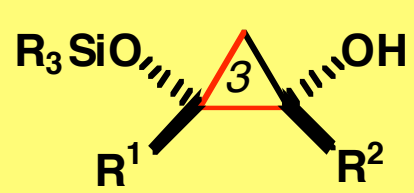
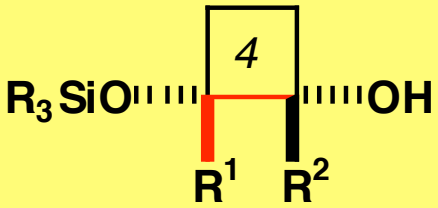
連続的炭素-炭素結合形成反応を用いる新規有機合成反応の開発

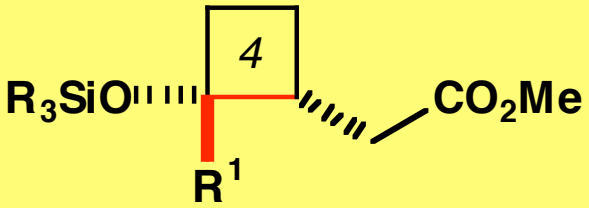
広島大学大学院
医歯薬学総合研究科薬学専攻
武　田　　敬

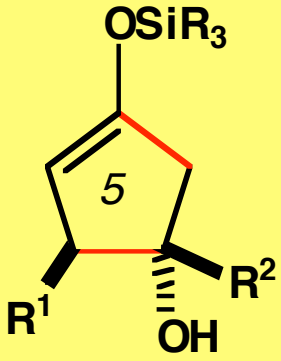
2002年4月26日，金沢大学薬学部

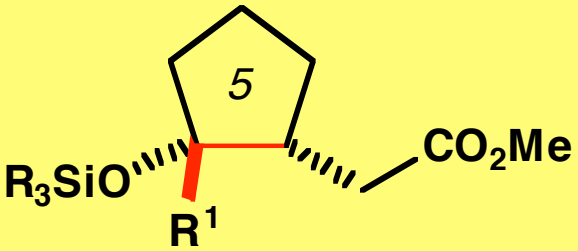
Brook Rearrangement-Mediated Formation of Carbocycles

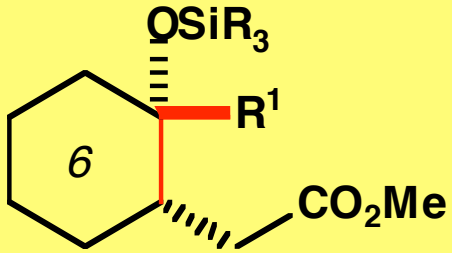


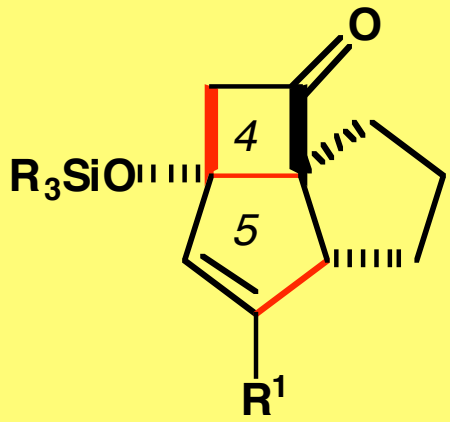


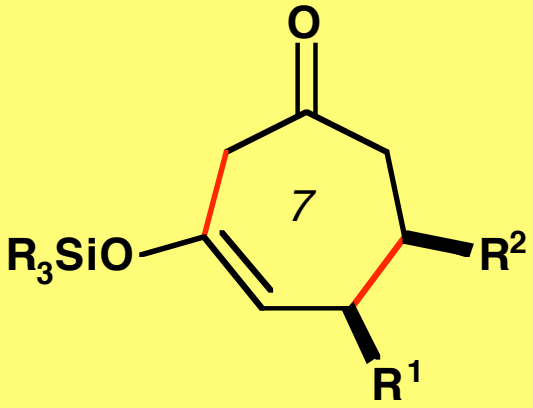


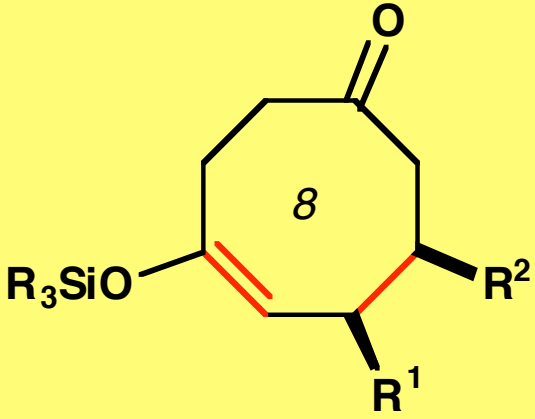


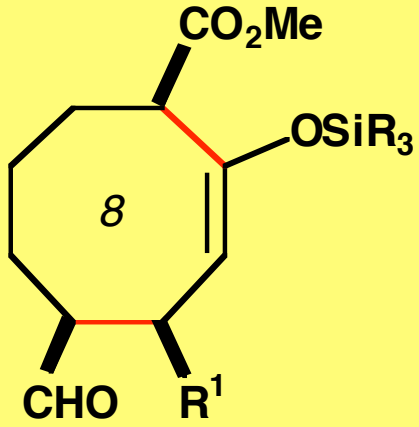




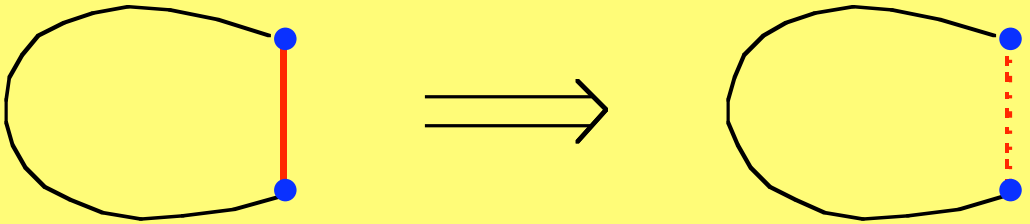




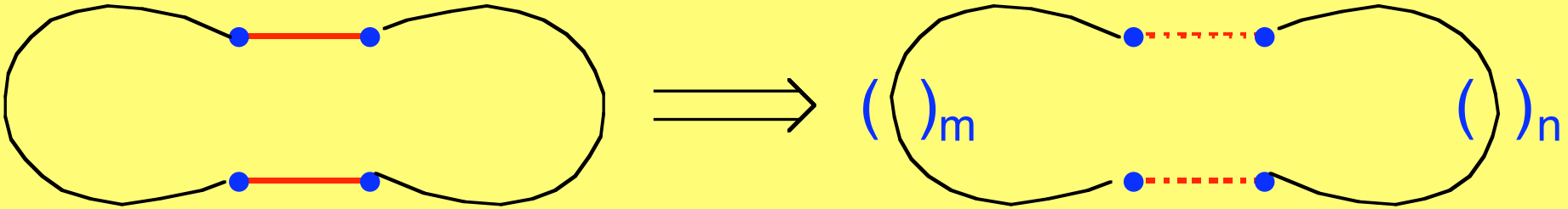




環形成法



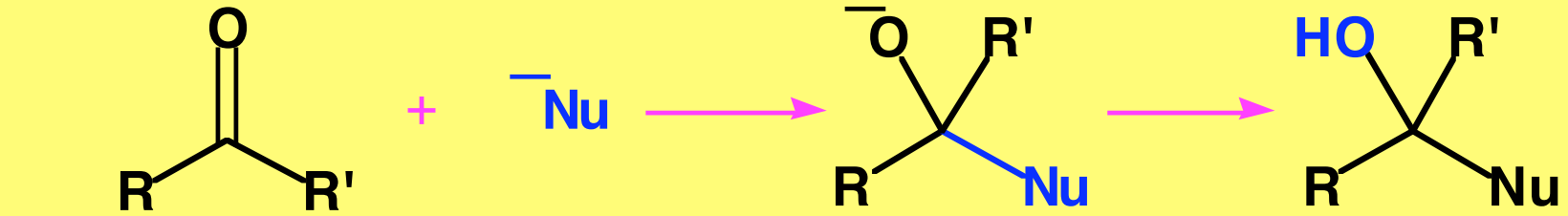
分子内環化法 (cyclization)

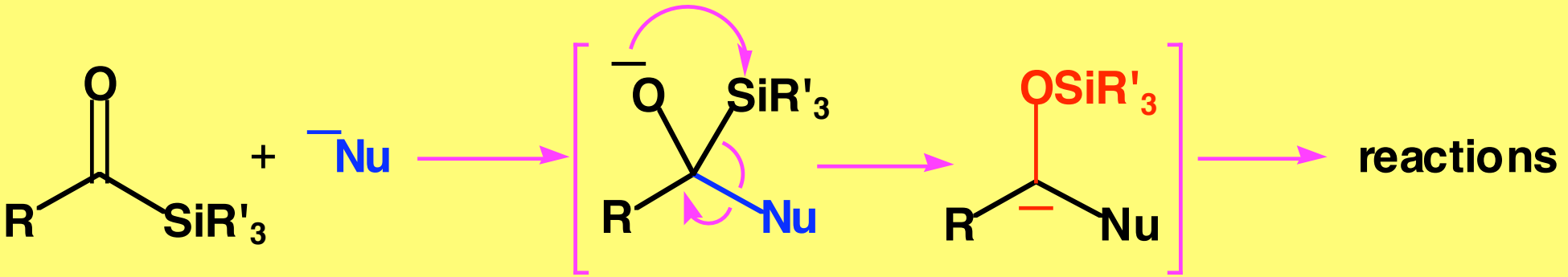


アニュレーション法 (annulation)

[m + n] annulation

Brook Rearrangement

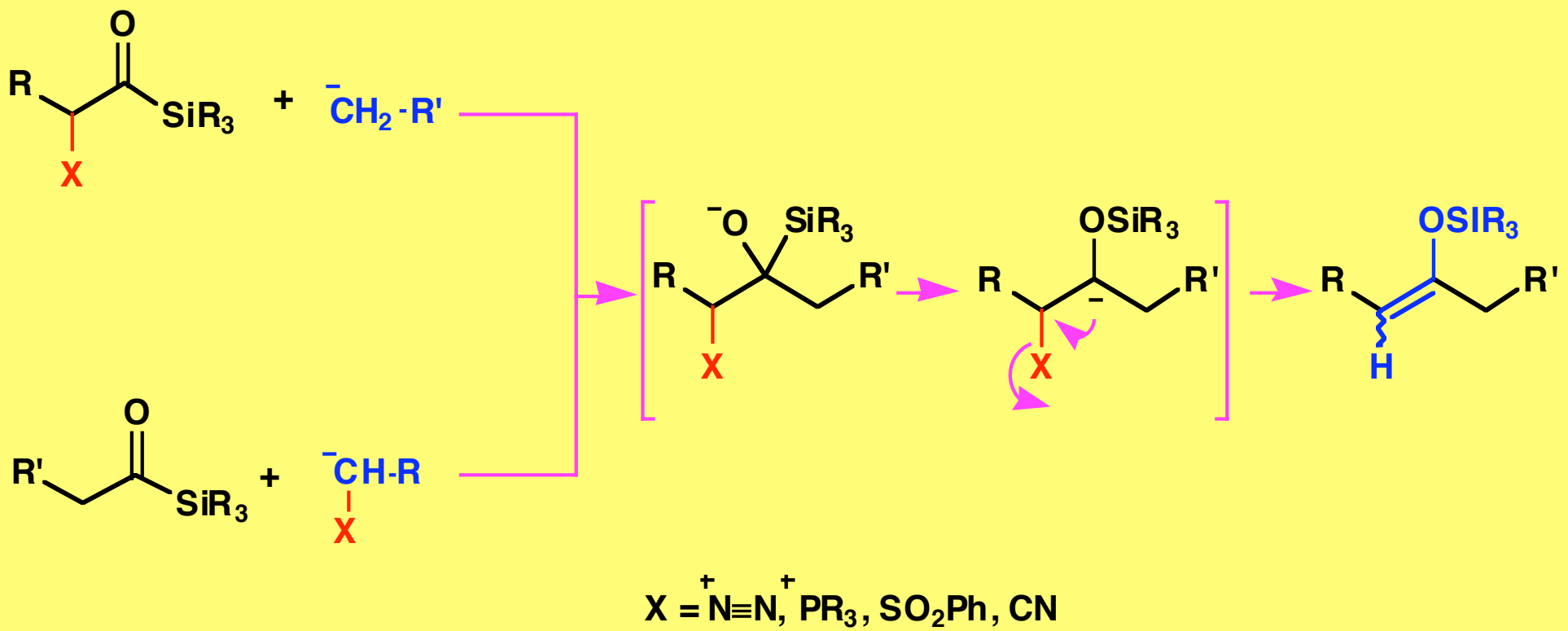




Brook rearrangement

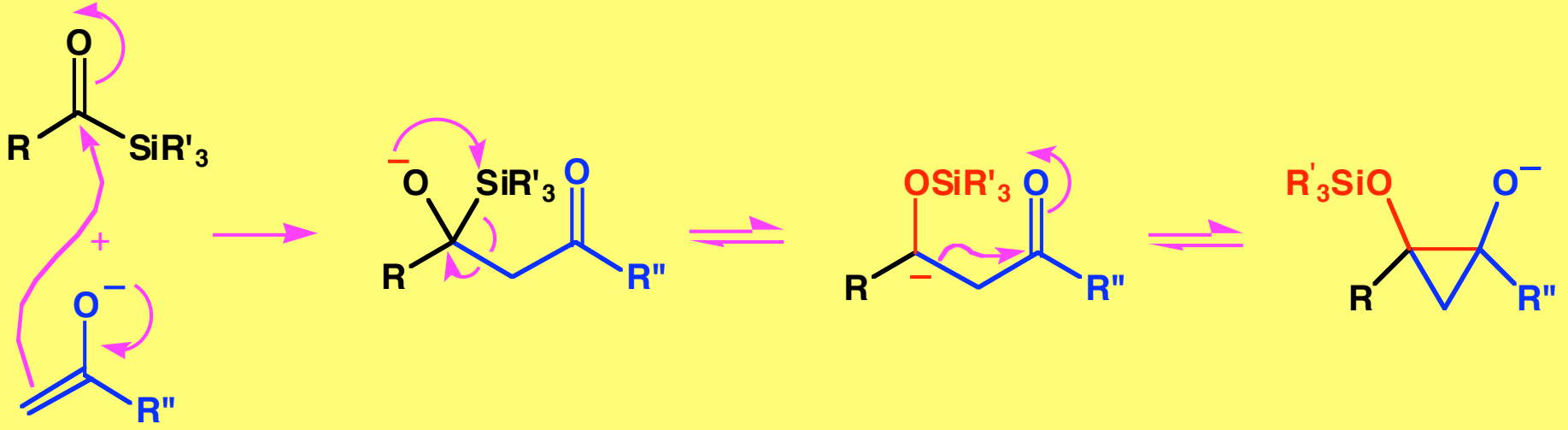
Brook, A.G. *J. Am. Chem. Soc.* **79**, 4373 (1957)

Reactions of Acylsilanes Bearing a Leaving Group with a Nucleophile
Reactions of Acylsilanes with a Nucleophile Bearing a Leaving

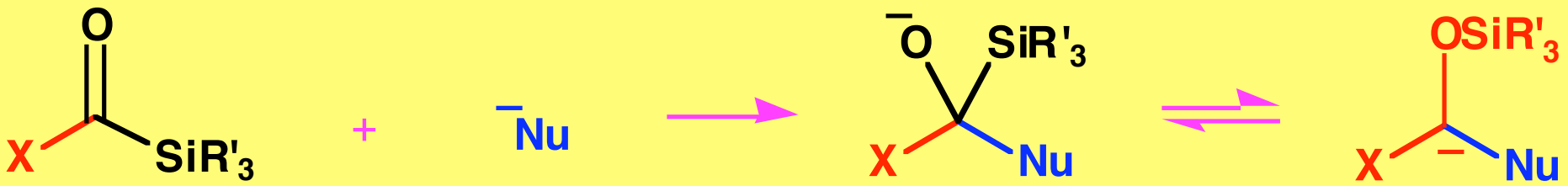


Brook, A. G.; Limburg, W. W.; MacRae, D. M.; Fieldhouse, S. A. *J. Am. Chem. Soc.* **1967**, *89*, 704.
Reich, H. G.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609-5617.
Nakajima, T.; Segi, M.; Sugimoto, F,; Hioki, R.; Yokota, S.; Miyashita, K. *Tetrahedron* **1993**, *37*, 8343.

Use of Ketone Enolate as a Nucleophile

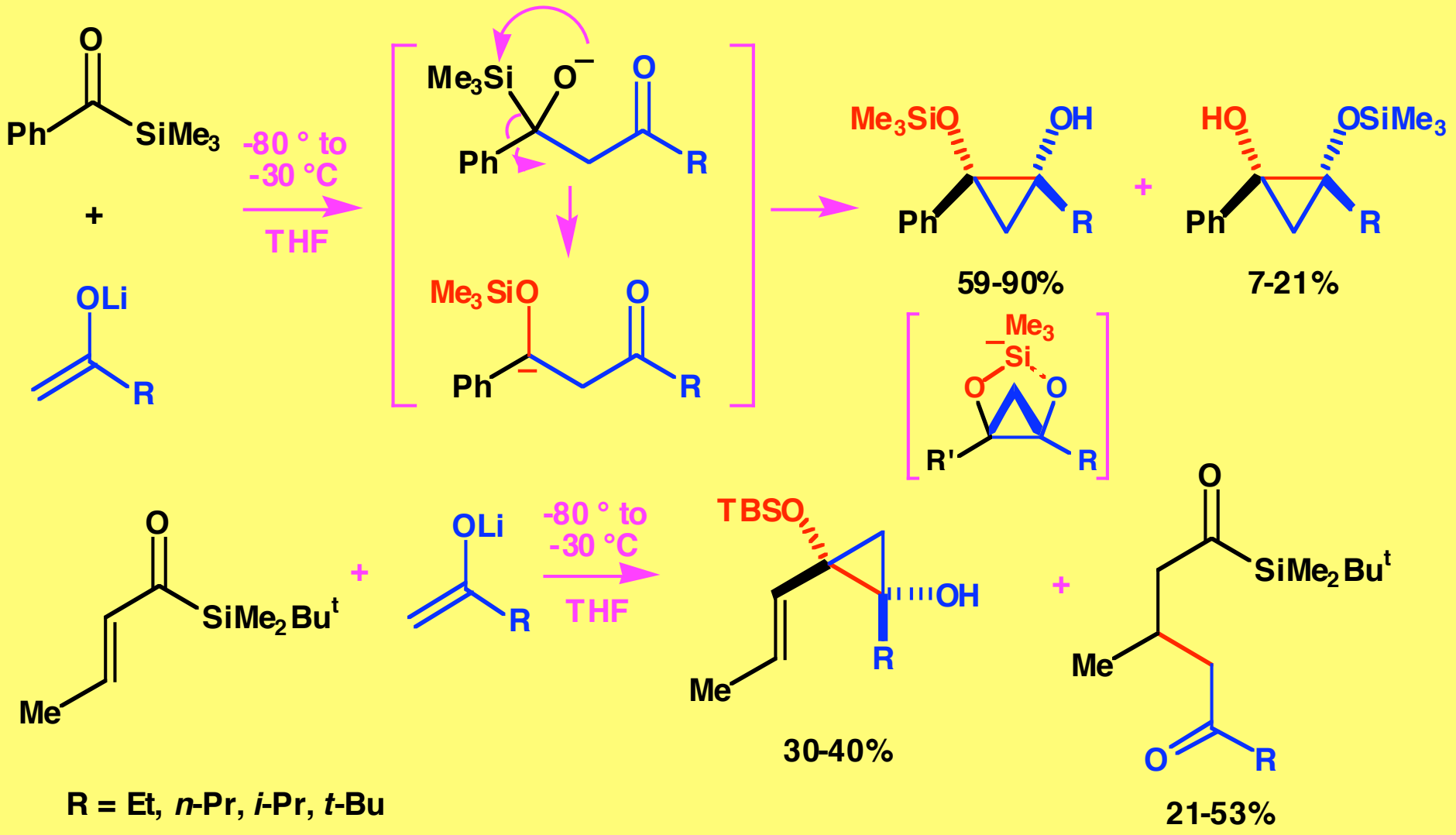


Introduction of a Carbanion-Stabilizing Heteroatom

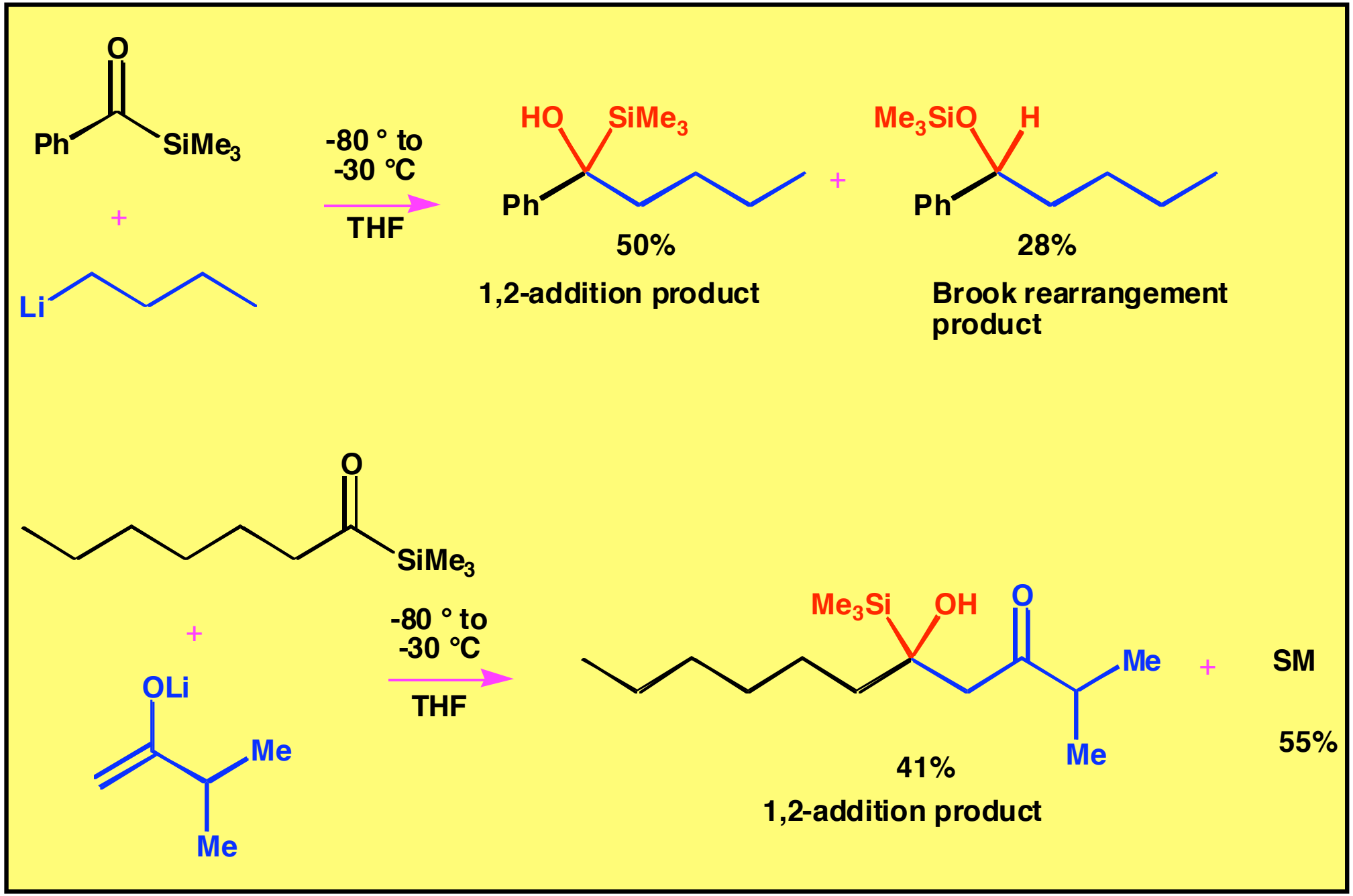


X = SPh, $SiMe_3$, $P(O)(OMe)_2$

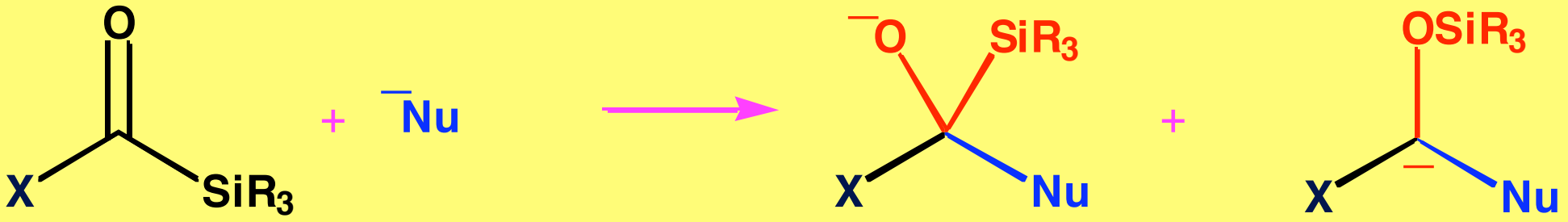
Reaction of α,β-Unsaturated Acylsilanes with Lithium Enolates



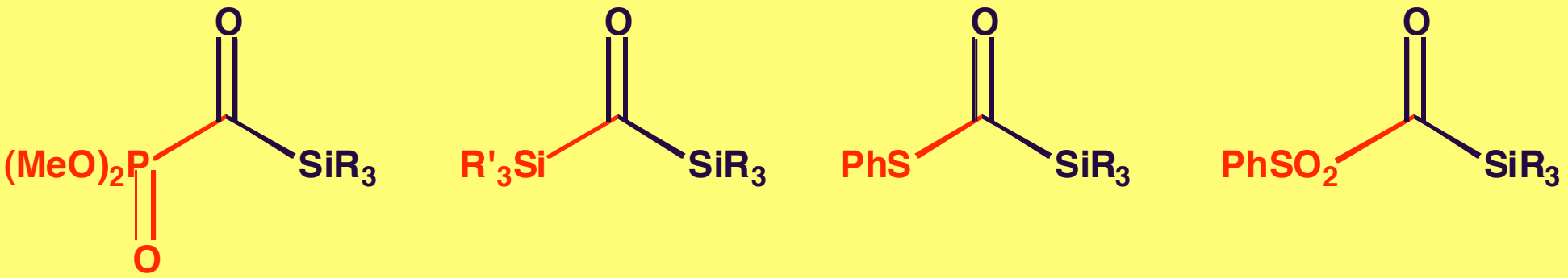
Takeda, K.; Nakatani, J.; Nakamura, H.; Sako, K.; Yoshii, E.; Yamaguchi, K. *Synlett* **1993**, 841-843.


O
Ph
SiMe3
+
Li
-80 ° to
-30 °C
THF
HO
SiMe3
Ph
50%
1,2-addition product
+
Me3SiO
H
Ph
28%
Brook rearrangement
product
O
SiMe3
+
OLi
Me
Me
-80 ° to
-30 °C
THF
Me3Si
OH
O
Me
Me
41%
1,2-addition product
+
SM
55%

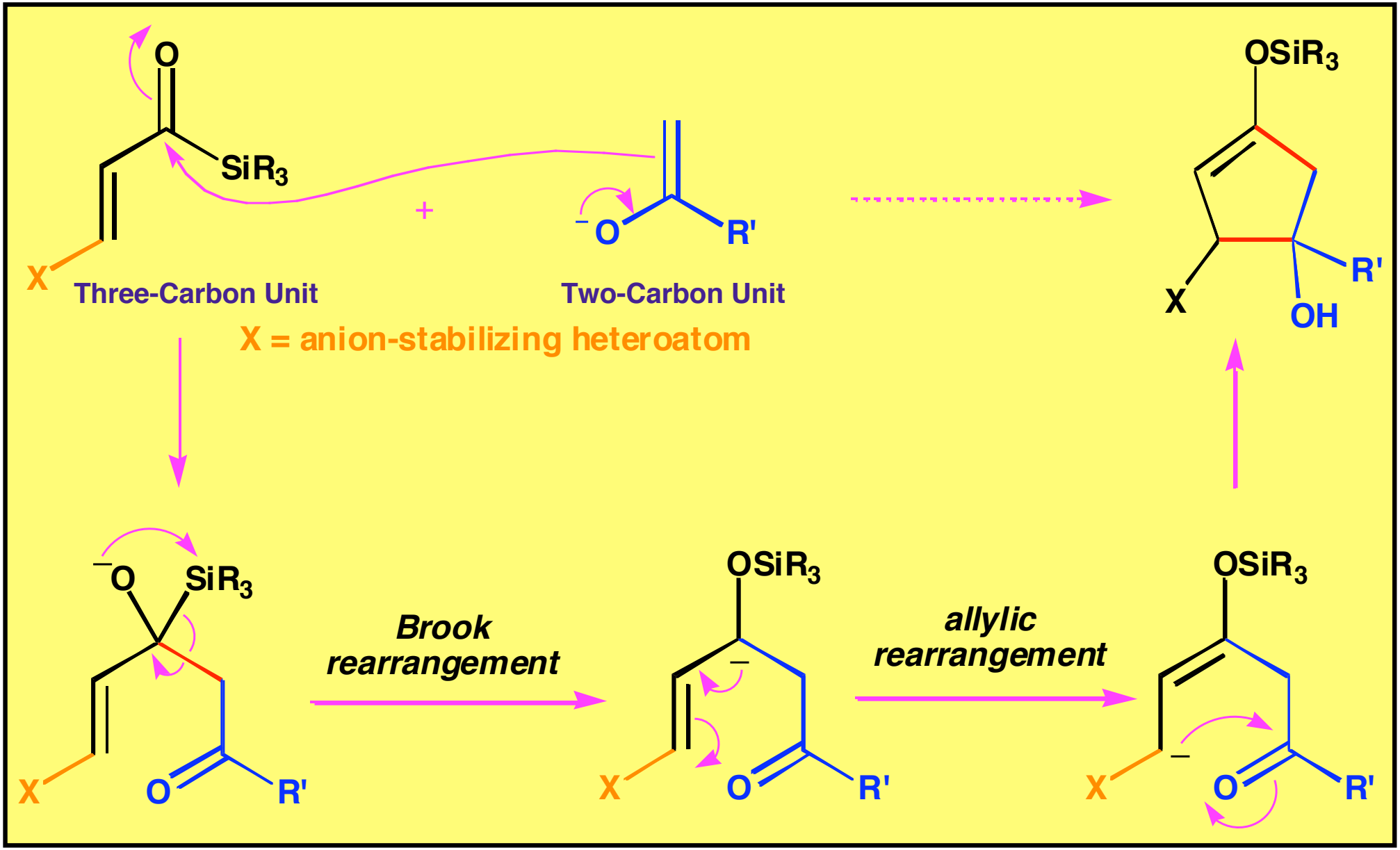
Attempted Synthesis of Heteroatom-Substituted Carbonylsilanes



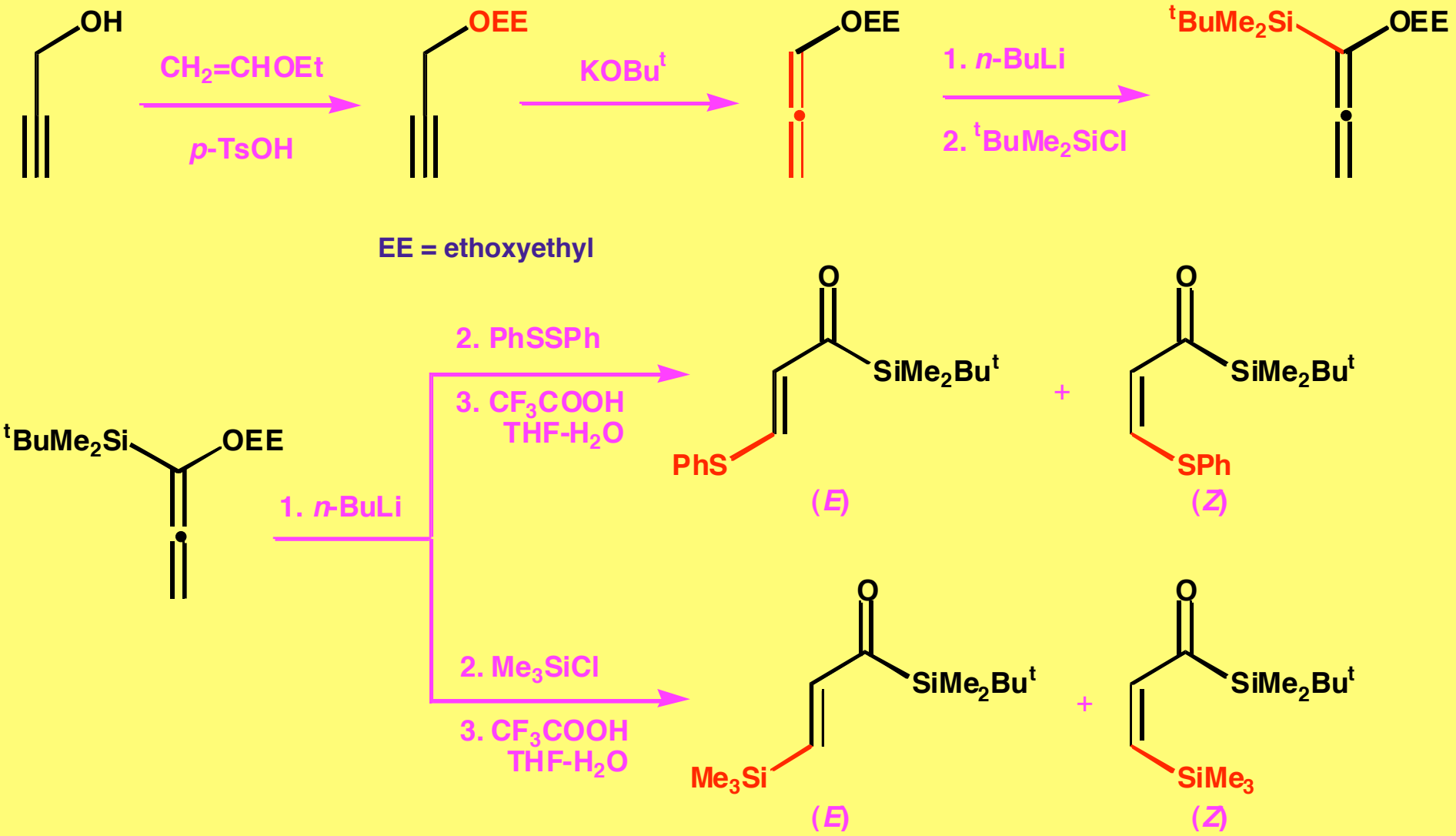
X = anion-stabilizing heteroatom



Brook Rearrangement-Mediated [3 + 2] Annulation

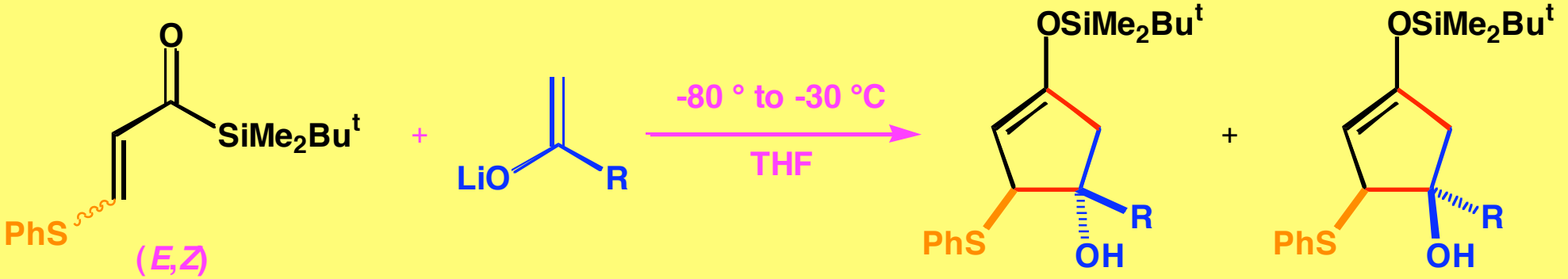


Preparation of β-(Phenylthio)- and β-(Trimethylsilyl)Acryloylsilanes

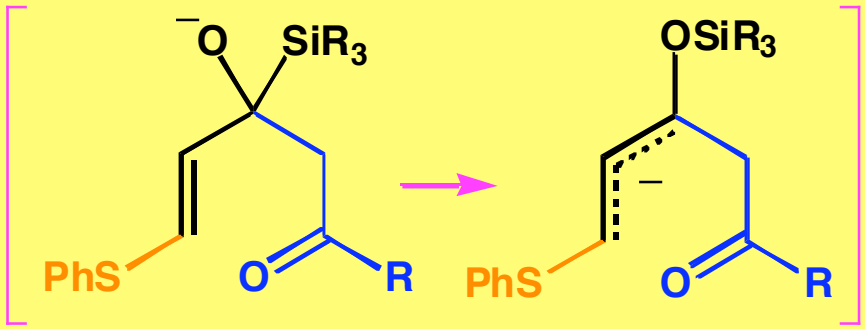


Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. *Tetrahedron* **1983**, *39*, 949-960.
Takeda, K.; Nakajima, A.; Takeda, M.; Yoshii, E. *Org. Synth.* **1999**, *76*, 199-213

[3 + 2] Annulation Using Reaction of (β-Phenylthio)acryloyl)silanes and Lithium Enolates

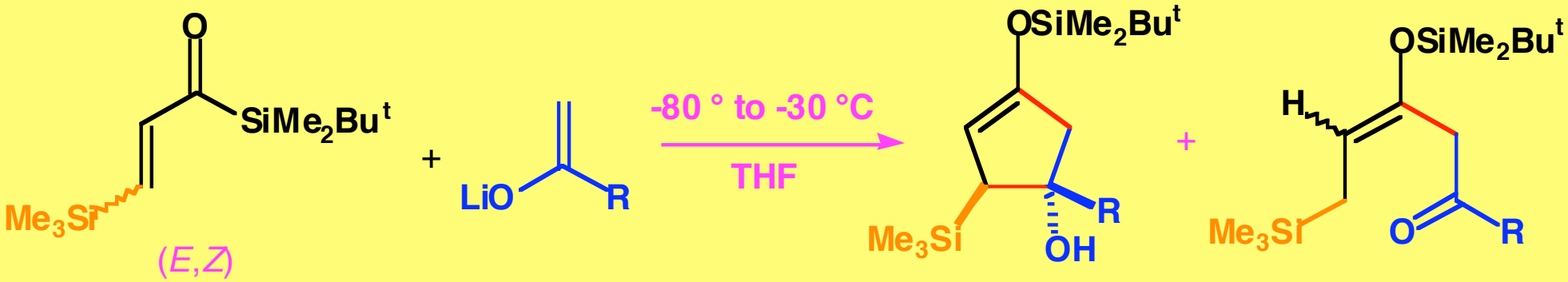


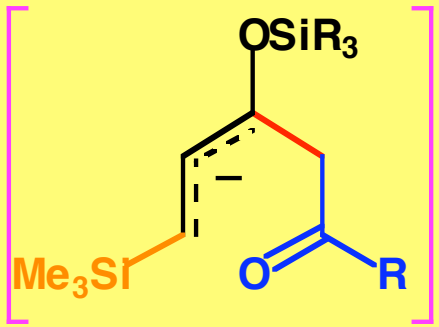
Et	70%	5%
Pr	74%	7%
i-Pr	55%	19%
n-octyl	71%	8%



Takeda, K.; Fujisawa, M.; Makino, T.; Yoshii, E.; Yamaguchi, K. *J. Am. Chem. Soc.* **1993**, *115*, 9351-9352.

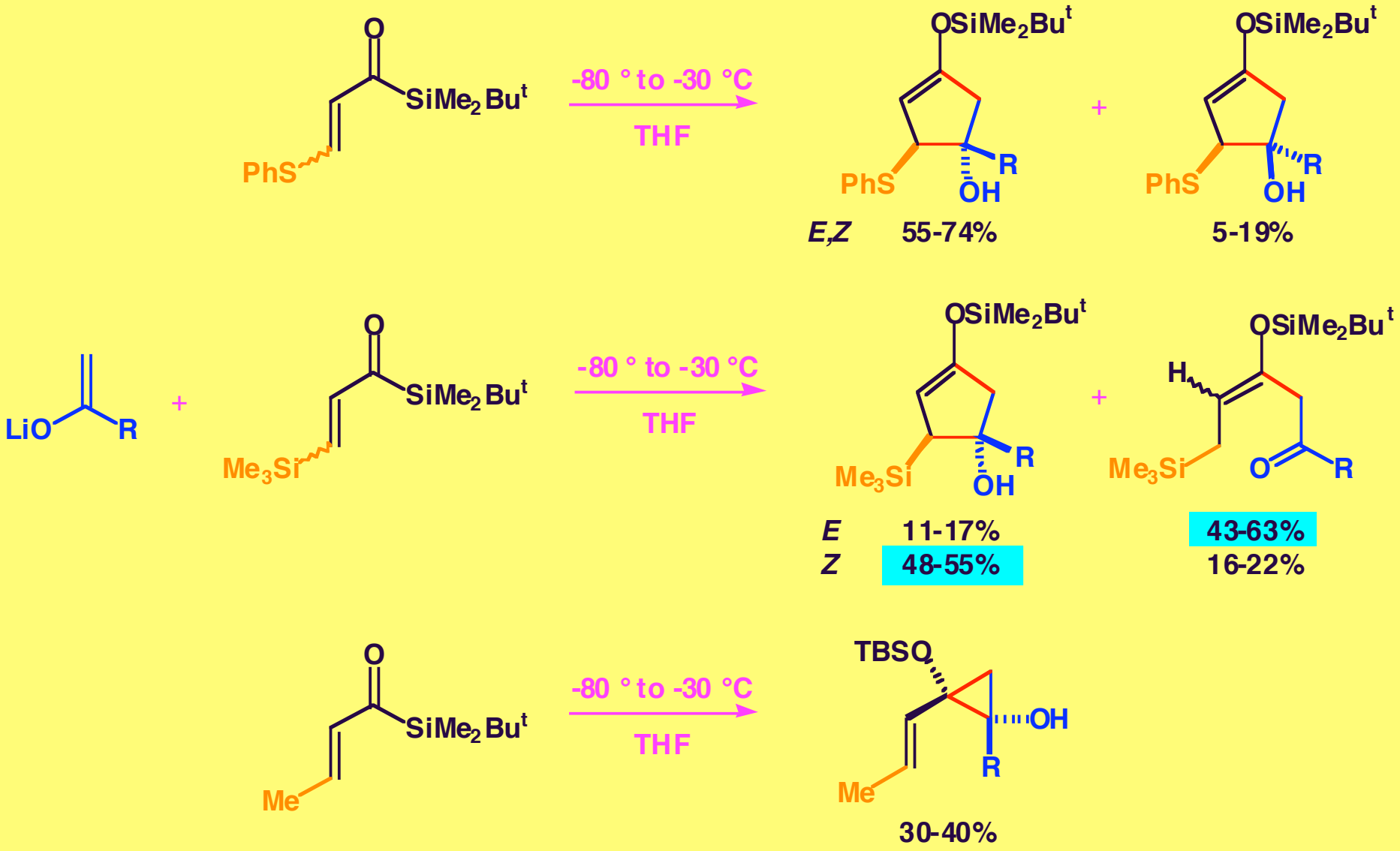
[3 + 2] Annulation Using Reaction of (β-Trimethylsilyl)acryloyl)silane and Lithium Enolates



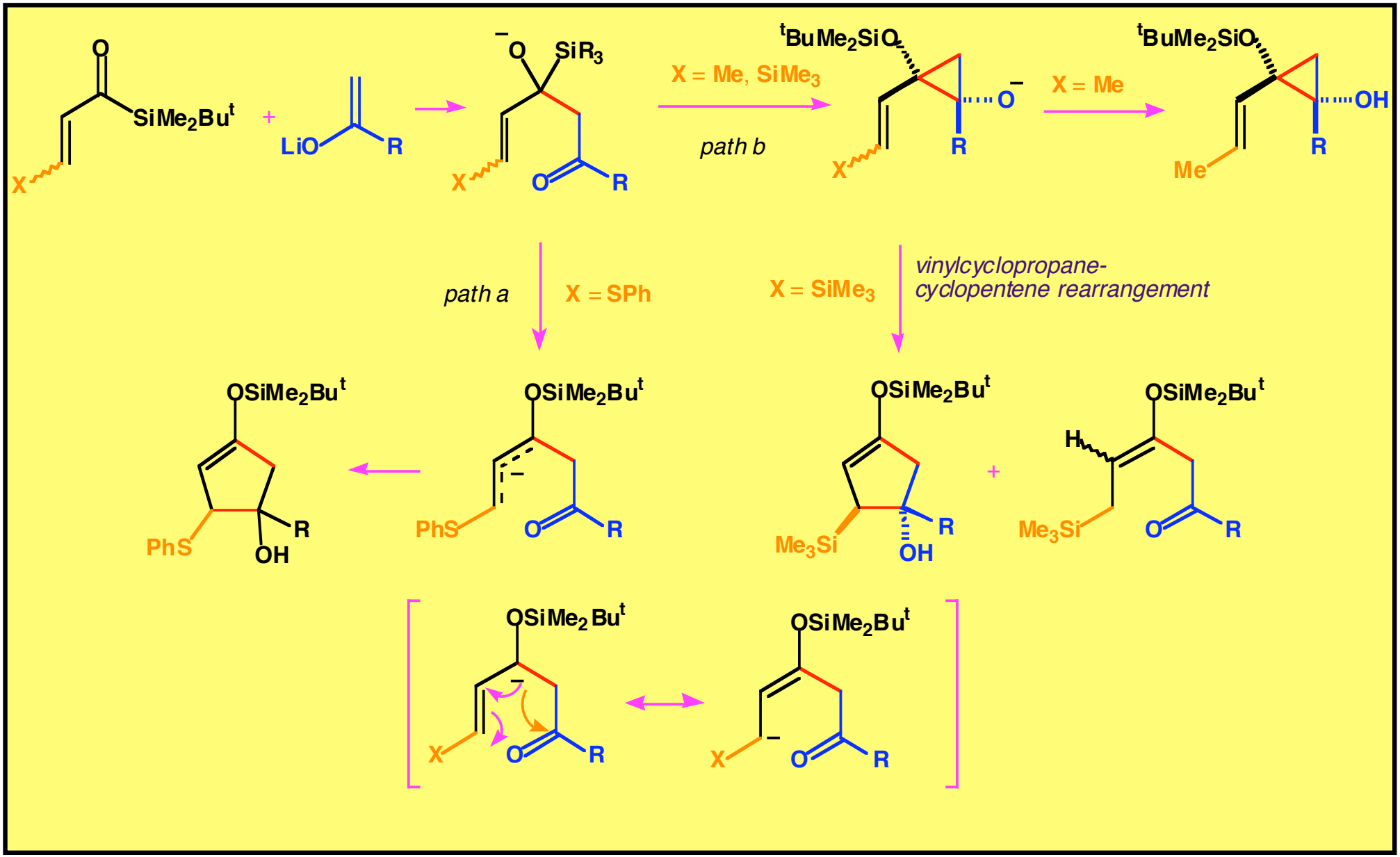


E	Et	17%	43%
	n-Pr	11%	57%
	i-Pr	14%	63%
Z	Et	48% (75)	16% (9)
	n-Pr	55% (70)	22% (19)
	i-Pr	51% (76)	21% (10)

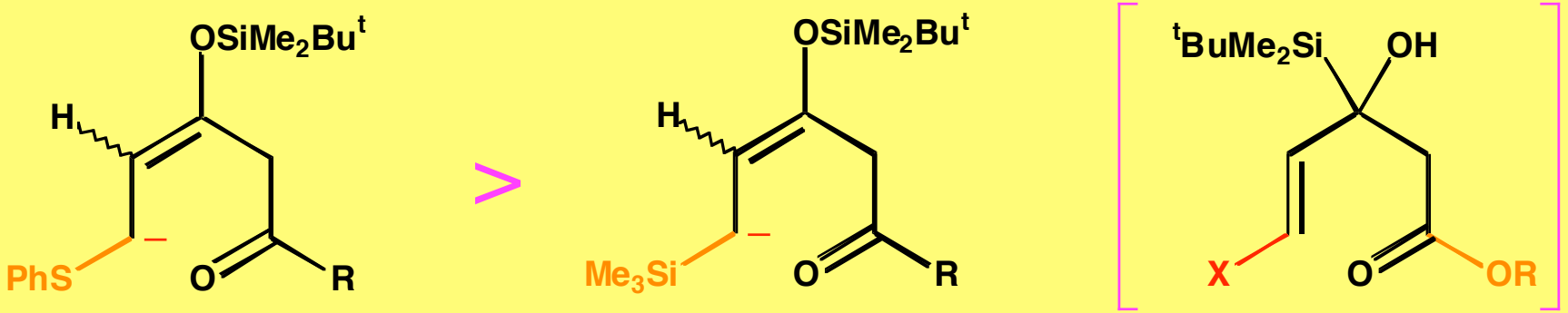
Summary of the Reaction of β-Substituted-Acryloylsilanes with Lithium Enolate of Methyl Ketones



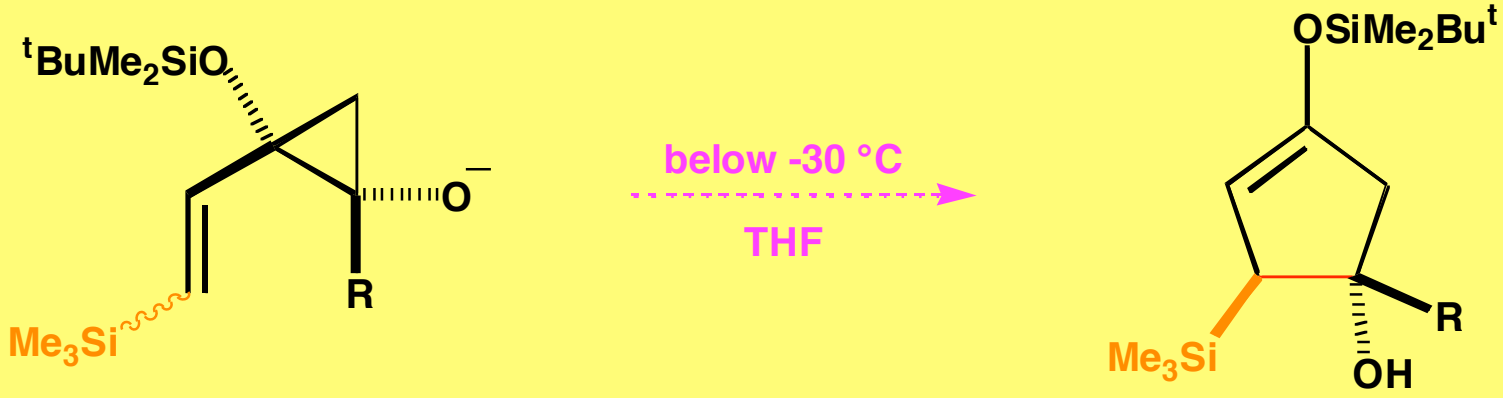
A Proposed Reaction Pathway for the [3 + 2] Annulation



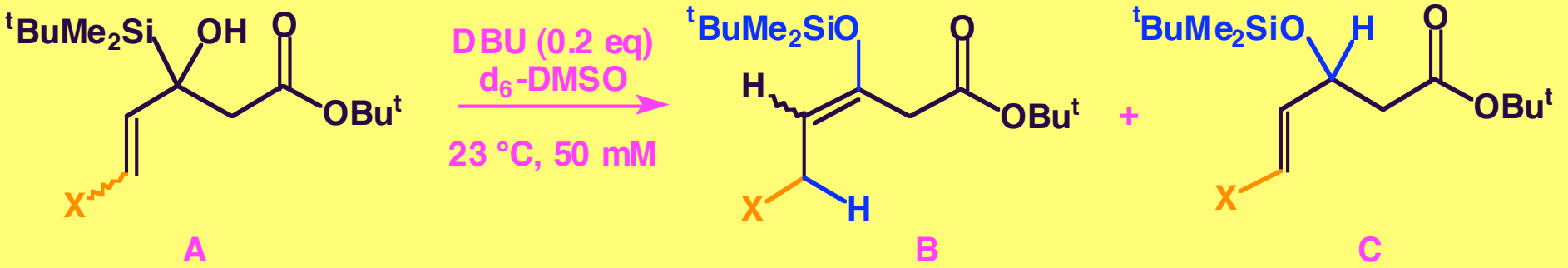
Does the phenylthio group stabilize the α-carbanion more strongly than does the trimethylsilyl group ?



Does the oxyanion accelerated vinylcyclopropane rearrangement occur at low temperatures below -30 °C?

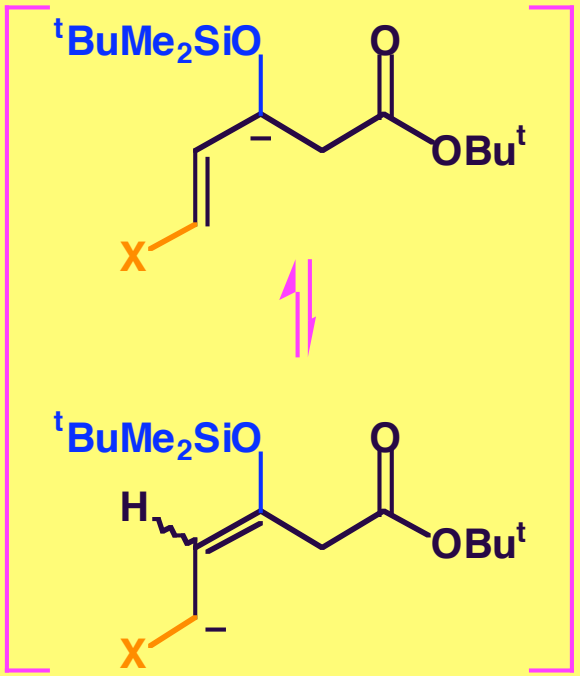


Comparison of the Rate of Base-Catalyzed Brook Rearrangement of β-Substituted α-Silyl Allyl Alcohol



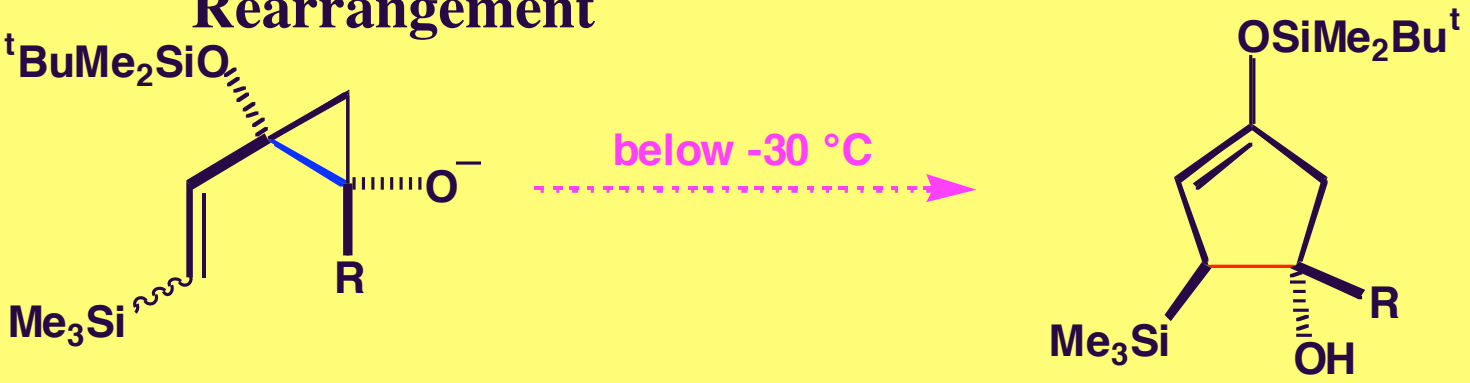
A B C

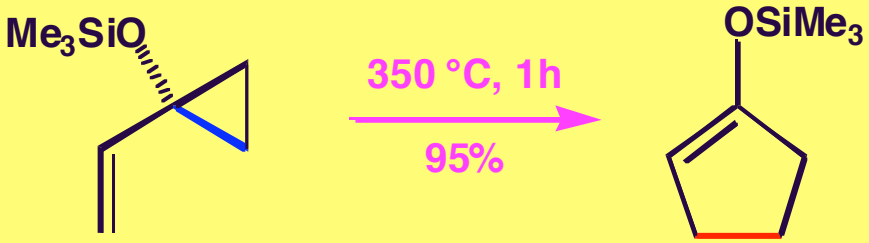
X	product	$t_{1/2}$ (min)
S(O)Ph	B	< 1
SPh	B	3.2
Ph	B	5.5
$SiMe_3$	B + C (~2 : 1)	27.5
Cl (*Z*)	A : C = 2.2 : 1 (25 h)	
Br	A : C = 4.5 : 1 (43 h)	



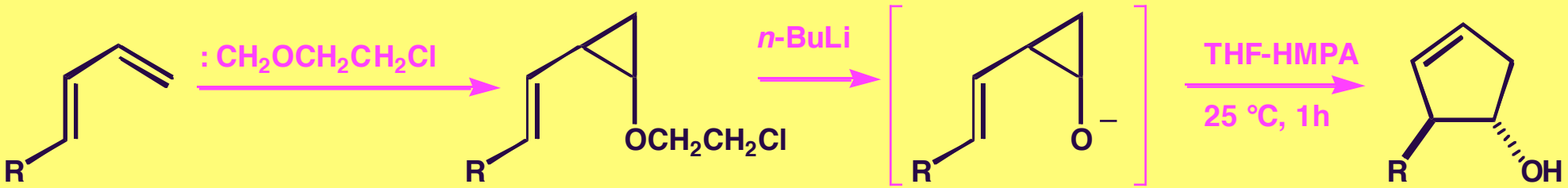
Kei Takeda, Haruka Ubayama, Ayako Sano, Eiichi Yoshii, Toru Koizumi *Tetrahedron Lett.***1998**, *39*, 5243-5246.

Vinylcyclopropane-Cyclopentene Rearrangement



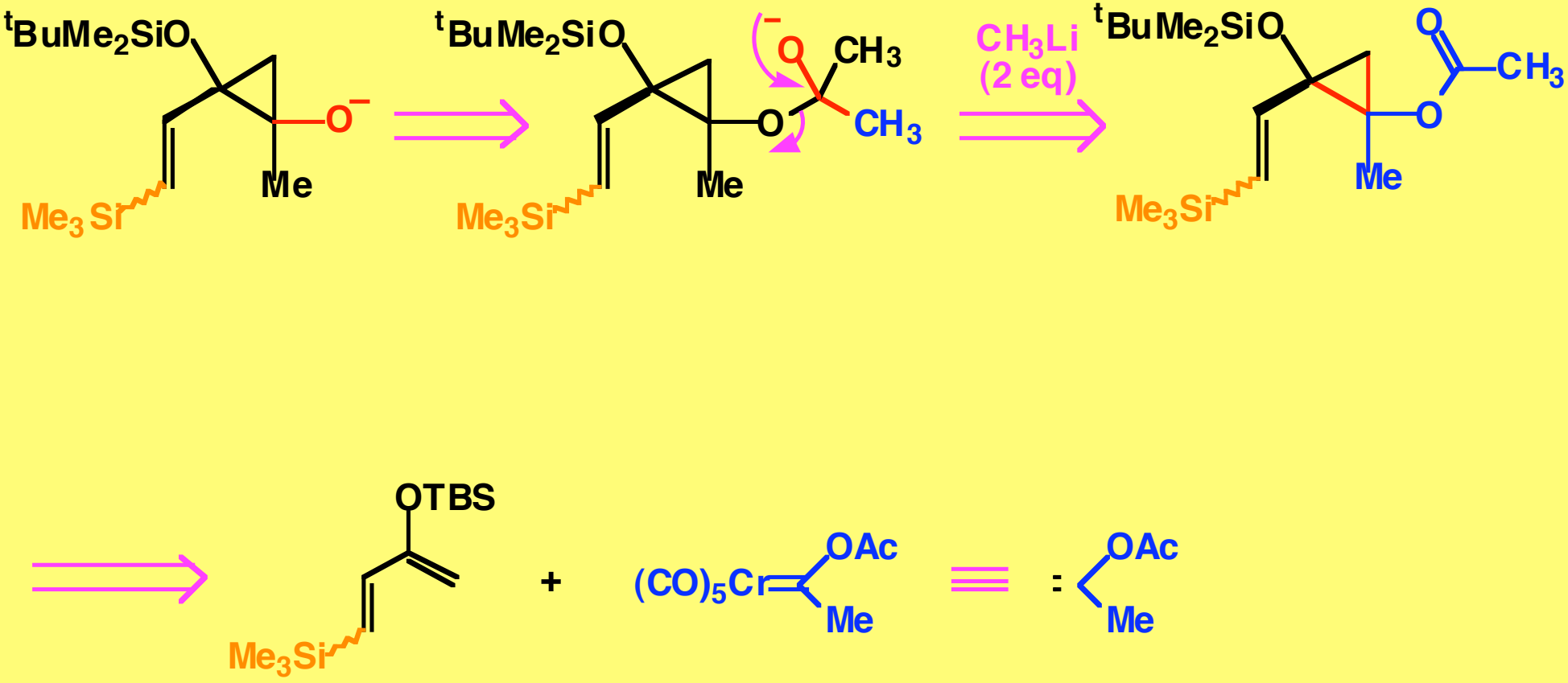


Girard, C.; Amice, P.; Barnier, J. P. Conia, J. M. *Tetrahedron Lett*. **1974**, 3329.

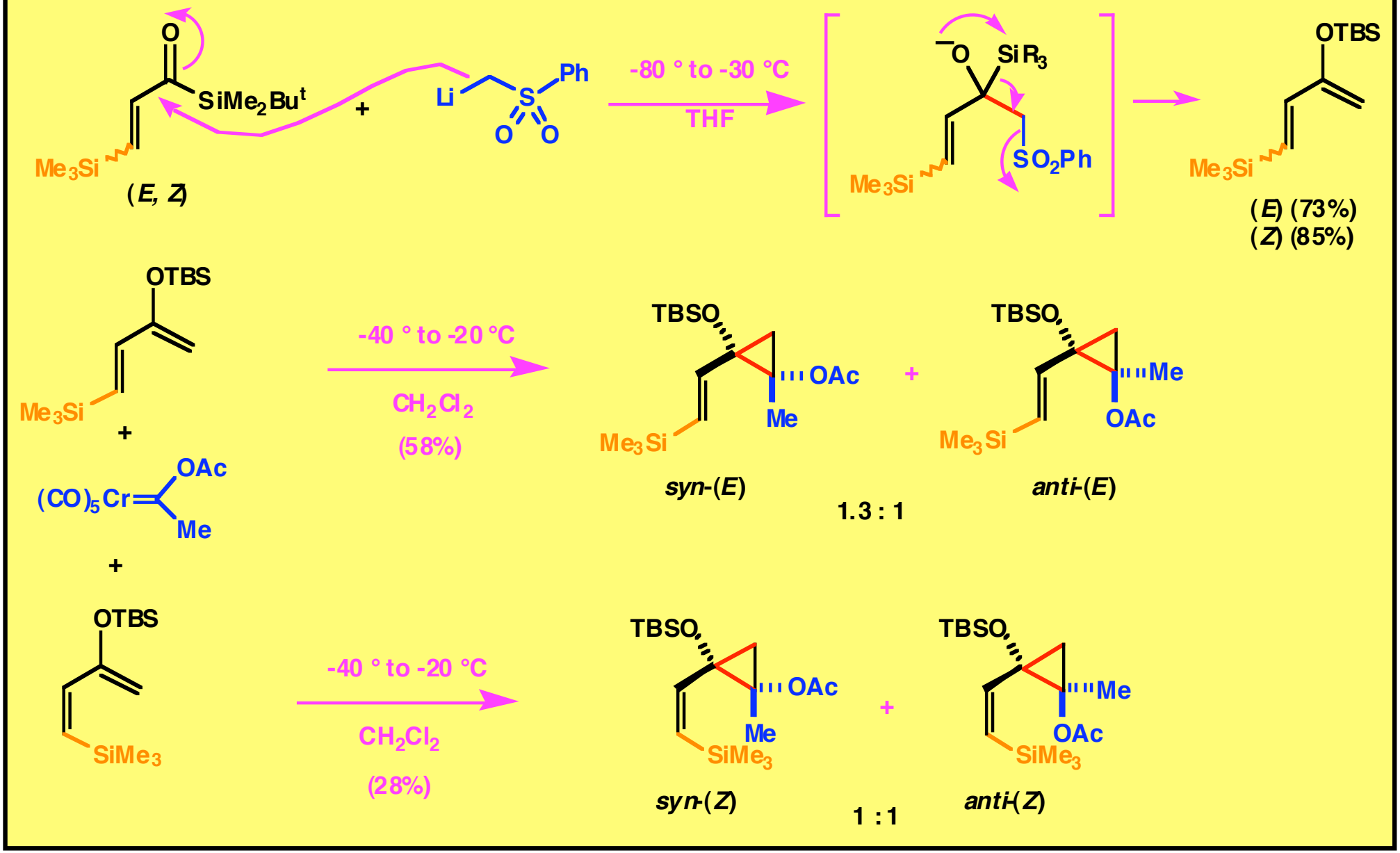


Danheiser, R. L.; Davilla, C. M.; Auchus, R. J.; Kadonaga, J. T. *J. Am. Chem. Soc*. **103**, 2443 (1981).

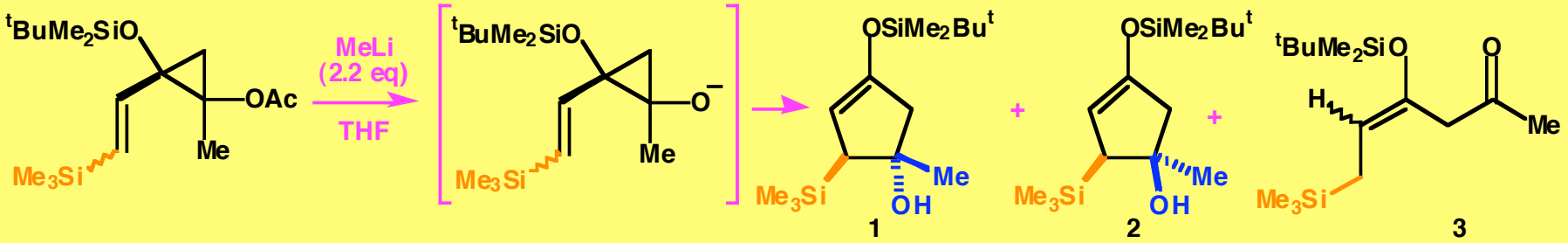
Synthesis of the Vinylcyclopropanolate Intermediates

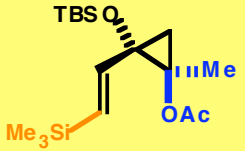
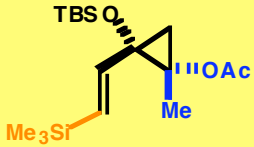
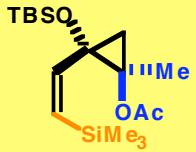


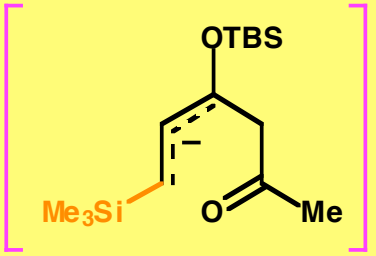
Synthesis of the Vinylcyclopropanolate Intermediates



Oxyanion Accelerated Vinylcyclopropane Rearrangement

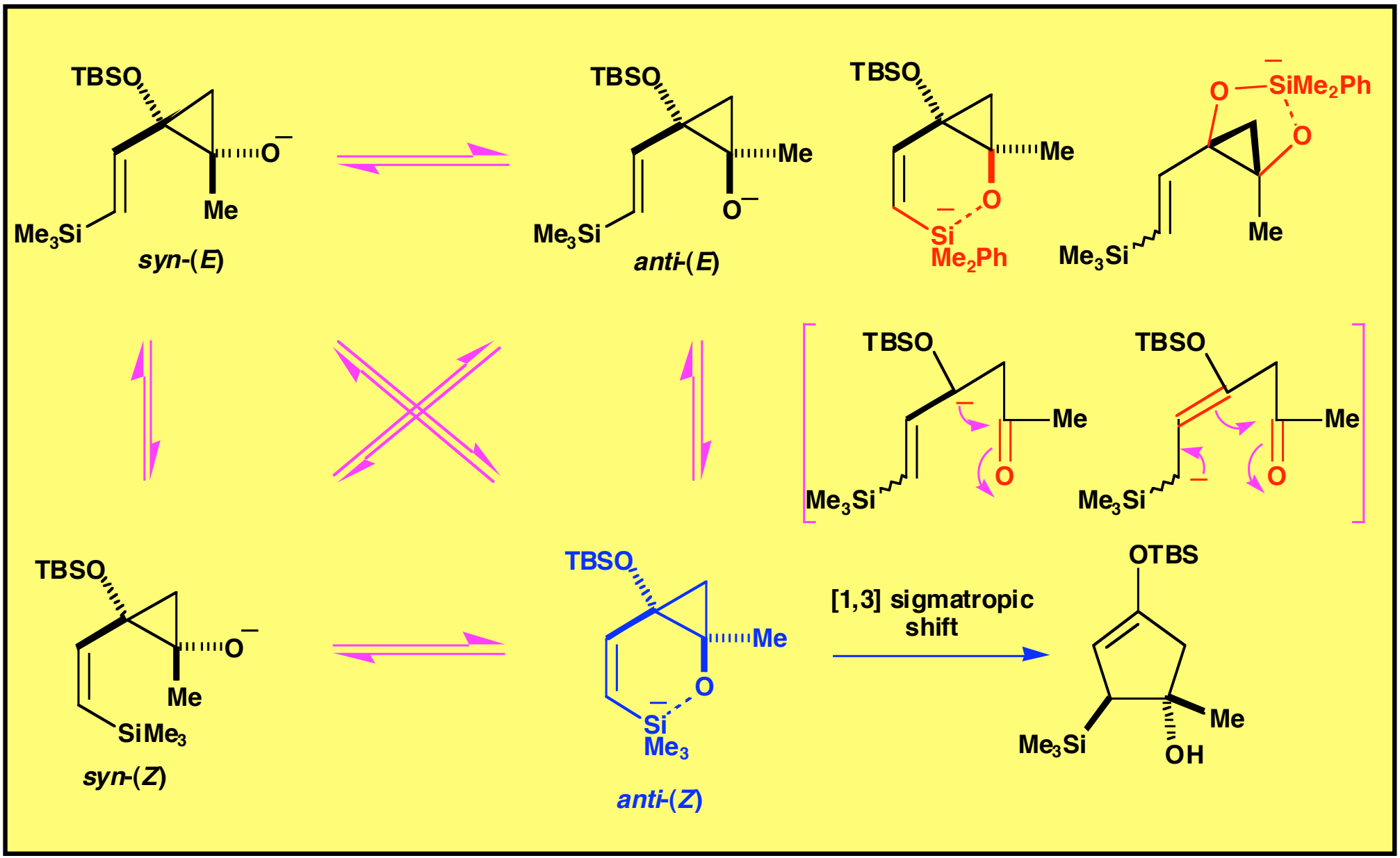


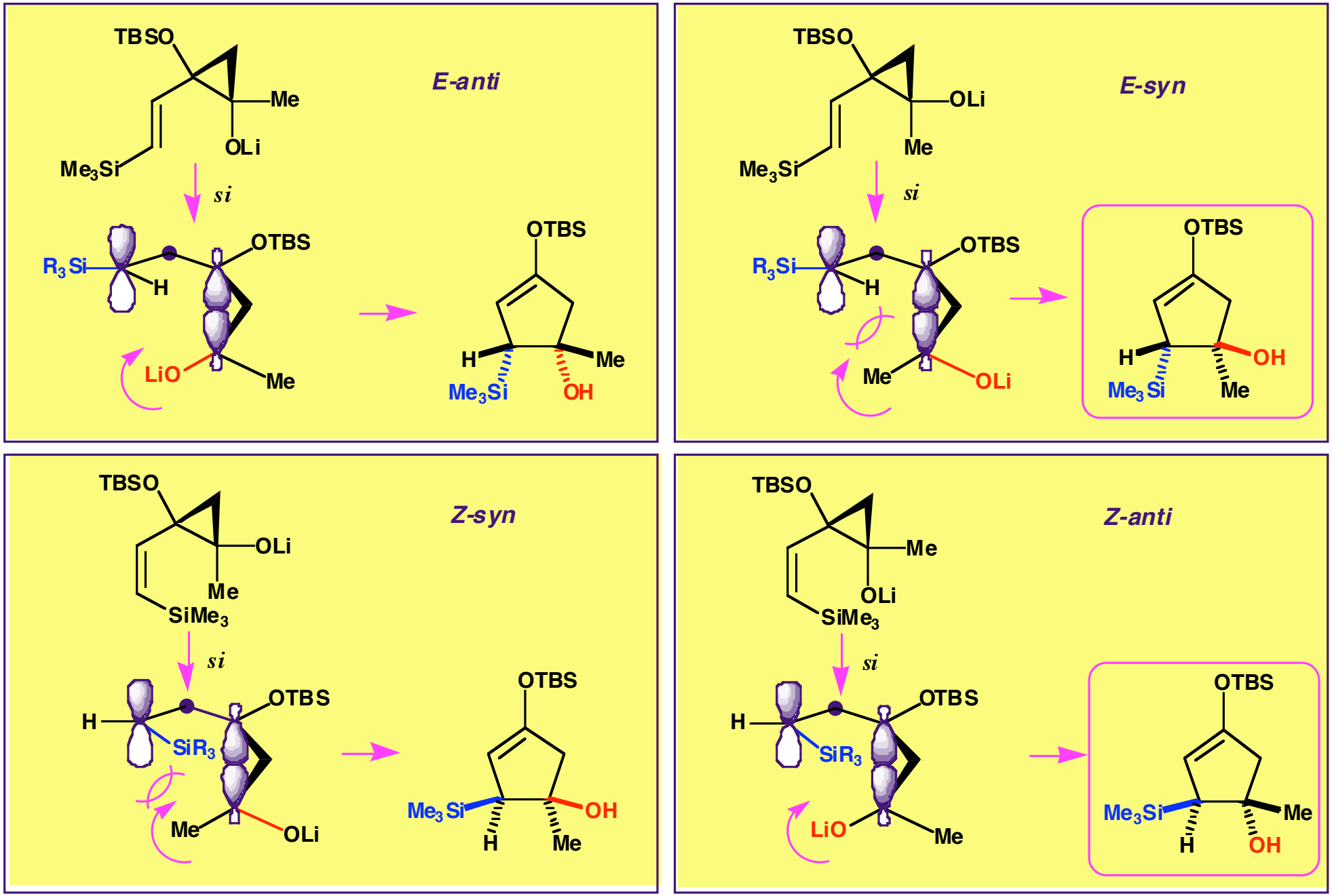
entry	cyclopropyl acetate	conditions	yield (%) 1	2	3 (*E*:*Z*)
1	 *anti-E*	-80 °C, 30 min	0	0	89 (1.1:1)
2		-80 ° to -30 °C	63	0	34 (only *E*)
3	 *syn-E*	-80 °C, 30 min	0	0	81 (1.1:1)
4		-80 ° to -30 °C	54	0	31 (17:1)
5	 *anti-Z*	-80 °C, 30 min	59	6	10 (1.7:1)
6		-80 ° to -30 °C	76	9	14 (5.7:1)
7	 *syn-Z*	-80 °C, 30 min	52	6	20 (1.7:1)
8		-80 ° to -30 °C	76	8	16 (only *E*)

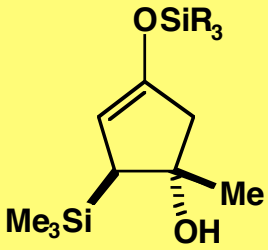
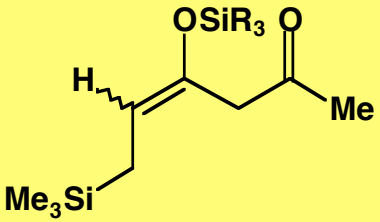


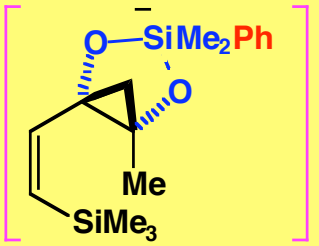
Kei Takeda, Keiki Sakurama, Eiichi Yoshii *Tetrahedron Lett.* **38** (18), 3257-3260 (1997).

A Proposed Reaction Pathway for the Vinylcyclopropane Rearrangement

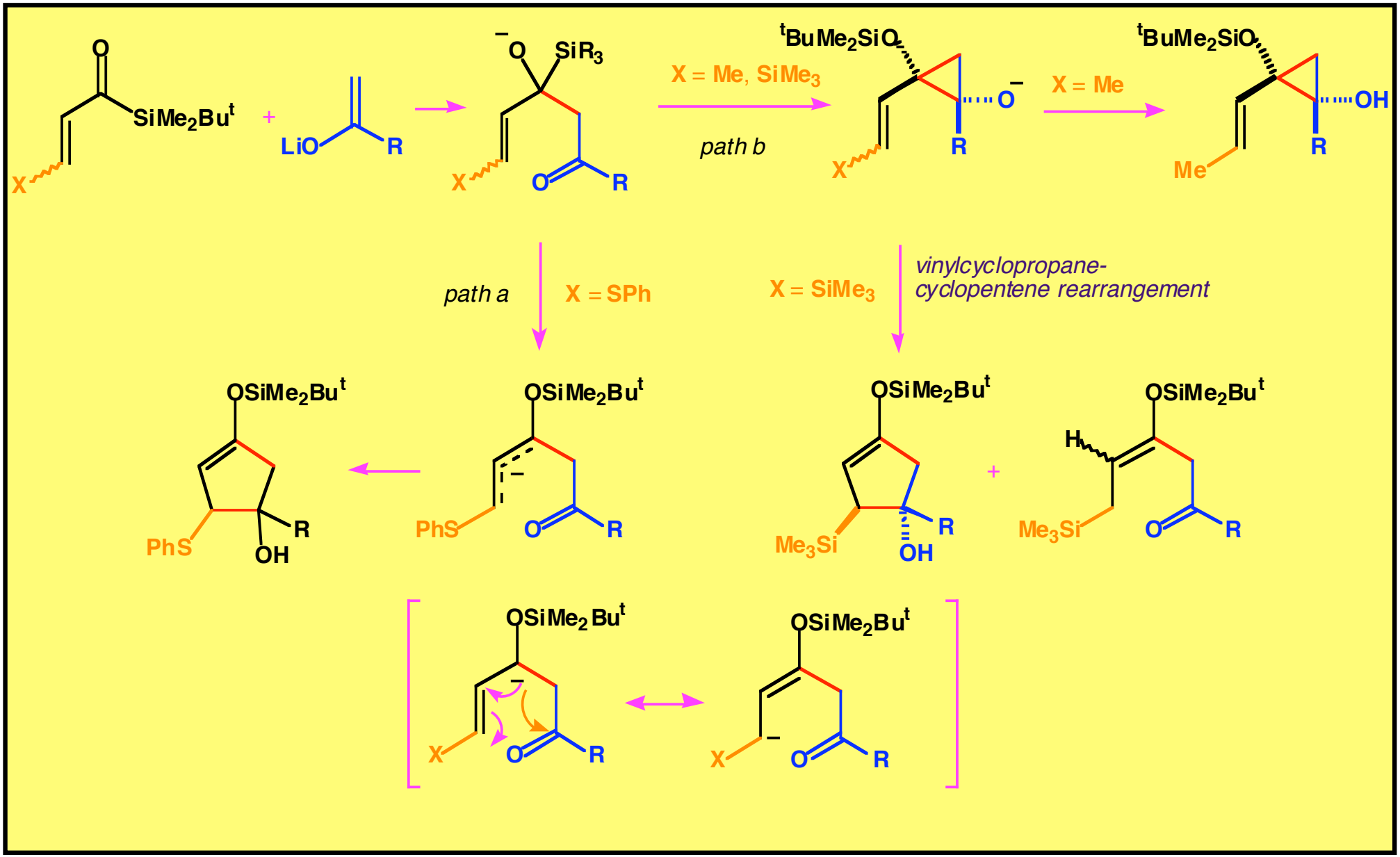



E-anti
TBSO
Me
OLi
Me3Si
si
OTBS
R3Si
H
LiO
Me
OTBS
H
Me
Me3Si
OH
E-syn
TBSO
OLi
Me
Me3Si
si
OTBS
R3Si
H
Me
OLi
OTBS
H
Me3Si
OH
Me
Z-syn
TBSO
OLi
Me
SiMe3
si
OTBS
H
SiR3
Me
OLi
OTBS
Me3Si
H
OH
Me
Z-anti
TBSO
Me
OLi
SiMe3
si
OTBS
H
SiR3
LiO
Me
OTBS
Me3Si
H
Me
OH

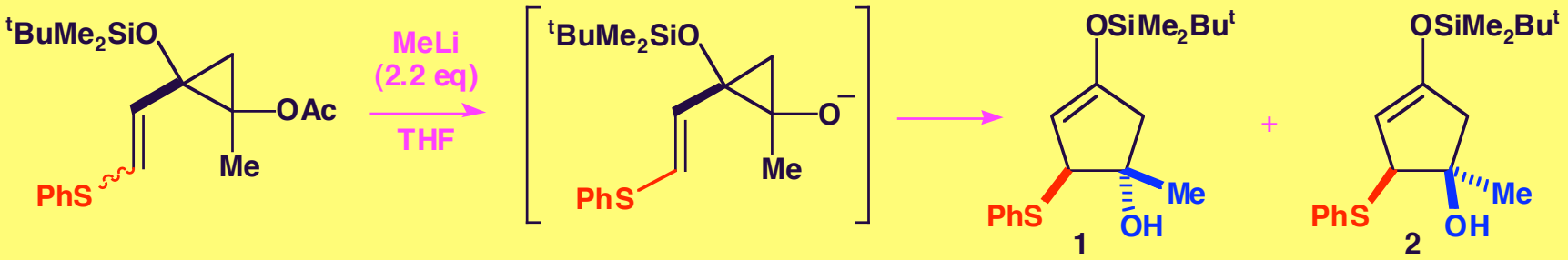
	conditions			
	toluene -80 ° to -30 °C	7%	54%	-
		30%	25%	-
	THF -80 °C, 30 min	8%	31%	53%
		20%	35%	21%

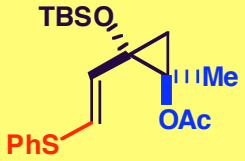
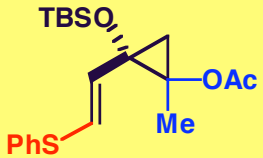


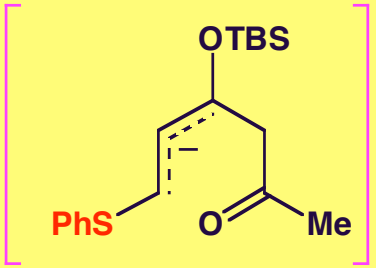
A Proposed Reaction Pathway for the [3 + 2] Annulation



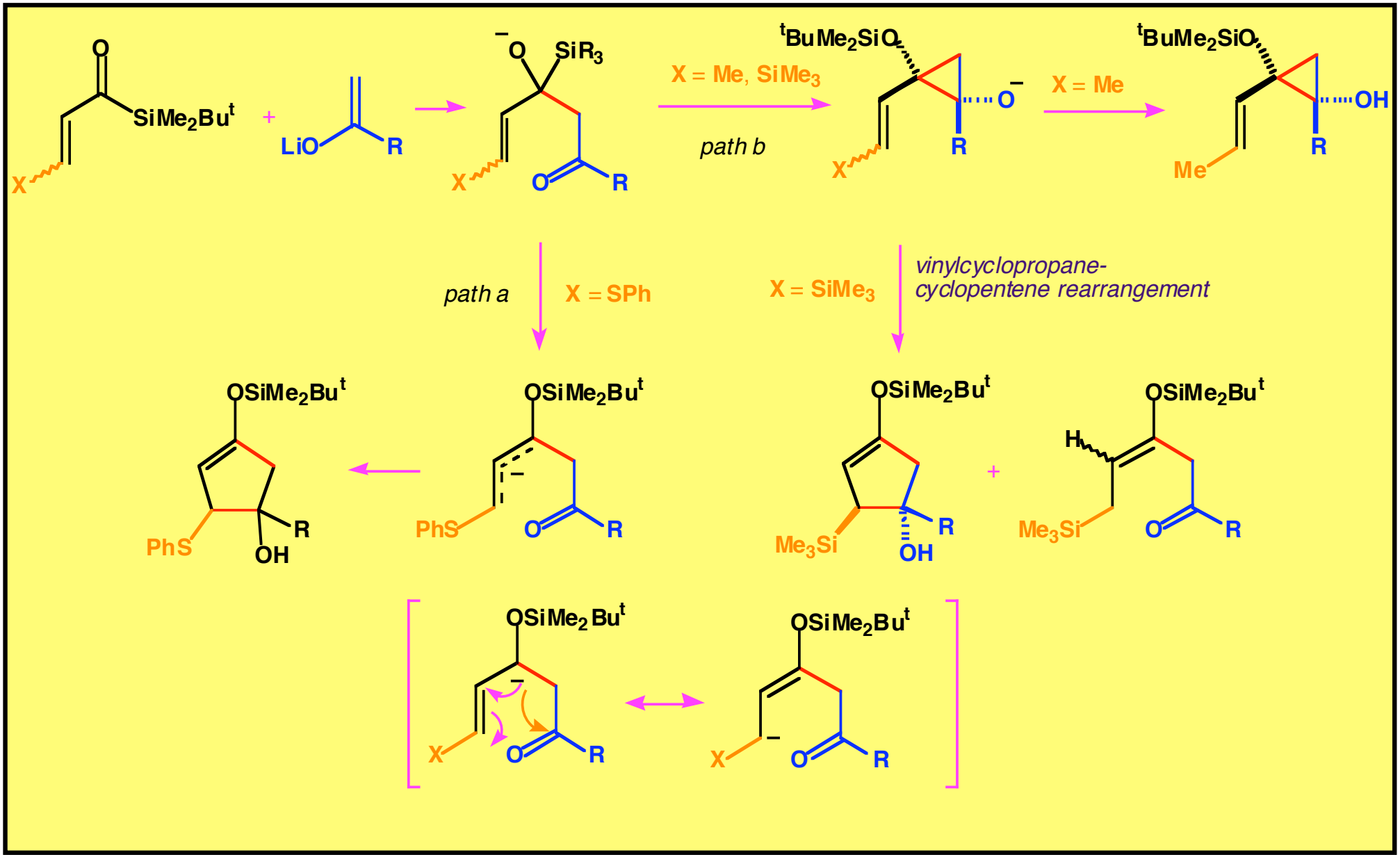
Oxyanion-Accelerated Vinylcyclopropane Rearrangement (2)



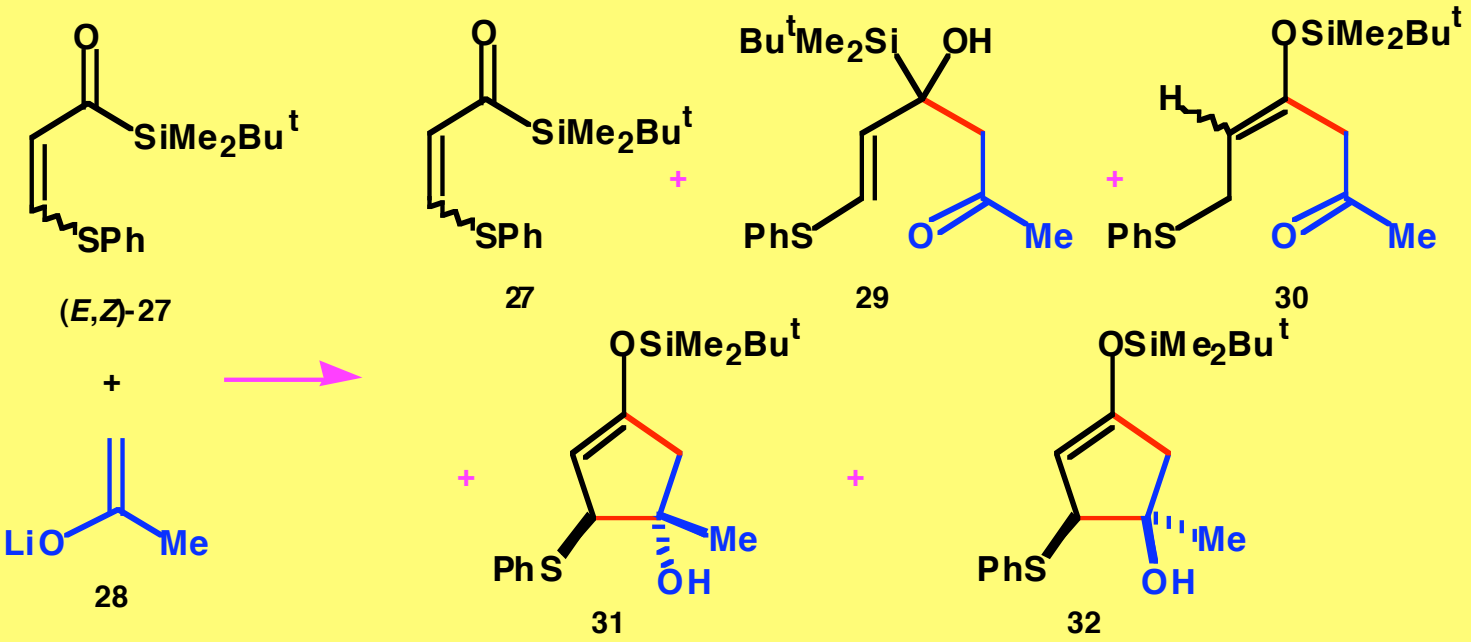
entry	cyclopropyl acetate	conditions	yield (%) 1	yield (%) 2
1	 *anti-E*	-80 °C, 30 min	84	2
2		-80 ° to -30 °C	85	3
3	 *anti-* : *syn-E* = 1 : 1.1	-80 °C, 30 min	87	1
4		-80 ° to -30 °C	87	2
5	 *anti-Z*	-80 °C, 30 min	50	39
6		-80 ° to -30 °C	48	39
7	 *syn-Z*	-80 °C, 30 min	48	35
8		-80 ° to -30 °C	48	40



A Proposed Reaction Pathway for the [3 + 2] Annulation

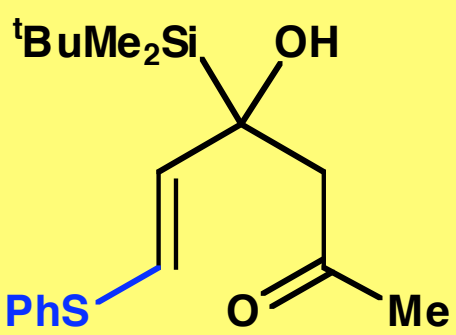


Low-Temperature Quenching of the [3 + 2] Annulation (1)



conditions	27	yield (%) 27 (*E*:*Z*)	29	30	31	32	27	yield (%) 27 (*E*:*Z*)	29	30	31	32
-80 °C, 10 min	*E*	23 (1:1.4)	14	12	33	-	*Z*	73 (1:1.9)	-	3	8	2
-80 ° to -70 °C	*E*	20 (1:1.2)	-	17	53	-	*Z*	66 (1:1.2)	-	9	21	2
-80 ° to -60 °C	*E*	12 (1:1.2)	-	24	48	1	*Z*	38 (1:1.2)	-	12	40	2
-80 ° to -50 °C	*E*	-	-	-	63	1	*Z*	24 (1:1.3)	-	8	42	2
-80 ° to -30 °C	*E*	-	-	-	68	2	*Z*	-	-	-	73	5

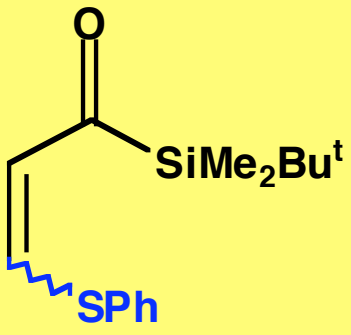
Reaction of (*E*)-1,2-Adduct (SPh) with LDA



E

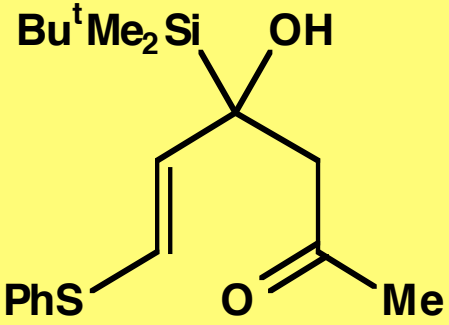
LDA
(1.05 eq)

THF
-80 °C
10 min

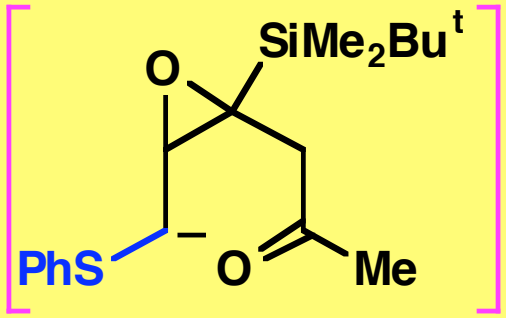


8% (*E*:*Z* = 1:1.3)

+

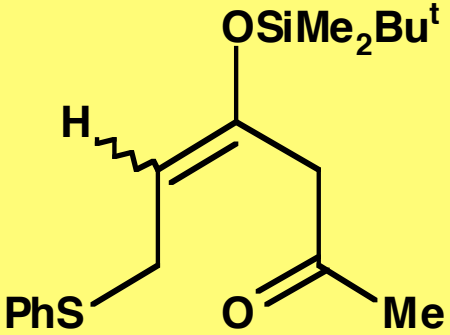


13%



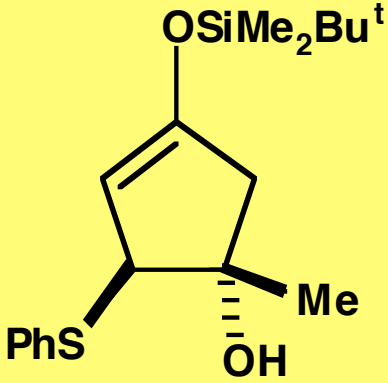
?

+



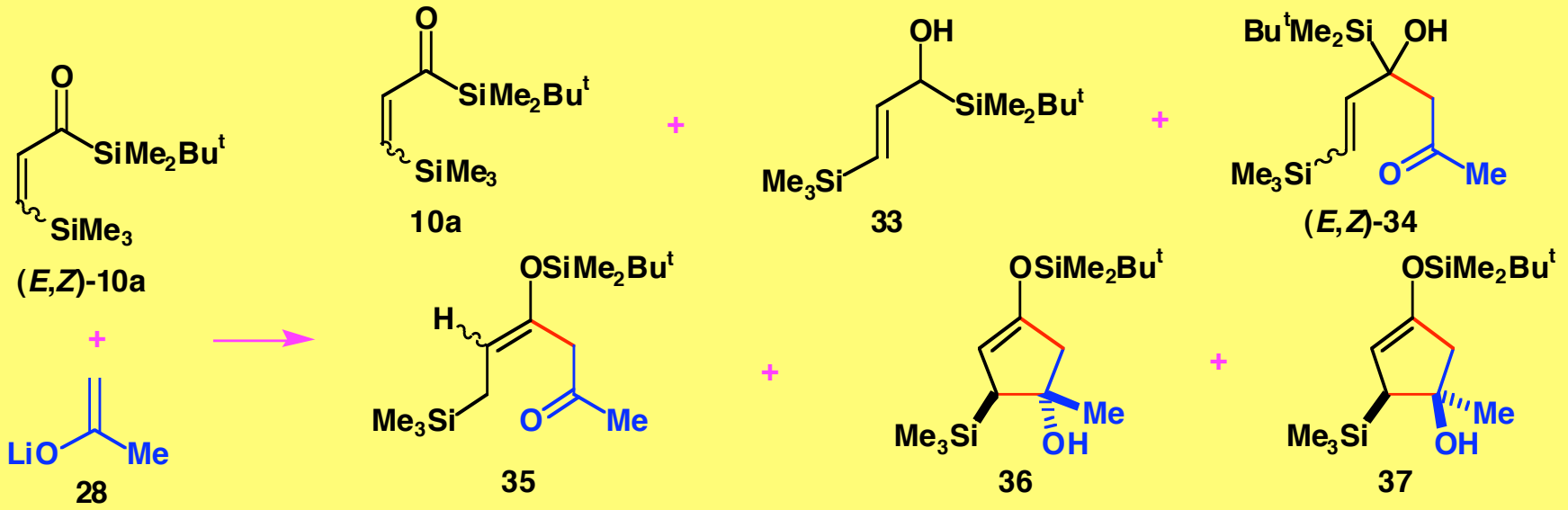
52%
(*E*:*Z* = 1:12.8)

+



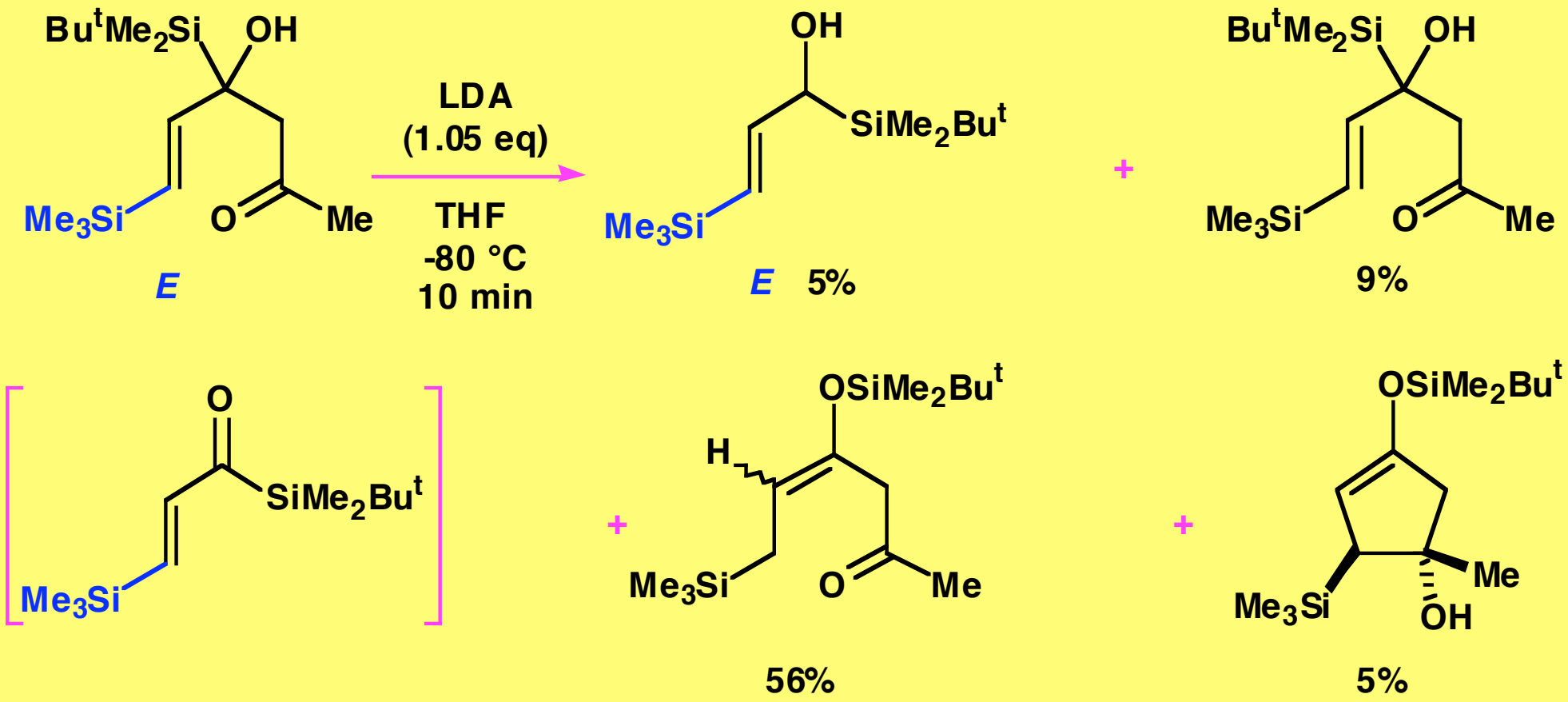
20%

Low-Temperature Quenching of the [3 + 2] Annulation (2)

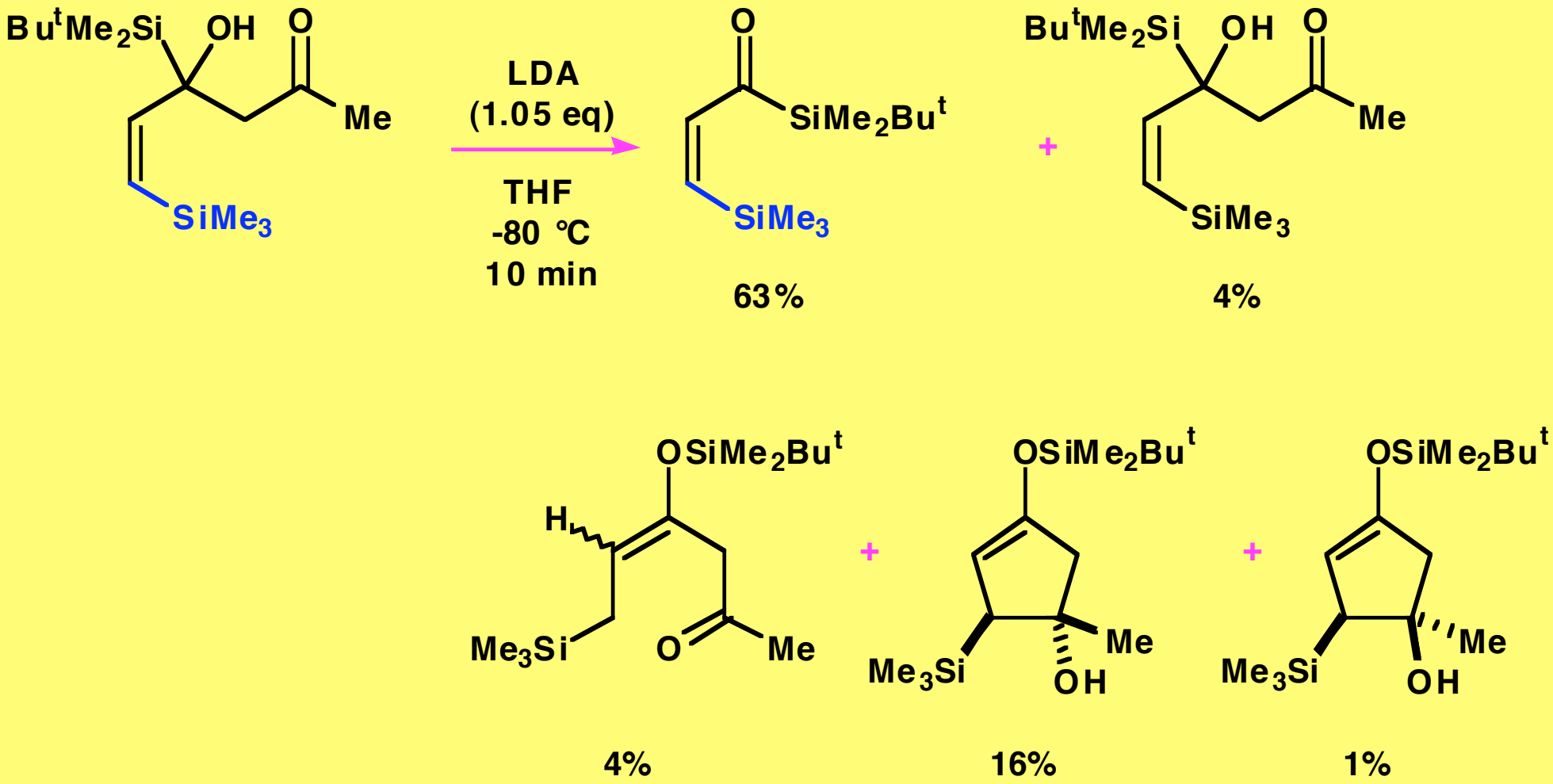


conditions		yield (%)							yield (%)					
	10a	33	(*E*)-34	35	(*E*:*Z*)	36	37	10a	(*Z*)-10a	(*Z*)-34	35	(*E*:*Z*)	36	37
-80 °C, 10 min	*E*	11	31	30	(1:1.8)	6	-	*Z*	65	12	2	(1:1.9)	6	-
-80 ° to -70 °C	*E*	9	18	35	(1:1.5)	9	-	*Z*	61	14	3	(1:1.8)	7	-
-80 ° to -60 °C	*E*	6	8	35	(1.7:1)	12	-	*Z*	56	-	7	(1.3:1)	12	-
-80 ° to -50 °C	*E*	4	-	35	(3.5:1)	15	-	*Z*	57	3	6	(2.0:1)	16	3
-80 ° to -30 °C	*E*	-	-	34	(5.6:1)	17	-	*Z*	32	-	7	(*E*)	42	5
-80 ° to 0 °C	*E*	-		34	(6.2:1)	19	-	*Z*	-	-	20	(*E*)	60	6

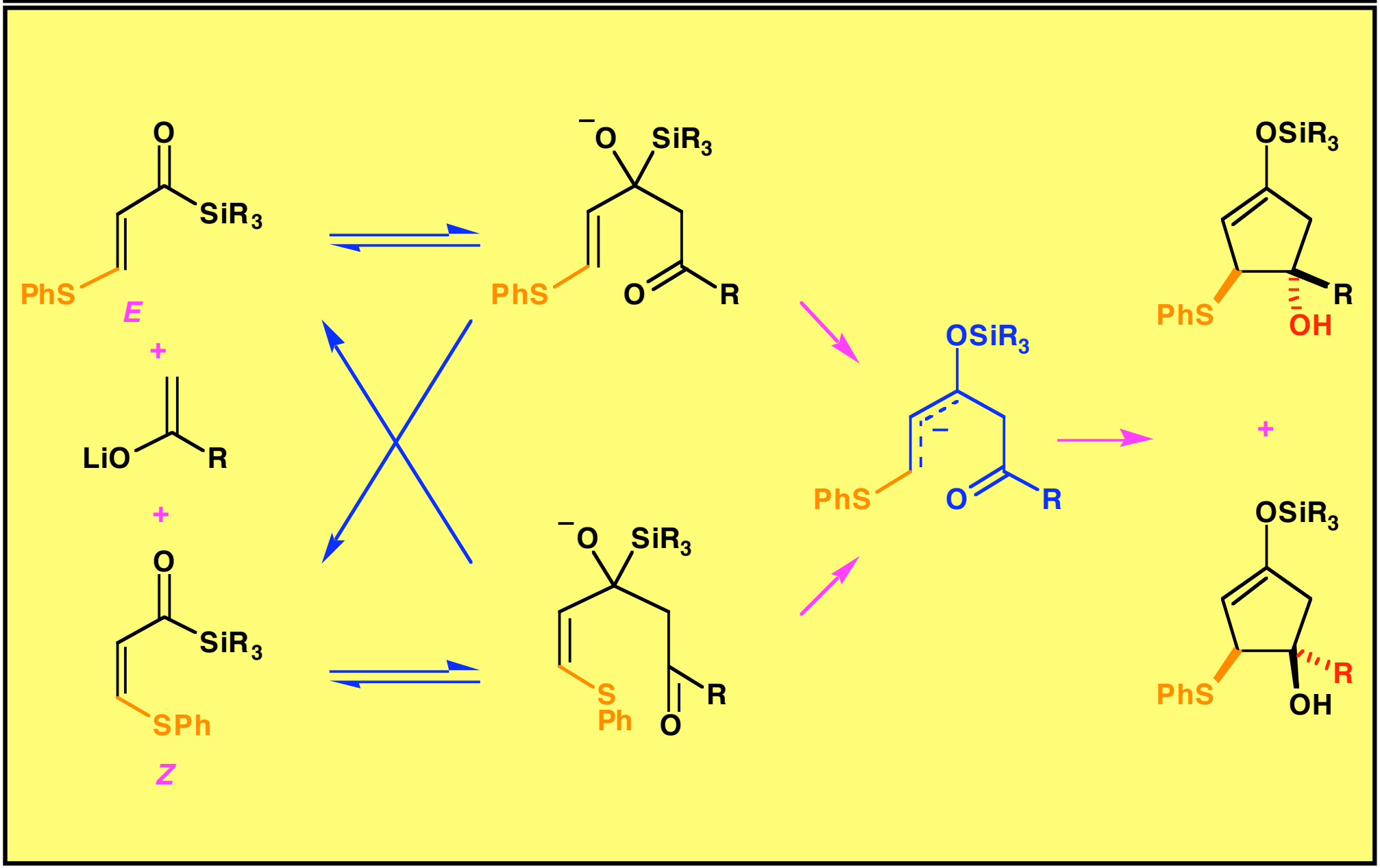
Reaction of (*E*)-1,2-Adduct with LDA



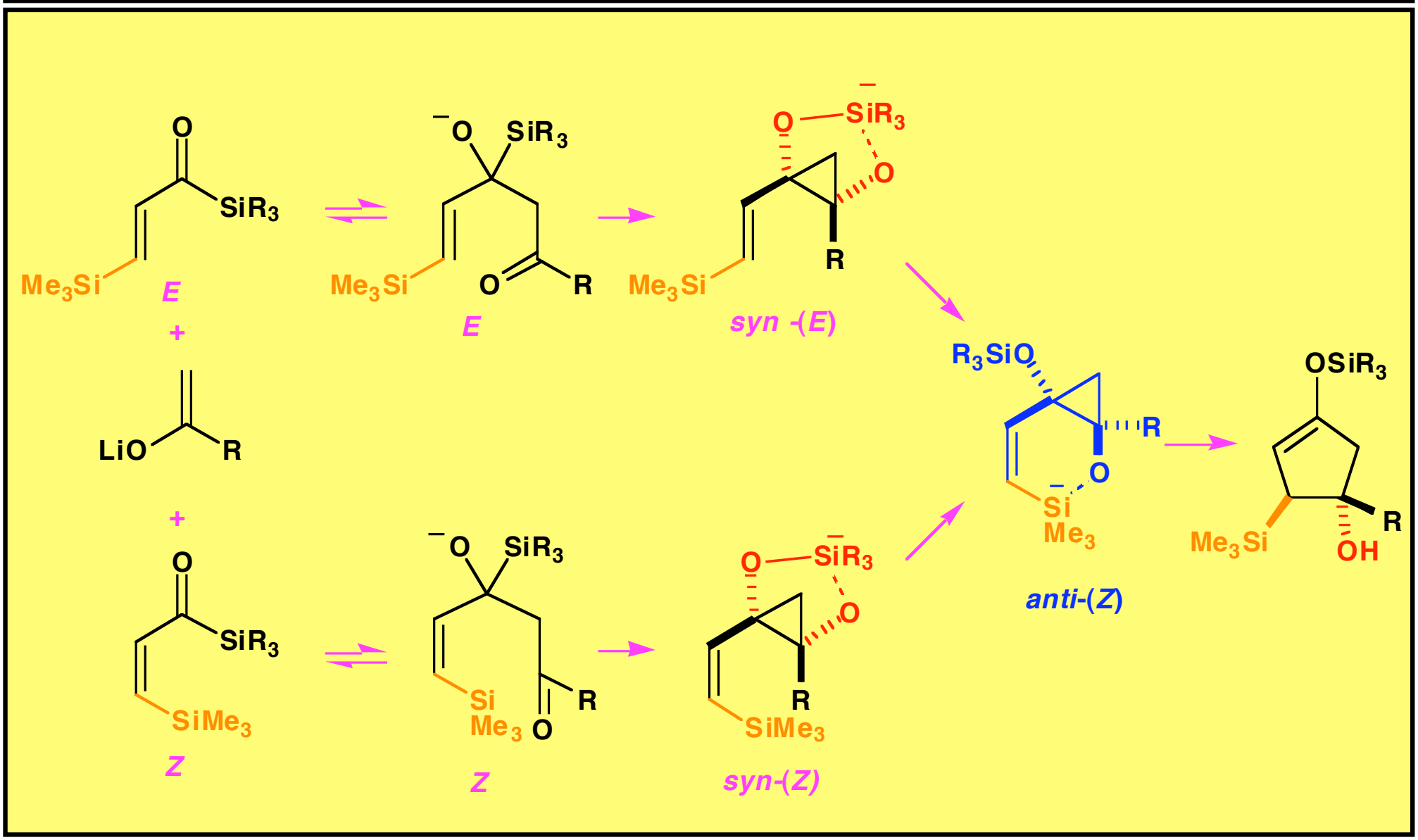
Reaction of (Z)-1,2-Adduct with LDA



A Proposed Reaction Pathway for the [3 + 2] Annulation Using (β-(Phenylthio)acryloylsilanes

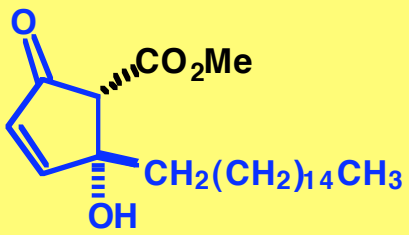


A Proposed Reaction Pathway for the [3 + 2] Annulation Using (β-(Trimethylsilyl)acryloylsilanes



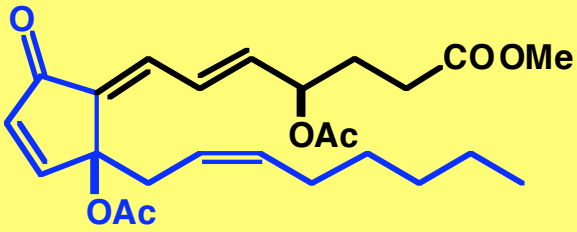
Kei Takeda, Kenji Yamawaki, Noriaki Hatakeyama *J. Org. Chem.* **67**, 1786-1794 (2002)

Application of the [3 + 2] Annulaton to the Synthesis of Biologically Important Molecules

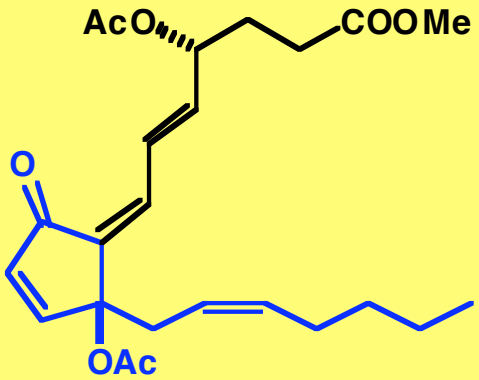


Untenone A[1]

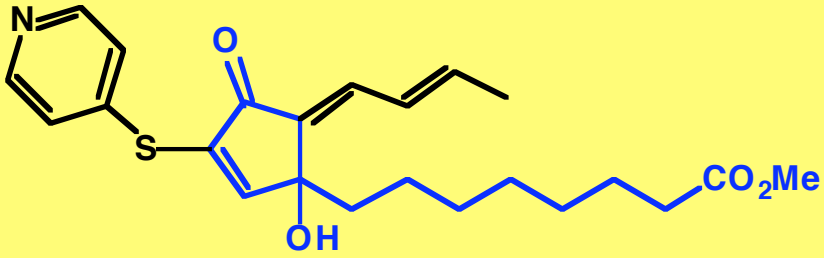
Chromomoric acid DII methyl ester[2]



Clavulone II[3]
(Claviridenone c)

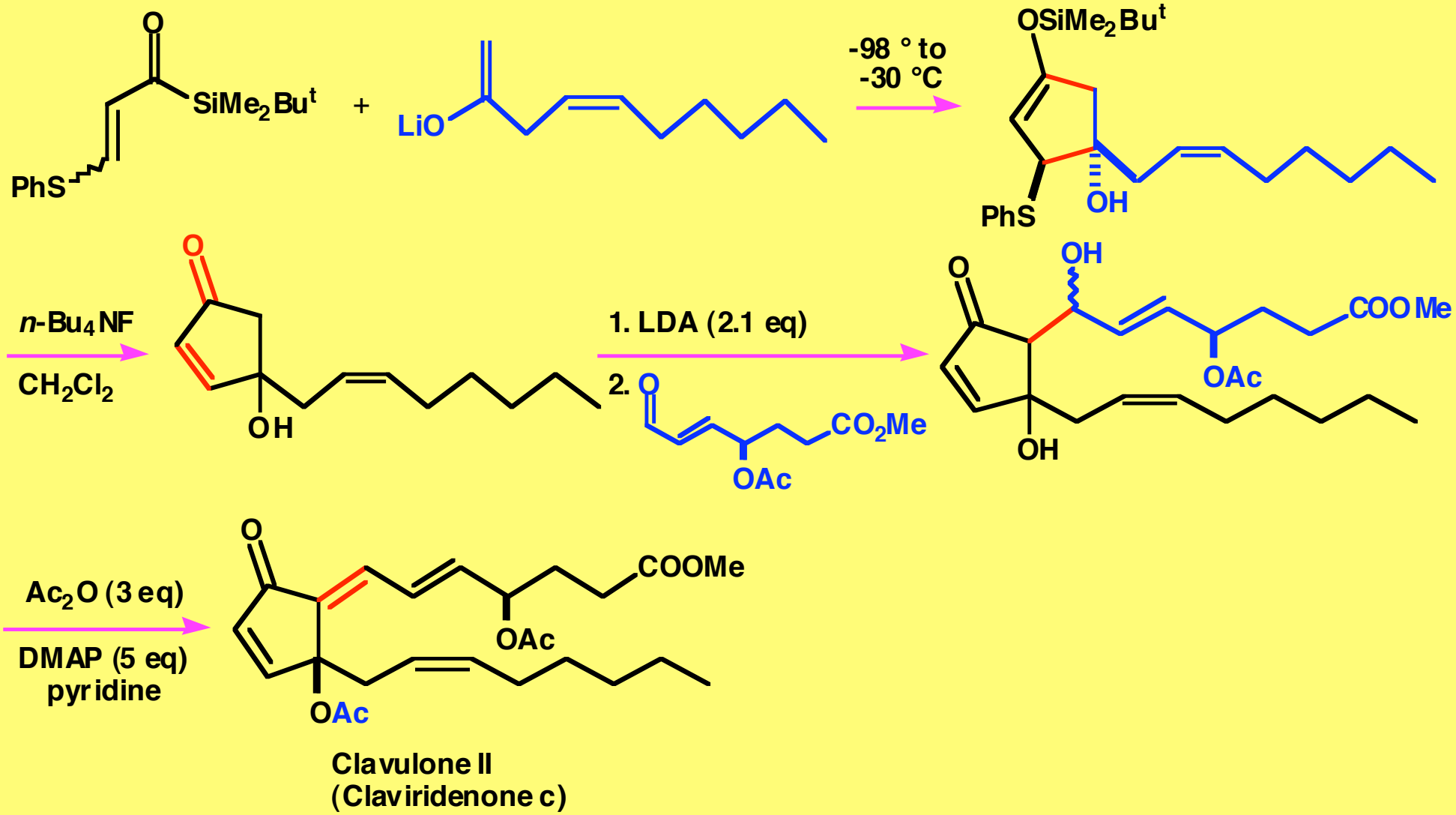


Clavulone III[3]
(Claviridenone b)



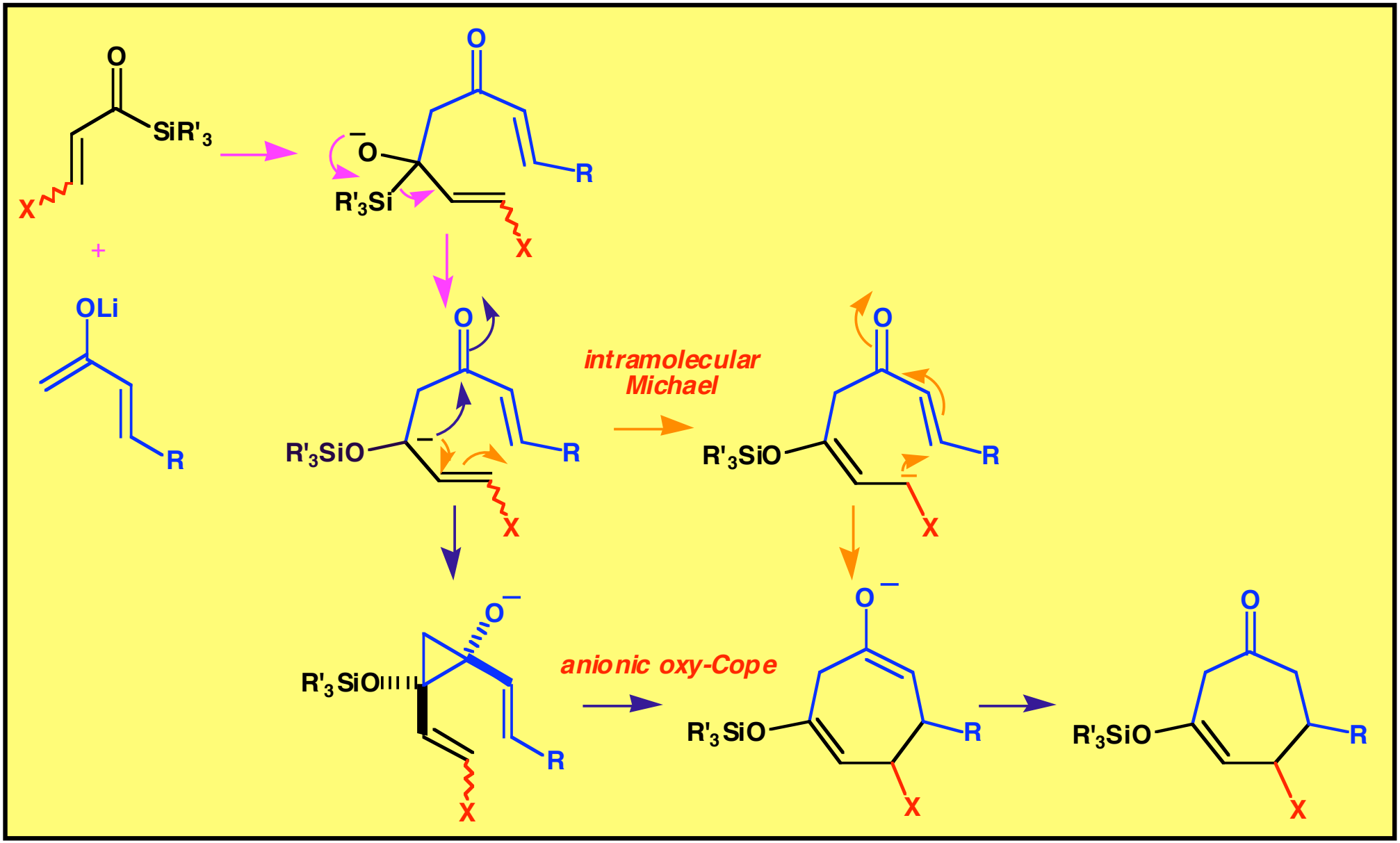
1. Takeda, K.; Nakayama, I.; Yoshii, E. *Synlett* **1994**, 178.
2. Takeda, K.; Fujisawa, M.; Makino, T.; Yoshii, E.; Yamaguchi, K. *J. Am. Chem. Soc*. **1993**, *115*, 9351-9352.
3. Takeda, K; Kitagawa, K.; Nakayama, I.; Yoshii, E. *Synlett* **1997**, 255-256.

Total Synthesis of Clavulones (Claviridenones) Using the [3 + 2] Annulation

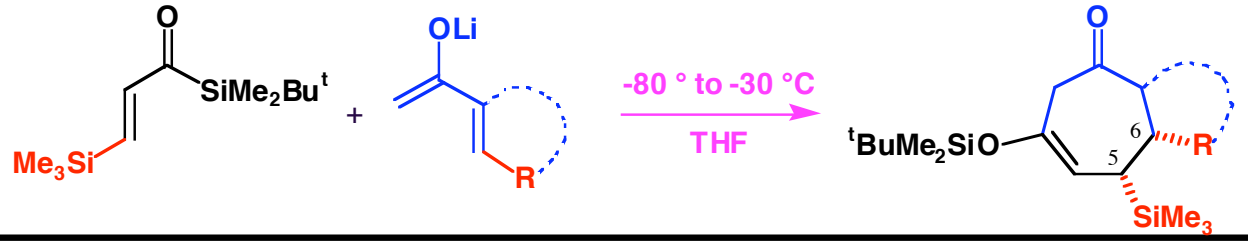


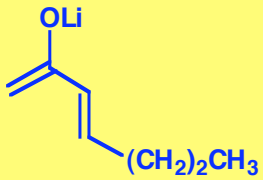
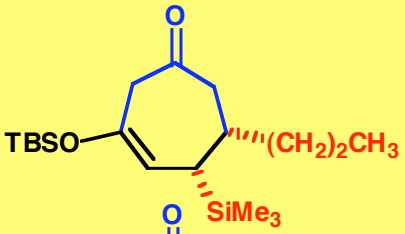
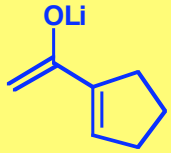
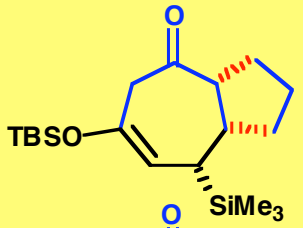
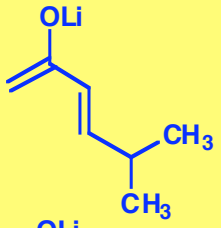
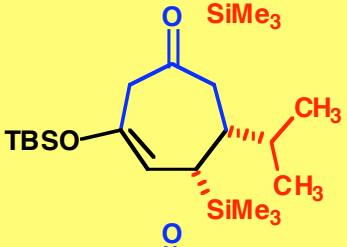
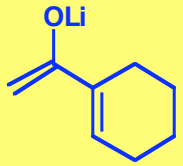
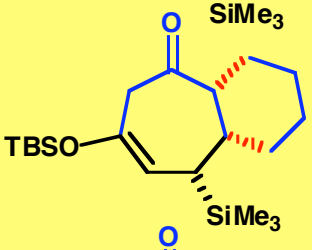
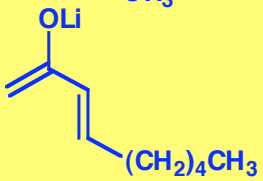
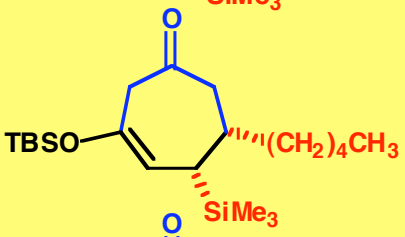
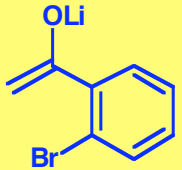
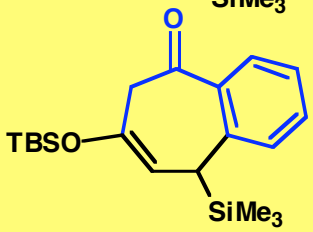
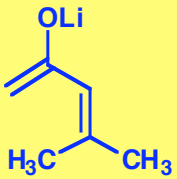
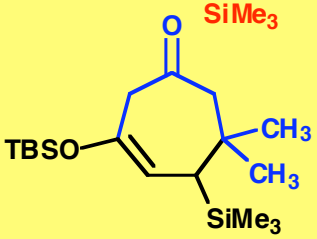
Clavulone II
(Claviridenone c)

[3 + 4] Annulation Using Reaction of Acryloylsilanes with the Lithium Enolate of Alkenyl Methyl Ketones

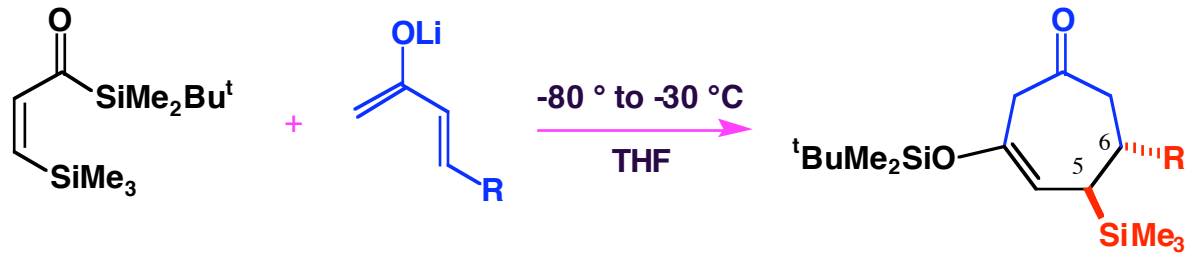


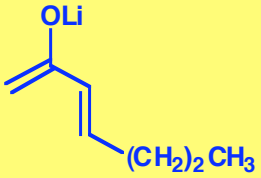
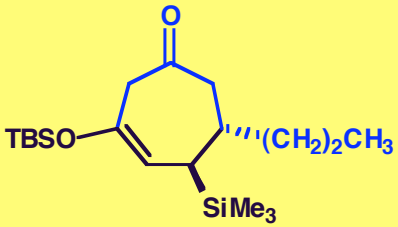
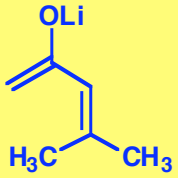
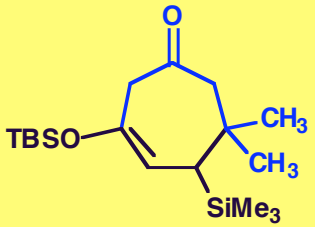
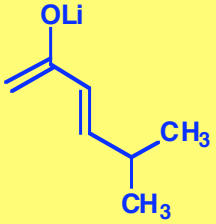
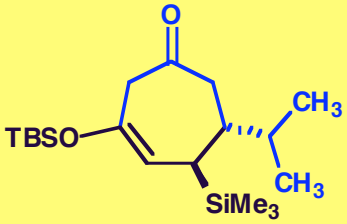
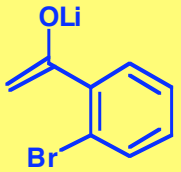
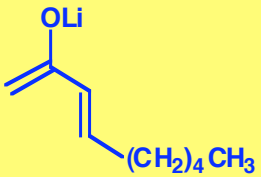
[3 + 4] Annulation Using (*E*)-(β-(Trimethylsilyl)acryloyl)silane



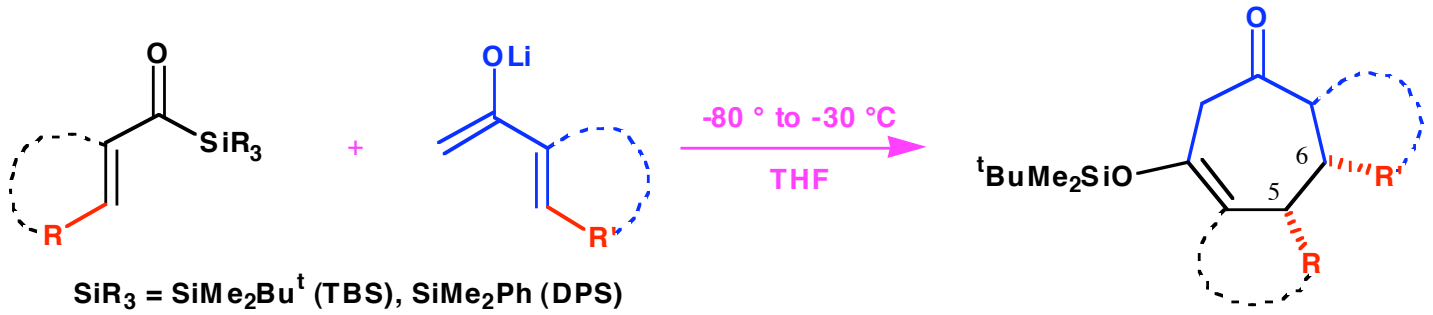
ketone enolate	product	yield	ketone enolate	product	yield
		73%			73%
		84%			82%
		84%			30%
		67%			

[3 + 4] Annulation Using (*Z*)-(β-(Trimethylsilyl)acryloyl)silane

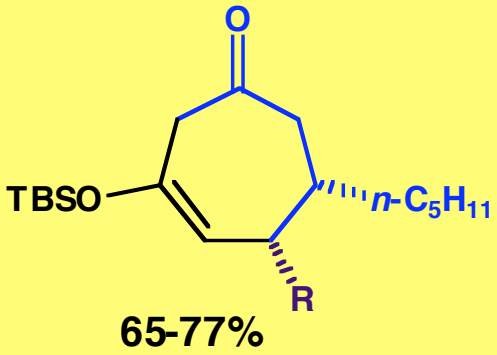


ketone enolate	product	yield (recovery of acylsilane)	ketone enolate	product	yield (recovery of acylsilane)
		31% (56%)			18% (31%)
		11% (59%)			0% (77%)
		29% (55%)			

[3 + 4] Annulation Using (β-(Alkyl)acryloyl)silanes

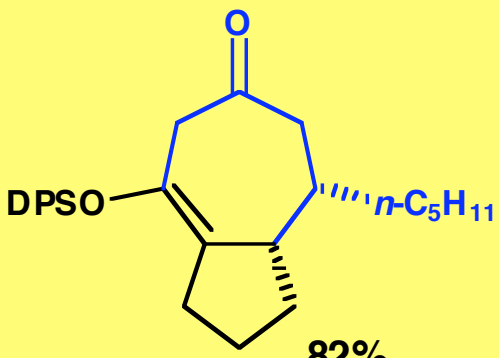


SiR_3 = $SiMe_2Bu^t$ (TBS), $SiMe_2Ph$ (DPS)

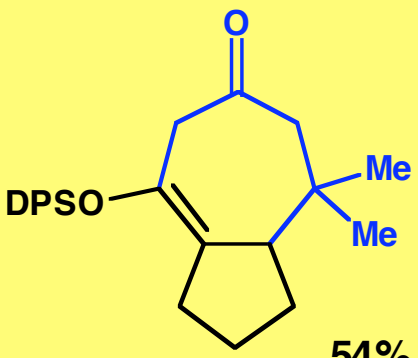


65-77%

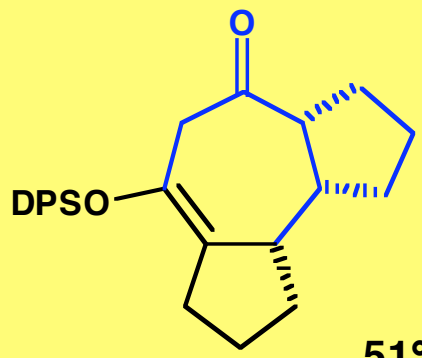
R = *i*-Pr, *n*-Pr, *t*-Bu, *c*-C_6H_{11}



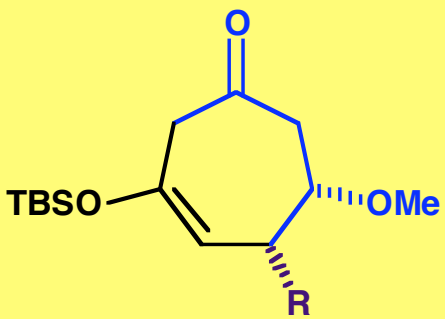
82%



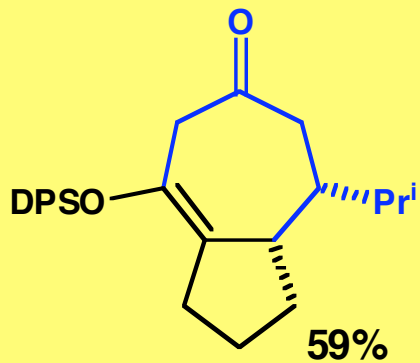
54%



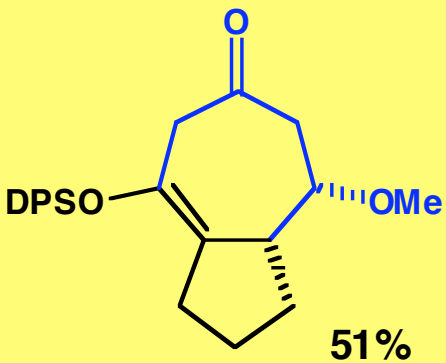
51%



44-70%



59%



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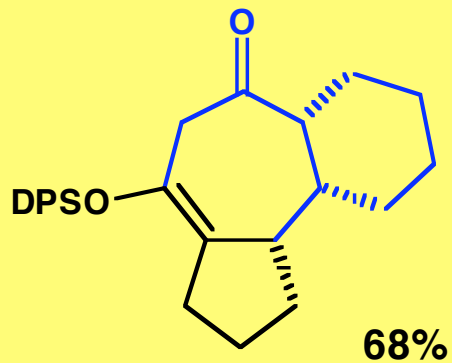
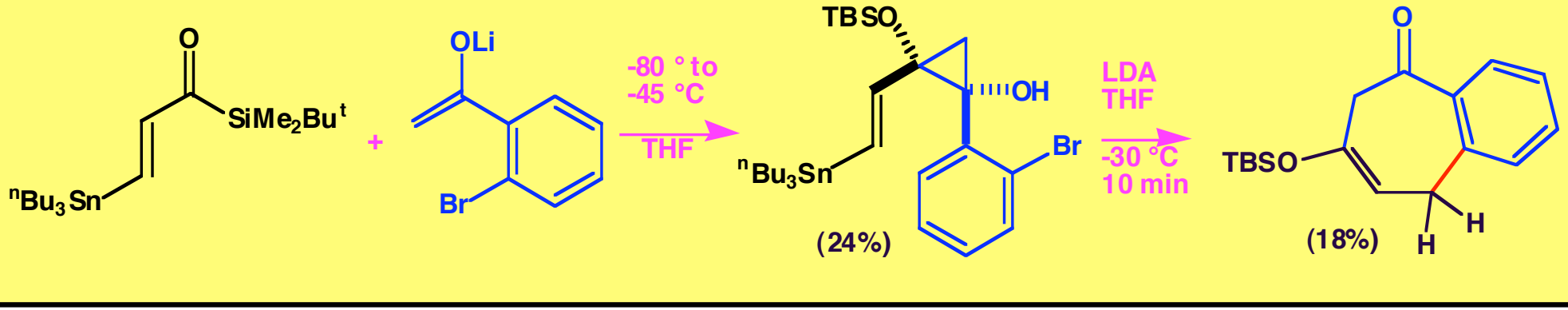
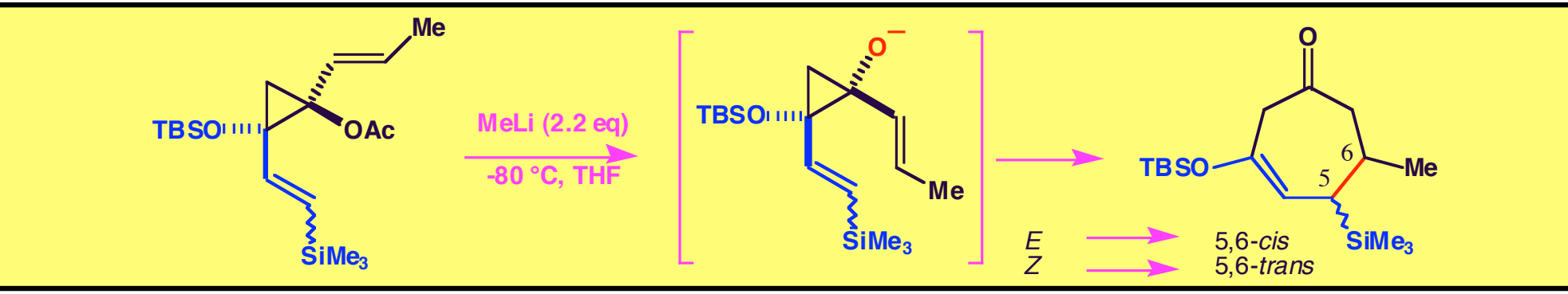
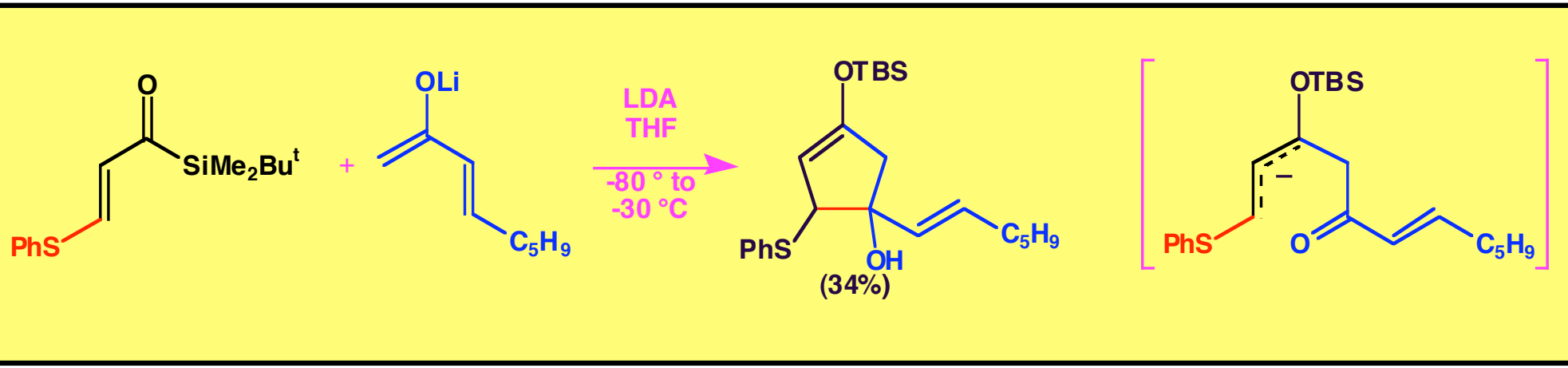


68%

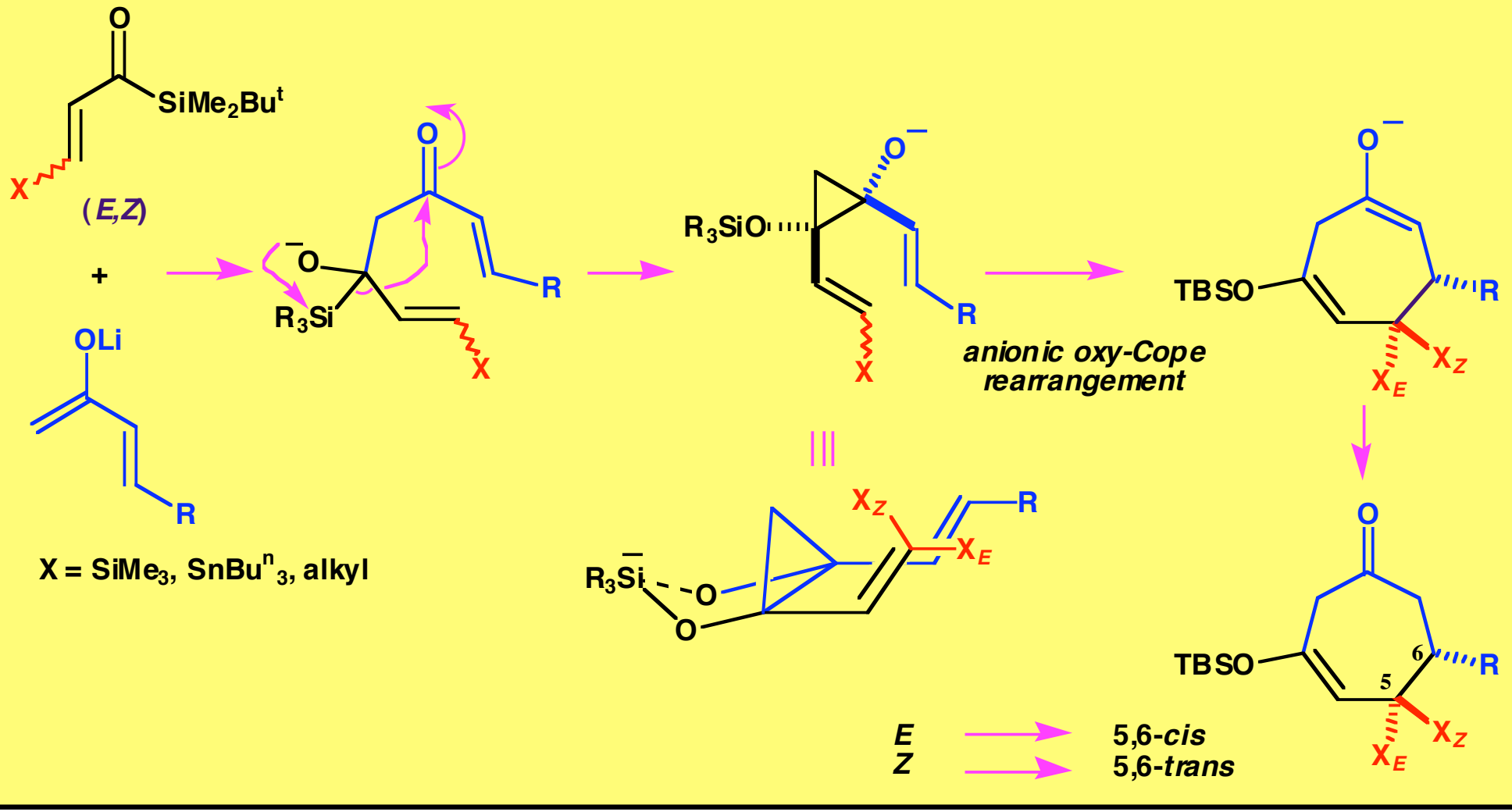
Mechanistic Studies of the [3 + 4] Annulation





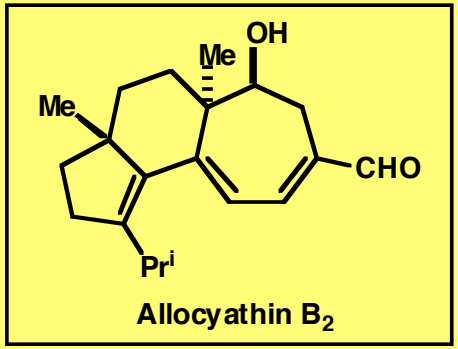


A Reaction Mechanism of the [3 + 4] Annulation Using the Reaction of Acryloylsilanes with the Lithium Enolates of Alkenyl Methyl Ketones

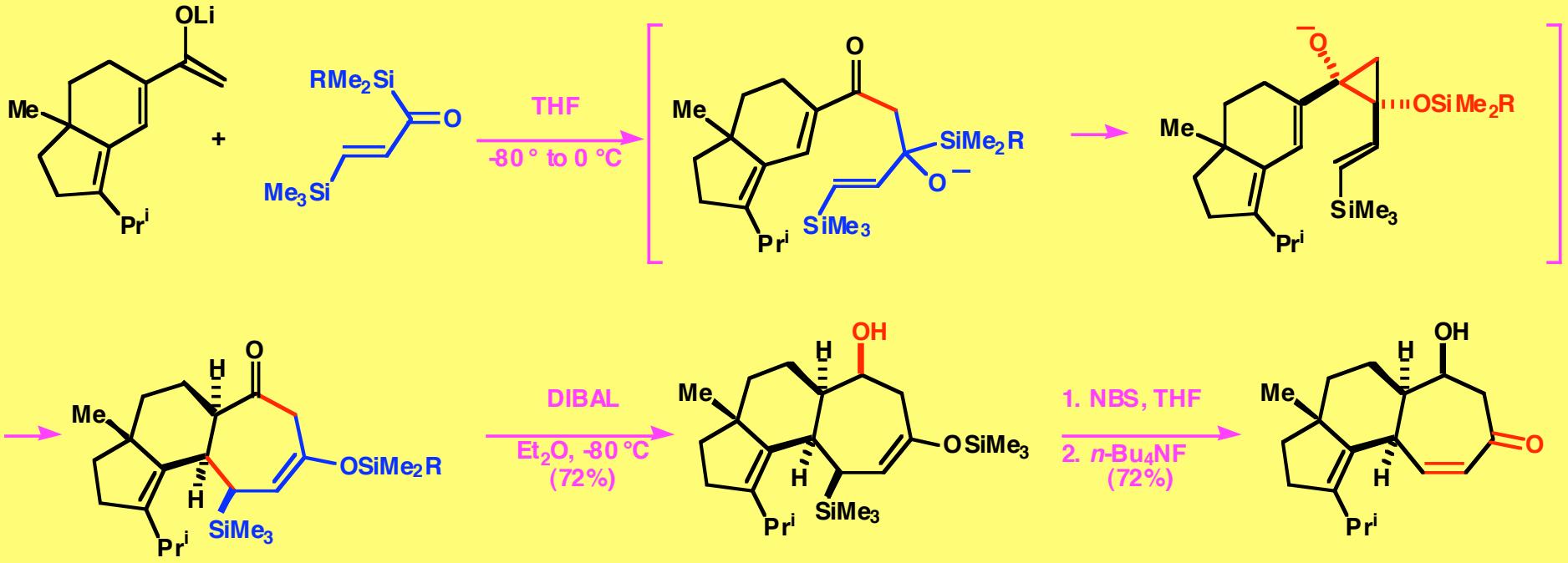


Takeda, K.; Takeda, M.; Nakajima, A.; Yoshii, E. *J. Am. Chem. Soc.* **1995**, *117*, 6400-6401.
Takeda, K.; Nakajima, A.; Takeda, M.; Okamoto, Y.; Sato, T.; Yoshii, E.; Koizumi, T. *J. Am. Chem. Soc.* **1998**, *120*, 4947-4959.
Takeda, K.; Nakajima, A.; Takeda, M.; Yoshii, E. *Org. Synth.* **1999**, *76*, 199-211.

Synthesis of the Tricyclic Skeleton of Cyathins Using Brook Rearrangement-Mediated [3 + 4] Annulation

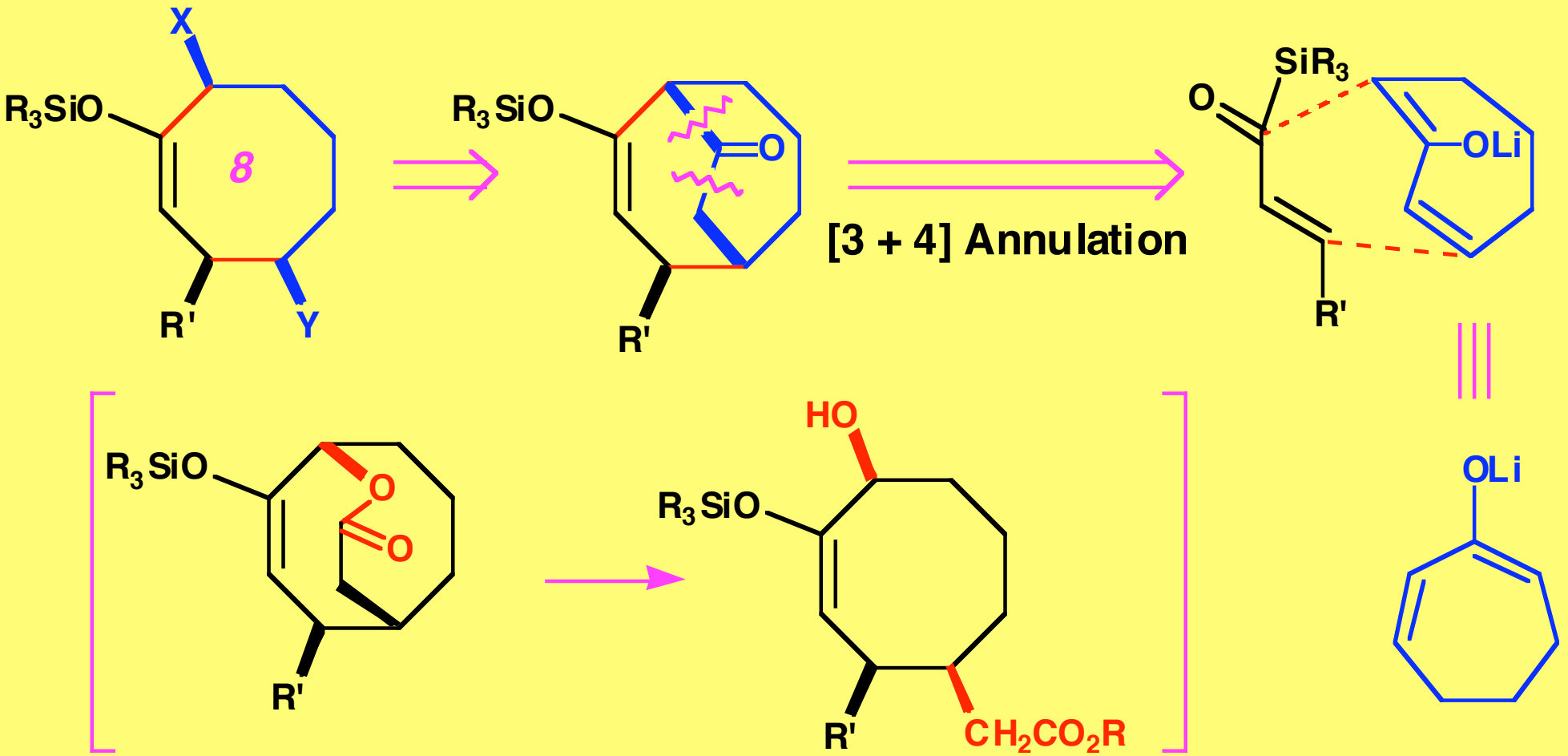


Allocyathin B_2

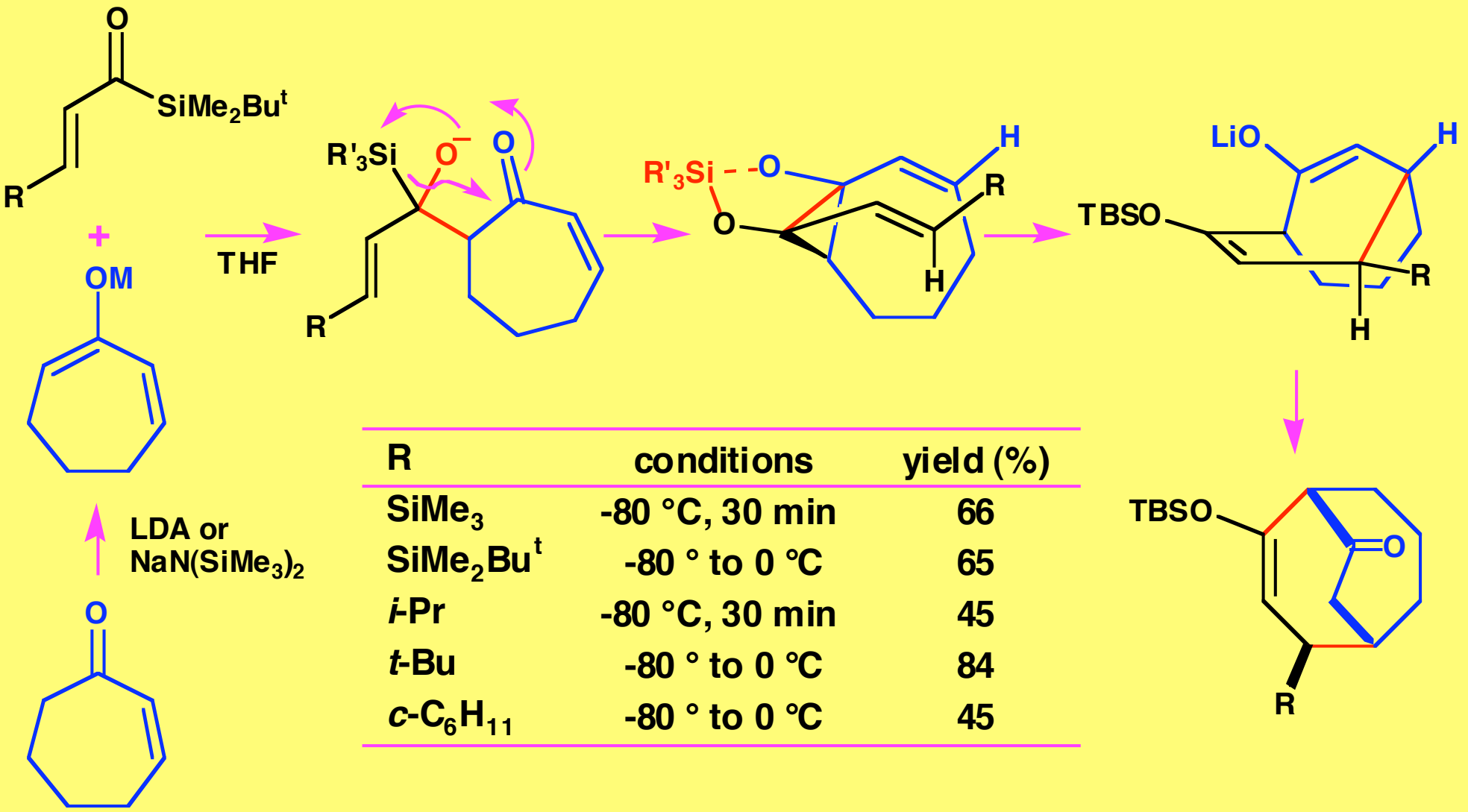


Kei Takeda, Daisuke Nakane, Mika Takeda *Org. Lett.* **2**, 1903-1905 (2000)

Formation of Eight-Membered Carbocycles by [3 + 4] Annulation (1)

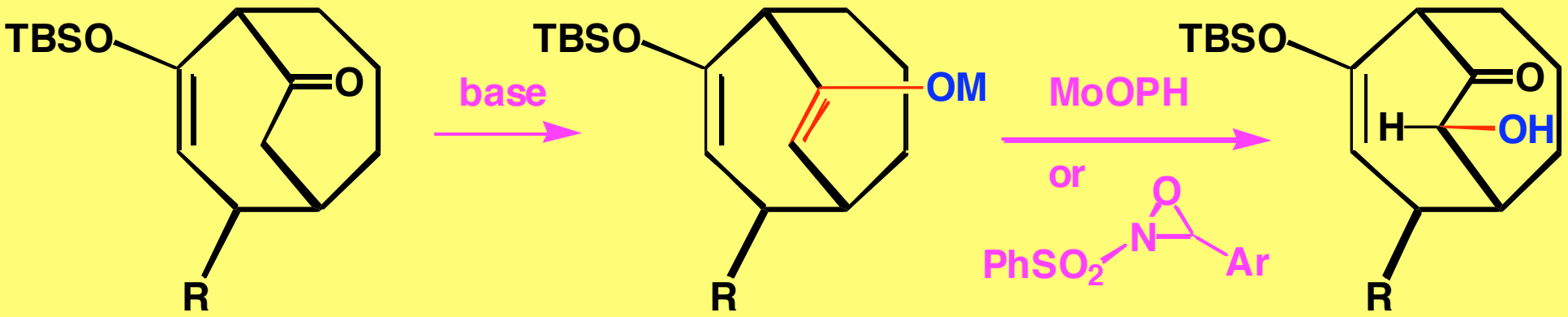


Formation of Eight-Membered Carbocycles by [3 + 4] Annulation (2)



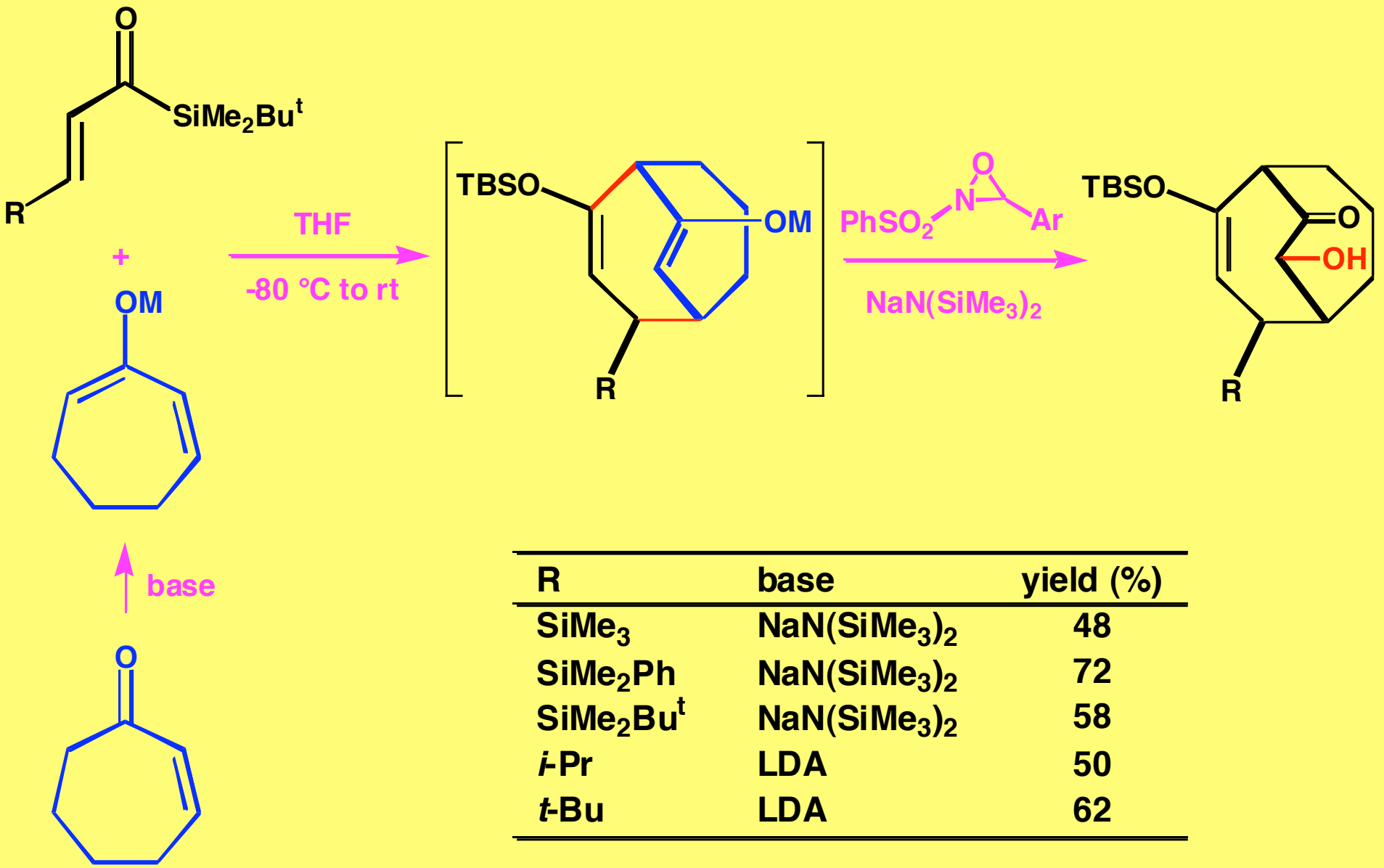
R	conditions	yield (%)
$SiMe_3$	-80 °C, 30 min	66
$SiMe_2Bu^t$	-80 ° to 0 °C	65
i-Pr	-80 °C, 30 min	45
t-Bu	-80 ° to 0 °C	84
c-C_6H_{11}	-80 ° to 0 °C	45

α-Hydroxylation of Bicyclo[2.2.2]decenones



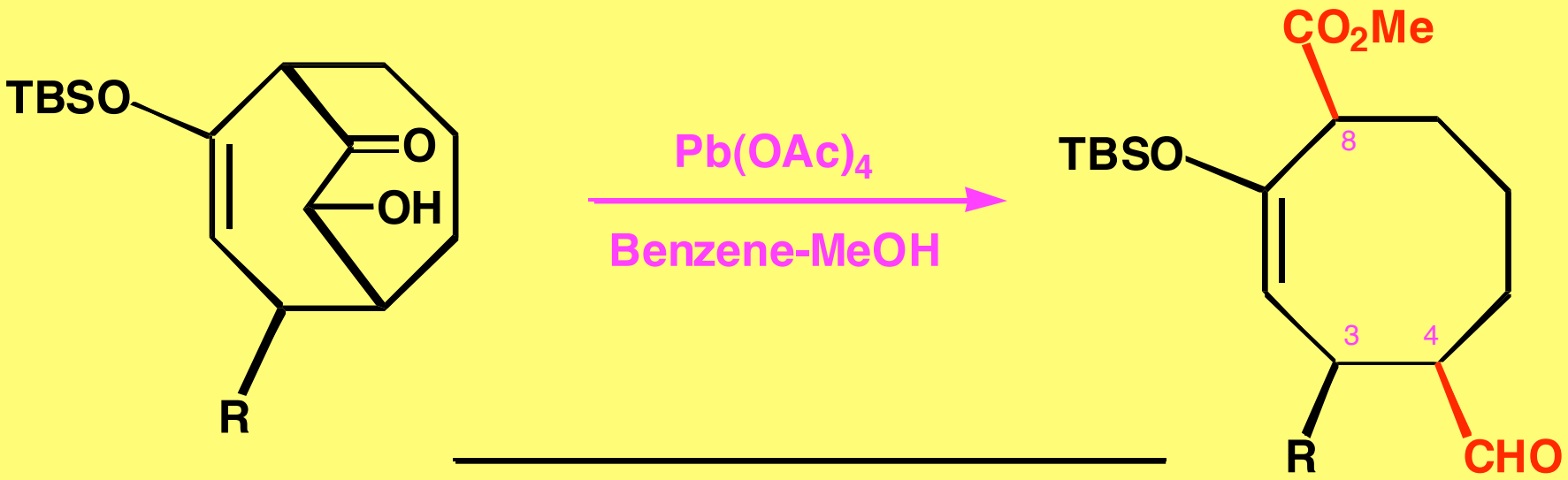
R	base	yield (%) Vedejs 法	yield (%) Davis 法
$SiMe_3$	LDA	52	
$SiMe_3$	$NaN(SiMe_3)_2$		76
t-Bu	LDA	66	
t-Bu	$NaN(SiMe_3)_2$		71

Tandem [3 + 4] Annulation /α-Hydroxylation



R	base	yield (%)
$SiMe_3$	$NaN(SiMe_3)_2$	48
$SiMe_2Ph$	$NaN(SiMe_3)_2$	72
$SiMe_2Bu^t$	$NaN(SiMe_3)_2$	58
i-Pr	LDA	50
t-Bu	LDA	62

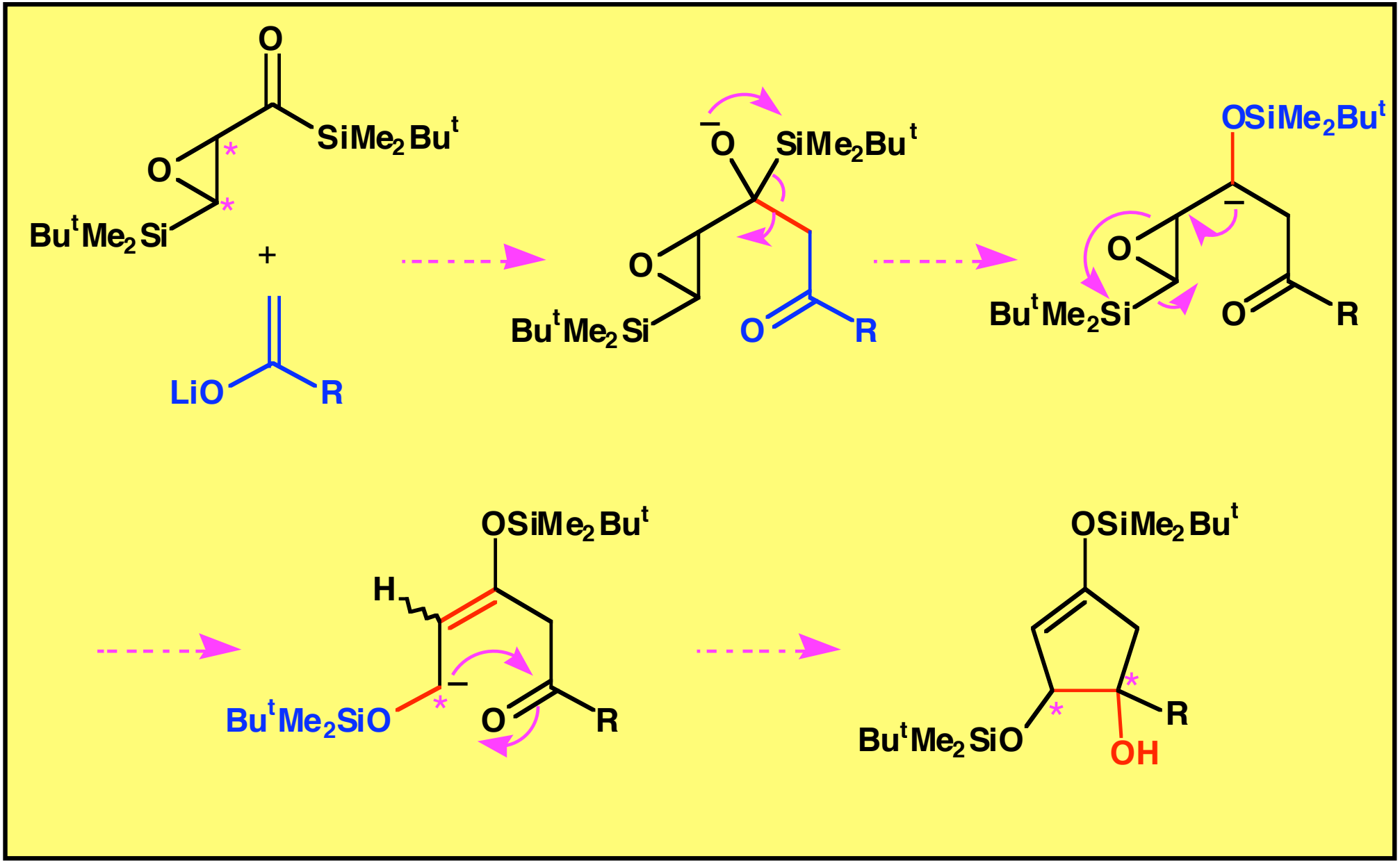
Tandem [3 + 4] Annulation /α-Hydroxylation



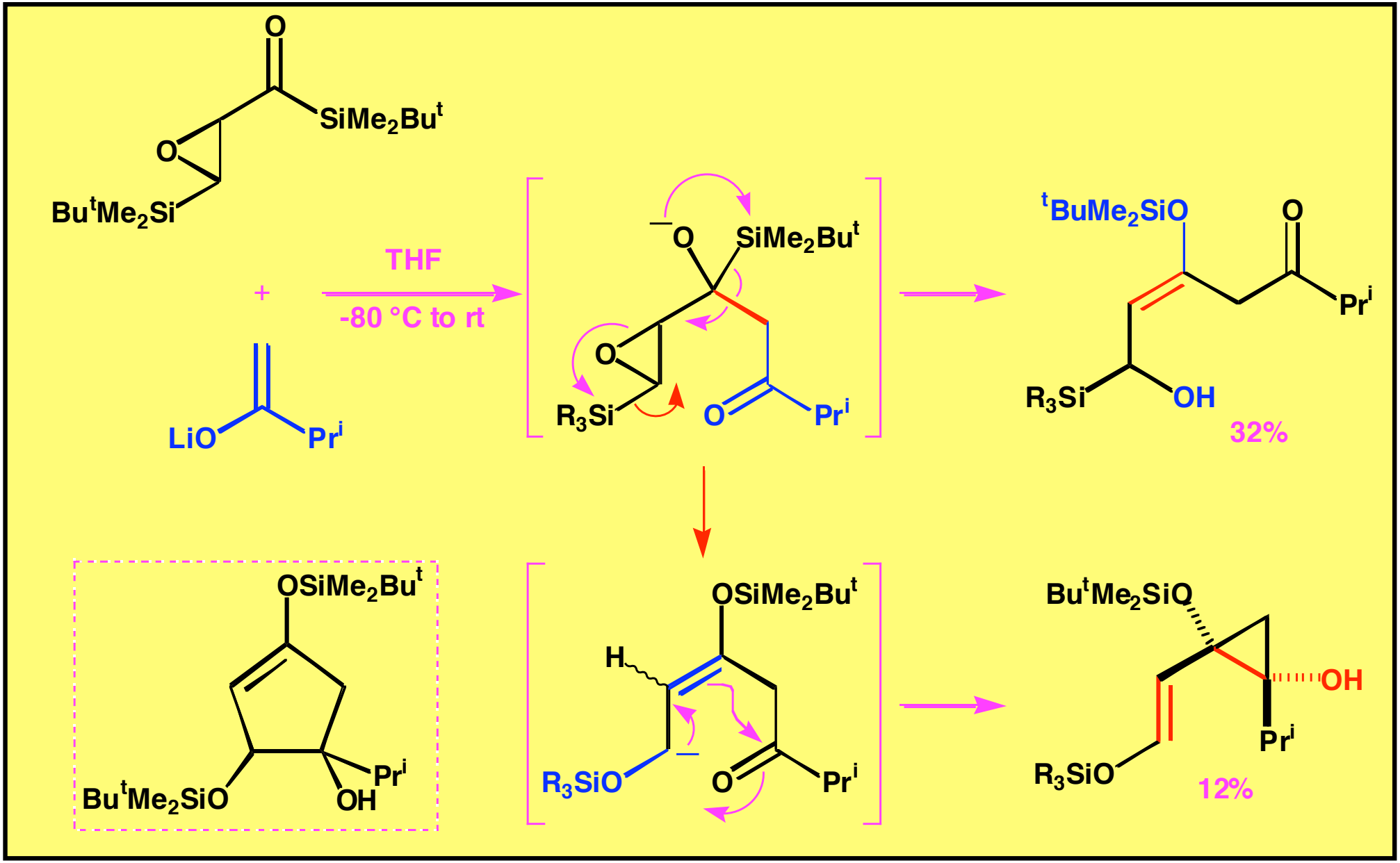
R	yield (%)
$SiMe_3$	95
$SiMe_2Ph$	96
$SiMe_2Bu^t$	95
i-Pr	97
t-Bu	93

Kei Takeda, Yuji Sawada, Koichi Sumi *Org. Lett.* **4**, 1031-1033 (2002)

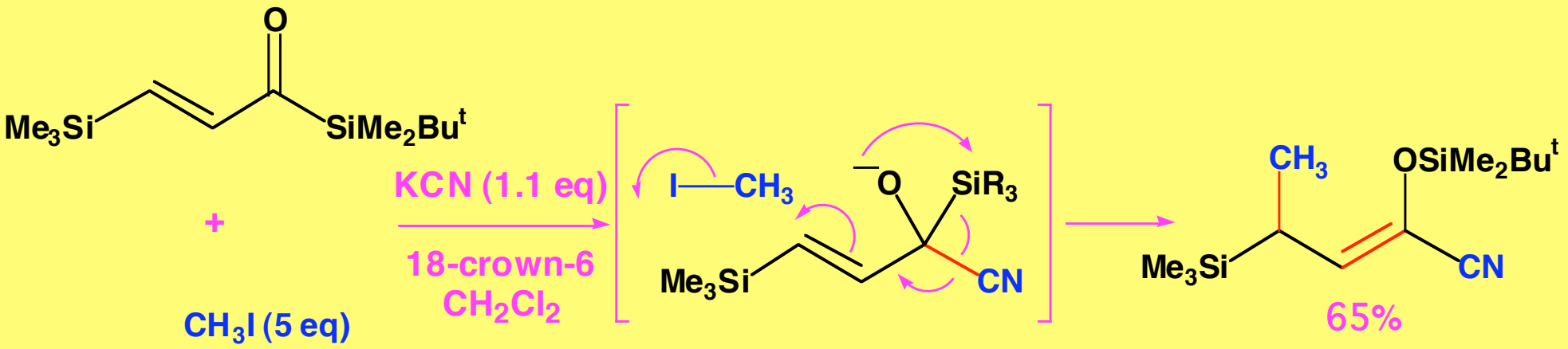
[3 + 2] Annulation Using a Double Brook Rearrangement (1)



[3 + 2] Annulation Using a Double Brook Rearrangement (2)

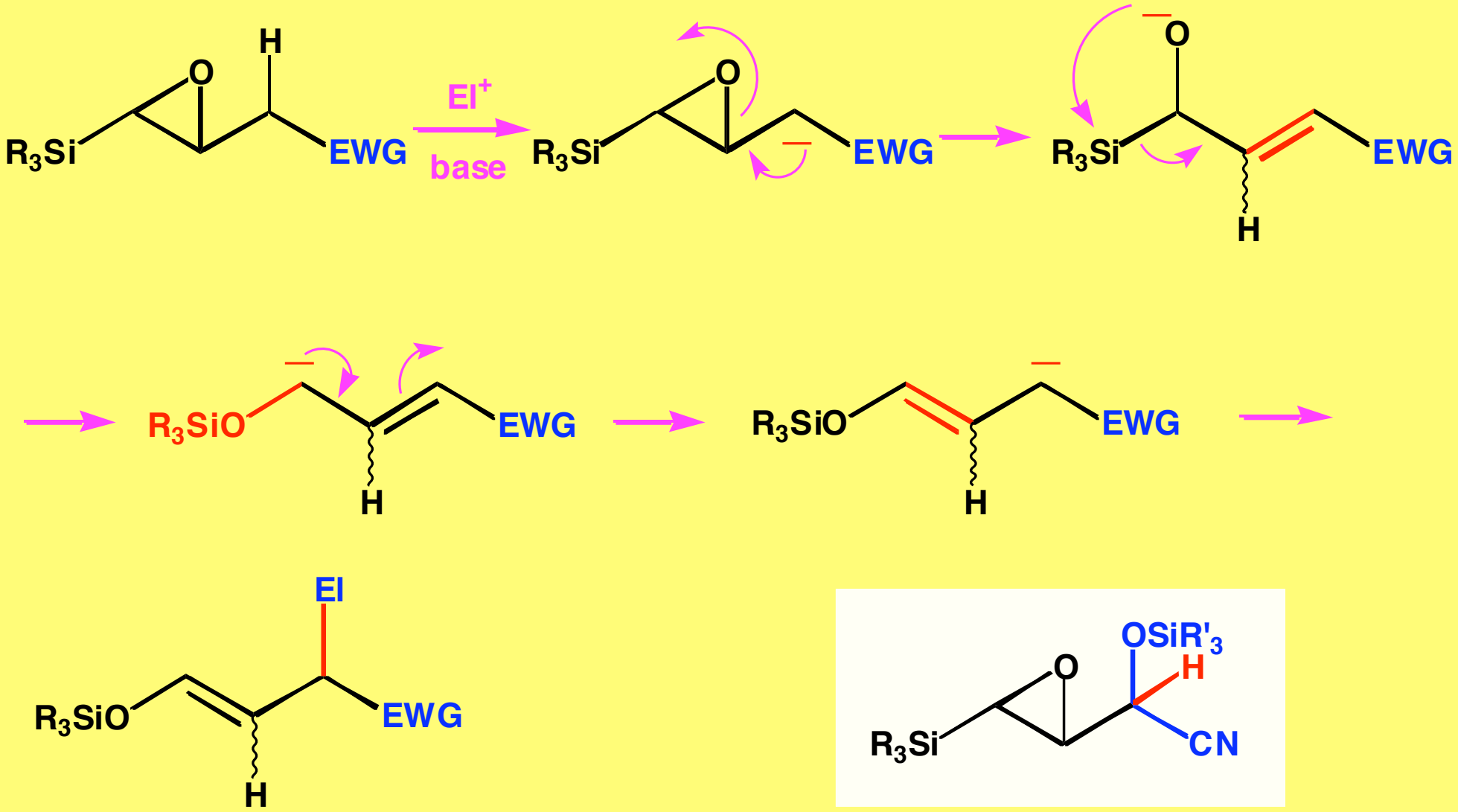


Reaction of Acryloylsilanes with KCN/18-crown-6 in the Presense of MeI

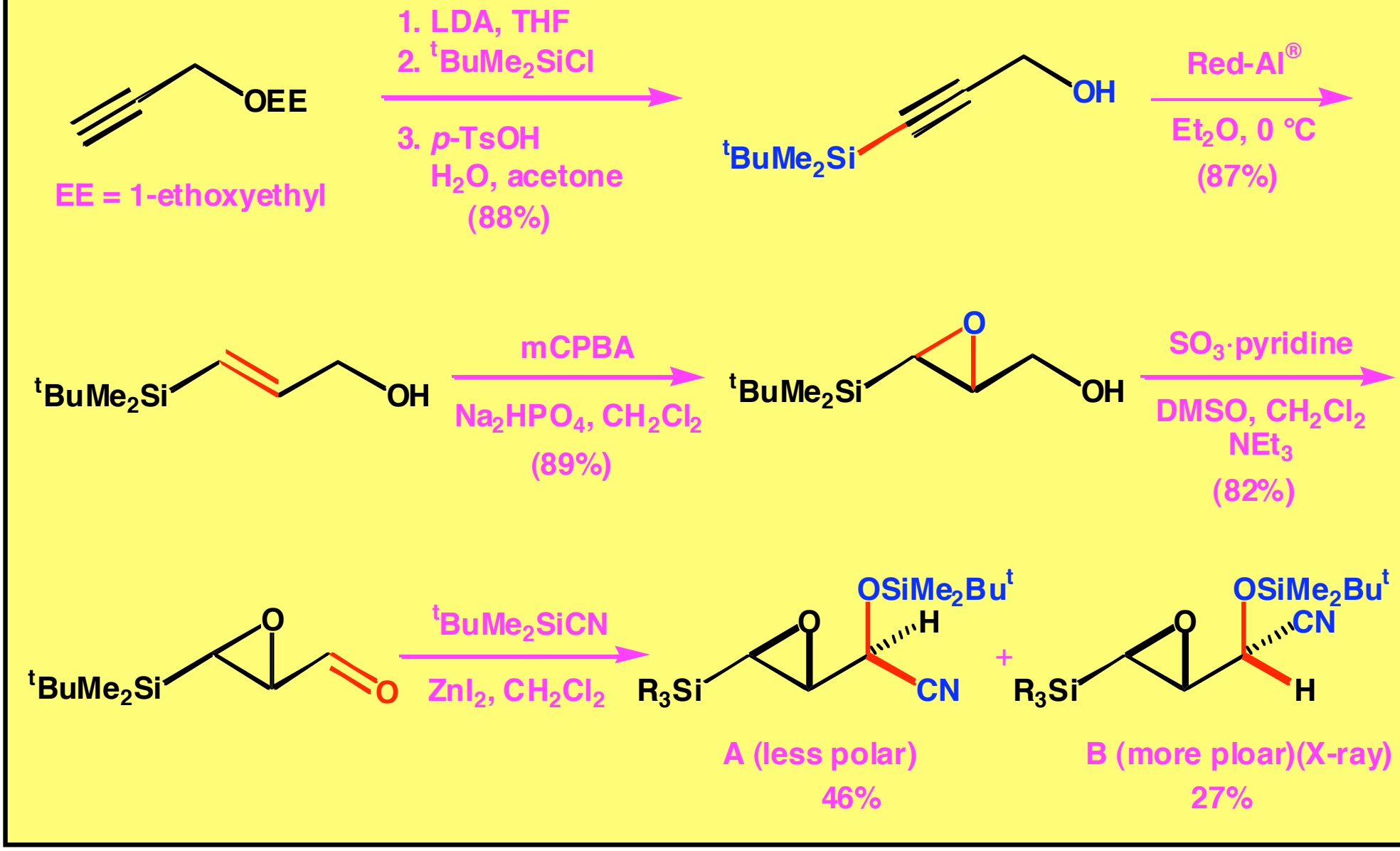


Kei Takeda, Yuji Ohnishi *Tetrahedron Lett*. **41**, 4169-4172 (2000).

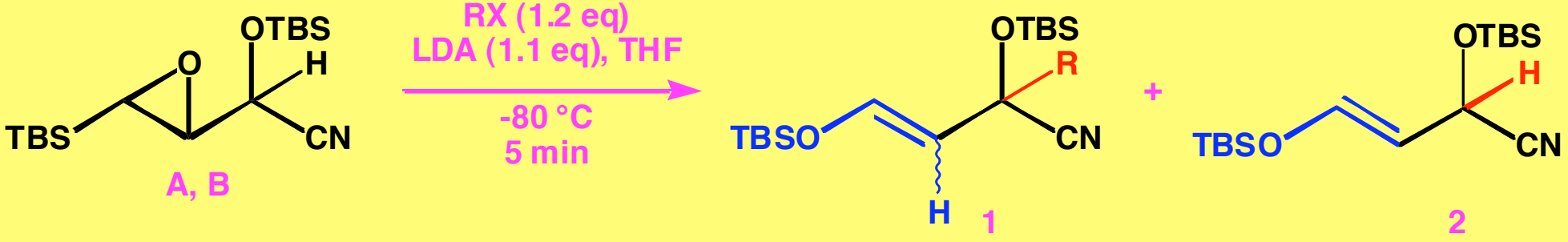
Reaction of Metalated β-Silyl-α,β-epoxides with Electrophiles



Preparation of β-Silyl-α,β-epoxyaldehyde Cyanohydrins

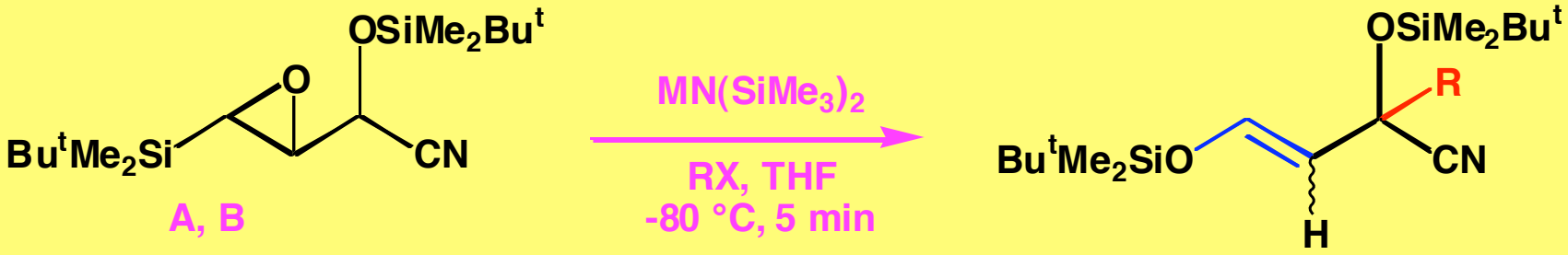


Reaction of Cyanohydrins of β-Silyl-α,β-epoxyaldehyde with LDA in the Presence of Alkylating Agents



	diastereomer A			diastereomer B		
RX	1 (yield, %)	*E*/*Z*	2 (yield, %)	1 (yield, %)	*E*/*Z*	2
MeI	82	2.5	-	84	22.0	-
EtI	76	2.9	-	74	28.0	-
i-PrI	58	2.8	12	74	31.0	-
$PhCH_2Br$	97	2.7	-	98	47.0	-
$CH_2=CHCH_2Br$	83	3.4	-	87	40.0	-

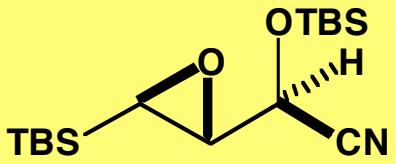
Reaction of Cyanohydrins of β-Silyl-α,β-epoxyaldehyde with $MN(SiMe_3)_2$ in the Presence of Alkylating Agents



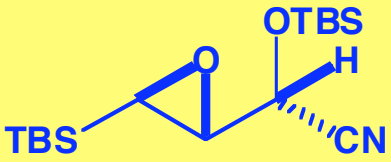
	yield (%) (*E*/*Z*)					
	from A			from B		
RX	LHMDS	KHMDS	NHMDS	LHMDS	KHMDS	NHMDS
MeI	44 (23.0)	84 (0.9)	96 (40.0)	83 (31.0)	87 (9.7)	98 (*E*)
EtI	24 (16.0)	76 (0.7)	90 (42.0)	64 (28.0)	81 (16.0)	89 (42.0)
i-PrI	15 (14.0)	42 (2.1)	80 (62.0)	44 (37.0)	73 (83.0)	89 (75.0)
$PhCH_2Br$	56 (30.0)	83 (0.8)	98 (65.0)	75 (82.0)	88 (13.0)	99 (67.0)
$CH_2{=}CHCH_2Br$	45 (31.0)	80 (1.1)	91 (39.0)	80 (89.0)	83 (14.0)	92 (41.0)

Kei Takeda, Eiji Kawanishi, Michiko Sasaki, Yuji Takahashi, Kentaro Yamaguchi *Org. Lett.* in press.

E/*Z* Ratios of the Alkylation Products Depending on the Bases Used

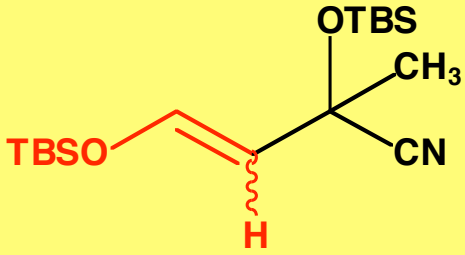


A (less polar)



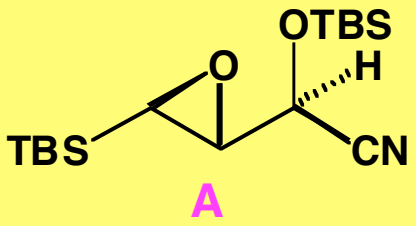
B (more ploar)

CH_3I (1.2 eq)
base (1.1 eq)
THF
-80 °C, 5 min

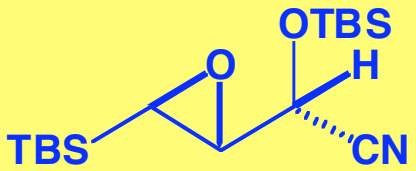


base	diastereomer	yield (%)	*E*/*Z*	SM
LDA (in Hexane/THF)	A	82	2.5	
	B	84	22.0	
$LiN(SiMe_3)_2$ (1.0M in THF)	A	44	23.0	40
	B	83	31.0	
$NaN(SiMe_3)_2$ (1.0M in THF)	A	91	40.0	
	B	92	47.0	
$KN(SiMe_3)_2$ (0.5M in toluene)	A	84	0.9	
	B	87	9.7	

Increased Z-Selectivity in Less-Polar Solvents



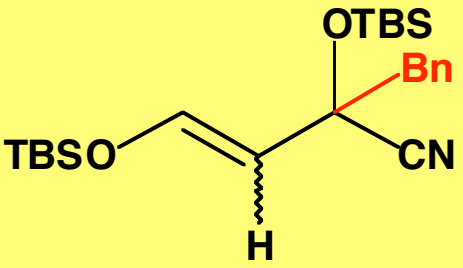
A



B

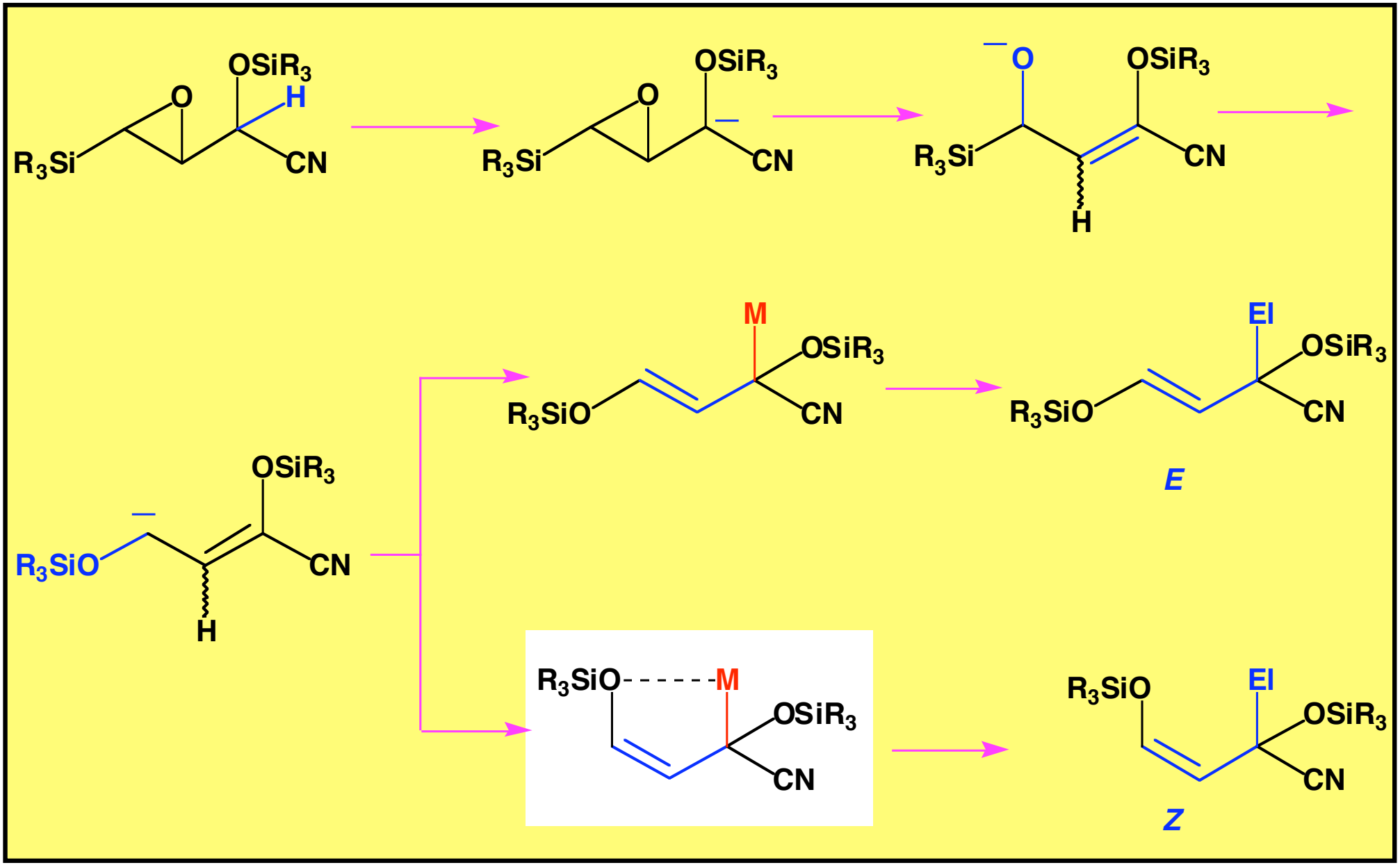
BnBr
NHMDS
(1.0M inTHF)

-80 °C, 5 min
solvent

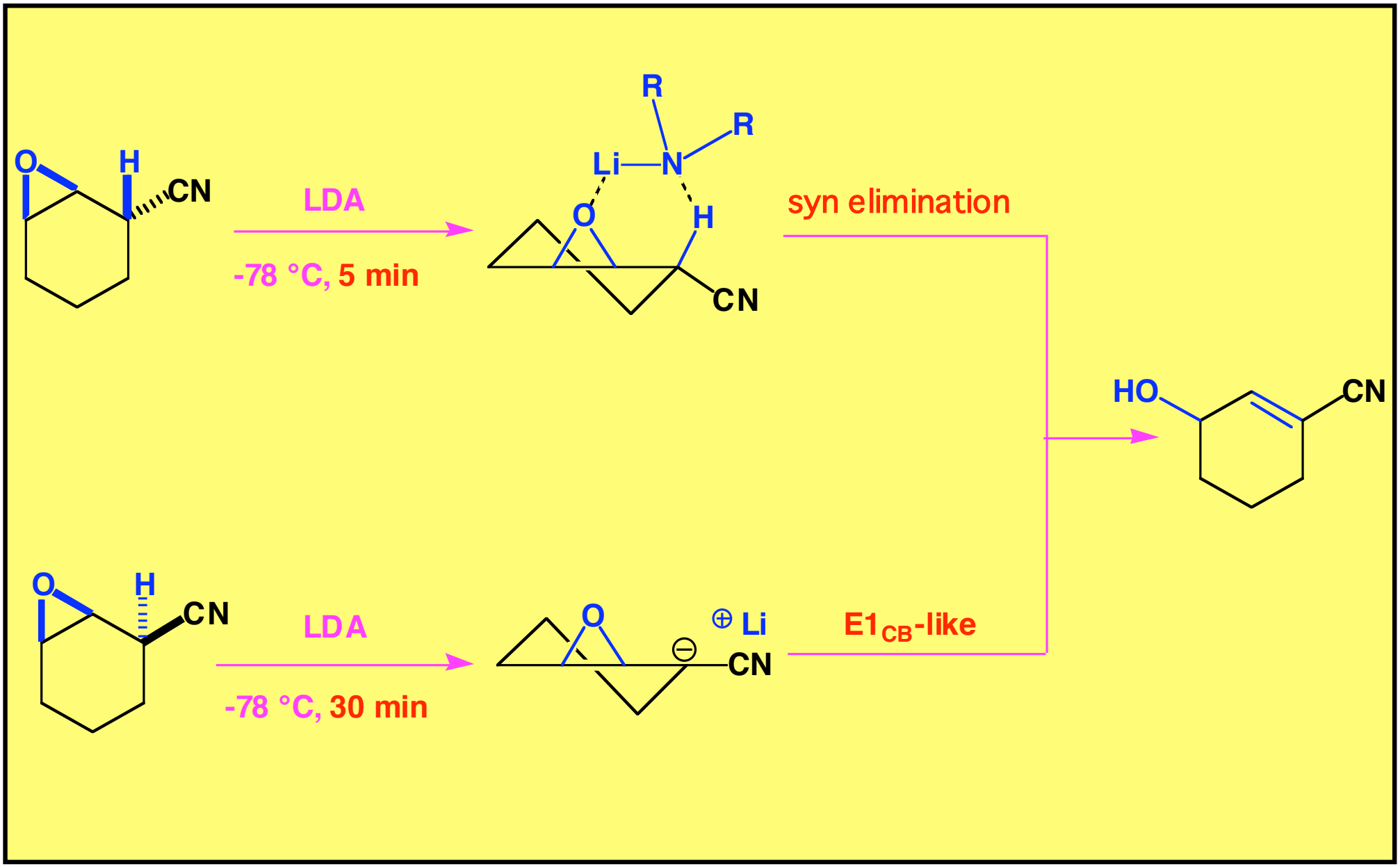


solvent	diastereomer	yield (%)	E/Z
hexane	A	93	1.5
	B	78	6.0
ether	A	84	1.9
	B	77	28.0
toluene	A	86	1.0
	B	83	24.0
THF	A	85	28.0
	B	84	52.0

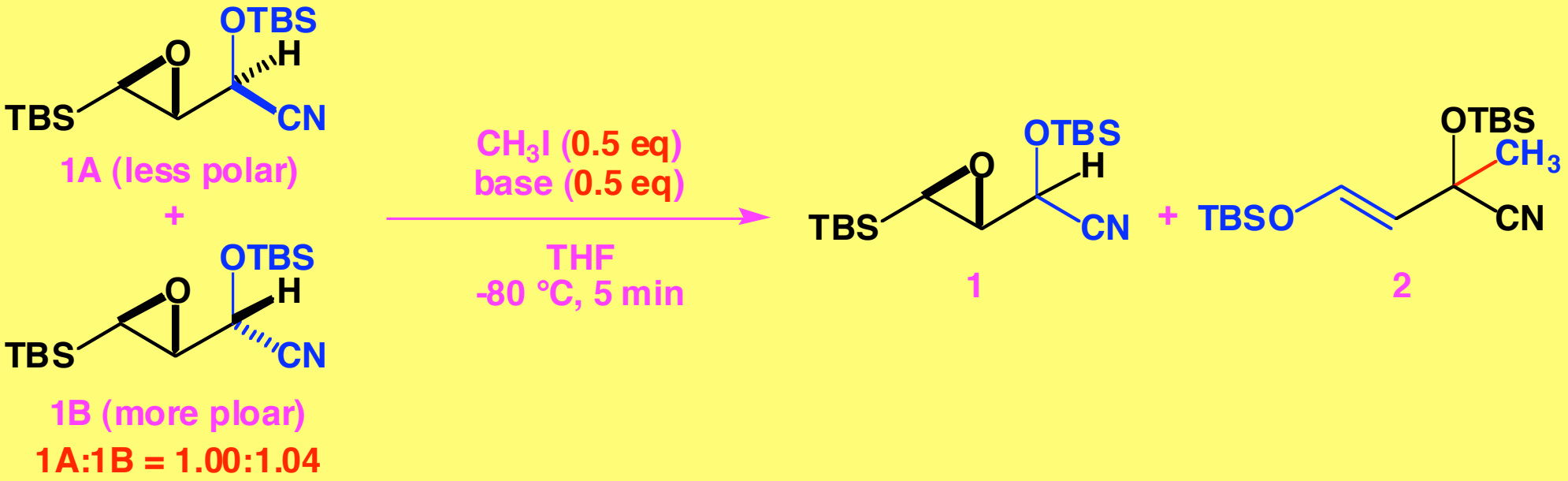
An Explanation for the Enhanced *Z*-Selectivity in Less-Polar Solvents



Chelation-Assisted Syn-Elimination Mechanism for a Base-Promoted Ring Opening of Epoxides



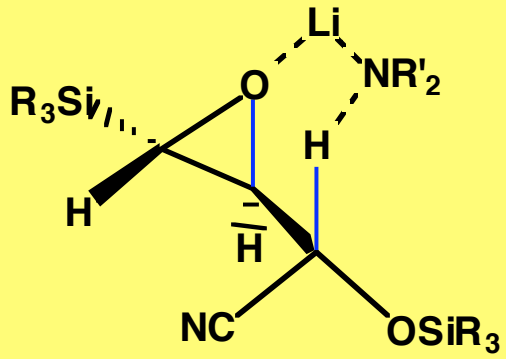
Comparison of the Relative Rates of Ring Opening of the Diasetereomers



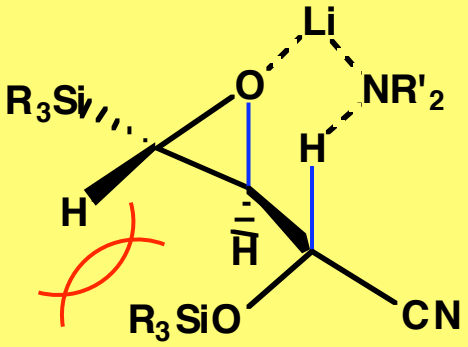
base	HMPA	yield (%) 1	A:B	yield (%) 2	*E/Z*
LDA	(-)	40	1.00:0.70	35	6.6
	(+)	67	1.00:0.76	26	25.0
NHMDS	(-)	52	1.00:0.79	40	41.0
	(+)	39	1.00:0.78	45	108.0

Plausible Mechanisms for the Base-Promoted Ring Opening of *O*-Silyl β-Silyl-α,β-epoxyaldehydes

syn-elimination

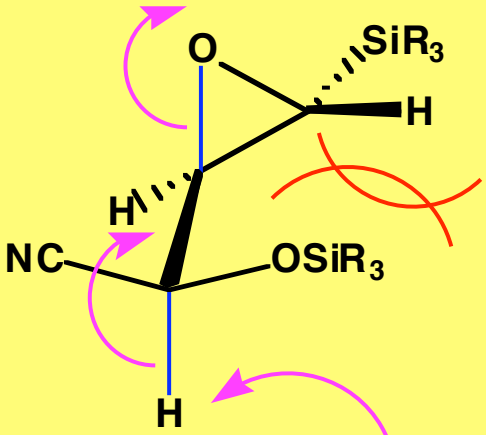


A (more stable)

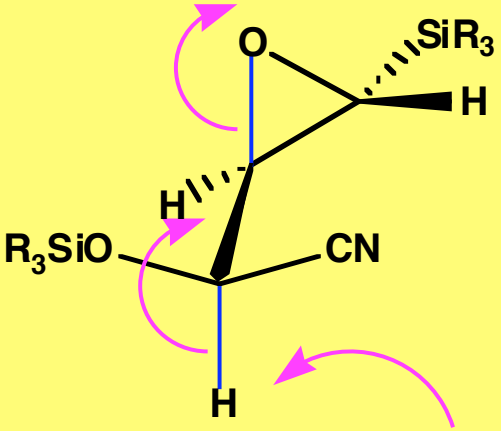


B (less stable)

anti-elimination

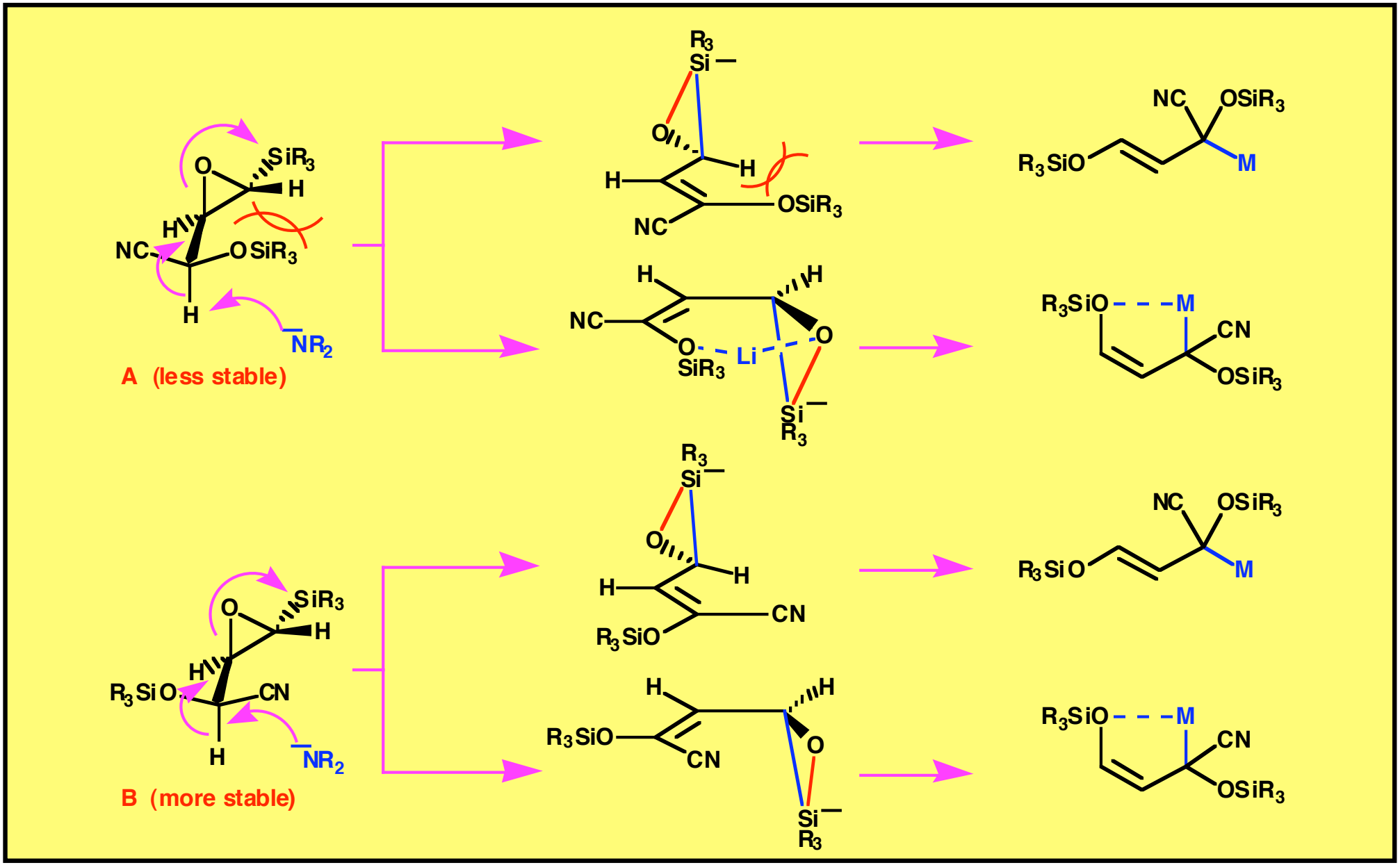


A (less stable) $\bar{N}R'_2$

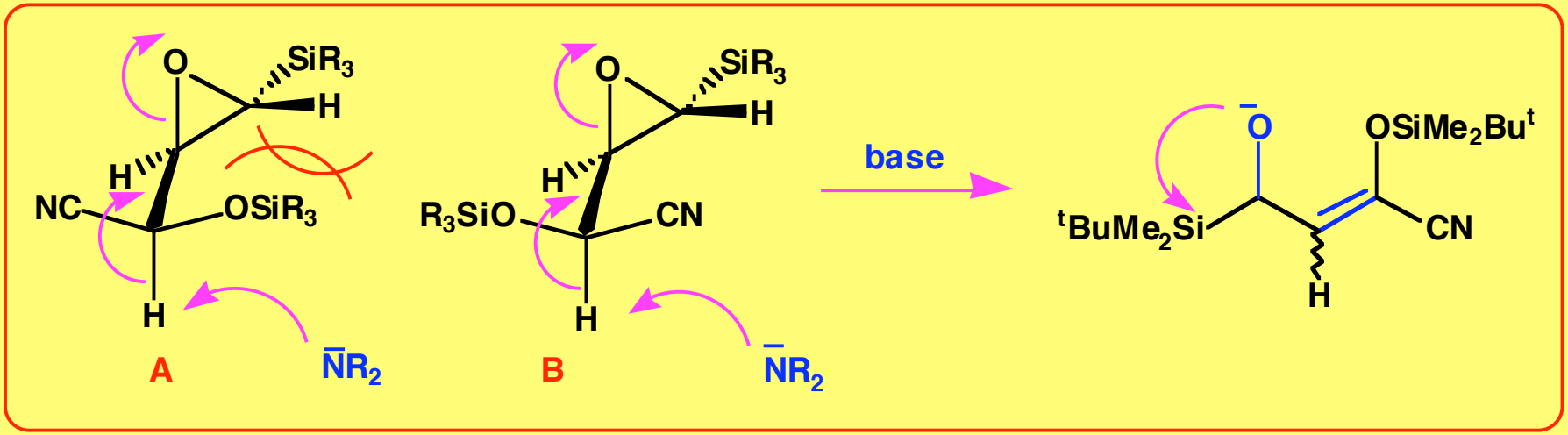


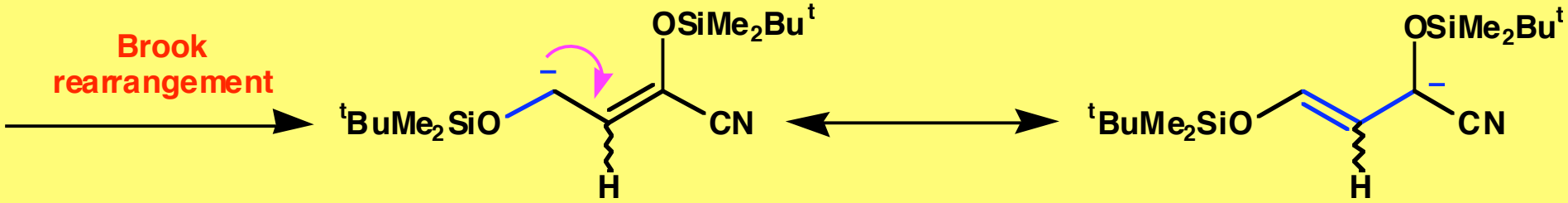
B (more stable) $\bar{N}R'_2$

An Explanation for Relatively Favorable Formation of (Z)-Derivatives from Diastereomer A



Summary


O
SiR3
H
H
NC
OSiR3
H
A
NR2
O
SiR3
H
H
R3SiO
CN
H
B
NR2
base
O
OSiMe2Bu^t
tBuMe2Si
CN
H


Brook
rearrangement
OSiMe2Bu^t
tBuMe2SiO
CN
H
OSiMe2Bu^t
tBuMe2SiO
CN
H


El
OSiMe2Bu^t
El
tBuMe2SiO
CN
H

Prof. Emeritus Eiichi Yoshii

[1 + 2] Annulation

Koichi Sako
Hitoshi Nakamura
Junko Nakatani

[3 + 2] Annulation

Tomoko Makino
Masato Fujisawa
Keiki Sakurama
Ayako Sano
Noriaki Hatakeyama
Haruka Ubayama
Emi Ando
Kenji Yamawaki

Reduction of Acylsilanes and Reactions with Cyanides

Yuji Ohnishi

Synthesis of Natural Products

Ichiro Nakayama
Kanji Kitagawa
Daisuke Nakane

The Late Prof. Toru Koizumi

[3 + 4] Annulation

Mika Takeda
Akemi Nakajima
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