Enolate Formation and Reactivity

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MacMillan Group Meeting
March 12, 2008

Aspects of Enolates that will be Discussed

- (*E*) versus (*Z*) selectivity
- Enolate formation regioselectivity
- O vs. C alkylation
- Factors that influence π-facial selectivity

Aspects of Enolates that will NOT be Discussed

- Aldol reactions
- Chiral auxiliaries
- Chiral catalysts

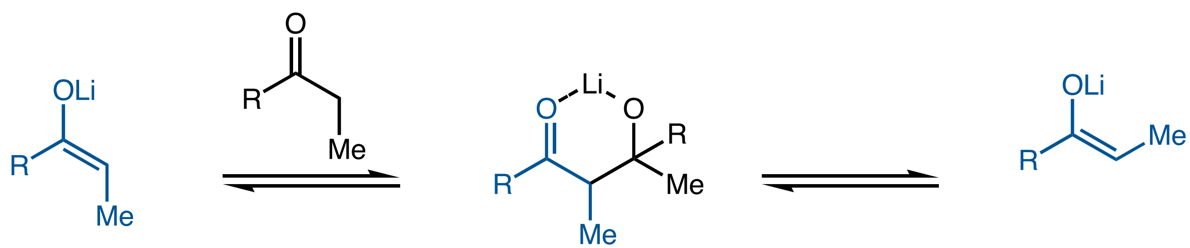
Important references:

Carey & Sundberg, Advanced Organic Chemistry, Part B, Ch. 1
Ian Fleming, Frontier Orbitals and Organic Chemical Reactions
David A. Evans, Asymmetric Synthesis, Volume 3, Stereodifferentiating Additions Reactions, Part B
Primary literature cited within

(E) vs. (Z) Selectivity

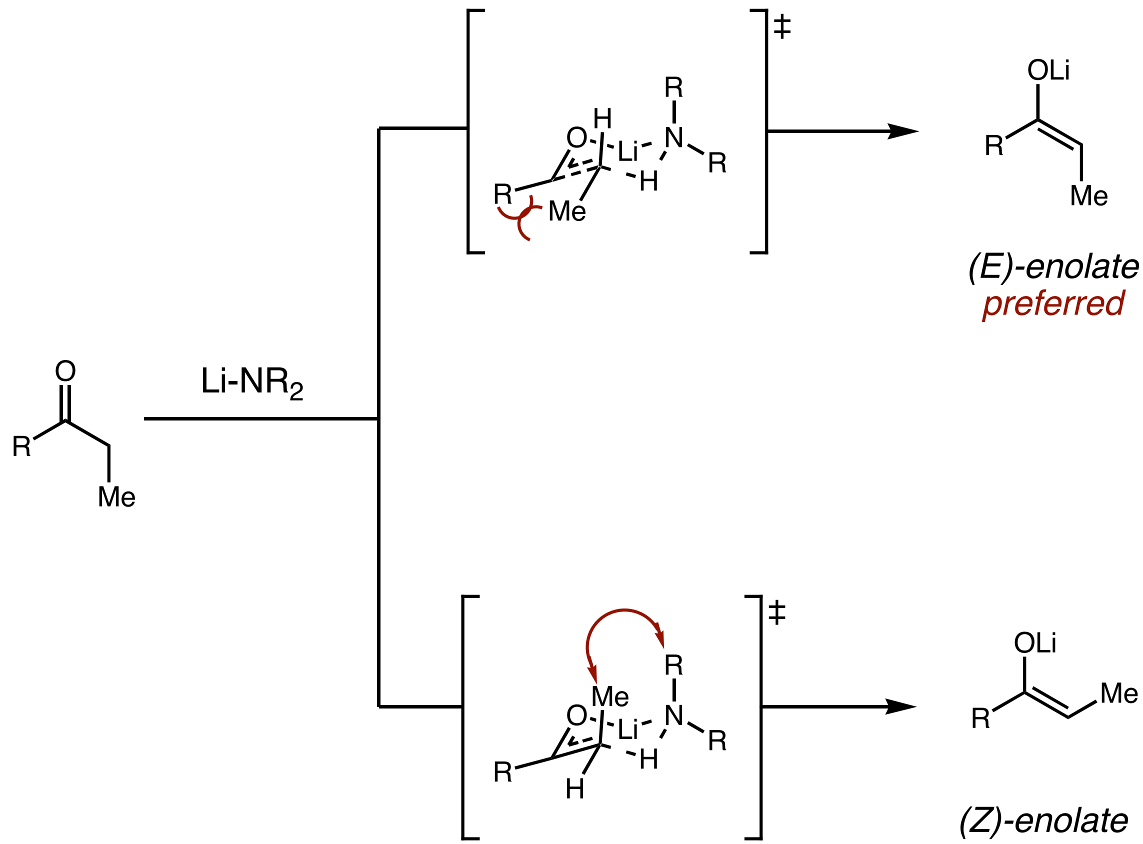
• In the absence of a catalyst or auxiliary, enolate selectivity can be difficult to maintain.

•Rathke proposes an aldol addition-reversion process for ketone enolate equilibrium:



Rathke, M. W. *JACS*, **1980**, *102*, 3959.

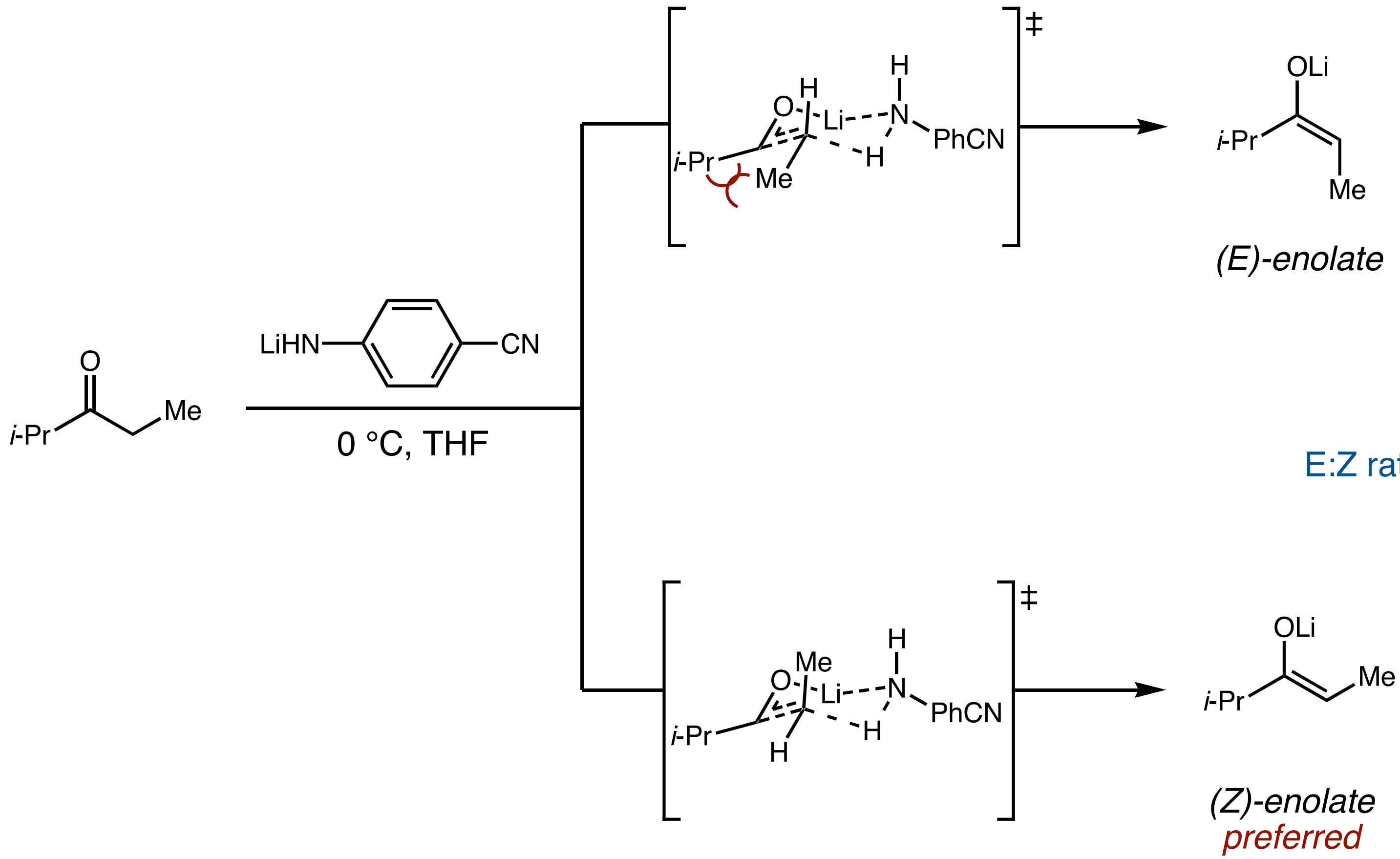
Sterics Affect Enolization by Lithium Amides



• Avoidance of a *syn*-pentane interaction in the transition state favors the (*E*)-enolate

Evans's 206 Notes, Lecture 24
Adaptation from Ireland, *et al.* *JACS*, **1976**, *98,* 2868.

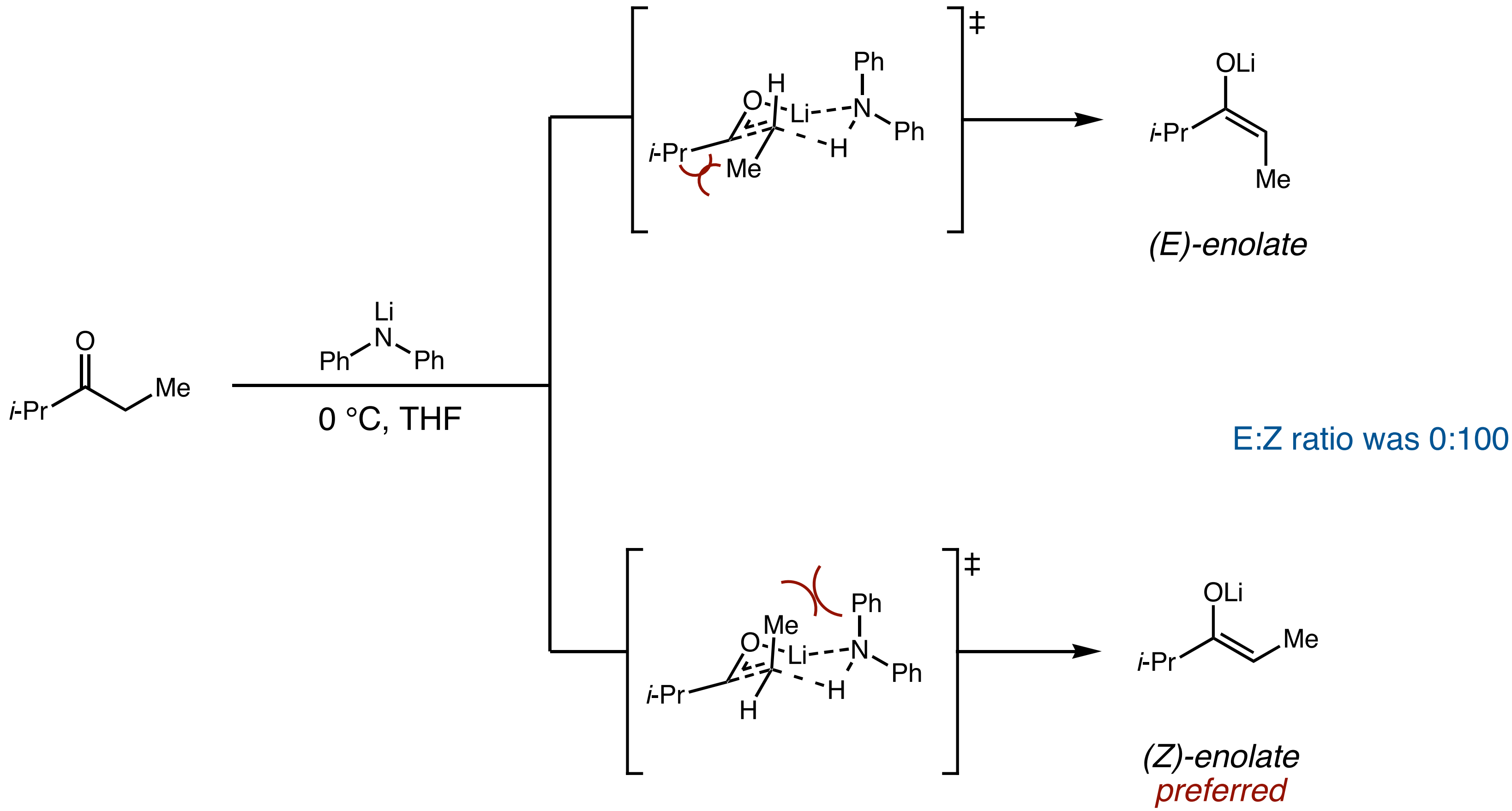
Stereoelectronics Also Affect Enolization



E:Z ratio was 2:98

Xie, L. *et al.* *JOC*, **2003**, *68*, 641-3.

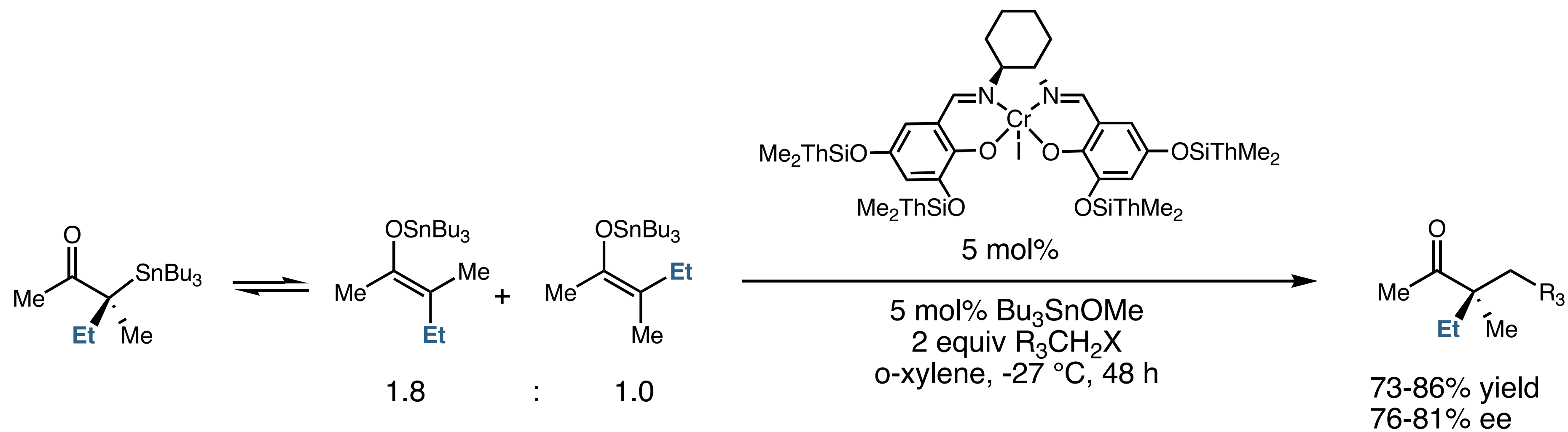
Stereoelectronics Also Affect Enolization

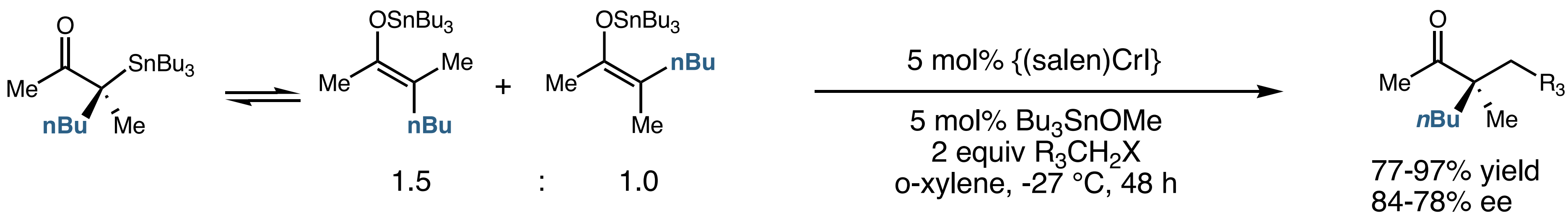


•Substantial stabilization of the electron density on the amide nitrogen leads to a significantly loose transition state, thus favoring the (*Z*)-enolate.

Xie, L. *et al.* *JOC*, **2003**, *68*, 641-3.

Enantioselective Alkylations of Tributyltin Enolates Catalyzed by a {Cr(salen)} Complex





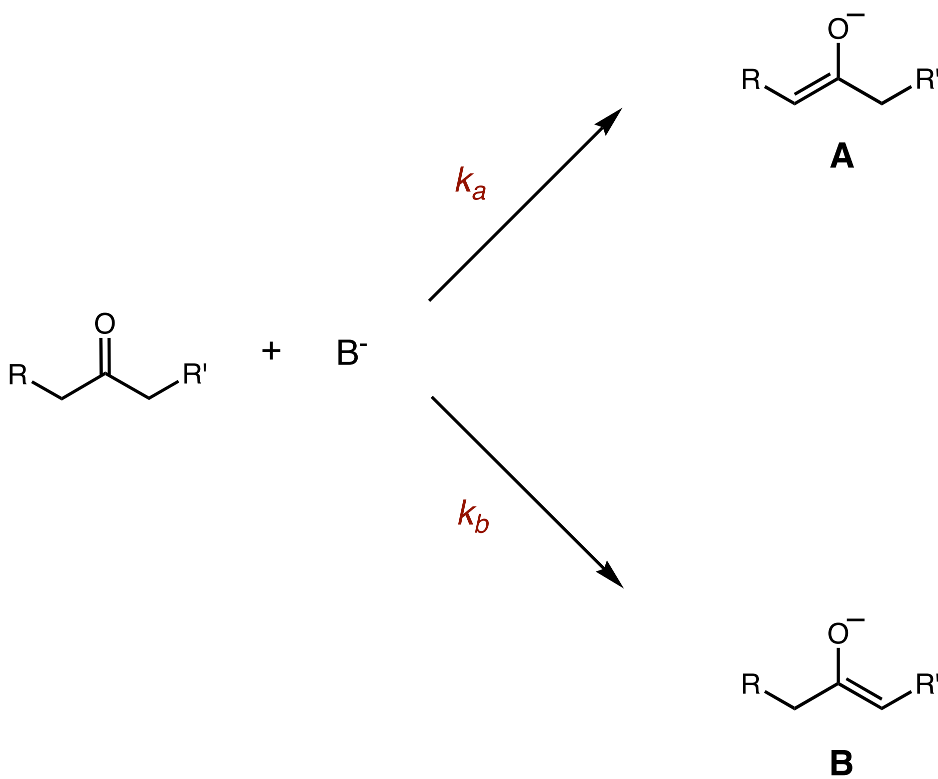
- A variety of sp^3 alkyl bromides and alkyl iodides used as electrophiles
- Enantioselectivity of disubstituted ketone product not limited by E/Z ratio of enolate isomers

Doyle, A. G.; Jacobsen, E. N. *ACIEE*, **2007**, *46*, 3701-5.

Regioselectivity in Enolate Formation

• Kinetic vs. thermodynamic control

Kinetic Control



$$\frac{[\mathbf{A}]}{[\mathbf{B}]} = \frac{k_a}{k_b}$$

• Product composition determined by relative rates of competing proton-abstraction reactions

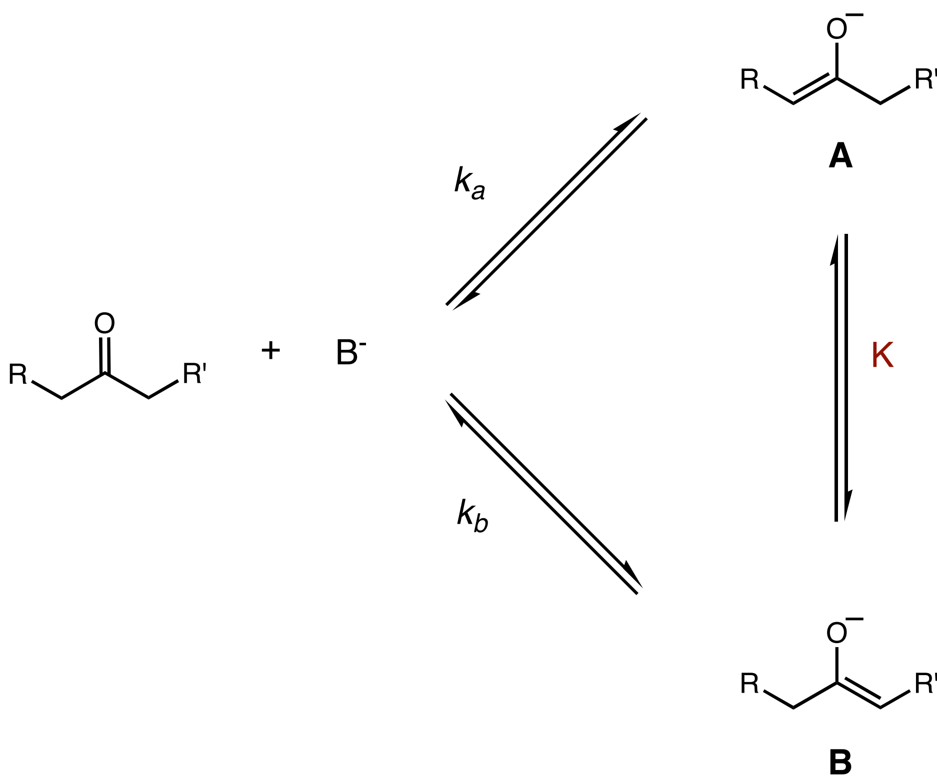
• Deprotonation is rapid, quantitative, and irreversible.

• Favors less substituted enolate

Regioselectivity in Enolate Formation

• Kinetic vs. thermodynamic control

Thermodynamic Control

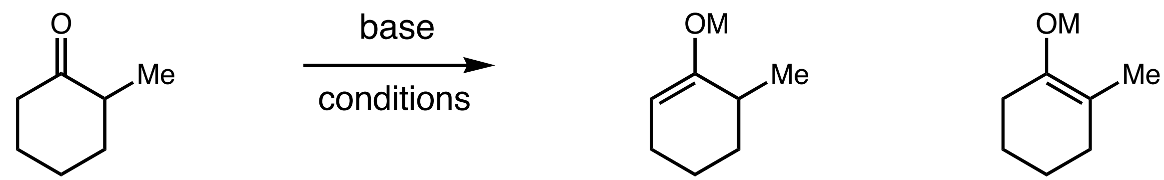


$$\frac{[A]}{[B]} = K$$

• Product composition determined by relative thermodynamic stability of the enolates.

• Favors more substituted enolate (Zaitzev's Rule)

Kinetic vs. Thermodynamic Control

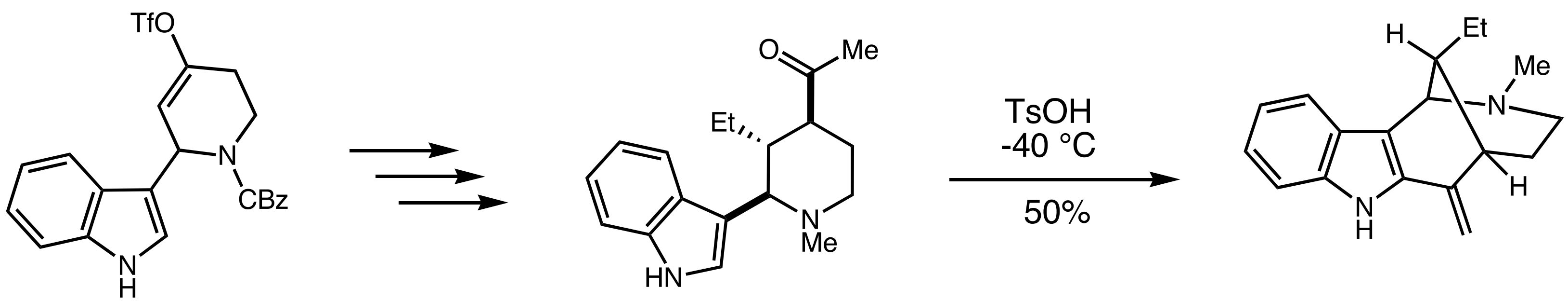


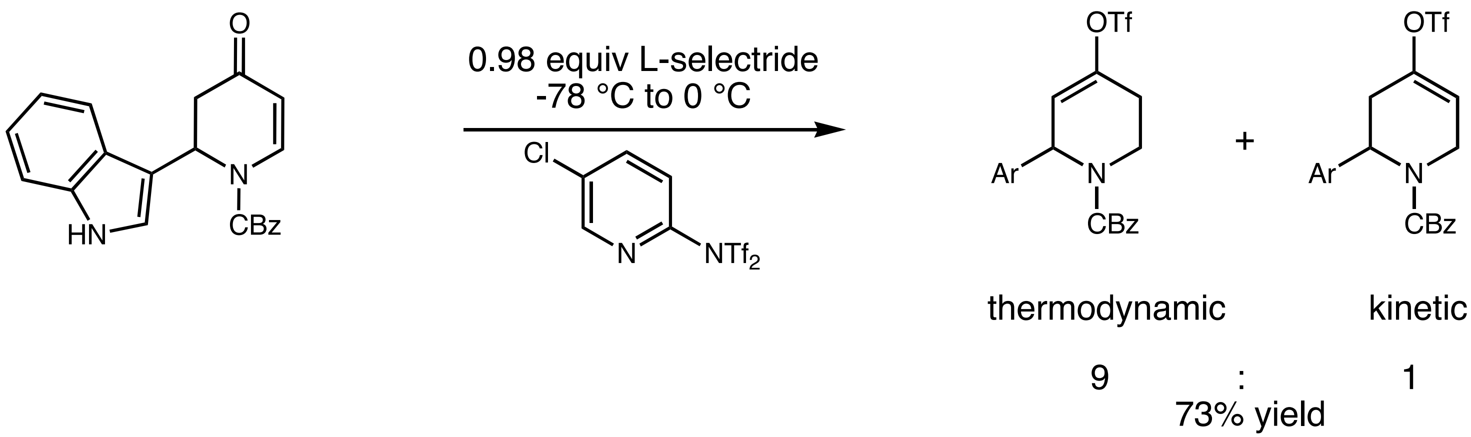
A **B**

base	**temp**	**ratio (A/B)**	**control**
$LiN(i\text{-}C_3H_7)_2$	0 °C	99:1	kinetic
$KN(SiMe_3)_2$	-78 °C	95:5	kinetic
Ph_3CLi	-78 °C	90:10	kinetic
Ph_3CK	25 °C	67:33	kinetic
Ph_3CK	25 °C	38:62	thermodynamic
NaH	25 °C	26:74	thermodynamic
Ph_3CLi	25 °C	10:90	thermodynamic

House, H. O. *et al.* *JOC*, **1969**, *34*, 2324.
Brown, C. A. *JOC*, **1974**, *39*, 3913.
Stork, G., Hudrlik, P. F. *JACS*, **1968**, *90*, 4464.

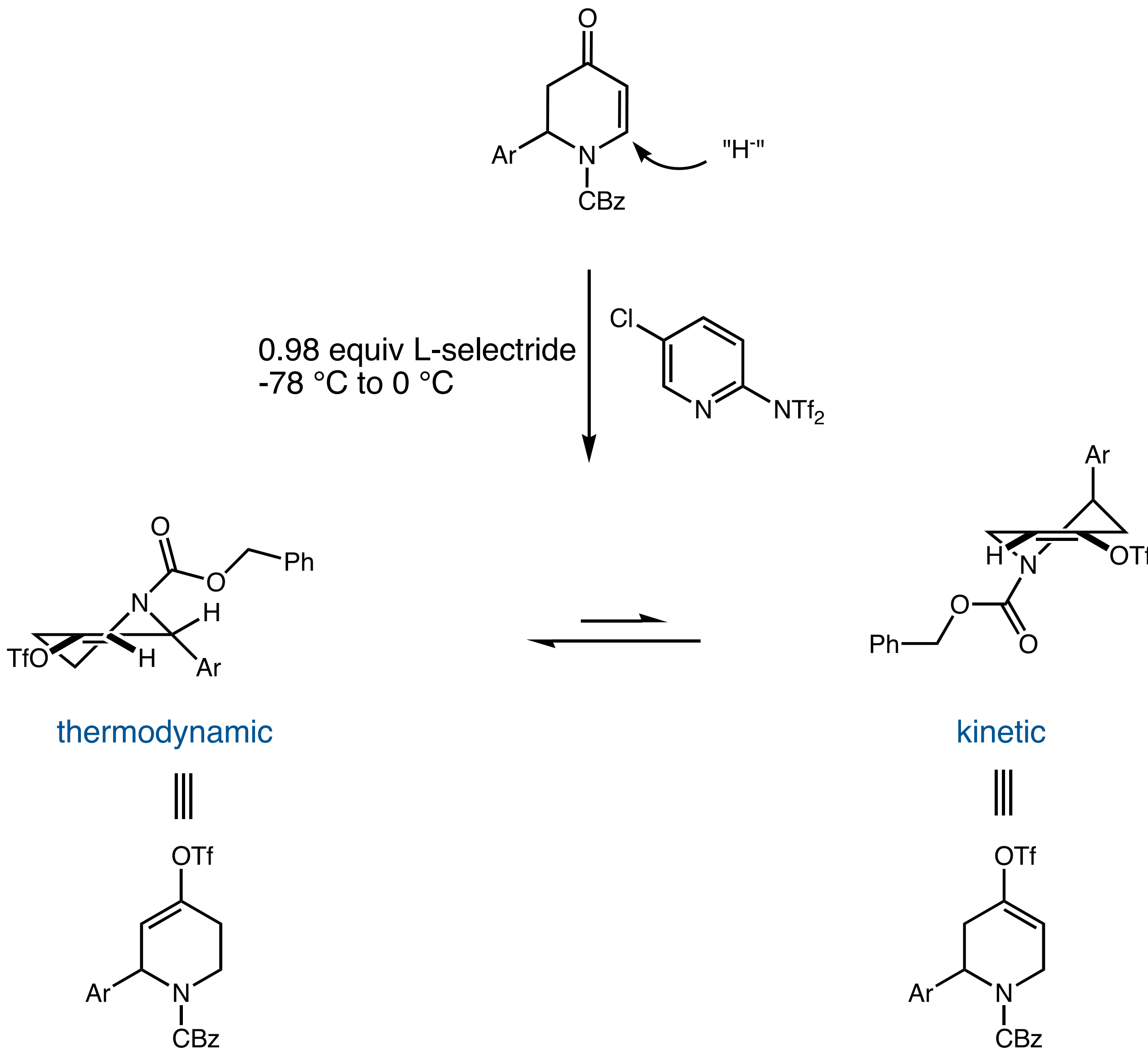
A-1, 3 Strain Controls Enolate Regioselectivity





Tasber, E. S.; Garbaccio, R. M. *TL*, **2003**, 44, *9185-8*.

A-1, 3 Strain Controls Enolate Regioselectivity

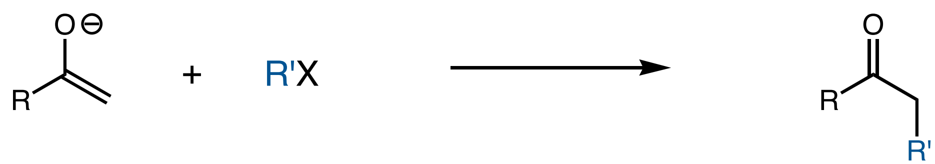


indole must adopt axial conformation to avoid syn-pentane interaction

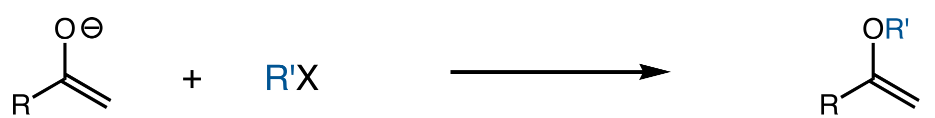
Tasber, E. S.; Garbaccio, R. M. TL, 2003, 44, 9185-8.

Enolates: Ambident Nucleophiles

• Alkylation of an enolate can occur at either carbon or oxygen



C-alkylation



O-alkylation

• What factors influence the C/O-alkylation ratio?

Elements that Dictate O-Alkylation vs. C-Alkylation Ratios

• Dissociation vs. clustering of ions	*Metal* *Solvent*
• Charge vs. Orbital Control	
• Hard-soft compatibility	*Leaving group*
• Stereoelectronics	*Orbital Overlap*

Dissociated versus Aggregated Enolates

- O-alkylation is prevalent when the enolate is dissociated
- C-alkylation is prevalent where ion clustering occurs

O-Alkylation

- Prevalent in polar, aprotic solvents
- Metal chelators are effective additives

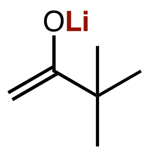
C-alkylation

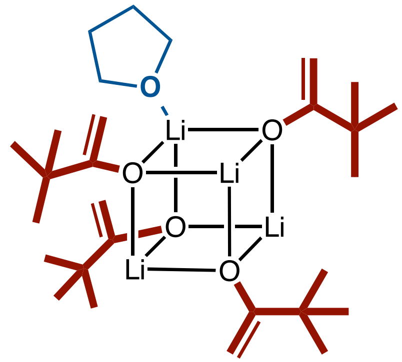
- Favors smaller, harder cations due to tighter coordination
- Prevalent in protic & apolar solvents
- Ideal in THF & DME

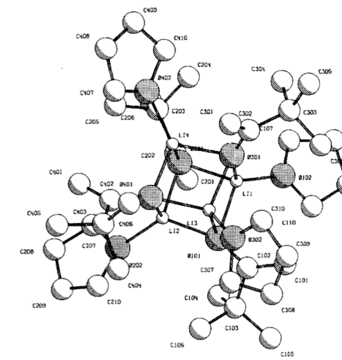
Lithium, Sodium, and Potassium Enolates of Pinacolone

Examples of Ion Clustering

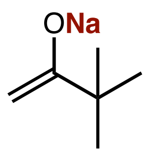
- Lithium enolate

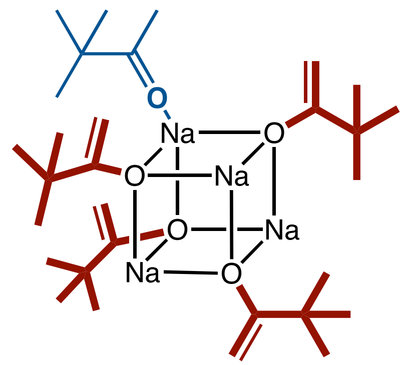


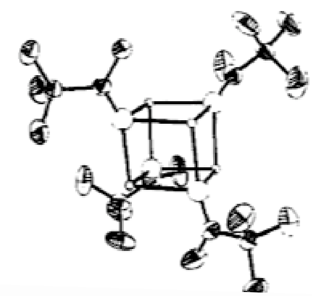


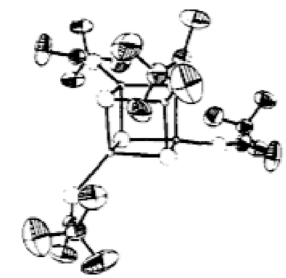


- Sodium enolate

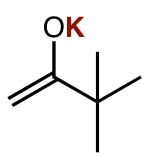


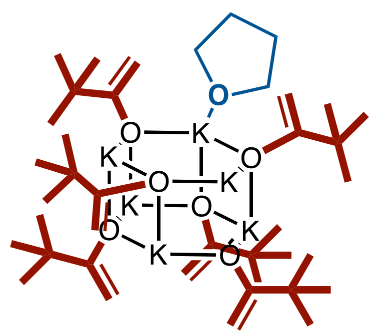


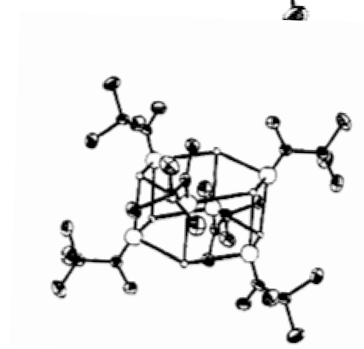


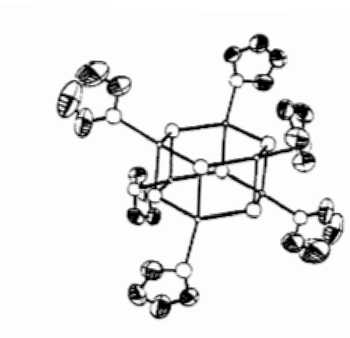


- Potassium enolate





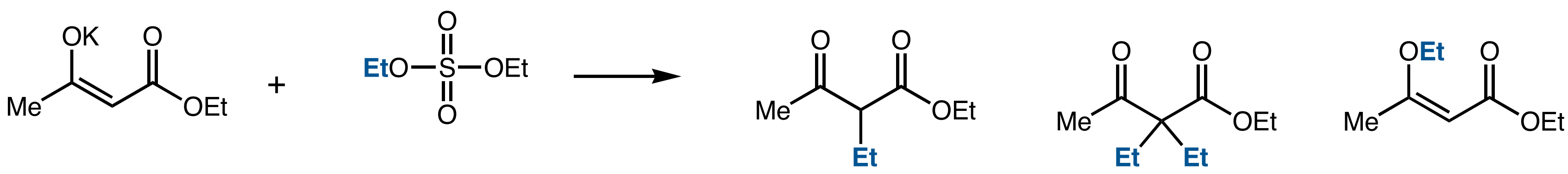




Williard, P.G. and Carpenter, G.B. *JACS*, **1986**, *108*, 462-8.
Seebach, D.; Dunitz, J.D. *et al.* *Helv. Chim. Acta*. **1981**, *64*, 2617.

Dissociation vs. clustering of ions

- O-alkylation is prevalent when the enolate is dissociated
- C-alkylation is prevalent where ion clustering occurs



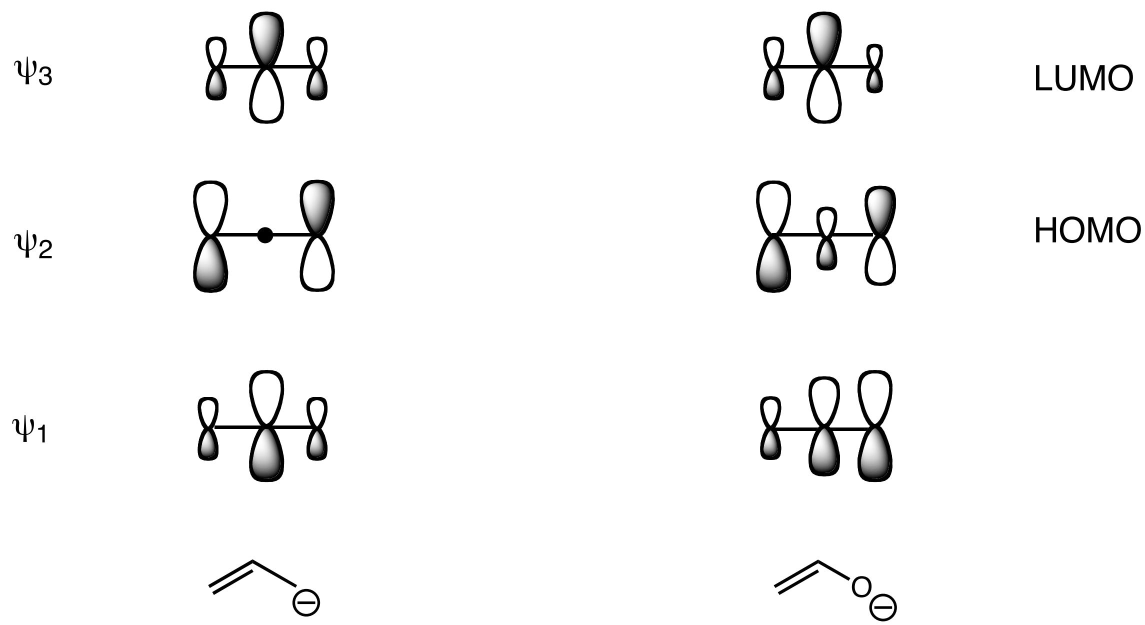
A B C

solvent	A	B	C
HMPA	15%	2%	83%
t-BuOH	94%	6%	0%
THF	94%	6%	0%

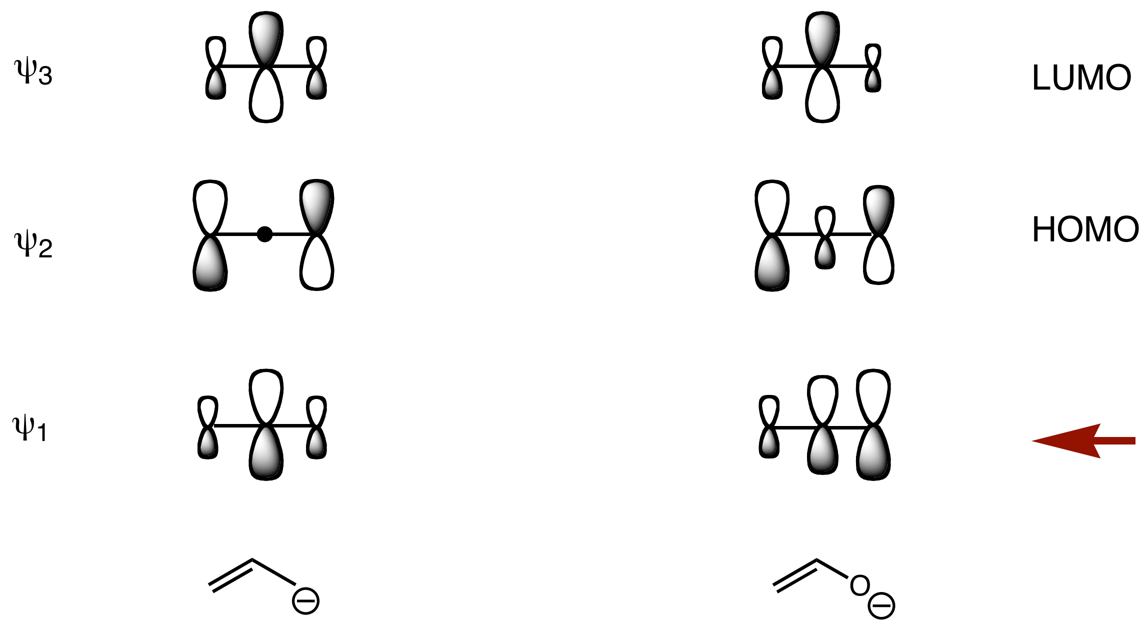
- HMPA promotes ion dissociation, favoring O-alkylation
- THF promotes ion clustering, favoring C-alkylation
- *t*-BuOH hydrogen-bonds with enolate anion, favoring C-alkylation

Kurts, A.L. *et al.* Dokl. Akad. Nauk. SSR (Engl. Transl.) 1969, 187, 595.

Using MO Theory to Understand Charge vs. Orbital Control



Using MO Theory to Understand Charge vs. Orbital Control

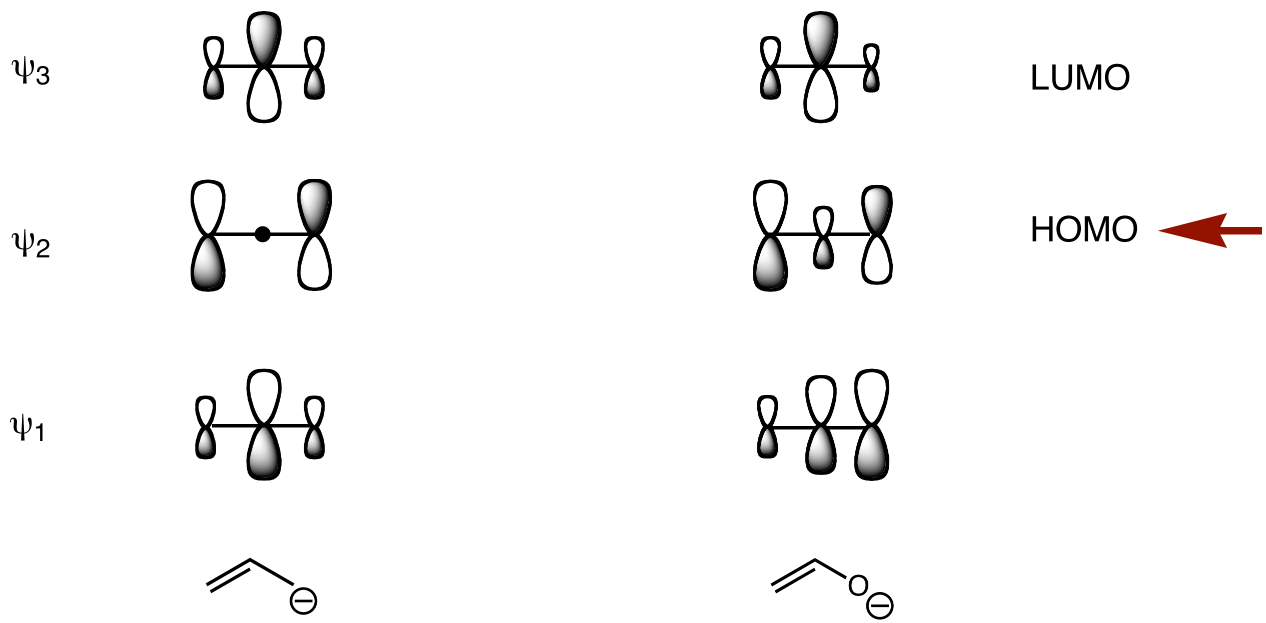


Charge control

- *Reaction occurs at the atom carrying the highest total electron density*
- *Predominant with charged electrophiles (e.g., H^+)*

Klopman, G.; Hudson, R. F. *Theoret. Chim. Acta (Berl.)* **1967**, *8*, 165-74.

Using MO Theory to Understand Charge vs. Orbital Control



Charge control

- *Reaction occurs at the atom carrying the highest total electron density*
- *Predominant with charged electrophiles (e.g., H^+)*

Orbital control

- *Reaction occurs at the atom whose frontier electron density is the highest*
- *Predominant with neutral electrophiles with relatively low-lying LUMOs*

Klopman, G.; Hudson, R. F. *Theoret. Chim. Acta (Berl.)* **1967**, *8*, 165-74.

Hard-Soft Acid Base Interactions (Leaving-Group Effects)

O-alkylation (charge control)

• Predominant with hard leaving groups

• Favored by an early transition state, where charge distribution is the most important factor

•Favored by conditions that afford a dissociated, more reactive enolate

C-alkylation (orbital control)

• Predominant with soft leaving groups

• Favored by a later transition state, where partial bond formation is the dominant factor

• More stable than the O-alkylation product

$$E\ (C{=}O + C{-}C) > E\ (C{=}C + C{-}O)$$

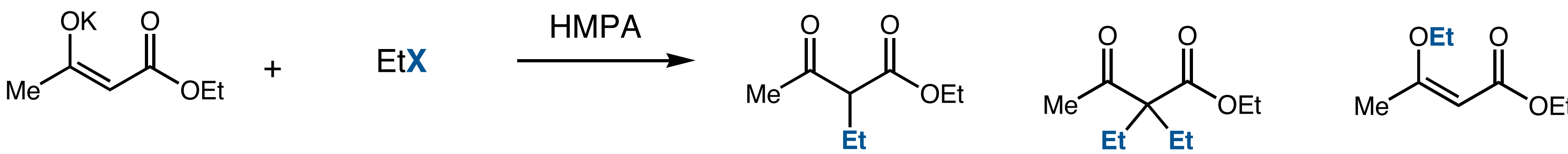
$$(745 + 347)\ \text{kJ/mol} > (614 + 358)\ \text{kJ/mol}$$

$$1097\ \text{kJ/mol} > 972\ \text{kJ/mol}$$

Bond energy values taken from Zumdahl, Chemical Principles, 5th ed.

Nature of the Leaving Group

• Of the two nucleophilic sites on the enolate, oxygen is harder than carbon



A B C

X	A	B	C
OTs	11%	1%	88%
Cl	32%	8%	60%
Br	38%	23%	39%
I	71%	16%	13%

• **Hard**---OTs > Cl > Br > I---**Soft**

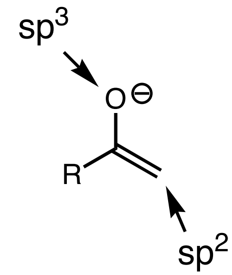
• Greater O-alkylation is observed with harder electrophiles

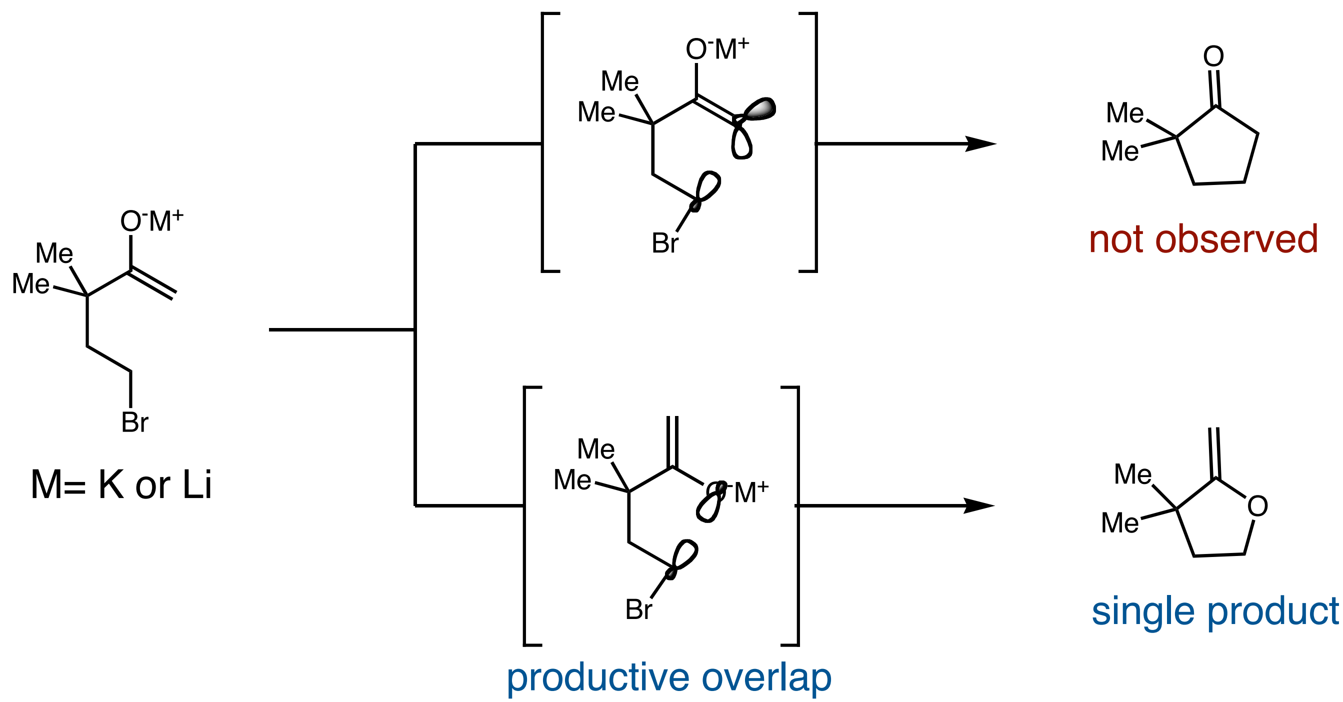
• Greater C-alkylation is observed with softer nucleophiles

Kurts, A. L. *et al.* *Tet.*, **1971**, *27*, 4777.

Orbital Overlap
(Baldwin's Suggestions)

- For enolate cyclizations, orbital overlap is imperative
- Oxygen and carbon sites on the enolate have different hybridizations
- Hybridization can have drastic effect on atom reactivity





Baldwin, J. E.; Kruse, L. I. J. Chem. Com. 1977, 233-35.

Elements that dictate enolate π-facial selectivity

• Intraannular Chirality Transfer

Asymmetric center is connected to the enolate framework through cyclic array of covalent bonds.

•Extraannular Chirality Transfer

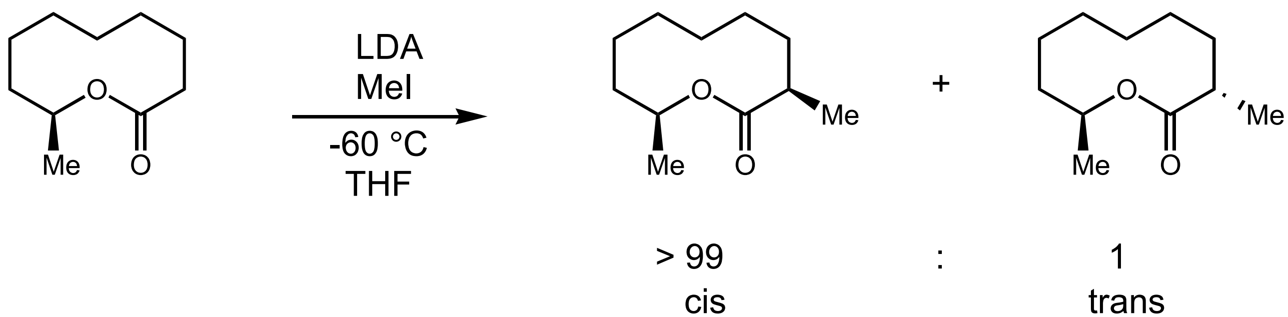
Chiral moiety is not conformationally locked at ≥2 more contact points via covalent bonds to enolate

• Chelate-Enforced Intraannular Chirality Transfer

Chelate provides organizational role in fixing orientation between resident asymmetric center and enolate system.

Evans, D. A. "*Stereoselective Alkylation Reactions of Chiral Metal Enolates*". Asymmetric Synthesis. Vol. *3*, 1-110.

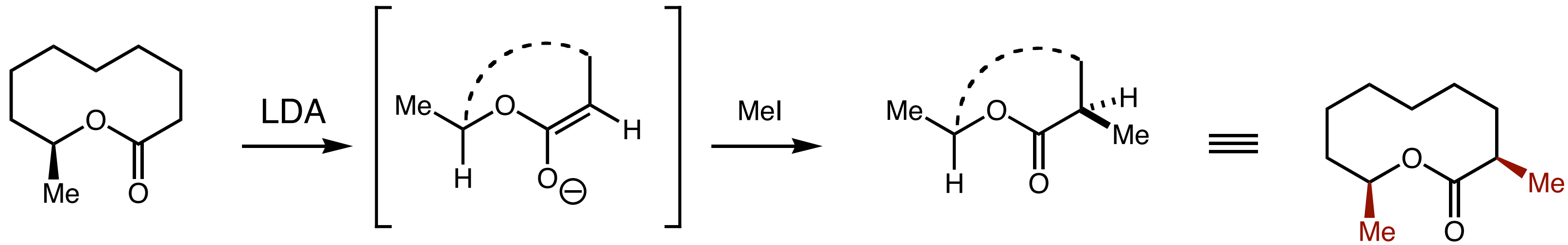
Intraannular Chirality Transfer
(Endocyclic Enolates)



Still, W. C.; Galynker, I. *Tetrahedron*, **1981**, *37*, 3981-96.

Intraannular Chirality Transfer

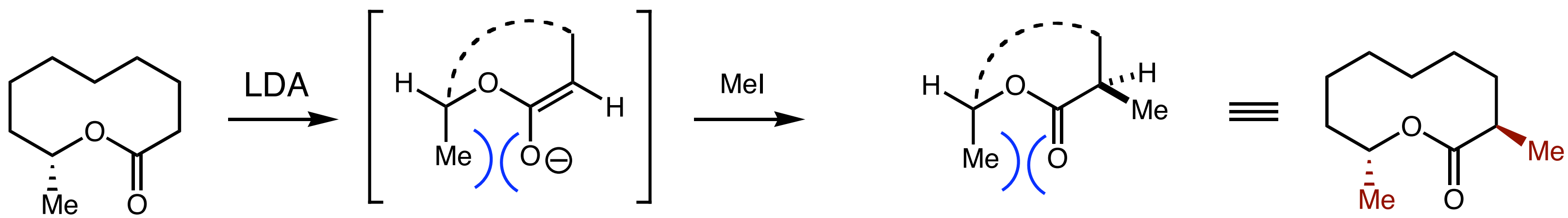
- Lactone affords only (*E*)-enolate
- Ring shields one face of the formed enolate



back face of enolate
shielded by ring

major product

- *Syn*-pentane interactions discourage transition state necessary for forming trans product



syn-pentane
interaction

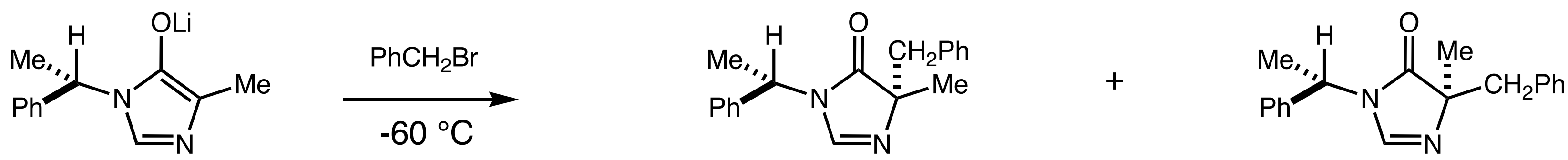
minor product

Still, W. C.; Galynker, I. *Tetrahedron*, **1981**, *37*, 3981-96.

Extraannular Chirality Transfer
(Exocyclic Enolates)

• A-1, 3 strain dictates conformation of the imidazolate

• Bulky phenyl group directs alkylation toward Re face



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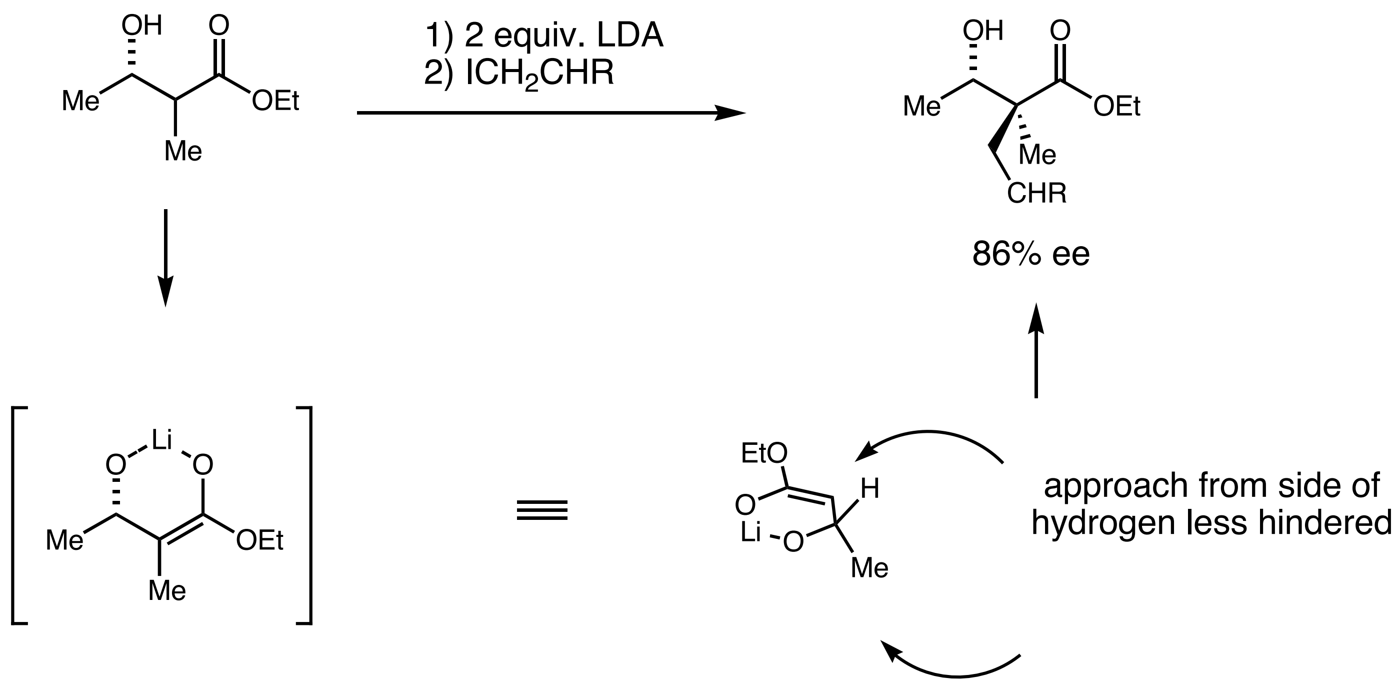
Schollkopf, U. *et al.* Liebigs. Ann. Chem. 1981, 439.

Chelation Affects Pi Facial Selectivity



Frater, G. *TL*, **1981**, *22*, 425.

Summary

• Enolate formation

• **(*E*) vs. (*Z*) selectivity** (*sterics, electronics*)

• **Regioselectivity** (*thermodynamics vs. kinetics, sterics*)

• Enolate Reactivity

• **O vs. C alkylation** (*dissociation vs. clustering of ions, charge vs. orbital control, hard-soft interactions, orbital overlap*)

• **Pi facial selectivity** (*intraannular chirality transfer, extraannular chirality transfer, chelation*)