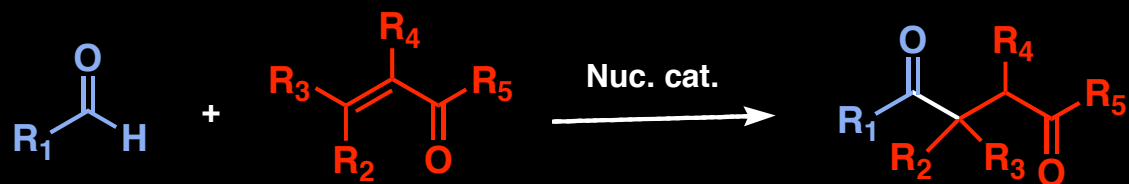

Michael Reactions with Acyl Anion Equivalents: The Stetter Reaction



Key Reviews:

Stetter, *ACIEE* (1976), 15, 639.

Seebach, *ACIEE* (1979), 18, 239.

Enders, *Acc. Chem. Res.* (2004), 37, 534.

Zeitler, *ACIEE* (2005), 44, 7506.

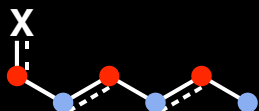
Rovis, *JOC* (2008), 73, 2033.

Adel ElSohly
Columbia Literature Seminar Series
May 2, 2008

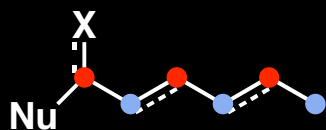


A Topological Synthetic Problem

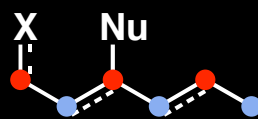
A Large number of organic reactions are controlled by polarity matching with nucleophiles attacking electrophiles. In systems with simple or conjugated π systems involving an electrophilic acceptor (usually a heteroatom), an interesting pattern emerges:



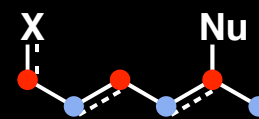
Positions with red dots are electrophilic and correspond to 1, n addition ($n = \text{even}$) while blue dots are nucleophilic. This leads to 1, n disubstituted products ($n = \text{odd}$) when general nucleophiles are introduced.



1,1 disubstitution

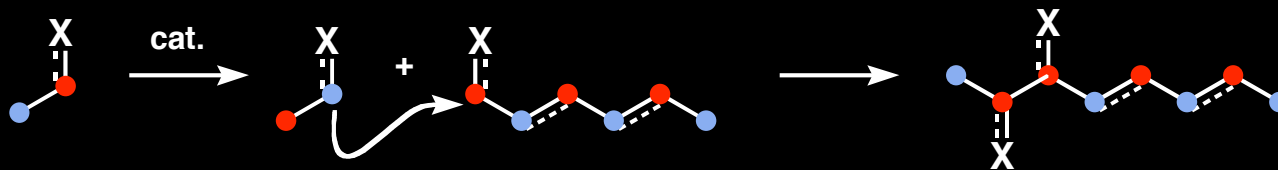


1,3 disubstitution



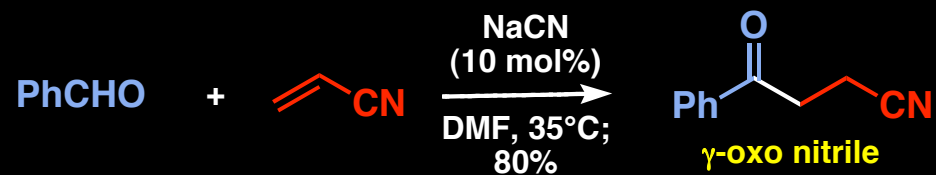
1,5 disubstitution

In order to synthesize molecules with an even number of carbons between FGs, a coupling of carbons of the **same** polarity would be required. Polarity reversal or *umpolung* allows such transformations to occur.

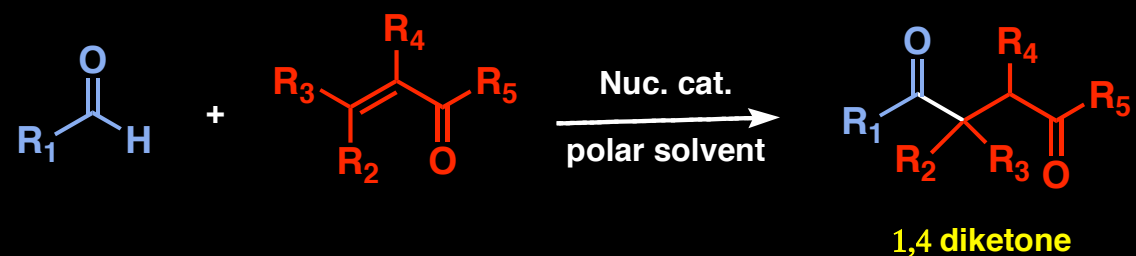


The Stetter Reaction

Early Example:



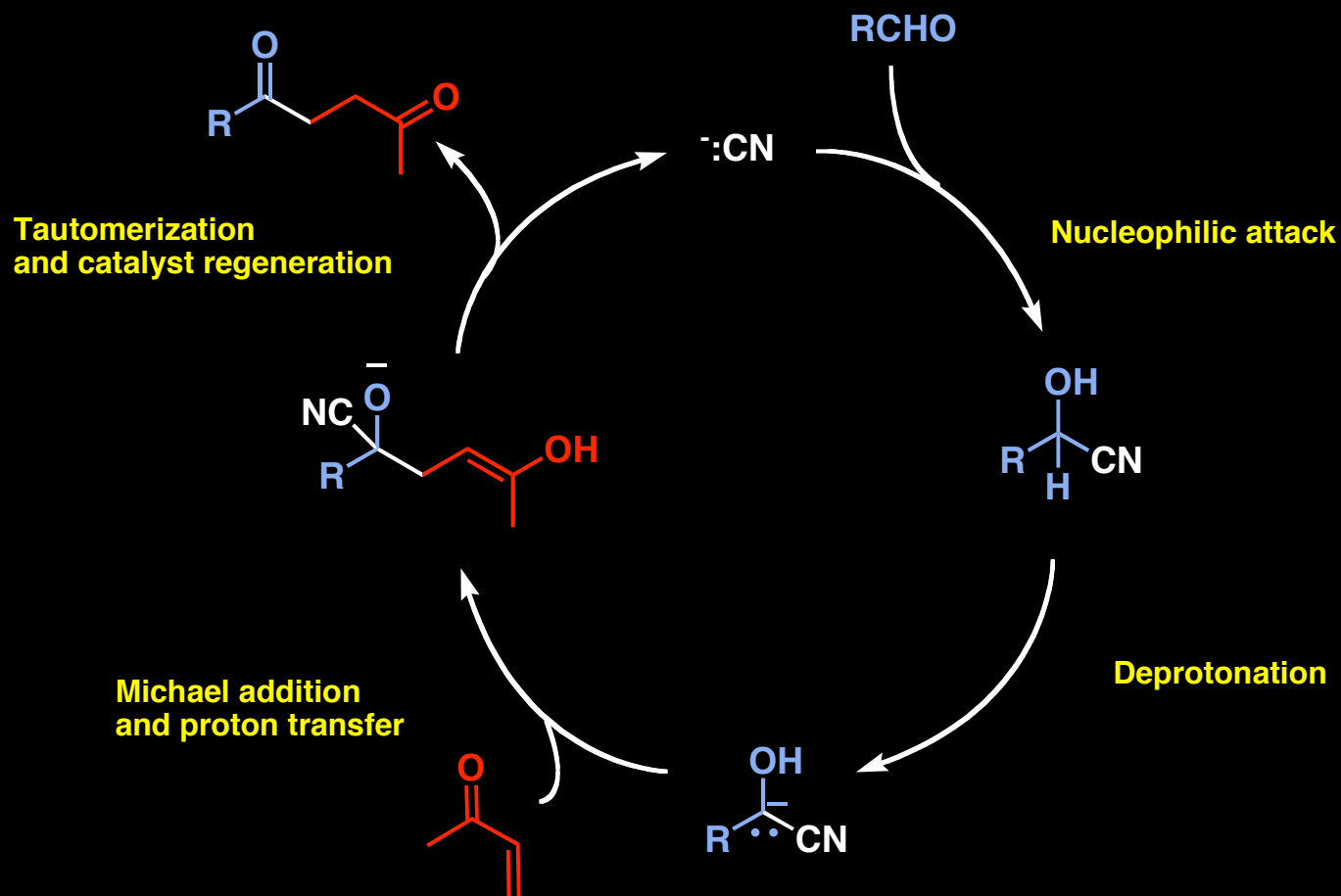
General Reaction:



Scope includes unsaturated esters, nitriles, ketones, and aldehydes

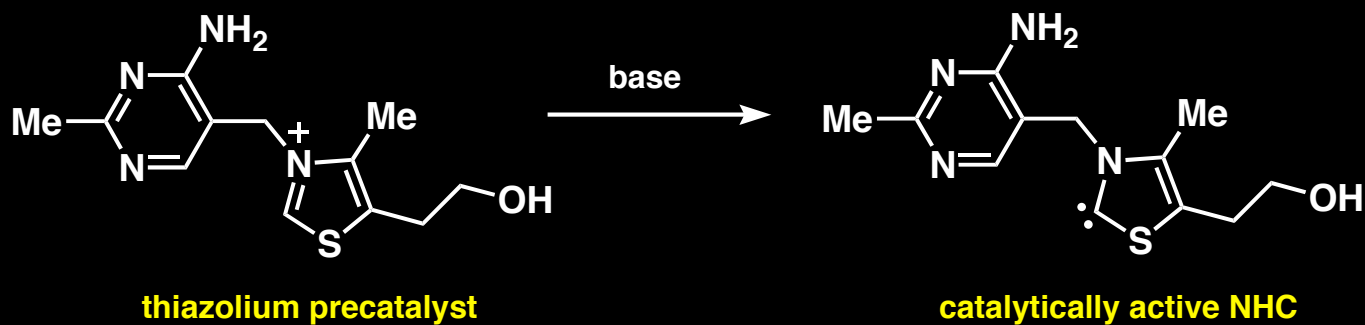
H. Stetter and M. Schreckenber, *Angew. Chem.* (1973), 85, 89.

Cyanide Catalytic Cycle



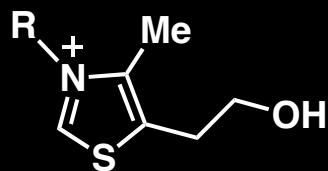
A Hint From Nature

Thiamine: Nature's NHC



Thiamine is an important cofactor in many biological processes and functions by performing polarity reversal at electrophilic centers

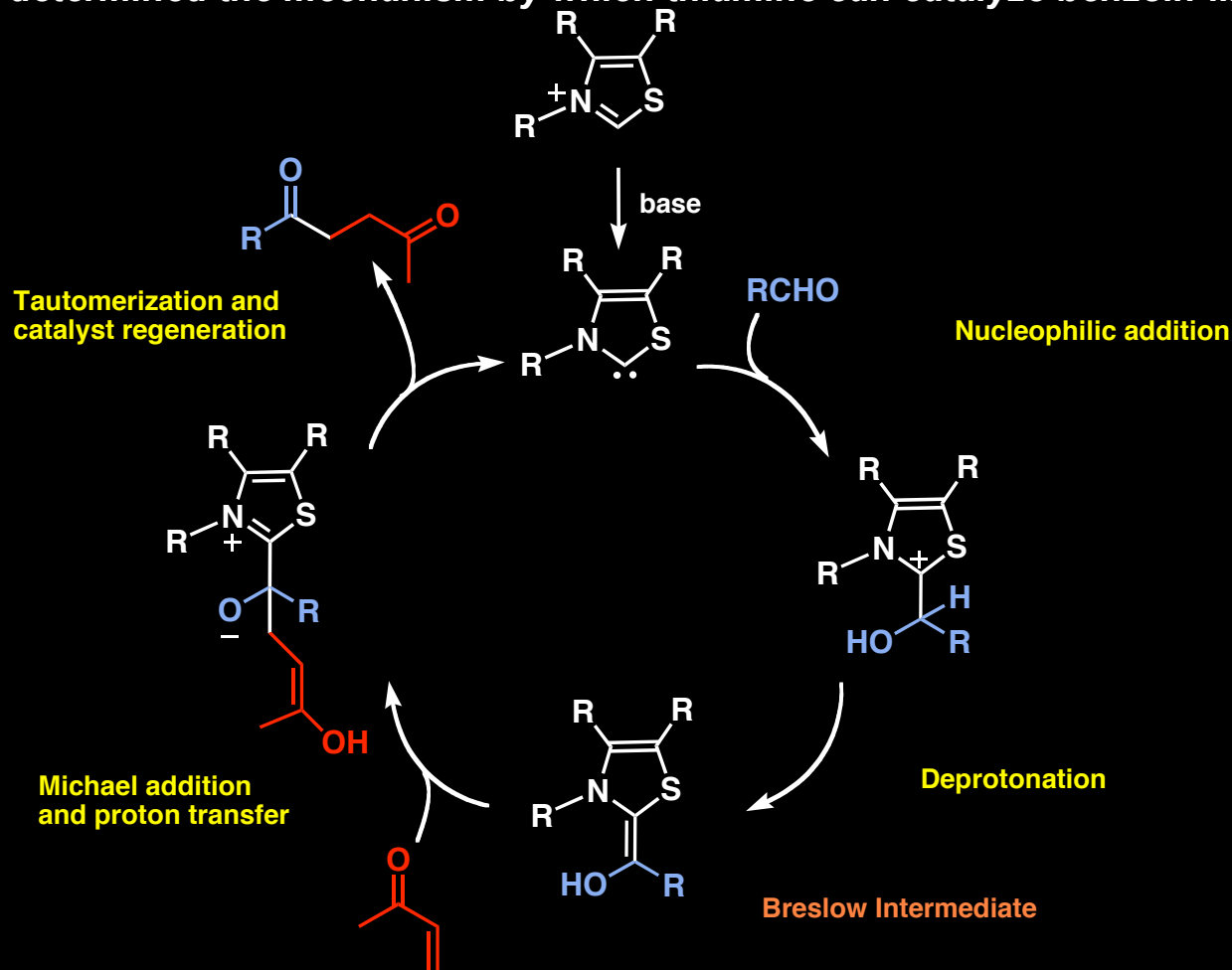
Stetter's Thiazolium Catalysts:



R = Bn, Et

Thiazolium Catalytic Cycle

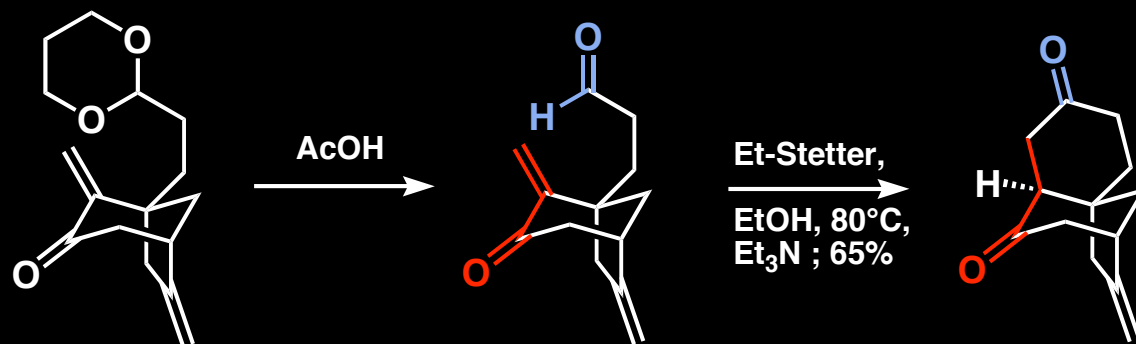
1958 - Breslow determined the mechanism by which thiamine can catalyze benzoin-like reactions



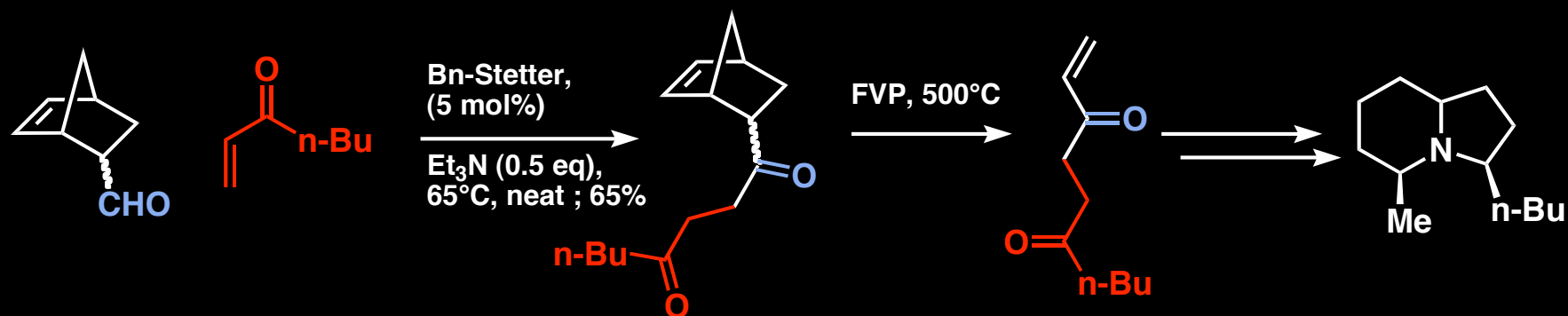
Breslow, JACS (1958), 80, 3719.

Examples from Synthesis

Nicolaou's Chiral Pool Platensimycin:



Blechert's synthesis of monomorine I

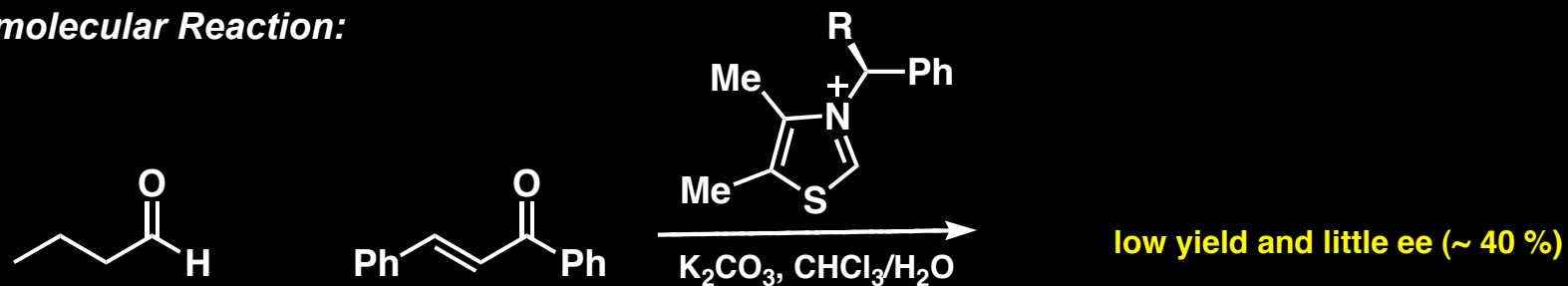


Nicolaou, *ACIEE* (2008), 120, 958

Blechert, *JOC* (2003), 68, 8879

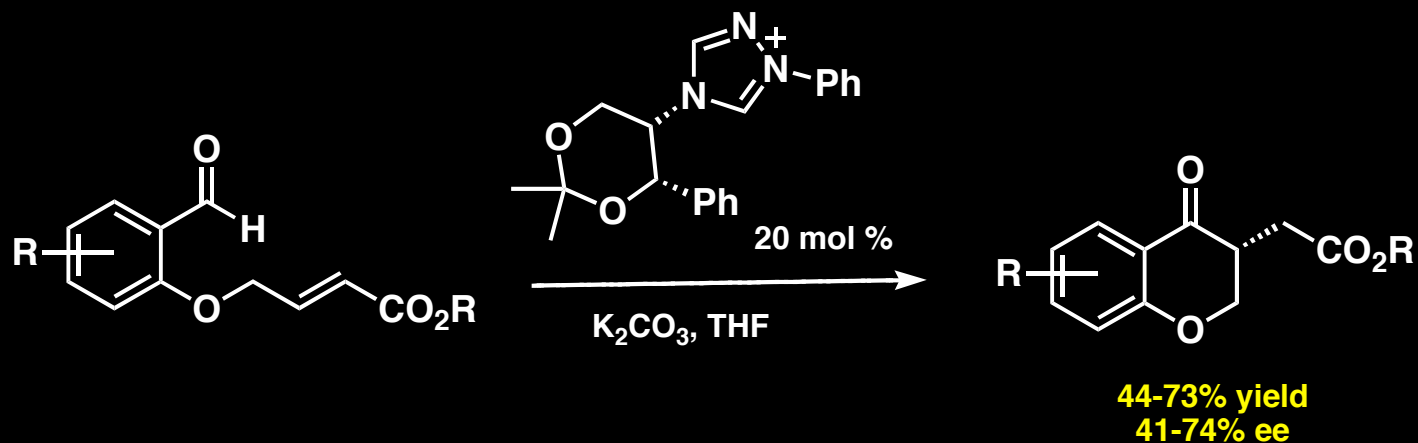
Achieving Asymmetry

Intermolecular Reaction:



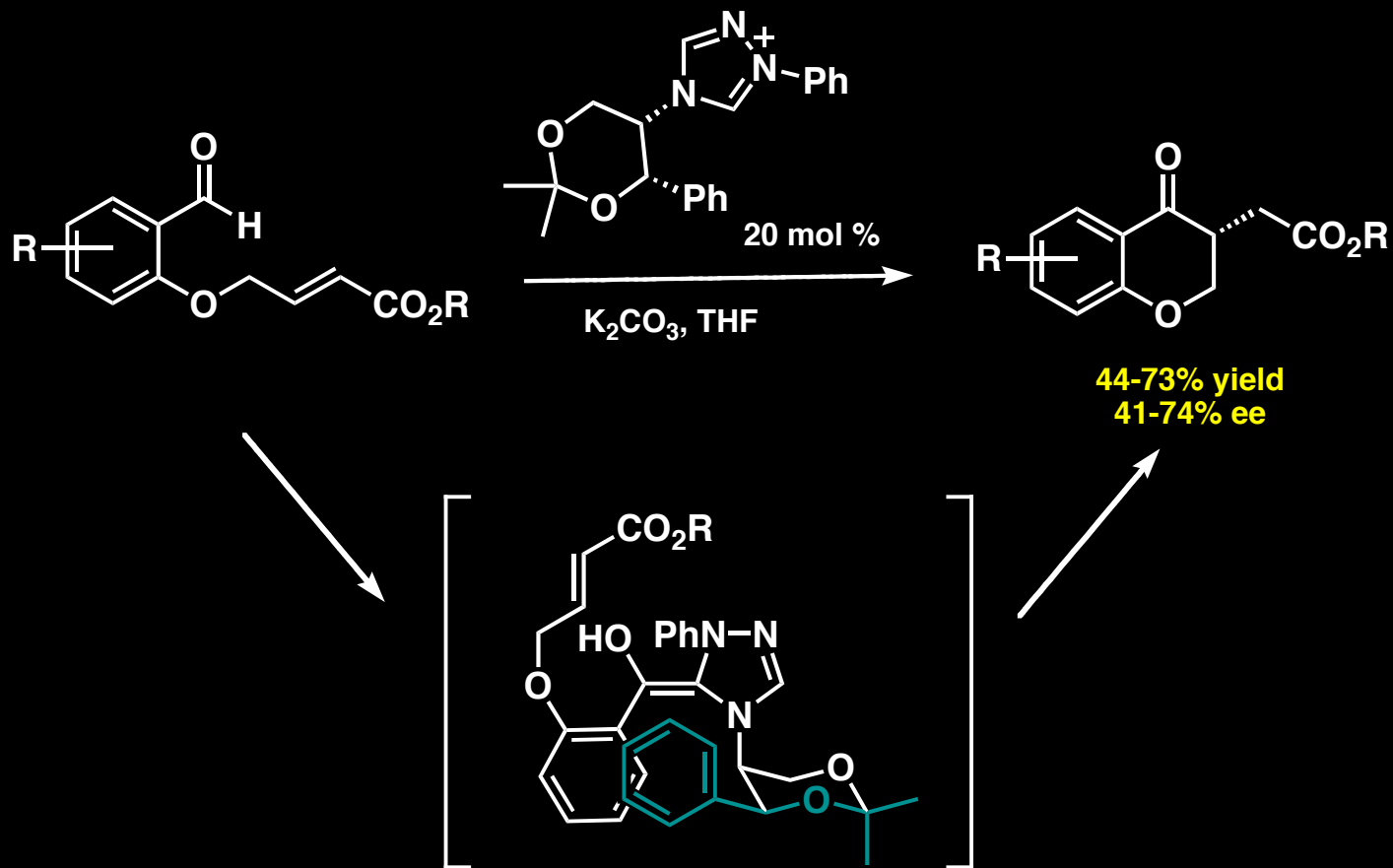
Other thiazolium based catalysts also gave low yields and poor ee

Intramolecular Reaction:



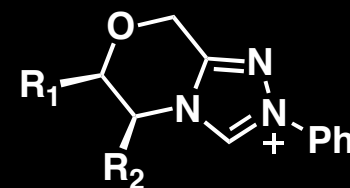
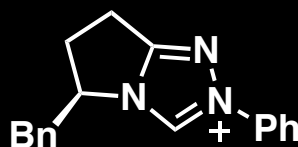
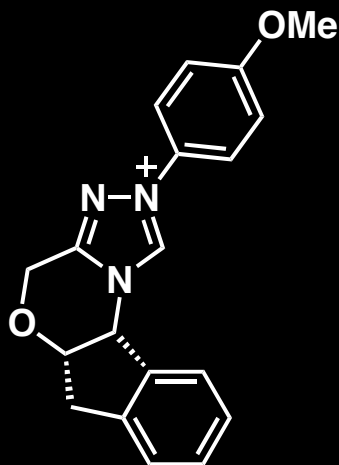
Rationale For Asymmetric Induction

Position of Phenyl ring shields one face of the olefin, allowing attack from the least hindered side



Recent Progress in Asymmetric Stetter Reactions

Triazolium-based catalysts:



These catalysts show good to excellent conversion (63-95 %) and **82-97 % ee**

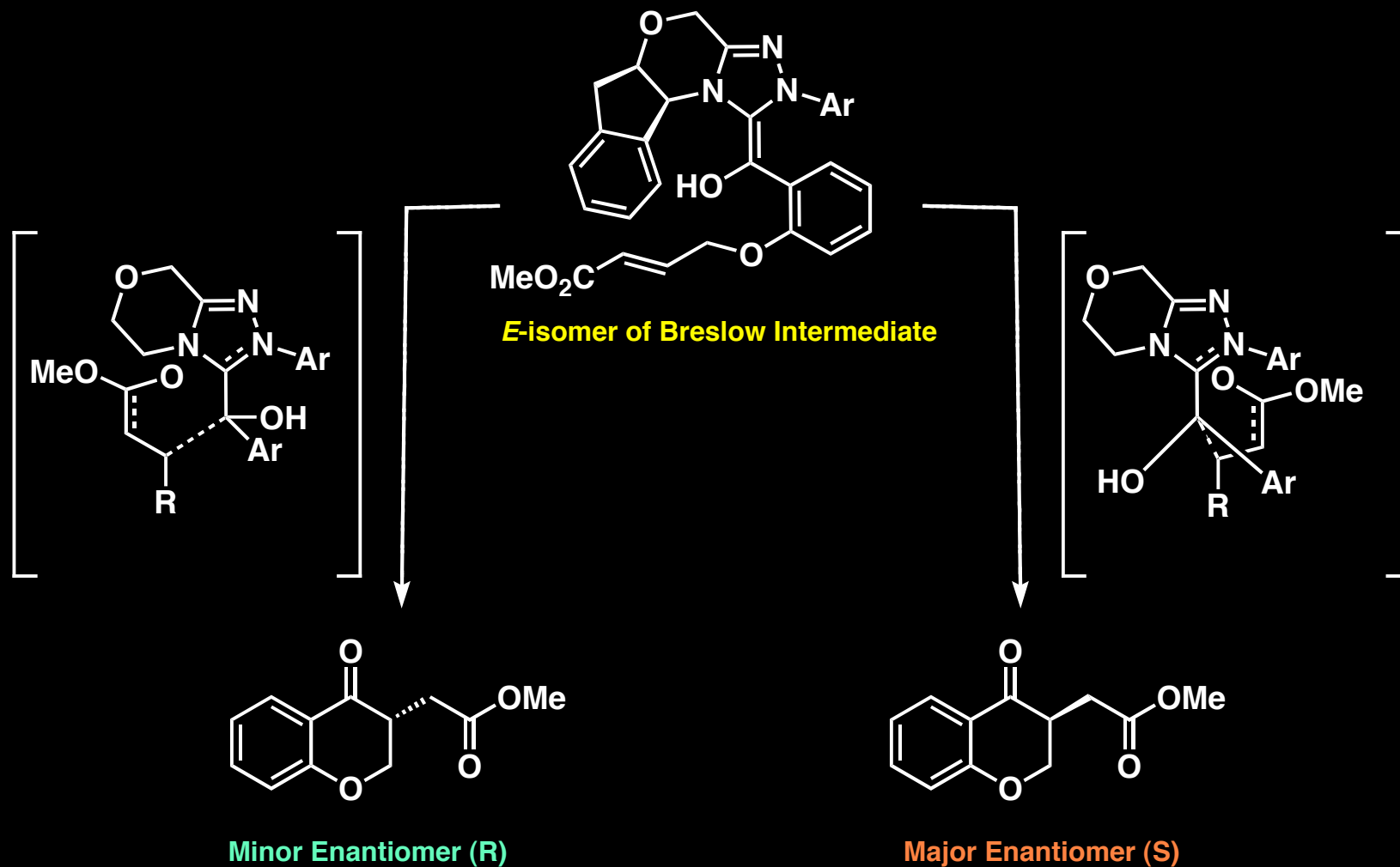
Five membered fully carbogenic rings are formed extremely well, but 6 membered rings require the use of extremely activated Michael acceptors

Quaternary stereocenters can also be forged with up to **99 % ee**

Rovis, *JACS* (2002), 124, 10298

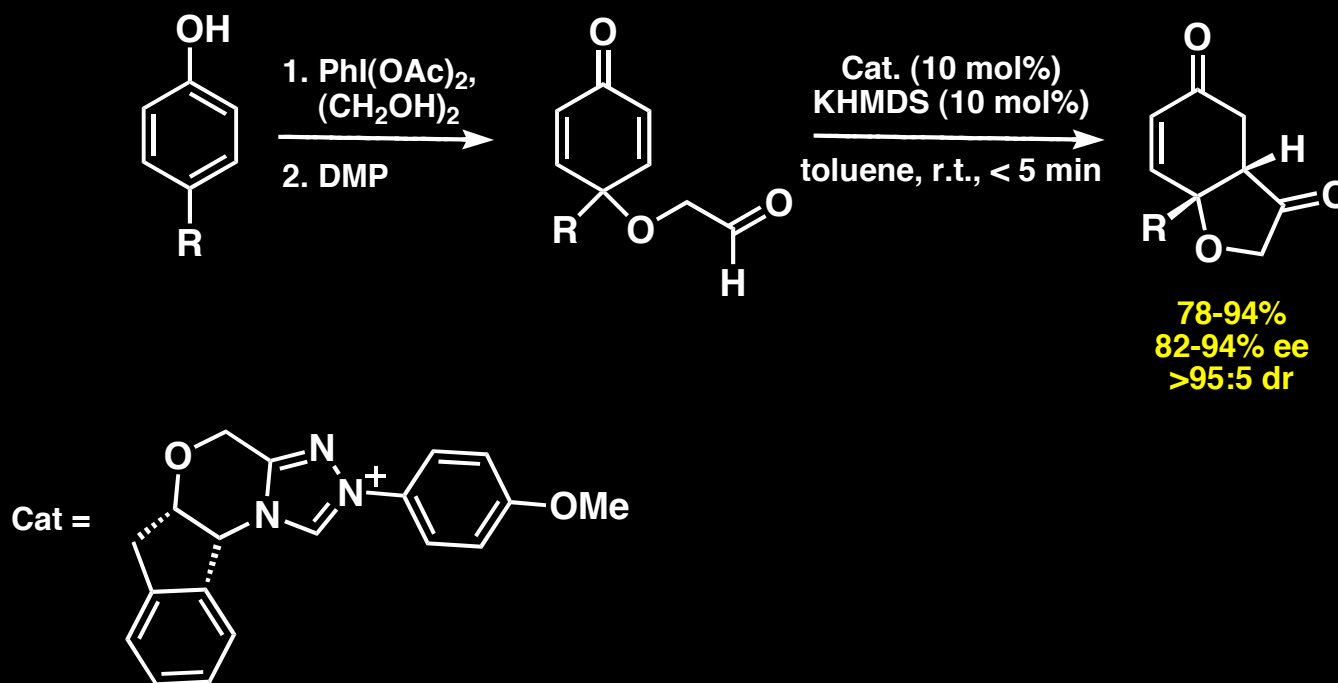
Rovis, *JOC* (2008), 73, 2033.

Stereochemical Model for Rovis' Catalysts



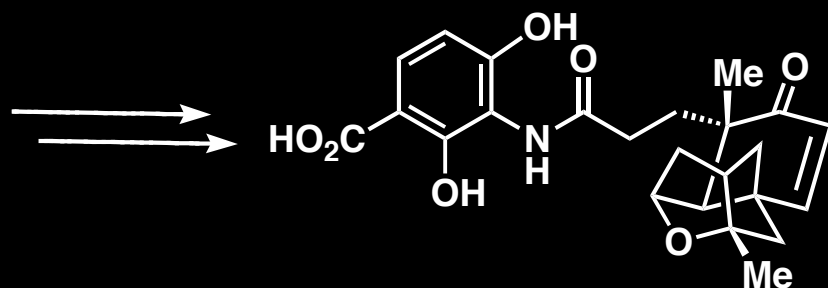
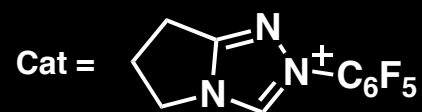
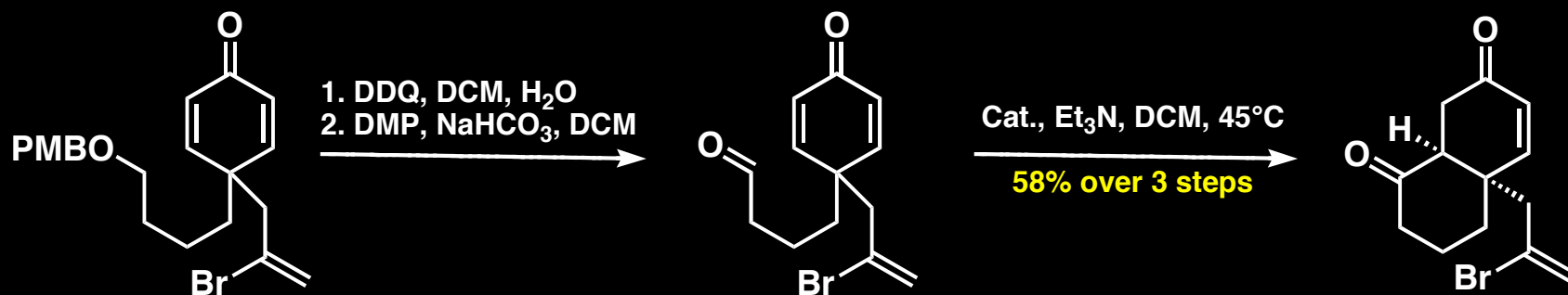
Rovis, *JOC* (2008), 73, 2033.

Desymmetrization with Asymmetric Catalysts



Fully carbogenic bicycles can also be forged in this manner with >90% ee.

Recent Example of Desymmetrization in Total Synthesis



Future Directions

*No general methods currently exist to apply asymmetric **intermolecular** Stetter reactions*

Better yield for reactions forging 6-membered rings in an intramolecular fashion

High chemoselectivity for systems incorporating multiple electrophilic centers
