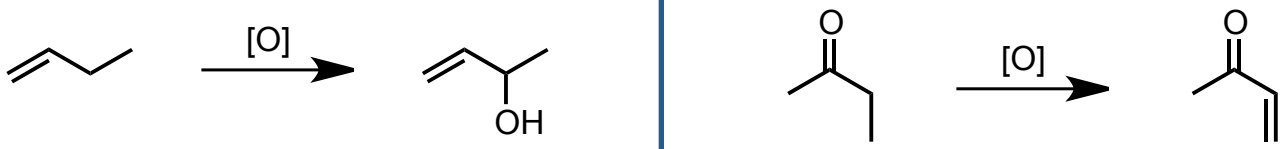
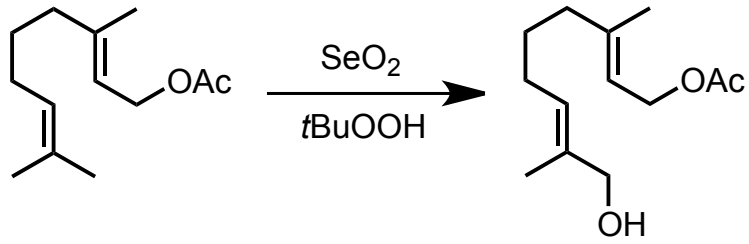
Allylic Oxidations
and
Oxidation of Ketones to Enones



Jeff Cannon
Chemistry Topics
May 3, 2011

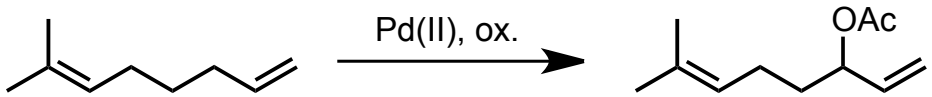
Common Allylic Oxidation Techniques

Selenium dioxide:

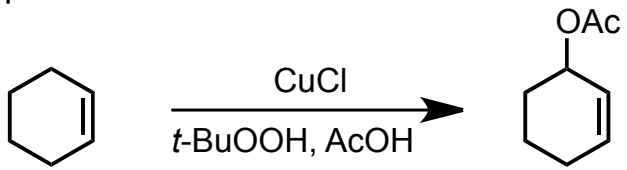


Transition Metal C–H Insertion:

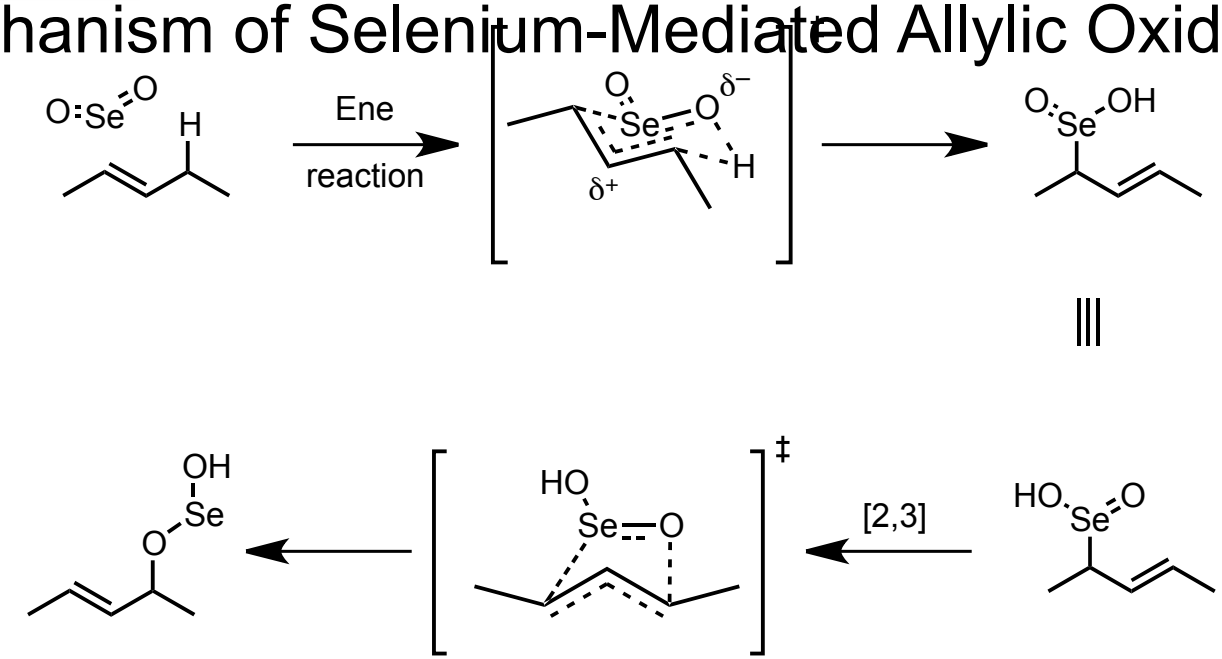
Palladium:



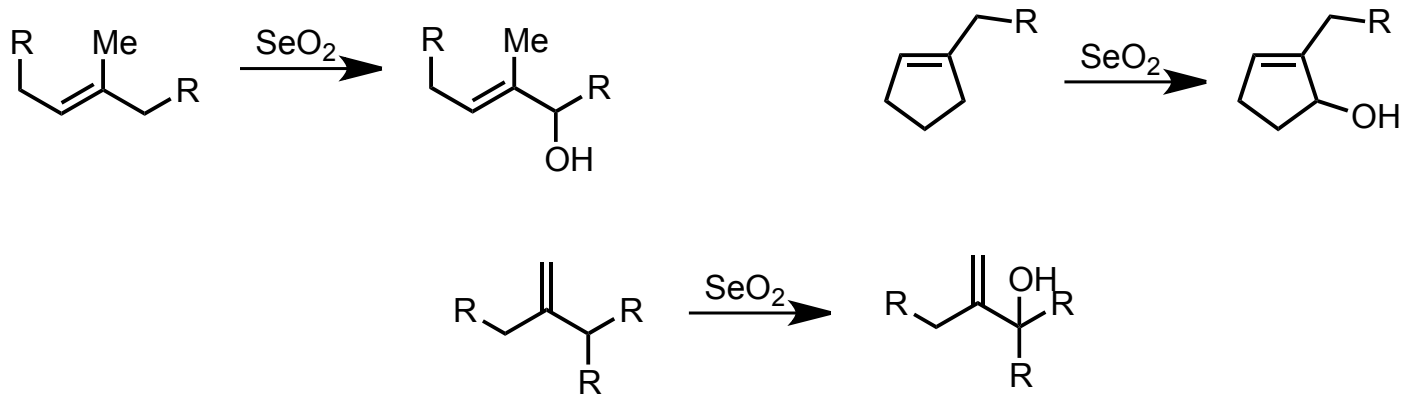
Copper:



Mechanism of Selenium-Mediated Allylic Oxidation

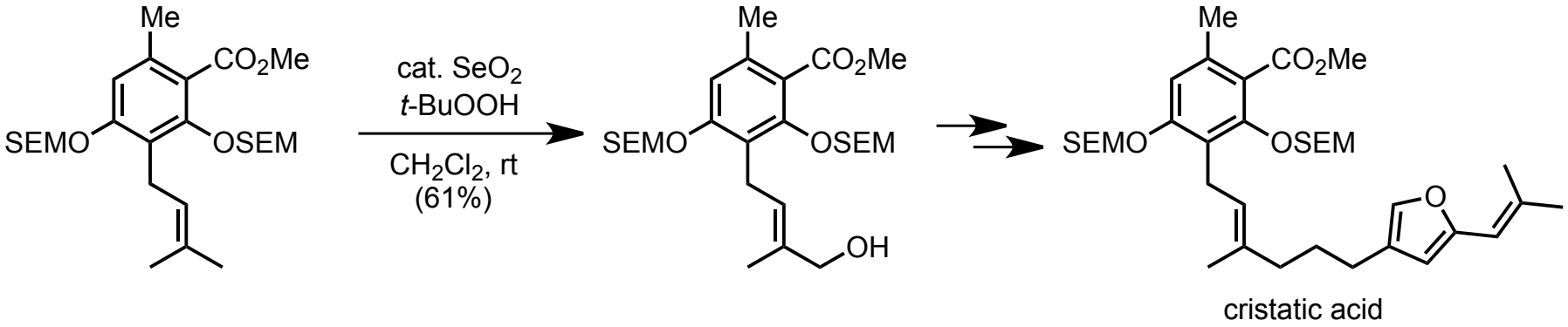


Displays good selectivity trends for substituted olefins:



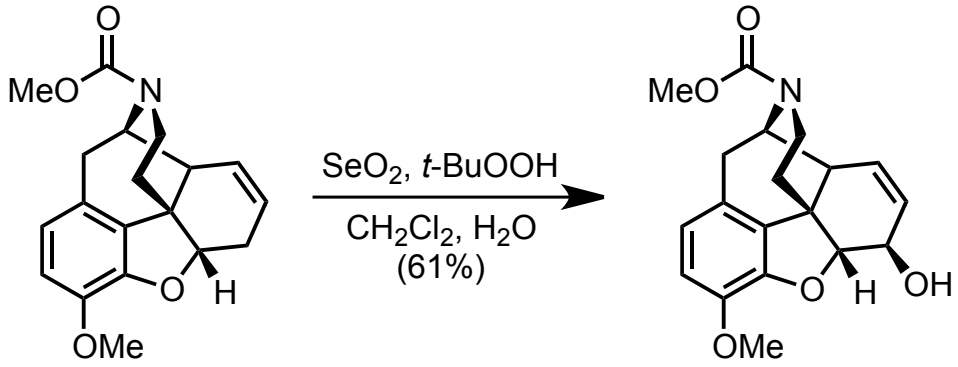
Examples of Selenium Dioxide Allylic Oxidation in Synthesis

Fürstner *Org. Lett.* **2000**, *2*, 2467:



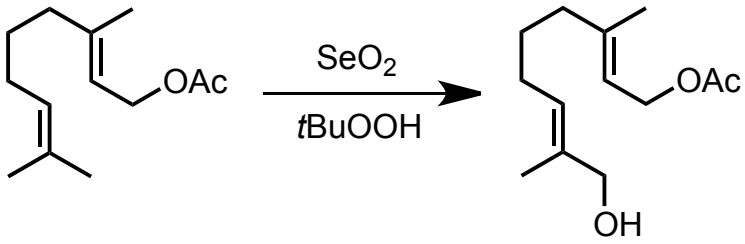
cristatic acid

Stork *J. Am. Chem. Soc.* **2009**, *131*, 11402:



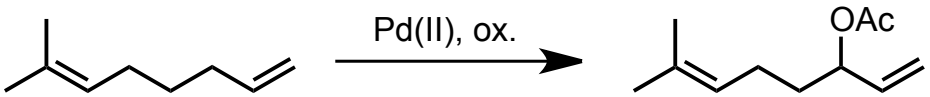
Common Allylic Oxidation Techniques

Selenium dioxide:

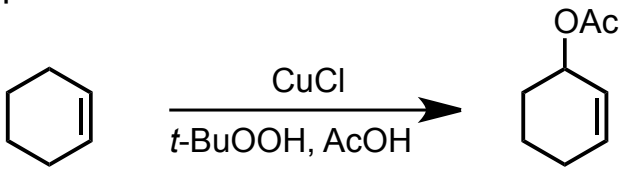


Transition Metal C–H Insertion:

Palladium:

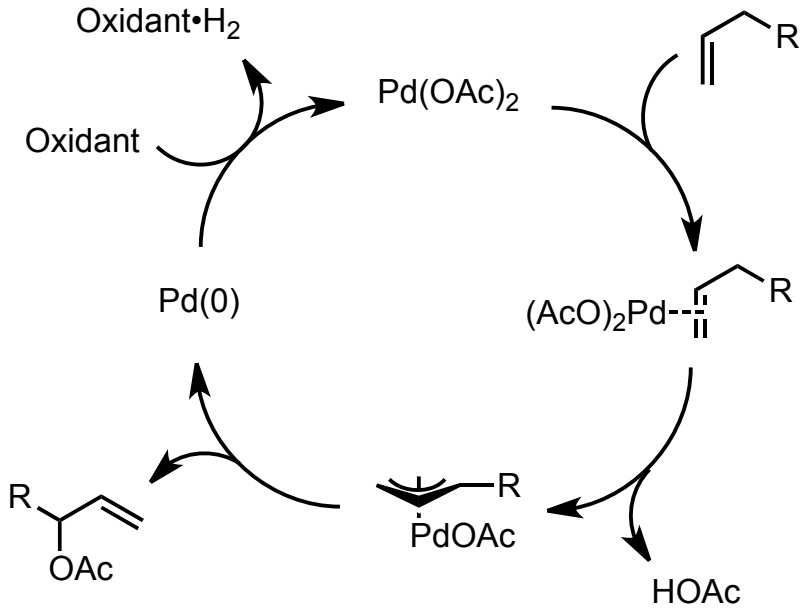


Copper:

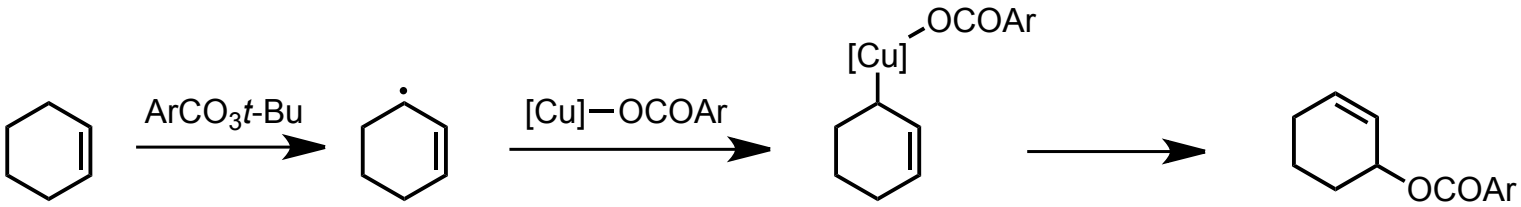


Mechanism of Transition Metal-Catalyzed Allylic Oxidation

Palladium:

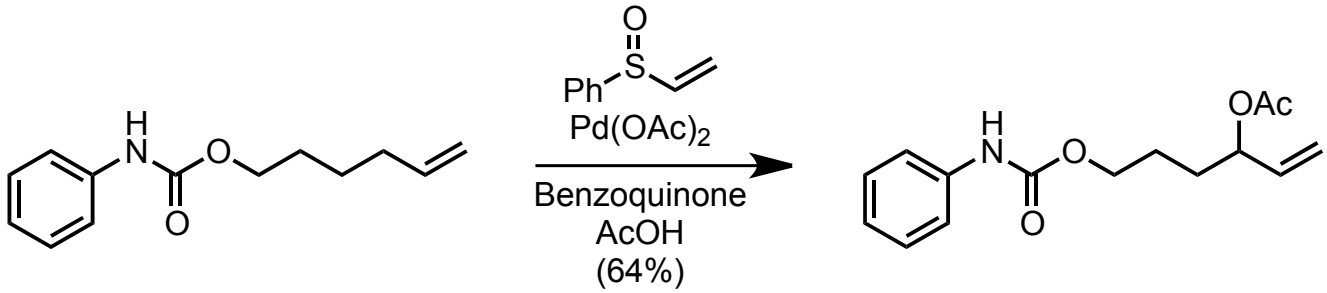


Copper:

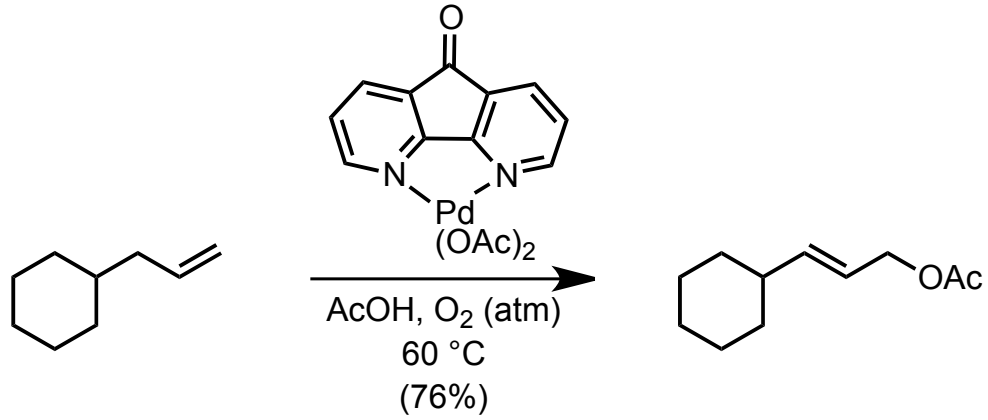


Examples of Transition Metal-Catalyzed Allylic Oxidation

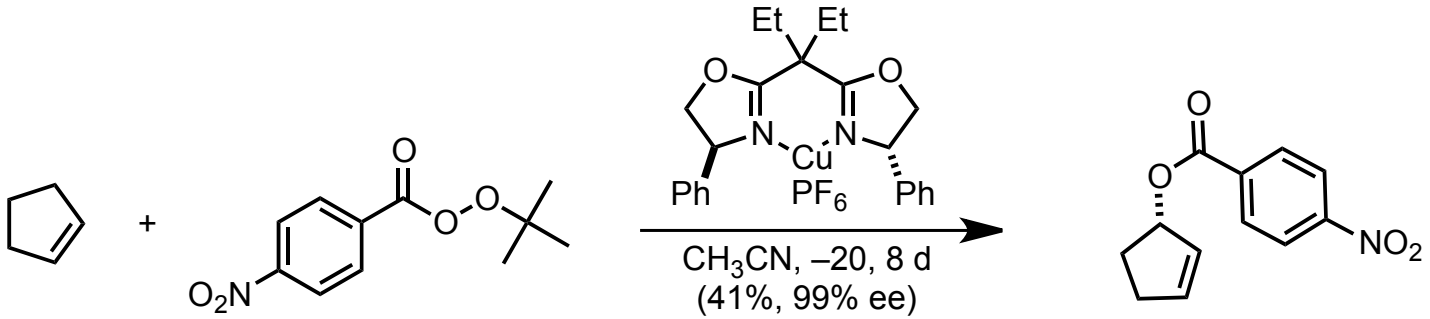
White:



Stahl:



Andrus:



Summary of Allylic Oxidation Reactions

Selenium dioxide mediated allylic oxidations:

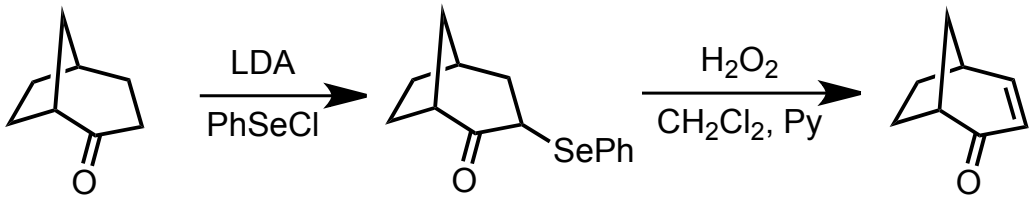
- Proceed through a double-pericyclic (ene, [2,3]) mechanism
- Are often highly selective
- Can have multiple byproducts:
  - Selenoxide elimination
  - Pummerer-type reactions
  - Selenium dioxide readily oxidizes ketones to 1,2-diketones
  - Overoxidation products can be problematic

Transition metal-catalyzed allylic oxidations:

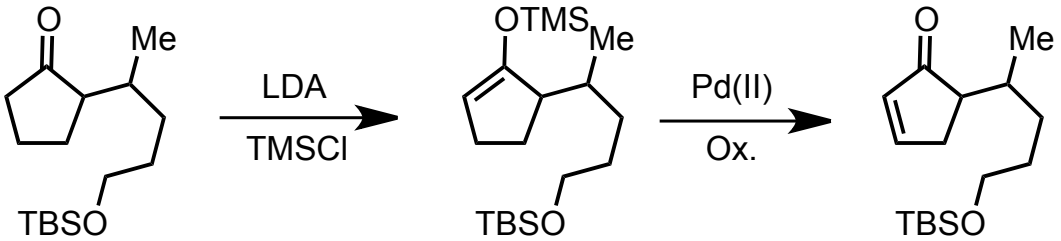
- Palladium-catalyzed reactions currently only effective on terminal olefins
- Palladium regioselectivity can be tuned by ligand selection
- Copper reacts with internal olefins, but regioselectivity is poor
- Enantioselectivity is possible, but not general yet

Common Ketone to Enone Techniques

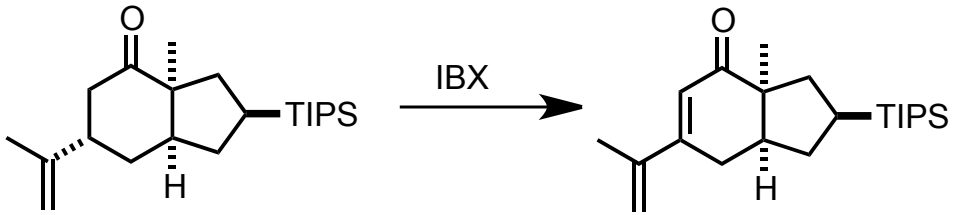
Selenoxide Elimination:



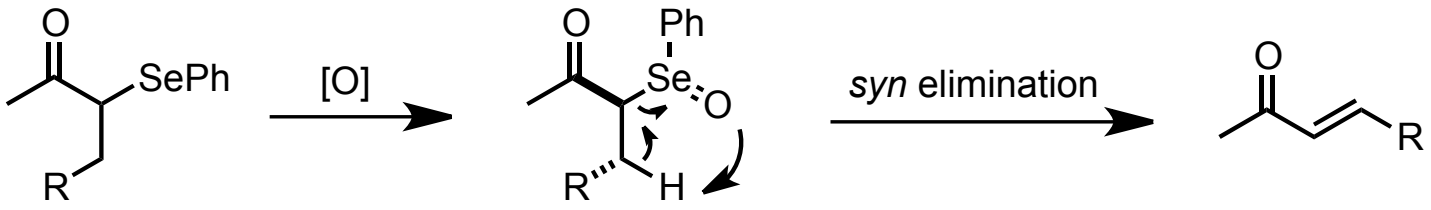
Saegusa Oxidation:



IBX Oxidation:



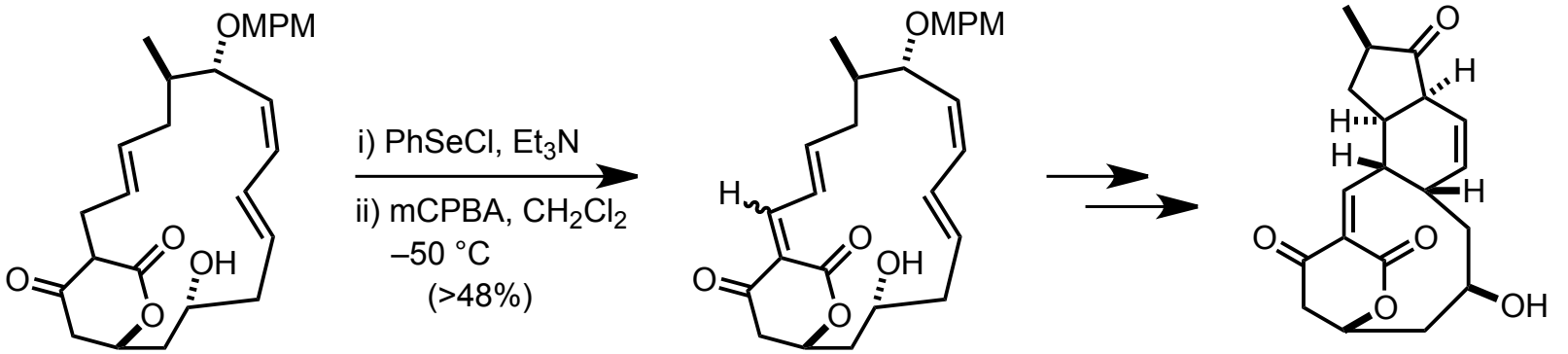
Mechanism of Selenoxide Elimination



- *Syn* elimination produces selectively the *trans* olefin in acyclic systems
- Endocyclic double-bonds formed selectively unless no *syn* hydrogen is available
- Conjugated products formed selectively

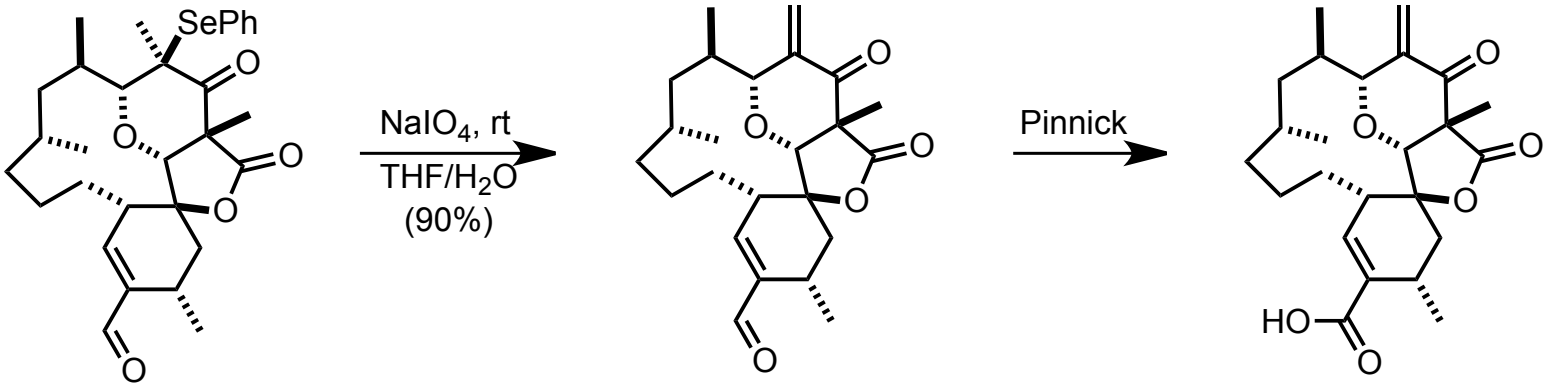
Examples of Selenoxide Elimination

Tadano, *J. Am. Chem. Soc.* **2003**, *125*, 14722:



(+)-macquarimicin A

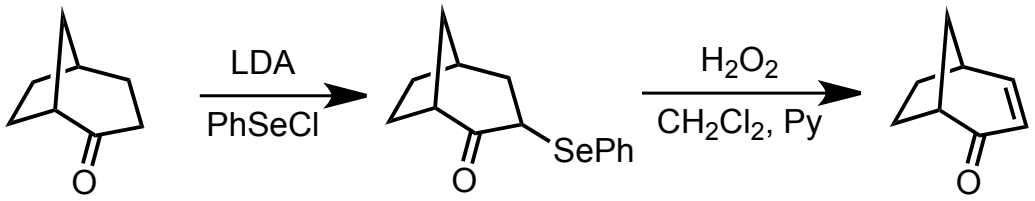
Smith, *J. Am. Chem. Soc.* **2009**, *131*, 2348:



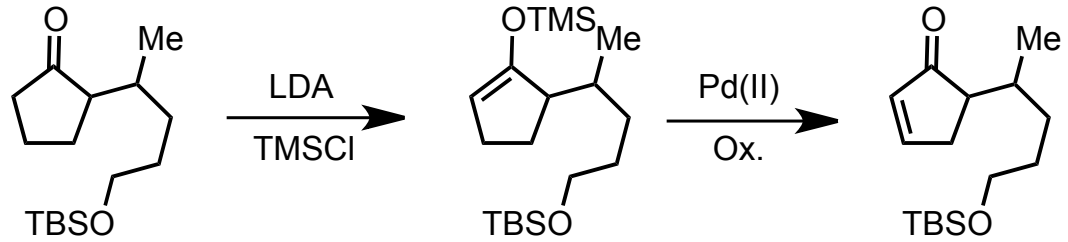
(–)-okilactomycin

Common Ketone to Enone Techniques

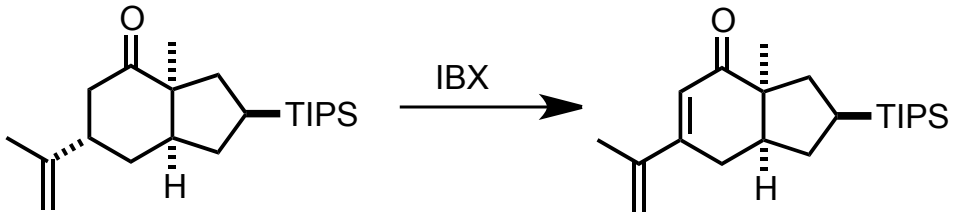
Selenoxide Elimination:



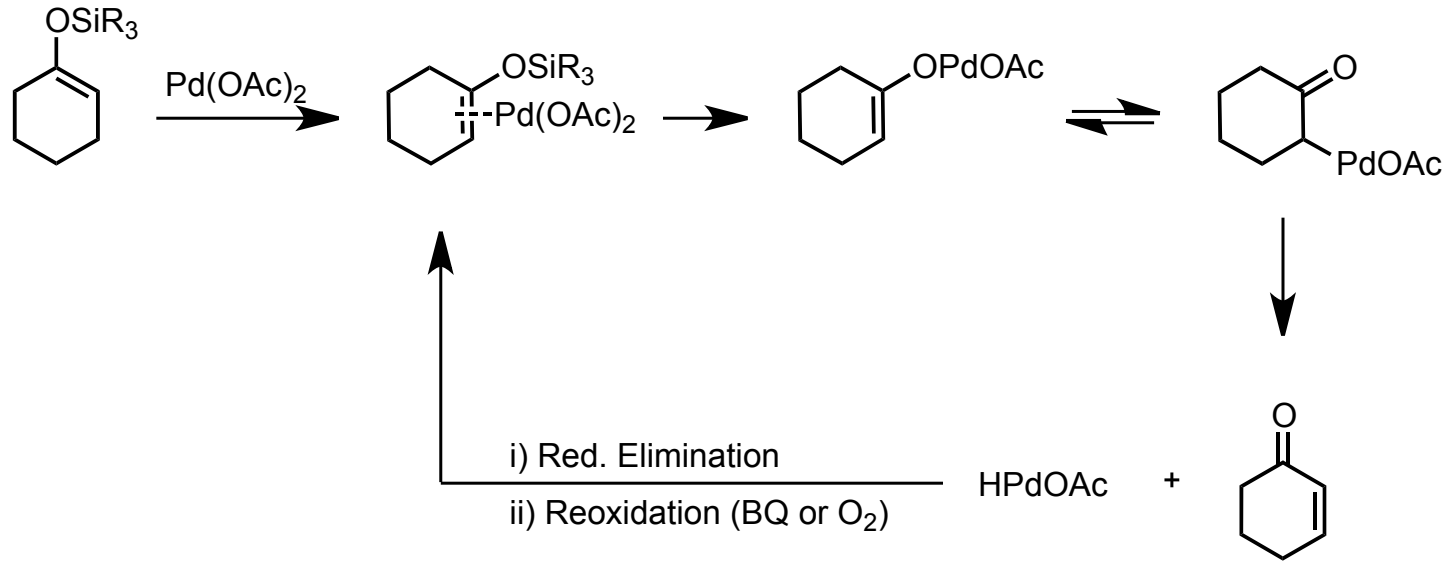
Saegusa Oxidation:



IBX Oxidation:



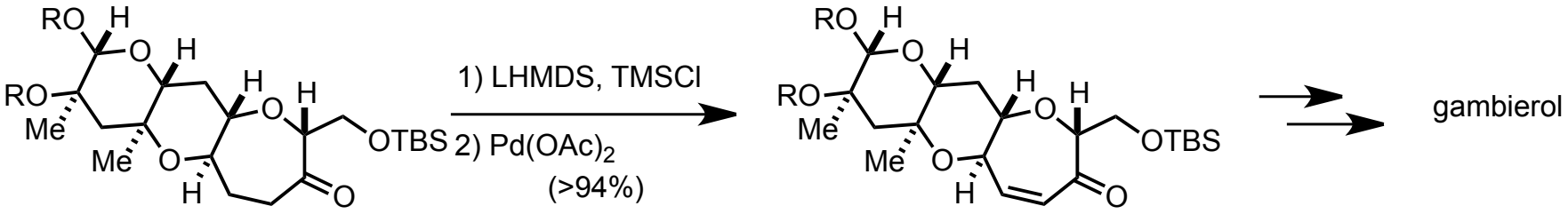
Mechanism of Saegusa Oxidation



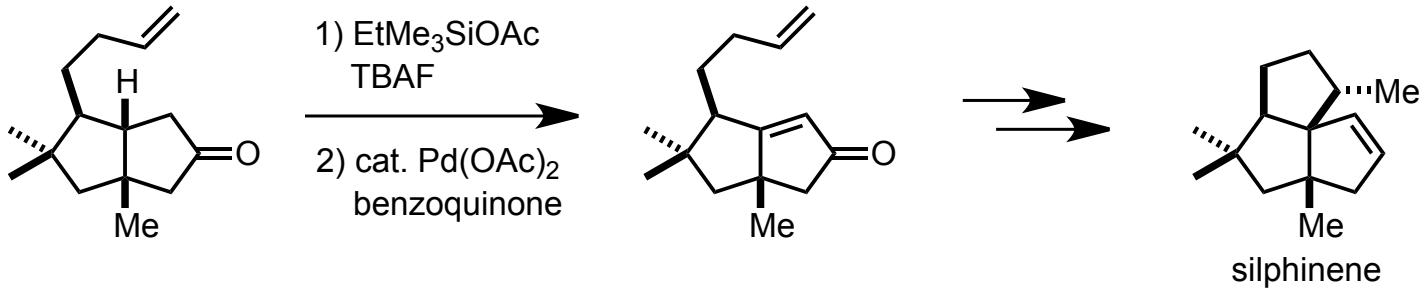
- Often requires a large amount of $Pd(OAc)_2$ (>0.5 equiv) to acquire a substantial rate
- Fairly mild oxidation conditions
- Enol silanes are easily formed from corresponding ketones

Examples of Saegusa Oxidation

Sasaki, *J. Am. Chem. Soc.* **2002**, *124*, 14983:

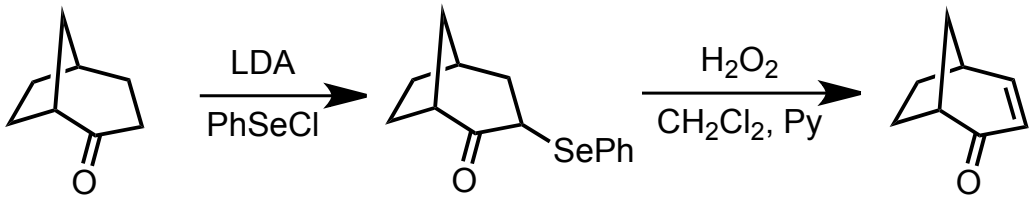


Crimmins, *J. Am. Chem. Soc.* **1986**, *108*, 3435:

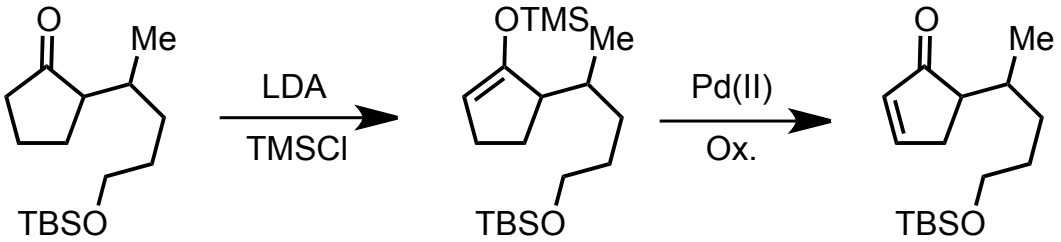


Common Ketone to Enone Techniques

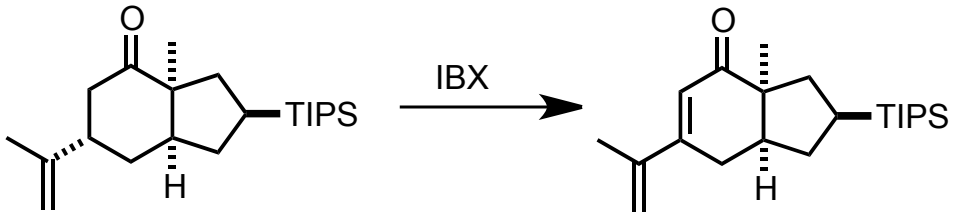
Selenoxide Elimination:



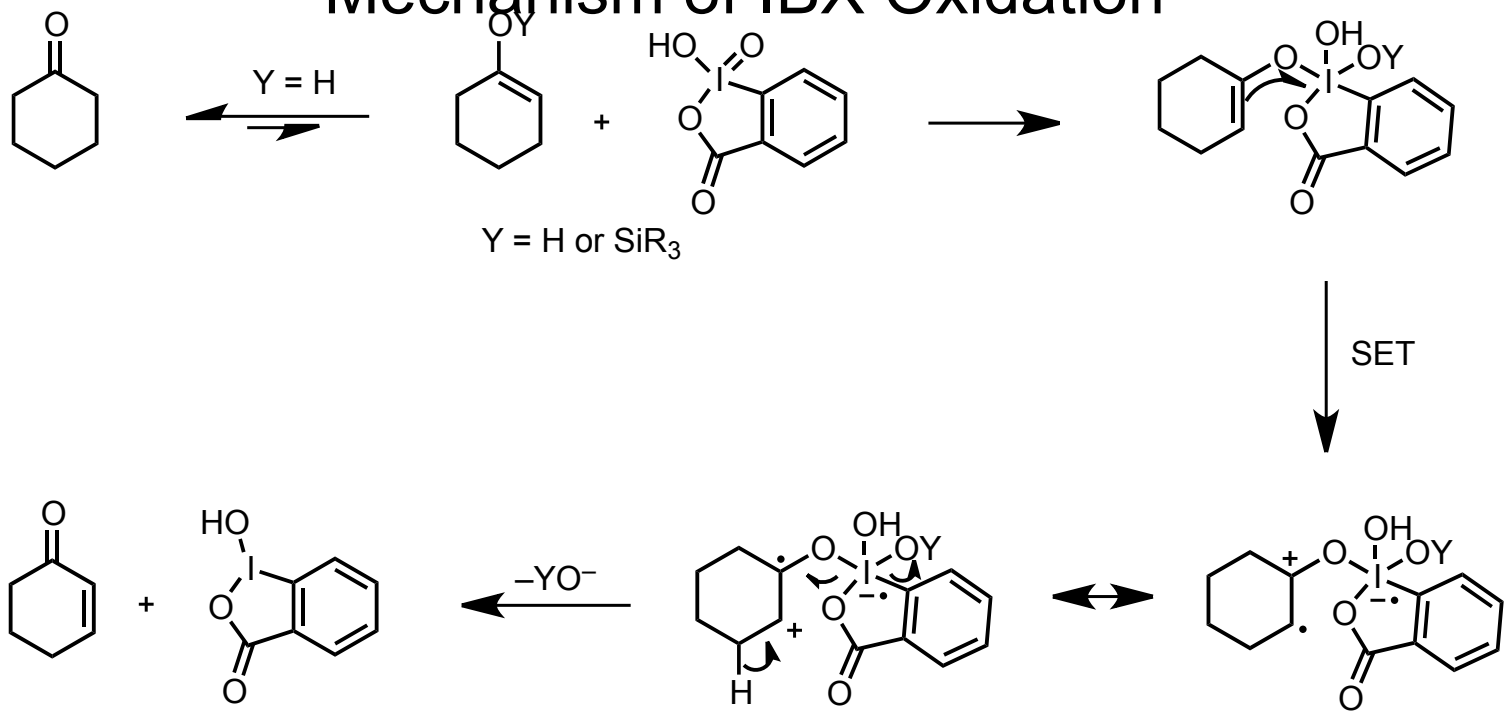
Saegusa Oxidation:



IBX Oxidation:



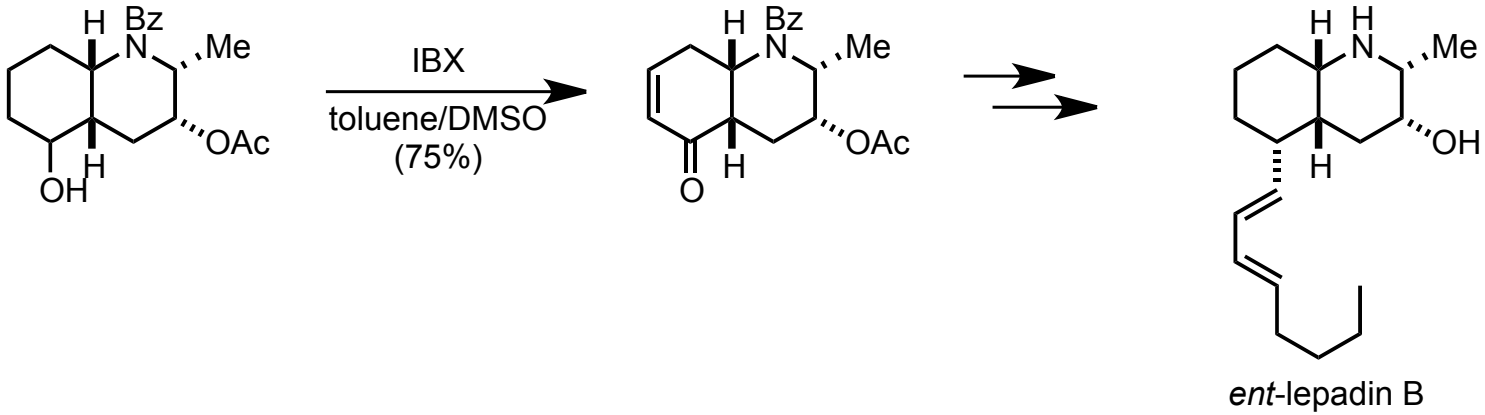
Mechanism of IBX Oxidation



- Will oxidize ketones, enol silanes, and alcohols directly to enones.
- More cost-effective than Saegusa conditions
- IBX will oxidize alcohols to ketones and aldehydes

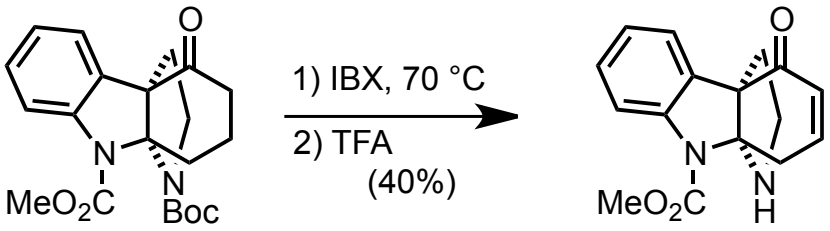
Examples of IBX Oxidation

Charette, *J. Am. Chem. Soc.* **2008**, *130*, 13873:



ent-lepadin B

Overman, *J. Am. Chem. Soc.* **2008**, *130*, 5368:



Summary of Oxidations of Ketones to Enones

Selenoxide Elimination:

- *Syn*-elimination mechanism usually provides high stereoselectivity
- Requires use of toxic and odorous selenium reagents
- Similar reactivity extends to sulfoxide elimination

Saegusa Oxidation:

- β-Hydride elimination of palladium enolate mechanism
- Often requires >0.5 equiv. of $Pd(OAc)_2$ to proceed, though truly catalytic examples exist
- Oxidation is site-selective if enol-silane can be generated selectively, including from conjugate addition reactions.

IBX oxidation:

- Single-electron transfer oxidation mechanism
- Mild reaction conditions can provide enone directly from ketone or alcohol
- Will react with other oxidizable alcohols in the molecule

Seminal References

Selenium Allylic Oxidation:

Guillemonat, A. *Annali di Chimica Applicata* **1939**, *11*, 143–211.

Metal-catalyzed allylic oxidation:

Campbell, A. N.; White, P. B.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 15116–15119.

Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970–6971.

Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845–866.

Selenoxide elimination:

Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447.

Saegusa oxidation:

Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.

IBX oxidation:

Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.