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Manganese-Catalyzed Direct Oxidation of Methyl Ethers to Ketones

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Dedicated to the 150th anniversary of Japan–UK diplomatic relations

Alkyl ether linkages generally exhibit high chemical stability under a wide array of synthetic procedures and reaction conditions. Therefore, such ethers are often employed as protective groups for hydroxyl functionalities,[1] which are present in a number of naturally occurring substances of biological and synthetic interest. During syntheses of multihydroxylated molecules, judicious choice of protective groups, and their selective introduction and removal, are extremely important issues. Accordingly, a number of ethereal protective groups have been designed and developed, and various substituted benzyl ethers are among the most frequently employed in organic synthesis. On the other hand, the simplest, most robust methyl ethers have received less attention mainly owing to the harsh acidic conditions required for deprotection.[2]

We envisioned that direct sp^3 C–H oxidation[3] under mild conditions should be useful for oxidative removal of methyl ethers, because C–H bonds in the position α to the oxygen atom are generally susceptible to oxidation.[4] A number of oxidizing agents have been reported to perform one-step oxidation of dialkyl ethers to the corresponding carbonyl products. Among them, dioxirane[5] and oxaziridine[6] are representative non-metallic stoichiometric reagents for oxidation of dialkyl ethers. Several metal catalysts, such as Ru, Cr, Mn, and Fe, are also reported to oxidize ethers when utilized with a stoichiometric amount of primary oxidant.[4,7] However, the starting ethers are restricted mainly to cyclic ethers, and systematic studies on metal-catalyzed oxidation of acyclic alkyl ethers are scarce.[8] We herein report a direct oxidation method of methyl ethers to ketones using a newly developed reagent system that involves a catalytic amount of Mn reagent and *m*-chloroperbenzoic acid (*m*CPBA).[9,10]

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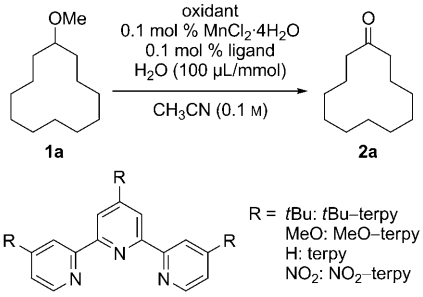
The reaction conditions for the C–H oxidation were screened and optimized using methyl cyclododecyl ether **1a** (Table 1). Treatment of methyl ether **1a** with four equivalents of reagent-grade *m*CPBA in the presence of 0.1 mol% of $MnCl_2 \cdot 4H_2O$ in CH_3CN produced the corresponding cyclododecanone **2a** in 32% yield (Table 1, entry 1), although the reaction was not complete even after 12 h at room temperature.[11] Use of 0.1 mol% of 2,2′:6′,2″-terpyridine (terpy, Table 1, entry 2) as a tridentate nitrogen ligand increased the reaction rate, and 50% of **2a** was isolated after 2 h at room temperature.[9b,c] To improve the oxidation ability of the catalyst even further, addition of a variety of ligands was examined (Table 1, entries 3–5). Complexation with ligands bearing electron-donating groups, such as 4,4′,4″-tri(*tert*-butyl)-2,2′:6′,2″-terpyridine (*t*Bu-terpy, entry 3) and 4,4′,4″-tri(methoxy)-2,2′:6′,2″-terpyridine[12] (MeO-terpy, entry 4) accelerated the ether oxidation, whereas addition of the ligand bearing an electron-withdrawing group, 4,4′,4″-tri(nitro)-2,2′:6′,2″-terpyridine (NO_2-terpy, entry 5), showed no beneficial effect for the conversion. Consequently, *t*Bu-terpy was selected as the ligand for further investigation, because of its high performance and commercial availability. As a primary oxidant, *m*CPBA was found to be far more reactive than magnesium monoperoxyphthalate (MMPP) and tetra-*n*-butylammonium oxone (TBA-oxone)[9b,c,13] (Table 1, entries 6 and 7). Overall, the optimized conditions (entry 3), which employed $MnCl_2 \cdot 4H_2O$ (0.1 mol%), *t*Bu-terpy (0.1 mol%) and *m*CPBA (4 equiv; 70 wt%) in CH_3CN (0.1 M), resulted in formation of **2a** in 50% yield within 2 h at 0 °C.[14] The reaction most likely occurs through insertion of oxygen into the tertiary C–H bond, which is generally more prone to oxidation than the methyl C–H bond (Scheme 1).[15] Ejection of methanol from the generated hemiacetal **3** would then lead to ketone **2a**. It is also important to note that *m*CPBA did not promote the Baeyer–Villiger type of oxidation of ketone **2a** under these mild conditions.

The procedure developed here is operationally simple. For instance, the reaction of **1a** to **2a** took place even in the presence of a small amount of water under aerobic atmos-

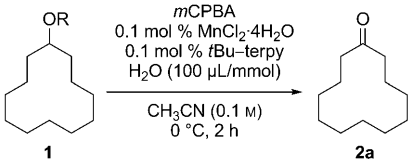
Table 1. Screening of ligand and oxidant for Mn-catalyzed oxidation of ether **1a**.[a]



Entry	Ligand	Oxidant	*T*, *t*	NMR Yield [%] (recovery of **1a**)
1	none	*m*CPBA[b]	0 °C, 2 h; then RT, 12 h	32 (36)
2	terpy	*m*CPBA[b]	0 °C, 2 h; then RT, 2 h	50[c]
3	*t*Bu-terpy	*m*CPBA[b]	0 °C, 2 h	50[c]
4	MeO-terpy	*m*CPBA[b]	0 °C, 2 h	41[c]
5	NO_2-terpy	*m*CPBA[b]	0 °C, 2 h; then RT, 2 h	31 (40)
6	*t*Bu-terpy	MMPP[d]	0 °C, 2 h	2.9 (94)
7	*t*Bu-terpy	TBA-oxone[e]	0 °C, 2 h	1.4 (90)

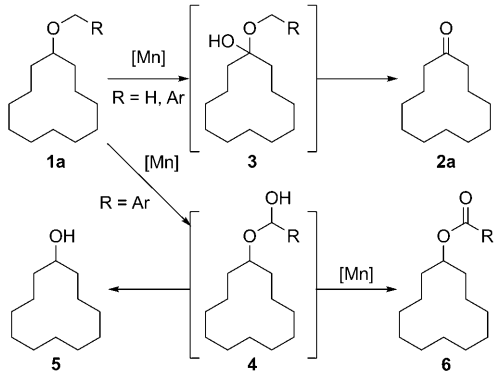
[a] Reaction conditions: **1a** (0.5 mmol), oxidant (2 mmol), $MnCl_2·4H_2O$ (0.5 μmol), ligand (0.5 μmol), H_2O (50 μL), CH_3CN (5 mL). [b] *m*CPBA (70 wt %) was used. [c] Yield of isolated product. [d] MMPP (65 wt %) was used. [e] TBA-oxone (30 wt %) was used.

Table 2. Mn-catalyzed oxidation of various cyclododecanol derivatives[a]



Entry	R	**1**	Yield [%] (recovery of **1**)
1	Me	**1a**	50
2	$PhCH_2$	**1b**	48[b]
3[c]	$(p\text{-MeO})C_6H_4CH_2$	**1c**	46[d]
4	$(p\text{-}NO_2)C_6H_4CH_2$	**1d**	55[e]
5[f]	$n\text{-}C_8H_{17}$	**1e**	59[g]
6[h]	*i*Pr	**1f**	29
7	*t*Bu	**1g**	trace (32)
8	$MeOCH_2$	**1h**	trace (73)
9	Bz	**1i**	0 (49)
10	Ts	**1j**	0 (51)

[a] Reaction conditions: **1** (0.5 mmol), *m*CPBA (2 mmol; 70 wt %), $MnCl_2·4H_2O$ (0.5 μmol), *t*Bu-terpy (0.5 μmol), H_2O (50 μL), CH_3CN (5 mL), 0 °C for 2 h. [b] The corresponding benzoate **6b** (trace) and cyclododecanol **5** (12 % yield) were obtained. [c] The reaction was completed in 1 h. [d] The corresponding benzoate **6c** (trace) and **5** (28 % yield) were obtained. [e] The corresponding benzoate **6d** (7.1 % yield) and **5** (trace) were obtained. [f] Five equivalents of *m*CPBA were employed. [g] Octanoic acid was obtained in 48 % NMR yield. [h] The reaction was further carried out at room temperature for 1 h.



Scheme 1. Plausible reaction mechanism of Mn-catalyzed oxidation.

phere utilizing a stock solution of the premixed manganese complex in CH_3CN.[16] The catalytic activity of the premixed catalyst was maintained at least for one month without any special precautions.

To investigate the reactivity of alkyl ethers toward oxidation, a variety of cyclododecanol derivatives were prepared and subjected to the optimized reagent system (Table 2). Similar to methyl ether (entry 1), oxidation of benzyl ethers **1b–d** proceeded to afford ketone **2a** as the major product in 46–55 % yields (Table 2, entries 2–4). The oxidation of the electron-rich *p*-methoxybenzyl ether **1c** (Table 2, entry 3) was completed in a shorter reaction time (1 h at 0 °C) than those of the other benzyl ethers, although similar yields of ketone **2a** were obtained irrespective of the electronic properties of the aromatic ring. In these reactions, cyclododecanol **5**, as well as the corresponding benzoates **6** [R = Ph, $(p\text{-MeO})C_6H_4$, or $(p\text{-}NO_2)C_6H_4$], were detected as minor byproducts (Scheme 1), indicating that direct hydroxylation at the reactive benzylic C–H bond occurred to generate hemiacetal **4** as an intermediate.[17] Nonetheless, formation of ketone **2a** as a major product from benzyl ethers **1b–d** is a striking difference of the Mn-catalyzed transformation compared to its RuO_4-catalyzed counterpart, which generally provides the corresponding benzoates as major products.

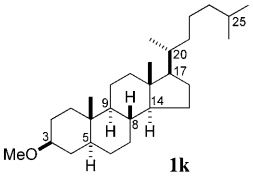
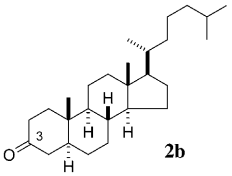
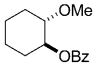
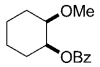
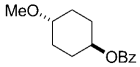
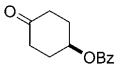
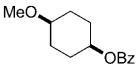
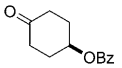
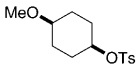
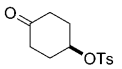
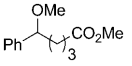
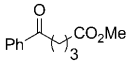
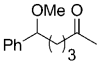
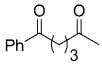
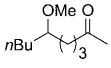
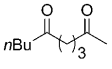
To assess the steric and electronic influences on the present oxidation, variously masked cyclododecanol derivatives were treated with the manganese catalyst and *m*CPBA (Table 2, entries 5–10). Entries 5, 6, and 7 demonstrated sensitivity of the transformation to the steric hindrance around the ether linkage. While cyclododecyl octyl ether **1e** (Table 2, entry 5) was converted into ketone **2a** in a similar efficiency to methyl ether **1a** (59 %),[18] the reaction of isopropyl ether **1f** was sluggish, affording the desired ketone **2a** only in 29 % yield (Table 2, entry 6), and oxidation of the bulkier *tert*-butyl ether **1g** gave only a trace amount of the ketone **2a** along with 32 % of recovered starting material **1g** (Table 2, entry 7). Entries 8, 9, and 10 clearly show that electron-poor substituents on the alcohol retarded the oxidation. The methoxymethyl- (MOM, entry 8), benzoyl- (Bz, entry 9), and tosyl- (Ts, entry 10) substituted cyclododecanols were all resistant to the oxidative conditions, and only the starting materials were recovered. These results imply that MOM, Bz, and Ts could be used as protective groups

for hydroxyl functionalities under these oxidative conditions.

We next tested the functional-group compatibility of the direct oxidation of the methyl ethers (Table 3). Entries 1–6 highlight the chemoselectivity of the present method. The reaction of the cholestanol derivative **1k**, possessing C5, 8, 9, 14, 17, 20, and 25 reactive tertiary C–H bonds in addition to the one at C3, resulted in formation of cholestanone **2b** in 46% yield in a site-selective fashion (Table 3, entry 1). Differentially protected diol systems were subjected to the oxidation, and the methyl ethers were preferentially oxidized in the presence of electron-poor substituents. The oxidation of *trans*-1-benzoyloxy-2-methoxycyclohexane **1l** and its *cis* isomer **1m** produced α-benzoyloxycyclohexanone **2c** in 47 and 30% yields, respectively (Table 3, entries 2 and 3). On the other hand, the methyl ethers **1n** and **1o**, prepared from monobenzoylated 1,4-cyclohexanediols, gave the corresponding ketone **2d** in 66 and 64% yields, respectively (Table 3, entries 4 and 5). The oxidation of tosylate **1p** proceeded selectively at the methyl ether moiety to provide **2e** (63% yield, Table 3, entry 6). These experiments clarified that Bz and Ts groups worked as orthogonal protective groups to the methyl group under these conditions. Entries 7–9 showed the compatibility of electron-withdrawing functional groups such as esters and ketones. The acyclic benzyl methyl ethers **1q** and **1r** bearing the ester and ketone groups afforded the corresponding ketoester **2f** and diketone **2g** in 80 and 76% yields, respectively (Table 3, entries 7 and 8), and the alkyl ether **1s** gave the corresponding diketone **2h** in 55% yield (Table 3, entry 9).

In conclusion, we have achieved direct C–H oxidation of methyl ethers using a reagent combination of the Mn/*t*Bu-terpy catalyst and *m*CPBA. The reactions are operationally simple, and chemoselectively oxidize dialkyl ethers under mild conditions without touching electron-deficient functionalities, such as benzyloxy, tosyloxy, ester, and ketone groups. This new method broadens the synthetic utility of methyl ethers not only as protective groups but also as precursors to carbonyl compounds. Synthetic applications of the present oxidation are ongoing in our laboratory.

Table 3. Mn-catalyzed oxidation of functionalized methyl ethers.[a]

Entry	Substrate	1	Product	2	Yield [%]
1[b]		**1k**		**2b**	46
2[c]		**1l**		**2c**	47
3[c]		**1m**		**2c**	30
4[c]		**1n**		**2d**	66
5[c]		**1o**		**2d**	64
6[c]		**1p**		**2e**	63
7		**1q**		**2f**	80
8		**1r**		**2g**	76
9		**1s**		**2h**	55

[a] Reaction conditions: **1** (0.5 mmol), *m*CPBA (2 mmol; 70 wt%), $MnCl_2{\cdot}4H_2O$ (0.5 μmol), *t*Bu-terpy (0.5 μmol), H_2O (50 μL), CH_3CN (5 mL), 0 °C for 2 h then room temperature for 2 h. [b] The reaction was carried out in $CH_3CN/CH_2Cl_2 = 1:1$ (0.04 M) at 0 °C for 3 h. [c] Racemic compound.

Experimental Section

General procedure for the Mn-catalyzed oxidation of ethers: A solution of $MnCl_2{\cdot}4H_2O$ (0.1 mg, 0.5 μmol), 4,4′,4″-tri(*tert*-butyl)-2,2′:6′,2″-terpyridine (*t*Bu-terpy; 0.2 mg, 0.5 μmol), and distilled water (50 μL) in CH_3CN (5 mL) was stirred at room temperature for 0.5 h. To the solution was added ether **1a** (99 mg, 0.5 mmol) at room temperature, and the resultant mixture was cooled to 0 °C. The solution was treated with *m*-chloroperbenzoic acid (*m*CPBA; 500 mg, 2.0 mmol; 70 wt%) and stirred for 2 h at 0 °C. The reaction mixture was filtered through an alumina short column (hexane/ethyl acetate 5:1), and the filtrate was concentrated. The residue was purified with flash column chromatography (SiO_2; hexane/ether 50:1–30:1) to provide cyclododecanone **2a** in 50% yield (45.5 mg).

Preparation of a stock solution of the premixed manganese complex: A stock solution of the premixed manganese complex was prepared by stirring a mixture of $MnCl_2{\cdot}4H_2O$ (0.99 mg, 5.0 μmol), *t*Bu-terpy (2.0 mg, 5.0 μmol), and distilled water (0.5 mL) in CH_3CN (40 mL) for 30 min at room temperature. The resulting pale yellow solution was used for oxidation of ethers. In the above case, the stock solution (4 mL) and CH_3CN (1 mL) were applied to **1a** (99 mg, 0.5 mmol) at room temperature.

Cyclododecanone (**2a**): [CAS 830–13–7]; colorless solid; ^1H NMR (495 MHz, $CDCl_3$): $\delta = 1.24$–1.31 (m, 14H), 1.71 (4H, quintet, $J = 6.2$ Hz), 2.46 ppm (4H, t, $J = 6.2$ Hz); ^{13}C NMR (124 MHz, $CDCl_3$): $\delta =$ 22.2, 22.4, 24.1, 24.5, 24.6, 40.3, 212.8 ppm.

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Keywords: C–H activation · ketones · manganese · methyl ethers · oxidation

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[16] See the Experimental Section.

[17] As a separate experiment, we found that alcohol **5** was also oxidized to ketone **2a** under these conditions in high yield, supporting the intermediacy of **5** via **4** in the reactions of entries 2–4.

[18] The oxidation of octyl methyl ether under the standard reaction conditions afforded octanoic acid in 47% NMR yield. This result shows that the present Mn-catalyzed oxidation of primary methyl ethers produces the corresponding carboxylic acids as a product.

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