

# Carbenes Part 1: *N*-Heterocyclic Carbenes and You

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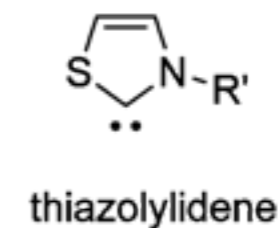
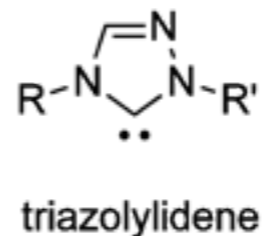
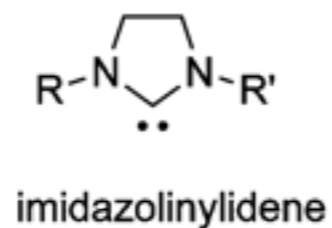
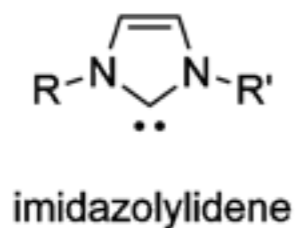
Tim Martin  
Lit. Group Meeting  
June 4th, 2010

## What is an NHC?

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- Nucleophilic carbenes; excellent ligands for metals, but also serve as excellent organocatalysts!
- Arduengo *et. al.* isolated a stable crystalline N-heterocyclic carbene and found to be thermally stable.
- Stabilized by “push-pull” effect.
- Cheaper than organometallic reagents, more environmentally friendly

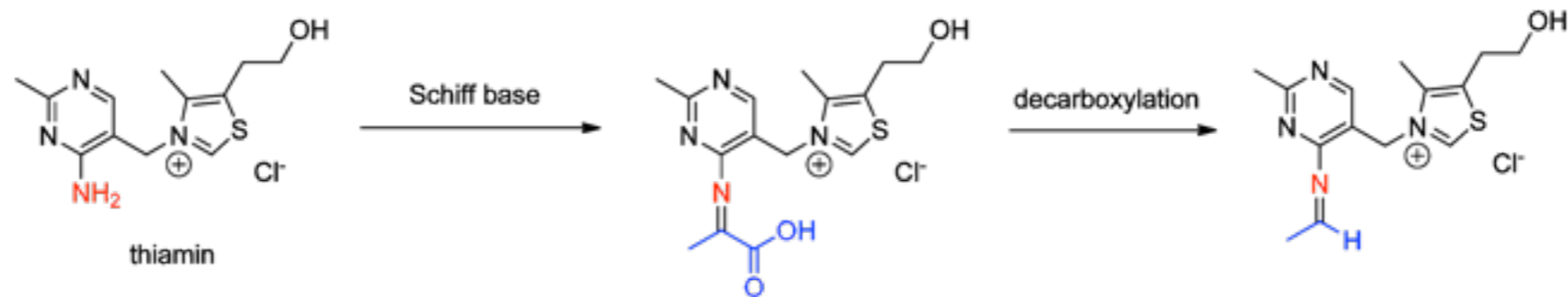
### Common NHCs



# Decarboxylation of Pyruvic Acid by Thiamin

- Significant discussion in literature about the mechanism:

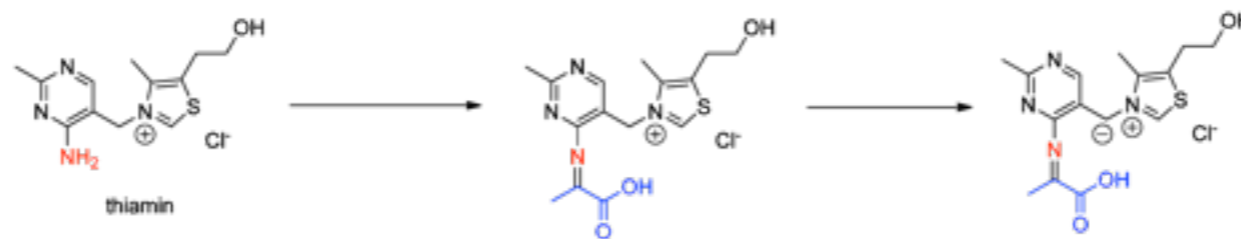
- Amine acting as a Schiff base?
  - Thiamin not effective under experimental conditions
  - Amine group is actually not very reactive



- Opening of the thiazole ring?



- Schiff base formation and tautomerization

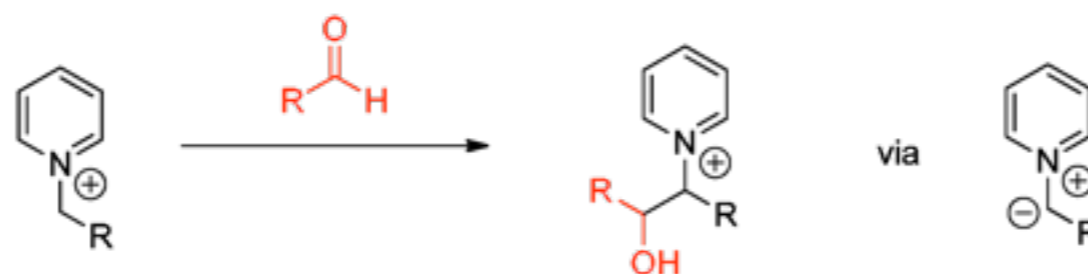


- Led to work by Ugai *et. al.*, Mizuhara gains some important info, Breslow for the put away.

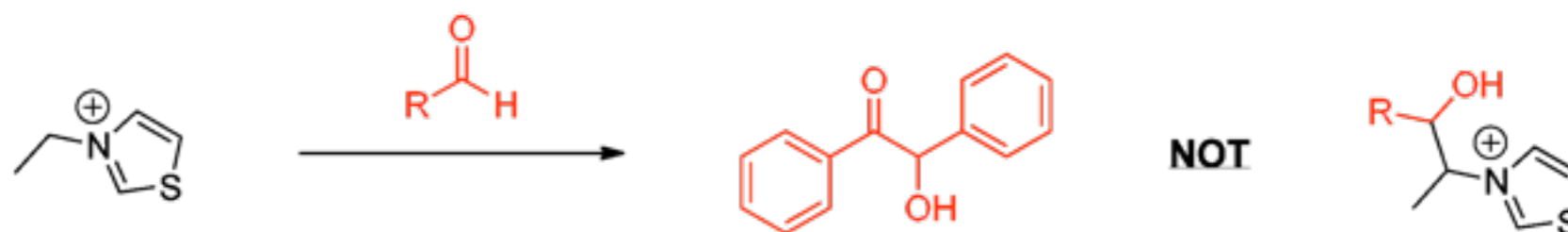
## Science in Action!

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- Krohnke showed pyridinium compounds can condense with aldehydes:



- Ugai expected thiazolium compounds to do as well...



- Mizuhara showed pH optimum for the benzoin reaction catalyzed by thiamin to be 8.4...but attributed it to the pseudobase formed from thiamin. Says everyone before this was wrong about Schiff bases or opening of the thiazole.
- Breslow's take: "He [Mizuhara] showed that the reaction exhibits a very pronounced optimum at pH 8.4, which is near the pK of pseudo-base formation by thiazolium compounds, and proposed an unusual and rather unlikely mechanism involving the *pseudo*-base of thiamin."

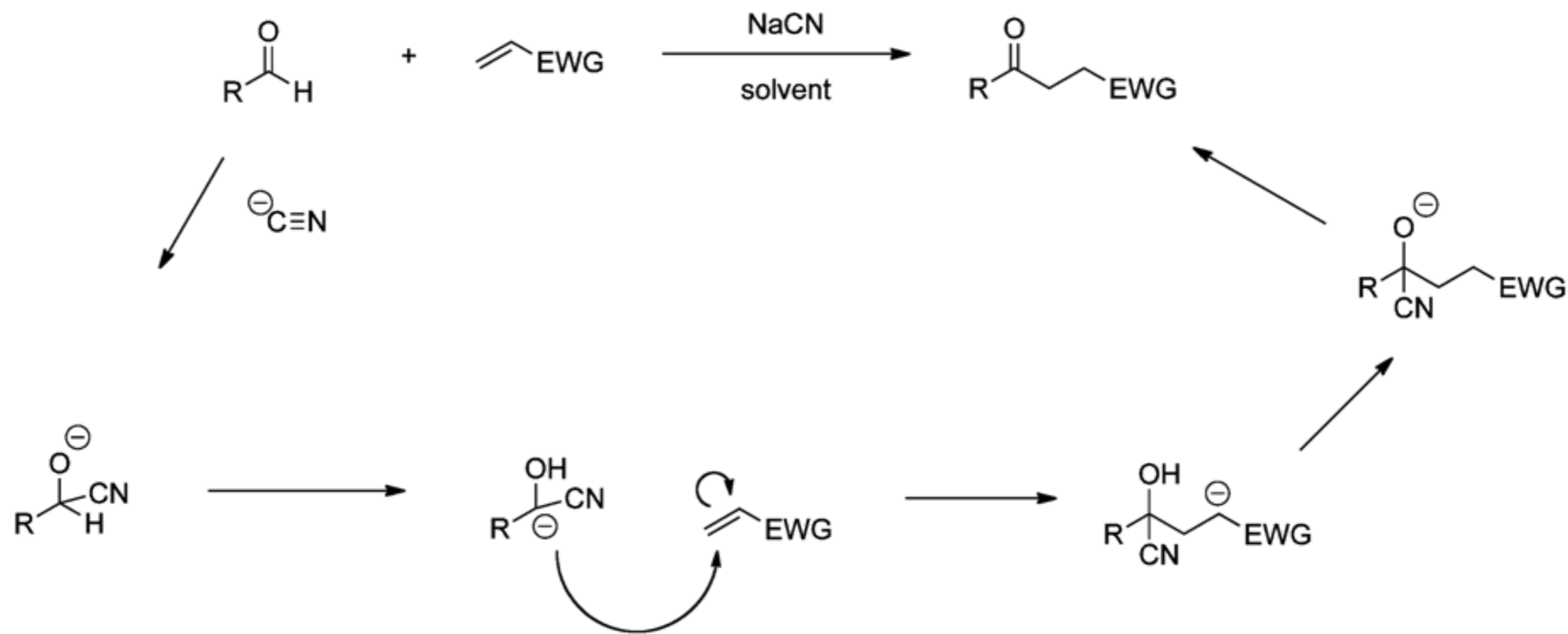


## What Can NHC's do for you?

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- Benzoin Condensation
- **Stetter Reaction**
- **Homoenolates**
- **Formal Cycloadditions and Cycloadditions**
- 1,2-Addition Reactions
- Transesterification/Acylation
- Ring Opening Reactions

# The Stetter Reaction



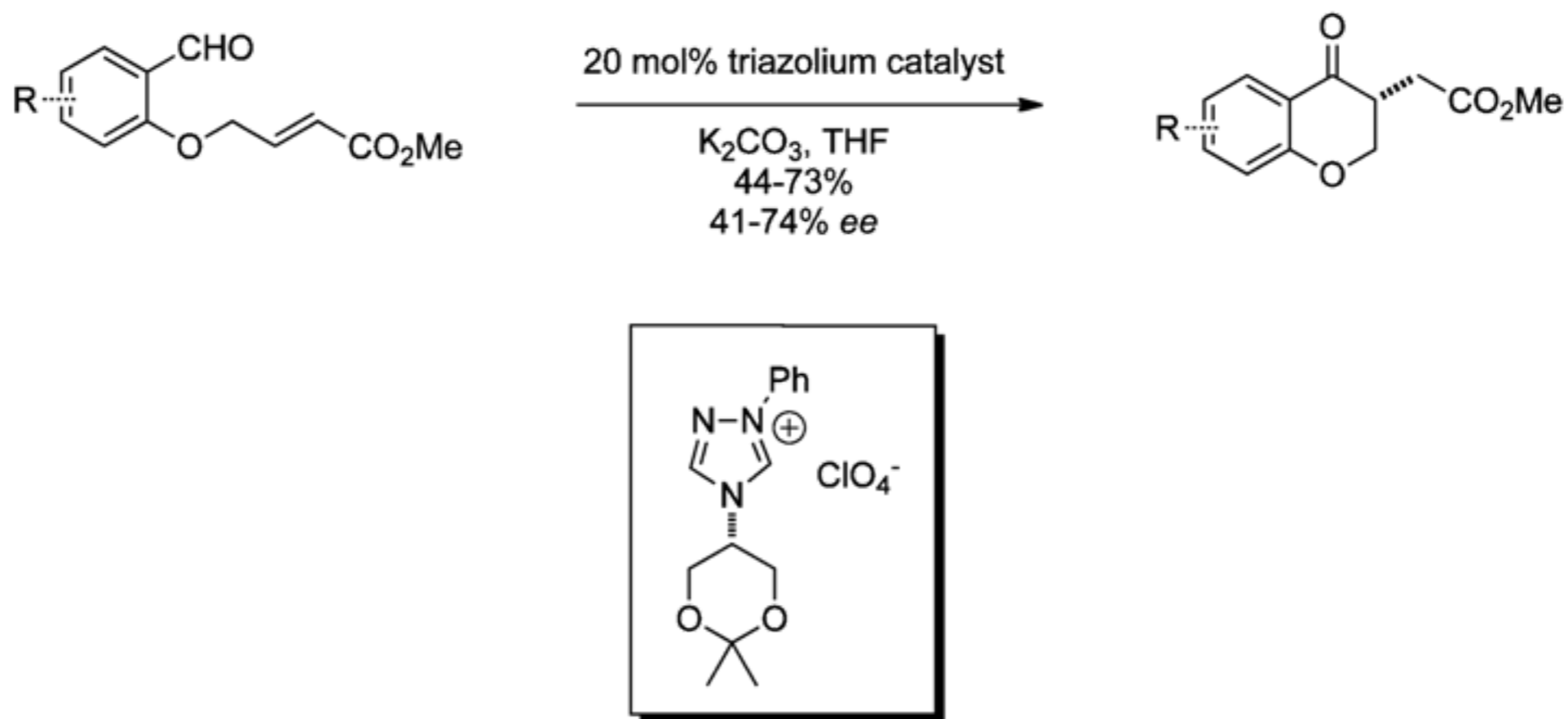
## NHCs in the Stetter Reaction

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- Allow for stereochemistry to be introduced to the reaction
- First asymmetric intramolecular Stetter reported by Enders in 1996 using NHC's, later improved by Rovis *et. al.*
- The intermolecular Stetter faces the problem of self condensation of the donor aldehyde, circumvented by Scheidt *et. al.* utilizing acyl silanes
- Asymmetric Intermolecular Stetter reports by Rovis *et. al.* utilizing fluorination of the NHC backbone to increase selectivity

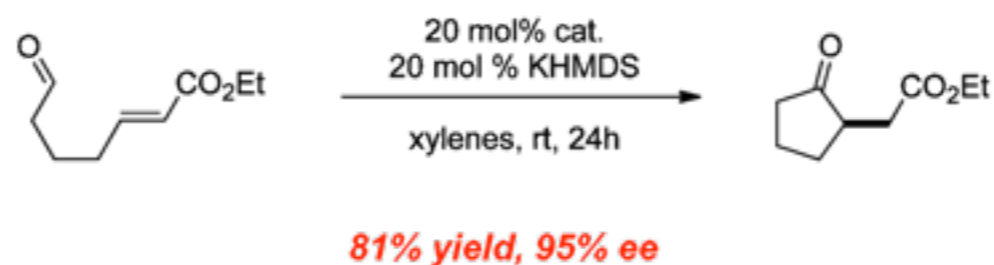
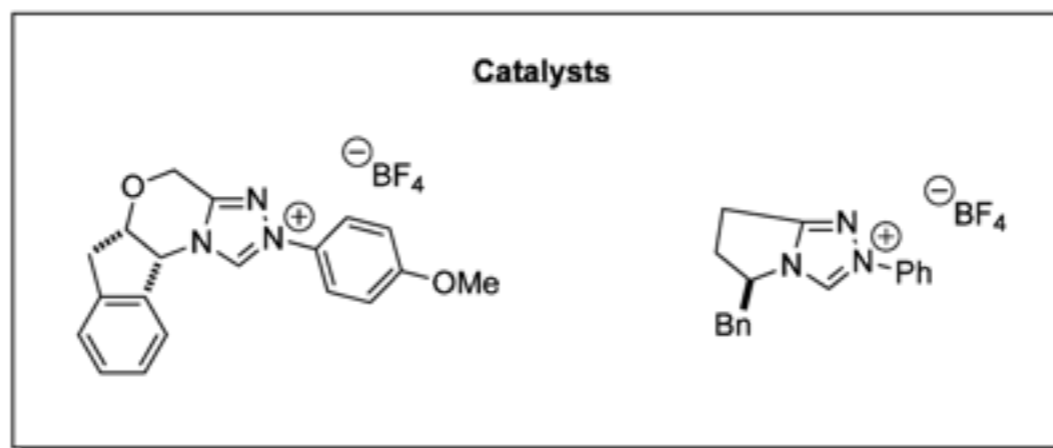
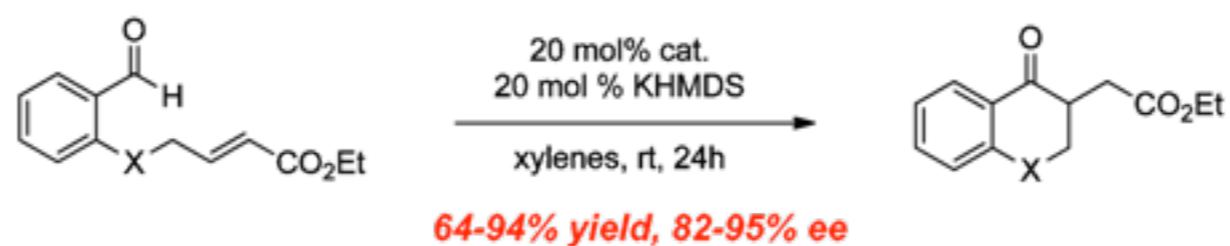
## NHCs in the Stetter Reaction

- Enders *et. al. Helv. Chim. Acta*, **1996**, 79, 1899-1902. Compounds generated are building blocks for compounds with strong fungicidal activity.
- Both enantiomers of catalyst available in large quantities. Rationalize selectivity via shielding of the *re*-face of the acceptor by the phenyl group of the dioxane moiety. Also note model simplifies things greatly...



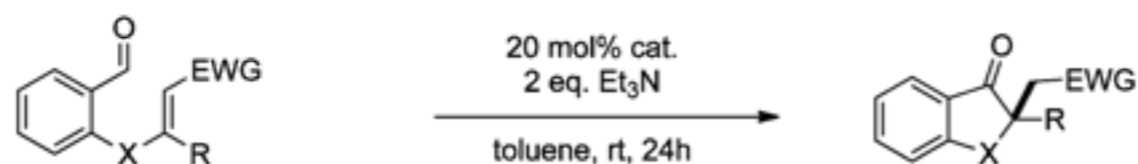
# A Highly Enantioselective Intramolecular Stetter Reaction

- Rovis *et. al.* found chiral triazolium salts that can be prepared from amino acids that are bench stable crystalline solids.
- Catalyze the intramolecular Stetter with good yields and moderate to high asymmetric induction.

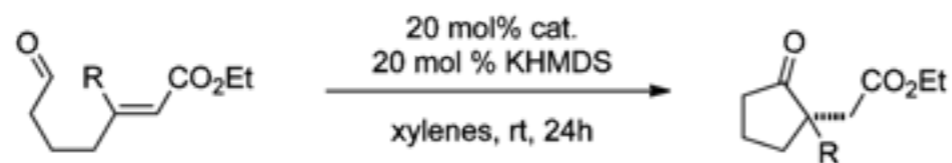


# Quaternary Centers!

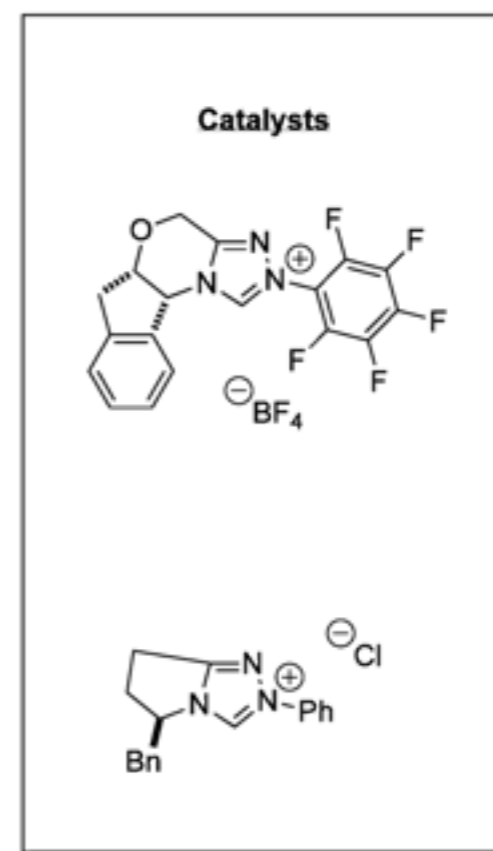
- Addition into a  $\beta,\beta$ -disubstituted Michael acceptor to introduce quat. centers



**55-96% yield, 89-99% ee**  
**X = O, S, CH<sub>2</sub>; R = Me, Et, Ph**  
**EWG = CO<sub>2</sub>Me, C(O)Me**



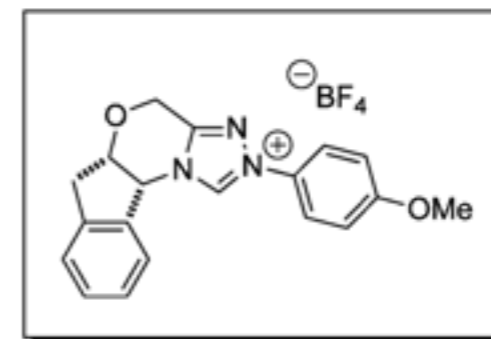
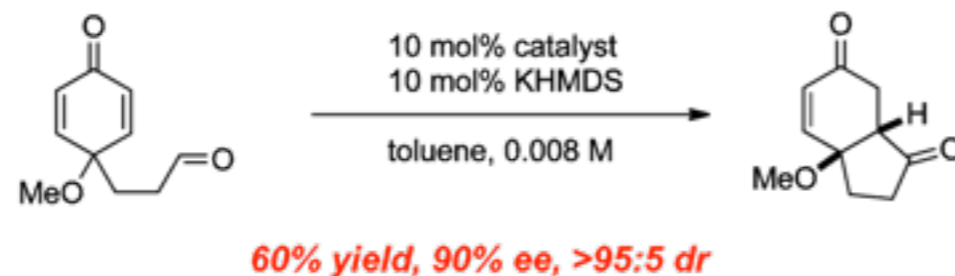
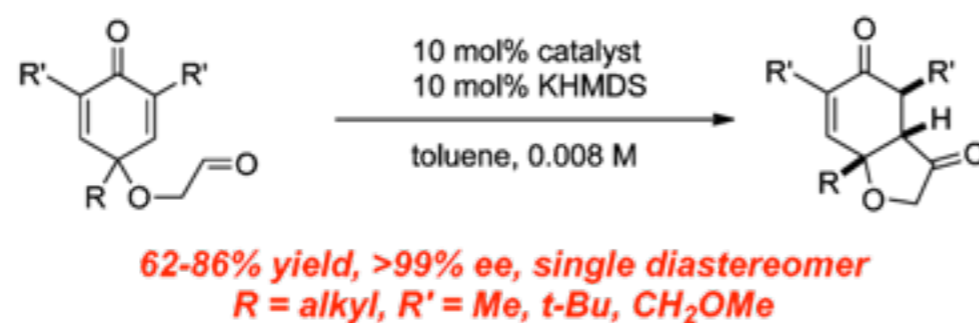
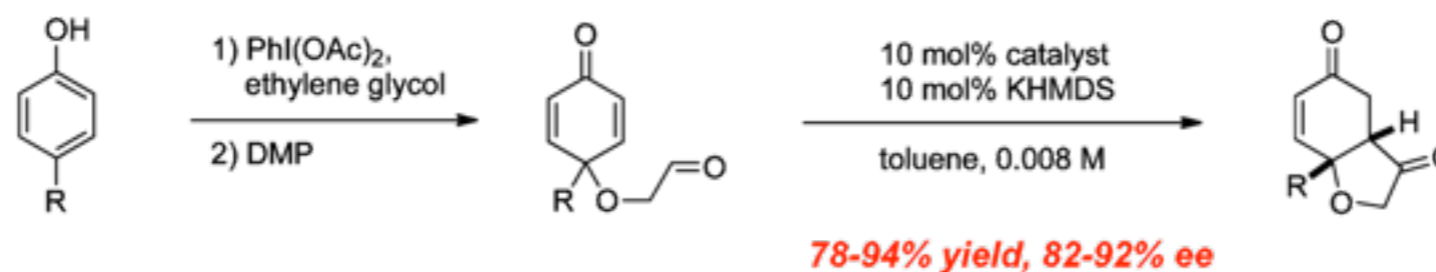
**63-90% yield, 84-99% ee**  
**R = Me, Bu, CO<sub>2</sub>Me**



- Found that E alkenes worked better than Z alkenes (proved to be sluggish and had lower selectivities).
- Can synthesize cyclopentanones with quaternary centers! Can cyclohexanones be done? Different EWG's? What about trisubstituted alkenes?

# Desymmetrization of Cyclohexadienones and NHCs

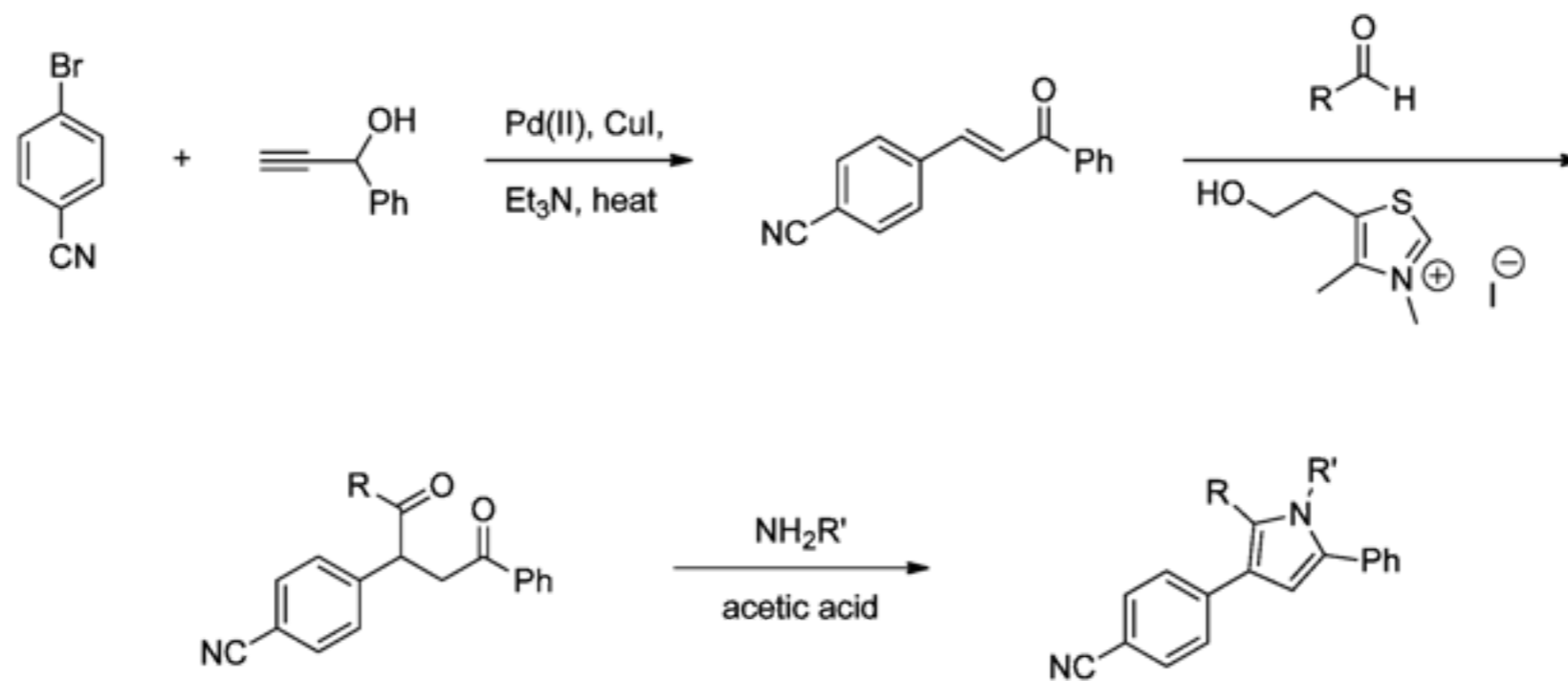
- Powerful way to access enantioenriched material from commonly available precursors



- Such hydrobenzofurans are core skeletons in many natural products. How far can the reaction be pushed?

# Intermolecular Stetter

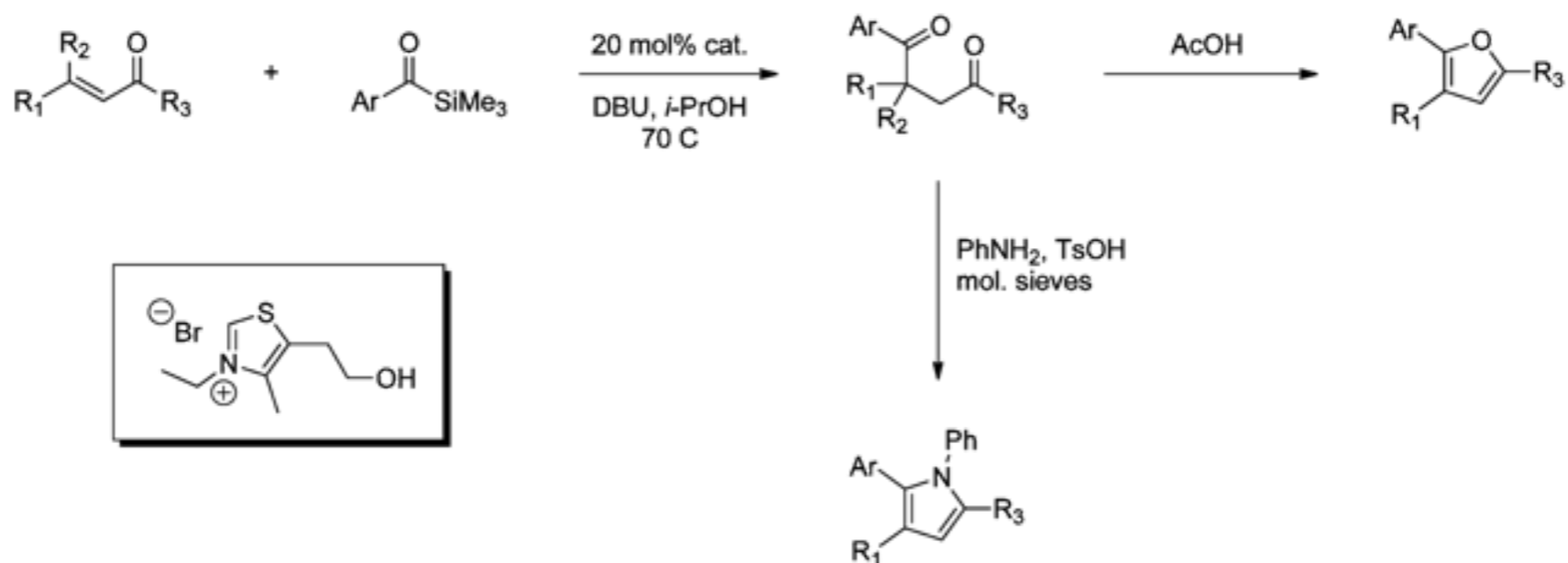
- 2001: Muller (Germany) publishes a novel one pot pyrrole synthesis using a Sonogashira coupling-isomerization-Stetter-Paal-Knorr sequence.



- Limited scope, yields range from 49-59%... not too bad after 4 transformations (recrystallized to greater than 95% purity).
- Future work “to extend these one-pot heterocycle syntheses to pharmaceutically and electronically interesting systems”.

# Intermolecular Stetter

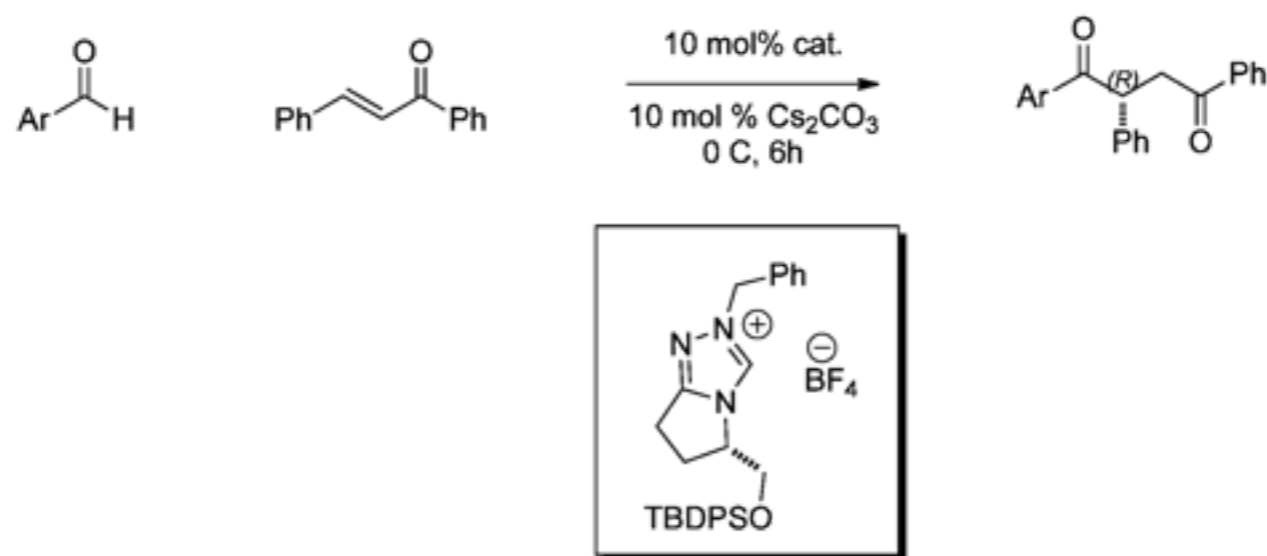
- 2004: Scheidt (Anita, too) exploited acyl silanes to effect an intermolecular Stetter. And expand upon Muller's initial work.



- One pot synthesis of furans and pyrroles, both important motifs for natural products, pharmaceuticals, and materials.

# Asymmetric Intermolecular Stetter

- Initial report by Enders in 2008, yields ranged from 49-98% with enantioselectivities from 56-78% ee (up to 90-99% ee upon recrystallization)... In 1993 they reported a version with 30% yield and 40% ee.



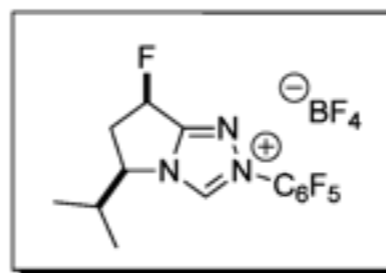
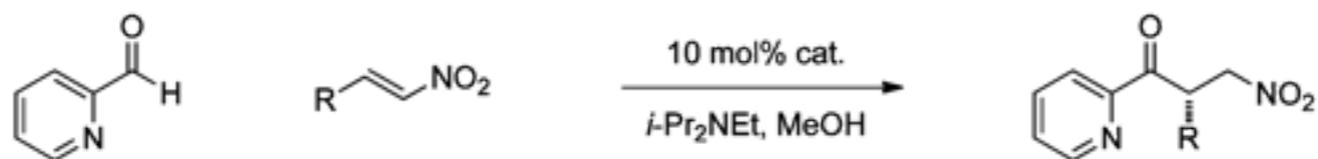
- Revealed some mechanistic details and proposed transition states explaining selectivity.



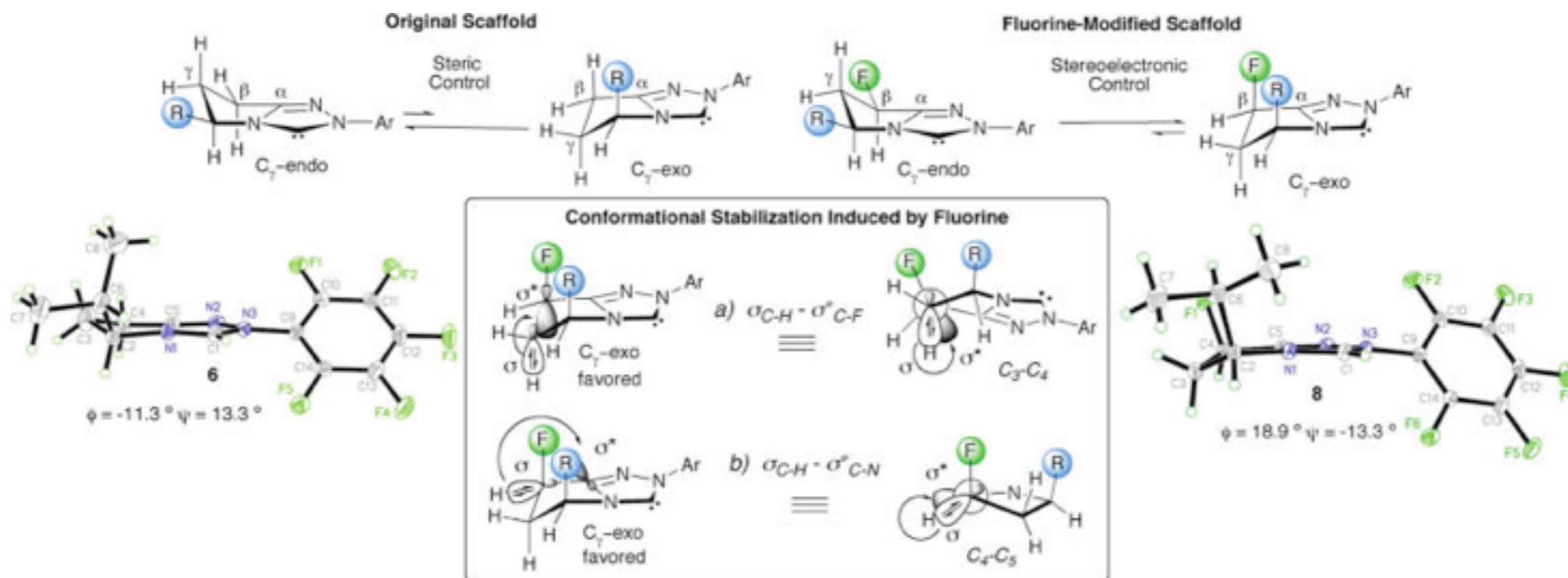
- What if you can't recrystallize your product? Several examples in the paper where this was the case. Albeit, a very nice first step.

# Asymmetric Intermolecular Stetter

- Rovis used back-bone fluorination to improve selectivity. Yields ranged from 62-99% with 83-99% ee. Alkyl R groups!



- Manipulation of stereoelectronics (gauche effect) causes conformation change of the catalyst and increases yield and enantioselectivity.



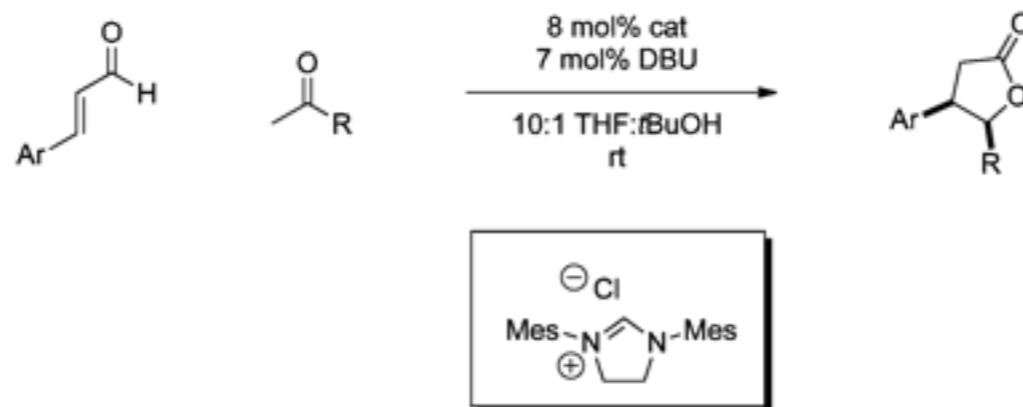
## NHC's in the formation of Homoenolates

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- Several ways to make “carbonyl anions”, many ways to make enolates, few approaches to make homoenolates in a direct, substoichiometric fashion
- Bode and Glorius first utilized NHC's to form homoenolates from  $\alpha,\beta$ -unsaturated aldehydes.
- Scheidt utilized NHC's for  $\beta$ -protonation and formation of enolates.

# Homoenolates from $\alpha,\beta$ -unsaturated aldehydes

- Bode reported the reaction in 2004, JACS



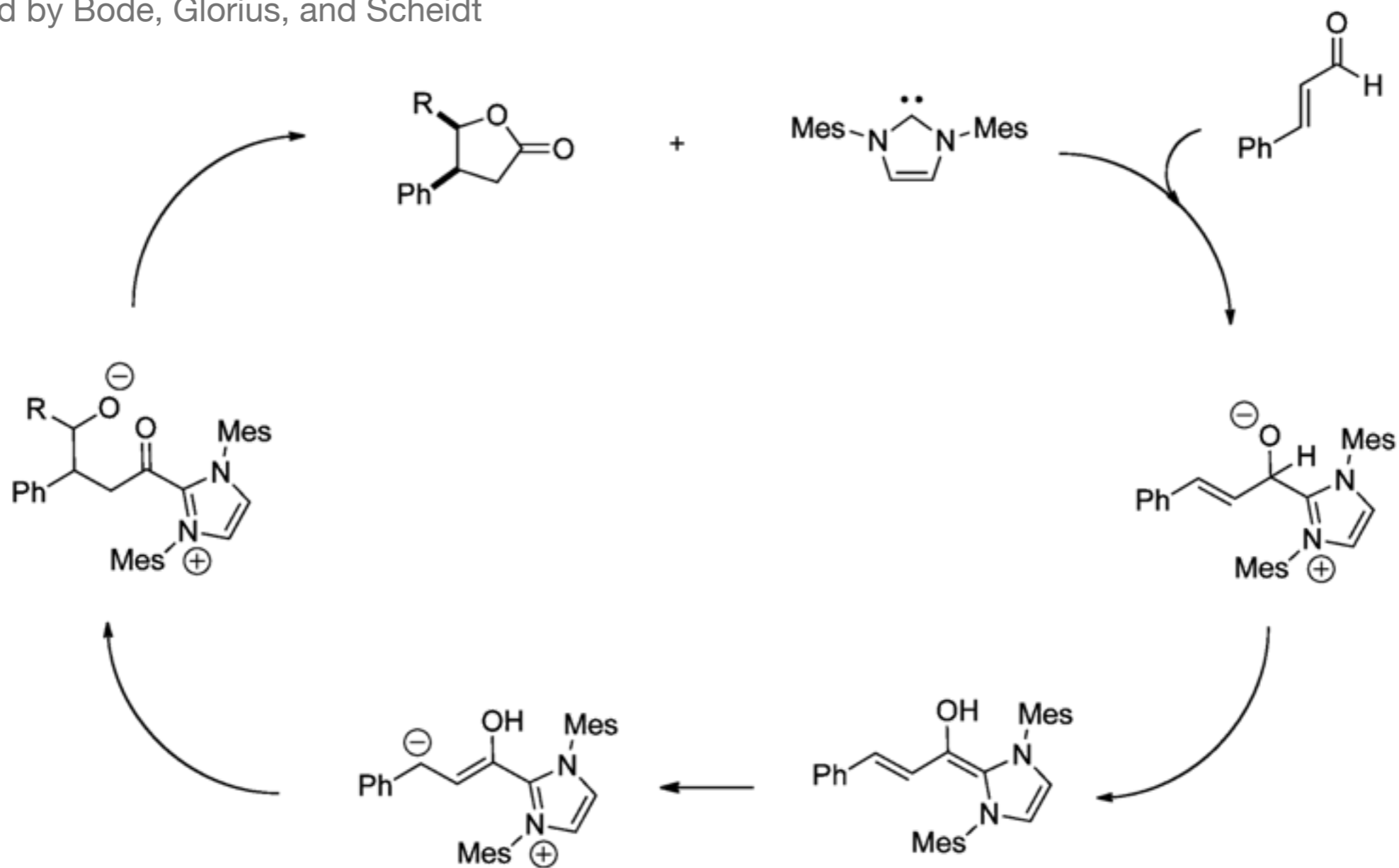
- Glorius reported the reaction in 2004, ACIE



- In both cases, limited scope, need aromatic aldehydes. Selectivities are around 3:1-5:1 in both reports. Both favoring *cis*.
- Glorius was able to extend to ketones, however required CF<sub>3</sub> as a substituent and 2 equivalents ketone.

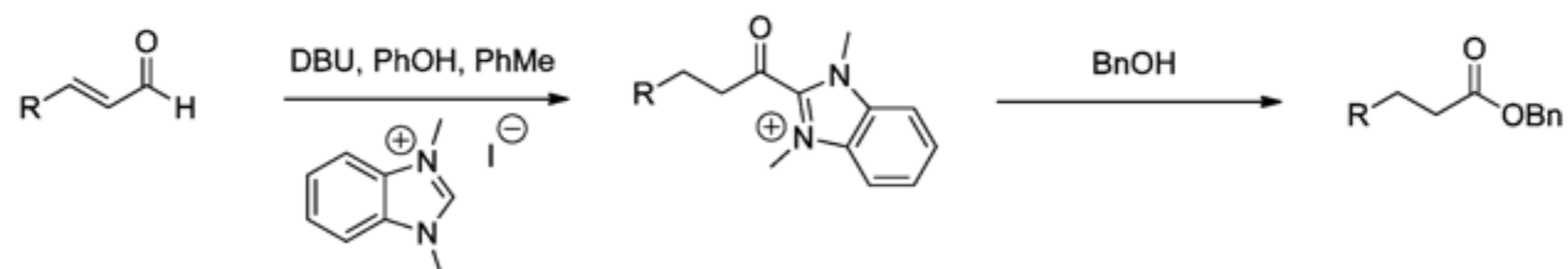
# General Mechanism

- Proposed by Bode, Glorius, and Scheidt

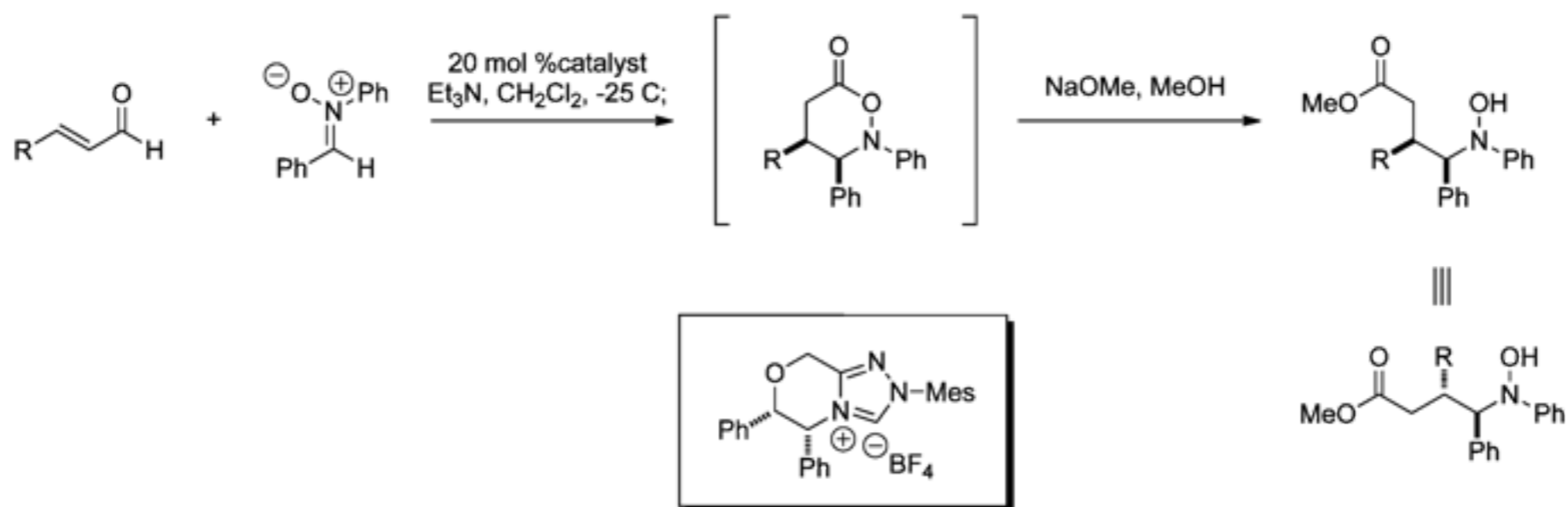


# Scheidt's Work with Homoenolates

- A reduction of sorts, or is it an oxidation...



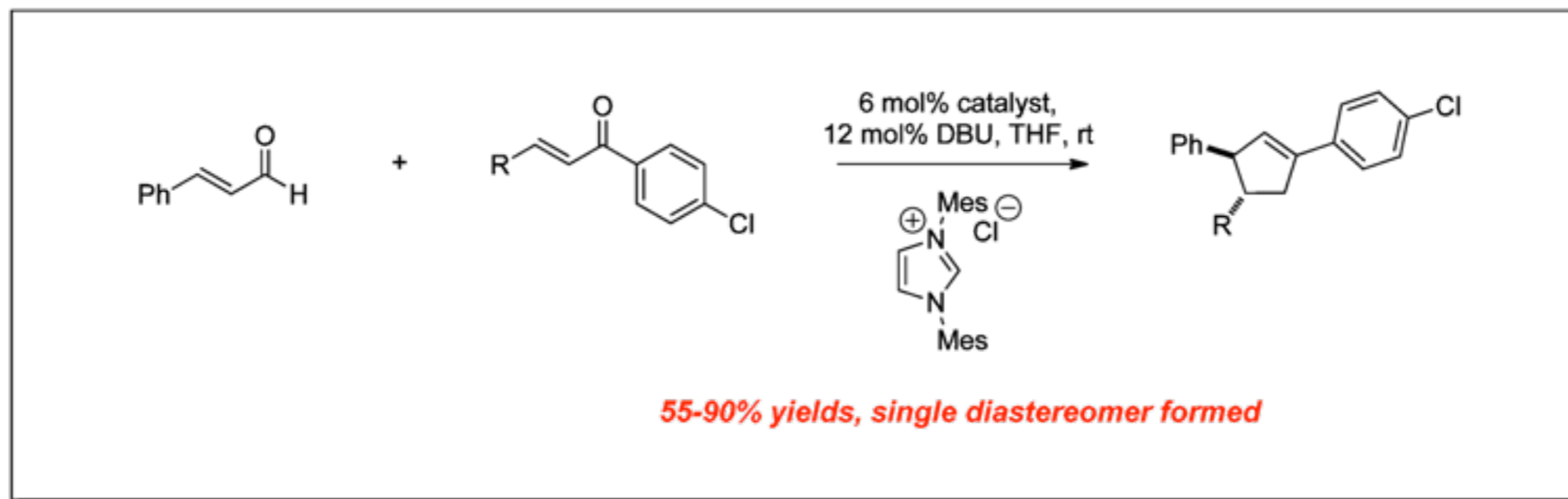
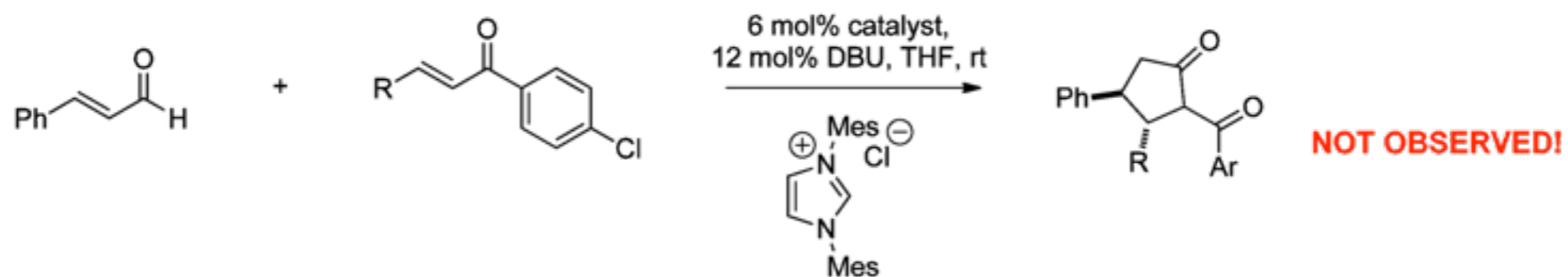
- Can more interesting electrophiles be used? Yes!  $>20:1$  dr, yield between 60-80%



- So? Can be elaborated into  $\gamma$ -amino acids: modulators of neurotransmission, pharmaceuticals, natural product scaffolds (lactacystin). Can cleave the N-O bond and cyclize to make lactams.

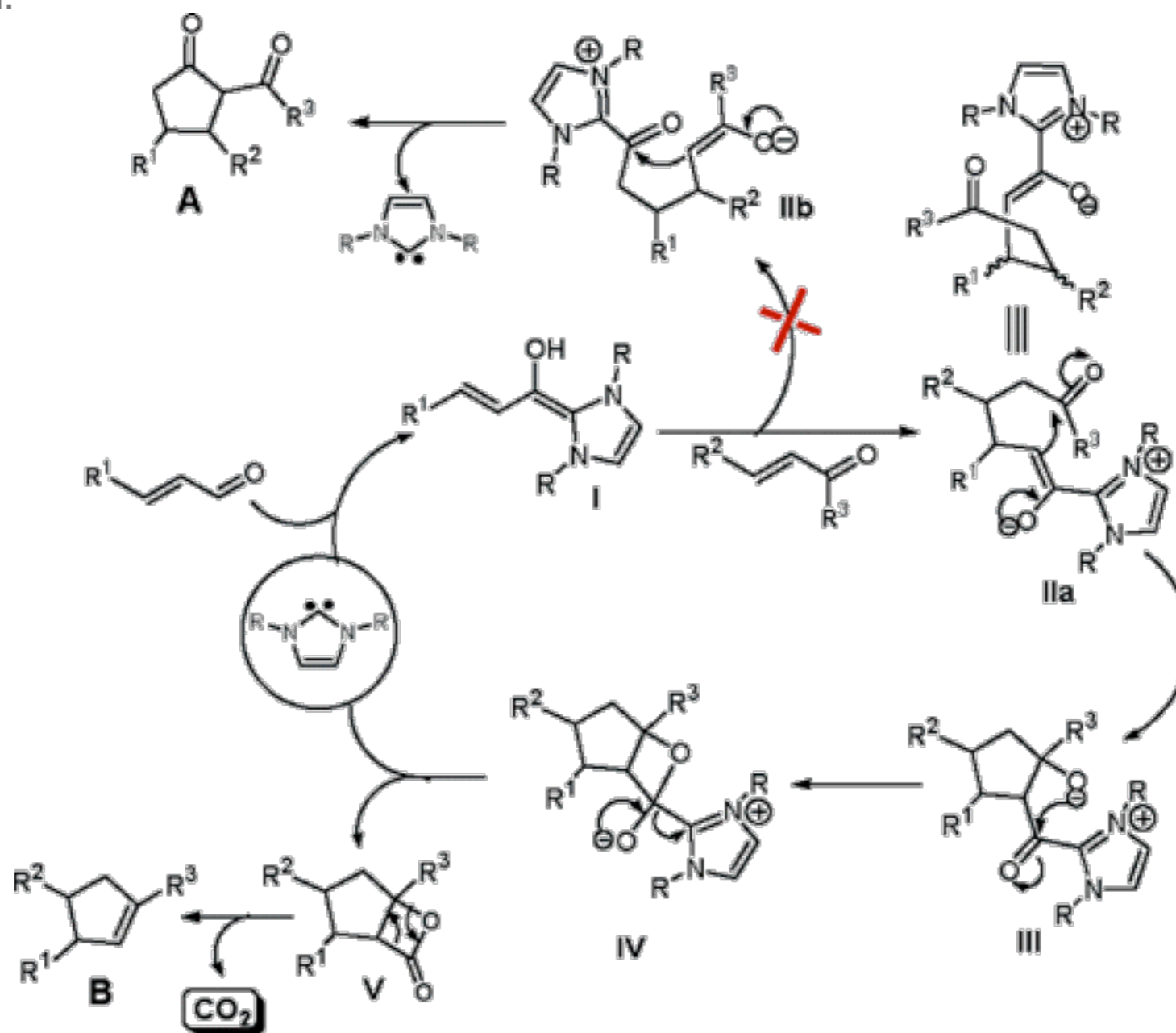
# Homoenolate Addition to Chalcones

- Expected a synthesis of cyclopentanones, however unexpected result was obtained.

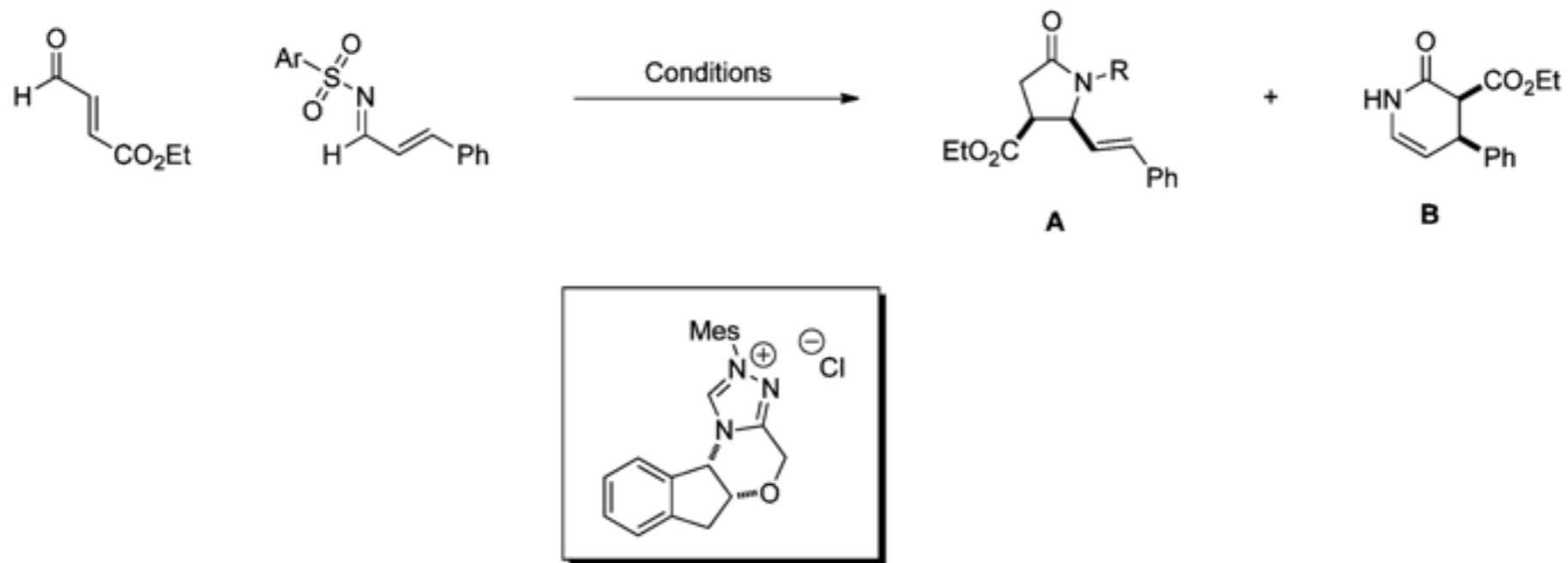


# Homoenolate Addition to Chalcones

- Proposed Mechanism:

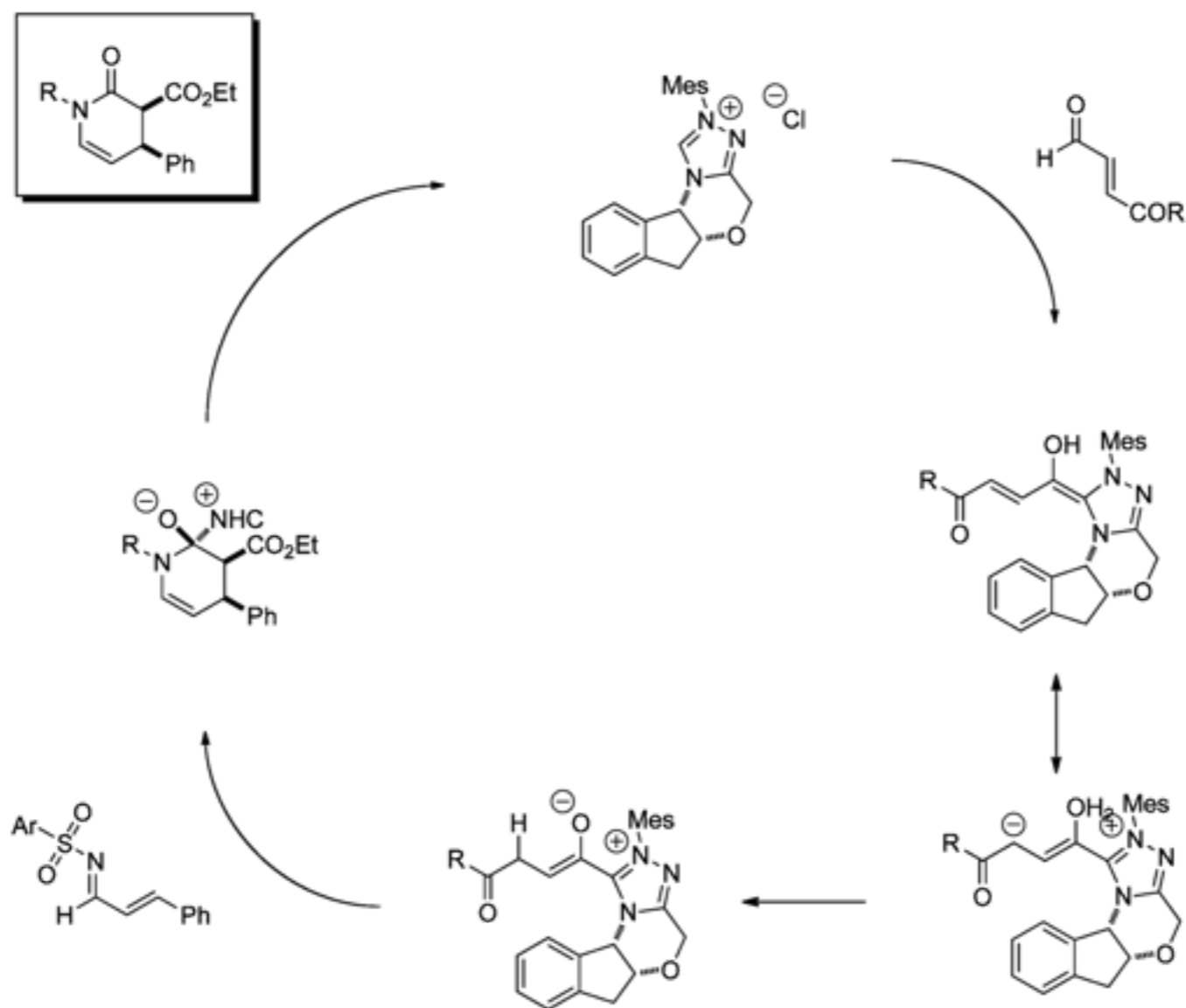


# NHCs in Cycloadditions



- Using the shown catalyst and DIPEA in toluene/THF results in exclusive formation of the dihydropyridinone
- >99% ee, >50:1 *cis* diastereoselectivity, No work-up required! (does require column chromatography though)
- Tolerates variety of imine substrates, including heteroaromatic and aliphatic; also varied the enal substrate to a methyl ketone and *t*-butyl ester.

# Proposed Mechanism and Origin of Selectivity



- *Cis* stereoselectivity explained by a *Z*-enolate or enol...postulated that protonation of the Breslow intermediate occurs only in fully conjugated, extended arrangement that leads to *Z*-enol.

## References

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