Novel Manganese-Catalyzed α-Oxidation of Cyclic β-Keto Esters with Molecular Oxygen

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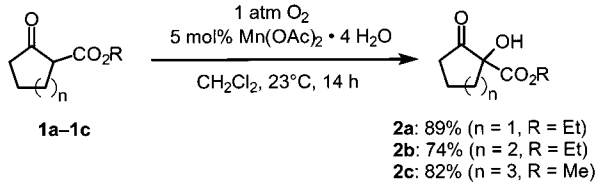
Oxidation is a common way of functionalizing organic compounds. In terms of economical and ecological considerations, molecular oxygen is the oxidant of choice. However, the reaction of O_2 with most organic materials is (fortunately) kinetically hindered[1] and must be catalyzed.[2] We report on a new chemoselective and regioselective oxidation of cyclic β-keto esters **1** with O_2 catalyzed by $Mn(OAc)_2 \cdot 4H_2O$ yielding the α-hydroxy derivatives **2** (Scheme 1).

The α-position of β-dicarbonyl compounds is naturally nucleophilic, and a number of electrophilic reagents can be utilized for introduction of an oxygen functionality at this position. Common examples are $Pb(OAc)_4$,[3] MOPH,[4] percarboxylic acids,[5] dimethyldioxirane,[6] or singlet oxygen.[7] In the course of our search for a chiral transition-metal catalyst for asymmetric Michael reactions,[8] we discovered that $Mn(OAc)_2 \cdot 4H_2O$ does catalyze the oxidation of ester **1a**, if air was not excluded. Optimization of this reaction gave a very simple protocol: Stirring of **1a** with 5 mol % $Mn(OAc)_2 \cdot 4\ H_2O$ under an atmosphere of O_2 in CH_2Cl_2 without an additional ligand or any other additive is sufficient to fully convert the starting material into product **2a**.[6] The reaction proceeds at room temperature, and after an induction period of about 1 h the mixture becomes dark colored and homogeneous, and within 1 d the conversion is quantitative. Separation of the product **2a** from the catalyst can be achieved by direct distillation from the reaction mixture under reduced pressure yielding 85−90% of a material, which contains only small amounts of **1a** and acetic acid as impurities.

Unfortunately, this very simple workup procedure of **1a** is an exceptional case. The oxidation of **1b** and **1c** proceeds with similar results as **1a**, but products **2b**[9] and **2c** are not as stable under reaction conditions as **2a**. Thus, small amounts of decomposition products are formed that have to be separated by chromatography. To figure out what kind of subsequent reactions are proceeding, we have stirred a reaction mixture of **1b** for 3 d at room temperature, after which period chromatographic workup yielded besides **2b** products **3** and **4**[5] (Scheme 2). Formation of **4** can be rationalized by Baeyer−Villiger oxidation of **2b** followed by retro-Claisen C−O bond cleavage. From a mechanistic point of view, the formation of compound **3** remains unclear and obscure.[10]

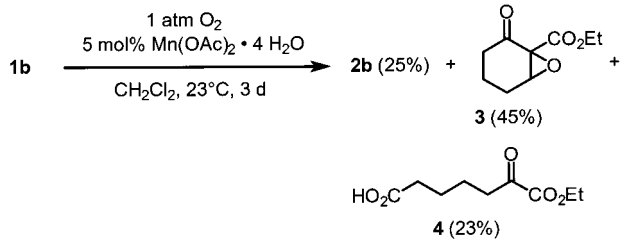
Scheme 1



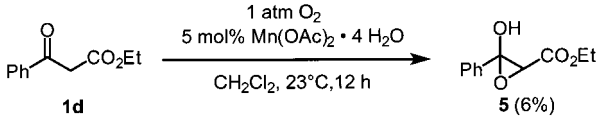
1a–1c

2a: 89% (n = 1, R = Et)
2b: 74% (n = 2, R = Et)
2c: 82% (n = 3, R = Me)

Scheme 2



Scheme 3



1d **5** (6%)

The mechanism of the conversion from **1** into **2** can be assumed to be the one-pot analoge to the sequence known as the Rubottom oxidation:[12] epoxidation of the enol tautomer of **1** by a Mn(V) oxo species[13] followed by rearrangement of the resulting hydroxy oxirane to the hydroxy ketone.[14]

Efforts to convert β-diketones or acyclic β-keto esters under similar or modified conditions as for **1a**−**c** have not been successful. Only in one case, the conversion of **1d**, an oxidation product (compound **5**, Scheme 3) was isolated in 6% yield. The constitution of **5**, which was deduced from a number of double-resonance NMR experiments, obviously supports the proposed mechanism leading to compounds **2** starting from **1**. The relative cis configuration of **5** was established by NOE between *o*-H and 2-H.

In summary, the new manganese-catalyzed oxidation of cyclic β-keto esters with O_2 offers an economically and

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ecologically friendly way for the chemo- and regioselective functionalization of compounds **1a**−**c**.

Experimental Section

General Methods. Column chromatography was accomplished with Merck silica gel (type 60, 0.063−0.200 mm) using *tert*-butyl methyl ether (MTB) and hexanes (PE). Multiplicity assignments of ^{13}C NMR resonances were made using DEPT experiments. All starting materials were commercially available.

Ethyl 2-Hydroxycyclopentanone-2-carboxylate (2a). Oxoester **1a** (1.00 g, 6.40 mol) was added to a suspension of $Mn(OAc)_2 \cdot 4H_2O$ (78 mg, 0.32 mmol) in CH_2Cl_2 (1 mL). The mixture was cooled with N_2(l), the flask was evacuated and equipped with a balloon of O_2 (ca. 500 mL, ca. 22 mmol), and finally the mixture was stirred for 14 h at room temperature. The solvent was removed in vacuo and the residue distilled in a Kugelrohr apparatus (1 mbar, oven temperature starting at 50 °C, finally raised to 150 °C) to yield a colorless oil (980 mg, 5.69 mmol, 89%): R_f (SiO_2, PE/MTB 1:1) = 0.35; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, J = 7.1 Hz, 3 H), 2.04−2.17 (m, 3 H), 2.40−2.52 (m, 3 H), 3.67 (s, 1 H), 4.24 (q, J = 7.1 Hz, 2 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz) δ 13.98 (CH_3), 18.33 (CH_2), 34.70 (CH_2), 35.78 (CH_2), 62.49 (CH_2), 79.70 (C), 171.54 (C=O), 213.34 (C=O) ppm; IR (ATR) 1/λ 3473 (s), 1756 (vs), 1729 (vs) cm^{-1}; mol. mass calcd 172.0736, found 172.0734 (HRMS). Anal. Calcd for $C_8H_{12}O_4$ (172.18): C, 55.81; H, 7.02. Found: C, 55.25; H, 7.11.

Ethyl 2-Hydroxycyclohexanone-2-carboxylate (2b). Following the procedure reported for **2a**, oxoester **1b** (1.00 g, 5.87 mmol) was converted with a suspension of $Mn(OAc)_2 \cdot 4H_2O$ (72 mg, 0.29 mmol) in CH_2Cl_2 (1 mL). After being stirred at room temperature, the reaction mixture was directly chromatographed (SiO_2, PE/MTB 1:1, R_f = 0.39) to yield **2b** (809 mg, 4.43 mmol, 74%) as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, J = 7.1 Hz, 3 H), 1.64−1.85 (m, 4 H), 1.95−2.07 (m, 1 H), 2.49−2.70 (m, 3 H), 4.22 (q, J = 7.1 Hz, 2 H), 4.31 (s, 1 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz) δ 13.95 (CH_3), 21.92 (CH_2), 26.99 (CH_2), 37.60 (CH_2), 38.83 (CH_2), 62.02 (CH_2), 80.61 (C), 169.99 (C=O), 207.29 (C=O) ppm; IR (ATR) 1/λ 3457 (m), 1720 (vs) cm^{-1}; mol. mass calcd 186.0892, found 186.0893 (HRMS). Anal. Calcd for $C_9H_{14}O_4$ (186.21): C, 58.05; H, 7.58. Found: C, 58.11; H, 7.57.

Methyl 2-Hydroxycycloheptanone-2-carboxylate (2c). Following the procedure reported for **2b**, oxoester **1c** (1.00 g, 5.88 mmol) was converted with $Mn(OAc)_2 \cdot 4H_2O$ (71 mg, 0.29 mmol) to yield after chromatography (SiO_2, PE/MTB 1:1, R_f = 0.35) **2c** (896 mg, 4.82 mmol, 82%) as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.21−1.47 (m, 3 H), 1.68−2.10 (m, 4 H), 2.21 (ddt, J = 14.9 Hz, J = 10.1 Hz, J = 1.3 Hz, 1 H), 2.52 (ddd, J = 12.0 Hz, J = 7.2 Hz, J = 1.4 Hz, 1 H), 2.90 (td, J = 12.0 Hz, J = 2.9 Hz, 1 H), 3.69 (s, 3 H), 4.29 (d, J = 1.3 Hz, 1 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz) δ 23.45 (CH_2), 27.01 (CH_2), 29.96 (CH_2), 34.36 (CH_2), 39.74 (CH_2), 52.84 (CH_3), 83.34 (C), 170.92 (C=O), 209.31 (C=O) ppm; IR (ATR) 1/λ 3474 (s), 1751 (vs), 1714 (vs) cm^{-1}; mol. mass calcd 186.0892, found 186.0987 (HRMS). Anal. Calcd for $C_9H_{14}O_4$ (186.21): C, 58.05; H, 7.58. Found: C, 58.21; H, 7.33.

Ethyl 2,3-Epoxycyclohexanone-2-carboxylate (3). The procedure reported for **2b** was repeated on the same scale. After the reaction mixture was stirred for 3 d at room temperature, chromatography on SiO_2 (PE/MTB 1:1) yielded three fractions: (1) R_f = 0.39, compound **2b** (273 mg, 1.47 mmol, 25%), (2) R_f = 0.26, compound **3** (487 mg, 2.64 mmol, 45%), and (3) R_f = 0.05 (PE/MTB 1:1), 0.35 (MTB), compound **4** (273 mg, 1.35 mmol, 23%): ^1H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, J = 7.2 Hz, 3 H), 1.68−2.10 (m, 3 H), 2.16 (d, J = 10.7, 6.5 Hz, 1 H), 2.21−2.34 (m, 1 H), 2.51 (dtd, J = 17.0, 4.3, 0.6 Hz, 1 H), 3.64 (t, J = 1.9 Hz, 1 H), 4.23 (q, J = 7.2 Hz, 2 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz) δ 13.91 (CH_3), 16.33 (CH_2), 22.71 (CH_2), 37.21 (CH_2), 58.57 (C), 59.82 (CH), 61.93 (CH_2), 165.95 (C=O), 199.39 (C=O) ppm; IR (ATR) 1/λ 1745 (vs), 1714 (vs) cm^{-1}; mol. mass calcd 184.0736, found 184.0717 (HRMS). Anal. Calcd for $C_9H_{12}O_4$ (184.19): C, 58.69; H, 6.57. Found: C, 58.22; H, 6.54.

2-Oxoheptanedioic acid 1-ethyl ester (4): R_f (SiO_2, PE/MTB 1:1) = 0.05, R_f (SiO_2, MTB) = 0.35; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.32 (t, J = 7.2 Hz, 3 H), 1.61−1.68 (m, 4 H), 2.32−2.38 (m, 2 H), 2.80−2.87 (m, 2 H), 4.27 (q, J = 7.2 Hz, 2 H), 10.3 (s, br., 1 H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz) δ 13.86 (CH_3), 22.15 (CH_2), 23.71 (CH_2), 33.52 (CH_2), 38.67 (CH_2), 62.37 (CH_2), 160.93 (C=O), 179.35 (C=O), 193.99 (C=O) ppm; IR (ATR) 1/λ 3500−2500 (s, br), 1727 (vs), 1710 (vs), 1406 (m), 1279 (s) cm^{-1}; mol. mass calcd 202.0841, found 202.0842 (HRMS). Anal. Calcd $C_9H_{14}O_5$ (202.21): C, 53.46; H, 6.98. Found: C, 53.88; H, 6.94.

Ethyl *cis*-2,3-Epoxy-3-hydroxy-3-phenylpropanoate (5). Following the procedure reported for **2b**, oxoester **1d** (1.00 g, 5.20 mmol) and $Mn(OAc)_2 \cdot 4H_2O$ (64 mg, 0.26 mmol) were stirred for 12 h at room temperature to yield after chromatography (SiO_2, PE/MTB 1:1, R_f = 0.38) compound **5** (66 mg, 0.32 mmol, 6%) as a colorless oil. As a first fraction, starting material **1d** was recovered (ca. 80%): ^1H NMR ($CDCl_3$, 200 MHz) δ 1.29 (t, J = 7.1 Hz, 3 H; CH_3), 1.65 (s, br, 1 H; OH), 4.17 (q, J = 7.1 Hz, 2 H; CH_2), 4.96 (s, 1 H; 2-H), 7.39−7.42 (m, 3 H; *p*- and *m*-H), 7.51−7.56 (m, 2 H; *o*-H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz) δ 14.54 (CH_3), 58.87 (CH_2), 84.59 (CH), 126.11 (CH), 128.77 (CH), 130.17 (CH), 137.64 (C), 160.44 (C), 170.38 (C) ppm; IR (ATR) 1/λ 3439 (m), 3327 (m), 1662 (s), 1615 (vs), 1576 (m), 1554 (vs), 1313 (s), 1174 (vs) cm^{-1}; MS (EI, 70 eV) *m*/*z* 191 (66), 146 (100), 119 (92), 104 (42).

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Supporting Information Available: NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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