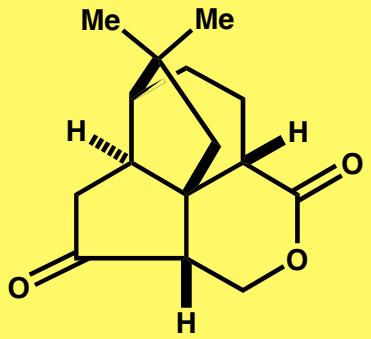
連続的結合形成反応を利用する八員環形成反応の開発

広島大学大学院医歯薬学総合研究科
薬学専攻創薬合成化学研究室
武田　敬

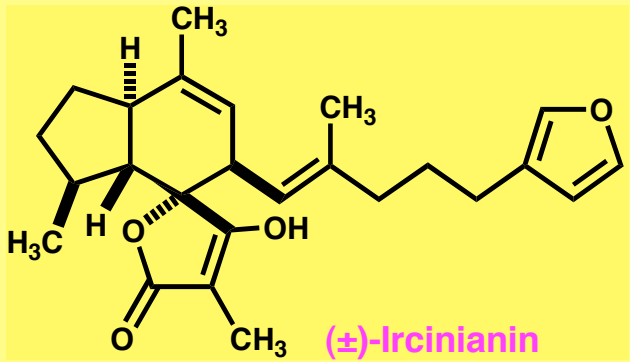
明治薬科大学　２００３年６月１６日

Total Synthesis of Natural Products



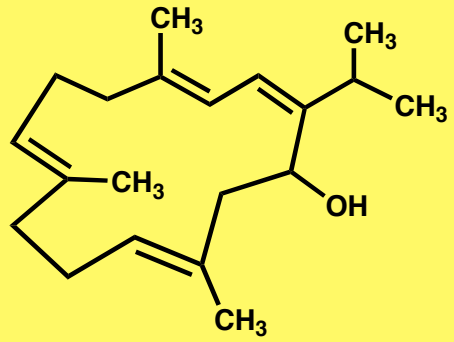
Quadrone

J. Am. Chem. Soc. **1983**, *105*, 563-568



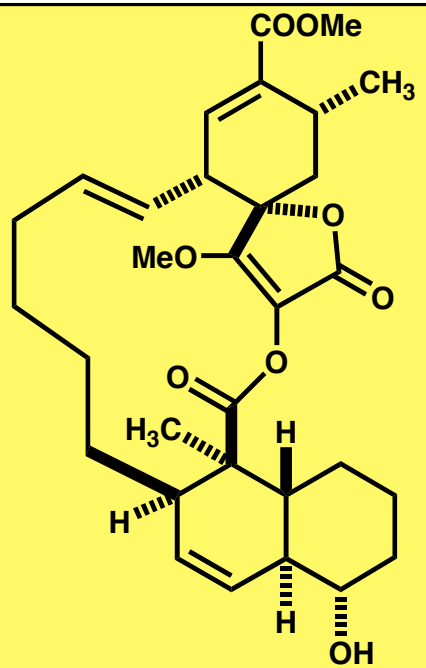
(±)-Ircinianin

Tetrahedron Lett. **1986**, *27*, 3903-3906

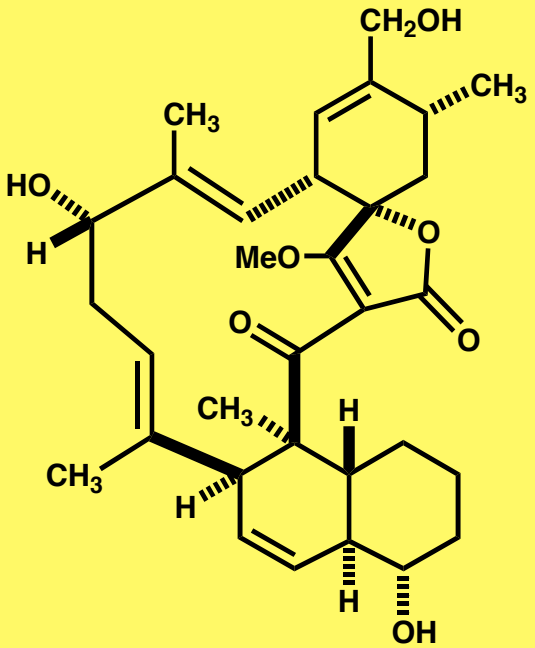


Sarcophytol A

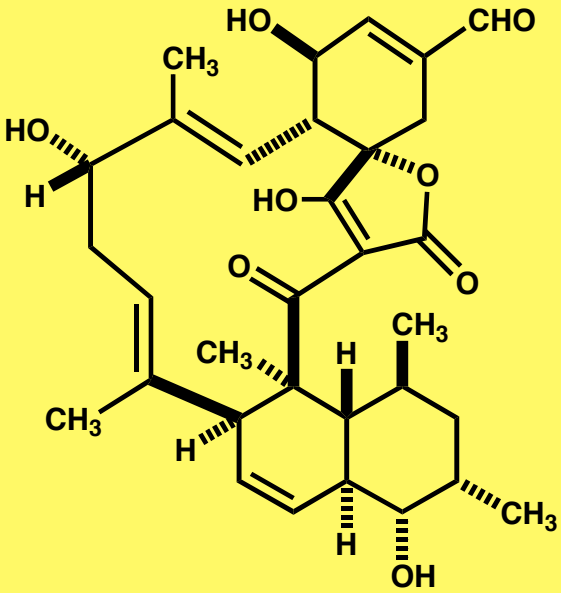
Synlett **1995**, 249-250 (1995)



O-Methyl Chlorothricolide Methyl Ester



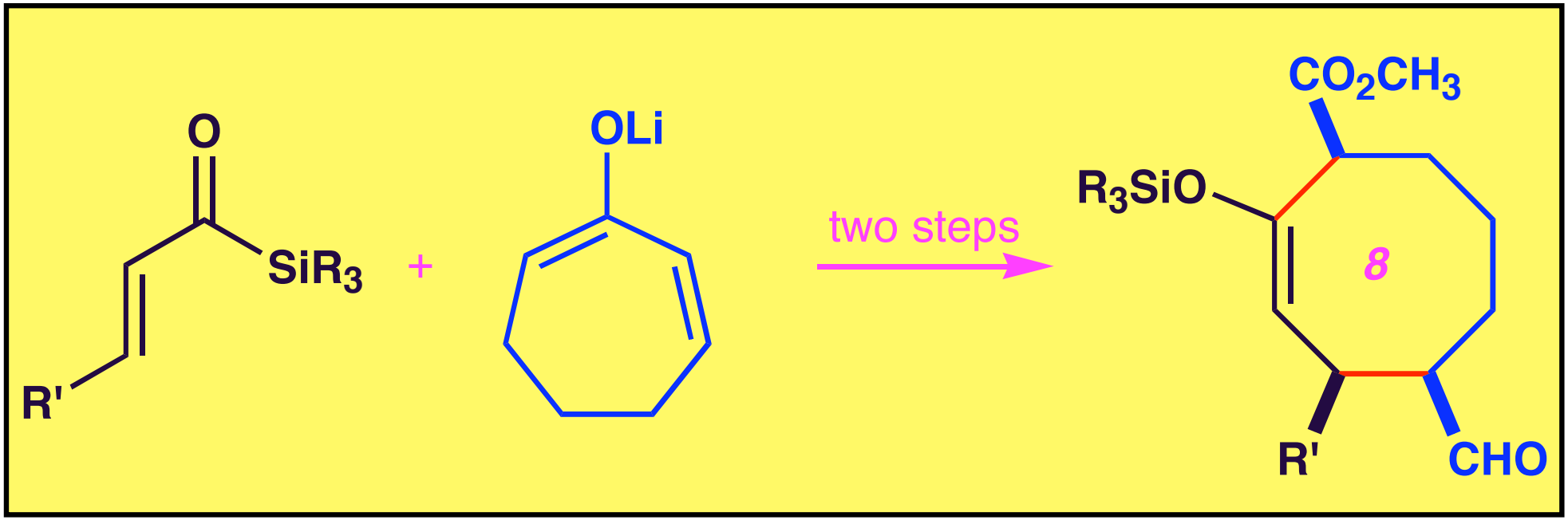
Bisnorkijanolide

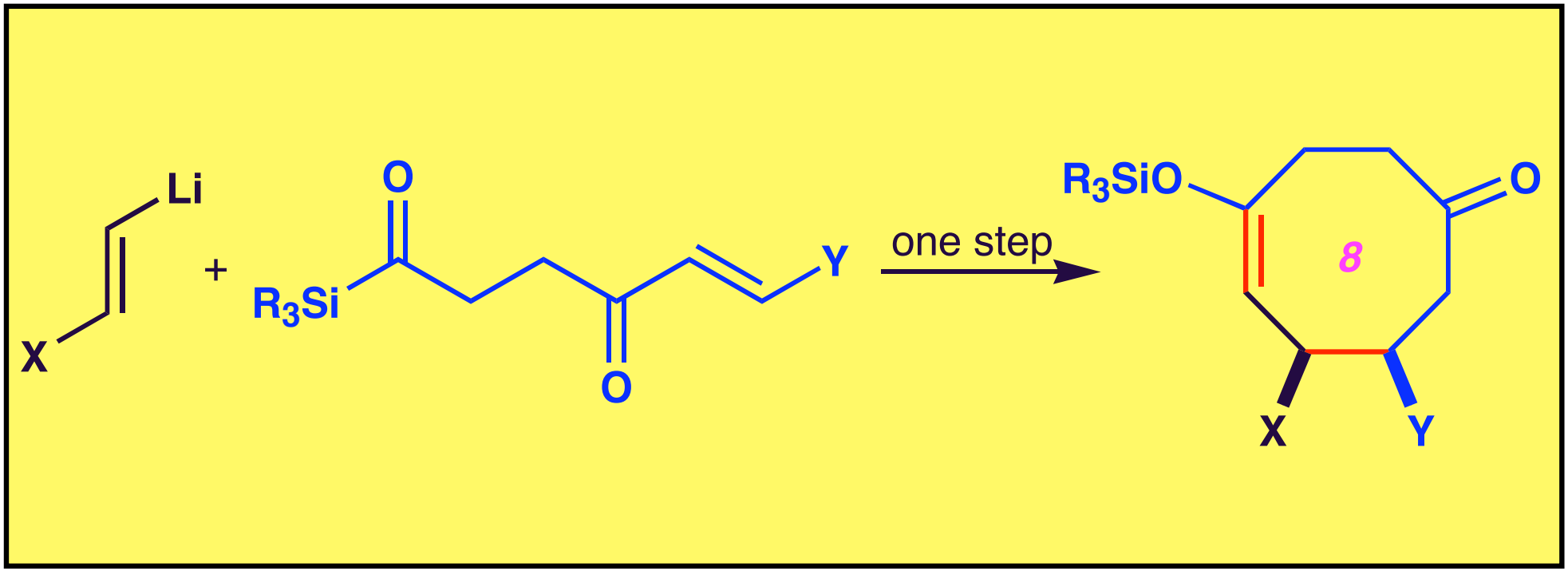


Tetronolide

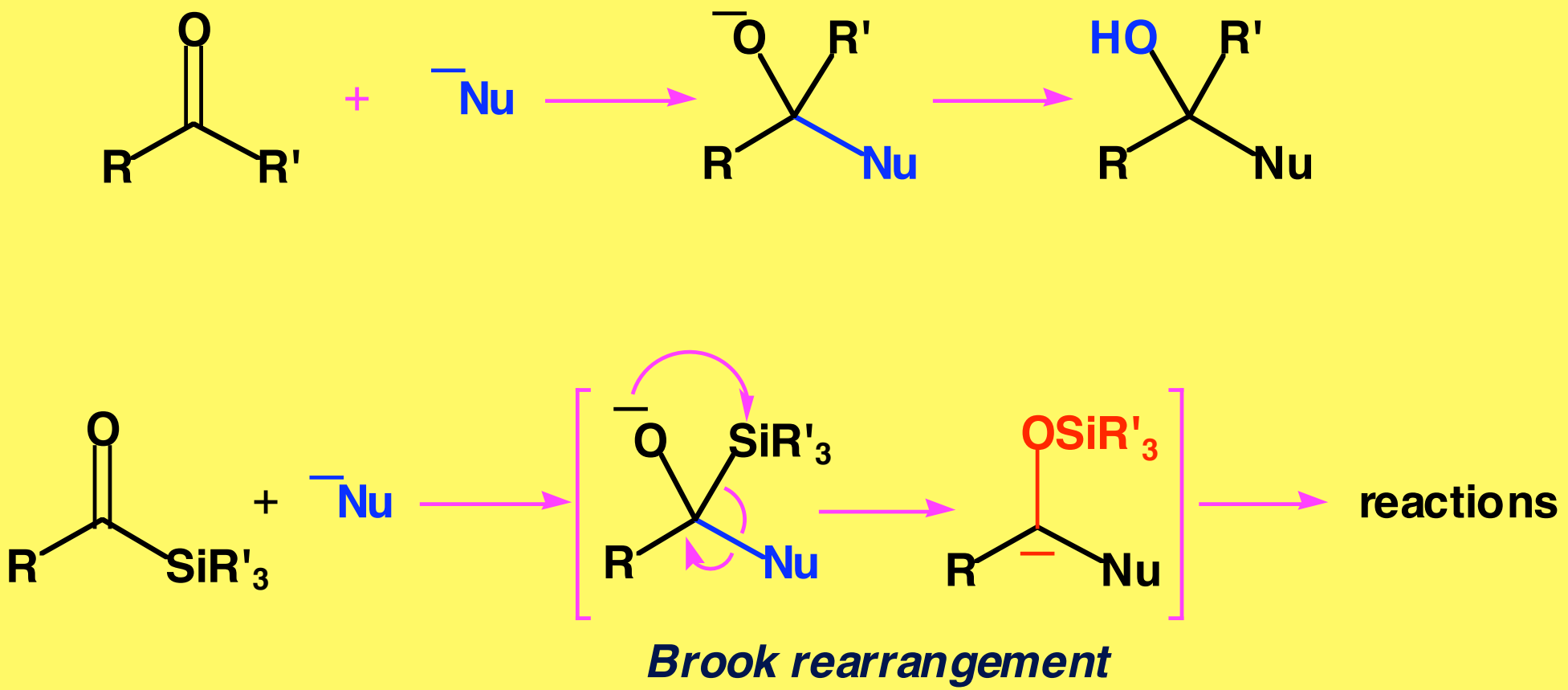
J. Org. Chem. **1985**, *50*, 4673-4681; *J. Org. Chem.* **1986**, *51*, 4735-4737; *J. Chem. Soc. Chem. Commun.* **1986**, 1197-1198; *J. Org. Chem.* **1987**, *52*, 4135-4137; *J. Org. Chem.* **1988**, *53*, 1092-1095; *Tetrahedron Lett.* **1988** *29*, 6951-6954; *J. Chem. Soc., Chem. Commun.* **1989**, 221-223; *J. Org. Chem.*. **1988**, *53*, 1092-1095; *J. Org. Chem.* **1990**, *55*, 3431-3432. *Tetrahedron Lett.* **1989** *30*, 2233-2236; *Tetrahedron Lett.* **1991** *32*, 4091-4094.

Formation of Eight-Membered Rings by [3 + 4] and [6 + 2] Annulation



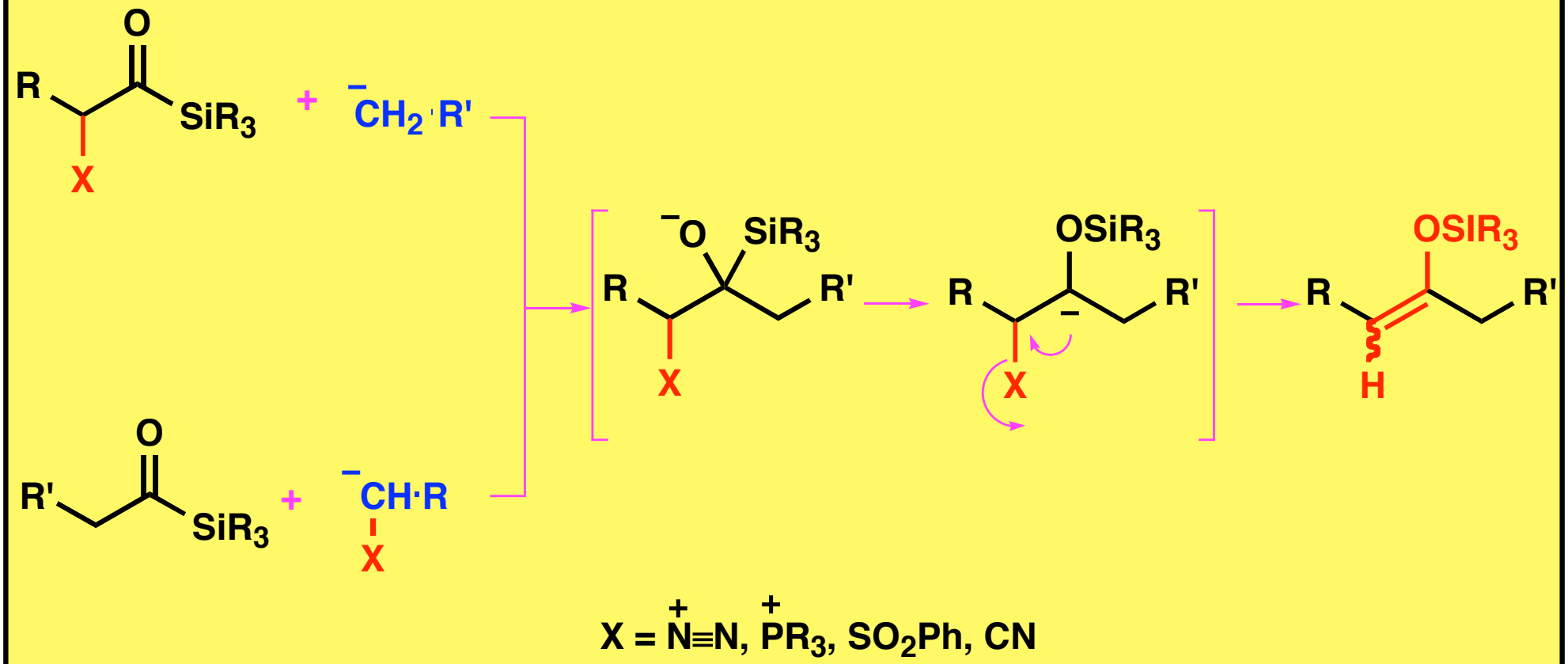


Brook Rearrangement



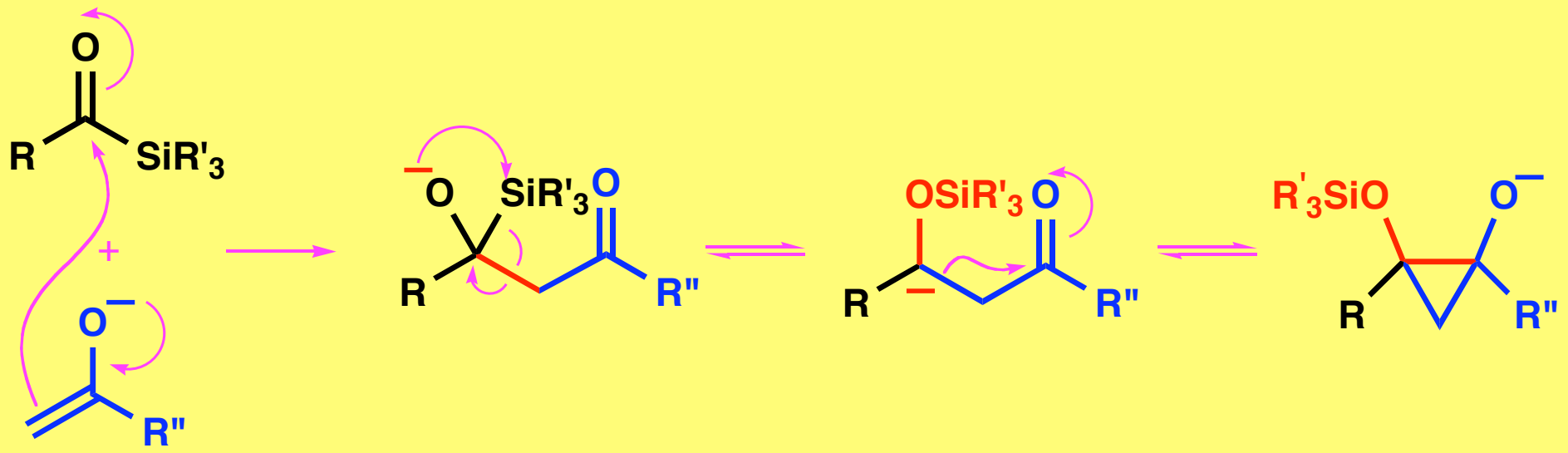
Brook, A.G. *J. Am. Chem. Soc.* **79**, 4373 (1957)

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

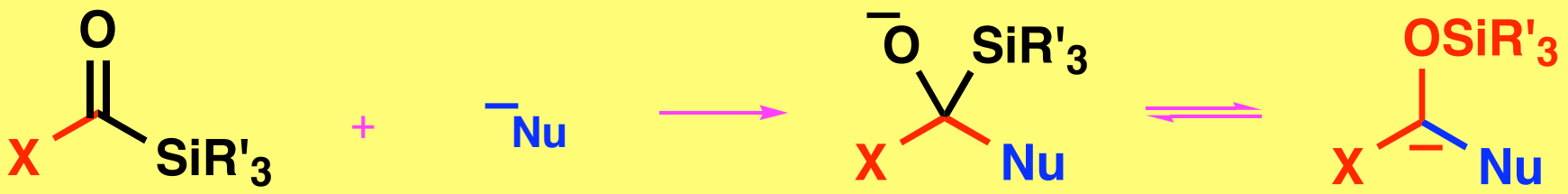


Brook, A. G.; Limburg, W. W.; MacRae, D. M.; Fieldhouse, S. A. *J. Am. Chem. Soc.* **1967**, *89*, 704.
Reich, H. G.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609-5617.
Nakajima, T.; Segi, M.; Sugimoto, F,; Hioki, R.; Yokota, S.; Miyashita, K. *Tetrahedron* **1993**, *37*, 8343.

Use of Ketone Enolate as a Nucleophile

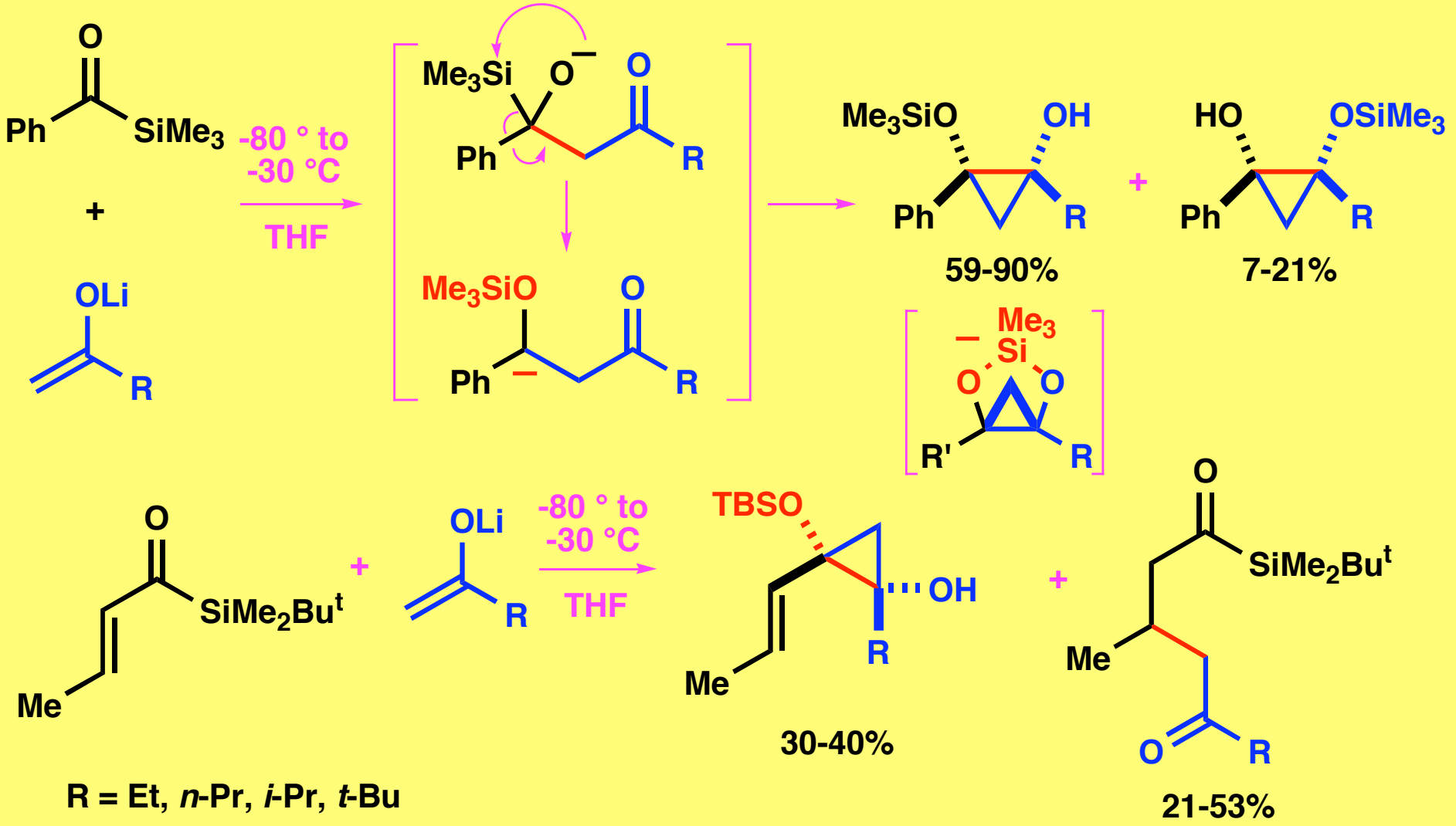


Introduction of a Carbanion-Stabilizing Heteroatom

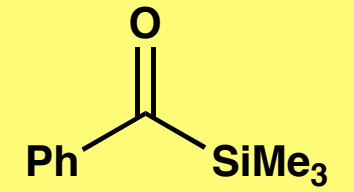


X = SPh, $SiMe_3$, $P(O)(OMe)_2$

Reaction of α,β-Unsaturated Acylsilanes with Lithium Enolates



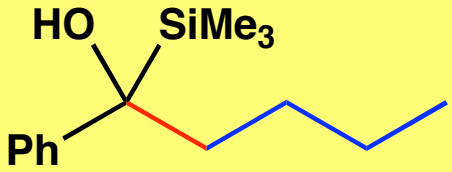
Takeda, K.; Nakatani, J.; Nakamura, H.; Sako, K.; Yoshii, E.; Yamaguchi, K. *Synlett* **1993**, 841-843.



+

-80 ° to
-30 °C

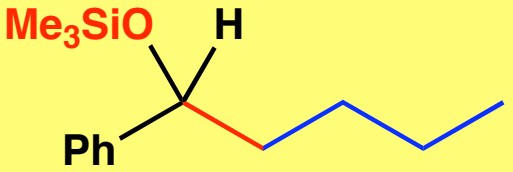
THF



50%

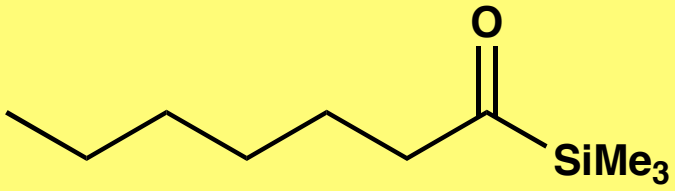
1,2-addition product

+

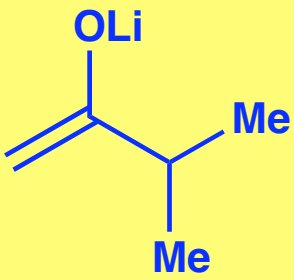


28%

Brook rearrangement product

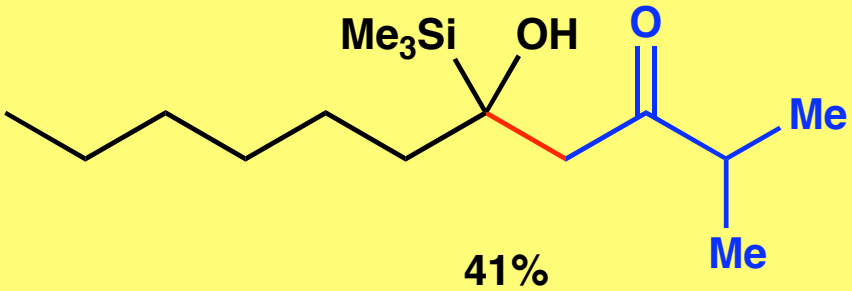


+



-80 ° to
-30 °C

THF



41%

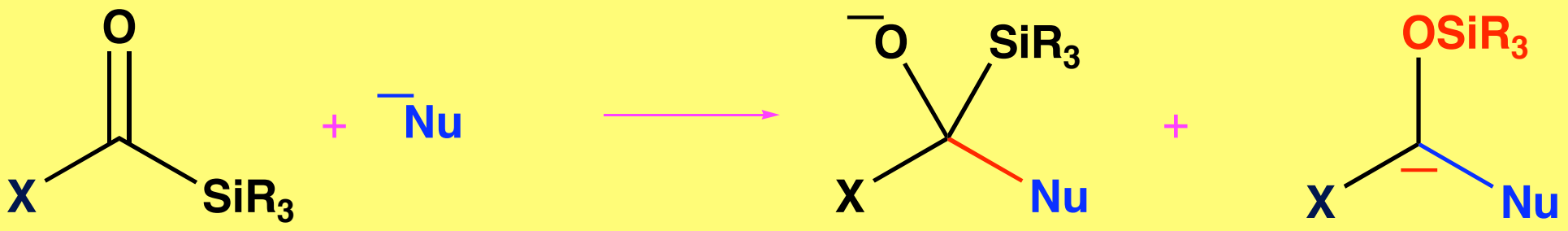
1,2-addition product

+

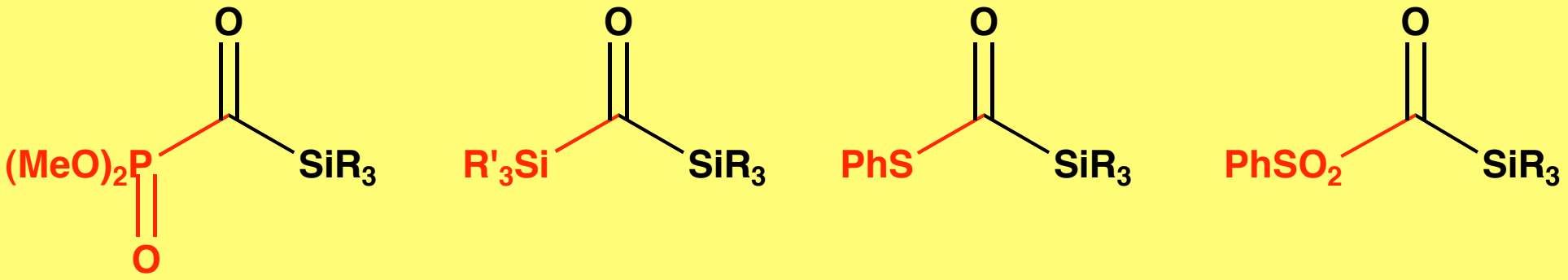
SM

55%

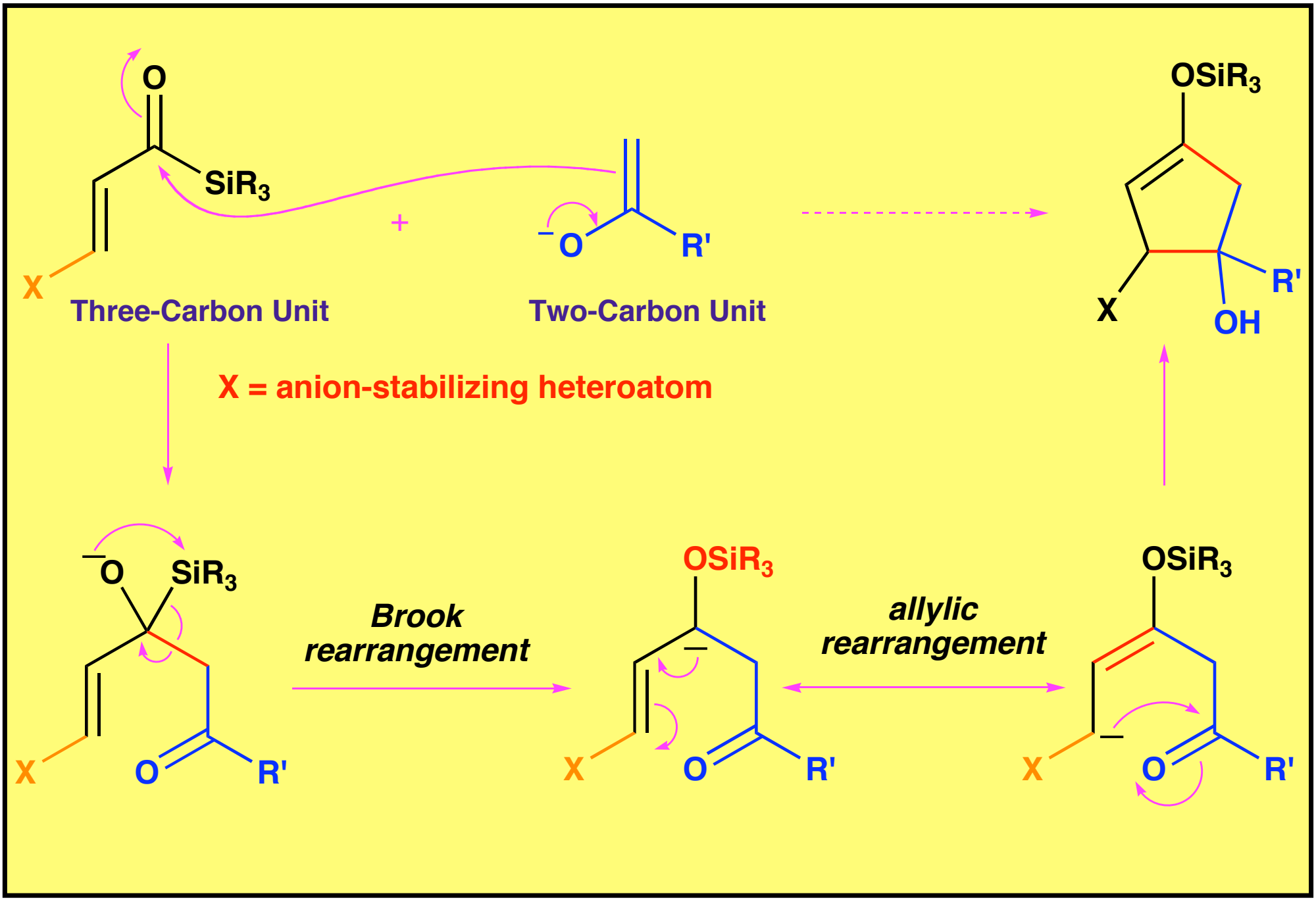
Attempted Synthesis of Heteroatom-Substituted Carbonylsilanes



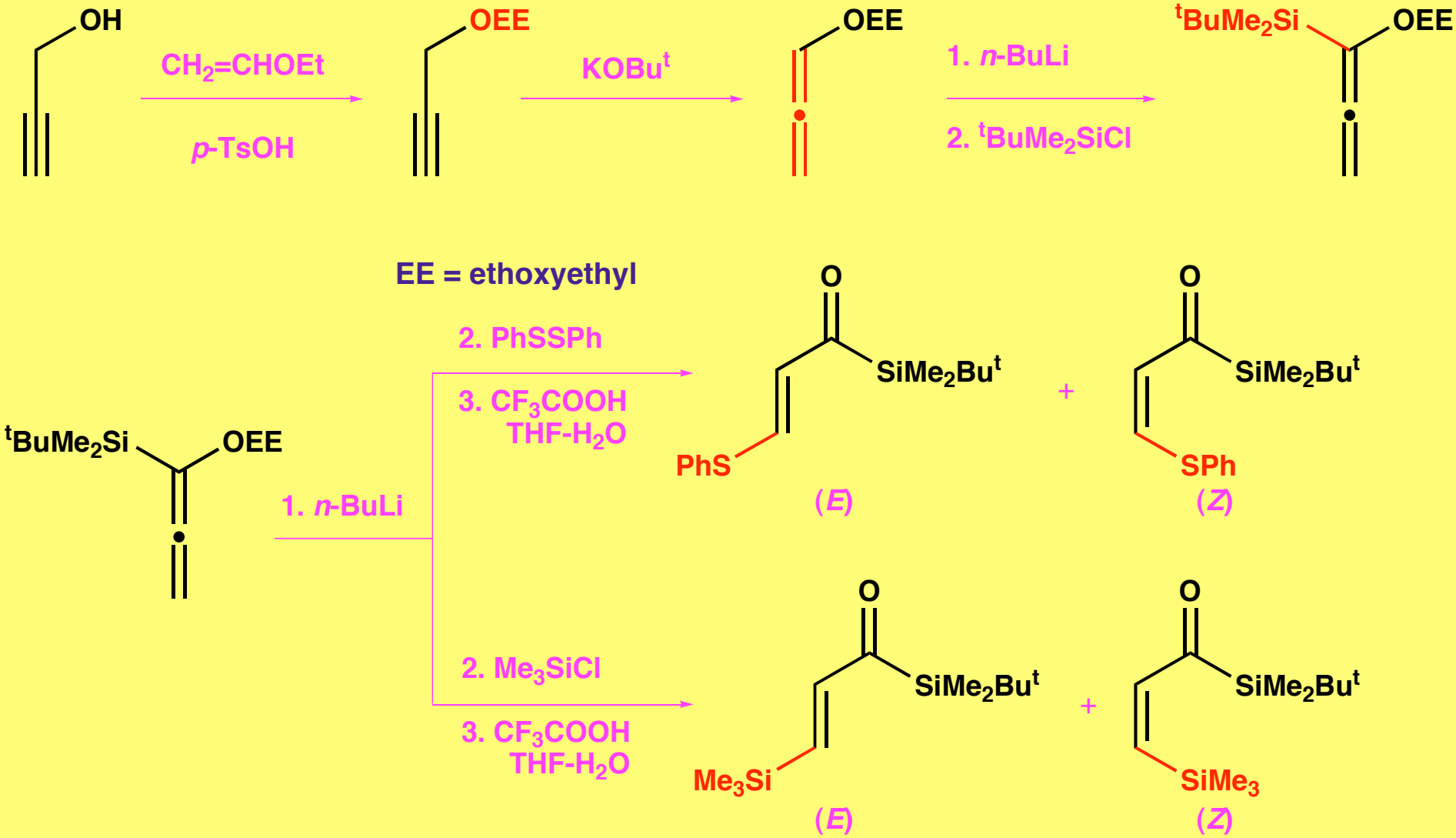
X = anion-stabilizing heteroatom



Brook Rearrangement-Mediated [3 + 2] Annulation

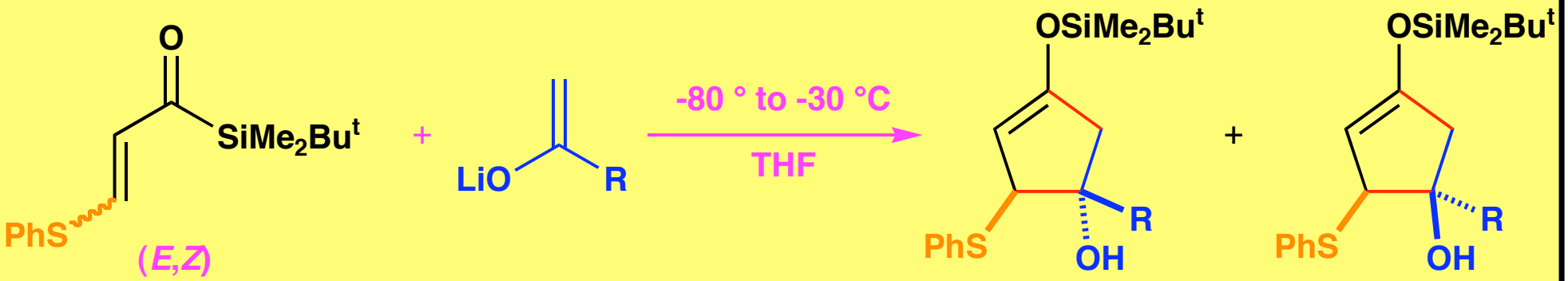


Preparation of β-(Phenylthio)- and β-(Trimethylsilyl)Acryloylsilanes

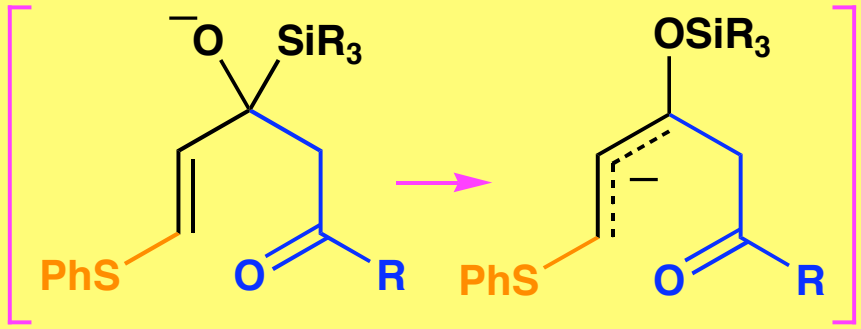


Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. *Tetrahedron* **1983**, *39*, 949-960.
Takeda, K.; Nakajima, A.; Takeda, M.; Yoshii, E. *Org. Synth.* **1999**, *76*, 199-213

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

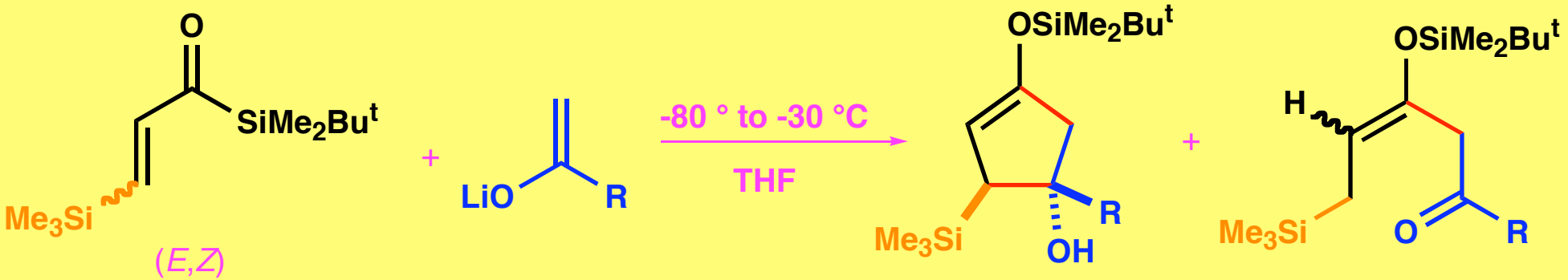


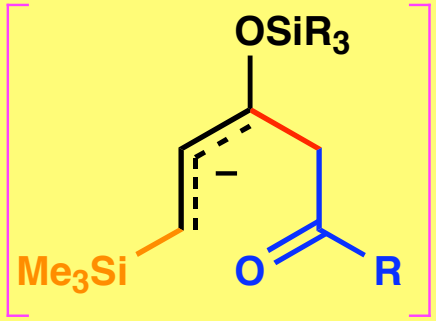
Et	**70%**	**5%**
Pr	**74%**	**7%**
***i*-Pr**	**55%**	**19%**
***n*-octyl**	**71%**	**8%**



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

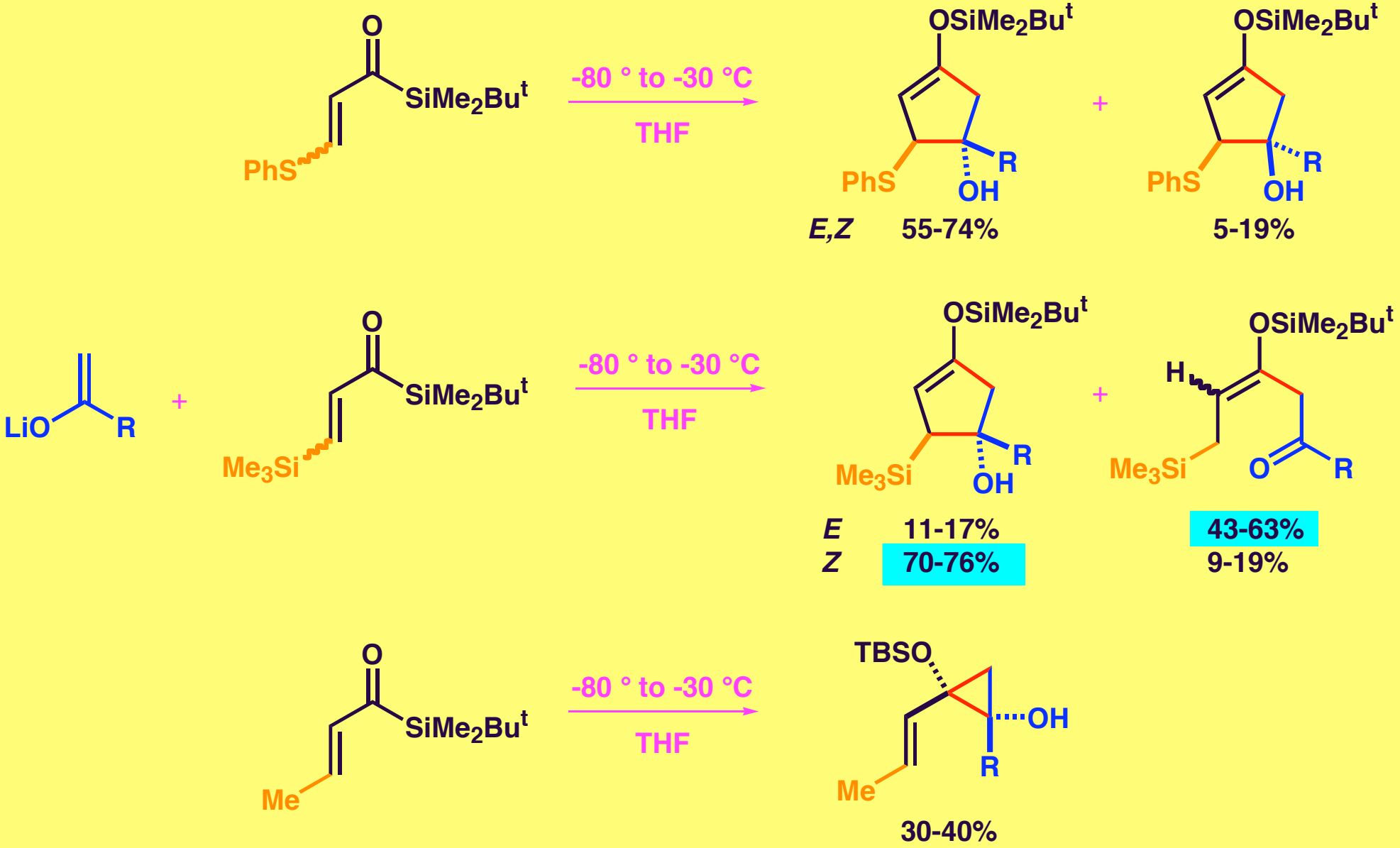
[3 + 2] Annulation Using Reaction of (β-Trimethylsilyl)acryloyl)silane and Lithium Enolates



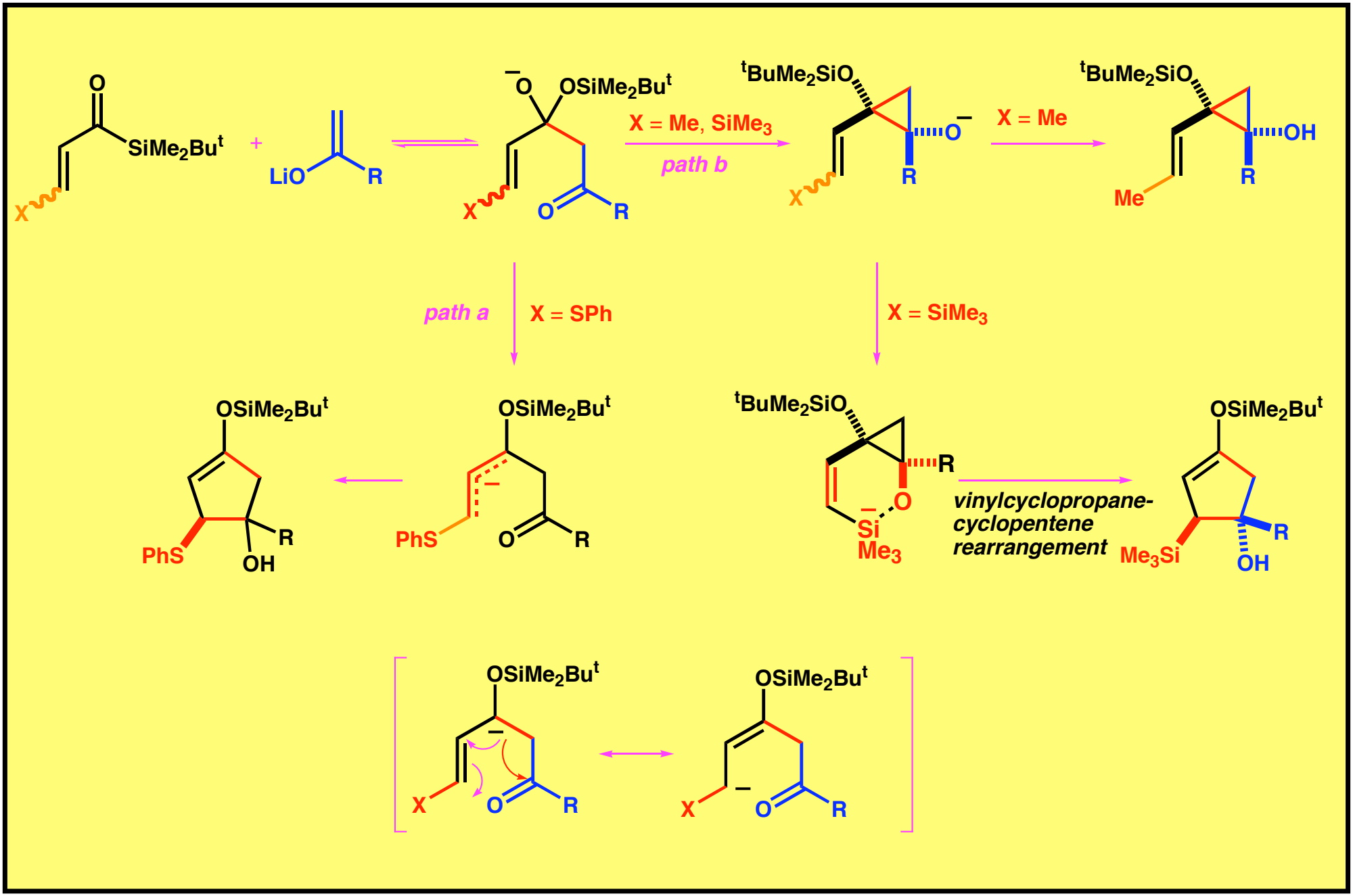


E	Et	17%	43%
	n-Pr	11%	57%
	i-Pr	14%	63%
Z	Et	75%	9%
	n-Pr	70%	19%
	i-Pr	76%	10%

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

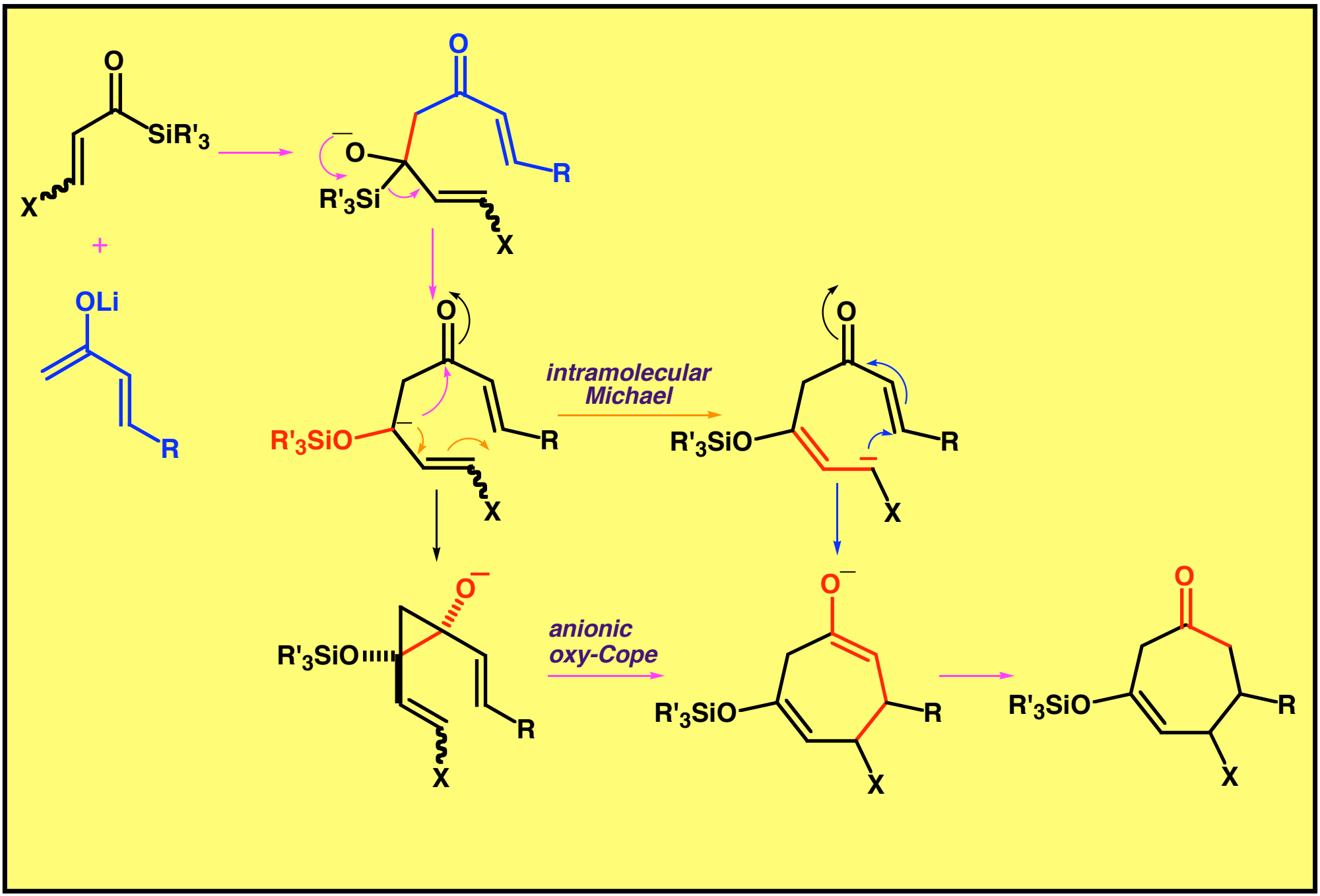


A Proposed Reaction Pathway for the [3 + 2] Annulation

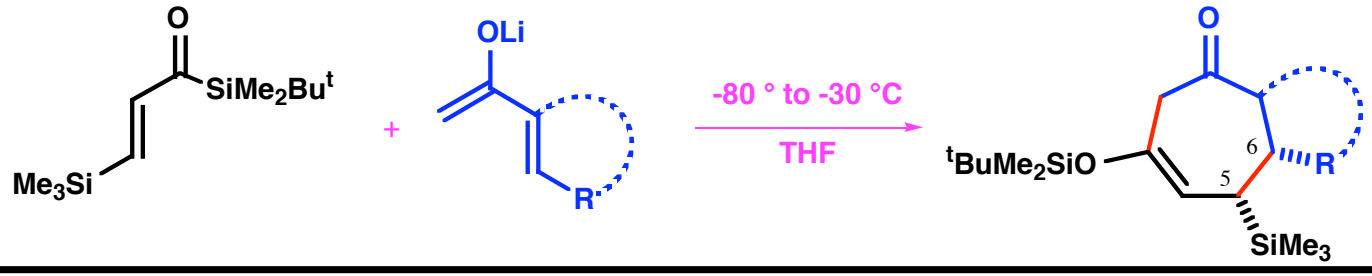


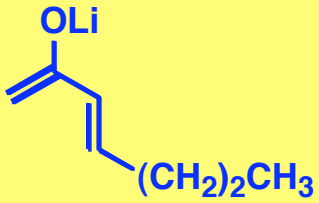
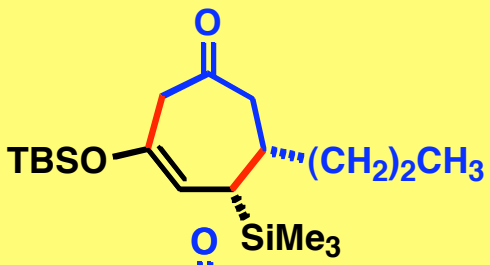
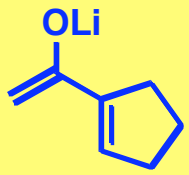
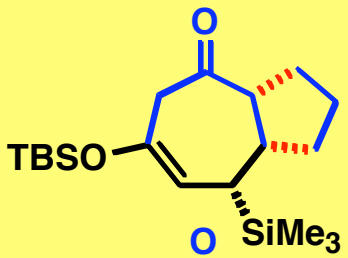
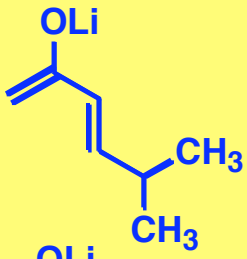
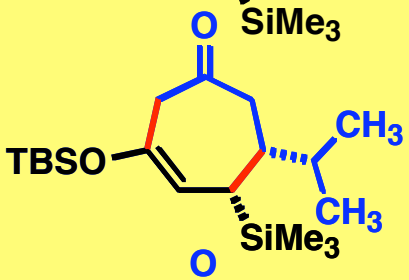
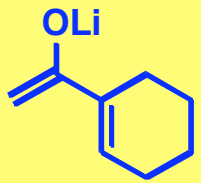
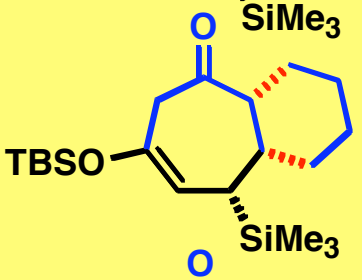
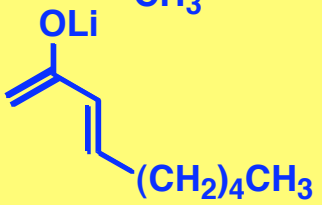
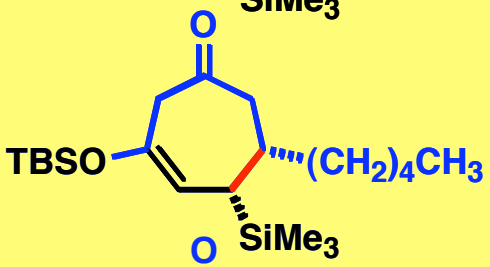
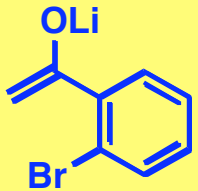
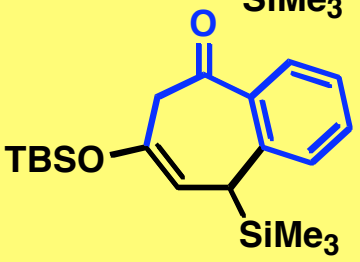
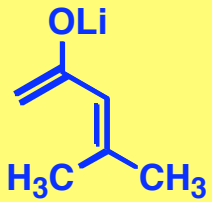
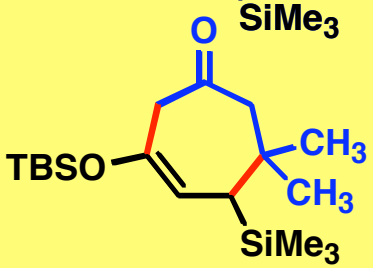
Kei Takeda, Kenji Yamawaki, Noriaki Hatakeyama *J. Org. Chem.* **67**, 1786-1794 (2002)

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

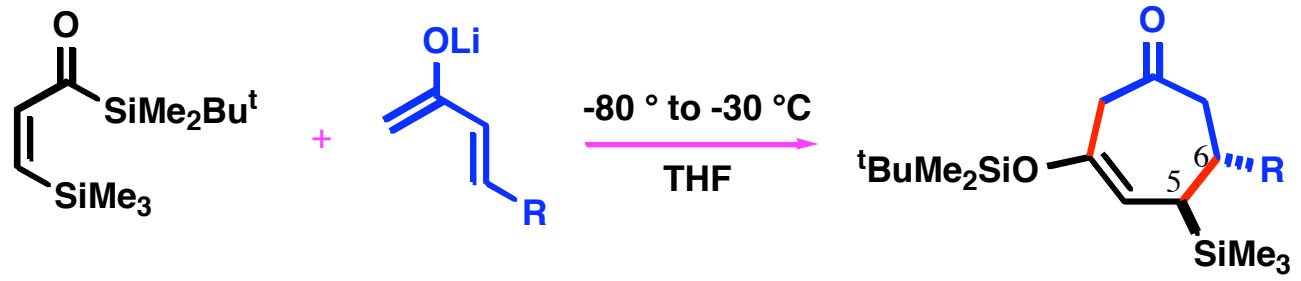


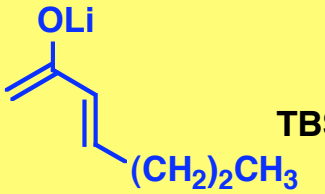
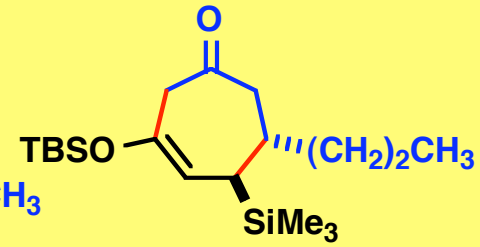
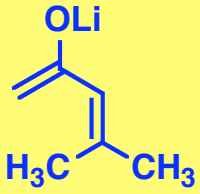
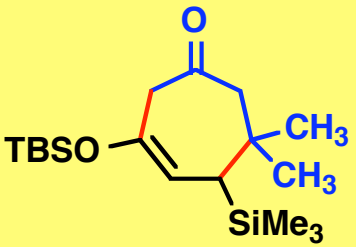
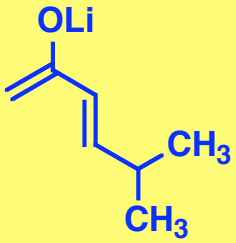
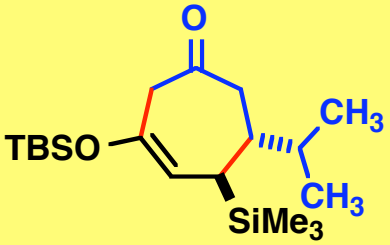
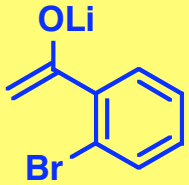
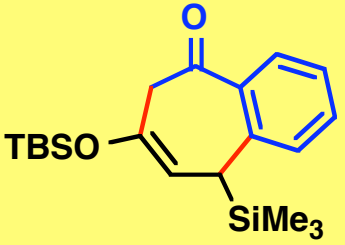
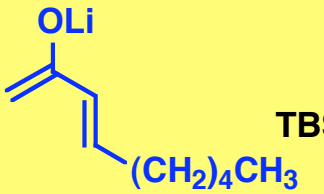
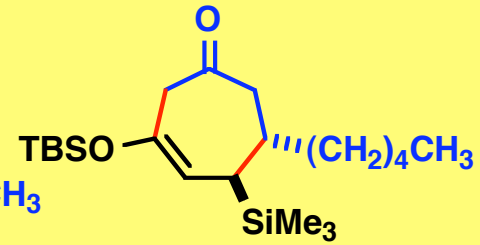
[3 + 4] Annulation Using (*E*)-(β-(Trimethylsilyl)acryloyl)silane



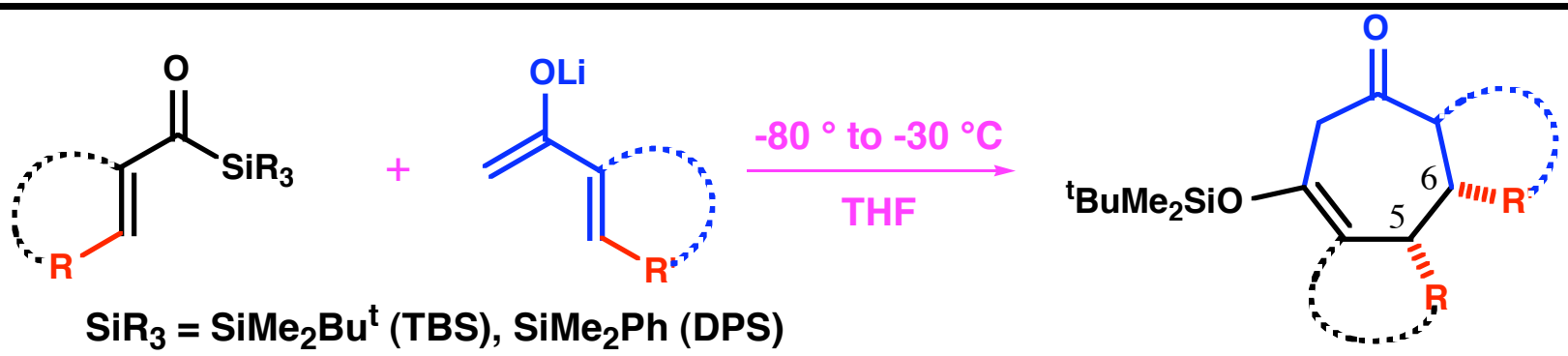
ketone enolate	product	yield	ketone enolate	product	yield
		73%			73%
		84%			82%
		84%			30%
		67%			

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

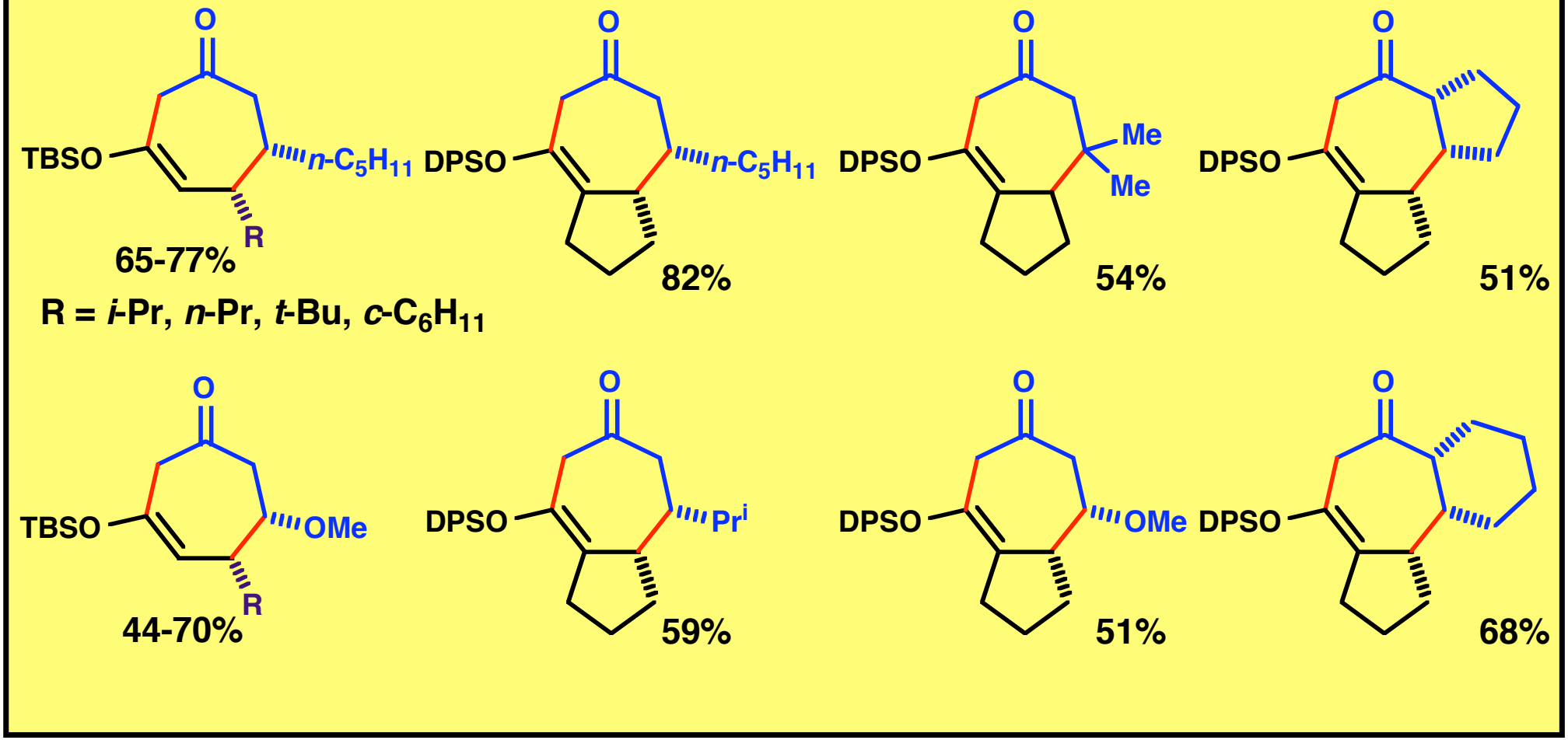


ketone enolate	product	yield (recovery of acylsilane)	ketone enolate	product	yield (recovery of acylsilane)
		31% (56%)			18% (31%)
		11% (59%)			0% (77%)
		29% (55%)			

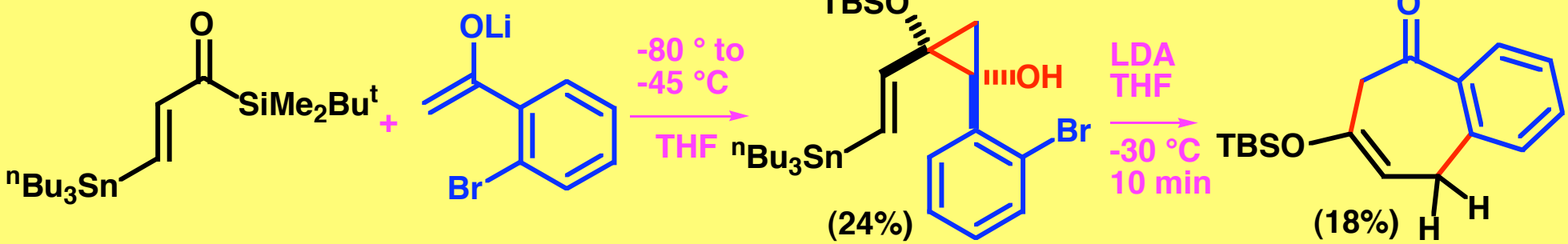
[3 + 4] Annulation Using (β-(Alkyl)acryloyl)silanes

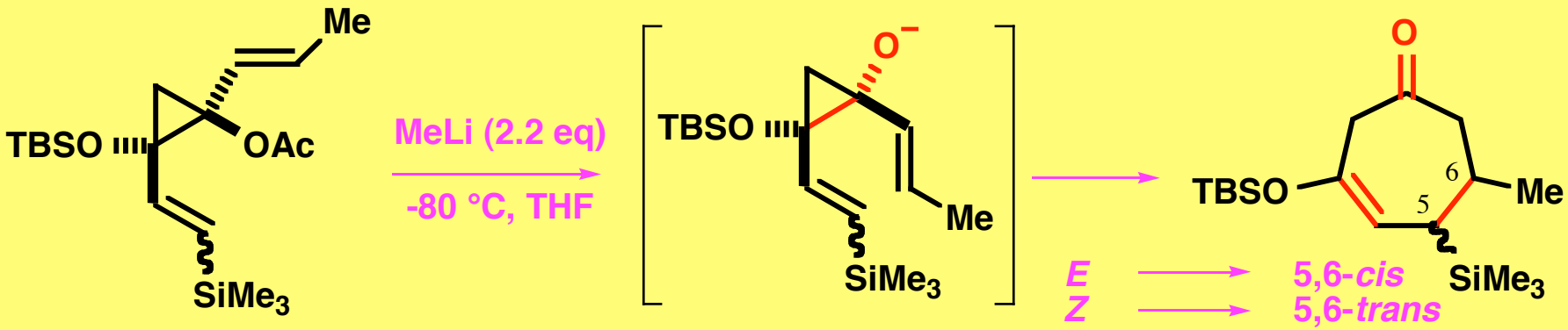


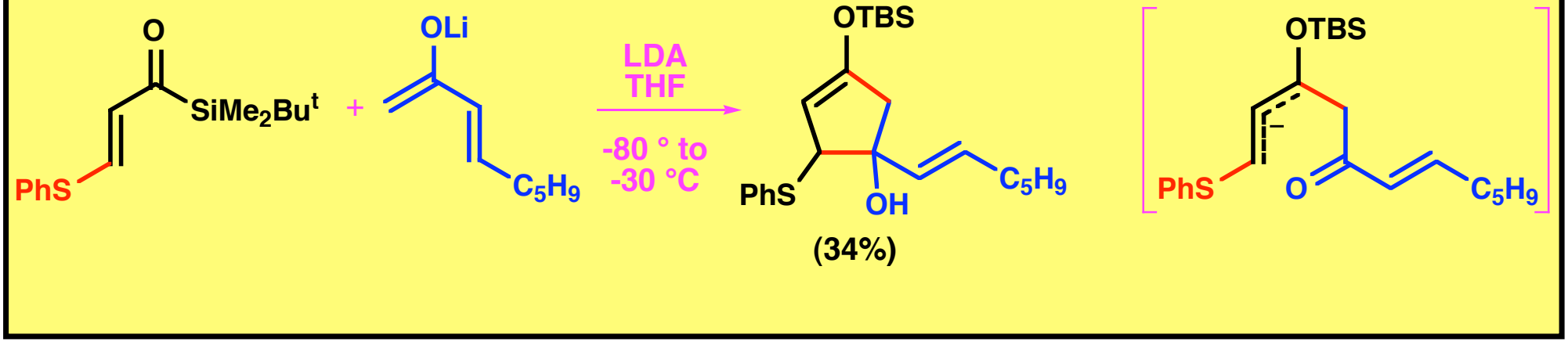
SiR_3 = $SiMe_2Bu^t$ (TBS), $SiMe_2Ph$ (DPS)



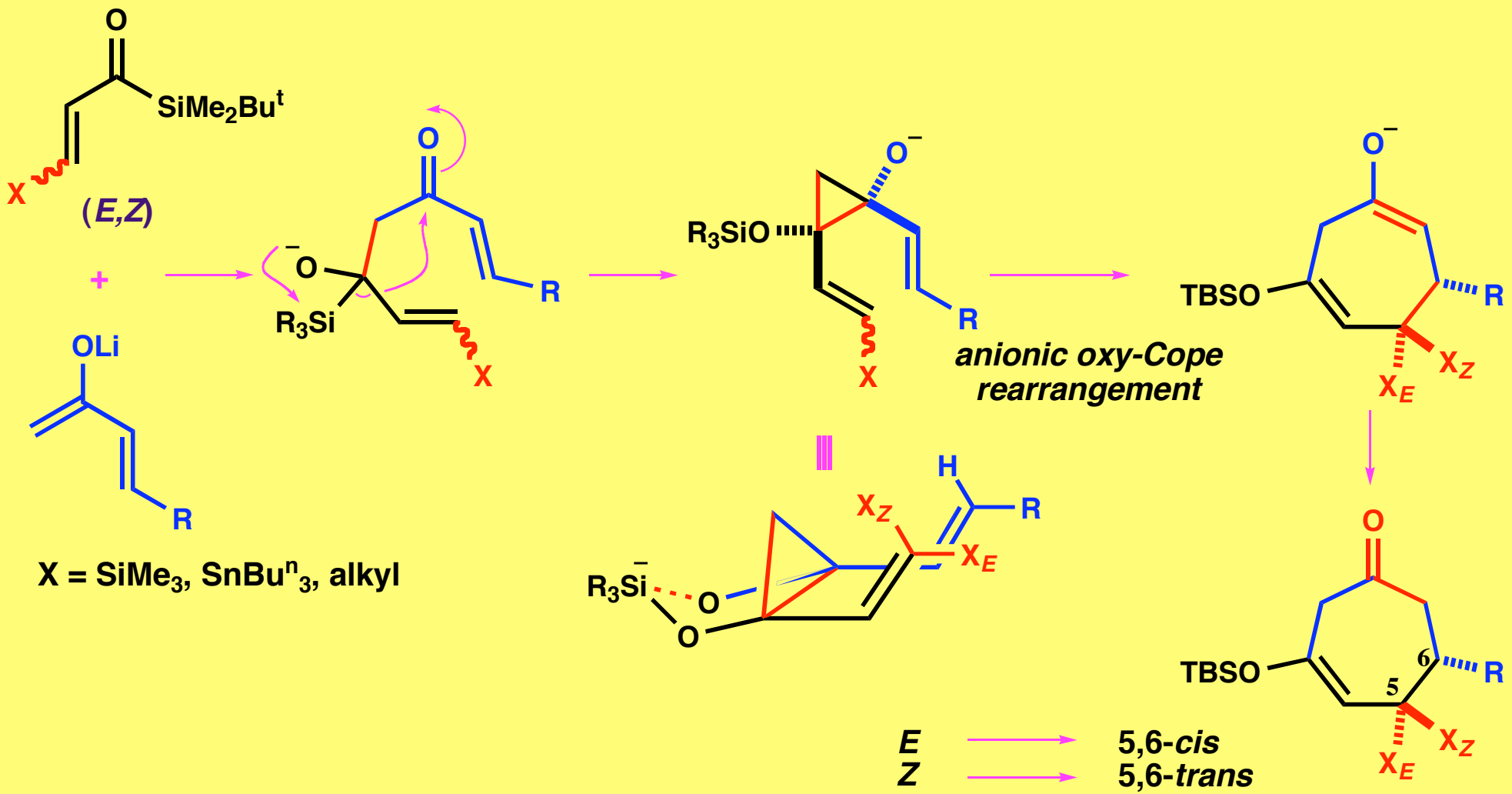
Mechanistic Studies of the [3 + 4] Annulation





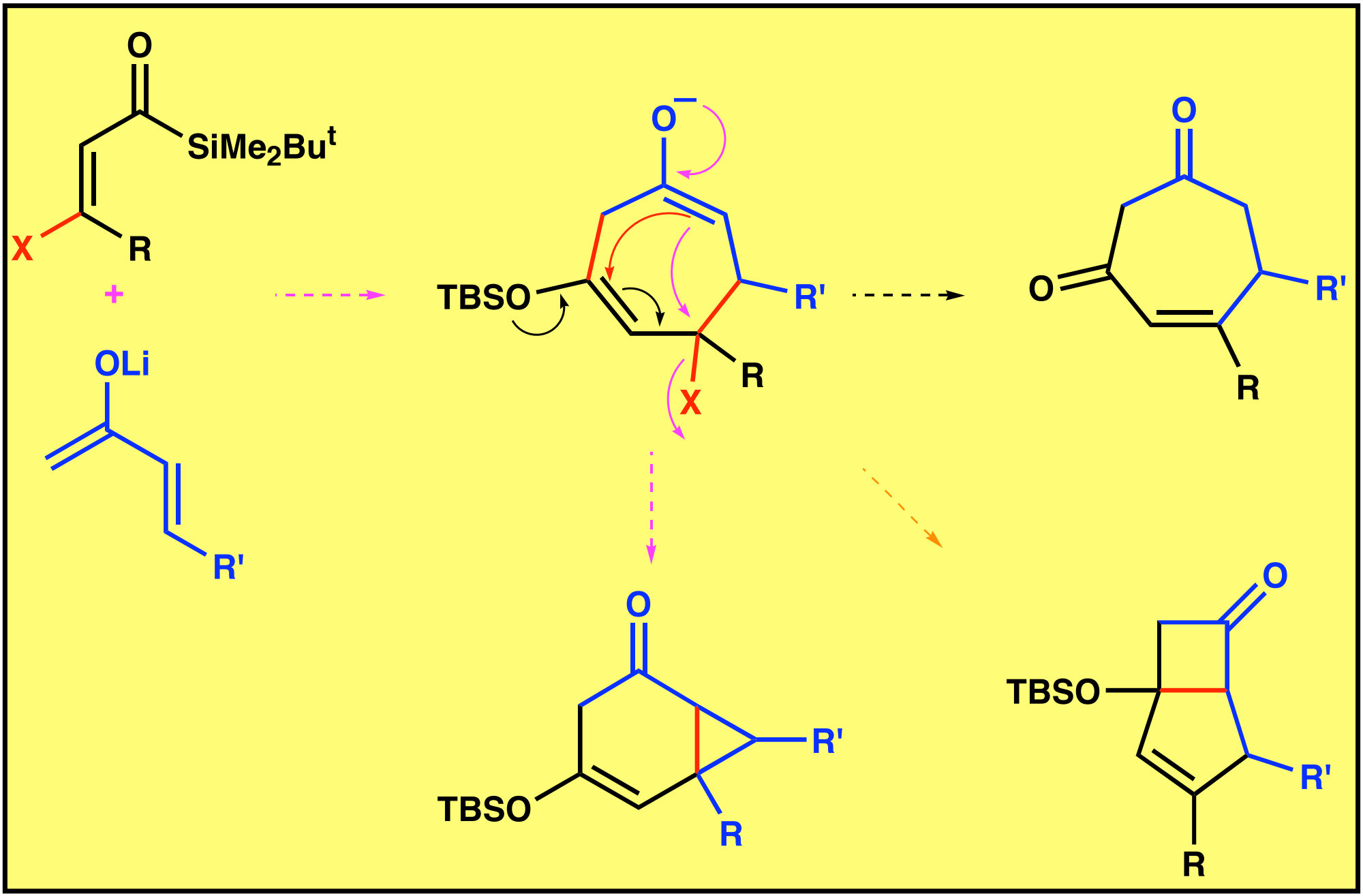


A Reaction Mechanism of the [3 + 4] Annulation Using the Reaction of Acryloylsilanes with the Lithium Enolates of Alkenyl Methyl Ketones



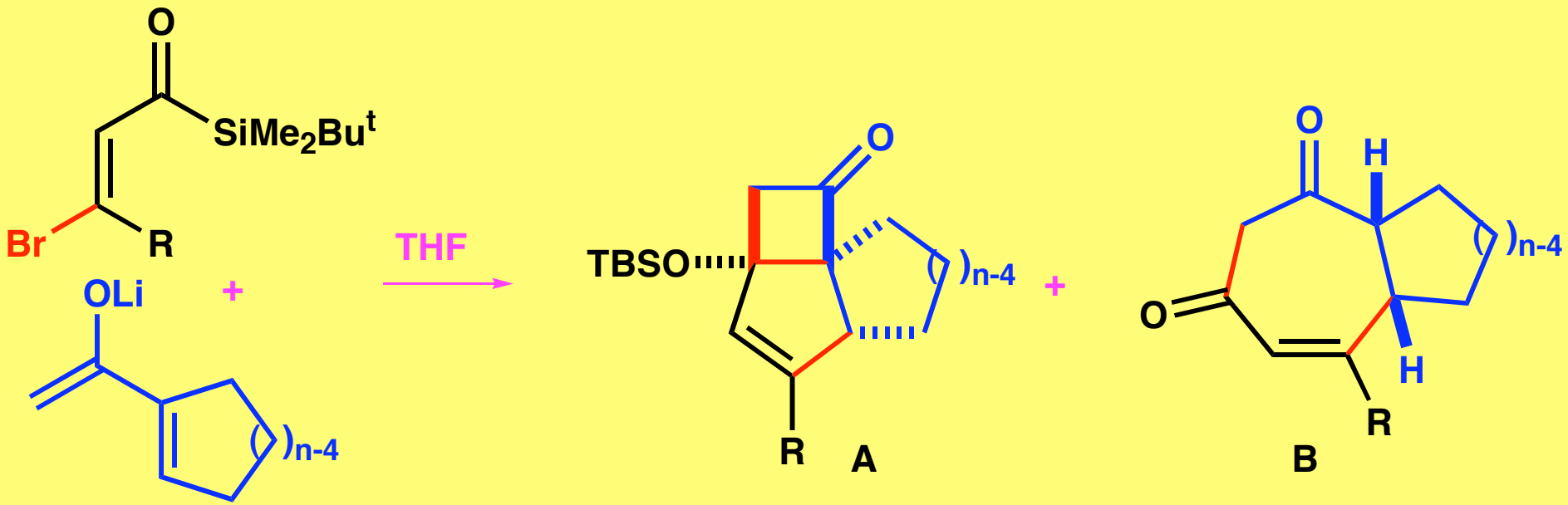
Takeda, K.; Takeda, M.; Nakajima, A.; Yoshii, E. *J. Am. Chem. Soc.* **1995**, *117*, 6400-6401.
Takeda, K.; Nakajima, A.; Takeda, M.; Okamoto, Y.; Sato, T.; Yoshii, E.; Koizumi, T. *J. Am. Chem. Soc.* **1998**, *120*, 4947-4959.
Takeda, K.; Nakajima, A.; Takeda, M.; Yoshii, E. *Org. Synth.* **1999**,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

[3 + 4] Annulation Using β-Haloacryloylsilanes



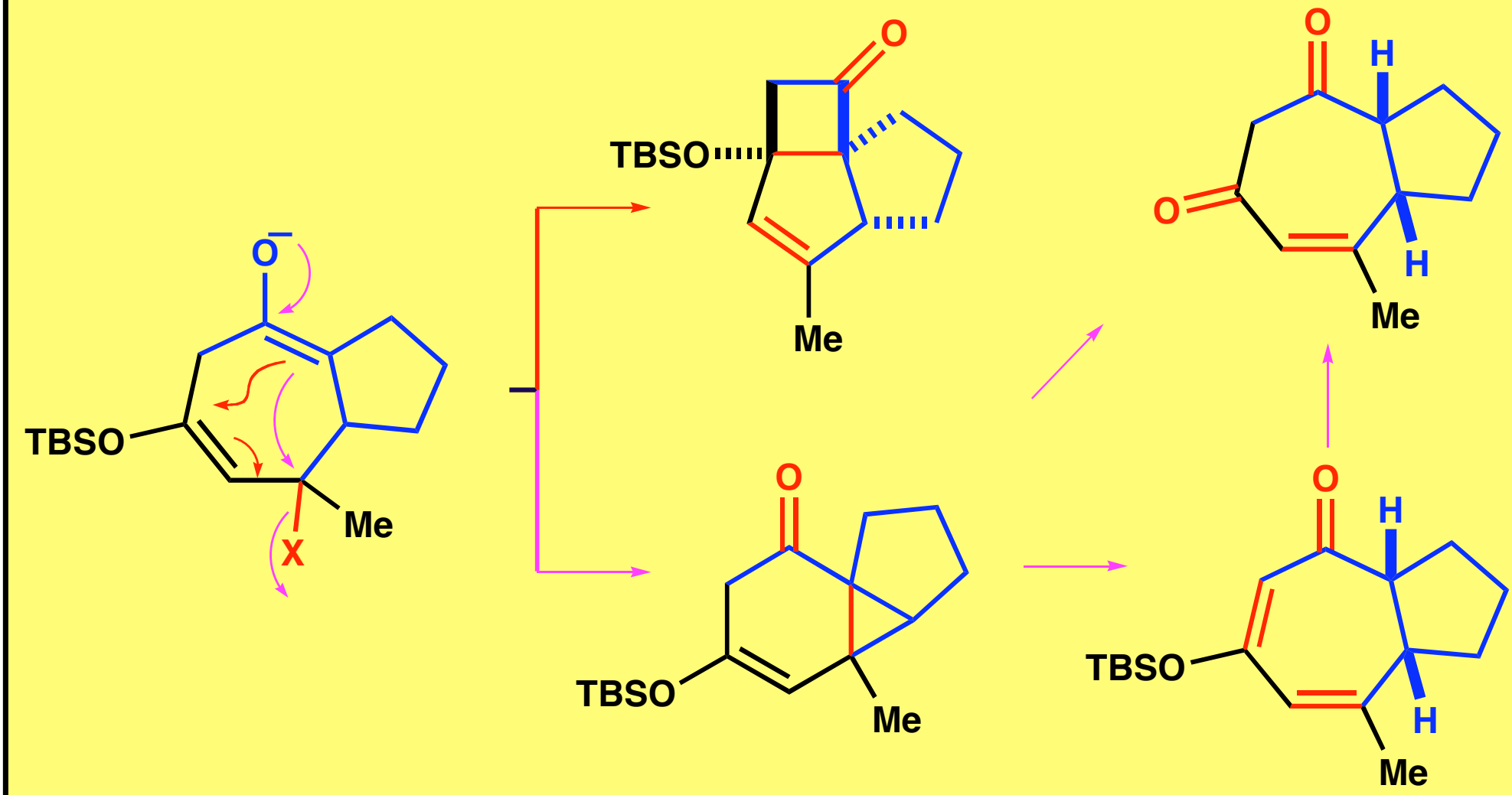
Takeda, K.; Ohtani, Y. *Org. Lett.* **1999**, *1*, 677-679.

[3 + 4] Annulation Using β-Bromoacryloylsilanes

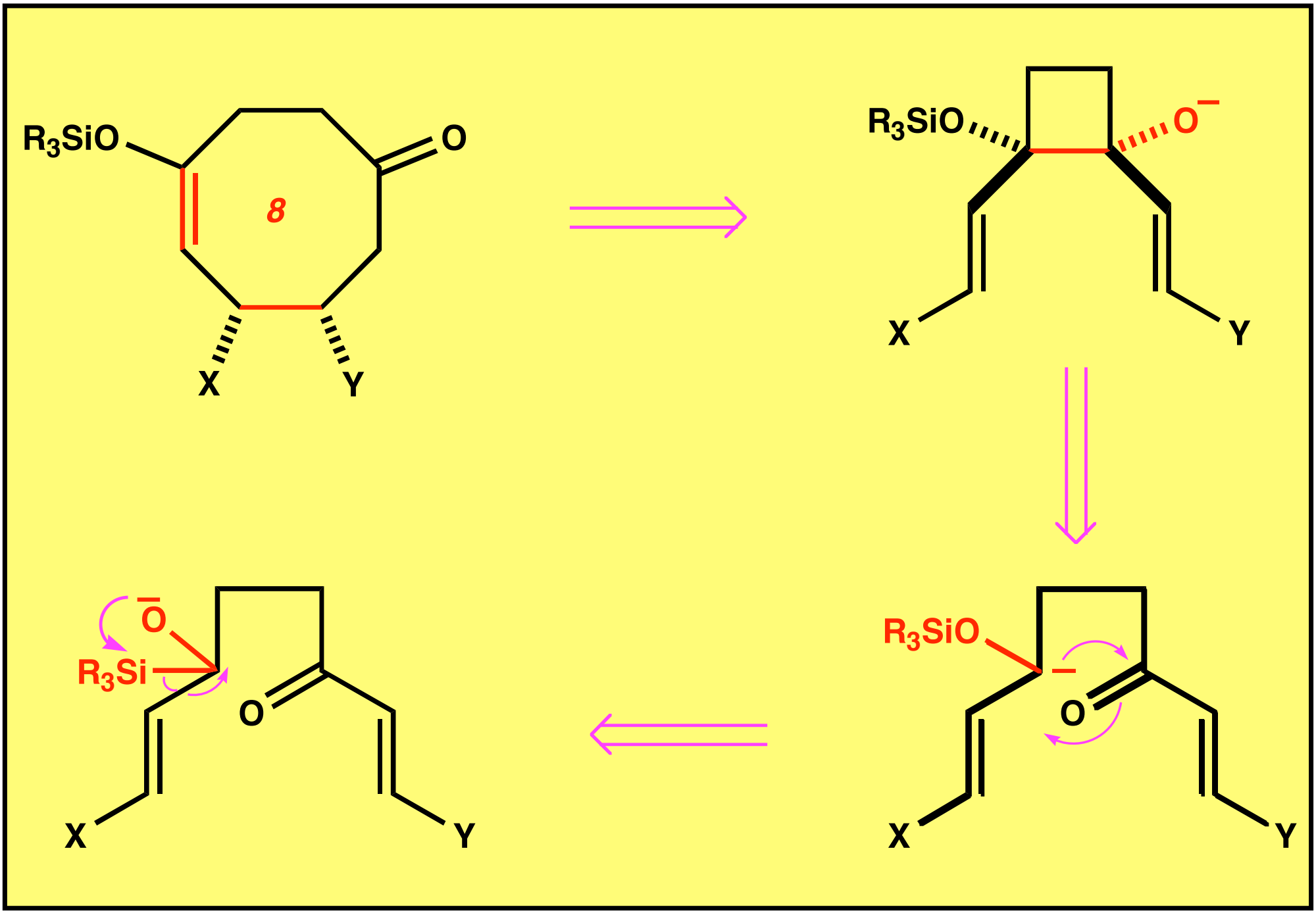


	R	conditions	yield (%) A n = 5	A n = 6	B n = 5	B n = 6
a	CH_3	-80 ° to 0 °C	68	27	0	45
b	*n*-Bu	-80 ° to 0 °C	49	27	0	14
c	*n*-hexyl	-80 ° to 0 °C	41	35	0	17
d	*t*-Bu	-80 ° to 0 °C	51	58	7	14
e	*c*-C_3H_5	-80 ° to 0 °C	56	39	0	32

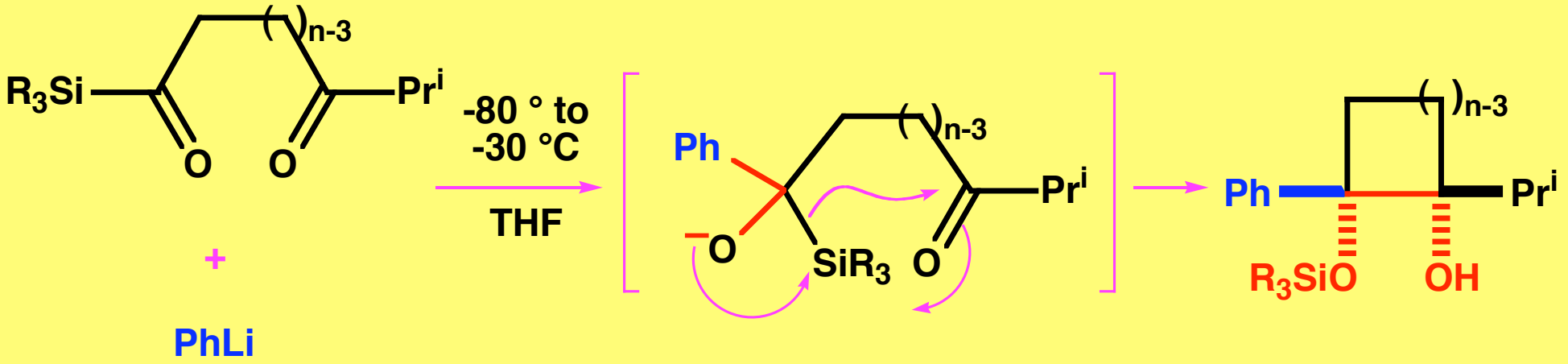
A Plausible Reaction Pathway for the [3 + 4] Annulation of β-Haloacryloylsilanes with Acetylcyclopentenone Enolates



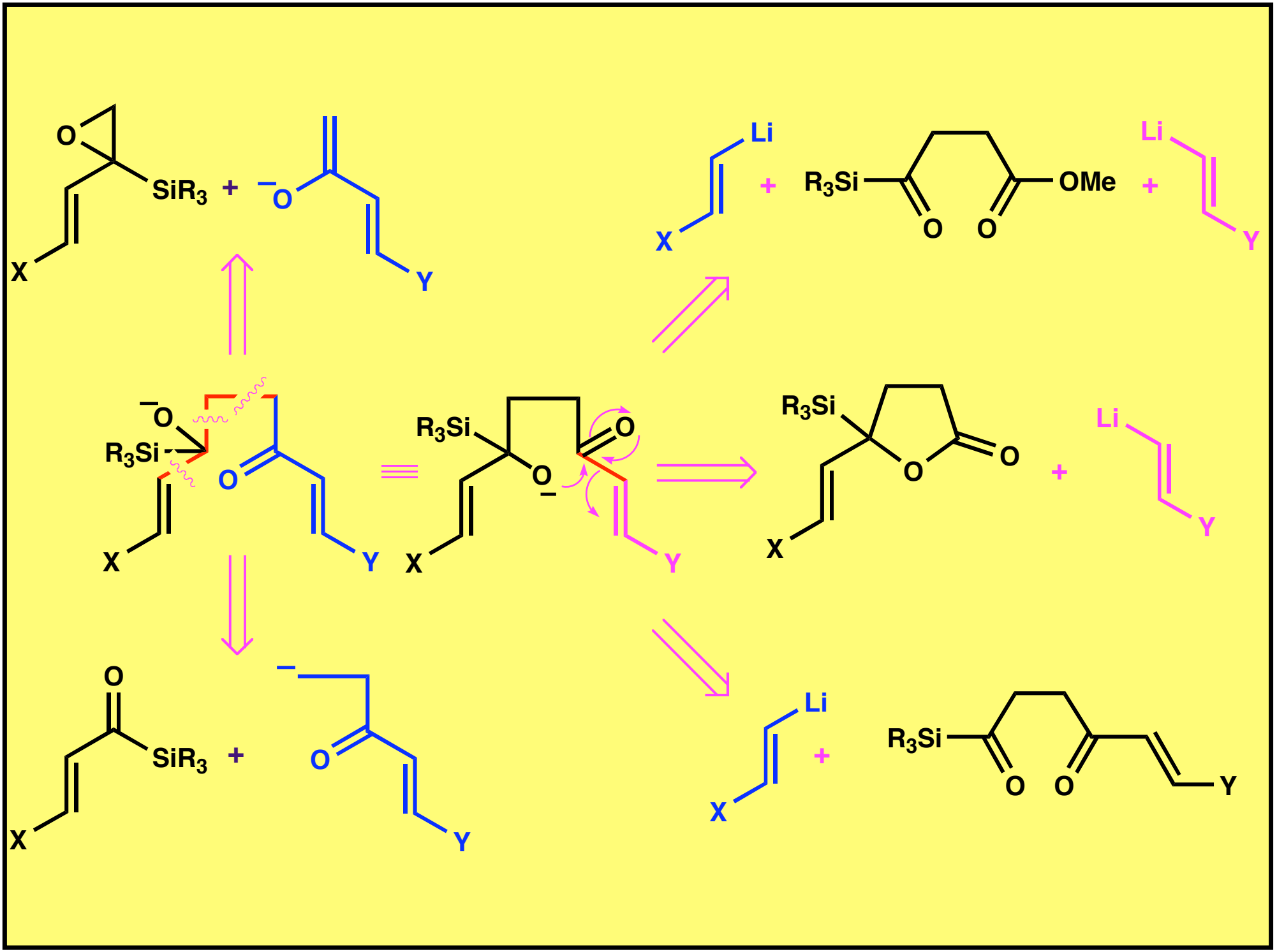
Brook Rearrangement-Mediated Formation of Eight-Membered Carbocycles



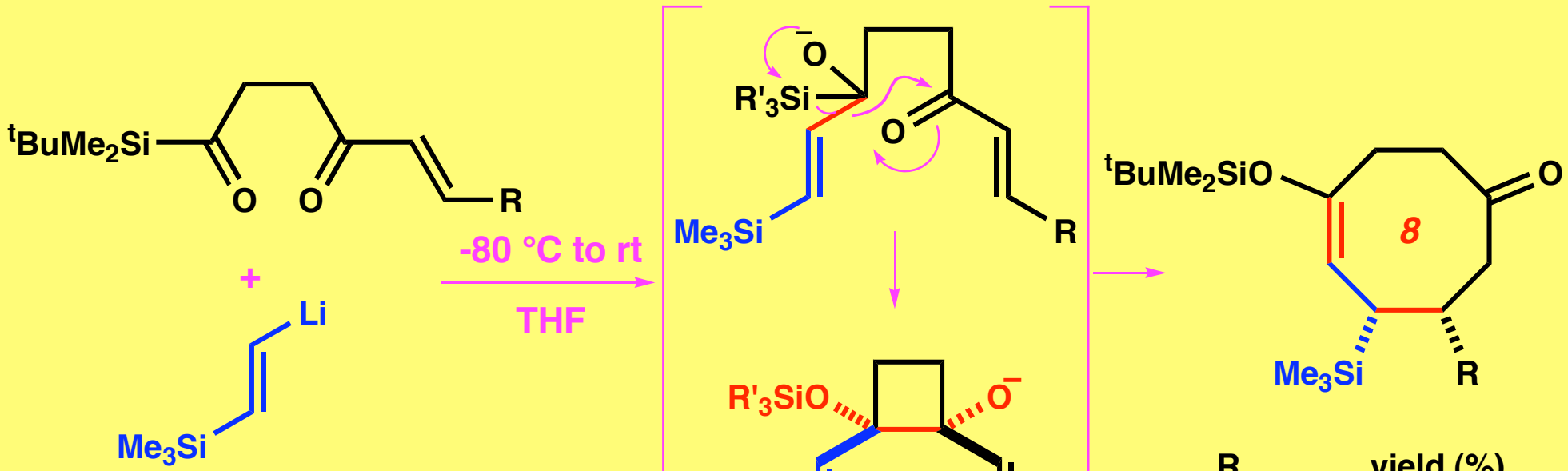
Formation of Four- to Seven-Membered Carbocycles by Tandem Brook Rearrangement-Intramolecular Aldol Reaction



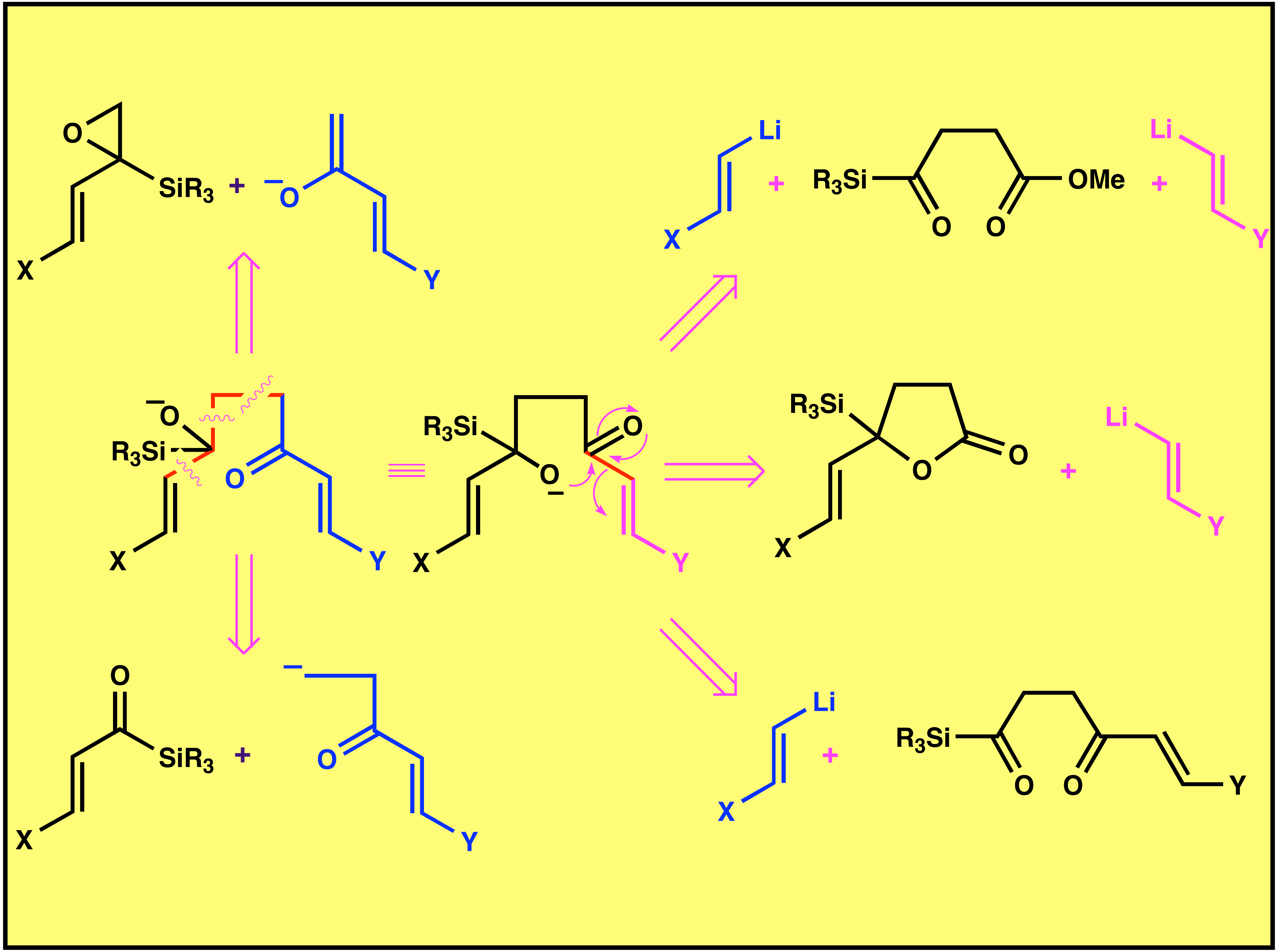
n	yield (%)
4	85
5	51
6	19
7	7


O
SiR3
X
Y
Li
OMe
R3Si

Formation of Eight-Membered Carbocycles by [6 + 2] Annulation

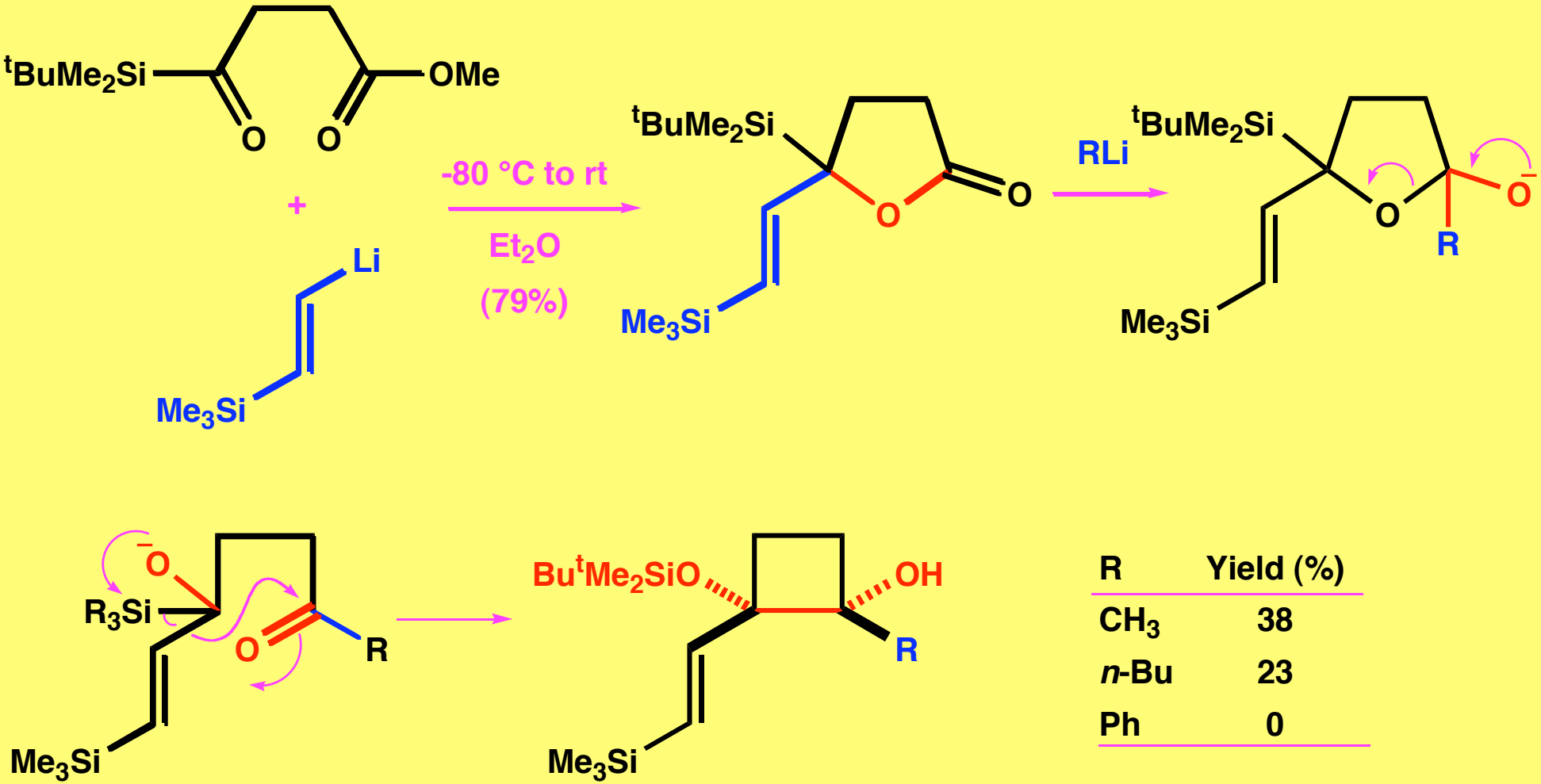


R	yield (%)
CH_3	45
n-Pr	42
c-hex	42
n-C_7H_{15}	45



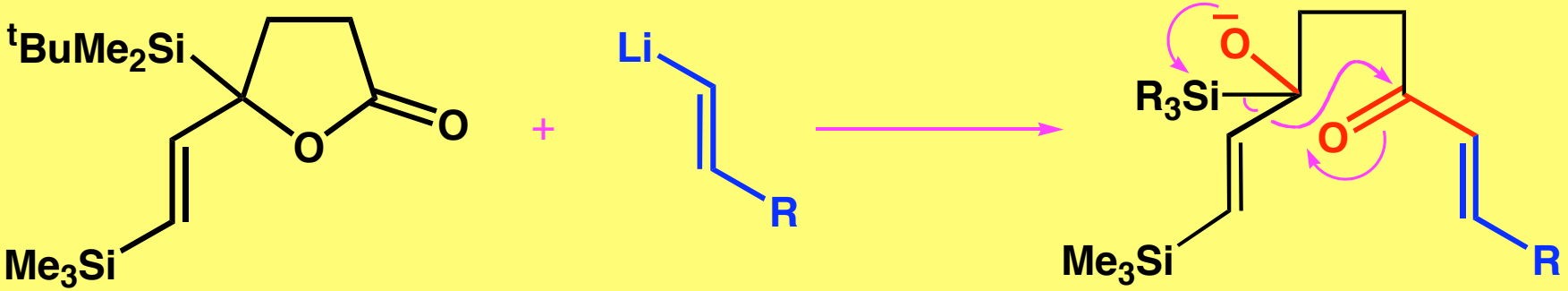
O
SiR3
+
O
Y
X
Li
X
+
R3Si
OMe
O
O
+
Li
Y
R3Si
O
X
Y
R3Si
O
O
X
Y
R3Si
O
O
X
+
Li
Y
O
SiR3
+
O
X
Y
Li
X
+
R3Si
O
O
Y

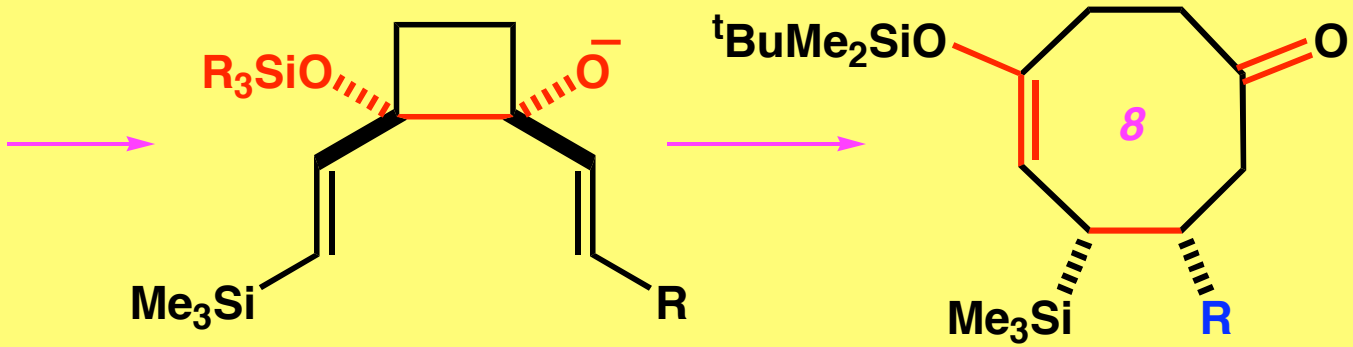
Formation of Four-Membered Carbocycles by γ-Silyl- γ-butyrolactone



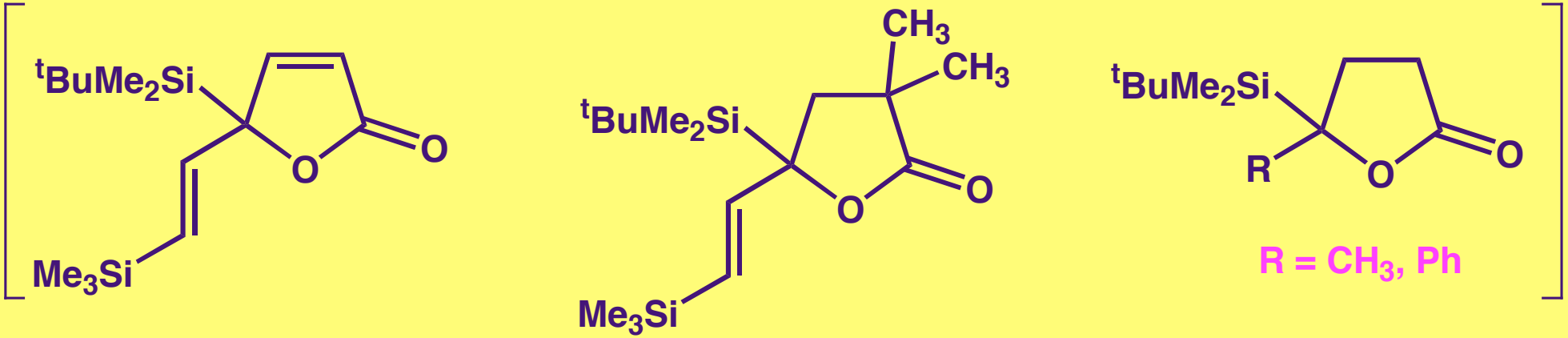
R	Yield (%)
CH_3	38
n-Bu	23
Ph	0

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

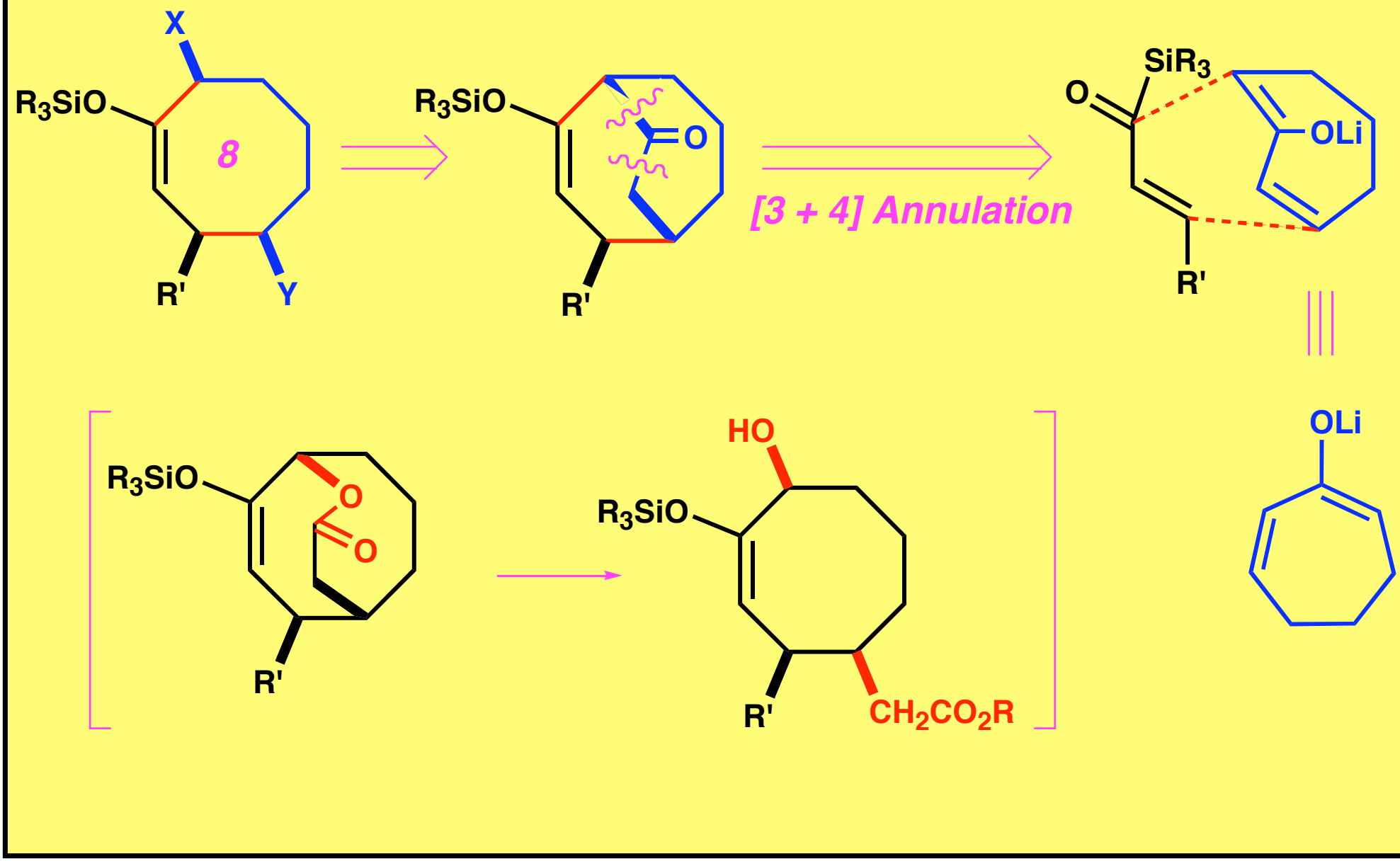




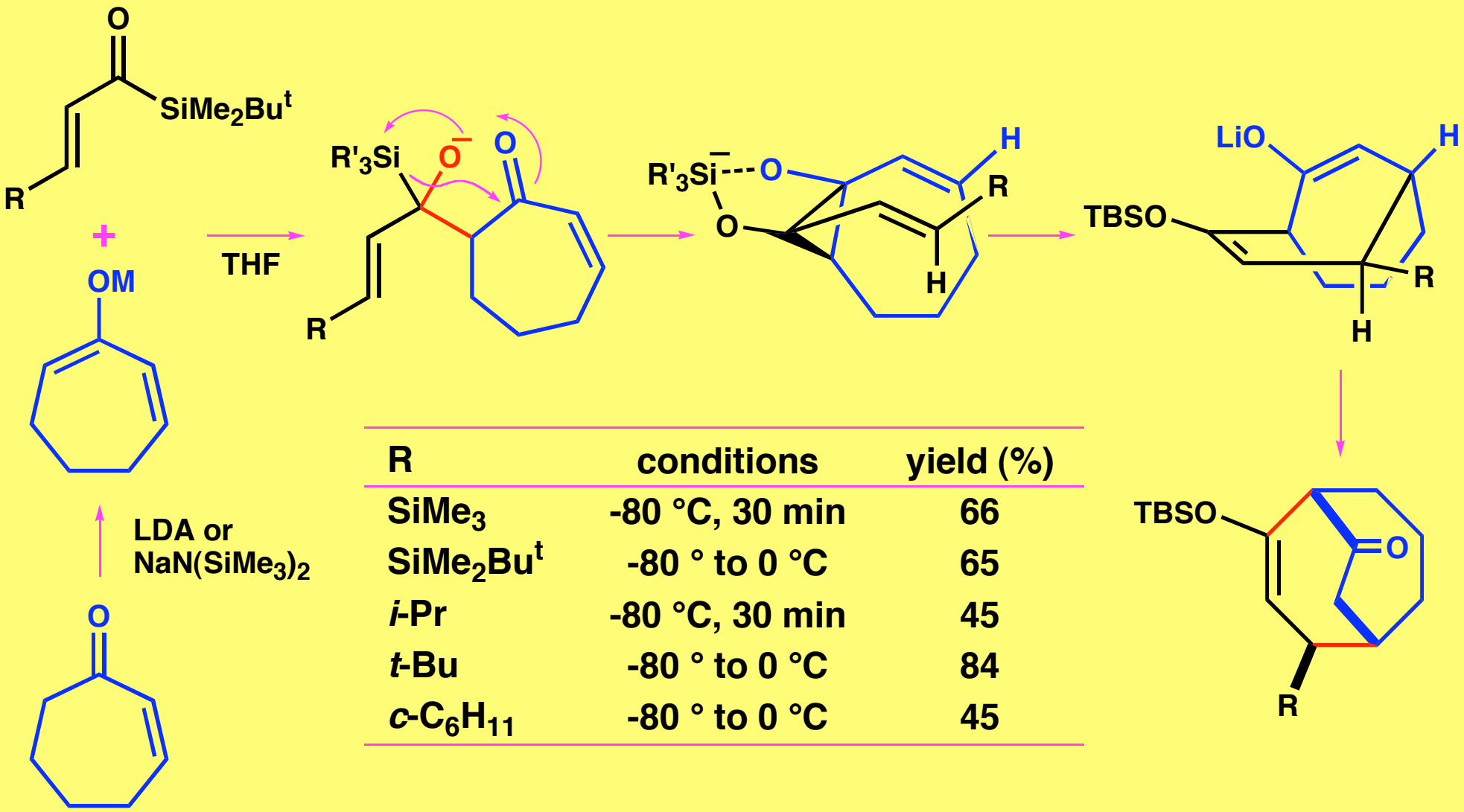
R	yield (%)
$SiMe_3$	8
CH_3	8



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

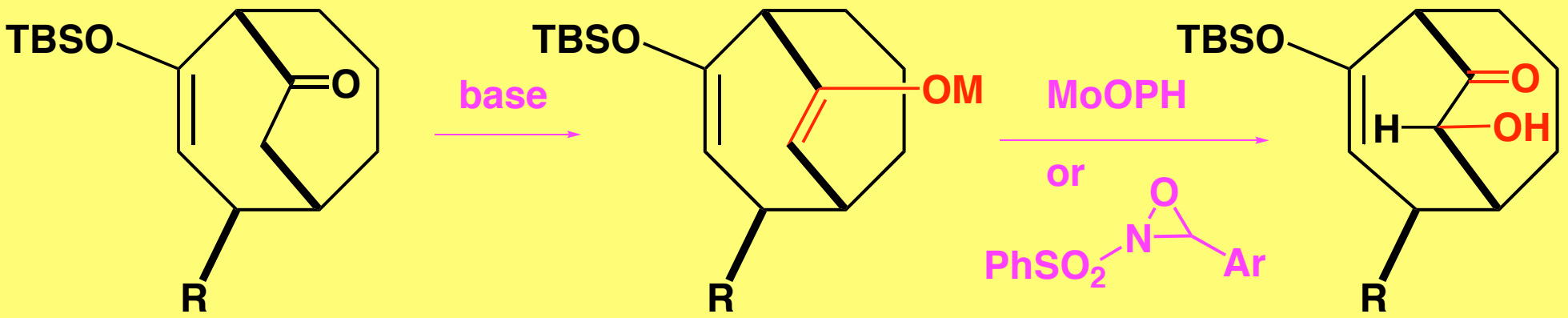


Formation of Eight-Membered Carbocycles by [3 + 4] Annulation



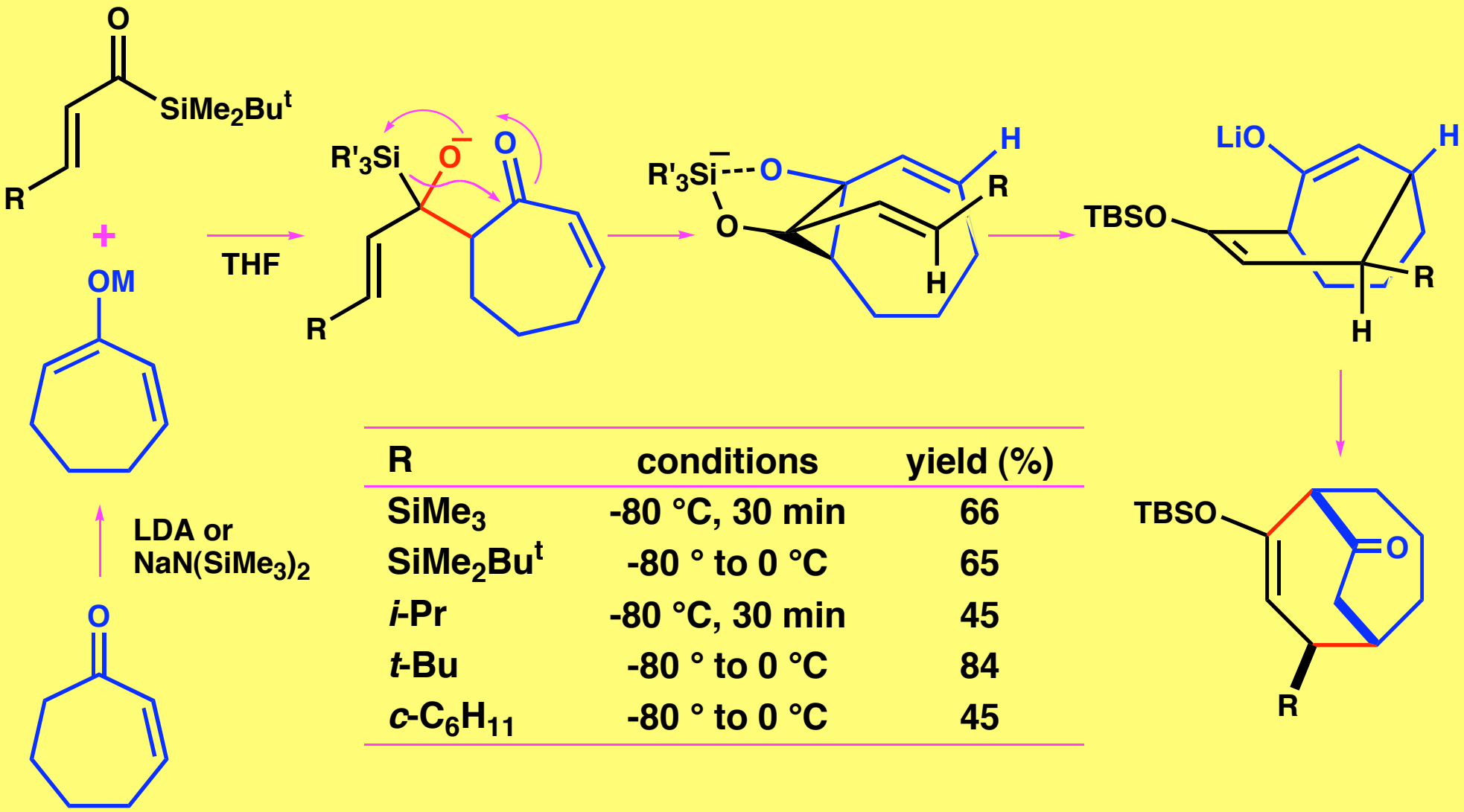
R	conditions	yield (%)
$SiMe_3$	-80 °C, 30 min	66
$SiMe_2Bu^t$	-80 ° to 0 °C	65
i-Pr	-80 °C, 30 min	45
t-Bu	-80 ° to 0 °C	84
c-C_6H_{11}	-80 ° to 0 °C	45

α-Hydroxylation of Bicyclo[2.2.2]decenones



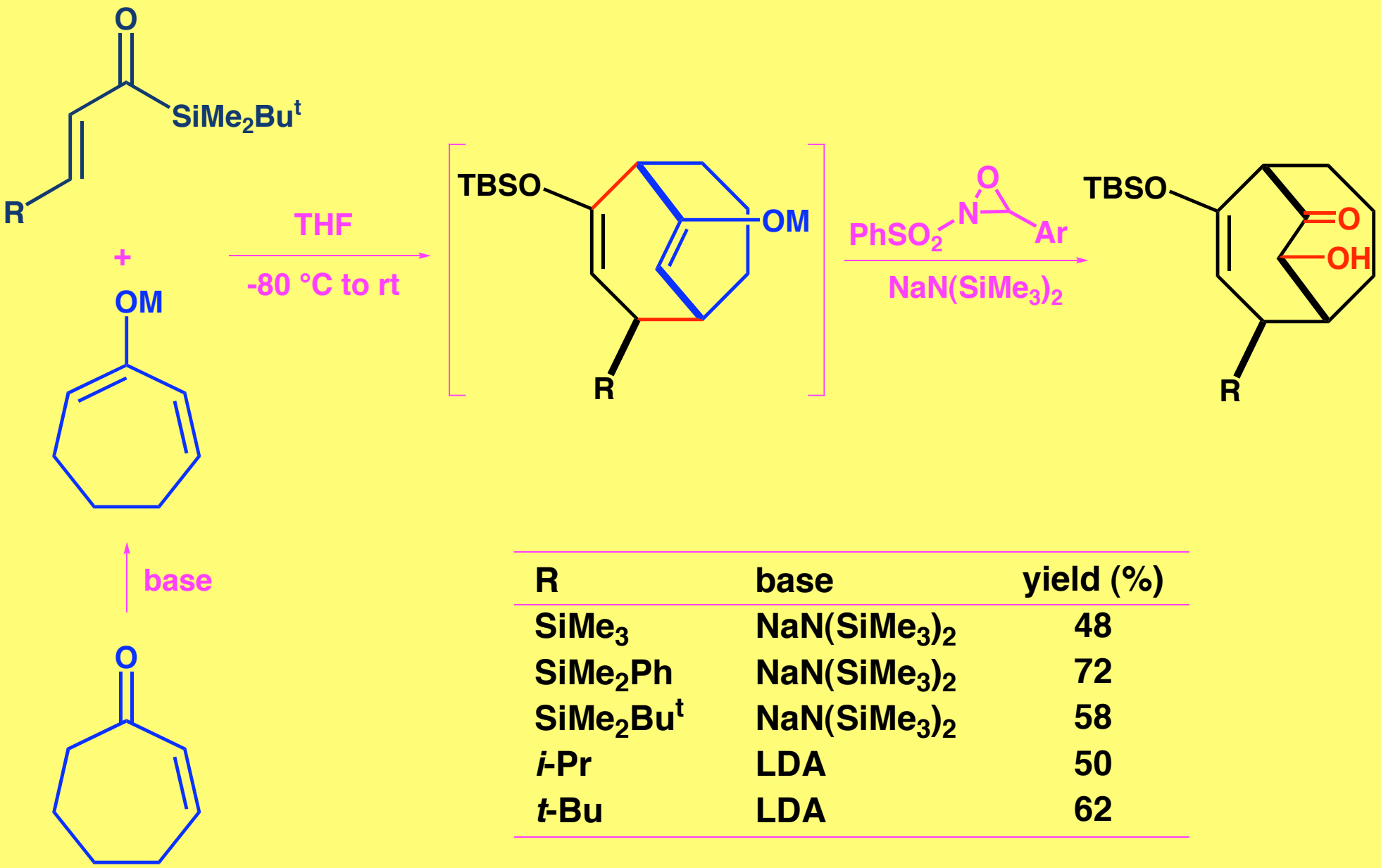
		yield (%)	
R	base	Vedejs 法	Davis 法
$SiMe_3$	LDA	52	
$SiMe_3$	$NaN(SiMe_3)_2$		76
t-Bu	LDA	66	
t-Bu	$NaN(SiMe_3)_2$		71

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



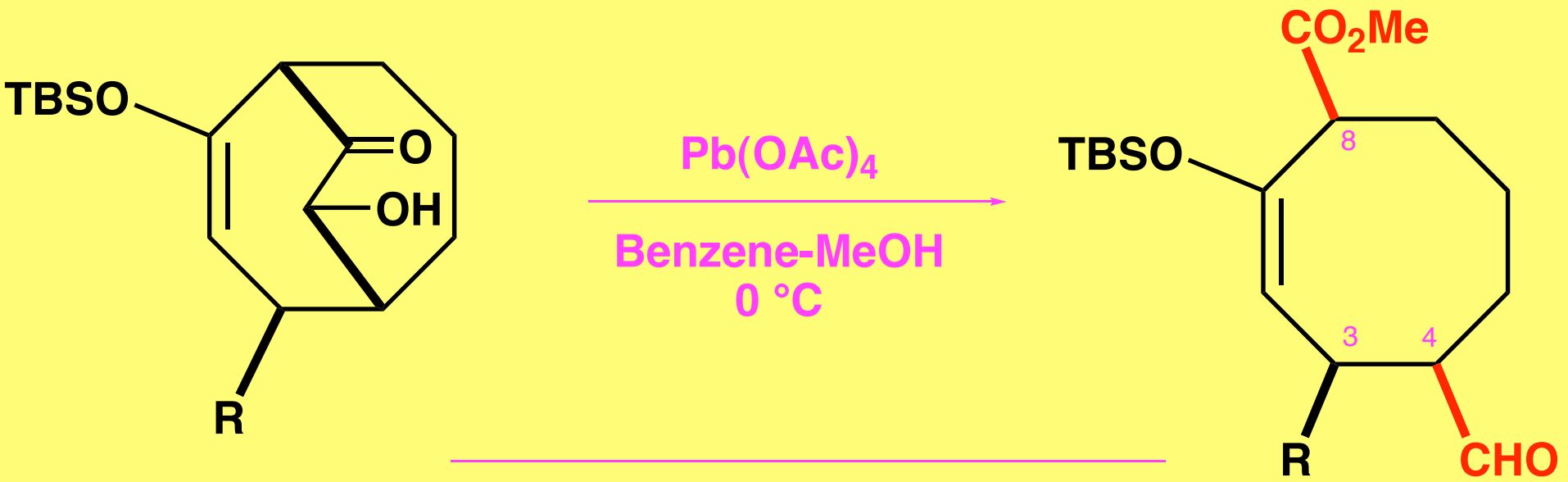
R	conditions	yield (%)
$SiMe_3$	-80 °C, 30 min	66
$SiMe_2Bu^t$	-80 ° to 0 °C	65
i-Pr	-80 °C, 30 min	45
t-Bu	-80 ° to 0 °C	84
c-C_6H_{11}	-80 ° to 0 °C	45

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

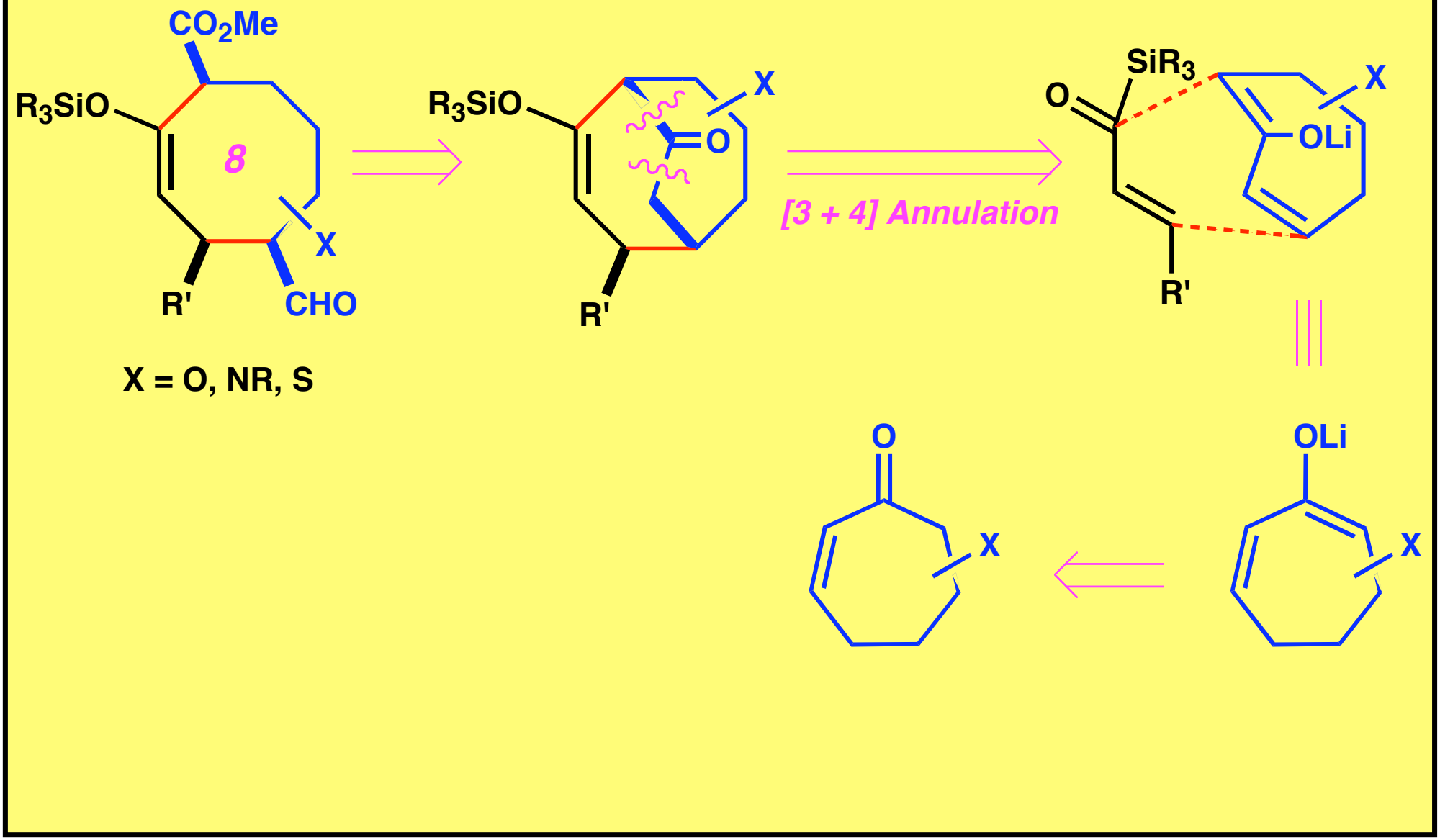
Oxidative Cleavage of α-Hydroxyketones



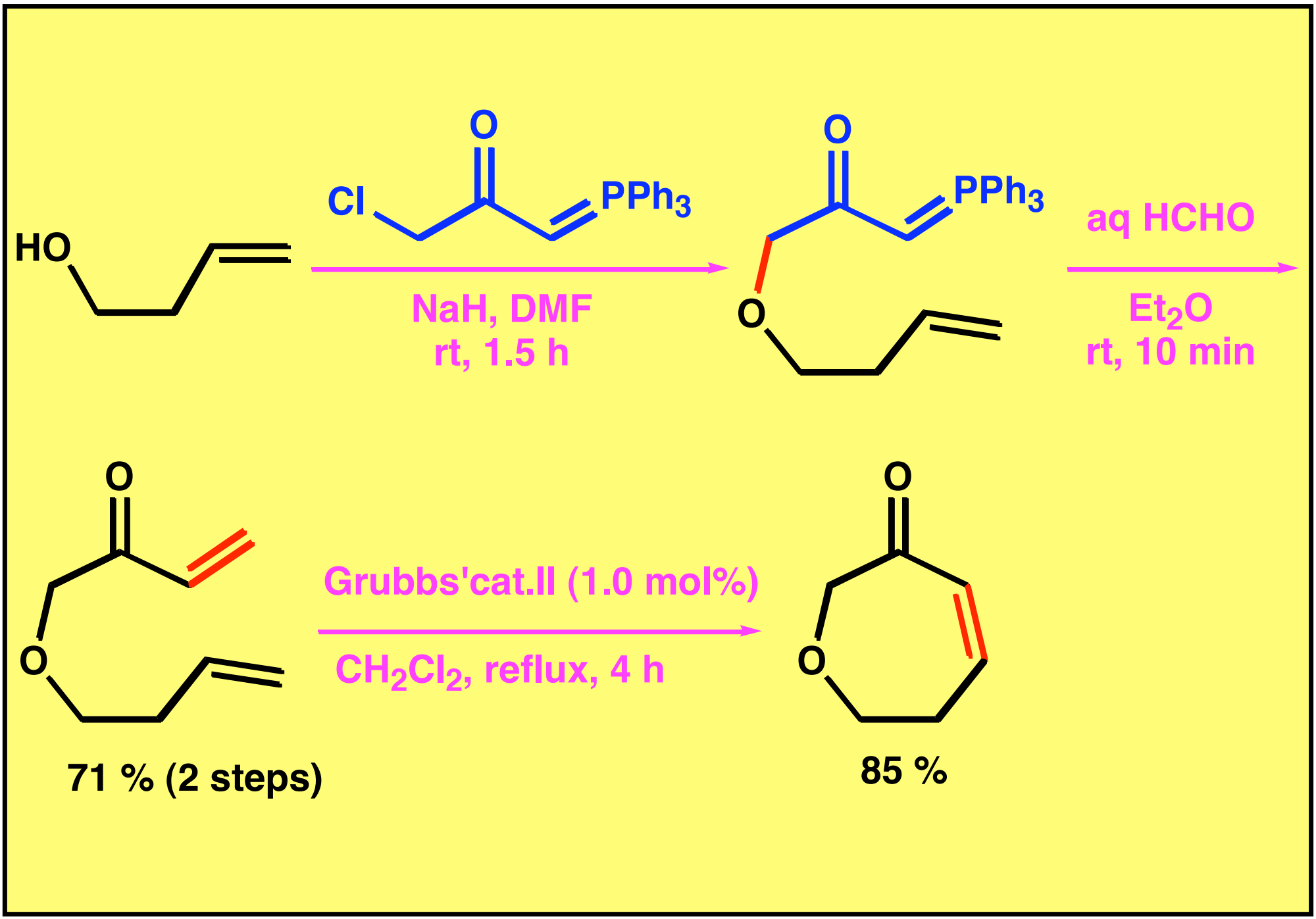
R	yield (%)
$SiMe_3$	95
$SiMe_2Ph$	96
$SiMe_2Bu^t$	95
i-Pr	97
t-Bu	93

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

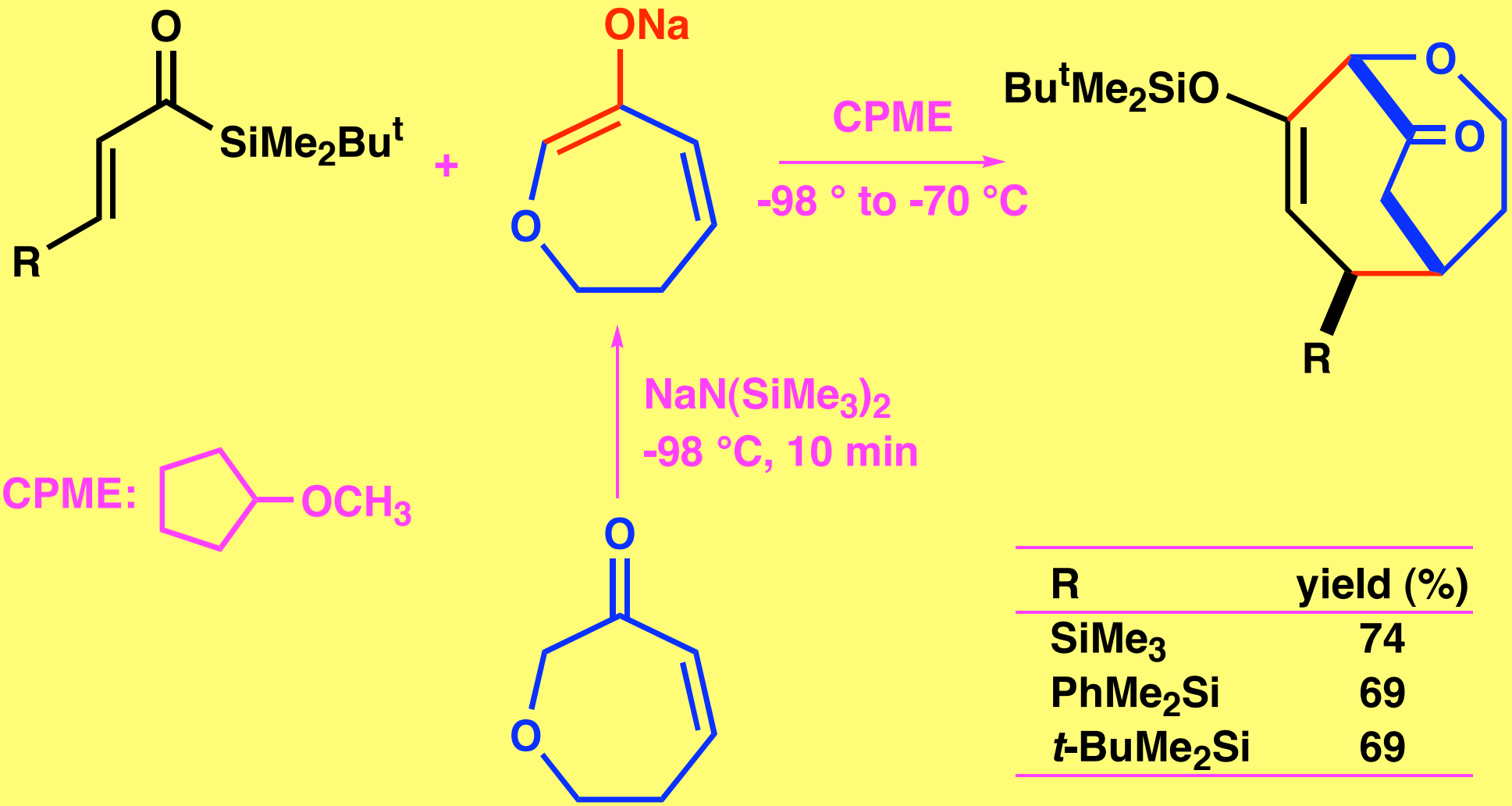
Formation of Eight-Membered Heterocycles by [3 + 4] Annulation



Preparation of 6-Oxa-2-cycloheptenone

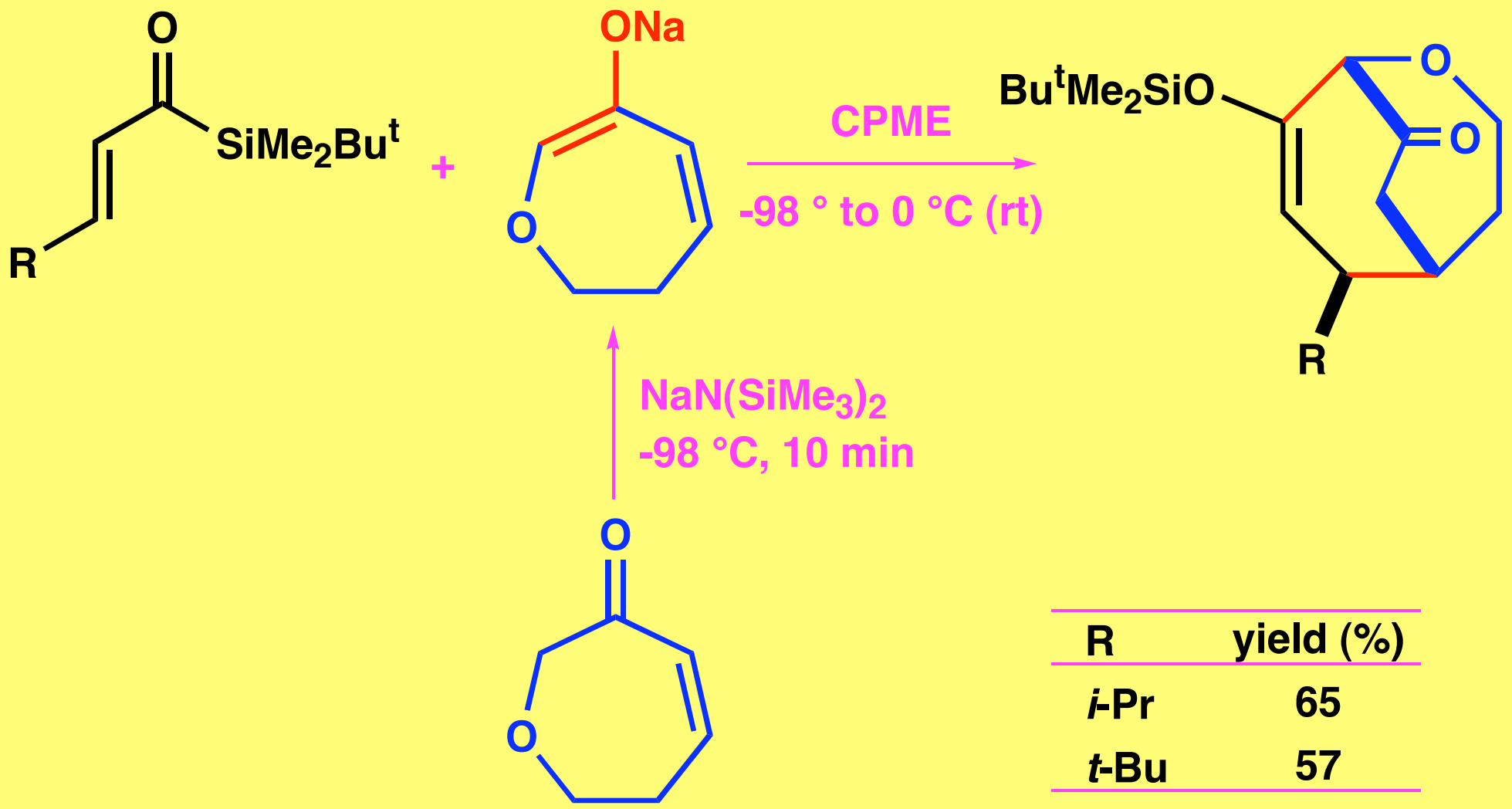


Formation of Eight-Membered Heterocycles by [3 + 4] Annulation (I)



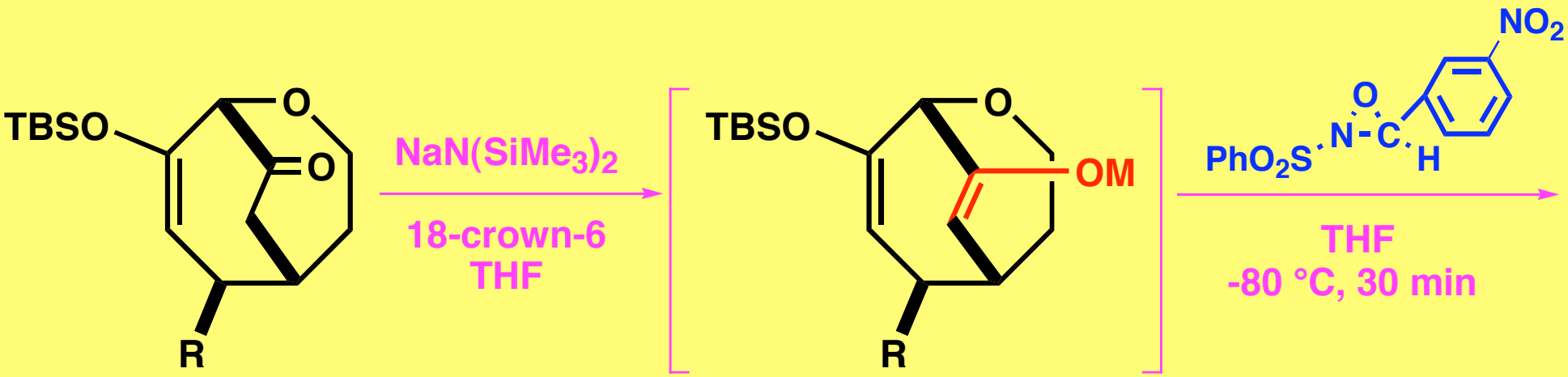
R	yield (%)
$SiMe_3$	74
$PhMe_2Si$	69
t-$BuMe_2Si$	69

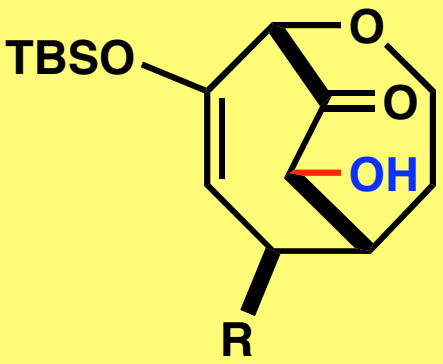
Formation of Eight-Membered Heterocycles by [3 + 4] Annulation (II)



R	yield (%)
i-Pr	65
t-Bu	57

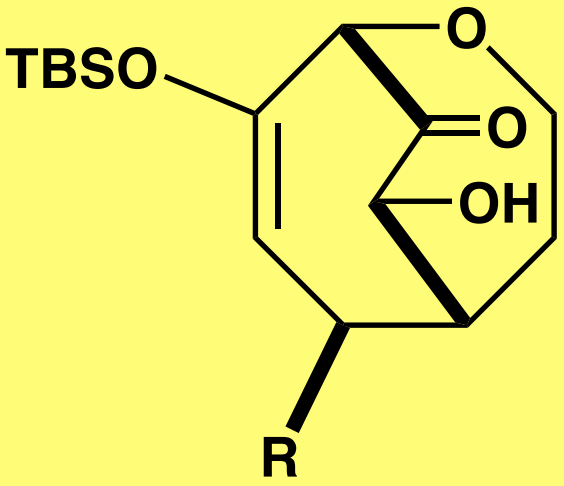
α-Hydroxylation of 2-Oxabicyclo[2.2.2]decene Derivatives





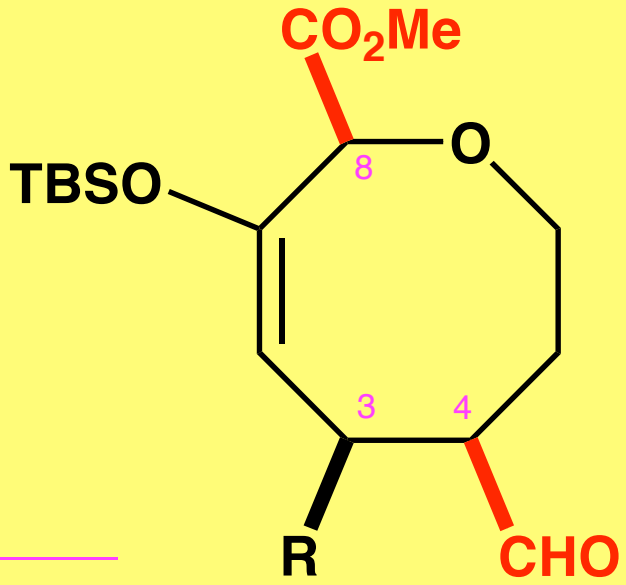
R	yield (%)
$SiMe_3$	66
$SiMe_2Ph$	86
$SiMe_2Bu^t$	76
i-Pr	66
t-Bu	86

Oxidative Cleavage of α-Hydroxyketones



$Pb(OAc)_4$

Benzene-MeOH
rt



R	yield (%)
$SiMe_3$	93
$SiMe_2Ph$	99
$SiMe_2Bu^t$	100
i-Pr	100
t-Bu	97

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
Yasuhiro Ohtani
Yasushi Okamoto
Koichi Sumi

Tandem Brook-Michael

Tadashi Tanaka

Eight-Membered Rings

Yasushi Okamoto
Emi Izumi
Koichi Sumi
Yuji Sawada
Hidekazu Haraguchi

Alkylation of Epoxysilanes

Yuji Ohnishi
Yuji Takahashi
Michiko Sasaki
Eiji Kawanishi
Yoshio Nakai
Tatsuya Matsumoto

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The Research Foundation for Pharmaceutical Sciences
The Naito Foundation
The Takeda Science Foundation
The Uehara Memorial Foundation
The Chiba-Geigy Foundation (Japan)
The Hoan-sha Foundation