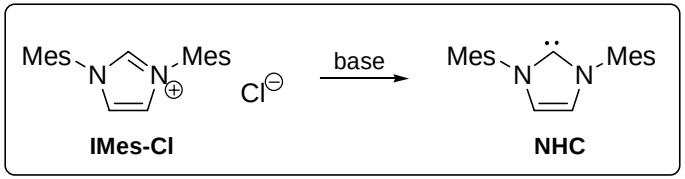
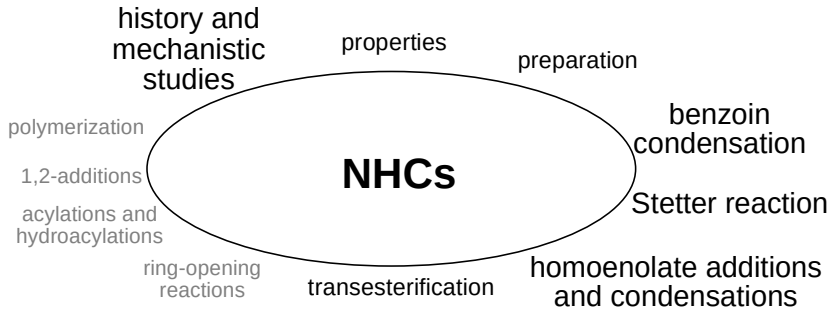
N-Heterocyclic Carbenes: Versatile Organocatalysts and Reagents

An Evans Group Afternoon Seminar
December 14, 2007



Scope of Seminar



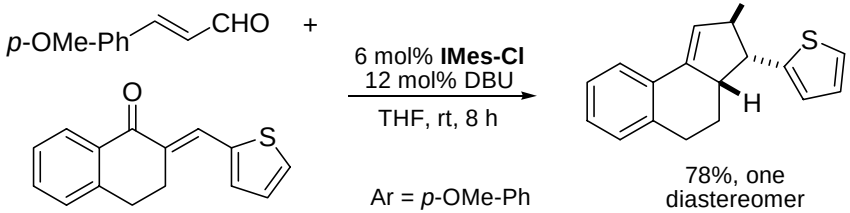
Outline

1. Benzoins 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." Ardugengo 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_a 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_a 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)**

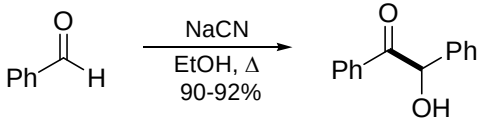
Reactions

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)**

Eugene Kwan

The Benzoin Condensation

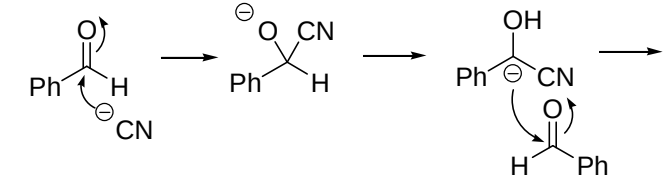
the original reaction

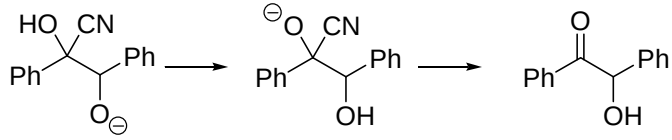


- incomplete condensation observed for aliphatic aldehydes
- electron deficient benzaldehydes are subject to side reactions

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

Lapworth Mechanism



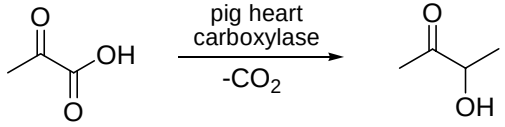


- intermediate cyanohydrins were isolated as crystalline K salts

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

Thiamine-Catalyzed Reactions

known in 1954:

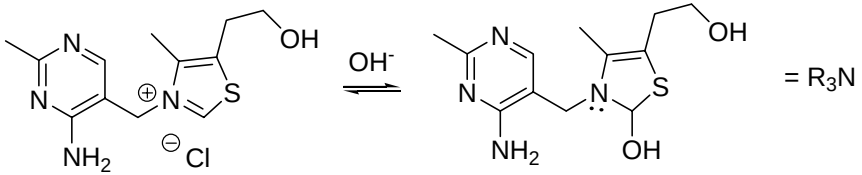


pyruvic acid — acetoin

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

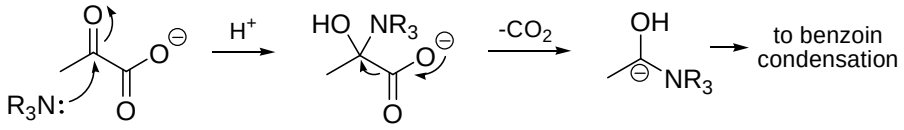
- addition of doubly ^{14}C labelled acetaldehyde gives doubly labelled acetoin

originally proposed mechanism:



thiamine (vitamin B_1) — "pseudobase"

Mizuhara *JACS* **1954** *76* 571

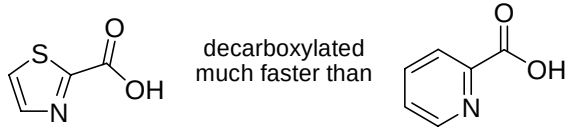


Breslow Mechanism

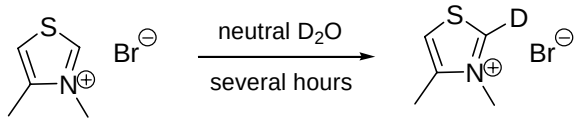
"[Mizuhara and coworkers] proposed an unusual and rather unlikely mechanism...we are thus forced to look elsewhere in the molecule for a site of potential reactivity..."

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

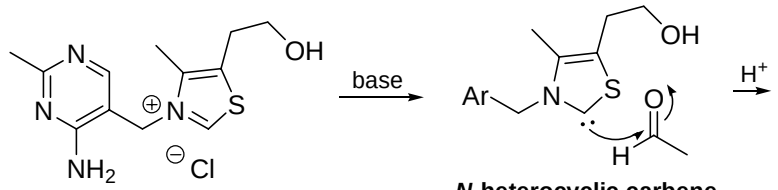
- carbon acidity of thiazolium compounds was known:



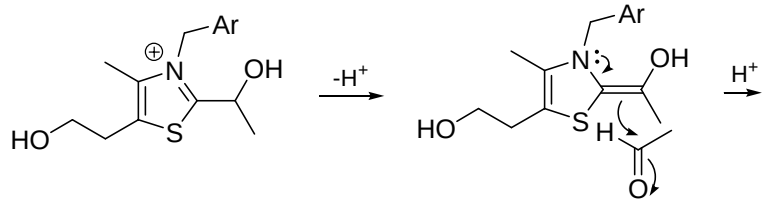
Schenkel *Helv. Chim. Acta.* **1948**, *31*, 924

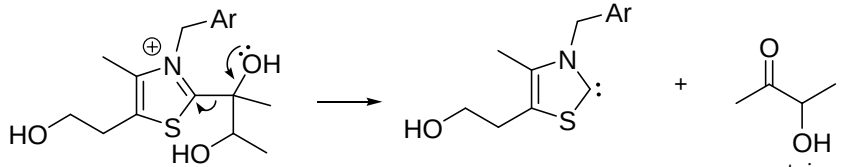


- could this be analogous to the Lapworth mechanism?



***N*-heterocyclic carbene**



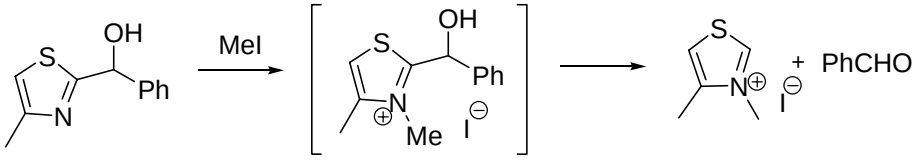


Eugene Kwan

N-Heterocyclic Carbenes: The Benzoin Condensation

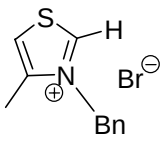
evidence for mechanism:

- independent generation of proposed intermediate gives product:

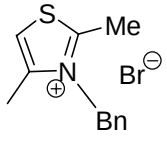


unstable

- various analogs of thiamine have varying efficacy:

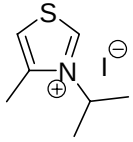


competent



ineffective

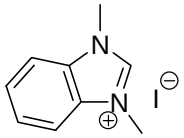
(cannot form NHC)



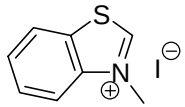
ineffective

(steric hindrance)

- an illuminating comparison:



competent

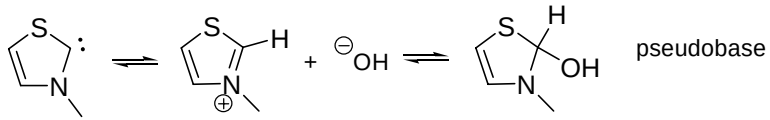


ineffective

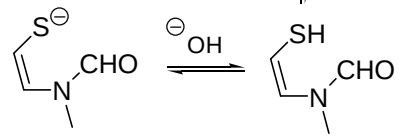
- both exchange with D_2O
- why is the thiazolium inactive?

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

- consider parent thiazolium first:



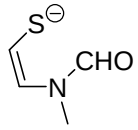
pseudobase



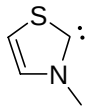
catalytically inactive
and non-aromatic

- prediction: at high pH, benzoin condensation should be supressed
- this has been found: Mizuhara *Proc. Japan Acad.* **1951** *27* 302

- another prediction:

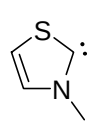
Compounds in which 

is especially stable compared to

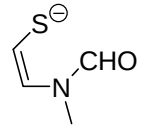


will be ineffective catalysts.

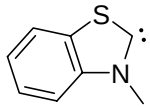
- aromaticity:



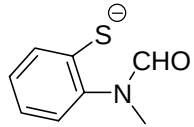
aromatic



not aromatic



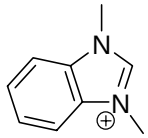
aromatic



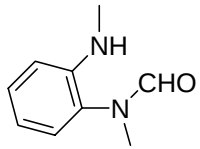
still aromatic

- the disruption of aromaticity is less significant here

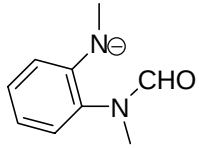
- comparison with imidazoliums:



could ring-open to



but

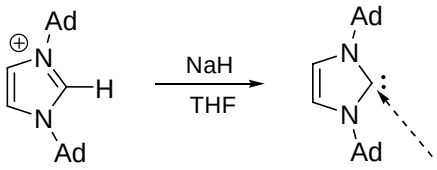


will not be formed.

Eugene Kwan

N-Heterocyclic Carbenes: Wanzlick Equilibrium

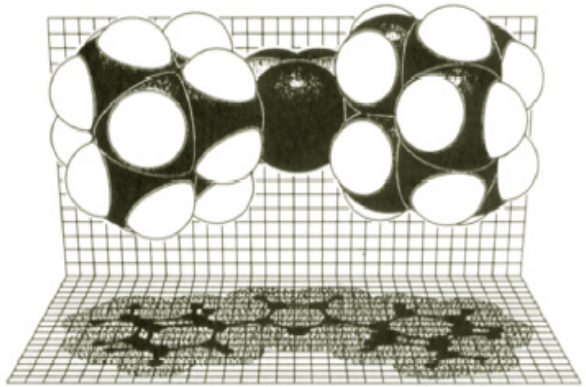
Isolation of a Stable Carbene



- stable if not exposed to moisture or O_2
- crystalline (mp=240-241 °C)

the first isolated stable carbene

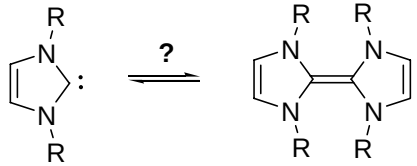
Arduengo *JACS* **1991** *113* 361



X-ray structure

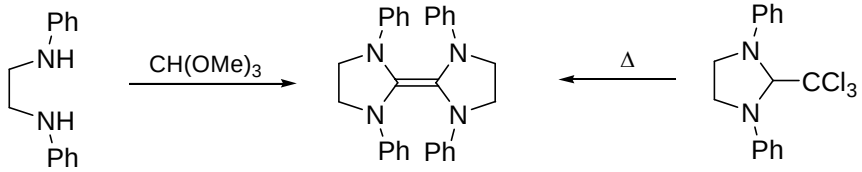
- a wide variety of stable carbenes have now been isolated (see Hermann *ACIE* **2000** 39 4036)

Carbene Dimerization



- the hypothesized mechanism of the formation of tetraaminoethylenes

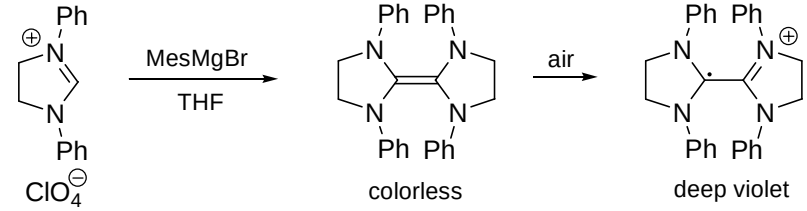
proposed by Wanzlick



- based on molecular weight measurements

Wanzlick *ACIE* **1960** *72* 494

no ordinary olefins

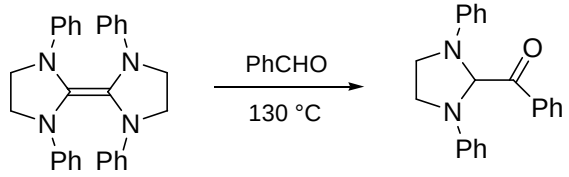


colorless — deep violet

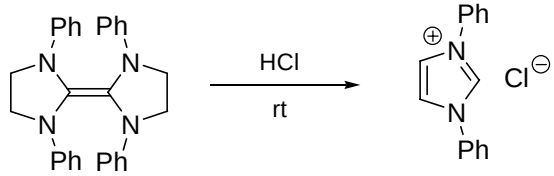
- incredibly electron rich, these dimers oxidize very easily

Lemal *JACS* **1962** *84* 1761

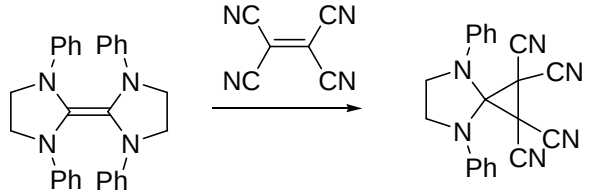
reactivity



90%



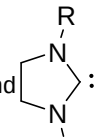
100%

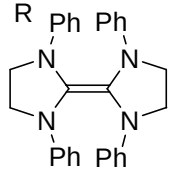


70%

Wanzlick *ACIE* **1962** *1* 75

what is the reactive species?

Wanzlick Proposal: There is an **equilibrium**, and  is the active species.

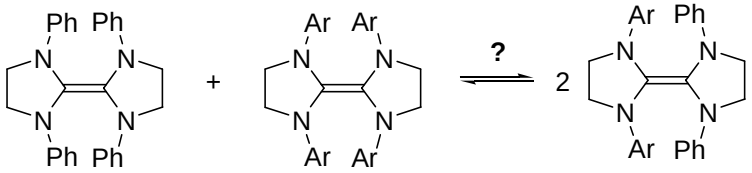
Lemal Proposal: There is **no equilibrium**, and  is the active species.

Lemal *JACS* **1964** *86* 2518

Eugene Kwan

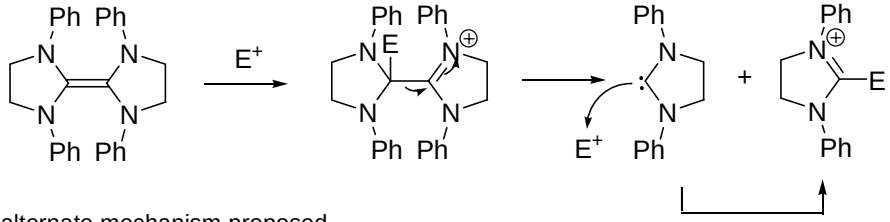
N-Heterocyclic Carbenes: Wanzlick Equilibrium

Crossover Experiements



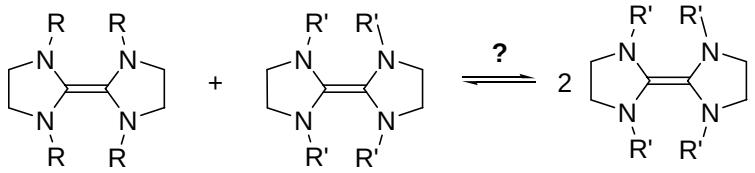
- 2 h reflux in xylene: **no crossover product observed** Lemal *JACS* **1964** *86* 2518

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



Denk *TL* **1999** *40* 2057

- statistical mixture (1:2:1) obtained

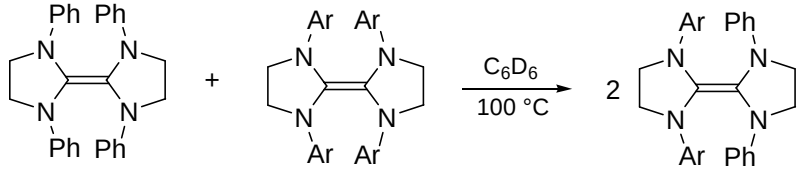
Do these findings prove the Wanzlick Equilibrium exists? No.

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

alternate possiblity: cycloaddition-cycloreversion

alternate possibility: contamination

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



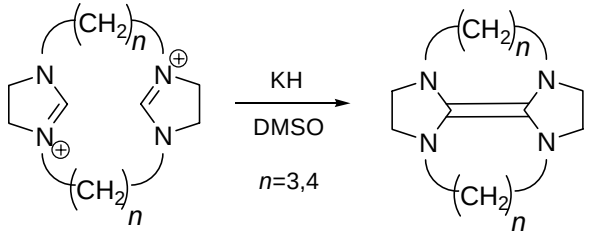
Lemal *TL* **2000** *41* 599

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 ΔG > 35 kcal/mol

- potential explanation: in the original 1964 work, substrates were prepared using tripheynlcarbinol 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

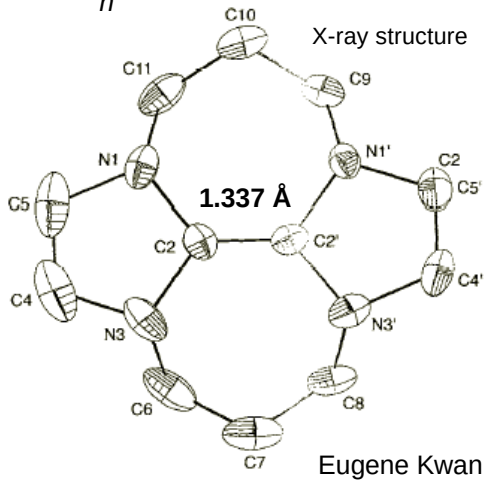


Chen *ACIEE* **1996** *35* 1011

- *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)

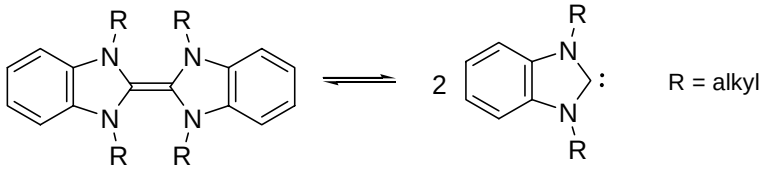
X-ray structure



Eugene Kwan

N-Heterocyclic Carbenes: The Benzoin Condensation Revisited

less aromatic carbenes



R = alkyl

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

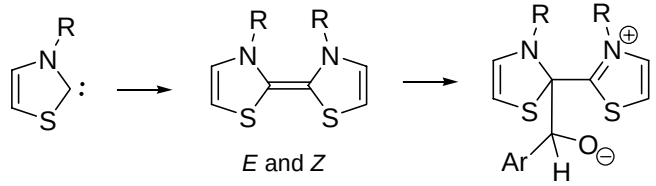
- aromatic carbenes do not dimerize as easily — Lemal *JACS* **1999** *121* 10626; Hahn *ACIE* **2000** *112* 541; Summary: Herrmann *ACIE* **2000** *39* 4036

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.

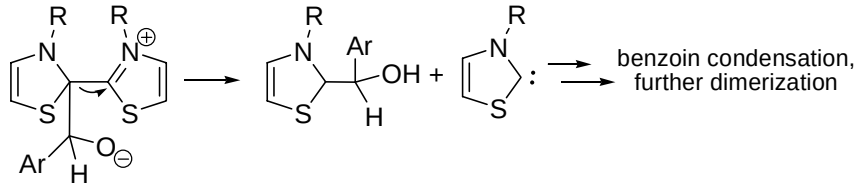
The Mechanism of Benzoin Condensation: A Controversy

a dimeric mechanism?



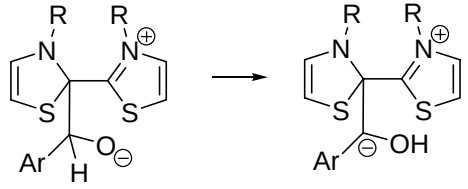
E and *Z*

option 1



benzoin condensation, further dimerization

option 2

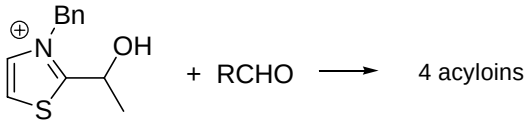


- is this anion significantly stabilized?

Castells *JOC* **1988** *53* 4433

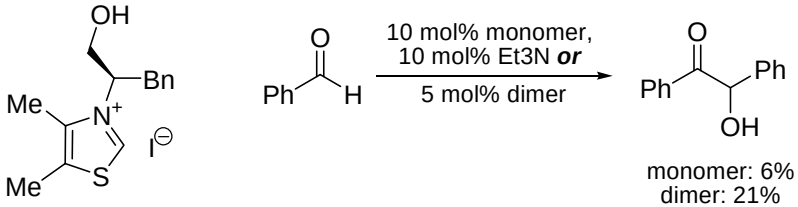
evidence for dimer involvement

(1) crossover is observed



- unclear how this implicates dimer

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

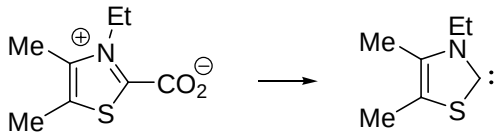


monomer: 6%
dimer: 21%

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

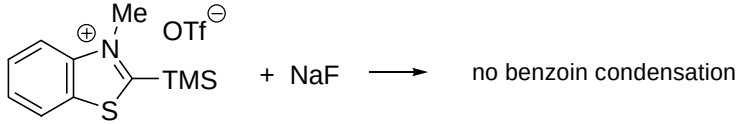
Castells *J Heterocyclic Chem* **1986** *23* 715

(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

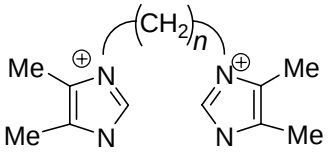
(4) behavior when NHC is generated via desilylation



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

Eugene Kwan

(5) bridged thiazolium salts



2 $Br^{\ominus}$

yields in the benzoin condensation

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

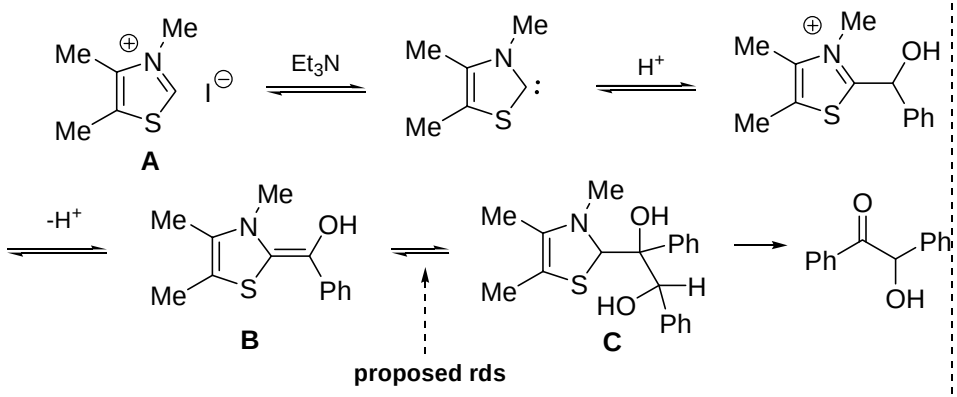
"this very clear dependency between yields and length of the polymethylene bridge supports our views on the relevant protagonism of bis(thiazolin-2-ylidenes)s as the catalytic species..."

- 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

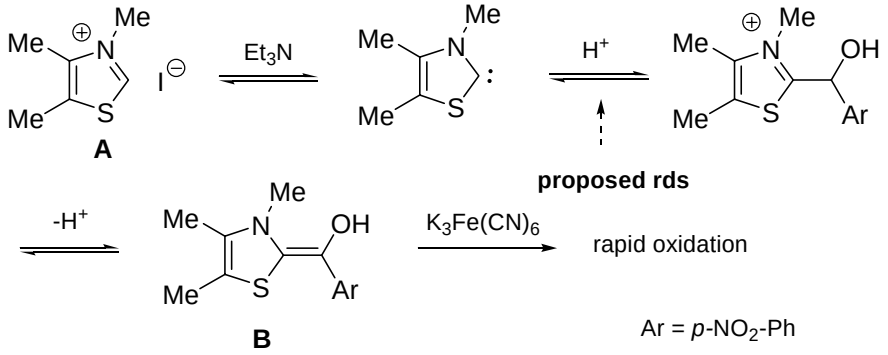
rate law: order in thiazolium ion

- 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

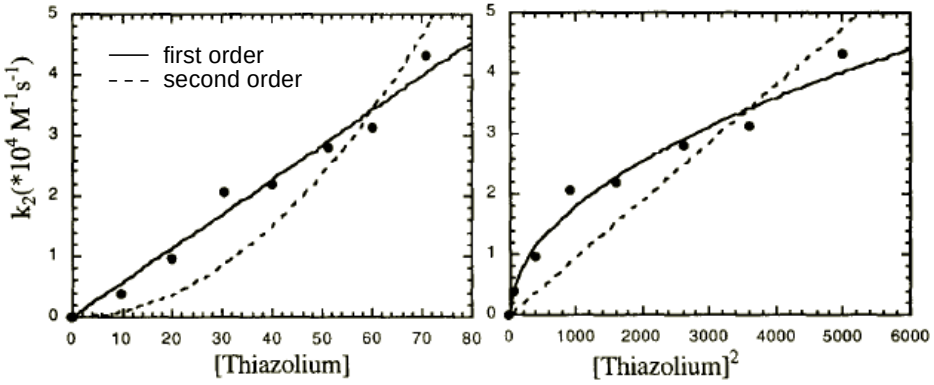
further confusion

- 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

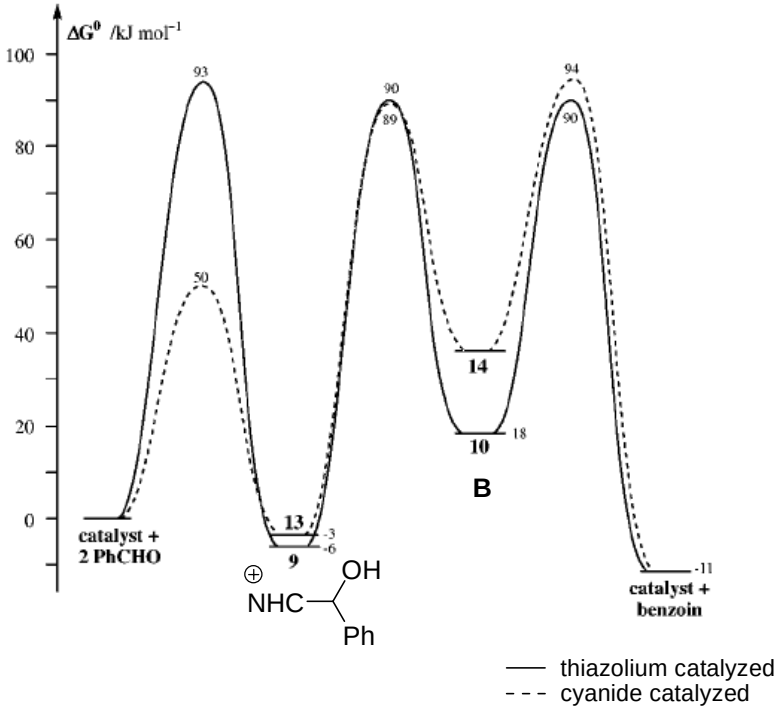


Eugene Kwan

N-Heterocyclic Carbenes: The Benzoin Condensation

modern data

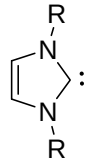
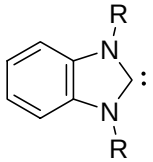
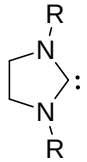
- primary kinetic isotope effect when PhCDO used: 3.4
- inverse solvent isotope effect when CD_3OD used: 5.9
- all rate constants have now been determined, confirming Breslow's position
- under many conditions, there is no single rate-determining step



Further Reading

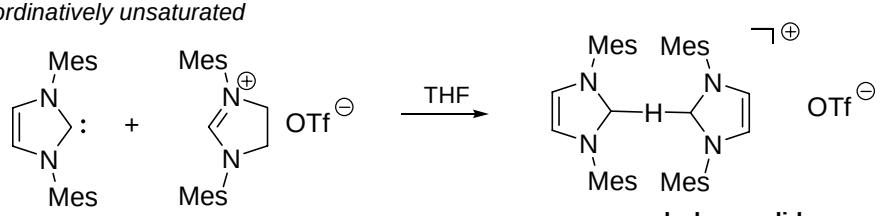
"Kinetics of the Thiazolium Ion-Catalyzed Benzoin Condensation." White, M.J.; Leeper, F.J. *J. Org. Chem.* **2001**, *66*, 5124-5131.

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	- nucleophiles - complex rapidly with most metals - moisture sensitive - do not react with triplet oxygen		

coordinatively unsaturated



colorless solid
(mp = 200 °C)

X-ray structure

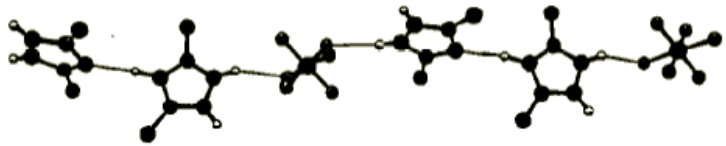
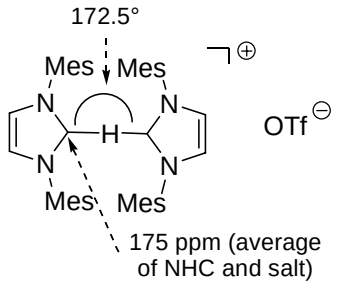


Figure 2. KANVAS[11] drawing of the extended structure of bis-(carbene)−proton complex in **3a**. Mesityl groups (except ipso-carbons) have been omitted for clarity.

Eugene Kwan

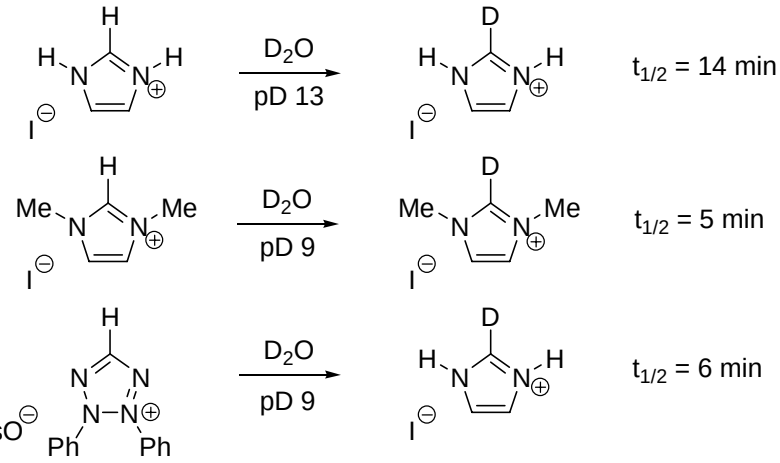


- bridging C-H bond length = 1.16 Å
- N-C-N bond angle = 107.6° (typical NHC: 102°)
- counterions form hydrogen-bonded bridges between imidazole C-H bonds
- a bridging iodine complex is also known

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

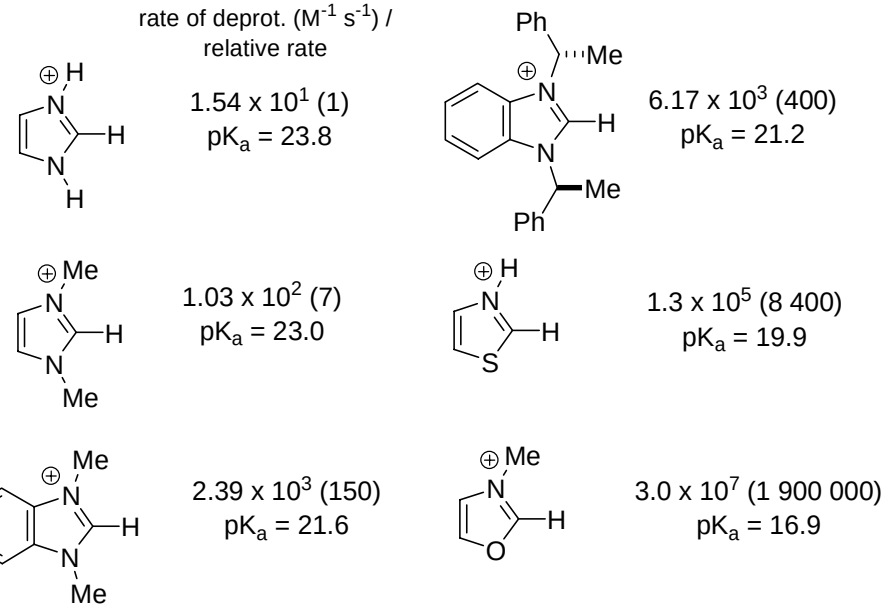
Olofson *JACS* **1964** *86* 1865

acidity in water: methods

- rate of H/D exchange measured in buffered D_2O with ^1H NMR
- this allows exchange at acidic CH to be distinguished from exchange at NH
- rate in H_2O extrapolated from known kinetic isotope effect k_{DO}/k_{HO} = 2.4 (Jencks *JACS* **1989** *111* 683)
- reverse rate, protonation of carbene, extrapolated from flash photolysis: $k_{HOH} = 10^{11}$ s^{-1}
- $pK_a = pK_w + \log(k_{HOH}/k_{HO})$, where $K_w = 10^{-14}$ and k_{HO} is the rate of deprotonation

Richard *JACS* **2004** *126* 4366

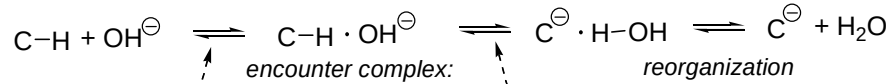
acidity in water: results



- 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



encounter complex: aligned for deprotonation

reorganization

work is done to bring reactants together

rate depends on "intrinsic Marcus barrier" energy:

- small primary KIEs are observed for imidazolium ion deprotonation

protonation of:	barrier (kcal/mol):
isobutylene	12
aryl ring	10
ethyl vinyl ether	6
carbonyl compounds	6
phenol, acetic acid	2

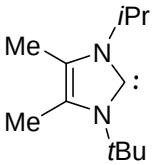
estimated barrier for azolium ions: 5 kcal/mol

Eisen *ACIEE* **1964** *3* 1 Kresge *Acc Chem Res* **1975** *8* 354

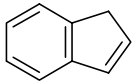
Eugene Kwan

Acid-Base Behavior in Organic Solvents

DMSO

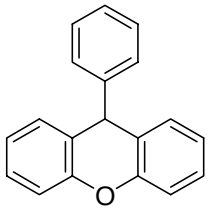


completely deprotonates



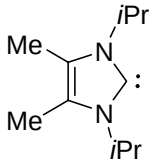
indene
pK_a = 20.1

and

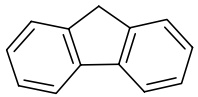


9-phenylxanthene
pK_a = 27.7

.



partially deprotonates



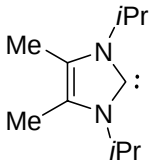
from which an apparent **pK_a of 24 can be derived** (corrected only for the number of protons).

- one of the strongest known neutral bases

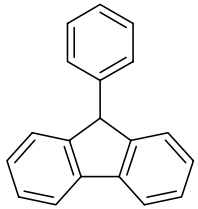
- carbene preparation (1. K/THF 2. filtration 3. evaporation)
- deprotonation monitored by NMR

THF

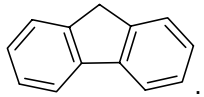
- a less polar solvent which disfavors the formation of ions



almost completely deprotonates



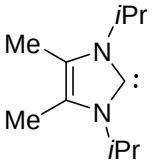
but fails to deprotonate



.

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

Basicity vs. Nucleophilicity



\+

DMSO →

elimination

\+

substitution

highly nucleophilic 20% 80%

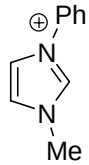
- cf. elimination/substitution ratios for DBN (91%) and DBU (21%) (Fritz *Chem. Ber.* **1994** *127* 2435)

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

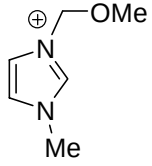
Compiled pK_a Values (DMSO)

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

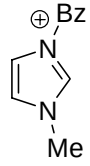
imidazolium core



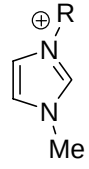
19.7



20.5

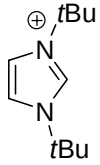


21.6

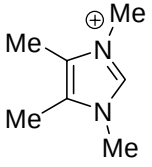


22.0-22.1

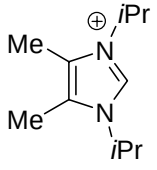
R = Me, Et, *n*Bu, *n*Oct



23.2



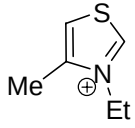
23.4



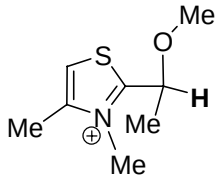
24

thiazolium and related cores

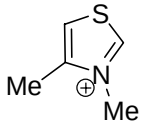
~9*



~13

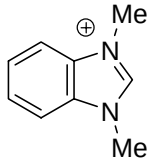


14.1

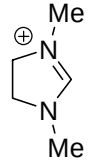


16.5

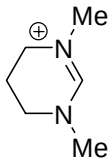
other



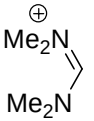
18.6



22.3**



27.1**



27.9**

references

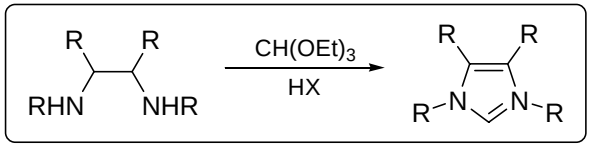
1. Jencks *JACS* **1989** *11* 683
2. Cheung *JOC* **2007** *72* 7790
3. Alder *JCS Chem Commun* **1995** 1267
4. Bordwell *JACS* **1991** *113* 985-990 + refs. therein
5. Yates *JACS* **2004** *126* 8717

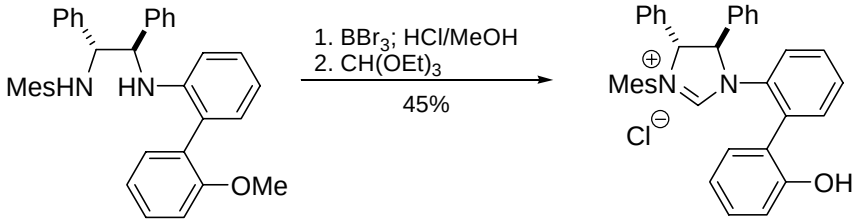
* complicated by dimerization
** estimated by computations (ref. 5)

Eugene Kwan

Imidazolium Salts

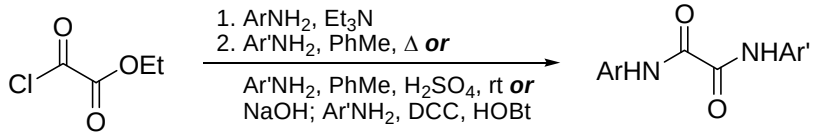
diamine precursor



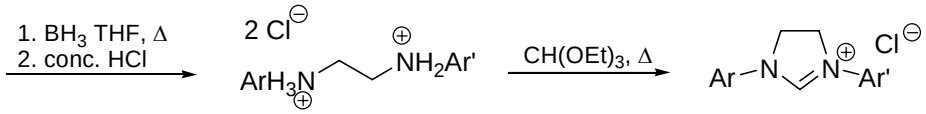


above: Hoveyda *JACS* **2005** *127* 6877
another example: Helmchen *Synlett* **2004** 1789

diamine precursor: variation

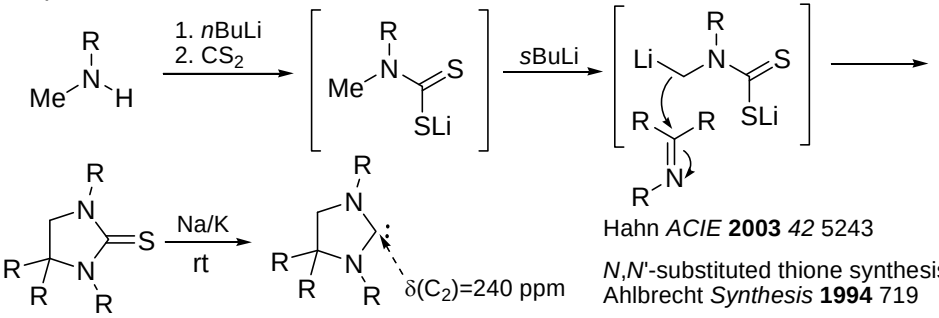


ethyl chlorooxoacetate



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

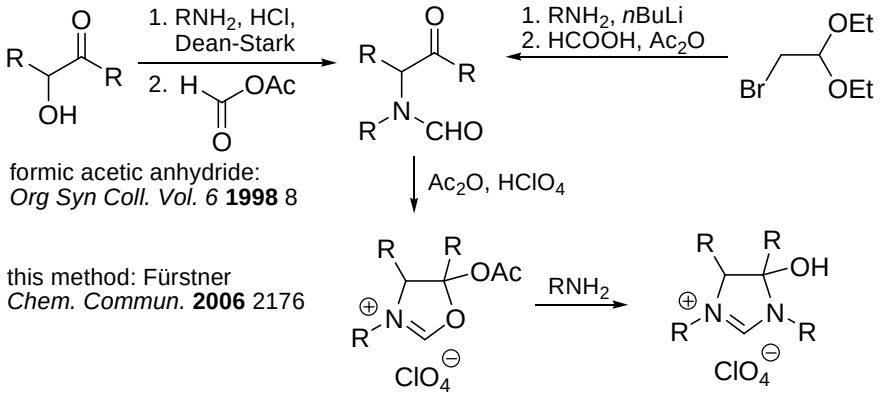
sequential lithiations



Hahn *ACIE* **2003** *42* 5243

N,*N*'-substituted thione synthesis:
Ahlbrecht *Synthesis* **1994** 719

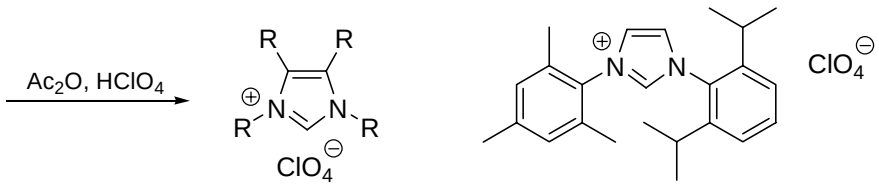
via oxazolium intermediate



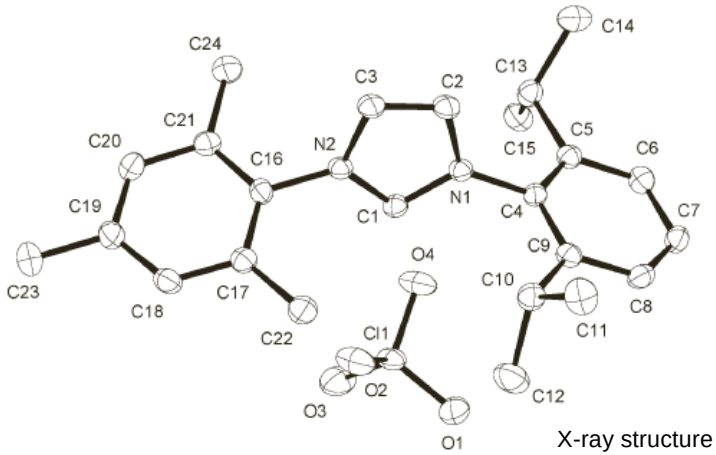
formic acetic anhydride:
Org Syn Coll. Vol. 6 **1998** 8

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

- does not aromatize



- sterically hindered amines are tolerated

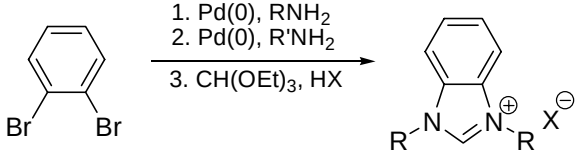


X-ray structure

Eugene Kwan

N-Heterocyclic Carbenes: Preparation

Benzoimidazolium Salts



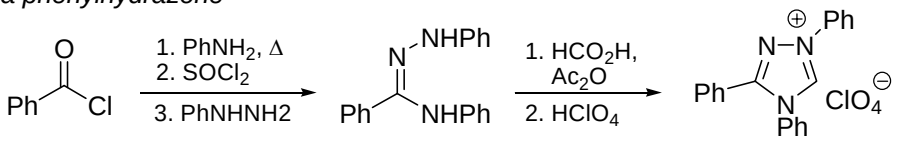
Diver *OL* **2001** *3* 2673

Buchwald-Hartwig Amination:
Pd_2dba_3, BINAP, NaO*t*Bu
Buchwald *JACS* **1996** *118* 7215
Hartwig *JACS* **1996** *118* 7217

- optimization was required to supress epimerization of chiral primary amines

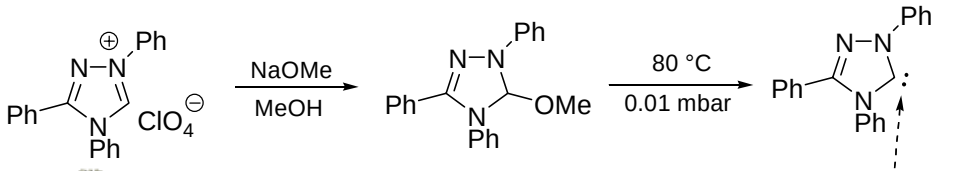
Triazolium Salts

via phenylhydrazone

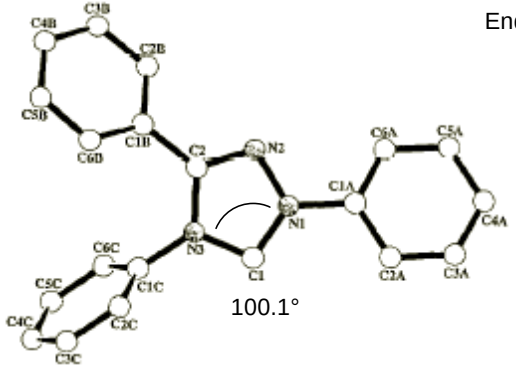


Enders *Synthesis* **2003** 1292

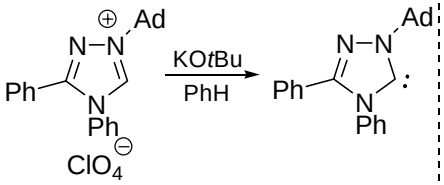
release of carbene



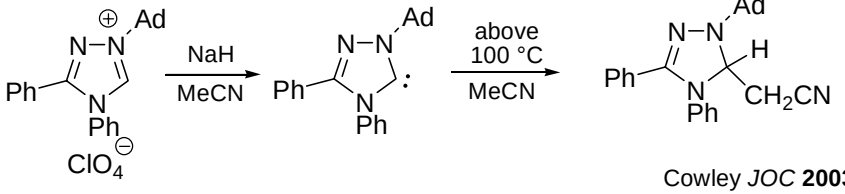
Enders ACIEE **1995** *34* 1021



- base is also effective:

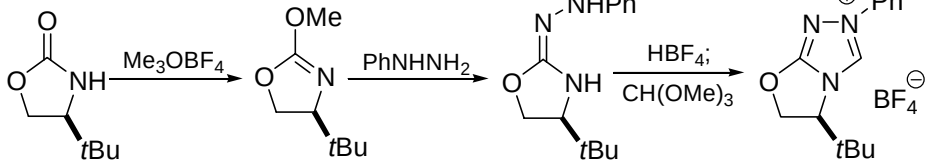


- reaction with acetonitrile:



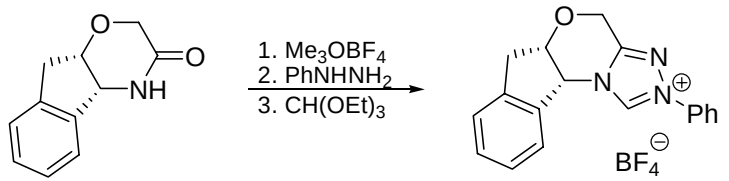
Cowley *JOC* **2003** *68* 5762

via oxazolidinone



Enders *ACIE* **2002** *41* 1743

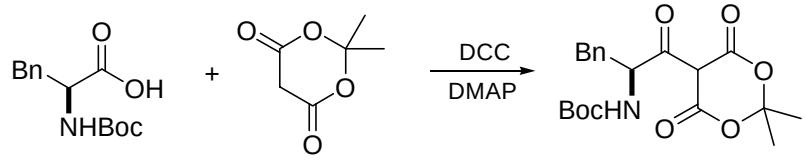
- amides are also useful:



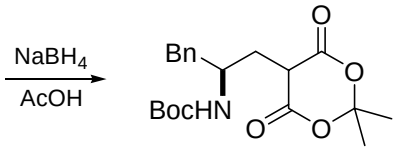
aminoindanol-derived

Leeper *JCS PT1* **1998** 1891
Rovis *JOC* **2005** *70* 5725

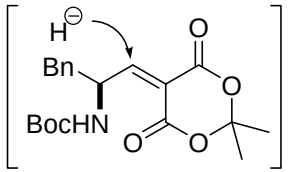
- from amino acids:



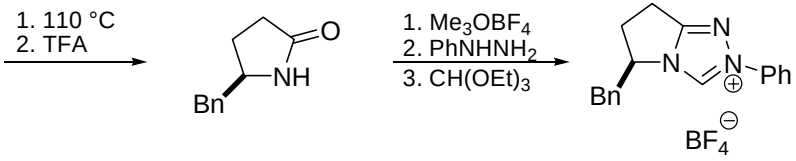
phenylalanine Meldrum's acid



presumably via:



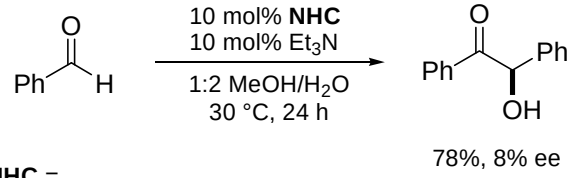
Smreina *Tet* **1997** *53* 12867



Eugene Kwan

N-Heterocyclic Carbenes: Asymmetric Benzoin Condensation

a first attempt



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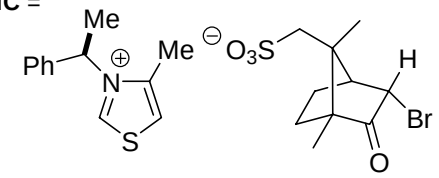
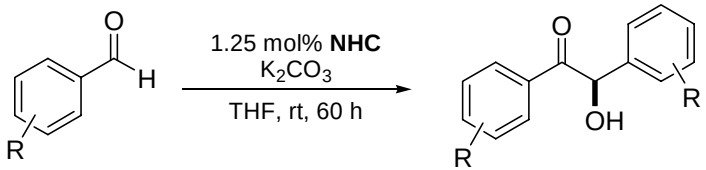
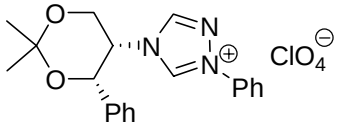


Sheehan *JACS* **1974** *39* 1196

an improved system

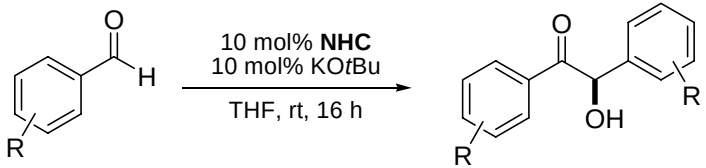


NHC =



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

an efficient system



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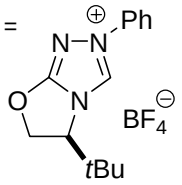
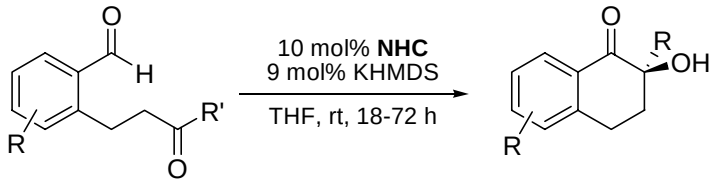


Enders *ACIE* **2002** *41* 1743

crossed-benzoin condensations



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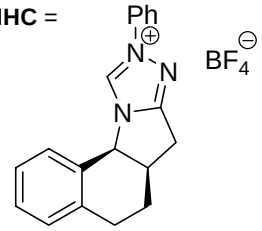
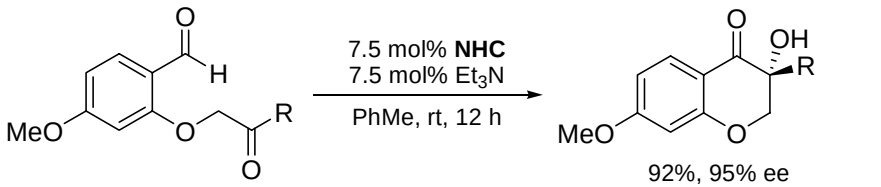
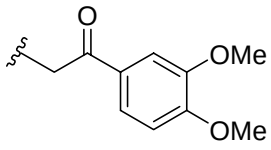


Enders *ACIE* **2006** *45* 1463
Enders *Synlett* **2006** *15* 2431



R =



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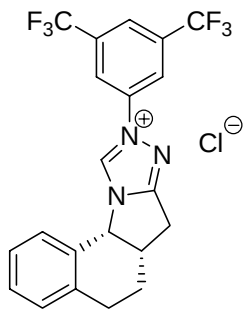
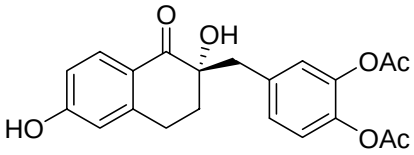


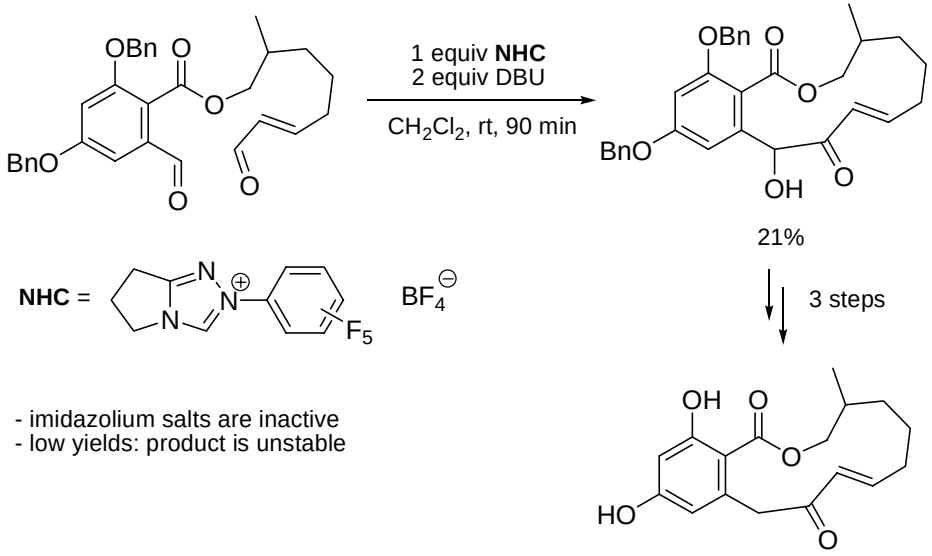


Suzuki *ACIE* **2006** *45* 3492
Suzuki *OL* **2007** *9* 2713

Eugene Kwan

N-Heterocyclic Carbenes: Benzoin Methodology

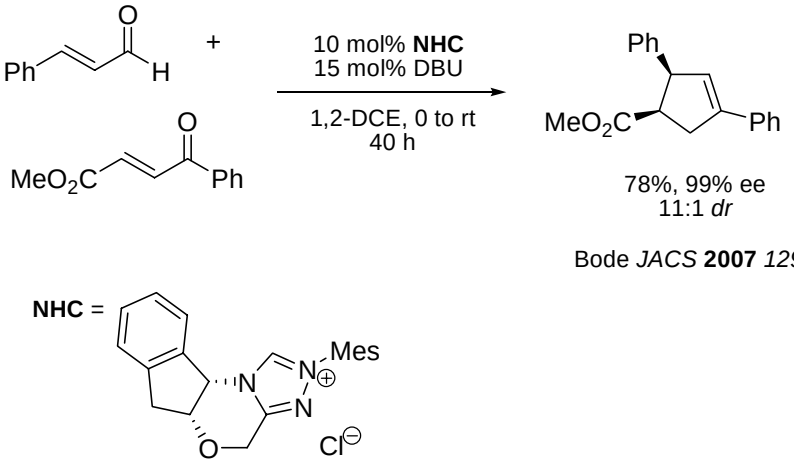
acyloin macrocyclization



- imidazolium salts are inactive
- low yields: product is unstable

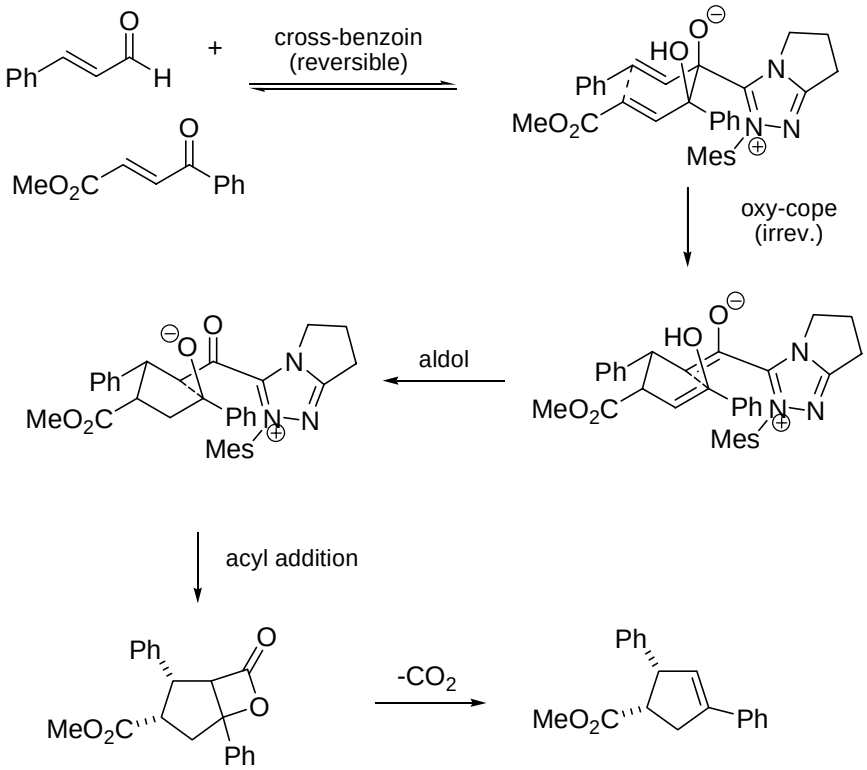
Miller *JOC* **2007** *72* 5260

tandem benzoin-oxy-Cope-aldol sequence



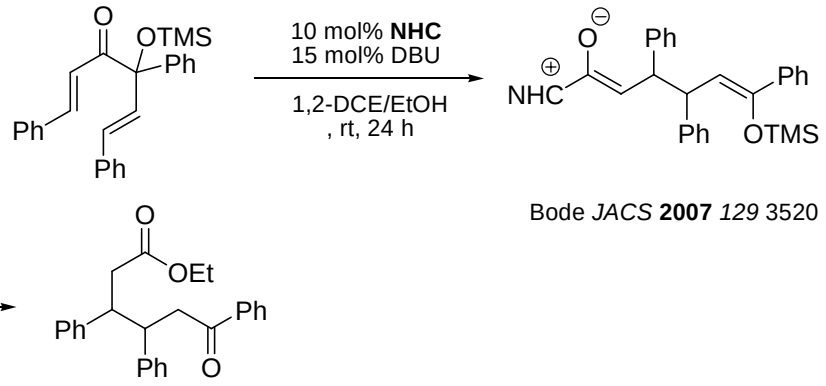
Bode *JACS* **2007** *129* 3520

- proposed mechanism:



- proposed mechanism:

- evidence for oxy-Cope:

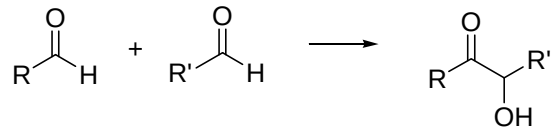


Bode *JACS* **2007** *129* 3520

Eugene Kwan

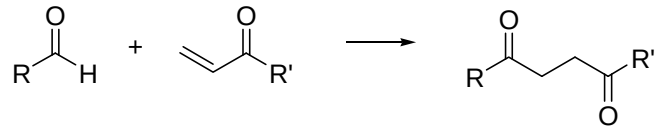
N-Heterocyclic Carbenes: The Stetter Reaction

benzoin



acyl anion aldehyde α-hydroxy ketones

Stetter

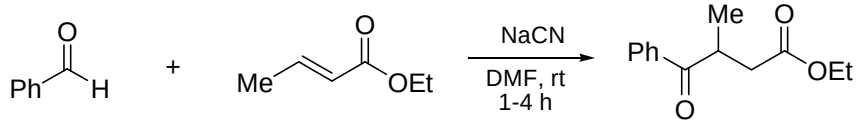


acyl anion Michael acceptor 1,4-dicarbonyl compounds

- 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



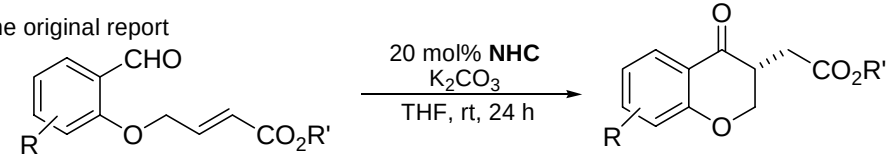
33%

- thiazolium salts were soon found to be useful as well

Stetter *ACIE* **1973** *12* 81

asymmetric Stetter reactions

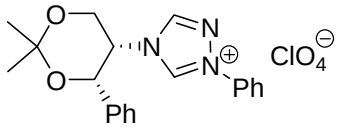
the original report



44-73%
56-74% ee

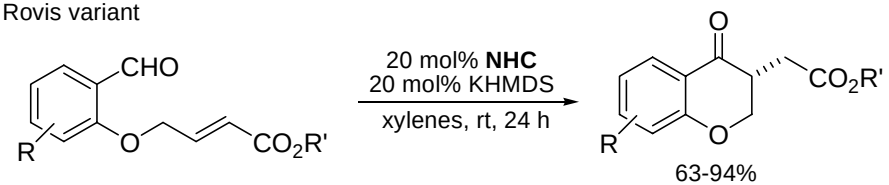
- R = H, Cl, OMe; R' = Me, Et
- key advance: triazolium salts are more active

NHC =



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

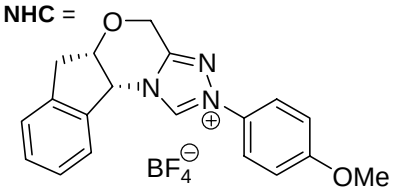
Rovis variant



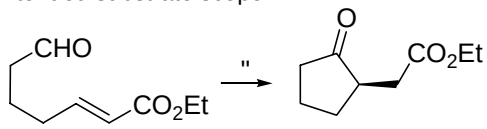
63-94%
82-97% ee

- significantly improved yields and ee's
- *Z* enoates do not react
- α,β-unsaturated aldehydes, carboxamides, and nitro compounds are inactive
- α,β-unsaturated ketones react more rapidly than corresponding esters

NHC =



- extended substrate scope:

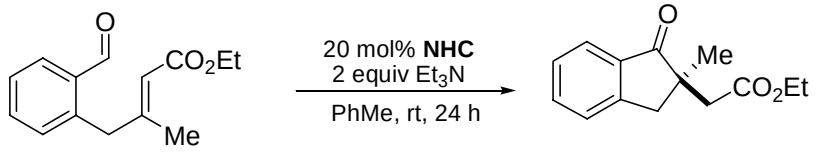


81%, 95% ee

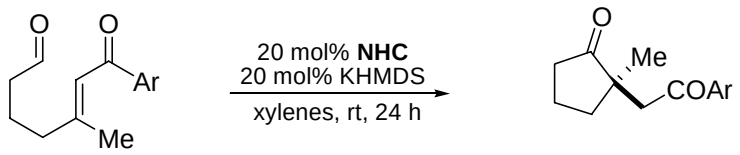
- six-membered variant: no reaction
- an unsolved problem: high catalyst loadings

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

formation of quaternary stereocenters

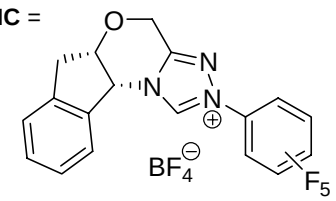


95%, 99% ee



90%, 84% ee

NHC =



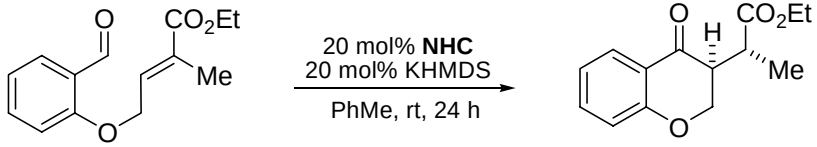
Rovis *JACS* **2004** *126* 8876

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

Eugene Kwan

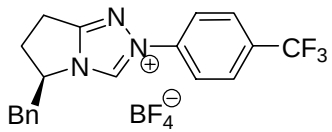
N-Heterocyclic Carbenes: The Stetter Reaction

diastereo- and enantioselective variant

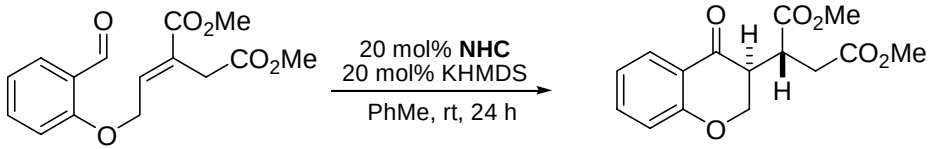


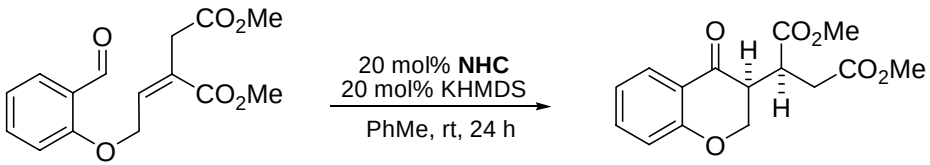
Rovis *JACS* **2005** *127* 6284

NHC =

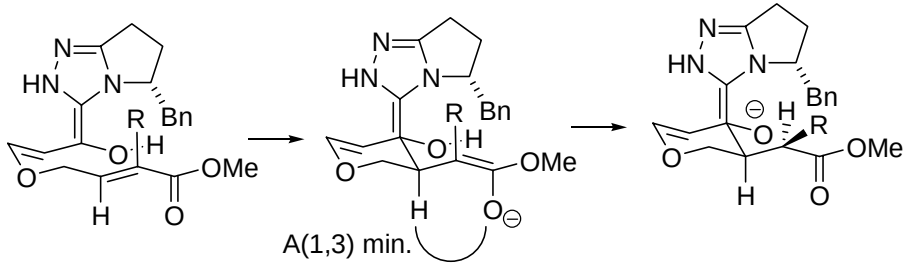


- mechanism of reaction?



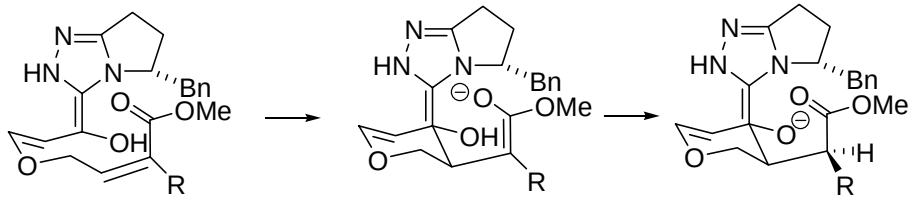


- proposed model for selectivity

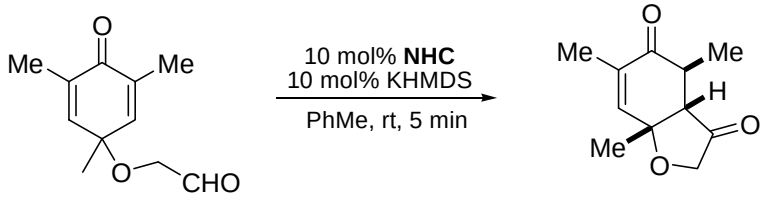


- evidently, intramolecular protonation is faster than intermolecular protonation

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



enantioselective desymmetrization



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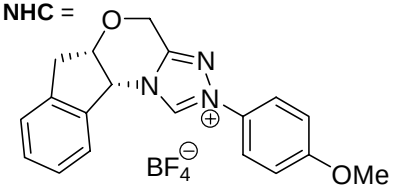
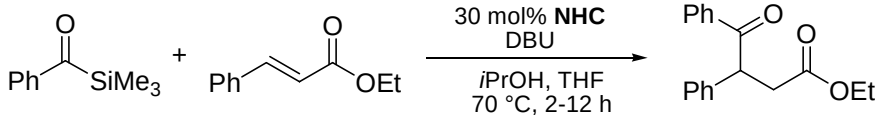


Rovis *JACS* **2006** *128* 2552
Rovis *Org Proc R&D* ***2007*** *11* 598

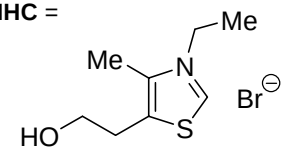
sila-Stetter reactions

- acylsilanes are competent nucleophiles



Scheidt *JACS* **2004** *126* 2314

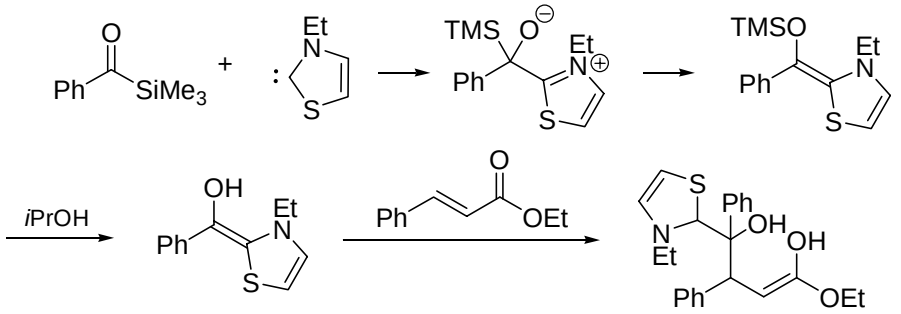
NHC =



- an analogue of thiamine diphosphate

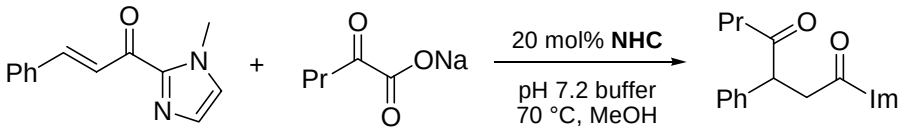
Eugene Kwan

- Brook rearrangement:



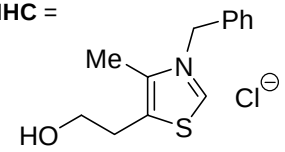
Scheidt *JOC* **2006** *71* 5715

acylimidazoles



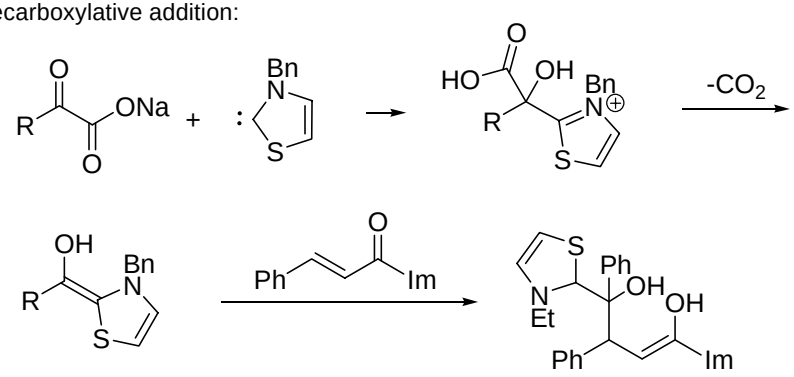
92%

NHC =



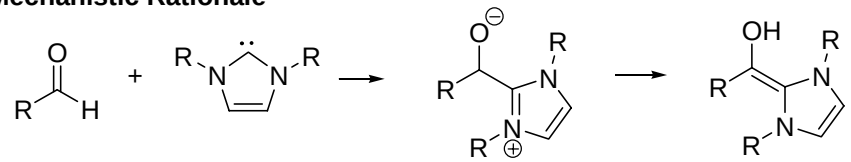
Scheidt *JACS* **2005** *127* 14675

- decarboxylative addition:

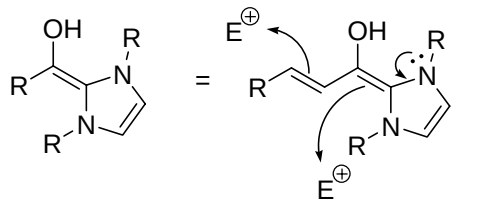


N-Heterocyclic Carbenes: Homoenolates

Mechanistic Rationale

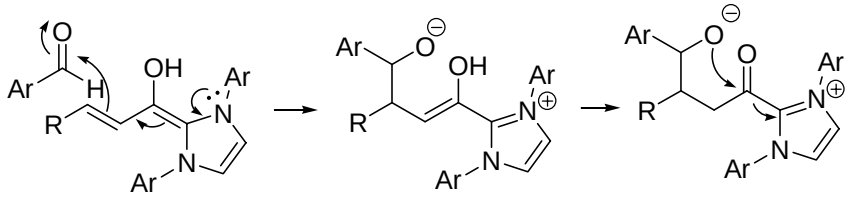


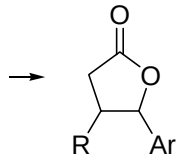
if aldehyde is α,β-unsaturated:



- potential for:
  (a) benzoin/Stetter (a^1 to d^1)
  (b) homoenolate (a^1 to d^3)
  reactivity patterns
- selectivity for dimerization vs. cross-addition?

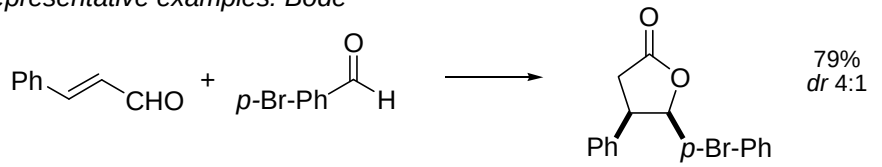
Intial Reports: γ-Butyrolactone Formation



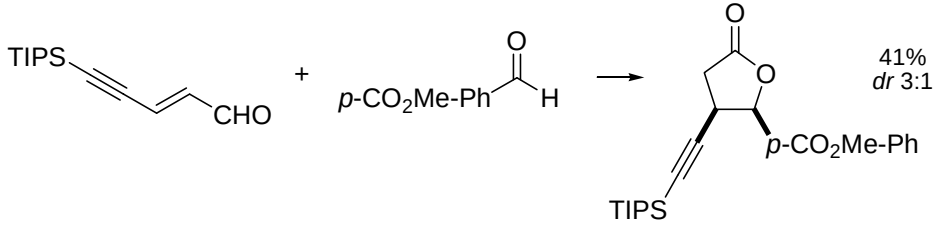


- moderate *cis* selectivity is observed
- simultaneously reported by Bode and Glorius groups
- steric bulk of NHC catalyst is important

representative examples: Bode



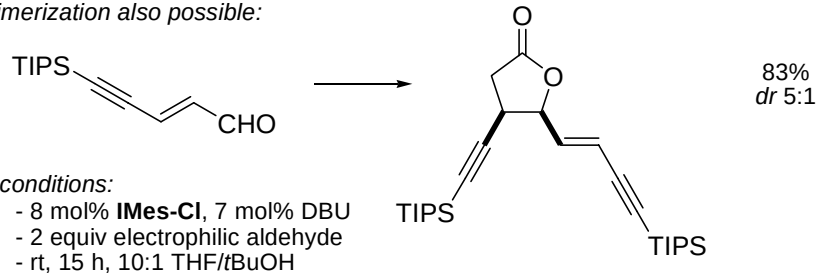
79%
dr 4:1



41%
dr 3:1

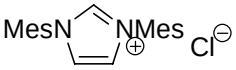
Bode *JACS* **2004** *126* 14370

- dimerization also possible:



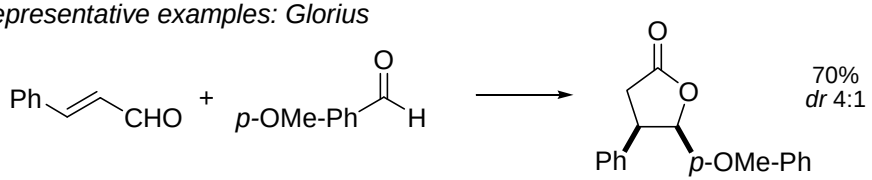
83%
dr 5:1

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

IMes-Cl = 

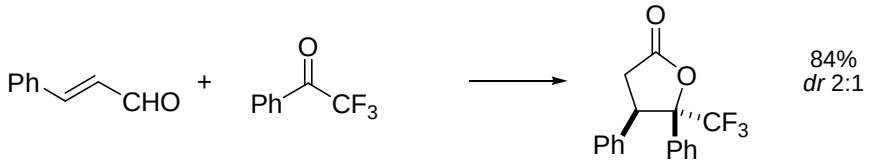
- aliphatic aldehydes are not effective
- slow addition of enal increases yields
- performing the reaction with *cis*-*p*-anisaldehyde still leads to the *cis* adduct
- if reaction is performed with *t*BuOD, D is incorporated exclusively at the α-position (no quenching of homoenolate by solvent)

representative examples: Glorius



70%
dr 4:1

- ketones are competent electrophiles:



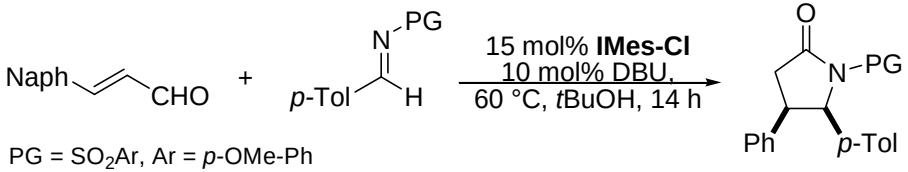
84%
dr 2:1

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

γ-lactams from N-sulfonylimines



PG = SO_2Ar, Ar = *p*-OMe-Ph

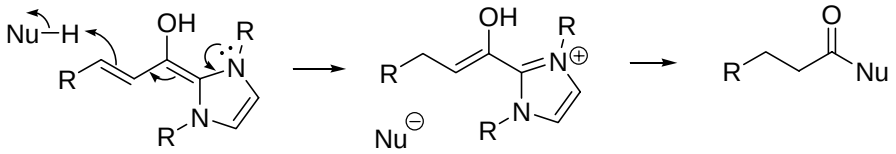
- choice of PG is important

Bode *OL* **2005** *7* 3131

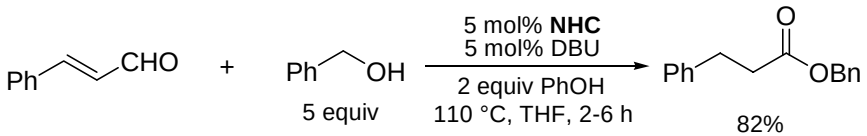
70%
dr 4:1

Eugene Kwan

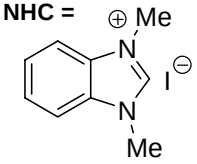
Redox Esterification



- a representative example:



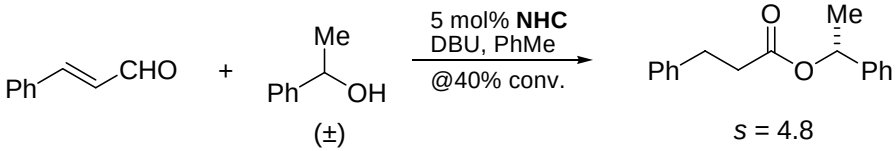
NHC =



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

Scheidt *OL* **2005** *7* 905

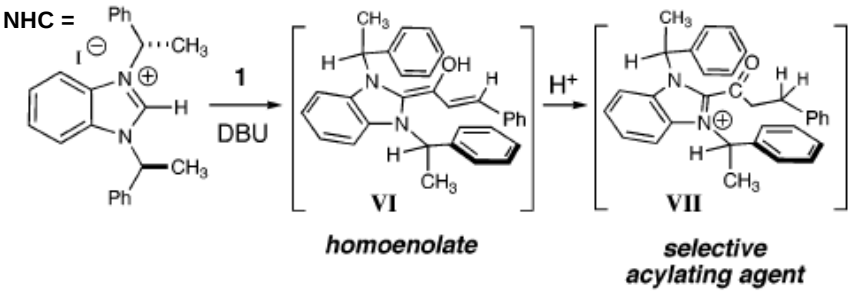
- kinetic resolution is possible:



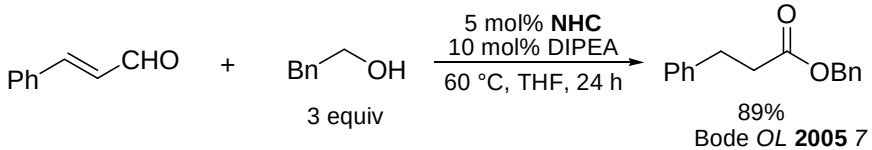
Scheidt *OL* **2005** *7* 905

- proposed stereochemical model:

NHC =

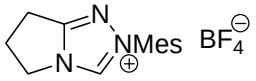


- an improved system:

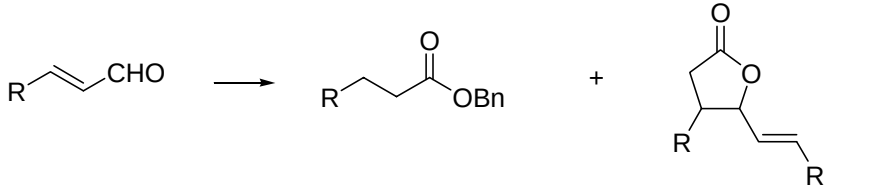


Bode *OL* **2005** *7* 3873

NHC =



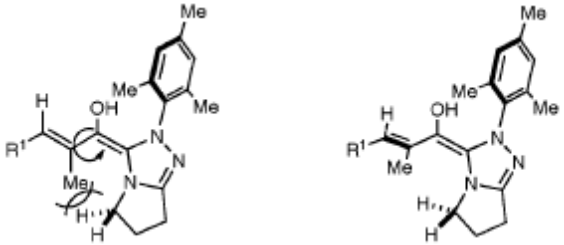
- selectivity between mechanistic pathways is dependent on the choice of base:



protonation pathway (slow) preferred for DIPEA

C-C bond formation (fast) preferred for tBuOK

- α-branched enals are unsuccessful due to A(1,3) strain:

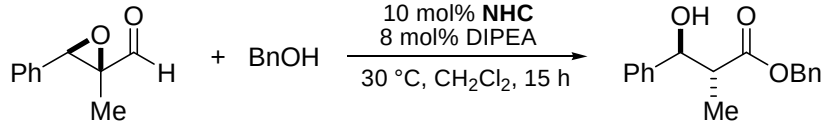


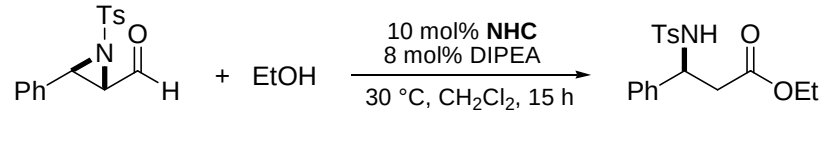
reactive for protonation, but suffers A(1,3)

unreactive for protonation, out of conjugation

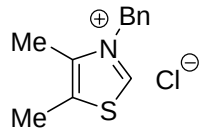
Bode *OL* **2005** *7* 3873

expoxyaldehydes and epoxyaziridines are also useful





NHC =

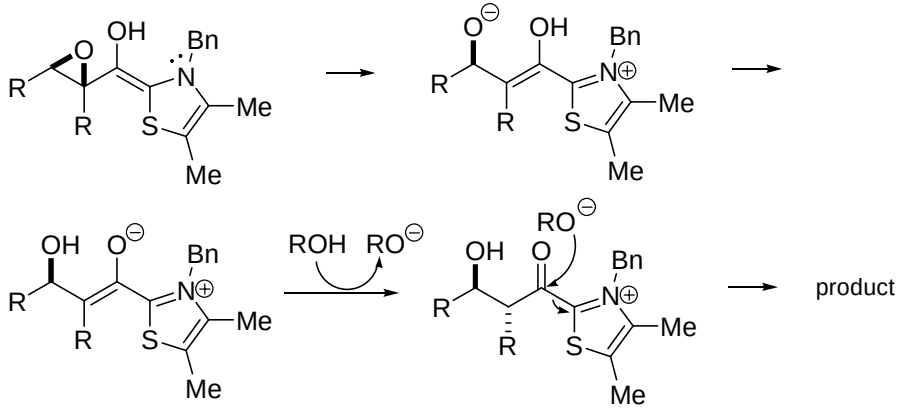


- acyloin dimers, C-C bond formation are supressed

Bode *JACS* **2004** *126* 8126

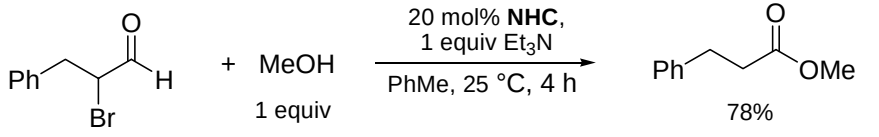
Eugene Kwan

- proposed mechanism:

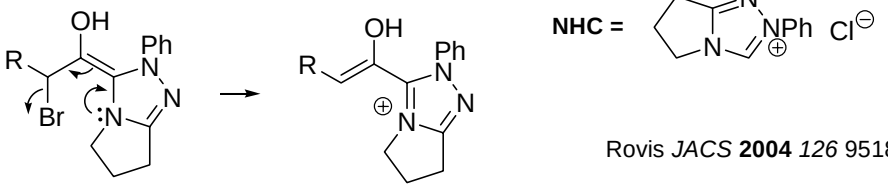


- if reaction is run in the presence of CD_3OD, recovered epoxide contains no deuterium
- implies concerted process or rate-determining deprotonation
- product has deuterium at the alpha position; no Favorskii or hydride-shift mechanism

Bode *JACS* **2004** *126* 8126

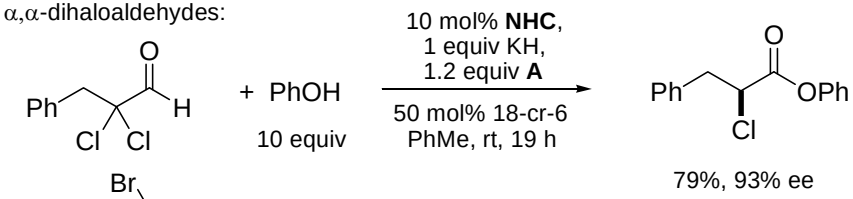


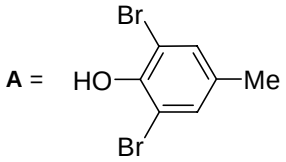
- presumably via:



Rovis *JACS* **2004** *126* 9518

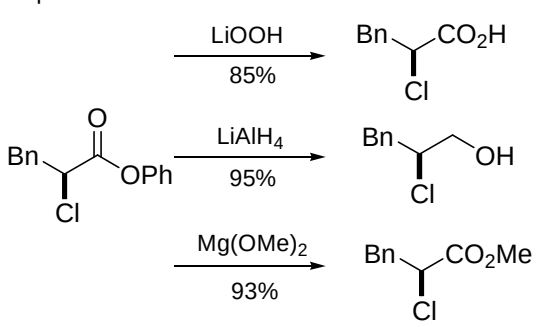
- α,α-dihaloaldehydes:



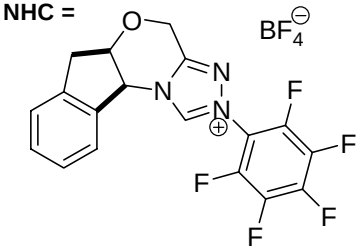


- 18-cr-6 required for solubility of KH in PhMe
- **A** acts to reduce background epimerization by acting as the "base reservoir"

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



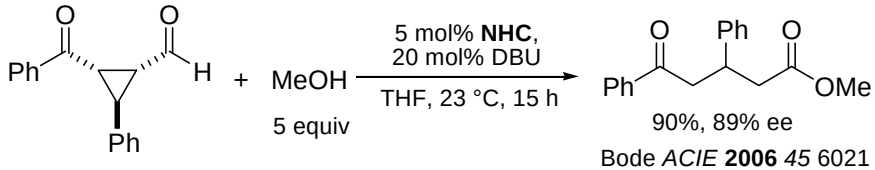
NHC =



- transformations preserve ee

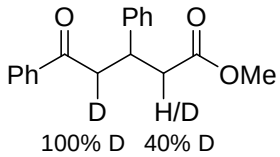
Rovis *JACS* **2005** *127* 16406

use of formylcyclopropanes



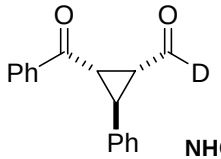
Bode *ACIE* **2006** *45* 6021

- range of aromatic, unsaturated, and aliphatic substrates are useful
- water and thiols are also useful nucleophiles
- if CD_3OD used:



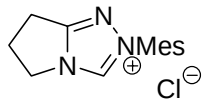
100% D 40% D

- recovered starting material:

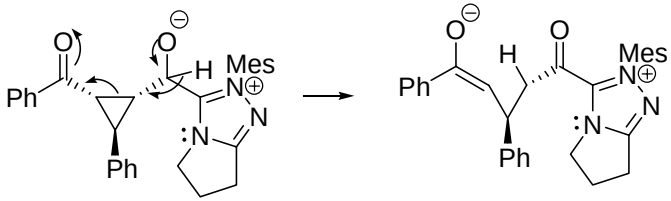


- indicates reversibility in intitial addition of NHC

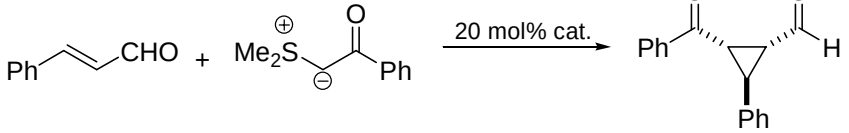
NHC =



- potential hydride shift mechanism:



- however, reaction with an enantioenriched substrate gives racemic product; actual mechanism remains unknown
- substrates are available using Macmillan protocol:

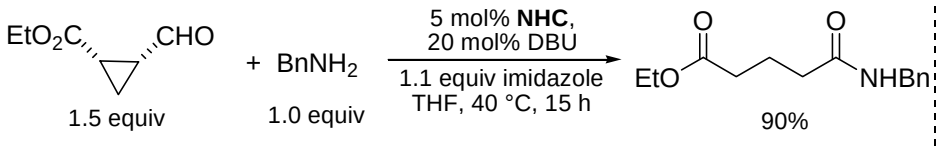


MacMillan *JACS* **2005** *127* 3240

Eugene Kwan

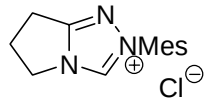
N-Heterocyclic Carbenes: Homoenolates

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



- presence of imidazole supresses 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

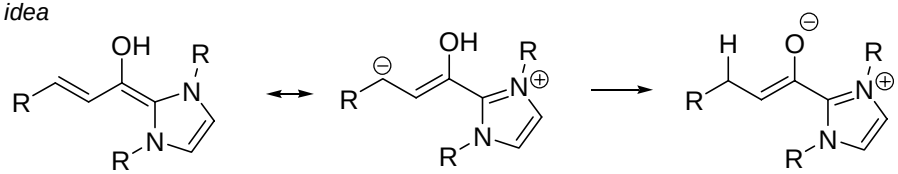
NHC =



Bode *JACS* **2007** *129* 13798

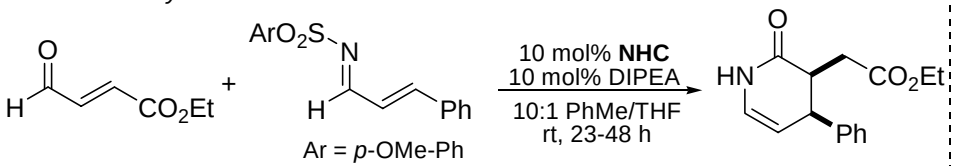
Diels-Alder Cycloadditions

the idea

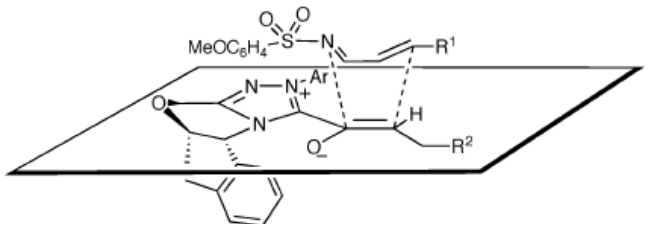


- problem: with imidazolium-derived NHCs, β-protonation is slow, even at elevated temperatures in protic solvents

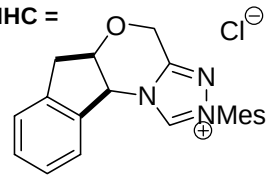
triazolium catalysts are successful



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



NHC =

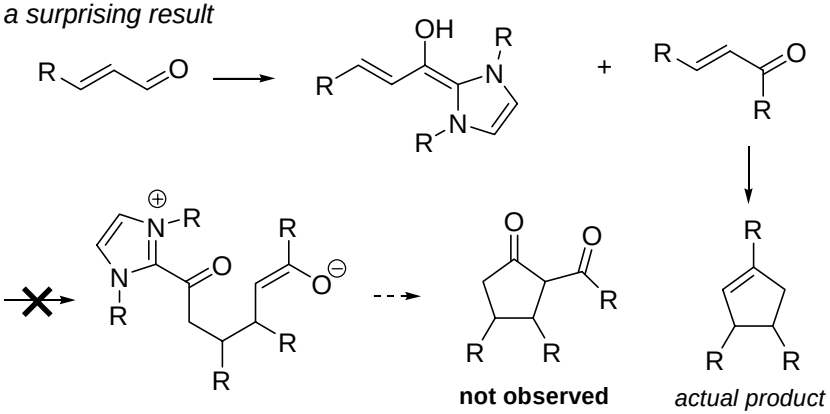


- if Mes is replaced by Ar, reaction fails

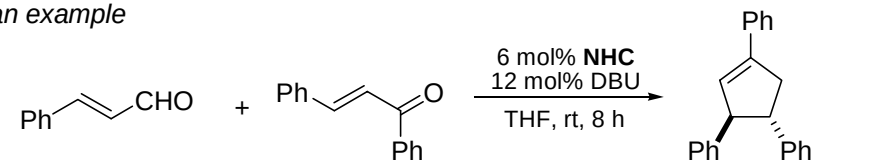
Bode *JACS* **2006** *128* 8418

α,β-Unsaturated Ketones

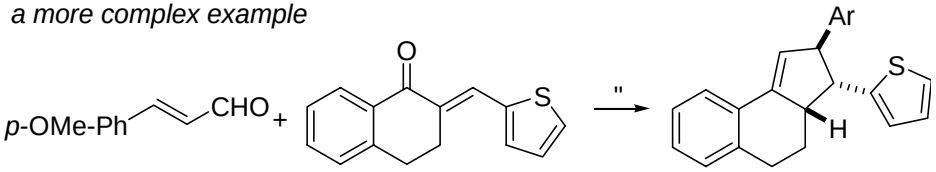
a surprising result



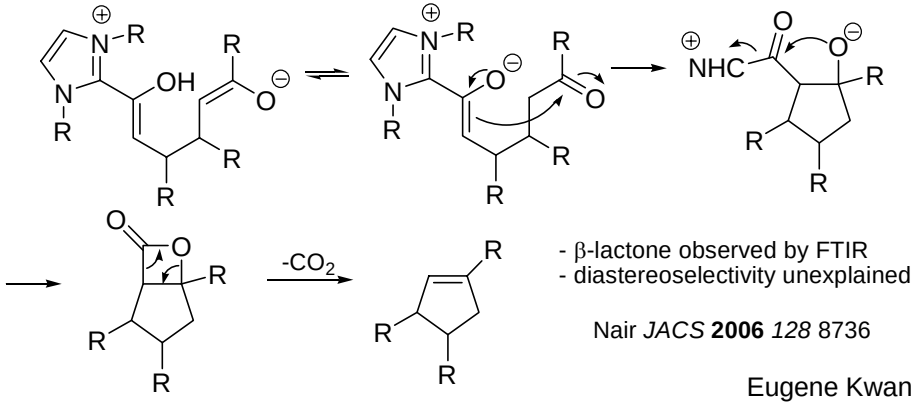
an example



a more complex example



mechanistic rationale



Nair *JACS* **2006** *128* 8736

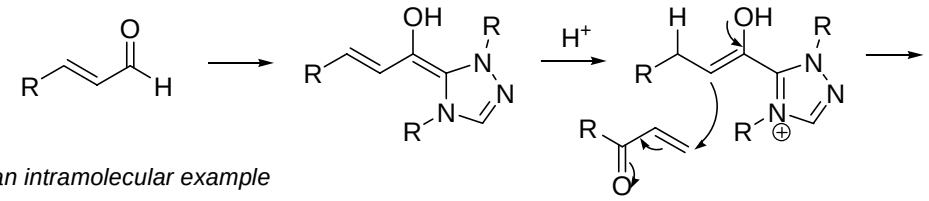
Eugene Kwan

N-Heterocyclic Carbenes: Homoenolates

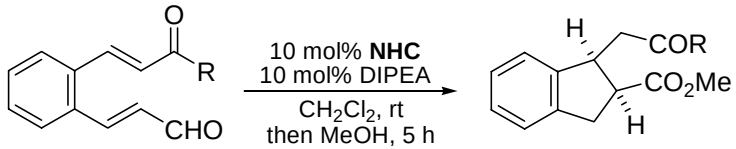
Intramolecular Michael Additions

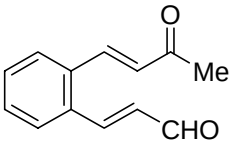
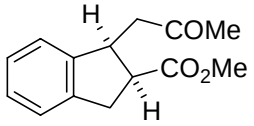
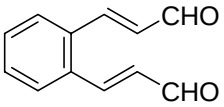
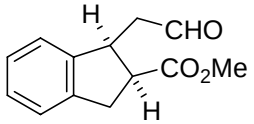
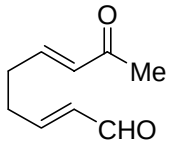
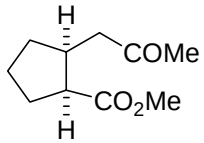
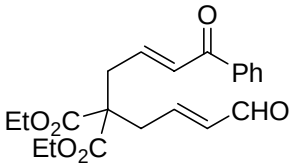
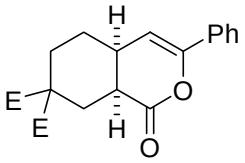
- NHC homoenolates can be β-quenched for use as nucleophiles in Michael additions

the idea



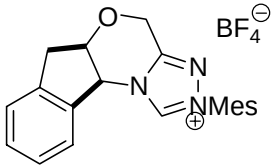
an intramolecular example



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

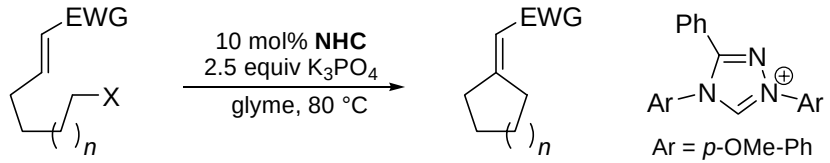
NHC =



Scheidt *ACIE* **2007** *46* 3107

α,β-Unsaturated Esters

- what if the NHC attacked the β-carbon of a Michael acceptor?

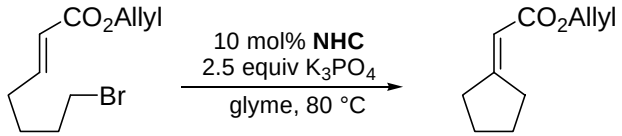


NHC =

Ar = *p*-OMe-Ph

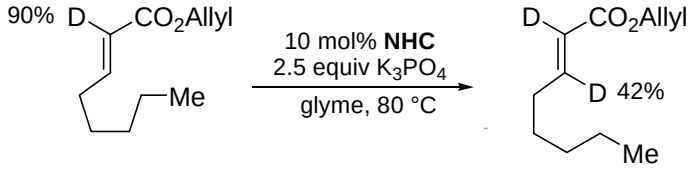
EWG = CO_2R, CN, Weinreb amide, X = OTs, Cl, Br, *n*=1,2

a representative example



8 h, 94%

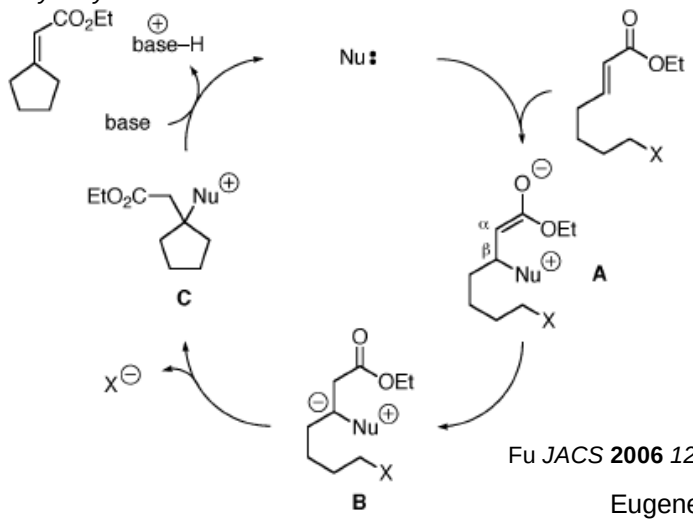
isotopic scrambling



12 h

- with PBu_3: <3% D at β-carbon

proposed catalytic cycle



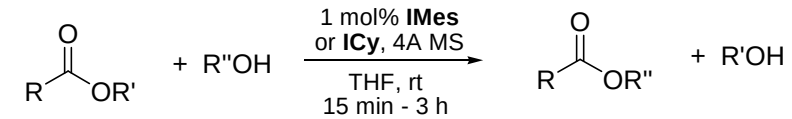
Fu *JACS* **2006** *128* 1472

Eugene Kwan

Transesterification Catalysts

- NHCs allow catalytic transesterification under mild conditions

primary alcohols



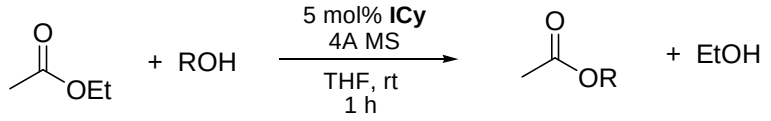
R' = Me, Et, vinyl

primary

95-100%

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

secondary alcohols



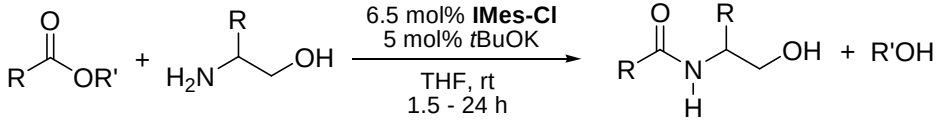
secondary

68-98%

Nolan *JOC* **2004** *69* 209

Amidation of Esters

substrate scope



R = alkyl, aryl, heterocyclic
R' = Me or lactone

- enantiopurity unchanged

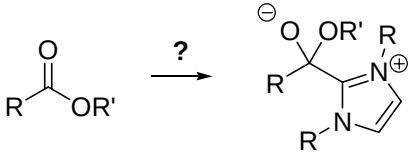
typical yields 90%

- numerous examples: see paper

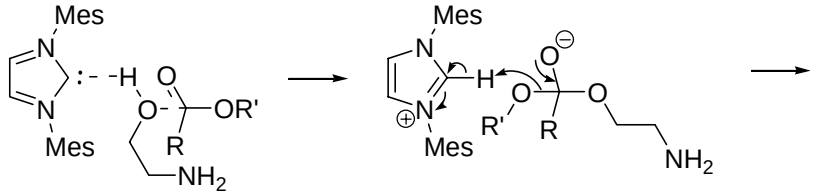
Movassaghi *OL* **2005** *7* 2453

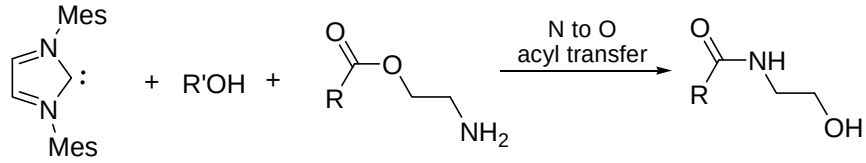
mechanism of action

- previously proposed: activated C2 imidazolium intermediates

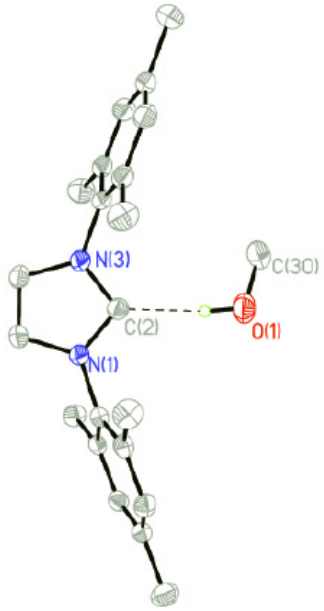


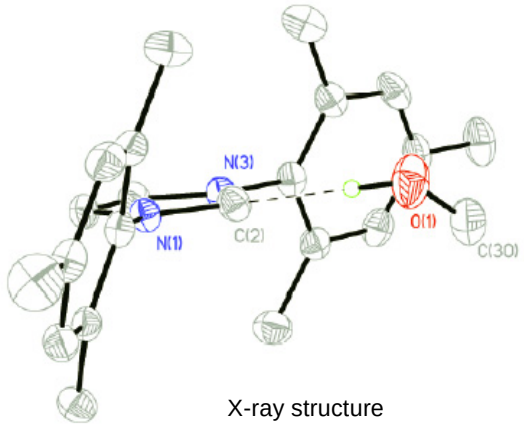
- another possibility: activation of alcohol nucleophile





- mixing an equimolar mixture of IMes and MeOH in C_6D_6 immediately produces Imes-MeOH complex (visible by NMR)
- complex is isolable:





X-ray structure

- reactIR and NMR show transient O-acylethanolamine intermediate

Movassaghi *OL* **2005** *7* 2453

Eugene Kwan