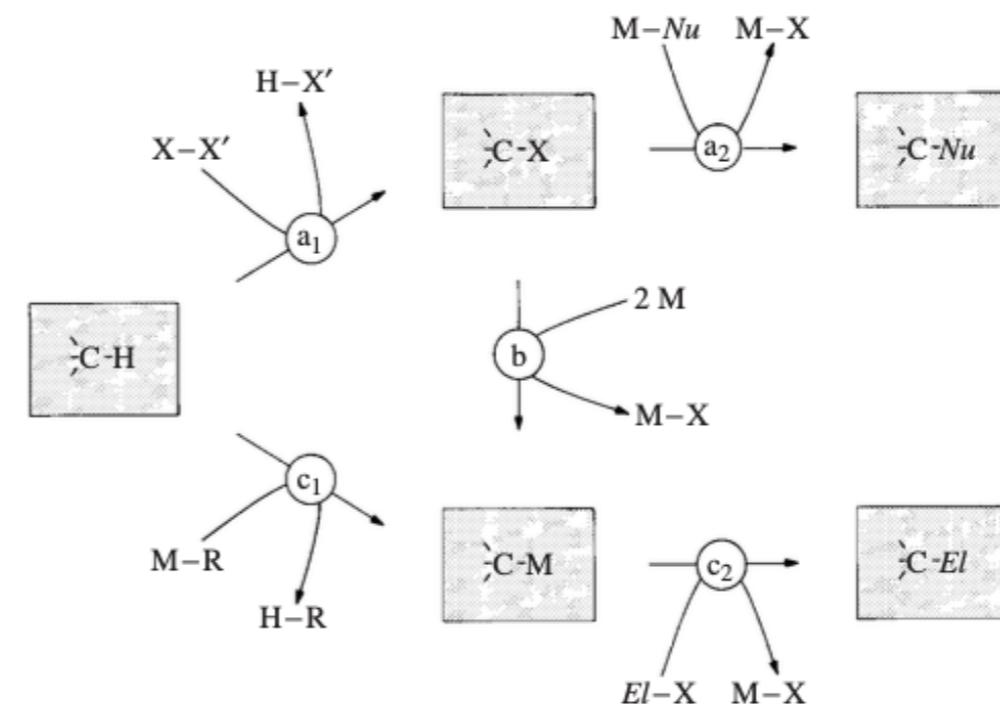


Organoalkali Metal Reagents: A Closer Look

Ximing Li

Jun 30, 2023

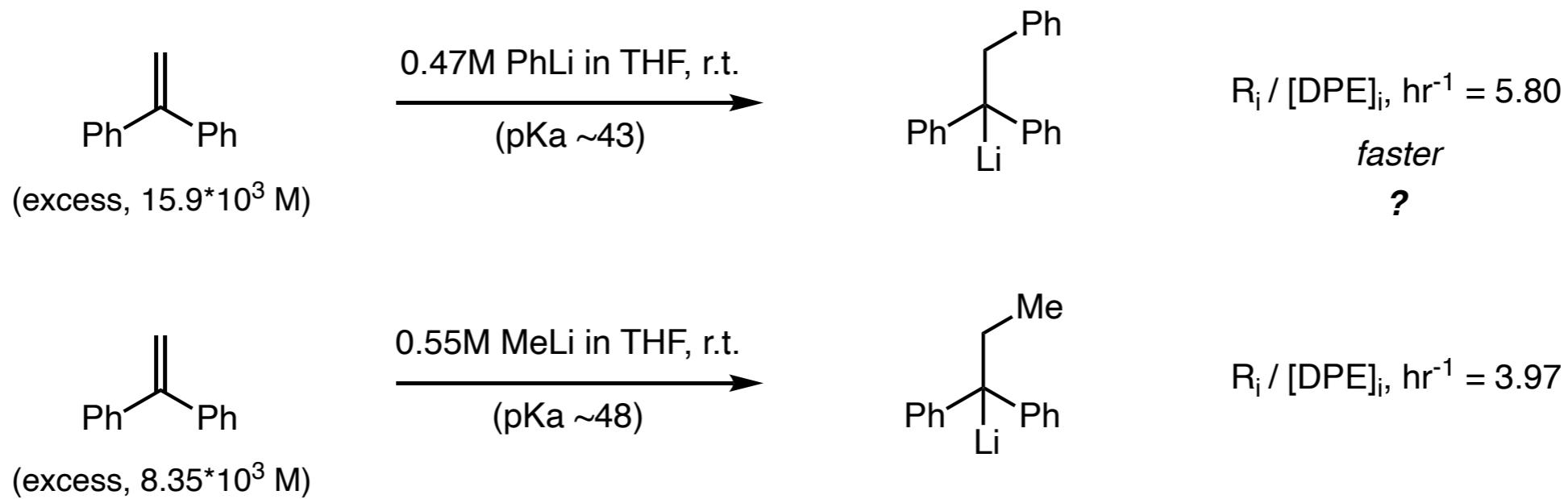


*M. Schlosser et. al.: Organometallics in Synthesis: A Manual, Wiley, Chichester, 2002;
ACIE. 2005, 44, 376–393; Chimia. 1996, 50, 650–652; JOC. 1996, 61, 5430–5434.*

H. J. Reich. Chem. Rev. 2013, 113, 7130–7178.

R. Waack, M. A. Doran. JACS. 1969, 91, 2456–2461. T. H. Chan, I. Fleming. Synthesis. 1979, 761–786.

Q1.



Q2.

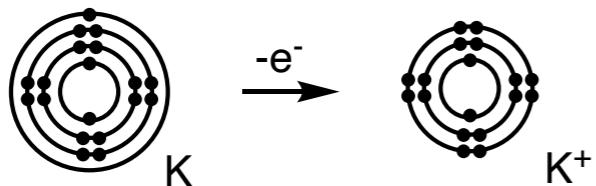
weaker base	stronger base
NaH	KH
$n\text{BuLi}$	$n\text{BuNa}$
<i>rarely used</i>	
?	

However,
Ionization potentials:

ionizing an electron from “electropositive” metals	energy required
$\text{Li} \xrightarrow{-e^-} \text{Li}^+$	124 kcal/mol
$\text{Na} \xrightarrow{-e^-} \text{Na}^+$	118 kcal/mol
$\text{K} \xrightarrow{-e^-} \text{K}^+$	100 kcal/mol
$\text{Ru} \xrightarrow{-e^-} \text{Ru}^+$	98 kcal/mol
$\text{Cs} \xrightarrow{-e^-} \text{Cs}^+$	90 kcal/mol

Nonspontaneous

In high school:



“...metals want to get rid of their valence electrons in order to become cations have the same electron shell as noble gas...”

Heat of formation, LiCl(g):

+H	-H
58 kcal/mol (1/2 dissociation energy of Cl ₂)	112 kcal/mol (binding energy)
~70 kcal/mol (fusion, vaporization & atomization of bulk Li)	

Endothermal

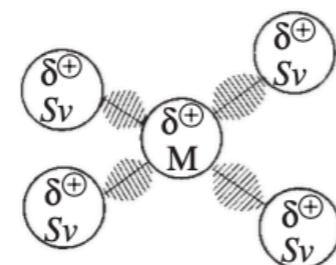
Key of metal binding: aggregation and coordination

**Diatomic Molecule
(Li^+Cl^-):**

energetically unfavorable
asymmetric charge distribution

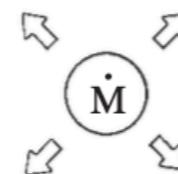


1

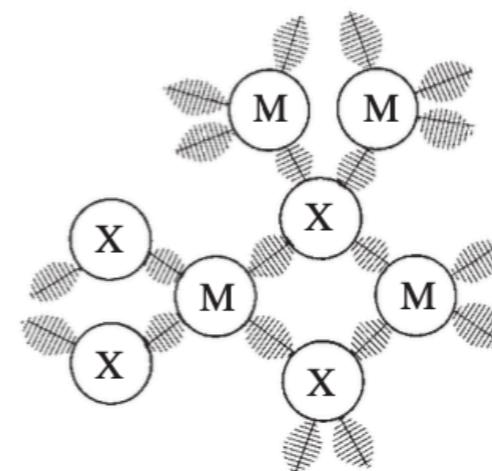


**Solvent “Coordination”
(LiL_n):**

Coordinating solvent molecule
further stabilizing metal



2



3

**Naked Metal Ion
(Li^+):**

extremely energetic

**Subunits “Aggregation”
($(\text{LiX})_n$):**

heteroatomic counterions sharing
valence electrons with metal

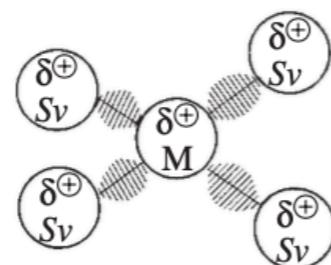
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1

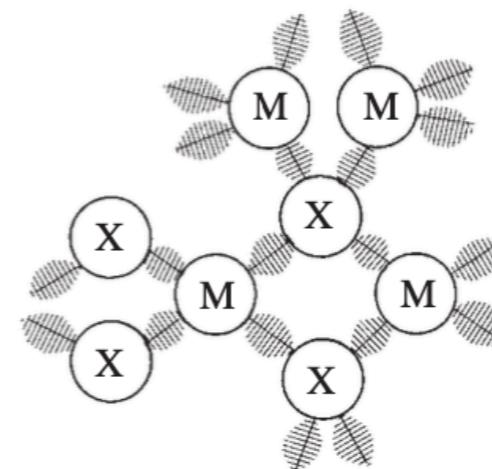


**Solvent "Coordination"
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Coordinating solvent molecule
further stabilizing metal



2



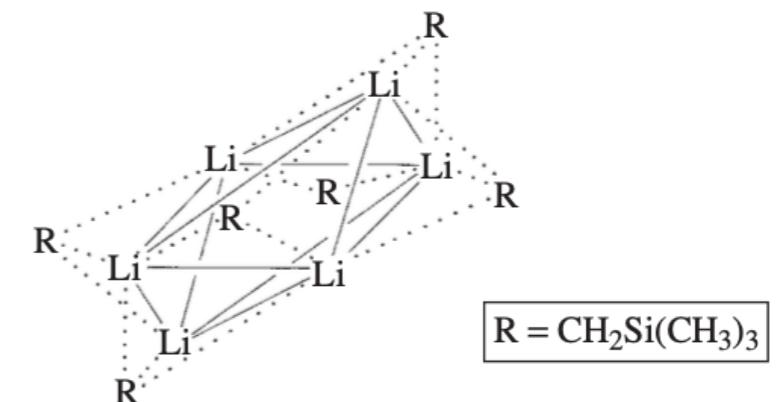
3

**Naked Metal Ion
(Li^+):**

extremely energetic

**Subunits "Aggregation"
($(\text{LiX})_n$):**

heteroatomic counterions sharing
valence electrons with metal



Ph_2Zn (dimer)
 $t\text{BuLi}$, MeLi , MeK (tetramer)
 $n\text{BuLi}$, TMSMeLi , CyhexLi (hexamer)

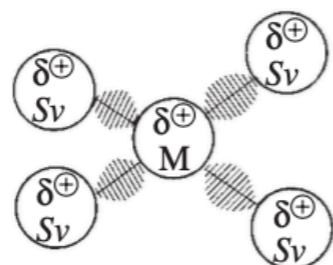
Key of metal binding: aggregation and coordination

**Diatomic Molecule
(Li^+Cl^-):**

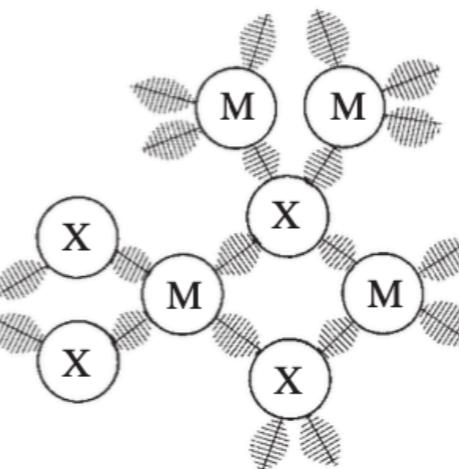
energetically unfavorable
asymmetric charge distribution



1



2



3

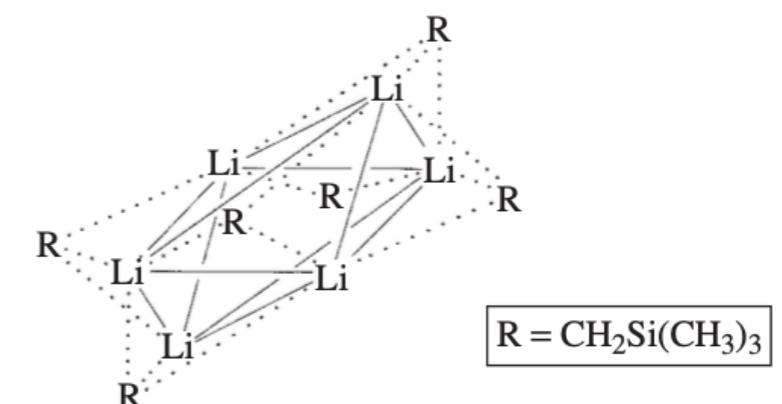
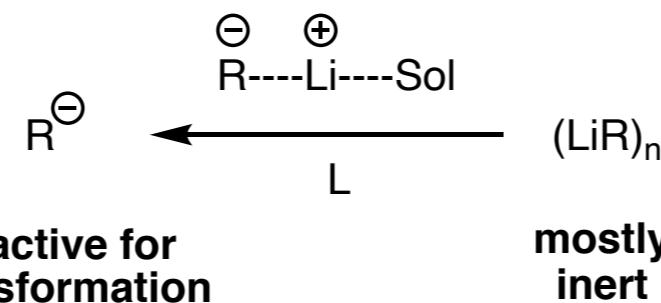
**Solvent “Coordination”
(LiL_n):**

Coordinating solvent molecule
further stabilizing metal

4

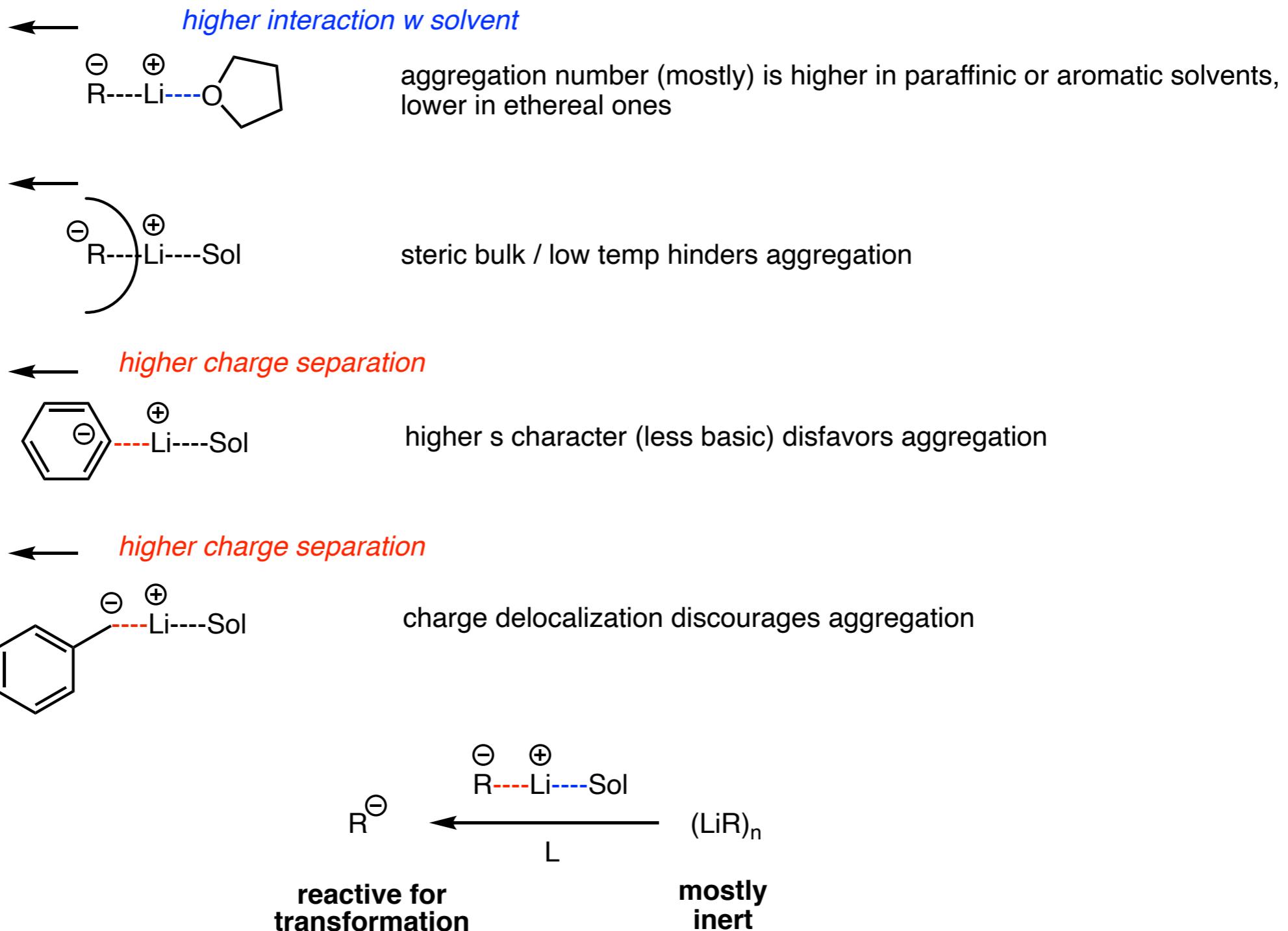
**Naked Metal Ion
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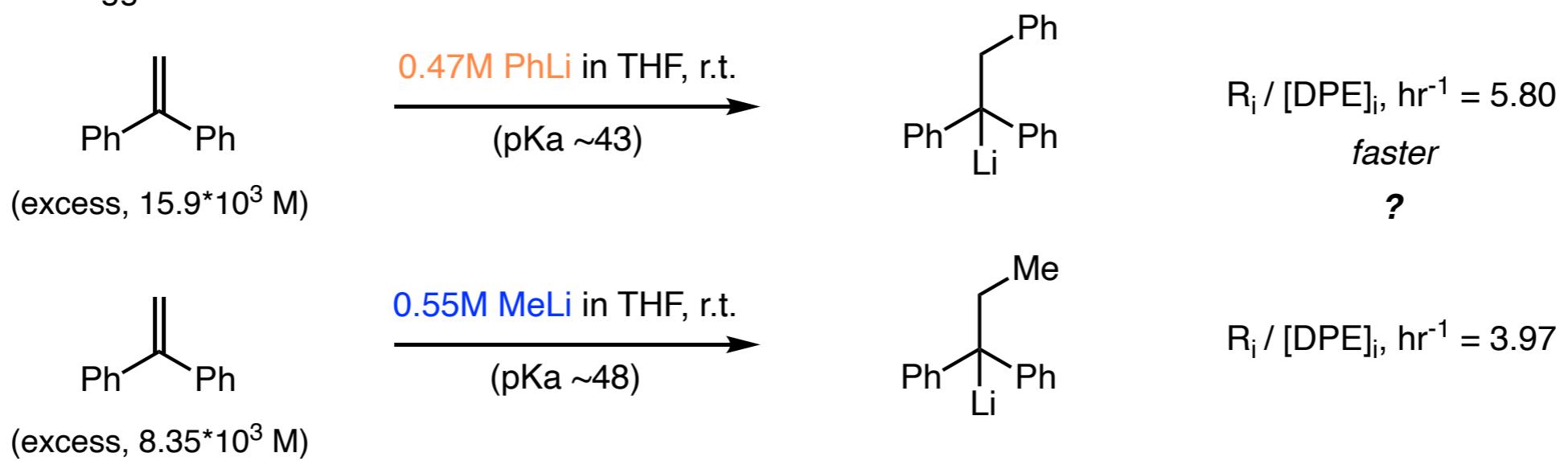


Ph₂Zn (dimer)
tBuLi, MeLi, MeK (tetramer)
nBuLi, TMSMeLi, CyhexLi (hexamer)

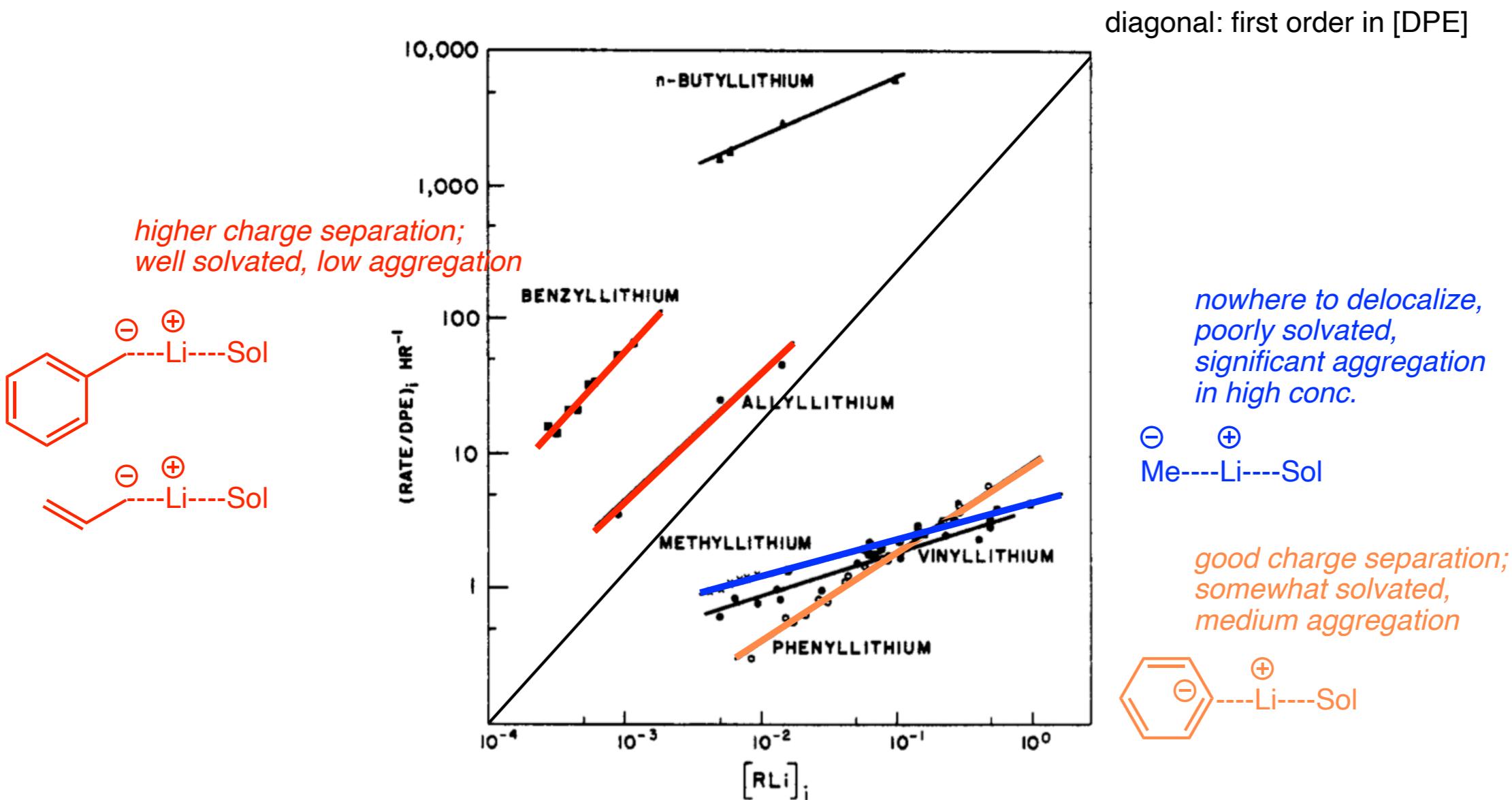
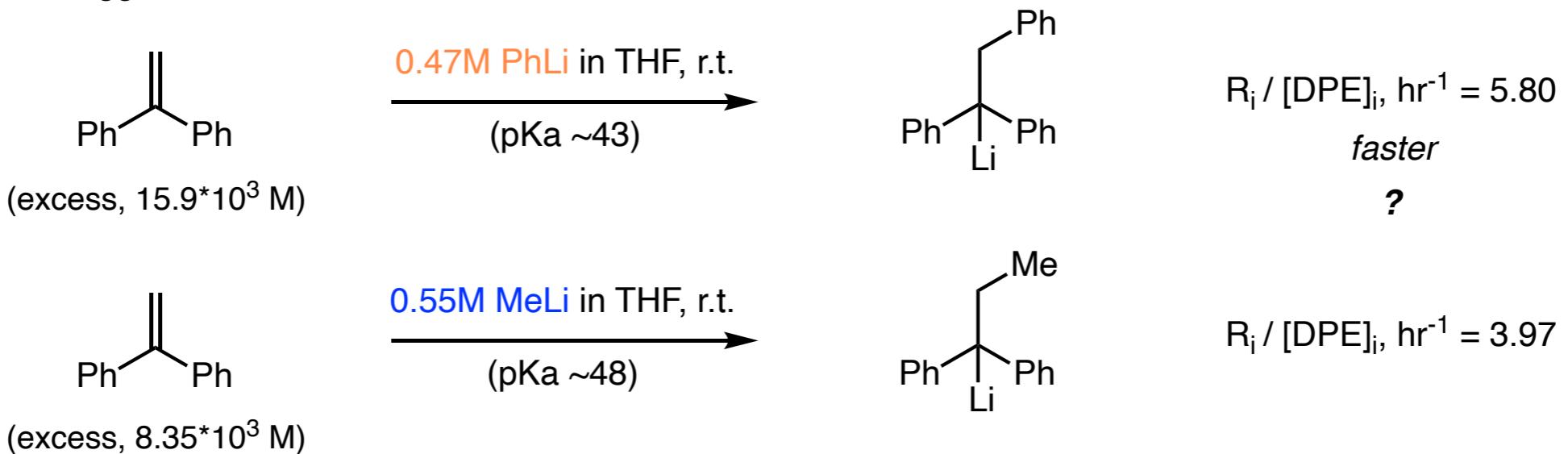
Key of metal binding: aggregation and coordination



Q1: why MeLi more sluggish than PhLi?



Q1: why MeLi more sluggish than PhLi?



Why Lithium?

Percentage Ionic Character of Carbon-Metal Bonds According to Pauling Electronegativities

Metal	K	Na	Li	Mg	Zn	Cd	Si	H
% Ionic Character	51	47	43	35	18	15	12	4



charge-separated
resonance
(exhibit **51%** of ionic C- character)



homopolar
resonance
(exhibit **18%** of ionic C- character)



covalent/
inert

multiply X

Gas Phase Acidities (enthalpy ΔH_g of deprotonation)

Anion	tBu	iPr	Et	Me	Vinyl	Ph	Al	Bn
kcal/mol ΔH_g	413.1	419.4	420.1	416.7	409.4	401.7	390.7	380.8

proton affinity: Me⁻ - Ph⁻ = 15 kcal/mol

MeK more basic than PhK: 15 * 51%

Why Lithium?

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Metal	K	Na	Li	Mg	Zn	Cd	Si	H
% Ionic Character	51	47	43	35	18	15	12	4

C-K⁺

charge-separated
resonance
(exhibit **51%** of ionic C- character)

C-Zn

homopolar
resonance
(exhibit **18%** of ionic C- character)

C-H

covalent/
inert

multiply X

Gas Phase Acidities (enthalpy ΔH_g of deprotonation)

Anion	tBu	iPr	Et	Me	Vinyl	Ph	Ali	Bn
kcal/mol ΔH_g	413.1	419.4	420.1	416.7	409.4	401.7	390.7	380.8

proton affinity: Me⁻ - Ph⁻ = **15** kcal/mol

how much is MeK more basic than PhK? **15 * 51%**

Why Lithium?

for basicity

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Metal	K	Na	Li	Mg	Zn	Cd	Si	H
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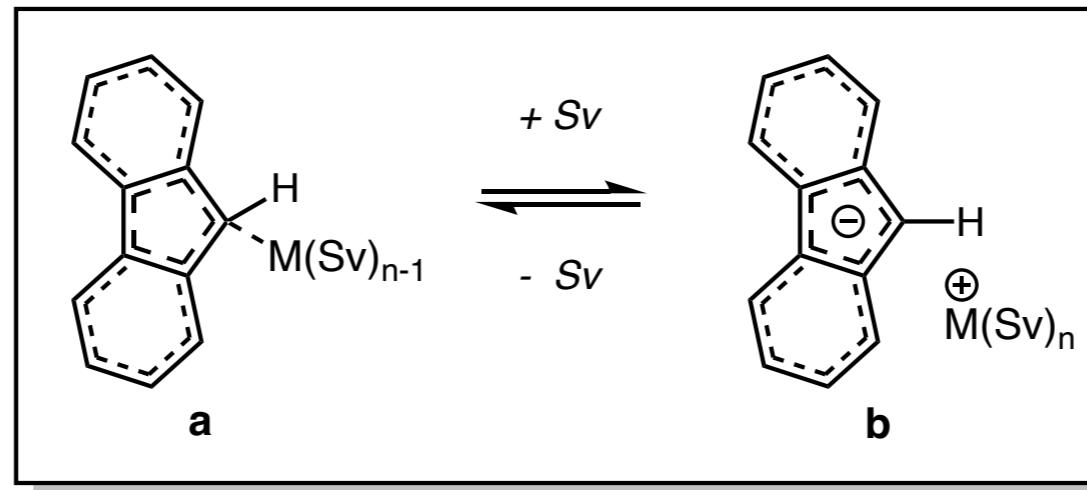
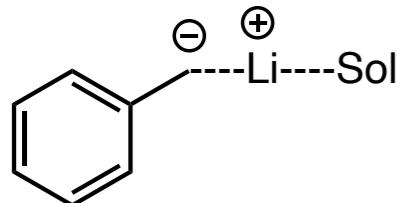
how much is MeK more basic than PhK? $15 * 51\%$

Most basic species: tBuCs?

Why Lithium?

Yet only small metals benefit from solvation enthalpies...

recall: higher charge separation easily solvated.



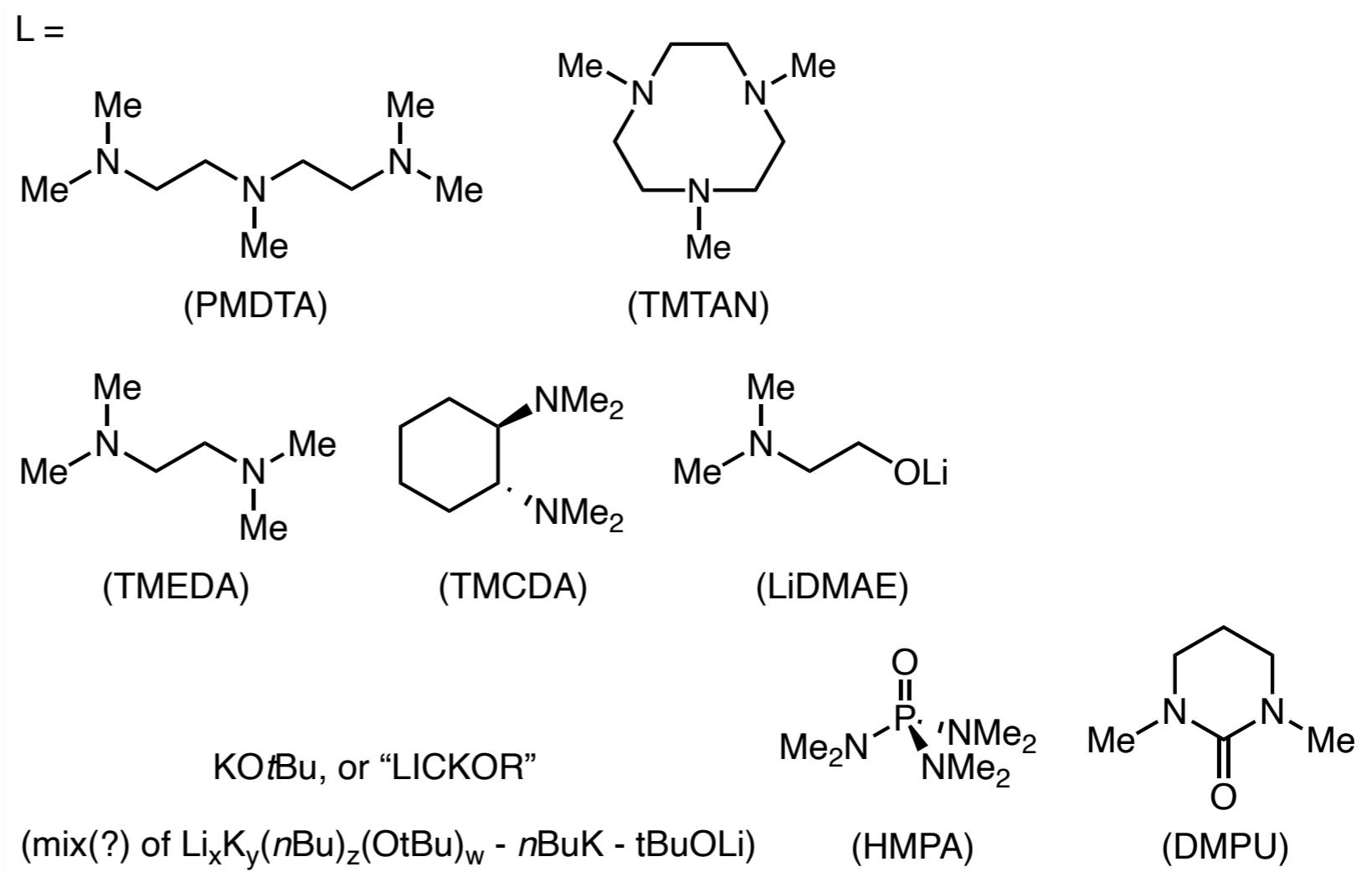
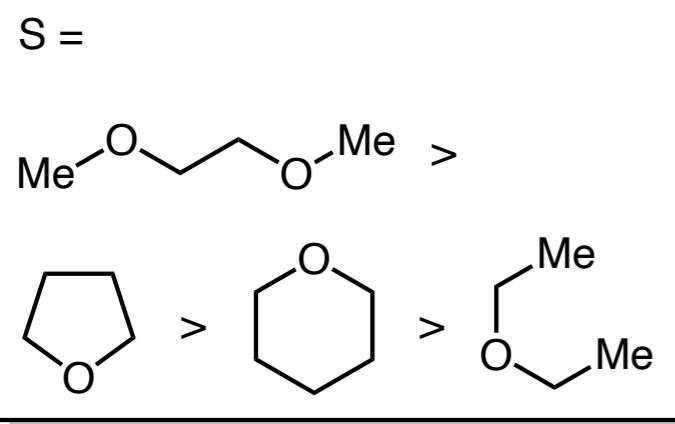
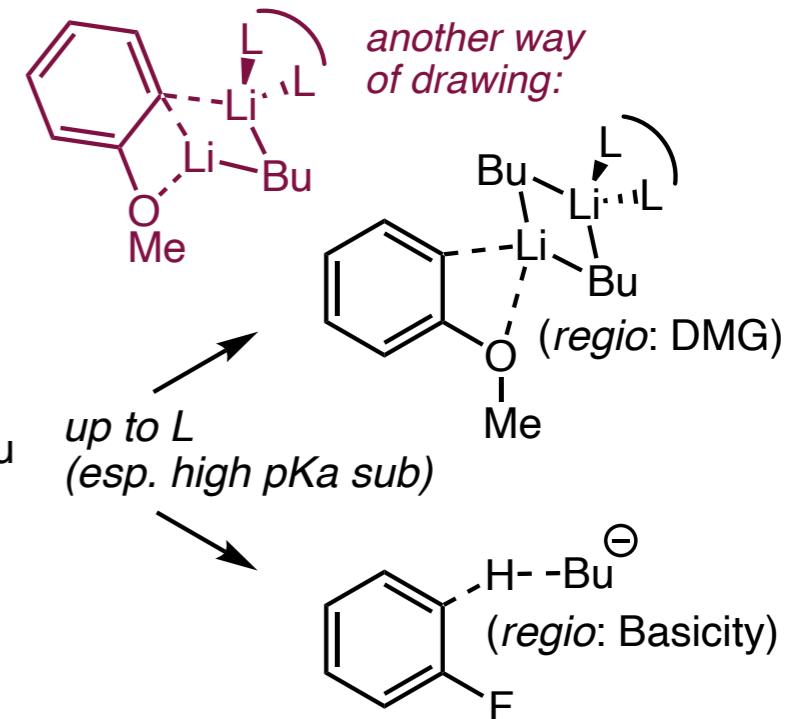
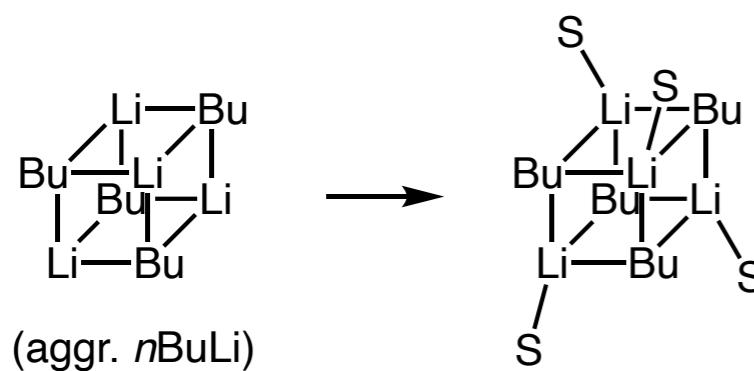
9-Fluorenylmetals: proportion of ion pairs **b** in equilibrium with contact species **a** at 25°C as a function of the solvent (THF, MEGME) and the metal (M)

M	Sv = THF (%)	Sv = MEGME (%)
Li	80	100
Na	5	95
K	0	0
Cs	0	0

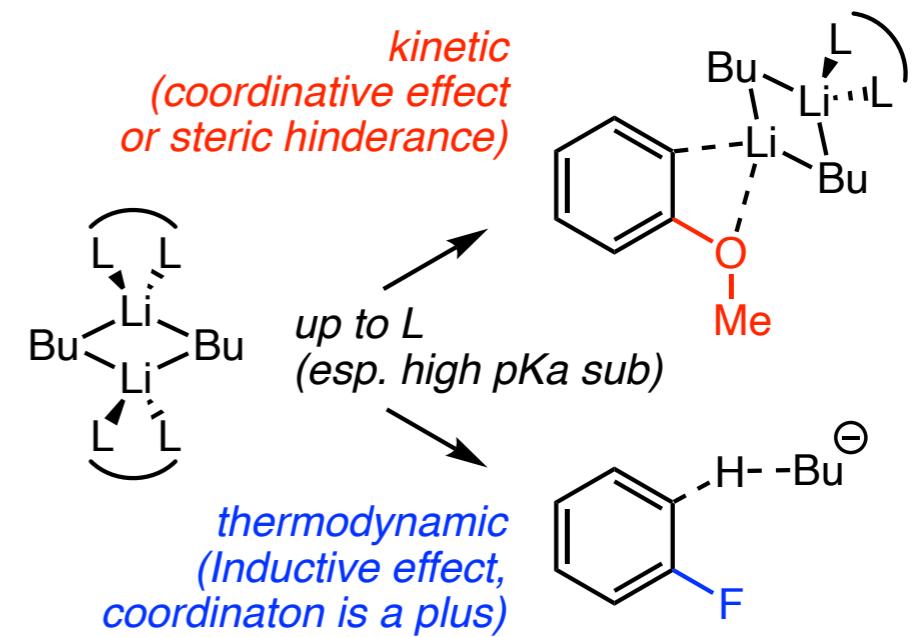
basicity
+

Q2: $n\text{BuNa}$ exists, but very prone to aggregation
(or, very high demand of solvation).

For better solvation / chelation

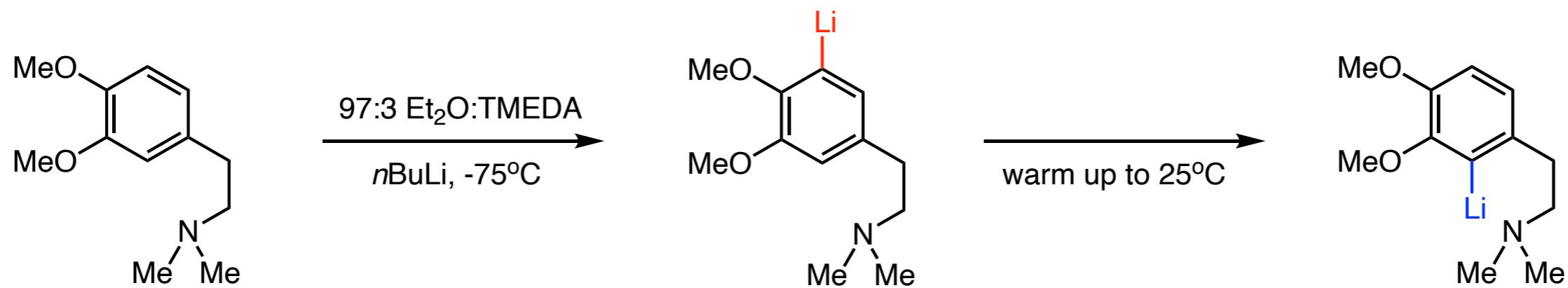


For better solvation / chelation

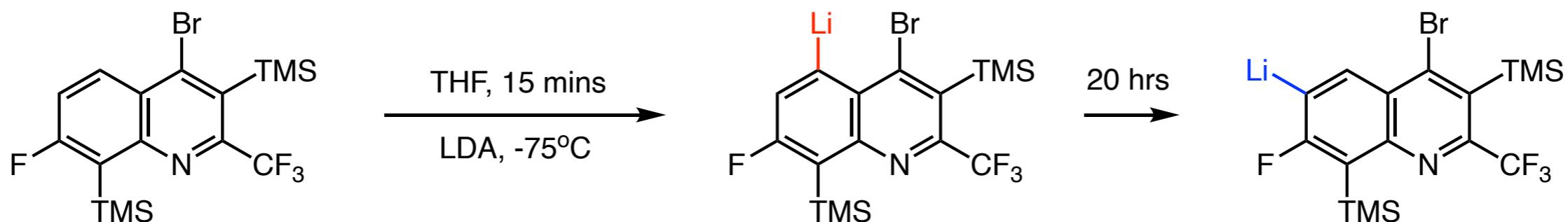


Ex. 1

Steric Hindrance vs. Electronic Stabilization (H-Li Exchange)

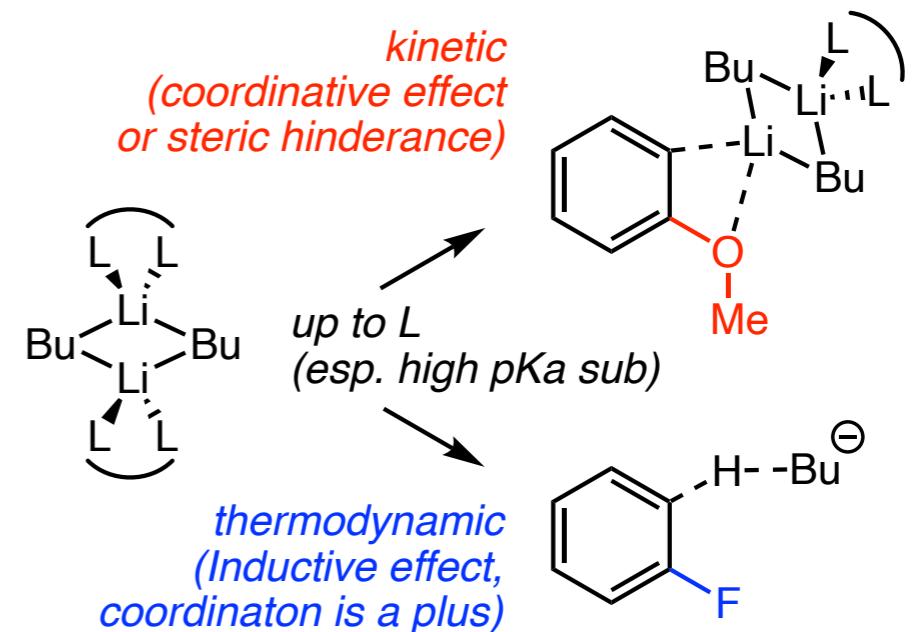


C. D. Liang. *Tet. Lett.* **1986**, 27, 1971–1974.



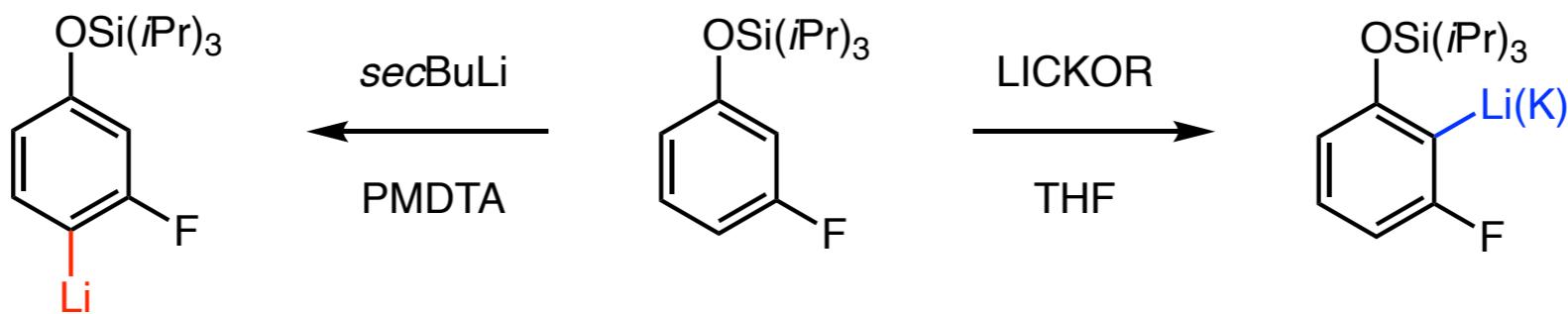
M. Marull, M. Schlosser. *Eur. J. Org. Chem.* **2004**, 1008–1013.

For better solvation / chelation

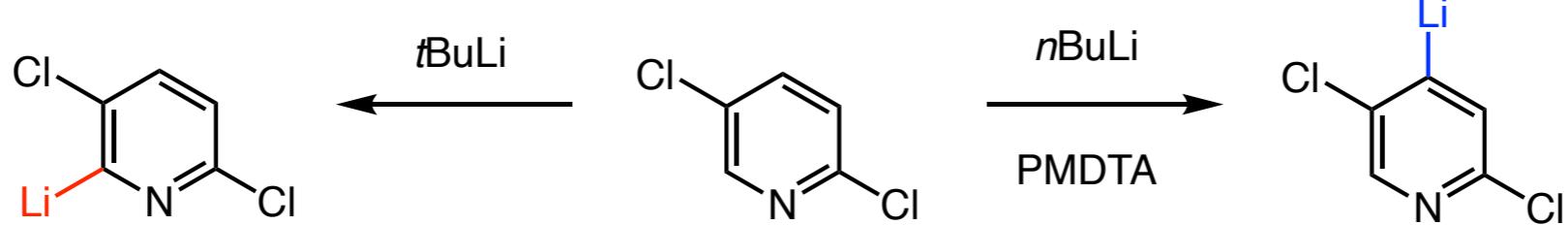


Ex. 2

Reagent-modulated Optional Site Selectivity (H-Li Exchange)



E. Marzi, J. Gorecka, M. Schlosser. *Synthesis*. **2004**, 1609–1614.



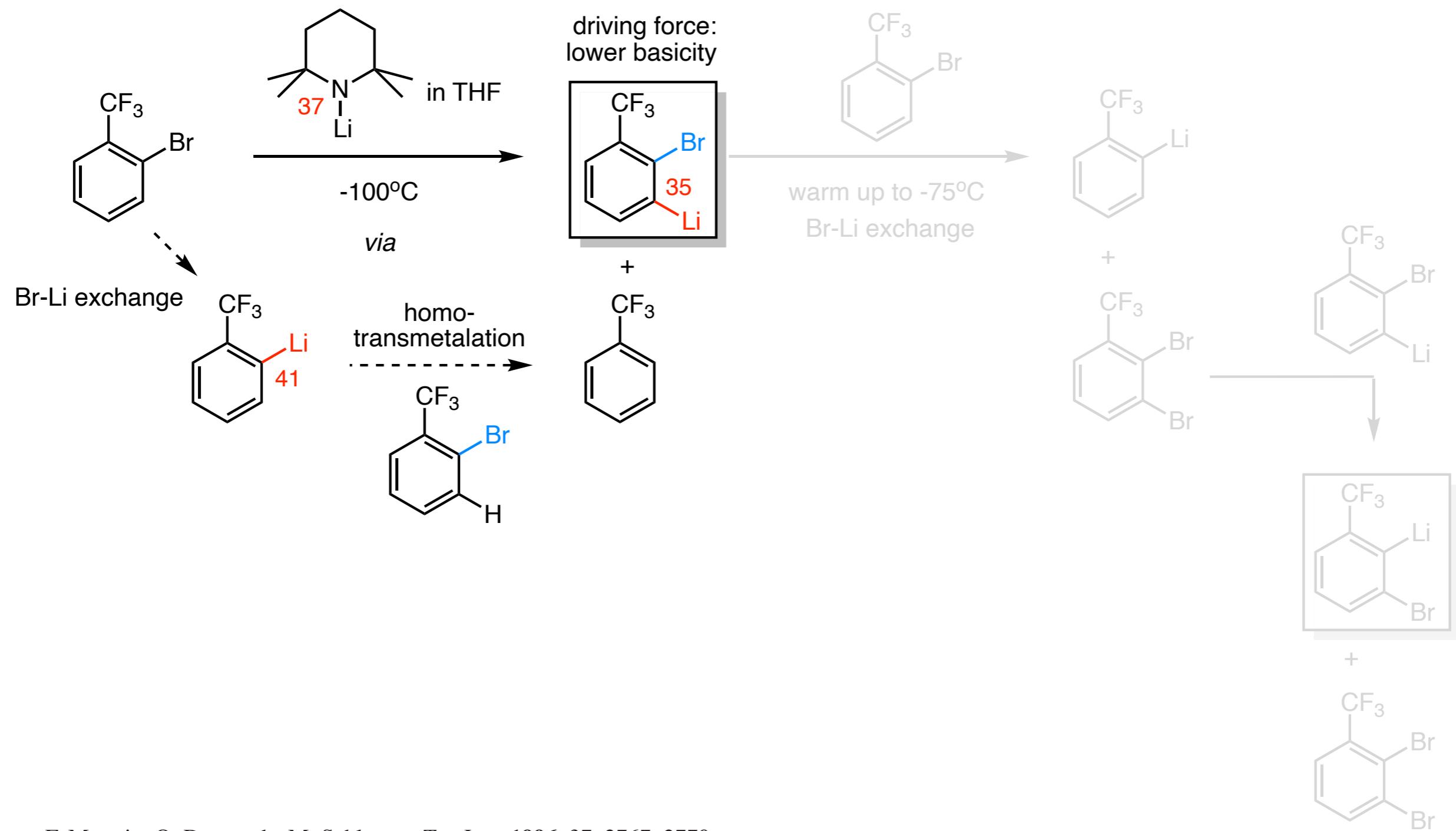
E. Marzi, A. Bigi, M. Schlosser. *Eur. J. Org. Chem.* **2001**, 1371–1376.
M. Hedidi. et al. *Tetrahedron*. **2016**, 72, 2196–2205.

pKa:	40.2
40.9	pyridine
44.1	N
35.7	37.8
34.0	40.2
32.1	36.8
37.9	41.6

For better solvation / chelation

Ex. 3

Deprotonation-triggered Heavy-halogen Migration (X-Li Exchange)

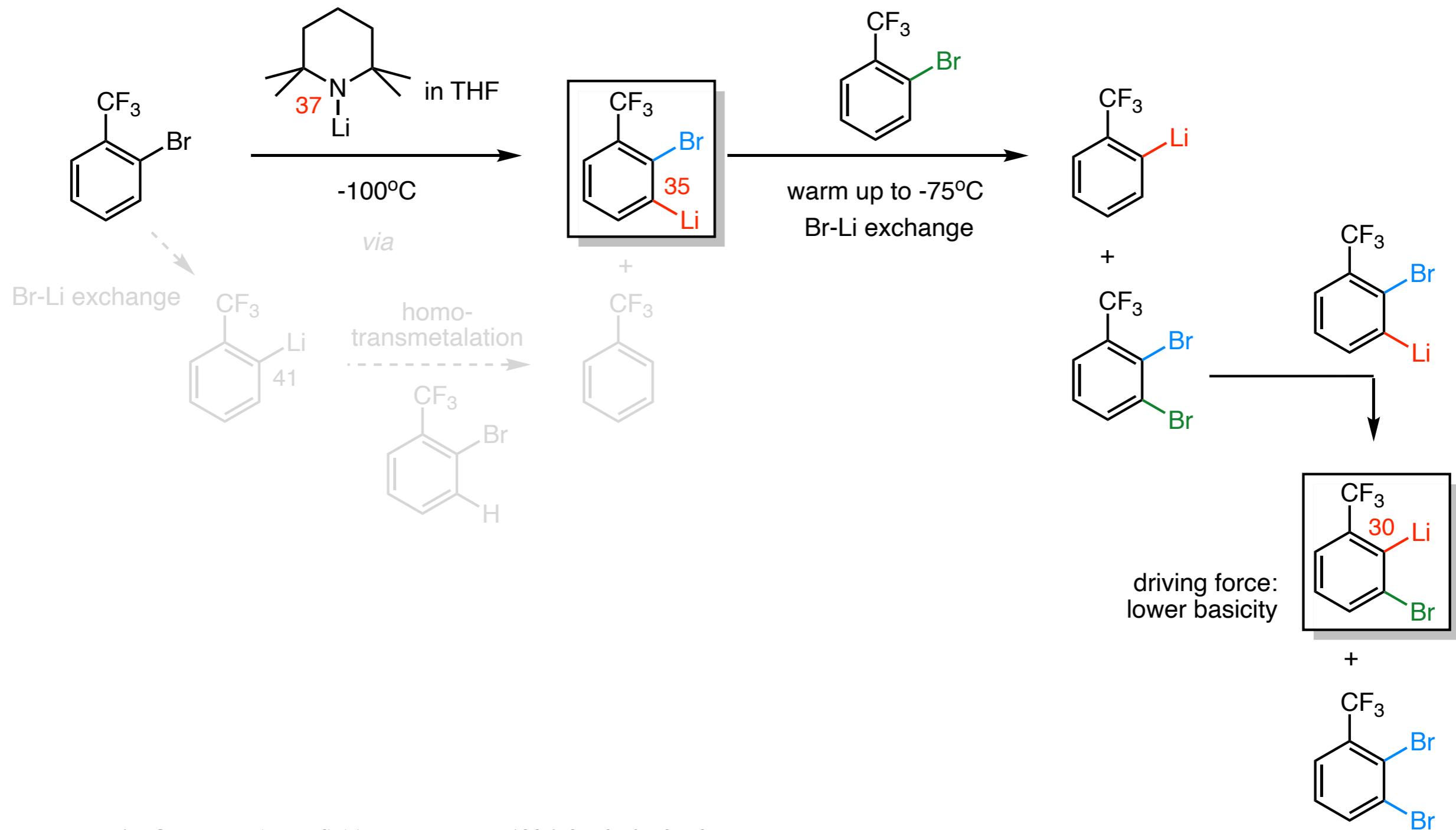


F. Mongin, O. Desponds, M. Schlosser. *Tet. Lett.* **1996**, 37, 2767–2770.
Mechanism: G. Queguiner. et al. *Adv. Heterocyc. Chem.* **1991**, 52, 187–304.

For better solvation / chelation

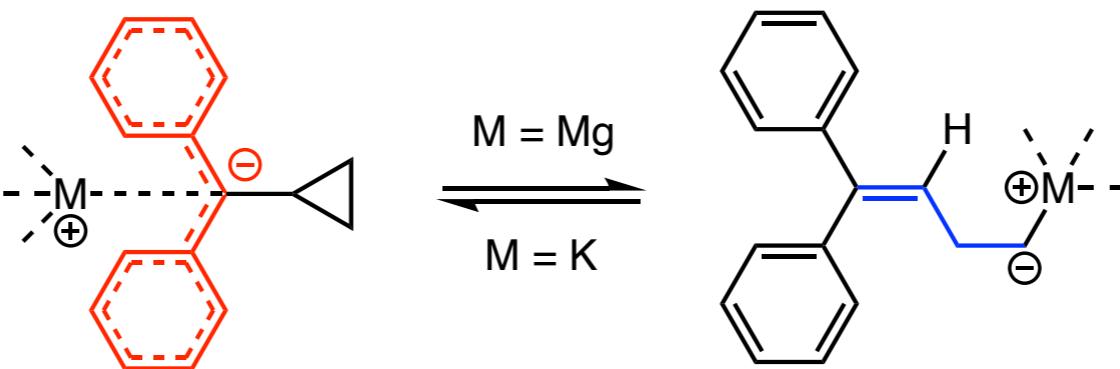
Ex. 3

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Mechanism: G. Queguiner. et al. *Adv. Heterocyc. Chem.* **1991**, 52, 187–304.

Metal Effects on Reactivity



Thermodynamic preference factor

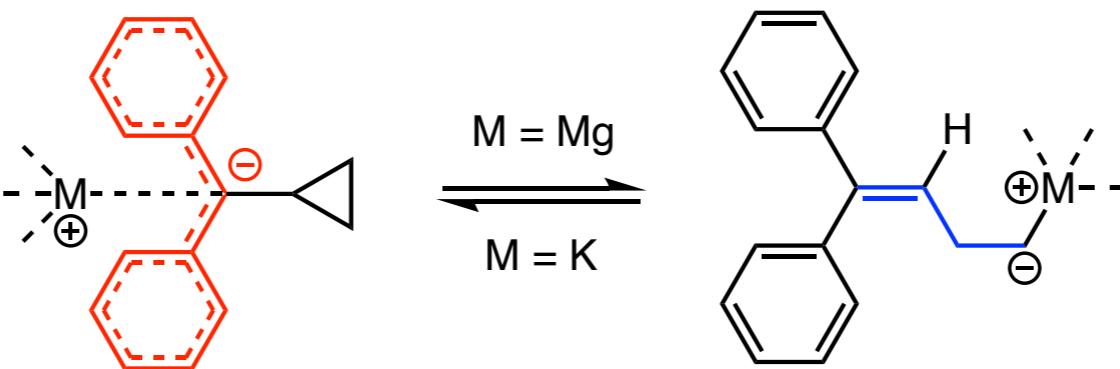


Li^+ in THF (better solvated, more ionic)

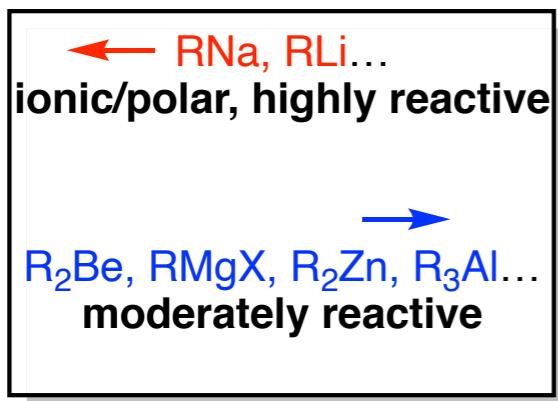


Li^+ in Et_2O (less ionic)

Metal Effects on Reactivity



Thermodynamic preference factor

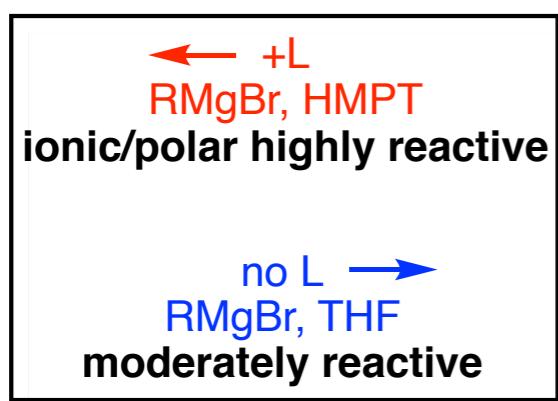


↑

Cs^+
 K^+
 Na^+
 Li^+
 ...
 Mg^+
 ...

delocalization of
 negative charge into
 two phenyl rings
 -45 kcal/mol
 times
 how basic metal is
 M more basic,
 \ominus more ionic

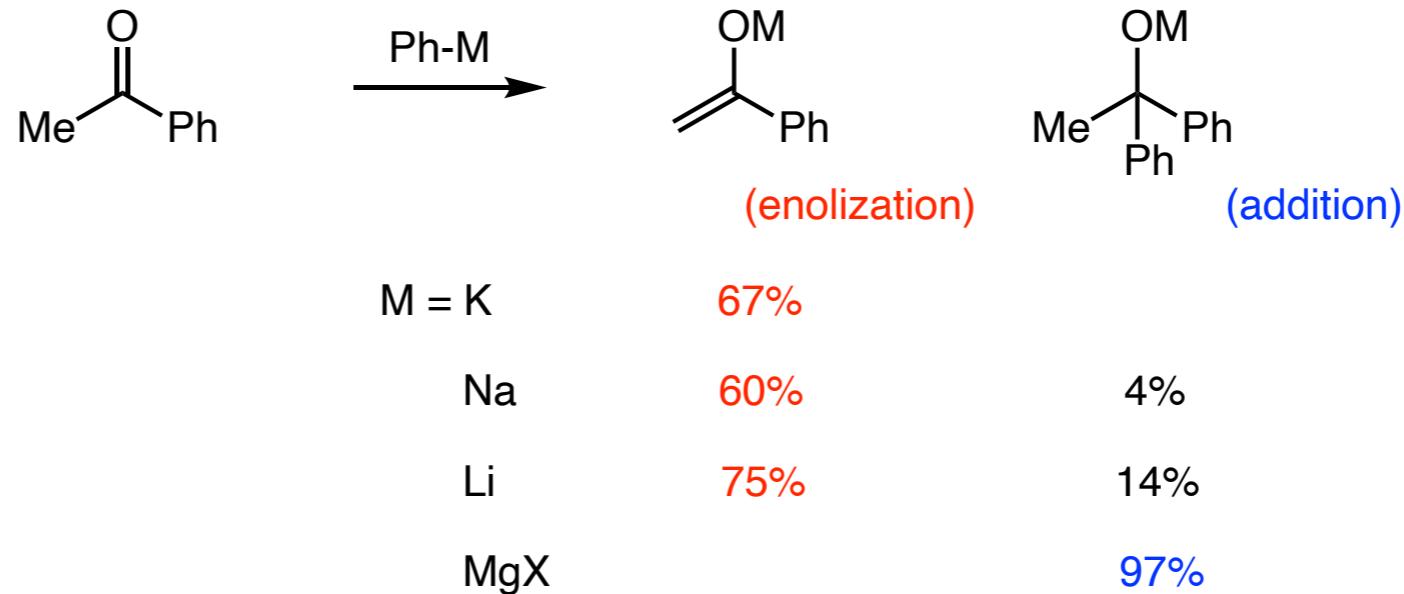
(hydrocarbon stability:
 olefinic > cyclopropyl)
 -15 kcal/mol
 metal invariant



Li^+ in THF (better solvated, more ionic)

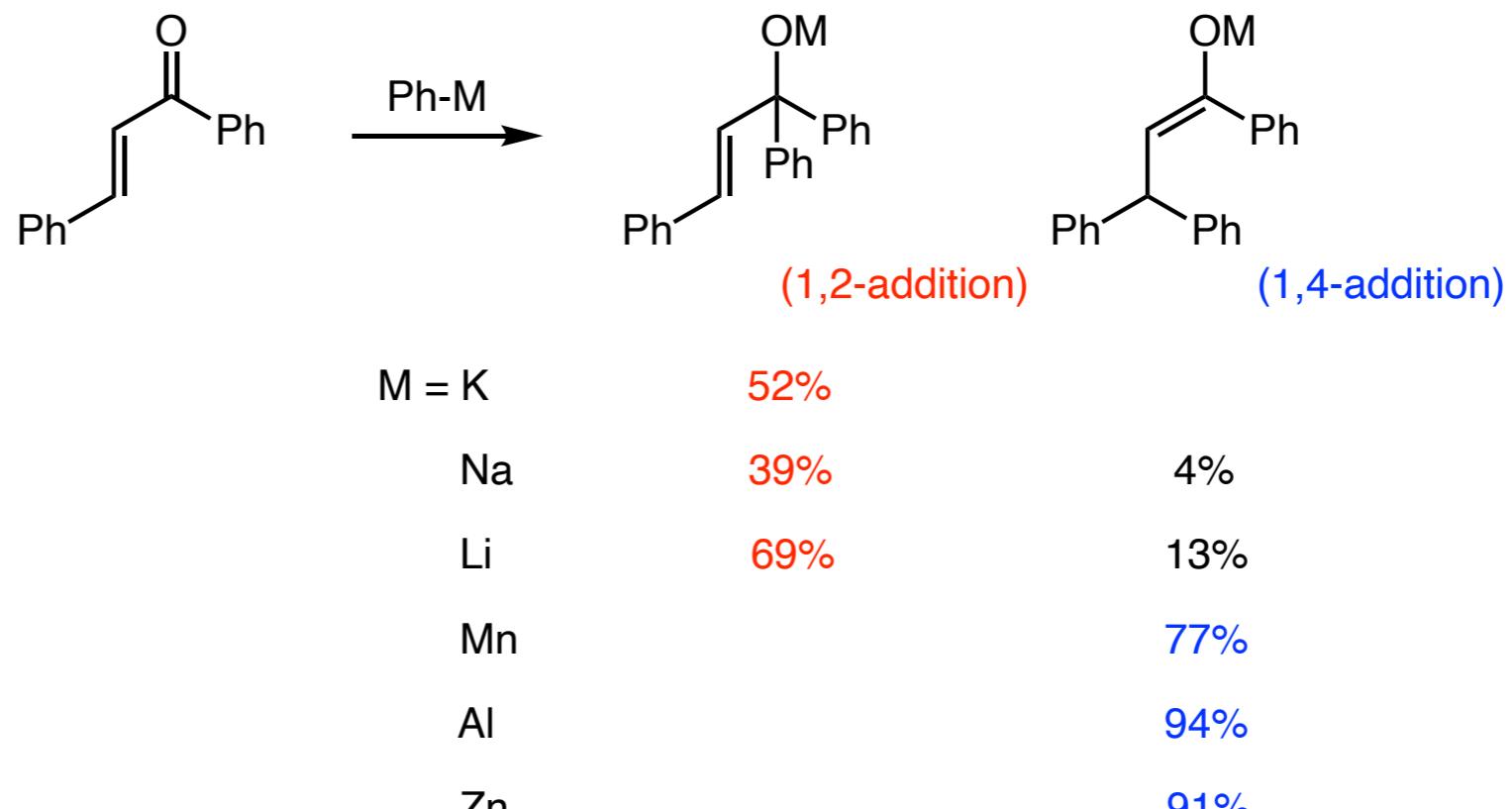
Li^+ in Et_2O (less ionic)

Metal Effects on Reactivity



RNa, RLi...
ionic/polar, highly reactive
enolization, 1,2-addition

R₂Be, RMgX, R₂Zn, R₃Al...
moderately reactive
addition, 1,4-addition

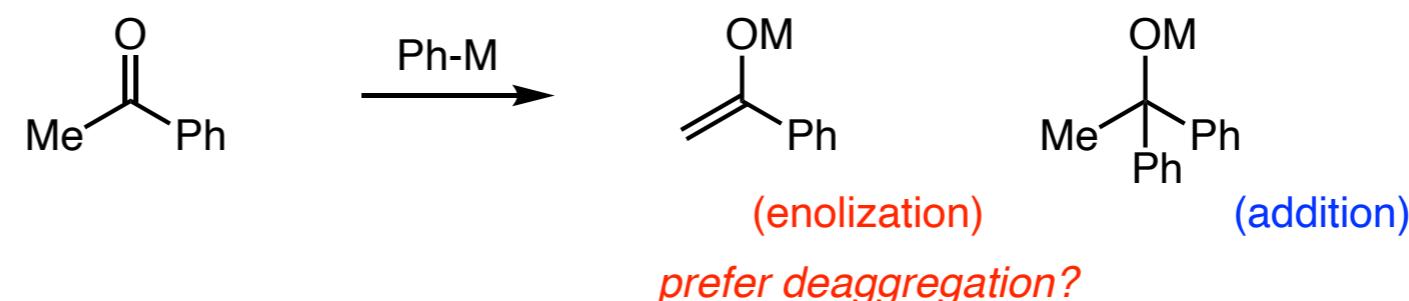


$+L$
RMgBr, HMPT
ionic/polar highly reactive

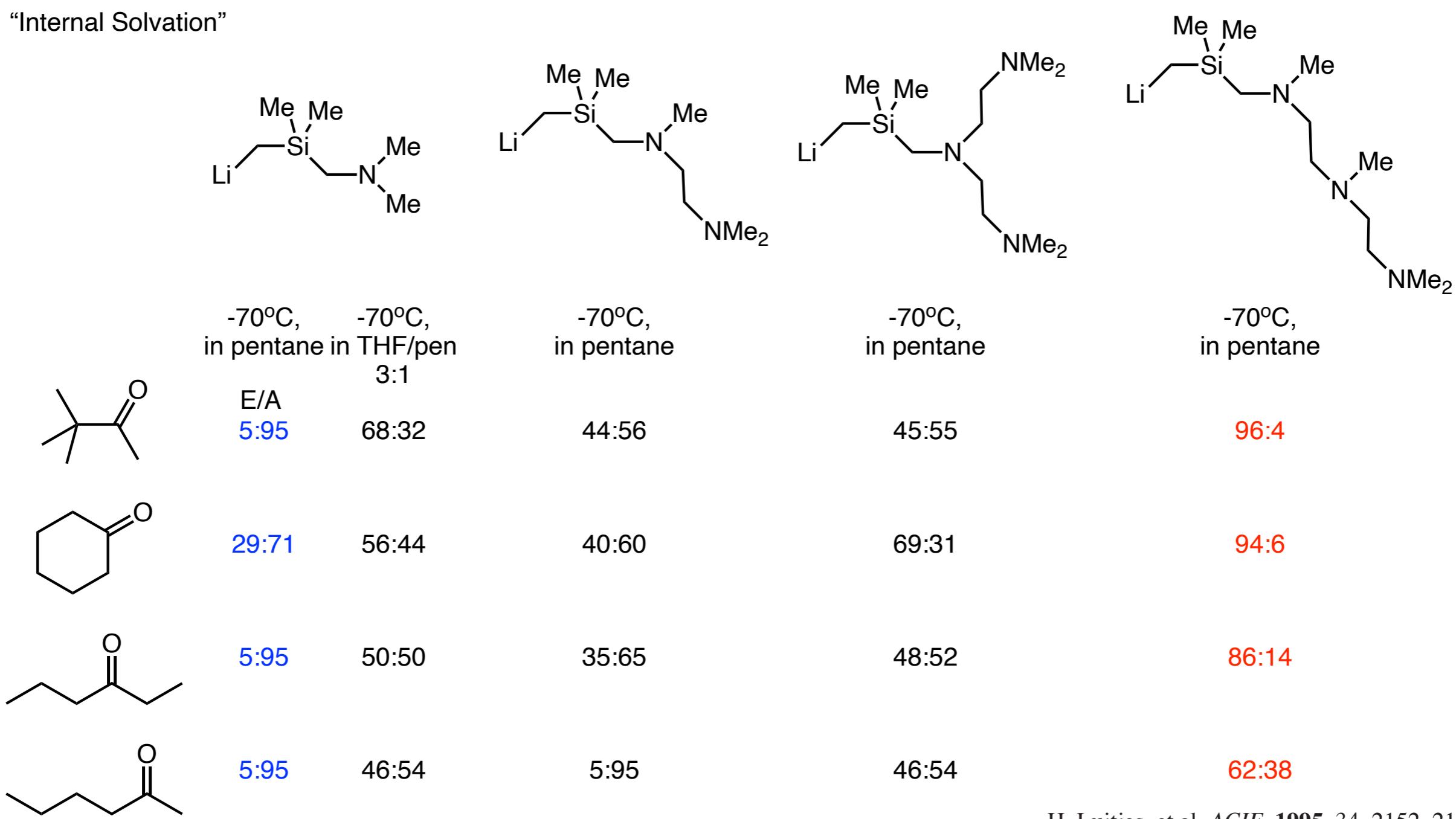
no L
RMgBr, THF
moderately reactive

does this mean enolization/1,2-addition prefer deaggregation?

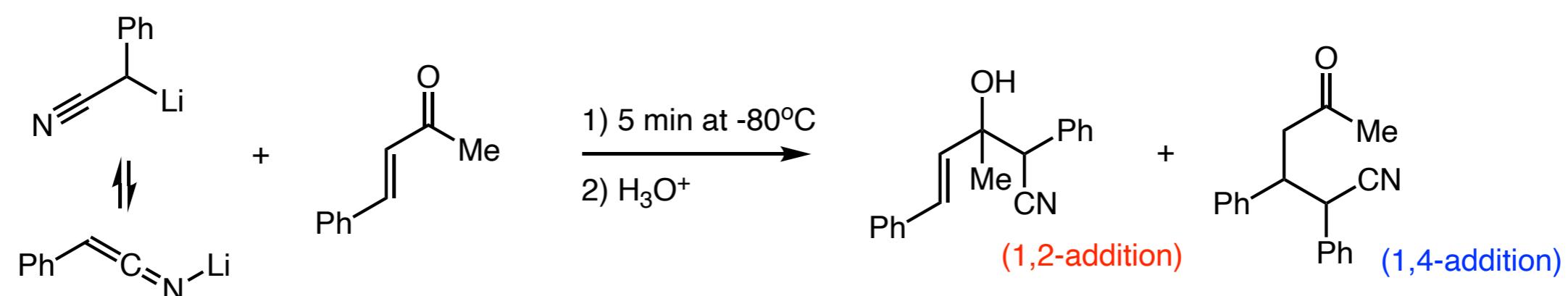
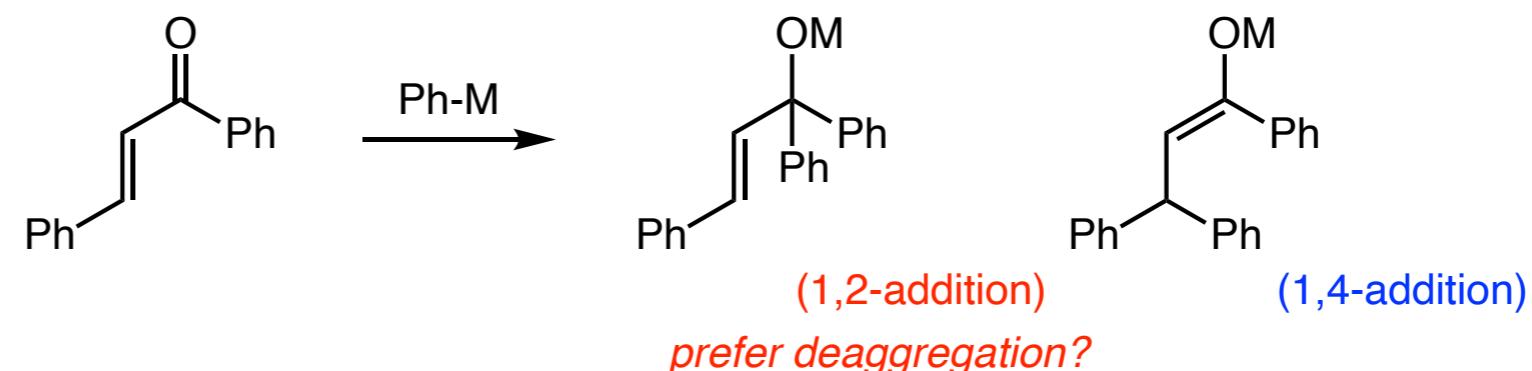
Metal Effects on Reactivity



“Internal Solvation”



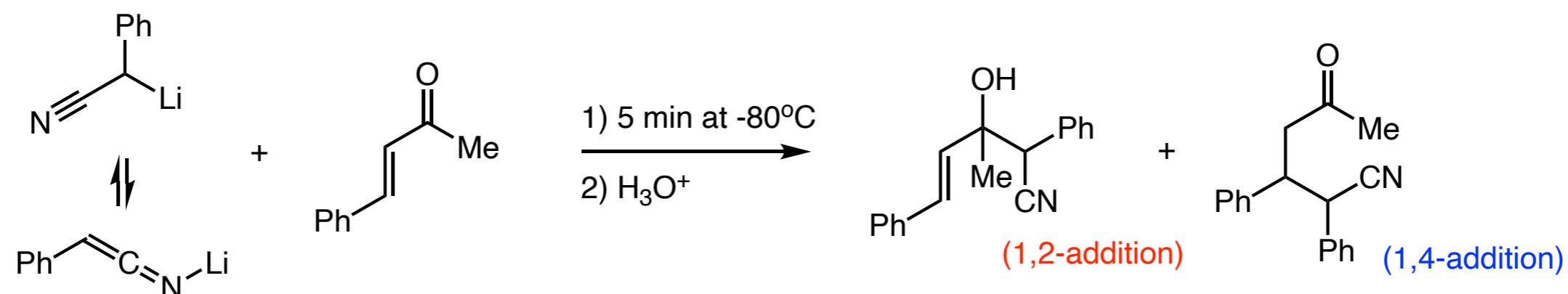
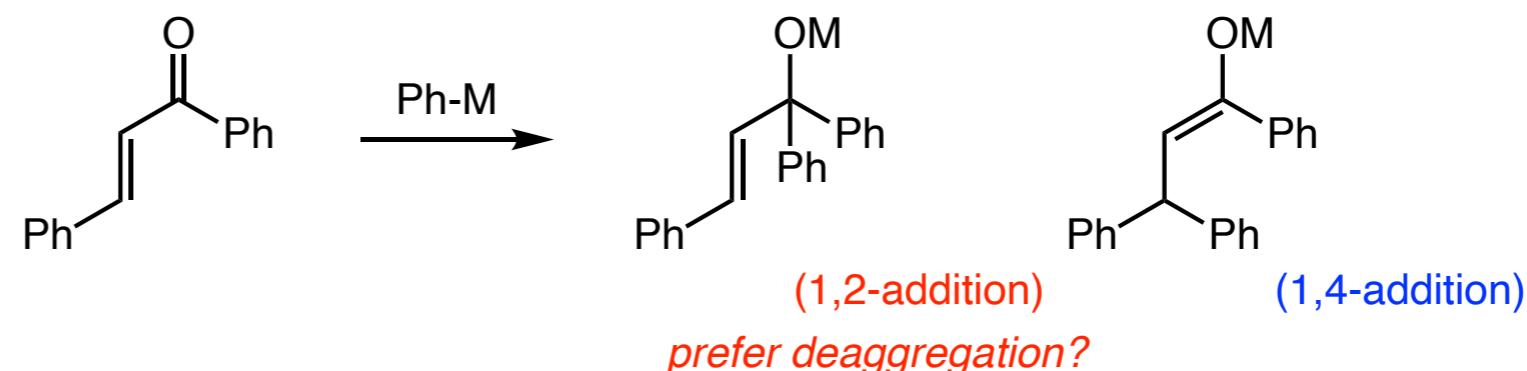
Metal Effects on Reactivity



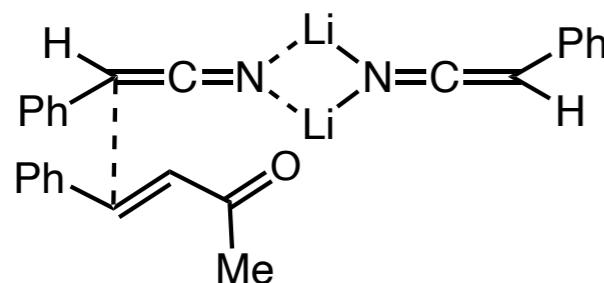
Solvent (THF/hexane v/v)	
100	95:5, 92% yield
80/20	75:25, 78% yield
70/30	47:53, 41% yield
60/40	25:75, 43% yield
50/50	8:92, 53% yield

T. Strzalko, et al. *Tet. Lett.* **1994**, 35, 3935–3936.
H. J. Reich, M. M. Biddle, R. J. Edmonston. *JOC*. **2005**, 70, 3375–3382.

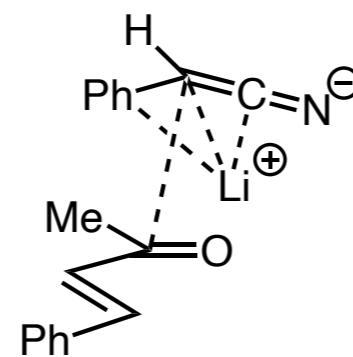
Metal Effects on Reactivity



1,4-addition extened TS (Dimer):



1,2-addition compact TS (Monomer):



Solvent
(THF/hexane v/v)

100	95:5, 92% yield
80/20	75:25, 78% yield
70/30	47:53, 41% yield
60/40	25:75, 43% yield
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Questions?