# The Beckmann Rearrangement

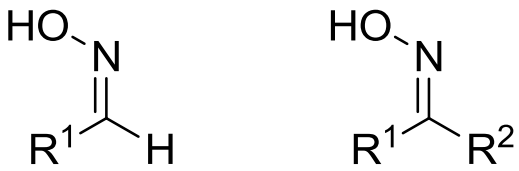
The Mona Lisa of Rearrangements

Jeremy Henle, 11/19/2013

# Outline

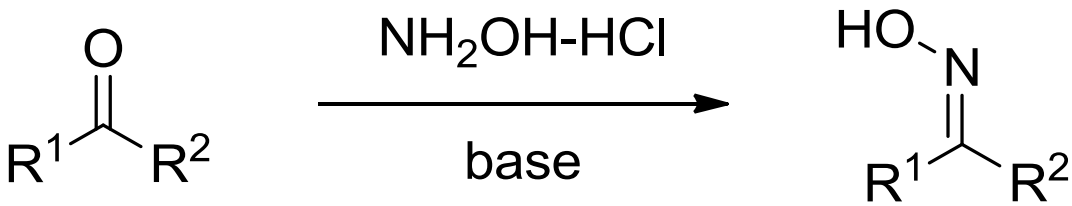
- Introduction
  - Oximes
  - Reactions of Oximes
- Discovery
- 100 years of the Beckmann Rearrangement
  - Mechanism Determination
- Organocatalyzed Beckmann Rearrangement
- Summary

# Oximes




aldoxime ketoxime

- Known to exist in isomeric forms (as of 1890, Hantzsch and Werner)
- Many are crystalline, air stable compounds
- Generally more stable to hydrolysis than hydrazones (2-3 times as stable)
- Preparation

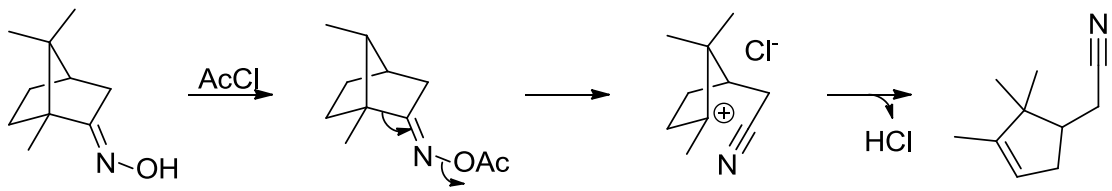



Hantzsch and Werner, *Ber.* **1890**, *23*, 11.

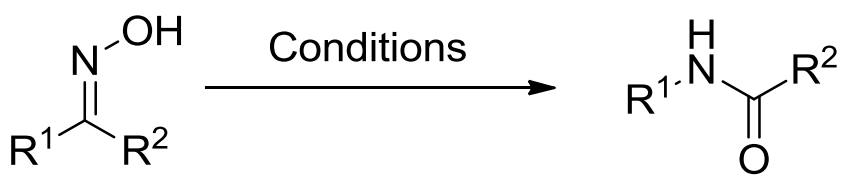
# Reactions of Oximes

- Neber Rearrangement


- Beckmann Fragmentation



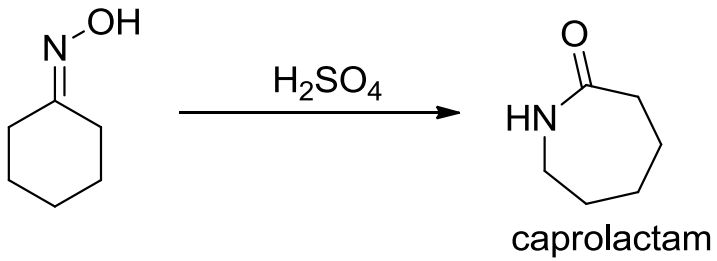

- Beckmann Rearrangement -1886 to present




Most widely used industrial process for lactam formation

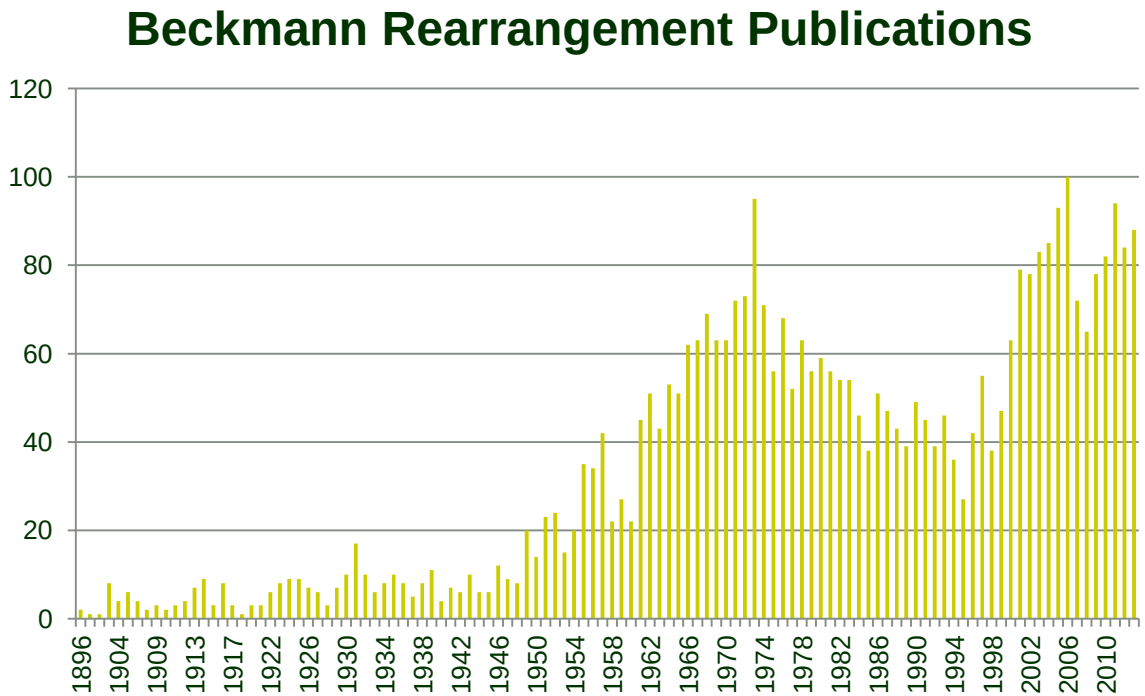
# Significance of the Beckmann Rearrangement

- Industrial Significance




Half of all produced cyclohexanone is converted to the oxime for this process. **Precursor to nylon-6**

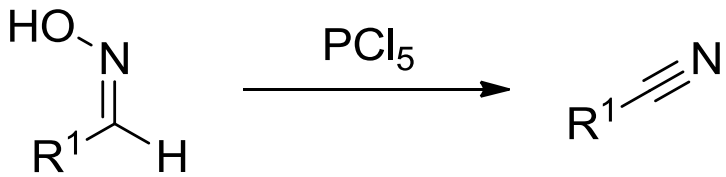
- Academic Significance
  - Mechanism still uncertain
  - Illustrated in numerous natural product syntheses



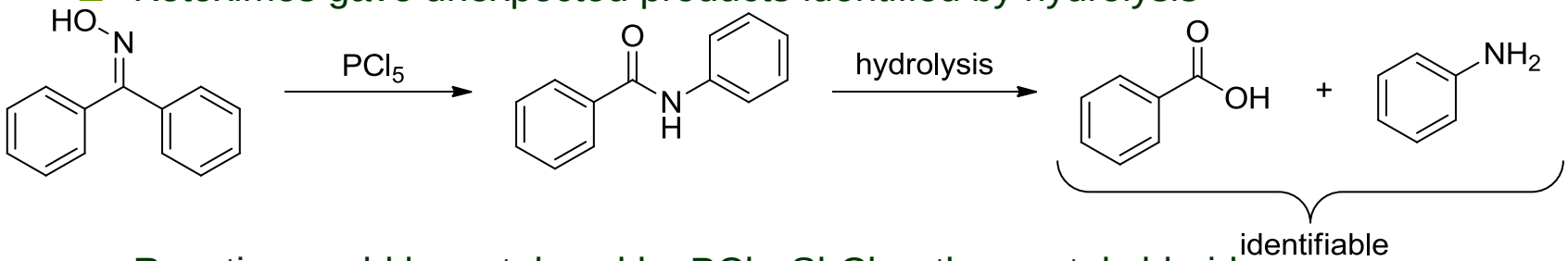
# Discovery

## 1886

- Ernst Beckmann
  - Attempting to find a novel method of distinguishing aldehydes and ketones from their corresponding aldoximes/ketoximes




  - Ketoximes gave unexpected products identified by hydrolysis

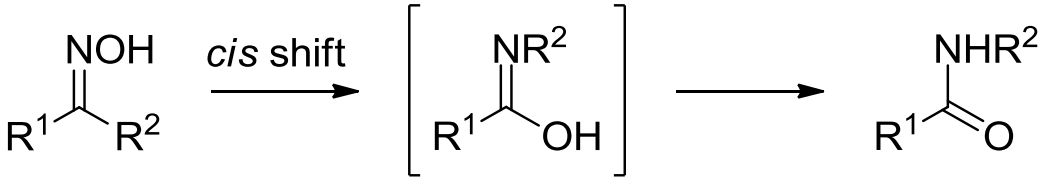



  - Reaction could be catalyzed by $PCl_5$, $SbCl_5$, other metal chlorides
  - Strong mineral acids could be used, catalytically if necessary
    - Beckmann solution: acetic acid, HCl, and acetic anhydride
  - Alkali metal hydroxides did not catalyze the reaction
- Beckmann expected the mechanism to be quite complex with many different intermediates due to generality and possible reagents

Beckmann, *Ber*. **1886**, 988. A. H. Blatt, *Chem. Rev.* **1933**, 215.

# Initial Mechanistic Assumptions

- Initial hypothesis that the reaction was formally an exchange of a “hydroxy radical” and “carbon radical” (Hantzsch, 1891)
- Isomeric oximes were shown to give different constitutional products
  - *Cis* shift assumed because the groups are closer in space

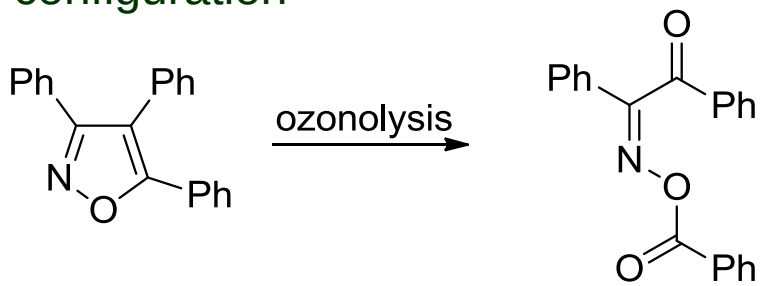



  - Mechanism unquestioned due to “inherent reasonableness”
    - Pfieffer (1904) and Bucherer (1914) suggested a *trans* shift
  - Reagents were simple catalysts of this process
- Until 1921, the *cis* shift assumption remained popular opinion
  - Used to identify the configuration of many ketoximes

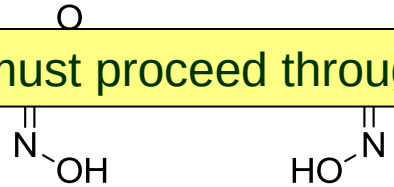

Hantzsch, *Ber*. **1891,** *24,* 13, 51
A. H. Blatt, *Chem. Rev.* **1933**, 215.

# Controversy in Configuration

- In 1921, Meisenheimer constructed a BKR-independent method of determining oxime configuration




- Beckmann had assigned the oximes based on the BKR



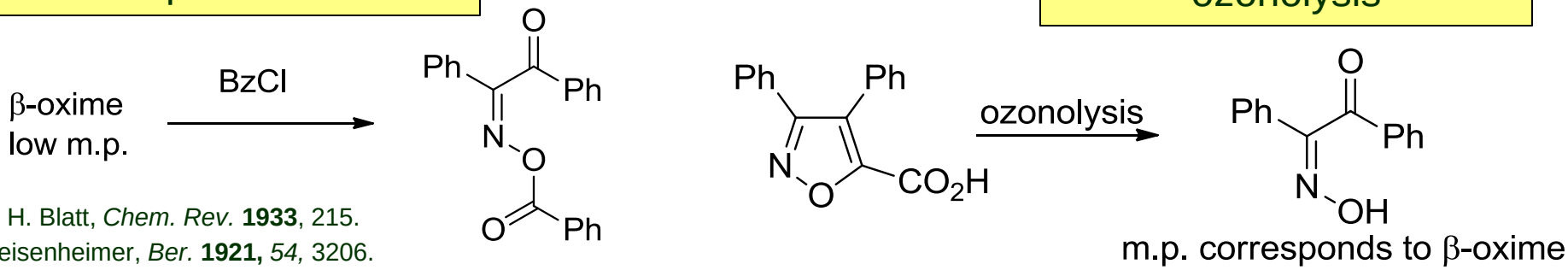

The BKR must proceed through a *trans* shift!

α-oxime
high m.p.

β-oxime
low m.p.

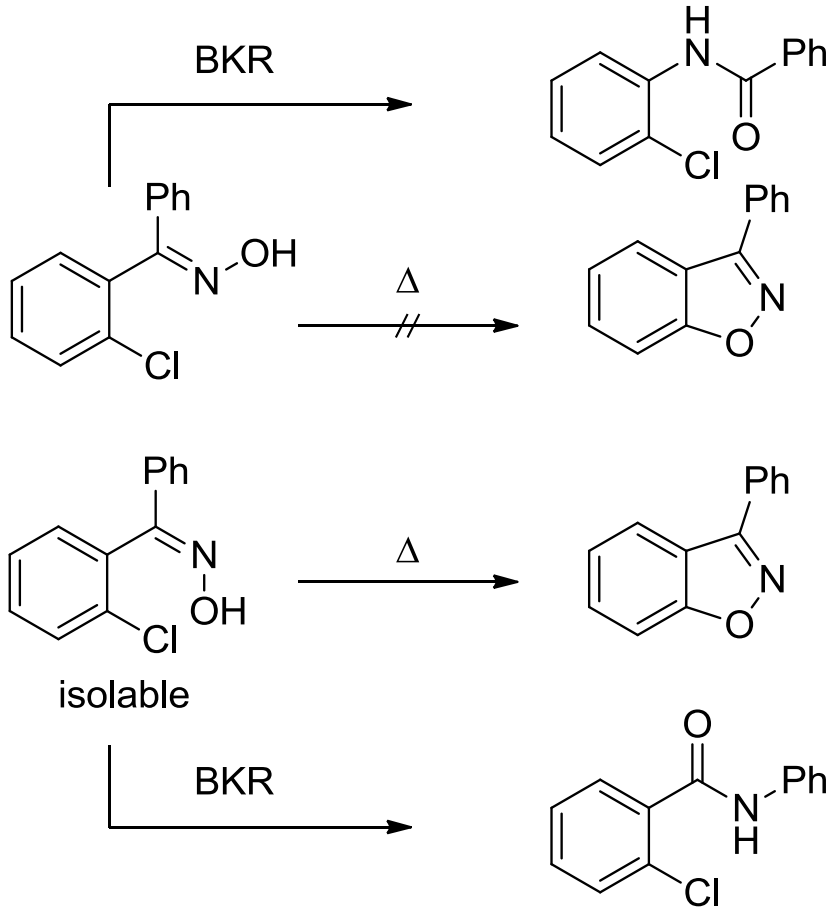
Benzoylation of β-oxime gave the Meisenheimer product

Meisenheimer was able to generate the oxime directly from an ozonolysis




A. H. Blatt, *Chem. Rev.* **1933**, 215.
Meisenheimer, *Ber.* **1921,** *54,* 3206.

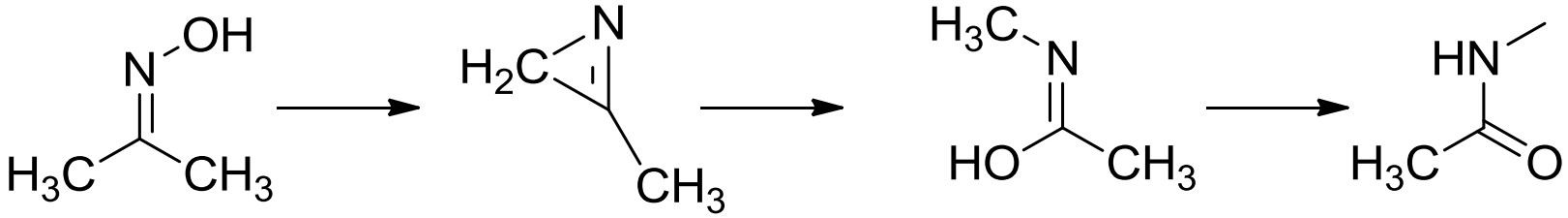
# Further Examples of Stereospecificity



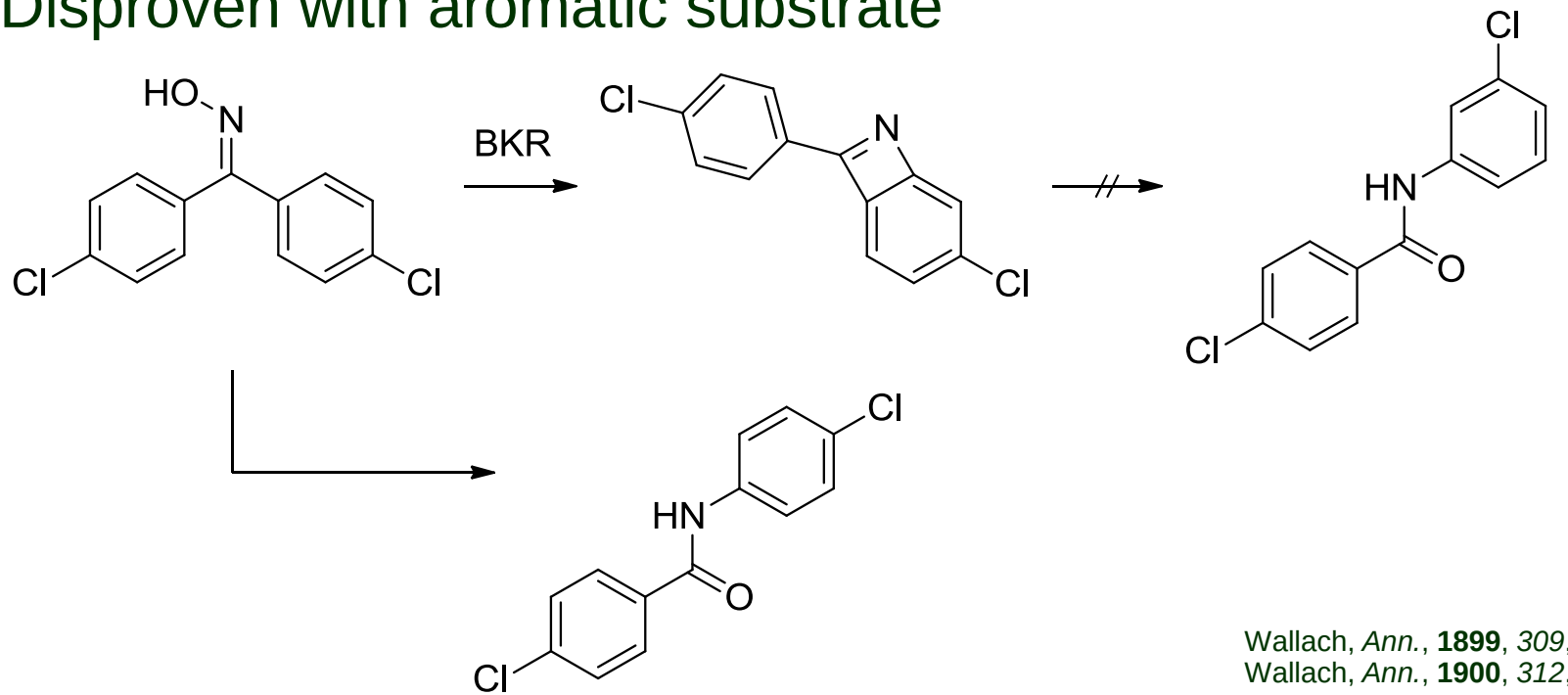

Meisenheimer, *Ber.* **1924,** *57,* 289.

# Kinetics and Mechanism (1933)

- Wallach



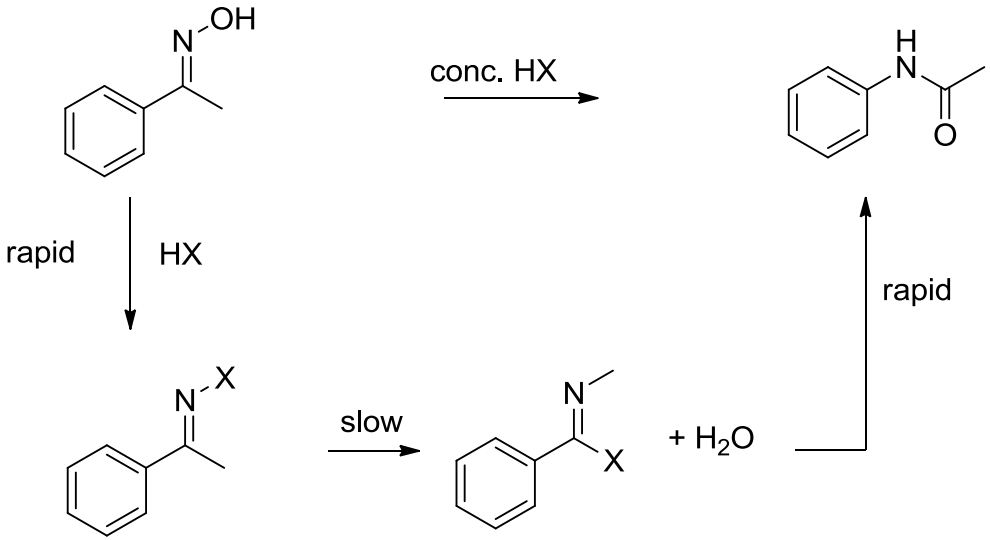

- Disproven with aromatic substrate




Wallach, *Ann.*, **1899**, *309*, 3
Wallach, *Ann.*, **1900**, *312*, 187
A. H. Blatt, *Chem. Rev.* **1933**, 215.

# Kinetics and Mechanism (1933)

- Sluiter kinetic data
  - BKR of acetophenone oximes is first order in oxime
  - Large temperature coefficient

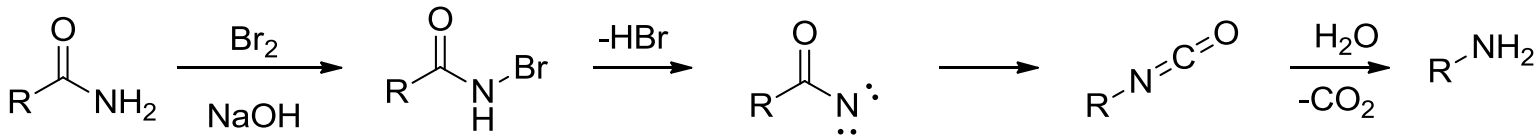



  - No supporting evidence for mechanism other than order of the reaction

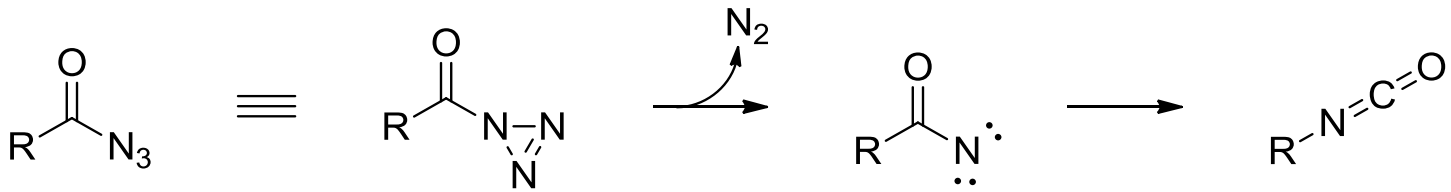
A. H. Blatt, *Chem. Rev.* **1933**, 215.
Sluiter, *Rec. trav. Chim.* **1905,** *25,* 372.

# “Univalent Nitrogen”
## Stieglitz

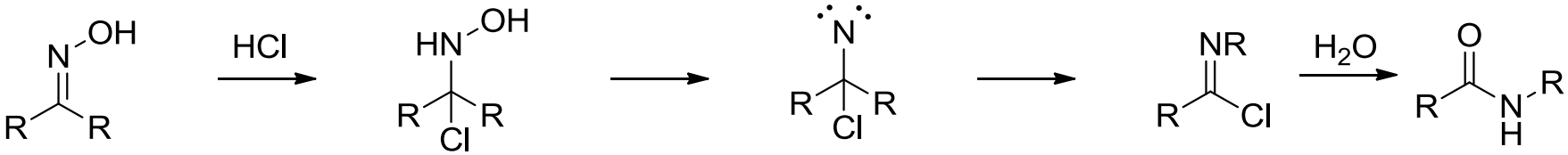
- Hoffmann




- Curtius




- Beckmann



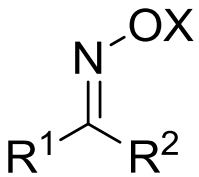

Stereospecificity would not arise from this mechanism!


Blatt, *Chem. Rev.* **1933**, 215.
Stieglitz, *Am. J. Chem.* **1896,** *18*, 751
Stieglitz, *Am. J. Chem.* **1910,** *43*, 782

# Oxime Ester Studies

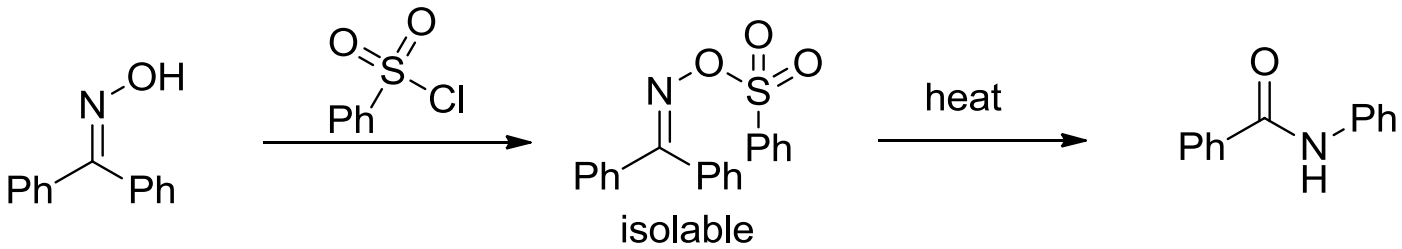
## Kuhara

- Postulated that acyl derivatives of oximes undergo rearrangement, not the original oximes

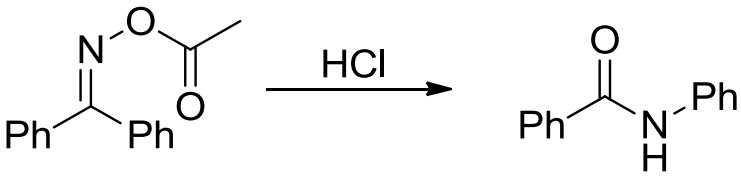



X must be EWG

- Careful synthesis of a variety of ester-like oxime compounds showed competency in the reaction
  - Spontaneous




  - Acid catalyzed

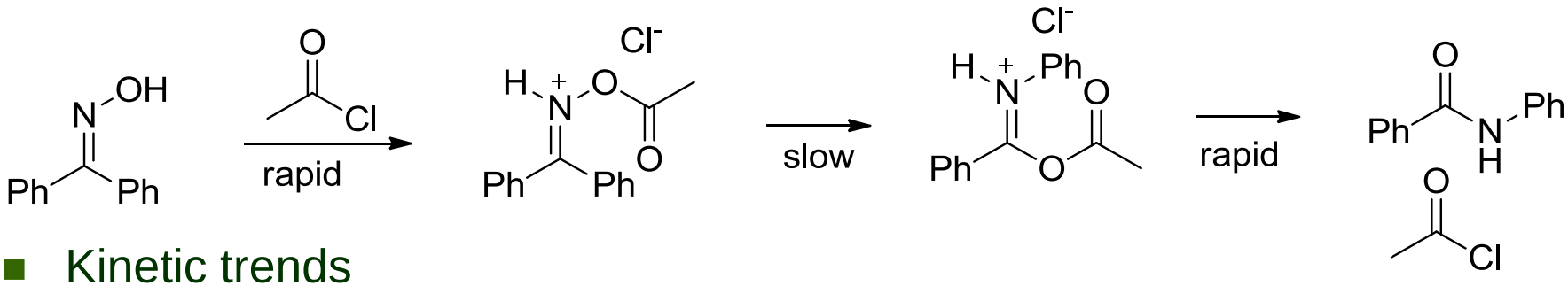




Blatt, *Chem. Rev.* **1933**, 215.
Kuhara, *Mem. Coll. Sci. Eng. Kyoto Imp. Univ.* **1906,** *1,* 25
Kuhara, *Mem. Coll. Sci. Eng. Kyoto Imp. Univ.* **1910,** *2,* 38
Kuhara, *Mem. Coll. Sci. Eng. Kyoto Imp. Univ.* **1914,** *1,* 10

# Kinetics of Oxime Ester Rearrangement

- Oximes treated with acetyl chloride undergo rearrangement




- Kinetic trends
  - Addition/Inc. HCl conc, inc. rate
  - Inc. “negativity” of acetyl group (lower pKa of conjugate acid), inc. rate. Sulfonyl esters rearrange without acid.

| Time | $CH_3COCl$ | $ClCH_2COCl$ | $C_6H_5SO_2Cl$ |
|---|---|---|---|
| 10 | 0.0% | 61.0% | 93.2% |
| 60 | 26.9% | 70.7% | - |
| 120 | 43.9% | 76.9% | - |


Blatt, *Chem. Rev.* **1933**, 215.
Kuhara, *Mem. Coll. Sci. Eng. Kyoto Imp. Univ.* **1906,** *1*, 254
Kuhara, *Mem. Coll. Sci. Eng. Kyoto Imp. Univ.* **1910,** *2*, 387
Kuhara, *Mem. Coll. Sci. Eng. Kyoto Imp. Univ.* **1914,** *1*, 105

# Summary

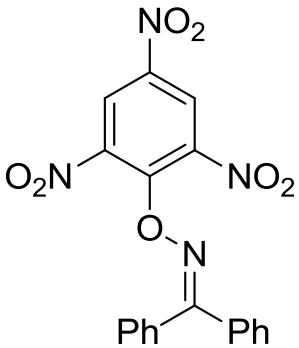
- Kuhara conclusions
  - If the “acid group” is sufficiently electron withdrawing, rearrangement will occur spontaneously. If not, salt formation is required to drive rearrangement.
  - Esters of oximes are capable of spontaneous rearrangement

- Problems:
  - Did not account for acid catalyzed BKR (without ester-like precursors)
  - Sulfonyl ester BKR products were oils that could not be purified or separated from sulfonic acids

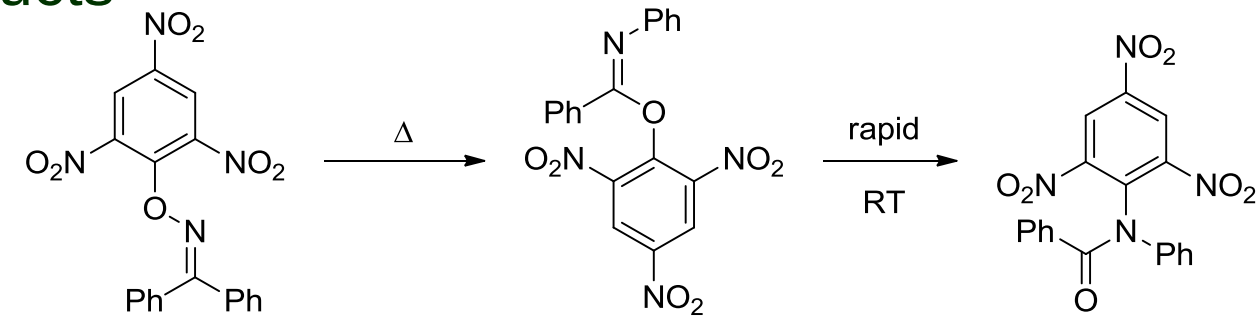
Blatt, *Chem. Rev.* **1933**, 215.
Kuhara, *Mem. Coll. Sci. Eng. Kyoto Imp. Univ.* **1906,** *1*, 254
Kuhara, *Mem. Coll. Sci. Eng. Kyoto Imp. Univ.* **1910,** *2*, 387
Kuhara, *Mem. Coll. Sci. Eng. Kyoto Imp. Univ.* **1914,** *1*, 105

# Oxime Picryl Ethers

- Chapman began to study the picryl ethers of oximes
  - Highly crystalline
  - Easy to isolate and purify



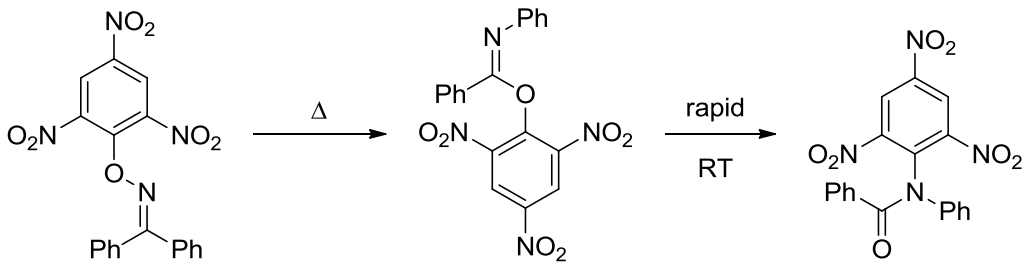

- Undergo spontaneous BKR upon heating to isolable products

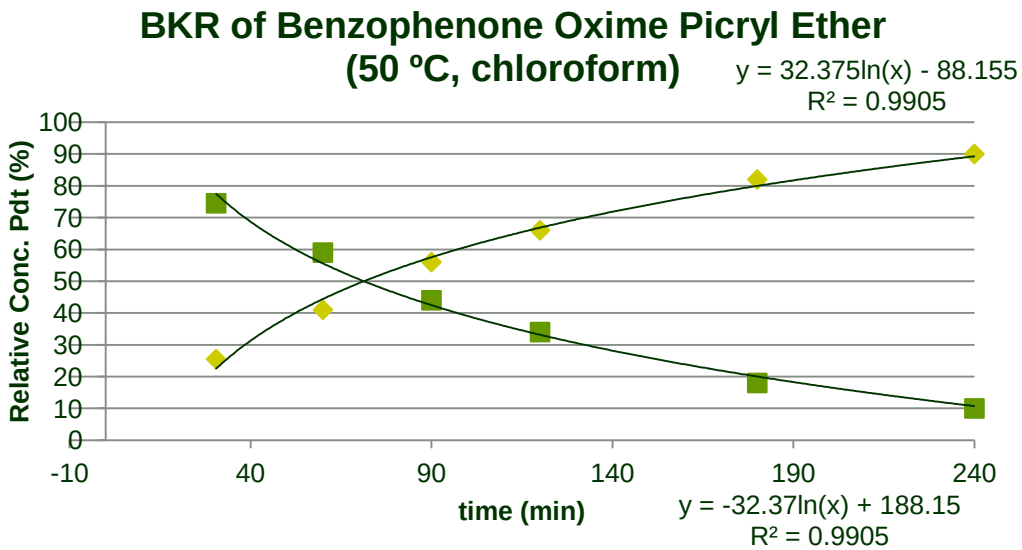



- Chapman suggests that sulfonyl esters go through similar process to the *N*-phenylsulfone

Chapman, *J. Chem. Soc.*, **1927,** 1743.
Chapman, *J. Chem. Soc.*, **1934,** 1550.

# Picryl Oxime Ethers Provide First Accurate Kinetics



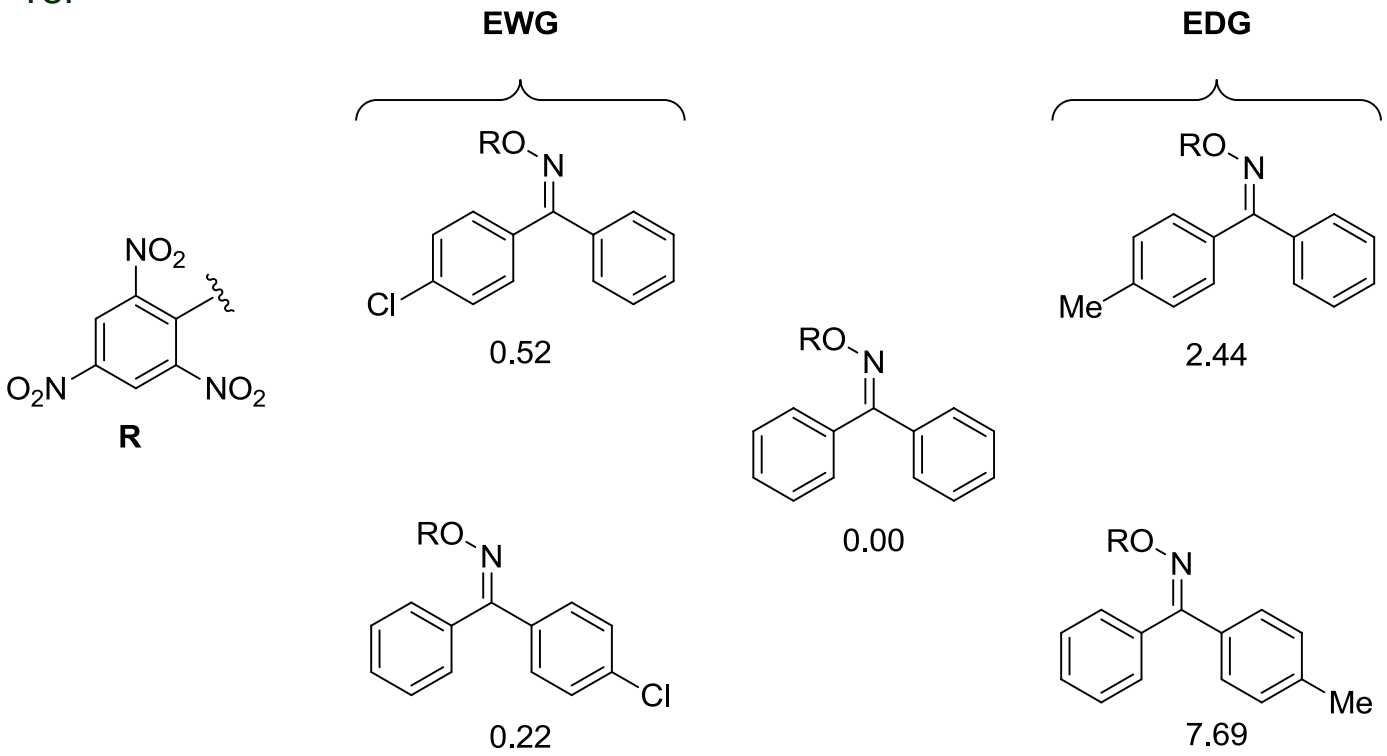

| Time (min) | $k_{obs}$(x10$^3$) |
|---|---|
| 30.5 | 4.2 |
| 60 | 3.8 |
| 90 | 3.95 |
| 120 | 3.9 |
| 180 | 4.15 |
| 240 | 4.1 |
| Avg | 4.0 |

- First order with respect to substrate
  - Unimolecular


Chapman, *J. Chem. Soc.*, **1935,** 1223.
Chapman, *J. Chem. Soc.*, **1935,** 1226.

# Substituent Effects

- $k_{rel}$

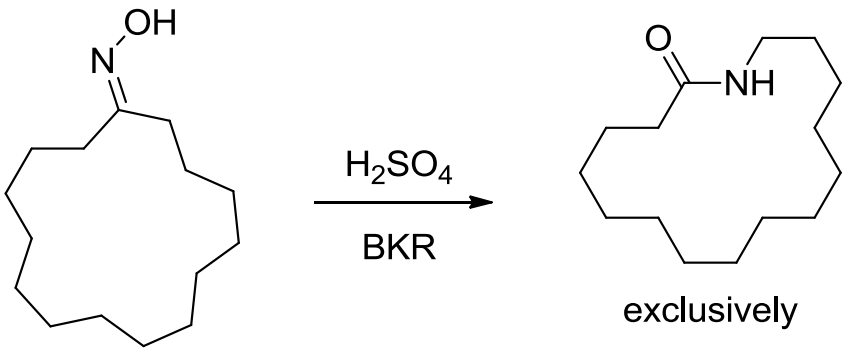



EWG retard reaction rate, while EWG accelerates
Effect is greater on the migrating group

Chapman, *J. Chem. Soc.*, **1935,** 1223.
Chapman, *J. Chem. Soc.*, **1936,** 448.

# Intramolecular or Intermolecular?

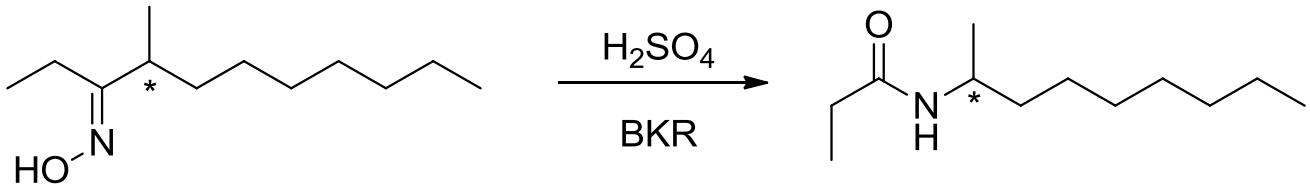
- Is the migrating carbon group kinetically “free”?
  - Entry of the migrating group into a separate molecule has never been observed
- Large ring expansion




exclusively

Unlikely that the ring opened as closure would be prohibitive

- Retention of stereochemistry




No loss of enantiomeric enrichment
No inversion of configuration

Kenyon and Young, *J. Chem. Soc.* **1941,** 263.

# Solvent Effects
## Picryl Oxime Ethers

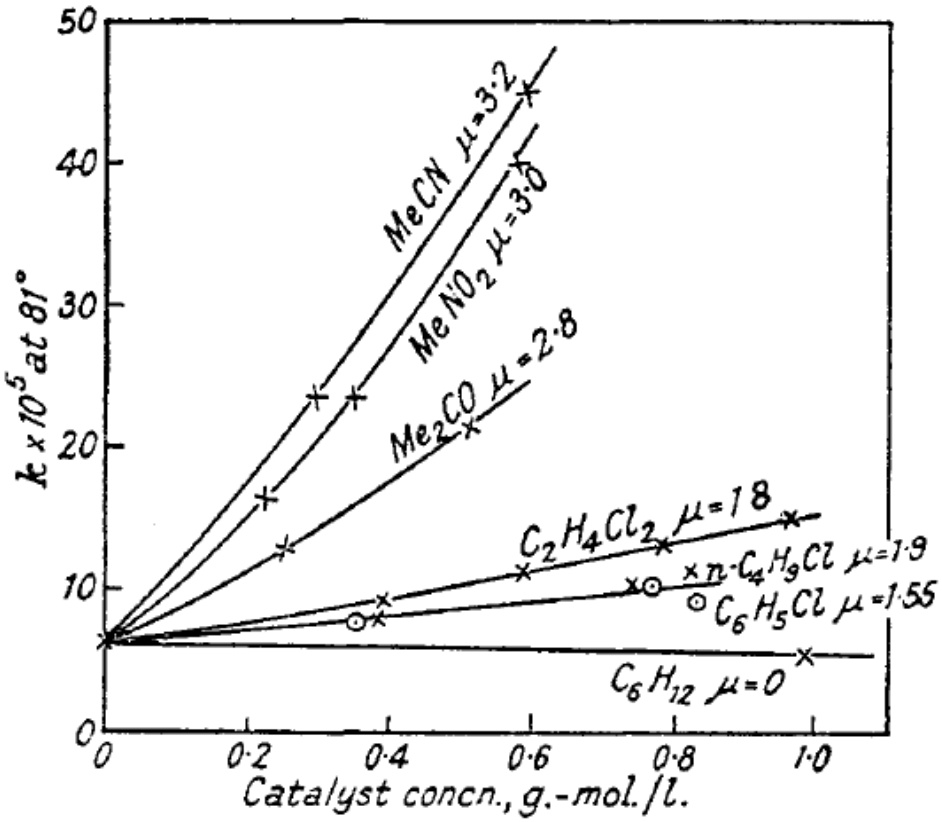
- Rate increases with increasing dielectric constant
  - $C_2H_4Cl_2 > CHCl_3 > CCl_4$
- Rate increases with increased concentration within solvent – first order kinetics
  - Discrepancy between energy of activation calculations and observed rates suggests catalytic activity of other solutes, and that their activity must be essentially equal.
    - Suggests oxime ether functions as a catalyst
  - Further experimentation showed significant discrepancy from observed rate and calculated $E_a$ based on substrate concentration/temp. rate data alone indicating catalytic effect of other solute/solvent molecules

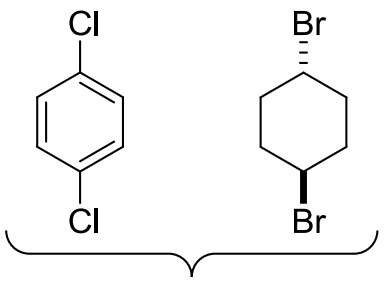
- If correct, it should stand to reason that the addition of "foreign polar molecules" should increase rearrangement rate

Chapman, *J. Chem. Soc.*, **1934,** 1550.

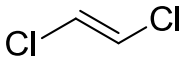
# Solvent Effects
## Polar Solvents as Catalysts

- Carbon tetrachloride as solvent doped with other solvents
  - Benzophenone oxime picryl ether rearrangement




non-polar, but individual dipoles far apart show rate enhancement

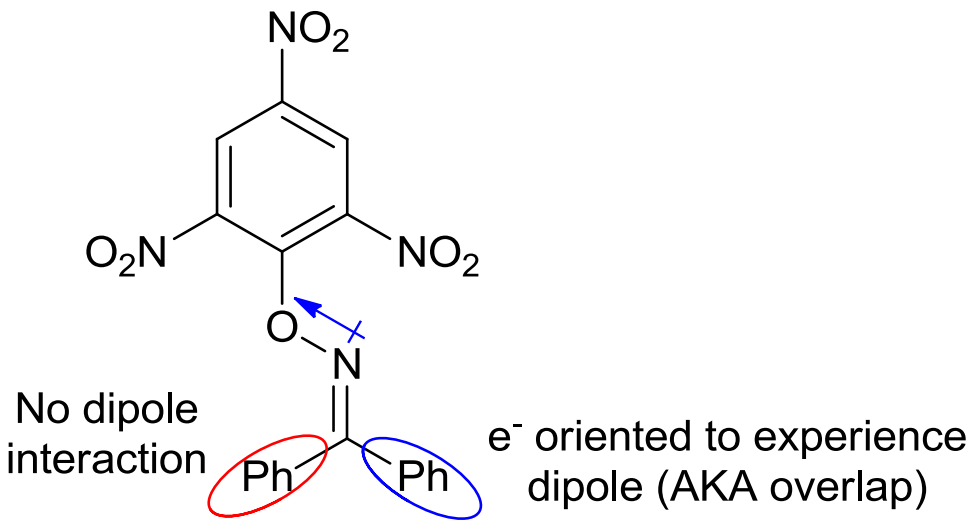


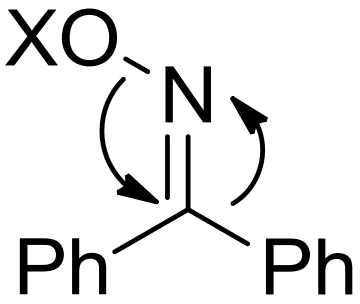

dipoles in close proximity
no rate enhancement observed

Chapman, *J. Chem. Soc.*, **1934,** 1550.

# Stereospecificity Explained

- 1944



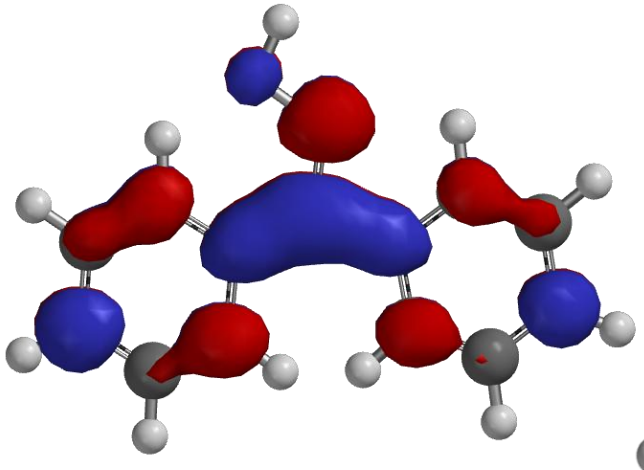

Nature of isomerization unclear

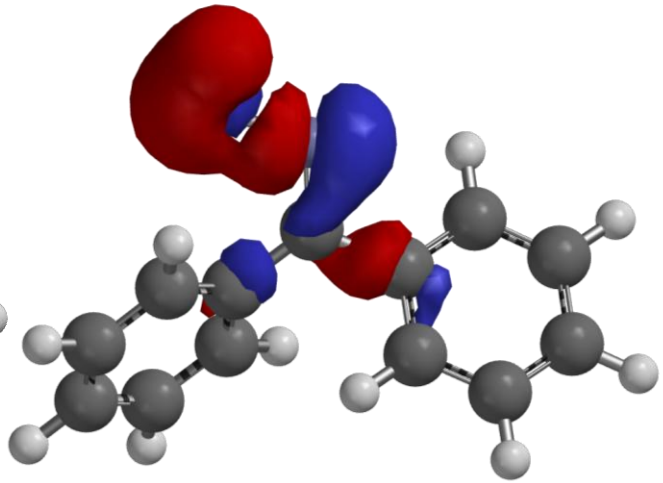
- Proposed as a concerted exchange
- The strength of the dipole dictates the energy required to force the rearrangement

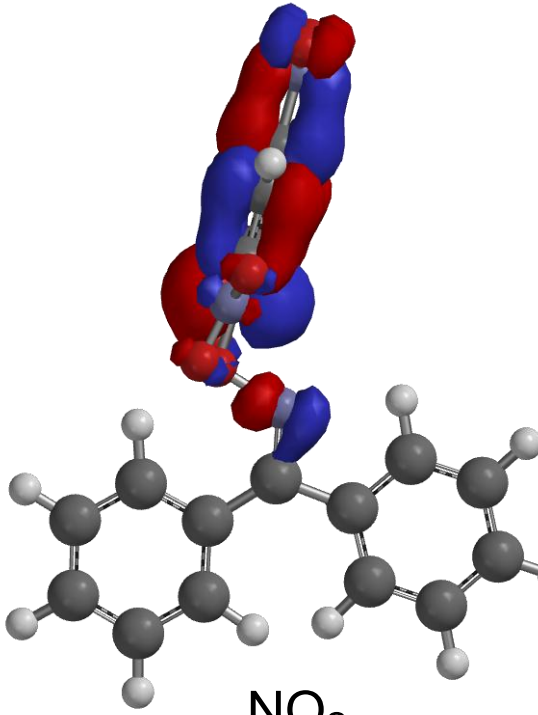
Jones, *Chem. Rev.* **1944,** 335

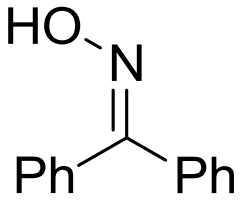
# Stereospecificity

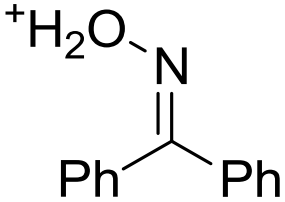
## FMO

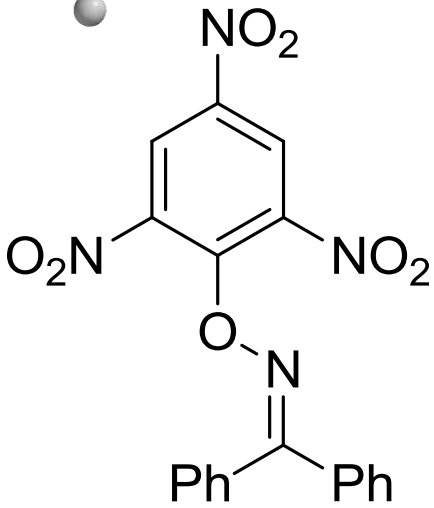








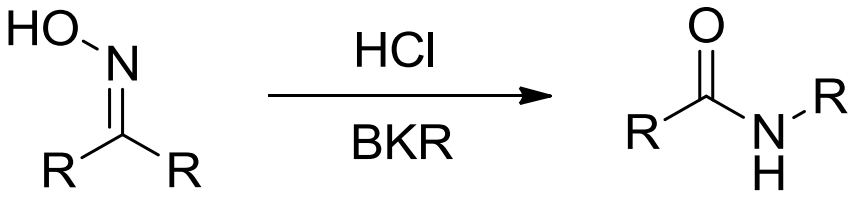



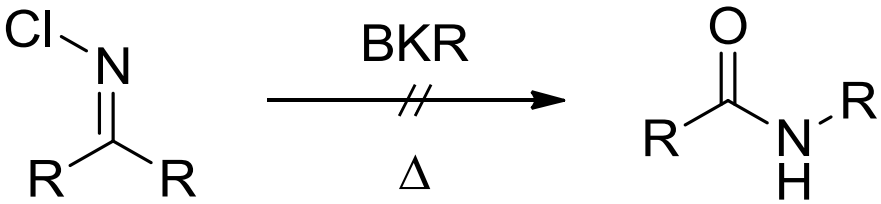

Addition of EWG on the oxime oxygen polarizes the LUMO contributions

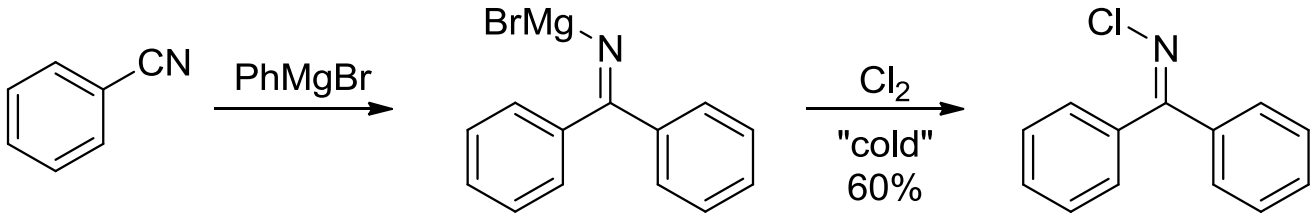
# The Problem of Acid-Promoted BKR

- How do mineral acids promote the rearrangement?




- *N*-chloroimines shown to be unable to rearrange



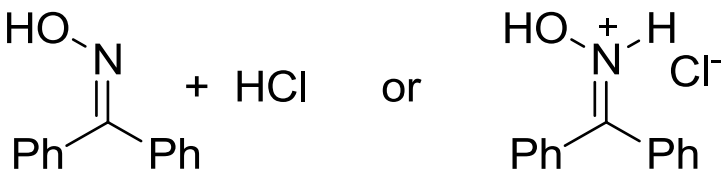




Stieglitz, *Am. Chem. J.* **1896,** *18,* 751.
Stieglitz, *J. Am. Chem. Soc.* **1914,** *36*, 272

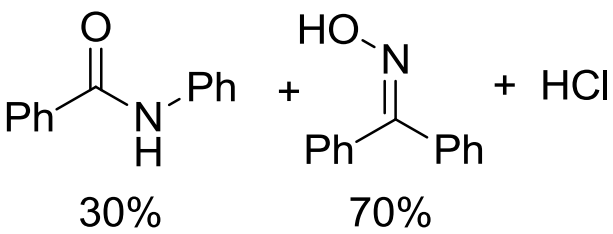
# Acid Catalysis

## HCl Kinetics

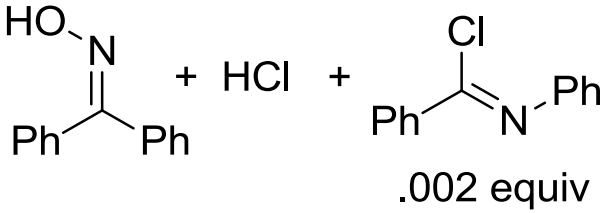
- **Curve I** (approx 0.4 eq HCl used)



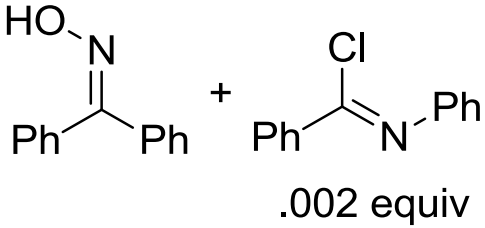

- **Curve II**

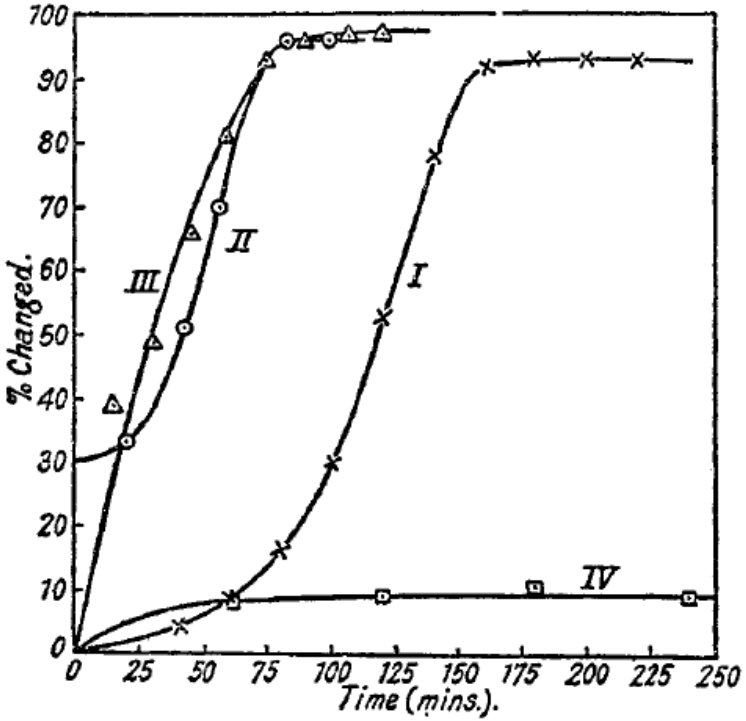


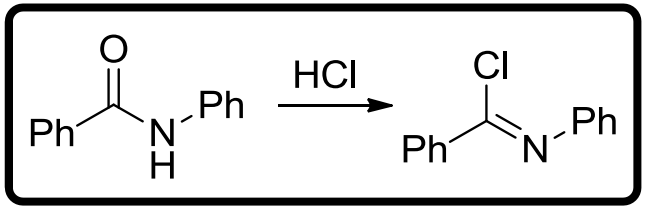

- **Curve III**




- **Curve IV**



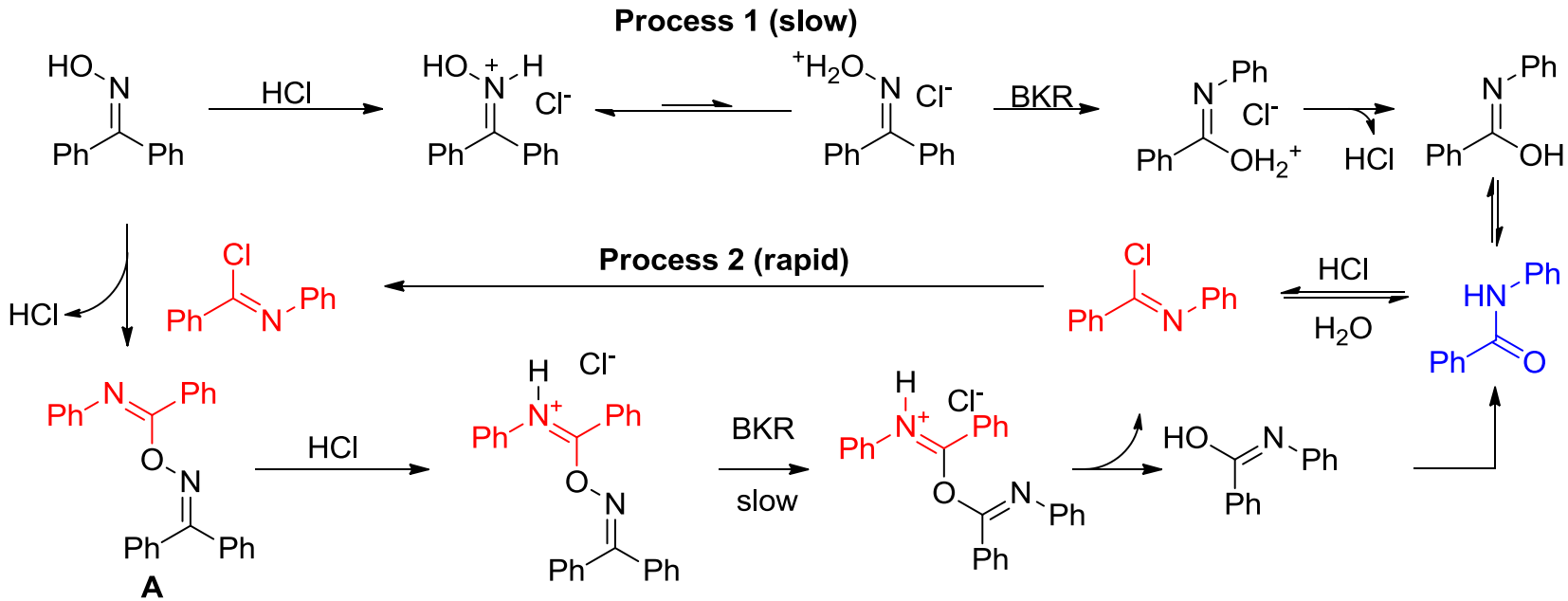




Chapman, *J. Chem. Soc.*, **1935,** 1223.
Chapman, *J. Chem. Soc.*, **1935,** 1226.

# Proposed HCl Catalysis Mechanism

- Chapman, 1935




Intermediate A was synthesized stoichiometrically and treated with aq HCl, and shown to convert quantitatively to product

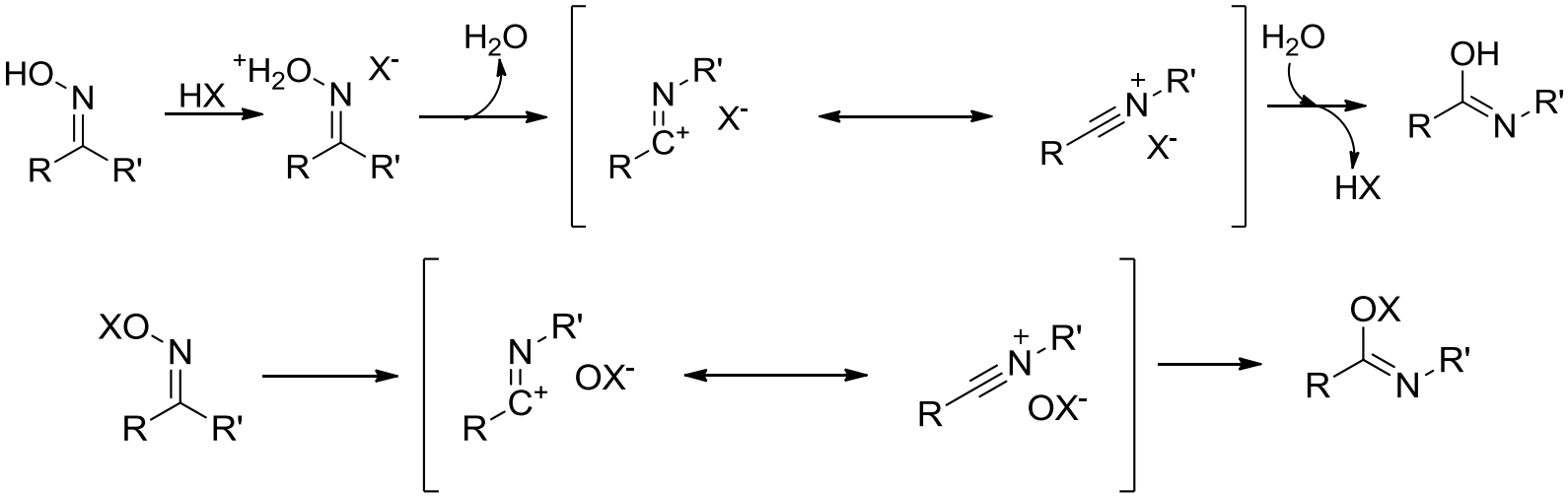
Chapman, *J. Chem. Soc.*, **1935,** 1223.
Chapman, *J. Chem. Soc.*, **1935,** 1226.

# Recap

- While many reagents catalyze the BKR, the mechanism likely requires the intermediate formation of an ester-like compound
- No evidence of dissociation of free ions in the mechanism
  - Migrating carbon is never kinetically free
- "…more needs to be discovered before the mechanism of this Mona Lisa of molecular rearrangements is fully understood" – Jones, 1944

# Introduction of Nitrilium Ion Intermediate

- Jones (Nature, 1946)
  - Recent reports had indicated $^{18}O$ incorporation into amides following $PCl_5$ catalyzed BKR – may arise from ionic intermediates

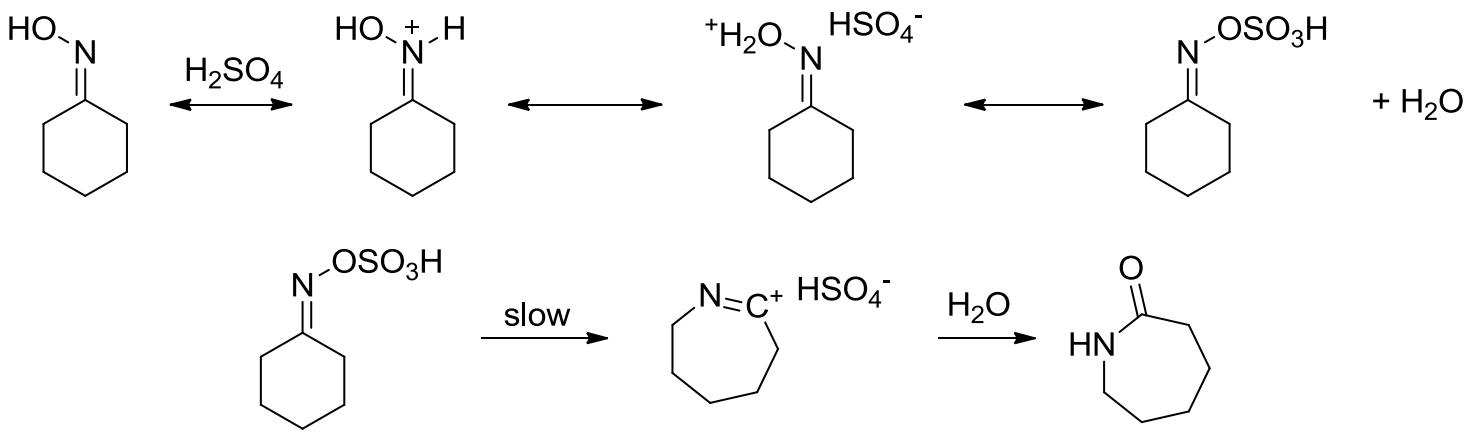



- If ionic intermediate is formed, it must be through a concerted process to preserve stereospecificity

Jones, *Nature*, **1946**, 519.

# Evidence of Nitrilium Intermediate

- Matsumoto (1955)

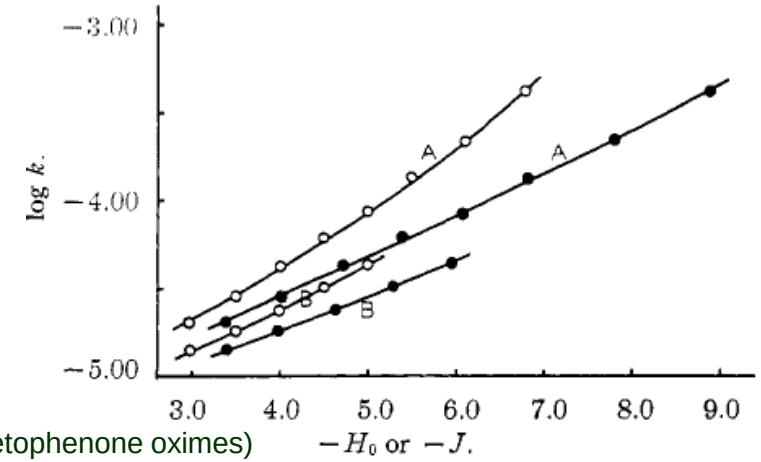



- Generated a potential kinetic equation for these steps, which condensed to a relationship between log k and the Hammett acidity property
- Derived eqn:

$$\log k = \log a_{H2SO4} - \log a_{H2O} + H_0 + const$$

$$H_0 = pKa + \log\left(\frac{c_B}{c_{BH+}}\right)$$

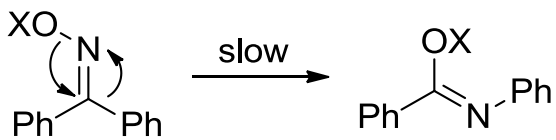
Observed data appear to support the derived relationship



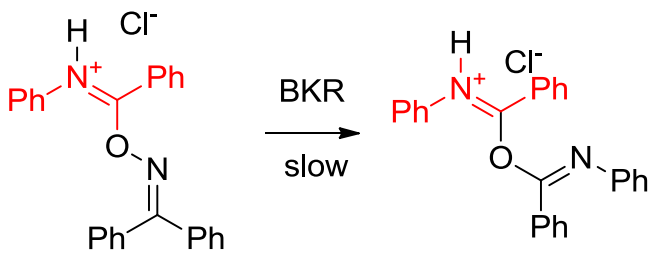

Matsumoto, *J. Chem. Soc.* **1955,** 4643. Schofield, *J. Chem. Soc.* **1970,** 338. (acetophenone oximes)

# Initial Evidence of Cationic Intermediate

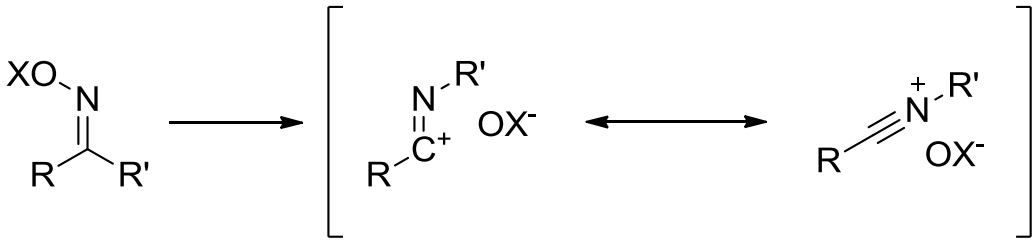
- Huisgen (1957)
  - ρ = -4.1
  - Build up of positive charge in the RDS transition state
- Review of RDS proposals
  - Kuhara – no dissociation

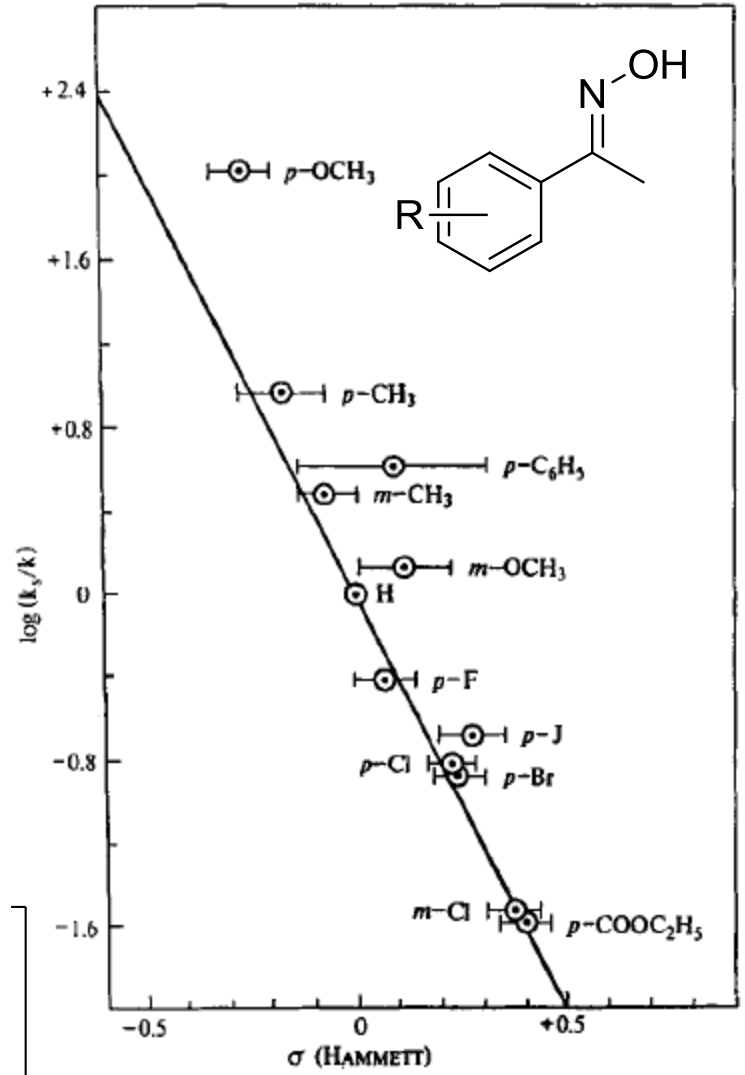



  - Chapman – no dissociation following isomerization




  - Jones – direct isomerization/ionization

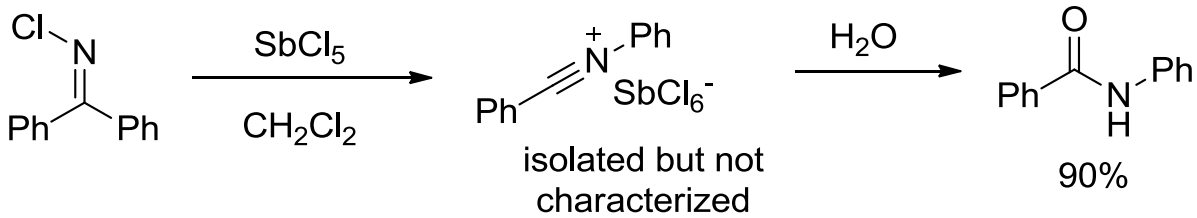


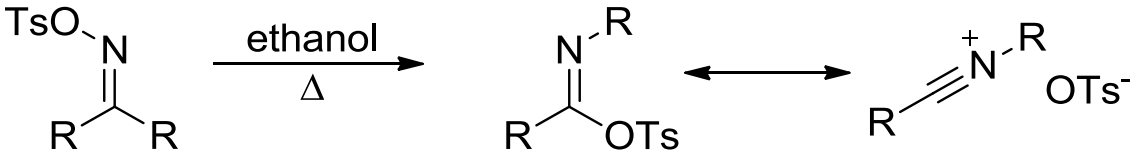

Huisgen, *Helv. Chim. Acta.* **1957,** 191

# Isolation of a Competent Intermediate

- First isolation of a “nitrilium salt” by Grob



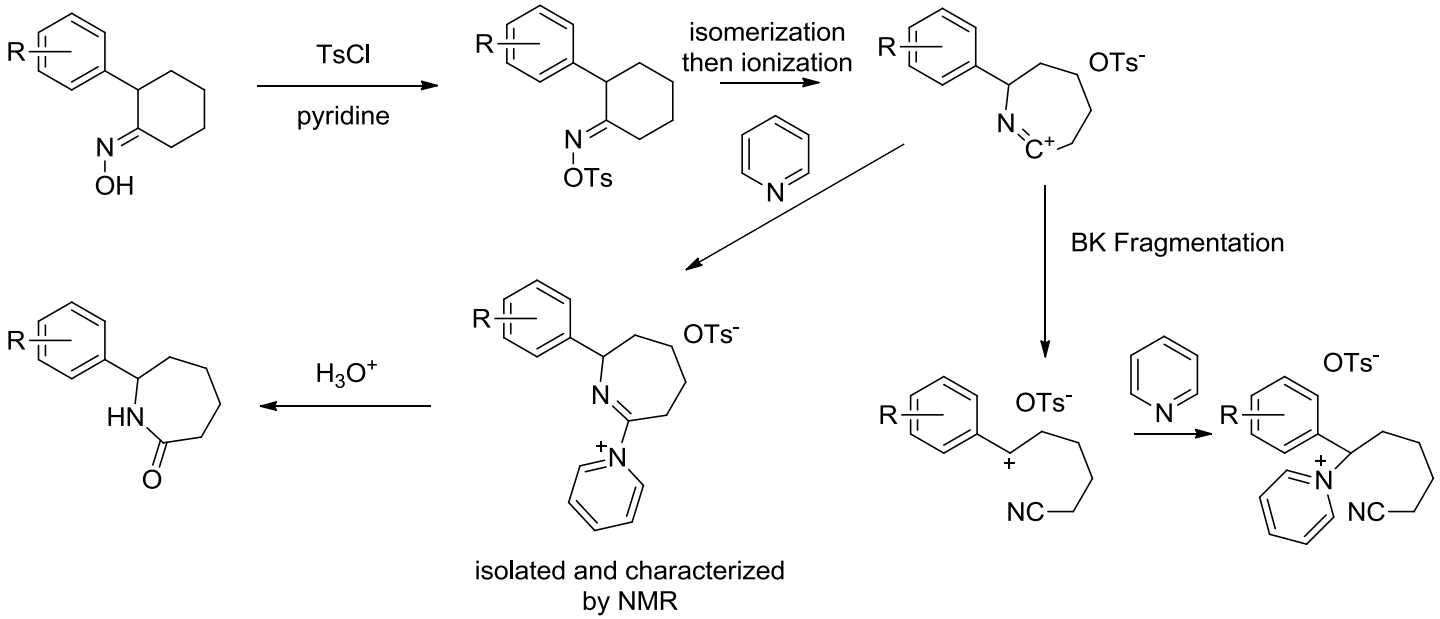

- Authors state competency in reaction precludes other intermediate structures
  - Recall: *N*-chloroimines do not undergo acid catalyzed BKR
- Futher kinetic studies indicate isomerization followed by ionization may be a stepwise course to the nitrilium cation



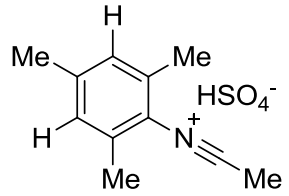

Grob, *Helv. Chim. Acta.* **1964,** *47*, 1003

# Further Support

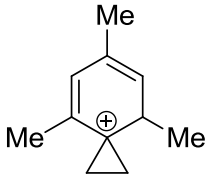
## Carbenium Ion Trapping and Observation



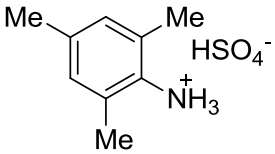

- R = EWG, fragmentation less favorable (stability of benzylic cation)
- o-methylacetophenone oxime
  - "More similar to anilinium than phenonium, and concluded to be nitrilium ion.."



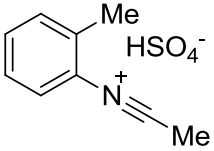

known
Ar-H 2.42 τ
Ref: TMS: 10.00 ppm




phenonium ion
2.34 τ




Anilinium Ion
Ar-H 2.00 τ

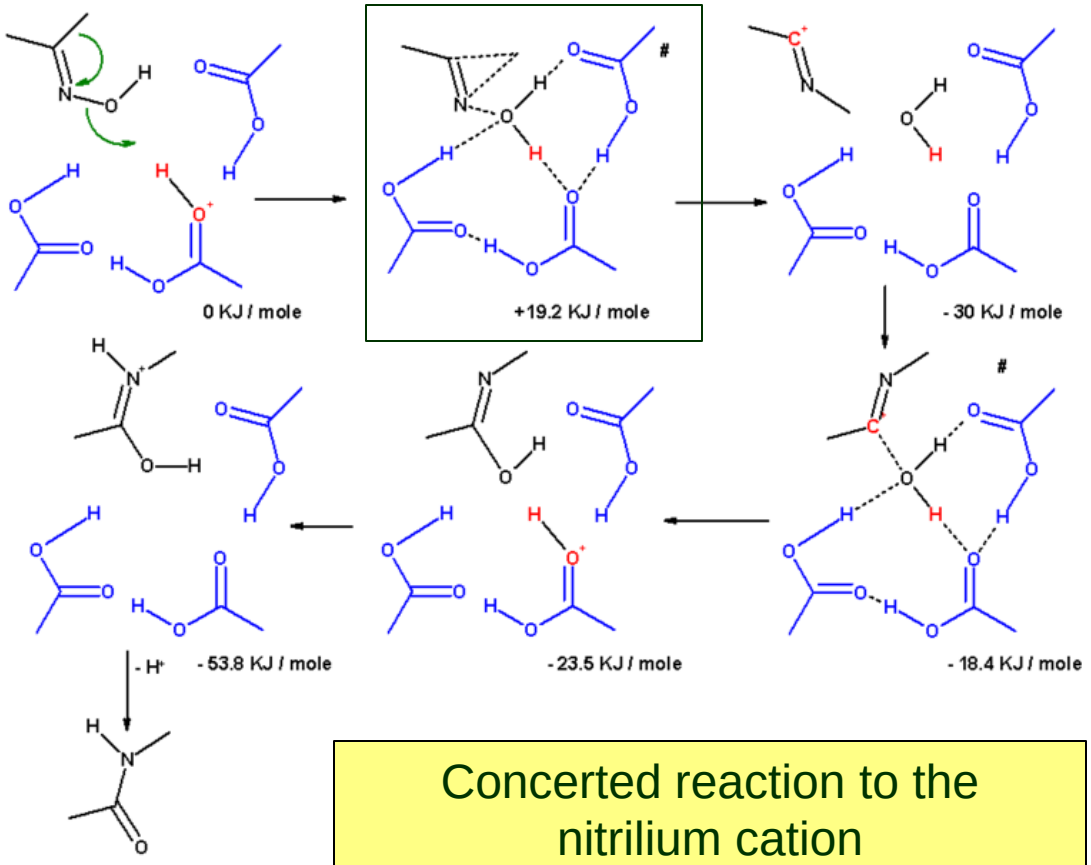



Observed Intermediate
Ar-H 2.1 τ
more similar to anilinium
than phenonium

Nelson, *JOC.*, **1969,** *1230*

# Concerted or Stepwise?

- Acetone oxime model $H^+(AcOH)_3$ (Beckman Solution)

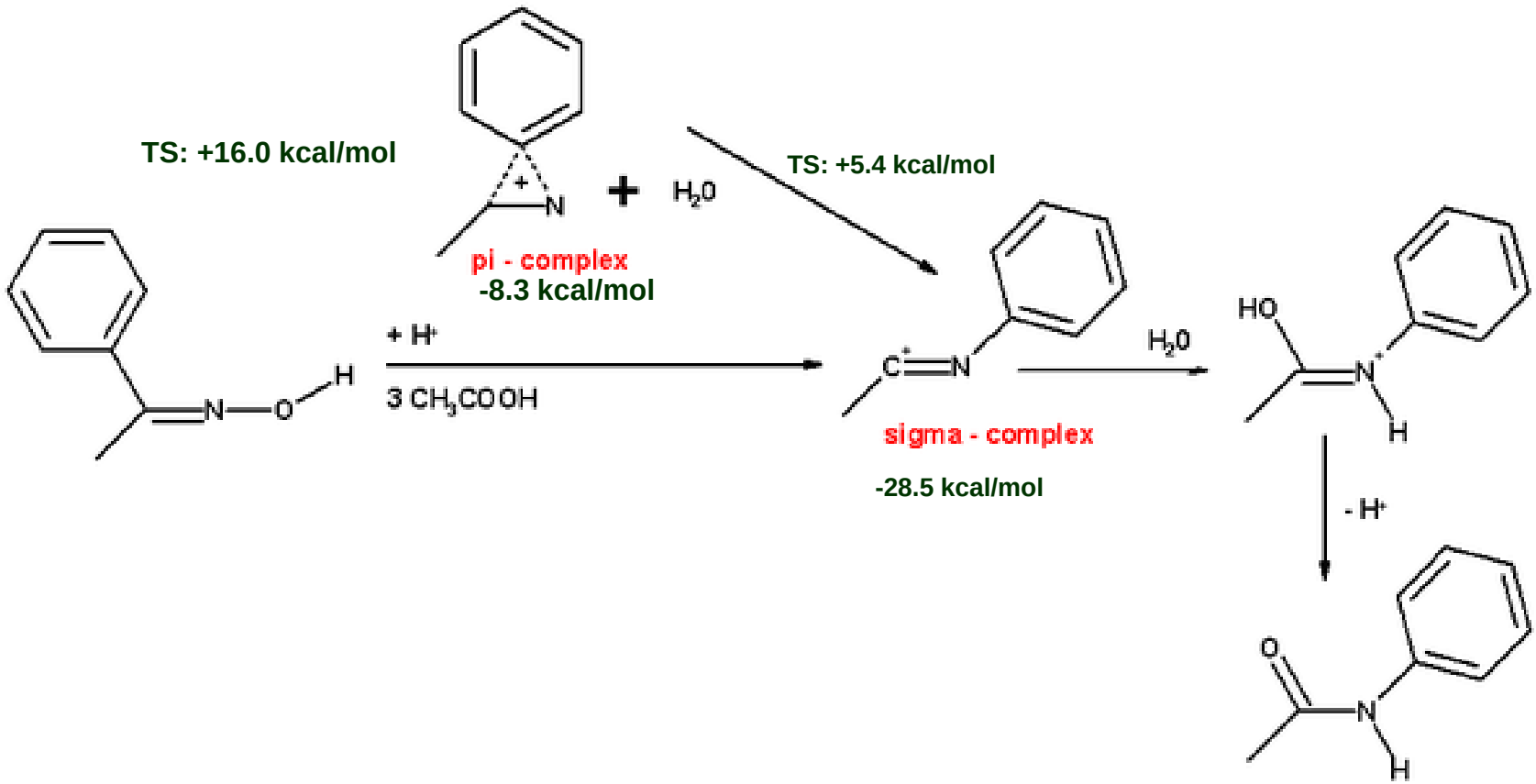



Concerted reaction to the nitrilium cation

Yamabe, *JOC.*, **2005,** *70*,10638.

# Concerted or Stepwise?

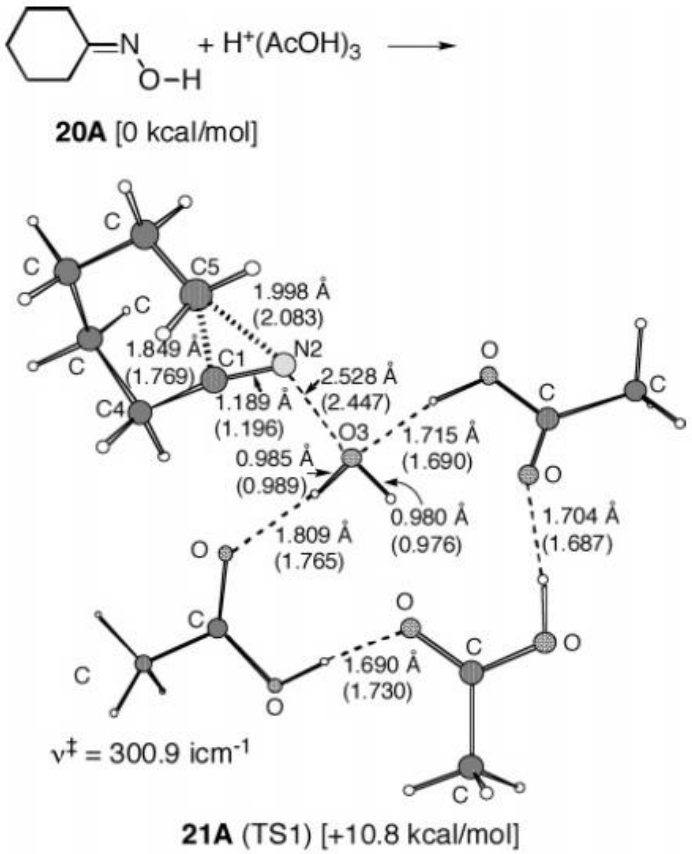
- Acetophenone Model $H^+(AcOH)_3$ (Beckman Solution)
  - Stepwise through pi-complex to nitrilium ion (sigma-complex)

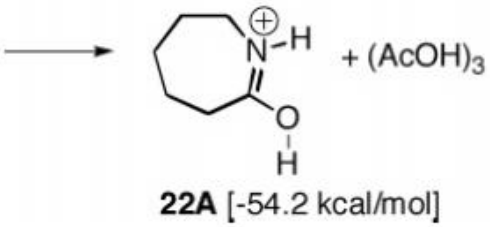



Yamabe, *JOC.*, **2005,** *70*,10638.

# Concerted or Stepwise

- Cyclohexanone model $H^+(AcOH)_3$ (Beckman Solution)



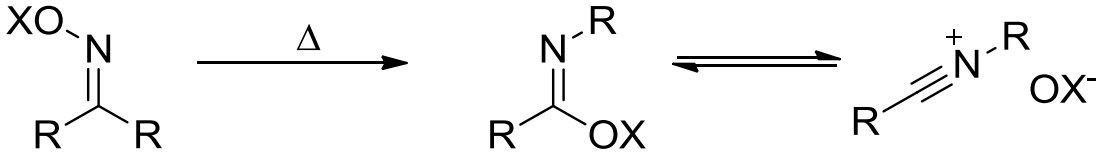

Concerted directly to protonated caprolactam due to relief of ring strain

Yamabe, *JOC.*, **2005,** *70*,10638.

# Classic BKR

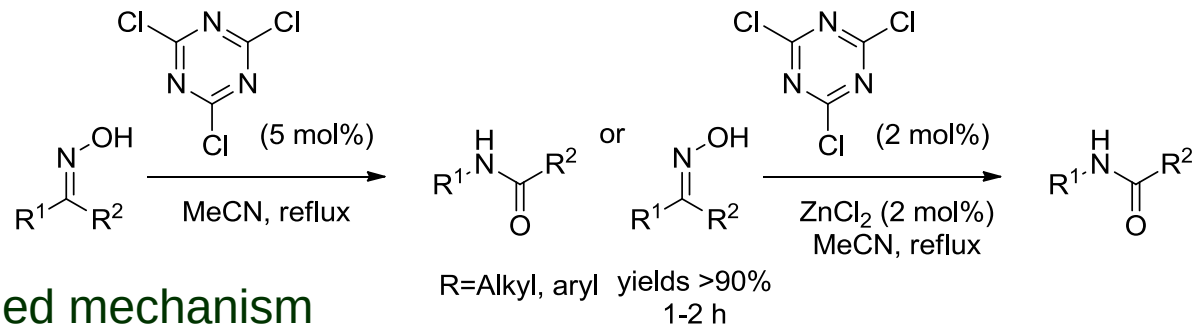
## Summary

- Rearrangement is a stereospecific *trans* shift
- Rearrangement occurs through an ester-like oxime intermediate (either EWG reagent or autocatalysis)
- The migrating carbon group is never kinetically free
  - Migration of chiral group does not decrease ee
- The migration step involves an isomerization followed by ionization to a nitrilium ion intermediate
  - Stabilization of this intermediate enhances rate (solvent, R properties)
- The isomerization/ionization step is a spectrum of step-wise and concerted processes

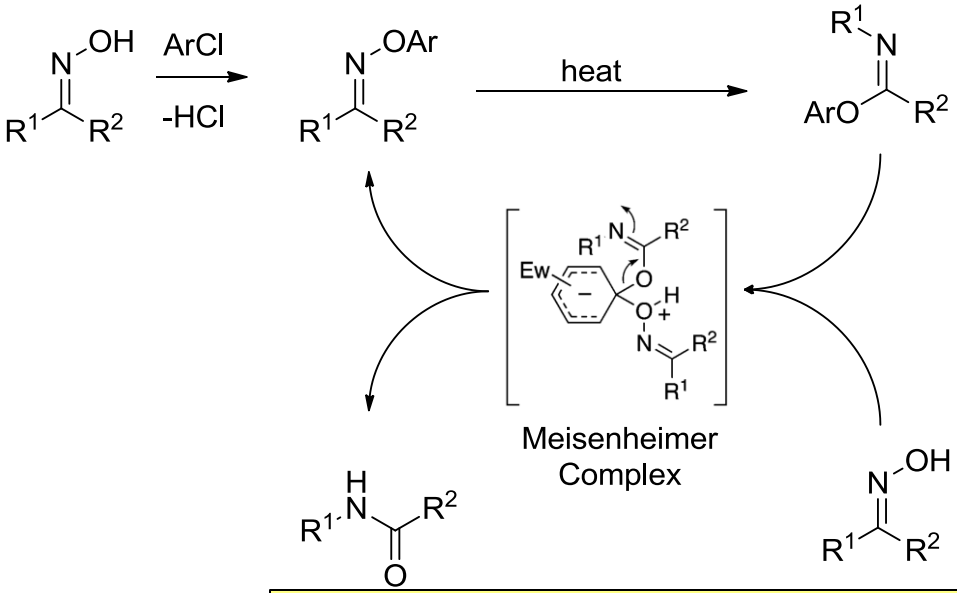


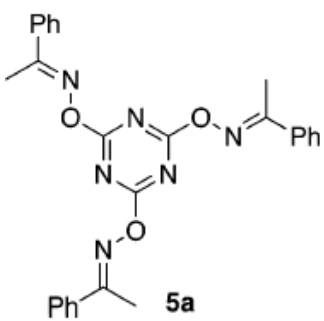
# Organocatalyzed BKR

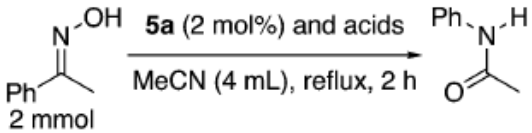
- First example, advertised as a milder method




- Proposed mechanism




| acids (mol%) | yield (%) of acetanilide |
|---|---|
| – | 2 |
| HCl (6) | 68 |
| $ZnCl_2$ (2) | 12 |
| HCl (6) + $ZnCl_2$ (2) | 96 |

5a requires addition of acid to act as a catalyst

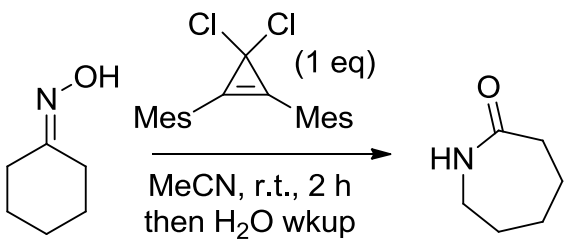
Propose Grob type isomerization but not ionization

Ishihara, *JACS*, **2005**, *127*, 11240

# Other Organocatalysts Lead To Mechanistic Questions

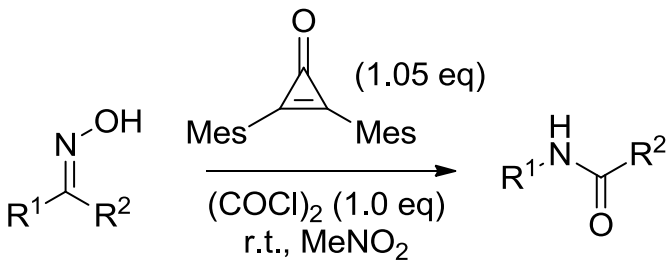
## Cyclopropenium Promoted

- Stoichiometric



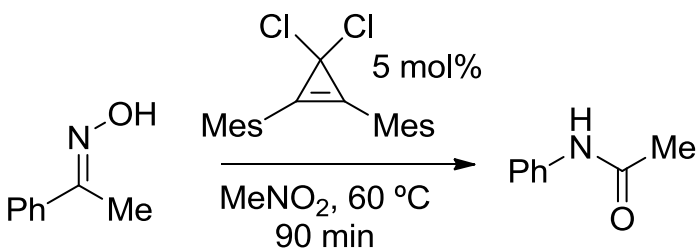

95%

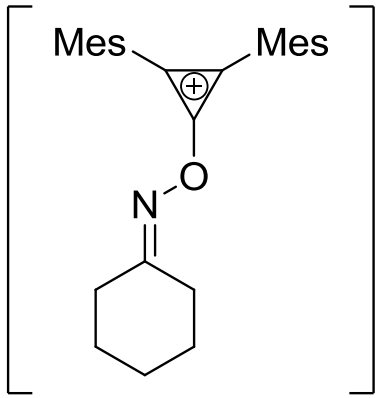
*In situ* generation prior to addition of oxime




10 ex, 85-99%

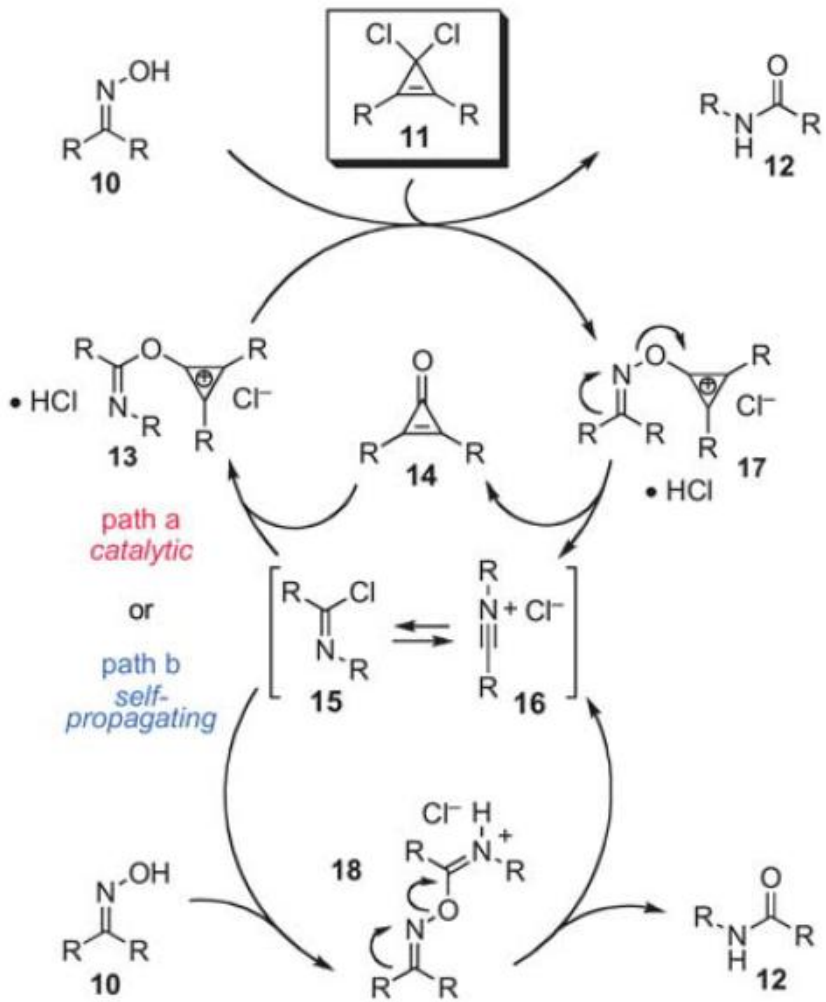
- Catalytic

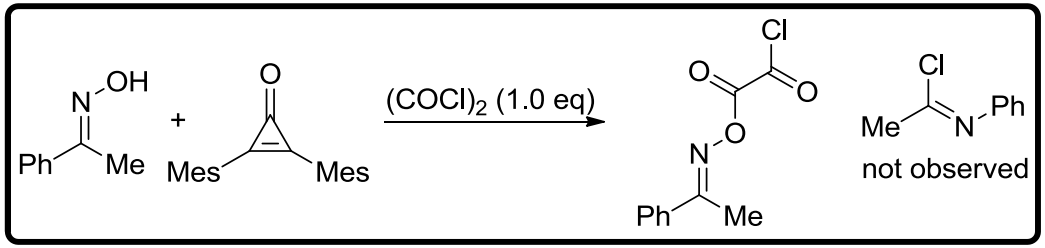


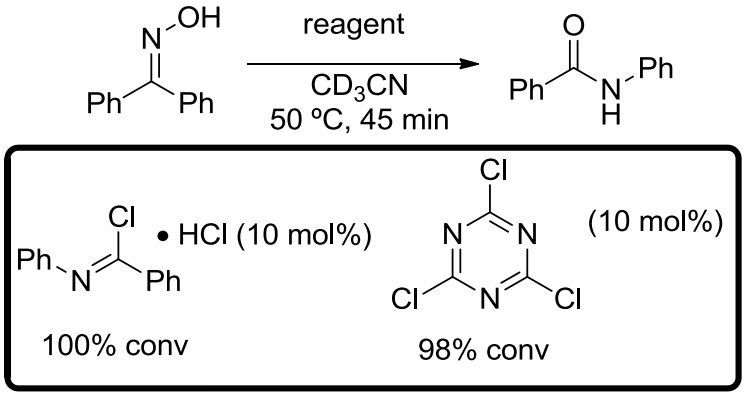

Lambert, *Chem. Sci.* **2010**, *1*, 705

# Catalytic Mechanism




Competition exp. shows cyclopropenone not nucleophilically competitive with oximes

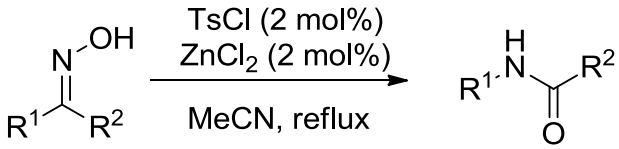



Essentially same rate for these catalysts
Recall: This is the catalytic species
Chapman proposed (1935)

Lambert, *Chem. Sci.* **2010**, *1*, 705

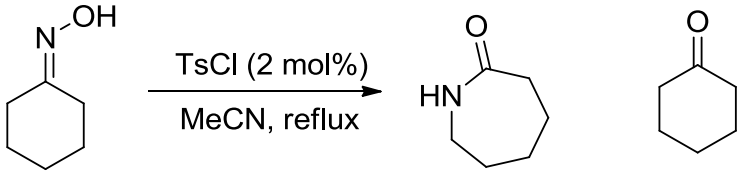
# Investigation of TsCl Catalysis

- Initially reported in 2009



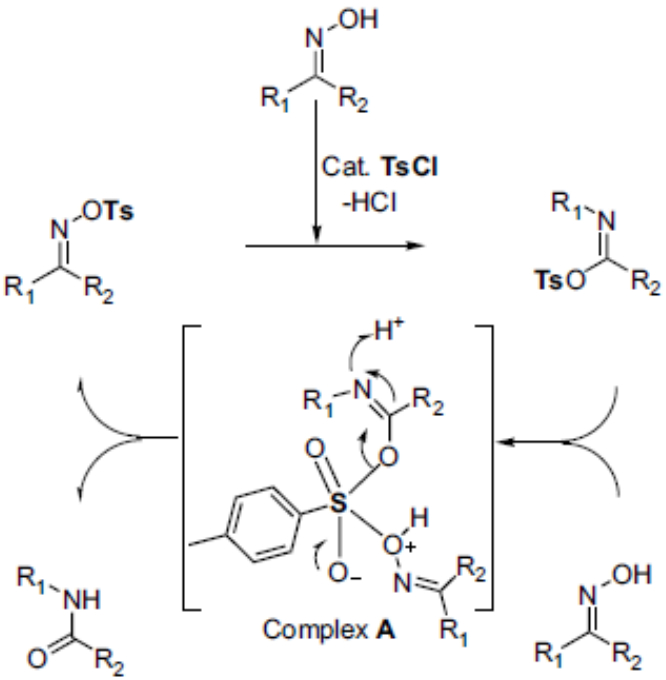

yields >90%
14 ex
Alkyl, aryl groups

- Major limitation



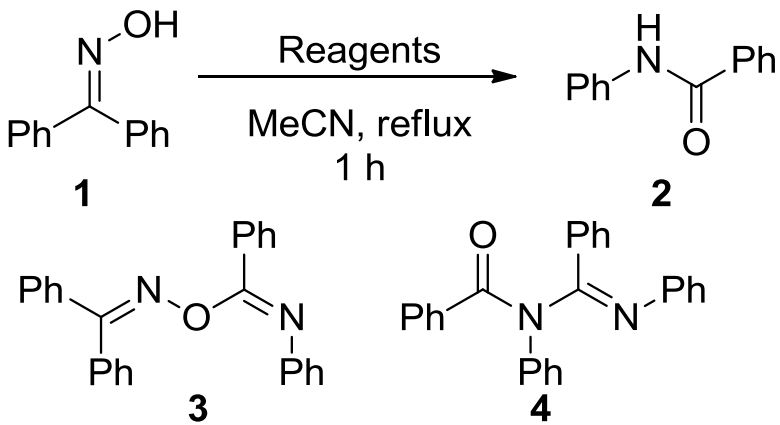

trace pdt 12%

  - Required 30 mol% loading of TsCl
  - Similar results seen with BOP-Cl, cyanuric chloride




Deng, *Tetrahedron*, **2009**, *65*, 7790.

# Reinvestigation of TsCl

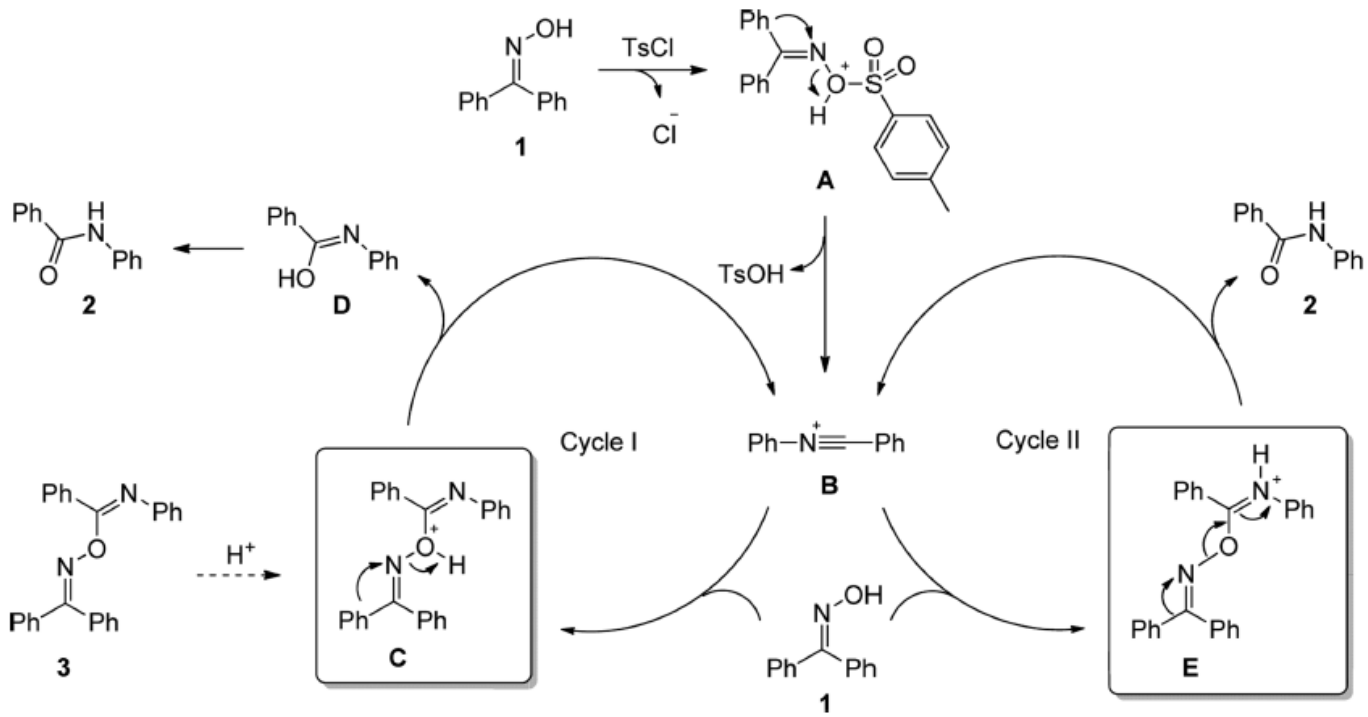


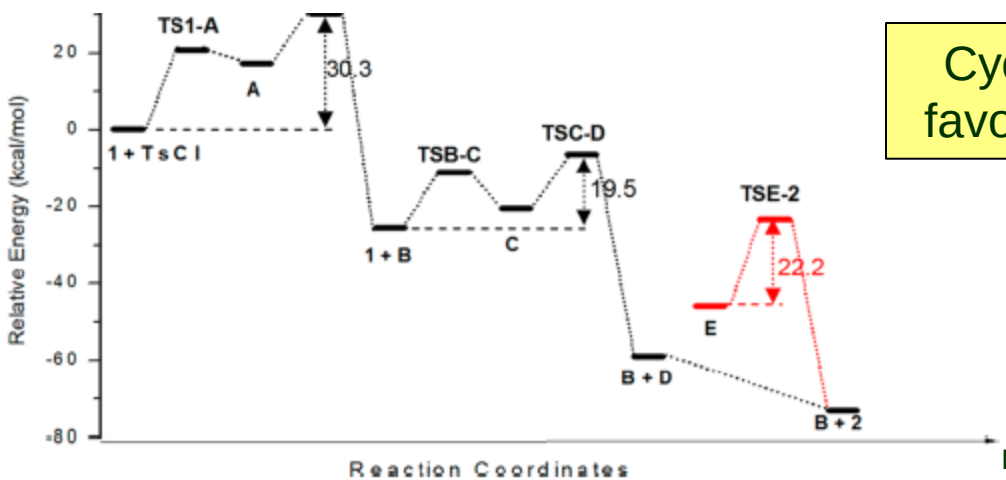

| Entry | Reagent (mol%) | Conv of 1 (%) | Yield of 4 (%) |
|---|---|---|---|
| 1 | 3 (10) | 0 | - |
| 2 | HCl (10) | 46 | - |
| 3 | 3 (10) + HCl (10) | 92 | 12 |
| 4 | TsCl (2) | 100 | - |

Authors also state an $^{18}O$ experiment that disproves the Meisenheimer complex Mechanism proposed by Ishihara, though it is unpublished

Deng, *JOC*, **2013** *78* 4297

# Proposed Mechanism: TsCl

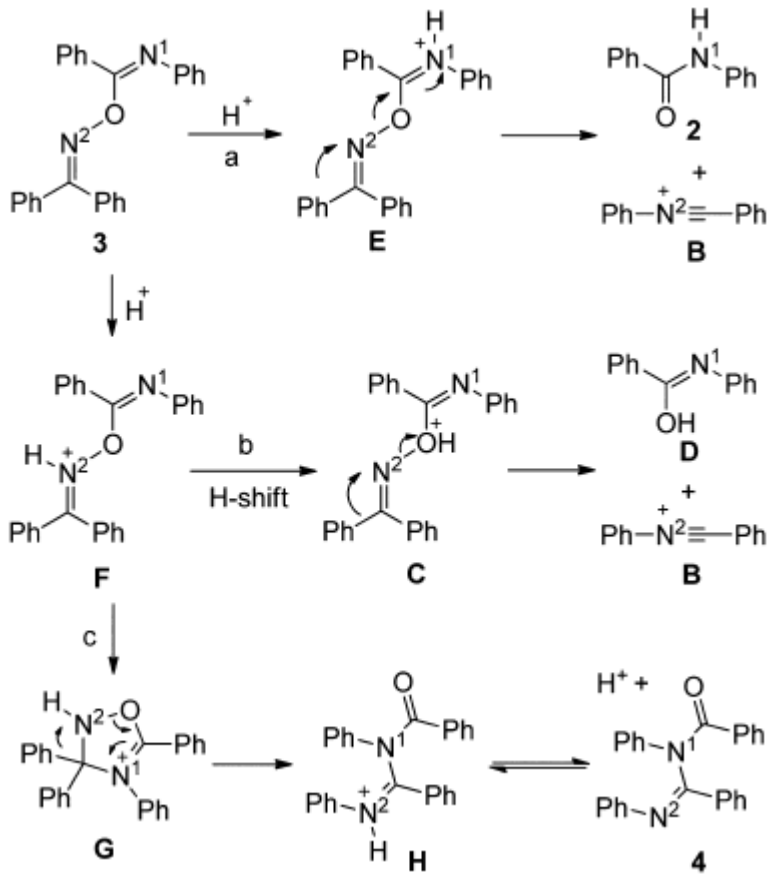


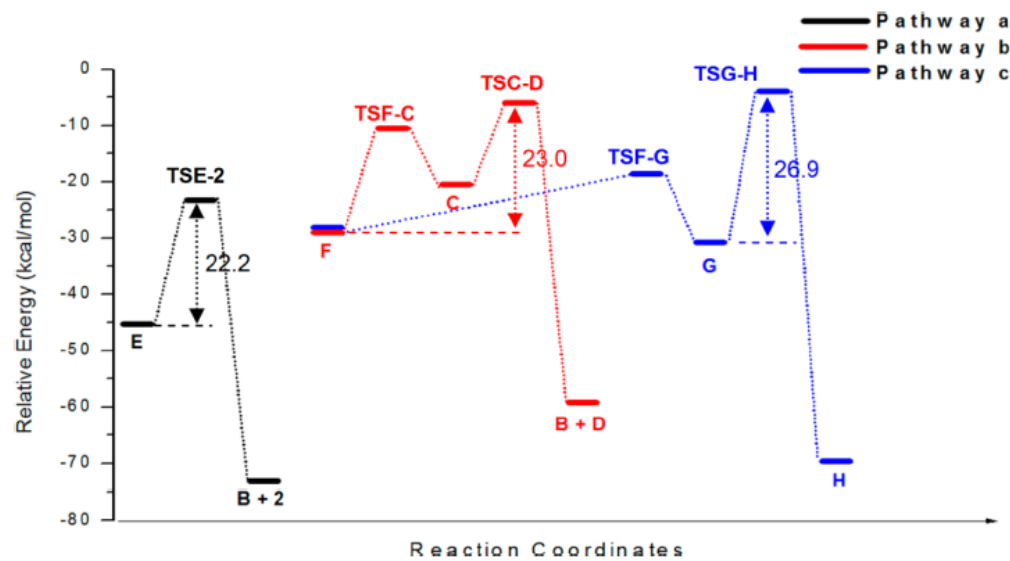




Cycle I the more favorable pathway

Deng, *JOC*, **2013** *78* 4297

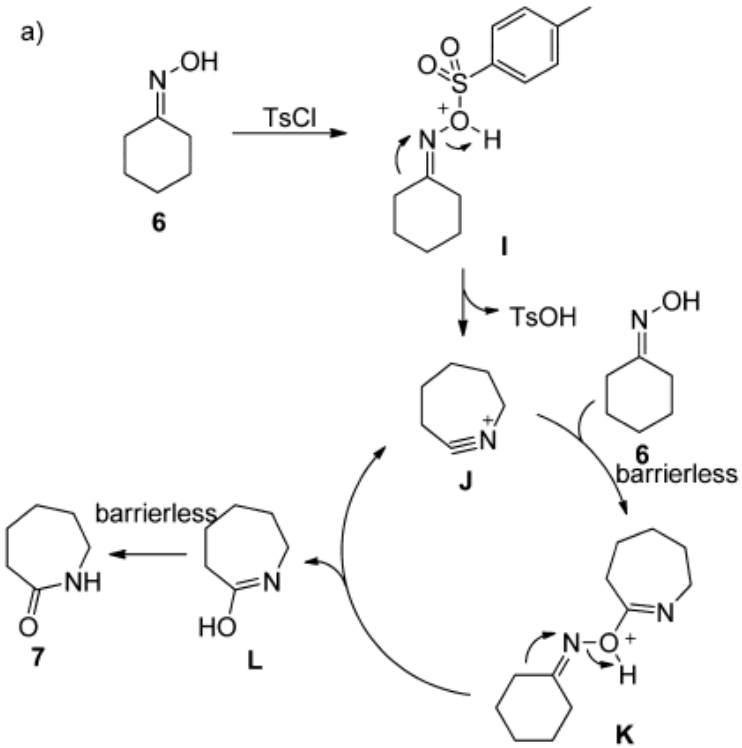
# Proposed Mechanism: HCl

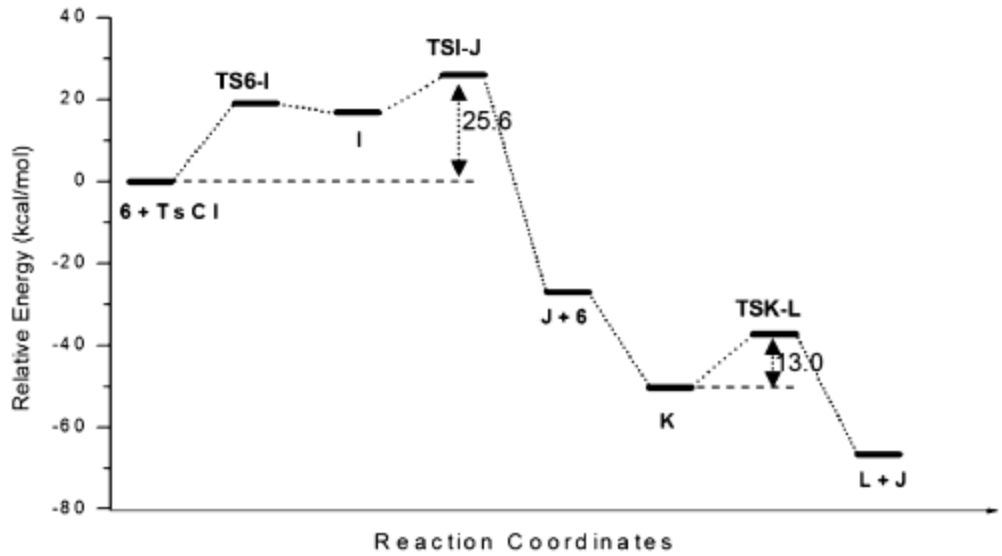


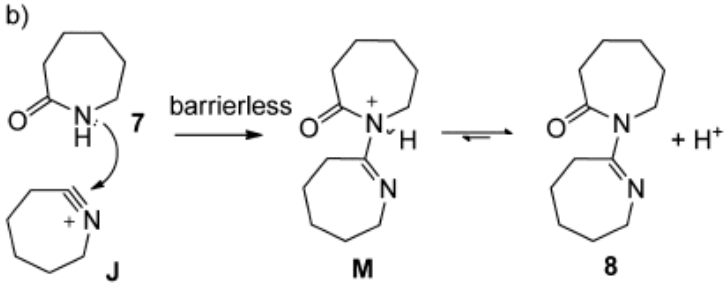



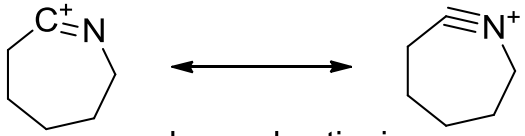

Deng, *JOC*, **2013** *78* 4297

# Organocatalyzed Cyclohexanone Oxime BKR



enhanced cationic character at carbon due to ring strain

**Sequestration of nitrilium ion leads to poor conversion**

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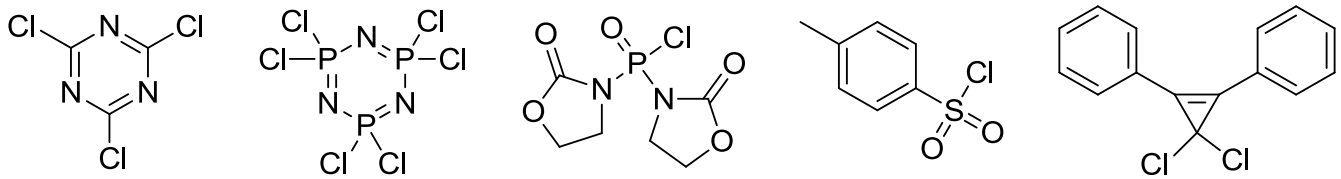
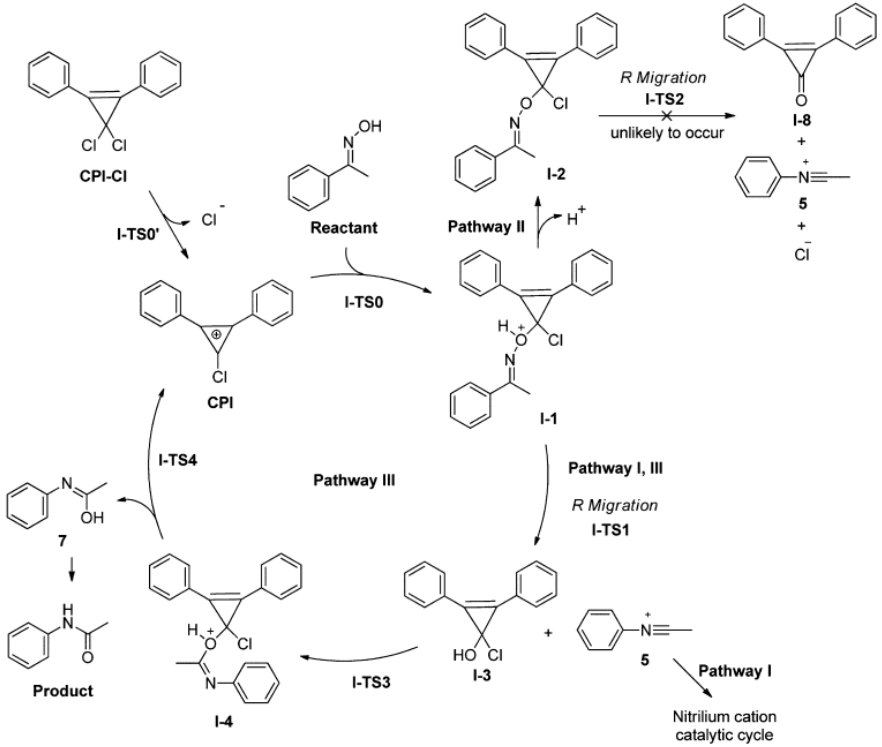
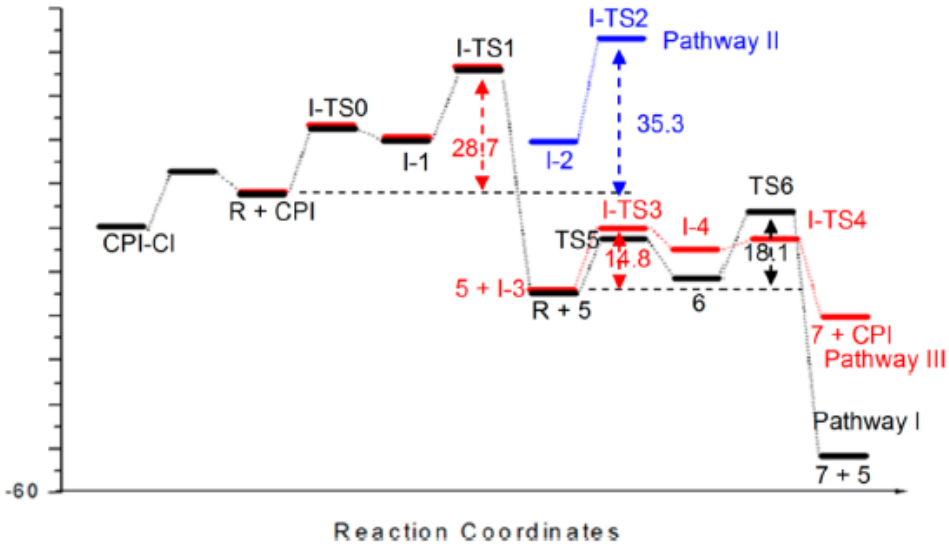
# Generality of Self-Propagation Mechanism



CNC TAPC BOP-Cl TsCl CPI-Cl

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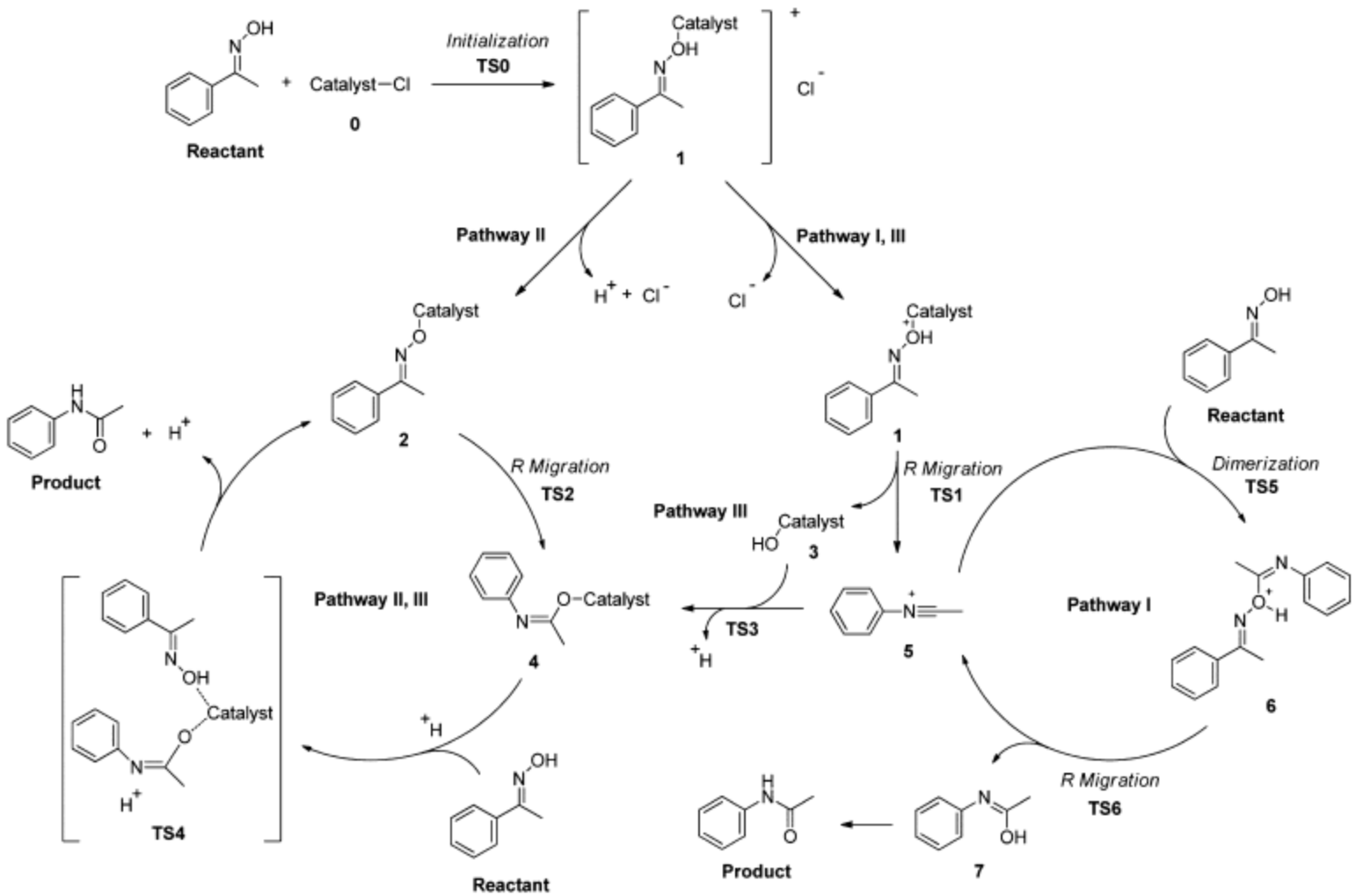
# Organocatalyzed BKR

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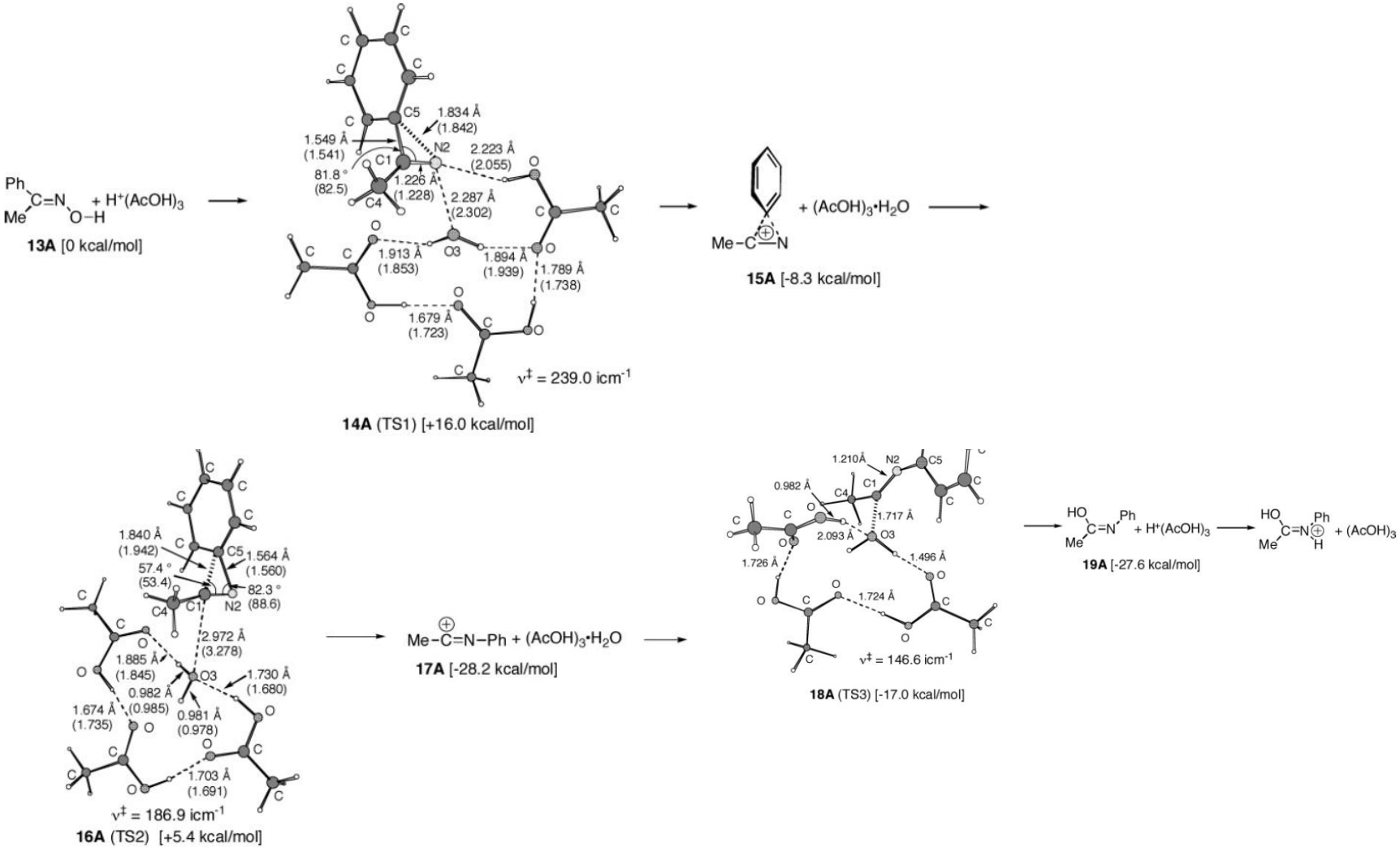
# Summary

- BKR is a general, stereospecific reaction of oximes that proceeds through an activated ester-like intermediate
- A Nitrilium ion is the common intermediate
  - To both the BKR and the BK fragmentation
- Catalyzed reactions appear increasingly likely to go through a self-propagation/promotion mechanism to regenerate the nitrilium ion.
- Even a 127 year old reaction can introduce new mechanistic insights.

# Rearrangement Step

## Concerted or Stepwise?

### Acetophenone: Three step process



# Concerted or Stepwise

Cyclohexanone: Concerted, one step process iminiu