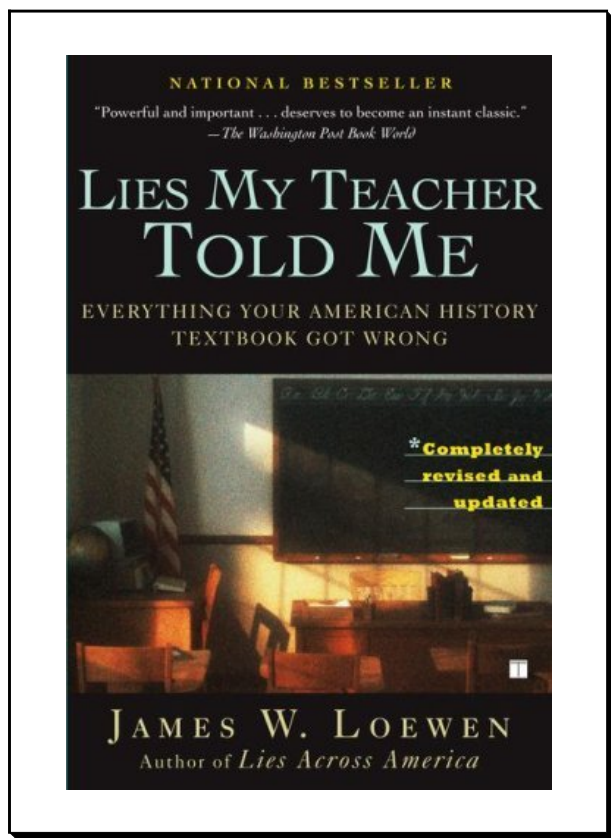


# Lies My Sophomore Organic Professor Told Me



**Group Meeting  
February 8th, 2012**

Christopher R. Jamison

## What Is This Talk About?

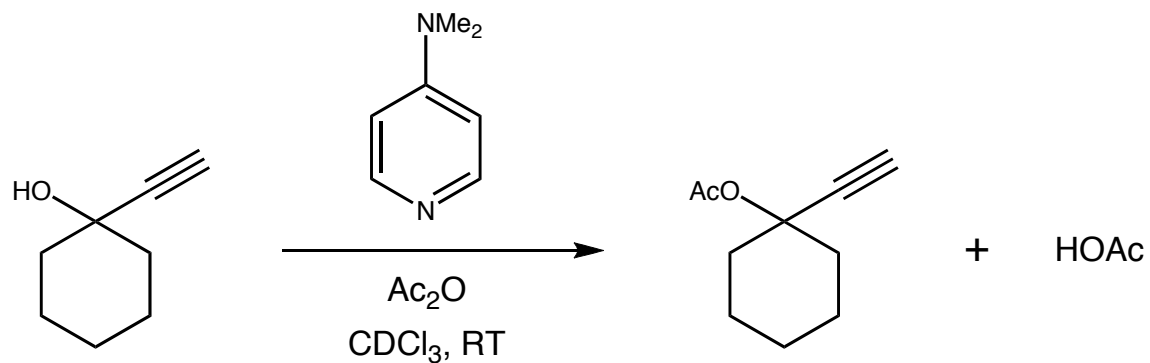
### 3 Mechanisms Taught to Organic Chemistry Students that are Incorrect

The traditional mechanism will be presented along with incompatible data

An alternate mechanism will be presented with proof to support it

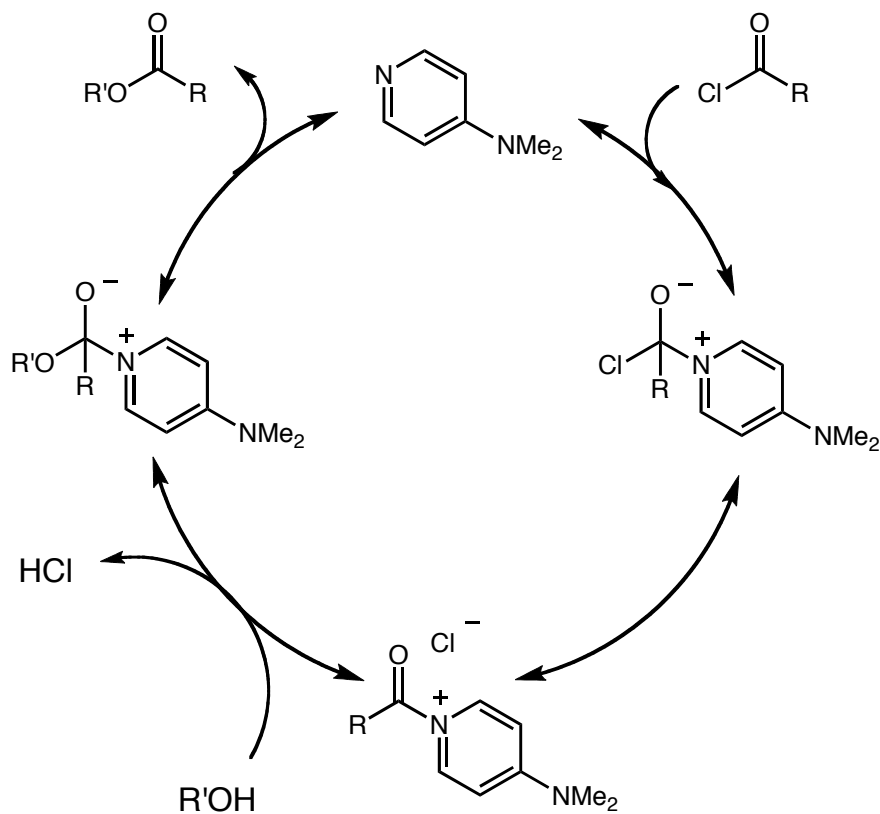
Examples will be presented wherein the alternate mechanism is instructive

## The Mechanism of DMAP Catalyzed Acylation of Alcohols



Recommended Reading: Spivey, A.; Arseniyadis, S. *ACIEE*, **2004**, 43, 5436

# The Traditionally Taught Mechanism

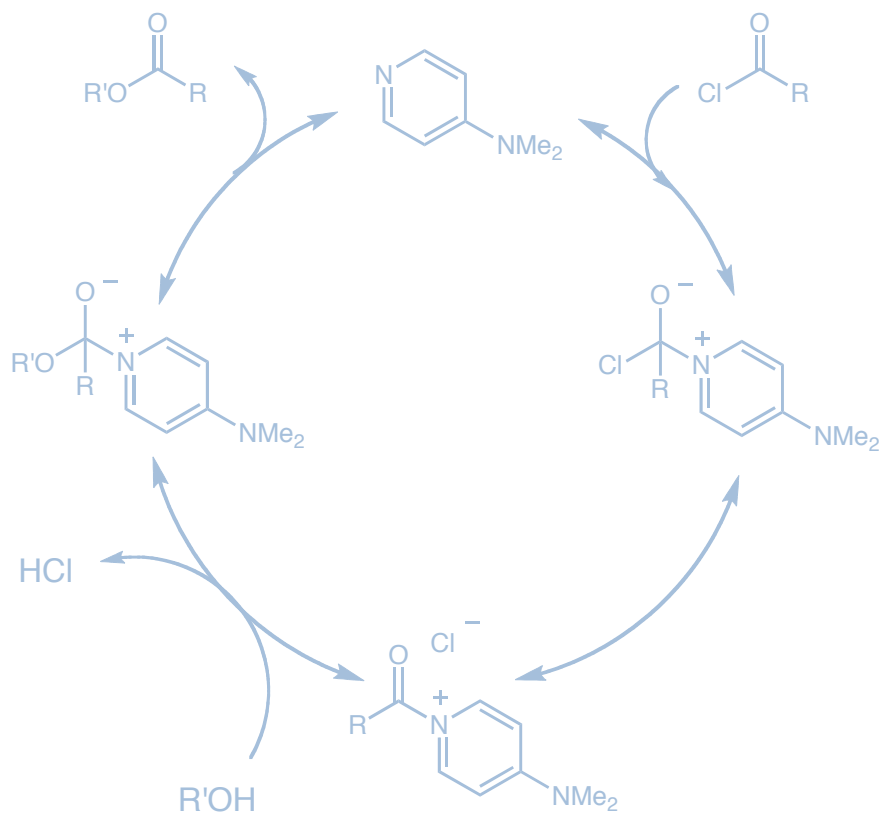


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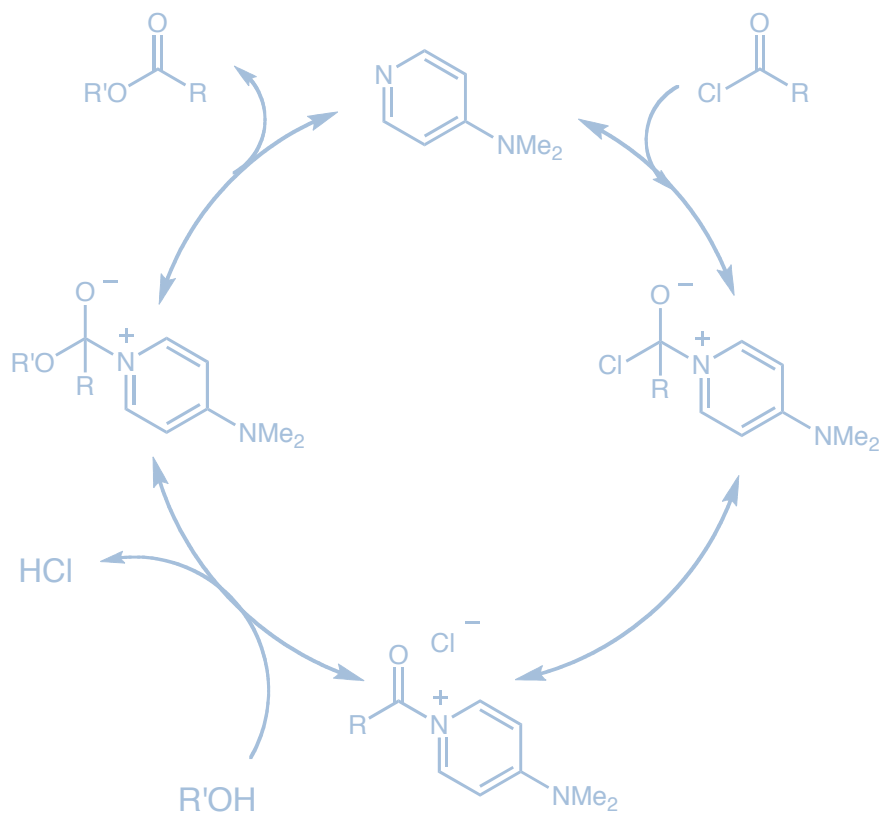


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# The Nucleophilicity of DMAP

Nucleophile	Mayr N value	pKa Conjugate Acid
DMAP	13.2	9.7
EtOH	7.5	-2.4

1. DMAP is more nucleophilic than the alcohol

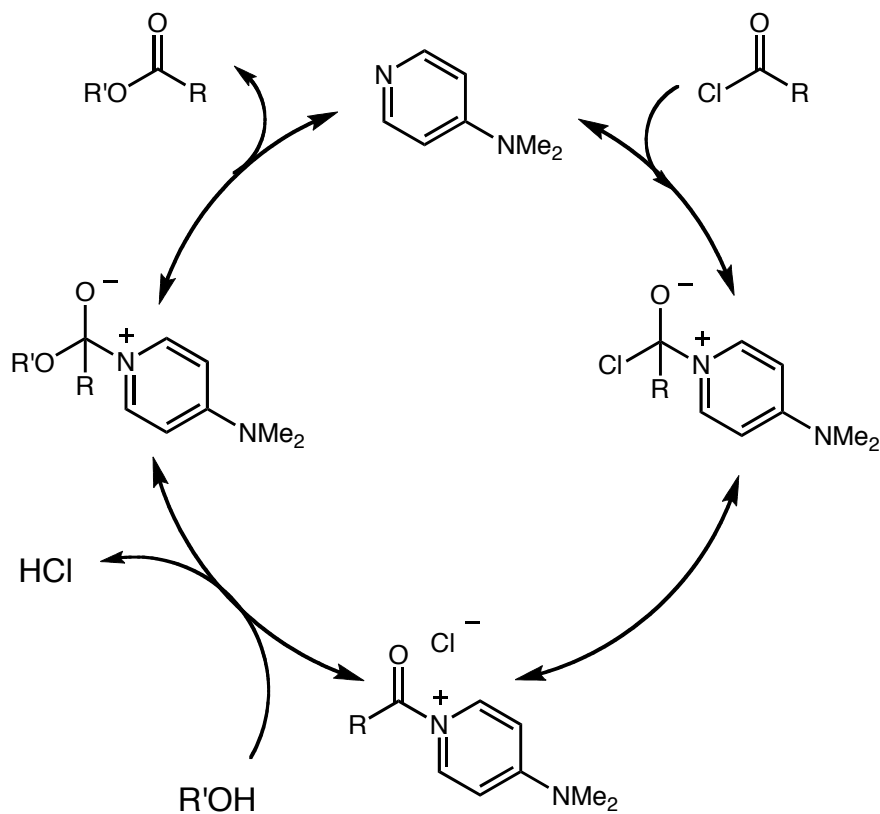
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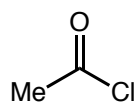
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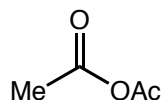


# IR Data for Various Acetyl Compounds

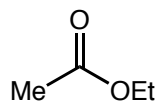
## IR C=O Stretch (cm<sup>-1</sup>)



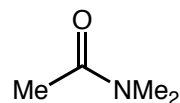
1806



1832, 1761



1743



1662

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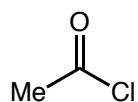
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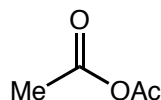
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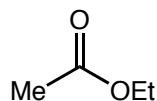
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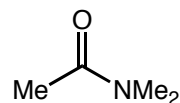
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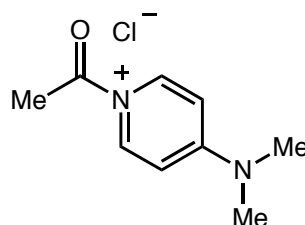
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**1755**

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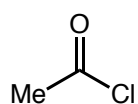
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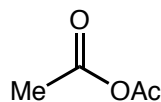
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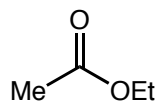
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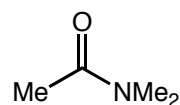
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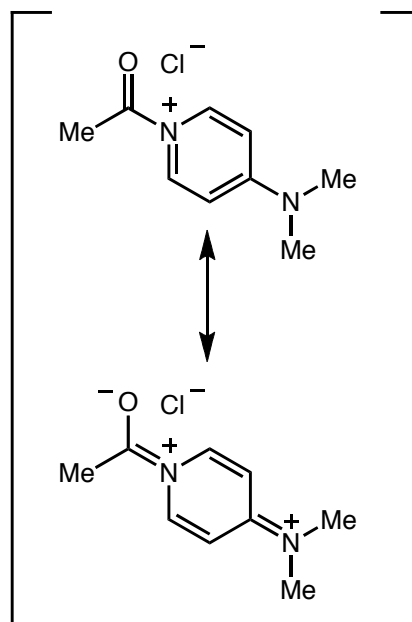


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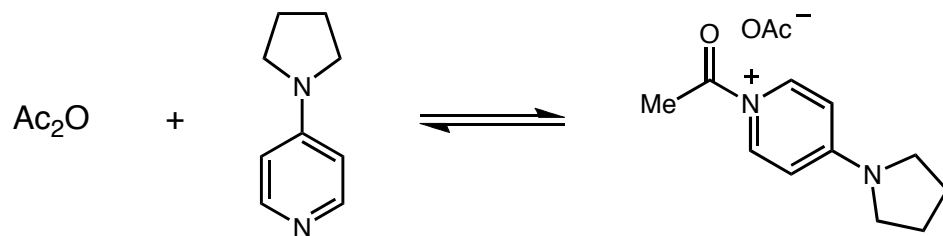
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# Thermodynamic Considerations



Equilibrium position is *ca.*  $\Delta H = -5.97 \text{ kcal/mol}$   
based on Van't Hoff analysis

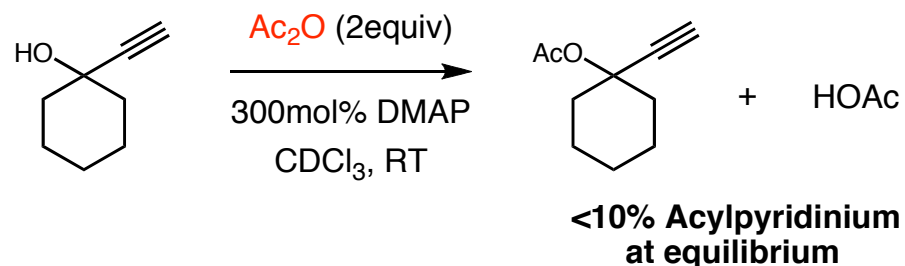
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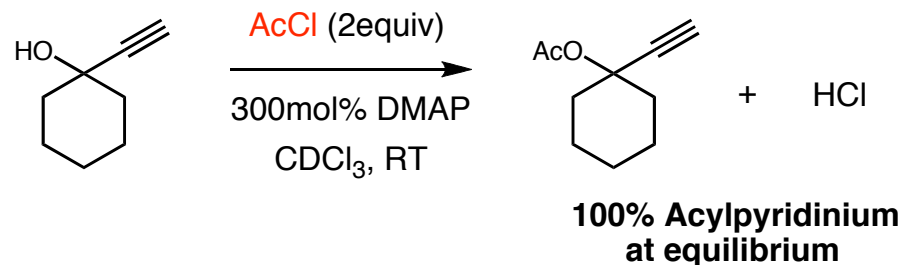
## Comparison of Different Acetyl Sources



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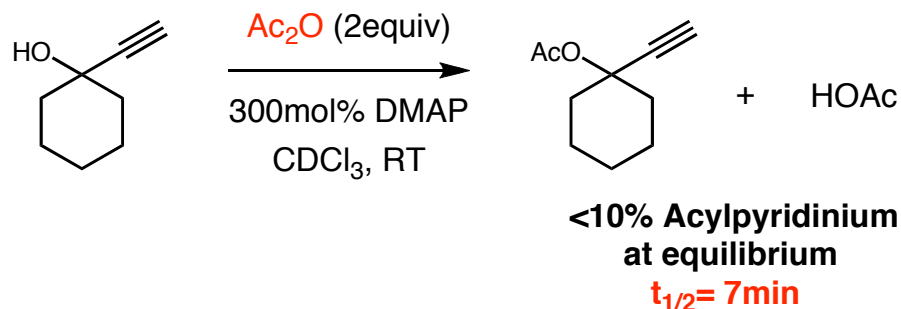
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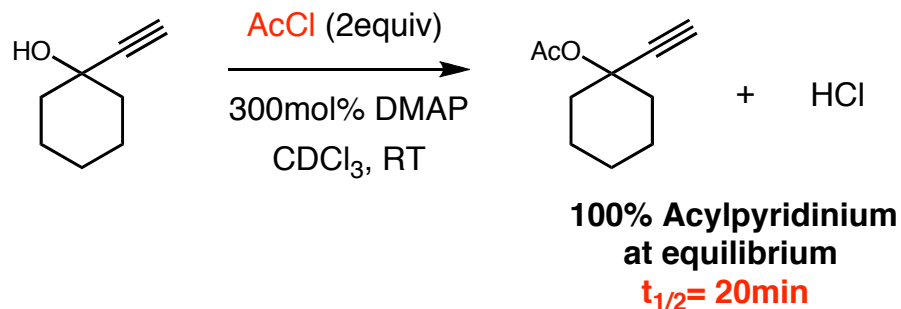
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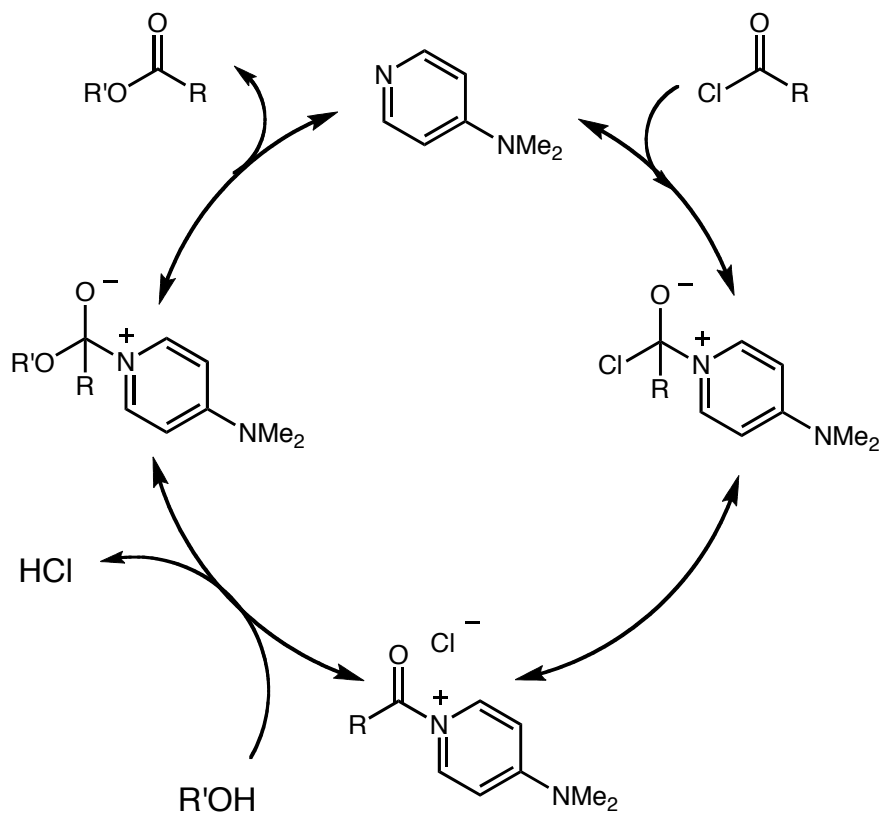
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"..reactivities of N-acylpyridinium salts do not correlate well with their intrinsic carbonyl activation as expected from resonance and spectrophotochemical properties. In particular, their reactivity is highly anion- and solvent-dependent."  
 -Spivey, A., Arseniyadis, S. *ACIEE*. **2004**, 43, 5436.

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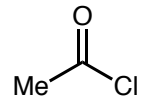
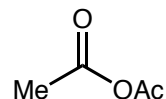
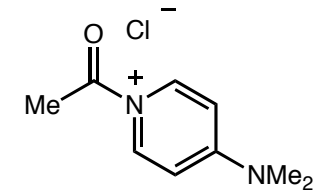
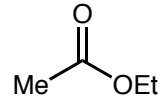
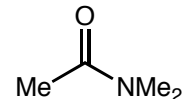


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# Relative pKa's of Various Leaving Groups

pKa of Leaving Group Conjugate Acid	
	-8.0
	4.8
	9.7
	15.5
	35

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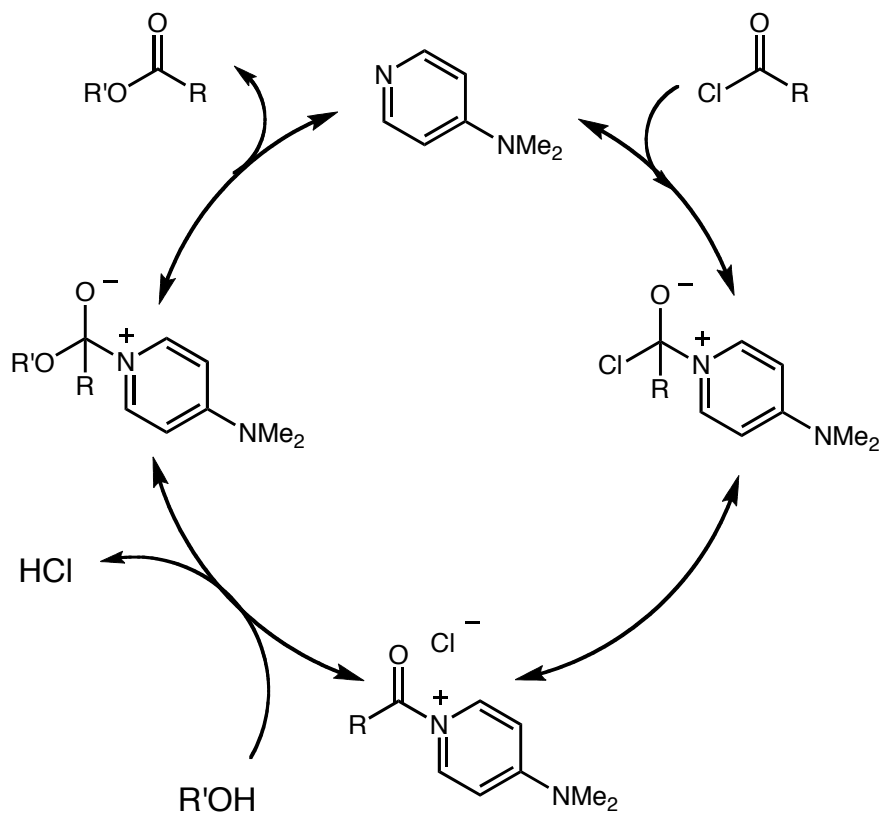
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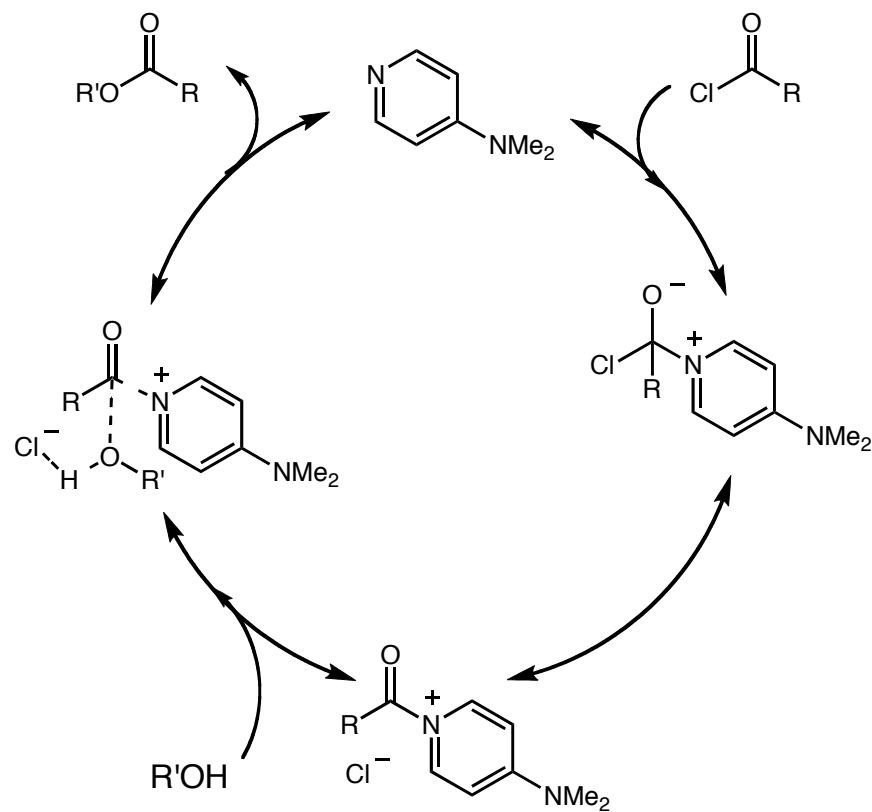
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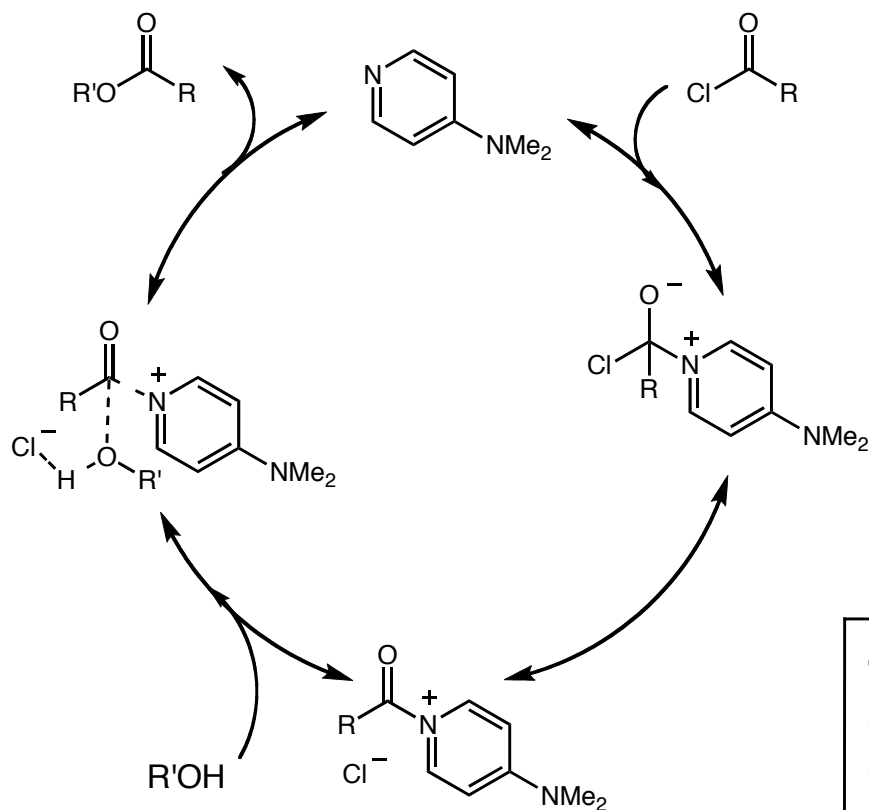
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## An Alternative Mechanism



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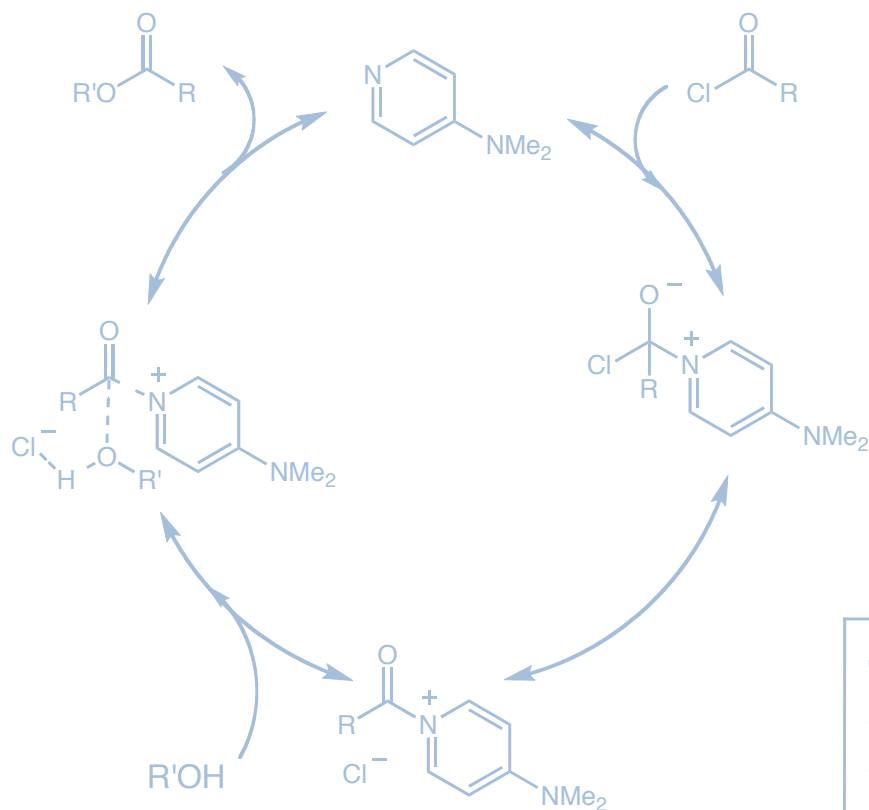
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**The activation mode is HOMO raising of the nucleophile, not LUMO lowering of the electrophile**

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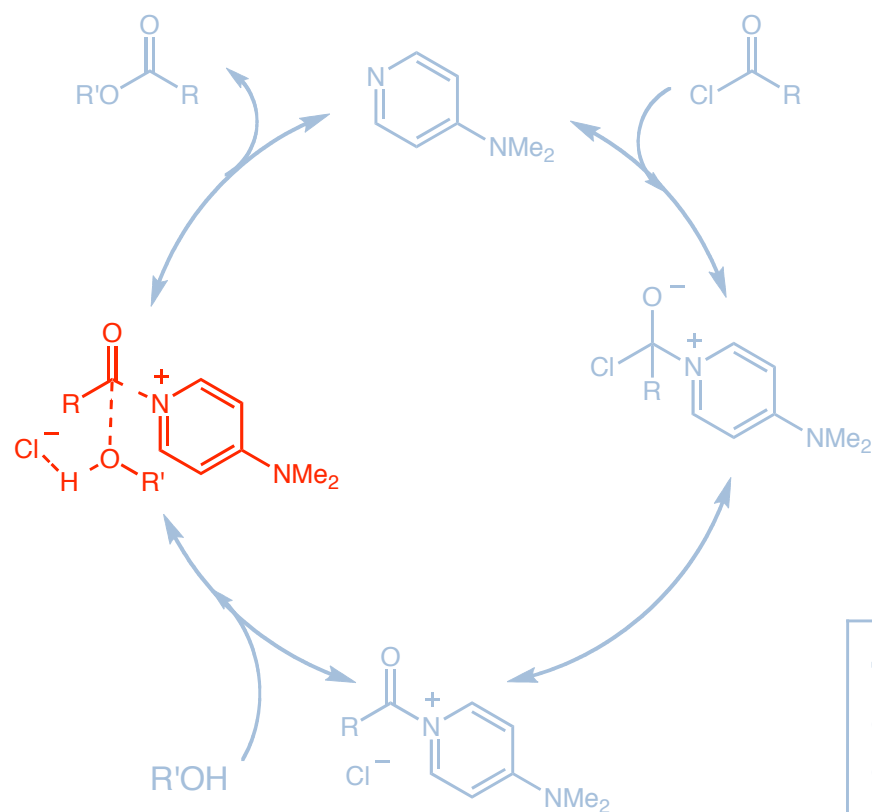


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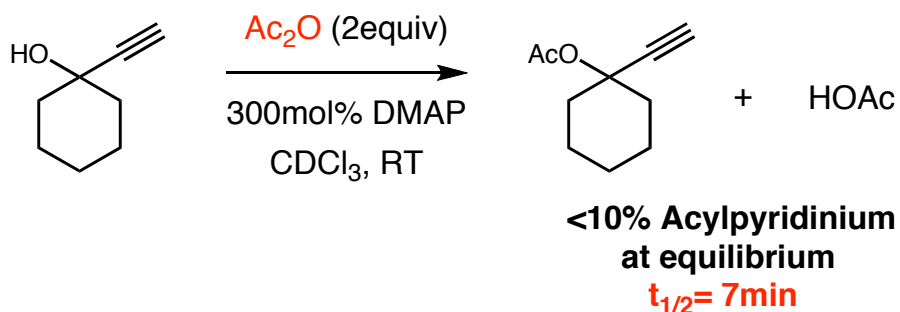
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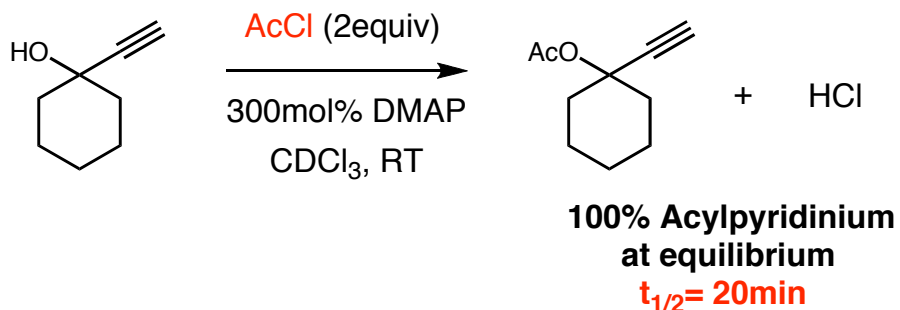
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## Explains the Rate Difference



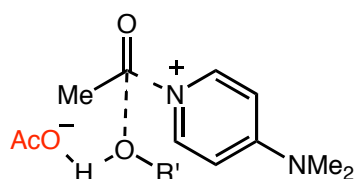
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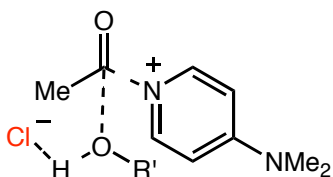
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# Explains the Rate Difference

**The more basic counterion compensates for the lower acylpyridinium concentration**



**<10% Acylpyridinium  
at equilibrium  
 $t_{1/2} = 7\text{min}$**



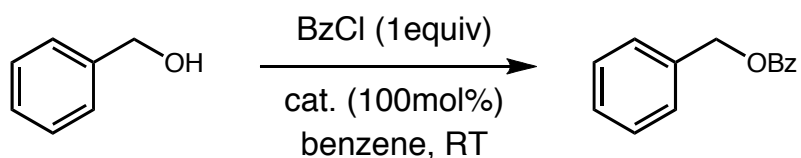
**100% Acylpyridinium  
at equilibrium  
 $t_{1/2} = 20\text{min}$**

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# A Point of Clarification

## DMAP is Not a General Base Catalyst



Base	pKa	rel. rate
Pyridine	5.2	80.9
2-methylpyridine	6.0	3.8
2,6-dimethylpyridine	6.7	1
DMAP	9.7	3.0 x 10 <sup>6</sup>

**There is no correlation between the rate constant and the pKa.**

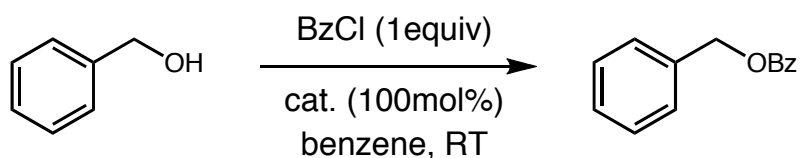
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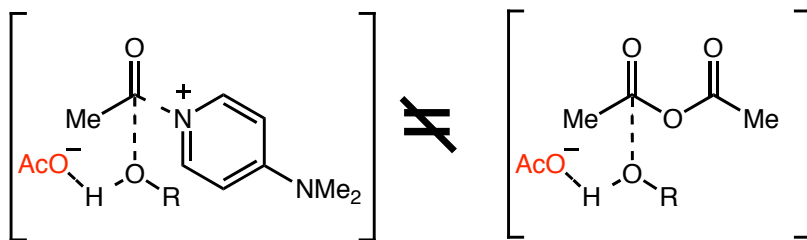
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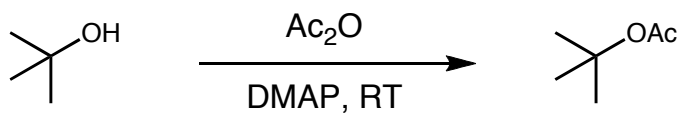
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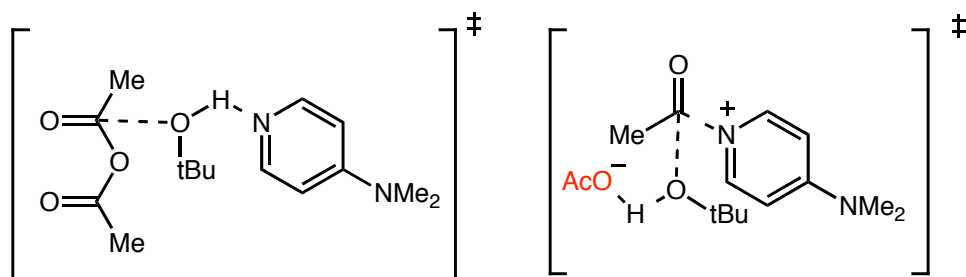
Spivey, A.; Arseniyadis, S. *ACIEE*, **2004**, 43, 5436

## DFT Model Supports Anion's Role



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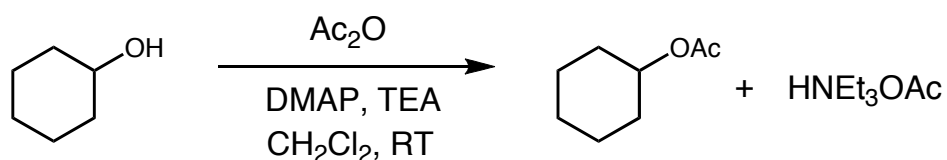
ca.  $\Delta H = +77.2$  kJ/mol

ca.  $\Delta H = +34.8$  kJ/mol

**The activation mode is HOMO raising of the nucleophile, not LUMO lowering of the electrophile**

Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. *Chem. Eur. J.* **2005**, 11, 4751.

## Kinetic Study of the Acetate's Role in the RDS



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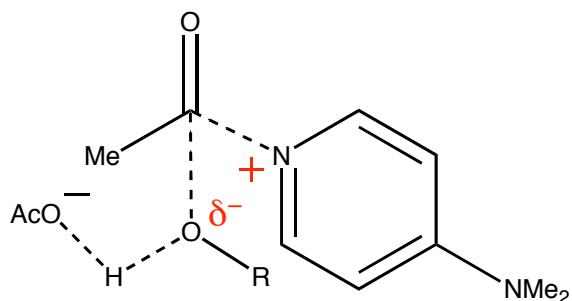
Reactant	Kinetic Order
Cyclohexanol	1
DMAP	1
Ac <sub>2</sub> O	1
triethylamine	0

**The acetate counterion is the only possible base involved in the RDS based on this data.**

**The activation mode is HOMO raising of the nucleophile, not LUMO lowering of the electrophile**

Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. *Chem. Eur. J.* **2005**, 11, 4751.

## Why is Acetate Able to Deprotonate an Alcohol?



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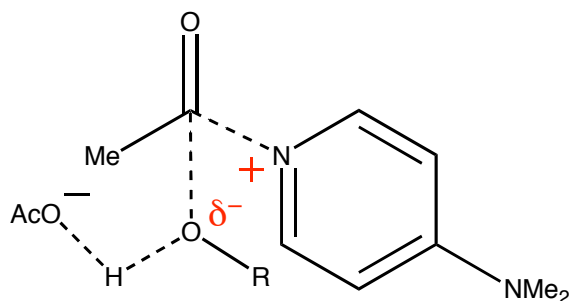
### Electrostatic Activation?

**The rate does have a known inverse dependence on the solvent polarity<sup>1</sup>**

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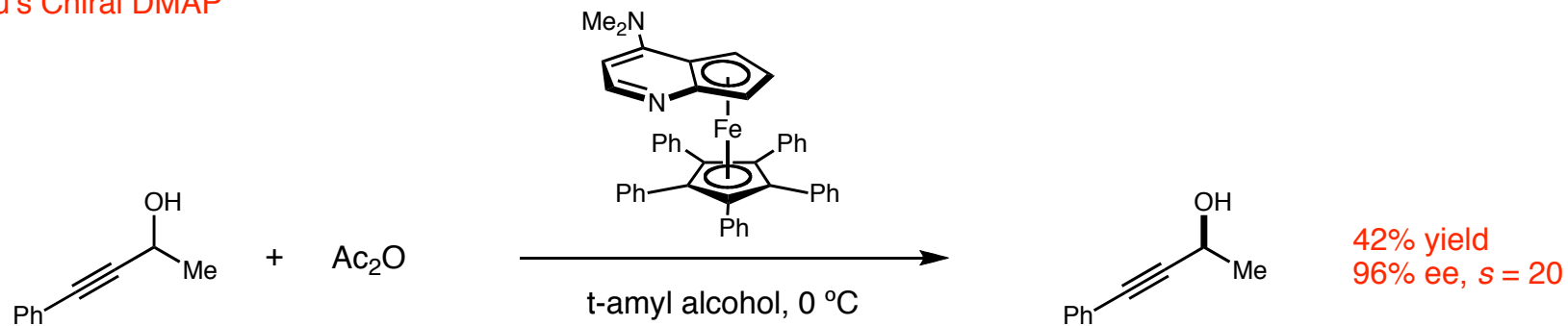
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**The activation mode is HOMO raising of the nucleophile, not LUMO lowering of the electrophile**

1. Spivey, A.; Arseniyadis, S. *ACIEE*, **2004**, 43, 5436

## Relevant Examples

Fu's Chiral DMAP

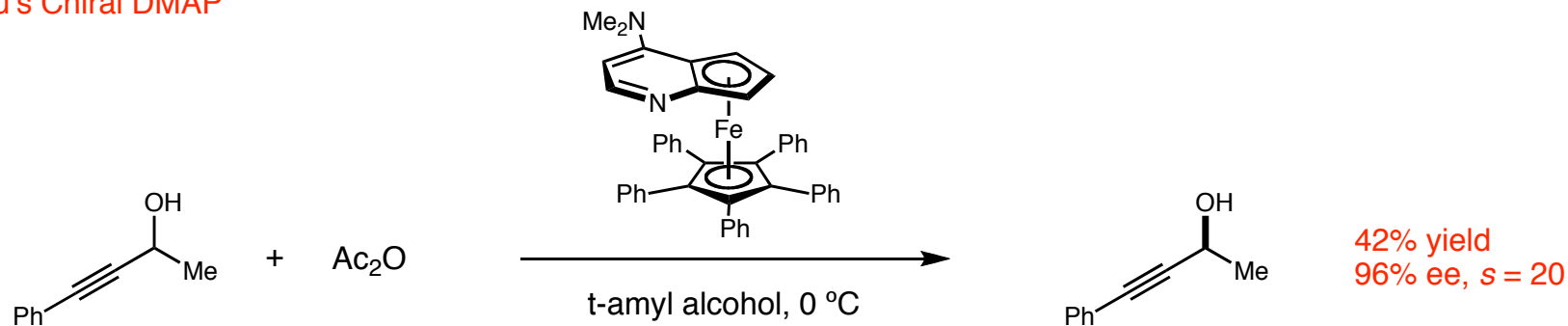


Fu, G. *et al.* *J. Am. Chem. Soc.* **1999**, 121, 5091

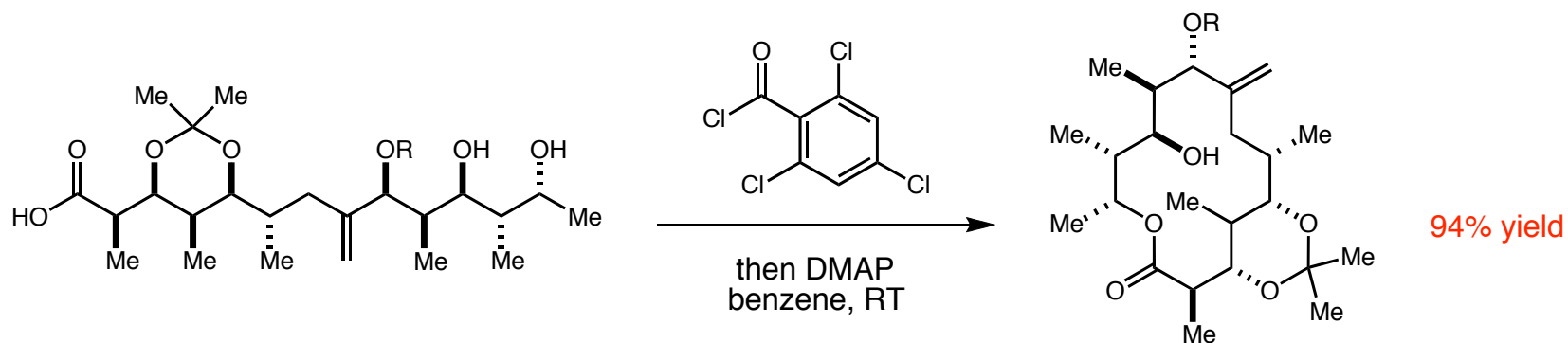
;

## Relevant Examples

### Fu's Chiral DMAP



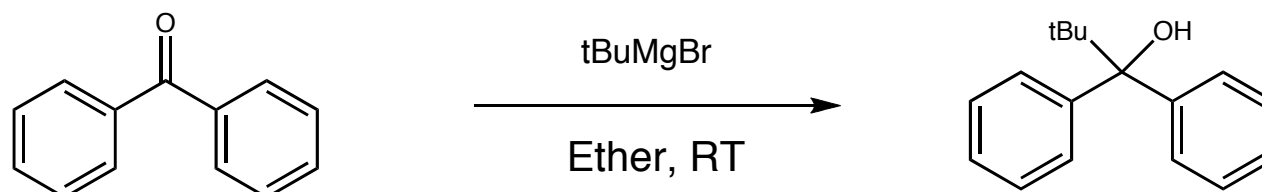
### Yamaguchi Macrolactonization



Fu, G. *et al.* *J. Am. Chem. Soc.* **1999**, 121, 5091

Panek, N. *et al.* *J. Am. Chem. Soc.* **2002**, 124, 12806

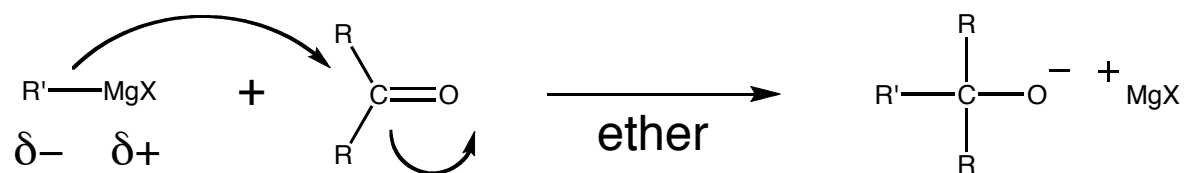
## The Mechanism of Addition of Grignard Reagents to Carbonyls



Recommended Reading: Ashby, E.; Bowers, J. *J. Am. Chem. Soc.*, **1981**, 103, 2242



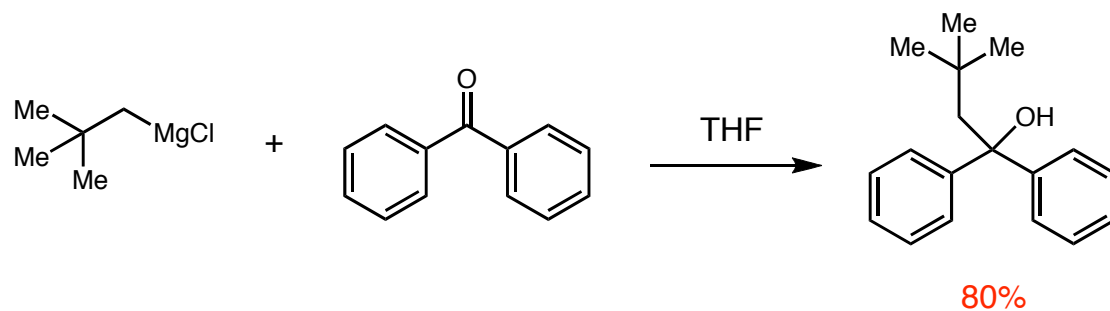
## The Traditionally Taught Mechanism



"Because they resemble carbanions, Grignard and organolithium reagents are strong **nucleophiles** and strong bases. Their most useful **nucleophilic** reactions are additions to carbonyl groups."

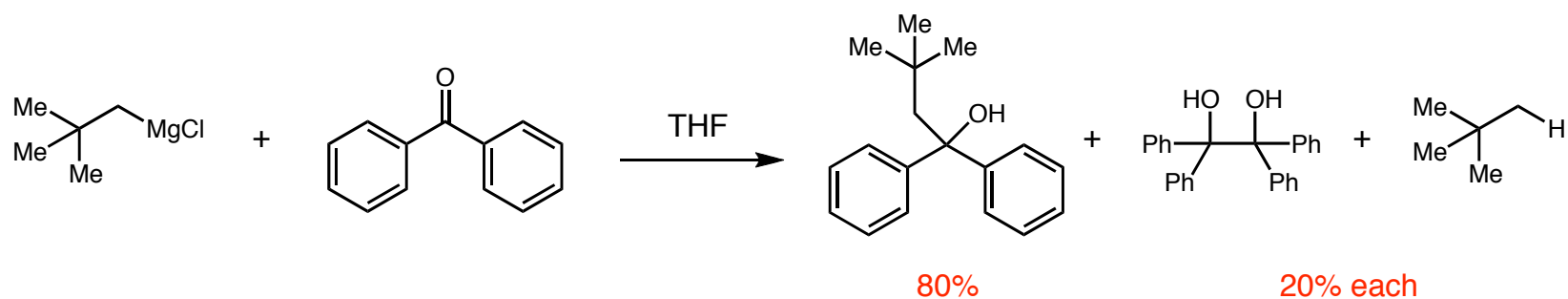
- Wade, L. G. *Organic Chemistry*.  
Prentice Hall, 2003.

## An Incompatible Observation



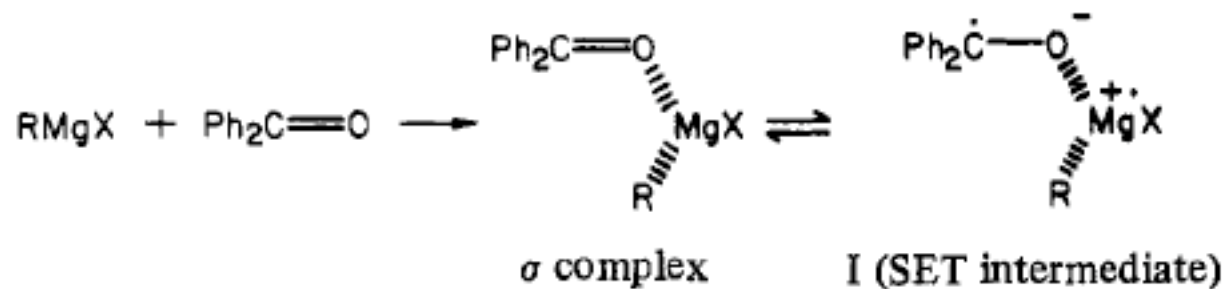
Blomberg, R. M. *et al. J. Org. Chem.* **1969**, 34, 2385.

## An Incompatible Observation



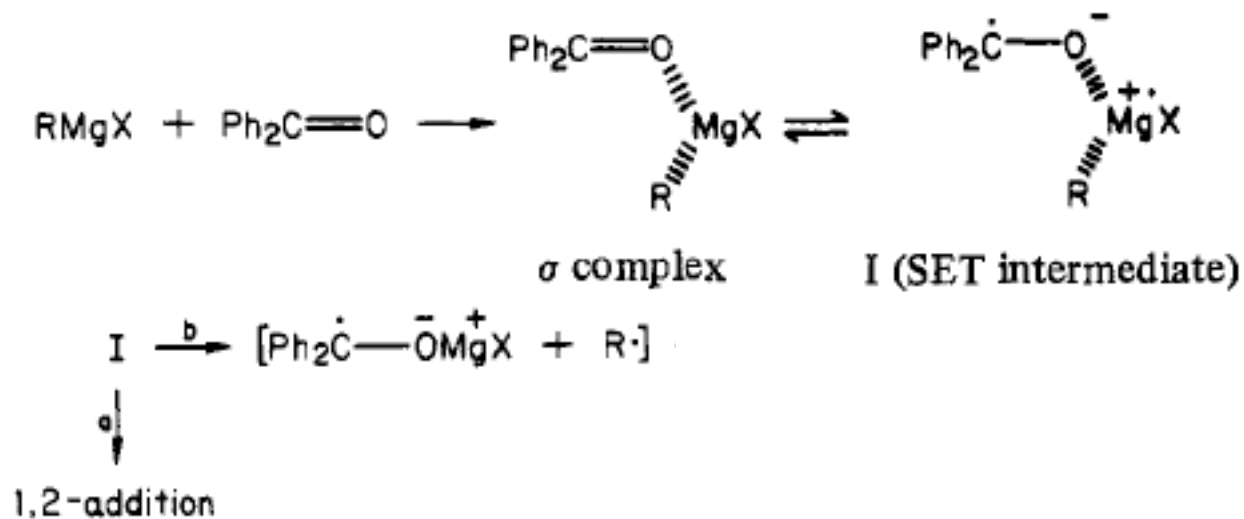
**This is highly suggestive of radical intermediates**

## An Alternative Mechanism



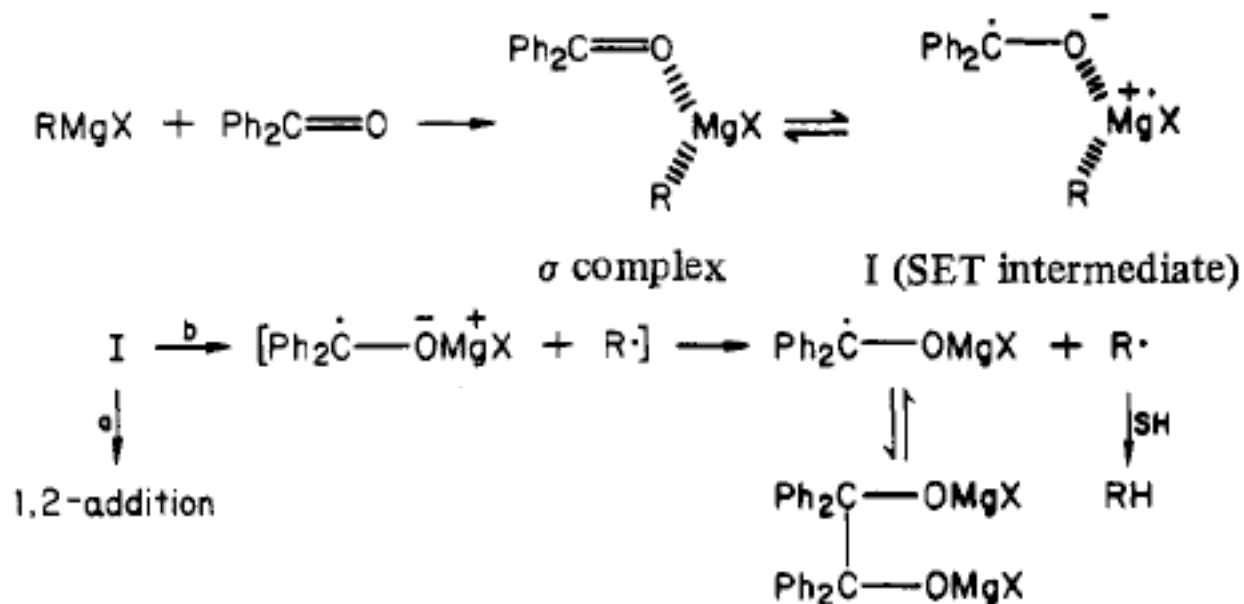
**The reaction is initiated by electron transfer, and radical recombination forms the new bond.**

## An Alternative Mechanism



**The reaction is initiated by electron transfer, and radical recombination forms the new bond.**

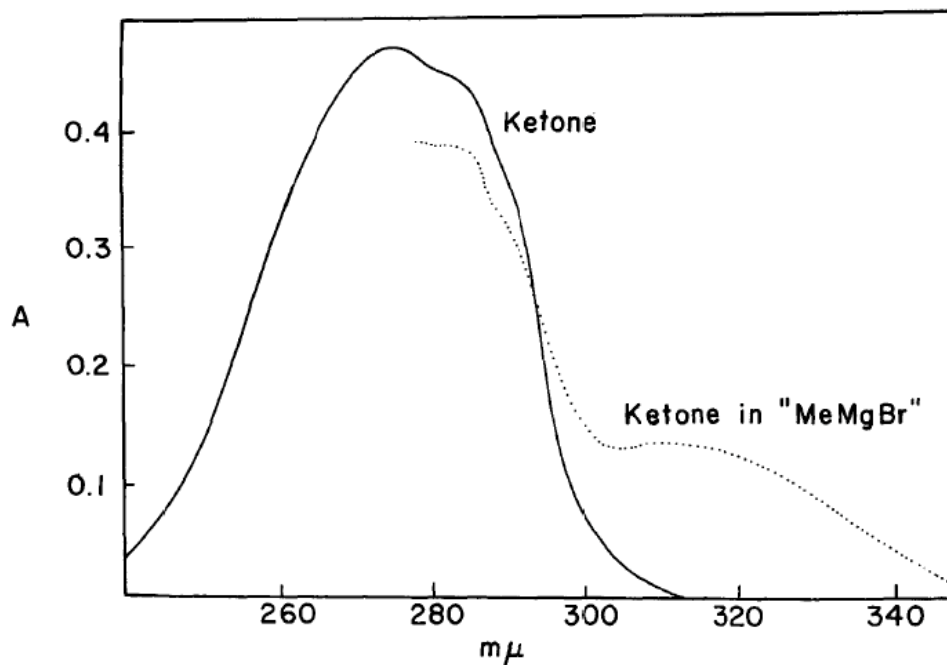
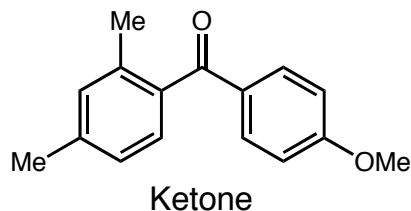
## An Alternative Mechanism



**The reaction is initiated by electron transfer, and radical recombination forms the new bond.**



## UV Evidence for the $\sigma$ -Complex



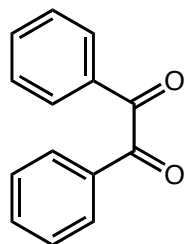
- 1. Both bands rapidly disappear when the Grignard solution is warmed to 25°C.**
- 2. Carbonyl band shifts in IR have also been recorded**

The reaction is initiated by electron transfer, and radical recombination forms the new bond.

1. Smith, S. *Tet. Lett.* **1963**, 103, 409
2. Ashby, E.; Bowers, J. *J. Am. Chem Soc.* **1981**, 103, 2242.



## EPR Evidence for the Ketyl Radical

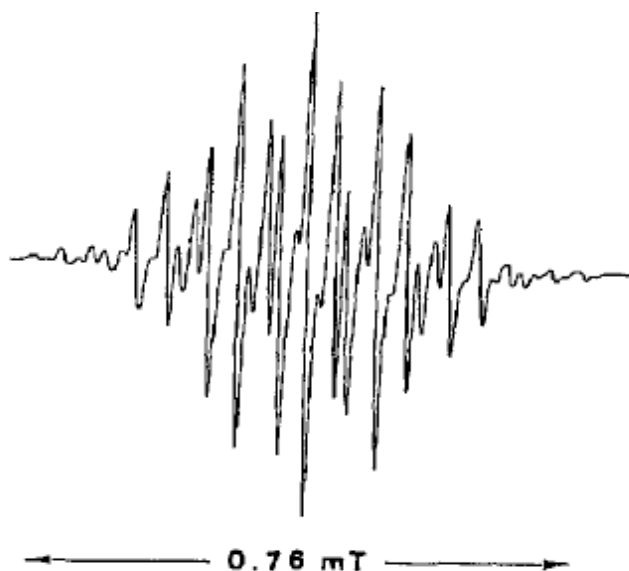


1equiv RMgBr

**R= Me, Et, Ph, allyl.**

**"purple colored radical"**

stable for years at RT

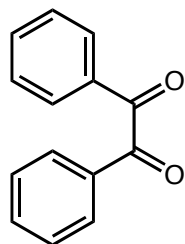


The reaction is initiated by electron transfer, and radical recombination forms the new bond.

**EPR spectrum of the "purple colored radical" from PhMgBr and Benzil in THF**

Maruyama, K.; Katagiri, T. *J. Phys. Org. Chem.* **1989**, 2, 205

## EPR Evidence for the Ketyl Radical

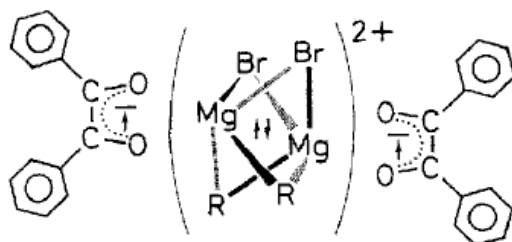


1equiv RMgBr

**R= Me, Et, Ph, allyl.**

**"purple colored radical"**

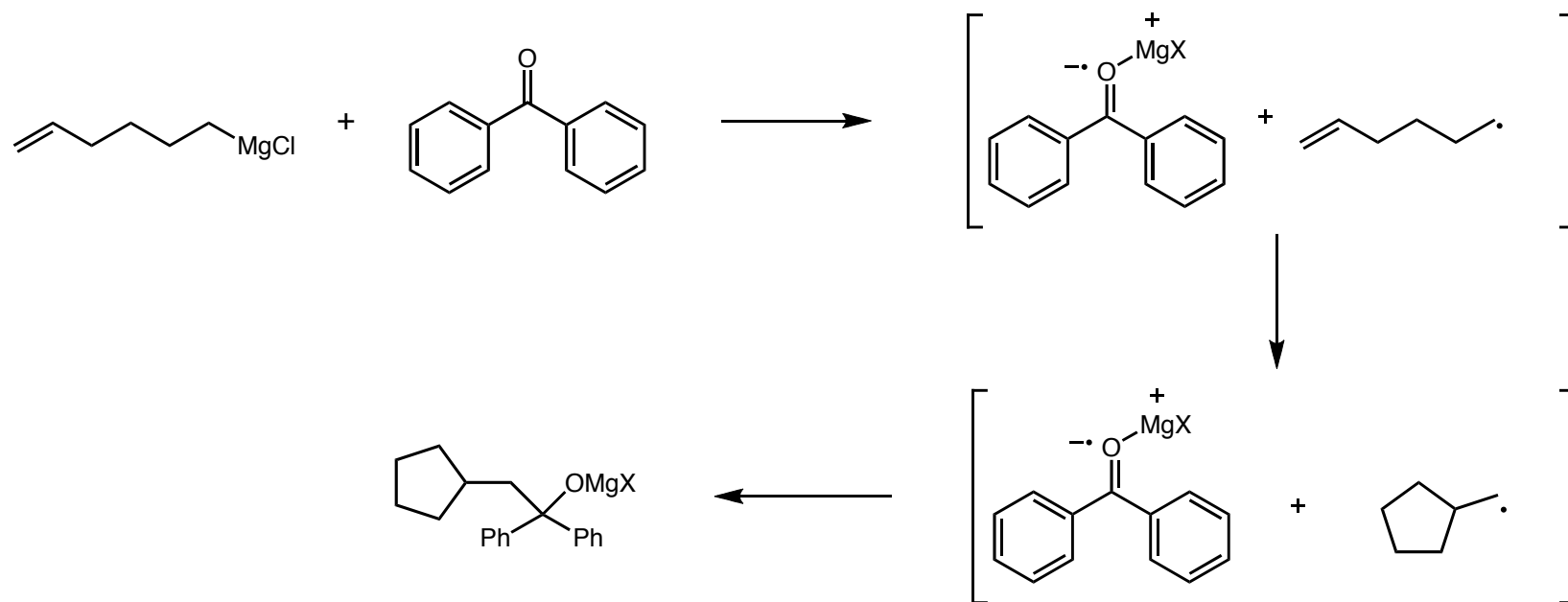
stable for years at RT



**Radical cation is not observed directly  
because it exists as a diamagnetic dimer**

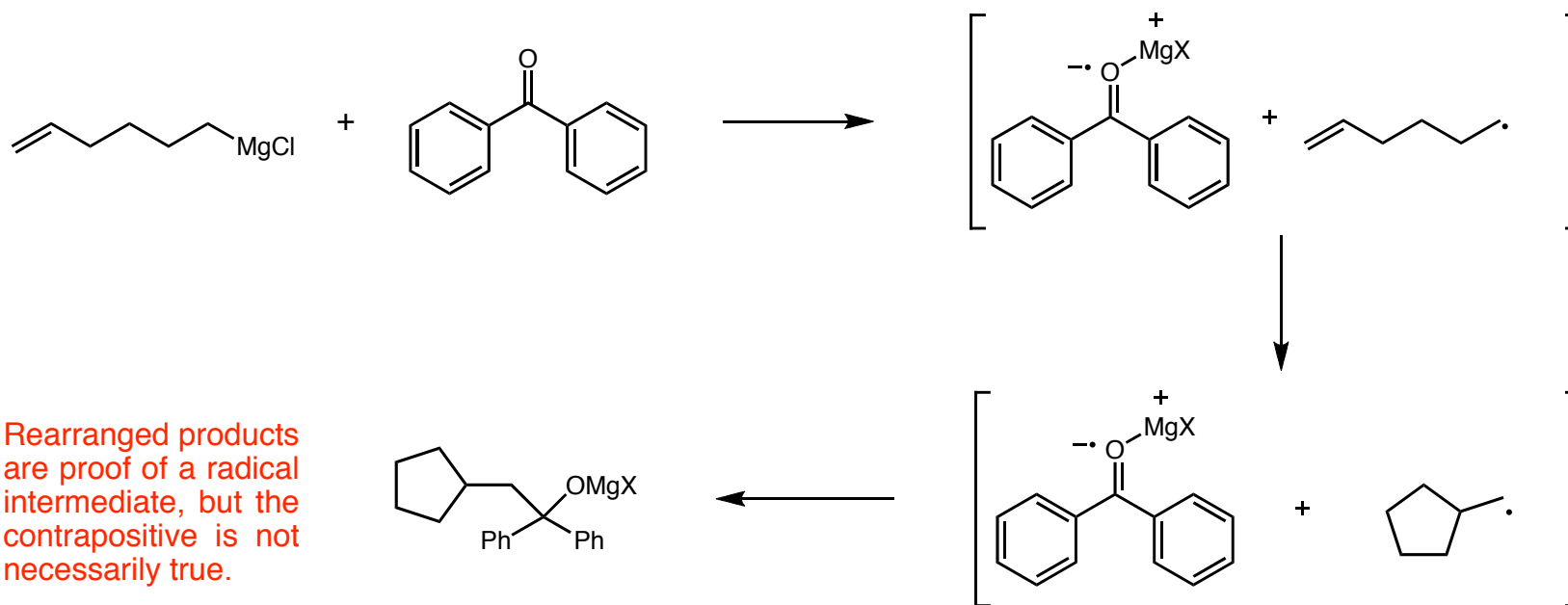
The reaction is initiated  
by electron transfer, and  
radical recombination  
forms the new bond.

## Radical Probes as Evidence of Electron Transfer



**The reaction is initiated by electron transfer, and radical recombination forms the new bond.**

## Radical Probes as Evidence of Electron Transfer



Rearranged products are proof of a radical intermediate, but the contrapositive is not necessarily true.

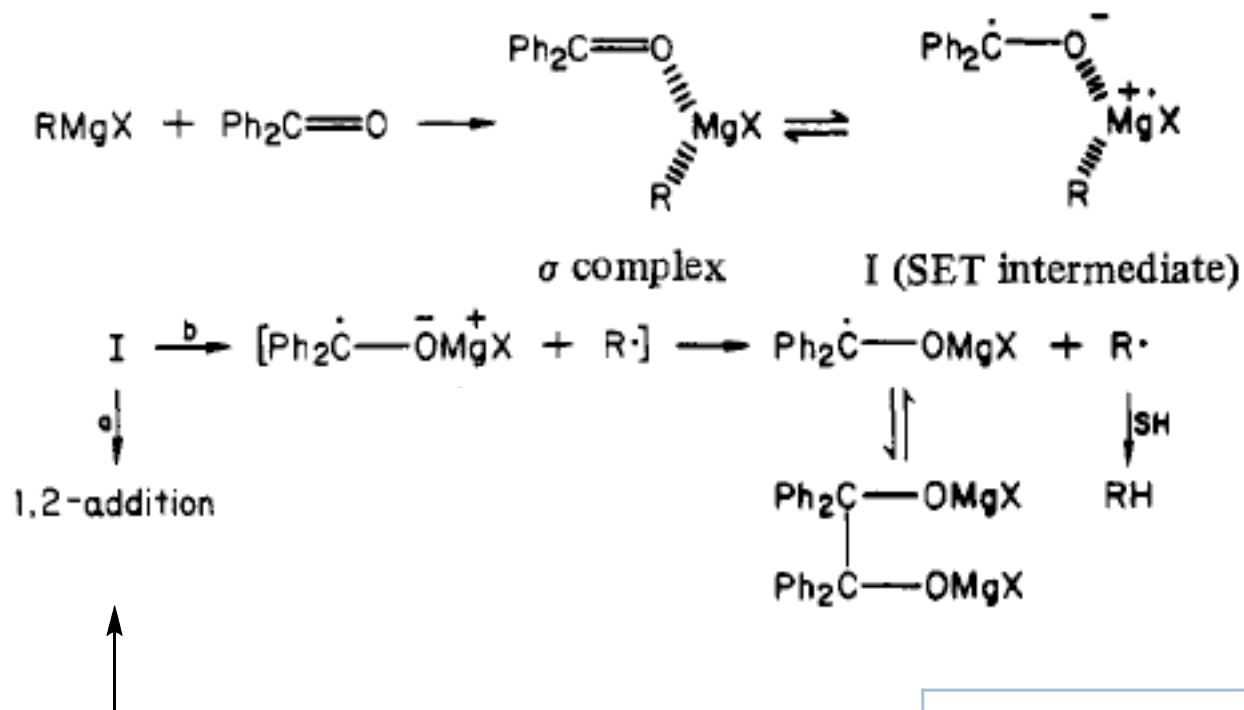
### Rate Constants for Competing Reactions

5-hexenyl radical cyclization =  $10^5 \text{ s}^{-1}$

alkyl radical + ketyl radical =  $10^7\text{-}10^9 \text{ L mol}^{-1} \text{ s}^{-1}$ .

The reaction is initiated by electron transfer, and radical recombination forms the new bond.

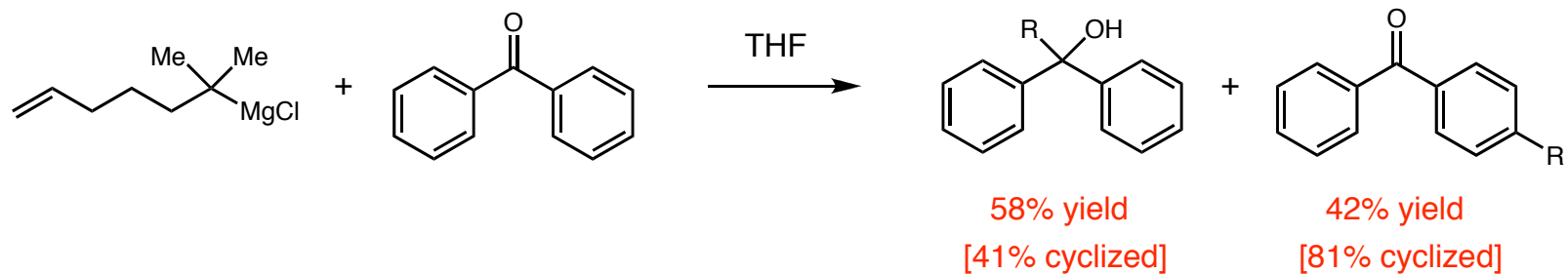
## Slowing Down "Path A"



"Path A" rate constant is estimated to be  $10^7$ - $10^9$  L mol<sup>-1</sup> s<sup>-1</sup> for a primary alkyl radical.

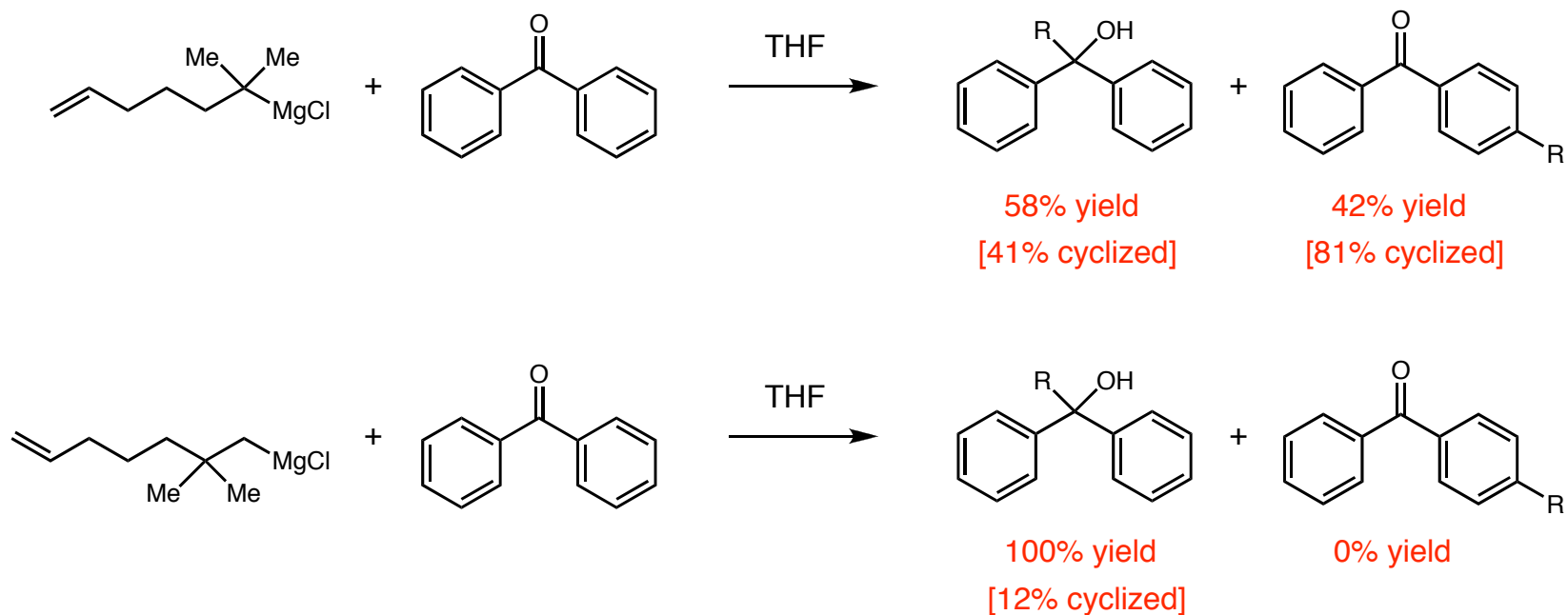
The reaction is initiated by electron transfer, and radical recombination forms the new bond.

## Radical Probes as Evidence of Electron Transfer



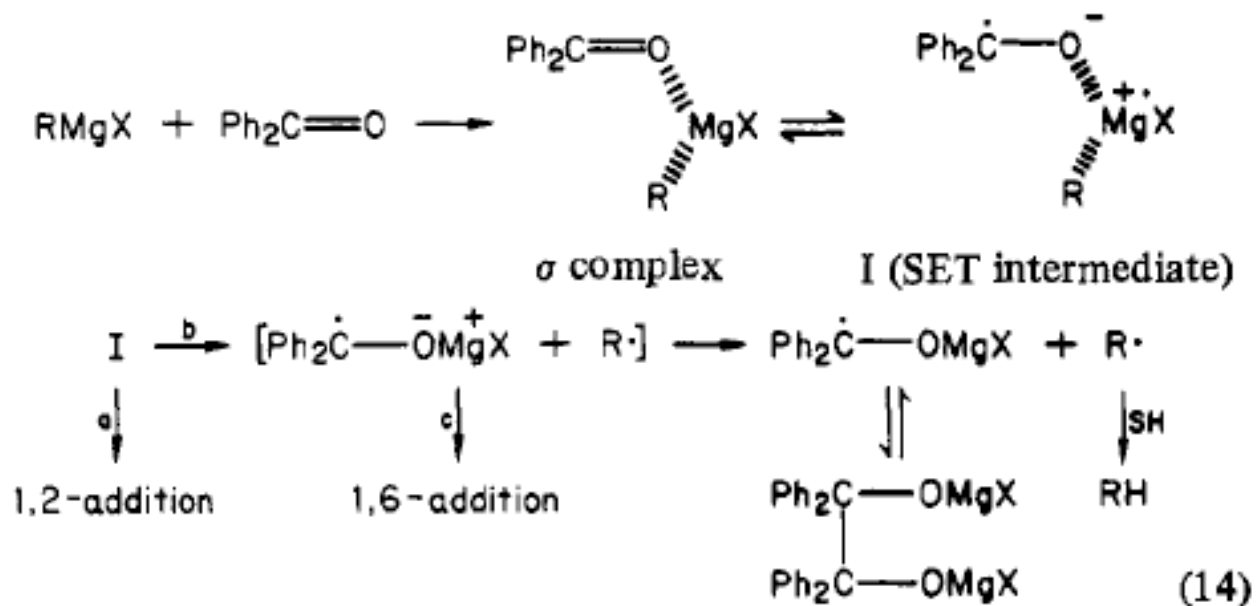
The reaction is initiated by electron transfer, and radical recombination forms the new bond.

## Radical Probes as Evidence of Electron Transfer



The reaction is initiated by electron transfer, and radical recombination forms the new bond.

# Can We Know if This Mechanism is General for All Grignards?



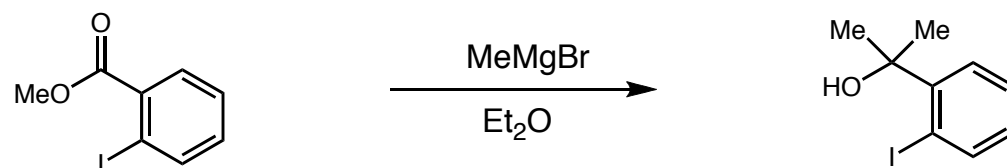
"Path A" rate constant is estimated to be  $10^7$ - $10^9$  L mol<sup>-1</sup> s<sup>-1</sup> for a primary alkyl radical.

**The reaction is initiated by electron transfer, and radical recombination forms the new bond.**



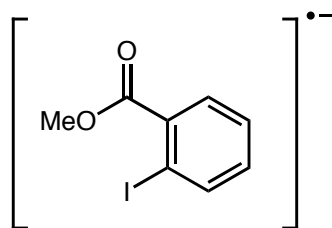
## Relevant Example

Synthesis of 3° Alcohol En Route to Togni Reagent



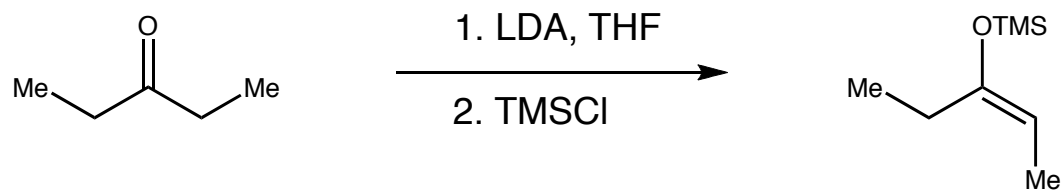
1M = 0% IY, decomp.

0.2M = >95% IY



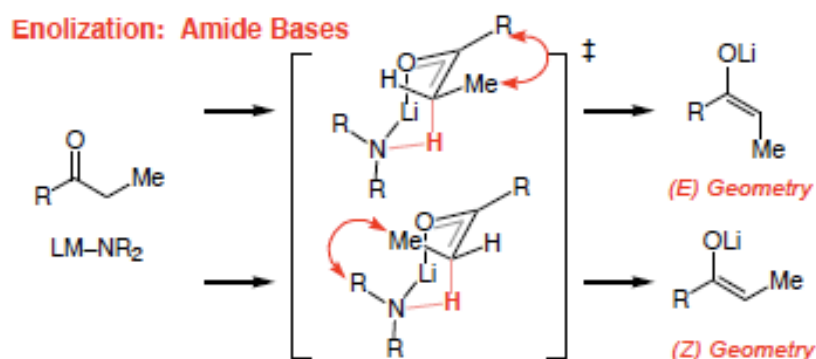
unpublished observation by the speaker

## The Mechanism of *E*-selective Enolization of Acyclic Carbonyls by LDA



Recommended Reading: Collum, D.; Romesberg, F. *J. Am. Chem. Soc.* **1995**, 117, 2166

## The Traditionally Taught Mechanism

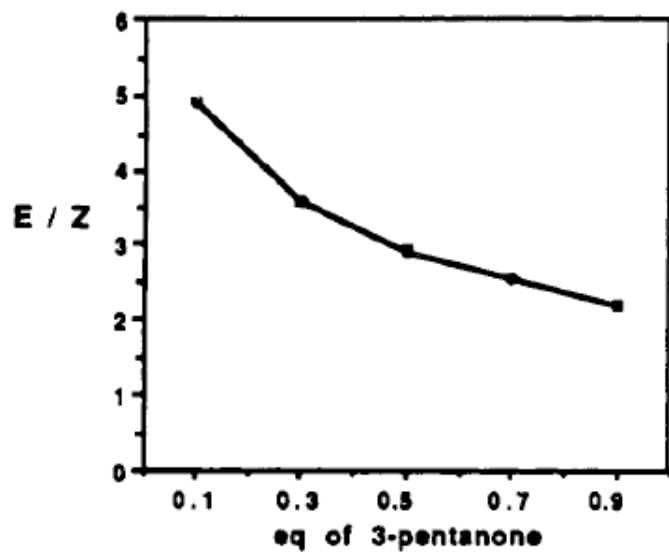


1. The *E*-selective TS<sup>‡</sup> is a monomeric cycle with minimized 1,3-diaxial strain favored by weakly coordinating solvents
2. The *Z*-selective TS<sup>‡</sup> is open monomer with minimized allylic strain favored by strongly coordinating solvents that "break-up" the lithium chelate.

"...the preferential formation of the *E*-enolate can be explained in terms of a cyclic transition state... Steric interaction between the base and the  $\alpha$ -substituent disfavors the TS for the *Z*-enolate... The switch to the *Z*-enolate with HMPA is attributed to a looser, perhaps acyclic, TS being favored as the result of the strong solvation of the lithium ion by the cosolvent."

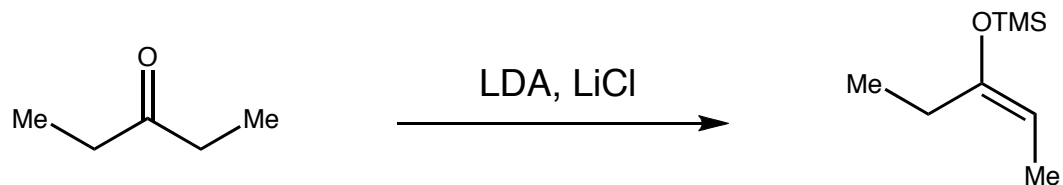
-Carey, F.; Sundberg, R. *Advanced Organic<sup>‡</sup> Chemistry*. Springer Science+Business Media, 2007.

## Incompatible Observations

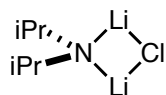
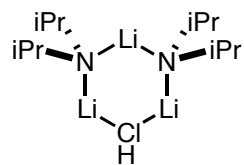


Rate of equilibration from E to Z is not significant

# Incompatible Observations



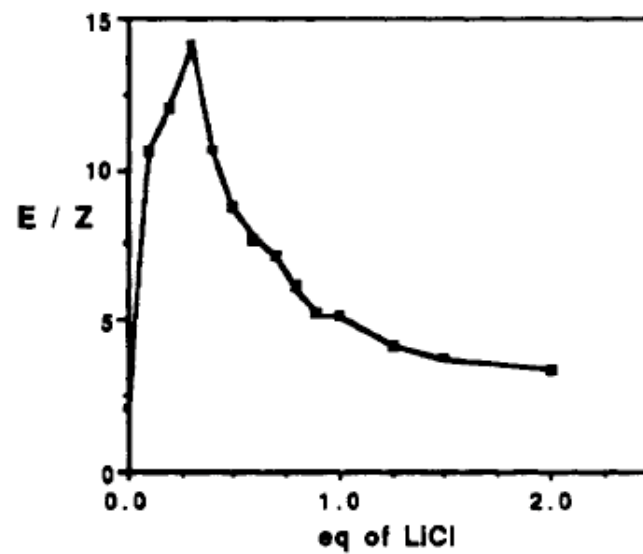
**Predominant Species**  
 **$^6\text{Li}$ ,  $^{15}\text{N}$  NMR**



**Equivalents**  
**of LiCl**

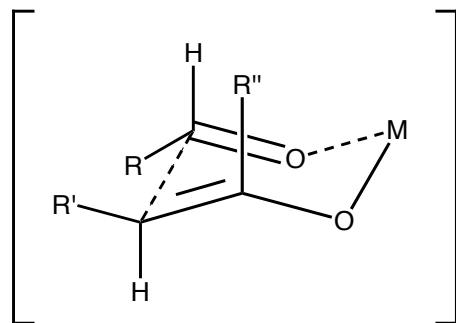
0.4eq

1.5eq



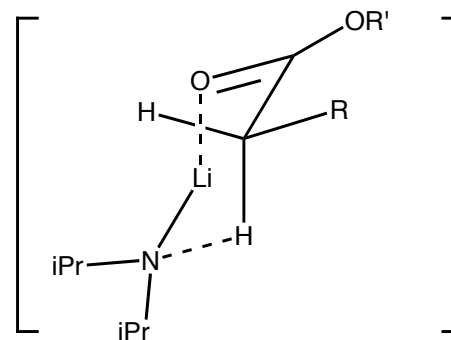
# A Major Oversight?

**Zimmerman-Traxler Model  
(1957)**



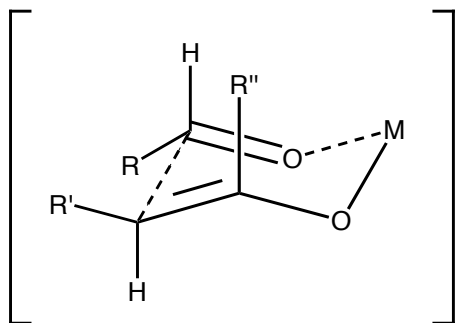
**vs.**

**Ireland Model  
(1976)**



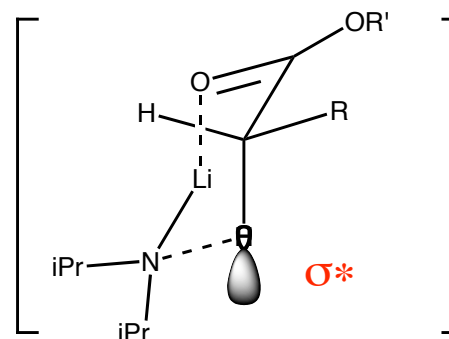
# A Major Oversight?

**Zimmerman-Traxler Model  
(1957)**



vs.

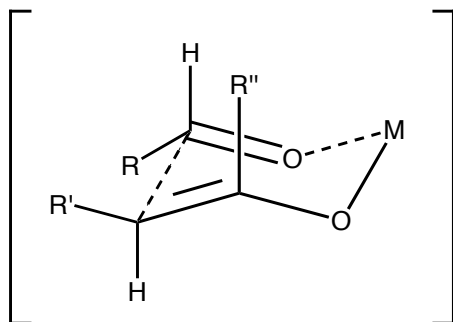
**Ireland Model  
(1976)**



"Although Ireland's model has an **enormous aesthetic appeal** in being a chair..., it fails to satisfy the stereoelectronic requirements of enolization (notice that the base does not approach along the axis of the correctly aligned  $\alpha$  C-H bond being broken)..." Narula, A. *Tet. Lett.* **1981**, 22, 4119.

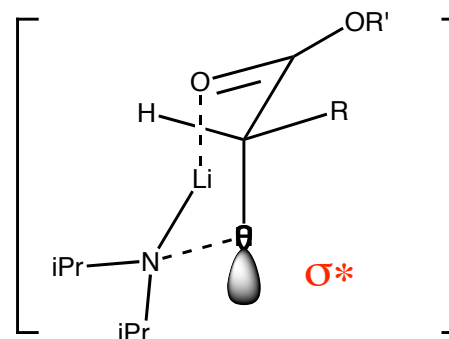
# A Major Oversight?

**Zimmerman-Traxler Model  
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vs.

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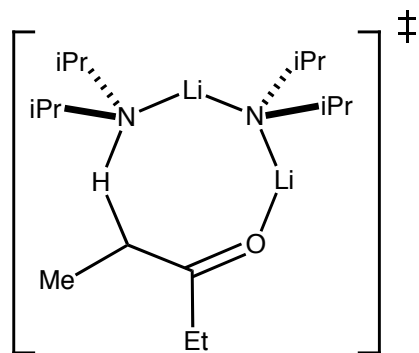
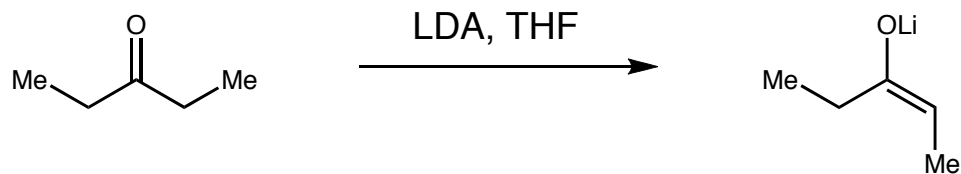


"Although Narula challenged the chair transition state model and received some support from *ab initio* calculations<sup>1</sup>, the chair model maintains wide popularity." Collum, D.; Romesberg, F. *J. Am. Chem. Soc.* **1995**, 117, 2166.

1. Personal correspondence between Houk and Collum.

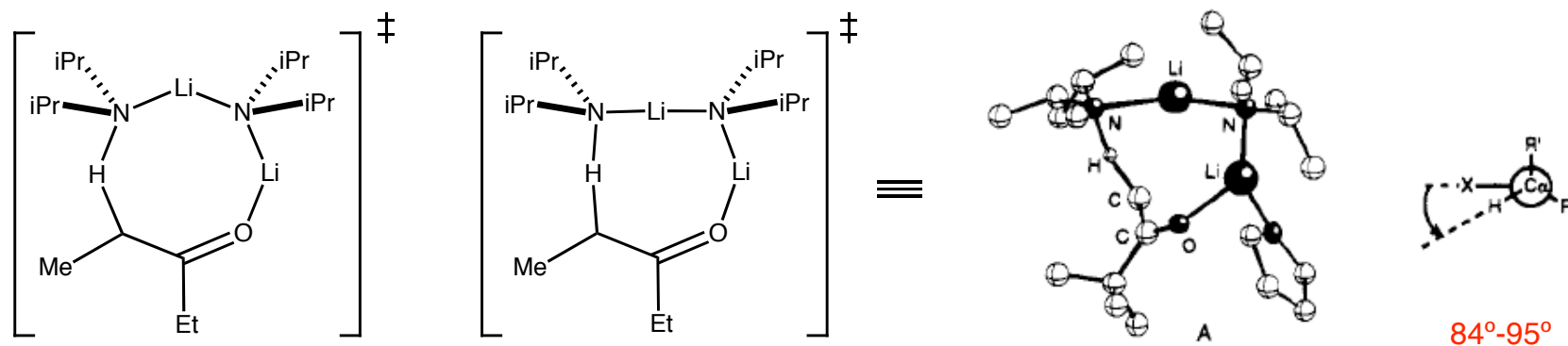
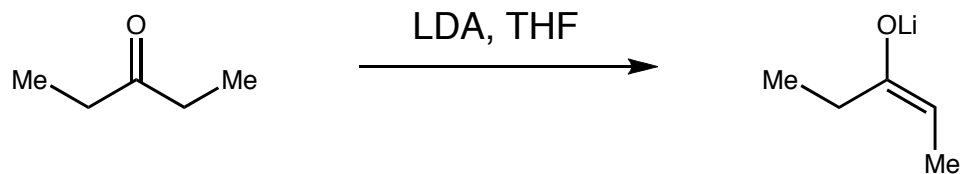


## An Alternative Mechanism



Reacts via the "open dimer" in a cyclic TS<sup>‡</sup>

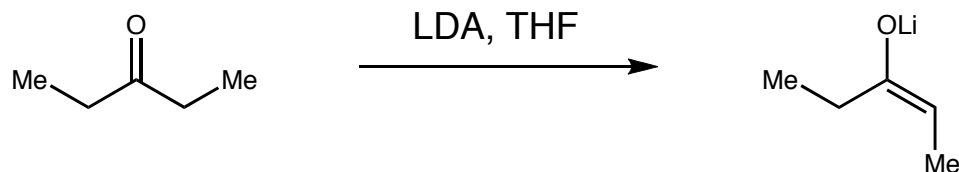
## An Alternative Mechanism



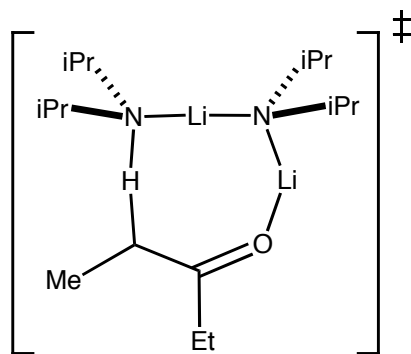
Reacts via the "open dimer" in a cyclic TS<sup>‡</sup>

Collum, D.; Romberg, F. *J. Am. Chem. Soc.* **1995**, 117, 2166.

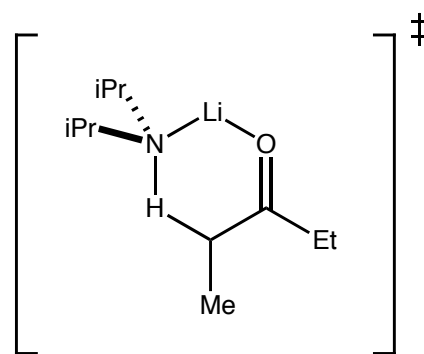
## Calculated Enthalpies Support the Dimer Transition State



amide/substrate/solvent	$H_f(\text{monomer})$	$H_f(\text{open dimer})$	$\Delta H^\ddagger_{(\text{monomer})}^a$	$\Delta H^\ddagger_{(\text{open dimer})}^a$	$\Delta\Delta H^\ddagger^b$
LDA/23/Me <sub>2</sub> O	-121.6 <sup>c</sup>	-167.71 <sup>c</sup>	31.6	29.0	-2.6
LDA/23/THF	-129.88 <sup>c</sup>	-175.47 <sup>c</sup>	31.8	29.9	-1.9
LDA/23/NMe <sub>3</sub>	-72.03 <sup>c</sup>	-116.71 <sup>c</sup>	26.6	19.2	-7.4
LDA/23/HMPA	-111.01 <sup>c</sup>	-156.25 <sup>c</sup>	27.5	27.8	0.3



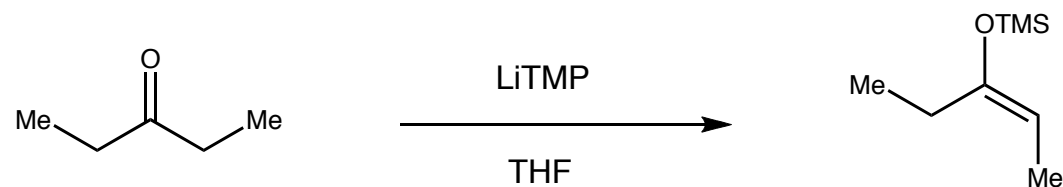
Dimer



Monomer

The calculated enthalpies favor the *E*-product TS in all solvents evaluated

## Relevant Example



Temperature	LiBr Additive	E : Z
-78 °C	none	5 : 1
-20 °C	none	20 : 1
-78 °C	1 eq	50 : 1

Is any of this truly surprising when thought about in the context of aggregates?

## Final Thought

Given that no mechanism can be known with 100% certainty,

does it matter if we keep teaching mechanisms that we know are wrong?