Supplementary Information for

Chemoselective Aliphatic C-H Bond Oxidation Enabled by Polarity Reversal

Valeria Dantignana,1§ Michela Milan,1§ Olaf Cussó,1 Anna Company,1,* Massimo Bietti,2,* and Miquel Costas1,*

1 QBIS-CAT Research Group, Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Universitat de Girona, Campus Montilivi, Girona E-17003, Catalonia, Spain.
2 Dipartimento di Scienze e Tecnologie Chimiche, Università “Tor Vergata”, Via della Ricerca Scientifica, 1 I-00133 Rome, Italy.

e-mail: miquel.costas@udg.edu
bietti@uniroma2.it
anna.company@udg.edu

§Both authors contributed equally to this work
Contents

1. Experimental Section ............................................................................................................ 2
   1.1. Materials .......................................................................................................................... 2
   1.2. Instrumentation ............................................................................................................... 2

2. Synthesis of the complexes ................................................................................................. 3

3. Synthesis of the substrates ................................................................................................... 4

4. Oxidation reactions ................................................................................................................ 5
   4.1 Reaction protocol for catalysis .......................................................................................... 5
   4.2. Screening of catalysts for the oxidation of hexane .......................................................... 7
   4.3. Blank experiments for the oxidation of hexane, cyclohexane and cyclohexanol .................. 9
   4.4. Screening of catalysts and carboxylic acid for enantioselective hydroxylation ............... 11
   4.5. Intermolecular competition experiment ....................................................................... 13
   4.6. Determination of kinetic isotopic effect (KIE) ................................................................ 13
   4.7. Oxidation of alcohols with Mn(TIPS,mcp) in TFE .......................................................... 14
   4.8. GC-MS spectra ............................................................................................................. 15

5. Characterization of the isolated products ............................................................................ 18
   5.1. $^1$H and $^{13}$C($^1$H) NMR spectra of substrates ............................................................. 20
   5.2 $^1$H and $^{13}$C($^1$H) NMR spectra of isolated products ..................................................... 21
   5.3 GC spectra of chiral products .......................................................................................... 28

6. References ............................................................................................................................ 31
1. Experimental Section

1.1. Materials

Reagents and solvents used were of commercially available reagent quality unless stated otherwise and were purchased from Aldrich, SDS, Scharlab and Fluorochem.

1.2. Instrumentation

Oxidation products were identified by comparison of their GC retention times and GC-MS with those of authentic compounds when commercially available, and/or by $^1$H and $^{13}$C-NMR analysis. GC spectra were performed with an Agilent 7820A gas chromatograph equipped with an HP-5 capillary column 30m × 0.32 mm × 0.25 μm and a flame ionization detector. GC-MS analyses were performed on an Agilent 7890A gas chromatograph equipped with an HP-5 capillary column interfaced with an Agilent 5975C mass spectrometer. For electron ionization (EI) the source was set at 70 eV, while a 50/50 NH$_3$:CH$_4$ mix was used as the ionization gas for chemical ionization (CI) analyses. NMR spectra were taken on BrukerDPX300 and DPX400 spectrometers using standard conditions. High resolution mass spectra (HRMS) were recorded on a Bruker MicroTOF-Q II instrument with an ESI source at Serveis Tècnics of the University of Girona. Samples were introduced into the mass spectrometer ion source by direct infusion through a syringe pump and were externally calibrated using sodium formate. Chromatographic resolution of enantiomers was performed on an Agilent 7820A gas chromatograph using a CYCLOSIL-B column.
2. Synthesis of the complexes

Scheme S1. Schematic representation of the complexes used in this work.

The manganese and iron complexes were prepared and purified according to the reported procedures:

\[
\begin{align*}
\text{[Fe(CF}_3\text{SO}_3]_2(pdp)} & ^1 (\text{Fe(pdp)}) \\
\text{[Fe(CF}_3\text{SO}_3]_2(mcp)} & ^2 (\text{Fe(mcp)}) \\
\text{[Fe(CF}_3\text{SO}_3]_2(\text{dMM}pdp), [Fe(CF}_3\text{SO}_3]_2(\text{dMM}mcp), [Fe(CF}_3\text{SO}_3]_2(\text{Cl}pdp)} & ^3 (\text{Fe(}^{\text{dMM}}\text{mcp), Fe(}^{\text{dMM}}\text{pdp), Fe(}^{\text{Cl}}\text{pdp)}) \\
\text{[Fe(CF}_3\text{SO}_3]_2(\text{TIPS}mcp), [Fe(CF}_3\text{SO}_3]_2(\text{TIPS}pdp)} & ^4 (\text{Fe(}^{\text{TIPS}}\text{mcp), Fe(}^{\text{TIPS}}\text{pdp)}) \\
\text{[Mn(CF}_3\text{SO}_3]_2(mcp)} & ^5 (\text{Mn(mcp)}) \\
\text{[Mn(CF}_3\text{SO}_3]_2(pdp)} & ^6 (\text{Mn(pdp)}) \\
\text{[Mn(CF}_3\text{SO}_3]_2(\text{dMM}pdp), [Mn(CF}_3\text{SO}_3]_2(\text{dMM}mcp), [Mn(CF}_3\text{SO}_3]_2(\text{Cl}mcp)} & ^7 (\text{Mn(}^{\text{dMM}}\text{pdp), Mn(}^{\text{dMM}}\text{mcp), Mn(}^{\text{Cl}}\text{mcp)}) \\
\text{[Mn(CF}_3\text{SO}_3]_2(\text{TIPS}mcp)} & ^8 (\text{Mn(}^{\text{TIPS}}\text{mcp)}) \\
\text{[Mn(salen)Cl]} & ^9 \\
\end{align*}
\]
3. Synthesis of the substrates

Substrates 1-15 and 22 were purchased from Aldrich and Fluorochem.

Substrates 16, 17, 18, 20, 21 and 23 were synthesized following the reported procedures.

Substrate 19 was prepared as described below:

A round-bottom flask capped with a rubber septum and kept under nitrogen was charged with a 0.20 M solution of 2-(4-methylpentyl)piperidine (1.1 equiv) in dichloromethane and cooled to 0 °C. Triethylamine (1.1 equiv) was added to the reaction flask. Pivaloyl chloride (1.0 equiv) was added dropwise and the reaction was stirred overnight at room temperature. At this point, a saturated aqueous Na₂CO₃ solution was added until pH ~ 10-11 and then diluted with dichloromethane. The organic layer was separated from the basic aqueous layer. The aqueous layer was extracted with dichloromethane (2x) and the organic layers were combined. The organic layer was washed with 1N HCl and dried over anhydrous sodium sulfate (Na₂SO₄). The organic layer was evaporated to dryness. The crude amide was purified by flash chromatography over silica gel with hexane:ethyl acetate 2:1 and the product was concentrated to dryness. Product 19 was isolated as a white solid (0.56 g, 88% yield). ¹H-NMR (CDCl₃, 400 MHz, 300 K) δ, ppm: 4.74 (s, 1H), 4.05 (s, 1H), 3.01 (s, 1H), 1.69 – 1.57 (m, 6H), 1.50 – 1.49 (m, 2H), 1.47 – 1.39 (m, 1H), 1.29 (s, 9H), 1.25 – 1.12 (m, 4H), 0.87 (dd, J = 6.6, 0.8 Hz, 6H). ¹³C-NMR (CDCl₃, 100 MHz, 300 K) δ, ppm: 176.2, 38.9, 38.8, 37.5, 29.7, 28.5, 27.8, 27.2, 26.2, 24.0, 22.6, 22.5, 19.0. HRMS(ESI+) m/z calculated for C₁₆H₃₁NO [M+Na]⁺ 276.2298, found 276.2302.
4. Oxidation reactions

Hydrogen peroxide solutions employed in the oxidation reactions were prepared by diluting commercially available hydrogen peroxide (30% H$_2$O$_2$ solution in water, Aldrich) in acetonitrile or fluorinated alcohols to achieve a 0.2 M final concentration. Commercially available glacial acetic acid (99-100%) purchased from Riedel-de-Haën was employed. The purity of the substrates synthetized as described above was in all cases >99%.

4.1 Reaction protocol for catalysis

- **Substrate 1** (entries 1-8, Scheme 2b)
  A 0.1 M solution (2 mL) of the substrate and the pertinent complex (1.0 mM) was prepared in a vial (10 mL) equipped with a stirring bar using the desired solvent (MeCN, TFE or HFIP). Acetic acid (2.0 equiv.) was added directly to the solution. Then hydrogen peroxide (0.2 equiv.) in the appropriate solvent was added by syringe pump over a period of 30 min. Afterwards, the solution was stirred for further 30 min. At this point, an internal standard was added and the solution was quickly filtered through a silica plug, which was subsequently rinsed with 2 x 1 mL AcOEt. GC analysis of the solution provided product yields relative to the internal standard. Calibration curves were obtained using commercially available pure compounds.

- **Substrates 1** (entries 9-14, Scheme 2b), 2-6 (Table 1), 7 (Scheme 3), 8-16 (Scheme 5), 2a and 3a (Scheme 5)
  A 0.1 M solution (2 mL) of the substrate and the pertinent complex (0.5 mM) was prepared in a vial (10 mL) equipped with a stirring bar using the desired solvent (MeCN, TFE or HFIP) and cooled at 0 °C in an ice bath. Acetic acid (2.0 equiv.) was added directly to the solution. Then hydrogen peroxide (0.5 equiv.) in the appropriate solvent was added by syringe pump over a period of 30 min. Afterwards, the solution was stirred for further 30 min. At this point, an internal standard was added and the solution was quickly filtered through a silica plug, which was subsequently rinsed with 2 x 1 mL AcOEt. GC analysis of the solution provided product yields relative to the internal standard. Calibration curves were obtained using commercially available pure compounds when available. For 8b, 9c, 10b, 11b, 11c, 2c, 3c and 3d the response factor of the corresponding commercially available 1,2-diols was used to calculate the yields. For 12b, 13c, 14 15b, 15c, 16c the response factor of the pure compounds synthetized following the reported procedures were used to calculate the yields.

The alcohol 4a$_{endo}$ was identified by $^1$H-NMR in CDCl$_3$ (4a$_{endo}$: δ (H$_{α}$) = 4.23 ppm$^{16}$). The axial and equatorial alcohols of 5a, 5b, 6a and 6b were identified by GC in combination with $^1$H-NMR. The NMR chemical shift of the alcohol α protons in CDCl$_3$ allowed the distinction of the different isomers, as previously reported (5b$_{ax}$:
\( \delta (H_a) = 4.05 \text{ ppm}; \ 17^5\text{b}_{eq}: \ \delta (H_a) = 3.58 \text{ ppm}; \ 17^5\text{a}_{ax}: \ \delta (H_a) = 4.19 \text{ ppm}; \ 18^6\text{a}_{eq}: \ \delta (H_a) = 3.57 \text{ ppm}; \ 18^6\text{a}_{ax}: \ \delta (H_a) = 3.76 \text{ ppm}; \ 19^6\text{a}_{eq}: \ \delta (H_a) = 3.2 \text{ ppm}; \ 19^6\text{b}_{eq}: \ \delta (H_a) = 3.58 \text{ ppm}. \)

- **Intermolecular competition experiment (Scheme 4 and Scheme S2)**

  A 0.05 M solution (2 mL) of each substrate and the pertinent complex (0.5 mM) was placed in a vial (10 mL) equipped with a stirring bar using the desired solvent (MeCN, TFE or HFIP) and cooled at 0 °C in an ice bath. Acetic acid (2.0 equiv.) was added directly to the solution. Then hydrogen peroxide (0.5 equiv.) in the appropriate solvent was added by syringe pump over a period of 30 min. Afterwards, the solution was stirred for further 30 min. At this point, an internal standard was added and the solution was quickly filtered through a silica plug, which was subsequently rinsed with 2 x 1 mL AcOEt. GC analysis of the solution provided product yields relative to the internal standard. Calibration curves were obtained using commercially available pure compounds.

- **Substrates 17-21 (Scheme 6 and Scheme 7):**

  A 25 mL round bottom flask was charged with catalyst (6 \( \mu \)mol, 1.0 mol%), substrate (1.0 equiv.), MeCN or HFIP (3.3 mL) and a magnetic stirring bar. Acetic acid was then added (13 equiv.) and the mixture was cooled at -40 °C in a N\(_2\)/MeCN bath or at 0 °C in an ice bath under magnetic stirring. Then, hydrogen peroxide solution in MeCN or HFIP (1.0 - 3.5 equiv.) was added by syringe pump over a period of 30 min. At this point, 15 mL of an aqueous NaHCO\(_3\) saturated solution were added to the mixture. The resulting solution was extracted with CH\(_2\)Cl\(_2\) (3 x 10 mL). The organic fractions were combined, dried over MgSO\(_4\), and the solvent was removed under reduced pressure to afford the oxidized product. The resulting residue was purified by column chromatography over silica gel to obtain the pure product.

- **Substrates 22-23 (Scheme 8):**

  A 25 mL round bottom flask was charged with catalyst (6 \( \mu \)mol, 1.0 mol%), substrate (1.0 equiv.), MeCN or HFIP (3.3 mL) and a magnetic stirring bar. Acetic acid was then added (13 equiv.) and the mixture was cooled at 0 °C in an ice bath under magnetic stirring. Then, hydrogen peroxide solution in HFIP or MeCN (1.0 equiv.) was added by syringe pump over a period of 30 min. At this point, the mixture was evaporated to dryness and charged with dichloromethane (15 mL) and cooled to 0 °C. Triethylamine (2.0 equiv) was added to the reaction flask. Pivaloyl chloride (2.0 equiv) was added dropwise and the reaction was stirred for 4 hours at room temperature. At this point, a saturated aqueous Na\(_2\)CO\(_3\) solution was added until pH~10-11 and then diluted with dichloromethane. The organic layer was separated from the basic aqueous layer. The aqueous layer was extracted with dichloromethane (2x) and the organic layers were combined. The organic layer was washed with 1N HCl and dried over anhydrous sodium sulfate (Na\(_2\)SO\(_4\)). The organic layer was evaporated to dryness and the crude amide was purified by flash chromatography over silica gel.
4.2. Screening of catalysts for the oxidation of hexane

Table S1. Oxidation of hexane (1) catalyzed by [Mn(salen)Cl] and [Mn(TCPP)Cl] in MeCN and HFIP.

| Catalyst          | 1a (%) | 1b (%) | 1c (%) | 1d (%) | Yield (%) | Solvent |
|-------------------|--------|--------|--------|--------|-----------|---------|
| [Mn(salen)Cl]c   | -      | -      | -      | -      | -         | MeCN    |
| [Mn(TCPP)Cl]d    | 3      | 3      | 4      | 4      | 14(60)    | MeCN    |
|                   | 3      | 3      | -      | -      | 6(100)    | HFIP    |

a Yields with respect to H$_2$O$_2$, determined by GC (FID) against an internal standard. Yields are calculated considering that 2 eq of H$_2$O$_2$ are necessary for the formation of the ketone products (1c and 1d). b $100 \times \frac{[1a]+[1b]}{([1a]+[1b]+[1c]+[1d])}$. c 21 eq hexane, 84 eq PhIO, 11 eq pyridine N-oxide, 0° C, 4 h. d 1000 eq hexane, 2 eq 4-tert-butylpyridine, RT, 1h.

Table S2. Oxidation of hexane (1) with different catalysts.

| Entry | Catalyst          | H$_2$O$_2$ (eq) | 1a (%) | 1b (%) | 1c (%) | 1d (%) | Yield (%) | Solvent |
|-------|-------------------|-----------------|--------|--------|--------|--------|-----------|---------|
| 1     | Fe(pdp)           | 0.2             | 8      | 8      | 24     | 14     | 54(46)    | MeCN    |
| 2     | Fe(pdp)           | 0.2             | 26     | 18     | 8      | 6      | 58(86)    | TFE     |
| 3     | Fe(pdp)           | 0.2             | 49     | 33     | 2      | 2      | 86(98)    | HFIP    |
| 4     | Mn(pdp)           | 0.2             | 7      | 5      | 26     | 14     | 52(38)    | MeCN    |
| 5     | Mn(pdp)           | 0.2             | 21     | 14     | 4      | 2      | 41(92)    | TFE     |
| 6     | Mn(pdp)           | 0.2             | 39     | 25     | 1      | 1      | 66(99)    | HFIP    |
| 7     | Fe(TIPS)mcp       | 0.2             | 30     | 19     | 6      | 8      | 63(91)    | TFE     |
| 8     | Mn(TIPS)mcp       | 0.2             | 34     | 20     | 4      | -      | 58(96)    | TFE     |
| 9c    | Fe(TIPS)mcp       | 0.5             | 3      | 2      | 36     | 18     | 59(16)    | MeCN    |
| 10c   | Fe(TIPS)mcp       | 0.5             | 22     | 14     | 8      | 4      | 48(86)    | TFE     |
| 11c   | Fe(TIPS)mcp       | 0.5             | 40     | 25     | 2      | 2      | 69(97)    | HFIP    |
| 12c   | Mn(TIPS)mcp       | 0.5             | 3      | 3      | 34     | 16     | 56(19)    | MeCN    |
| 13c   | Mn(TIPS)mcp       | 0.5             | 29     | 18     | 8      | 4      | 59(89)    | TFE     |
| 14c   | Mn(TIPS)mcp       | 0.5             | 34     | 21     | 2      | 2      | 59(97)    | HFIP    |

*Yields with respect to H$_2$O$_2$, determined by GC-FID against an internal standard. Yields are calculated considering that 2 eq of H$_2$O$_2$ are necessary for the formation of the ketone products (1c and 1d). b $100 \times \frac{[1a]+[1b]}{([1a]+[1b]+[1c]+[1d])}$. c 0.5 mol% catalyst was used; oxidations performed at 0° C.
Table S3. Catalyst screening for the oxidation of hexane (1) in TFE.

![Catalyst Screening Diagram]

| Catalyst            | 1a (%)<sup>a</sup> | 1b (%)<sup>a</sup> | 1c (%)<sup>a</sup> | 1d (%)<sup>a</sup> | Yield (%)<sup>a</sup> (% alcohol)<sup>b</sup> |
|---------------------|---------------------|---------------------|---------------------|---------------------|-----------------------------------------------|
| Fe(mcp)             | 18                  | 12                  | 6                   | 4                   | 40(86)                                        |
| Mn(mcp)             | 23                  | 14                  | 2                   | 2                   | 41(95)                                        |
| Fe(dMM pdp)         | 22                  | 16                  | 4                   | 2                   | 44(93)                                        |
| Mn(dMM pdp)         | 23                  | 17                  | 4                   | 2                   | 46(93)                                        |
| Fe(dMM mcp)<sup>c</sup> | 22              | 17                  | 4                   | 4                   | 47(91)                                        |
| Mn(Cl pdp)<sup>c</sup> | 24              | 17                  | 4                   | 2                   | 47(93)                                        |
| Fe(TIPS pdp)        | 18                  | 14                  | 8                   | 8                   | 48(80)                                        |
| Mn(Cl mcp)          | 26                  | 16                  | 6                   | -                   | 48(93)                                        |
| Fe(TIPS pdp)        | 21                  | 14                  | 4                   | 4                   | 43(90)                                        |

<sup>a</sup>Yields with respect to H<sub>2</sub>O<sub>2</sub>, determined by GC (FID) against an internal standard. Yields are calculated considering that 2 eq of H<sub>2</sub>O<sub>2</sub> are necessary for the formation of the ketone products (1c and 1d).

<sup>b</sup>100 x[(1a)+1b]/[(1a)+1b]+(1c)+(1d)].
4.3. Blank experiments for the oxidation of hexane, cyclohexane and cyclohexanol

Table S4. Control experiment for the oxidation of hexane (1).

| Solvent          | Mn(TIPS)mcp (mol%) | 1a (%)<sup>a</sup> | 1b (%)<sup>a</sup> | 1c (%)<sup>a</sup> | 1d (%)<sup>a</sup> |
|------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| MeCN (reference) | 1                  | 7                  | 5                  | 14                 | 6                  |
| MeCN (blank)     | 0                  | 0                  | 0                  | 0                  | 0                  |
| TFE (reference)  | 1                  | 34                 | 20                 | 4                  | 0                  |
| TFE (blank)      | 0                  | 0                  | 0                  | 0                  | 0                  |
| HFIP (reference)<sup>b</sup> | 1         | 30                 | 18                 | 2                  | 1                  |
| HFIP (blank)<sup>b</sup> | 0         | 0                  | 0                  | 0                  | 0                  |

<sup>a</sup>Yields with respect to H₂O₂, determined by GC (FID) against an internal standard. Yields are calculated considering that 2 eq of H₂O₂ are necessary for the formation of 1c and 1d. <sup>b</sup>0.5 equiv. of H₂O₂ was used.

Table S5. Control experiment for the oxidation of cyclohexane (2).

| Solvent          | Mn(TIPS)mcp (mol%) | AcOH (eq) | 2a (%)<sup>a</sup> | 2b (%)<sup>a</sup> |
|------------------|--------------------|-----------|--------------------|--------------------|
| TFE (reference)  | 0.5                | 2         | 68                 | 6                  |
| TFE (blank)      | 0                  | 2         | 0                  | 0                  |
| TFE (blank)      | 0.5                | 0         | 7                  | 2                  |
| HFIP (reference) | 0.5                | 2         | 68                 | 4                  |
| HFIP (blank)     | 0.5                | 2         | 0                  | 0                  |
| HFIP (blank)     | 0.5                | 0         | 39                 | 2                  |

<sup>a</sup>Yields with respect to H₂O₂, determined by GC (FID) against an internal standard. Yields are calculated considering that 2 eq of H₂O₂ are necessary for the formation of 2b.
Table S6. Control experiment for the oxidation of cyclohexanol (2a).

![Chemical structure diagram]

| Solvent       | Mn(TIPS\textsubscript{mcp}) (mol\%) | AcOH (eq) | 2b (%)\textsuperscript{a} | 2c (%)\textsuperscript{a} |
|---------------|-------------------------------------|-----------|----------------|-----------------|
| TFE (reference)| 0.5                                 | 2         | 53             | 18              |
| TFE (blank)   | 0                                   | 2         | 3              | 0               |
| TFE (blank)   | 0.5                                 | 0         | 1              | 0               |
| HFIP (reference)| 0.5                               | 2         | 36             | 30              |
| HFIP (blank)  | 0                                   | 2         | 2              | 0               |
| HFIP (blank)  | 0.5                                 | 0         | 15             | 6               |

\textsuperscript{a}With respect to H\textsubscript{2}O\textsubscript{2}, determined by GC (FID) against an internal standard.
### 4.4. Screening of catalysts and carboxylic acid for enantioselective hydroxylation

**Table S7.** Screening of catalysts and/or additives in the enantioselective hydroxylation of benzylic C–H bonds in TFE.

| Substrate | Products | Catalyst | RCO₂H | Product yields (%) | Hydroxylation selectivity (%) | ee (%) |
|-----------|----------|----------|-------|-------------------|-----------------------------|--------|
| ![Substrate](image.png) | ![Product](image.png) | ![Catalyst](image.png) | AcOH | ![Yield](image.png) | ![Selectivity](image.png) | ![ee](image.png) |
| ![Substrate](image.png) | ![Product](image.png) | ![Catalyst](image.png) | AcOH | ![Yield](image.png) | ![Selectivity](image.png) | ![ee](image.png) |
| ![Substrate](image.png) | ![Product](image.png) | ![Catalyst](image.png) | AcOH | ![Yield](image.png) | ![Selectivity](image.png) | ![ee](image.png) |
| ![Substrate](image.png) | ![Product](image.png) | ![Catalyst](image.png) | AcOH | ![Yield](image.png) | ![Selectivity](image.png) | ![ee](image.png) |

*S1* and *S2* were oxidized following the procedure reported in Section 4.1 for substrate 7.
Table S8. Comparison of the oxidation of propylbenzene (7) catalyzed by Mn(\textsuperscript{dMM}pdp) and Mn(\textsuperscript{Me2N}pdp) in MeCN, TFE and HFIP.

![Diagram of reaction](image)

| Catalyst     | Solvent | Product yields (%)\(^a\) | hydroxylation selectivity (%)\(^b\) | ee (%)\(^c\) |
|--------------|---------|--------------------------|-----------------------------------|-------------|
| Mn(\textsuperscript{dMM}pdp) | MeCN    | 7/26                     | 37                                | 39          |
|              | TFE     | 24/2                     | 96                                | 66          |
|              | HFIP    | 12/0.3                   | 99                                | 46          |
| Mn(\textsuperscript{Me2N}pdp) | MeCN    | 7/39                     | 26                                | 10          |
|              | TFE     | 44/7                     | 93                                | 60          |
|              | HFIP    | 12/1                     | 96                                | 40          |

\(^a\)Yields with respect to H\textsubscript{2}O\textsubscript{2}, determined by GC (FID) against an internal standard. Yields are calculated considering that 2 eq of H\textsubscript{2}O\textsubscript{2} are necessary for the formation of the ketone products. Yields of 7\texttext{a} and 7\texttext{b} calculated with the response factor of P\text{1a} and P\text{1b} (Table S7), respectively.  
\(^b\)100x([7\texttext{a}] / ([7\texttext{a}]+[7\texttext{b}])).  
\(^c\)ee of 7\texttext{a} determined by GC with a chiral stationary phase.
4.5. Intermolecular competition experiment

\[
\begin{align*}
\text{MeCN} & : 11\% & 18\%^a & 3\% & 38\% \\
\text{TFE} & : 40\% & 4\%^a & 11\% & 4\% \\
\text{HFIP} & : 41\% & 4\%^a & 10\% & 3\%
\end{align*}
\]

Scheme S2. Intermolecular competition experiment. Yields calculated with respect to H\textsubscript{2}O\textsubscript{2}, determined by GC (FID) against an internal standard. \textsuperscript{a}Yields shown below each of the products are calculated considering that 2 eq of H\textsubscript{2}O\textsubscript{2} are necessary for the formation of 3b.

4.6. Determination of kinetic isotopic effect (KIE)

- Procedure
A 0.05 M solution (2 mL) of each substrate and the pertinent complex (0.5 mM) was prepared in a vial (10 mL) equipped with a stirring bar using the desired solvent (MeCN, TFE or HFIP) and cooled at 0 °C in an ice bath. Acetic acid (2.0 equiv.) was added directly to the solution. Then hydrogen peroxide (0.5 equiv.) in the appropriate solvent was added by syringe pump over a period of 30 min. Afterwards, the solution was stirred for further 30 min. At this point, an internal standard was added and the solution was quickly filtered through a silica plug, which was subsequently rinsed with 2 x 1 mL AcOEt. GC analysis of the solution provided product yields relative to the internal standard.

\[
\begin{align*}
\text{MeCN: KIE}^a &= 3.8 \\
\text{HFIP: KIE}^a &= 3.3
\end{align*}
\]

Scheme S3. Determination of KIE. \textsuperscript{a}KIE = ([2a]+[2b])/ ([S3a]+[S3b]). [S3a] and [S3b] calculated with the response factor of 2a and 2b respectively.
4.7. Oxidation of alcohols with Mn(TIPS-mcp) in TFE

Scheme S4. Catalytic oxidation of alkanols in TFE.
4.8. GC-MS spectra

The diols 8b, 9c, 10b, 11b and 11c were identified through their molecular mass peak ascertained by GC-MS in the CI mode. The position of the hydroxyl groups along the chain were defined by analyzing the fragmentation pattern of the mass spectra recorded using the GC-MS in the EI mode.21

Figure S1. MS (EI) spectra of 8b (Cl: [8b + NH₄]⁺ m/z = 136.1)
Figure S2. MS (EI) spectra of 9c (Cl: [9c + NH₄]⁺ m/z = 134.1)

Figure S3. MS (EI) spectra of 10b (Cl: [10b + NH₄]⁺ m/z = 150.1)
Figure S4. MS (EI) spectra of 11b (Cl: [11b + NH₄]^+ m/z = 164.1)

Figure S5. MS (EI) spectra of 11c (Cl: [11c + NH₄]^+ m/z = 164.1)
5. Characterization of the isolated products

\[ \text{N-}(1\text{-hydroxy})\text{pentylacetamide (17a):} \]
Following the general conditions, the crude mixture was purified by flash chromatography over silica with hexane:ethyl acetate 1:1 and the product was concentrated to dryness. The product was isolated as a white solid (35% yield with Mn([\text{MM}])\text{dpd}) in MeCN and 16% yield with Mn([\text{TIPS}])\text{mcp} in HFIP). \(^1\text{H}-\text{NMR (CDCl}_3, 400 \text{ MHz, 300 K)} \) \(\delta\), ppm: 6.46 (d, \(J = 7.8 \text{ Hz, 1H}\)), 5.29 (td, \(J = 8.6, 4.5 \text{ Hz, 1H}\)), 4.34 (d, \(J = 3.5 \text{ Hz, 1H}\)), 2.00 (s, 3H), 1.74 \(-\) 1.62 (m, 1H), 1.62 \(-\) 1.50 (m, 1H), 1.46 \(-\) 1.26 (m, 4H), 0.97 \(-\) 0.85 (m, 3H). \(^{13}\text{C}-\text{NMR (CDCl}_3, 100 \text{ MHz, 300 K)} \) \(\delta\), ppm: 171.6, 74.3, 34.9, 27.0, 23.3. HRMS(ESI+) \(m/z\) calculated for C\(_{17}\)H\(_{33}\)NO\(_{2}\) [M+Na]\(^+\) 168.0995, found 168.0991.

\[ \text{N-}(4\text{-oxo})\text{pentylacetamide (17b):} \]
Following the general conditions, the crude mixture was purified by flash chromatography over silica with hexane:ethyl acetate 1:1 and the product was concentrated to dryness. The product was isolated as a white solid (51% yield). \(^1\text{H}-\text{NMR (CDCl}_3, 400 \text{ MHz, 300K)} \) \(\delta\), ppm: 5.93 (s, 1H), 3.28 \(-\) 3.18 (m, 2H), 2.52 (t, \(J = 6.9 \text{ Hz, 2H}\)), 2.16 (s, 3H), 1.97 (d, \(J = 4.5 \text{ Hz, 3H}\)), 1.79 (q, \(J = 6.9 \text{ Hz, 2H}\)). \(^{13}\text{C}-\text{NMR (CDCl}_3, 100 \text{ MHz, 300 K)} \) \(\delta\), ppm: 208.8, 170.3, 41.1, 39.2, 30.0, 23.3, 23.27. HRMS(ESI+) \(m/z\) calculated for C\(_{17}\)H\(_{23}\)NO\(_{2}\) [M+Na]\(^+\) 166.0838, found 166.0843.

\[ \text{N-1-(1-hydroxy-3-methylbutyl)acetamide (18a):} \]
Following the general conditions, the crude mixture was purified by flash chromatography over silica with hexane:ethyl acetate 1:4 and the product was concentrated to dryness. The product was isolated as a white solid (65% yield). \(^1\text{H}-\text{NMR (CDCl}_3, 400 \text{ MHz, 300K)} \) \(\delta\), ppm: 6.68 (d, \(J = 8.2 \text{ Hz, 1H}\)), 5.38 (td, \(J = 7.7, 5.9 \text{ Hz, 1H}\)), 4.64 (s, 1H), 1.97 (s, 3H), 1.81 \(-\) 1.66 (m, 1H), 1.57 (dt, \(J = 13.8, 7.1 \text{ Hz, 1H}\)), 1.43 \(-\) 1.33 (m, 1H), 0.91 (dd, \(J = 6.6, 2.8 \text{ Hz, 6H}\)). \(^{13}\text{C}-\text{NMR (CDCl}_3, 100 \text{ MHz, 300 K)} \) \(\delta\), ppm: 171.4, 72.6, 44.1, 29.7, 24.4, 23.3, 22.2. HRMS(ESI+) \(m/z\) calculated for C\(_{15}\)H\(_{35}\)NO\(_{2}\) [M+Na]\(^+\) 168.0995, found 168.0992.

\[ \text{N-}(3\text{-hydroxy})\text{pentylacetamide (18b):} \]
Following the general conditions, the crude mixture was purified by flash chromatography over silica with hexane:ethyl acetate 1:4 and the product was concentrated to dryness. The product was isolated as a white solid (62% yield). \(^1\text{H}-\text{NMR (CDCl}_3, 400 \text{ MHz,}

Following the general conditions, the crude mixture was purified by flash chromatography over silica with hexane:ethyl acetate 3:1 and the product was concentrated to dryness. The product was isolated as a pale yellow oil (46% yield). \[^1\text{H-}	ext{NMR}\ (\text{CDCl}_3, 400 \text{ MHz, 300 K}) \quad \delta, \text{ ppm: } 4.82 \ (s, 1H),
4.09 \ (s, 1H), 3.01 \ (s, 1H), 1.75 – 1.56 \ (m, 9H), 1.50 – 1.42 \ (m, 3H), 1.29 \ (s, 9H),
1.22 \ (s, 3H), 1.19 \ (s, 3H). \[^{13}\text{C-NMR}\ (\text{CDCl}_3, 100 \text{ MHz, 300 K}) \quad \delta, \text{ ppm: } 176.7, 70.6, 43.3, 38.9, 30.9, 29.9, 29.7, 28.6, 28.5, 26.2, 20.3, 19.1. \] HRMS(ESI+) \text{ m/z calculated for C}_{16}H_{31}NO_2 [\text{M+Na}^+] 292.2247, \text{ found 292.2242.}

Following the general conditions, the crude mixture was purified by flash chromatography over silica with ethyl acetate and the product was concentrated to dryness. The product was isolated as a white solid (44% yield). \[^1\text{H-}	ext{NMR}\ (\text{CDCl}_3, 400 \text{ MHz, 300 K}) \quad \delta, \text{ ppm: } 3.27 \ (dd, J = 8.6, 5.4
Hz, 2H), 2.81 \ (s, 3H), 2.38 \ (qd, J = 8.7, 4.9 Hz, 1H), 2.21 – 2.12 \ (m, 1H), 2.05 \ (d, J = 17.7 Hz, 1H),
1.87 \ (tt, J = 12.3, 5.2 Hz, 1H), 1.65 \ (dq, J = 12.7, 8.4 Hz, 1H), 1.58 – 1.37 \ (m, 3H), 1.20 \ (s, 3H),
1.19 \ (s, 3H). \[^{13}\text{C-NMR}\ (\text{CDCl}_3, 100 \text{ MHz, 300 K}) \quad \delta, \text{ ppm: } 176.8, 70.6, 47.7, 41.7, 40.9, 29.7, 29.4, 29.0, 26.2, 24.9. \] HRMS(ESI+) \text{ m/z calculated for C}_{16}H_{19}NO_2 [\text{M+Na}^+] 208.1308, \text{ found 208.1312.}

Following the general conditions, the crude mixture was purified by flash chromatography over silica with ethyl acetate and the product was concentrated to dryness. The product was isolated as a pale yellow oil (49% yield). \[^1\text{H-}	ext{NMR}\ (\text{CDCl}_3, 400 \text{ MHz, 300 K}) \quad \delta, \text{ ppm: } 3.27 \ (dd, J = 8.6, 5.4
Hz, 2H), 2.81 \ (s, 3H), 2.38 \ (qd, J = 8.7, 4.9 Hz, 1H), 2.21 – 2.12 \ (m, 1H), 2.05 \ (d, J = 17.7 Hz, 1H),
1.87 \ (tt, J = 12.3, 5.2 Hz, 1H), 1.65 \ (dq, J = 12.7, 8.4 Hz, 1H), 1.58 – 1.37 \ (m, 3H), 1.20 \ (s, 3H),
1.19 \ (s, 3H). \[^{13}\text{C-NMR}\ (\text{CDCl}_3, 100 \text{ MHz, 300 K}) \quad \delta, \text{ ppm: } 176.8, 70.6, 47.7, 41.7, 40.9, 29.7, 29.4, 29.0, 26.2, 24.9. \] HRMS(ESI+) \text{ m/z calculated for C}_{16}H_{19}NO_2 [\text{M+Na}^+] 208.1308, \text{ found 208.1312.}
5.1. $^1$H and $^{13}$C{$_1^H$} NMR spectra of substrates

Figure S6. $^1$H-NMR of 19 in CDCl$_3$

Figure S7. $^{13}$C{$_1^H$}-NMR of 19 in CDCl$_3$
5.2 $^1$H and $^{13}$C{$^1$H} NMR spectra of isolated products

![Figure S8. $^1$H-NMR of 17a in CDCl$_3$](image)

![Figure S9. $^{13}$C{$^1$H}-NMR of 17a in CDCl$_3$](image)
Figure S10. $^1$H-NMR of 17b in CDCl$_3$

Figure S11. $^{13}$C($^1$H)-NMR of 17b in CDCl$_3$
Figure S12. $^1$H-NMR of 18a in CDCl$_3$.

Figure S13. $^{13}$C[$^1$H]-NMR of 18a in CDCl$_3$. 
Figure S14. $^1$H-NMR of 18b in CDCl$_3$

Figure S15. $^{13}$C($^1$H)-NMR of 18b in CDCl$_3$
Figure S16. $^1$H-NMR of 20c in CDCl$_3$

Figure S17. $^{13}$C($^1$H)-NMR of 20c in CDCl$_3$
Figure S18. $^1$H-NMR of 19b in CDCl$_3$.

Figure S19. $^{13}$C($^1$H)-NMR of 19b in CDCl$_3$.
Figure S20. $^1$H-NMR of 21a in CDCl$_3$

Figure S21. $^{13}$C($^1$H)-NMR of 21a in CDCl$_3$
5.3 GC spectra of chiral products

The GC spectra of the racemic products were obtained by using the racemic Mn(dMM pdp) complex as catalyst in the oxidation of the corresponding substrates (Figures S22, S24 and S26). The representative GC spectra of chiral products shown in Figures S23, S25 and S27 were obtained using chiral Mn(dMM pdp) complex as catalysts using 2-ethylhexanoic acid (2-eha) as acid additive in TFE as solvent.

Figure S22. GC spectrum of racemic 1-phenylethanol (P1a)

Figure S23. GC spectrum of chiral 1-phenylethanol (P1a)
**Figure S24.** GC spectrum of racemic 4-methyl-1-phenylethanol (P2a)

**Figure S25.** GC spectrum of chiral 4-methyl-1-phenylethanol (P2a)
Figure S26. GC spectrum of racemic 1-phenyl-1-propanol (7a)

Figure S27. GC spectrum of chiral 1-phenyl-1-propanol (7a)
6. References

(1) Chen, M. S.; White, M. C. A Predictably Selective Aliphatic C – H Hydroxylation Reaction. *Science 2007*, *318*, 783-787.

(2) Costas, M.; Tipton, A. K.; Chen, K.; Jo, D.-H.; Que Jr., L. Modeling Rieske Dioxygenases. The First Example of Iron-Catalyzed Asymmetric cis-Dihydroxylation of Olefins. *J. Am. Chem. Soc. 2001*, *123*, 6722-6723.

(3) Cussó, O.; Garcia-Bosch, I.; Ribas, X.; Lloret-Fillol, J.; Costas, M. Asymmetric Epoxidation with H2O2 by Manipulating the Electronic Properties of Non-heme Iron Catalysts. *J. Am. Chem. Soc. 2013*, *135*, 14871-14878.

(4) Font, D.; Canta, M.; Milan, M.; Cussó, O.; Ribas, X.; Klein Gebbink, R. J. M.; Costas, M. Readily Accessible Bulky Iron Catalysts exhibiting Site Selectivity in the Oxidation of Steroidal Substrates. *Angew. Chem. Int. Ed. 2016*, *55*, 5776-5779.

(5) Murphy, A.; Dubois, G.; Stack, T. D. P. Efficient Epoxidation of Electron-Deficient Olefins with a Cationic Manganese Complex. *J. Am. Chem. Soc. 2003*, *125*, 5250-5251.

(6) Ottenbacher, R. V.; Bryliakov, K. P.; Talsi, E. P. Non-Heme Manganese Complexes Catalyzed Asymmetric Epoxidation of Olefins by Peracetic Acid and Hydrogen Peroxide. *Adv. Synth. Catal. 2011*, *353*, 885-889.

(7) Cussó, O.; Garcia-Bosch, I.; Font, D.; Ribas, X.; Lloret-Fillol, J.; Costas, M. Highly Stereoselective Epoxidation with H2O2 Catalyzed by Electron-Rich Aminopyridine Manganese Catalysts. *Org. Lett. 2013*, *15*, 6158-6161.

(8) Milan, M.; Bietti, M.; Costas, M. Highly Enantioselective Oxidation of Nonactivated Aliphatic C–H Bonds with Hydrogen Peroxide Catalyzed by Manganese Complexes. *ACS Cent. Sci. 2017*, *3*, 196-204.

(9) Deng, L.; Jacobsen, E. N. A practical, highly enantioselective synthesis of the taxol side chain via asymmetric catalysis. *The Journal of Organic Chemistry 1992*, *57*, 4320-4323.

(10) Nishimoto, Y.; Yasuda, M.; Baba, A. Coupling Reaction of Alkyl Chlorides with Silyl Enolates Catalyzed by Indium Trihalide. *Organic Letters 2009*, *9*, 4931-4934.

(11) Milan, M.; Carboni, G.; Salamone, M.; Costas, M.; Bietti, M. Tuning Selectivity in Aliphatic C–H Bond Oxidation of N-Alkylamides and Phthalimides Catalyzed by Manganese Complexes. *ACS Catalysis 2017*, *7*, 5903-5911.

(12) Nanjo, T.; de Lucca, E. C.; White, M. C. Remote, Late-Stage Oxidation of Aliphatic C–H Bonds in Amide-Containing Molecules. *Journal of the American Chemical Society 2017*, *139*, 14586-14591.

(13) Howell, J. M.; Feng, K. B.; Clark, J. R.; Trzepkowski, L. J.; White, M. C. Remote Oxidation of Aliphatic C–H Bonds in Nitrogen-Containing Molecules. *J. Am. Chem. Soc. 2015*, *137*, 14590-14593.

(14) Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. Total Synthesis of Vinblastine, Vincristine, Related Natural Products, and Key Structural Analogues. *Journal of the American Chemical Society 2009*, *131*, 4904-4916.

(15) Kim, H.; Lee, C. Nickel-Catalyzed Reductive Cyclization of Organohalides. *Organic Letters 2011*, *13*, 2050-2053.

(16) Abraham, R. J.; Mobli, M. *Modelling 1H NMR Spectra of Organic Compounds*; John Wiley & Sons: Wiltshire, 2008.

(17) Kamata, K.; Yonehara, K.; Nakagawa, Y.; Uehara, K.; Mizuno, N. Efficient stereo- and regioselective hydroxylation of alkanes catalysed by a bulky polyoxometalate. *Nat. Chem. 2010*, *2*, 478-483.

(18) Shiner, V. J.; Ensinger, M. W.; Kriz, G. S.; Halley, K. A. .tau.-Silicon stabilization of carbonium ions in solvolysis. 4. Solvolysis of cis- and trans-3-(trimethylsilyl)cyclohexyl and -3-tert-butylcyclohexyl p-bromobenzenesulfonates. *J. Org. Chem. 1990*, *55*, 653-661.

(19) Solladié-Cavallo, A.; Ahmed, B.; Schmitt, M.; Garin, F. Heterogeneous hydrogenation of 1-naphtol and 2-naphtol over Ru/Al2O3: a simple 1H NMR method for determination of the diastereoselectivity. *C. R. Chimie 2005*, *8*, 1975-1980.

(20) Gómez, L; Bioinspired iron and manganese catalysts for the effective and selective oxidation of alkanes and alkenes. *PhD thesis. University of Girona, 2010*.

(21) Horváth, G.; Kuszmann, J. The mass spectral fragmentation of 1,4-butandiol. *Org. Mass. Spectrom. 1977*, *12*, 45-50.
