エポキシシランを利用する合成反応の開発

広島大学大学院医歯薬学総合研究科

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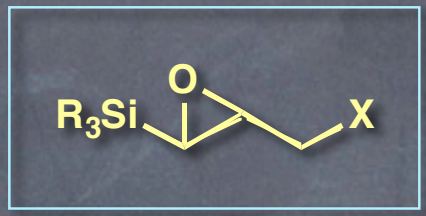
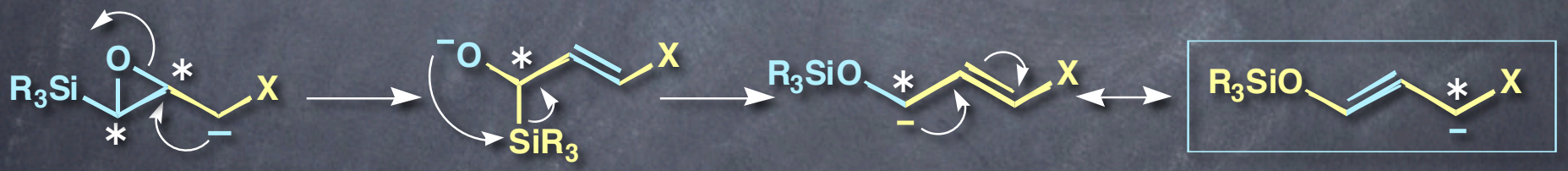
岐阜薬科大学　２００５年５月１３日

HIROSHIMA UNIVERSITY

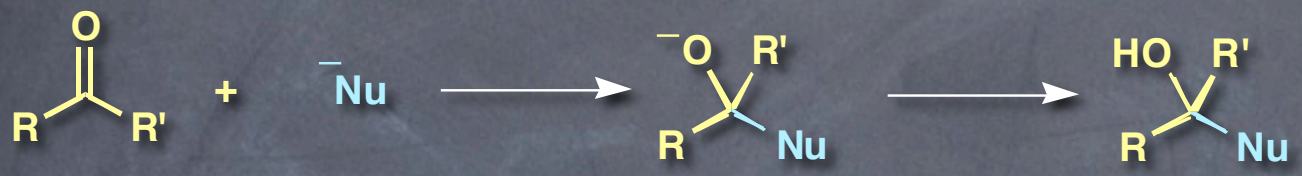
Reactions of Epoxysilanes

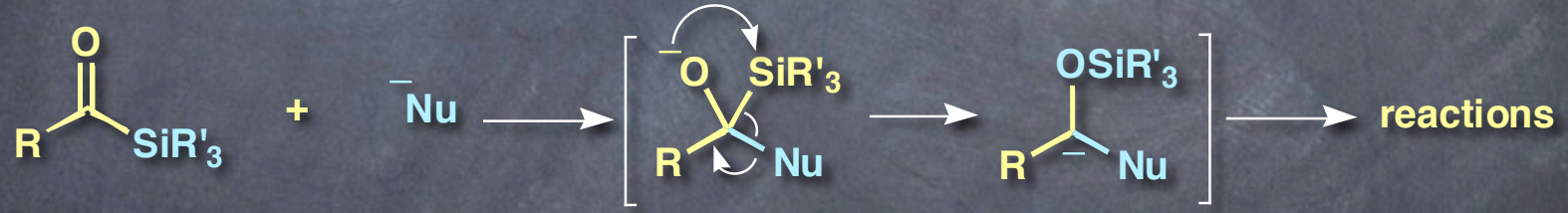




Brook rearrangement

Brook Rearrangement





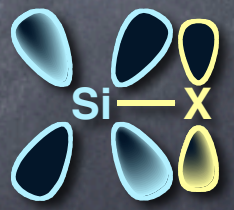
Brook, A.G. *J. Am. Chem. Soc.* **1957**, *79*, 4373.

Properties of Organosilicon Compounds

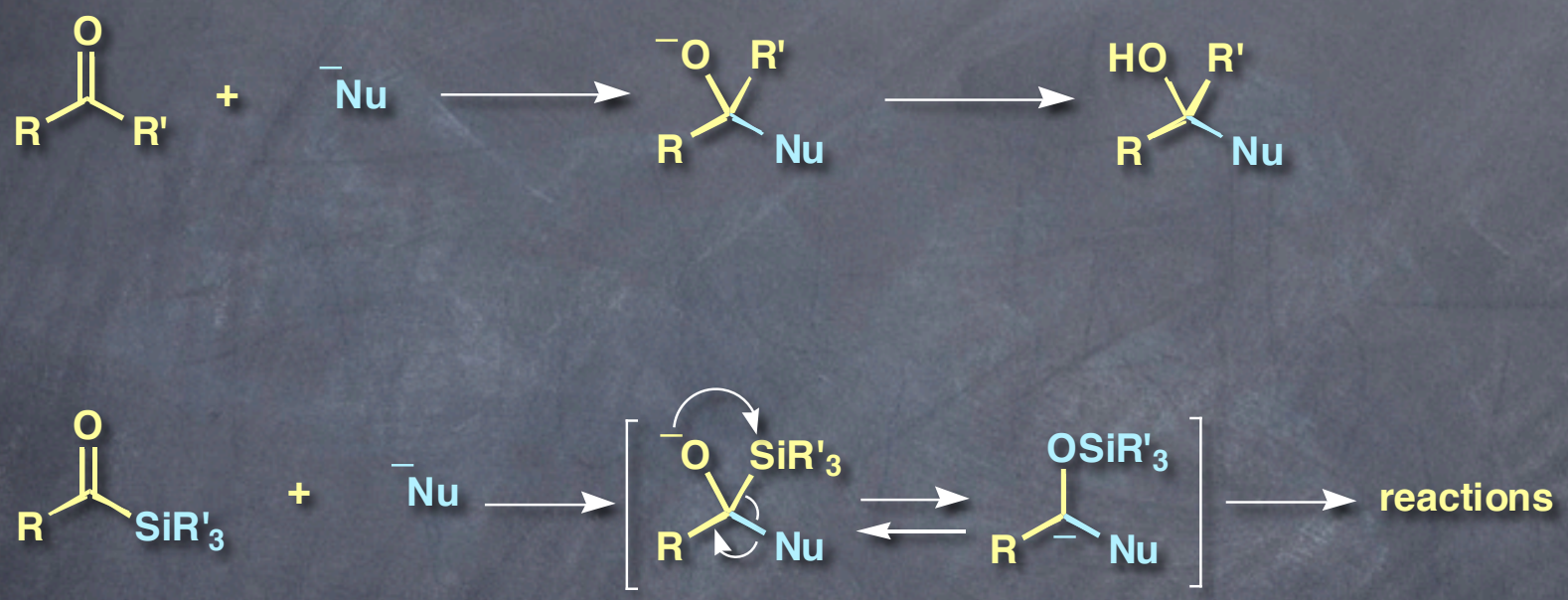
Bond strength and Bond lengths

Bonds	*Bond Dissociation Energy (kcal/mol)*	*Bond Length (Å)*
C-H	100	1.09
SiH	81 (x 0.81)	1.48 (x 1.36)
C-C	80	1.54
Si-C	76 (x 0.95)	1.89 (x 1.23)
C-O	81	1.41
Si-O	127 (x 1.57)	1.63 (x 1.16)
C-F	108	1.39
Si-F	193 (x 1.79)	1.60 (x 1.15)

p*p*-d*p* Bonding

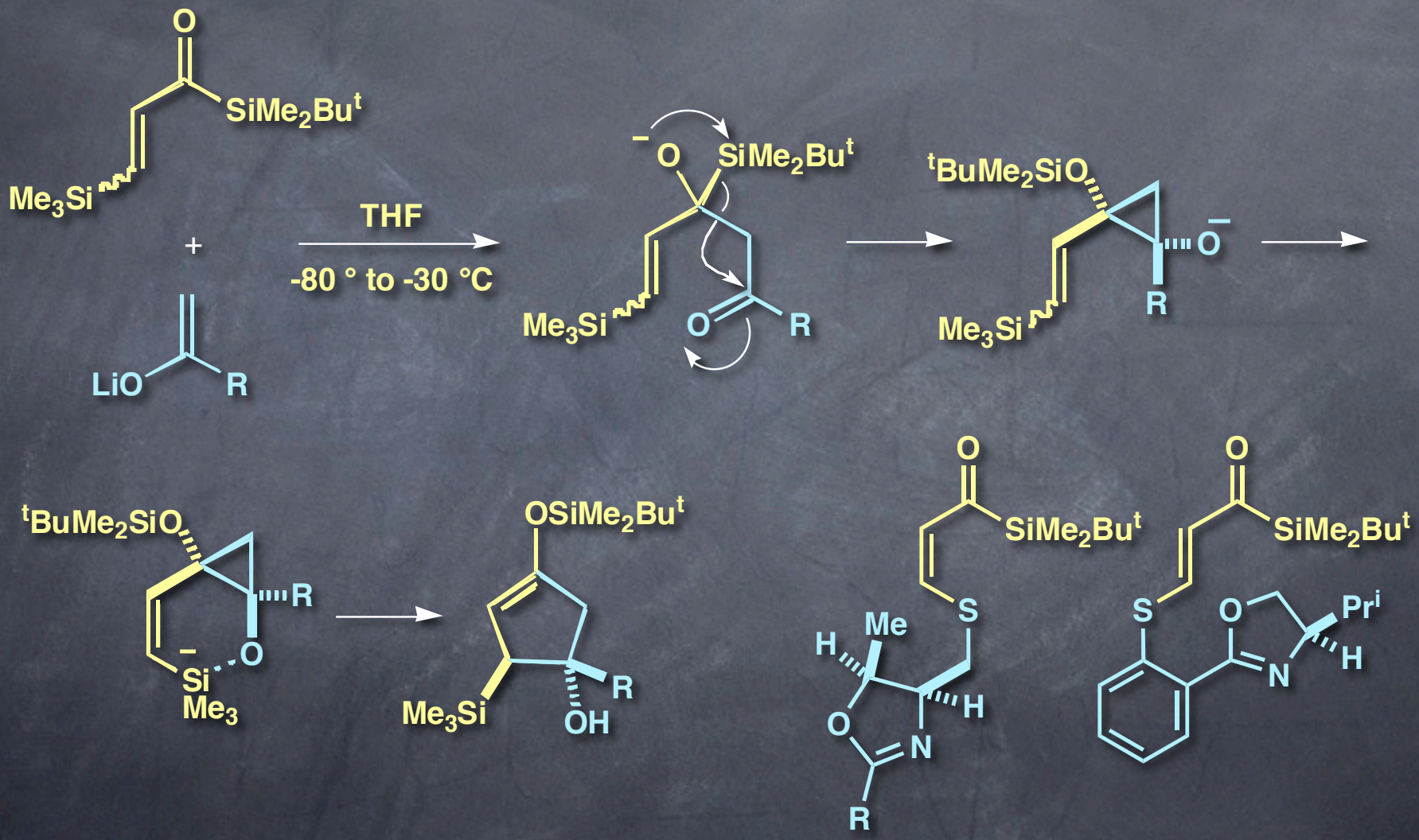


Brook Rearrangement



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

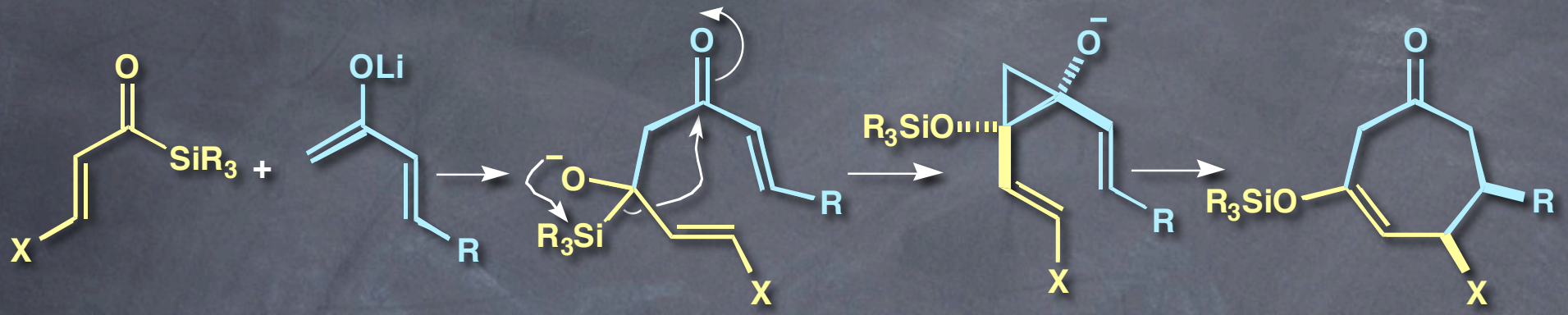
Brook Rearrangement-Mediated [3 + 2] Annulation



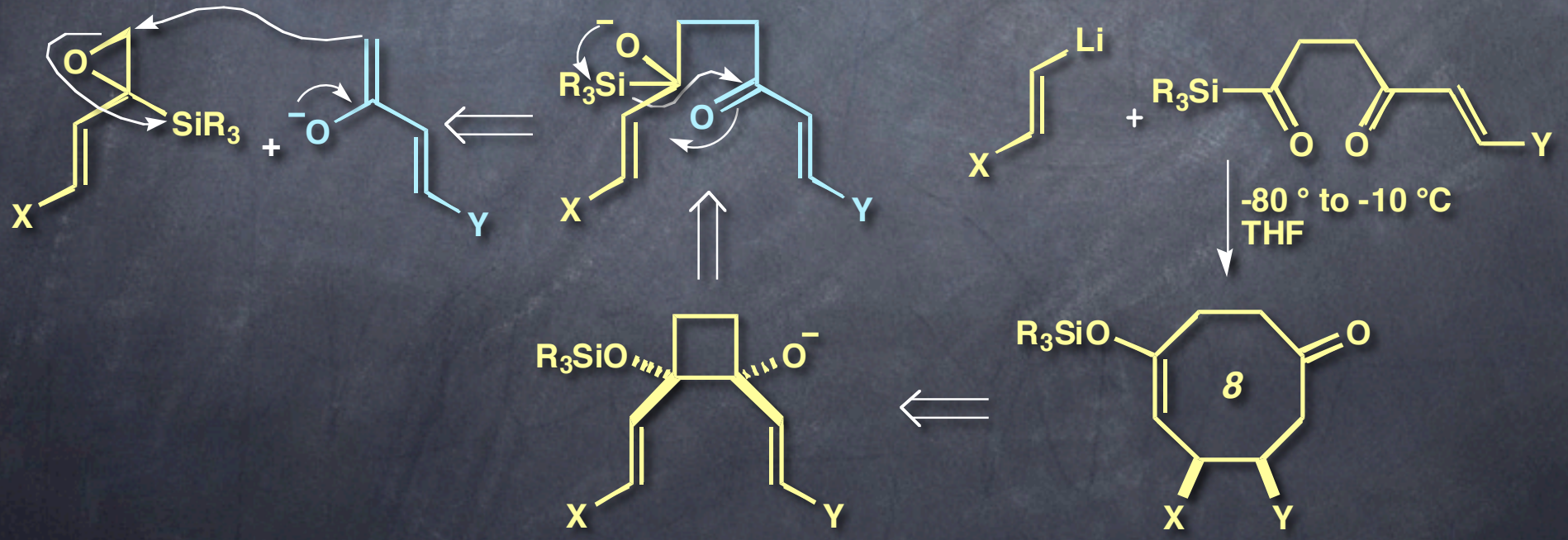
Takeda, K.; Fujisawa, M.; Makino, T.; Yoshii, E.; Yamaguchi, K. *J. Am. Chem. Soc.* **1993**, *115*, 9351-9352.
Takeda, K.; Yamawaki, K.; Hatakeyama, N. *J. Org. Chem.* **2002**, *67*, 1786-1794.

Extension of the [3 + 2] Annulation to Asymmetric Versions

Brook Rearrangement-Mediated [3 + 4] and [6 + 2] Annulations

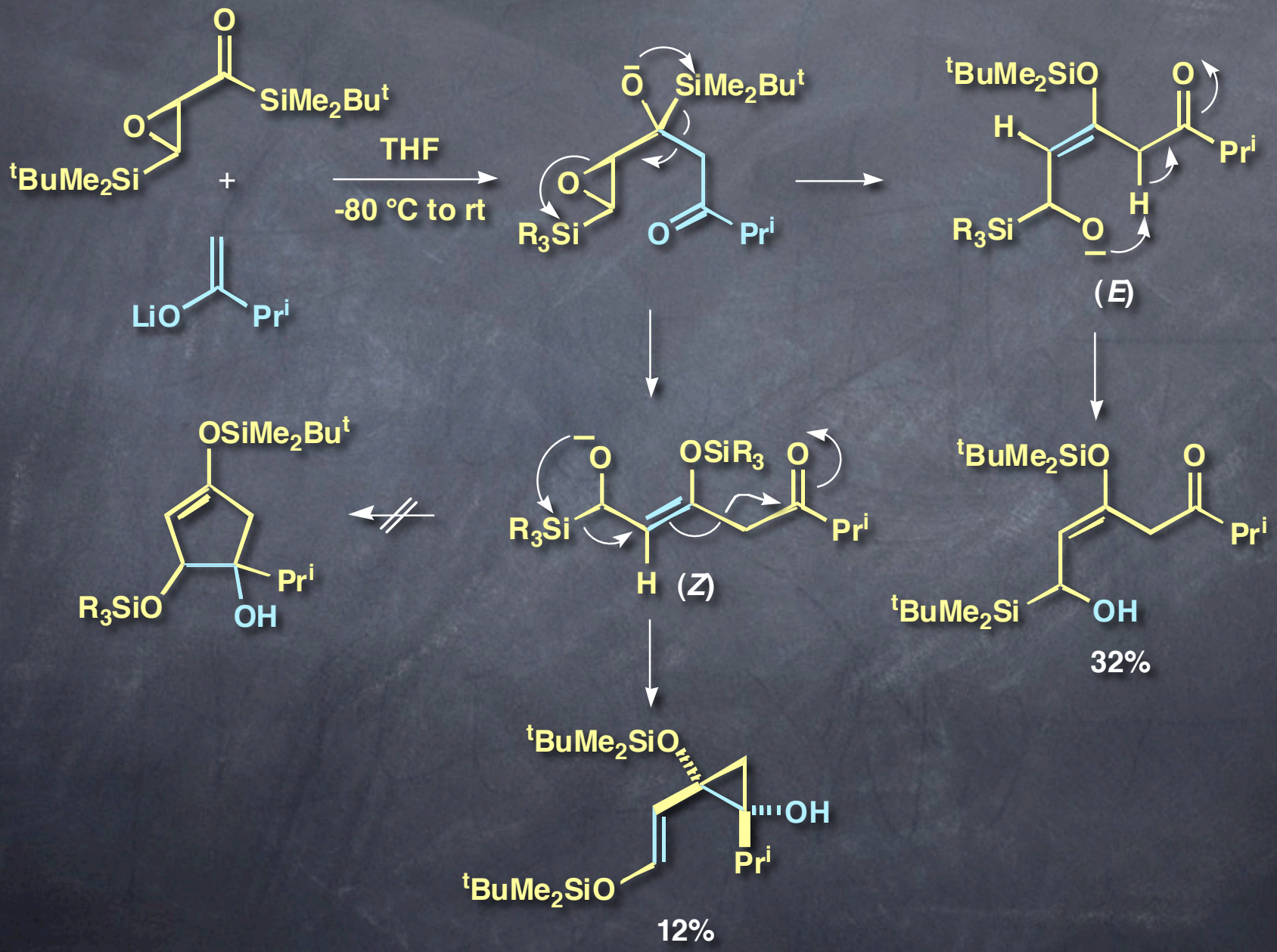


Takeda, K.; Takeda, M.; Nakajima, A.; Yoshii, E. *J. Am. Chem. Soc.* **1995**, *117*, 6400-6401.
Takeda, K.; Nakajima, A.; Takeda, M.; Okamoto, Y.; Sato, T.; Yoshii, E.; Koizumi, T. *J. Am. Chem. Soc.* **1998**, *120*, 4947-4959.
Takeda, K.; Nakajima, A.; Takeda, M.; Yoshii, E. *Org. Synth.* **1999**,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

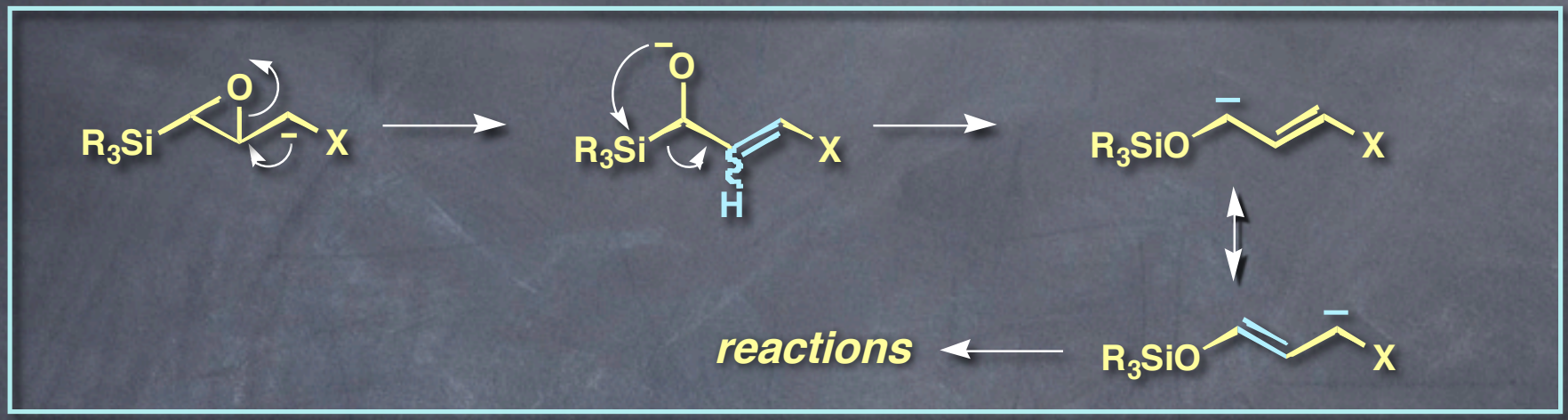


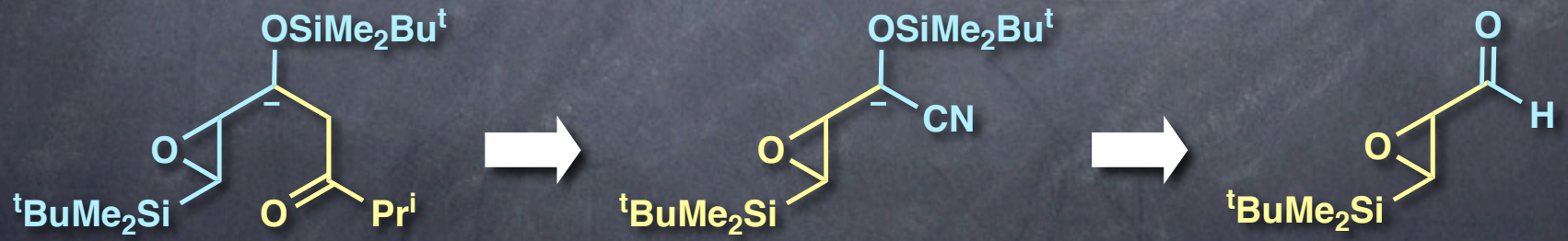
Takeda, K.; Haraguchi, H.; Okamoto, Y. *Org. Lett.* **2003**, *5*, 3705-3707.

Reaction of β-Silyl-α,β-epoxyacylsilane with Ketone Enolates

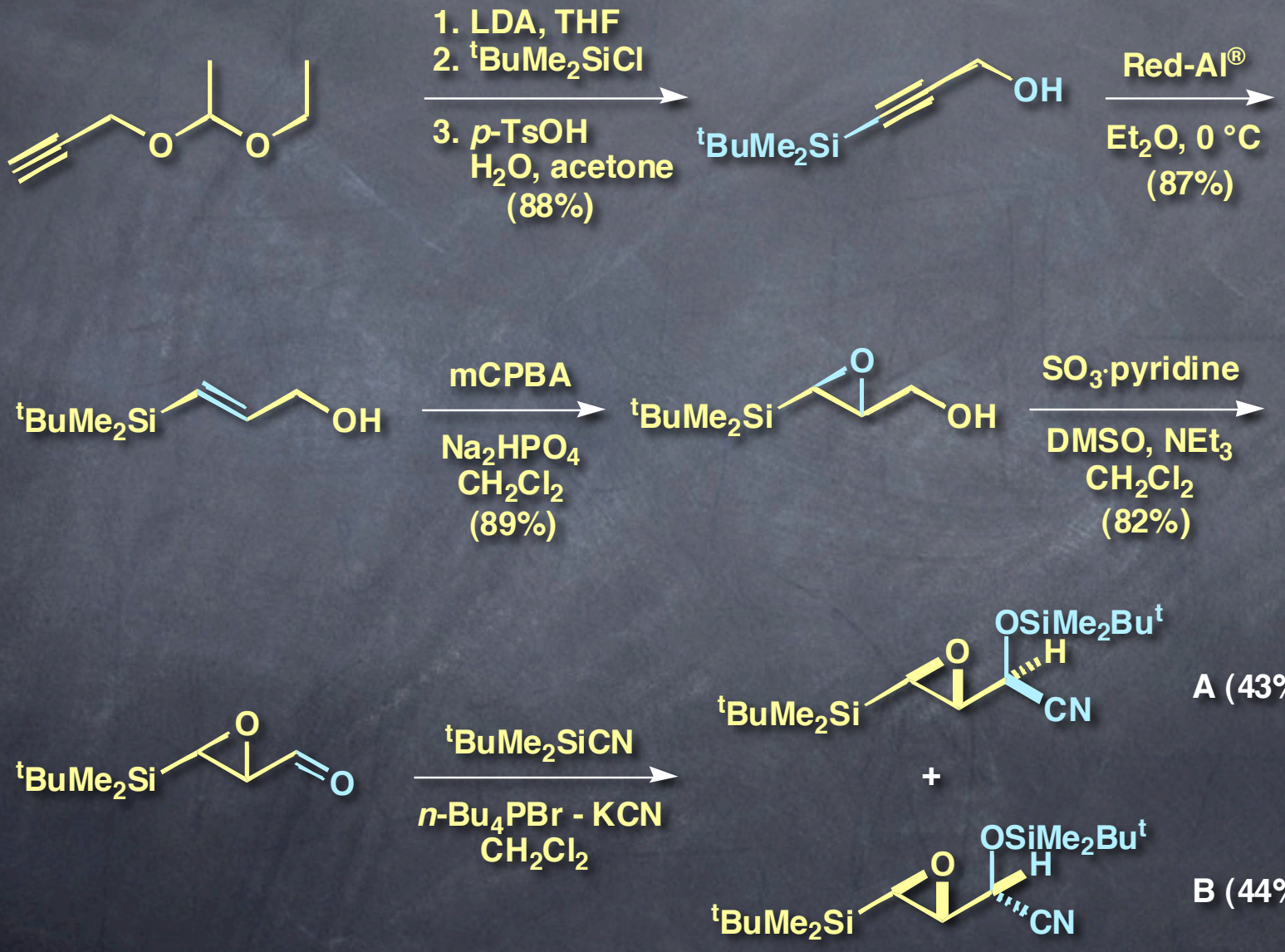


Epoxysilanes as an Efficient Trigger in Tandem Reactions

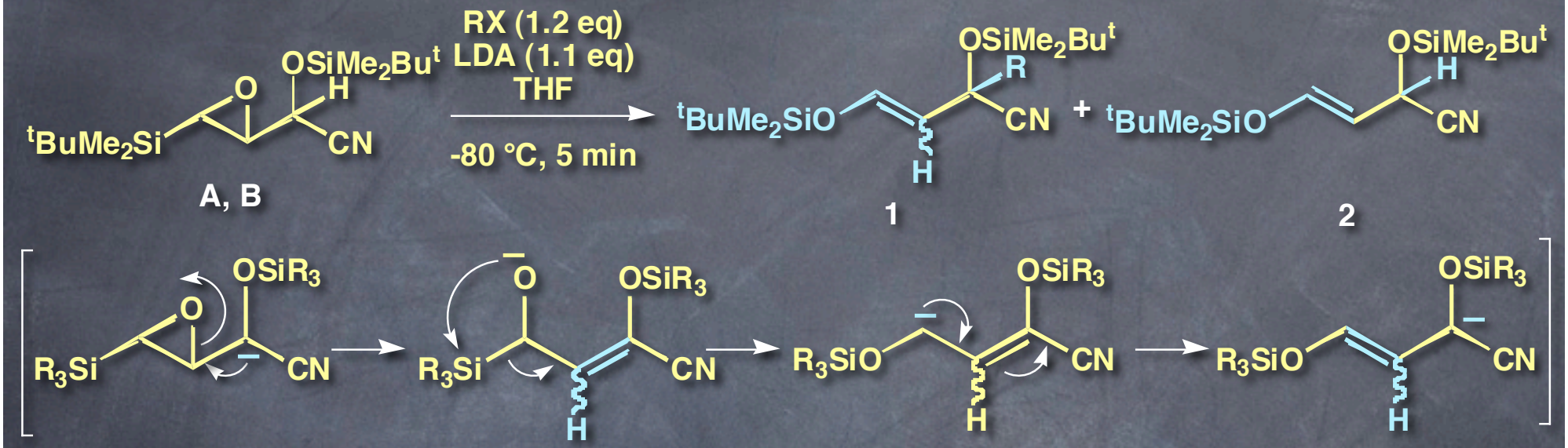




Preparation of *O*-Silyl Cyanohydrins of *trans*-β-Silyl-α,β-epoxyaldehydes



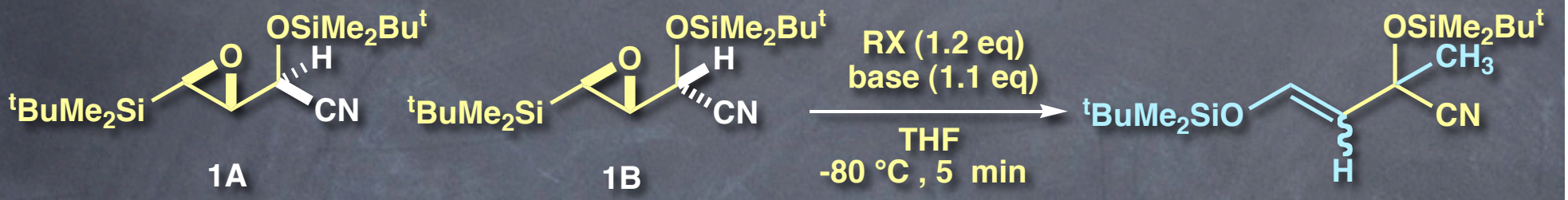
Reaction of Cyanohydrins of β-Silyl-α,β-epoxyaldehyde with LDA in the Presence of Alkylating Agents



RX	diastereomer A			diastereomer B		
	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	-

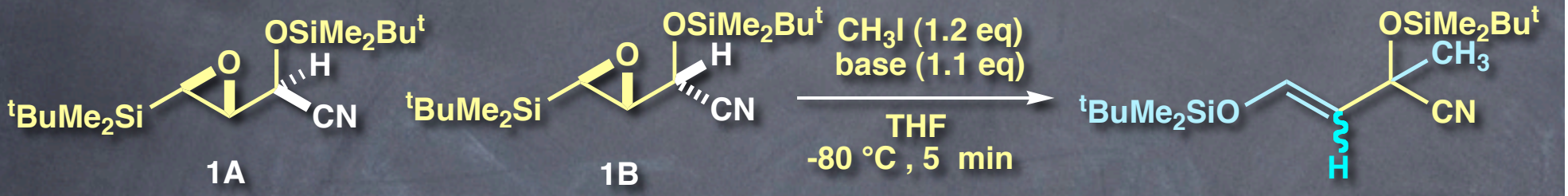
Kei Takeda, Eiji Kawanishi, Michiko Sasaki, Yuji Takahashi, Kentaro Yamaguchi *Org. Lett.* **2002**, *4*, 1511-1514.

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

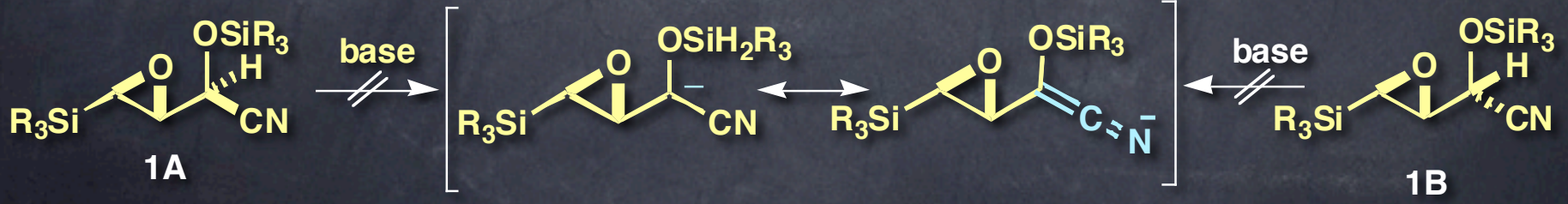


	yield (%) (*E*/*Z*)					
	from A			from B		
RX	$LiN(SiMe_3)_2$	$KN(SiMe_3)_2$	$NaN(SiMe_3)_2$	$LiN(SiMe_3)_2$	$KN(SiMe_3)_2$	$NaN(SiMe_3)_2$
MeI	44 (23.0)	84 (0.9)	96 (40.0)	83 (31.0)	87 (9.7)	98 (*E*)
EtI	24 (16.0)	76 (0.7)	90 (42.0)	64 (28.0)	81 (16.0)	89 (42.0)
i-PrI	15 (14.0)	42 (2.1)	80 (62.0)	44 (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)

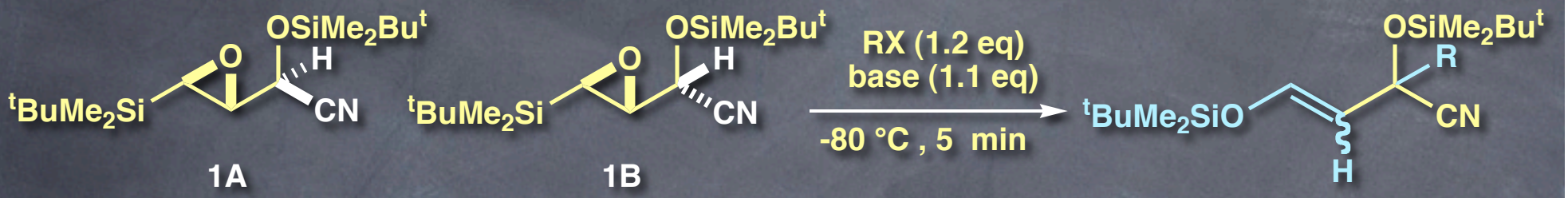
Summary of Methylation of Metalated *O*-Silyl Cyanohydrins of *trans*-β-Silyl-α,β-epoxyaldehydes



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



Solvent Effect on *E*/*Z* Selectivity

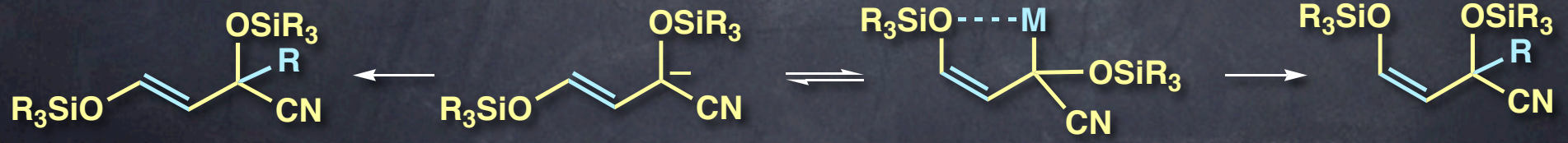


solvent	SM	yield (%)	*E*/*Z*
hexane	1A	93	1.5
	1B	78	6.0
ether	1A	84	1.9
	1B	77	28.0
toluene	1A	86	1.0
	1B	83	24.0
THF	1A	85	28.0
	1B	84	52.0

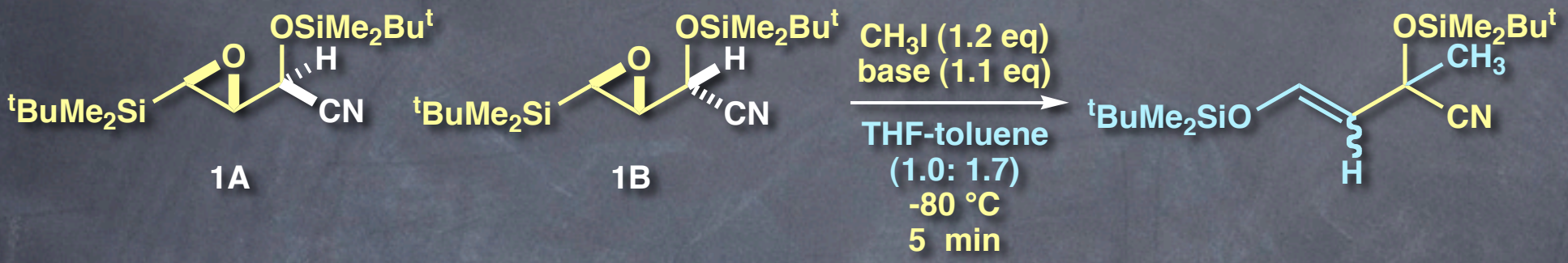
Base: NHMDS (in THF), RX: BnBr

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*	-

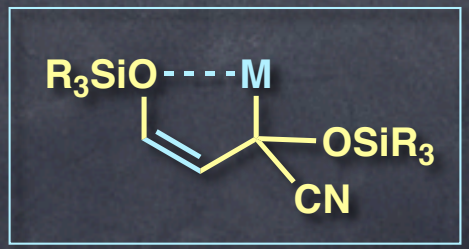
solvent: THF, RX: CH_3I

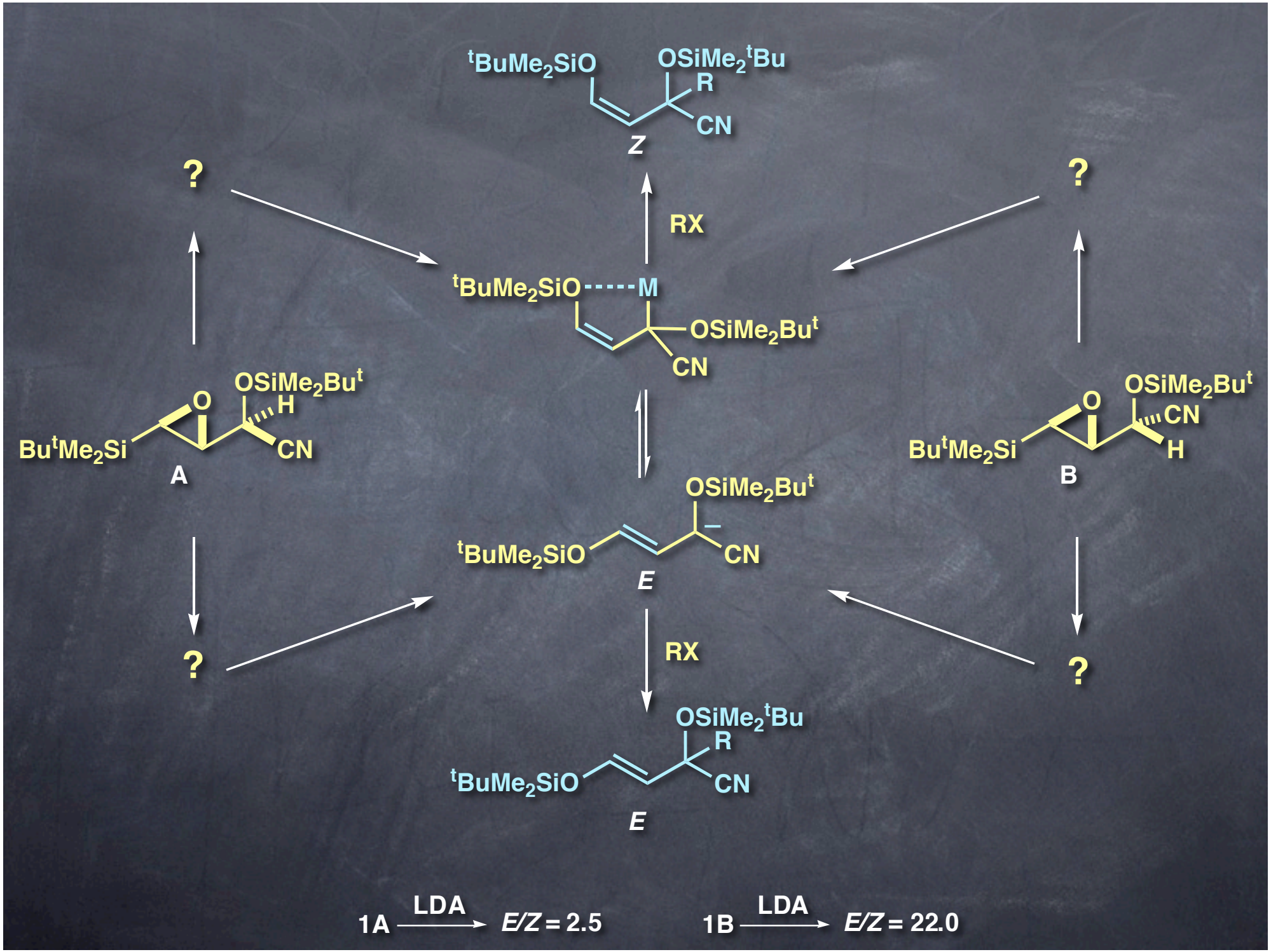


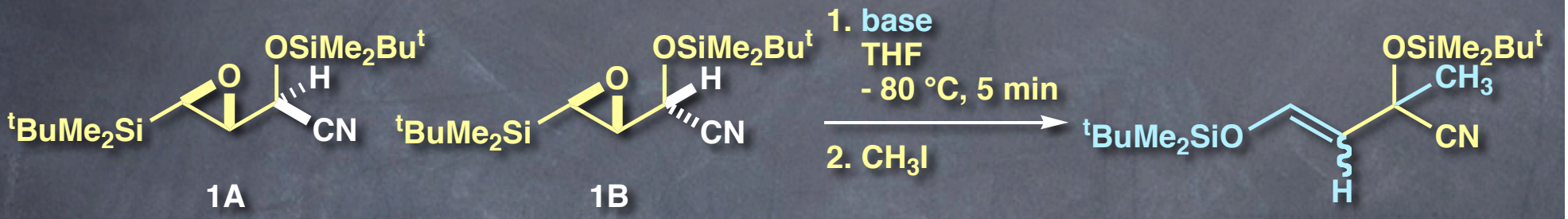
The Effect of the Counter Cations on *the E/Z* Selectivity



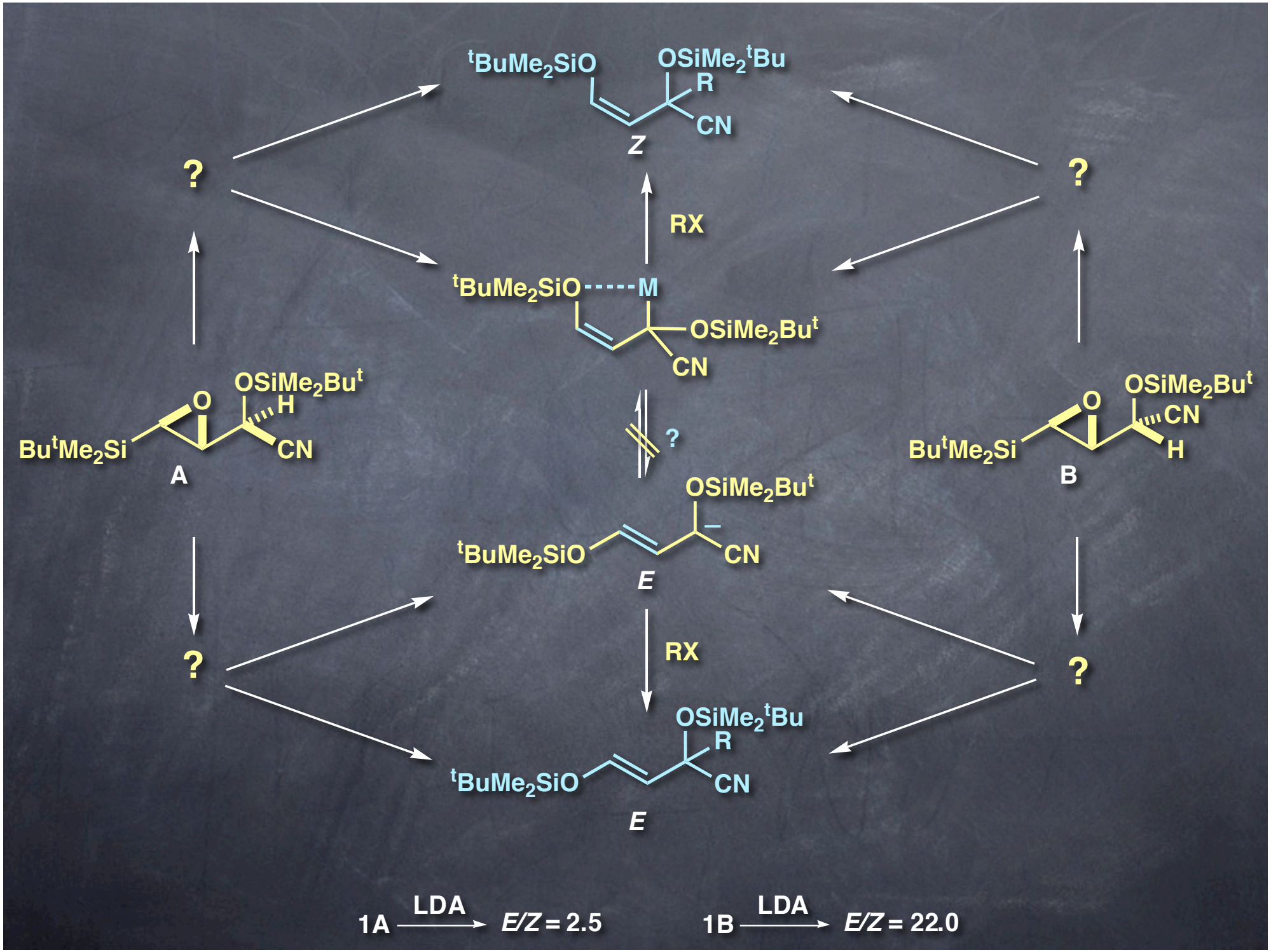
base	diastereomer	yield (%)	*E/Z*	SM
$LiN(SiMe_3)_2$	A	19	0.4	67
$LiN(SiMe_3)_2$	B	18	34.0	63
$NaN(SiMe_3)_2$	A	86	1.4	
$NaN(SiMe_3)_2$	B	97	16.0	

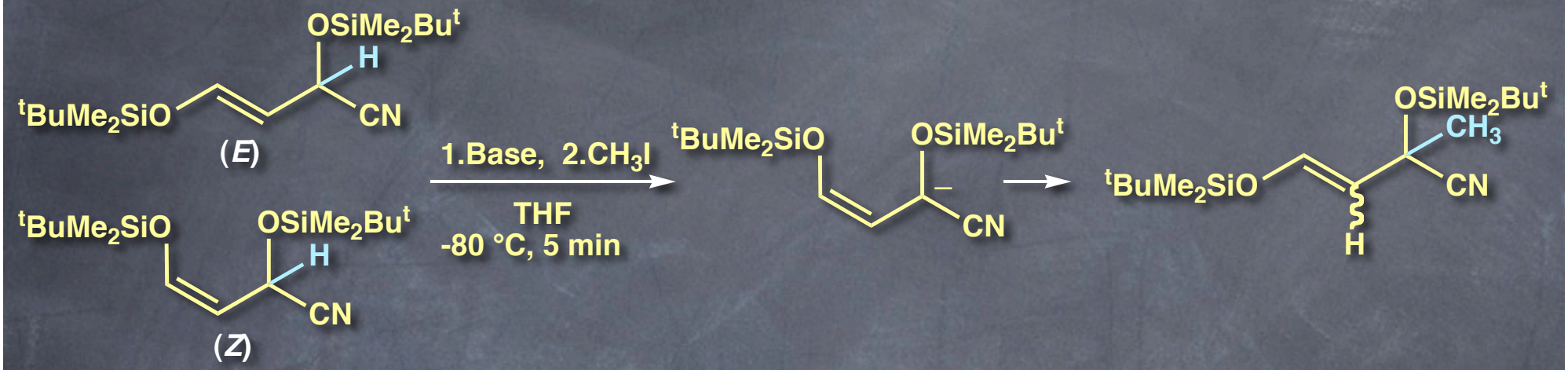



tBuMe2SiO
OSiMe2tBu
R
CN
Z
RX
?
tBuMe2SiO
M
OSiMe2But
CN
OSiMe2But
O
H
ButMe2Si
CN
A
OSiMe2But
O
CN
ButMe2Si
H
B
OSiMe2But
tBuMe2SiO
CN
E
RX
?
?
?
OSiMe2tBu
R
tBuMe2SiO
CN
E
1A
LDA
E/Z = 2.5
1B
LDA
E/Z = 22.0

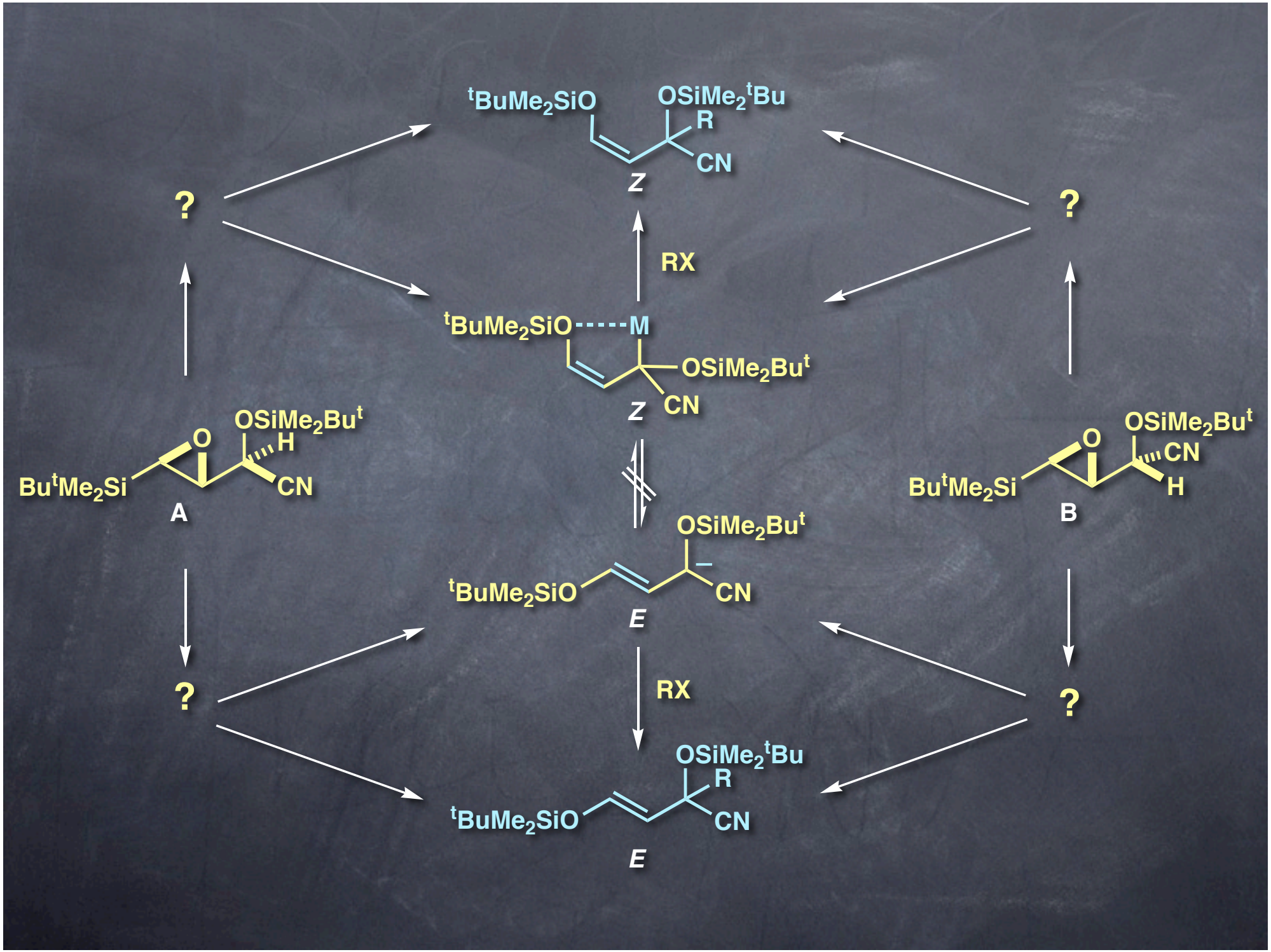


	from A		from B	
base	yield (%)	*E*/*Z*	yield (%)	*E*/*Z*
LDA	76 (82)	2.9 (2.5)	69 (84)	38.0 (22.0)
LHMDS	36 (44)	39.0 (23.0)	68 (83)	54.0 (31.0)
NHMDS	86 (91)	38.0 (40.0)	85 (92)	124.0 (47.0)
KHMDS	78 (84)	0.3 (0.9)	66 (87)	12.0 (9.7)

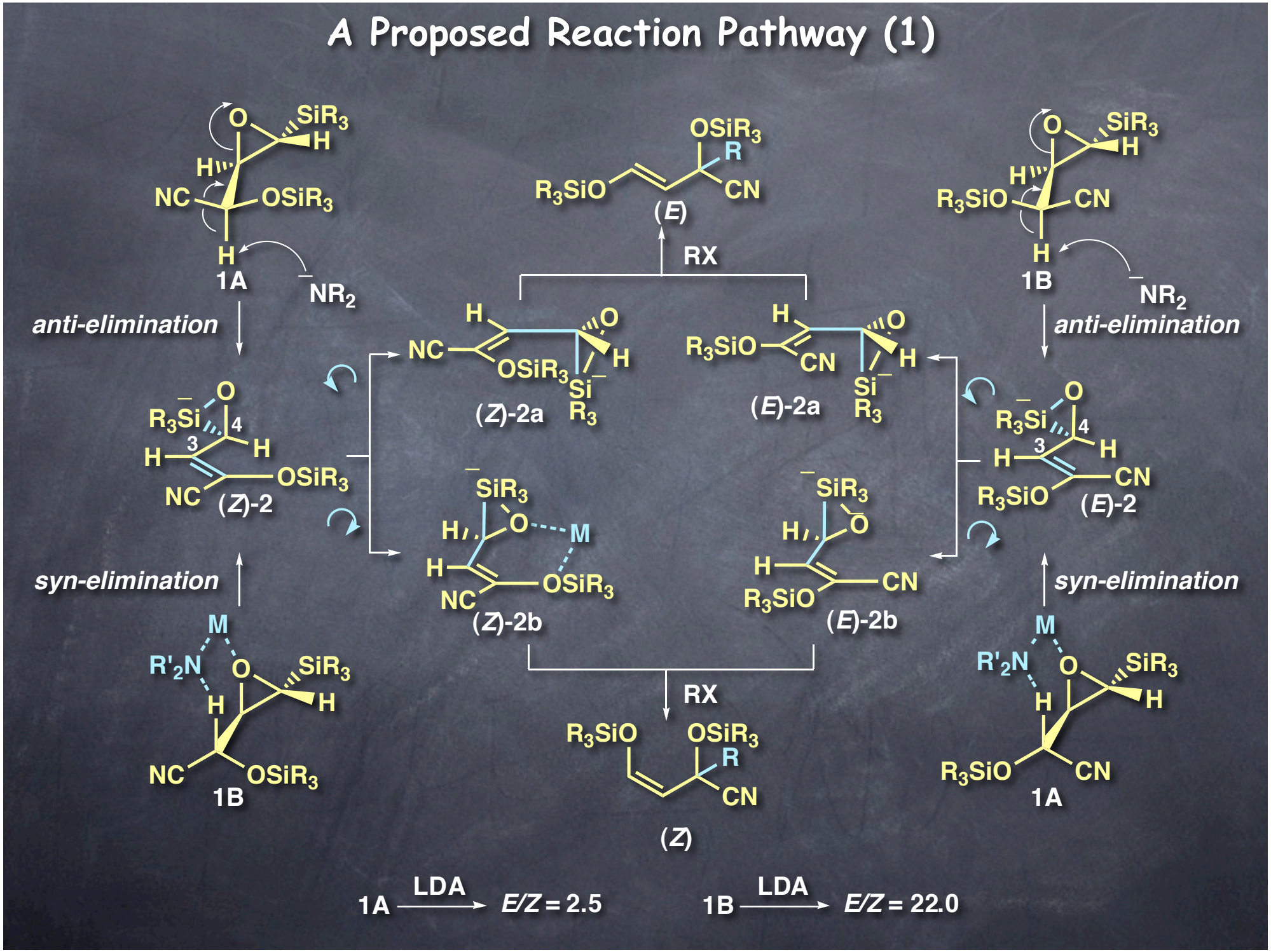

tBuMe2SiO
OSiMe2tBu
R
CN
Z
?
?
RX
tBuMe2SiO
M
OSiMe2But
CN
OSiMe2But
O
H
CN
ButMe2Si
A
?
OSiMe2But
O
CN
H
ButMe2Si
B
OSiMe2But
tBuMe2SiO
CN
E
?
?
RX
?
OSiMe2tBu
R
tBuMe2SiO
CN
E
1A
LDA
E/Z = 2.5
1B
LDA
E/Z = 22.0



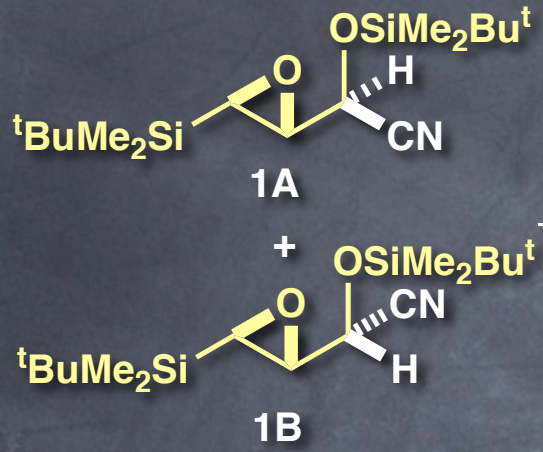
Base	SM	yield (%)	*E/Z*	SM, yield (%)
LDA	*E*	76	58.0	-
LHMDS	*E*	46	*E*	47
NHMDS	*E*	81	*E*	6
KHMDS	*E*	75	*E*	8
LDA	*Z*	41	0.01	18
LHMDS	*Z*	0	-	87
NHMDS	*Z*	30	0.02	59
KHMDS	*Z*	76	0.01	8


tBuMe2SiO
OSiMe2tBu
R
CN
Z
?
?
RX
tBuMe2SiO
M
OSiMe2But
CN
Z
OSiMe2But
O
H
CN
ButMe2Si
A
OSiMe2But
O
CN
H
ButMe2Si
B
OSiMe2But
tBuMe2SiO
CN
E
?
?
RX
OSiMe2tBu
R
tBuMe2SiO
CN
E

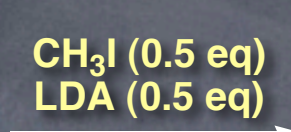
A Proposed Reaction Pathway (1)

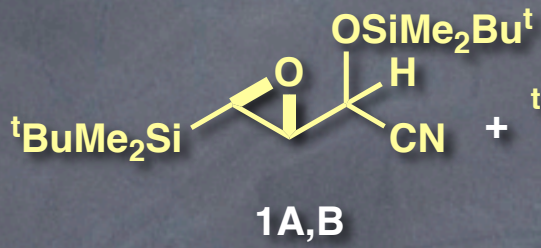


Base-Promoted Ring-Opening of Cyanohydrins of β-Silyl α,β-Epoxyaldehyde (1)



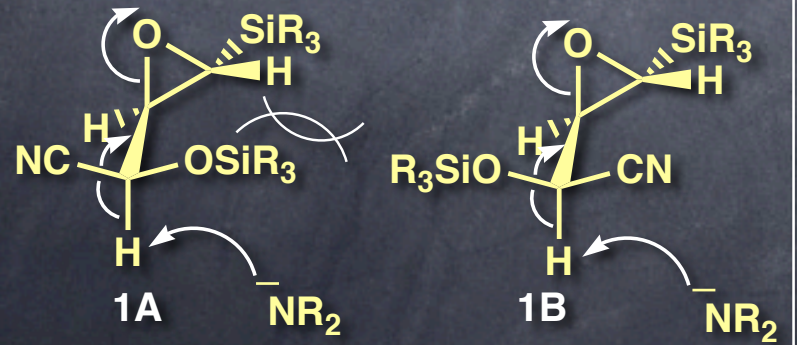
1A:1B = 1.00:1.04



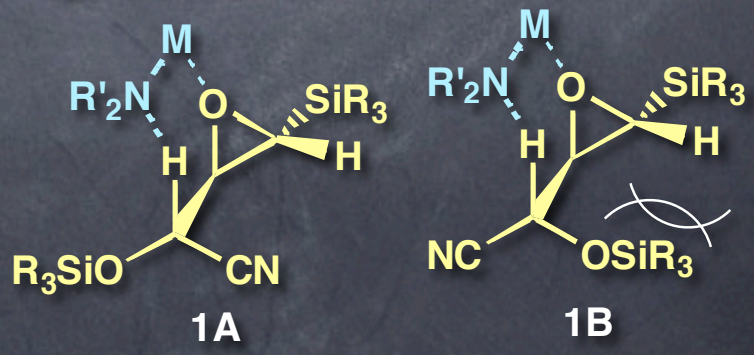


	yield (%)		yield (%)	
HMPA	1	A:B	2	*E/Z*
(–)	40	1.00:0.70	35	6.6
(+)	67	1.00:0.76	26	25.0

anti-elimination

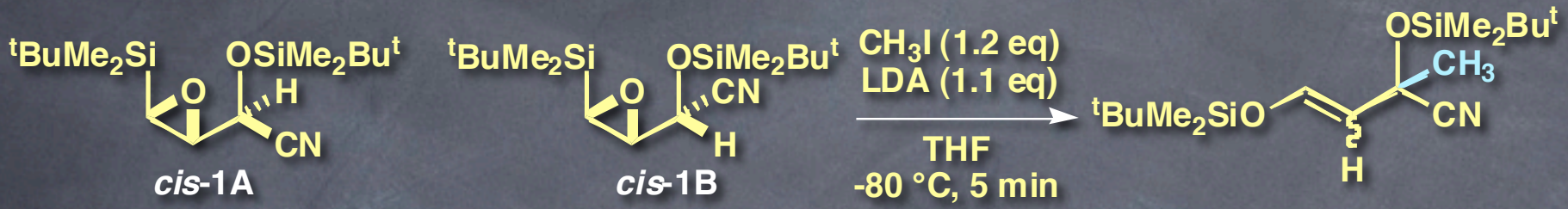


syn-elimination

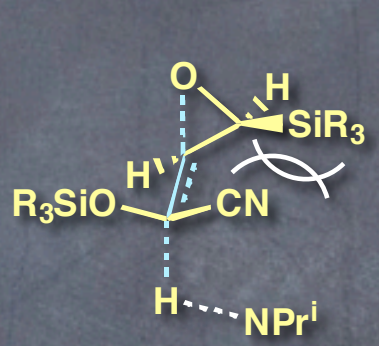


A-value: OTMS = 0.7
CN = 0.2

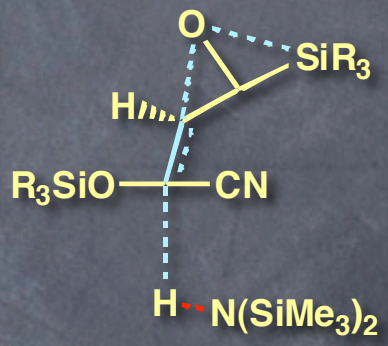
Base-Promoted Ring-Opening of Cyanohydrins of β-Silyl α,β-Epoxyaldehyde (2)



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

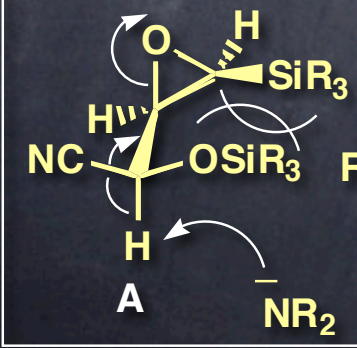


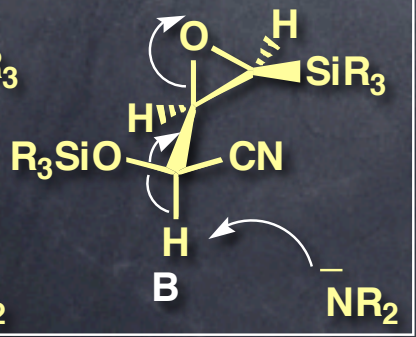
reactant-like transition state



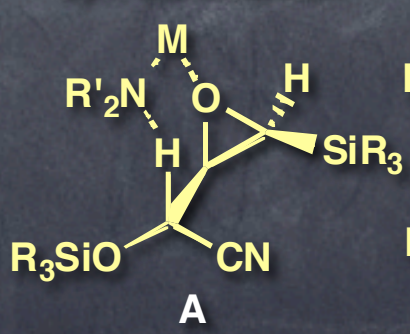
less reactant-like transition state

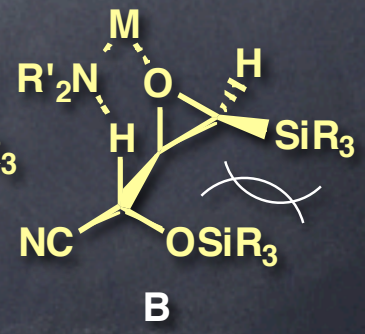
anti-elimination

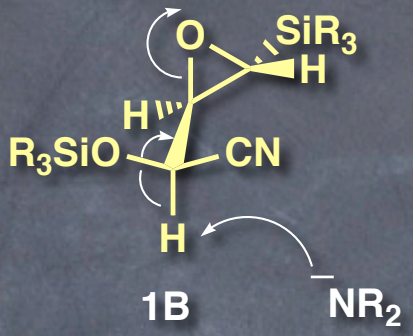




syn-elimination

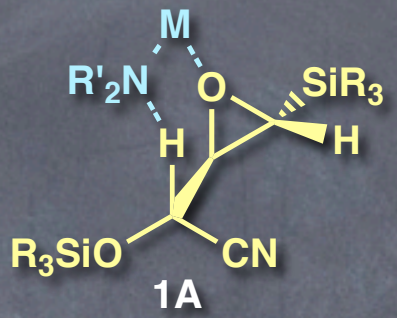






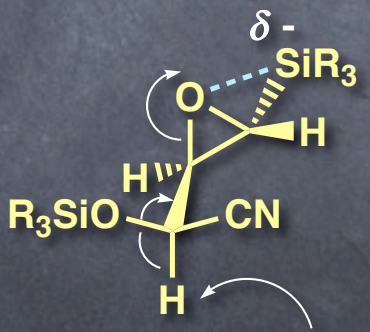
1B

anti-elimination



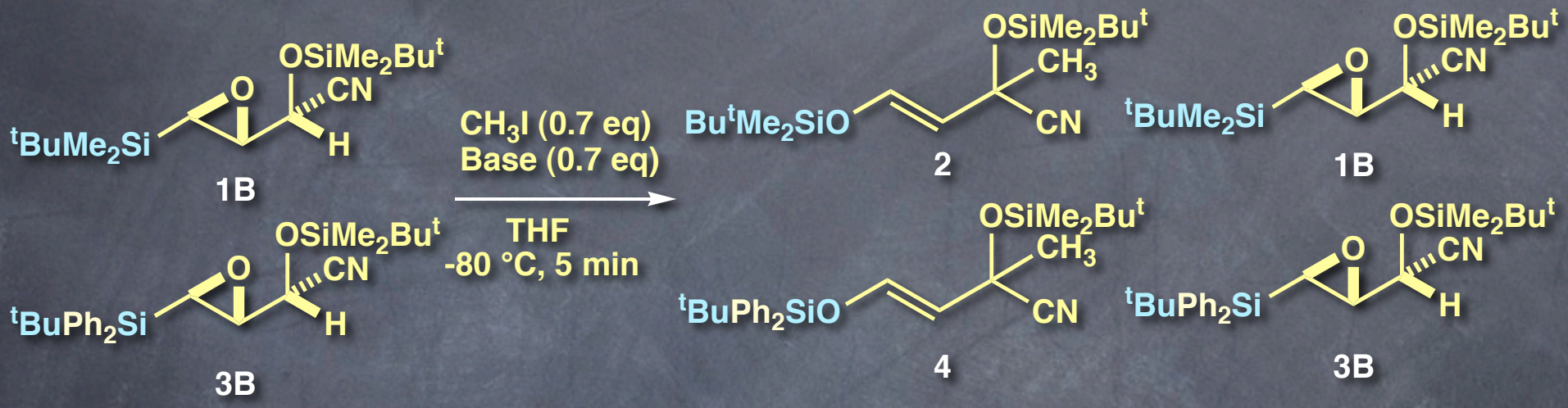
1A

syn-elimination

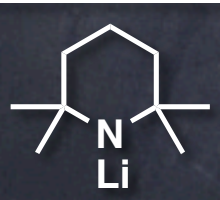


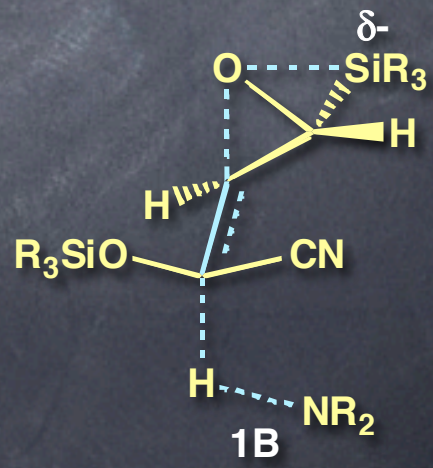
1B

Substituent Effect of the Silyl Group on Rates of Ring Opening

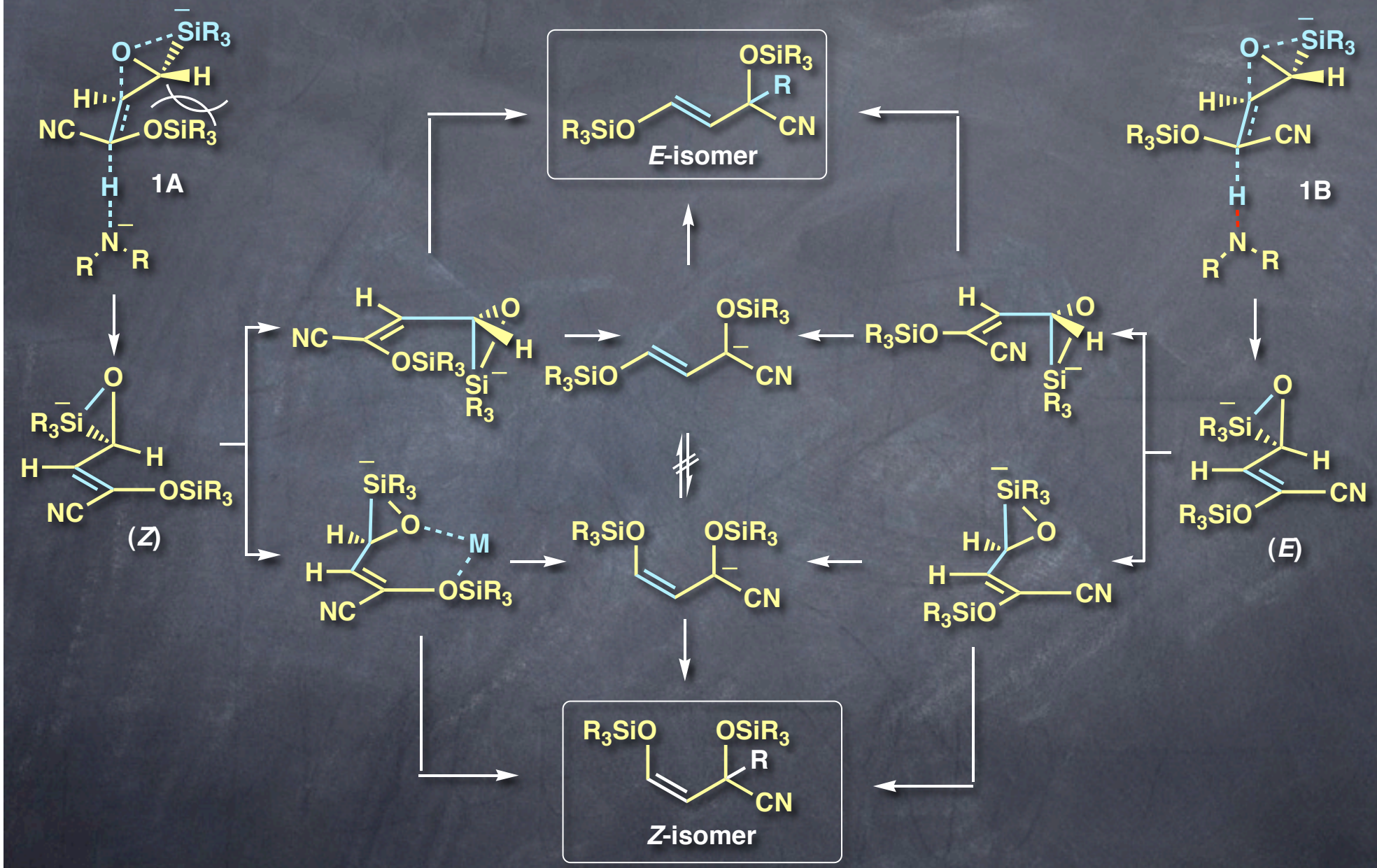


	yield (%)			yield (%)	
base	2	4	4 (TBDPS)/2 (TBS)	1B	3B
LDA	22	7	0.31	18	40
$LiNEt_2$	19	6	0.32	24	39
LTMP	22	15	0.67	19	30

LTMP = 

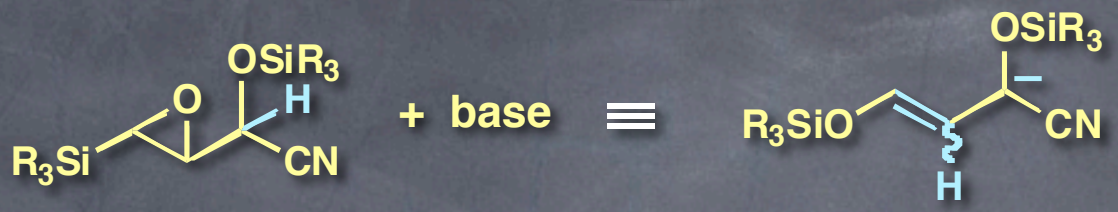


A Proposed Reaction Pathway (2)

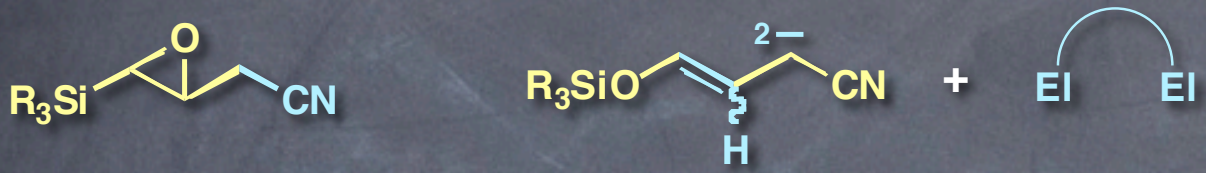


Michiko Sasaki, Eiji Kawanishi, Yoshio Nakai, Tatsuya Matsumoto, Kentaro Yamaguchi, Kei Takeda
J. Org. Chem. **2003**, *68*, 9330-9339.

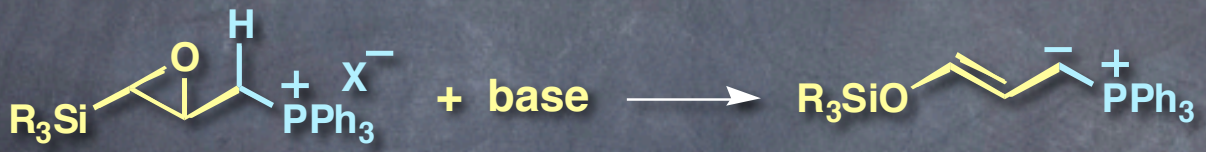
Epoxysilanes as an Efficeint Trigger in Tandem Reactions (2)



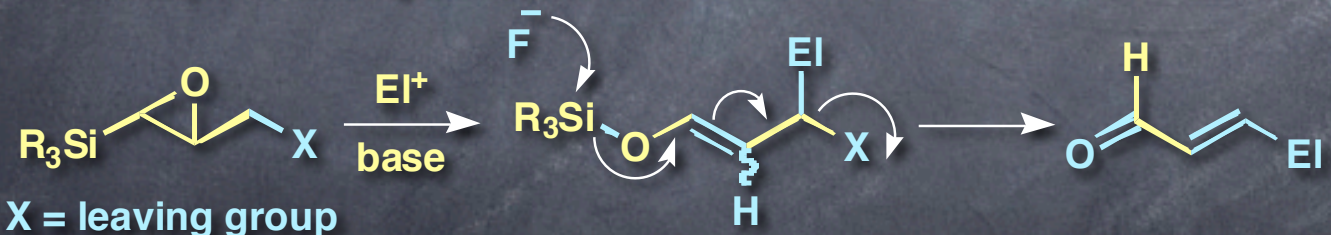
- *Reactions with bis-electrophiles*



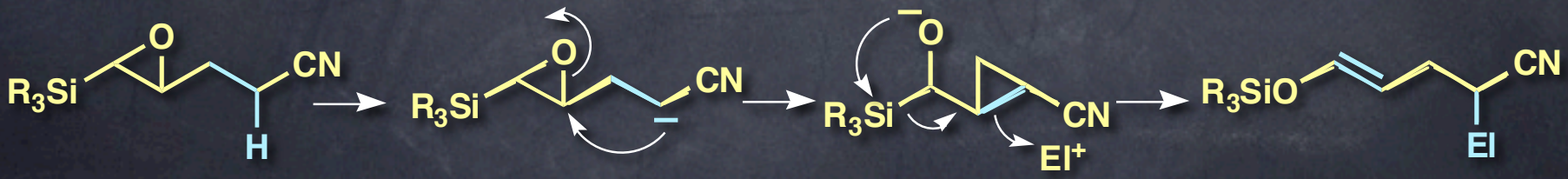
- *Wittig-type reactions*



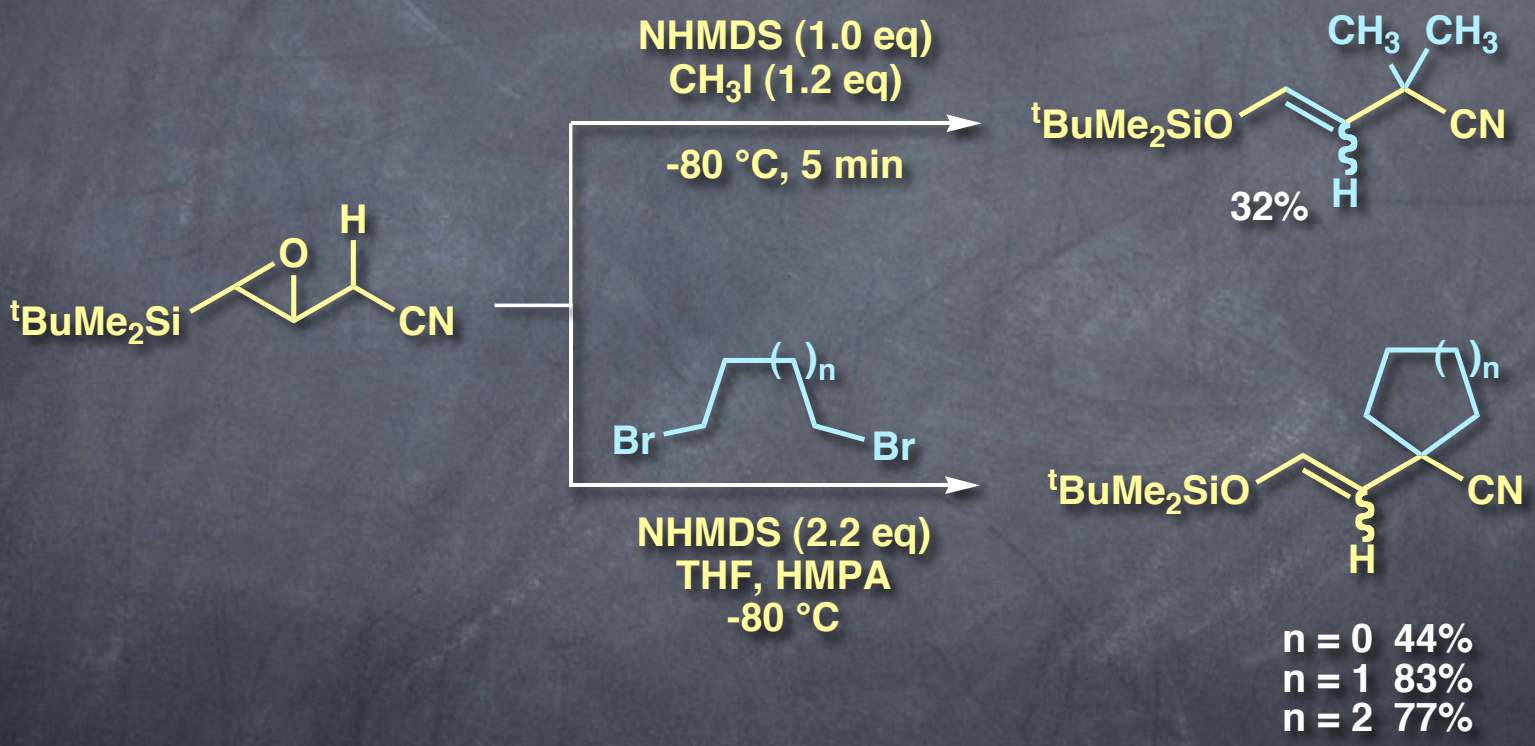
- *Acrolein β-anion equivalent*



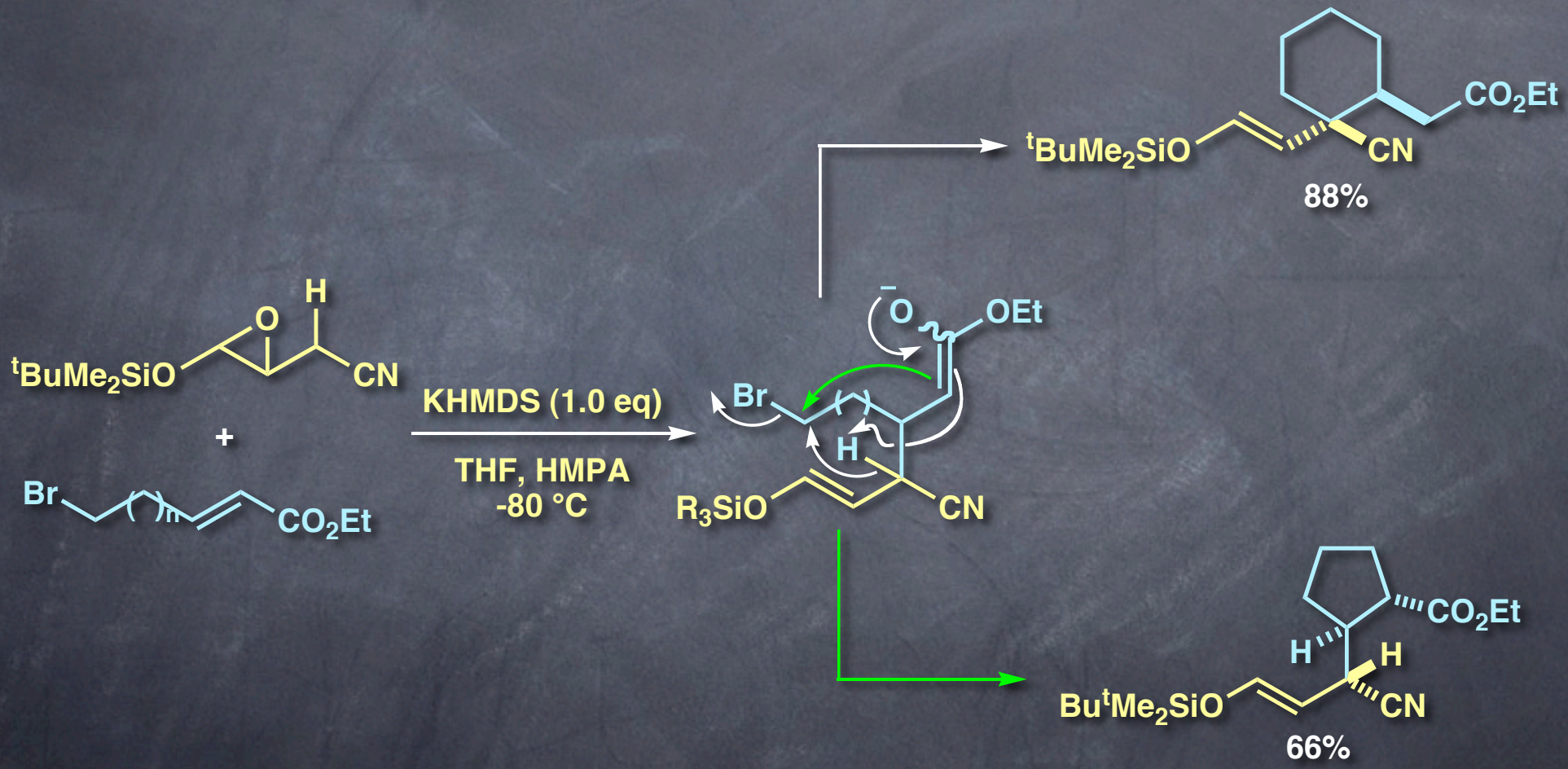
- *Introduction of one more carbon atom between epoxide and nitrile group*



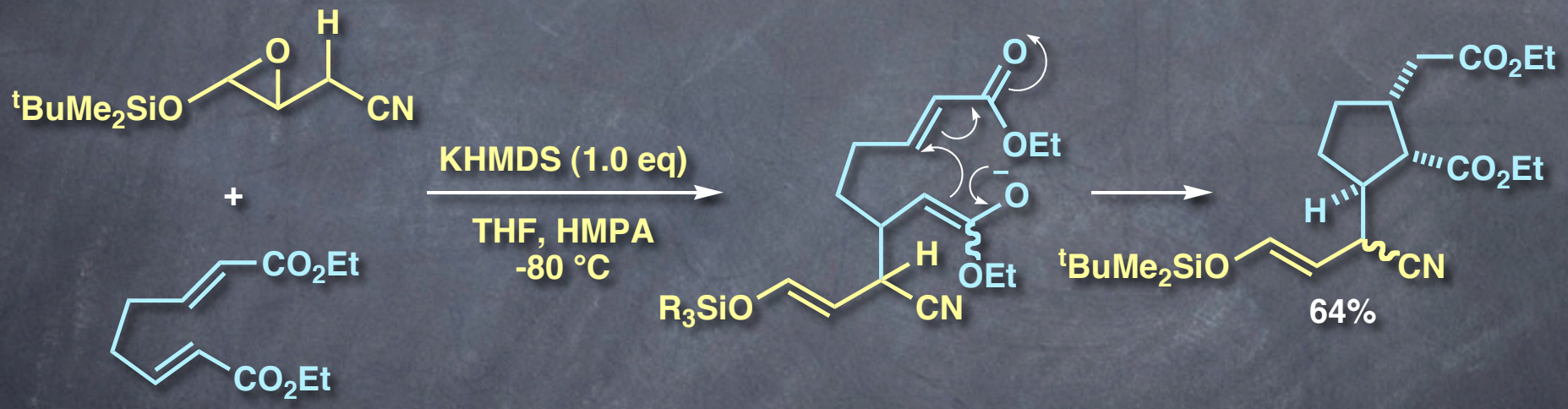
Tandem Formation of Functionalized Carbocycles via Reactions with Bis-Electrophiles (1)



Tandem Formation of Functionalized Carbocycles via Reactions with Bis-Electrophiles (2)

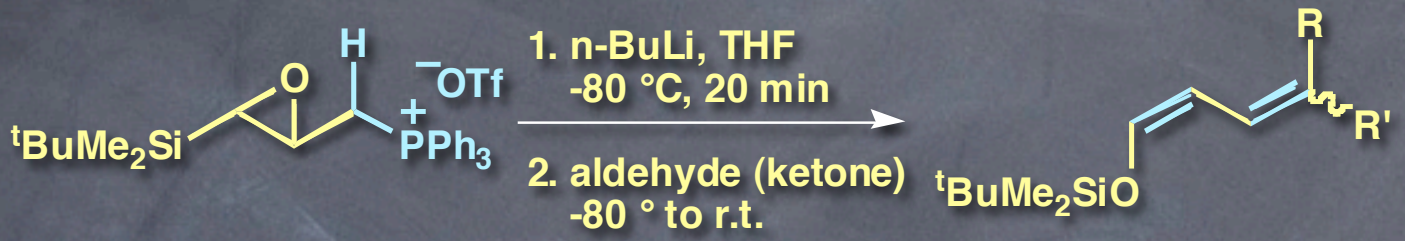


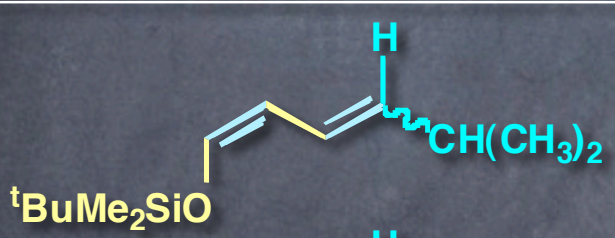
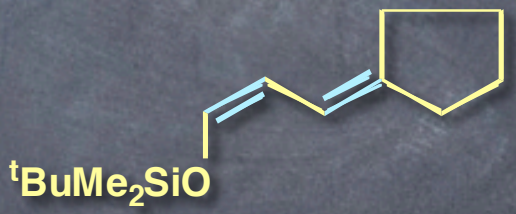
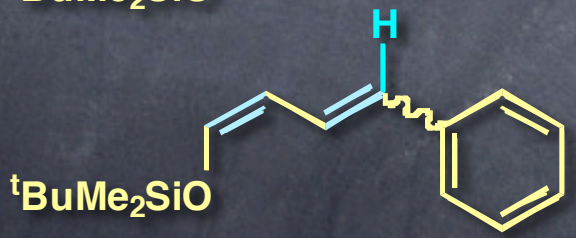
Tandem Formation of Functionalized Carbocycles via Reactions with Bis-Electrophiles (3)



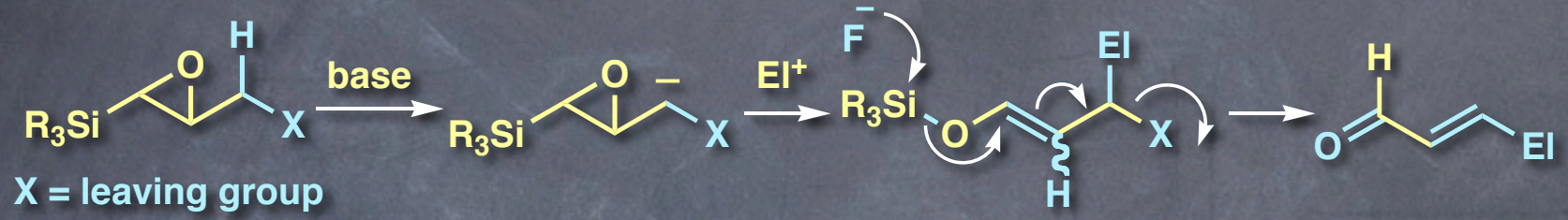
Tatsuya Matsumoto, Hyuma Masu, Kentaro Yamaguchi, and Kei Takeda *Org. Lett.* **2004**, ***6***, 4367-4369.

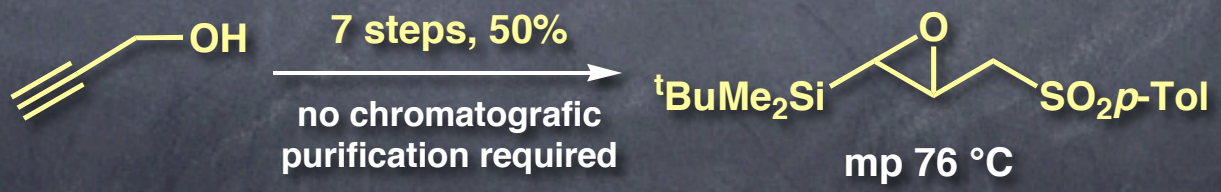
γ-Phosphonio-α,β-epoxysilane: A New Wittig-Type Reagent



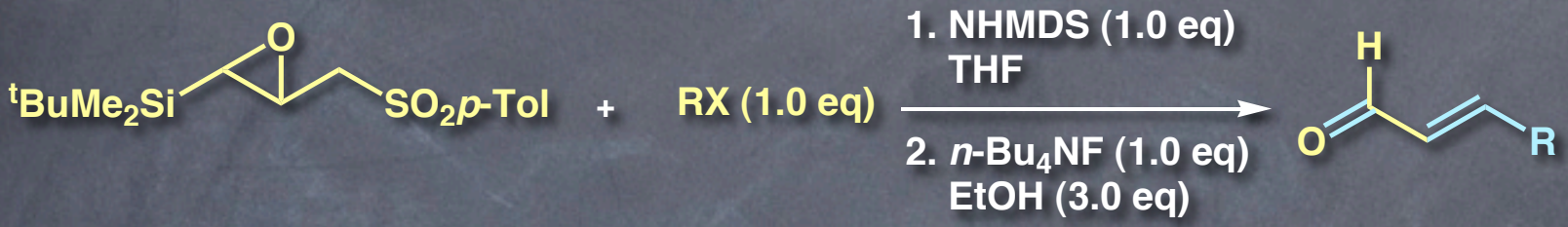
	yield (%) (*E*/*Z*)		yield (%)
	63 (1.0)		36
	66 (1.0)		

γ-*p*-Toluenesulfonyl-α,β-epoxysilane
A New and Practical Acrolein β-Anion Equivalent (1)



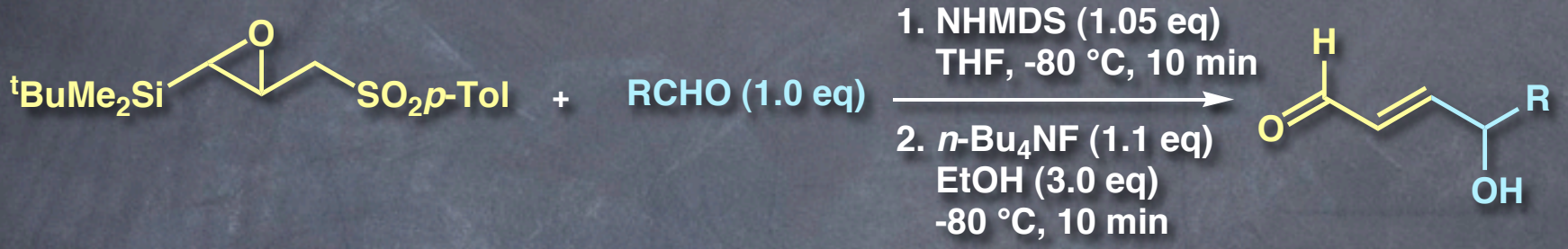


γ-*p*-Toluenesulfonyl-α,β-epoxysilane
A New and Practical Acrolein β-Anion Equivalent (2)



RX	conditions	yield (%)
$BrCH_2Ph$	1. -80 ° to -60 °C, 30 min	85
	2. -80 ° to -70 °C, 15 min	
$ICH_2(CH_2)_6CH_3$	1. -80 ° to -50 °C, 40 min	84
	2. -80 ° to -70 °C, 20 min	
$BrCH_2CH{=}CH(CH_2)_3CH_3$	1. -80 ° to -50 °C, 30 min	82
	2. -80 ° to -40 °C, 15 min	
$ICH_2CH_2CH_2CH_2OSiMe_2Bu^t$	1. -80 ° to -40 °C, 45 min	68
	2. -80 ° to -70 °C, 15 min	
$ICH_2CH_2CH_2CO_2Et$	1. -80 ° 5 min, then RX -40 °C, 45 min	74
	2. -80 ° to -70 °C, 20 min	

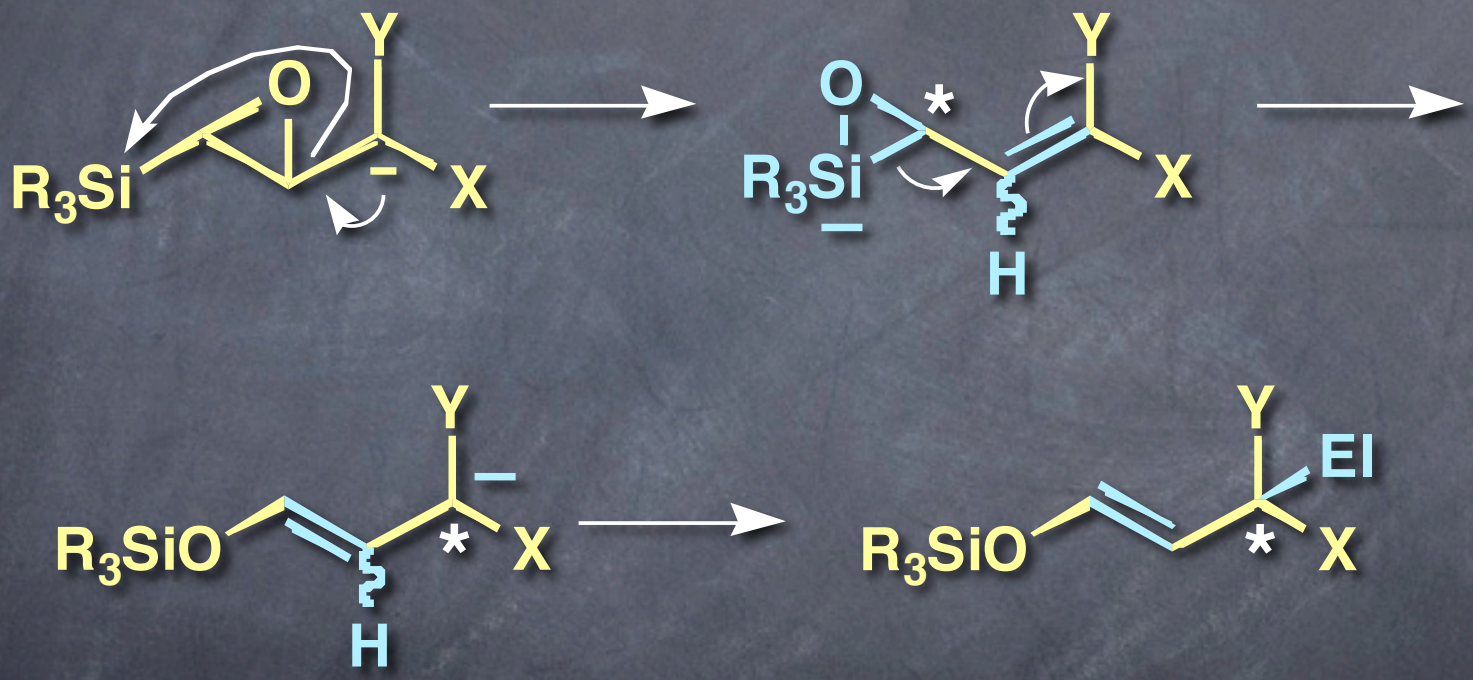
γ-*p*-Toluenesulfonyl-α,β-epoxysilane
A New and Practical Acrolein β-Anion Equivalent (3)



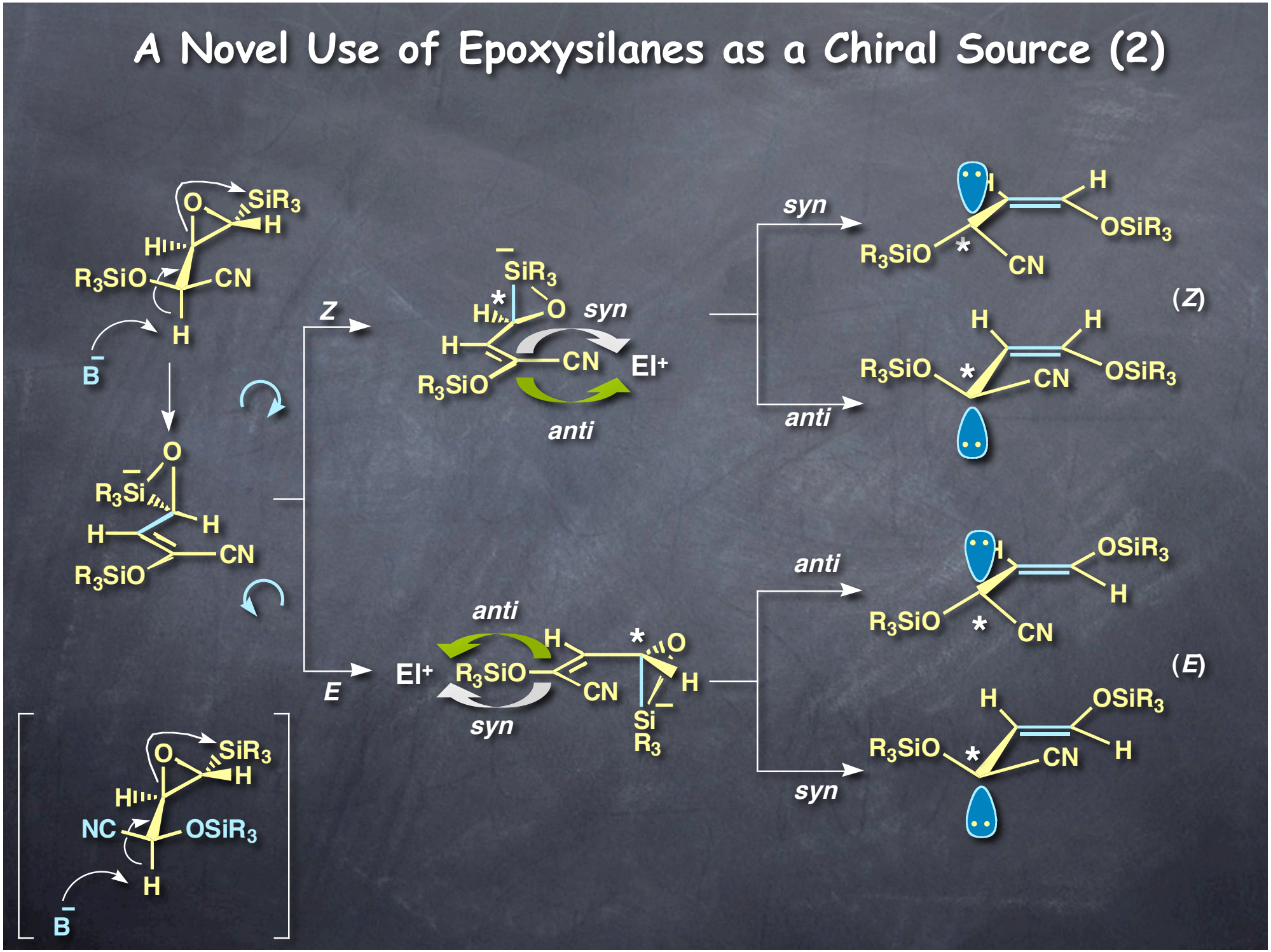
RCHO	yield (%)
$CH_3(CH_2)_4CH$	77
$(CH_3)_2CHCHO$	71
$(CH_3)_3CCHO$	80

Michiko Sasaki, Kei Takeda *Org. Lett.* **2004**, *6*, 4849-4851.

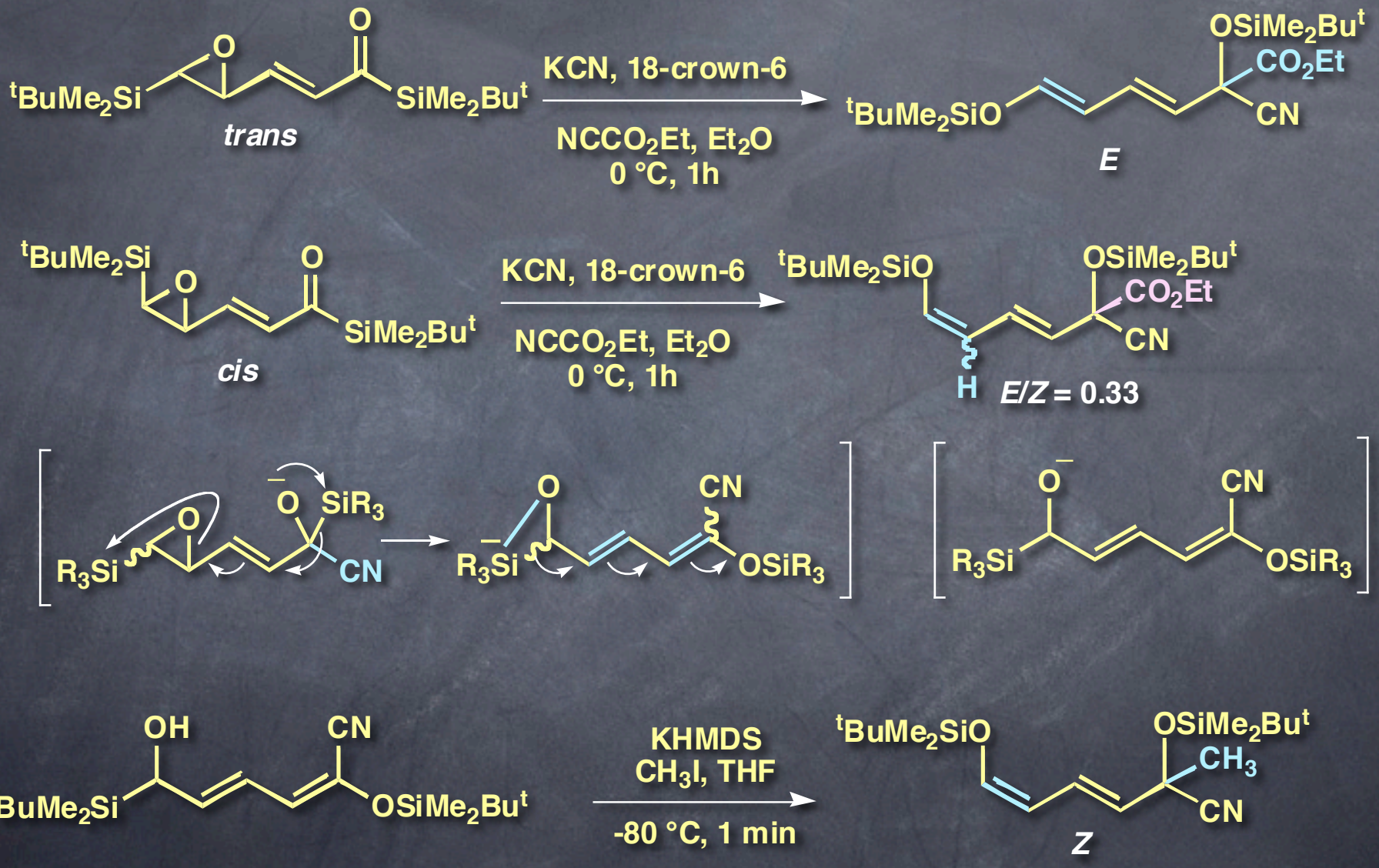
A Novel Use of Epoxysilanes as a Chiral Source (1)



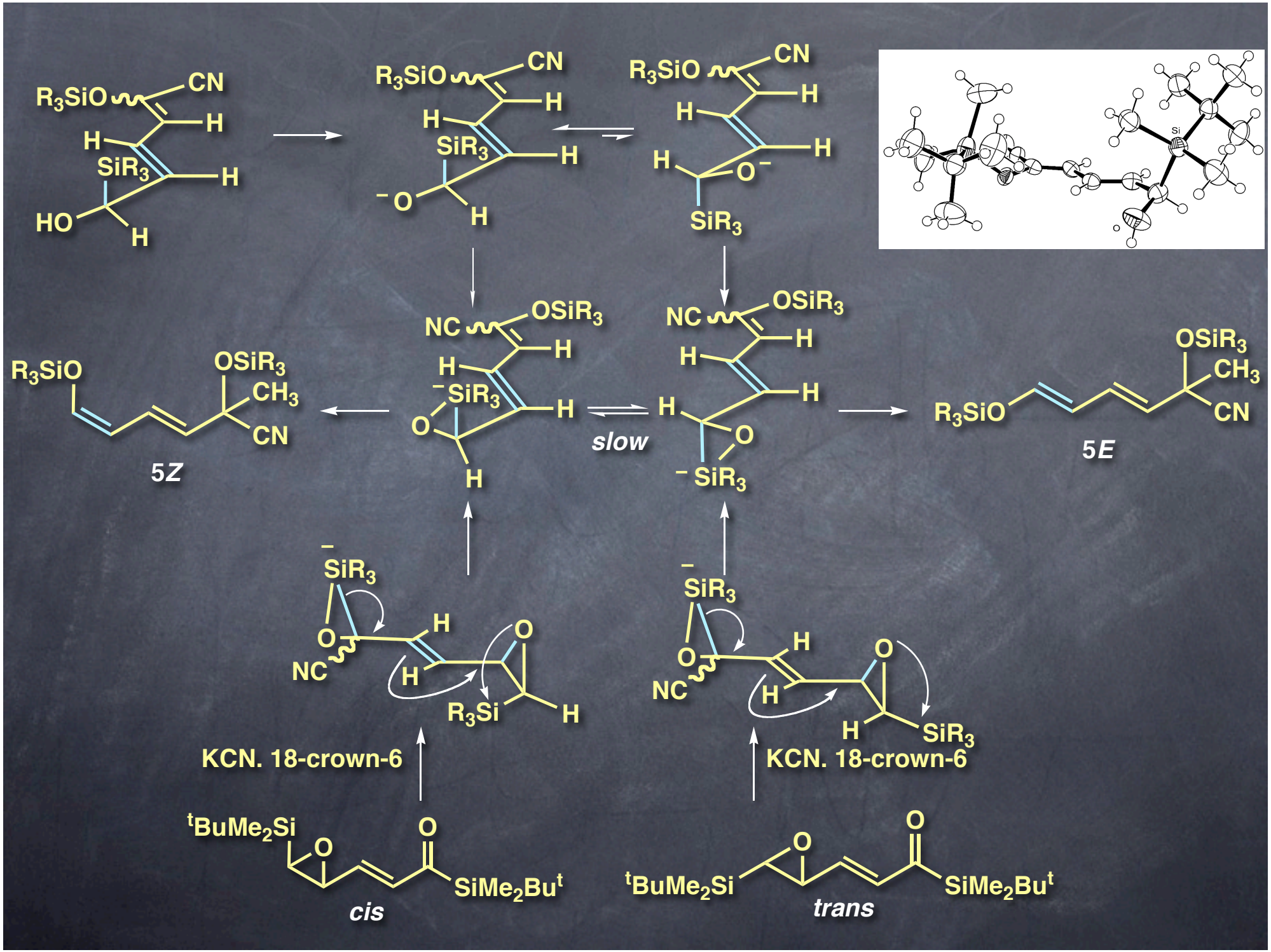
A Novel Use of Epoxysilanes as a Chiral Source (2)



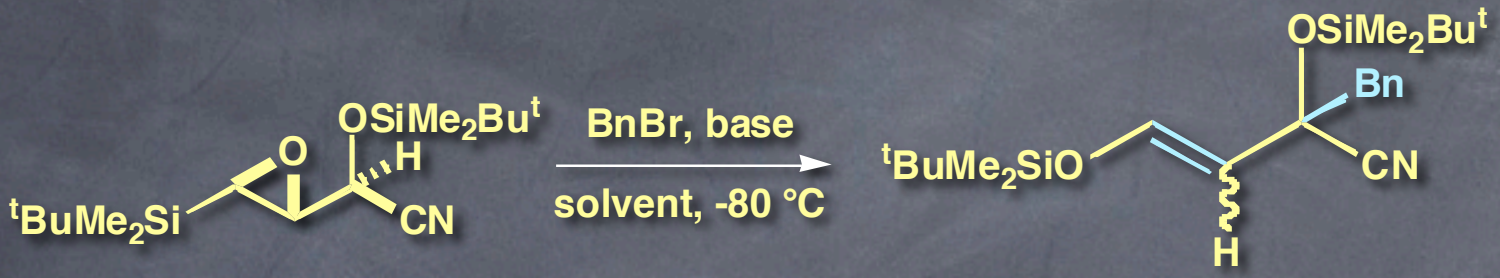
A Novel Use of Epoxysilanes as a Chiral Source (3)

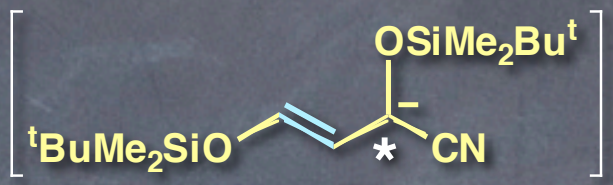


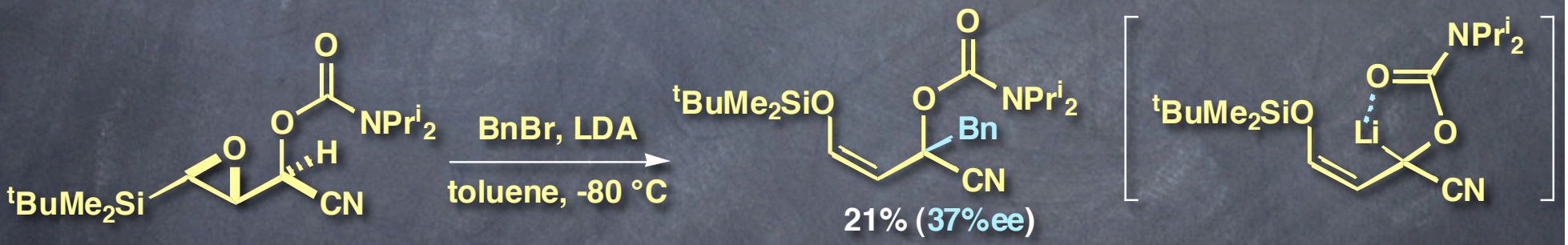
Koudai Tanaka, Kei Takeda *Tetrahedron Lett.* **2004**, *45*, 7859-7861
Koudai Tanaka, Kei Takeda. *unpublished results*

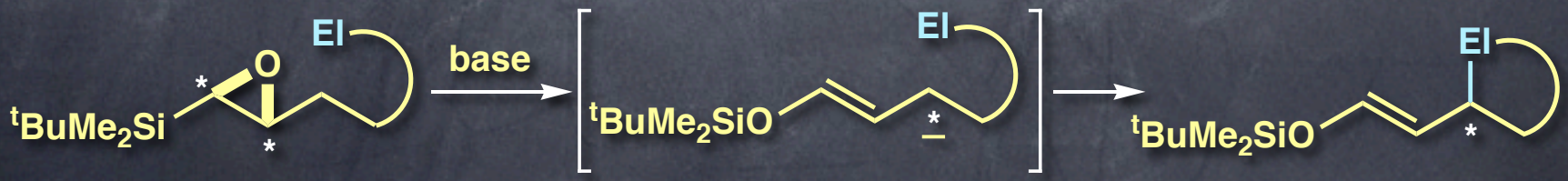

R3SiO
CN
H
SiR3
HO
O
OSiR3
NC
CH3
5Z
5E
slow
KCN. 18-crown-6
KCN. 18-crown-6
tBuMe2Si
SiMe2But
cis
trans
Si

Chirality Transfer of Epoxides to Carbanions



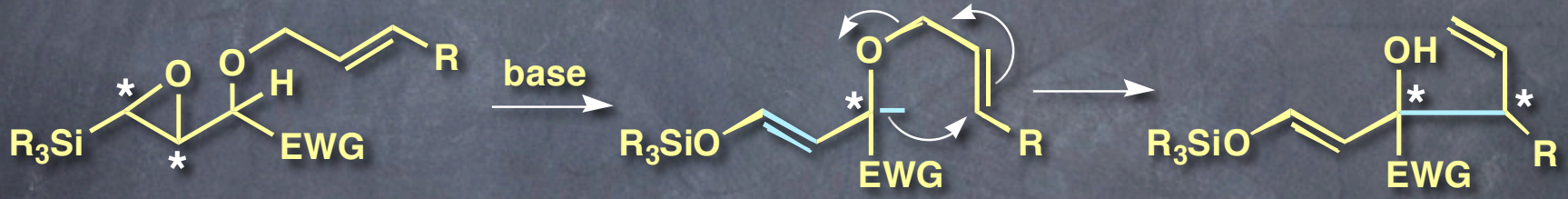




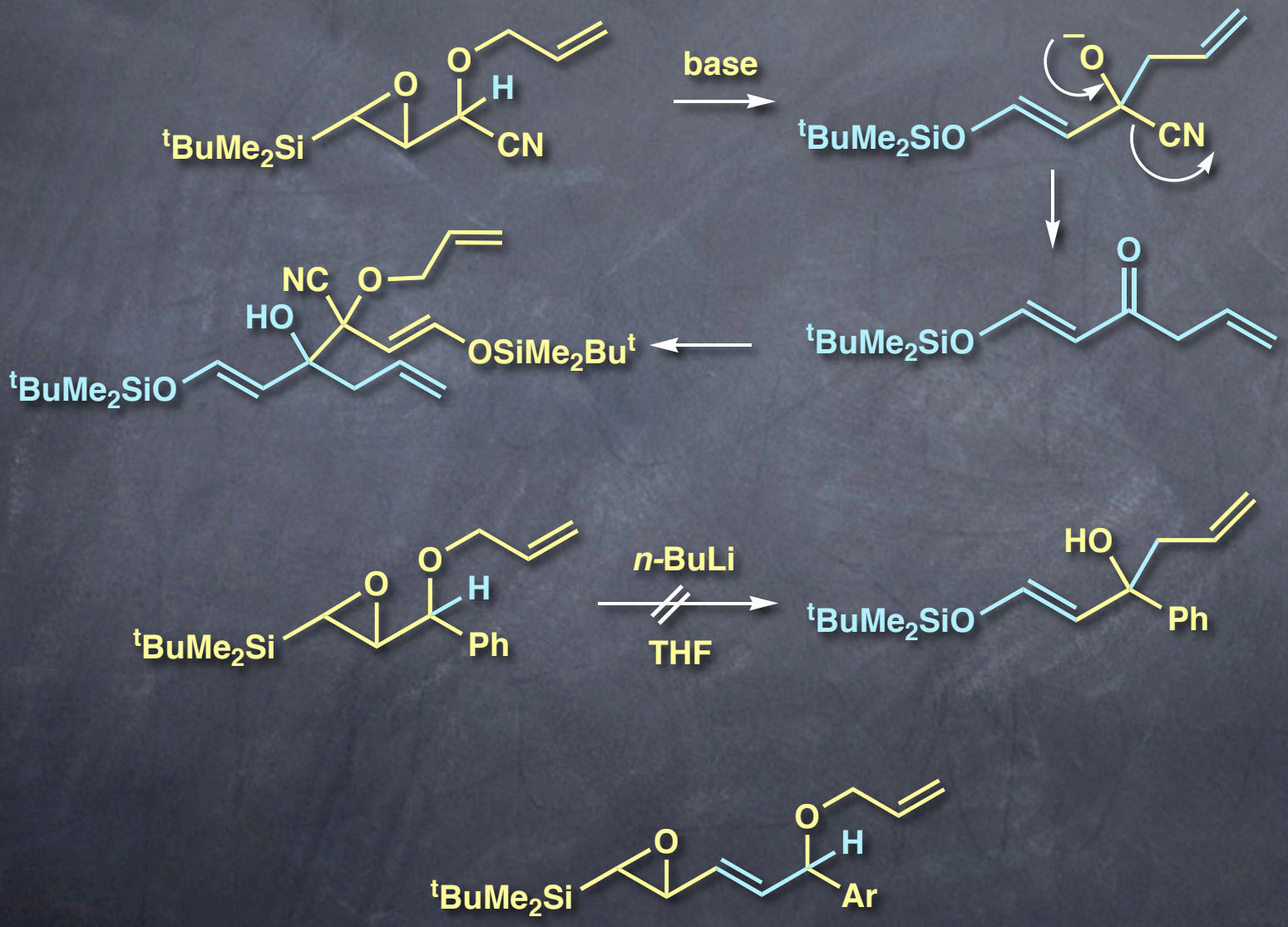


Eiji Kawanishi, Kei Takeda *unpublished results*

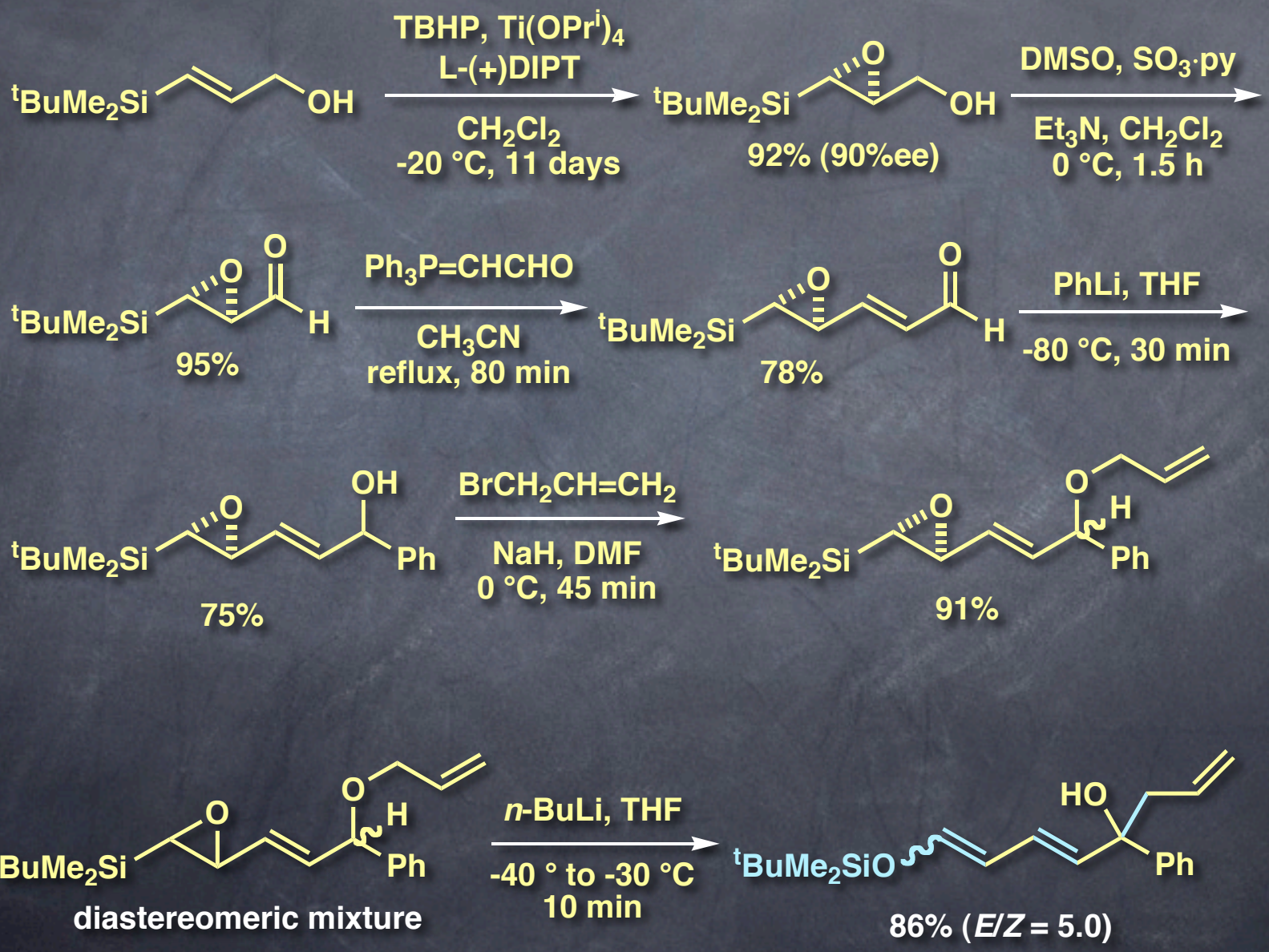
Intramolecular Trapping of Chiral cabanions by [2,3] Wittig Rearrangement (1)



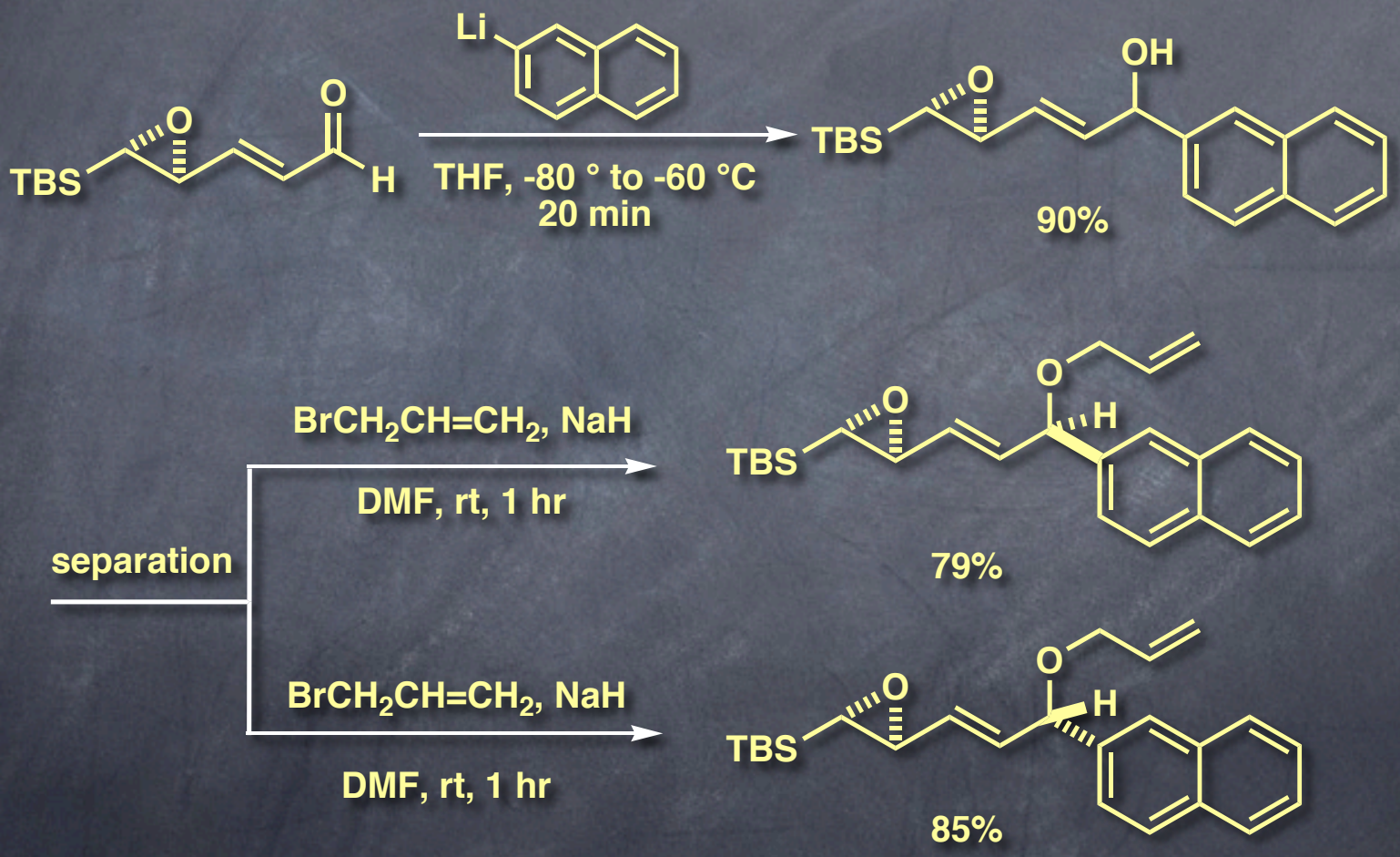
Intramolecular Trapping of Chiral Carbanions by [2,3]-Wittig Rearrangement (2)



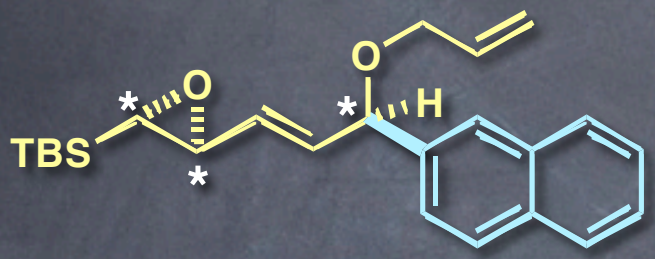
Intramolecular Trapping of Chiral Carbanions by [2,3]-Wittig Rearrangement (3)



Intramolecular Trapping of Chiral Carbanions by [2,3]-Wittig Rearrangement (4)



Intramolecular Trapping of Chiral cabanions by [2,3] Wittig Rearrangement (3)

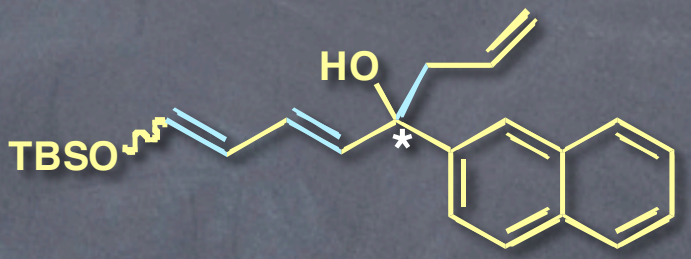


A (90%ee)

n-BuLi (1.5 eq)

Et_2O

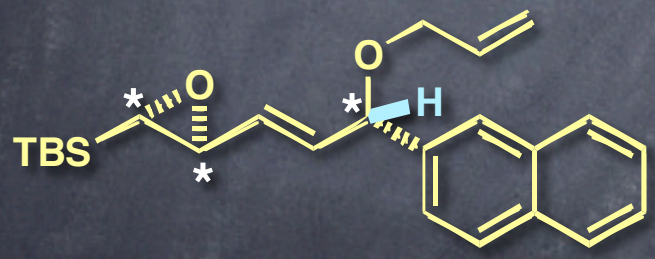
27 ° to 30 °C, 7 min



B (70% (*E*/*Z* = 0.19))

(*E*) 81%ee (90%ee)

(*Z*) 73%ee (81%ee)

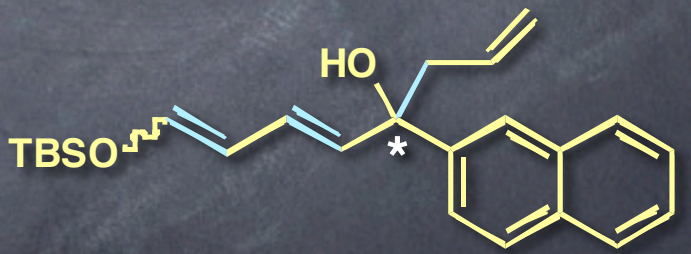


A' (90%ee)

n-BuLi (1.5 eq)

Et_2O

27 ° to 30 °C, 7 min



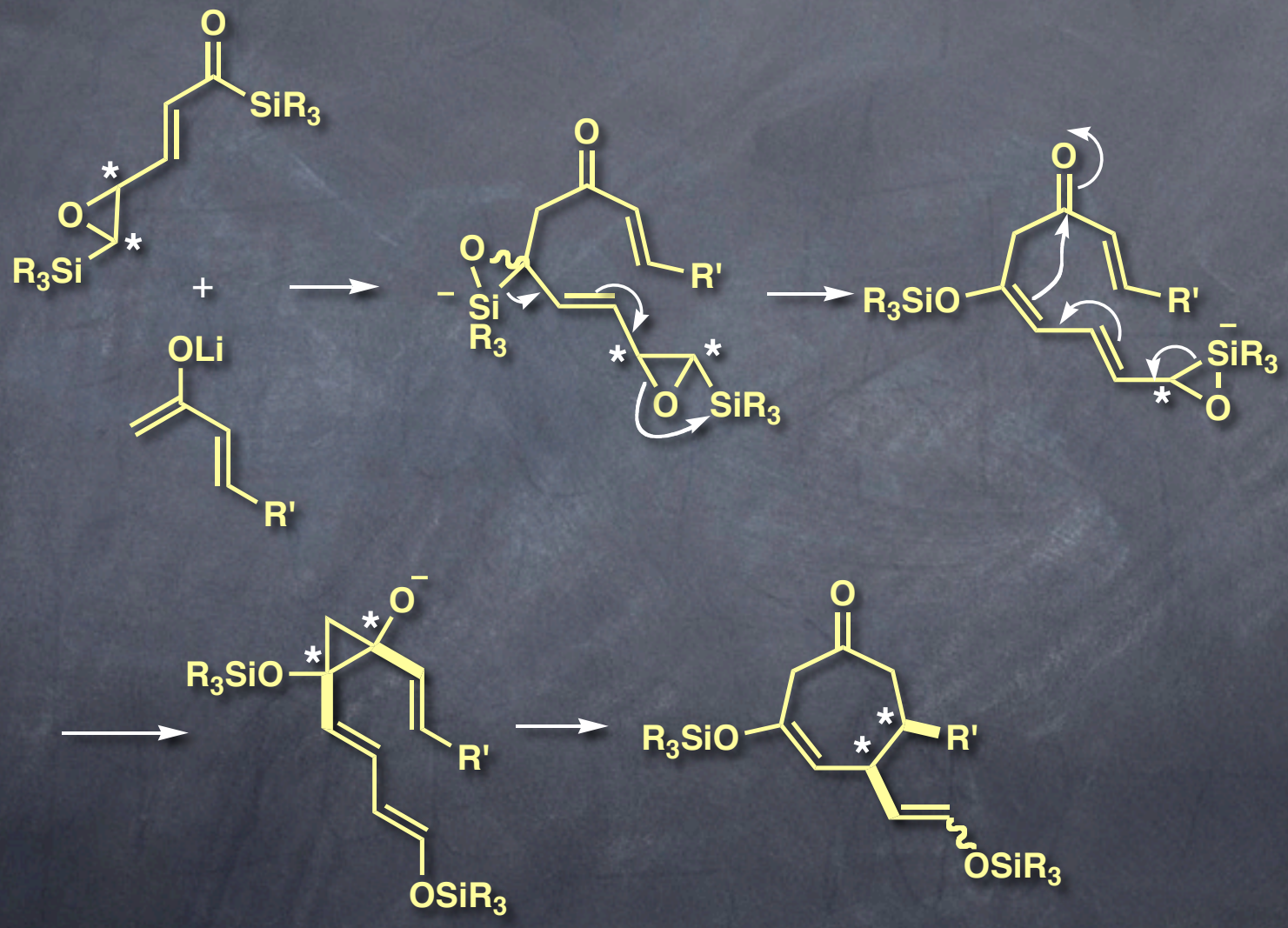
ent-B (77% (*E*/*Z* = 2.2))

(*E*) 81%ee (90%ee)

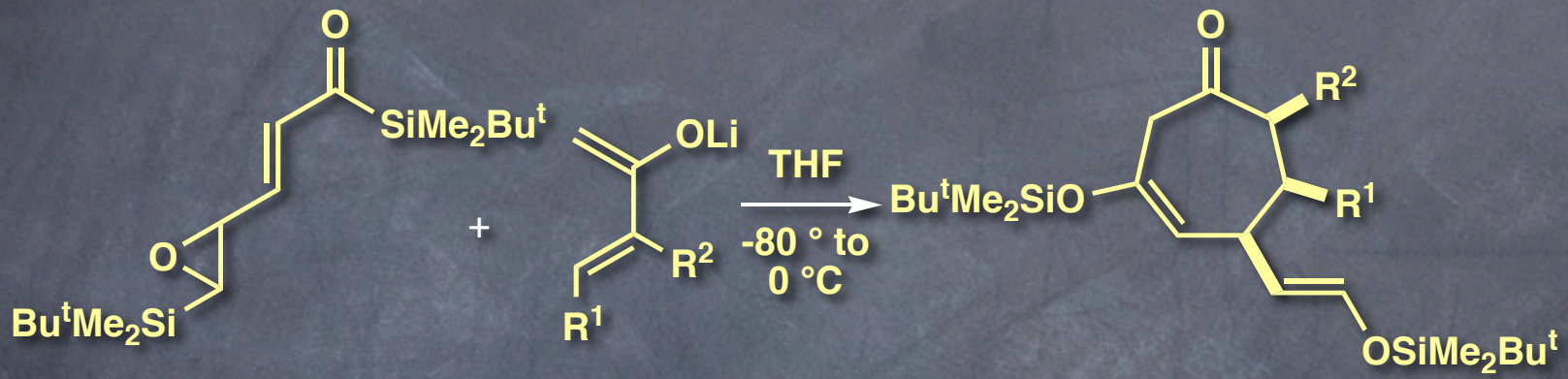
(*Z*) 56%ee (62%ee)

Michiko Sasaki, Kei Takeda, *unpublished results*

Intramolecular Trapping of Chiral cabanions Using [3 + 4] Annulation (1)

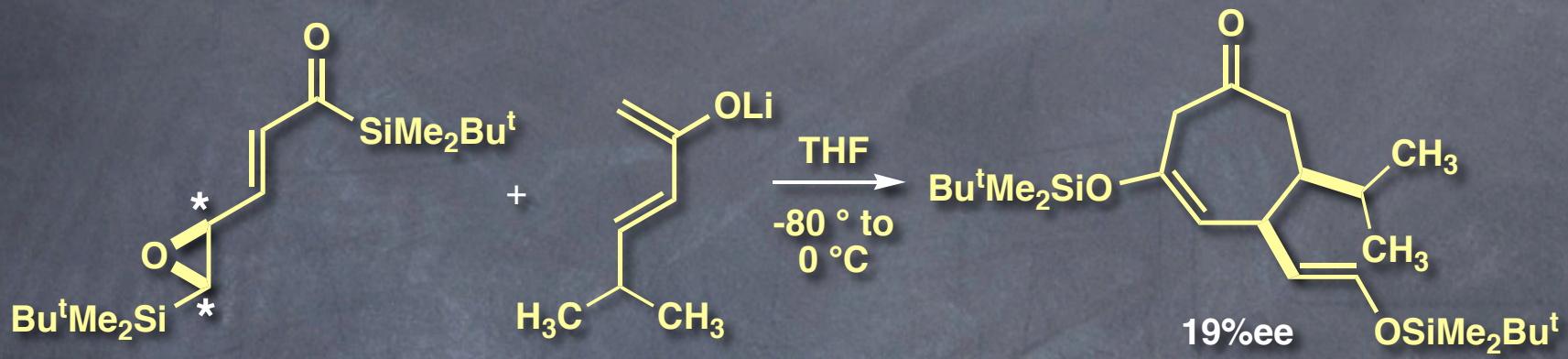


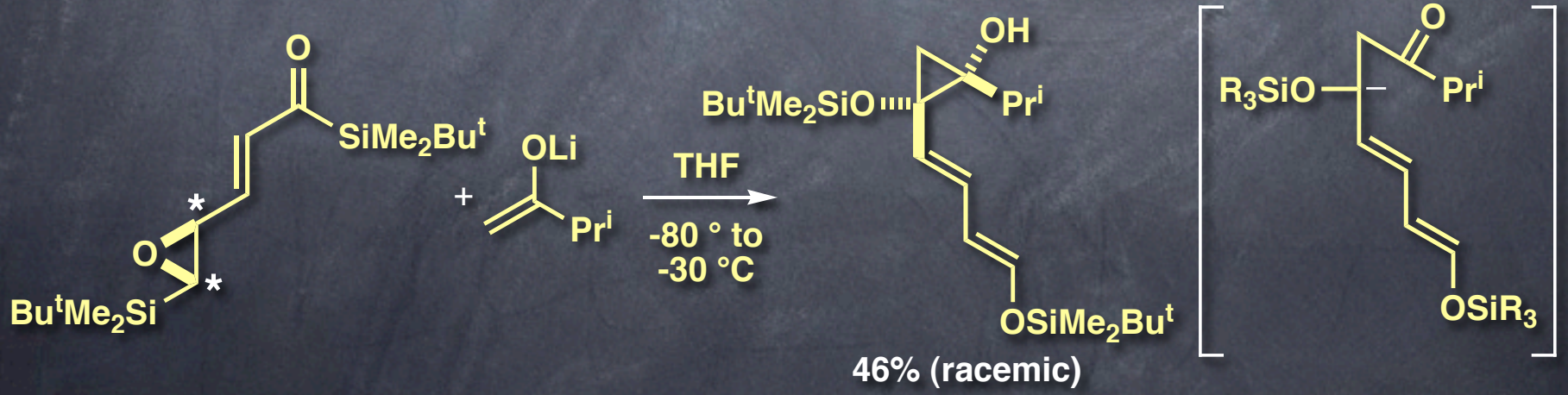
Intramolecular Trapping of Chiral cabanions Using [3 + 4] Annulation (2)



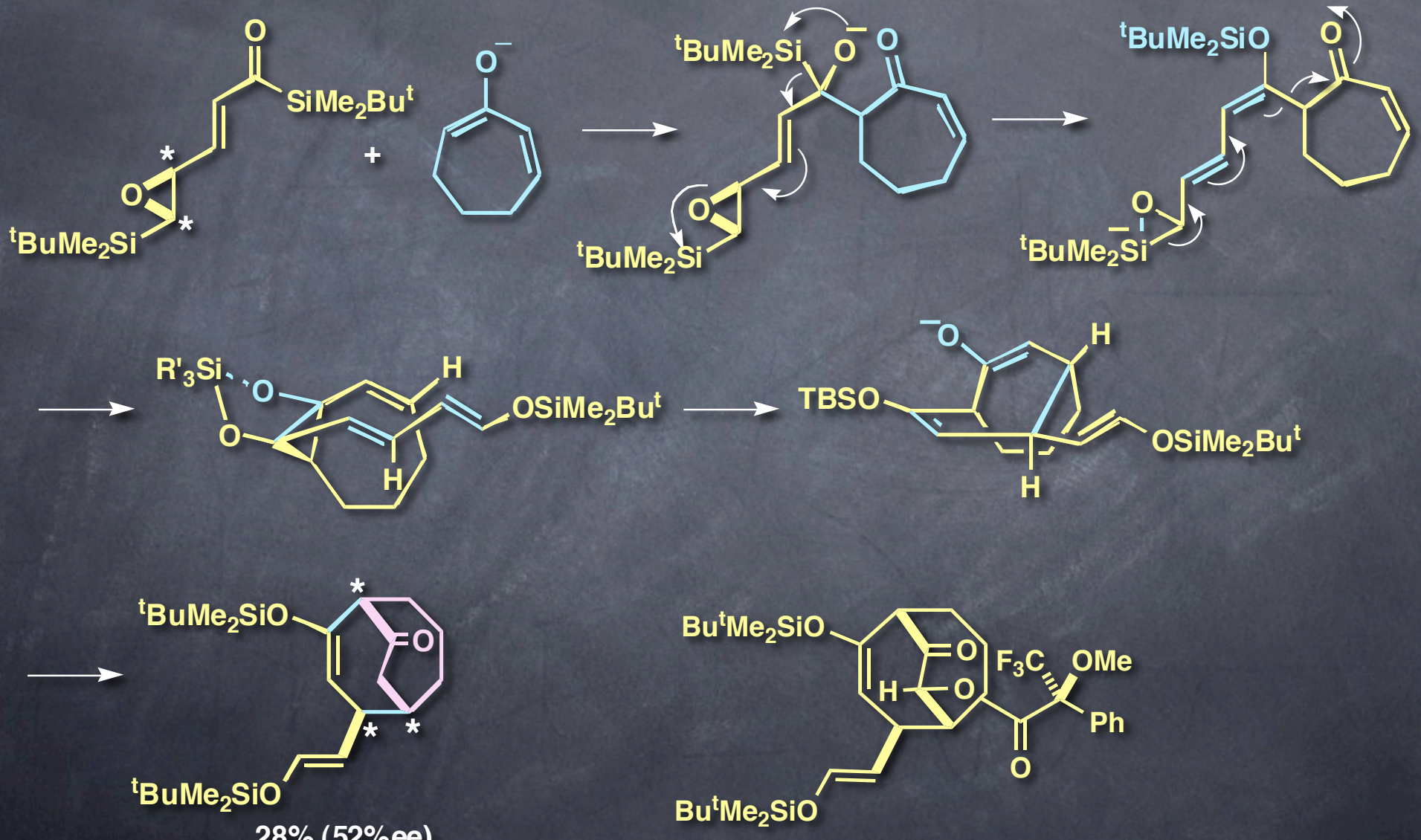
R^1	R^2	yield (%)
$CHMe_2$	H	60
$(CH_2)_4Me$	H	30
OMe	H	35
Bn	H	31
$-(CH_2)_4-$		55

Intramolecular Trapping of Chiral cabanions Using [3 + 4] Annulation (3)

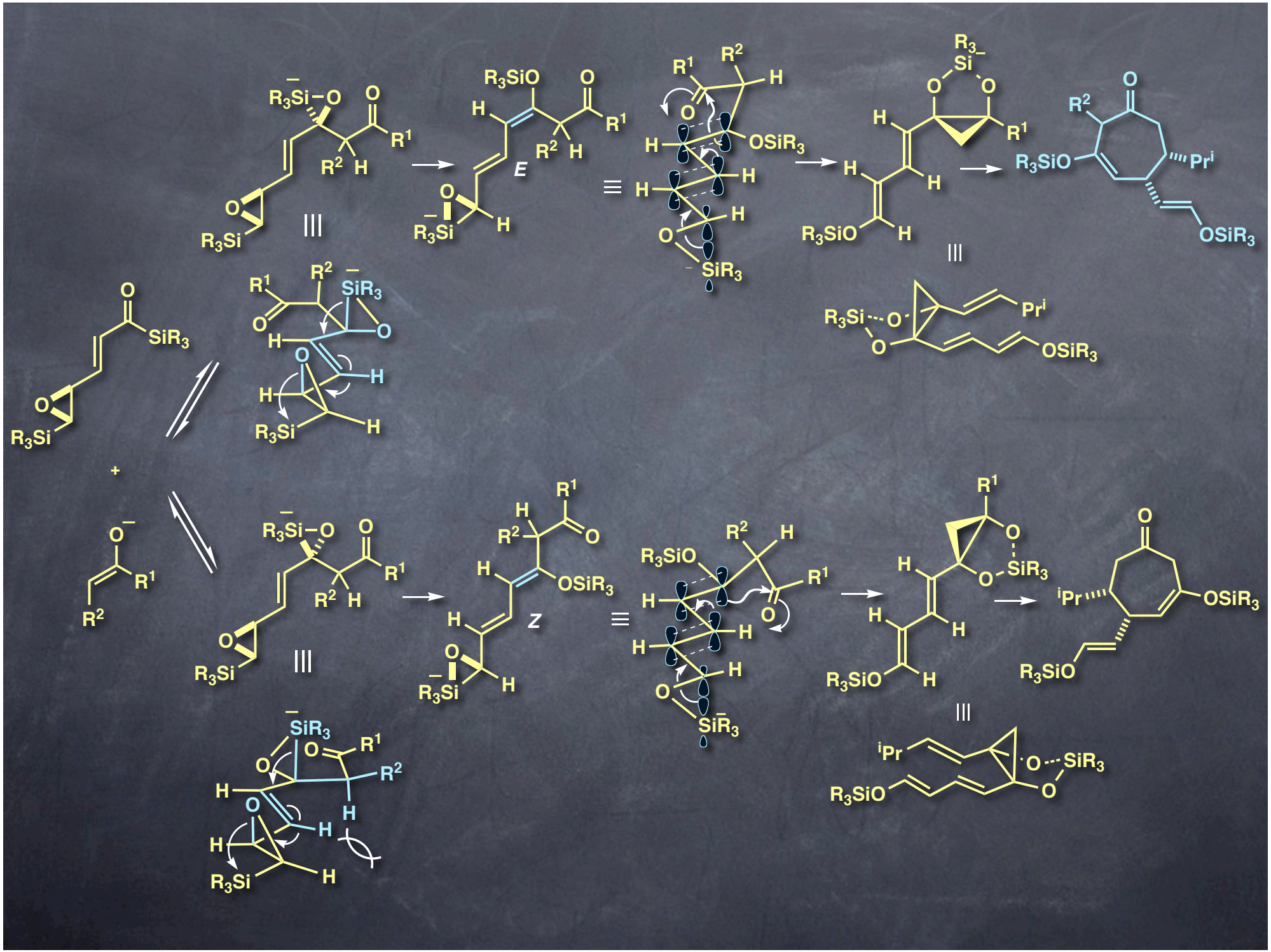




Intramolecular Trapping of Chiral cabanions Using [3 + 4] Annulation (4)



Yoshio Nakai, Kei Takeda *unpublished results*


R3Si
SiR3
R1
R2
E
Z
OSiR3
Pri
iPr

Development, Scope, Limitation and Mechanistic Studies

Michiko Sasaki

Asymmetric Version (Intermolecular)

Eiji Kawanishi

Reactions with Bis-Electrophiles

Tatsuya Matumoto

Wittig-Type Reaction

Michiko Sasaki, Mai Horai

Extention to One-Carbon Homologues

Seigo Okugawa

Acrolein β-Anion Equivalent

Michiko Sasaki

Tandem Asymmetric [2,3]-Wittig Rearrangement

Michiko Sasaki

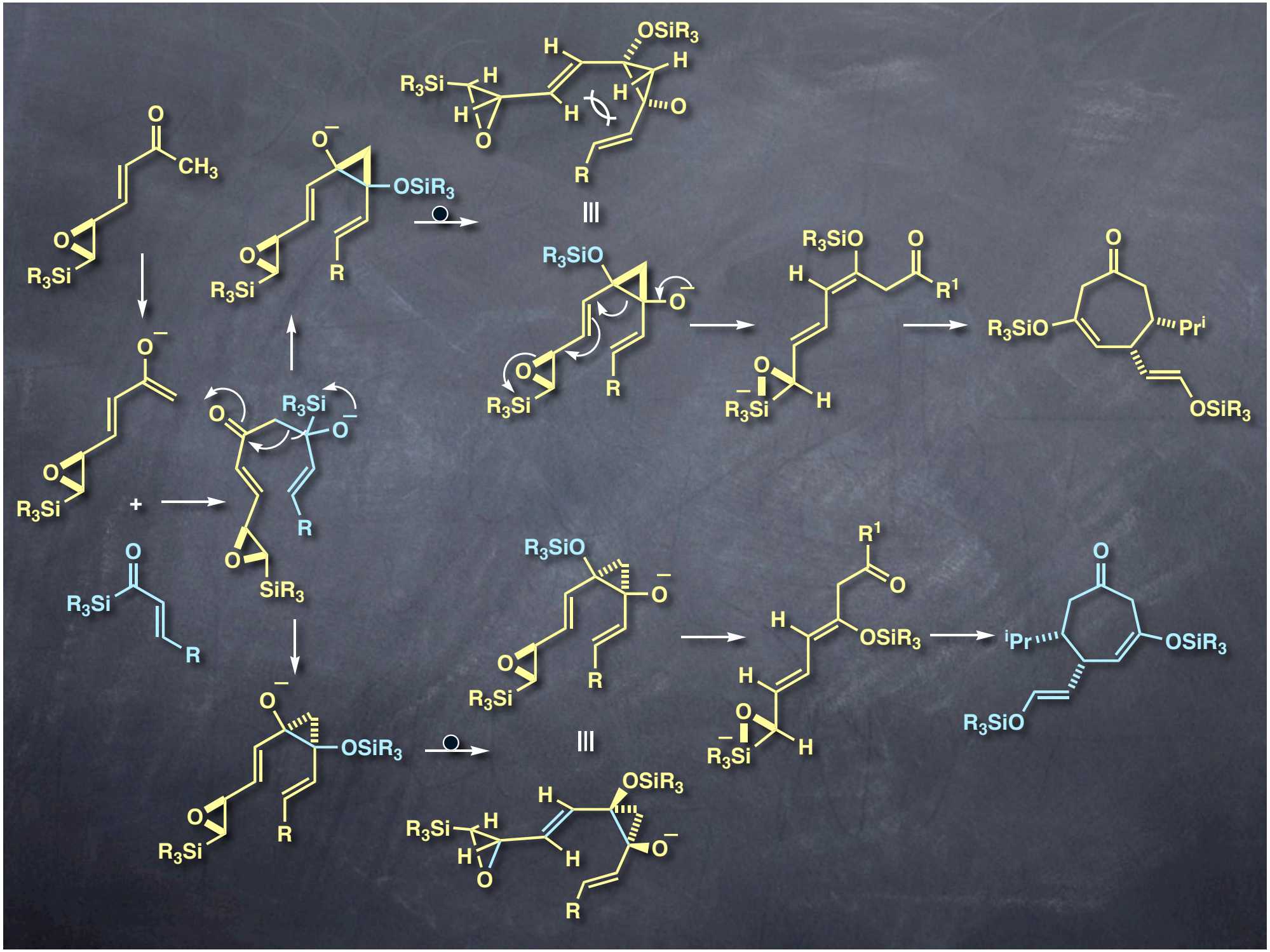
Reactions with KCN/18-crown-6

Koudai Tanaka

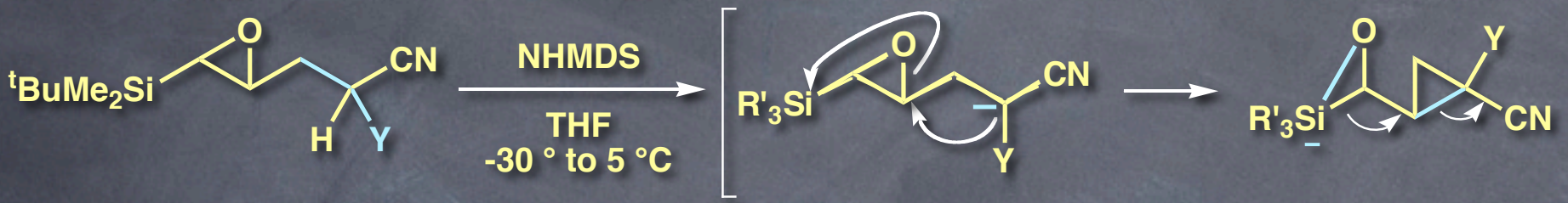
Asymmetric [3 + 4] Annulation

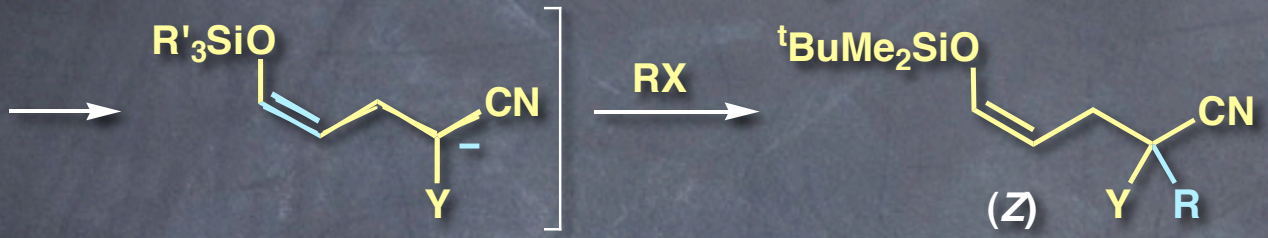
Yoshio Nakai

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

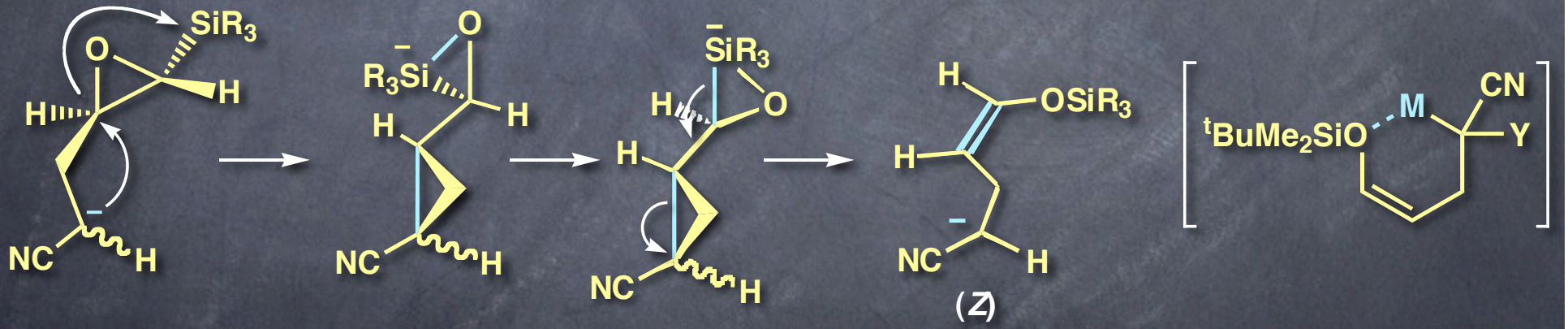

O
CH3
R3Si
O
O−
OSiR3
R
+
SiR3
III
H
R3SiO
R1
Pri
iPr

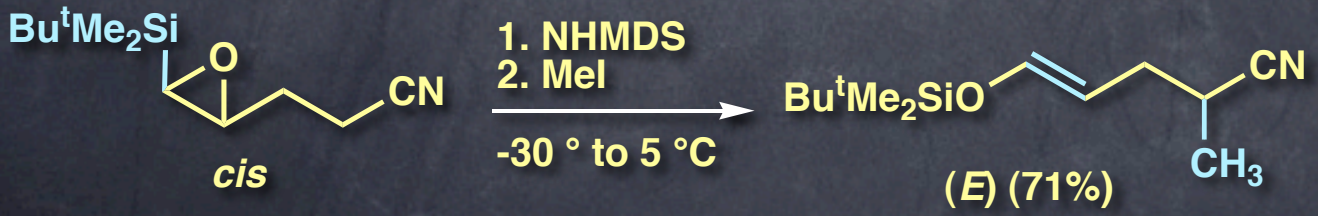
Nitrile Anion Cyclization with Epoxysilanes Followed by Brook Rearrangement/Ring-Opening of Cyclopropane Nitriles/Alkylation





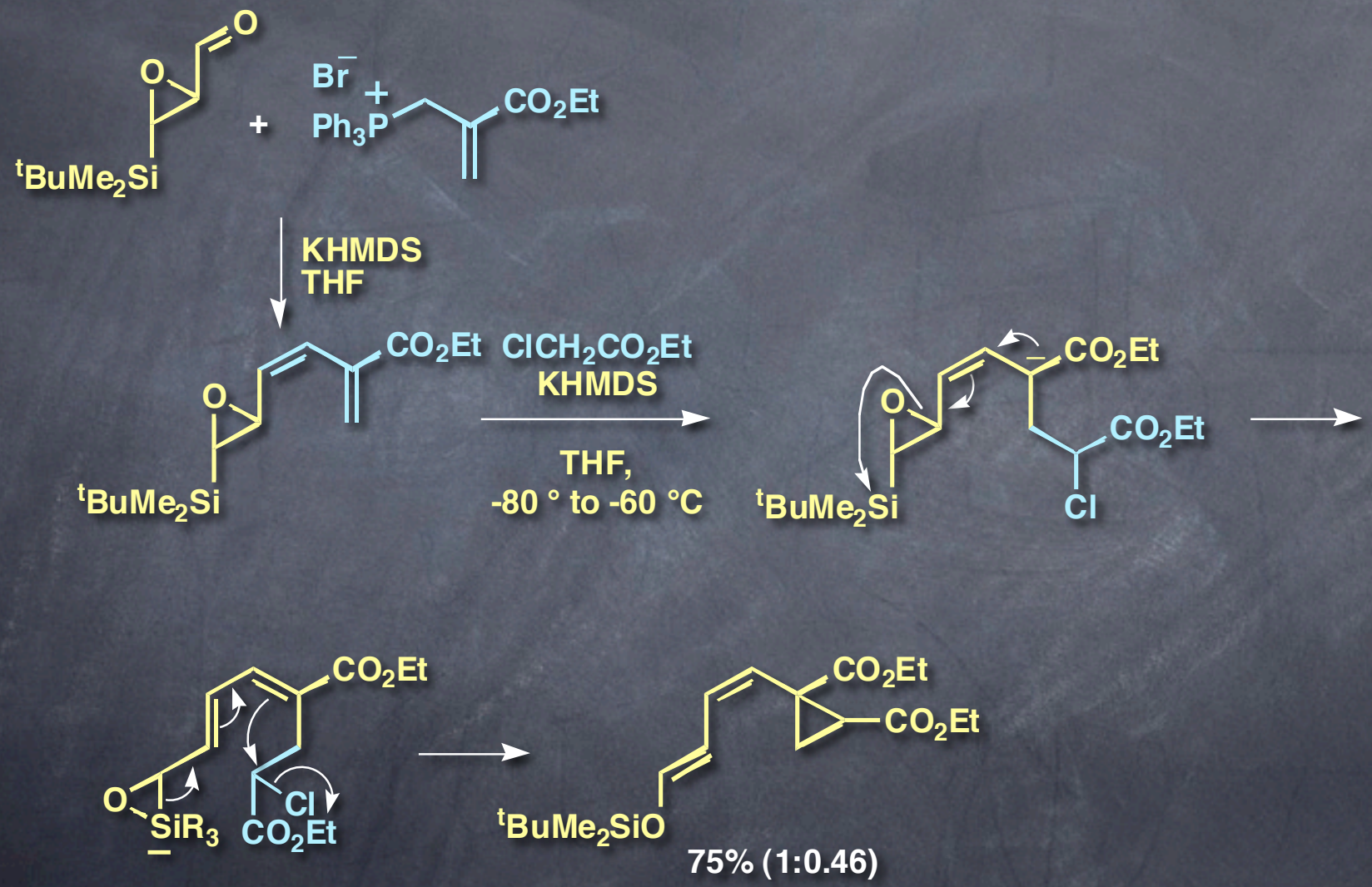
Y = H: 73% (R = H)
Y = Ph: 65-84%
(R = alkyl (1°, 2°), Bn





Seigo Okugawa, Kei Takeda *Org. Lett.* **2004**, *6*, 2973-2975.

Nitrile Anion Cyclization with Epoxysilanes Followed by Brook Rearrangement/Ring-Opening of Cyclopropane Nitriles/Alkylation



Noriko Okamoto, Kei Takeda, unpubished results