

# *The Mechanism of Lithium-Halogen Exchange*



MacMillan Group Meeting  
February 22, 2007  
Sandra Lee

## [Key Articles:](#)

Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, 352, 1–46.

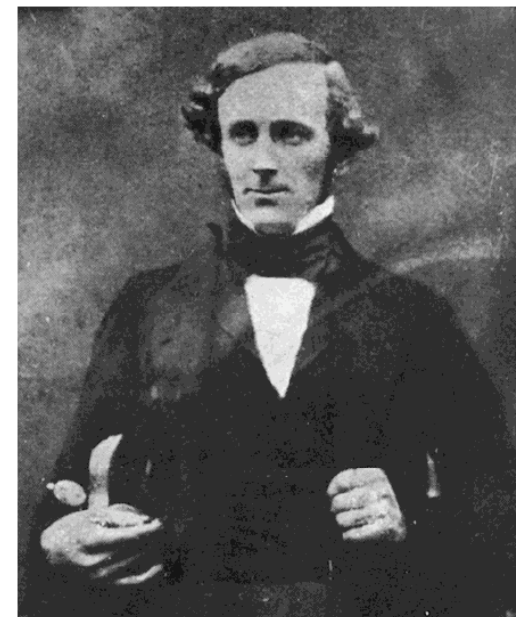
Seyferth, D. *Organometallics* **2006**, 25, 2–24.

Schlosser, M. Organoalkali Chemistry. In *Organometallics in Synthesis, A Manual*: Schlosser, M., Ed; Wiley & Sons LTD: West Sussex, U. K. 2002, pp 5–352.

## Beginnings of Main-Group Organometallic Chemistry

- $\text{Me}_2\text{Zn}$ : The first main group organometallic compound was discovered by Frankland in 1849

" When, on July 28, 1848, Edward Frankland, then a 23-year-old faculty member of Queenwood College in Hampshire, England, filled a thick-walled glass tube with finely granulated zinc and ethyl iodide and then sealed it, he did not realize that he had set up the reaction that would produce the first main-group organometallic compounds, ethylzinc iodide and diethylzinc... His goal was the preparation and isolation of the ethyl "radical". "

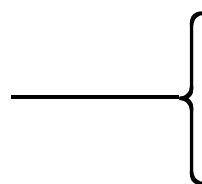


- Lithium organic compounds: physical and chemical properties

The small size of  $\text{Li}^+$  compared to other the other alkali-metal cations results in a much greater polarizing power (i.e. charge density)

$$\Phi \text{ (ionic potential)}^* = Z / r$$

Z = ionic charge (+1)  
r = ionic radius (Å)



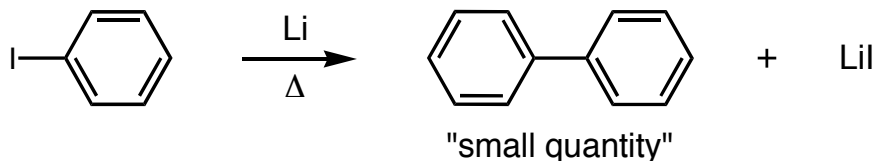
$\text{Li}^+ = 1.66$   
 $\text{Na}^+ = 1.04$   
 $\text{K}^+ = 0.76$

covalent	ionic
high positive charge	low positive charge
small cation	large cation
large anion	small anion
(e.g. $\text{AlI}_3$ )	(e.g. $\text{NaCl}$ )

Thus, organolithium compounds are more covalent (less ionic as per Fajans' rule), less reactive and more soluble in organic solvents than Na or K counterparts (ie. easier to handle)

## Missed Opportunities: The Discovery of the Lithium–Halogen Exchange Reaction

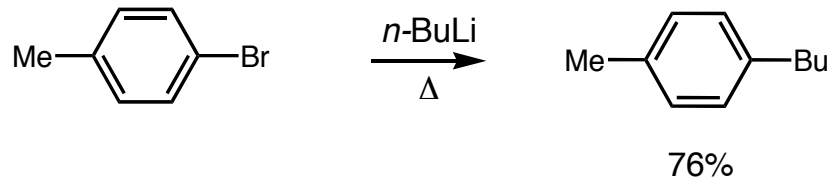
- The first study of metallic lithium with organic halides did not consider the formation of PhLi



"The reaction between iodobenzene and lithium was also tried in absolute ether solution under the usual Grignard conditions. No compound other than diphenyl and lithium iodide could be isolated from the reaction products, so that it may be taken that lithium and halogen derivatives in ether solution react according to the Wurtz reaction and not according to the Grignard reaction."

Spencer, J. F.; Price, G. M. *J. Chem. Soc.* **1910**, 97, :

- In an article entitled "The mechanism of the reaction between lithium *n*-butyl and various organic halogen compounds" and misses the connection



"While no butene or butane has been isolated from any of the reaction mixtures, as would be required to establish definitely the exact course of the reaction, there seems to be little doubt that free radicals are first produced when a halogen compound reacts with a lithium alkyl."

Marvel, C. S.; Hager, F. D.; Coffman, D. D. *J. Am. Chem. Soc.* **1927**, 49, 2

- Ziegler tried to determine the concentration of alkyl lithium solutions in benzene... Another would be discoverer

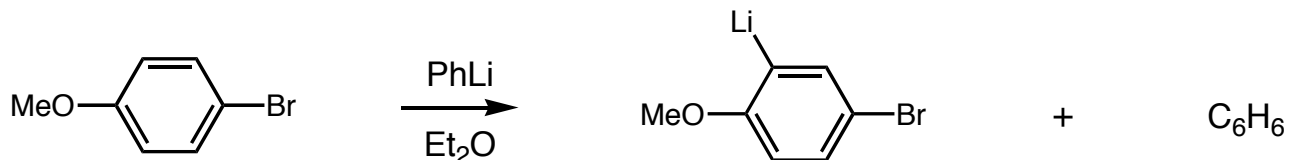


Ziegler, K.; Crössman, F.; Kleiner, H.; Schäfer, O. *Liebigs Ann. Chem.* **1929**, 47

## The First Lithium–Halogen Exchange Reaction

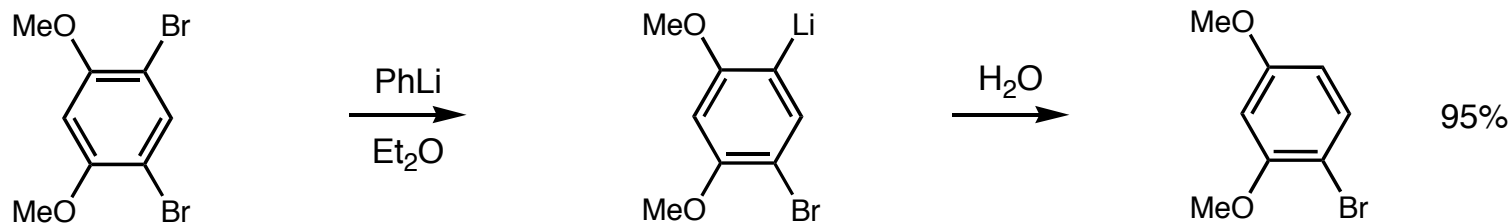
- In 1938 Wittig is surprised by his discovery of lithium–halogen interconversion:

After observing lithiation of *p*-Bromo anisole by phenyl lithium (via Li–hydrogen exchange)



They were surprised when 1,3-dimethoxy-4,6-dibromobenzene reacted differently (ie. not by Li–hydrogen exchange but lithium–bromine exchange). Wittig called the reaction contrary to every chemical intuition:

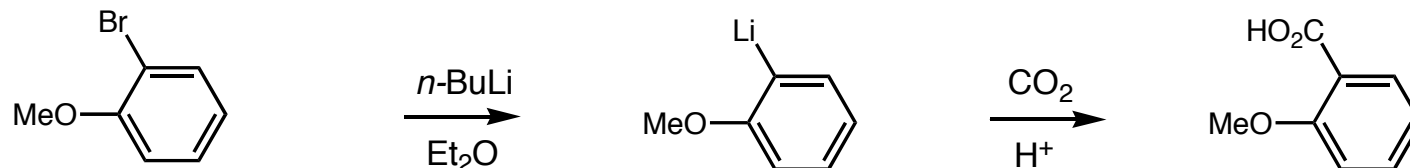
" Es hat sich also die folgende, jedem chemischen Gefühl widerstrebende Reaktion abgespielt."



- Subsequent studies of the reactions of PhLi with fluorobenzene led to the first example of a reaction proceeding via a benzyne intermediate

## A Simultaneous Independent Discovery

- Three months after Wittig's publication, Gilman reported an independent result in a carbonation reaction to form *o*-methoxybenzoic acid



- By a gentleman's agreement, Wittig restricted his research to phenyllithium and Gilman carried out studies with alkyllithiums\*
- Gilman conducted broader studies of lithium–halogen exchange reactions and made some early observations:

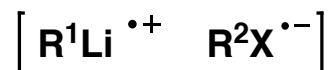
- ① aryl fluorides do not undergo exchange
- ② rates of interchange decrease from  $\text{I} > \text{Br} > \text{Cl}$
- ③ interchange is a reversible process that leads to an equilibrium favoring the more stable RLi

\*Wittig, G.; Fuhrmann, G. *Ber. Dtsch. Chem. Ges.* **1940**, *73*, 1000.  
Gilman, H.; Langham, W.; Moore, F. W. *J. Am. Chem. Soc.* **1939**, *61*, 2000.  
Gilman, H.; Jones, R. G. *Org. React.* **1951**, *6*, 1.

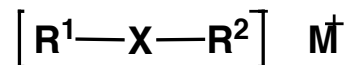
## Mechanistic Postulates for Li-Halogen Exchange



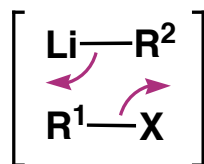
### Electron transfer (radical) process



### Nucleophilic mechanism via halogen "ate"-type intermediate



### Four-centered transition state model



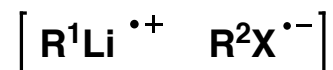
- Complications associated with investigating the mechanism of lithium–halogen exchange: side-product formation and aggregation.

"... any study which probes the reaction of an organolithium substrate should consider the fundamental question of the nature of the species (i.e. monomer, dimer, tetramer, etc.) that is responsible for the observed chemistry. Unfortunately, due to the inherent practical difficulties associated with obtaining such data for even the simplest of systems, most studies of the metal-halogen interchange do not address the problem of relating organolithium association with observed reactivity."

## Mechanistic Postulates for Li-Halogen Exchange



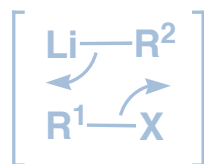
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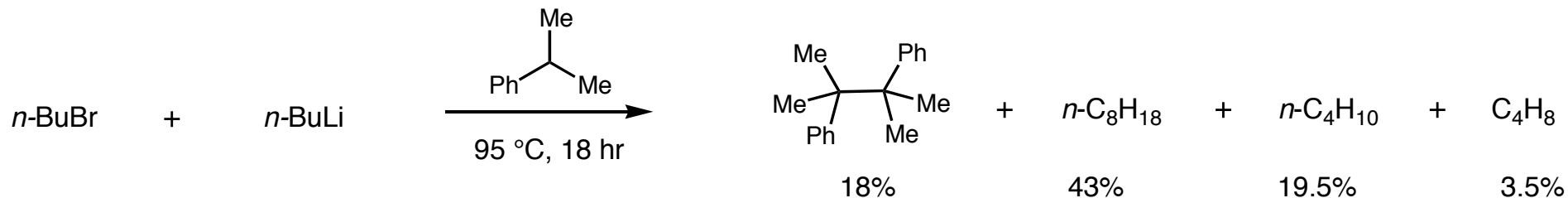


- Complications associated with investigating the mechanism of lithium–halogen exchange: side-product formation and aggregation.

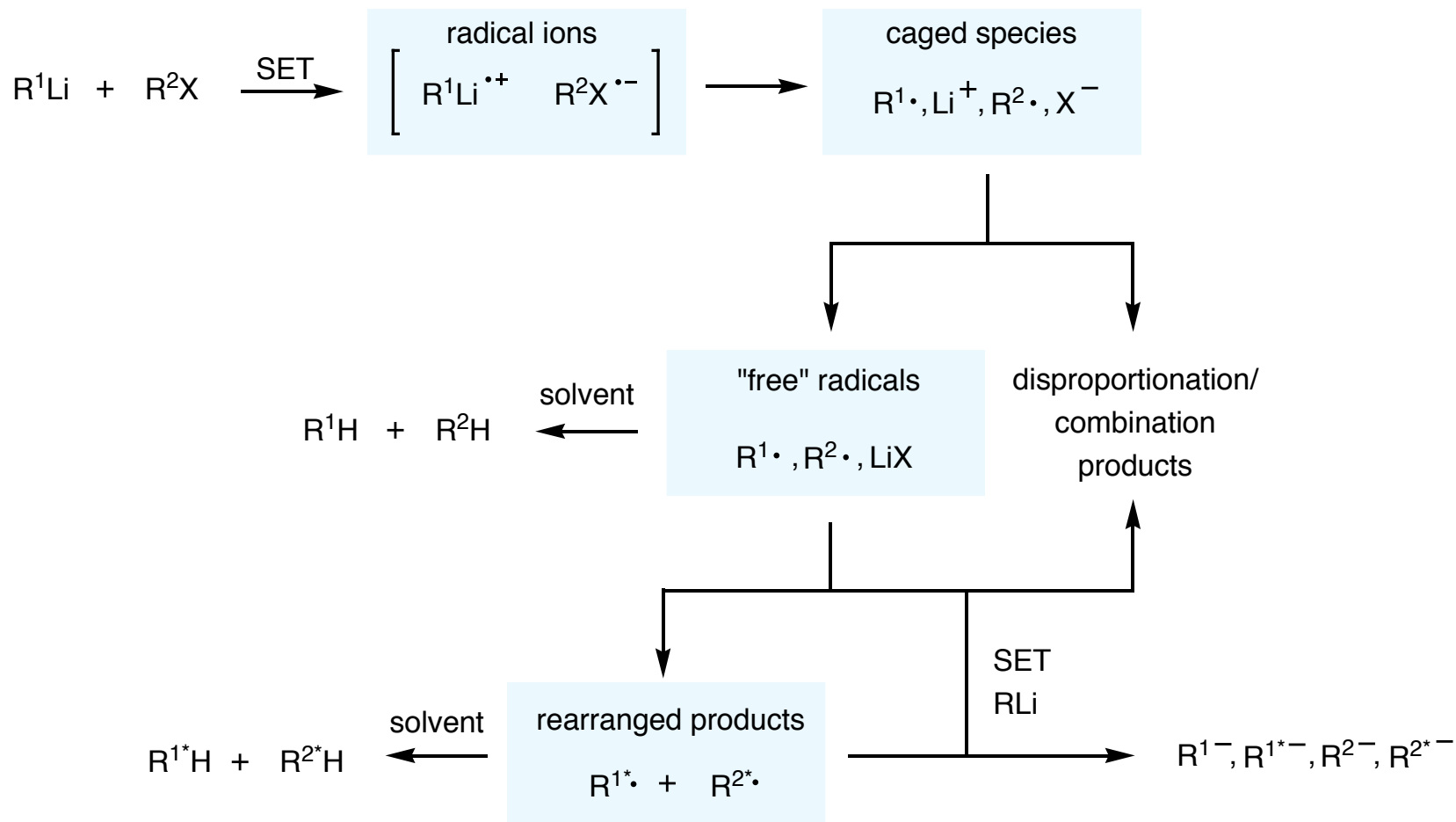
"... any study which probes the reaction of an organolithium substrate should consider the fundamental question of the nature of the species (i.e. monomer, dimer, tetramer, etc.) that is responsible for the observed chemistry. Unfortunately, due to the inherent practical difficulties associated with obtaining such data for even the simplest of systems, most studies of the metal-halogen interchange do not address the problem of relating organolithium association with observed reactivity."

## Radical-Mediated Mechanism

- In 1956 Bryce-Smith attributed this result to a radical mechanism

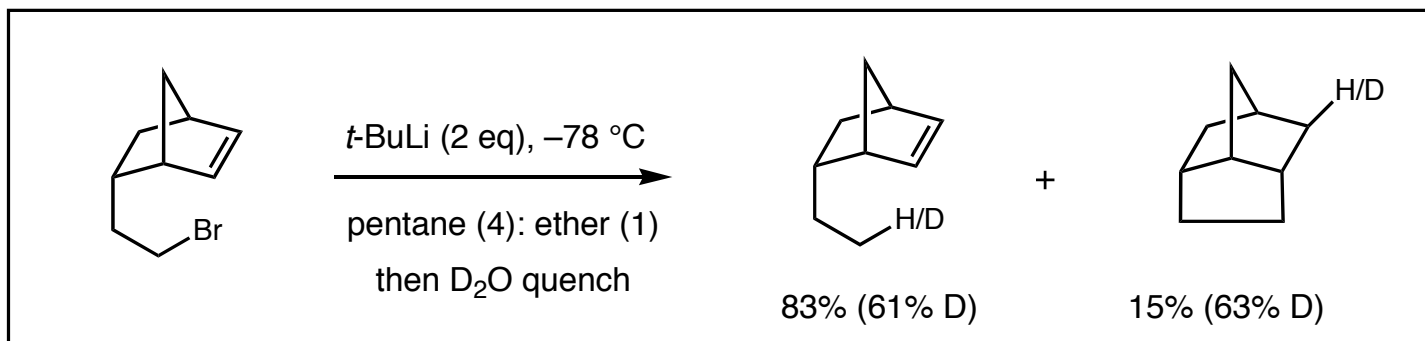


- A SET mediated mechanism provides an explanation for the observation of "dicumene"

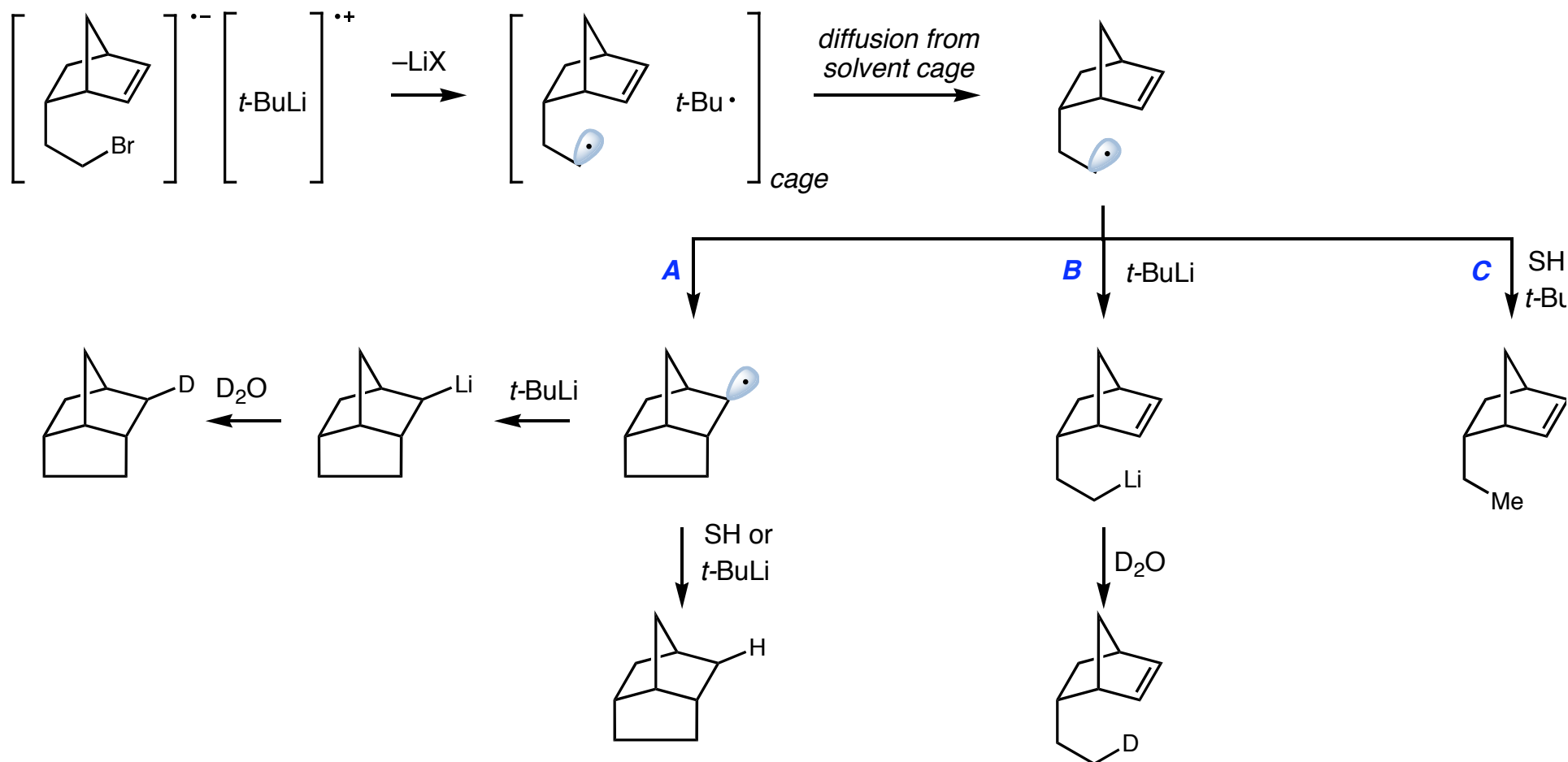




## A Case Study: Norbornene and *t*-BuLi

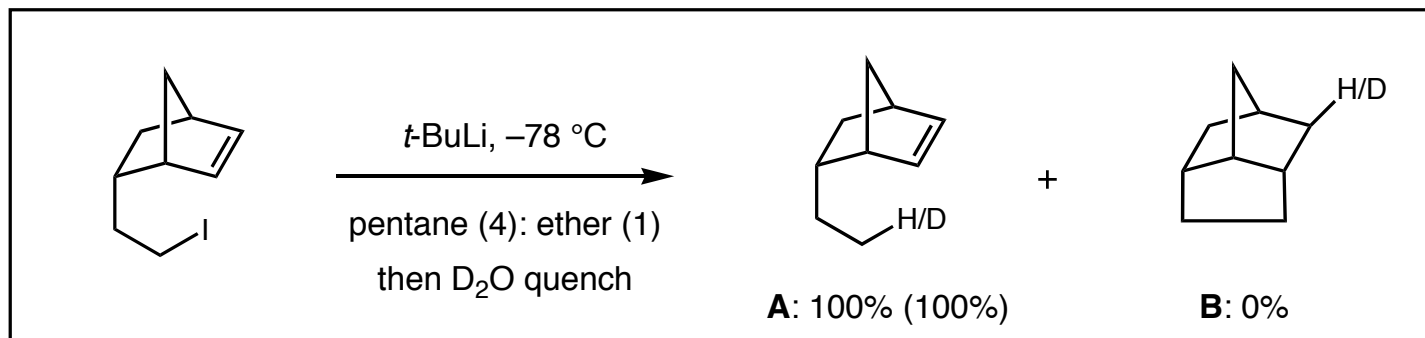


■ Ashby studies "cyclizable" probes to confirm the formation of radical intermediates



## A Case Study: Norbornene and *t*-BuLi

- Cyclization was not observed in the case of the the iodide analog, heterolytic mechanism?



- Temperature studies

entry	temp ( $^\circ\text{C}$ )	A	B
1	-78	100 (100)	0
2	-45	95 (95)	3 (46)
3	-23	90 (96)	6 (22)
4	0	72 (36)*	30 (22)*

Higher temperatures led more to a radical mechanism except in the case at  $0\text{ }^\circ\text{C}$ , when the cyclization occurred even after the reaction was complete.

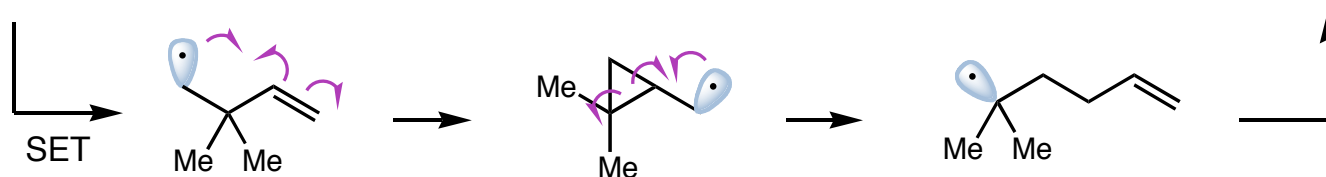
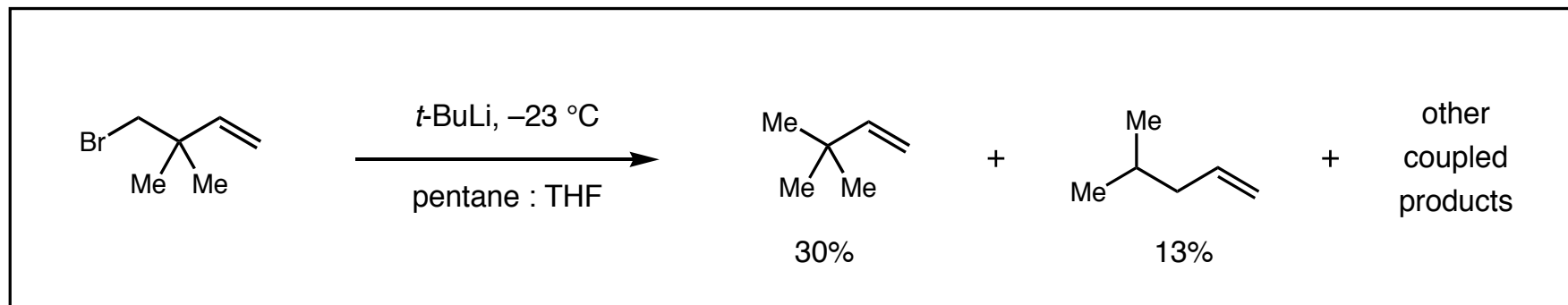
- Solvent studies

entry	solvent	A	B
1	pentane:ether	100 (100)	0
2	pentane only	88 (66)	10 (12.1)
3	pentane:ether + HMPA	99 (61)	0.1
4	pentane:ether + TMEDA	92 (84)	5 (5.2)

Decreasing the coordinating ability of solvent increases the extent of SET pathway. Complexing agents increase carbanionic character and to yield cyclization products

## In Search of Radical Intermediates

- Looking for skeletal rearrangements as a validation of the radical mechanism



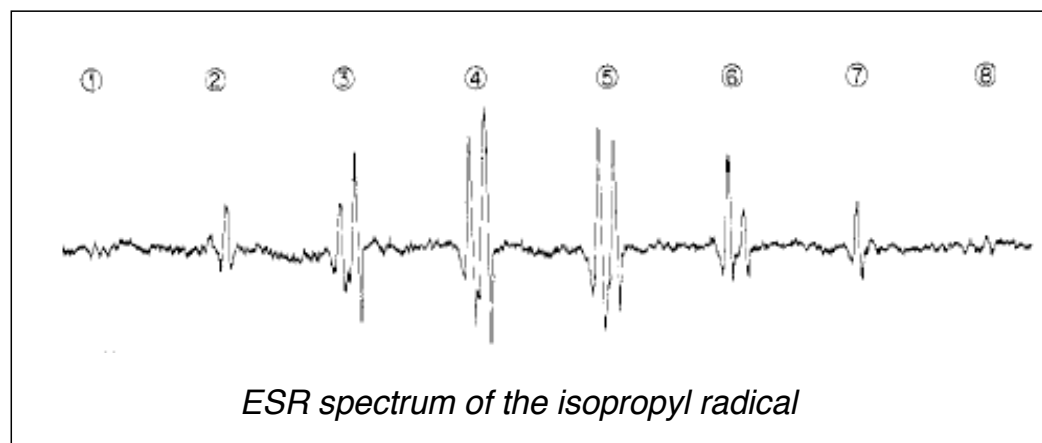
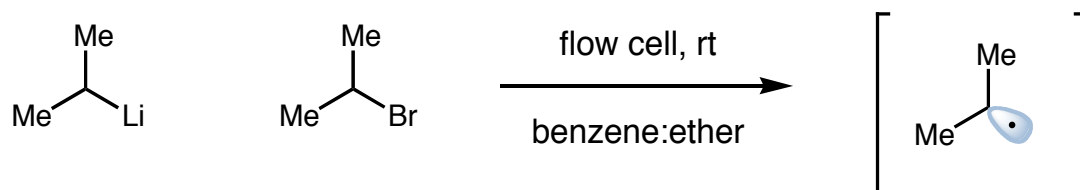
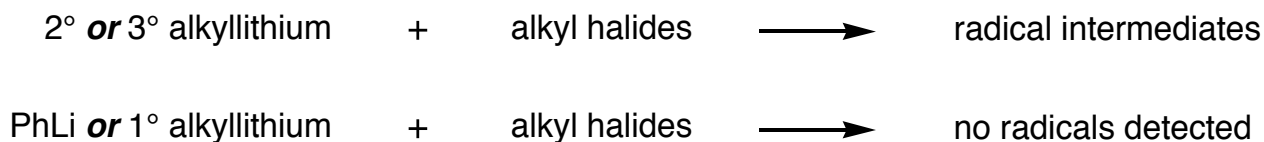
- Some conclusions from this study:

- SET mechanism is at least a minor pathway but there must exist a metal-exchange pathway not involving SET
- It is possible that the radical was reduced in a bimolecular reaction (at a rate constant greater than  $1 \times 10^7 \text{ M}^{-1}\text{sec}^{-1}$  at  $-23 \text{ }^\circ\text{C}$ ).

## Other Evidence for the Electron Transfer Mechanism

### ■ ESR (Electron-Spin Resonance) Spectroscopy experiments support free-radical mechanism

radical concentrations for a variety of organolithiums were detected to be between  $10^{-6}$ – $10^{-5}$  M under the reaction conditions



### ■ ESR demonstrates radicals may be generated but it is not definitive that radicals are involved as intermediates in the metal-halogen exchange

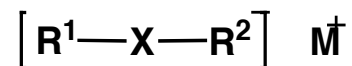
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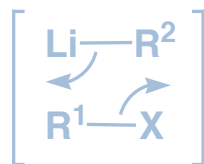
Electron transfer (radical) process



Nucleophilic mechanism via halogen "ate"-type intermediate

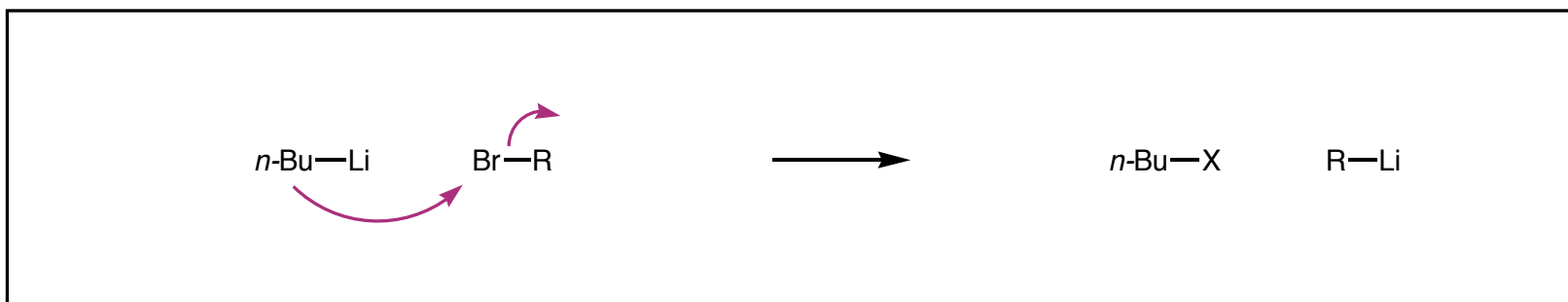


Four-centered transition state model

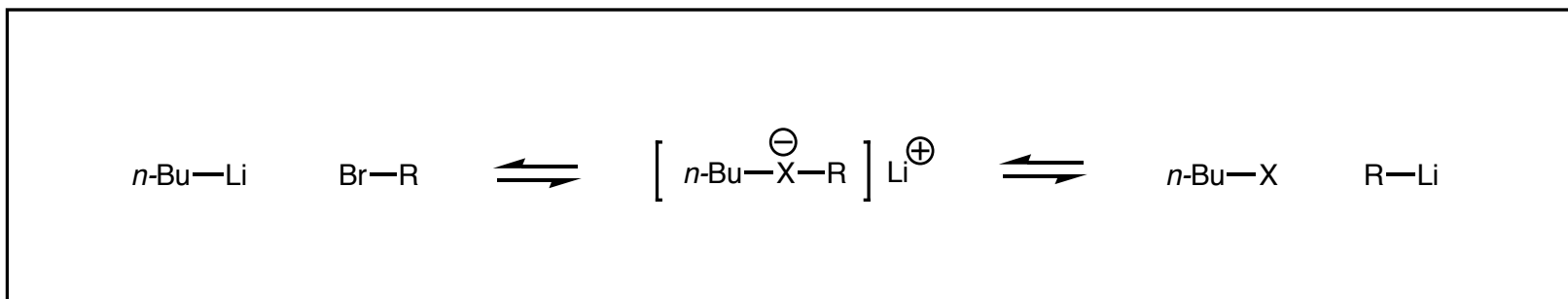


## Nucleophilic Reaction Pathway?

- Gilman suggests a nucleophilic mechanism involving a carbanion leaving group

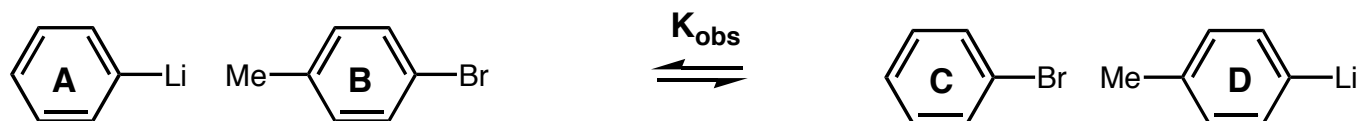


- Wittig postulated a reversible formation of an "ate-complex" (a term coined by Wittig)



## Lithium-Halogen Exchange is an Equilibrium Process

- Winkler and Winkler demonstrate interconversions are an equilibrium process

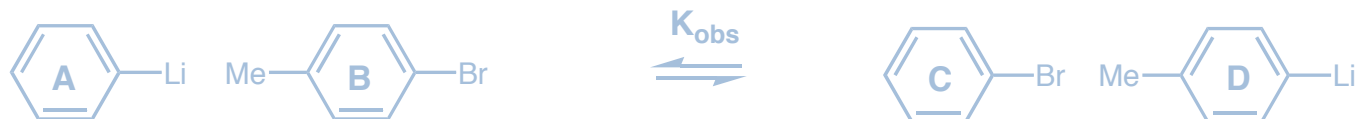


entry	A	B	C	D	$K_{\text{obs}}$
1	0.6 ( $t_0$ )	0.6 ( $t_0$ )	0.0 ( $t_0$ )	0.0 ( $t_0$ )	0.60
	0.3 ( $t_{\text{eq}}$ )	0.3 ( $t_{\text{eq}}$ )	0.3 ( $t_{\text{eq}}$ )	0.3 ( $t_{\text{eq}}$ )	
2	0.0 ( $t_0$ )	0.0 ( $t_0$ )	0.5 ( $t_0$ )	0.5 ( $t_0$ )	0.67
	0.2 ( $t_{\text{eq}}$ )	0.3 ( $t_{\text{eq}}$ )	0.2 ( $t_{\text{eq}}$ )	0.2 ( $t_{\text{eq}}$ )	

Winkler, H. J. S.; Winkler, H. J. *Am. Chem.* **1965**, *8*

## Lithium-Halogen Exchange is an Equilibrium Process

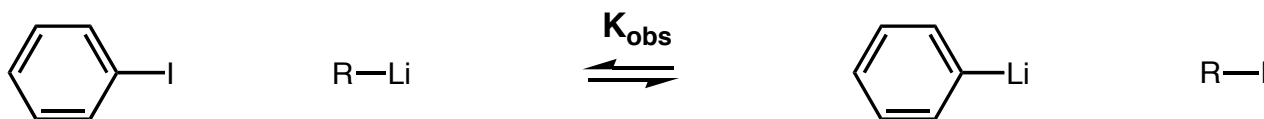
- Winkler and Winkler demonstrate interconversions are an equilibrium process



entry	A	B	C	D	$K_{obs}$
1	0.6 ( $t_0$ )	0.6 ( $t_0$ )	0.0 ( $t_0$ )	0.0 ( $t_0$ )	0.60
	0.3 ( $t_{eq}$ )	0.3 ( $t_{eq}$ )	0.3 ( $t_{eq}$ )	0.3 ( $t_{eq}$ )	
2	0.0 ( $t_0$ )	0.0 ( $t_0$ )	0.5 ( $t_0$ )	0.5 ( $t_0$ )	0.67
	0.2 ( $t_{eq}$ )	0.3 ( $t_{eq}$ )	0.2 ( $t_{eq}$ )	0.2 ( $t_{eq}$ )	

Winkler, H. J. S.; Winkler, H. J. *Am. Chem.* **1965**, *8*

- Equilibrium is a reflective measure of relative carbanion stability ( $sp \gg sp_2 \gg sp_3$ )

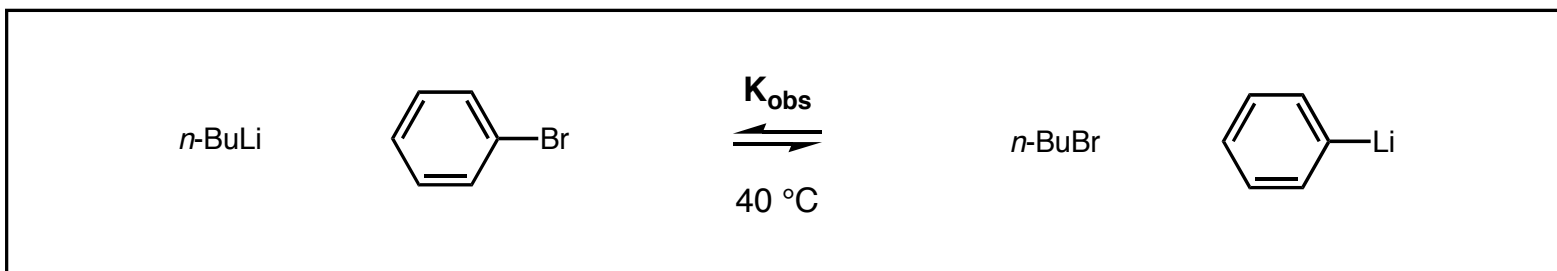


R	$K_{obs}$	$pK_a$	R	$K_{obs}$	$pK_a$	R	$K_{obs}$	$pK_a$
	0.004	36.5	Me-	3200	42	<i>t</i> -Bu-	$3 \times 10^5$	42
Ph-	1.0	37	Et-	7600	42		$1 \times 10^6$	43
	9.5	39	( $H_3C$ ) <sub>2</sub> HC-	$4 \times 10^4$	42		$8 \times 10^7$	44

Annlequist, D. E.; O'Brien, D. E. *J. Am. Chem. Soc.* **1962**, *8*

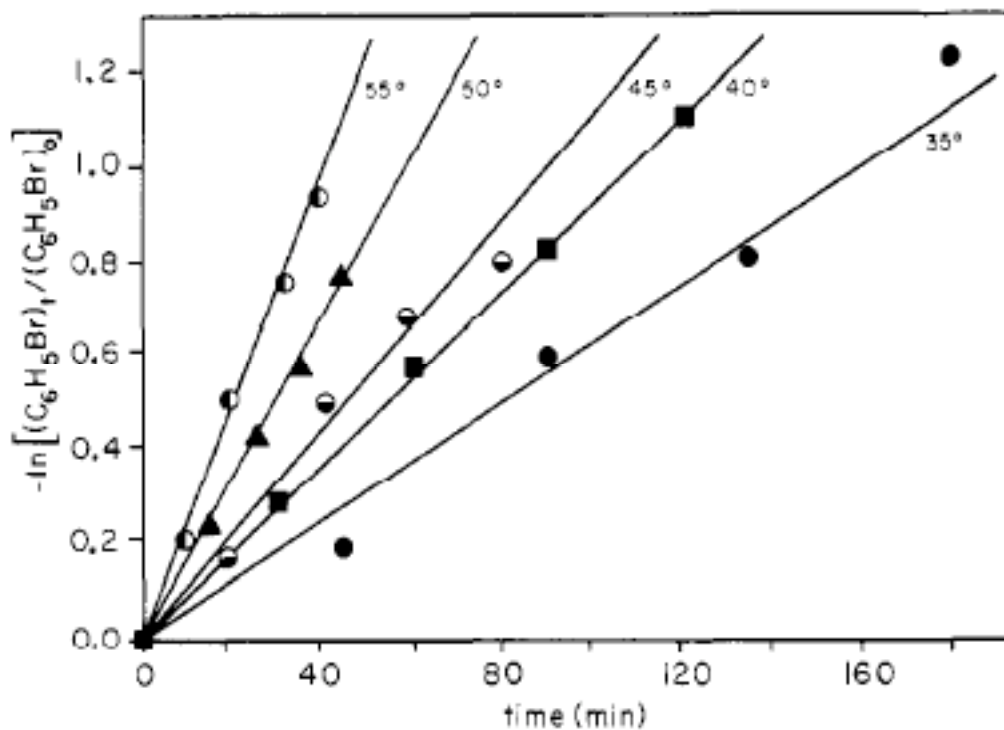


## Kinetic Studies to Probe the Mechanism

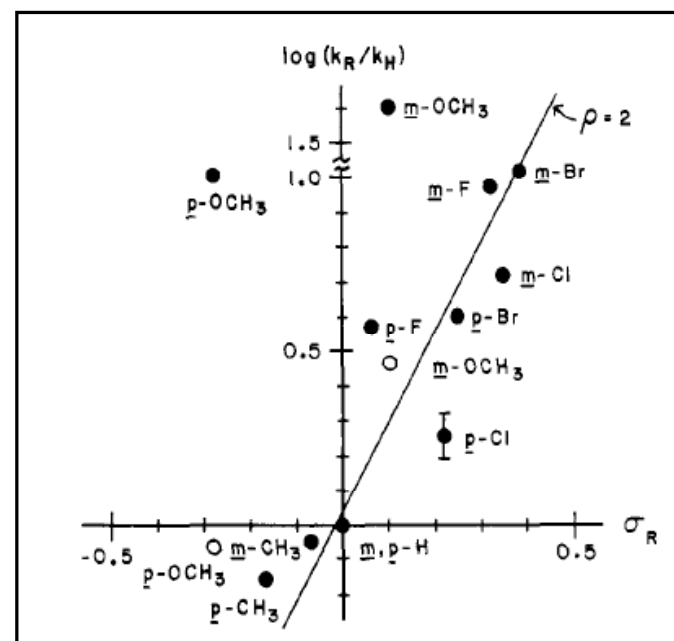


$$\text{rate} = -d[\text{ArBr}]/dt = k[\text{ArBr}]^1[n\text{-BuLi}]^1$$

- Reaction is first order in bromobenzene and *n*-BuLi

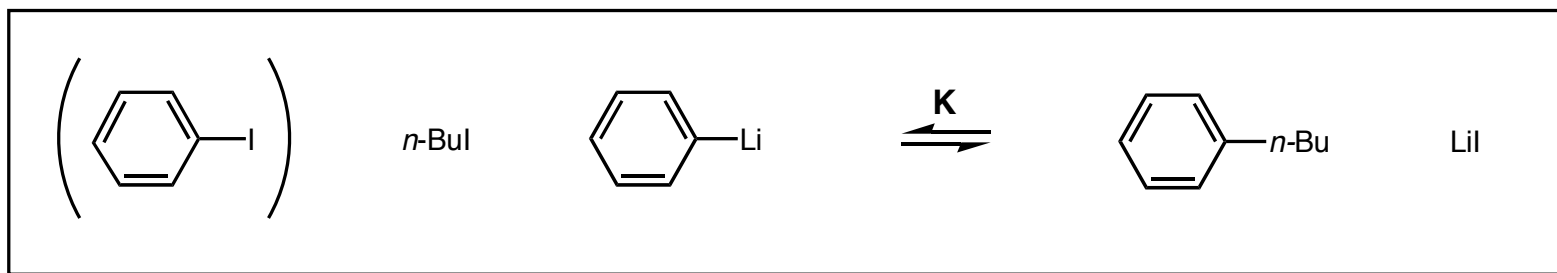


- Hammett relationship for the reaction of substituted bromobenzenes suggests a negative character in the transition state ( $\rho \approx 2$ ) for the slow step of the reaction

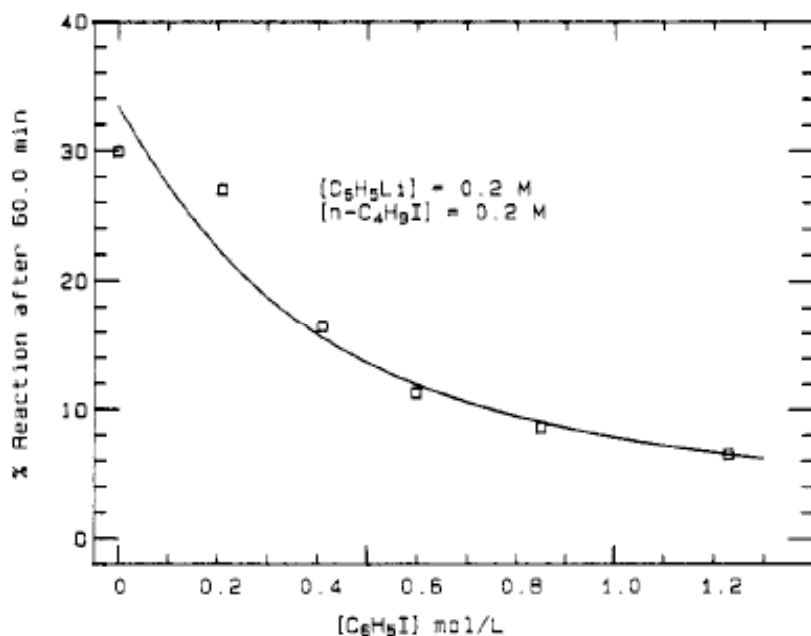


- Results are consistent with a concerted exchange of lithium and halogen with nucleophilic attack of a carbanion-like aryllithium on the bromine atom of the aryl halide

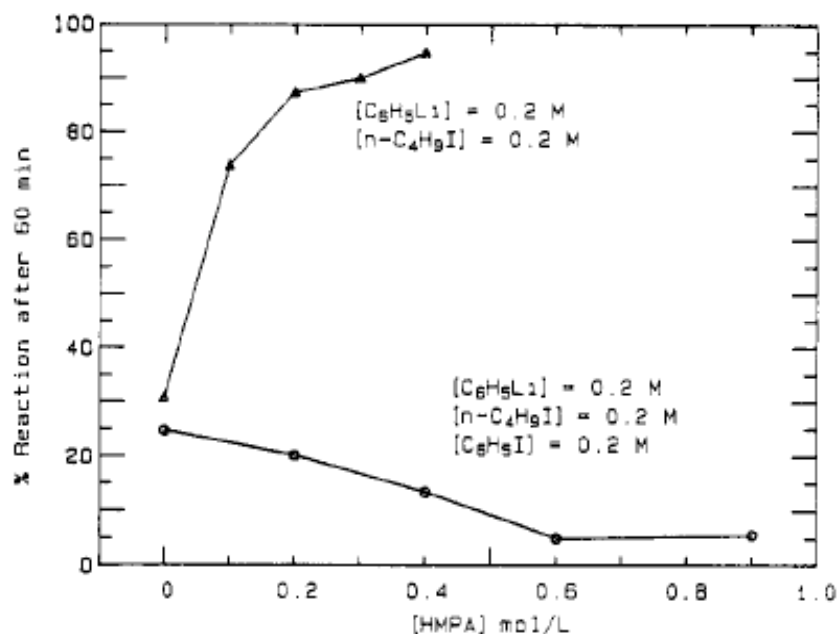
## Evidence for the Formation of an Intermediate "ate-complex"



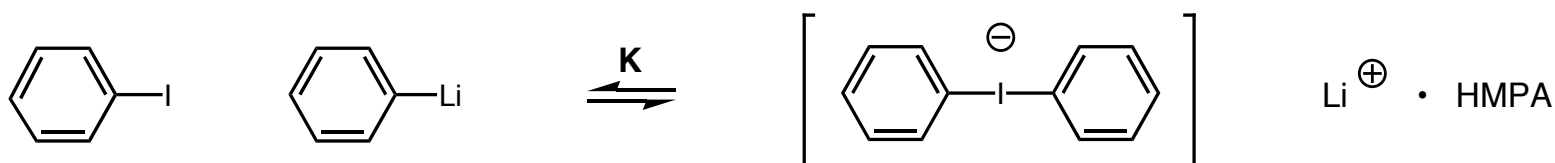
- Increasing concentration of iodobenzene decreased the rate of alkylation



- The addition of HMPA lowers the reactivity

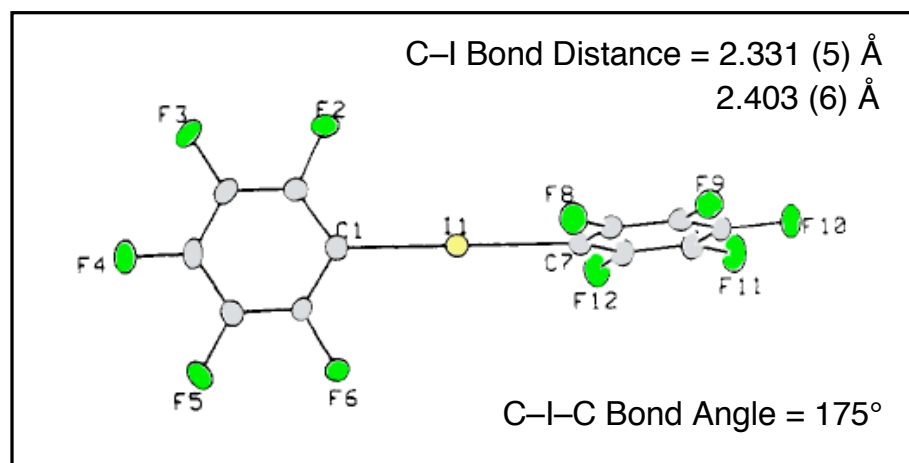
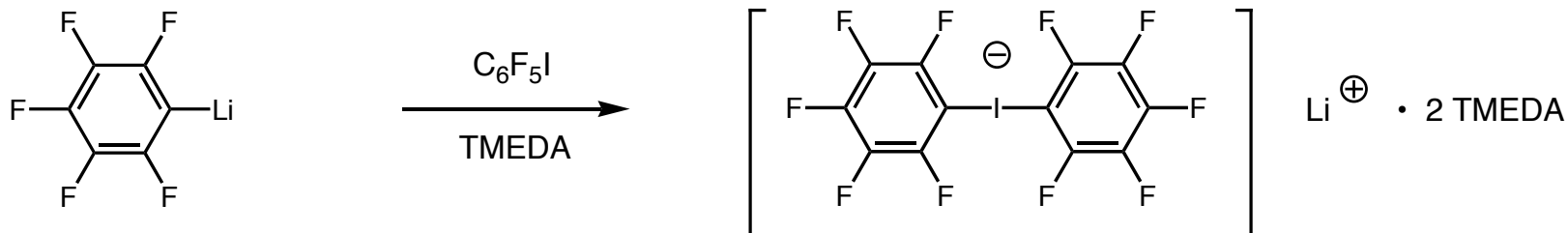


- It was postulated that a relatively unreactive "ate-complex" intermediate was formed and that HMPA preferentially coordinates to the Li cation to lower the rate of alkylation

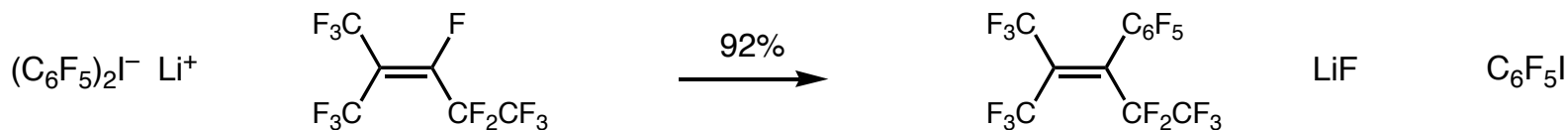


## Evidence for the Intermediacy of an "ate-complex"

- Farnham isolates a hypervalent (10-I-2) structure from a Li-Halogen exchange reaction



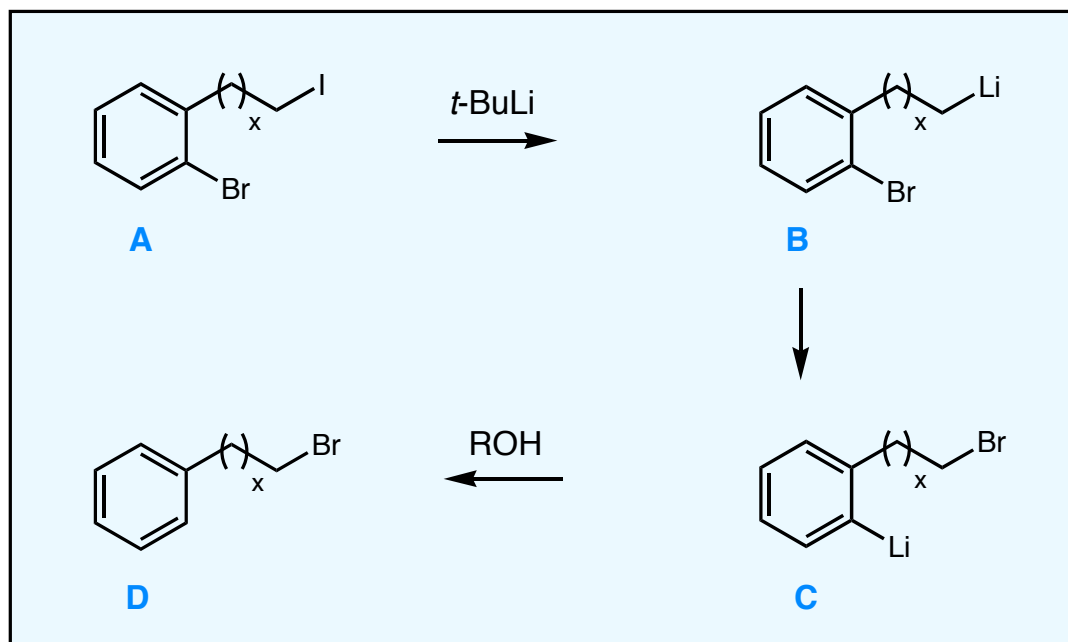
- The isolated "ate-complex" was found to be a competent nucleophile



- Analogous stable hypervalent 10-Br-2 anions have since been established

## Probing the Transition Structure Geometry: The Endocyclic Restriction Test

- 10-X-2 "ate-complexes" favor linear geometries, which has also been suggested to be favored in nucleophilic substitution reaction at the halogen center

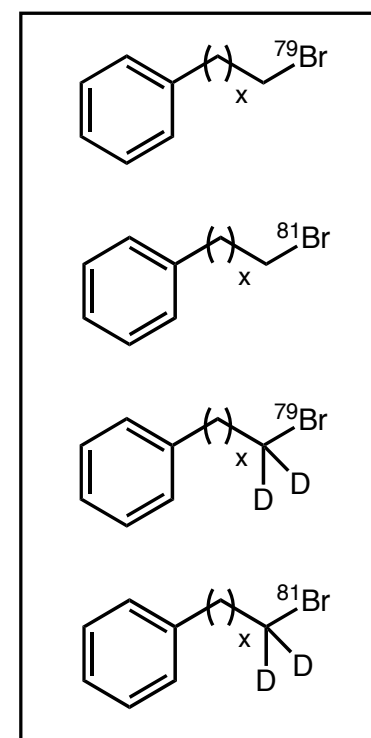
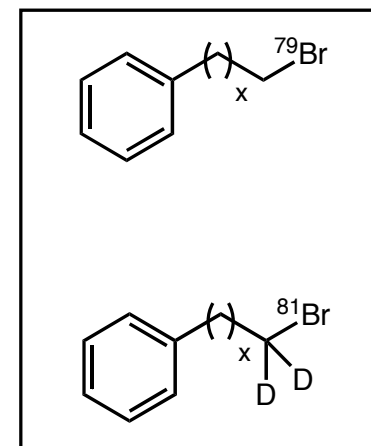
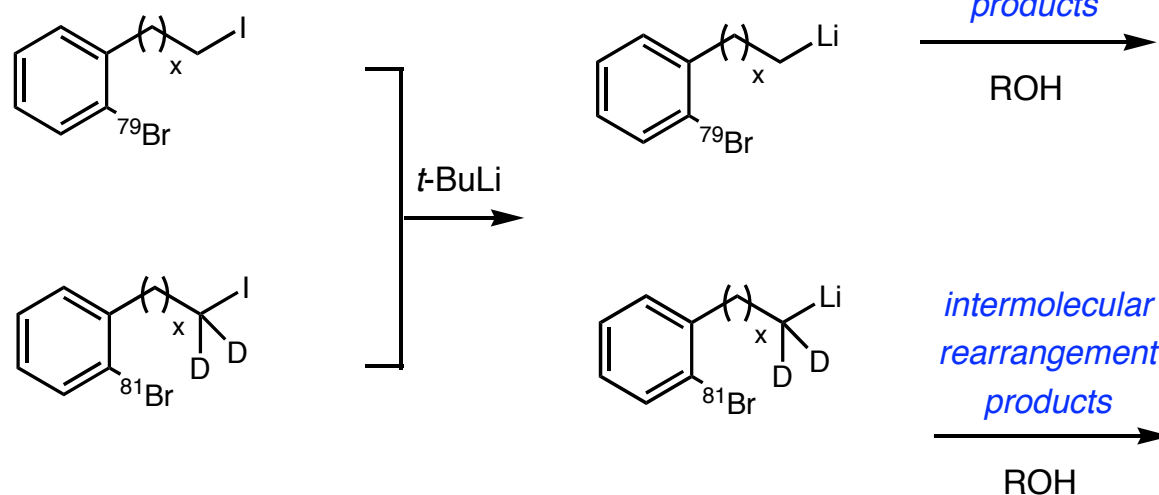


### ■ The game plan:

- The rearrangement of **B** to **C** requires a TS geometry which allows an endocyclic reaction.
- If the geometry requirement can not be met, an intermolecular reaction is expected.
- A geometrical dependance for the reaction can be established by a change in the tether length
- Therefore, a lack of geometrical dependance would reveal no change in the intra/intermolecularity of the reaction with systematic variation of the tether.

# Probing the Transition Structure Geometry: The Endocyclic Restriction Test

- How to distinguish between an inter- and intramolecular reaction?



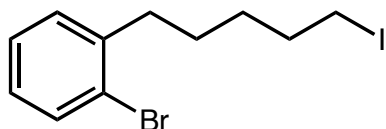
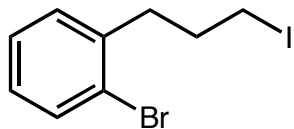
## Double-Double Labelling Experiments

**Intramolecular– isotopic distribution will be the same as the reactants**

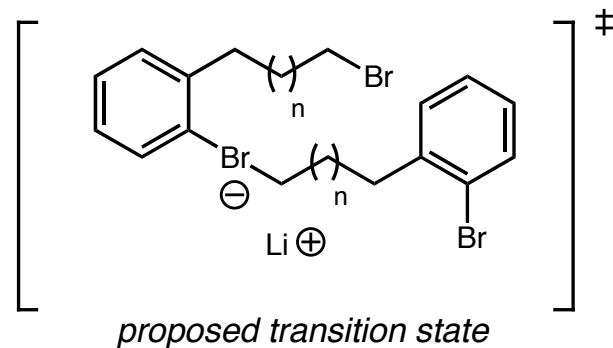
**Intermolecular– a statistically distributed ratio of products will be obtained which can be determined by MS**

## Probing the Transition Structure Geometry: The Endocyclic Restriction Test

- Intermolecular reactions are observed for systems that would have a 6 or 8 membered endocyclic transition structure

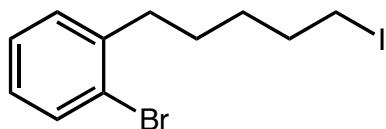
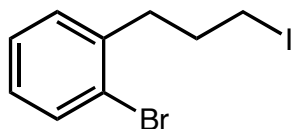


**intermolecular  
only**

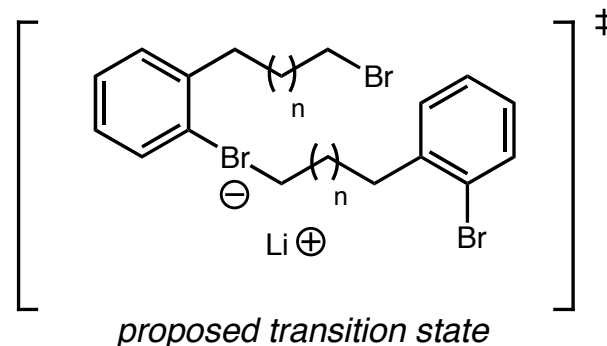


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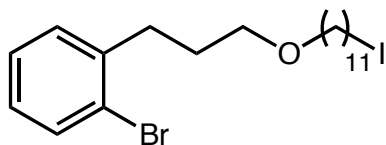
- Intermolecular reactions are observed for systems that would have a 6 or 8 membered endocyclic transition structure



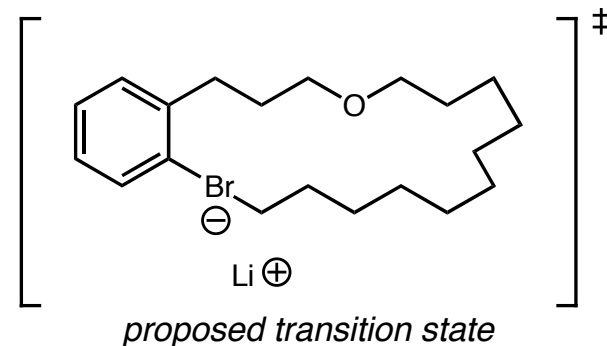
**intermolecular  
only**



- Intramolecular reactions is allowed in an 18 membered endocyclic transition state demonstrating the geometrical requirement for large bond angles around the entering and leaving groups for  $S_N2$  reaction

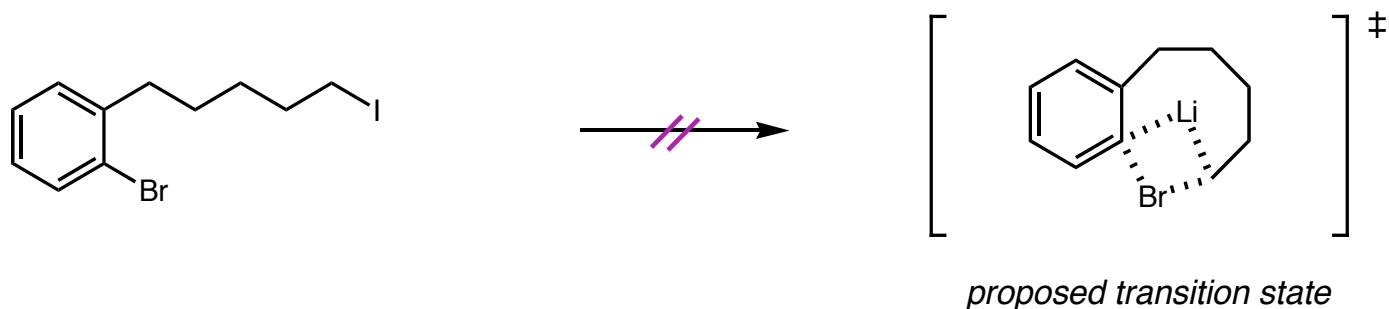


**intermolecular (55%)  
intramolecular (45%)**

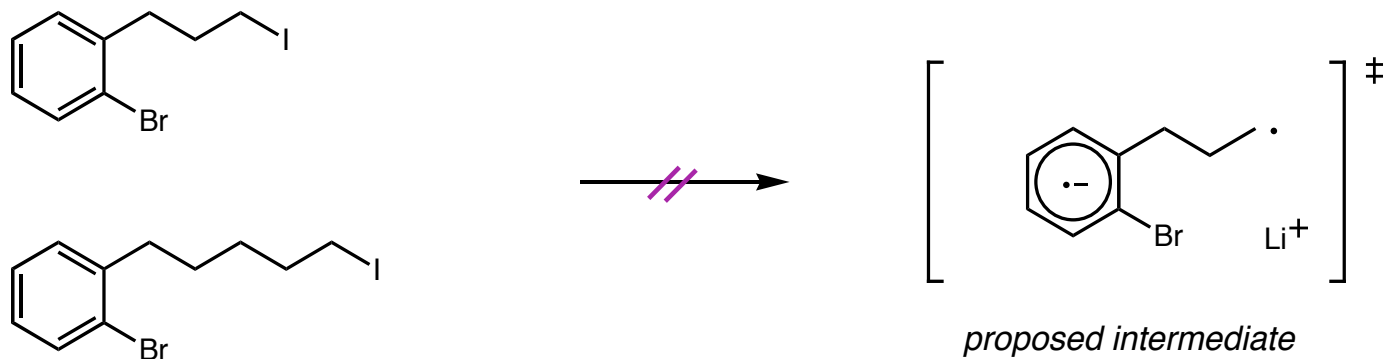


## Probing the Transition Structure Geometry: Other Mechanistic Conclusions

- Authors discount the four-centered transition state mechanism on the basis that the requisite C–Br–C bond would be small and an intramolecular transition state would have been accessible



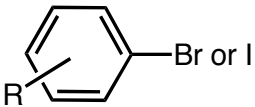




- SET mechanism is also ruled out as there was no intramolecular exchange observed in two cases





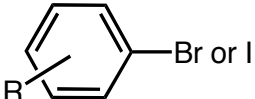




## The Mechanism of Lithium–Halogen Exchange: Conclusions

- Mechanism of lithium–halogen exchange is still under debate in the literature, the balance of evidence suggests:

		nucleophilic ("ate–complex") mechanism
1° alkyl iodide		nucleophilic ("ate–complex") mechanism
2° alkyl iodide		nucleophilic ("ate–complex")/ radical competition
alkyl bromide		radical mechanism

## The Mechanism of Lithium–Halogen Exchange: Conclusions

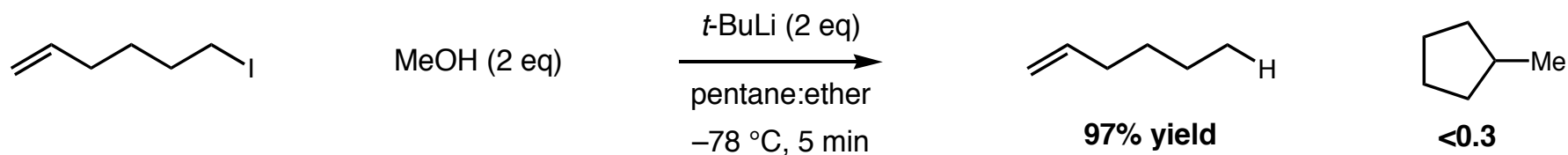
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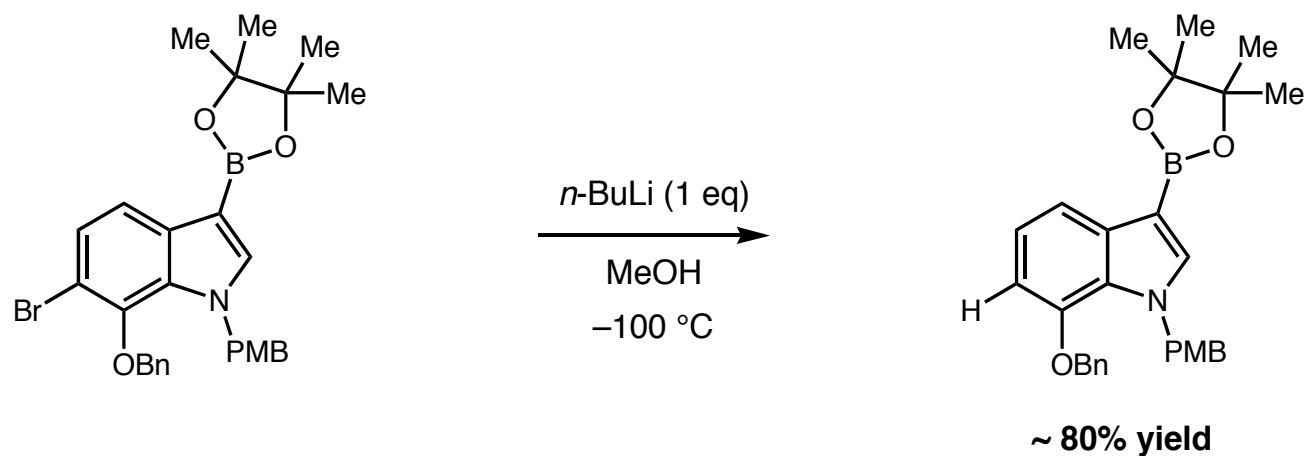
- What of the reactivity of lithium–halogen exchange relative to other processes?

# A Competition: Reaction of Organolithium Reagents

## Lithium-Halogen exchange versus proton transfer

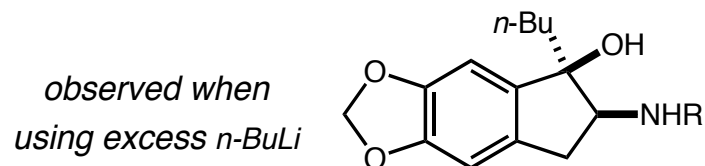
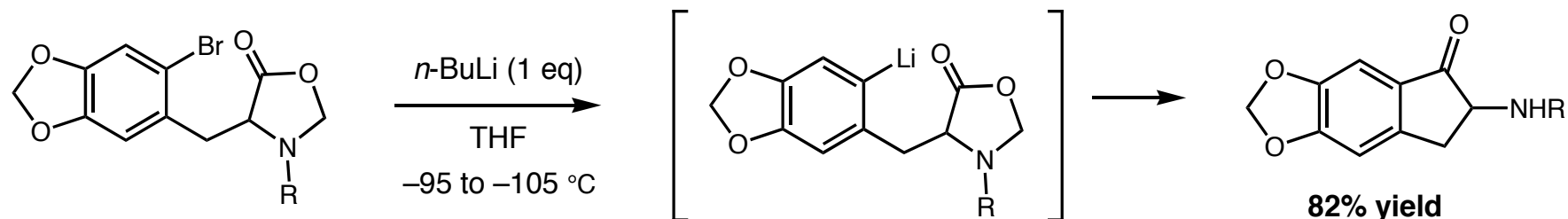


## Exchange can exceed the rate of proton transfer in some cases\*

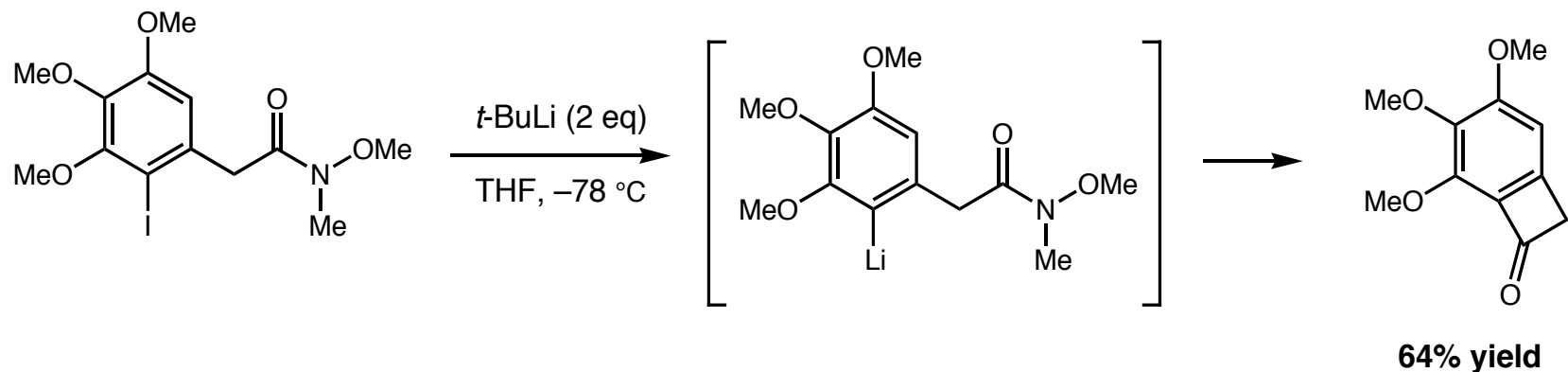


## A Competition: Reaction of Organolithium Reagents

### Lithium–Halogen exchange versus nucleophilic addition:



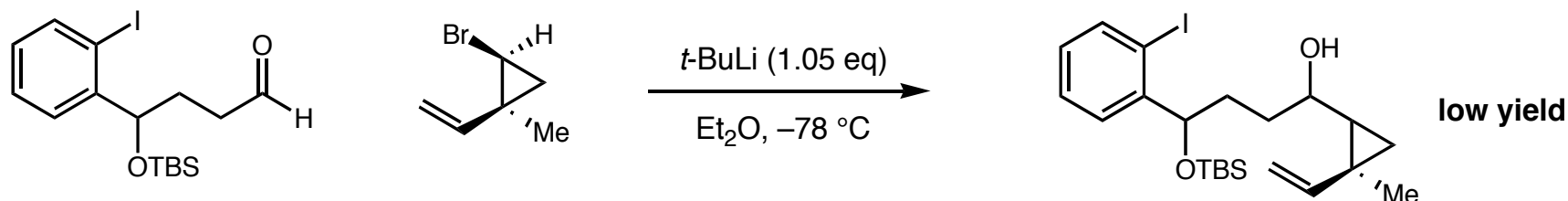
### Exchange reaction is more rapid than addition in some cases



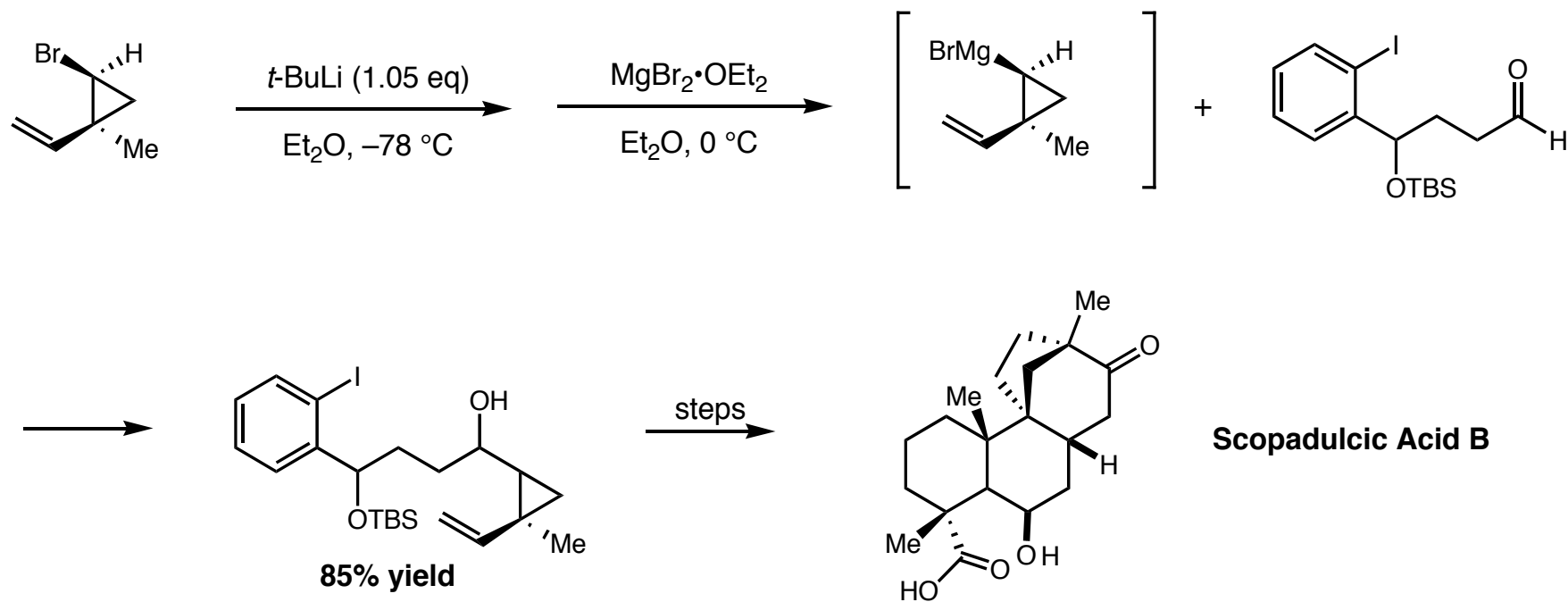
# Applications in Total Synthesis

## Synthesis of Scopadulic Acid B

Competitive lithium–halogen exchange is faster with the aryl iodide than reaction with the terminal aldehyde

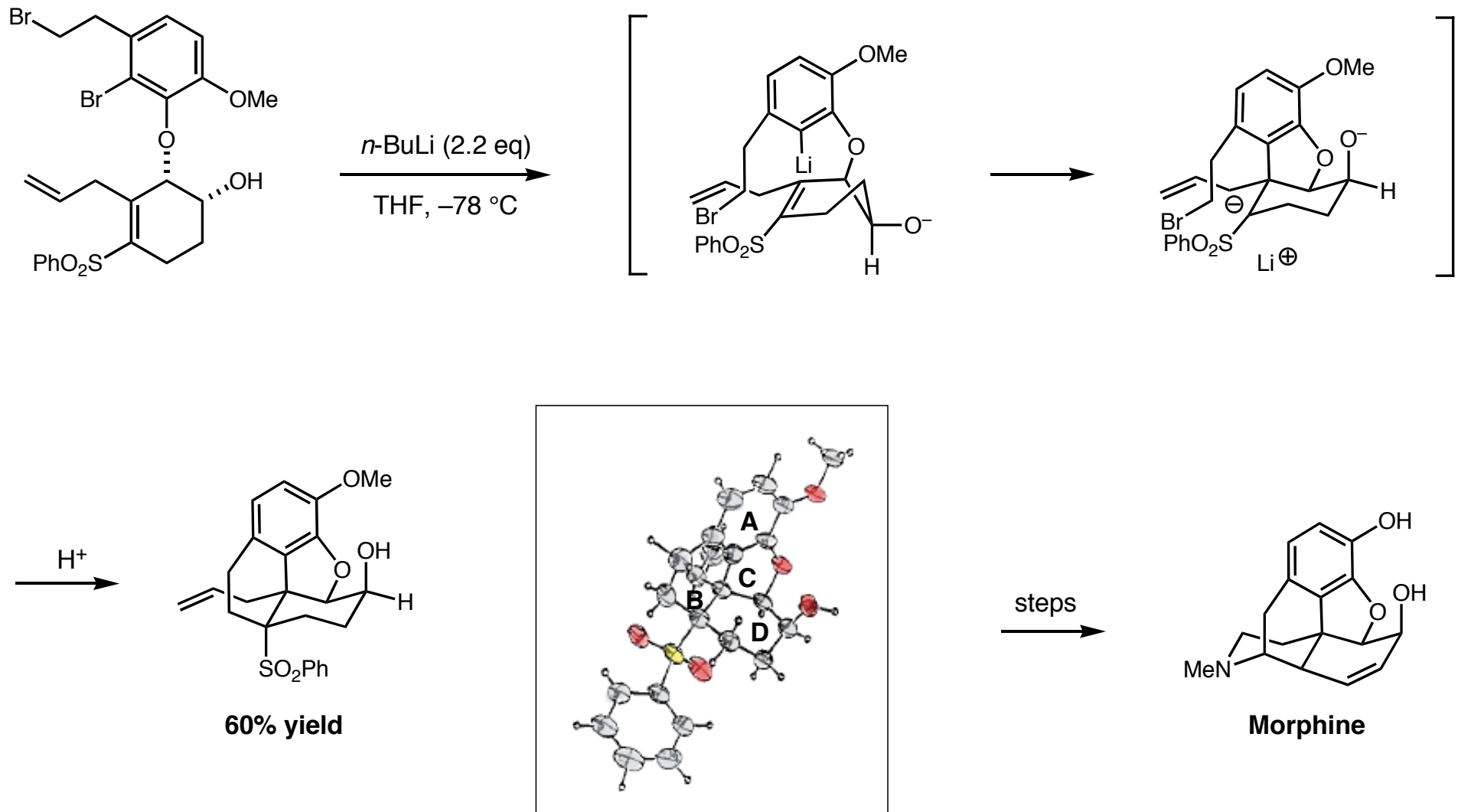


## Transmetalation gives a more nucleophilic organometallic species



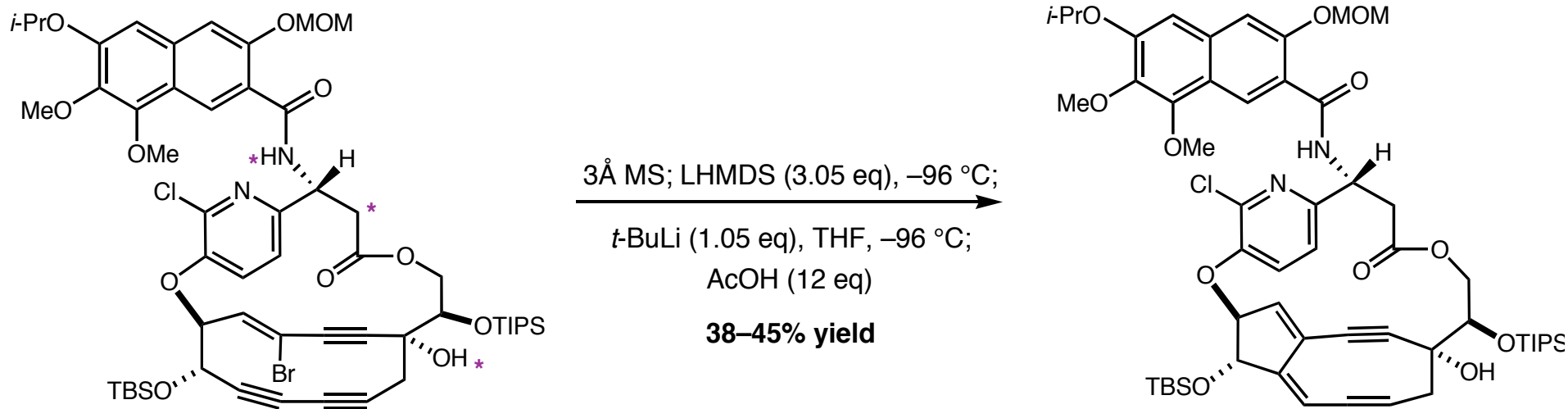
# Applications in Total Synthesis

## ■ Synthesis of Morphine: Formation of the tetracyclic core

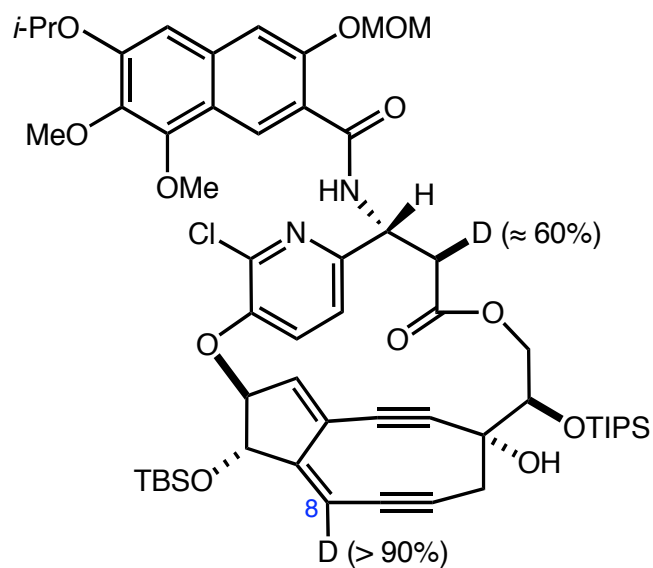


# Applications in Total Synthesis

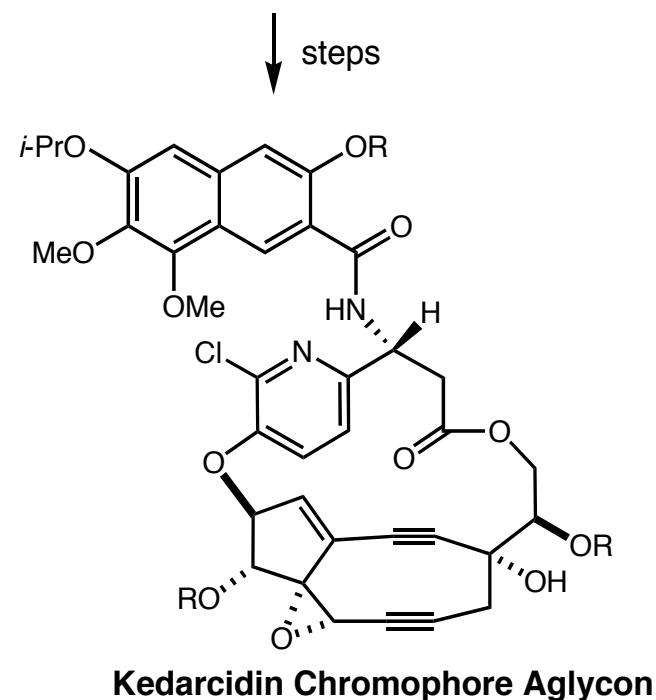
## ■ Synthesis of the Kedarcidin Chromophore Aglycon by an anionic transannular ring closure



## ■ Deuterium-labelling experiment: [D<sub>4</sub>]acetic acid quench

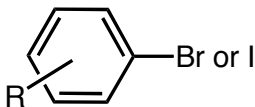






*The authors conclude that the transannular cyclization had proceeded through a tetraanion intermediate*



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- Lithium-halogen reactions have found broad use by synthetic organic chemists