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A high performance oxidation method for secondary alcohols by inductive activation of TEMPO in combination with pyridine–bromine complexes

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ABSTRACT

A new TEMPO-mediated catalytic oxidation method in combination with Py·HBr_3 (stoichiometric) is developed for oxidation of secondary alcohols to the corresponding ketones. The performance of this oxidizing system is better compared with that of TEMPO method combined with R_4NBr_3. Poly(4-vinylpyridine)·HBr_3 can be used in place of Py·HBr_3. The electron-withdrawing substituent at the C-4 position of TEMPO increases the reactivity of TEMPO significantly in the oxidation of electron-deficient alcohols such as polyhaloalkylmethanols. Inductive effect of the substituent of TEMPO is discussed through the characterization of the redox potential of N–O radical by cyclic voltammetry.

1. Introduction

Various oxidation methods of alcohols with metallic and non-metallic reagents,[1] performed in a stoichiometric or catalytic manner,[2,3] meeting with the demand in synthetic transformations have been developed. However, the examples of catalytic oxidation methods relied on non-metallic reagent are scarce in spite of increasing importance in view of green chemistry. In this context, the use of TEMPO in combination with a non-toxic co-oxidant[4] is practically meaningful especially for process chemistry producing pharmaceutical substances,[5] since the TEMPO is recoverable organic catalyst after the oxidation. In addition, the TEMPO and its *N*-oxoammonium intermediate, an active form for alcohol oxidation, can be featured by fair durability and safety in conducting the operation at ambient temperature.[6]

Although TEMPO is selective in the oxidation of primary hydroxy group in the presence of secondary ones,[6c] which is cumbersome to the oxidation of sterically hindered secondary alcohols. Accordingly, several modifications by reface of the reaction site of TEMPO have been devised in order to avoid steric repulsion in the nucleophilic addition of alcohol to the *N*-oxoammonium intermediate, as exemplified by using 2,2,6-trimethylpiperidine assembled in the adamantane framework[7] or 2,6-dialkylpiperidine on the 9-azabicylo[3.3.1]nonane structure as well as its homologues,[8] and acyclic derivatives.[9] However, the activation of 2,2,6,6-tetramethylpiperidine-*N*-oxoammonium intermediate through an inductive effect of electron-withdrawing appendage at the C-4 position would be a viable approach for a high performance oxidation of alcohols because of commercial availability of 4-hydroxy-TEMPO. Although the effects of the substituent such as CN and amides at the C-4 position of TEMPO were examined on reduction rate of ascorbate,[10] the activation of the *N*-oxoammonium intermediate for oxidations based on the same protocol has not been attempted so far. Thus, we examined the effect of the substituent at the C-4 position to attain smooth oxidations of secondary alcohols.

Previously, we developed convenient catalytic oxidation methods of alcohols with TEMPO in combination with following activation procedures and co-oxidants: (a) electrooxidation in the presence of bromide ion,[11a] (b) aerobic oxidation in the presence of ruthenium catalyst,[11b] and cheap co-oxidants such as (c) $NaBrO_2$,[11c] (d) R_4NBr_3,[11d] and (e) $Ca(OCl)_2$.[11c] Now, we examined the use of pyridinium hydrobromide perbromide (Py·HBr_3) as a co-oxidant,[12a] since this commercially available and stable reagent is less expensive than R_4NBr_3,[12b] and more advantageously polymer-supported pyridinium hydrobromide perbromide is now available, though its oxidizing ability is not well characterized until now.[13]

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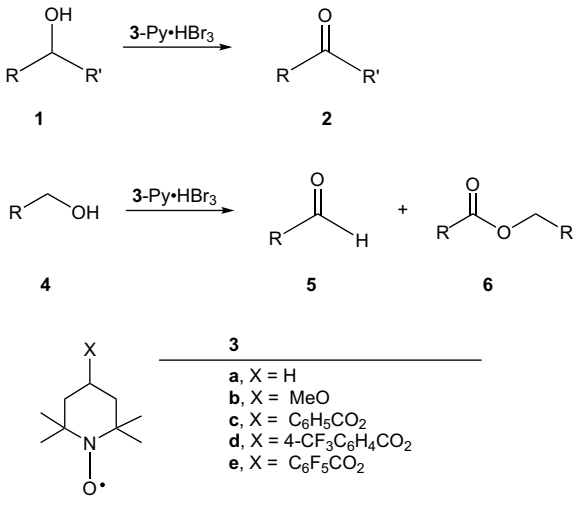
Bromine and its amine complexes are capable of oxidation of alcohols, producing the corresponding carbonyls and thus far various methods and bromine-intercalated reagents have been developed.[14,15] In general, the bromine oxidation of alcohol proceeds slowly even with respect to electron-rich secondary alcohols. Accordingly, in executing the catalytic oxidation of alcohols with TEMPO by the aid of Py·HBr_3 (stoichiometric) as a co-oxidant, concurrent oxidation of the substrate with Py·HBr_3 is an issue to be discussed (Scheme 1).



Scheme 1. TEMPO-mediated oxidation of alcohols with **3**-Py·HBr_3.

2. Results and discussion

2.1. TEMPO-mediated oxidation of aliphatic secondary alcohols

We firstly examined the reactivity of Py·HBr_3 as a co-oxidant in the TEMPO-mediated catalytic oxidation of secondary alcohols. As shown in Figure 1, the reaction of 2-undecanol (**1a**, R=C_9H_{19}, R′=CH_3) with a mixture of 4-BzOTEMPO (**3c**,[16] X=$C_6H_5CO_2$, 10 mol %) and Py·HBr_3 (1.5 equiv) in a CH_2Cl_2/aqueous $NaHCO_3$ system completes within 15 min to form the corresponding 2-undecanone (**2a**, R=C_9H_{19}, R′=CH_3) in 99% (curve a). The amount of **3c** can be reduced to 1 mol % for this conversion (curve b), though the reaction becomes somewhat sluggish. The oxidation of **1a** to **2a**, which is presumably due to oxidizing ability of Py·HBr_3, was observed in the reaction system that lacks the presence of **3c** (curve c), though being of no synthetic potential. Noteworthy is that the oxidation of **1a** to **2a** by the combination of **3c** and R_4NBr_3 as co-oxidant proceeds much slower compared with Py·HBr_3 (curve d).[17]

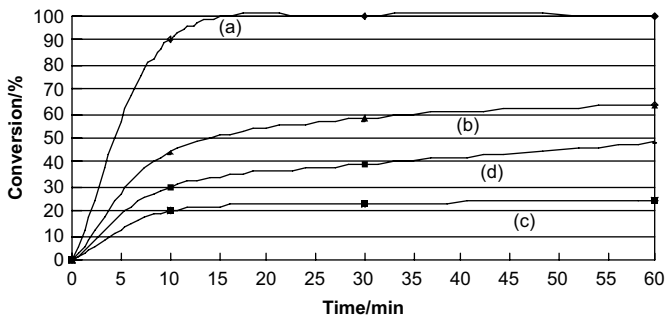
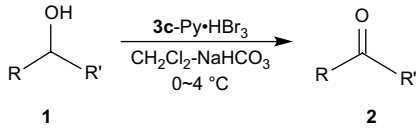


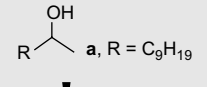
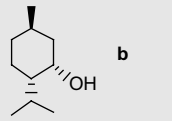
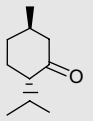
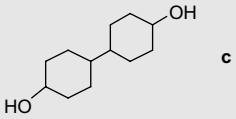
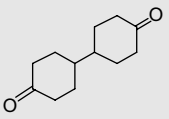
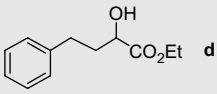
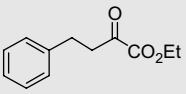
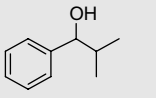
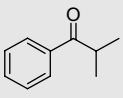
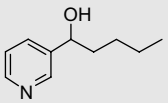
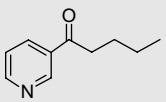
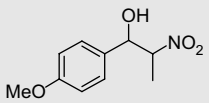
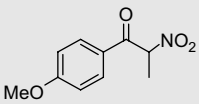
Figure 1. Time-conversion curves for oxidation of **1a** to **2a** under varying the amount of **3c** with Py·HBr_3 (1.5 equiv) at 0–4 °C. Symbols are as follows: (a) = 10 mol %, (b) = 1.0 mol %, (c) = no addition, (d) = 10 mol %–Bu_4NBr_3. Data points were obtained by GC analyses.

The present oxidizing system comprised of **3c** (3–10 mol %) and Py·HBr_3 (1.5 equiv) was applied to the oxidation of various secondary alcohols **1**. As shown in Table 1, most of secondary alcohols **1** can be oxidized at 0–4 °C, giving the corresponding ketones **2** in good yields. The reaction of sterically hindered alcohol such as menthol (**1b**) is best achieved at room temperature (entry 2). In place of chromate[18] or Swern oxidation methods, 2-nitroalcohol **1g**, accessible by Henry reaction, was smoothly oxidized to synthetically useful 2-nitroketone **2g** by the present method, though a small of amount of bromination at the C-2 position was accompanied (ca. 5%, entry 7).

In contrast to high performance in secondary alcohols, the oxidation of primary alcohol **4a** (R=$C_{10}H_{21}$) with a **3c** (catalytic)–Py·HBr_3 (stoichiometric) system led to a mixture of the desired undecanal (R=$C_{10}H_{21}$, **5a**) and the corresponding dimeric ester **6a** in a ratio of 4:1 in 90% yield. For further insight into the effect of co-oxidant, two bromine compounds, i.e., Py·HBr_3 and Bu_4NBr_3,[11d] were compared in the competitive oxidation of primary and

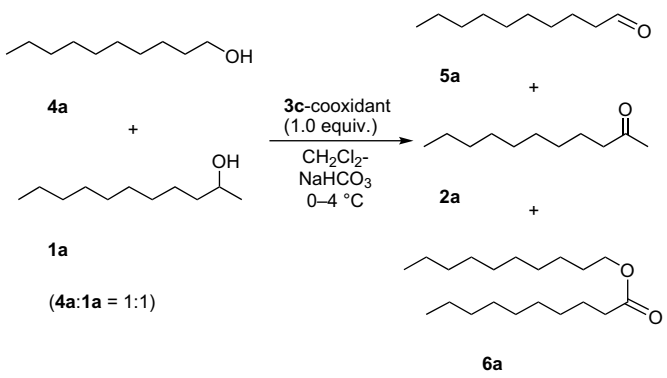
Table 1
Oxidation of secondary alcohols with a combination of 4-BzOTEMPO (**3c**) and Py·HBr_3[a]



Entry	Alcohol **1**	Product **2**	Yield[b,d] (%)
1	 **a**, R = C_9H_{19}		79 (78)
2[c]	 **b**		76
3	 **c**		93
4	 **d**		81 (69)
5	 **e**		80 (64)
6	 **f**		84 (74)
7	 **g**		87[e]

[a] Carried out by the reaction of **1** (1 mmol) with **3c** (5 mol %) and Py·HBr_3 (1.5–2 equiv) at 0–4 °C.
[b] Based on isolated products after column chromatography.
[c] Carried out at room temperature.
[d] Numbers in parenthesis are the data obtained with a **3c**–poly(4-vinylPy)·HBr_3 system.
[e] Bromination at the C-2 was accompanied (ca. 5%).

secondary alcohols. As shown in Scheme 2, the oxidation of a mixture of **4a** and **1a** with a **3c**–Py·HBr_3 (1.0 equiv) system produces a mixture of the corresponding aldehyde **5a**, ketone **2a**, and dimeric ester **6a** in a ratio of 94:2:4, while the same run with a **3c**–Bu_4NBr_3 (1.0 equiv) system afforded **5a**, selectively (**5a**/**6a**=99:1). Thus, the problem forming dimeric ester **6a** from primary alcohol with a **3c**–Py·HBr_3 system can be avoided by employing Bu_4NBr_3 as a co-oxidant.



Cooxidant	Product/ratio **5a**:**2a**:**6a**
Py•HBr_3	94:2:4
Bu_4NBr_3	99:1:0

Scheme 2. Competitive oxidation of primary and secondary alcohols.

Merit of Py·HBr_3 as a co-oxidant lies in its easy extension to the polymer-supported derivative,[19] poly(4-vinylPy)·HBr_3, which is commercially available. Thus, we examined the use of this polymer-supported reagent in place of Py·HBr_3 and the results for oxidation of secondary alcohols are shown in the parenthesis of Table 1. Although slightly inferior results than that with Py·HBr_3 are obtained with this supported reagent, the present TEMPO (**3c**)-mediated oxidation was smoothly performed and the solid pyridine support was recovered quantitatively only by filtration.

2.2. TEMPO-mediated oxidation of aryl polyhaloalkyl alcohols

In the course of our study on synthesis of fluorine-containing building blocks (Scheme 3), we met with somewhat low yields in the oxidation of 1-aryl-2,2-dichloro-2-fluoroethyl alcohols **7** to the corresponding ketones **8** with conventional methods such as Swern and chromium(VI) oxidation.[20] Since these unfavorable results seemed to be due to strong electron-withdrawing nature of dichlorofluromethyl group, we attempted to employ TEMPOs bearing an EWG group at the C-4 position as an appendage, which would result in enhancement of electronic polarity of reaction site of *N*-oxoammonium intermediate.

Thus, effect of the appendage on TEMPOs is examined by dictating the time-course of the conversion of **7a** (Ar=C_6H_5) to **8a** (Ar=C_6H_5) by changing the kind of substituent at the C-4 position. As shown in Figure 2, the oxidation of **7a** is fairly facilitated by appendage of an arenecarboxy group on TEMPO, curves (c), (d),

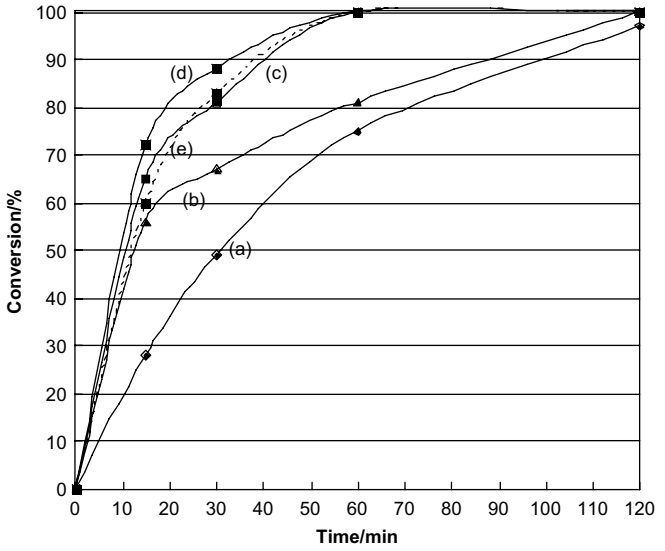


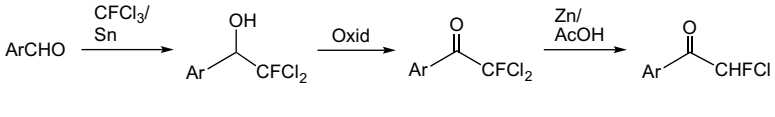
Figure 2. Time-conversion curves for oxidation of **7a** to **8a** under various TEMPO catalysts **3a**–**d**. Carried out by reaction of **7a** (1 mmol) with **3** (5 mol %) and Py·HBr_3 (1.5–2 equiv) at room temperature. Symbols are as follows: (a) = **3a**, (b) = **3b**, (c) = **3c**, (d) = **3d**, and (e dotted) = **3e**. Data points were obtained by GC analyses.

and (e), compared with the TEMPO bearing no appendage, curve (a). Among them, the most favorable conversion was attained with 4-(4-trifluoromethylbenzoyl)-substituted **3d** (curve (d)), prepared by 4-trifluoromethylbenzoylation of 4-hydroxyTEMPO. Similar enhancement in the conversion was also observed in the oxidation of 2-octanol, being classified as electron-rich alcohol compared with 2,2-dichloro-2-fluoroethyl derivatives, in which the best conversion was also attained with **3d**.

Based on these results, we next attempted the oxidation of carbinol with an electron-withdrawing group. As shown in Table 2, the dichlorofluoro and dichlorotrifluoromethyl, dichlorocarboxy alcohols[21] are cleanly oxidized under the conditions developed above.

2.3. Characterization of redox properties of C4-substituted TEMPOs

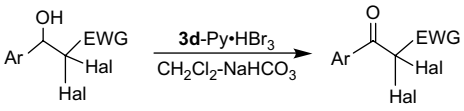
The enhanced reactivity of the electronically activated TEMPOs was rationalized by the characterization of their redox properties. The cyclic voltammetry of C4-substituted TEMPOs (**3a**–**e**) was performed in dichloromethane, the same solvent as in the catalytic reactions. All TEMPOs (**3a**–**e**) exhibited an oxidation peak and the reduction peak of C4-substituted $TEMPO^+$ on the reverse scan, in a reversible system at the scan rate of 0.5 V s^{-1} (Table 3). From the potential values, it emerges that the redox properties of C4-substituted TEMPOs are affected by the electronic properties of the substituents. The oxidation peak potentials of TEMPOs substituted by ester groups (**3c**–**e**) are very similar and are more positive than for H and OMe substituents (**3a**,**b**). The reduction peak potentials of their oxidized forms, N–O^+ are also more positive for ester substituents. Consequently, the $TEMPO^+$ substituted by the ester

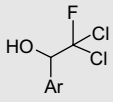
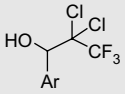
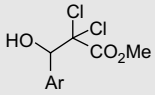
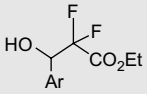
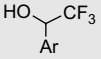


7 **8**

Scheme 3. Synthesis of α-fluoroketones from fluorohaloketones.

Table 2
Oxidation of (aryl)polyhaloalkylmethanols with a combination of 4-(4-CF_3BzO)-TEMPO (**3d**) and Py·HBr_3[a]



Entry	Alcohol		Ar	Product	Yield[b] (%)
1		**7a**	C_6H_5	**8a**	91
2		**8b**	4-$MeOC_6H_5$	**8b**	94
3		**8c**	4-ClC_6H_5	**8c**	92
4		**8d**	4-MeC_6H_5	**8d**	93
5		**9a**	C_6H_5	**10a**	69
6		**9b**	4-$MeOC_6H_5$	**10b**	86
7		**11a**	C_6H_5	**12a**	79
8		**11b**	4-$MeOC_6H_5$	**12b**	78
9		**13a**	C_6H_5	**14a**	80
10		**13b**	4-$MeOC_6H_5$	**14b**	72
11		**15**	4-$MeOC_6H_5$	**16**	70

[a] Carried out by reaction of polyhalocarbinol (1 mmol) with **3d** (5 mol%) and Py·HBr_3 (1.5–2 equiv) at room temperature.
[b] Isolated yield based on separated products.

Table 3
Oxidation peak potentials of C4-X-substituted TEMPO (2 mM) in CH_2Cl_2 (containing Bu_4NBF_4, 0.3 M) and reduction peak potentials of C4-X-substituted TEMPO$^+$

	X	X-TEMPO	X-TEMPO$^+$	
		E^p_{ox}	E^p_{red}	E^0
		(V vs SCE)[a]	(V vs SCE)[a]	(V vs SCE)[a]
3a	H	+0.852	+0.766	+0.809
3b	MeO	+0.885	+0.803	+0.844
3c	$C_6H_5CO_2$	+0.970	+0.887	+0.928
3d	4-$CF_3C_6H_4CO_2$	+0.966	+0.885	+0.925
3e	$C_6F_5CO_2$	+0.974	+0.886	+0.930

[a] Potentials were determined at a gold disk electrode (d=0.5 mm), at the scan rate of 0.5 V^{-1} at 22 °C.

groups at the C-4 position generated by the oxidation of the C4-substituted TEMPOs (**3c**–**e**) are more powerful oxidants for the oxidation of alcohols than those substituted by H or MeO. This is in agreement with the results of the catalytic reactions in which Py·HBr_3 acts as an oxidant for the TEMPOs.

3. Conclusion

In summary, a high performance oxidation method of alcohols with TEMPO substituted with an EWG at the C-4 position, which is useful for the electron-deficient secondary alcohols such as $ArCH(OH)CFCl_2$, has been developed by using Py·HBr_3 as a co-oxidant. Reactivity of Py·HBr_3 was discussed in terms of efficiency and selectivity in comparison with similar bromine compounds such as Bu_3NBr_3, and the method was easily extended to the polymer-supported bromine reagents as a co-oxidant. Inductive activation of TEMPO by the appendage of electron-withdrawing group at the C-4 position was shown to facilitate the reaction rate, which was rationalized by measuring the cyclic voltammetry of the C-4-substituted TEMPOs.

4. Experimental section

4.1. General

IR spectra were obtained with a Shimazu, FT-IR 8400, and only major absorptions are cited. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on Varian instruments with $CDCl_3$ as a solvent unless otherwise indicated.

4.2. General procedure for oxidation of secondary alcohols to the ketones

A solution of 2-undecanol (**1a**, 172 mg, 1 mmol) and **3c** (28 mg, 0. 1 mmol) in CH_2Cl_2 (6 mL) was covered with aqueous saturated $NaHCO_3$ (12 mL). To this biphase mixture was added portionwise Py·HBr_3 (480 mg, 1.5 mmol) under a vigorous stirring at 0–4 °C. The mixture was stirred for an additional 30 min. The reaction was quenched with aqueous 5% $Na_2S_2O_3$. The products were extracted with CH_2Cl_2 and the aqueous layer was again extracted with AcOEt. Extracts were washed separately with aqueous NH_4Cl, dried ($MgSO_4$), and concentrated. The combined crude product was purified by column chromatography (SiO_2, hexane–AcOEt 10:1 to 5:1) to give 135 mg (79% yield) of **2a** (R_f=0.79, hexane–AcOEt 3:1); IR (neat): 1719, 1466, 1410, 1358, 1228, 1163, 758, 719 cm^{-1}; ^1H NMR (300 MHz): δ 0.87 (t, J=7.4 Hz, 3H), 1.26 (br s, 12H), 1.56 (m, 2H), 2.13 (s, 3H), 2.41 (t, J=7.4 Hz, 2H); ^{13}C NMR (75.5 MHz): δ 13.9, 22.5, 23.9, 29.1, 29.2, 29.31, 29.33, 29.6, 31.8, 43.7, 208.9.

4.2.1. 4,4′-Bicyclohexanone (**2c**)

Yield 93% (R_f=0.47, hexane–AcOEt 1:2); mp 113–115 °C (from hexane) (lit.[22] 112–116 °C); IR (KBr): 1705, 1464, 1439, 1418, 1354, 1333, 1321, 1302, 1281, 1267, 1244, 1215, 1167, 1155, 1115, 1069, 1011, 980, 932, 858, 816, 762, 704 cm^{-1}; ^1H NMR (300 MHz): δ 1.45–1.60 (m, 4H), 1.63–1.79 (m, 2H), 2.02–2.12 (m, 4H), 2.27–2.46 (m, 8H); ^{13}C NMR (75.5 MHz): δ 29.8 (4C), 40.3 (2C), 40.7 (4C), 211.0 (2C).

4.2.2. Ethyl 2-Oxo-4-phenylbutanoate (**2d**)

Yield 81% (R_f=0.5, hexane–AcOEt 5:1); IR (neat): 1728, 1605, 1497, 1454, 1400, 1370, 1304, 1271, 1250, 1190, 1067, 1030, 856, 750, 700 cm^{-1}; ^1H NMR (300 MHz): δ 1.35 (t, J=7.1 Hz, 3H), 2.96 (t, J=7.7 Hz, 2H), 3.18 (t, J=7.7 Hz, 2H), 4.31 (q, J=7.1 Hz, 2H), 7.18–7.32 (m 5H); ^{13}C NMR (75.5 MHz): δ 13.9, 28.9, 40.7, 62.1, 125.9, 127.9 (2C), 128.1 (2C), 139.6, 160.4, 192.8.

4.2.3. 3-Pentanoylpyridine (**2f**)

Yield 84% (R_f=0.41, hexane–AcOEt 1:1); IR (neat): 1690, 1586, 1466, 1458, 1420, 1374, 1350, 1269, 1223, 1117, 1011, 970, 797, 704 cm^{-1}; ^1H NMR (300 MHz): δ 0.94 (t, J=7.9 Hz, 3H), 1.41 (m, 2H), 1.72 (m, 2H), 2.97 (t, J=7.2 Hz, 2H), 7.41 (d,d,d, J=7.9, 4.7, 1.1 Hz, 1H), 8.23 (ddd, J=7.9, 2.2, 2.2 Hz, 1H), 8.76 (dd, J=4.9, 1.6 Hz, 1H), 9.15 (d, J=2.2 Hz, 1H); ^{13}C NMR (75.5 MHz): δ 13.6, 22.2, 26.0, 38.4, 123.4, 132.2, 135.1, 149.4, 153.1, 198.9.

4.2.4. 2-Nitro-1-phenylpropanone (**2g**) and 2-bromo-2-nitro-1-phenylpropanone (byproduct)

Compound **2g**: yield 87% (R_f=0.31, hexane–AcOEt 3:1); IR (neat): 3534, 2843, 1686, 1601, 1560, 1512, 1452, 1389, 1364, 1325, 1269, 1229, 1175, 1123, 1026, 966, 845, 752, 683 cm^{-1}; ^1H NMR (300 MHz) (absorptions based on major isomer):[23] δ 1.82 (d, J=7.1 Hz, 3H), 3.90 (s, 3H), 6.13 (q, J=7.1 Hz, 2H), 6.99 (d, J=8.8 Hz, 2H), 7.94 (d, J=8.8 Hz, 2H); ^{13}C NMR (75.5 MHz) (absorptions based on major isomer): δ 16.0, 55.6, 84.5, 114.4 (2C), 126.4, 131.2 (2C), 164.8, 188.1. 2-Bromo-2-nitro-1-phenylpropanone: yield 5% (R_f=0.65, hexane–AcOEt 3:1); IR (neat): 2843, 1686, 1601, 1560,

1512, 1458, 1441, 1424, 1381, 1333, 1317, 1258, 1180, 1140, 1121, 1080, 1028, 957, 845 cm^{-1}; ^1H NMR (300 MHz): δ 2.49 (s, 3H), 3.88 (s, 3H), 6.92 (d, J=9.1 Hz, 2H), 7.94 (d, J=9.1 Hz, 2H); ^{13}C NMR (75.5 MHz): δ 30.2, 55.6, 92.2, 114.2 (2C), 123.8, 132.1 (2C), 164.4, 183.1.

4.3. Time-course for the oxidation of 2a with a 3c-co-oxidants system

A mixture of **1a** (172 mg, 1 mmol), **3c** (28 mg, 0. 1 mmol), and Py·HBr_3 (480 mg, 1.5 mmol) in CH_2Cl_2 (6 mL)–aqueous saturated $NaHCO_3$ (12 mL) was allowed to react and the aliquots at the prescribed time were analyzed by GC and the selectivity was calculated based on the peak areas (Fig. 1). Similarly, the time-course of the oxidation of **7a** was achieved by using Py·HBr_3 in combination with various **3a–d** (Fig. 2).

4.4. A typical procedure for oxidation of secondary alcohols to the ketones with poly(4-vinylPy)·HBr_3

A solution of **1a** (86 mg, 0.5 mmol) and **3c** (28 mg, 0. 1 mmol) in CH_2Cl_2 (3 mL) was covered with aqueous saturated $NaHCO_3$ (6 mL). To this biphase mixture was added portionwise poly(4-vinylpyridinium) tribromide (300 mg) under a vigorous stirring at room temperature. The stirring was continued at room temperature until **1a** was consumed, for about 2 h as monitored with TLC. The mixture was filtered off to leave poly(4-vinylpyridine) (107 mg) and the filtrate was worked up in the usual manner to give 67 mg (78% yield) of **2a** after purification by column chromatography.

4.5. Preparation of 4-(4-trifluoromethylbenzoyloxy)-2,2,6,6-tetramethylpiperidine-1-oxyl (3d)

To a solution of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (1.72 g, 10 mmol) and pyridine (1.62 mL, 20 mmol) in THF (10 mL) was added dropwise a solution of 4-trifluoromethylbenzoyl chloride (1.63 mL, 11 mmol) in THF (3 mL) at 0–4 °C. The mixture was stirred at room temperature overnight and worked up in the usual manner. The crude product was purified by column chromatography (SiO_2, hexane–AcOEt 10:1 to 5:1) to give 3.2 g (93% yield) of **3d** as solids; mp 74–75 °C (from hexane) (R_f=0.55 hexane–AcOEt 3:1); IR (KBr): 1721, 1585, 1512, 1466, 1412, 1331, 1283, 1242, 1167, 1138, 1128, 1101, 1067, 1017, 963, 862, 775, 705 cm^{-1}; ^1H NMR, treated with $PhNHNH_2$ (300 MHz): δ 1.176 and 1.181 (s, 12H), 1.68 (m 2H), 1.94–2.00 (m, 2H), 5.23 (m, 1H), 7.60 (d, J=8.2 Hz, 2H), 8.03 (d, J=8.24 Hz, 2H); ^{19}F NMR, treated with $PhNHNH_2$ (282.3 MHz): δ −63.3 (s). HRMS (ESI) calcd for $C_{17}H_{21}F_3NO_3$ (M^+) 344.1474, found 344.1499 (M^+).

4.6. 4-(2,3,4,5,6-Pentafluorobenzoyloxy)-2,2,6,6-tetramethylpiperidine-1-oxyl (3e)

Compound **3e** was prepared by the reaction of 2,3,4,5,6-pentafluorobenzoic acid and 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl in the presence of carbon tetrabromide, PPh_3, pyridine in CH_2Cl_2; mp 109–110 °C (from hexane–AcOEt 10:1) (R_f=0.64 hexane–AcOEt 3:1); IR (KBr): 1728, 1651, 1526. 1495, 1416, 1368, 1337, 1232, 1177, 1107, 1092, 1069, 1007, 957, 770 cm^{-1}; ^1H NMR, treated with $PhNHNH_2$ (300 MHz): δ 1.152 and 1.158 (s, 12H), 1.64 (m 2H), 1.93–1.99 (m, 2H), 5.24 (m, 1H); ^{19}F NMR, treated with $PhNHNH_2$ (282.3 MHz): δ −160.6 (m), −149.0 (m), −138.9 (m). HRMS (ESI) calcd for $C_{16}H_{17}F_5NO_3$ (M^+) 366.1129, found 366.1121 (M^+).

4.7. Electrochemical set-up and electrochemical procedure for cyclic voltammetry

Cyclic voltammetry was performed with a home made potentiostat and a wave-form generator, PAR Model 175. The cyclic voltammograms were recorded on a Nicolet 3091 digital oscilloscope. Experiments were carried out in a three-electrode cell. The working electrode was a steady gold disk electrode (d=0.5 mm). The counter electrode was a platinum wire of ca. 1 cm^2 apparent surface area. The reference was a saturated calomel electrode separated from the solution by a bridge filled by 2 mL of dichloromethane containing Bu_4NBF_4 (0.3 M). Distilled and degassed dichloromethane (15 mL) containing Bu_4NBF_4 (0.3 M) was poured into the cell, followed by 4.68 mg (0.03 mmol, 2 mM) of TEMPO (**3a**). The cyclic voltammetry was performed at the scan rate of 0.5 V s^{-1} in the potential range between 0 and +1.2 V.

Similar experiments were performed from **3b** (5.6 mg), **3c** (8 mg), **3d** (10 mg), and **3e** (11 mg).

4.8. General procedure for oxidation of polyhaloalkyl alcohols to the ketones with 3d–Py·HBr_3

A solution of 2,2-dichloro-3,3,3-trifluoro-1-(4-methoxyphenyl)propanol[21] (**9b**, 288 mg, 1.0 mmol) and 4-(4-$CF_3C_6H_4CO_2$)-TEMPO (**3d**, 35 mg, 0.1 mmol) in CH_2Cl_2 (6 mL) was covered with aqueous 5% $NaHCO_3$ (12 mL). To this biphase mixture was added portionwise Py·HBr_3 (480 mg, 1.5 mmol) under a vigorous stirring at room temperature. The mixture was stirred for an additional 1.5 h and the reaction was quenched with aqueous 5% $Na_2S_2O_3$ (5 mL). The products were extracted with CH_2Cl_2 and the aqueous layer was again extracted with AcOEt. Extracts were separately washed with brine, dried ($MgSO_4$), and concentrated. The combined crude product was purified by column chromatography (SiO_2, hexane–AcOEt 10:1 to 3:1) to give 245 mg (86% yield) of **10b** (R_f=0.65, hexane–AcOEt 5:1); IR (neat): 2845, 1697, 1601, 1574, 1512, 1460, 1425, 1316, 1261, 1207, 1180, 1124, 1045, 1026, 930, 870, 847, 829, 737, 702, 673 cm^{-1}; ^1H NMR (300 MHz): δ 3.91 (s, 3H), 6.97 (d, J=9.2 Hz, 2H), 8.27 (d, J=9.2 Hz, 2H); ^{13}C NMR (75.5 MHz): δ 55.5, 78.7 (q, $^2J_{CF}$=31.1 Hz), 113.8 (2C), 121.3 (q, $^1J_{CF}$=283.3 Hz), 122.7, 133.4 (2C), 164.7, 181.3; ^{19}F NMR (282.3 MHz): δ −75.2 (s).

4.8.1. *Methyl 2,2-dichloro-3-oxo-3-phenylpropanoate (**12a**)*

Yield 79% (R_f=0.53, hexane–AcOEt 5:1); IR (neat): 2957, 1769, 1746, 1713, 1690, 1597, 1449, 1437, 1252, 1217, 1186, 1015, 864, 824, 795, 689 cm^{-1}; ^1H NMR (300 MHz): δ 3.87 (s, 3H), 7.45–7.52 (m, 2H), 7.60–7.65 (m, 1H), 8.02–8.07 (m, 2H); ^{13}C NMR (75.5 MHz): δ 54.8, 81.6, 128.6 (2C), 130.0 (2C), 130.8, 134.1, 164.5, 183.3. HRMS (ESI) calcd for $C_{10}H_9Cl_2O_3$ (MH^+) 246.9929, found 246.9887 (MH^+).

4.8.2. *Methyl 2,2-dichloro-3-oxo-3-(4-bromophenyl)-propanoate (**12b**)*

Yield 78% (R_f=0.62, hexane–AcOEt 5:1); IR (neat): 1769, 1746, 1713, 1690, 1584, 1485, 1437, 1398, 1250, 1217, 1184, 1074, 1007, 928, 868, 824, 760, 725 cm^{-1}; ^1H NMR (300 MHz): δ 3.89 (s, 3H), 7.63 (d, J=8.8 Hz, 2H), 7.92 (d, J=8.8 Hz, 2H); ^{13}C NMR (75.5 MHz): δ 55.0. 81.4, 129.6, 129.7, 131.5 (2C), 132.1 (2C), 164.3, 182.7. HRMS (ESI) calcd for $C_{10}H_7BrCl_2O_3$ (MH^+) 324.9034, found 324.8992 (MH^+).

4.8.3. *Ethyl 2,2-difluoro-3-(4-methoxyphenyl)-3-oxo-propanoate (**14b**)*

Yield 72% (R_f=0.59, hexane–AcOEt 5:1); IR (neat): 2845, 1771, 1694, 1690, 1600, 1573, 1514, 1464, 1447, 1427, 1395, 1373, 1316, 1269, 1182, 1159, 1122, 1099, 1076, 1026, 924, 910, 847, 791, 712, 698 cm^{-1}; ^1H NMR (300 MHz): δ 1.32 (t, J=7.1 Hz, 3H), 3.90 (s, 3H), 4.38 (q, J=7.1 Hz, 2H), 6.98 (d, J=9.1 Hz, 2H), 8.07 (d, J=9.1 Hz, 2H);

^{13}C NMR (75.5 MHz): δ 13.7, 55.6, 63.5, 110.1 (t, $^{1}J_{CF}$=264.3 Hz), 114.3 (2C), 124.0, 132.5 (t, $^{4}J_{CF}$=2.9 Hz, 2C), 162.0 (t, $^{2}J_{CF}$=30.5 Hz), 165.1, 183.8 (t, $^{2}J_{CF}$=27.1 Hz); ^{19}F NMR (282.3 MHz): δ −107.6 (s). HRMS (ESI) calcd for $C_{12}H_{13}F_2O_4$ (MH^+) 259.0782, found 259.0749 (MH^+).

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Supplementary data

IR, ^{1}H NMR, and ^{13}C NMR spectra of the compounds **2a**–**g**, **8a**–**d**, **10a**,**b**, **12a**,**b**, **14a**,**b**, **16**, and **3c**,**d**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.08.051.

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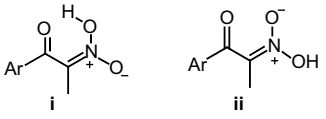
23. Two isomers **i** and **ii** are conceived for **2g**.



i **ii**