Mechanism of Selective C-H Hydroxylation Mediated by Manganese-Aminopyridine Enzyme Models

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Supporting Information

Materials and Methods

Materials

All chemicals and solvents were purchased from either Aldrich, Acros Organics, Alfa Aesar commercial reagents (used without additional purification unless noted otherwise), or were prepared according to literature procedures. For catalytic epoxidation experiments, 30% analytical grade aqueous H_2O_2 was dissolved in acetonitrile. The exact oxidant concentrations in the prepared reagents were determined by iodometric titration under argon. Chiral Mn catalysts **1**,[1] and **4**, **5**[2] were prepared as described and were recrystallized from acetonitrile/diethyl ether. $H_2{}^{18}O$ (97 atom % ^{18}O) was purchased form Sigma-Aldrich.

Instrumentation.

^1H and ^{13}C NMR spectra were measured on Bruker Avance 400 at 400.13 and 100.613 MHz, respectively, or on Bruker DPX-250 at 250.13 and 62.903 MHz, respectively. Chemical shifts were internally referenced to tetramethylsilane. For precise integration of ^{13}C NMR peaks during the NMR analyses of mixtures of cumene/α-D-cumene and *p*-methoxycumene/α-D-cumene-*p*-methoxycumene, inverse-gated $^{13}C\{^1H\}$ NMR spectra were measured on a Bruker DPX-250 at 62.903 MHz, with a 14 µs 90° pulse and with a 90 s delay between pulses; number of scans 512-1024.

The incorporation of ^{18}O into the products of oxidation of adamantane, *cis*-1,2-dimethylcyclohexane, cyclohexane, cumene, and the corresponding yields were determined by GC-MS using Agilent 7000B GC/MS with Triple Quad detector, EI - 70 eV, chromatograph Agilent 7890 equipped with a capillary column ZB-WAX [30 m × 0.25 mm × 0.25μm, He carrier gas].

Synthetic procedures

***α*-D-cumene** was prepared according to a modified procedure adopted from Ref. 3: a suspension of cumene (2.0mmol, 0.28 mL) and Pd/C (25 mg, 6 wt. % Pd) in D_2O (1.0 mL) in a 18 mL Schlenk tube was flushed with H_2, closed and stirred overnight at 50 °C. The mixture was cooled to room temperature and 10 mL of diethyl ether was added. Pd/C was filtered off, and the organic phase was separated. The aqueous phase was extracted with diethyl ether (10 mL). The combined organic extracts were dried with $CaSO_4$ and volatiles were removed on a rotary evaporator. Collected yield: 87 mg (36 %), the mixture contained 84% of *α*-D-cumene and 16 % of *α*-H-cumene. For oxidation experiments, the mixture was diluted with *α*-H-cumene to obtain a 31.2:68.8 mixture of *α*-H-cumene:*α*-D-cumene (by ^{13}C NMR).

α-D-Cumene: ^{13}C NMR{^1H} (CD_3CN, 20 °C), *δ*: 150.43 (s, 1C, aryl-*C*), 130.95 (s, 2C, aryl-*C*H), 127.84 (s, 1C, aryl-*C*H), 127.26 (s, 2C, aryl-*C*H), 34.96 (t, 1C, *C*DMe$_2$, $^1J_{CD}$= 19.6 Hz), 24.74 (s, 2C, CD(*C*H$_3$)$_2$).

α-H-Cumene: ^{13}C NMR{^1H} (CD_3CN, 20 °C), *δ*: 150.43 (1C, aryl-*C*), 130.95 (2C, aryl-*C*H), 127.84 (1C, aryl-*C*H), 127.26 (2C, aryl-*C*H), 35.40 (1C, C*H*Me$_2$), 24.85 (2C, CH(*C*H$_3$)$_2$).

Alkane oxidations

Catalytic C-H oxidations with H_2O_2.

The solution of the appropriate substrate (100 *μ*mol) and of manganese complex (0.1 *μ*mol) in CH_3CN (0.50 mL in case of using **4** or **5**, 0.40 mL using **1**) and AcOH (34 *μ*L, 600 *μ*mol in case of using **4** or **5**, 80 *μ*L, 1400 *μ*mol using **1**) were thermostated at 0 °C, and 130 *μ*mol of 30% aqueous H_2O_2 (dissolved in CH_3CN, total volume 100 *μ*L) were added to this mixture with a syringe pump over 30-60 min at 0 °C. The mixture was stirred for additional 3-4 h at 0 °C. Then the reaction was quenched with aqueous $NaHCO_3$, the products were extracted with 3×2ml of pentane, the solvent was carefully removed at 0 °C, and the residue was dissolved in $CDCl_3$ and analyzed by GC-MS.

Table S1. Catalytic oxidation of *cis*-1,2-dimethylcyclohexane with H_2O_2. [a]

No	catalyst	temperature, °C	*RC*, % [b]	conversion, %	selectivity, % [c]
1	**1**	20 °C	> 99	56.7	72.7
2	**4**	20 °C	98.6	53.4	71.0
3	**5**	20 °C	97.1	55.3	74.7
4	**1**	30 °C	> 99	48.3	78.8
5	**4**	30 °C	98.6	49.5	76.2
6	**5**	30 °C	94.3	48.5	75.2

[a] [substrate]:[H_2O_2]:[AcOH]:[Mn]= 100 μmol : 130 μmol : 600 μmol : 0.1 μmol, oxidant added via syringe pump over 30 min and the mixture stirred for an additional 3 h, products analyzed by GC-MS.

[b] RC = 100%×[(1*R*,2*R*) + (1*S*,2*S*)) - ((1*R*,2*S*) + (1*S*,2*R*))]/ [(1*R*,2*R*) + (1*S*,2*S*)) + ((1*R*,2*S*) + (1*S*,2*R*))].

[c] **(1*RS*, 2*RS*)-1,2-dimethylcyclohexanol *s*electivity. The** RC values determination uncertainty was not higher than ±0.1 %.

Catalytic oxidations of alkanes in the presence of $H_2{}^{18}O$.

Substrate (100 μmol) and $H_2{}^{18}O$ (2.0 mmol) were added to the solution of Mn catalyst **5** (1.0 μmol, 0.68 mg) in CH_3CN (400 μL), and the mixture was thermostated at 0 ºC. Then, 100 μL of the 88% H_2O_2 solution in CH_3CN (100 μmol of H_2O_2, 1 equiv. vs. substrate) was injected by a syringe pump over 2 h upon stirring (555 rpm). The resulting mixture was stirred for additional 1 h at 0 ºC. An internal standard (1,4-dioxane) was added and the mixture was subjected to GC-MS analysis.

k_H/k_D measurements: cyclohexane/d_{12}-cyclohexane.

Cyclohexane (200 μmol) and D_{12}-cyclohehane (200 μmol) were added to the solution of the **Mn** catalyst (0.1 μmol) in CH_3CN (500 μL). Acetic acid (34 μL, 600 μmol) was added and the mixture was thermostated at 0 ºC. Then, 100 μL of the 30 % H_2O_2 solution in CH_3CN (250 μmol of H_2O_2) was injected by a syringe pump over 1 h upon stirring (555 rpm). The resulting mixture was stirred for 3 h at 0 ºC. The internal standard (1,4-dioxane) was added and the reaction mixture was directly analyzed by GC-MS.

Table S2. Catalytic oxidation of cyclohexane/d_{12}-cyclohexane with H_2O_2.

No	catalyst	cyclohexane			d_{12}-cyclohexane		
		A, TON [a]	K, TON [b]	E, TON [c]	A, TON [a]	K, TON [b]	E, TON [c]
1	**1**	141.4	216.1	10.5	61.0	32.4	3.5
2	**4**	183.6	383.4	8.0	77.3	59.4	2.4
3	**5**	170.4	168.7	-	68.8	27.0	-

[a] Cyclohexanol, turnover numbers for catalyst. [b] Cyclohexanone, turnover numbers for catalyst. [c] Cyclohexene epoxide, turnover numbers for catalyst.

k_H/k_D measurements.

Cumene/α-D-cumene.

A mixture of cumene (31.2 %) and α-D-cumene (68.8 %) (200 μmol, 27.8 μL) was added to the solution of the **Mn** catalyst (0.2 μmol in case of using **4** or **5**, 1.0 μmol using **1**) in the mixture CD_3CN/CH_3CN (450 μL / 50 μL). Acetic acid (34 μL, 600 μmol in case of using **4** or **5**, 80 μL, 1400 μmol using **1**) was added and the mixture was thermostated at 0 ºC. Then, 50 μL of the 30 % H_2O_2 solution in CH_3CN (260 μmol of H_2O_2 in case of using **4** or **5**, 200 μmol using **1**) was injected by a syringe pump over 1 h upon stirring (555 rpm). The resulting mixture was stirred for 3 h at 0 ºC, and then the mixture was transferred into a 5 mm NMR tube and analyzed by quantitative (inverse gated) ^{13}C NMR. Along with residual cumene and α-D-cumene, two oxidation products were found: 2-phenylpropan-2-ol and 2-phenylpropan-2-yl acetate (in a ca. 10:1 ratio).

2-Phenylpropan-2-ol: ^{13}C NMR{^1H} (CD_3CN, 20 °C), δ: 151.28 (1C, aryl-*C*), 129.47 (2C, aryl-*C*H), 127.76 (1C, aryl-*C*H), 125.92 (2C, aryl-*C*H), 73.31 (1C, *C*(OH)Me_2), 32.54 (2C, C(OH)(CH_3)$_2$).

2-phenylpropan-2-yl acetate: ^{13}C NMR{^1H} (CD_3CN, 20 °C), δ: 147.71 (1C, aryl-*C*), 130.12 (2C, aryl-*C*H), 129.71 (2C, aryl-*C*H), 125.74 (1C, aryl-*C*H), 82.72 (1C, *C*(OAc)Me_2), 29.61 (s, 2C, C(OAc)($\mathit{C}H_3)_2$), 22.91 (1C, OC(O)CH_3).

Competitive catalytic oxidations of *para*-substituted cumenes (Figure 2a).

Cumene (100 μmol) and desired *p*-substituted cumene (100 μmol) were added to the solution of the catalyst **5** (0.1 μmol) in CH_3CN (500 μL). Acetic acid (600 μmol, 34 μL) was added and the mixture was thermostated at 0 ºC. Then, 100 μL of the 30 % H_2O_2 solution in CH_3CN (130 μmol of H_2O_2) was injected by a syringe pump over 30 min upon stirring (555 rpm). The resulting mixture was stirred for 3 h at 0 ºC. The internal standard (1,4-dioxane) was added and the reaction mixture was directly analyzed by GC-MS.

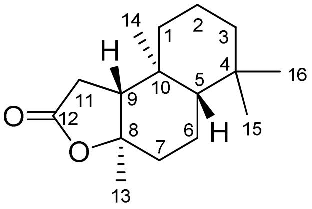
Competitive catalytic oxidations of hydrocarbons with various BDEs (Figure 2b).

Cumene (100 μmol) and desired hydrocarbon (100 μmol) were added to the solution of the catalyst **5** (0.1 μmol) in CH_3CN (500 μL). Acetic acid (600 μmol, 34 μL) was added and the mixture was thermostated at 0 ºC. Then, 100 μL of the 30 % H_2O_2 solution in CH_3CN (130 μmol of H_2O_2) was injected by a syringe pump over 30 min upon stirring (555 rpm). The resulting mixture was stirred for 3 h at 0 ºC. The internal standard (1,4-dioxane) was added and the reaction mixture was directly analyzed by GC-MS (except the oxidation of cumene/triphenylmethane, for which the mixture was analyzed by quantitative (inverse gated) ^{13}C NMR.

The k_{rel} values were referenced to k_{cumene}, i.e. calculated as $Ln(Cx/Cx_0)/Ln(C_{cumene}/C_{cumene0})$ for all substrates used except ethylbenzene: for the latter, the resulting k_{rel} was normalized via dividing by a factor of 2 (to take into account two equivalent C-H bonds in PhEt). Bond dissociation energies were taken from the literature.[4,5]

Catalytic oxidation of (−)-Ambroxide.

(−)-Ambroxide (500 *μ*mol, 118.2 mg) was added to the solution of the catalyst **4** (0.5 *μ*mol, 0.1 mol. %) in CH_3CN (2.5 mL). Acetic acid (2500 *μ*mol, 143 *μ*L, 5 equiv. vs. substrate) was added and the mixture was thermostated at +15 ºC. Then, 500 *μ*L of the 30 % H_2O_2 solution in CH_3CN (1500 *μ*mol of H_2O_2) was injected by a syringe pump over 30 min upon stirring (555 rpm). The resulting mixture was stirred for 2 h at +15 ºC. Solvent was carefully evaporated under vacuum and the residue was purified on SiO_2 column (eluent: EtOAc:hexane = 1:10) to yield (+)-sclareolide (65.5 mg, 52 %). NMR data of the isolated (+)-sclareolide (see below) were consistent with the literature data.[6,7]



(+)-sclareolide

^{1}H NMR ($CDCl_3$, 20 °C), *δ*: 2.41 (dd, *J* = 16.3, 14.7 Hz, 1H), 2.23 (dd, *J* = 16.3, 6.4 Hz, 1H), 2.08 (dt, *J* = 11.6, 3.3 Hz, 1H), 1.96 (dd, *J* = 14.7, 6.5 Hz, 1H), 1.88 (dq, *J* = 13.8, 3.6 Hz, 1H), 1.7 (m, 2H), 1.35-1.53 (m, 4H), 1.33 (s, 3H), 1.24 (m, 2H), 1.06 (m, 1H), 0.92 (s, 3H), 0.88 (s, 3H), 0.84 (s, 3H).

^{13}C NMR ($CDCl_3$, 20 °C), *δ*: 175.97 (1C, C, C=O), 85.88 (1C, C, C-8), 59.11 (1C, CH, C-9), 56.73 (1C, CH, C-5), 42.25 (1C, CH_2, C-3), 39.56 (1C, CH_2, C-7), 38.78 (1C, CH_2, C-1), 36.25 (1C, CH_3, C-15), 33.17 (1C, C, C-4), 28.59 (1C, CH_2, C-11), 21.61 (1C, CH_3, C-14), 20.99 (1C, CH_3, C-13), 20.58 (1C, CH_2, C-6), 18.12 (1C, CH_2, C-2), 15.10 (1C, CH_2, C-16).

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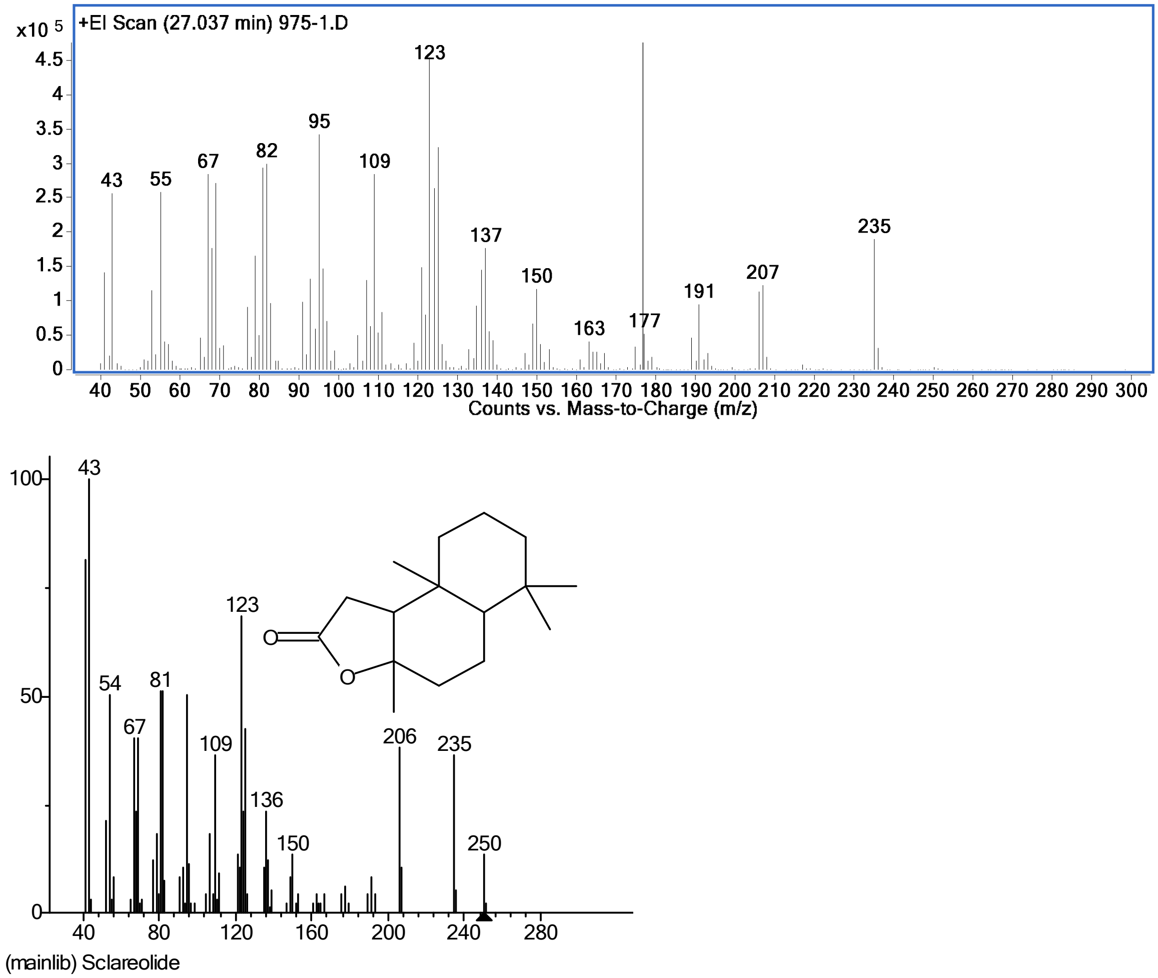

Figure S1. Experimental mass spectrum of (+)-sclareolide (upper picture) and spectrum from the library (lower picture).

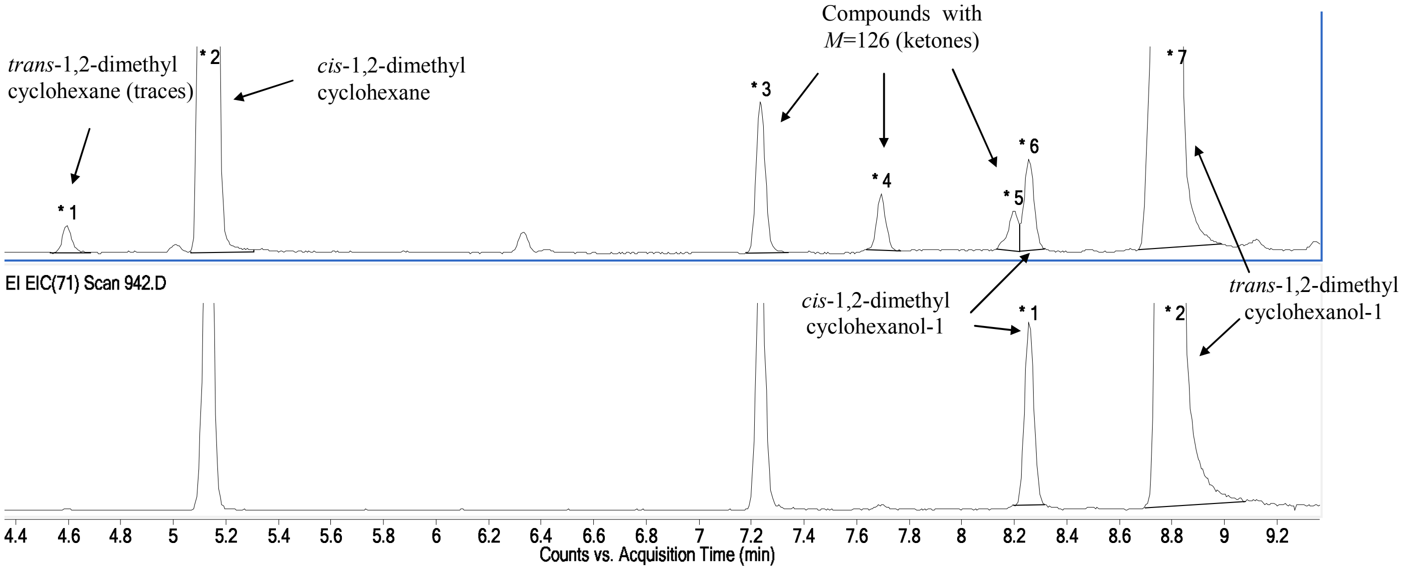

Figure S2. GC-MS chromatograms of the reaction mixture for the oxidation of cis-1,2-dimethylcyclohexane with H_2O_2 on catalyst **5** at +30 °C: total ion current chromatogram (upper curve) and selected ion chromatogram (m/z = 71) chromatogram (lower curve). The S/N and peak separation is much better in the second case.

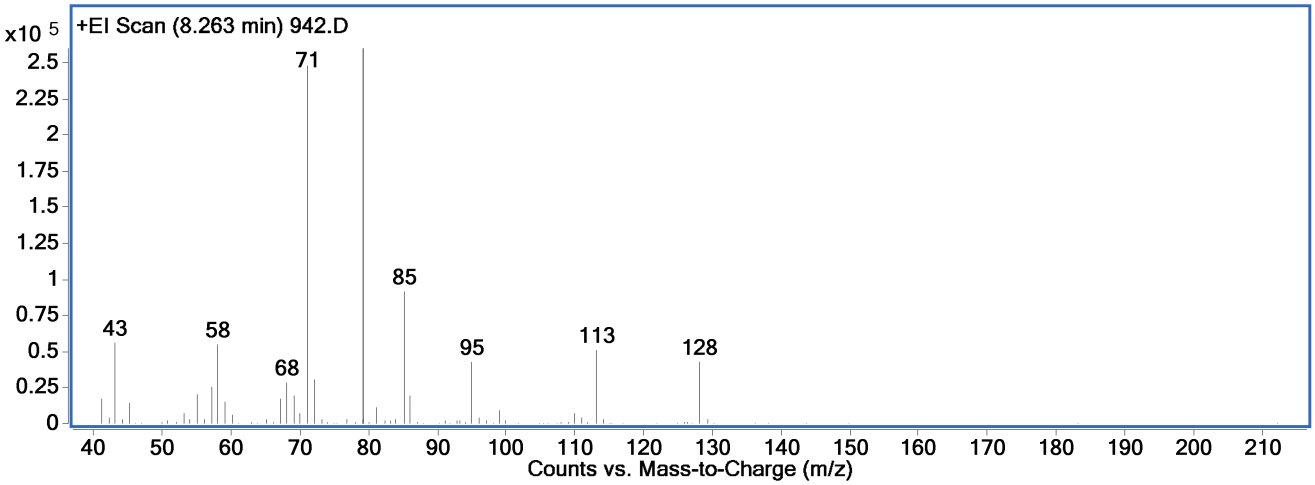

Figure S3. Mass spectrum of *trans*-1,2-dimethylcyclohexanol {(1*R*,2*R*)-1,2-dimethylcyclohexanol + (1*S*,2*S*)-1,2-dimethylcyclohexanol} (t_R = 8.82 min).