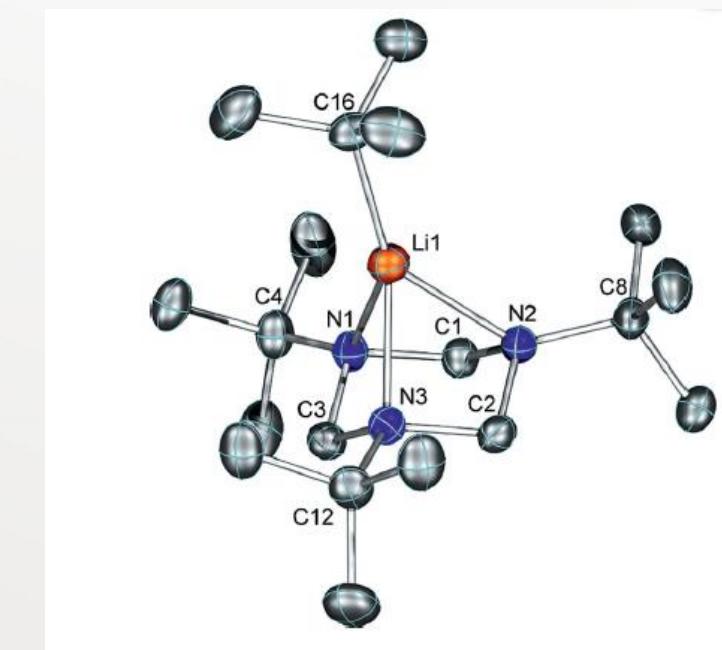


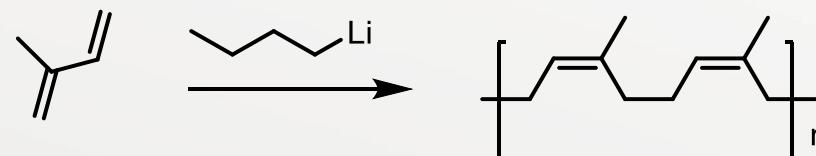
Advanced Organolithium Chemistry



Report: Zhe Dong
Advisor: Prof. Guangbin Dong
Sept 03rd 2014

A short history for BuLi

n-Butyllithium was first prepared in 1949
It was not commercial available until 1970s.
The industry found it can polymerize isoprene
stereospecifically.



tert-Butyllithium was first prepared in 1974

Novis Smith Jr, W. J. *Organomet. Chem.* **1974**, 82, 1.

All the alkylolithium can deprotonize
the THF or ether at r.t and has the potential to
Catch the fire in the presence of air!!

What is the most powerful synthetic tool?

Price: nBuLi 800ml 2.5M \$50
\$25/mol

High reactivity, require set up skills

Pd(OAc)₂ \$2352/mol

Highly chemo selective, No skills

[Rh(cod)₂Cl]₂ \$143500/mol

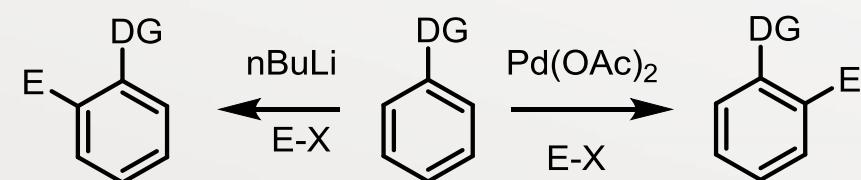
Seldom used for substrate synthesis

1eq BuLi vs 1%Pd(OAc)2 vs 0.02% Rh

TON requirement: **100** vs **5000**

Ligand price:

TMEDA	VS	Pyridine ligand
HPMA	VS	Phosphine ligand
(-)Sparteine	VS	Segphos

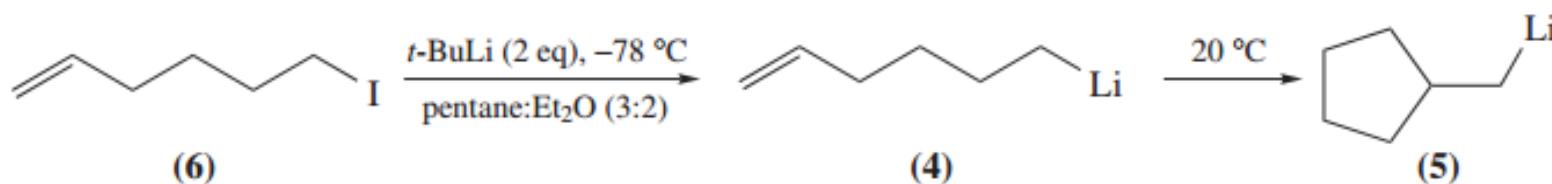


Which route is more Practical?
Maybe still is BuLi at this stage

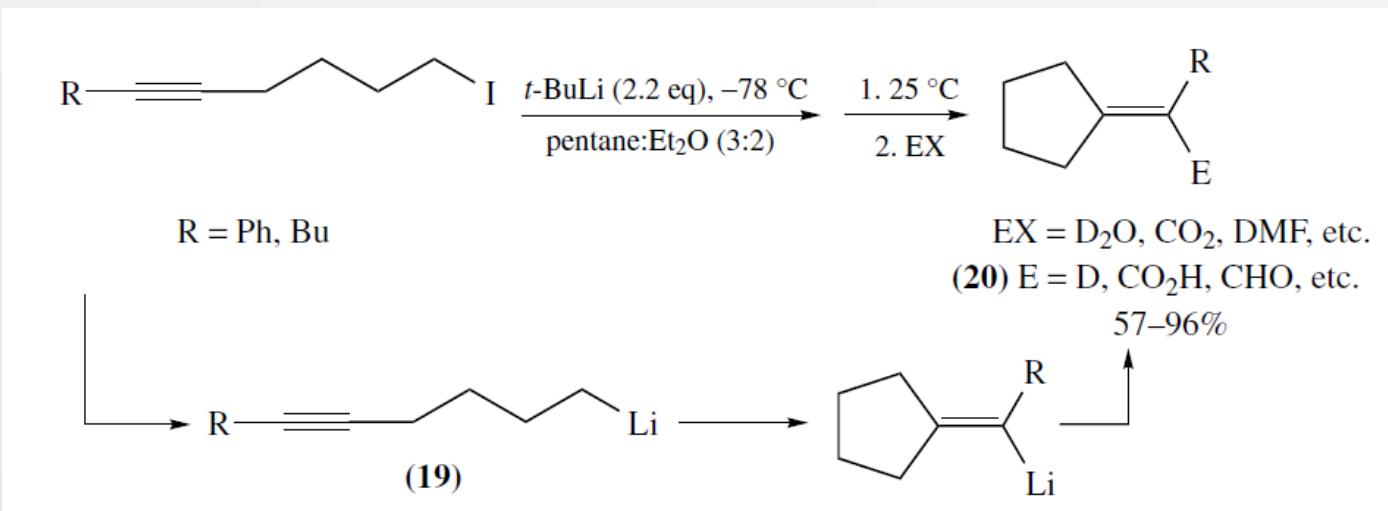
Outline

- 1. “Migratory insertion” of Organolithium**
- 2. Halogen dance reaction**
 - 2.1 Discovery and Modern Mechanism**
 - 2.2 Halogen dance on the Benzene**
 - 2.3 Halogen dance on the Heterocycle**
- 3. Conclusion and Outlook**

Migratory insertion with alkene and alkyne

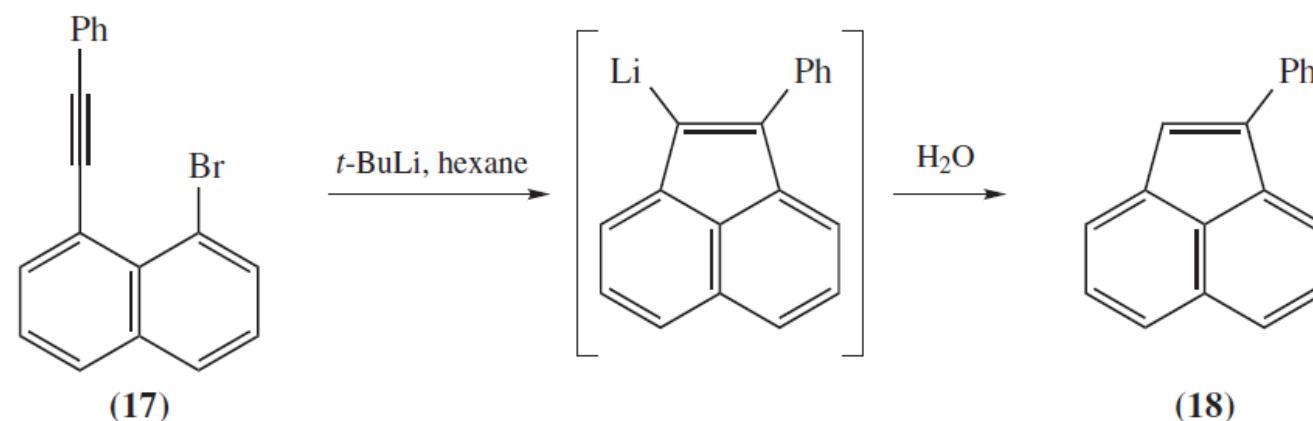
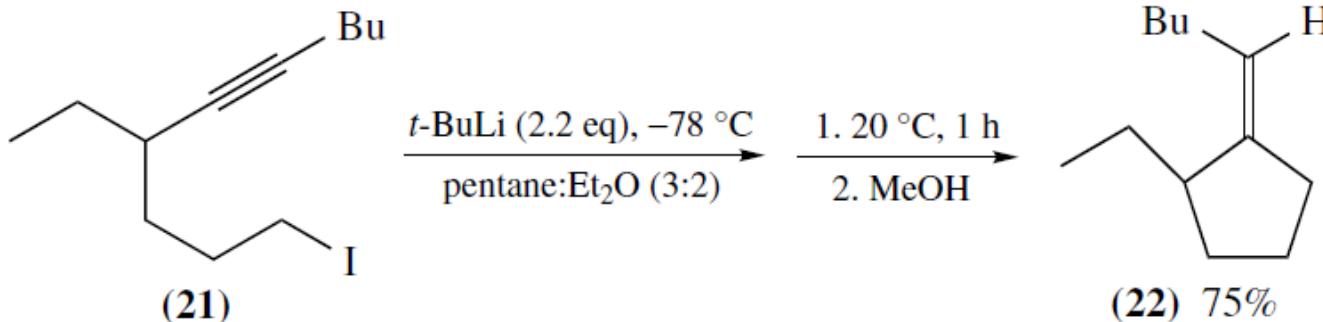


W. F. Bailey, J. J. Patricia, V. C. DelGobbo, R. M. Jarret and P. J. Okarma, *J. Org. Chem.*, **1984**, 50, 1999



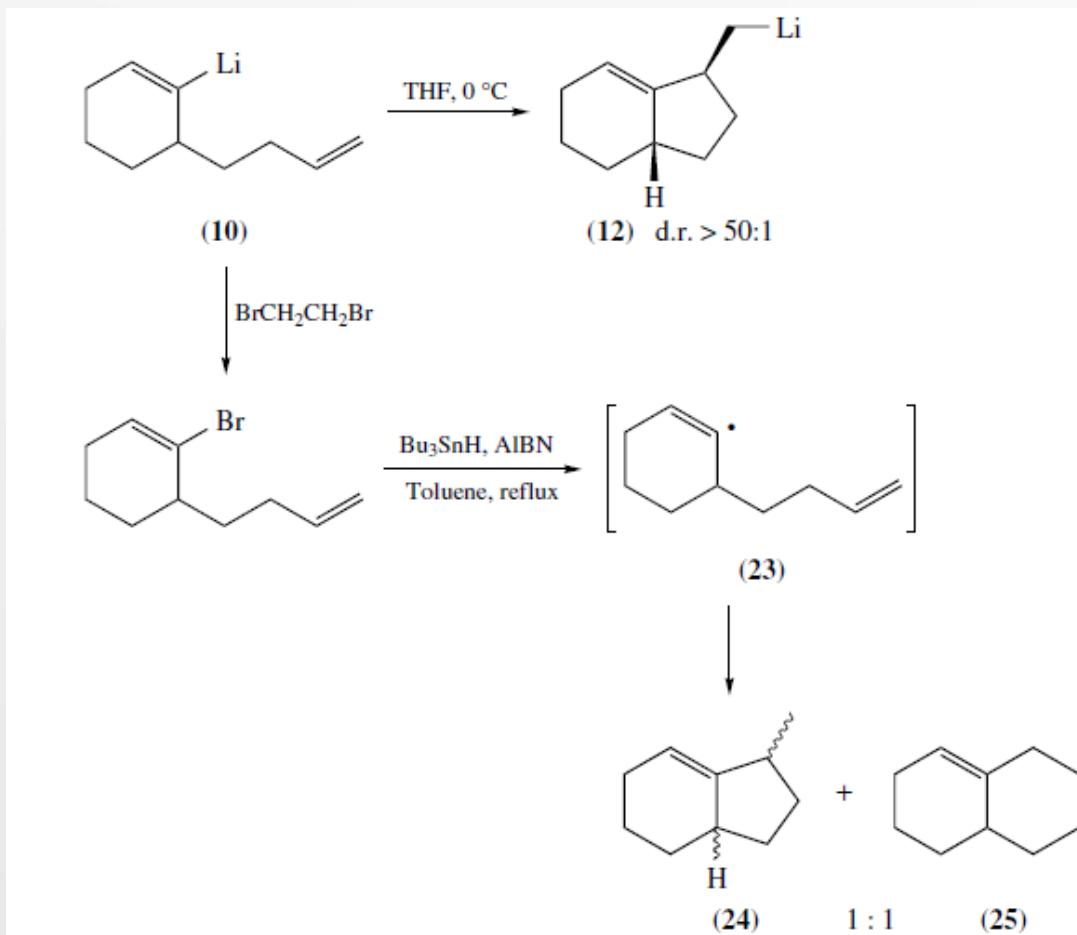
Bailey, W. F.; Ovaska, T. V.; Leipert, T. K. *Tetrahedron Lett.* **1989**, 30, 3901.

Migratory insertion with Alkyne



Bailey, W. F.; Ovaska, T. V.; Leipert, T. K. *Tetrahedron Lett.* **1989**, 30, 3901.

Anionic or radical ?



A. R. Chamberlin and S. H. Bloom, *Tetrahedron Lett.*, 1986, 27, 551

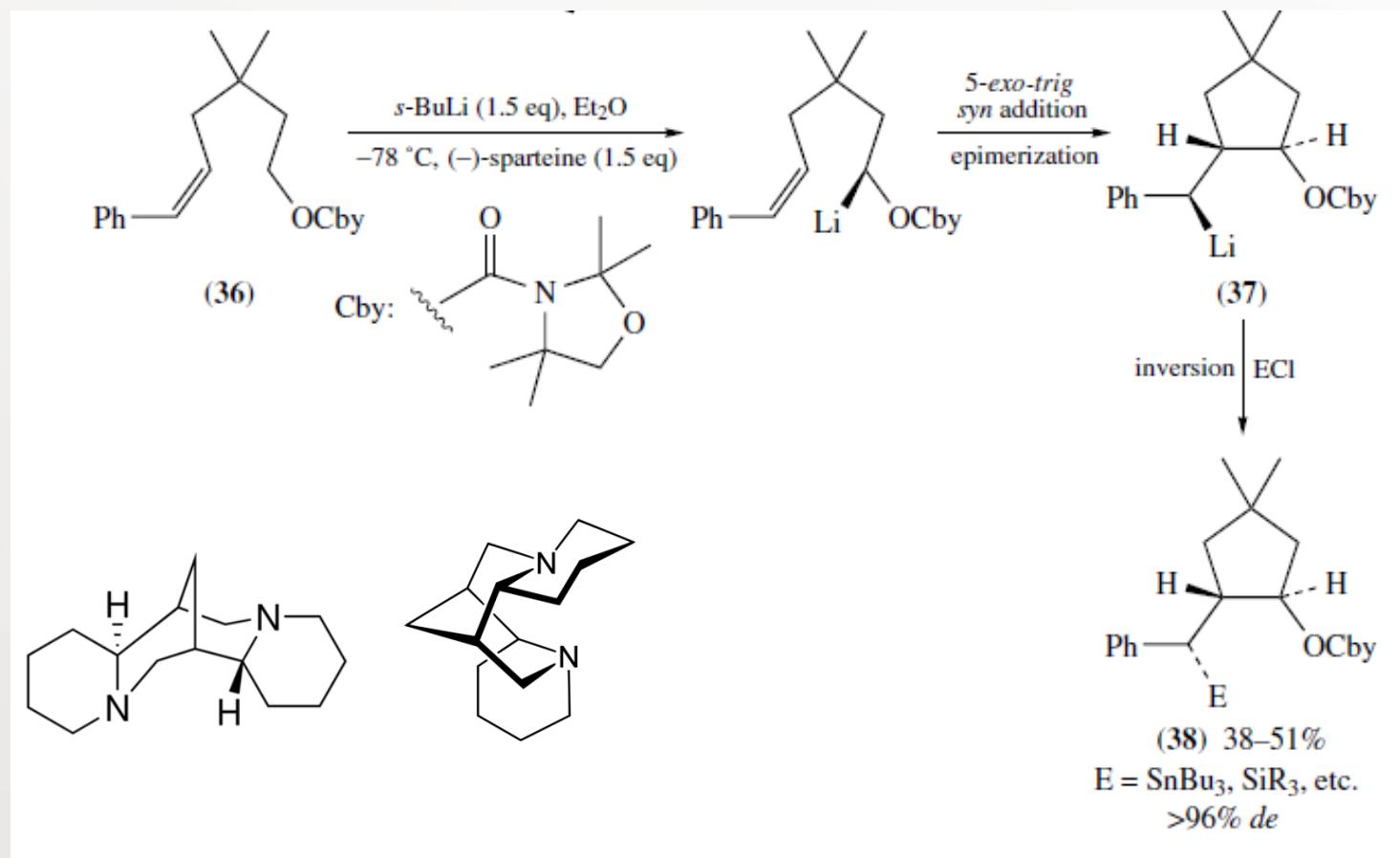
Anionic or radical ?

Starting material	<i>cis</i> -Product	<i>trans</i> -Product	Ratio (organolithium cyclization) ^a <i>cis/trans</i>	Ratio (radical cyclization) ^b <i>cis/trans</i>
			1:10	1:1.8
			10:1	2.5:1
			1:12	1:5

^a Conditions: 1) *t*-BuLi (2 eq), pentane: Et₂O, -78 °C; 2) TMEDA (2.2 eq), -78 °C; 3) -78 to 20 °C; 4) MeOH.

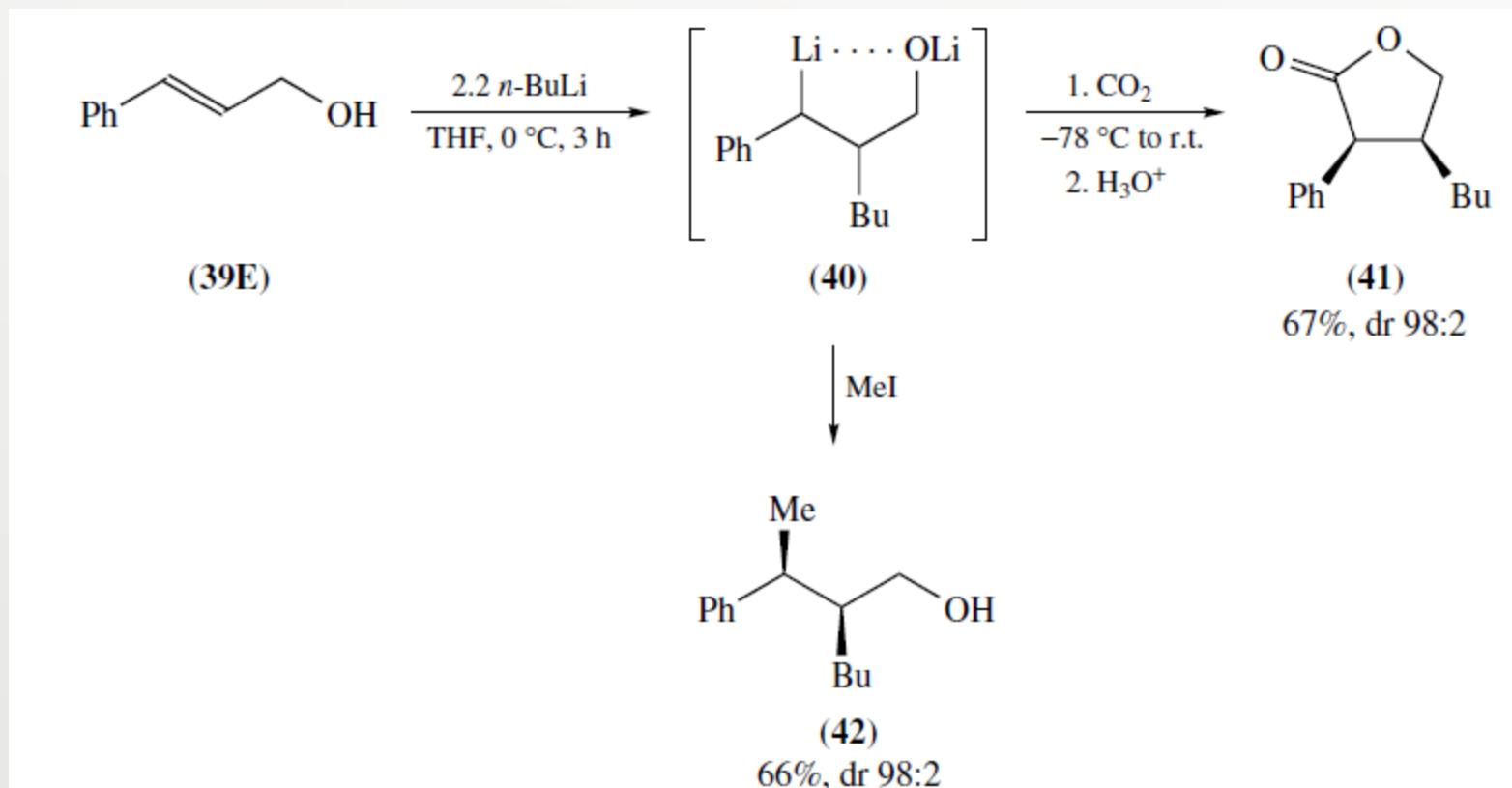
^b Conditions: Bu₃SnH, benzene, 80 °C.

Enantioselective Version

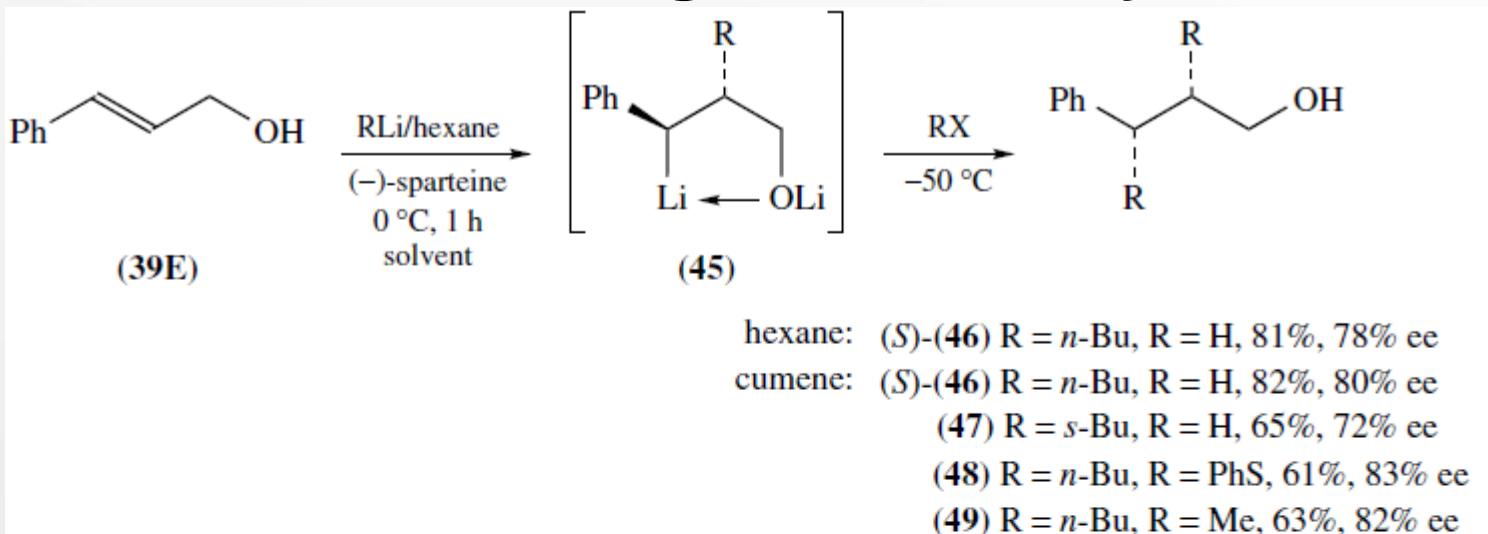


D. Hoppe, F. Hintze and P. Tebben, *Angew. Chem., Int. Ed.* **1990**, 29, 1422

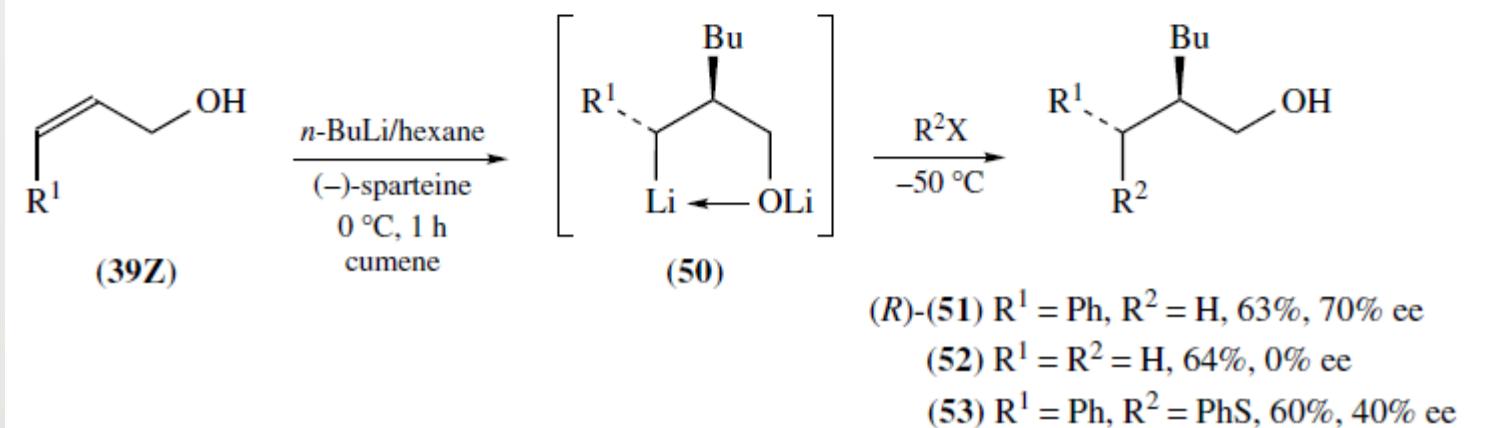
Novel regio-selectivity



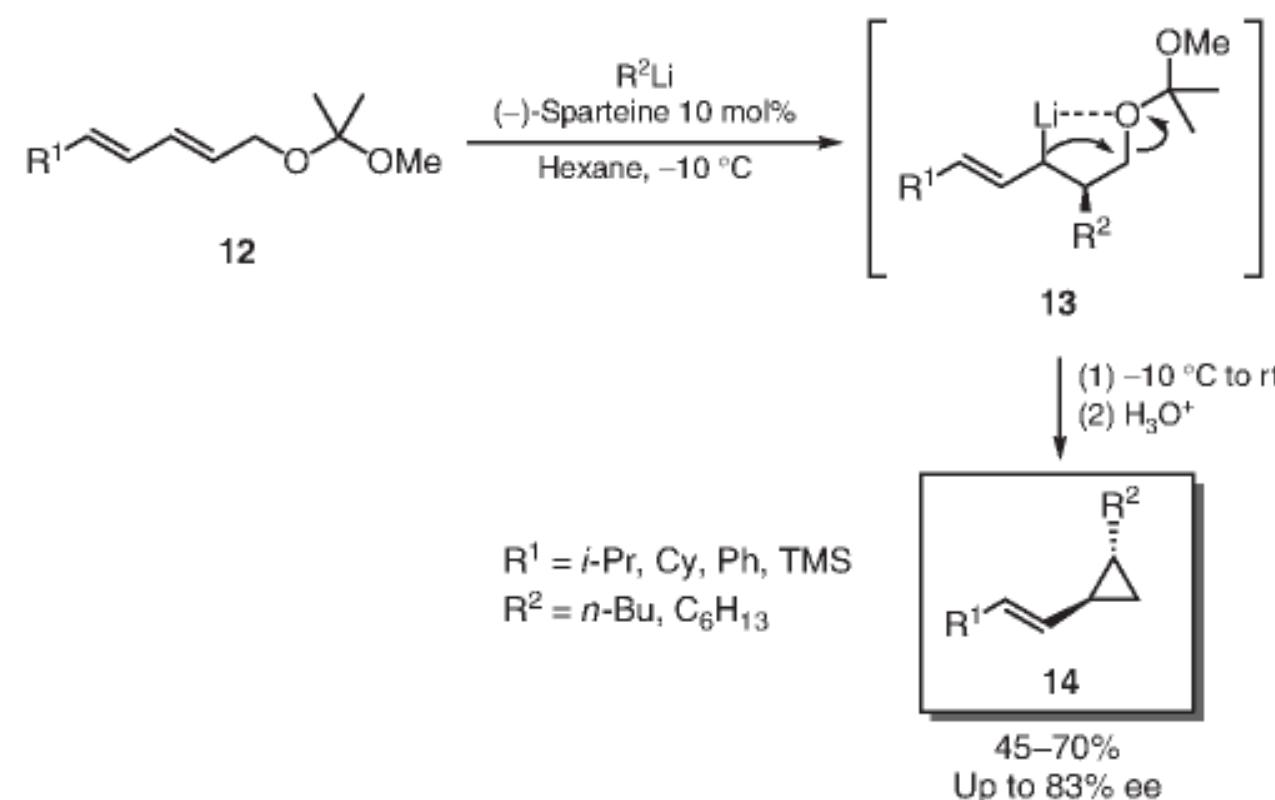
Novel regio-selectivity



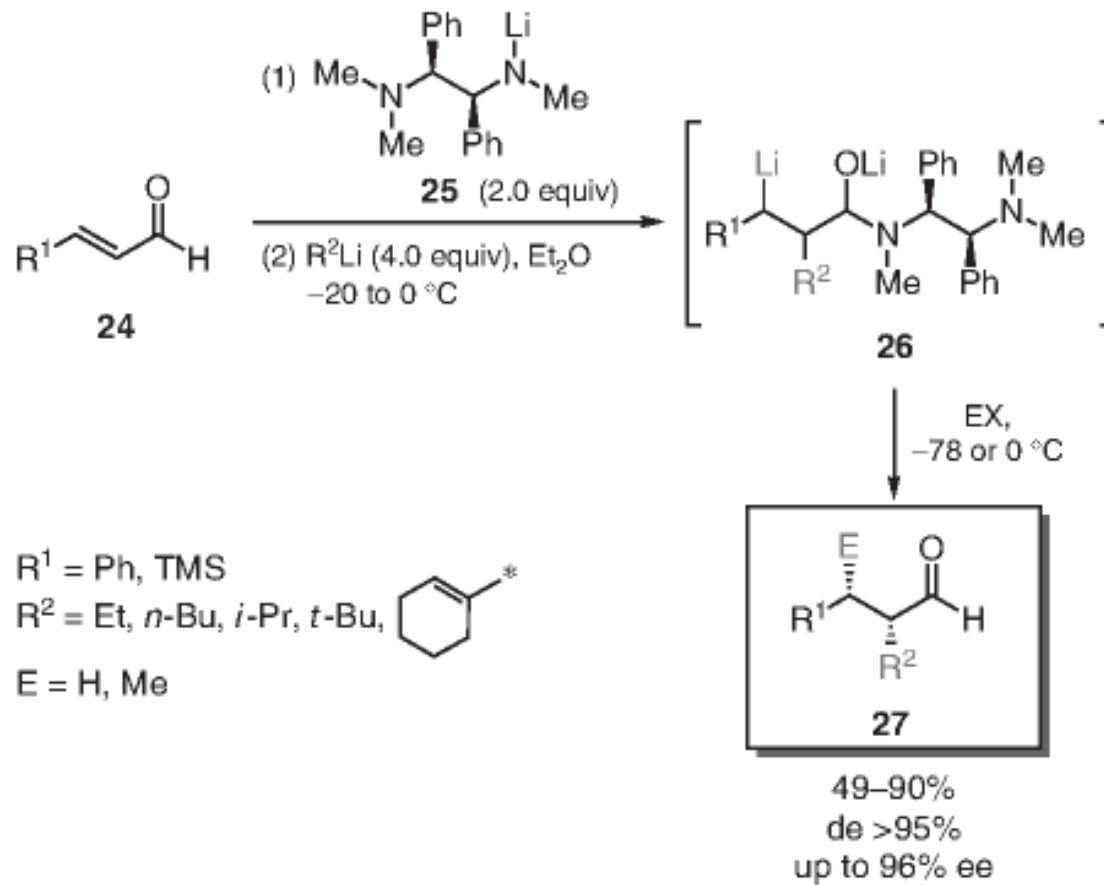
SCHEME 19



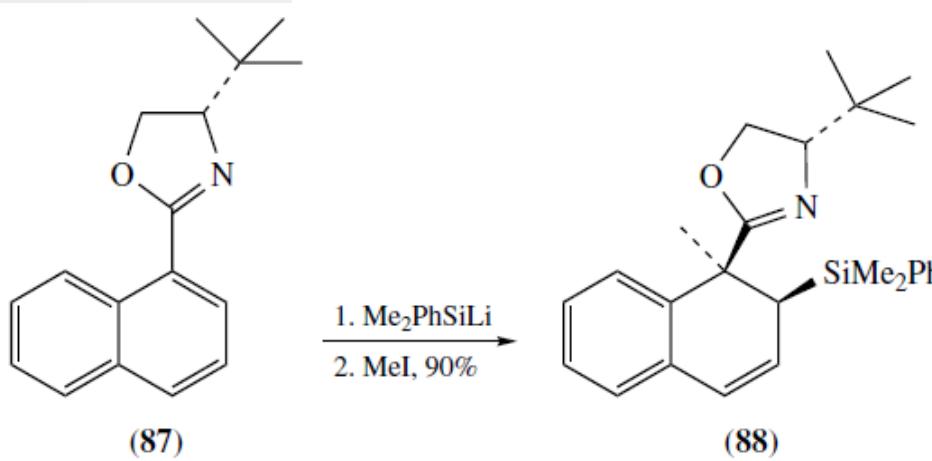
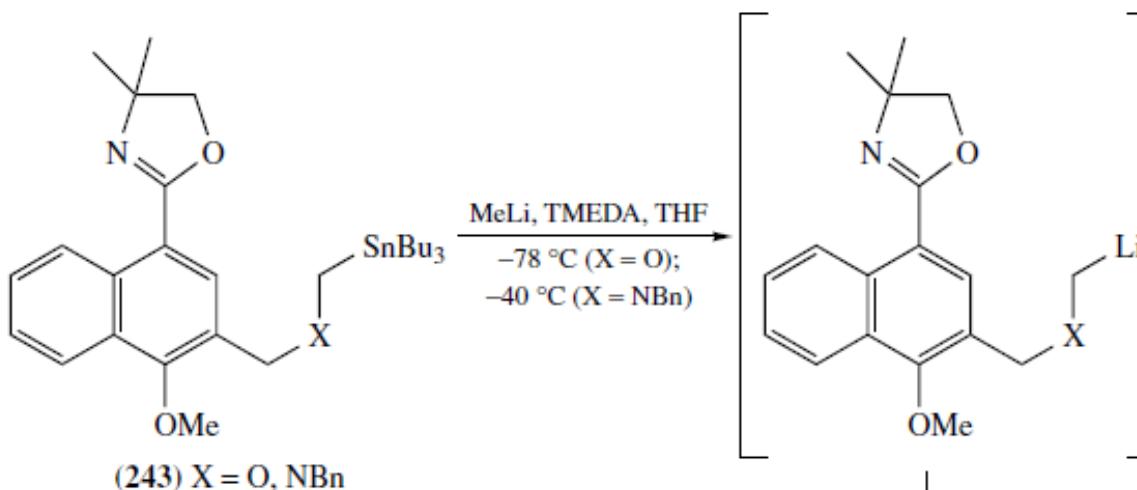
Novel regio-selectivity



Novel regio-selectivity

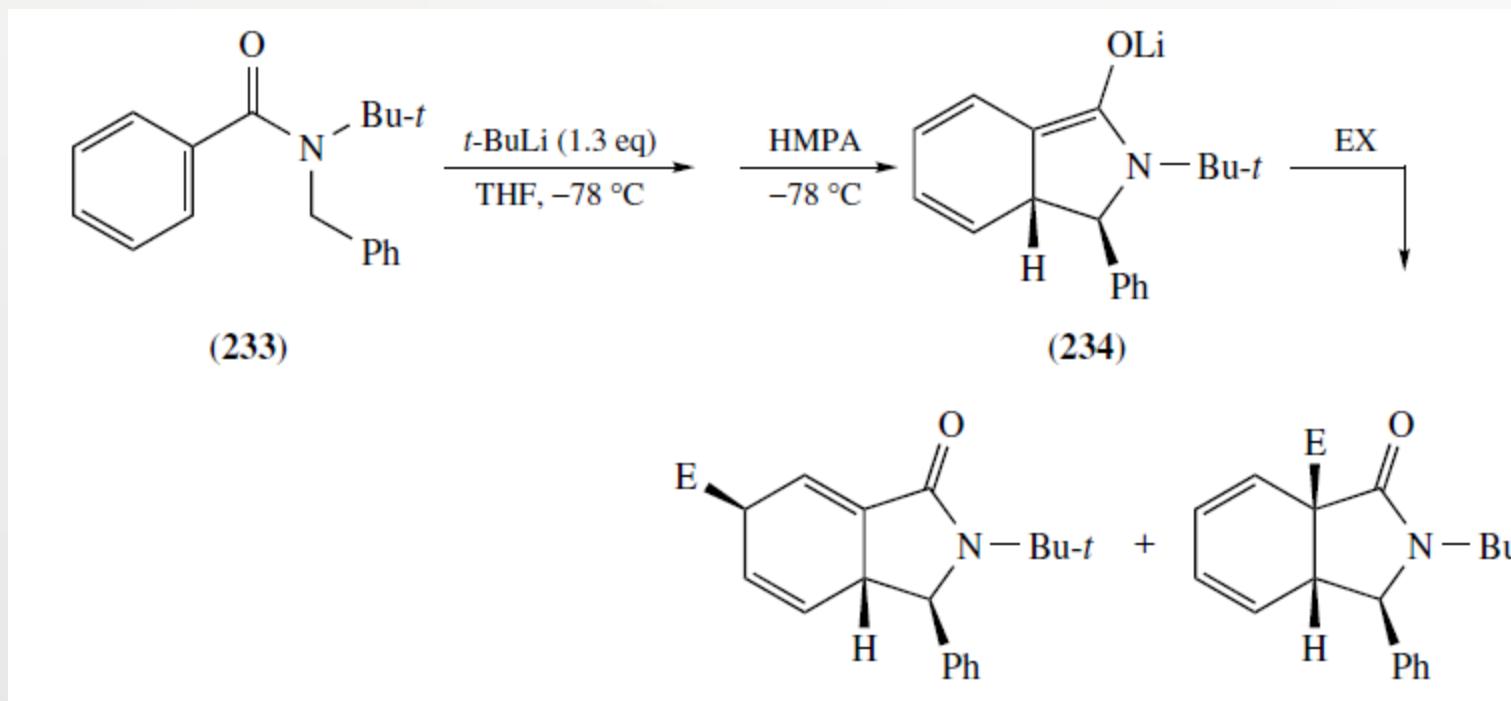


Deamortization



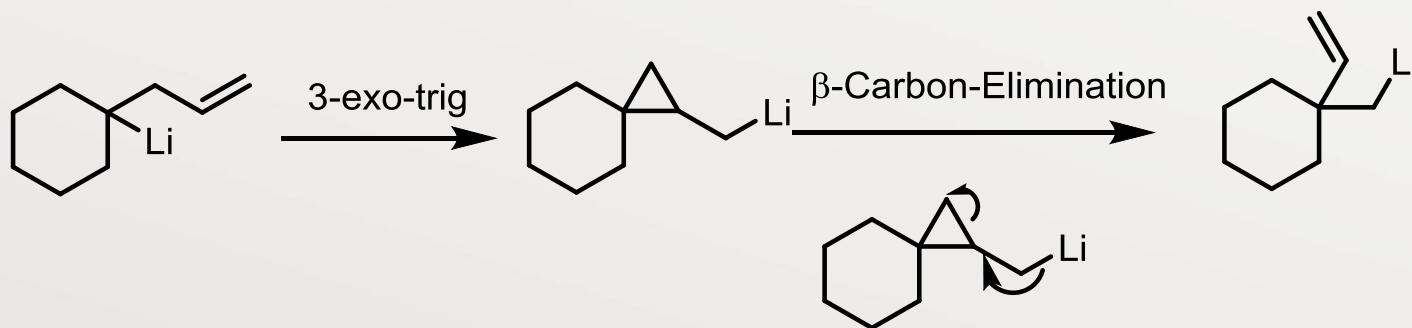
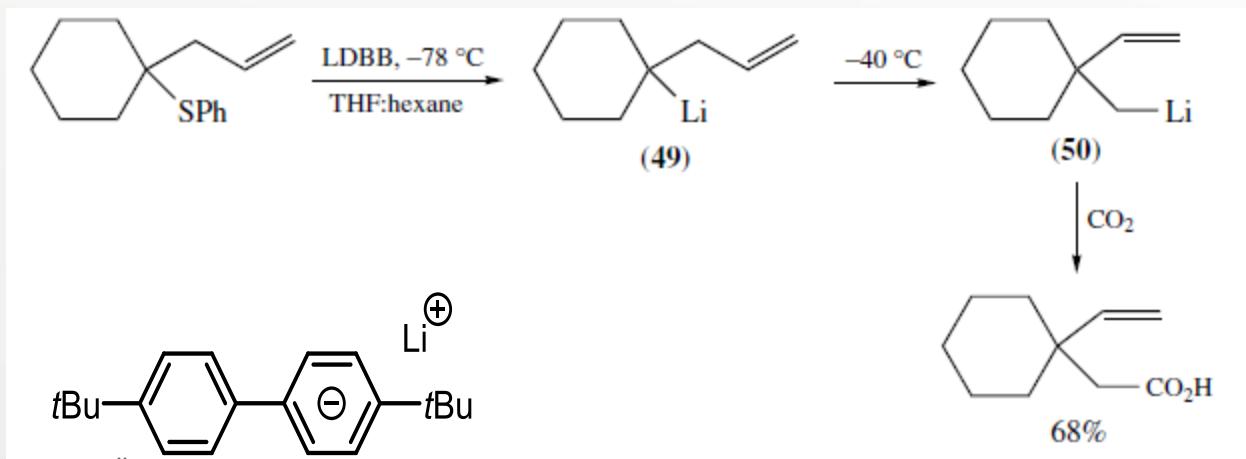
EX = $\text{H}_2\text{O}, \text{MeI}, \text{PhCHO}$, etc.
(244) E = H, Me, $\text{CH}(\text{OH})\text{Ph}$, etc.
41–80%

Deamortization



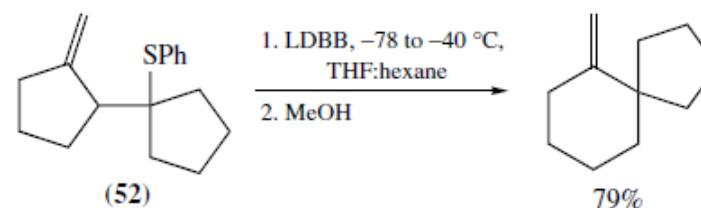
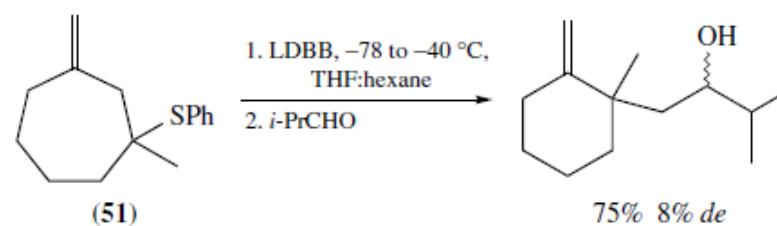
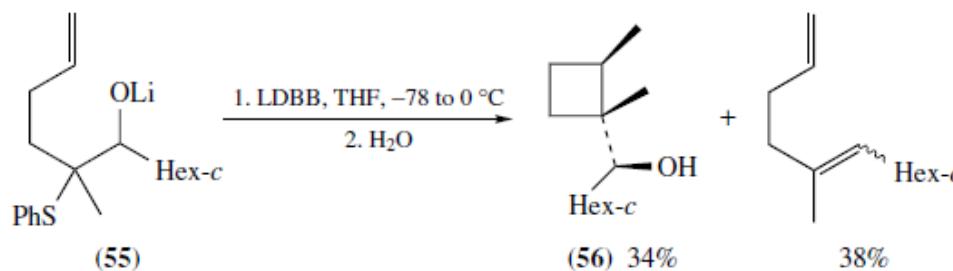
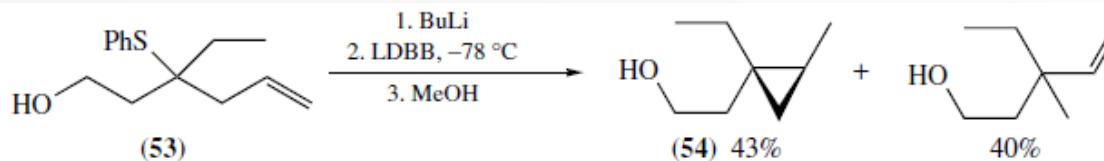
. A. Ahmed, J. Clayden and M. Rowley, *Tetrahedron Lett.*, 1998, 39, 6103

“ β -Carbon-Elimination”



B. Mudryk and T. Cohen, *J. Am. Chem. Soc.* **1993**, 115, 3855

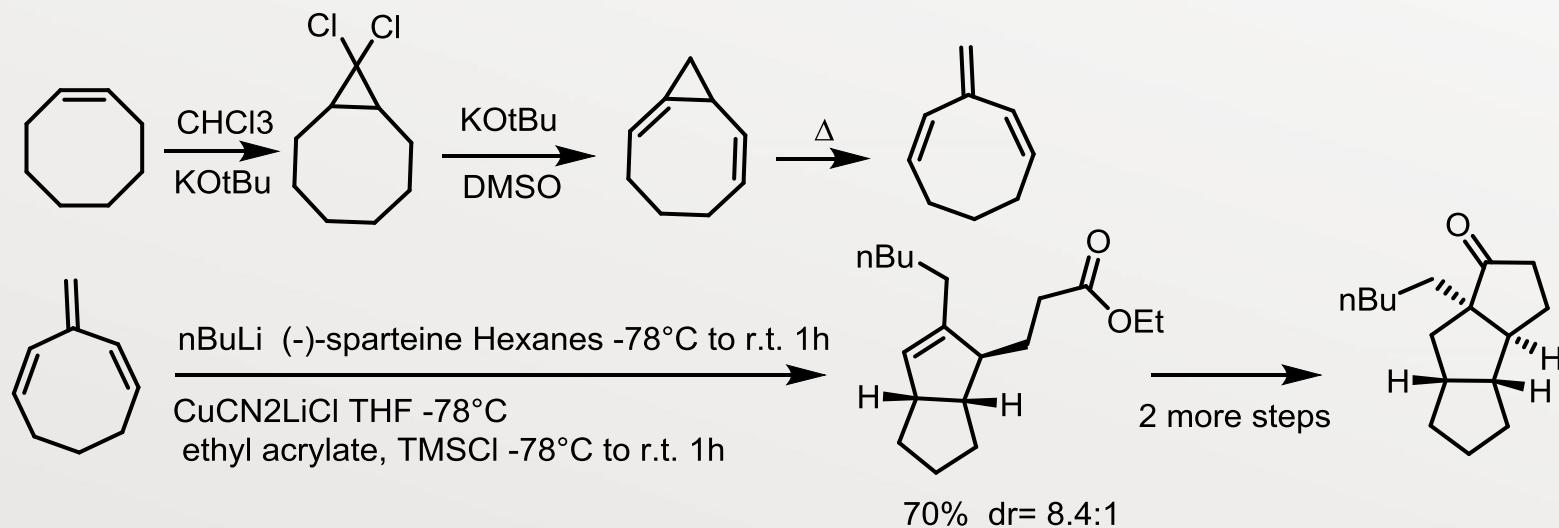
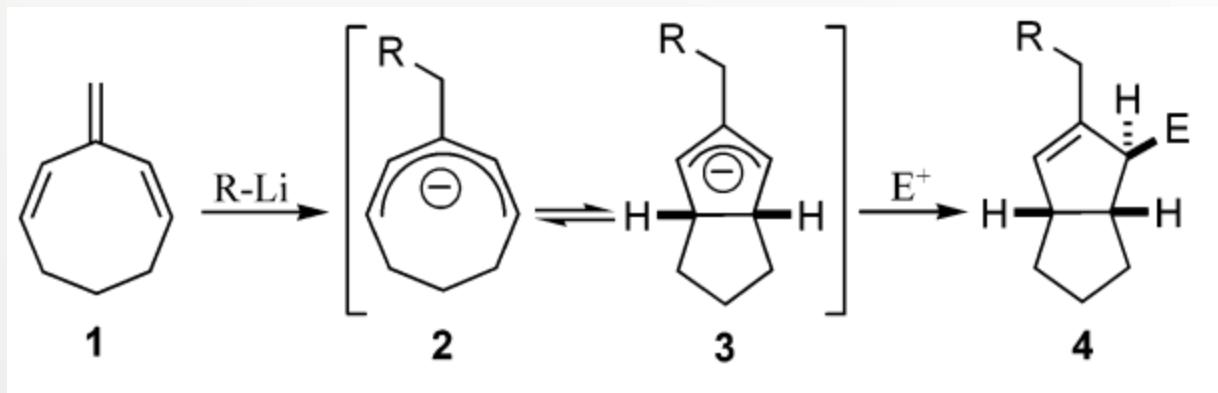
“ β -Carbon-Elimination”



B. Mudryk and T. Cohen, *J. Am. Chem. Soc.* **1993**, 115, 3855

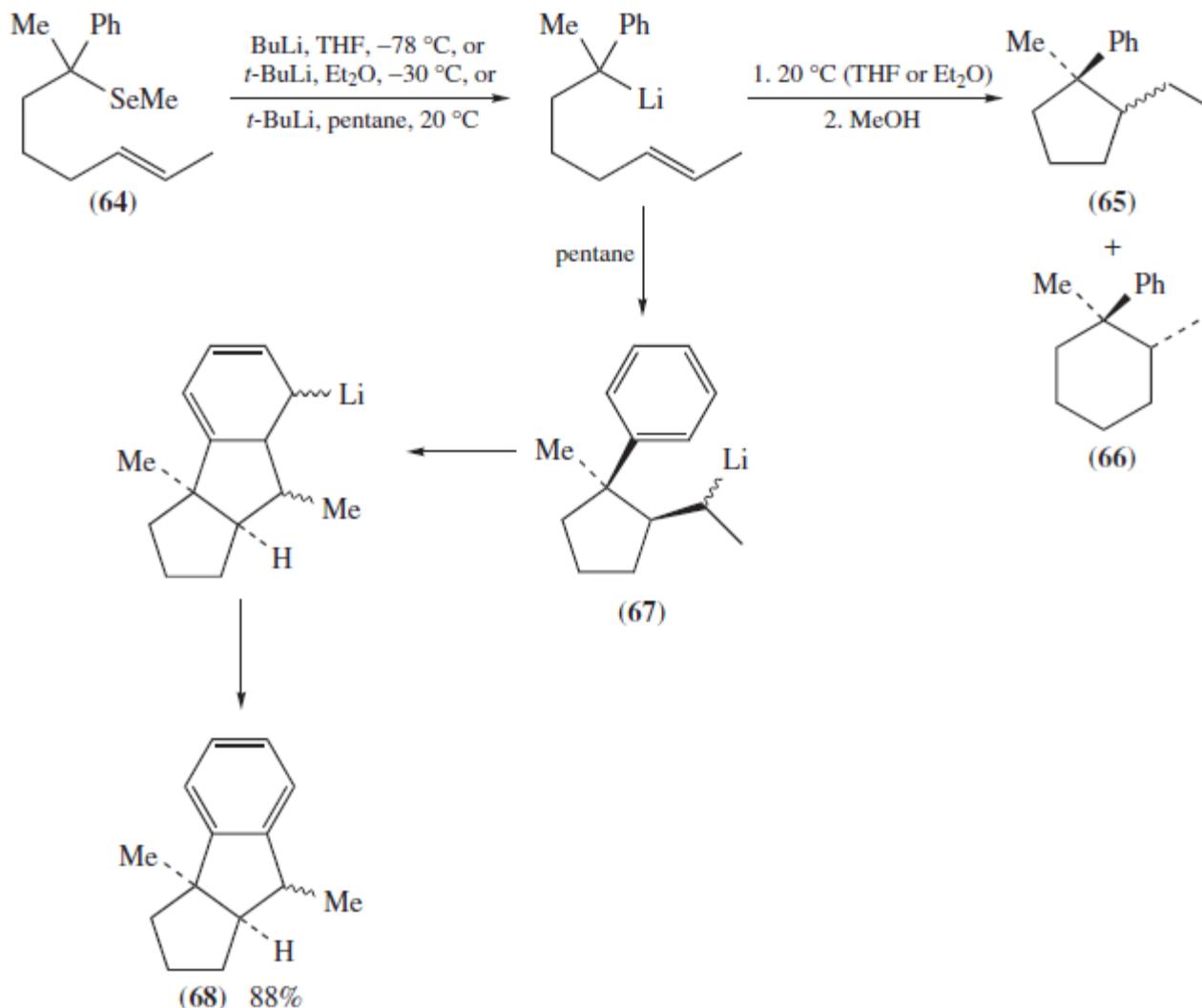
F. Chen, B. Mudryk and T. Cohen, *Tetrahedron*, **1994**, 50, 12793

Cascade Cyclization

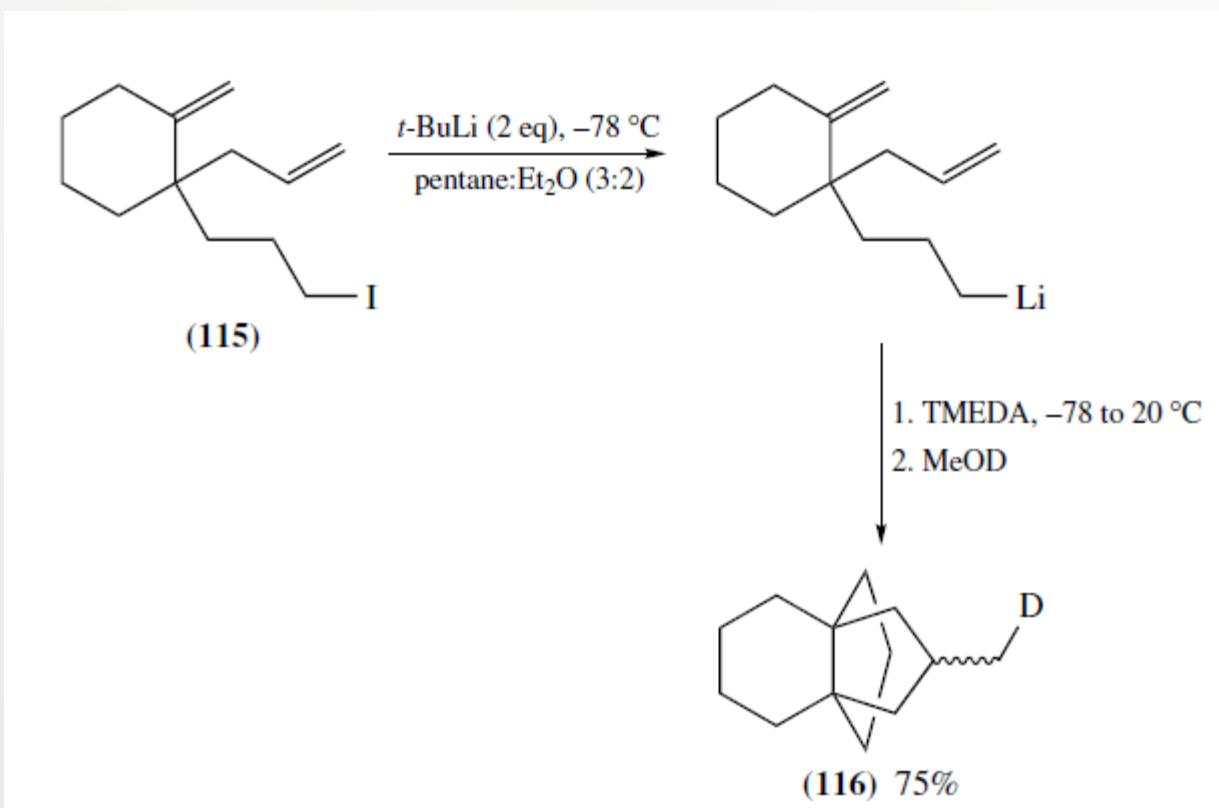


Williams, D. R.; Reeves, J. T. *J. Am. Chem. Soc.* **2004**, 126, 3434.

Cascade Cyclization

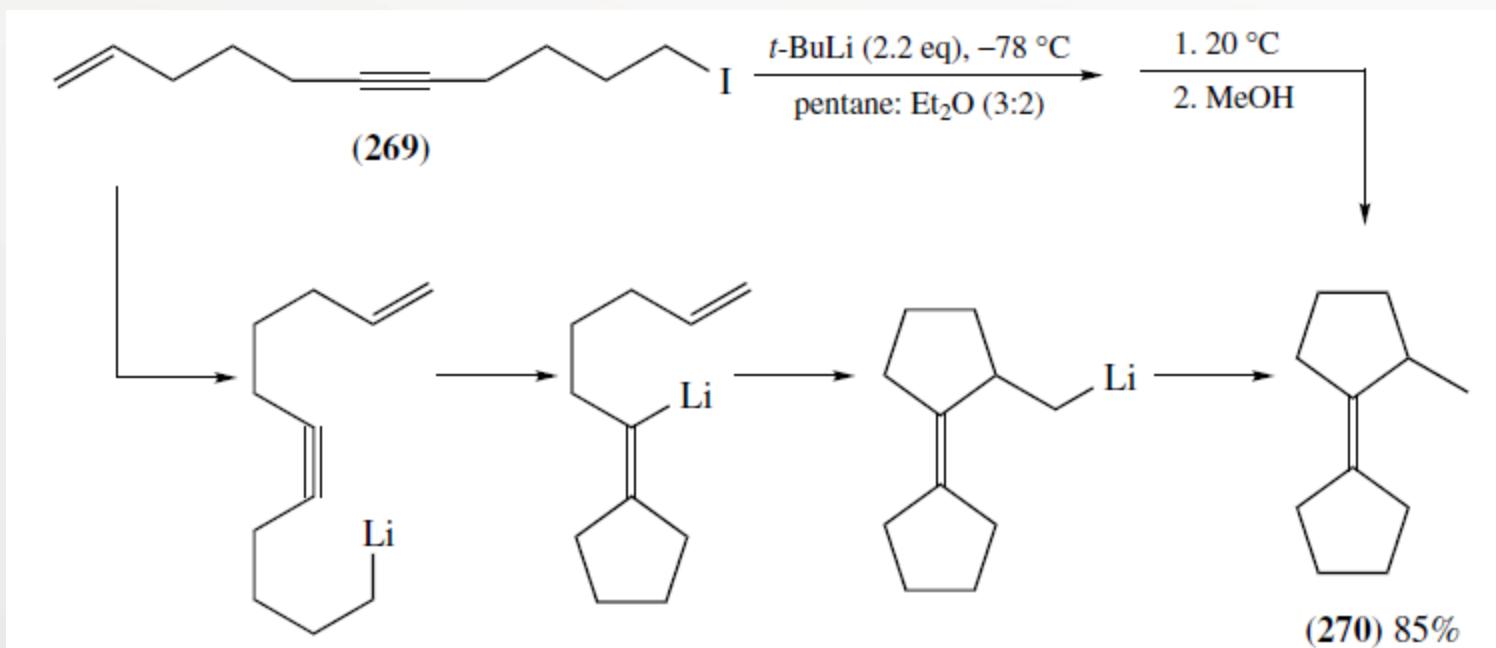


Cascade Cyclization



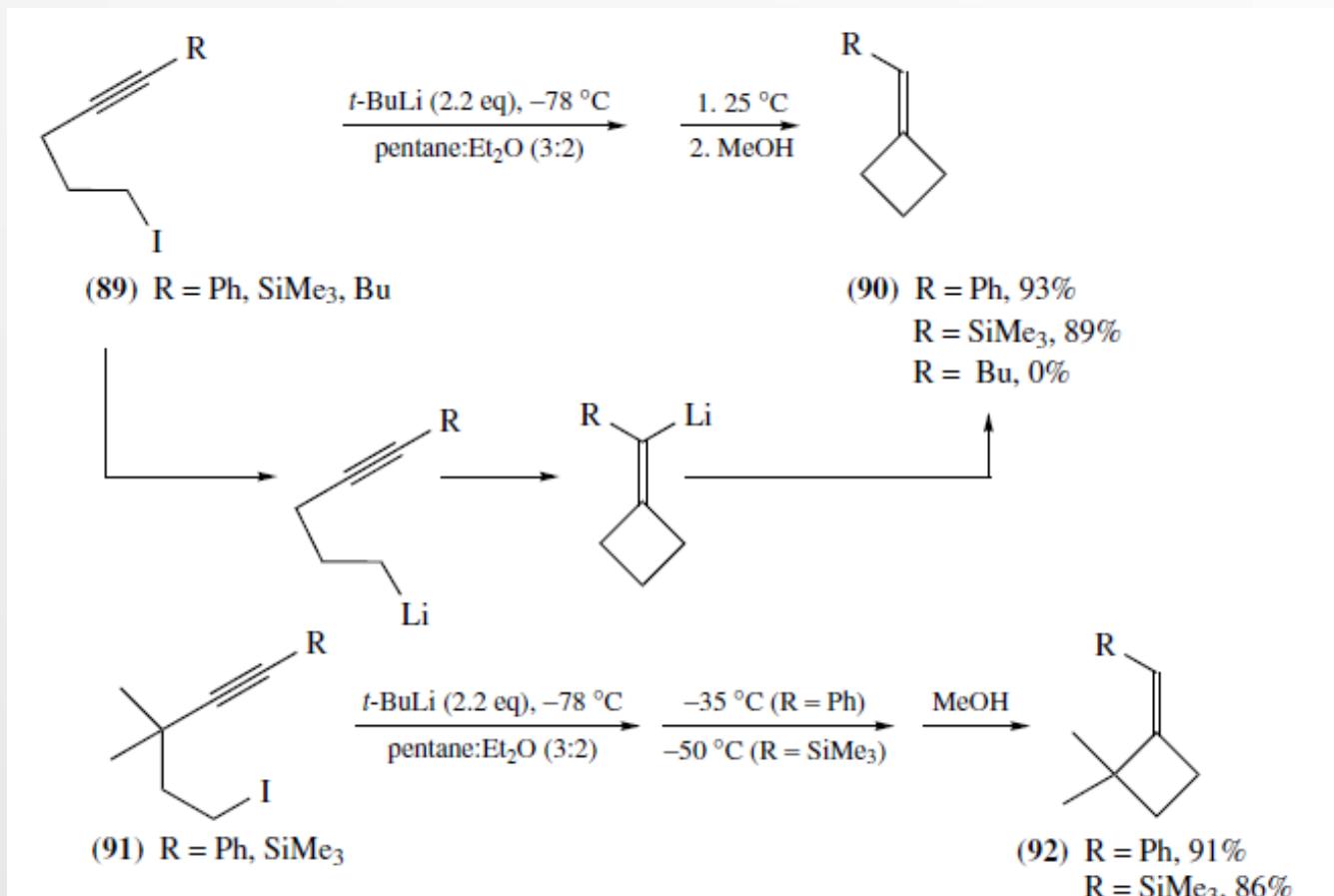
W. F. Bailey and K. Rossi, *J. Am. Chem. Soc.*, **1989**, 111, 765

Cascade Cyclization



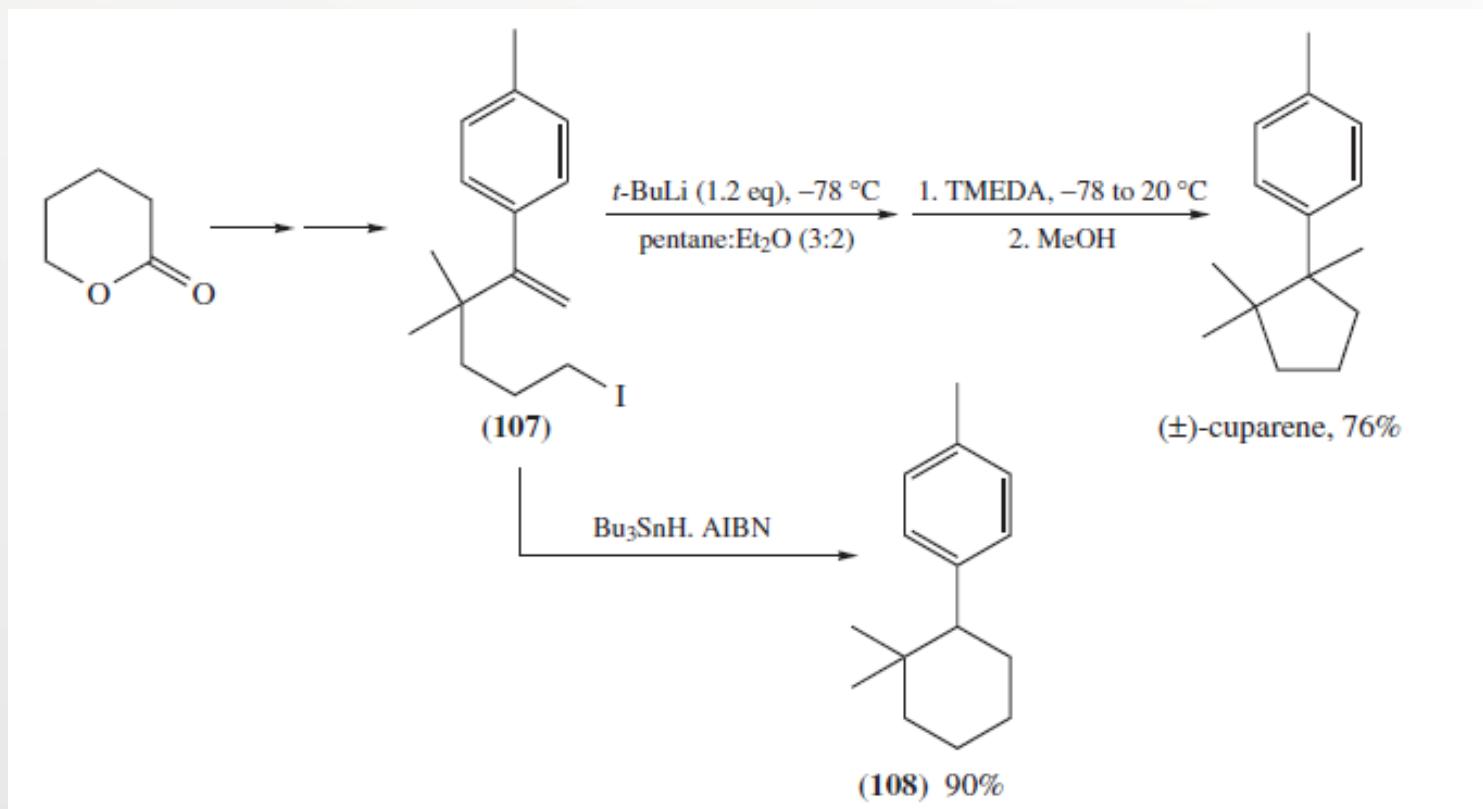
W. F. Bailey and T. V. Ovaska, *Chem. Lett.*, **1993**, 819

Cyclobutane synthesis



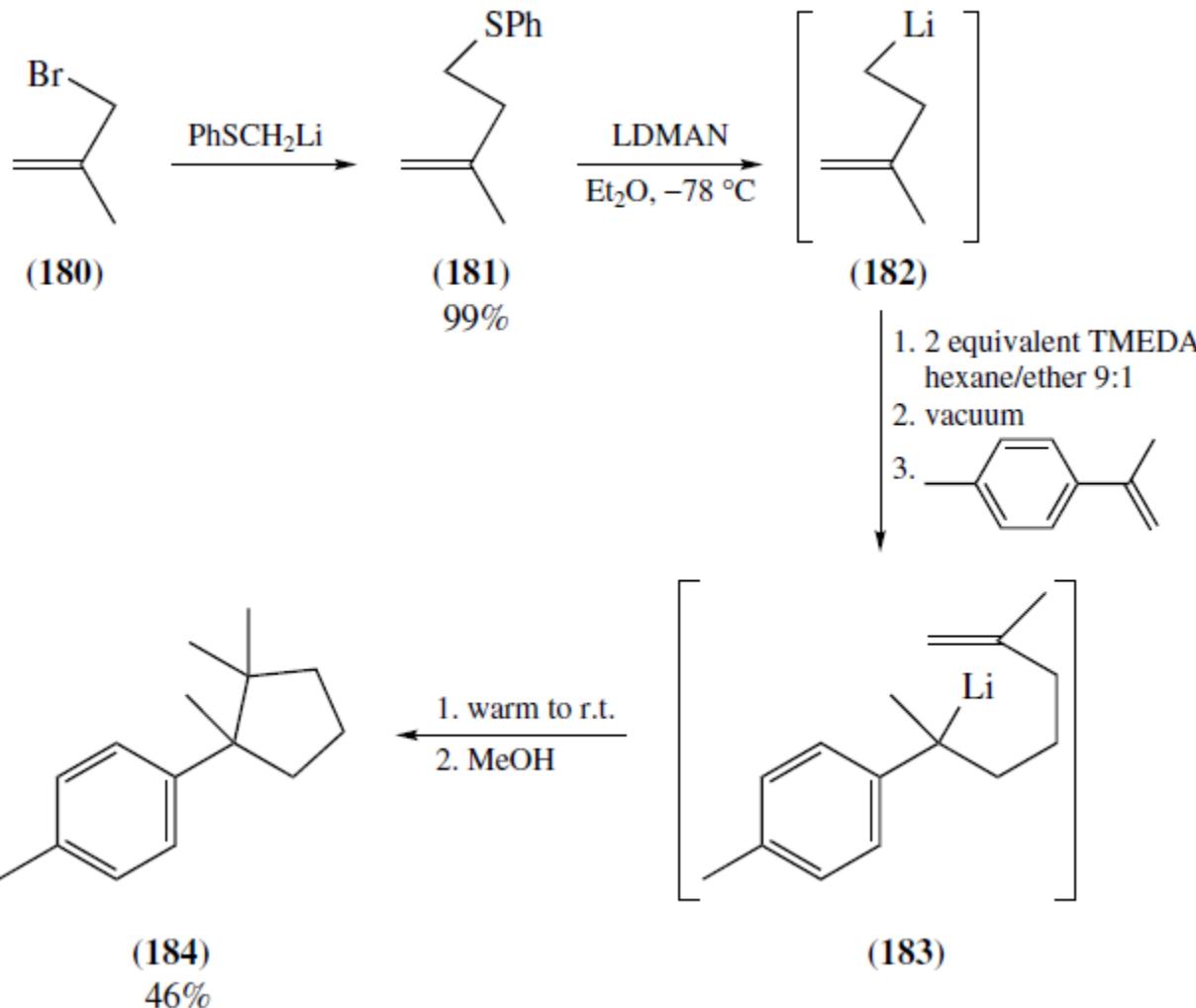
W. F. Bailey and T. V. Ovaska, *J. Am. Chem. Soc.* **1993**, 115, 3080

Unique Advantages



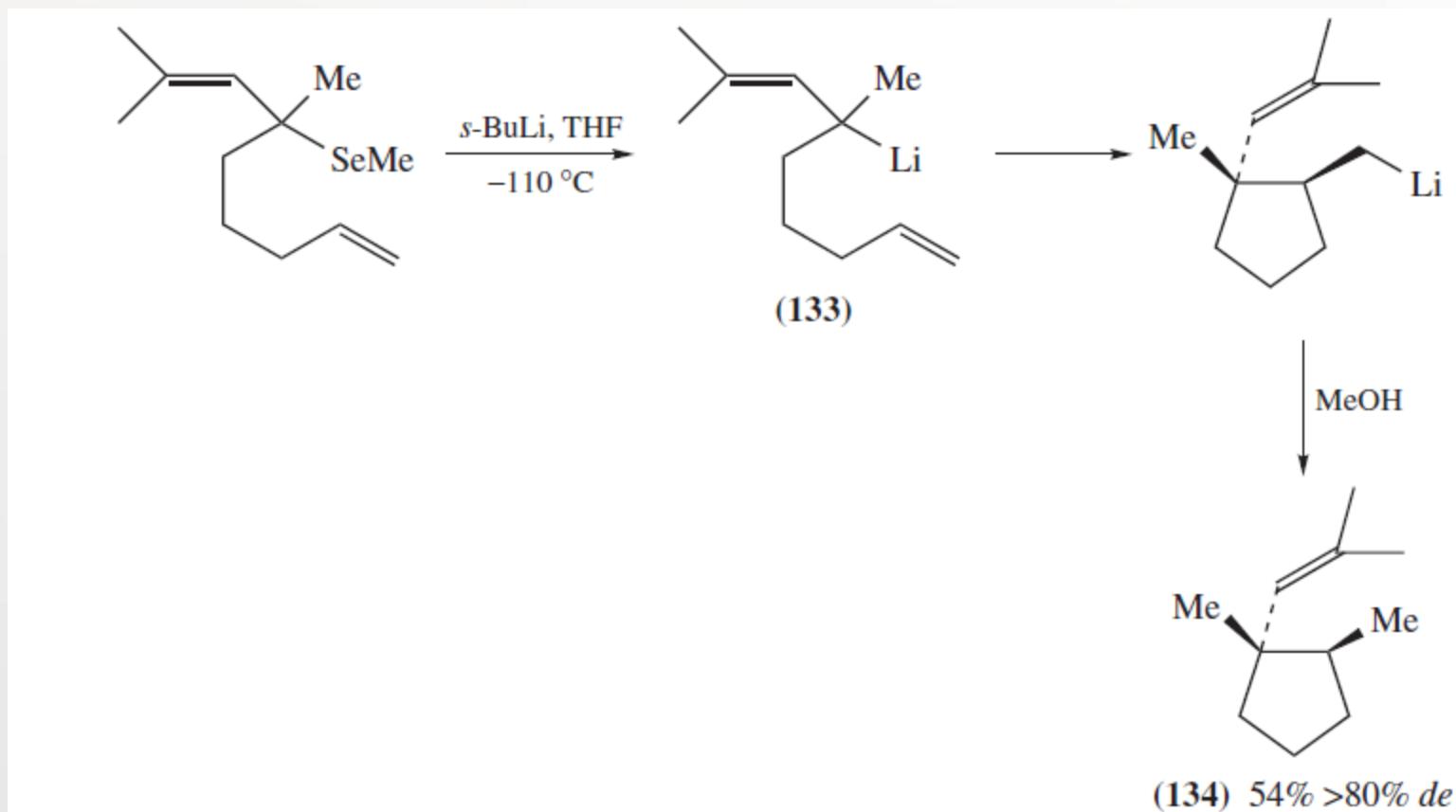
W. F. Bailey and A. D. Khanolkar, *Tetrahedron*, 1991, 47, 7727 .

Unique Advantages



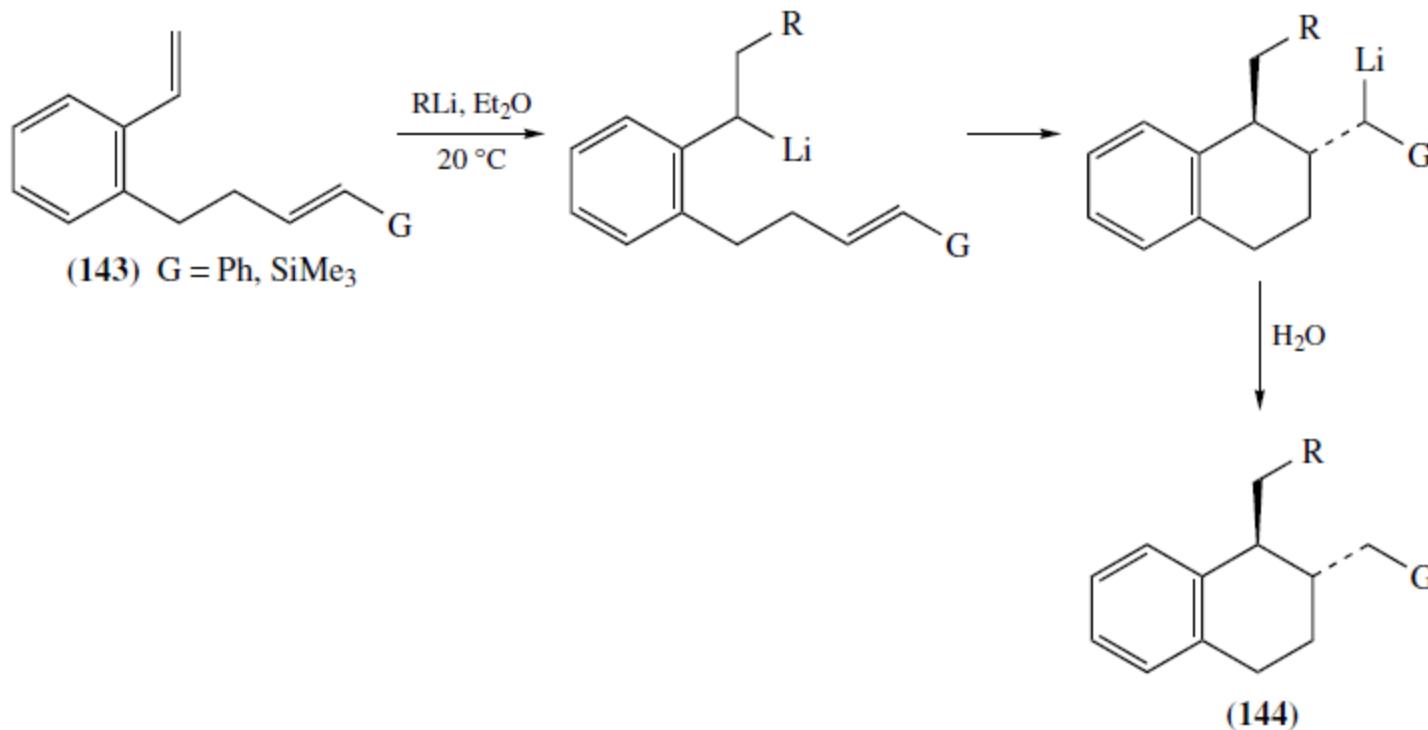
A. Krief and P. Barbeaux, *Synlett*, **1990**, 511 .

Unique Advantages



A. Krief, D. Derouane and W. Dumont, *Synlett*, **1992**, 907.

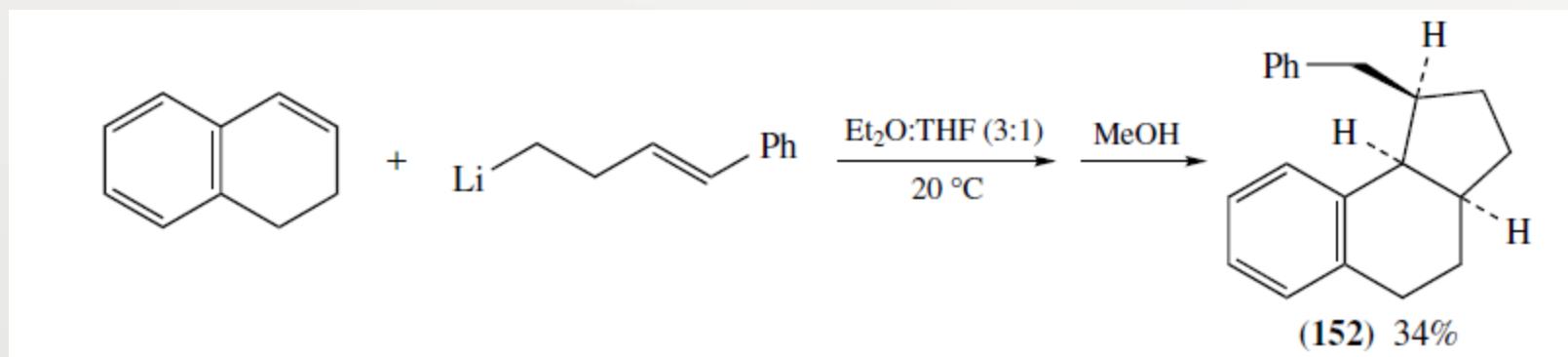
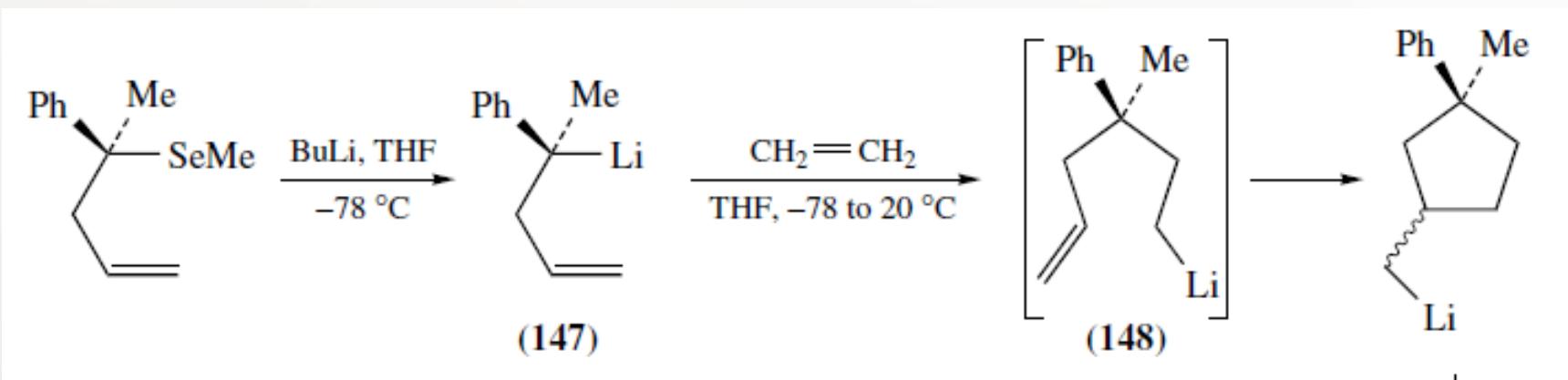
Intermolecular Reaction with Alkene



R	G	Yield (%)
Bu	Ph	71 (<i>trans/cis</i> = 2.2:1)
Bu	SiMe ₃	75
Hex	SiMe ₃	71

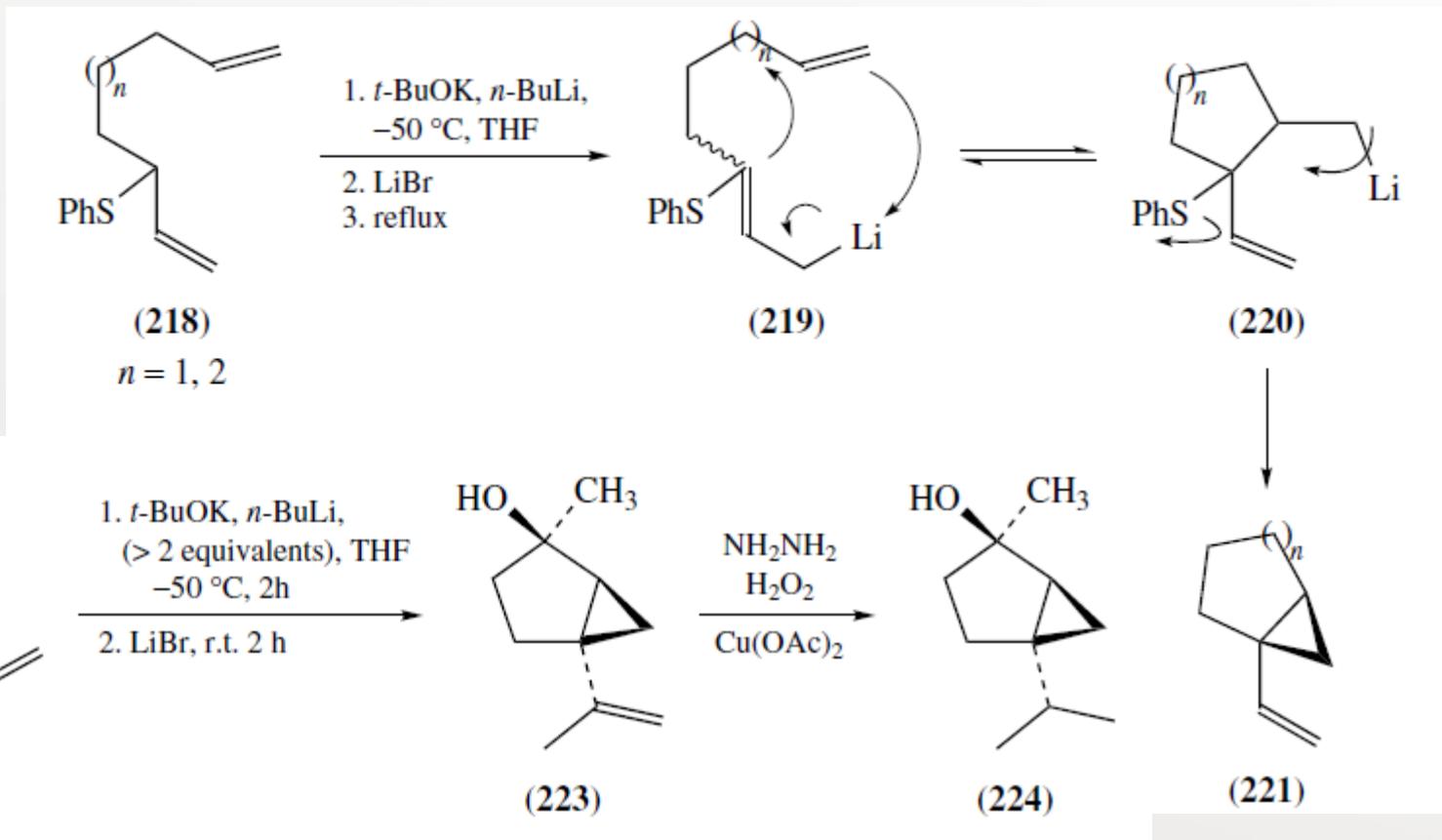
X. Wei and R. J. K. Taylor, *Tetrahedron Lett.*, 1997, 38, 6467.

Intermolecular Reaction with Alkene



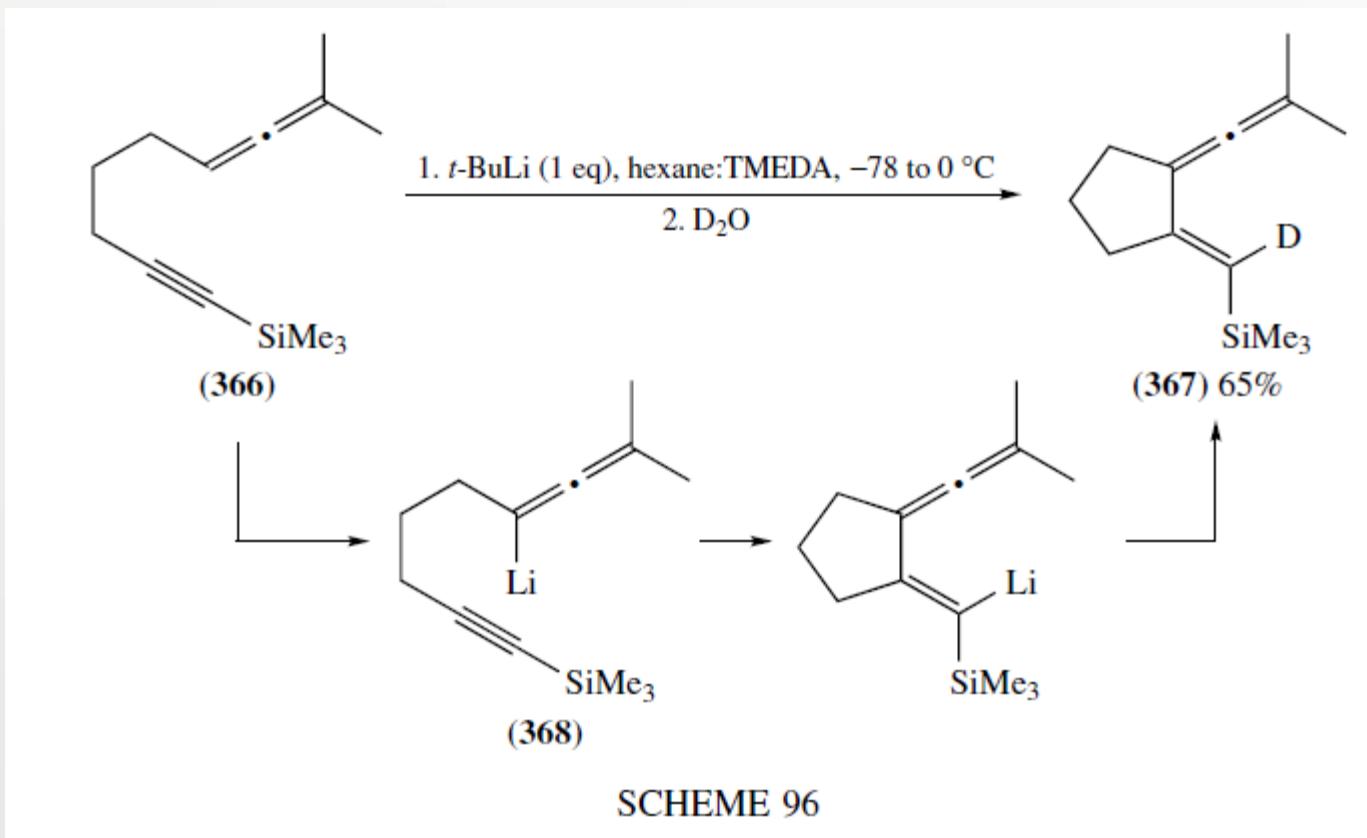
A. Krief and P. Barbeaux, *Synlett*, **1990**, 511.

Allylic C-H Functionalization



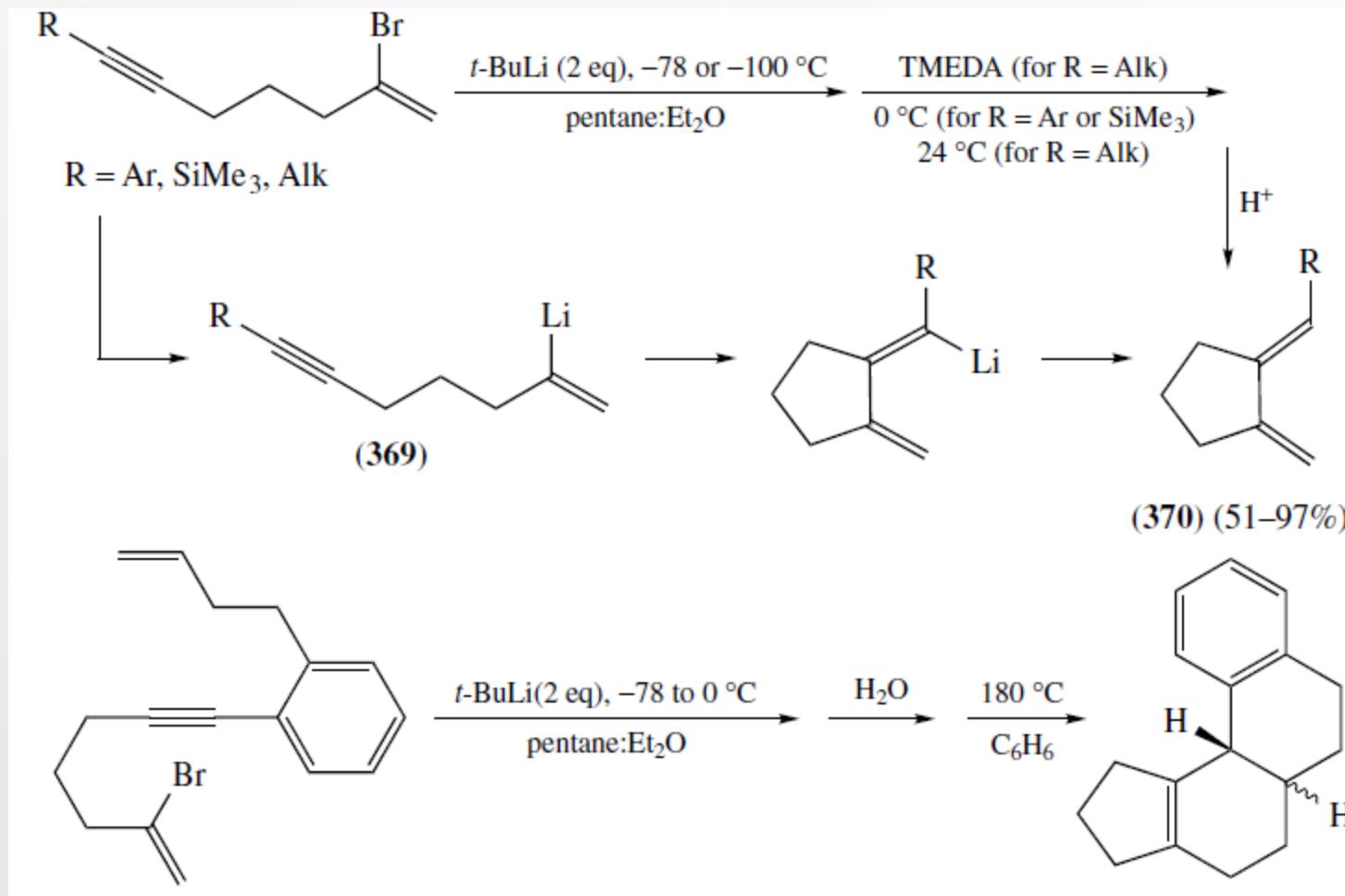
S. J. Lange, J. W. Sibert, C. L. Stern, A. G. M. Barret and B. M. Hoffmann, *Tetrahedron*, 1990, 51 8175

Directly deprotonation with Allene



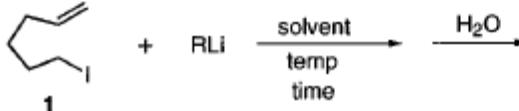
G. Wu, F. E. Cederbaum and E. Negishi, *Tetrahedron Lett.*, **1990**, 31, 493.

Lithium type Enyne metathesis

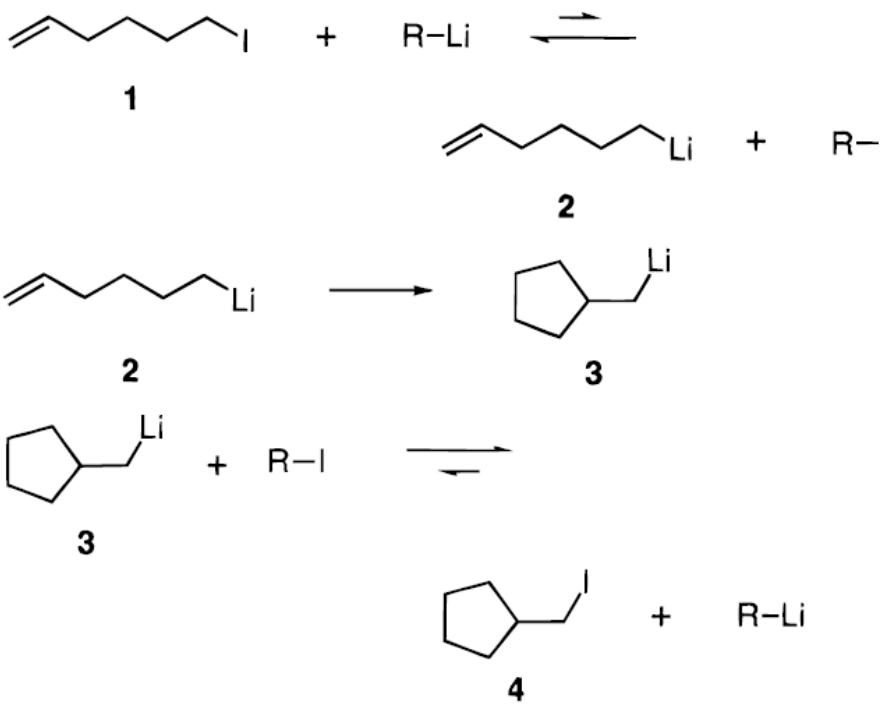
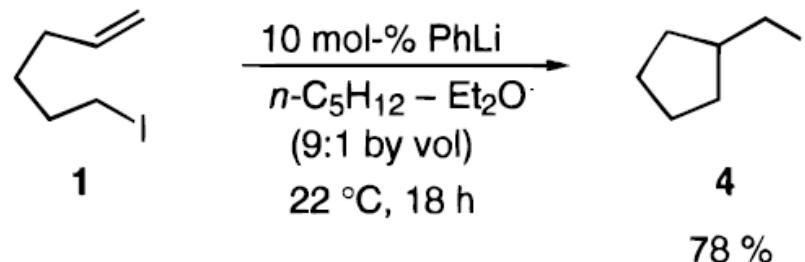


W. F. Bailey, N. M. Wachter-Jurcsak, M. R. Pineau, T. V. Ovaska, R. R. Warren and C. E. Lewis,
J. Org. Chem., 1996, 61, 8216.

Lithium catalyzed Atom Transfer

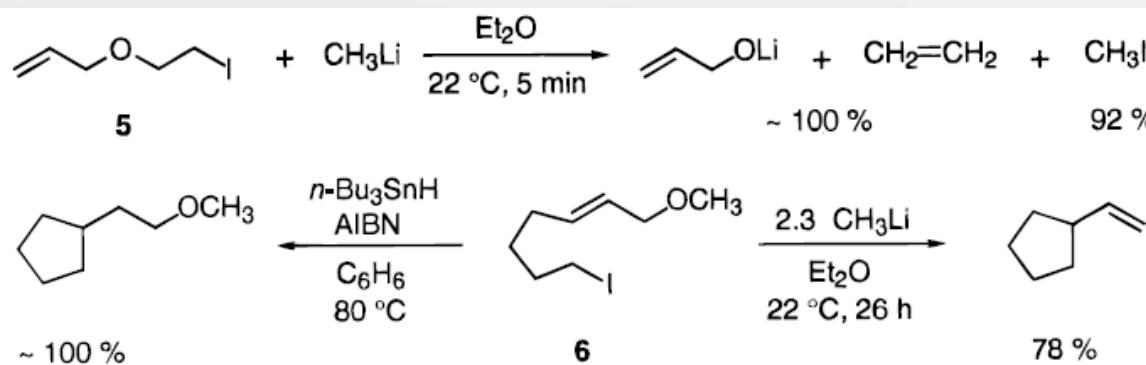
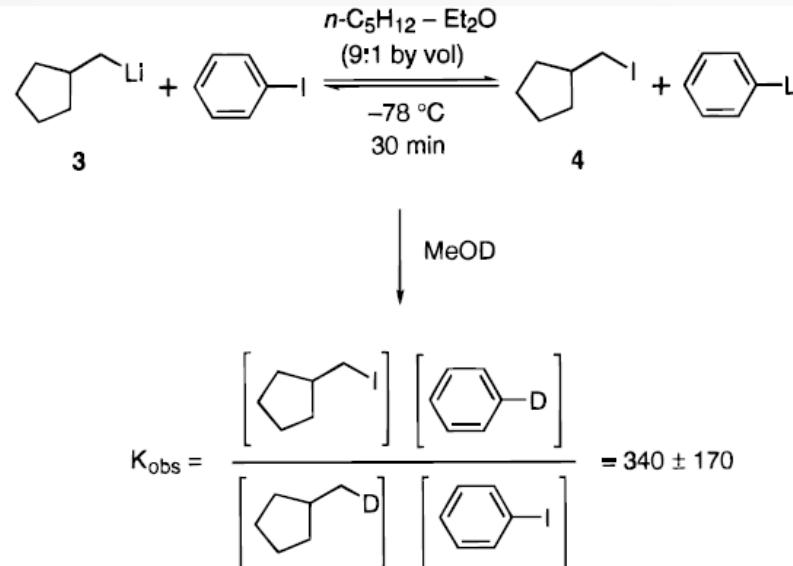
				products, % yield ^b					
entry	RLi	solvent	temp, °C	time, h					dimers ^c
1	MeLi	Et ₂ O	22	21	22	3	5	60	3
2		Et ₂ O	35	3.5	15	2	14	62	3
3		MTBE	55	0.25	7	2	13	67	9
4		<i>n</i> -C ₅ H ₁₂ – TMEDA ^d	22	0.5	5	1	20	53	8
5		THF	22	0.25	16	2			62 ^e
6	PhLi	Et ₂ O	22	24	54	2	13	34	2
7		<i>n</i> -C ₅ H ₁₂ – Et ₂ O (9:1 by vol)	22	4	2	1	1	87	2
8		<i>n</i> -C ₅ H ₁₂ – Et ₂ O (50:1 by vol)	22	10	4	1	2	86	1
9		<i>n</i> -C ₅ H ₁₂ – Et ₂ O (9:1 by vol) ^f	22	50	9	1	4	86	
10		c-C ₆ H ₁₂ – MTBE (9:1 by vol) ^f	50	0.5	11		34	55	
11		c-C ₆ H ₁₂ – MTBE (9:1 by vol) ^f	50	2	12		12	75	

Lithium catalyzed Atom Transfer



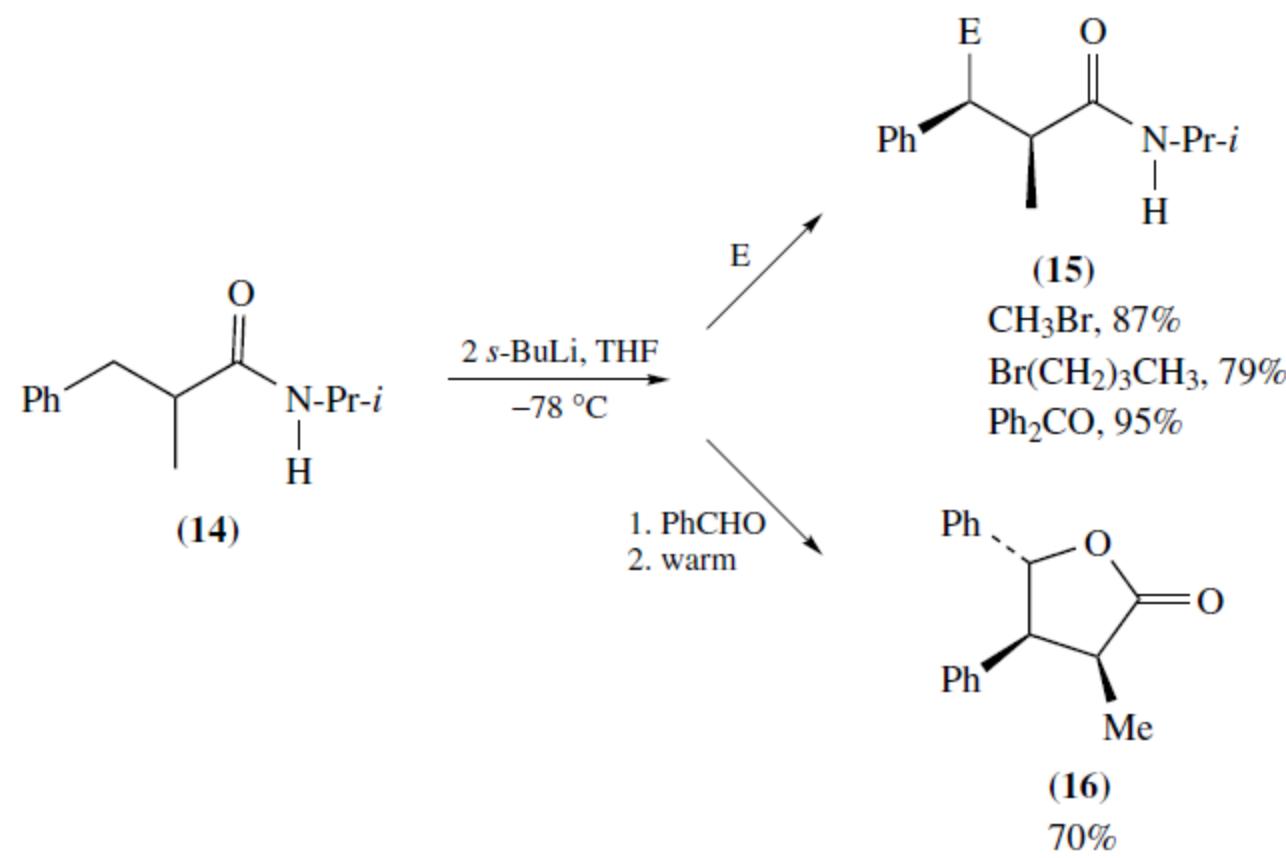
Bailey, W. F.; Carson, M. W. *J. Org. Chem.* **1998**, *63*, 361.

Lithium catalyzed Atom Transfer



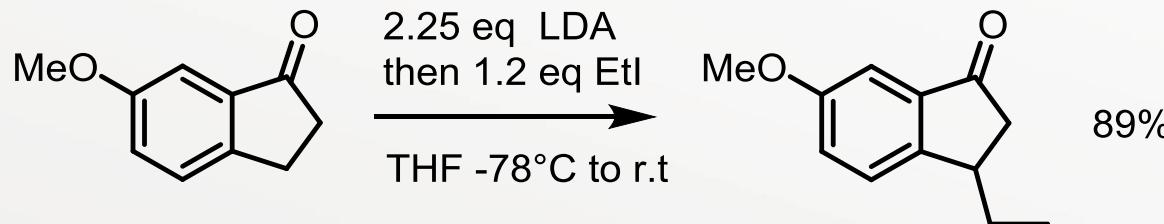
Bailey, W. F.; Carson, M. W. *J. Org. Chem.* **1998**, *63*, 361.

β -alkylation of amide

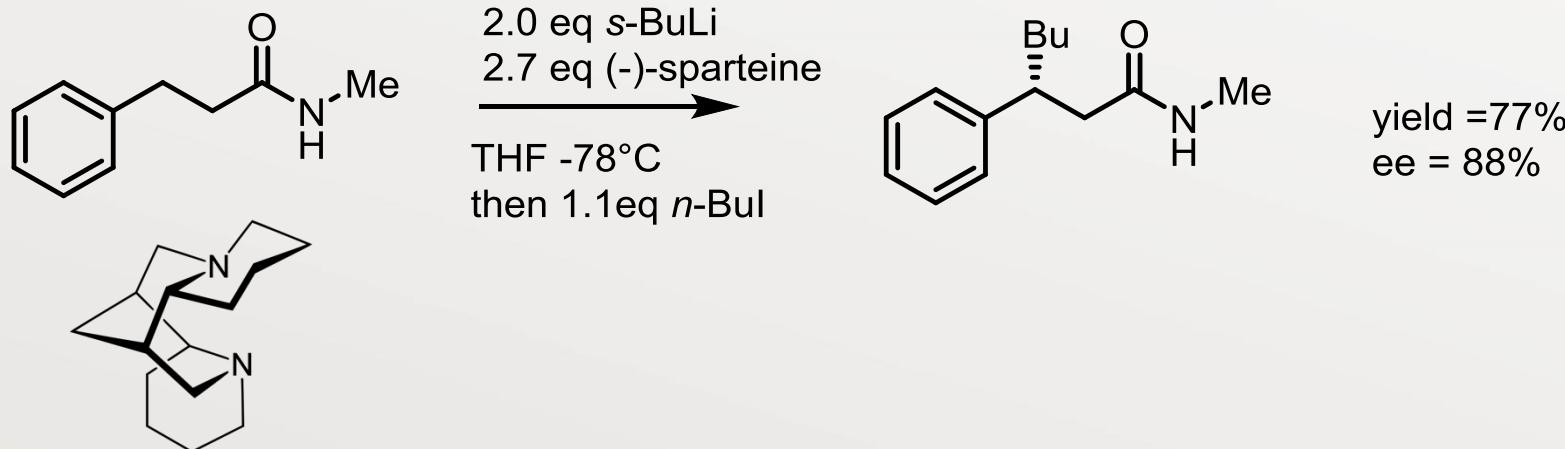


Lutz, G. P.; Wallin, A. P.; Kerrick, S. T.; Beak, P. *J. Org. Chem.* **1991**, *56*, 493

β -alkylation of ketone

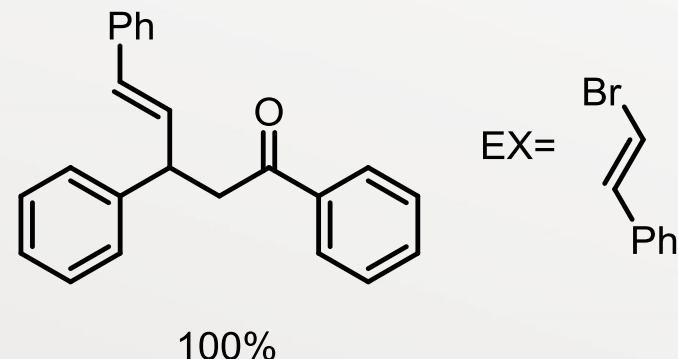
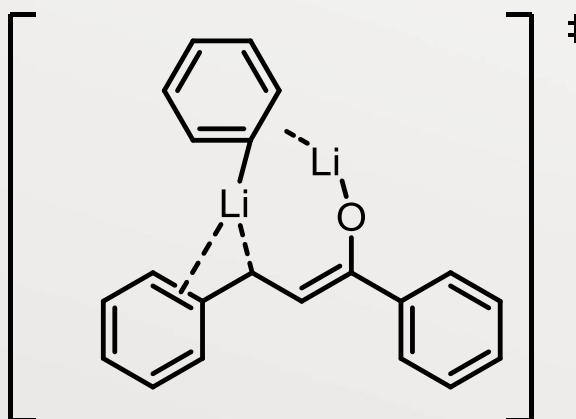
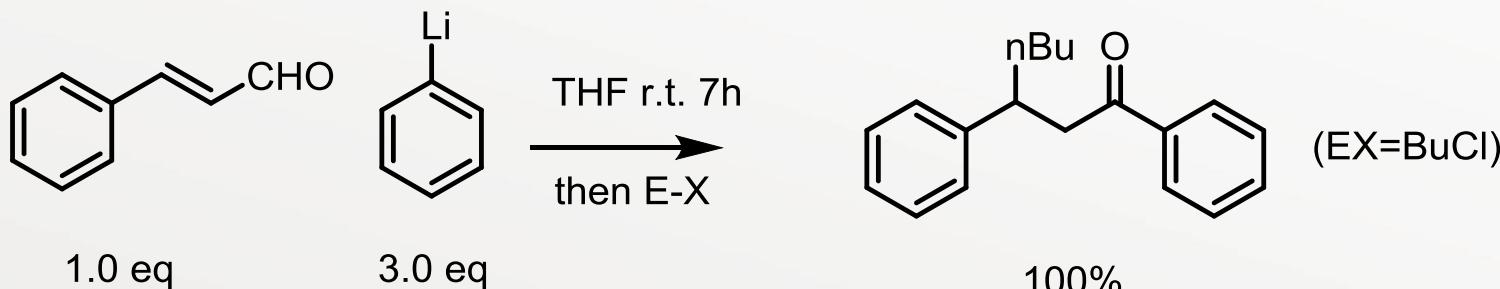


Trost, B. M.; Latimer, L. H. *J. Org. Chem.* **1977**, *42*, 3212.



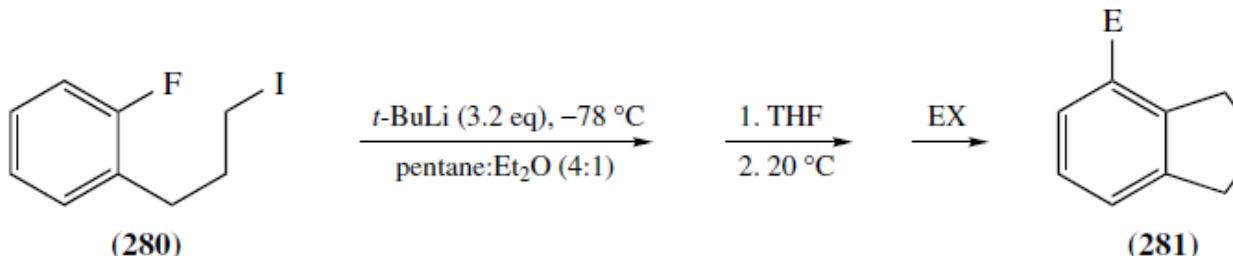
Gallagher, D. J.; Du, H.; Long, S. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 11391.

β -alkylation of ketone

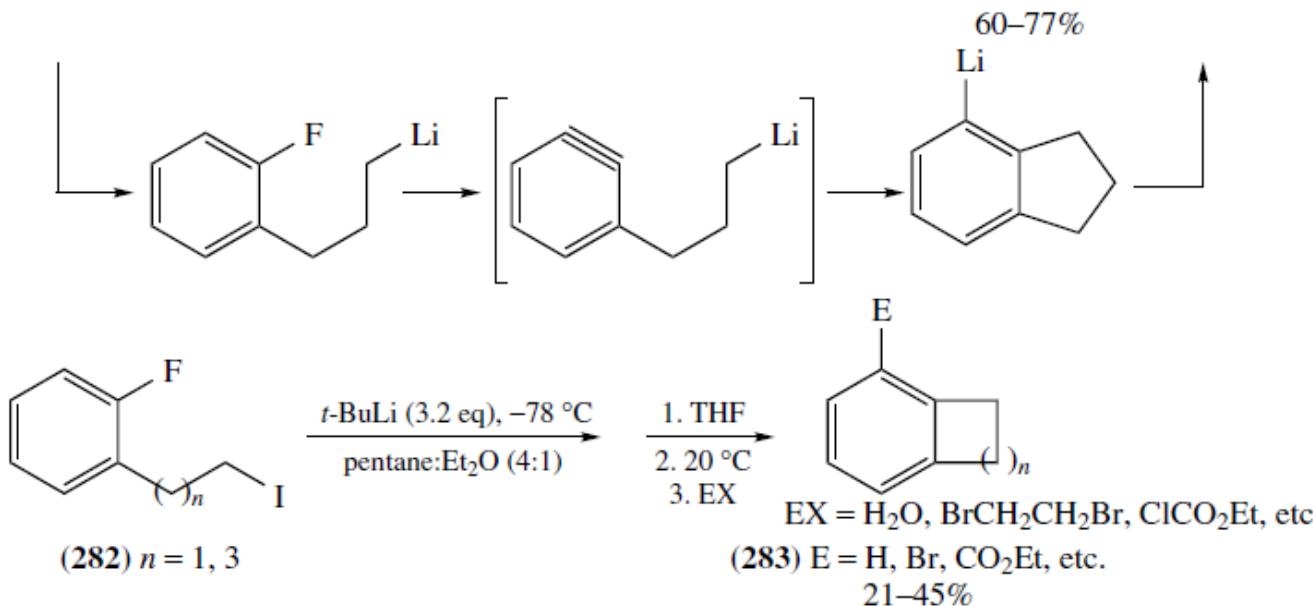


Nudelman, N. S.; García, G. V.; Schulz, H. G. *J. Org. Chem.* **1998**, *63*, 5730.

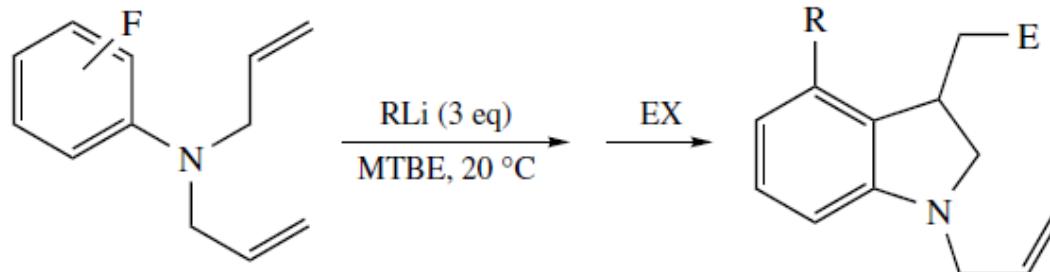
Lithium mediated Catellani Reaction



EX = H₂O, BrCH₂CH₂Br, DMF, etc.
E = H, Br, CHO, etc.

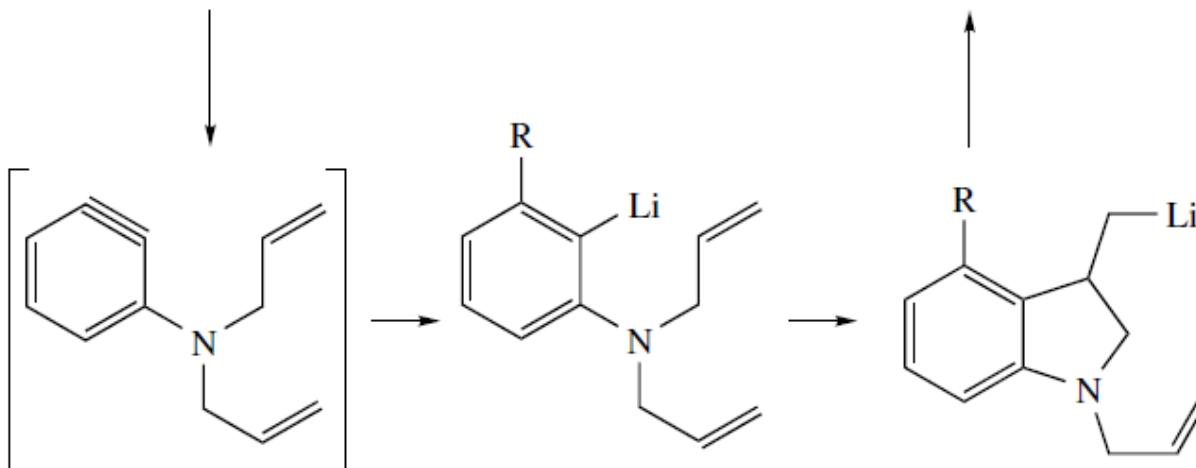


Lithium mediated Catellani Reaction



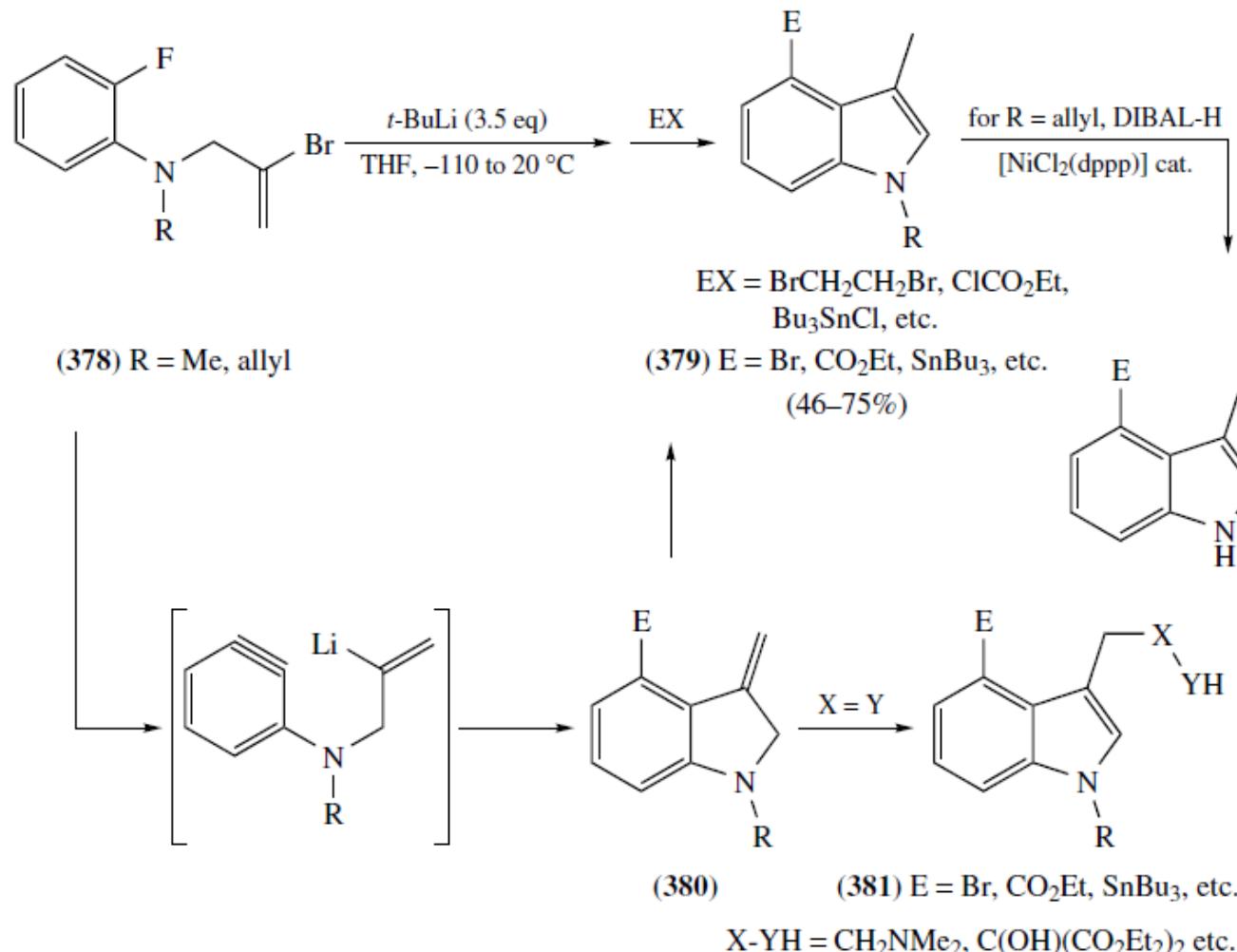
(335)

EX = H₂O, Me₃SiCl
(336) E = H, SiMe₃
R = Bu, Ph, t-Bu
(20–51%)

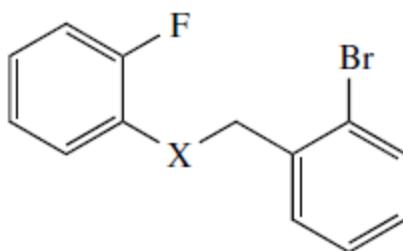


Bailey, W. F.; Longstaff, S. C. *Tetrahedron Lett.* **1999**, *40*, 6899.

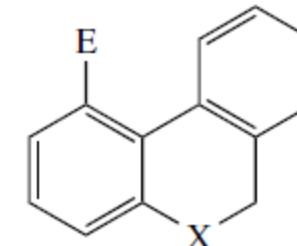
Lithium mediated Catellani Reaction



Lithium mediated Catellani Reaction



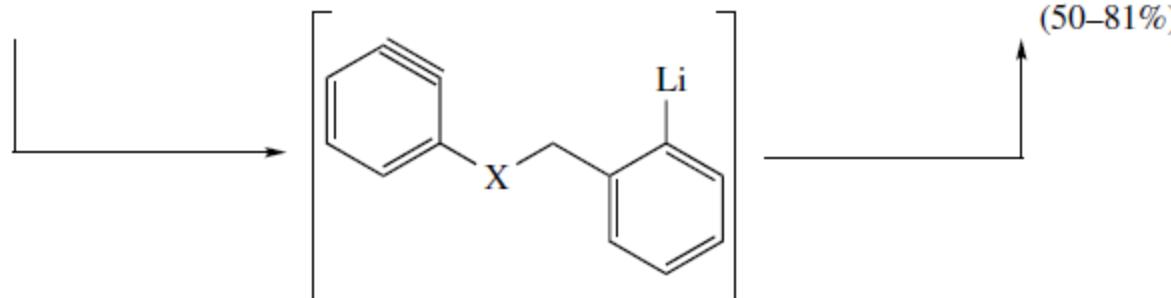
1. *t*-BuLi (3.5 eq), THF, -110 to 20 °C
2. EX



(382) X = NR, O, S

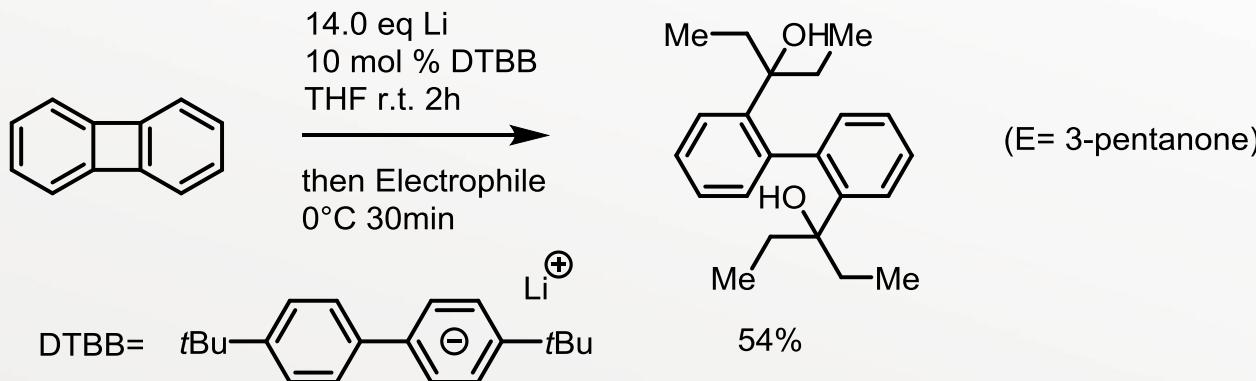
EX = BrCH₂CH₂Br, Bu₃SnCl,
Ph₂S₂, etc.

(383) E = Br, SnBu₃, SPh, etc.

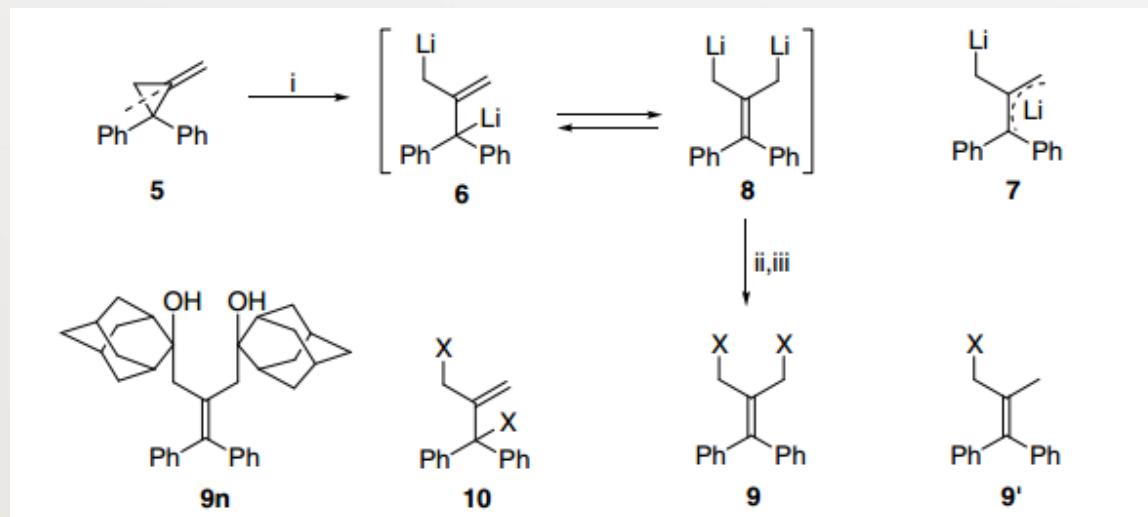


Barluenga, J.; Fañanás, F. J.; Sanz, R.; Fernández, Y. *Chem. Eur. J.* **2002**, 8, 2034.

Lithium mediated C-C activation

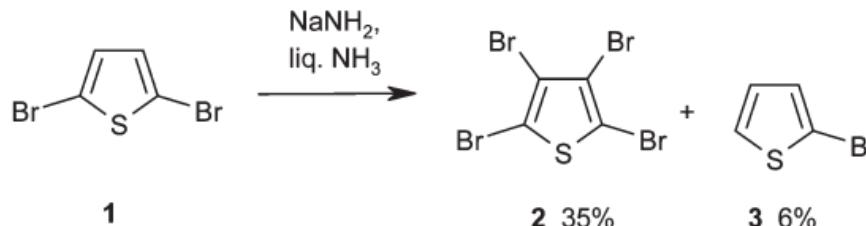


Lillo, V. J.; Gómez, C.; Yus, M. *Tetrahedron Lett.* **2009**, *50*, 2266.



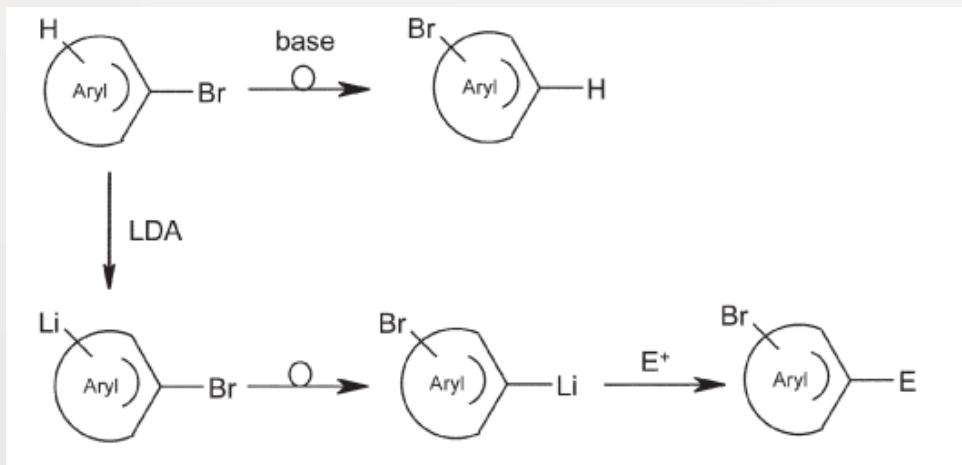
Lillo, V. J.; Gómez, C.; Yus, M. *Tetrahedron Lett.* **2008**, *49*, 5182.

Halogen dance reaction-Discovery



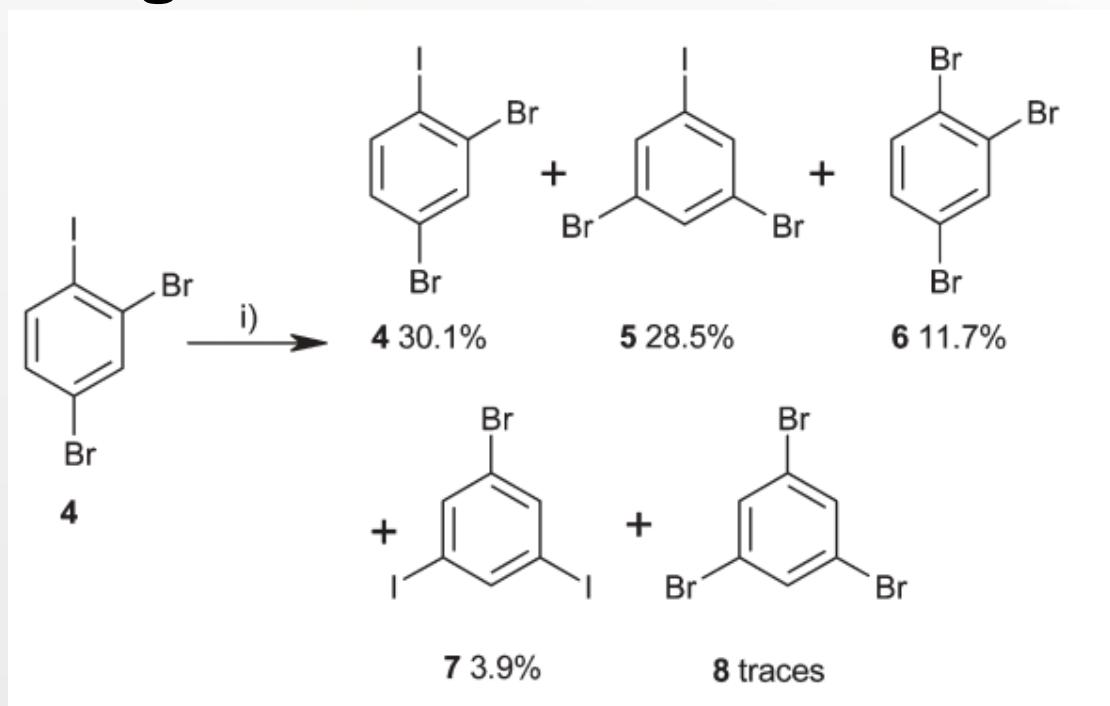
Aryne pathway was ruled out very soon.

A. Vaitiekunas and F. F. Nord, *Nature*, 1951, 168, 875–876



Schnurch, M.; Spina, M.; Khan, A. F.; Mihovilovic, M. D.; Stanetty, P. *Chem. Soc. Rev.* 2007, 36, 1046.

Halogen dance reaction-mechanism

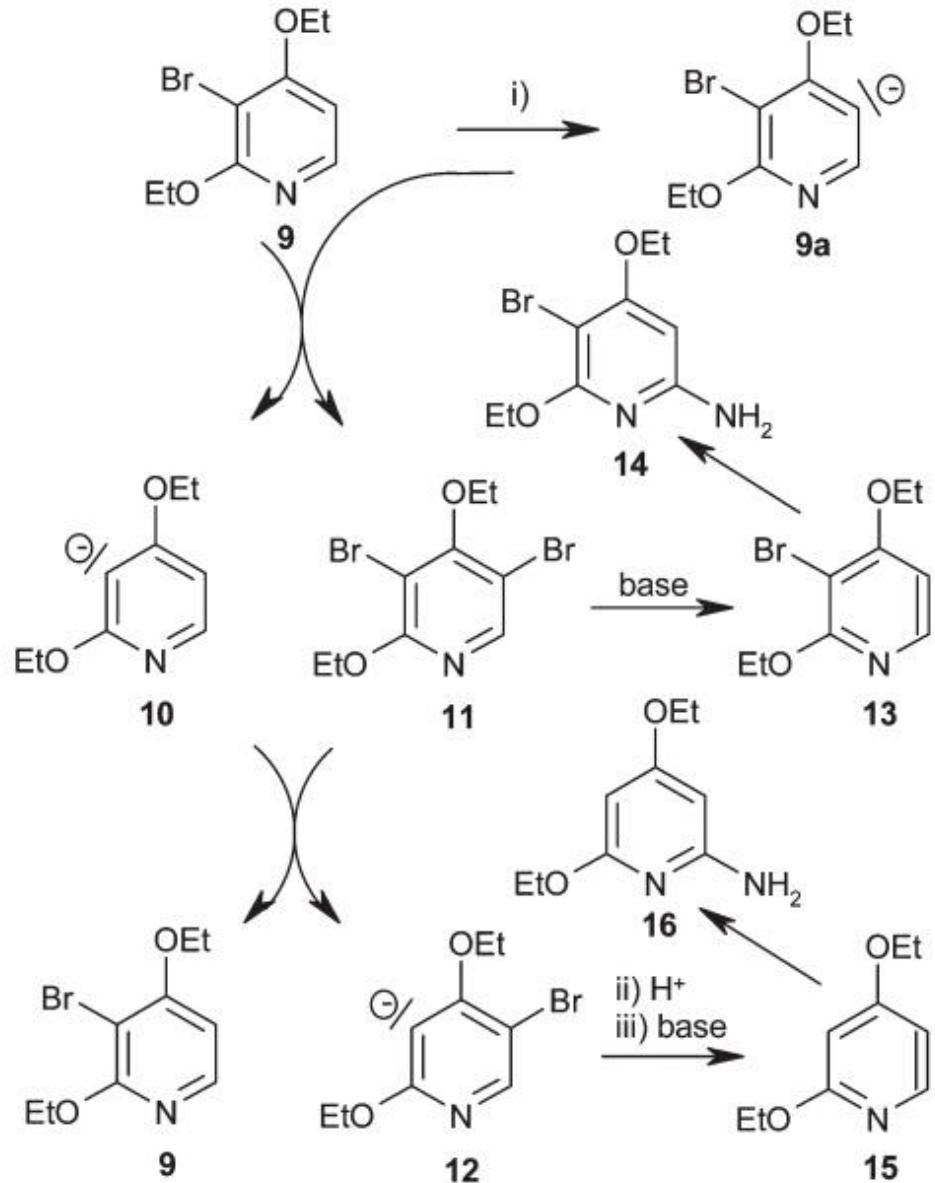


Adding
KBr or KI
Doesn't
Change
Rate or
product
contribution

i) C_6H_5NHK in liq. NH_3 , reflux, 30 min.

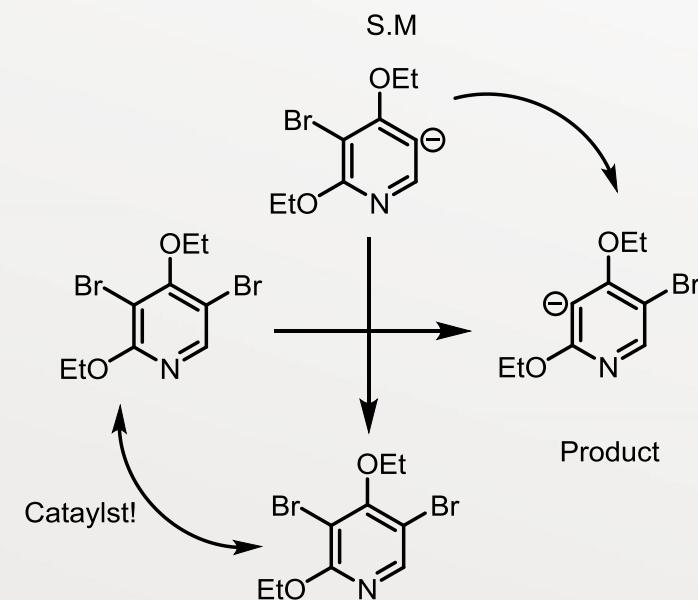
C. E. Moyer, Jr. and J. F. Bennett, *J. Am. Chem. Soc.*, **1963**, 85, 1891–1893.

Halogen dance reaction-mechanism

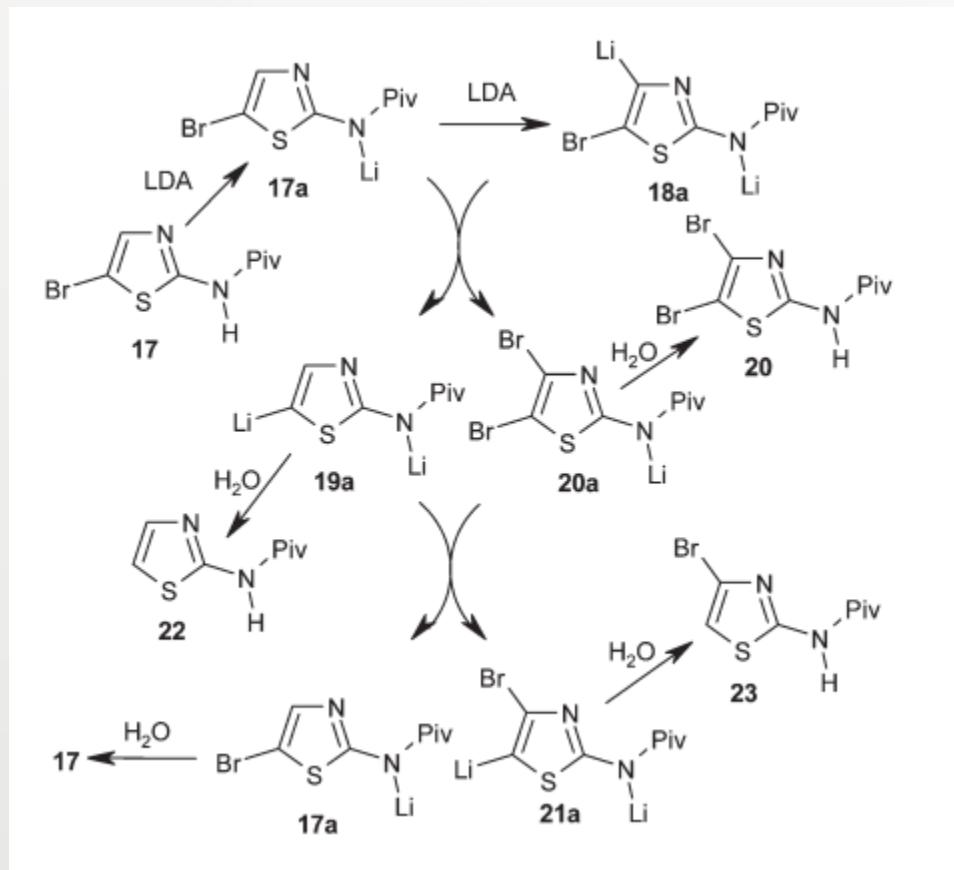


i) $\text{C}_6\text{H}_5\text{NHK}$ in liq. NH_3 , reflux, 30 min.

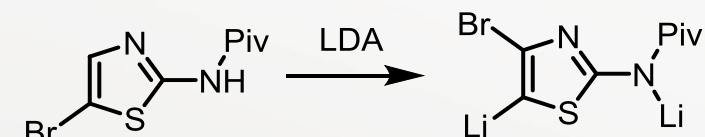
M. J. Pieterse and H. J. den Hertog,
Recl. Trav. Chim. Pays-Bas, 1962, 81,
855–863



Halogen dance reaction-mechanism

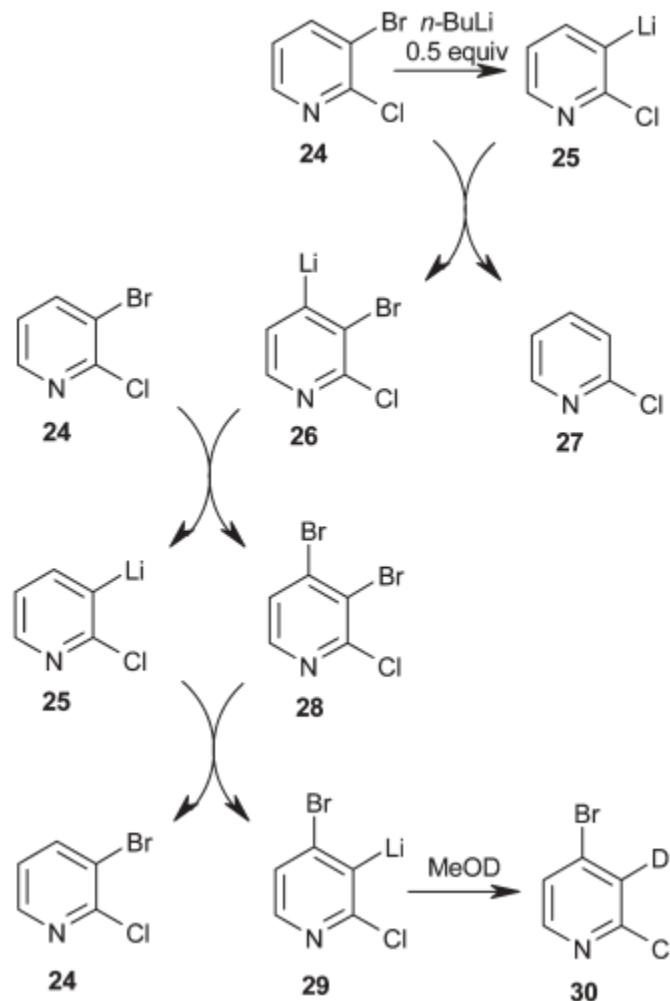


Net reaction:

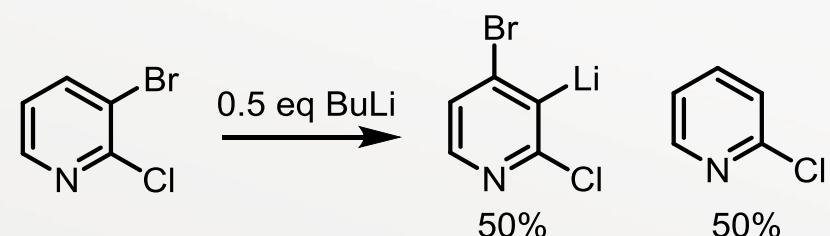


P. Stanetty, M. Schnurch, K. Mereiter and M. D. Mihovilovic, *J. Org. Chem.*, **2005**, 70, 567–574

Halogen dance reaction-mechanism

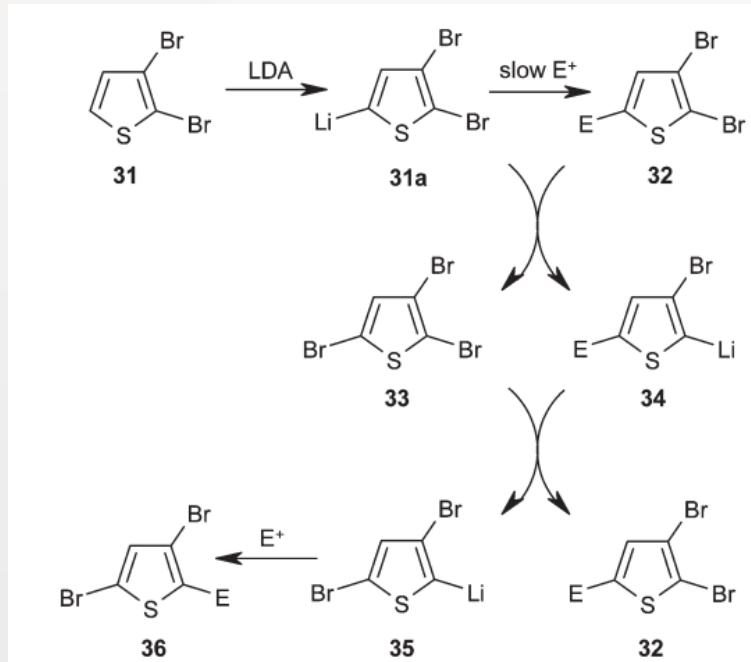


Net reaction:



Due to the Metal halogen exchange
Initiated “catalytic cycle”
The theoretical yield can only
reach 50%

Halogen dance reaction-mechanism



- 1.Excess of Aryl halide is critical
- 2.all the reactions were the Thermodynamics control.
- 3.The possible way to change the Selectivity is the base.

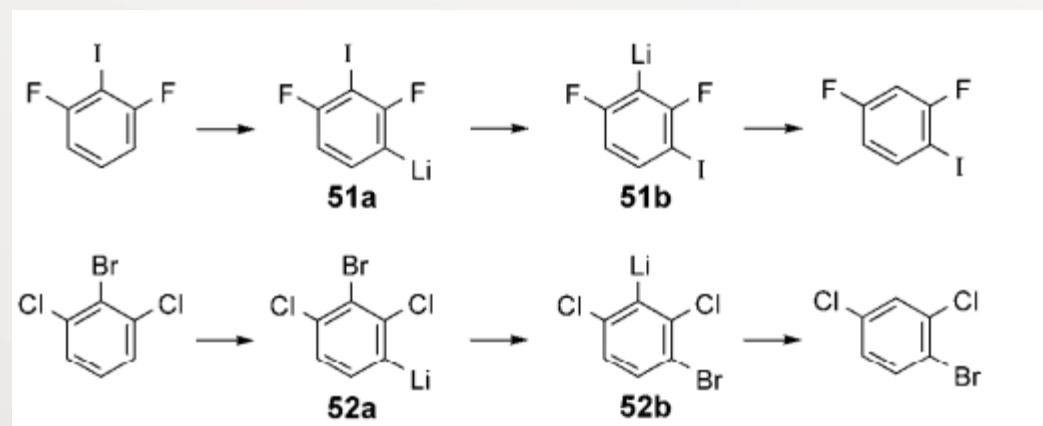
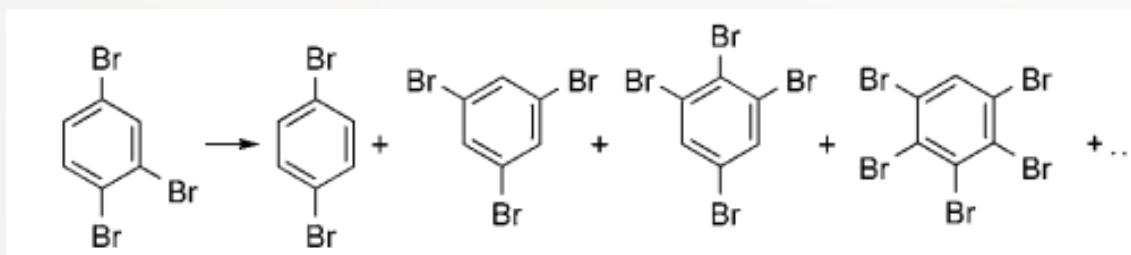
HD Promotion

Low temperatures
No excess of base
Addition of base to the halide
THF
Slow reacting electrophile

HD Prevention

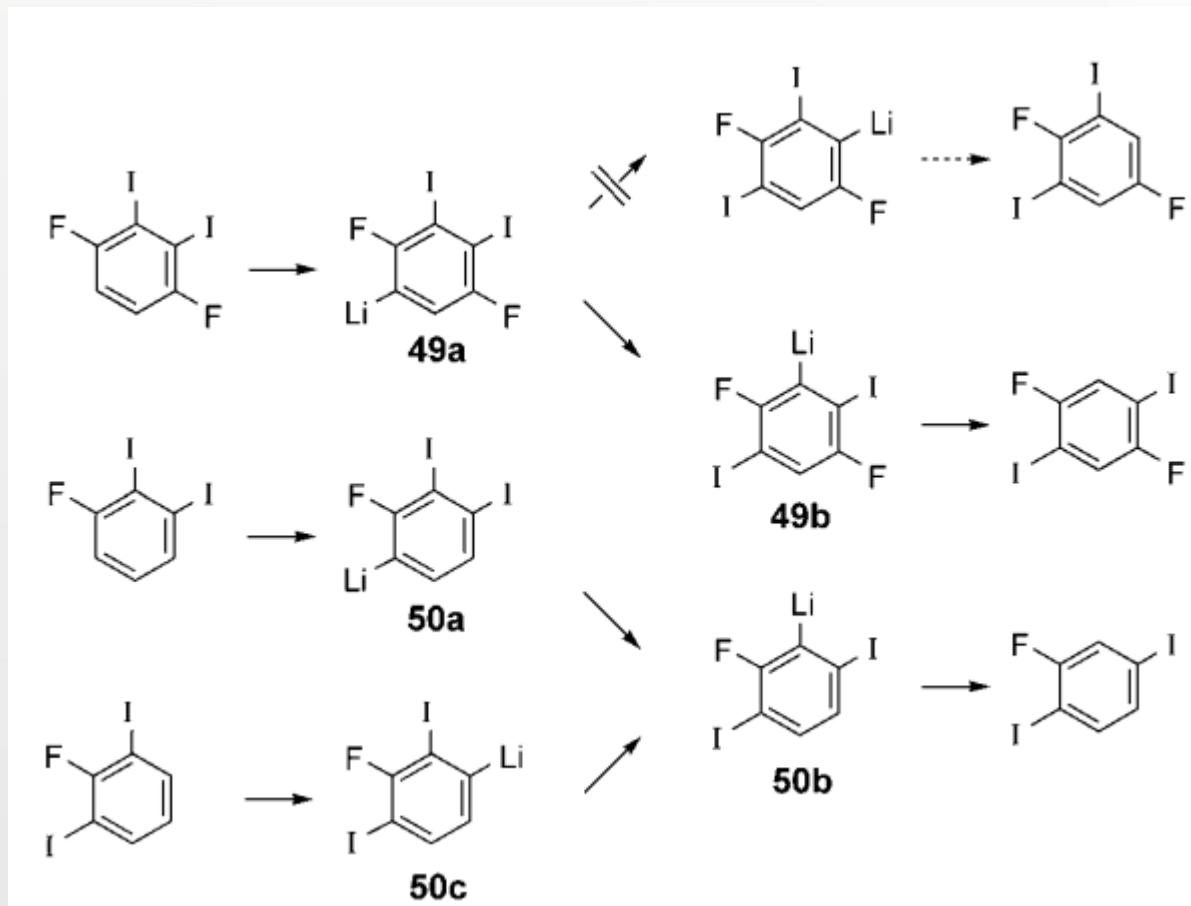
High temperatures
Excess of base
Addition of halide to the base
THP
Fast reacting electrophile

Halogen dance on the Benzene



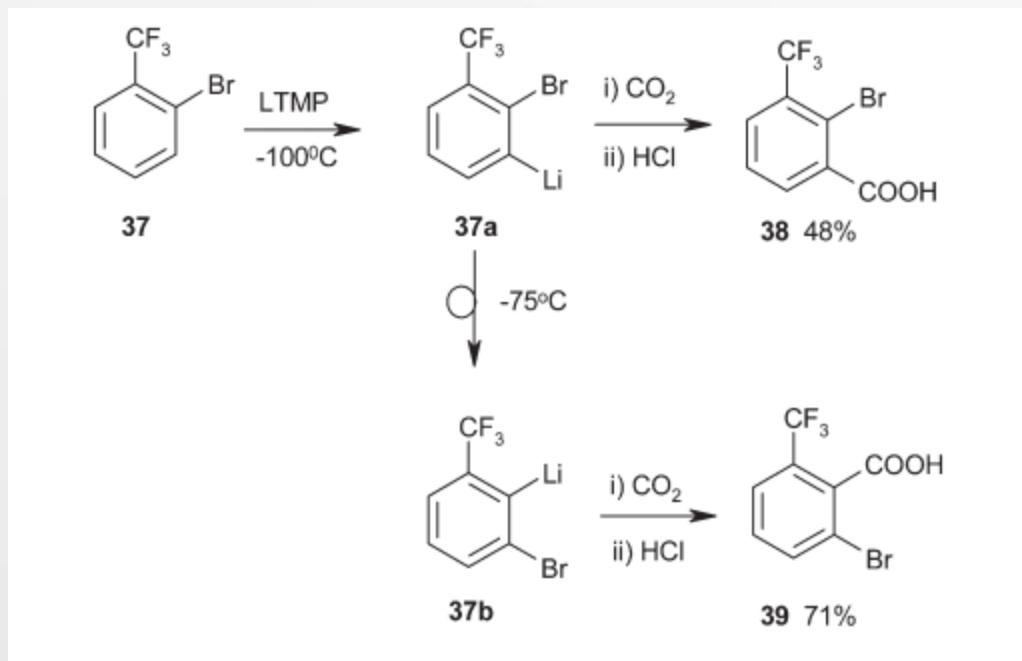
T. Rausis, M. Schlosser, *Eur. J. Org. Chem.* **2002**, 3351 – 4458.

Halogen dance on the Benzene

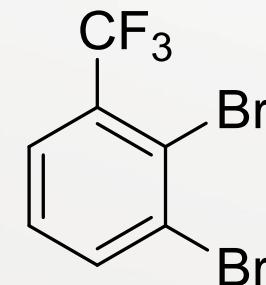


T. Rausis, M. Schlosser, *Eur. J. Org. Chem.* **2002**, 3351 – 4458.

Halogen dance on the Benzene

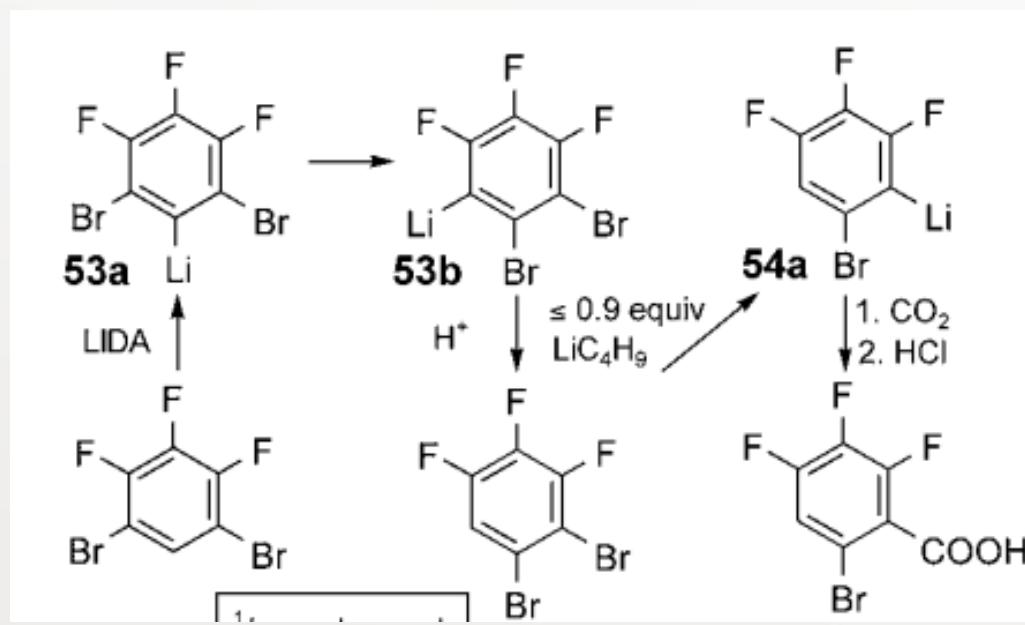


Real catalyst



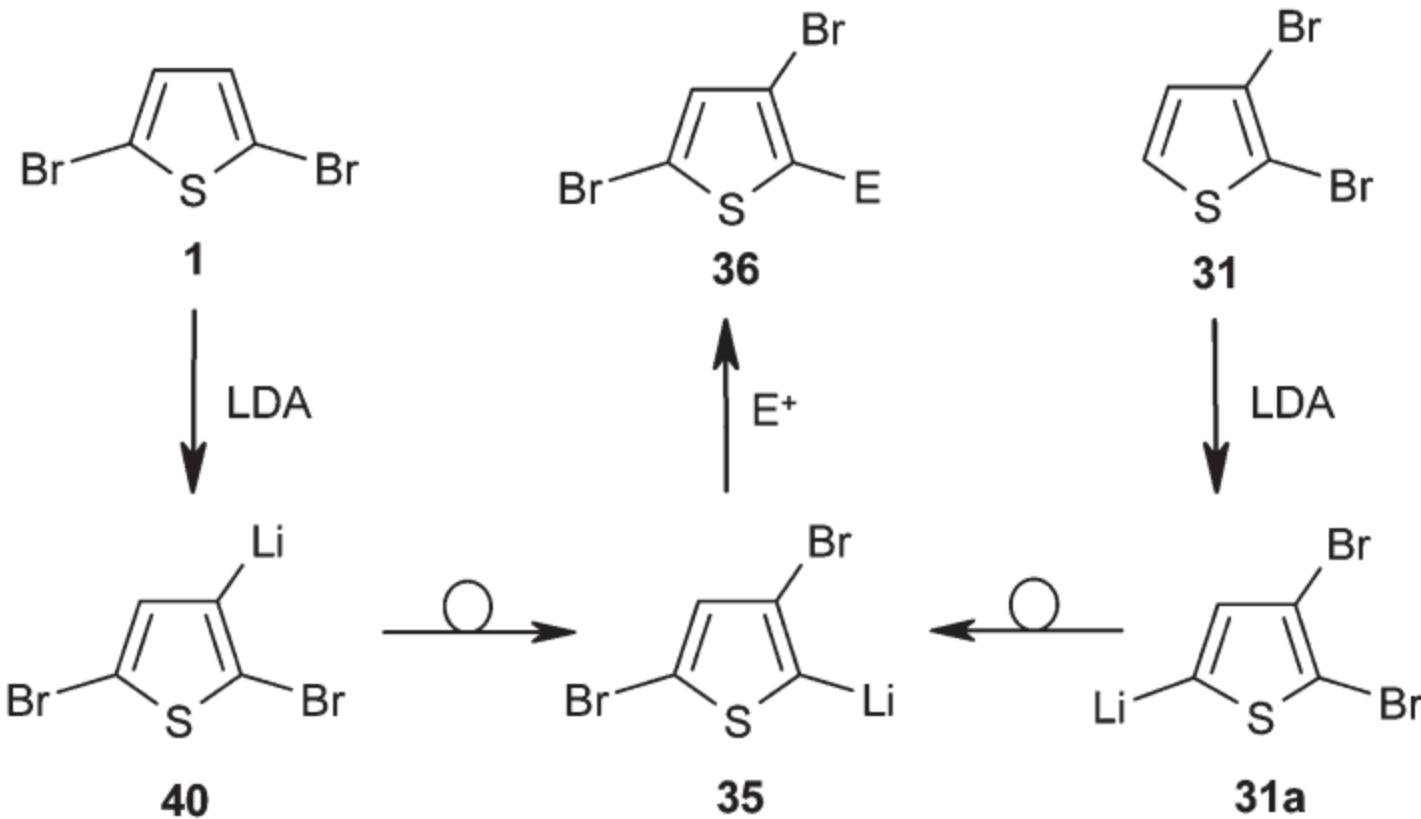
F. Mongin, O. Desponds, M. Schlosser, *Tetrahedron Lett.* **1996**, 37, 2767-2770.

Halogen dance on the Benzene

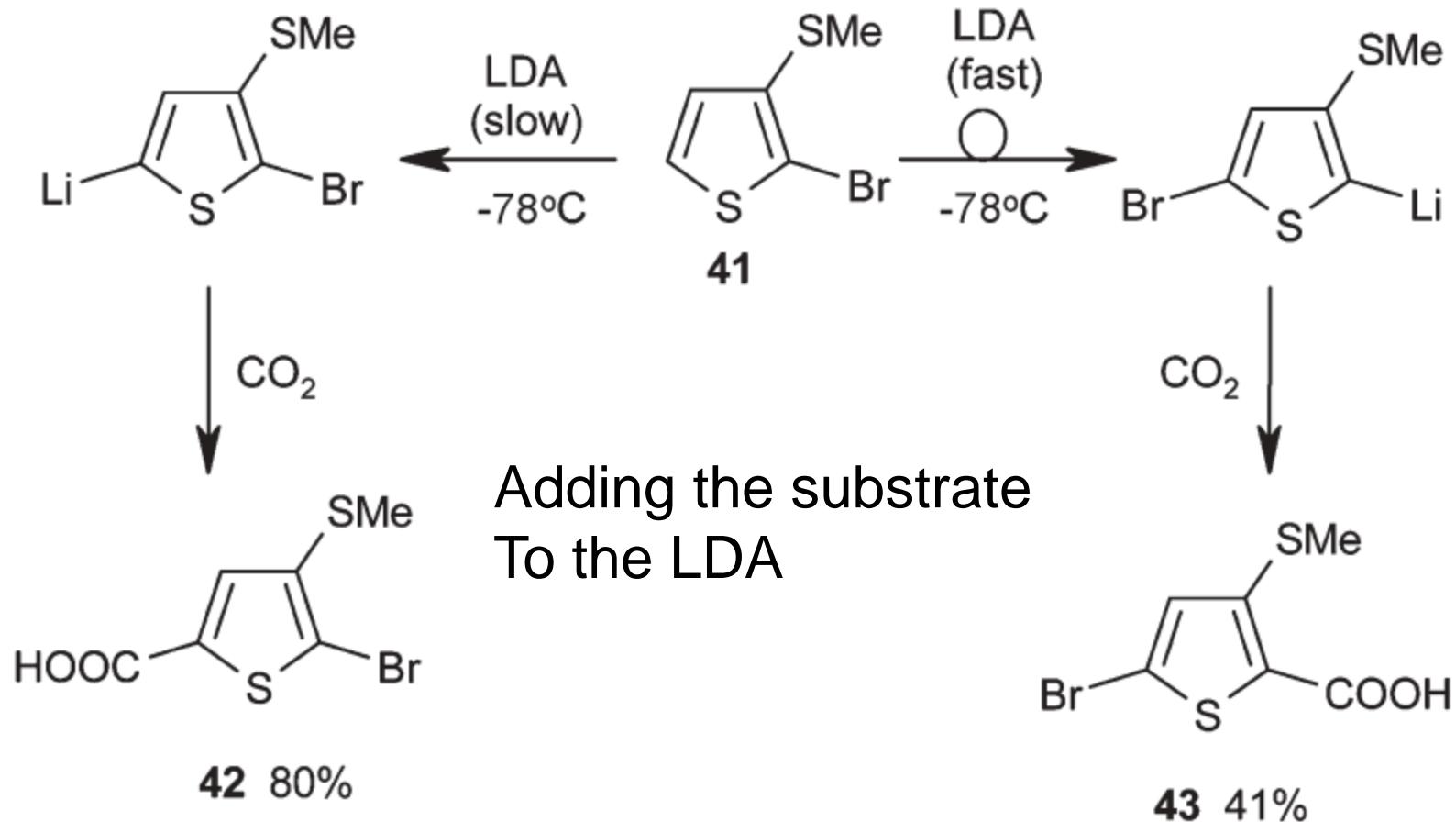


C. Heiss, M. Schlosser, *Eur. J. Org. Chem.* **2003**, 447 – 451

Halogen dance on the Thiophene

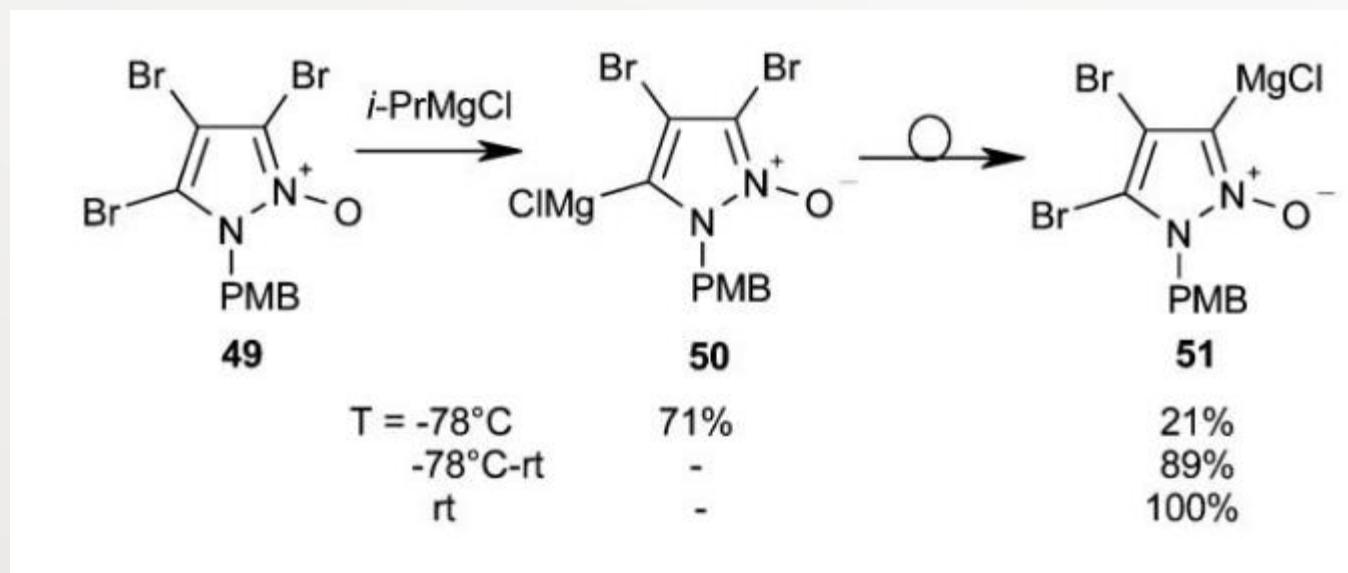


Halogen dance on the Thiophene



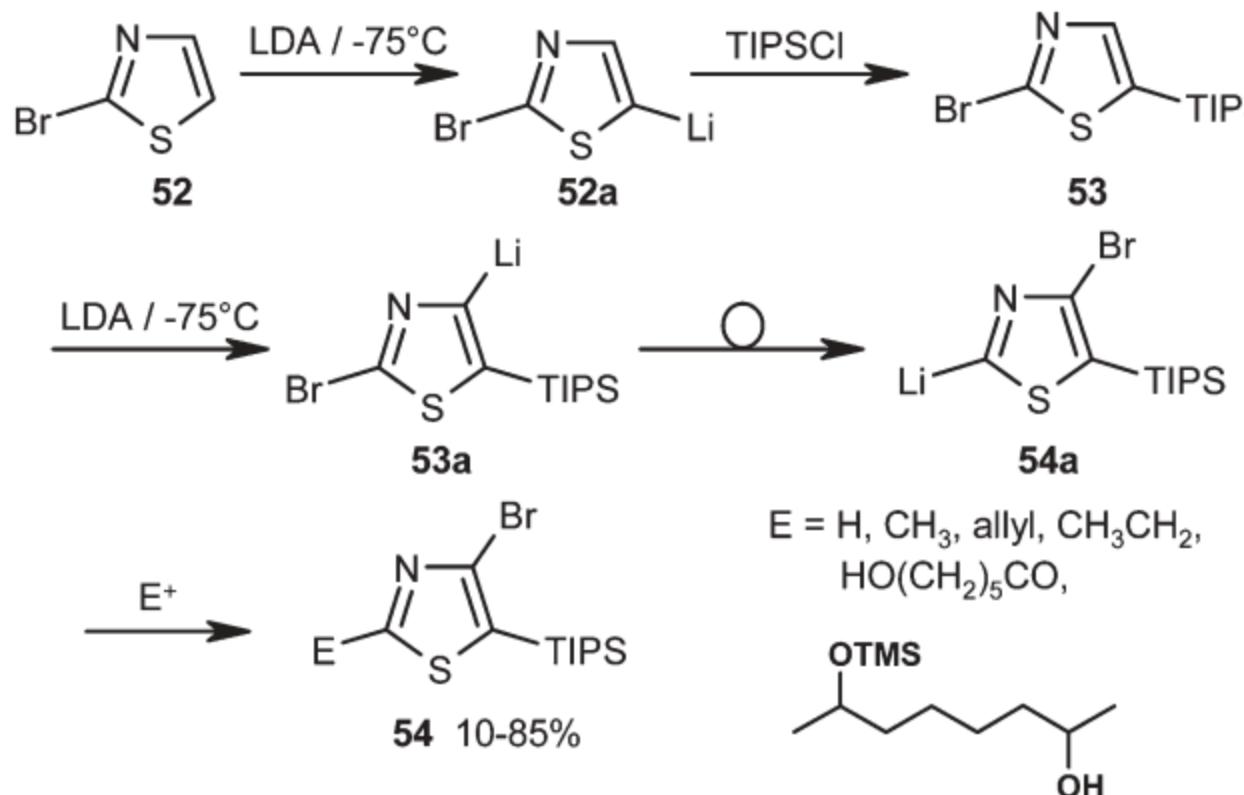
E. C. Taylor and D. E. Vogel, *J. Org. Chem.*, **1985**, 50, 1002–1004.

Halogen dance on the Pyrazole



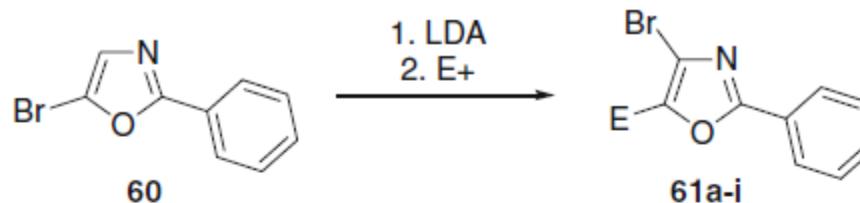
J. Eskildsen, N. Ostergaard, P. Vedso and M. Begtrup, *Tetrahedron*, 2002, 58, 7635–7644.

Halogen dance on the Thiazole



E. L. Stangeland and T. Sammakia, *J. Org. Chem.*, 2004, 69, 2381–2385.

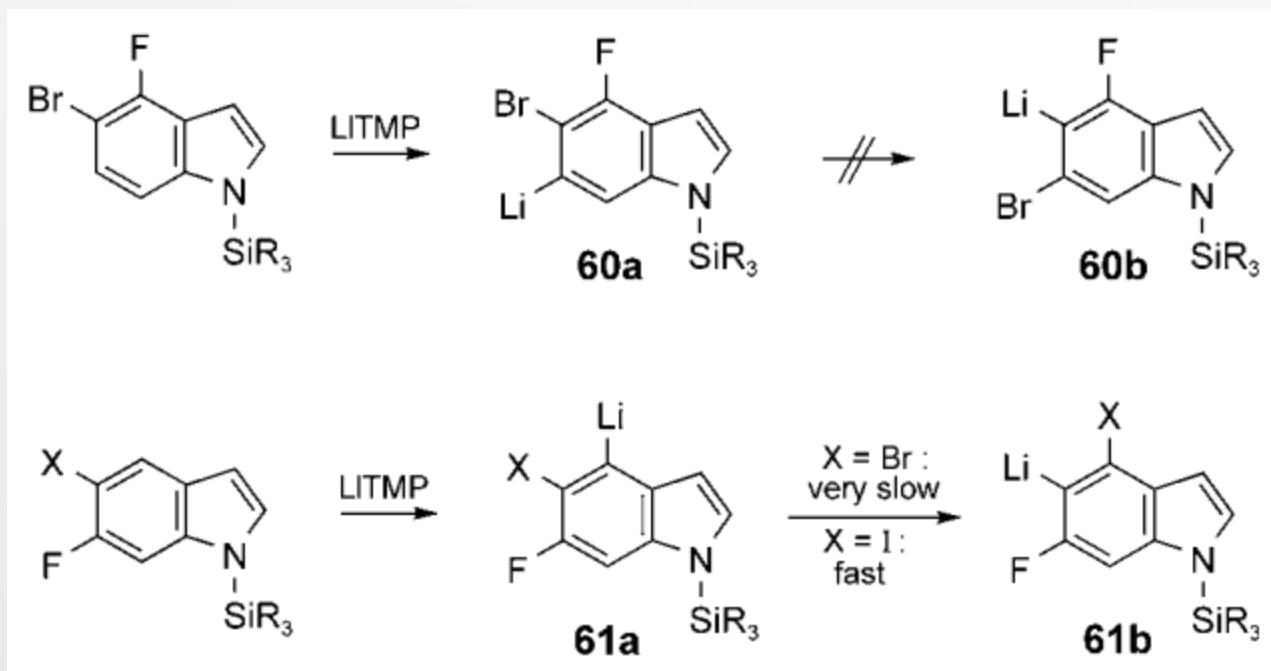
Halogen dance on the Oxazole



Entry	E+	E	Compd	Yield (%)
1	H ₂ O	H	61a	60
2	C ₆ H ₅ CHO	C ₆ H ₅ (OH)	61b	78
3	TMSCl	TMS	61c	68
4	C ₂ Cl ₆	Cl	61d	68
5	Br ₂	Br	61e	30
6	BrCH ₂ CH ₂ Br	Br	61e	11
7	C ₂ Br ₂ Cl ₄	Br	61e	76
8	I ₂	I	61f	66
9	DMF	CHO	61g	58
10	CO ₂	COOH	61h	63
11	Cyclohexanone	C ₆ H ₁₀ OH	61i	69

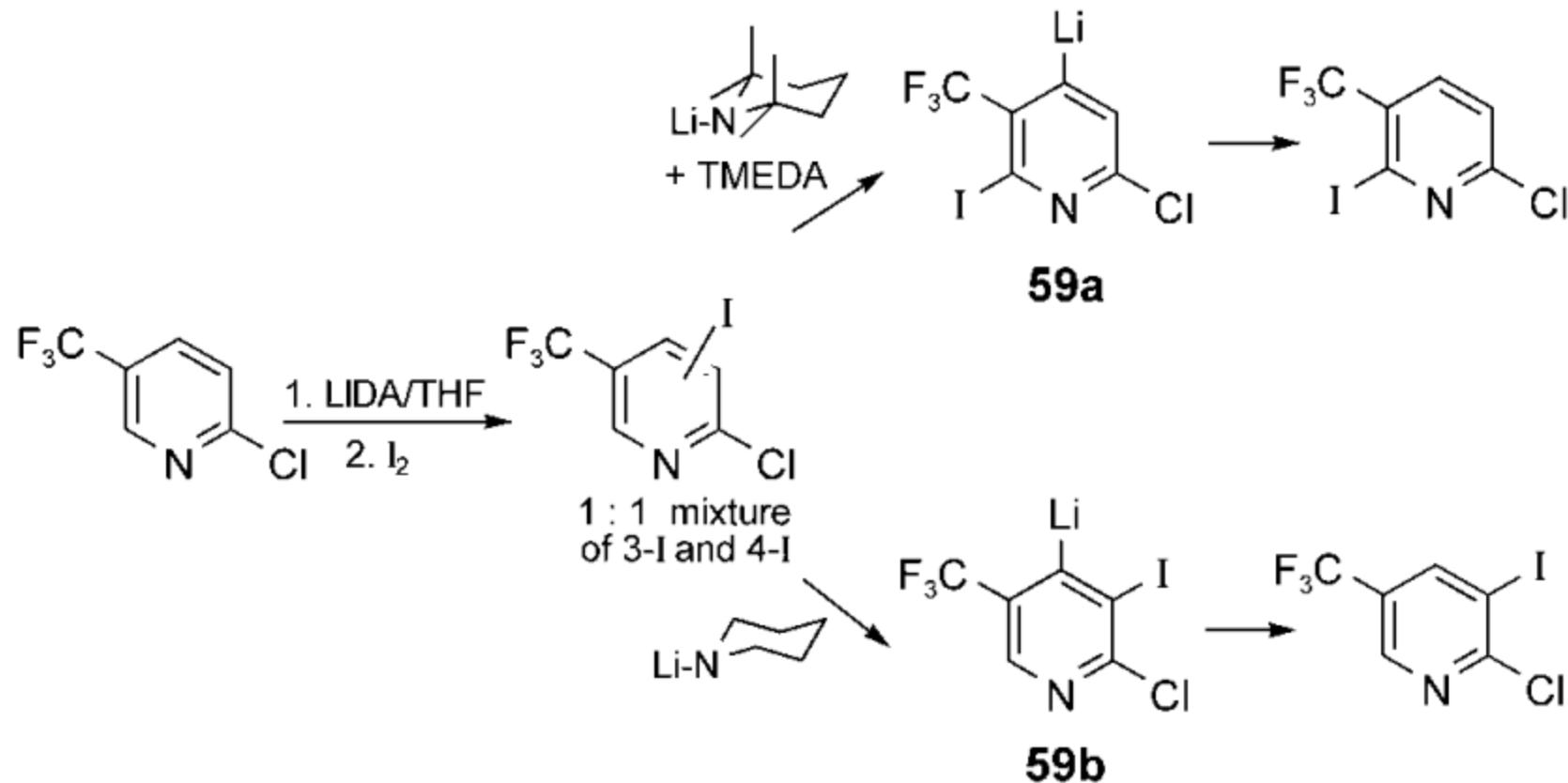
P. Stanetty, M. Spina and M. D. Mihovilovic, *Synlett*, **2005**, 9, 1433–1434..

Halogen dance on the Indole



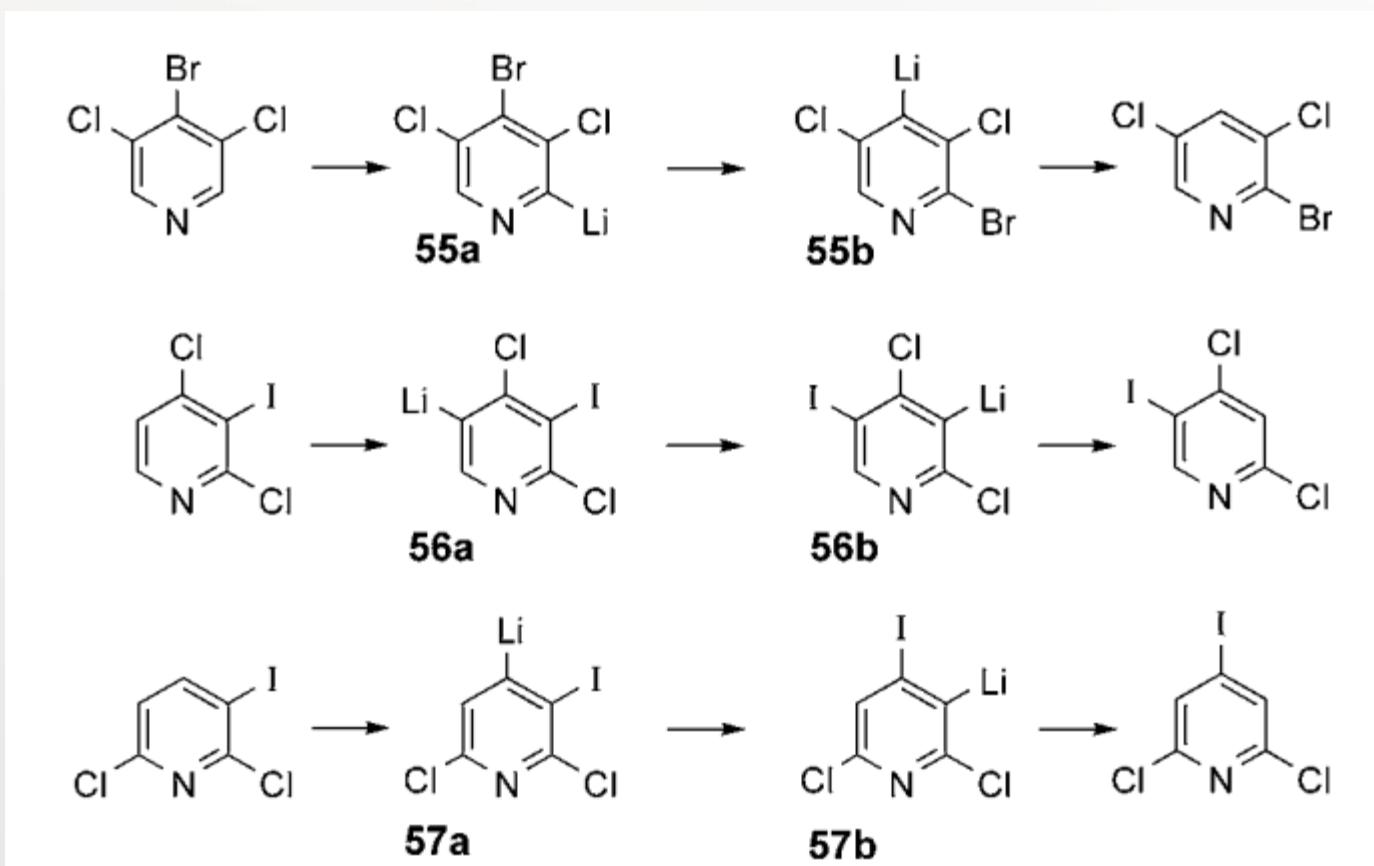
A. Ginanneschi, M. Schlosser, unpublished results, 2002.

Halogen dance on the Pyridine



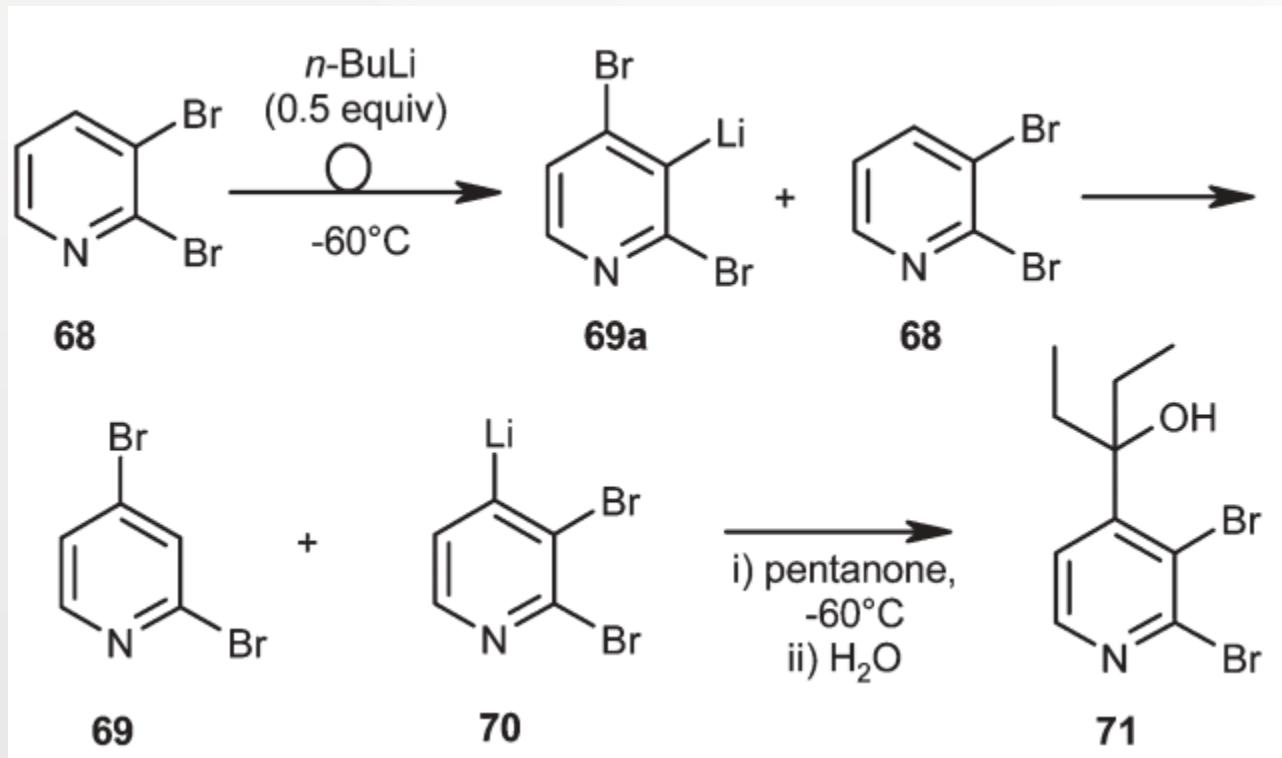
F. Cottet, M. Schlosser, unpublished results, 2002–2003

Halogen dance on the Pyridine



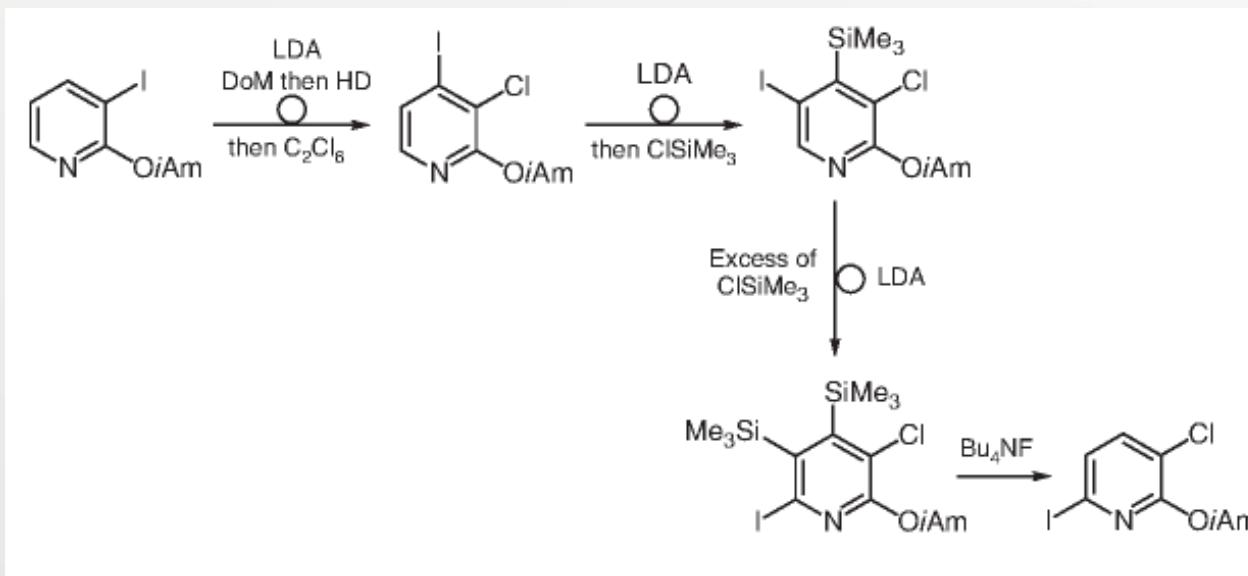
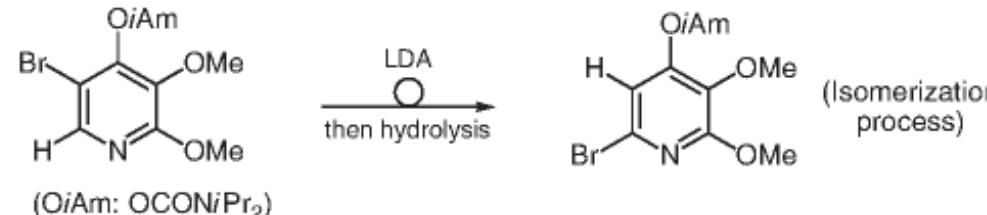
E. Marzi, A. Bigi, M. Schlosser, *Eur. J. Org. Chem.* **2001**, 1371–1376.

Halogen dance on the Pyridine



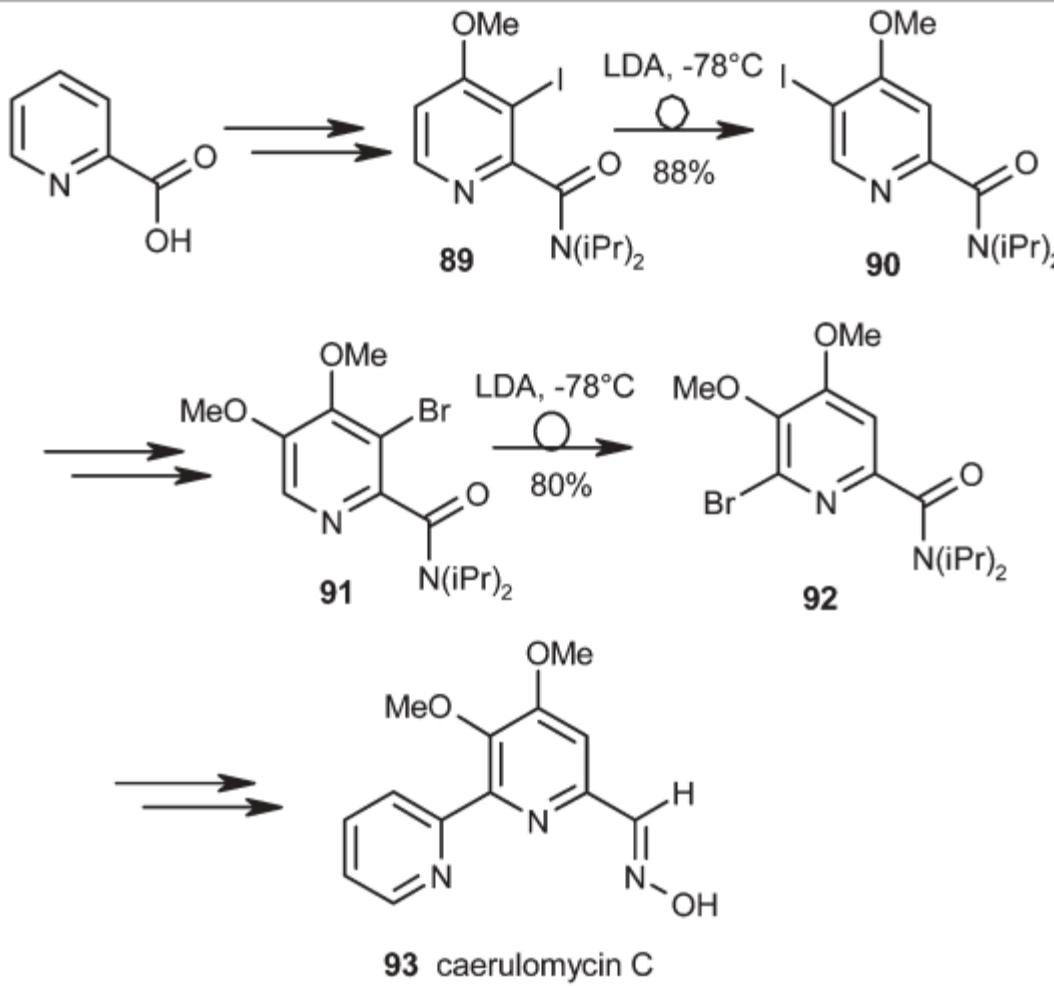
M. Mallet, G. Branger, F. Marsais and G. Queguiner, *J. Organomet. Chem.*, **1990**, 328, 319–332.

Halogen dance on the Pyridine



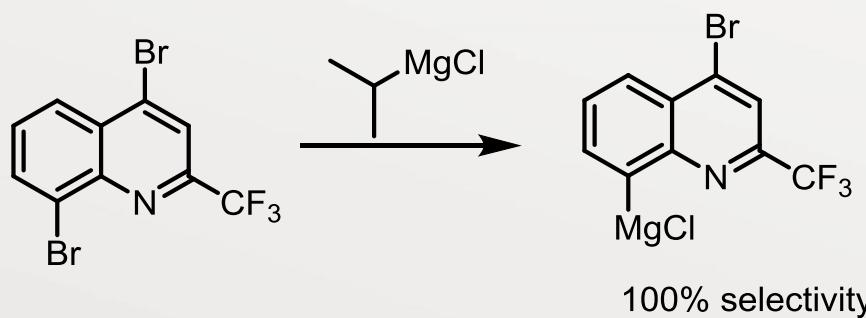
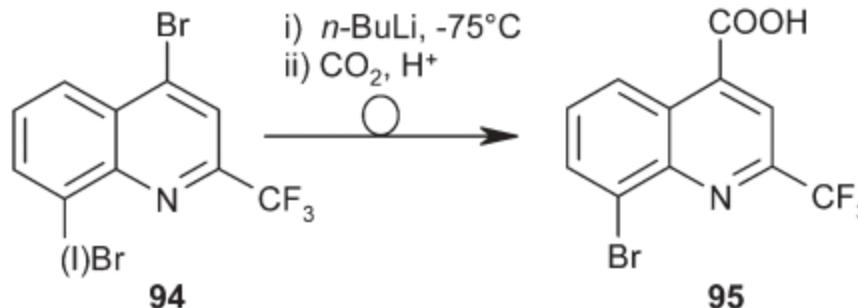
Miller, R. E.; Rantanen, T.; Ogilvie, K. A.; Groth, U.; Snieckus, V. *Org. Lett.* **2010**, 12, 2198–2201.

Halogen dance on the Pyridine



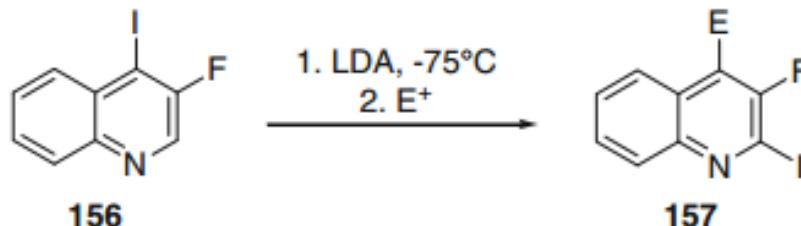
T. Sammakia, E. L. Stangeland and M. C. Withcomb, *Org. Lett.*, 2002, 4, 2385–2388.

Halogen dance on the Pyridine



M. Marull and M. Schlosser, *Eur. J. Org. Chem.*, 2003, 1576–1588..

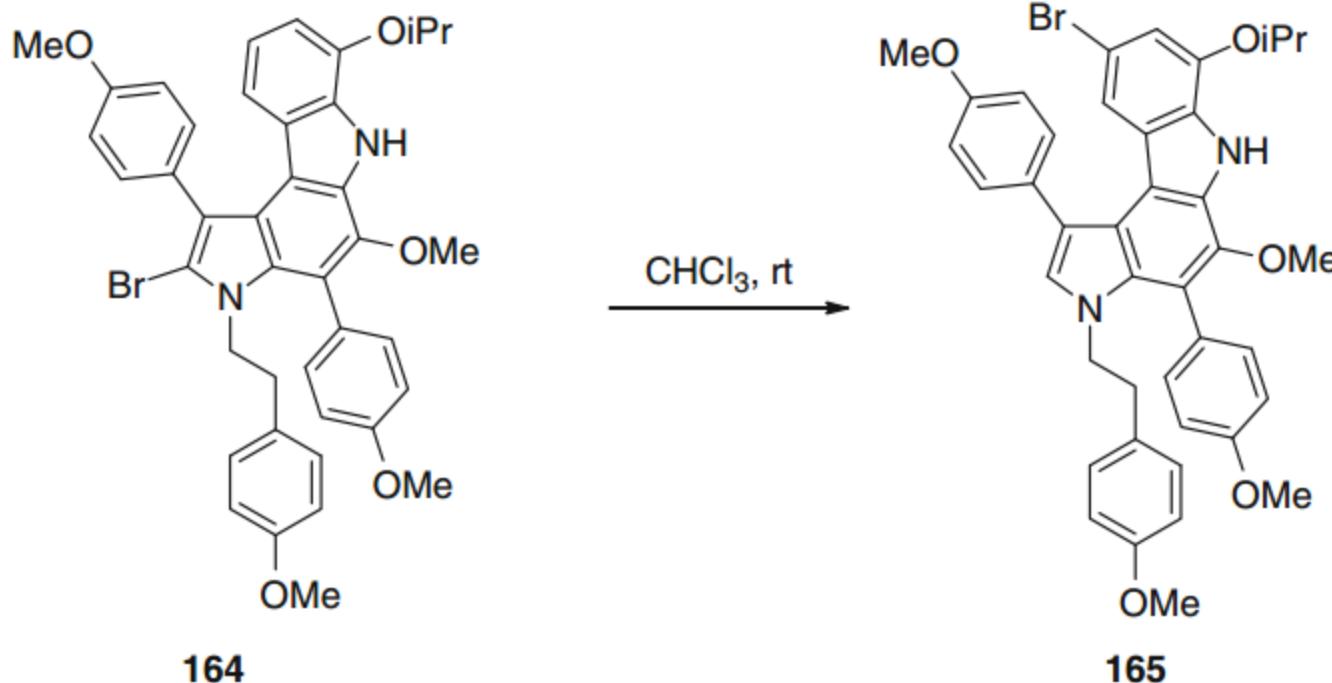
Halogen dance on the Quinoline



Entry	E+	E	Compd	Yield (%)
1	H ₂ O	H	157a	95
2	D ₂ O	D	157b	95
3	I ₂	I	157c	98
4	C ₂ Cl ₆	Cl	157d	74
5	MeI	Me	157e	65
6	MeCHO	MeCH(OH)	157f	79
7	C ₆ H ₅ CHO	C ₆ H ₅ CH(OH)	157g	75
8	HCO ₂ Et	CHO	157h	95

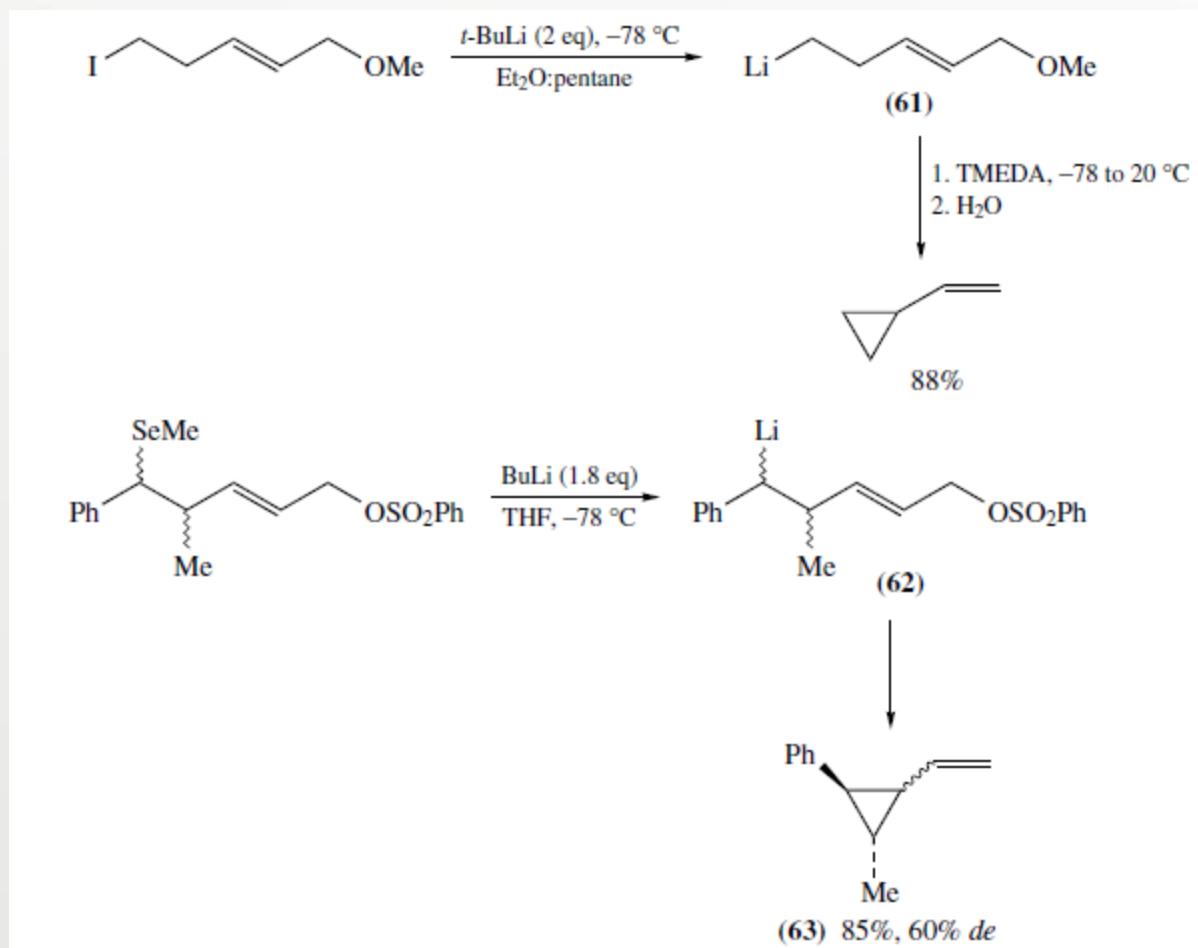
Arzel, E.; Rocca, P.; Grellier, P.; Labaeïd, M.; Frappier, F.; Guérinne, F.; Gaspard, C.; Marsais, F.; Godard, A.; Quéguiner, G. *J. Med. Chem.* **2001**, *44*, 949.

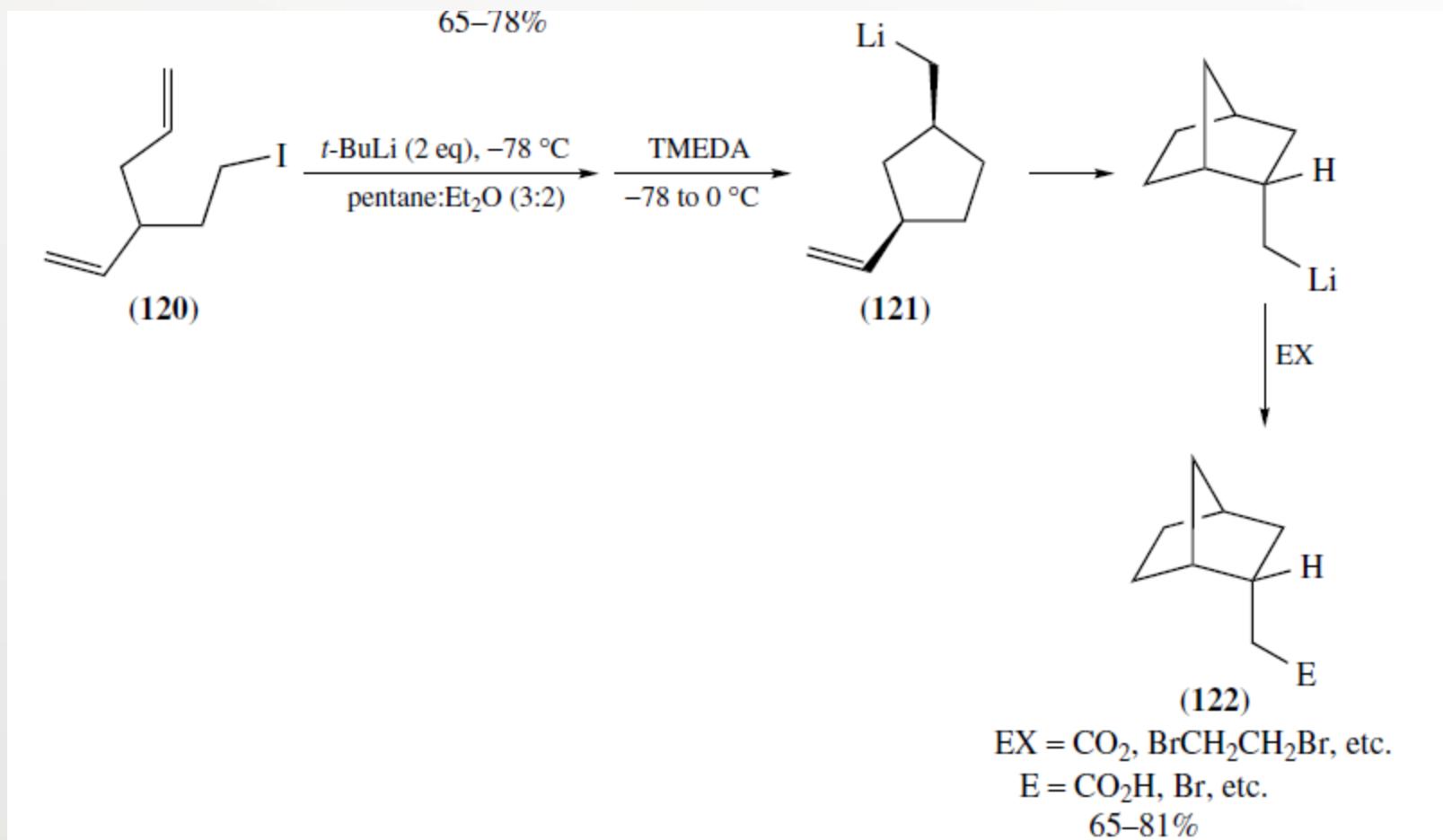
Unusual Halogen dance

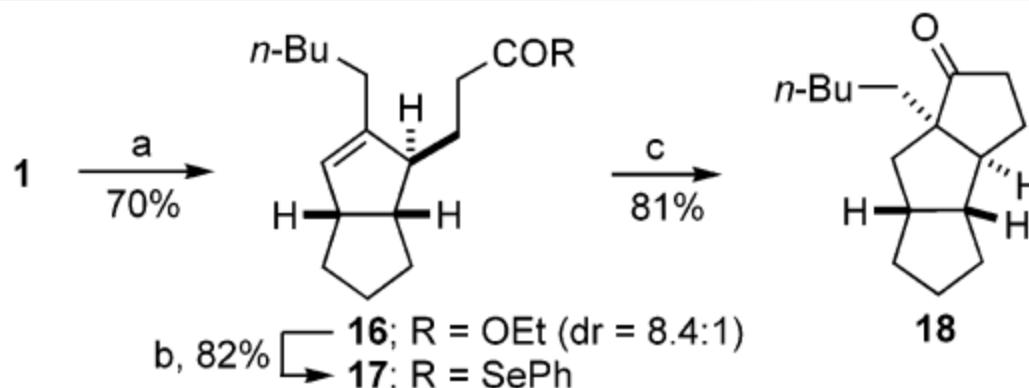


Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2006**, 128, 8087

Thank you for your attention
Welcome the first year student again







^a Conditions: (a) *n*-BuLi, (–)-sparteine, hexanes, –78 °C to room temperature, 1 h; CuCN·2 LiCl, THF, –78 °C; ethyl acrylate, TMSCl, –78 °C to room temperature. (b) i. LiOH, THF/H₂O; ii. *N*-(phenylselenyl)phthalimide, *n*-Bu₃P, THF. (c) *n*-Bu₃SnH, AIBN, PhH, reflux.

