

## Chiral $\alpha$ -Heteroatom Substituted Lithio Compounds

DAE Evening Seminar

March 8, 1996

Bernard Côté



X = O, N, S, Se

Leading references :

Aggarwal, V. K. *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 175-177.

Muci, A. R. *DAE Evening Seminar*, Feb. 21, **1995**.

Beak, P. J. *Am. Chem. Soc.* **1996**, 118, 715-721.

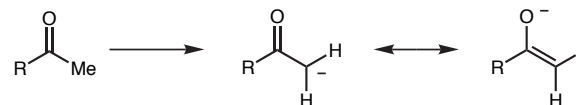
Macdonald, T. L. and McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, 110, 842-853.

## Carbanion : Stability and Structure



- The structure of a carbanion is directly related to his stabilizing substituent(s).
- Several factors are known to stabilize a carbanion :

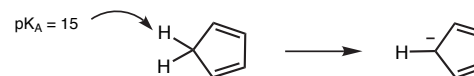
- Resonance :  $\pi$  acceptor is in conjugation with the lone pair inducing planarity of the carbanion.



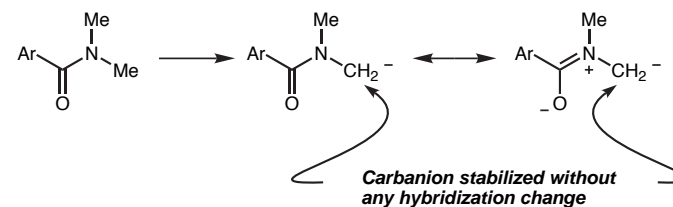
- s character : Increase of s character of the carbanion result in more stable carbanion.



- Aromaticity : Conjugation of the lone pair results in planarity of the carbanion

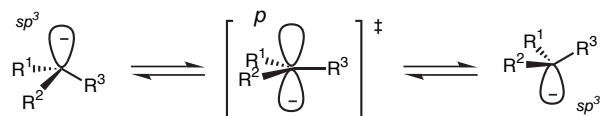


- Field (dipole) or Inducing effect : Electronegative substituents on the carbanion increases s character.



## $sp^3$ Carbanion : Barrier of Inversion

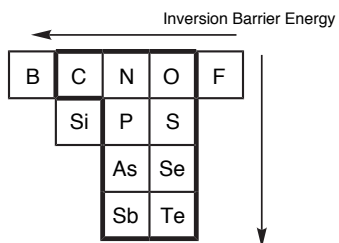
### Pyramidal atomic inversion



An atom bonded to three substituents in a pyramidal geometry and possessing one unshared electron pair may spontaneously undergo an inversion of configuration.

Lambert *Top. Stereochem.* **1971**, 6, 19.

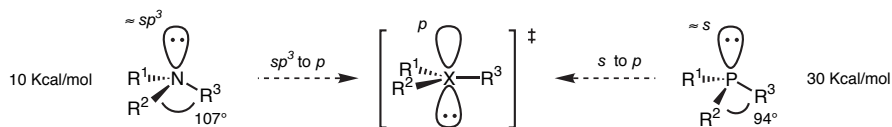
### General trend



| Inversion Barrier Kcal/mol |     |
|----------------------------|-----|
| $H_3O^+$                   | < 1 |
| $NR_3$                     | 10  |
| $PR_3$                     | 30  |
| $SR_3^+$                   | 30  |
| $ArS(O)R$                  | 40  |

For R = alkyl Ar =  $C_6H_5$

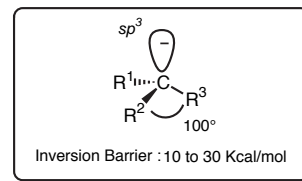
**The geometric argument :** Inversion happens more rapidly for ground-state bond angles closer from the transition state ( $120^\circ$ ).



The lone pair of nitrogen ( $sp^3$ ) is also closer in energy to the transition state than the lone pair of phosphorus (s).

## $sp^3$ Carbanion : Barrier of Inversion

### Do carbanion follow the trend?



**YES BUT...**

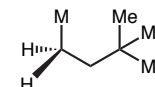
- Because the carbanion is linked to the metal by a partially covalent bond, it is not clear whether a carbanion undergoes a unimolecular pyramidal inversion analogous to nitrogen.
- Aggregation, nature of the C-metal bond as well as possible internal chelation should be considered in the configurational stability of the carbanion.

### Height of the barrier to pyramidal inversion is affected by :

#### - Counterion



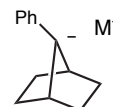
vs



| M = | Inversion Barrier |
|-----|-------------------|
| Li  | 15 Kcal/mol       |
| Mg  | 20 Kcal/mol       |
| Zn  | 26 Kcal/mol       |
| Al  | no inversion      |
| Hg  | no inversion      |

Roberts *J. Am. Chem. Soc.* **1966**, 88, 737.

- The fact that a pyramidal inversion necessitates a complete dissociation of the counterion contribute to an increase of the energy inversion barrier, for more strongly associating metal.



For  $M^+$  = K or Cs anion is planar;  
Li anion is pyramidal

Grutzner *J. Am. Chem. Soc.* **1980**, 102, 4709.

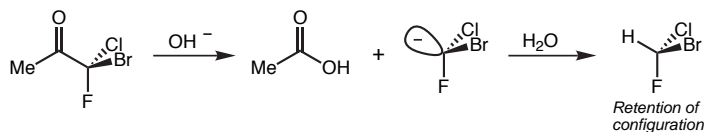
## $sp^3$ Carbanion : Barrier of Inversion

■ Height of the barrier to pyramidal inversion is affected by :

### - Solvent and Complexation:

- For some system, low-dielectric solvent prevents inversion because the carbanion is closely paired with its counterion.
- A high-dielectric solvent can stabilize the carbanion or disrupt an essential internal chelate.
- Internal chelate sometimes are responsible for racemization as well as retention of configuration.

### - Electronegativity of the substituents

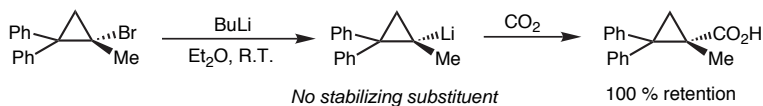


Hargreaves *J. Chem. Soc. C* **1971**, 1013

The analogy...

|                                 |    |                                |
|---------------------------------|----|--------------------------------|
| NH <sub>3</sub><br>5.8 Kcal/mol | vs | NF <sub>3</sub><br>50 Kcal/mol |
|---------------------------------|----|--------------------------------|

### - Angle strain

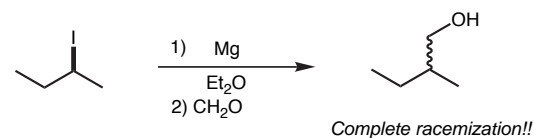


Walborsky *J. Am. Chem. Soc.* **1974**, 96, 3711.

Walborsky *J. Am. Chem. Soc.* **1977**, 99, 2631.

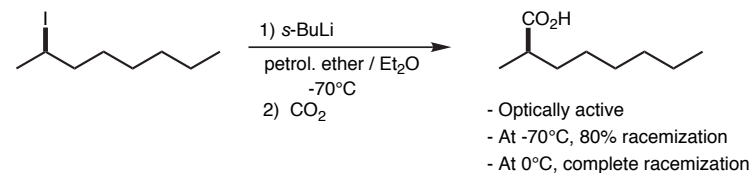
## Chiral Carbanion : First Attempt

■ Grignard reagent



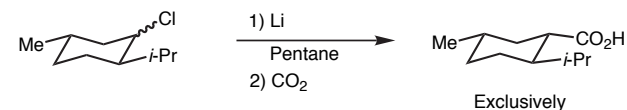
Pickard and Kenyon *J. Chem. Soc.* **1911**, 99, 45.

■ Transmetalation



Letsinger *J. Am. Chem. Soc.* **1950**, 72, 4842.

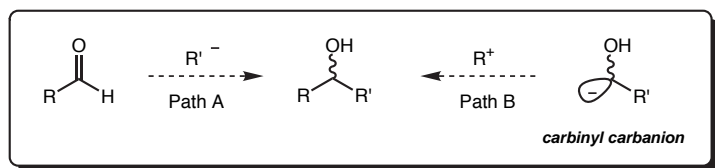
■ Reductive lithiation



Glaze *J. Org. Chem.* **1968**, 33, 1967.

## *$\alpha$ -Alkoxyorganolithium Reagent*

■ General concept : a carbinyllithium

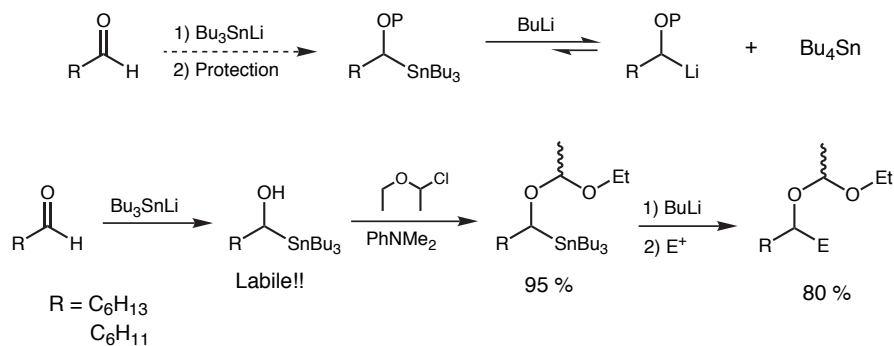


Path A : Subject to chiral induction from aldehyde substituent  
see : Evans, *J. Am. Chem. Soc.* **1995**, 117, 6619.

Path B : Chirality already set by the nucleophile. But for this path to be efficient the carbinyllithium should be :

1. Easily accessible with high diastereo/enantiomeric purity.
2. Configurationally stable under reaction condition.
3. Trapped by the electrophile with complete retention or inversion of configuration.

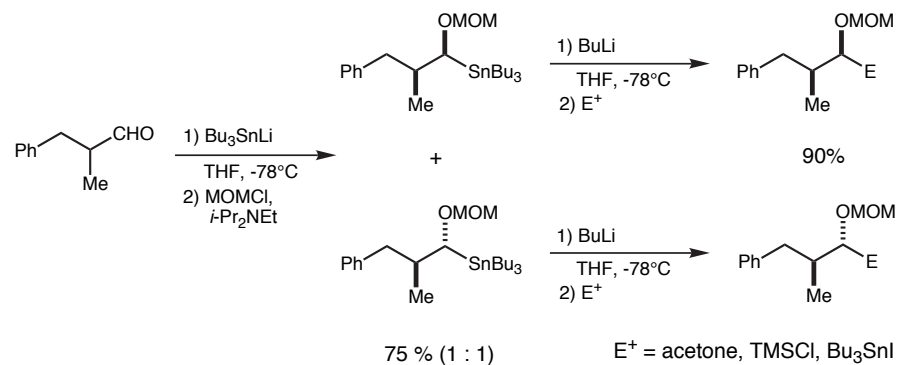
■ The stannylation/destannylation strategy



Still *J. Am. Chem. Soc.* **1978**, 100, 1481.

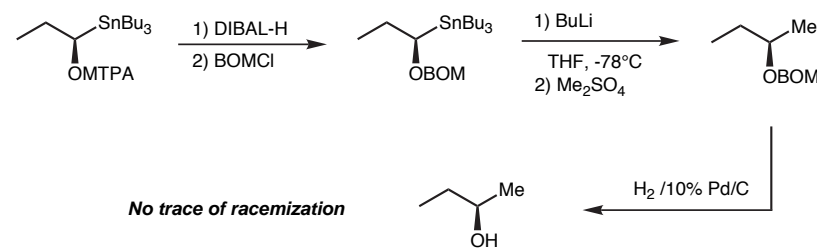
## *Configurationally Stable $\alpha$ -Alkoxyorganolithium Reagent*

■ The key experiment!



**- Only one stereoisomer with full retention of configuration**  
**-  $\alpha$ -Alkoxyorganolithium reagent are configurationally stable from -78°C to -30°C**

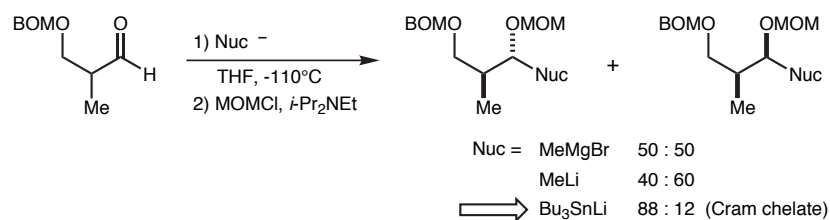
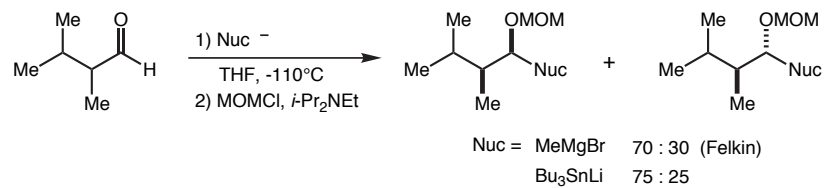
■ Enantiomerically pure  $\alpha$ -alkoxyorganostannane



Still *J. Am. Chem. Soc.* **1980**, 102, 1201.

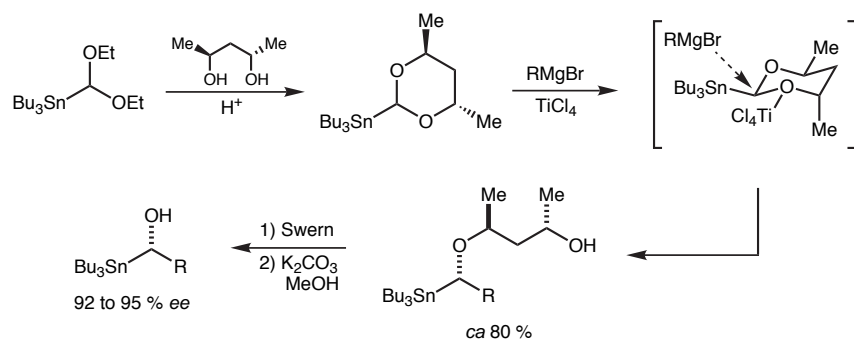
## Synthesis of Enantio and Diastereochemically Pure $\alpha$ -Alkoxyorganolithium Reagent

### ■ $\alpha$ -Induction for the addition of $\text{Bu}_3\text{SnLi}$



Still *J. Am. Chem. Soc.* **1980**, *102*, 1201.

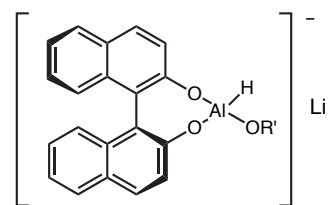
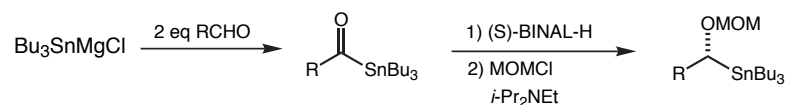
### ■ Chiral acetal opening



Nakai *Tetrahedron Lett.* **1994**, *35*, 1913.

## Synthesis of Enantiopure $\alpha$ -Alkoxyorganolithium Reagent

### ■ Enantioselective reduction

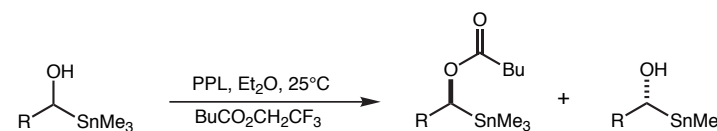


(S)-BINAL-H

| R                              | Yield | ee % |
|--------------------------------|-------|------|
| Me                             | 58%   | 94   |
| Et                             | 69%   | 96   |
| <i>i</i> -Pr                   | 52%   | 96   |
| C <sub>5</sub> H <sub>11</sub> | 53%   | 92   |
| <i>t</i> -Bu                   | 55%   | 80   |

Chong *J. Org. Chem.* **1988**, *53*, 5586.

### ■ Enzymatic resolution

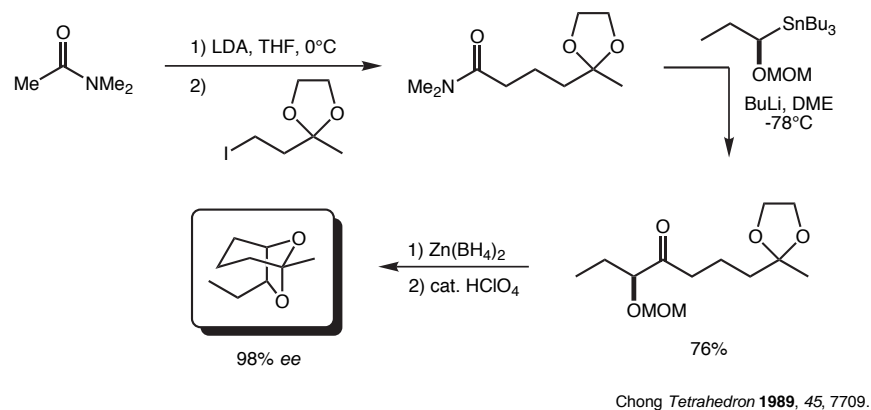


| R  | ee % ester (yield) | ee % alcohol (yield) |
|----|--------------------|----------------------|
| Me | 98 (38%)           | 97 (41%)             |
| Et | 99 (36%)           | 56 (36%)             |
| Pr | 97 (7%)            | 7 (68%)              |

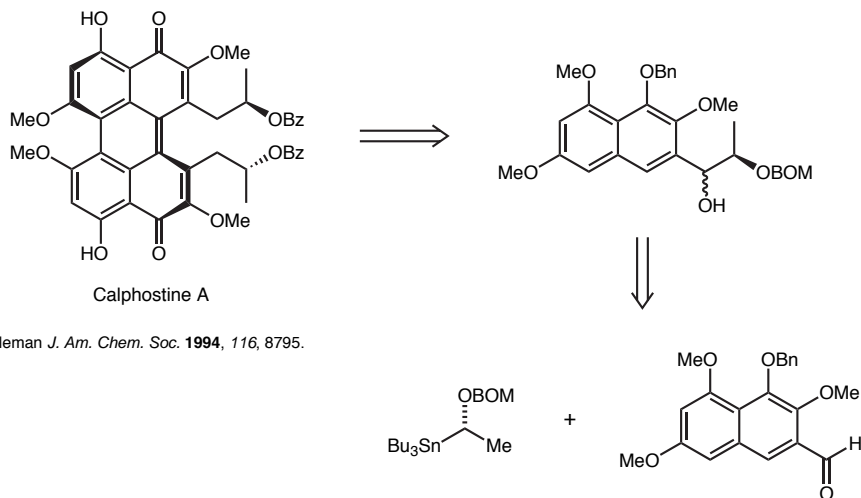
Chong *Tetrahedron Lett.* **1991**, *32*, 5683.

## Synthetic Application

### ■ Synthesis of *endo*-Brevicommin



### ■ Synthesis of the protein kinase C inhibitor Calphostin A



## Physical Properties of $\alpha$ -Alkoxyorganolithium : Stabilizing Effects

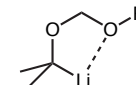
### ■ Stabilizing effect of the $\alpha$ -alkoxy substituent

- **Inductive** : According to calculation (vapor phase)  $\begin{matrix} \text{OH} \\ | \\ \text{CH}_2^- \end{matrix}$  is 15.8 Kcal/mol  
more stable than  $\text{CH}_3^-$   
 $\Rightarrow$  Stabilizing  $\sigma$ -inductive effect is more important than destabilizing  $\pi$ -effect

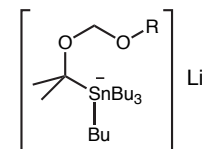
- **Stereoelectronic** : Anion delocalized in  $\sigma^*$  of C-O?

- **Bridging** : According to calculation (vapor phase)  $\begin{matrix} \text{H} \\ | \\ \text{O} \\ | \\ \text{H}_2\text{C}-\text{Li} \end{matrix}$  is 9 Kcal/mol  
more stable than  $\text{CH}_3\text{Li}$

- **Internal Chelate** : As acetals were found to be optimal protecting groups, the stabilizing effect might come from :

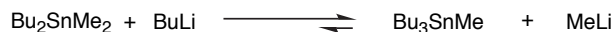
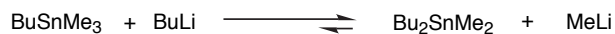


- **Ate Complex** : Selective transfer of the  $\alpha$ -alkoxy ligand from the ate complex



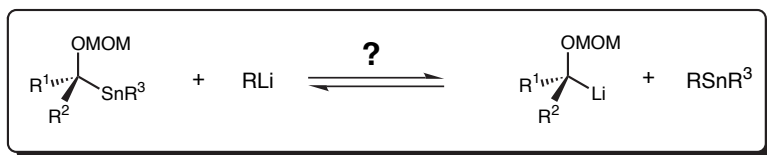
## Physical Properties of $\alpha$ -Alkoxyorganolithium : The Tin-Lithium Exchange

### Relative thermodynamic stabilities of organolithium species

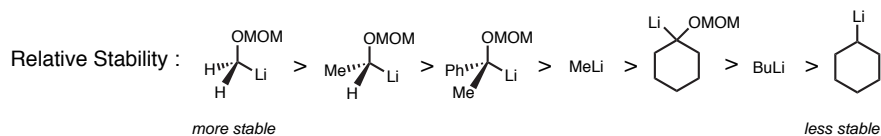


- Thermodynamic relationship lies far to the right (>95 : 5)
- No ate complex observed

What is the relative stability of primary, secondary and tertiary  $\alpha$ -alkoxystannanes as a function of the tin substituent and the alkylolithium?



|           |                    |              |            |
|-----------|--------------------|--------------|------------|
| primary   | $R^1=H, R^2=H$     | $R^3=Me, Bu$ | $R=Me, Bu$ |
| secondary | $R^1=Me, R^2=H$    |              |            |
| tertiary  | $R^1R^2=C_5H_{10}$ |              |            |

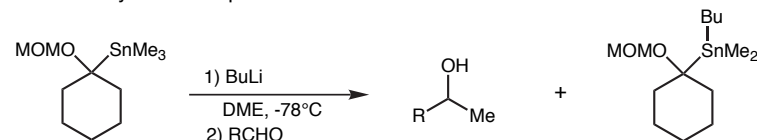


- Each species is separated by  $\approx 2$  Kcal/mol which represents  $\approx 1.5$  pK<sub>A</sub> unit.
- Alkyl substitution represents a destabilizing effect of 3-4 Kcal/mol.
- Alkoxy substitution represents a stabilizing effect of 5-6 Kcal/mol.
- No ate complexes were observed.
- Rate of exchange is influenced by trialkylstannyl substituent : Me > Bu > cyclohexyl
- Rate of exchange is influenced by solvent : DME > THF > Et<sub>2</sub>O.
- Reaction with tertiary  $\alpha$ -alkoxyorganolithium *must* be run in DME.

Macdonald, T. L. and McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.

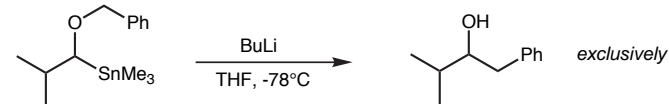
## Physical Properties of $\alpha$ -Alkoxyorganolithium : The Tin-Lithium Exchange

### Relative stability : an example

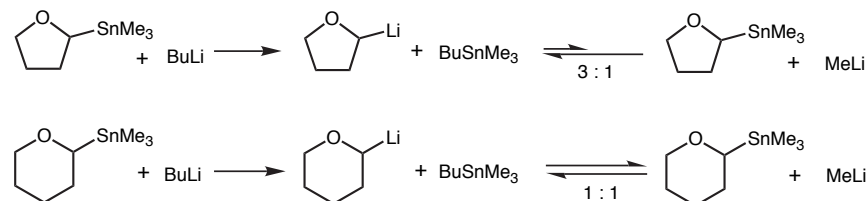


### Internal chelate

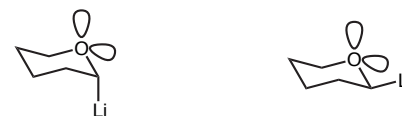
Unfortunately, the contribution of this factor cannot be addressed in the acyclic series because of an unavoidable Wittig rearrangement :



### Stereoelectronic effect



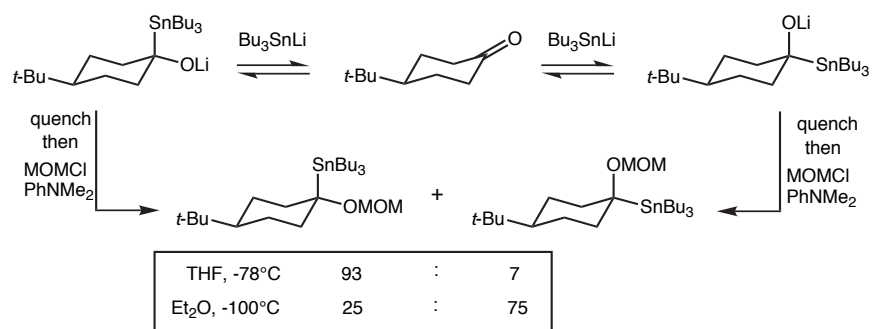
Lone pair orientation is clearly affecting the stability of the carbanion



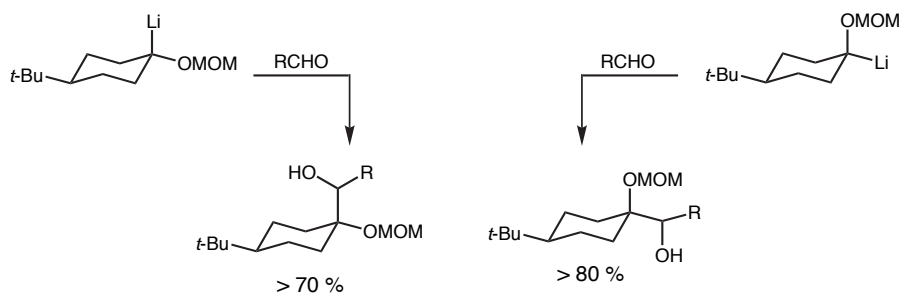
Macdonald, T. L. and McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.

■  $\alpha$ -alkoxy organolithium derived from conformationally biased cyclic ketone

- Addition to cyclohexanone is reversible. Equatorial addition is obtained under kinetic condition and axial addition under equilibrium conditions.

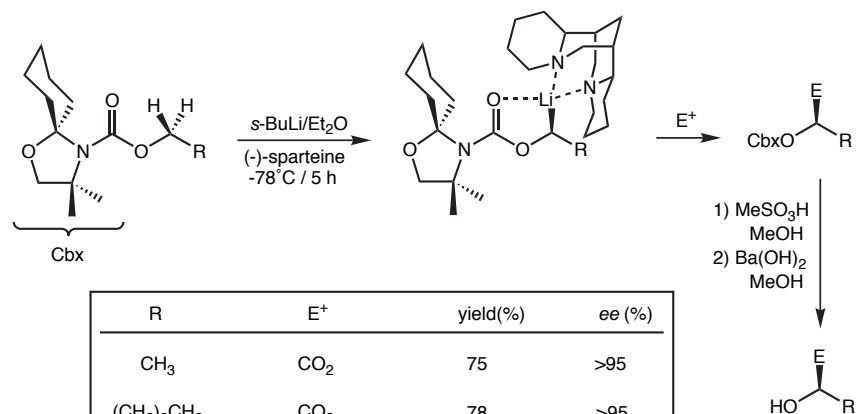


- Tin-Lithium exchange operate with full retention of configuration



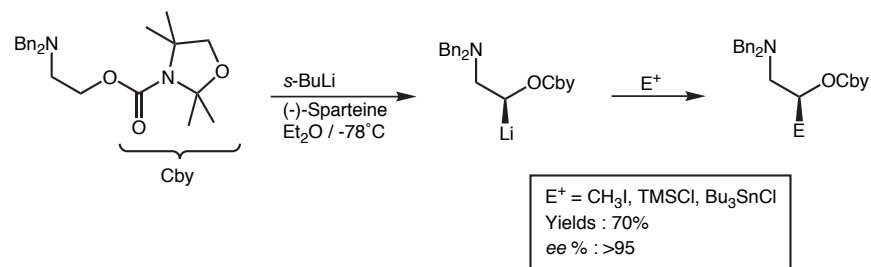
Macdonald, T. L. and McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.

### Synthesis of chiral Lithium-1-oxyalkanides by Asymmetric Deprotonation



| R   | E <sup>+</sup>       | yield(%) | ee (%) |
|---|----------------------|----------|--------|
| CH <sub>3</sub>                                 | CO <sub>2</sub>      | 75       | >95    |
| (CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub> | CO <sub>2</sub>      | 78       | >95    |
| CH <sub>3</sub>                                 | Me <sub>3</sub> SnCl | 76       | >95    |
| CH(CH <sub>3</sub> ) <sub>2</sub>               | Me <sub>3</sub> SnCl | 62       | >95    |
| (CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub> | CH <sub>3</sub> I    | 81       | >95    |

D. Hoppe, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1422-1424.

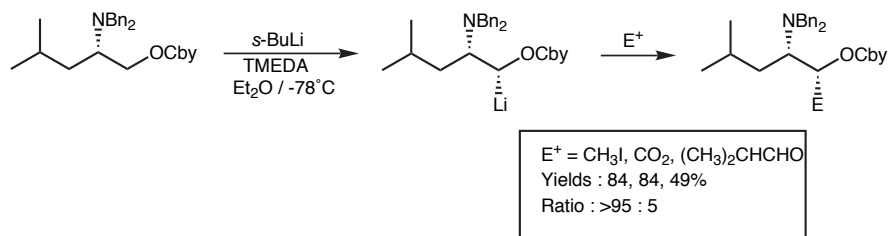


D. Hoppe, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1505-1507.

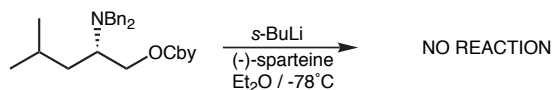


## Substrate Control Deprotonation

### ■ Diastereoselective deprotonation

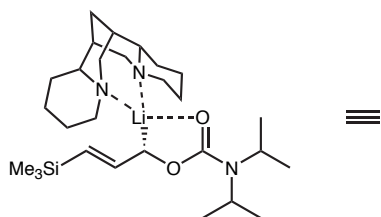


The Mismatch...



Hoppe, *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 1505-1507.

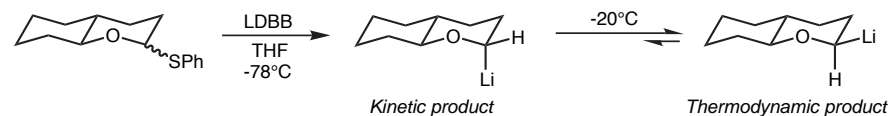
### ■ X-Ray structure of the complex



Boche, *Angew. Chem. Int. Ed. Engl.* **1991**, 1991, 321-322.

## 2-Lithiotetrahydropyran via Reductive Lithiation

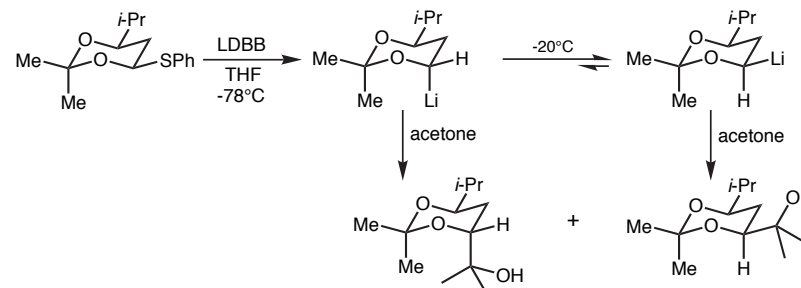
### ■ Kinetic and thermodynamic products



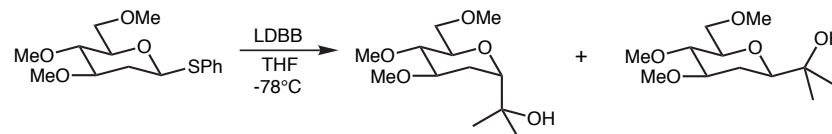
- Lithiation proceeds through a more stable "pyramidal" axial radical intermediate

Cohen, *J. Am. Chem. Soc.* **1984**, 1130.  
Cohen, *Acc. Chem. Res.* **1989**, 152.

### ■ The synthetic application



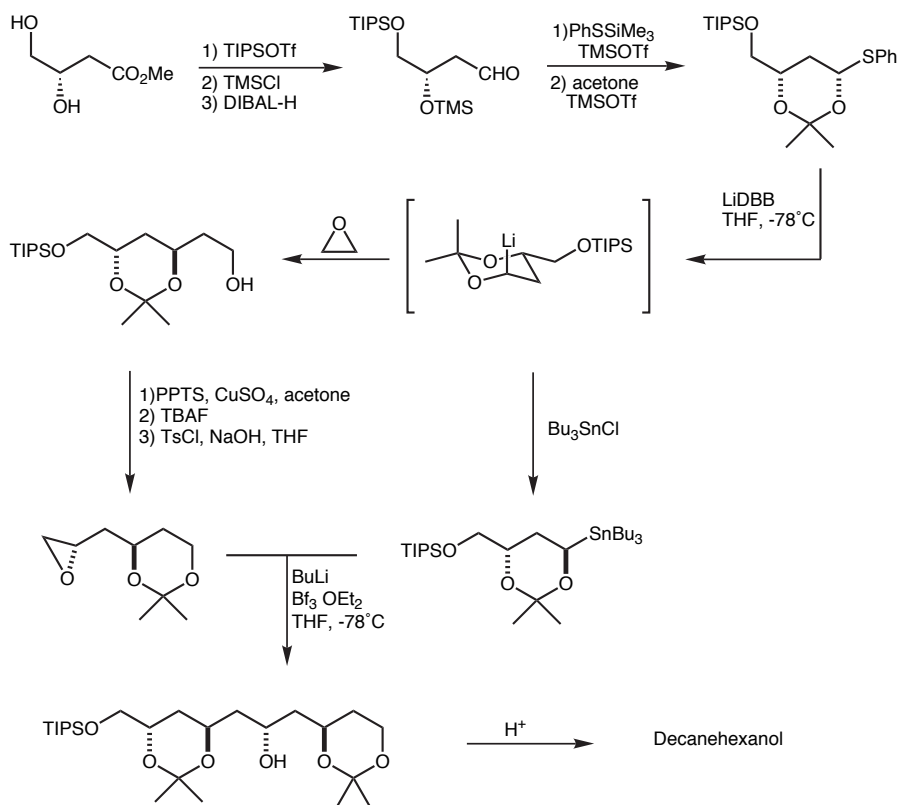
|                             |    |   |          |
|-----------------------------|----|---|----------|
| Kinetic -78°C               | 98 | : | 2 (78%)  |
| Thermodynamic -20°C, 30 min | 4  | : | 96 (54%) |



|                             |    |   |          |
|-----------------------------|----|---|----------|
| Kinetic -78°C               | 98 | : | 2 (81%)  |
| Thermodynamic -20°C, 30 min | 1  | : | 99 (60%) |

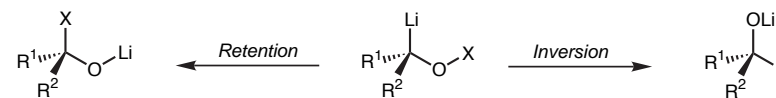
Rychnovsky, *Tetrahedron Lett.* **1989**, 30, 3011.  
Rychnovsky, *J. Am. Chem. Soc.* **1992**, 114, 8375.  
Rychnovsky, *Tetrahedron Lett.*, **1994**, 35, 6799.

## Synthesis of Lienomycin Decanehexanol



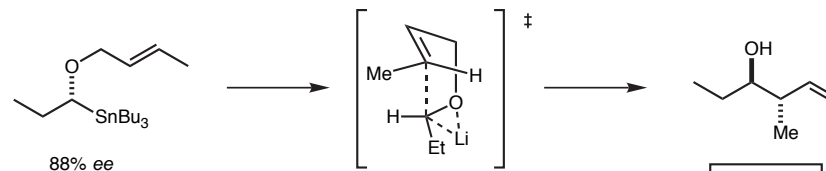
S. D. Rychnovsky, *J. Org. Chem.* **1989**, 4982-4984.  
see also : Linderman, *J. Org. Chem.* **1991**, 5491.

## Rearrangement of Lithioalkyl Ether



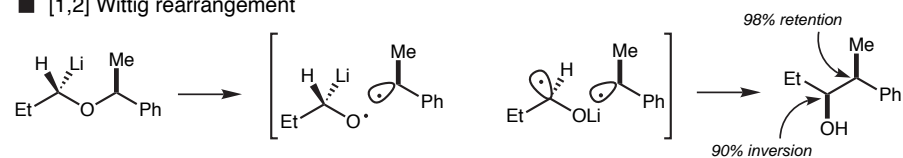
| X                | Rearrangement     | Stereochemistry | references   |
|------------------|-------------------|-----------------|--|
| SiR <sub>3</sub> | retro-[1,2]-Brook | retention       | Linderman, <i>J. Am. Chem. Soc.</i> <b>1990</b> , 112, 2392. |
| SiR <sub>3</sub> | retro-[1,2]-Brook | inversion       | West, <i>J. Am. Chem. Soc.</i> <b>1974</b> , 96, 3227.       |
| crotyl           | [1,2]-Wittig      | inversion       | Cohen, <i>J. Am. Chem. Soc.</i> <b>1992</b> , 114, 375.      |
| crotyl           | [2,3]-Wittig      | inversion       | Cohen, <i>J. Am. Chem. Soc.</i> <b>1992</b> , 114, 375.      |
| allyl            | [1,2]-Wittig      | inversion       | Brückner <i>Chem. Ber.</i> <b>1992</b> , 125, 1957.          |
| crotyl           | [2,3]-Wittig      | inversion       | Nakai <i>Tetrahedron Lett.</i> <b>1992</b> , 33, 5795.       |
| Benzyl           | [1,2]-Wittig      | inversion       | Brückner <i>Tetrahedron Lett.</i> <b>1993</b> , 34, 297.     |

### ■ [2,3] Wittig rearrangement (T. Nakai)



- Complexation of the Li counterion with oxygen induces planarity of the carbanion followed by inversion to form the new C-C bond.
- Ethyl substituent is *exo* in the envelope transition state according to Houk and Marshall calculation (*J. Org. Chem.* **1990**, 55, 1421)

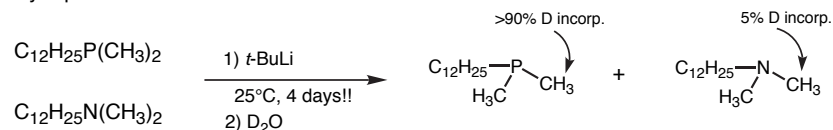
### ■ [1,2] Wittig rearrangement



Nakai, *Tetrahedron Lett.* **1993**, 34, 8139.

## $\alpha$ -Aminoorganolithium

### Early report

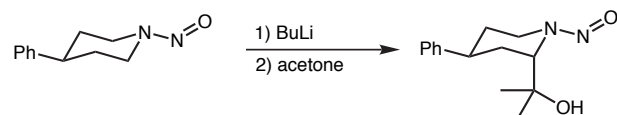


- In this competitive experiment metallation of the amine was expected based on electronegativity. The author rationalized this result by delocalization of the anion in the *d* orbital of the phosphorus which was not possible for the amine.

Peterson, *J. Org. Chem.* **1965**, 30, 1939.

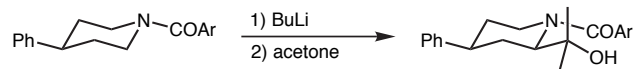
For first Sn-Li exchange see : Peterson *J. Am. Chem. Soc.* **1971**, 93, 4027

### First evidence for chiral $\alpha$ -aminoorganolithium



- Carbanion was postulated to be  $sp^2$  to give the more stable axial product of addition.

Fraser, *Can. J. Chem.* **1975**, 53, 2473.

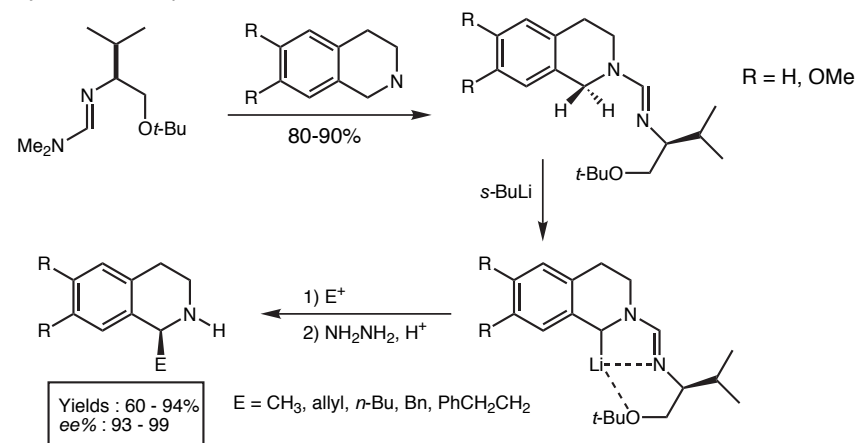


- Since the equatorial isomer is the less stable it was postulated that the carbanion was configurationally stable

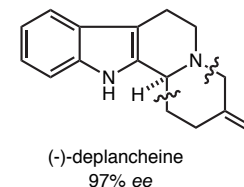
Seebach, *Helv. Chim. Acta.* **1978**, 61, 3100.

## Alkylation of Chiral Formamidines

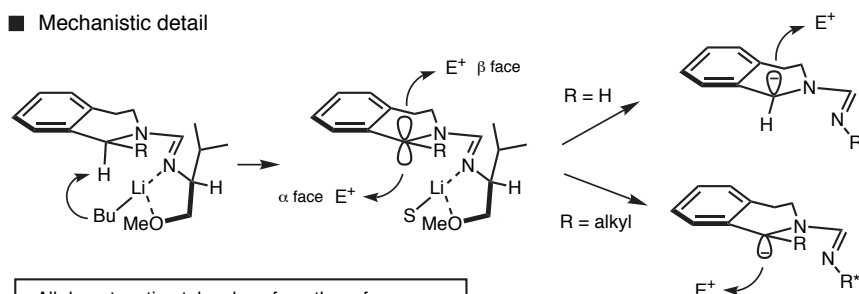
### Synthesis of isoquinoline alkaloids



- This strategy was also applied to the synthesis of indole framework :



### Mechanistic detail



- All deprotonation take place from the  $\alpha$  face

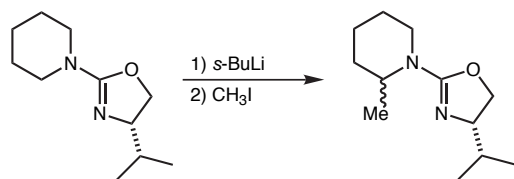
- Alkylation of 2° carbanion from the  $\beta$  face (99% ee)

- Alkylation of 3° carbanion from the  $\alpha$  face (93% ee)

A. I. Meyers, *Tetrahedron* **1992**, 48, 2589.

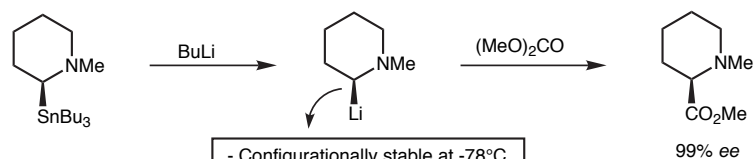
## 2-Lithio-N-Methylpiperidine

### ■ Piperidine oxazoline



- very low diastereoselectivities
- TMEDA doesn't have any effect on selectivity.
- Alkylation was postulated to take place through a SET mechanism.

### ■ Unchelated $\alpha$ -aminoorganolithium

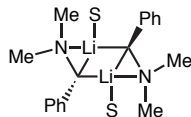
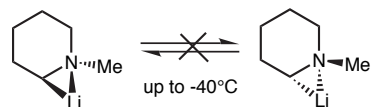


- Configurationally stable at  $-78^\circ\text{C}$  **without** TMEDA  
 - Configurationally stable at  $-40^\circ\text{C}$  with TMEDA

- First example of a configurationally stable  $\alpha$ -aminoorganolithium not stabilized by chelation or a dipole or both.
- Also observed for *N*-methylpyrrolidine.

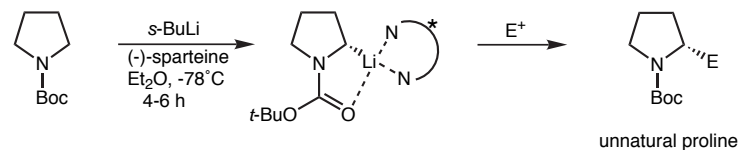
Gawley *J. Am. Chem. Soc.* **1993**, *115*, 7515.  
 Gawley *Tetrahedron* **1994**, *50*, 6077.  
 Gawley *J. Org. Chem.* **1995**, *60*, 5763.

### ■ The explanation : internal bridging

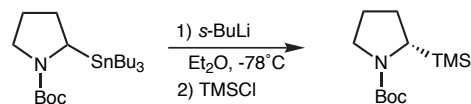


Boche *Chem. Ber.* **1993**, *126*, 1887.

## Asymmetric Deprotonation of BOC-pyrrolidines



| E                   | Yield% | ee%       |
|---------------------|--------|-----------|
| Me <sub>3</sub> Si  | 76     | 96        |
| Ph <sub>2</sub> COH | 75     | 90 (99.3) |
| CO <sub>2</sub> H   | 55     | 88        |
| CH <sub>3</sub>     | 76     | 95        |
| Bu <sub>3</sub> Sn  | 70     | 94        |

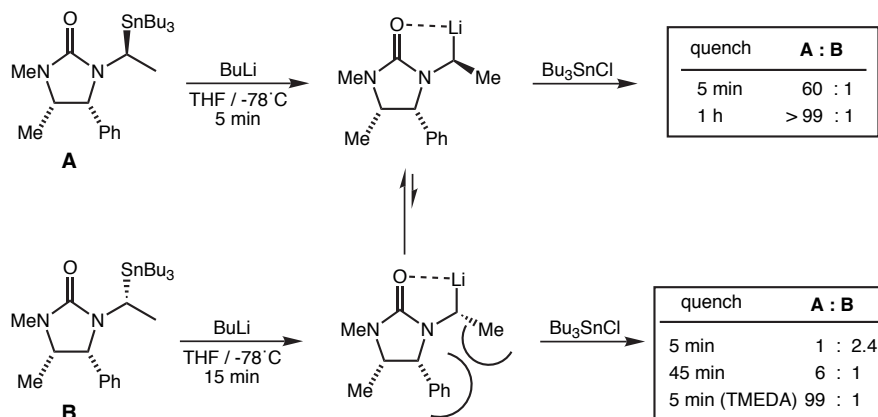


- Complexing agent is essential to stabilize the anion.
- Enantioselective deprotonation of one of two protons.

| Diamine | Yield%        | ee% |
|---------|---------------|-----|
|         | none          | 8   |
|         | (-)-sparteine | 60  |
|         | TMEDA         | 62  |

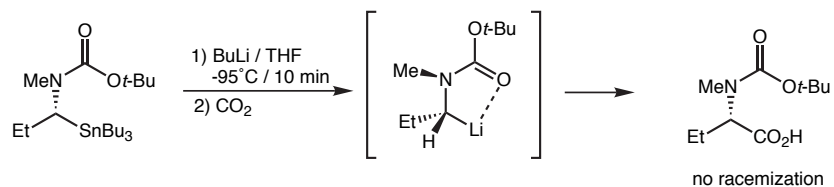
P. Beak, *J. Am. Chem. Soc.* **1991**, *113*, 9708-9710.

## Acyclic $\alpha$ -Aminoorganolithium



- Syn pentane interaction disrupts the chelate of one isomer generating a non-configurationally stable carbanion that can slowly equilibrate to the more stable isomer (internal chelate).
- TMEDA is also believed to break down the less stable chelate and accelerate the inversion.

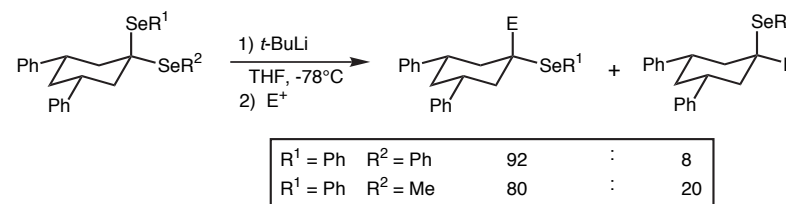
Pearson *J. Am. Chem. Soc.* **1993**, 115, 2622.



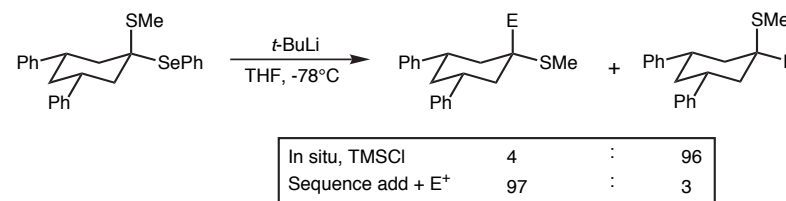
- Carbanion starts to racemize above -78°C.
- HMPA disrupts the intramolecular coordination and dramatically accelerates the rate of racemization.

Chong, *J. Org. Chem.* **1992**, 57, 2220.

## $\alpha$ -Lithiosulfides and $\alpha$ -Lithioselenides

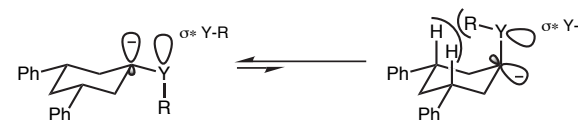


- Ratio doesn't change with any E<sup>+</sup>
- If C-SeMe is cleaved first, axial lithiation product might arise from a rapid equilibration favors the axial configuration.



- As C-Se is cleaved faster than C-S, equatorial  $\alpha$ -lithiosulfide is in fact generated but a fast equilibration favors the axial  $\alpha$ -lithiosulfide.

### ■ Stabilization of the axial carbanion : hyperconjugation

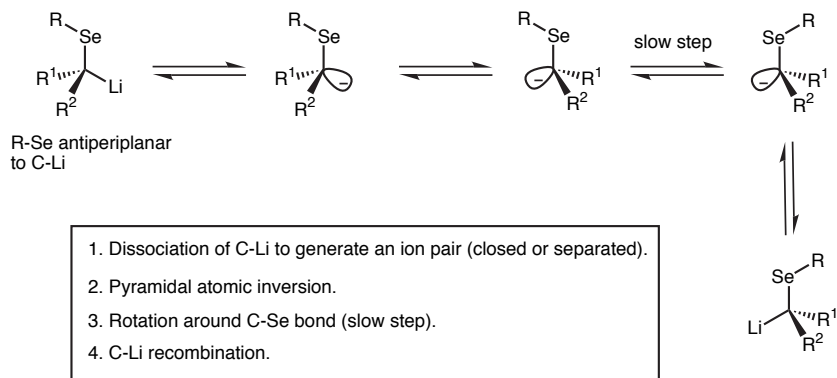


- Rotation around the C-Y bond becomes very important for that stereoelectronic effect.

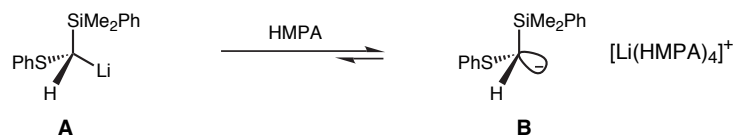
Reich *J. Am. Chem. Soc.* **1990**, 112, 8994.  
Krief *Tetrahedron Lett.* **1989**, 5636.

## Racemization of Lithioselenide : Mechanism

- Based on experimental data Hoffmann and Reich concluded that hyperconjugation is the major effect to consider in the racemization mechanism.



### Supplementary evidence

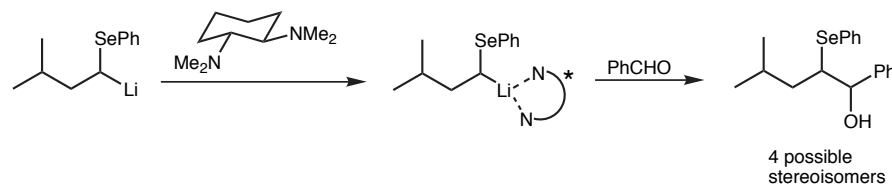


- **A** racemize 20 times faster than **B**
- Dissociation of ions is not the rate limiting step
- Anion is more easily delocalised in the  $\sigma^*$  S-Ph

Hoffmann *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1467.  
 Reich *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1469.  
 Hoffmann *Chem. Ber.* **1995**, 128, 861.

## Enantioselective Transformation of Configurationally Labile $\alpha$ -Phenylselenoalkyllithium Compound

- Knowing that  $\alpha$ -phenylselenoorganolithium are not configurationally stable one can imagine a chiral ligand that would shift the equilibrium to only one chiral anion.



- Unfortunately **3a** and **3b** are reacting faster than they equilibrate
- Moreover, the ligand is strongly binded to the product of the reaction.

**Désolé... no catalyst!!!**

Hoffmann *J. Chem. Soc. Perkin Trans. 2* **1993**, 1409.