Catalyst-Controlled Aliphatic C-H oxidation: Prediction and Experiment

Paul E. Gormisky and M. Christina White

JACS, *135*, 14052-14055

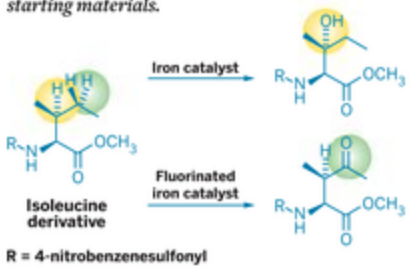
Wipf Group Current Literature 11/9/13

John Milligan

CATALYST CALLS THE SHOTS

ORGANIC SYNTHESIS: Iron-based catalyst controls selectivity in C–H oxidations

Iron catalysts selectively oxidize different C–H bonds (yellow and green) in the same isoleucine substrate, reactions that would otherwise require independent synthetic routes from different starting materials.



CHEMISTS HAVE DEVELOPED a new catalyst that accelerates oxidation of C–H bonds selectively in nonaromatic compounds such as terpenes, rather than relying on the inherent properties of the reactant molecules. The catalyst could boost the versatility with which organic compounds can be synthesized for drug discovery and other applications.

"C–H functionalization is becoming a more important synthetic methodology for drug discovery by expanding options for late-stage lead diversification," says Pfizer researcher Mark C. Noe, who was not involved with the work. "This new methodology enables late-stage oxidative functionalization at sites that were previously inaccessible by known C–H functionalization methods."

Several years ago, M. Christina White of the University of Illinois, Urbana-Champaign, and coworkers discovered an inexpensive iron-based catalyst with enzymelike capabilities (C&EN, Nov. 5, 2007, page 8). The catalyst, called Fe(PDP), oxidizes specific C–H bonds in aliphatic compounds with several such bonds. This type of selectivity is difficult to achieve: C–H bonds are strong and relatively unreactive, and their ubiquity in organic molecules makes them difficult for catalysts to distinguish.

A drawback of Fe(PDP) is that it has no control over the site to be oxidized—subtle property differences between reactant molecule C–H sites control site selectivity. For example, the C–H bond that is most electron-rich, less hindered sterically, or experiences the greatest strain tends to get the attention from the catalyst instead of other C–H bonds in the same substrate molecule.

By tweaking Fe(PDP)'s structure with four trifluoromethyl groups, White and coworkers have now produced a catalyst that shows substrates who's boss (*J. Am. Chem. Soc.* 2013, DOI: 10.1021/ja407388y). The added groups block substrate access to the catalyst's iron-based active site so only specific C–H bonds conforming to the catalyst's nonnegotiable steric and electronic demands get oxidized there.

The researchers showed that Fe(CF_3-PDP) oxidizes the antimalarial drug artemisinin and other substrates at C–H bonds that were before inaccessible to chemical oxidation. The catalyst's reactivity is modest, but White hopes to solve that issue in future work.—STU BORMAN

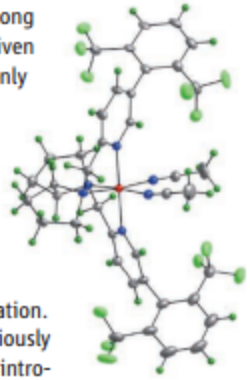
C&EN News of the Week- 7 October

CREDITS (TOP TO BOTTOM): A. GOSTYNSKI ET AL., JOURNAL OF INVESTIGATIVE DERMATOLOGY 133 (15 AUGUST 2013) © 2013 THE SOCIE

CHEMISTRY

Telling O Where to Go

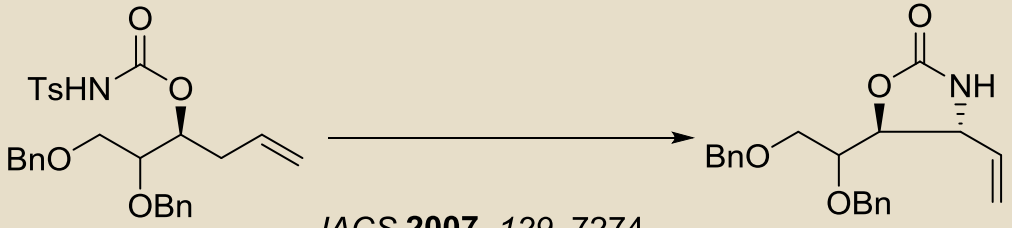
The abundance of aliphatic C-H bonds in organic molecules poses an enticing, yet maddening challenge to synthetic chemists. On the one hand, direct oxidation protocols are prospectively applicable to an immense range of substrates; on the other hand, genuinely useful methods must achieve selectivity among numerous sites in a given substrate that differ only subtly. Gormisky and White tackle this challenge through the use of a pair of complementary ligands on an iron catalyst that activates peroxide for C-H oxidation. Elaborating on a previously reported ligand, they introduce bulky bis(trifluoromethyl) phenyl groups that roughly halve the conical angle-bounding substrate approach to the metal center. As a result, this bulkier catalyst favors oxidation at sterically unhindered sites on a substrate, whereas the previous catalyst manifested selectivity governed by



Science Editor's Choice- 4 October

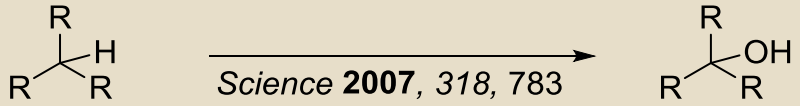
White Group

Allylic C-H oxidation:

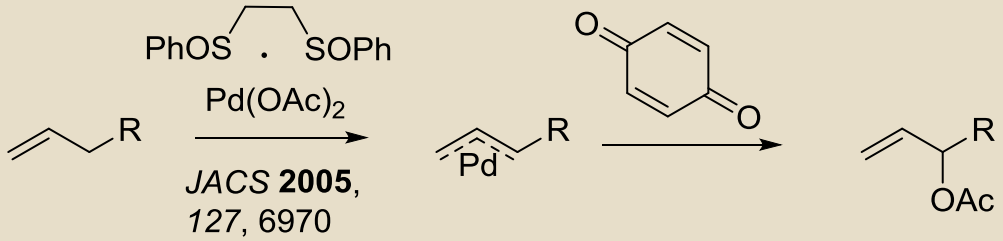


JACS **2007**, *129*, 7274

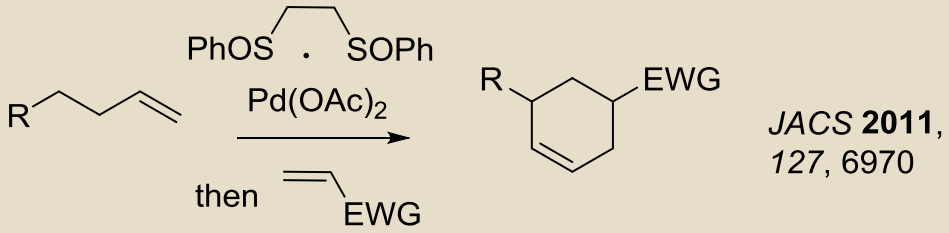
Aliphatic C-H oxidation:



Tandem Sulfoxide/
Quinone Oxidation:



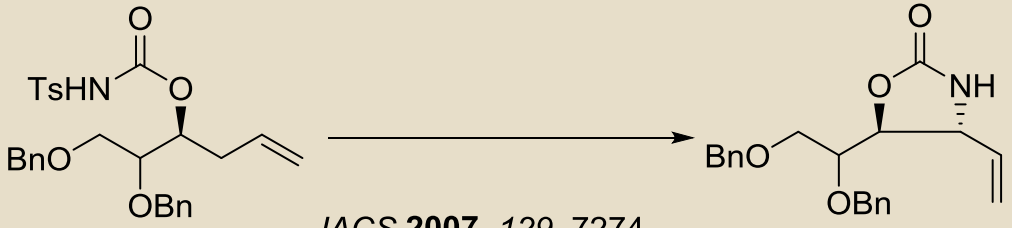
Dehydrogenative
DA reactions:



JACS **2011**,
127, 6970

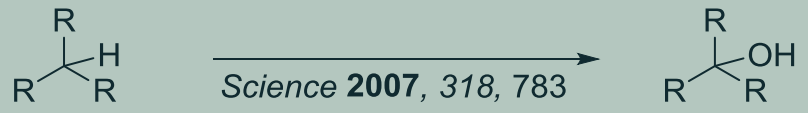
White Group

Allylic C-H oxidation:

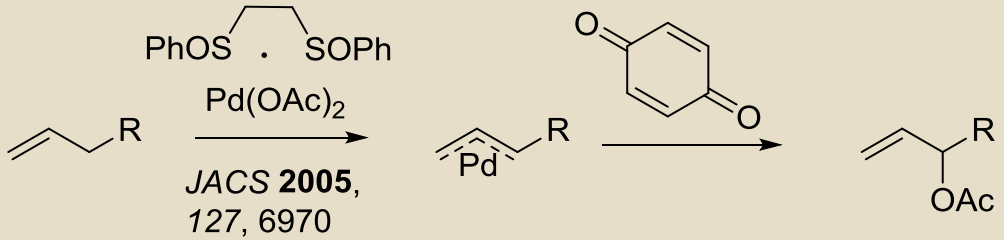


JACS **2007**, *129*, 7274

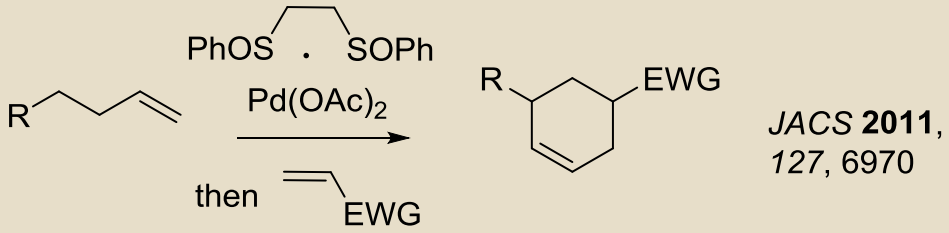
Aliphatic C-H oxidation:



Tandem Sulfoxide/
Quinone Oxidation:

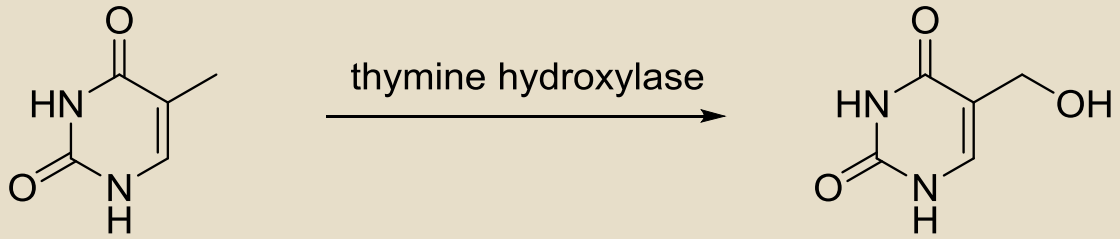


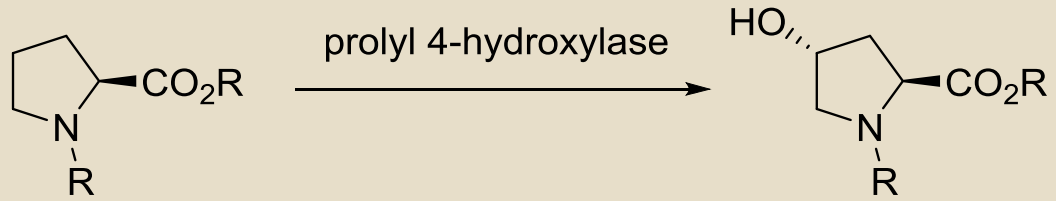
Dehydrogenative
DA reactions:

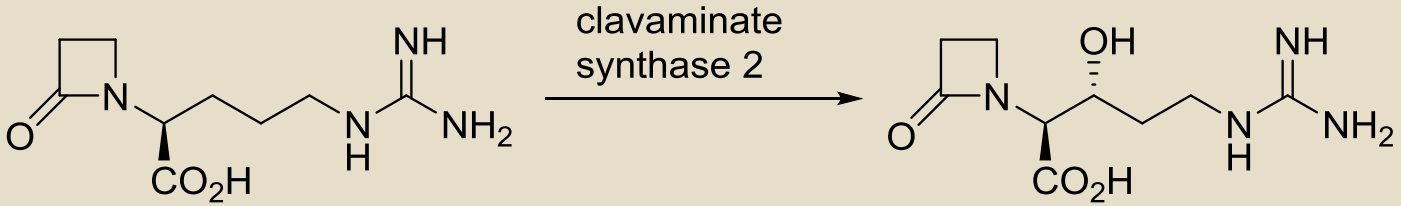


JACS **2011**,
127, 6970

Nature's C-H oxidation





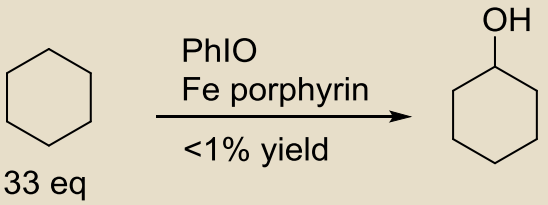


Active Oxidant:

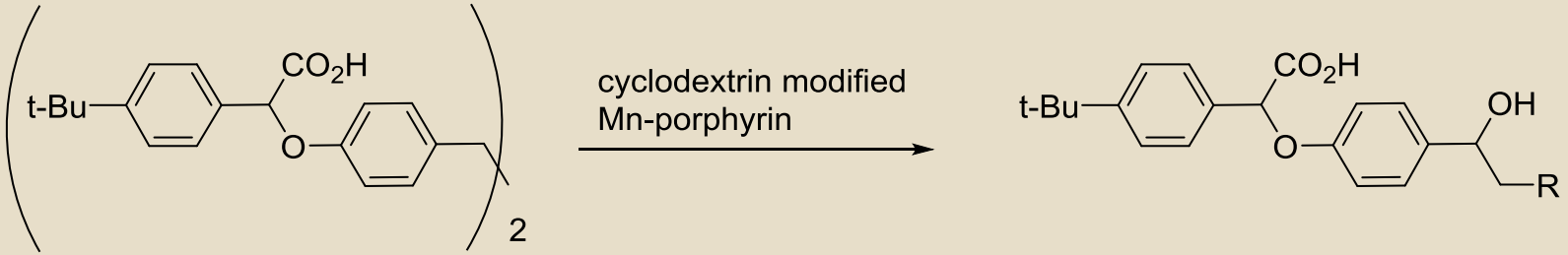
$L_nFe^{=}O$

Costas et al. *Chem Rev.* **2004**, *104*, 939-986

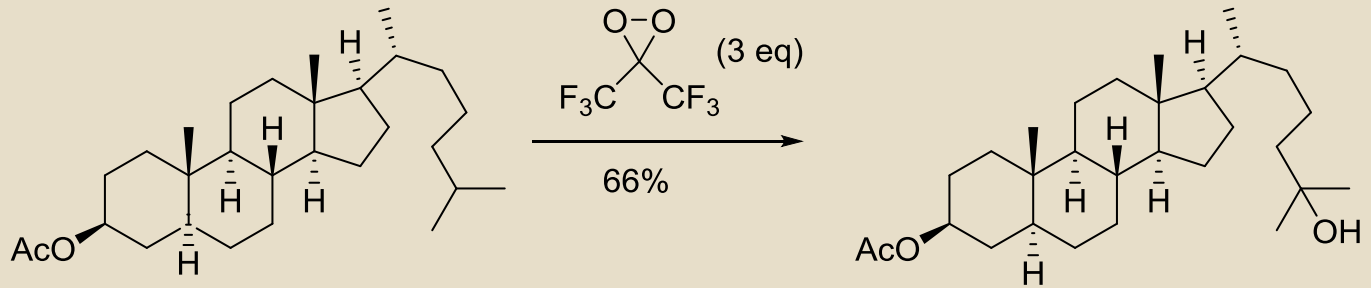
Previous Strategies



Grooves et al. *JACS* **1979**, *101*, 1032

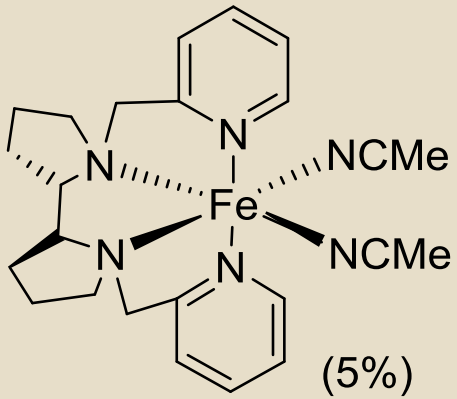


Breslow et al. *PNAS* **1997**, *94*, 11156

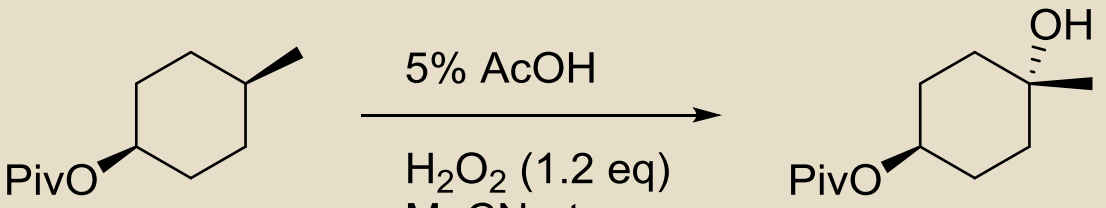


Curci et al. *JOC* **1992**, *57*, 5052.

White's Non-heme iron catalyst



(5%)

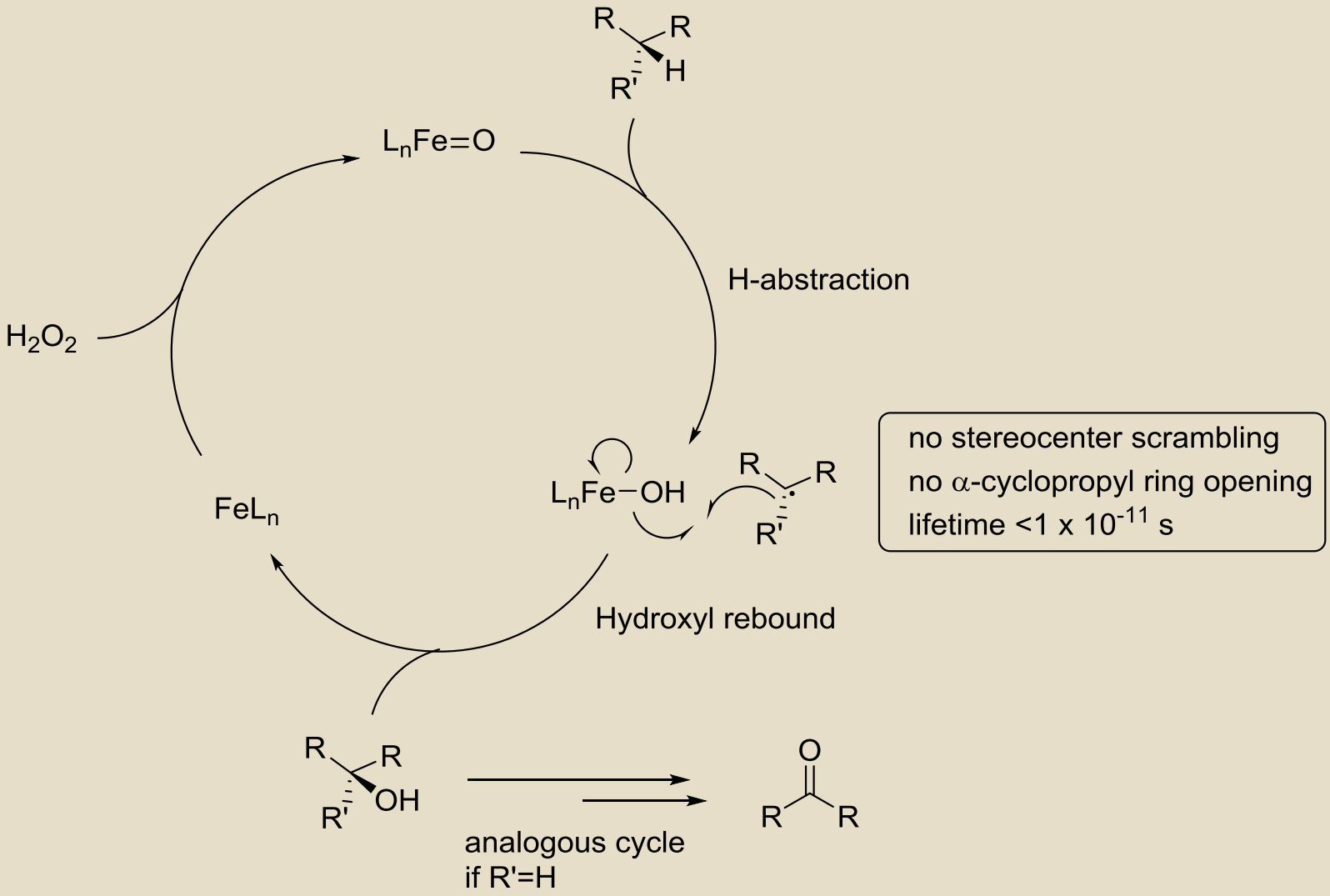


42%, 9:1 regioselectivity
single diasteromer

Science top 10 breakthrough of the year: 2007

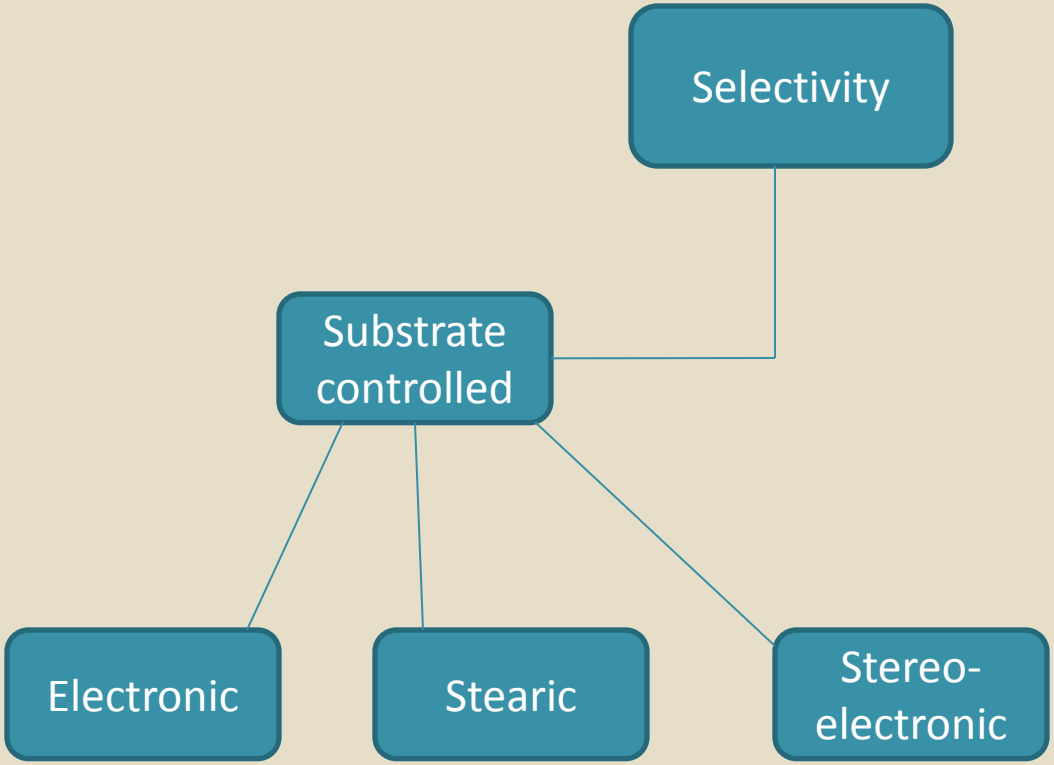
Chen and White, *Science* **2007**, *318*, 783

Mechanism

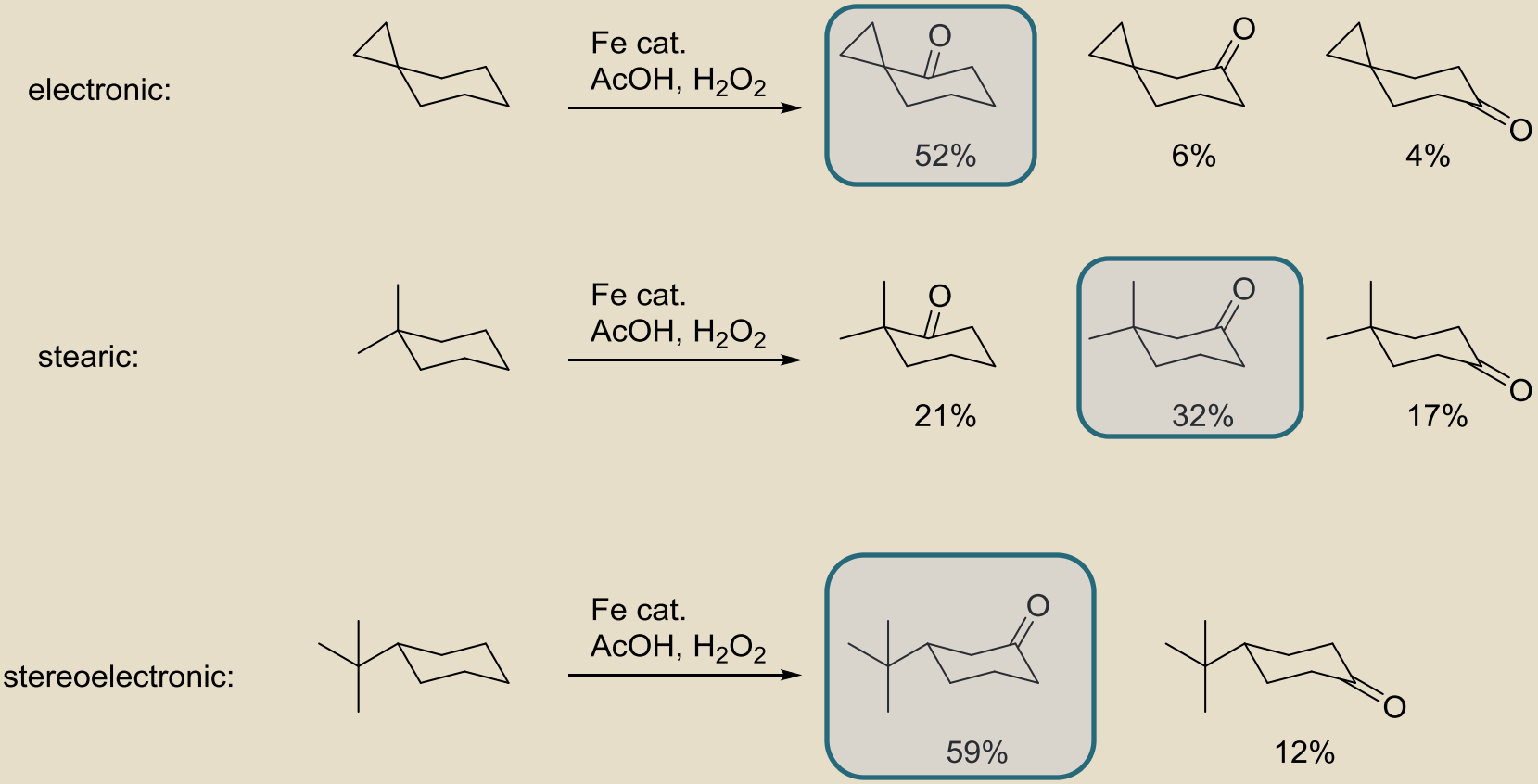


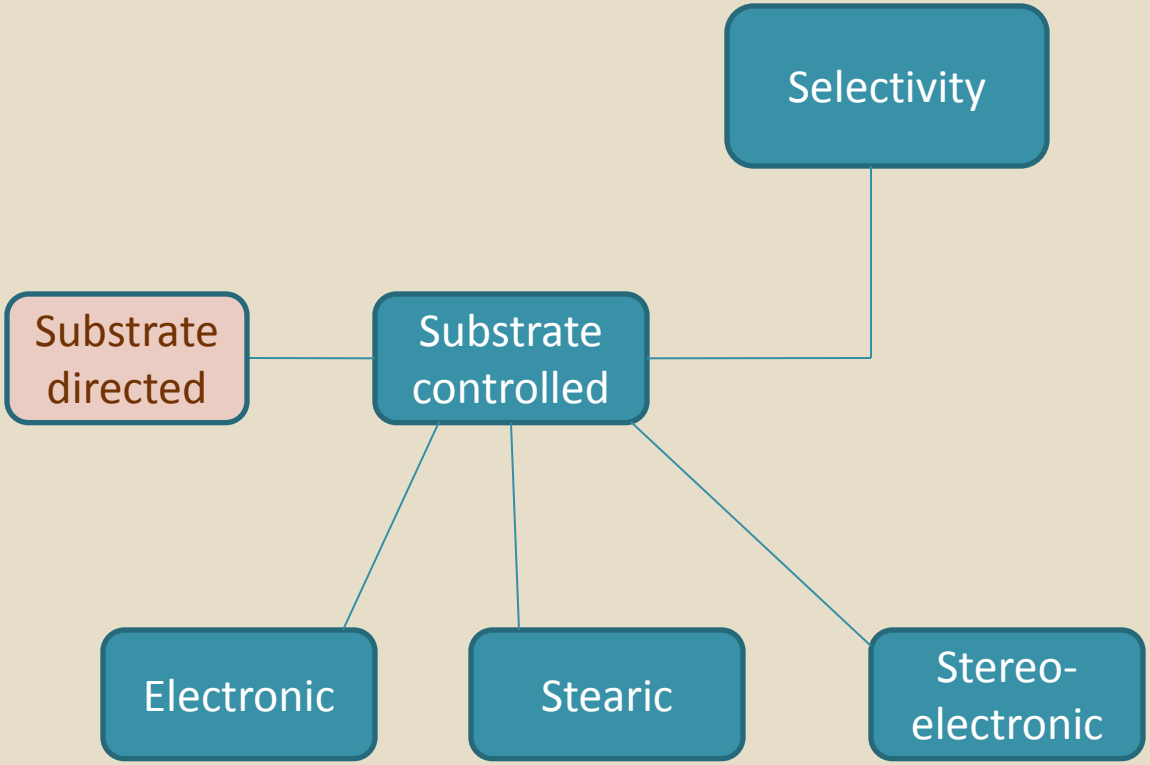
no stereocenter scrambling
no α-cyclopropyl ring opening
lifetime <1 x 10^{-11} s

Bigi, Reed, and White, *Nat. Chem.* **2007**, *3*, 216

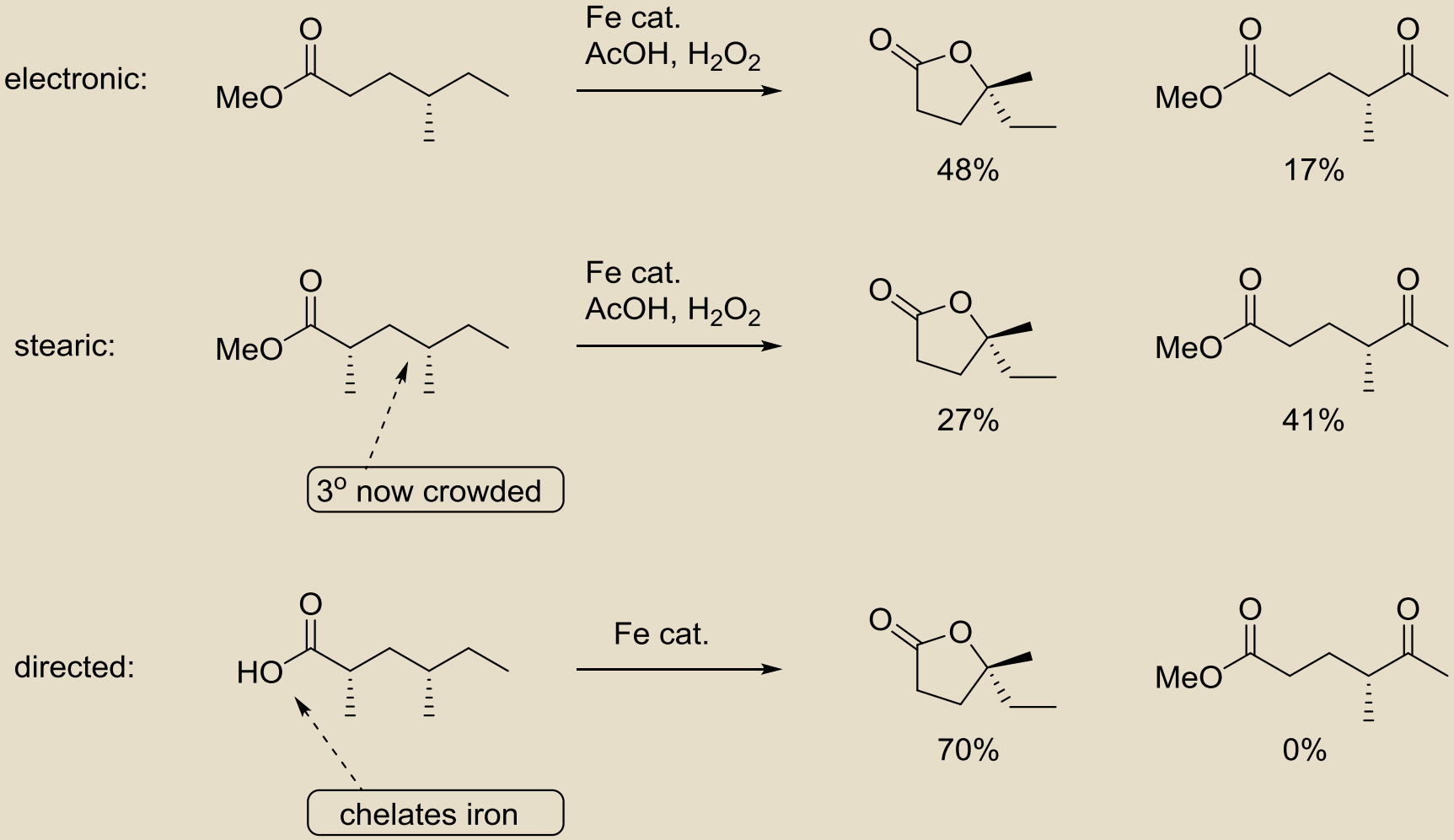

Selectivity
Substrate controlled
Electronic
Stearic
Stereo-electronic

Methylene Oxidation: Selectivity



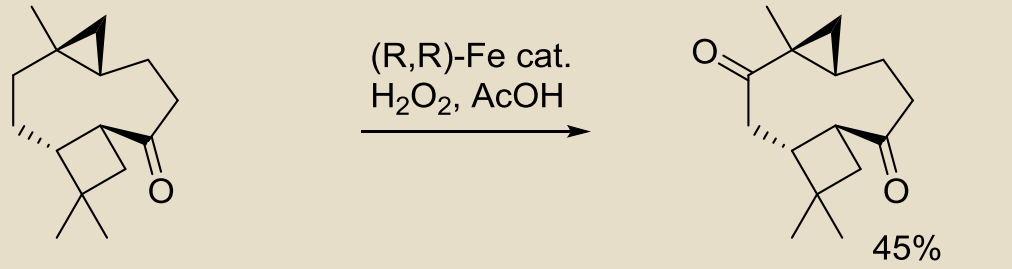

Selectivity
Substrate directed
Substrate controlled
Electronic
Stearic
Stereo-electronic

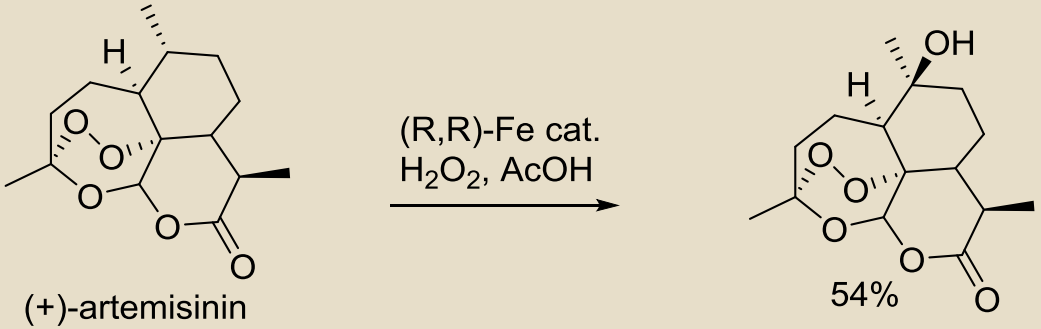
Acid Directing Effect

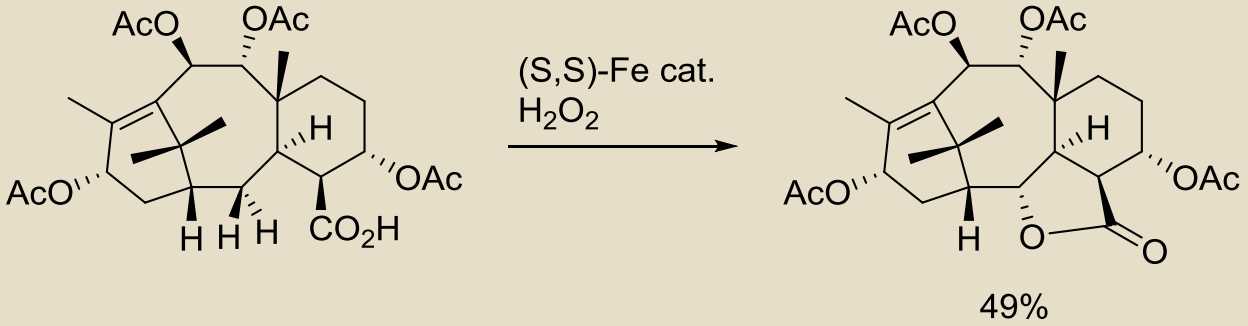


Chen and White, *Science* **2007**, *318*, 783

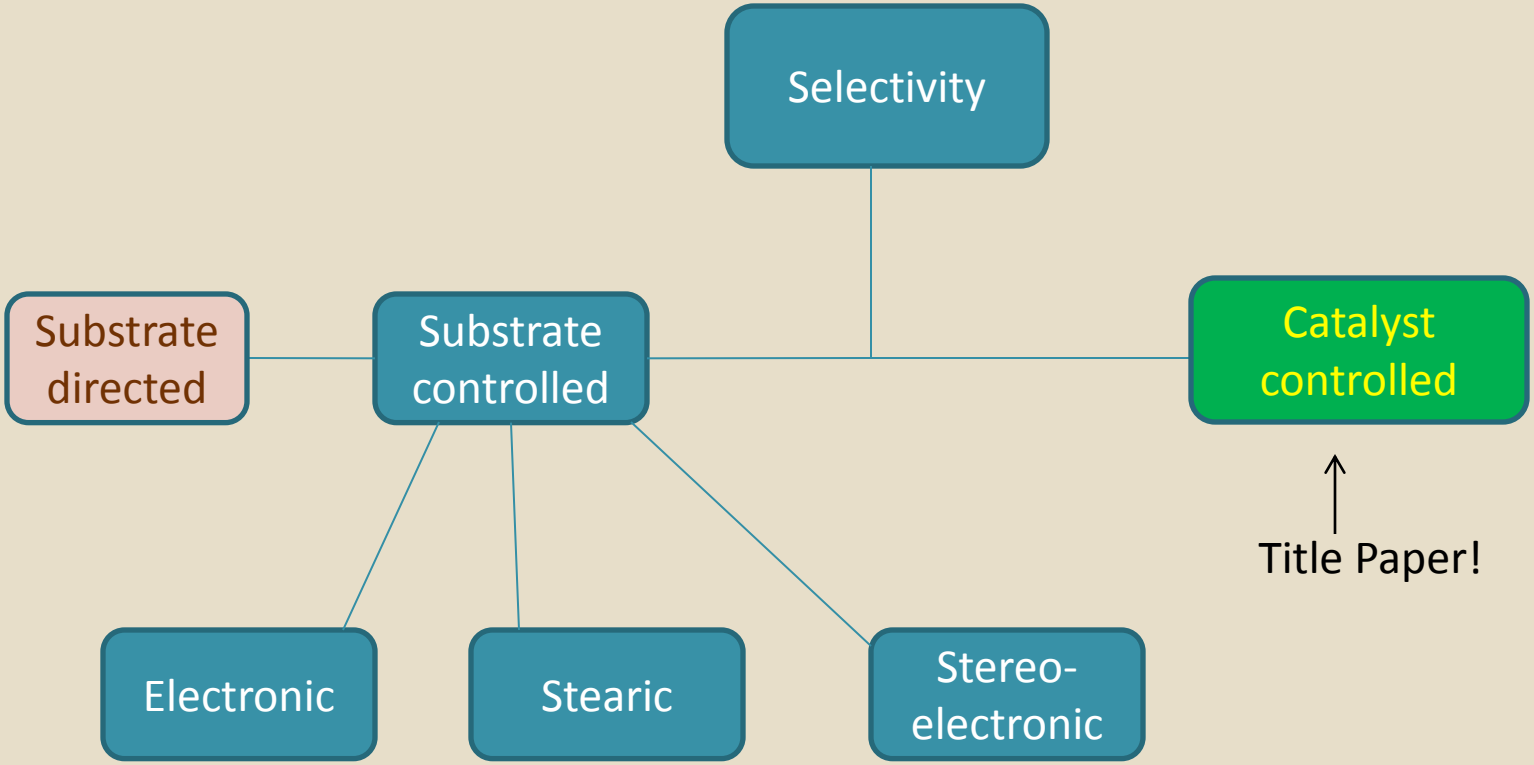
Complex Systems



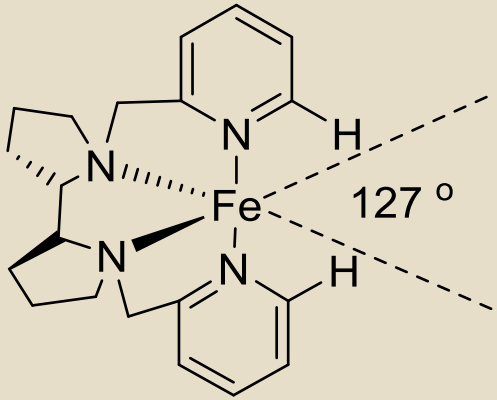




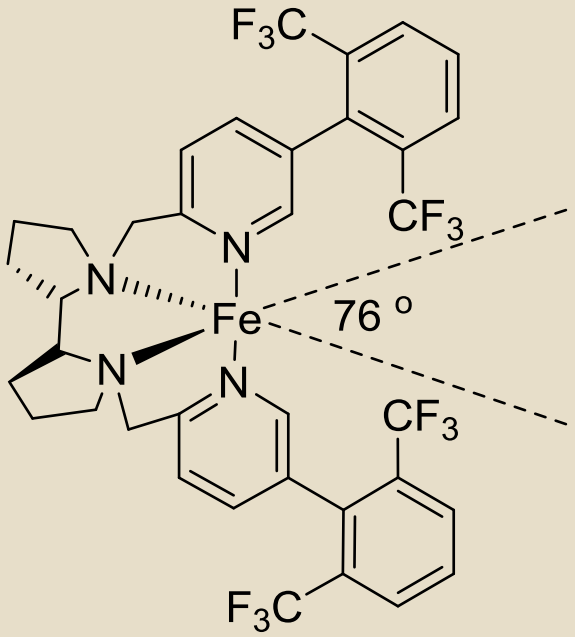
Chen and White, *Science* **2007**, *318*, 783; Chen and White, *Science* **2010**, *327*, 566; Bigi, Reed, and White, *JACS* **2012**, *134*, 9721


Selectivity
Substrate directed
Substrate controlled
Catalyst controlled
Title Paper!
Electronic
Stearic
Stereo-electronic

Re-designing a constrained catayst

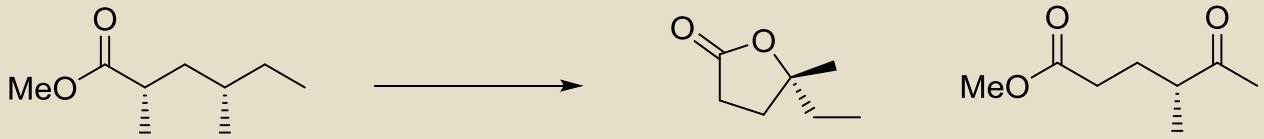


original

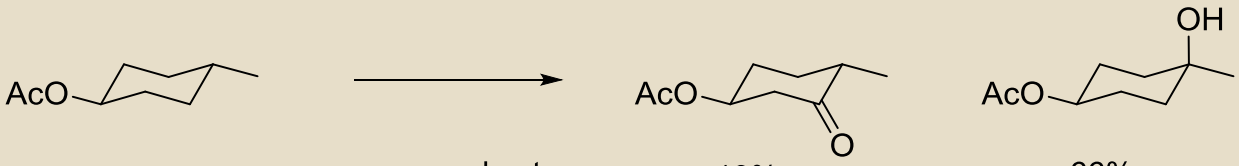


selectivity by stearic restriction

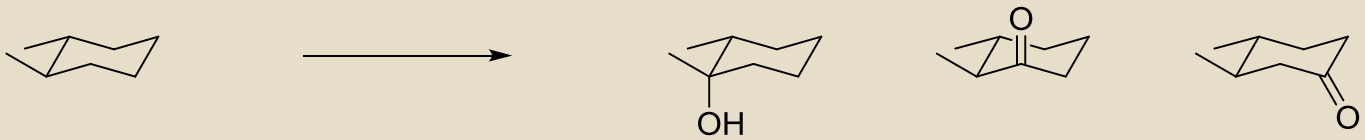
Modulating Selectivity



normal cat.	27%	41%
constrained cat.	11%	51%

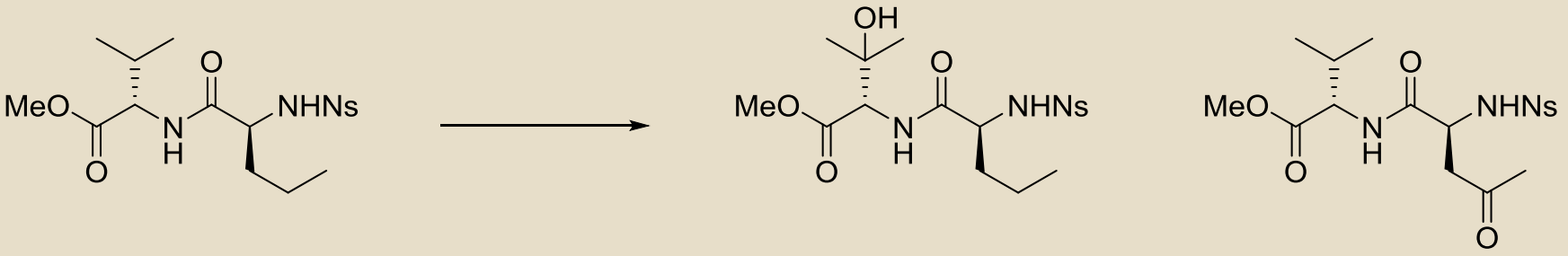


normal cat.	19%	66%
constrained cat.	51%	28%



normal cat.	29%	22%	28%
constrained cat.	7%	26%	44%

Modulating Selectivty



normal cat	27%	24%
constrained cat	6%	51%

Computational Model

- Model selectivity based on:
  - Electronics (E): from DFT analysis
  - Stearics (S): From A value
- Site selectivity between H_a and H_b:

$$\Delta\Delta G^{\ddagger} = f_{cat}(\Delta E_{ab}, \Delta S_{ab}) = 1.36\ log\ (a:b)$$

TS free energy

Computational function of catalyst

Experimental ratio

Predictability

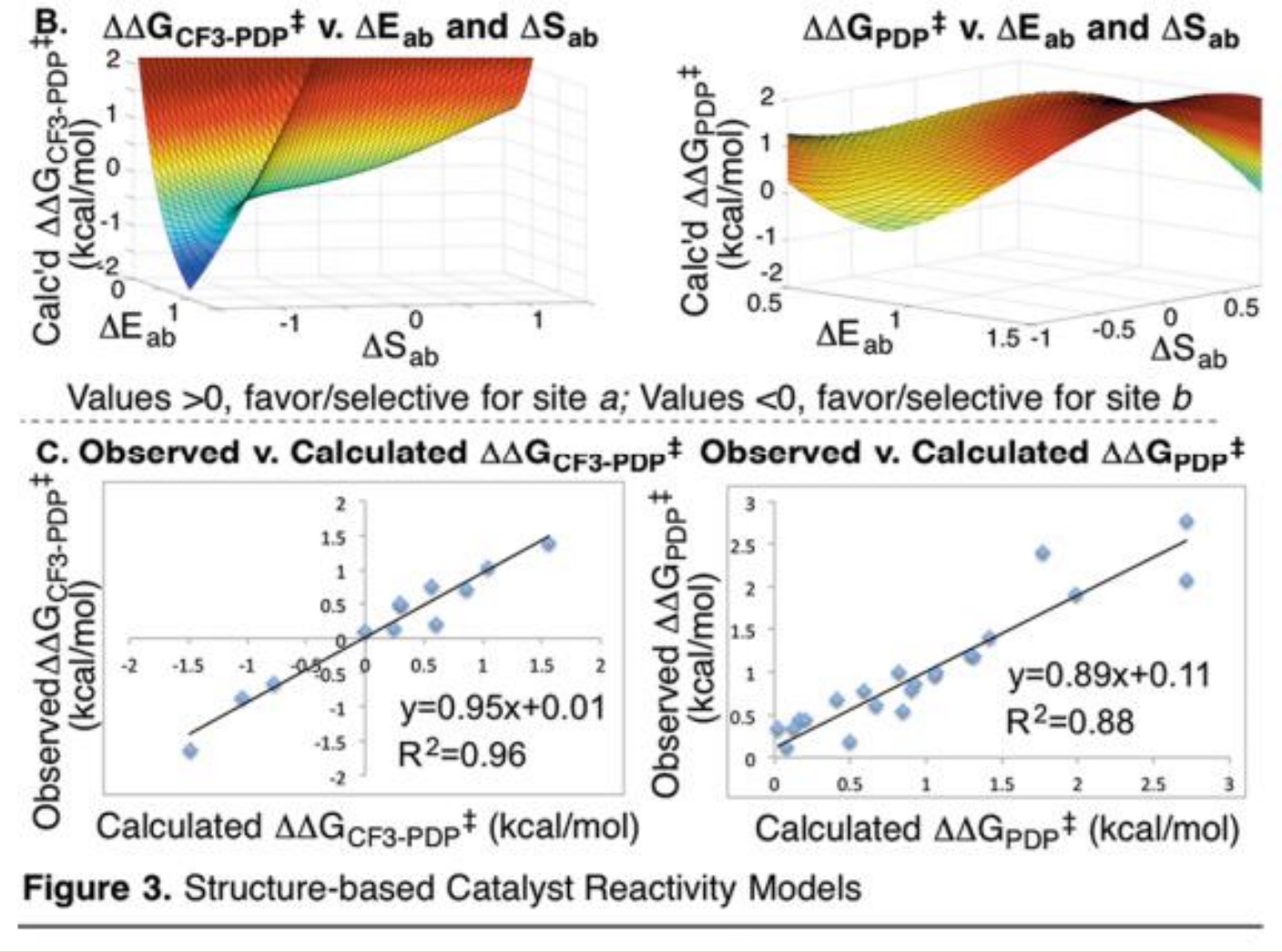
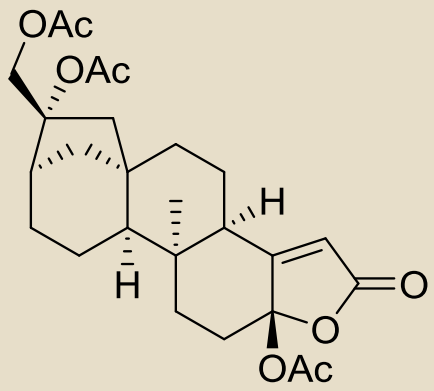
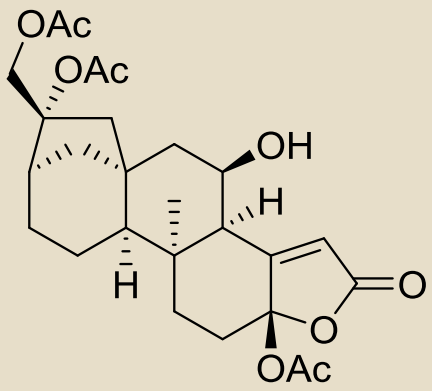


Figure 3. Structure-based Catalyst Reactivity Models

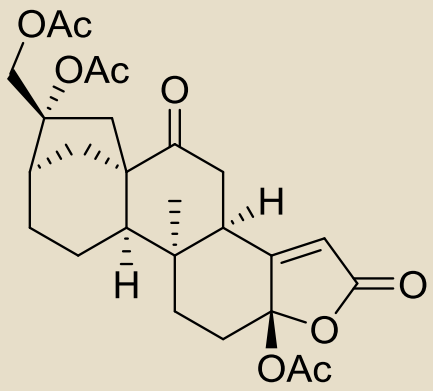
Testing the theory



acetoxytricalysiolide B
(from coffee)



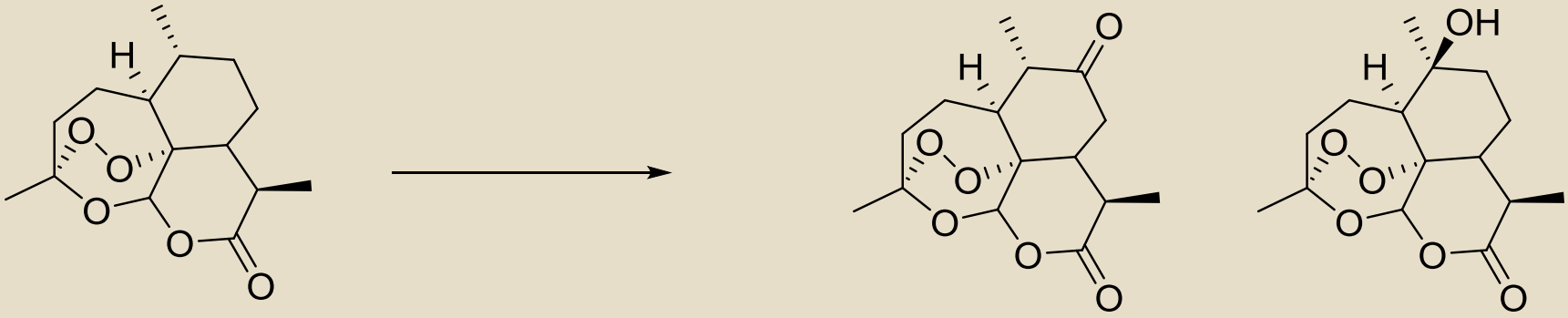
A



B

	predicted $\Delta\Delta G_{TS}$ A:B	Predicted A:B	Observed A:B
normal catalyst	-0.1 kcal/mol	1:1	1:1
constrained catalyst	1.4 kcal/mol	11:1	>10:1

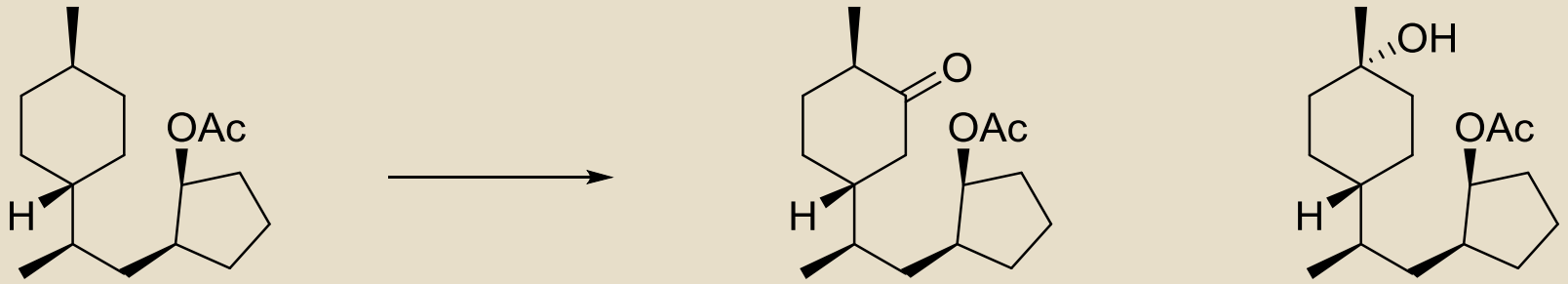
Overriding Selectivity



(+)-artemisinin **A** **B**

	Predicted A:B	Observed A:B
normal catalyst	1:1.3	1:2
constrained catalyst	17:1	11:1

Overriding Selectivty



nectaryl derivative

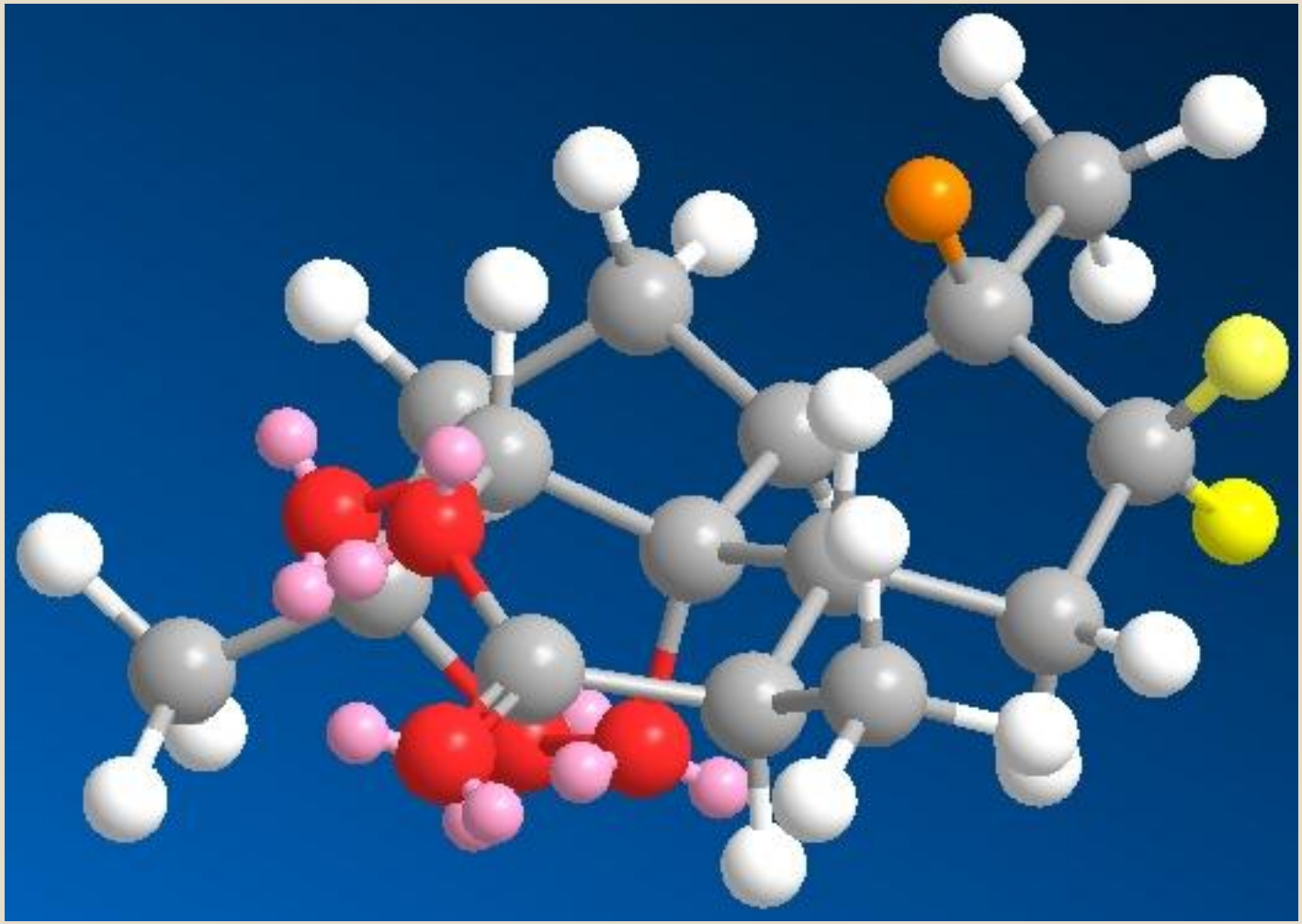
A

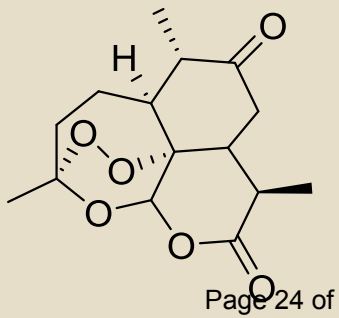
B

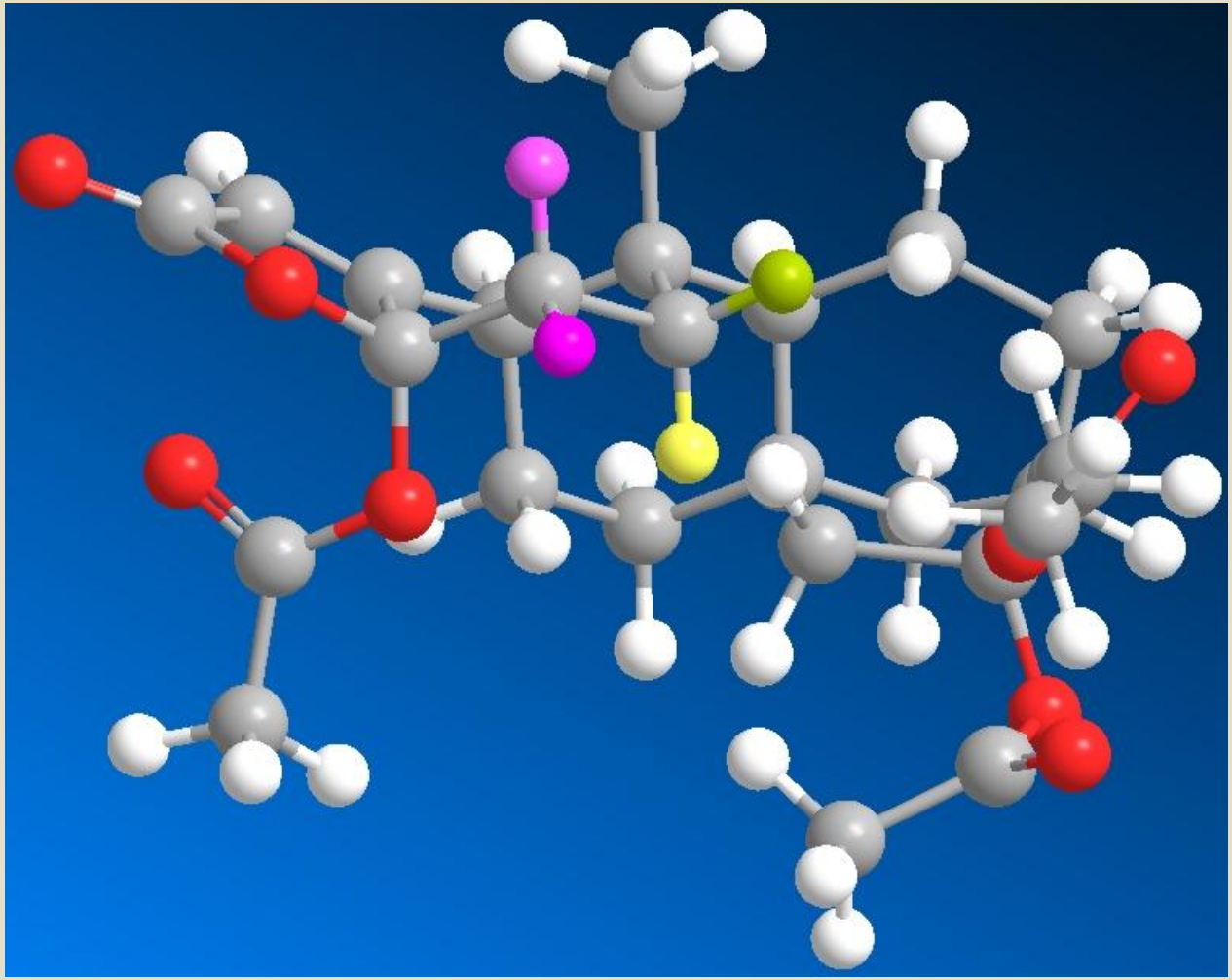
	Predicted A:B	Observed A:B
normal catalyst	1:1.5	1:1.3
constrained catalyst	3:1	6:1

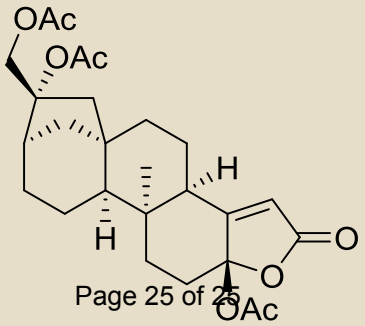
Conclusion

- From the 2007 paper: “Will fundamentally alter the way in which complex molecules are synthesized”
- Increasing predictability and compatibility bode well for an increased role of C-H oxidation in synthesis




H
O
O
O
O
O
O




OAc
OAc
H
H
O
O
OAc