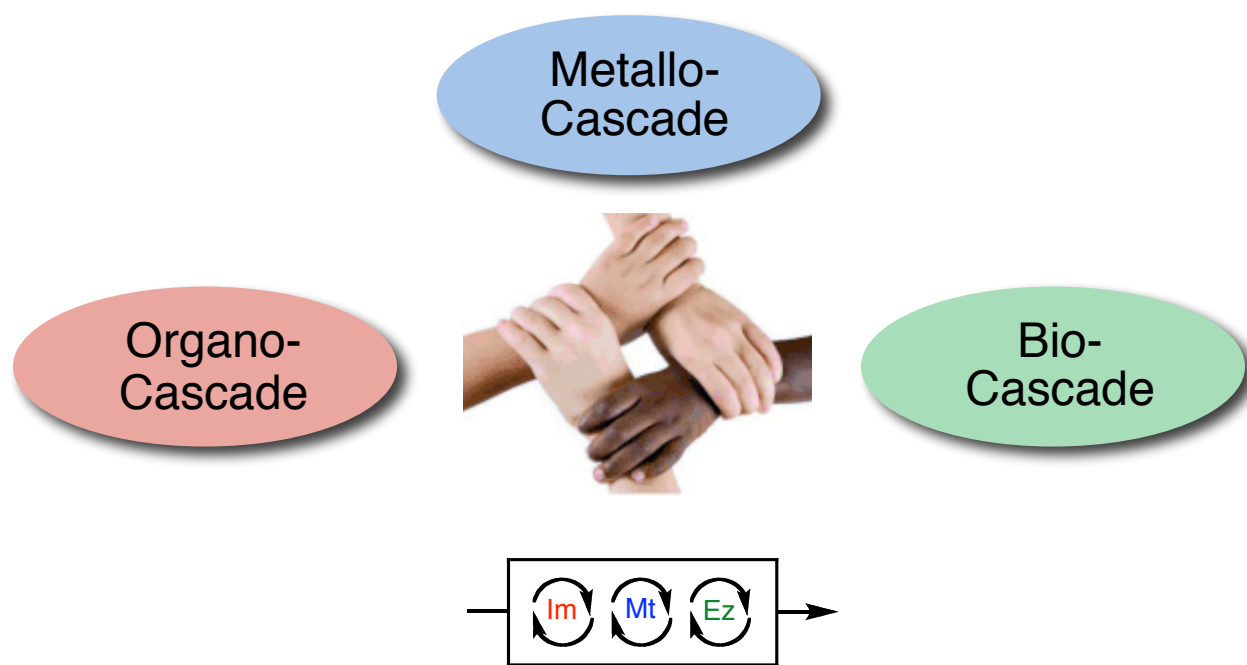


# *Recent Developments in Cascade Catalysis*

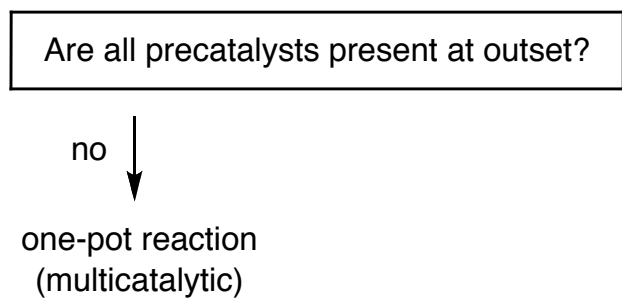


MacMillan Group Meeting

July 7, 2010

Spencer Jones

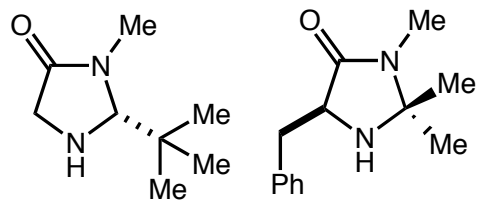
## *Defining Cascade Catalysis: Flowchart of One-Pot Processes*



# One Pot, Multicatalytic Reaction: Both Catalysts not Present at Outset

## catalyst combination A

enamine catalyst and **E**  
added after consumption of **Nu**

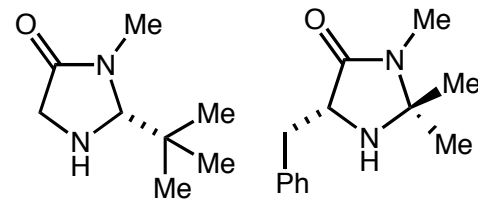


(5*S*)-iminium  
catalyst  
(7.5 mol%)

(2*R*)-enamine  
catalyst  
(30 mol%)

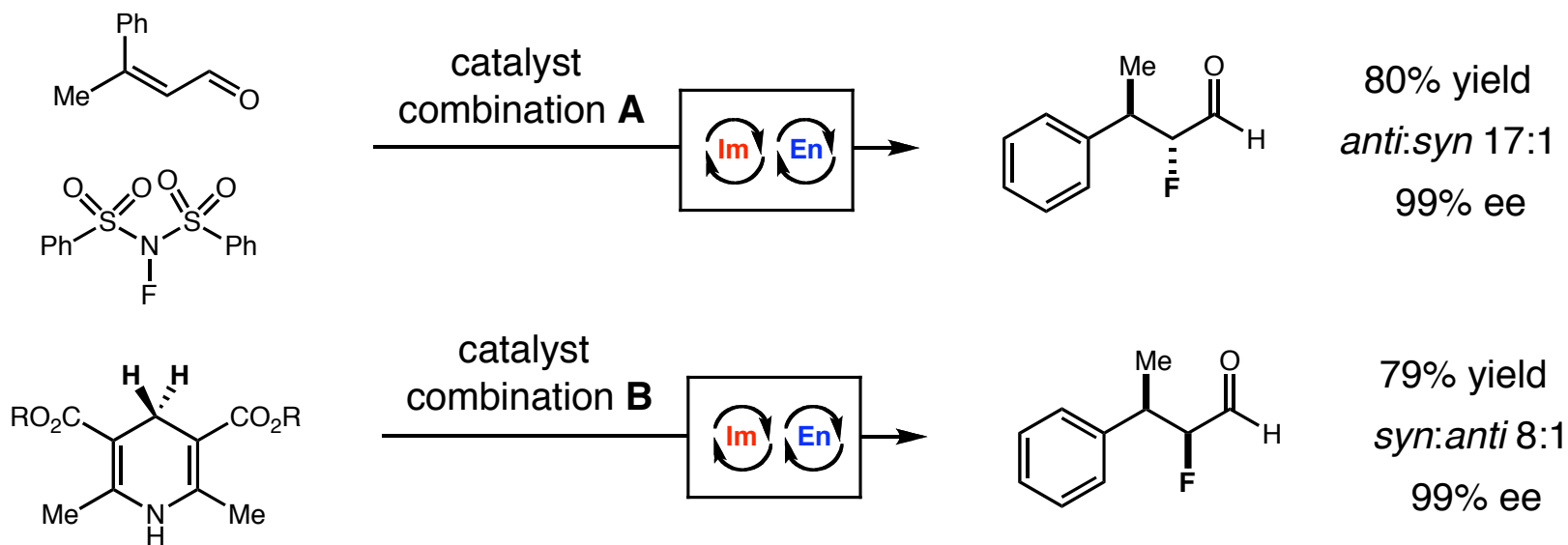
## catalyst combination B

enamine catalyst and **E**  
added after consumption of **Nu**



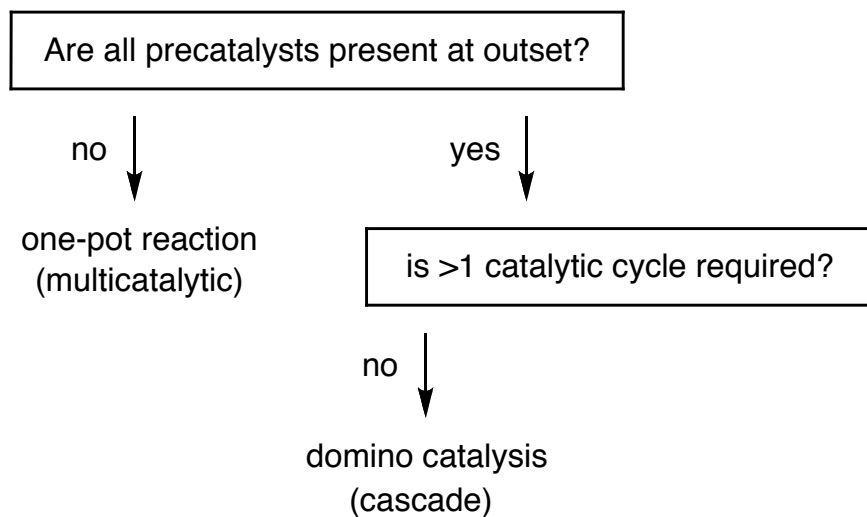
(5*S*)-iminium  
catalyst  
(7.5 mol%)

(2*S*)-enamine  
catalyst  
(30 mol%)

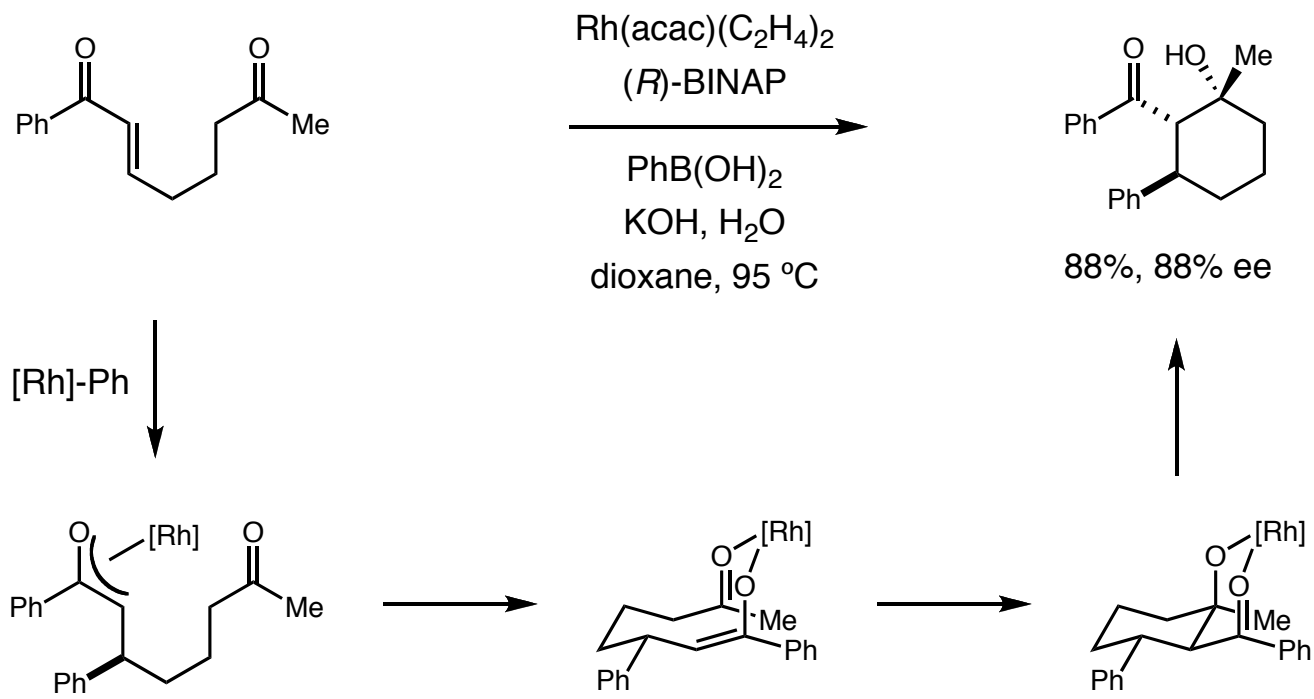


Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051

## Defining Cascade Catalysis: Flowchart of One-Pot Processes



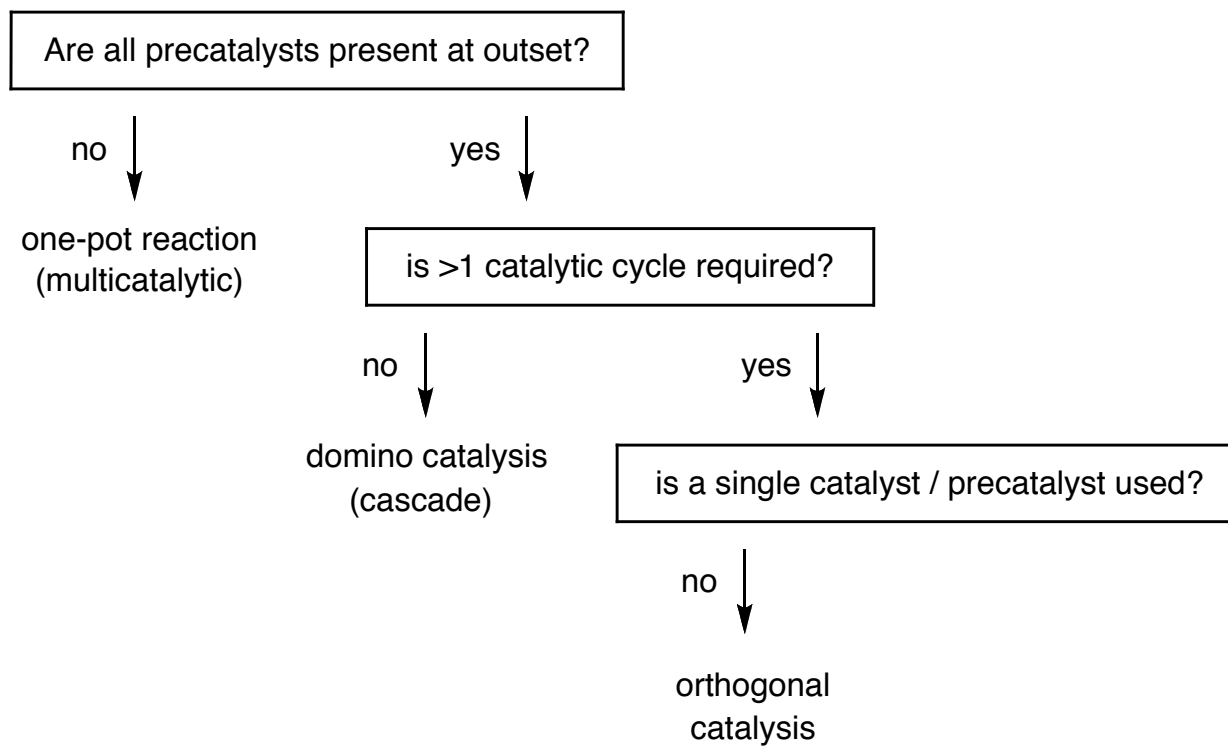
## Domino Catalysis: Conjugate Addition/Aldol Cascade



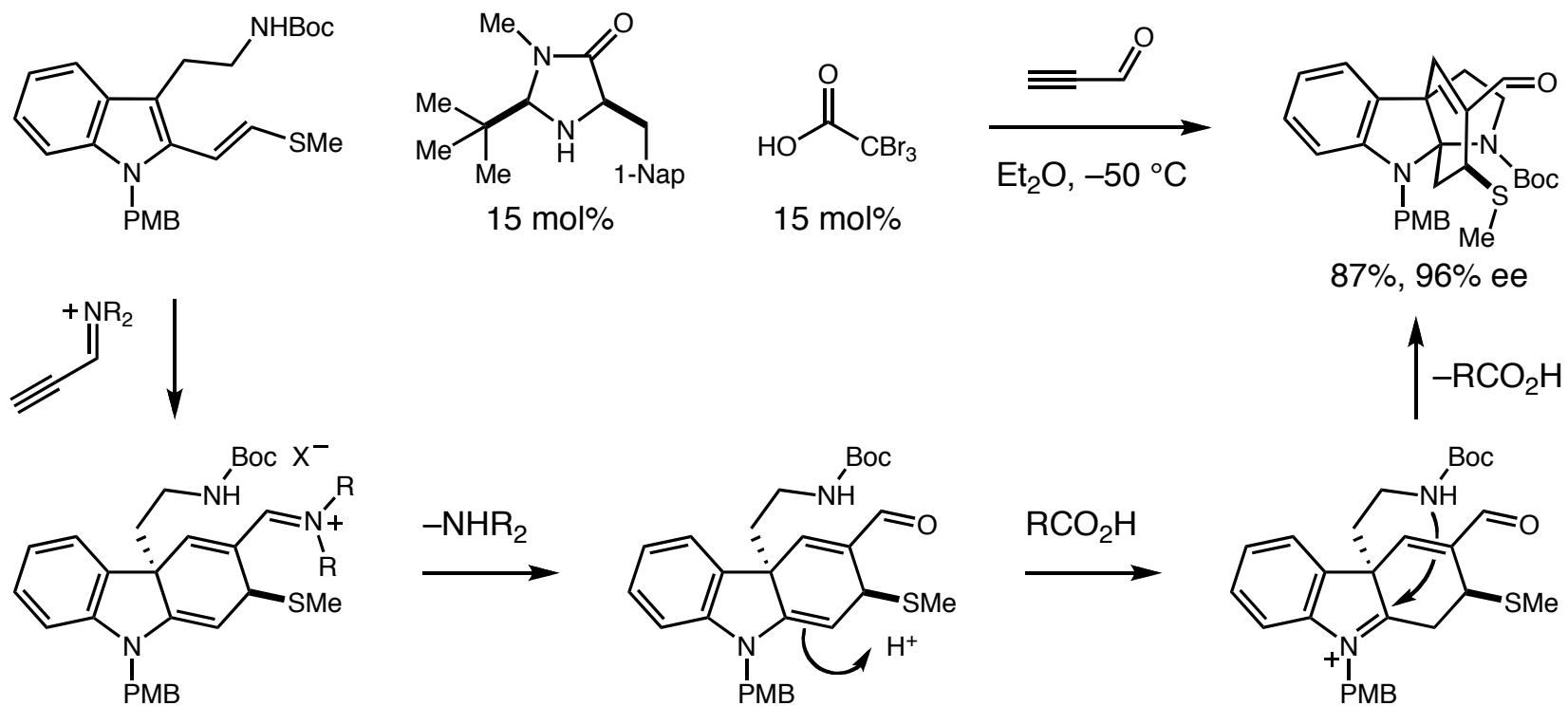
- The rate of aldol cyclization is faster than rhodium enolate hydrolysis: single catalytic cycle

Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, 125 (5), 1110.

## Defining Cascade Catalysis: Flowchart of One-Pot Processes

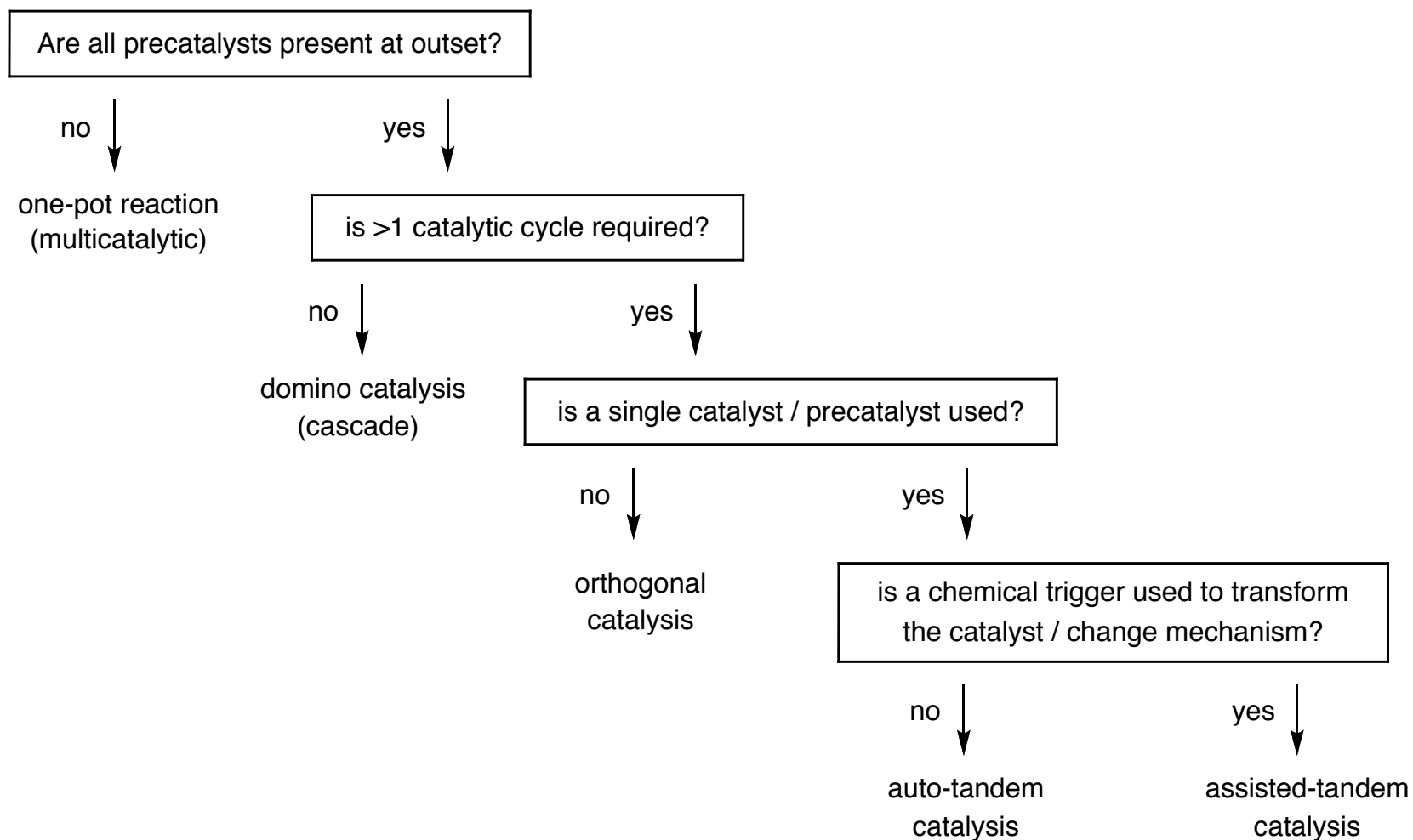


## Orthogonal Catalysis: Multiple Catalysts Present from Outset



- Both iminium and Brønsted acid catalysts are present at the beginning of the reaction and catalyze separate steps

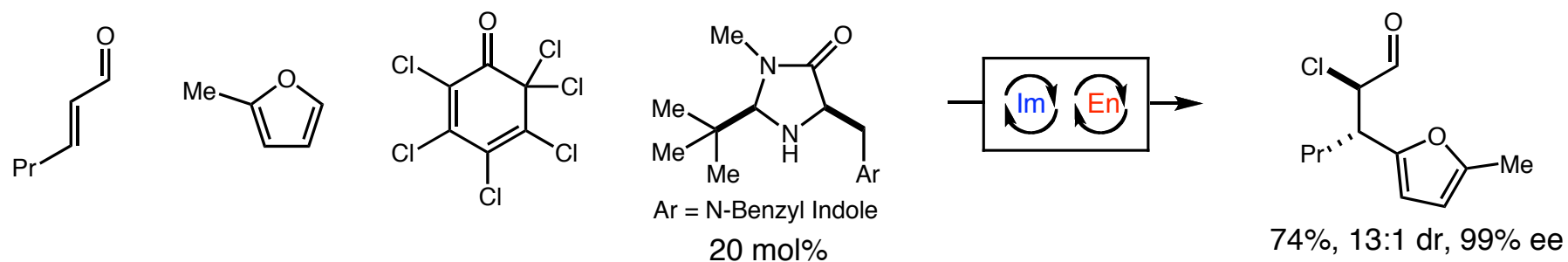
## Defining Cascade Catalysis: Flowchart of One-Pot Processes





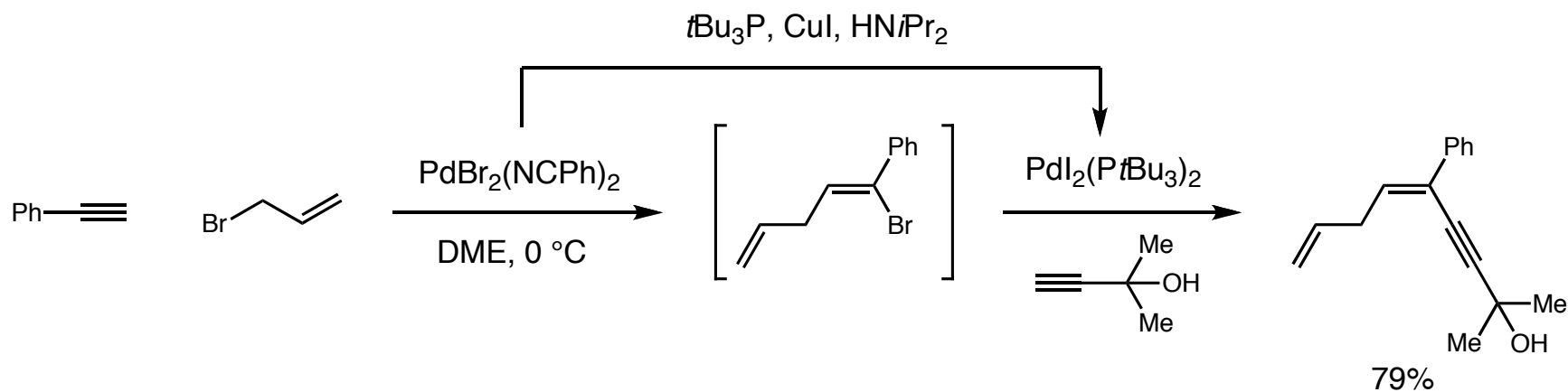
## Tandem Catalysis: Single Catalyst, Mechanistically Distinct Transformations

- Auto tandem catalysis: Single catalyst directly performs multiple catalytic transformations



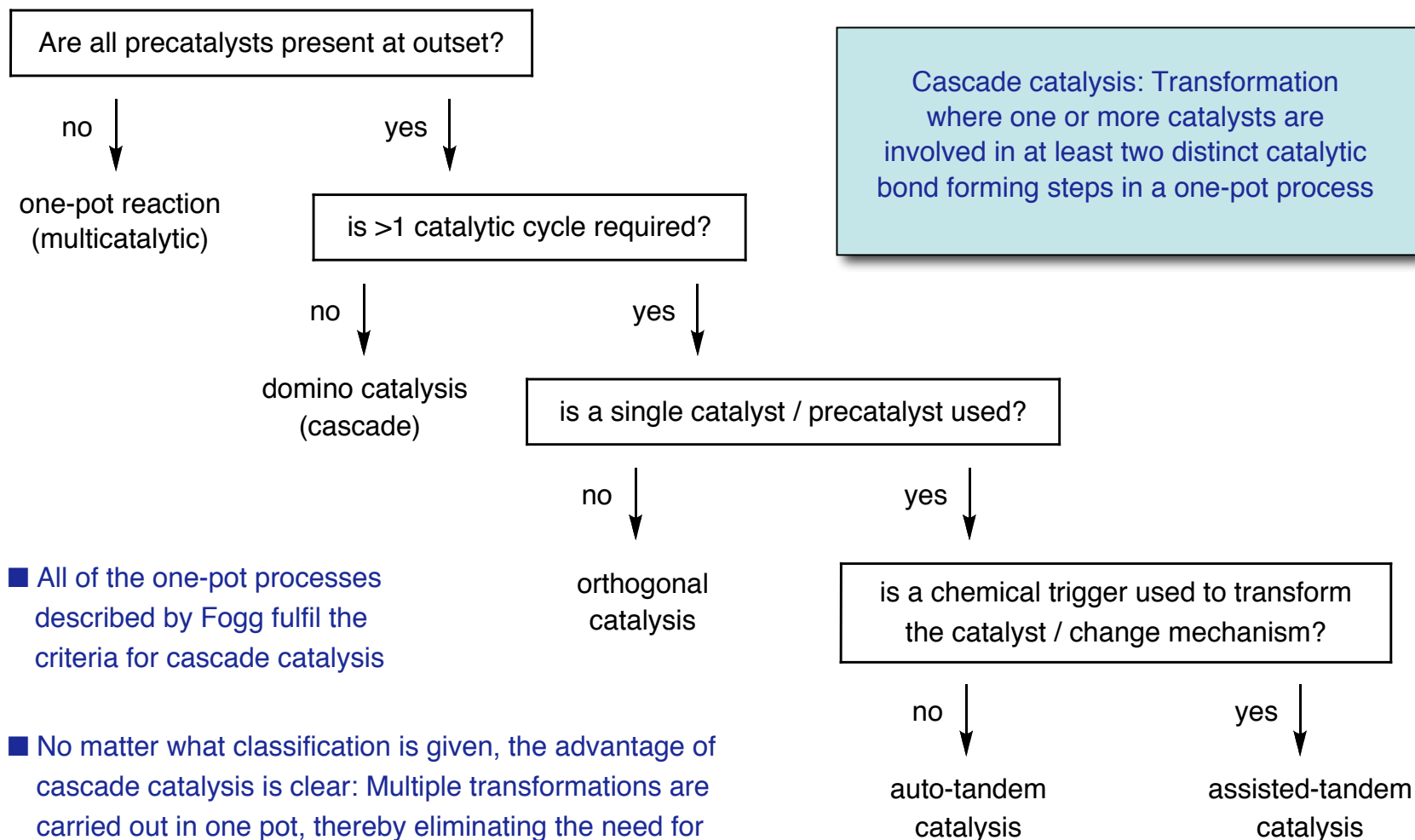
Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127* (43), 15051.

- Assisted tandem catalysis: Mechanistic change induced by addition of chemical trigger



Thadani, A. N.; Rawal, V. H. *Org. Lett.* **2002**, *4* (24), 4321.

## Defining Cascade Catalysis: Flowchart of One-Pot Processes



## *Selected Examples of Enantioselective Cascade Catalysis*

Organocascade



Organometallo Cascade



Metallo Cascade



OrganoBio Cascade



MetalloBio Cascade



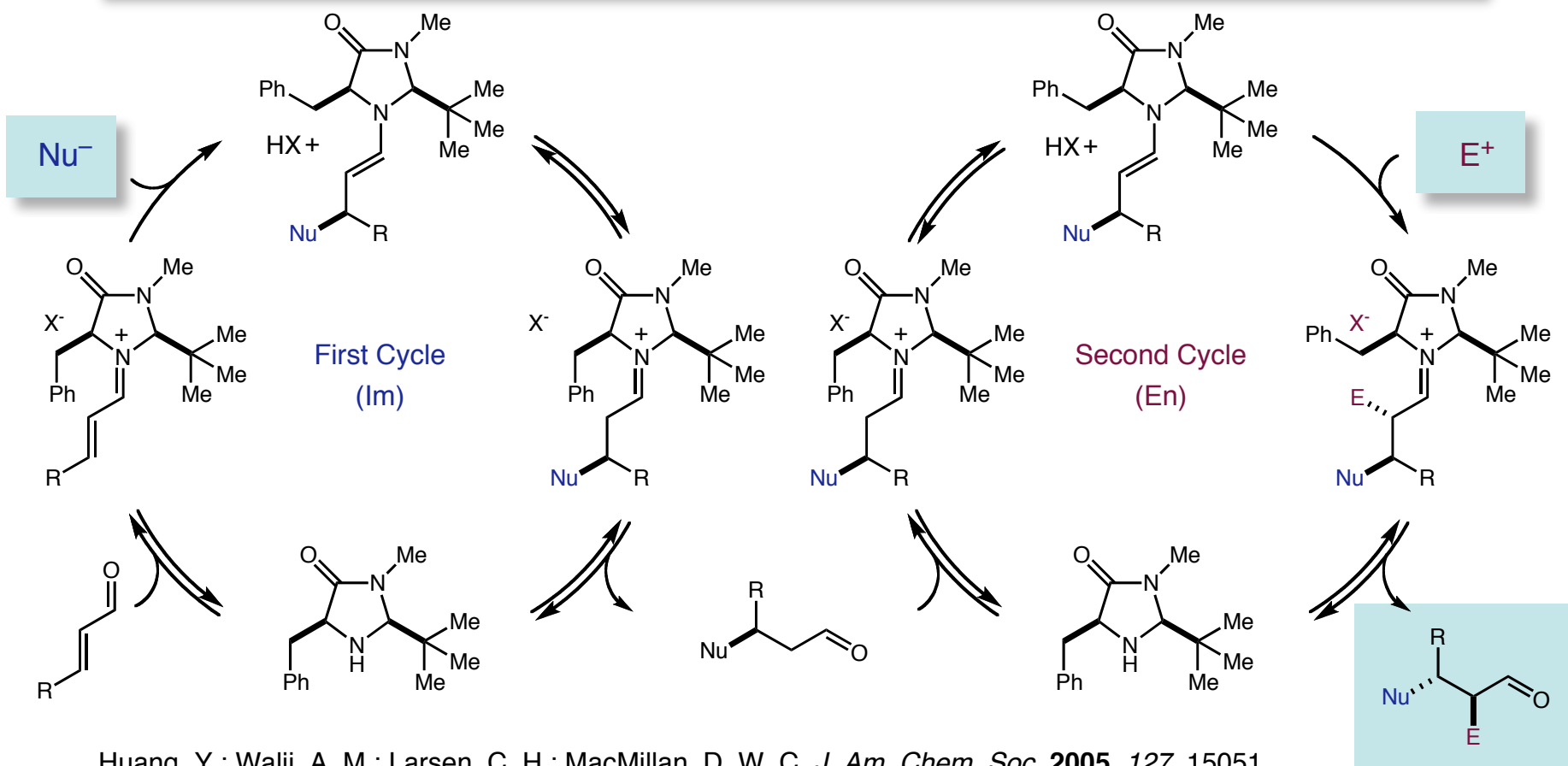
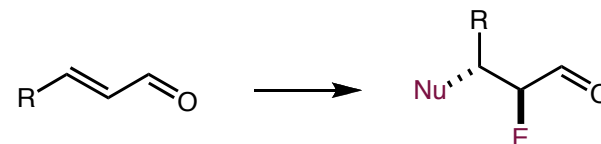
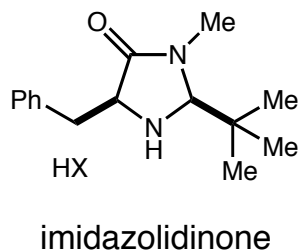
Biocascade



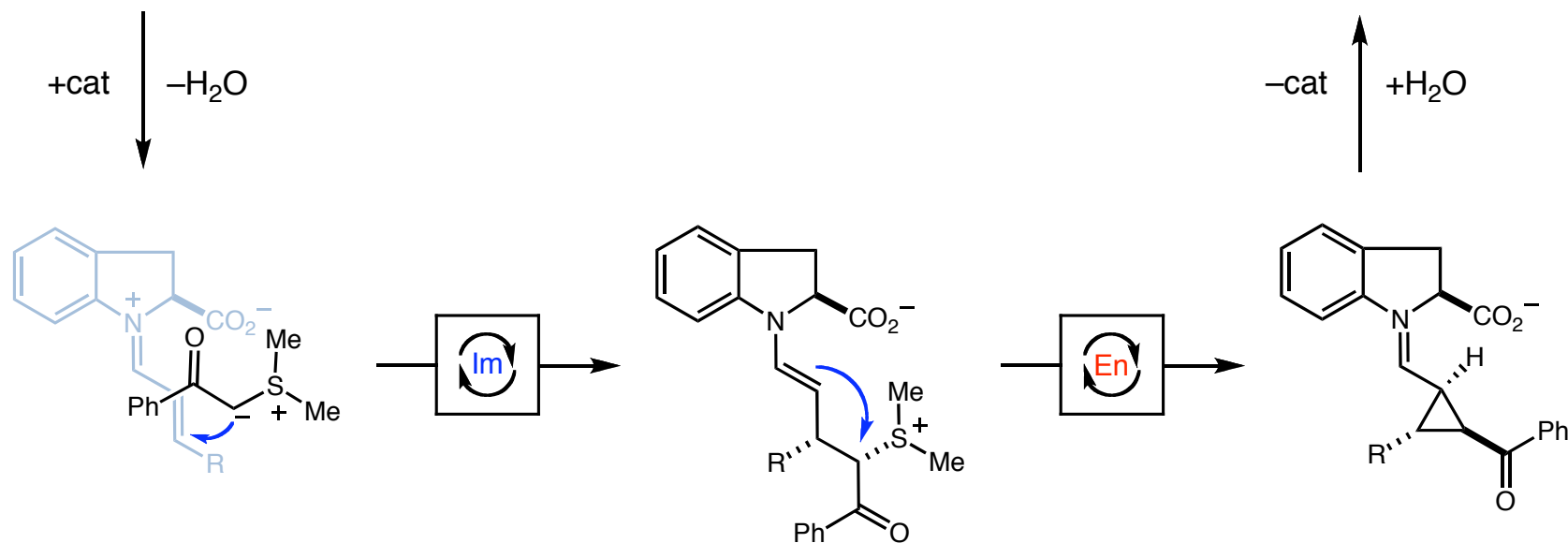
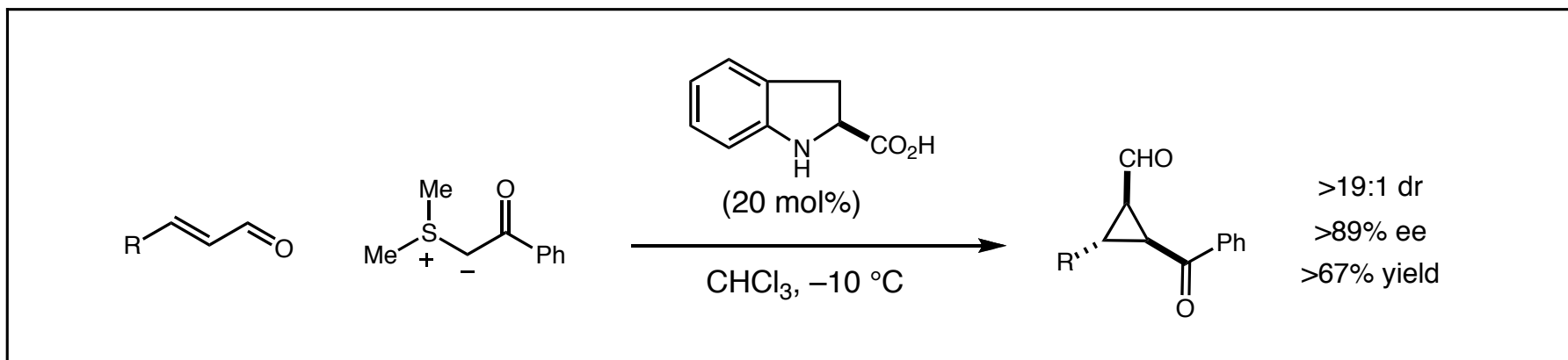
## Merging LUMO-lowering and HOMO-raising with one catalyst

■ **First step:**  
Iminium catalysis

■ **Second step:**  
Enamine catalysis

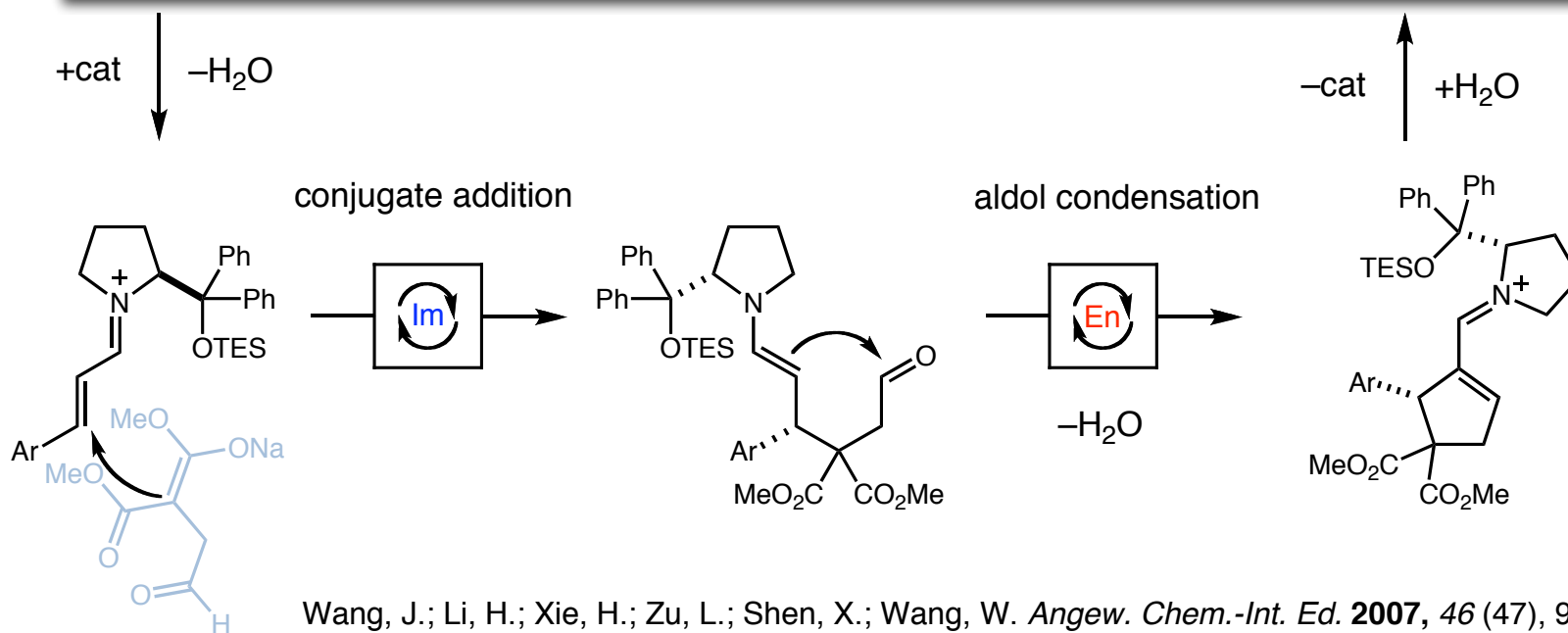
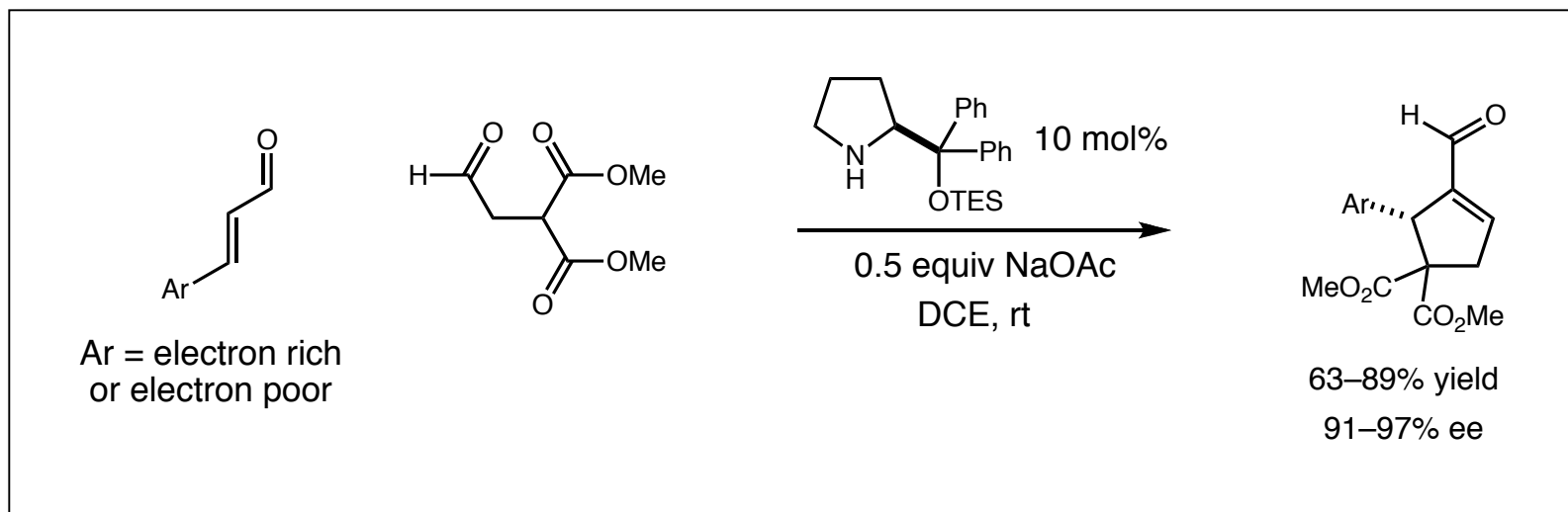


## Organocascade Catalysis: Before the Name

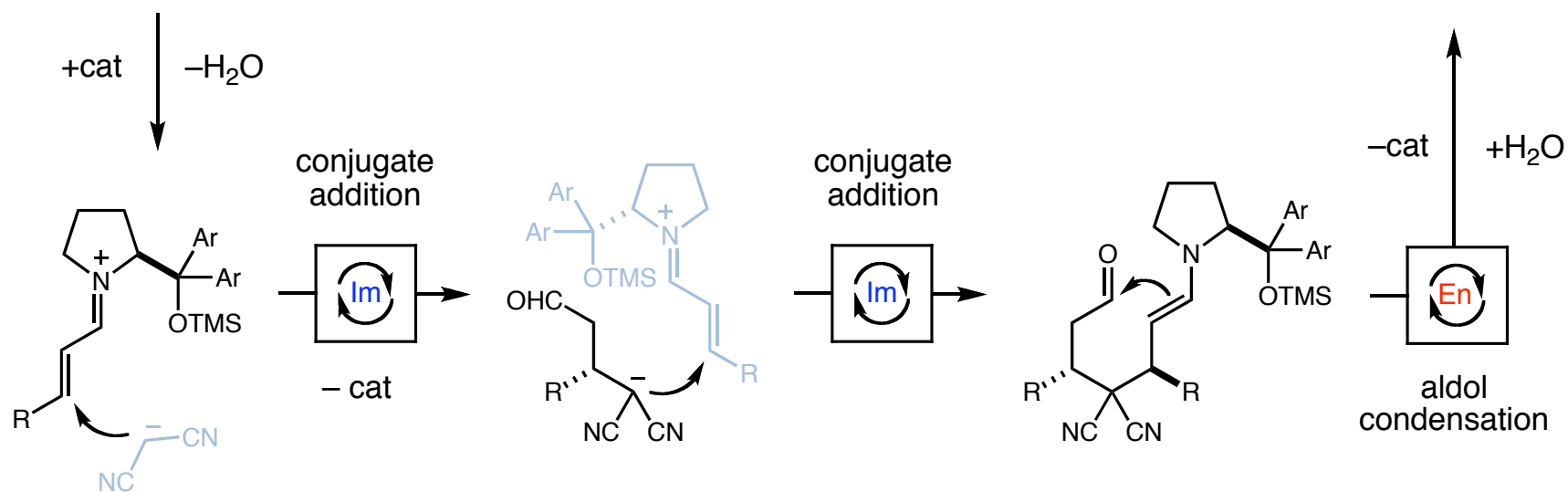
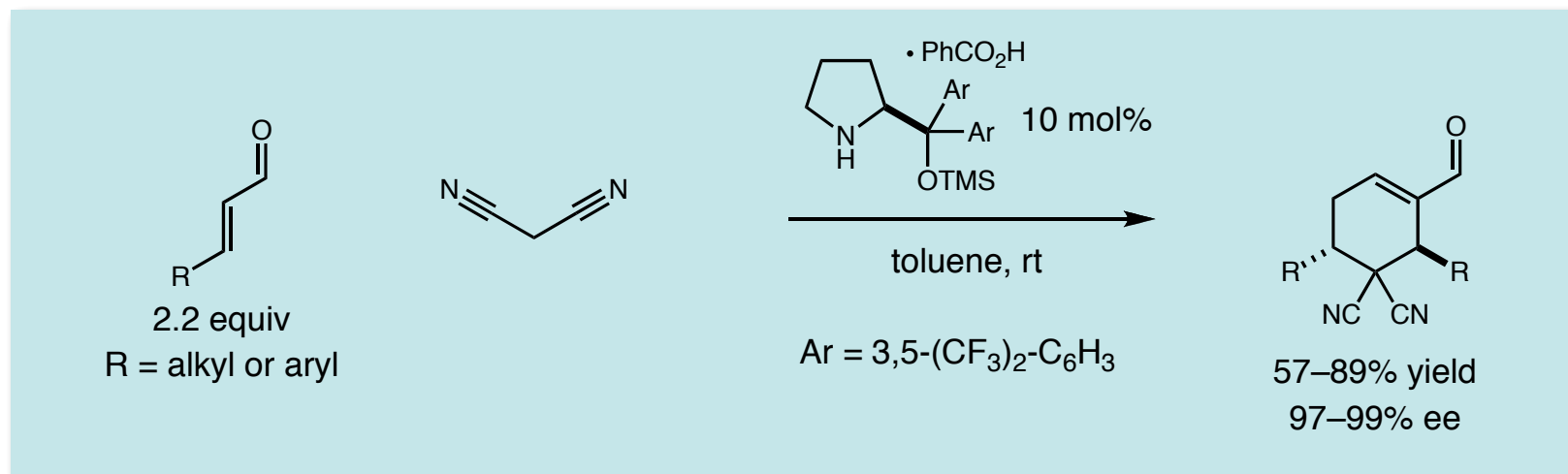


■ Indoline carboxylic acid facilitates the formation of cyclopropanes via iminium-enamine cascade catalysis

## Double Organocascade Catalysis: Wang Group

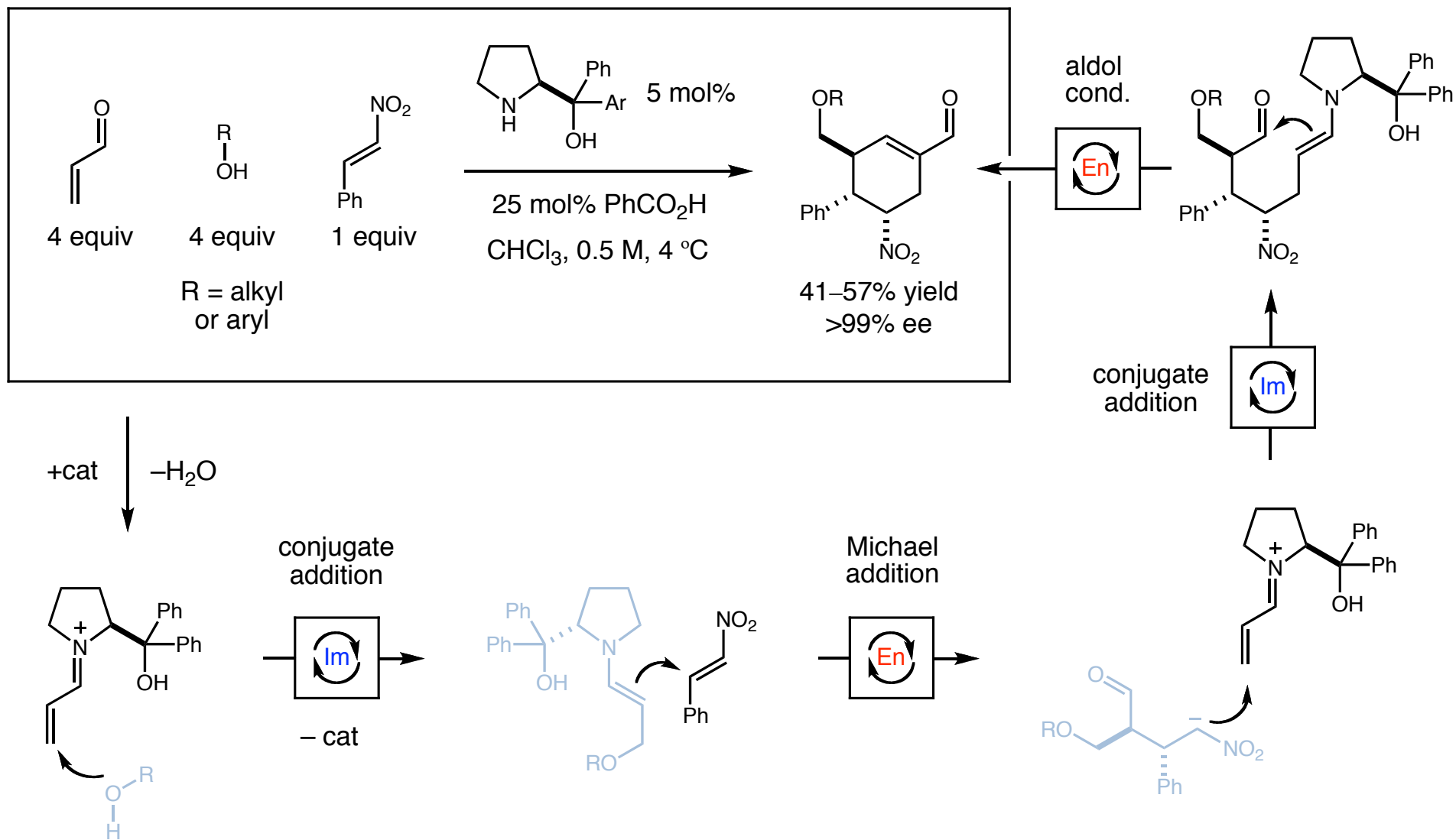


## Triple Organocascade Catalysis: Jørgensen Group



Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem.-Int. Ed.* **2007**, 46 (7), 1101

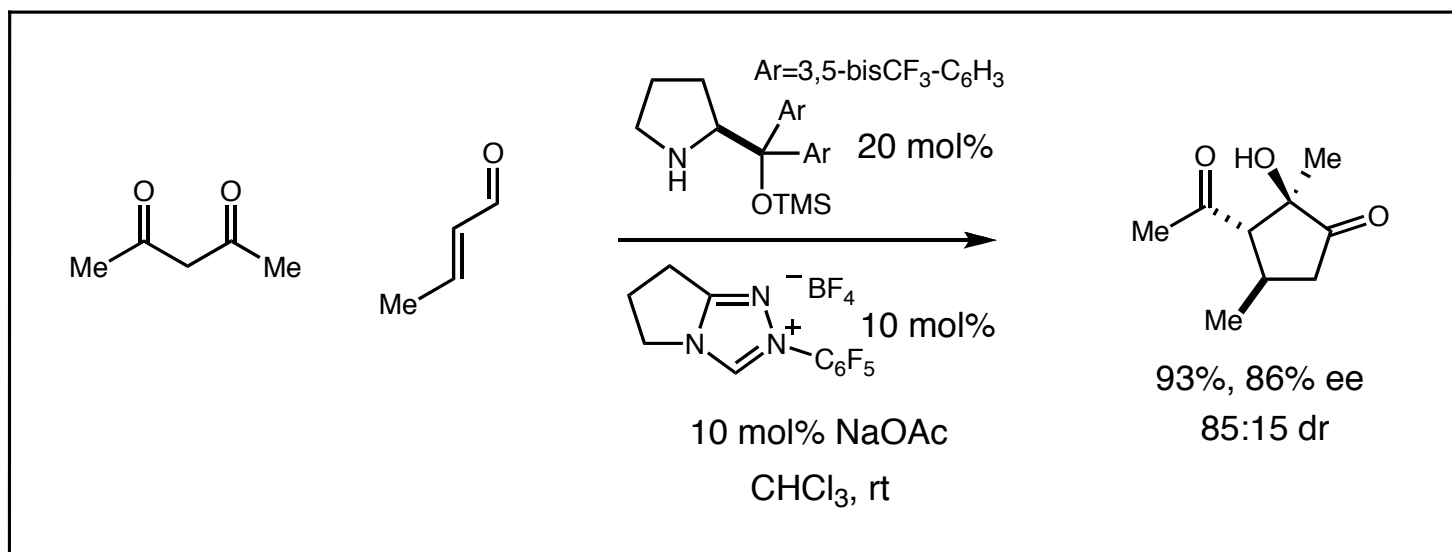
## Quadruple Organocascade Catalysis: Zhang Group



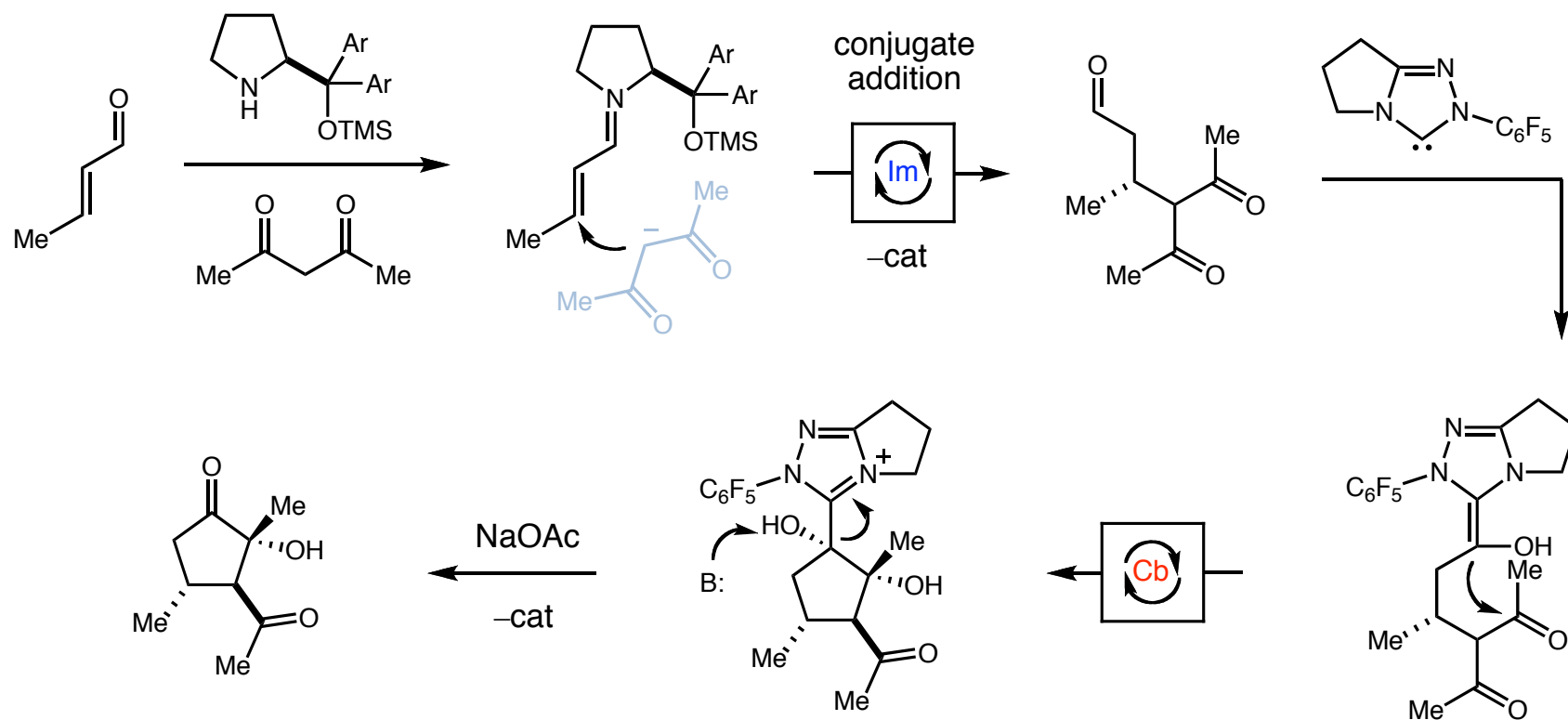
Zhang, F. L.; Xu, A. W.; Gong, Y. F.; Wei, M. H.; Yang, X. L. *Chem. Eur. J.* **2009**, *15* (28), 6815



## *Iminium-Carbene Cascade Catalysis: Synthesis of Functionalized Cyclopentanones*

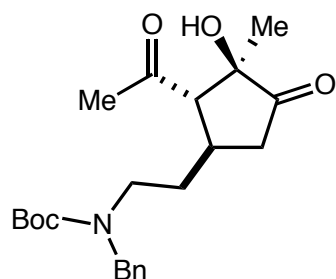
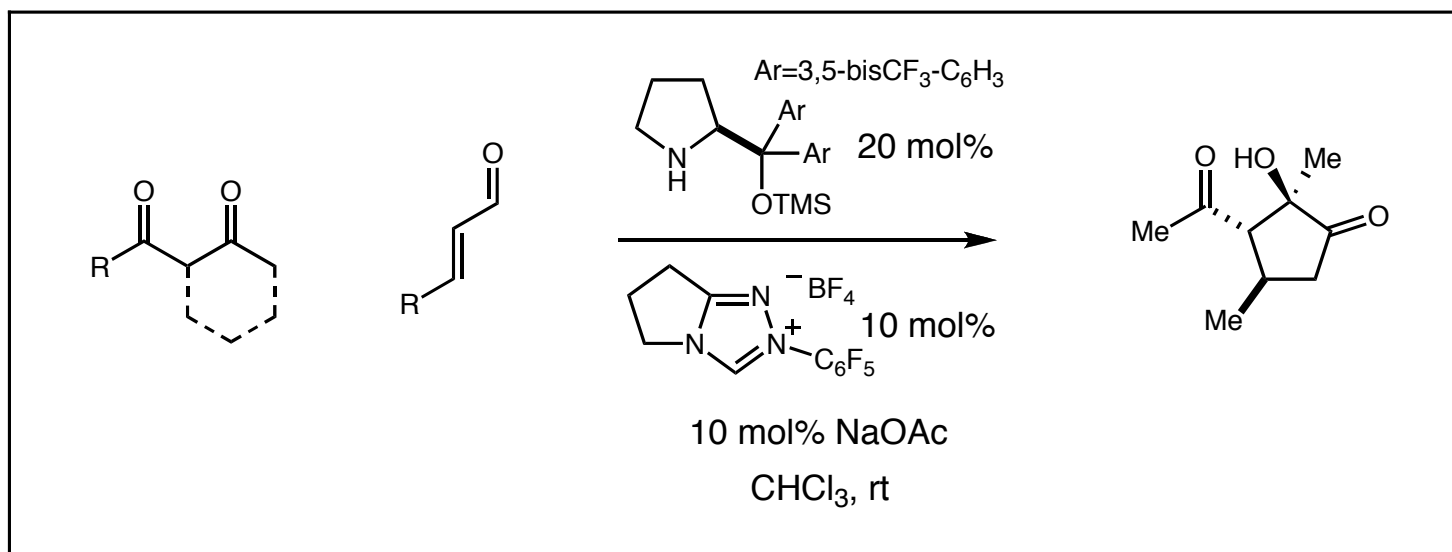


## Iminium-Carbene Cascade Catalysis: Synthesis of Functionalized Cyclopentanones



■ Triazolium salt mediates Benzoin type cyclization to give functionalized cyclopentanones

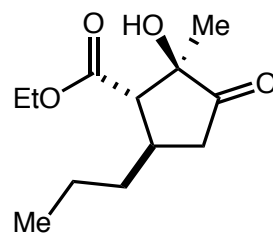
# Iminium-Carbene Cascade Catalysis: Synthesis of Functionalized Cyclopentanones



60% yield

90% ee

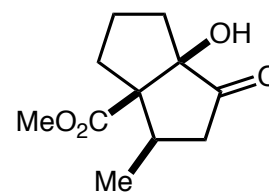
85:15 dr



80% yield

93% ee

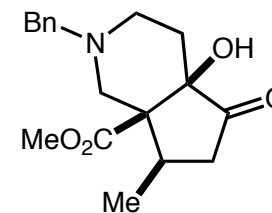
60:30:8:2 dr



79% yield

94% ee

80:20 dr

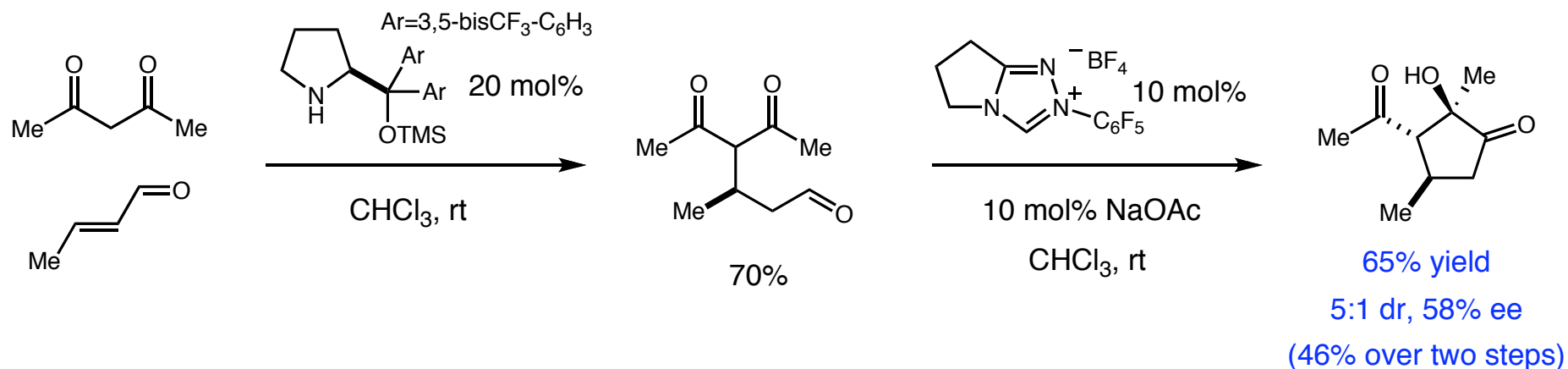
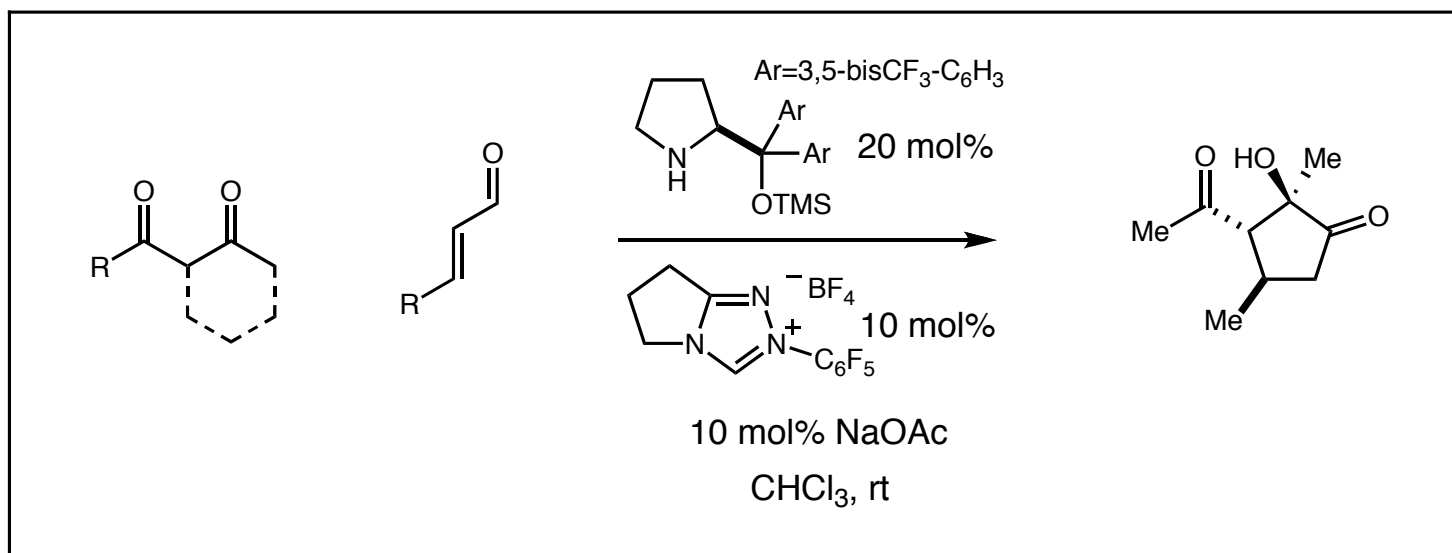


76% yield

90% ee

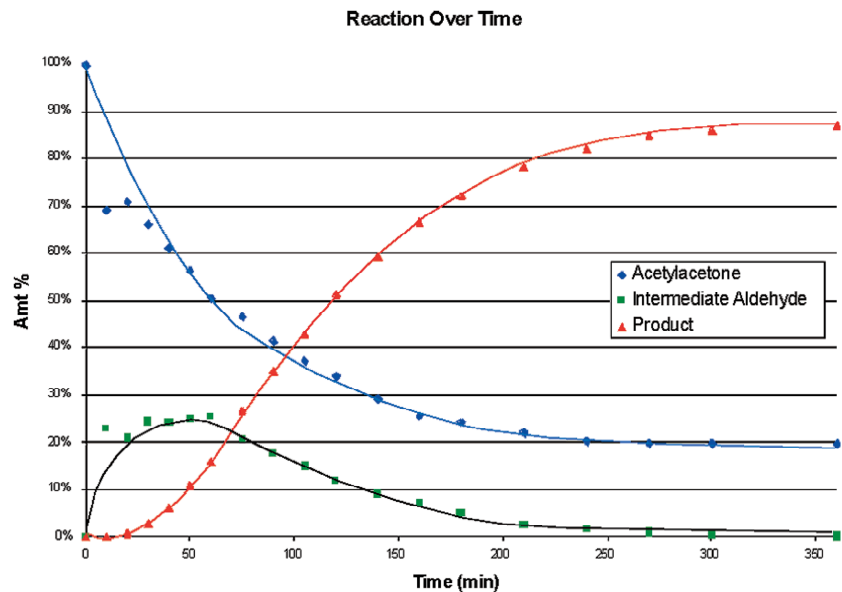
85:15 dr

# Iminium-Carbene Cascade Catalysis: Synthesis of Functionalized Cyclopentanones

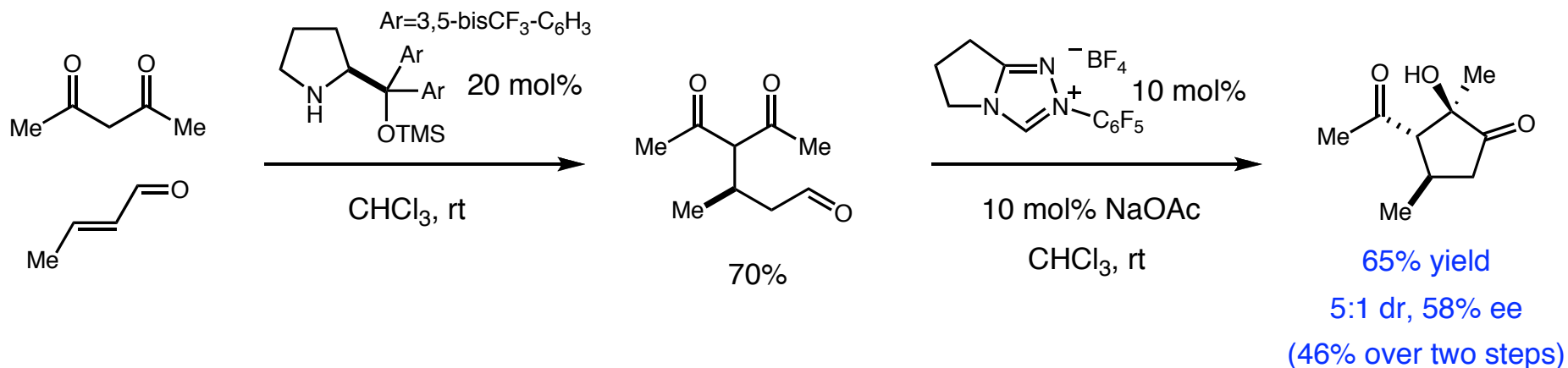


■ Carrying out the cascade as separate reactions gives the product with lower yield and selectivity

# Iminium-Carbene Cascade Catalysis: Synthesis of Functionalized Cyclopentanones

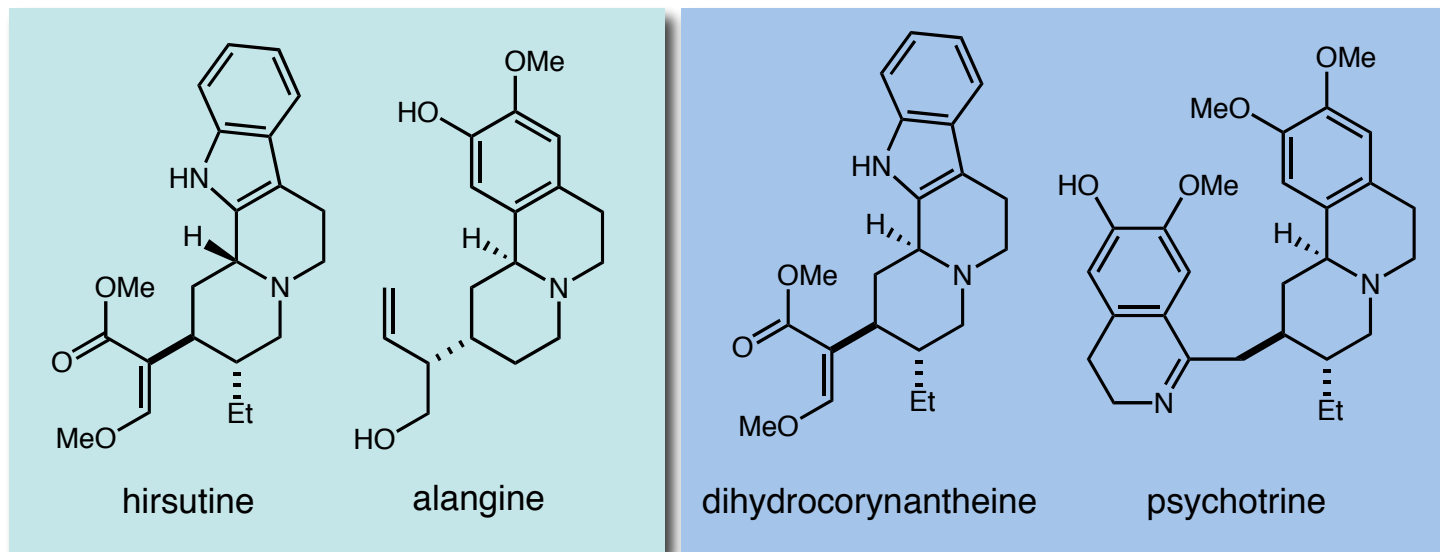


- Reaction of 2,4-pentanedione with crotonaldehyde is reversible
- Optimal yields and selectivities are obtained only when triazolium salt is present to funnel off the conjugate addition adduct to product



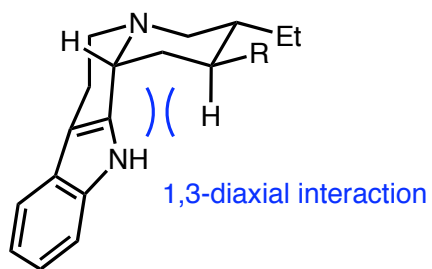
- Carrying out the cascade as separate reactions gives the product with lower yield and selectivity

# Organocascade Catalysis Synthesis of Quinolizidine Derivatives

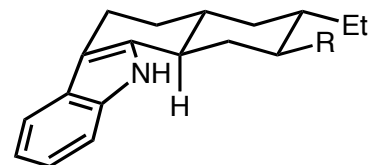


*cis* quinolizidines

*trans* quinolizidines



"kinetic" product

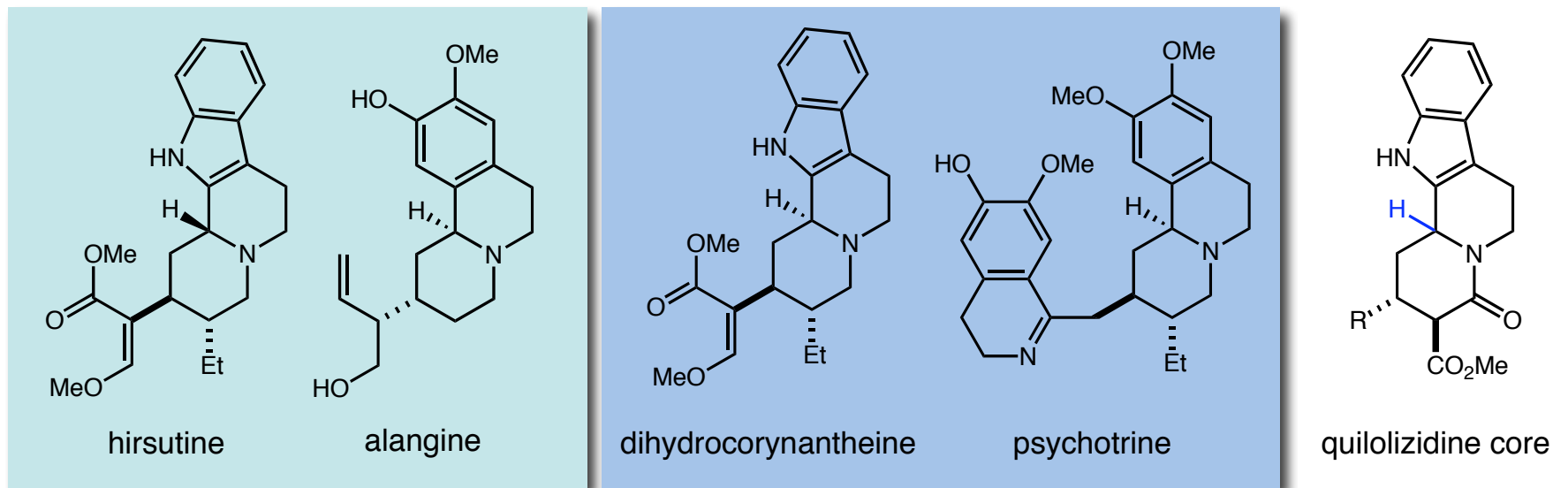


"thermodynamic" product

Zhang, W.; Franzen, J. *Adv. Synth. Catal.* **2010**, 352 (2-3), 499.

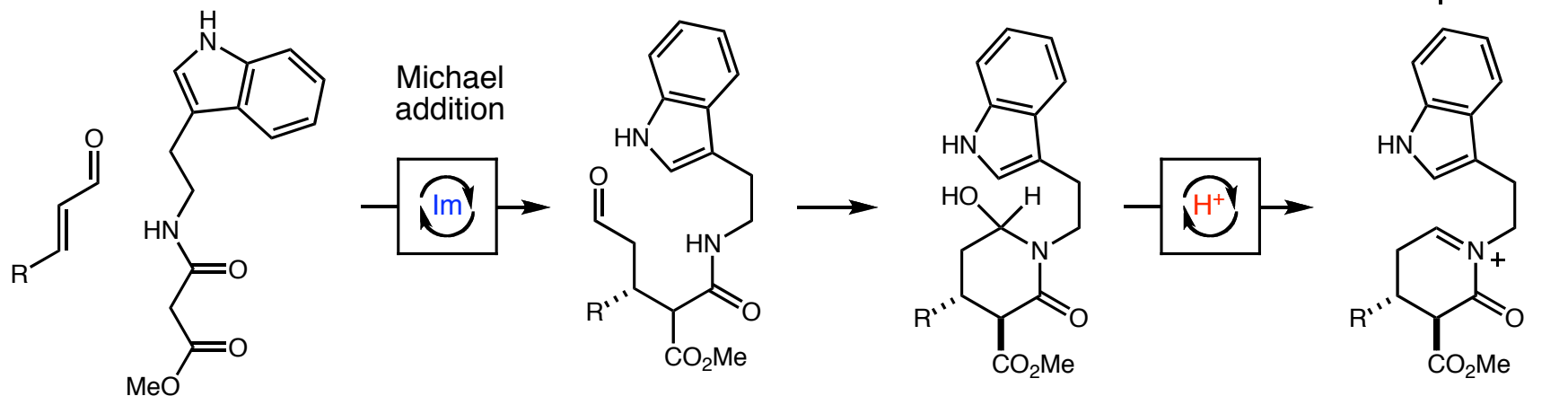
Franzen, J.; Fisher, A. *Angew. Chem.-Int. Ed.* **2009**, 48 (4), 787.

# Organocascade Catalysis Synthesis of Quinolizidine Derivatives



*cis* quinolizidines

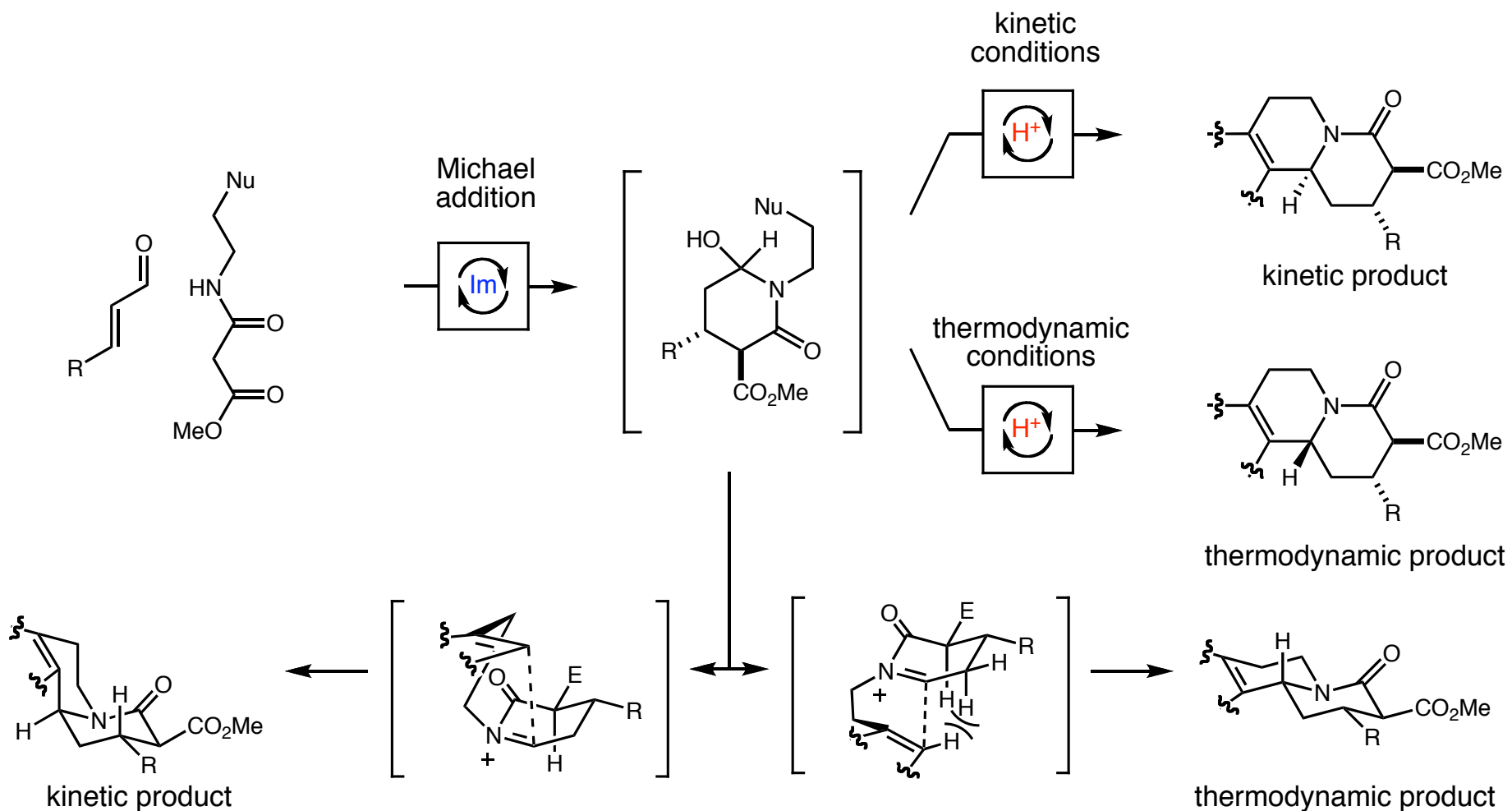
*trans* quinolizidines



Zhang, W.; Franzen, J. *Adv. Synth. Catal.* **2010**, 352 (2-3), 499.

Franzen, J.; Fisher, A. *Angew. Chem.-Int. Ed.* **2009**, 48 (4), 787.

## Organocascade Catalysis Synthesis of Quinolizidine Derivatives



■ Kinetic product favored due to free approach of aryl group onto iminium ion

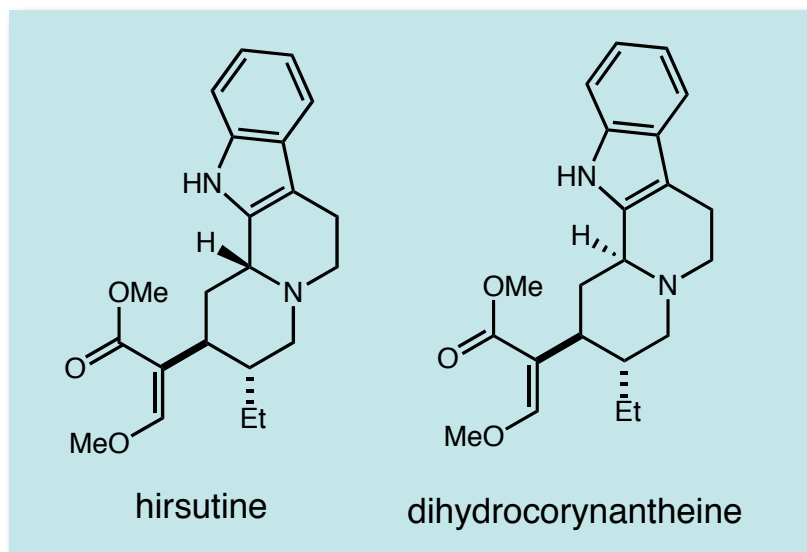
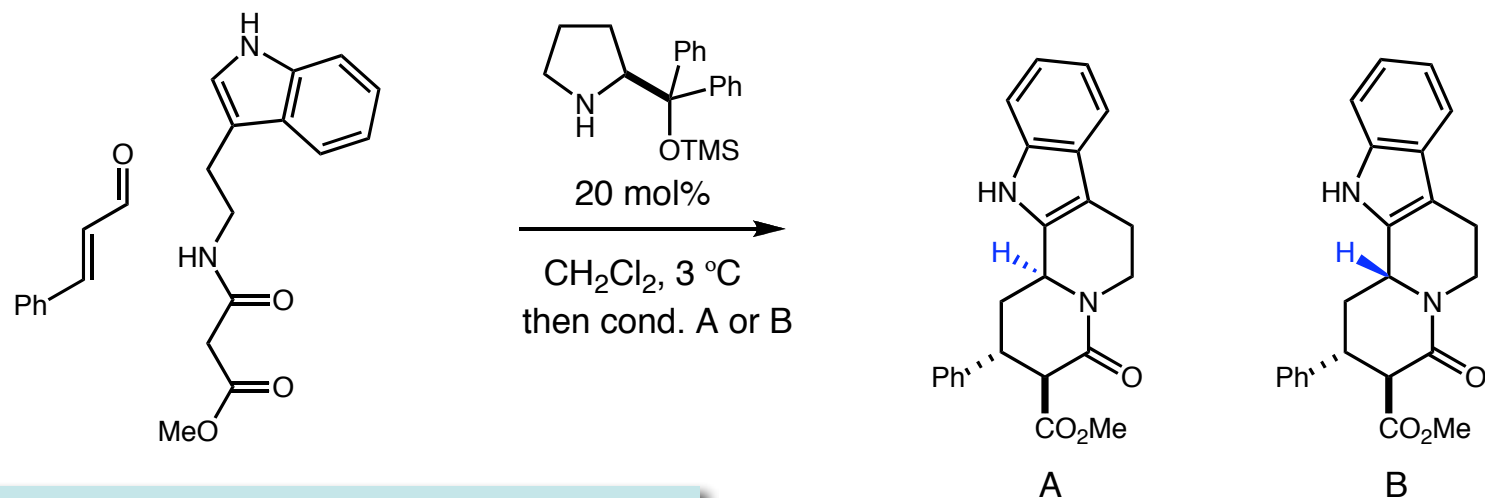
■ Thermodynamic product favored due to all equatorial arrangement of substituents

Zhang, W.; Franzen, J. *Adv. Synth. Catal.* **2010**, 352 (2-3), 499.

Franzen, J.; Fisher, A. *Angew. Chem.-Int. Ed.* **2009**, 48 (4), 787.



## Organocascade Catalysis Synthesis of Quinolizidine Derivatives



condition	yield	ee	dr A:B
A	69%	94%	85:15
B	64%	94%	18:82

Kinetic method A: 20 mol% HCl, rt.

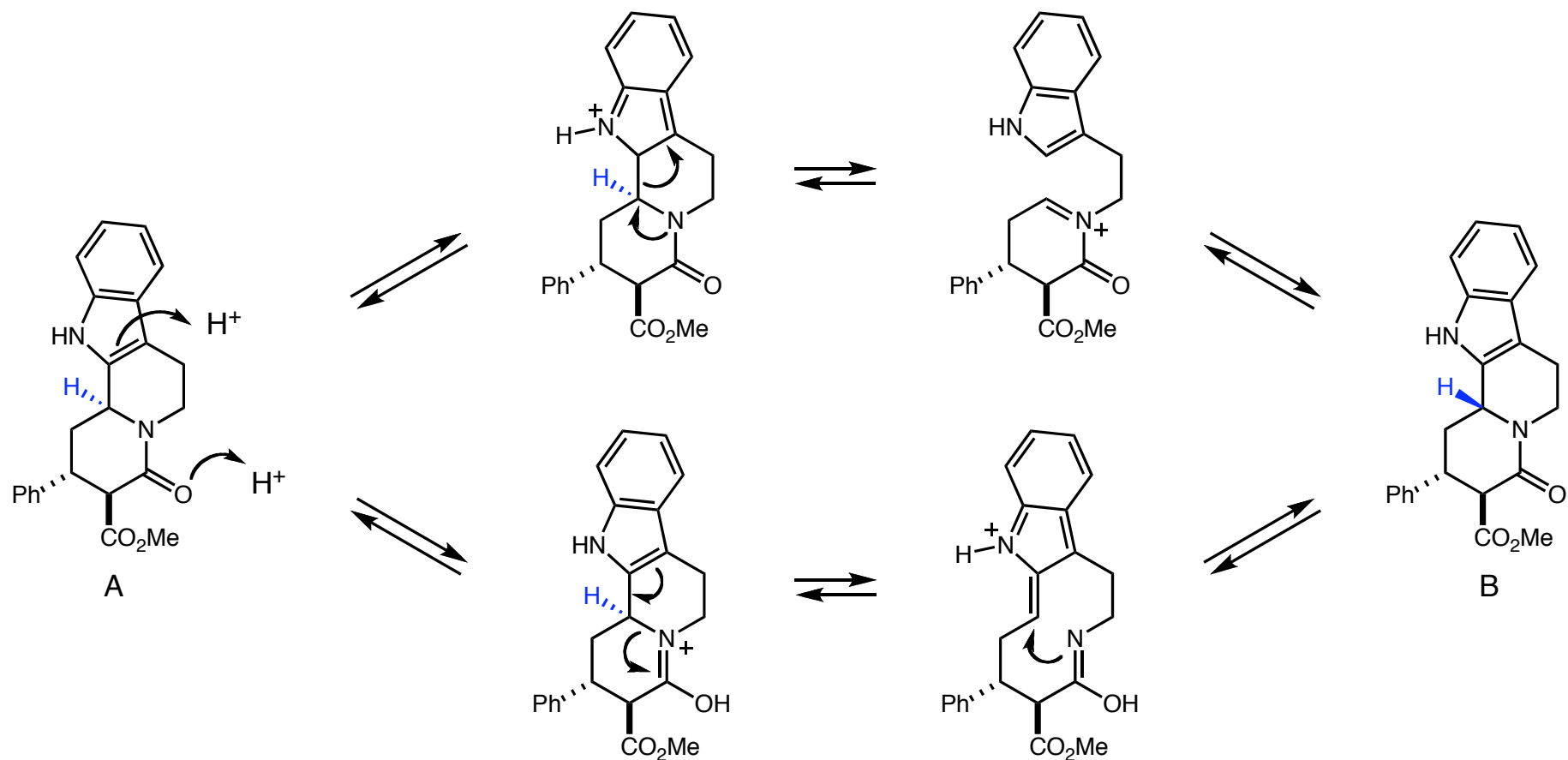
Thermodynamic method B: conc. TFA, 70 °C

- Kinetic cyclization induced by catalytic HCl gives rise to predominantly the *cis* isomer A
- Thermodynamic cyclization induced by excess TFA gives predominantly the *trans* isomer A

Zhang, W.; Franzen, J. *Adv. Synth. Catal.* **2010**, 352 (2-3), 499.

Franzen, J.; Fisher, A. *Angew. Chem.-Int. Ed.* **2009**, 48 (4), 787.

## Organocascade Catalysis Synthesis of Quinolizidine Derivatives

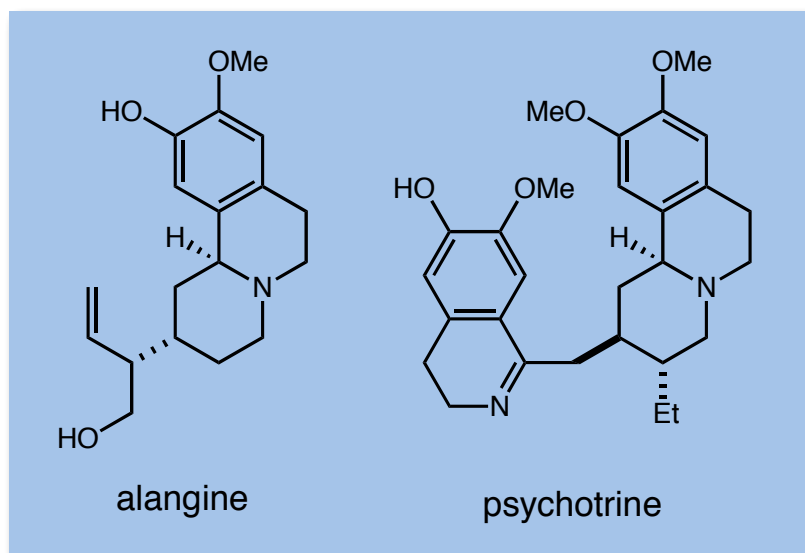
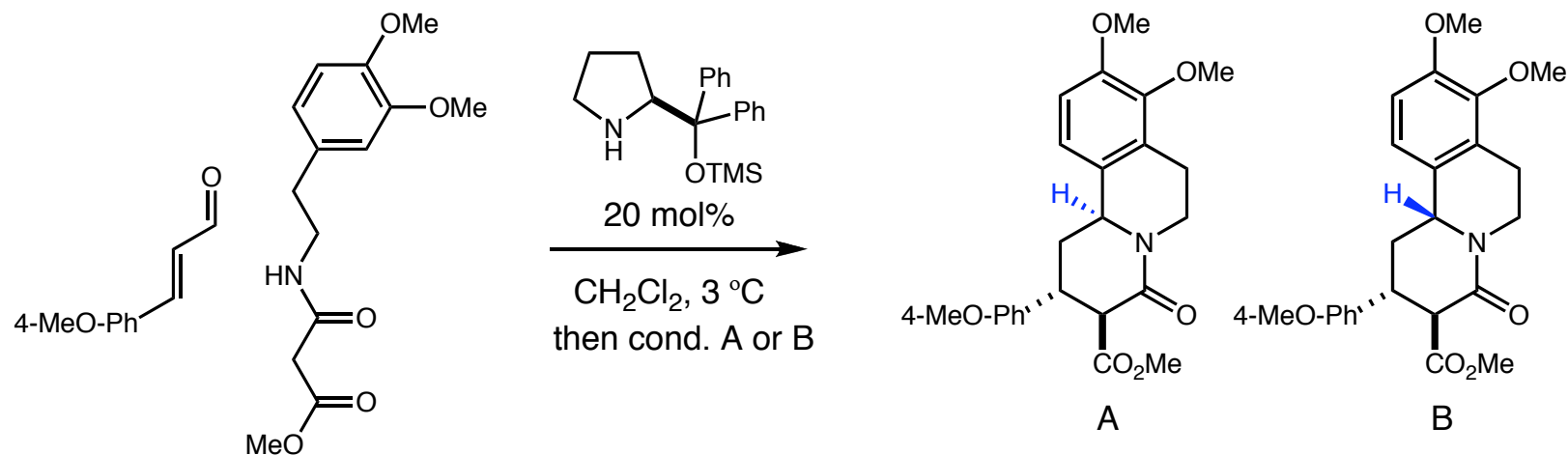


- Thermodynamic equilibration of the *cis* product to the *trans* product might go via regeneration of the acyl iminium ion or via an intermediate 10-membered ring.

Zhang, W.; Franzen, J. *Adv. Synth. Catal.* **2010**, 352 (2-3), 499.

Franzen, J.; Fisher, A. *Angew. Chem.-Int. Ed.* **2009**, 48 (4), 787.

## Organocascade Catalysis Synthesis of Quinolizidine Derivatives



condition	yield	ee	dr A:B
A	71%	89%	76:24
B	75%	89%	24:76

Method A: 20 mol% HCl, rt.

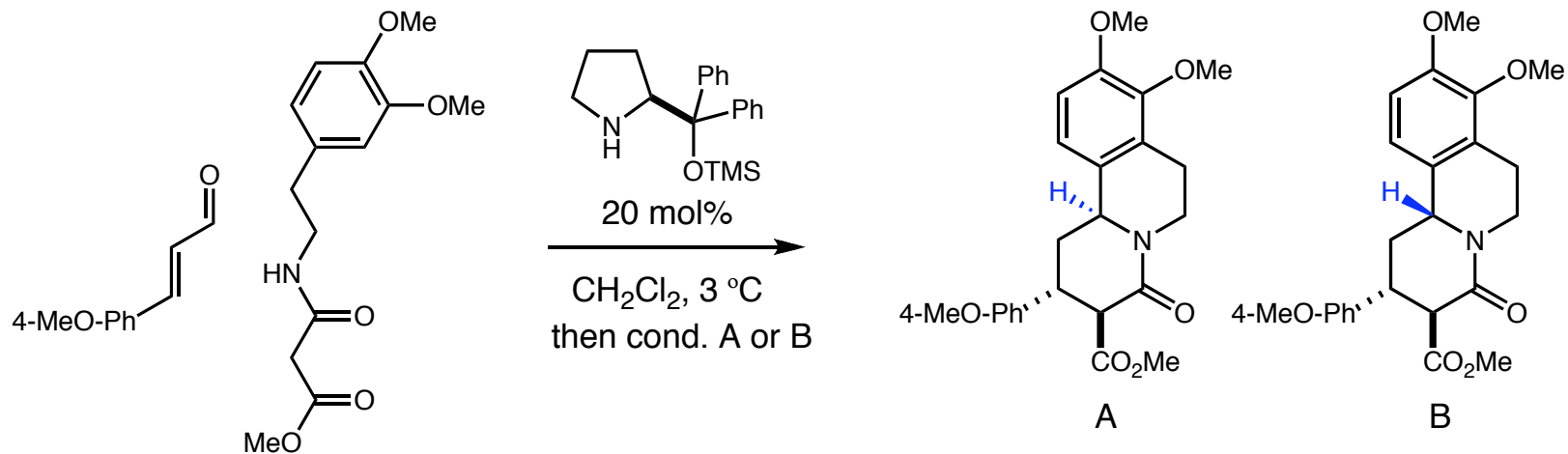
Method B: 40 mol% SnCl<sub>4</sub>, rt

- SnCl<sub>4</sub> reaction does not achieve *trans* selection by equilibration: aliquots at low conversion still have 1:3 ratio

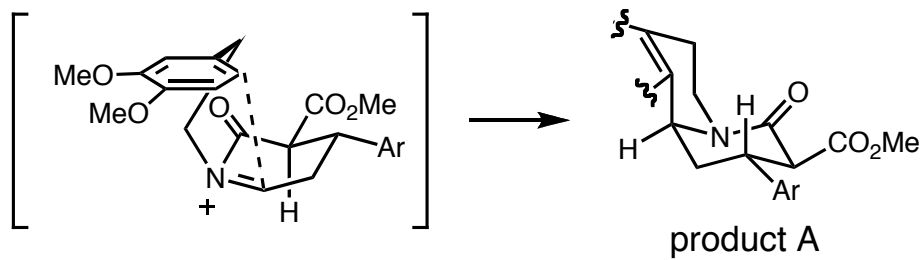
Zhang, W.; Franzen, J. *Adv. Synth. Catal.* **2010**, 352 (2-3), 499.

Franzen, J.; Fisher, A. *Angew. Chem.-Int. Ed.* **2009**, 48 (4), 787.

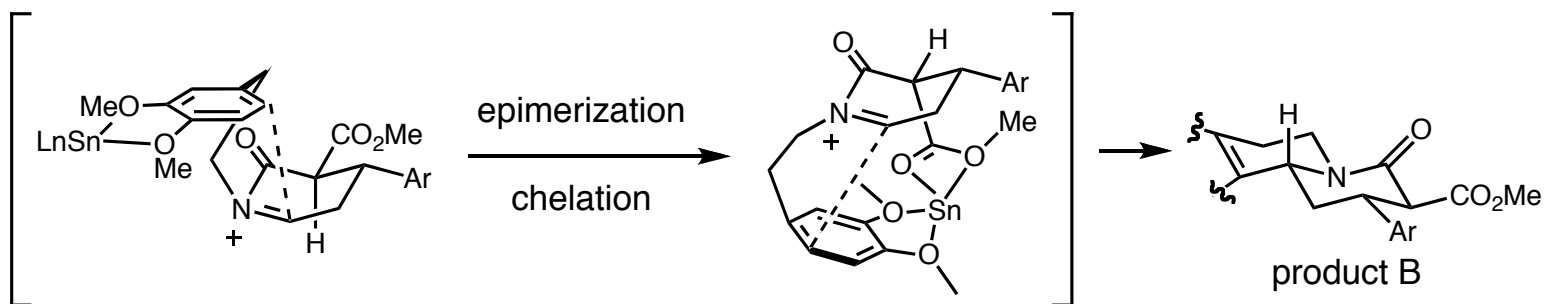
# Organocascade Catalysis Synthesis of Quinolizidine Derivatives



Method A  
Kinetic control



Method B  
Chelation control



Zhang, W.; Franzen, J. *Adv. Synth. Catal.* **2010**, 352 (2-3), 499.

Franzen, J.; Fisher, A. *Angew. Chem.-Int. Ed.* **2009**, 48 (4), 787.

## *Selected Examples of Enantioselective Cascade Catalysis*

Organocascade



Organometallo Cascade



Metallo Cascade



OrganoBio Cascade



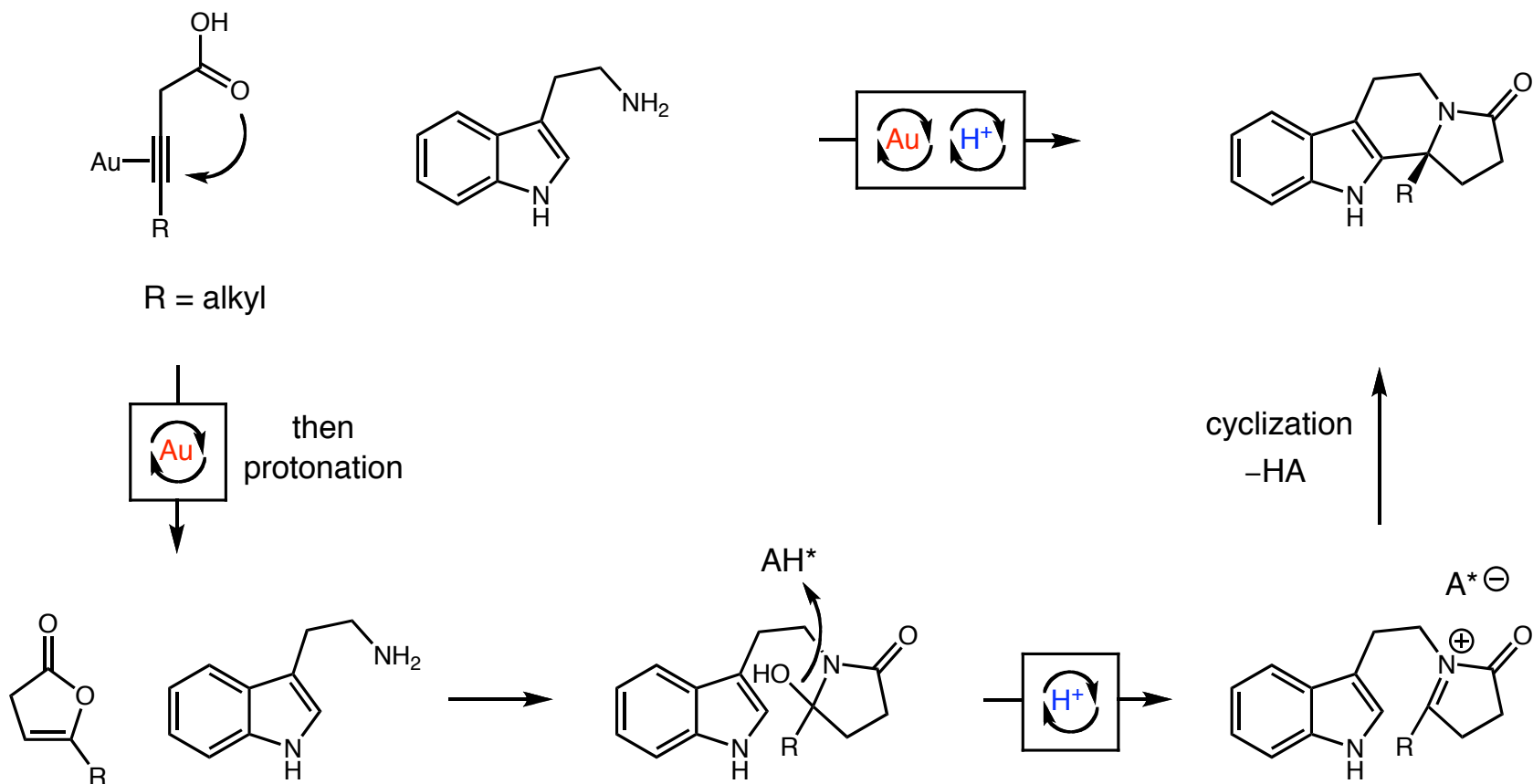
MetalloBio Cascade



Biocascade

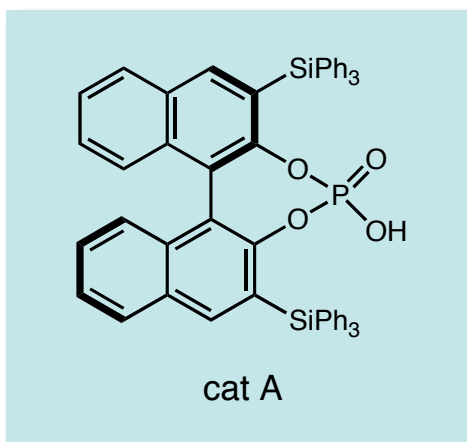
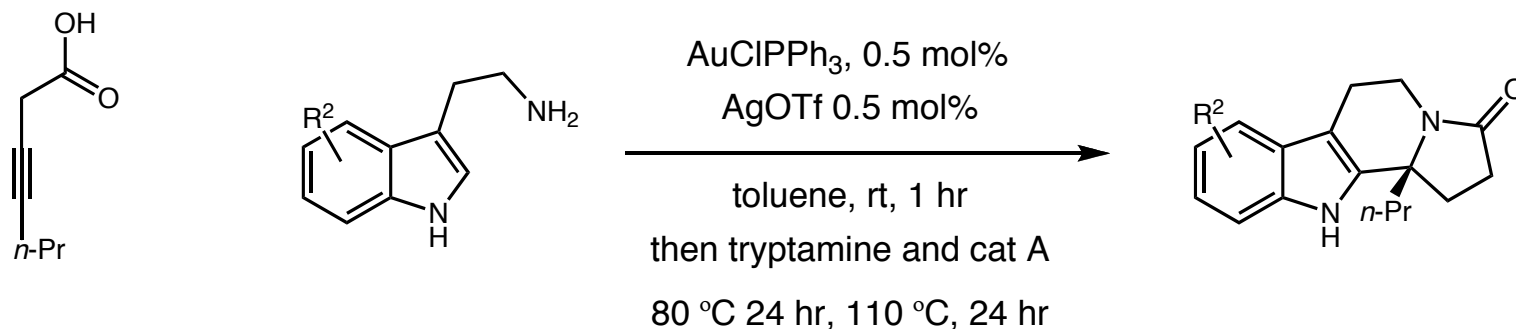


## Brønsted Acid/Gold (I) Multicatalyst Cascade: Dixon Group



- Gold catalysis facilitates  $\beta,\gamma$  unsaturated lactone via activation of the alkyne toward 5-endo-*dig* cyclization
- Brønsted acid catalyzed N-acyl iminium cyclization generates enantioenriched heterocycles

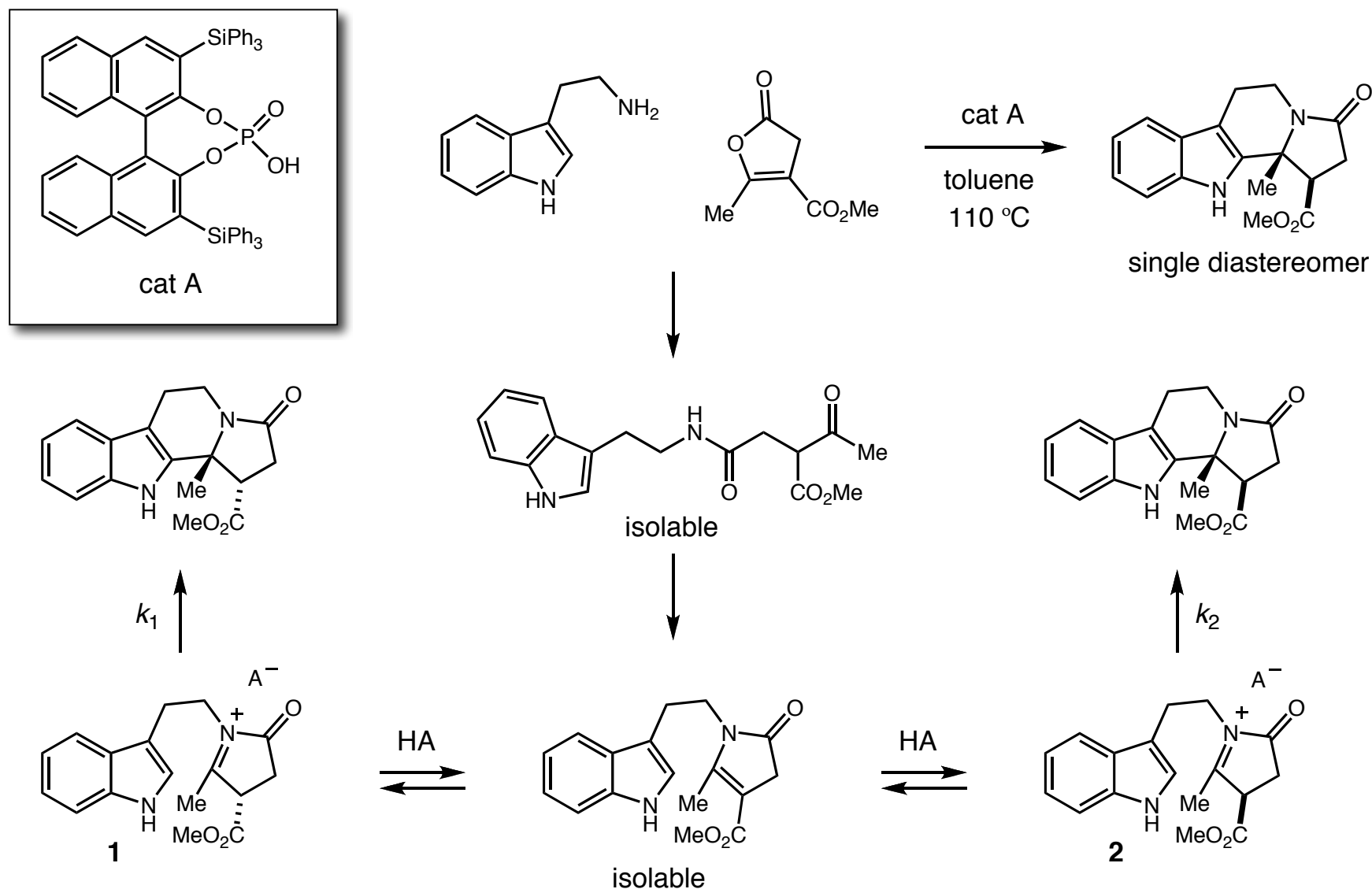
## Brønsted Acid/Gold (I) Multicatalyst Cascade: Dixon Group



R <sup>2</sup>	yield (%)	ee (%)
H	79	84
5-Br	77	89
7-Me	96	95

- Organometallo cascade proceeds in good selectivity only at high temperatures. Lower temperatures (i.e., rt to 50 °C gave around 30 to 50% ee.
- Bulky phosphoric acid catalyst required for good selectivity. Aryl substituted Binol phosphoric acid catalysts gave < 55% ee.

## Brønsted Acid/Gold (I) Multicatalyst Cascade: Dixon Group

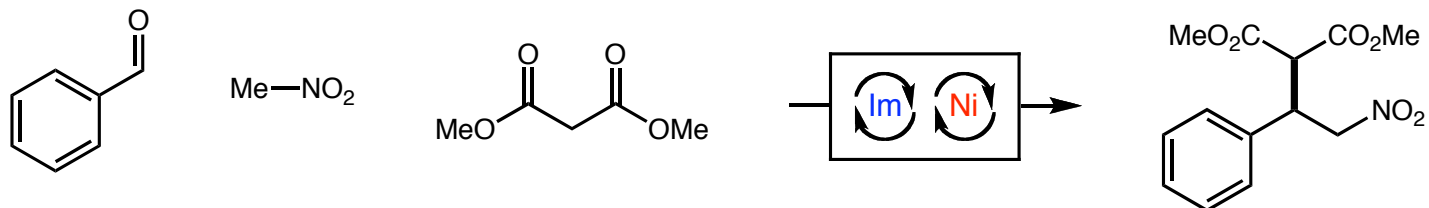


■ Because only a single diastereomer is formed, equilibration of **1**, **2** must be fast relative to cyclization and  $k_2 \gg k_1$ .

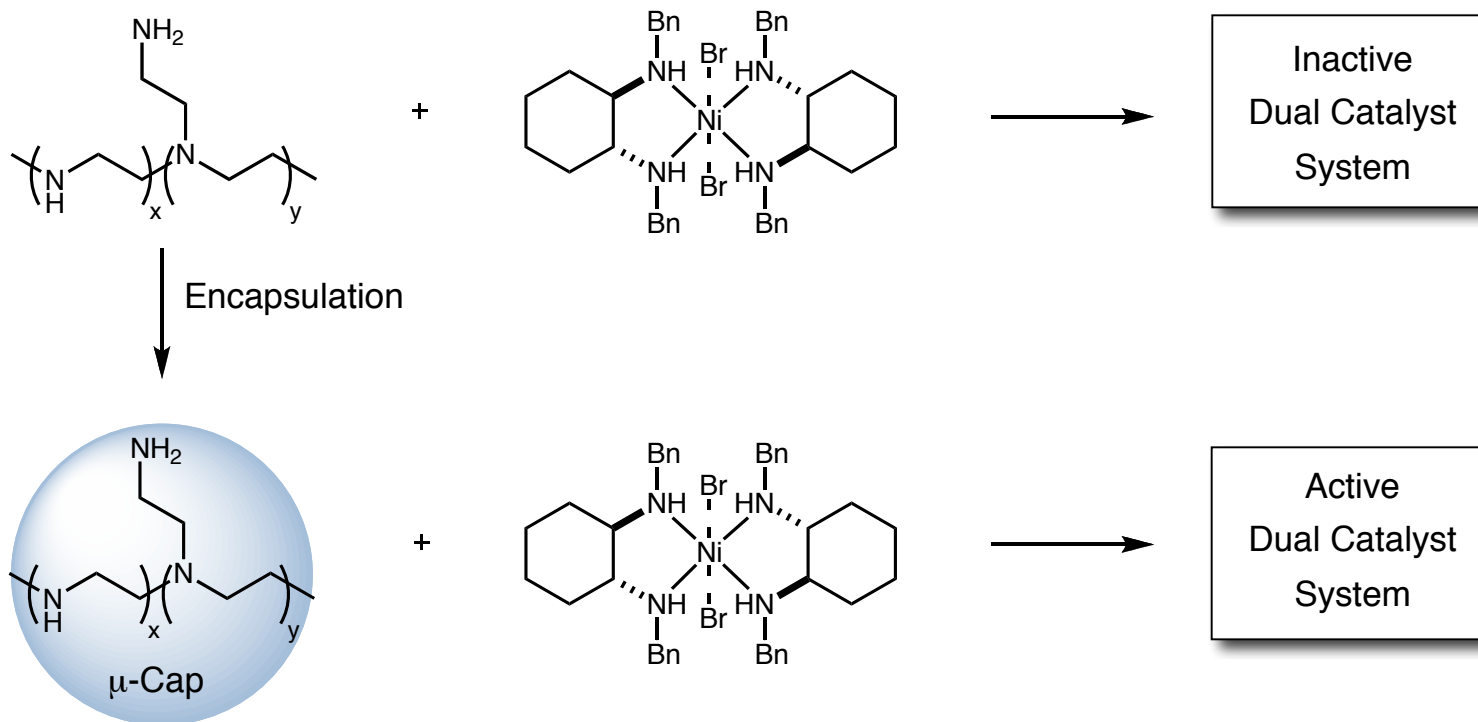
Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J., *J. Am. Chem. Soc.* **2009**, *131* (31), 10796.



## Microencapsule Enabled Multicatalyst System



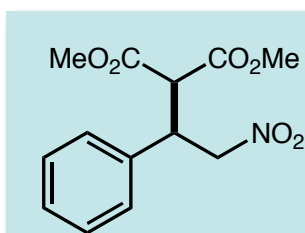
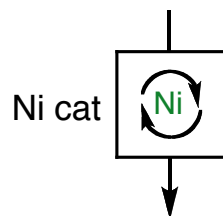
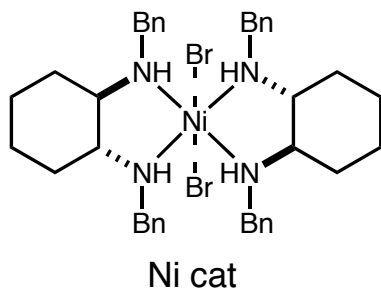
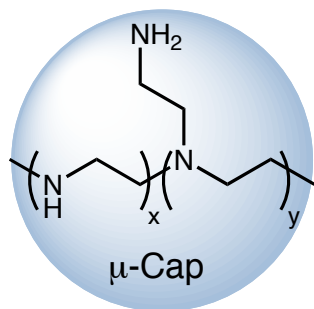
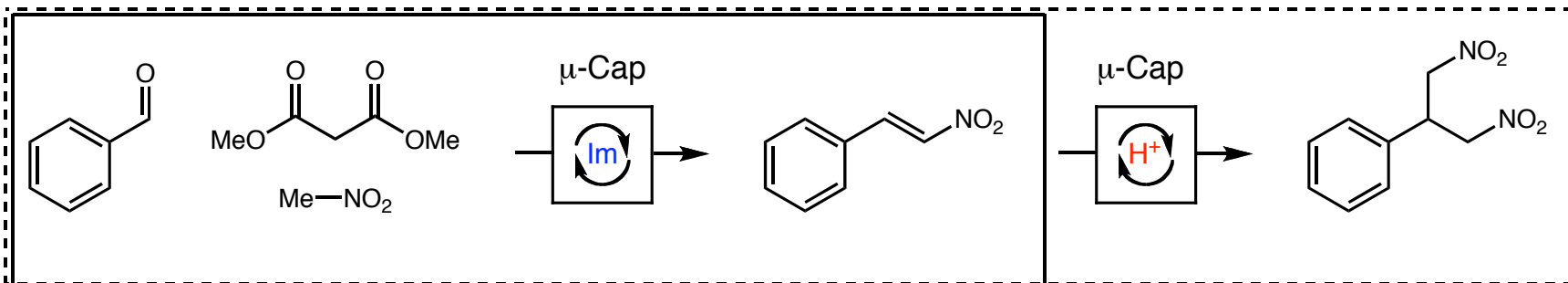
Is it possible to use two incompatible catalysts for a tandem reaction?



Poe, S. L.; Kobaslija, M.; McQuade, D. T. *J. Am. Chem. Soc.* **2006**, *128* (49), 15586.

Poe, S. L.; Kobaslija, M.; McQuade, D. T. *J. Am. Chem. Soc.* **2007**, *129* (29), 9216.

## Microencapsule Enabled Multicatalyst System



■ Dinitro compound predominates when no Ni cat is present

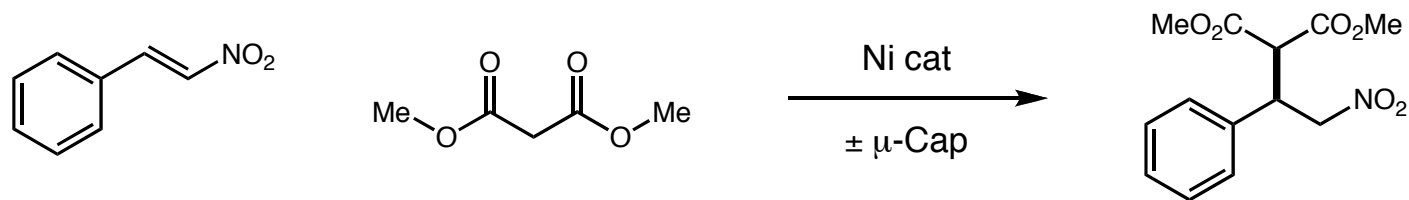
Catalyst system	Yield of malonate
$\mu$ -Cap alone	2%
$\mu$ -Cap and Ni cat	80%
Ni cat alone	8%
amine cat and Ni cat	5%

■ In the absence of either one of the catalysts, virtually no malonate addition product is formed

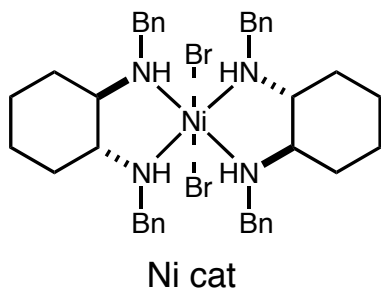
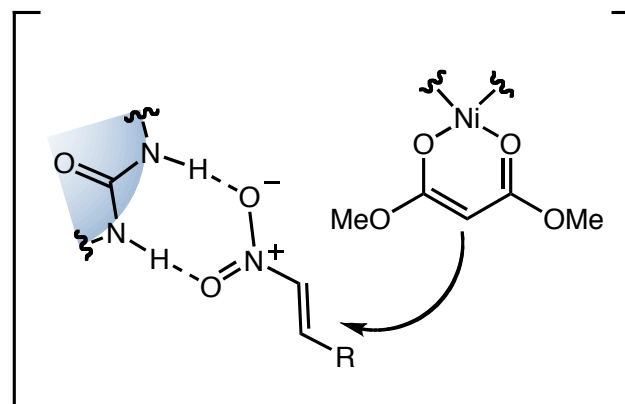
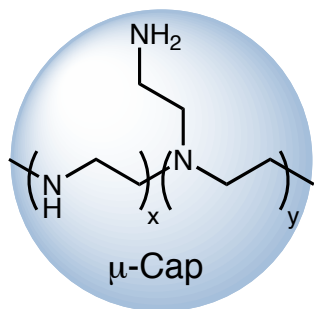
Poe, S. L.; Kobaslija, M.; McQuade, D. T. *J. Am. Chem. Soc.* **2006**, *128* (49), 15586.

Poe, S. L.; Kobaslija, M.; McQuade, D. T. *J. Am. Chem. Soc.* **2007**, *129* (29), 9216.

## Microencapsule Enabled Multicatalyst System



significant rate enhancement  
when  $\mu\text{-Cap}$  present

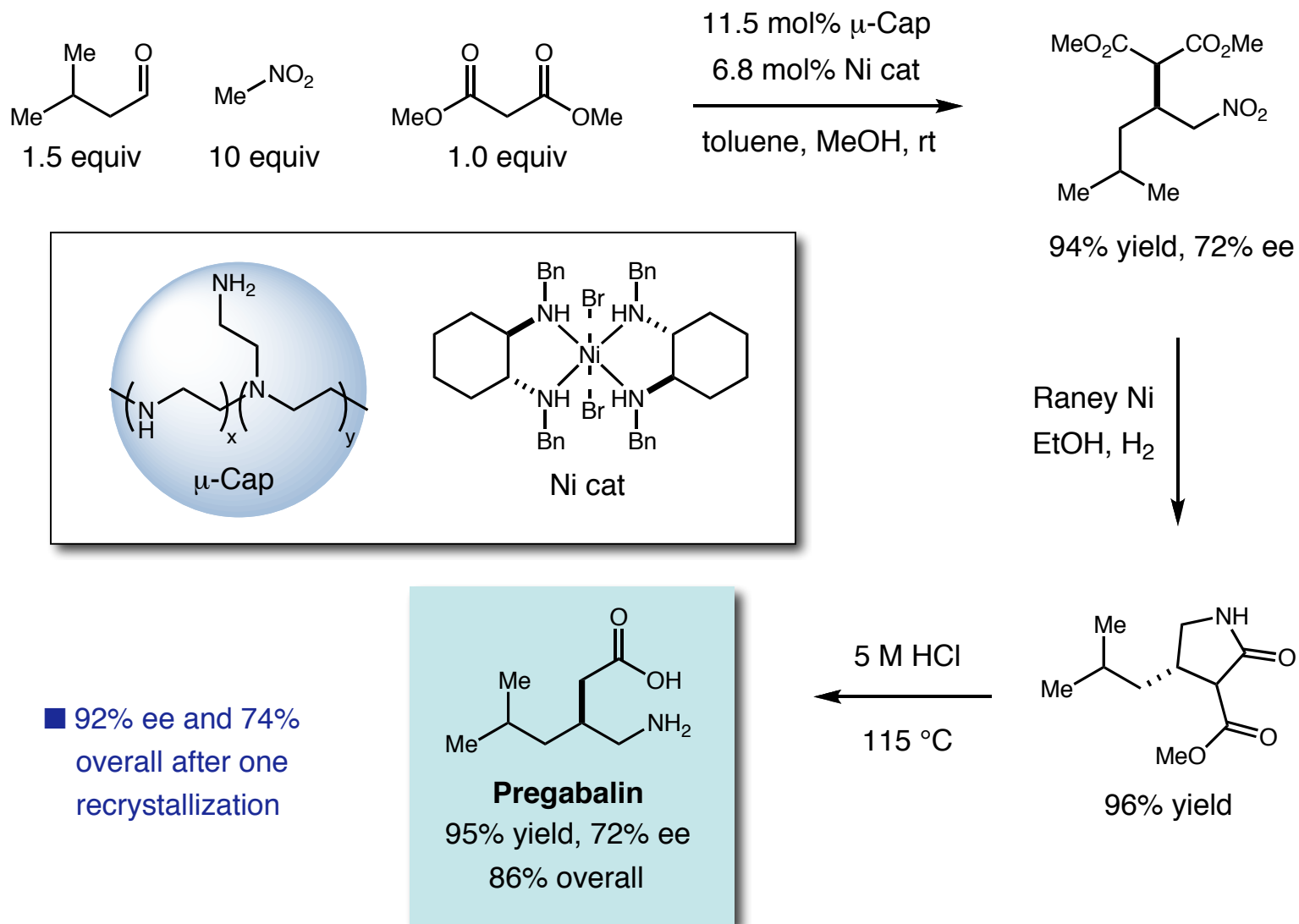


- Encapsulating material is a polyurea made from a diisocyanate.
- H-bonding activation of the nitroolefin is responsible for rate acceleration
- The urea and not the NH groups of the catalyst were shown to be active by exhaustive acetylation. The acetylated  $\mu\text{-Cap}$  showed similar rates

Poe, S. L.; Kobaslija, M.; McQuade, D. T. *J. Am. Chem. Soc.* **2006**, *128* (49), 15586.

Poe, S. L.; Kobaslija, M.; McQuade, D. T. *J. Am. Chem. Soc.* **2007**, *129* (29), 9216.

## Microencapsule Enabled Multicatalyst System



Poe, S. L.; Kobaslija, M.; McQuade, D. T. *J. Am. Chem. Soc.* **2006**, *128* (49), 15586.

Poe, S. L.; Kobaslija, M.; McQuade, D. T. *J. Am. Chem. Soc.* **2007**, *129* (29), 9216.

## *Selected Examples of Enantioselective Cascade Catalysis*

Organocascade



Organometallo Cascade



Metallo Cascade



OrganoBio Cascade



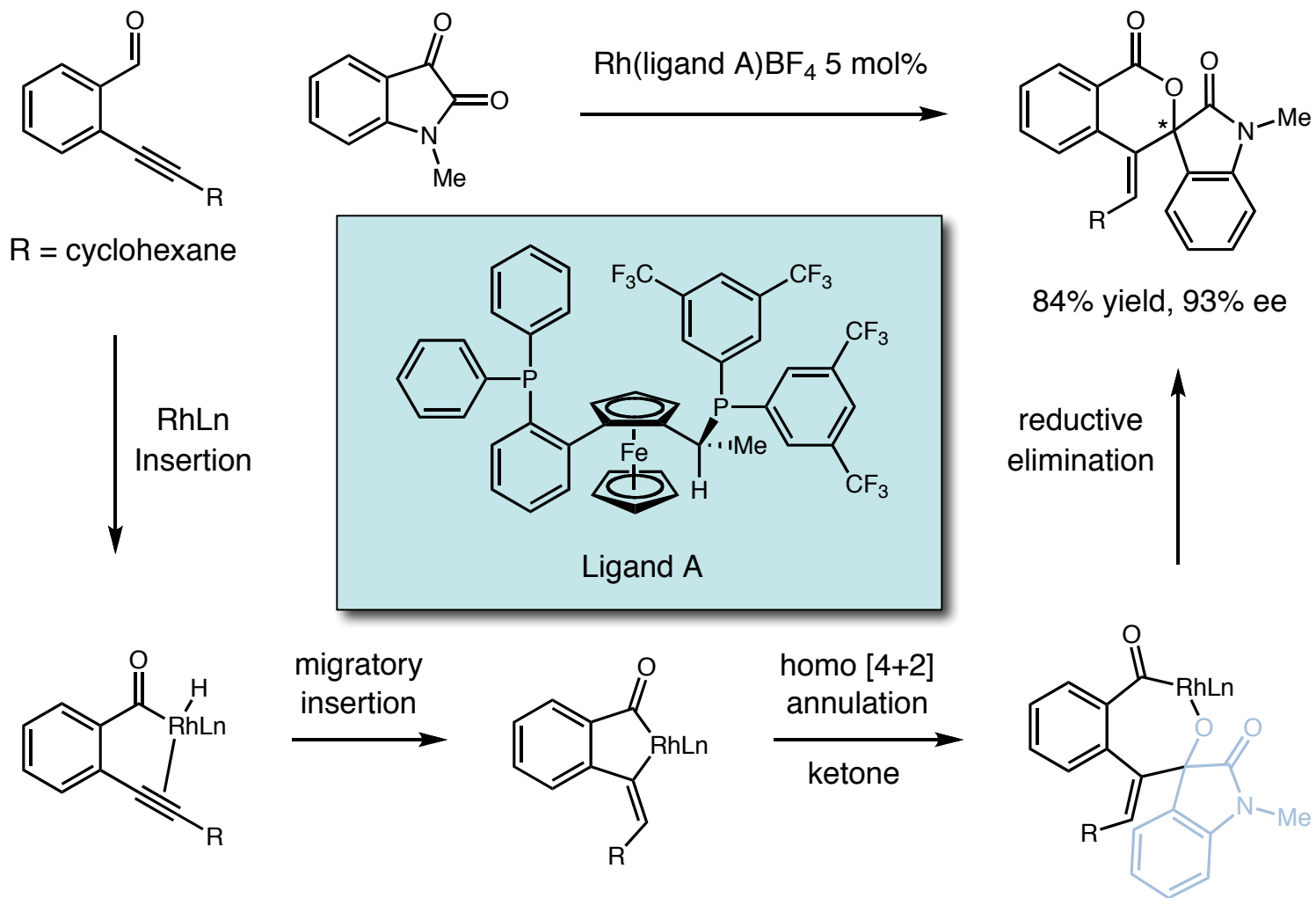
MetalloBio Cascade



Biocascade



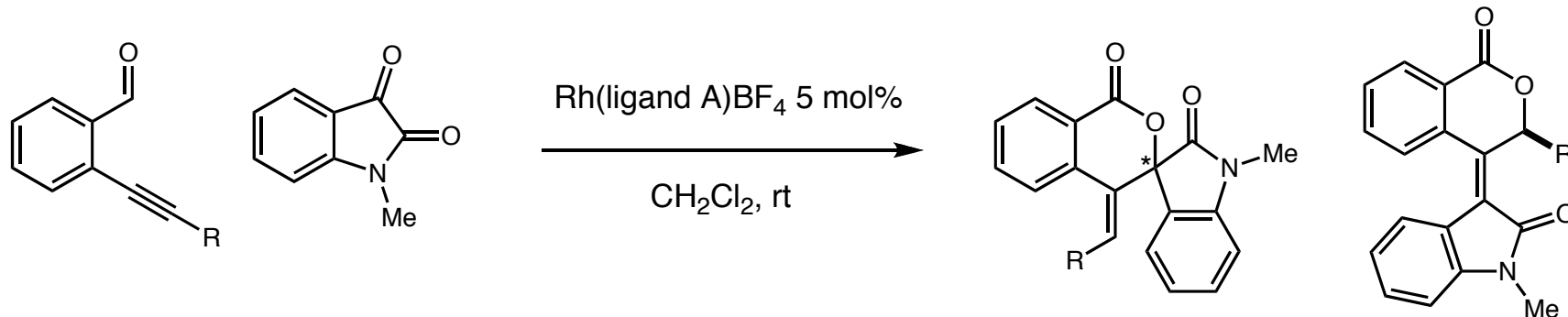
# Tetrasubstituted Alkenes via Cooperative Rhodium and Silver Catalysis



Hojo, D.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem. -Int. Ed.* **2008**, 47, 8129.

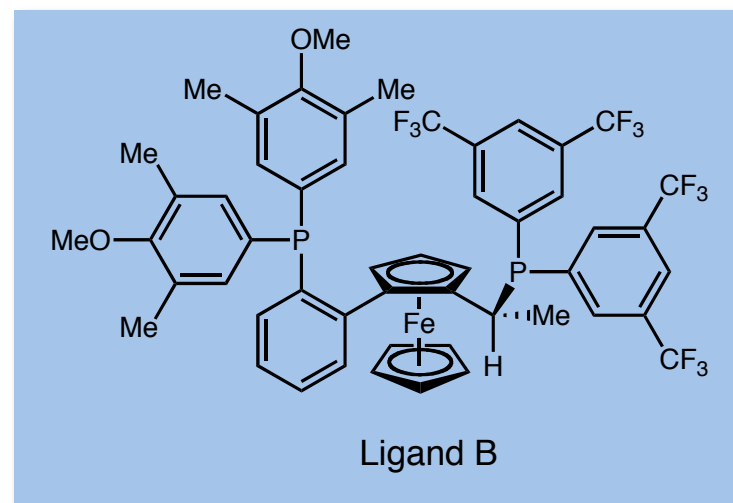
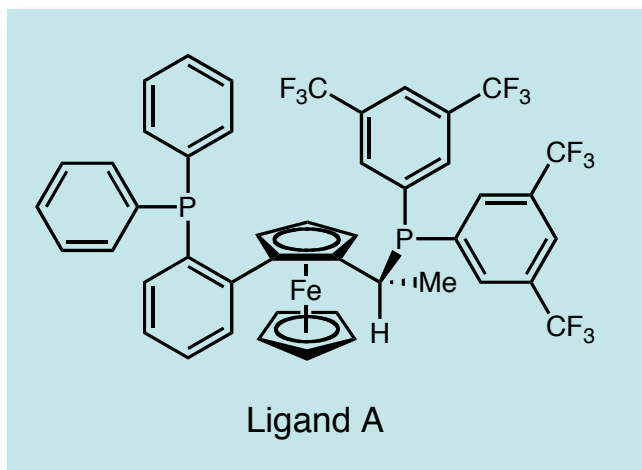
Hojo, D.; Noguchi, K.; Tanaka, K. *Angew. Chem. -Int. Ed.* **2009**, 48, 8129.

## Tetrasubstituted Alkenes via Cooperative Rhodium and Silver Catalysis



■ Only the cyclohexenyl system gave the tetrasubstituted olefin

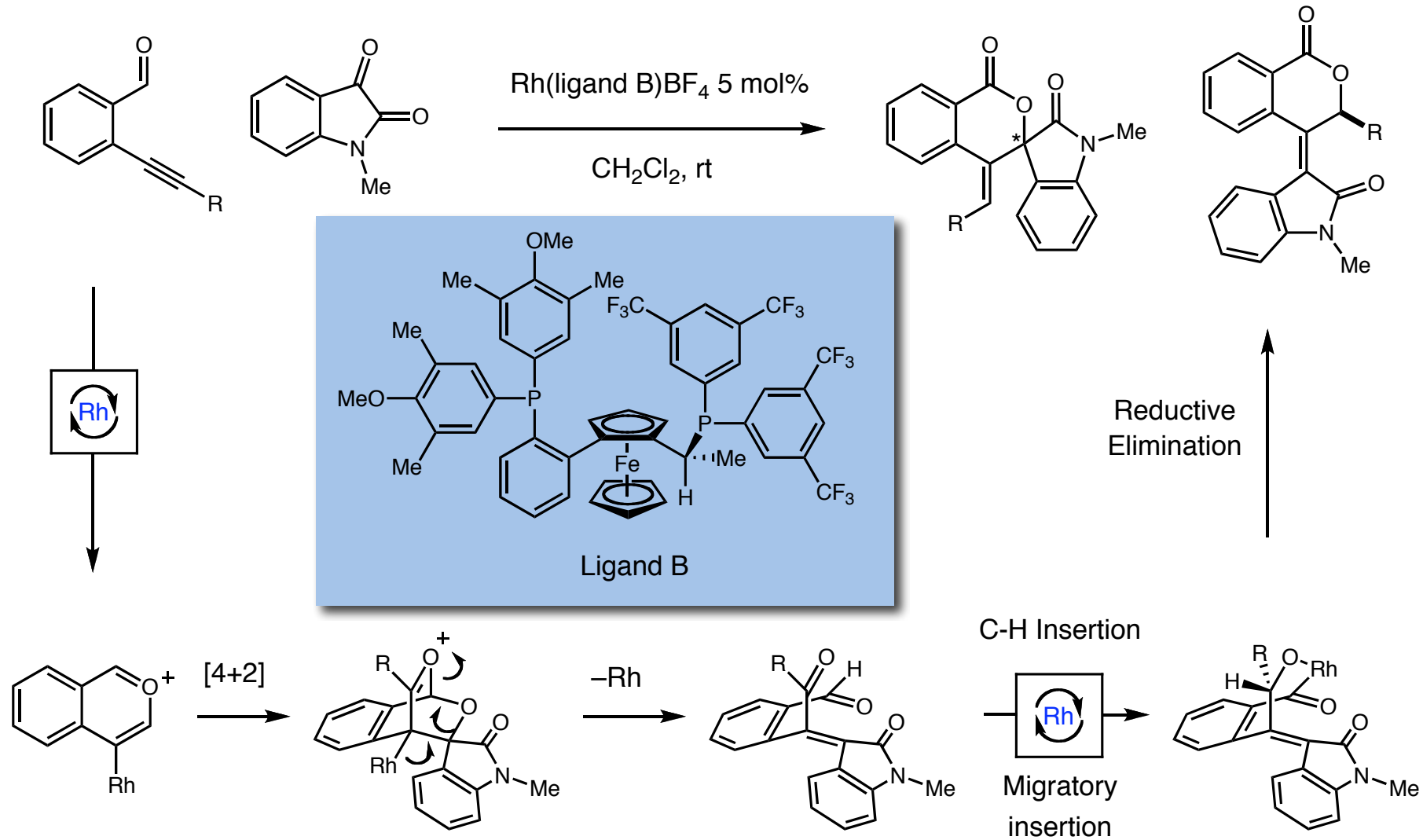
R = cyclohexane	84%, 93% ee	not detected
R = 1-cyclohexenyl	40%, 61% ee	60%, 85% ee
(Ligand B) R = 1-cyclohexenyl	<1%, --	99%, 95% ee
R = isopropenyl, alkyl, aryl	"High"	< 2%



Hojo, D.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem. -Int. Ed.* **2008**, *47*, 8129.

Hojo, D.; Noguchi, K.; Tanaka, K. *Angew. Chem. -Int. Ed.* **2009**, *48*, 8129.

## Tetrasubstituted Alkenes via Cooperative Rhodium and Silver Catalysis



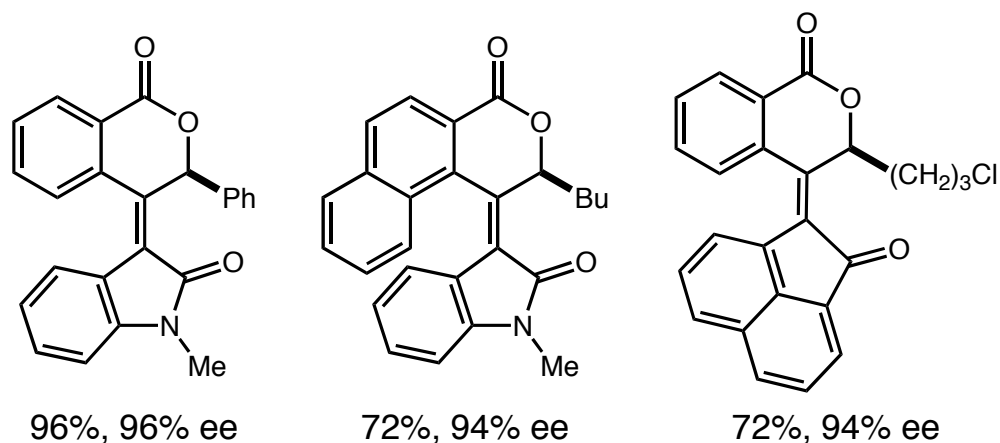
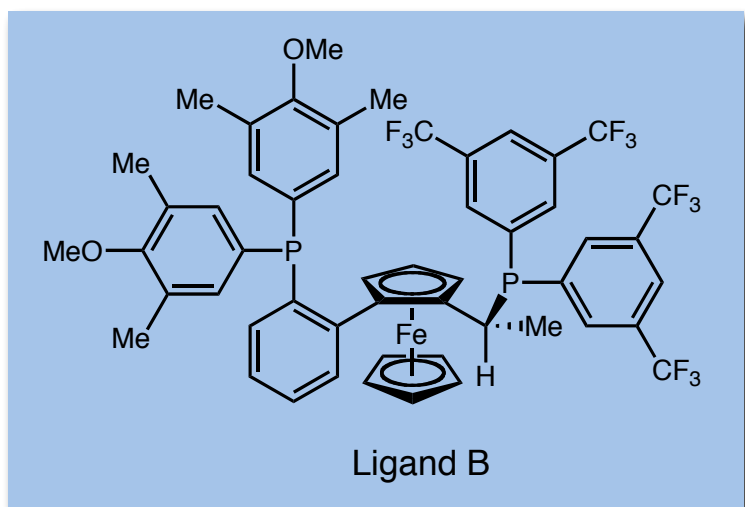
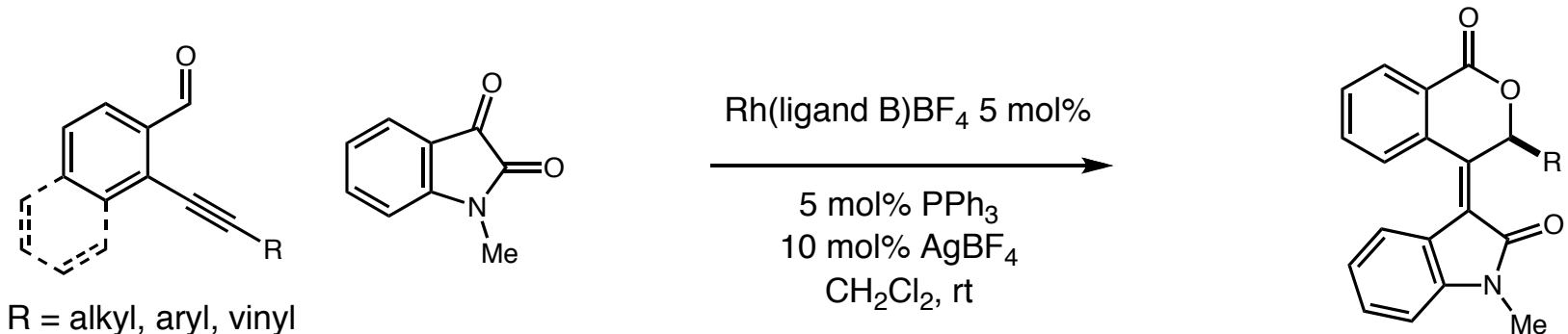
■ Reason for the mechanistic change is not known. ■ Model for the asymmetric induction has not been proposed.

Hojo, D.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem. -Int. Ed.* **2008**, 47, 8129.

Hojo, D.; Noguchi, K.; Tanaka, K. *Angew. Chem. -Int. Ed.* **2009**, 48, 8129.



## Tetrasubstituted Alkenes via Cooperative Rhodium and Silver Catalysis

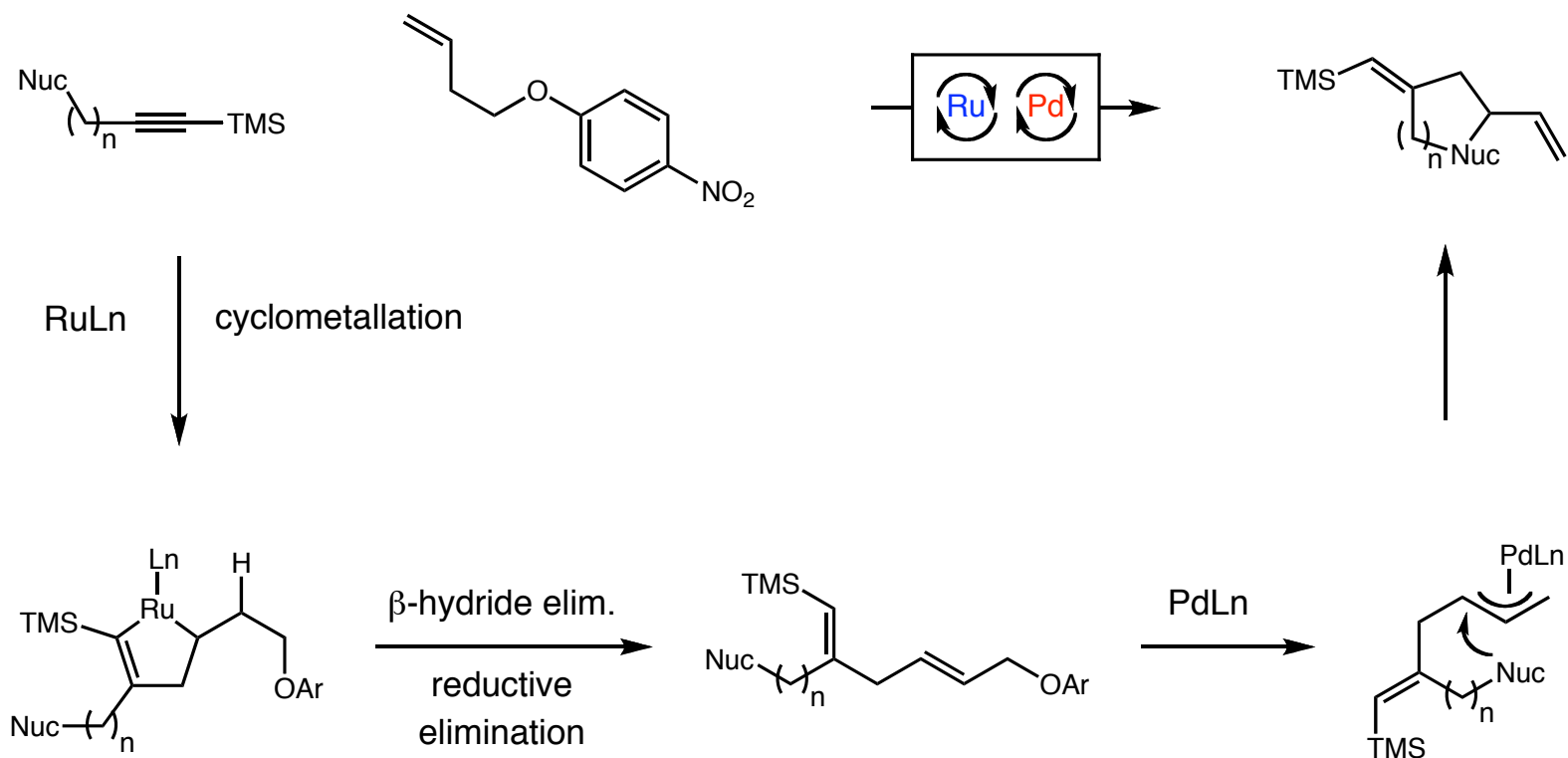


- Role of silver is unknown. Initially it was suspected that it might act as a Lewis acid to enable cyclization of the aldehyde onto the alkyne. However, subjecting the SM to silver did not produce any cyclization derived products

Hojo, D.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem. -Int. Ed.* **2008**, *47*, 8129.

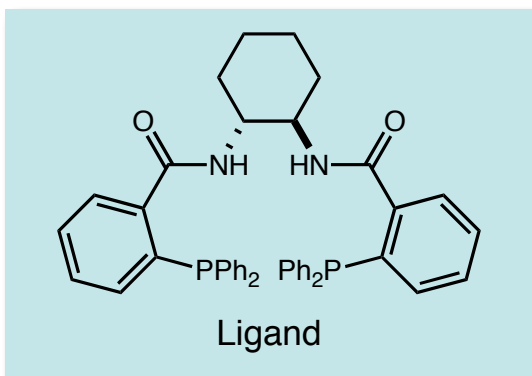
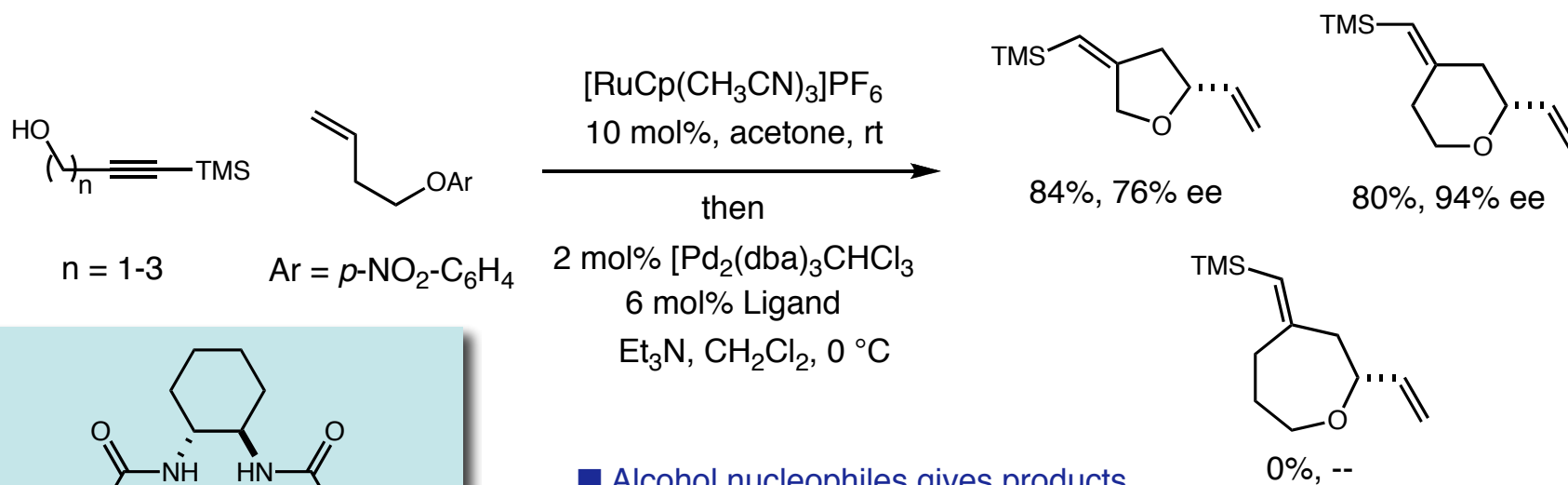
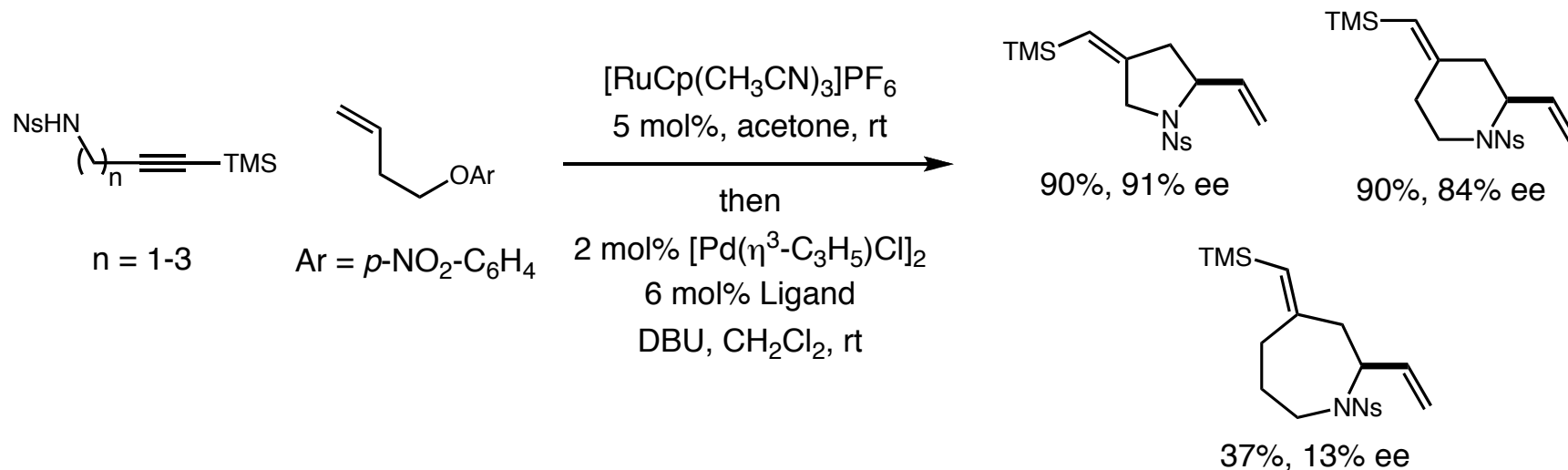
Hojo, D.; Noguchi, K.; Tanaka, K. *Angew. Chem. -Int. Ed.* **2009**, *48*, 8129.

## Heterocycle Synthesis via Ruthenium and Palladium Cascade Catalysis



- Alkyne regioselectivity is dictated by the TMS group
- Allylic leaving group not present until after ene-yne coupling reaction
- Key criterion: Ru catalyst must not be able to ionize allylic group (racemic pathway)

## Heterocycle Synthesis via Ruthenium and Palladium Cascade Catalysis

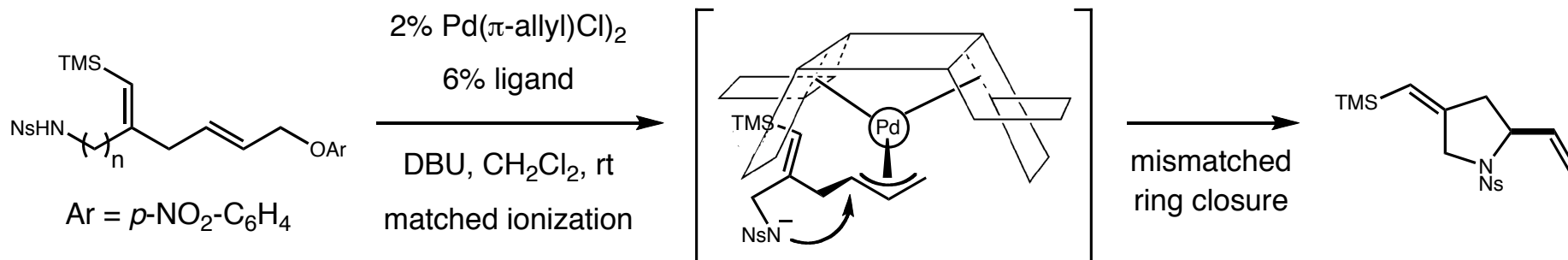


■ Alcohol nucleophiles gives products  
 with opposite sense of enantioinduction

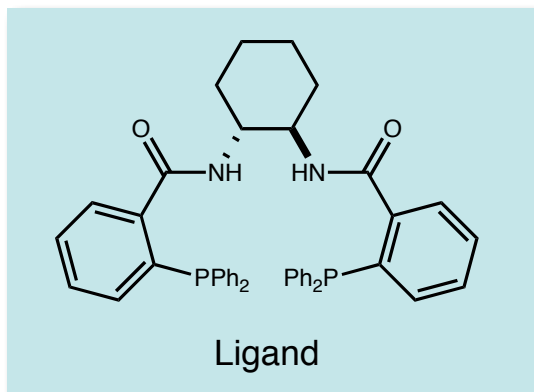
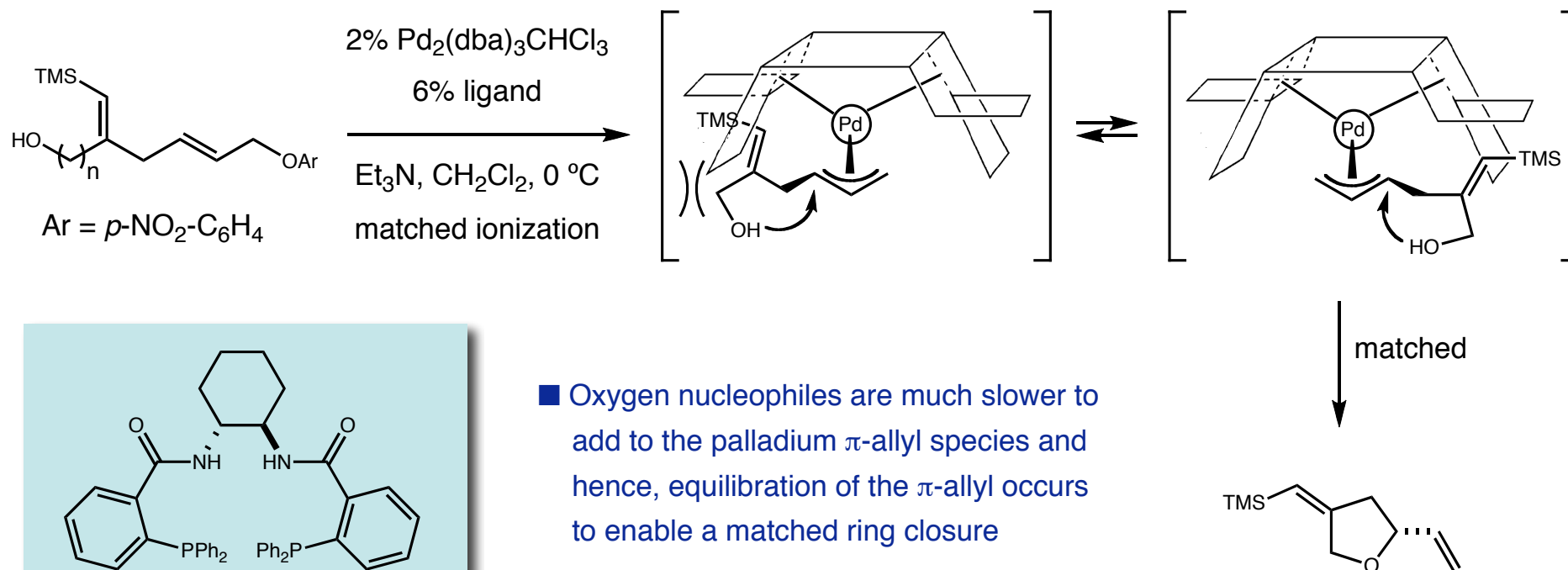
Trost, B. M.; Machacek, M. R.; Faulk, B. D. *J. Am. Chem. Soc.* **2006**, *128* (20), 6745.

# Heterocycle Synthesis via Ruthenium and Palladium Cascade Catalysis

- For nitrogen nucleophiles, ionization is the enantiodetermining step

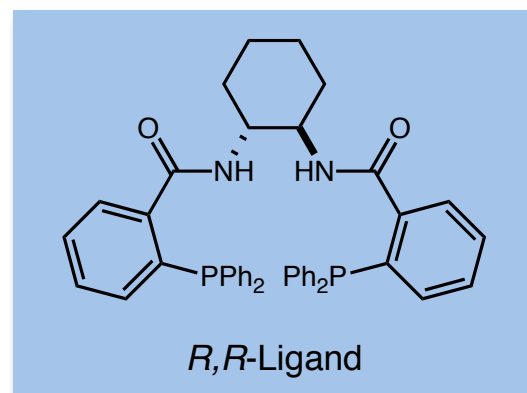
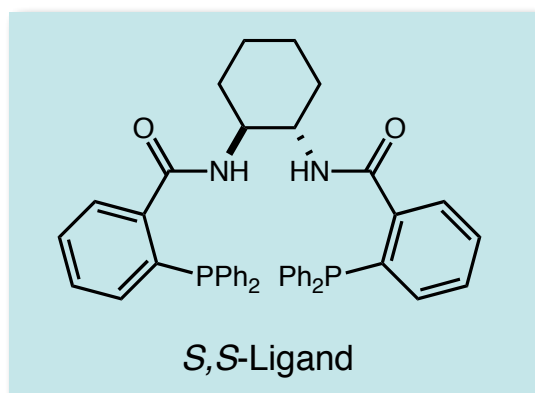
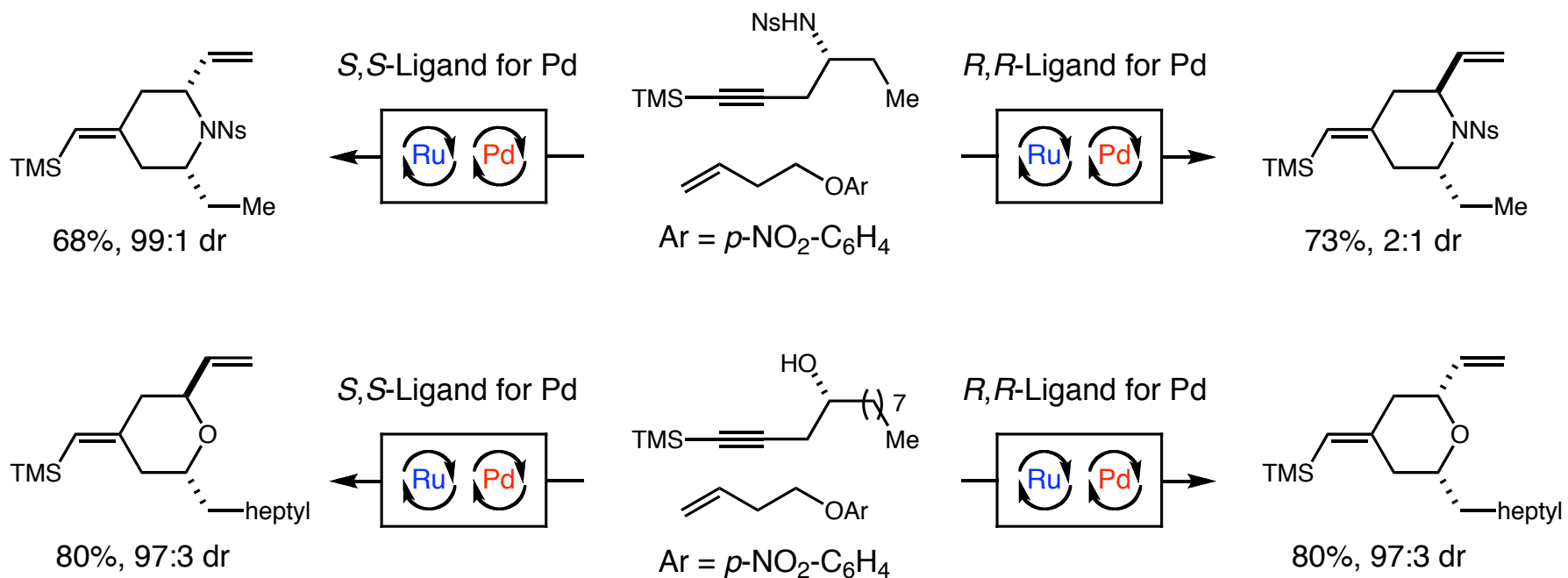


- For oxygen nucleophiles, ring closure is the enantiodetermining step

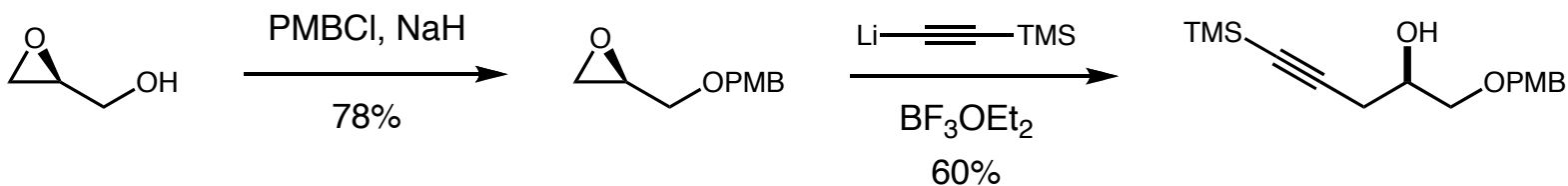


- Oxygen nucleophiles are much slower to add to the palladium  $\pi$ -allyl species and hence, equilibration of the  $\pi$ -allyl occurs to enable a matched ring closure

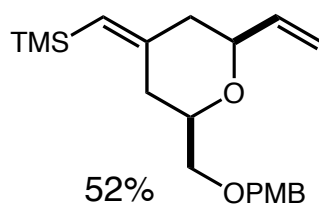
# Heterocycle Synthesis via Ruthenium and Palladium Cascade Catalysis



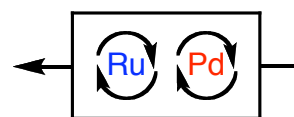
## Heterocycle Synthesis via Ruthenium and Palladium Cascade Catalysis



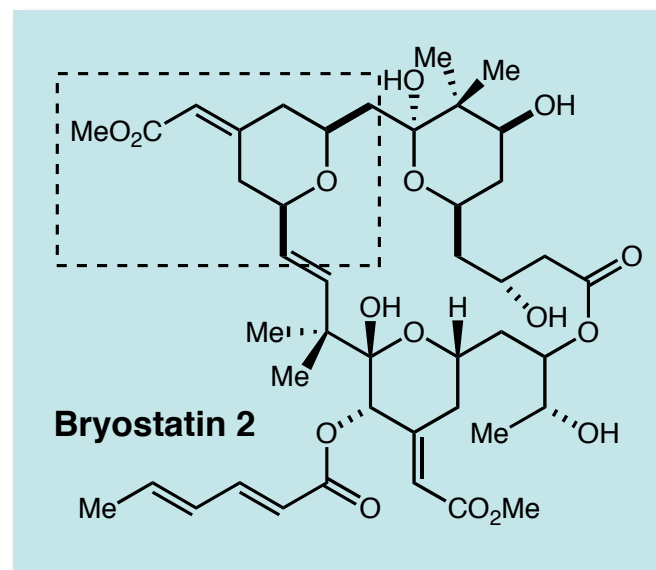
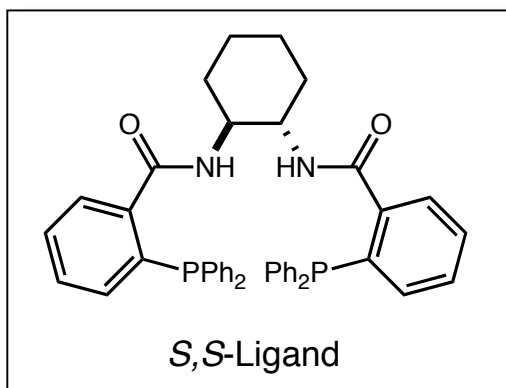
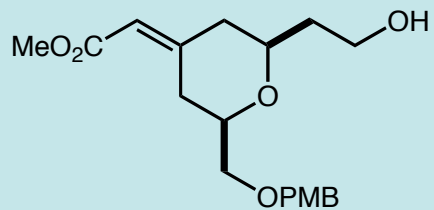
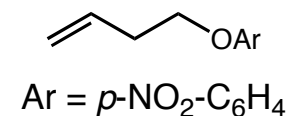
1. NIS
2. 9-BBN, H<sub>2</sub>O<sub>2</sub>
3. Pd<sub>2</sub>(dba)<sub>3</sub>, CO, MeOH  
50%



10% [RuCp(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub>



2% Pd<sub>2</sub>(dba)<sub>3</sub>  
6% S,S-ligand



## *Selected Examples of Enantioselective Cascade Catalysis*

Organocascade



Organometallo Cascade



Metallo Cascade



OrganoBio Cascade



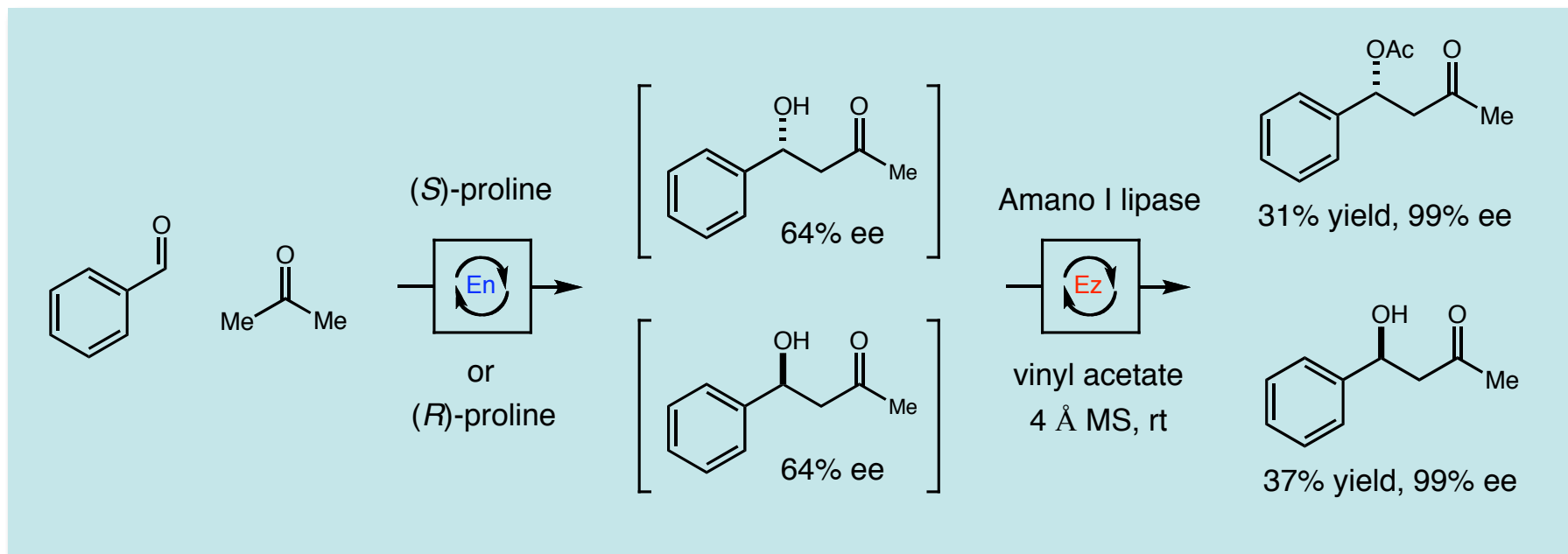
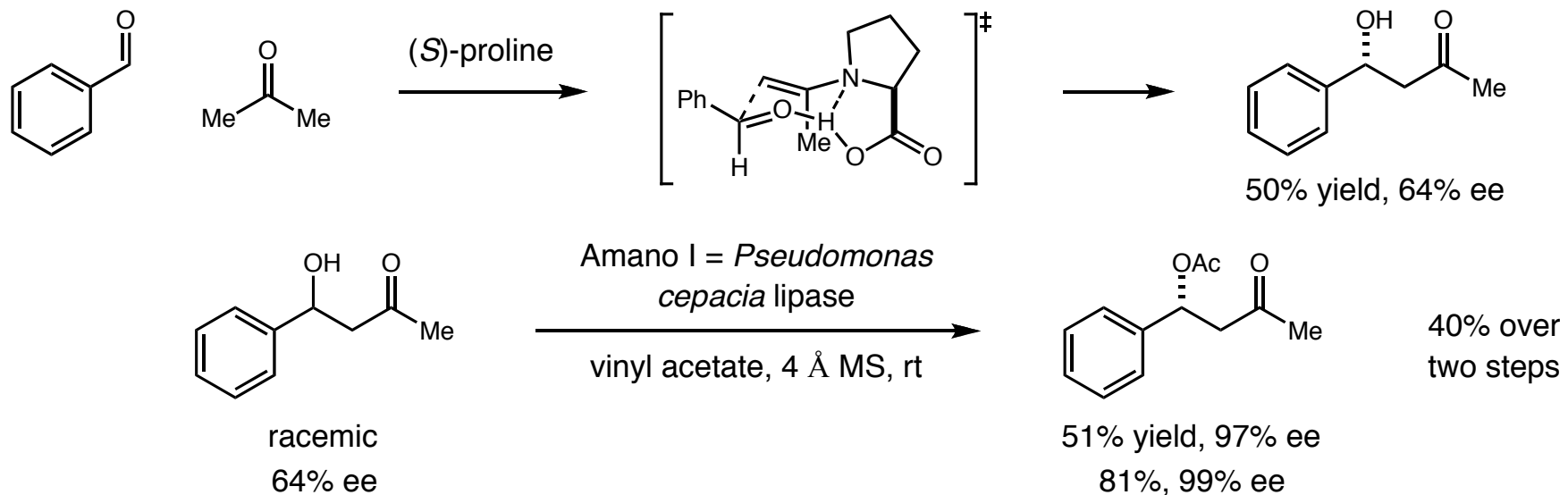
MetalloBio Cascade



Biocascade

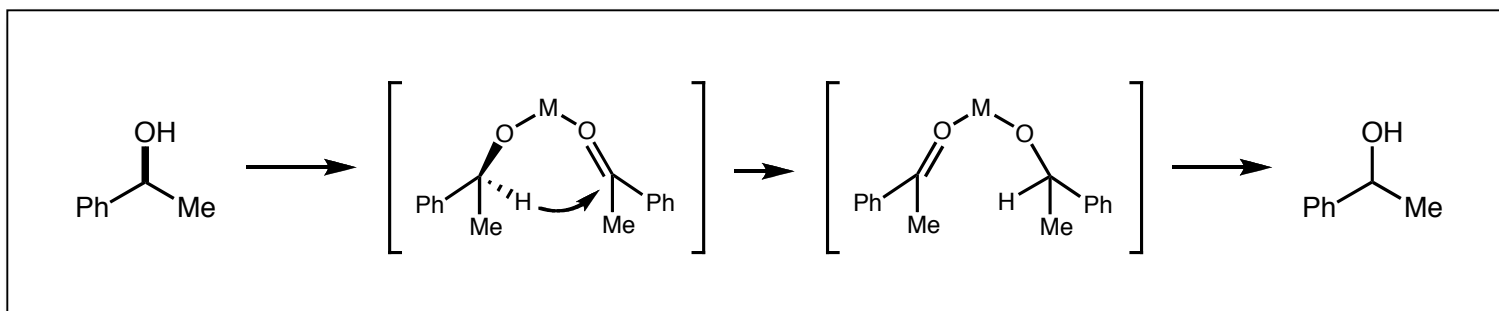
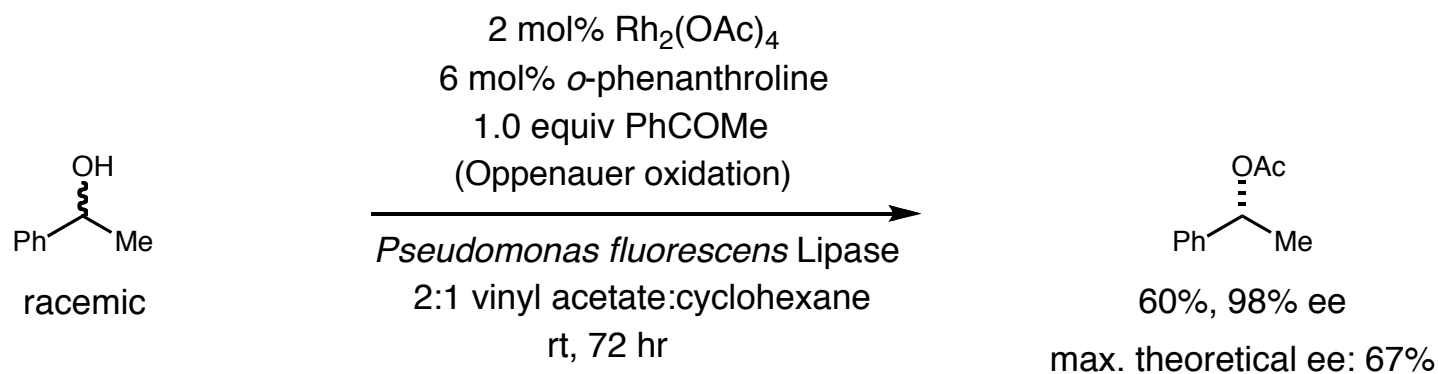
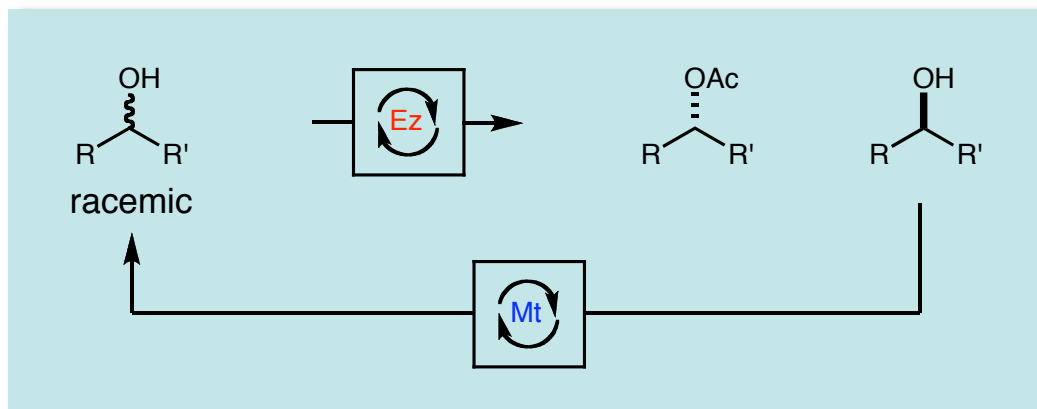


## OrganoBio Cascade Catalysis: $\beta$ -Hydroxy Ketone Synthesis

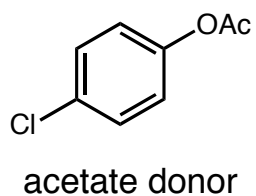
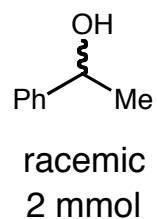
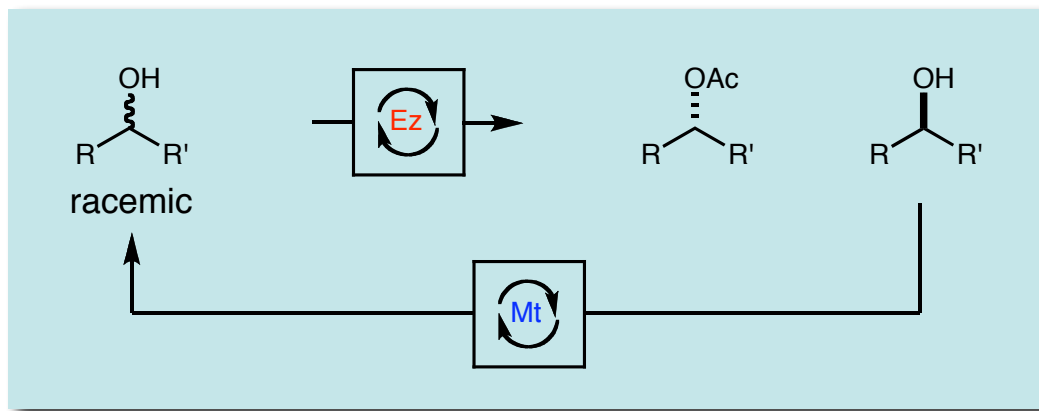




## MetalloBio Cascade Catalysis: Dynamic Kinetic Resolutions

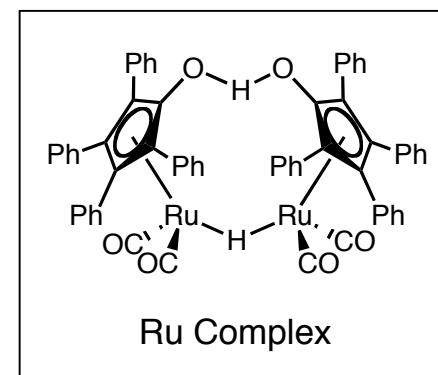
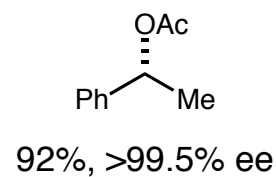


## MetalloBio Cascade Catalysis: Dynamic Kinetic Resolutions



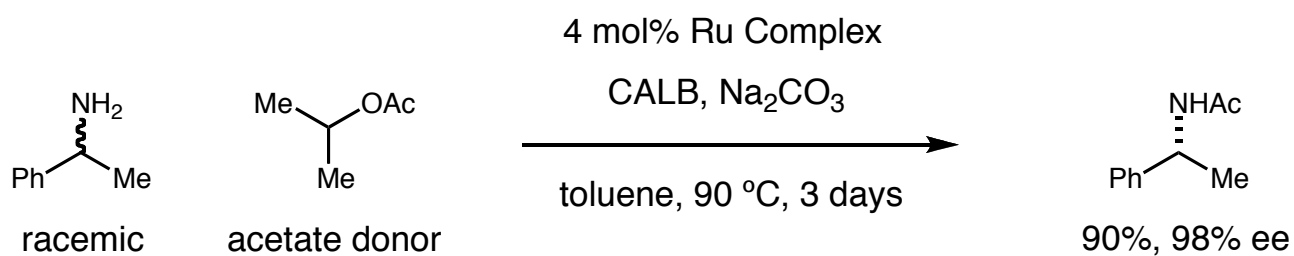
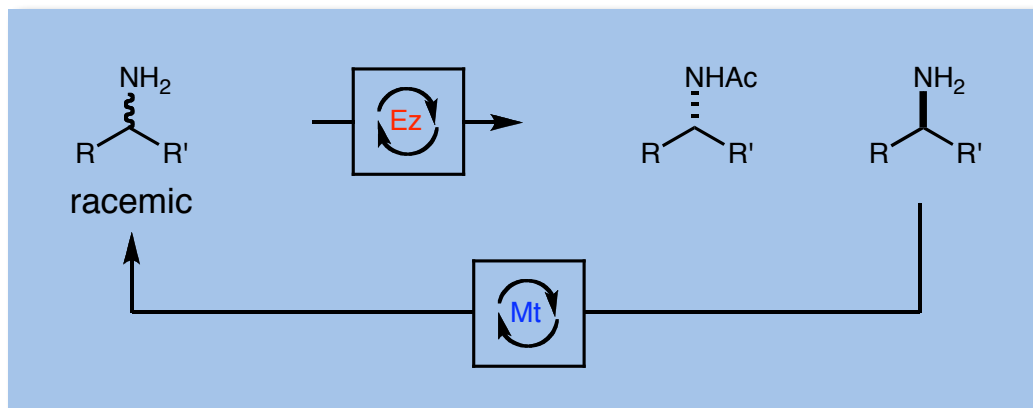
2 mol% Ru Complex  
 1.0 equiv PhCOMe  
 (*Oppenauer oxidation*)

50 mg CALB  
*t*-BuOH, 70 °C, 87 hr

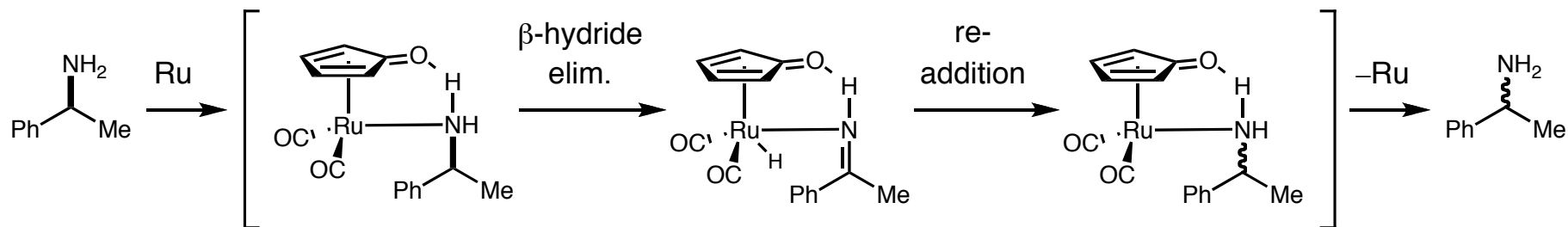
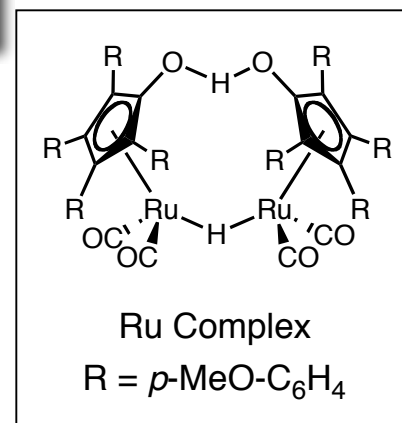


CALB = *Candida antarctica* lipase B

# MetalloBio Cascade Catalysis: Dynamic Kinetic Resolutions



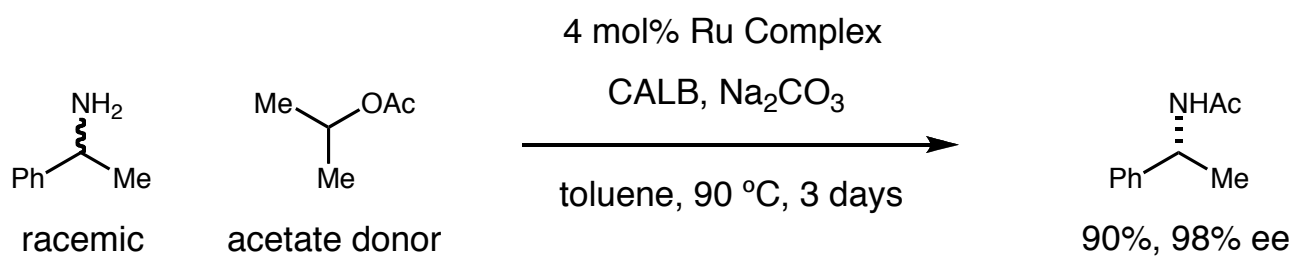
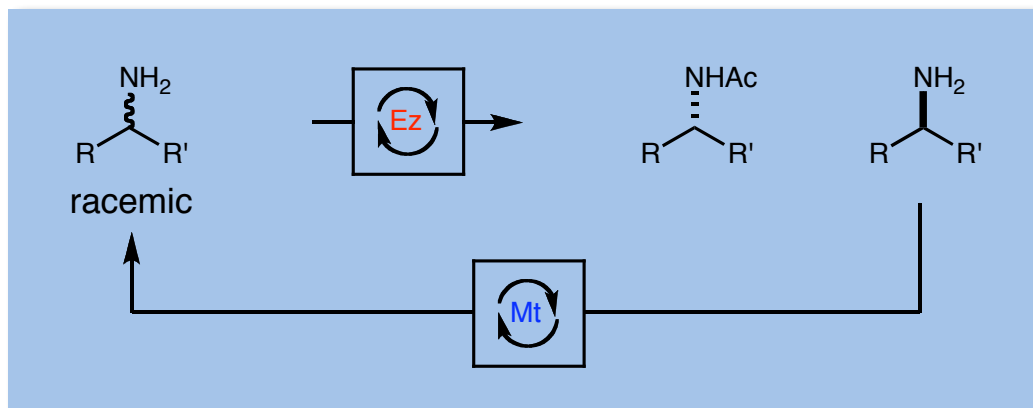
CALB = *Candida antarctica* lipase B



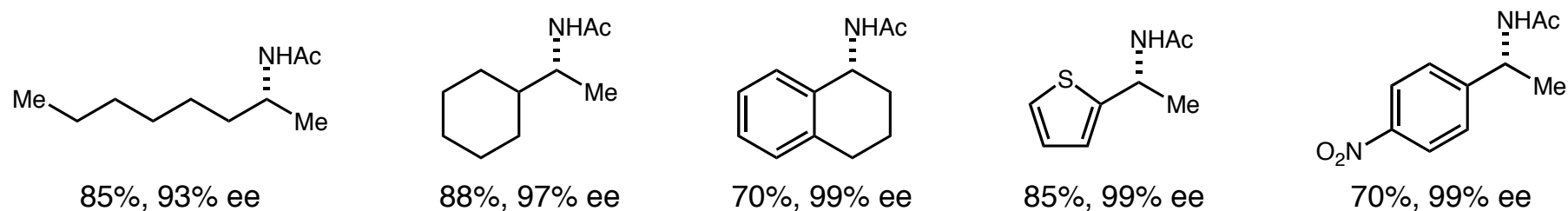
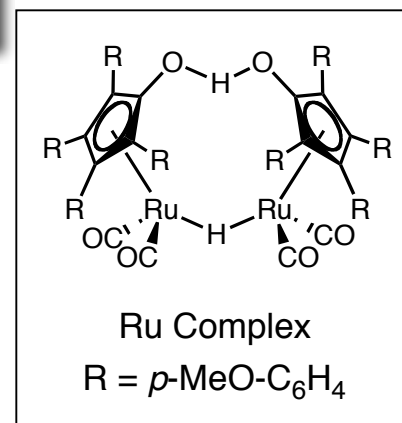
Paetzold, J.; Backvall, J. E. *J. Am. Chem. Soc.* **2005**, *127* (50), 17620.

Thalen, L. K.; Zhao, D. B.; Sortais, J. B.; Paetzold, J.; Hoben, C.; Backvall, J. E. *Chem. Eur. J.* **2009**, *15* (14), 3403.

# MetalloBio Cascade Catalysis: Dynamic Kinetic Resolutions



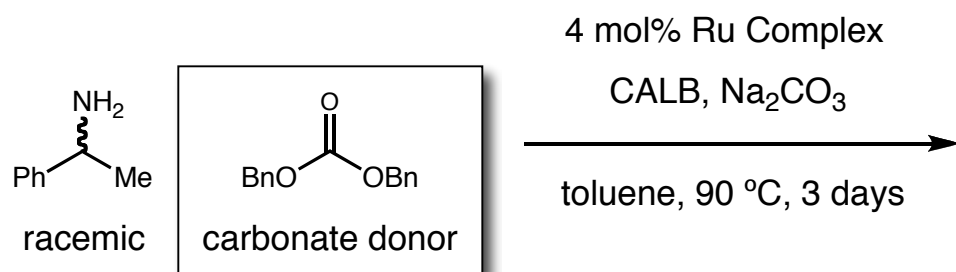
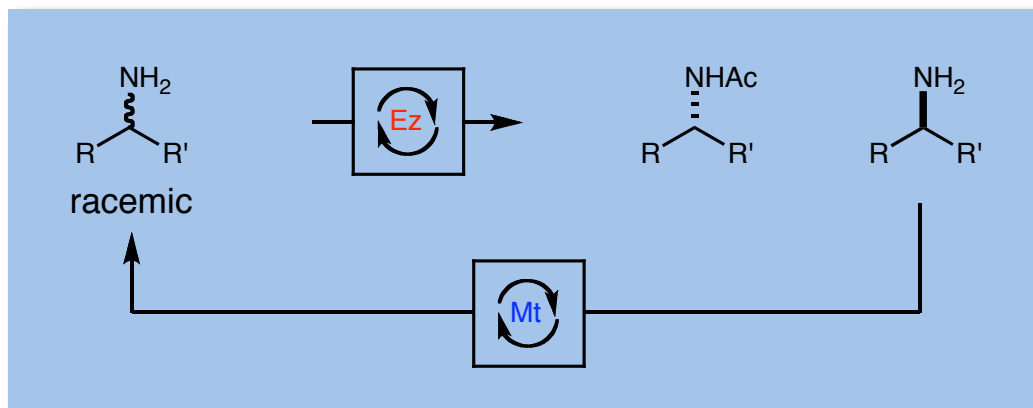
CALB = *Candida antarctica* lipase B



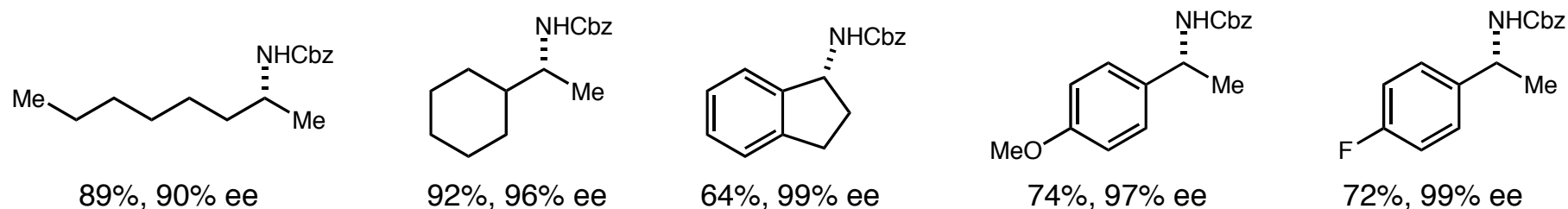
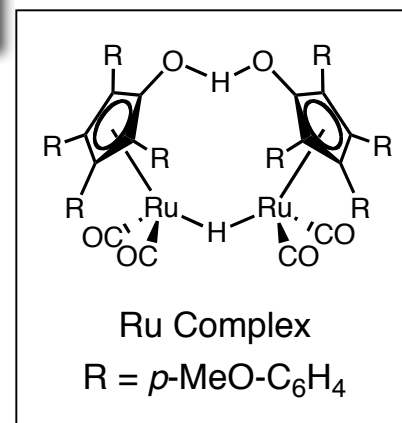
Paetzold, J.; Backvall, J. E. *J. Am. Chem. Soc.* **2005**, *127* (50), 17620.

Thalen, L. K.; Zhao, D. B.; Sortais, J. B.; Paetzold, J.; Hoben, C.; Backvall, J. E. *Chem. Eur. J.* **2009**, *15* (14), 3403.

# MetalloBio Cascade Catalysis: Dynamic Kinetic Resolutions



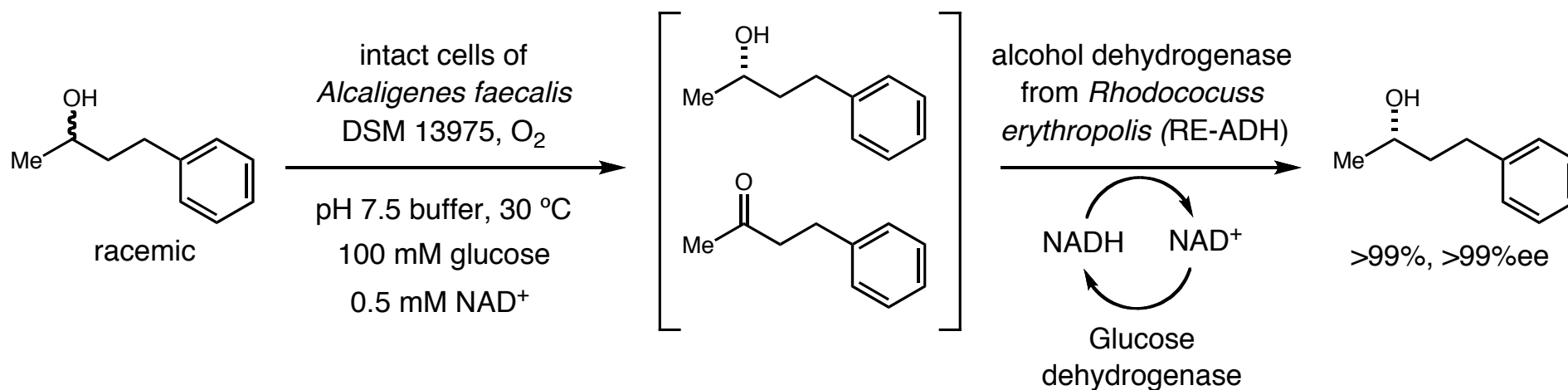
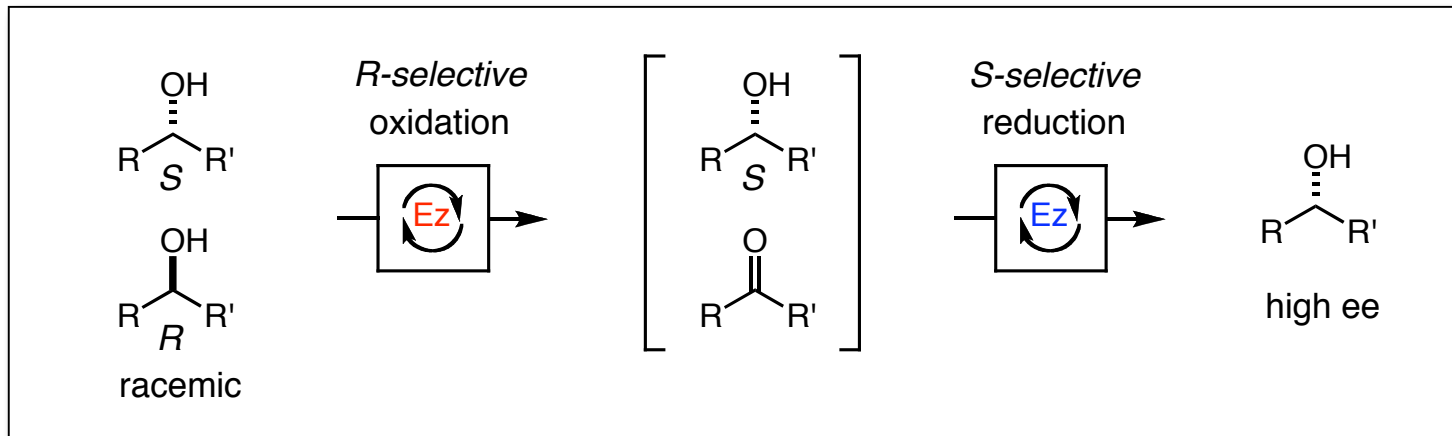
CALB = *Candida antarctica* lipase B



Paetzold, J.; Backvall, J. E. *J. Am. Chem. Soc.* **2005**, *127* (50), 17620.

Thalen, L. K.; Zhao, D. B.; Sortais, J. B.; Paetzold, J.; Hoben, C.; Backvall, J. E. *Chem. Eur. J.* **2009**, *15* (14), 3403.

## Deracemization of Secondary Alcohols via Biocascade Catalysis



- When lysed cells were used, racemization of enantiopure secondary alcohols was observed
- They concluded that the oxidation and reduction cycles must be separated: intact cell membrane

## Deracemization of Secondary Alcohols via Biocascade Catalysis

