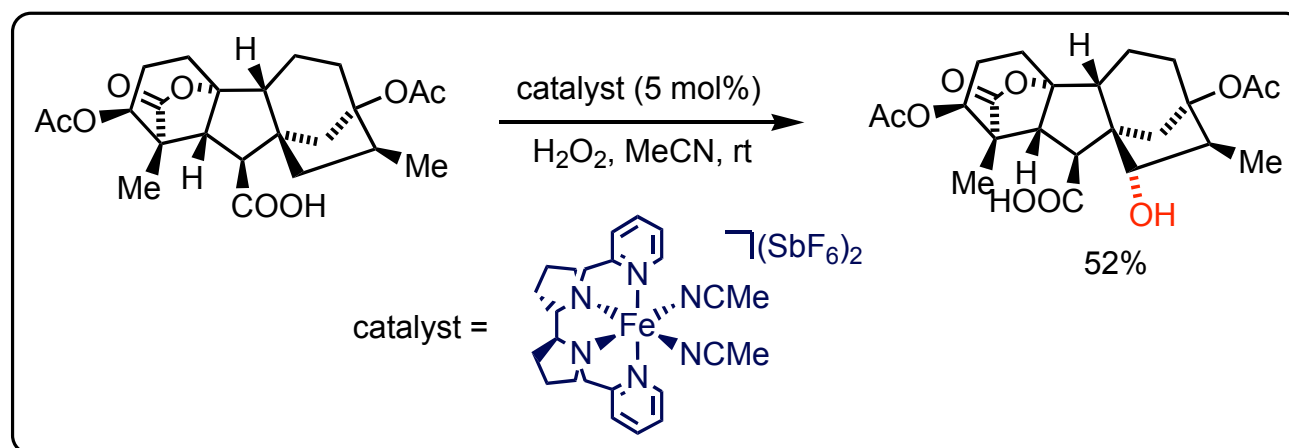


# A Predictably Selective Aliphatic C–H Oxidation Reaction for Complex Molecule Synthesis

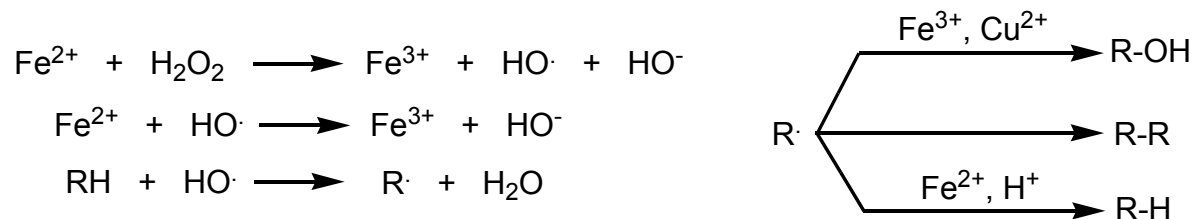


Mark S. Chen and M. Christina White  
*Science* **2007**, 318, 783-787

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.

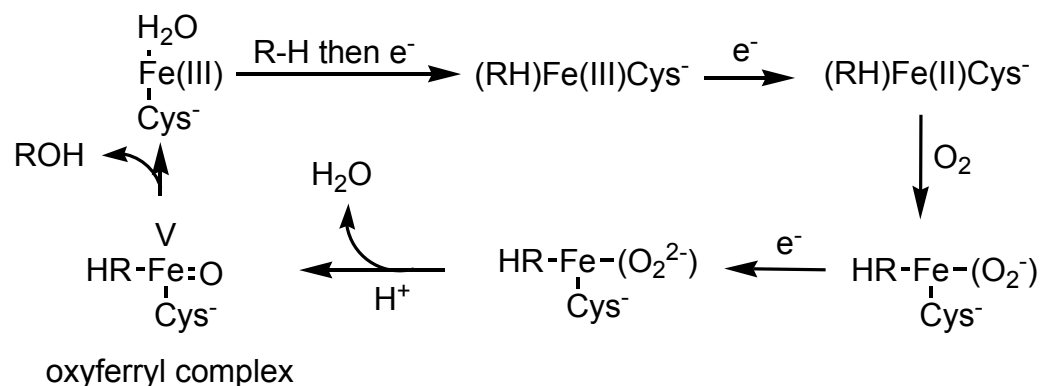
For relevant discussion, see:

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

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

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

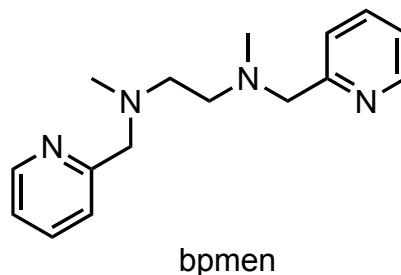
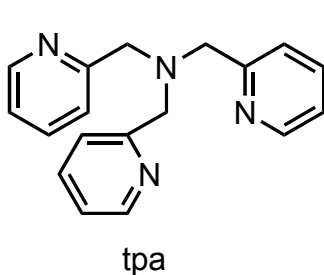
# Iron in High Oxidation States



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

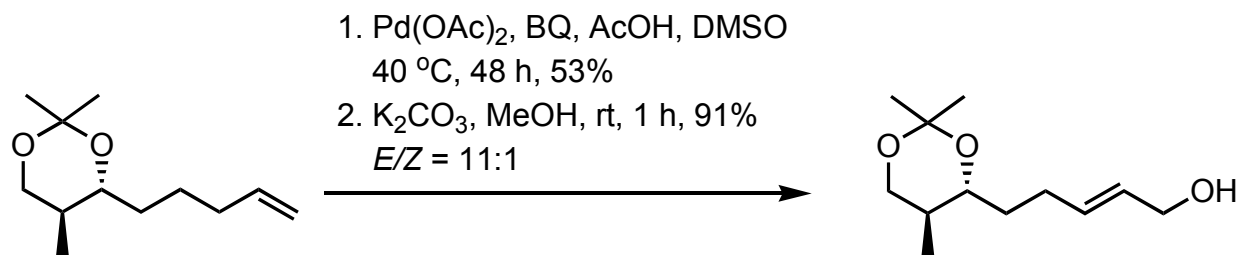
**Cytochromes** operate via shuttling iron between different oxidation states Fe(II)-Fe(V).

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  $HO\cdot$ .

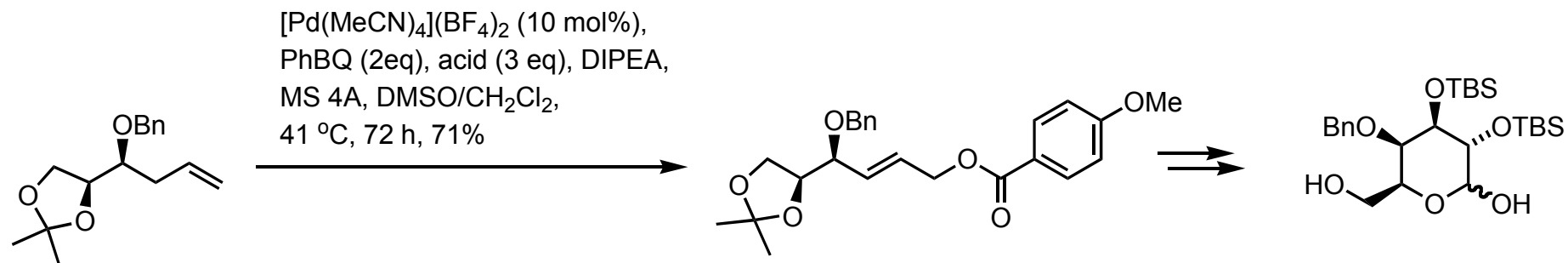


Chen, Que *Chem. Comm.* **1999**, 1375  
 Nishida et al. *Dalton Trans.* **1997**, 3547  
 Que, Ho *Chem. Rev.* **1996**, 96, 2607  
 Que et al. *J. Am. Chem. Soc.* **1997**, 119, 5964

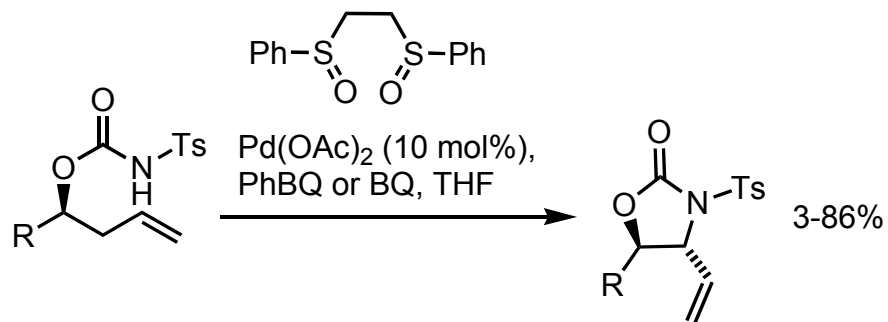
# CH Activation in the White Group



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

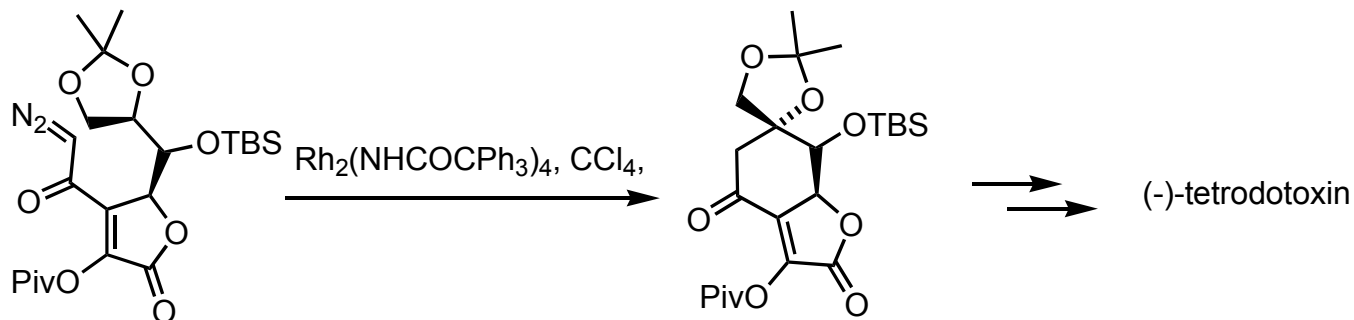


White et al. *Angew. Chem. Int. Ed.* **2006**, 45, 8217

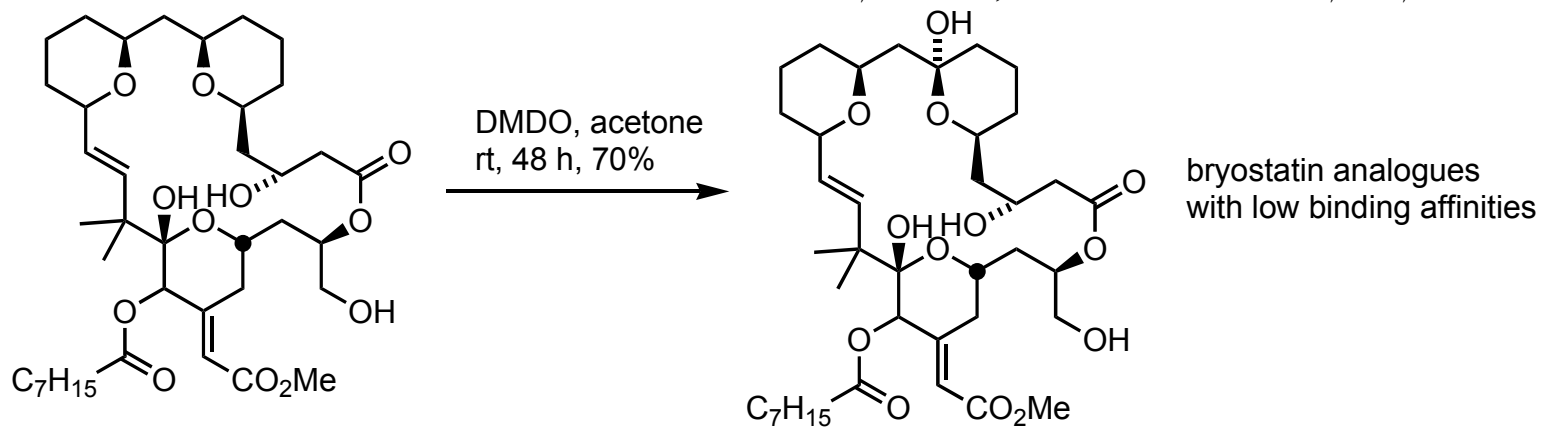


Fraunhofer, White *J. Am. Chem. Soc.* **2007**, 129, 7274

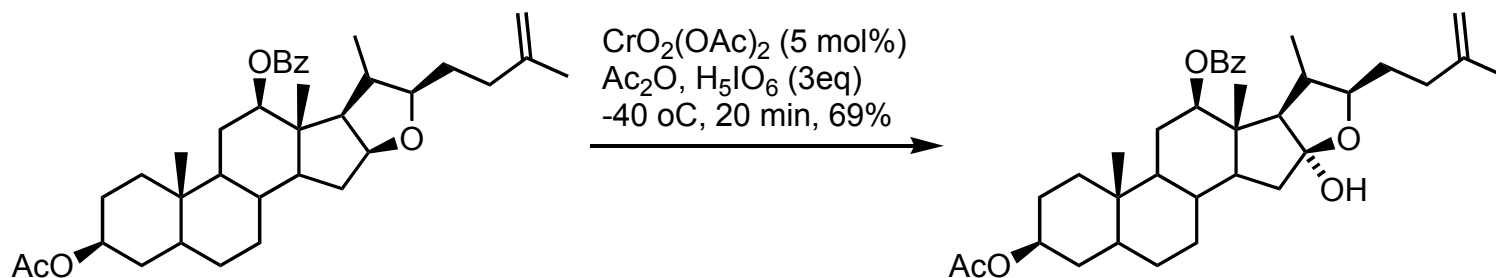
# CH Activation in Complex Molecule Synthesis



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

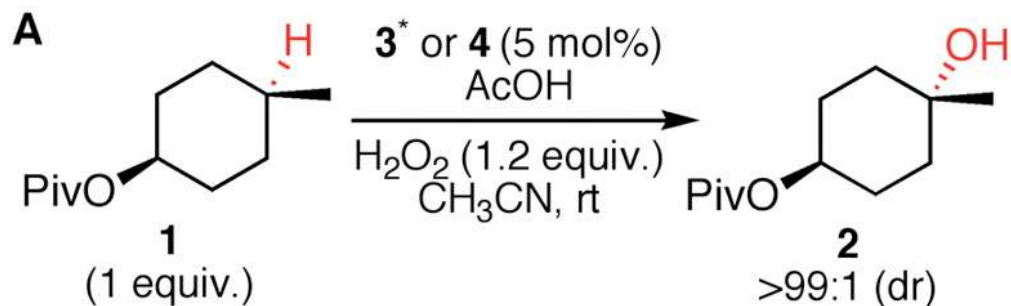


Wender, Hilinski, Mayweg *Org. Lett.* **2005**, *7*, 79



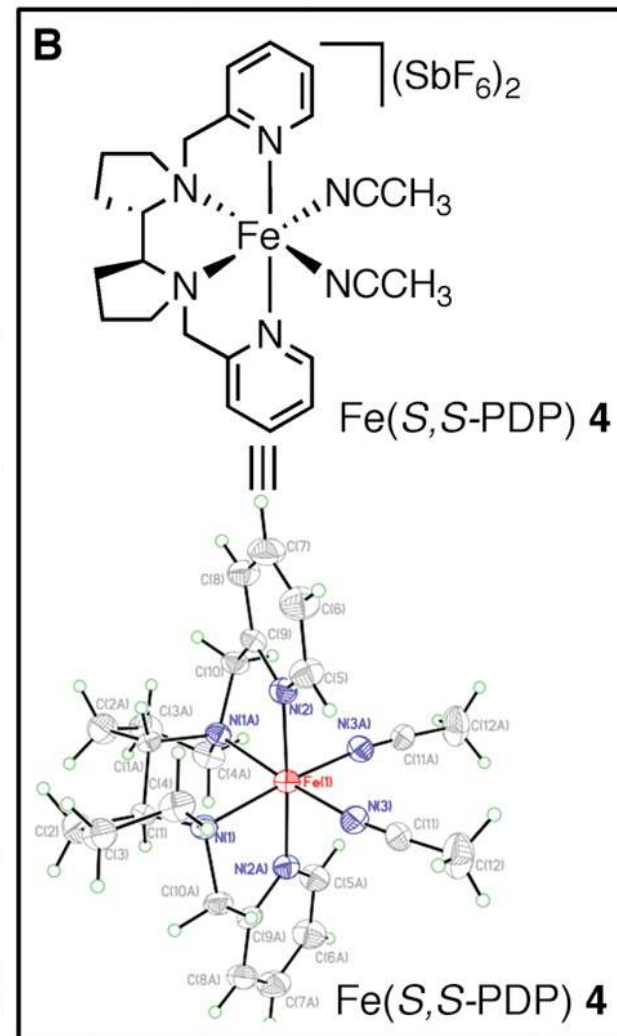
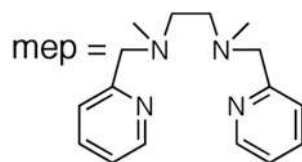
Lee, Fuchs *J. Am. Chem. Soc.* **2002**, *124*, 13978

# Catalyst Optimization

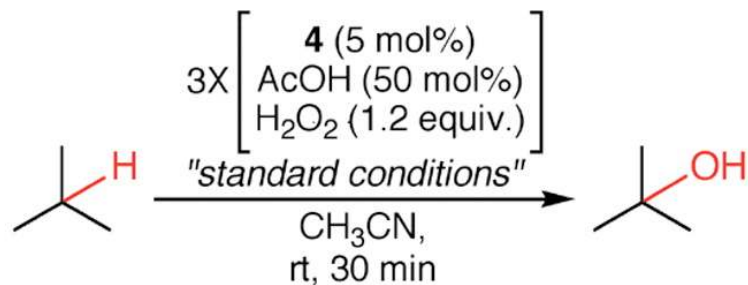


Entry	Catalyst	AcOH (equiv.)	Yield (%)	Conv. <sup>†</sup> (%)	Select. <sup>‡</sup> (%)
1	<b>3</b> *	0	7	12	56
2	<b>4</b>	0	14	15	92
3	<b>3</b> *	0.5	26	41	62
4	<b>4</b>	0.5	38	42	90
5 <sup>§</sup>	<b>4</b>	0.5	51	-	-

<sup>\*</sup>[Fe(mep)(CH<sub>3</sub>CN)<sub>2</sub>](SbF<sub>6</sub>)<sub>2</sub> (**3**). <sup>†</sup>Conversion of starting material. <sup>‡</sup>Selectivity for desired product (yield/conversion). <sup>§</sup>Iterative addition protocol (isolated yield).



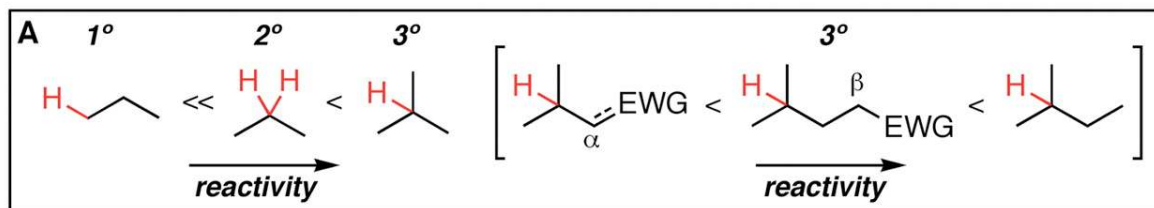
# Reaction Scope



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

\*rsm = % recovered unoxidized starting material. <sup>†</sup>Starting material was recycled five times. <sup>‡</sup>GC yield.

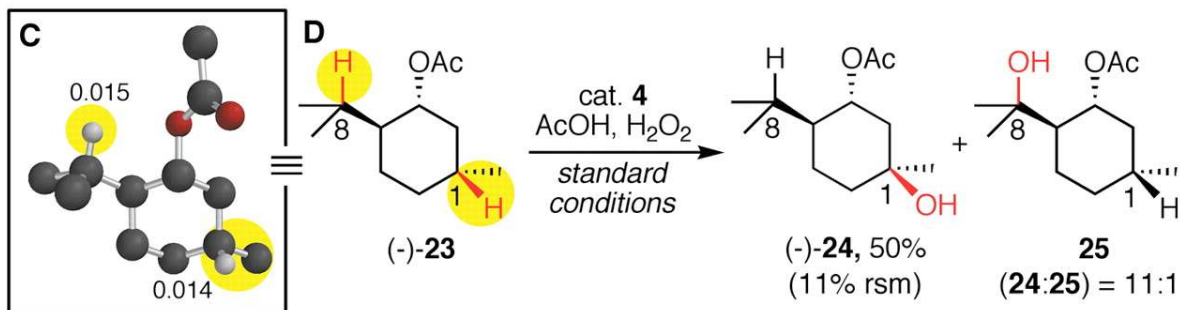
# Reaction Scope



**B**

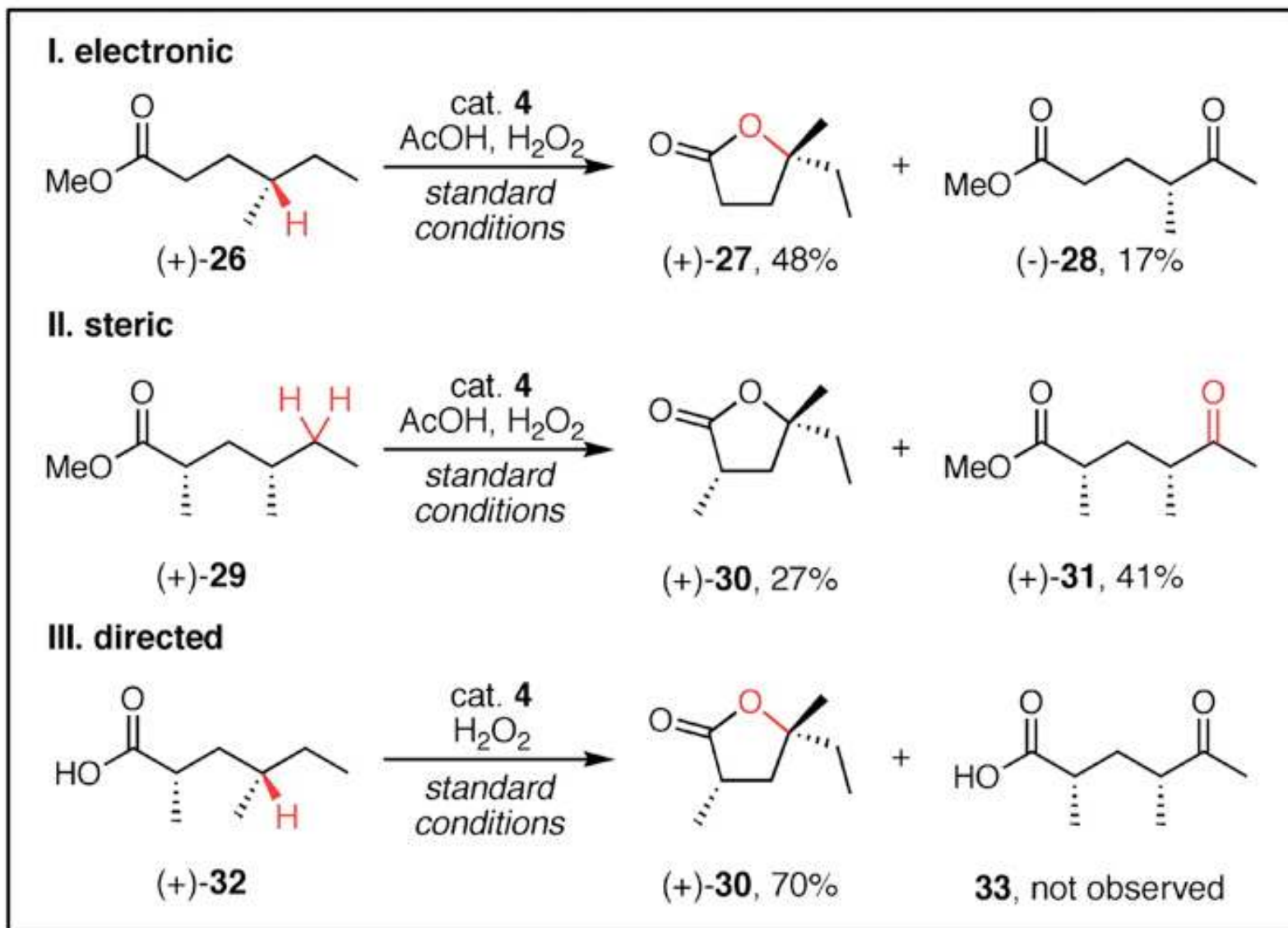
Entry	Substrate	Major Product	Isolated %Yield* (rsm) <sup>†</sup>	[Remote: Proximal] <sup>‡</sup>	
1	remote proximal	<b>15</b> , X = H	48 <sup>§</sup> (29)	1:1	
2			<b>16</b> , X = OAc	43 (35)	5:1
3			<b>17</b> , X = Br	39 (32)	9:1
4			<b>18</b> , X = F	43 (20)	6:1
5			<b>19</b> , X = OAc	49 (21)	29:1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

\*Unless otherwise noted, isolated yields are of pure major product isolated from the entire reaction mixture.  
<sup>†</sup>rsm = % recovered unoxidized starting material. <sup>‡</sup>GC analysis of crude reaction mixture using authentic standards. <sup>§</sup>Isolated as a 1:1 mixture of remote:proximal.



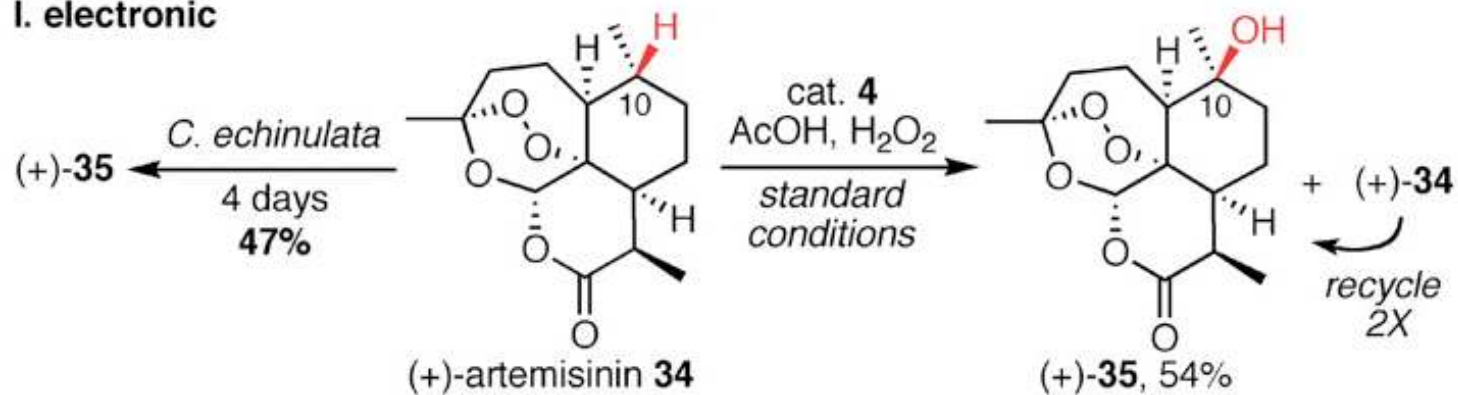


# Directing Group Selectivity

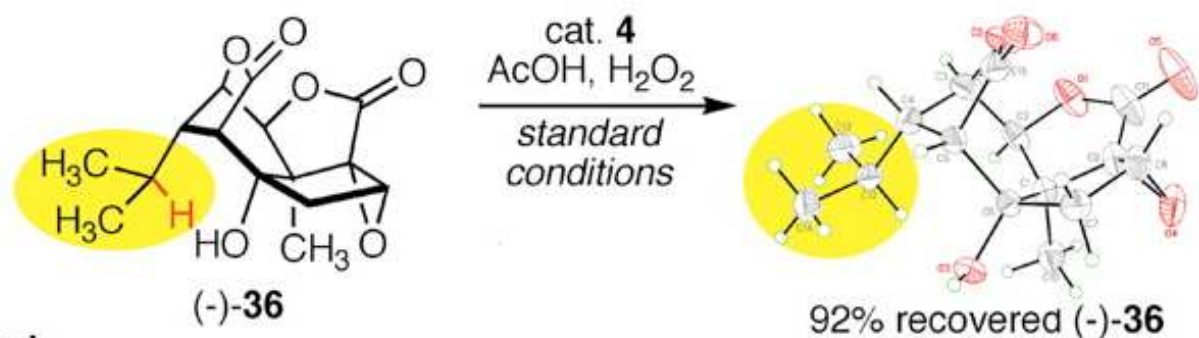


# Advanced Applications

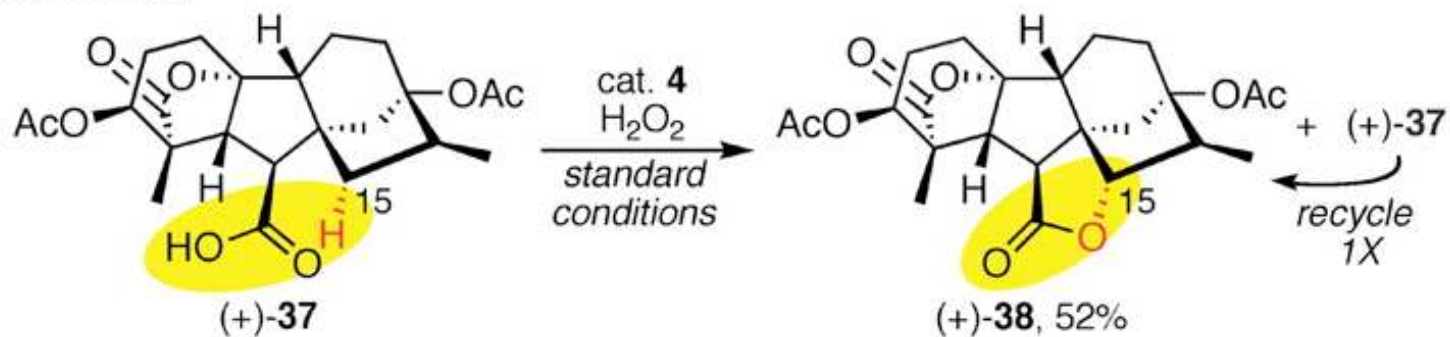
## I. electronic



## II. steric



## III. directed



## Summary

- Fe(II) based catalyst with  $\text{H}_2\text{O}_2$  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.