エポキシシランを用いる新規合成反応の開発

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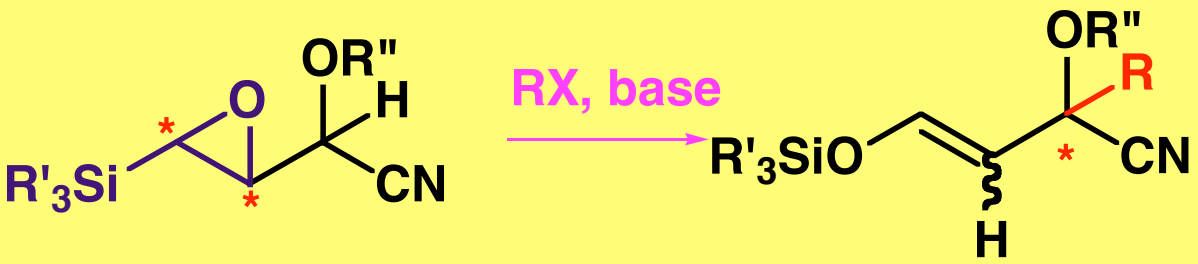
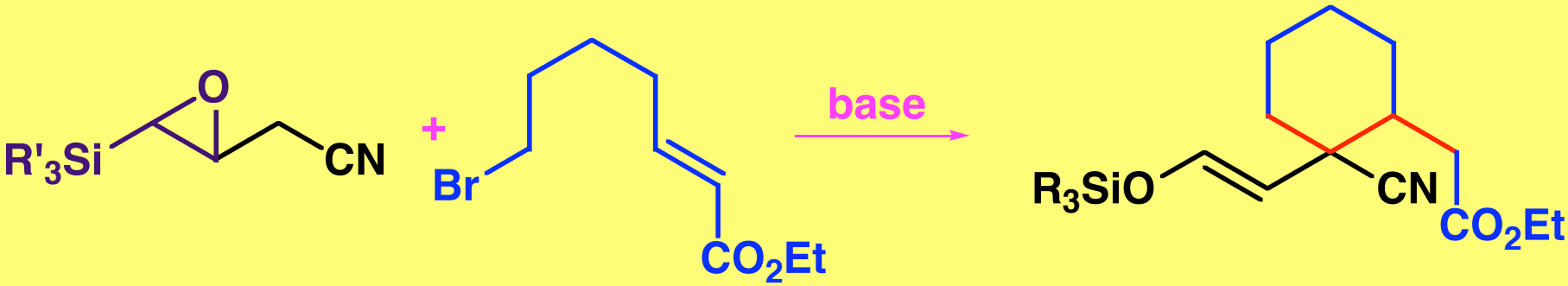
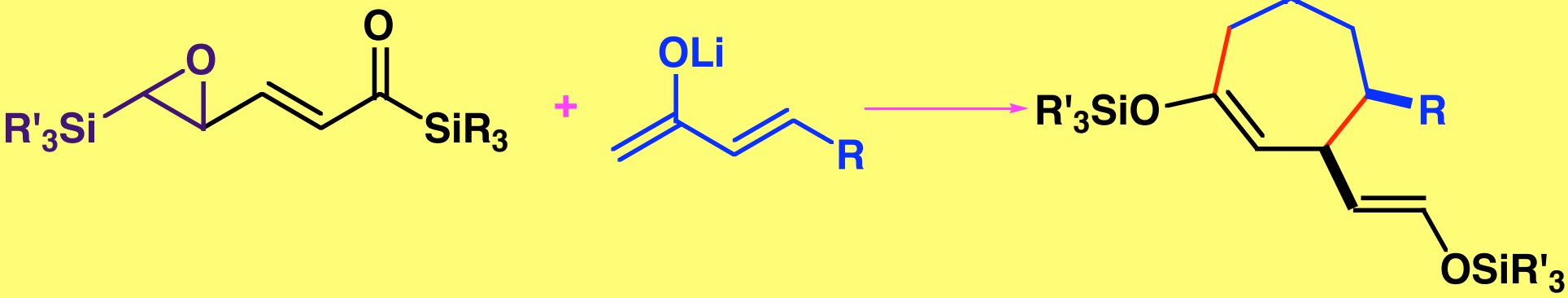
東京理科大学　２００３年6月１７日

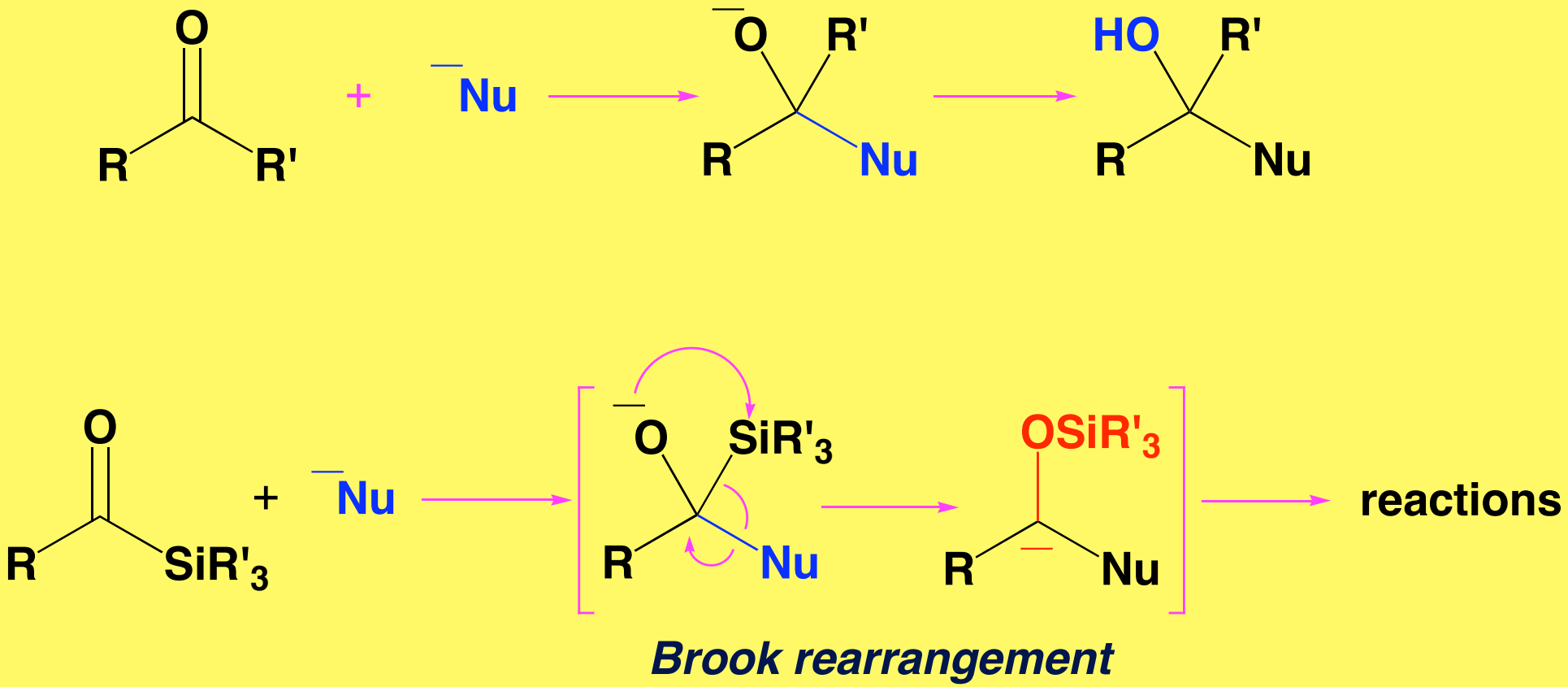
Development of New Synthetic Reactions Using Epoxysilanes





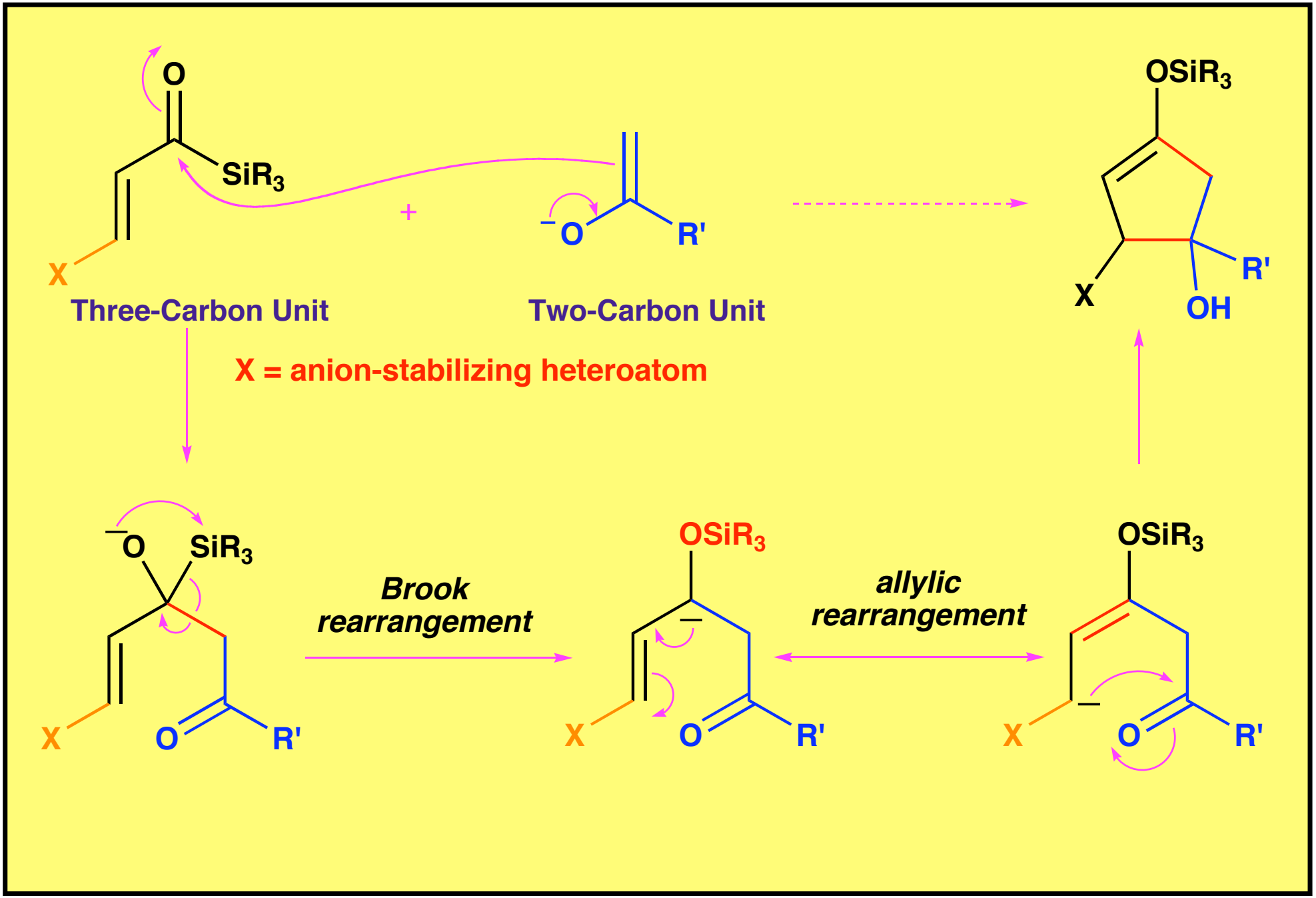


Brook Rearrangement

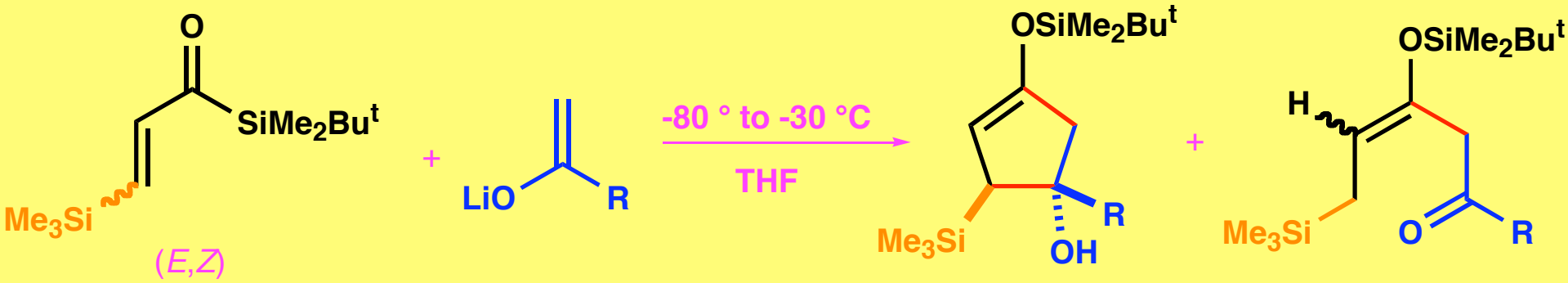


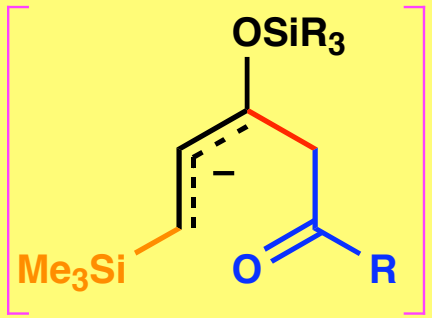
Brook, A.G. *J. Am. Chem. Soc.* **79**, 4373 (1957)

Brook Rearrangement-Mediated [3 + 2] Annulation



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

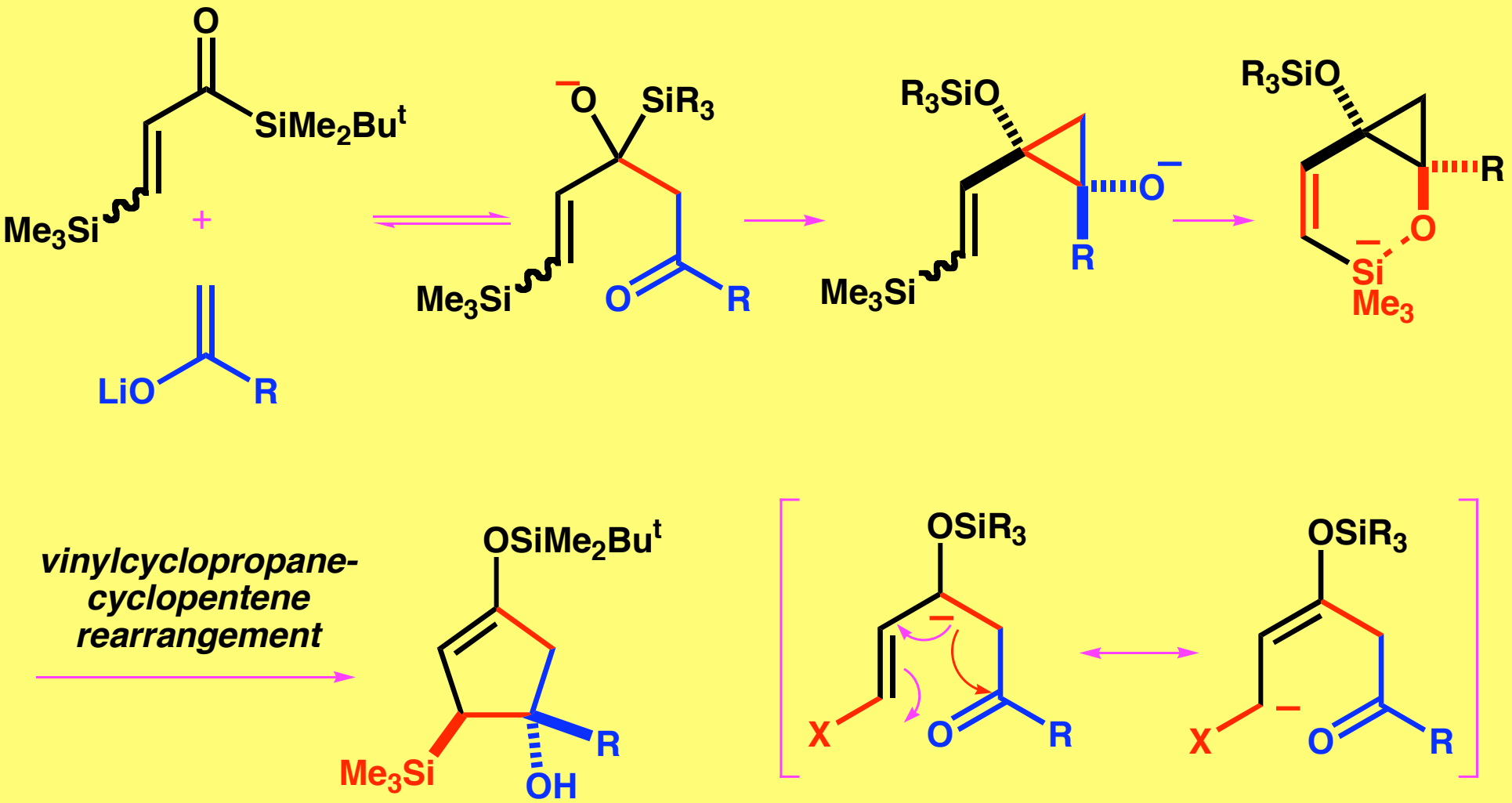




E	Et	17%	43%
	n-Pr	11%	57%
	i-Pr	14%	63%
Z	Et	75%	9%
	n-Pr	70%	19%
	i-Pr	76%	10%

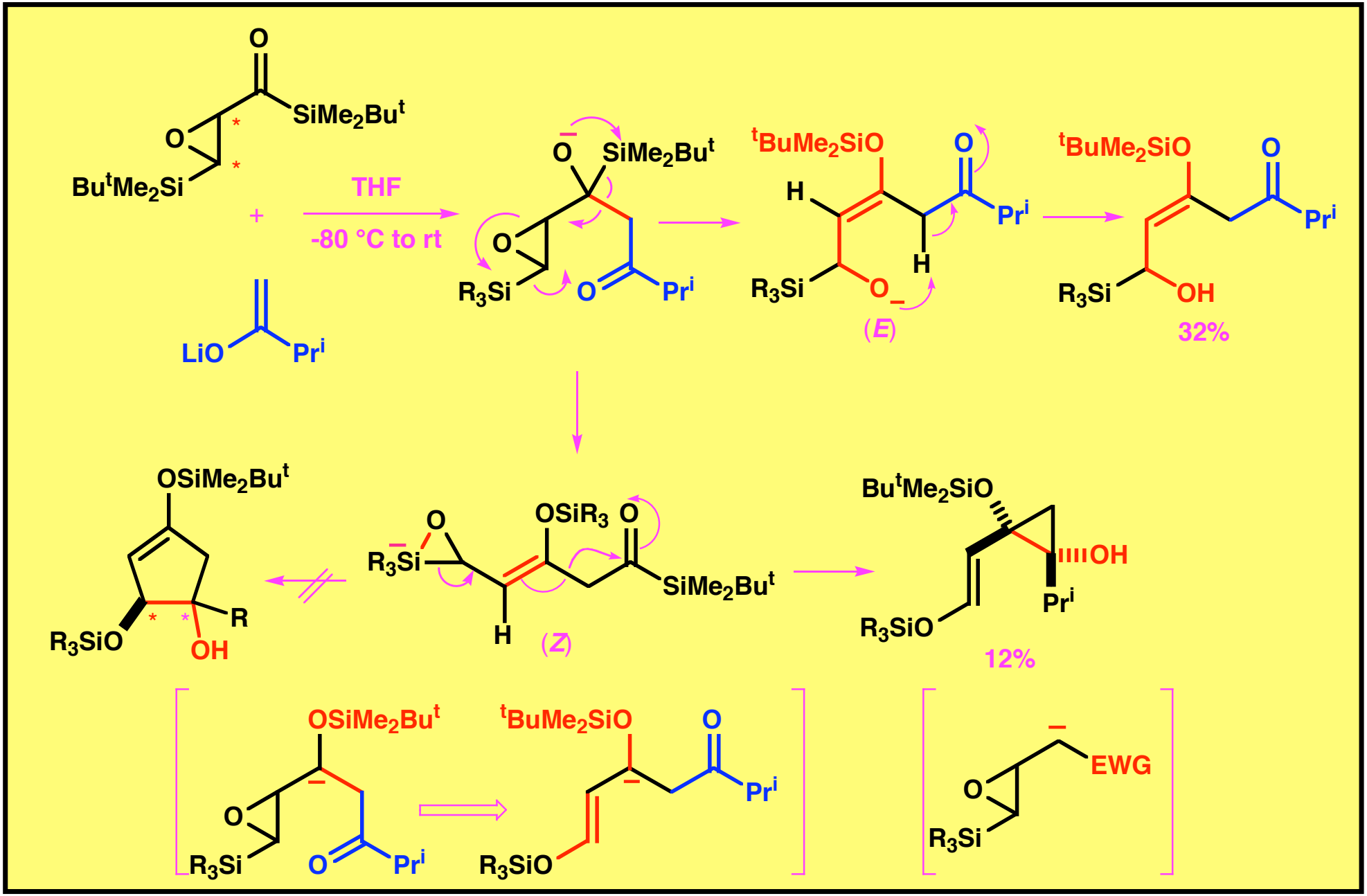
Takeda, K.; Fujisawa, M.; Makino, T.; Yoshii, E.; Yamaguchi, K. *J. Am. Chem. Soc.* **1993**, *115*, 9351-9352.

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



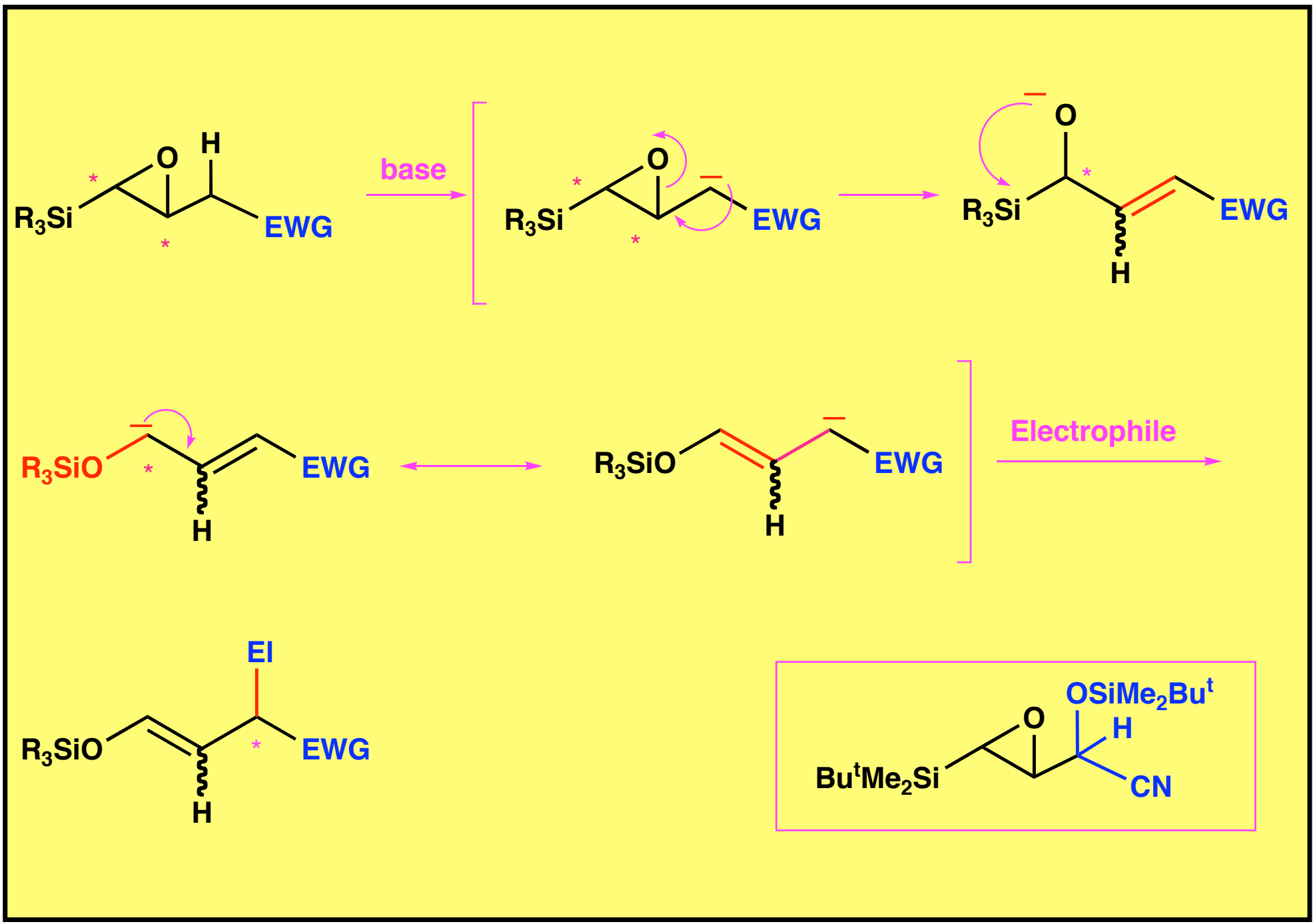
Kei Takeda, Kenji Yamawaki, Noriaki Hatakeyama *J. Org. Chem.* **67**, 1786-1794 (2002)

Attempted Double Brook Rearrangement-Mediated [3 + 2] Annulation

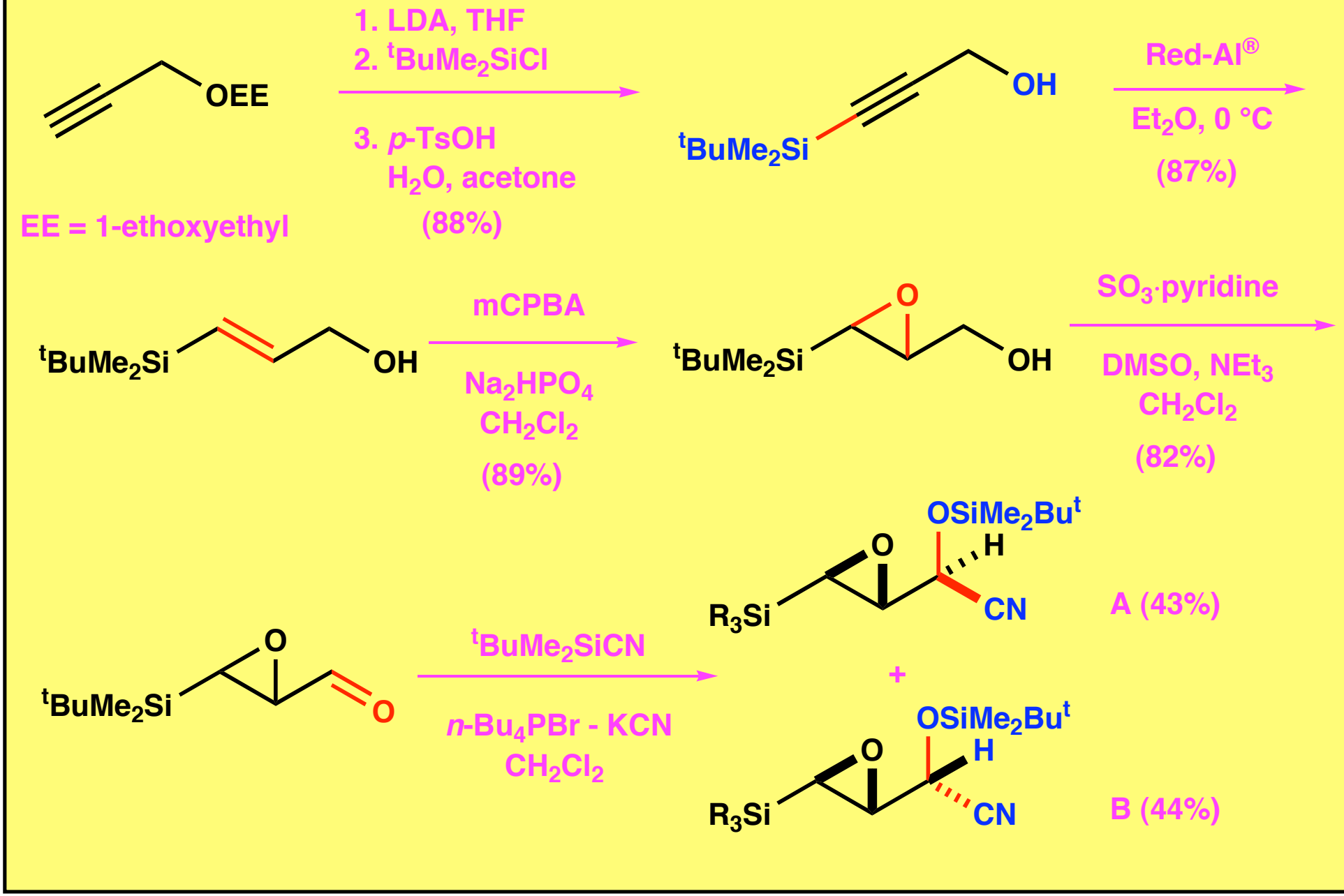


Kei Takeda, Yuji Ohnishi unpublished result.

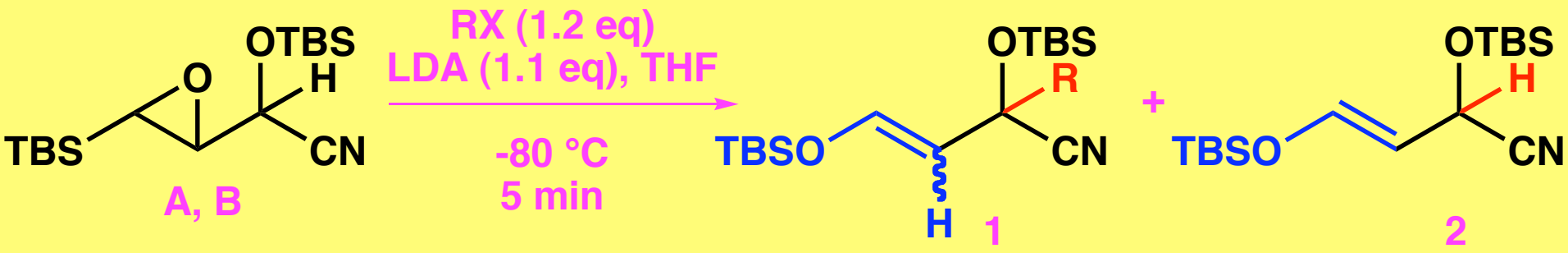
Formation of γ-Alkylated Enol Silyl Ether via Brook Rearrangement-Mediated Tandem Process



Preparation of *O*-Silyl Cyanohydrins of *trans*-β-Silyl-α,β-epoxyaldehydes

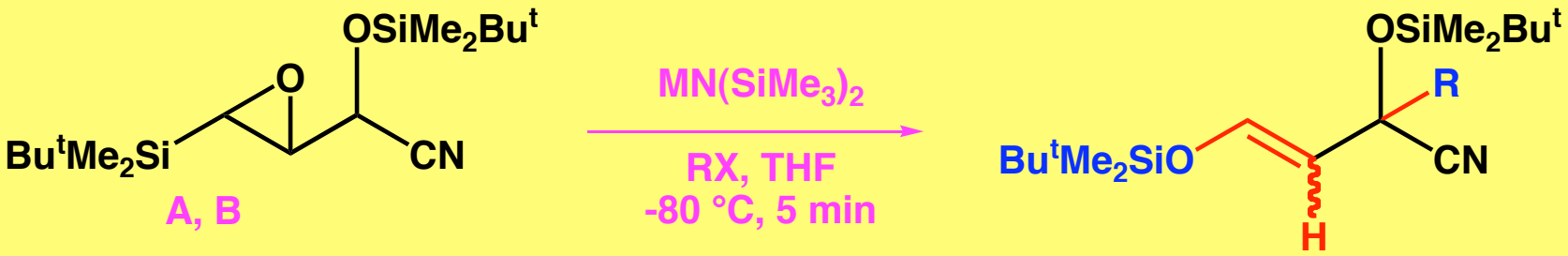


Reaction of Cyanohydrins of β-Silyl-α,β-epoxyaldehyde with LDA in the Presence of Alkylating Agents



	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	-

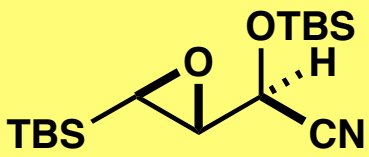
Reaction of Cyanohydrins of β-Silyl-α,β-epoxyaldehyde with $MN(SiMe_3)_2$ in the Presence of Alkylating Agents



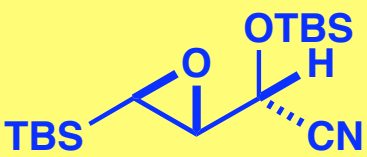
	yield (%) (*E*/*Z*)					
	from A			from B		
RX	LHMDS	KHMDS	NHMDS	LHMDS	KHMDS	NHMDS
MeI	44 (23.0)	84 (0.9)	96 (40.0)	83 (31.0)	87 (9.7)	98 (*E*)
EtI	24 (16.0)	76 (0.7)	90 (42.0)	64 (28.0)	81 (16.0)	89 (42.0)
i-PrI	15 (14.0)	42 (2.1)	80 (62.0)	44 (37.0)	73 (83.0)	89 (75.0)
$PhCH_2Br$	56 (30.0)	83 (0.8)	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.* **2002**, 4, 1511-1514.

Methylation of Metalated *O*-Silyl Cyanohydrins of *trans*-β-Silyl-α,β-epoxyaldehydes

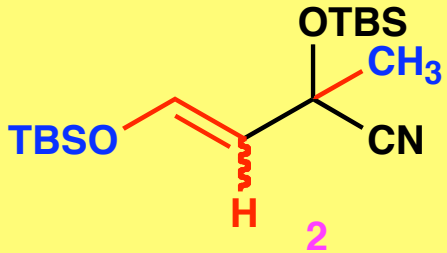


1A



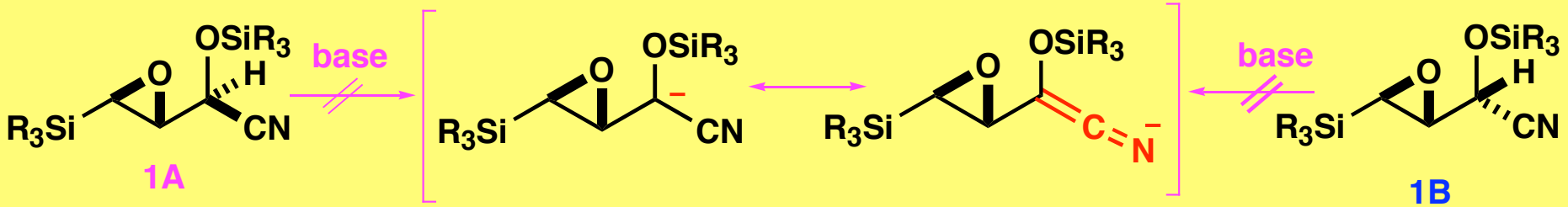
1B

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



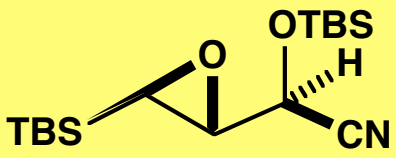
2

base	diastereomer	yield (%)	*E/Z*	SM
LDA (in hexane/THF)	1A	82	2.5	
	1B	84	22.0	
$LiN(SiMe_3)_2$ (1.0M in THF)	1A	44	23.0	40
	1B	83	31.0	
$NaN(SiMe_3)_2$ (1.0M in THF)	1A	91	40.0	
	1B	92	47.0	
$KN(SiMe_3)_2$ (0.5M in toluene)	1A	84	0.9	
	1B	87	9.7	

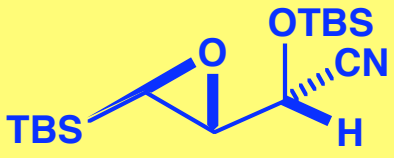


1A 1B

Solvent Effect on *E*/*Z* Selectivity

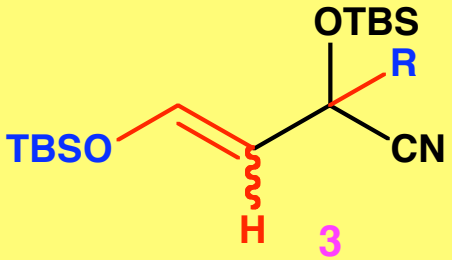


1A



1B

RX (1.2 eq)
Base (1.1 eq)
solvent/HMPA
-80 °C, 5 min



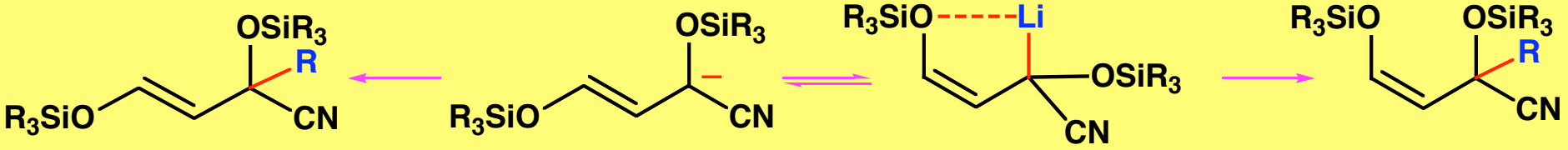
3

solvent	SM	yield (%)	E/Z
hexane	1A	93	1.5
	1B	78	6.0
ether	1A	84	1.9
	1B	77	28.0
toluene	1A	86	1.0
	1B	83	24.0
THF	1A	85	28.0
	1B	84	52.0

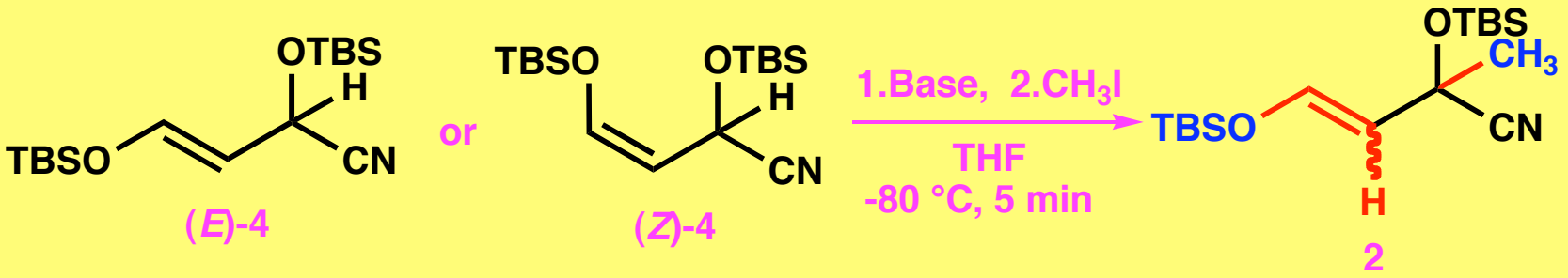
Base: NHMDS, RX: BnBr

base	SM	HMPA	yield (%)	E/Z	SM (%)
LDA	1A	(–)	82	2.5	-
	1A	(+)	61	28.0	26
	1B	(–)	84	22.0	-
	1B	(+)	85	*E*	8
KHMDS	1A	(–)	84	0.9	-
	1A	(+)	92	15.0	-
	1B	(–)	87	9.7	-
	1B	(+)	84	*E*	-

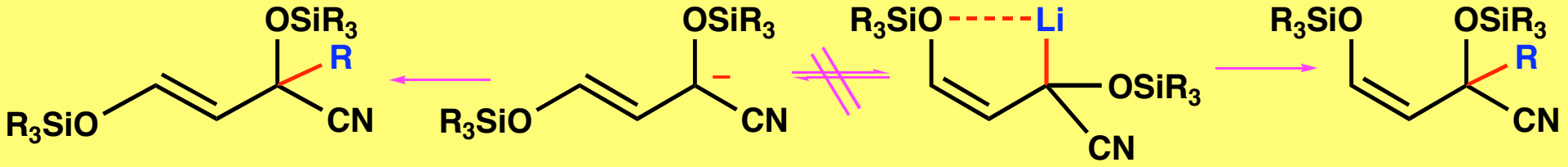
solvent: THF, RX: CH_3I



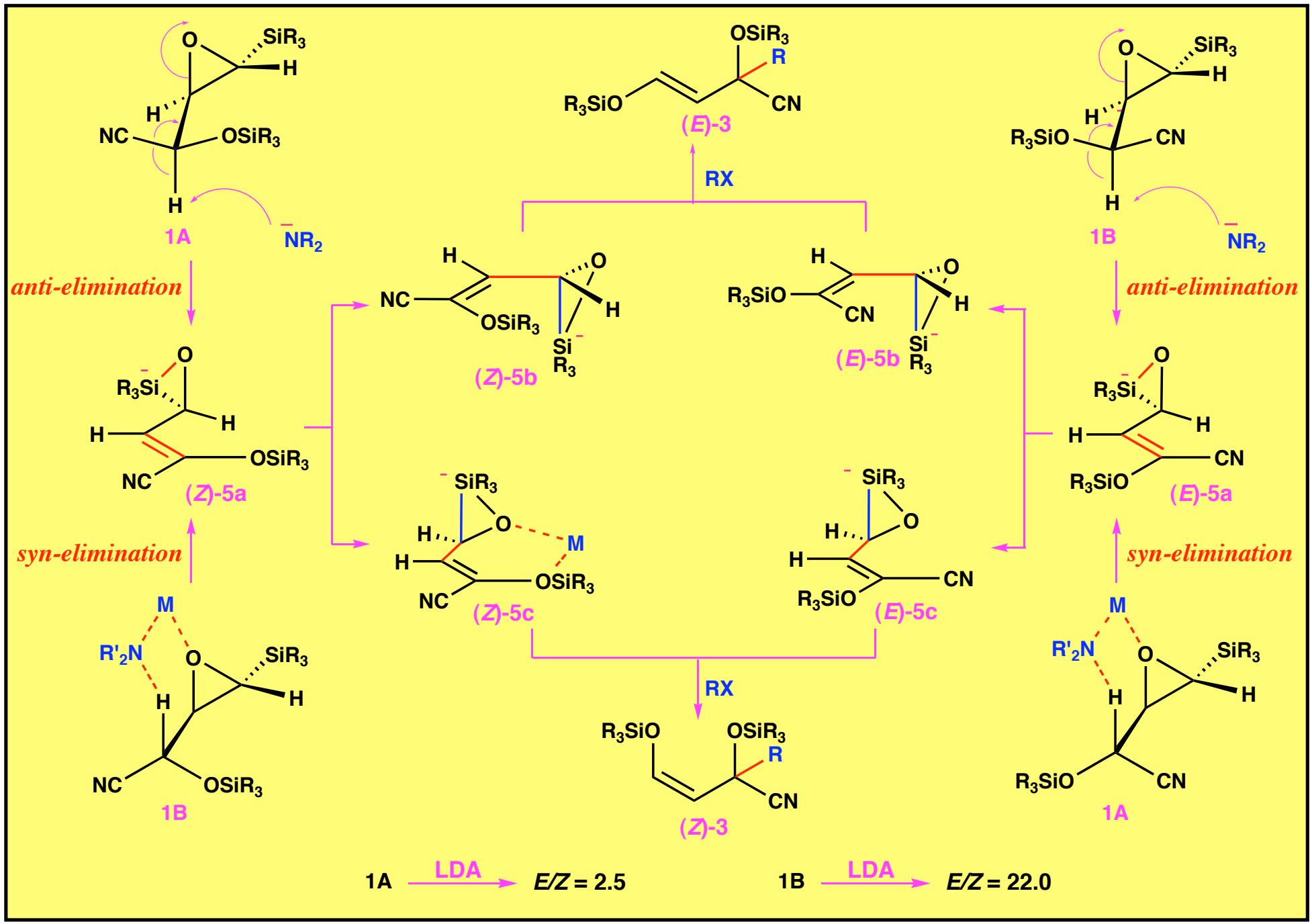
Alkylation of *O*-Silyl Cyanohydrins of β-Siloxyacrolein



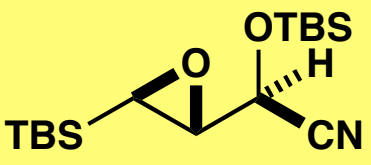
		2		SM
Base	SM	yield (%)	*E/Z*	yield (%)
LDA	*E*	76	58.0	-
LHMDS	*E*	46	*E*	47
NHMDS	*E*	81	*E*	6
KHMDS	*E*	75	*E*	8
LDA	*Z*	41	0.01	18
LHMDS	*Z*	0	-	87
NHMDS	*Z*	30	0.02	59
KHMDS	*Z*	76	0.01	8



A Proposed Reaction Pathway

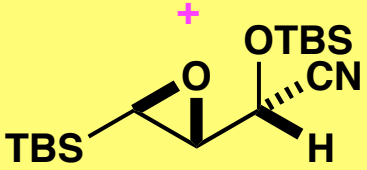


Base-Promoted Ring-Opening of Cyanohydrins of β-Silyl α,β-Epoxyaldehyde (1)



1A

+

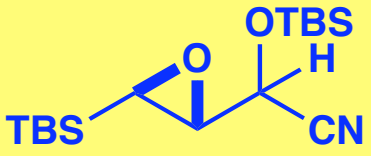


1B

1A:1B = 1.00:1.04

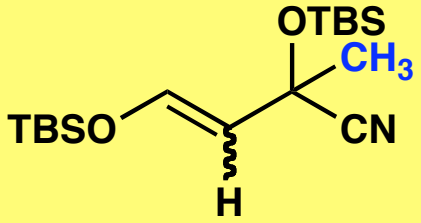
CH_3I (0.5 eq)
LDA (0.5 eq)

THF
-80 °C, 5 min



1

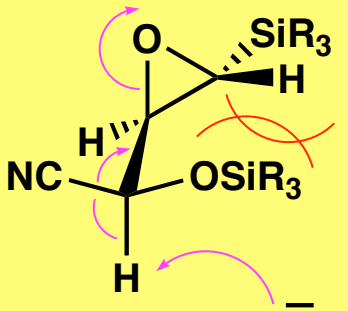
+



2

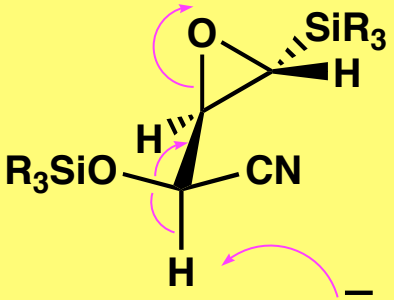
	yield (%)		yield (%)	
HMPA	1	A:B	2	*E/Z*
(–)	40	1.00:0.70	35	6.6
(+)	67	1.00:0.76	26	25.0

***anti*-elimination**



1A

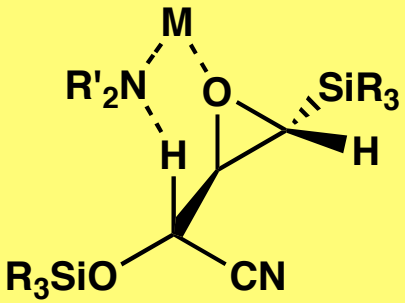
$\overline{N}R_2$



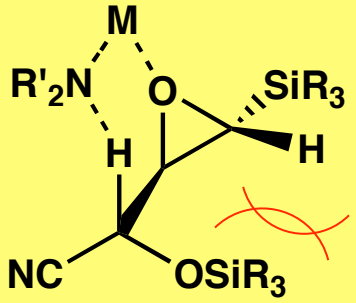
1B

$\overline{N}R_2$

***syn*-elimination**



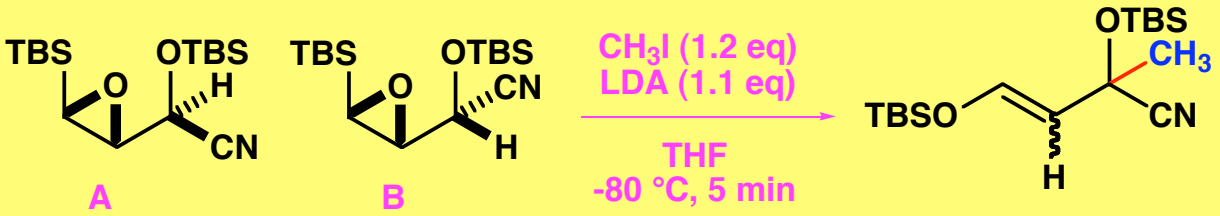
1A



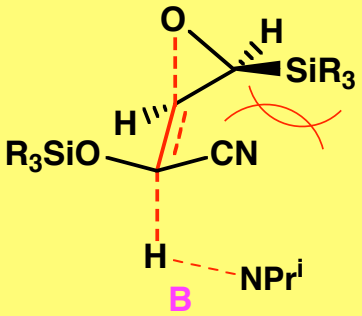
1B

A-value: OTMS = 0.7
CN = 0.2

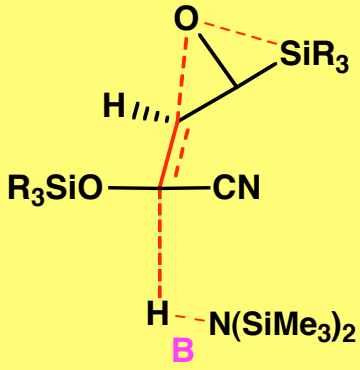
Base-Promoted Ring-Opening of Cyanohydrins of β-Silyl α,β-Epoxyaldehyde (2)



base	diastereomer	yield (%)	E/Z
LDA	A	3	0.9
(in hexane/THF)	B	22	6.3
$NaN(SiMe_3)_2$	A	7	6.5
(1.0M in THF)	B	87	5.0
$KN(SiMe_3)_2$	A	45	1.1
(0.5M in toluene)	B	86	3.2

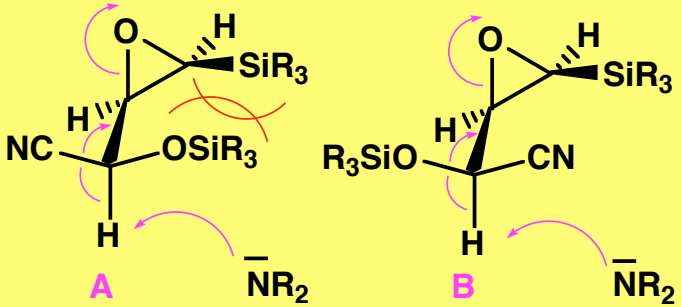


reactant-like transition state

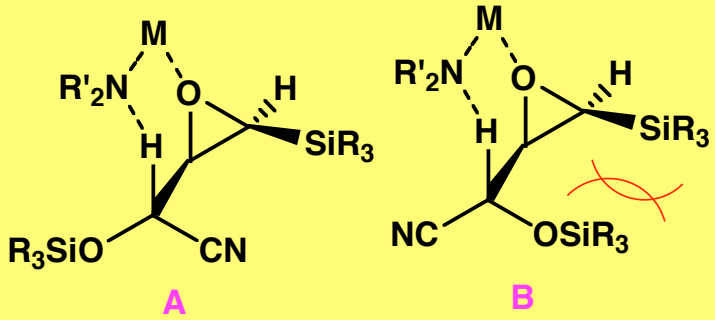


less reactant-like transition state

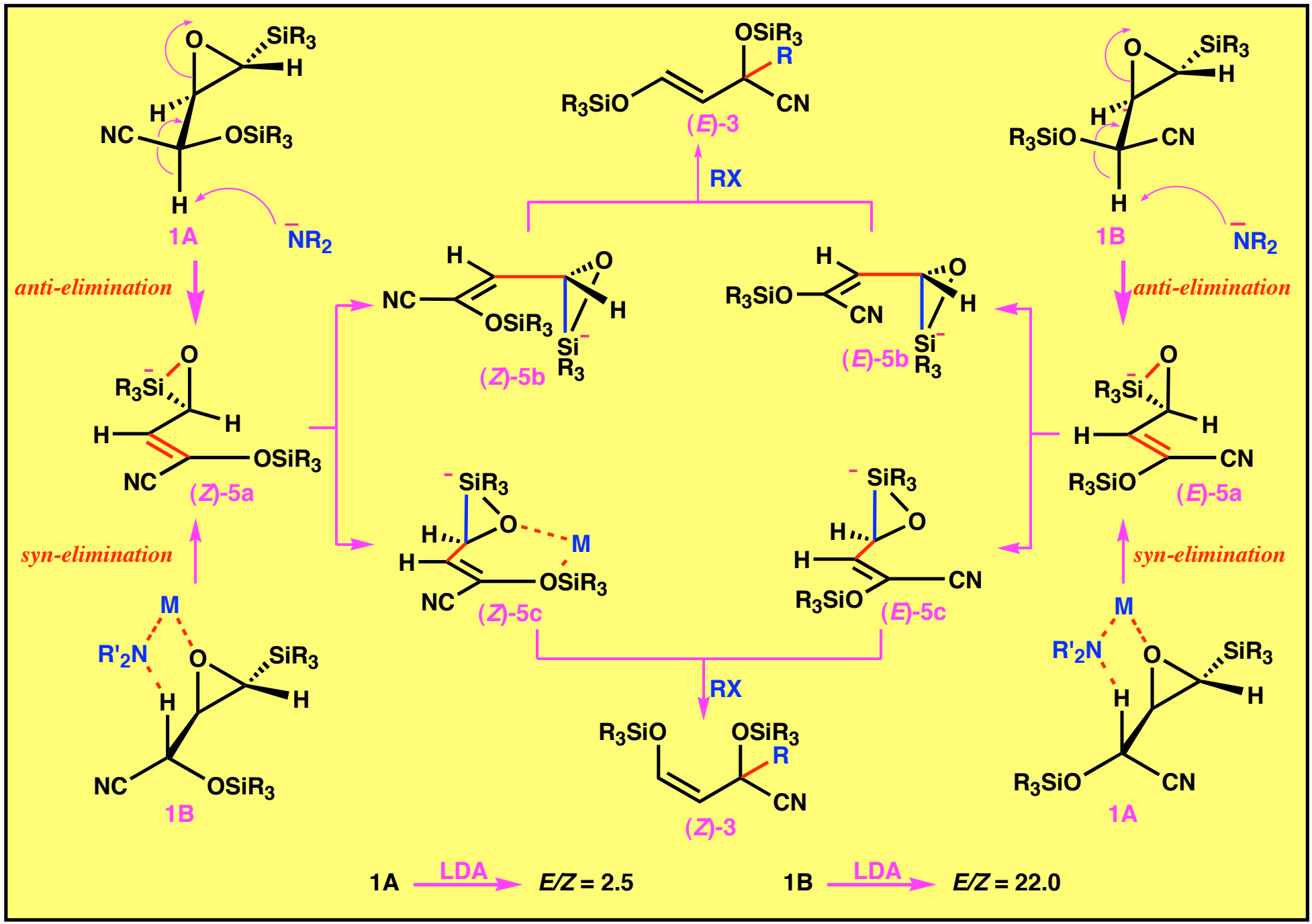
***anti*-elimination**



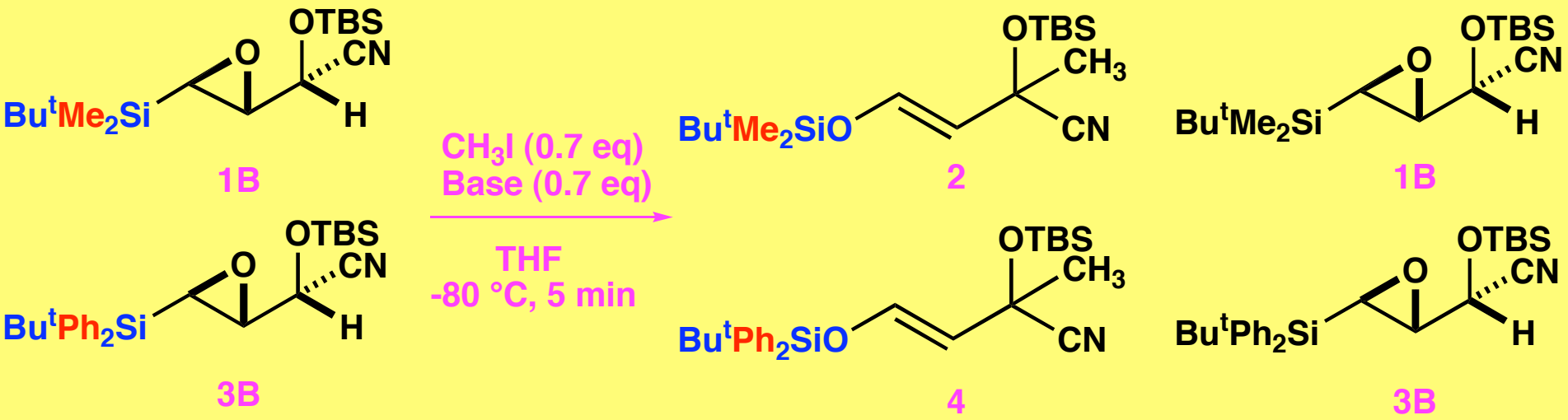
***syn*-elimination**



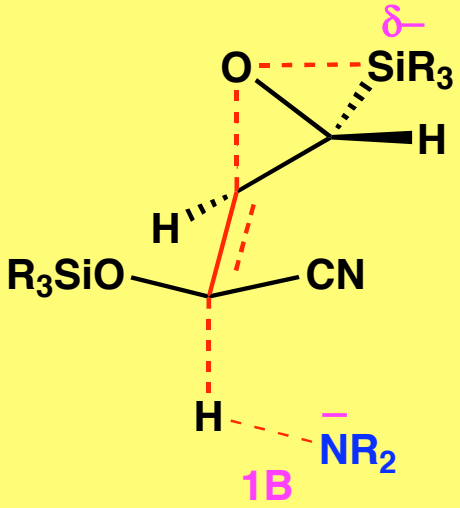
A Proposed Reaction Pathway

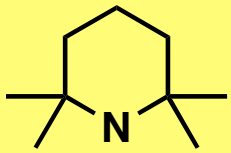


Substituent Effect of the Silyl Group on Rates of Ring Opening



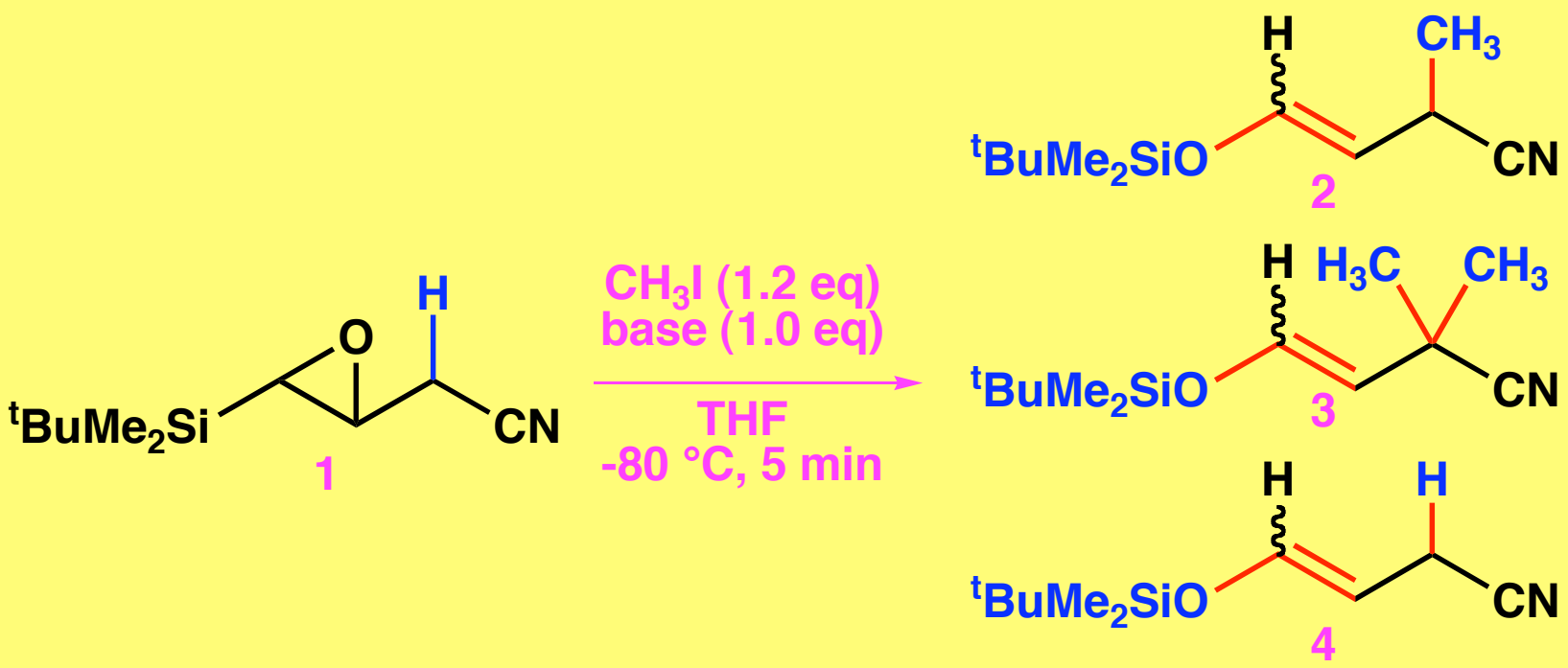
	yield (%)			yield (%)	
base	2	4	4 (TBDPS)/2 (TBS)	1B	3B
LDA	21.5	6.7	0.31	18.1	39.8
$LiNEt_2$	18.8	6.0	0.32	24.4	39.1
LTMP	22.1	14.8	0.67	19.4	29.8



LTMP = 

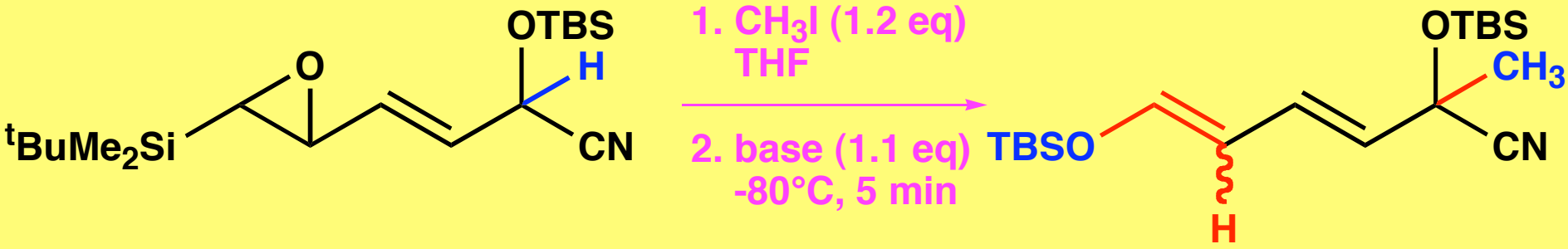
TBS = Bu^tMe_2Si
TBDPS = Bu^tPh_2Si

Reactions of γ-Silyl-β,γ-epoxybutyronitirile with Bases in the Presence of Methyl Iodide



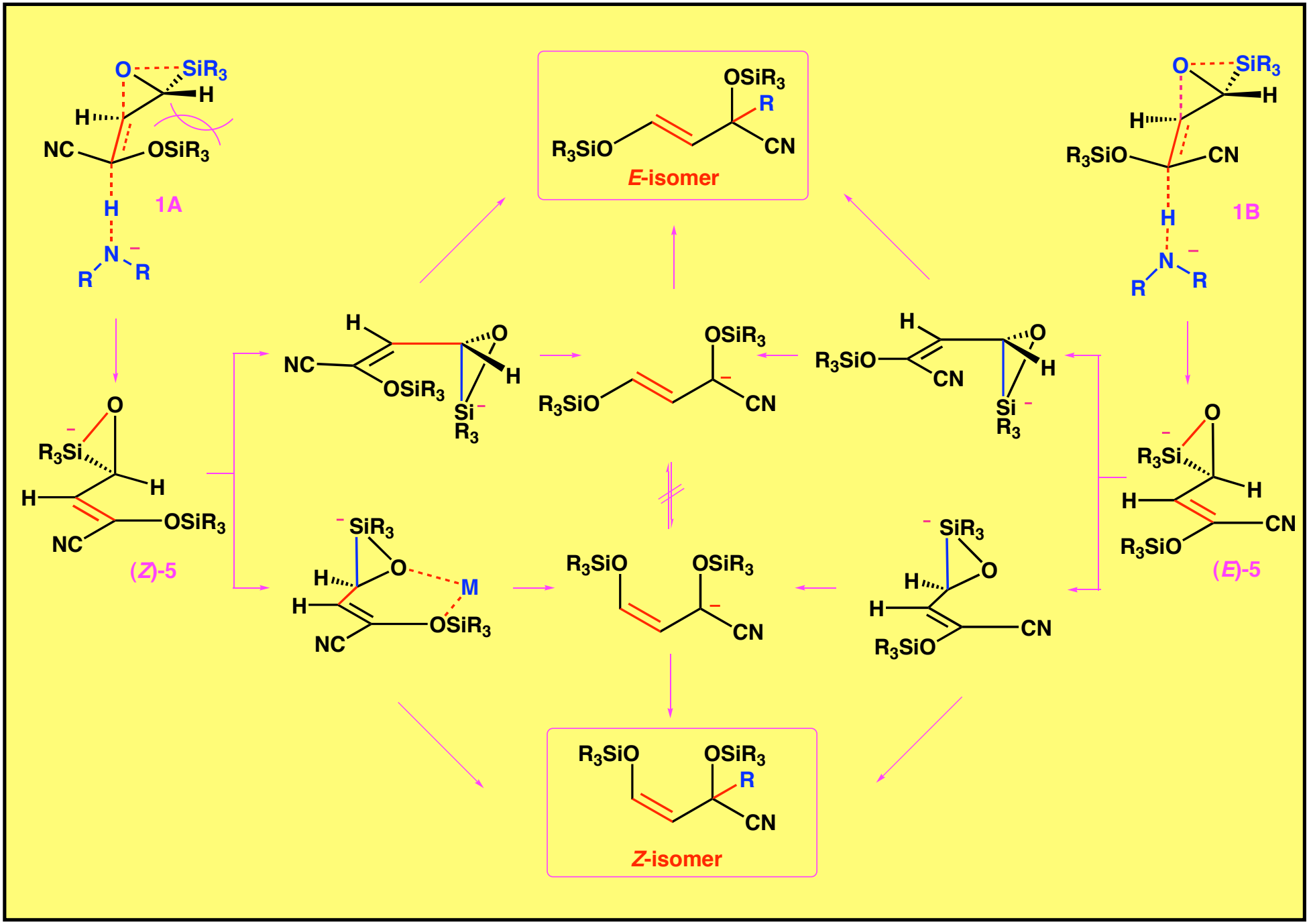
	yield (%)			
base	2	3	4	total
LDA (THF-hexane)	33 (2.1)	28 (5.2)	1 (*Z*)	62 (2.8)
$LiN(SiMe_3)_2$ (THF)	74 (2.5)	4 (*E*)	3 (0.4)	81 (2.5)
$NaN(SiMe_3)_2$ (THF)	26 (0.7)	32 (6.0)	9 (0.2)	67 (1.5)
$KN(SiMe_3)_2$ (toluene)	18 (0.1)	35 (0.5)	14 (0.1)	67 (0.3)

Reaction of Cyanohydrins of δ-Silyl-γ,δ-epoxy-α,β-unsaturated Aldehyde with Base in the Presence of Methyl Iodide

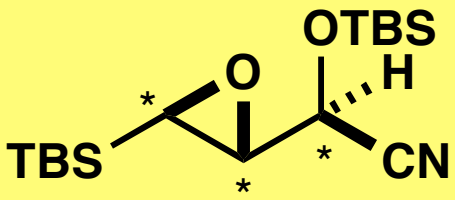


base	yield (%)	*E/Z*
LDA (in hexane/THF)	87	9.8
$LiN(SiMe_3)_2$ (in THF)	91	16.5
$NaN(SiMe_3)_2$ (in THF)	97	16.5
$KN(SiMe_3)_2$ (in toluene)	92	7.2

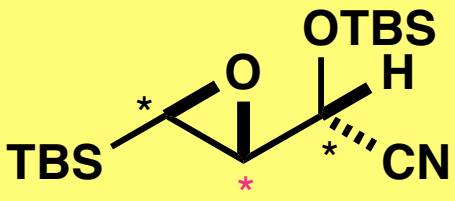
A Proposed Reaction Pathway



Reactions of Enantiomerically Pure *O*-Silyl Cyanohydrins of β-Silyl-α,β-Epoxyaldehyde with LDA in the Presense of Benzyl Bromide



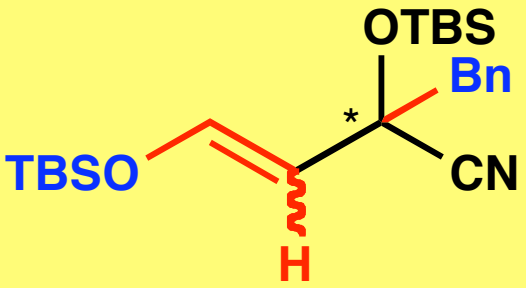
1A
93%ee



1B
93%ee

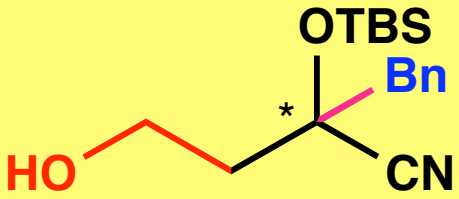
$PhCH_2Br$
base

additive, solvent
-80 °C , 5 min



1. AcOH, THF, H_2O
60 °C , 24 h

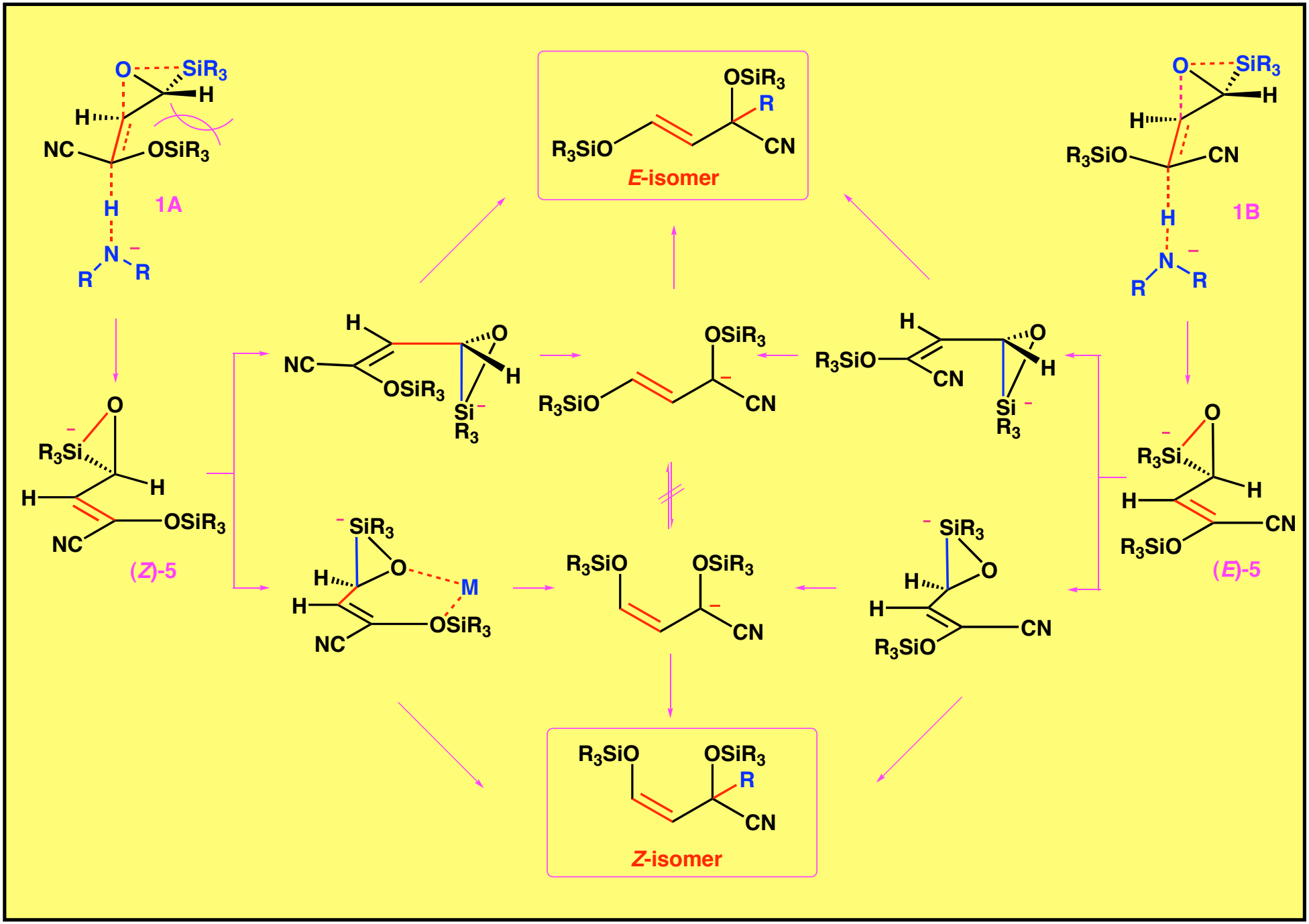
2. $NaBH_4$, EtOH



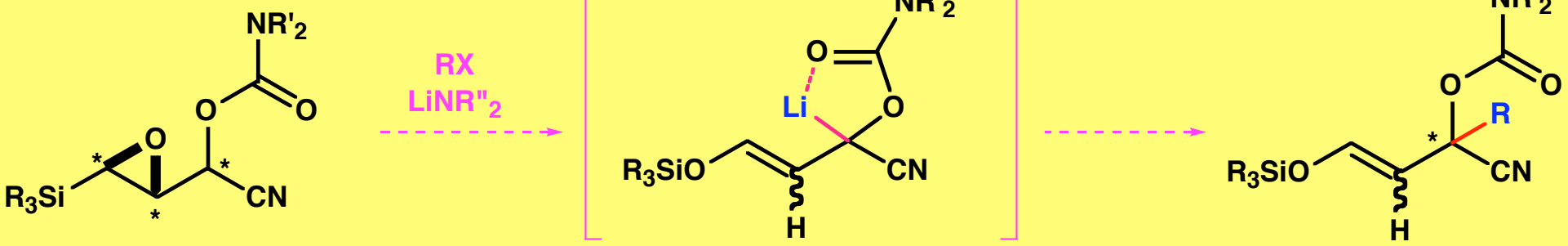
< 1% ee

base
LDA, LiHMDS, NaHMDS, KHMDS
solvent
THF, Et_2O, toluene, hexane
additive
TMEDA

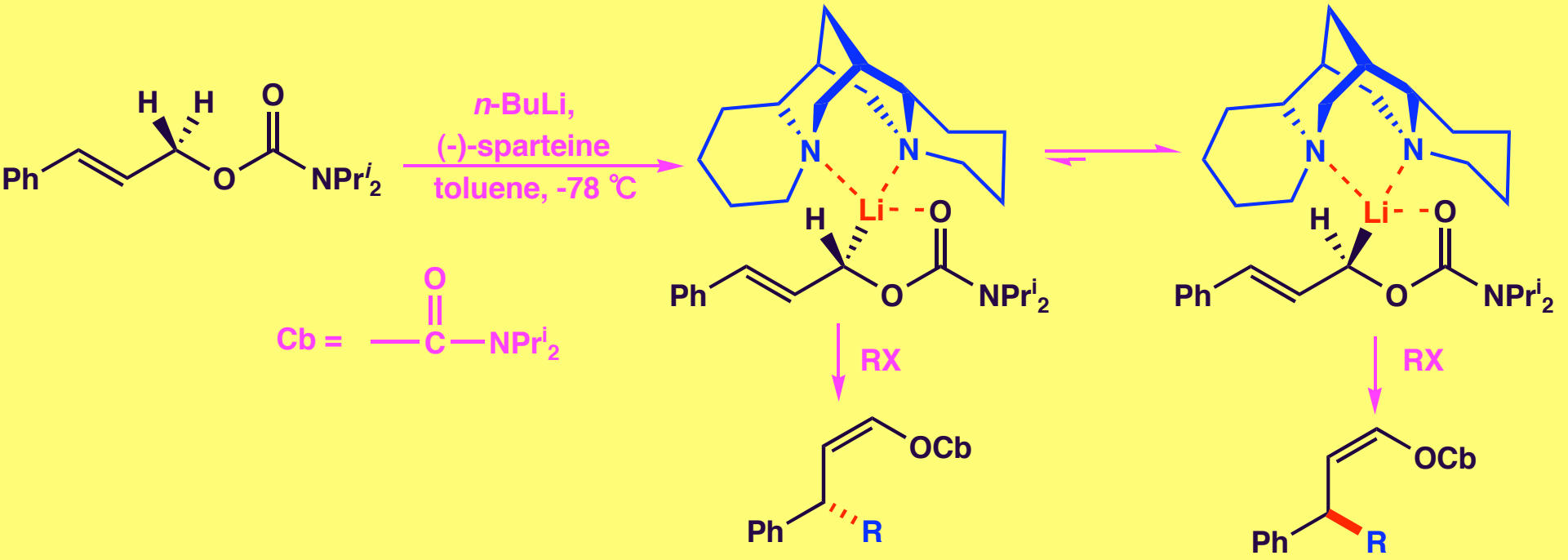
A Proposed Reaction Pathway



Reactions of Enantiomerically Pure *O*-Carbamoyl Cyanohydrins of β-Silyl-α,β-Epoxyaldehyde with LDA in the Presense of Alkylating Reagent

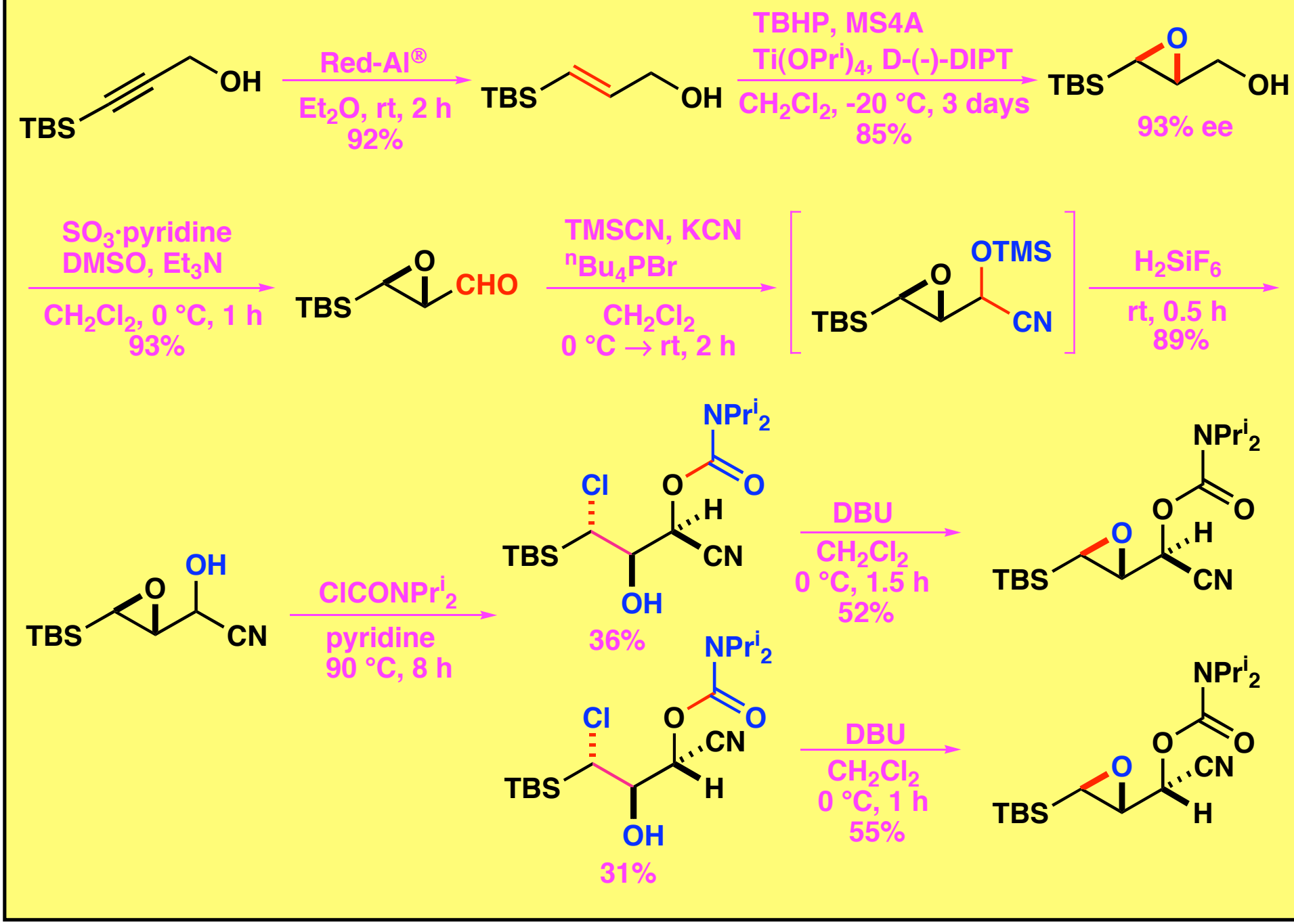


Chiral Homoenolate Equivalent

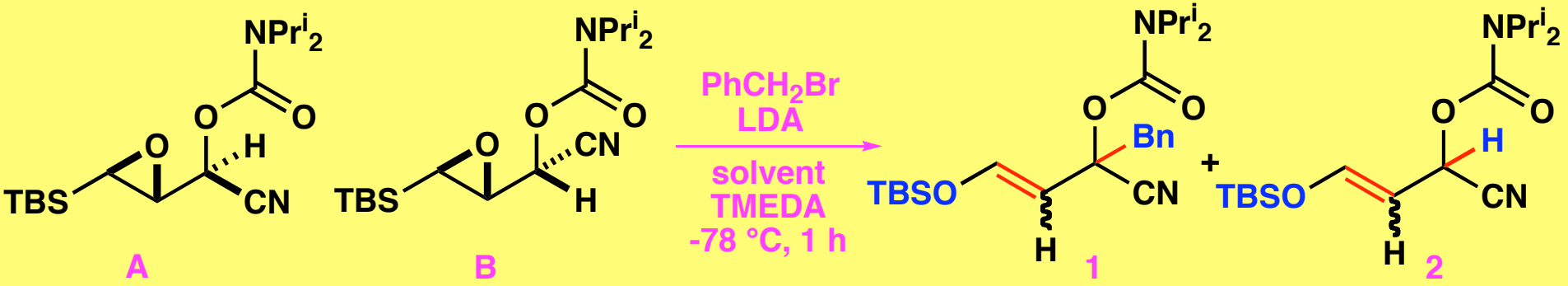


Hoppe, D. ; Hense, T. *Angew. Chem. Int. Ed. Engl.*, **1997**, 36, 2282-2316.

Preparation of Enantiomerically Pure *O*-Carbamoyl Cyanohydrins of β-Silyl-α,β-Epoxyaldehydes



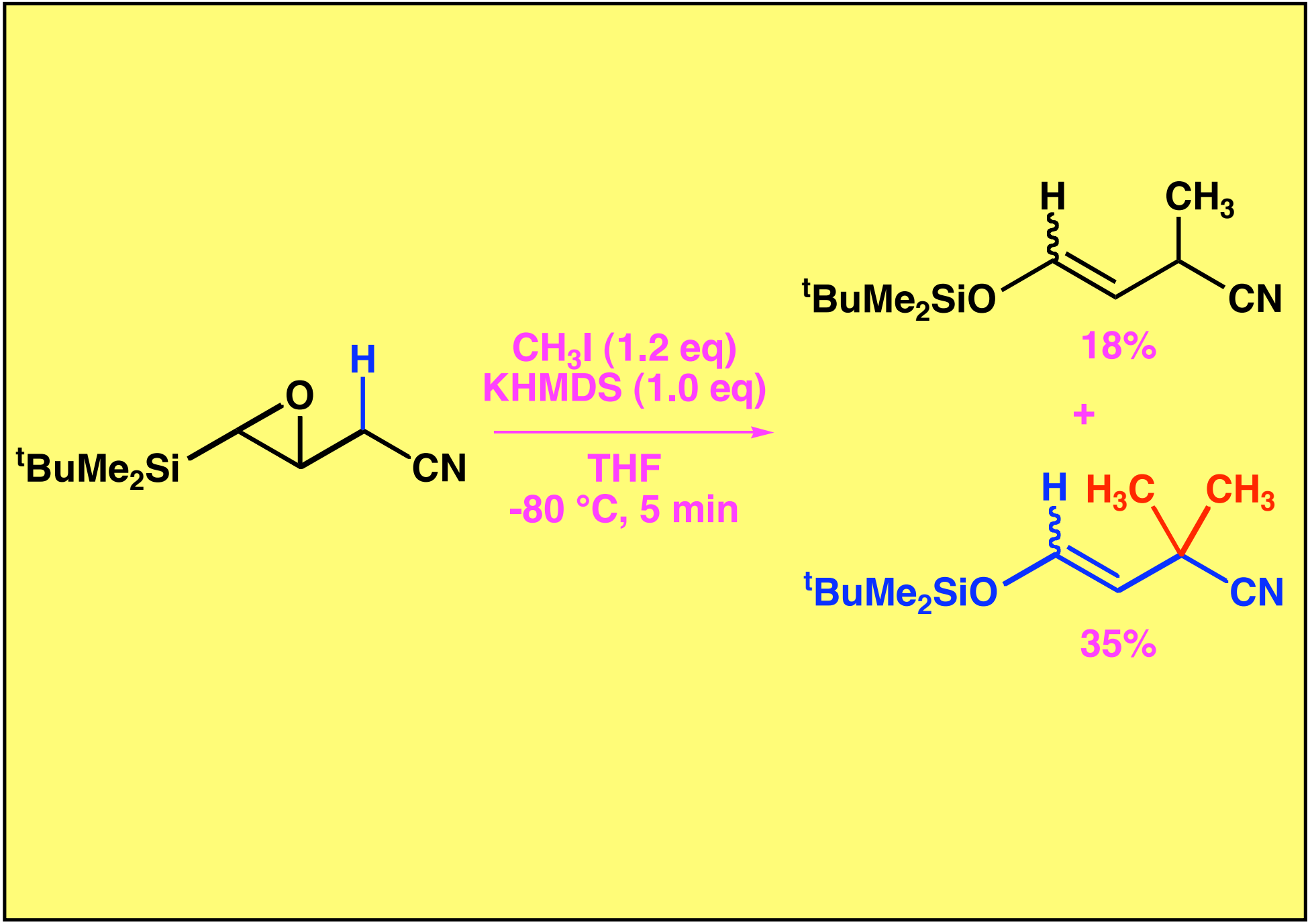
Reactions of Enantiomerically Pure *O*-Silyl Cyanohydrins of β-Silyl-α,β-Epoxyaldehyde with LDA in the Presense of Benzyl Bromide



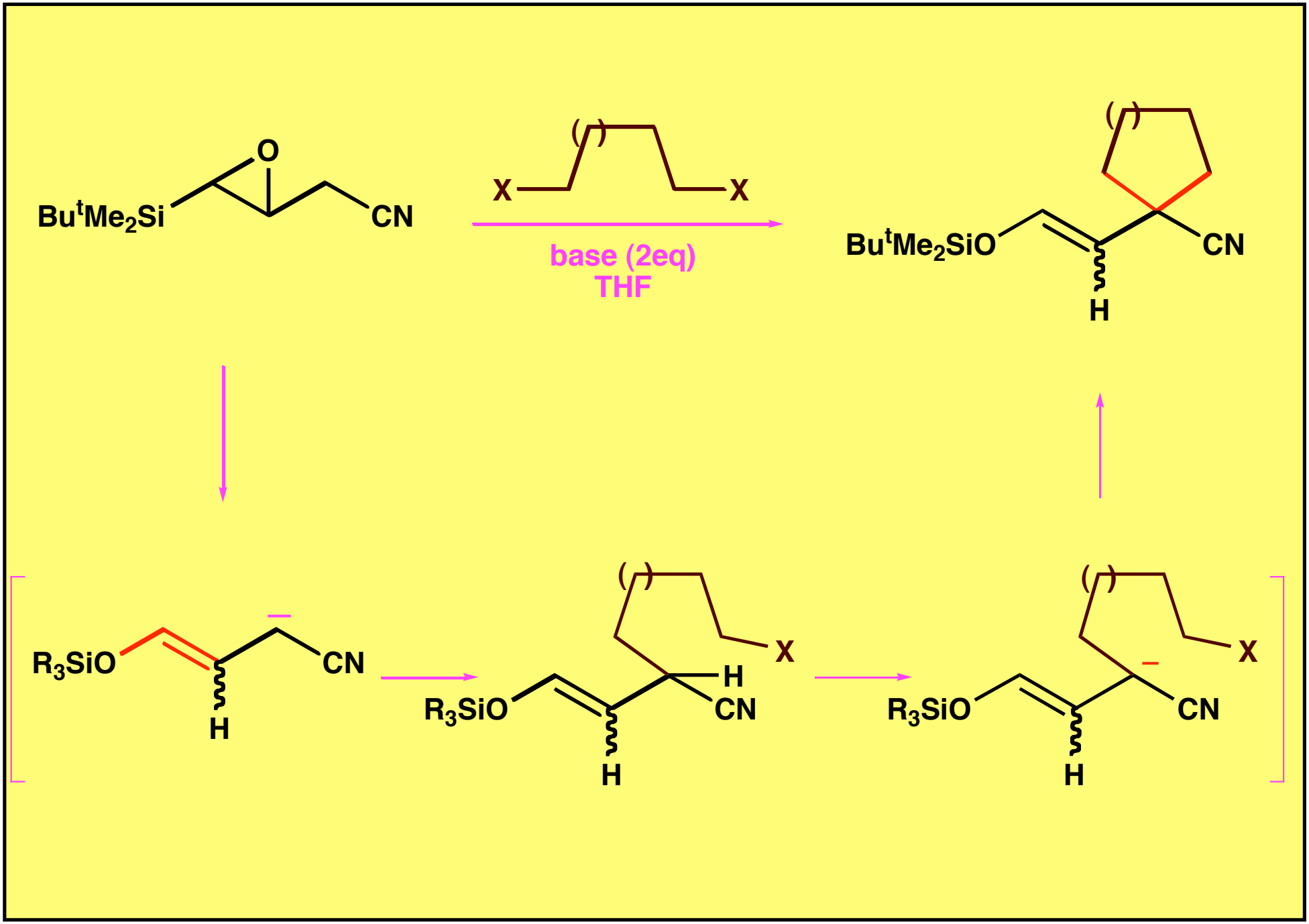
solvent	SM	TMEDA	(*E*)-1 yield (%)	(*Z*)-1 yield (%)	(*Z*)-1 ee (%)	(*E*)-2 yield (%)	(*Z*)-2 yield (%)	total yield (%)
THF	A	(–)	30	36	0	2	7	75
	B	(–)	52	-	-	7	-	59
Et_2O	A	(–)	6	44	30.0	1	11	62
	B	(–)	23	-	-	35	-	58
	A	(+)	8	25	0	3	18	54
	B	(+)	39	-	-	26	-	65
toluene	A	(–)	11	21	37.3	2	11	46
	B	(–)	26	-	-	33	-	59
	A	(+)	25	29	0	2	9	65
	B	(+)	49	9	2.4	10	-	68

(*E*)-**1**, (*E*)-**2**, and (*Z*)-**2** were inseparable.
Enantiomeric purity was determined by chiral HPLC using a CHIRALPAK AD®.

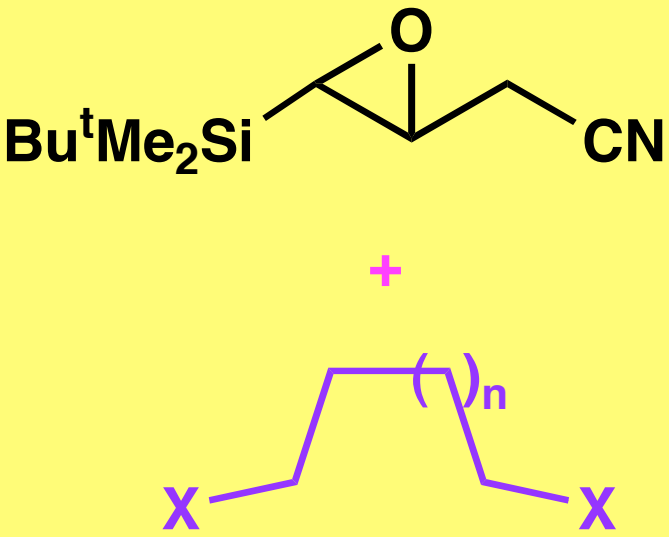
Reactions of γ-Silyl-β,γ-epoxybutyronitirile with Bases in the Presence of Methyl Iodide

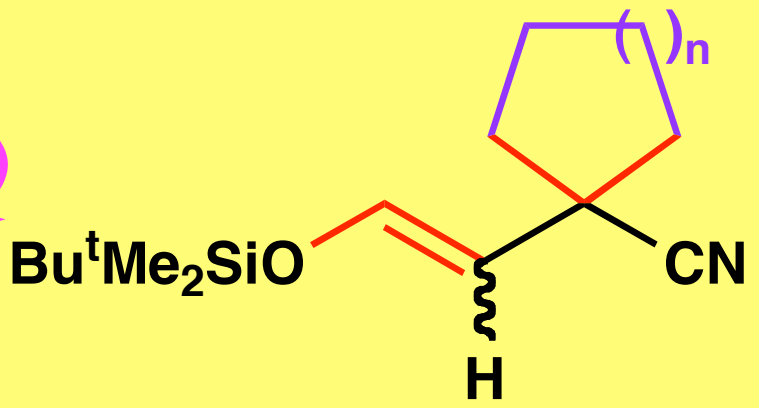


Application of the Tandem Sequence to the Synthesis of Carbocycles (1)



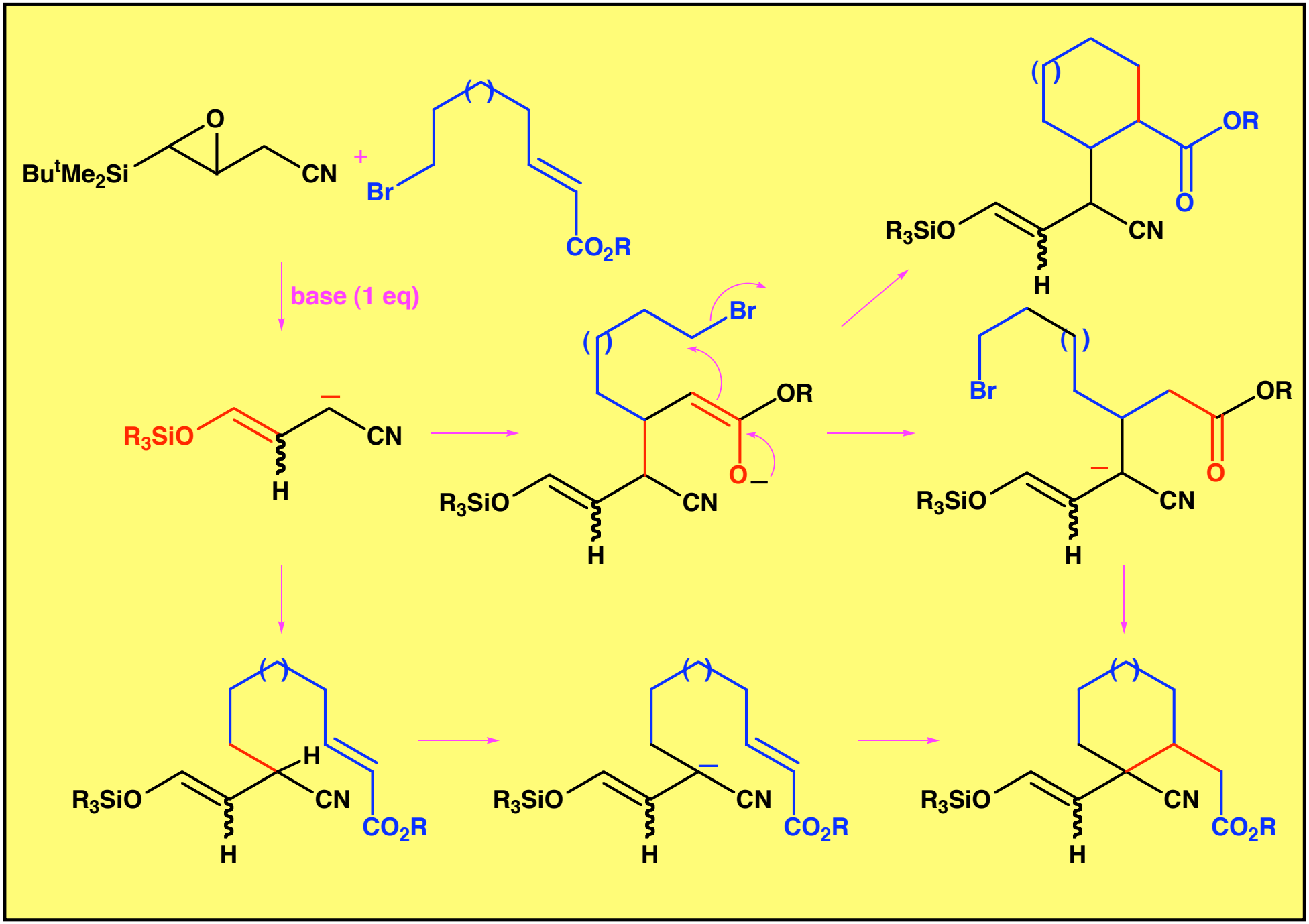
Formation of Four- to Seven-Membered Carbocycles Using the Tandem Sequence



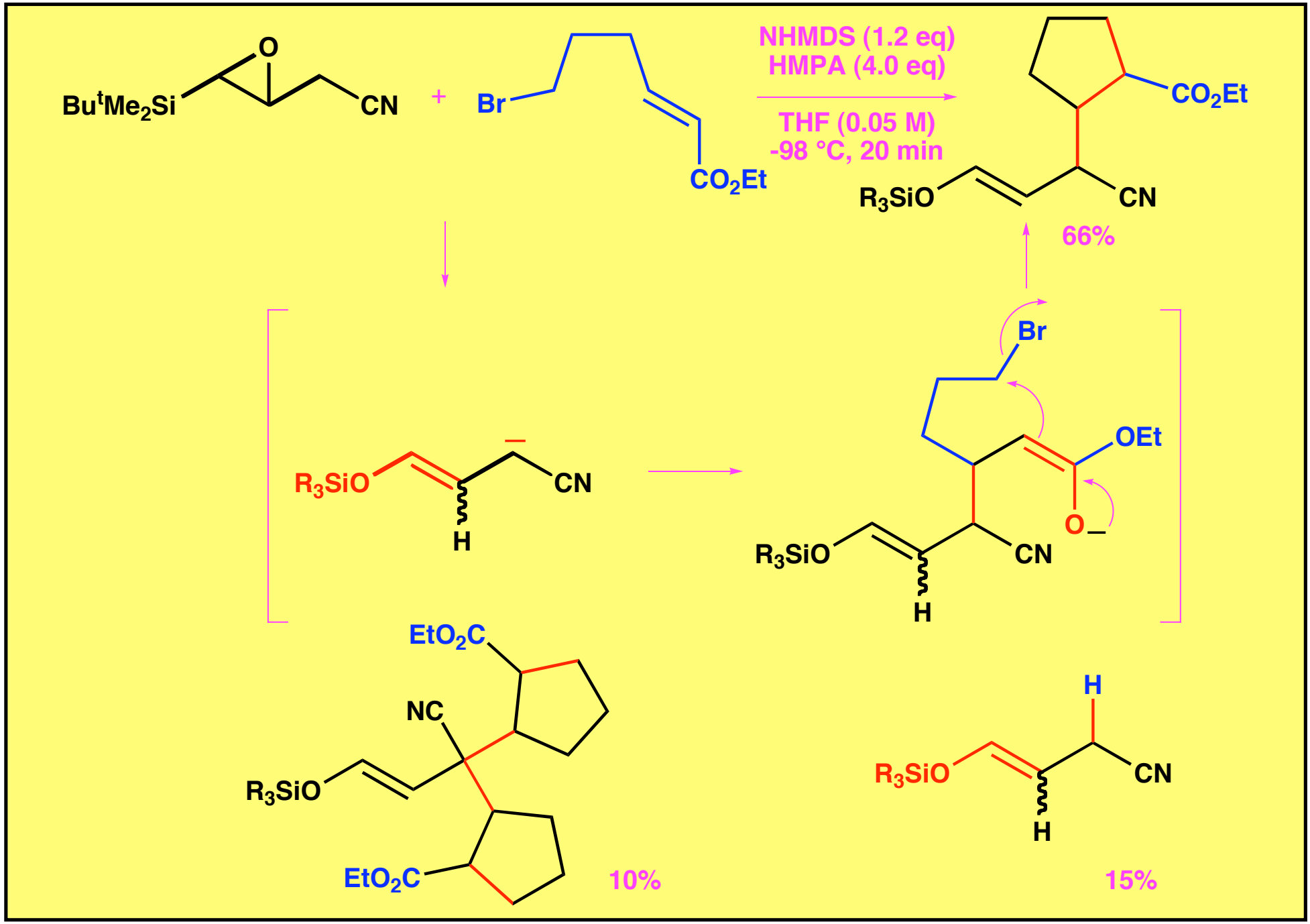


n	yield(%)
4	44
5	83
6	77
7	53

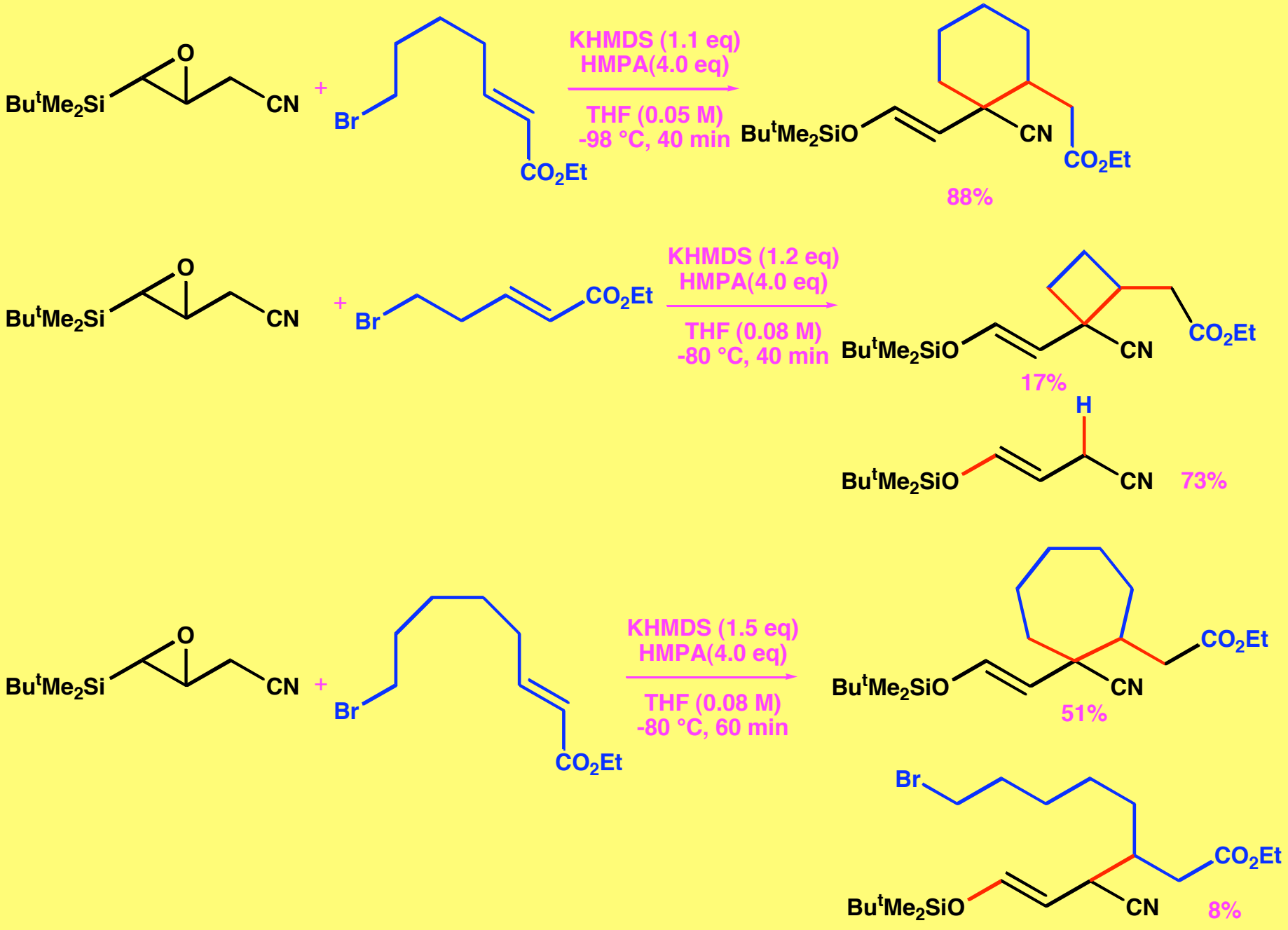
Application of the Tandem Sequence to the Synthesis of Carbocycles (2)



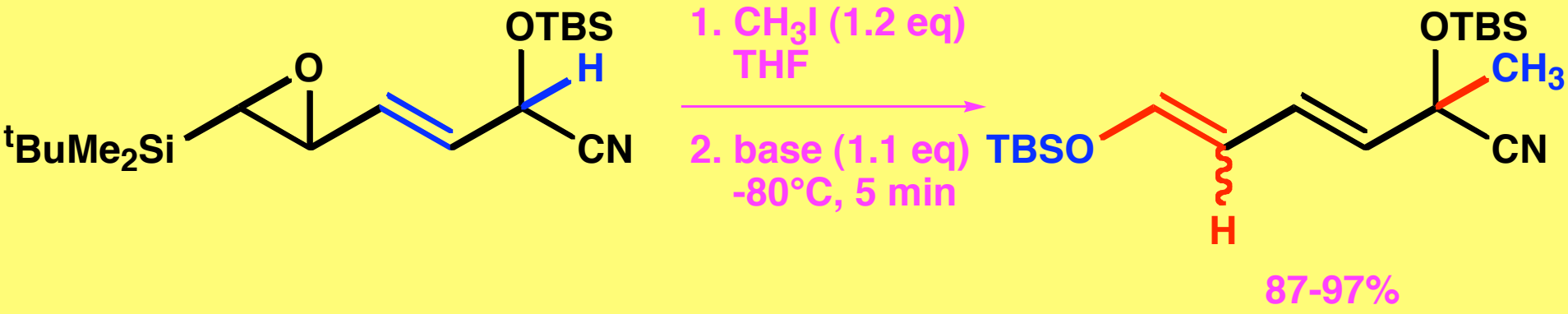
Formation of Five-Membered Carbocycles via the Tandem Sequence



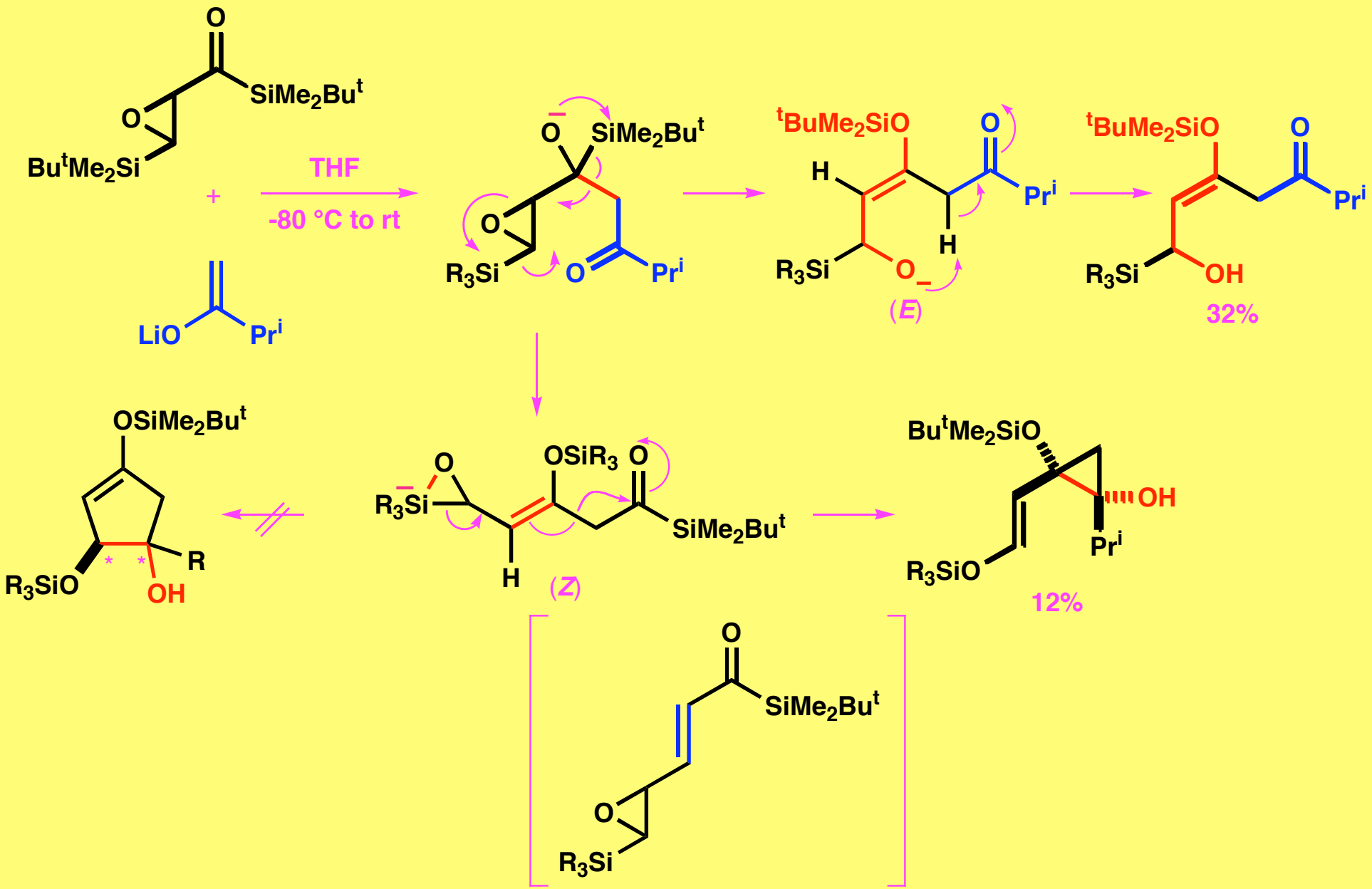
Formation of Four-, Six- and Seven-Membered Carbocycles via the Tandem Sequence



Reaction of Cyanohydrins of δ-Silyl-γ,δ-epoxy-α,β-unsaturated Aldehyde with Base in the Presence of Methyl Iodide

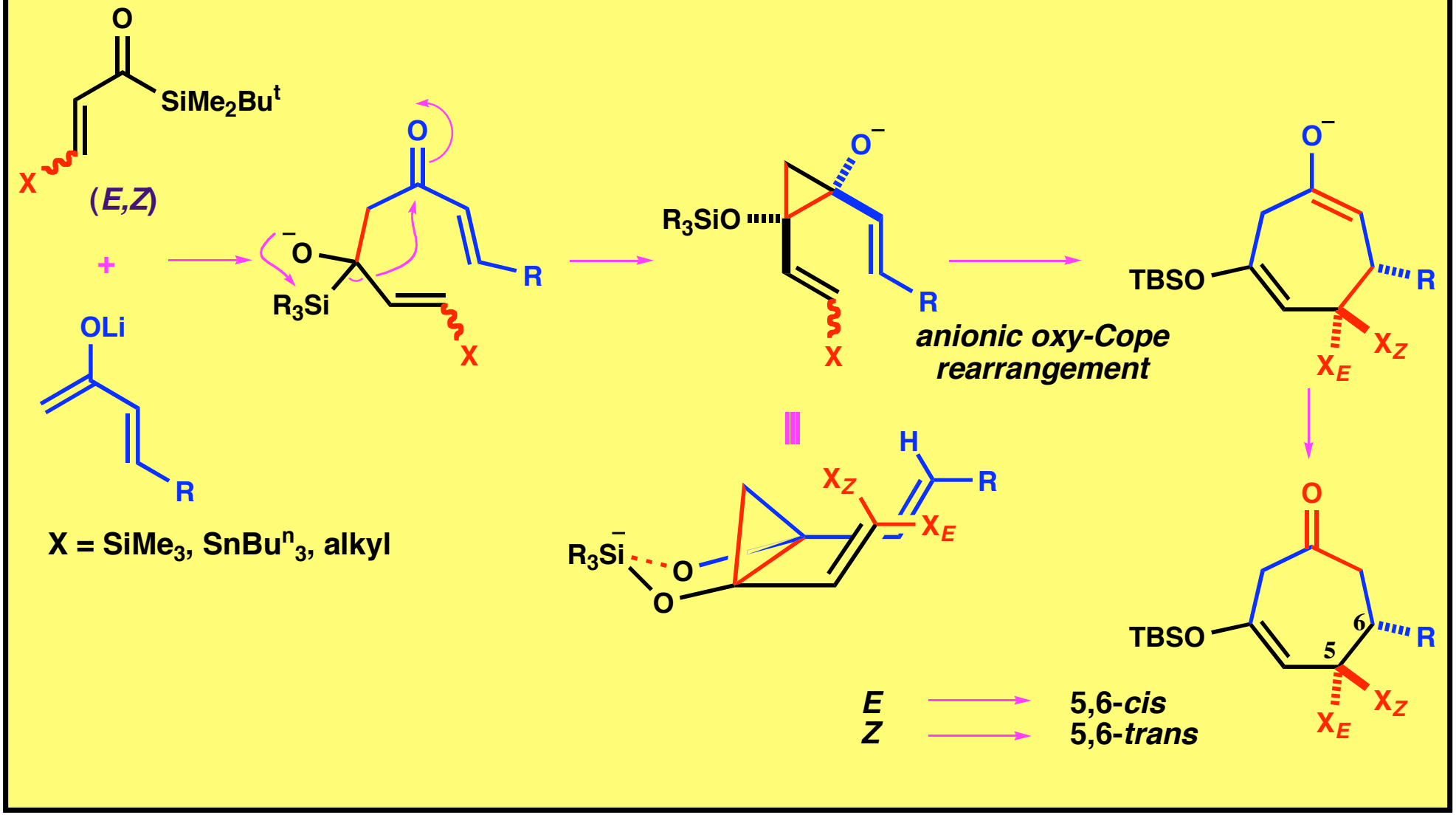


Attempted Double Brook Rearrangement-Mediated [3 + 2] Annulation



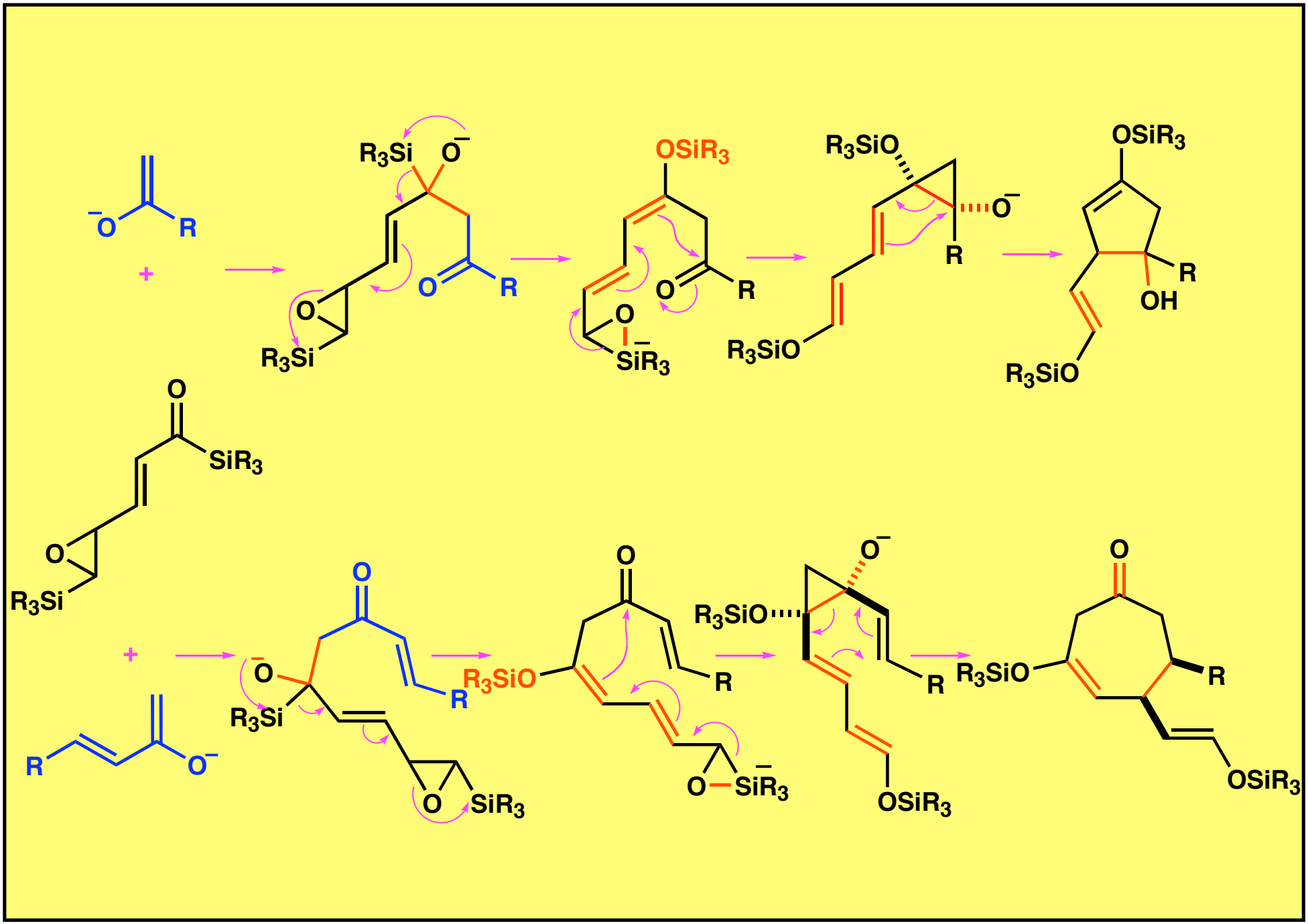
Kei Takeda, Yuji Ohnishi unpublished result.

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

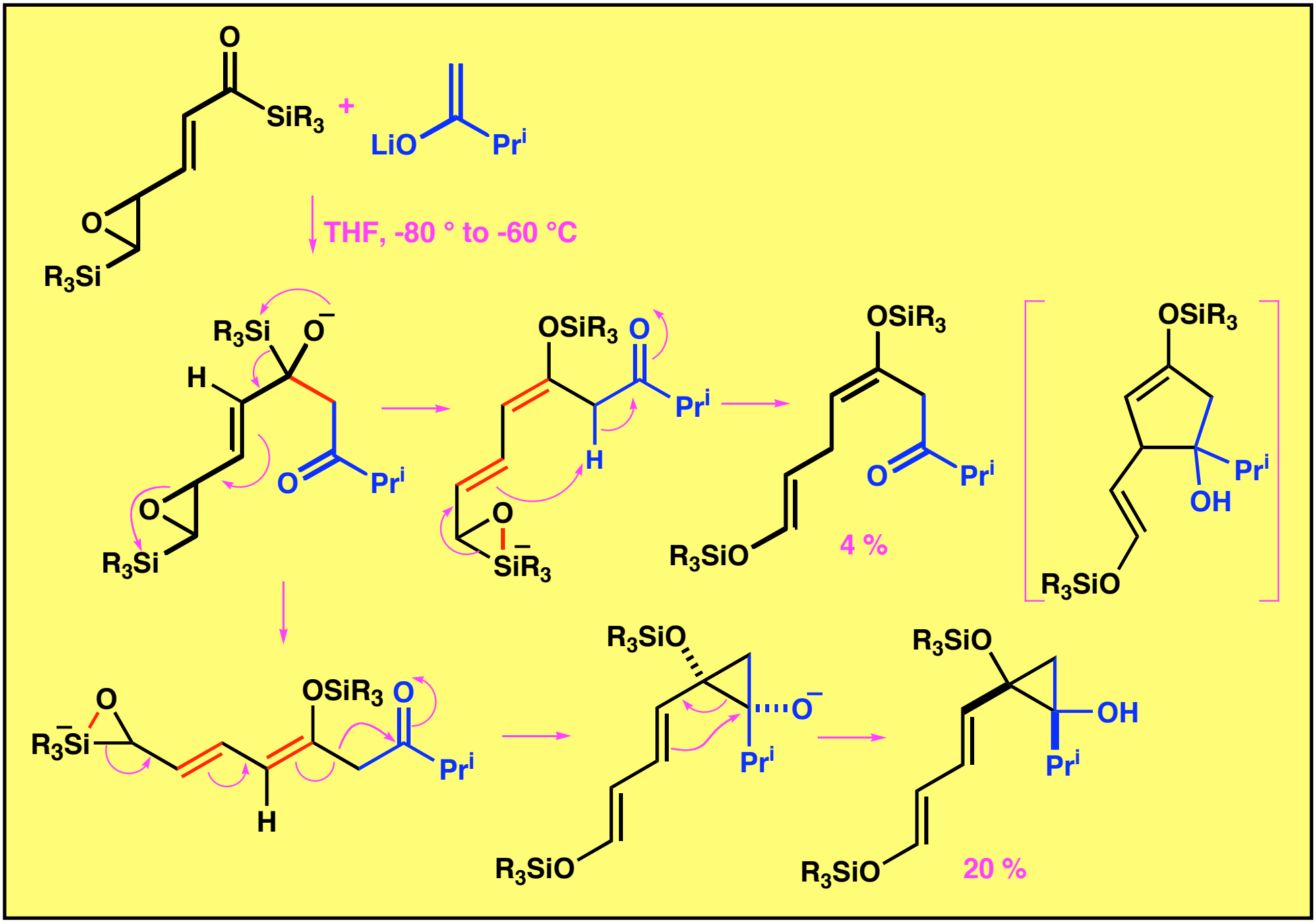


Takeda, K.; Takeda, M.; Nakajima, A.; Yoshii, E. *J. Am. Chem. Soc.* **1995**, *117*, 6400-6401.
Takeda, K.; Nakajima, A.; Takeda, M.; Okamoto, Y.; Sato, T.; Yoshii, E.; Koizumi, T. *J. Am. Chem. Soc.* **1998**, *120*, 4947-4959.
Takeda, K.; Nakajima, A.; Takeda, M.; Yoshii, E. *Org. Synth.* **1999**,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

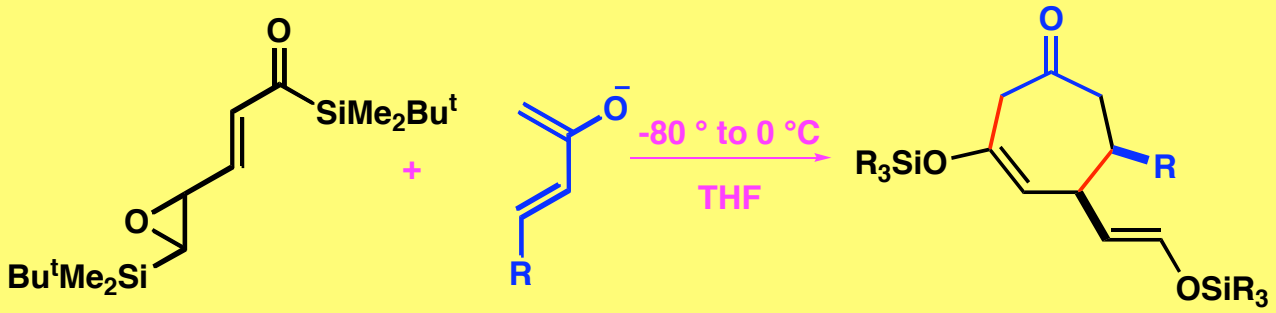
[3 +2] and [3 + 4] Annulations Using δ-silyl-γ,δ-epoxy-α,β-unsaturated Acylsilanes

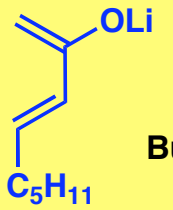
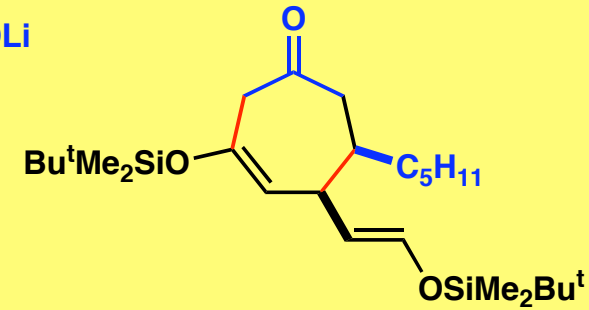
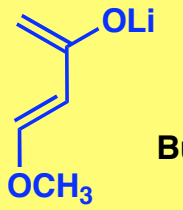
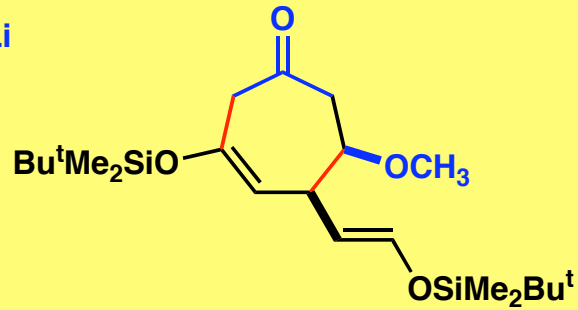
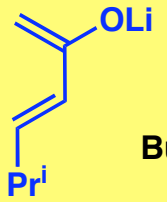
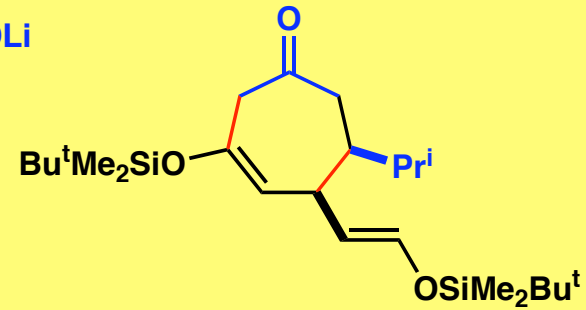
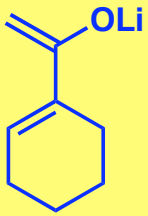
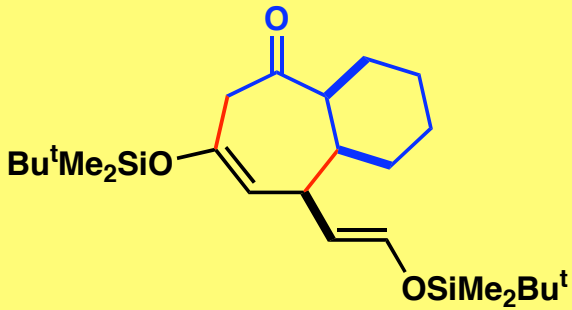


[3 +2] Annulations Using δ-silyl-γ,δ-epoxy-α,β-unsaturated Acylsilanes

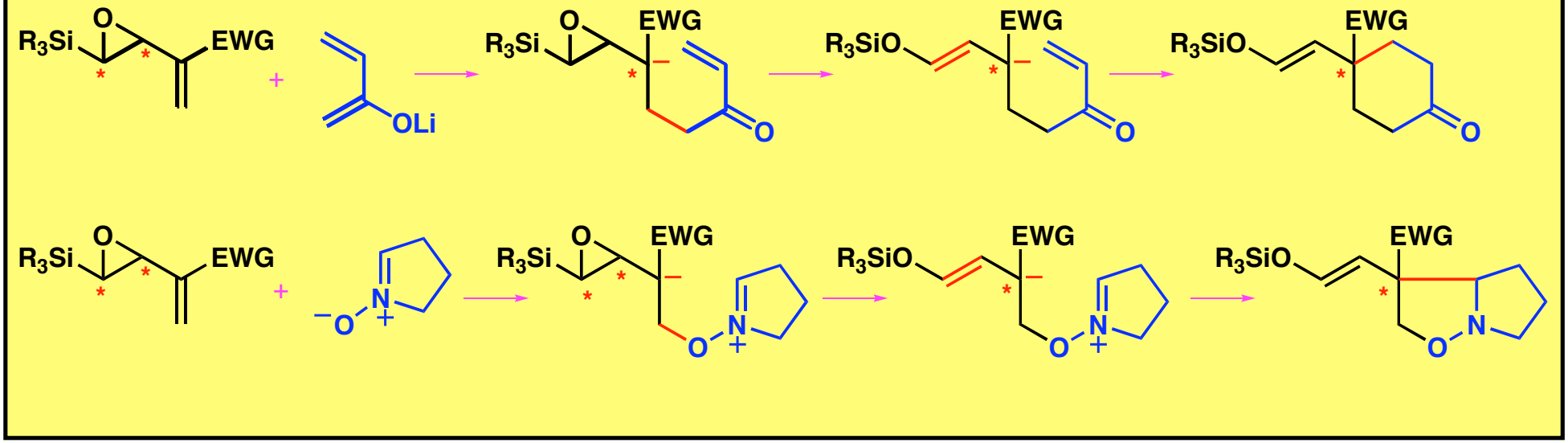


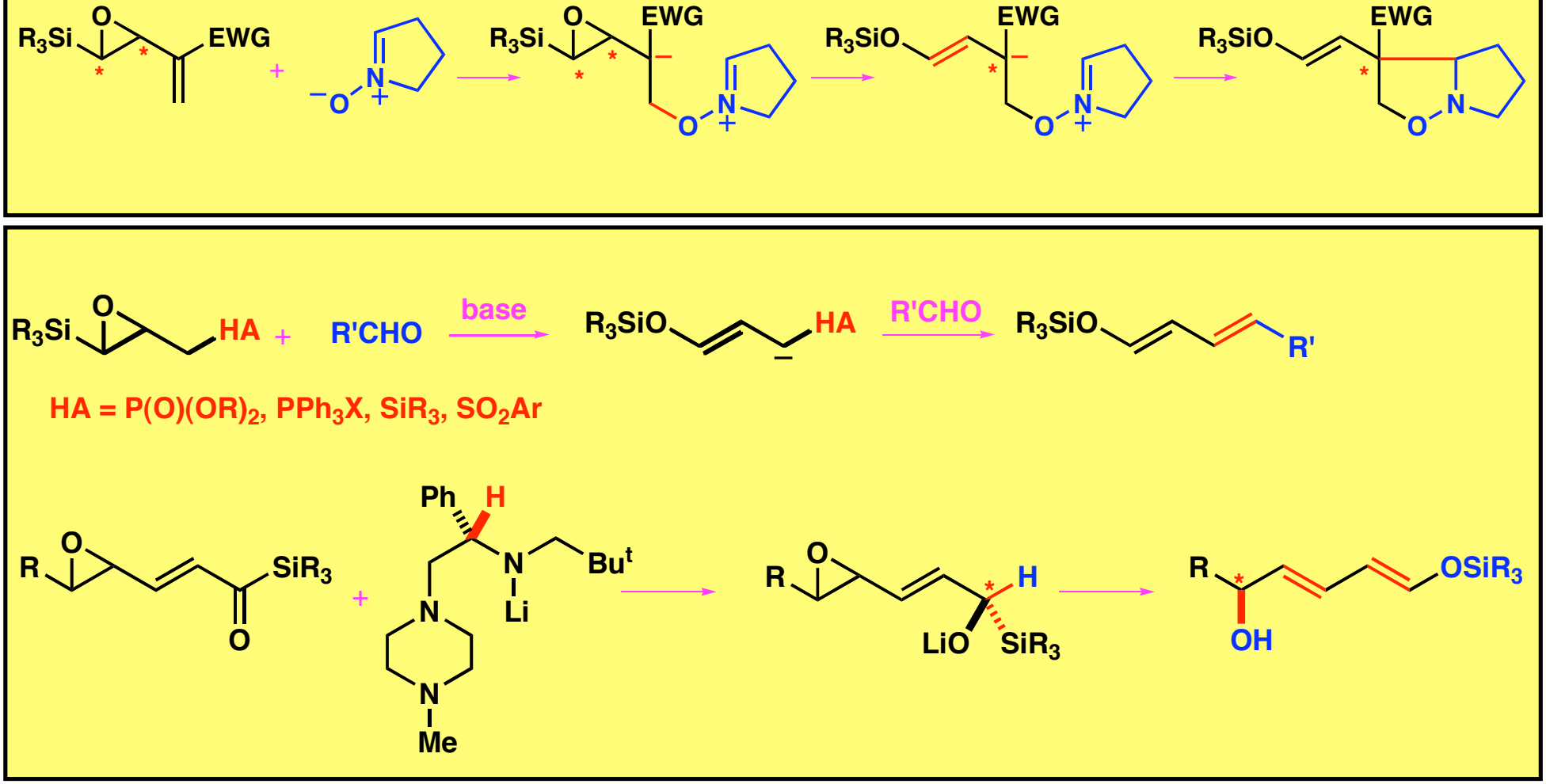
[3 + 4] Annulations Using δ-Silyl-γ,δ-epoxy-α,β-unsaturated Acylsilanes



ketone enolate	product	yield (%)	ketone enolate	product	yield (%) (*E*/*Z*)
		30%			25%
		55%			55%

Use of Epoxysilanes as Chiral Carbanion Generator





Development of New Synthetic Reactions Using Epoxysilanes

Scope, Limitation and Mechanistic Studies

Michiko Sasaki (D1)

Asymmetric Version

Eiji Kawanishi (D3)

Ring Forming Reactions

Tatsuya Matumoto (M1)

[3 + 4] Annulation

Yoshio Nakai (M1)

Grant-in-Aid for Scientific Research
The Uehara Memorial Foundation
The Naito Foundation