Unified Oxidation Protocol for the Synthesis of Carbonyl Compounds Using a Manganese Catalyst

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Abstract: We have developed a unified protocol for the oxidation of ethers, benzylic compounds, and alcohols to carbonyl compounds. The protocol uses catalytic amounts of manganese(II) chloride tetrahydrate and 4,4′,4″-tri(*t*-butyl)-2,2′:6′,2″-terpyridine in combination with a stoichiometric amount of either *m*-chloroperbenzoic acid (MCPBA) or potassium hydrogen peroxysulfate ($KHSO_5$). A reagent system consisting of the Mn catalyst and MCPBA permitted the chemoselective sp^3 C–H oxidation of alkyl ethers and benzylic compounds to generate the corresponding ketones. Alternatively, the water-soluble inorganic salt $KHSO_5$ in combination with the Mn catalyst was used to oxidize alcohols to ketones or carboxylic acids. Importantly, the Mn catalyst/$KHSO_5$ system eliminates technical difficulties associated with the isolation of carboxylic acid products. All the oxidations presented in this feature article proceed at sub-ambient temperature in an aerobic atmosphere, and can therefore be used in practical syntheses of complex organic molecules.

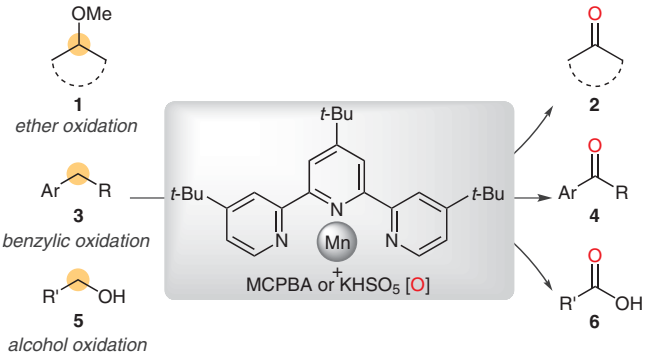
Key words: catalysis, oxidation, ethers, alcohols, ketones, carboxylic acids

Introduction

The oxidation of activated or nonactivated hydrocarbons to the corresponding carbonyl compounds is a fundamental transformation in organic synthesis.[1] The resulting aldehydes, ketones, carboxylic acids, and lactones are valuable intermediates for further elaboration into complex organic molecules. Excellent methods and a variety of reagents have been developed to achieve chemoselective oxidative transformations, but most of these methods require more than a stoichiometric amount of reagent to give a high yield of the oxidized product. Consequently, catalytic methods for various oxidations have been a subject of recent interest.

The scope and variety of methods for the catalytic oxidation of sp^3 C–H bonds in saturated carbon skeletons are especially limited, despite the prevalence of such bonds in organic chemistry.[2,3] This is mainly because of the high chemical stability of sp^3 C–H bond under a wide array of conditions. In this context, we initiated our research into metal-catalyzed chemoselective techniques for the introduction of polar functionalities, such as hydroxy or carbonyl groups, onto carbon skeletons through direct oxidation of sp^3 C–H bonds.[4] In principle, such transformation should increase efficiency in syntheses of structurally complex and densely functionalized organic compounds by minimizing the number of functional group manipulations, reducing the number of adjustments of oxidation states, and restricting the need to use protecting groups. Furthermore, the resulting hydroxy and carbonyl groups can serve as versatile handles for further elaboration of the carbon framework and for the installation of other functionalities.

To explore suitable catalysts for sp^3 C–H oxidation, we focused on manganese complexes, because a range of oxidative transformations can be effected by using manganese-based reagents, such as potassium permanganate or manganese dioxide, in stoichiometric amounts.[5] In this feature article, we report a new manganese-catalyzed reagent system for the chemoselective oxidation of sp^3 C–H bonds of ethers or benzylic compounds. A combination of a manganese catalyst composed of manganese(II) chloride tetrahydrate and 4,4′,4″-tri(*tert*-butyl)-2,2′:6′,2″-terpyridine (*t*-Bu-terpy), in combination with a stoichiometric amount of *m*-chloroperbenzoic acid (MCPBA) was shown to oxidize alkyl ethers or benzylic compounds chemoselectively to give the corresponding ketones (Scheme 1). During the course of this investigation we found that a similar reaction using the inorganic oxidant, potassium hydrogen peroxysulfate ($KHSO_5$), instead of MCPBA gave high yields of ketones or carboxylic acids from alcohols. The development and the optimization of these three oxidation reactions are described in detail.



Scheme 1 Unified oxidation protocol using a manganese catalyst

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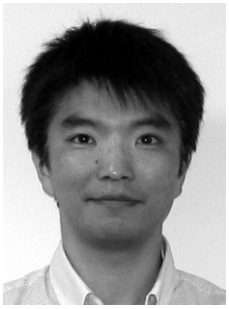
Direct Oxidation of Methyl Ethers to Ketones by Using the Manganese Catalyst/*m*-Chloroperbenzoic Acid System[6]

Because alkyl ether linkages generally exhibit a high chemical stability in a wide range of synthetic procedures under a variety of reaction conditions, such ethers are widely in protecting hydroxy groups,[7] which are present in many naturally occurring substances of biological and synthetic interest. In syntheses of polyhydroxy compounds, the judicious choice of protecting groups and the selection of appropriate methods for 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 have become some of the most frequently used protecting groups in organic synthesis. On the other hand, simple robust methyl ethers have received less attention, mainly because of the harsh acidic conditions that are required for deprotection.[8]

We envisaged that direct sp^3 C–H oxidation could be useful for the chemoselective oxidative cleavage of methyl ethers, because C–H bonds located in a position α to an oxygen atom are generally susceptible to oxidation.[9] A number of oxidizing agents bring about one-step oxidation reactions of dialkyl ethers to form the corresponding carbonyl products. Among these agents, dioxirane[10] and oxaziridine[11] are representative nonmetallic stoichiometric reagents for the oxidation of dialkyl ethers. Several metal catalysts based on ruthenium, chromium, manganese, or iron have also been reported to effect the oxidation of ethers when used in conjunction with a stoichiometric amount of a primary oxidant.[9,12] However, the choice of the starting ether is restricted mainly to cyclic ethers, and there have been few systematic studies on metal-catalyzed oxidation of acyclic alkyl ethers.[13]

Biographical Sketches



Shin Kamijo was born in 1973 in Yamaguchi, Japan. He received his B.Sc. (1997) and Ph.D. (2002) degrees from Tohoku University under the supervision of Professor Yoshinori Yamamoto, and was appointed as a Research Associate in the same group (2002–2004). After spending two years as a JSPS Postdoctoral Fellow with Professor Gregory B. Dudley at Florida State University (2004–2006) and one year as a Postdoctoral Associate with Professor Masakatsu Shibasaki at the University of Tokyo (2006–2007), he joined the research group of Professor Masayuki Inoue at the University of Tokyo as an Assistant Professor in 2007. His research interests are focused on the development of methods involving the activation and functionalization of unreactive bonds, and the use of these methods in organic synthesis.

Yuuki Amaoka was born in 1987 in Yokohama, Japan. He received his bachelor's degree from the University of Tokyo in 2009. He is currently studying for a Ph.D. under the guidance of Professor Masayuki Inoue in the Graduate School of Pharmaceutical Sciences at the same university. His current researches are focused on the development of reactions that can be applied to the synthesis of structurally complex organic molecules.

Masayuki Inoue was born in 1971 in Tokyo, Japan. He received a B.Sc. degree in chemistry from the University of Tokyo in 1993. In 1998, he obtained his Ph.D. from the same university, working under the supervision of Professors K. Tachibana and M. Sasaki. After spending two years with Professor S. J. Danishefsky at the Sloan–Kettering Institute for Cancer Research (1998–2000), he joined the Graduate School of Science at Tohoku University as an assistant professor in the research group of Professor M. Hirama. At Tohoku University, he was promoted to associate professor in 2004 and concurrently served as a PRESTO researcher of the Japan Science and Technology Agency (2005–2008). In 2007, he moved to the Graduate School of Pharmaceutical Sciences of the University of Tokyo as a full professor. He has been honored with the First Merck–Banyu Lectureship Award (2004), The Chemical Society of Japan Award for Young Chemists (2004), the Thieme Journal Award 2005, the Novartis Lectureship 2008/2009, and the 5th JSPS Prize (2009). His research interests include the synthesis, design, and study of biologically important molecules, with particular emphasis on the total synthesis of structurally complex natural products.

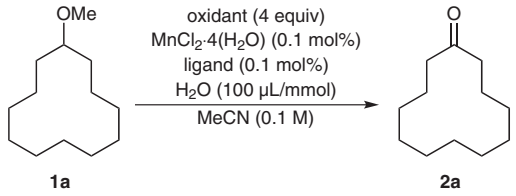
We found that a catalytic amount of a manganese reagent and MCPBA efficiently transformed methyl ethers into the corresponding carbonyl compounds. The reaction conditions for C–H oxidation were screened and optimized by using cyclododecyl methyl ether (**1a**) (Table 1).[14,15] Treatment of ether **1a** with four equivalents of reagent-grade MCPBA (70 wt%) in the presence of 0.1 mol% of manganese dichloride tetrahydrate ($MnCl_2·4H_2O$) in acetonitrile gave cyclododecanone (**2a**) in 32% yield (entry 1), although the reaction was not complete even after twelve hours at room temperature. The attempted oxidation of **1a** in acetonitrile by MCPBA in the absence of the manganese salt resulted in quantitative recovery of the starting material. The use of 0.1 mol% of 2,2′:6′,2″-terpyridine (terpy, entry 2) as a tridentate nitrogen ligand increased the reaction rate, and **2a** was isolated in 50% yield after two hours at room temperature.[14] A variety of ligands were examined in attempts to improve the oxidative power of the catalyst (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) or 4,4′,4″-trimethoxy-2,2′:6′,2″-terpyridine[16] (MeO-terpy, entry 4), accelerated the oxidation, whereas the addition of a ligand bearing an electron-withdrawing group, 4,4′,4″-trinitro-2,2′:6′,2″-terpyridine (NO_2-terpy, entry 5), produced no beneficial effect on the conversion. Because of its good performance and commercial availability, *t*-Bu-terpy was selected as the ligand for further investigation. As a primary oxidant, MCPBA was found to be far more reactive than magnesium monoperoxyphthalate (MMPP) or tetrabutylammonium Oxone (TBA-Oxone)[14,17] (entries 6 and 7). Overall, the optimized conditions (entry 3), which employed $MnCl_2·4H_2O$ (0.1 mol%), *t*-Bu-terpy (0.1 mol%), water (50 μL), and MCPBA (4 equiv; 70 wt%) in acetonitrile (0.1 M), resulted in the exclusive formation of **2a** in 50% yield within two hours at 0 °C.[18,19]

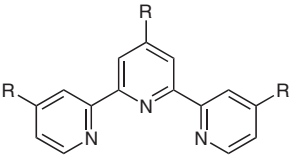
The procedure developed here is operationally simple. For instance, the reaction of **1a** to **2a** took place even under an aerobic atmosphere by using a stock solution of the manganese complex premixed in acetonitrile containing a small amount of water.[20] The catalytic activity of the premixed catalyst was retained for at least one month without any special precautions. It is also important to note that MCPBA did not promote the Baeyer–Villiger-type oxidation of product **2a** under these mild conditions.

Scheme 2 shows plausible intermediates for the oxidation reaction. It has been frequently demonstrated that the reactivity of sp^3 C–H bonds toward C–H bond functionalization increases with increasing electron density (R_3CH > R_2CH_2 > RCH_3).[21] Therefore, the reaction of methyl ether **1a** probably occurs through insertion of oxygen into the tertiary C–H bond, which is more prone to oxidation than the other C–H bond. The ejection of methanol from the generated hemiacetal **A** then leads to ketone **2a**.

To investigate the reactivity of alkyl ethers toward oxidation, a variety of cyclododecanol derivatives were pre-

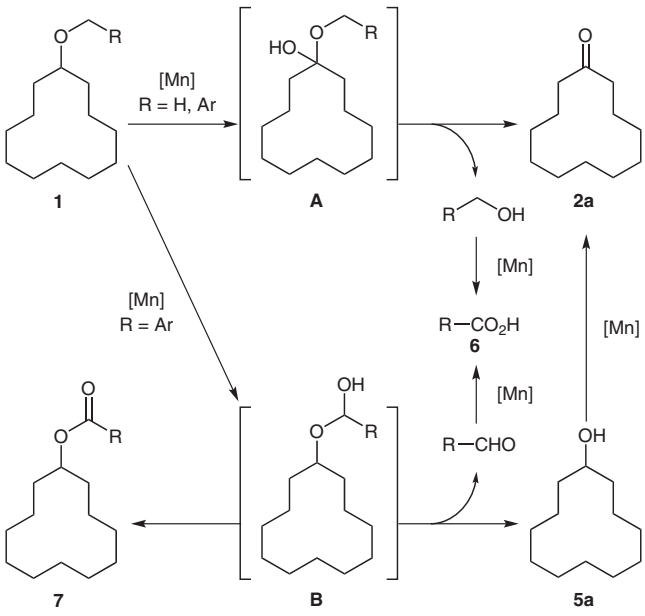
Table 1 Screening of Ligands and Oxidants for the Manganese-Catalyzed Oxidation of Ether **1a**





Entry	Ligand	Oxidant	Conditions[a]	Yield (%)[b]
1	none	MCPBA[c]	0 °C, 2 h; r.t., 12 h	32 (36)
2	terpy	MCPBA[c]	0 °C, 2 h; r.t., 2 h	50[d]
3	*t*-Bu-terpy	MCPBA[c]	0 °C, 2 h	50[d]
4	MeO-terpy	MCPBA[c]	0 °C, 2 h	41[d]
5	NO_2-terpy	MCPBA[c]	0 °C, 2 h; r.t., 2 h	31 (40)
6	*t*-Bu-terpy	MMPP[e]	0 °C, 2 h	2.9 (94)
7	*t*-Bu-terpy	TBA-Oxone[f]	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), MeCN (5 mL).
[b] Yield calculated by ^1H NMR analysis of the crude mixture, unless otherwise noted. The recovery of the starting material **1a** is shown in parentheses.
[c] MCPBA (70 wt%) was used.
[d] Yield of isolated product.
[e] MMPP (65 wt%) was used.
[f] TBA-Oxone (30 wt%) was used.

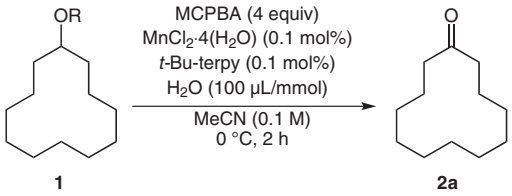


Scheme 2 Plausible intermediates for manganese-catalyzed oxidation of ethers **1**

pared and subjected oxidation by the optimized reagent system (Table 2). The oxidation of cyclododecyl octyl ether (**1b**) proceeded in a similar way to that of methyl ether **1a** (entry 1), and the formation of ketone **2a** and octanoic acid (**6a**) was identified by analysis of the crude reaction mixture (entry 2). The observation of acid **6a** indicated that octan-1-ol eliminated from **A** was further oxidized to give octanoic acid under the reaction conditions (Scheme 2).[22] The oxidation of benzyl ethers **1c–e** gave ketone **2a** as the major product in 46–55% yield (entries 3–5). The oxidation of the electron-rich 4-methoxybenzyl ether **1d** (entry 4) was completed in a shorter reaction time (1 h at 0 °C) than that 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 (**5a**) and benzoates **7** (R = Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$) were detected as byproducts. These minor products were probably formed from hemiacetal **B** (Scheme 2); oxidation of **1** at the reactive benzylic position generates hemiacetal **B**, which then undergoes either hydrolysis to produce alcohol **5a** or further oxidation to produce benzoate **7**. As a separate experiment (see above), we found that alcohol **5a** was oxidized to ketone **2a** in high yield under these conditions. Thus, the main product **2a** in entries 3–5 was potentially delivered by two pathways via intermediates **A** and **B**, respectively. Nevertheless, the isolation of ketone **2a** as a major product from benzyl ethers **1c–e** represents a striking difference between the manganese-catalyzed transformation and its ruthenium tetroxide-catalyzed counterpart, which generally provides the corresponding benzoate as the major product.[12]

To assess steric and electronic effects on the oxidation, various masked cyclododecanol derivatives were treated with the manganese catalyst and MCPBA (entries 6–11). Entries 6 and 7 showed that the transformation is sensitive to steric hindrance around the ether linkage. In contrast to the case with the methyl ether (entry 1), the oxidation of the isopropyl ether **1f** was sluggish, affording the desired ketone **2a** in only 29% yield (entry 6), and the oxidation of the bulkier *tert*-butyl ether **1g** gave only a trace amount of ketone **2a** along with 32% of recovered starting material **1g** (entry 7). Entries 8, 9, and 10 clearly show that the presence of electron-deficient substituents on the alcohol retards the oxidation. The benzoylated (entry 8), tosylated (entry 9), and methoxymethylated (entry 10) cyclododecanols were all resistant to the oxidative conditions, and the starting materials were recovered exclusively. These results suggest that benzoyl, tosyl, or methoxymethyl groups could be used as protecting groups for hydroxy groups under these oxidative conditions. On the other hand, the oxidation of the *t*-butyldimethylsilyl (TBS) ether **1k** led to a complex mixture, presumably because of its instability under both acidic and oxidative reaction conditions (entry 11).

Table 2 Manganese-Catalyzed Oxidation Reactions of Cyclododecanol Derivative[a]

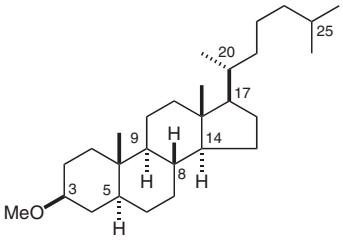
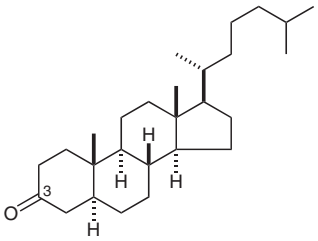
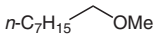
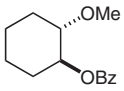
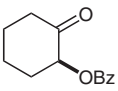
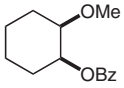
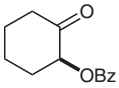
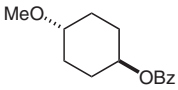
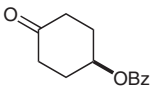
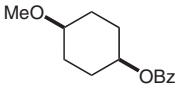
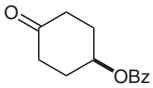
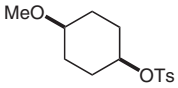
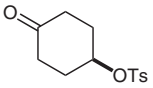
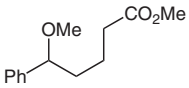
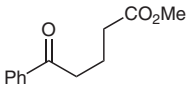
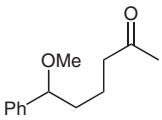
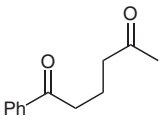
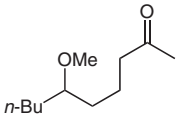
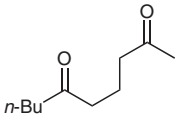


Entry	R	Ether	Yield (%)[b]
1	Me	**1a**	50
2	$(CH_2)_7Me$[c]	**1b**	59[d]
3	Bn	**1c**	48[e]
4	4-methoxybenzyl[f]	**1d**	46[g]
5	4-nitrobenzyl	**1e**	55[h]
6	*i*-Pr[i]	**1f**	29
7	*t*-Bu	**1g**	trace (32)
8	Bz	**1h**	0 (49)
9	Ts	**1i**	trace (73)
10	CH_2OMe	**1j**	0 (49)
11	TBS	**1k**	–[j]

[a] Reaction conditions: **1** (0.5 mmol), MCPBA (2 mmol, 70 wt%), $MnCl_2·4H_2O$ (0.5 μmol), *t*-Bu-terpy (0.5 μmol), H_2O (50 μL), MeCN (5 mL), 0 °C for 2 h.
[b] Yield of isolated product. The recovery of the starting material **1** is shown in parentheses.
[c] MCPBA (5 equiv) was used and the reaction was further carried out at r.t. for 2 h.
[d] Octanoic acid (**6a**) was observed in the crude reaction mixture [48% yield (NMR)].
[e] The corresponding benzoate **7c** (trace) and cyclododecanol **5a** (12%) were obtained.
[f] The reaction was completed in 1 h.
[g] The corresponding benzoate **7d** (trace) and **5a** (28%) were obtained.
[h] The corresponding benzoate **7e** (7.1%) and **5a** (trace) were obtained.
[i] The reaction was further carried out at r.t. for 1 h.
[j] A complex mixture was obtained.

Next, we examined the range of substrates that are compatible with the direct oxidation of methyl ethers (Table 3). Entries 1–7 highlight the chemoselectivity of the present method. The reaction of the cholestanol derivative **1l**, which has reactive tertiary C–H bonds at the C5, C8, C9, C14, C17, C20, and C25 positions, in addition to the one at C3, gave (5α)-cholestan-3-one (**2b**) in 46% yield in a site-selective manner (entry 1). Oxidation of the primary methyl ether **1m** gave the carboxylic acid **6a** (entry 2). When differentially protected diol systems were subjected to the oxidation, methyl ether groups were oxidized preferentially in the presence of electron-deficient substituents. Thus, oxidation of *trans*-1-(benzoyloxy)-2-methoxycyclohexane (**1n**) and its *cis*-isomer **1o** produced 2-oxocyclohexyl benzoate (**2c**) in 47 and 30% yield, respectively (entries 3 and 4). On the other hand, the methyl

Table 3 Manganese-Catalyzed Oxidation of Functionalized Methyl Ethers[a]

Entry	Substrate	Product	Yield (%)[b]
1[c]			46
	1l	**2b**	
2[d]			47[e]
	1m	**6a**	
3[f]			47
	1n	**2c**	
4[f]			30
	1o	**2c**	
5[f]			66
	1p	**2d**	
6[f]			64
	1q	**2d**	
7[f]			63
	1r	**2e**	
8			80
	1s	**2f**	
9			76
	1t	**2g**	
10			55
	1u	**2h**	

[a] Reaction conditions: **1** (0.5 mmol), MCPBA (2 mmol, 70 wt%), $MnCl_2 \cdot 4H_2O$ (0.5 μmol), *t*-Bu-terpy (0.5 μmol), H_2O (50 μL), MeCN (5 mL), 0 °C for 2 h then r.t. for 2 h.
[b] Yield of isolated product unless otherwise noted.
[c] The reaction was carried out in MeCN–CH_2Cl_2 (1:1) (0.04 M) at 0 °C for 3 h.
[d] MCPBA (5 equiv) was used.
[e] Yield calculated by ^1H NMR analysis of the crude mixture.
[f] Racemic compound.

ethers **1p** and **1q**, prepared from the corresponding monobenzoylated cyclohexane-1,4-diols, gave ketone **2d** in 66 and 64% yields, respectively (entries 5 and 6). The oxidation of tosylate **1r** proceeded selectively at the methyl ether moiety to provide **2e** in 63% yield (entry 7). These experiments confirmed that benzoyl and tosyl groups operate as orthogonal protecting groups to the methyl group under these conditions. Entries 8–10 show the compatibility of electron-withdrawing functional groups, such as esters and ketones. The acyclic benzyl methyl ethers **1s** and **1t**, bearing ester and ketone groups, respectively, gave the keto ester **2f** and diketone **2g** in 80 and 76% yield, respectively (entries 8 and 9), whereas the alkyl ether **1u** gave the corresponding diketone **2h** in 55% yield (entry 10).

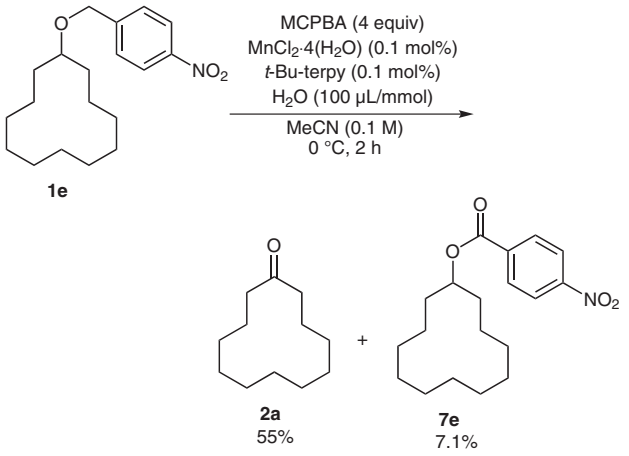
We therefore achieved chemoselective sp^3 C–H oxidation of methyl ethers by using a reagent combination of a Mn/*t*-Bu-terpy catalyst and MCPBA. The reactions are operationally simple and dialkyl ethers are oxidized chemoselectively under mild conditions without affecting electron-deficient functionalities such as benzoyloxy, tosyloxy, ester, or ketone groups. This method broadens the synthetic utility of methyl ethers, not only as stable protective groups, but also as precursors to ketones.

Direct Oxidation of Benzylic Compounds to Aryl Ketones by Using the Manganese Catalyst/*m*-Chloroperbenzoic Acid System

The chemoselective oxidation of sp^3 C–H bonds at benzylic positions is an important transformation in organic synthesis.[23–26] Classically, stoichiometric quantities of an oxidant such as potassium permanganate ($KMnO_4$) or potassium dichromate ($K_2Cr_2O_7$) are used in these reactions. The main disadvantages of the classical methods are the tedious workup and the production of voluminous amounts of environmentally hazardous metal-containing residues that result from the use of a large excess of the reagent. Recent decades have seen the development of various oxidation catalysts that are designed to circumvent these problems.

During our research on ether oxidation, we observed the concomitant formation of benzoate **7e** upon transformation of cyclododecyl 4-nitrobenzyl ether (**1e**) into cyclododecanone (**2a**) (Scheme 3). This showed that the manganese catalyst/MCPBA reagent system can oxidize an sp^3 C–H bond at a benzylic position. We therefore set about developing a new protocol for the oxidation of nonethereal benzylic C–H bonds by using the manganese catalyst.

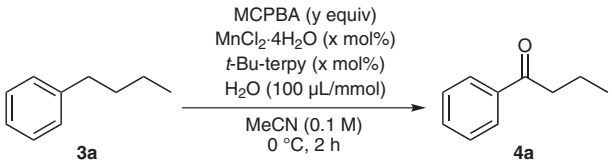
The reaction conditions were optimized for the oxidation of the benzylic C–H bond of butylbenzene (**3a**; Table 4). As anticipated, the Mn catalyst/MCPBA combination directly oxidized the benzylic position. The reaction of **3a** under the conditions used for the oxidation of ethers generated phenyl propyl ketone (**4a**) in 15% yield; the starting material **3a** was also recovered (entry 1). To improve the yield, the amounts of the reagents were modified (entries



Scheme 3 Oxidation of cyclododecyl 4-nitrobenzyl ether (**1e**) to cyclododecanone (**2a**) and cyclododecyl 4-nitrobenzoate (**7e**)

2 and 3). Oxidation using 1.0 mol% of Mn catalyst gave **4a** in 40% isolated yield (entry 2), whereas a reduction in the number of equivalents of MCPBA decreased the conversion ratio (entry 3). The reaction conditions for benzylic oxidation were therefore fixed as shown in entry 2: $MnCl_2·4H_2O$ (1.0 mol%), *t*-Bu-terpy (1.0 mol%), water (50 μL), and MCPBA (4 equiv; 70 wt%) in acetonitrile (0.1 M).[27]

Table 4 Optimization of Amounts of Manganese Catalyst and MCPBA for Oxidation of Butylbenzene (**3a**)[a]



Entry	Catalyst (mol%)	MCPBA (equiv)	Yield (%)[b]
1	0.1	4	15 (36)
2	1.0	4	40[c] (trace)
3	1.0	3	29 (21)

[a] Reaction conditions: BuPh (**3a**; 0.5 mmol), MCPBA (70 wt%), $MnCl_2·4H_2O$, *t*-Bu-terpy, H_2O (50 μL), MeCN (5 mL), 0 °C for 2 h.
[b] Yield calculated by ^1H NMR analysis of the crude mixture unless otherwise noted. The recovery of the starting material **3a** is shown in parentheses.
[c] Yield of isolated product.

The results for Mn-catalyzed benzylic C–H oxidation reactions are summarized in Table 5. The oxidation of butylbenzene derivatives **3a–c** gave the corresponding aryl ketones **4a–c** in 21–44% yield (entries 1–3). The introduction of an electron-donating methoxy substituent at the *para*-position of the aromatic ring (**3b**) increased the rate of oxidation, and consequently the reaction was completed in a shorter time than the corresponding reaction of butylbenzene (**3a**; entry 2). On the other hand, the introduction of an electron-withdrawing substituent (**3c**) retarded the oxidation. Even after extra stirring at room

temperature for two hours, only a low yield of **4c** was obtained, and a large amount of starting material was recovered (entry 3). These results showed that the reactivity of a benzylic C–H bond increases with increasing electron density on the aromatic ring.

Next, we evaluated the tolerance of various functional groups to the oxidation conditions to determine the applicability of this method in syntheses of structurally complex and functionalized organic molecules. Oxidation of substrates having electron-withdrawing functionalities, such as the ester group in **3d** or the nitrile group in **3e** and **3f**, gave the corresponding ketones **4d–f** in 30–45% yield (entries 4–6). The reactions of acetate **3g** and benzoate **3h** led to ketones **4g** and **4h**, respectively (entries 7 and 8), showing that ester-protected hydroxy groups survive the conditions. The oxidation of ibuprofen methyl ester (**3i**) proceeded site-selectively to give the corresponding ketone **4i** (entry 9).[14b] Apparently, the electron-withdrawing ester group in **3i** suppresses the reactivity of the adjacent benzylic C–H bond, and the oxidation takes place at the more-electron-rich alkyl-substituted benzylic position. The reaction of diphenylmethane (**3j**) was completed in two hours at 0 °C to give benzophenone (**4j**; entry 10). Triphenylmethane (**3k**) and cumene (**3l**), each of which contains a tertiary C–H benzylic bond, gave the corresponding tertiary benzyl alcohols **4k** and **4l**, respectively (entries 11 and 12).

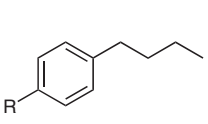
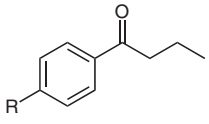
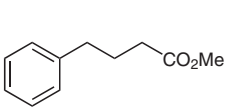
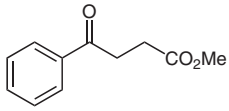
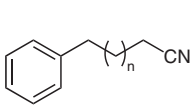
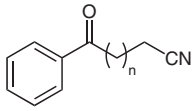
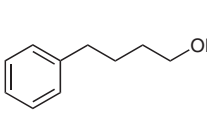
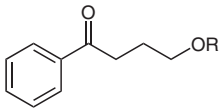
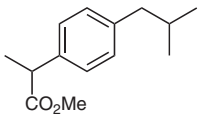
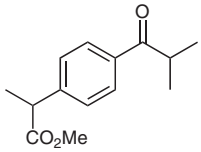
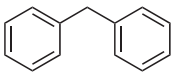
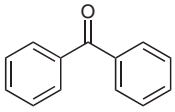
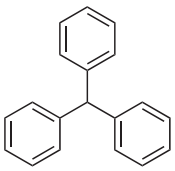
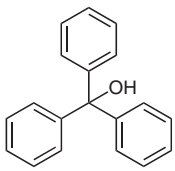
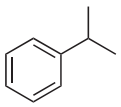
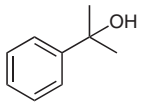
We have therefore shown that a reagent system consisting of Mn/*t*-Bu-terpy catalyst and MCPBA can be used for the direct oxidation of benzylic C–H bonds. The oxidation takes place chemoselectively at the electron-rich benzylic position at sub-ambient temperatures in an aerobic atmosphere. This operationally simple method expands the synthetic utility of benzylic compounds as protected aryl ketones.

Oxidation of Alcohols to Ketones and Carboxylic Acids by Using the Manganese Catalyst/Potassium Hydrogen Peroxysulfate System

The oxidation of an alcohol to the corresponding aldehyde, ketone, or carboxylic acid is a key transformation in synthetic organic chemistry. A variety of methods have been devised for this reaction, but there is still a need for new and efficient catalytic oxidations that are compatible with various functional groups.[1] We therefore examined the possibility of developing a new method by using the Mn/*t*-Bu-terpy catalyst system.

The formation of octanoic acid (**6a**) during the manganese-catalyzed direct oxidation of ether **1b** to ketone **2a** (Scheme 4) suggested that the oxidation of a primary alcohol to a carboxylic acid occurs under these conditions.[28,29] However, it was not possible to isolate pure octanoic acid by chromatography on silica gel because the mixture was contaminated with *m*-chlorobenzoic acid formed from MCPBA. Therefore, to develop a simple and practical oxidation protocol, it appeared to be necessary to

Table 5 Manganese-Catalyzed Oxidation of Various Benzylic Compound[a]

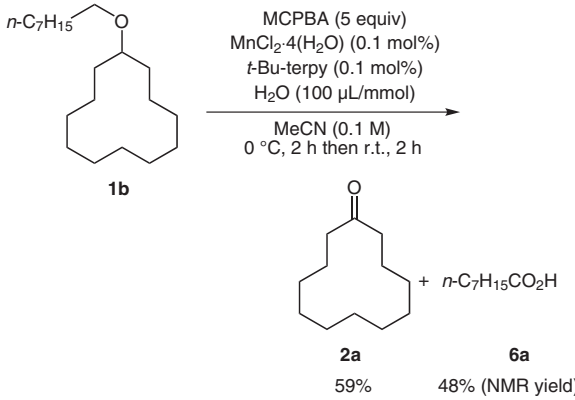
Entry	Substrate	Product	Yield (%)[b]
			
1[c]	**3a**: R = H	**4a**	40
2[d]	**3b**: R = OMe	**4b**	44
3	**3c**: R = Ac	**4c**	21 (25)
4	 **3d**	 **4d**	41 (14)
5	 **3e**: n = 1	 **4e**	30 (31)
6	**3f**: n = 2	**4f**	45 (18)
7	 **3g**: R = Ac	 **4g**	45 (11)
8	**3h**: R = Bz	**4h**	40 (30)
9	 **3i**	 **4i**	37 (20)
10[c]	 **3j**	 **4j**	53
11[d]	 **3k**	 **4k**	39
12[c]	 **3l**	 **4l**	21

[a] Reaction conditions: **3** (0.5 mmol), MCPBA (2 mmol, 70 wt%), $MnCl_2 \cdot 4H_2O$ (5.0 μmol), *t*-Bu-terpy (5.0 μmol), H_2O (50 μL), MeCN (5 mL), 0 °C for 2 h then r.t. for 2 h.

[b] Yield of isolated product. The recovery of the starting material **3** is shown in parentheses.

[c] The reaction was complete after 2 h at 0 °C.

[d] The reaction was complete after 20 min at 0 °C.



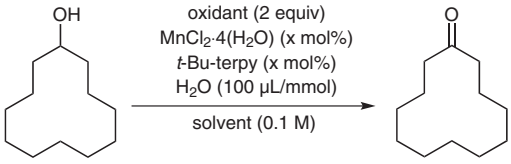
Scheme 4 Formation of octanoic acid (**6a**) during oxidation of cyclododecyl octyl ether (**1b**)

replace MCPBA with another primary oxidant that could be easily separated from the reaction mixture.

To optimize the oxidation conditions, alcohol **5a** was used as a substrate (Table 6). Oxidation of **5a** proceeded smoothly under the standard conditions for direct ether oxidation, resulting in the formation of ketone **2a** in 76% yield (entry 1). Having confirmed that the alcohol is sufficiently reactive, we examined various primary oxidants as alternatives to MCPBA that would simplify the purification procedure. We focused on water-soluble inorganic oxidants that would not contaminate the ketone or carboxylic acid products. After several trials, we found that $KHSO_5$[30] worked as a primary oxidant in combination with the Mn catalyst derived from $MnCl_2·4H_2O$ and *t*-Bu-terpy (19% yield; entry 2). The oxidative ability of the Mn catalyst/$KHSO_5$ system appeared to be lower than that of its Mn catalyst/MCPBA counterpart. An increase in the amount of Mn catalyst helped to improve the yield of ketone **2a**, although a significant quantity of the starting material was recovered (entries 3 and 4).

Because we believed that the slow reaction rate observed in entries 2–4 originated from the low solubility of $KHSO_5$ in acetonitrile, we examined a range of solvents (entries 5–9). The reaction was found to be retarded in a less-polar solvent (CH_2Cl_2, entry 5), whereas a higher conversion of alcohol **5a** was observed in polar solvents such as ethyl acetate or acetone (entries 6 and 7). The use of a 1:1 mixture of acetone and water did not improve the activity of the reagent (entry 8), although this result clearly showed that the presence of excess water did not interfere with oxidation of the alcohol. Furthermore, exclusion of water during the preparation of the manganese catalyst

Table 6 Screening of Primary Oxidant and Reaction Conditions for Manganese-Catalyzed Oxidation of Alcohol **5a**



Entry	Oxidant	Catalyst (mol%)	Conditions[a]	Solvent	Yield (%)[b]
1	MCPBA[c]	0.1	0 °C, 2 h; r.t., 2 h	MeCN	76[d] (trace)
2	$KHSO_5$	0.1	0 °C, 2 h; r.t., 2 h	MeCN	19 (81)
3	$KHSO_5$	0.5	0 °C, 2 h; r.t., 2 h	MeCN	49 (45)
4	$KHSO_5$	1.0	0 °C, 2 h; r.t., 2 h	MeCN	70 (23)
5	$KHSO_5$	0.5	0 °C, 2 h; r.t., 2 h	CH_2Cl_2	28 (72)
6	$KHSO_5$	0.5	0 °C, 2 h; r.t., 2 h	EtOAc	80
7	$KHSO_5$	0.5	0 °C, 2 h; r.t., 2 h	acetone	83 (17)
8	$KHSO_5$	0.5	0 °C, 2 h; r.t., 2 h	acetone–H_2O (1:1)	78 (19)
9	$KHSO_5$	0.5	0 °C, 2 h; r.t., 2 h	acetone[e]	82[d] (16)
10	$KHSO_5$	0.5	r.t., 4 h	*t*-BuOH	77
11	Oxone[f]	0.5	0 °C, 2 h; r.t., 2 h	acetone	61 (38)

[a] Reaction conditions: **5a** (0.5 mmol), oxidant (1 mmol), $MnCl_2·4H_2O$, *t*-Bu-terpy, H_2O (50 μL), solvent (5 mL).
[b] Yield calculated by ^1H NMR analysis of the crude mixture unless otherwise noted. The recovery of the starting material **5a** is shown in parentheses.
[c] MCPBA (70 wt%) was used.
[d] Yield of isolated product.
[e] The reaction was conducted without addition of H_2O.
[f] $2KHSO_5·KHSO_4·K_2SO_4$.

had no effect on the yield or reproducibility (entry 9). Protic *tert*-butyl alcohol was found to be a good solvent for this manganese-catalyzed oxidation (entry 10). Interestingly, the use of Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as the primary oxidant instead of $KHSO_5$ reduced the oxidation yield slightly (entry 11). On the basis of these results, the conditions for alcohol oxidation were set as indicated in entry 9: $MnCl_2 \cdot 4H_2O$ (0.5 mol%), *t*-Bu-terpy (0.5 mol%), and $KHSO_5$ (2 equiv) in acetone (0.1 M).[31]

Having identified the optimal conditions, we surveyed the oxidation of various secondary alcohols (Table 7). As described above, treatment of cyclododecanol (**5a**) with the Mn catalyst/$KHSO_5$ system gave ketone **2a** in 82% yield, along with 16% of the recovered starting material (entry 1). Oxidation of the substituted cyclohexanol diastereomers **5b** and **5c** gave menthone (**2i**) in 59% and 39% yield, respectively (entries 2 and 3). Changing the nitrogen ligand from *t*-Bu-terpy to the less-bulky 2,2′:6′,2″-terpyridine (terpy) slightly improved the yield of **2i** from **5c**, indicating that the steric bulk of the Mn/*t*-Bu-terpy catalyst might have a negative influence on this particular transformation (entry 3). The propargylic alcohol **5d** and the homopropargylic alcohol **5e** were converted into the corresponding alkynones **2j** and **2k** (entries 4 and 5). The formation of the relatively unstable homopropargylic ketone **2k** highlighted the mildness of the Mn catalyst/$KHSO_5$ system. The absence of the formation of arylketones in entries 4 and 5 showed that the hydroxy groups are oxidized faster than benzylic C–H groups under the present conditions. Diol **5f** was oxidized chemoselectively at the secondary hydroxy group to give the conjugated alkynone **2l** (entry 6).

Table 7 Manganese-Catalyzed Oxidation of Alcohols[a]

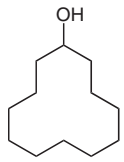
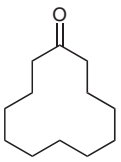
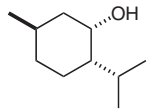
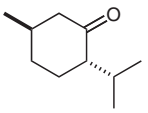
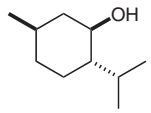
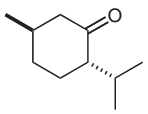
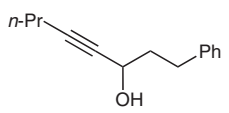
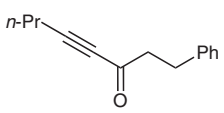
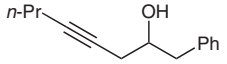
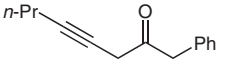
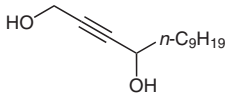
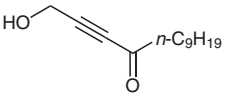
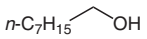
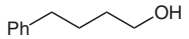
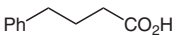
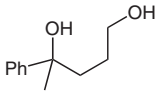
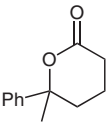
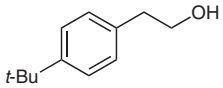
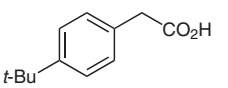
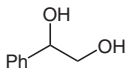
Entry	Substrate	Product	Yield (%)[b]
1	 **5a**	 **2a**	82 (16)
2	 **5b**	 **2i**	59 (29)
3	 **5c**	 **2i**	39 (46) 53 (36)[c]
4	 **5d**	 **2j**	58 (22)

Table 7 Manganese-Catalyzed Oxidation of Alcohols[a] (continued)

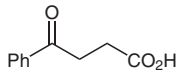
Entry	Substrate	Product	Yield (%)[b]
5	 **5e**	 **2k**	38 (36)
6	 **5f**	 **2l**	48
7	 **5g**	n-$C_7H_{15}CO_2H$ **6a**	72
8	 **5h**	 **6b**	58 (17)[d]
9	 **5i**	 **6c**	59 (4.0)
10	**5j**: R = H	**6d**	87
11	**5k**: R = *t*-Bu	**6e**	89
12	**5l**: R = OBz	**6f**	83
13	 **5m**	 **6g**	41 (9)[e]
14	 **5n**	 **6d**	68 (14)

[a] Reaction conditions: **5** (0.5 mmol), $KHSO_5$ (1 mmol), $MnCl_2 \cdot 4H_2O$ (2.5 μmol), *t*-Bu-terpy (2.5 μmol), acetone (5 mL), 0 °C for 2 h then r.t. for 2 h.

[b] Yield of isolated product. The recovery of the starting material **5** is shown in parentheses.

[c] 2,2′:6′,2″-Terpyridine (terpy) was used instead of *t*-Bu-terpy.

[d] The oxo carboxylic acid **6b′** was obtained in ~3.4% yield.

 **6b′**

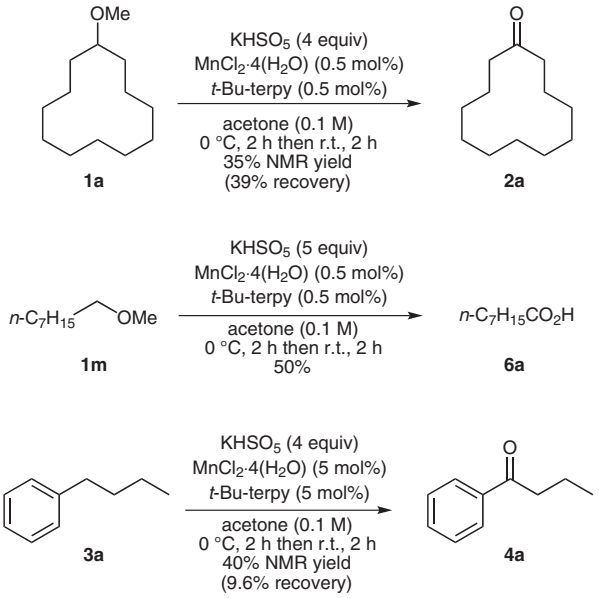
[e] Compound **6e** was obtained in 13% yield.

Next, we examined the oxidation of primary alcohols to carboxylic acids (entries 7–14). Oxidation of octanol (**5g**) gave octanoic acid (**6a**) in 72% yield (entry 7). In contrast to the reaction in Scheme 4, pure **6a** was isolated exclusively by extraction and subsequent silica gel chromatography, demonstrating that $KHSO_5$ has practical advantages over MCPBA. Oxidation of alcohol **5h**, which contains a phenyl group, produced the expected carboxylic acid **6b** along with a minute amount of the oxo carboxylic acid **6b′** (entry 8). The reaction of diol **5i** afforded

lactone **6c** as a single isolable product, presumably via the six-membered hemiacetal (entry 9).

Treatment of the benzylic alcohols **5j–l** with the Mn catalyst/$KHSO_5$ system gave the corresponding benzoic acids **6d–f** in yields of over 83% (entries 10–12). Oxidation of the one-carbon homologated phenethyl alcohol **5m** gave the phenylacetic acid derivative **6g** as a major product, accompanied by a small amount of 4-*tert*-butylbenzoic acid (**6e**; entry 13). Although over-oxidation to **6e** was not completely suppressed, it is noteworthy that the Mn-catalyzed oxidation could be used in the preparation of the relatively unstable phenylacetic acid **6g**. Oxidative cleavage of the glycol moiety took place in the case of 1,2-diol **5n**, and benzoic acid (**6d**) was the sole product (entry 14).

We have therefore developed a new reagent system consisting of a Mn/*t*-Bu-terpy catalyst and $KHSO_5$ for the oxidation of alcohols. Changing the primary oxidant to $KHSO_5$ from MCPBA simplifies the isolation of the product, particularly in the case of carboxylic acids. Furthermore, this reagent system is effective for synthesizing relatively unstable carbonyl compounds, such as propargylic ketones and phenylacetic acid derivatives.



Scheme 5 Oxidation of methyl ethers and a benzylic compound

Oxidation of Methyl Ethers and Benzylic Compounds by Using the Manganese Catalyst/Potassium Hydrogen Peroxysulfate System

Next, we examined the oxidation of methyl ethers and benzylic compounds by using the Mn/*t*-Bu-terpy catalyst in combination with $KHSO_5$ as the reagent. Although increased amounts Mn catalyst were required with $KHSO_5$ to obtain yields that were comparable to those obtained by using MCPBA, cyclododecyl methyl ether (**1a**), methyl octyl ether (**1m**), and butylbenzene (**3a**) were transformed into the oxidized products **2a**, **6a**, and **4a**, respectively (Scheme 5). [For comparison, see entry 3 (Table 1), entry 2 (Table 3), and entry 1 (Table 5).] Most importantly, this alternative reagent system allowed chromatographic isolation of octanoic acid (**6a**) produced by one-step oxidation of the corresponding primary ether **1m**. Overall, the Mn catalyst/$KHSO_5$ system proved to be effective for the oxidation, not only of alcohols, but also of ethers and benzylic compounds.[32]

Conclusion

We have developed a unified protocol for the oxidation of ethers, benzylic compounds, and alcohols to carbonyl compounds by using a catalytic amount of $MnCl_2{\cdot}4H_2O$ and *t*-Bu-terpy. The reagent system, which consists of the Mn catalyst and MCPBA, has a high reactivity in oxidizing the sp^3 C–H bonds of methyl ethers and benzylic compounds to form ketones. For the oxidation of alcohols, we developed a Mn catalyst/$KHSO_5$ reagent system, in which the replacement of MCPBA by $KHSO_5$ eliminates technical difficulties associated with the isolation of the oxidized products. The Mn catalyst/$KHSO_5$ system is especially advantageous for one-step preparation of carboxylic acids from primary alcohols or ethers. All the oxidation reactions presented in this feature article are operationally simple and predictable, and they proceed under very mild reaction conditions at sub-ambient temperatures in an aerobic atmosphere. In addition, carbon center adjacent to alkoxy, hydroxy, or aryl groups are oxidized chemoselectively in the presence of electron-withdrawing functionalities such as benzoate, tosylate, ketone, ester, or nitrile groups. The present Mn-catalyzed oxidation methods broaden the utility not only of alcohols, but also of methyl ethers and benzylic compounds, as precursors to carbonyl compounds.

All the reactions were carried out under an aerobic atmosphere at 0 °C to r.t. MCPBA was used as supplied (~70 wt%) without further purification, and purified $KHSO_5$ was obtained by recrystallization of Oxone according to the reported procedure.[30] Analytical TLC was performed on E. Merck silica gel 60 F254 pre-coated plates. Flash column chromatography was performed by using 40–63 μm silica gel 60 (Merck). The ^1H and ^{13}C NMR spectra were recorded on JEOL JNM-ECX-500 (500 MHz), JNM-ECA-500 (500 MHz), and JNM-ECS-400 (400 MHz) spectrometers. Chemical shifts are reported in δ (ppm) with reference to residual solvent signals [^1H NMR: $CHCl_3$ (7.26); ^{13}C NMR: $CDCl_3$ (77.0)]. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. HRMS were recorded on a Bruker Daltonics BioTOF-Q spectrometer (ESI) or a JEOL JMS-T100LP AccuTOF LC-plus spectrometer (DART). The yields are reported in the corresponding tables.

Direct Oxidation of Methyl Ethers by Using the Manganese Catalyst/MCPBA System; Typical Procedure

A soln of $MnCl_2{\cdot}4H_2O$ (0.1 mg, 0.5 μmol), *t*-Bu-terpy (0.2 mg, 0.5 μmol), and distilled H_2O (50 μL) in MeCN (5 mL) was stirred at r.t. for 0.5 h. Ether **1a** (99 mg, 0.5 mmol) was added to the soln at r.t., and the mixture was cooled to 0 °C. The soln was treated with MCPBA (70 wt%, 500 mg, 2.0 mmol) and stirred for 2 h at 0 °C. The mixture was then filtered through a short column of alumina

[hexane–EtOAc (5:1)], and the filtrate was concentrated. The residue was purified by flash column chromatography [silica gel, hexane–Et_2O (50:1 to 30:1)]; yield: 45.5 mg (50%).

Preparation of a Stock Solution of the Premixed Manganese Complex for Oxidation of Ethers

A stock soln of the premixed Mn complex was prepared by stirring a mixture of $MnCl_2·4H_2O$ (0.99 mg, 5.0 μmol), *t*-Bu-terpy (2.0 mg, 5.0 μmol), and H_2O (0.5 mL) in MeCN (40 mL) for 30 min at r.t. The resulting pale yellow soln was used for oxidation of ethers. In the case of ether **1a**, the stock soln (4 mL) and MeCN (1 mL) were used to oxidize **1a** (99 mg, 0.5 mmol).

Cyclododecanone (2a)

[CAS 830-13-7]; colorless solid.

^{1}H NMR (495 MHz, $CDCl_3$): δ = 1.24–1.31 (m, 14 H), 1.71 (quin, *J* = 6.2 Hz, 4 H), 2.46 (t, *J* = 6.2 Hz, 4 H).

^{13}C NMR (124 MHz, $CDCl_3$): δ = 22.2, 22.4, 24.1, 24.5, 24.6, 40.3, 212.8.

(5α)-Cholestan-3-one (2b)

[CAS 566-88-1]; colorless solid.

^{1}H NMR (495 MHz, $CDCl_3$): δ = 0.64 (s, 3 H), 0.70 (m, 1 H), 0.83 (d, *J* = 7.0 Hz, 3 H), 0.84 (d, *J* = 7.0 Hz, 3 H), 0.88 (d, *J* = 6.5 Hz, 3 H), 0.98 (s, 3 H), 0.94–1.40 (m, 17 H), 1.46–1.58 (m, 5 H), 1.67 (dq, *J* = 13.0, 3.0 Hz, 1 H), 1.80 (m, 1 H), 1.98 (m, 2 H), 2.06 (ddd, *J* = 15.0, 3.5, 2.0 Hz, 1 H), 2.20–2.30 (m, 2 H), 2.36 (ddd, *J* = 15.0, 6.5, 6.5 Hz, 1 H).

^{13}C NMR (124 MHz, $CDCl_3$): δ = 11.3, 11.9, 18.5, 21.3, 22.4, 22.7, 23.7, 24.1, 27.9, 28.1, 28.8, 31.6, 35.3, 35.5, 35.7, 36.0, 38.0, 38.4, 39.4, 39.8, 42.4, 44.6, 46.5, 53.7, 56.1, 211.8.

2-Oxocyclohexyl Benzoate (2c)

[CAS 7472-23-3]; colorless solid.

^{1}H NMR (490 MHz, $CDCl_3$): δ = 1.66 (dtt, *J* = 12.5, 12.5, 3.5 Hz, 1 H), 1.82 (dtt, *J* = 12.5, 12.5, 3.5 Hz, 1 H), 1.92 (ddt, *J* = 12.5, 12.5, 3.5 Hz, 1 H), 2.02 (m, 1 H), 2.11 (m, 1 H), 2.38–2.48 (m, 2 H), 2.55 (m, 1 H), 5.39 (br dd, *J* = 12.5, 6.0 Hz, 1 H), 7.42 (br t, *J* = 7.3 Hz, 2 H), 7.55 (tt, *J* = 7.3, 1.5 Hz, 1 H), 8.07 (dd, *J* = 7.3, 1.5 Hz, 2 H).

^{13}C NMR (123 MHz, $CDCl_3$): δ = 23.7, 27.1, 33.1, 40.7, 76.9, 128.3, 129.6, 129.8, 133.1, 165.5, 204.3.

4-Oxocyclohexyl Benzoate (2d)

[CAS 23510-95-4]; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13–2.31 (m, 4 H), 2.44 (ddd, *J* = 16.0, 6.2, 6.2 Hz, 2 H), 2.66 (ddd, *J* = 16.0, 10.5, 6.2 Hz, 2 H), 5.44 (tt, *J* = 6.2, 3.1 Hz, 1 H), 7.46 (dd, *J* = 8.0, 8.0 Hz, 2 H), 7.59 (t, *J* = 8.0 Hz, 1 H), 8.06 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.5, 37.3, 69.0, 128.5, 129.5, 130.1, 133.2, 165.7, 209.9.

4-Oxocyclohexyl Tosylate (2e)

[CAS 23511-04-8]; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89–1.98 (m, 2 H), 2.10–2.18 (m, 2 H), 2.27 (ddd, *J* = 15.0, 5.0, 5.0 Hz, 2 H), 2.44 (s, 3 H), 2.55 (ddd, *J* = 15.0, 11.0, 5.9 Hz, 2 H), 4.86 (tt, J = 5.2, 2.7 Hz, 1 H), 7.34 (d, *J* = 8.3 Hz, 2 H), 7.80 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 31.0, 36.4, 76.5, 127.5, 129.9, 133.8, 144.9, 208.6.

Methyl 5-Oxo-5-phenylpentanoate (2f)

[CAS 1501-04-8]; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (quin, *J* = 7.0 Hz, 2 H), 2.45 (t, *J* = 7.0 Hz, 2 H), 3.06 (t, *J* = 7.0 Hz, 2 H), 3.68 (s, 3 H), 7.46 (dd, *J* = 7.7, 7.0 Hz, 2 H), 7.56 (t, *J* = 7.0 Hz, 1 H), 7.96 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 33.1, 37.4, 51.6, 128.0, 128.6, 133.1, 136.7, 173.7, 199.4.

1-Phenylhexane-1,5-dione (2g)

[CAS 6303-82-8]; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99 (quin, *J* = 7.0 Hz, 2 H), 2.13 (s, 3 H), 2.55 (t, *J* = 7.0 Hz, 2 H), 2.99 (t, *J* = 7.0 Hz, 2 H), 7.43 (dd, *J* = 8.0, 7.5 Hz, 2 H), 7.53 (t, *J* = 7.5 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0, 29.9, 37.3, 42.5, 127.9, 128.5, 133.0, 136.6, 199.6, 208.5.

Decane-2,6-dione (2h)

[CAS 103984-05-0]; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3 H), 1.28 (sext, *J* = 7.2 Hz, 2 H), 1.53 (tt, *J* = 7.5, 7.2 Hz, 2 H), 1.82 (quin, *J* = 7.0 Hz, 2 H), 2.12 (s, 3 H), 2.37 (t, *J* = 7.5 Hz, 2 H), 2.43 (t, *J* = 7.0 Hz, 2 H), 2.46 (t, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 17.6, 22.3, 25.9, 29.9, 41.4, 42.5, 42.5, 208.6, 210.9.

Cyclododecyl 4-Nitrobenzoate (7e)

[CAS 622836-12-8]; colorless solid.

^{1}H NMR (495 MHz, $CDCl_3$): δ = 1.20–1.40 (m, 18 H), 1.69 (m, 2 H), 1.89 (m, 2 H), 5.33 (m, 1 H), 8.18 (br d, *J* = 8.5 Hz, 2 H), 8.32 (br d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (124 MHz, $CDCl_3$): δ = 20.8, 23.0, 23.2, 23.9, 24.1, 29.0, 74.3, 123.4, 130.5, 136.3, 150.3, 164.3.

Direct Oxidation of Benzylic Compounds by Using the Mn Catalyst/MCPBA System; Typical Procedure

A soln of $MnCl_2·4H_2O$ (1.0 mg, 5.0 μmol), *t*-Bu-terpy (2.0 mg, 5.0 μmol), and distilled H_2O (50 μL) in MeCN (5 mL) was stirred at r.t. for 0.5 h. BuPh (**3a**; 78 μL, 0.5 mmol) was added to the soln at r.t., and the mixture was cooled to 0 °C. The soln was treated with MCPBA (70 wt%, 500 mg, 2.0 mmol) and stirred for 2 h at 0 °C. The mixture was then filtered through a short column of alumina [hexane–EtOAc (10:1)], and the filtrate was concentrated. The residue was purified with flash column chromatography [silica gel, hexane–EtOAc (80:1 to 60:1)]; yield: 29.7 mg (40%).

1-Phenylbutan-1-one (4a)

[CAS 495-40-9]; colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.2 Hz, 3 H), 1.78 (m, 2 H), 2.95 (t, *J* = 7.2 Hz, 2 H), 7.46 (t, *J* = 7.0 Hz, 2 H), 7.56 (dt, *J* = 7.0, 1.0 Hz, 1 H), 7.96 (dd, *J* = 7.0. 1.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 17.8, 40.5, 128.0, 128.5, 132.8, 137.1, 200.4.

1-(4-Methoxyphenyl)butan-1-one (4b)

[CAS 4160-51-4]; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 6.2 Hz, 3 H), 1.75 (tt, *J* = 6.5, 6.2 Hz, 2 H), 2.89 (t, *J* = 6.5 Hz, 2 H), 3.86 (s, 3 H), 6.92 (d, *J* = 7.6 Hz, 2 H), 7.94 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 18.0, 40.2, 55.4, 113.6, 130.1, 130.3, 163.2, 199.1.

1-(4-Acetylphenyl)butan-1-one (4c)

Colorless solid.

IR (neat): 1677, 1464, 830 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.1 Hz, 3 H), 1.75 (quin, *J* = 7.1 Hz, 2 H), 2.63 (s, 3 H), 2.96 (t, *J* = 7.1 Hz, 2 H), 7.97–8.04 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 17.5, 26.9, 40.8, 128.1, 128.4, 139.9, 140.1, 197.5, 199.8.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{14}NaO_2$: 213.0886; found: 213.0887.

Methyl 4-Oxo-4-phenylbutanoate (4d)
[CAS 25333-24-8]; colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.76 (t, *J* = 6.8 Hz, 2 H), 3.32 (t, *J* = 6.8 Hz, 2 H), 3.71 (s, 3 H), 7.46 (dd, *J* = 7.8, 7.5 Hz, 2 H), 7.56 (t, *J* = 7.5 Hz, 1 H), 7.98 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9, 33.3, 51.8, 128.0 128.6, 133.2, 136.4, 173.4, 198.0.

4-Oxo-4-phenylbutanenitrile (4e)
[CAS 5343-98-6]; colorless solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.79 (t, *J* = 7.0 Hz, 2 H), 3.40 (t, *J* = 7.0 Hz, 2 H), 7.50 (t, *J* = 7.1 Hz, 2 H), 7.62 (t, *J* = 7.1 Hz, 1 H), 7.96 (d, *J* = 7.1 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8, 34.2, 119.2, 128.0, 128.8, 133.9, 135.6, 195.3.

5-Oxo-5-phenylpentanenitrile (4f)
[CAS 10413-00-0]; colorless solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.11 (quin, *J* = 7.0 Hz, 2 H), 2.52 (t, *J* = 7.0 Hz, 2 H), 3.17 (t, *J* = 7.0 Hz, 2 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.58 (t, *J* = 7.6 Hz, 1 H), 7.95 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6, 19.6, 36.2, 119.4, 127.9, 128.7, 133.4, 136.3, 198.1.

4-Oxo-4-phenylbutyl Acetate (4g)
[CAS 39755-06-1]; colorless solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.03 (s, 3 H), 2.09 (tt, *J* = 6.0, 5.5 Hz, 2 H), 3.06 (t, *J* = 6.0 Hz, 2 H), 4.16 (t, *J* = 5.5 Hz, 2 H), 7.45 (t, *J* = 6.5 Hz, 2 H), 7.56 (t, *J* = 6.5 Hz, 1 H), 7.95 (d, *J* = 6.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.9, 23.1, 34.8, 63.7, 127.9, 128.6, 133.1, 136.7, 171.0, 199.0.

4-Oxo-4-phenylbutyl Benzoate (4h)
[CAS 62973-33-5]; colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.26 (tt, *J* = 7.0, 6.5 Hz, 2 H), 3.17 (t, *J* = 7.0 Hz, 2 H), 4.44 (t, *J* = 6.5 Hz, 2 H), 7.41–7.56 (m, 6 H), 7.93–8.07 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 34.9, 64.3, 128.0, 128.3, 128.6, 129.5, 130.2, 132.9, 133.2, 136.7, 166.5, 199.1.

Methyl 2-(4-Isobutyrylphenyl)propanoate (4i)
[CAS 1009647-55-5]; colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 7.0 Hz, 6 H), 1.51 (d, *J* = 7.0 Hz, 3 H), 3.52 (septet, *J* = 7.0 Hz, 1 H), 3.66 (s, 3 H), 3.78 (q, *J* = 7.0 Hz, 1 H), 7.38 (d, *J* = 8.2 Hz, 2 H), 7.91 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 19.1, 35.2, 45.3, 52.2, 127.7, 128.7, 135.0, 145.4, 174.3, 203.9.

Benzophenone (4j)
[CAS 119-61-9]; colorless solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (t, *J* = 6.1 Hz, 4 H), 7.59 (t, *J* = 6.1 Hz, 2 H), 7.81 (d, *J* = 6.1 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.2, 130.0, 132.3, 137.5, 196.7.

Triphenylmethanol (4k)
[CAS 76-84-6]; colorless solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.84 (br s, 1 H), 7.27–7.36 (m, 15 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 82.0, 127.2, 127.8, 127.9, 146.8.

2-Phenyl-2-propanol (4l)
[CAS 617-94-7]; colorless oil.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.59 (s, 6 H), 1.79 (br s, 1 H), 7.25 (t, *J* = 7.1 Hz, 1 H), 7.35 (t, *J* = 7.1 Hz, 2 H), 7.50 (d, *J* = 7.1 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.7, 72.5, 124.3, 126.7, 128.2, 149.1.

Oxidation of Alcohols by Using the Manganese Catalyst/Potassium Hydrogen Peroxysulfate System; Typical Procedure
A soln of $MnCl_2·4H_2O$ (0.5 mg, 2.5 μmol) and *t*-Bu-terpy (1.0 mg, 2.5 μmol) in acetone (5 mL) was stirred at r.t. for 0.5 h. Cyclododecanol (**5a**; 92 mg, 0.5 mmol) at r.t. was added to the soln, and the mixture was cooled to 0 °C. The soln was treated with $KHSO_5$ (152 mg, 1.0 mmol) and stirred for 2 h at 0 °C, then warmed to r.t. and stirred for an additional 2 h. The mixture was then filtered through a Celite pad [hexane–EtOAc (10:1)], and the filtrate was concentrated. The residue was purified by flash column chromatography [silica gel, hexane–EtOAc (80:1 to 60:1)]; yield; 74.3 mg (82%).

Menthone (2i)
[CAS 89-80-5]; colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.0 Hz, 3 H), 0.90 (d, *J* = 6.0 Hz, 3 H), 1.00 (d, *J* = 5.5 Hz, 3 H), 1.25–1.43 (m, 2 H), 1.80–2.17 (m, 6 H), 2.34 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7, 21.2, 22.3, 25.9, 27.8, 33.9, 35.4, 50.9, 55.9, 212.4.

1-Phenyloct-4-yn-3-one (2j)
[CAS 412022-19-6]; colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.2 Hz, 3 H), 1.61 (sext, *J* = 7.2 Hz, 2 H), 2.34 (t, *J* = 7.2 Hz, 2 H), 2.87 (t, *J* = 7.2 Hz, 2 H), 2.99 (t, *J* = 7.2 Hz, 2 H), 7.17–7.22 (m, 3 H), 7.26–7.31 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 20.9, 21.2, 30.0, 47.0, 80.9, 94.7, 126.2, 128.3, 128.5, 140.4, 187.1.

1-Phenyloct-4-yn-2-one (2k)
Colorless oil.

IR (neat): 1726, 1455, 735, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 7.1 Hz, 3 H), 1.54 (sext, *J* = 7.1 Hz, 2 H), 2.20 (tt, *J* = 7.2, 2.5 Hz, 2 H), 3.27 (t, *J* = 2.5 Hz, 2 H), 3.88 (s, 2 H), 7.21–7.35 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.5, 20.8, 22.1, 33.6, 48.1, 72.2, 85.3, 127.1, 128.7, 129.5, 133.8, 202.8.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{16}NaO$: 223.1093; found: 223.1093.

1-Hydroxytridec-2-yn-4-one (2l)
Colorless oil.

IR (neat): 3397, 2217, 1677 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 5.9 Hz, 3 H), 1.20–1.35 (m, 12 H), 1.60–1.73 (m, 2 H), 1.75–1.85 (br s, 1 H), 2.56 (t, *J* = 6.1 Hz, 2 H), 4.44 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 23.9, 28.9, 29.2, 29.3, 29.4, 31.8, 45.3, 50.9, 84.6, 89.1, 187.7.

HRMS (DART): *m/z* [M + H]$^+$ calcd for $C_{13}H_{23}O_2$: 211.1693; found: 211.1702.

Octanoic Acid (6a)
[CAS 124-07-2]; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.25–1.35 (m, 8 H), 1.63 (quin, *J* = 7.5 Hz, 2 H), 2.34 (t, *J* = 7.5 Hz, 2 H), 10.1 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.7, 28.9, 29.0, 31.6, 34.0, 180.1.

4-Phenylbutanoic Acid (6b)
[CAS 1821-12-1]; colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (quin, *J* = 7.9 Hz, 2 H), 2.37 (t, *J* = 7.9 Hz, 2 H), 2.67 (t, *J* = 7.9 Hz, 2 H), 7.16–7.30 (m, 5 H), 9.90 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2, 33.3, 35.0, 126.0, 128.4, 128.5, 141.2, 179.8.

4-Oxo-4-phenylbutanoic Acid (6b′)
[CAS 2051-95-8]; colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.82 (t, *J* = 6.9 Hz, 2 H), 3.33 (t, *J* = 6.9 Hz, 2 H), 7.47 (t, *J* = 7.2 Hz, 2 H), 7.58 (t, *J* = 7.2 Hz, 1 H), 7.99 (d, *J* = 7.2 Hz, 2 H).

The signal of the carboxyl group is missing, probably because of the presence of small amounts of inseparable impurities; the data listed above are otherwise identical to those reported in the literature.[33]

6-Methyl-6-phenyltetrahydro-2*H*-pyran-2-one (6c)
Colorless oil.

IR (neat): 1731, 1257, 1066, 765, 702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.61 (m, 1 H), 1.68 (s, 3 H), 1.79 (m, 1 H), 2.01 (ddd, *J* = 14.1, 11.5, 4.5 Hz, 1 H), 2.32 (dt, *J* = 14.1, 4.5 Hz, 1 H), 2.43 (ddd, *J* = 18.0, 7.0, 4.5 Hz, 1 H), 2.49 (ddd, *J* = 18.0, 8.5, 7.5 Hz, 1 H), 7.27–7.38 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5, 29.0, 31.3, 34.3, 85.3, 124.4, 127.3, 128.6, 144.5, 171.5.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{14}NaO_2$: 213.0886; found: 213.0884.

Benzoic Acid (6d)
[CAS 65-85-0]; colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (t, *J* = 7.8 Hz, 2 H), 7.62 (t, *J* = 7.8 Hz, 1 H), 8.11 (d, *J* = 7.8 Hz, 2 H), 13.1 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.5, 129.4, 130.3, 133.8, 172.8.

4-*tert*-Butylbenzoic Acid (6e)
[CAS 98-73-7]; colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 9 H), 7.50 (d, *J* = 8.7 Hz, 2 H), 8.06 (d, *J* = 8.7 Hz, 2 H), 12.1 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.1, 35.2, 125.5, 126.5, 130.1, 157.6, 172.3.

4-Benzoylbenzoic Acid (6f)
[CAS 28547-23-1]; colorless solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.43 (d, *J* = 8.5 Hz, 2 H), 7.61 (t, *J* = 7.8 Hz, 2 H), 7.76 (t, *J* = 7.8 Hz, 1 H), 8.05 (d, *J* = 8.5 Hz, 2 H), 8.14 (d, *J* = 7.8 Hz, 2 H), 13.0 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 122.2, 128.6, 128.6, 129.0, 129.9, 131.0, 134.3, 154.1, 164.2, 166.7.

(4-*tert*-Butylphenyl)acetic Acid (6g)
[CAS 32857-63-9]; colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 9 H), 3.62 (s, 2 H), 7.21 (d, *J* = 7.1 Hz, 2 H), 7.36 (d, *J* = 7.1 Hz, 2 H), 10.0 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.3, 34.5, 40.4, 125.6, 129.0, 130.2, 150.2, 177.2.

Direct Oxidation of Methyl Octyl Ether to Octanoic Acid by Using the Manganese Catalyst/$KHSO_5$ System
A soln of $MnCl_2·4H_2O$ (0.5 mg, 2.5 μmol) and *t*-Bu-terpy (1.0 mg, 2.5 μmol) in acetone (5 mL) was stirred at r.t. for 0.5 h. Methyl octyl ether (**1m**; 72 mg, 0.5 mmol) was added to the soln at r.t., and the mixture was cooled to 0 °C. The soln was treated with $KHSO_5$ (380 mg, 2.5 mmol) and stirred for 2 h at 0 °C, then warmed to r.t. and stirred for an additional 2 h. The mixture was then filtered through a Celite pad [hexane–EtOAc (1:1)], and the filtrate was concentrated. The residue was purified by flash column chromatography [silica gel, hexane–EtOAc (10:1 to 3:1)]; yield: 36.1 mg (50%).

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(18) The addition of a small amount of water during preparation of the Mn catalyst helped to give reproducible results. Water dissolves the $MnCl_2$ salt and promotes the formation of the Mn catalyst.

(19) Over-oxidation took place to produce cyclodocecane-1,5-dione as a byproduct (<5% yield).

(20) See the experimental section for details.

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(22) Because methine C–H bonds have a higher intrinsic reactivity toward oxidation than do methylene C–H bonds, and no formation of octanoate ester was observed, we assumed that octanoic acid was generated through intermediate **A**; however, we cannot rule out the possibility of the involvement of intermediate **B**.

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(26) For pioneering works on benzylic C–H oxidation with a Mn/terpy catalyst and tetrabutylammonium Oxone (TBA-Oxone), see reference 14.

(27) A stock solution of the premixed manganese complex in acetonitrile can be used.

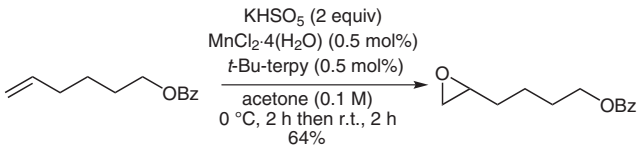
(28) For examples of Mn-catalyzed oxidation of alcohols, see: (a) Berkessel, A.; Sklorz, C. A. *Tetrahedron Lett.* **1999**, *40*, 7965. (b) Brinksma, J.; Rispens, M. T.; Hage, R.; Feringa, B. L. *Inorg. Chim. Acta* **2002**, *337*, 75. (c) Bagherzadeh, M. *Tetrahedron Lett.* **2003**, *44*, 8943. (d) Bahramian, B.; Mirkhani, V.; Moghadam, M.; Amin, A. H. *Appl. Catal., A* **2006**, *315*, 52. (e) Mardani, H. R.; Golchoubian, H. *Tetrahedron Lett.* **2006**, *47*, 2349. (f) Rezaeifard, A.; Jafarpour, M.; Moghaddam, G. K.; Amini, F. *Bioorg. Med. Chem.* **2007**, *15*, 3097. (g) Romakh, V. B.; Therrien, B.; Süss-Fink, G.; Shul'pin, G. B. *Inorg. Chem.* **2007**, *46*, 1315.

(29) For the oxidation of alcohols by stoichiometric amounts of $MnSO_4$ and Oxone, see: Sánchez, A. V.; Zárrage, J. G. *J. Mex. Chem. Soc.* **2007**, *51*, 213.

(30) Travis, B. R.; Ciaramitaro, B. P.; Borhan, B. *Eur. J. Org. Chem.* **2002**, 3429.

(31) The reaction in the absence of the Mn catalyst gave no oxidized product **2a**, and quantitative recovery of alcohol **5a** was observed. This result eliminates the possibility that dioxirane is formed from acetone under the reaction conditions.

(32) Treatment of an olefin with the Mn catalyst/$KHSO_5$ system resulted in clean formation of an epoxide (Scheme 6).



Scheme 6 Formation of an epoxide from an olefin

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