

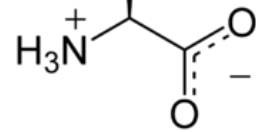
## Organocatalysis

Definition: a type of catalysis where the catalyst in the chemical reaction is an organic (non-metallic) compound.

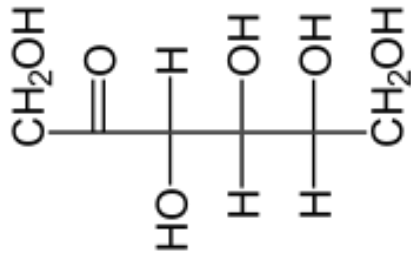
Origins from 3 places

- Aldolase**

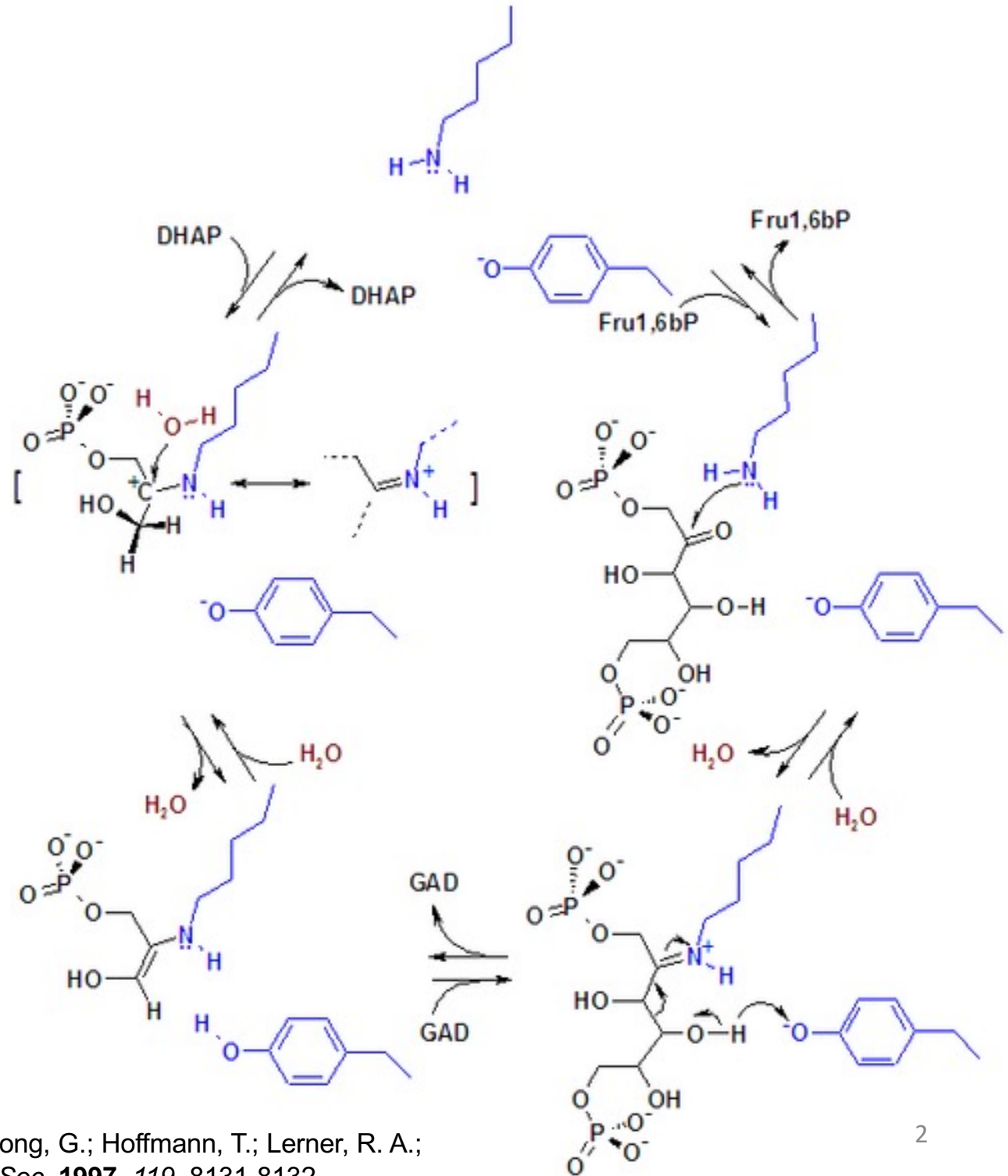
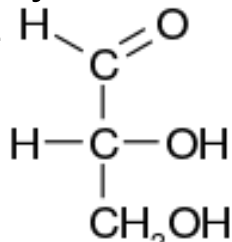
- Lysine<sup>+</sup>NH<sub>3</sub>



- Reversible conversion
- Fructose

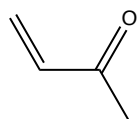
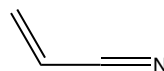
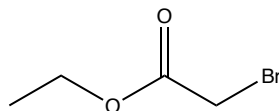
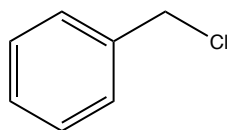
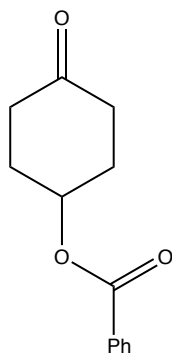
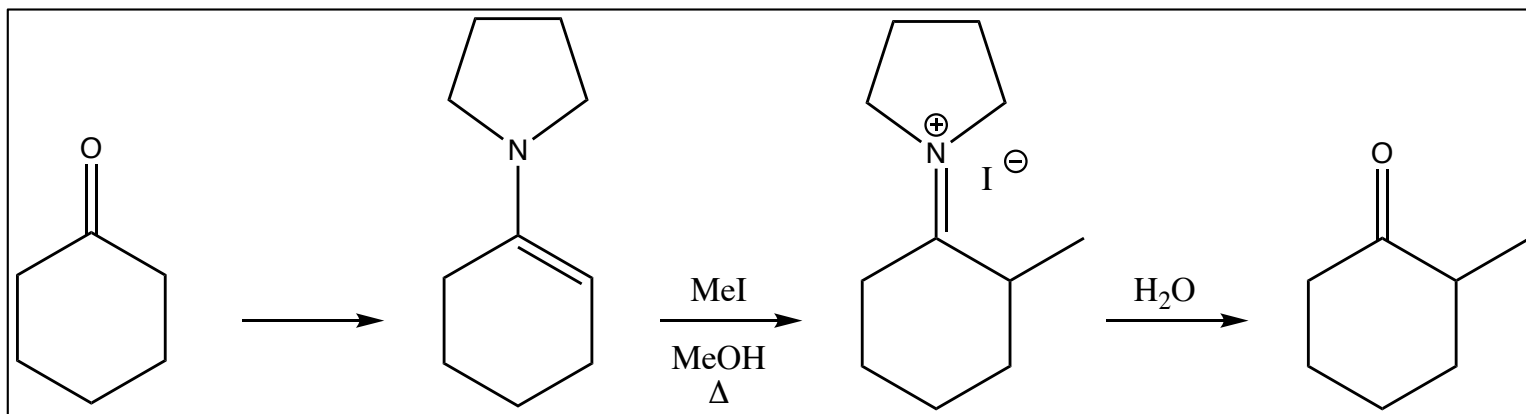


- Dihydroxy acetone phosphate
- Glyceraldehyde phosphate



Antibodies (aldol) and Robinson annulation: Zhong, G.; Hoffmann, T.; Lerner, R. A.; Danishefsky, S.; Barbas III, C. F. *J. Am. Chem. Soc.* **1997**, *119*, 8131-8132.

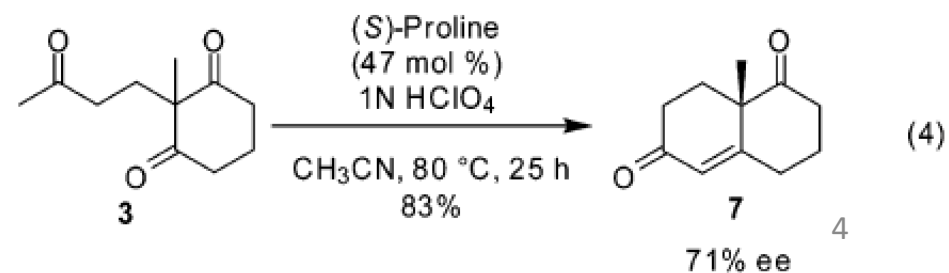
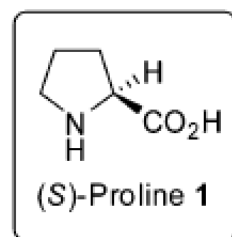
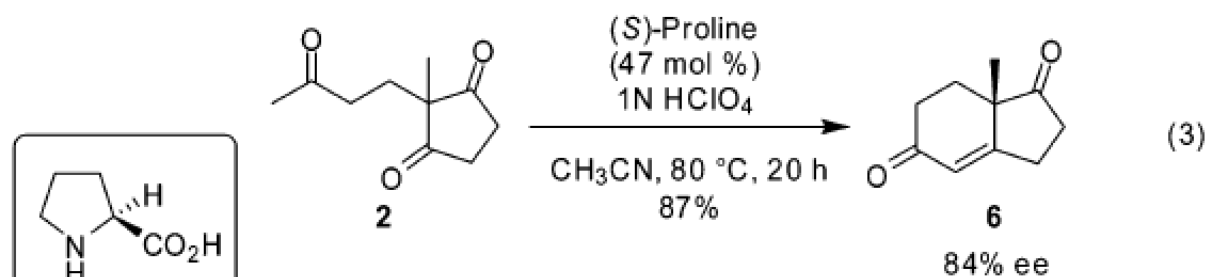
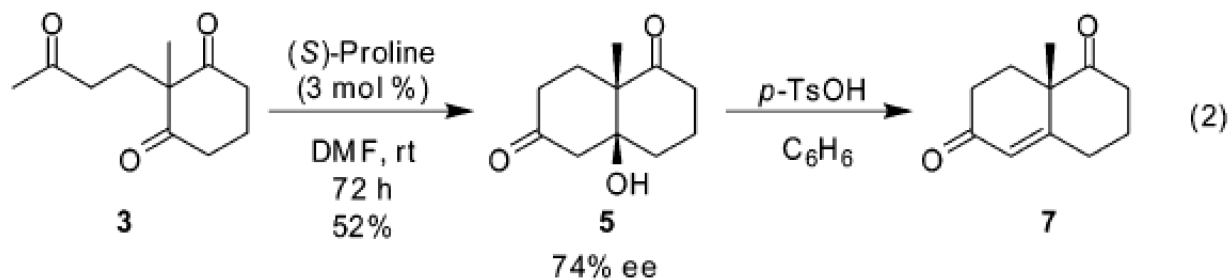
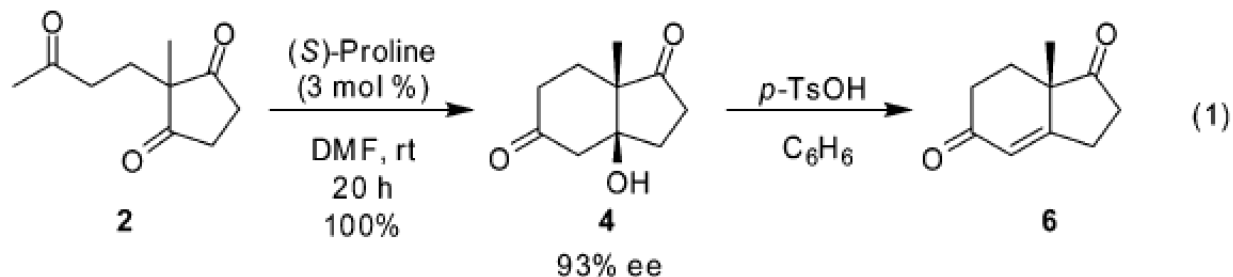
- **Stork preformed enamines**
  - *J. Am. Chem. Soc.* **1954**, 76, 2029-2030.
- Reaction at C vs. N



(Robinson annulation)

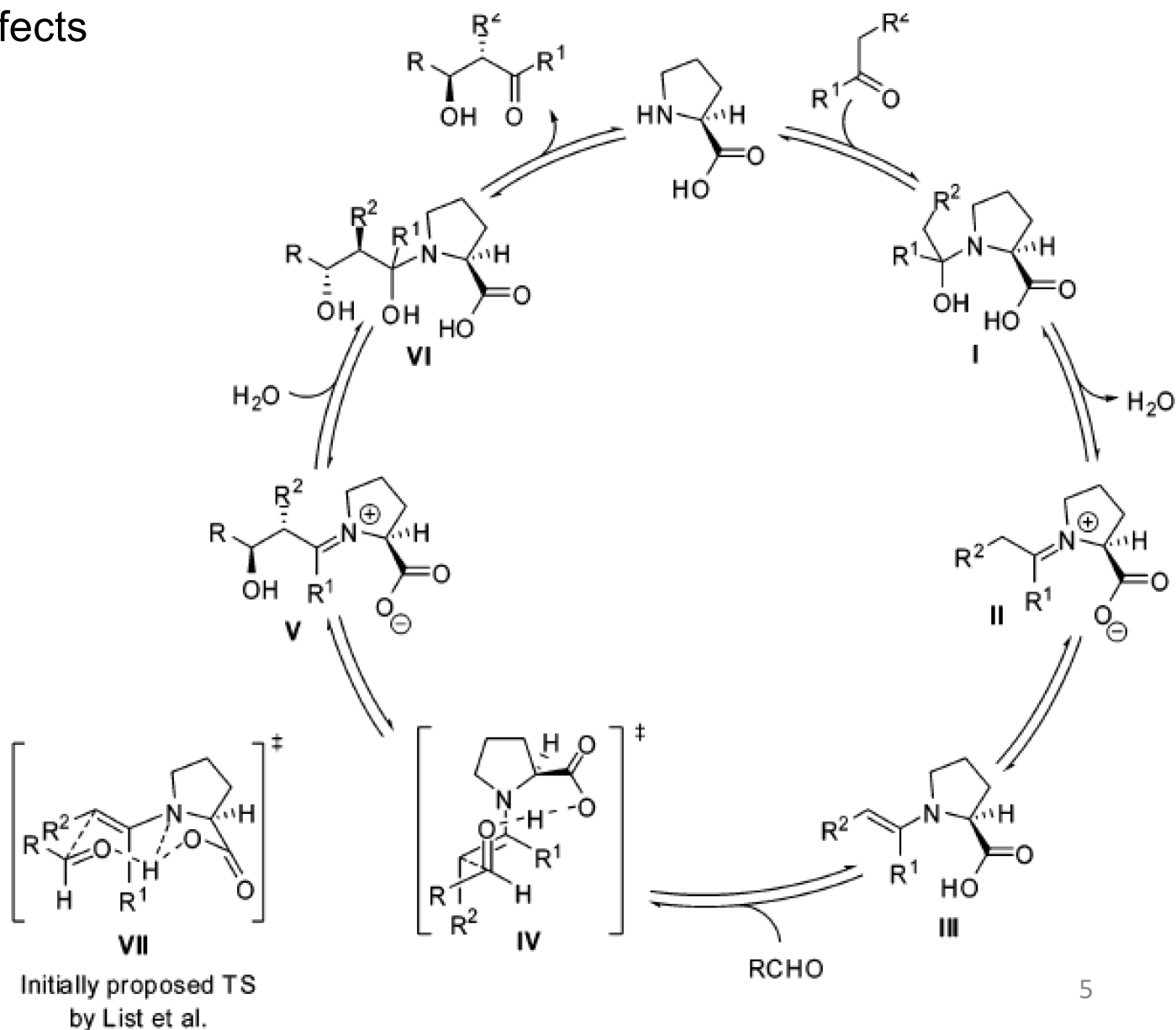
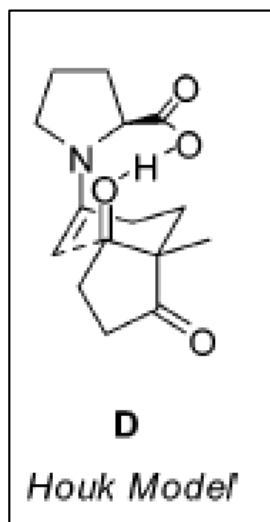
- **Hajos-Parrish-Eder-Sauer-Wiechert**
  - *J. Org. Chem.* **1974**, 39, 1615-1621.
  - *Angew. Chem. Int. Ed.* **1971**, 10, 496-497.

- Wieland-Miescher ketone



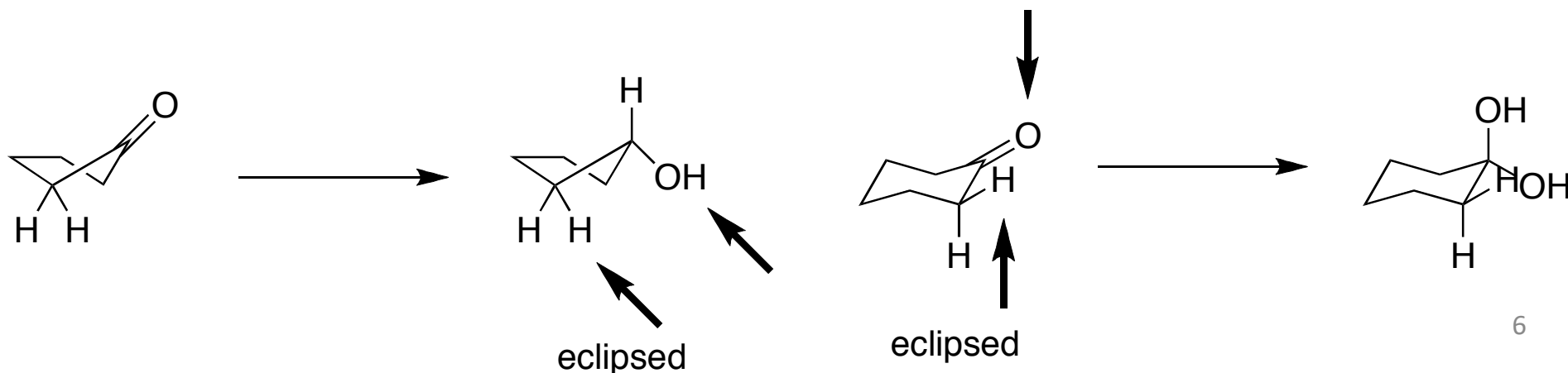
List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.  
 Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 12911-12912.

- Enamine geometry
- Proline = directing effects
- Aldol = anti selective

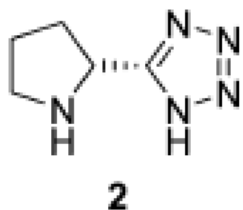


# Chapter 3: Torsional and Stereoelectronic Effects on Reactivity

- pyrrolidine reacts faster than piperidine
- hybridization changes at a ring atom (II on previous slide)
- $sp^2 \rightarrow sp^3$  are faster in 6-membered rings vs. 5-membered rings
  - reduction of cyclohexanone vs. cyclopentanone
- cyclohexanone has an eclipsing interaction between C=O and  $\alpha$ -equatorial H's which is relieved upon reduction of carbonyl
- cyclopentanone has eclipsing interactions between C-OH and adjacent H's which are introduced upon reduction of carbonyl

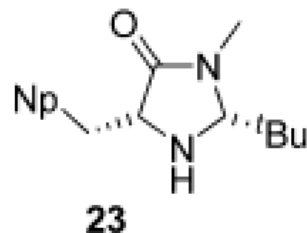


- Examples of catalysts

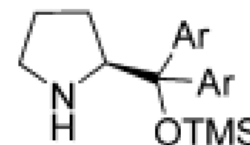


Yamamoto  
Ley

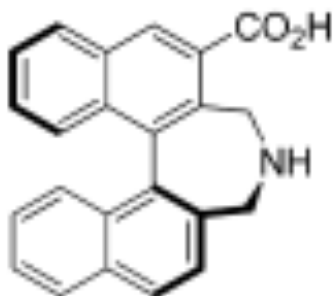
(isostere for carboxylic acid)



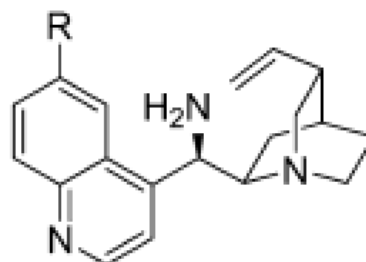
MacMillan  
(imidazolidinone-  
amino acids + aldehydes)



Jorgensen  
Hayashi  
(see next slide)



Maruoka  
(binaphthyl based)



27: R = H  
28: R = OMe

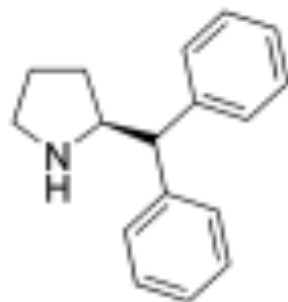
Cinchona alkaloids

Chen, *ACIE* **2007** p. 389  
Melchiorre, *Org. Lett.* **2007** p. 1403  
Connon, *Org. Lett.* **2007** p. 599

Pioneering studies:  
Ishihara, *JACS* **2005**

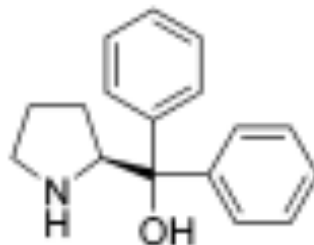
Consider: iminium can simply be  
deprotonated to form imine

- Examples of catalysts



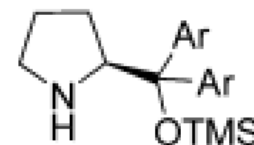
(S)-1

Good yield  
Poor ee

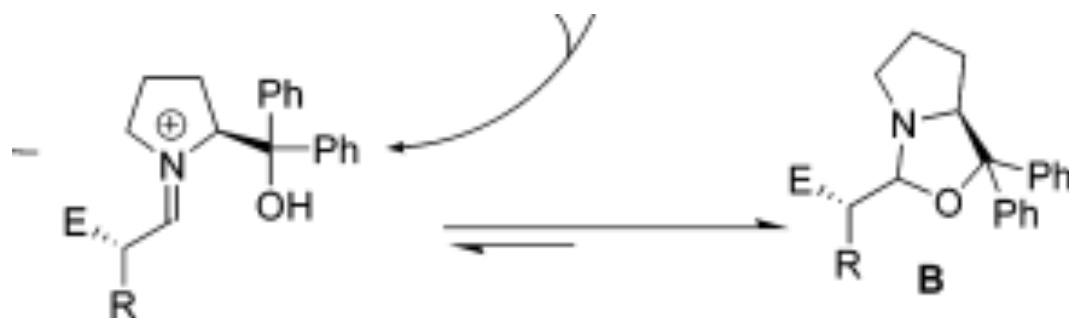


(S)-2a

Low yield  
Good ee



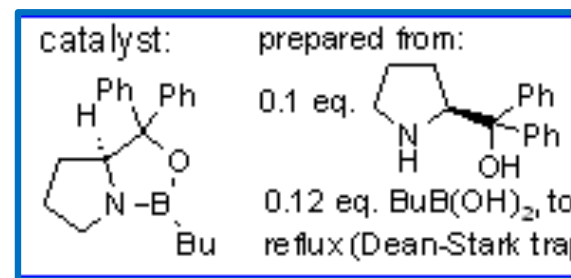
Jørgensen  
Hayashi



Low yield due to poor turnover because catalyst is sequestered as the stable hemiaminal species **B**

Jørgensen's  $\text{CF}_3$  groups exert steric (not electronic) effect

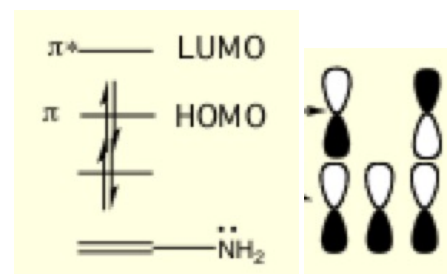
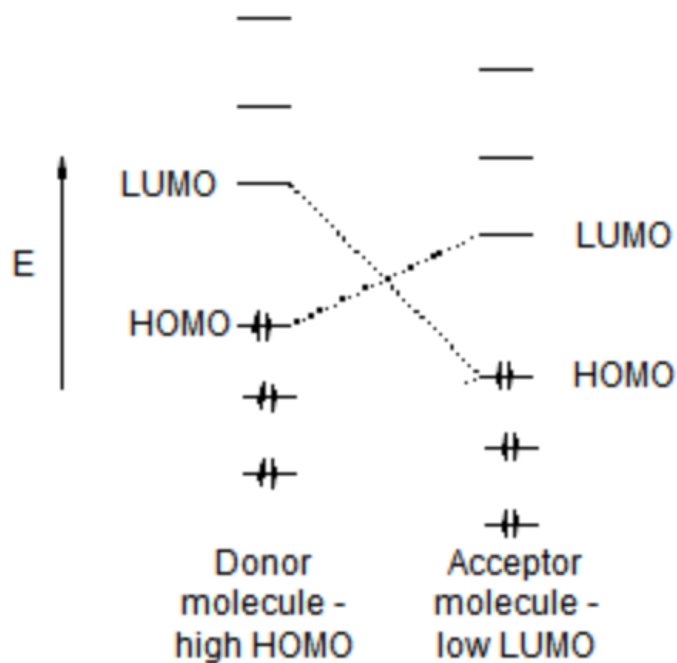
Good discussion in: Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296-18304.



Corey-Bakshi-Shibata  
80's and 90's



- **HOMO raising**
- Frontier Molecular Orbital Theory
- HOMO = electron rich = nucleophile
- LUMO = electron deficient = electrophile
- The closer in energy the HOMO of the nucleophile and the LUMO of the electrophile, the more effectively they can interact; the more electronically “matched” they are
- Enamines are isoelectronic with allyl anions
- HOMO has node in the center; electron density resides on termini



- **Scope of Reactions**
- Aldol (i.e., Hajos-Parrish-Eder-Sauer-Wiechert)
- Mannich
- Michael additions
- $\alpha$ -functionalizations

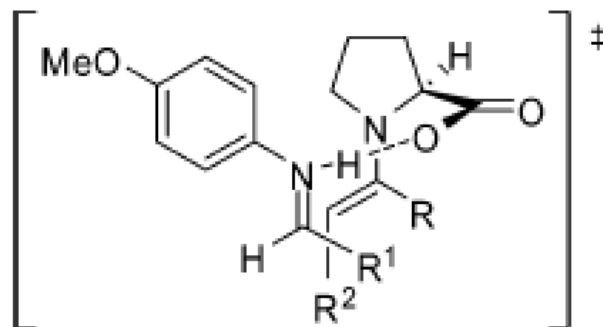
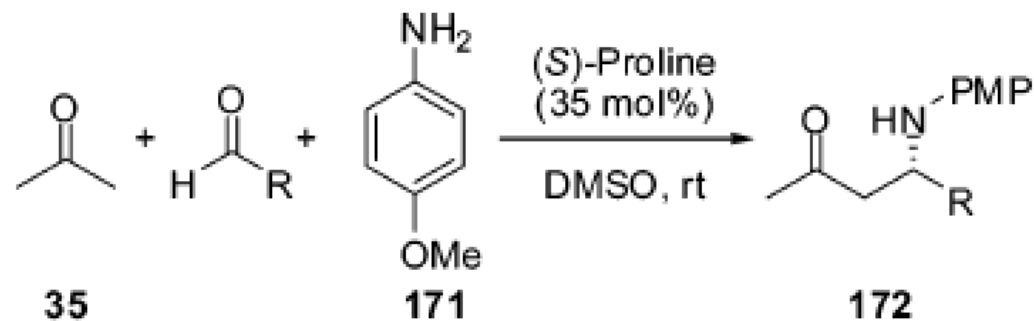
- **Scope of Reactions**

- Aldol (intra and inter)

- Mannich

- Syn selective

- Boc (List)

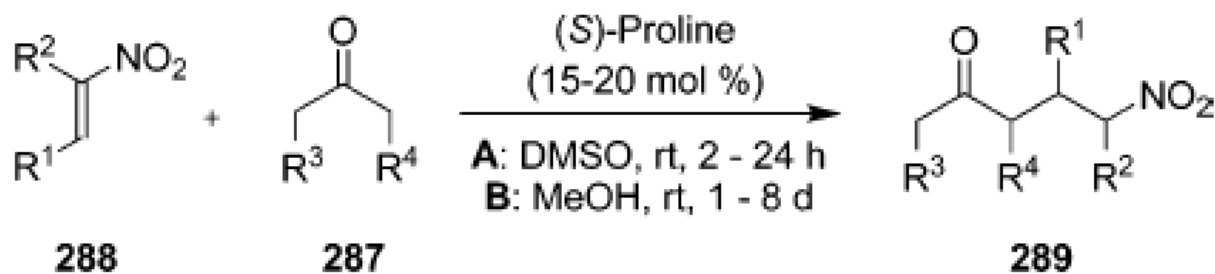


List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.

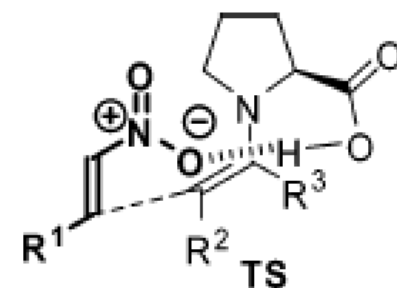
- **Scope of Reactions**

- Michael additions (to enones, nitroolefins)

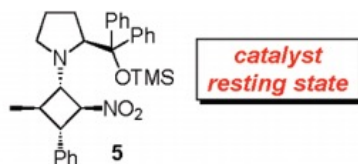
- List, B.; Pojarliev, P.; Martin, H. *J. Org. Lett.* **2001**, 3, 2423.
- Nitro group versatility (amine, Nef → ketone)
- *Synclinal* transition state
  - staggered conformation
  - gauche relationship between pi donor/acceptor systems
  - electrostatic interaction between  $\delta^+$  enamine N and  $\delta^-$  nitro group



**Proposed Transition State**

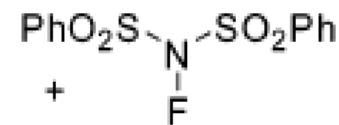


- Mechanistic insight: Bures, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2011**, 133, 8822.



- **Scope of Reactions**
- $\alpha$ -functionalizations (aminations, oxygenations, halogenations, selenation, sulfenylation)

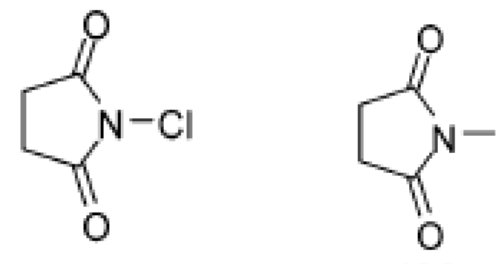
Jørgensen  
MacMillan



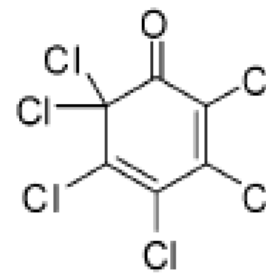
402

Ketone fluorination: Kwiatkowski, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 1738-1741.

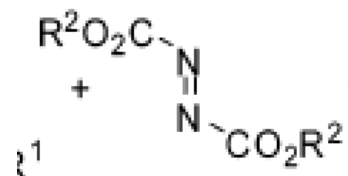
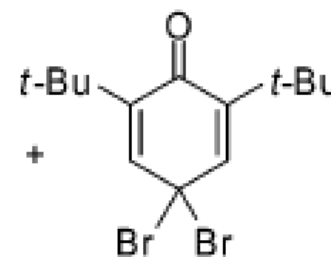
Jørgensen



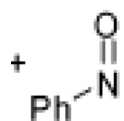
MacMillan



Jørgensen

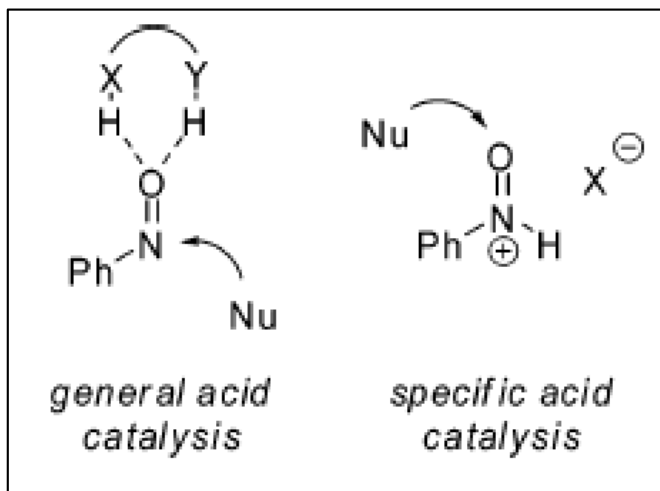


Jørgensen  
List



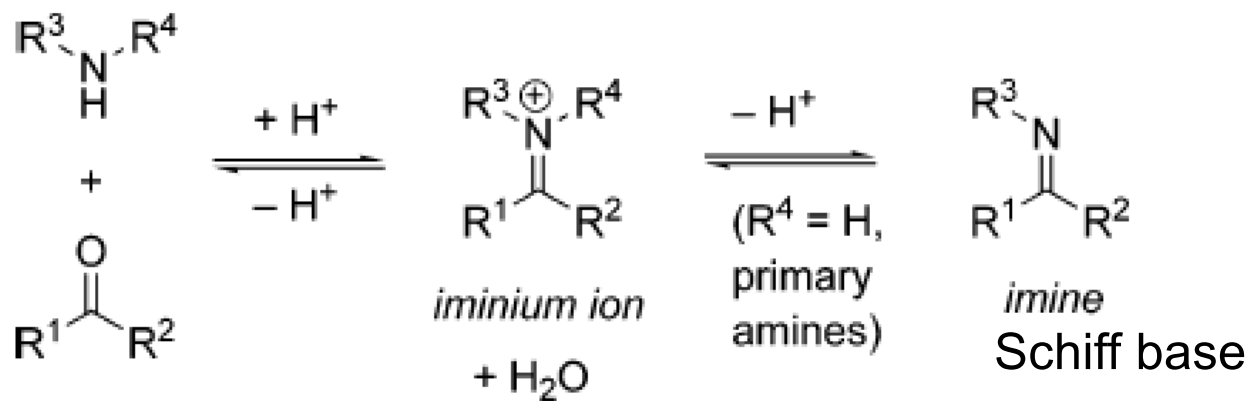
Zhong  
MacMillan  
Hayashi

(N- or O- electrophile)



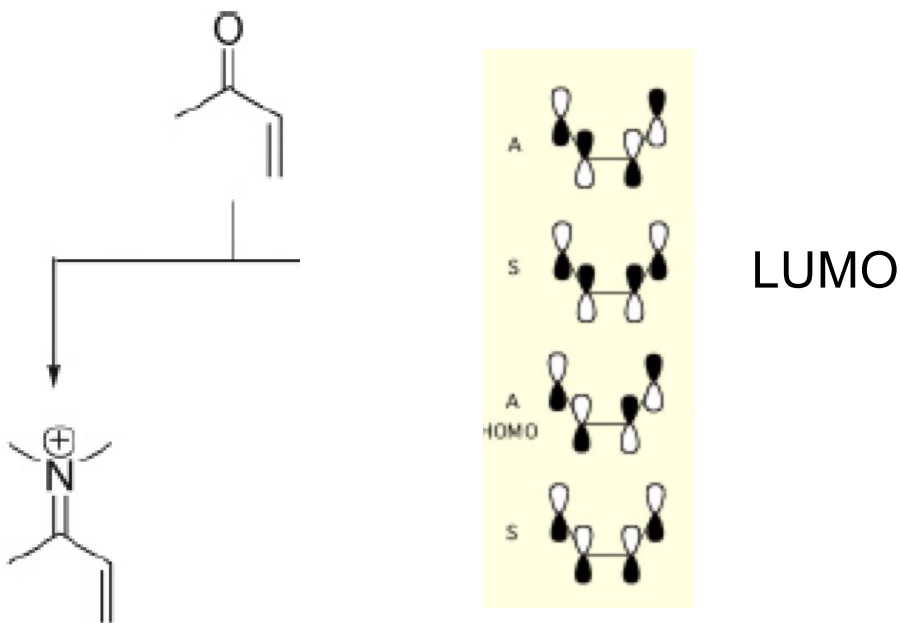
In GAC protonation is rate determining, in SAC it is not.

- **Iminium catalysis**



- LUMO lowering

- Conjugated iminium ion is more electrophilic than enal/enone

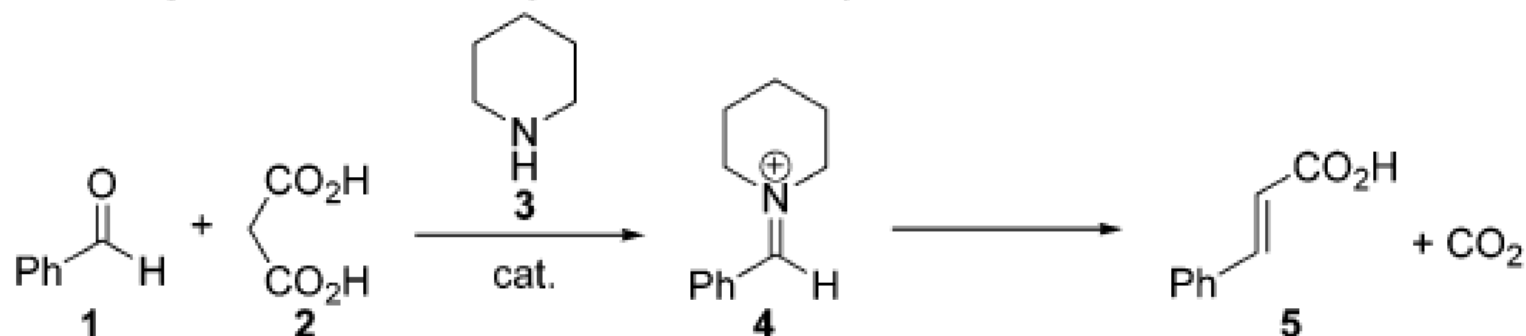


- **Iminium catalysis: History**

- First example

1894-  
1898

Knoevenagel discovers a family of iminium-catalyzed condensation reactions:

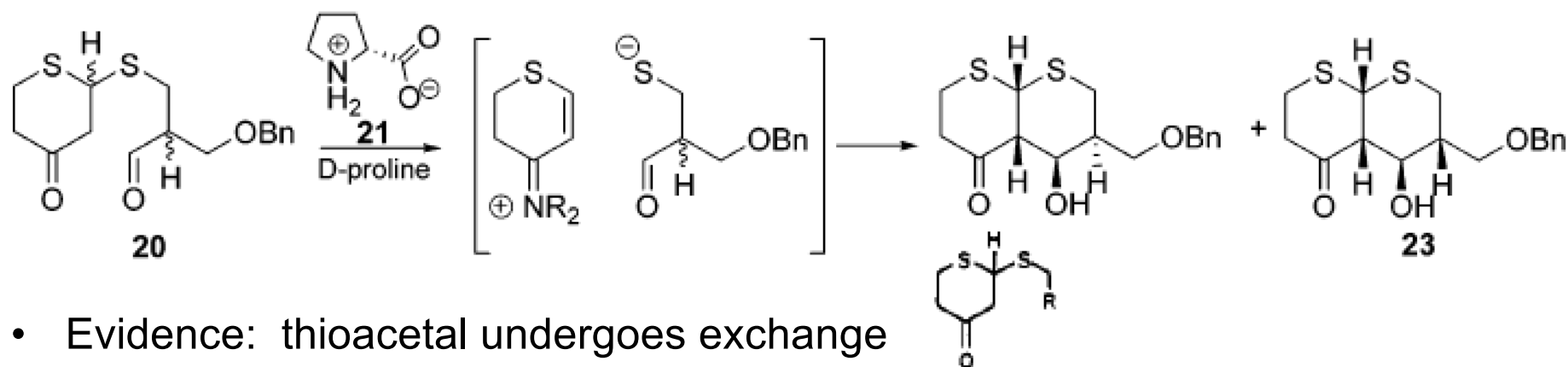


- Notable example

- Woodward's synthesis of erythromycin

1981

Woodward and co-workers use asymmetric proline catalysis to effect an iminium-catalyzed deracemization and intramolecular aldol reaction in the total synthesis of erythromycin



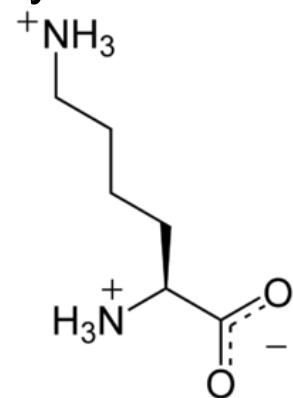
- Evidence: thioacetal undergoes exchange upon exposure to proline and benzyl thiol

iii R = CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>  
iv R = C<sub>6</sub>H<sub>5</sub>

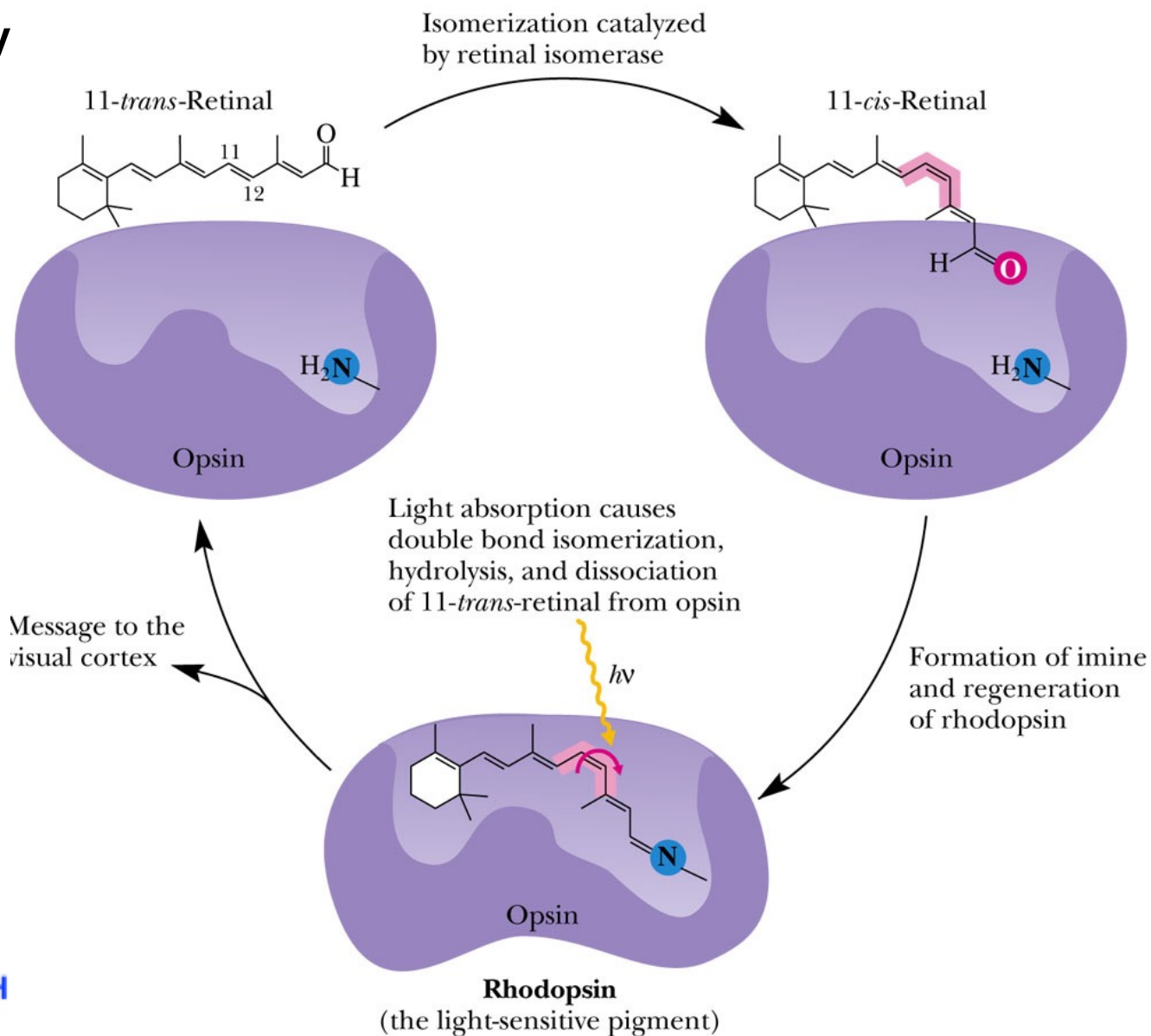
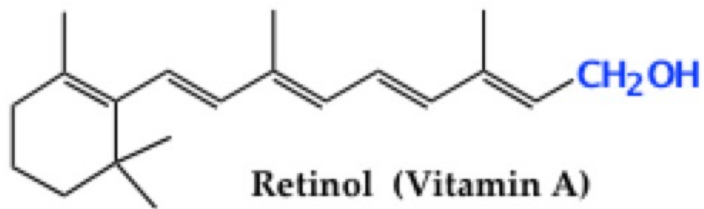
- **Iminium catalysis: History**

- Vision

- Lysine



- isomerization via protonated imine (iminium; retinilidene)



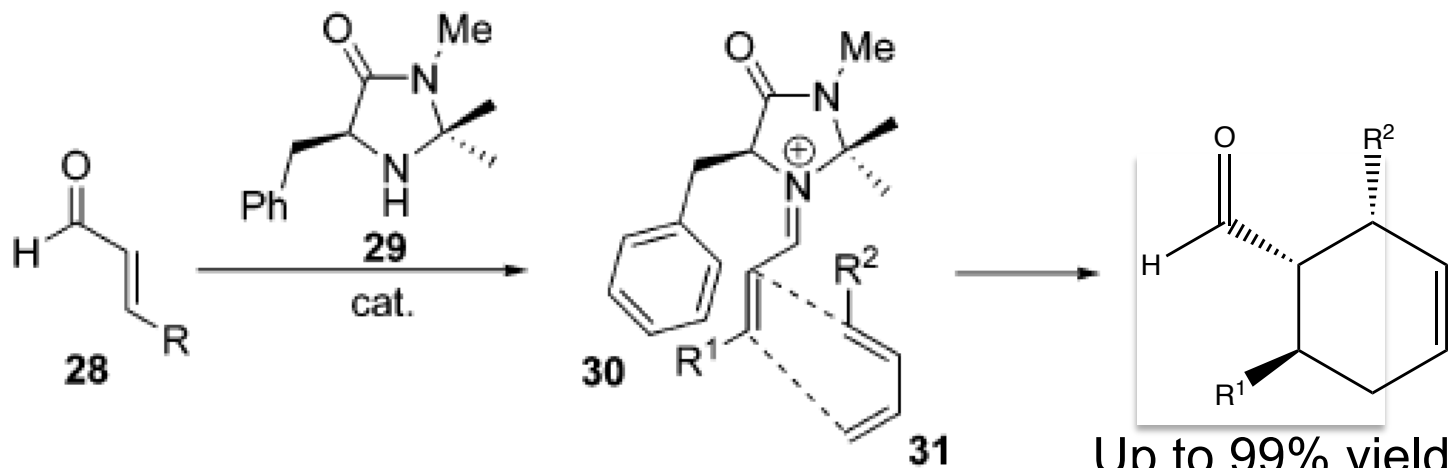


- **Iminium catalysis: History**

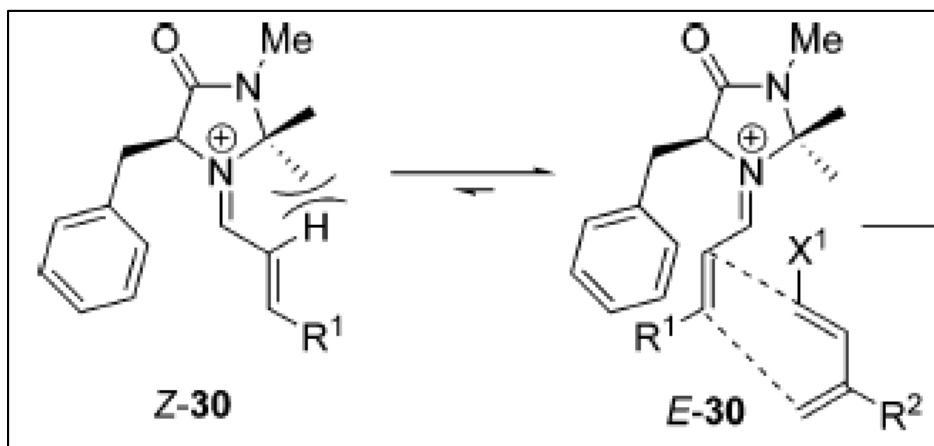
- What started it all

2000

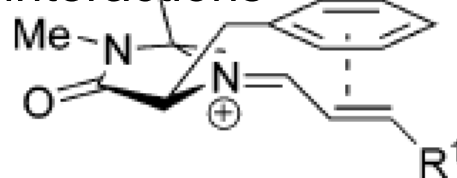
MacMillan reports the first asymmetric iminium-catalyzed cycloaddition reactions



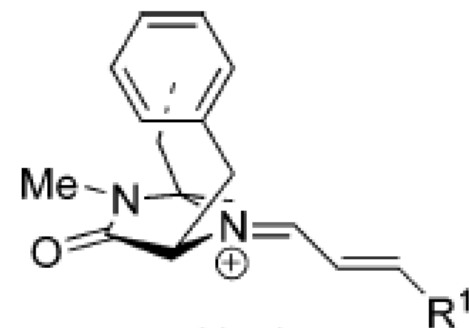
Up to 99% yield  
Up to 14:1 endo:exo  
Up to 94% ee



$\pi$ -stacking vs C-H  $\pi$ -interactions



MacMillan

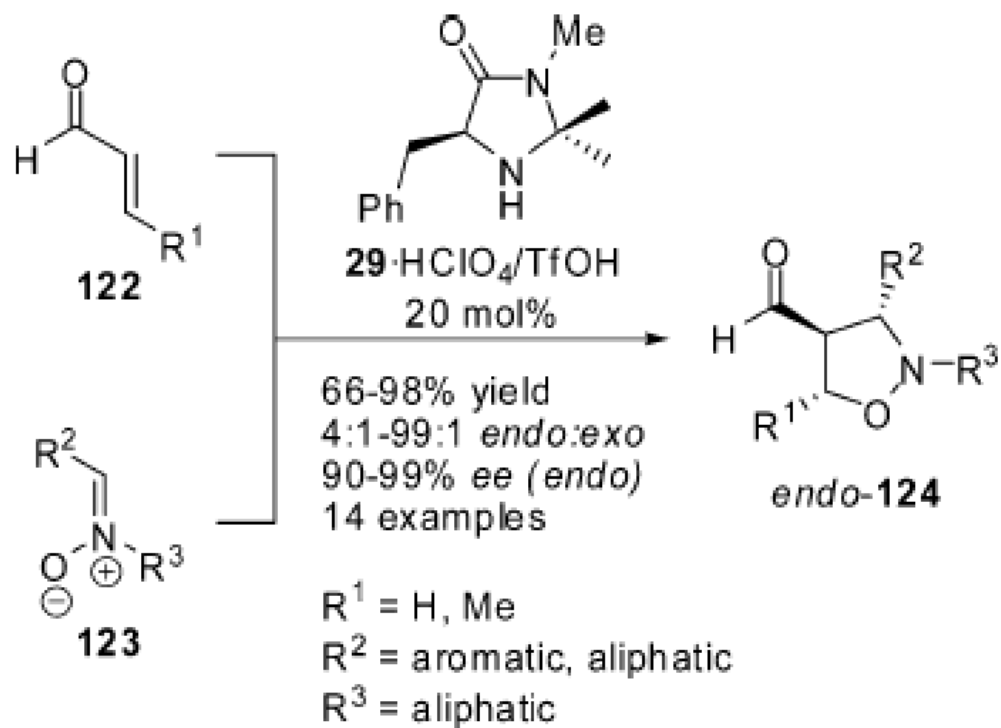


Houk

Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.  
Gordillo, R.; Houk, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 3543.

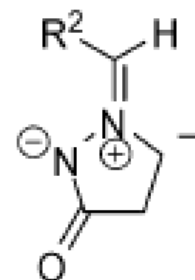
- **Scope of Reactions**
- Cycloadditions
  - Diels-Alder (MacMillan example)
  - [3+2]
  - [5+2] (our group)
- Michael additions (C-, H-, S-, N-, O-nucleophiles)

- **Scope of Reactions**
- [3+2] cycloadditions

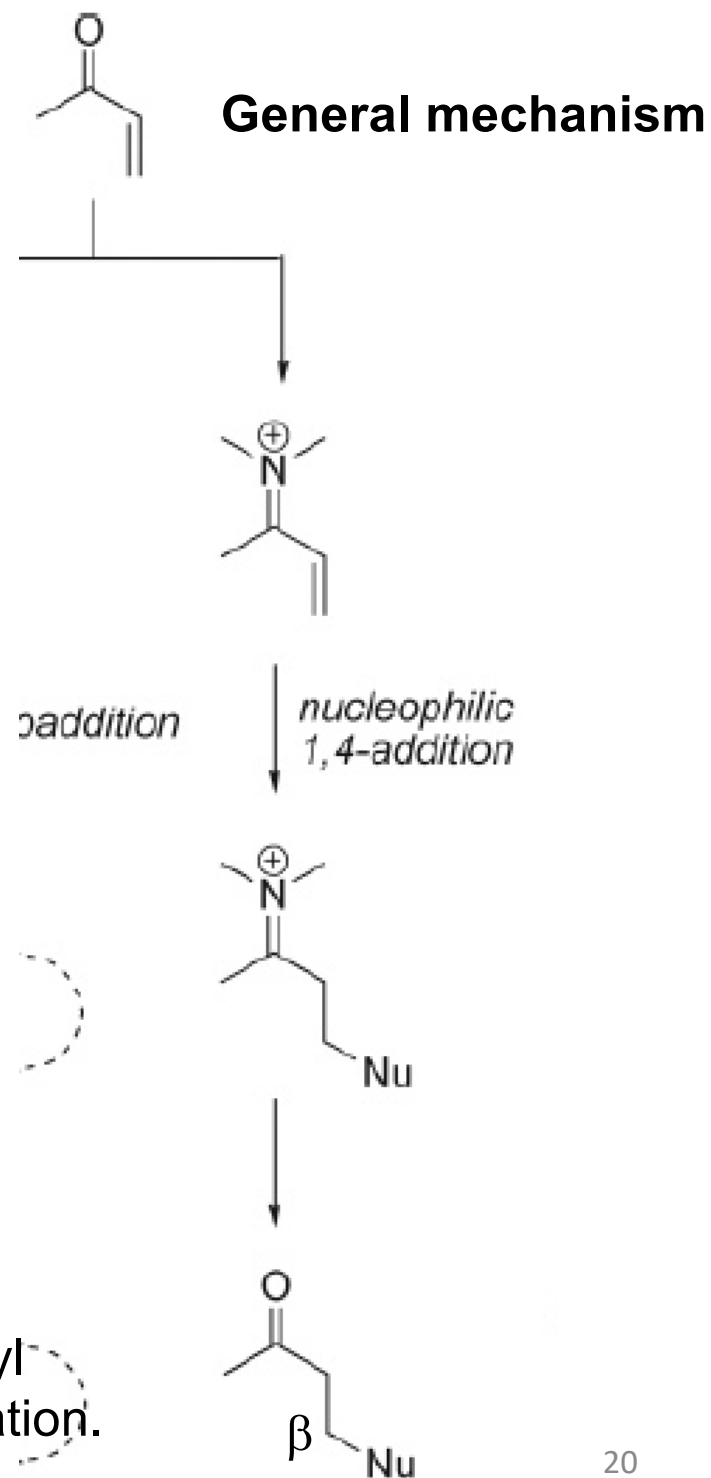


Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.

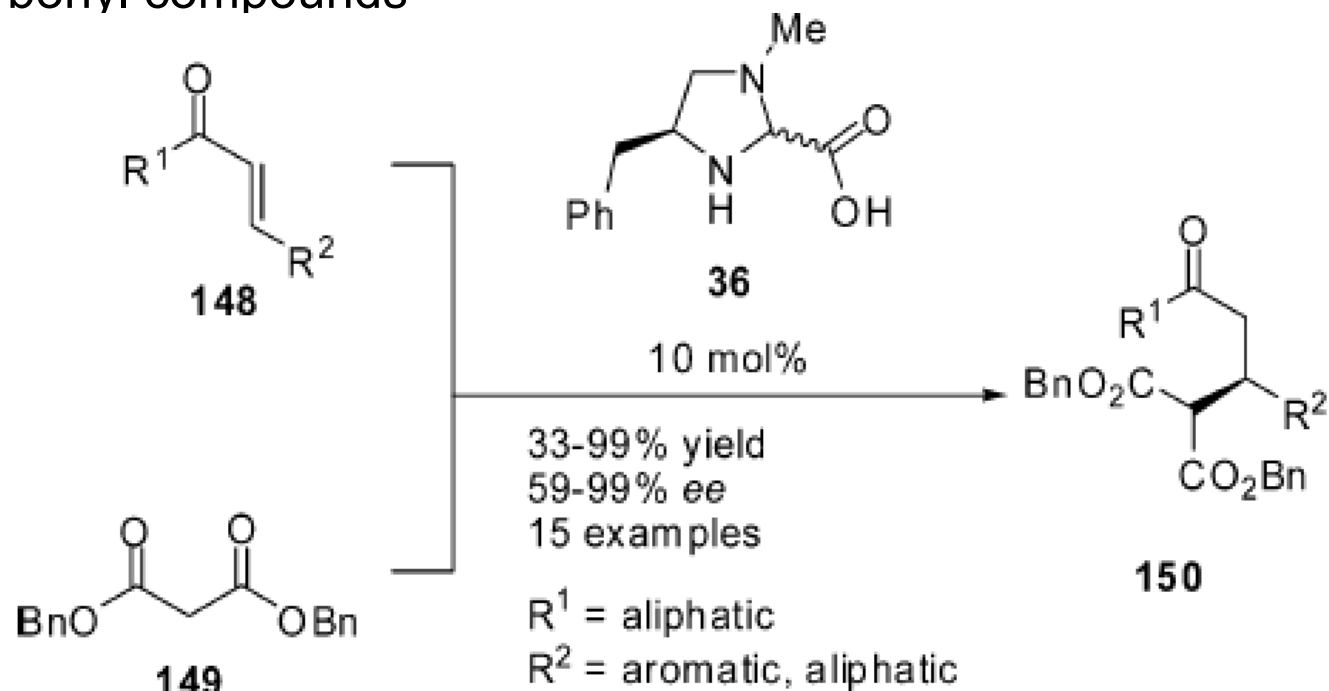
Azomethine imines



- **Scope of Reactions**
- Cycloadditions
  - Diels-Alder (MacMillan example)
  - [3+2]
  - [5+2] (our group)
- Michael additions (C-, H-, S-, N-, O-nucleophiles)



- **Scope of Reactions**
- Michael additions (C-nucleophiles)
  - 1,3-dicarbonyl compounds

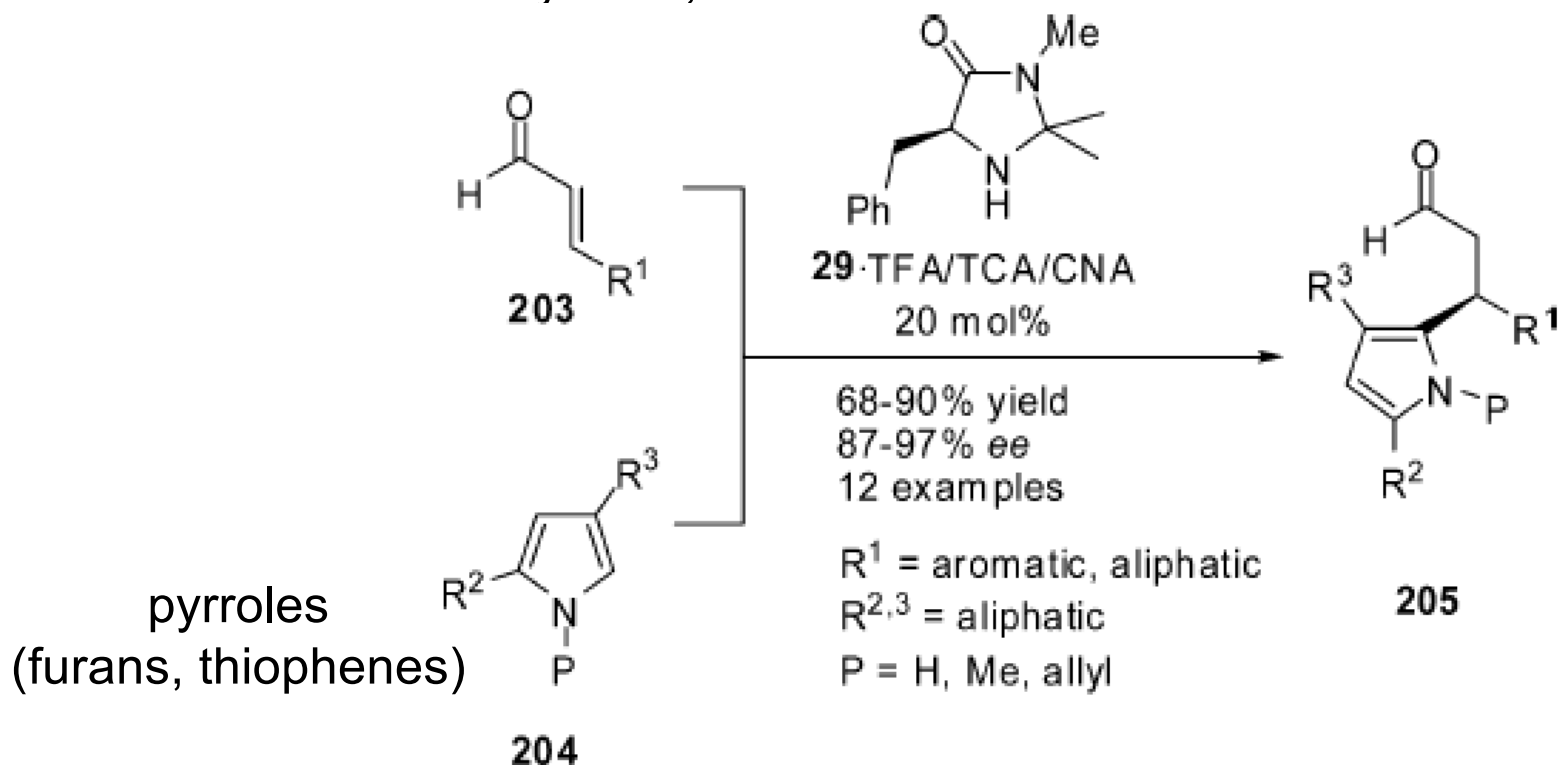


Halland, N.; Aburel, P. S.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, 42, 661.

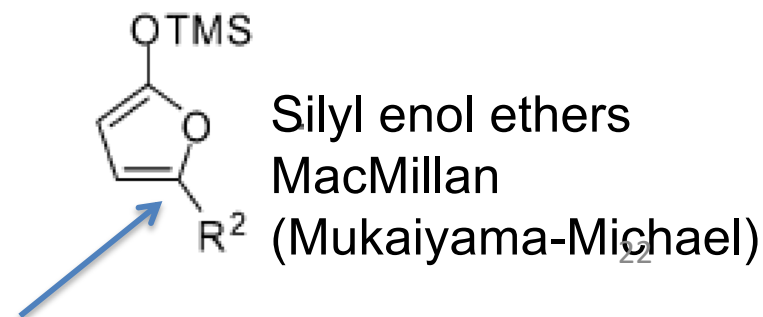
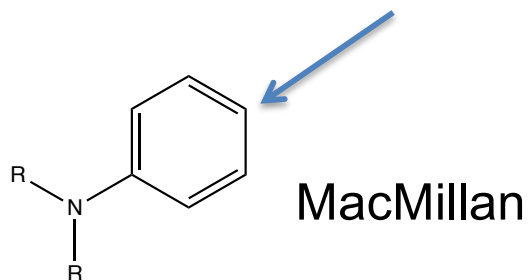
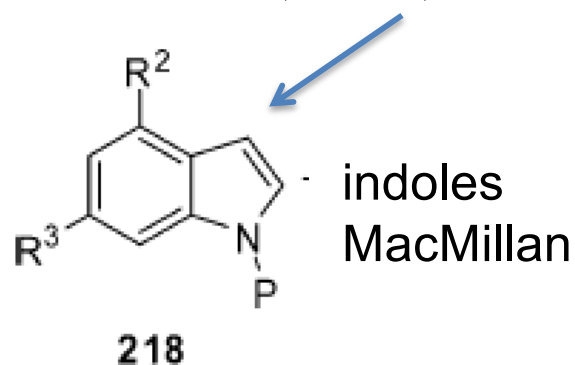


Hanessian, S.; Pham, V. *Org. Lett.* **2000**, 2, 2975.

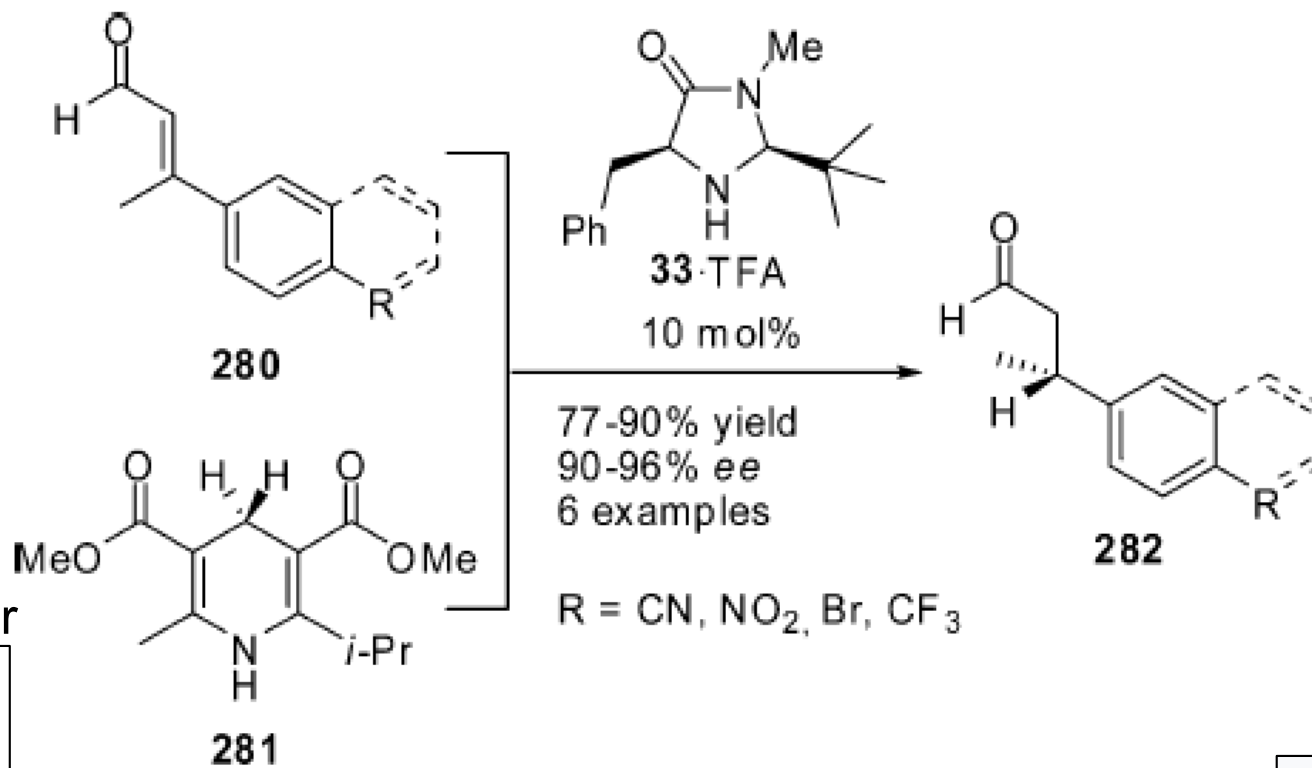
- **Scope of Reactions**
- Michael additions (C-nucleophiles)
  - Friedel-Crafts alkylation, etc.



Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, 123, 4370.

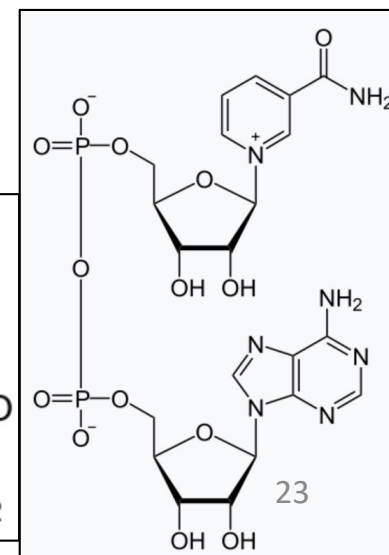
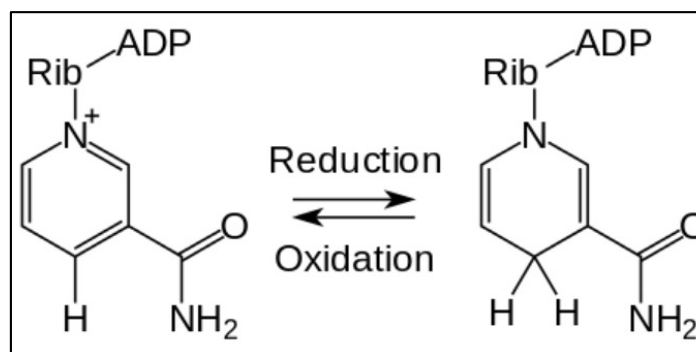


- **Scope of Reactions**
- Michael additions (H-nucleophiles)
  - Biomimetic transfer hydrogenation

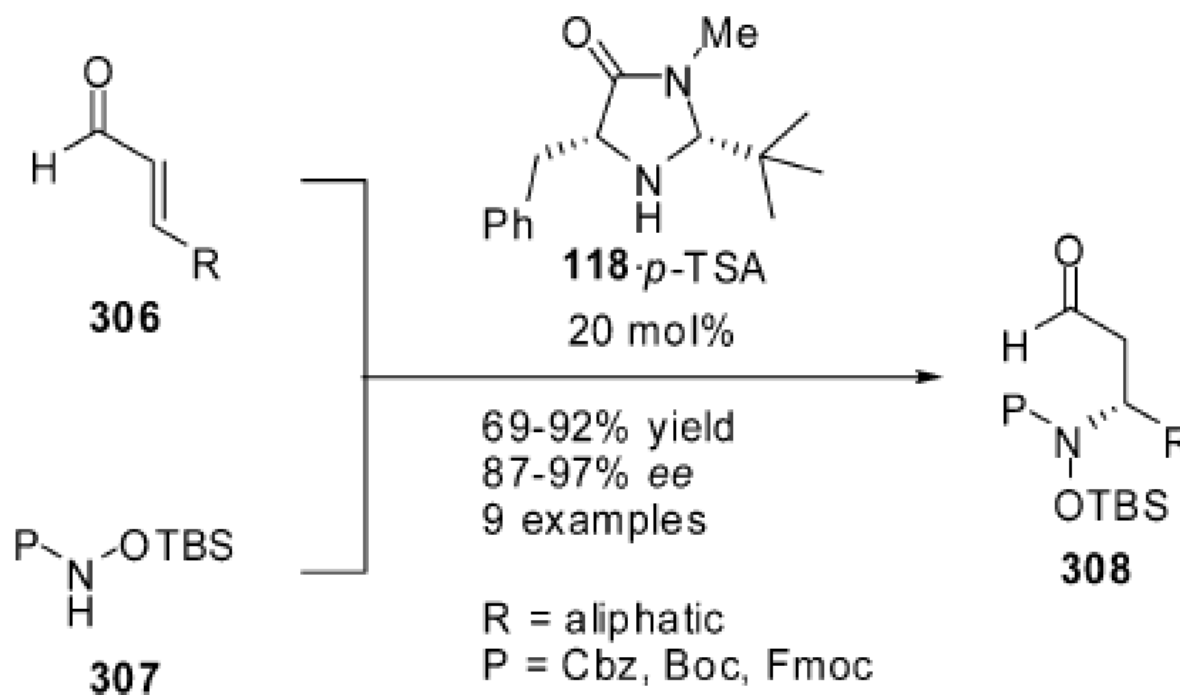


Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B.  
*Angew. Chem. Int. Ed.* **2005**, *44*, 108.

Nicotinamide adenine dinucleotide  
 (NAD<sup>+</sup> and NADH)



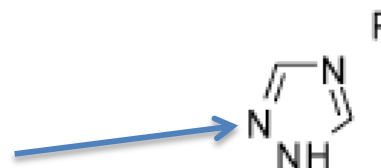
- **Scope of Reactions**
- Michael additions (N-nucleophiles)
  - aza-Michaels



Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328.

The indicated N reacts bc:

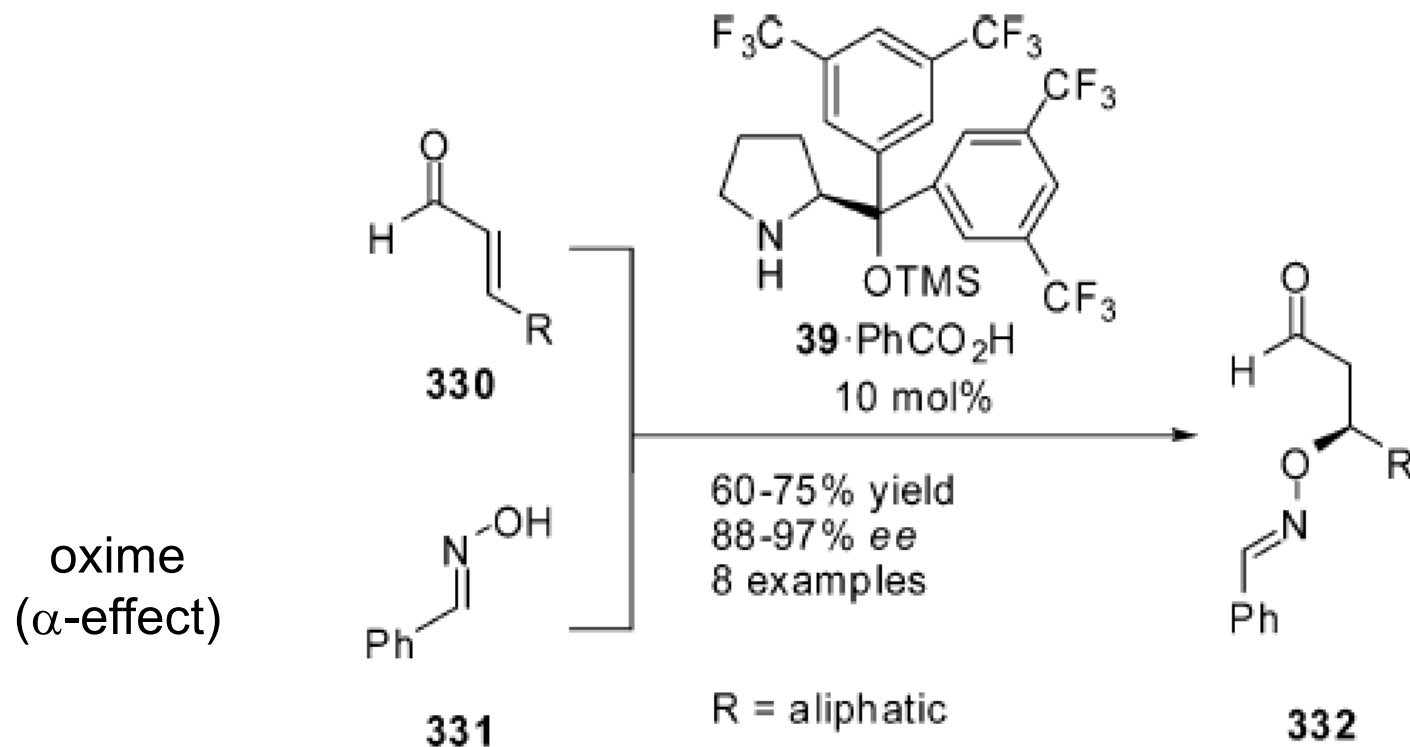
- 1) lone pair not aromatic
- 2) resonance stabilized by allylic N
- 3)  $\alpha$ -effect



Jørgensen  
(triazoles)



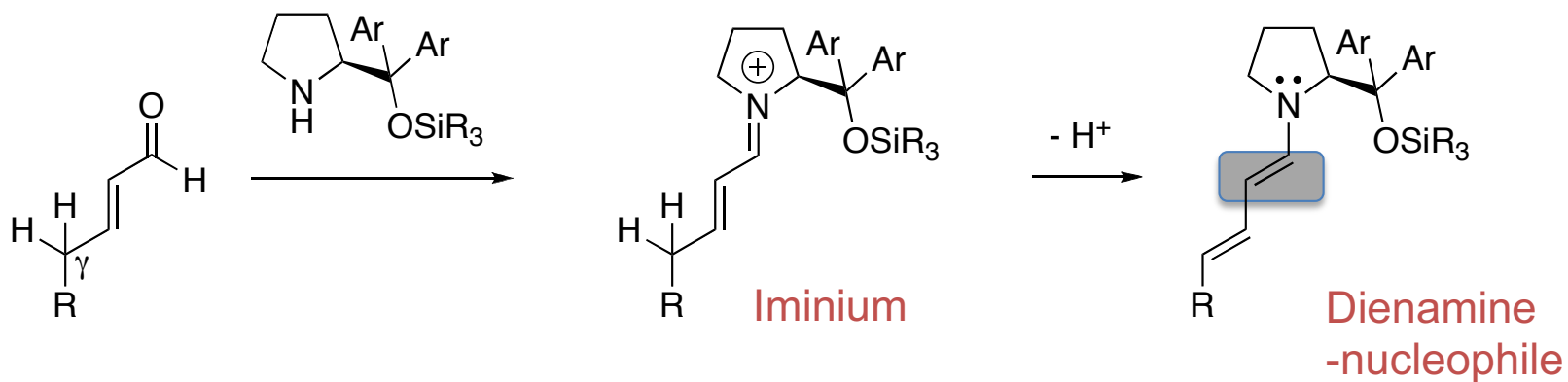
- **Scope of Reactions**
- Michael additions (O-nucleophiles)
  - oxa-Michaels
  - Reversibility is a big problem



Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A.  
*J. Am. Chem. Soc.* **2007**, *129*, 1536.

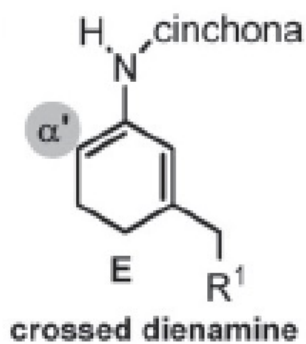
aliphatic thiols Jørgensen  
(sulfa-Michael)

- Dienamines (vinylogous enamines)



- **Dienamines**

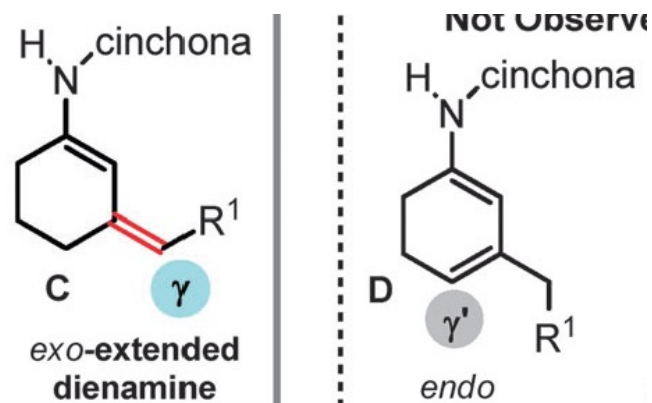
- Issues (ketones)



2-amino-1,3-diene

Barbas

kinetic

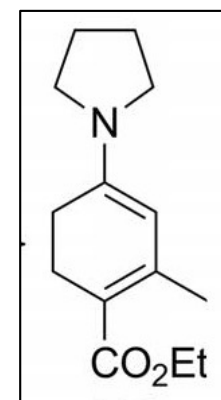


1-amino-1,3-diene

Serebryakov

thermodynamic  
(think resonance:  
N can push electron density into both olefins)

Special case



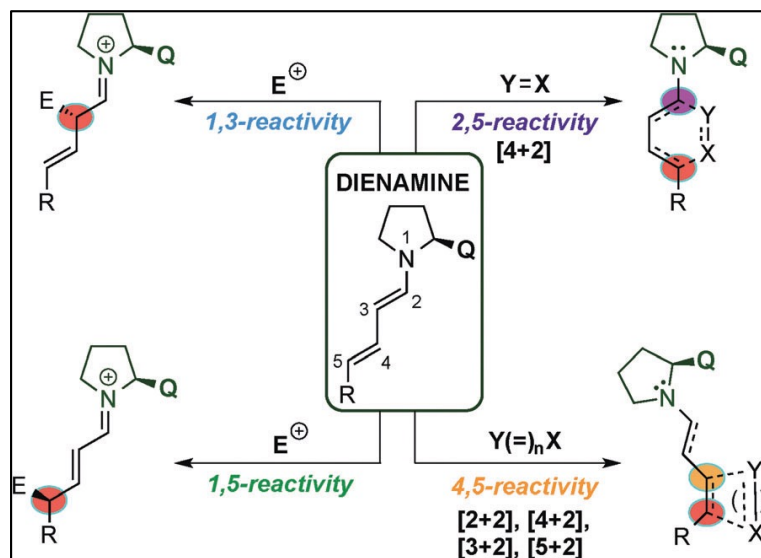
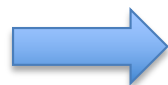
push-pull dienamine

Ramachary

(a Barbas postdoc)

- **Dienamines**

- Even if you form just the Serebryakov dienamine (enals), there are still issues.
- Serebryakov dienamine is the only one enabling remote (i.e.,  $\gamma$ -) functionalization.

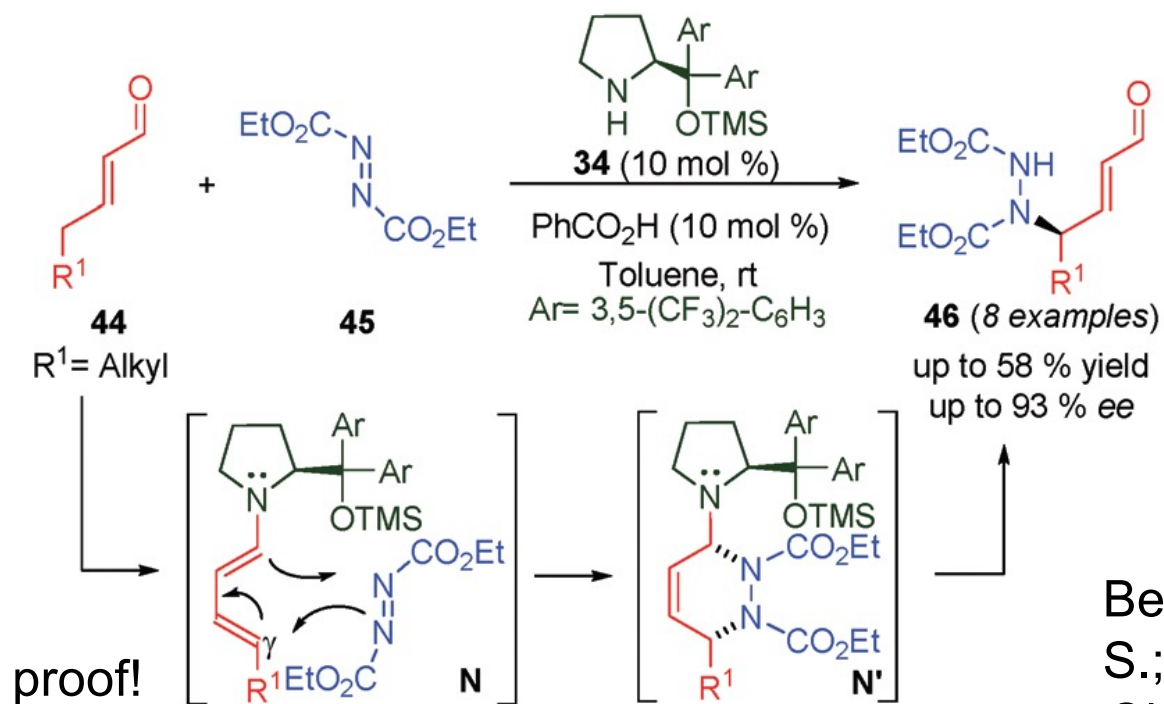
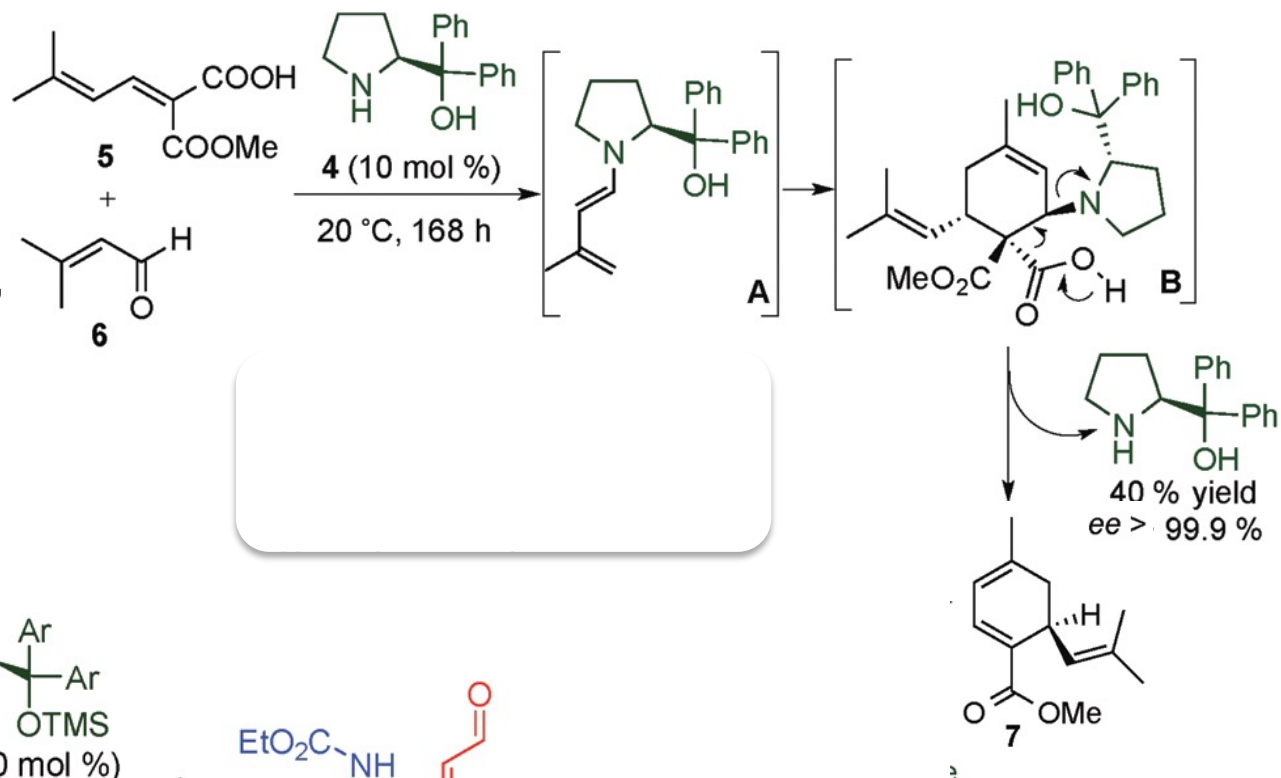


- Will focus on these. Will highlight “tricks” people use to achieve remote,  $\gamma$ -functionalization
- Stereochemistry: geometry of remote olefin (Z?)
  - Seegerer, A.; Hioe, J.; Hammer, M. M.; Morana, F.; Fuchs, P. J. W.; Gschwind, R. M. *J. Am. Chem. Soc.* **2016**, *138*, 9864-9873.

- **Dienamines**

- Background

Serebryakov, E. P.; Nigmatov, A. G.; Shcherbakov, M. A.; Struchkova, M. I. *Russ. Bull. Chem.* **1998**, *47*, 82-90.



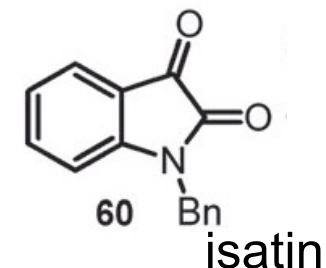
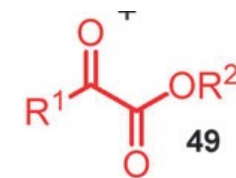
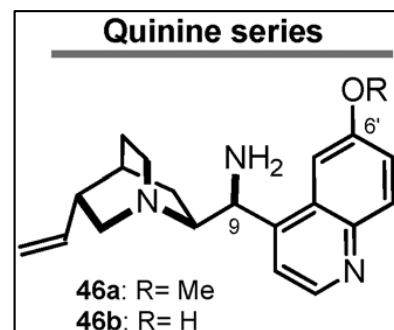
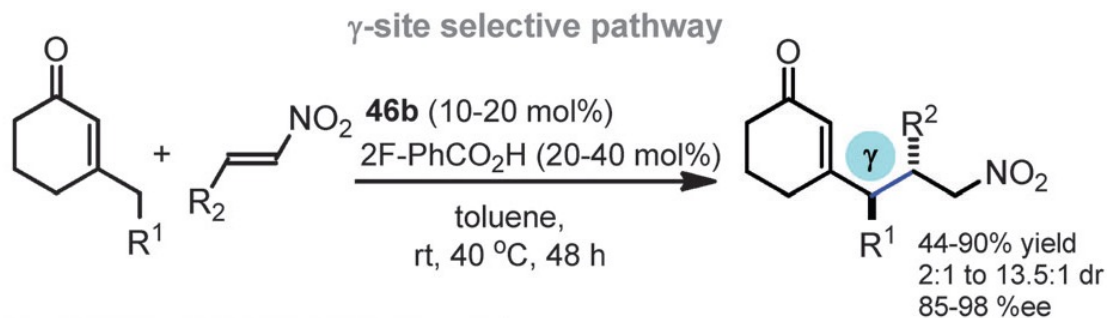
**Trick 1:  $\gamma$ -functionalization via co-functionalization (i.e., cycloaddition)**

Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.

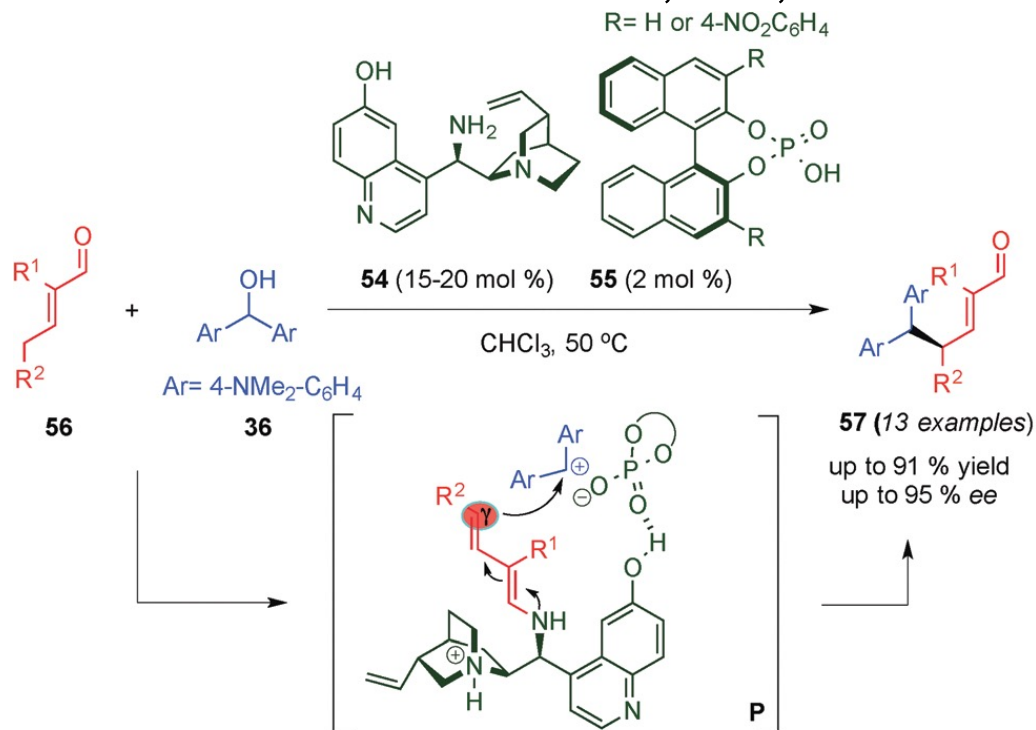
**Trick 2: Substrate control (dienamine).** *Exo* extended dienamine favored for 3-Me-cyclohexenones.  $\alpha$ -blocking group on linear dienamines.

## Dienamines

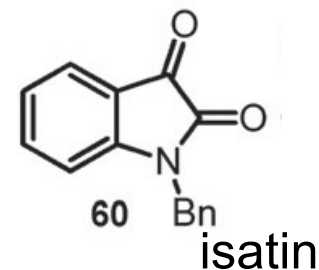
- Few intramolecular exclusive  $\gamma$ -functionalizations (i.e., non-cascade)
- Melchiorre



Bencivenni, G.; Galzerano, P.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20642.

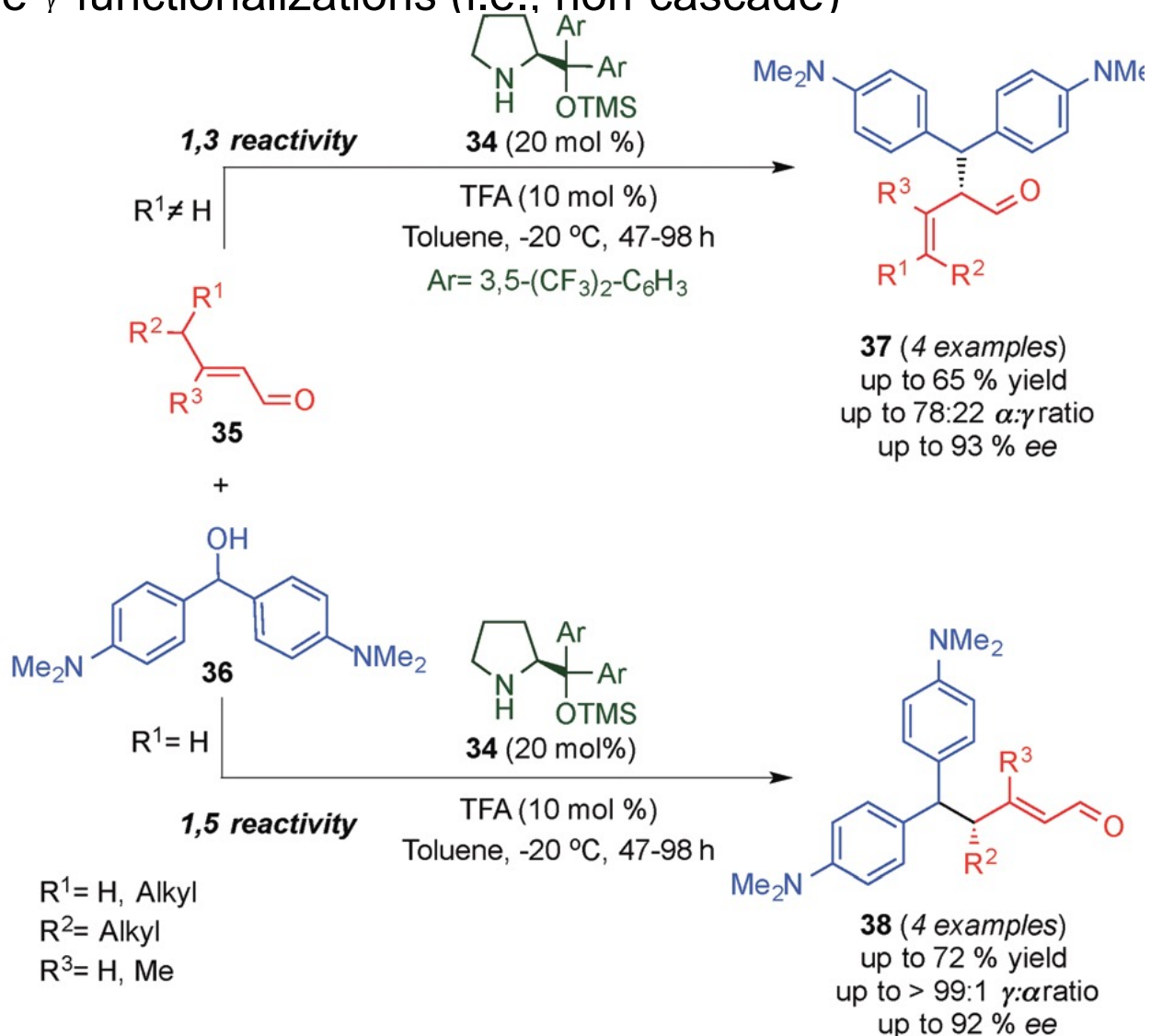


Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 9685.



## • Dienamines

- Few intramolecular exclusive  $\gamma$ -functionalizations (i.e., non-cascade)
- Christmann (concurrent; a lot of work in this area as well)
- $\gamma,\gamma$ -disubstituted enals favor  $\alpha$ -alkylation (2:1 to 4:1)
- Other enals favor  $\gamma$ -alkylation, but with poor selectivity (3:1 to 5:1)

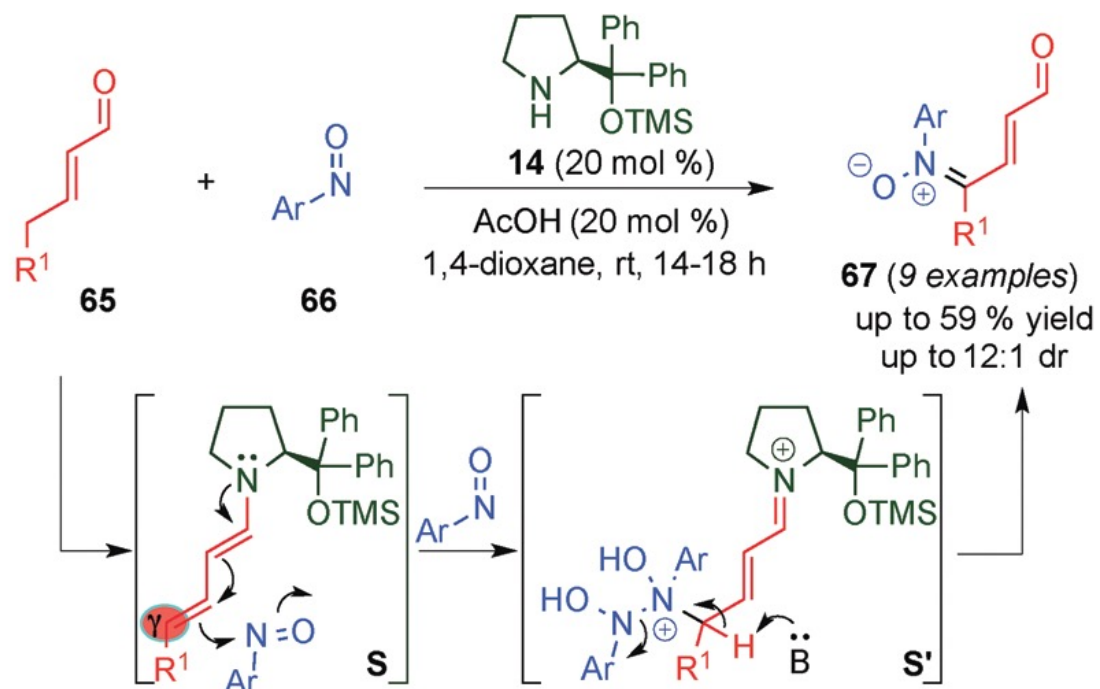


**Trick 2: Substrate control (dienamine).**  $\gamma$ -blocking group on linear dienamines.  $\beta$ -activating group on linear dienamines (99:1  $\gamma$ : $\alpha$ ).

**Trick 3: Substrate control (electrophile).** Bulky electrophiles favor alkylation at position more remote from bulky catalyst.

- **Dienamines**

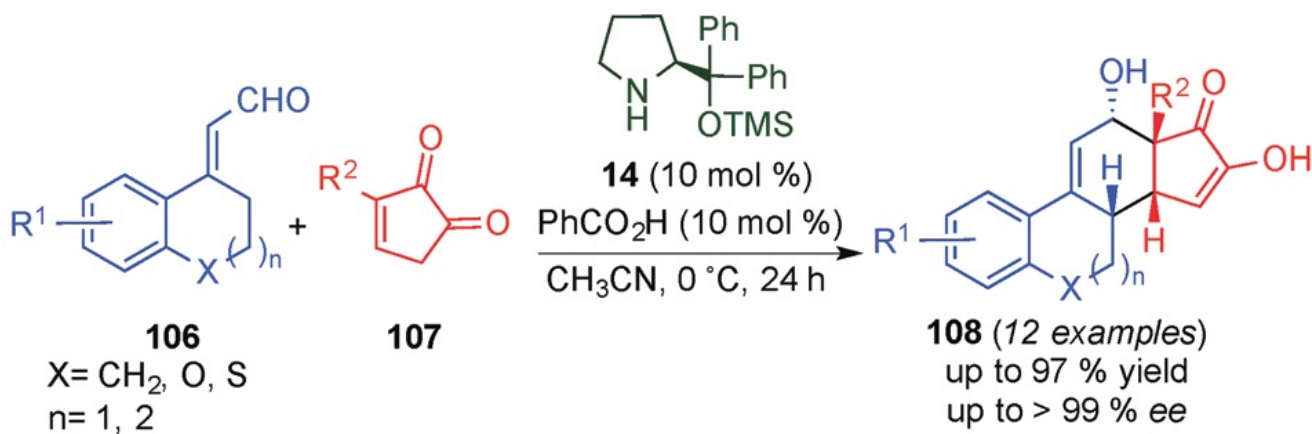
- Few intramolecular exclusive  $\gamma$ -functionalizations (i.e., non-cascade)
- Our group
- **Trick 1**
- supported by structural determination of byproduct and HRMS studies





- **Dienamines**

- Mostly used in cycloadditions (**Trick 1**)
- Some highlights:
  - Original Serebryakov example ([4+2])
  - Jørgenson's synthesis of steroids



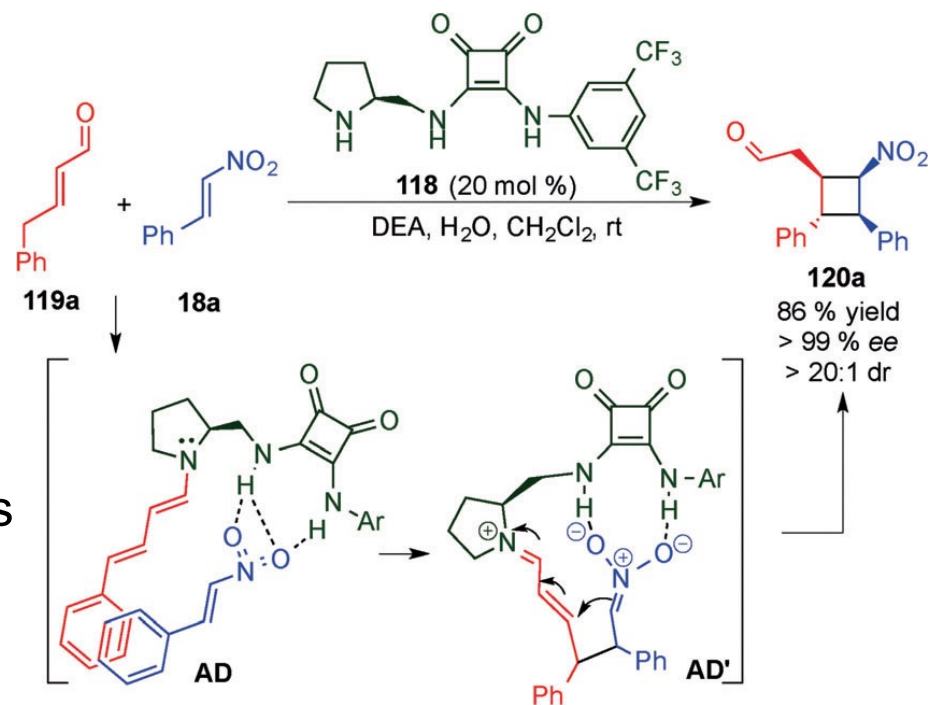
- **Dienamines**

- Mostly used in cycloadditions (**Trick 1**)
- Some highlights:

- [2+2]

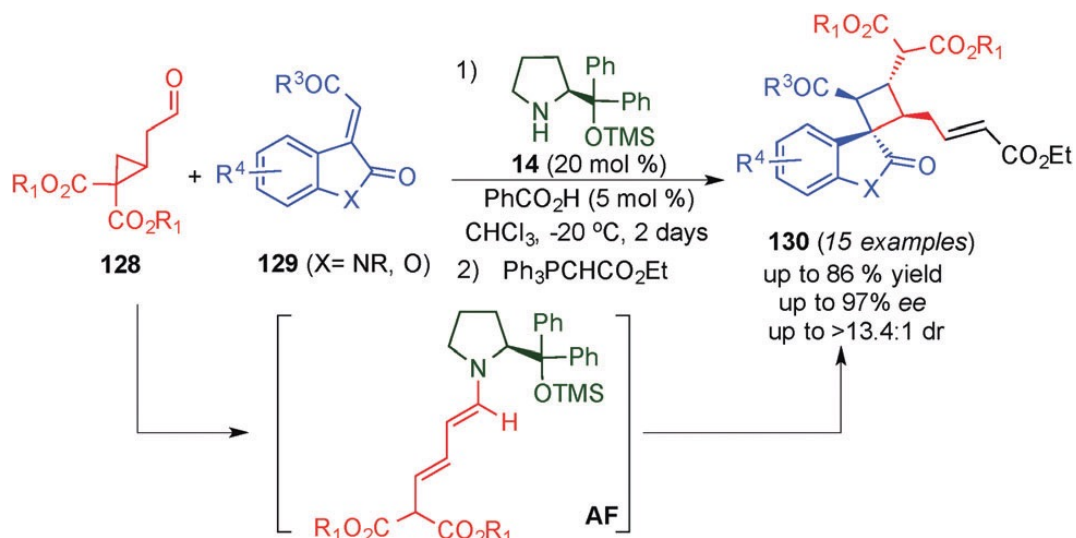
- Albrecht, Ł.; Dickmeiss, G.; Cruz Acosta, F.; Rodríguez-Esrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543.

- The claim is that H-bonding situates electrophile for  $\gamma$ -alkylation of dienamine, however...



- **Dienamines**

- Mostly used in cycloadditions (**Trick 1**)
- Some highlights:
  - [2+2]
  - An interesting way to access dienamines

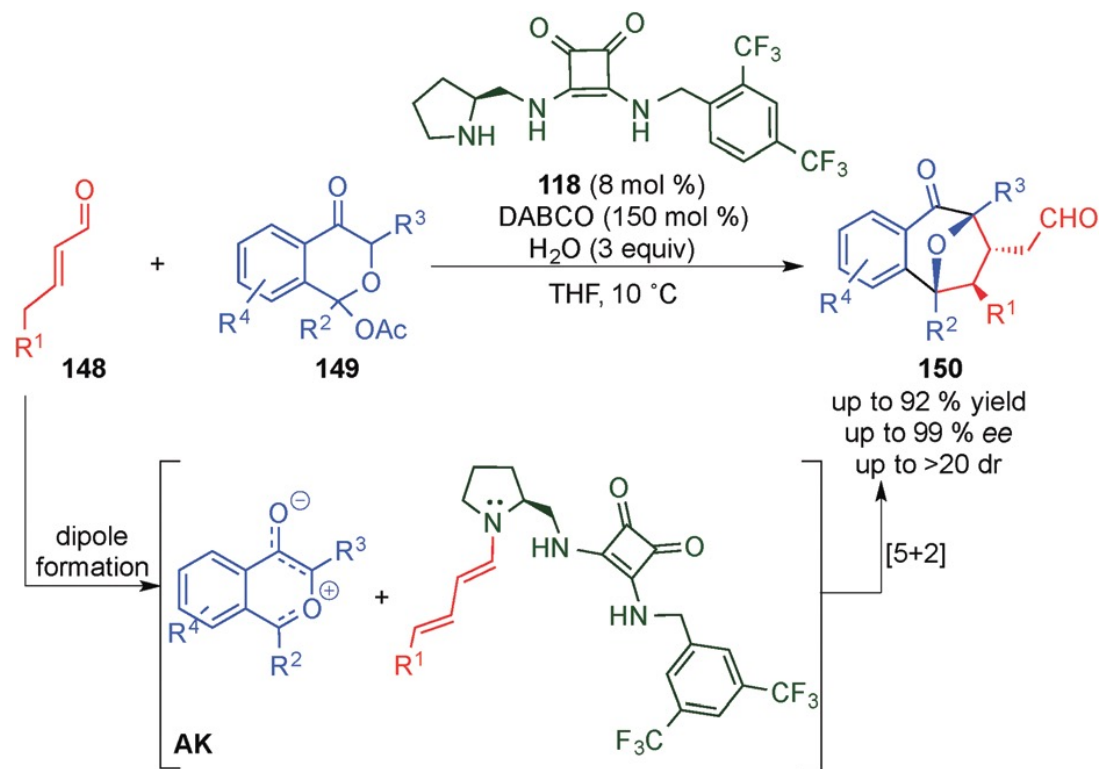


Halskov, K. S.; Kniep, F.; Lauridsen, V. H.; Iversen, E. H.; Donslund, B. S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2015**, *137*, 1685.

- [4+2] using only remote olefin of diene enables inverse electron demand DA and HAD reactions

- **Dienamines**

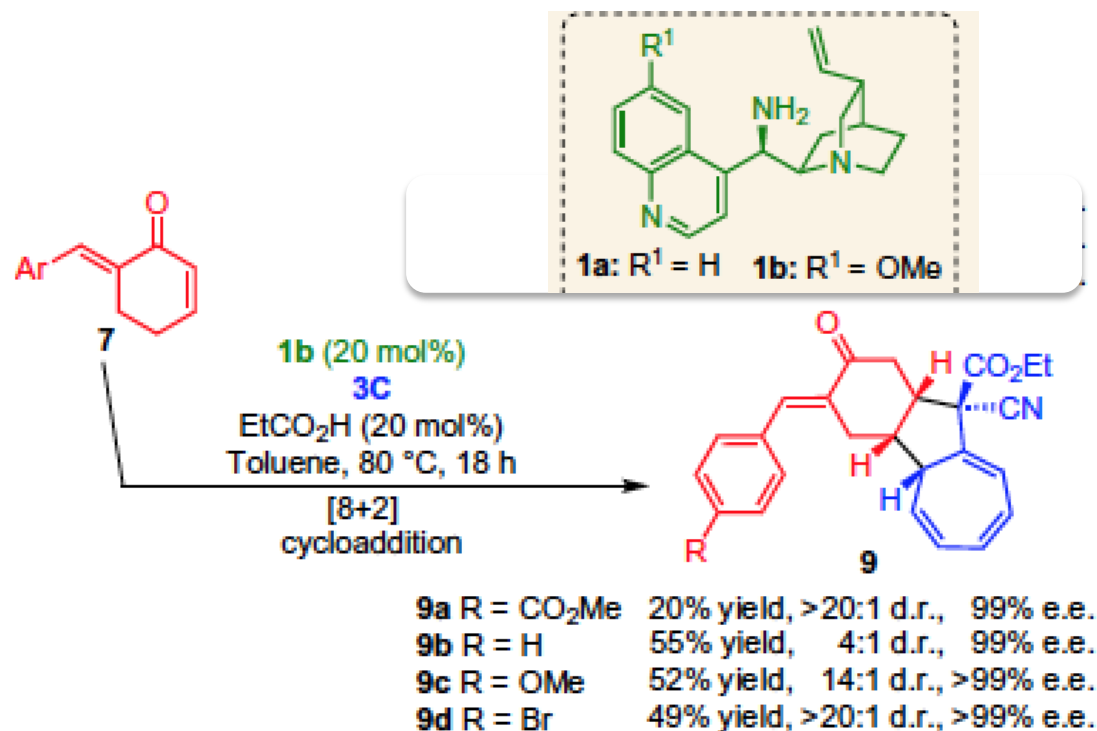
- Mostly used in cycloadditions (**Trick 1**)
- Some highlights:
  - [5+2]
  - Only 2<sup>nd</sup> example of catalytic enantioselective [5+2] dipolar cycloaddition of oxidopyrylium ylides



Orue, A.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 3043.

- **Dienamines**

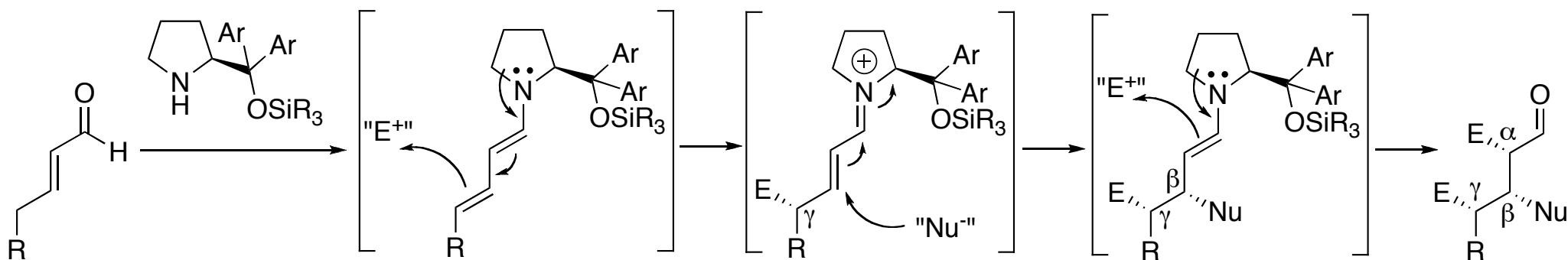
- Mostly used in cycloadditions (**Trick 1**)
- Some highlights:
  - [8+2]



Mose, R.; Preegel, G.; Larsen, J.; Jakobsen, S.; Iverson, E. H.; Jørgensen, K. A. *Nat. Chem.* **2017**, *9*, 487-492.

# CASCADE REACTIONS

two (or more) consecutive reactions in a single flask



- Dienamine-, iminium-, and enamine catalyzed reactions have complementary mechanisms that facilitate combining more than one transformation into one flask

Domino: two or more bond-forming reactions under **identical conditions**, in which the subsequent transformation takes place at the functionalities obtained in the former transformation.

Tandem: only two bond-forming reactions

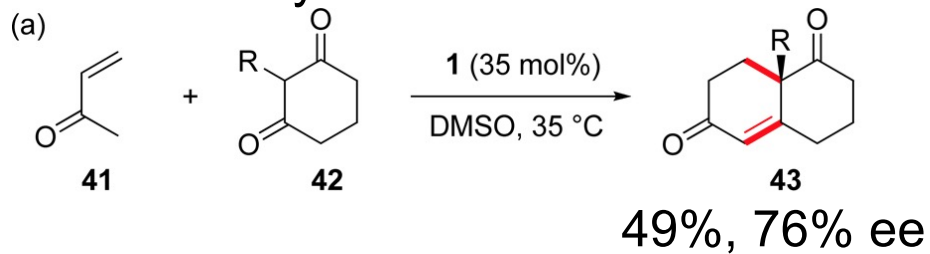
They are multicomponent reactions; can be multicatalytic or employ a single catalyst.

- **Domino reactions**

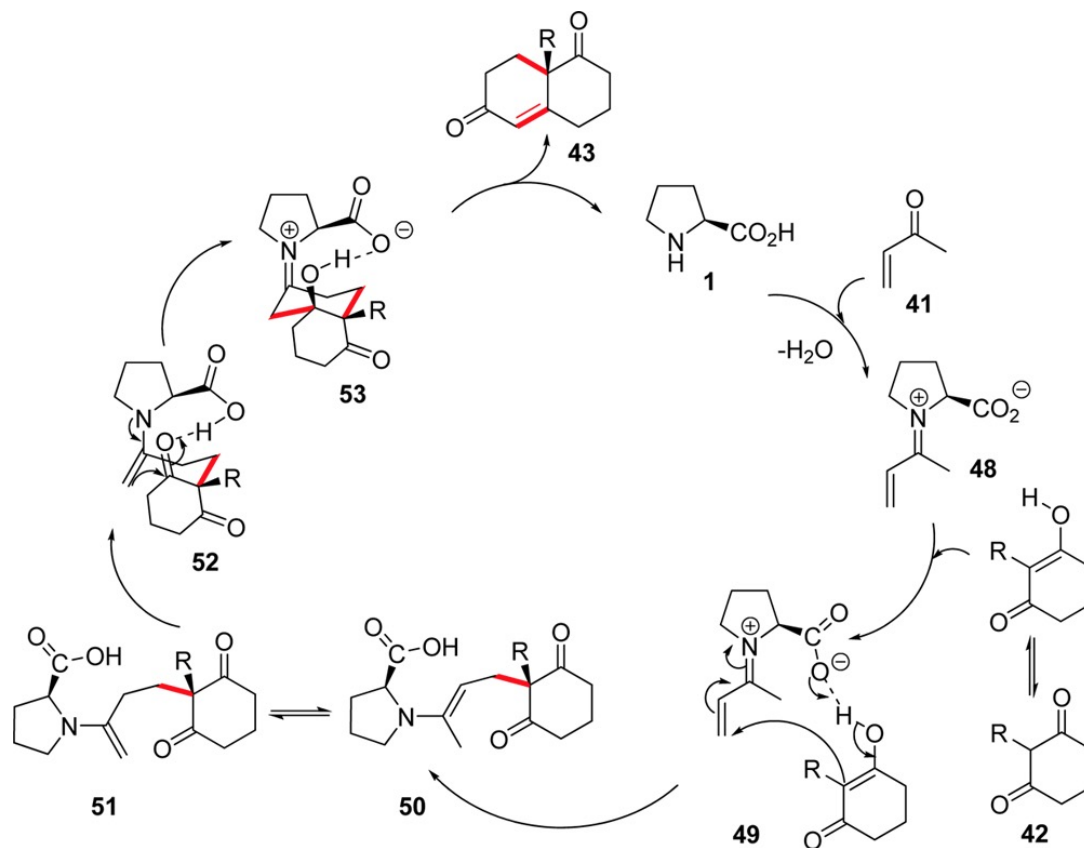
- Early example

- Barbas

- Proline-catalyzed Robinson annulation

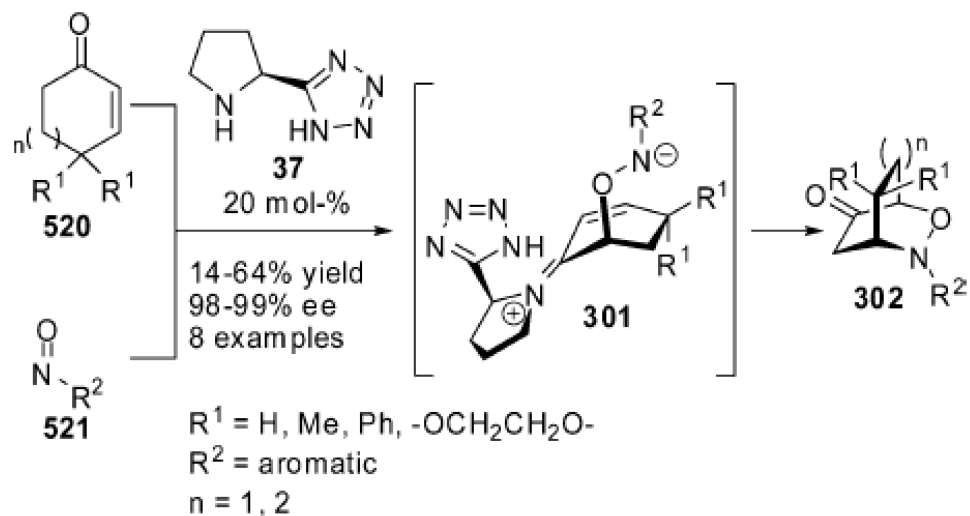


Bui, T.; Barbas, C. F.  
*Tetrahedron Lett.* **2000**, *41*, 6951.



- **Domino reactions**

- Early example of dienamine catalysis in a cascade reaction
- Barbas (cross conjugated) dienamine
  - O-nitroso aldol—aza-Michael



Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962.

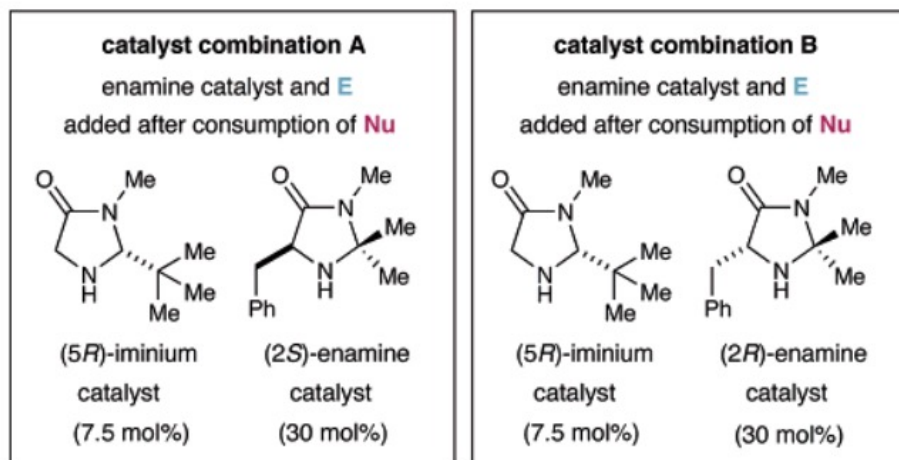
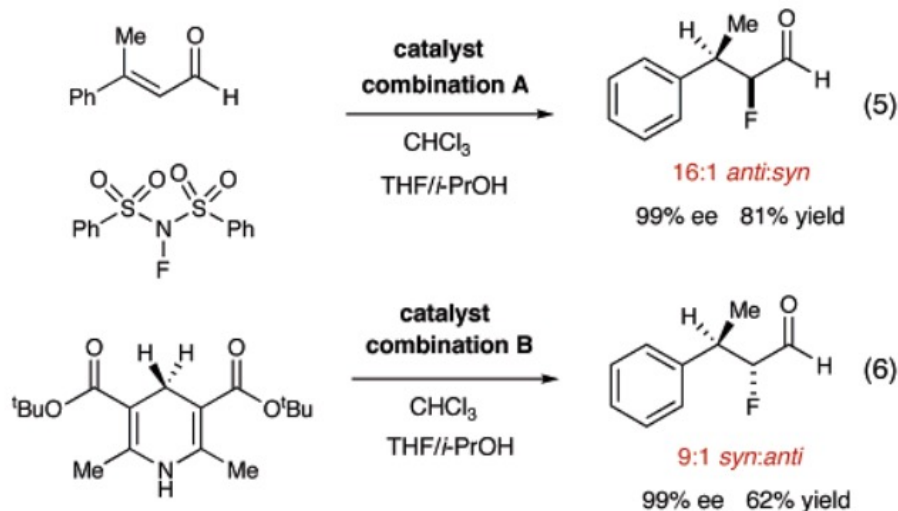


- **Domino reactions**

- MacMillan

- “organomulticatalysis” (cycle specific)
    - Allows access to all stereoisomers (both enantiomers of **both diastereomers**)

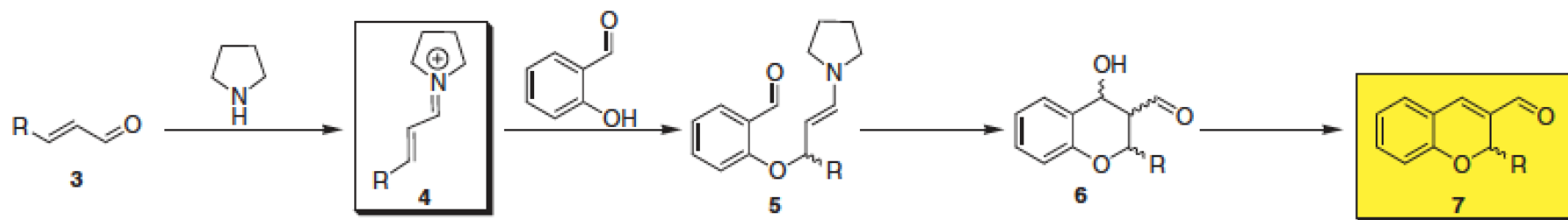
- Intermolecular cascades



Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051-15053.

- **Domino reactions**

- Easy access to ring systems
  - 3-, 5-, 6-membered rings; carbocycles, heterocycles; fused, spiro, and bridged ring systems
- Cascade reactions provide a way to overcome reversible, nonselective addition of Nu to conjugated iminium ions (i.e., oxa-Michael)

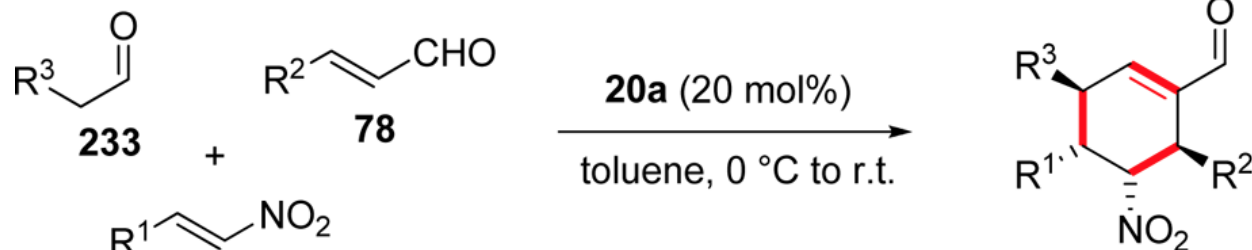


Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I.  
*Tetrahedron: Asymm.* **2006**, *17*, 1763-1767. and others

- benzopyran (chromene) = a structural core of natural and synthetic bioactive compounds

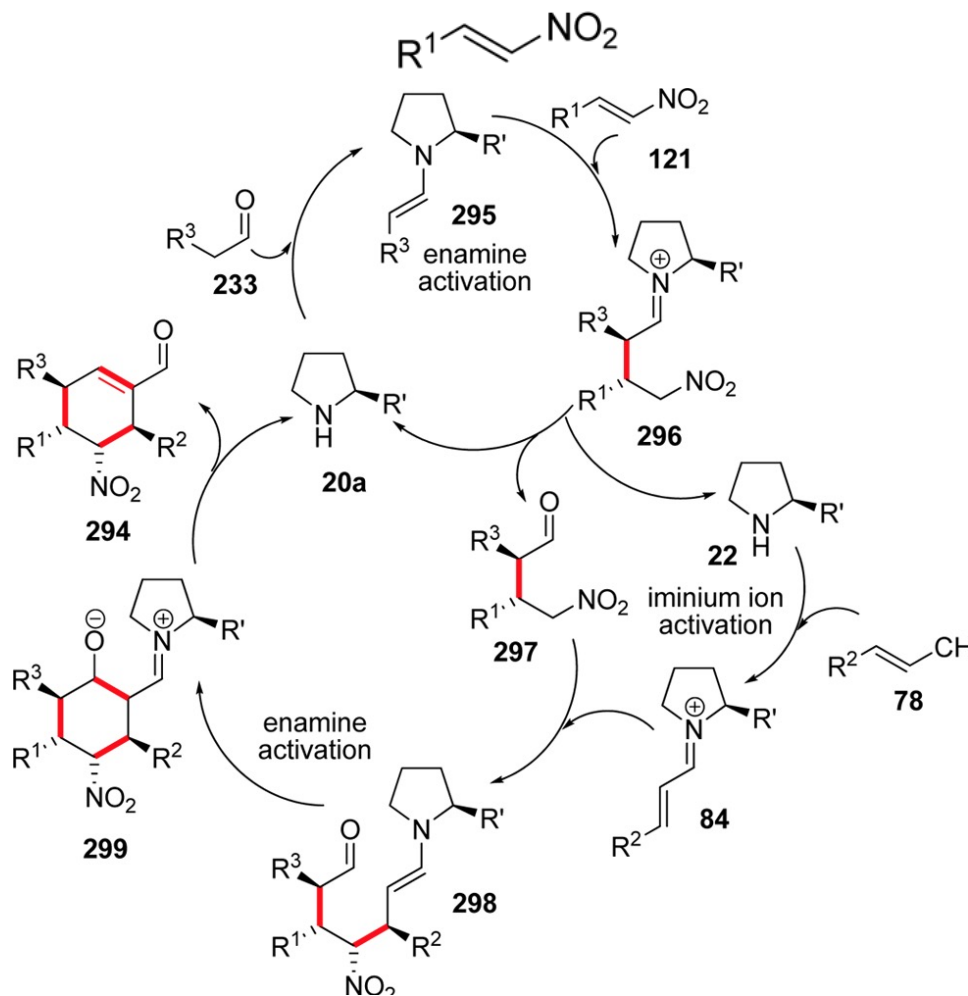
- **Domino reactions**

- Multicomponent (triple cascade)



**294**: 25 examples: 18-60%  
 65:35 to 89:11dr, 97-99% ee

Enders, D.; Hüttl, M. R. M.; Grondal, C.;  
 Raabe, G. *Nature* **2006**, *44*, 861.

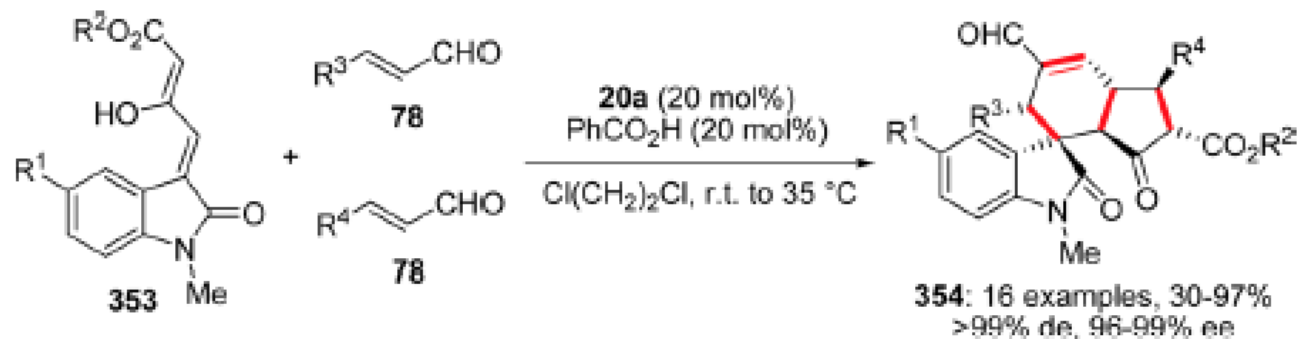


- **Domino reactions**

- 3-component, quadruple cascade (iminium-enamine-iminium-enamine)
- Rapidly build complex systems
  - Multiple ring systems, multiple stereocenters, quaternary stereocenters

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**Scheme 104. Spirocyclic Oxindoles through a Quadruple Cascade Reaction**



Jiang, K.; Jia, Z.-J.; Yin, X.; Wu, L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 2766.

- **Conclusion**

- Later on...
  - Will see some of these catalysts/mechanisms used in conjunction with other catalysts, both organic and transition metal.
  - Will see application of some of these transformations in total syntheses.