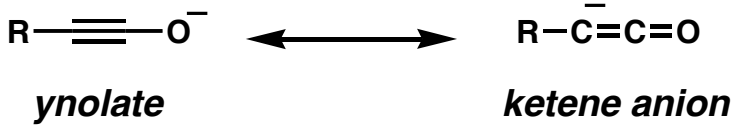
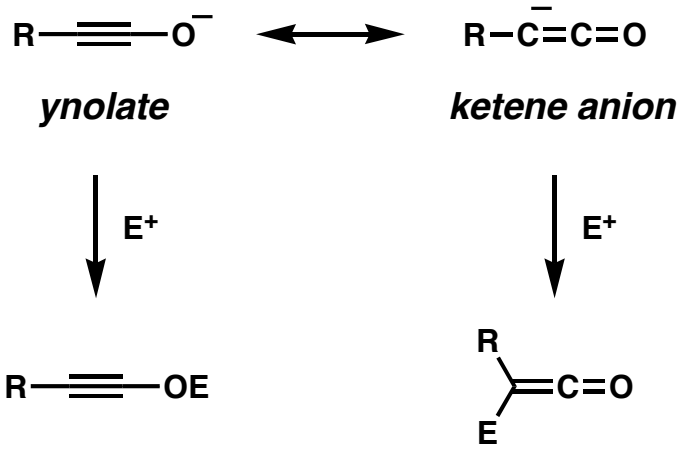
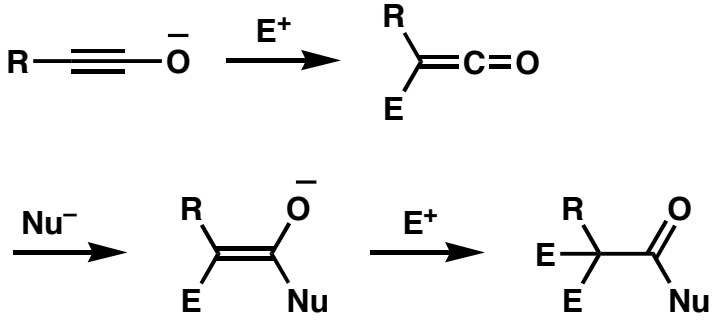
Synthesis and Synthetic Utility of Ynolates



Narae Park
06/02/2008
Stoltz Group
Literature Meeting

Ynolates - Outline





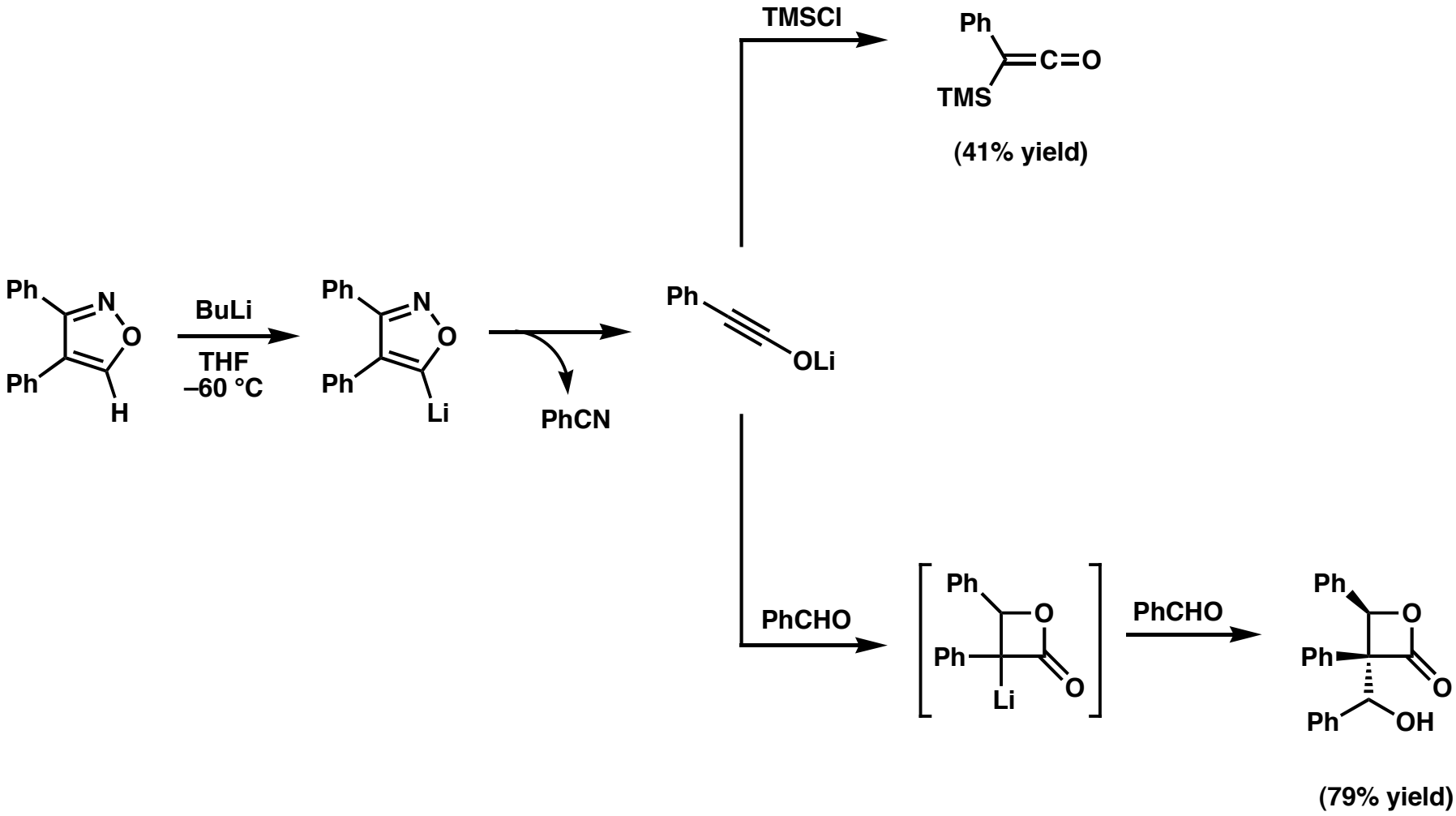
Synthesis of Ynolates

- **Phenyl-substituted ynolates**
- **Silyl-substituted ynolates**
- **Alkyl-substituted ynolates**

Reactions with Ynolates

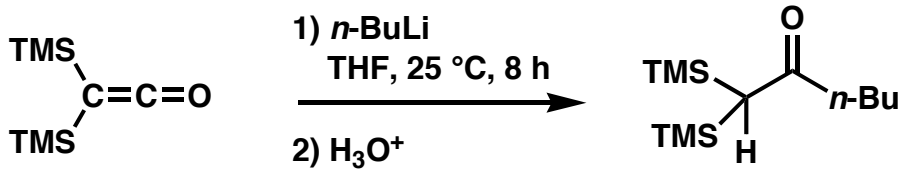
- **Reactions with Carbonyl Compounds**
- **Reactions with Imines**
- **Reactions with Isocyanates**
- **Reactions with Nitrones**
- **Reactions with Oxiranes and Aziridines**
- **Reactions with Silylvinyl Ketenes**

First Synthesis of Ynolates - Fragmentation of Isoxazolyl Lithium

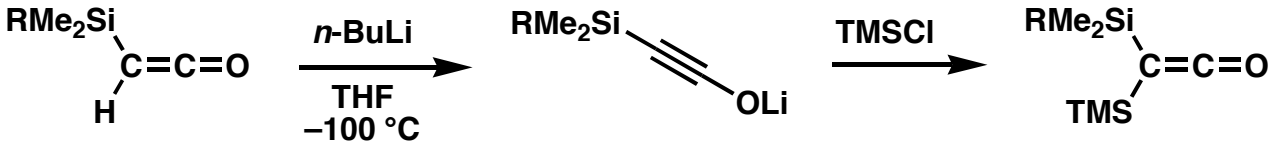


Schöllkopf, U.; Hoppe, I. *Angew. Chem., Int. Ed. Engl.* **1975**, 14, 765.

Synthesis of Ynolates via Deprotonation of Silylketenes

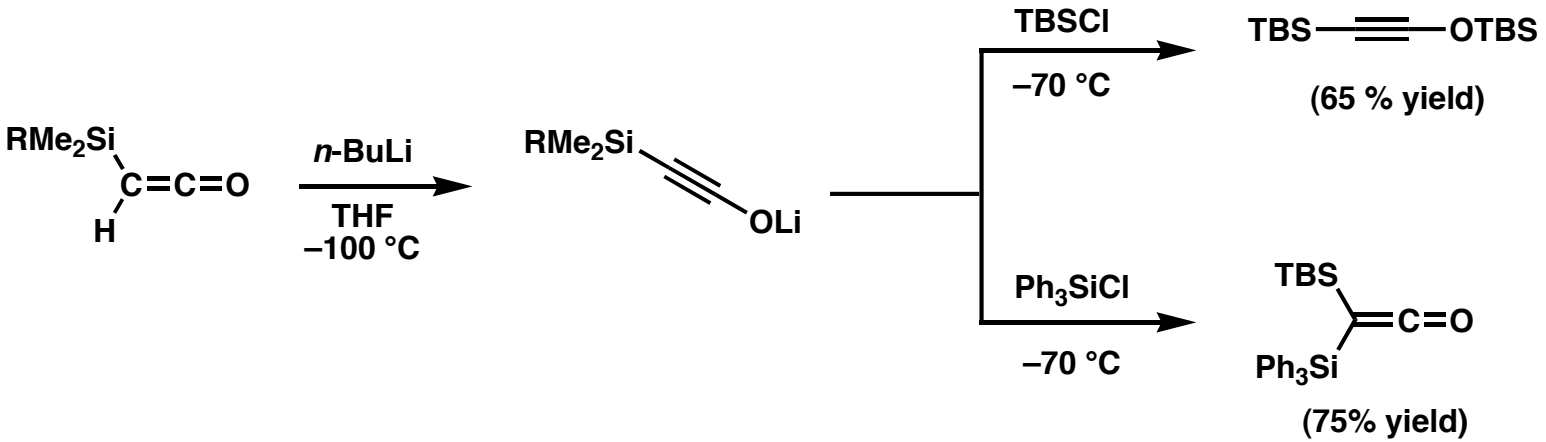


(85% yield)



(80-90% yield)

Woodbury, R. P.; Long, N. R.; Rathke, M. W. *J. Org. Chem*. 1978, 43, 376.

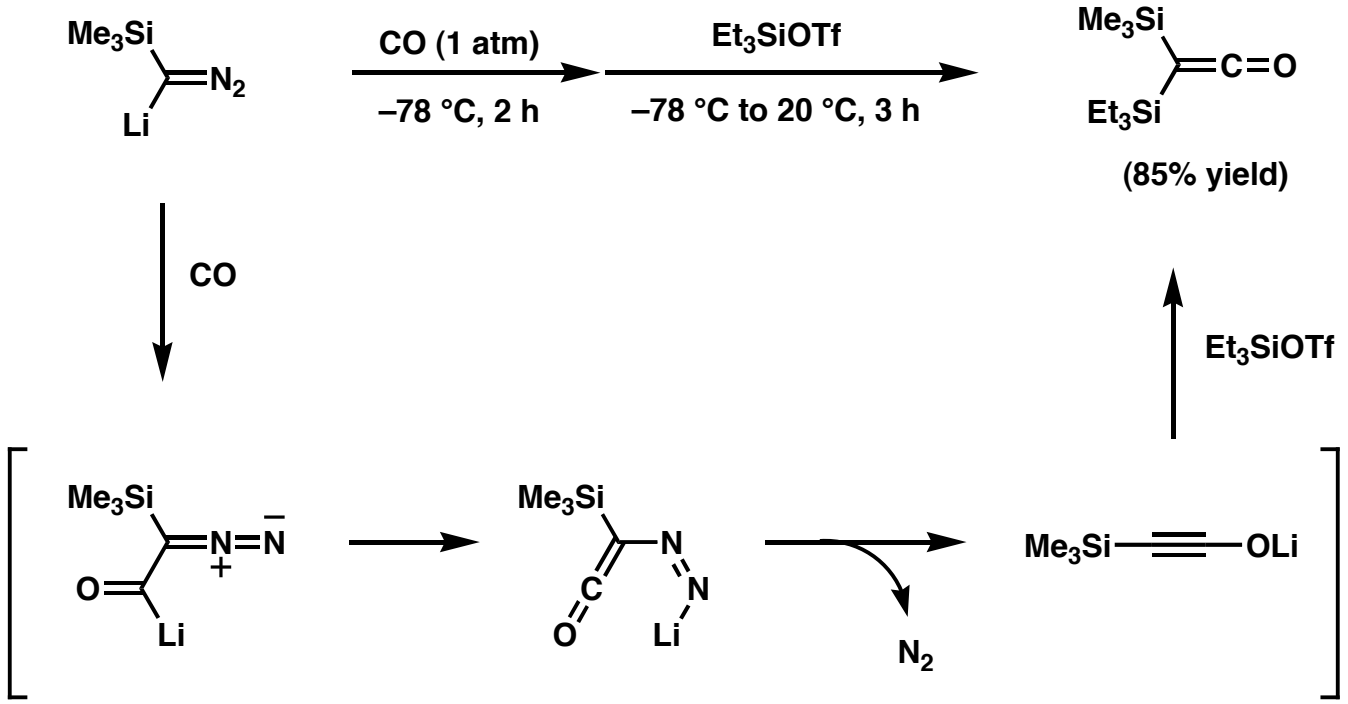


(65 % yield)

(75% yield)

Akai, S.; Kitagaki, S.; Naka, T.; Yamamoto, K.; Tsuzuki, Y. Matsumoto, K. Kita, Y.; *J. Chem. Soc. Perk. Trans. 1* **1996**, 1705.

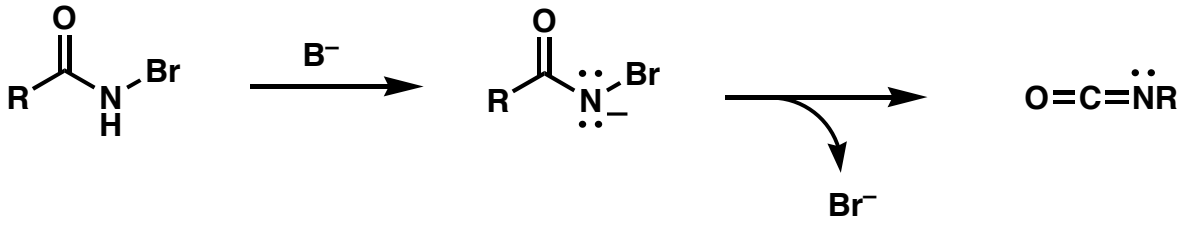
Synthesis of Silyl Ynolates from α-Diazoacyllithium



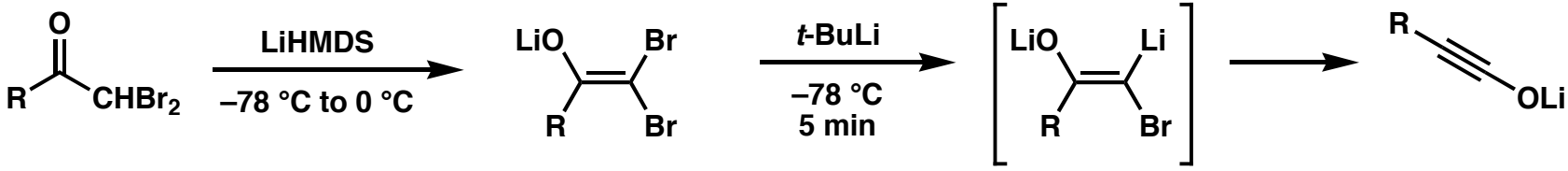
Kai, H.; Iwamoto, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **1996**, 118, 7634.

Synthesis of Ynolates via Rearrangement of α-Keto Dianions

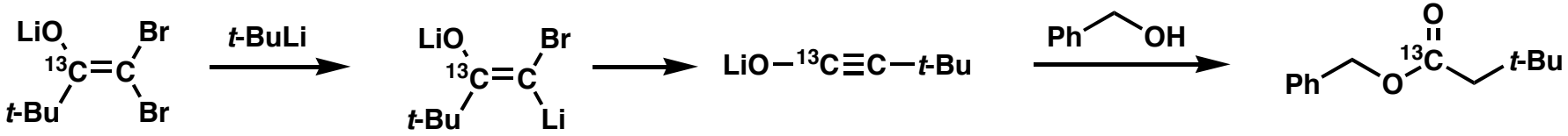
Classical Hofmann Rearrangement



Carbon analogue of Hofman Rearrangement



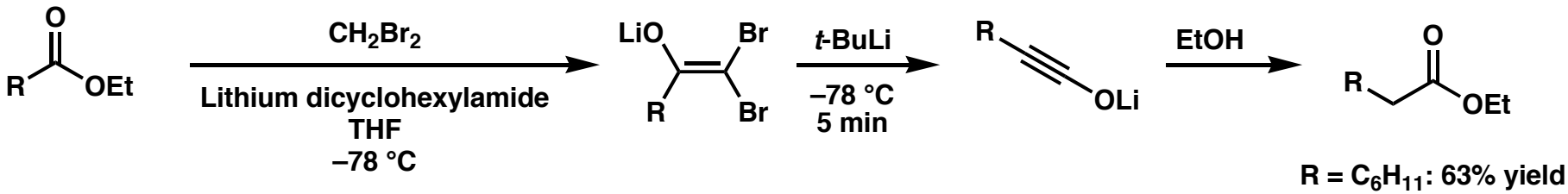
^{13}C labeling experiment



Kowalski, C. J.; Fields, K. W. *J. Am. Chem. Soc.* **1982,** 104, 321.

Synthesis of Ynolates via Rearrangement of α-Keto Dianions

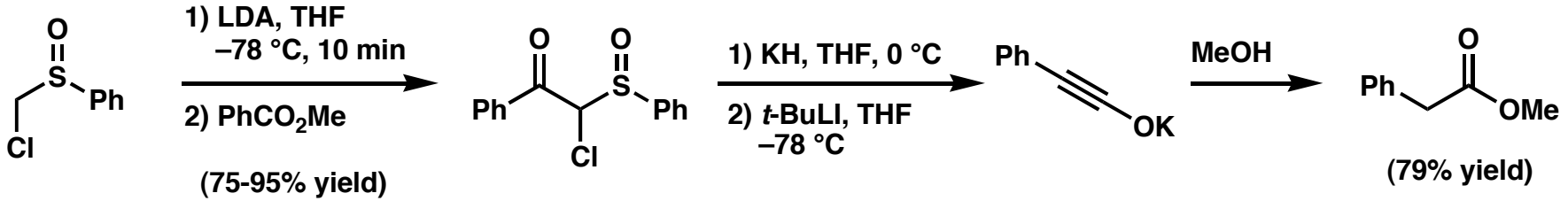
Single-step one carbon homologation of esters



R = C_6H_{11}: 63% yield

Kowalski, C. J.; Fields, K. W. *J. Am. Chem. Soc*. **1982,** 104, 321.

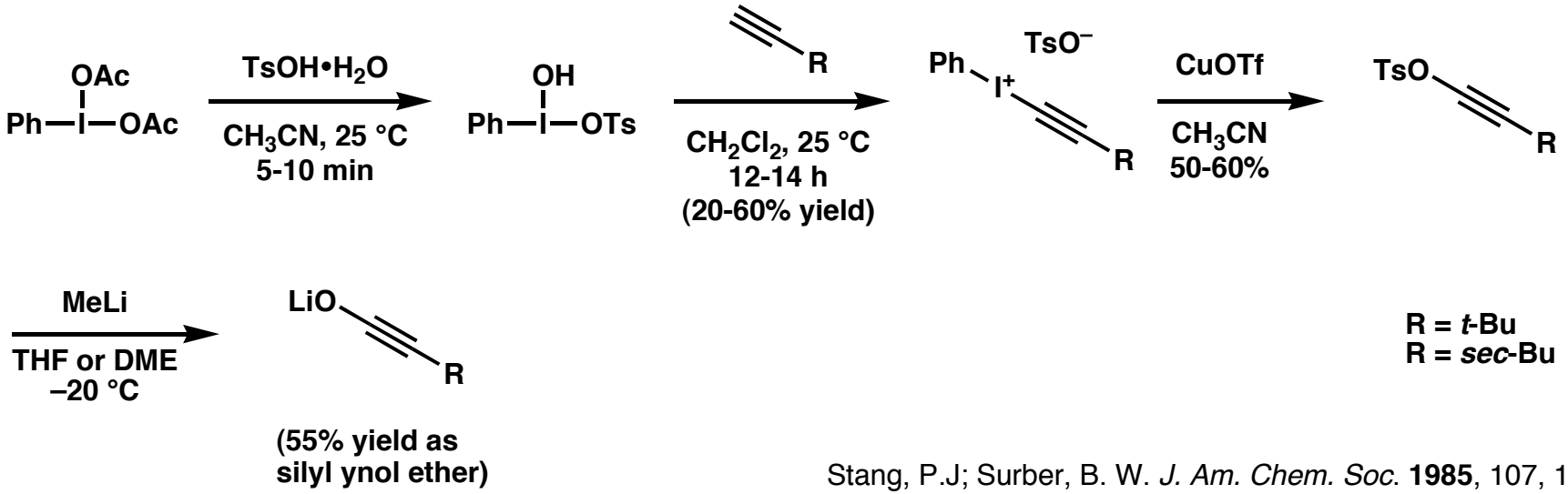
Homologation of esters using chloromethyl phenyl sulfoxide



Satoh, T.; Mizu, Y.; Kawashima, T.; Yamakawa, K. *Tetrahedron* **1995**, 51, 703.
Satoh, T.; Nakamura, A.; Iruchijima, A.; Hayashi, Y.; Kubota, K. *Tetrahedron* **2001**, 57, 9689.

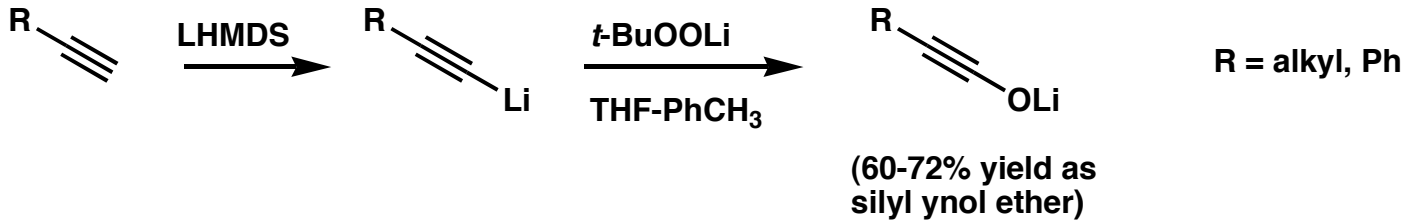
Synthesis of Ynolates via Oxidation of Terminal Alkynes

Synthesis of ynolates via ynol tosylates



Stang, P.J; Surber, B. W. *J. Am. Chem. Soc*. **1985**, 107, 1452.
Stang, P. J.; Roberts, K. *J. Am. Chem. Soc*. **1986**, 108. 7125.

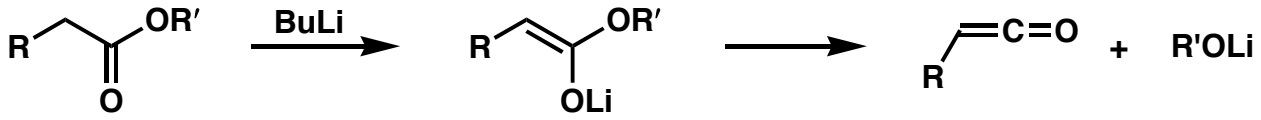
Synthesis of ynolates vis lithium acetylides



Julia, M.; Saint-Jalmes, V.P.; Verpeaux, J. N. *Synlett* **1993**, 233.

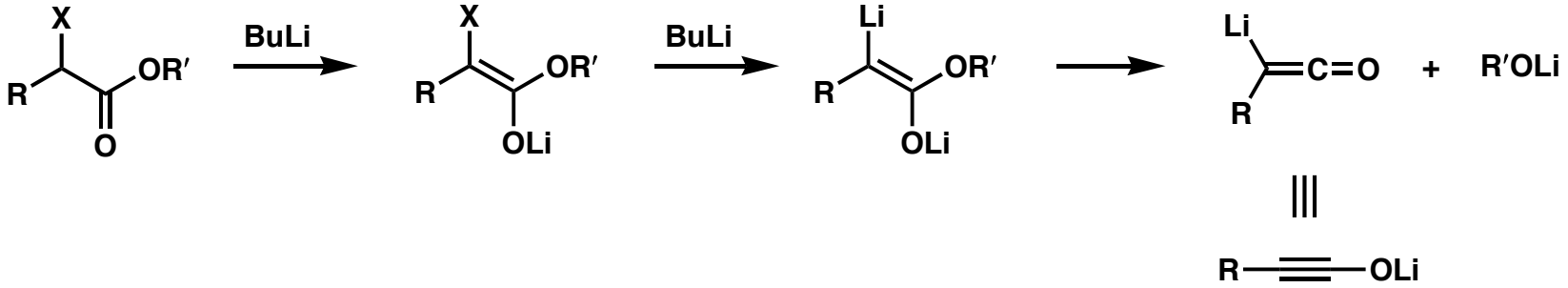
Synthesis of Ynolates via Cleavage of Ester Dianions

Cleavage of lithium ester enolates



Häner, R.; Laube, T.; Seebach, D.; *J. Am. Chem. Soc*. **1985**, 107, 5396.
Sullivan, D. F.; Woodbury, R. P.; Rathke, M. W. *J. Org. Chem*. **1977**, 42, 2038.

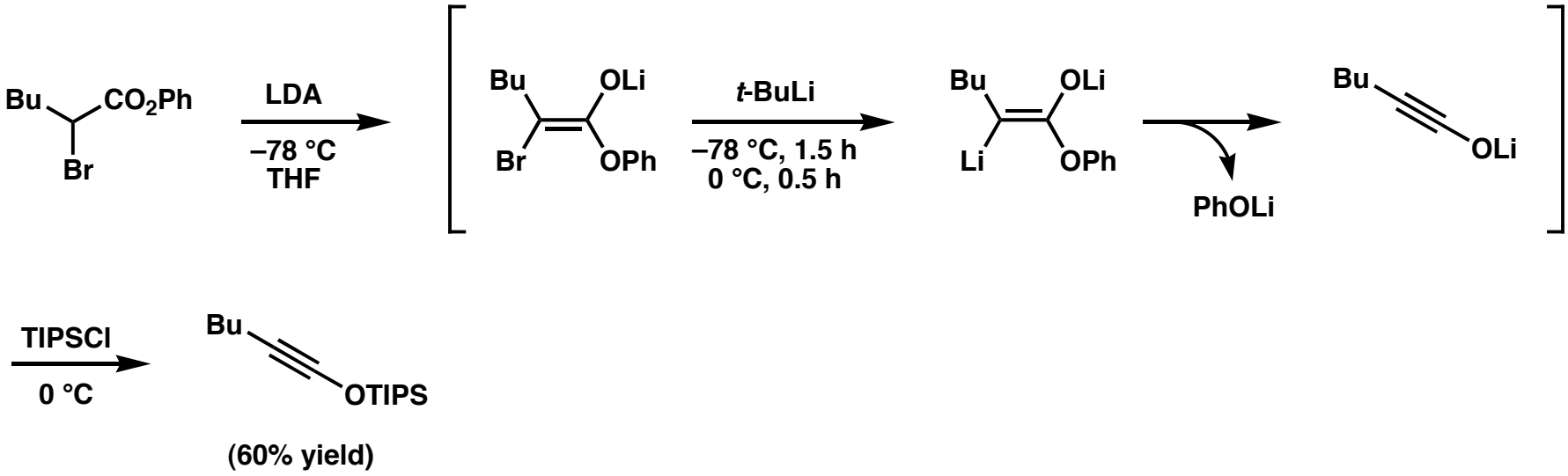
Cleavage of ester dianions



Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, 54, 2411.

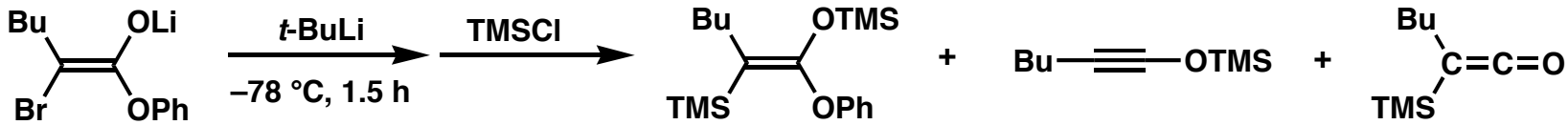
Synthesis of Ynolates via Cleavage of Ester Dianions

Ynolate generation from α-bromoester



(60% yield)

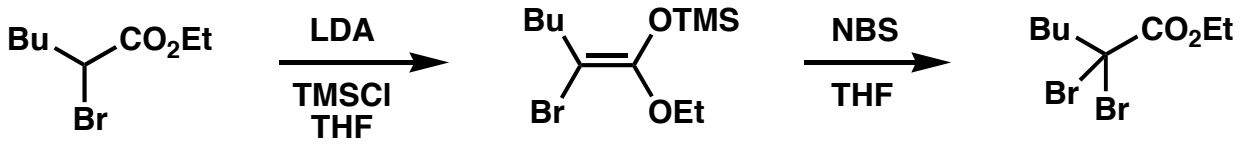
Attempts at trapping of the ester dianion



Shindo, M. *Tetrahedron Lett.* **1997**, 38, 4433.

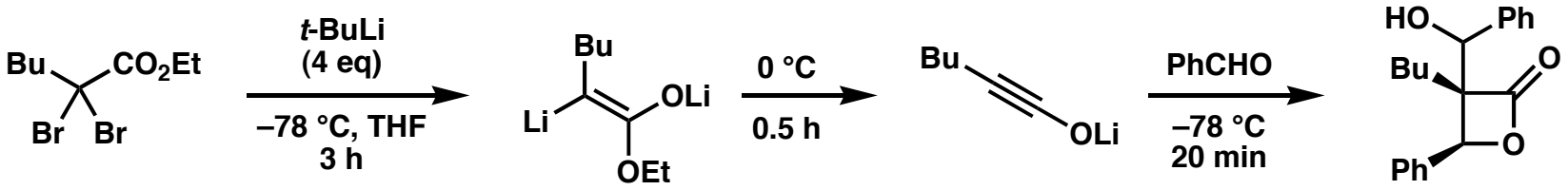
Synthesis of Ynolates via Cleavage of Ester Dianions

Synthesis of α,α-dibromoester



(51% over 2 steps)

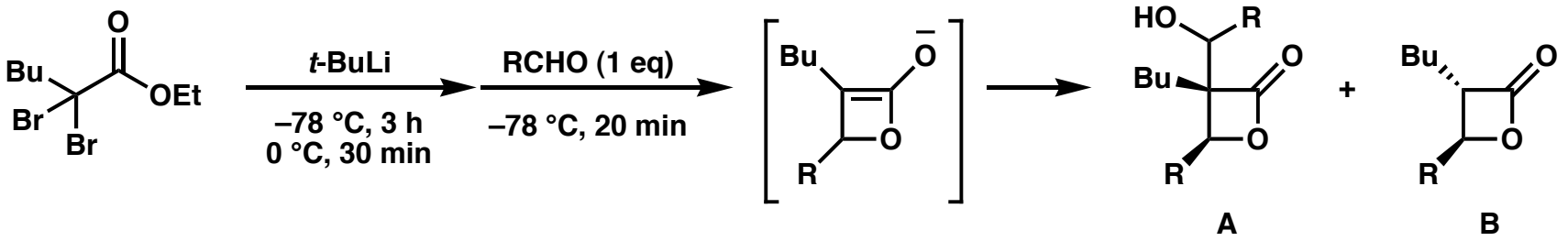
Ynolate generation from α,α-dibromoester



(70-85% yield)

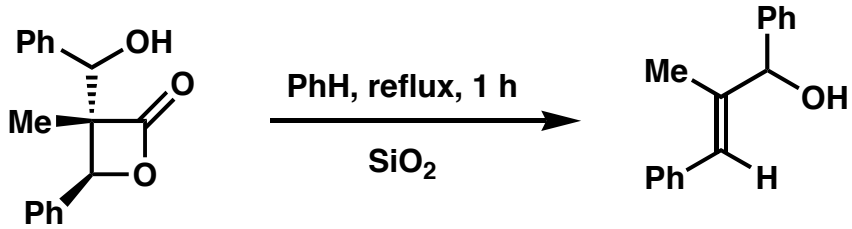
Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, 54, 2411.

[2+2] Cycloaddition with Aldehydes



R	A (%)	B (%)
Ph	36	0
Et	25	0
*i*Pr	30	0
t-Bu	0	74

Thermal decarboxylation of tri-substituted β-lactone

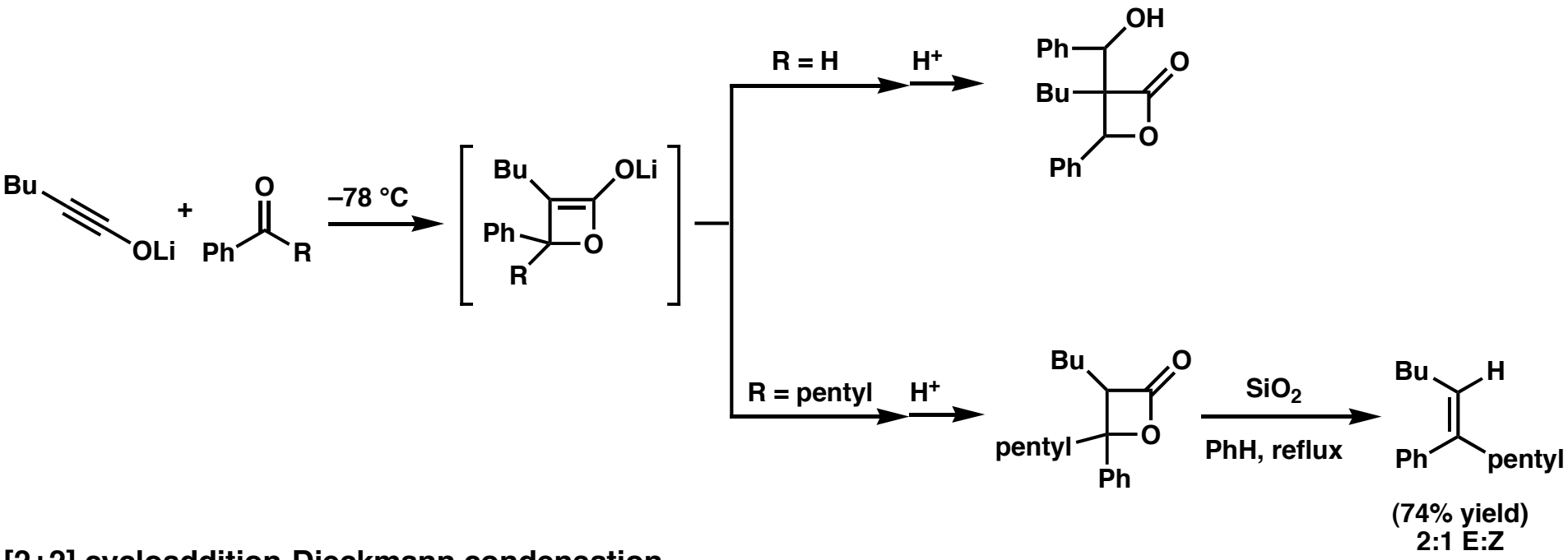


(85% yield)

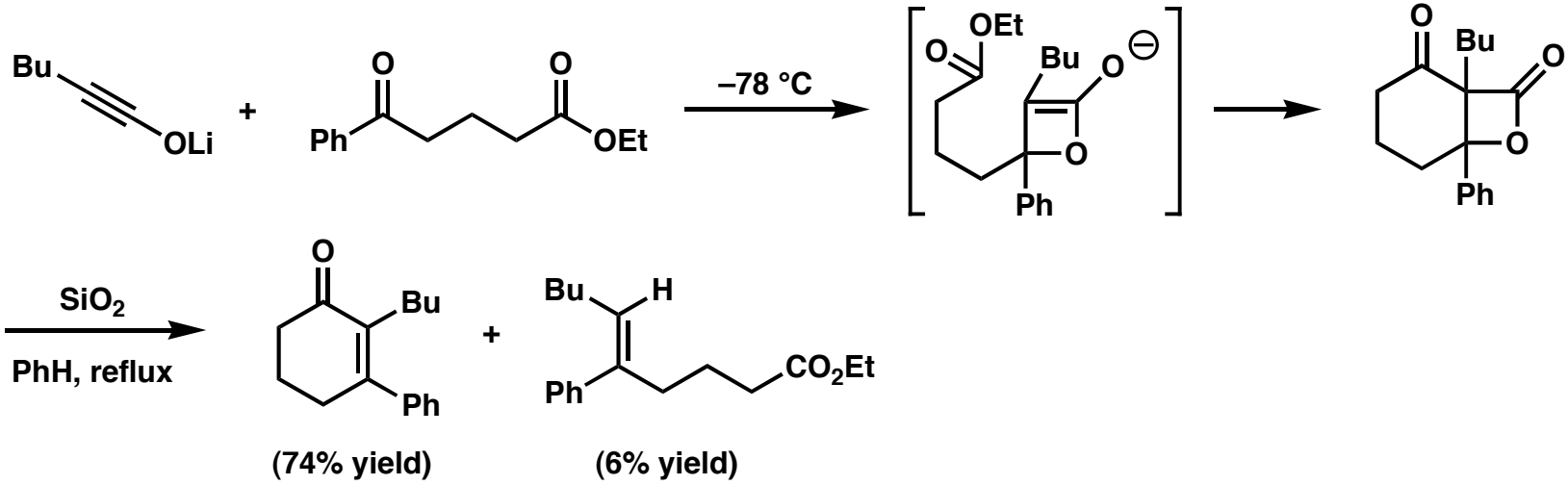
***cis*-eleimination**

Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, 54, 2411.

[2+2] Cycloadditions-Dieckmann Condensation



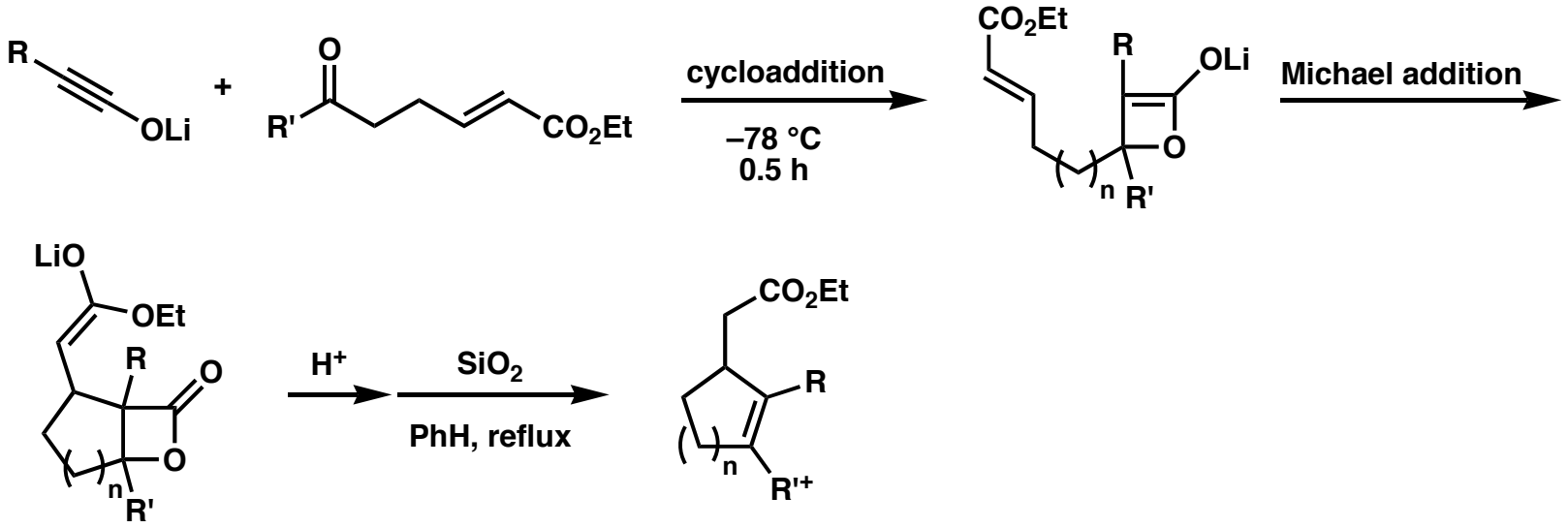
[2+2] cycloaddition-Dieckmann condensation



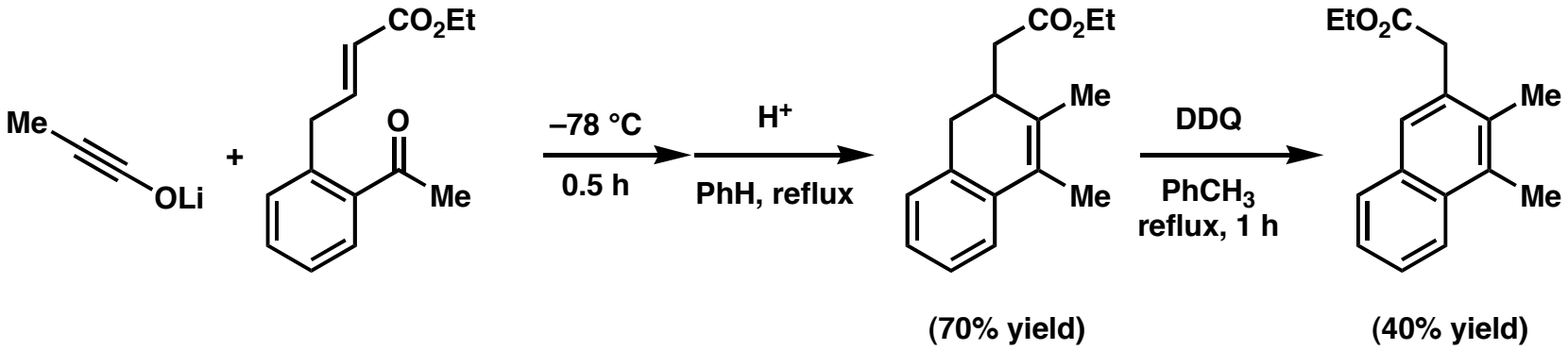
Shindo, M.; Sato, Y.; Shishindo, K. *J. Am. Chem. Soc*. **1999**, 121, 6507**.**

[2+2] Cycloaddition-Michael Reaction

Synthesis of polysubstituted cycloalkenes

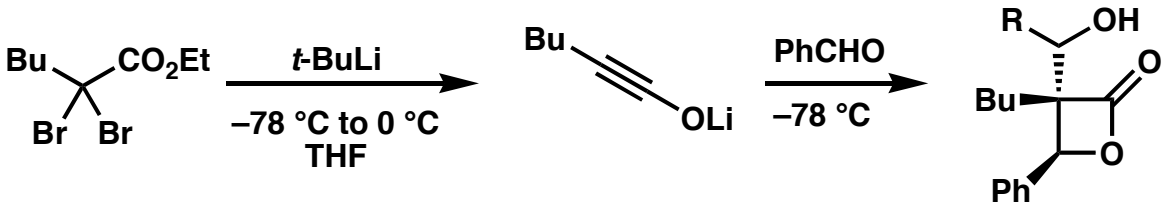


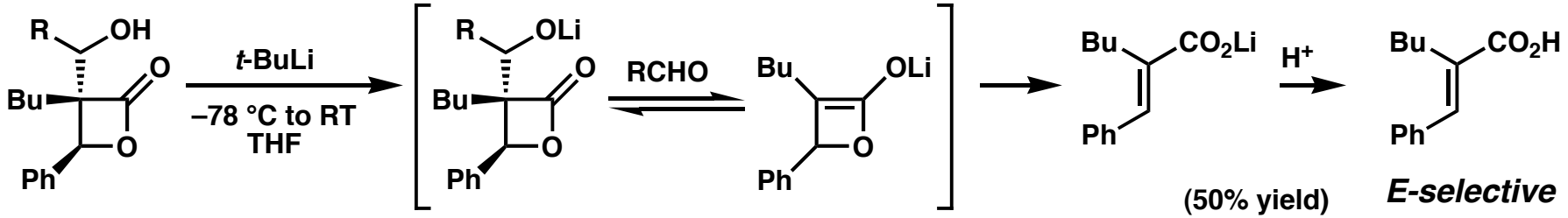
Synthesis of polysubstituted naphthalenes



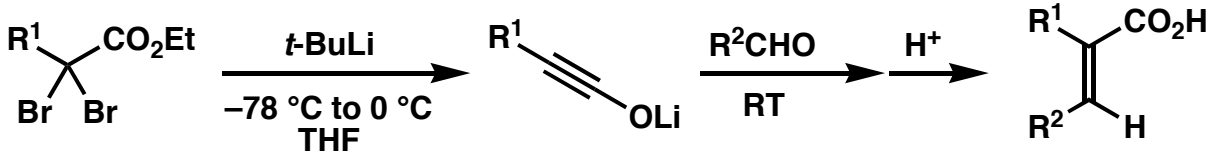
Shindo, M.; Matsumoto, K.; Sato, Y.; Shishido, K. *Org. Lett.* **2001**, 3, 2029.

Olefination of Aldehydes





Synthesis of tri-substituted olefins

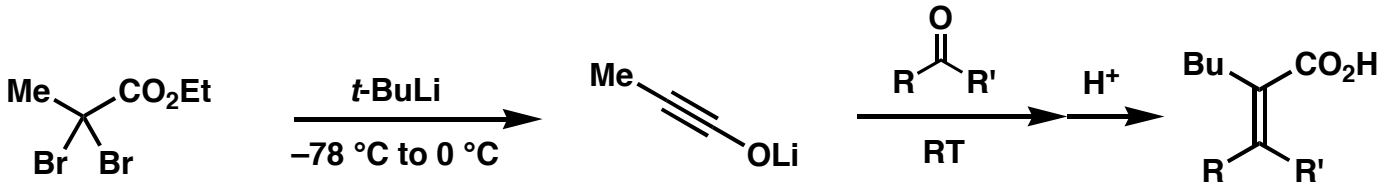


R^1	R^2	Product	
		E:Z	Yield
Bu	Ph	>99:1	73
Bu	t-Bu	>99:1	51
Bu	Et	>99:1	24
cyclohexyl	Ph	>99:1	62
t-Bu	Ph	20:1	58

Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **1998**, 39, 4857.

Olefination of Ketones

Synthesis of tetrasubstituted olefins

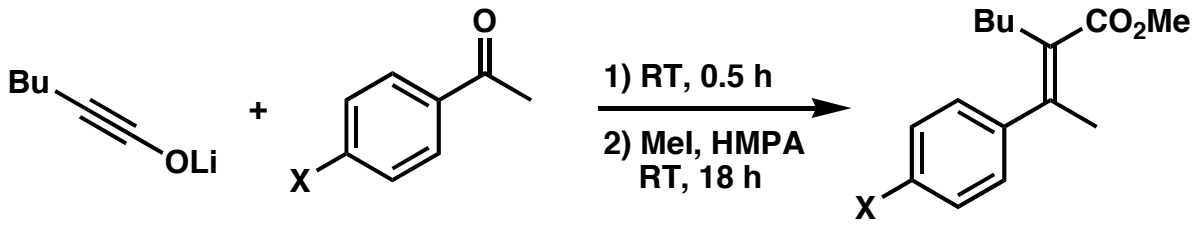


Ketone		Product		
R	R'	E:Z	Yield (%)	
α-tetralone		83:17	96	E-selective with aryl alkyl ketones
Ph	Me	80:20	>99	
Ph	Et	86:14	89	
Ph	*i*Pr	73:27	86	
Ph	*t*-Bu	85:15	74	
Ph	CHCHPh	21:79	66	
Me	*t*-Bu	19:81	67	

Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. *J. Org. Chem.* **2004**, 69, 3912.

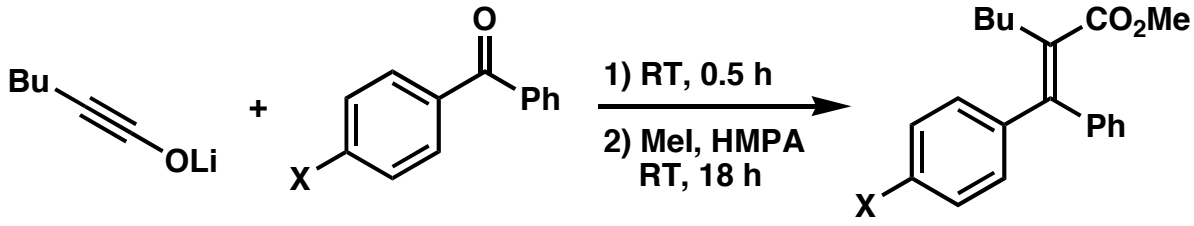
Olefination of Ketones - Stereoelectronic Effect

Acetaphenones



X	Yield (%)	E:Z
NO_2	61	40:60
Cl	68	70:30
F	88	80:20
H	82	85:15
Me	89	91:9
MeO	80	95:5
Me_2N	64	>99:1

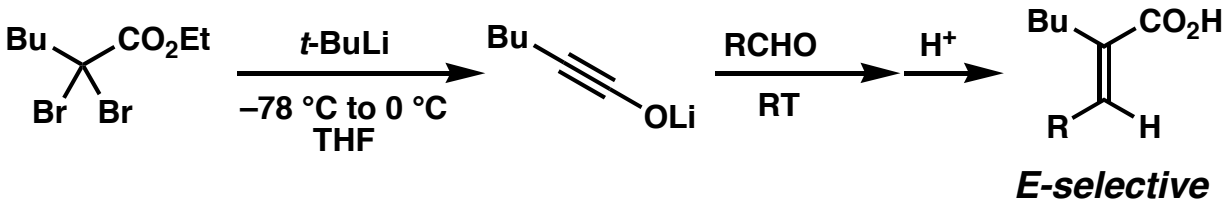
Benzophenones



X	Yield (%)	E:Z
NO_2	92	25:75
Cl	92	40:60
F	>99	50:50
H	82	–
Me	90	60:40
MeO	99	67:33
Me_2N	90	83:17

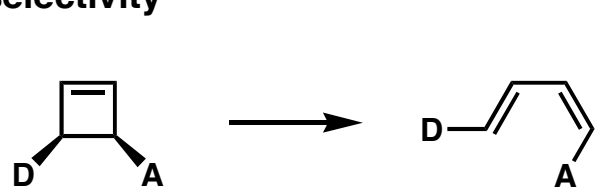
Shindo, M.; Sato, Y.; Shishido, K. *J. Org. Chem.* **2000**, 65, 5443.

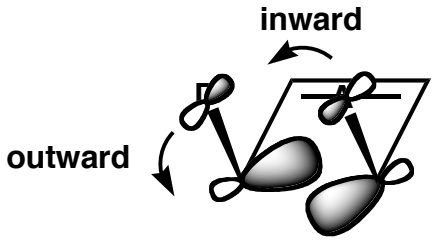
Torquoselective Olefination of Carbonyl Compounds



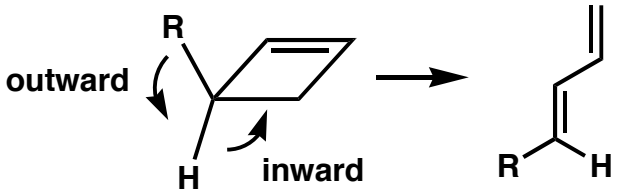
E-selective

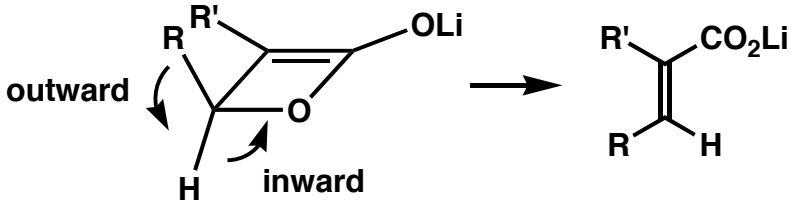
Houk's torquoselectivity





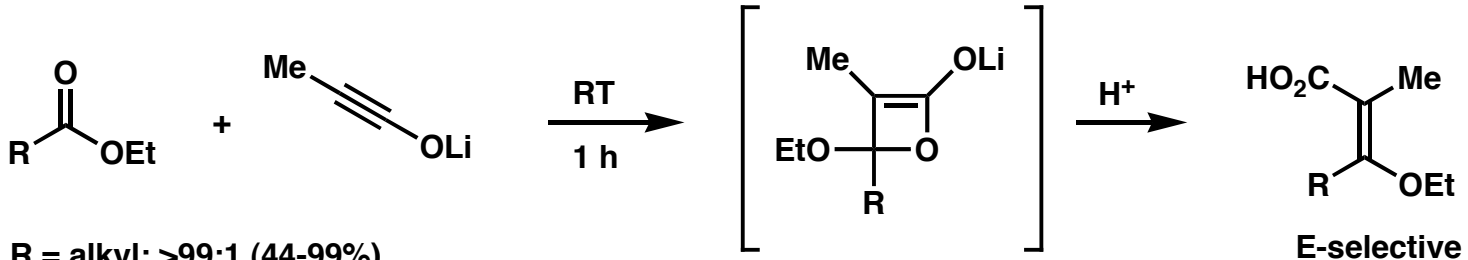
Electrocyclic ring-opening of 3-alkylcyclobutenes and β-lactone enolates





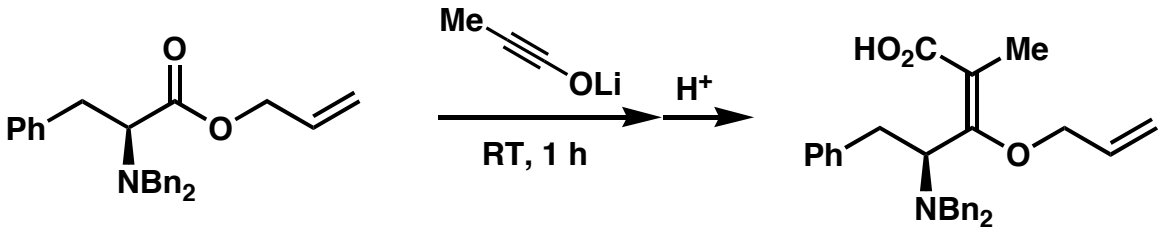
Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. *J. Org. Chem.* **2004**, 69, 3912.

Olefination of Esters

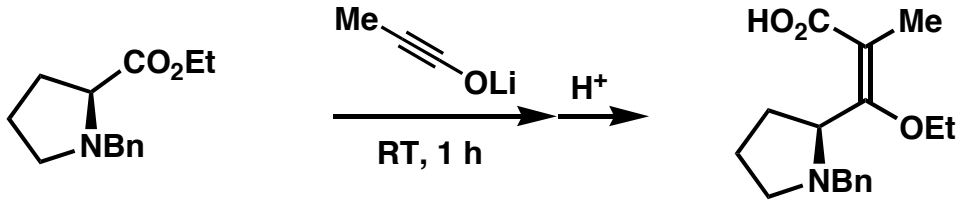


R = alkyl: >99:1 (44-99%)
Ph: 89:11 (94%)
***p*-MeO-C_6H_4: 77:23 (90%)**
***p*-O_2N-C_6H_4: 98:2 (95%)**

E-selective



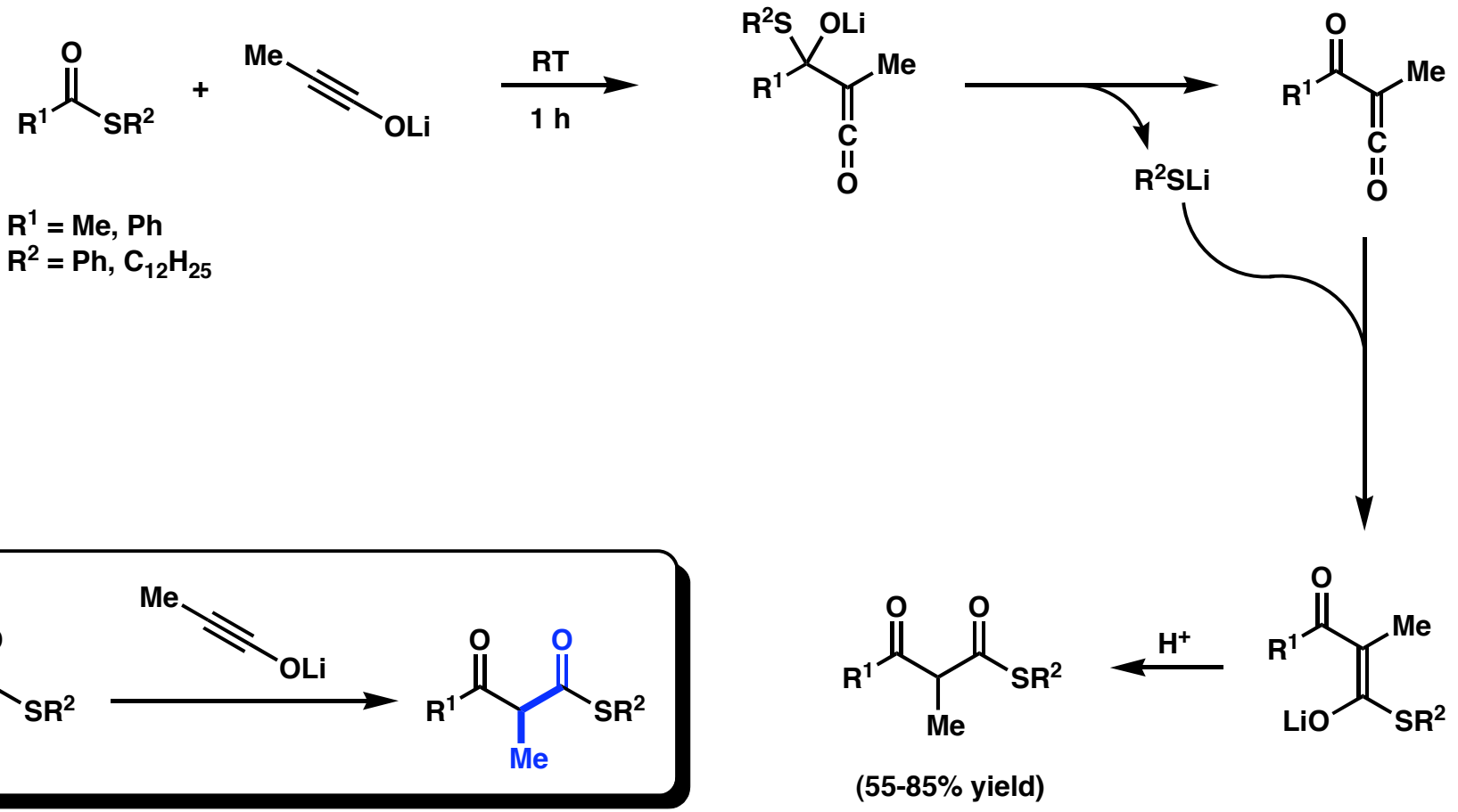
>99:1 (92% yield)



>99:1 (>99% yield)

Shindo, M.; Kita, T.; Kumagai, T.; Matsumoto, K. Shishido, K. *J. Am. Chem. Soc*. **2006**, 128, 1062.

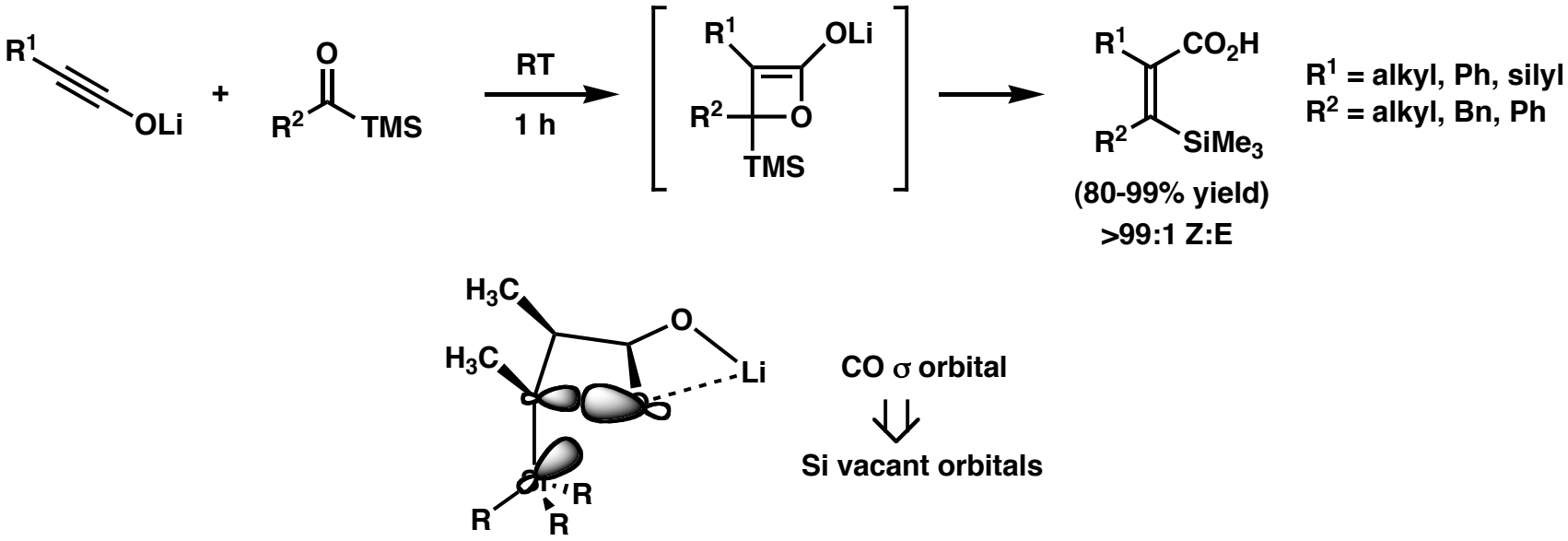
Homologation of Thioesters

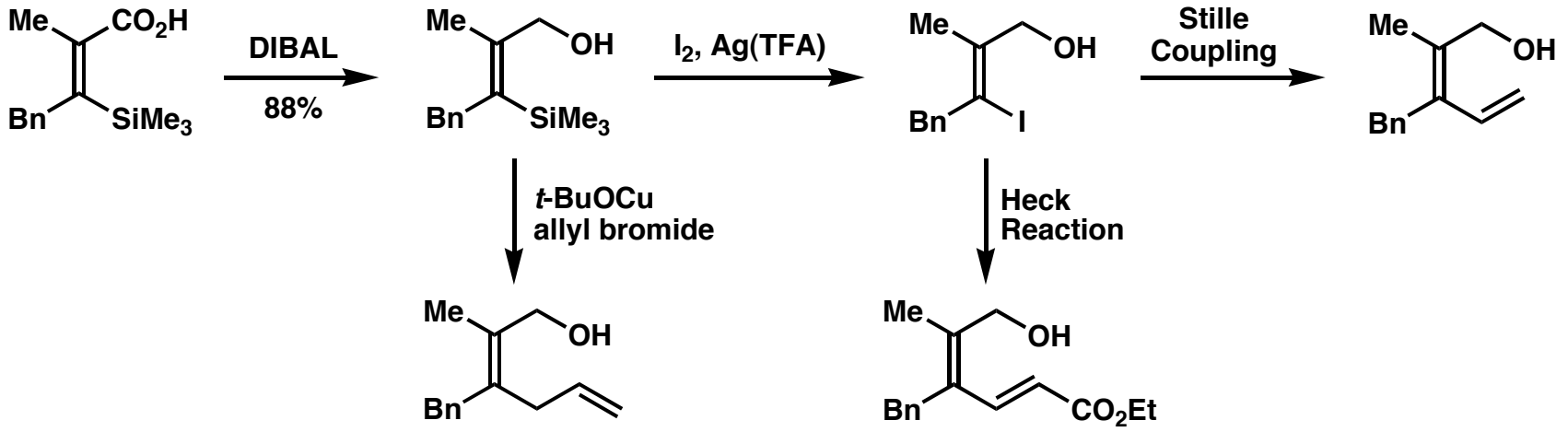


R^1 = Me, Ph
R^2 = Ph, $C_{12}H_{25}$

Shindo, M.; Kita, T.; Kumagai, T.; Matsumoto, K.; Shishido, K. *J. Am. Chem. Soc.* **2006**, 128, 1062.

Olefination of Acylsilanes

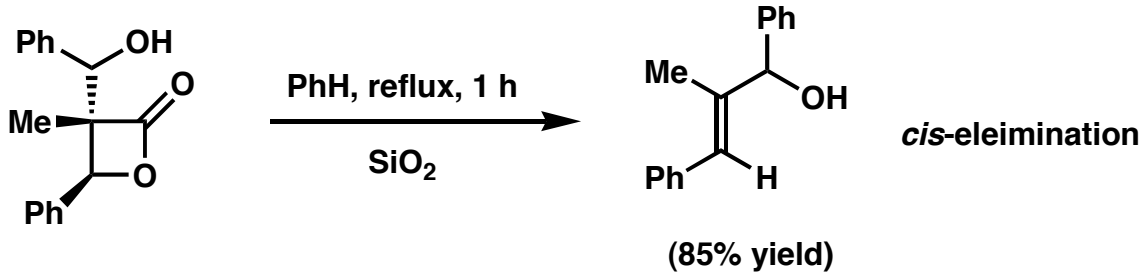




Shindo, M.; Matsumoto, K., Mori, S.; Shishido, K. *J. Am. Chem. Soc*. **2002**, 124, 6840.

Decarboxylative Olefination of Acylsilanes

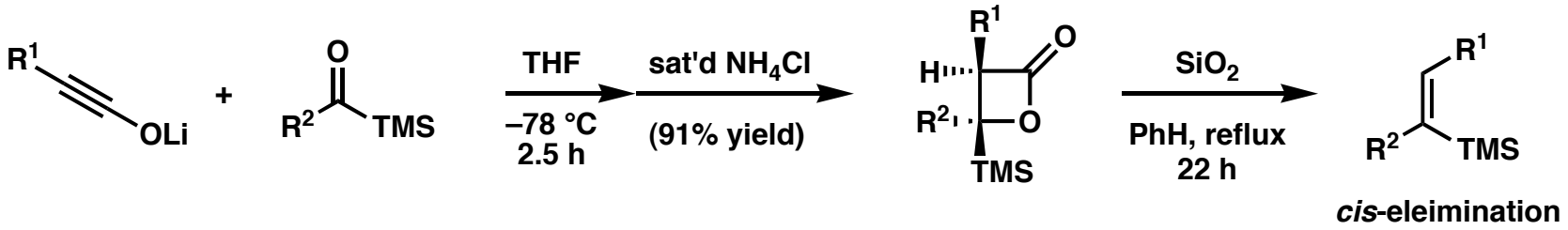
Decarboxylation of disubstituted β-lactone



(85% yield)

Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, 54, 2411.

Decarboxylation of disubstituted β-silyl-β-lactone

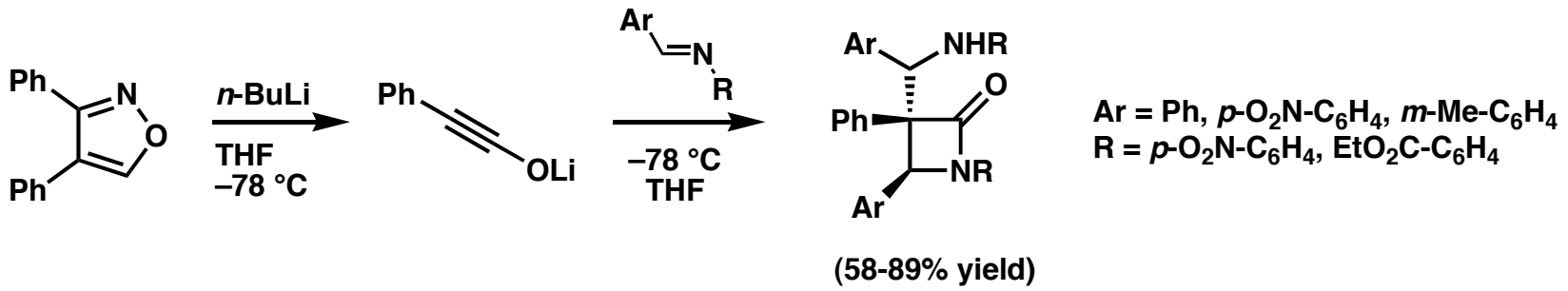


R^1	R^2	Z:E	Yield (%)
Me	Bn	98:2	72
*i*Pr	Bn	94:6	78
Me	Ph	92:8	62
Me	CH_2=CH$(CH_2)_3$	94:6	72

Shindo, M.; Matsumoto, K.; Shishido, K. *Chem. Commun*. **2005**, 2477.

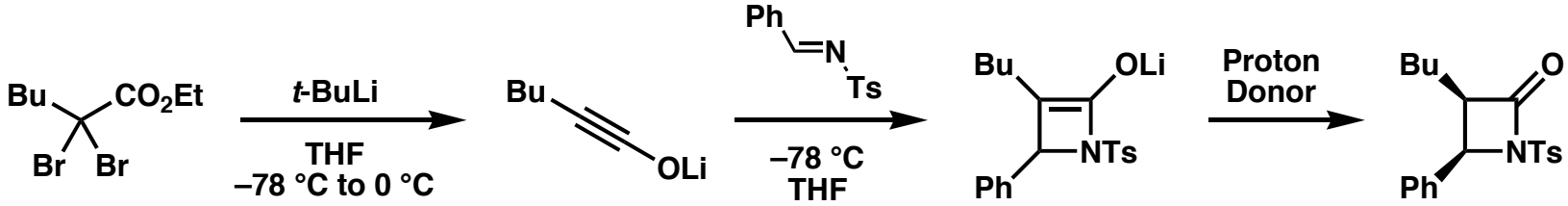
Reactions with Imines

Barrett



Adlington, R. M.; Barrett, A. G. M.; Quayle, P.; Walker, A. *J. Chem. Soc. Chem. Comm.* **1981**, 404.

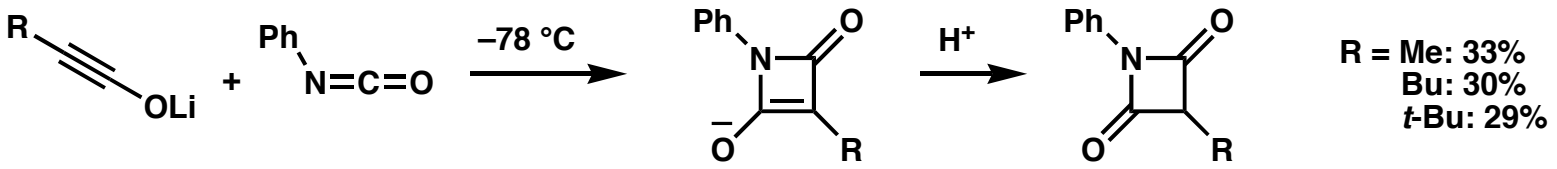
Shindo



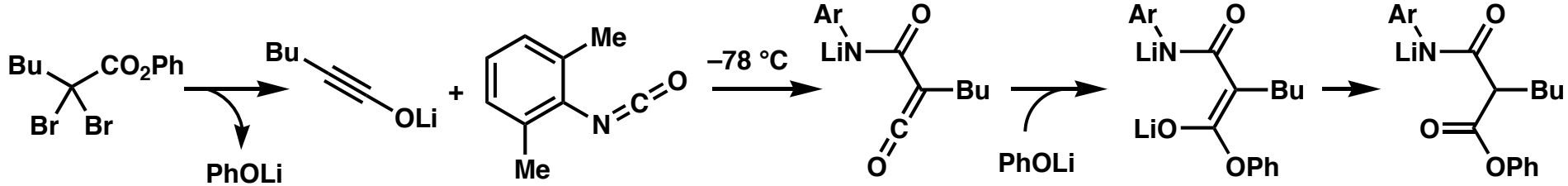
Proton Donor	*cis*/*trans*	Yield (%)
Sat'd. NH_4Cl	3:1	58
AcOH	4:1	73
PhOH	11:1	68

Shindo, M.; Oya, S.; Sato, Y.; Shishido, K. *Heterocycles* **1998**, 49, 113.

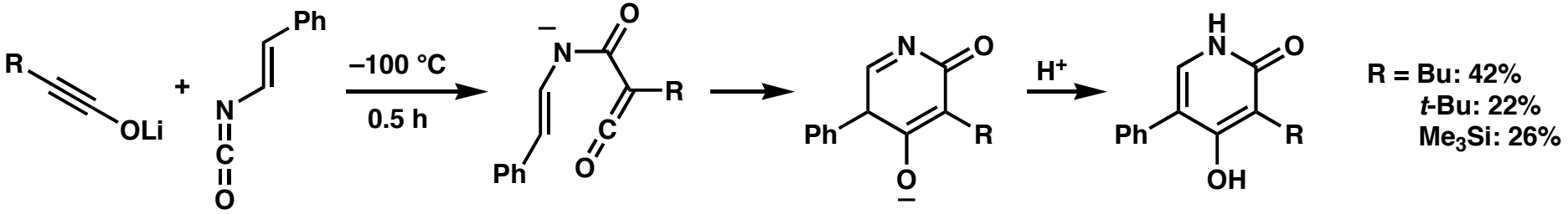
Reactions with Isocyanates



Evidence for ketene intermediate



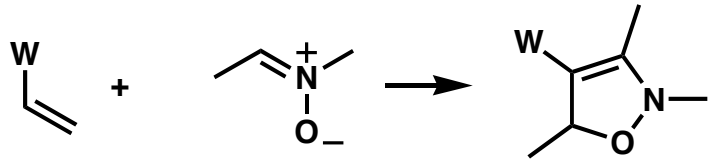
Formal [4+2] cycloaddition



Shindo, M.; Harada, A.; Matsumoto, K.; Shishido, K. *Heterocycles*. **2005**, 66, 39.

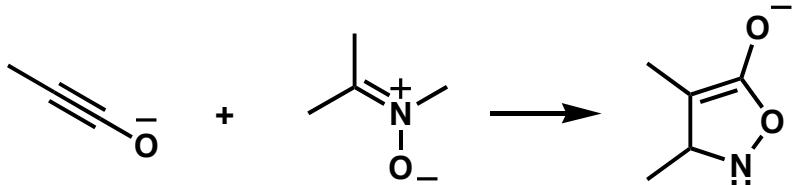
[3+2] Dipolar Additions with Nitrones

Normal 1,3-dipolar cycloaddition

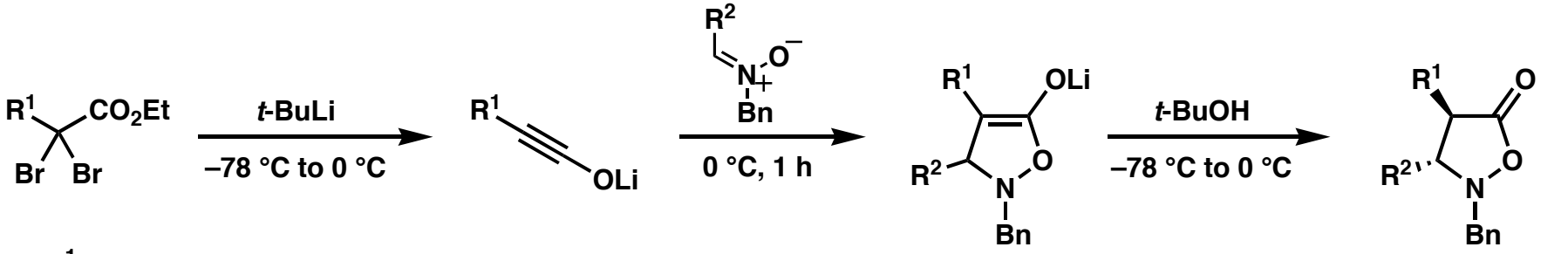


LUMO **HOMO**

Inverse electron-demand 1,3-dipolar cycloaddition



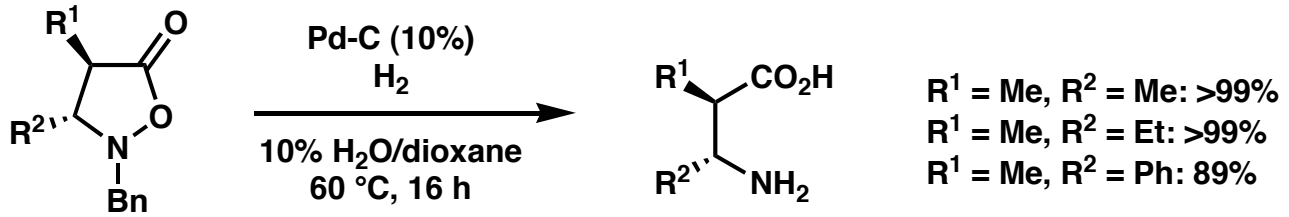
HOMO **LUMO**



R^1 = Me, Bu, *i*Pr
R^2 = Me, Et, iPr, *t*-Bu, Ph, CO_2Et

(15-85% yield)

Synthesis of β-amino acids

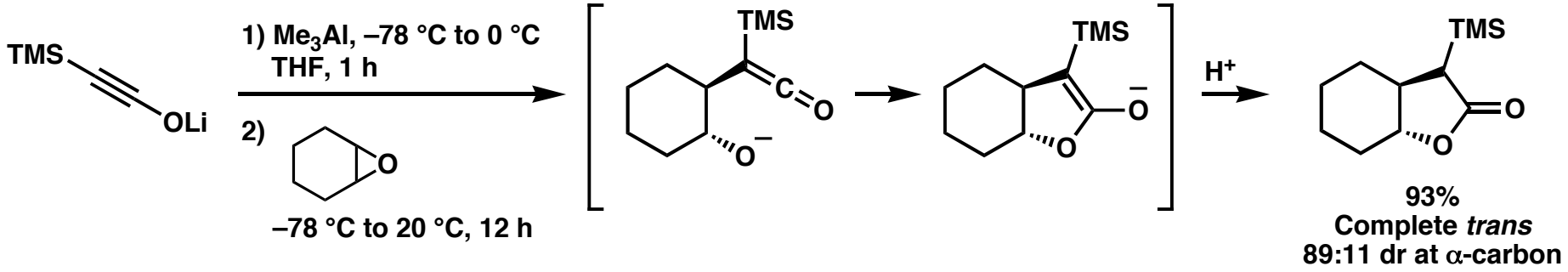


R^1 = Me, R^2 = Me: >99%
R^1 = Me, R^2 = Et: >99%
R^1 = Me, R^2 = Ph: 89%

Shindo, M.; Itoh, K.; Tsuchiya, C, Shishindo, K. *Org. Lett.* **2002**, 4, 18, 3119.

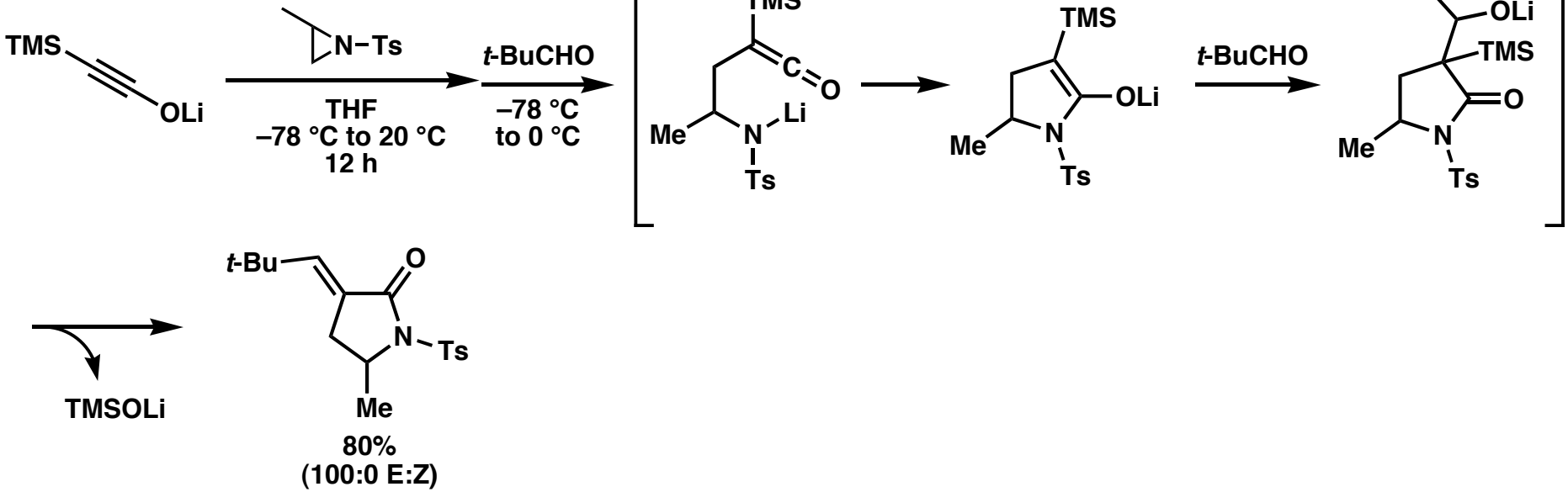
Formal [3+2] with Oxiranes and Aziridines

Reaction with oxiranes



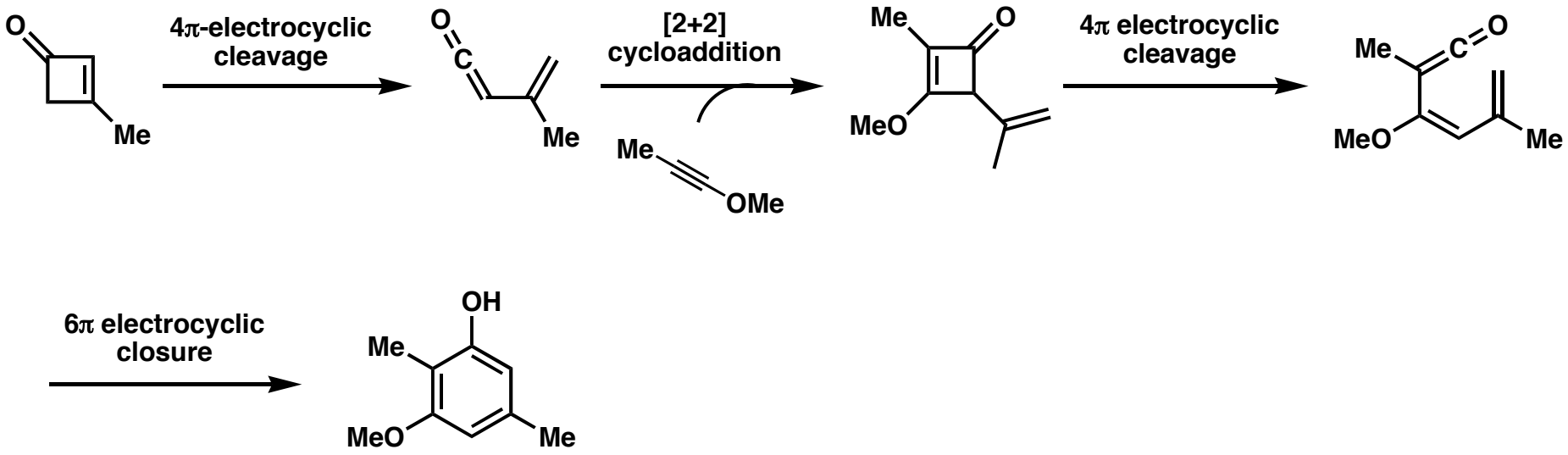
Kai, H.; Iwamoto, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc*. **1996**, 118, 7634.

Reaction with aziridines



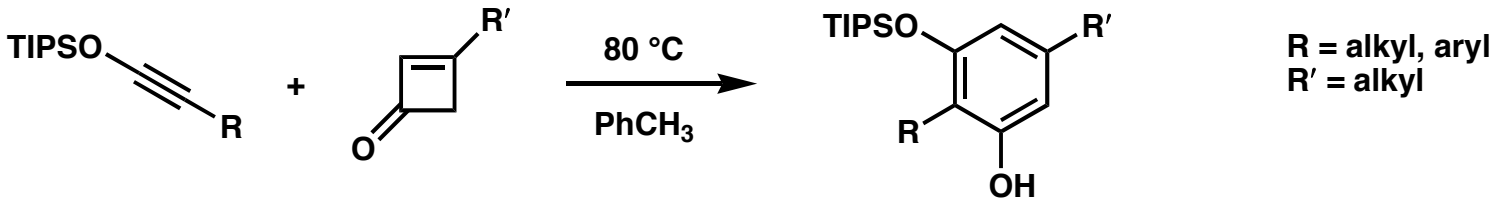
Iwamoto, K.; Kojima, M.; Chatani, N.; Murai, S. J. *Org. Chem*. **2001**, 66, 169.

Benzannulation with Silyl Ynol Ether and Vinyl Ketenes



R. L. Danheiser; Gee, S. K. *J. Org. Chem.* **1984**, 49, 1672.

Resorcinol Synthesis

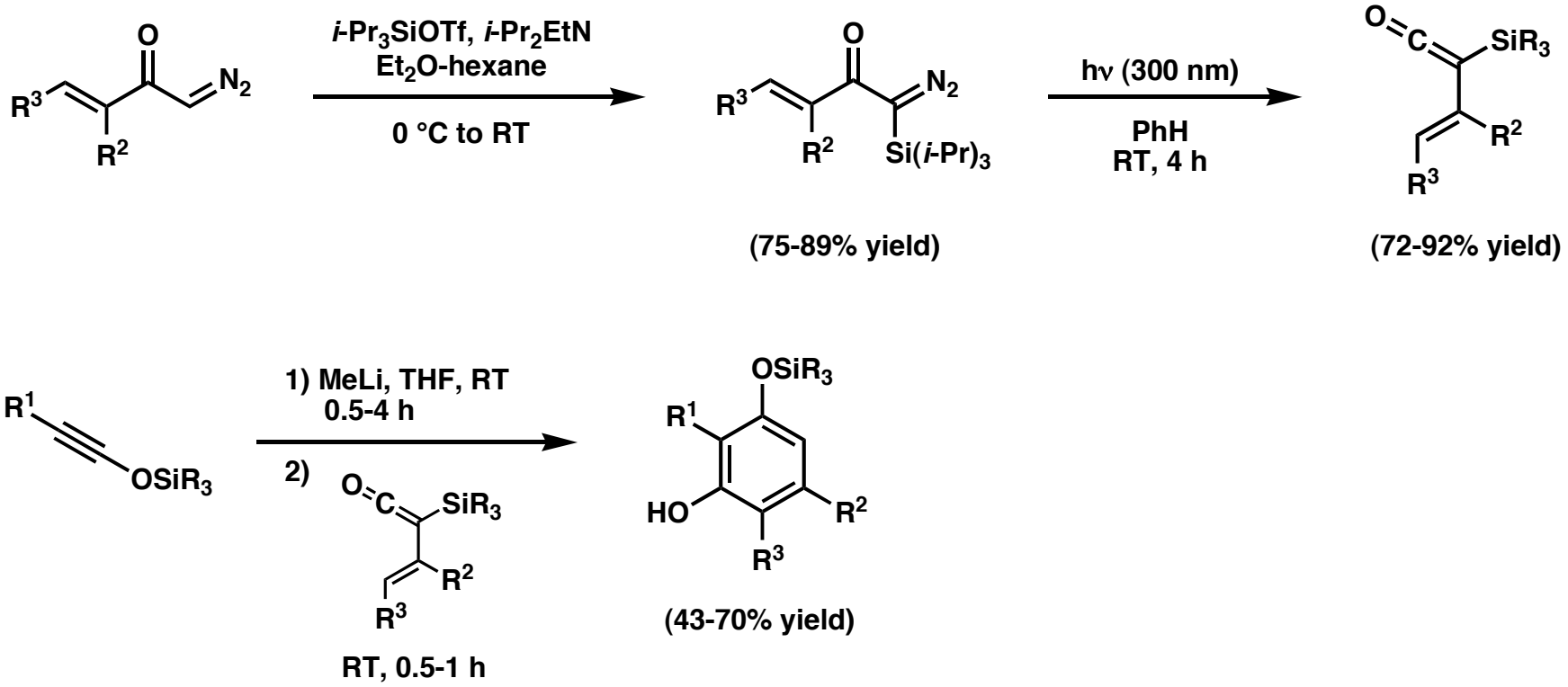


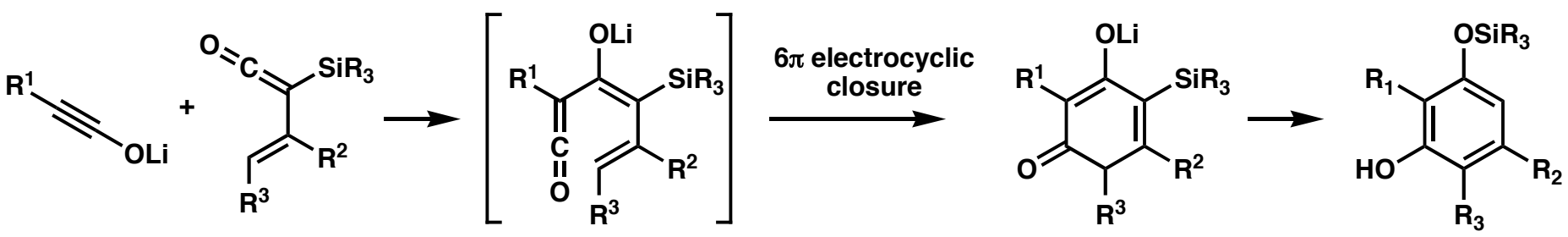
R = alkyl, aryl
R′ = alkyl

(75-90% yield)

Kowalski, C.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, 110, 3693.

Benzannulation with Ynolates and Silylvinylketenes

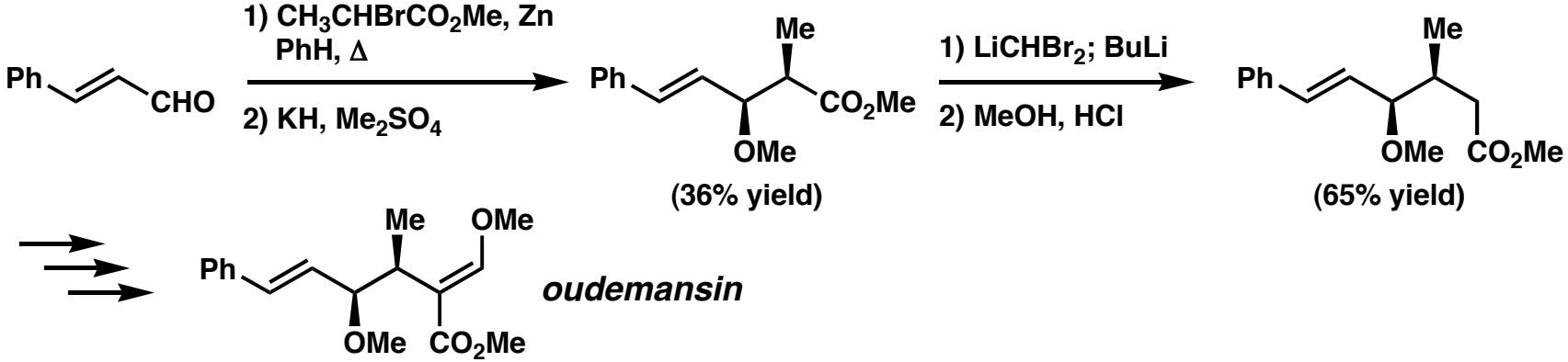




Austin, W. F.; Zhang, Y.; Danheiser, R. L. *Org. Lett.* **2005**, 7, 18, 3905.

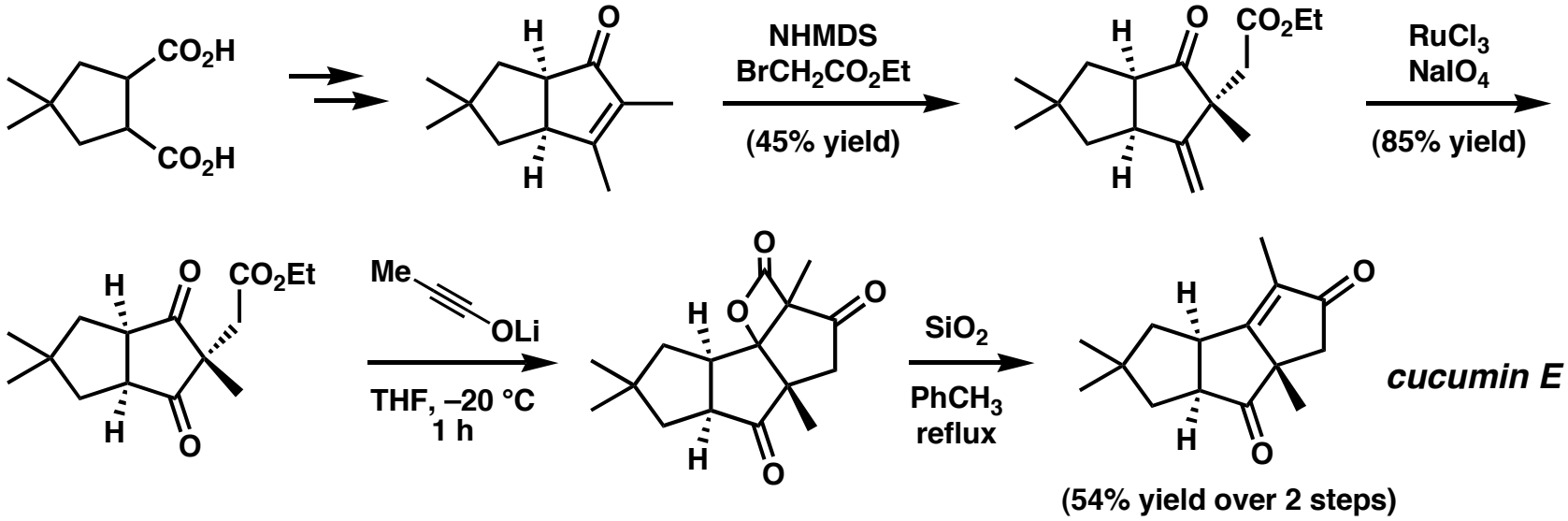
Natural Products

Formal total synthesis of oudemansin



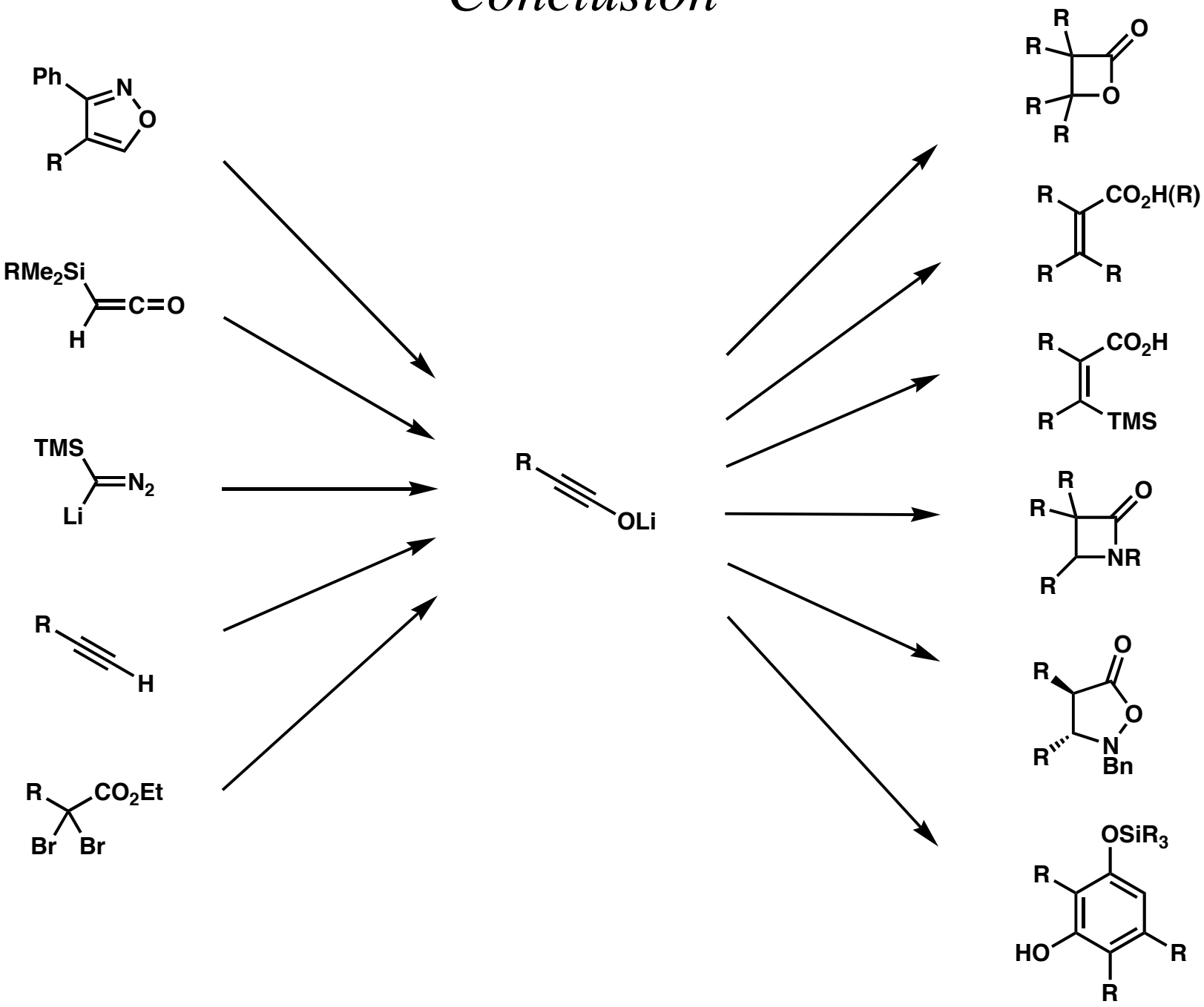
Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, 107, 1429.

Total synthesis of cucumin E



Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron Lett.* **2002**, 43, 5039.

Conclusion


Ph
N
O
R
RMe2Si
C=O
H
TMS
N2
Li
R
H
R
CO2Et
Br
Br
R
OLi
R
R
O
R
O
R
R
R
CO2H(R)
R
R
R
CO2H
R
TMS
R
R
O
NR
R
O
R
O
N
Bn
R
OSiR3
R
HO
R
R

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Stoltz Group