ANION RELAY CHEMISTRY

Zachery Matesich 17 April 2012

Roadmap

- Brook Rearrangement
- Overview of anion relay chemistry (ARC)
- Type 1 ARC
- Type 2 ARC
- New directions in ARC
- Conclusions

Brook Rearrangement

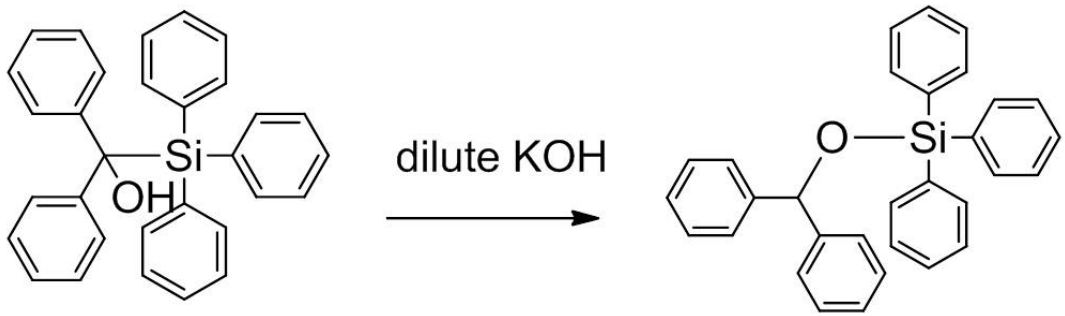
- First observed in early 1950 by Henry Gilman

$$Ph_3SiK + Ph_2CO \longrightarrow Ph_3SiOCHPh_2$$

- Suggested migration of Si group

Gillman, *JACS*, **1953**, *75*, 2935

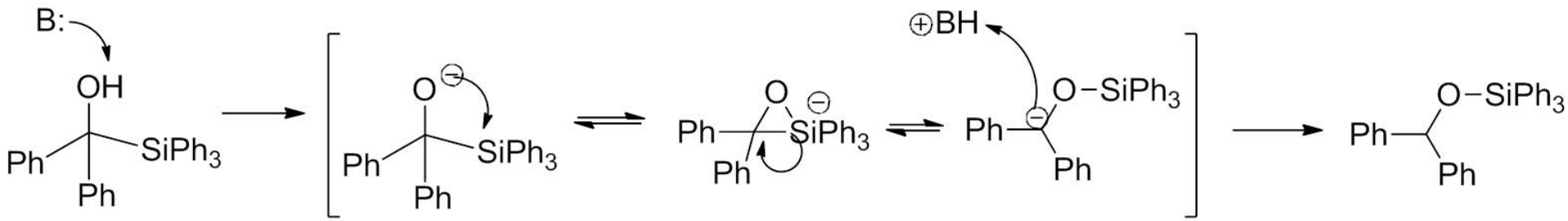
- Extensively developed in 1957 by Adrian G Brook

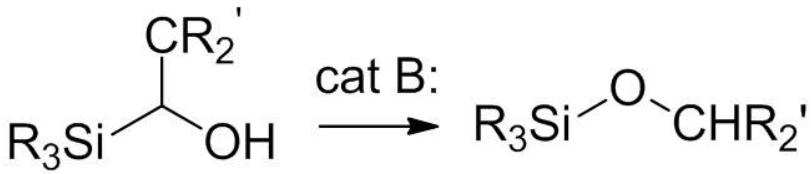


- Proposed a nucleophilic attack of oxygen to α-silicon atom ([1,2] Brook)

Brook et al, *JACS*, **1958**, *80*, 1886

[1,2] Brook Rearrangement





R = aryl, alkyl
R' = aryl, alkyl, hydrogen
Additive = Na-K, Na, NaH, RLi, Et_2NH, R_3N

- [1,2] involves retention of configuration at silicon and inversion at carbinol carbon

Brook, *Acc. Chem. Res.* **1974**, *7*, *77*

Brook Rearrangement (kinetics)

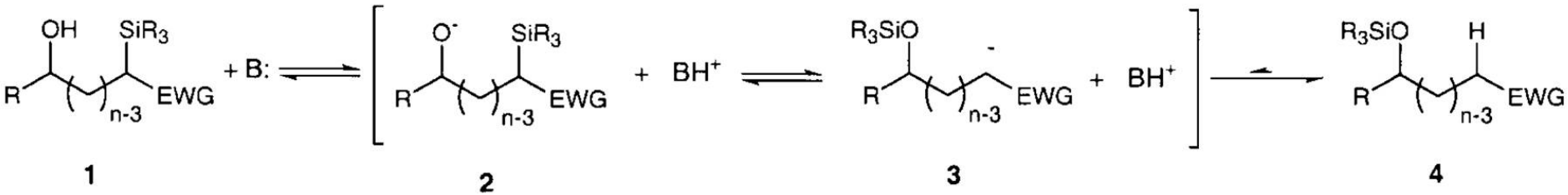
Table I
Approximate Rates of Rearrangement of Silylcarbinols in Me_2SO by Et_2NH at 36°

Carbinol	Rate, l. mol^{-1} sec^{-1}
Ph_3SiCPh_2OH	7.6
$Ph_3SiCMePhOH$	6.7×10^{-3}
$Ph_3SiCHPhOH$	5.7×10^{-3}
$Ph_3SiC(CH_2Ph)PhOH$	1.1×10^{-1}
Ph_3SiCMe_2OH	Too slow to measure
$MePh_2SiCPh_2OH$	1.2
$Me_2PhSiCPh_2OH$	2×10^{-1}
Me_3SiCPh_2OH	3.3×10^{-2}

- Anionic character is built up on carbinol carbon in transition state

Brook, *Acc. Chem. Res.* **1974**, *7*, *77*

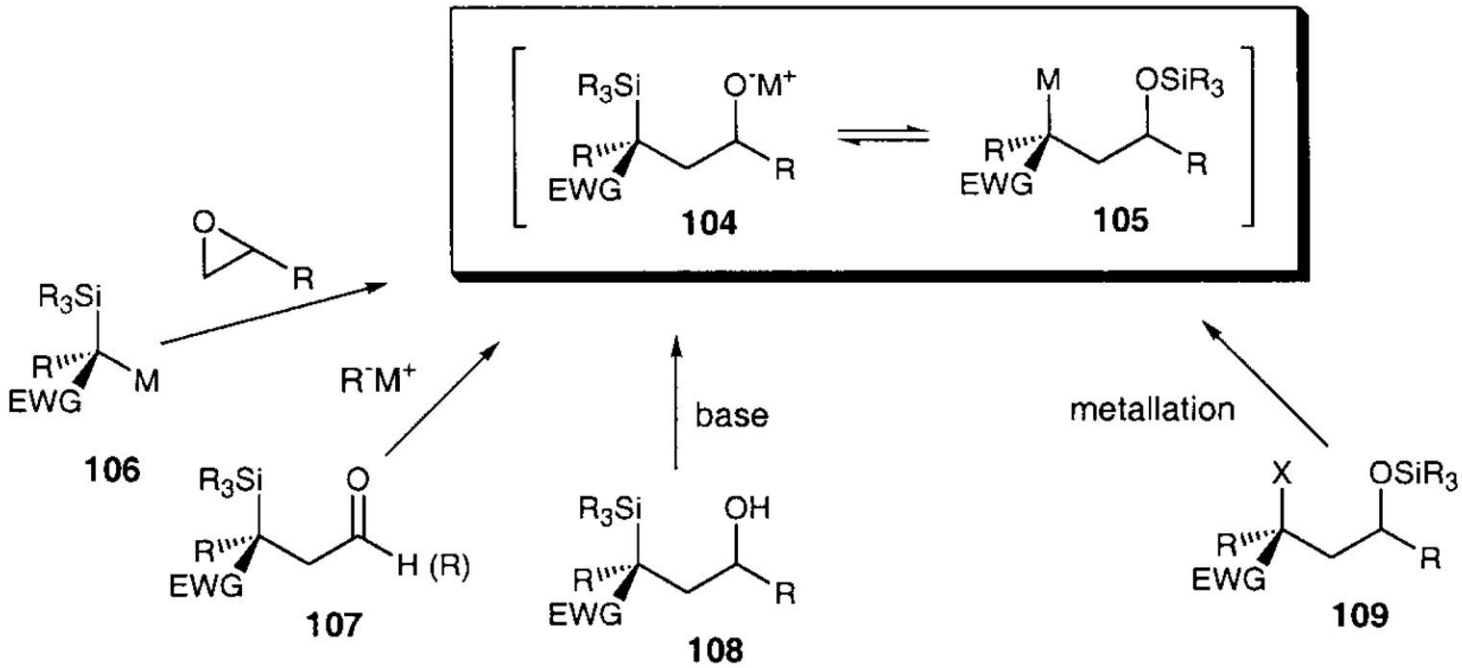
Brook Rearrangement (thermodynamics)



- Weak base:
  - O-Si bond (120-130 kcal/mol)
  - C-Si bond (75-85 kcal/mol)
  - Stability of **1** vs **4**
- Strong base:
  - Basicity of carbanion and identity of counterion
  - Reactivity of alkoxide
  - Stability of **2** vs **3**

Moser, Tetrahedron **2001**, *57, 2065*

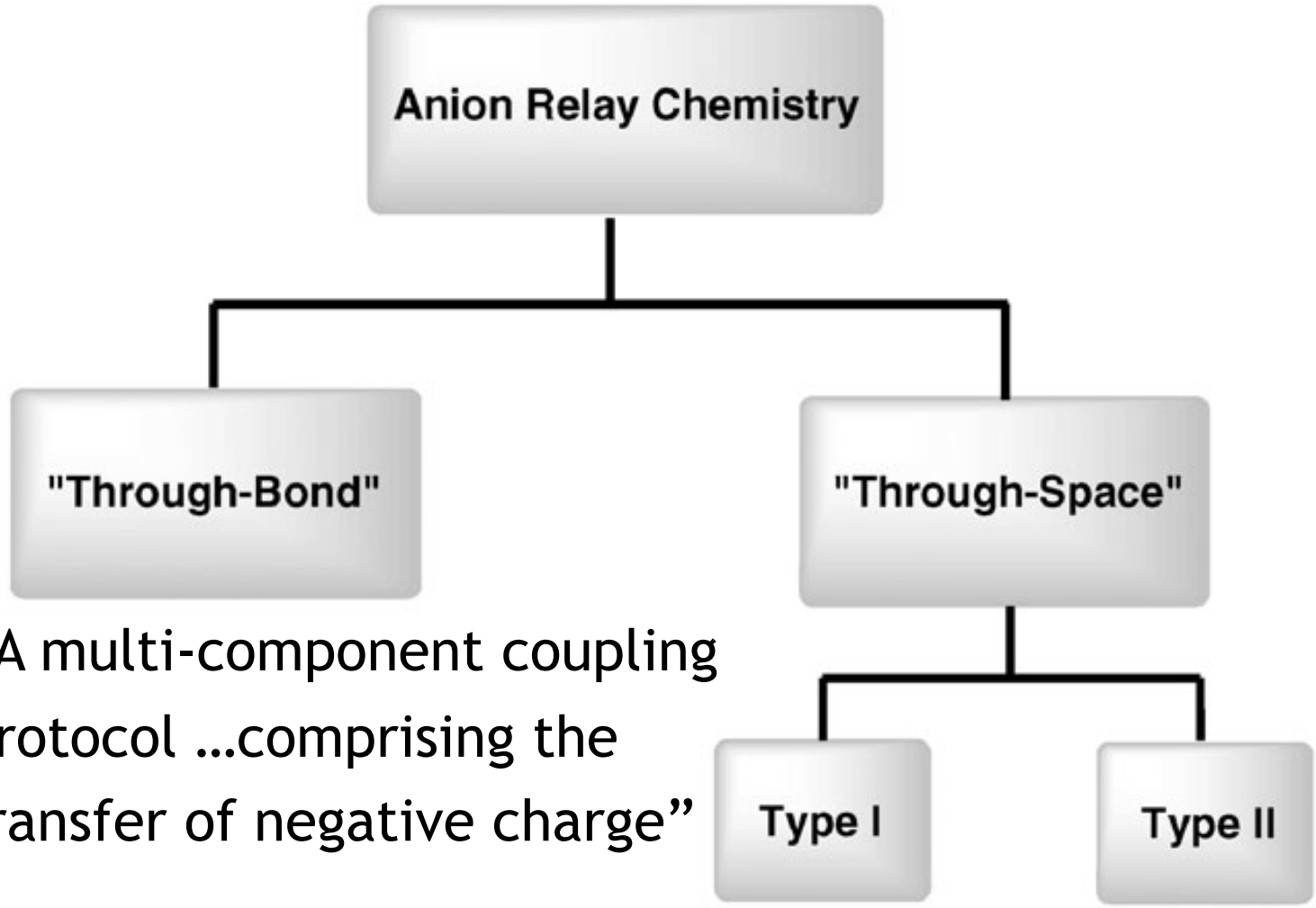
[1,4] Brook Rearrangement



- [1,4] Brook rearrangement can be initiated via several different methods

Moser, Tetrahedron **2001**, *57, 2065*

Anion Relay Chemistry (ARC)

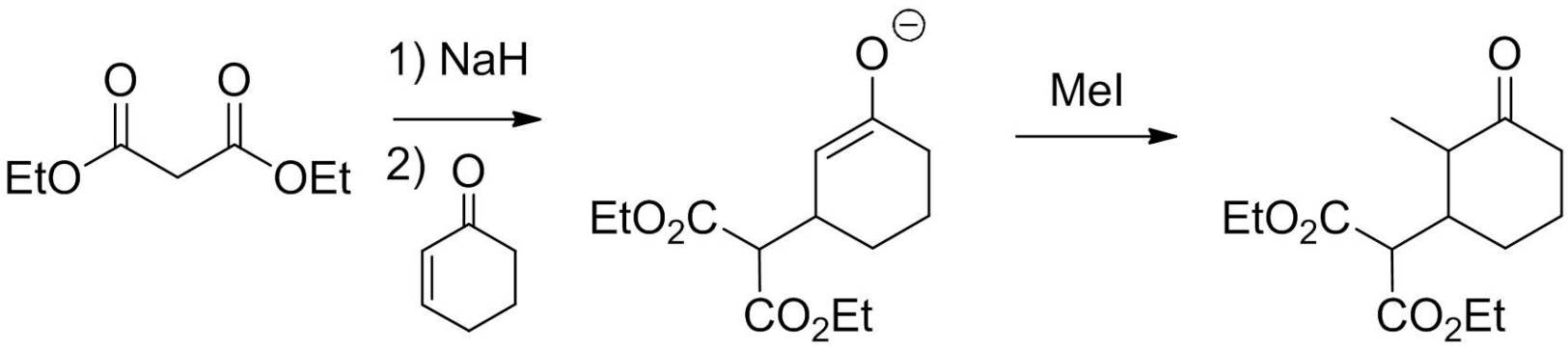


- "A multi-component coupling protocol …comprising the transfer of negative charge"

Smith et al, *Chem. Commun.*, **2008**, 5883

“Through-bond” ARC

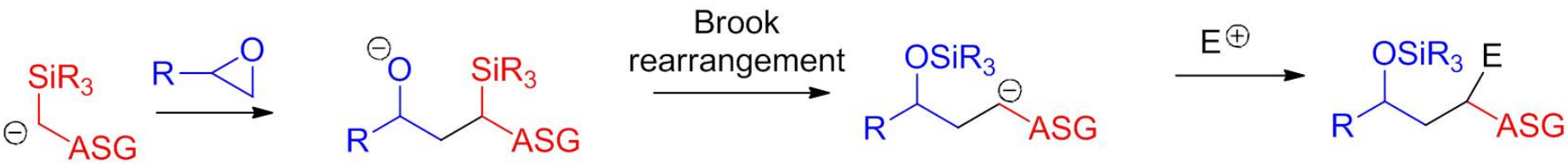
- Transfer of negative charge through π-system
- Essential example: enolate chemistry



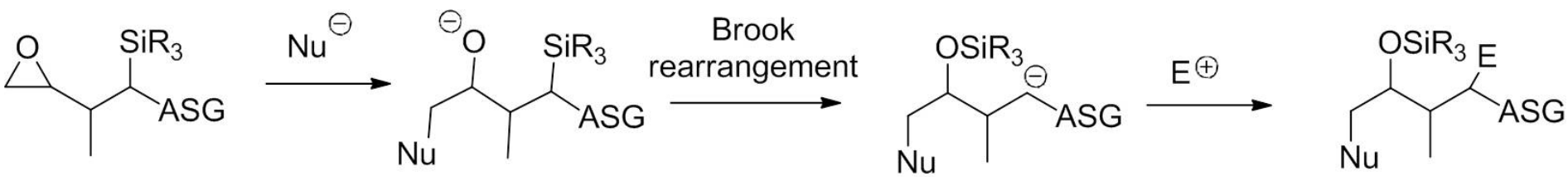
Smith et al, *Chem. Commun.*, **2008**, 5883

“Through-space” ARC

- Type I: Involves relaying of anion back to original location after rearrangement



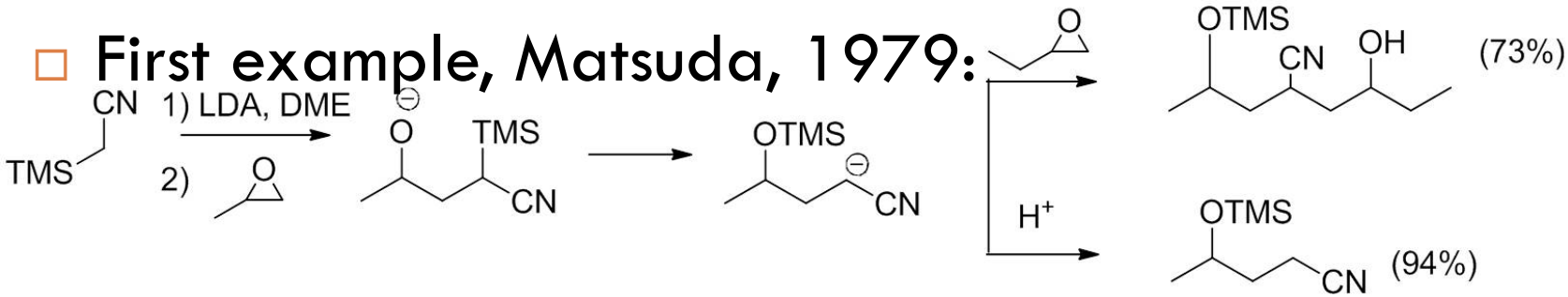
- Type 2: Anion is relayed to a new position on the molecule after rearrangement with the aid of a transfer agent



Smith et al, *Chem. Commun.*, **2008**, 5883

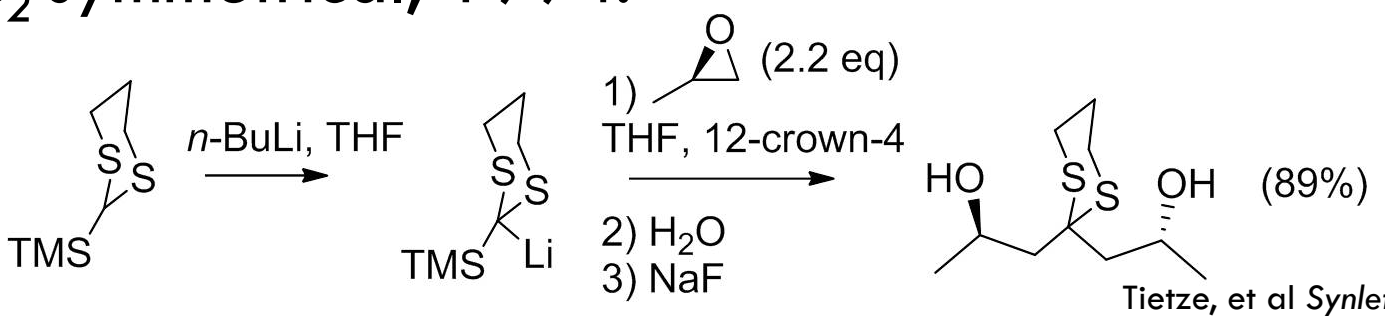
Type 1 ARC First Beginnings

- First example, Matsuda, 1979:



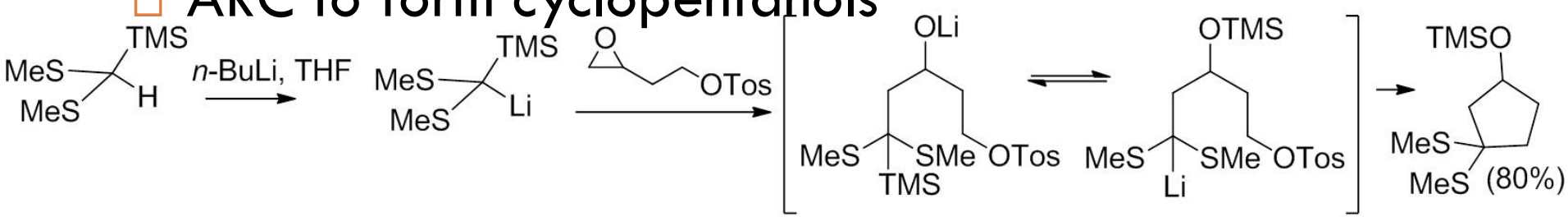
Matsuda et al, *Perkin. Trans. 1*, **1979**, 26

- C_2 symmetrical, 1994:



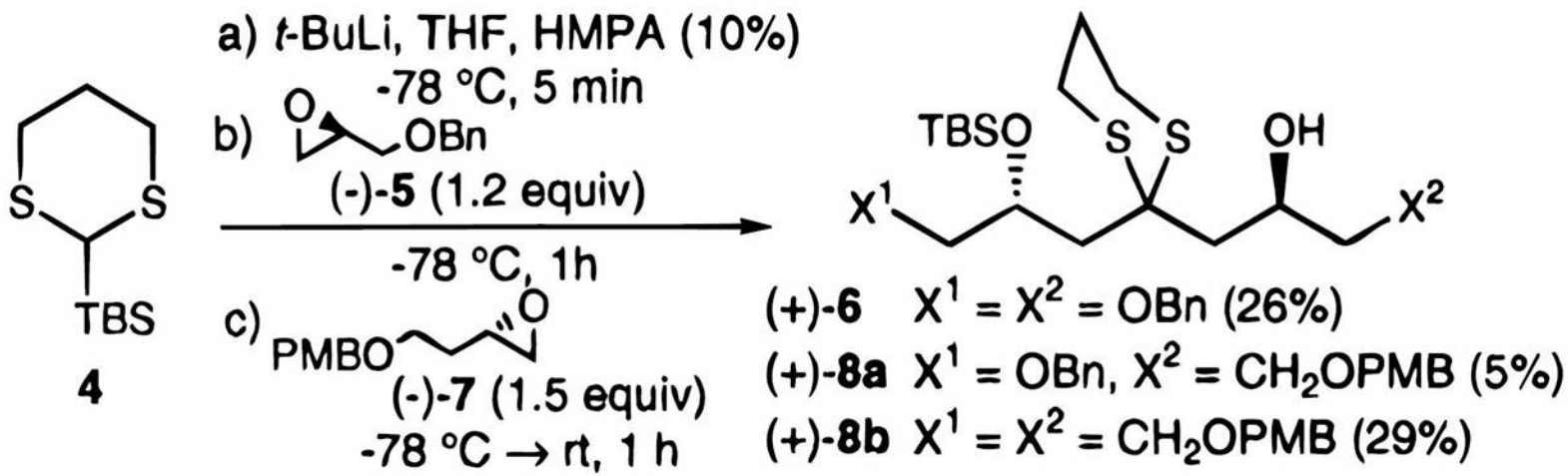
Tietze, et al *Synlett*, **1994**, 511

- ARC to form cyclopentanols



Schaumann et al, *Angew. Chem. Int. Ed. Eng.* **1994**, *33*, 217

Solvent/Additive Dependence

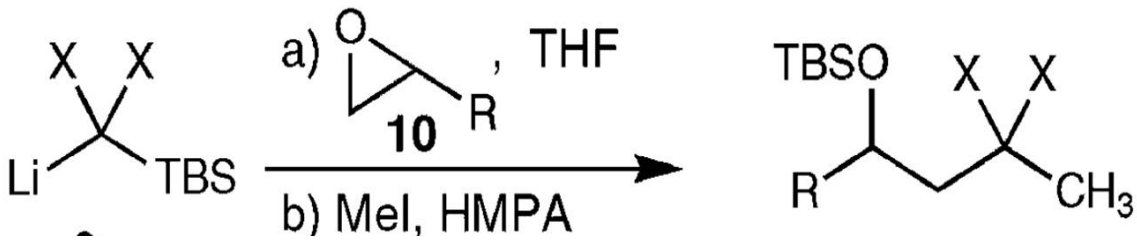


Product	X^1	X^2	Yield Ratio
(+)-6	OBn	OBn	26%
(+)-8a	OBn	CH_2OPMB	5%
(+)-8b	CH_2OPMB	CH_2OPMB	29%

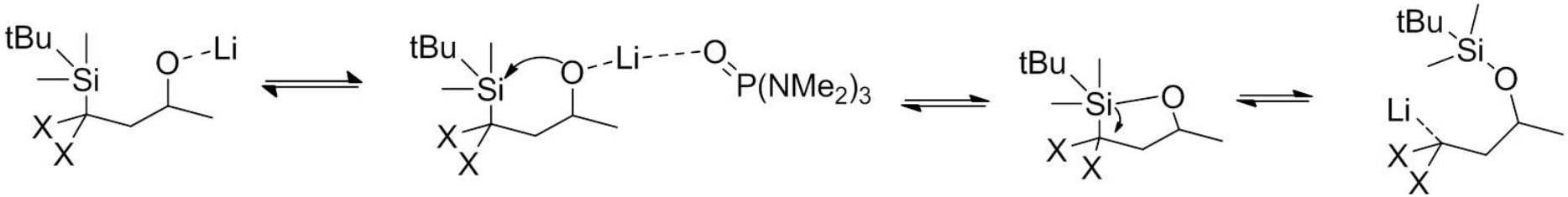
- Lack of control of [1,4] onset leads to mixtures of products

Smith et al, *J. Am. Chem. Soc.*, **1997**, *119*, 6925

Solvent/Additive Dependence



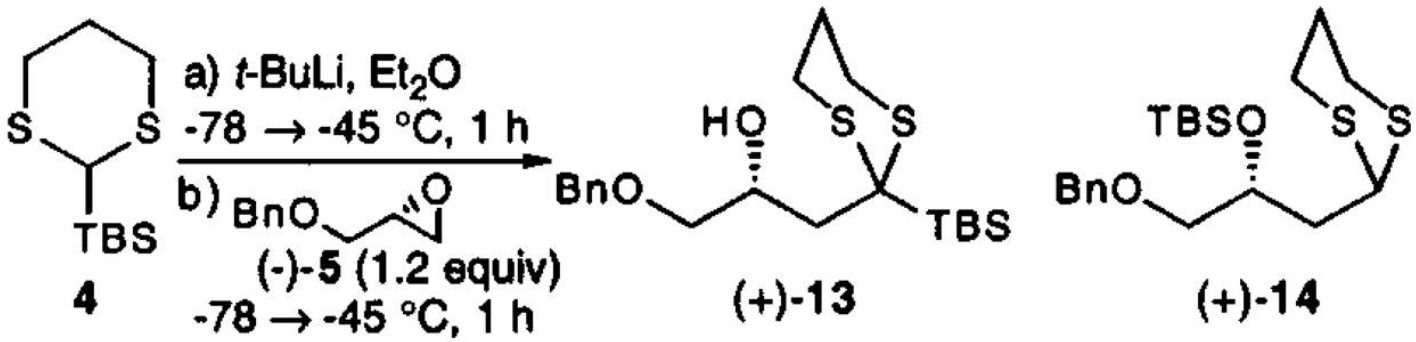
11, R=H, X=Cl (80%)
12, R=Me, X=Cl (68%)
13, R=Me, X=Br (60%)



- Use of HMPA to "trigger" onset of [1,4] Brook allows sequential addition of dissimilar components

Oshima et al, *Tetrahedron*, **1996**, *52*, 503

Solvent/Additive Dependence

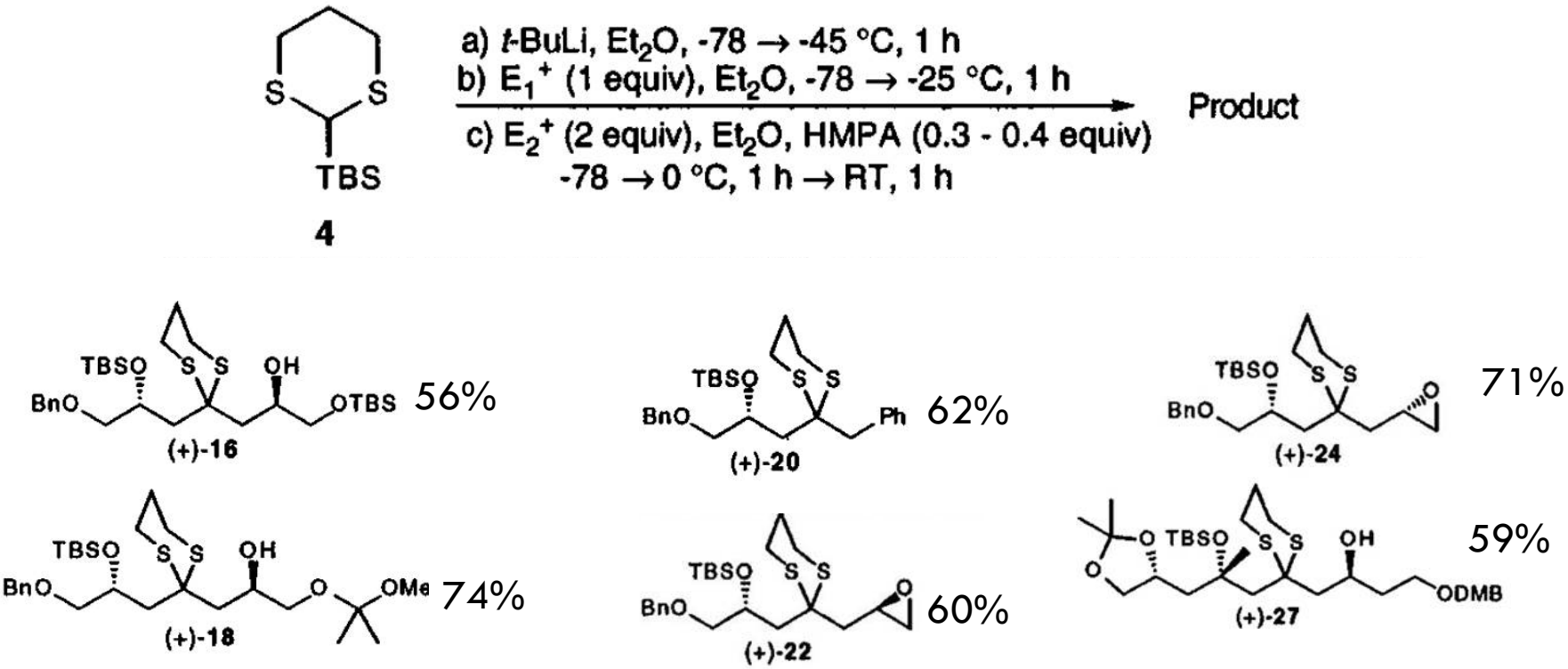


Entry	Solvent	Additive[a]	Yield **13** (%)	Yield **14** (%)
1	THF	-	60	-
2	Et_2O	-	74	-
3	Et_2O	HMPA	9	56
4	Et_2O	DMPU	12	66

- Use of HMPA or DMPU increases yield of [1,4] Brook rearrangement product

Smith et al, *J. Am. Chem. Soc.*, **1997**, *119*, 6925

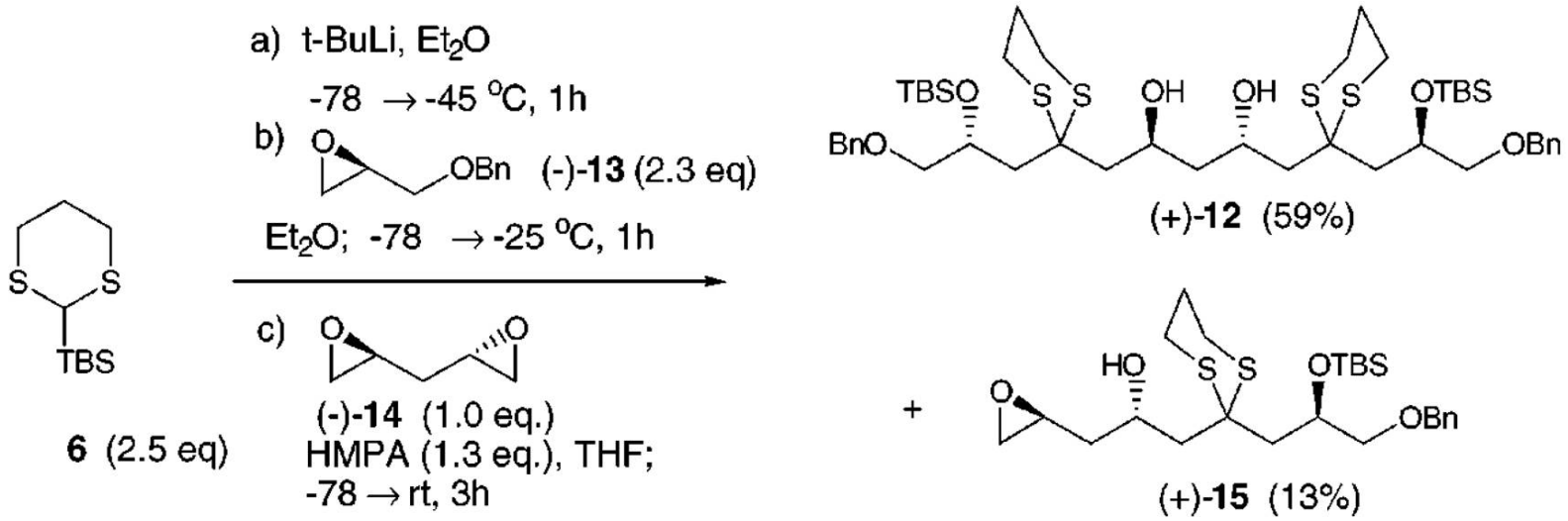
Expansion of ARC Type 1



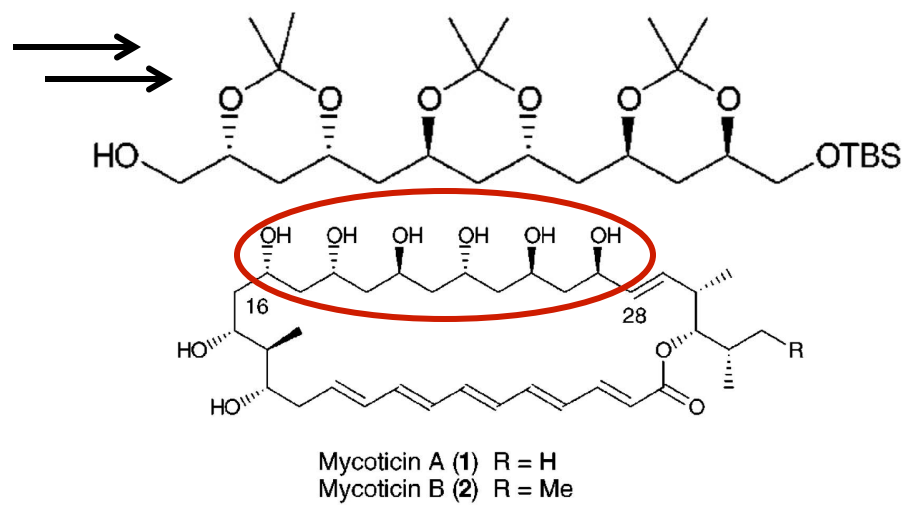
- Expanded use of dissimilar epoxides with HMPA allowed for unsymmetrical products

Smith et al, *J. Am. Chem. Soc.*, **1997**, *119*, 6925

Applications of ARC Type 1

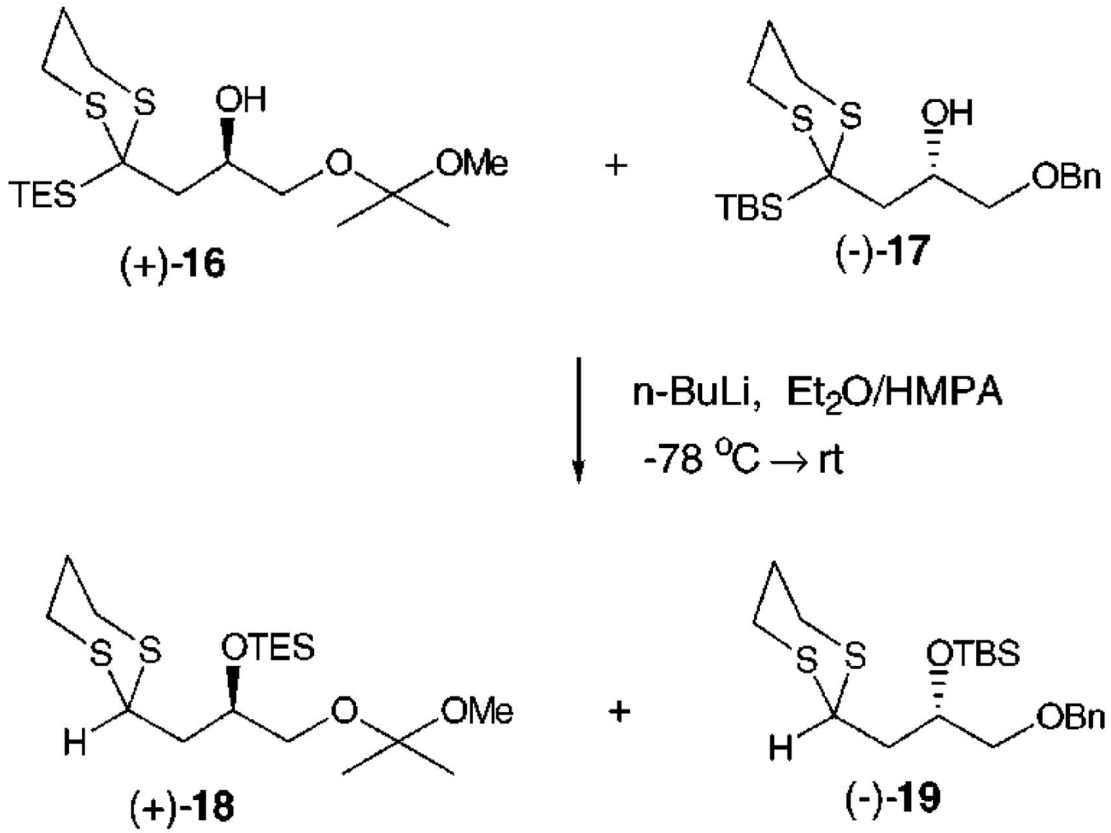


- Five-component synthesis of Mycoticin (A & B) fragment
- Total of 8 steps, 5 fewer than previous method with a total yield of 17% (compared to 3.3%)



Smith et al, *Org. Lett.* **1999**, *1*, 2001

Crossover Study

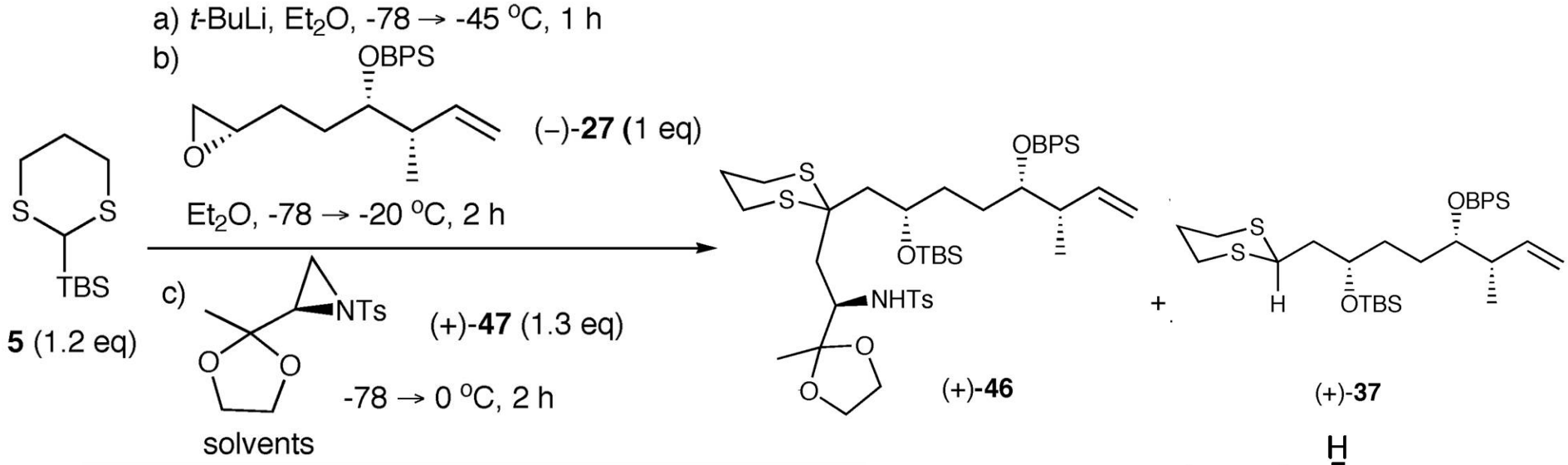


- No observed crossover product → Intramolecular!

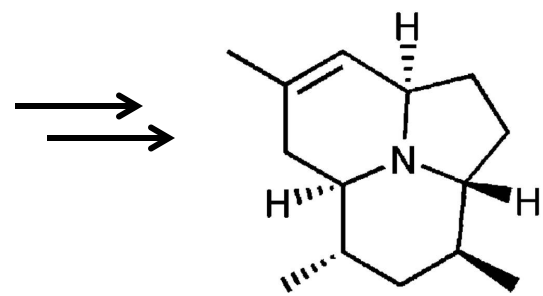
Smith, et al *Org. Lett.* **1999**, *1*, 2001

Further Applications of ARC Type 1

- Used in synthesis of frog toxin Alkaloid (-)-205B



solvents	yield (%)	
	(+)-**46**	(+)-**37**
Et_2O, HMPA (0.7 equiv)	6	56
THF, HMPA (0.4 equiv)	12	70
THF, DMPU (1 equiv)	no desired product	
THF	39	24
THF, DME (3.2 equiv)	53	31



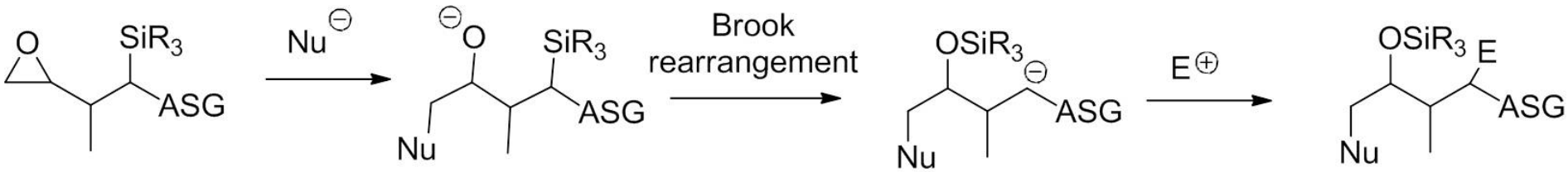
Alkaloid (–)–205B (**2**)

Smith et al, *J. Org. Chem.*, **2006**, *71*, 2547

ARC Type 1 Summary

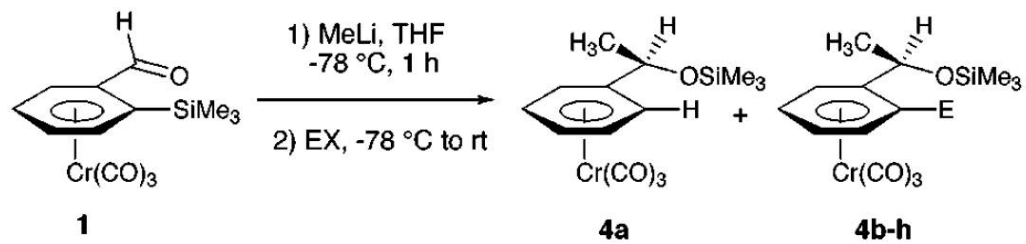
- Dependent on the [1,4] Brook intramolecular rearrangement with a pentavalent silicon
- Use of HMPA or DMPU to trigger [1,4] Brook
- C_2 symmetrical molecules can easily be assembled using 1,3 dithiane moiety, unsymmetrical with careful control of [1,4] Brook
- Successful use in natural product synthesis
- Formed basis for ARC type 2

Type 2 ARC

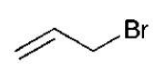
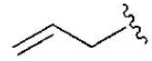
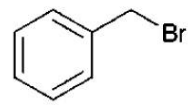
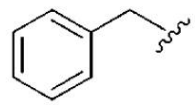


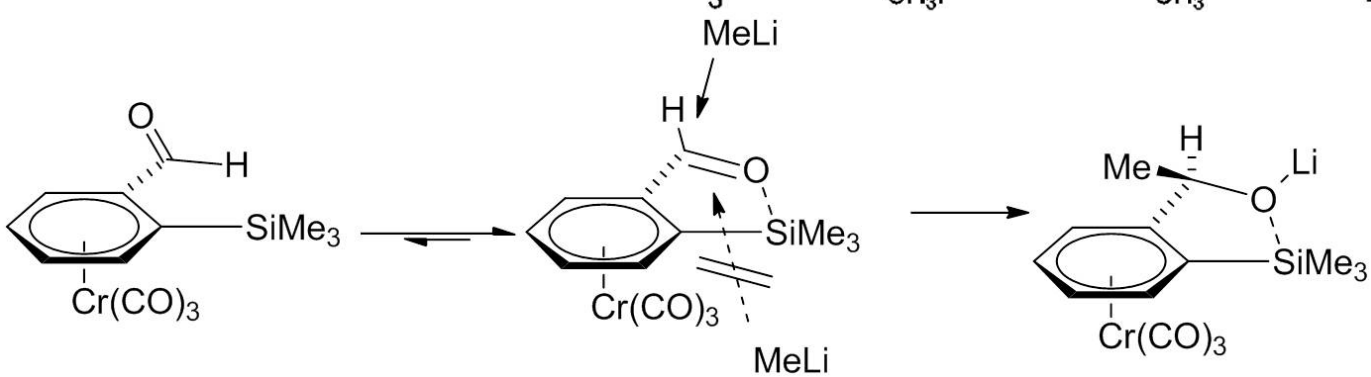
- Type 2: Anion is relayed to a new position on the molecule after rearrangement with the aid of a transfer agent

Type 2 ARC Beginnings



- First example from Moser in 2000 with Cr species:
- Prochiral face

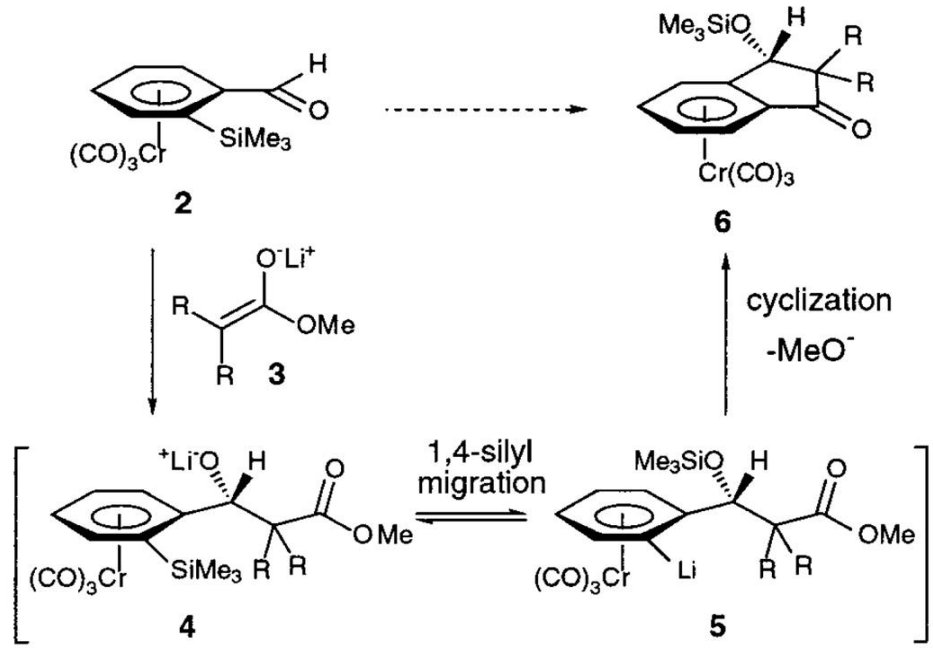
Entry	EX	E	Products[a] (% yield)
1			**4b** (58) + **4a** (36)
2			**4c** (52) + **4a** (33)
3	CH_3I	CH_3	**4d** (65) + **4a** (15)

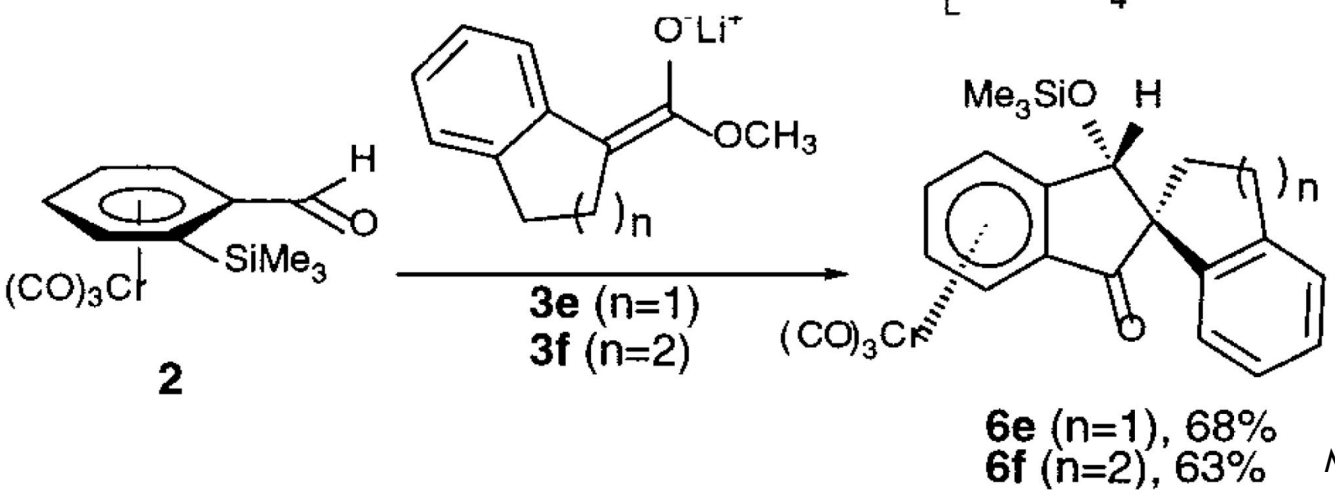


Moser et al, *J. Org. Chem.*, **2006**, *71*, 2547

Formal [3+2] Annulation with Cr

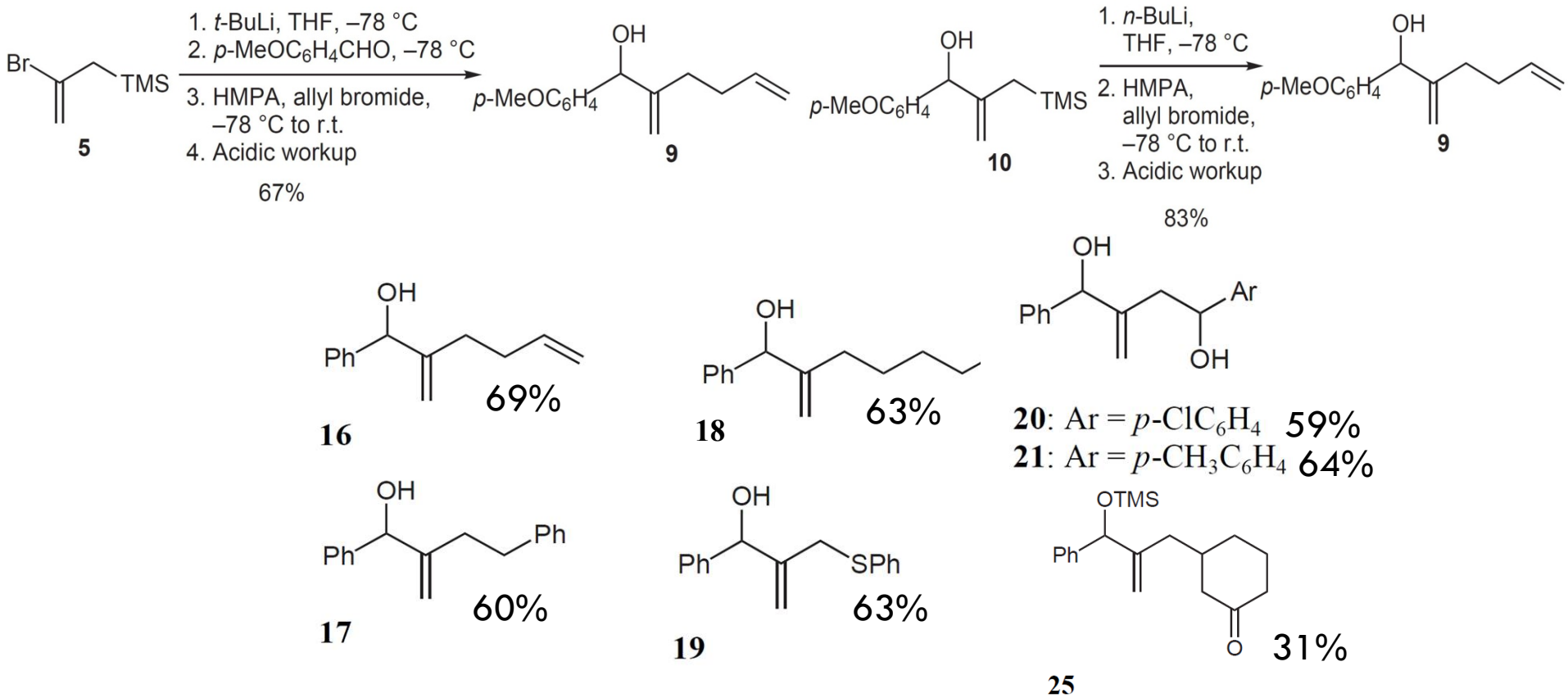
- Symmetrical and unsymmetric ester enolates capable of forming spiro compounds





Moser et al, *Org. Lett.* **2002,** *4,* 1981

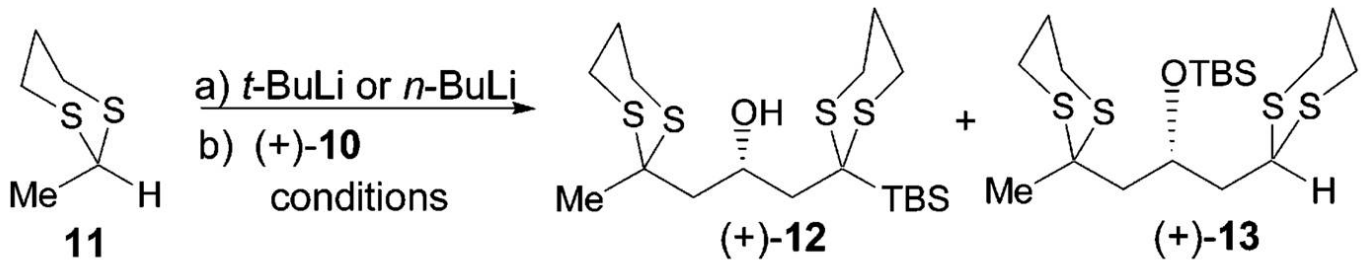
Type 2 ARC Linchpins

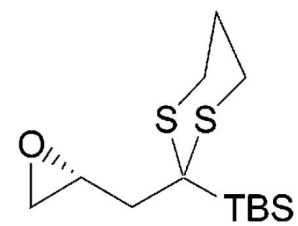


- New linchpin capable of diverse reactions

Smith et al *Synlett* **2004,** *8,* 1363

Further Linchpin Design





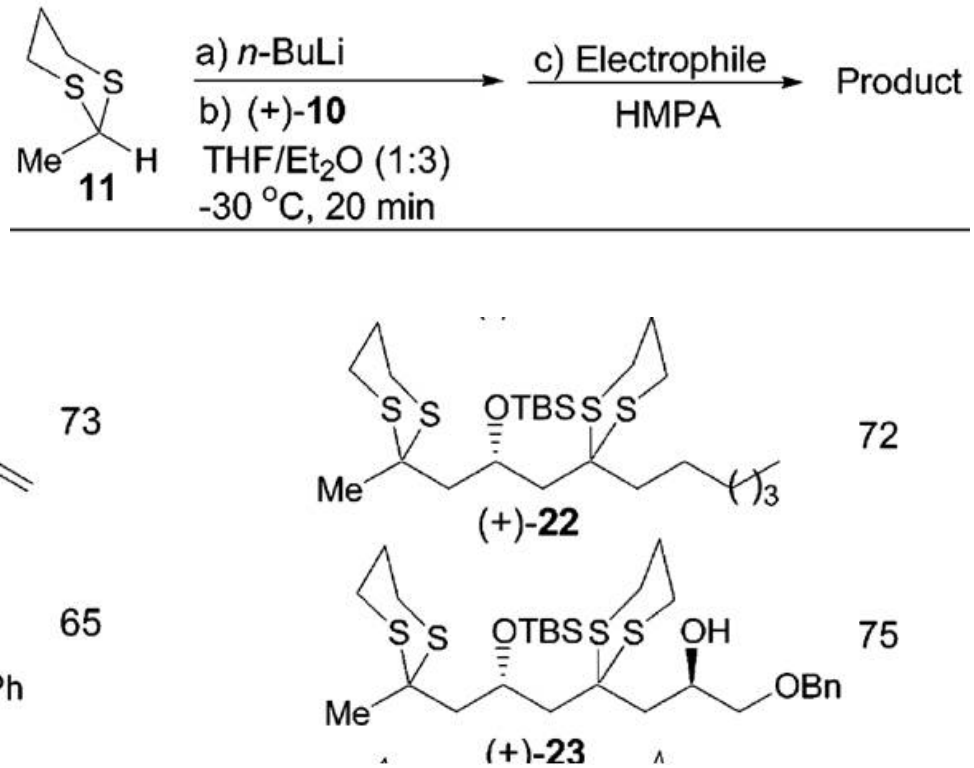
(+)-10

Entry	Solvent	Reaction temperature/time	Yield **12** (%)	Yield **13** (%)
1	Et_2O	−78 to −20 °C	0	0
2	Et_2O	r.t./3 h	71	<5
3	THF	−30 °C/20 min	47	24
4	THF/Et_2O (1:3)	−30 °C/20 min	87	<5

- Solvent choice of THF/Et_2O (1:3) allows completed addition of first epoxide, avoiding mixture of products upon addition of second epoxide

Smith et al, *J. Am. Chem. Soc.* **2006,** *128*, 66

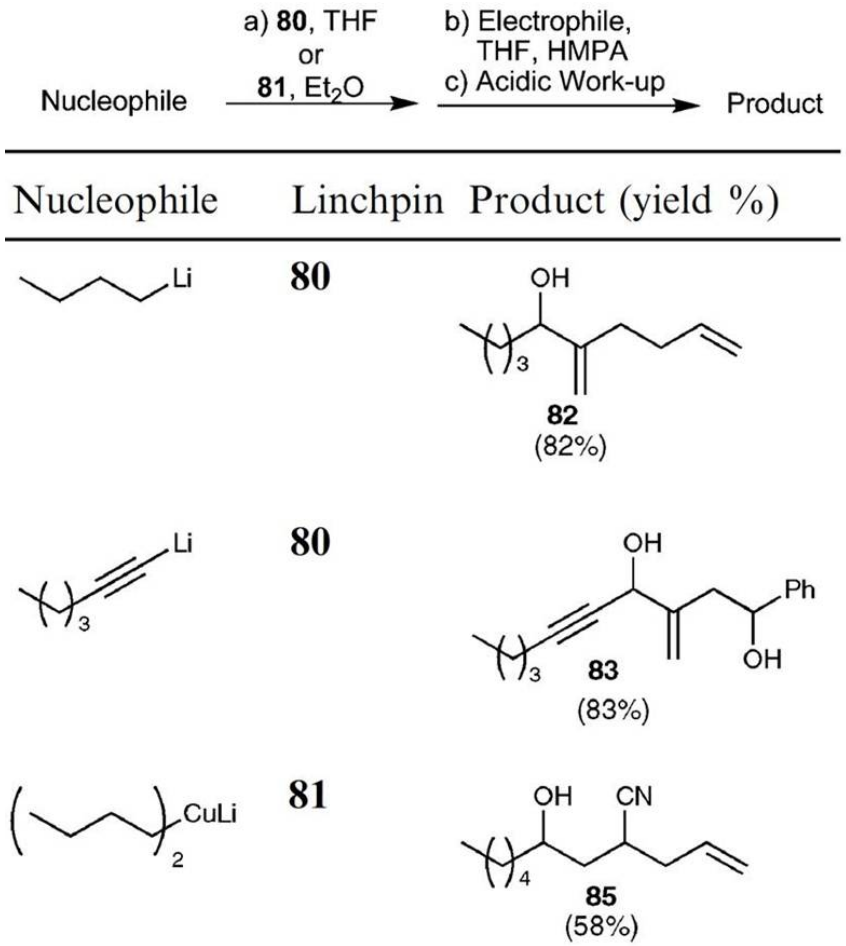
Further Linchpin Design (continued)

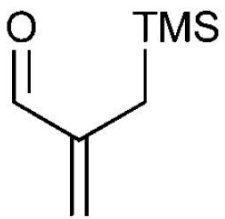


- Three component systems with defined stereo centers possible using ARC Type 2 linchpins

Smith et al, *J. Am. Chem. Soc.* **2006,** *128*, 66

Further Linchpin Design (continued)





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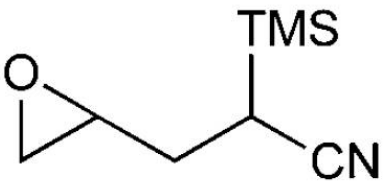
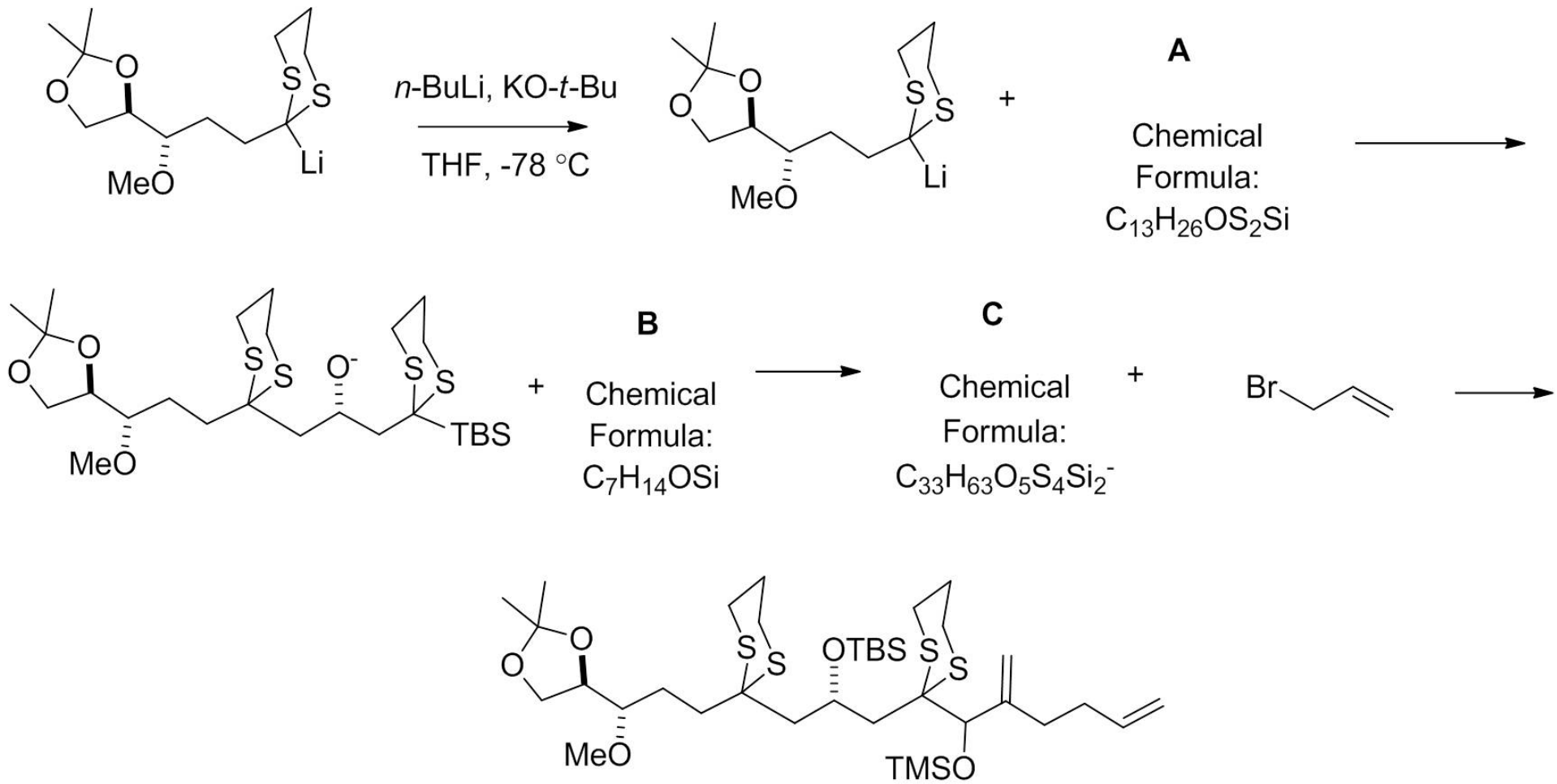


81

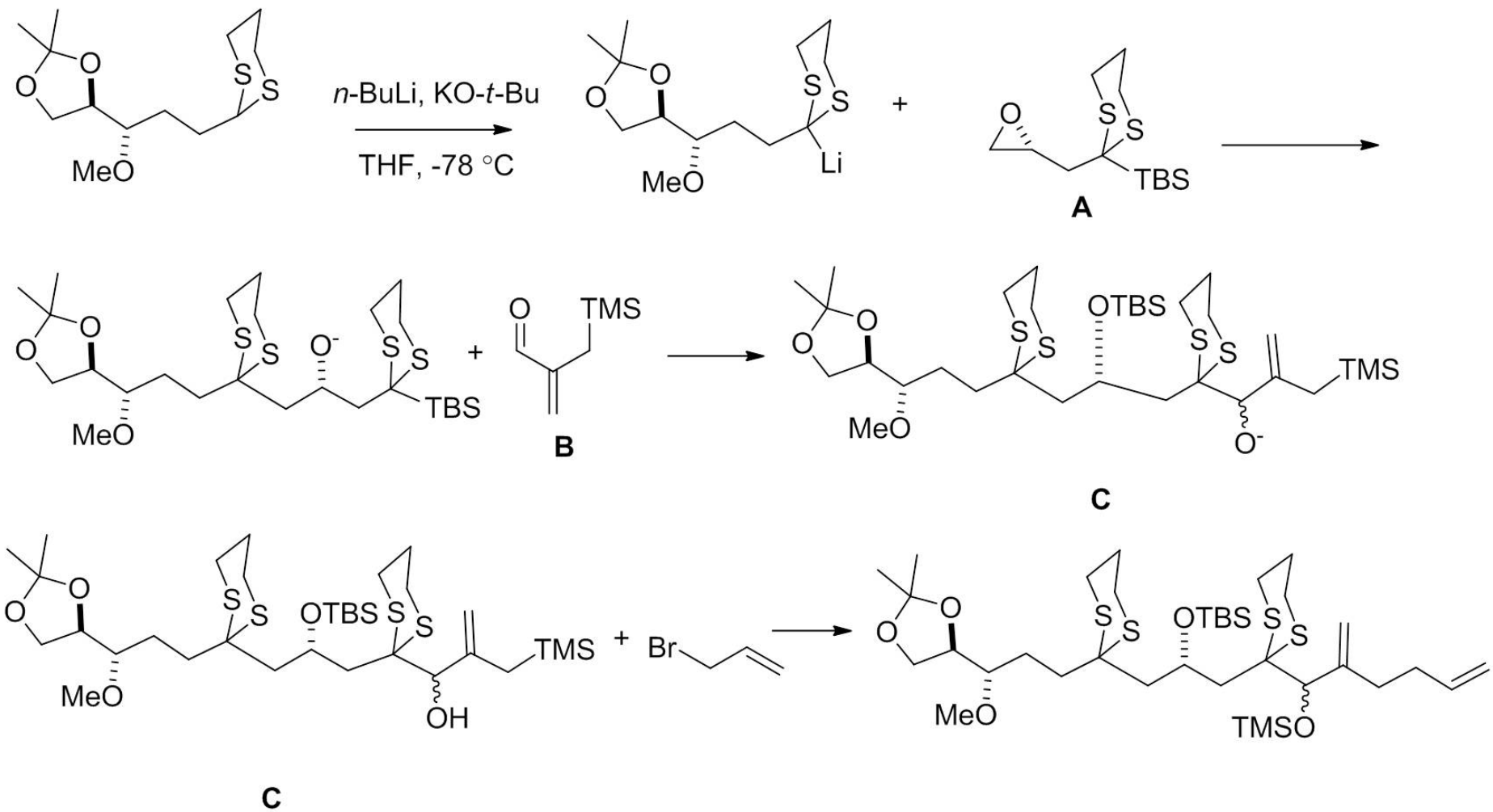
- Linchpins with cation/anion synthon functionalities capable of linkages, including Cu species

Smith et al, *Org. Lett.* **2007**, *9*, 3307

Group Problem

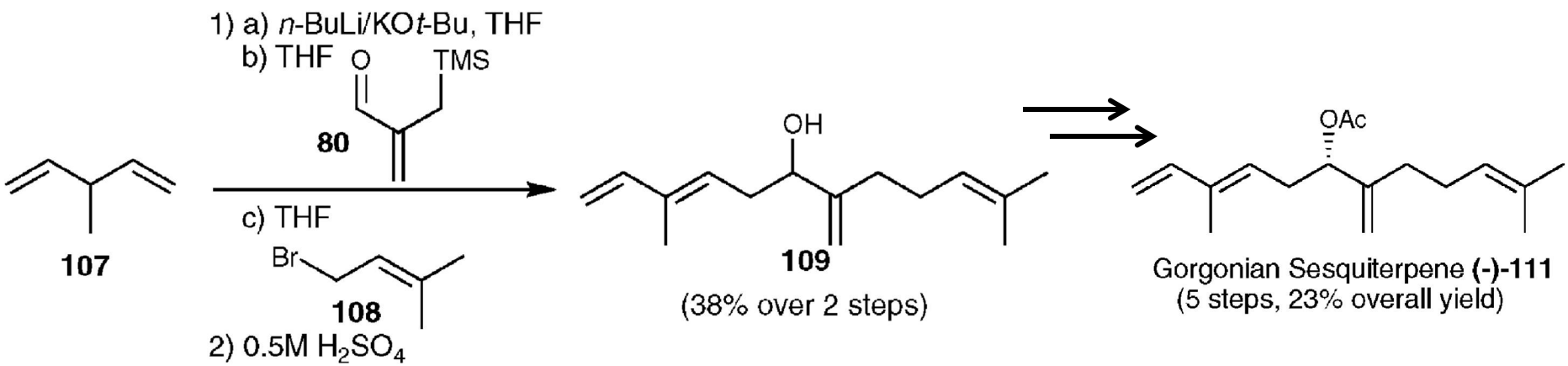


Group Problem



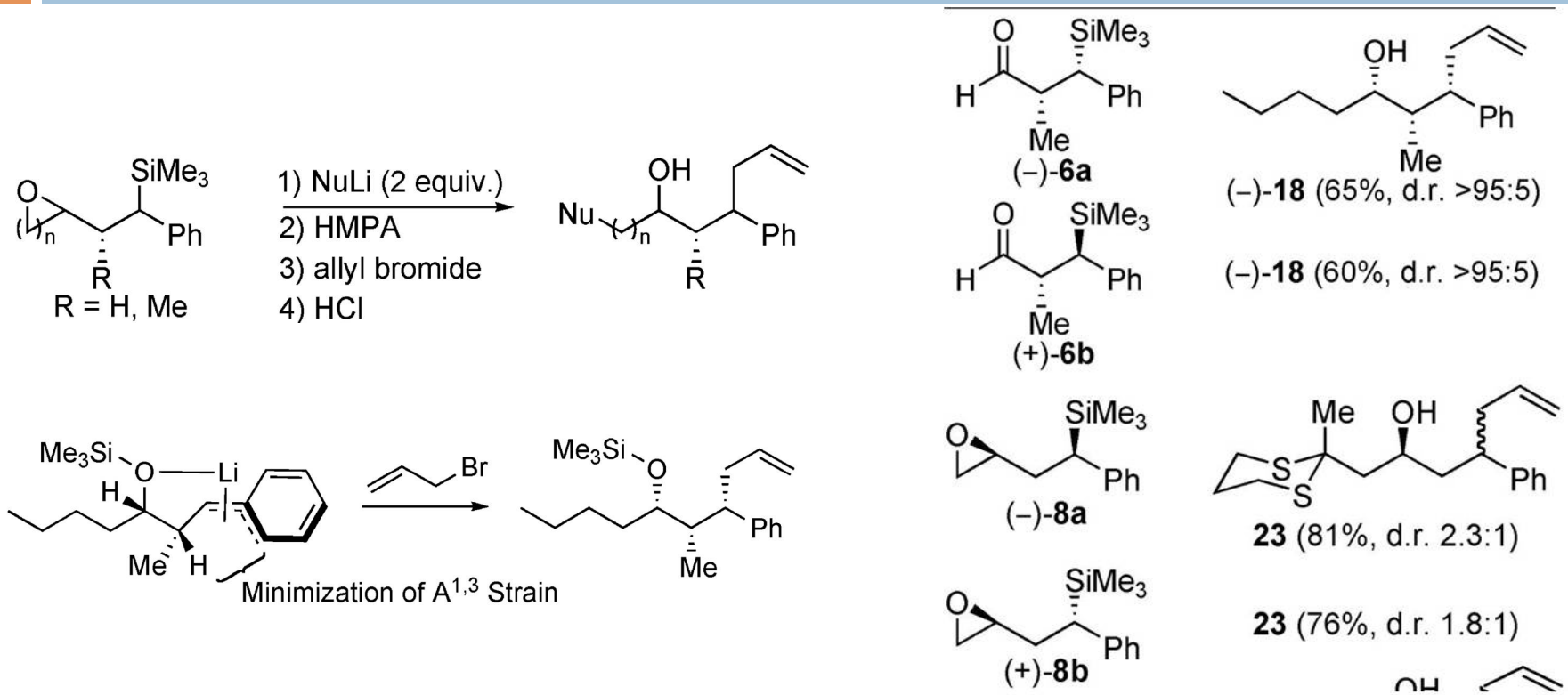
Smith et al, *Org. Lett.* **2007**, *9*, 3307

Further Application of new linchpins



Smith et al, *Org. Lett.* **2007**, *9*, 3307

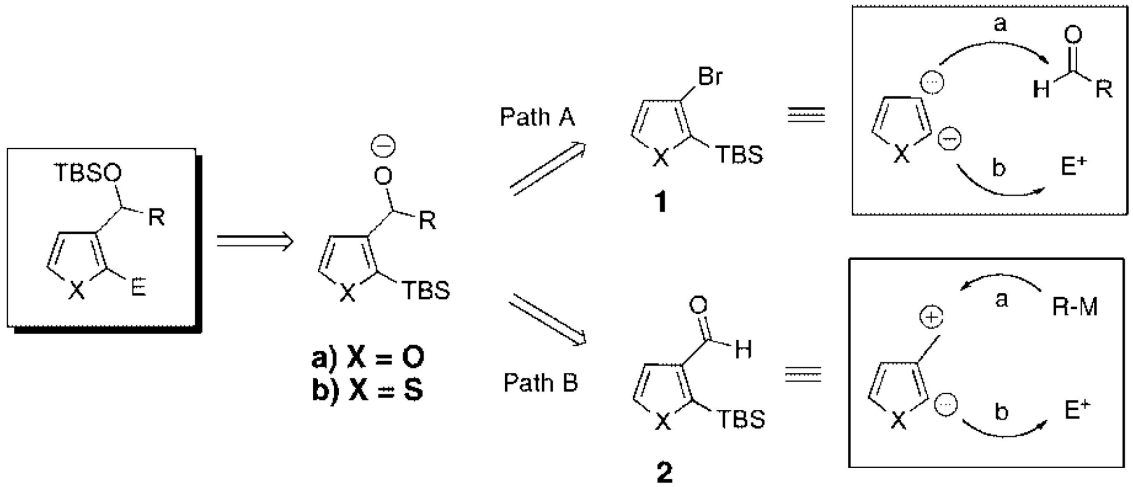
Diastereoselective ARC linchpin



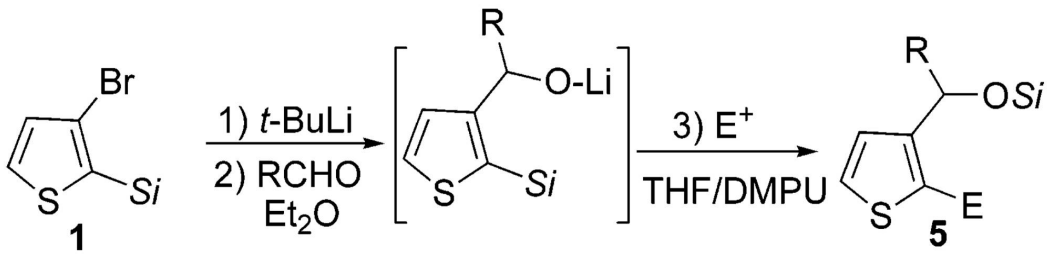
- Phenyl containing linchpin able to introduce diastereoselective to ARC Type 2 when adjacent to a stereocenter

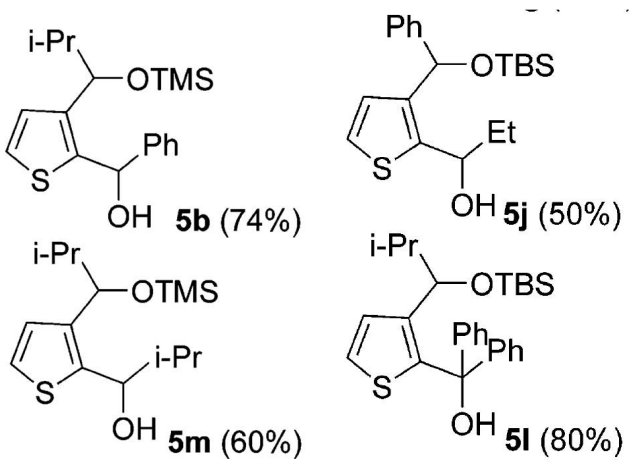
Smith et al, *Org. Lett.* **2010,** *12,* 1260

Thiophenes and Furans (Br-Li exchange)



Si = TMS

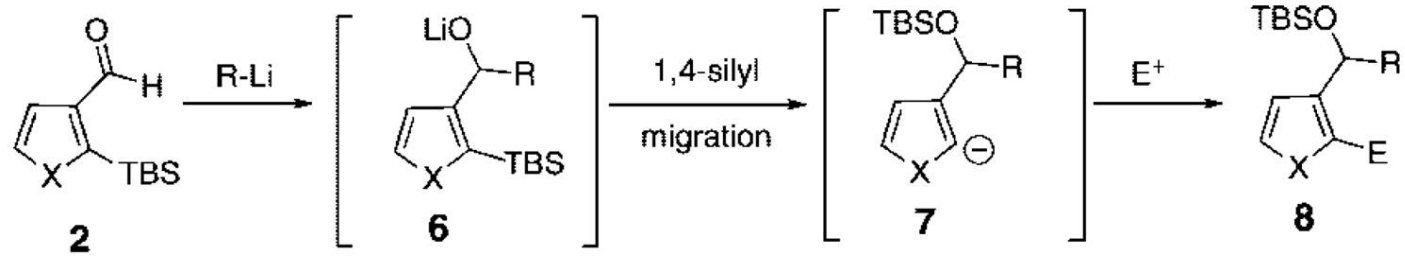




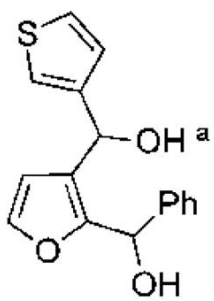
- sp^2 carbanion source with a stabilizing group in the ring

Xian et al, *Org. Lett.* **2007**, *9*, 4655 & **2009**, *11*, 1861

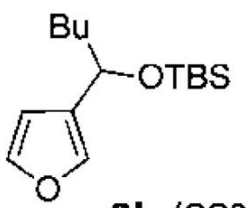
Thiophenes and Furans Couplings



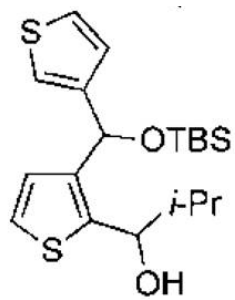
E^+ = *i*-Pr-CHO



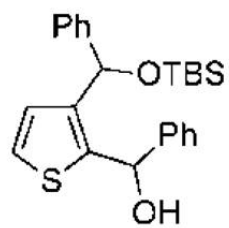
9f (62%)



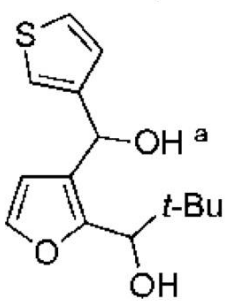
9h (82%)



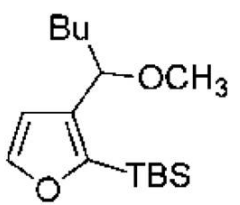
15g (76%)



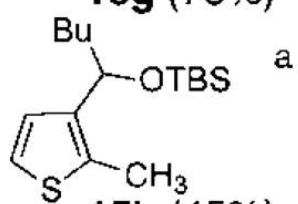
15e (77%)



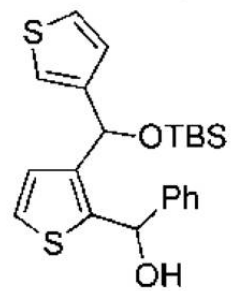
9g (65%)



9i (85%)



15h (45%)



15f (76%)

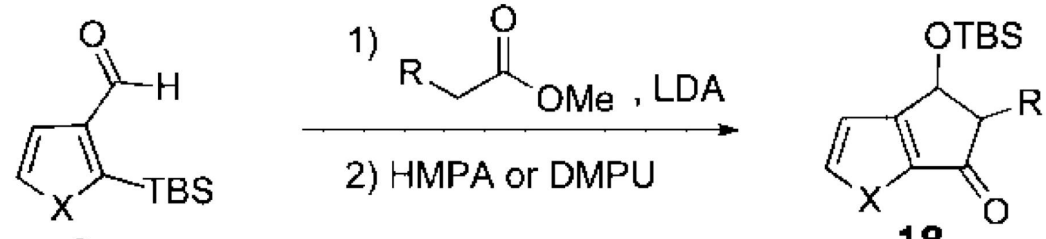
HMPA:Et_2O (1:1)

DMPU:THF (1:1)

Xian et al, *Org. Lett.* **2009**, *11*, 1861

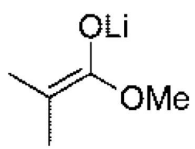
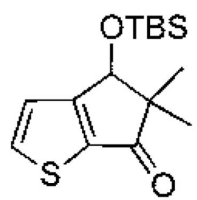
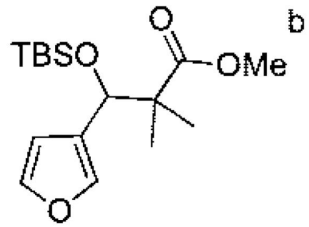
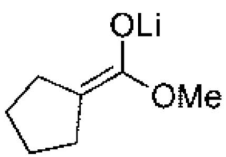
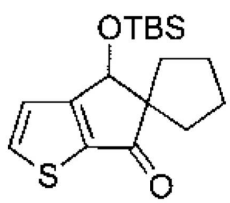
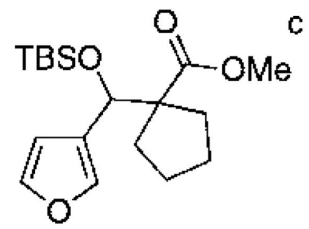
Thiophenes and Furans Cyclizations

- Use of enolates to form bicyclics



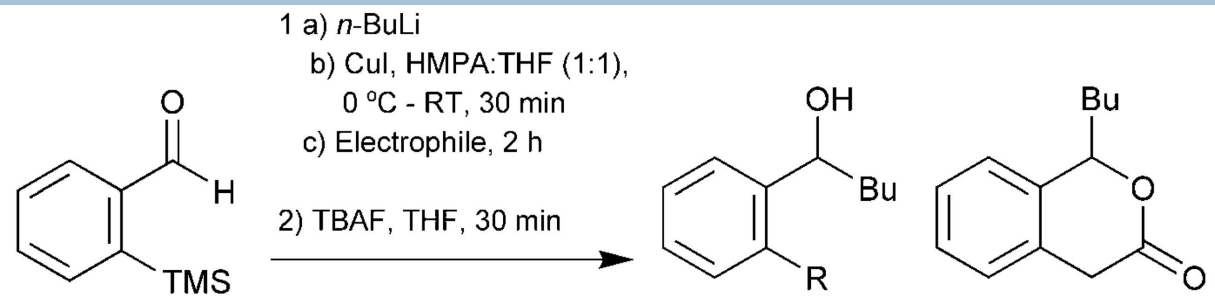
2
a) X = O
b) X = S

18

Enolate	Product(yield)
	 a **18a** (69%)  b **19a** (52%)
	 a **18b** (88%)  c **19b** (57%)

Xian et al, *Org. Lett.* **2009**, *11*, 1861

Ortho-TMS-benzaldehye

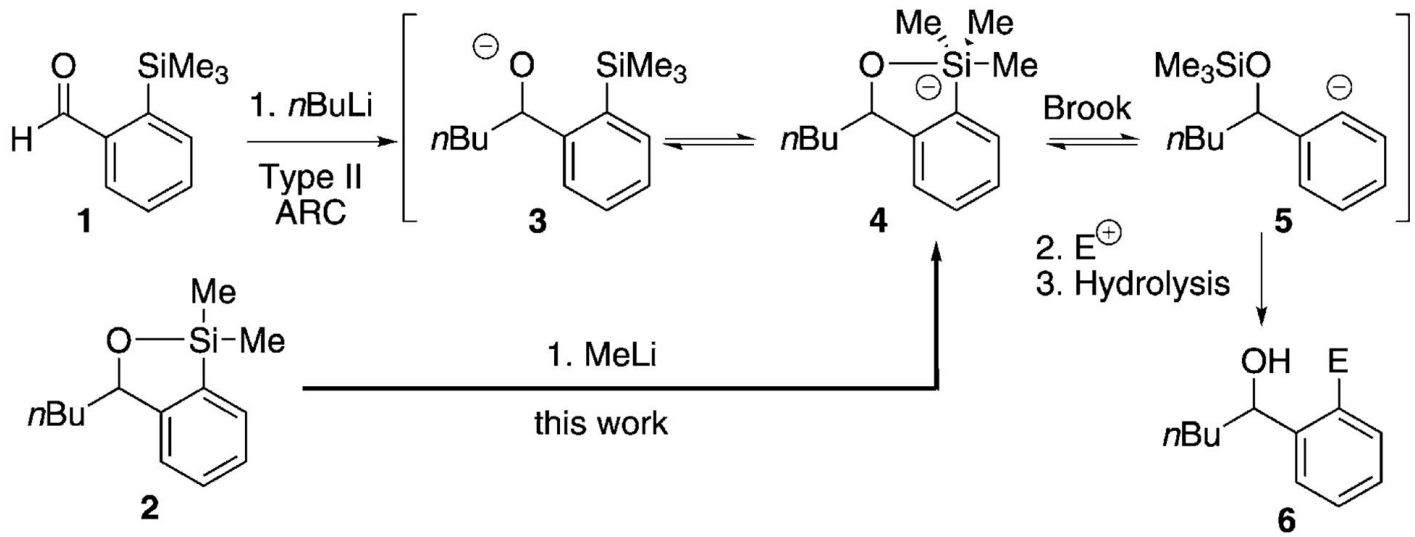


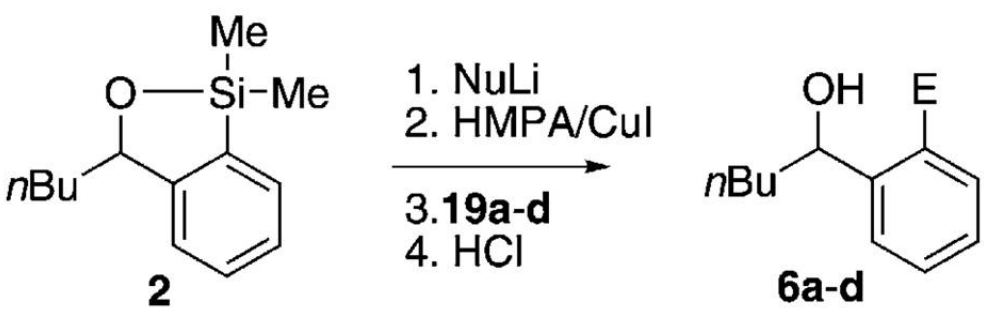
Electrophile	R	Product	Yield [%]
Br		**6a**	69
Br Ph	Ph	**6b**	55
Br		**6c**	58[a]
PhS-SPh	SPh	**6e**	71
Bu_3SnCl	$SnBu_3$	**6f**	65
Br O OEt		**7**	50[b]
Br		**6g**	56[c]

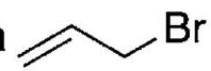
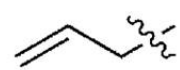
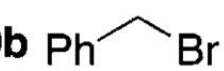
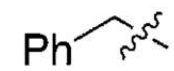
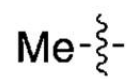
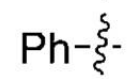
- Linchpin enables sp^2 carbon additions and cyclilizations

Smith et al, *Angew. Chem. Int. Ed.*, **2008**, *47*, 7082

Different ARC Type 2 Pathway



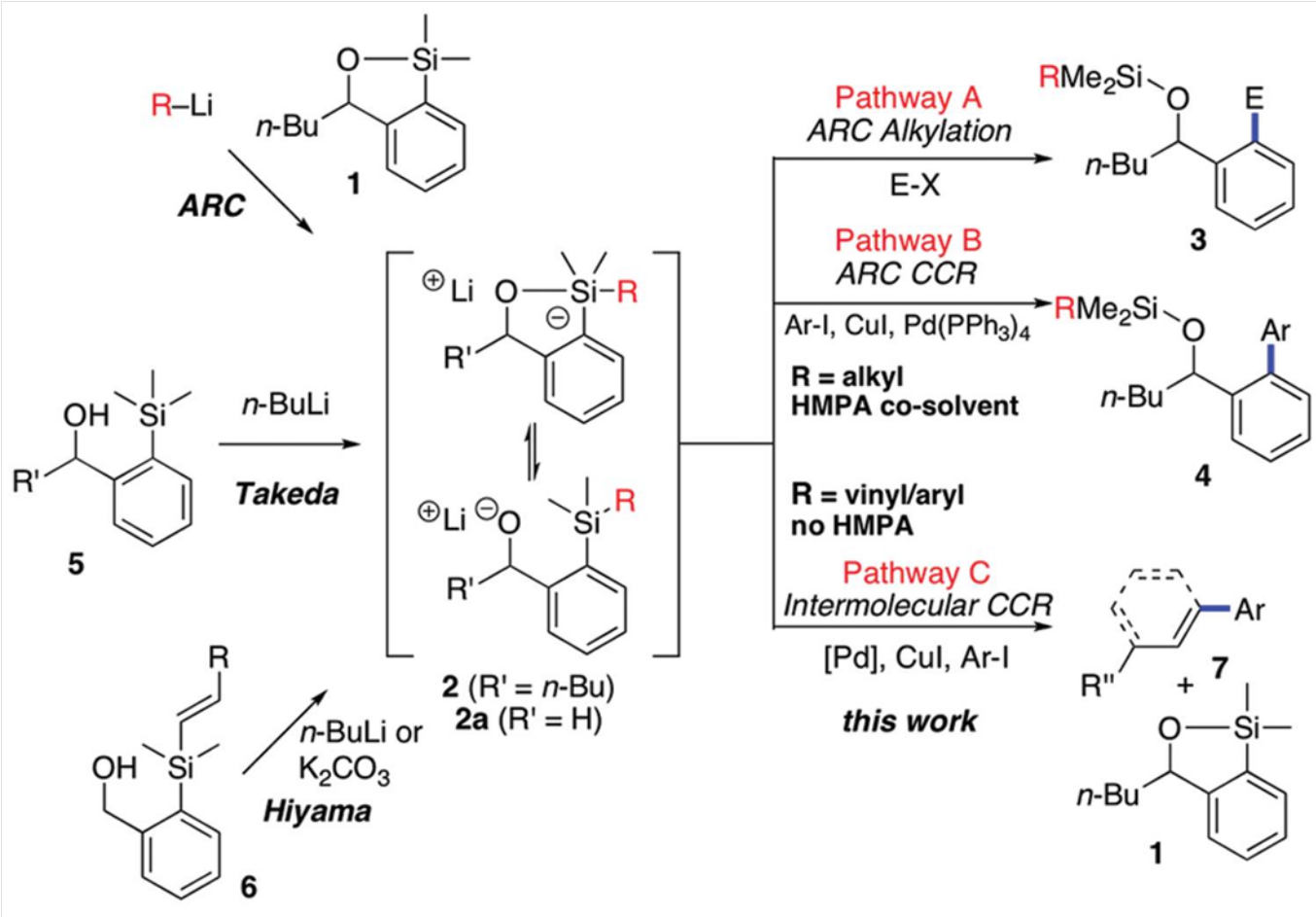


Electrophile		E	yield
19a			**6a**, 66%
19b			**6e**, 74%
19c	Me—I		**6c**, 78%
19d	Ph—I*		**6d**, 65%

- Pre-coordinated Si-O bond can act as a means to achieve [1,4] like rearrangements

Smith et al, *Angew. Chem. Int. Ed.*, **2011**, *50*, 8904

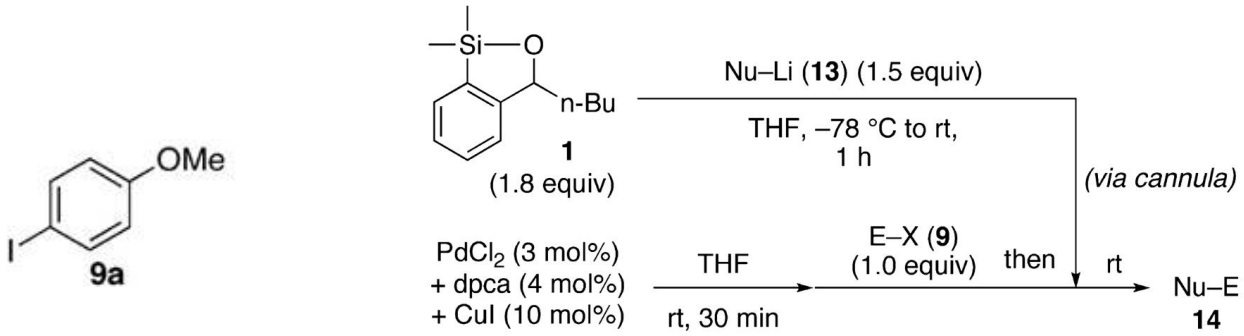
Pd Crosscoupling ARC Type 2



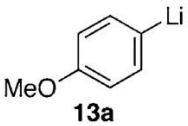
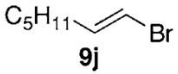
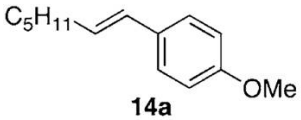
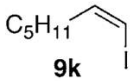
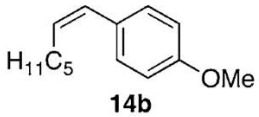
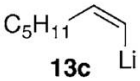
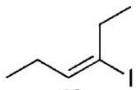
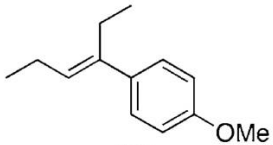
- Attempt to access ARC products via Pd coupling route

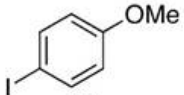
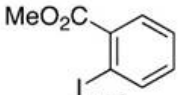
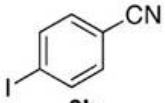
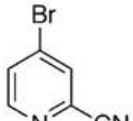
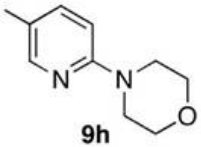
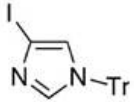
Smith et al, *J. Am. Chem. Soc.* **2012**, *134, 4533*

Pd Crosscoupling ARC Type 2



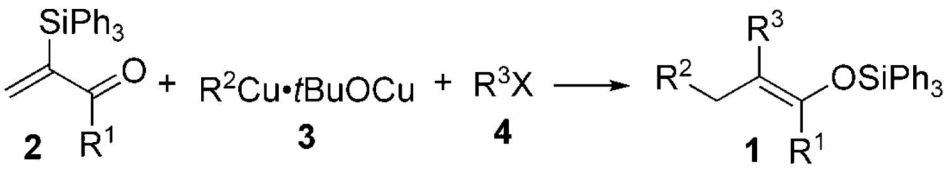
Nu-Li = Ph-Li

Nu–Li	E–X	Product	Yield[a]
 13a	 9j	 14a	81%
13a	 9k	 14b	84%
 13c	9a	14b	82%
13a	 9l	 14c	79%

Ar–X	Yield[a]	Ar–X	Yield[a]
 9a	96% (10a)	 9f	76% (10d)
 9b	92% (10b)	 9g	85% (10e)
 9h	95% (10f)	 9i	67% (10g)

Smith et al, *J. Am. Chem. Soc.* **2012**, *134, 4533*

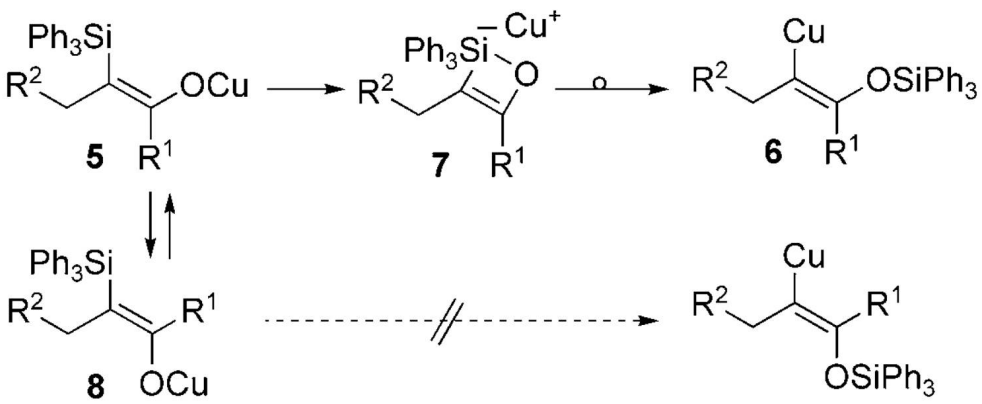
Stereoselective ARC

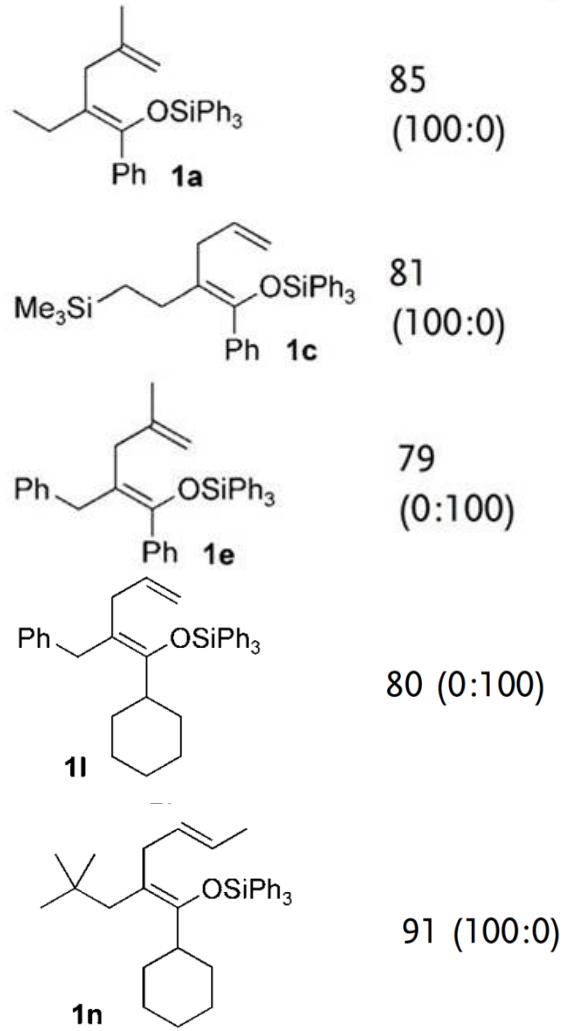


R^1 = Ph (**2a**), $PhCH_2CH_2$ (**2b**), Cy (**2c**)

R^2 = Me (**3a**), *i*Pr (**3b**), $TMSCH_2$ (**3c**), vinyl (**3d**), Ph (**3e**), *t*Bu (**3f**)

R^3 = $H_2C{=}CMeCH_2$ (**4a**), $H_2C{=}CHCH_2$ (**4b**), $PhCH_2$ (**4c**), Me (**4d**),



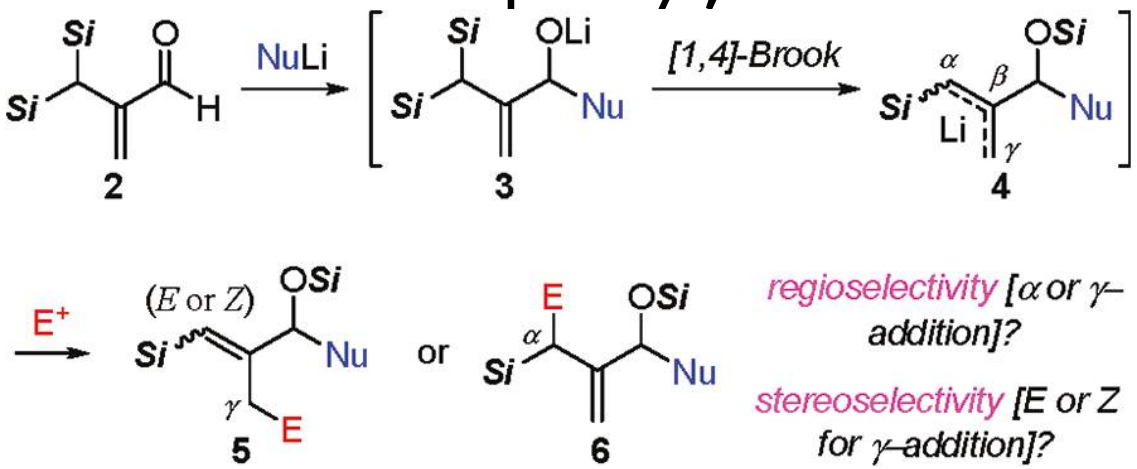


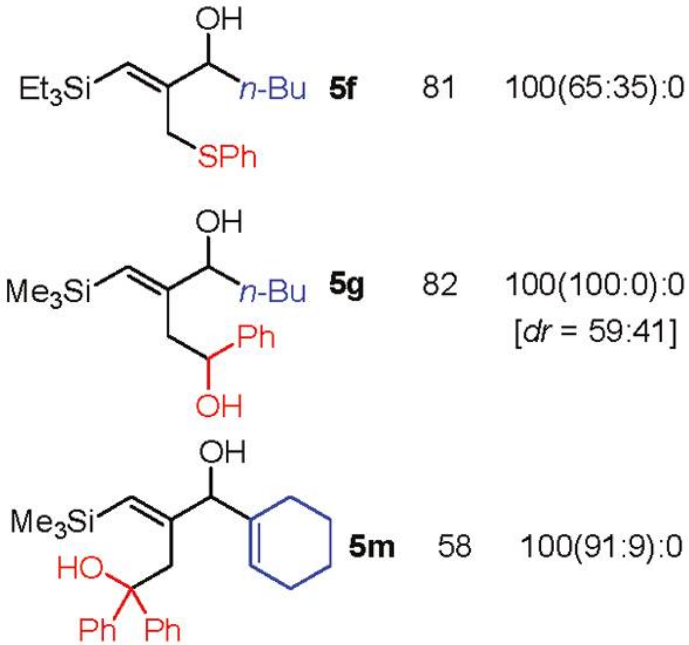
- Can achieve complete stereoselectivity through closed transition state

Takeda et al, *Angew. Chem. Int. Ed.*, **2010**, *49*, 7089

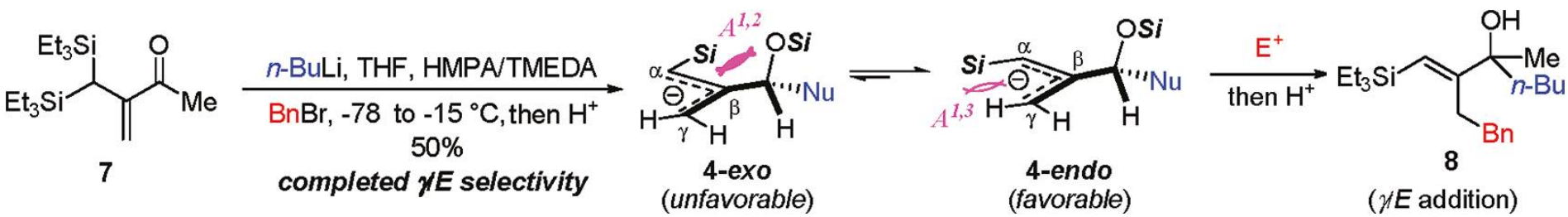
Silyl group as anion stabilizer

- Use of silyl groups to stabilize anion formation, instead of phenyl, dithianes





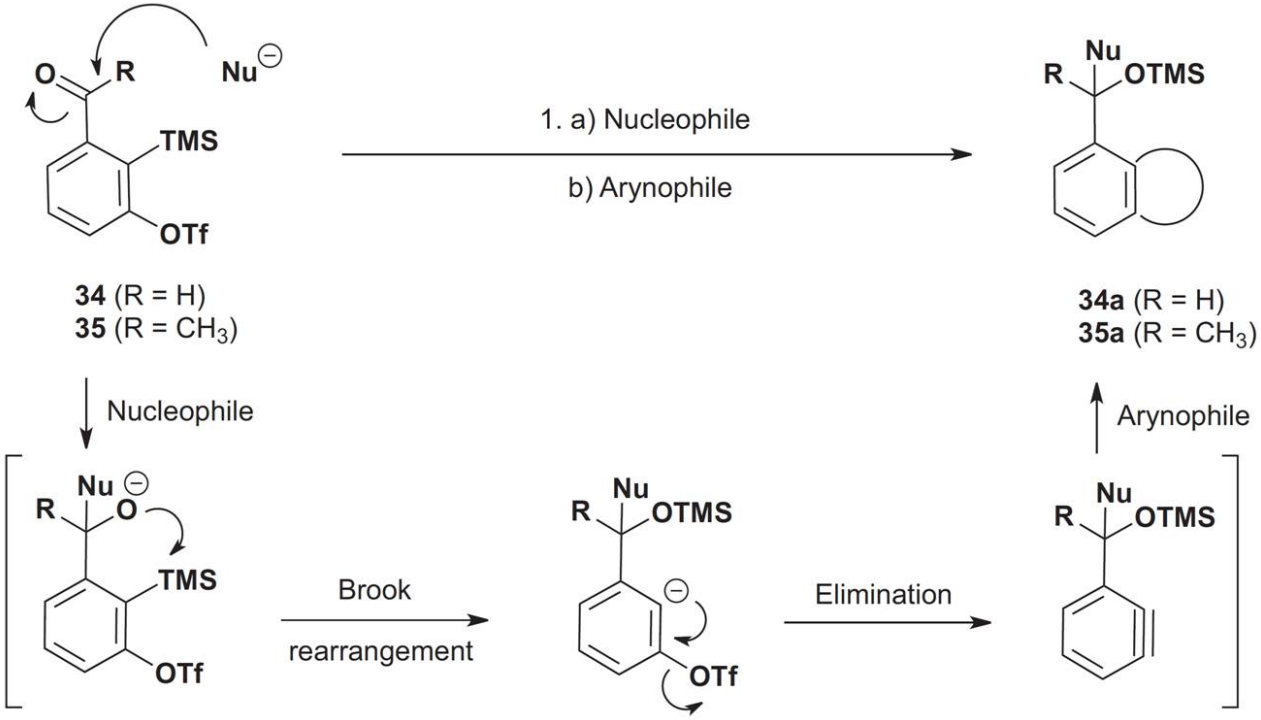
- Nearly all E addition



Song et al, *Org. Lett.* **2012,** *14,* 158

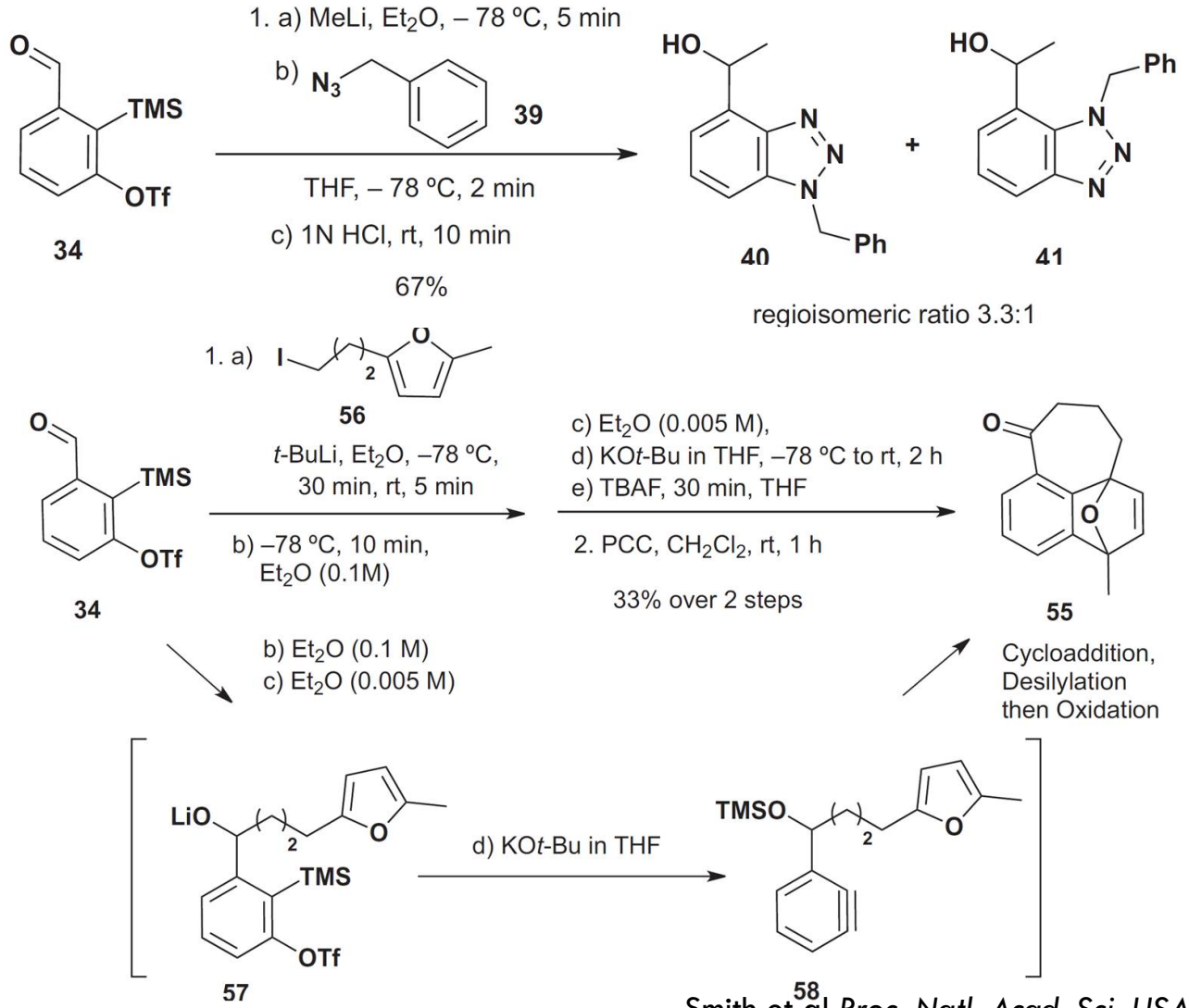
Cyclizations with ARC and Benzyne

- Application of previous o-TMS-benzaldehye



Smith et al *Proc. Natl. Acad. Sci. USA*, **2011**, *108*, 6782

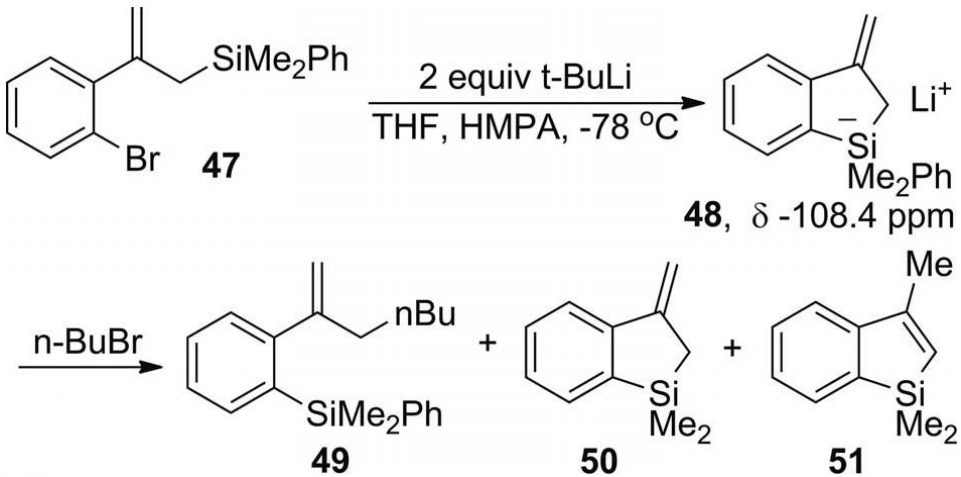
Cyclizations with ARC and Benzyne



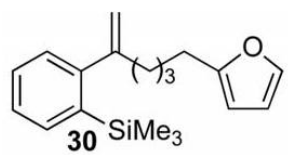
Smith et al *Proc. Natl. Acad. Sci. USA*, **2011**, *108*, 6782

Carbon-Carbon ARC

- Novel C-C forming reaction using ARC principles

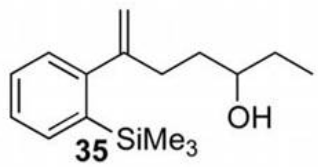


94%



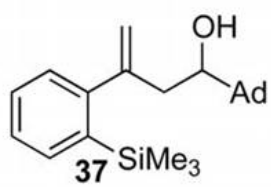
77%

75%

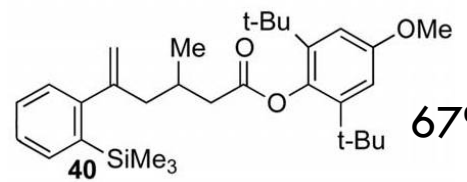


70%

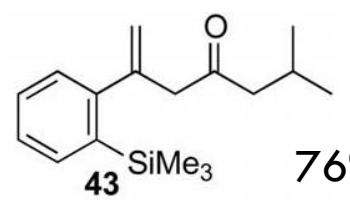
68%



72%



67%

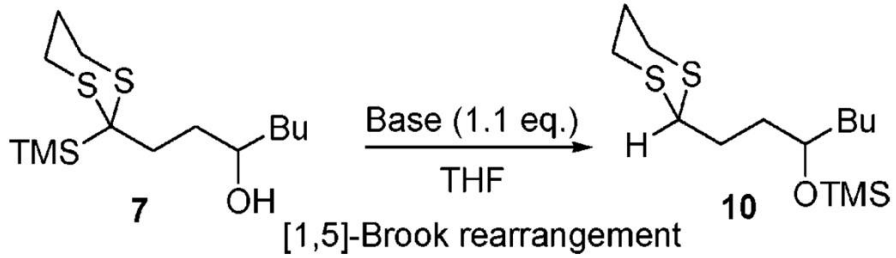


76%

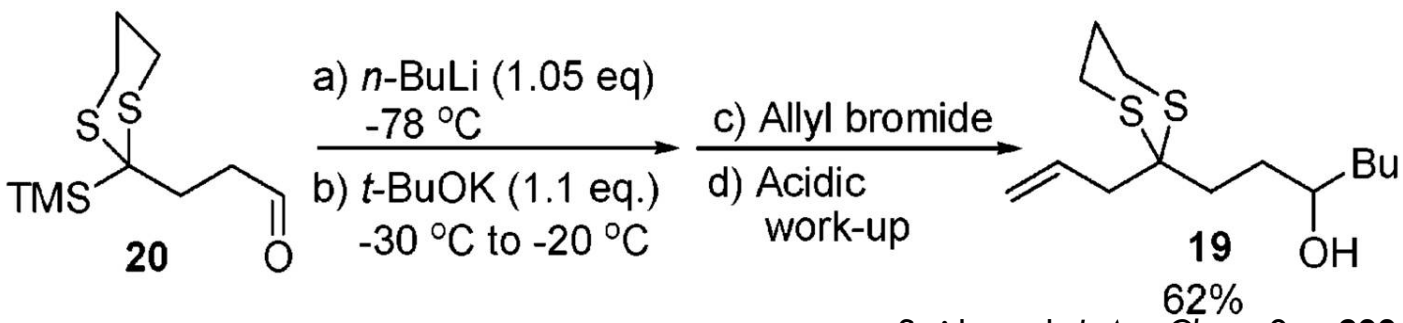
Schreiner, Harmata et al. *Eur. J. Org. Chem.*, ***2011***, *5255*

[1,5] Brook Rearrangement & ARC

- Expansion of [1,4] Brook ARC work

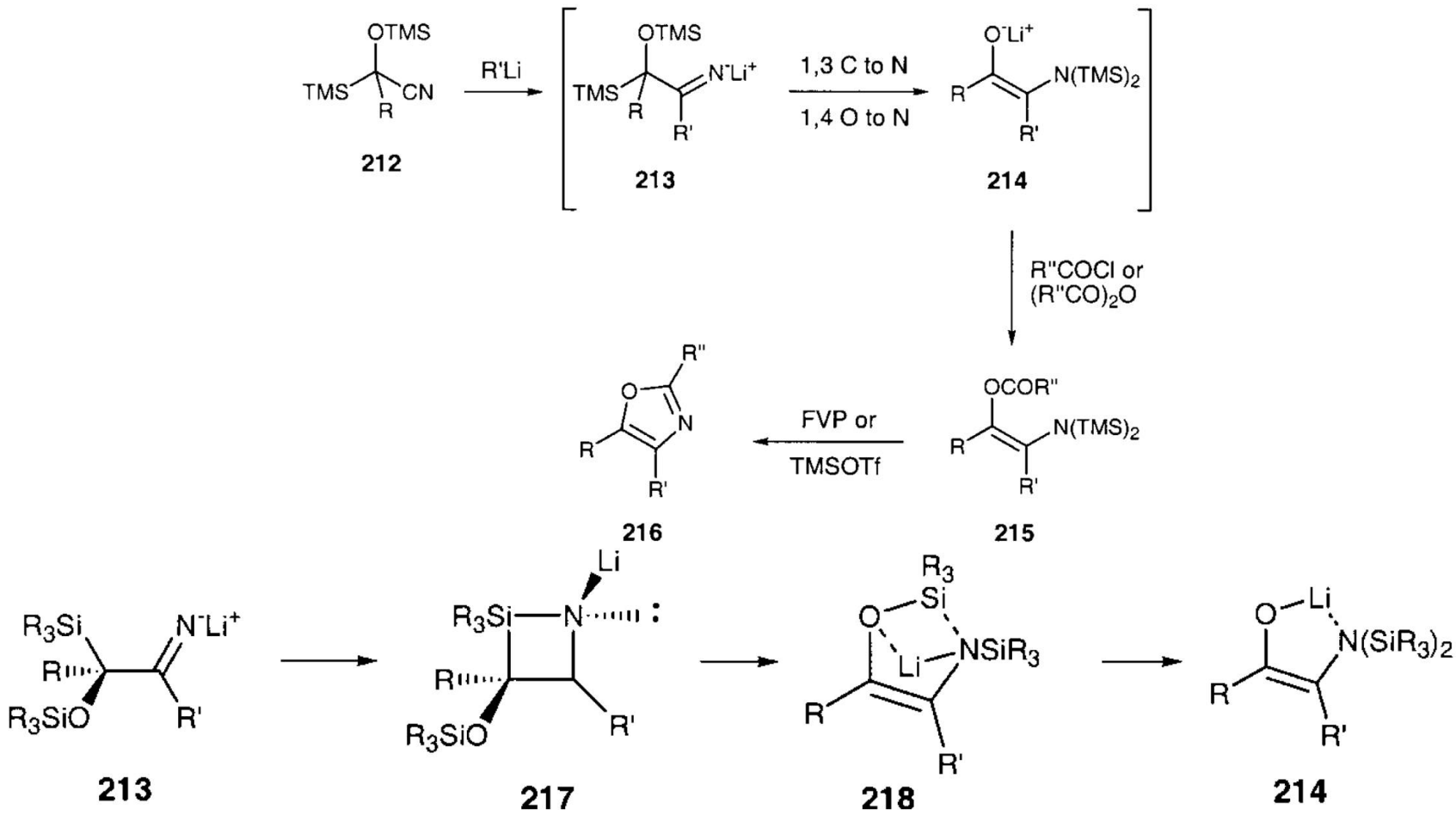


entry	base	temp	time	yield of **10**
1	*t*-BuLi or *n*-BuLi	rt	overnight	<30%
2	LHMDS	rt	overnight	40%
3	NaHMDS	0 °C	30 min	88%
4	KHMDS	0 °C	30 min	92%
5	*t*-BuOK/*n*-BuLi	0 °C	60 min	89%



Smith et al, *J. Am. Chem. Soc.* **2006**, *128, 12368*

Aza-Brook ARC



- Viable method for synthesis of oxazoles

Moser, Tetrahedron **2001**, *57, 2065*

ARC Type 2 Conclusions

- Solvent and additives important in controlling of [1,4] Brook onset in addition of dissimilar electrophiles
- Synthesis of unsymmetrical carbon backbones
- Diverse set of linchpins
- Broad cyclization scope
- Stereoselective variants
- Potential for use in Pd coupling
- Extensions to non C-Si-O Brook
- Limited to Brook rearrangement