP$), *E*:*Z* = ca. 2:1, **d**: *m*CPBA, CH_2Cl_2 (78%)

Scheme 4. Allylic oxidation via halogenation and substitution with the TEMPO anion followed by mCPBA oxidation.

Alternatively, the conversion of *O*-acylated TEMPOs **6** to the corresponding aldehydes **3** was examined by a hydride reduction.[21] Thus, the treatment of **6f** (R = PhCH=CH) with DIBAL-H (3 equivalents) at -78 to -50 °C for 75 min afforded cleanly the corresponding aldehyde **3f** (91% yield) (run 3), the overreduction to carbinol was negligibly small, while ethyl *trans*-cinnamate, an analogue of **6f**, produced the corresponding primary alcohol under the same conditions.[22] Examples of the selective reduction of **6** to aldehydes, including aldol derivative (run 5), are shown in Table 3.

Table 3. Reduction of *O*-acylated 2,2,6,6-tetramethylpiperidinyl-1-oxyls with DIBAL-H to Aaldehydes[a]

Entry	Substrates	Products	Yield %[b]
1	 **6a**	 **3a**	95
2	 **6i**	$(Me)_2CH-CHO$ **3i**	72[c]
3	 **6f**	 **3f**	91
4[d]	 **6j**	Ar–CHO **3j**	92
5[d.e]	 **20**	 **21**	94[f]

[a] Carried out by using excess DIBAL-H (2-3 equv.) in toluene at -78~ -50 °C for 30 to 1 h.

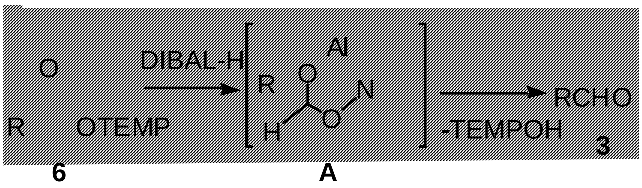
[b] Yields are based on isolated products.

[c] Yield calculated by comparing with an internal standard (PhCH=CHCHO, added after the reaction) due to volatility of the product.

[d] Ar = 4-MeOC_6H_4.

[e] The substrate *anti*-**20** was prepared by the aldol reaction of **6** (R = Et) and 4-MeOC_6H_4CHO with LDA (ca. 7:1 ds.mixture) followed by protection of the *anti*-adduct, purified by recrystallization, as a THP ether. [f]Overreduction to the carbinol (4%) was found.

Accordingly, it is conceived that the DIBAL-H reduction of **6** proceeds through the chelated intermediate **A** with close resemblance with the case of *N*-methoxy-*N*-methylamdies developed by Weinreb et al,[23] which explain the lack of over-reduction (Scheme 5).



Scheme 5. A proposed mechanism for reduction of *O*-acyl TEMPOs **6** with DIBAL-H.

3. Conclusion

The TEMPO-attached carbon was shown to be a synthon of carbonyl group. Haloalkanes were efficiently converted to aldehyde via *O*-alkylated TEMPOs by oxidation with *m*CPBA (up to 98% yields for two steps). The *O*-acyl TEMPOs were selectively reduced to the aldehydes even with excess DIBAL-H owing to chelating ability of tetramethylpiperidine group for stabilization of the hydride-adduct intermediate.

4. Experimental

4.1. General

IR spectra were obtained with a Horiba, Model FT-210, or a JASCO, Model FT/IR-230, fourier transform infrared spectrometer instrument, and only major absorptions are cited. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-AL400 and Varian Mercury-300 instruments with $CDCl_3$ as a solvent unless otherwise indicated.

4.2. General procedure for preparation of *O*-alkyl TEMPOs 2.

In a 50 mL one-necked flask were placed $C_{10}H_8$ (221 mg, 1.72 mmol), TEMPO• (2.7 g, 17.3 mmol), and THF (15 mL). To this solution was added Na metal (477 mg, 20.7 mmol) and the mixture was stirred at room temperature until Na dissolved and blue-black color of $Na^+[C_{10}H_8]^{-\bullet}$ persisted. To a solution of *n*-$C_{11}H_{23}Br$ (**1a**, 3.66 g, 15.5 mmol) in THF (5 mL), placed in a 100 mL one-necked flask, was transferred by double-ended needle the above TEMPO anion with cooling at 0-4 °C. The mixture was allowed to warm gradually to room temperature and to 50 °C, stirred for 2 h, and then heated at reflux for 18 h. The reaction was quenched with cold aqueous $NaHCO_3$ and products were extracted with AcOEt. Extracts were washed with brine, dried ($MgSO_4$), and concentrated. The products were purified by distillation and the fraction of boiling range 137-138 °C (0.15 Torr, bath temperature 150-155 °C) was collected; 4.47 g (92% yield). **2a**: IR (neat) 1467, 1373, 1263, 1133, 1047, 759, 711 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.88 (complex t, J = 6.9 Hz, 3H), 1.09, 1.14 (s, 12H), 1.23-1.56 (m, 24H, brs at 1.26), 3.71 (t, J = 6.6 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 14.1, 17.2, 20.1 (2C), 22.7, 26.5, 28.7, 29.4, 29.6, 29.7 (2C), 29.8, 31.9, 33.0 (2C), 39.6 (2C), 59.5 (2C), 76.8. HRMS (EI) calcd for $C_{20}H_{41}NO$ 311.3188, found 311.3205.

Similarly, the compound **2c** was prepared as follows. A solution of the TEMPO anion, prepared from TEMPO• (2.59 g, 16.6 mmol), $C_{10}H_8$ (240 mg, 1.87 mmol), and Na (420 mg, 18.3 mmol) in THF (20 mL), was added to a solution of $BrCH_2C(OMe)_2CH_3$ (**1c**, 3.5 g, 19.2 mmol) in THF (10 mL) and DMI (3.6 mL) at 0 °C. The mixture was gradually raised to room temperature and then heated at reflux for 110 h, during which solids precipitated. Usual workup and the removal of volatile materials including the unreacted TEMPO• (1.65 g) by distillation of the crude product at 62 °C (1.5 Torr, bath temperature 90 °C), which was followed by column chromatography (SiO_2, hexane and hexane-AcOEt 10:1) of the residual oil to give the TEMPO substituted acetal **2c** (2.9 g, 67% yield based on the starting TEMPO•): IR (neat) 2933, 2829, 1469, 1454, 1375, 1360, 1261, 1242, 1178, 1132, 1090, 958, 849, 800, 702 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.13, 1.19 (s, 12H), 1.41(s, 3H), 1.42-1.59 (m, 6H), 3.23 (s, 6H), 3.77 (s, 2H); ^{13}C NMR (75.5 MHz) δ 16.9, 20.0, 20.3, 32.9 (2C), 39.7 (2C), 48.1 (2C), 59.8 (2C), 77.4, 100.0. HRMS (EI) calcd for $C_{14}H_{29}NO_3$ 259.2147, found 259.2169.

2b: bp 78-82 °C (0.1 Torr); IR (neat) 2831, 1469, 1359, 1245, 1135, 1081, 970, 923, 856, 786, 713 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.10, 1.17 (s, 12H), 1.25-1.55 (m, 6H), 3.39 (s, 6H), 3.84 (d, *J* = 5.2 Hz, 2H), 4.49 (t, *J* = 5.2 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 16.6, 19.5 (2C), 32.4 (2C), 39.1 (2C), 53.3 (2C), 59.3 (2C), 76.7, 101.9. HRMS (EI) calcd for $C_{13}H_{27}NO_3$ 245.1991, found 245.1959.

2d: mp 82.5-83.5 °C; IR (KBr) 3003, 2976, 2927, 2868, 1477, 1360, 1263, 1186, 1132, 1039, 933, 829, 775, 750, 706 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.04, 1.08 (s, 12H), 1.20-1.59 (m, 6H), 4.72 (s, 2H), 7.19-7.65 (m, 9H); ^{13}C NMR (100 MHz) δ17.5, 20.7 (2C), 33.2 (2C), 40.1 (2C), 60.2 (2C), 77.5, 127.1, 127.3, 127.4, 128.1 (2C), 129.1, 129.4 (2C), 129.9, 135.8, 141.2, 141.8. HRMS (EI) calcd for $C_{22}H_{29}NO$ 323.2249, found 323.2277.

2e: mp 88-89 °C; IR (KBr) 3003, 2974, 2931, 2889, 1485, 1469, 1448, 1373, 1360, 1261, 1182, 1132, 1030, 991, 862, 823, 764, 702 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.25, 1.37 (s, 12H), 1.20-1.70 (m, 6H), 4.95 (s, 2H), 7.37-7.47 (m, 9H); ^{13}C NMR (100 MHz) δ17.2, 20.4 (2C), 33.2 (2C), 39.8 (2C), 60.0 (2C), 78.4, 126.8 (2C), 126.9 (2C), 127.0, 127.7 (2C), 128.5 (2C), 137.1, 140.1, 140.8. HRMS (EI) calcd for $C_{22}H_{29}NO$ 323.2249, found 323.2216.

18 (*E*/*Z* mixture): IR (Neat) 2929, 1454, 1373, 1358, 1261, 1201, 1184, 1134, 1078, 1030, 991, 908, 870, 814, 735 cm^{-1}; ^{1}H NMR (400 MHz) δ0.87, 0.90 (d, *J* = 6.8 Hz, 3H), 1.09, 1.15, 1.19 (s, 12H), 1.65, 1.79 (s, 3H), 1.25-2.12 (m, 19H), 3.33-3.52 (m, 2H), 3.70-3.90 (m, 2H), 4.11, 4.25 (s, 2H), 4.56, 4.81 (s, 1H, OCH), 5.25, 5.37 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz) δ14.3, 17.0, 19.5, 20.0 and 20.1 (2C), 24.8, 25.3, 29.5, 30.6 (2C), 32.8 and 32.9, 36.4 and 36.5, 37.2 and 37.3, 39.5 (2C), 59.5 (2C), 62.0, 65.6 and 65.7, 75.1, 82.3, 98.4 and 98.6, 128.3, 131.4 and 131.5. HRMS (EI) calcd for $C_{24}H_{45}NO_4$ 395.3399, found 395.3310.

4.3. General procedure for oxidation of *O*-alkyl TEMPOs 2 to aldehydes and ketones 3. To a solution of the *O*-alkyl TEMPO **2a** (R = $C_{10}H_{21}$, 311 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added portionwise mCPBA (70~75% assay, 296 mg, 1.2

equivalent) over 10 min at 0~4 °C. The reaction was exothermic and the temperature was kept at under 8 °C. The mixture was stirred at the same temperature for 30 min, and the reaction was quenched with cold aqueous $Na_2S_2O_3$, and the products were extracted with CH_2Cl_2 (first) and AcOEt (second). Extracts were washed with aqueous $NaHCO_3$ and with brine, dried ($MgSO_4$), and concentrated. The crude products were purified by column chromatography (SiO_2, hexane-AcOEt, 7:1, 5:1, 3:1, 2:1, then 1:1) to give 150 mg (88%) of the aldehyde **3a** (R = $C_{10}H_{21}$, R_f= 0.52, hexane-AcOEt 7:1), 10 mg of TEMPO•, and 101 mg (64%) of a mixture of TEMPO• and the *N*-hydroxypiperidine (R_f= 0.12, hexane-AcOEt 7:1).

2-Phenylbenzaldehyde 3d: IR (neat) 3062, 2848, 2754, 2252, 1655, 1597, 1473, 1394, 1254, 1196, 1009, 910, 827, 733, 704, 646 cm^{-1}; ^1H NMR (400 MHz) δ 7.35-8.04 (m, 9H, Ph), 9.97 (s, 1H, CHO); ^{13}C NMR (100 MHz) δ127.4, 127.6, 128.0, 128.3 (2C), 129.9 (2C), 130.6, 133.4, 133.5, 137.5, 145.8, 192.2.

4-Phenylbenzaldehyde 3e: IR (neat) 3059, 3032, 2827, 2735, 2252, 1699, 1604, 1566, 1487, 1450, 1412, 1385, 1308, 1215, 1171, 1007, 910, 839, 762, 731, 696 cm^{-1}; ^1H NMR (400 MHz) δ 7.35-7.96 (m, 9H, Ph), 10.04(s, 1H, CHO); ^{13}C NMR (100 MHz) δ127.1 (2C), 127.4 (2C), 128.2, 128.5 (2C), 130.0 (2C), 134.9, 139.4, 146.9, 191.5.

1-Acetoxy-2-undecanone 10: mp 51.5-52.5 °C; IR (KBr) 1862, 1724, 1467, 1409, 1378, 1232, 1130, 1079, 1037, 985, 873, 838, 717 cm^{-1}; ^1H NMR (300 MHz) δ 0.87 (complex t, *J* = 6.2 Hz, 3H), 1.26 (brs, 12H), 1.60 (m, 2H), 2.17 (s, 3H), 2.40 (t, *J* = 7.4 Hz, 2H), 4.65 (s, 2H); ^{13}C NMR (75.5 MHz) δ 14.1, 20.5, 22.6, 23.3, 29.1, 29.2, 29.28, 29.33, 31.8, 38.8, 67.9, 170.2, 204. HRMS (EI) calcd for $C_{13}H_{24}O_3$ 228.1725, found 228.1772.

Ethyl 4-Oxotridec-2-enoate 14: IR (neat) 1727, 1689, 1635, 1465, 1367, 1301, 1182, 1095, 1031, 981, 867, 723 cm-1; ^1H NMR (300 MHz) δ 0.88 (complex t, *J* = 6.9 Hz, 3H), 1.27 (brs, 12H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.64 (m, 2H), 2.63 (t, *J* = 7.4 Hz, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 6.67 (d, *J* = 15.9 Hz, 1H), 7.07 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (300 MHz) δ 12.1, 12.2, 20.6, 21.7, 27.1, 27.2, 27.3, 27.4, 29.8, 39.5, 59.4, 128.6, 137.3, 163.5, 197.8.

Enal 19 (*E*-isomer): IR (neat) 2943, 2871, 1685, 1645, 1454, 1381, 1354, 1265, 1201, 1184, 1136, 1120, 1076, 1034, 910, 868, 812, 733 cm^{-1}; ^1H NMR (400 MHz) δ0.92 (d, *J* = 6.4 Hz, 3H), 1.73 (s, 3H), 1.25-1.82(m, 11H), 2.25-2.40 (m, 2H), 3.33-3.50 (m, 2H), 3.70-3.85 (m, 2H), 4.50-4.55 (m, 1H), 6.45 (t, *J* = 7.2 Hz, 1H), 9.35 (s, 1H);

13C NMR (100 MHz) δ9.3, 19.4 and 19.5, 19.6 and 19.8, 25.6, 26.6, 29.8, 30.8, 35.5 and 35.7, 36.5, 62.4, 65.5 and 65.6, 98.7 and 99.0, 139.0, 154.7, 194.9

4.4. Hydrolysis of 2c to 4c. To a solution of **2c** (3.96 g, 15.3 mmol) in THF (80 mL) was added at 0~4 °C cold 1N HCl (15 mL). The mixture was allowed to warm to room temperature and stirred for 5 h. The reaction was quenched with aqueous $NaHCO_3$ and products were extracted with AcOEt. Usual workup followed by purification on column chromatography (SiO_2, hexane-AcOEt 10:1 and 7:1) gave 2.44 g (75%) of the TEMPO-substituted acetone **4c**: IR (neat) 1720, 1359, 1234, 1133, 1081, 995, 923, 702 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.13, 1.15 (s, 12H), 1.30-1.60 (m, 6H), 2.21 (s, 3H), 4.38 (s, 2H); ^{13}C NMR (75.5 MHz) δ 16.8, 19.9 (2C), 27.0, 32.7 (2C), 39.4 (2C), 59.8 (2C), 83.1, 206.6.

4b: yield 70%; IR (neat) 2976, 2933,1736, 1469, 1375, 1362, 1263, 1246, 1134, 1080, 912, 735 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.12 (s, 12H), 1.20-1.67 (m, 6H), 4.41 (s, 2H), 9.73 (s, 1H); ^{13}C NMR (100 MHz) δ 17.1, 20.2 (2C), 32.9 (2C), 39.7 (2C), 60.2 (2C), 83.6, 200.6.

4.5. Preparation of *O*-acyl TEMPOs 6. To a cooled (0~4 °C) solution of *p*-anisoyl chloride **5j** (R = $MeOC_6H_4$, 3.5 g, 20.5 mmol) in THF (10 mL) was added dropwise a chilled solution of the TEMPO anion, prepared from TEMPO• (3.12 g, 20 mmol), $C_{10}H_8$ (150 mg, 1.17 mmol), and Na metal (506 mg, 22 mmol). The mixture was allowed to warm to room temperature and stirred for 4 h. The reaction was quenched with cold aqueous $NaHCO_3$ and products were extracted with AcOEt, worked up in a usual manner, and purified by distillation; fraction of 147-152 °C (0.03 Torr) was collected: 5.12 g (88% based on TEMPO•). **6j**: mp 89-91 °C (from hexane-AcOEt); IR (KBr) 1747, 1604, 1510, 1459, 1442, 1317, 1249, 1160, 1130, 1072, 1024, 912, 846, 765, 692, 607 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.10, 1.26 (s, 12H), 1.42-1.48 (m, 1H), 1.54-1.84 (m, 5H), 3.87 (s, 3H), 6.94 (d, *J* = 9.1 Hz, 2H), 8.03 (d, *J* = 9.1 Hz, 2H); ^{13}C NMR (75.5 MHz) δ 16.9, 20.7 (2C), 31.8 (2C), 38.9 (2C), 55.3, 60.2 (2C), 113.6 (2C), 121.8, 131.3 (2C), 163.2, 166.0. HRMS (EI) calcd for $C_{17}H_{25}NO_3$ 291.1834, found 291.1849.

6a: 85% yield; IR (neat) 2927, 2854, 1770, 1466, 1377, 1363, 1265, 1246, 1209, 1182, 1134, 1101, 1045, 935, 721 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.85 (complex t, *J* = 6.8 Hz, 3H), 1.02, 1.12 (s, 12H), 1.20-1.73 (m, 22H), 2.31 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz) δ 14.2, 17.1, 20.6 (2C), 22.8, 25.4, 29.3, 29.4, 29.5 (2C), 29.6, 32.0 (2C), 33.1

(2C), 39.0 (2C), 59.9 (2C), 173.0. HRMS (EI) calcd for $C_{20}H_{39}NO_2$ 325.2981, found 325.2986.

6f: 75% yield; mp 104-105 °C; IR (KBr) 3066, 1739, 1575, 1450, 1307, 1203, 1124, 1042, 1012, 973, 923, 864, 804, 767, 715, 675 cm^{-1}; ^1H NMR (300 MHz) δ 1.10, 1.22 (s, 12H), 1.40-1.48 (m, 1H), 1.53-1.80 (m, 5H), 6.49 (d, *J* = 16.0 Hz, 1H), 7.37-7.42 (m, 3H), 7.55-7.59 (m, 2H), 7.76 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 16.8, 20.4 (2C), 31.8 (2C), 38.8 (2C), 60.0 (2C), 116.5, 127.9 (2C), 128.7 (2C), 130.1, 134.3, 144.9, 167.0. HRMS (EI) calcd for $C_{18}H_{25}NO_2$ 287.1885, found 287.1924.

4.6. General procedure for reduction of *O*-acyl TEMPOs 6 to aldehydes 3. To a cooled (-78 °C) solution of **6f** (R = PhCH=CH, 723 mg, 2.5 mmol) in toluene (10 mL) was added dropwise DIBAL-H (1.0 N in toluene, 7.9 mL, 3.1 equivalents) over 5 min. The mixture was stirred at -78 to -50 °C for 75 min and excess DIBAL-H was decomposed with AcOEt and the reaction was quenched with aqueous $NaHCO_3$ (1.0 mL). The mixture was diluted with AcOEt, treated with a Celite, and filtered from a short Celite pad. The filtrate was washed with cold 2N HCl, brine, dried ($MgSO_4$), and concentrated. The crude products were analyzed by ^1H NMR (300 MHz) to ensure the amount of aldehyde over carbinol and purified by column chromatography (SiO_2, hexane-AcOEt, 10:1, 7:1, 5:1, 3:1, 2:1, then 1:1) to give 308 mg (91%) of **3f** (R_f= 0.36, hexane-AcOEt 5:1), identical in all respects with that obtained above. The structures of the aldehydes **3a**, **3i**, **3f**, and **3j** in Table 3 were confirmed by comparison of their spectral data with those of authentic samples.

Aldol **21**: IR (neat) 2715, 1727, 1612, 1586, 1513, 1303, 1251, 1116, 1035, 1022, 968, 906, 869, 817 cm^{-1}; ^1H NMR (300 MHz) δ 0.85 (d, *J* = 6.9 Hz, 3H), 1.35-1.85 (m, 6H), 2.70-2.85 (m, 1H), 3.15-3.80 (m, 2H), 3.809 and 3.813 (s, 3H), 4.40 and 4.80 (m, 1H), 4.64 (d, *J* = 8.5 Hz) and 4.78 (d, *J* = 9.6 Hz, 1H), 6.85-6.90 (m, 2H), 7.21-7.28 (m, 2H), 9.82 (d, *J* = 2.5 Hz) and 9.90 (d, *J* = 3.3 Hz, 1H). HRMS (EI) calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1484.

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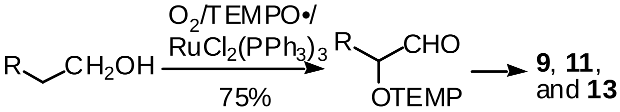
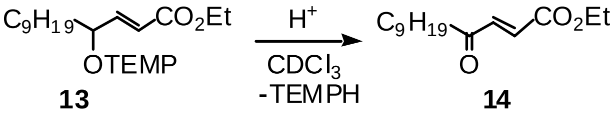
17. The liberated TEMPOH can be recovered and reused.

18. The 2-TEMPO-substituted undecanal was prepared by the reaction of undecanol with the TEMPO•/$RuCl_2(PPh_3)_3/O_2$ system in toluene.[12] This compound was converted to **9** by treatment with $NaBH_4$ (94% yield) followed with Ac_2O (95% yield), to **11** with $CH(OMe)_3$/*p*TsOH in MeOH (82% yield), and to **13** with (*i*-PrO)$_2P(O)CH_2CO_2Et$/NaH (97% yield).



19. The same compound **14** was produced on standing **13** under very weak acidic conditions (in $CDCl_3$) at room temperature for a long period.[5]



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