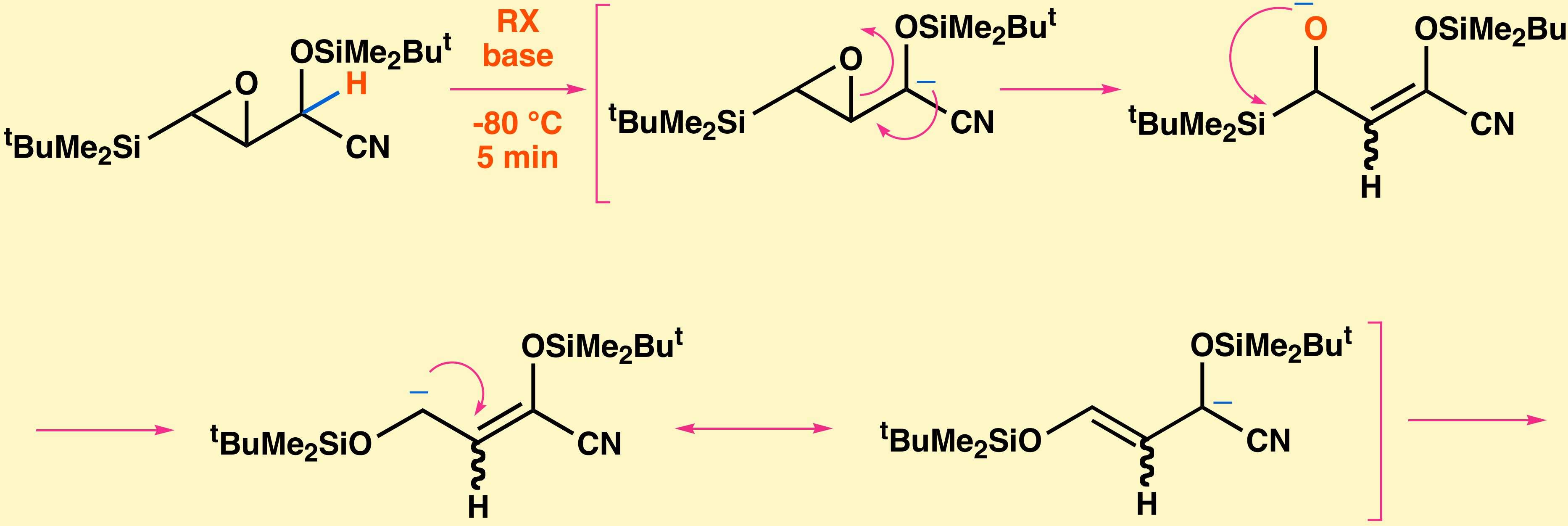
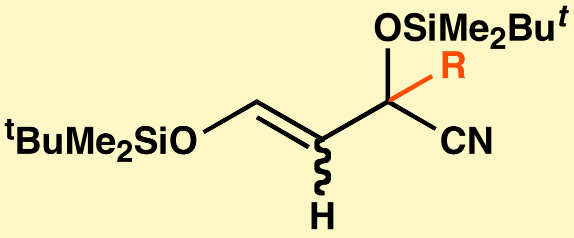
エポキシドからカルバニオンへの不斉転写：エポキシシランの連続的開環－転位反応を利用するアルキル化反応

広島大学大学院医歯薬学総合研究科
○佐々木　道子，川西　英治，中井　良雄
松本　龍弥，武田　敬

Alkylation of Metalated *O*-Silyl Cyanohydrins of β-Silyl-α,β-Epoxyaldehydes



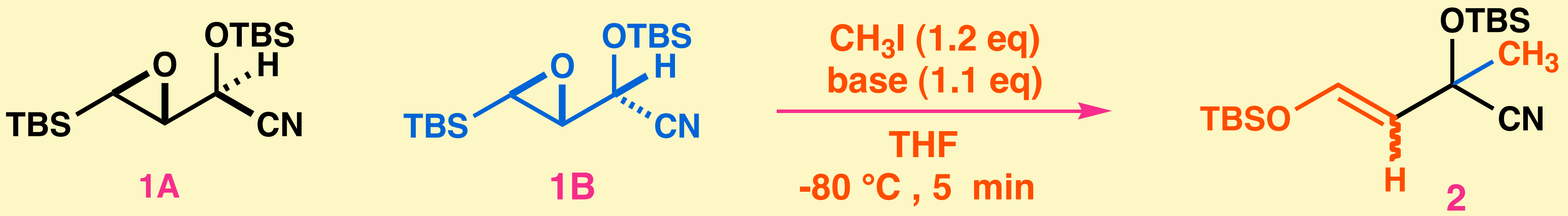


R = Me, Et, *i*-Pr, $CH_2CH{=}CH_2$, CH_2Ph

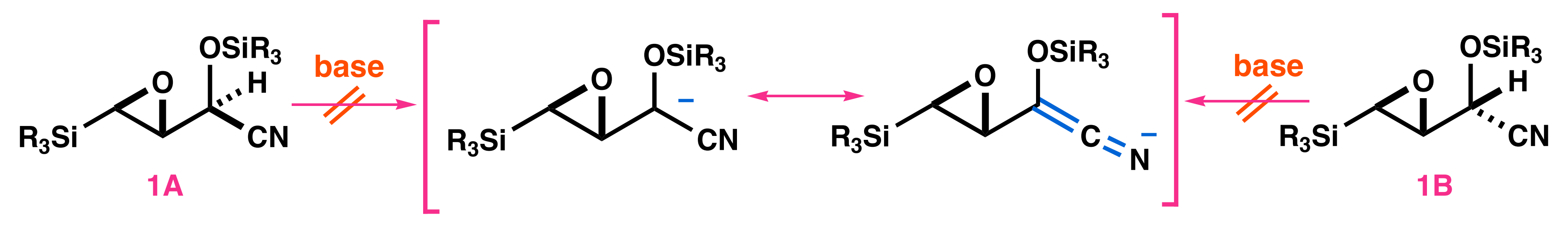
base	yield (%)
LiN^iPr_2 (LDA)	58 - 98
$LiN(SiMe_3)_2$ (LHMDS)	15 - 90
$NaN(SiMe_3)_2$ (NHMDS)	80 - 98
$KN(SiMe_3)_2$ (KHMDS)	80 - 95

Takeda, K.;Kawanishi, E.;Sasaki, M.;Takahasi, Y.;Yamaguchi, K. *Org*. *Lett*. **2002**, 4, 1511-1514.

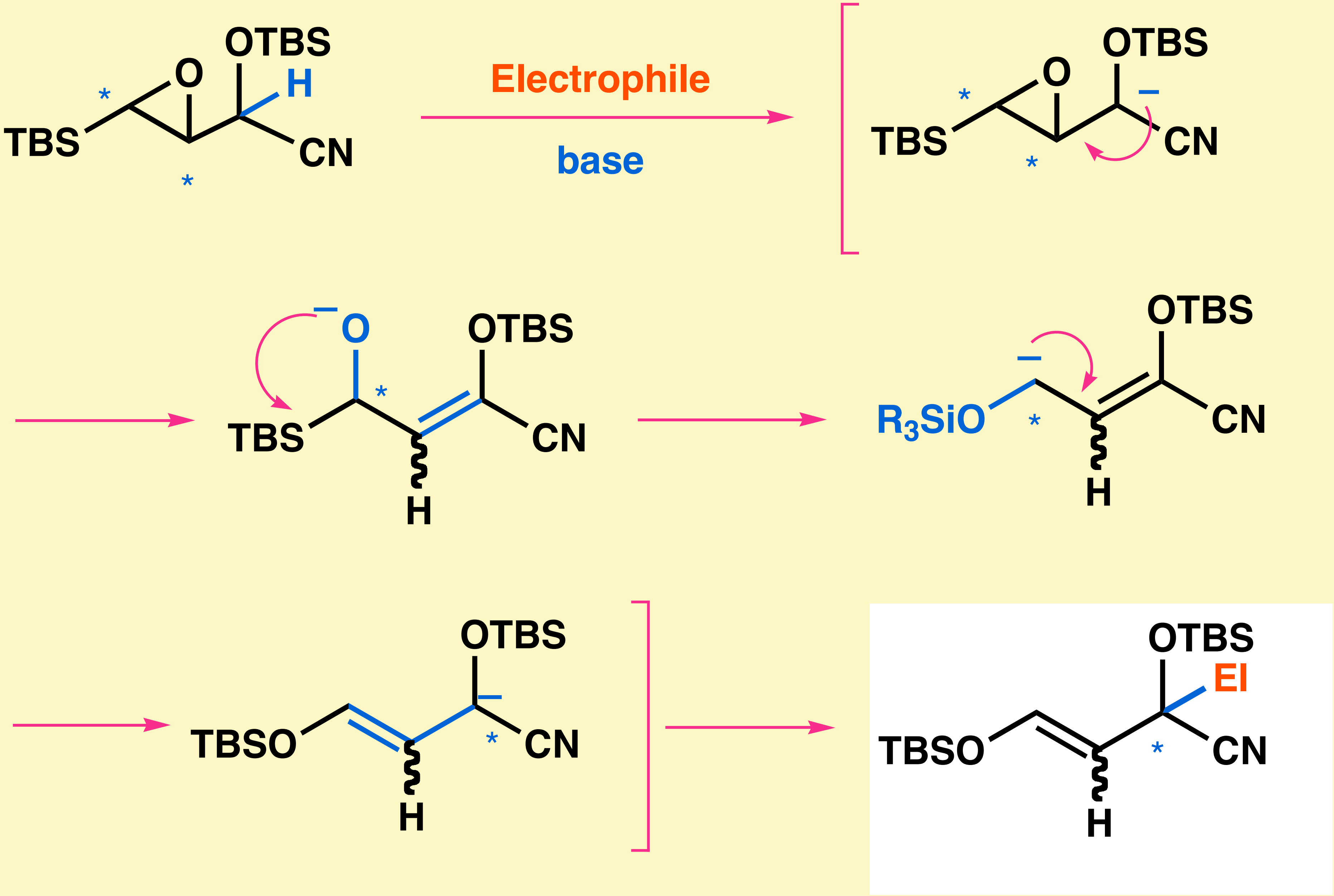
Methylation of Metalated *O*-Silyl Cyanohydrins of *trans*-β-Silyl-α,β-epoxyaldehydes



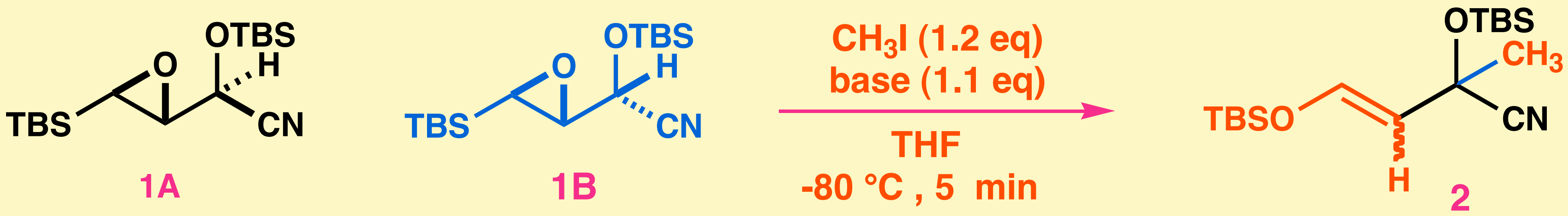
base	diastereomer	yield (%)	*E/Z*	SM
LDA (in hexane/THF)	1A	82	2.5	
	1B	84	22.0	
LiN(SiMe$_3$)$_2$ (1.0M in THF)	1A	44	23.0	40
	1B	83	31.0	
NaN(SiMe$_3$)$_2$ (1.0M in THF)	1A	91	40.0	
	1B	92	47.0	
KN(SiMe$_3$)$_2$ (0.5M in toluene)	1A	84	0.9	
	1B	87	9.7	



Alkylation of Asymmetric *O*-Silyl Cyanohydrins of β-Silyl-α,β-epoxyaldehydes

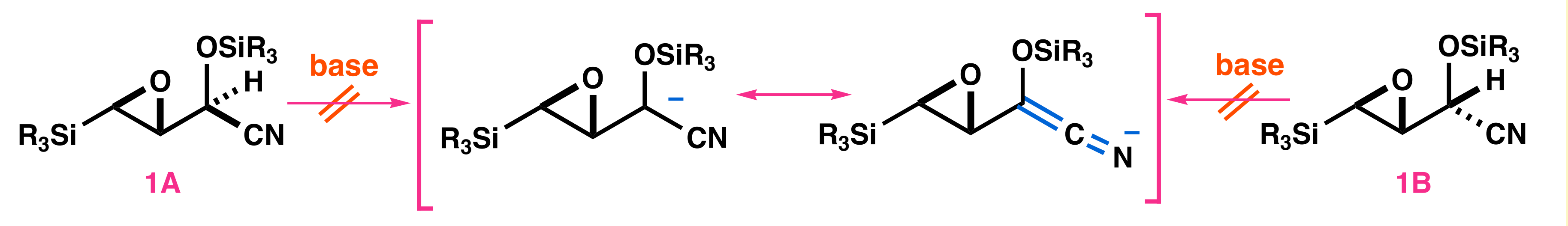


Methylation of Metalated *O*-Silyl Cyanohydrins of *trans*-β-Silyl-α,β-epoxyaldehydes

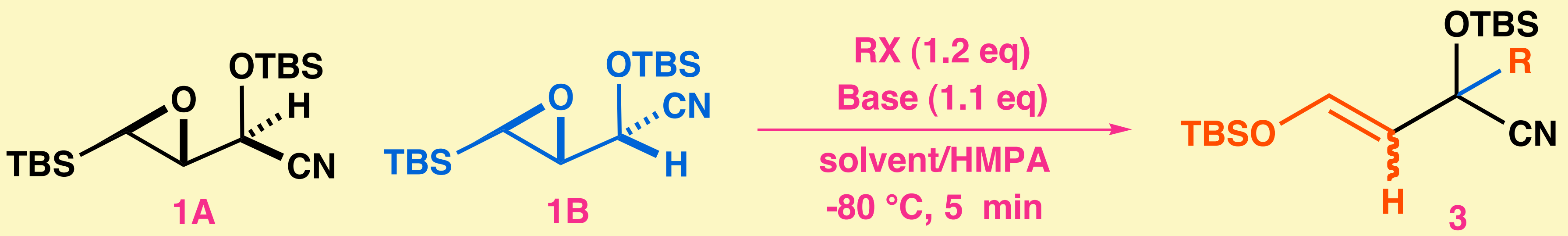


CH_3I (1.2 eq)
base (1.1 eq)
THF
-80 °C , 5 min

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	



Solvent Effect on *E*/*Z* Selectivity

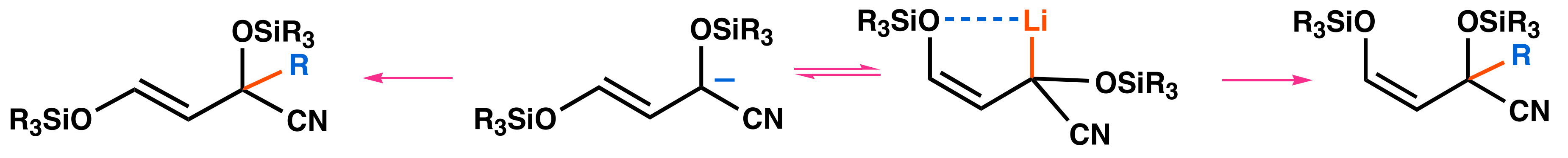


solvent	SM	yield (%)	E/Z
hexane	1A	93	1.5
	1B	78	6.0
ether	1A	84	1.9
	1B	77	28.0
toluene	1A	86	1.0
	1B	83	24.0
THF	1A	85	28.0
	1B	84	52.0

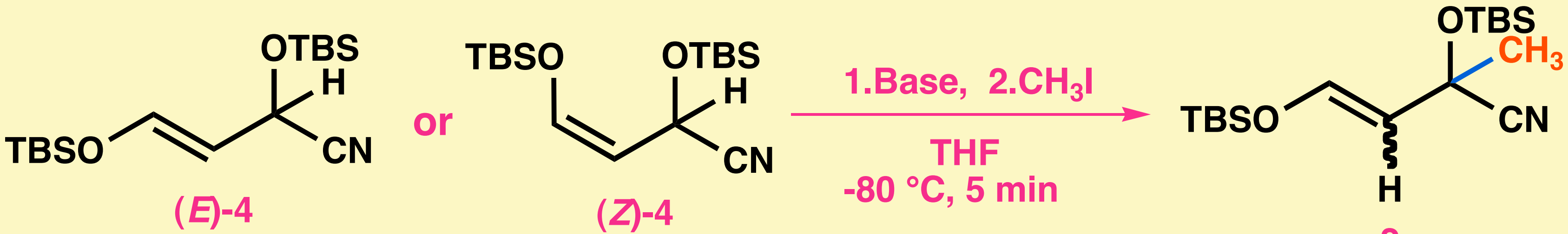
Base: NHMDS, RX: BnBr

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

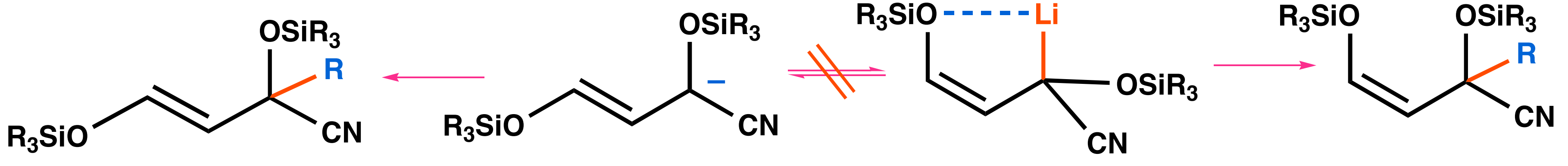


(*E*)-4

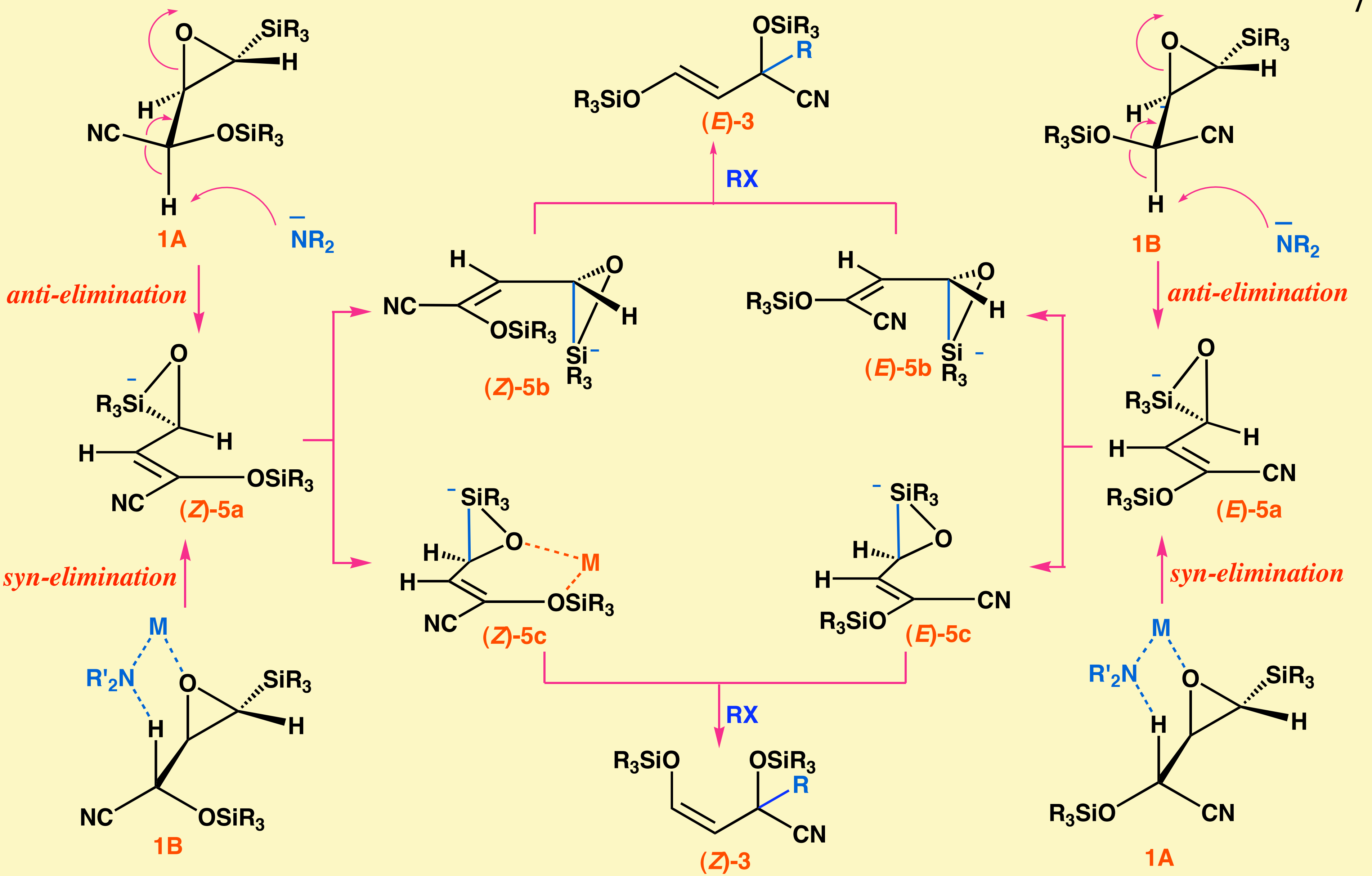
(*Z*)-4

2

		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

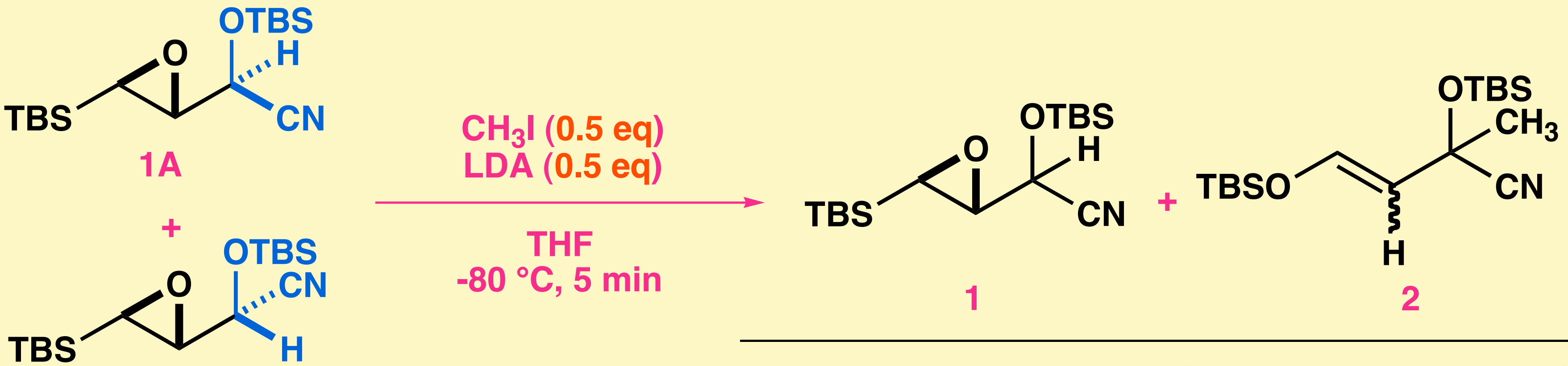


A Proposed Reaction Pathway



1A $\xrightarrow{\text{LDA}}$ $E/Z = 2.5$ 1B $\xrightarrow{\text{LDA}}$ $E/Z = 22.0$

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



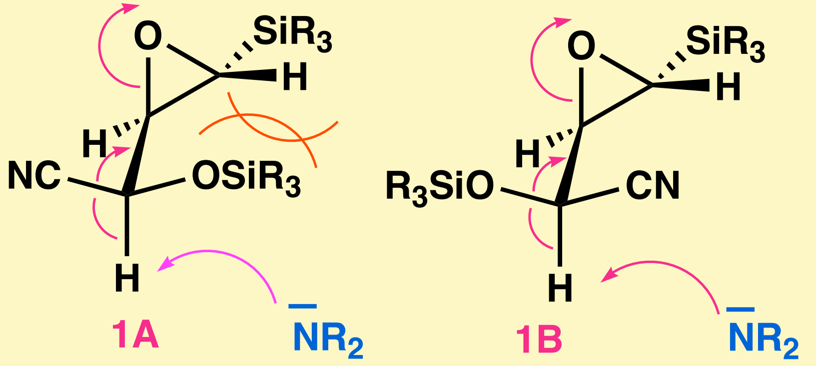
CH_3I (0.5 eq)
LDA (0.5 eq)

THF
-80 °C, 5 min

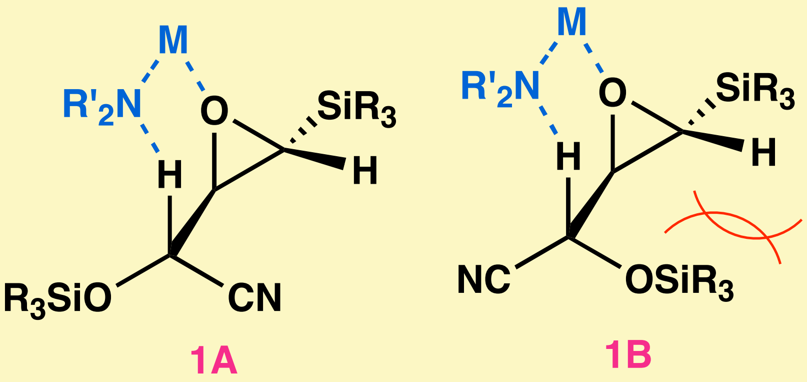
1A:1B = 1.00:1.04

	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

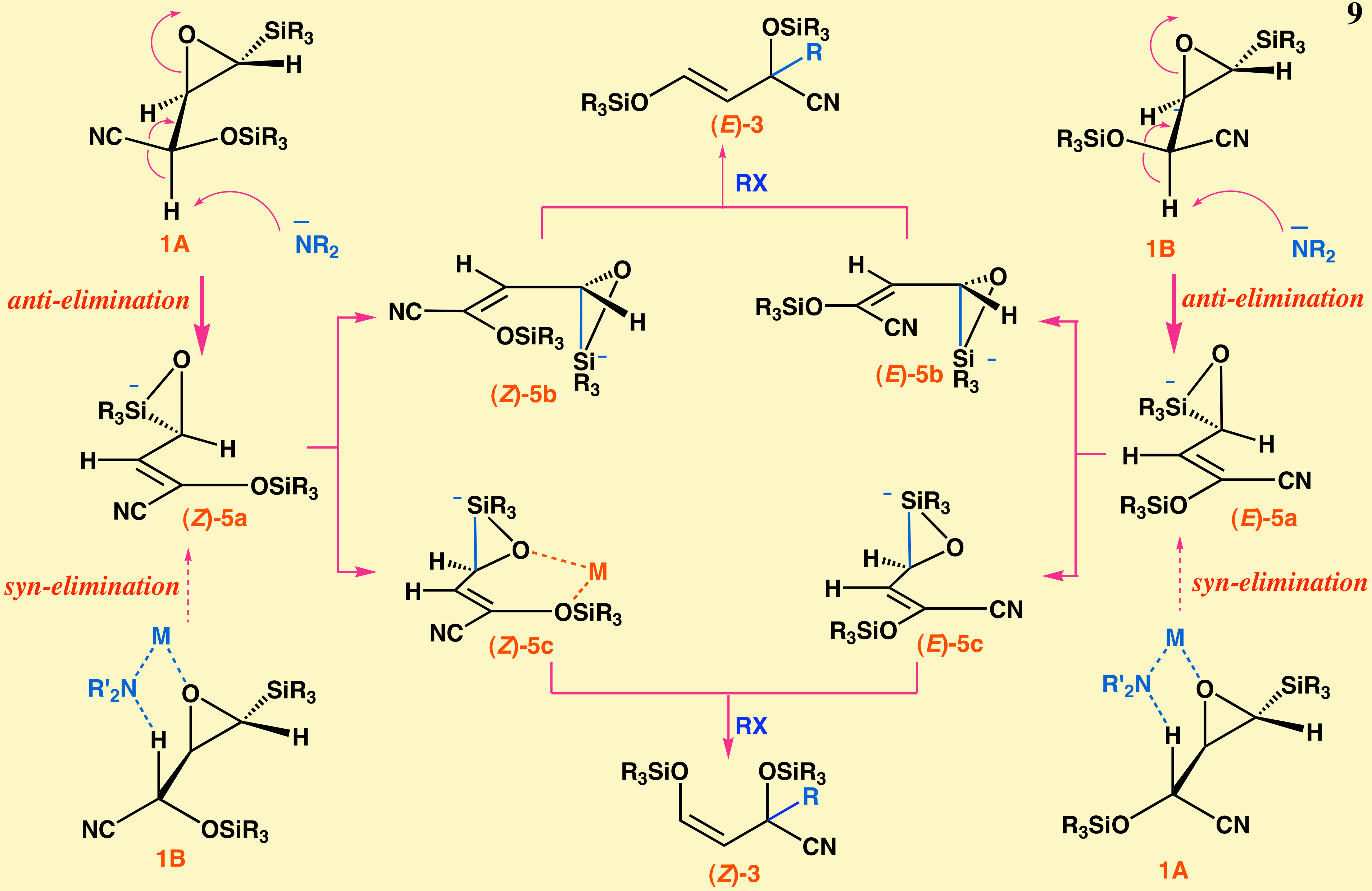


syn-elimination



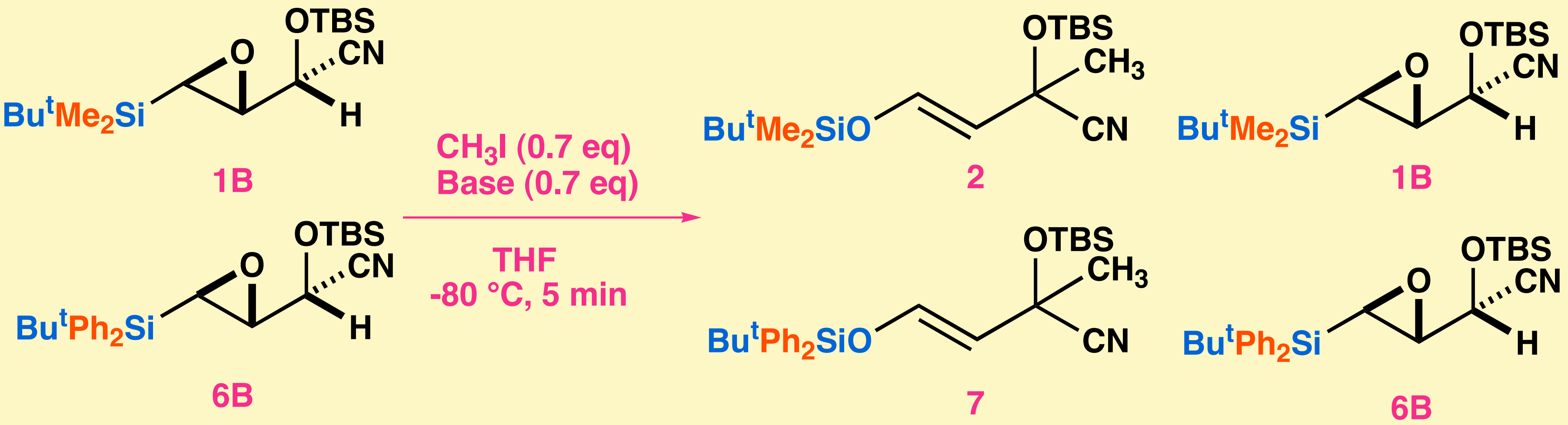
A-value: OTMS = 0.7
CN = 0.2

A Proposed Reaction Pathway

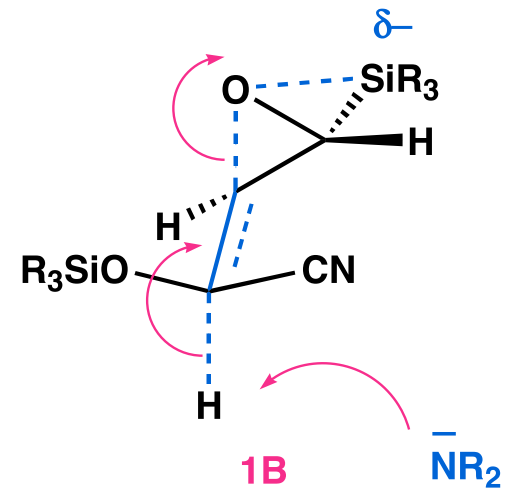


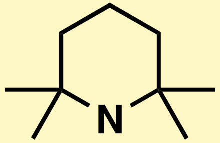
1A $\xrightarrow{\text{LDA}}$ *E*/*Z* = 2.5 1B $\xrightarrow{\text{LDA}}$ *E*/*Z* = 22.0

Substituent Effect of the Silyl Group on Rates of Ring Opening



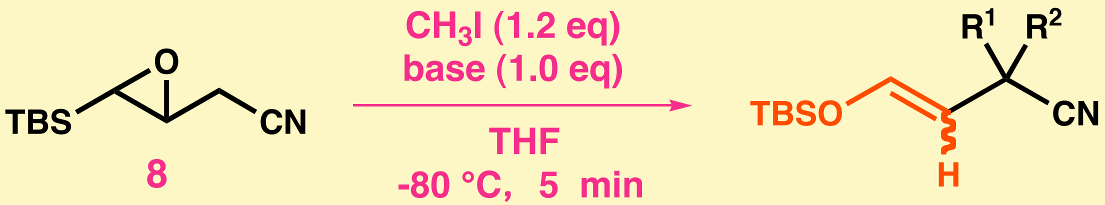
	yield (%)			yield (%)	
base	2	7	7 (TBDPS)/2 (TBS)	1B	6B
$LiNEt_2$	18.8	6.0	0.32	24.4	39.1
LDA	21.5	6.7	0.31	18.1	39.8
LTMP	22.1	14.8	0.67	19.4	29.8



LTMP = 

TBS = Bu^tMe_2Si
TBDPS = Bu^tPh_2Si

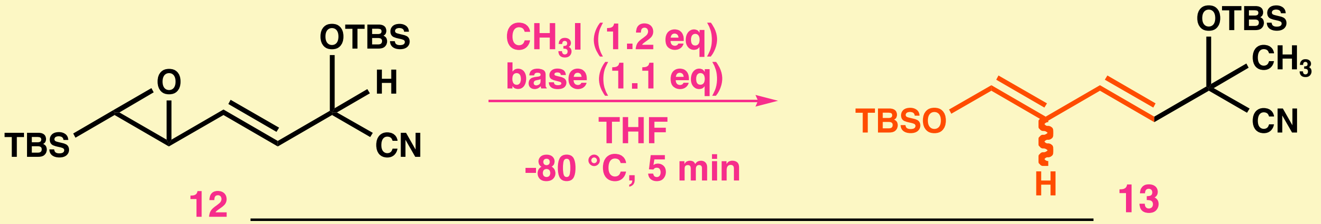
Methylation of Metalated γ-Silyl-β,γ-butyronitrile



9; $R^1 = R^2 = Me$
10; $R^1 = Me$, $R^2 = H$
11; $R^1 = R^2 = H$

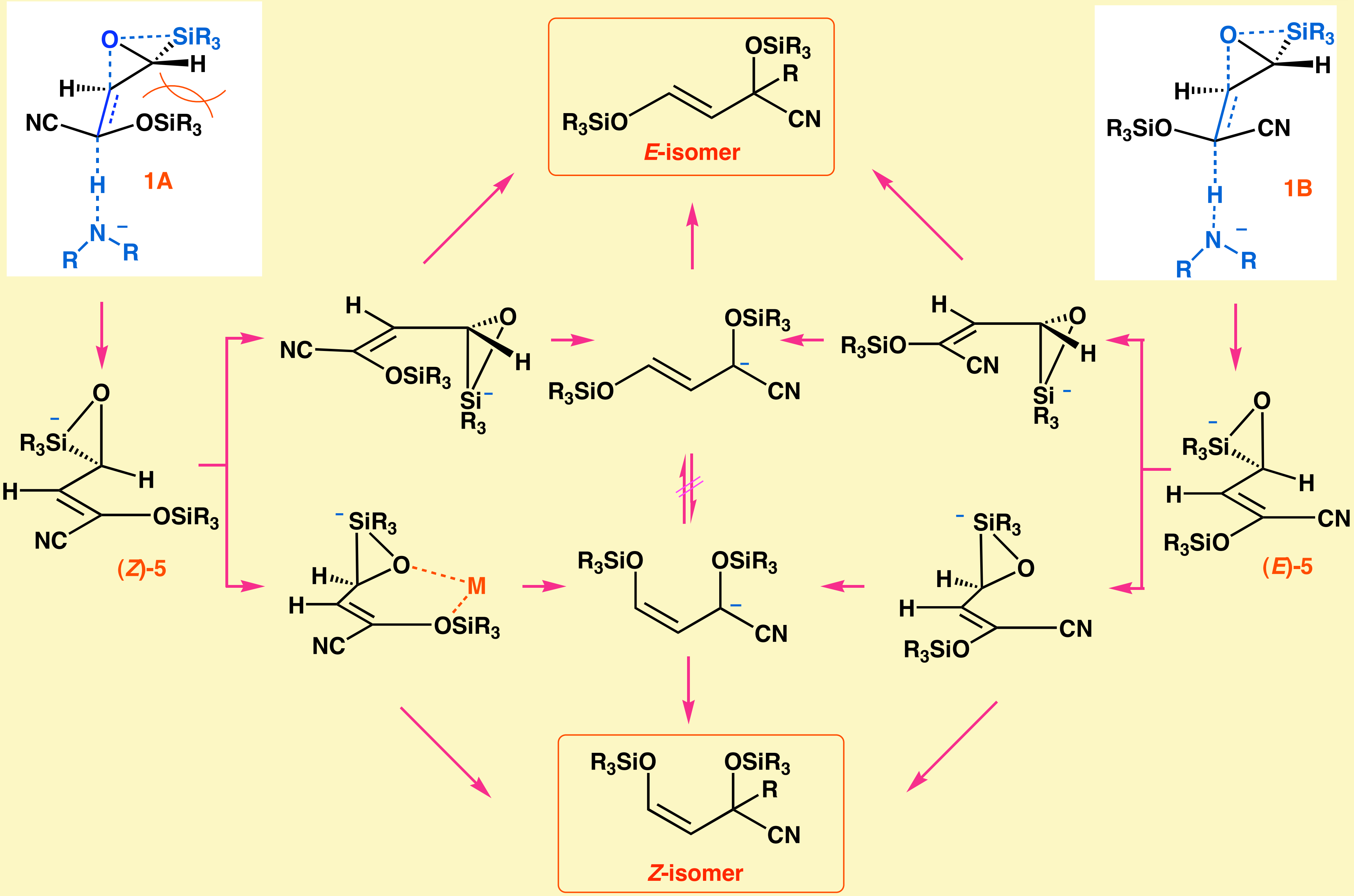
	9		10		11		total	
base	yield (%)	*E/Z*	yield (%)	*E/Z*	yield (%)	*E/Z*	yield (%)	*E/Z*
LDA	2	5.7	77	9.7	8	E	87	11.0
LHMDS	8	*E*	82	8.4	0	-	90	9.3
NHMDS	30	238	38	3.8	5	2.3	73	6.7
KHMDS	38	18	24	1.2	21	0.8	83	2.4

Methylation of Metalated Cyanohydrins of δ-Silyl-γ,δ-epoxy-α,β-unsaturated Aldehyde

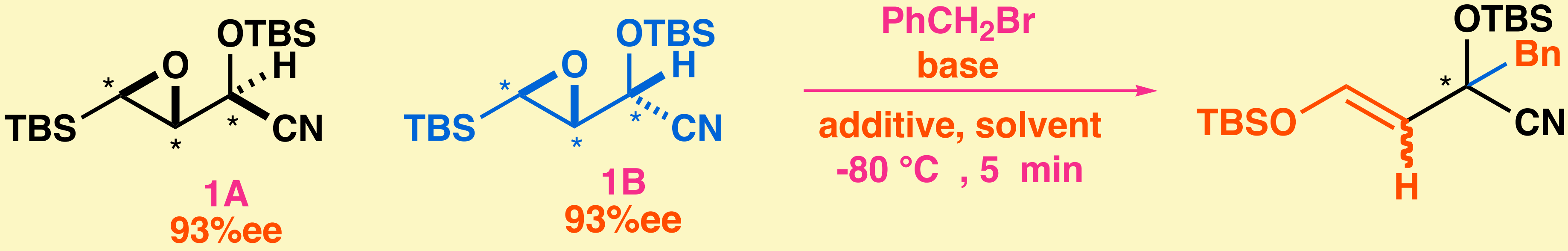


base	yield (%)	*E/Z*
LDA	87	9.8
LHMDS	91	16.5
NHMDS	97	16.5
KHMDS	92	7.2

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

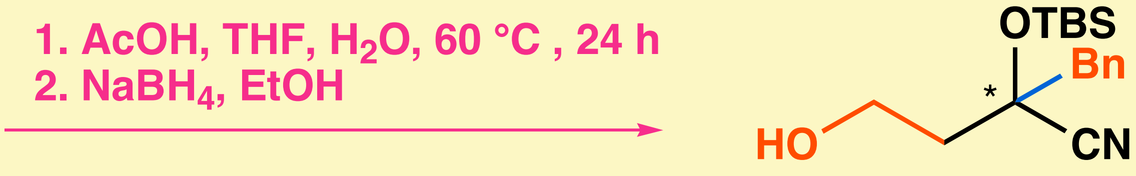


1A 93%ee

1B 93%ee

$PhCH_2Br$
base

additive, solvent
-80 °C , 5 min

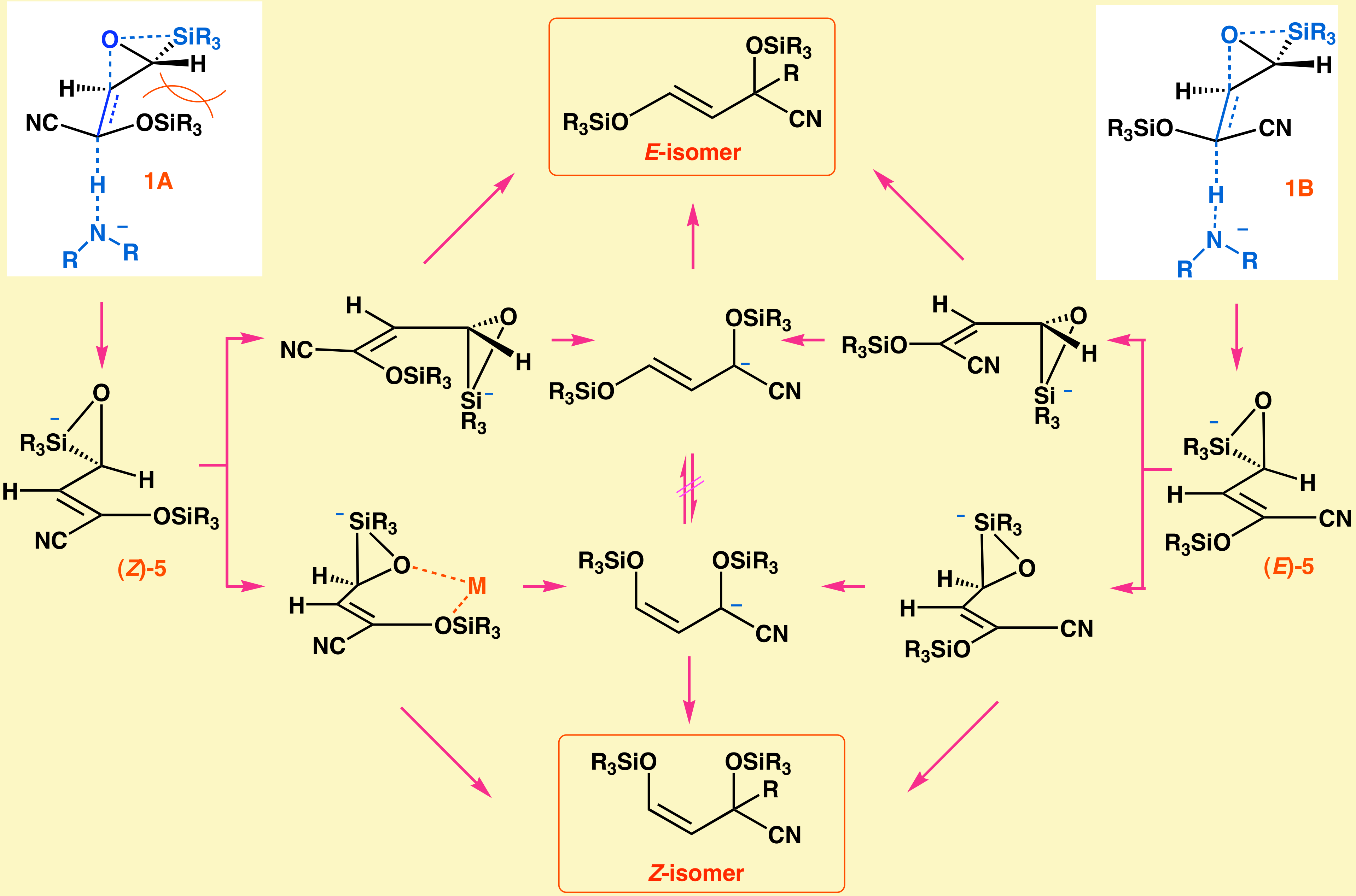


1. AcOH, THF, H_2O, 60 °C , 24 h
2. $NaBH_4$, EtOH

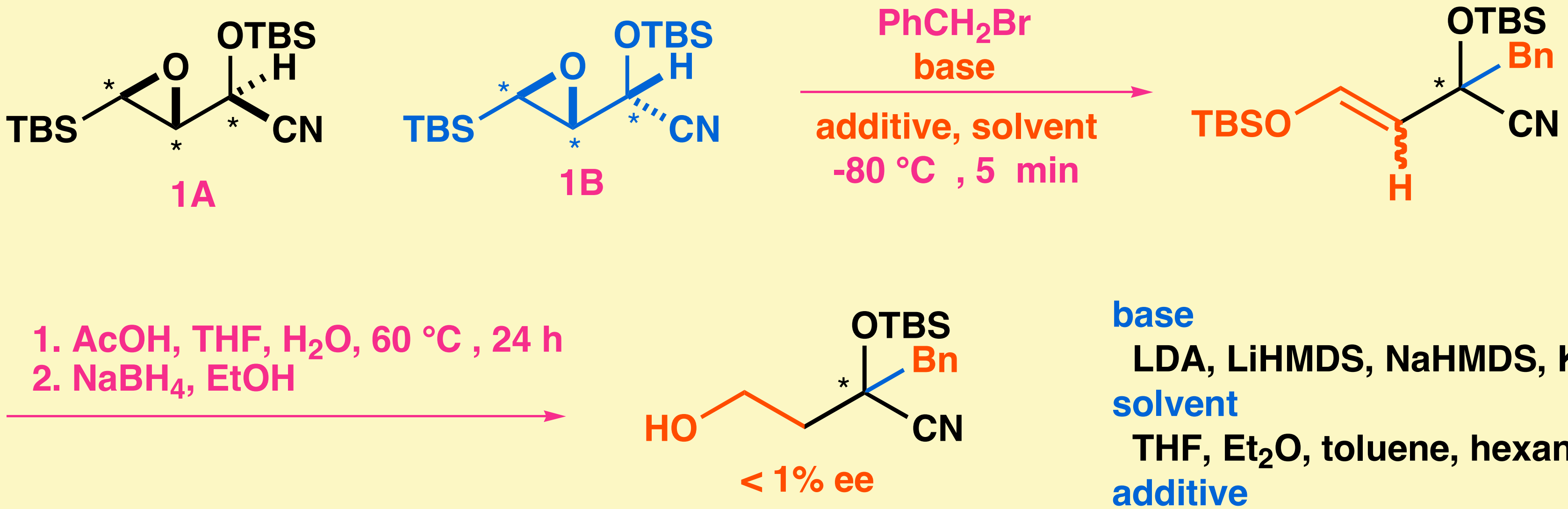
< 1% ee

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

A Proposed Reaction Pathway



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



1A

1B

$PhCH_2Br$
base

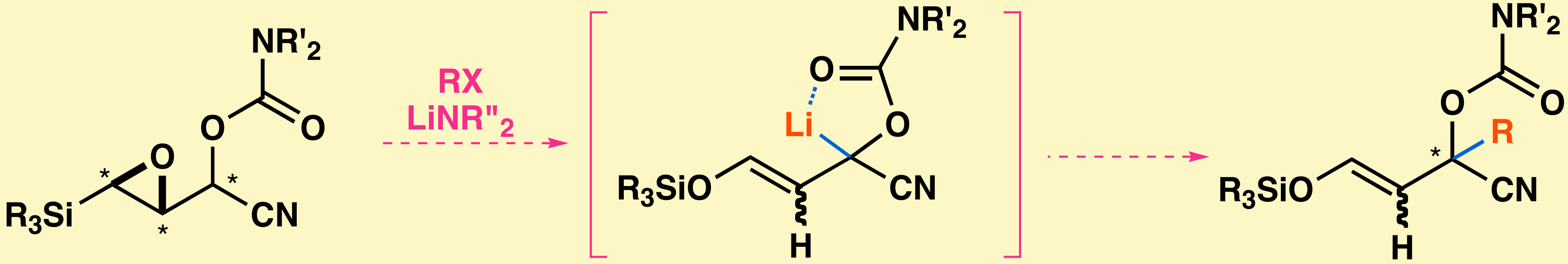
additive, solvent
-80 °C , 5 min

1. AcOH, THF, H_2O, 60 °C , 24 h
2. $NaBH_4$, EtOH

< 1% ee

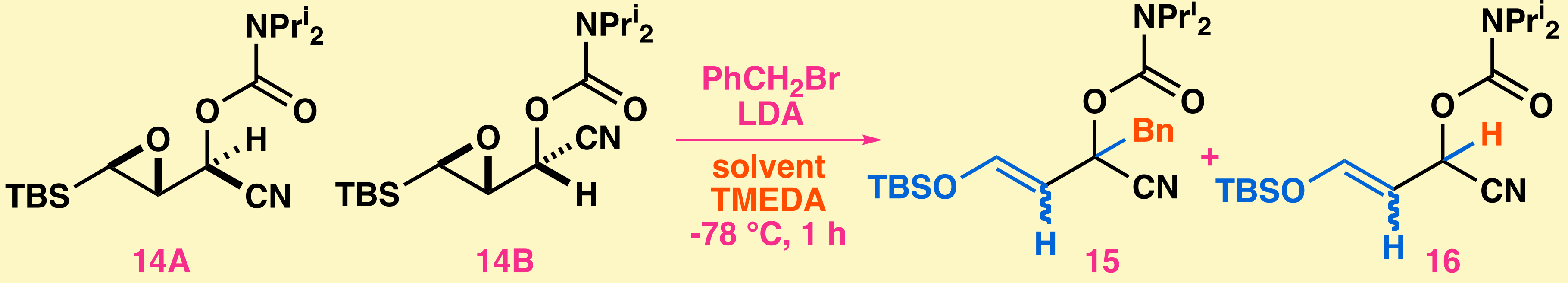
base
LDA, LiHMDS, NaHMDS, KHMDS
solvent
THF, Et_2O, toluene, hexane
additive
TMEDA

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



RX
$LiNR''_2$

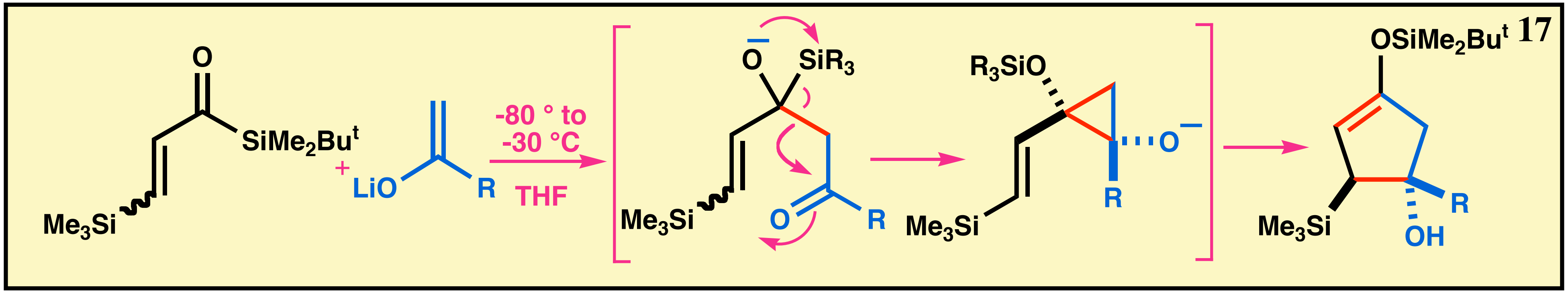
Reactions of Enantiomerically Pure *O*-Silyl Cyanohydrins of β-Silyl-α,β-Epoxyaldehyde with LDA in the Presense of Benzyl Bromide



			(*E*)15	(*Z*)15		(*E*)-16	(*Z*)-16	total
solvent	SM	TMEDA	yield (%)	yield (%)	ee (%)	yield (%)	yield (%)	yield (%)
THF	14A	(–)	30	36	0	2	7	75
	14B	(–)	52	-	-	7	-	59
Et_2O	14A	(–)	6	44	30.0	1	11	62
	14B	(–)	23	-	-	35	-	58
	14A	(+)	8	25	0	3	18	54
	14B	(+)	39	-	-	26	-	65
toluene	14A	(–)	11	21	37.3	2	11	46
	14B	(–)	26	-	-	33	-	59
	14A	(+)	25	29	0	2	9	65
	14B	(+)	49	9	2.4	10	-	68

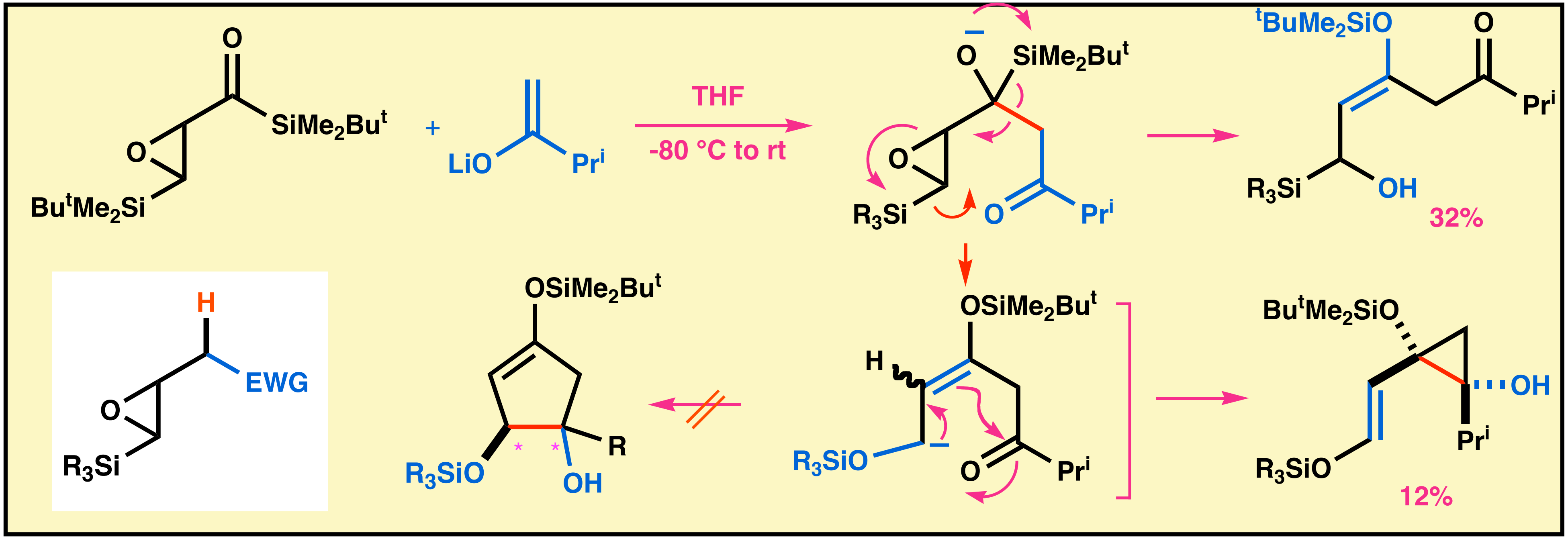
(*E*)-**15**, (*E*)-**16**, and (*Z*)-**16** were inseparable.
The enantiomeric purity was determined by chiral HPLC using a CHIRALPAK AD®.

[3 + 2] Annulation Using Reaction of (β-(Trimethylsilyl)acryloyl)silanes and Lithium Enolate of Methyl Ketones



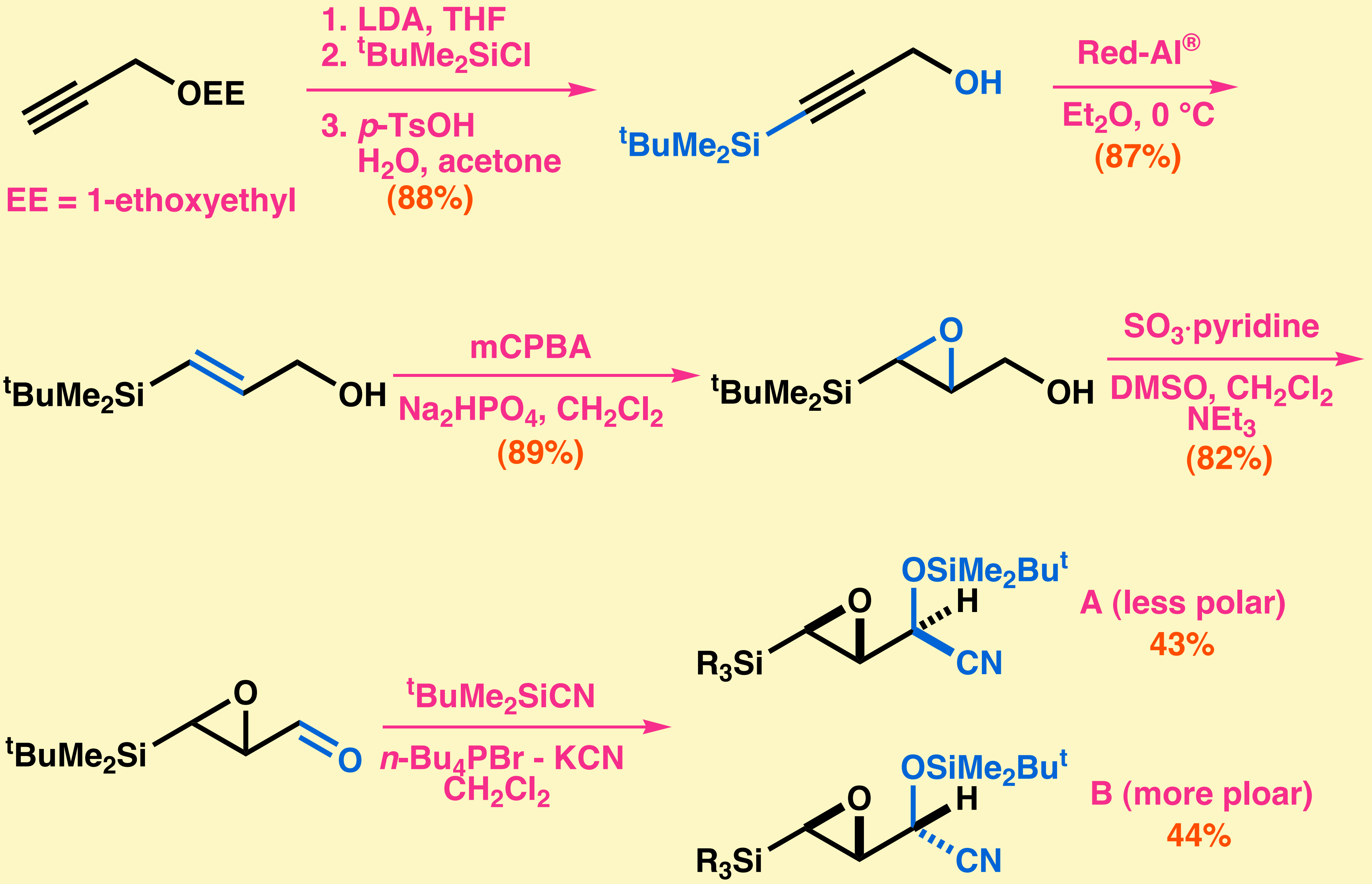
17

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



1. Takeda, K.; Fujisawa, M.; Makino, T.; Yoshii, E.; Yamaguchi, K. *J. Am. Chem. Soc.* **1993**, *115*, 9351-9352.
2. Takeda, K.; Yamawaki, K.; Hatakeyama, N. *J. Org. Chem.* **2002**, 67, 1786-1794.
3. 武田　敬，大西裕司，未発表データ

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



EE = 1-ethoxyethyl

1. LDA, THF
2. $^{t}BuMe_2SiCl$
3. *p*-TsOH, H_2O, acetone
(88%)

Red-Al®
Et_2O, 0 °C
(87%)

mCPBA
Na_2HPO_4, CH_2Cl_2
(89%)

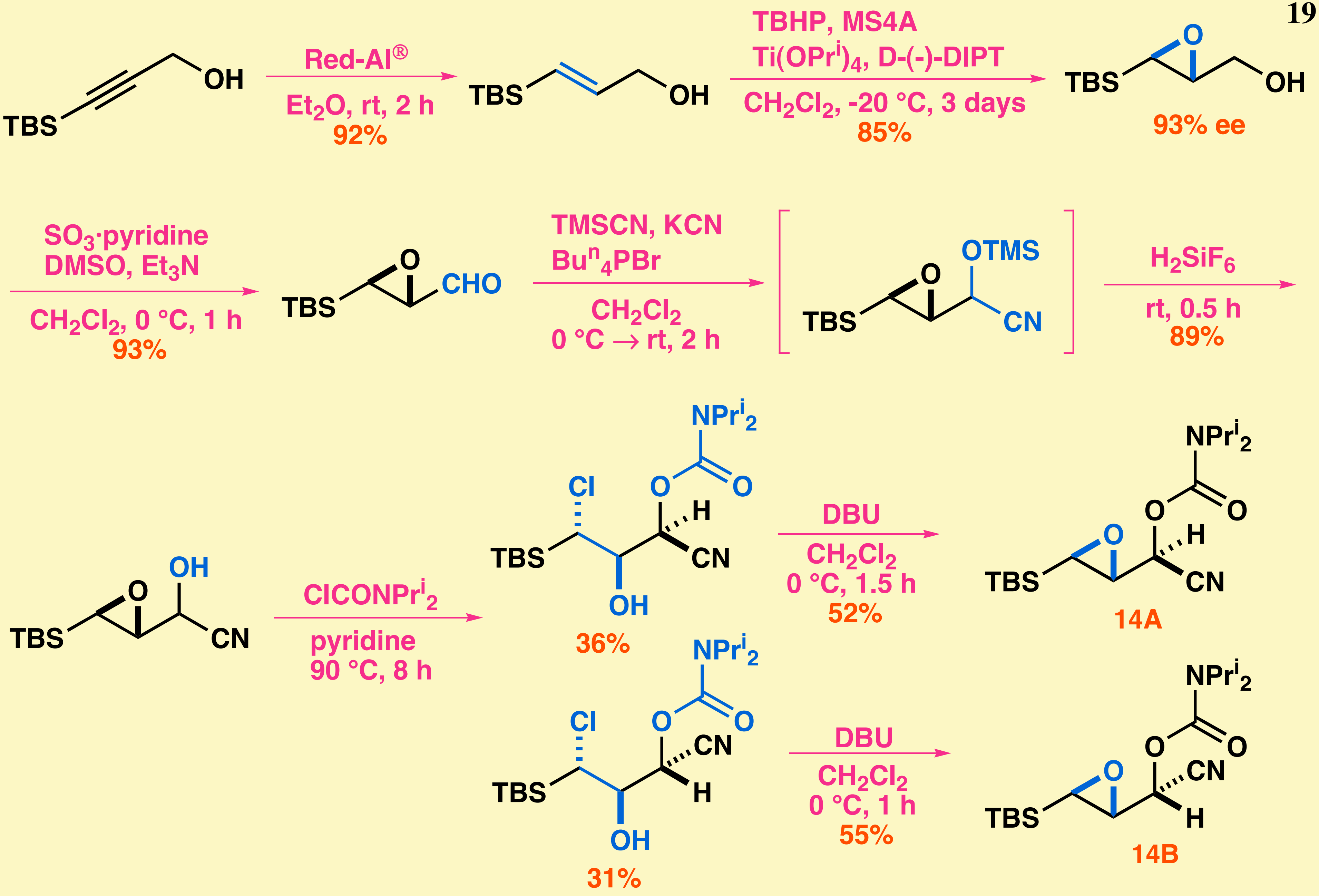
SO_3·pyridine
DMSO, CH_2Cl_2
NEt_3
(82%)

$^{t}BuMe_2SiCN$
n-Bu_4PBr - KCN
CH_2Cl_2

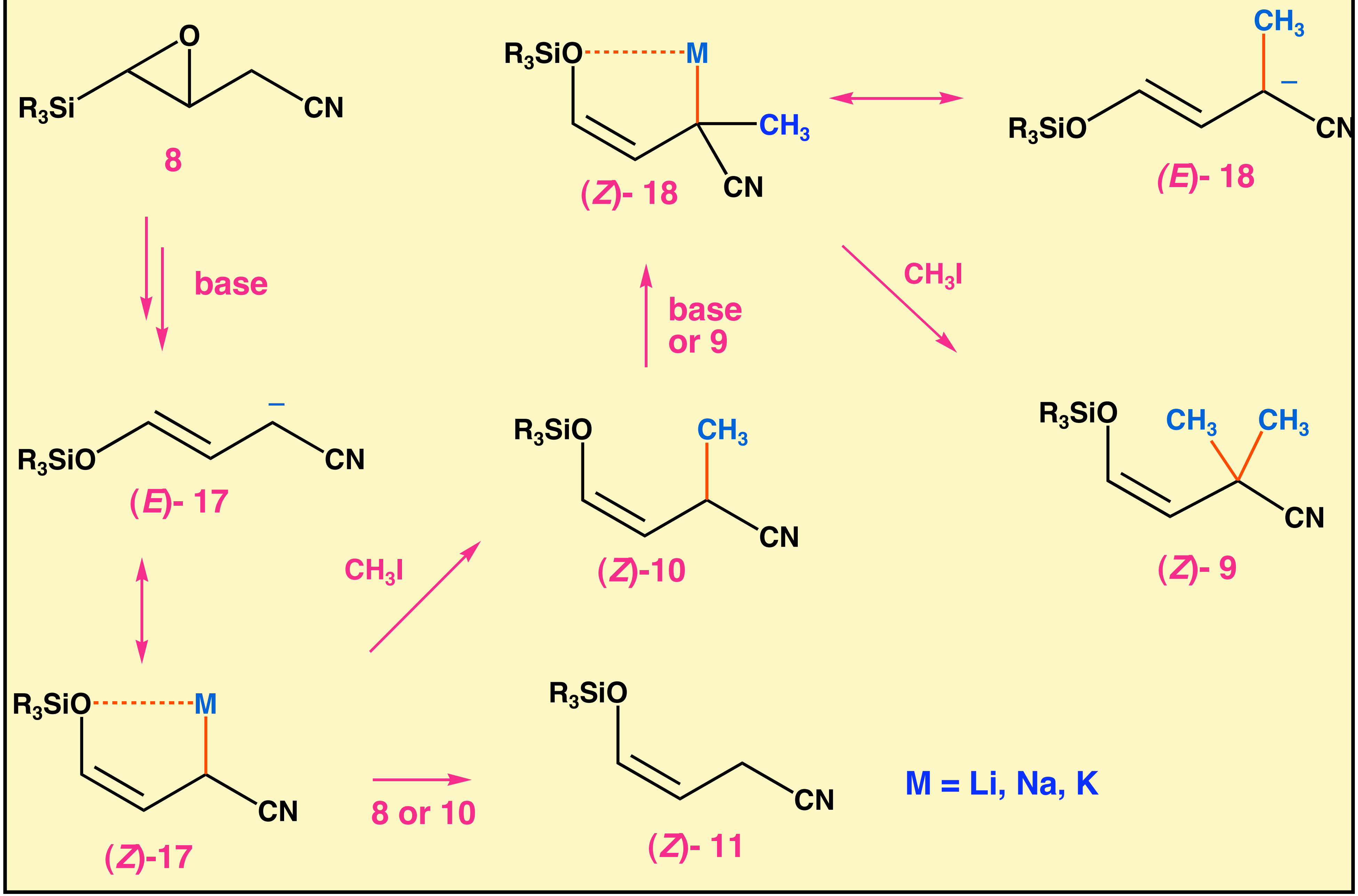
A (less polar)
43%

B (more ploar)
44%

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

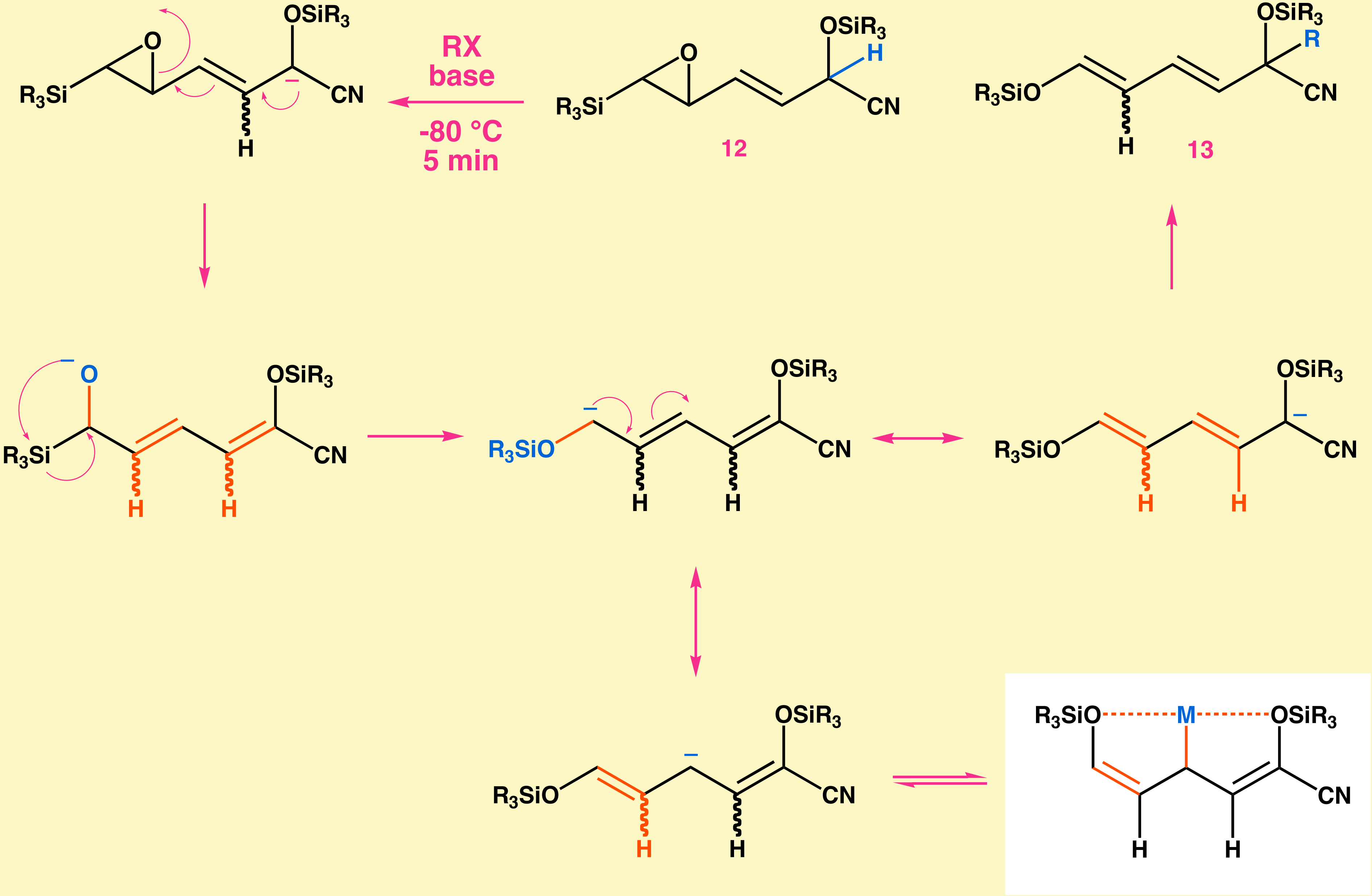


An Explanation for the Enhanced *Z*-Selectivity in Less-Polar Solvents



M = Li, Na, K

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



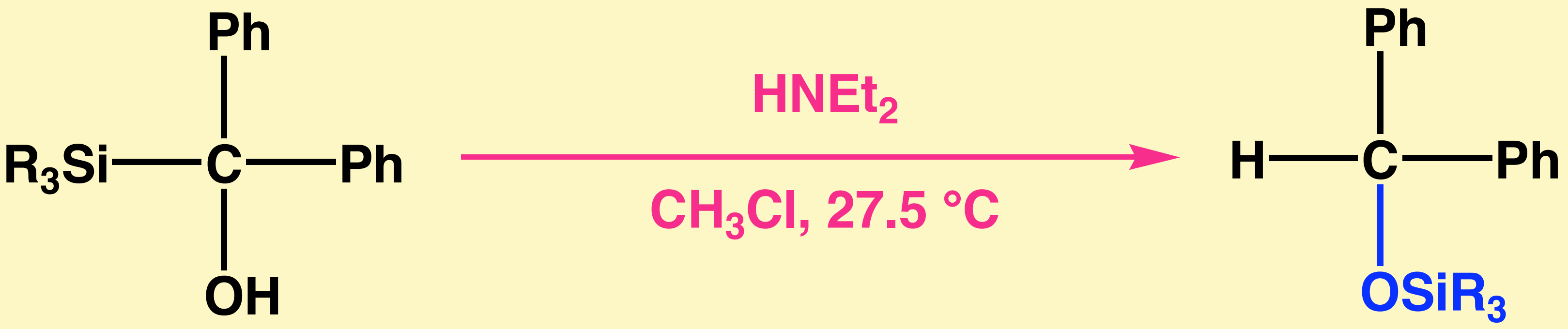
RX
base

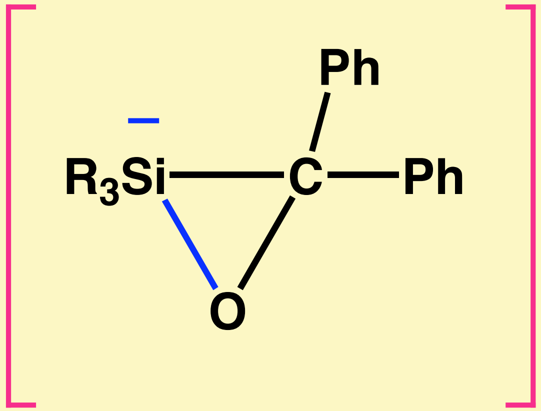
-80 °C
5 min

12

13

Rates of Brook Rearrangement of α-Silyldiphenylcarbinol

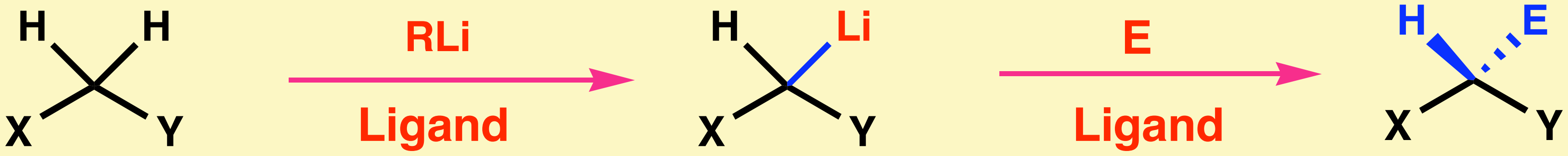




SiR_3	k_2 (l mole^{-1} s^{-1})
$SiPh_3$	6.10×10^{-3}
$SiPh_2Me$	0.98×10^{-3}
$SiPhMe_2$	0.15×10^{-3}
$SiMe_3$	0.25×10^{-4}

Brook, A. G.; LeGrow, G. E.; MacRae, D. M. *Can. J. Chem.* **1967,** 45, 239-253.

Enantioselective Lithiation-Substitution Sequence

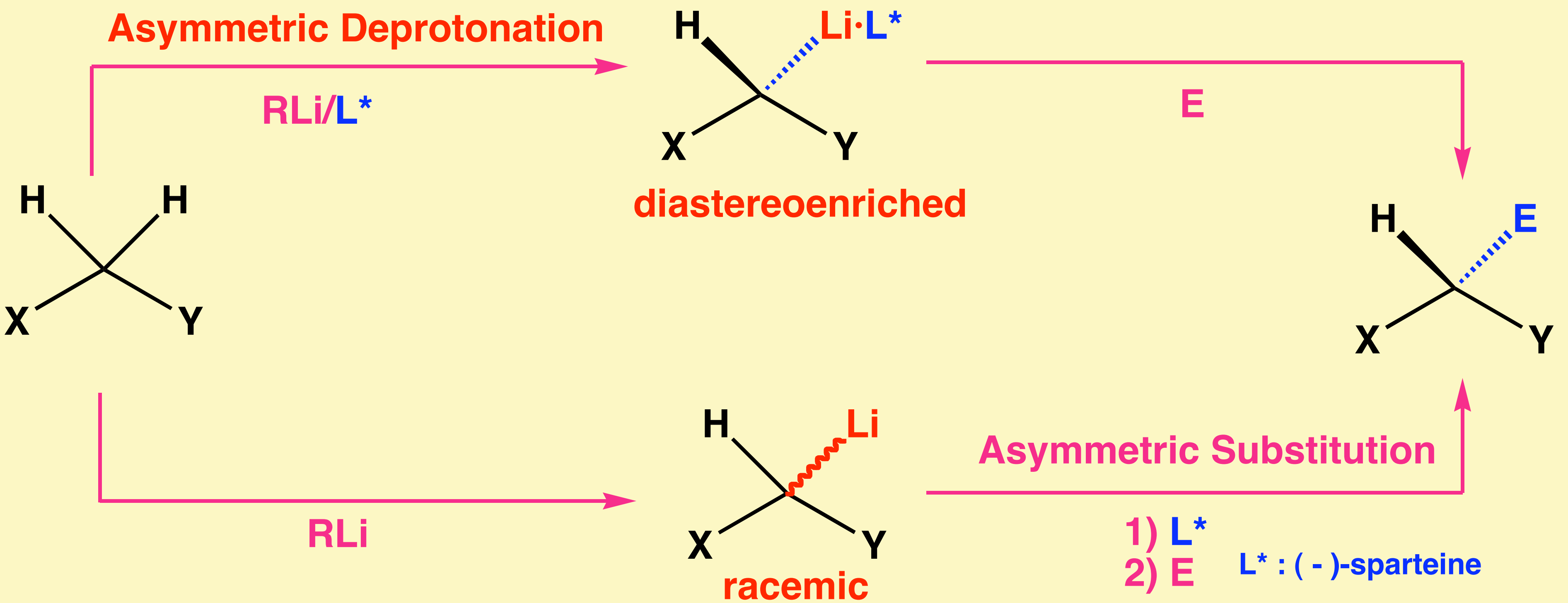


RLi

Ligand

E

Ligand



Asymmetric Deprotonation

RLi/L*

diastereoenriched

E

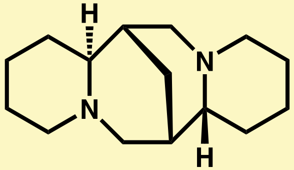
RLi

racemic

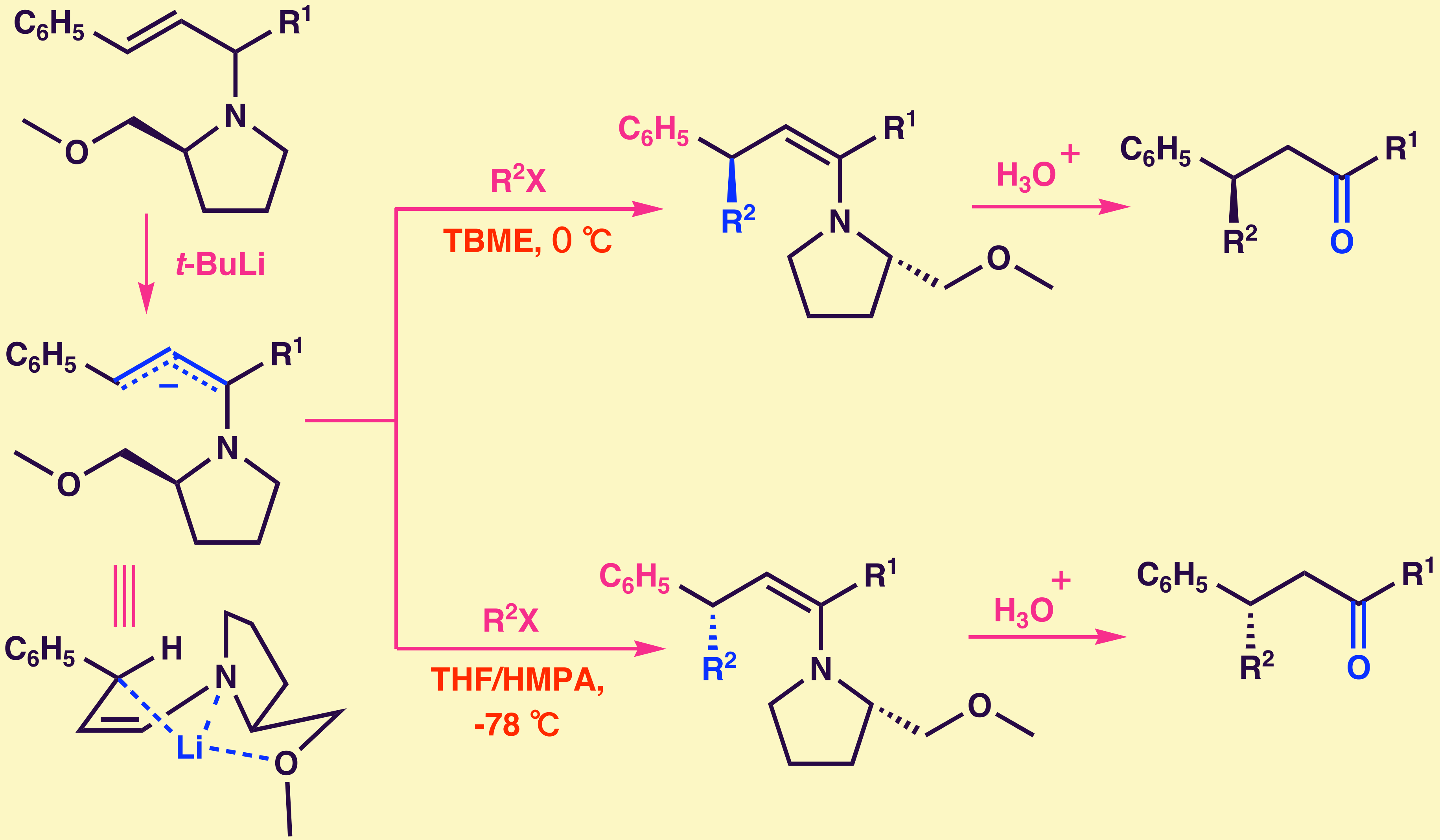
Asymmetric Substitution

1) L*
2) E

L* : (-)-sparteine

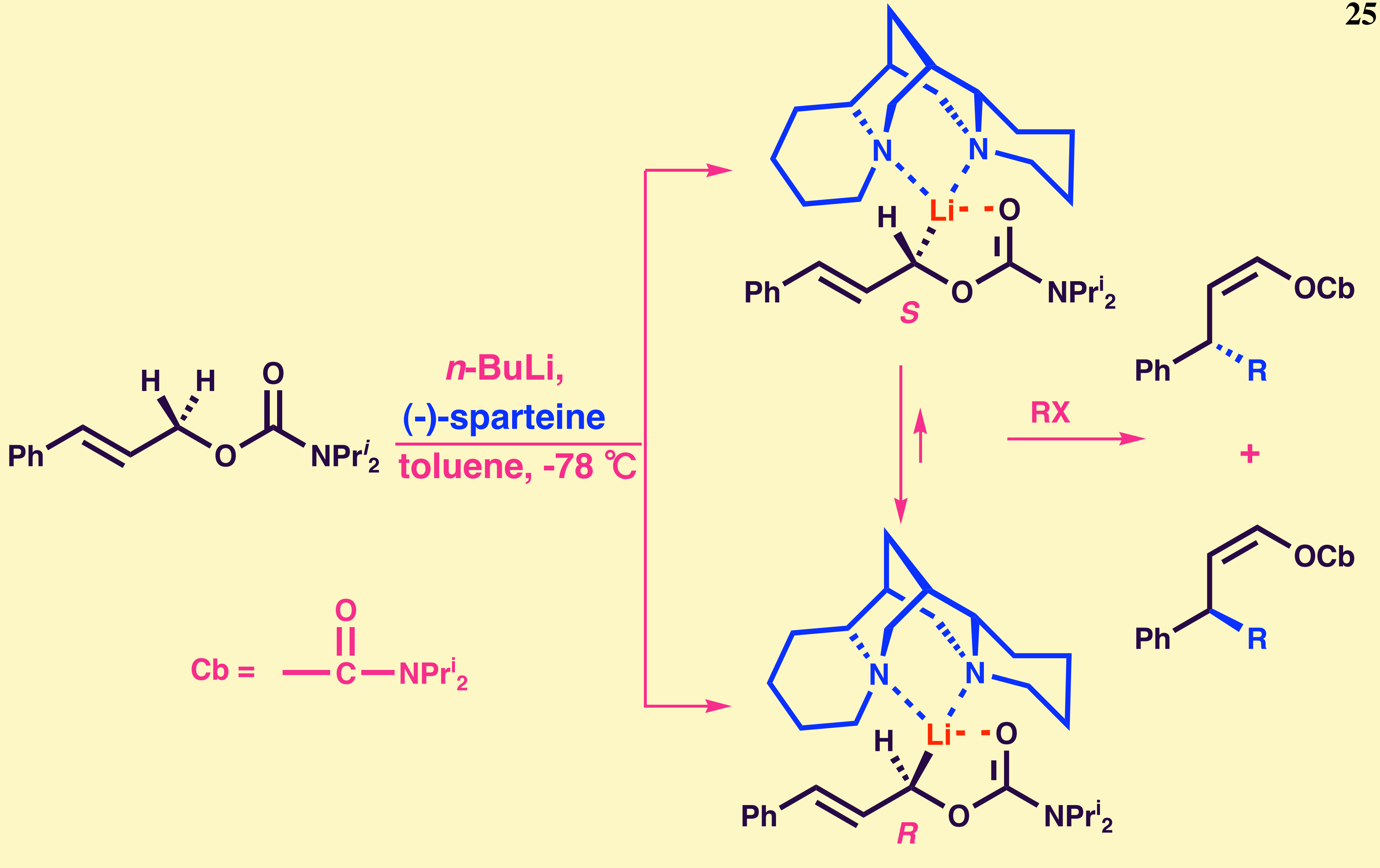


Chiral Homoenolate Equivalent (1)



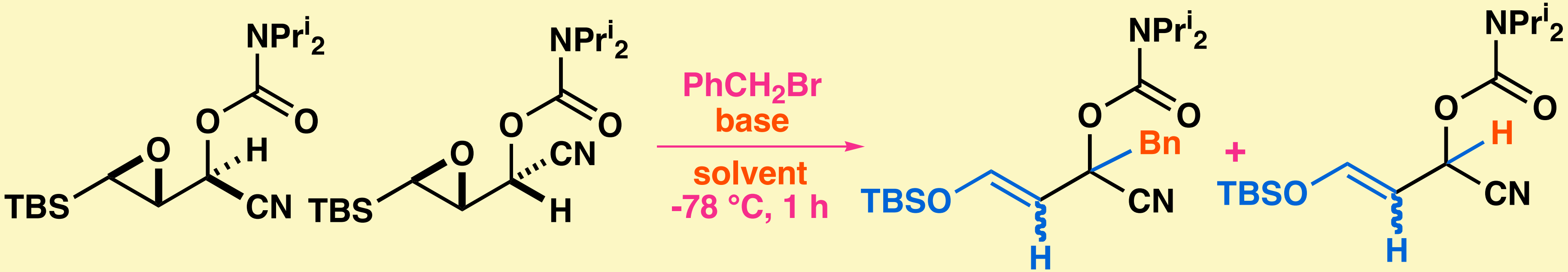
Ahlbrecht, H. ; Beyer, U. *Synthesis* **1999**, 365-390.

Chiral Homoenolate Equivalent (2)



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

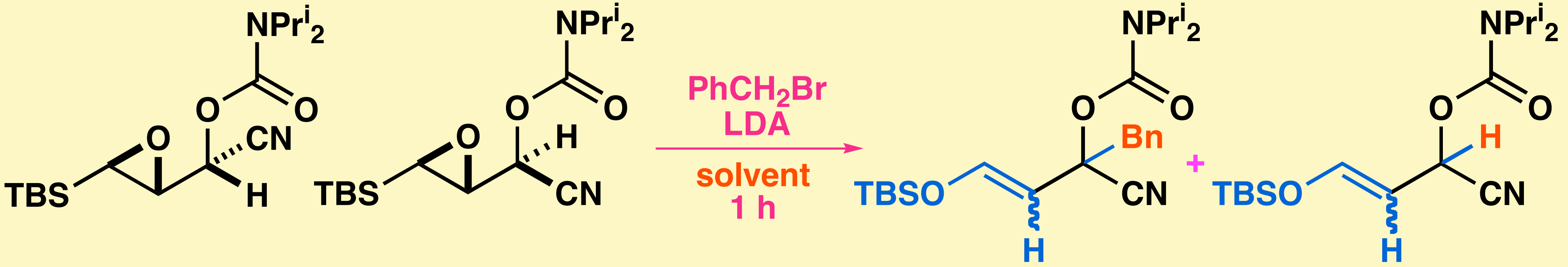
Reactions of Enantiomerically Pure *O*-Carbamoyl Cyanohydrins of β-Silyl-α,β-Epoxyaldehyde with Bases in the Presense of Benzyl Bromide : Effect of Bases



14A 14B 15 16

Base	SM	solvent	(*E*)-15 yield (%)	(*Z*)-15 yield (%)	(*Z*)-15 ee (%)	(*E*)-16 yield (%)	(*Z*)-16 yield (%)	total yield (%)
LHMDS	7A	Et_2O	22	35	22.6	3	4	64
	7B		51	-	-	12	-	63
	7A	toluene	49	6	0	4	-	59
	7B		46	-	-	-	7	53
NHMDS	7A	Et_2O	39	33	4.3	-	-	69
	7B		53	-	-	19	-	72
	7A	toluene	47	27	2.5	-	-	74
	7B		59	5	0	-	-	64
KHMDS	7A	Et_2O	50	24	0	-	-	74
	7B		23	-	-	40	-	63
	7A	toluene	47	21	1.8	-	-	68
	7B		60	6	0	-	-	66

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



14A 14B 15 16

solvent	SM	temp (°C)	(*E*)-15	(*Z*)-15		(*E*)-16	(*Z*)-16	total
			yield (%)	yield (%)	ee (%)	yield (%)	yield (%)	yield (%)
Et_2O	7A	-110	-	6	27.8	9	61	76
	7A	-78	6	44	30.0	1	11	62
	7A	-40	8	46	27.8	2	11	67
	7A	0	7	44	0	3	16	70
	7B	-110	24	-	-	37	-	61
	7B	-78	23	-	-	35	-	58
toluene	7A	-78	11	21	37.3	2	11	46
	7A	-40	8	32	15.9	3	16	59
	7A	0	8	36	5.6	2	16	62
	7B	-78	26	-	-	33	-	59