### Literature

#### General
2. "N-Heterocyclic Carbenes." Eastman, K.J. *Baran Group Seminar*

#### History

#### Properties

#### Preparation

#### Reactions

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**Scope of Seminar**
- History and mechanistic studies
- Properties of NHCs
- Preparation of NHCs
- Benzoin condensation
- Stetter reaction
- Homoenolate additions and condensations
- Transesterification

**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**

\[
\begin{align*}
\text{p-OMe-Ph} & \xrightarrow{p-OCH_3-Ph} \text{CHO} + 6 \text{ mol}\% \text{IMes-Cl} \\
& \xrightarrow{12 \text{ mol}\% \text{DBU}} \text{THF, rt, 8 h} \\
& \text{Ar} = \text{p-OMe-Ph}
\end{align*}
\]

78\%, one diastereomer

**Problem of the Day Solution**

\[
\text{Ar} = \text{p-OMe-Ph}
\]

**References**

- *JACS* 2006, 128, 8736
- Nair, *JACS* 2006
**The Benzoin Condensation**

**the original reaction**

\[
\begin{align*}
\text{PhCHO} + \text{NaCN} & \xrightarrow{\text{EtOH, } \Delta} \text{PhC(O)OH} \\
90-92\% & \ 
\end{align*}
\]

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

**Wohler/Liebig Ann. Pharm. 1832 3 249**


**Lapworth Mechanism**

\[
\begin{align*}
\text{PhCN} & \rightarrow \text{PhNHCOCN} \\
\text{PhCN} & \rightarrow \text{PhC(O)OH}
\end{align*}
\]

- intermediate cyanohydrins were isolated as crystalline K salts

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

**Thiamine-Catalyzed Reactions**

known in 1954:

\[
\begin{align*}
\text{HOOC} & \xrightarrow{\text{pig heart carboxylase}} \text{HOCH}_2\text{COOH} \\
\text{pyruvic acid} & \rightarrow \text{acetoine}
\end{align*}
\]

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


- carbon acidity of thiazolium compounds was known:

**Breslow Mechanism**

\[
\begin{align*}
\text{R}_3\text{N}: & \rightarrow \text{NR}_3\text{CO}^{-}\text{H}^+ \\
\text{H}^+ & \rightarrow \text{OH}^{-} \rightarrow \text{benzoin condensation}
\end{align*}
\]

**Breslow JACS 1958, 80, 3719**

**[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...**

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

**Mizuhara JACS 1954 76 571**

"[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..."

- could this be analogous to the Lapworth mechanism?

**N-heterocyclic carbene**

**thiamine is regenerated**

Eugene Kwan
evidence for mechanism:
- independent generation of proposed intermediate gives product:

\[
\begin{align*}
\text{OH} & \quad \text{Me}^+ \\
\text{Ph} & \quad \text{OH} \\
\text{S} & \quad \text{N} \\
\text{N} & \quad \text{Me} \\
\text{Ph} & \quad \text{I} \\
\end{align*}
\]

- various analogs of thiamine have varying efficacy:

\[
\begin{align*}
\text{S} & \quad \text{N} \\
\text{N} & \quad \text{Br} \\
\text{Bn} & \quad \text{Me} \\
\text{Me}^+ & \quad \text{Bn} \\
\end{align*}
\]

competent   ineffective

(steric hindrance)

- an illuminating comparison:

\[
\begin{align*}
\text{S} & \quad \text{N} \\
\text{N} & \quad \text{H} \\
\text{Bn} & \quad \text{I} \\
\text{Me}^+ & \quad \text{Bn} \\
\end{align*}
\]

competent   ineffective

NHC (cannot form NHC)

- both exchange with D\(_2\)O
- why is the thiazolium inactive?

Breslow JACS 1958, 80, 3719

- aromaticity:

\[
\begin{align*}
\text{S} & \quad \text{N} \\
\text{N} & \quad \text{CHO} \\
\text{CHO} & \quad \text{N} \\
\end{align*}
\]

aromatic

not aromatic

- the disruption of aromaticity is less significant here

- consider parent thiazolium first:

\[
\begin{align*}
\text{S} & \quad \text{N} \\
\text{N} & \quad \text{H} \\
\text{Me}^+ & \quad \text{OH} \\
\end{align*}
\]

pseudobase

catalytically inactive and non-aromatic

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

- another prediction:

\[
\begin{align*}
\text{S} & \quad \text{N} \\
\text{N} & \quad \text{CHO} \\
\end{align*}
\]

is especially stable compared to

\[
\begin{align*}
\text{S} & \quad \text{N} \\
\text{N} & \quad \text{Me}^+ \\
\end{align*}
\]

will be ineffective catalysts.

- comparison with imidazoliums:

\[
\begin{align*}
\text{S} & \quad \text{N} \\
\text{N} & \quad \text{CHO} \\
\text{CHO} & \quad \text{N} \\
\end{align*}
\]

could ring-open to

\[
\begin{align*}
\text{S} & \quad \text{N} \\
\text{N} & \quad \text{CHO} \\
\text{CHO} & \quad \text{N} \\
\end{align*}
\]

will not be formed.
**Isolation of a Stable Carbene**

- stable if not exposed to moisture or O₂
- crystalline (mp=240-241 °C)

- the first isolated stable carbene

**Carbene Dimerization**

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

- based on molecular weight measurements
  Wanzlick *ACIE* 1960 72 494

- the hypothesized mechanism of the formation of tetraaminoethylenes

**Wanzlick Proposal:** There is an equilibrium, and

[Active Species]

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

[Active Species]

**no ordinary olefins**

**reactivity**

- incredibly electron rich, these dimers oxidize very easily

**Lemal JACS 1962 84 1761**

**Wanzlick ACIE 1962 1 75**
Crossover Experiments

\[
\begin{align*}
\text{Ph Ph} & \quad \text{N N} \\
\text{Ar Ar} & \quad \text{Ph Ph} \\
\text{Ar Ar} & \quad \text{Ph Ph}
\end{align*}
\]

- 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

\[
\begin{align*}
\text{R, R'} = \text{Me/Et; Et/iPr; iPr/Me; Ph/pTol}
\end{align*}
\]

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

\[
\begin{align*}
\text{Ph Ph} & \quad \text{N N} \\
\text{Ar Ar'} & \quad \text{Ph Ph'} \\
\text{Ar Ar'} & \quad \text{Ph Ph'}
\end{align*}
\]

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 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

\[
\begin{align*}
\text{CH}_2 \quad \text{CH}_2
\end{align*}
\]

- 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)

1.337 Å

Eugene Kwan
**N-Heterocyclic Carbenes: The Benzoin Condensation Revisited**

*Less aromatic carbenes*

\[
\begin{align*}
\text{R} \quad & \quad \text{R} \quad & \quad \text{R} \\
\text{N} \quad & \quad \text{N} \quad & \quad \text{N}
\end{align*}
\]

- Equilibrium is observed (NMR)
- Bulky R favors carbene (R=IPr, 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

*Further Reading*


**The Mechanism of Benzoin Condensation: A Controversy**

*a dimeric mechanism?*

*Option 1*

\[
\begin{align*}
\text{S} \quad & \quad \text{S} \\
\text{R} \quad & \quad \text{R} \quad & \quad \text{R} \\
\text{S} \quad & \quad \text{S} \quad & \quad \text{S}
\end{align*}
\]

- Benzoin condensation, further dimerization

*Option 2*

- Is this anion significantly stabilized?

*Evidence for dimer involvement*

1. Crossover is observed

\[
\begin{align*}
\text{S} \quad & \quad \text{N} \quad & \quad \text{N} \quad & \quad \text{N} \\
\text{R} \quad & \quad \text{R} \quad & \quad \text{R} \\
\text{S} \quad & \quad \text{S} \quad & \quad \text{S}
\end{align*}
\]

- Unclear how this implicates dimer

2. Dimers give higher yields than thiazolium salt + base

\[
\begin{align*}
\text{S} \quad & \quad \text{N} \quad & \quad \text{N} \quad & \quad \text{N} \\
\text{R} \quad & \quad \text{R} \quad & \quad \text{R} \\
\text{S} \quad & \quad \text{S} \quad & \quad \text{S}
\end{align*}
\]

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

3. Behavior when NHC is generated via decarboxylation

\[
\begin{align*}
\text{S} \quad & \quad \text{N} \quad & \quad \text{N} \quad & \quad \text{N} \\
\text{R} \quad & \quad \text{R} \quad & \quad \text{R} \\
\text{S} \quad & \quad \text{S} \quad & \quad \text{S}
\end{align*}
\]

- 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

\[
\begin{align*}
\text{S} \quad & \quad \text{N} \quad & \quad \text{N} \quad & \quad \text{N} \\
\text{R} \quad & \quad \text{R} \quad & \quad \text{R} \\
\text{S} \quad & \quad \text{S} \quad & \quad \text{S}
\end{align*}
\]

- Reaction performed in dioxane at 100 °C
- Solubility of NaF under these conditions?

*Further Reading*

Castells *J Heterocyclic Chem* 1986 23 715

Castells *JOC* 1988 53 4433
N-Heterocyclic Carbenes: The Benzoin Condensation

(5) bridged thiazolium salts

![Chemical structure]

*yields in the benzoin condensation

<table>
<thead>
<tr>
<th>n</th>
<th>Salt</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>44%</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Breslow's Reply

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

![Chemical reactions]

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

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

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?

![Chemical reactions]

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

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

Graphs showing reaction rate law:

- first order
- second order

[Chemical structures and reactions are depicted in the image]
modern data
- primary kinetic isotope effect when PhCDO used: 3.4
- inverse solvent isotope effect when CD$_3$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
**N-Heterocyclic Carbenes: Acidity**

**Facile Deuterium Exchange**

*the seminal report*

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

\[
\text{Arduengo JACS 1995 117 572}
\]

**Acidity in water: results**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Rate of Deprot. ((M^{-1} \text{ s}^{-1}))</th>
<th>Relative Rate</th>
<th>pK_a</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHC</td>
<td>(1.54 \times 10^1) (1)</td>
<td></td>
<td>23.8</td>
</tr>
<tr>
<td>NHC</td>
<td>(1.03 \times 10^2) (7)</td>
<td></td>
<td>23.0</td>
</tr>
<tr>
<td>NHC</td>
<td>(2.39 \times 10^3) (150)</td>
<td></td>
<td>21.6</td>
</tr>
<tr>
<td>NHC</td>
<td>(1.3 \times 10^5) (8 400)</td>
<td></td>
<td>19.9</td>
</tr>
<tr>
<td>NHC</td>
<td>(3.0 \times 10^7) (1 900 000)</td>
<td></td>
<td>16.9</td>
</tr>
</tbody>
</table>

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

**Eisen mechanism**

\[
\text{C-H} + \text{OH}^{-} \rightarrow \text{C-H} \cdot \text{OH}^{-} \rightarrow \text{C}^+ \cdot \text{H-OH} \rightarrow \text{C}^+ + \text{H}_2\text{O}
\]

- work is done to bring reactants together
- rate depends on "intrinsic Marcus barrier" energy

<table>
<thead>
<tr>
<th>Protonation of:</th>
<th>Barrier (kcal/mol):</th>
</tr>
</thead>
<tbody>
<tr>
<td>isobutylene</td>
<td>12</td>
</tr>
<tr>
<td>aryl ring</td>
<td>10</td>
</tr>
<tr>
<td>ethyl vinyl ether</td>
<td>6</td>
</tr>
<tr>
<td>carbonyl compounds</td>
<td>6</td>
</tr>
<tr>
<td>phenol, acetic acid</td>
<td>2</td>
</tr>
</tbody>
</table>

- small primary KIEs are observed for imidazolium ion deprotonation

**Acidity in water: methods**

- rate of H/D exchange measured in buffered D_2O with \(^1\text{H}\) NMR
- this allows exchange at acidic CH to be distinguished from exchange at NH
- rate in H_2O extrapolated from known kinetic isotope effect \(k_{\text{D2O}}/k_{\text{H2O}} = 2.4\)
  (Jencks JACS 1989 111 683)
- reverse rate, protonation of carbene, extrapolated from flash photolysis: \(k_{\text{H2O}} = 10^{11} \text{ s}^{-1}\)
- \(pK_a = pK_w + \log(k_{\text{H2O}}/k_{\text{H2O}}), \text{ where } K_w = 10^{14}\) and \(k_{\text{H2O}}\) is the rate of deprotonation

\[
\text{Richard JACS 2004 126 4366}
\]
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)

Compiled $pK_a$ Values (DMSO)

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

**imidazolium core**

- one of the strongest known neutral bases

**thiazolium and related cores**

**other**

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

references

1. Jencks JACS 1989 11 683
2. Cheung JOC 2007 72 7790
4. Bordwell JACS 1991 113 985-990 + refs. therein
5. Yates JACS 2004 126 8717

Alder JCS Chem Commun 1995 1267

Eugene Kwan
**N-Heterocyclic Carbenes: Preparation**

**Imidazolium Salts**

*diamine precursor*

\[
\begin{align*}
\text{RHN} & \quad \text{NHR} \\
\text{MesHN} & \quad \text{HN} \quad \text{Ph} \\
\text{MeO} & \quad \text{Ph}
\end{align*}
\]

1. \( \text{BBR}_3; \text{HCl/MeOH} \)
2. \( \text{CH(OEt)}_3 \)

\( \text{45\%} \)

above: Hoveyda *JACS* 2005 127 6877

another example: Helmchen *Synlett* 2004 1789

**Diamine precursor: variation**

\[
\begin{align*}
\text{Cl} & \quad \text{ArNH}_2, \text{Et}_3\text{N} \\
\text{ArNH}_2, \text{PhMe}, \Delta \text{ or} \\
\text{NaOH; ArNH}_2, \text{DCC}, \text{HOBT}
\end{align*}
\]

via oxazolium intermediate

\[
\begin{align*}
\text{R} & \quad \text{N} \quad \text{CHO} \\
\text{R} & \quad \text{N} \quad \text{CHO}
\end{align*}
\]

1. \( \text{RNH}_2, \text{HCl, Dean-Stark} \)
2. \( \text{HCOOH, Ac}_2\text{O} \)

formic acetic anhydride:

*Org Syn Coll. Vol. 6* 1998 8

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

\[
\begin{align*}
\text{ArHN} & \quad \text{NHAr'} \\
\text{ArH}_3\text{N} & \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \quad \text{Cl}
\end{align*}
\]

- does not aromatize

via oxazolium intermediate

\[
\begin{align*}
\text{R} & \quad \text{N} \quad \text{CHO} \\
\text{R} & \quad \text{N} \quad \text{CHO}
\end{align*}
\]

1. \( \text{RNH}_2, \text{nBuLi} \)
2. \( \text{Ac}_2\text{O, HClO}_4 \)

ethyl chlorooxoacetate

\[
\begin{align*}
\text{Cl} & \quad \text{OEt} \\
\text{Cl} & \quad \text{OEt}
\end{align*}
\]

1. \( \text{ArNH}_2, \text{PhMe}, \text{H}_2\text{SO}_4, \text{rt} \text{ or} \\
\text{NaOH; ArNH}_2, \text{DCC}, \text{HOBT}
\]

sequential lithiations

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{H} \\
\text{R} & \quad \text{N} \quad \text{S}
\end{align*}
\]

1. \( \text{nBuLi} \)
2. \( \text{CS}_2 \)

\[
\begin{align*}
\text{Li} & \quad \text{N} \quad \text{S}
\end{align*}
\]

\( \delta(C_2)=240 \text{ ppm} \)

above: Grubbs *Orgmet* 2004 23 3105

further examples: Gilbertson *OL* 2005 7 4605

Maudit *JOMC* 2005 690 5237

- sterically hindered amines are tolerated

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} \\
\text{ClO}_4 & \quad \text{ClO}_4
\end{align*}
\]

\( \delta(C_2)=240 \text{ ppm} \)

*Hahn ACIE* 2003 42 5243

\( N,N\)-substituted thione synthesis:

*Ahlbrecht Synthesis* 1994 719

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} \\
\text{ClO}_4 & \quad \text{ClO}_4
\end{align*}
\]

- sterically hindered amines are tolerated
N-Heterocyclic Carbenes: Preparation

Evans Group Seminar

Benzoimidazolium Salts

\[
\begin{align*}
&\text{1. Pd(0), RNH}_2 \\
&\text{2. Pd(0), R'}\text{NH}_2 \\
&\text{3. CH(OEt)}_3, \text{HX}
\end{align*}
\]

Buchwald-Hartwig Amination:
Pd\text{dba}_3, \text{BINAP}, \text{NaO}t\text{Bu}
Buchwald JACS 1996 118 7215
Hartwig JACS 1996 118 7217

- optimization was required to suppress epimerization of chiral primary amines

Triazolium Salts

\[
\begin{align*}
&\text{O-Cl} \\
&\text{1. PhNH}_2, \Delta \\
&\text{2. SOCl}_2 \\
&\text{3. PhNHNH}_2
\end{align*}
\]

via phenylhydrazone

- amides are also useful:

\[
\begin{align*}
&\text{1. Me}_3\text{OBF}_4 \\
&\text{2. PhNHNH}_2 \\
&\text{3. CH(OEt)}_3
\end{align*}
\]

Enders ACIE 2002 41 1743

- from amino acids:

\[
\begin{align*}
&\text{Bn} \quad \text{O} \\
&\text{Bn} \quad \text{O} \\
&\text{O} \\
&\text{O}
\end{align*}
\]

phenylalanine
Meldrum's acid
presumably via:

Rovis JOC 2005 70 5725

via oxazolidinone

\[
\begin{align*}
&\text{O} \\
&\text{NH} \quad \text{O} \\
&\text{O} \\
&\text{O}
\end{align*}
\]

Enders ACIEE 1995 34 1021

214.6 ppm

Amide are also useful:

Enders Synthesis 2003 1292

- reaction with acetonitrile:

\[
\begin{align*}
&\text{N}^+ \quad \text{Ph} \\
&\text{ClO}_4^- \\
&\text{NaOMe} \quad \text{MeOH}
\end{align*}
\]

Enders ACIE 1995 34 1021

110 °C
2. TFA

Cowley JOC 2003 68 5762

Eugene Kwan
\textit{N}-Heterocyclic Carbenes: Asymmetric Benzoin Condensation

\textbf{a first attempt}

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{H} & \quad \text{H} \\
\xrightarrow{10 \text{ mol}\% \text{ NHC}, 10 \text{ mol}\% \text{ Et}_3\text{N}} & \quad \text{Ph} \quad \text{Ph} \\
& \quad \text{OH} \\
\text{1.2 MeOH/H}_2\text{O} & \quad 30 \degree \text{C}, 24 \text{h} \\
& \quad 78\%, 8\% \text{ ee}
\end{align*}
\]

\textbf{an improved system}

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{H} & \quad \text{H} \\
\xrightarrow{1.25 \text{ mol}\% \text{ NHC}, \text{ K}_2\text{CO}_3} & \quad \text{Ph} \quad \text{Ph} \\
& \quad \text{OH} \\
\text{THF, rt, 60 h} & \quad 22-72\%, 20-86\% \text{ ee}
\end{align*}
\]

\textbf{an efficient system}

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{H} & \quad \text{H} \\
\xrightarrow{10 \text{ mol}\% \text{ NHC}, 10 \text{ mol}\% \text{ KOtBu}} & \quad \text{Ph} \quad \text{Ph} \\
& \quad \text{OH} \\
\text{THF, rt, 16 h} & \quad 8-100\%, 80-95\%
\end{align*}
\]

\textbf{crossed-benzoin condensations}

\[
\begin{align*}
\text{R} & \quad \text{R'} \\
\xrightarrow{10 \text{ mol}\% \text{ NHC}, 9 \text{ mol}\% \text{ KHMDS}} & \quad \text{R} \quad \text{R'} \\
\text{THF, rt, 18-72 h} & \quad 24-93\%, 71-99\% \text{ ee}
\end{align*}
\]

\textit{Sheehan JACS 1974 39 1196}

\textit{Enders Helv Chim Acta 1996 79 1217}

\textit{Enders ACIE 2002 41 1743}

\textit{Enders ACIE 2006 45 1463}

\textit{Enders Synlett 2006 15 2431}

\textit{Suzuki ACIE 2006 45 3492}

\textit{Suzuki OL 2007 9 2713}

Eugene Kwan
**N-Heterocyclic Carbenes: Benzoin Methodology**

**Acyloin Macrocyclization**

- **NHC =** [Diagram of NHC structure]

- Proposed mechanism:
  - Evidence for oxy-Cope:

**Tandem Benzoin-oxy-Cope-aldol Sequence**

- Proposed mechanism:
  - Cross-benzoin (reversible)
  - Oxy-Cope (irreversible)

**References**

- Miller JOC 2007 72 5260
- Bode JACS 2007 129 3520
**N-Heterocyclic Carbenes: The Stetter Reaction**

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**benzoin**

\[
\text{RCHO} + \text{R'}\text{CO}_2\text{R} \rightarrow \text{RCHO}_2\text{R}'
\]

**acyl anion** aldehyde \(\alpha\)-hydroxy ketones

**Stetter**

\[
\text{RCHO} + \text{R'}\text{C}=\text{O} \rightarrow \text{RCHO}_2\text{R}'
\]

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

**the original reaction**

\[
\text{PhCO}_2\text{H} + \text{MeC}=\text{OEt} \xrightarrow{\text{NaCN, DMF, rt}} \text{PhCO}_2\text{Me}
\]

- thiazolium salts were soon found to be useful as well

**asymmetric Stetter reactions**

**the original report**

\[
\text{CHO} \xrightarrow{20\text{ mol}\% \text{NHC, } \text{K}_2\text{CO}_3, \text{THF, rt, 24 h}} \text{NHC}
\]

- \(R = \text{H, Cl, OMe; } R' = \text{Me, Et}\)
- key advance: triazolium salts are more active

Enders *Helv Chim Acta* 1996 79 1899

**Rovis variant**

\[
\text{RCHO} \xrightarrow{2\text{ mol}\% \text{NHC, } 2\text{ equiv Et}_3\text{N, PhMe, rt, 24 h}} \text{NHC}
\]

- 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:

**formation of quaternary stereocenters**

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

Rovis *JACS* 2002 124 10298

Rovis *Synlett* 2003 12 1934

- some kinetic resolution can also be obtained with racemic \(g\)-substituted substrates

Rovis *Tet* 2005 67 6368

**Eugene Kwan**
**N-Heterocyclic Carbenes: The Stetter Reaction**

---

### Diastereo- and Enantioselective Variant

![Chemical Structure](image1)

**Rovis JACS 2005 127 6284**

- **Mechanism of reaction?**

![Chemical Structure](image2)

- **Proposed model for selectivity**

![Chemical Structure](image3)

- Evidently, intramolecular protonation is faster than intermolecular protonation

---

### Enantioselective Desymmetrization

![Chemical Structure](image4)

**Rovis JACS 2006 128 2552**

- **Sila-Stetter reactions**

![Chemical Structure](image5)

- Acylsilanes are competent nucleophiles

---

**Eugene Kwan**
N-Heterocyclic Carbenes: The Stetter Reaction

- Brook rearrangement:

\[
\begin{align*}
\text{Ph} & \quad \text{SiMe}_3 + \text{EtN} & \rightarrow & \text{TMSO} \quad \text{Et} \\
\text{Ph} & \quad \text{Ph} \quad \text{OH} \quad \text{Et} & \rightarrow & \text{TMSO} \quad \text{Et} \quad \text{Et}
\end{align*}
\]

Scheidt *JOC* 2006 71 5715

- decarboxylative addition:

\[
\begin{align*}
\text{RCOONa} & + \text{EtN} & \rightarrow & \text{R} \quad \text{OH} \quad \text{Bn} \quad \text{N} \\
\text{Ph} & \quad \text{Ph} \quad \text{OH} \quad \text{Im} & \rightarrow & \text{Ph} \quad \text{OH} \quad \text{Bn} \quad \text{N}
\end{align*}
\]

Scheidt *JACS* 2005 127 14675

acylimidazoles

\[
\begin{align*}
\text{Ph} & \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{Pr} & + \text{PrCOONa} & \rightarrow & \text{Ph} \quad \text{O} \quad \text{CO} \quad \text{Im} \\
\text{NHC} & = & \text{Me} & \quad \text{Ph} \quad \text{N} \quad \text{Cl} \quad \text{S}
\end{align*}
\]

Scheidt *JACS* 2005 127 14675

Eugene Kwan
**Mechanistic Rationale**

If aldehyde is α,β-unsaturated:

- Potential for:
  - benzoin/Stetter (a₁ to d₁)
  - homoenolate (a₁ to d₃) reactivity patterns
- Selectivity for dimerization vs. cross-addition?

**Initial 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

**Extending the Scope of the Electrophile**

γ-lactams from N-sulfonylimines

- TIPS = MesN\(\equiv\)NMes
- PG = SO₂Ar, Ar = p-OMe-Ph
- Choice of PG is important

**Conditions:**
- 5 mol% IMes-Cl, 10 mol% KOtBu
- 1 equiv electrophilic aldehyde
- 16 h, rt, THF

**Representative examples:**
- Bode
- Glorius ACIE 2004 43 6205

**Dimerization also possible:**

- TIPS = MesN\(\equiv\)NMes

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

- 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 tBuOD, D is incorporated exclusively at the α-position (no quenching of homoenolate by solvent)

**Representative examples:**
- Glorius
- Bode JACS 2004 126 14370

**Ketones are competent electrophiles:**

**Conditions:**
- 5 mol% IMes-Cl, 10 mol% KOtBu
- 1 equiv electrophilic aldehyde
- 15 mol% IMes-Cl, 10 mol% DBU, 60 °C, tBuOH, 14 h

**Representative examples:**
- Bode
- Oligo 2005 7 3131

- Eugene Kwan
**Redox Esterification**

\[
\begin{align*}
\text{NHC} = \begin{array}{c}
\text{NMe} \\
\text{Ar}\\
\ell \\
\end{array} \\
\end{align*}
\]

- a representative example:

\[
\begin{align*}
\text{Ph} & \equiv \text{CHO} + \text{Ph} \equiv \text{OH} \\
& \xrightarrow{5 \text{ mol\% NHC}, 5 \text{ mol\% DBU}} \\
& \xrightarrow{2 \text{ equiv PhOH} \text{, THF, } 110^\circ \text{C, 2-6 h}} \\
& \xrightarrow{82\%} \\
\end{align*}
\]

- 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

- kinetic resolution is possible:

\[
\begin{align*}
\text{Ph} & \equiv \text{CHO} + \text{Ph} \equiv \text{OH}^{\dagger} \\
& \xrightarrow{5 \text{ mol\% NHC, DBU, PhMe \@40\% conv.}} \\
& \xrightarrow{s = 4.8} \\
\end{align*}
\]

- proposed stereochemical model:

\[
\begin{align*}
\text{NHC} = \begin{array}{c}
\text{NMe} \\
\text{Ar}\\
\ell \\
\end{array} \\
\end{align*}
\]

- an improved system:

\[
\begin{align*}
\text{Ph} & \equiv \text{CHO} + \text{Bn} \equiv \text{OH} \\
& \xrightarrow{5 \text{ mol\% NHC, 10 mol\% DIPEA \text{, THF, 24 h}}} \\
& \xrightarrow{89\%} \\
\end{align*}
\]

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

\[
\begin{align*}
\text{R} & \equiv \text{CHO} \rightarrow \text{R} \equiv \text{COBn} + \text{C-C bond formation (fast)} \text{ preferred for tBuOK} \\
\text{R} & \equiv \text{CHO} \rightarrow \text{R} \equiv \text{COBn} + \text{protonation pathway (slow)} \text{ preferred for DIPEA} \\
\end{align*}
\]

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

\[
\begin{align*}
\text{epoxyaldehydes and epoxyaziridines are also useful}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \equiv \text{CHO} + \text{BnOH} \rightarrow \text{Ph} \equiv \text{COBn} \rightarrow \text{Ph} \equiv \text{COEt} \\
& \xrightarrow{30 \text{ C, CH}_2\text{Cl}_2, 15 \text{ h}} \\
& \xrightarrow{89\%, \text{dr} > 10:1} \\
\end{align*}
\]

- acyloin dimers, C-C bond formation are suppressed

\[
\begin{align*}
\text{Ph} & \equiv \text{CHO} + \text{EtOH} \rightarrow \text{Ph} \equiv \text{COEt} \\
& \xrightarrow{30 \text{ C, CH}_2\text{Cl}_2, 15 \text{ h}} \\
& \xrightarrow{53\%} \\
\end{align*}
\]
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**N-Heterocyclic Carbenes: Homoenoates**

- Proposed mechanism:
  
  \[
  \begin{align*}
  \text{R} & \quad \text{O} & \quad \text{Bn} & \quad \text{Me} \\
  \text{OH} & \quad \text{OH} & \quad \text{N} & \quad \text{S} & \quad \text{N} & \quad \text{Bn} & \quad \text{Me} \\
  \text{S} & \quad \text{N} & \quad \text{Bn} & \quad \text{Me} & \quad & \quad & \quad \\
  \text{Me} & \quad & \quad & \quad & \quad & \quad & \quad \\
  \end{align*}
  \]

  - If reaction is run in the presence of CD\textsubscript{3}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.

- Proposed mechanism:
  
  \[
  \begin{align*}
  \text{R} & \quad \text{O} & \quad \text{Bn} & \quad \text{Me} \\
  \text{OH} & \quad \text{OH} & \quad \text{N} & \quad \text{S} & \quad \text{N} & \quad \text{Bn} & \quad \text{Me} \\
  \text{S} & \quad \text{N} & \quad \text{Bn} & \quad \text{Me} & \quad & \quad & \quad \\
  \text{Me} & \quad & \quad & \quad & \quad & \quad & \quad \\
  \end{align*}
  \]

  \[\text{ROH}\]

- Use of formylcyclopropanes:

- Range of aromatic, unsaturated, and aliphatic substrates are useful.
- Water and thiols are also useful nucleophiles.
- If CD\textsubscript{3}OD used:
  - Recovered starting material:
  - Indicates reversibility in initial addition of 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
**Eugene Kwan**

**N-Heterocyclic Carbenes: Homoenolates**

Evans Group Seminar

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

\[
\text{EtO}_2\text{C} = \text{CHO} \xrightarrow{1.5 \text{ equiv}} \text{BnNH}_2 \xrightarrow{1.0 \text{ equiv}} \text{NHC} \quad \begin{array}{c}
\text{5 mol\% NHC,} \\
\text{20 mol\% DBU} \\
\text{THF, 40 °C, 15 h}
\end{array} \\
\text{EtO}_2\text{C} = \text{C}(\text{O})\text{NHBN} \\
\text{90%}
\]

- 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 hydroxylamines are tolerated

**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

\[
\text{ArO}_2\text{S} \quad \begin{array}{c}
\text{10 mol\% NHC} \\
\text{10 mol\% DIPEA} \\
\text{10:1 PhMe/THF} \\
\text{rt, 23-48 h}
\end{array} \\
\text{HO} \xrightarrow{\text{H}} \text{CO}_2\text{Et} \\
\text{10 mol\% NHC} \quad \begin{array}{c}
\text{12 mol\% DBU} \\
\text{THF, rt, 8 h}
\end{array} \\
\text{Ph} \text{CHO} \\
\text{6 mol\% NHC} \quad \begin{array}{c}
\text{p-OMe-Ph} \\
\text{CHO}
\end{array}
\]

- 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

**α,β-Unsaturated Ketones**

A surprising result

\[
\text{Ph} \xrightarrow{\text{CHO}} \text{Ph} \xrightarrow{\text{CHO}} \\
\text{NHC} = \text{IMes-Cl}
\]

Not observed

Actual product - typically, R=aryl

An example

\[
\text{Ph} \xrightarrow{\text{CHO}} \text{Ph} \\
\text{NHC} = \text{IMes-Cl}
\]

78%, one diastereomer

A more complex example

\[
\text{p-OMe-Ph} \text{CHO} + \text{Ph} \xrightarrow{\text{CHO}} \text{Ph} \xrightarrow{\text{CHO}} \\
\text{NHC} = \text{IMes-Cl}
\]

90%, >99% ee, dr >50:1

Mechanistic rationale

- β-lactone observed by FTIR
- Diastereoselectivity unexplained

Nair JACS 2006 128 8736

Eugene Kwan
**N-Heterocyclic Carbenes: Homoenolates**

**Evans Group Seminar**

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

\[
R-\text{C}R' \text{=N} \rightarrow R-\text{C}R' \text{=N} R
\]

*an intramolecular example*

### α,β-Unsaturated Esters
- what if the NHC attacked the β-carbon of a Michael acceptor?

\[
\begin{align*}
\text{EWG} & \quad 2.5 \text{ equiv } \text{K}_3\text{PO}_4 \\
\text{glyme}, 80 ^\circ \text{C} & \\
\text{NHC} & \quad \text{Ar} - \text{N} - \text{N}^{\ominus} - \text{Ar} \\
\text{Ar} & = p-\text{OMe-Ph} \\
\end{align*}
\]

EWG = CO$_2$R, CN, Weinreb amide, X = OTs, Cl, Br, n=1,2

*a representative example*

\[
\begin{align*}
\text{CO}_2\text{Allyl} & \quad 10 \text{ mol\% NHC} \\
\text{glyme}, 80 ^\circ \text{C} & \\
\text{X} & = \text{OTs}, \text{Cl}, \text{Br} \\
\end{align*}
\]

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

**Scheidt ACIE 2007 46 3107**

**Fu JACS 2006 128 1472**

Eugene Kwan
**Transesterification Catalysts**

- NHCs allow catalytic transesterification under mild conditions
  - primary alcohols
    \[ RO + R'OH \rightarrow R'O + R''OH \]
    
    \( R' = \text{Me, Et, vinyl} \)
    
    - secondary alcohols are not viable nucleophiles
    - simultaneous report: Waymouth/Hedrick 2002 4 3587
    - sieves may absorb liberated alcohols
  - secondary alcohols
    \[ ROEt + ROH \rightarrow ROC + EtOH \]
    
    \( 5 \text{ mol}\% ICy, 4A MS \)
    
    Nolan JOC 2004 69 209

**Amidation of Esters**

- **substrate scope**
  \[ RO + R'OH + H_2N \rightarrow R'N + ROH \]
  
  \( R = \text{alkyl, aryl, heterocyclic} \)
  \( R' = \text{Me or lactone} \)
  
  - typical yields 90%
  - numerous examples: see paper Movassaghi OL 2005 7 2453

- **mechanism of action**
  - previously proposed: activated C2 imidazolium intermediates
  
  \[ ROOR' \rightarrow RO \rightarrow R'N \]

- another possibility: activation of alcohol nucleophile
  
  \[ \text{Imes} + R'OH \rightarrow R'N + ROH \]
  
  Movassaghi OL 2005 7 2453

- mixing an equimolar mixture of IMes and MeOH in C_6D_6 immediately produces Imes-MeOH complex (visible by NMR)
  
  - complex is isolable:
  
  \[ \text{Imes-MeOH complex} \]
  
  Movassaghi OL 2005 7 2453

Eugene Kwan