

A Predictably Selective Aliphatic C-H Oxidation Reaction for Complex Molecule Synthesis

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TAMING THE FORCE OF OXIDATION

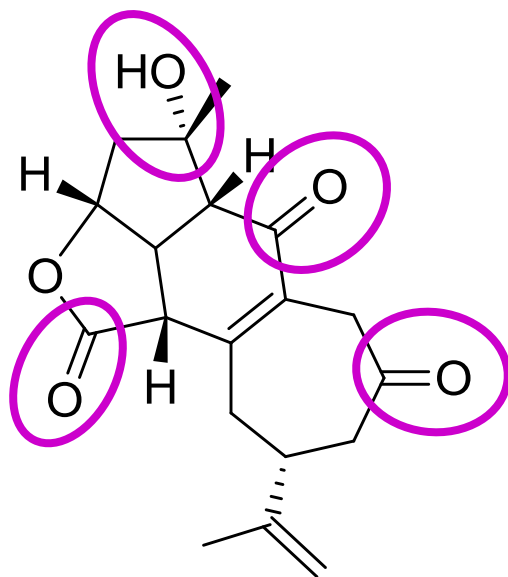
What are they trying to do?

- They are trying to find a small molecule catalyst that can oxidize sp^3 C-H bonds using a cheap oxidizing agent.
 - Optimize the metal
 - Optimize the oxidizing agent
 - Make selective

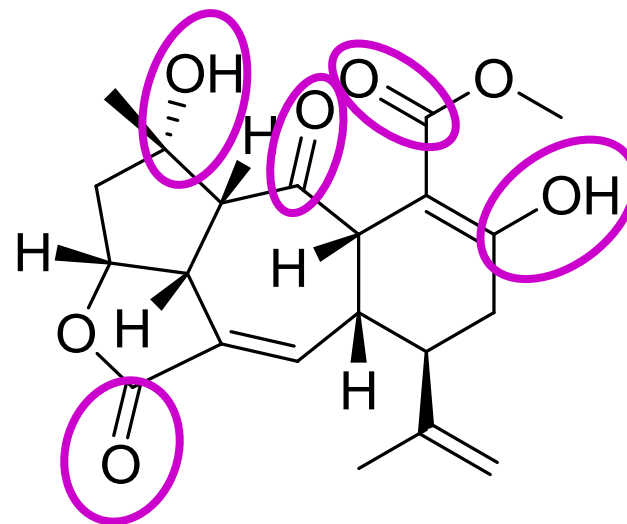
Why do we care?

- A lot of bio-active molecules have oxidized hydrocarbons
- Opportunity to install them at late phases in synthetic schemes
 - ▣ Less maintenance
- Selective reactivity

Bio-active Molecules



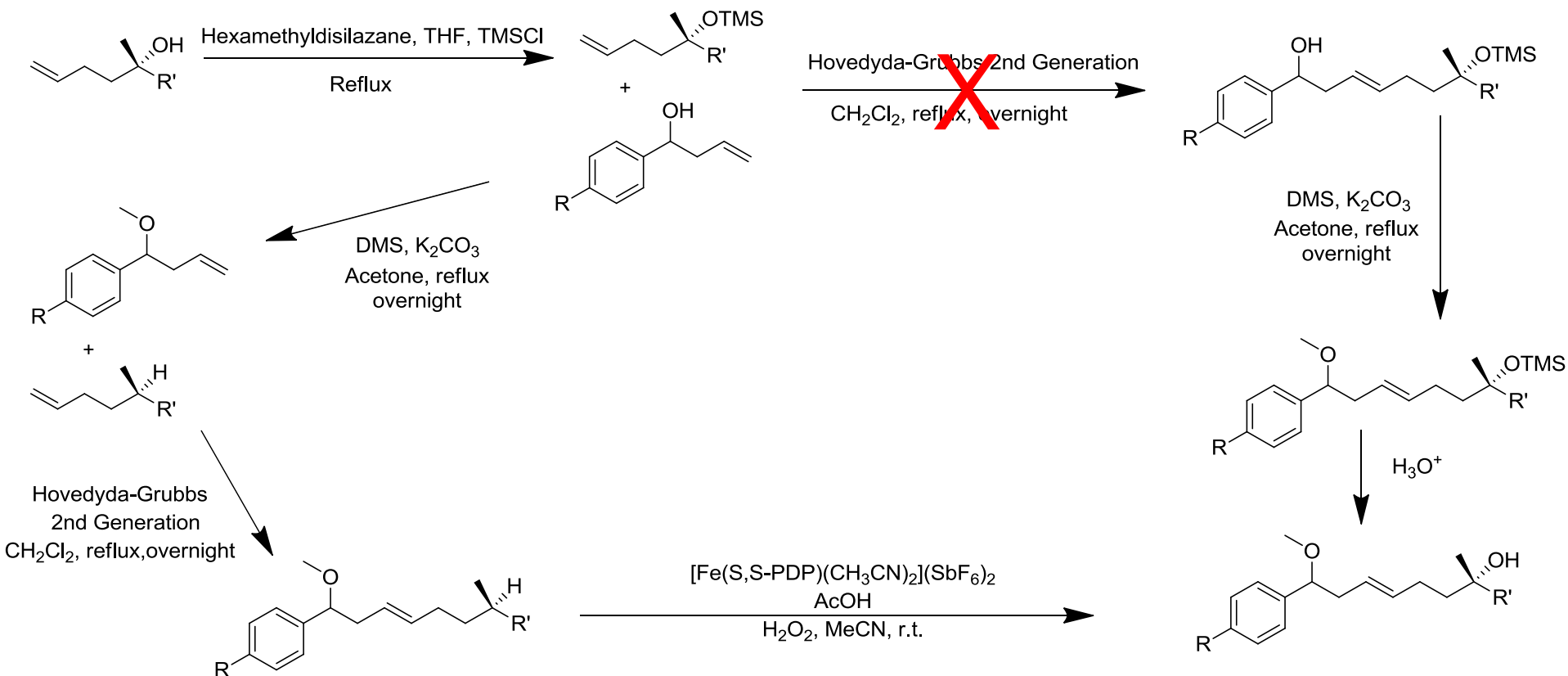
Scabrolide A



Rameswaralide

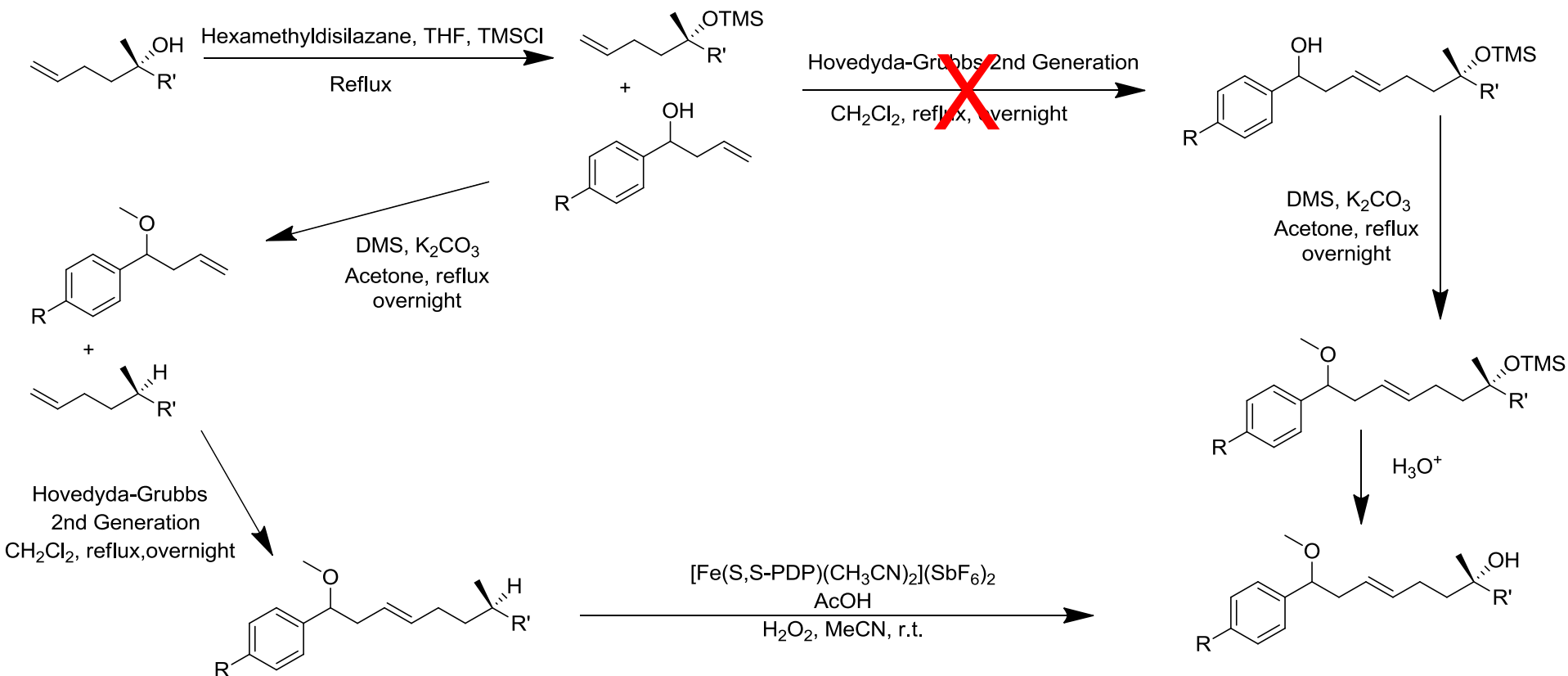
Previous Methods

□ Unproductive chemical manipulations



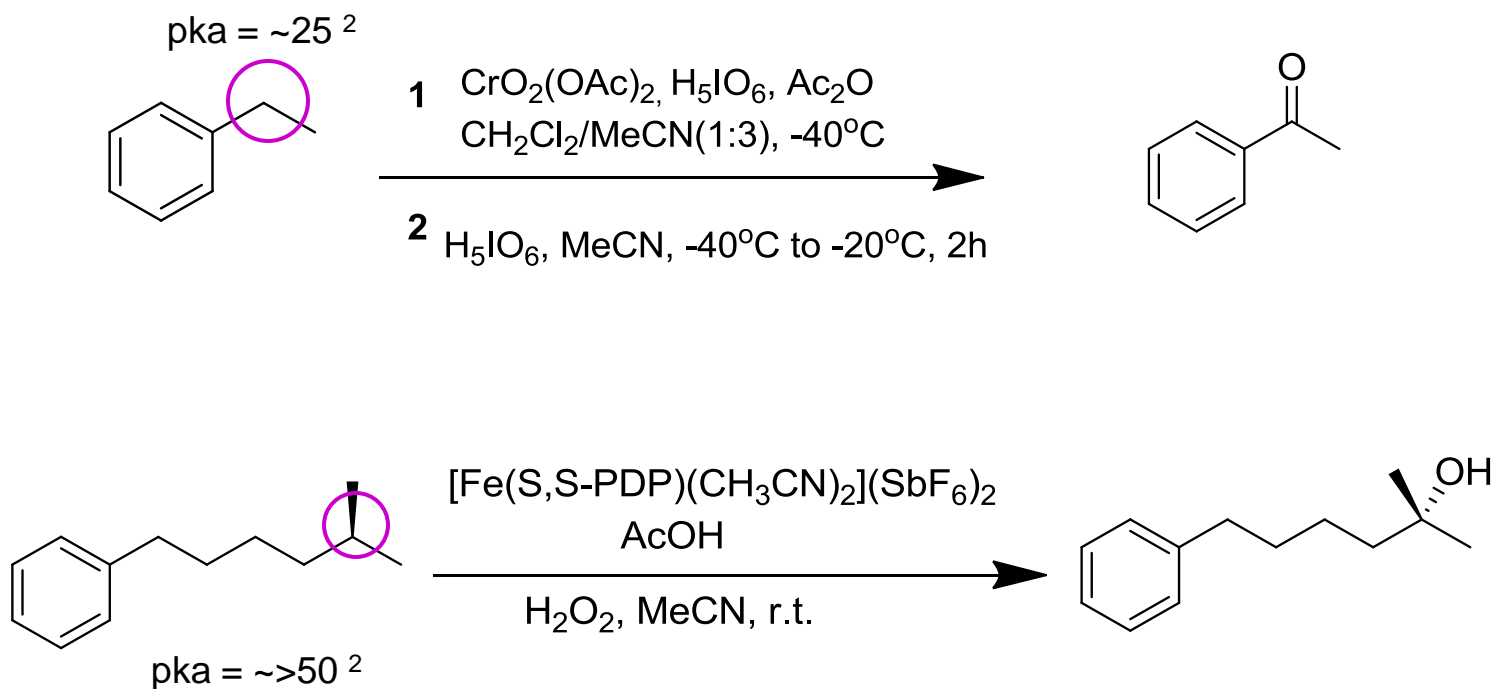
Previous Methods

□ Unproductive chemical manipulations



Previous Methods

□ Using activated C-H bonds¹



¹ S. Lee, P.L. Fuchs, *J. Am. Chem. Soc.* **124**, 13978 (2002).

² Bordwell pKa Table (Acidity in DMSO), University of Wisconsin. <http://www.chem.wisc.edu/areas/reich/pkatable/index.htm>

Previous Methods

□ Using directing groups

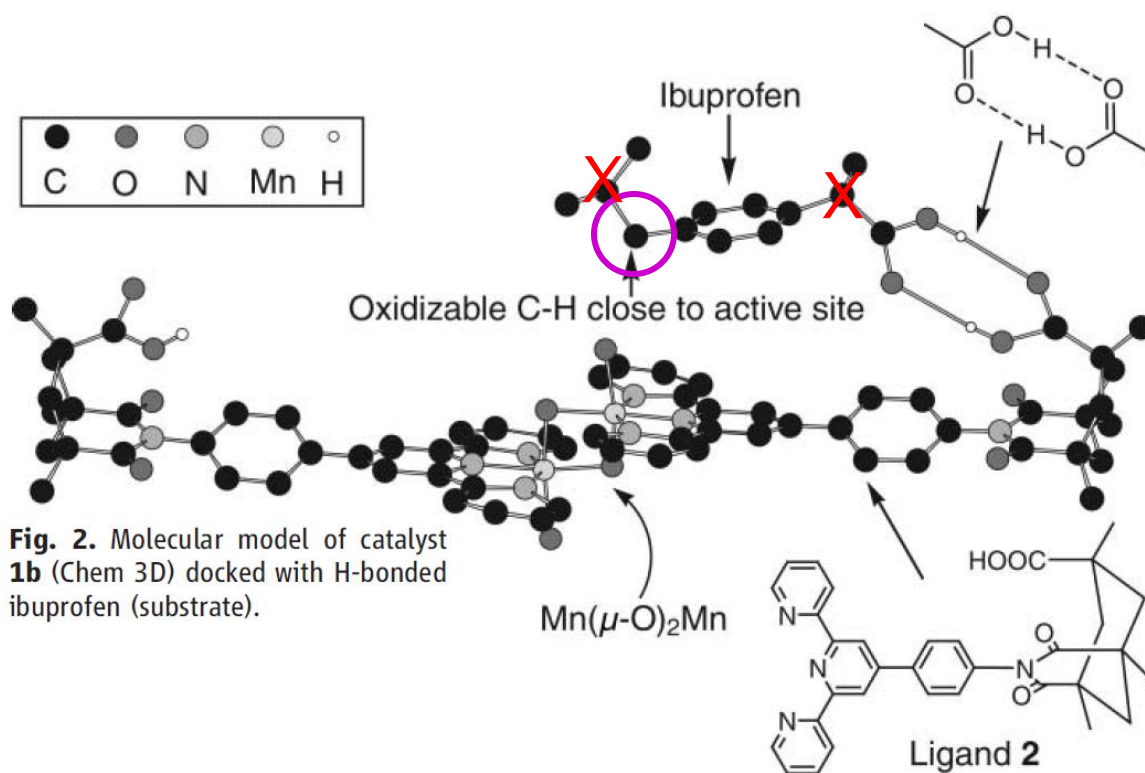
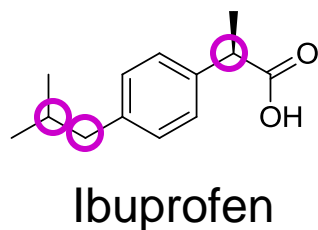


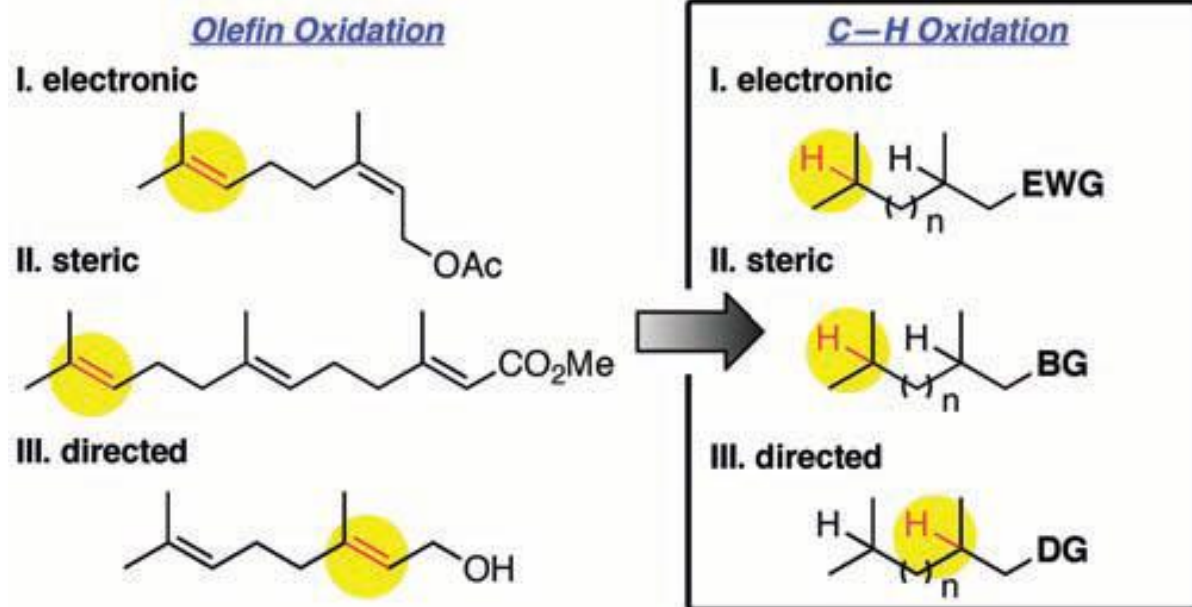
Fig. 2. Molecular model of catalyst **1b** (Chem 3D) docked with H-bonded ibuprofen (substrate).

How do they do it?

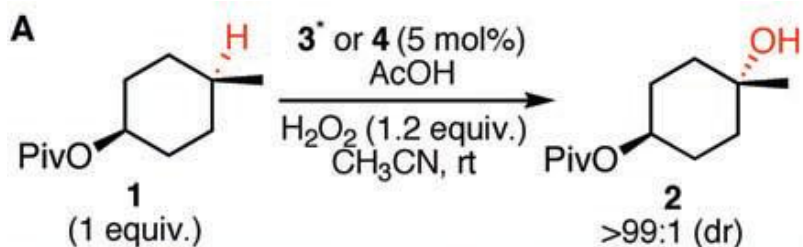
- Based off site-selective olefin oxidations and epoxidation work

- Can control via 4 methods

- Overall conditions
- Electronics
- Sterics
- Directing groups

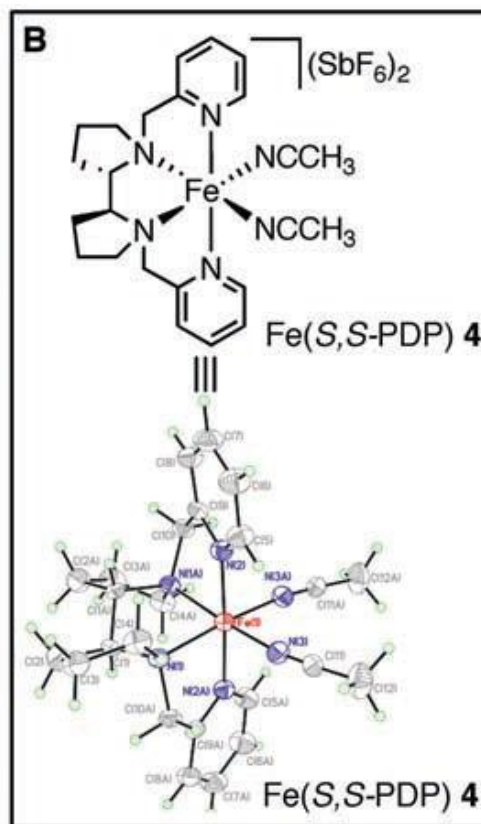
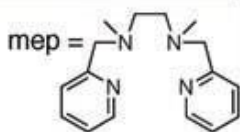


Conditions



| Entry | Catalyst | AcOH (equiv.) | Yield (%) | Conv. [†] (%) | Select. [‡] (%) |
|----------------|------------|---------------|-----------|------------------------|--------------------------|
| 1 | 3 * | 0 | 7 | 12 | 56 |
| 2 | 4 | 0 | 14 | 15 | 92 |
| 3 | 3 * | 0.5 | 26 | 41 | 62 |
| 4 | 4 | 0.5 | 38 | 42 | 90 |
| 5 [§] | 4 | 0.5 | 51 | - | - |

[†][Fe(mep)(CH₃CN)₂](SbF₆)₂ (**3**). [†]Conversion of starting material. [‡]Selectivity for desired product (yield/conversion). [§]Iterative addition protocol (isolated yield).



Fe ox. St. = Fe⁺²
 CN = 6
 e⁻ count = 18e⁻

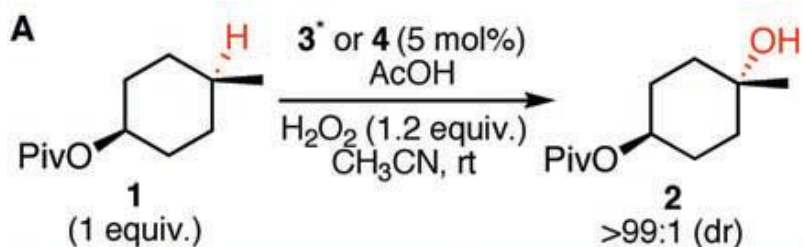
Mechanism

- Limited Understanding¹
- Thought to be Fenton-type reactivity
- Fenton Reaction²:
 - $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{OH}\cdot + \text{OH}^-$
 - $\text{Fe}^{3+} + \text{H}_2\text{O}_2 \rightarrow \text{OOH}\cdot + \text{H}^+$

¹ J.England, G.J.P. Britovesk, N. Rabadia, A.J.P. White, *Inorg. Chem.* **46**, 3752 (2007).

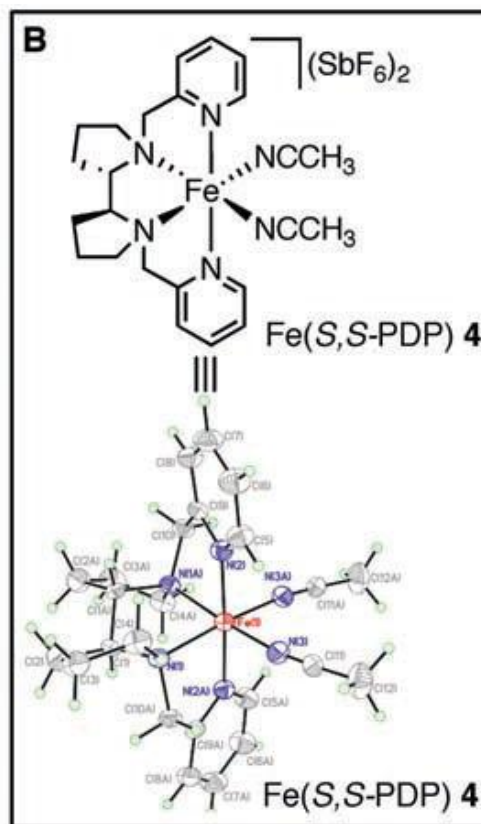
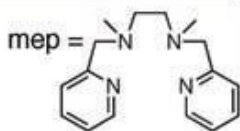
² Fenton's Reagent, Wikipedia, http://en.wikipedia.org/wiki/Fenton%27s_reagent

Conditions



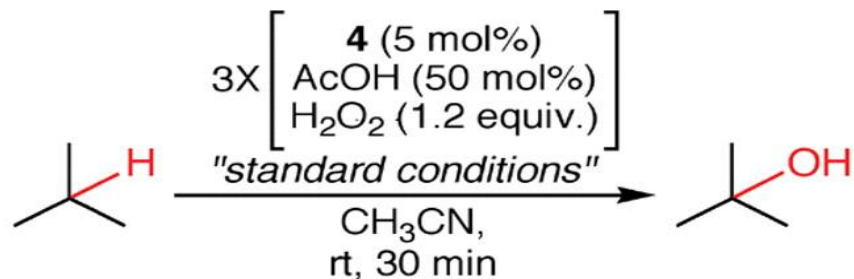
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[†][Fe(mep)(CH₃CN)₂](SbF₆)₂ (**3**). [†]Conversion of starting material. [‡]Selectivity for desired product (yield/conversion). [§]Iterative addition protocol (isolated yield).



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Fig 3



| Entry | Product | Isolated % Yield (rsm)* | Entry | Product | Isolated % Yield (rsm)* |
|-------|------------------------|-------------------------|-------|-----------------------------|--------------------------------|
| 1 | 5 , X = Br | 46 (26) | 6 | (+)-10 , Z = H | 57 (27) |
| 2 | 6 , X = OAc | 53 (43) | 7 | (+)-11 , Z = OAc | 43 (42) |
| 3 | 7 | 60 (18) | 8 | (-)-12 | 33 (67) 90 [†] (8) |
| 4 | 8 | 43 (33) | 9 | 13 | 52 (20) |
| 5 | 9 | 52 (21) | 10 | 14 | 92 [‡] |

*rsm = % recovered unoxidized starting material. [†]Starting material was recycled five times. [‡]GC yield.

Preliminary Evaluation of Functional Group Compatibility and Substrate Scope

- Hydroxylation occurred preferentially at the most electron-rich tertiary C-H bond
- Lewis basic groups were surprisingly well tolerated
- Retention of stereochemistry was retained upon hydroxylation
- When no tertiary sites were available, oxidation occurred at a secondary site

Fig 4B

| Entry | Substrate | Major Product | Isolated %Yield* (rsm) [†] | [Remote: Proximal] [‡] | |
|-------|-----------|---------------|-------------------------------------|---------------------------------|-------|
| 1 | | | | | |
| 2 | | | 15, X = H | 48 [§] (29) | 1:1 |
| 3 | | | 16, X = OAc | 43 (35) | 5:1 |
| 4 | | | 17, X = Br | 39 (32) | 9:1 |
| 5 | | | 18, X = F | 43 (20) | 6:1 |
| 6 | | | 19, X = OAc | 49 (21) | 29:1 |
| 7 | | | 20, X = Br | 48 (17) | 20:1 |
| 8 | | | 21, R = CH ₃ | 52 (18) | >99:1 |
| 9 | | | 22, R = OCH ₃ | 56 (32) | >99:1 |

*Unless otherwise noted, isolated yields are of pure major product isolated from the entire reaction mixture.

[†]rsm = % recovered unoxidized starting material. [‡]GC analysis of crude reaction mixture using authentic standards. [§]Isolated as a 1:1 mixture of remote:proximal.

Substrate Electronic Effects on Site Selectivity of Multiple Tertiary C-H Bonds

- Substrates without electronic bias
 - ▣ Equimolar mixtures of both products
- Substrates with electronic bias
 - ▣ Hydroxylation occurred preferentially at tertiary C-H bond remote from the EWGs
 - ▣ β -position gave modest selectivity
 - ▣ α -position gave excellent selectivity

Noted Reactivity Trends Based on the Electronics of the C-H Bond

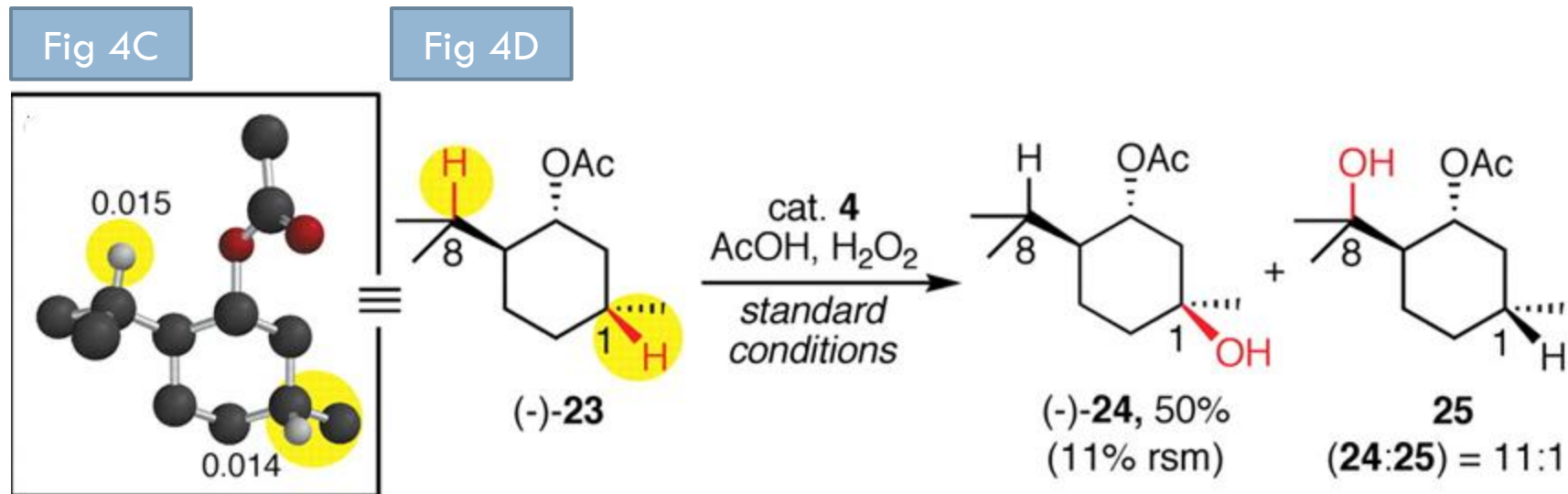
- Electronic effects
- site
- EWG
- react
- EWG
- site
- effe



reactivity



Investigation of Site Selectivity in Steric Environments of the Tertiary C-H Bond

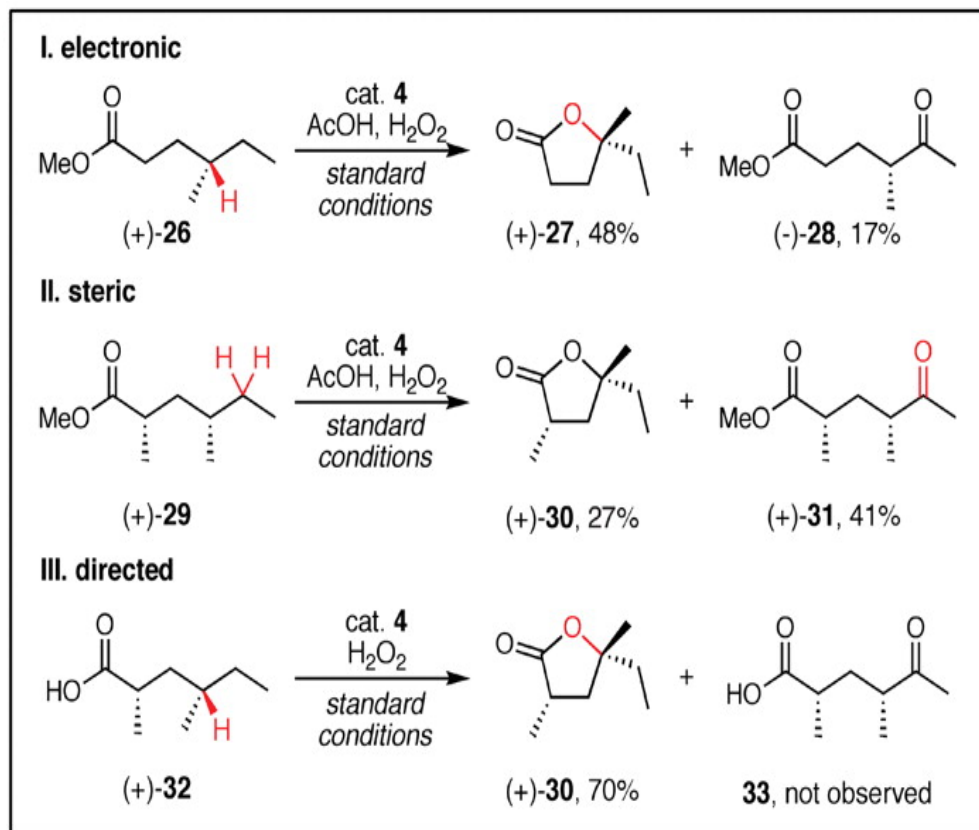


- Energy minimization calculations showed the two tertiary C-H bonds to have similar atomic charges in the γ -position
- Strong preference for oxidation at the C-1 site was observed potentially due to lack of steric hindrance

Interplay Between Electronic and Steric Factors in Determining Selectivity

- Steric bulk trumps electronics
- Oxidation at secondary sites may operate similarly to tertiary sites
- Directing groups trumps sterics and electronics

Fig 5A

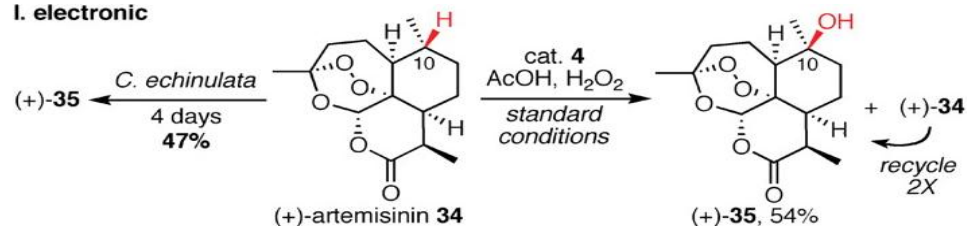


How Predictive are these Modes of Selectivity in Complex Molecular Settings

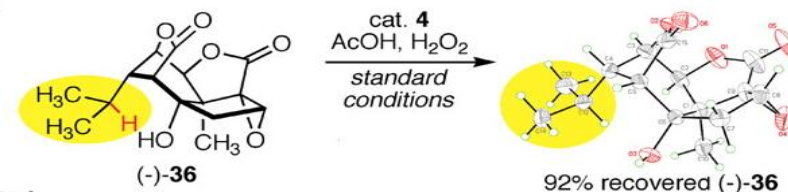
- Selectivity rules for oxidation held true
- Catalyst 4 gives greater yield, shorter reaction time, and higher volume throughput

Fig 5B

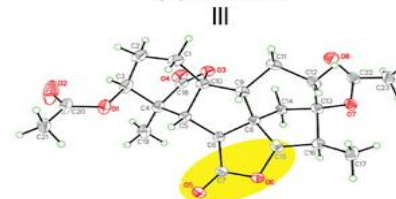
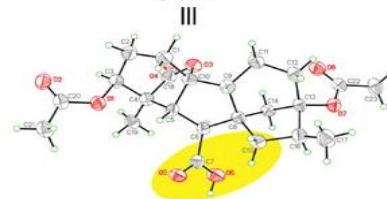
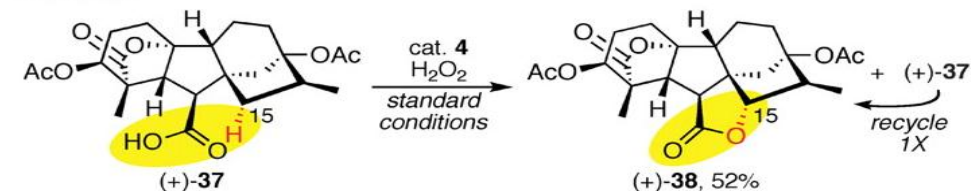
I. electronic



II. steric



III. directed



Where will it/has it gone since?

- Will fundamentally alter ways in which complex molecules are synthesized
- More research has been completed on the secondary C-H bonds (1)
- Regio- and stereoselective oxidation of un-activated sp^3 C-H bonds with the P450 enzyme (2)

Questions

- What was the most reactive type of C-H?
- What are two problems that this catalyst addressed?
- What are the 4 areas that were addressed to optimize the reaction?
- Who has the coolest organometallic research group?