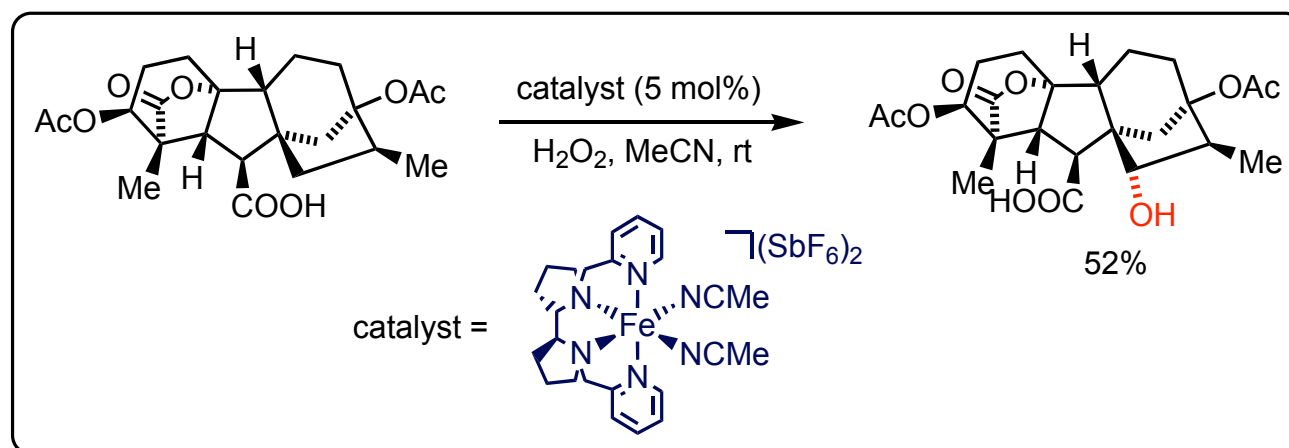


A Predictably Selective Aliphatic C–H Oxidation Reaction for Complex Molecule Synthesis

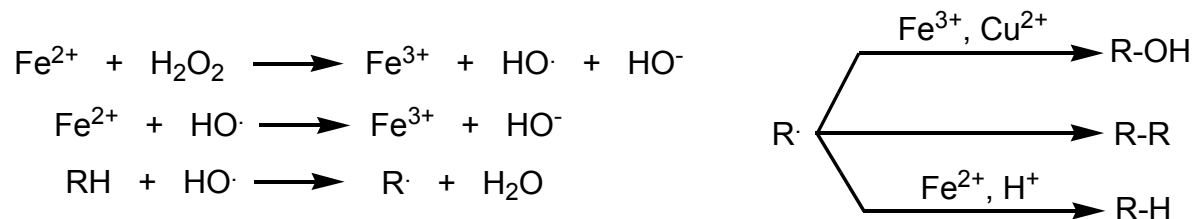


Mark S. Chen and M. Christina White
Science **2007**, 318, 783-787

For commentary: R. H. Crabtree *Science* **2007**, 318, 756

Fenton Reaction

- Combination of Fe(II) and peroxide is considered as Fenton reagent.



- Initial ligand displacement by nucleophilic peroxide initiates presumably internal one-electron oxidation-reduction process.
- Note a different behavior of highly oxidized metals (Mo(VI), V(V), Ti(IV)) which complexes with peroxides show properties of peracids.

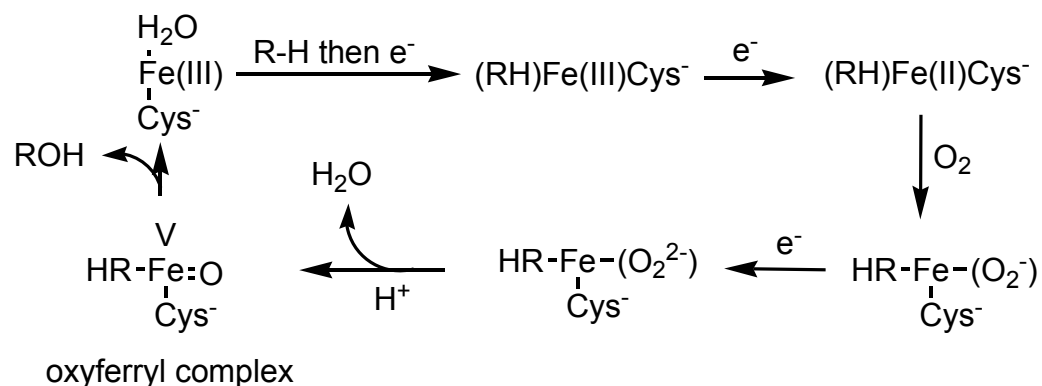
For relevant discussion, see:

Acc. Chem. Res. **1998**, 31, 155

Acc. Chem. Res. **1996**, 29, 409

Walling, C. *Acc. Chem. Res.* **1975**, 8, 125

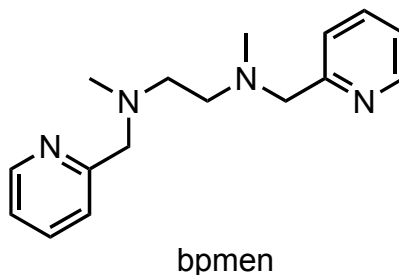
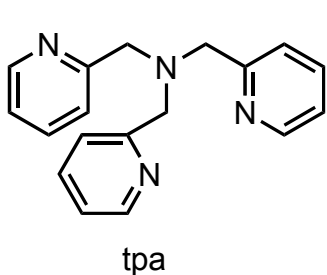
Iron in High Oxidation States



Iron porphyrin proteins are responsible for transport and storage of O_2 , oxidation of organic molecules as well as electron transport.

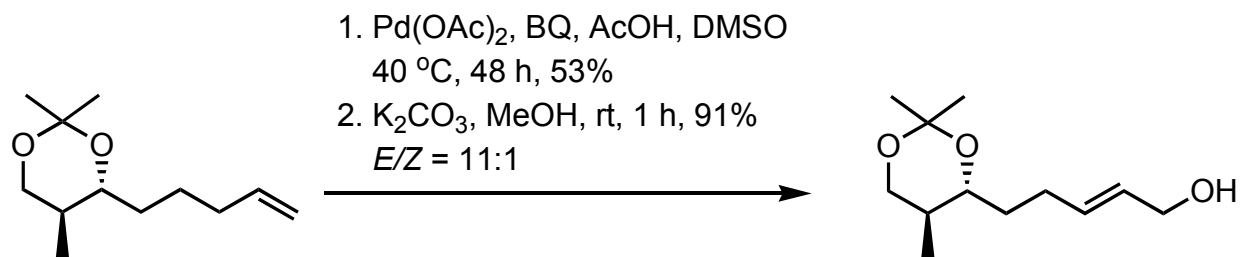
Cytochromes operate via shuttling iron between different oxidation states Fe(II)-Fe(V).

Synthetic pyridine-based polydentate ligands in combination with Fe(II) and H_2O_2 most likely operate via **Fe(V)** species. Labeling studies, lack of O_2 involvement as well as high stereospecificity in the oxidation reaction exclude $\text{HO}\cdot$.

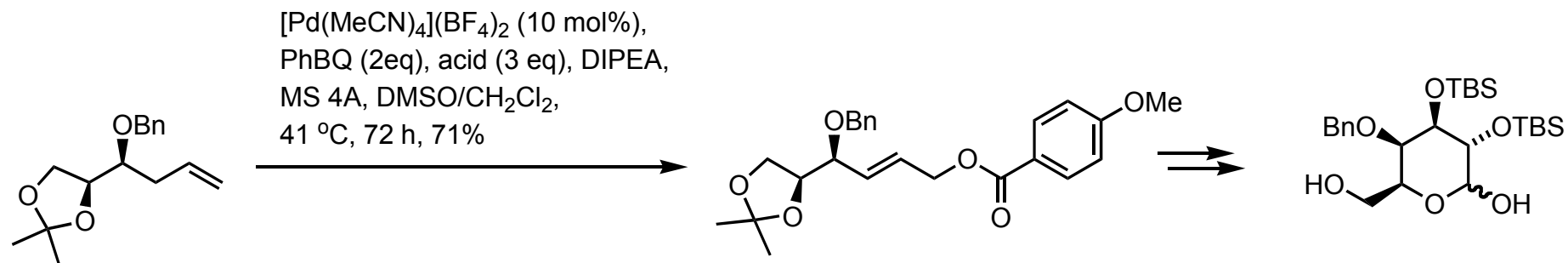


Chen, Que *Chem. Comm.* **1999**, 1375
 Nishida et al. *Dalton Trans.* **1997**, 3547
 Que, Ho *Chem. Rev.* **1996**, 96, 2607
 Que et al. *J. Am. Chem. Soc.* **1997**, 119, 5964

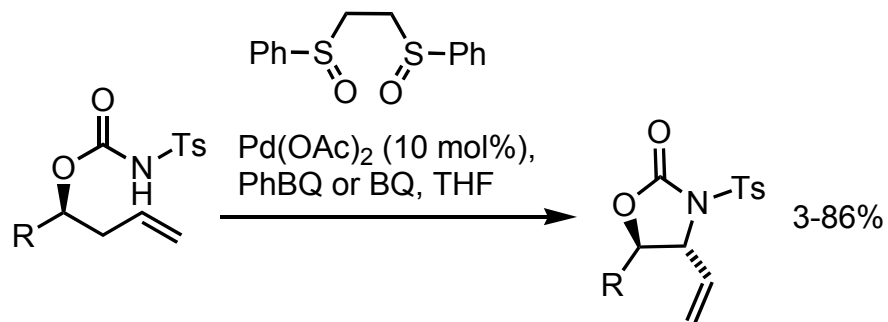
CH Activation in the White Group



White et al. *Org. Lett.* **2005**, 7, 223

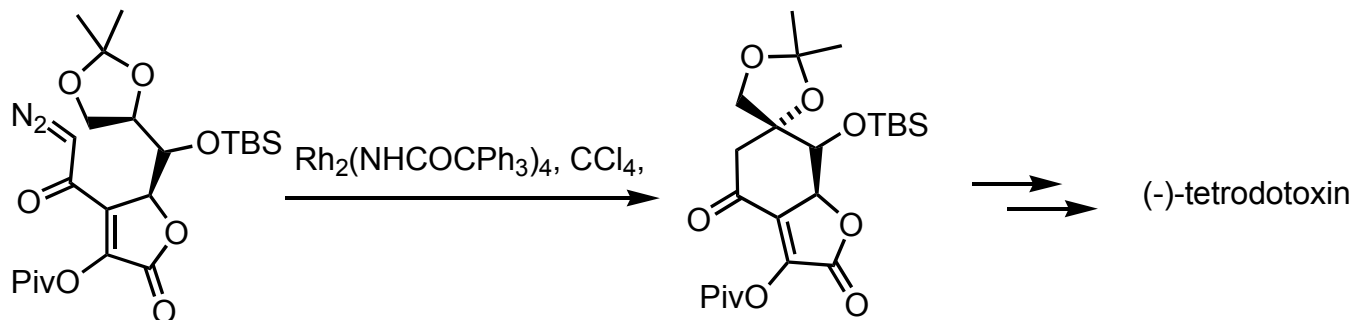


White et al. *Angew. Chem. Int. Ed.* **2006**, 45, 8217

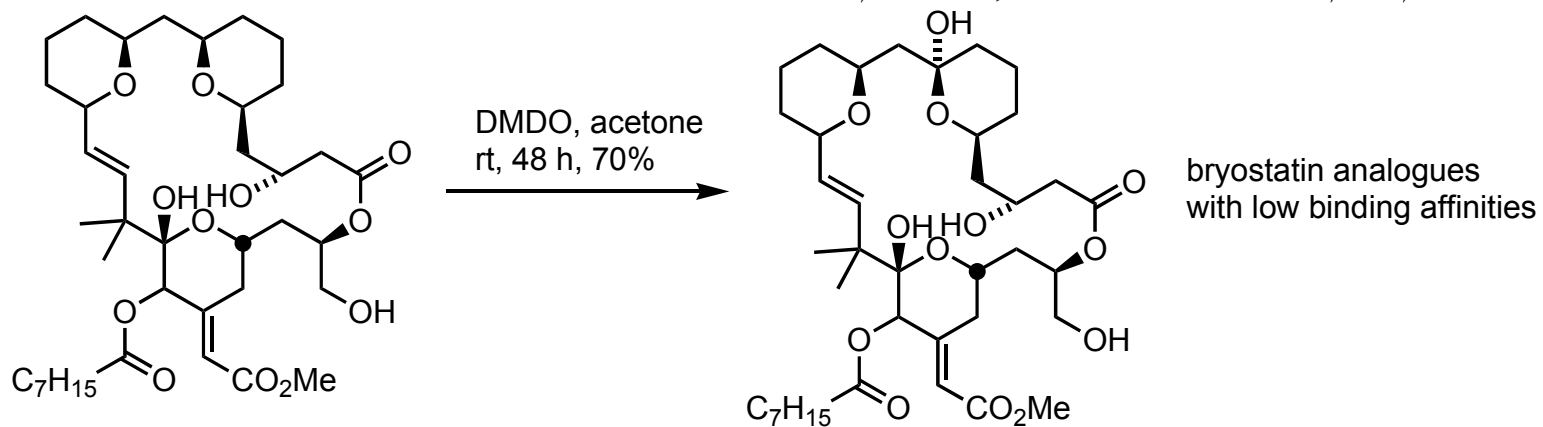


Fraunhofer, White *J. Am. Chem. Soc.* **2007**, 129, 7274

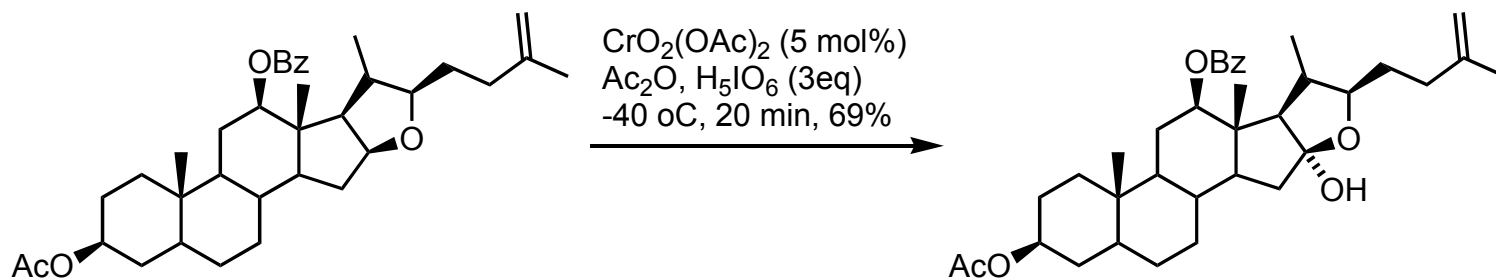
CH Activation in Complex Molecule Synthesis



Hinman, Du Bois *J. Am. Chem. Soc.* **2003**, *125*, 11510

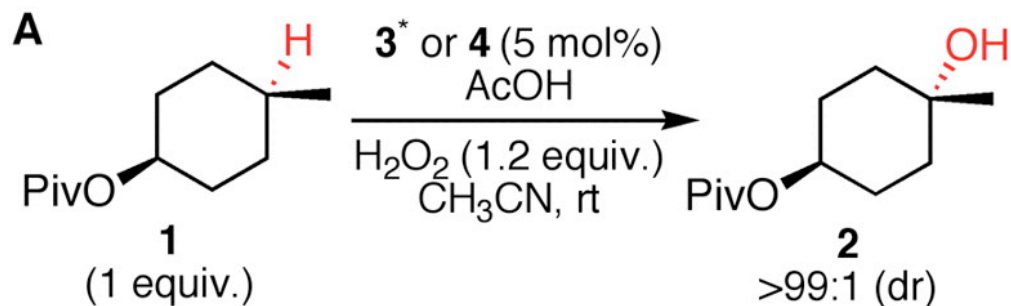


Wender, Hilinski, Mayweg *Org. Lett.* **2005**, *7*, 79



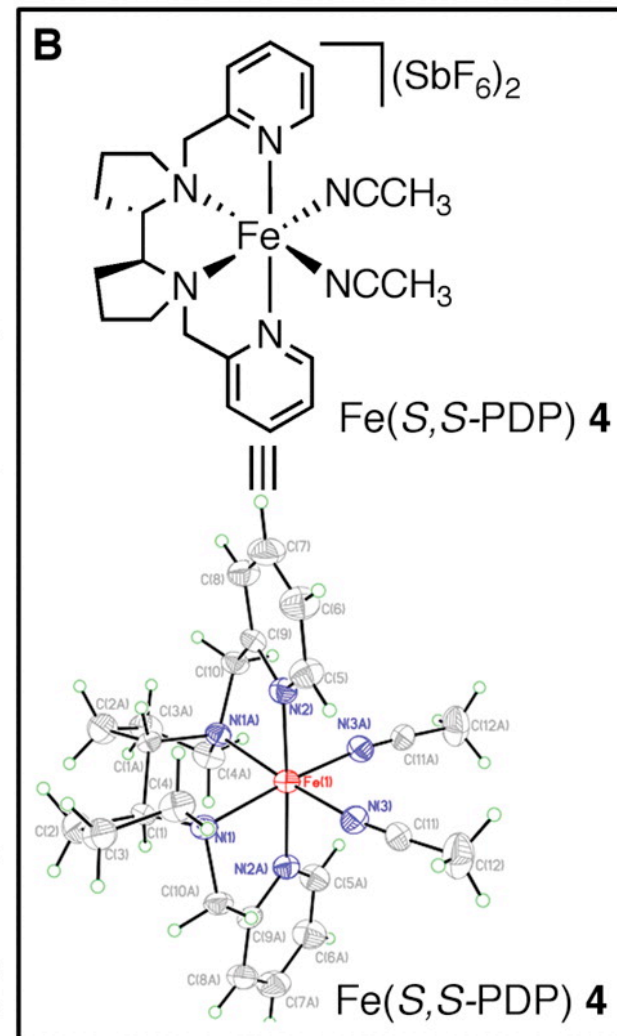
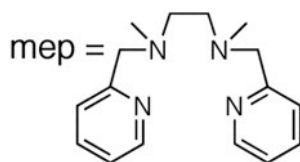
Lee, Fuchs *J. Am. Chem. Soc.* **2002**, *124*, 13978

Catalyst Optimization

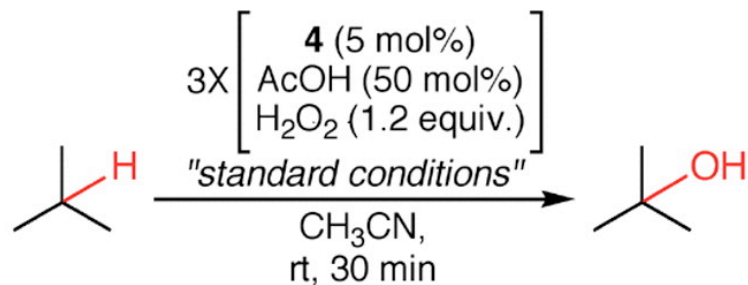


Entry	Catalyst	AcOH (equiv.)	Yield (%)	Conv. [†] (%)	Select. [‡] (%)
1	3*	0	7	12	56
2	4	0	14	15	92
3	3*	0.5	26	41	62
4	4	0.5	38	42	90
5 [§]	4	0.5	51	-	-

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



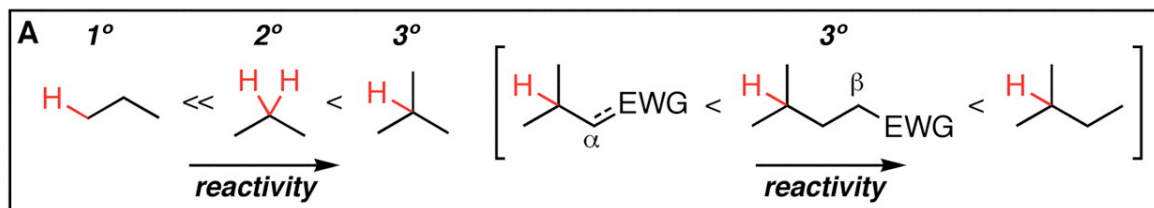
Reaction Scope



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.

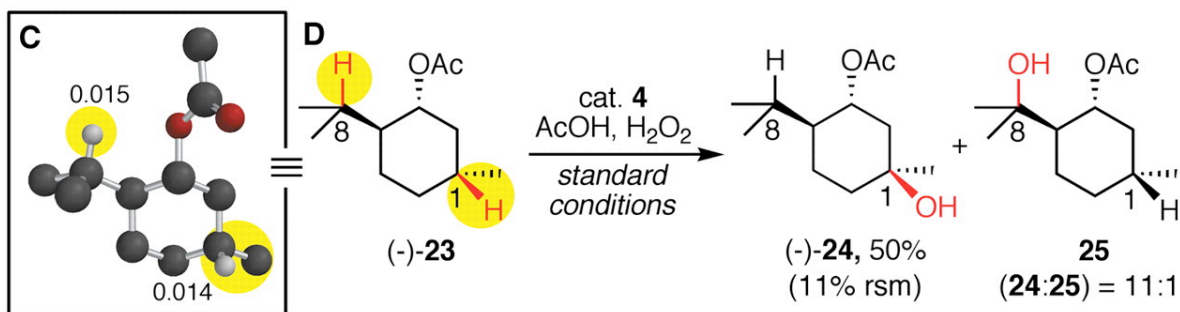
Reaction Scope



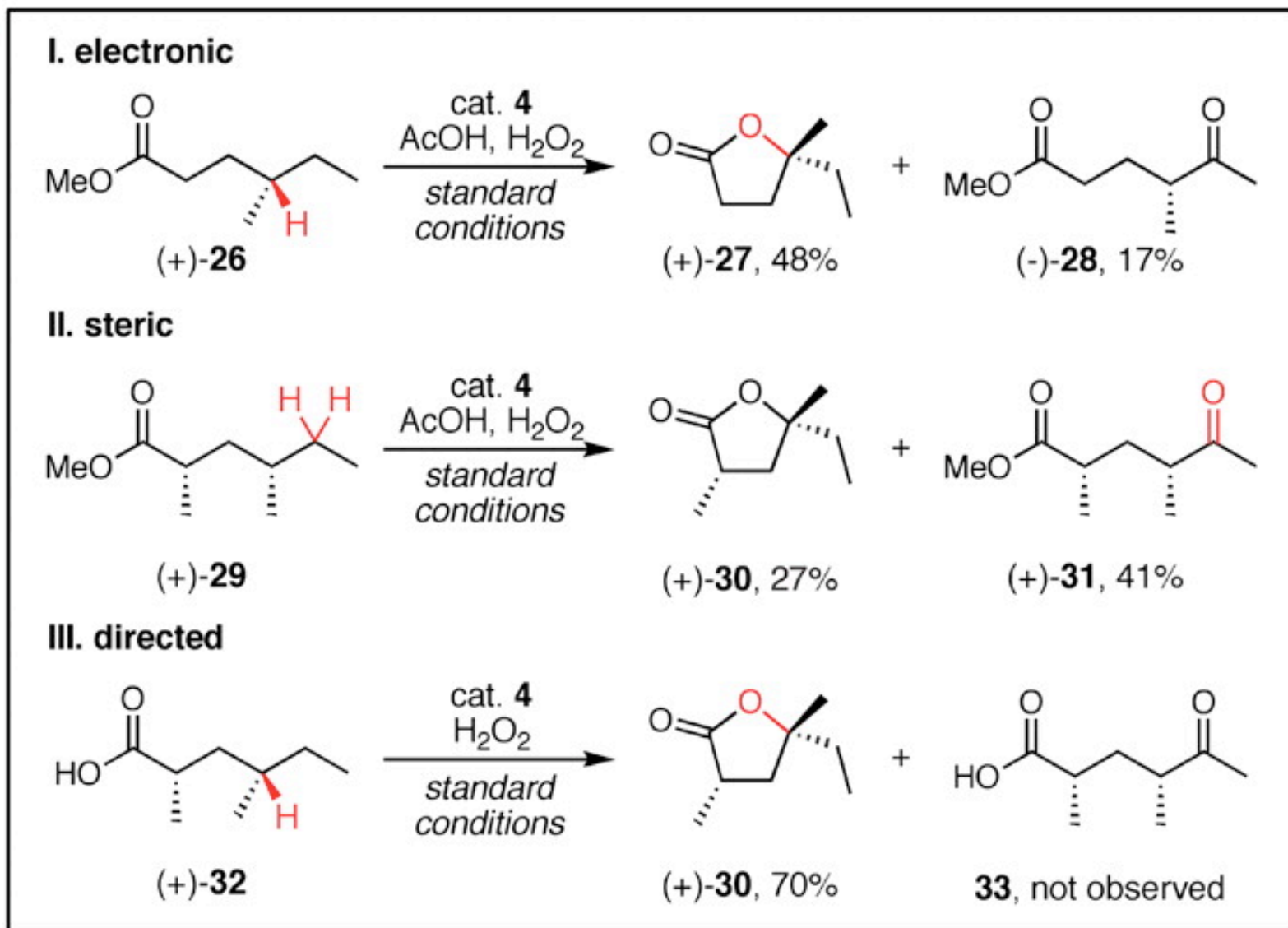
B

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

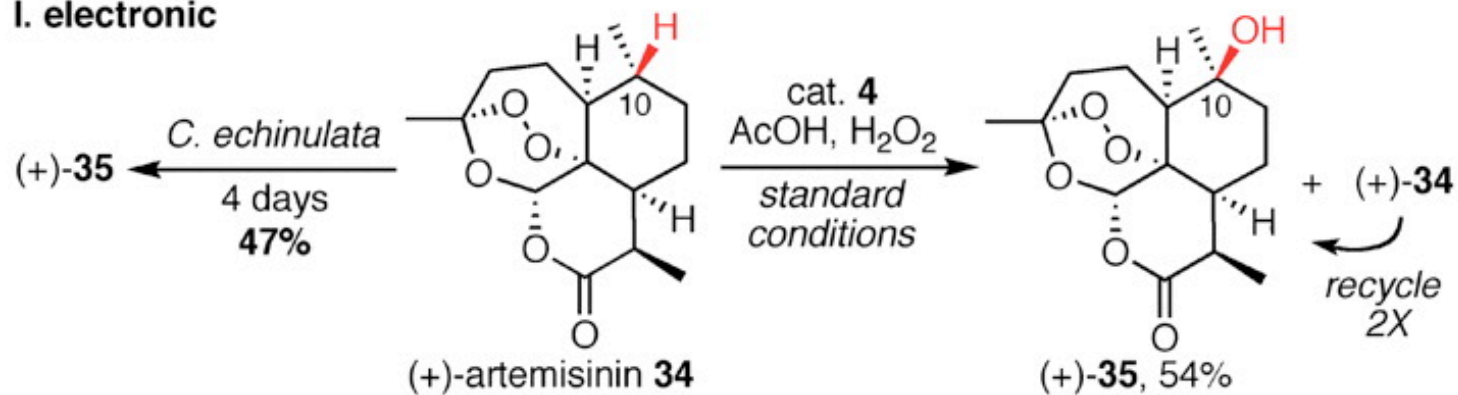


Directing Group Selectivity

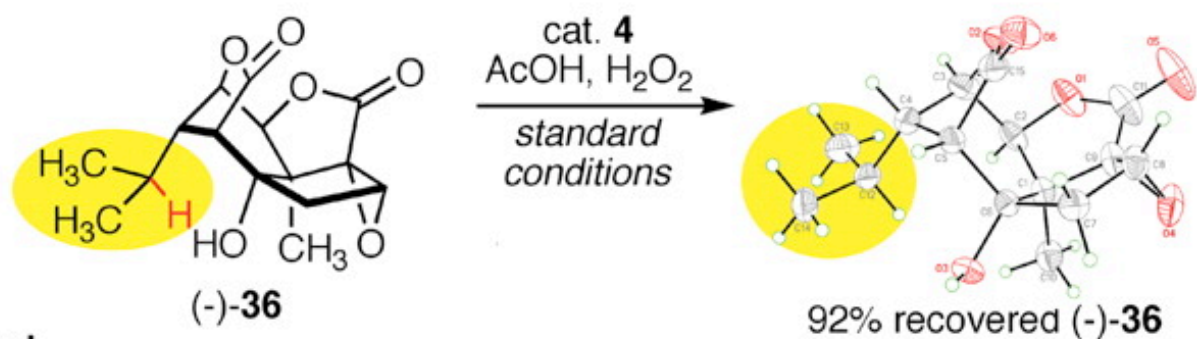


Advanced Applications

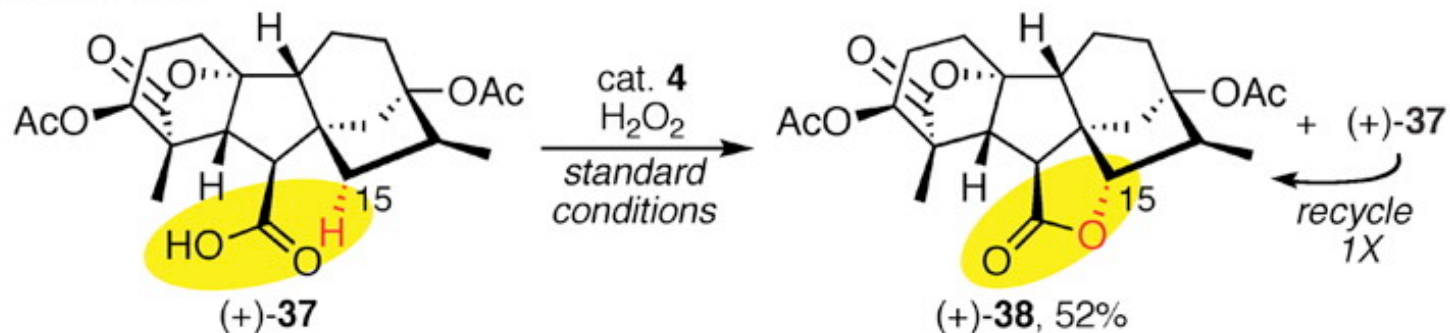
I. electronic



II. steric



III. directed



Summary

- Fe(II) based catalyst with H_2O_2 as an oxidant has been utilized in oxidation of CH bonds.
- Selectivity in these reactions has been achieved via electronic and steric bias of CH bonds.
- Additional mechanistic studies may provide better understanding of the catalyst reactivity and selectivity.