Oxidation of *unactivated* and *isolated* C-H bonds

Literature Review
June 2011
Liz Rayment

Talk overview

1. Introduction

2. Biological inspiration to C-H activation

3. The Organic perspective – previous attempts to selectively activate C-H bonds

4. Chemistry of the White Group
    1. Aliphatic C-H oxidation reactions, hydoxylation reactions in complex molecule synthesis
    2. Methylene oxidation, selectivity results
    3. Biomimetic catalysis, hydoxylation/desaturation switches

5. Conclusion

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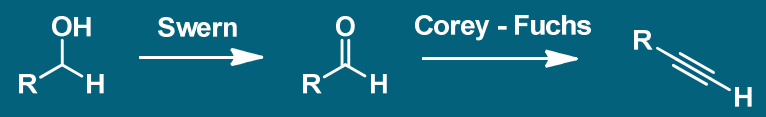
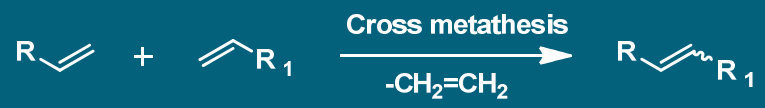
1. Introduction

How do we commonly prepare oxidized hydrocarbon centres?

- **Functional group interconversions**



- **C-C bond forming reactions of preoxidized fragments**



"With these reactions, modern synthetic planning often centres around the use of and maintenance of pre-existing oxidized functionality"[1]

1. Chen, M. S.; White, M. C.; *Science* **2007,** *318* (5851), 783-787.

1. Introduction

Is it possible to oxidise *unactivated* C-H bonds?

- **Advantages of the approach**

  "Streamlining synthesis" – C-H bonds remain unactivated and inert until selective oxidation, reducing inefficient chemical manipulations (protecting group chemistry).

- **Difficulties**

  Reactivity – How do you oxidise an inert C-H bond?
  Selectivity – How do you single out one unactivated C-H bond from many?

1. Chen, M. S.; White, M. C.; *Science* **2007,** *318* (5851), 783-787.

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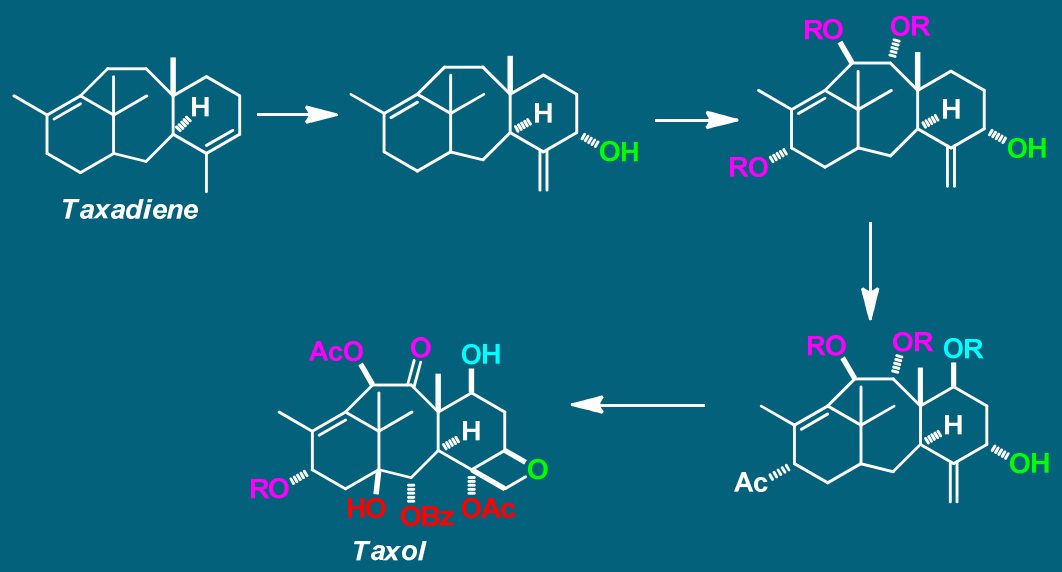
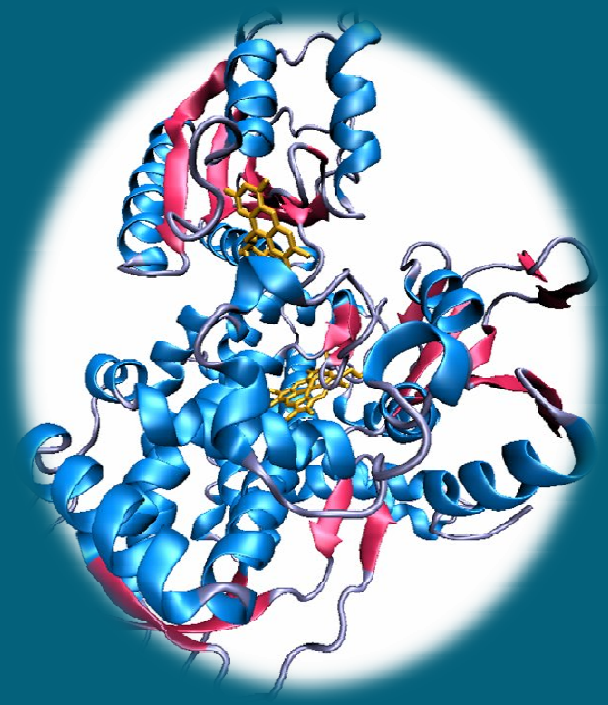
2. Biological inspiration to C-H activation

- Learning from nature
  - Nature is incredibly good at selecting and oxidising inert C-H bonds



Eight oxygen atoms are introduced to the scaffold by cytochrome P450 mono-oxygenases, which are further modified into carbonyl, ether or ester links. (The intermediates shown have been identified, but not all the responsible enzymes have been characterised).[1]



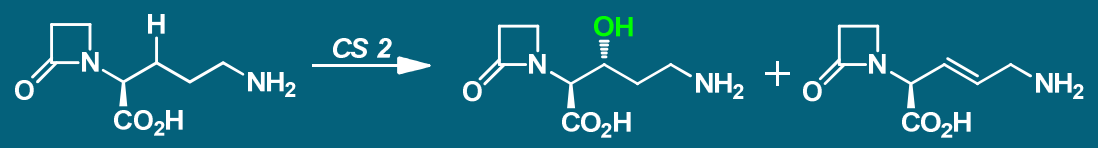
Monoxygenase P450 BM-3 from *Bacillus megaterium*[2]

1. Clardy, J.; Walsh, C., Lessons from natural molecules. *Nature* **2004,** *432* (7019), 829-837; 2. Nazor, J.; Schwaneberg, U., Laboratory Evolution of P450 BM-3 for Mediated Electron Transfer. *ChemBioChem* **2006,** *7* (4), 638-644.

2. Biological inspiration to C-H activation

•Chemical switches – natural enzymes can catalyse different forms of C-H oxidation depending only on the chemistry of the substrate

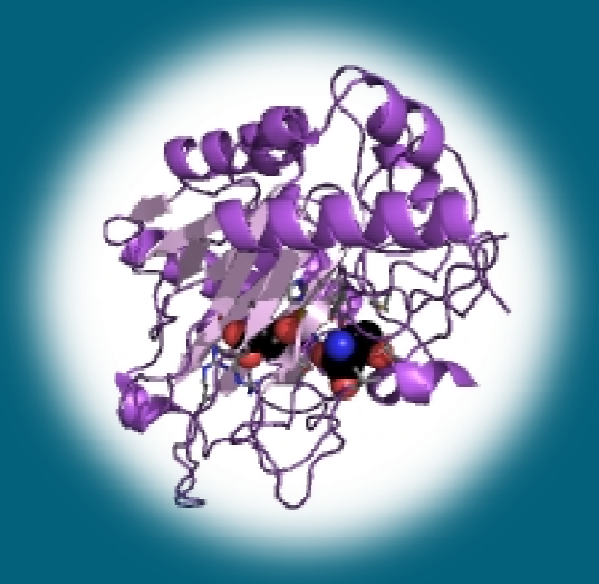
•CS 2 is an enzyme able to catalyze three different types of reaction from the same non-haem iron active site: hydroxylation, oxidative ring closure and desaturation, dependant upon substrate



Only hydroxylation observed for protected amine

•In the case of this proclavaminic substrate, the enzyme normally catalyzes hyroxylation α- to the carboxylate group, however, upon exposure of the free amine a mixture of hydroxylation and desaturation takes place

•One explanation for this selectivity involves the alignment of the C-H bond to the active iron site – a condition controlled by intramolecular ligation of other functional groups in the substrate



Clavaminate synthase 2

Zhou, J.; Kelly, W. L.; Bachmann, B. O.; Gunsior, M.; Townsend, C. A.; Solomon, E. I., Spectroscopic Studies of Substrate Interactions with Clavaminate Synthase 2, a Multifunctional α-KG-Dependent Non-Heme Iron Enzyme: Correlation with Mechanisms and Reactivities. *Journal of the American Chemical Society* **2001,** *123* (30), 7388-7398.

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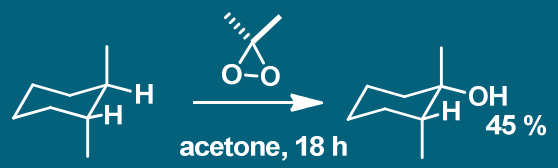
3. The Organic perspective – previous attempts to selectively activate C-H bonds

•Dioxiranes, O-atom insertion reagents [1-2]

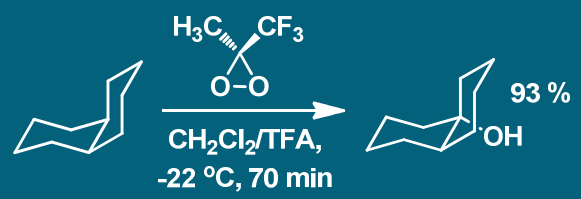
Dimethyldioxiranes[1]



+
+
–

Very early example of C-H bond activation
Stereospecific – equatorial alcohol product always preferred
Unstable stoichiometric reagent, can only be prepared in solution.

Methyl(trifluoromethyl)dioxirane[2]



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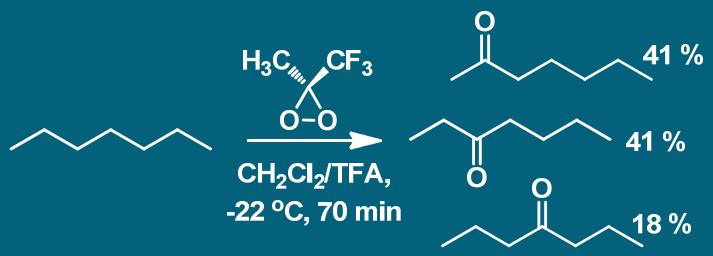


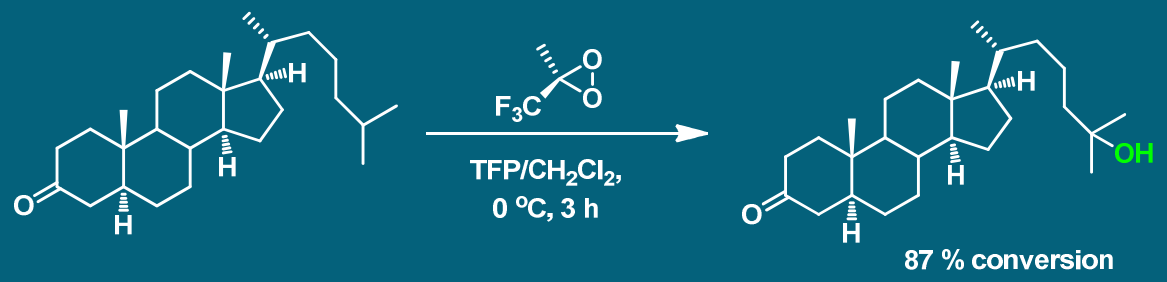
–

ca. 600 times more reactive than dimethyldioxirane
greater range of substrates tested, good selectivity observed for unsymmetrical compounds – strong preference for equatorial attack on ring systems
No selectivity in aliphatic systems

1. Murray, R. W.; Jeyaraman, R.; Mohan, L., Chemistry of dioxiranes. 4. Oxygen atom insertion into carbon-hydrogen bonds by dimethyldioxirane. *Journal of the American Chemical Society* **1986,** *108* (9), 2470-2472; 2. Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R., Oxidations by methyl(trifluoromethyl)dioxirane. 2. Oxyfunctionalization of saturated hydrocarbons. *Journal of the American Chemical Society* **1989,** *111* (17), 6749-6757.

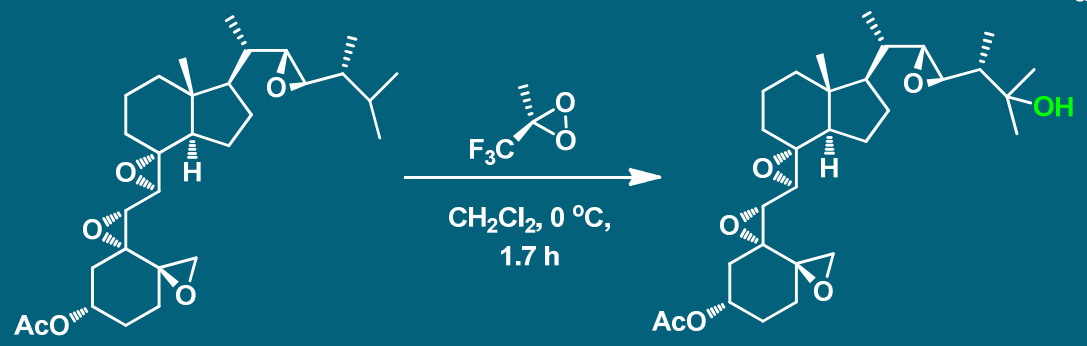
3. The Organic perspective – previous attempts to selectively activate C-H bonds

•Cholestane derivatives



•Some evidence that dioxiranes show preference for attack at 3° C-H bonds bearing geminal methyl groups (although this is also just the least sterically hindered 3° carbon you can find!)

•Vitamin D derivative, biomimetic reactivity



•These dioxiranes also commonly form epoxides from alkenes

Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T.; Curci, R.,*The Journal of Organic Chemistry* **1992,** *57* (7), 2182-2184. Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T.; Curci, R *The Journal of Organic Chemistry* **1992,** *57* (19), 5052-5054. Curci, R.; Detomaso, A.; Lattanzio, M. E.; Carpenter, G. B. *Journal of the American Chemical Society* **1996,** *118* (45), 11089-11092. Curci, R.; D'Accolti, L.; Fusco, C., *Accounts of Chemical Research* **2005,** *39* (1), 1-9.

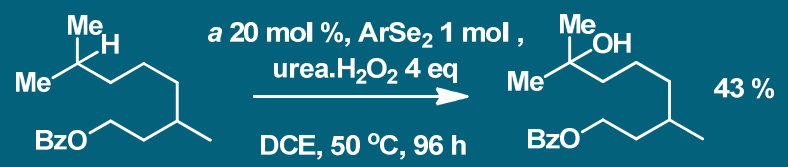
3. The Organic perspective – previous attempts to selectively activate C-H bonds

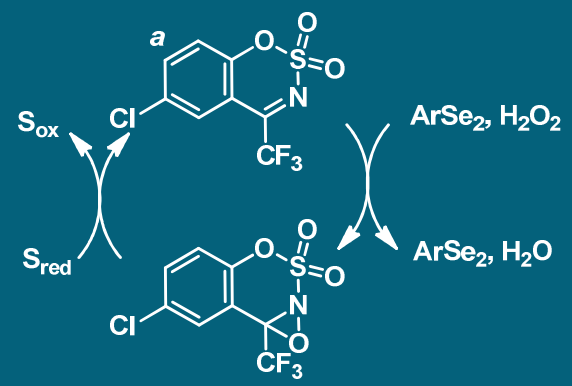
•Oxaziridines

Perfluorodialkyloxaziridines[1]

+ Oxaziridine far more stable than dioxirane analogues
– Substrates as before, no new selectivity

Catalytic hydroxylation of 3° C-H bonds[2]



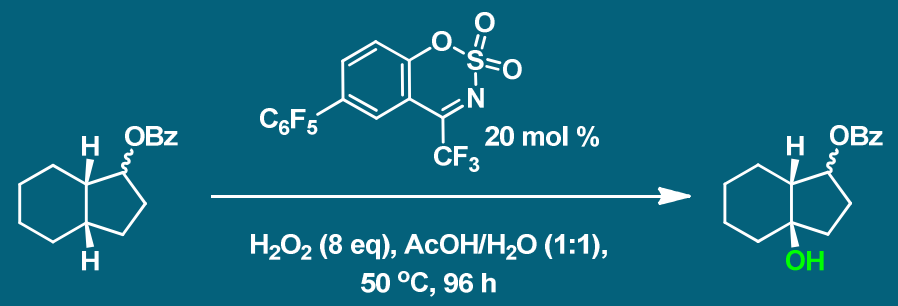


+ Strained heterocycle oxaziridines easy to prepare, and could perform oxidation under catalytic conditions with $ArSe_2$ and H_2O_2 co-catalyst.
+ As above, a stereospecific reaction; evidence for concerted oxaziridine *O*-atom transfer
– Limited to 3° C-H bonds, although selectivity between them observed.

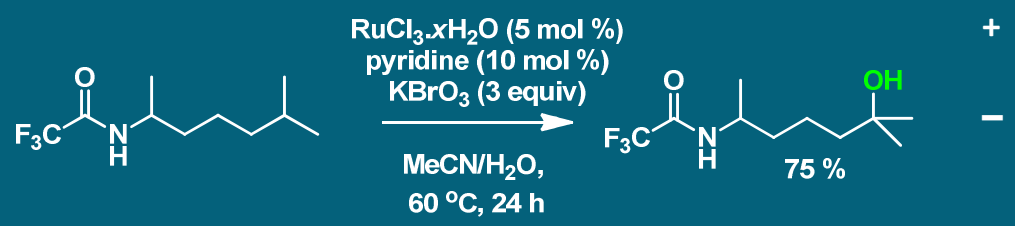
1. DesMarteau, D. D.; Donadelli, A.; Montanari, V.; Petrov, V. A.; Resnati, G., Mild and selective oxyfunctionalization of hydrocarbons by perfluorodialkyloxaziridines. *Journal of the American Chemical Society* **1993,** *115* (11), 4897-4898. 2. Brodsky, B. H.; Du Bois, J., Oxaziridine-Mediated Catalytic Hydroxylation of Unactivated 3° C–H Bonds Using Hydrogen Peroxide. *Journal of the American Chemical Society* **2005,** *127* (44), 15391-15393.

3. The Organic perspective – previous attempts to selectively activate C-H bonds

Later work from the Du Bois group differentiated between 3° bonds by varying the electronic environment of the C-H bond[1]



•More recently they have developed a Ruthenium catalytic C-H hydroxylation

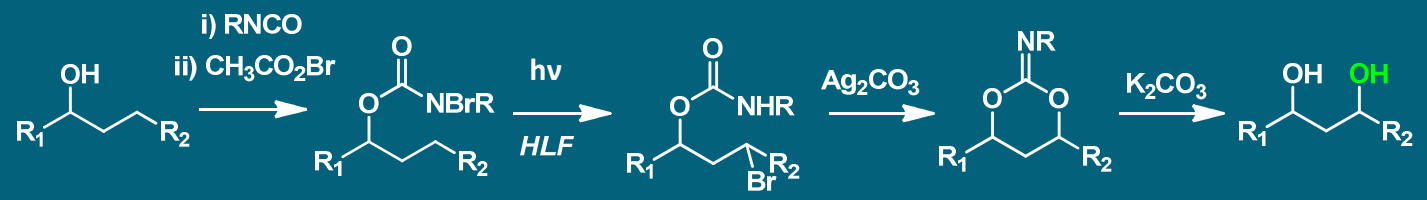


catalytic system over decent range of substrates
selective for 3° C-H bonds only, no example of differentiation between 3° bonds

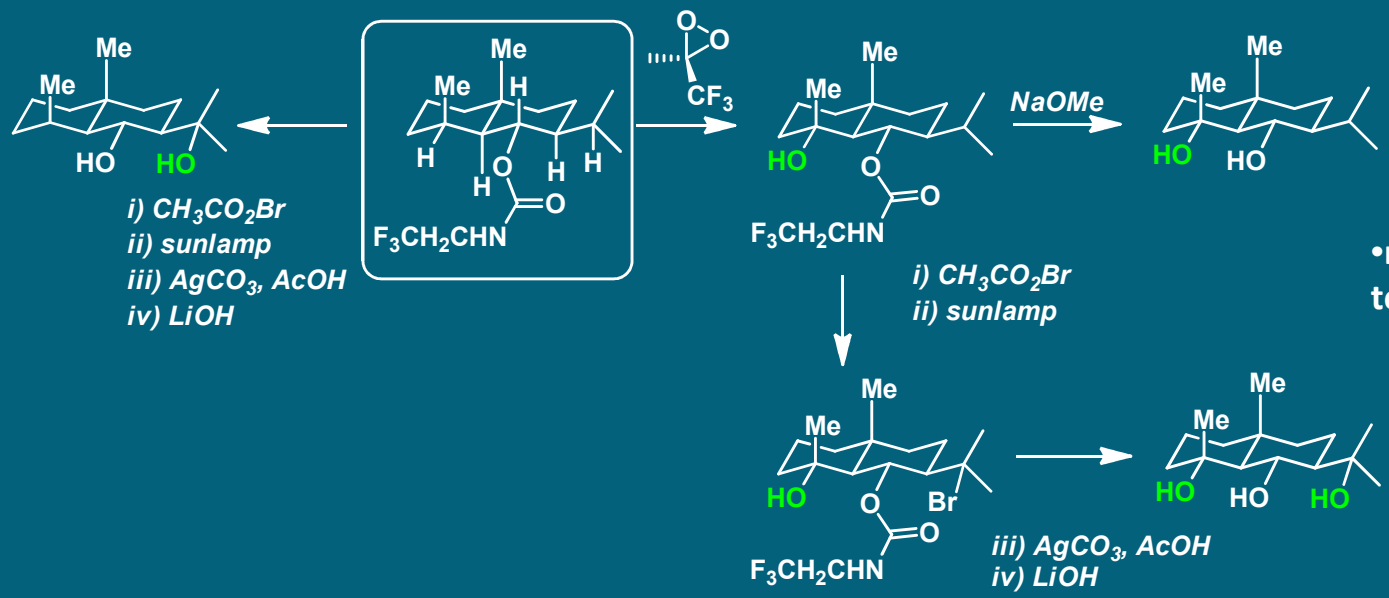
1. Litvinas, N. D.; Brodsky, B. H.; Du Bois, J., CH Hydroxylation Using a Heterocyclic Catalyst and Aqueous H2O2. *Angewandte Chemie International Edition* **2009,** *48* (25), 4513-4516. McNeill, E.; Bois, J. D., Ruthenium-Catalyzed Hydroxylation of Unactivated Tertiary C–H Bonds. *Journal of the American Chemical Society* **2010,** *132* (29), 10202-10204.

3. The Organic perspective – previous attempts to selectively activate C-H bonds

- **Baran group chemsitry – doesn't quite qualify (arguably activated C-H bonds, or multi-step intramolecular activation) but worth a mention**
- **Stoichiometric multi-step Hoffman Loffler Freytag based C-H activation – doesn't really compete**



- **But nice total synthesis using this CH activation and Curci chem**

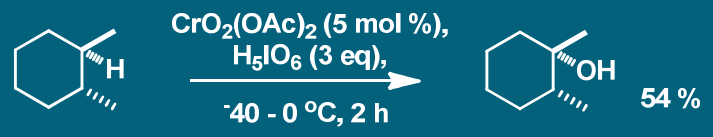


- **multiple eudesemane terpene syntheses**

Chen, K.; Eschenmoser, A.; Baran, P. S., Strain Release in CH Bond Activation? *Angewandte Chemie International Edition* **2009,** *48* (51), 9705-9708. Chen, K.; Richter, J. M.; Baran, P. S., 1,3-Diol Synthesis via Controlled, Radical-Mediated C–H Functionalization. *Journal of the American Chemical Society* **2008,** *130* (23), 7247-7249. Chen, K.; Baran, P. S., Total synthesis of eudesmane terpenes by site-selective C-H oxidations. *Nature* **2009,** *459* (7248), 824-828;

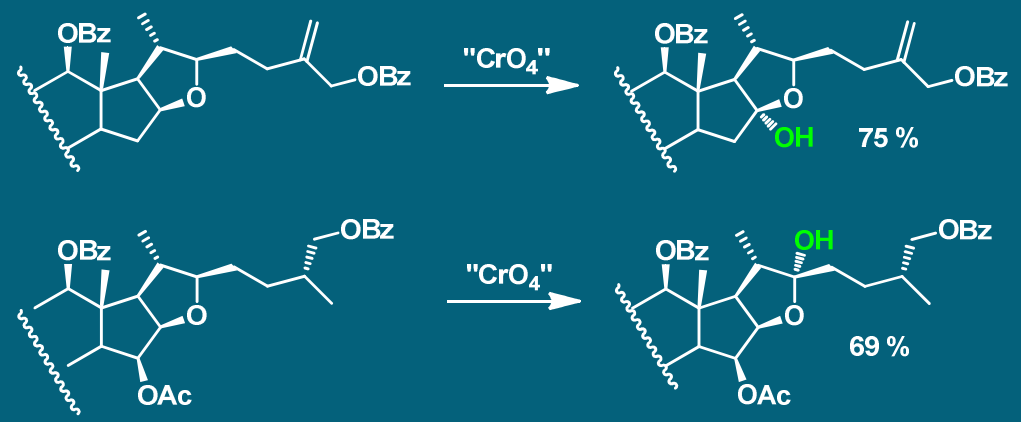
3. The Organic perspective – previous attempts to selectively activate C-H bonds

•Chromium (VI) catalysed hydroxylation of C-H bonds at $^{-}40$ °C[1]

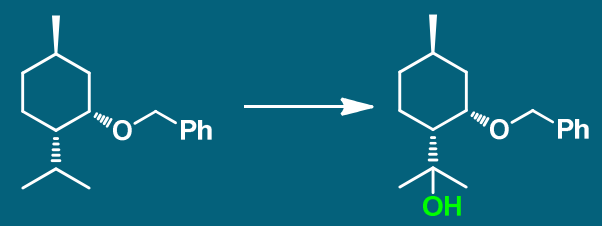


+ Stereospecific reaction – retention of stereochemistry
– Mainly given examples of 3° C-H bond oxidation
– Simple range of substrates – no examples of selectivity between 3° C-H bonds

•A later paper explored the oxidation of many steroid derivatives, at 3° alkoxy centres[2]



Their only example of an unactivated 3° C-H activation is selective over a *benzylic alkoxy* C-H bond



Selective C-H oxidation according to electronic factors

1.Lee, S.; Fuchs, P. L., Chemospecific Chromium[VI] Catalyzed Oxidation of C–H Bonds at –40 °C1. *Journal of the American Chemical Society* **2002,** *124* (47), 13978-13979.; 2. Lee, S.; Fuchs, P. L., An Efficient C–H Oxidation Protocol for α-Hydroxylation of Cyclic Steroidal Ethers. *Organic Letters* **2004,** *6* (9), 1437-1440.

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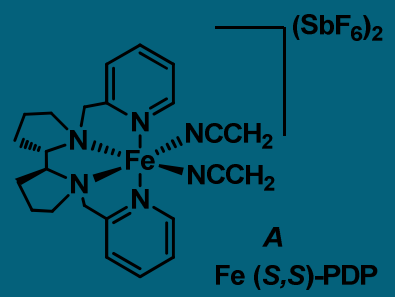
4. Chemistry of the White Group

1. Aliphatic C-H oxidation reactions, hydoxylation reactions in complex molecule synthesis

"The paradoxical challenge in solving this problem lies in discovering a catalyst that is both highly reactive and predictably selective for oxidising these inert and ubiquitous C-H bonds."[1]

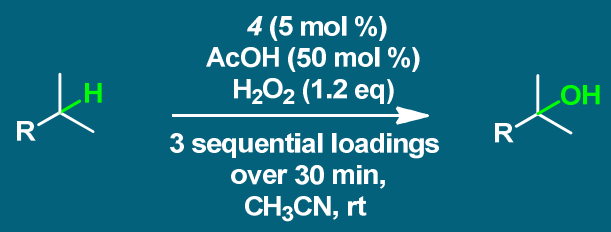
- **Non-haem iron complexes alongside inexpensive, enviromentaly friendly, H_2O_2, were identified as promising, selective catalysts for C-H hydroxylations**
- **Previous work on these compounds found unactivated sp^3 centres could be functionalised, however poor catalyst turnovers and selectivity limited the work[2]**

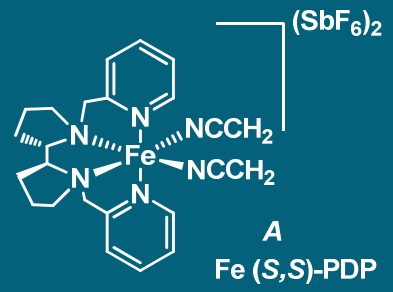


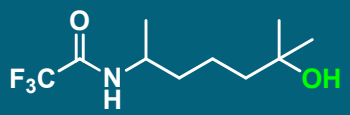
- **Electrophonic catalyst *A* was developed by the group**
- **Initially the catalyst had contained a mep ligand, but increasing the rigidity of the ligands drastically improved both the selectivity and yield of selective oxidations**
- **Acetic acid was also found to aid the catalytic turnover of the reaction**
- **Portionwise addition of catalyst, H_2O_2, and acetic acid produced the best yields**

1. Chen, M. S.; White, M. C.; *Science* **2007,** *318* (5851), 783-787; 2. a) Okuno, T.; Ito, S.; Ohba, S.; Nishida, Y., [small micro]-Oxo bridged diiron(III) complexes and hydrogen peroxide: oxygenation and catalase-like activities. *Journal of the Chemical Society, Dalton Transactions* **1997,** (19), 3547-3551. b) Company, A.; Gómez, L.; Fontrodona, X.; Ribas, X.; Costas, M., A Novel Platform for Modeling Oxidative Catalysis in Non-Heme Iron Oxygenases with Unprecedented Efficiency. *Chemistry – A European Journal* **2008,** *14* (19), 5727-5731.

Optimised conditions;



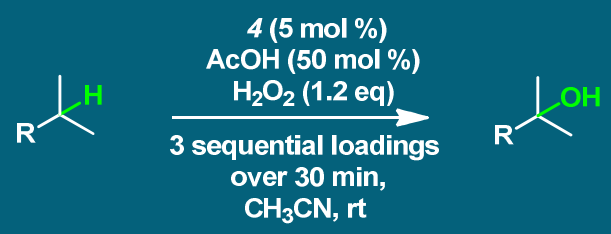


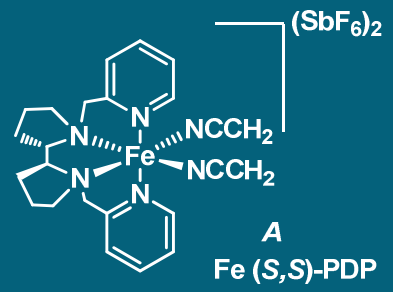
R	% Yield (rsm)
	46 (26)
	53 (43)
	60 (18)
	43 (33)
	52 (21)

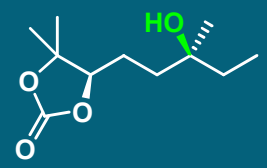
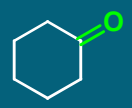
+ Hydroxylation occurs preferentially at 3° C-H bonds
+ Lewis basic groups tolerated (despite Lewis acidic catalyst)
– Similar to previous work

Chen, M. S.; White, M. C.; *Science* **2007,** *318* (5851), 783-787;

Optimised conditions;





R	% Yield (rsm)
	57 (27)
	92 (sm recycled 5 times)

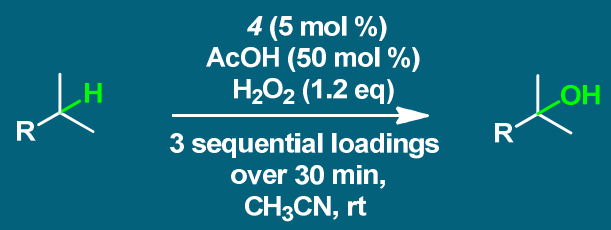
+ Retention of stereochemistry

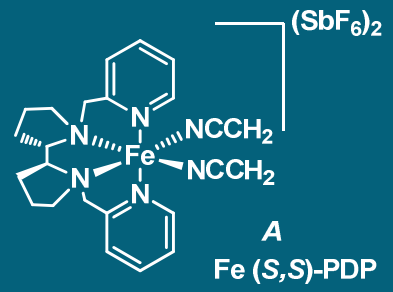
+ methylene hydrogens activated when no 3° C-H bonds present

– 2° alcohols oxidised to ketone under reaction conditions

Chen, M. S.; White, M. C.; *Science* **2007,** *318* (5851), 783-787;

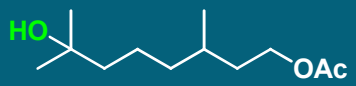
Optimised conditions;





But can the catalyst differentiate between multiple 3° C-H bonds?

Electronic selectivity?

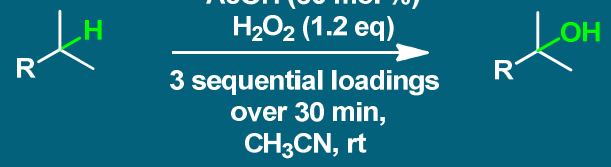
Major product	% Yield (rsm)	3° C-H bond selectivity
	48 (29)	1:1
	43 (35)	5:1
	39 (32)	6:1

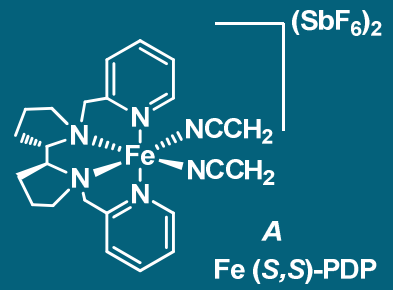
- No selectivity – indistinguishable 3° C-H bonds

- β – EWG deactivates the C-H bonds towards electrophilic catalyst attack – average selectivity

Chen, M. S.; White, M. C.; *Science* **2007,** *318* (5851), 783-787;

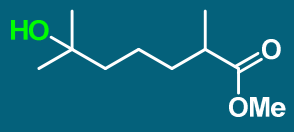
Optimised conditions;





But can the catalyst differentiate between multiple 3° C-H bonds?

Electronic selectivity?

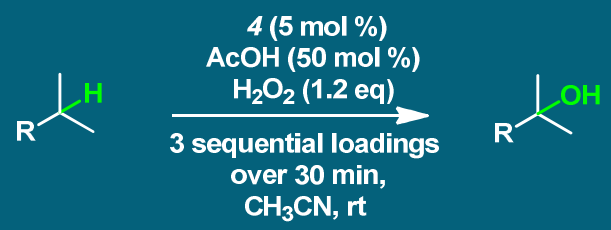
	% Yield (rsm)	3° C-H bond selectivity
	49 (21)	29:1
	48 (17)	20:1
	52 (18)	>99:1
	56 (32)	>99:1

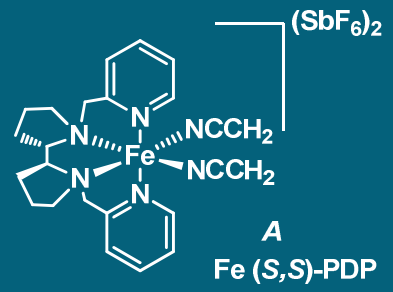
- α – EWG strongly deactivates C-H bonds towards electrophilic catalyst attack, good selectivity

- α – mesomerically EWG strongly deactivates C-H bonds towards electrophilic catalyst attack, complete selectivity!

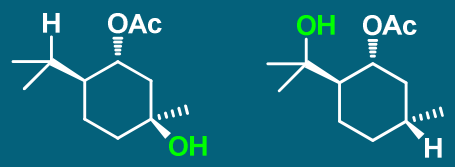
Chen, M. S.; White, M. C.; *Science* **2007**, *318* (5851), 783-787;

Optimised conditions;





But can the catalyst differentiate between multiple 3° C-H bonds?
Steric selectivity?

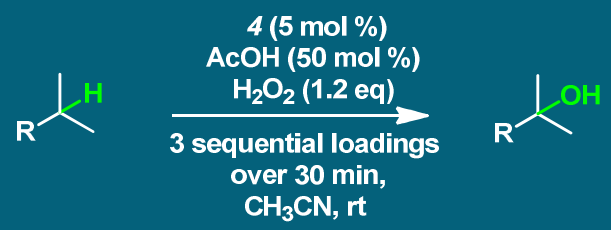


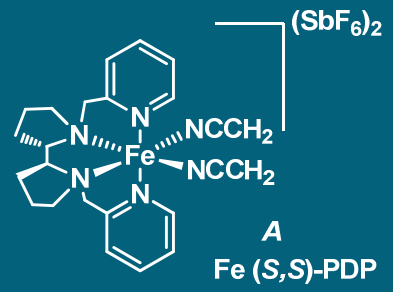
% Yield (rsm)	3° C-H bond selectivity
50 (11)	11:1

- Electronically similar C-H bonds (DFT calculations)
- C-H bond of the isopropyl group is directed towards the acetate group to relieve steric strain of the SM but decrease accessibility to the C-H bond.

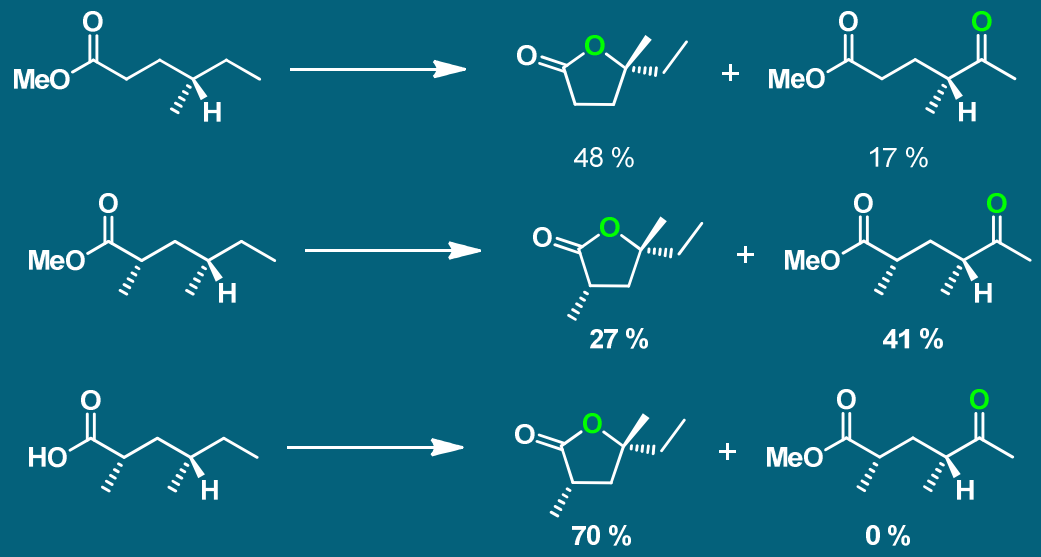
Chen, M. S.; White, M. C.; *Science* **2007,** *318* (5851), 783-787;

Optimised conditions;





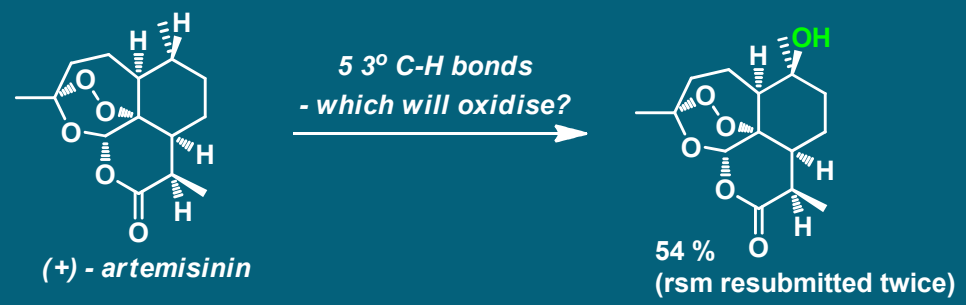
Sterics v electronics



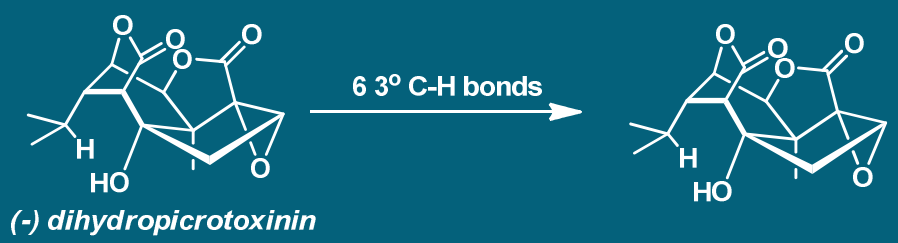
- 3° C-H bond selected
- Reversed selectivity -less hindered 2° C-H bond selected
- Directed attack – back to 3° C-H bond selection

Chen, M. S.; White, M. C.; *Science* **2007,** *318* (5851), 783-787;

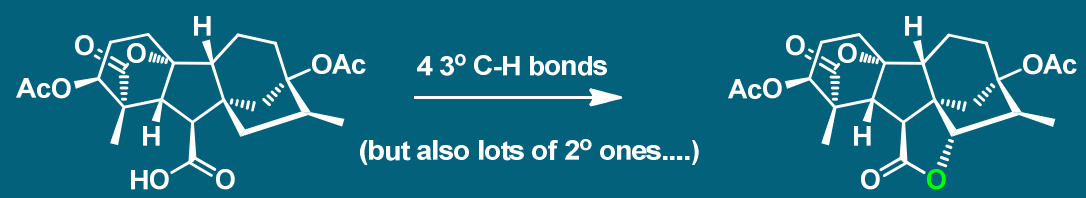
Complex molecule reactivity – predicting C-H activation



- The 4 remaining 3° C-H bonds were α- or β- to electron withdrawing groups, and on the crowded face of the compound
- Enzymatic equivalent – 4 days, 47 %!!



- No reaction!! X-ray structure reveals the only electron rich C-H bond is directed into the ring system, rendering it inaccessible to the catalyst



- Carboxylate directed activation on the closest C-H bond

Chen, M. S.; White, M. C.; *Science* **2007,** *318* (5851), 783-787;

Summary

- Tertiary bonds are electronically preferred over 2° bonds. Although they have an example of 2° preference due to steric hindrance of 3° centre
- Steric factors can direct selectivity between tertiary bonds
- Directing groups can overide steric factors to select the site of hydroxylation

Chen, M. S.; White, M. C.; *Science* **2007,** *318* (5851), 783-787;

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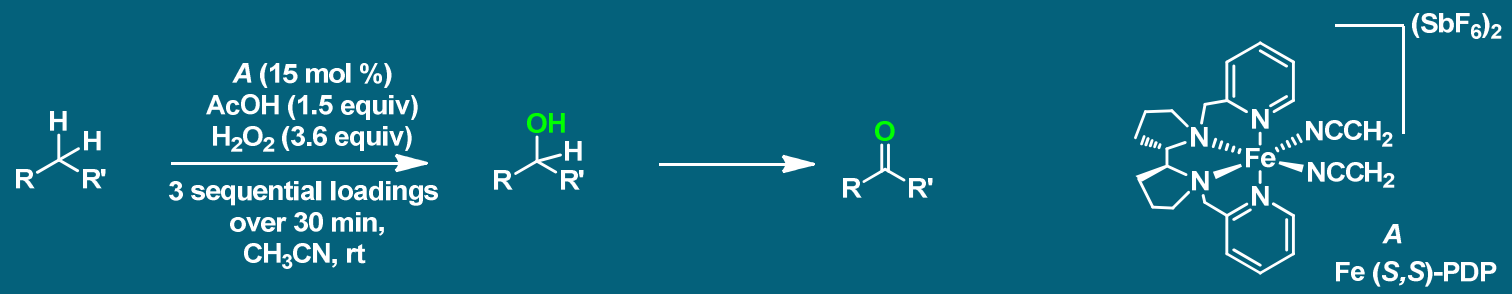
5. Conclusion

"Methylene (seondary) C-H bonds are ubiquitous in organic structures and are often viewed by organic chemists as the inert scaffold upon which the traditional chemistry "reactive" functional groups is performed"

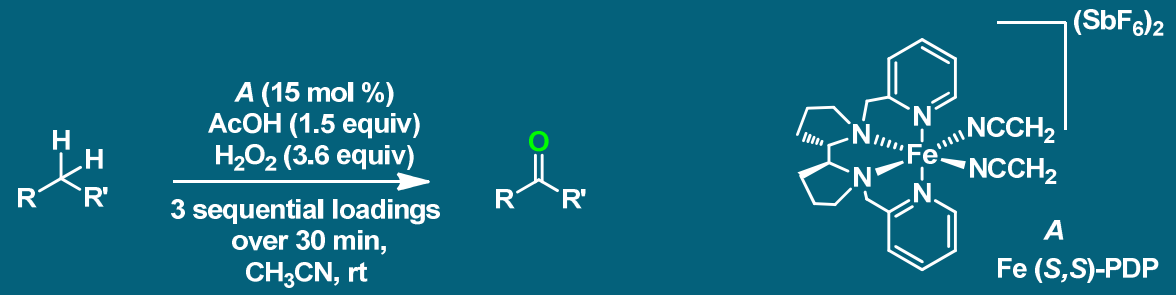
- Under the same conditions as previously reported, the non-haem iron catalyst will oxidise 2° C-H bonds. The product alcohol contains a highly activated 3° C-H bond which will oxidise to form a ketone

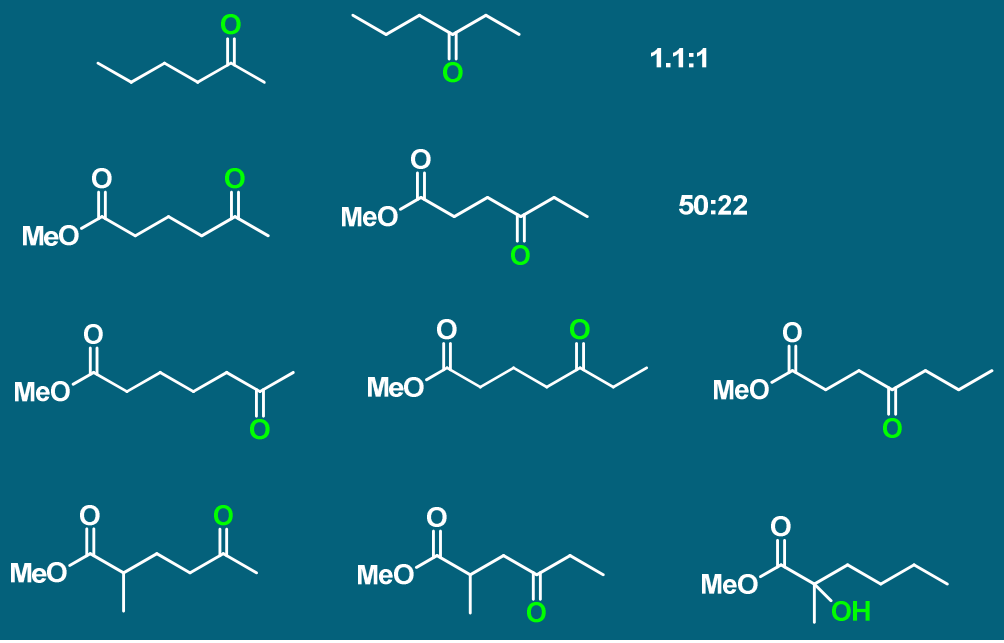


- The alcohol intermediate was only observed when the substrate was in excess

Chen, M. S.; White, M. C., Combined Effects on Selectivity in Fe-Catalyzed Methylene Oxidation. *Science* **2010**, *327* (5965), 566-571.

Further work with the catalyst *selectively* oxidised methylene C-H bonds



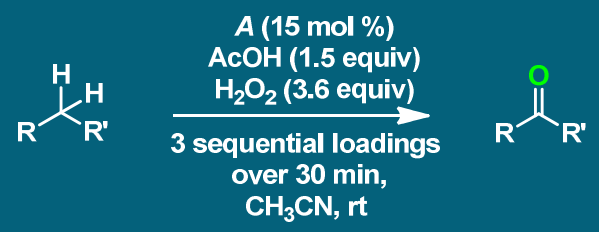


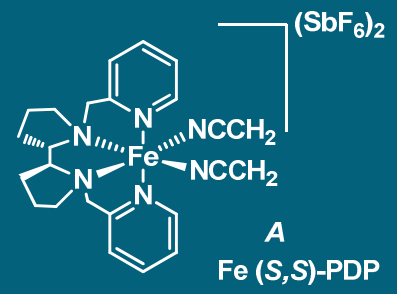
- No selectivity for aliphatic chains
- Upon introduction of an EWG, the proximal C-H bonds were suitably de-activated to allow for selective oxidation
- Oxidation of a 2° C-H bond was favoured over an α –EWG substitued 3° C-H bond

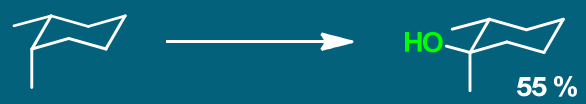
Chen, M. S.; White, M. C., Combined Effects on Selectivity in Fe-Catalyzed Methylene Oxidation. *Science* **2010**, *327* (5965), 566-571.

Further work with the catalyst selectively oxidised methylene C-H bonds

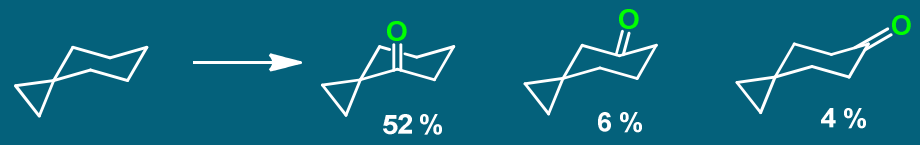
- Back to original iterative addition protocol



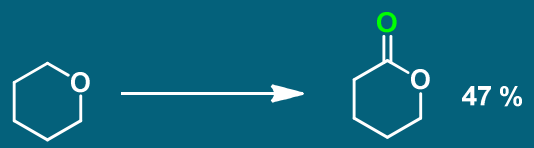




ketone products - 15 % combined

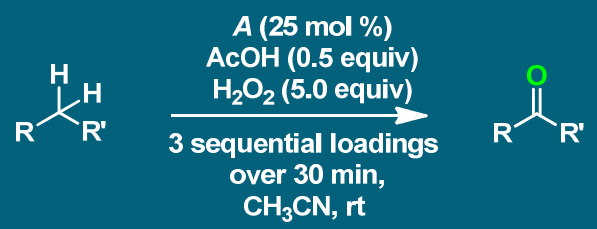


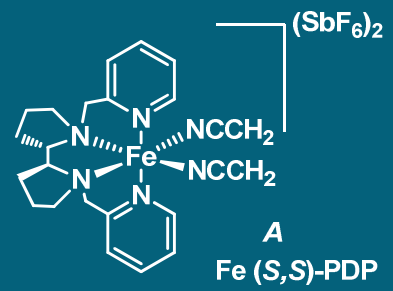
- Cyclic systems show the influence of sterics, hyperconjugation and C-H activation

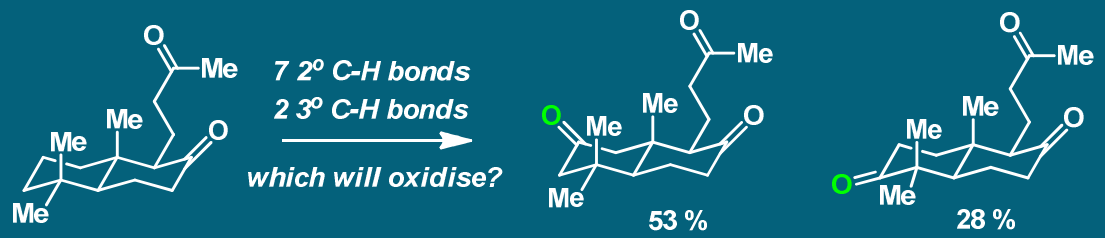


Chen, M. S.; White, M. C., Combined Effects on Selectivity in Fe-Catalyzed Methylene Oxidation. *Science* **2010**, *327* (5965), 566-571.

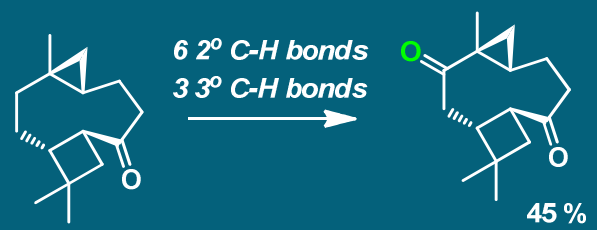
Further work with the catalyst selectively oxidised methylene C-H bonds







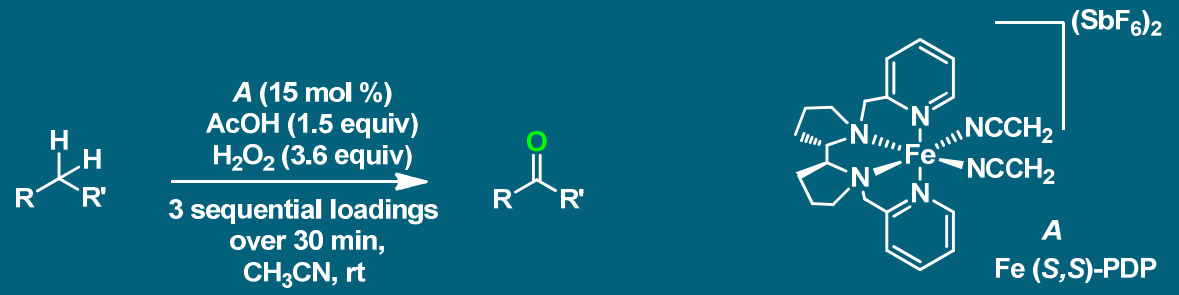
- 3° C-H bonds either stereoelectronically unfavoured, or α- to an EWG.
- Methylene C-H bond selected by a combination of electronic and steric factors

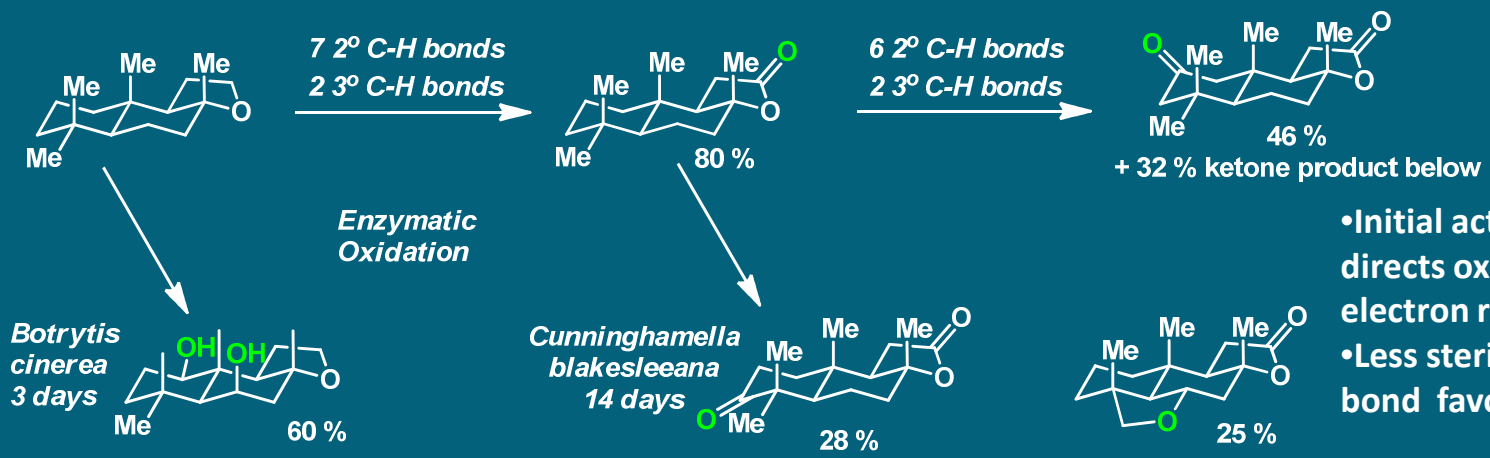


- 3° C-H bonds all sterically unfavoured
- Methylene C-H bond favoured due to cyclopropane hyperconjugation and remoteness to ketone moiety
- (*R,R*) catalyst produced the higher yield and selectivity shown

Chen, M. S.; White, M. C., Combined Effects on Selectivity in Fe-Catalyzed Methylene Oxidation. *Science* **2010**, *327* (5965), 566-571.

Further work with the catalyst selectively oxidised methylene C-H bonds





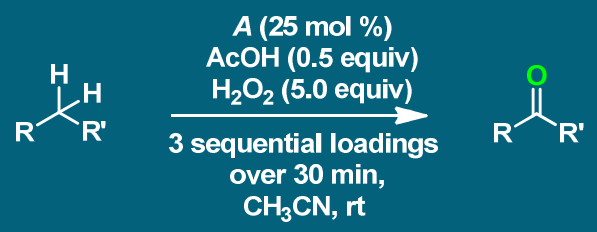
- Initial activated C-H bond then directs oxidation to the more electron rich ring
- Less sterically strained C-H bond favoured

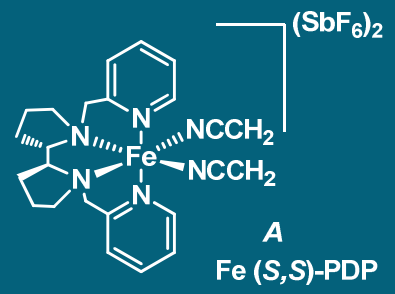
- These oxidations offer fast alternative and complementary oxidation system to enzymatic options.

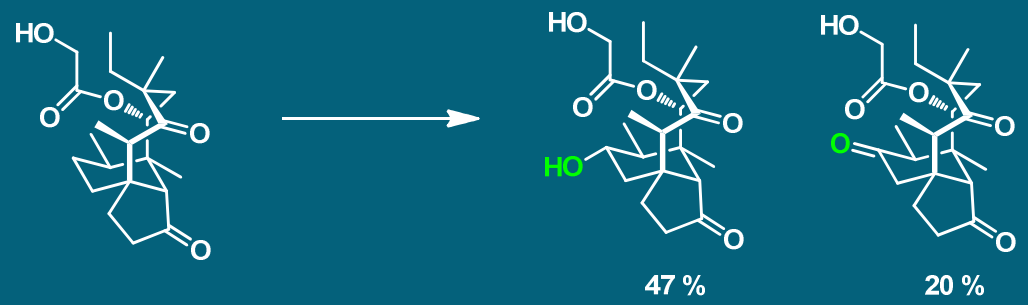
Chen, M. S.; White, M. C., Combined Effects on Selectivity in Fe-Catalyzed Methylene Oxidation. *Science* **2010**, *327* (5965), 566-571.

Further work with the catalyst selectively oxidised methylene C-H bonds

- Back to original iterative addition protocol







- Although the major product is highly activated towards a second oxidation, the site is so hindered that the alcohol product can be isolated

- The primary alcohol provides a methylene group also highly activated towards oxidation, but the α-ester group completely deactivates the site

- 3 3° C-H sites remain intact presumably due to steric hindrance

Chen, M. S.; White, M. C., Combined Effects on Selectivity in Fe-Catalyzed Methylene Oxidation. *Science* **2010**, *327* (5965), 566-571.

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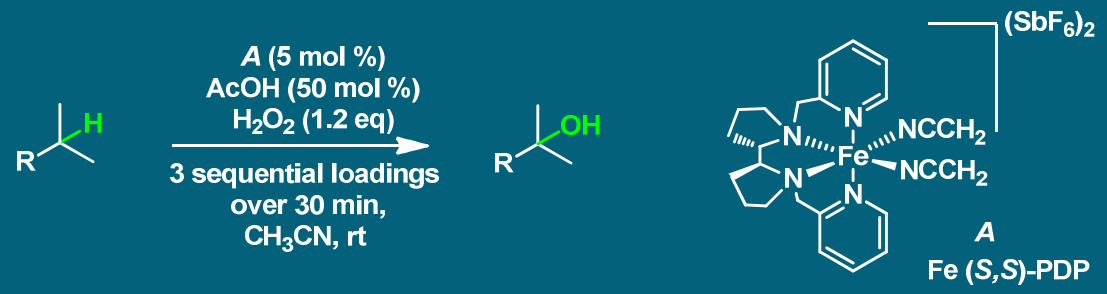
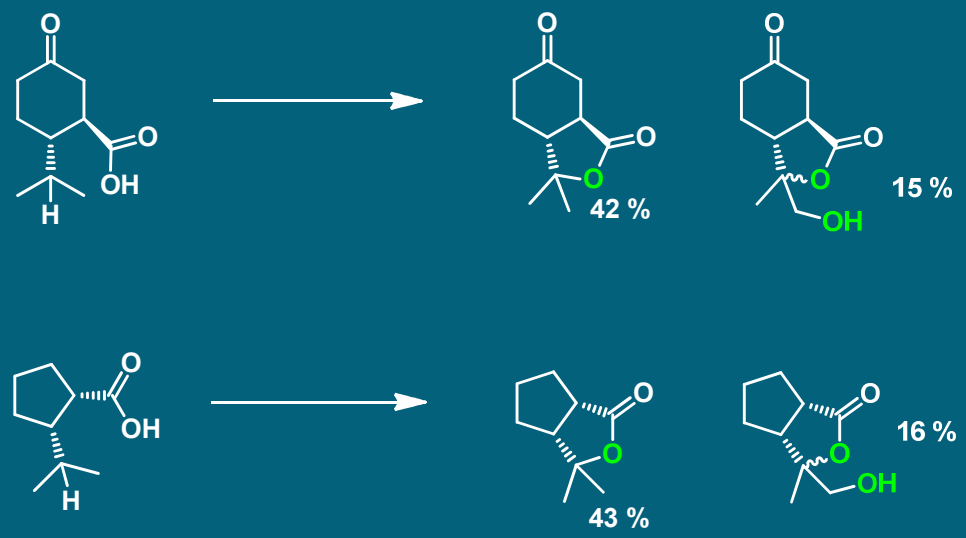
5. Conclusion

"A non-haem iron hydroxylase catalyst [Fe(PDP)] can also be divefted to catalytic, mixed hydroxylase/desaturase acvtivity with aliphatic C-H bonds"



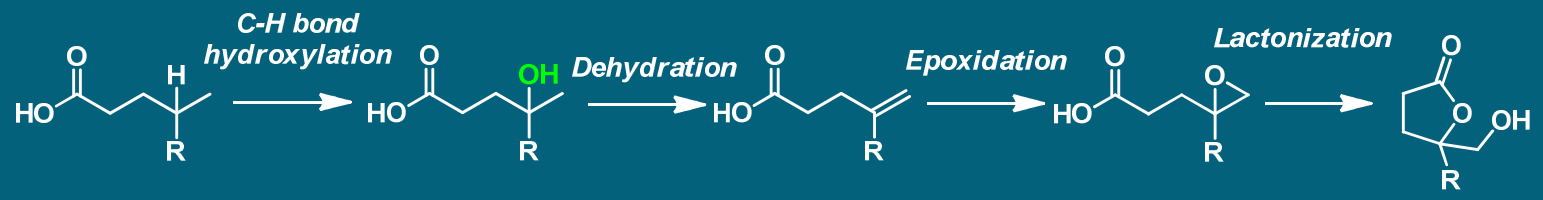


- During further investigations of carboxylate directed oxidations, unexpected products were observed

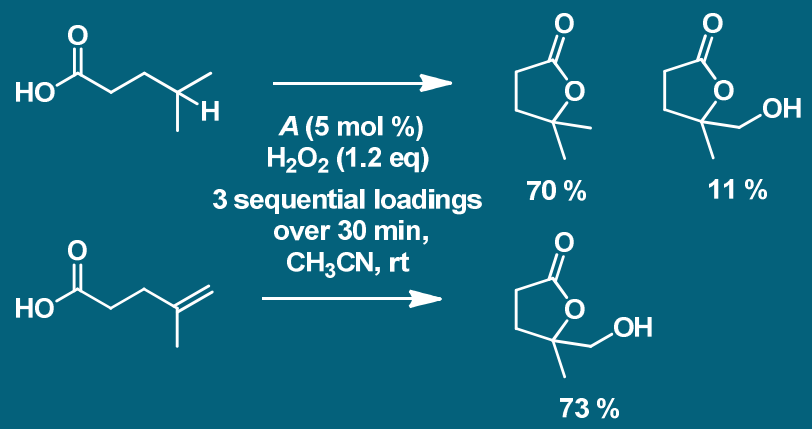
- It was not thought possible these "double oxidation" products were forming *via* a second selective C-H bond hydroxylation, these sites shoud be inert as 1° C-H bonds and α- to an EWG

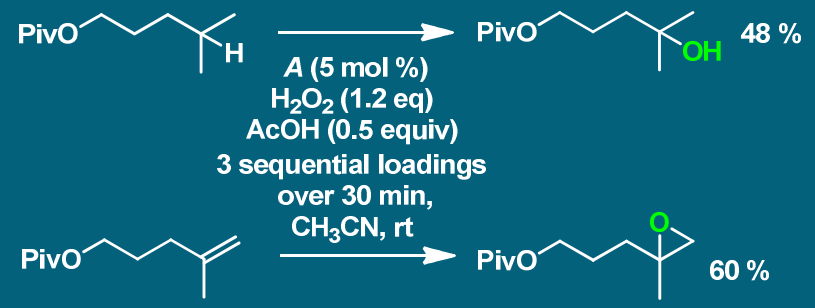
Bigi, M. A.; Reed, S. A.; White, M. C., Diverting non-haem iron catalysed aliphatic C–H hydroxylations towards desaturations. *Nat Chem* **2011,** *3* (3), 216-222.

Bigi *et al* postulated that these products were formed from olefins generated *in situ* by the Fe(PDP) catalyst through desaturation, epoxidation and lactonisation



The hypothesis was tested with simpler carboxylate substrates



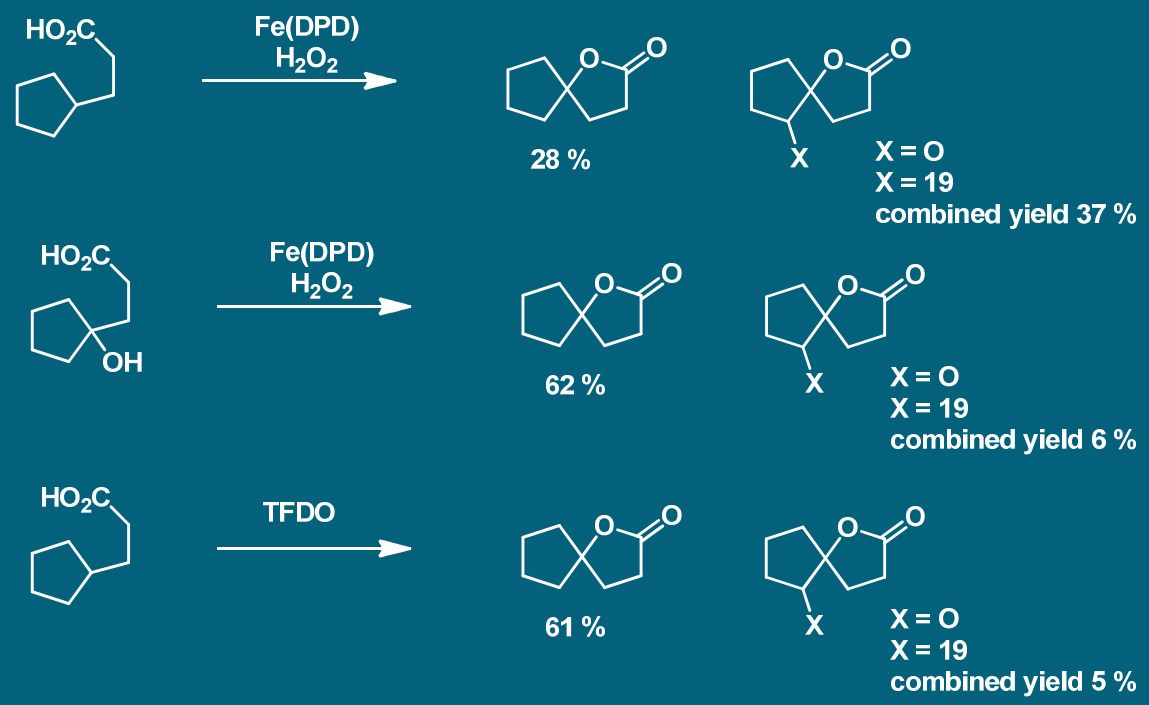


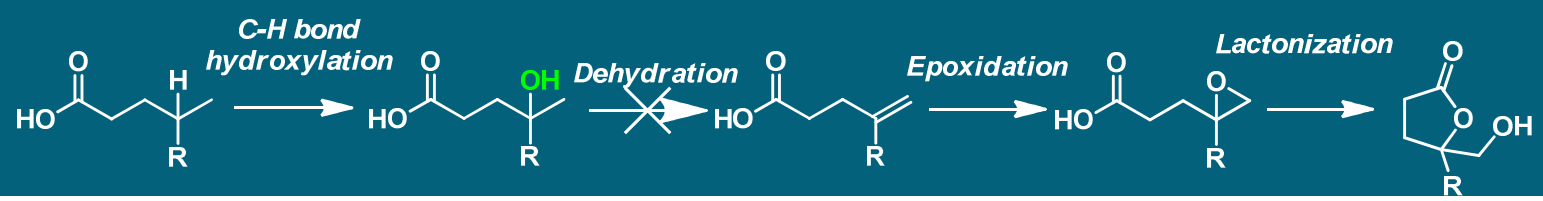
- Another "double oxidation" product
- Confirmation of alkene as viable intermediate to hydroxylactone

- Although epoxidation of alkene intermediate is proven possible, not epoxide observed, suggesting non-carboxylate substrates do not support desaturation.
- This substrate dependant oxygenase/desaturase acitivty is highly reminiscant of non-haem iron enzymes!

Bigi, M. A.; Reed, S. A.; White, M. C., Diverting non-haem iron catalysed aliphatic C–H hydroxylations towards desaturations. *Nat Chem* **2011**, *3* (3), 216-222.

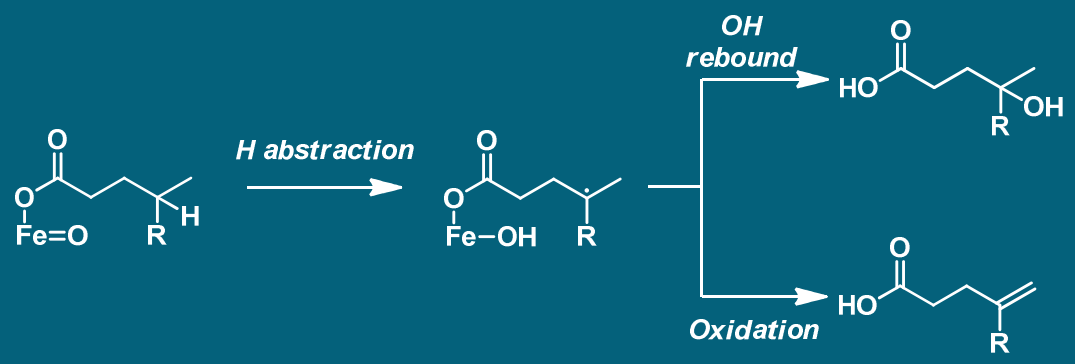
However, comparison with dioxiranes suggested desaturation was not occuring *via* dehydration of an alcohol intermediate





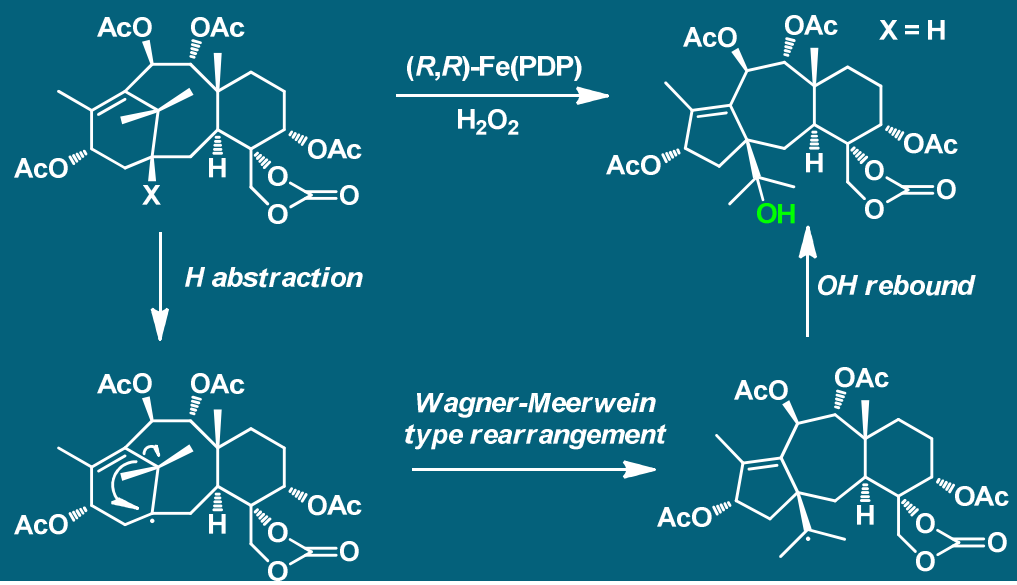
Bigi, M. A.; Reed, S. A.; White, M. C., Diverting non-haem iron catalysed aliphatic C–H hydroxylations towards desaturations. *Nat Chem* **2011,** *3* (3), 216-222.

•An alternative mechanism involves initial hydrogen abstraction, to form a radical intermediate which can transform to either hydroxylated or desaturated products



•Carbon centred radical intermediate can either pick up a hydroxyl group, or undergo further oxidation.

The presence of a radical intermediate was confirmed by submitting a taxane-based radical trap to the catalytic oxidation conditions



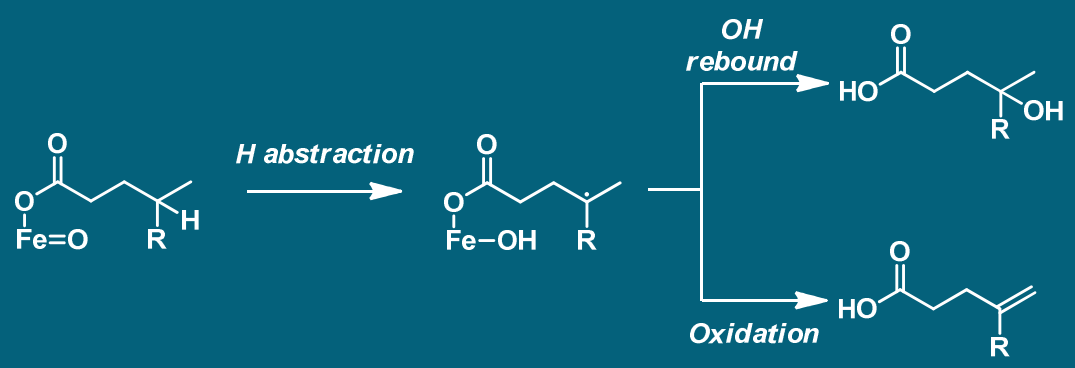
•Submitting substrate X = OH produced no products – ruling out C-H hydroxylation followed by a cationic rearrangement

Bigi, M. A.; Reed, S. A.; White, M. C., Diverting non-haem iron catalysed aliphatic C–H hydroxylations towards desaturations. *Nat Chem* **2011,** *3* (3), 216-222.

- These observations only prove a radical pathway exists for hydroxylation reactions, but the group favour the simple conclusion that both reactions occur *via* a common intermediate – the carbon based radical

- This reactivity takes us all the way back to the enzymatic systems seen earlier, providing further interest in the reactivity of this small molecule catalyst (a biomimetic system)

- Final question – what determines the end product of this carbon centred radical?



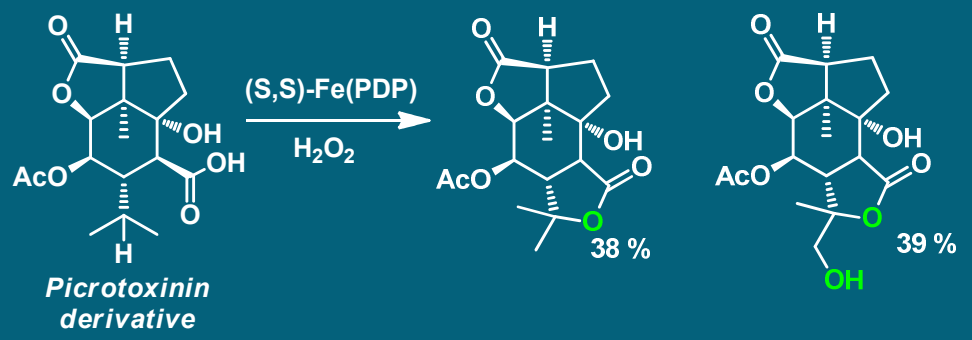
- Desaturation reactions are only observed when the carboxylate moeity creates an intramolcular like oxidation.

- The group suggest carboxylate ligation may change the orientation of the iron centre to the carbon radical and alter the rate of the OH rebound step

- A prolonged life of the radical may promote the dehydrogenative pathway

Bigi, M. A.; Reed, S. A.; White, M. C., Diverting non-haem iron catalysed aliphatic C–H hydroxylations towards desaturations. *Nat Chem* **2011,** *3* (3), 216-222.

•Finally, an example of the two pathways in complex molecule synthesis



- Electron rich, carboxylate directed, 3° C-H bond selected for oxidation
- Total oxidation 77%, and the products easily separable
- Treatment of substrate with methyl(trifluoromethyl)dioxirane affords no such products

•Summary

- The non-haem iron catalyst Fe(DPD) has shown further versatility by switching reaction catalyst upon changing substrate
- The mechanism has been proven to follow a radical pathway, and both products are believed to form *via* the same radical intermediate

Bigi, M. A.; Reed, S. A.; White, M. C., Diverting non-haem iron catalysed aliphatic C–H hydroxylations towards desaturations. *Nat Chem* **2011,** *3* (3), 216-222.

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Conclusion

- The white group have successfully realised a method of selectively oxidizing C-H bonds in simple and complex systems.

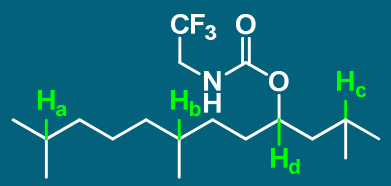
- Their complex molecule transformations have been both biomimetic and complementary to natural enzymes

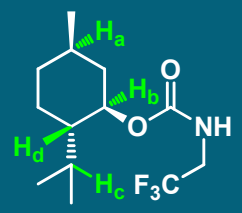
Future work

- They promise to explore other common functionalities which may switch catalytic activity as a carboxylate group has proven to and increase substrate scope of these reactions

Points for discussion

- Should the potential manipulation of “inert” C-H bonds change the way organic chemists approach synthesis? – Can atom economy excuse poor yields?
- Are protecting groups on the way out?!





Chen, K.; Richter, J. M.; Baran, P. S., 1,3-Diol Synthesis via Controlled, Radical-Mediated C–H Functionalization. *Journal of the American Chemical Society* **2008,** *130* (23), 7247-7249.

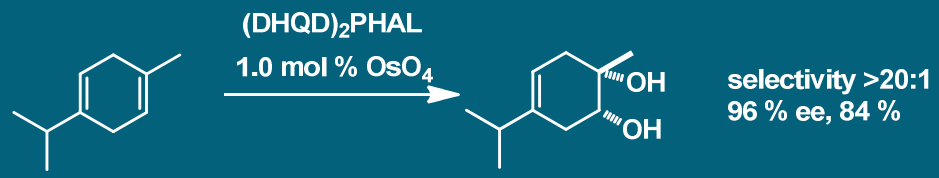
Site selective olefin oxidations – the extent of research on olefin oxidation chemistry has created a library of conditions which can selectively mono-dihydroxylate alkenes though electronics, sterics or directing groups.[1]

Electronic selectivity

- Osmylation of unsymmetrical polyenes preferentially occurs at the more electron rich double bonds, conjugated or otherwise

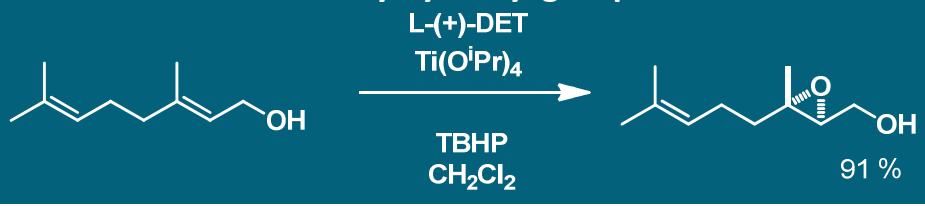
Steric selectivity

- Steric effects will control reactivity towards AD when alkenes are electronically similar



Directed reactivity

- Olefins can be differentiated in AE reactions by hydroxyl groups[2]



1. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B., Catalytic Asymmetric Dihydroxylation. *Chemical Reviews* **1994,** *94* (8), 2483-2547; 2. Hanson, R. M.; Sharpless, K. B., Procedure for the catalytic asymmetric epoxidation of allylic alcohols in the presence of molecular sieves. *The Journal of Organic Chemistry* **1986,** *51* (10), 1922-1925.

- **Enzymes are constructed to select very specific chemical structures into their active site, inherently limiting the generality of these approaches**
  - **Some attempts to mimic oxygenase activity have been successful[1];**

1. a) Yang, J.; Gabriele, B.; Belvedere, S.; Huang, Y.; Breslow, R., Catalytic Oxidations of Steroid Substrates by Artificial Cytochrome P-450 Enzymes†. *The Journal of Organic Chemistry* **2002,** *67* (15), 5057-5067; b) Mas-Ballesté, R.; Que, L., Targeting Specific C-H Bonds for Oxidation. *Science* **2006,** *312* (5782), 1885-1886; c) Das, S.; Incarvito, C. D.; Crabtree, R. H.; Brudvig, G. W., Molecular Recognition in the Selective Oxygenation of Saturated C-H Bonds by a Dimanganese Catalyst. *Science* **2006,** *312* (5782), 1941-1943.