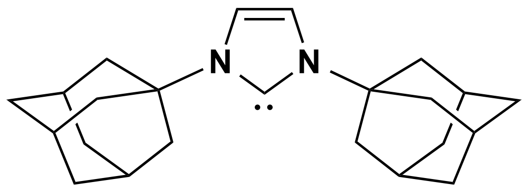
Selected topics in metal-free catalysis:
Carbenes (and Lewis Base) Catalysis



Martin Smith
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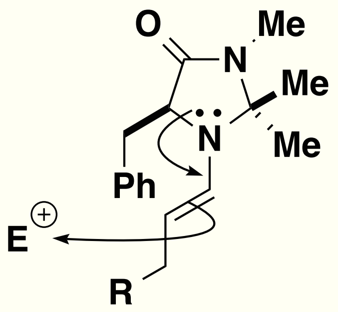
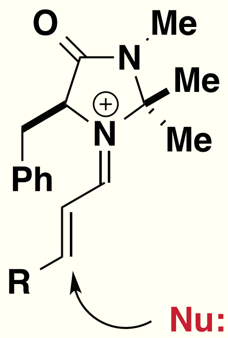
UNIVERSITY OF OXFORD

Selected topics

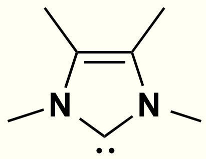
Enamine



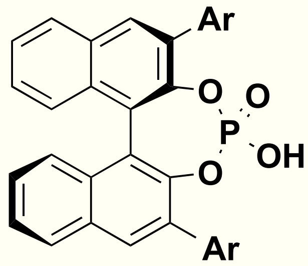
Iminium



Lewis/ Brønsted Base



Brønsted Acid



All of these topics are of direct relevance to contemporary synthetic chemistry

This is a very selective treatment of topics that are not a focus of most undergraduate courses

Course outline and contents

1. General considerations: types of reaction, scope and focus of this (truncated) course

2. N-heterocyclic carbenes: This course will focus on:

(i) background and history of carbene-mediated reactions

(ii) application in catalysis (both asymmetric and racemic examples)

This is a very selective treatment of what is a large and complex area: the aim is to focus on contemporary developments in (mostly) catalytic reactions and understand how and why these processes are effective

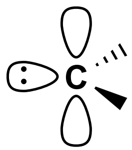
N-Heterocyclic Carbenes

What is a carbene?

A neutral molecule containing a divalent carbon atom with six electrons in its valence shell

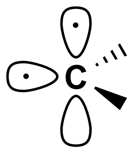
Two possible ground-state electronic structures::

Singlet Carbene



Filled sp^2 hybridised orbital
Empty p-orbital
Nucleophilic and electrophilic (ambiphilic)
Most important ground state for catalysis

Triplet Carbene

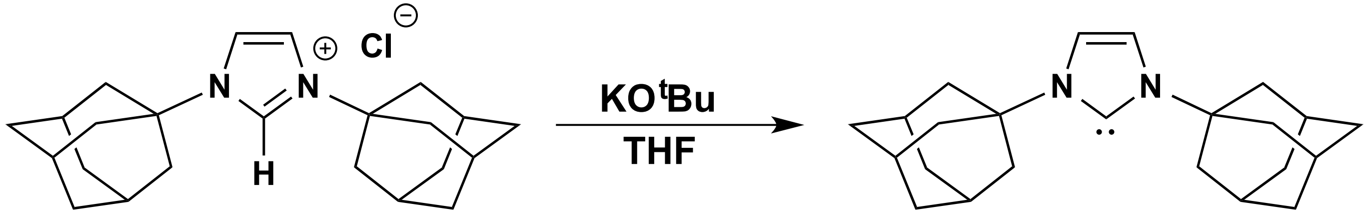


Two singly occupied orbitals
React as diradicals
More reactive, but less stable
Of less direct relevance to synthetic chemistry

Stability and reactivity of carbenes depends on electronic and steric factors

Carbene stabilization

Isolation and preparation of a free carbene



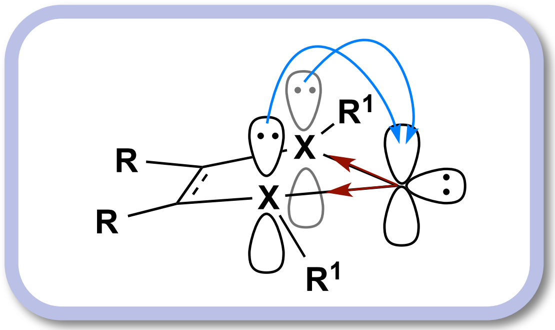
Use bulky groups to stabilize carbene

Stable solid (m.p. 240˚C)
in absence of H_2O and O_2

J. Am. Chem. Soc. **1991**, *113*, 361

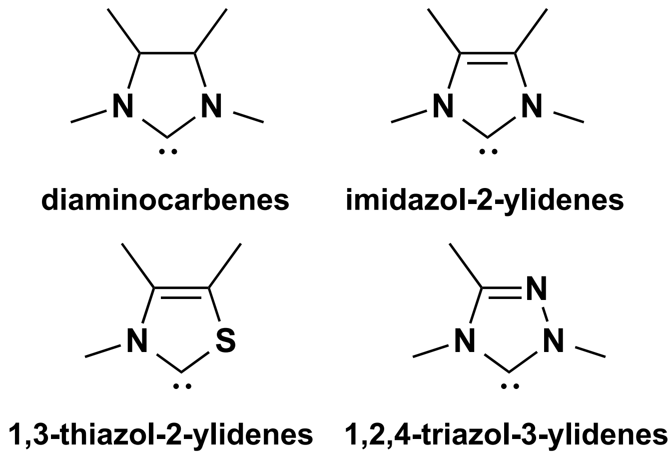
Electronic Stabilization operates in both σ- and π- framework

π-donation into empty p-orbital from adjacent heteroatoms stabilizes electrophilic reactivity



σ-withdrawal by adjacent electronegative atoms stabilizes nucleophilic reactivity

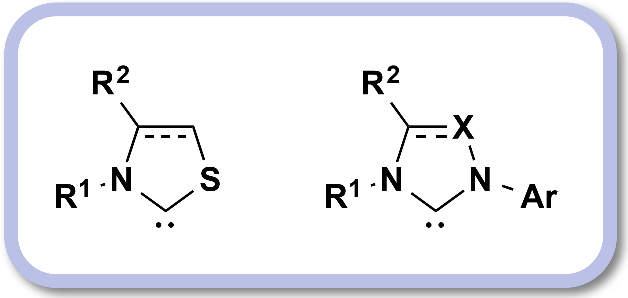
"Push-Pull" synergistic effect stabilizes singlet carbenes



Aldrichimica Acta **2009**, *42*, 55; *Chem. Rev.* **2000**, *100*, 39

NHC reactivity

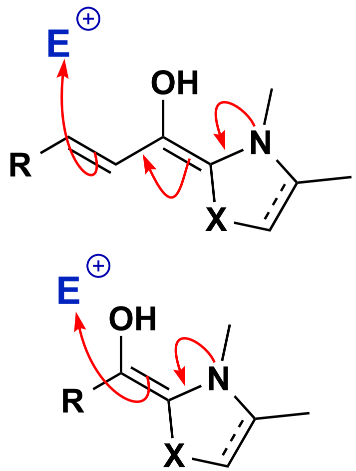
- **Nucleophilic character of NHCs makes them good Lewis base organocatalysts**



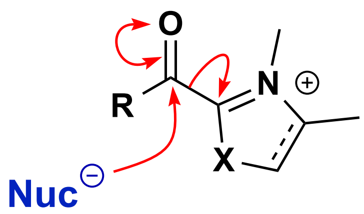
Many variations possible – sterics and electronics of substituents are important

- **Typical modes of reactivity:**

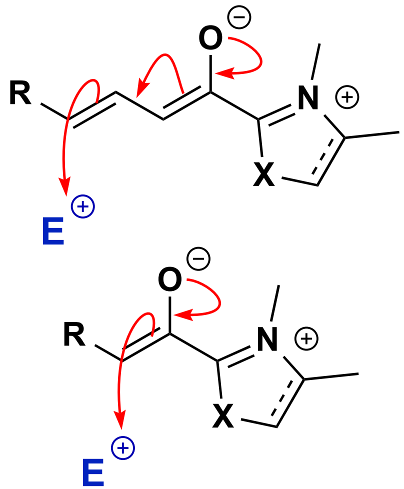
Umpolung



Acyl Transfer



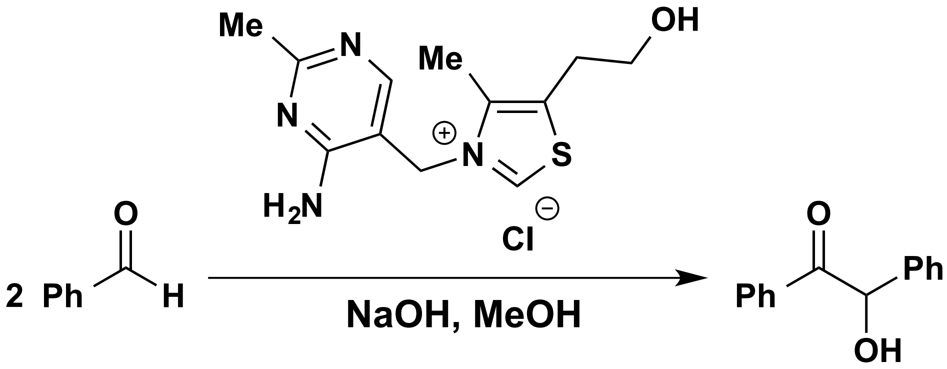
Enolate reactivity



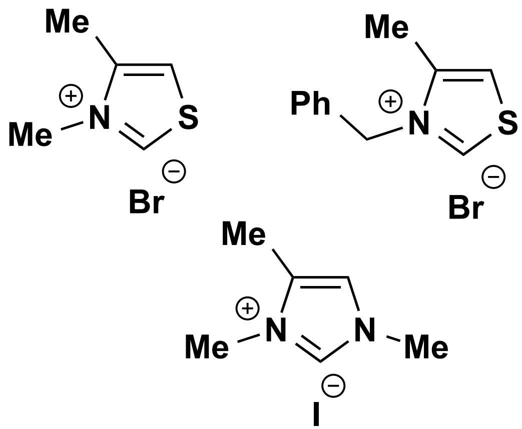
Chem. Rev. **2009**, *109*, 3612

Thiamine catalysed benzoin reaction

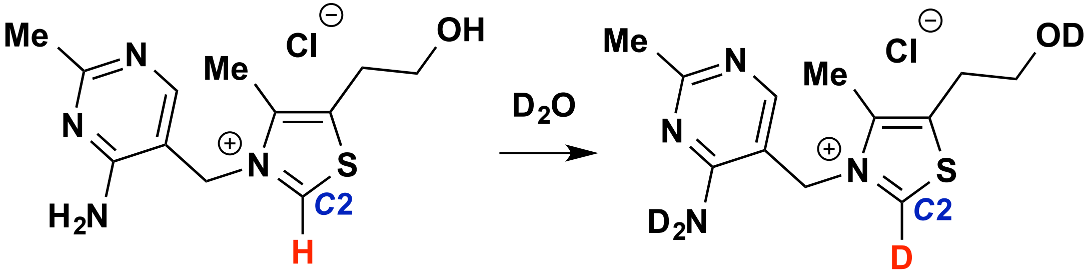
- **1943: Ugai demonstrates that vitamin B1 catalyses the Benzoin reaction (unknown mech.)**



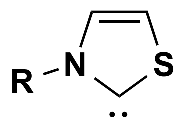
Other related salts also effective:



- **1958: Breslow shows that the C2 proton of thiamine undergoes H/D exchange**



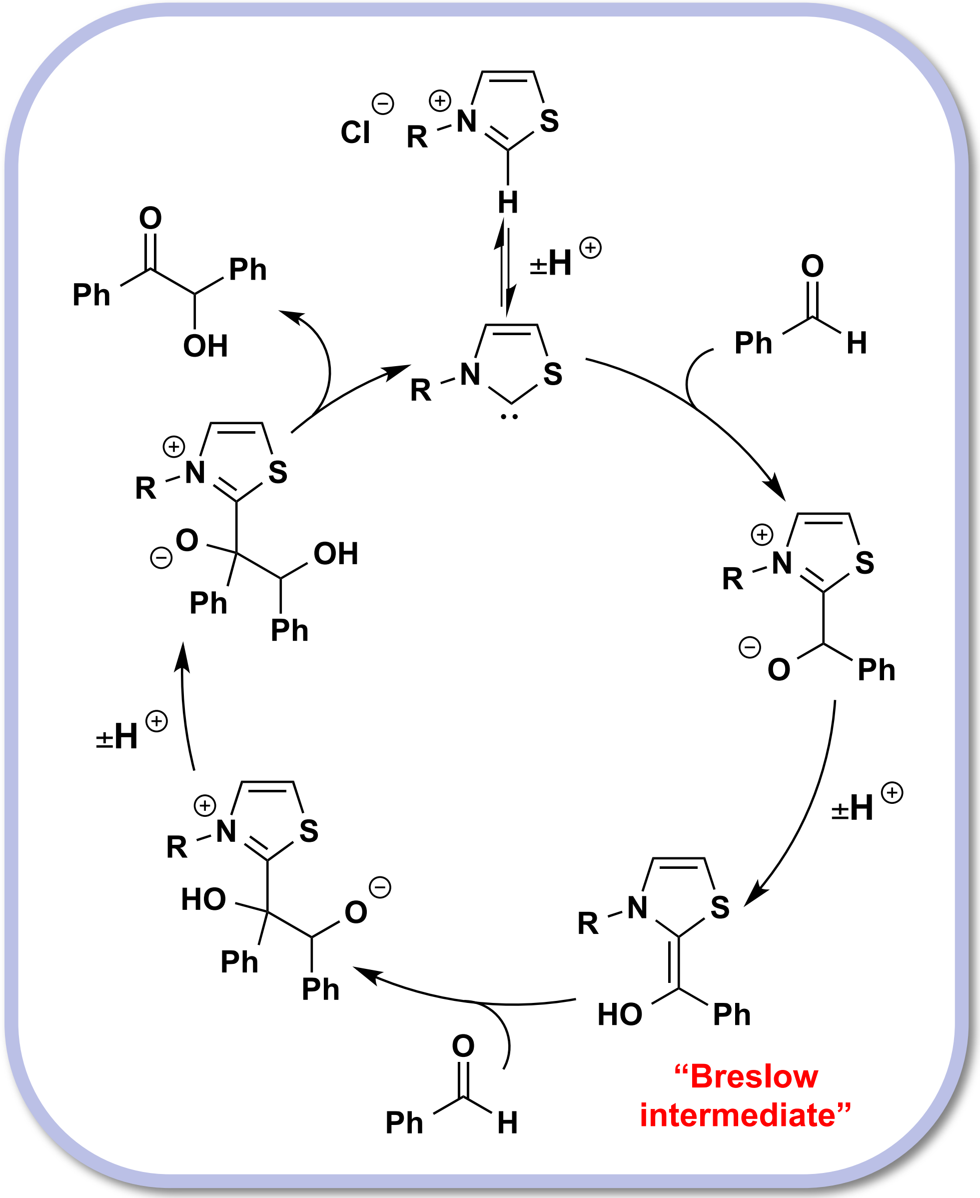
Suggests that "Zwitterion" (*aka* a carbene) is responsible for catalysis

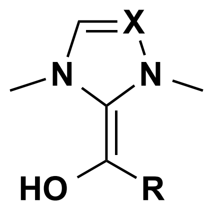


N-Heterocyclic Carbene

J. Pharm. Soc. Jpn. **1943**, *63*, 296; *J. Am. Chem. Soc.* **1958**, *80*, 3719

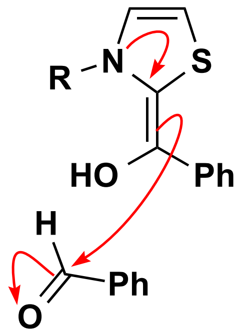
Proposed mechanism





Breslow intermediate

This (postulated) intermediate acts as an acyl anion equivalent

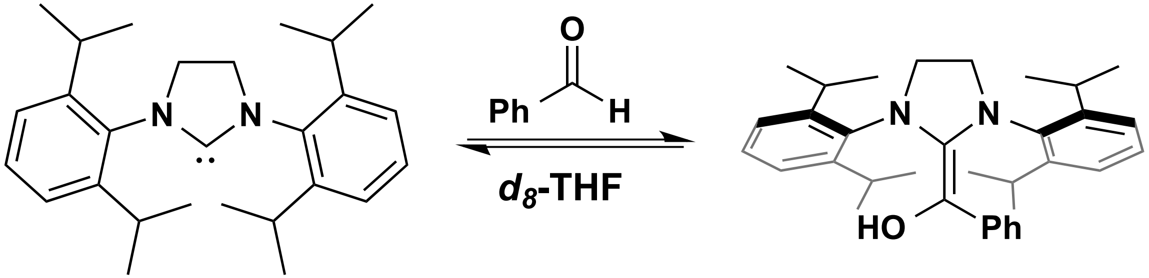


Umpolung reactivity

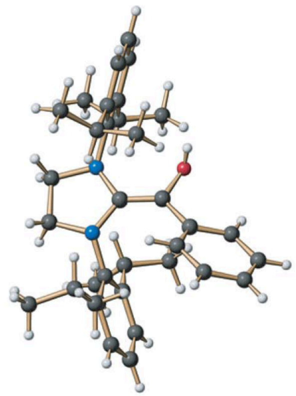
All steps reversible to some extent
No single step fully rate-determining

Isolation of the Breslow intermediate

2012: First direct (spectroscopic) evidence for Breslow intermediate

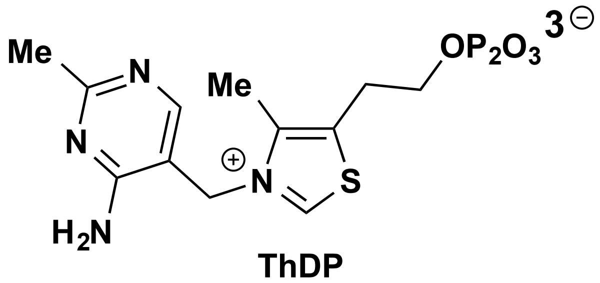


Breslow intermediate can be observed under strictly anhydrous conditions; requires very specific carbene

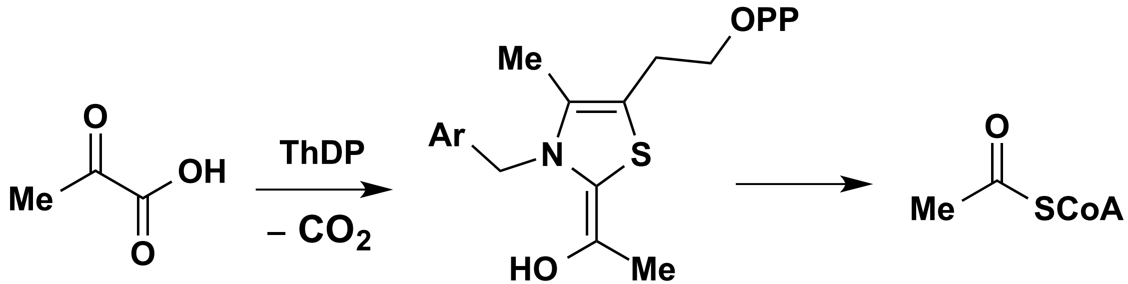


X-ray

Pyruvate decarboxylase



Cofactor mediates a range of reactions via a Breslow type intermediate

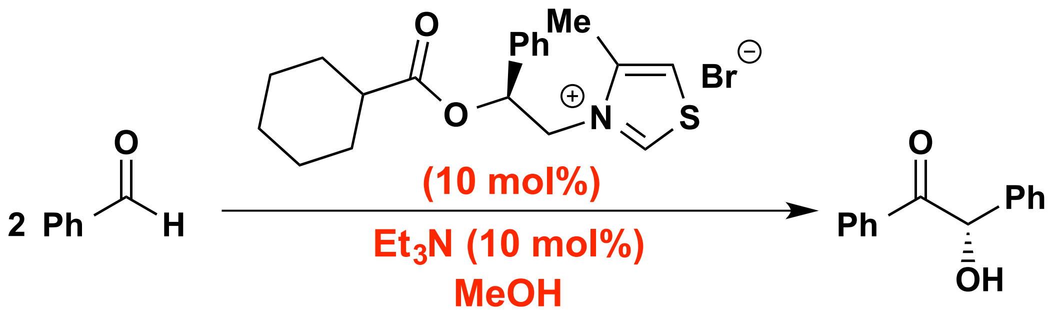


Breslow Intermediate

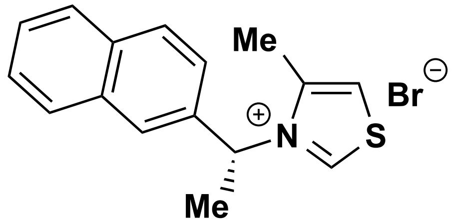
Angew. Chem. Int. Ed. **2012**, *51*, 12370; *Angew. Chem. Int. Ed.* **2013**, *52*, 11158; *Nat. Prod. Rep.* **2003**, *20*, 184

Asymmetric benzoin condensation

- **First examples using chiral NHC reported by Sheehan (1966 & 1974)**

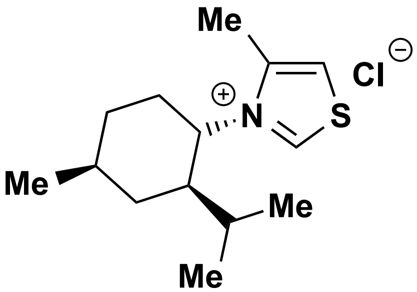


9% yield
22% ee

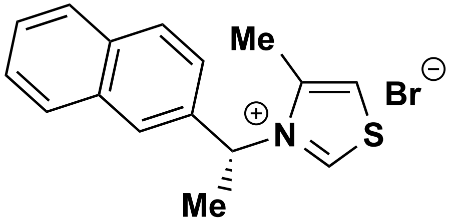


Higher ee at the expense of yield (6% yield, 52% ee)

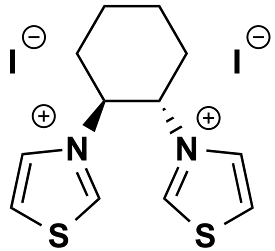
- **Other thiazolium salts examined but yield and selectivity still a problem**



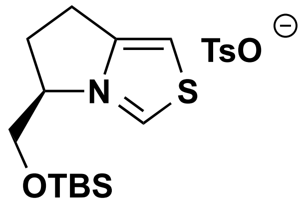
Takagi (1980)
up to 20% yield
up to 35% ee



Zhao (1988)
up to 30% yield
up to 57% ee



López-Calahorra (1993)
21% yield
27% ee

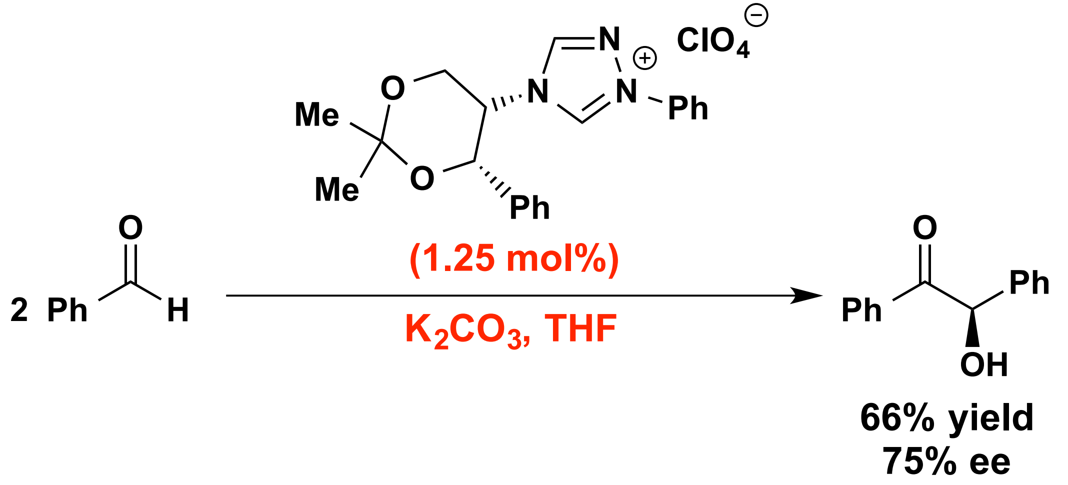


Leeper (1997)
up to 50% yield
up to 21% ee

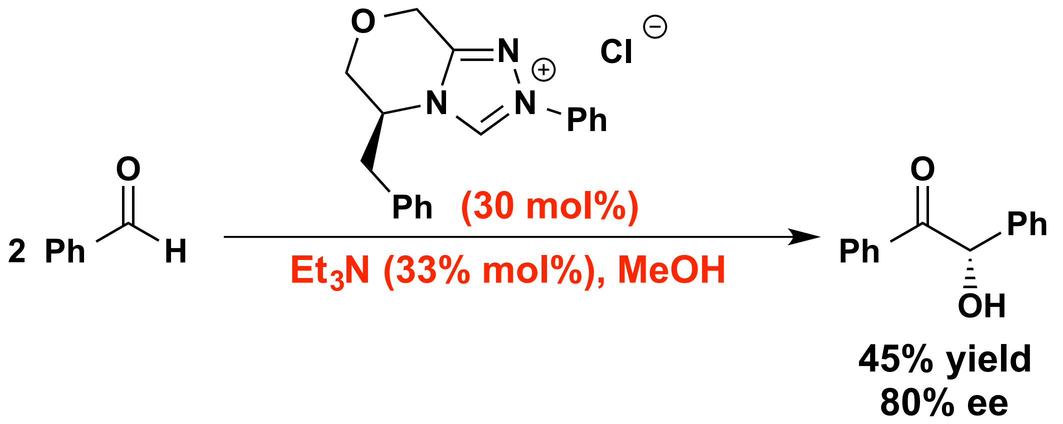
Acc. Chem. Res. **2004**, *37*, 534

Asymmetric benzoin condensation

- **Breakthrough using enantiometrically pure triazolium salt (Enders, 1996)**



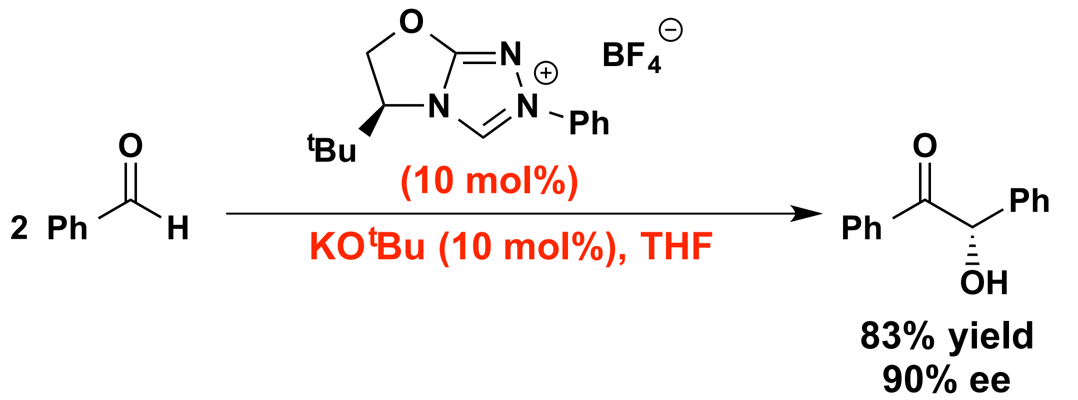
- **A bicyclic variant can also be used to give high enantioselectivity (Leeper, 1998)**



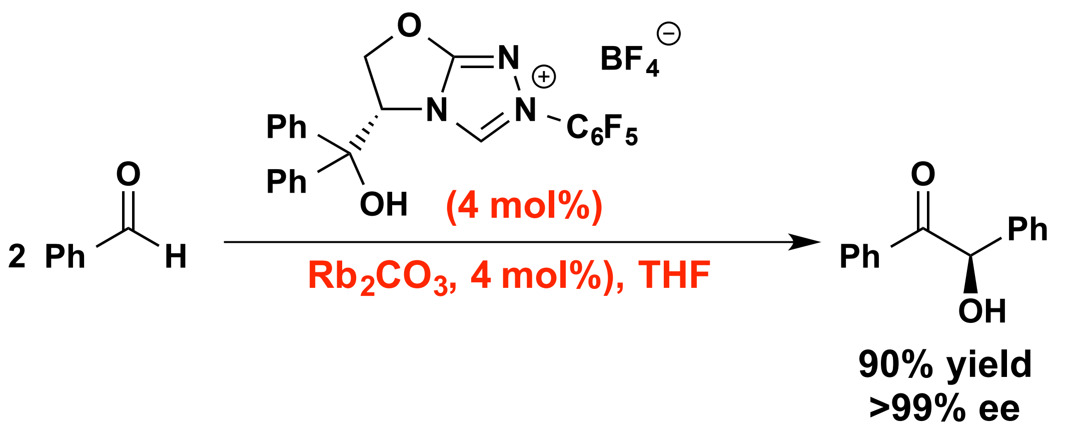
Helv. Chim. Acta **1996**, *79*, 1217; *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891

Asymmetric benzoin condensation

- **Evolution of bicyclic triazolium (pre) catalyst gives improved yield and enentioselctivity**

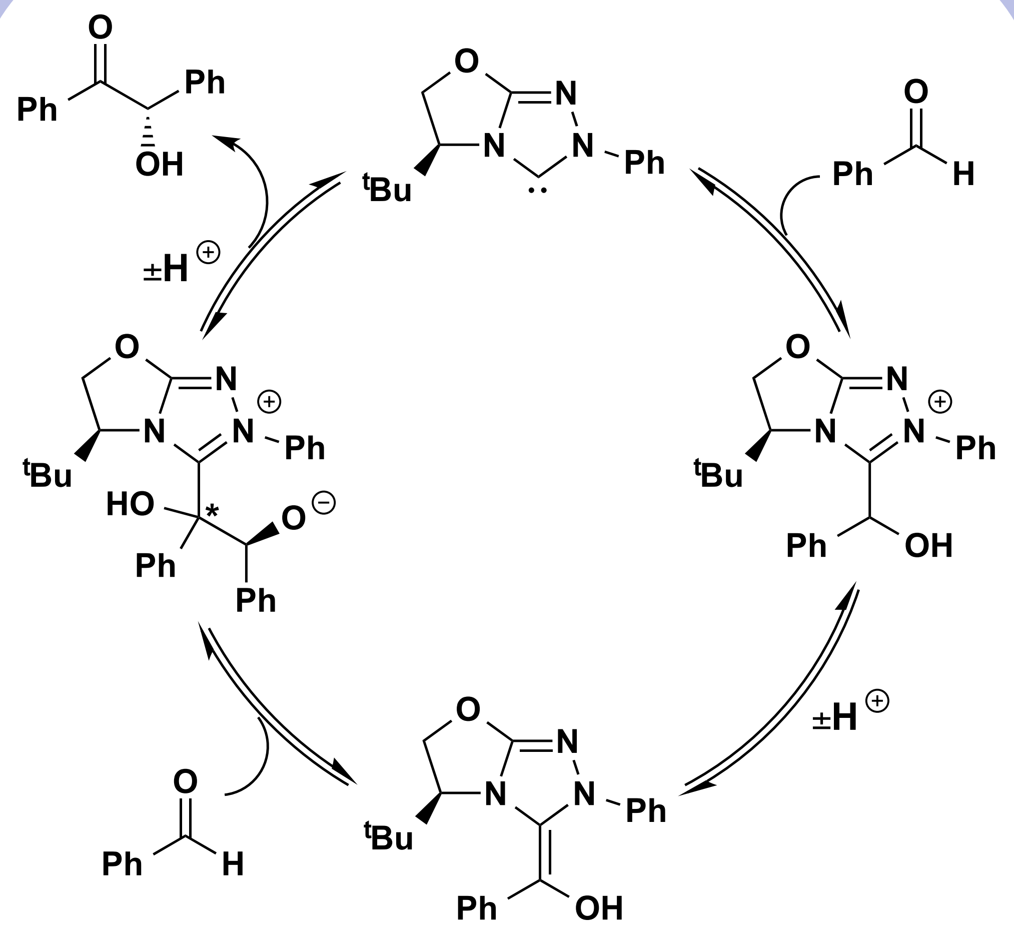


- **….and incorporation of a directing group gives excellent overall yield and selectivity**



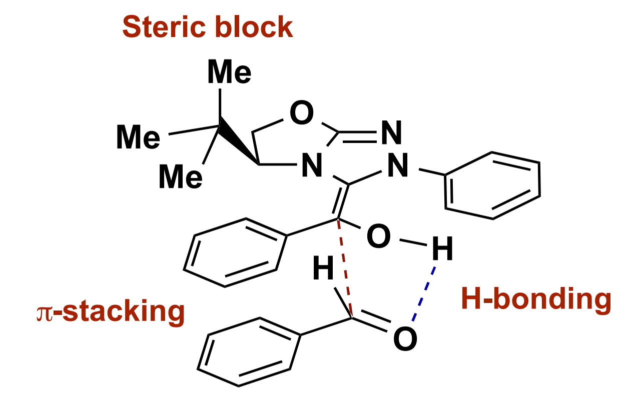
Angew. Chem. Int. Ed. **2002**, *41*, 1743; *J. Org. Chem.* **2009**, *74*, 9214

Stereochemical rationale (for bicyclic catalysts)



Stereochemistry determined during attack of Breslow intermediate onto the aldehyde

Stereochemistry obtained from *Re* face attack of the Breslow intermediate onto the *Re* face of the aldehyde

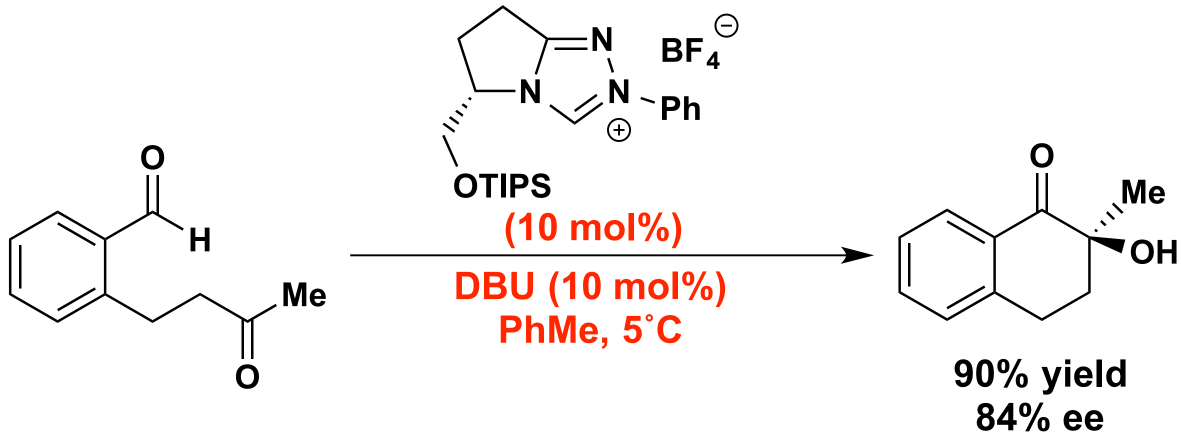


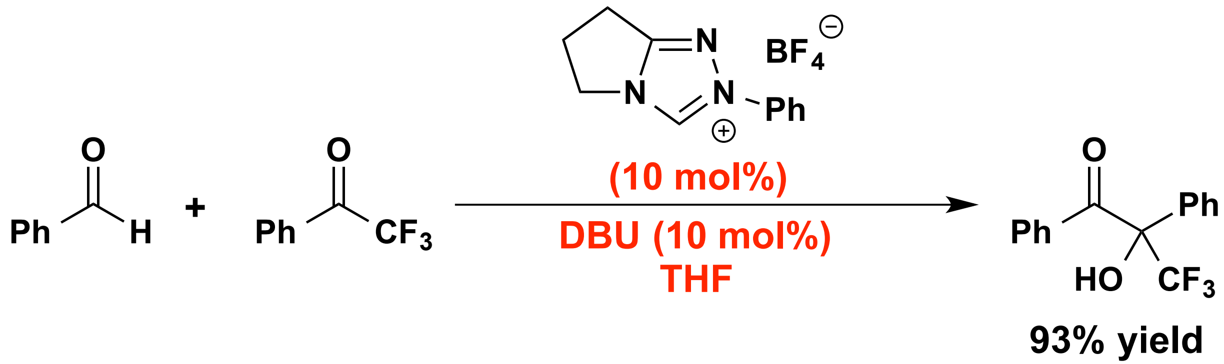
However, *E/Z* geometry of Breslow intermediate is unknown

Computational work suggests an alternative transition state with no π-stacking

Crossed Benzoin

- **Use electrophilic components of differing reactivity to get selectivity**

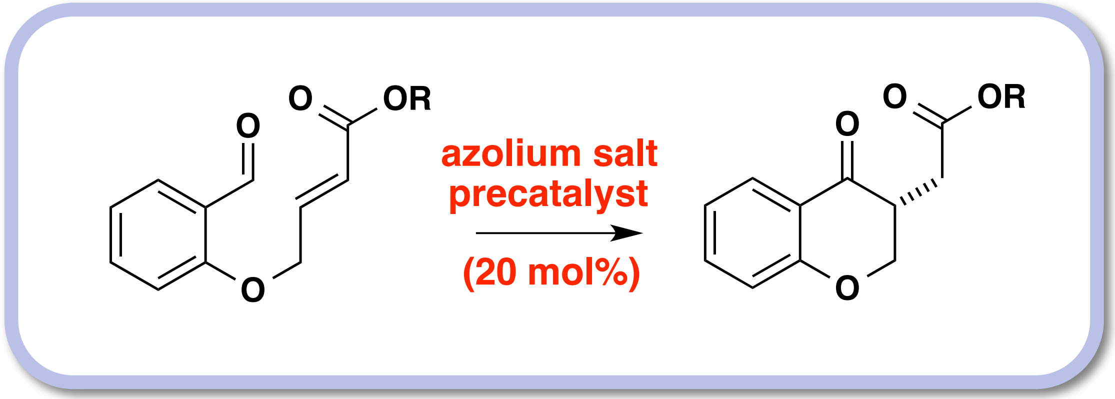




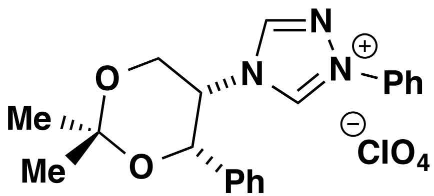
Angew. Chem. Int. Ed. **2006**, *45*, 1463; *Adv. Synth. Catal.* **2009**, *351*, 1749

Stetter reaction: another acyl anion equivalent

Intramolecular Stetter reaction

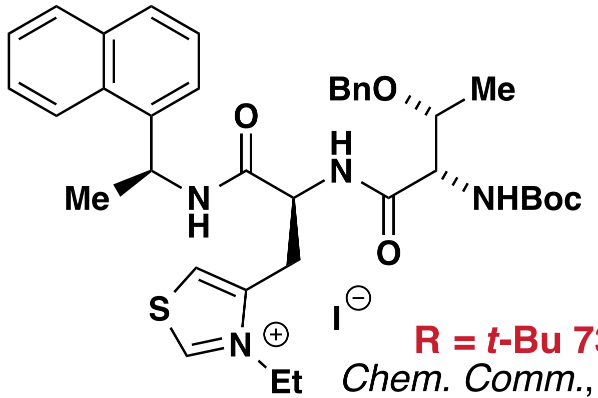


Triazolium salts are very effective (pre)catalysts



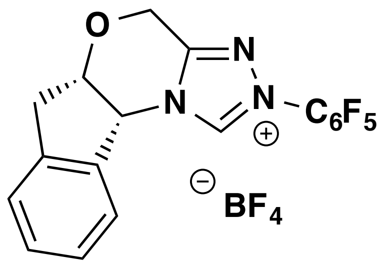
R = Me 60% ee

Helv. Chim. Acta, **1996**, *79*, 1899



R = *t*-Bu 73% ee

Chem. Comm., **2005**, 195

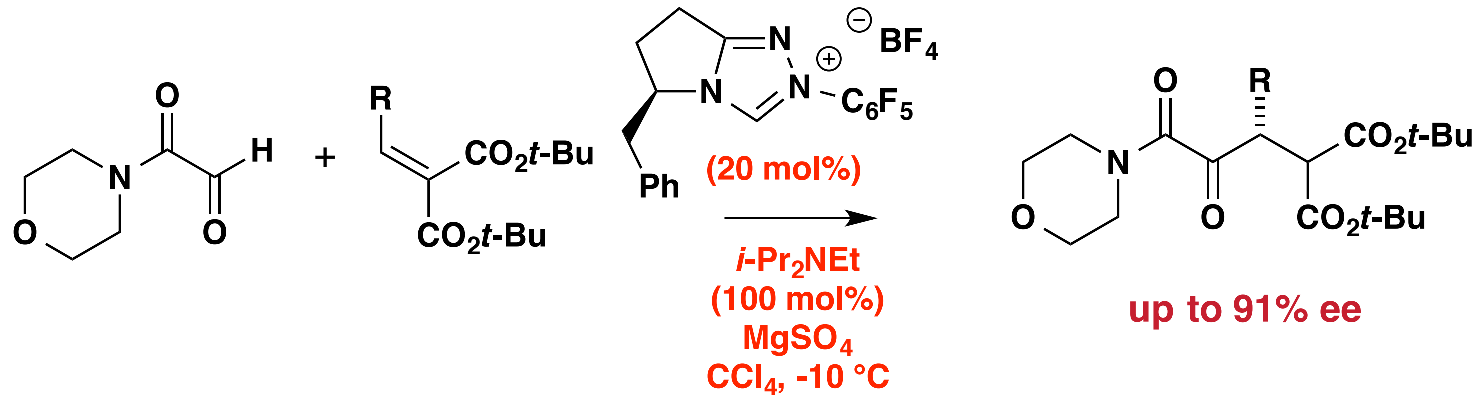


R = *t*-Bu, 94%, 97% ee

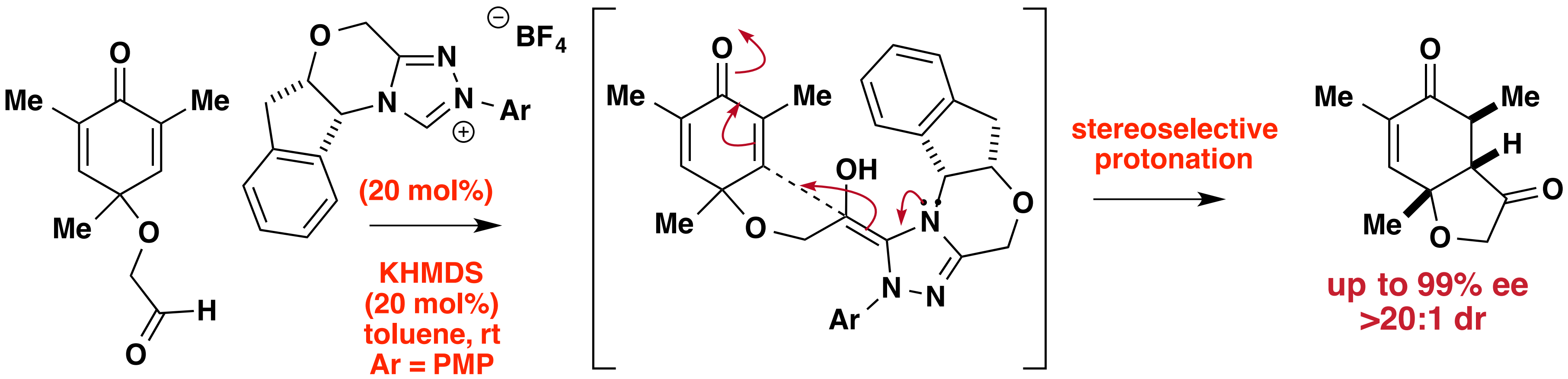
JACS **2002**, *124*, 10299

Stetter reaction: another acyl anion equivalent

Intermolecular Stetter reaction(s): Glyoxaldehydes and alkylidene malonates



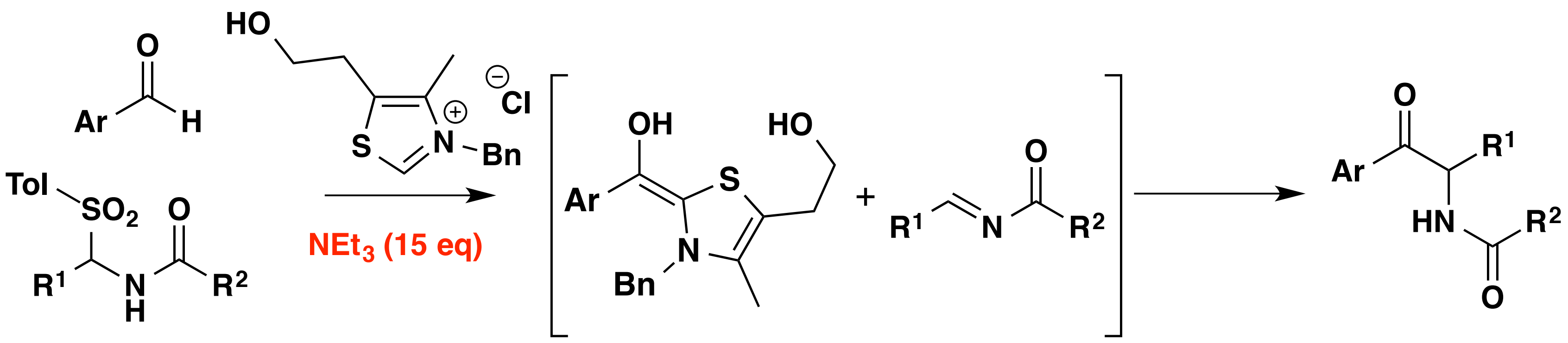
Desymmetrisation of cyclohexadienones



J. Am. Chem. Soc., **2008**, *130*, 14066 *J. Am. Chem. Soc.*, **2006**, *128*, 2522

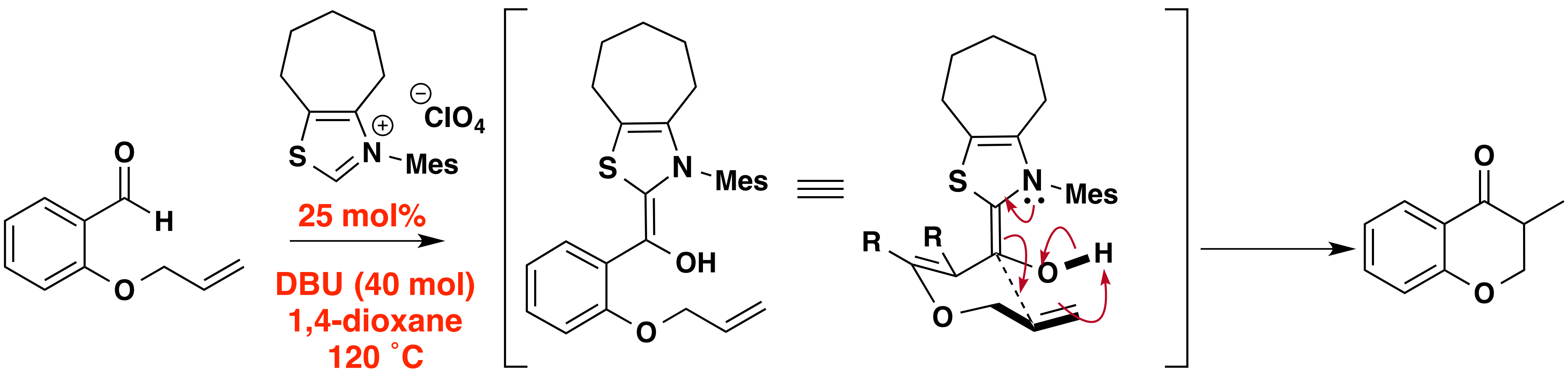
Alternative acyl anion equivalent applications

Cross-coupling of aldehydes and acyl imines



JACS **2001**, *123*, 9697

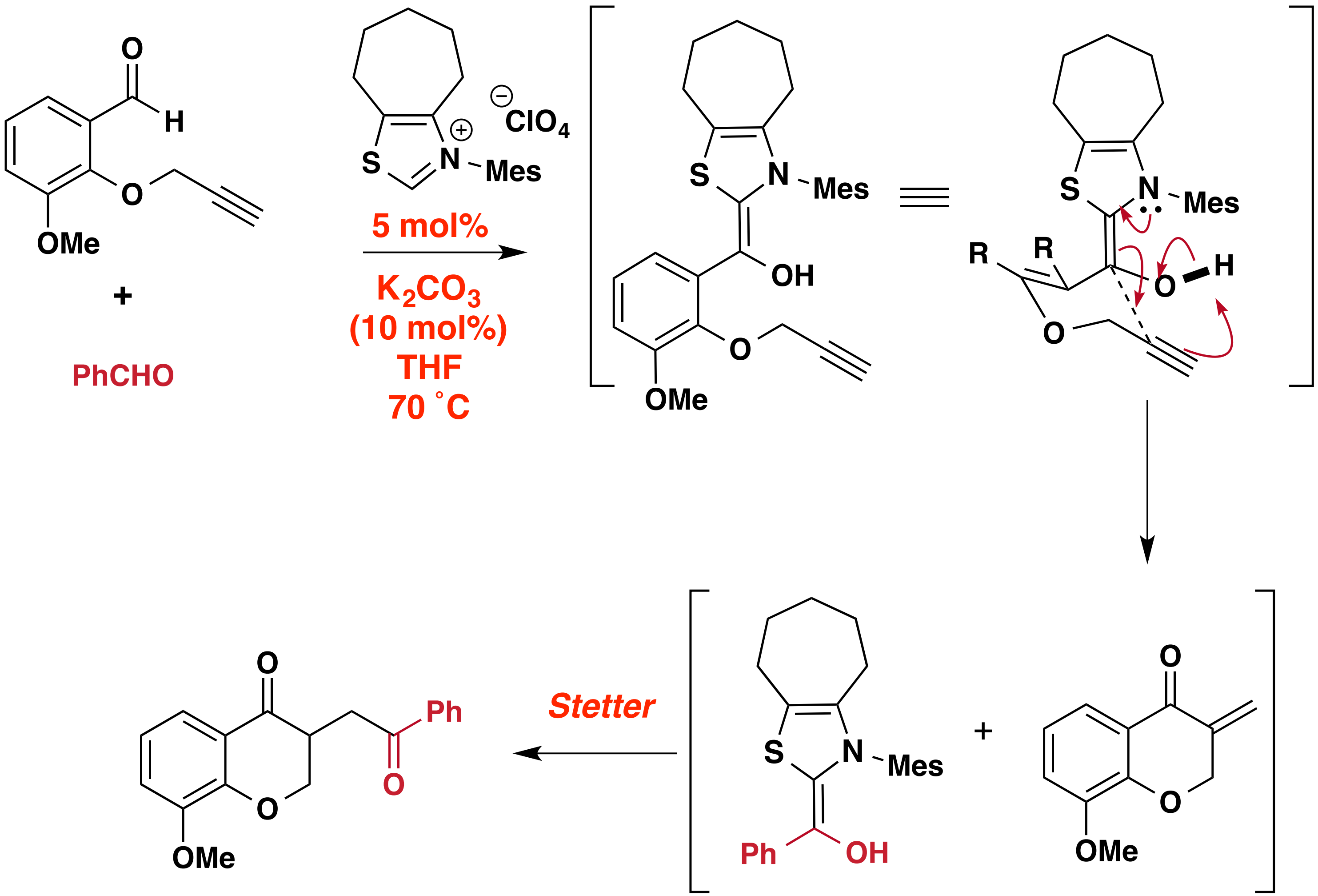
Recent Progress: Hydroacylation of Unactivated Double bonds



JACS **2009**, *131*, 14191

Alternative acyl anion equivalent applications

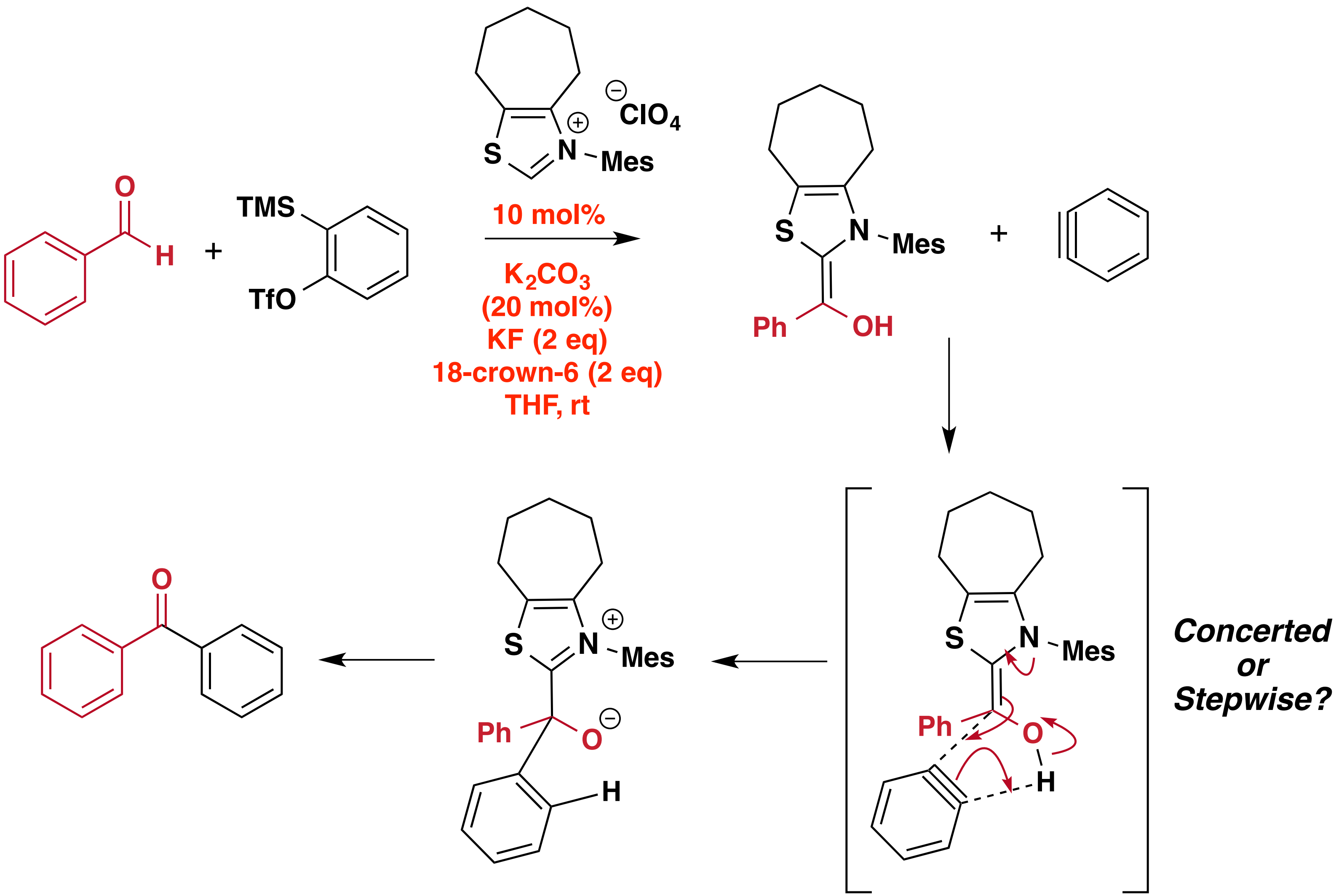
- **Extension: Cascade catalysis involving hydroacylation of unactivated alkynes**



JACS **2010**, *132*, 5970

Alternative acyl anion equivalent applications

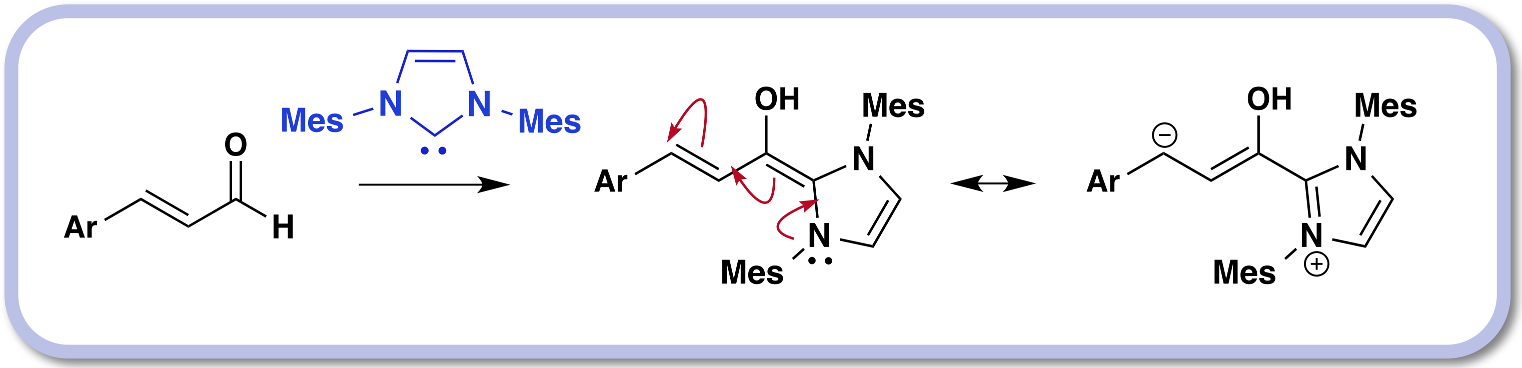
- **Hydroacylation of arynes**



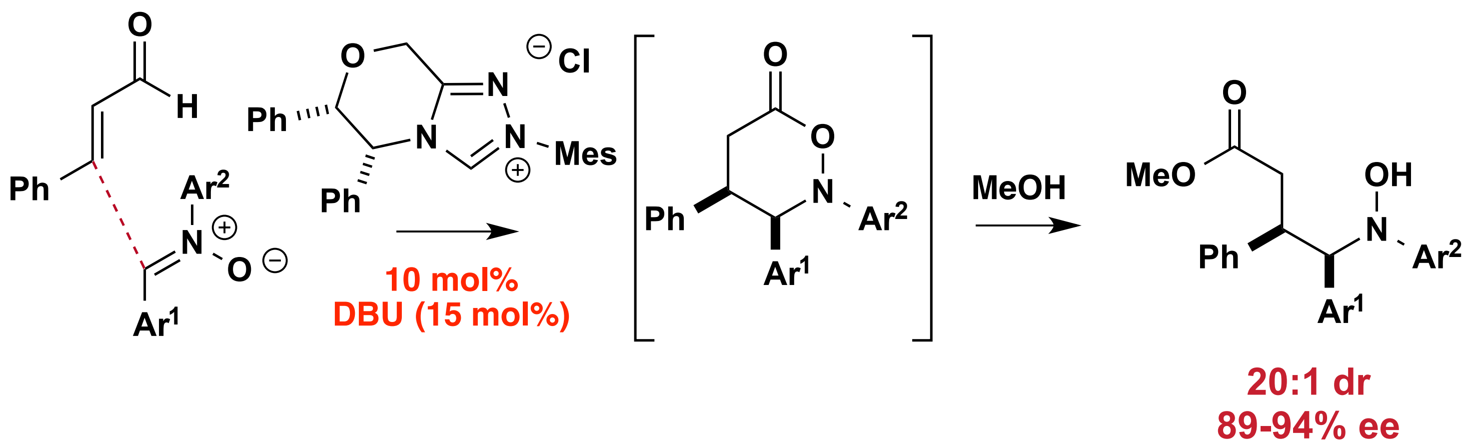
Angew. Chem. Int. Ed, **2010**, 49, 9761

Homoenolate Reactivity

- **Principle:**



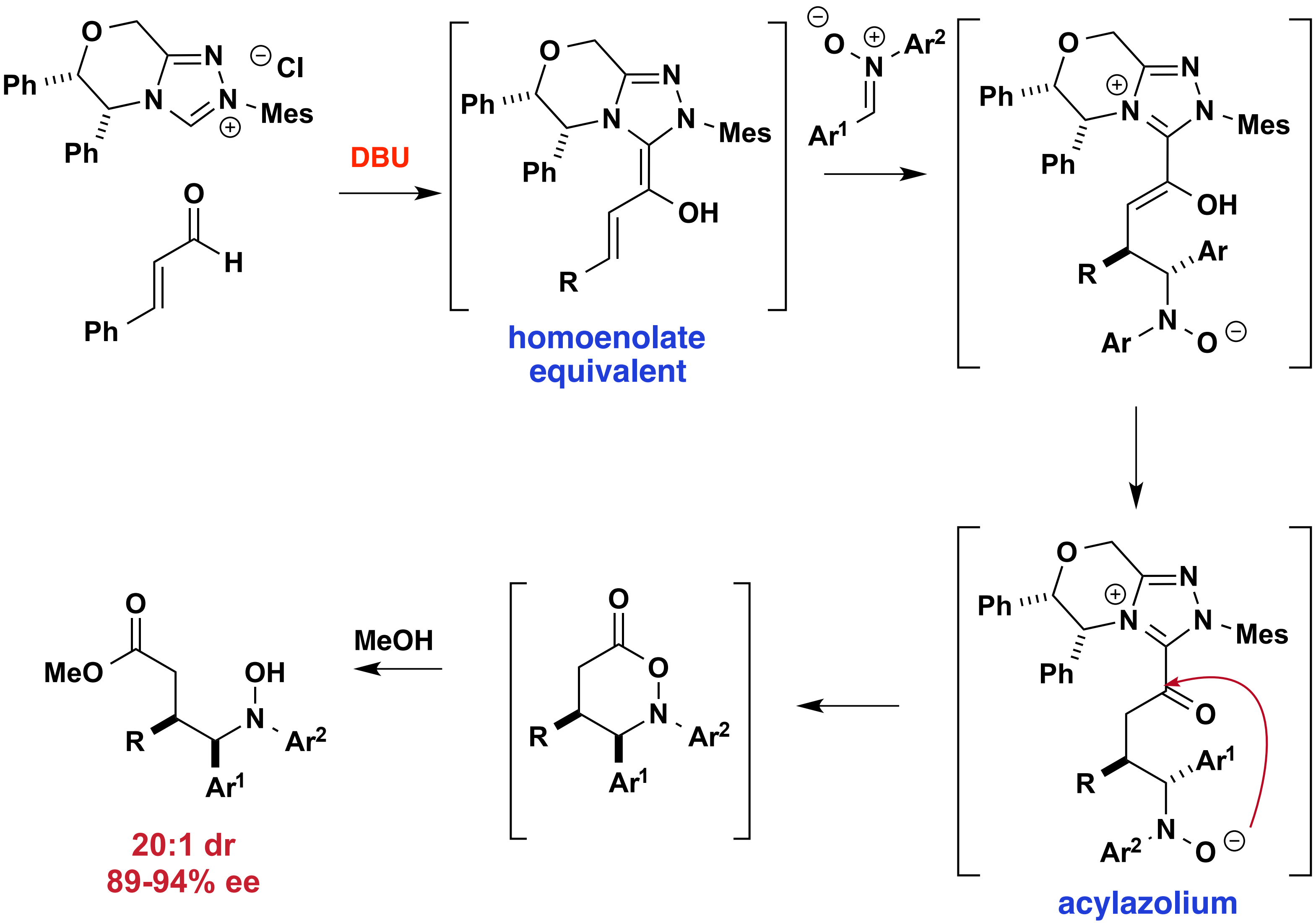
- **In practice:**



J. Am. Chem. Soc., **2008**, *130*, 2416

Homoenolate Reactivity

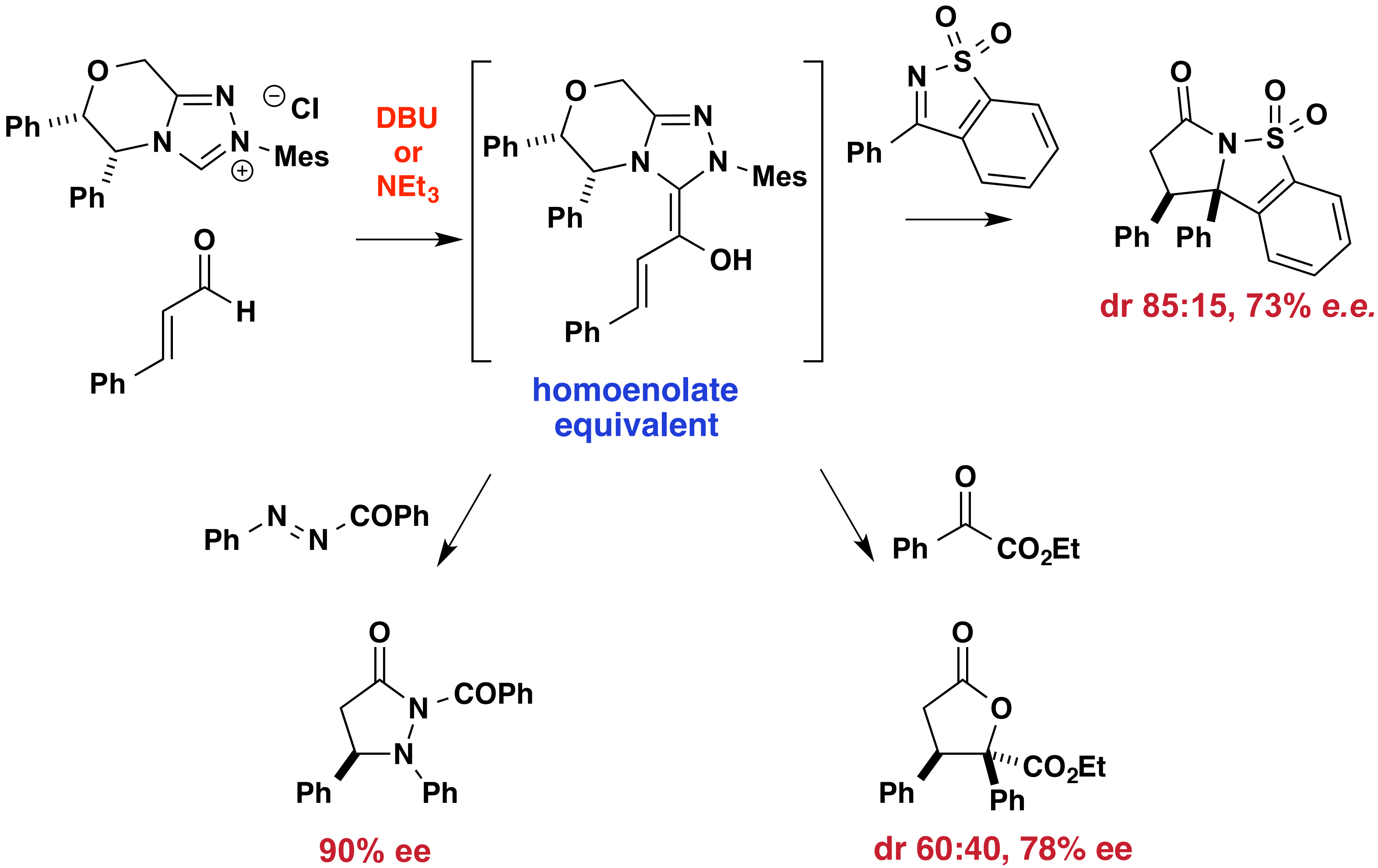
- **Homoenolate equivalents: mechanistic pathway:**



J. Am. Chem. Soc., **2008**, *130*, 2416

Homoenolate Reactivity

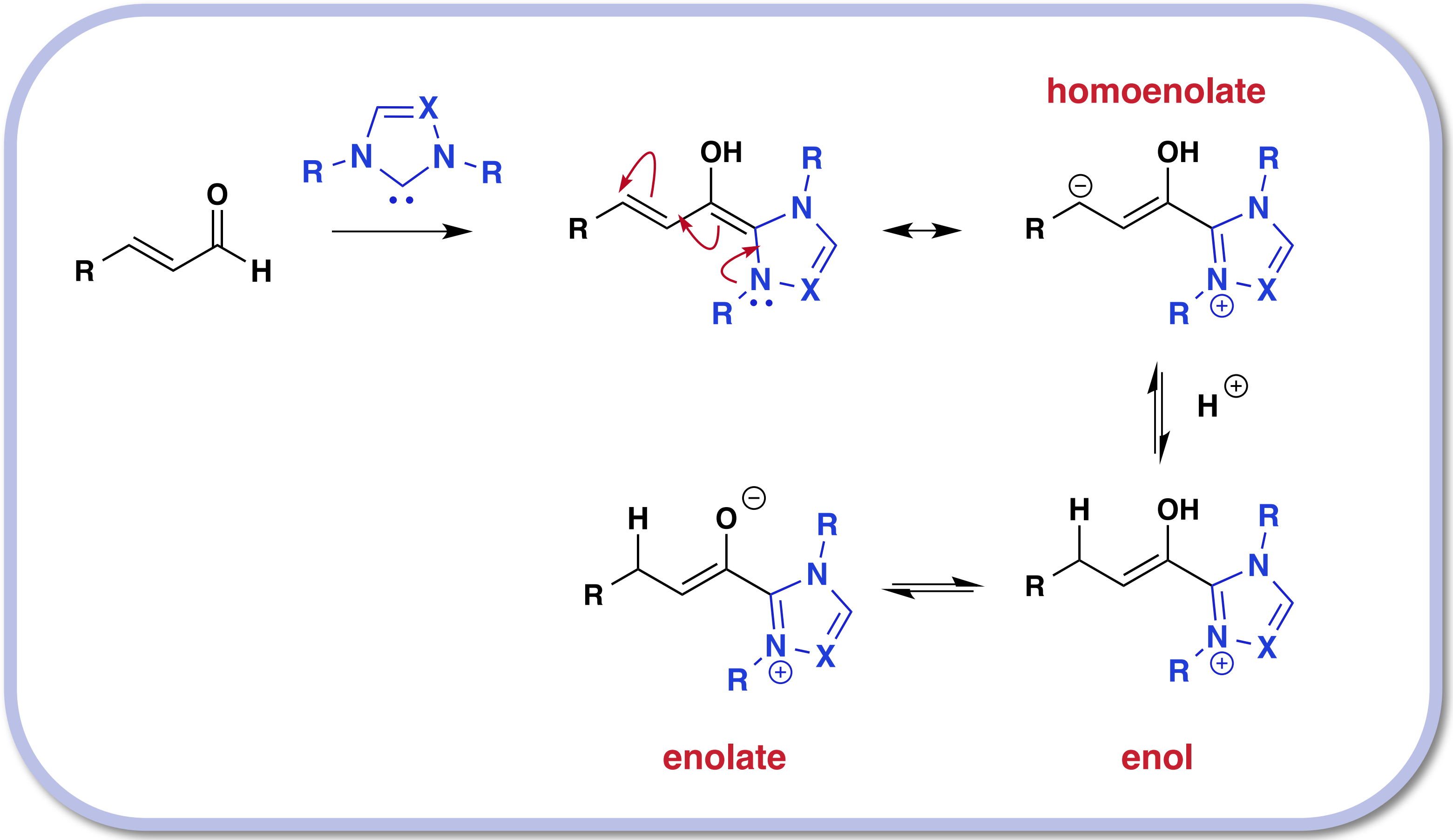
- **Other homoenolate examples:**



JACS **2008**, *130*, 2740; *Adv. Synth. Catal.*, **2008**, *350*, 1885; *JACS*, **2008**, *130*, 2416.

Enolates from NHCs

- **Can the reactivity of enals be controlled by NHCs to allow homoenolate or enolate reactivity?**



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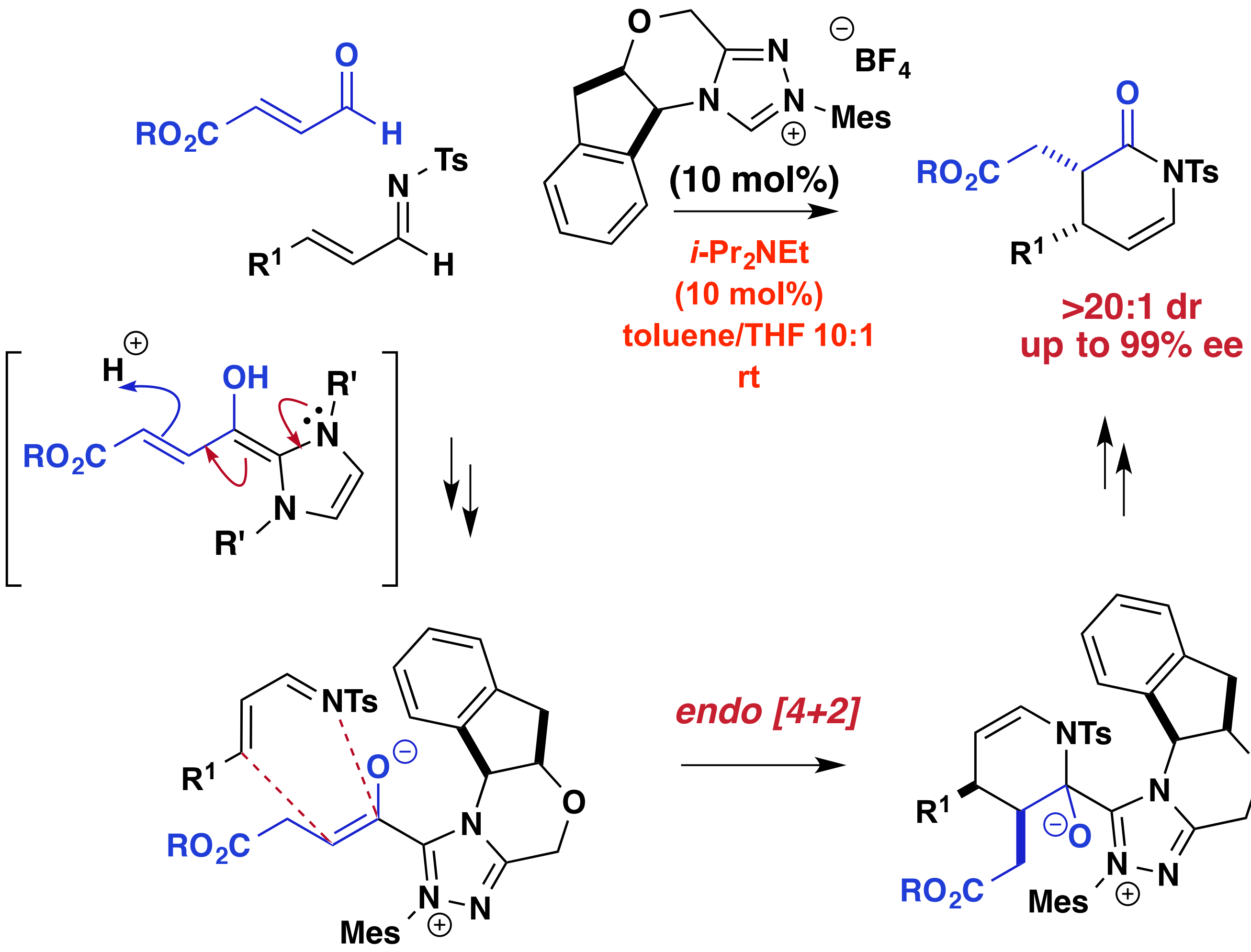
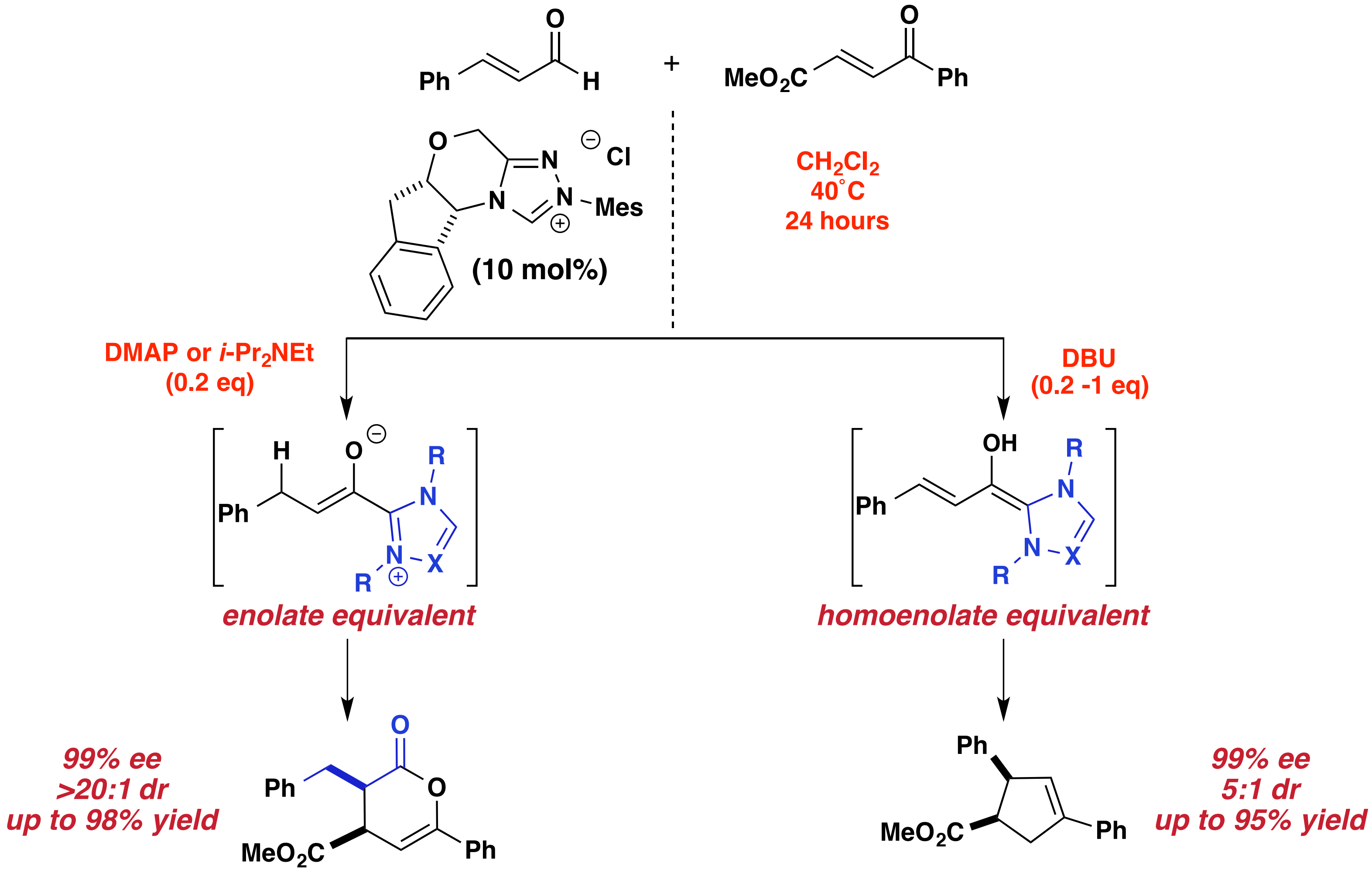


JACS **2006**, *128*, 8418

Enolates from NHCs

- **The base (or its conjugate acid) can play a determining role in the mode of reactivity**



PNAS **2010**, *107*, 20661

Enolates from NHCs

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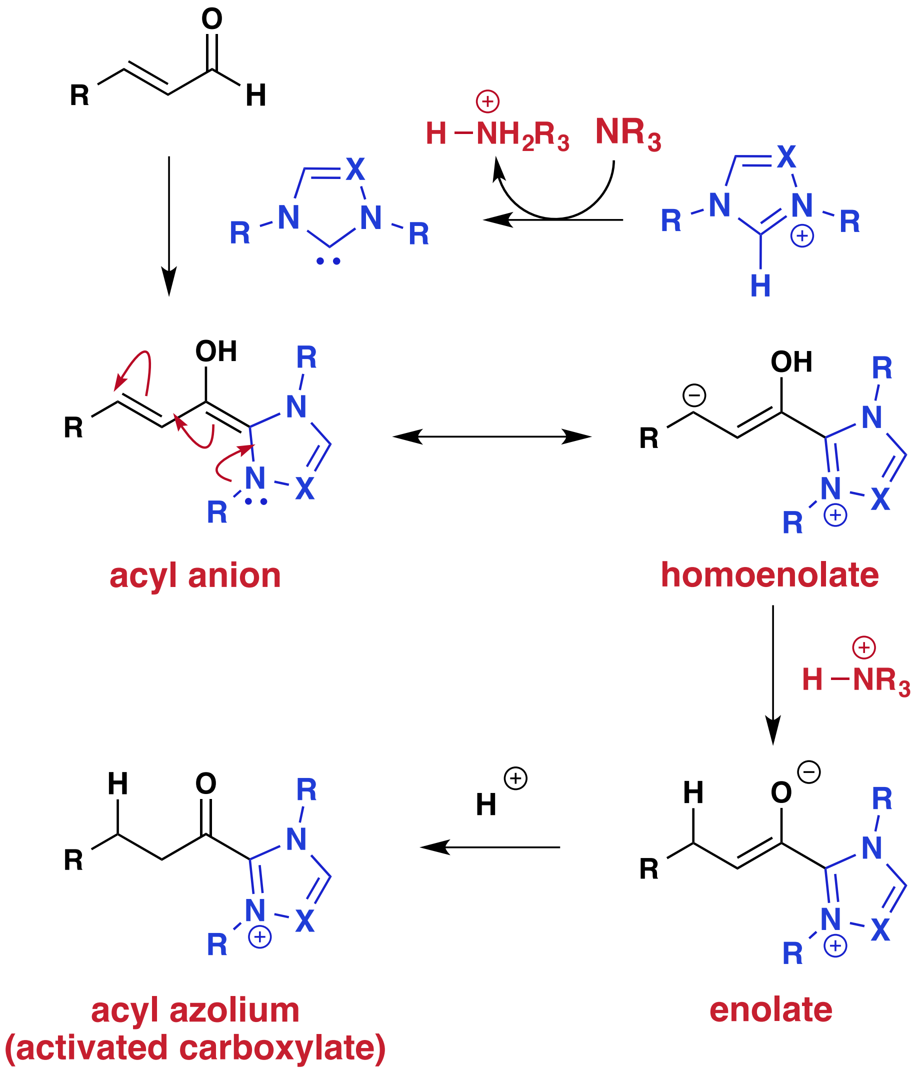


Product distribution is determined by relative rates of C-C bond formation and protonation steps

homoenolates

Favoured by strong bases (DBU)
Weaker conjugate acid
Protonation relatively disfavoured

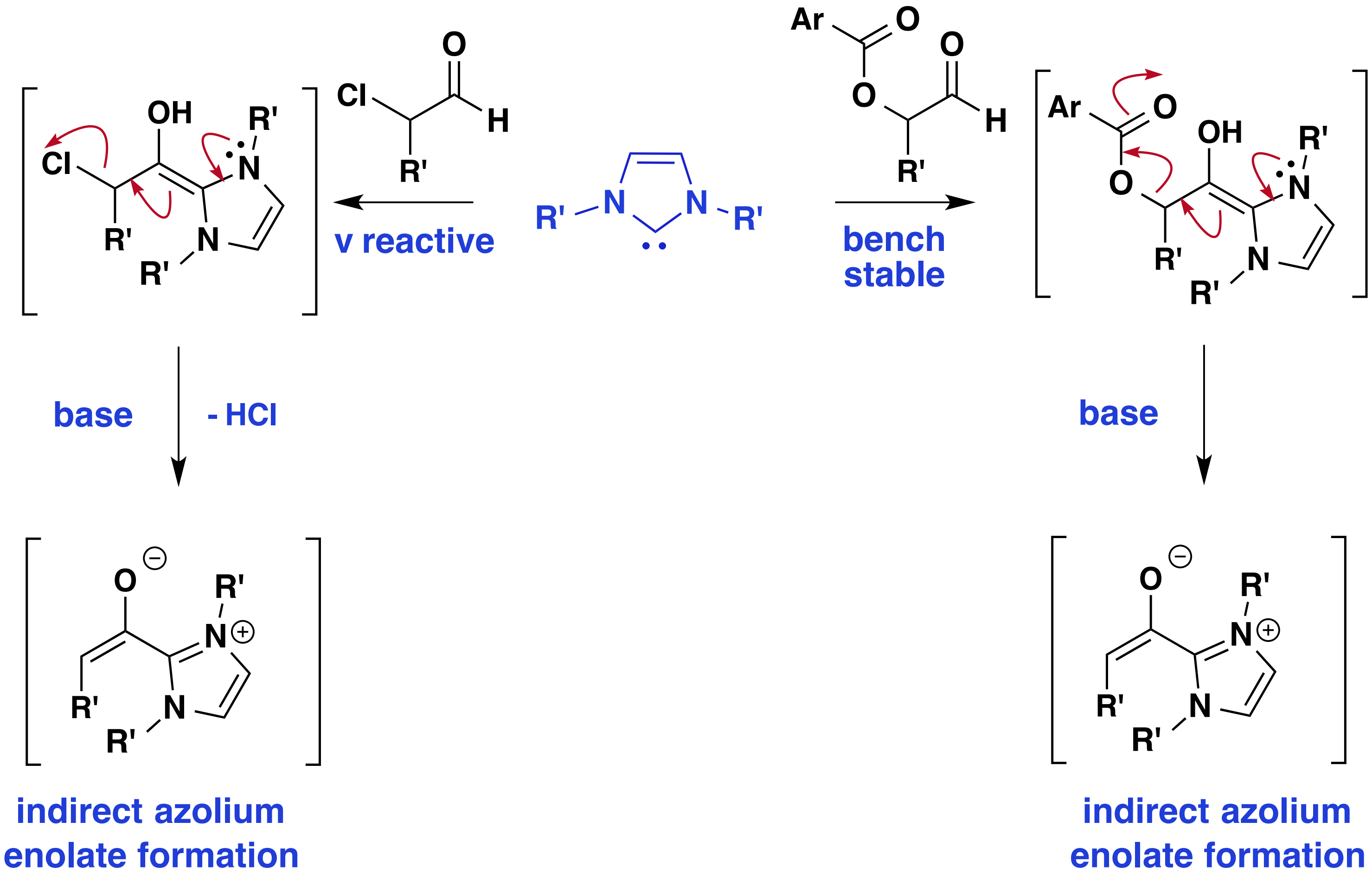
enolates

Favoured by weak bases (DMAP, i-Pr_2NEt)
Stronger conjugate acid
Protonation relatively favoured

PNAS **2010**, *107*, 20661

Enolates from NHCs

- **Alternative Strategy : From aldehydes containing an adjacent leaving group**

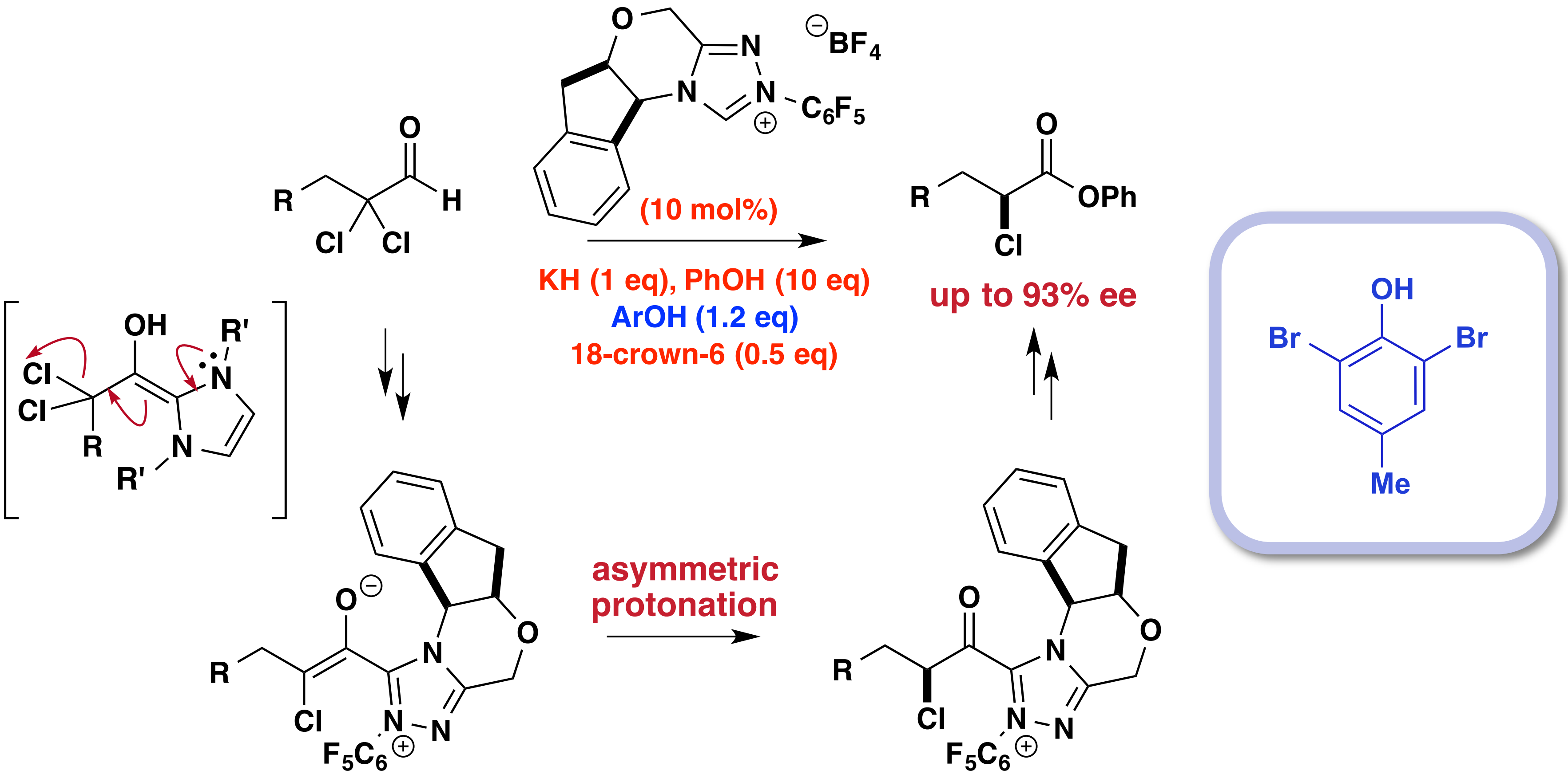


Bode, Scheidt, Rovis

Chem. Comm. **2011**, *47*, 373.

Enolates from NHCs

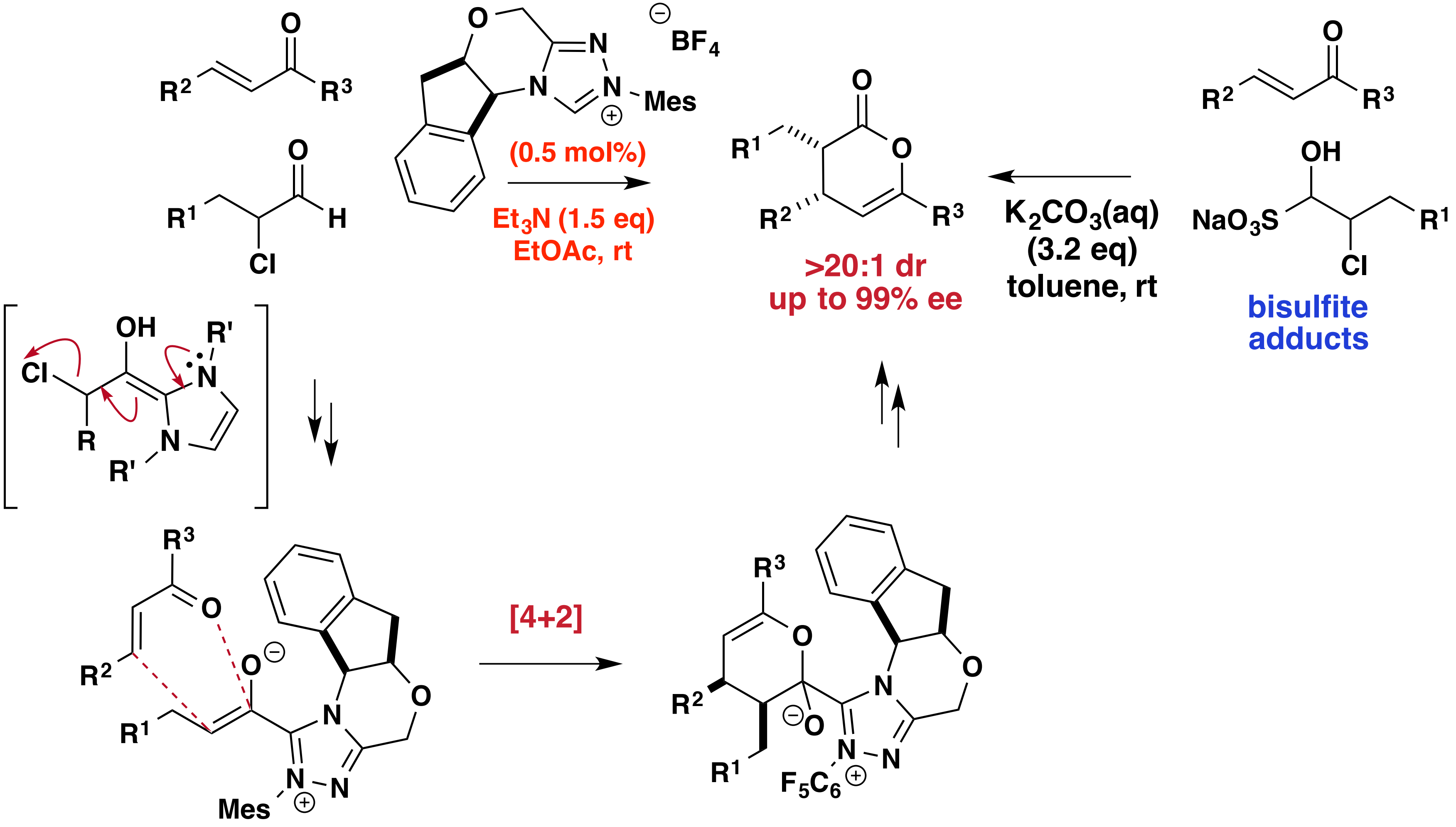
- Applications: asymmetric protonation of azolium enolates



JACS **2005**, *127*, 16406

Enolates from NHCs

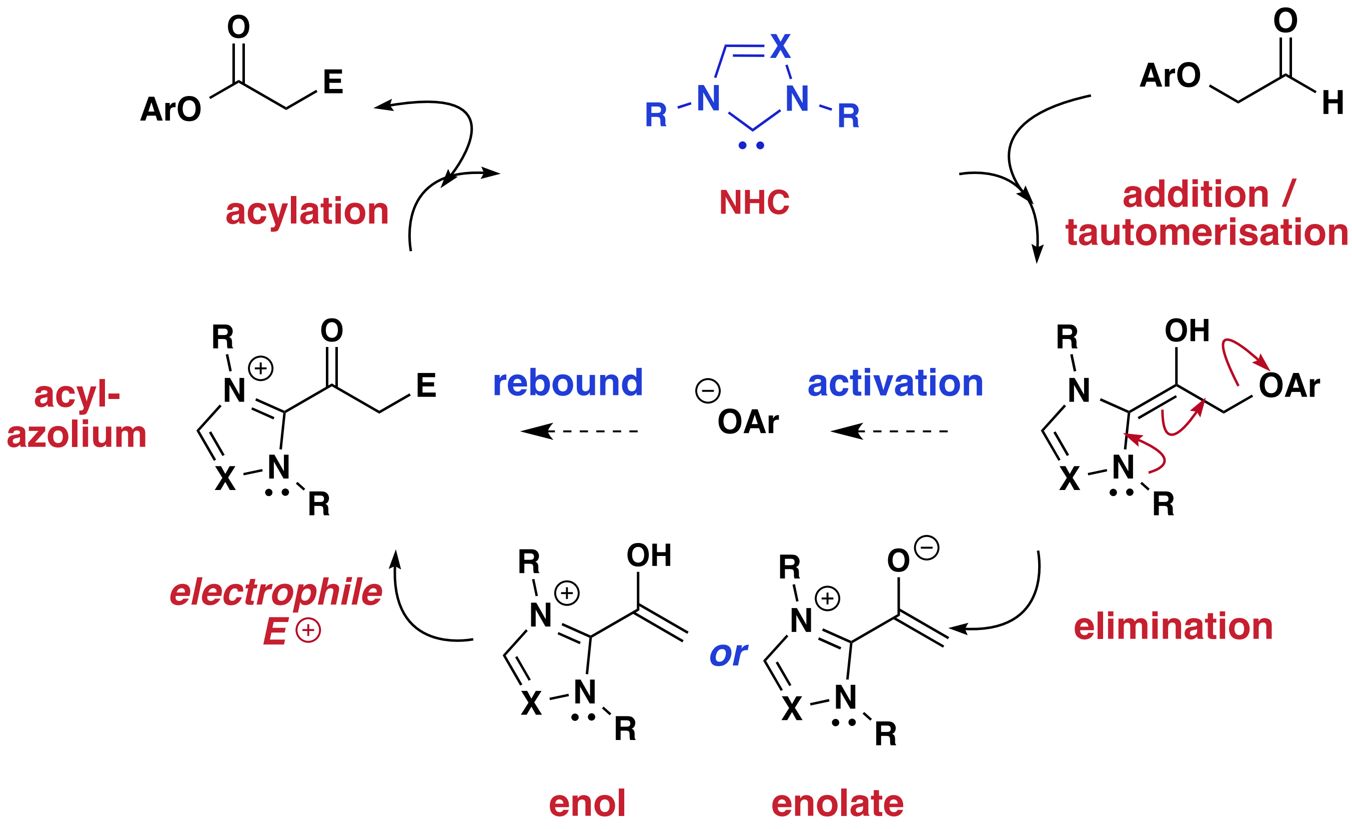
- **Applications: asymmetric [4+2] cycloadditions**



JACS **2006**, *128*, 15088; *Org. Lett.* **2008**, *10*, 3817

Enolates from NHCs

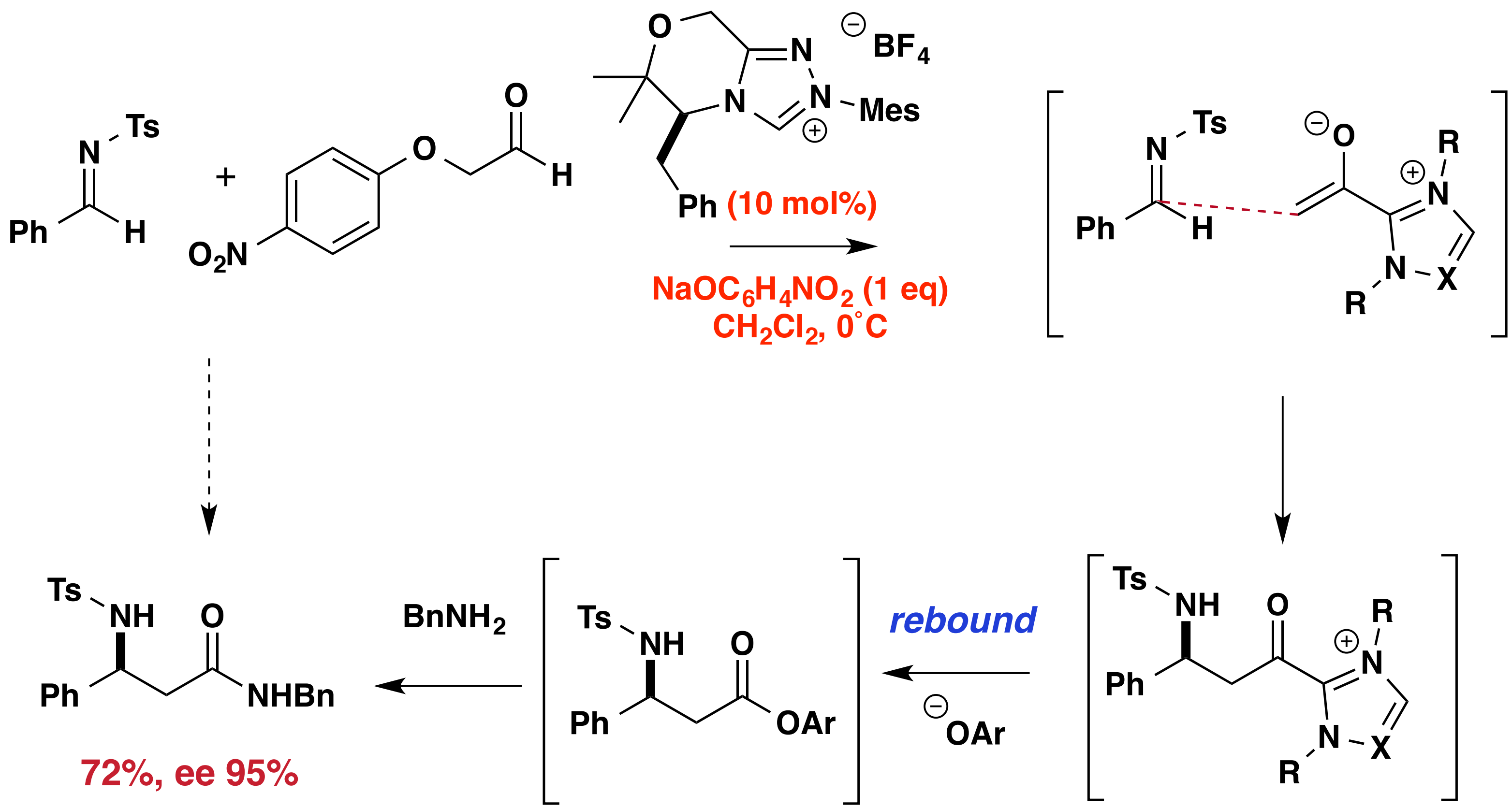
- **"Rebound catalysis": Strategy incorporates a leaving group that can regenerate NHC**



JACS **2009**, *131*, 18028

Enolates from NHCs

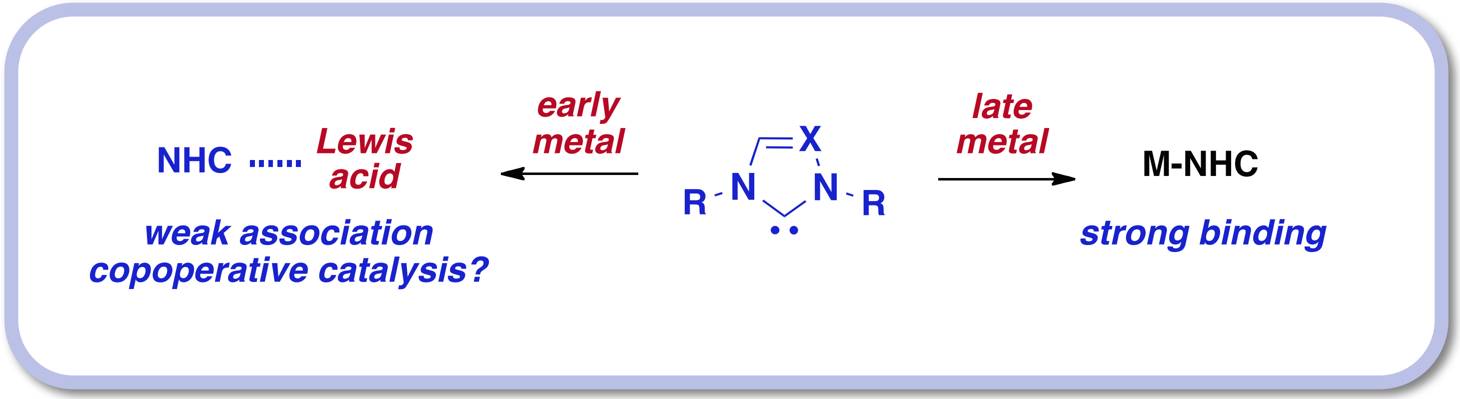
- Application of “rebound catalysis” - asymmetric Mannich reaction

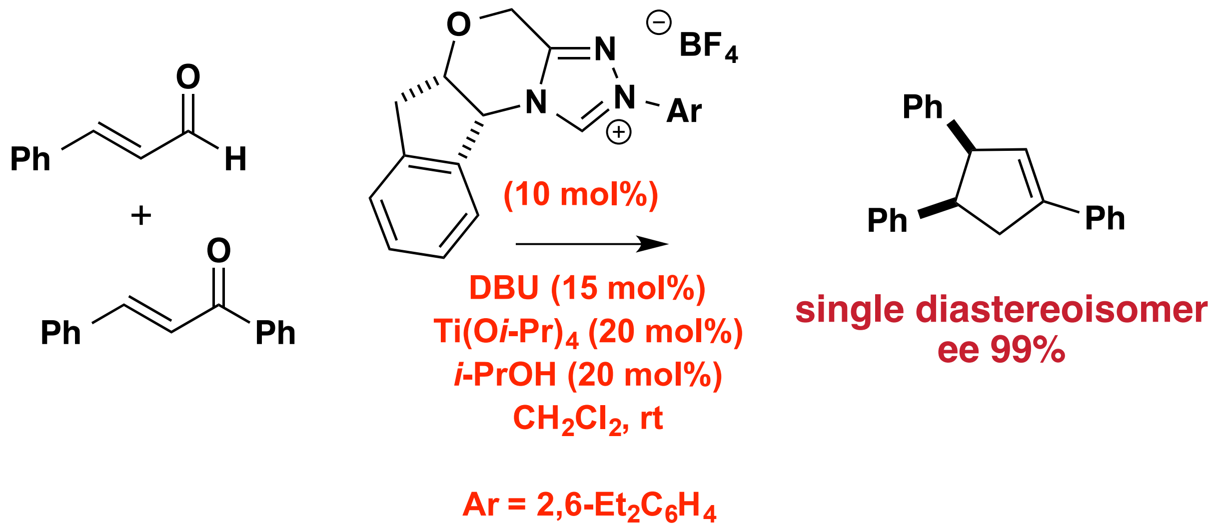


JACS **2009**, *131*, 18028

Enolates from NHCs

- **Co-operative catalysis - can a Lewis acid *and* an NHC be beneficial to a catalytic system?**

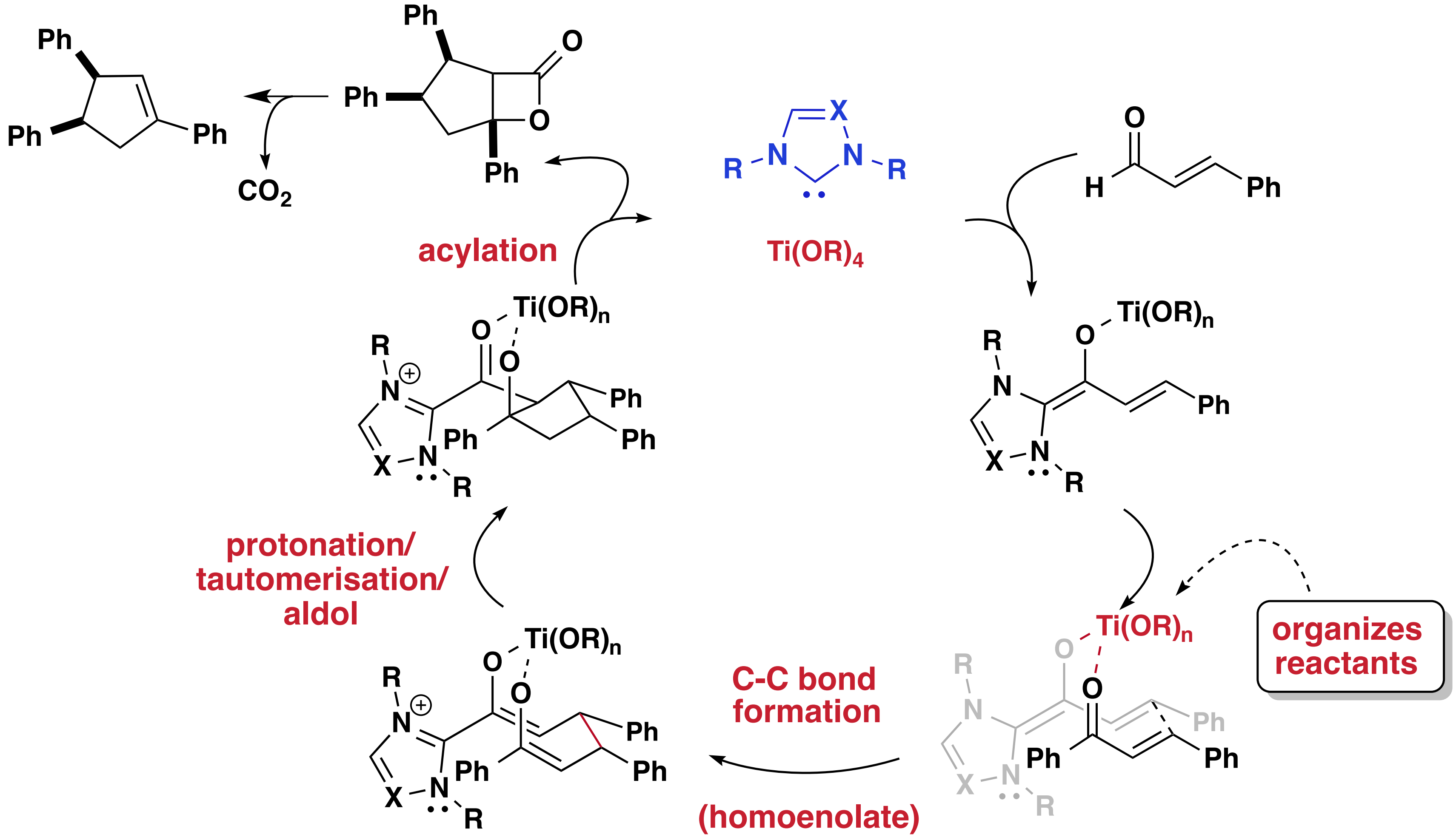




JACS **2010**, *132*, 5345

Enolates from NHCs

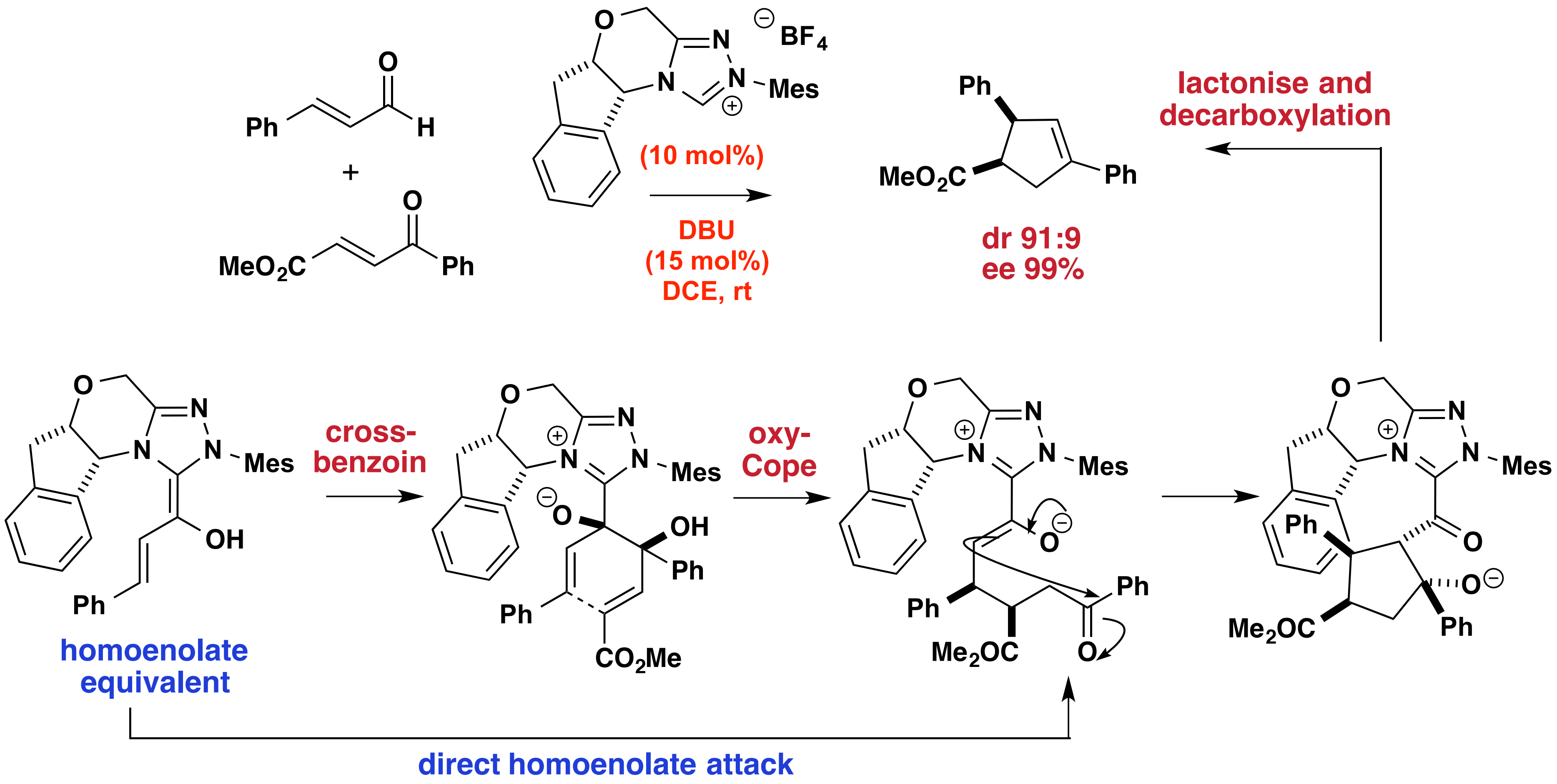
- **Rationale:**



JACS **2010**, *132*, 5345

Enolates from NHCs

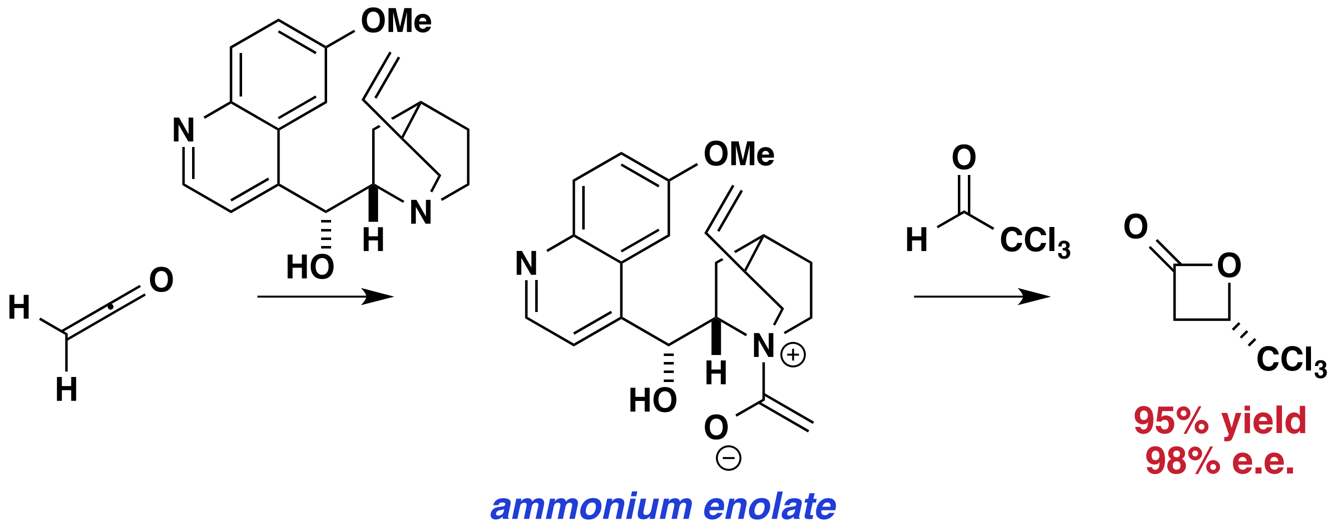
- **Homoenolate vs cross-benzoin - a mechanistic ambiguity?**



JACS **2007**, *129*, 3520

Enolates from NHCs

- **Generation of enolates from Ketenes (via ammonium enolates, for comparison)**

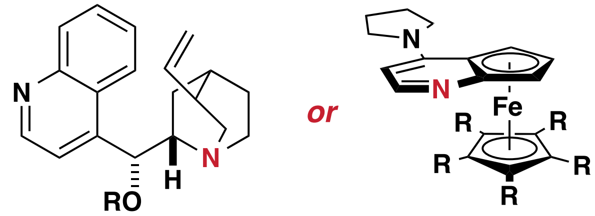


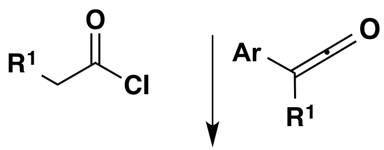
Enolates from NHCs

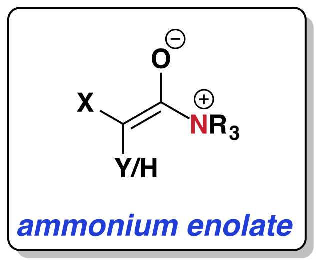
Generation of enolates from Ketenes (via ammonium enolates, for comparison)

mono-substituted in-situ generated "ketene enolates"

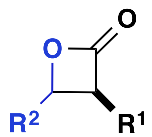
di-substituted enolates from isolable carbenes



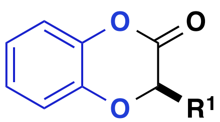




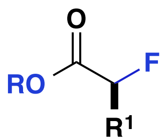
up to 93% ee
Nelson et al.
J. Am. Chem. Soc., **2004**, *126*, 5352



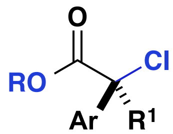
up to 99% ee
Lectka et al.
J. Am. Chem. Soc., **2006**, *128*, 1810



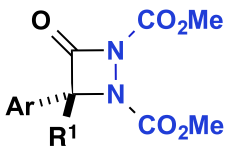
up to 99% ee
Lectka et al.
J. Am. Chem. Soc., **2008**, *130*, 17260
J. Org. Chem. **2010**, *75*, 969



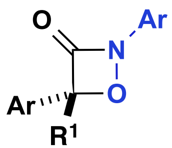
For reviews
1. "ketene enolate" chemistry
Lectka et al. *Tetrahedron*, **2009**, *65*, 6771
2. For ammonium enolates
Gaunt and Johansson, *Chem. Rev.*, **2007**, *107*, 5596



up to 94% ee
Fu et al.
Angew. Chem. Int. Ed., **2007**, *46*, 977



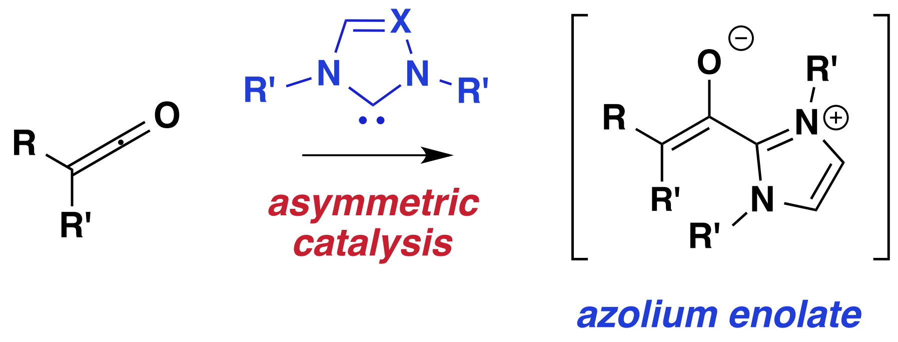
up to 93% ee
Fu et al.
Angew. Chem. Int. Ed., **2008**, *47*, 7048



up to 96% ee
Fu et al.
Angew. Chem. Int. Ed., **2009**, *48*, 2391

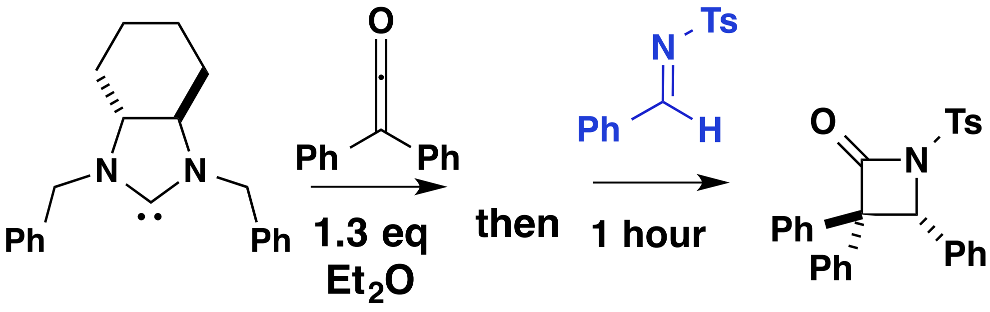
Enolates from NHCs

- **Similar reactivity from azolium enolates**



Enolates from NHCs

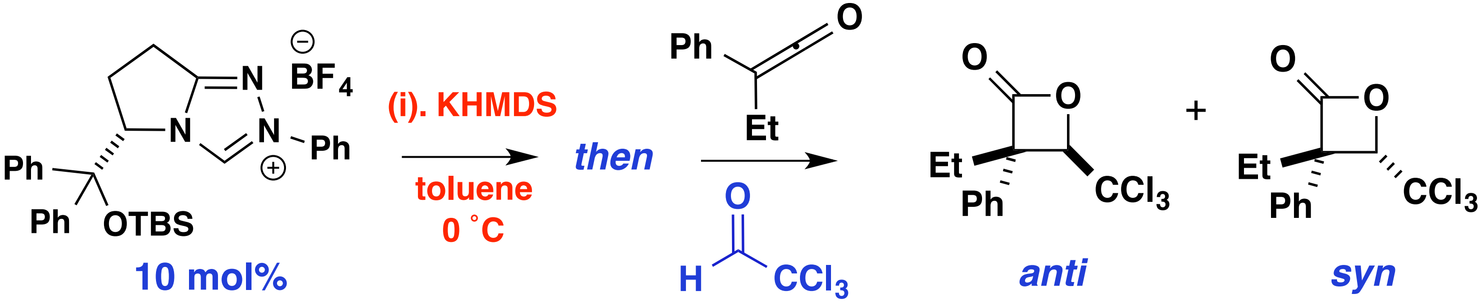
- **Similar reactivity from azolium enolates**



90%
76% e.e.

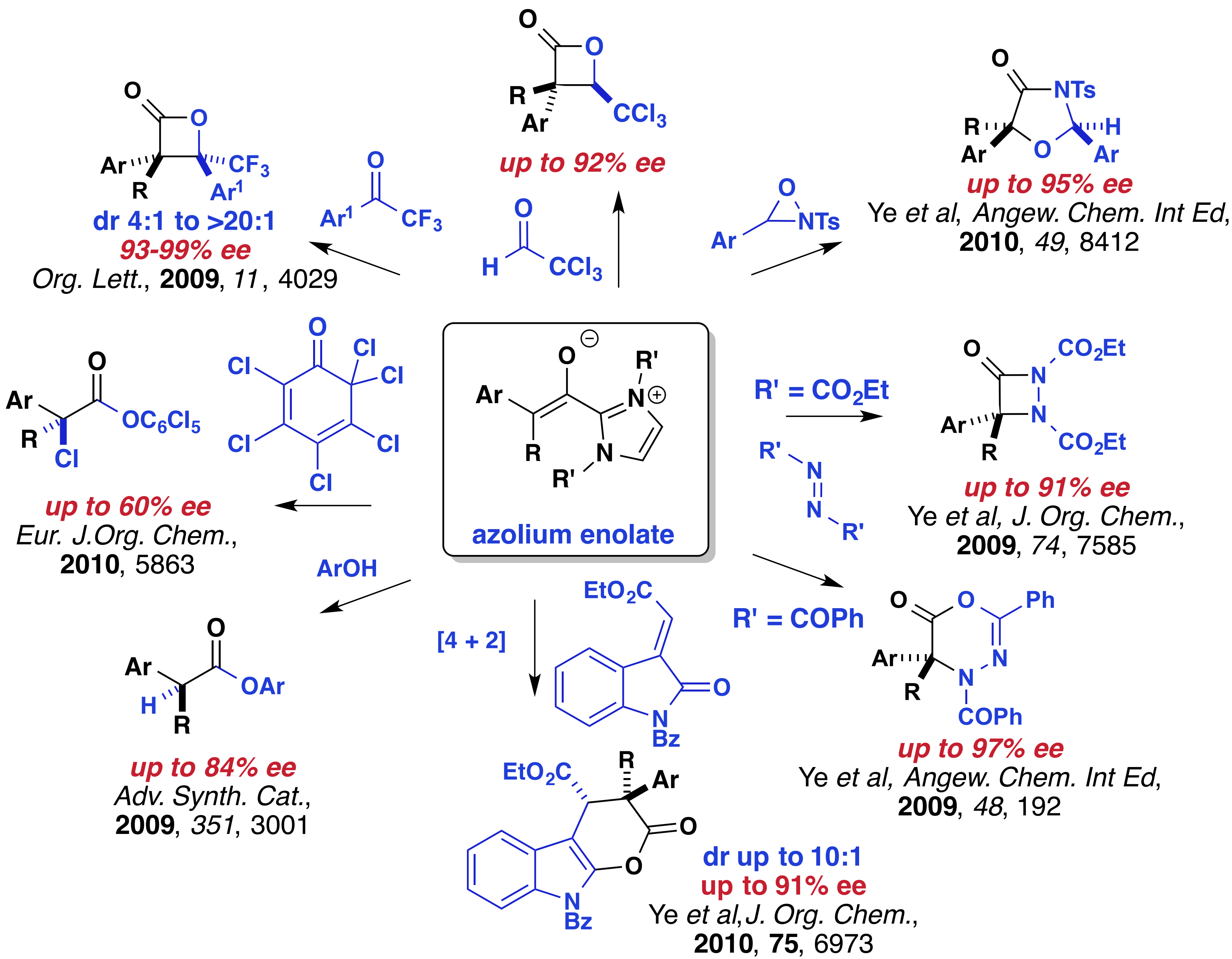
Org. Biomol. Chem., **2008**, *6*, 1108
Tetrahedron: Asymmetry, **2010**, *21*, 582
Tetrahedron: Asymmetry, **2010**, *21*, 601

>99% e.e.

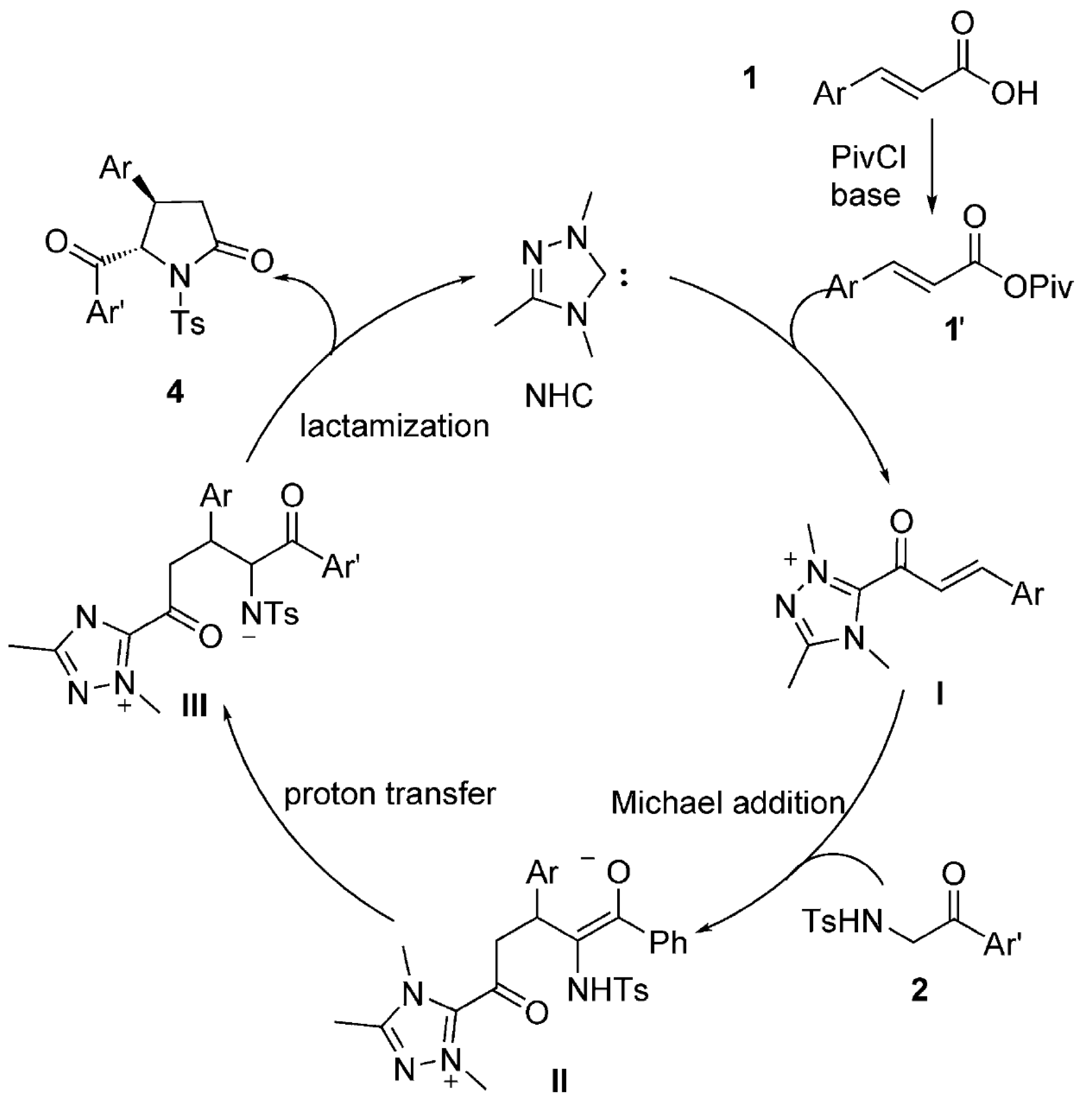


dr 75:25
ee (*anti*) 92%, 61%
ee (*syn*) 88%, 16%

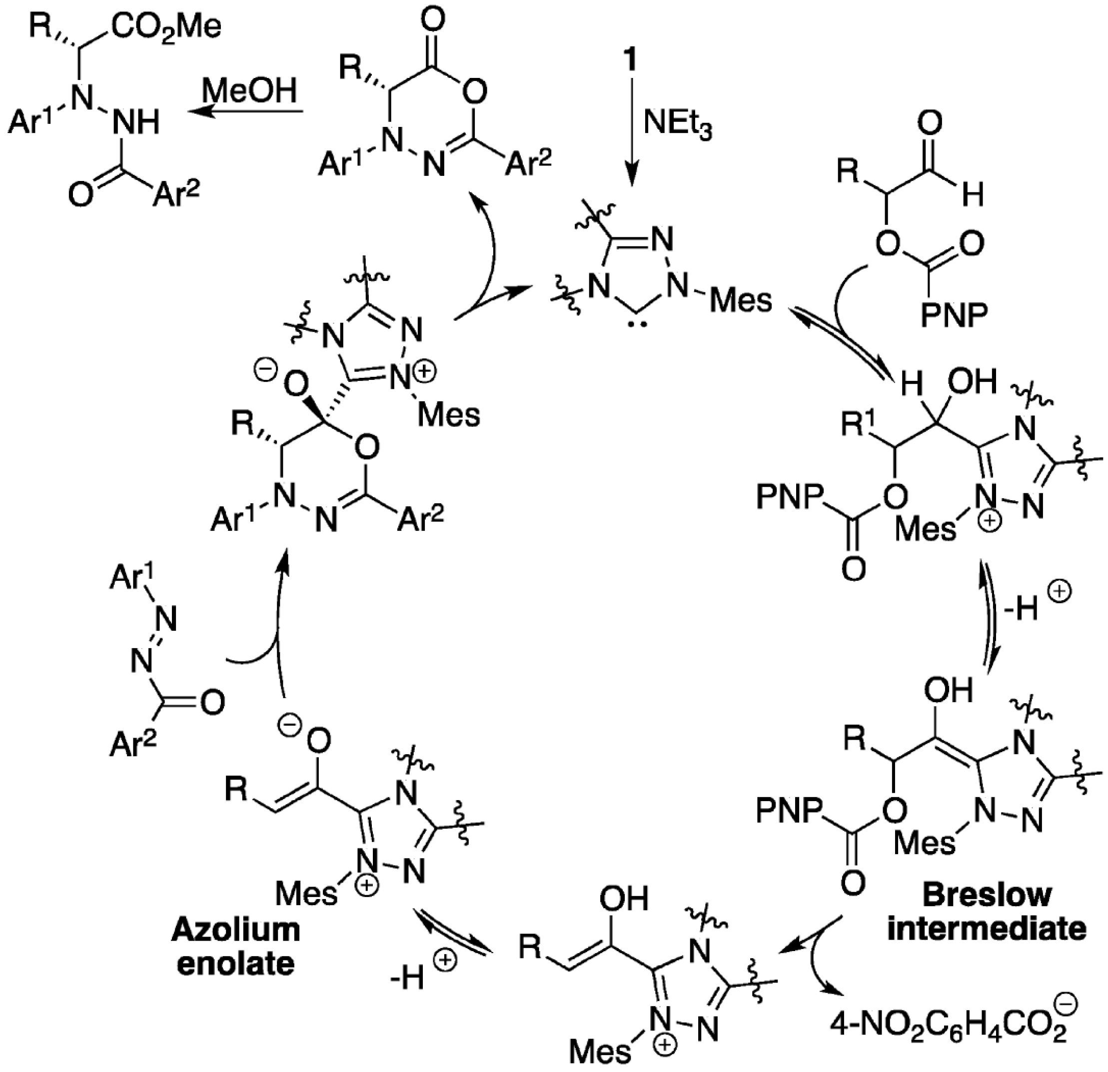
Enolates from NHCs



Q1

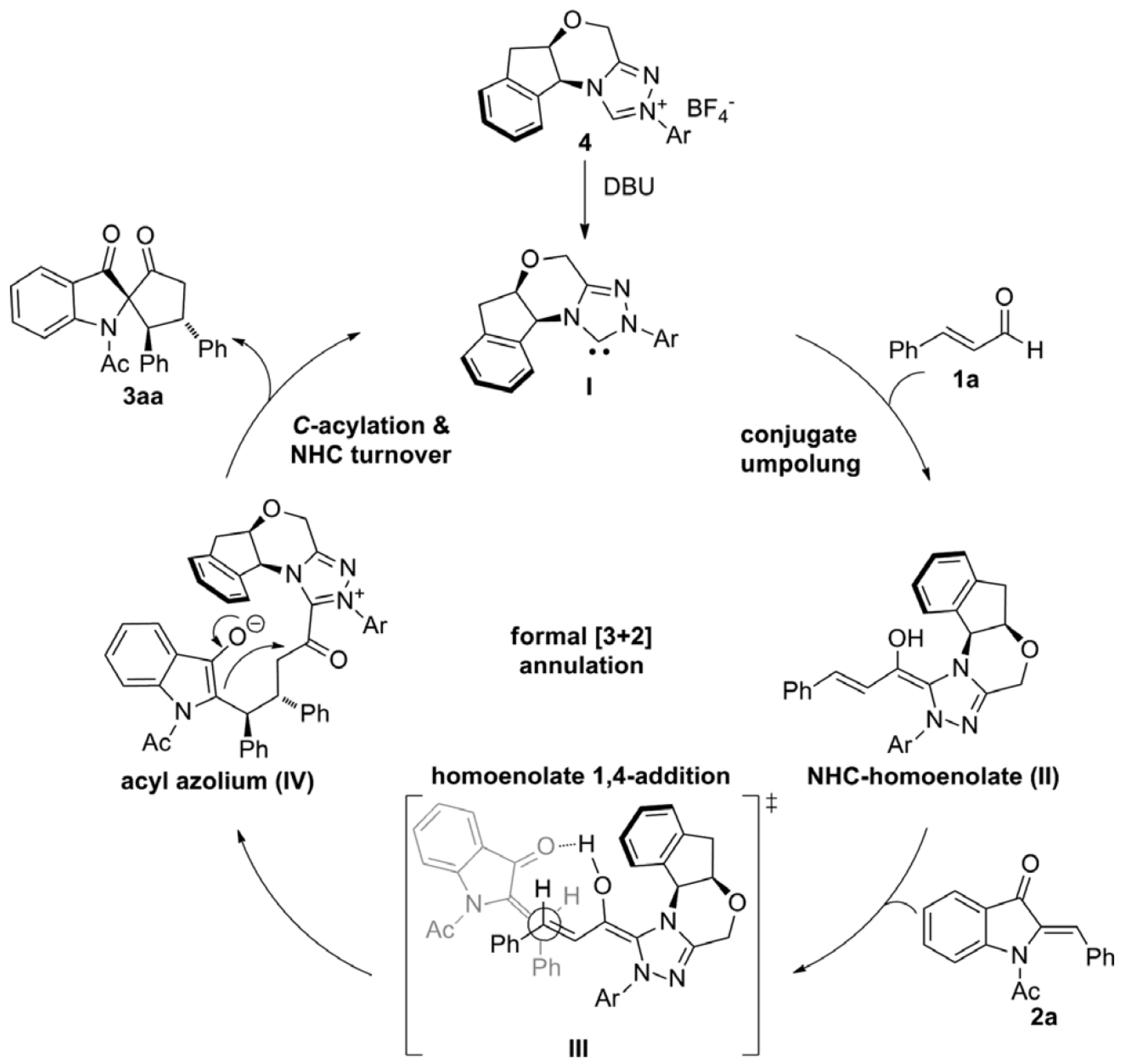

1
Ar
O
OH
PivCl
base
O
Ar
OPiv
1'
Ar
O
N
Ar'
Ts
O
4
N
N
N
:
NHC
lactamization
Ar
O
Ar'
NTs
N
O
N
N
III
+
N
N
N
O
Ar
I
Michael addition
proton transfer
Ar
O
Ph
N
O
NHTs
N
N
II
TsHN
O
Ar'
2

Q2



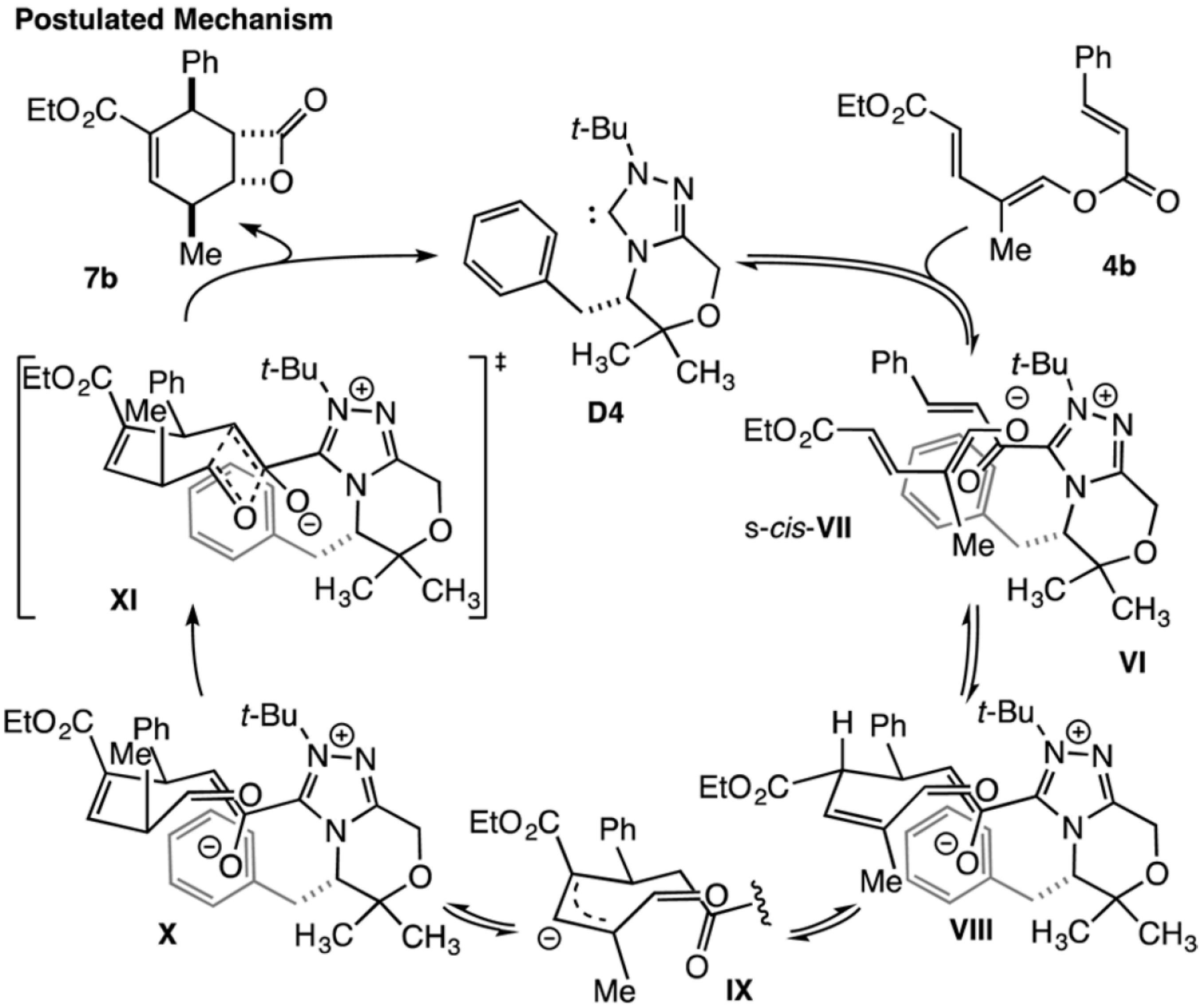
R
CO_2Me
MeOH
Ar1
N
NH
O
Ar2
1
NEt_3
Mes
PNP
H
OH
R1
-H ⊕
Breslow intermediate
Azolium enolate
$4\text{-}NO_2C_6H_4CO_2^{\ominus}$

Q3

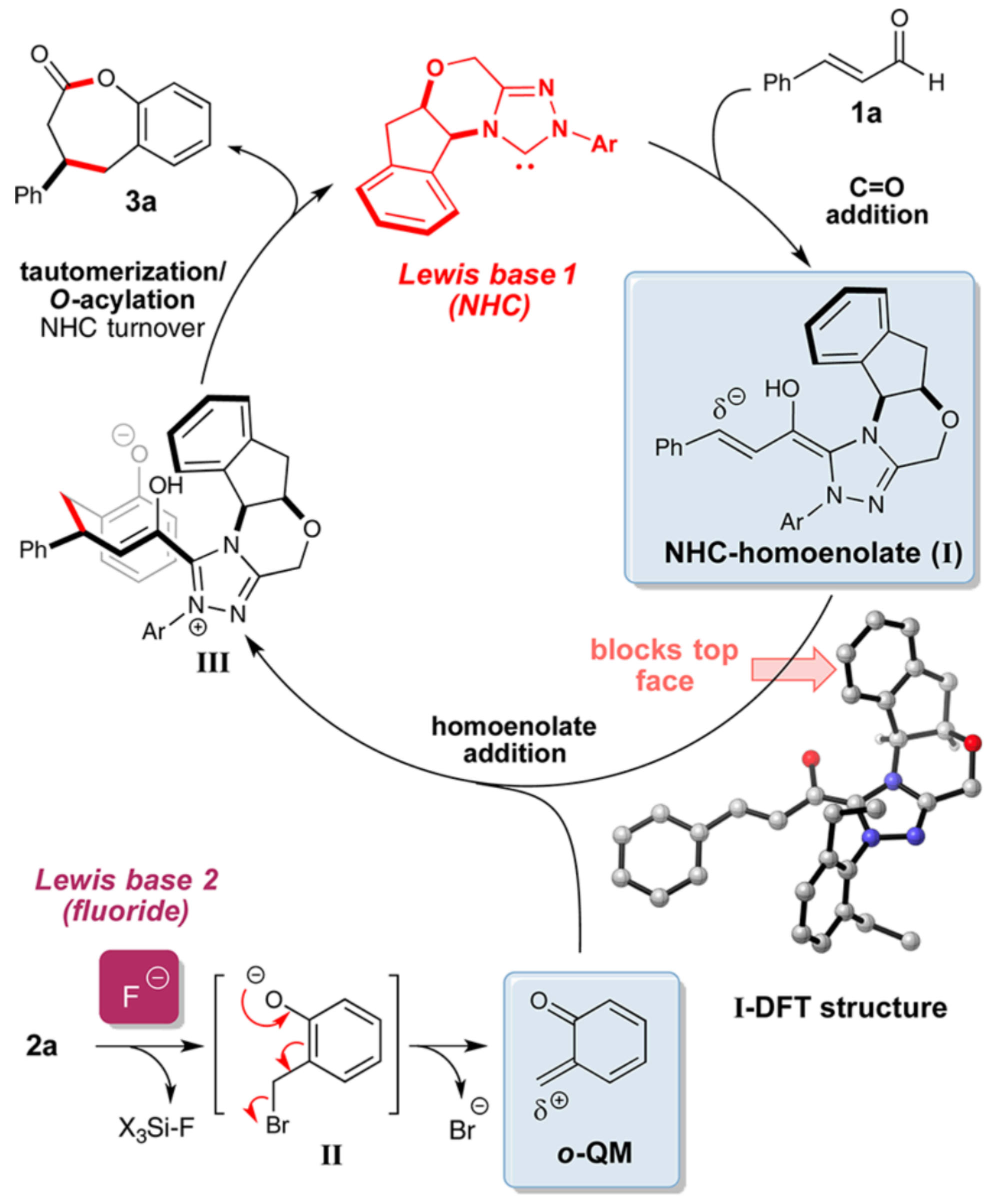


4
DBU
BF4-
I
1a
conjugate umpolung
NHC-homoenolate (II)
2a
homoenolate 1,4-addition
III
formal [3+2] annulation
acyl azolium (IV)
C-acylation & NHC turnover
3aa

Q4



Q5



3a
Ph
Lewis base 1
(NHC)
Ar
Ph
H
1a
C=O
addition
tautomerization/
O-acylation
NHC turnover
HO
Ph
Ar
NHC-homoenolate (I)
OH
Ph
Ar
III
blocks top
face
homoenolate
addition
I-DFT structure
Lewis base 2
(fluoride)
F
2a
X3Si-F
Br
II
Br
o-QM