

## 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.

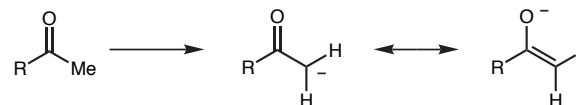
Macdonald, T. L. and McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, 110, 842-853.

## 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 :

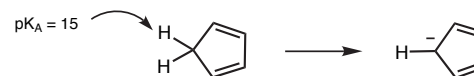
- Resonance :  $\pi$  acceptor is in conjugation with the lone pair inducing planarity of the carbanion.



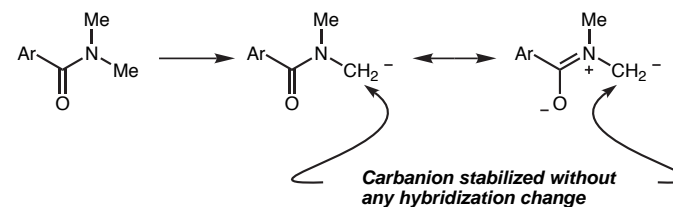
- s character : Increase of s character of the carbanion result in more stable carbanion.



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

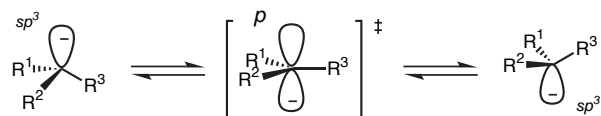


- Field (dipole) or Inducing effect : Electronegative substituents on the carbanion increases s character.



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

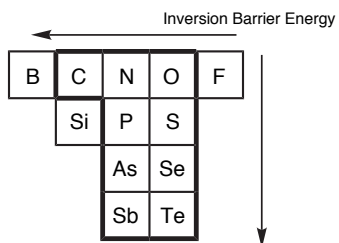
### Pyramidal atomic inversion



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.

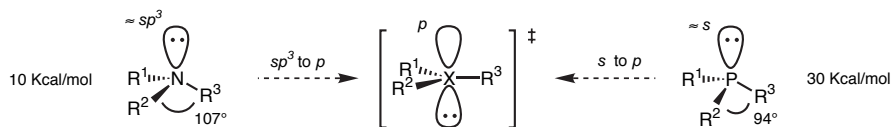
### General trend



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

For R = alkyl Ar =  $C_6H_5$

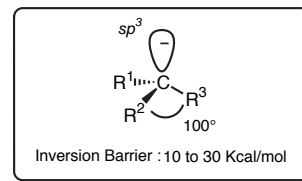
**The geometric argument :** Inversion happens more rapidly for ground-state bond angles closer from the transition state ( $120^\circ$ ).



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...**

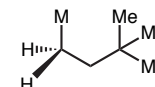
- Because the carbanion is linked to the metal by a partially covalent bond, it is not clear whether a carbanion undergoes a unimolecular pyramidal inversion analogous to nitrogen.
- Aggregation, nature of the C-metal bond as well as possible internal chelation should be considered in the configurational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

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

#### - Counterion



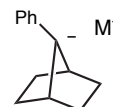
vs



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.

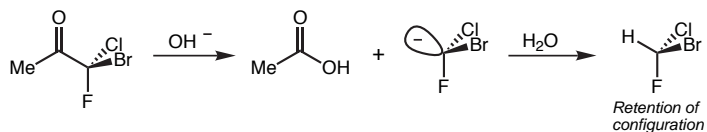
## $sp^3$ Carbanion : Barrier of Inversion

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

### - Solvent and Complexation:

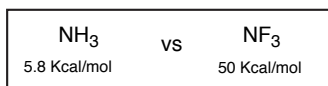
- For some system, low-dielectric solvent prevents inversion because the carbanion is closely paired with its counterion.
- A high-dielectric solvent can stabilize the carbanion or disrupt an essential internal chelate.
- Internal chelate sometimes are responsible for racemization as well as retention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

### - Electronegativity of the substituents

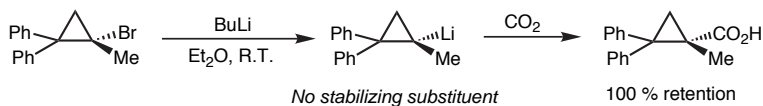


Hargreaves *J. Chem. Soc. C* **1971**, 1013

The analogy...



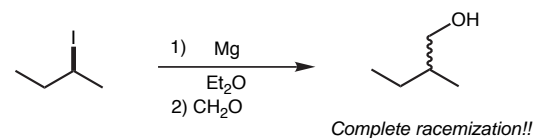
### - Angle strain



Walborsky *J. Am. Chem. Soc.* **1974**, 96, 3711.  
Walborsky *J. Am. Chem. Soc.* **1977**, 99, 2631.

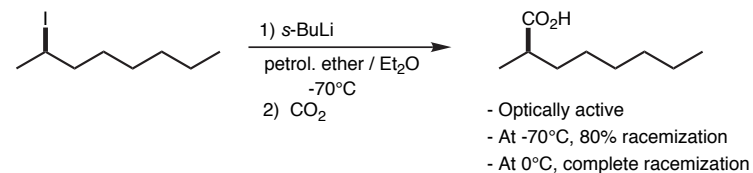
## Chiral Carbanion : First Attempt

■ Grignard reagent



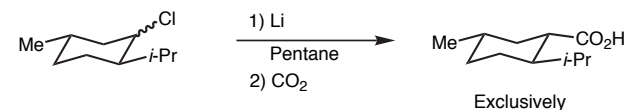
Pickard and Kenyon *J. Chem. Soc.* **1911**, 99, 45.

■ Transmetalation



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

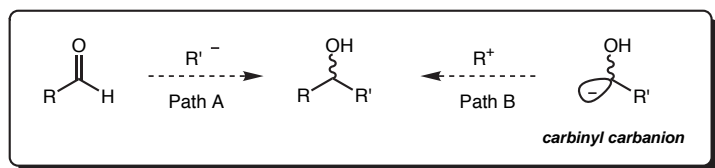
■ Reductive lithiation



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

## *$\alpha$ -Alkoxyorganolithium Reagent*

■ General concept : a carbinyllithium

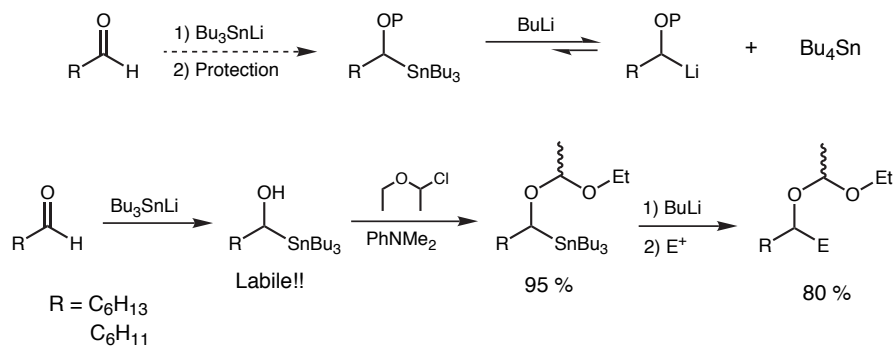


Path A : Subject to chiral induction from aldehyde substituent  
see : Evans, *J. Am. Chem. Soc.* **1995**, 117, 6619.

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.

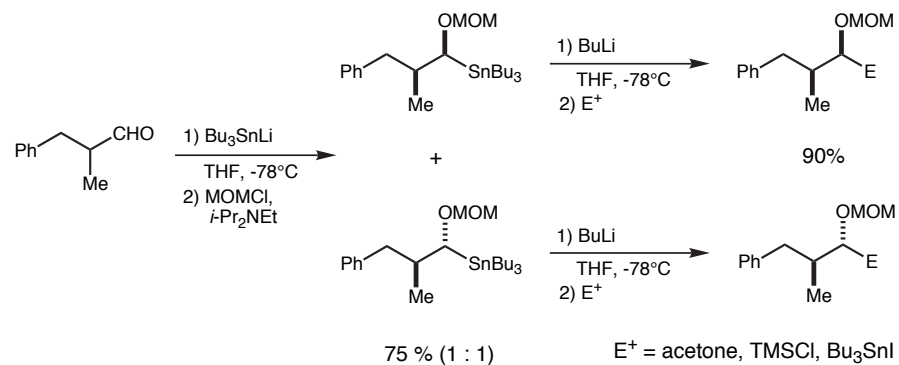
■ The stannylation/destannylation strategy



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

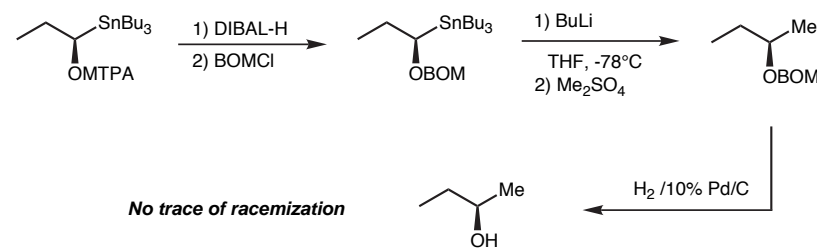
## *Configurationally Stable $\alpha$ -Alkoxyorganolithium Reagent*

■ The key experiment!



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

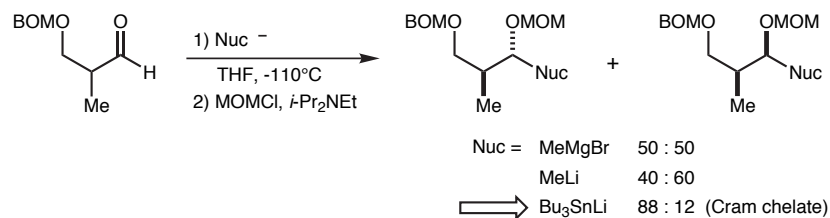
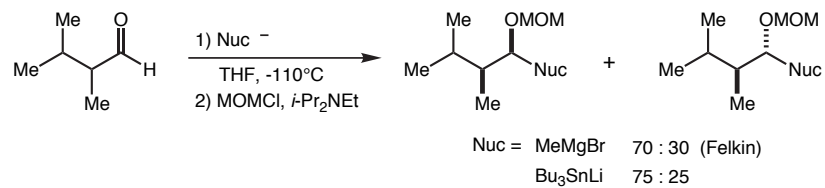
■ Enantiomerically pure  $\alpha$ -alkoxyorganostannane



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

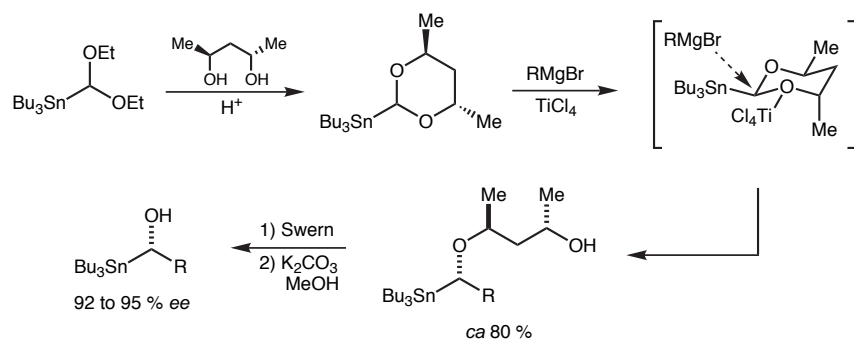
## Synthesis of Enantio and Diastereochemically Pure $\alpha$ -Alkoxyorganolithium Reagent

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



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

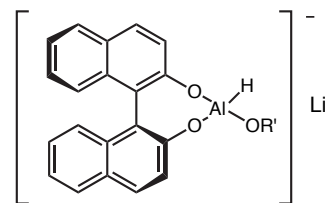
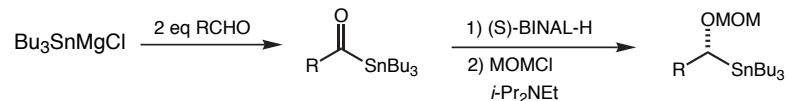
### ■ Chiral acetal opening



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

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

### ■ Enantioselective reduction

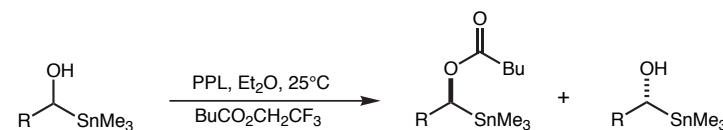


(S)-BINAL-H

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



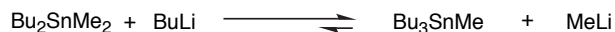
R	ee % ester (yield)	ee % alcohol (yield)
Me	98 (38%)	97 (41%)
Et	99 (36%)	56 (36%)
Pr	97 (7%)	7 (68%)

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



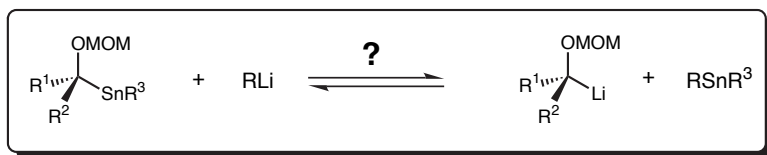
## Physical Properties of $\alpha$ -Alkoxyorganolithium : The Tin-Lithium Exchange

### Relative thermodynamic stabilities of organolithium species

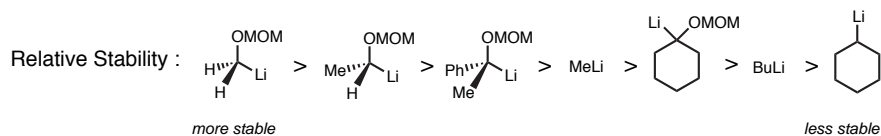


- Thermodynamic relationship lies far to the right (>95 : 5)
- No ate complex observed

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



primary	$\text{R}^1=\text{H}, \text{R}^2=\text{H}$	$\text{R}^3=\text{Me, Bu}$	$\text{R}=\text{Me, Bu}$
secondary	$\text{R}^1=\text{Me}, \text{R}^2=\text{H}$		
tertiary	$\text{R}^1\text{R}^2=\text{C}_5\text{H}_{10}$		

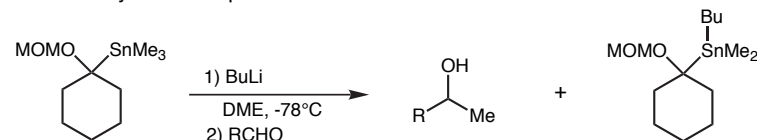


- Each species is separated by  $\approx 2$  Kcal/mol which represents  $\approx 1.5$  pK<sub>A</sub> unit.
- Alkyl substitution represents a destabilizing effect of 3-4 Kcal/mol.
- Alkoxy substitution represents a stabilizing effect of 5-6 Kcal/mol.
- No ate complexes were observed.
- Rate of exchange 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.

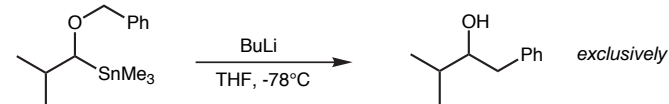
## Physical Properties of $\alpha$ -Alkoxyorganolithium : The Tin-Lithium Exchange

### Relative stability : an example

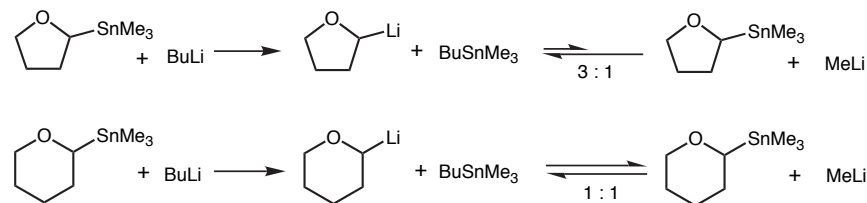


### Internal chelate

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



### Stereoelectronic effect



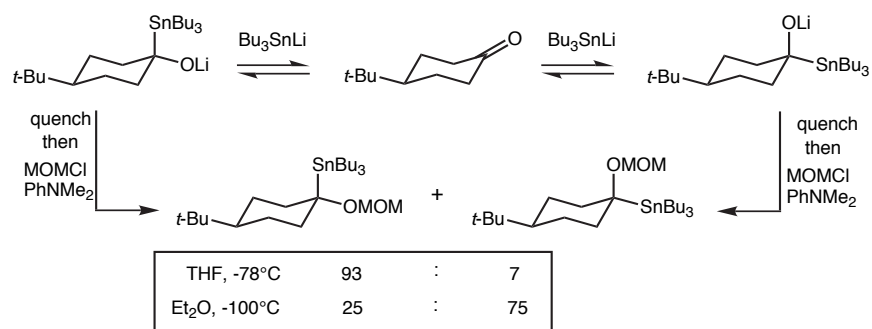
Lone pair orientation is clearly affecting the stability of the carbanion



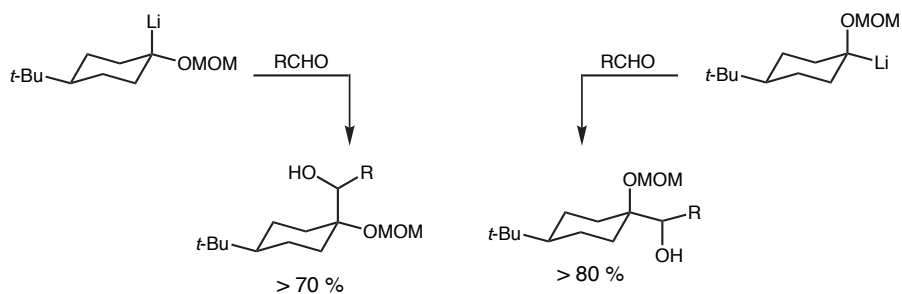
Macdonald, T. L. and McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.

■  $\alpha$ -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.

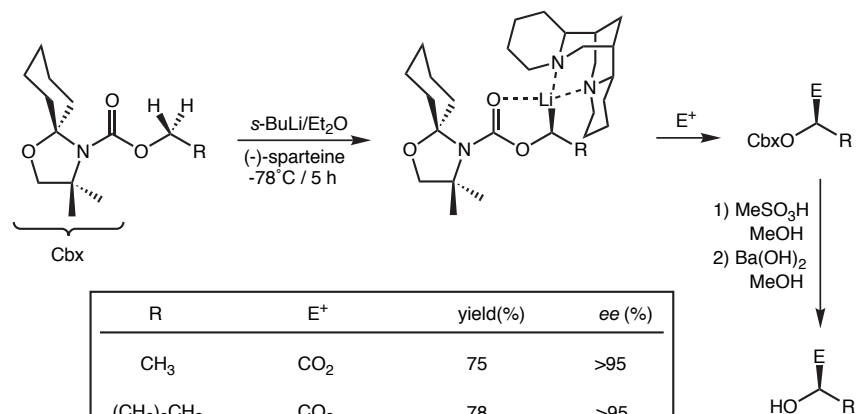


- Tin-Lithium exchange operate with full retention of configuration



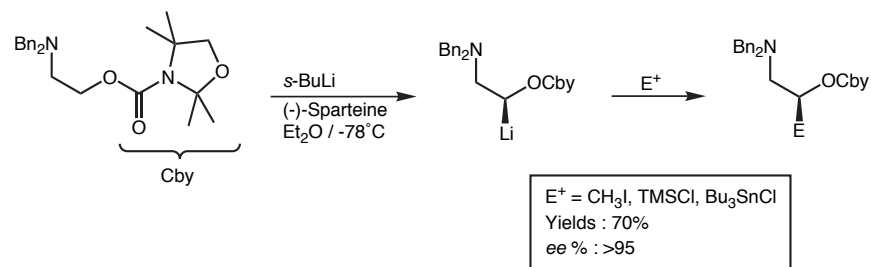
Macdonald, T. L. and McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.

### 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

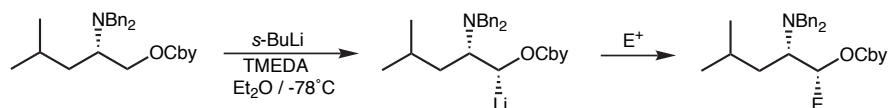
D. Hoppe, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1422-1424.



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

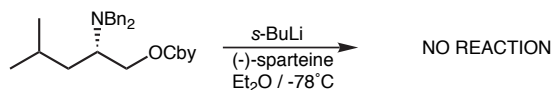
## Substrate Control Deprotonation

### ■ Diastereoselective deprotonation



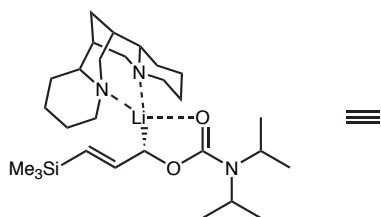
$E^+ = \text{CH}_3\text{I}, \text{CO}_2, (\text{CH}_3)_2\text{CHCHO}$   
 Yields : 84, 84, 49%  
 Ratio : >95 : 5

The Mismatch...



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

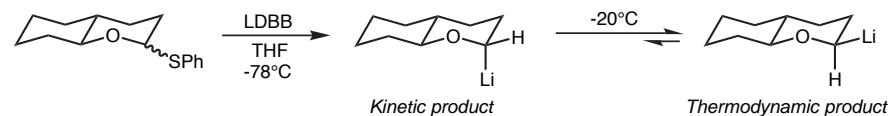
### ■ X-Ray structure of the complex



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

## 2-Lithiotetrahydropyran via Reductive Lithiation

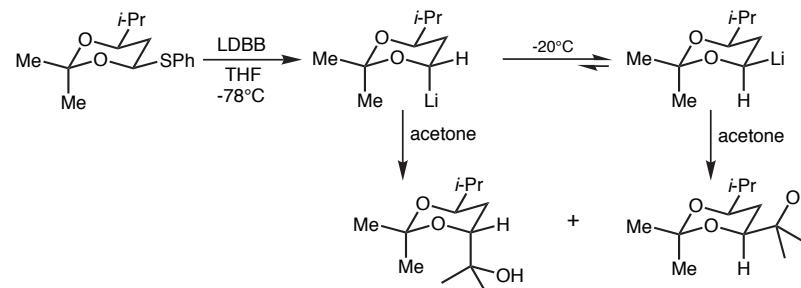
### ■ Kinetic and thermodynamic products



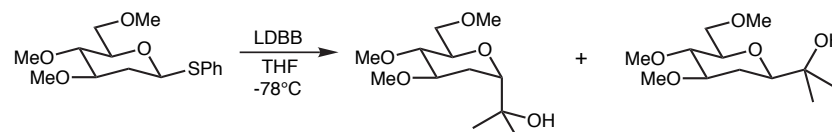
- Lithiation proceeds through a more stable "pyramidal" axial radical intermediate

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

### ■ The synthetic application



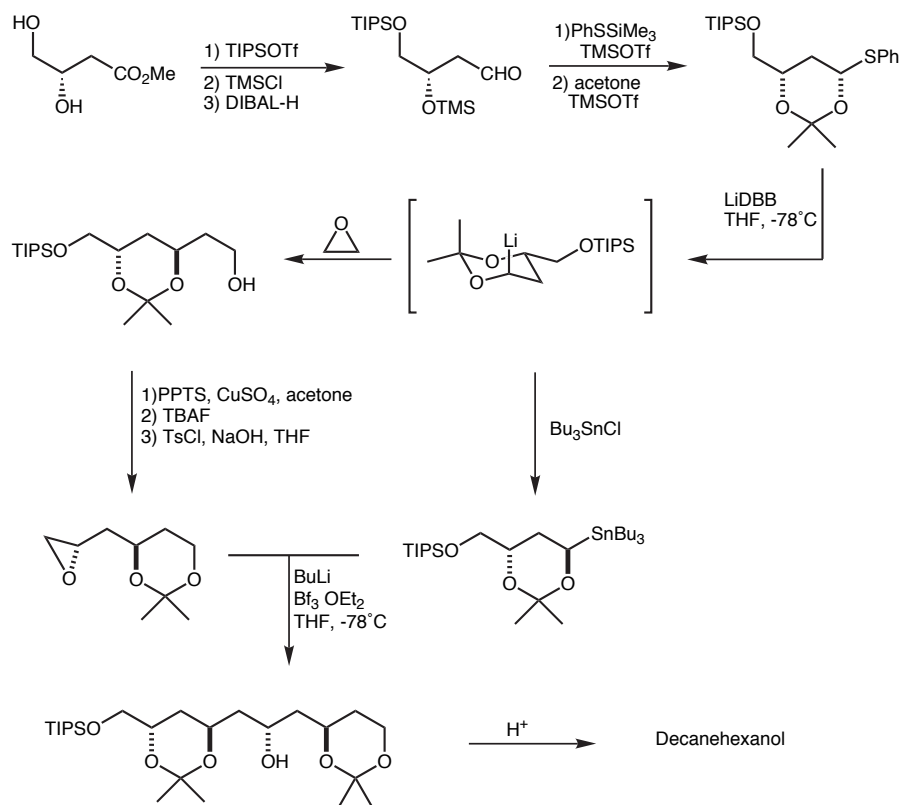
Kinetic -78°C	98	:	2 (78%)
Thermodynamic -20°C, 30 min	4	:	96 (54%)



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

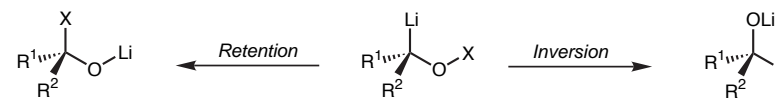
Rychnovsky, *Tetrahedron Lett.* **1989**, 30, 3011.  
 Rychnovsky, *J. Am. Chem. Soc.* **1992**, 114, 8375.  
 Rychnovsky, *Tetrahedron Lett.*, **1994**, 35, 6799.

## Synthesis of Lienomycin Decanehexanol



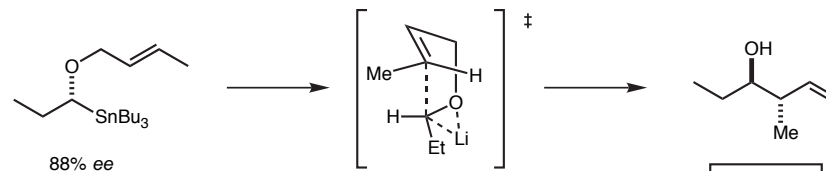
S. D. Rychnovsky, *J. Org. Chem.* **1989**, 4982-4984.  
see also : Linderman, *J. Org. Chem.* **1991**, 5491.

## Rearrangement of Lithioalkyl Ether



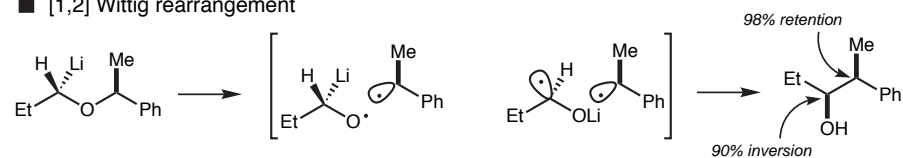
X	Rearrangement	Stereochemistry	references
SiR <sub>3</sub>	retro-[1,2]-Brook	retention	Linderman, <i>J. Am. Chem. Soc.</i> <b>1990</b> , 112, 2392.
SiR <sub>3</sub>	retro-[1,2]-Brook	inversion	West, <i>J. Am. Chem. Soc.</i> <b>1974</b> , 96, 3227.
crotyl	[1,2]-Wittig	inversion	Cohen, <i>J. Am. Chem. 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)

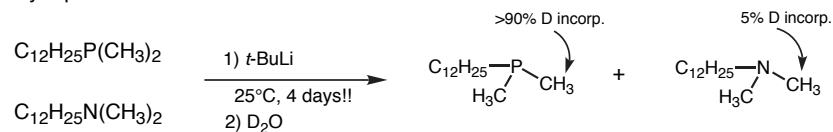
### ■ [1,2] Wittig rearrangement



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

## $\alpha$ -Aminoorganolithium

### Early report

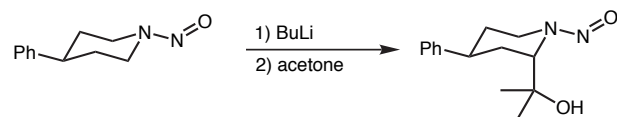


- In this competitive experiment metallation of the amine was expected based on electronegativity. The author rationalized this result by delocalization of the anion in the *d* orbital of the phosphorus which was not possible for the amine.

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

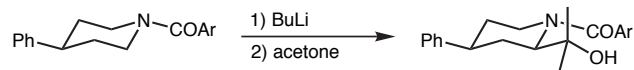
For first Sn-Li exchange see : Peterson *J. Am. Chem. Soc.* **1971**, 93, 4027

### 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.

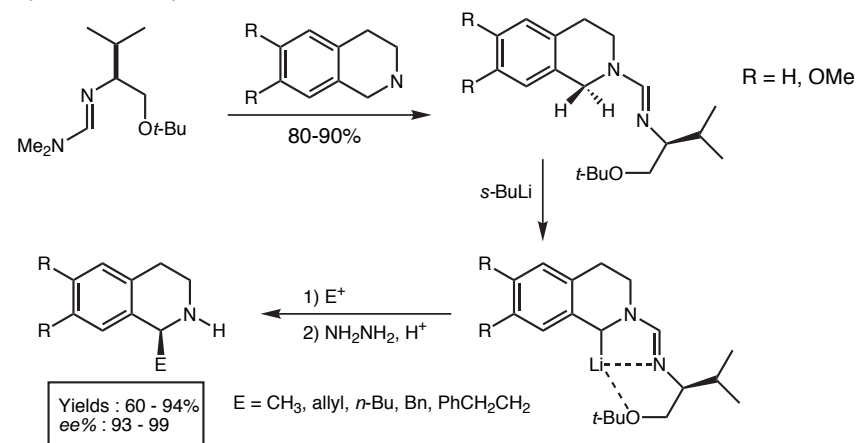


- Since the equatorial isomer is the less stable it was postulated that the carbanion was configurationally stable

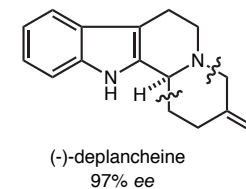
Seebach, *Helv. Chim. Acta.* **1978**, 61, 3100.

## Alkylation of Chiral Formamidines

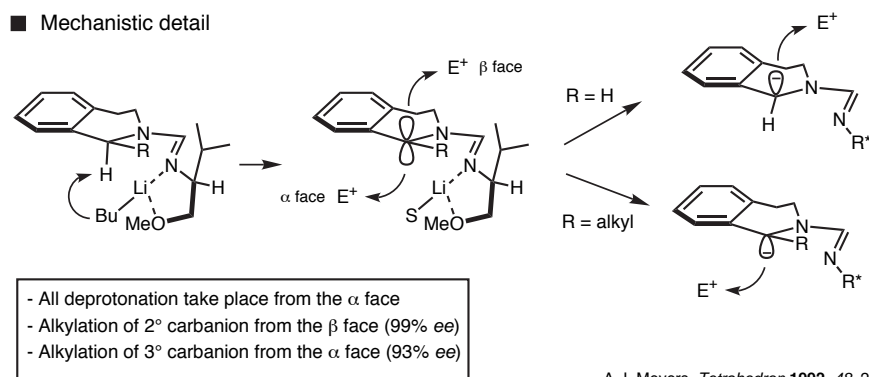
### Synthesis of isoquinoline alkaloids



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

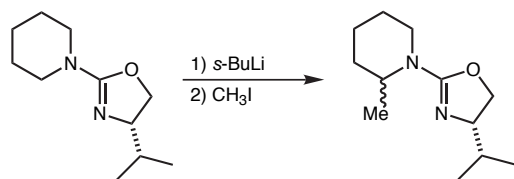


### Mechanistic detail



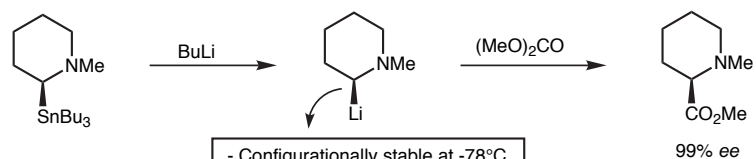
## 2-Lithio-N-Methylpiperidine

### ■ 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

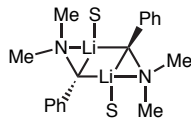
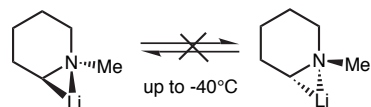


- Configurationally stable at  $-78^\circ\text{C}$  **without** TMEDA  
 - Configurationally stable at  $-40^\circ\text{C}$  with TMEDA

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

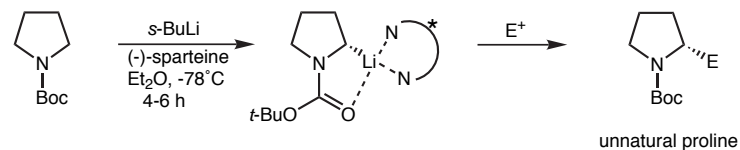
Gawley *J. Am. Chem. Soc.* **1993**, *115*, 7515.  
 Gawley *Tetrahedron* **1994**, *50*, 6077.  
 Gawley *J. Org. Chem.* **1995**, *60*, 5763.

### ■ The explanation : internal bridging

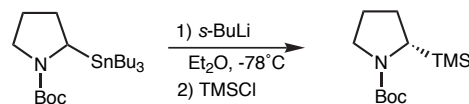


Boche *Chem. Ber.* **1993**, *126*, 1887.

## 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

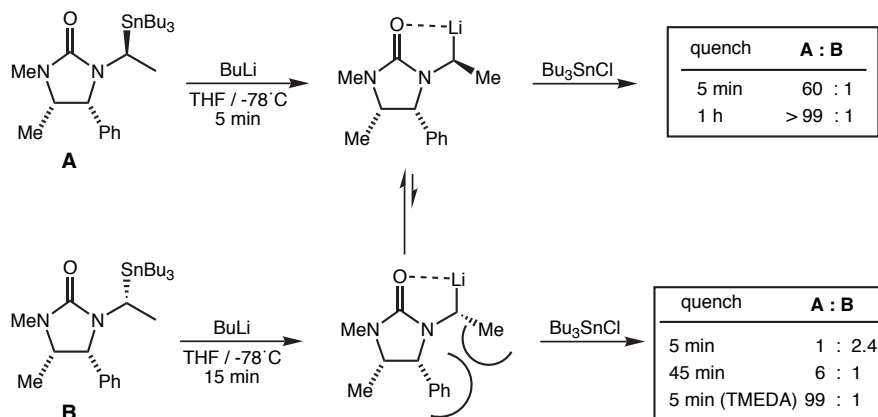


- Complexing agent is essential to stabilize the anion.
- Enantioselective deprotonation of one of two protons.

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

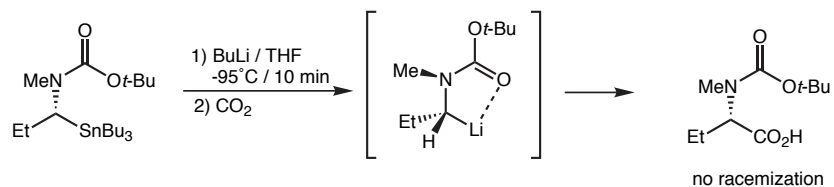
P. Beak, *J. Am. Chem. Soc.* **1991**, *113*, 9708-9710.

### 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.

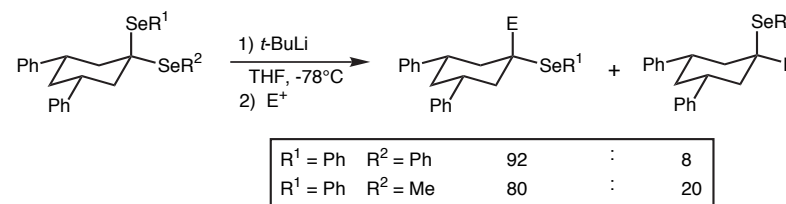
Pearson *J. Am. Chem. Soc.* **1993**, 115, 2622.



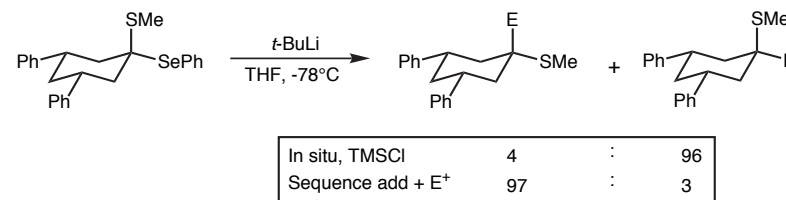
- Carbanion starts to racemize above  $-78^\circ\text{C}$ .
- HMPA disrupts the intramolecular coordination and dramatically accelerates the rate of racemization.

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

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

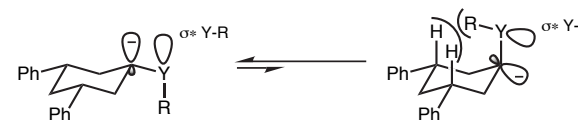


- Ratio doesn't change with any E<sup>+</sup>
- If C-SeMe is cleaved first, axial lithiation product might arise from a rapid equilibration favors the axial configuration.



- 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

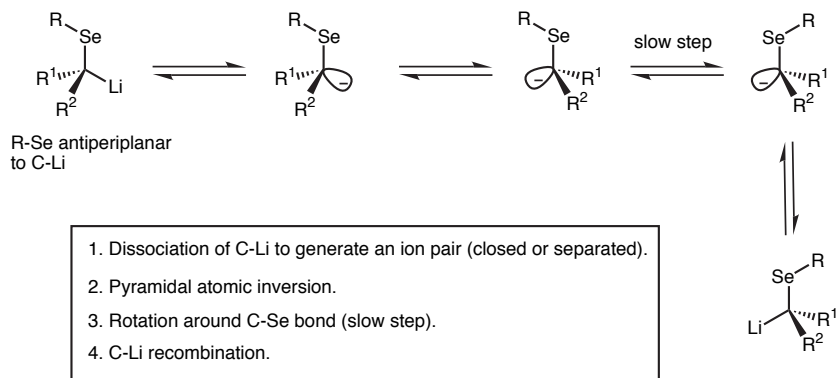


- Rotation around the C-Y bond becomes very important for that stereoelectronic effect.

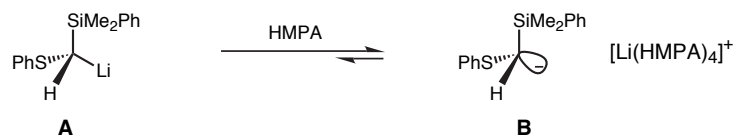
Reich *J. Am. Chem. Soc.* **1990**, 112, 8994.  
Krief *Tetrahedron Lett.* **1989**, 5636.

## 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

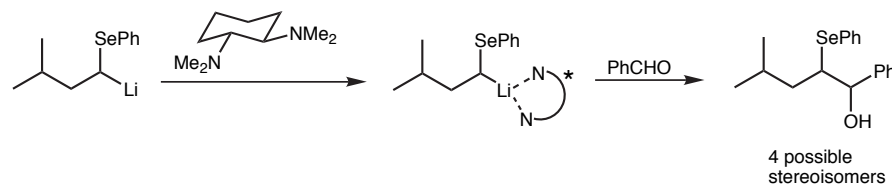


- **A** racemize 20 times faster than **B**
- Dissociation of ions is not the rate limiting step
- Anion is more easily delocalised in the  $\sigma^*$  S-Ph

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.