

Mechanism of Lithium-Halogen Exchange and Related Reactions

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Outline

Introduction

Single electron transfer (SET) mechanism

Nucleophilic ("ate-complex") mechanism

Structure and reactivity of organolithium

Summary

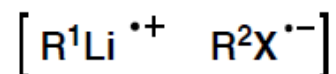
Acknowledgement

Introduction

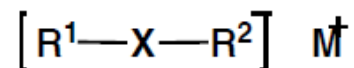
Mechanistic Postulates for Li-Halogen Exchange



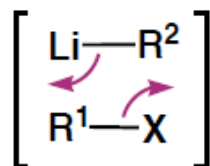
Electron transfer (radical) process



Nucleophilic mechanism via halogen "ate"-type intermediate

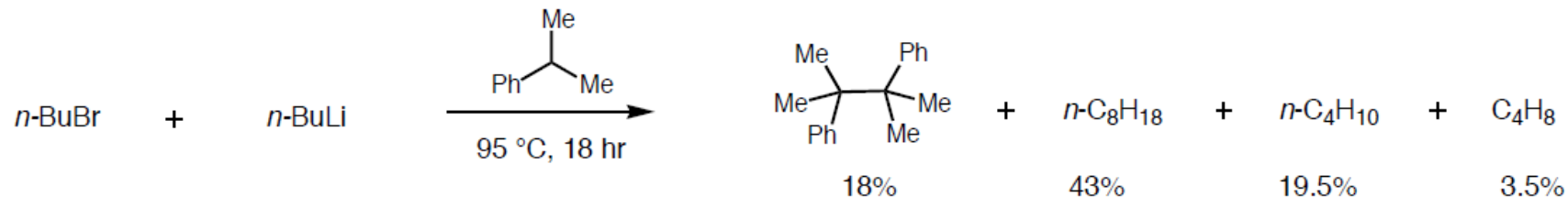


Four-centered transition state model

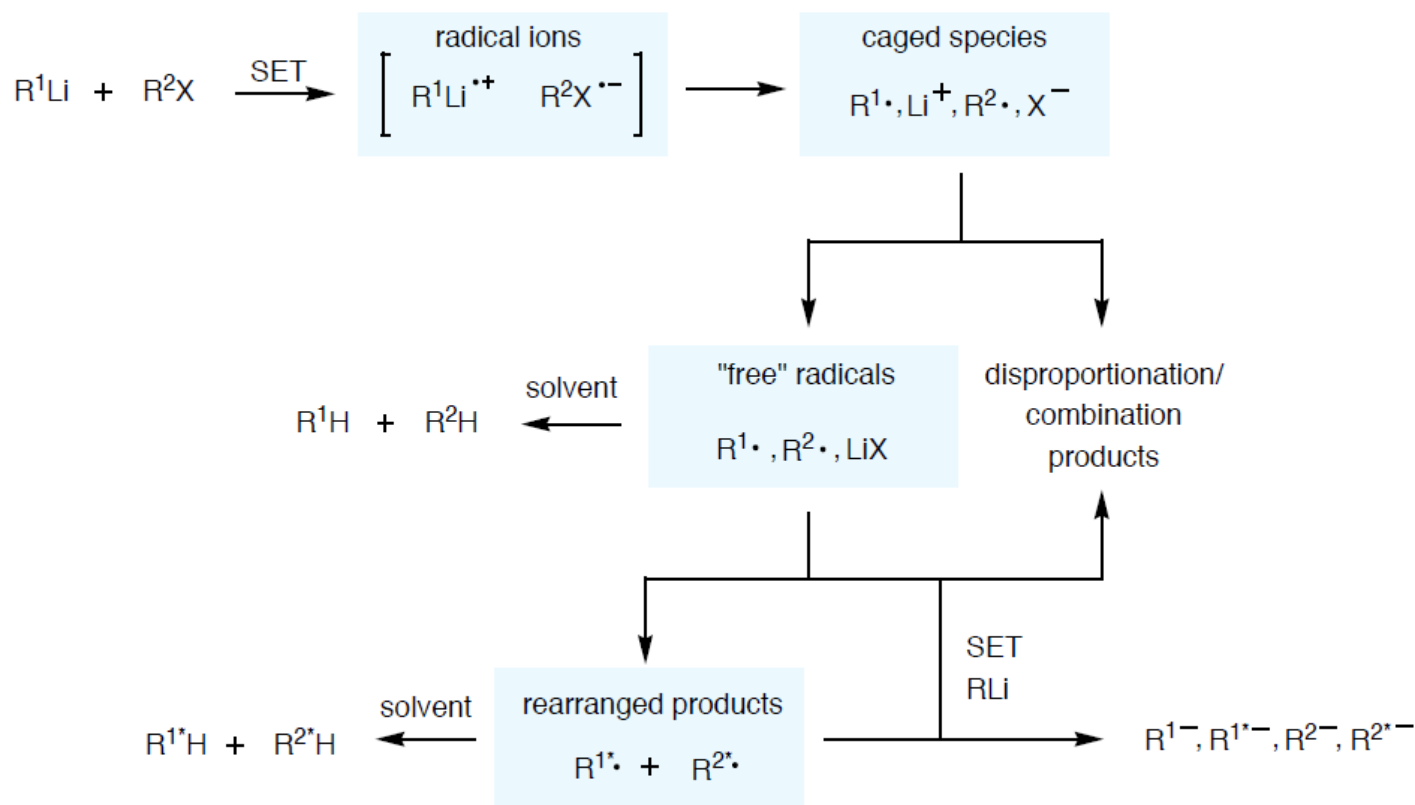


Single Electron Transfer Mechanism

- First evidence for radical mechanism in 1956



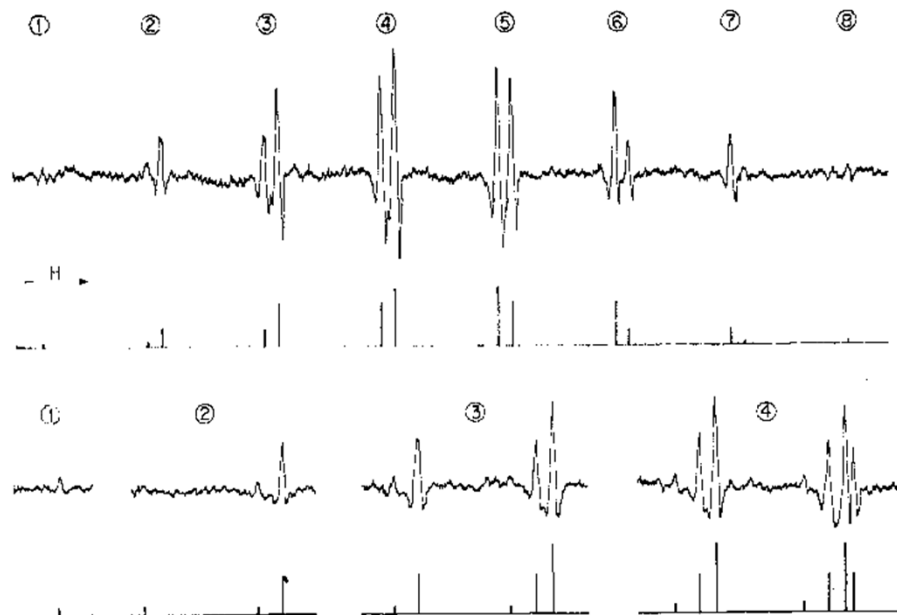
- Proposed mechanism



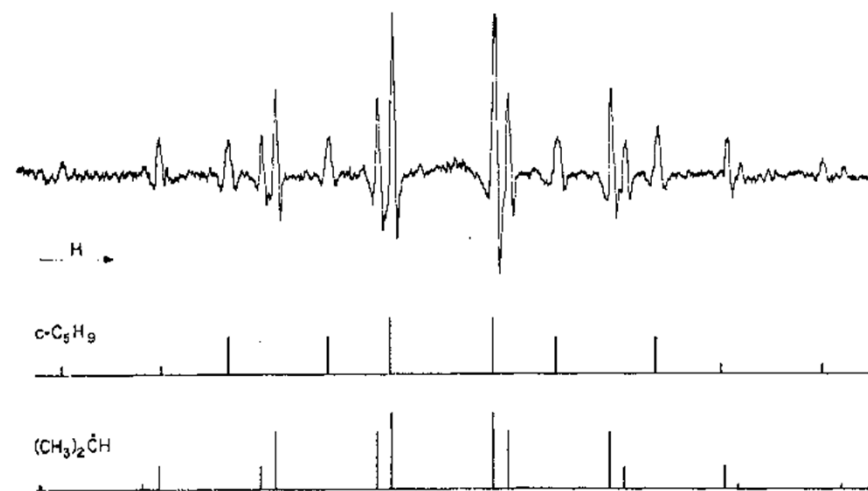
J. Chem. Soc. **1956**, 1603.

Luo Group Meeting (CCME@PKU)
J. Organomet. Chem. **1988**, 352, 1.

Electron-Spin Resonance Spectroscopy



isopropyllithium (1.86 M in n-pentane)
with isopropyl bromide (0.66 M in a 6:1
benzene-diethyl ether mixture)



isopropyllithium with cyclopentyl
bromide (second derivative presentation)

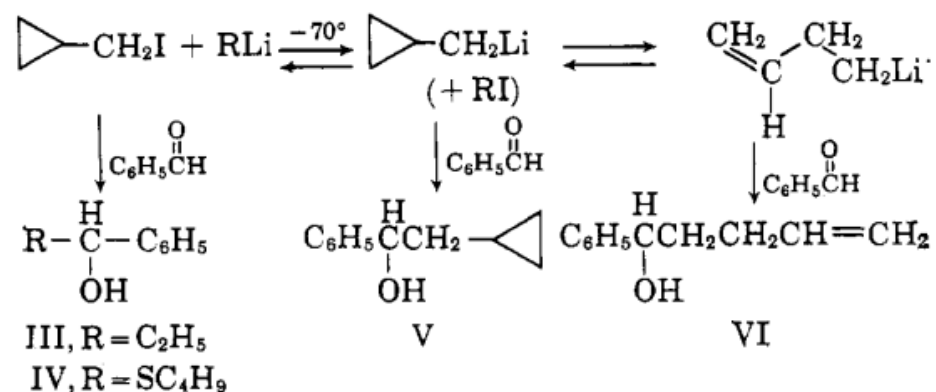
Fischer, H. *J. Phys. Chem.* **1969**, 73, 3834.

Luo Group Meeting (CCME@PKU)

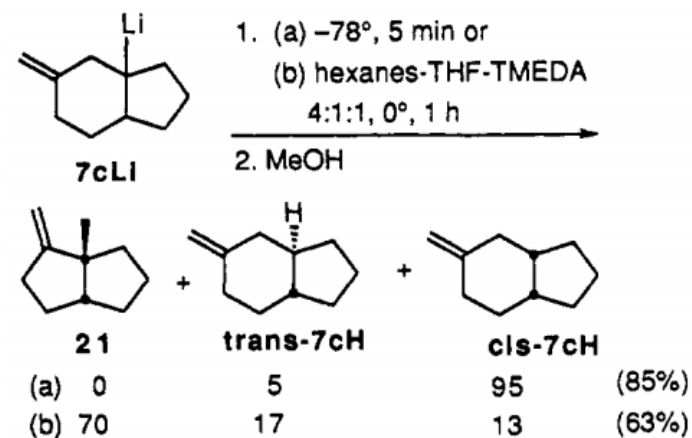
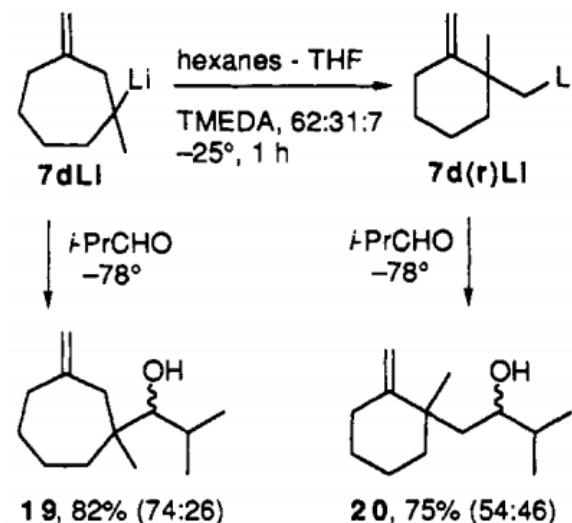
Radical Clock Experiments

TABLE I

PREPARATION OF I BY METAL-HALOGEN EXCHANGE AT -70°

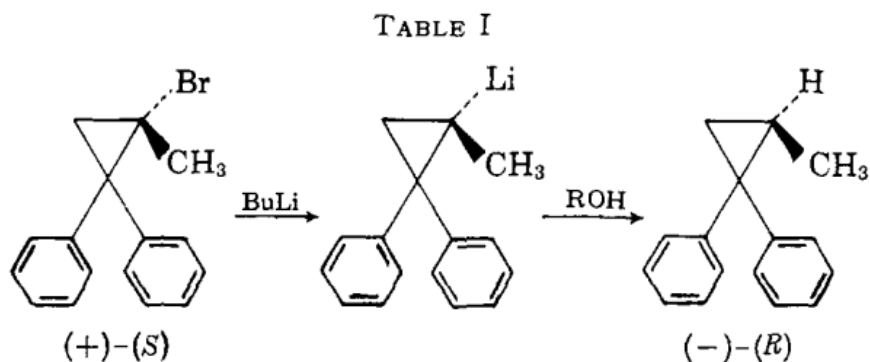


Run	mmoles RLi	mmoles C ₄ H ₇ I	Ex-change time, min.	% III (IV)	% V	% VI	% alcohols
A. RLi = ethyllithium in ether ^a							
1	1.0	1.0	5	35	49	16	..
2	1.0	1.0	30	11	51	38	..
3	1.0	1.0	120	3	17	80	..
4	10.0	10.0	5	66	22	12	82
B. RLi = <i>sec</i> -butyllithium in 10:1 petroleum ether-ether							
5	1.0	1.2	2	1	95	4	89
6 ^b	1.0	1.2	2	1	93	6	83
7 ^c	1.0	1.2	2	<1	94	6	82
8	1.0	1.2	60	0	84	16	60
9	1.0	1.2	240	0	55	45	33
10 ^d	1.0	1.2	240	0	53	47	41
11 ^e	1.0	1.2	2	0.5	71	28.5	



Is SET Mechanism the Only Pathway?

Retention of configuration at the carbon center connected to the halogen atom



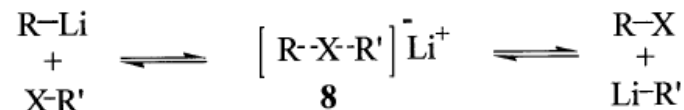
Run	$[\alpha]_D$ of bromide	Solvent	Temp., °C.	Time, min.	Yield, %	Optical purity, ^a %
1	106.0	Ether-benzene-petr. ^d	6	30	43	60 ^c
2	106.2 ^b	2:1:1	35	10	44	77
3	107.1	Ether	35	10	61	84
4	107.1	Ether	-3 to 0	30	73 ^e	76
5	91.9	Petr-DME ^f	28-33	10	69	85

^a The maximum rotation of the bromide is taken to be 111.6° and of the hydrocarbon¹⁸ 128°. ^b Enantiomer used. ^c Low value¹⁹ due to contamination with (+)-bromide. ^d Petroleum ether (30-60°). ^e Yield based on recovered bromide. ^f 1,2-Dimethoxyethane.

J. Am. Chem. Soc. **1964**, *86*, 3283.

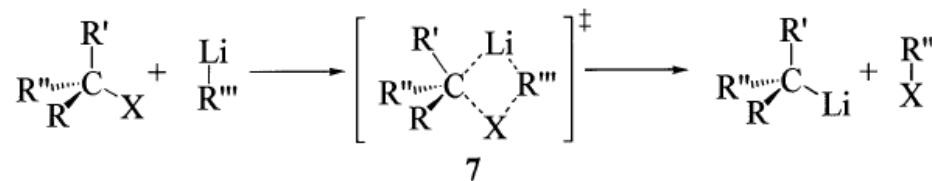
Proposed other mechanism

➤ Nucleophilic ("ate-complex") mechanism



Angew. Chem. **1958**, *70*, 65.

➤ four-center transition state



Tetrahedron **1958**, *3*, 91.

X-ray Structure of Ate-Complex

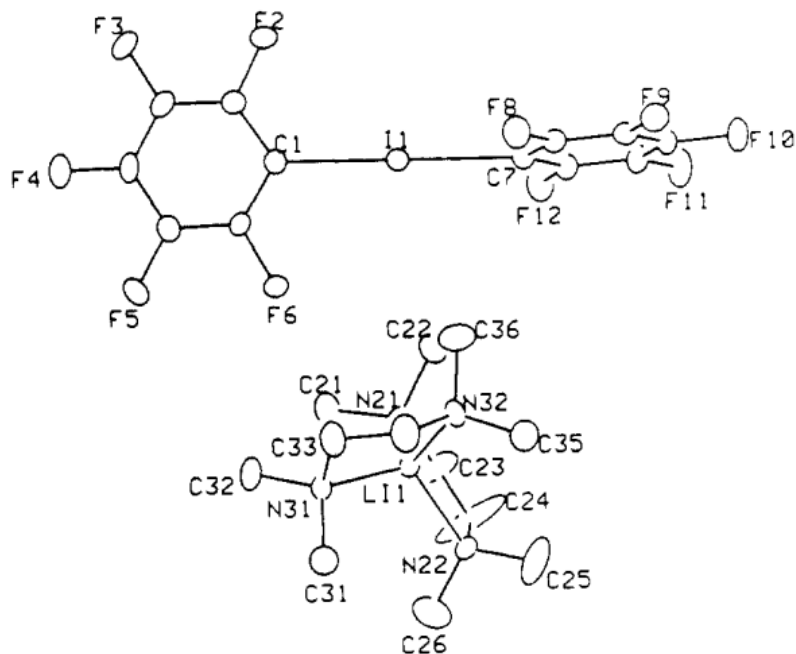
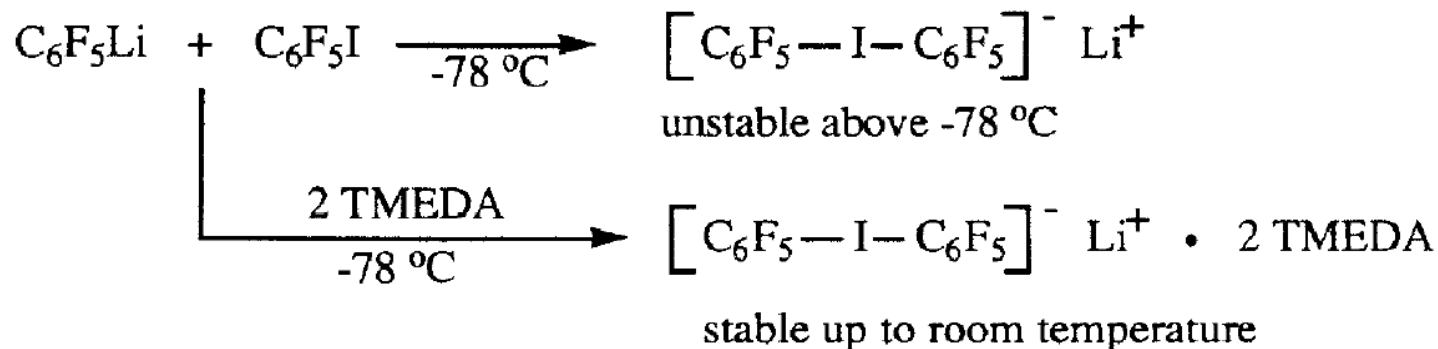


Table I. Selected Bond Distances (Å) and Angles (deg) for **2**

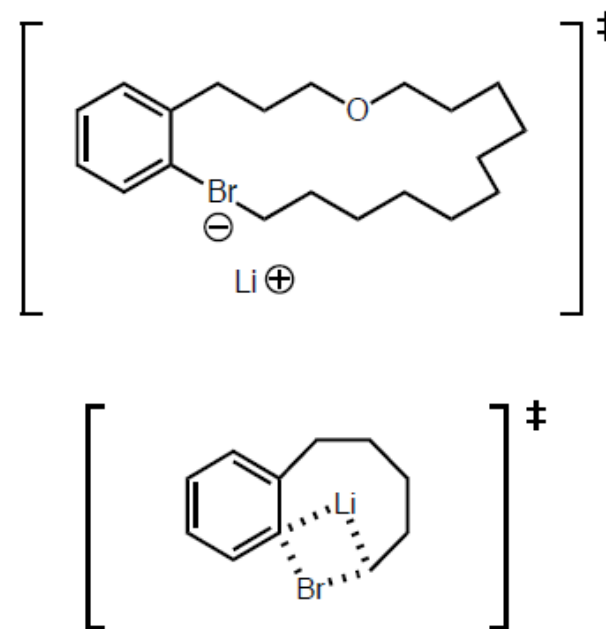
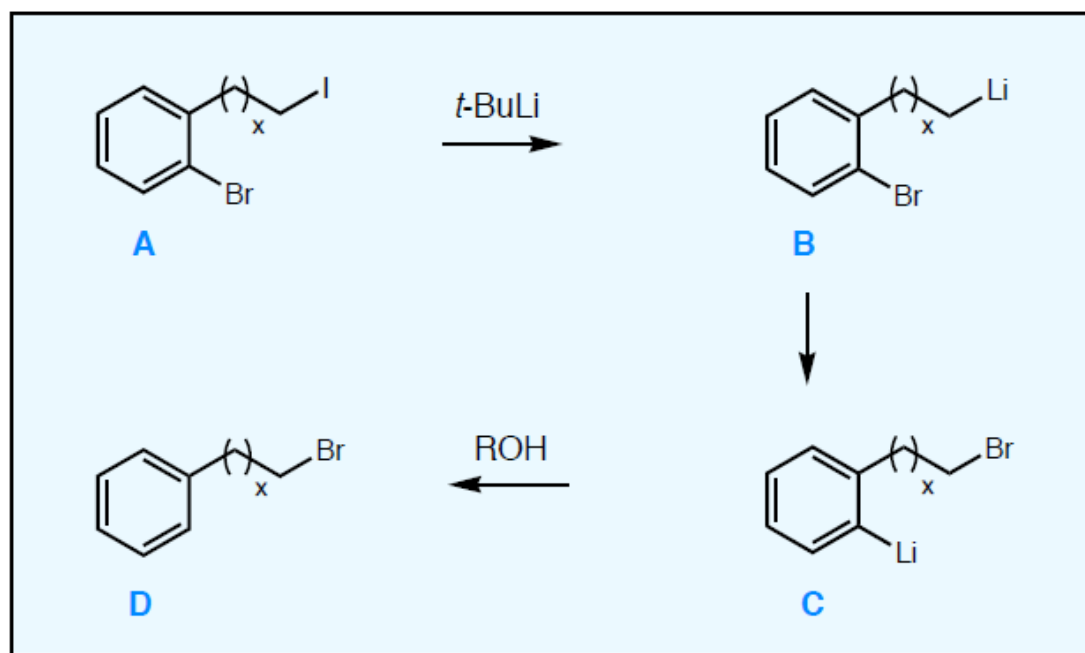
C(7)–I(1)	2.403 (6)	C(3)–C(4)	1.367 (7)
C(1)–I(1)	2.331 (5)	C(2)–F(2)	1.366 (5)
C(1)–C(2)	1.375 (7)	C(3)–F(3)	1.348 (6)
C(2)–C(3)	1.370 (7)	C(4)–F(4)	1.340 (6)
C(1)–I(1)–C(7)	175.2 (2)	C(2)–C(1)–C(6)	114.8 (5)
I(1)–C(1)–C(2)	123.6 (3)	C(3)–C(2)–F(2)	116.6 (5)
C(1)–C(2)–F(2)	119.5 (5)		

"ate-complexes" favor linear geometries

Does Four-centered Transition State Exist?

- "ate-complexes" favor linear geometries, which has also been suggested to be favored in nucleophilic substitution reaction at the halogen center
- intermolecular reaction requires a TS geometry TS geometry is dependent on the tether length

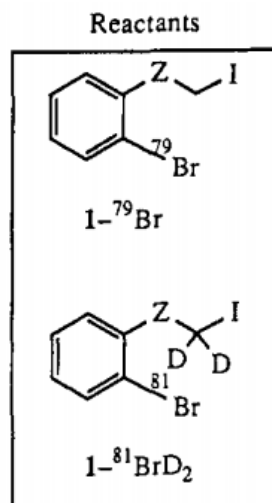
Probing the Transition Structure Geometry



J. Am. Chem. Soc. **1992**, *114*, 3420.

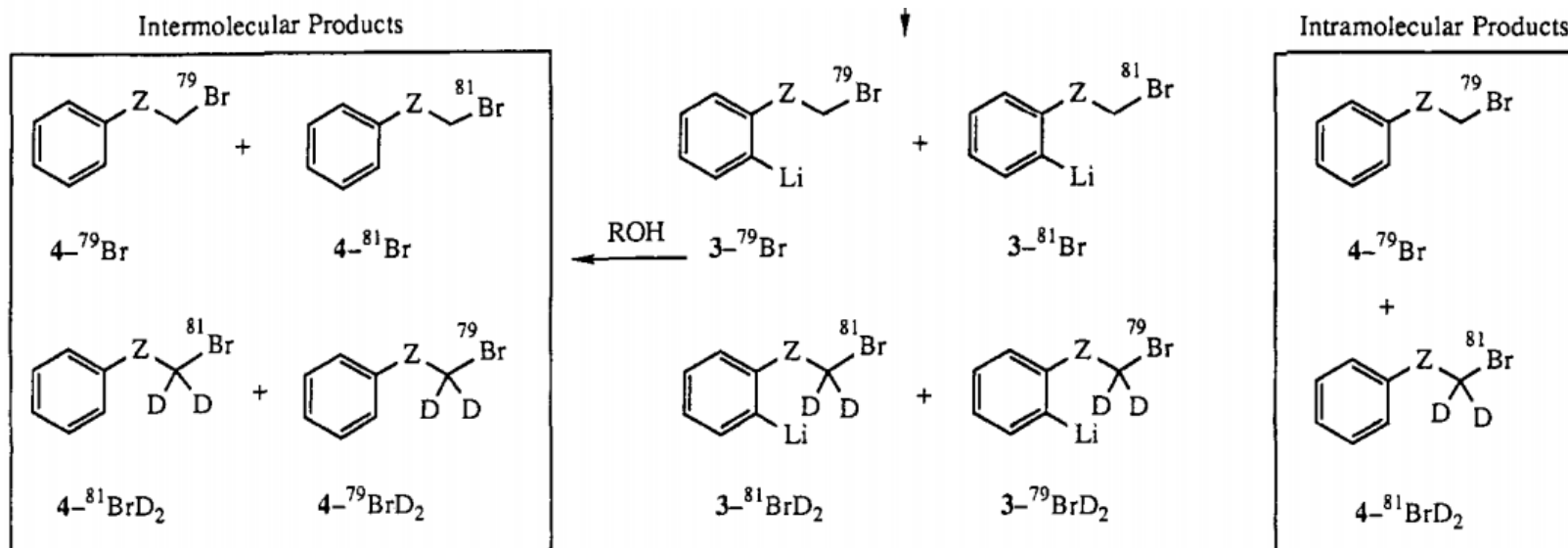
Luo Group Meeting (CCME@PKU)

Double-Double Labelling Experiments



Expectation based on reactant labeling

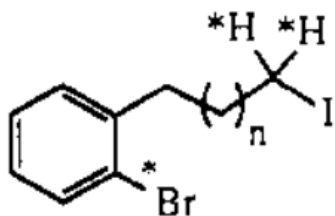
isotopic composition ^a	reactant 11	intramolecular reaction ^b	intermolecular reaction ^b
⁷⁹ Br	45	45	25
⁸¹ Br and ⁷⁹ BrD ₂	10	10	50
⁸¹ BrD ₂	45	45	25



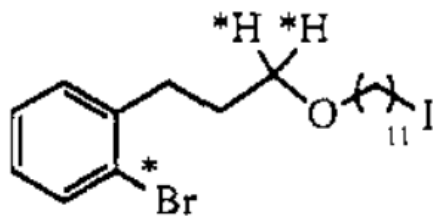
J. Am. Chem. Soc. **1992**, *114*, 3420.

Luo Group Meeting (CCME@PKU)

Double-Double Labelling Experiments



- 11-⁷⁹Br, n = 1, *Br = ⁷⁹Br *H = H
 11-⁸¹BrD₂, n = 1, *Br = ⁸¹Br *H = D
 12-⁷⁹Br, n = 3, *Br = ⁷⁹Br *H = H
 12-⁸¹BrD₂, n = 3, *Br = ⁸¹Br *H = D



- 13-⁷⁹Br, *Br = ⁷⁹Br *H = H
 13-⁸¹BrD₂, *Br = ⁸¹Br *H = D

Table I. Composition of **15** from Isotopic Labeled **11**

isotopic composition ^a	reactant 11	product 15	intramolecular reaction ^b	intermolecular reaction ^b
⁷⁹ Br	45	24	45	25
⁸¹ Br and ⁷⁹ BrD ₂	10	52	10	50
⁸¹ BrD ₂	45	24	45	25

^a Error is ±5%. ^b Expectation based on reactant labeling.

Table II. Composition of **20** from Isotopic Labeled **12**

isotopic composition ^a	reactant 12	product 20	intramolecular reaction ^b	intermolecular reaction ^b
⁷⁹ Br	45	28	45	25
⁸¹ Br and ⁷⁹ BrD ₂	10	50	10	50
⁸¹ BrD ₂	45	22	45	25

^a Error is ±5%. ^b Expectation based on reactant labeling.

Table III. Composition of **26** from Isotopic Labeled **13**

isotopic composition ^a	reactant 13	product		intramolecular reaction ^d	intermolecular reaction ^d
		26^b	26^c		
⁷⁹ Br	48	34	47	48	28
⁸¹ Br and ⁷⁹ BrD ₂	11	32	13	11	50
⁸¹ BrD ₂	42	34	41	42	22

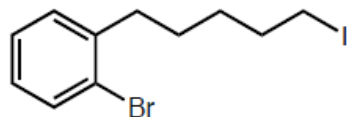
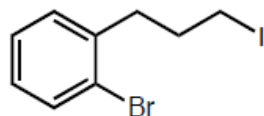
^a Error is ±5%. ^b The values expected for a reaction at 0.02 M which is 45% intramolecular and 55% intramolecular are ⁷⁹Br, ⁸¹Br and ⁷⁹BrD₂, and ⁸¹BrD₂ 36:33:30. ^c At 0.001 M. ^d Expectation based on reactant labeling.

J. Am. Chem. Soc. **1992**, *114*, 3420.

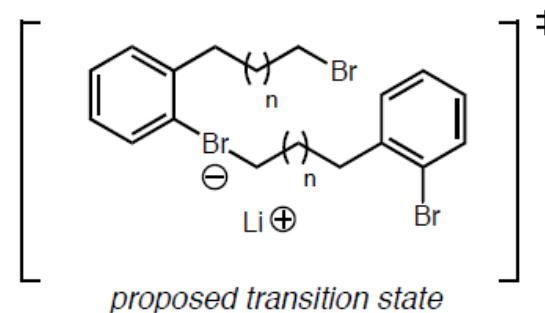
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Transition Structure Geometry

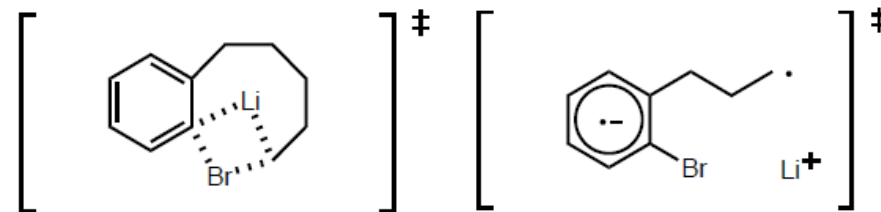
- Intermolecular reactions are observed for systems that would have a 6 or 8 membered endocyclic transition structure



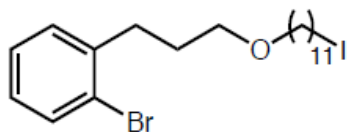
intermolecular
only



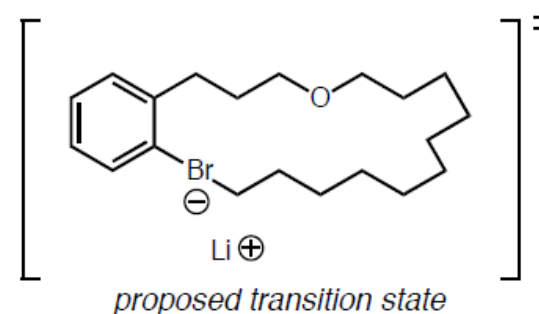
Four-centered transition state mechanism and SET mechanism are not observed in two cases



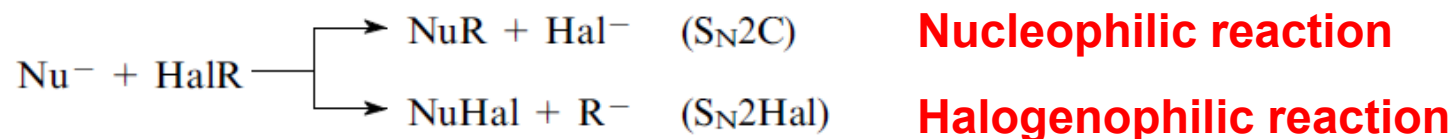
- Intramolecular reactions is allowed in 18 membered endocyclic transition state



intermolecular (55%)
intramolecular (45%)

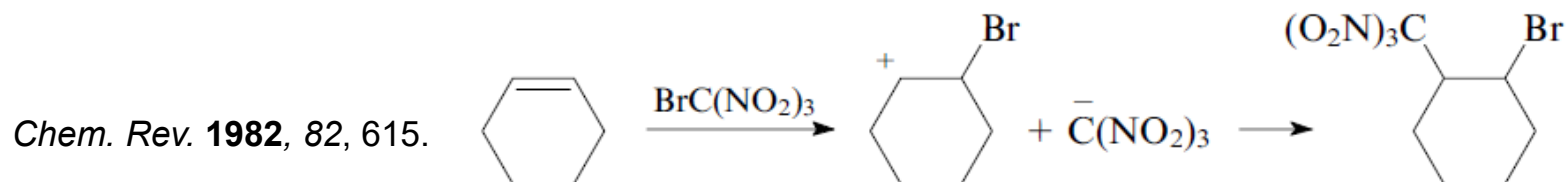


Halogenophilic Reaction

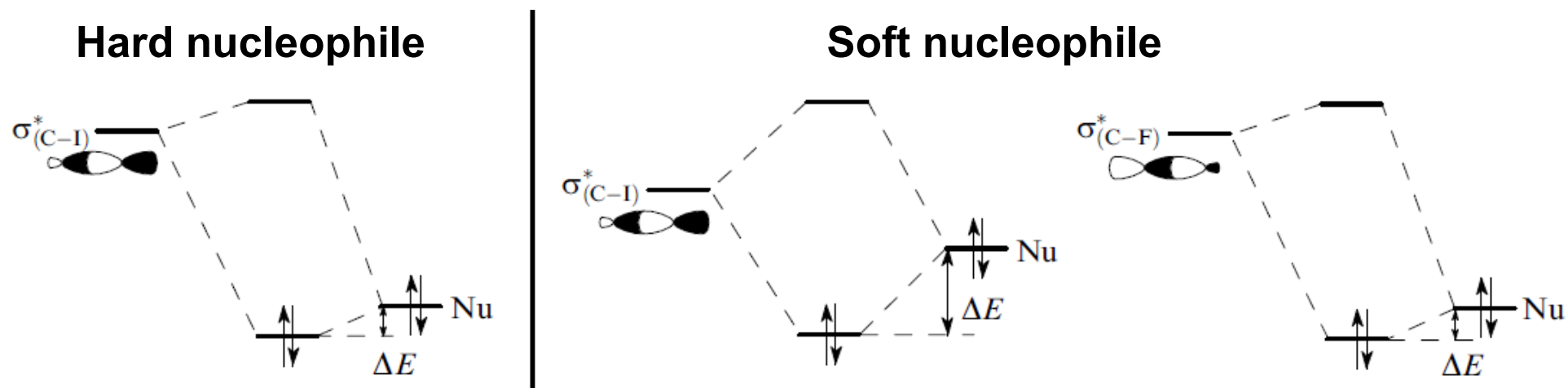


- the general susceptibility for halogenophilic processes increases in the order $\text{C}(\text{sp}^3) < \text{C}(\text{sp}^2) < \text{C}(\text{sp})$
- The carbanion forming in the halogenophilic reaction may also be stabilized by electron-withdrawing substituents in the molecule of organic halide.

Compound RH (bond)	$\text{p}K_{\text{a}}$	Compound RH	$\text{p}K_{\text{a}}$
Alkane $[\text{C}(\text{sp}^3) - \text{H}]$, CH_4	≥ 45	$\text{CH}_3\text{SO}_2\text{X}$	~ 26
Alkene $(\text{C}(\text{sp}^2) - \text{H})$, $\text{CH}_2=\text{CH}_2$	36	CHCl_3	15
Arene $(\text{C}(\text{sp}^2) - \text{H})$, PhH	37	CHF_3	26
Alkyne $(\text{C}(\text{sp}) - \text{H})$, $\text{CH}\equiv\text{CH}$	25	$\text{CF}_2=\text{CFH}$	~ 25
Toluene $(\text{C}(\text{sp}^3) - \text{H})$, PhCH_3	35	$\text{C}_6\text{F}_5\text{H}$	24
CH_3COOEt	~ 27	$(\text{CF}_3)_3\text{CH}$	7
CH_3CN	29	$(\text{NO}_2)_3\text{CH}$	< -1



Reactivity of Nucleophiles



- A general trend is higher reactivity of soft, easily polarizable nucleophiles.

R	K_{obs}	pK_a	R	K_{obs}	pK_a	R	K_{obs}	pK_a
	0.004	36.5		3200	42		3×10^5	42
	1.0	37		7600	42		1×10^6	43
	9.5	39		4×10^4	42		8×10^7	44

Nucleophiles for Halogenophilic Reactions

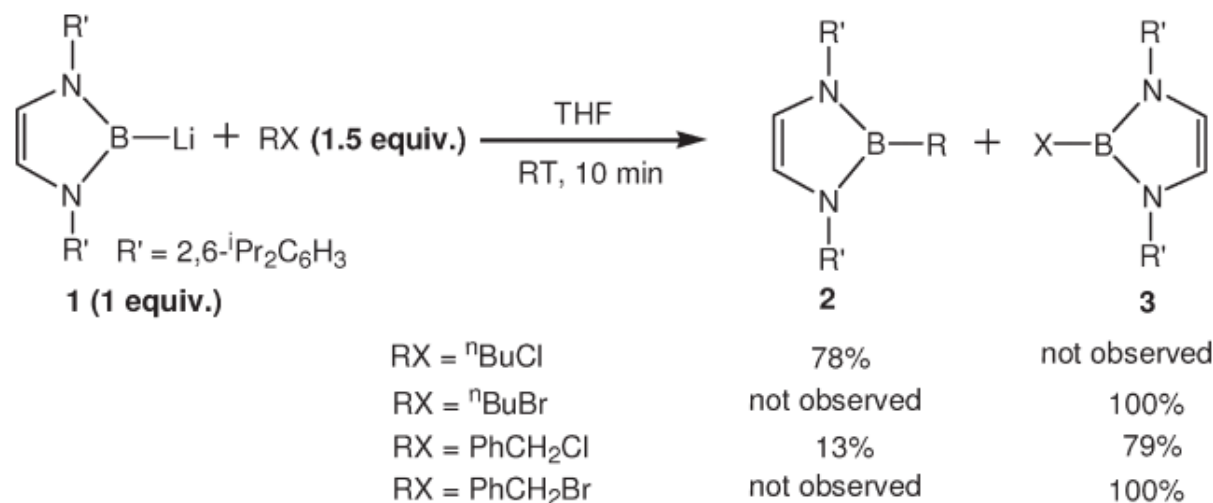
Group 13 elements: R_2B^- ;

Group 14 elements: carbanions, R_3Si^- , R_3Sn^- ;

Group 15 elements: trivalent phosphorus, R_2P^- , R_2As^- ;

Group 16 elements: RS^- , RSe^- , RTe^- ;

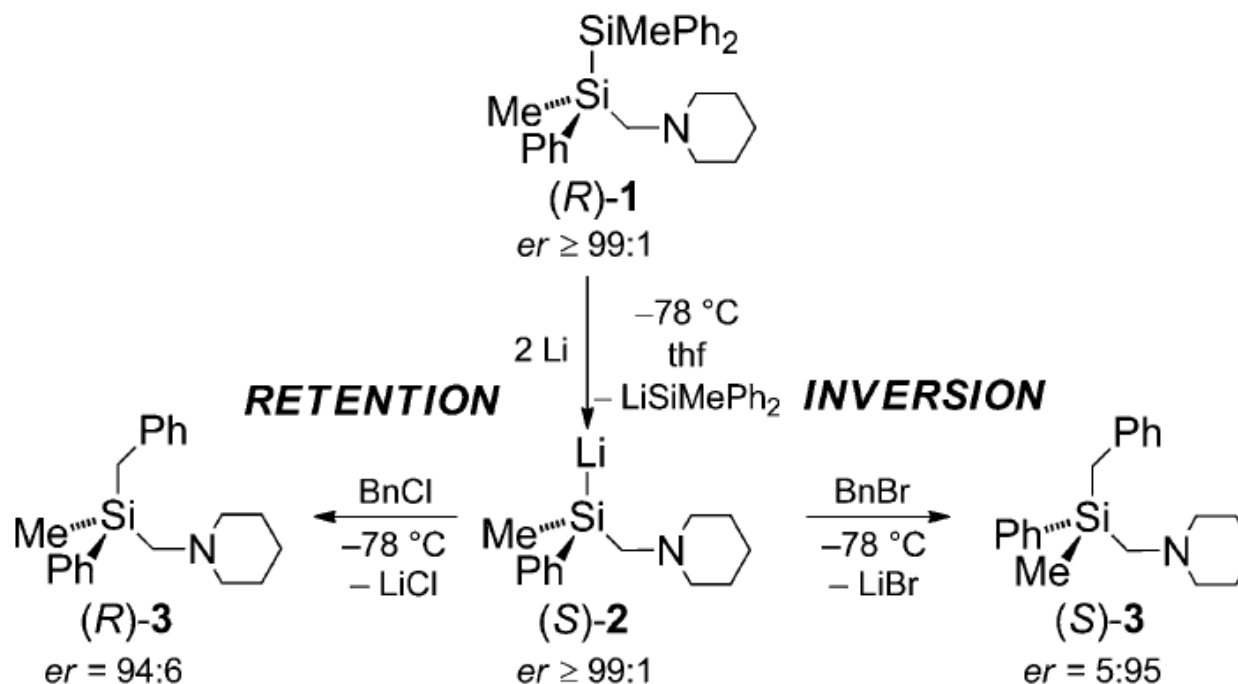
Transition metal carbonyl anions: $[CpFe(CO)_2]^-$ and so on



Organometallics **2011**, 30, 3018

Silicon Anions as Nucleophiles

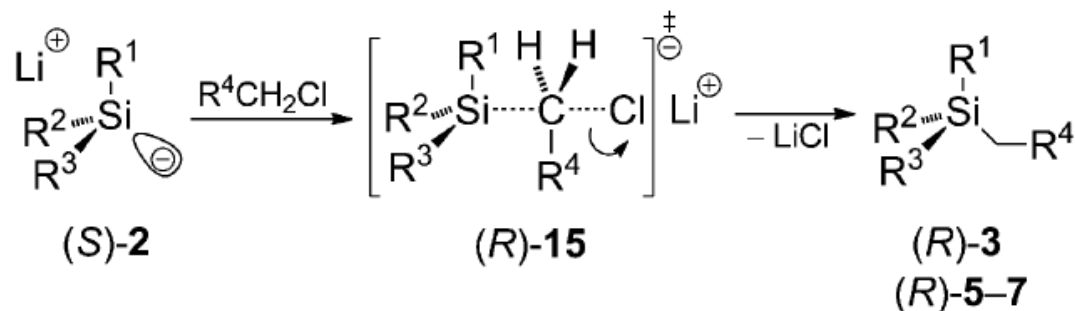
- S_N2 reaction on carbon results in **retention** of configuration on silicon
- Halide–lithium exchange and a subsequent S_N2 reaction on silicon leads to **inversion** of configuration on silicon



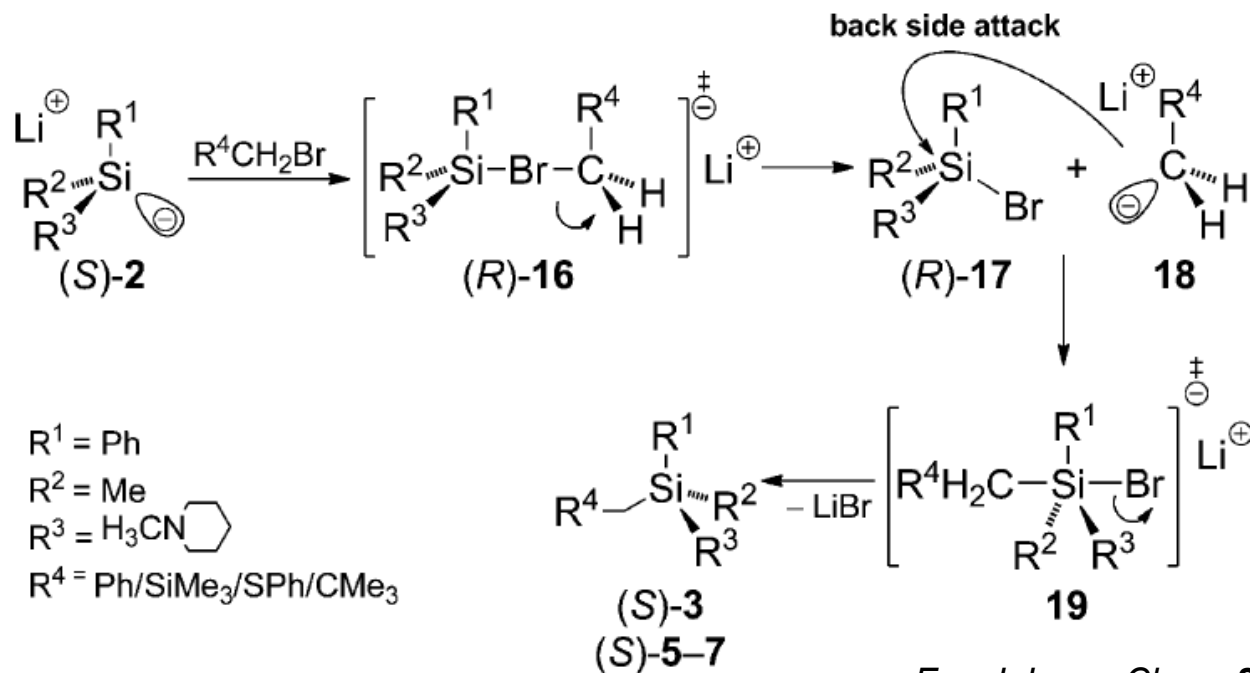
Eur. J. Inorg. Chem. **2011**, 1454.

Competition Between S_N2C and S_N2Hal

S_N2 mechanism: *RETENTION* on silicon



Halide–lithium exchange via an ate complex: *INVERSION* on silicon



Eur. J. Inorg. Chem. **2011**, 1454.

Calculated Transition State Energy

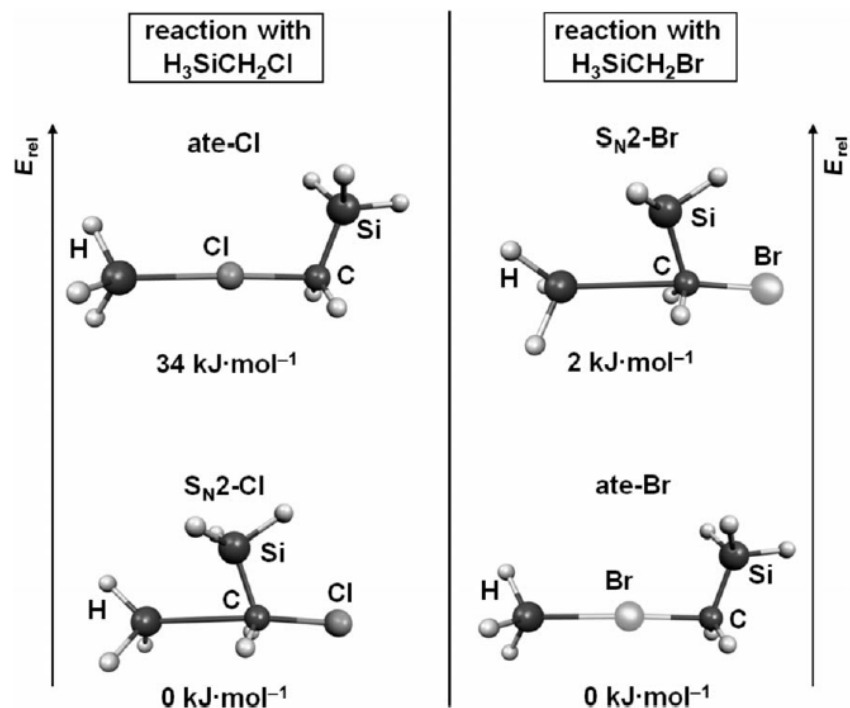


Figure 2. Calculated stationary points for the studied model systems $\text{H}_3\text{Si}^-/\text{Me}_3\text{SiCH}_2\text{Cl}$ (left) and $\text{H}_3\text{Si}^-/\text{Me}_3\text{SiCH}_2\text{Br}$ (right) [B3LYP/6-31+G(d), CPCM]; in both cases, an ate complex (ate-X, X = Cl, Br) and the $\text{S}_{\text{N}}2$ mechanism ($\text{S}_{\text{N}}2\text{-X}$, X = Cl, Br) were optimized; *Molekel* plots.^[36]

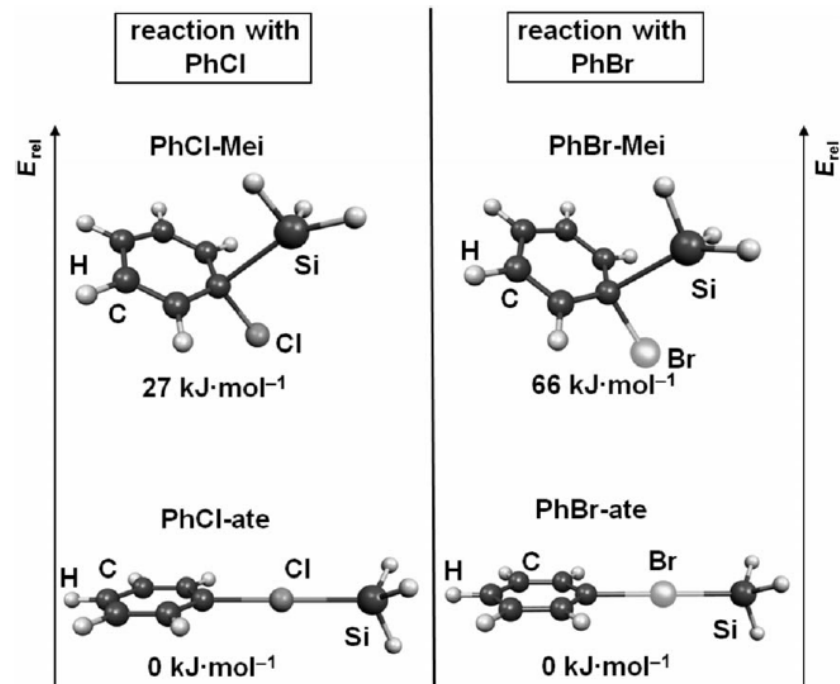
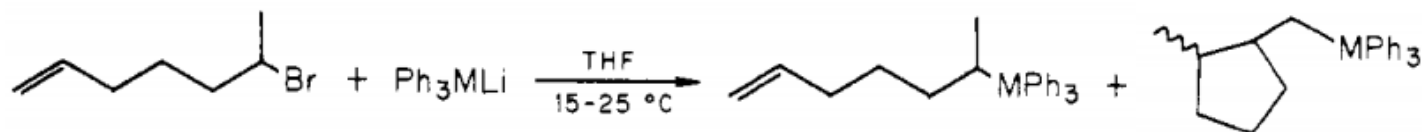
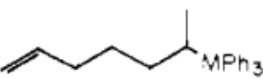
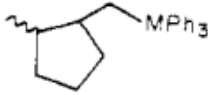


Figure 3. Calculated stationary points for the studied model systems $\text{H}_3\text{Si}^-/\text{PhCl}$ (left) and $\text{H}_3\text{Si}^-/\text{PhBr}$ (right) [B3LYP/6-31+G(d), CPCM]; in both cases, an ate complex and a reaction via an intermediate analogous to a Meisenheimer complex were optimized; *Molekel* plots.^[36]

Comparison of Group 14 Elements



entry	M	order of additn	yield, ^a %		ee, ^c %	ref
						
1	C	normal	>99	<1	94	<i>b</i>
		inverse	>99	<1	97	<i>b</i>
2	Si	normal	11	89	24	<i>b</i>
		inverse	37	63	50	<i>b</i>
3	Ge	normal	66	34	85	<i>b</i>
		inverse	84	16	99	<i>b</i>
4	Ge	normal	68 (18)	32 (9)		7
5	Sn	normal	>99	<1	98	<i>b</i>
6	Sn	normal	>99 (83)	<1		7

^a Relative yields; absolute yields are in parentheses.
^b This work; see also ref 16. ^c Reference 16. ee = enantiometric excess.

Ate Complexes of Other Elements

- Besides halogens, Se, Te, Sb and Sn also formed easily detectable ate complexes in the more polar ethereal solvents

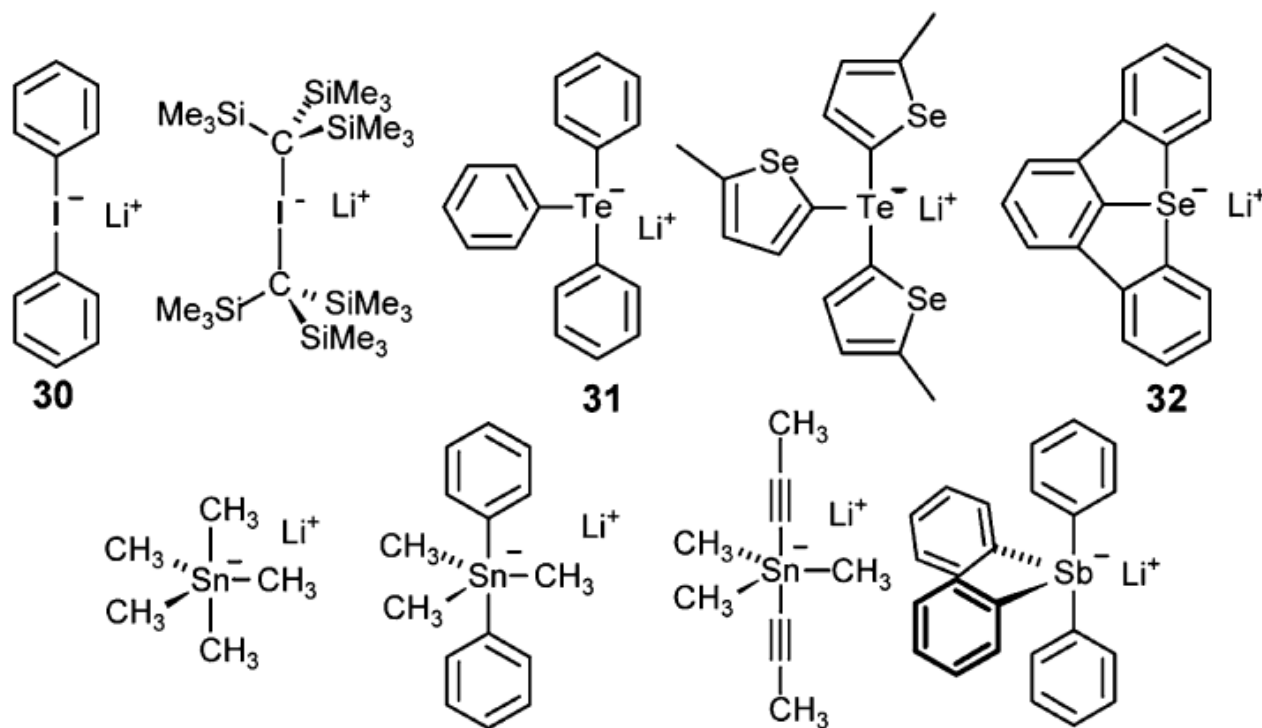


Figure 5. Some of the spectroscopically characterized ate complexes.

NMR Spectrum of Ate Complexes

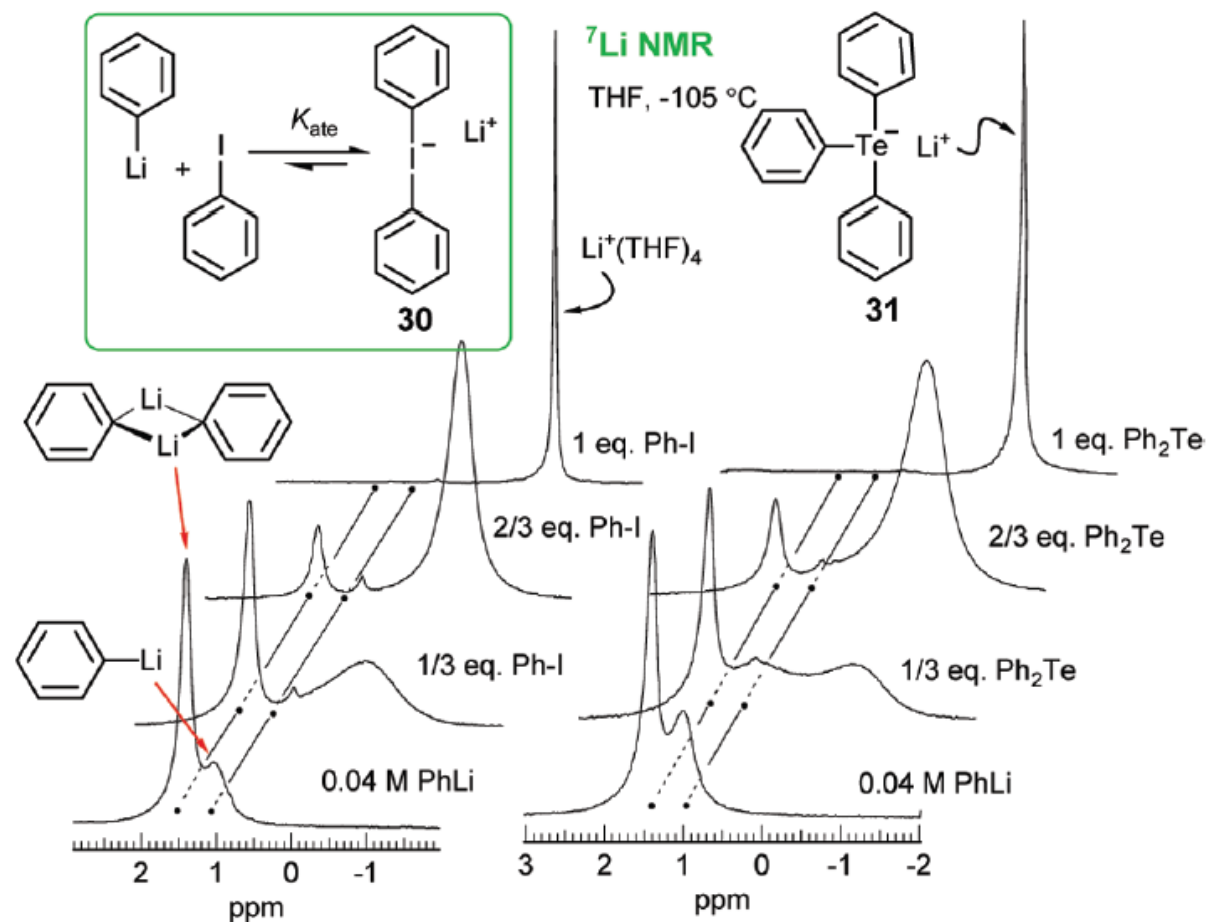
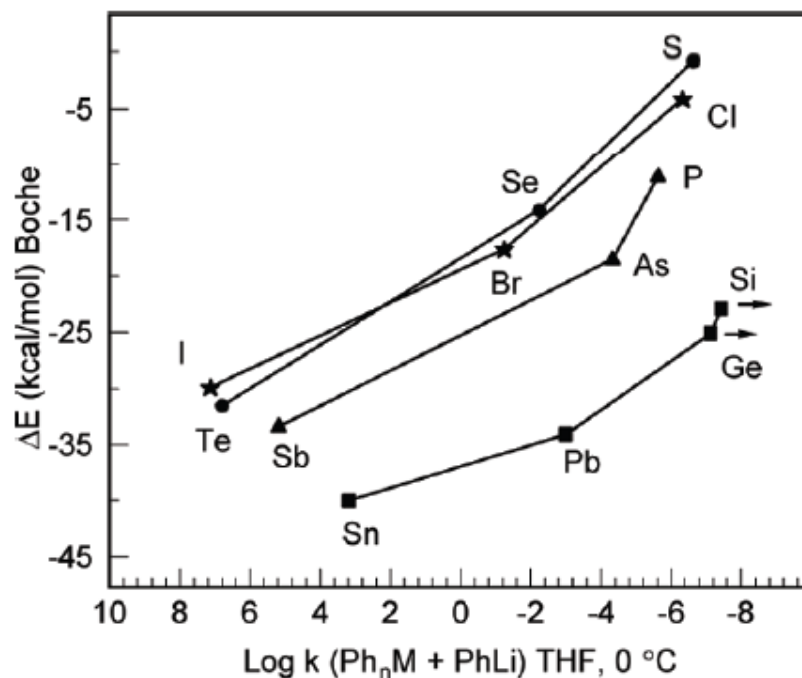
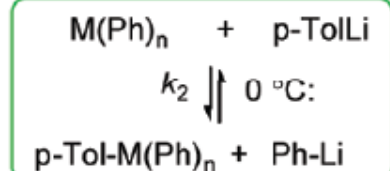


Figure 6. ^7Li NMR study of the exchange of PhLi with PhI and Ph_2Te at -105°C in THF. At this temperature K_{ate} is large, and only the ate complexes 30 and 31 (no PhLi) can be detected when a full equivalent of PhI or Ph_2Te is added.^{34c}

Reactivity of Lithium/Metalloid Exchange



For Cl, Br, S, Se, P, As, Pb:



For I, Te, Sb, Sn:

DNMR studies of PhLi + Ph_nM degenerate exchange (extrapolated from < -90 °C)

For Sn:

Extrapolated from rate of ArLi + Ar₄Sn → R₅SnLi by RINMR at -90 °C

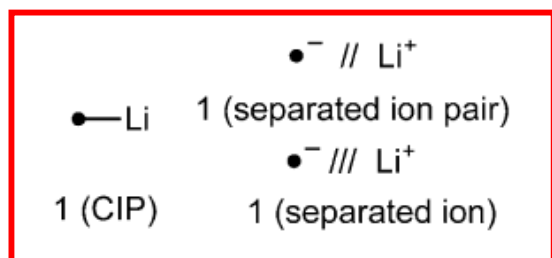
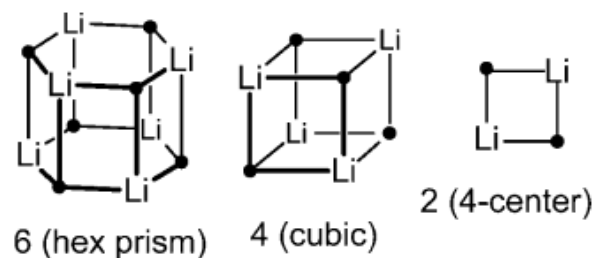
For Si and Ge:

No exchange detected

Figure 7. Rates of lithium/metalloid exchange reactions, compared with calculated ate complex energies.

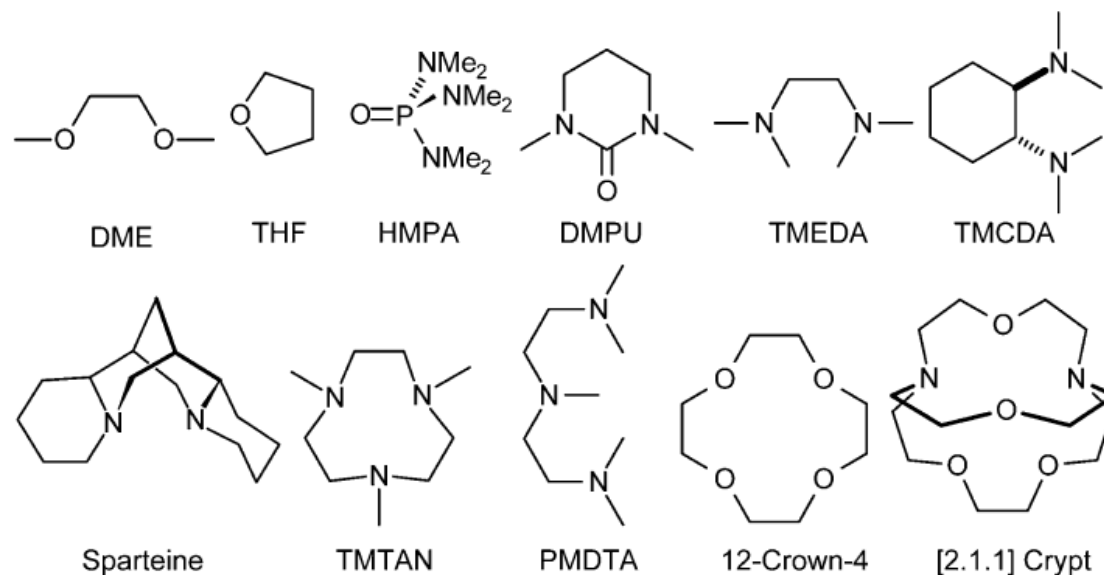
Structure of Organolithium Reagents

- Most organolithium reagents are aggregated in solution
- Degree of aggregation is strongly dependent on carbanion structure, solvent polarity, and the presence of donor ligands like TMEDA, PMDTA, HMPA and so on.



CIP: contact ion pair
SIP: separated ion pair

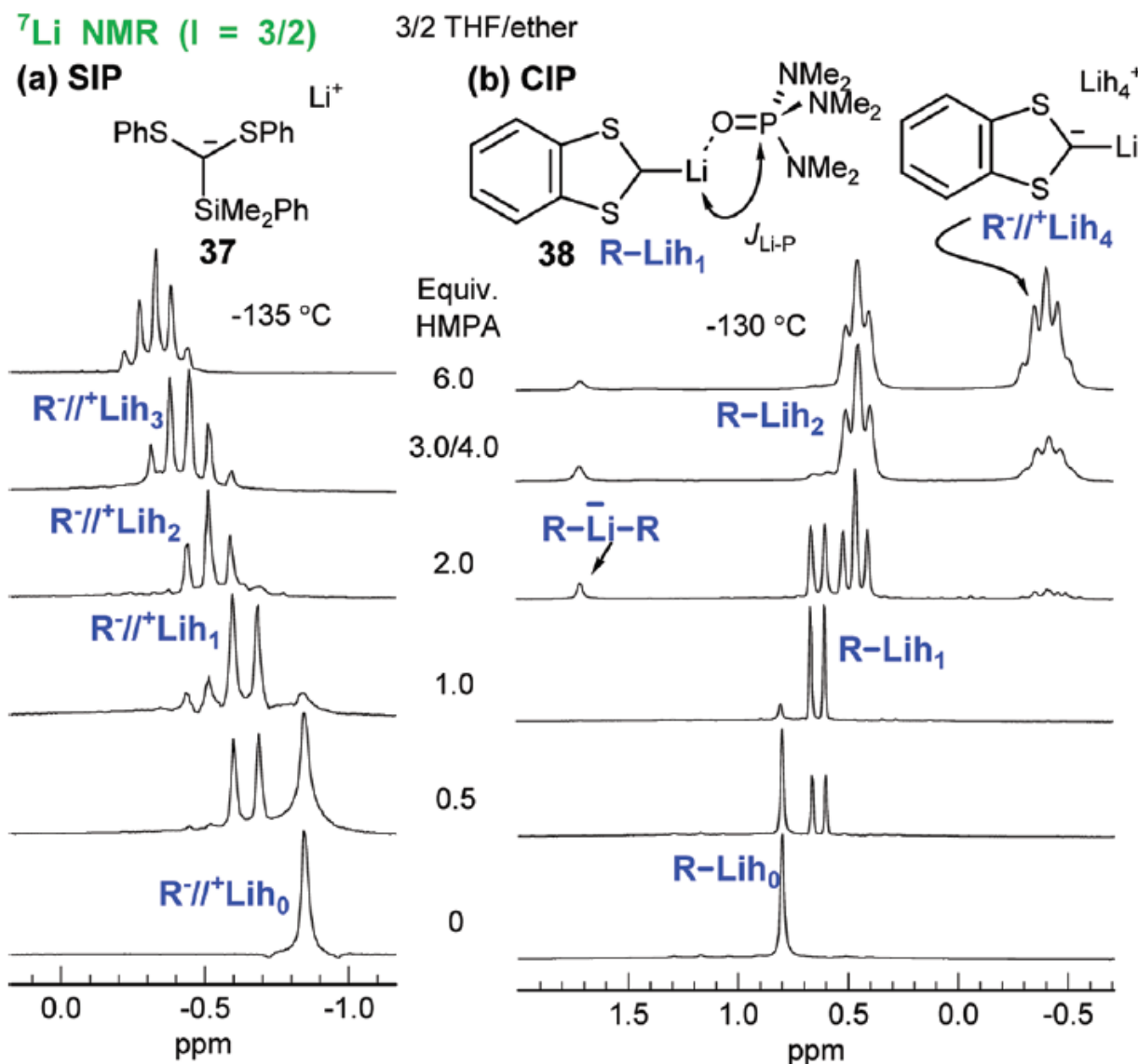
Some structural types of organolithium reagents



Coordination solvents or cosolvents

J. Org. Chem. **2012**, *77*, 5471
Chem. Rev. **2013**, *113*, 7130

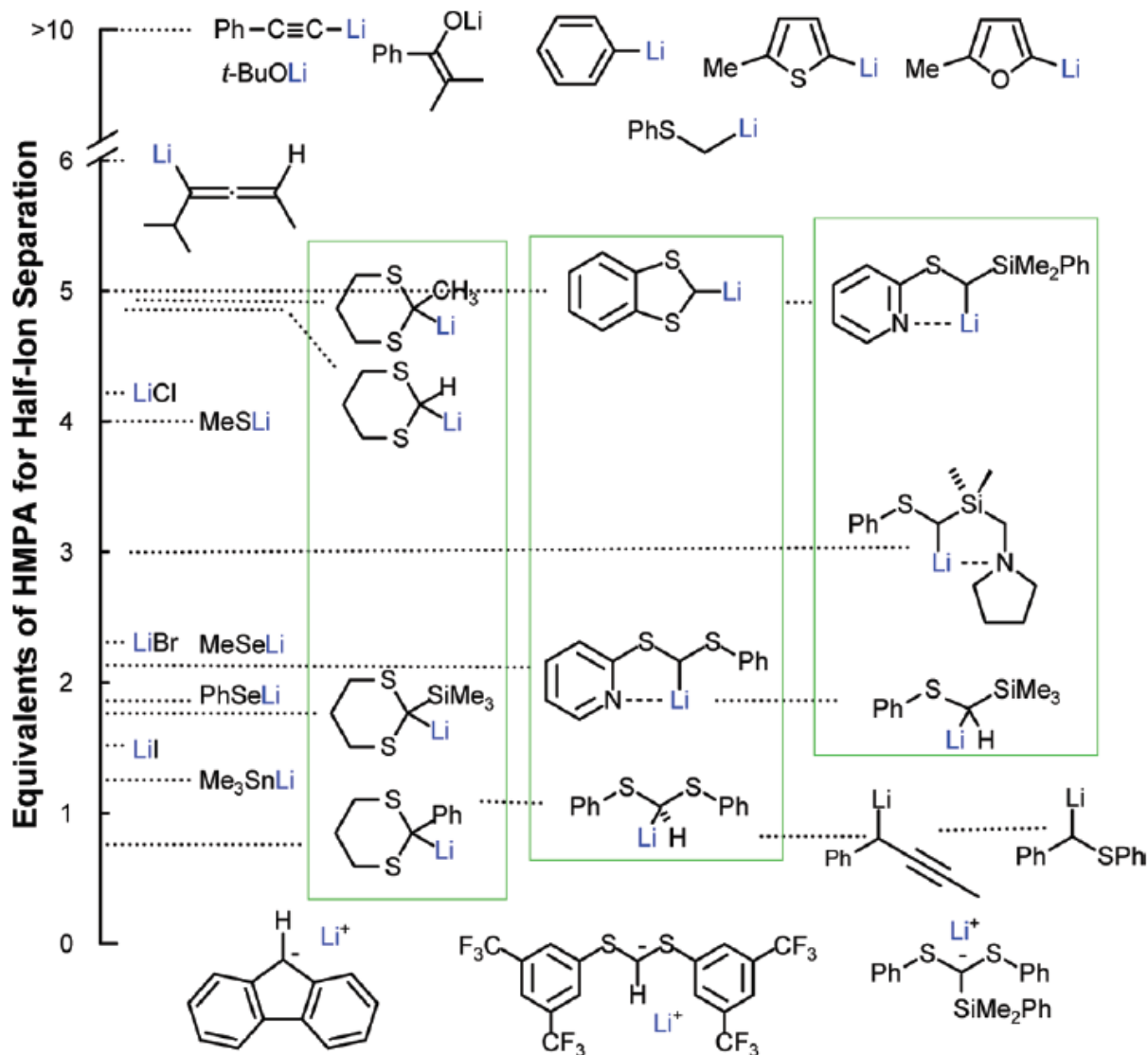
HMPA Titrations of a SIP and CIP



J. Org. Chem. **2012**, *77*, 5471.

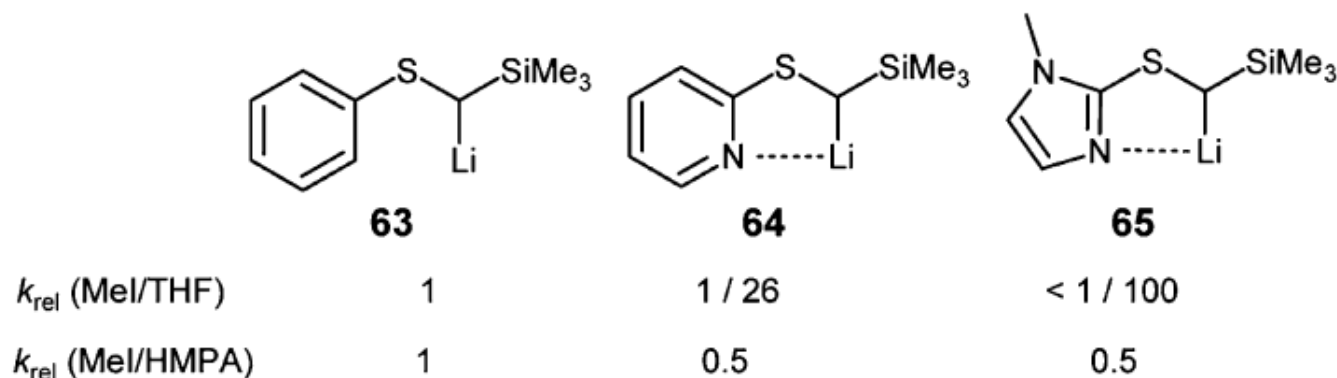
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Equivalents of HMPA for 1:1 CIP/SIP



S_N2 Reactivity of Chelated Reagents

- When the S_N2 reactivity of chelated and nonchelated reagents was compared, the chelated ones were typically 1–3 orders of magnitude less reactive.
- Chelation may reduce the equilibrium concentration of the SIP, which we believe is the reactive nucleophile in most such reactions.

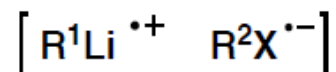


J. Org. Chem. **2012**, 77, 5471.

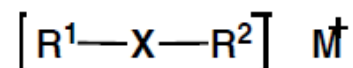
Summary

- Mechanism of lithium–halogen exchange includes at least radical mechanism and nucleophilic ("ate–complex") mechanism

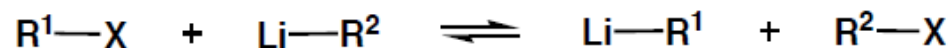
Electron transfer (radical) process



Nucleophilic mechanism via halogen "ate"-type intermediate



- Halogenophilic reactions are possible for many organic halides, in the presence of sufficiently active halogenophilic reagent
- ate complexes of many main group elements are key intermediates in halogen-(metalloid)-lithium exchange reactions



X=Br, I, TeR, SbR₂, SnR₃ and so on

R²=R-, R₂B-, R₃Si-, R₃Sn-, R₃P and so on