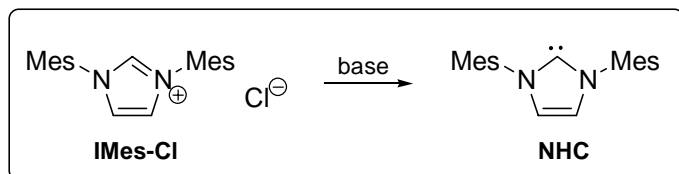
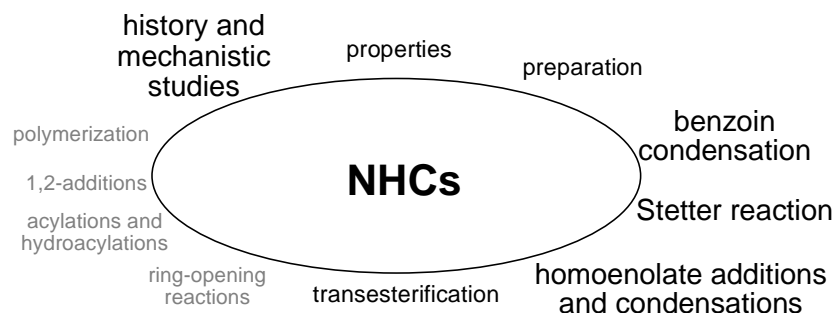


## N-Heterocyclic Carbenes: Versatile Organocatalysts and Reagents

An Evans Group Afternoon Seminar  
December 14, 2007



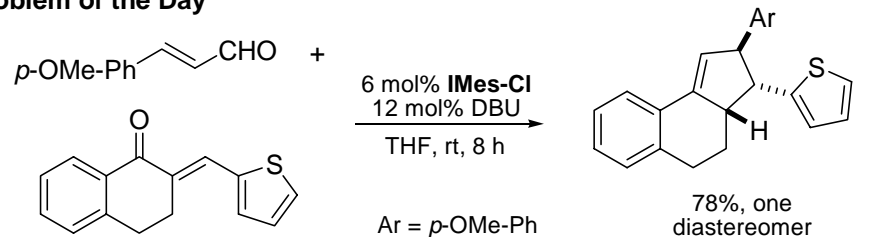
### Scope of Seminar



### Outline

1. Benzoin and the Breslow Mechanism
2. The Wanzlick Equilibrium
3. Properties of NHCs
4. Preparation of NHCs
5. The Benzoin Condensation
6. The Stetter Reaction
7. NHC-derived Homoenolates
8. NHC-catalyzed Transesterification

### Problem of the Day



Nair *JACS* **2006** 128 8736

### Literature

#### General

1. "N-Heterocyclic Carbenes as Organocatalysts." Marion, N.; Diez-Gonzalez, S.; Nolan, S.P. *Angew. Chem. Int. Ed.* **2007**, *26*, 2988. (**general review**)
2. "N-Heterocyclic Carbenes." Eastman, K.J. *Baran Group Seminar*

#### History

3. "Nucleophilic Carbenes: An Incredible Renaissance." Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 725-728. (**discovery**)
4. "Looking for Stable Carbenes: The Difficulty in Starting Anew." Arduengo III, A.J. *Acc. Chem. Res.* **1999**, *32*, 913-921. (**discovery**)

#### Properties

5. "Formation and Stability of N-Heterocyclic Carbenes in Water: The Carbon Acid pK<sub>a</sub> of Imidazolium Cations in Aqueous Solution." Amyes, T.; Diver, S.T.; Richard, J.P.; Rivas, F.M.; Toth, K. *J. Am. Chem. Soc.* **2004**, *126*, 4366-4374. (**pK<sub>a</sub> of NHCs**)
6. "Stable Carbenes." Bourissou, D.; Guerret, O.; Gabbai, F.P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39-91. (**general review**)
7. "When and How Do Diaminocarbenes Dimerize?" Alder, R.W.; Blake, M.E.; Chaker, L.; Harvey, J.N.; Paolini, F.; Schutz, J. *ACIE* **2004** 43 5896-5911. (**general review**)

#### Preparation

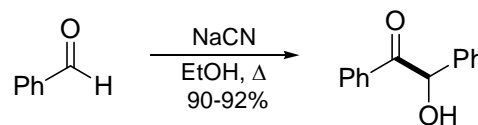
8. "Convenient, Scalable, and Flexible Method for the Preparation of Imidazolium Salts With Previously Inaccessible Substitution Patterns." *Chem. Commun.* 2006, 2176-2178. (**synthesis of imidazolium salts**)
9. "An Efficient Synthesis of Achiral and Chiral 1,2,4-Triazolium Salts: Bench Stable Precursors for N-Heterocyclic Carbenes." Kerr, M.S.; de Alaniz, J.R.; Rovis, T. *J. Org. Chem.* 2005, *70*, 5725-5728. (**synthesis of triazolium salts**)

#### Reactions

10. "Catalyzed Reactions of Acyl Anion Chemistry." Johnson, J.S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1326-1328. (**benzoin, Stetter**)
11. "Nucleophilic Carbenes in Asymmetric Organocatalysis." Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534-541. (**asymmetric benzoin, Stetter**)
12. "Extending Mechanistic Routes in Heterazolium Catalysis--Promising Concepts for Versatile Synthetic Methods." Zeitler, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 7506-7510. (**homoenolates**)

## The Benzoin Condensation

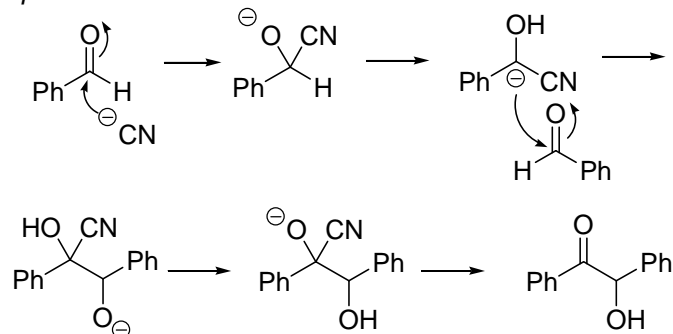
the original reaction



- incomplete condensation observed for aliphatic aldehydes
- electron deficient benzaldehydes are subject to side reactions

Wohler/Liebig *Ann. Pharm.* **1832** 3 249  
Adams *Org. Syn. Coll. Vol. 1* **1941** 94

## Lapworth Mechanism

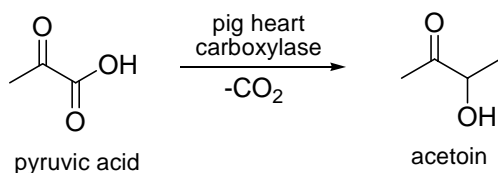


- intermediate cyanohydrins were isolated as crystalline K salts

Lapworth *J. Chem. Soc.* **1903** 83 995

## Thiamine-Catalyzed Reactions

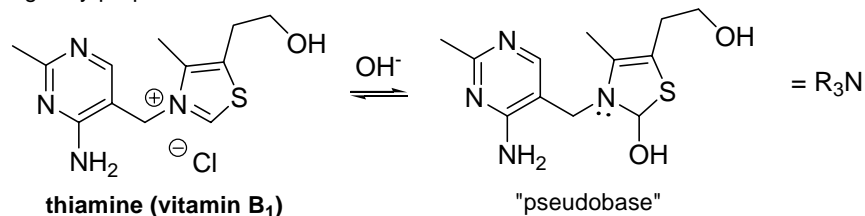
known in 1954:



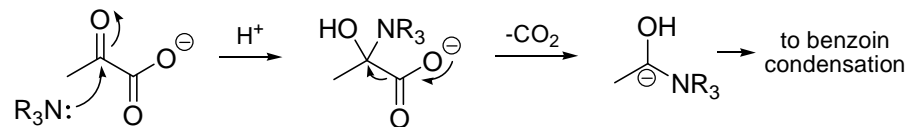
- known that these reactions were possible in protein-free systems if thiamine was present
- reaction is optimal at pH 8.4

- addition of doubly  $^{14}\text{C}$  labelled acetaldehyde gives doubly labelled acetoin

originally proposed mechanism:



Mizuhara *JACS* **1954** 76 571

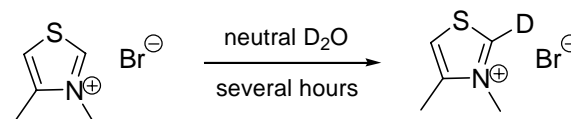
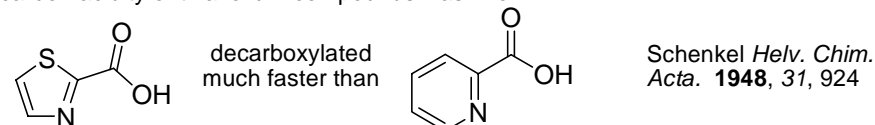


## Breslow Mechanism

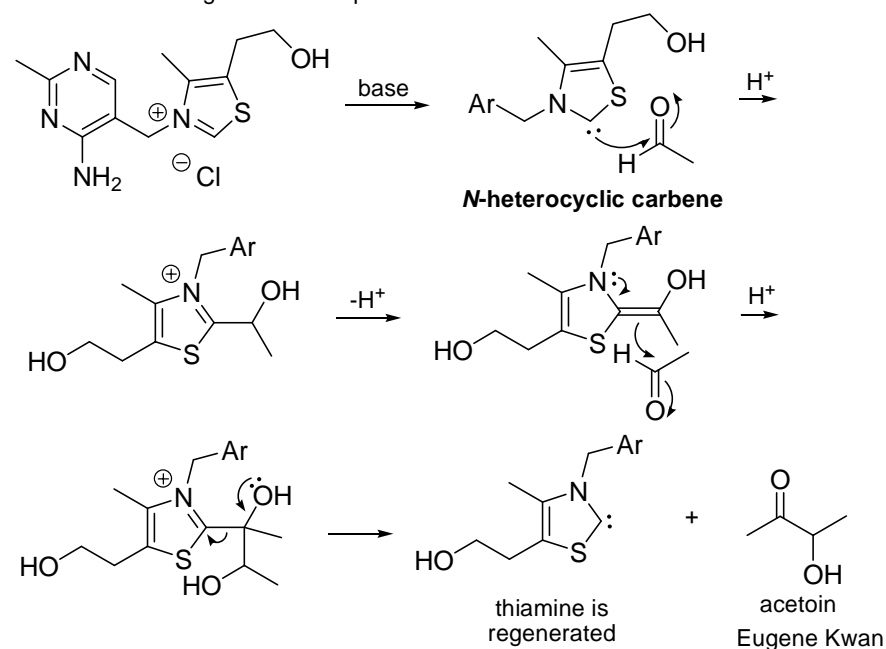
"[Mizuhara and coworkers] proposed an unusual and rather unlikely mechanism...we are thus forced to look elsewhere in the molecule for a site of potential reactivity..."

Breslow *JACS* **1958**, *80*, 3719

- carbon acidity of thiazolium compounds was known:

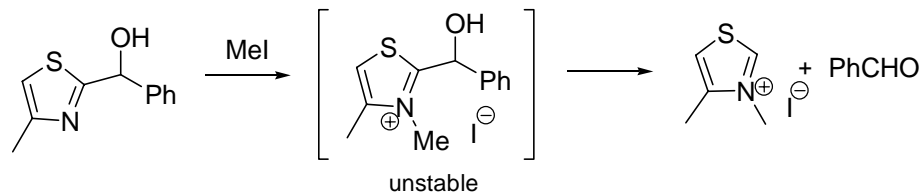


- could this be analogous to the Lapworth mechanism?

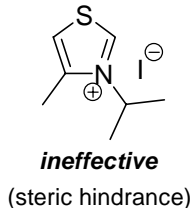
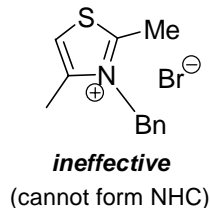
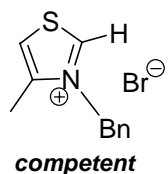


evidence for mechanism:

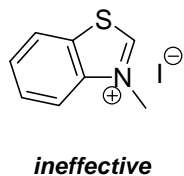
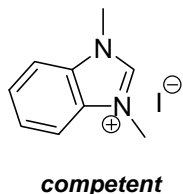
- independent generation of proposed intermediate gives product:



- various analogs of thiamine have varying efficacy:



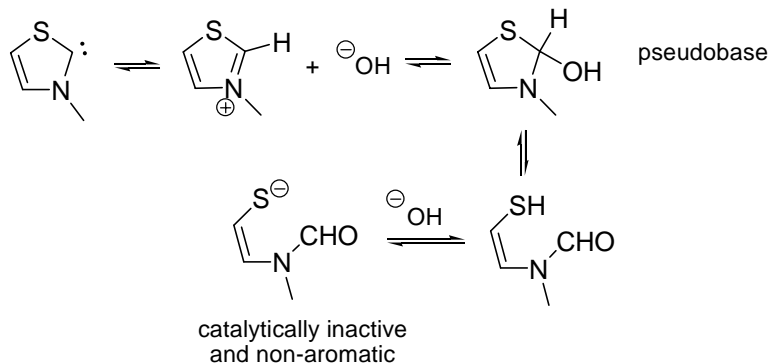
- an illuminating comparison:



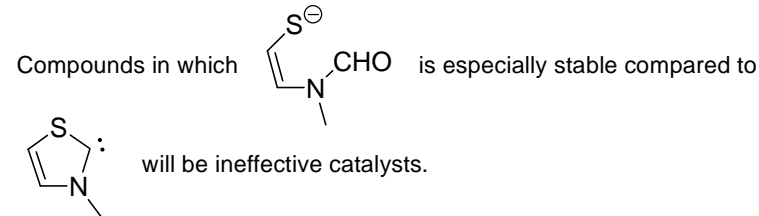
- both exchange with D<sub>2</sub>O  
- why is the thiazolium inactive?

Breslow *JACS* **1958**, *80*, 3719

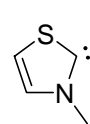
- consider parent thiazolium first:



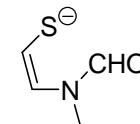
- another prediction:



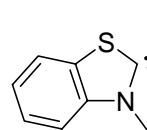
- aromaticity:



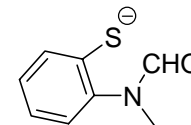
aromatic



not aromatic



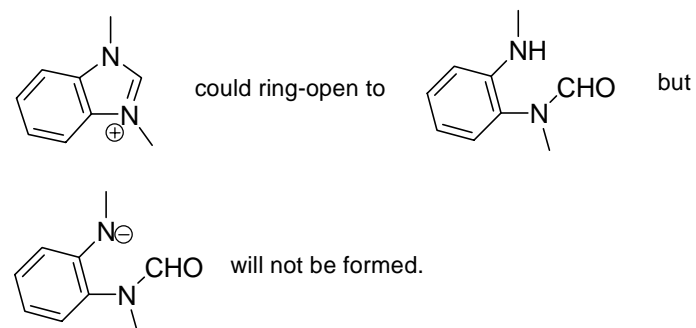
aromatic



still aromatic

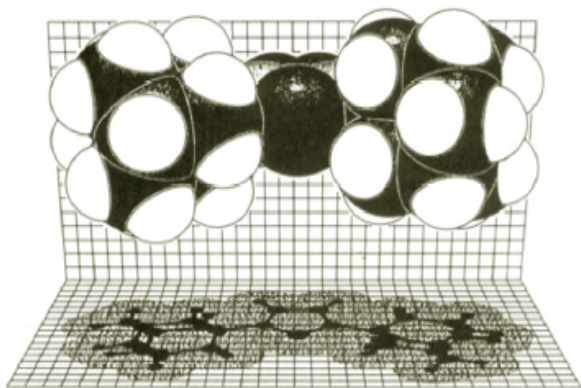
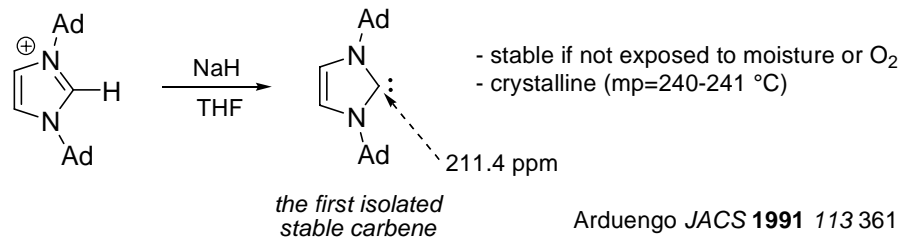
- the disruption of aromaticity is less significant here

- comparison with imidazoliums:



- prediction: at high pH, benzoin condensation should be suppressed  
- this has been found: Mizuhara *Proc. Japan Acad.* **1951** 27302

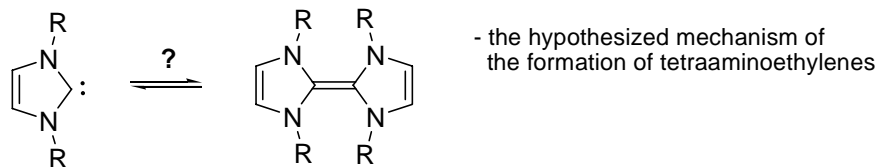
Isolation of a Stable Carbene



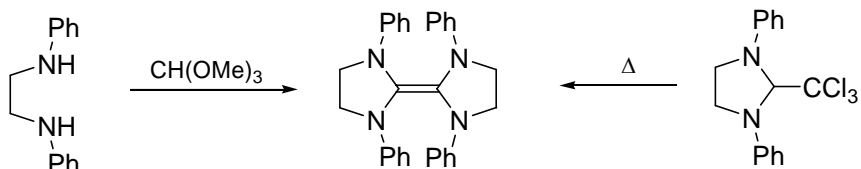
X-ray structure

- a wide variety of stable carbenes have now been isolated (see Hermann *ACIE* **2000** 39 4036)

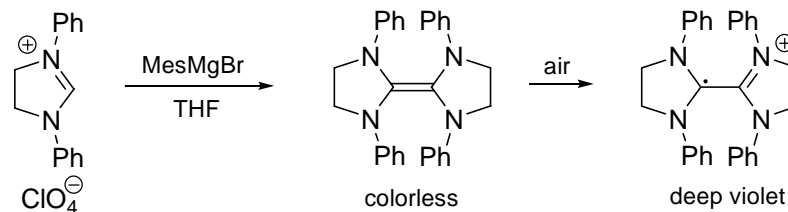
Carbene Dimerization



proposed by Wanzlick



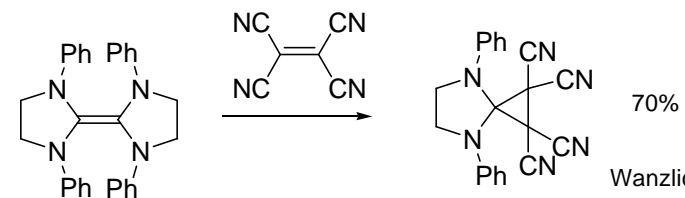
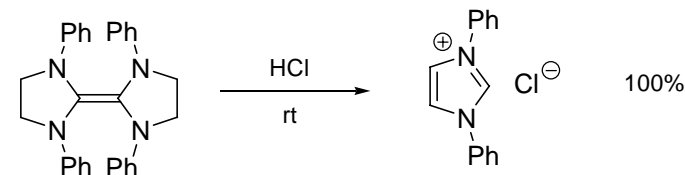
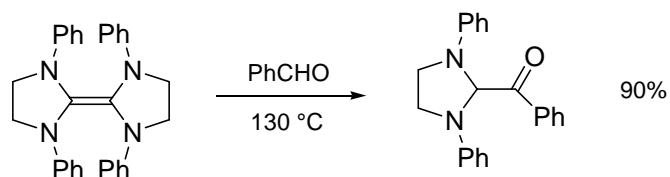
no ordinary olefins



- incredibly electron rich, these dimers oxidize very easily

Lemal *JACS* **1962** 84 1761

reactivity



Wanzlick *ACIE* **1962** 1 75

what is the reactive species?

**Wanzlick Proposal:** There is an **equilibrium**, and C1CN(C1)C2=CC=CC=C2 is the active species.

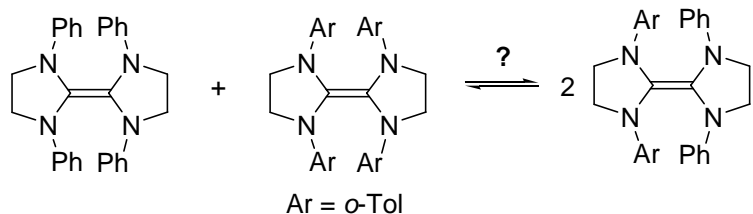
**Lemal Proposal:** There is **no equilibrium**, and

C1CN(C1)C2=CC=CC=C2 is the active species.

Lemal *JACS* **1964** 86 2518

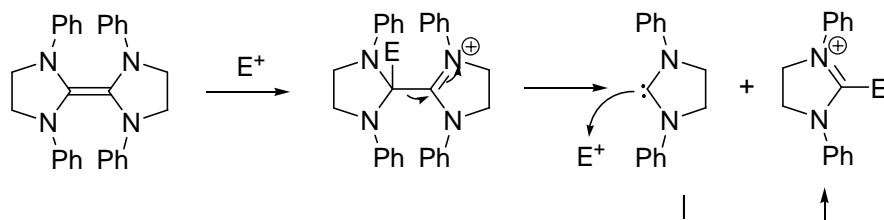
Eugene Kwan

## Crossover Experiments



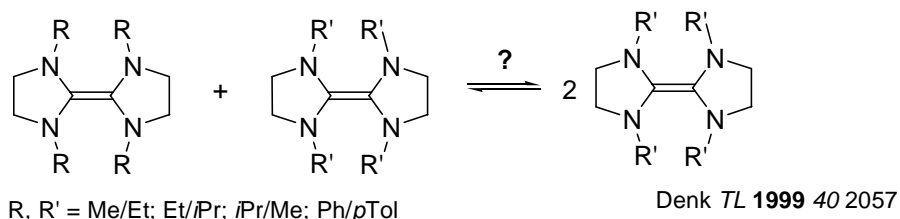
- 2 h reflux in xylene: **no crossover product observed** Lemal *JACS* **1964** 86 2518

an electrophilic addition mechanism



- alternate mechanism proposed
- requires: rate(dimerization) << rate (carbene + electrophile)
- further crossover experiments with alkyl and aryl tetraaminoethylenes confirmed the lack of crossover: Wiberg *JACS* **1965** 87 2055

a reinvestigation

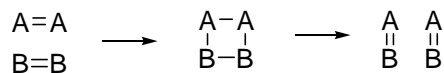


- **statistical mixture (1:2:1) obtained**

Do these findings prove the Wanzlick Equilibrium exists? No.

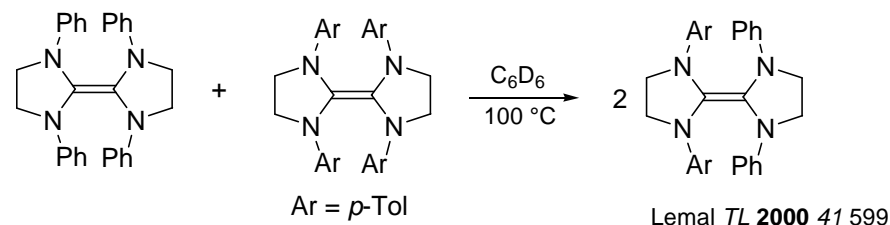
Negative Crossover = Definitely no equilibrium  
Positive Crossover = Might be an equilibrium

alternate possibility: cycloaddition-cycloreversion



alternate possibility: contamination

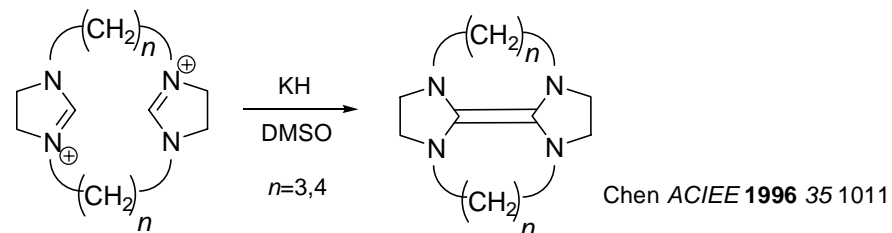
- to investigate the possibility that a contaminant catalyzes crossover, the experiments were repeated:



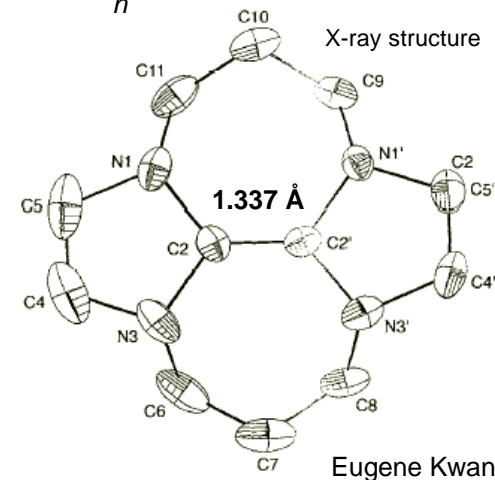
**as drawn:** 19% crossover after 6 h  
**with KH:** no crossover product

- after 22 h at 140 °C with KH, still no crossover product
- implies  $\Delta G > 35$  kcal/mol
- potential explanation: in the original 1964 work, substrates were prepared using triphenylcarbinol oxide, rather than heating the diamines with triethyl orthoformate as was done in the more recent studies
- confirmation: addition of acid catalyzed equilibrium (Hu *Mol Physics* **2004** 102 2617)

bridged carbenes

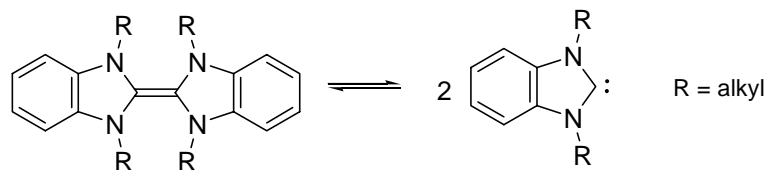


- *n*=3: no dissociation even at 100 °C
- *n*=4: dimer at -33 °C, carbenes at rt



- C=C bond length is normal, despite being extremely weak! (a few kJ/mol)

less aromatic carbenes



- equilibrium is observed (NMR)
- bulky R favors carbene (R=*i*Pr, neopentyl)
- for R=Et,  $\Delta H^\circ = 13.7 \pm 0.6 \text{ kcal/mol}$ ,  $\Delta S^\circ = 30.4 \pm 1.7 \text{ cal mol}^{-1} \text{ K}^{-1}$
- at 25 °C, this corresponds to  $\Delta G = 5 \text{ kcal/mol}$

- aromatic carbenes do not dimerize as easily

Lemal *JACS* **1999** 121 10626

Hahn *ACIE* **2000** 112 541

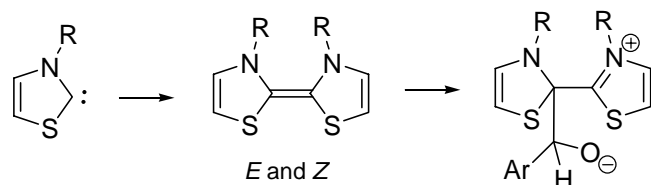
Summary: Herrmann *ACIE* **2000** 39 4036

## Further Reading

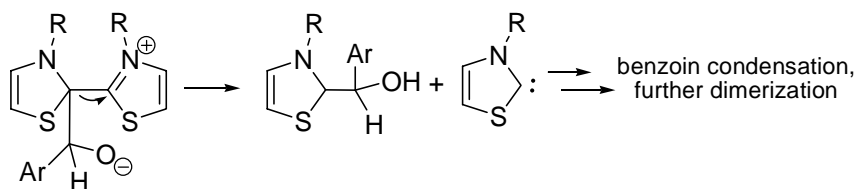
"When and How Do Diaminocarbenes Dimerize?" Alder, R.W.; Blake, M.E.; Chaker, L.; Harvey, J.N.; Paolini, F.; Schutz, J. *ACIE* **2004** 43 5896-5911.

## The Mechanism of Benzoin Condensation: A Controversy

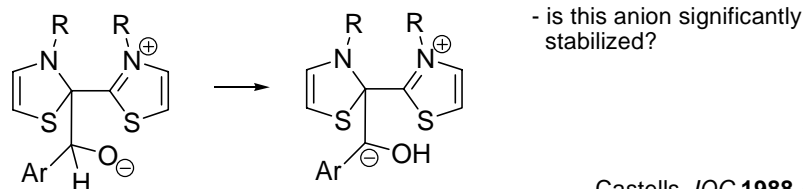
a dimeric mechanism?



option 1



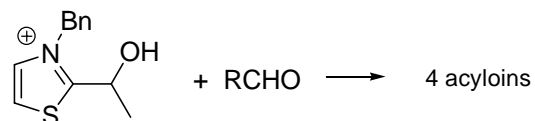
option 2



Castells *JOC* **1988** 53 4433

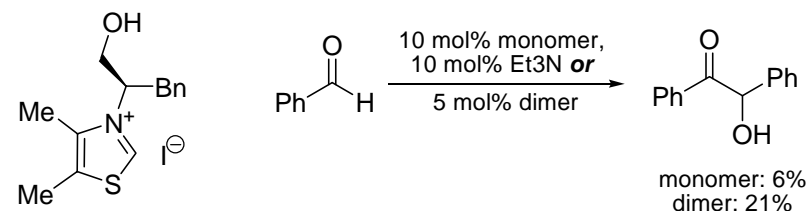
evidence for dimer involvement

(1) crossover is observed



- unclear how this implicates dimer

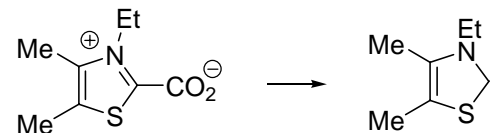
(2) dimers give higher yields than thiazolium salt + base



- dimers prepared by passing solution of salt in methanol through basic ion exchange resin

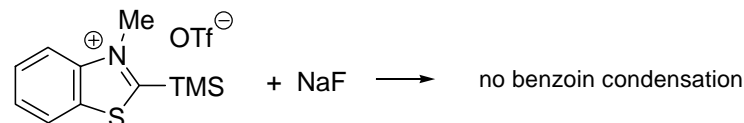
Castells *J Heterocyclic Chem* **1986** 23 715

(3) behavior when NHC is generated via decarboxylation



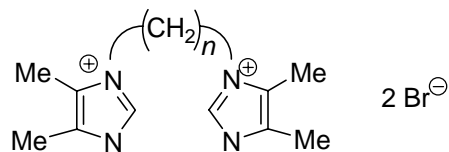
- argument: this should generate NHC is much higher concentrations
- however, same loadings of carboxylate are needed to effect reaction

(4) behavior when NHC is generated via desilylation



- reaction performed in dioxane at 100 °C
- solubility of NaF under these conditions?

## (5) bridged thiazolium salts



yields in the benzoin condensation

parent salt	yield
$n=3$	69%
$n=4$	59%
$n=5$	14%
$n=6$	40%
	44%

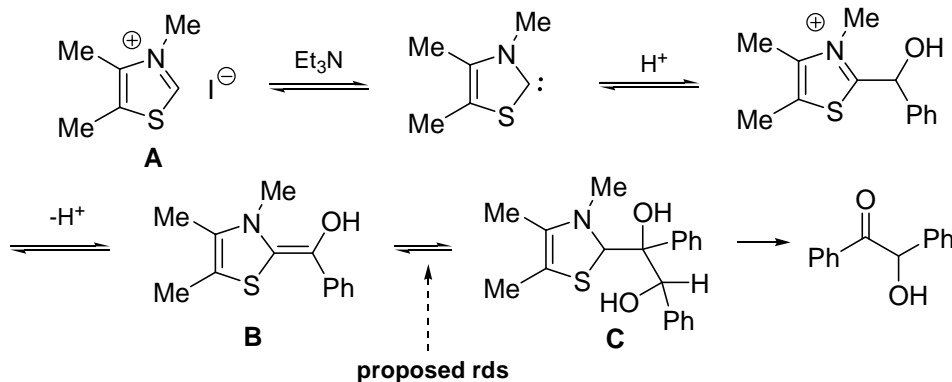
"this very clear dependency between yields and length of the polymethylene bridge supports our views on the relevant protagonism of bis(thiazolin-2-ylidenes)s as the catalytic species..."

- conditions: 10 mol% salt, 30 mol% DIPEA, dioxane, 100 °C, 24 h

Castells *TL* **1993** 34 517

## Breslow's Reply

- study the kinetics (UV, NMR) of the benzoin condensation:



rate law: order in benzaldehyde

- **B** is formed rapidly before much benzoin is produced
- in the early part of the reaction, **A** and **B** are in semi-equilibrium
- as ArCHO is consumed, **B/A** ratio decreases
- if **B** to **C** is the rds, then the order in PhCHO depends on the state of the thiazolium ion: first order if in form **B** but second order if in form **A**
- indeed, the order in PhCHO is between first and second order, depending on the initial concentrations

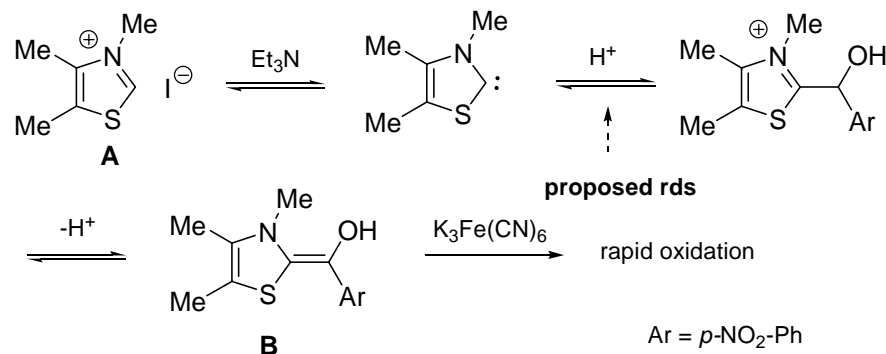
rate law: order in thiazolium ion

- NMR shows no trace of dimer
- rate law is **first order in total thiazolium ion**
- this excludes *option 2*

Jordan *JOC* **1991** 56 5029  
Breslow *TL* **1994** 35 699

## reaction with ferricyanide present

- *option 1* is not excluded, because it generates **B**
- what if the process is changed to make the formation of **B** rate determining?



- rate law is first order in aldehyde, **first order in A**, and zero-order in ferricyanide

"The thiazolium catalyzed benzoin condensation with mild base does not involve a 'dimer' intermediate."

Breslow *TL* **1994** 35 699

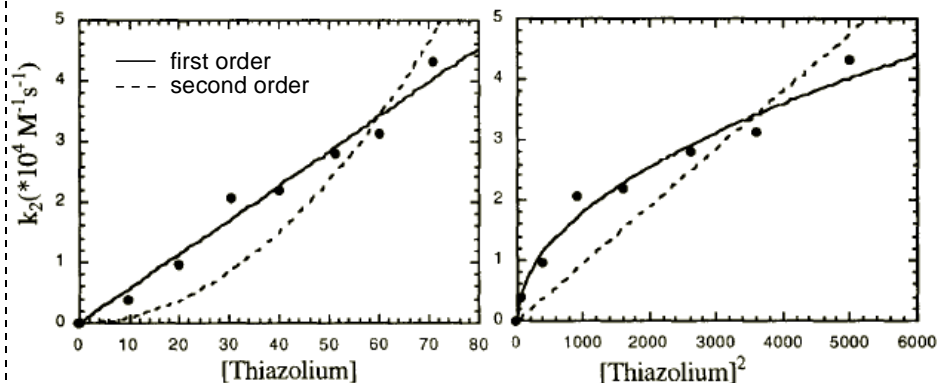
## further confusion

- contradictory reports appeared that the reaction might actually be second-order in both aldehyde and thiazolium ion

Lopez-Calahorra *Tet* **1995** 35 9713

"Contrary to recent reports, the catalysis of the benzoin condensation is first-order in thiazolium ion, even based on the results recently reported by others. Thus there is no need to propose an unusual anion intermediate in the reaction."

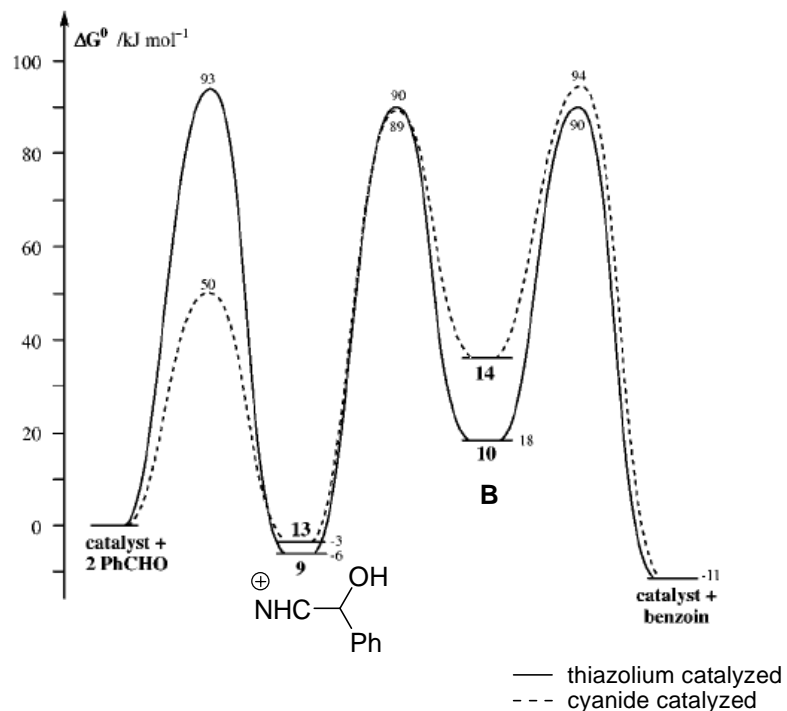
Breslow *TL* **1996** 37 8421



Eugene Kwan

modern data

- primary kinetic isotope effect when PhCDO used: 3.4
- inverse solvent isotope effect when CD<sub>3</sub>OD used: 5.9
- all rate constants have now been determined, confirming Breslow's position
- under many conditions, there is no single rate-determining step



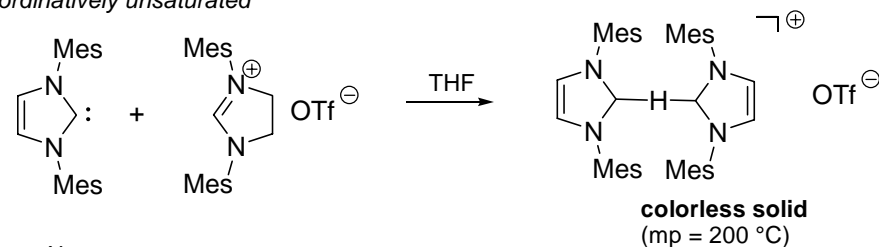
Further Reading

"Kinetics of the Thiazolium Ion-Catalyzed Benzoin Condensation." White, M.J.; Leeper, F.J. *J. Org. Chem.* **2001**, 66, 5124-5131.

Summary of Reactivity

dimerization potential	do not dimerize	dimerize reversibly	dimerize irreversibly
singlet-triplet gap (kJ/mol)	354		290
dimer C=C bond strength (kJ/mol)	4		130
general reactivity	<ul style="list-style-type: none"> <li>- nucleophiles</li> <li>- complex rapidly with most metals</li> <li>- moisture sensitive</li> <li>- do not react with triplet oxygen</li> </ul>		

coordinatively unsaturated



X-ray structure

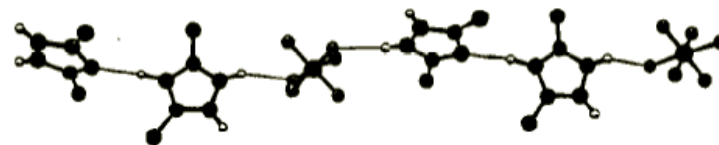
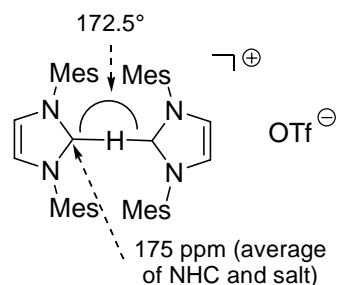


Figure 2. KANVAS<sup>11</sup> drawing of the extended structure of bis-(carbene)-proton complex in 3a. Mesityl groups (except ipso-carbons) have been omitted for clarity.

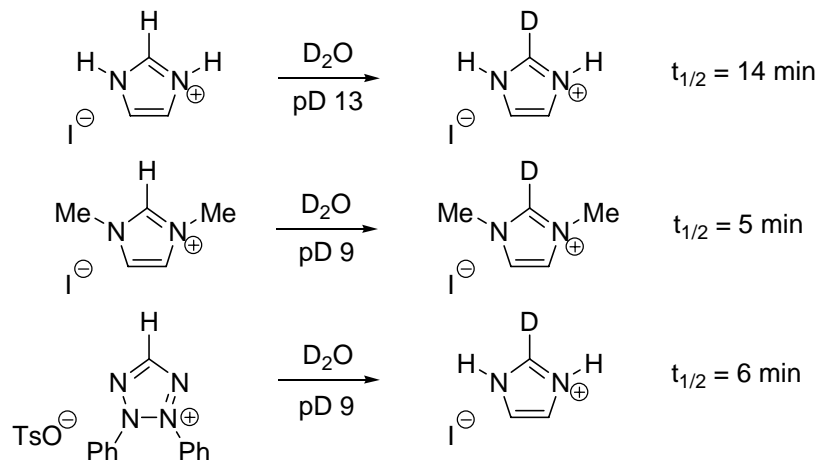




- bridging C-H bond length = 1.16 Å
- N-C-N bond angle = 107.6° (typical NHC: 102°)
- counterions form hydrogen-bonded bridges between imidazole C-H bonds
- a bridging iodine complex is also known

 Arduengo *JACS* **1995** 117 572

## Facile Deuterium Exchange

*the seminal report*


- rate varies by less than a factor of 2 for various buffer concentrations and types

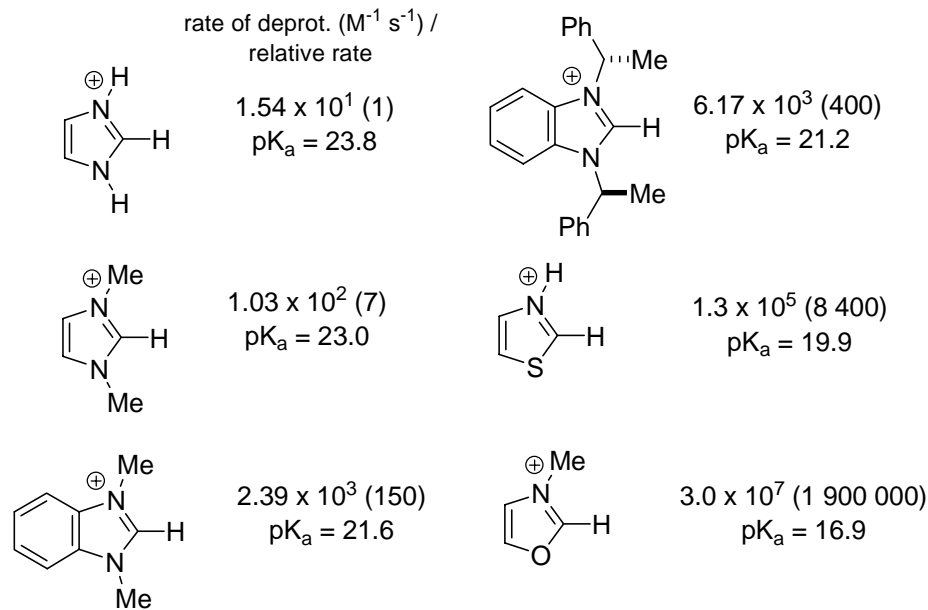
 Olofson *JACS* **1964** 86 1865

## acidity in water: methods

- rate of H/D exchange measured in buffered D<sub>2</sub>O with <sup>1</sup>H NMR
- this allows exchange at acidic CH to be distinguished from exchange at NH
- rate in H<sub>2</sub>O extrapolated from known kinetic isotope effect  $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}} = 2.4$  (Jencks *JACS* **1989** 111 683)
- reverse rate, protonation of carbene, extrapolated from flash photolysis:  $k_{\text{HOH}} = 10^{11} \text{ s}^{-1}$
- $\text{p}K_{\text{a}} = \text{p}K_{\text{w}} + \log(k_{\text{HOH}}/k_{\text{H}_2\text{O}})$ , where  $K_{\text{w}} = 10^{-14}$  and  $k_{\text{H}_2\text{O}}$  is the rate of deprotonation

 Richard *JACS* **2004** 126 4366

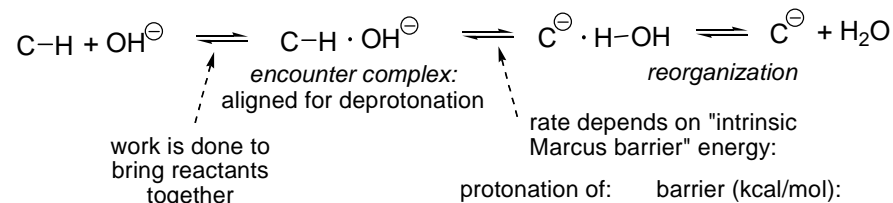
## acidity in water: results



- determined by relating rate of H/D exchange to solvent kinetic isotope effect
- kinetic and thermodynamic acidity are correlated

 Richard *JACS* **2004** 126 4366

## Eisen mechanism



- small primary KIEs are observed for imidazolium ion deprotonation

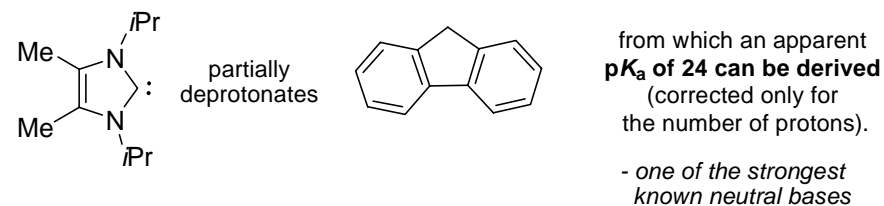
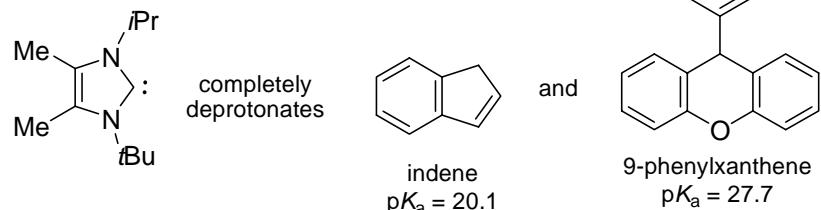
estimated barrier for azolium ions: 5 kcal/mol

 Eisen *ACIEE* **1964** 3 1

 Kresge *Acc Chem Res* **1975** 8 354

Acid-Base Behavior in Organic Solvents

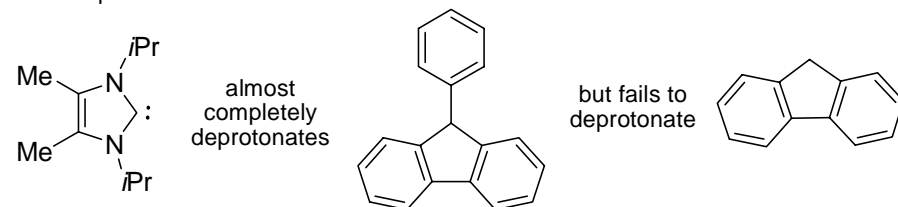
DMSO



- carbene preparation (1. K/THF 2. filtration 3. evaporation)
- deprotonation monitored by NMR

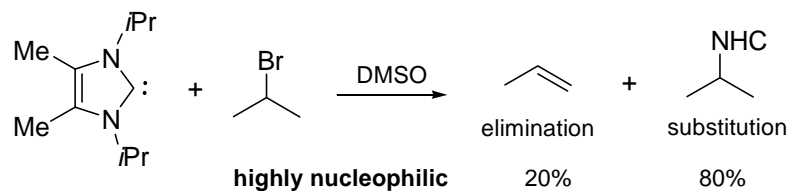
THF

- a less polar solvent which disfavors the formation of ions



- spectra show only slight broadening: rapid proton transfer on NMR timescale

Basicity vs. Nucleophilicity



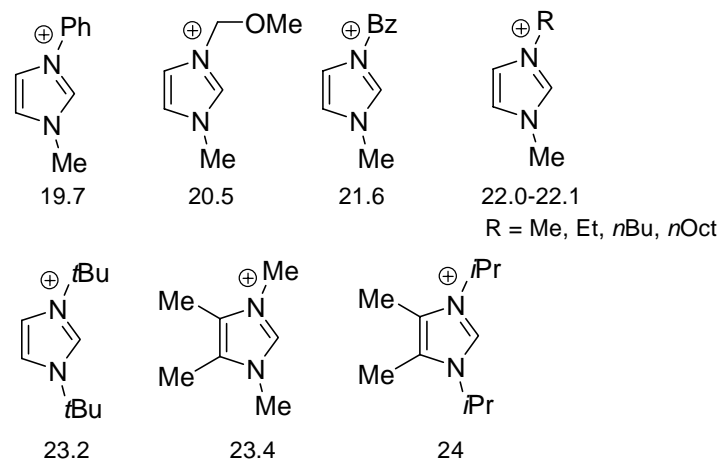
- cf. elimination/substitution ratios for DBN (91%) and DBU (21%) (Fritz *Chem. Ber.* **1994** 127 2435)

Alder *JCS Chem Commun* **1995** 1267

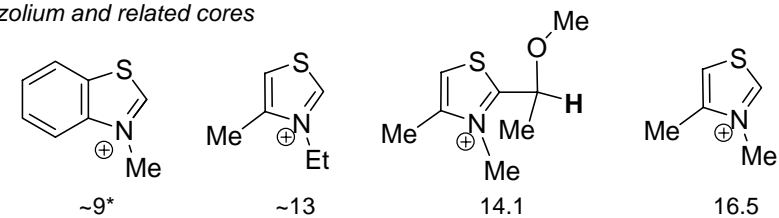
Compiled  $pK_a$  Values (DMSO)

- primarily determined from titrations with indicators
- little dependence on counterion (not shown)

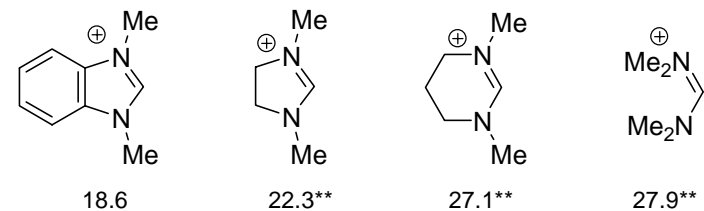
imidazolium core



thiazolium and related cores



other



references

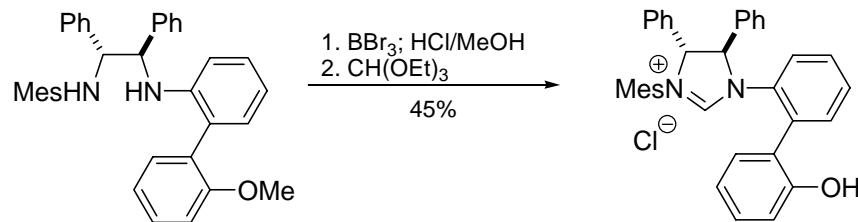
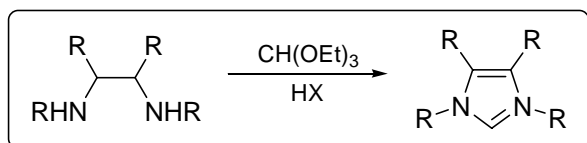
1. Jencks *JACS* **1989** 11 683
2. Cheung *JOC* **2007** 72 7790
3. Alder *JCS Chem Commun* **1995** 1267
4. Bordwell *JACS* **1991** 113 985-990 + refs. therein
5. Yates *JACS* **2004** 126 8717

\* complicated by dimerization

\*\* estimated by computations (ref. 5)

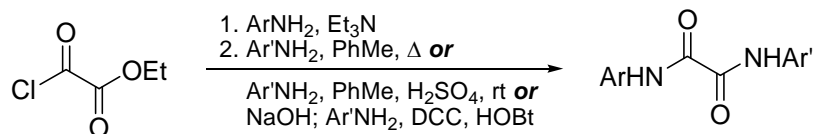
Imidazolium Salts

diamine precursor

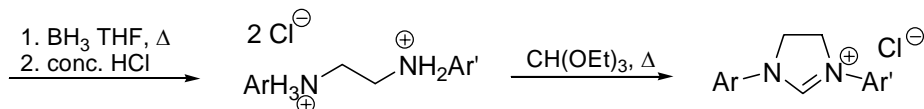


above: Hoveyda *JACS* **2005** 127 6877  
another example: Helmchen *Synlett* **2004** 1789

diamine precursor: variation

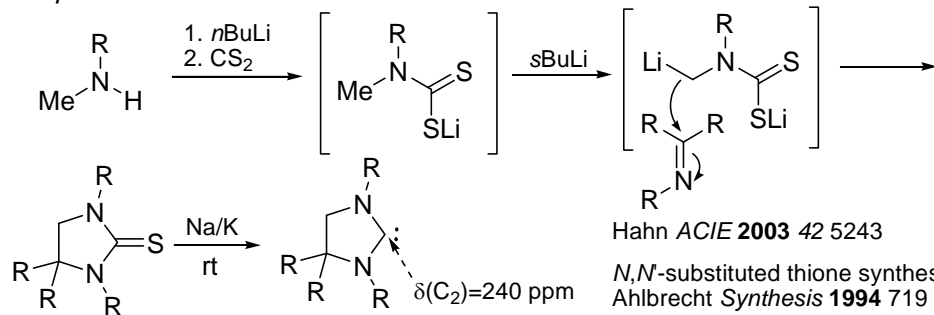


ethyl chlorooxoacetate

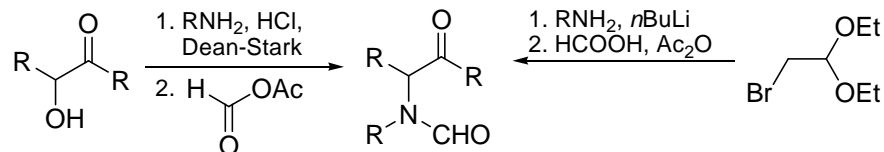


above: Grubbs *Orgmet* **2004** 23 3105  
further examples: Gilbertson *OL* **2005** 7 4605  
Mauditt *JOMC* **2005** 690 5237

sequential lithiations

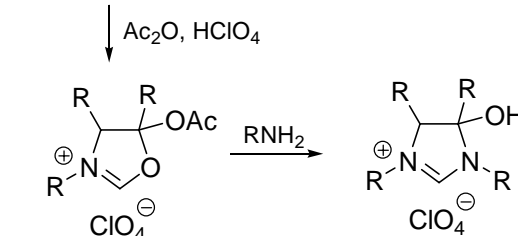


via oxazolium intermediate

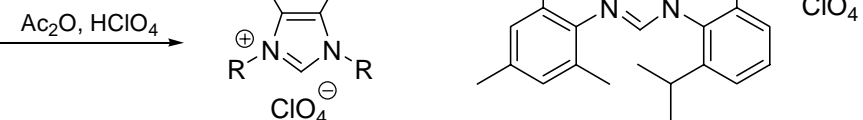


formic acetic anhydride:  
*Org Syn Coll.* Vol. 6 **1998** 8

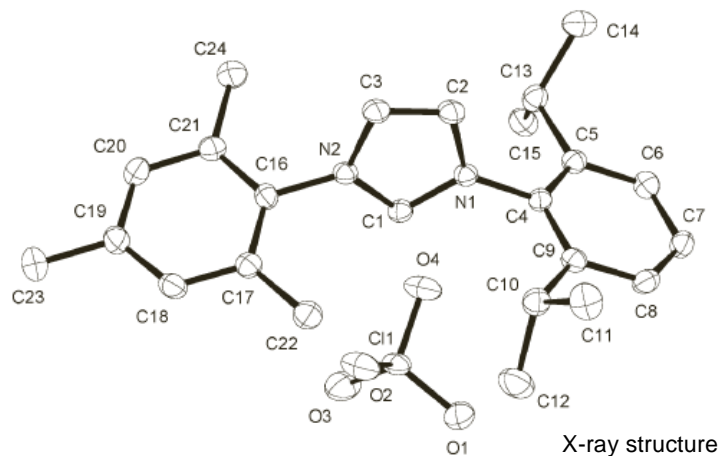
this method: Fürstner  
*Chem. Commun.* **2006** 2176



- does not aromatize

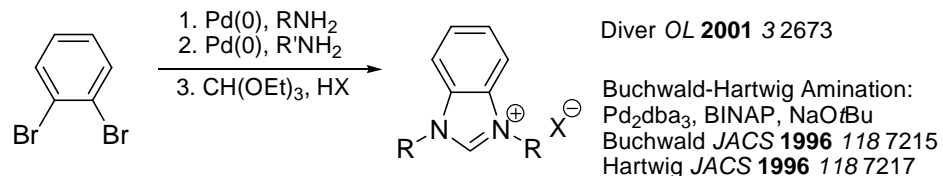


- sterically hindered amines are tolerated



X-ray structure

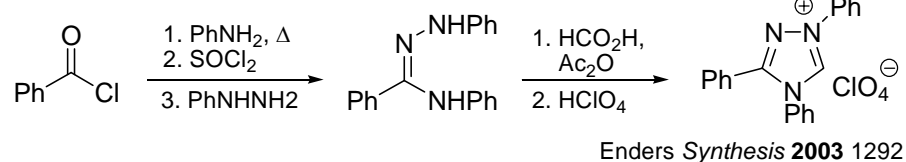
## Benzoimidazolium Salts



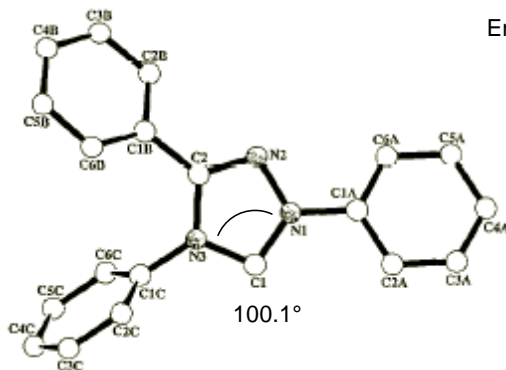
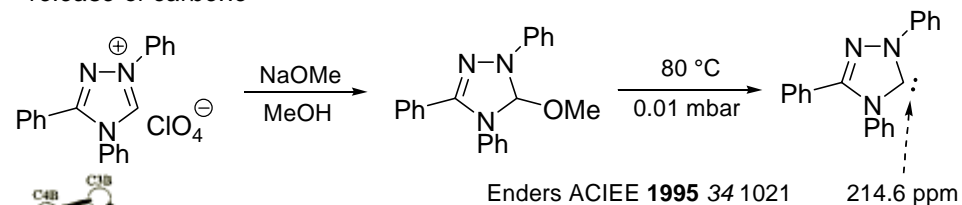
- optimization was required to suppress epimerization of chiral primary amines

## Triazolium Salts

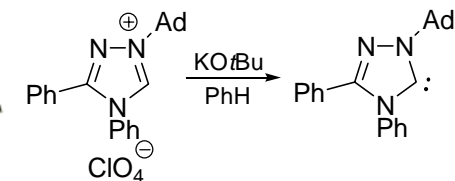
via phenylhydrazone



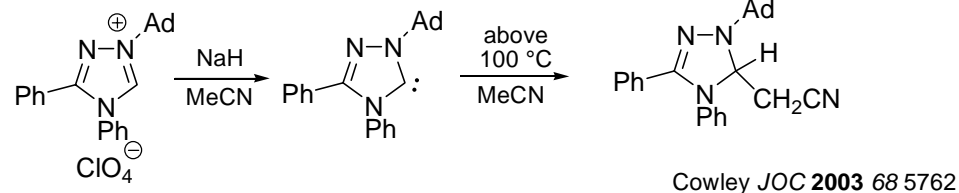
release of carbene



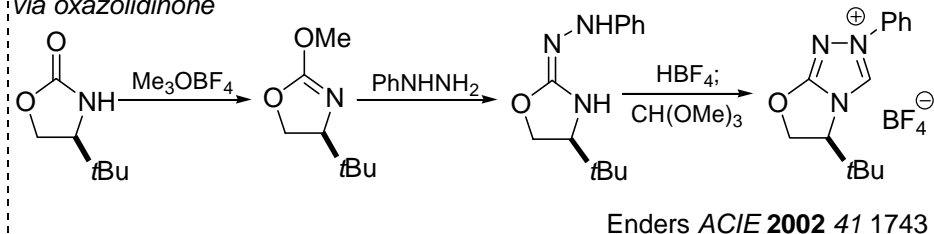
- base is also effective:



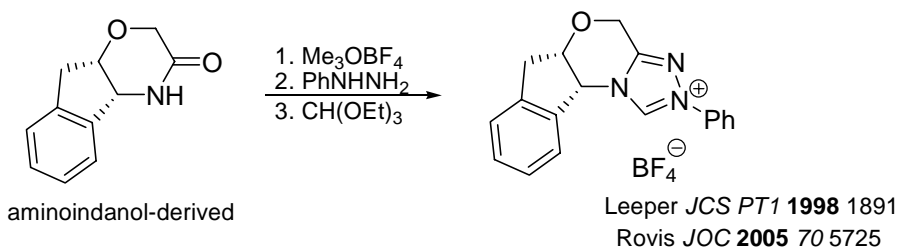
- reaction with acetonitrile:



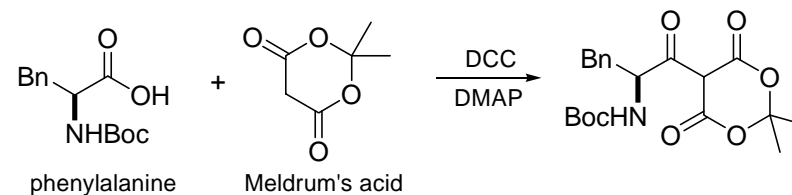
via oxazolidinone



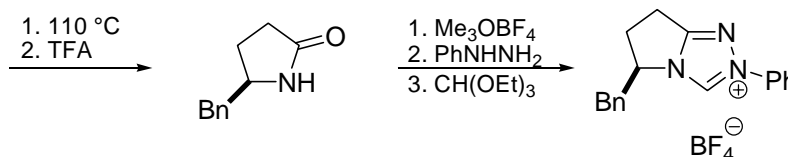
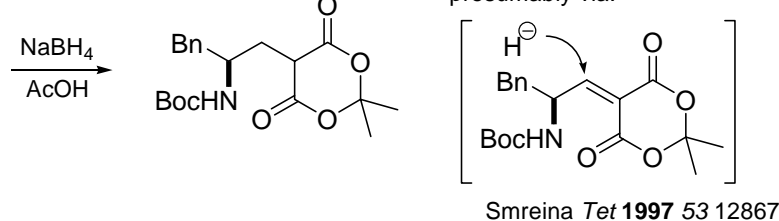
- amides are also useful:



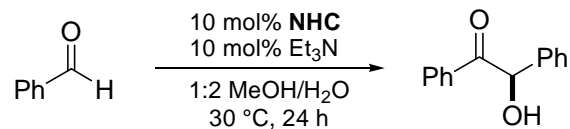
- from amino acids:



presumably via:

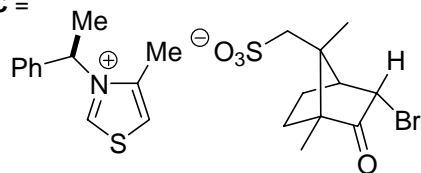


a first attempt



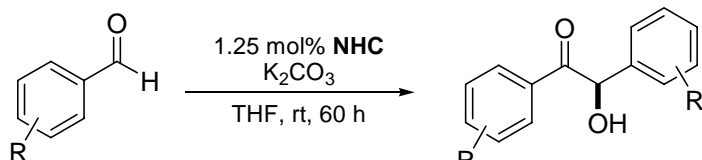
78%, 8% ee

NHC =



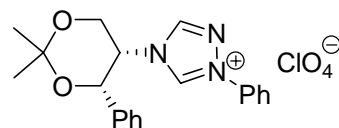
Sheehan *JACS* **1974** 39 1196

an improved system



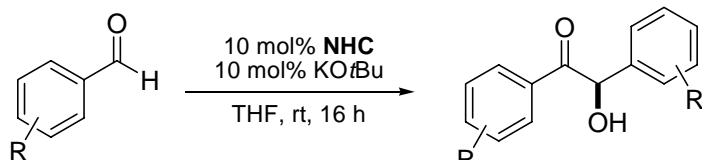
22-72%, 20-86% ee

NHC =



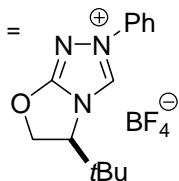
Enders *Helv Chim Acta* **1996** 79 1217

an efficient system



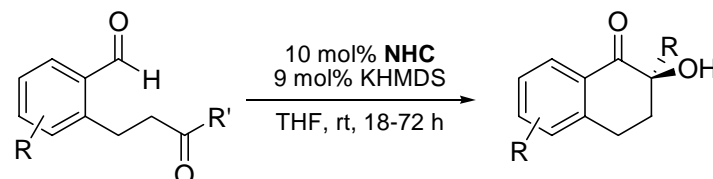
8-100%, 80-95%

NHC =



Enders *ACIE* **2002** 41 1743

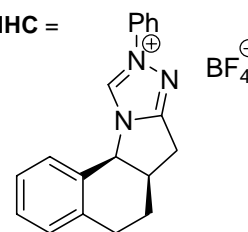
crossed-benzoin condensations



24-93%, 71-99% ee

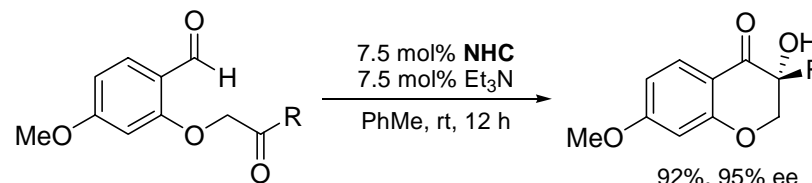
R'=alkyl

NHC =

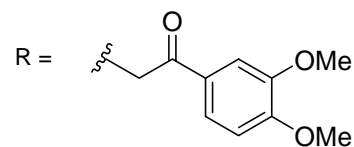


Enders *ACIE* **2006** 45 1463

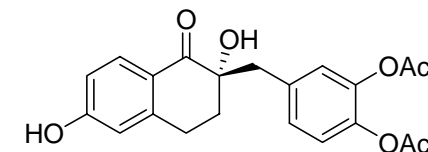
Enders *Synlett* **2006** 15 2431



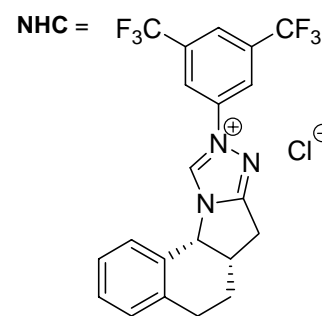
92%, 95% ee



3 steps



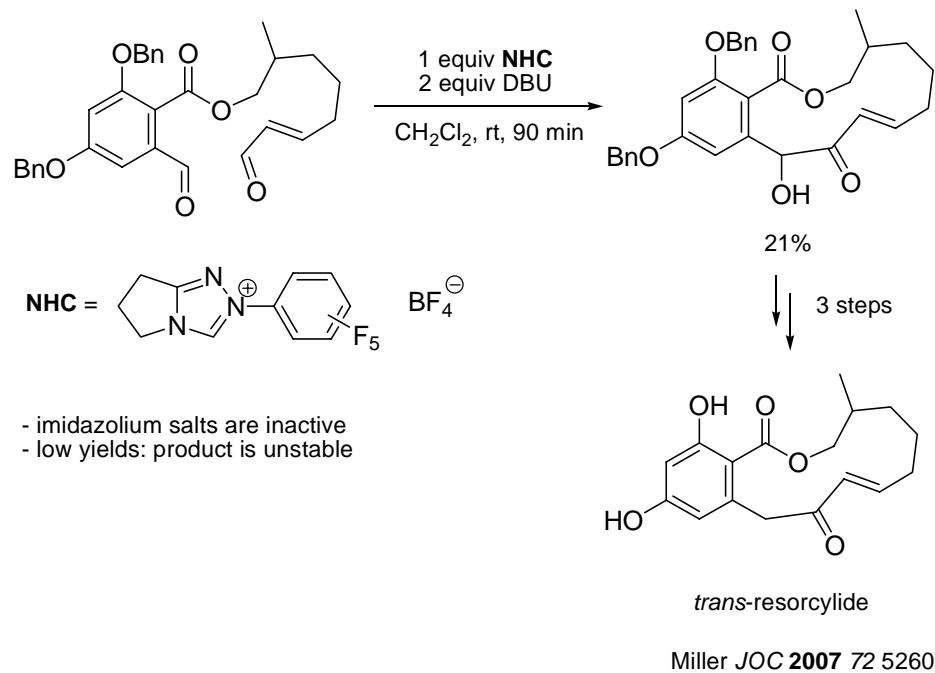
(+)-sappanone B



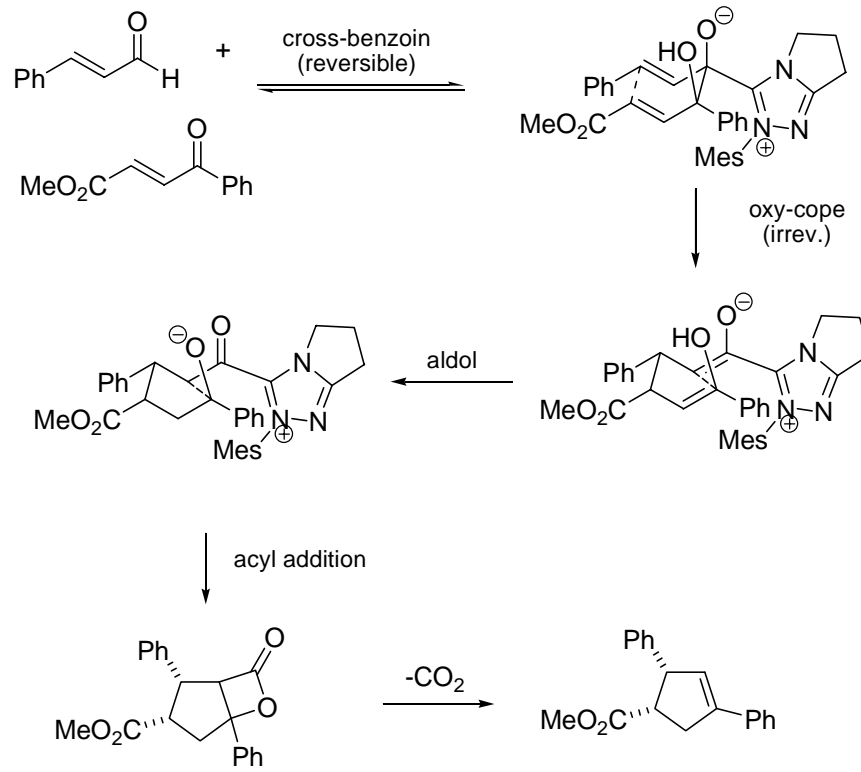
Suzuki *ACIE* **2006** 45 3492

Suzuki *OL* **2007** 9 2713

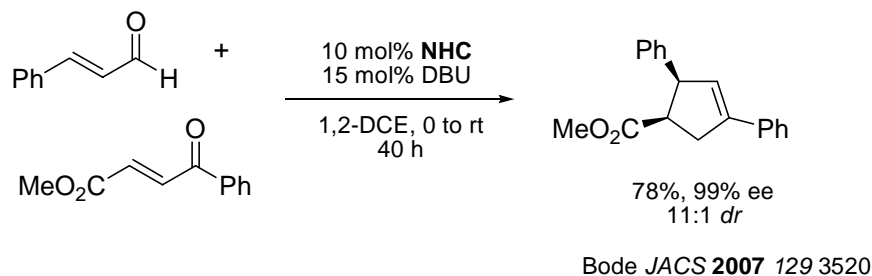
acyloin macrocyclization



- proposed mechanism:

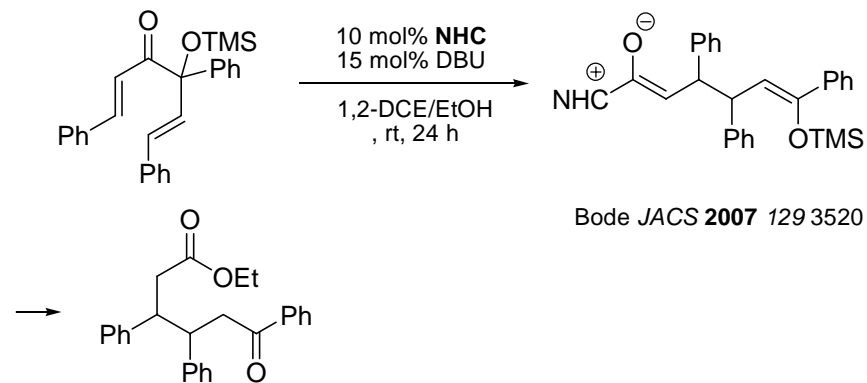


tandem benzoin-oxy-Cope-aldol sequence

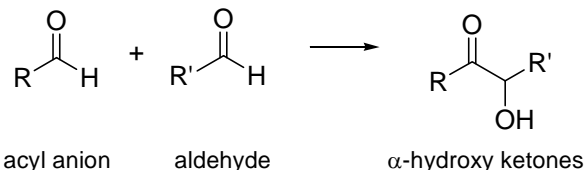


- proposed mechanism:

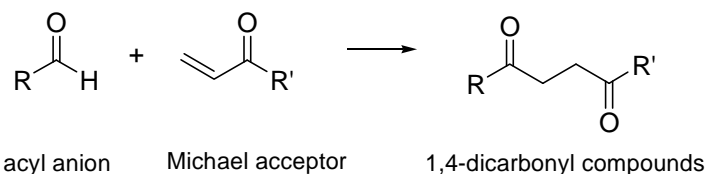
- evidence for oxy-Cope:



## benzoin



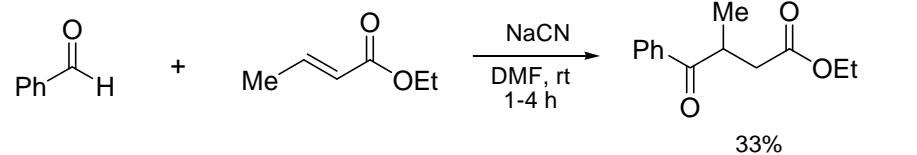
## Stetter



- essentially a vinylogous Stetter reaction
- removes problem of self vs. crossed additions
- the NHC-catalyzed process is a useful alternative to the radical process

Stetter *ACIEE* **1976** 15 639  
 Christmann *ACIE* **2005** 44 2632 } useful reviews

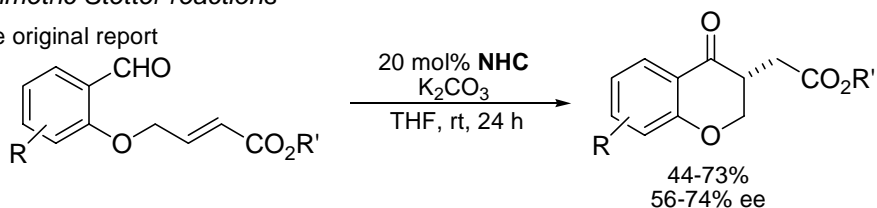
## the original reaction



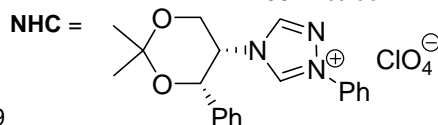
- thiazolium salts were soon found to be useful as well

## asymmetric Stetter reactions

the original report

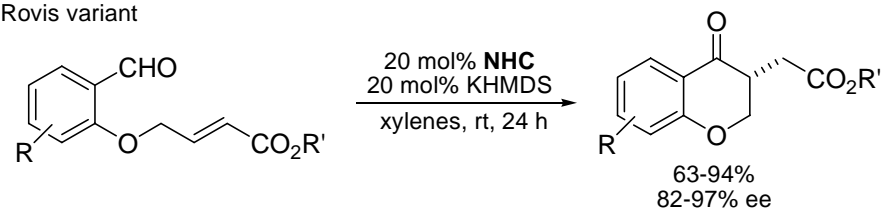


- R = H, Cl, OMe; R' = Me, Et
- key advance: triazolium salts are more active

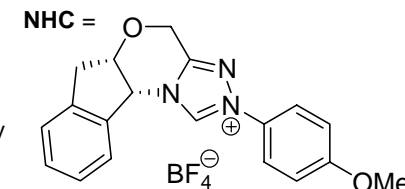


Enders *Helv Chim Acta* **1996** 79 1899

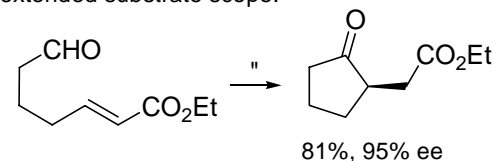
## Rovis variant



- significantly improved yields and ee's
- Z enoates do not react
- $\alpha,\beta$ -unsaturated aldehydes, carboxamides, and nitro compounds are inactive
- $\alpha,\beta$ -unsaturated ketones react more rapidly than corresponding esters



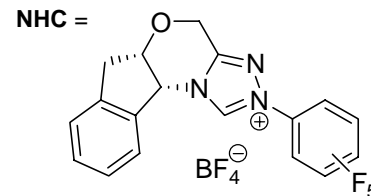
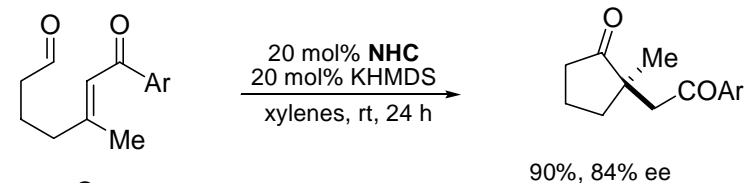
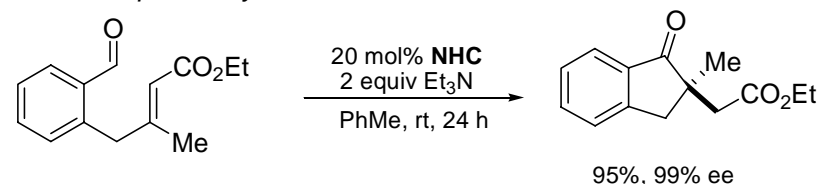
- extended substrate scope:



- six-membered variant: no reaction
- an unsolved problem: high catalyst loadings

Rovis *JACS* **2002** 124 10298  
 Rovis *Synlett* **2003** 12 1934

## formation of quaternary stereocenters

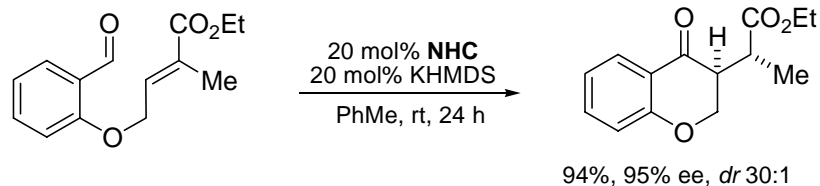
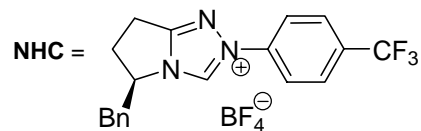


Rovis *JACS* **2004** 126 8876

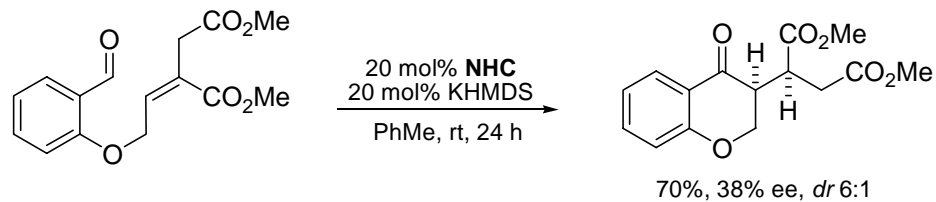
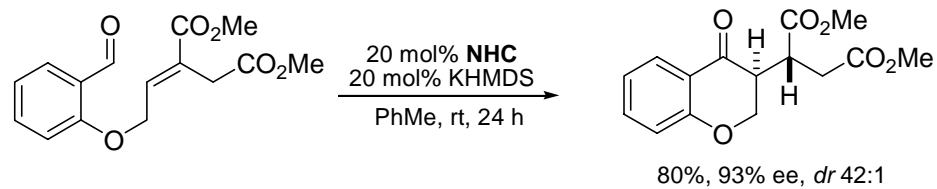
- some kinetic resolution can also be obtained with racemic g-substituted substrates
- Rovis *Tet* **2005** 61 6368

Eugene Kwan

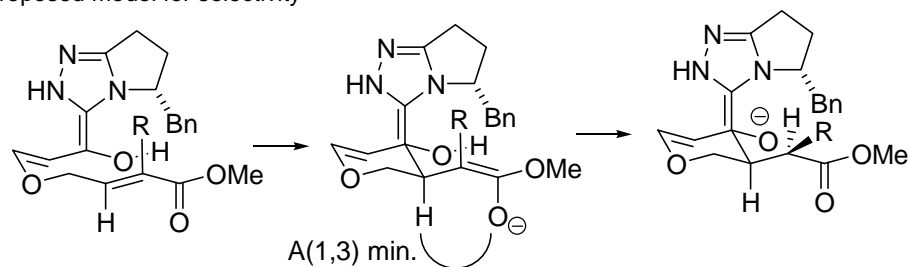
## diastereo- and enantioselective variant


 Rovis *JACS* **2005** 127 6284


- mechanism of reaction?

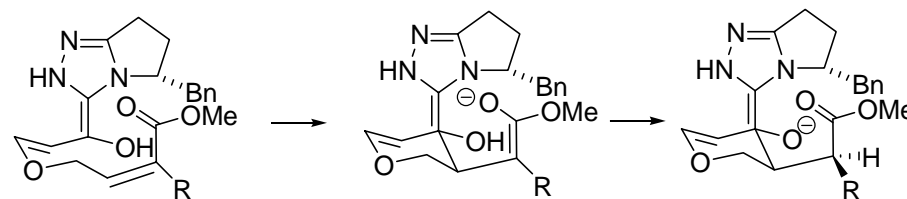


- proposed model for selectivity

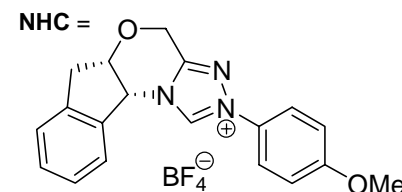
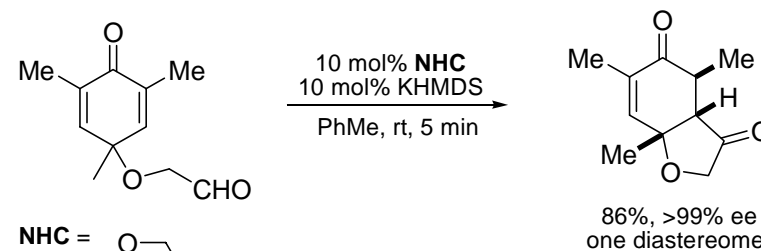


- evidently, intramolecular protonation is faster than intermolecular protonation

- Z acceptor: Stetter addition from the same face, but protonation from the opposite face

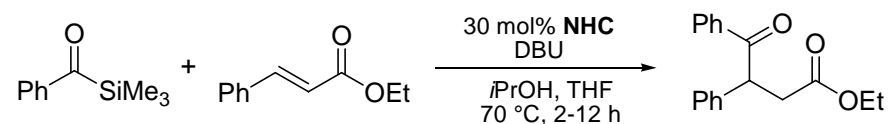
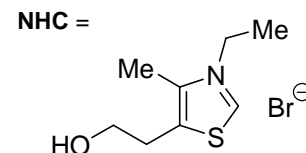


## enantioselective desymmetrization


 Rovis *JACS* **2006** 128 2552  
Rovis *Org Proc R&D* **2007** 11 598

## sila-Stetter reactions

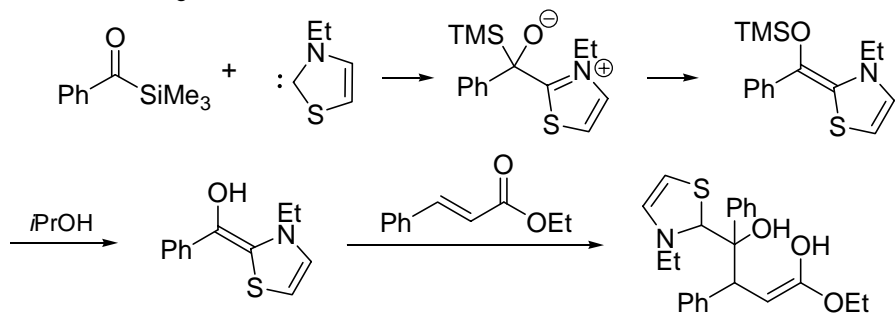
- acylsilanes are competent nucleophiles


 Scheidt *JACS* **2004** 126 2314


- an analogue of thiamine diphosphate

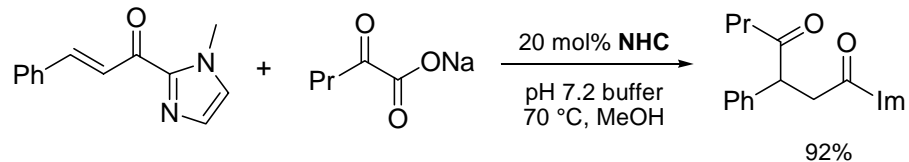


- Brook rearrangement:

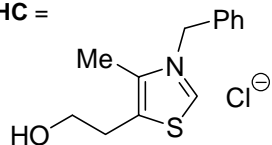


Scheidt *JOC* **2006** 71 5715

acylimidazoles

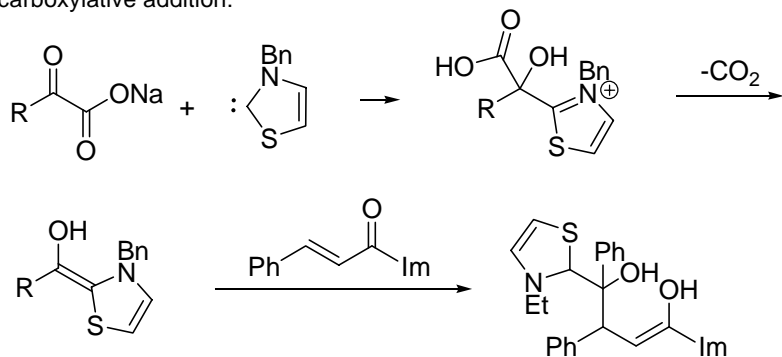


NHC =

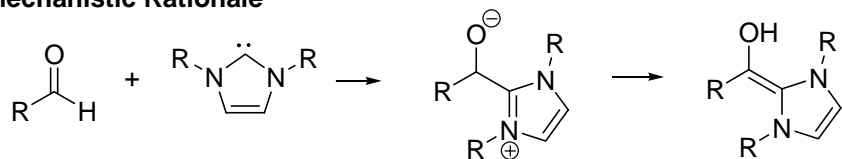


Scheidt *JACS* **2005** 127 14675

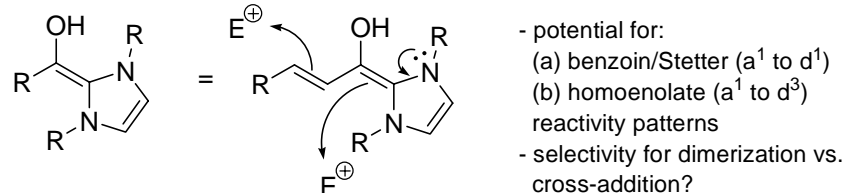
- decarboxylative addition:



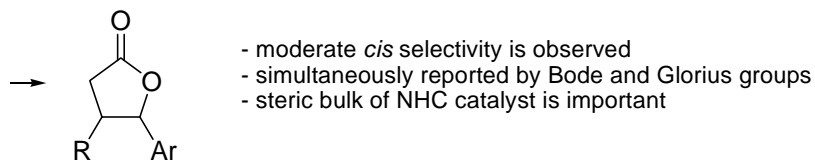
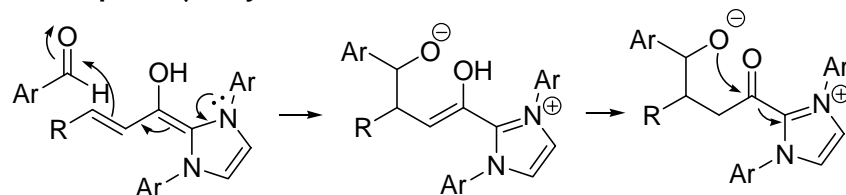
Mechanistic Rationale



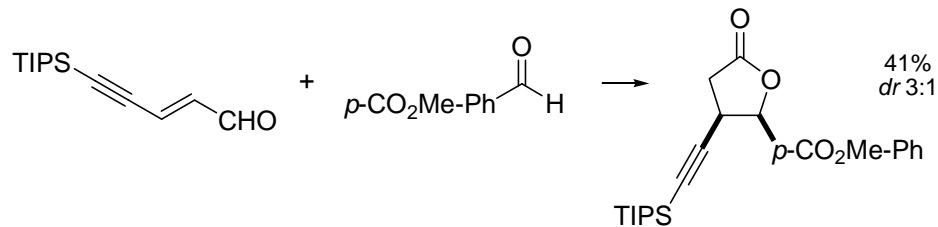
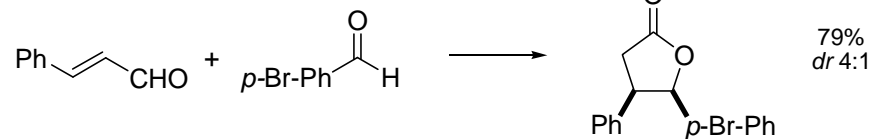
if aldehyde is  $\alpha,\beta$ -unsaturated:



Initial Reports:  $\gamma$ -Butyrolactone Formation

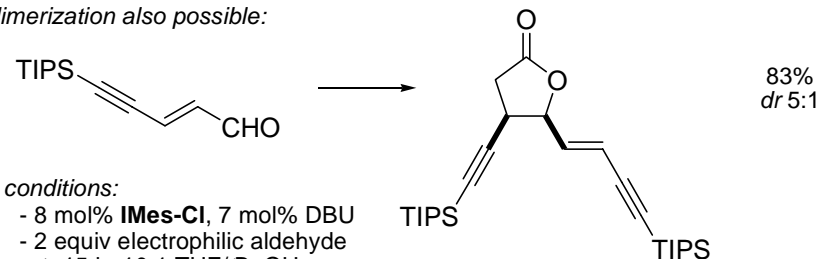


representative examples: Bode



Bode JACS 2004 126 14370

- dimerization also possible:



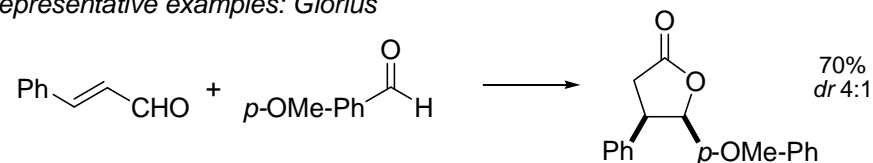
conditions:

- 8 mol% **IMes-Cl**, 7 mol% DBU
- 2 equiv electrophilic aldehyde
- rt, 15 h, 10:1 THF/*t*BuOH

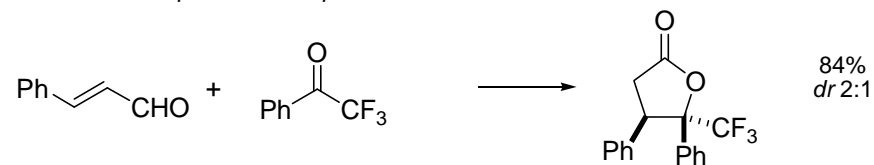


- aliphatic aldehydes are not effective
- slow addition of enal increases yields
- performing the reaction with *cis*-*p*-anisaldehyde still leads to the *cis* adduct
- if reaction is performed with *t*BuOD, D is incorporated exclusively at the  $\alpha$ -position (no quenching of homo-enolate by solvent)

representative examples: Glorius



- ketones are competent electrophiles:



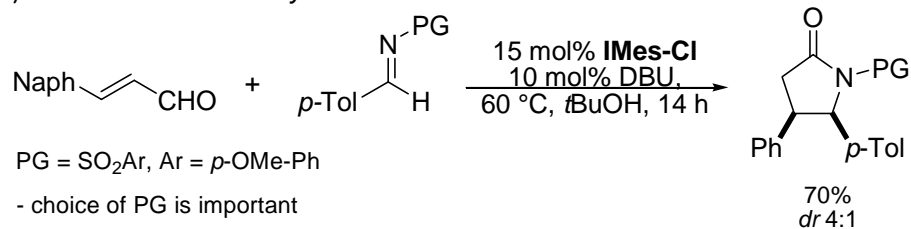
conditions:

- 5 mol% **IMes-Cl**, 10 mol% KO*t*Bu
- 1 equiv electrophilic aldehyde
- 16 h, rt, THF

Glorius ACIE 2004 43 6205

Extending the Scope of the Electrophile

$\gamma$ -lactams from N-sulfonylimines



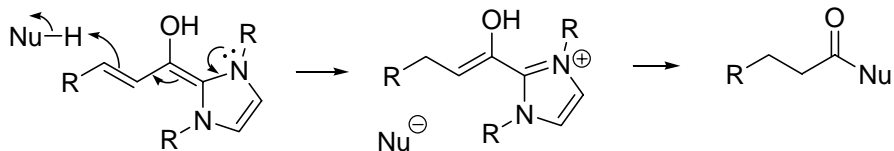
PG = SO<sub>2</sub>Ar, Ar = *p*-OMe-Ph

- choice of PG is important

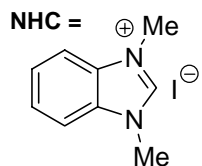
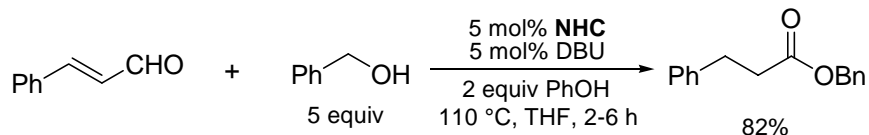
Bode OL 2005 7 3131

Eugene Kwan

Redox Esterification



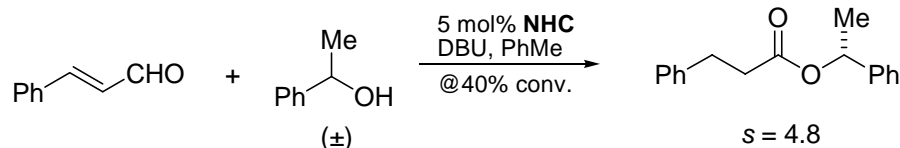
- a representative example:



- primary and secondary alcohols are tolerated
- nitrogen nucleophiles are not useful: sulfonamides, amides, azides, and anilines give other products
- $\beta,\beta$ -disubstitution of the enal gives no reaction

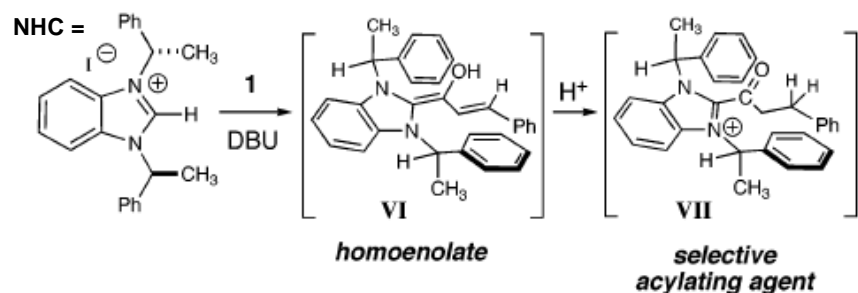
Scheidt OL 2005 7 905

- kinetic resolution is possible:

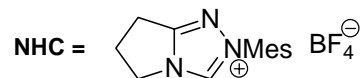
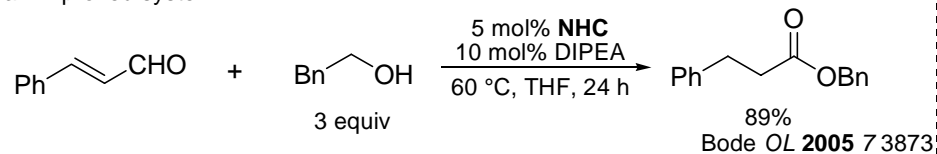


Scheidt OL 2005 7 905

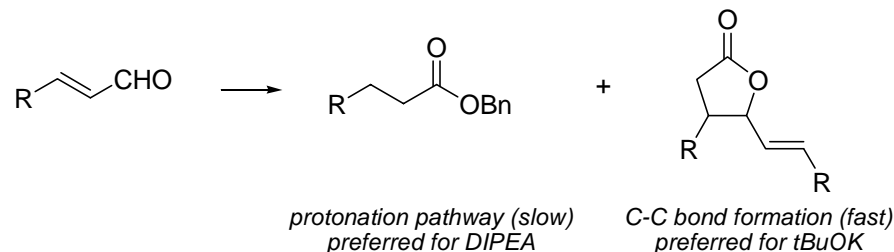
- proposed stereochemical model:



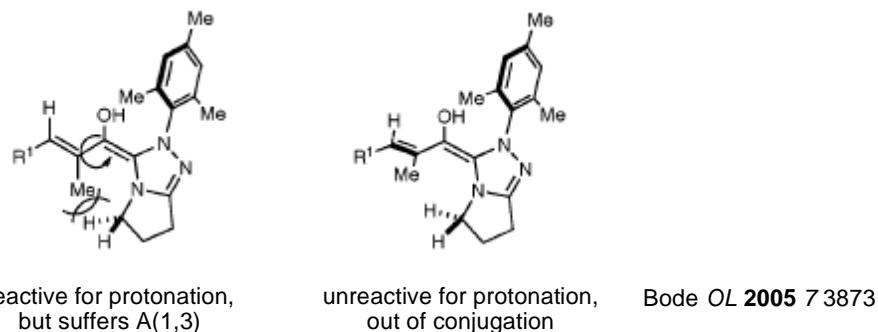
- an improved system:



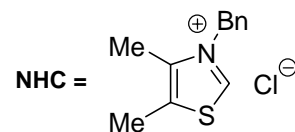
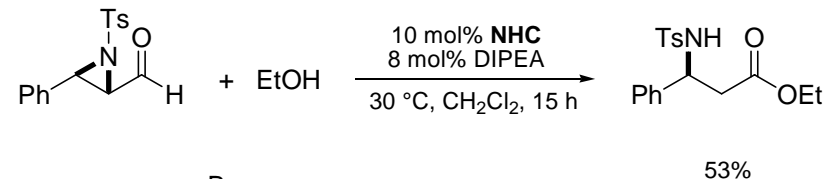
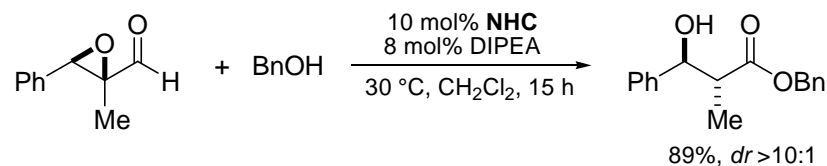
- selectivity between mechanistic pathways is dependent on the choice of base:



-  $\alpha$ -branched enals are unsuccessful due to A(1,3) strain:



epoxyaldehydes and epoxyaziridines are also useful



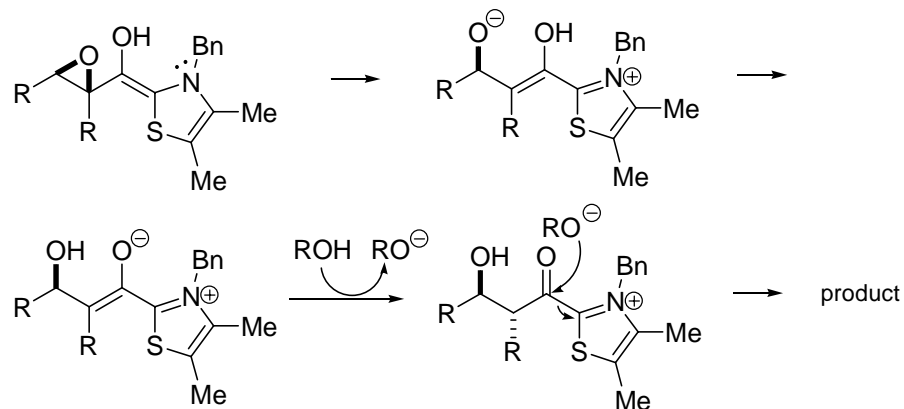
- acyloin dimers, C-C bond formation are suppressed

Bode JACS 2004 126 8126

Eugene Kwan

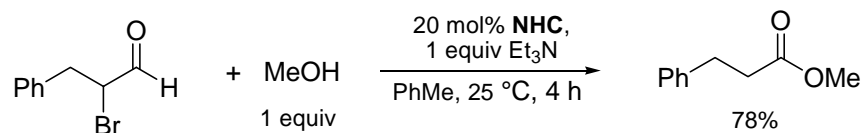
# N-Heterocyclic Carbenes: Homoenolates

- proposed mechanism:

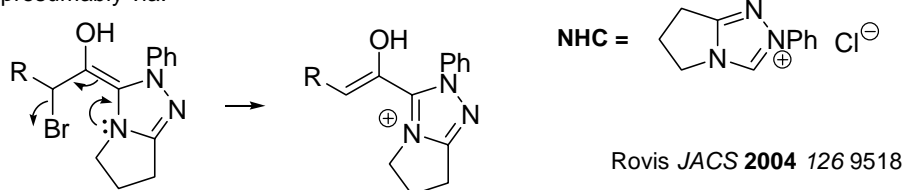


- if reaction is run in the presence of  $\text{CD}_3\text{OD}$ , recovered epoxide contains no deuterium  
 - implies concerted process or rate-determining deprotonation  
 - product has deuterium at the alpha position; no Favorskii or hydride-shift mechanism

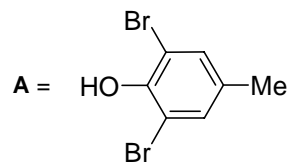
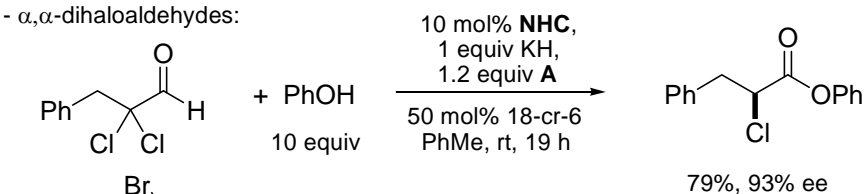
Bode *JACS* **2004** 126 8126



- presumably via:

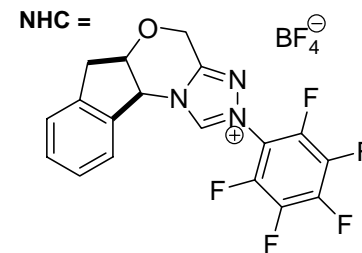
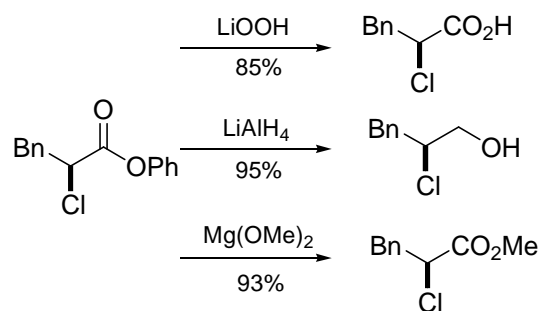


-  $\alpha,\alpha$ -dihaloaldehydes:



- 18-cr-6 required for solubility of KH in PhMe  
 - A acts to reduce background epimerization by acting as the "base reservoir"

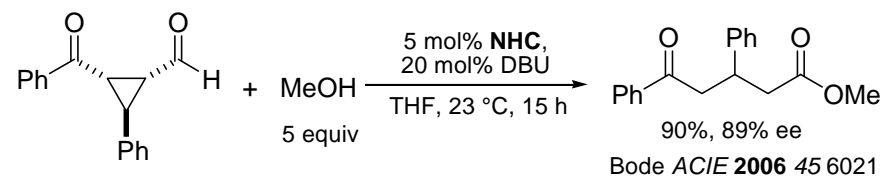
- enantioselective protonation leads to product  
 - products are useful in further transformations:



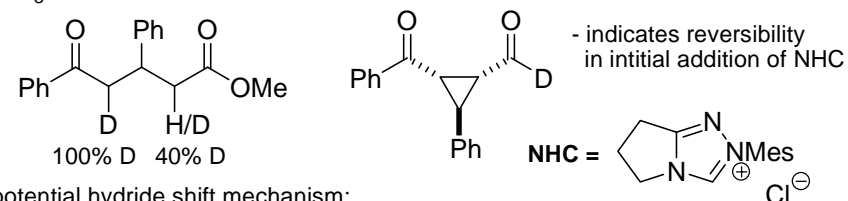
- transformations preserve ee

Rovis *JACS* **2005** 127 16406

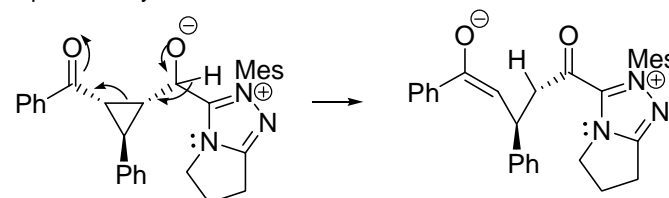
use of formylcyclopropanes



- range of aromatic, unsaturated, and aliphatic substrates are useful  
 - water and thiols are also useful nucleophiles  
 - if  $\text{CD}_3\text{OD}$  used:

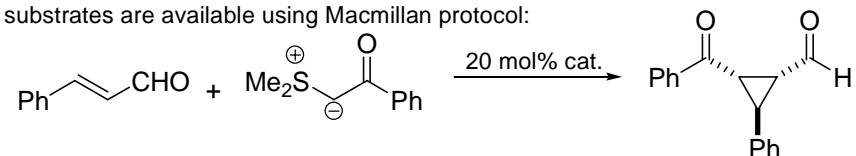


- potential hydride shift mechanism:



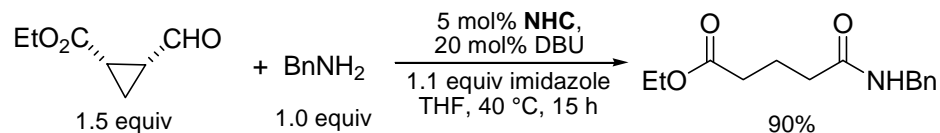
- however, reaction with an enantioenriched substrate gives racemic product; actual mechanism remains unknown

- substrates are available using Macmillan protocol:

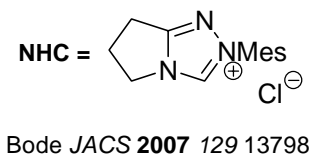


MacMillan *JACS* **2005** 127 3240 Eugene Kwan

- redox amidation is also possible (difficult with other methods)

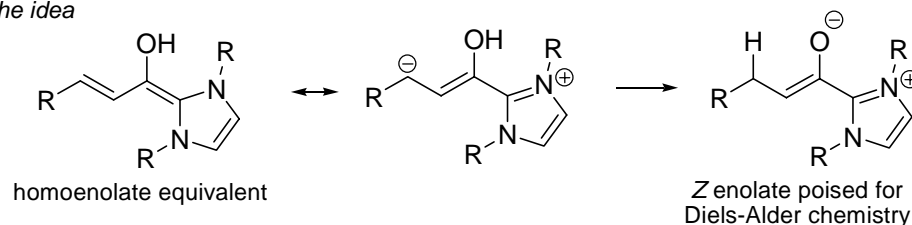


- presence of imidazole suppresses formation of undesired imine
- believed imidazole forms a transient hemiaminal which acts to protect the aldehyde
- range of primary, secondary, anilinic, and hydroxyl- amines are tolerated



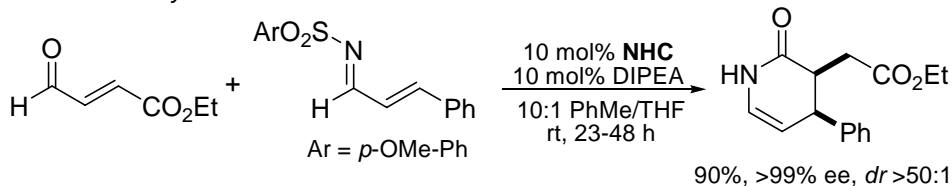
## Diels-Alder Cycloadditions

the idea

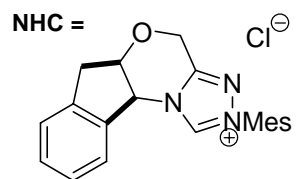
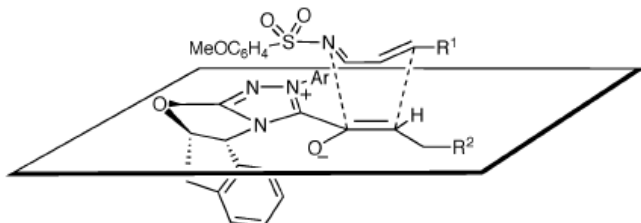


- problem: with imidazolium-derived NHCs,  $\beta$ -protonation is slow, even at elevated temperatures in protic solvents

triazolium catalysts are successful



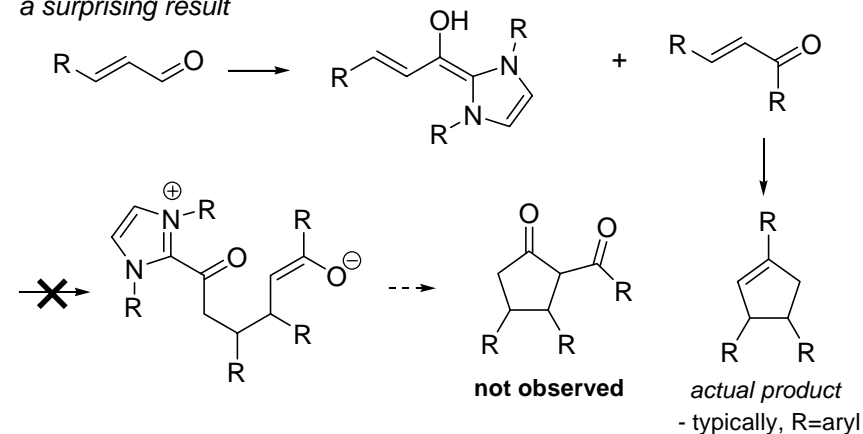
- exclusively *endo* dihydropyridinone products formed in high yields
- *cis* selectivity rationalized by Z enolate
- $\alpha$ -chloro aldehydes are also viable dienophiles
- fumarates and other non-aldehyde dienophiles are not reactive, arguing against a Morita-Baylis-Hillman-type pathway



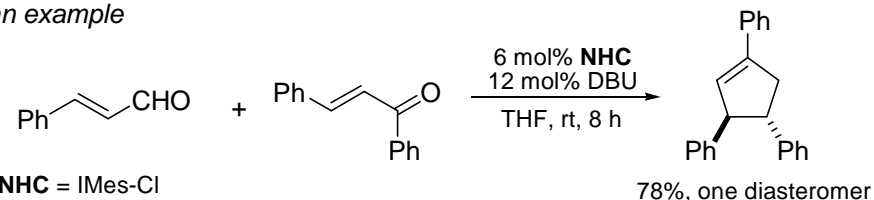
Bode *JACS* **2006** 128 8418

## $\alpha,\beta$ -Unsaturated Ketones

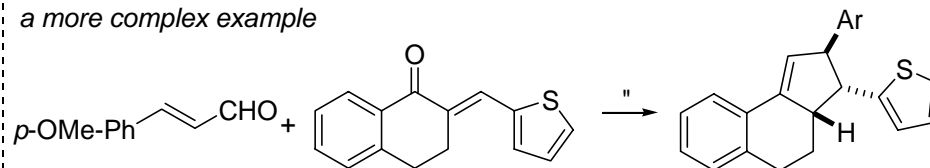
a surprising result



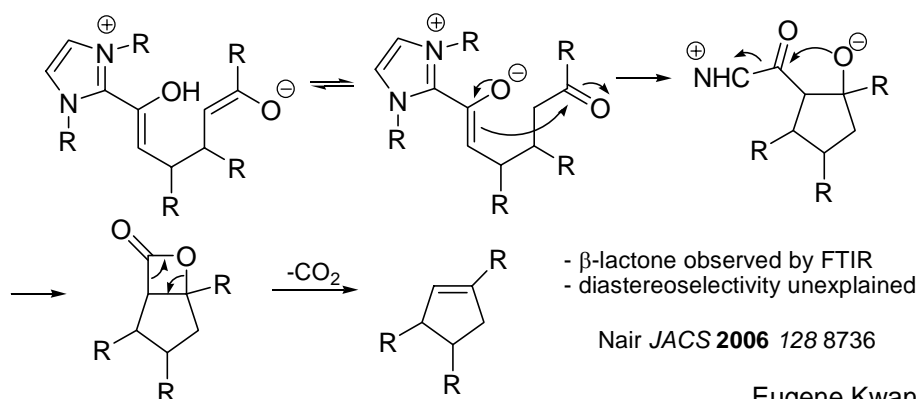
an example



a more complex example



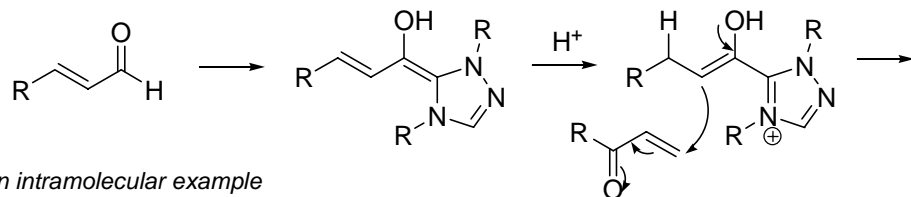
mechanistic rationale



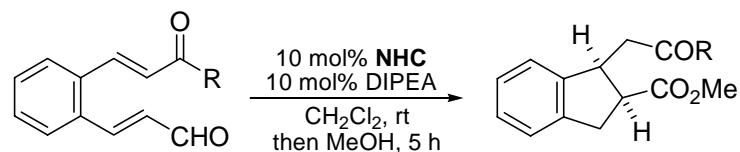
Eugene Kwan

**Intramolecular Michael Additions**

- NHC homoenolates can be  $\beta$ -quenched for use as nucleophiles in Michael additions  
*the idea*

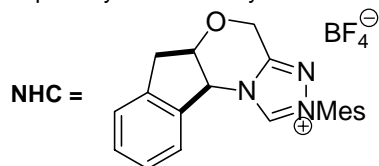


*an intramolecular example*



substrate	product	yield	ee
		59	99
		68	99
		66	99
		52	62

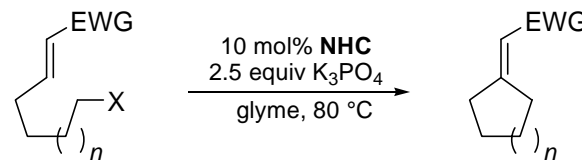
- primary or secondary amides are accessed if amines are used instead of MeOH



Scheidt *ACIE* 2007 46 3107

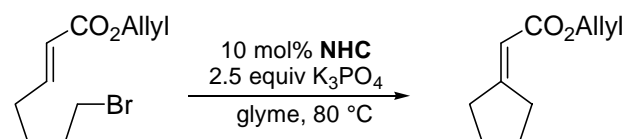
**$\alpha,\beta$ -Unsaturated Esters**

- what if the NHC attacked the  $\beta$ -carbon of a Michael acceptor?

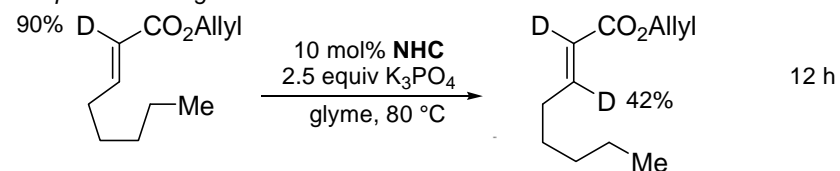


EWG = CO<sub>2</sub>R, CN, Weinreb amide, X = OTs, Cl, Br, n=1,2

*a representative example*

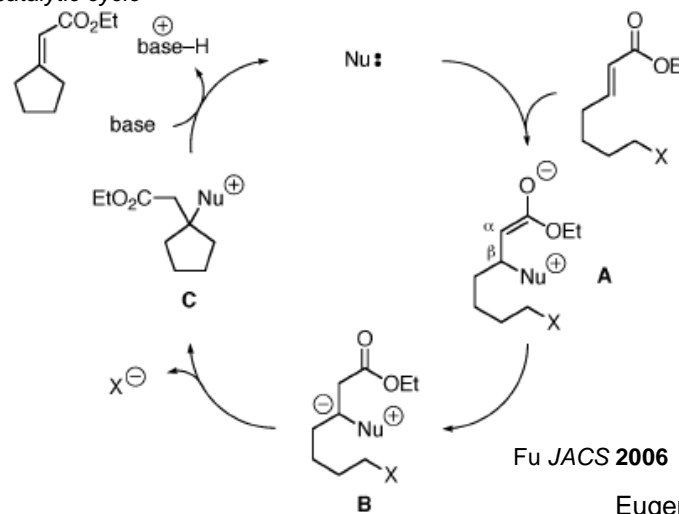


*isotopic scrambling*



- with PBU<sub>3</sub>: <3% D at  $\beta$ -carbon

*proposed catalytic cycle*



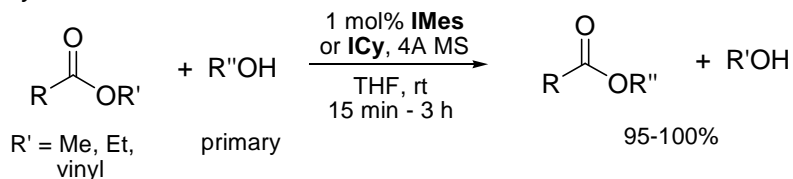
Fu *JACS* 2006 128 1472

Eugene Kwan

**Transesterification Catalysts**

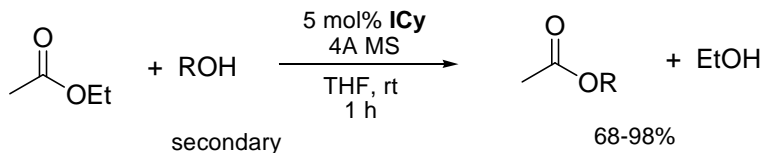
- NHCs allow catalytic transesterification under mild conditions

*primary alcohols*



- secondary alcohols are not viable nucleophiles  
 - simultaneous report: Waymouth/Hedrick **2002** 4 3587  
 - sieves may absorb liberated alcohols  
 Nolan *OL* **2002** 4 3583  
 Nolan *JOC* **2003** 68 2812

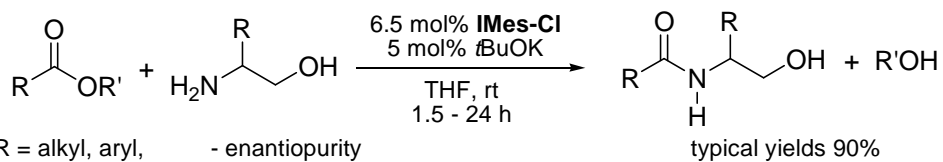
*secondary alcohols*



Nolan *JOC* **2004** 69 209

**Amidation of Esters**

*substrate scope*

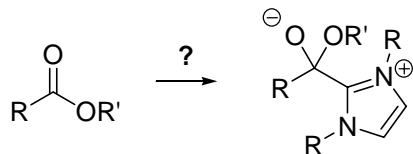


- numerous examples: see paper

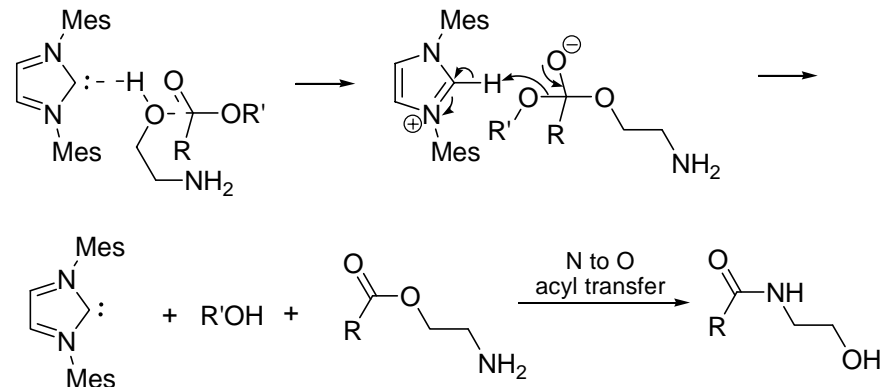
Movassaghi *OL* **2005** 7 2453

*mechanism of action*

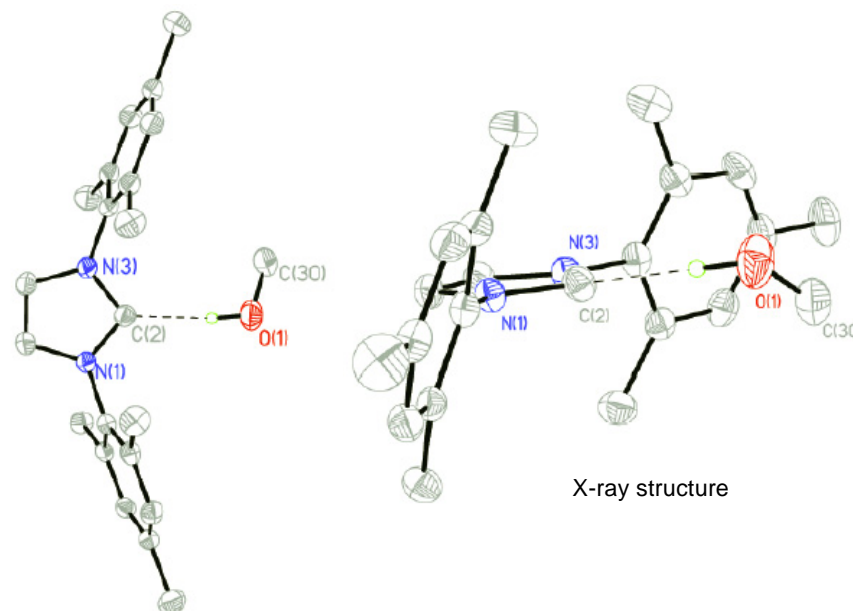
- previously proposed: activated C2 imidazolium intermediates



- another possibility: activation of alcohol nucleophile



- mixing an equimolar mixture of IMes and MeOH in C<sub>6</sub>D<sub>6</sub> immediately produces Imes-MeOH complex (visible by NMR)  
 - complex is isolable:



- reactIR and NMR show transient O-acylethanolamine intermediate

Movassaghi *OL* **2005** 7 2453

Eugene Kwan