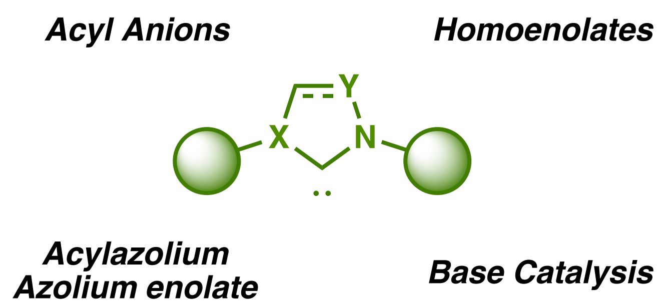
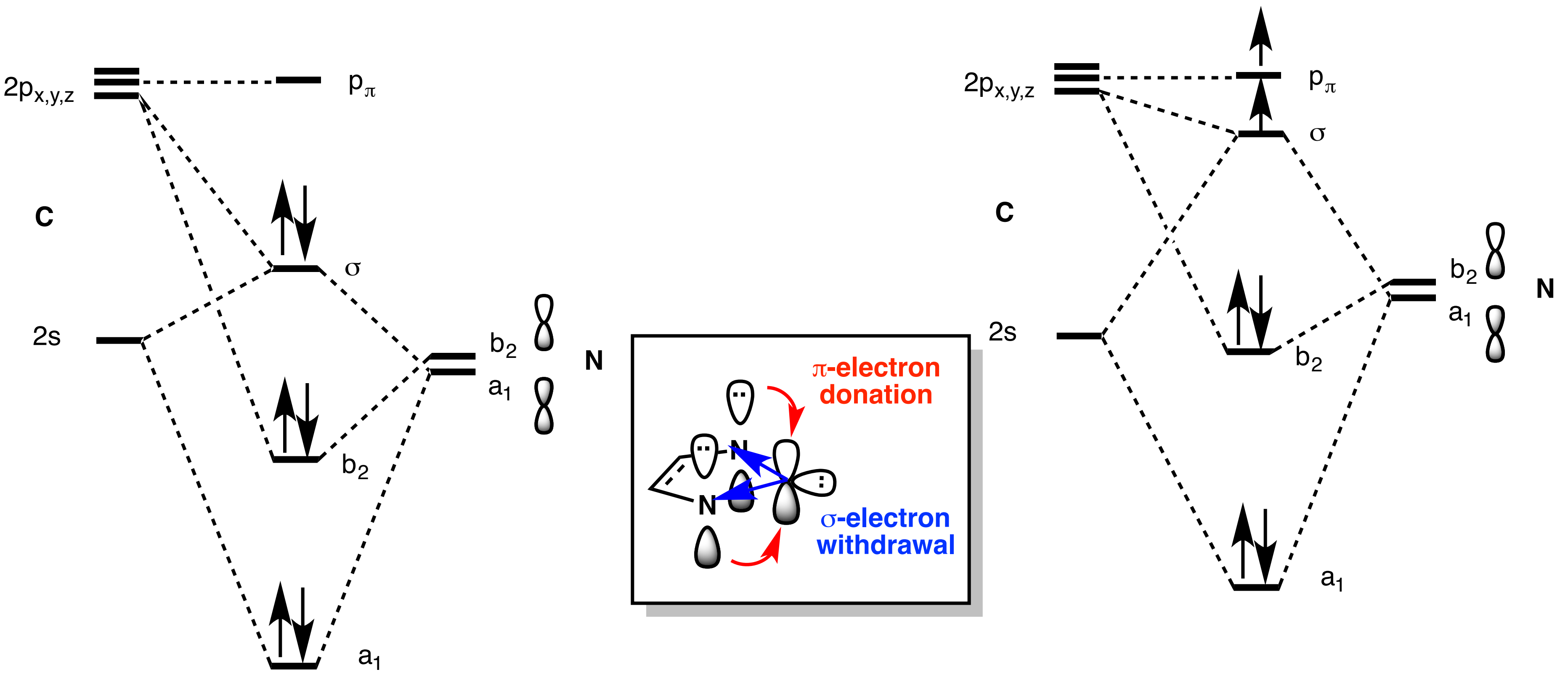
Organocatalysis Enabled by N-Heterocyclic Carbenes



Jiaming Li

2018/04/27

Stability of N-heterocyclic Carbenes

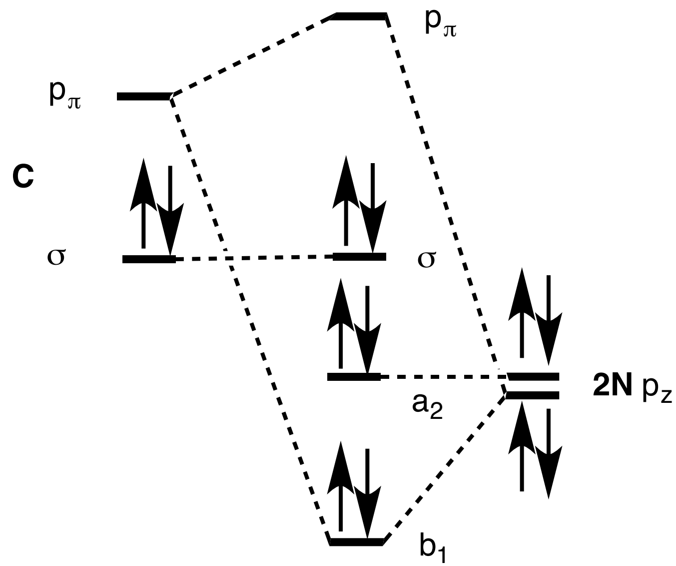


σ-electron-withdrawing substitutents **σ-electron-donating substitutents**

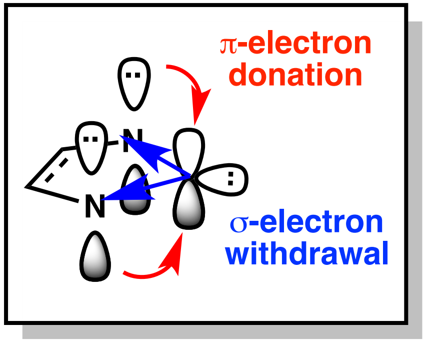
- σ-electron withdrawing substitutents favor the singlet state over the triplet state
- σ-electron withdrawing substitutents inductively stablize the σ non-bonding orbital by increasing its s character and leaving the p_π orbital unchanged
- σ-electron donating substitutents induce a smaller σ-p_π gap, favoring a triplet state

Bertrand, *Chem. Rev.* **2000**, 100, 39

Stability of N-heterocyclic Carbenes



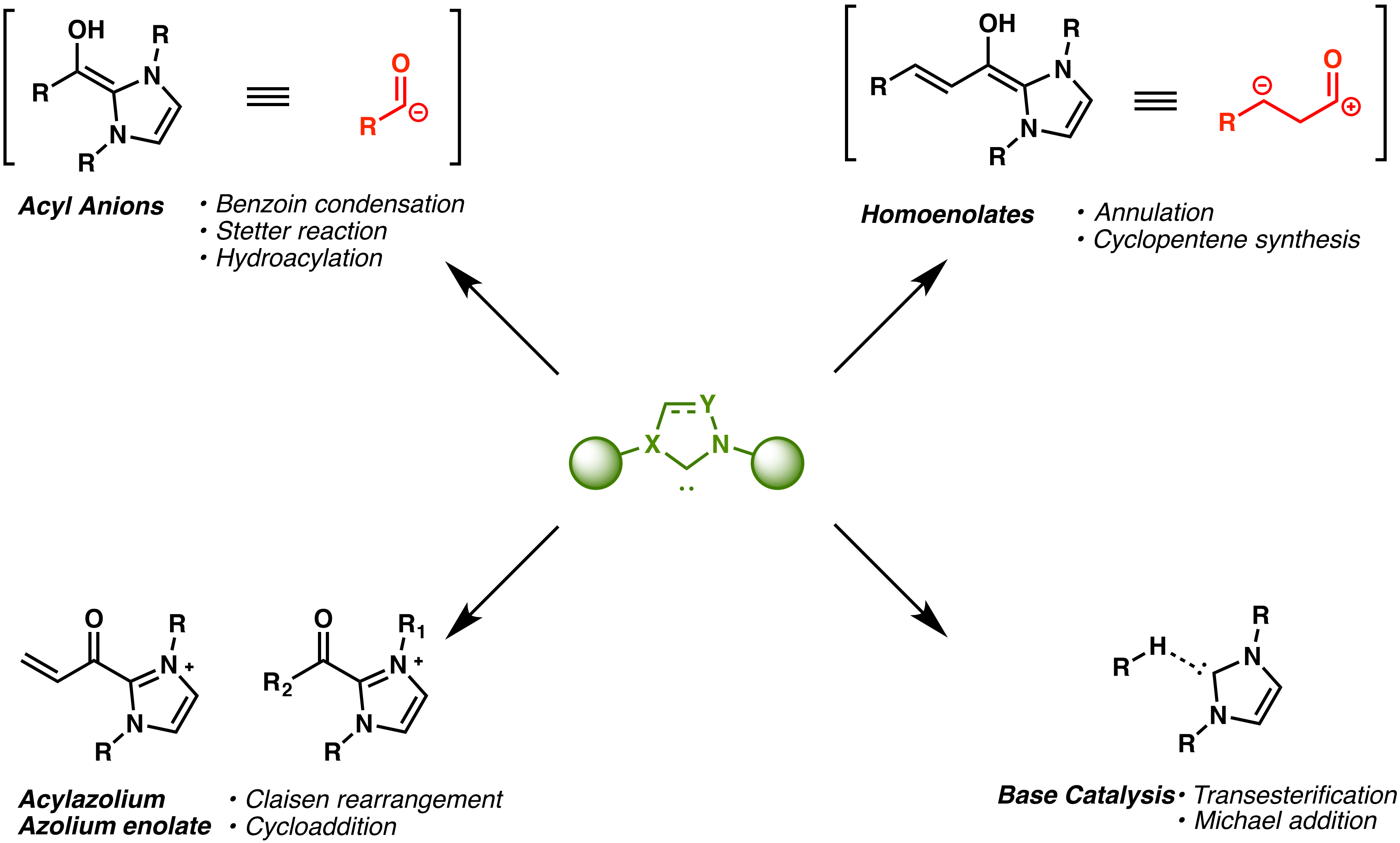
π-electron donation



- The energy of p_π orbital is increased by the interaction with the symmetric combination of the substitutent lone pairs.
- Combined effect is to increase the σ–p_π gap and stablize the singlet-state carbene over the more reactive triplet-state carbene.

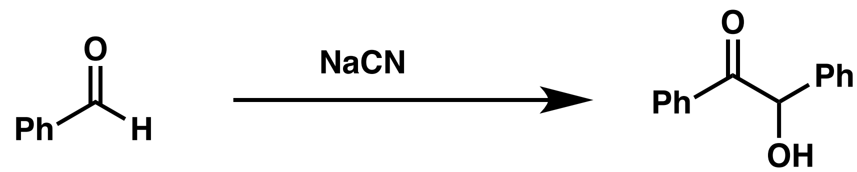
Bertrand, *Chem. Rev.* **2000**, 100, 39

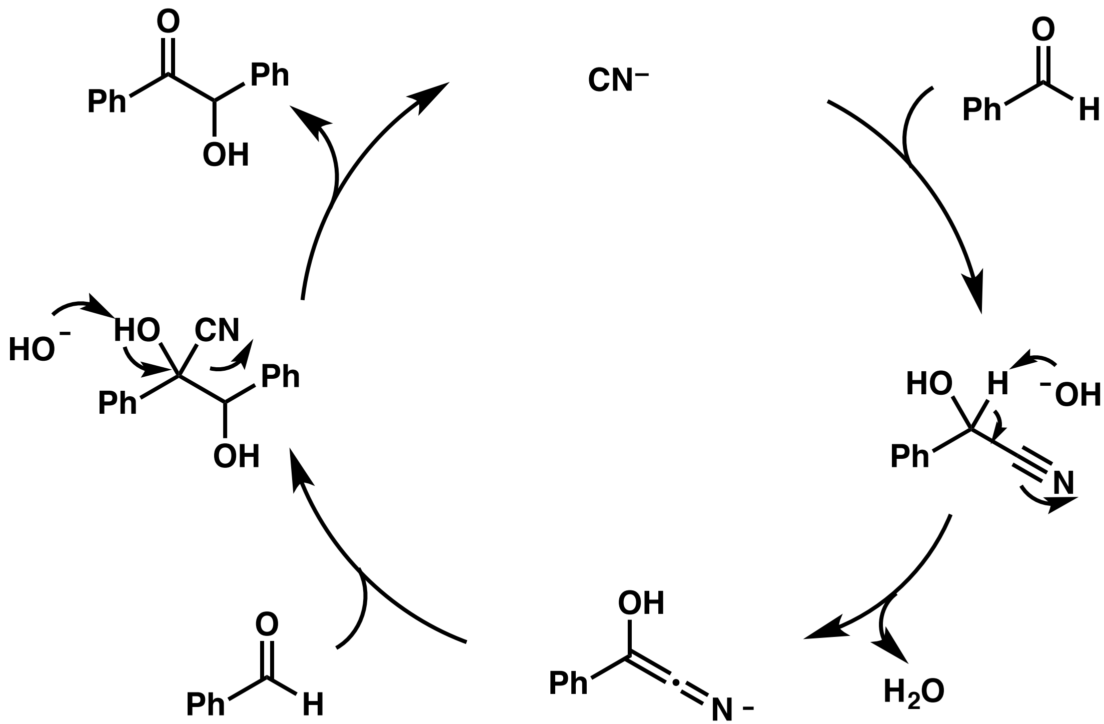
Overview


OH
R
N
R
N
R
O
R
Acyl Anions
• Benzoin condensation
• Stetter reaction
• Hydroacylation
OH
R
R
N
N
R
O
R
Homoenolates
• Annulation
• Cyclopentene synthesis
Y
X
N
O
R
N+
N
R
O
R1
R2
N+
N
R
Acylazolium
Azolium enolate
• Claisen rearrangement
• Cycloaddition
R
R
H
N
N
R
Base Catalysis
• Transesterification
• Michael addition

Benzoin condensation

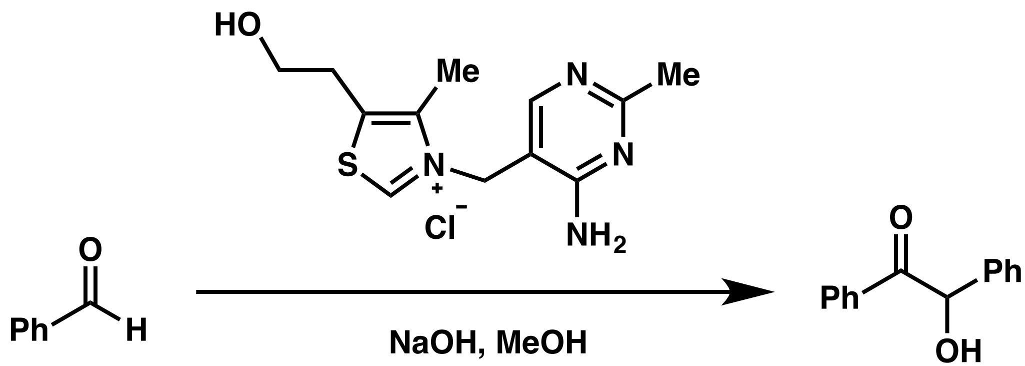
- **First reported benzoin condensation (Wohler, Liebig, 1832)**

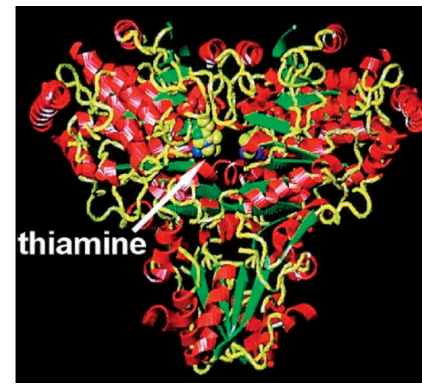




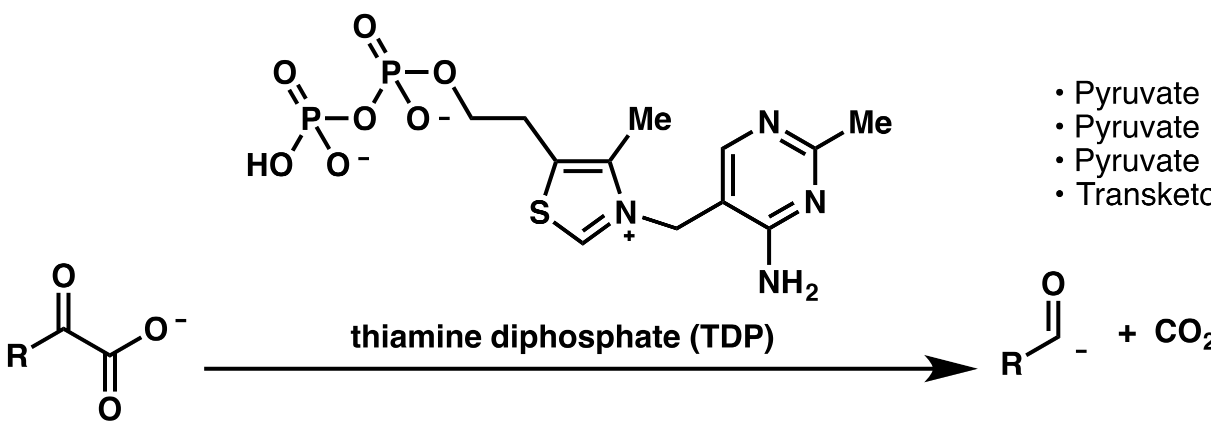
Benzoin condensation

- **Ugai discovered thiazolium salts could catalyze benzoin condensation (1943)**





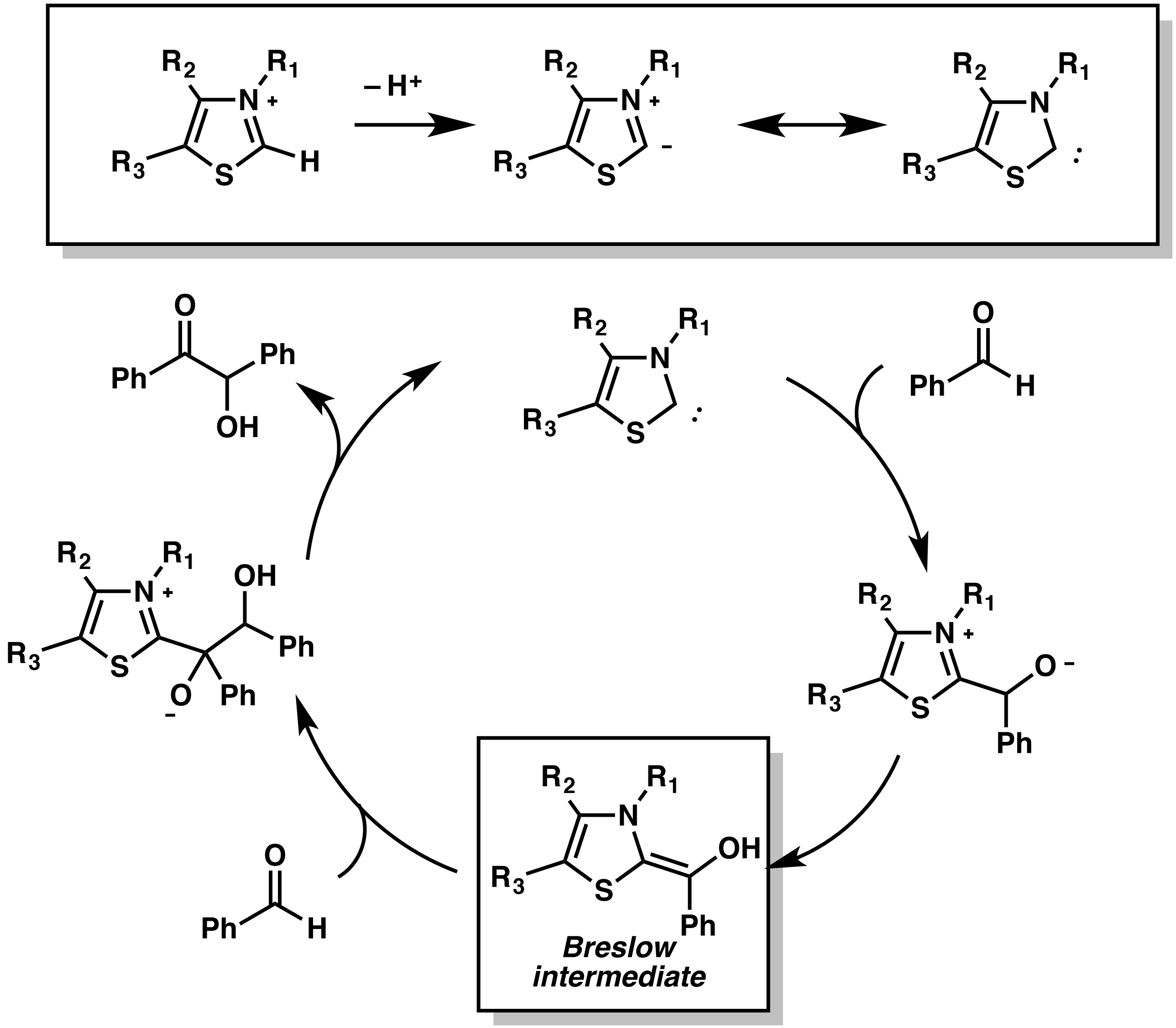
- **Co-enzyme thiamine diphosphate is responsible for the generation of acyl anion**



- Pyruvate decarboxylase
- Pyruvate oxidase
- Pyruvate dehydrogenase
- Transketolase

Ugai, T.; Tanaka, R.; Dokawa, T. *J. Pharm. Soc. Jpn.* **1943**, 63, 296.

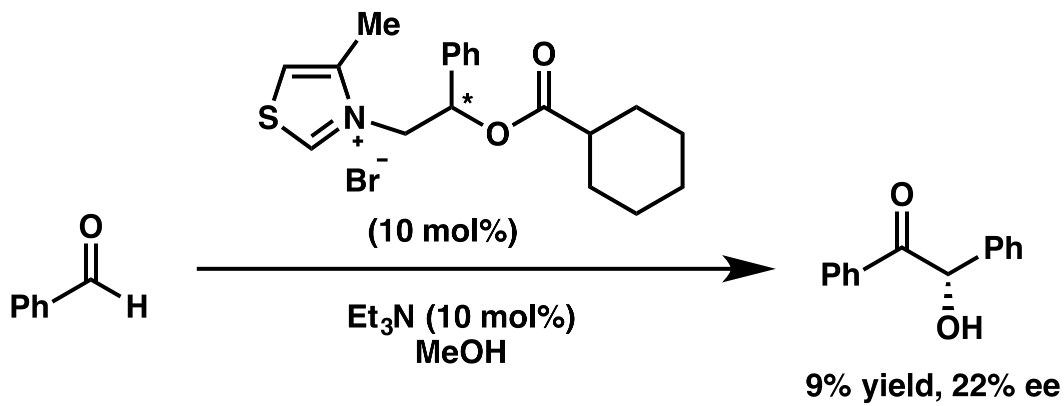
Proposed Mechanism by Breslow



Breslow, R. *J. Am. Chem. Soc.*. **1958**, 80, 3719

Enantioselective Benzoin Condensation

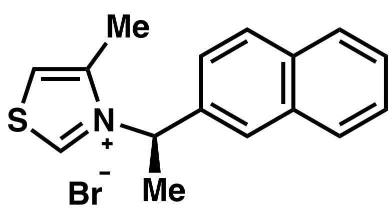
- **First asymmetric benzoin condensation catalyzed by chiral thiazolium salts (Sheehan, 1966)**



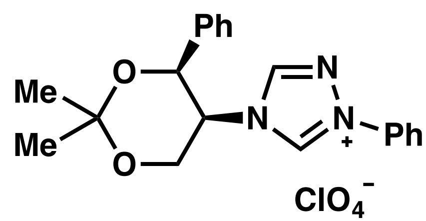
Sheehan, J. C.; Hunneman, D. H. *J. Am. Chem. Soc.* **1966**, 88, 3666

Enantioselective Benzoin Condensation

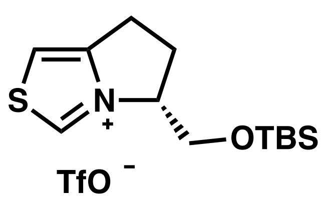
- **Improvement in the enantioselectivity of benzoin condensation**



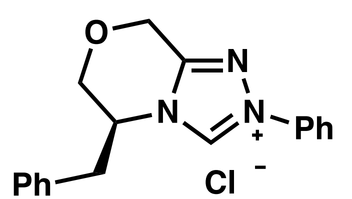
6% yield, 52% ee
Sheehan, 1974



66% yield, 75% ee
Enders, 1996



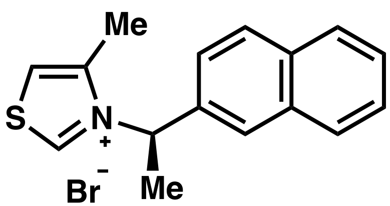
50% yield, 21% ee
Leeper, 1997



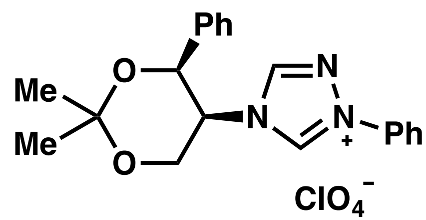
45% yield, 80% ee
Leeper, 1998

Enantioselective Benzoin Condensation

• **Improvement in the enantioselectivity of benzoin condensation**

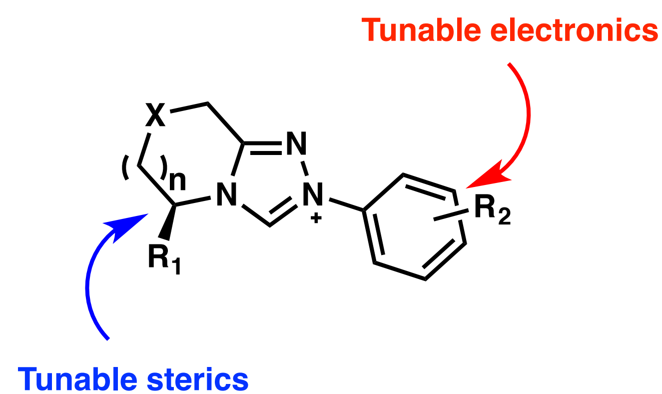


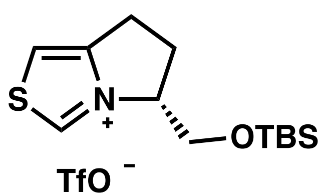
6% yield, 52% ee
Sheehan, 1974



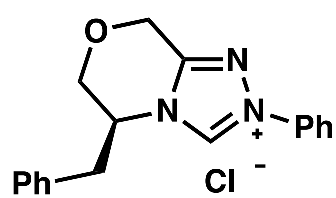
66% yield, 75% ee
Enders, 1996

• **N-aryl-bicyclic triazolium structure**

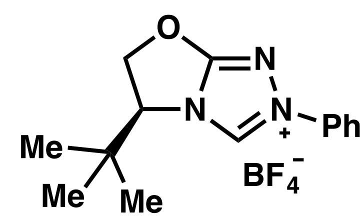




50% yield, 21% ee
Leeper, 1997

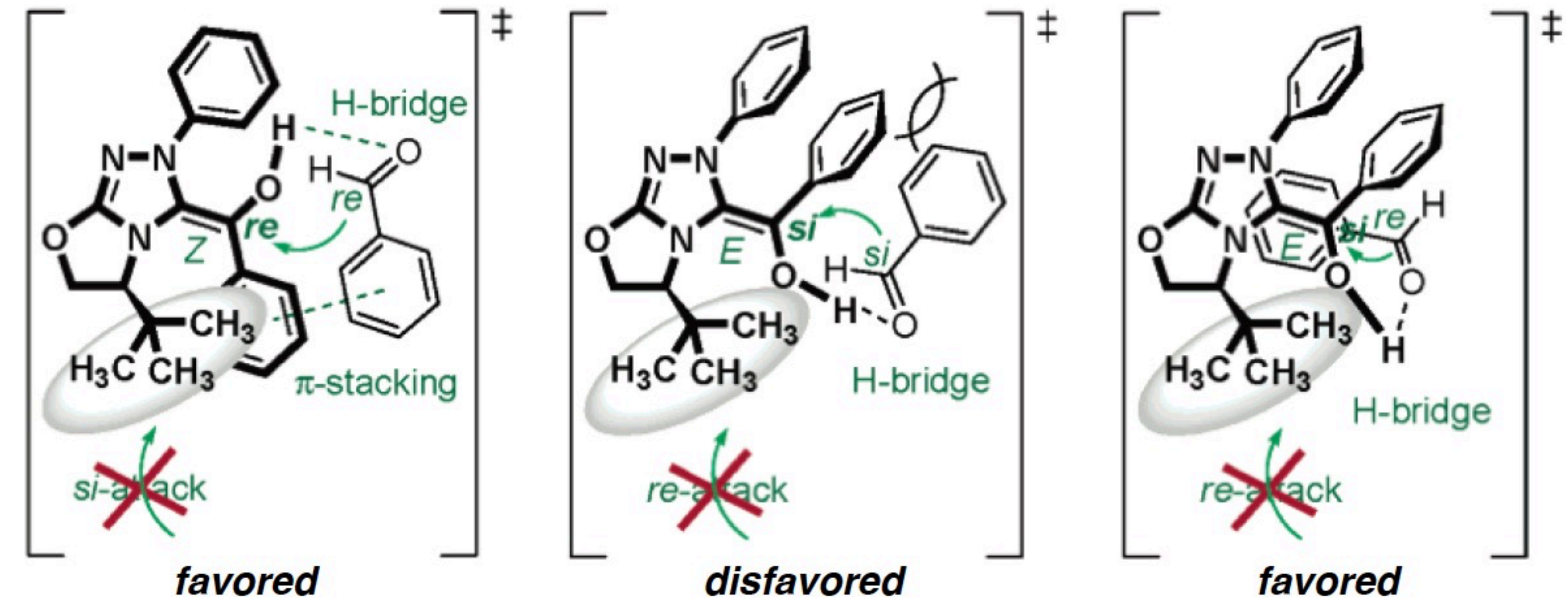


45% yield, 80% ee
Leeper, 1998



83% yield, 90% ee
Enders, 2002

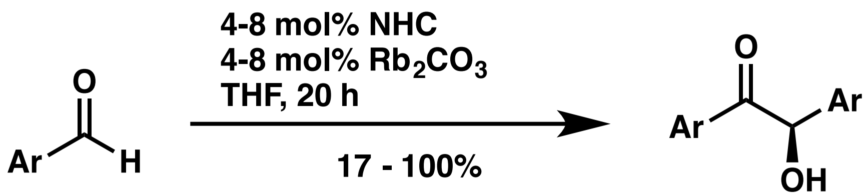
Model

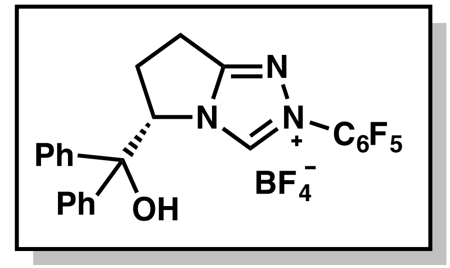


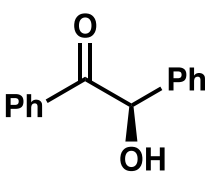
Enders, *Chem. Rev.* **2007**, *107*, 5606-5655

Enantioselective Benzoin Condensation

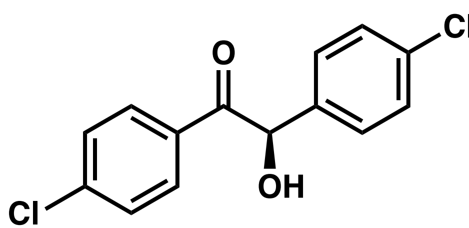
- **Highly efficient system for the enantioselective benzoin reaction (Connon, 2009)**



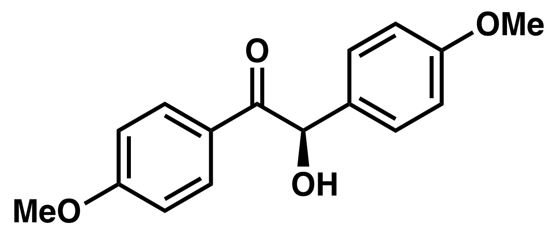




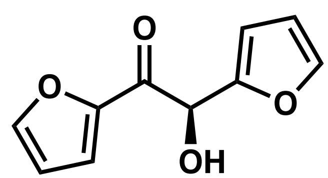
90% yield,
>99% ee



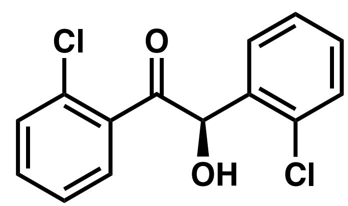
91% yield,
92% ee



26% yield,
97% ee



92% yield,
90% ee

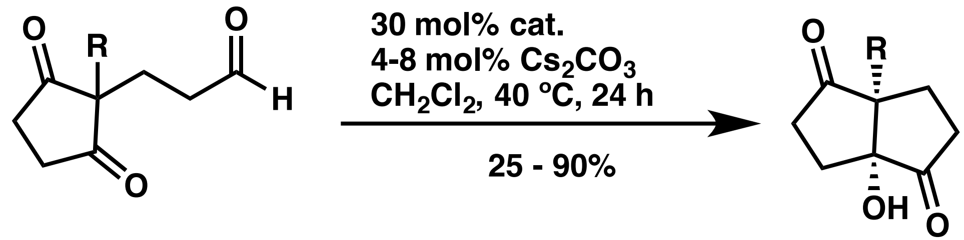


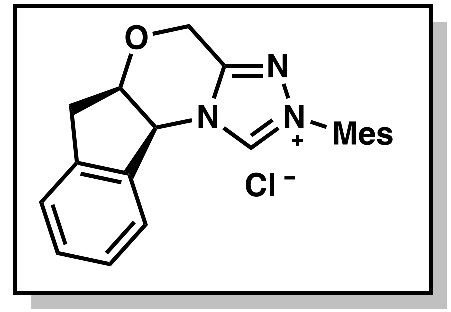
17% yield,
43% ee

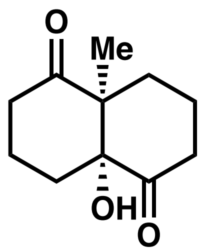
Connon, S. J. *J. Org. Chem.* **2009**, 74, 9214

Aldehyde-Ketone Cross-Benzoin Reaction

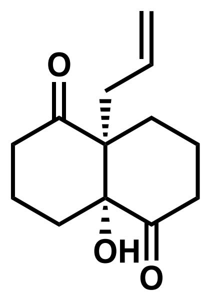
- **Synthesis of Bicyclic Tertiary Alcohols**



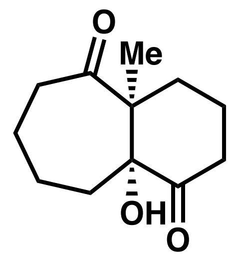




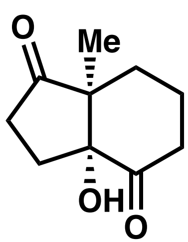
67% yield,
>99% ee



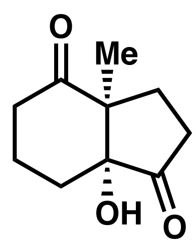
37% yield,
94% ee



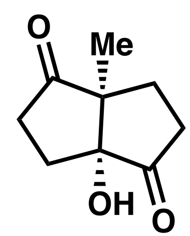
47% yield,
86% ee



43% yield,
95% ee



50% yield,
78% ee

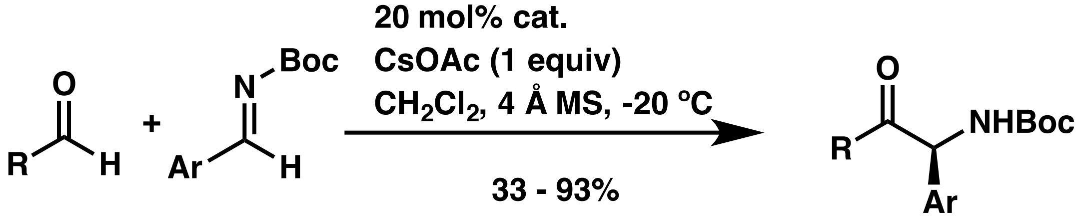


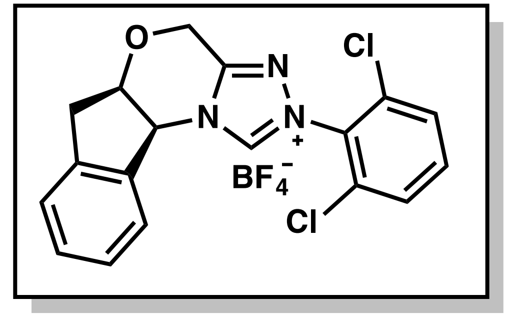
32% yield,
26% ee

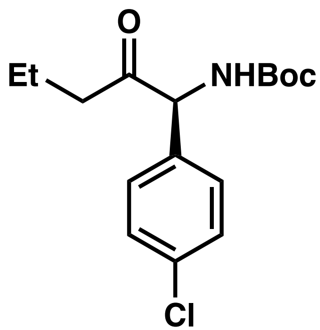
Sakai, *Org. Lett.* **2009**, 11, 4866-4869

Aldehyde-Imine Cross-Benzoin Reaction

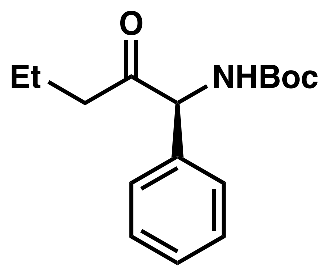
- **Cross Aza-Benzoin Reaction with N-Boc Imines**



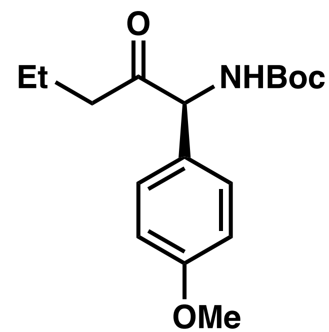




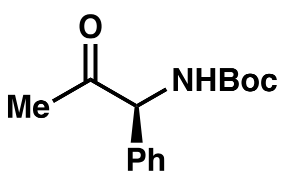
83% yield,
96% ee



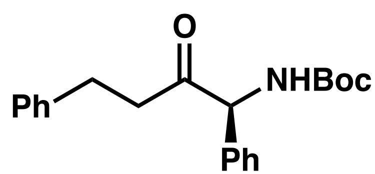
89% yield,
96% ee



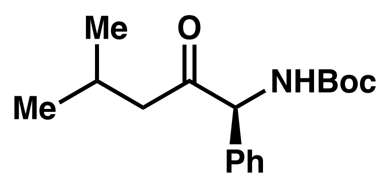
84% yield,
96% ee



86% yield,
84% ee



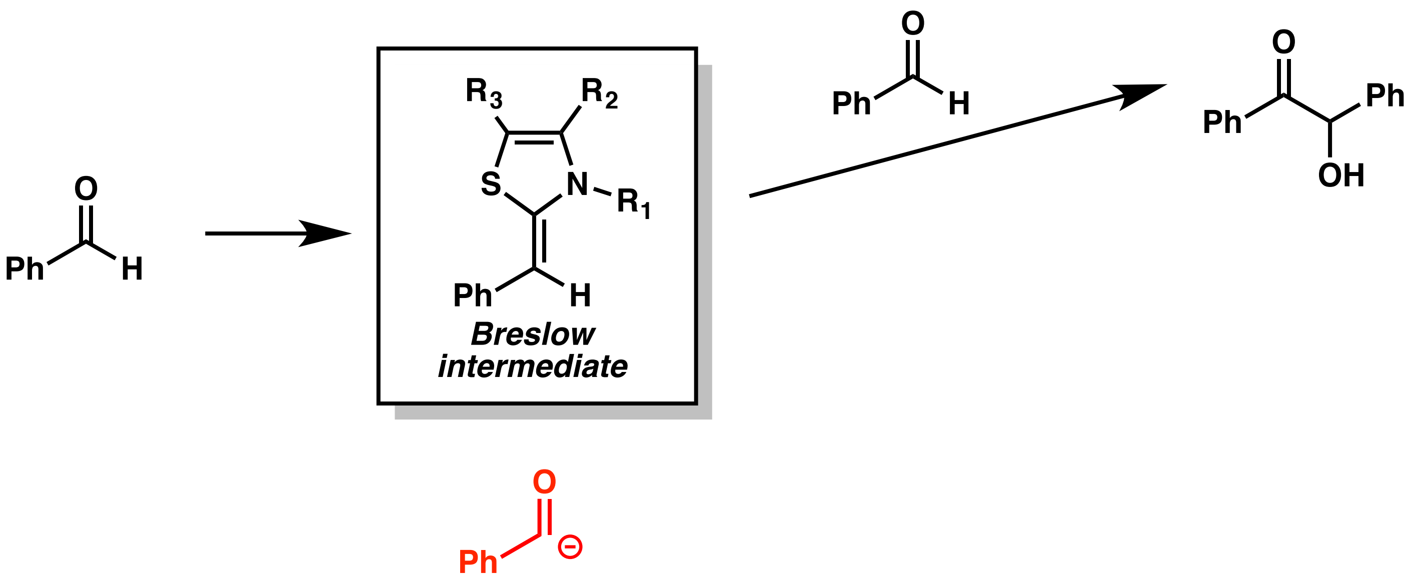
71% yield,
92% ee



33% yield,
98% ee

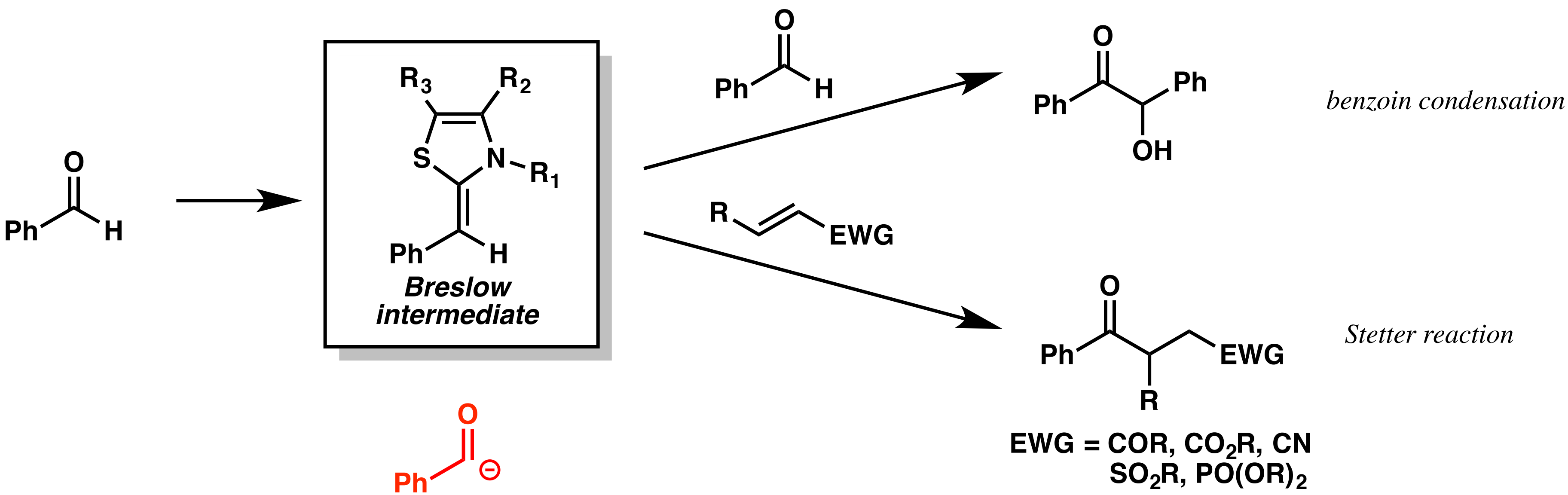
Rovis, *Angew. Chem., Int. Ed.* **2012**, 51, 5904-5906

Acyl Anion Equivalent



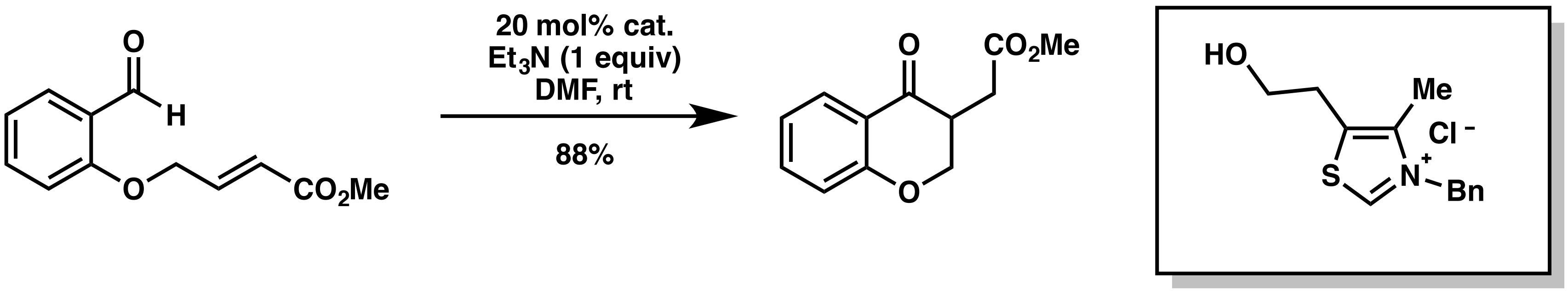
benzoin condensation

Acyl Anion Equivalent

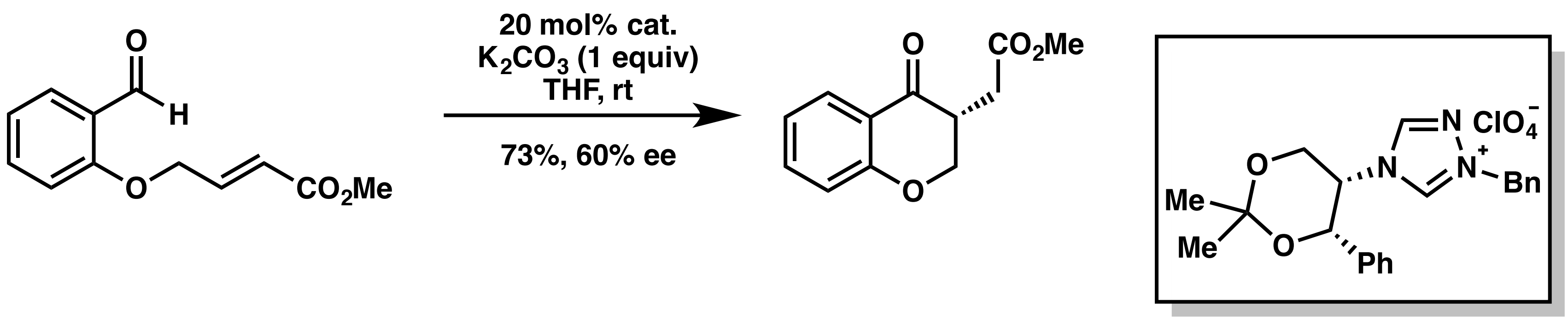


Seminal Works of Stetter Reaction

• **First general intramolecular Stetter reaction catalyzed by NHC (Ciganek, 1995)**



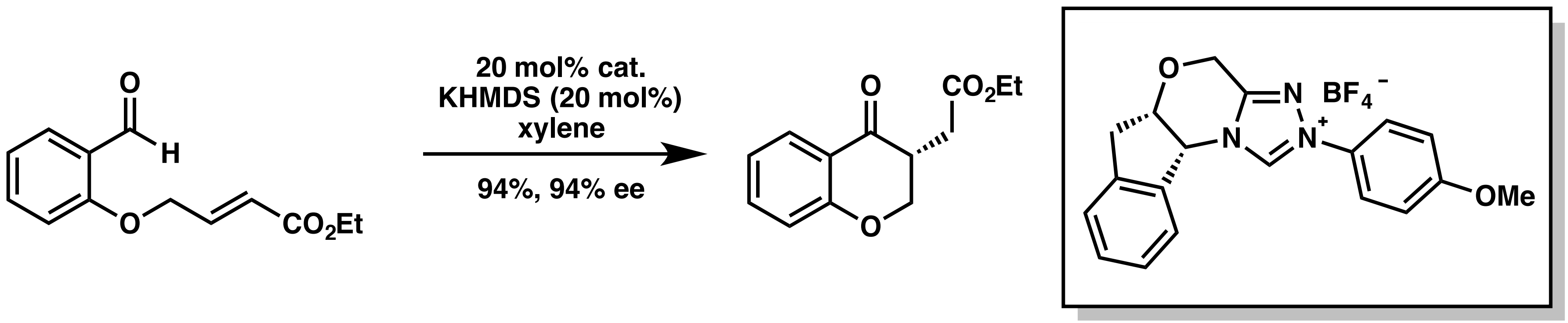
• **First asymmetric intramolecular Stetter reaction (Enders, 1995)**

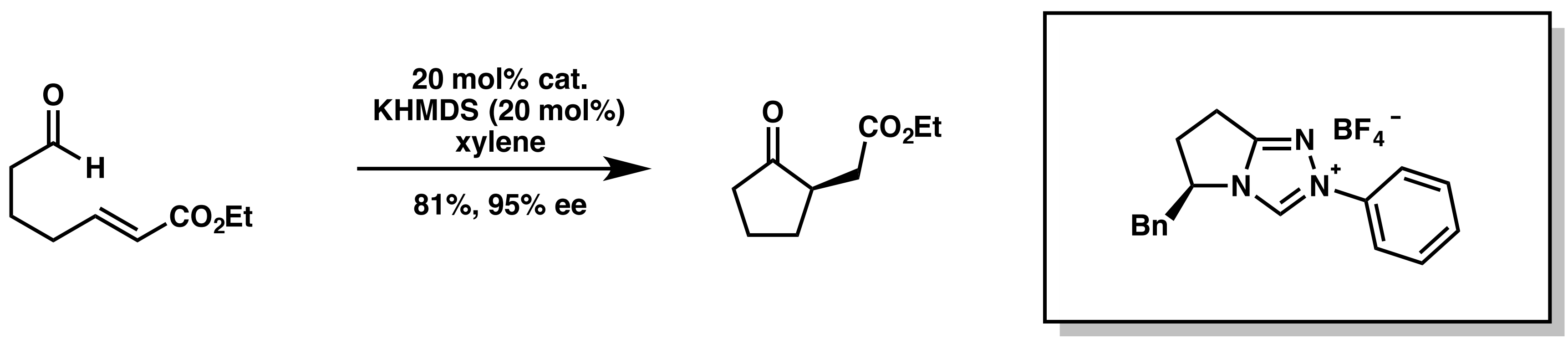


Ciganek, *Synthesis* **1995**, 1311-1314
Enders, *Angew. Chem., Int. Ed*. **1995**, 34, 1021-1023

Improved Asymmetric Intramolecular Stetter Reaction

• **Highly enantioselective Stetter reaction (Rovis, 2002)**

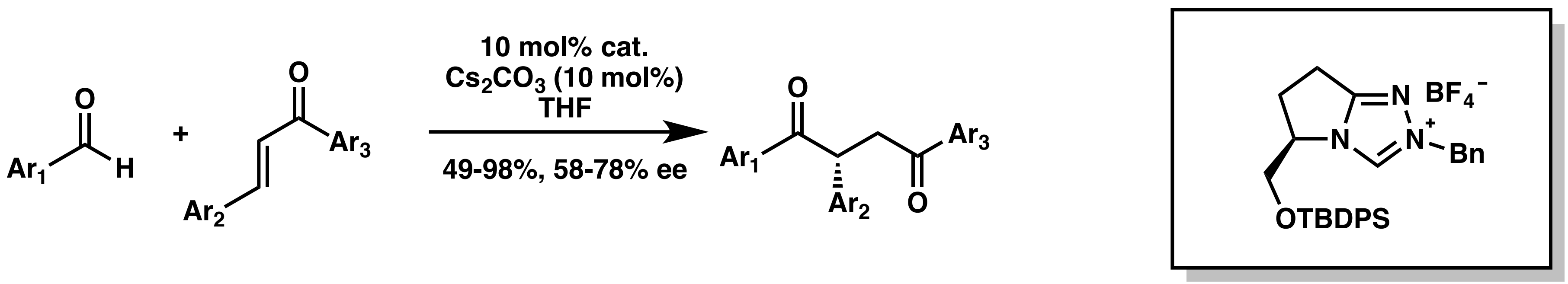




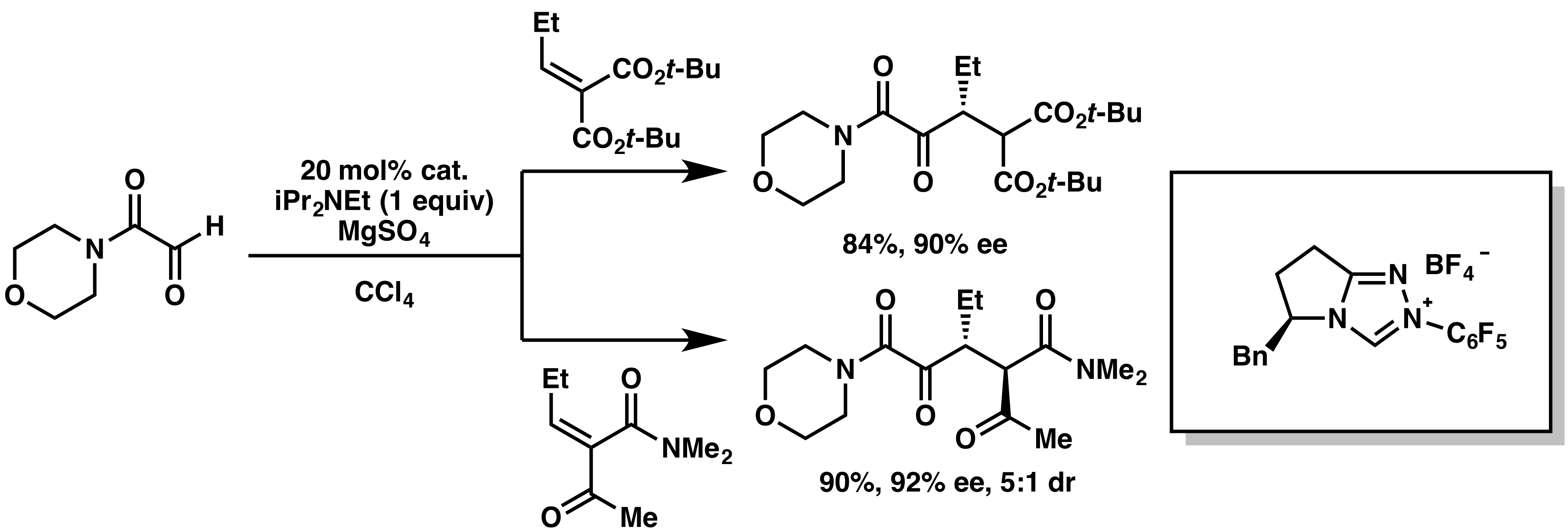
Rovis, *J. Am. Chem. Soc.* **2002**, 124, 10298

Asymmetric Intermolecular Stetter Reaction

- **Intermolecular Stetter reaction with Chalcones (Enders, 2008)**



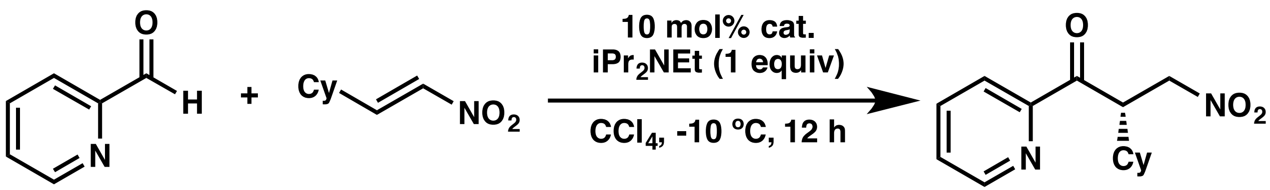
- **Intermolecular Stetter reaction with highly activated alkylidene dicarbonyls (Rovis, 2008)**

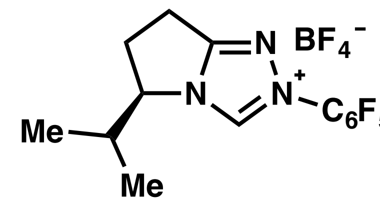


Rovis, T. *J. Am. Chem. Soc.* **2008**, 130, 14066

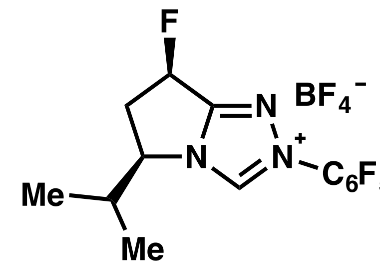
Asymmetric Intermolecular Stetter Reaction

• **Intermolecular Stetter reaction with nitroalkenes**



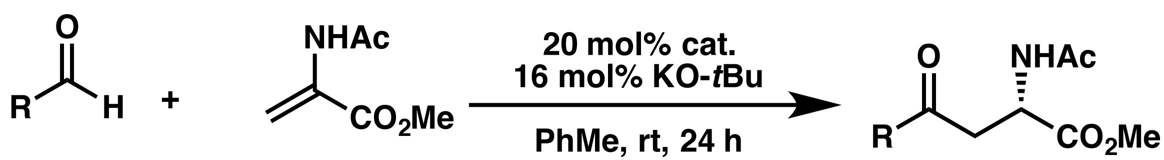


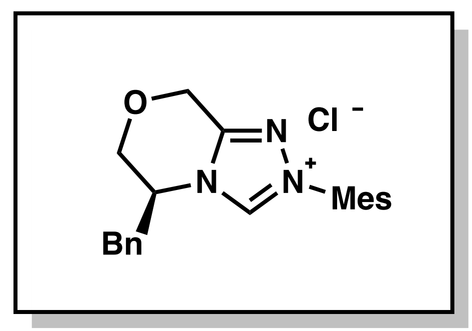
90% yield, 88% ee



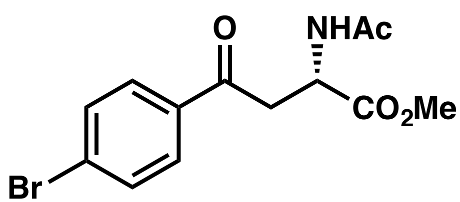
95% yield, 95% ee

• **Stetter reaction of Methyl 2-Acetamidoacrylate**

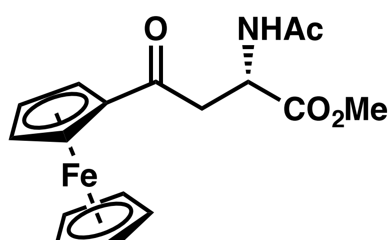




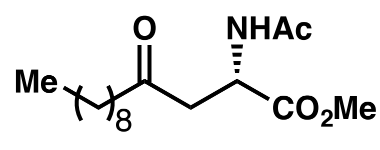
Selected Examples:



98%, 96% ee



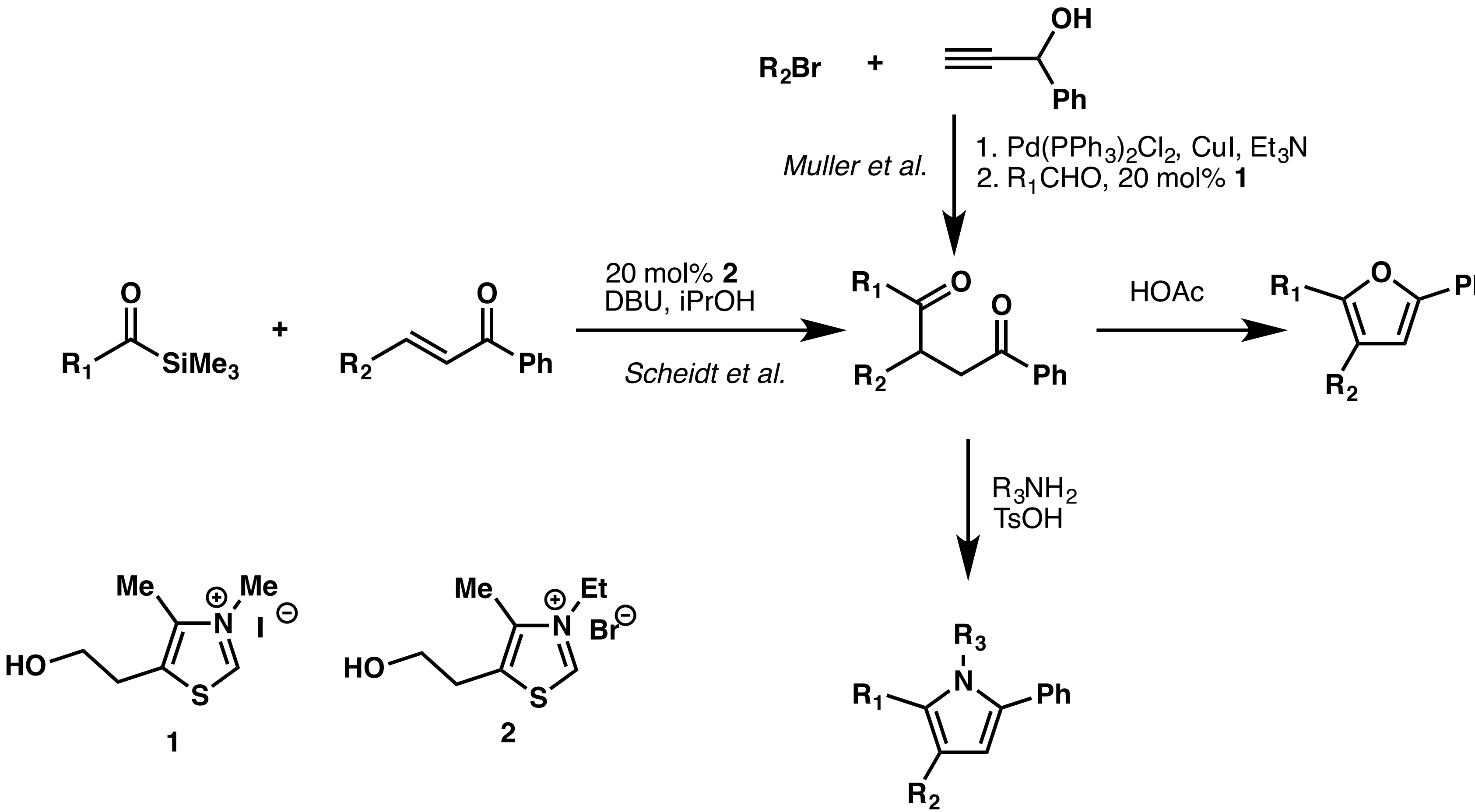
56%, 99% ee



52%, 97% ee

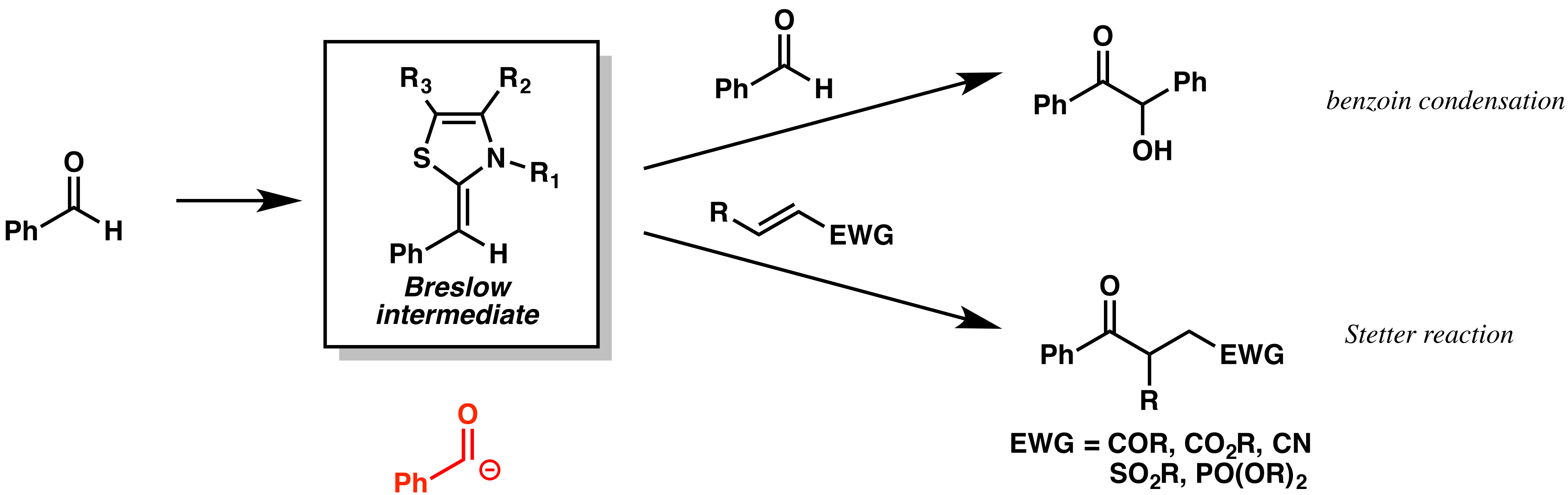
Rovis, *J. Am. Chem. Soc.* **2011**, 133, 10402-10405.
Glorius, *Angew. Chem., Int. Ed.* **2011**, 50, 1410-1414

One-Pot Synthesis of Pyrrols and Furans

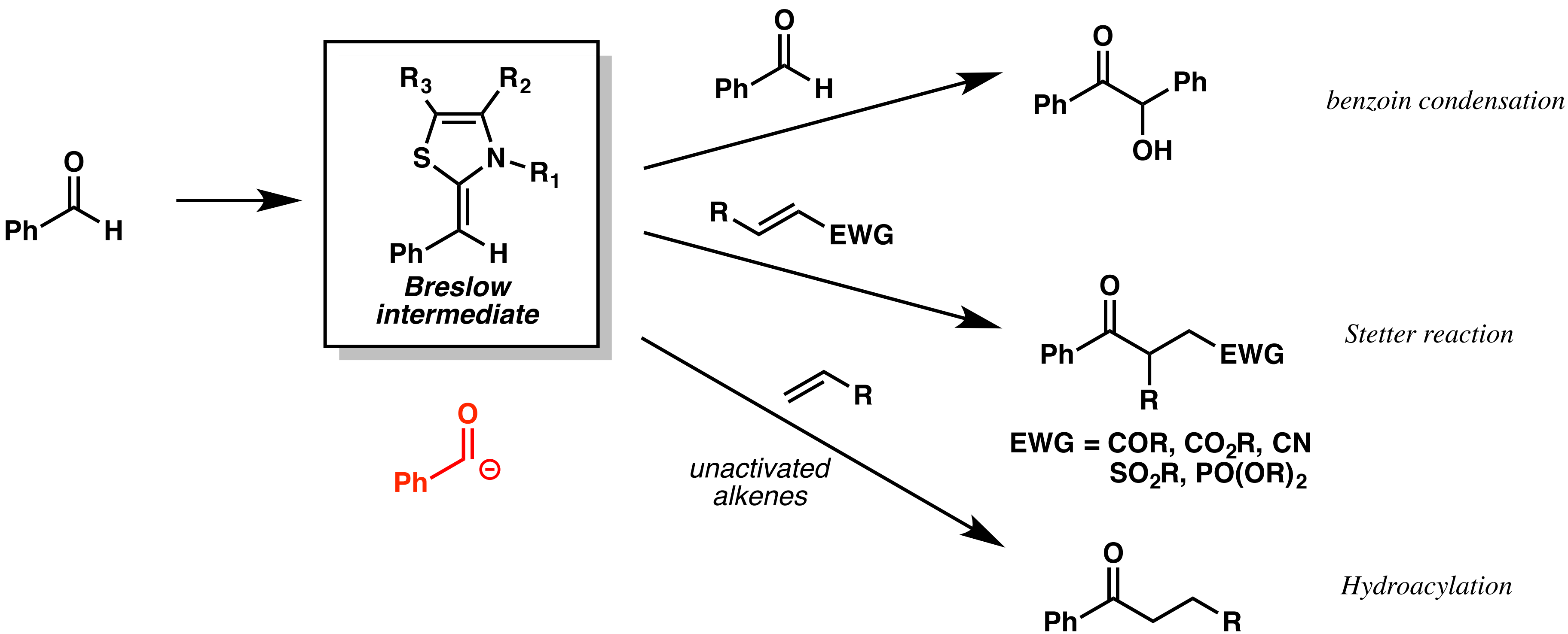


Müller, T. J. J. *Org. Lett.* **2001**, 3, 3297
Scheidt, K. A. *Org. Lett.* **2004**, 6, 2465

Acyl Anion Equivalent

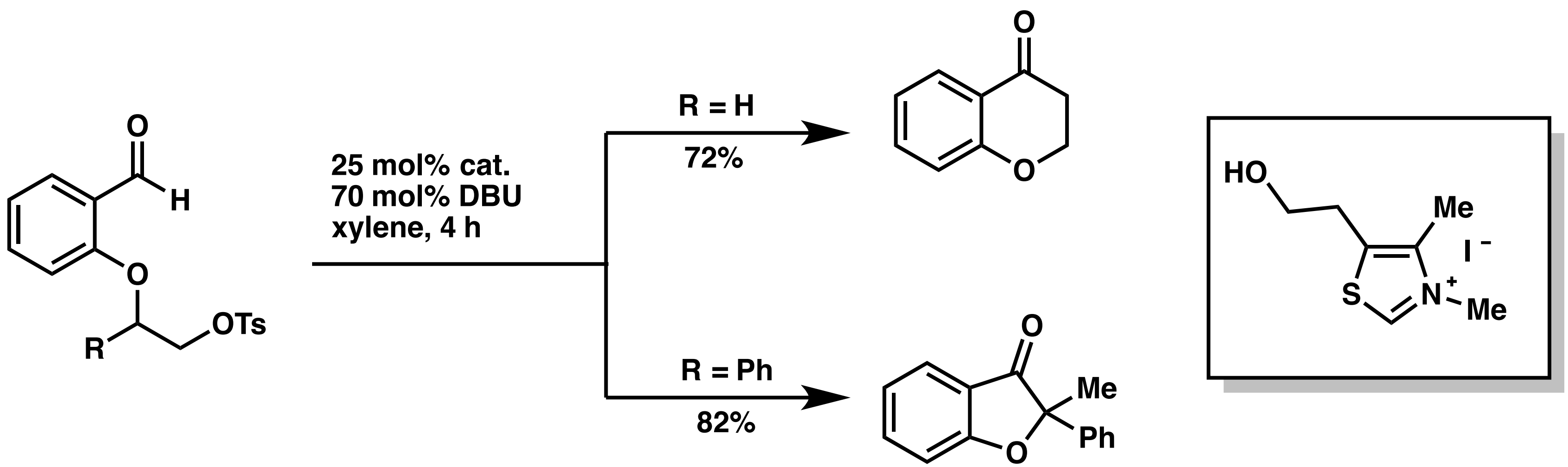


Hydroacylation



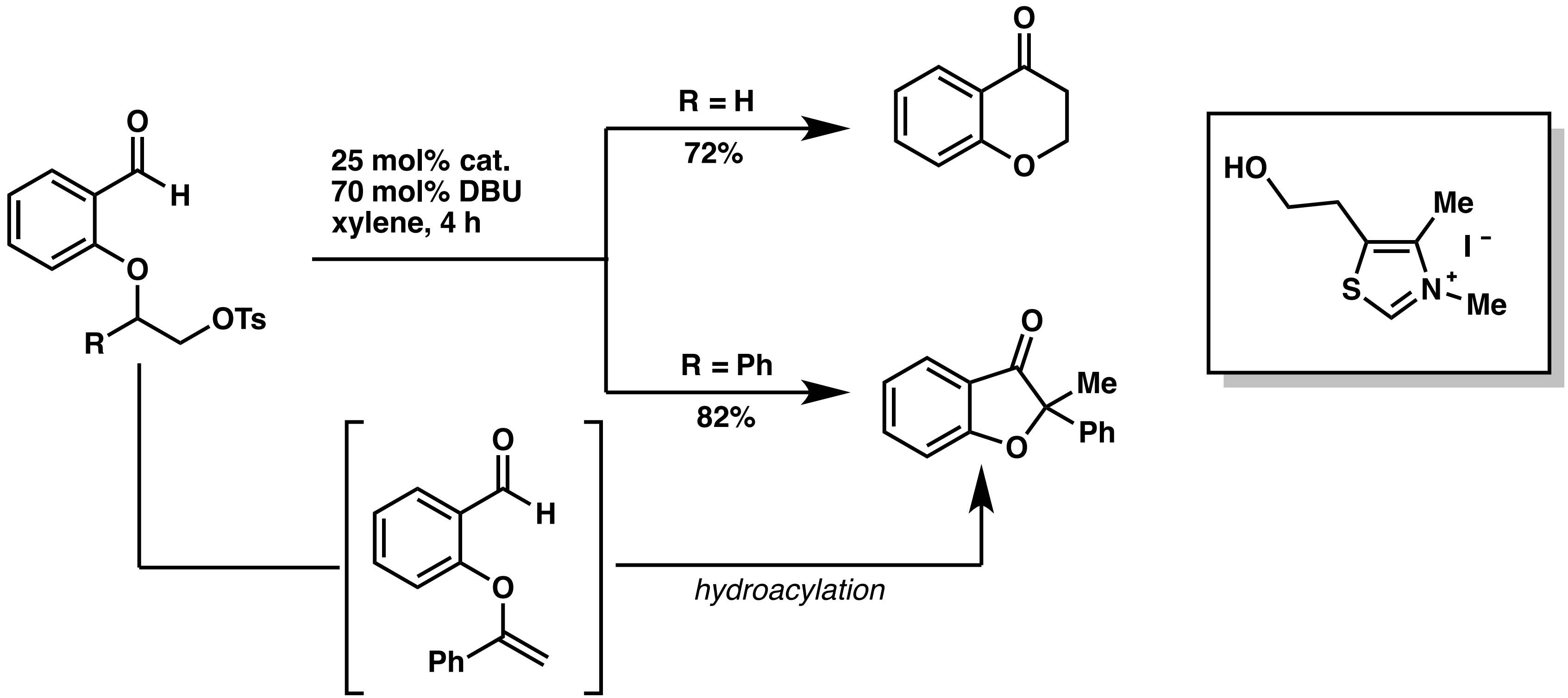
Hydroacylation

- **First hydroacylation precedent (She, 2008)**



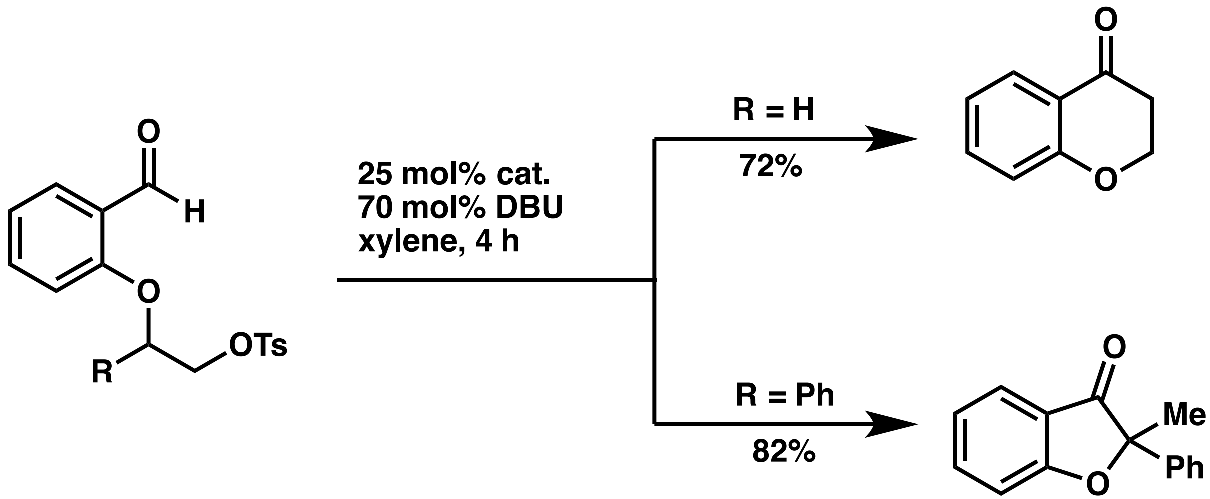
Hydroacylation

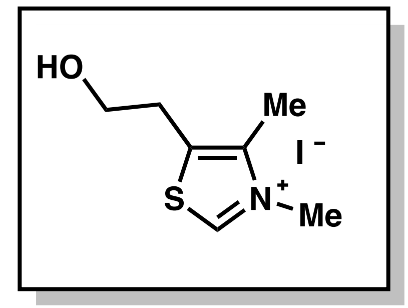
• **First hydroacylation precedent (She, 2008)**



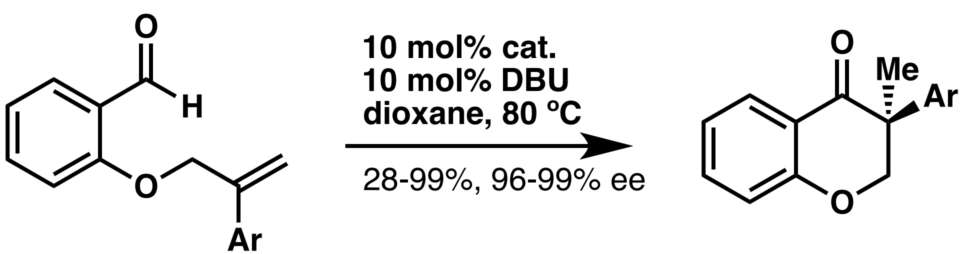
Hydroacylation

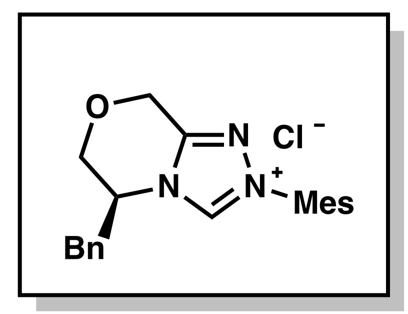
- **First hydroacylation precedent (She, 2008)**





- **Asymmetric intramolecular hydroacylation (Glorius, 2011)**

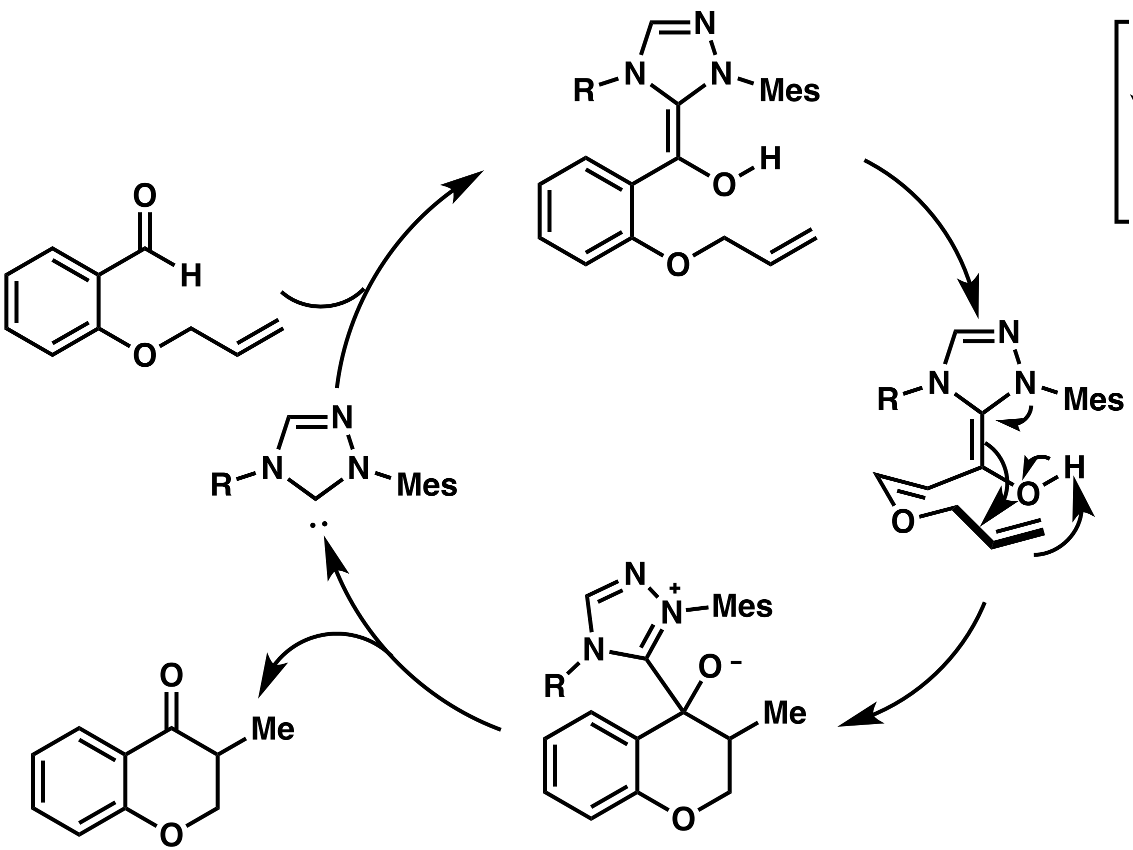


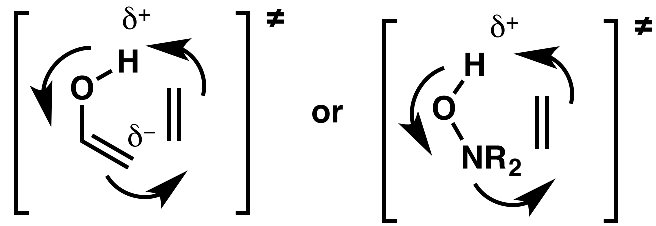


Glorius, F. *Angew. Chem. Int. Ed.* **2011**, 50, 4983
She, X. *Tetrahedron* **2008**, 64, 8797

Hydroacylation Mechanism

•**Concerted but highly asynchronous transition state (Glorius, Grimme)**

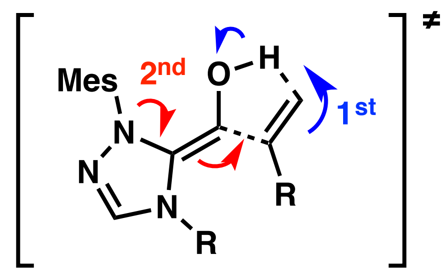




Conia-ene *Reverse-Cope elimination*

concerted mechanisms

vs.

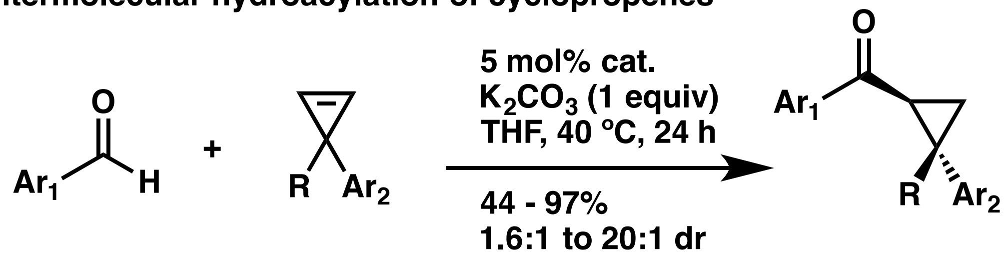


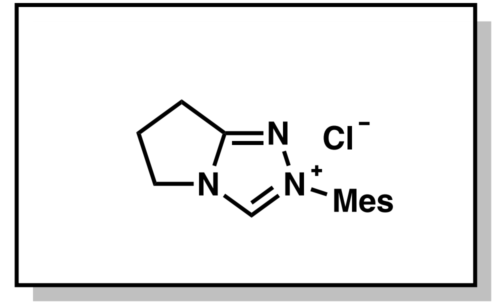
concerted but asynchronous mechanism
(Computation)

Glorius, F. *J. Am. Chem. Soc.* **2009**, 131, 14190.
Glorius, F. *Angew. Chem. Int. Ed.* **2011**, 50, 4983

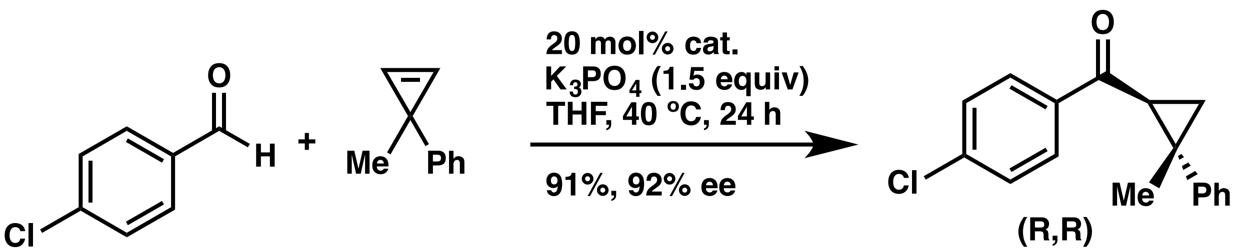
Intermolecular Hydroacylation

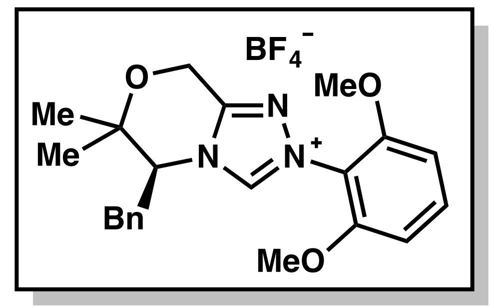
• **Intermolecular hydroacylation of cyclopropenes**





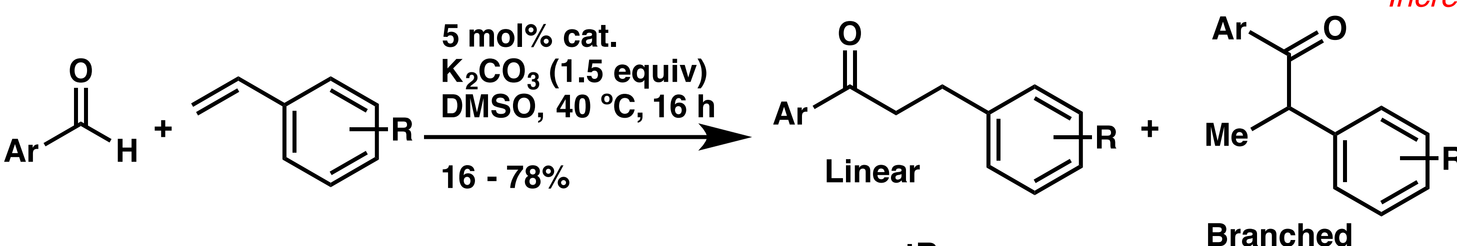
• **Asymmetric intramolecular hydroacylation**

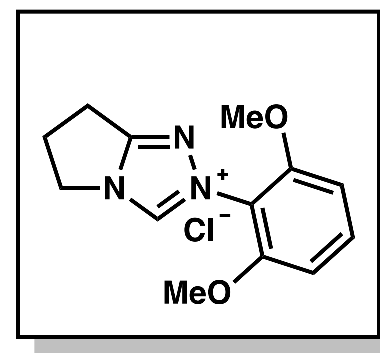


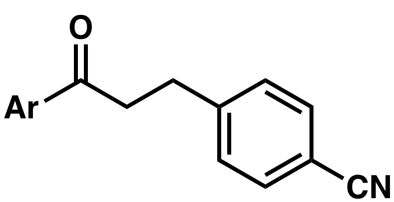


• **Intermolecular hydroacylation of styrenes**

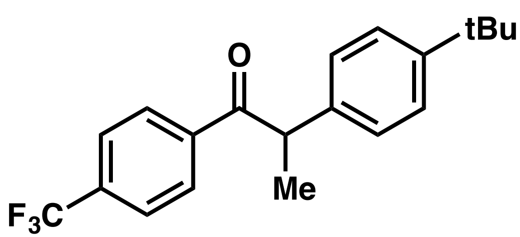
Increased reactivity with OMe







49% yield
L:B = > 20:1

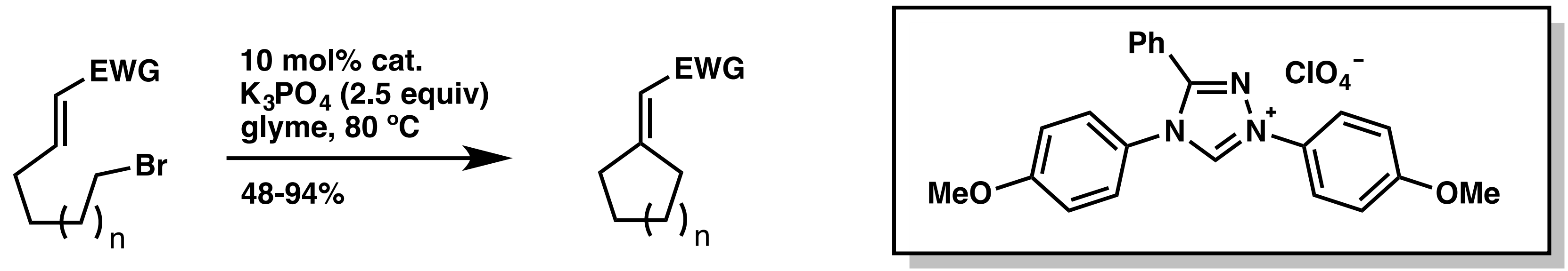


39% yield
L:B = < 1:20

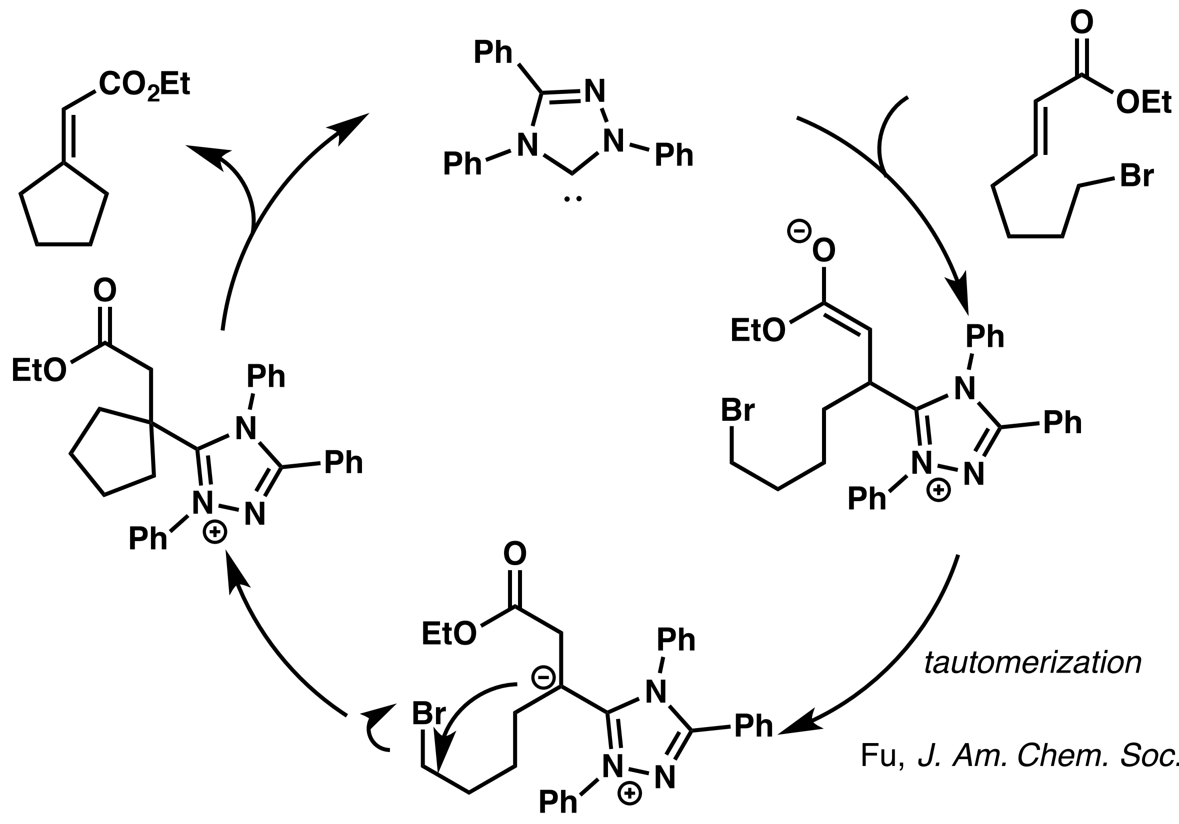
Glorius, *Angew. Chem., Int. Ed.* **2010**, 49, 9761-9764.
Glorius, *Angew. Chem., Int. Ed.* **2011**, 50, 12626-12630.
Glorius, *Angew. Chem., Int. Ed.* **2013**, 52, 2585-2589.

Umpolung of Michael Acceptor

· **Heck-type cyclization (Fu, 2006):**

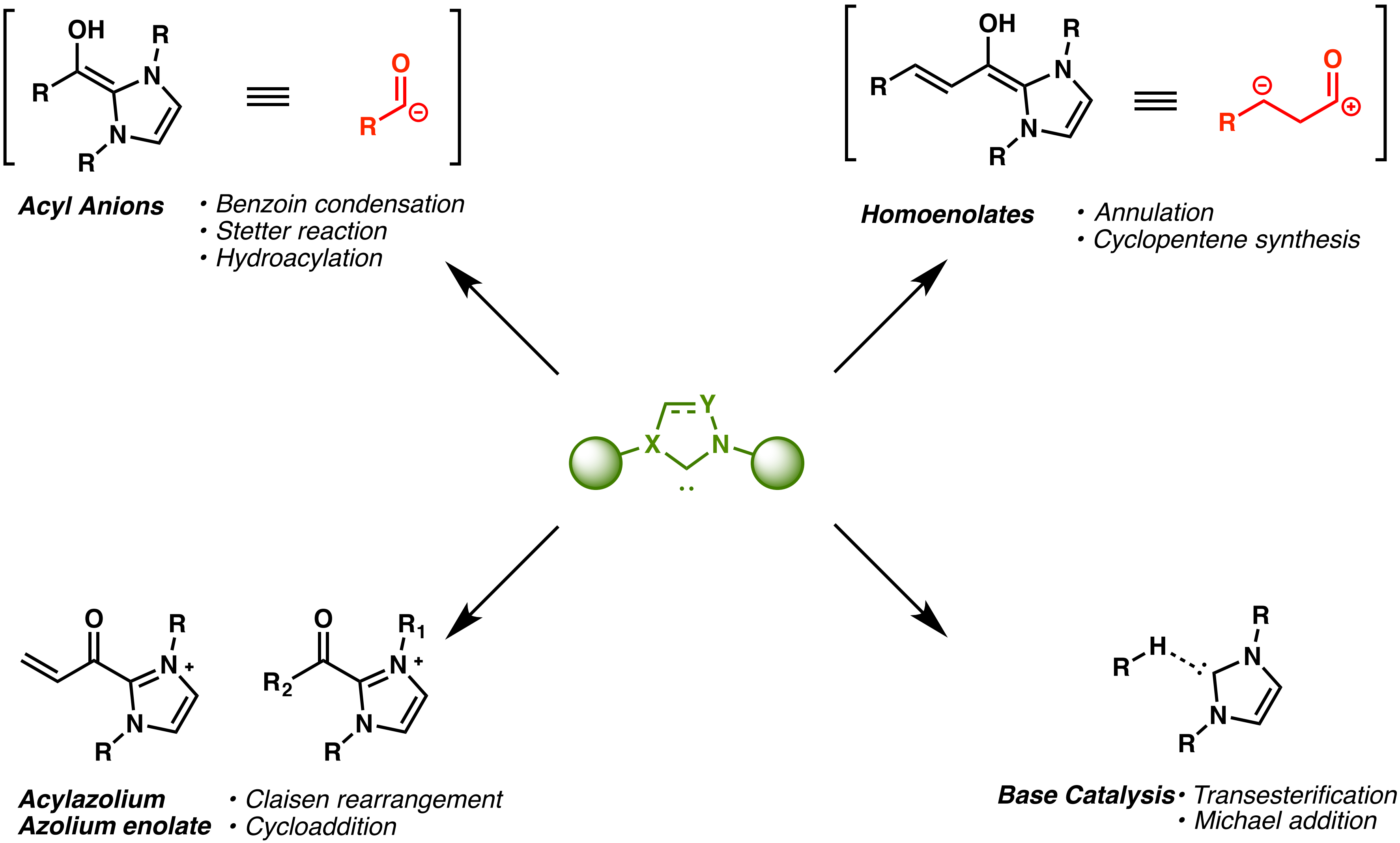


EWG = CO_2Et, CO_2allyl, $CO_2N(Me)OMe$, CN
n = 1,2



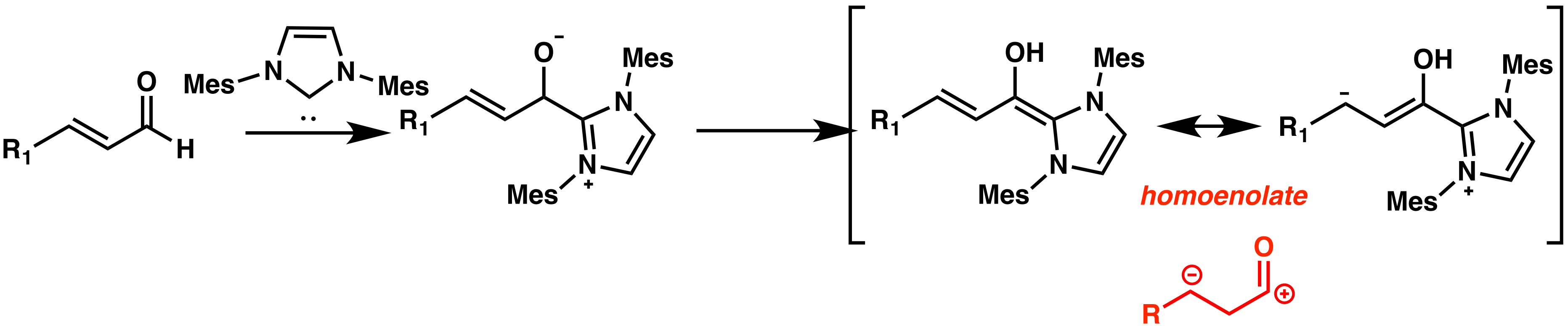
Fu, *J. Am. Chem. Soc.*, **2006**, 128,1472–1473

Overview

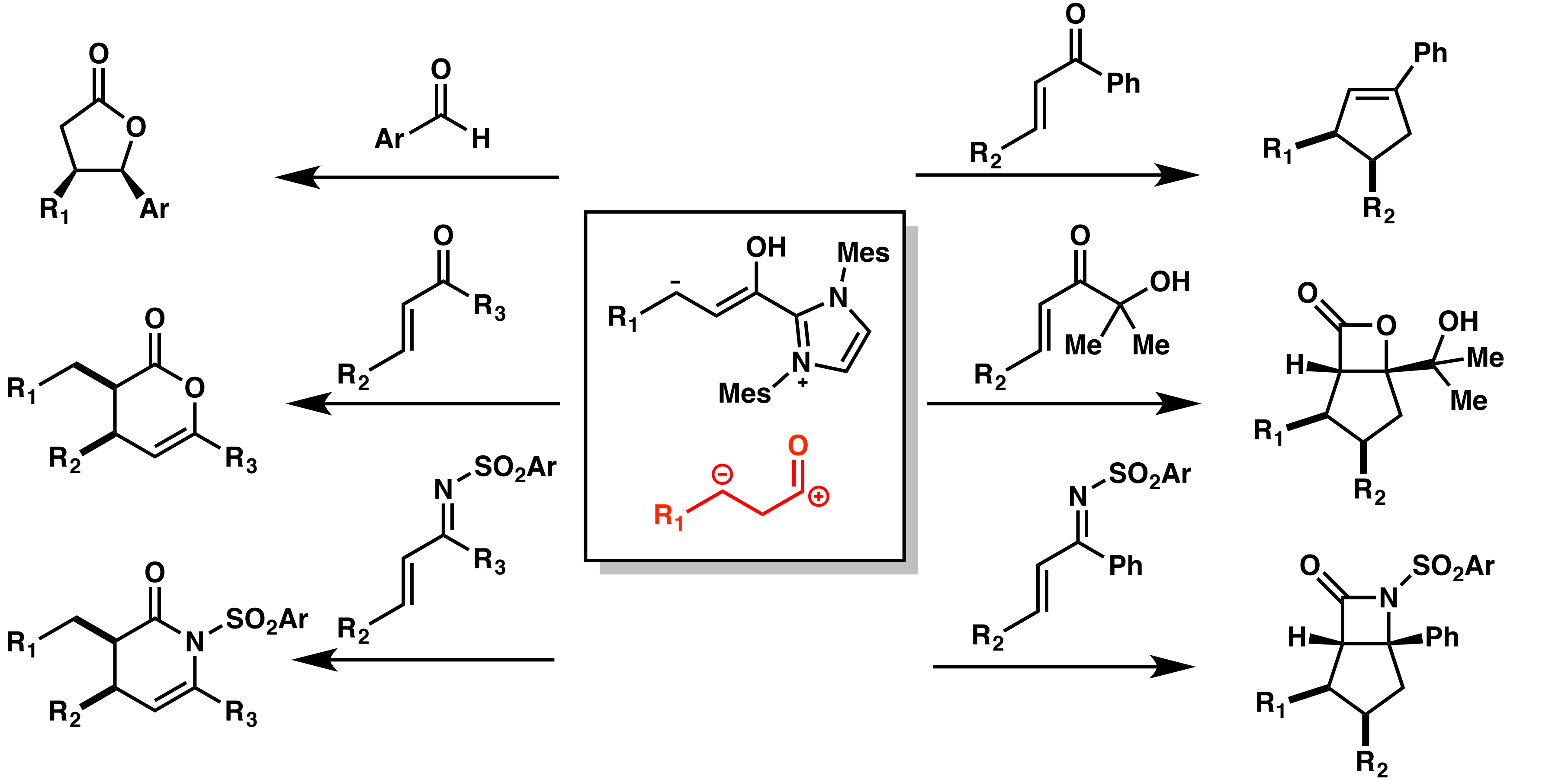


OH
R
N
N
R
O
R
Acyl Anions
• Benzoin condensation
• Stetter reaction
• Hydroacylation
OH
R
N
N
R
O
R
Homoenolates
• Annulation
• Cyclopentene synthesis
Y
X
N
O
R
N+
N
R
O
R1
R2
N+
N
R
Acylazolium
Azolium enolate
• Claisen rearrangement
• Cycloaddition
R
H
R
N
N
R
Base Catalysis
• Transesterification
• Michael addition

Generation of Homoenolate

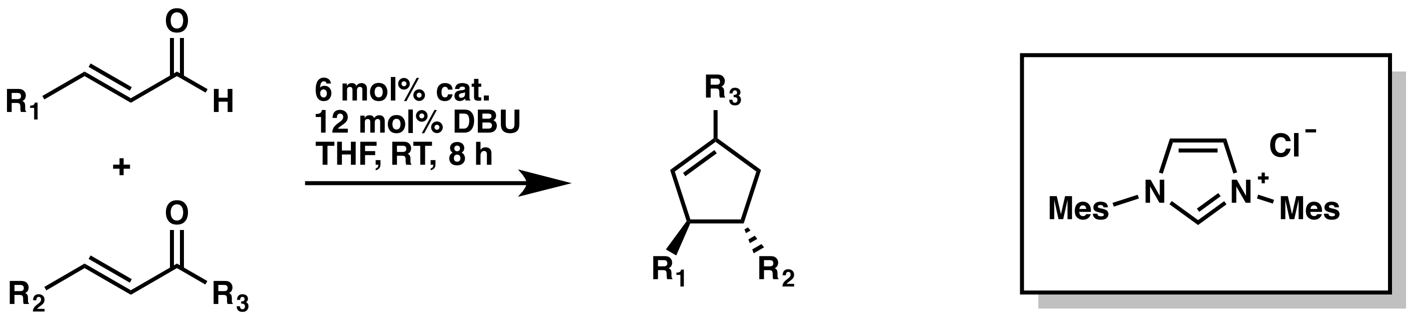


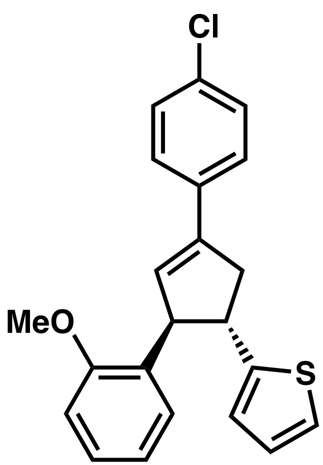
Annulation Reactions



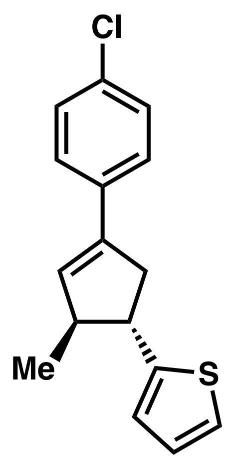
Cyclopentene Synthesis

• **1,3,4-trisubstituted Cyclopropene Synthesis by NHC (Nair, 2006)**

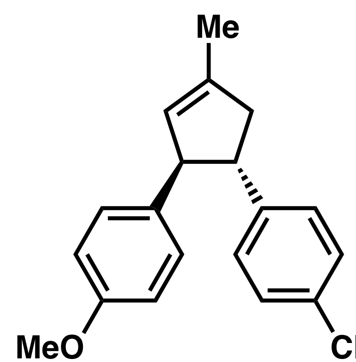




88% yield
> 20:1 dr



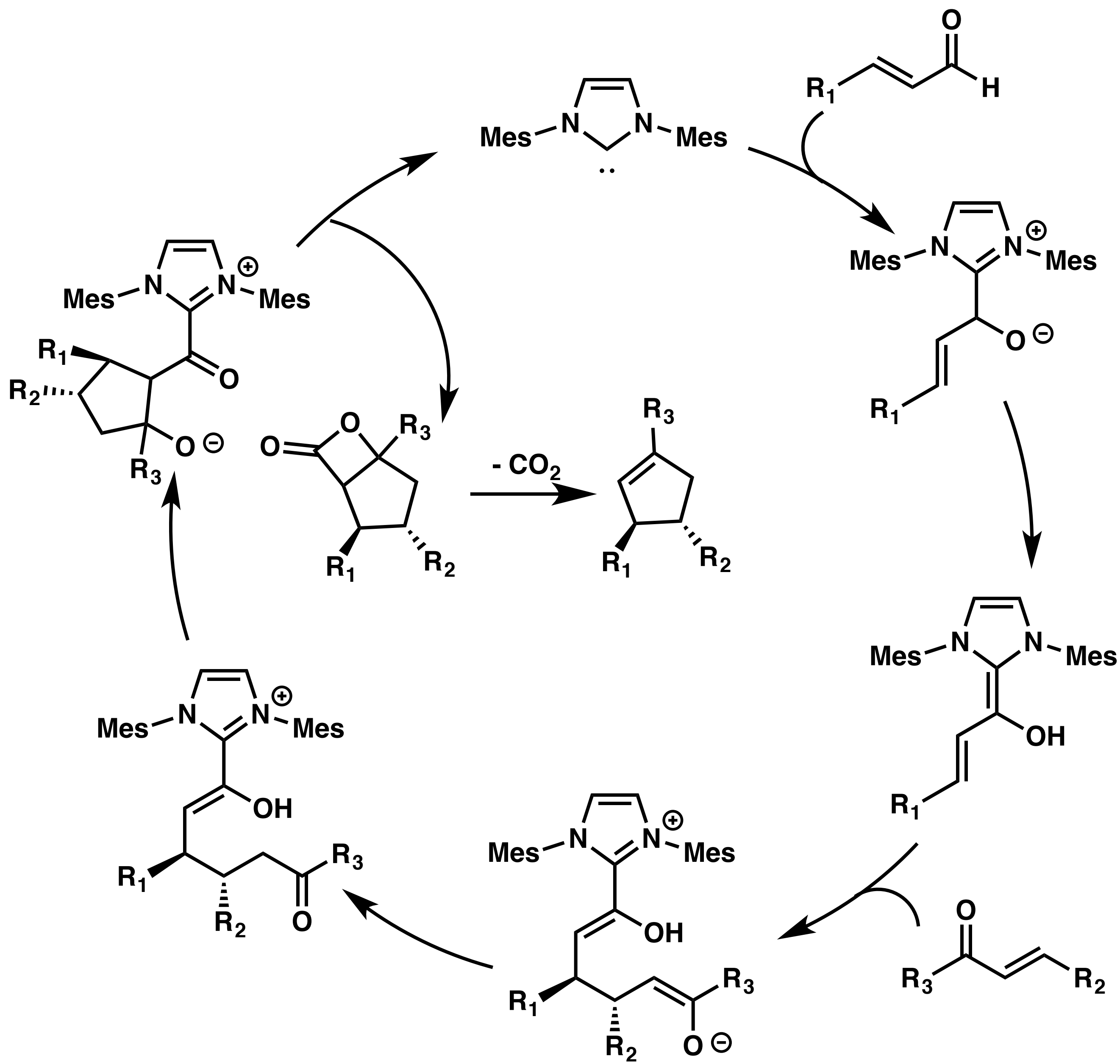
73% yield
> 20:1 dr



55% yield
> 20:1 dr

Nair, *J. Am. Chem. Soc.* **2006**, 128, 8736-8737.

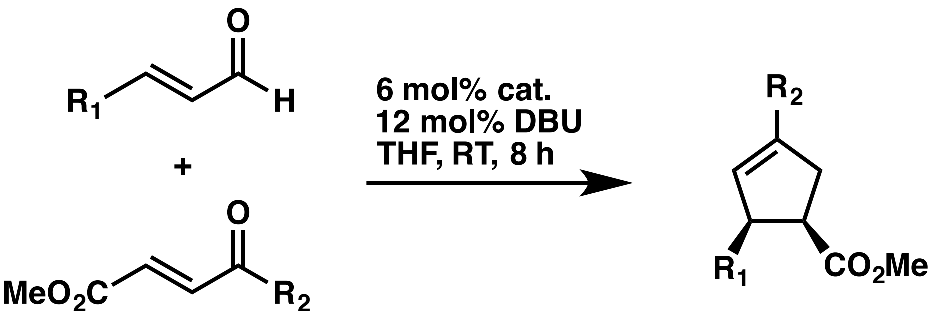
Mechanism

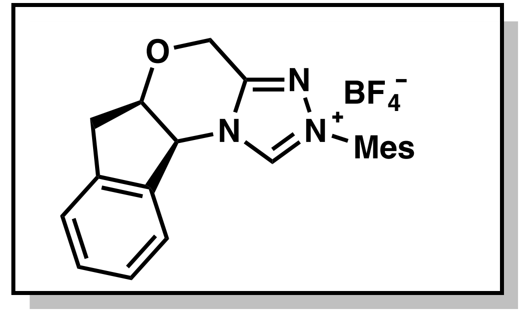


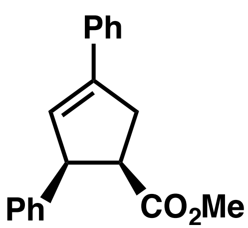
Mes
N
N
Mes
O
R1
H
Mes
N
N
Mes
O
R1
Mes
N
N
Mes
OH
R1
O
R3
R2
Mes
N
N
Mes
OH
R1
R2
R3
O
Mes
N
N
Mes
OH
R1
R2
O
R3
Mes
N
N
Mes
R1
R2
O
O
R3
O
O
R3
R1
R2
- CO2
R3
R1
R2

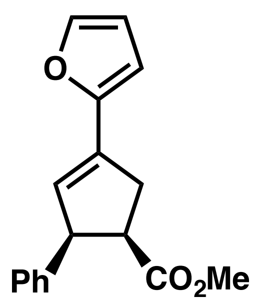
Cyclopentene Synthesis

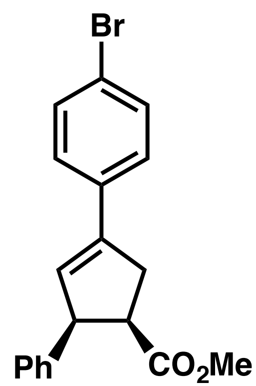
- **Enantioselective Synthesis Cyclopropene by NHC (Bode, 2007)**

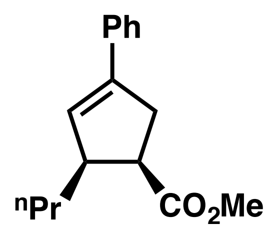












78% yield
11:1 dr
99% ee

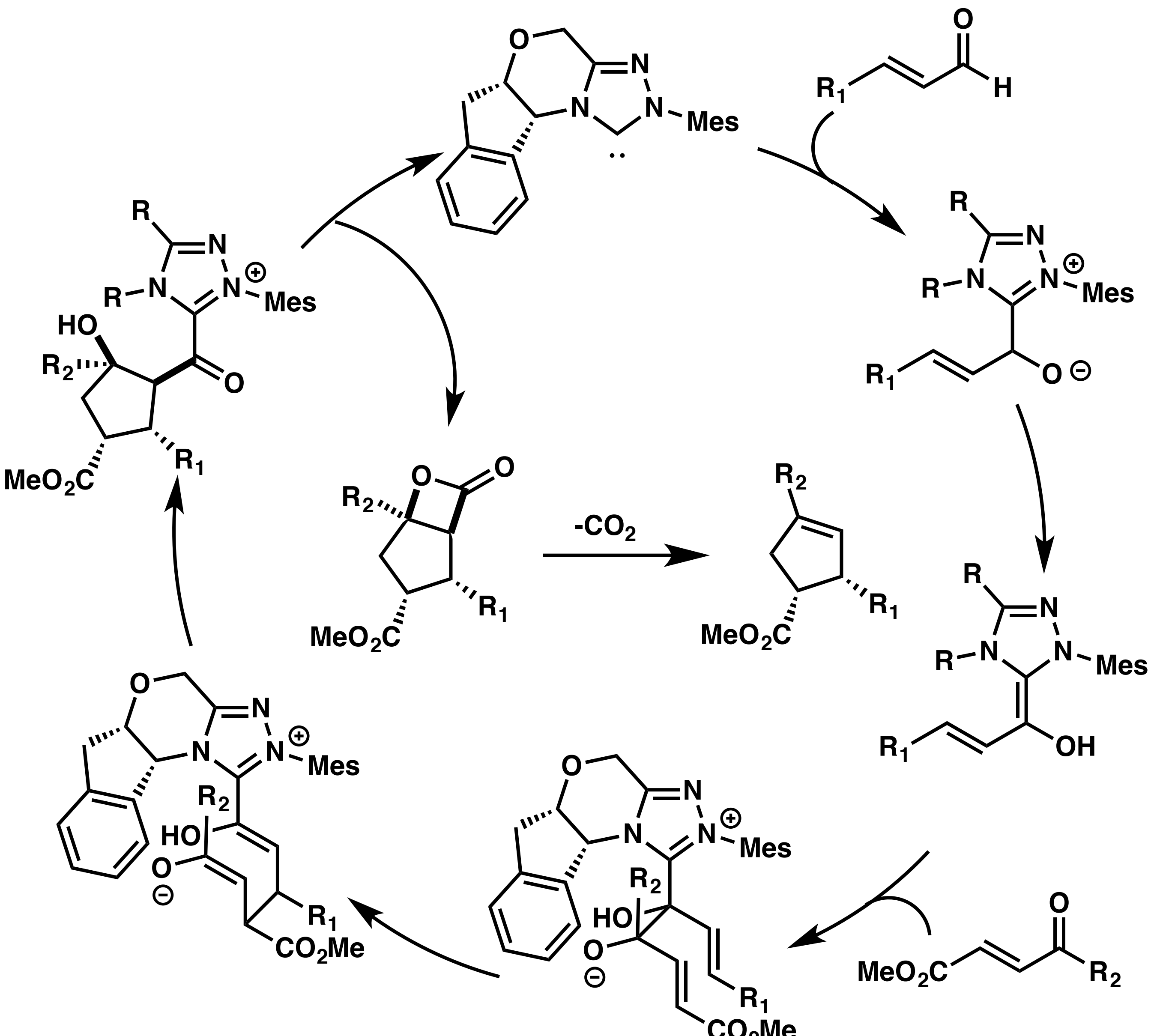
93% yield
>20:1 dr
98% ee

50% yield
11:1 dr
99% ee

25% yield
14:1 dr
96% ee

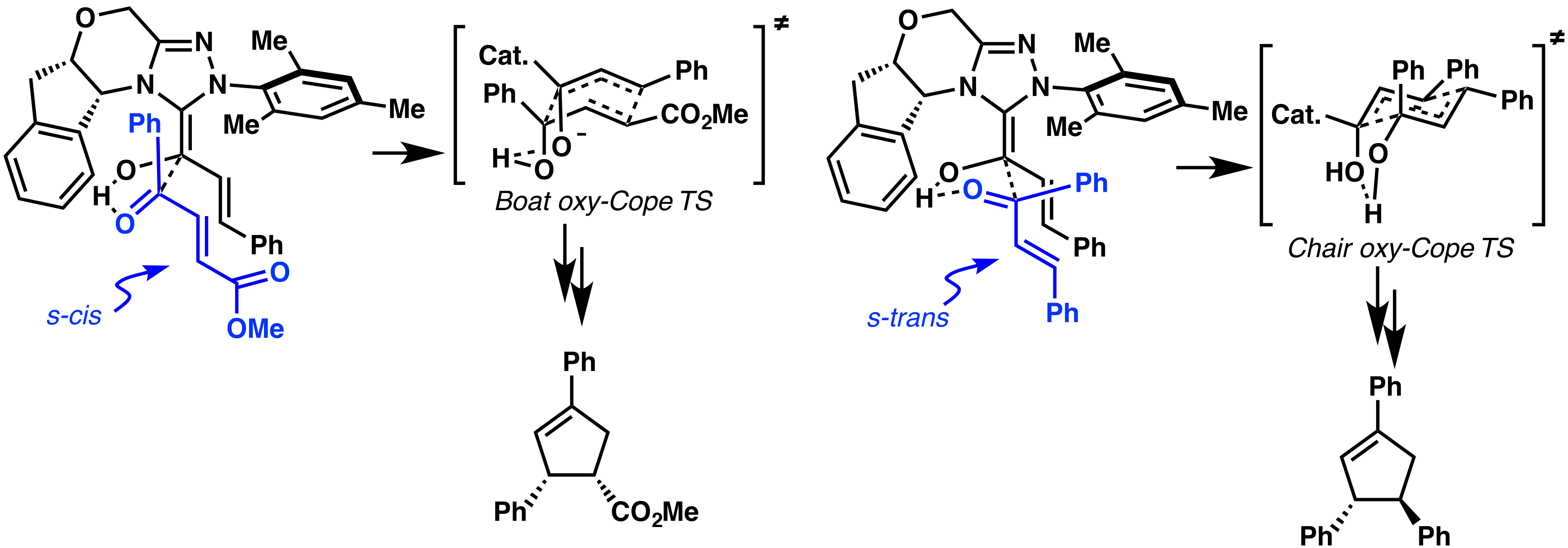
Bode, *J. Am. Chem. Soc.* **2007**, 129, 3520-3521

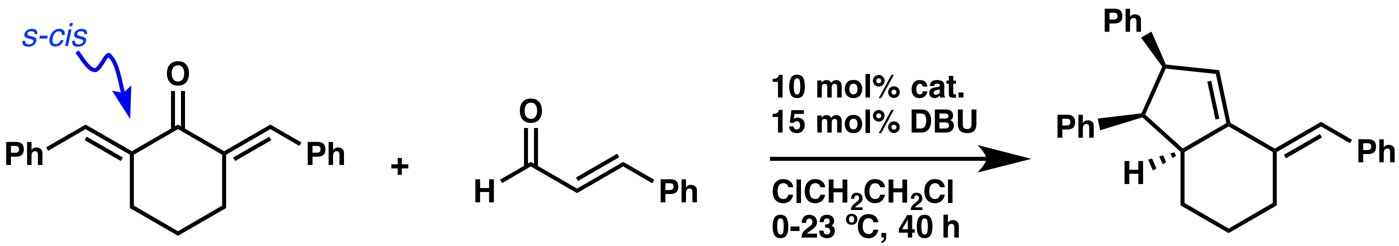
Mechanism



Mechanism

- **Origin of *cis/trans* stereoselectivity**

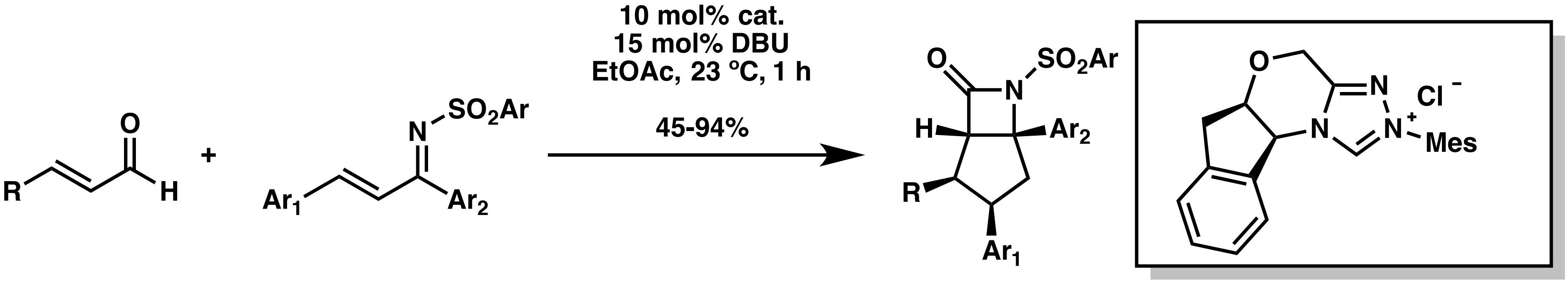


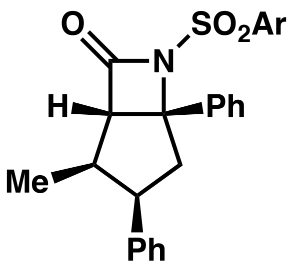


> 20:1 dr (72% ee)

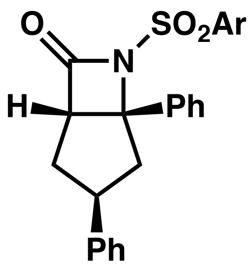
β-lactam Formation

- **Scope of β-lactam formation**

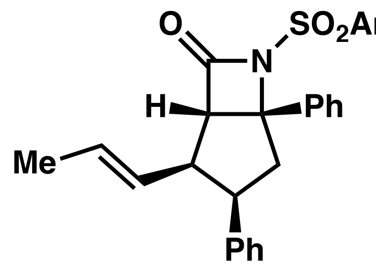




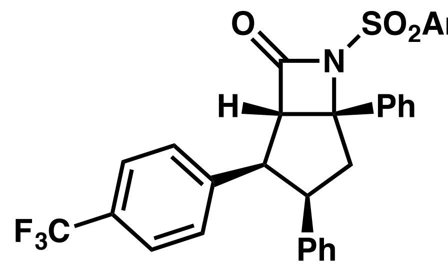
94% yield
>20:1 dr
99% ee



45% yield
>20:1 dr
98% ee



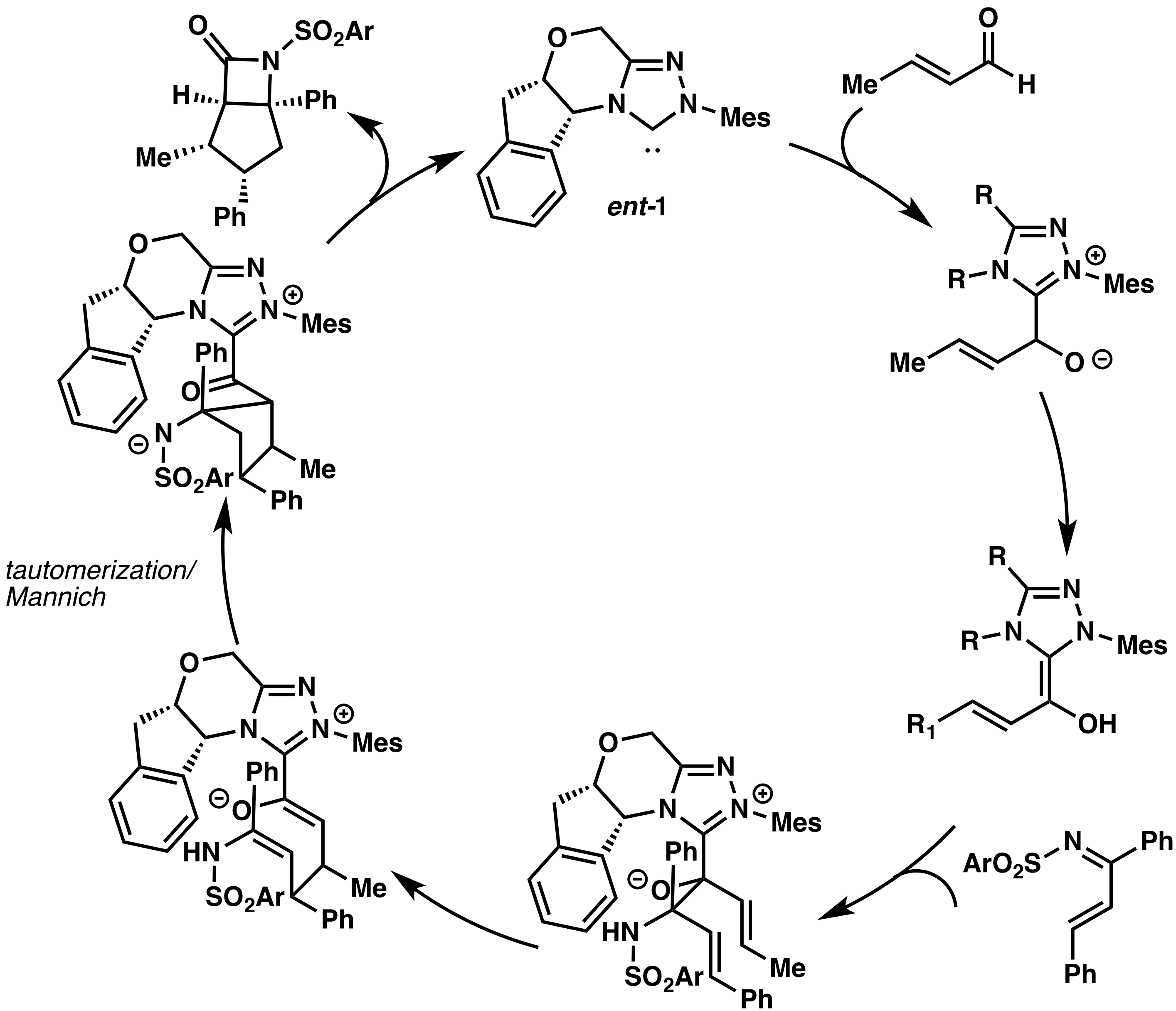
76% yield
5:1 dr
99% ee



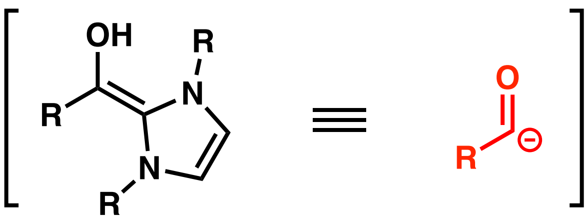
72% yield
>20:1 dr
88% ee

Bode, *J. Am. Chem. Soc.* **2008**, 130, 418-419

Aza-Benzoin-Oxy-Cope Rearrangement Mechanism

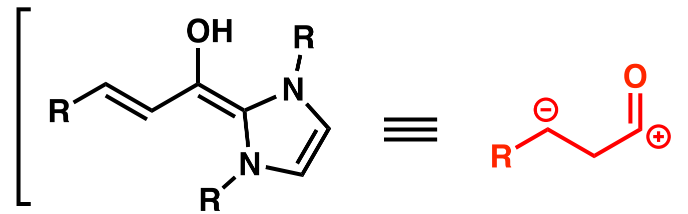


Overview



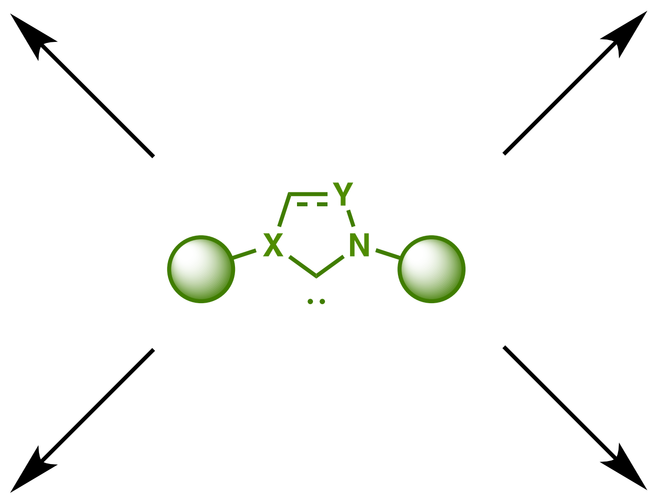
Acyl Anions

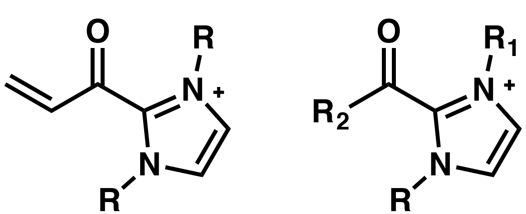
- *Benzoin condensation*
- *Stetter reaction*
- *Hydroacylation*



Homoenolates

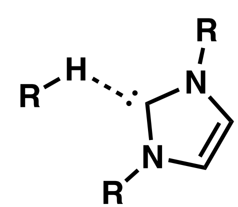
- *Annulation*
- *Cyclopentene synthesis*





Acylazolium
Azolium enolate

- *Claisen rearrangement*
- *Cycloaddition*

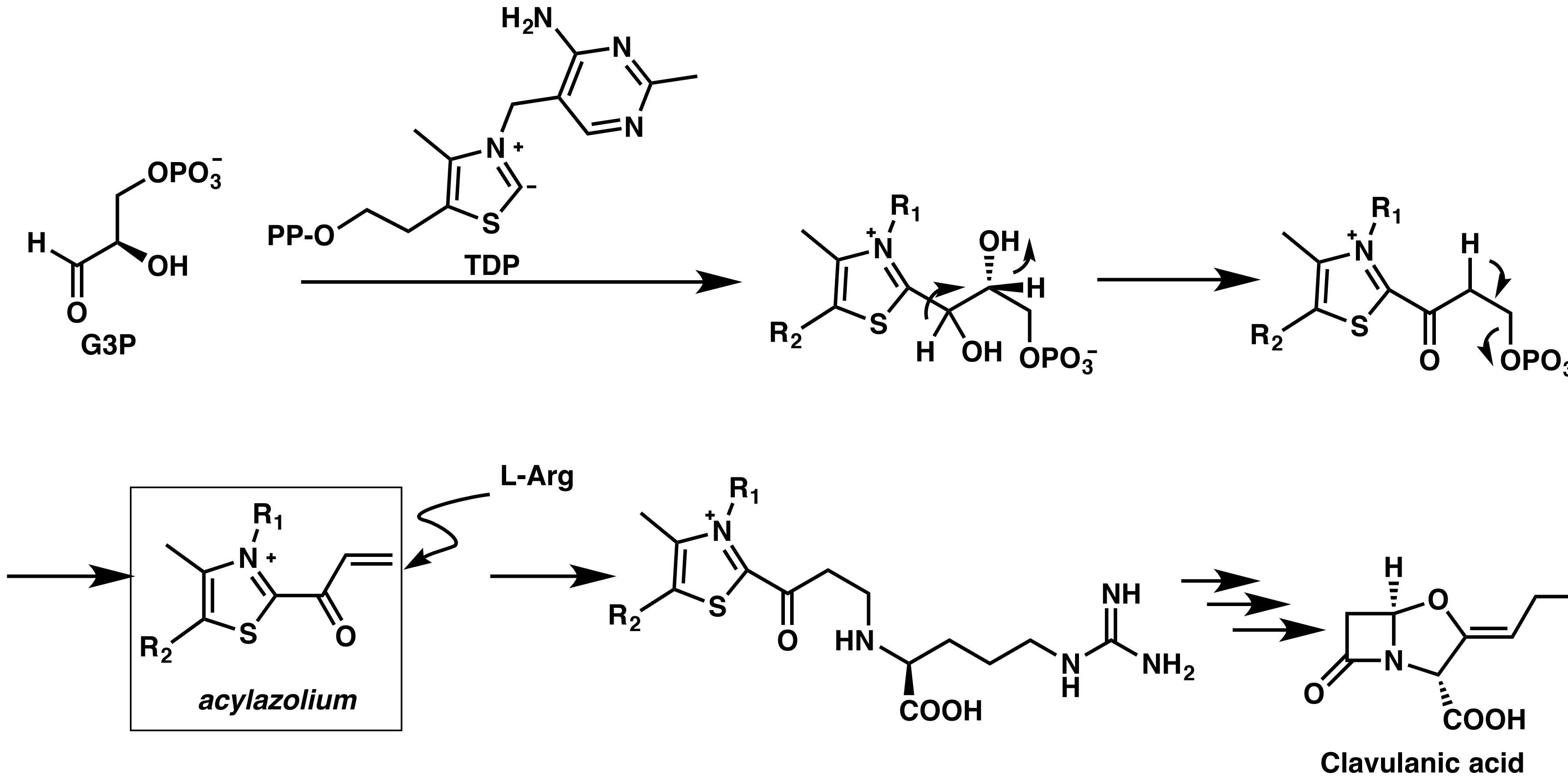


Base Catalysis

- *Transesterification*
- *Michael addition*

Biomimetic Origin of Acylazolium Reactivity

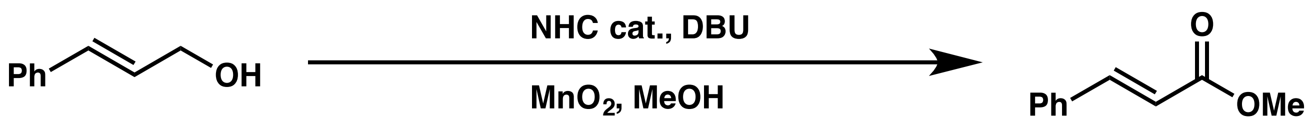
- **Clavulanic acid biosynthesis through acylazolium intermediate**



Townsend, *J. Am. Chem. Soc.* **1999**, 121, 9223-9224

Generation of Acylazolium

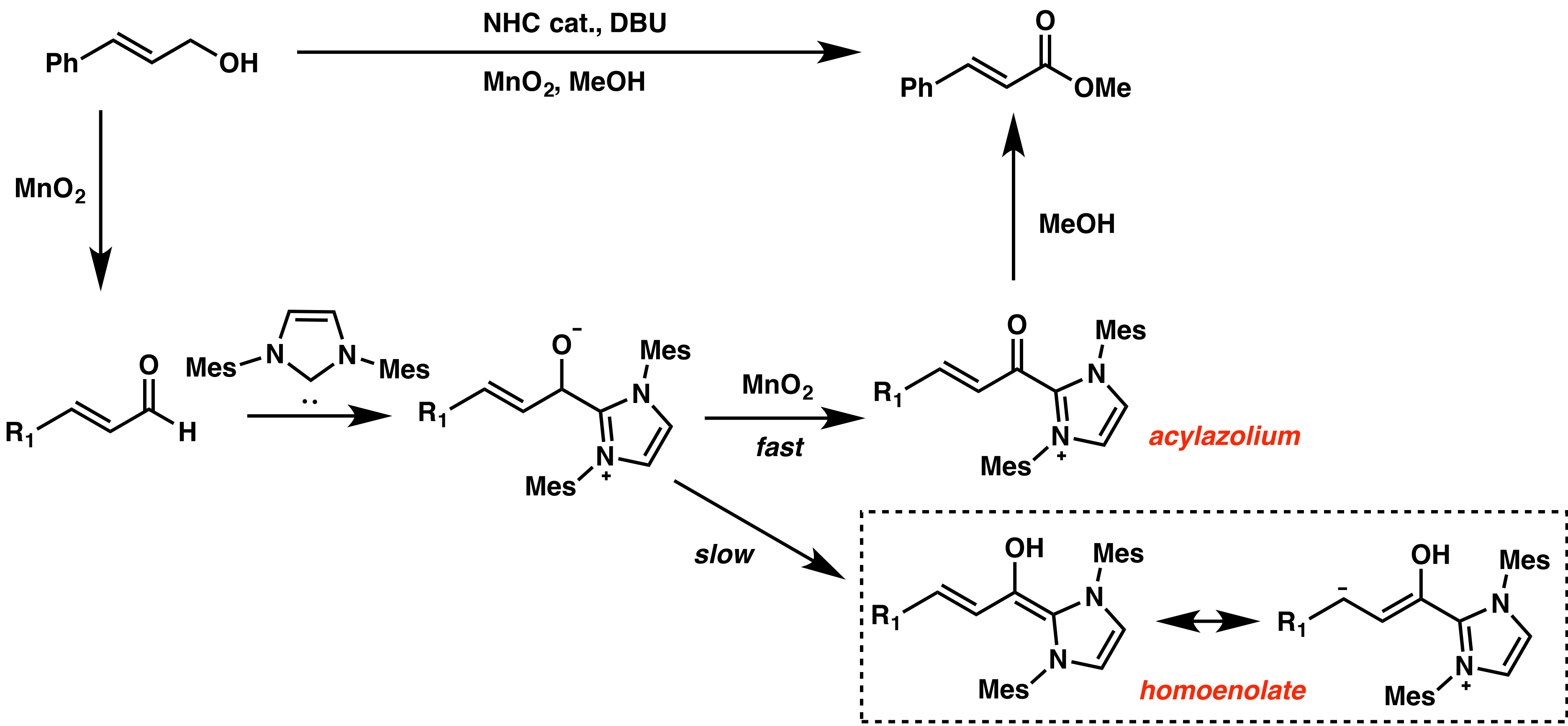
- **Genertion of acylazolium intermediate by MnO_2 oxidation (Scheidt, 2007)**



Scheidt, *Org. Lett.*, **2007**, 9, 371-374

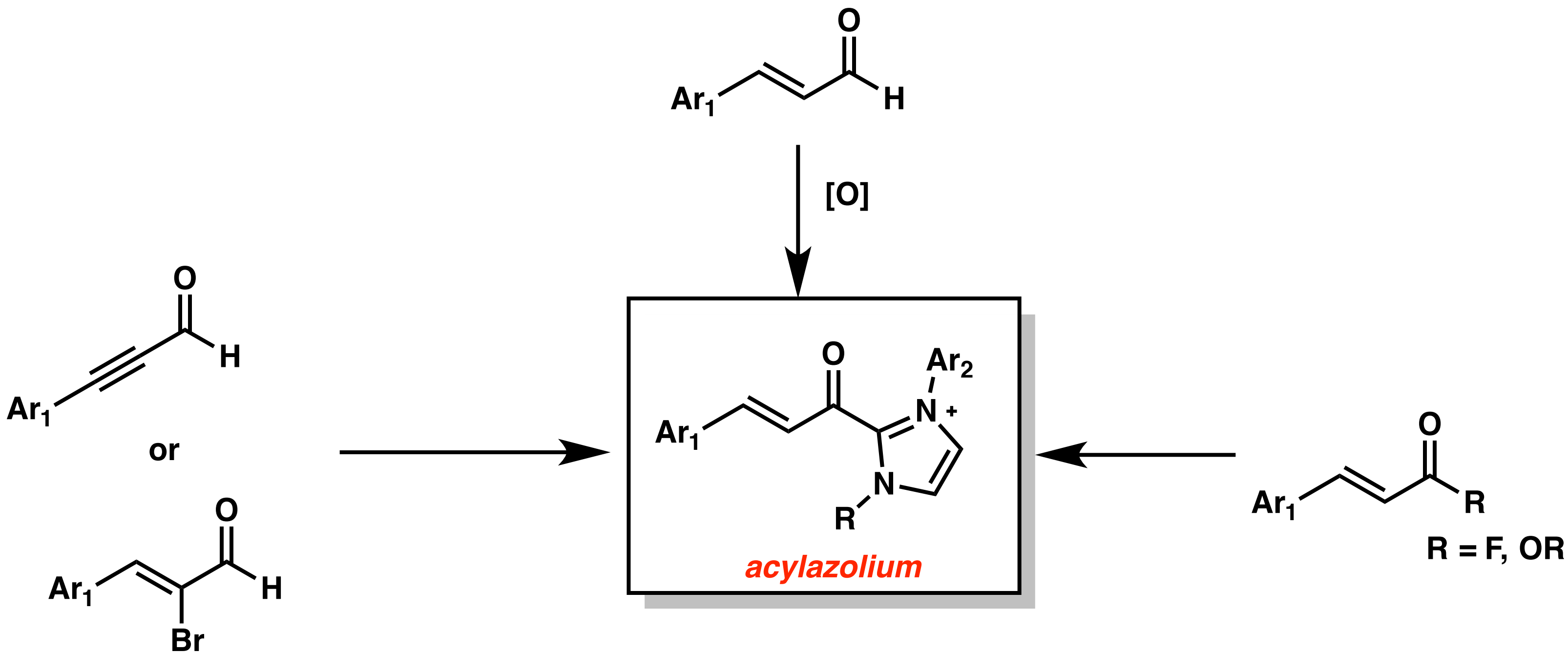
Generation of Acylazolium

- **Genertion of acylazolium intermediate by MnO_2 oxidation (Scheidt, 2007)**

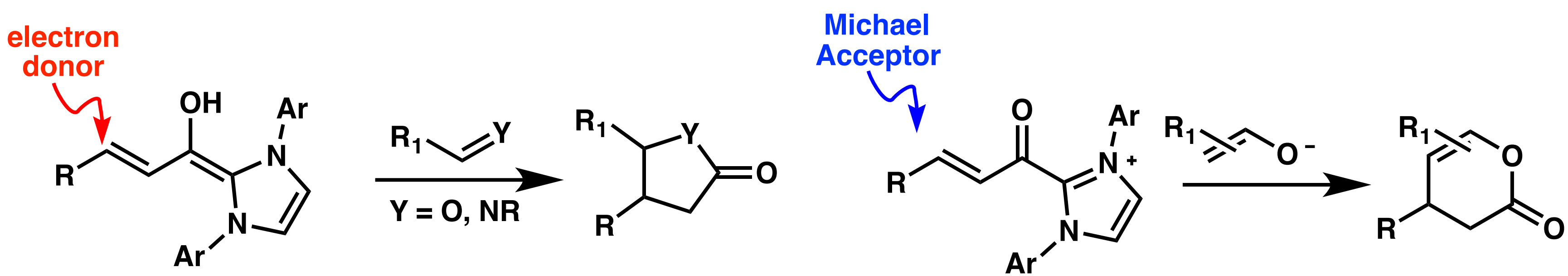


Scheidt, *Org. Lett.*, **2007**, 9, 371-374

Generation of Acylazolium

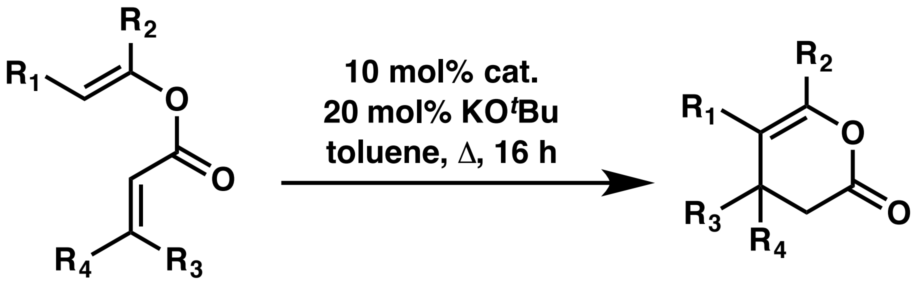


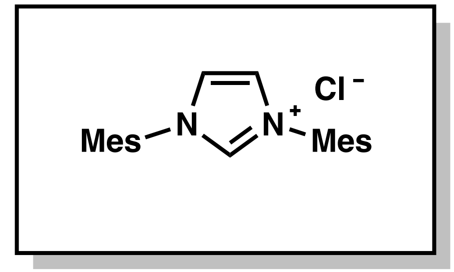
- comparison of homoenolate/acylazolium reactivity



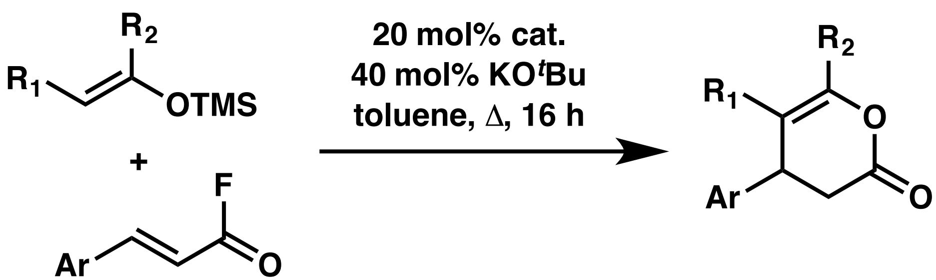
Dihydropyranone Synthesis Through Acylazolium

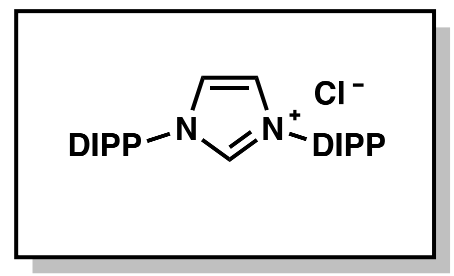
- **Intramolecular Rearrangement**





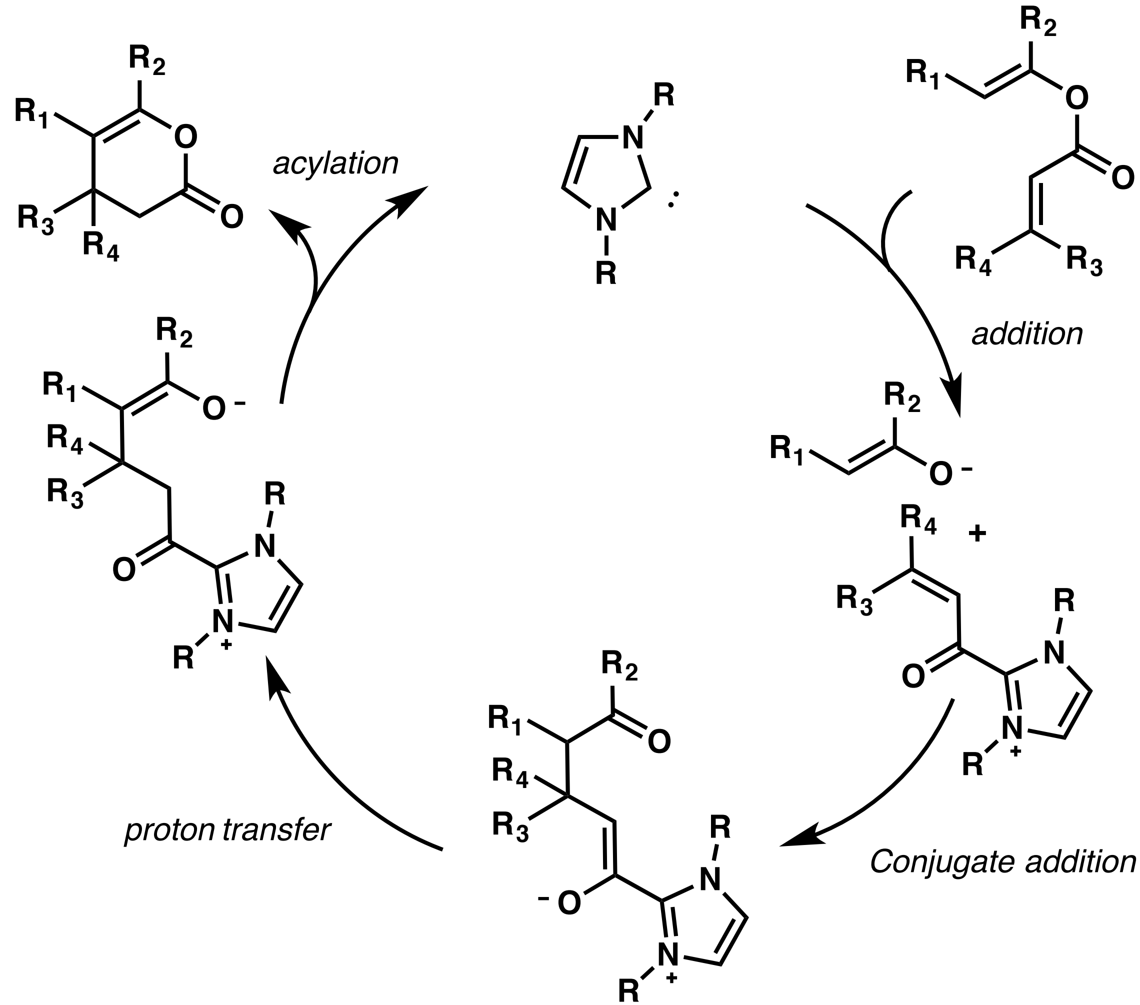
- **Intermolecular Reaction**





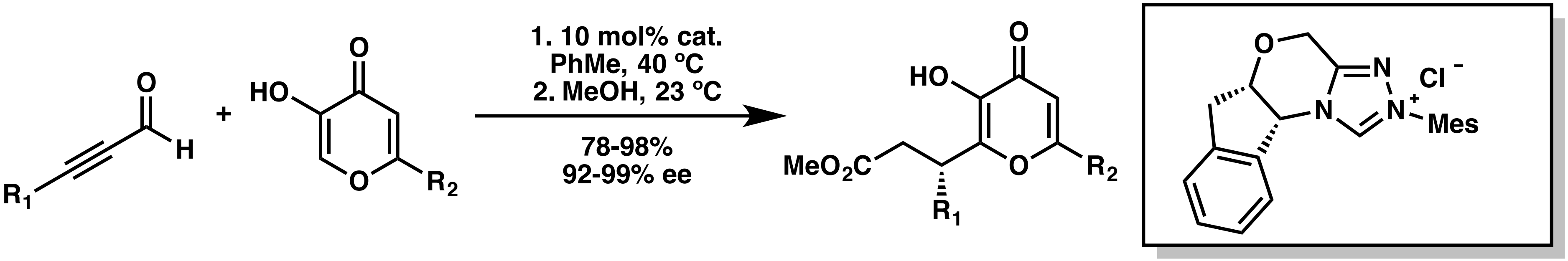
Lupton, *J. Am. Chem. Soc.* **2009**, 131, 14176-14177

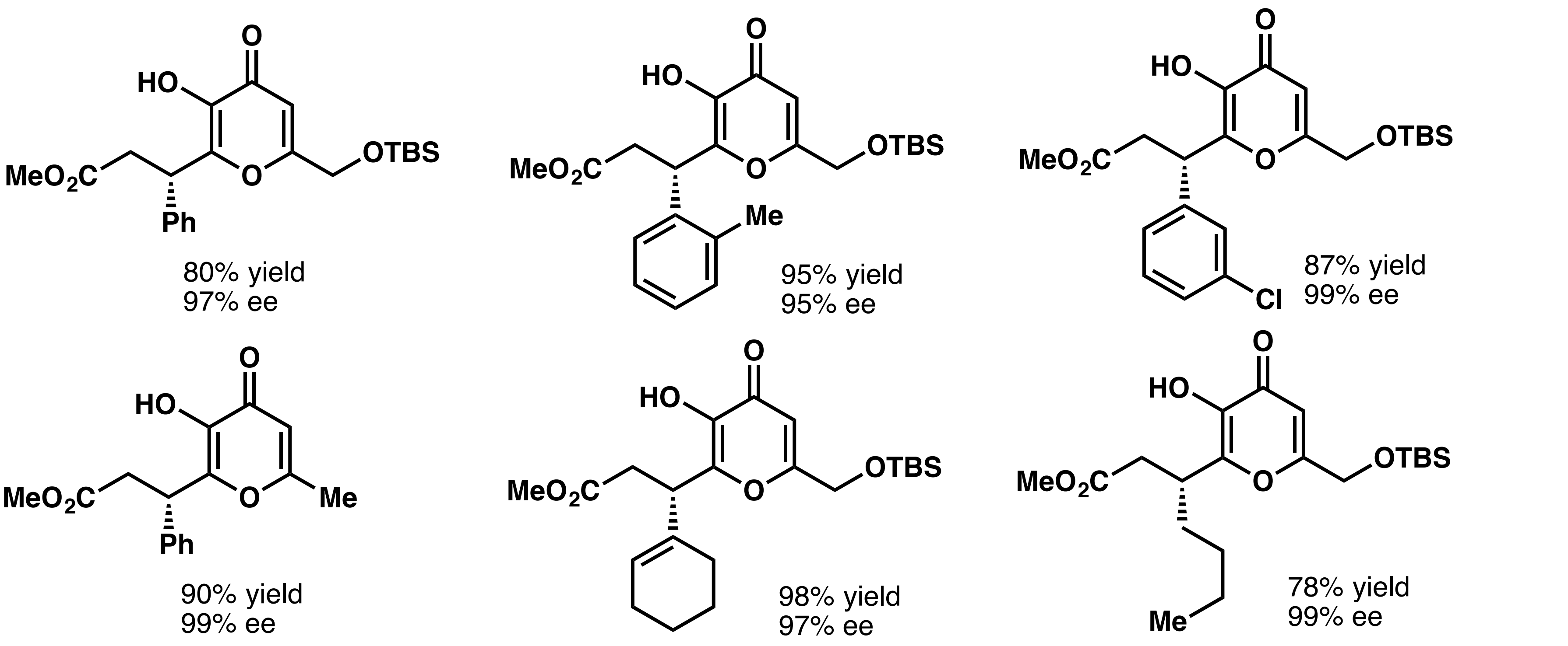
Mechanism



Enantioselective Coates-Claisen Rearrangement

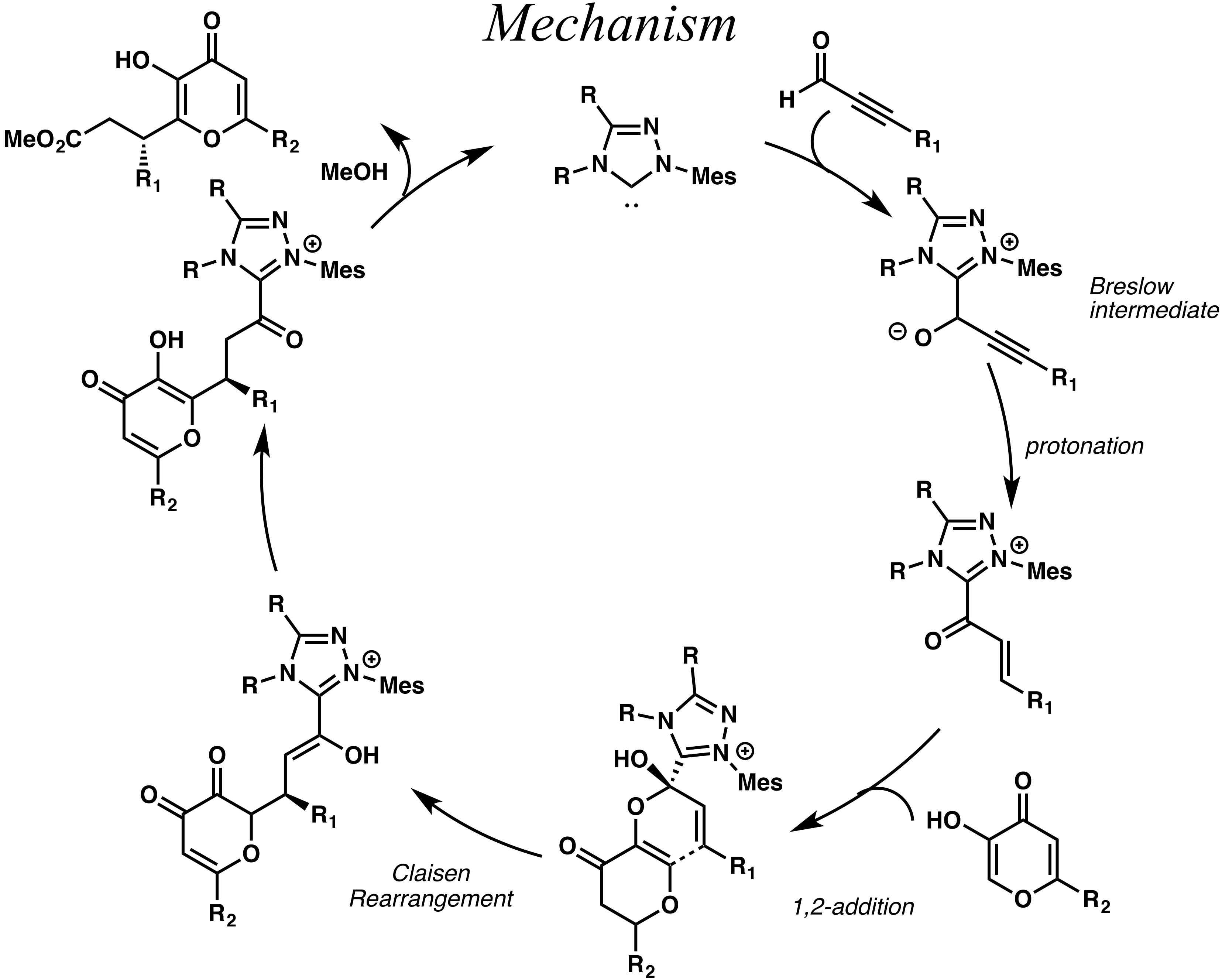
- **Catalytic, Enantioselective Couplings with Kojic Acids (Bode, 2010)**





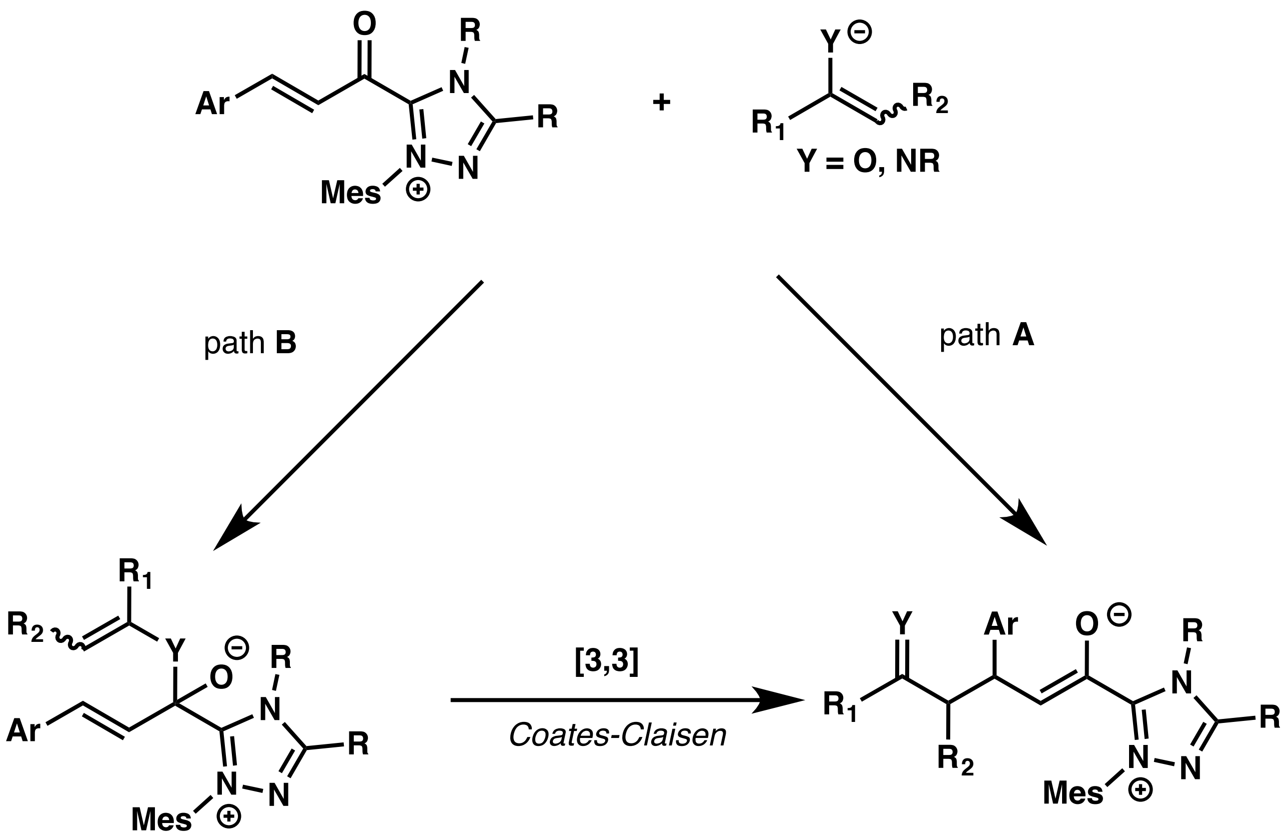
Bode, *J. Am. Chem. Soc.* **2010**, 132, 8810-8812

Mechanism



Breslow intermediate
protonation
1,2-addition
Claisen Rearrangement
MeOH

Mechanistic Dichotomy

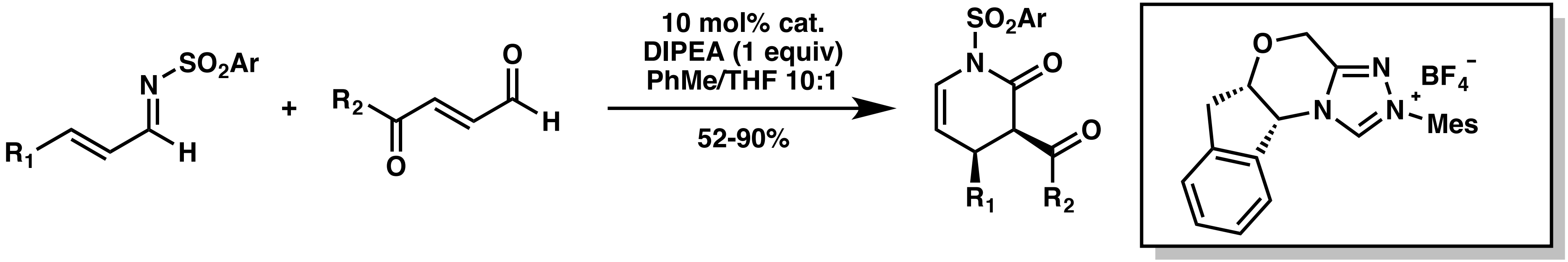


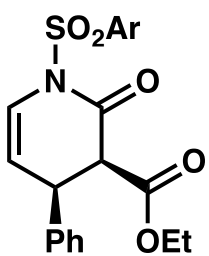
Schoenebeck, Bode
(loose ion pair)

Mayr, Studer
(contact ion pair)

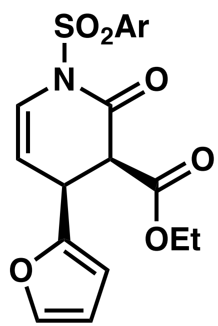
Mayr, *Angew. Chem., Int. Ed*. **2012**, 51, 5234-5238
Schoenebeck, *Chem. Sci*. **2012**, 3, 2346-2350.

Enantioselective Hetero-Diels-Alder Reaction

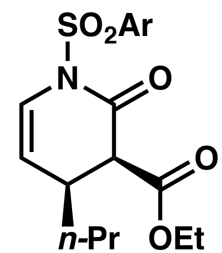




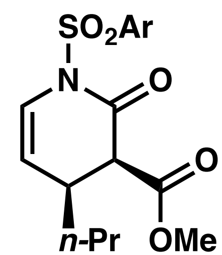
90% yield
99% ee



71% yield
99% ee



58% yield
99% ee

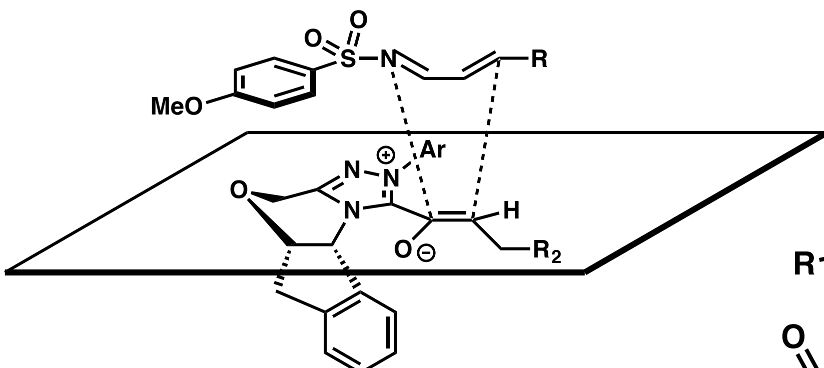


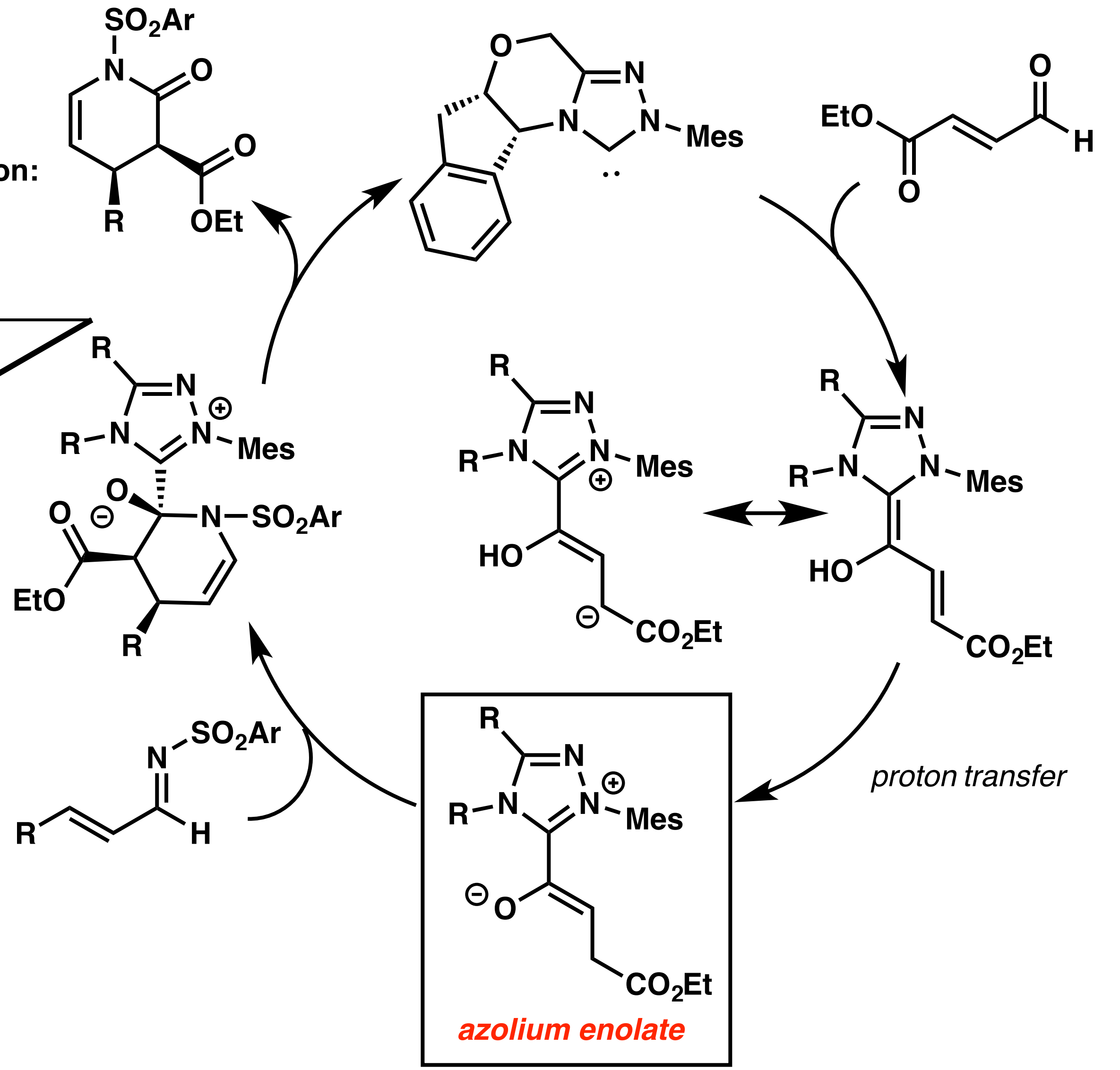
71% yield
99% ee

Bode, *J. Am. Chem. Soc.* **2006**, 128, 8418-8420

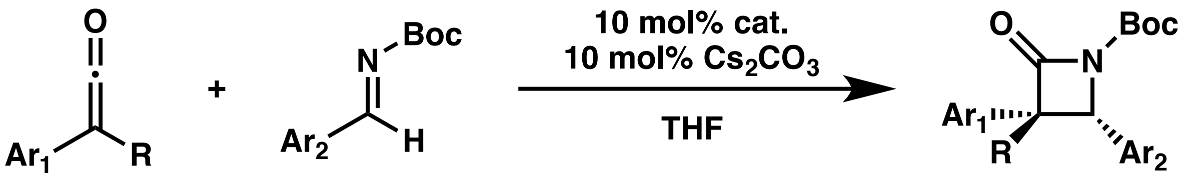
Enantioselective Hetero-Diels-Alder Reaction

Transition State of Azadiene Diels-Alder Reaction:

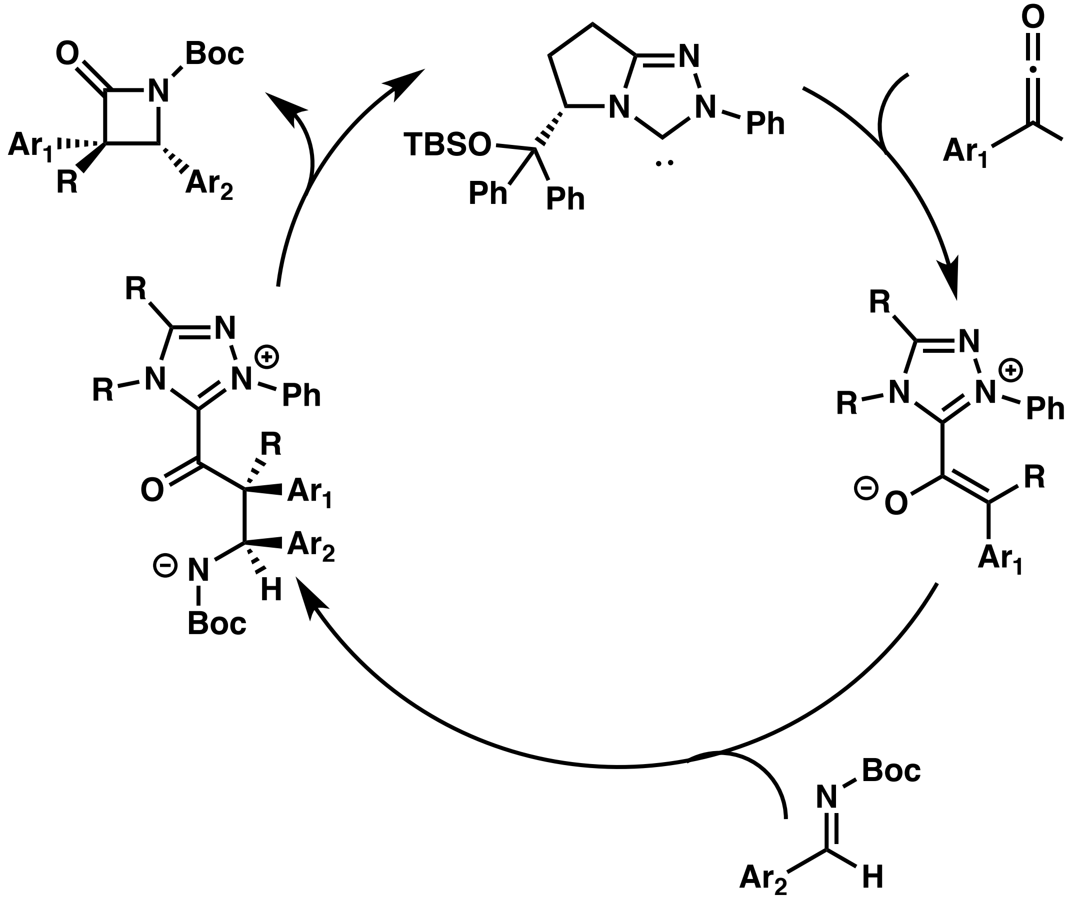




Ketene Cycloaddition



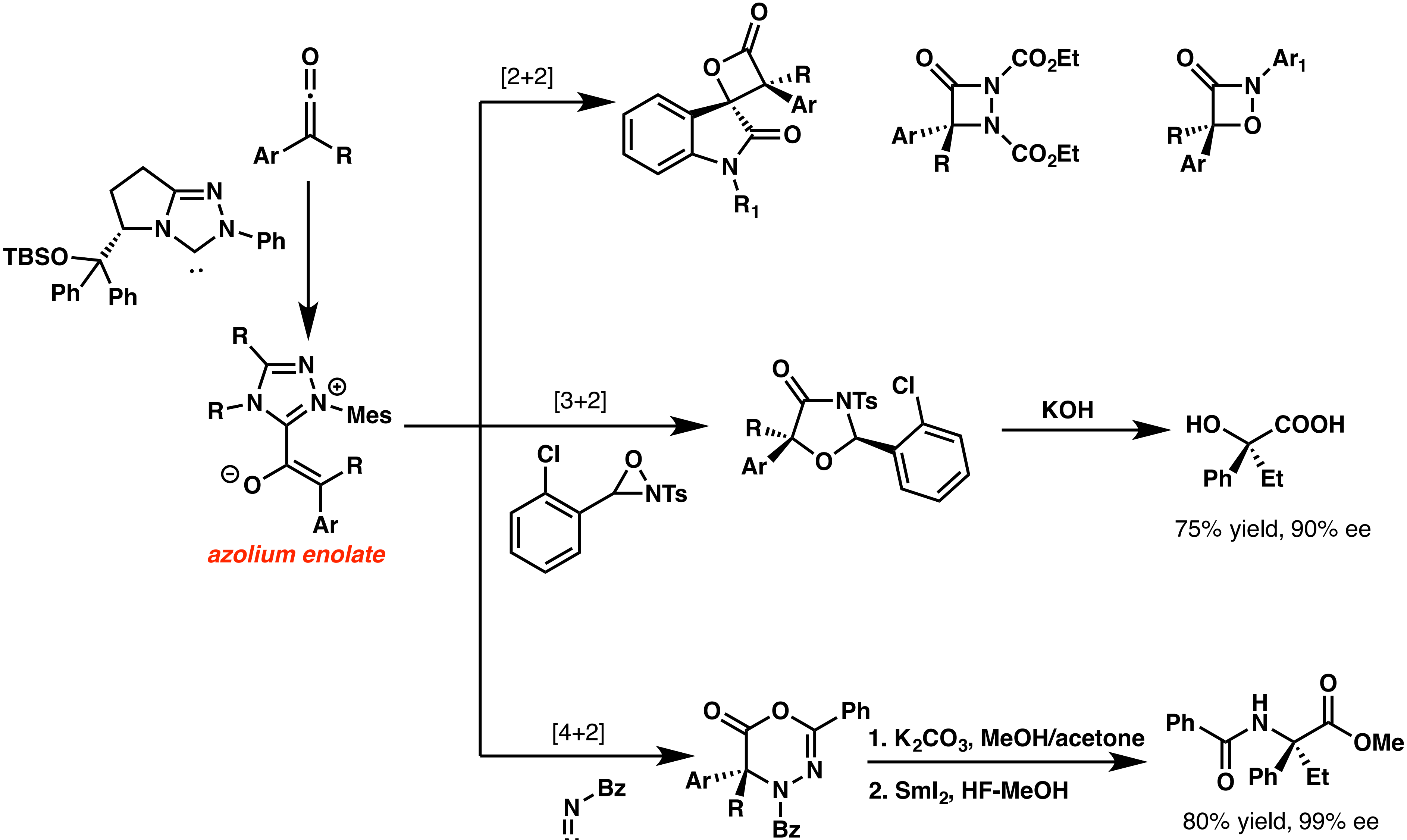
53-98% yield
91-99% ee
2.5-99:1 dr



azolium enolate

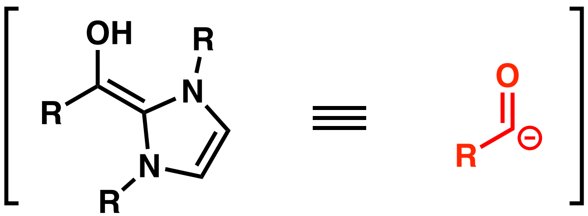
Ye, S.; *Org. Lett.* **2008**, 10, 277.

Ketene Cycloaddition



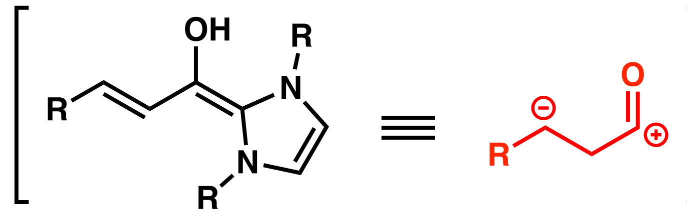
Ye, S. *Synlett* **2013**, 1614

Overview



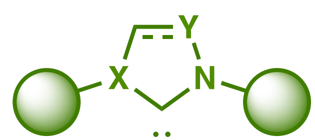
Acyl Anions

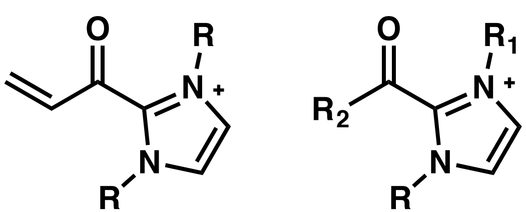
- *Benzoin condensation*
- *Stetter reaction*
- *Hydroacylation*



Homoenolates

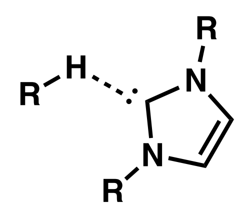
- *Annulation*
- *Cyclopentene synthesis*





Acylazolium
Azolium enolate

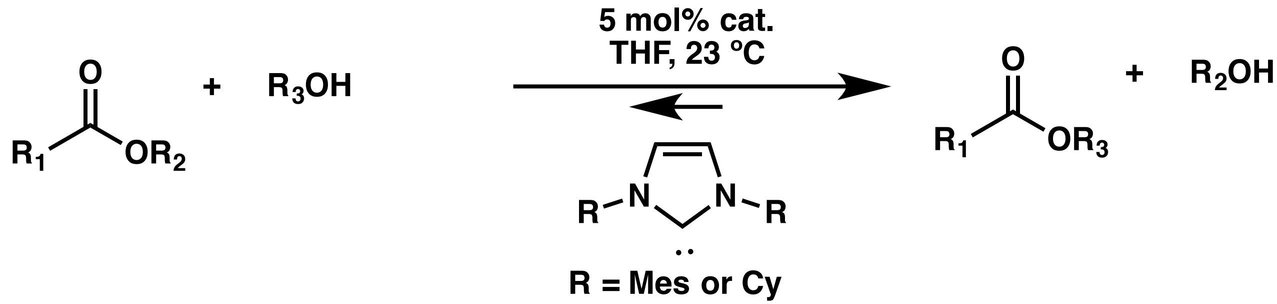
- *Claisen rearrangement*
- *Cycloaddition*

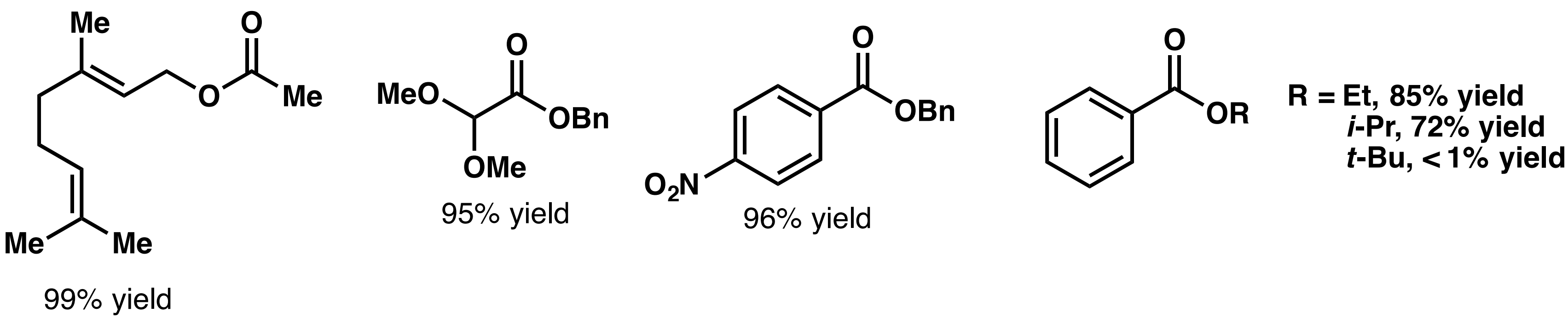


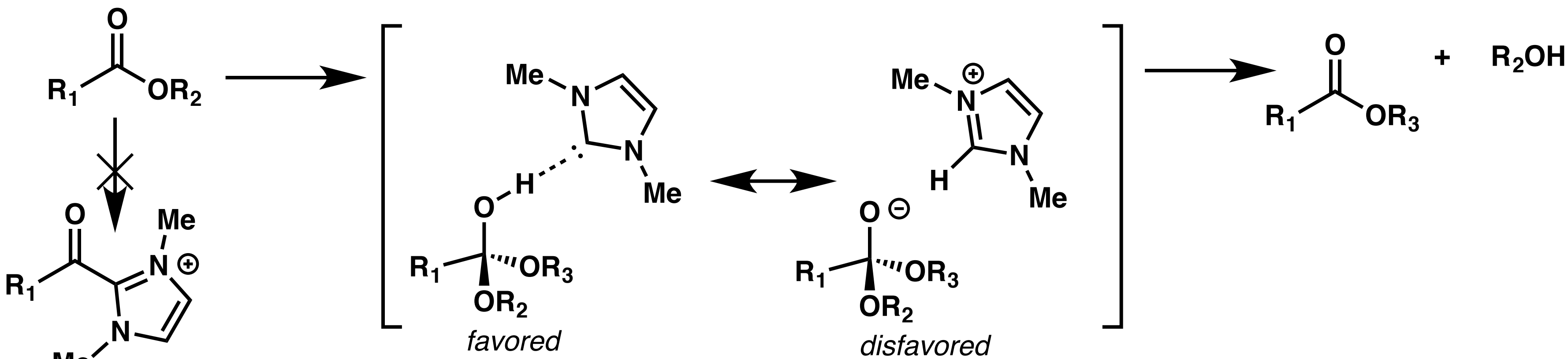
Base Catalysis

- *Transesterification*
- *Michael addition*

Transesterification



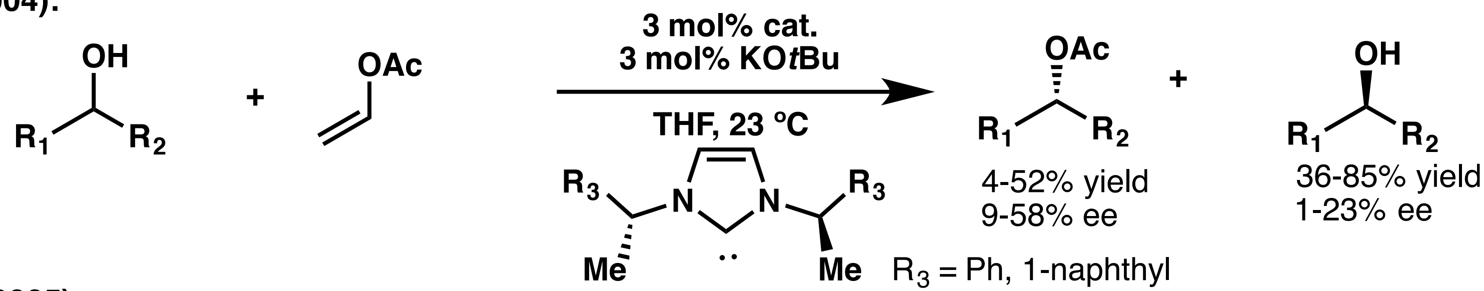




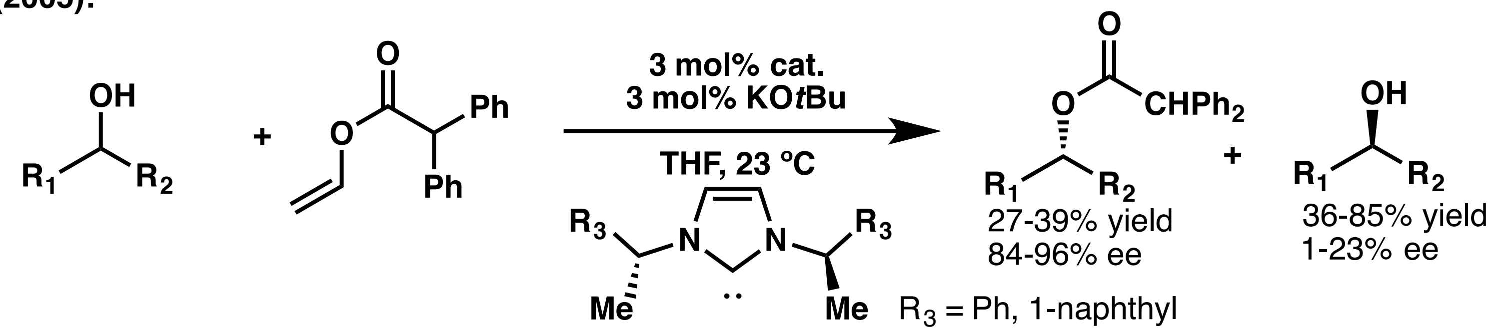
Nolan, *Org. Lett.* **2002**, 4, 3583-3586
Hedrick, *Org. Lett.* **2002**, 4, 3587-3590

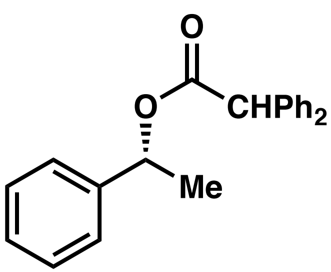
Kinetic Resolution of Secondary Alcohols

Suzuki (2004):

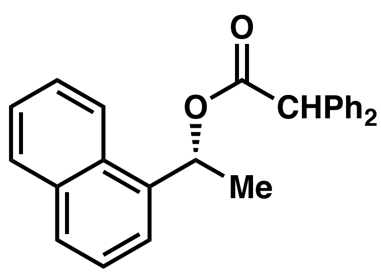


Maruoka (2005):

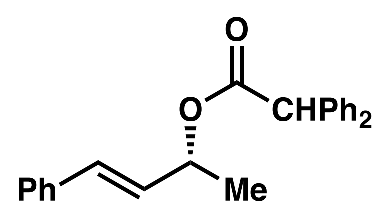




32% yield
96% ee
s = 80



29% yield
94% ee
s = 47

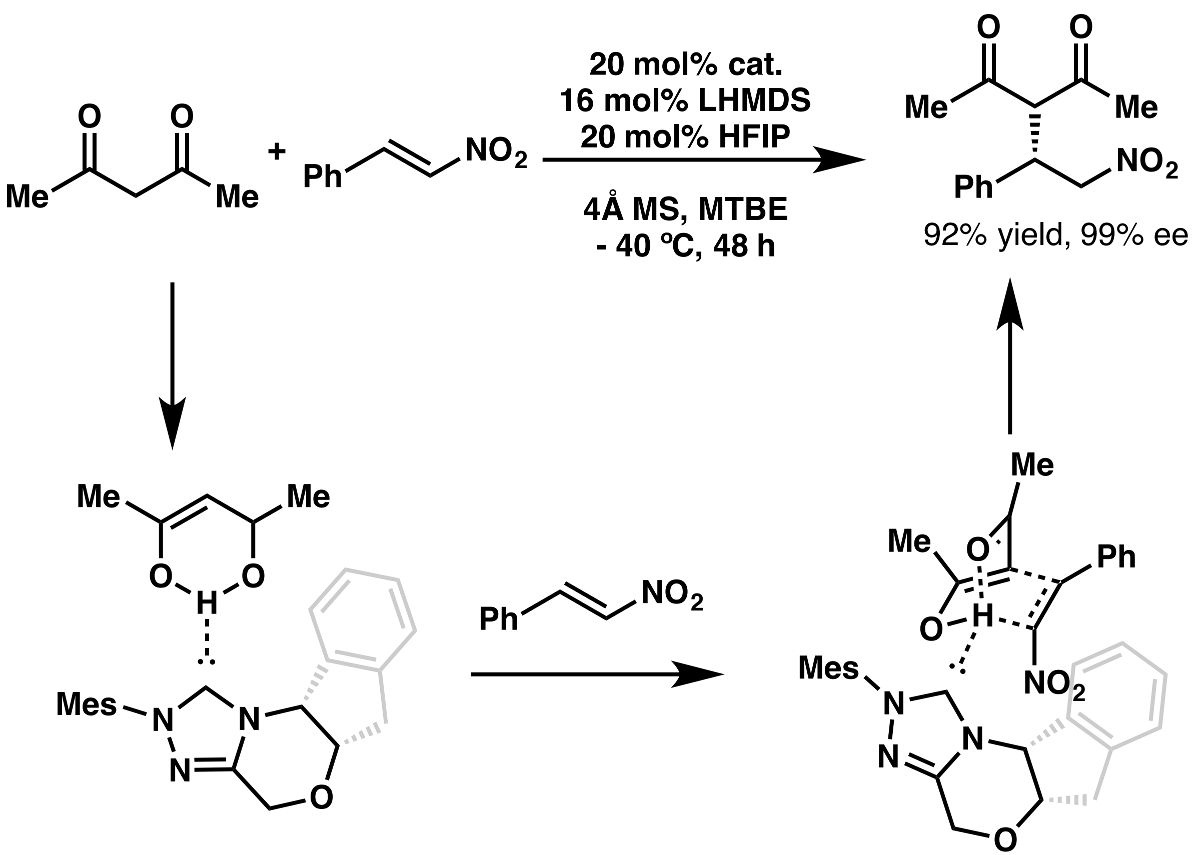


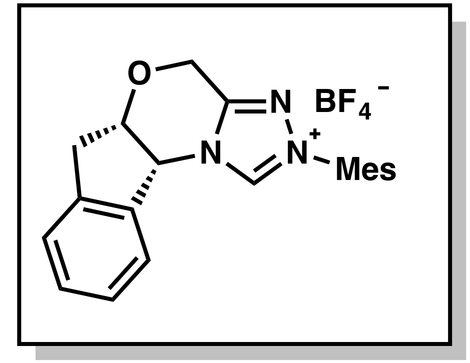
27% yield
84% ee
s = 16

Suzuki, *Chem. Commun.* **2004**, 2770-2771
Maruoka, *Org. Lett*. **2005**, 7, 1347-1349

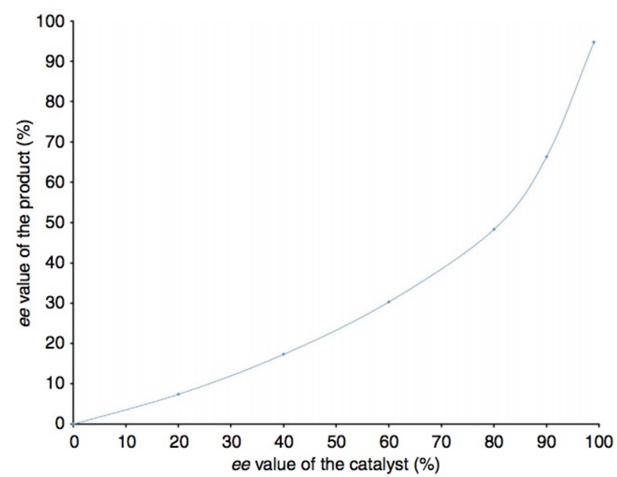
Asymmetric Conjugate Addition of 1,3-Dicarbonyls

• **NHC as non-covalent chiral templates (Huang, 2014)**



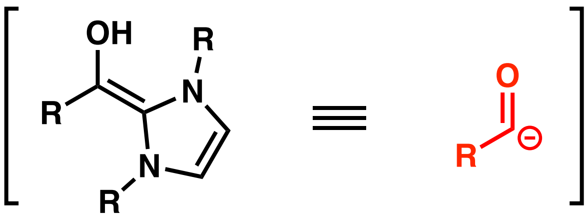


negative non-linear effects:



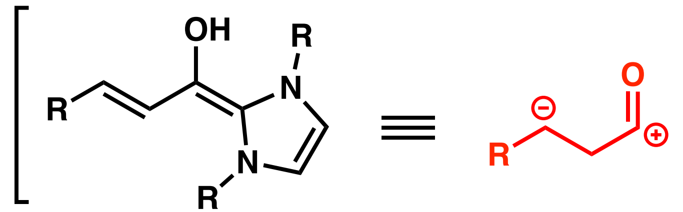
Huang, *Nat. Commun.* **2014**, 5, 3437

Overview



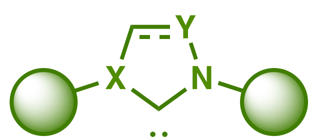
Acyl Anions

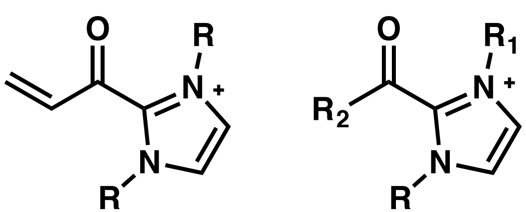
- *Benzoin condensation*
- *Stetter reaction*
- *Hydroacylation*



Homoenolates

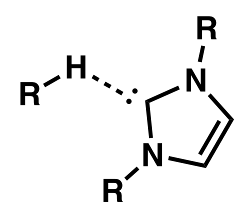
- *Annulation*
- *Cyclopentene synthesis*





Acylazolium
Azolium enolate

- *Claisen rearrangement*
- *Cycloaddition*



Base Catalysis

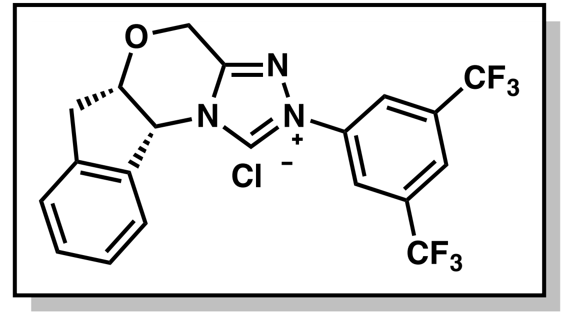
- *Transesterification*
- *Michael addition*

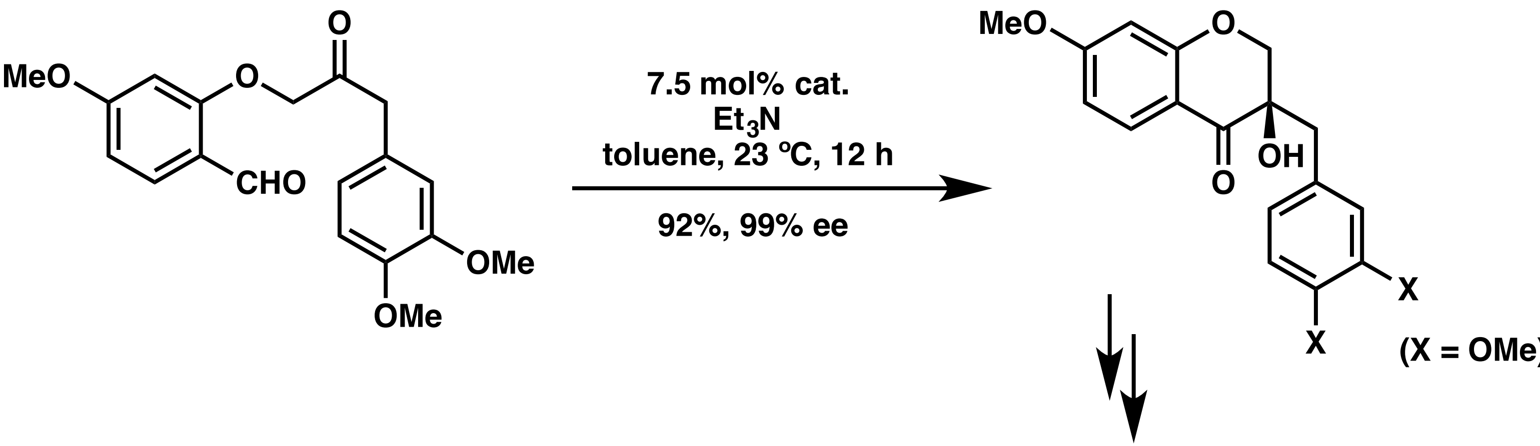
QUIZ TIME!

Application in Total Synthesis

•**Synthesis of (+)-sappanone B**

reaction type:





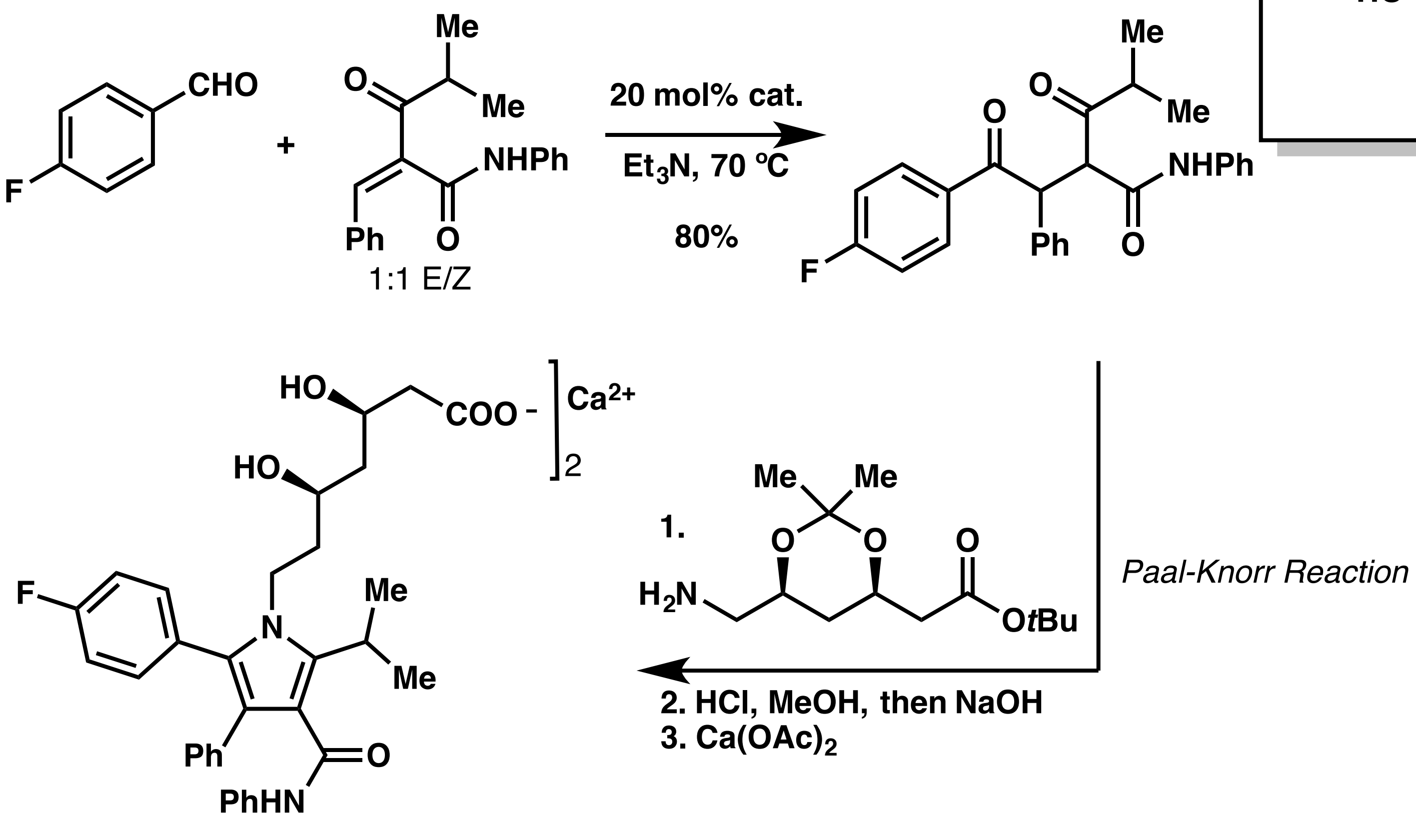
(+)-sappanone B (X = OH)

Suzuki, *Org. Lett.* **2007**, 9, 2713-2716

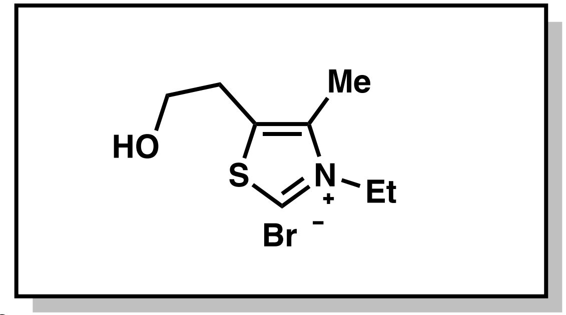
Application in Total Synthesis

•**Synthesis of atorvastatin (Lipitor)**

reaction type:



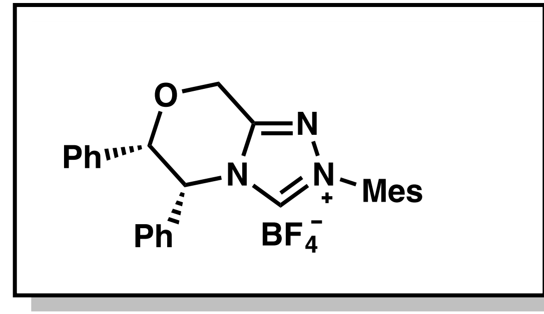
atorvastatin (Lipitor)

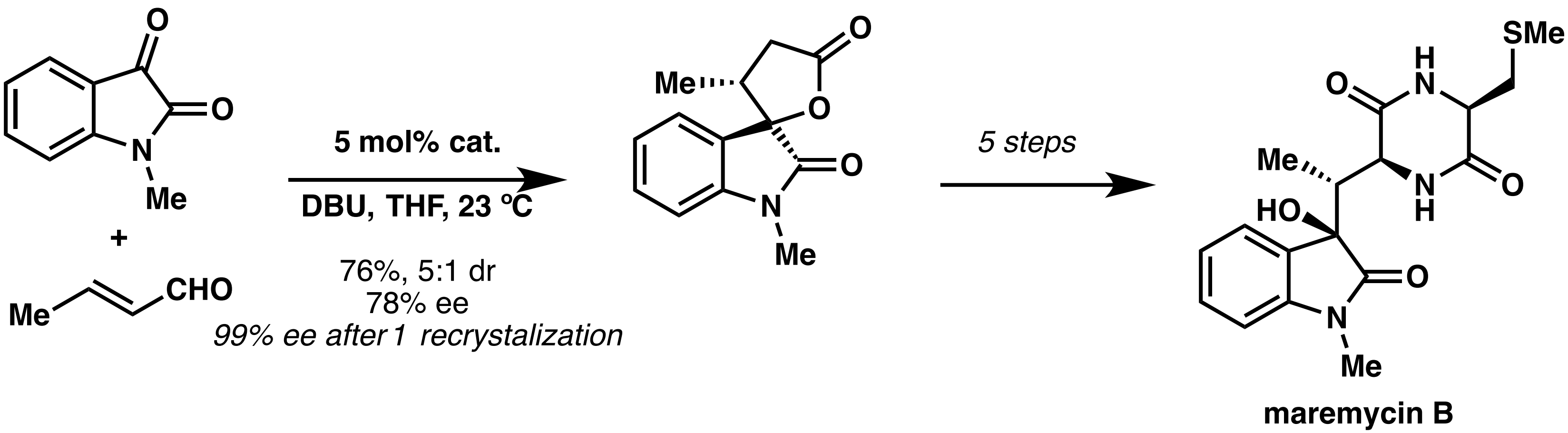


Roth, *Tetrahedron Lett.* **1992**, 33, 2283-2284

Application in Total Synthesis

•**Synthesis of maremycin B**
reaction type:

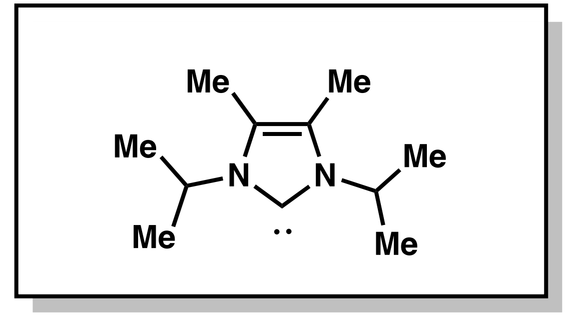


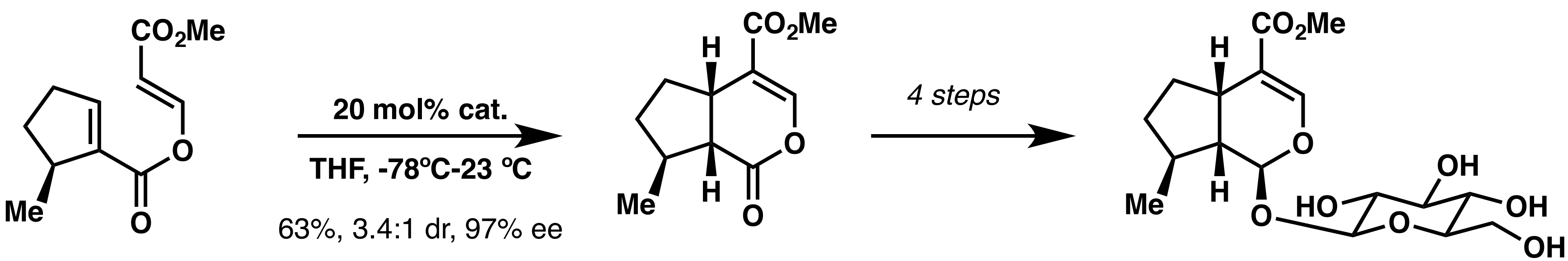


Scheidt, *Angew. Chem. Int. Ed.* **2012**, 51, 4963-4967

Application in Total Synthesis

•**Synthesis of (–)-7-deoxyloganin**
reaction type:



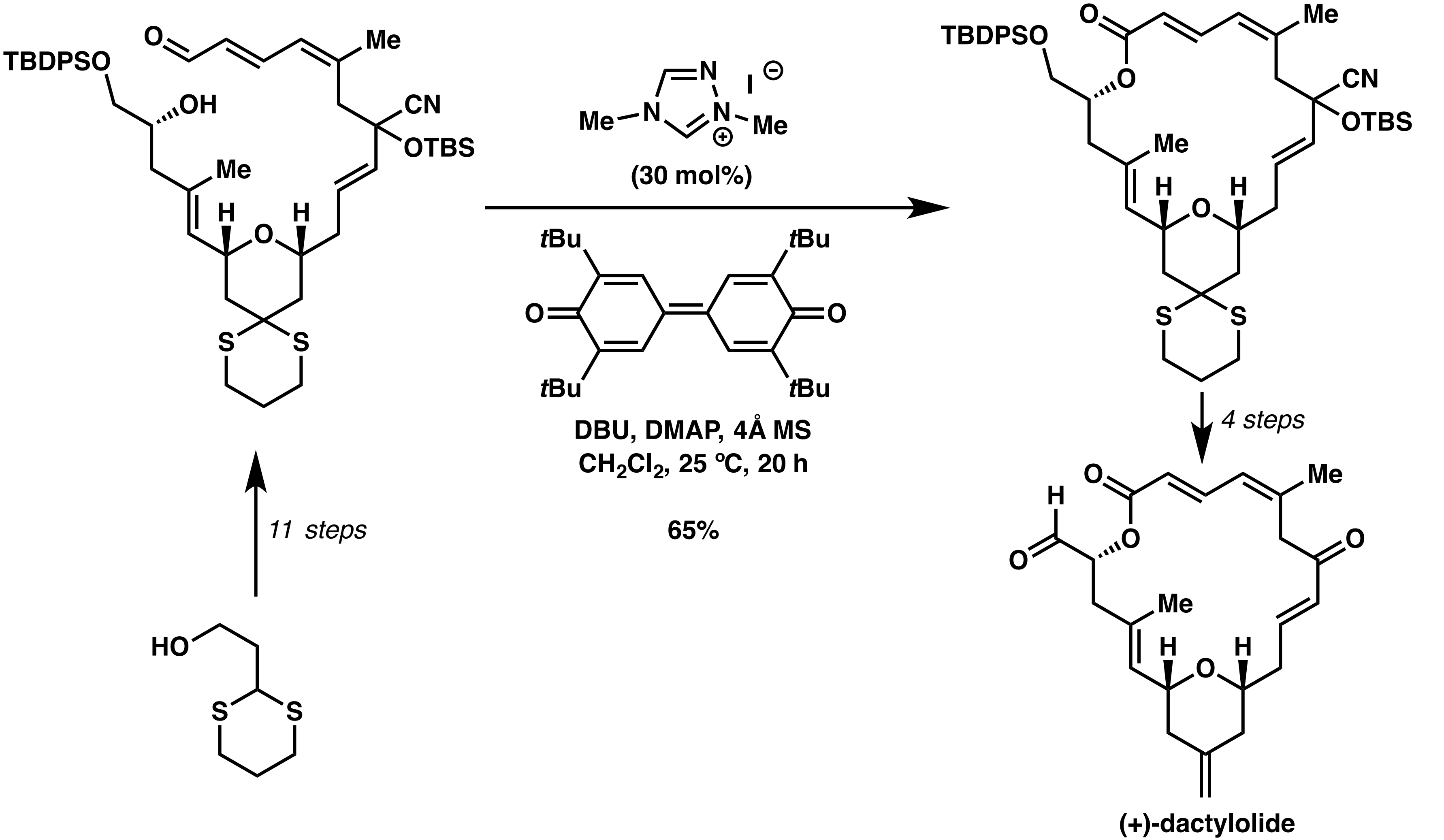


Candish, Lupton, *Org. Lett.* **2010**, 12, 4836-4839.

Application in Total Synthesis

•**Synthesis of (+)-Dactylolide**

reaction type:



Hong, *Angew. Chem. Int. Ed.* **2012**, 51, 5735-5738.

Reviews

1. N-Heterocyclic Carbenes as Organocatalysts
Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988 – 3000

2. Organocatalysis by N-Heterocyclic Carbenes
Enders, *Chem. Rev.* **2007**, *107*, 5606-5655

3. A Continuum of Progress: Applications of N-Hetereocyclic Carbene Catalysis in Total Synthesis
Sheidt, *Angew. Chem. Int. Ed*. **2012**, *51*, 11686 – 11698

4. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes
Rovis, *Chem. Rev.* **2015**, *115*, 9307–9387