

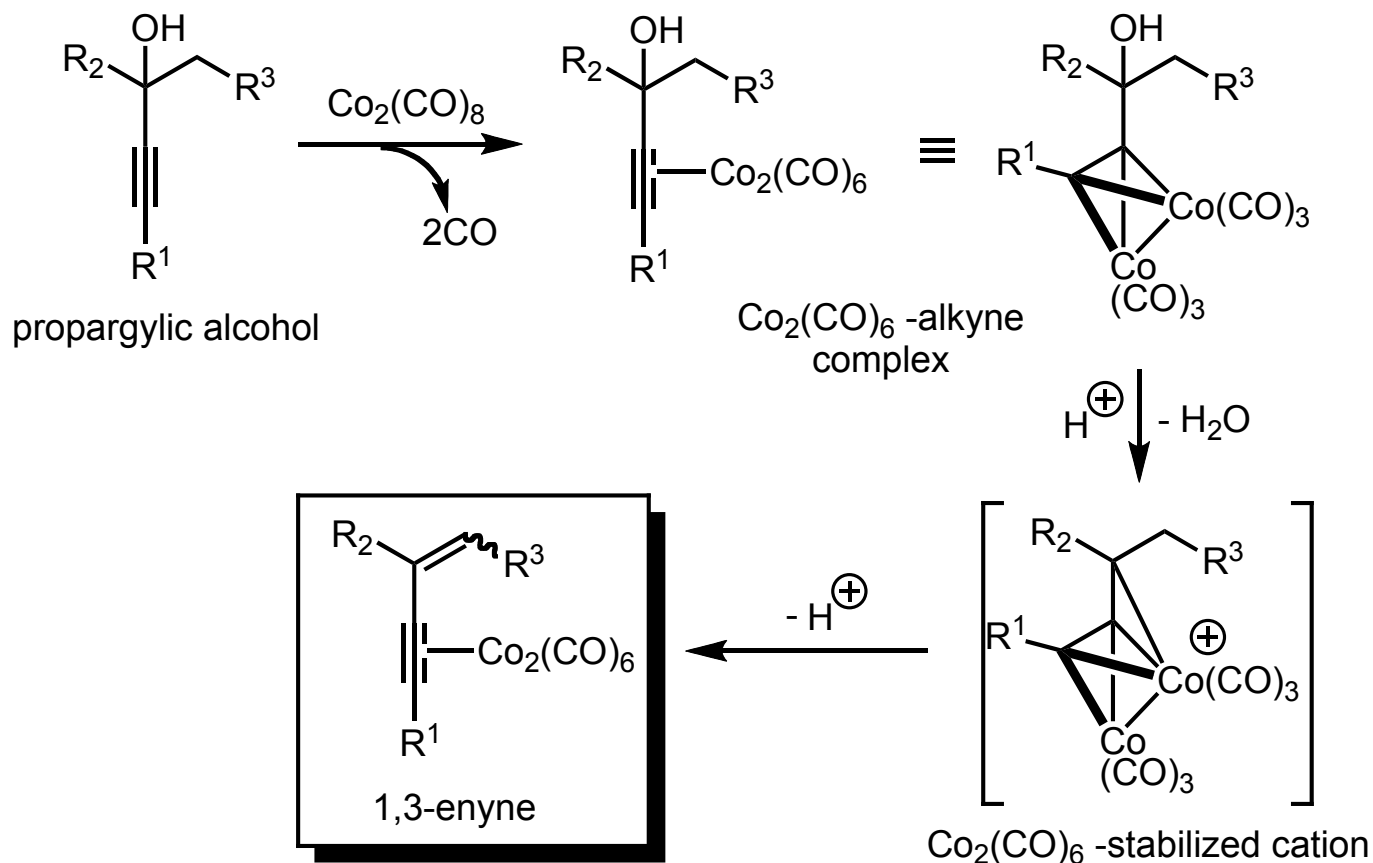
Nicholas Reaction

Munmun Mukherjee

Wulff Group

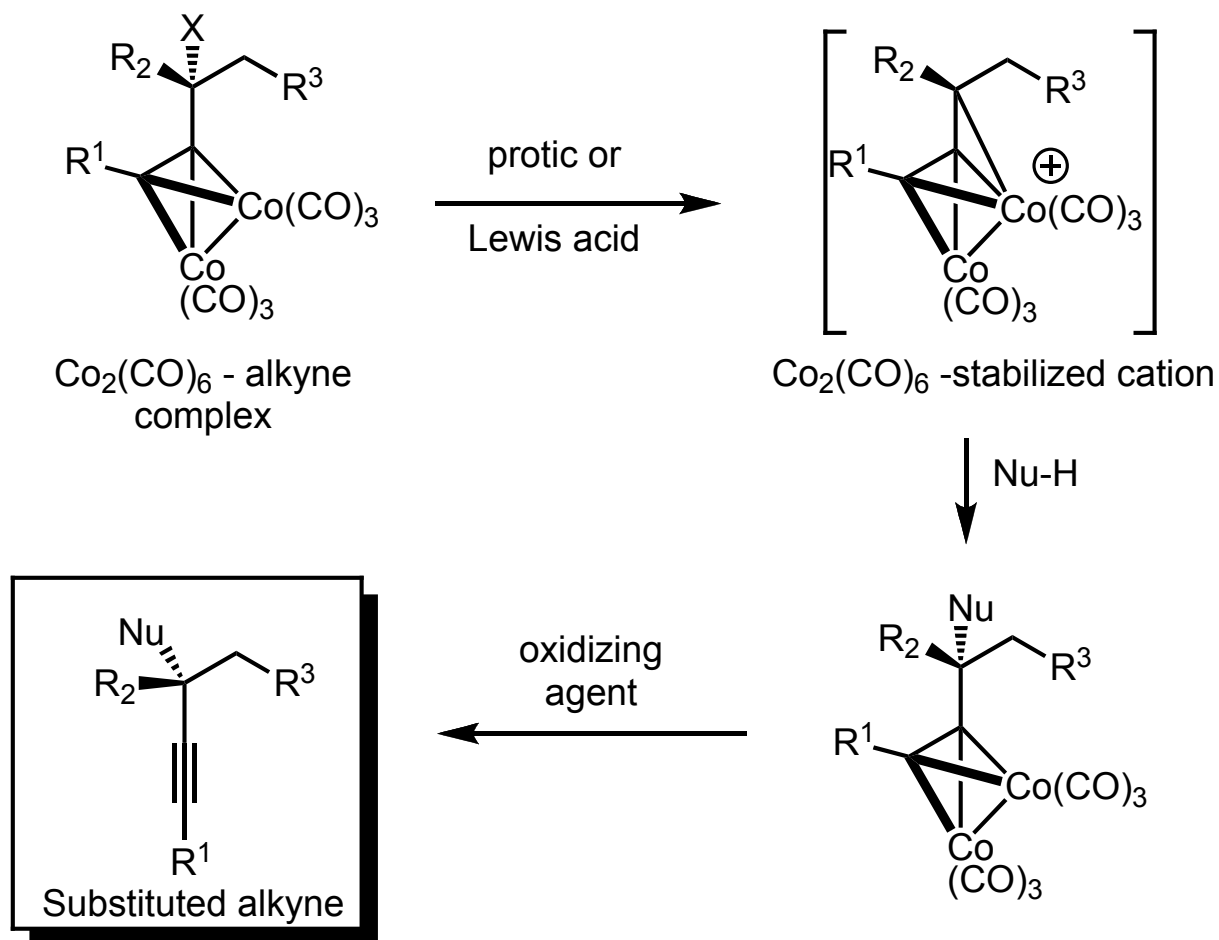
March 13, 2009

Nicholas - Pettit Reaction



Nicholas, K. M.; Pettit, R. *Tetrahedron Lett.* **1971**, 37, 3475.

Nicholas Reaction



Nu-H = e-rich aromatics, alkenes, allyl silanes, enol ether, silyl ketene acetal, ROH, R_2NH , RSH
 X = OH, OR, Cl

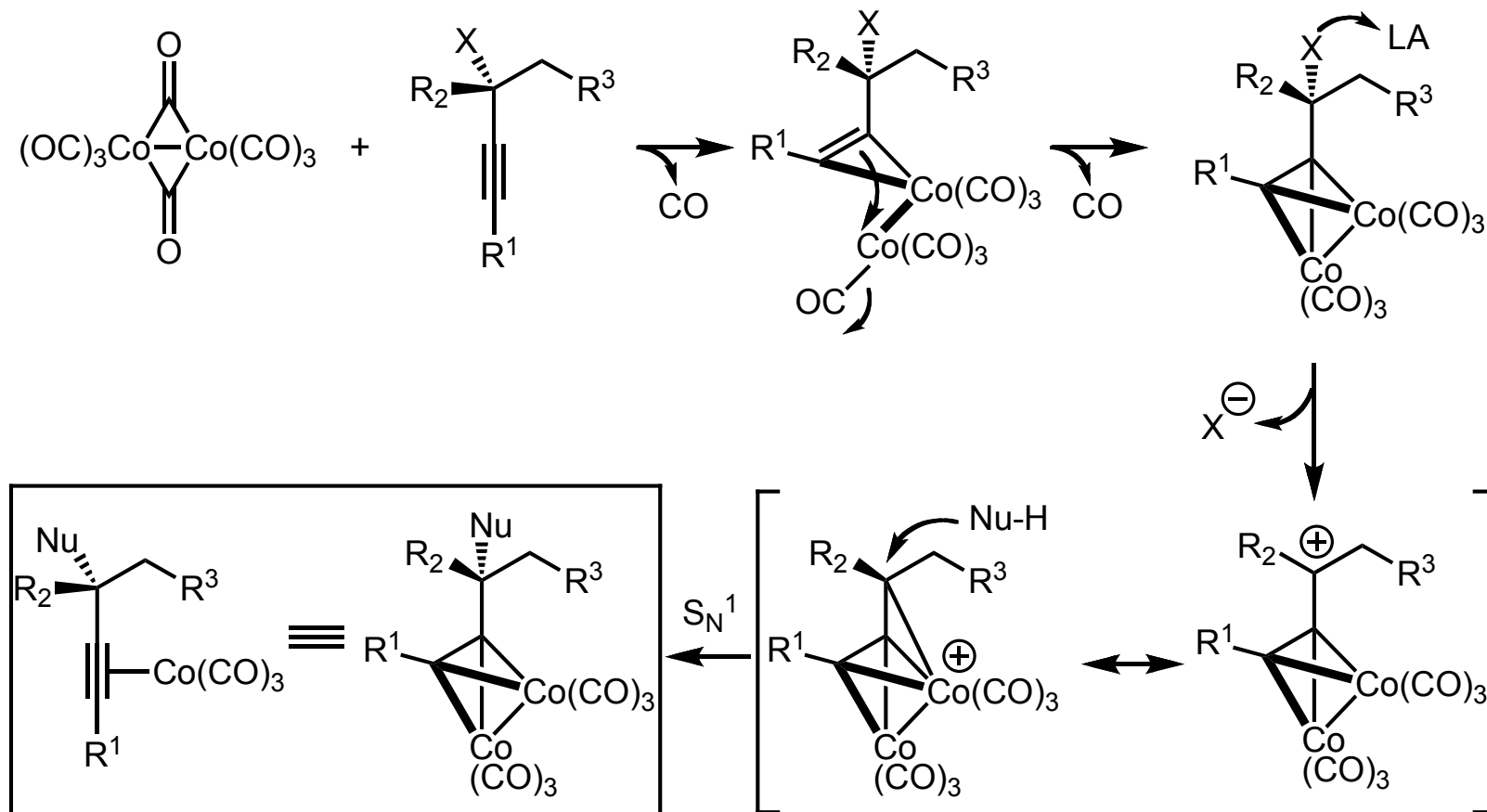
Lockwood, R. F.; Nicholas, K. M. *Tetrahedron Lett.* **1977**, *18*, 4163

Kenneth. M. Nicholas

- ❖ Born in Jamaica, NY, in 1947
- ❖ B.S. (S.U.N.Y. at Stony Brook) 1969
- ❖ Ph.D. (University of Texas) 1972 (with Rowland Pettit)
- ❖ Postdoctoral Fellow (Brandeis University) 1972-1973 (with M. Rosenblum)
- ❖ Assistant Professor, Boston College, 1973
- ❖ Professor, University of Oklahoma, 1984
- ❖ Alfred P. Sloan Foundation Fellow, 1980-1984.
- ❖ Regents' Award for Superior Accomplishment in Research, 1989.
- ❖ George Lynn Cross Research Professor, University of Oklahoma, 1993.



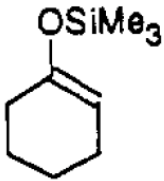
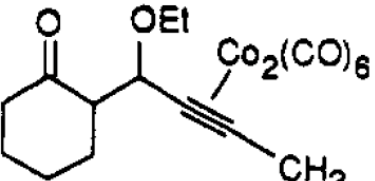
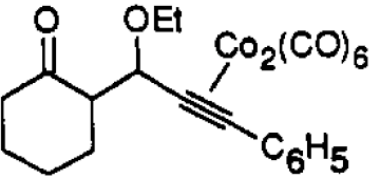
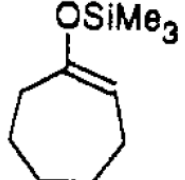
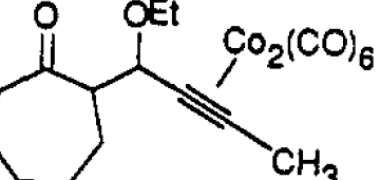
Nicholas Reaction : Mechanism



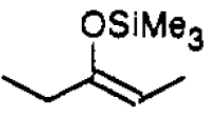
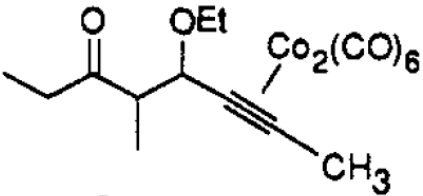
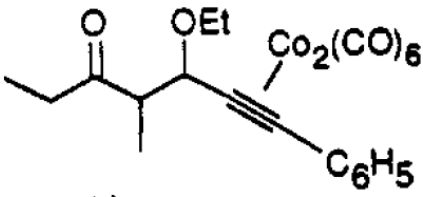
Asymmetric Nicholas Reaction:

1. Use of Chiral Starting Material
2. Use of Chiral Nucleophile
3. Use of Chiral Ligands

Stereoselective Coupling with Enol Silanes

entry	enol silane	$T, ^\circ\text{C}$	product	% yield ^b (syn)
1		-78		89 (8:1)
2		0		91 (9:1)
3		-78		82 (6:1)
4		0		73 (4.5:1)
5		-78		91 (1.1:1)

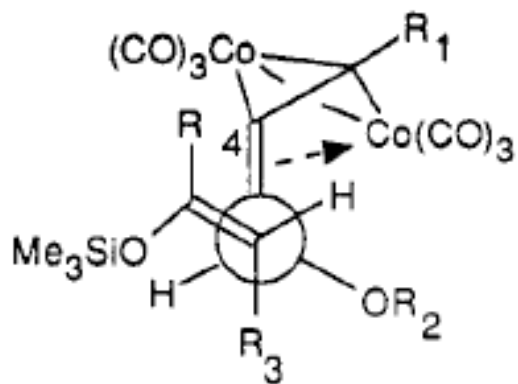
Stereoselective Coupling with Enol Silanes

entry	enol silane	$T, ^\circ\text{C}$	product	% yield ^b (syn/anti)
8		0		96 (1.9:1)
9	 <p>5</p>	-78	 <p>10</p>	100 (10.5:1)
10		0		100 (11.2:1)
11		-78	 <p>11</p>	93 (>15:1)
12		0		96 (12.5:1)

Khan, M.; Tester, R.; Varghese, A.M.; Nicholas, K. M. *J.Org. Chem.* **1990**, *55*, 186.

Transition States for Acyclic Enol Ethers

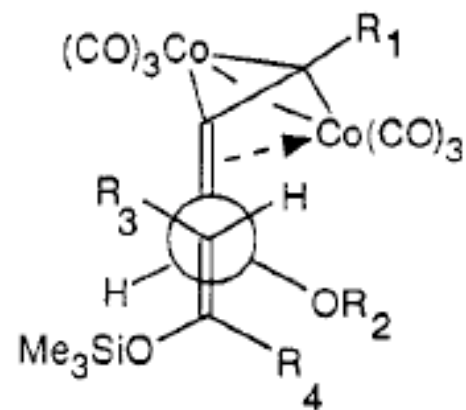
Transition States for Acyclic Enol Ethers



synclinal

A

(producing syn isomer)



anticlinal

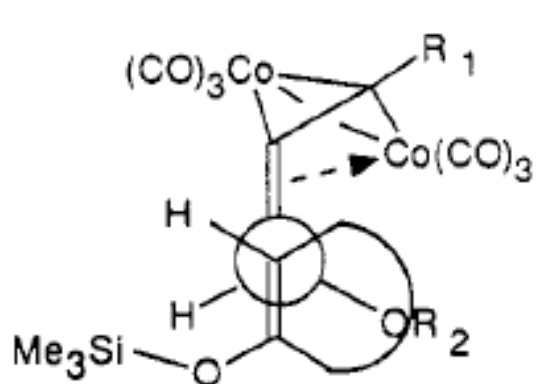
B

(producing anti isomer)

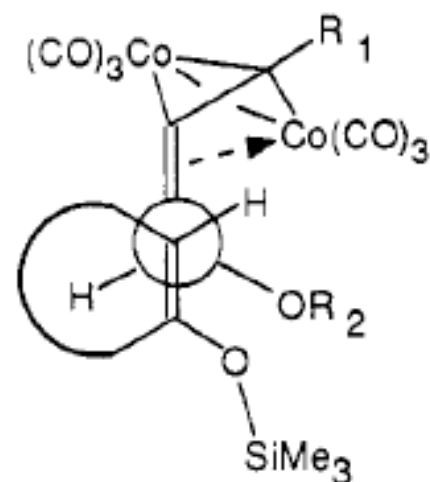
Favored (stereoelectronic effect)

Transition States for Cyclic Enol Ethers

Transition State for Cyclic Enol Ethers



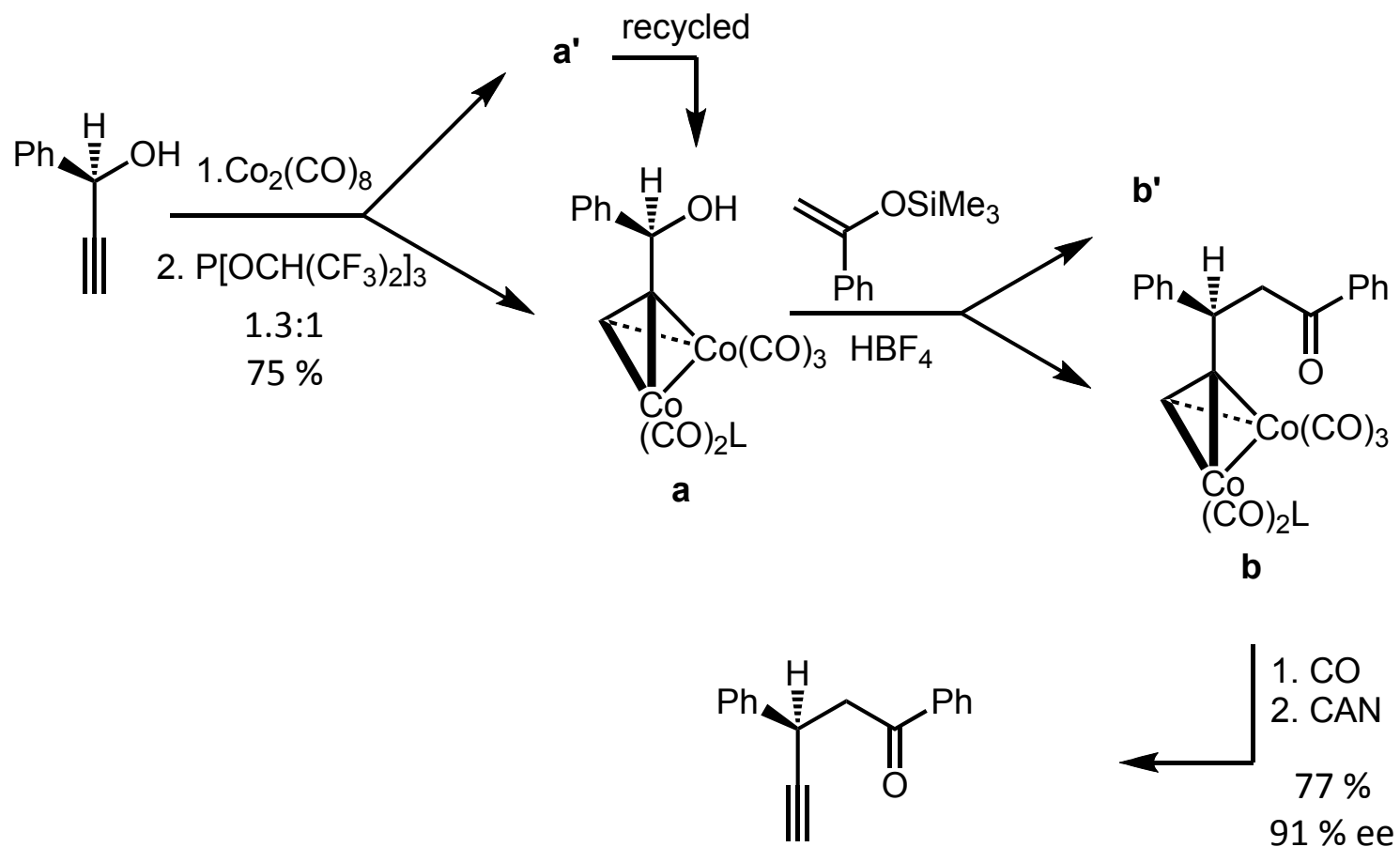
C
(producing syn isomer)



D
(producing anti isomer)
Disfavored(dipolar interaction)

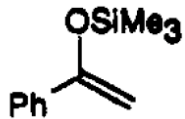
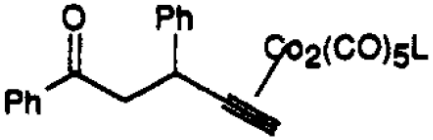
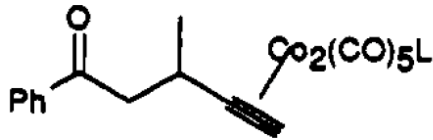
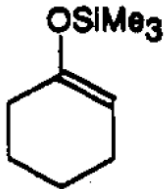
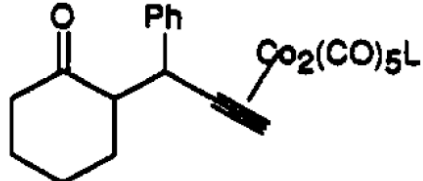
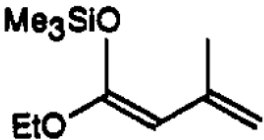
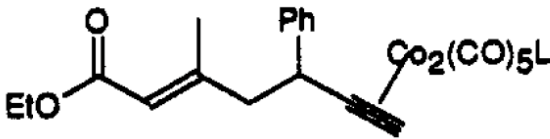

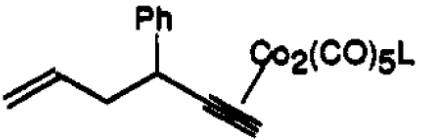
Synclinal orientation not possible : steric interaction

Stereoselective Propargylation Mediated by a Chiral Metal Cluster (Reaction with Chiral SM)



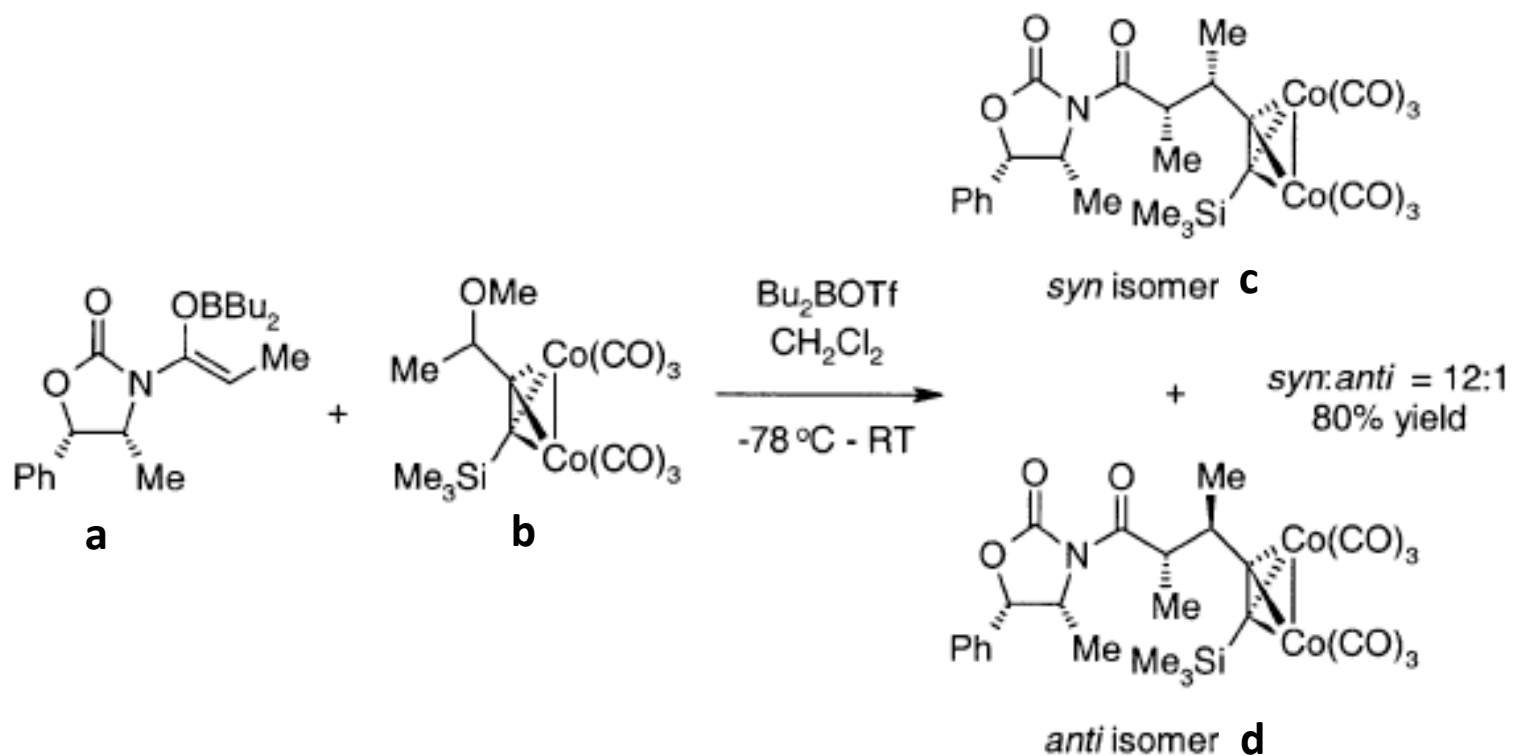
Caffyn, A. J. M.; Nicholas, K. M. J. *Am. Chem. Soc.* **1993**, *115*, 6438.

Substrate Scope

entry	nucleophile	product	yield, % ^a (diastereomer ratio)
1			85 (1:9)
2			47 (1:1.2)
3			30 (1:1.2)
4			90 (1:1.1) ^b
5			73 (1:7.1)
6			94 (1:10.5)

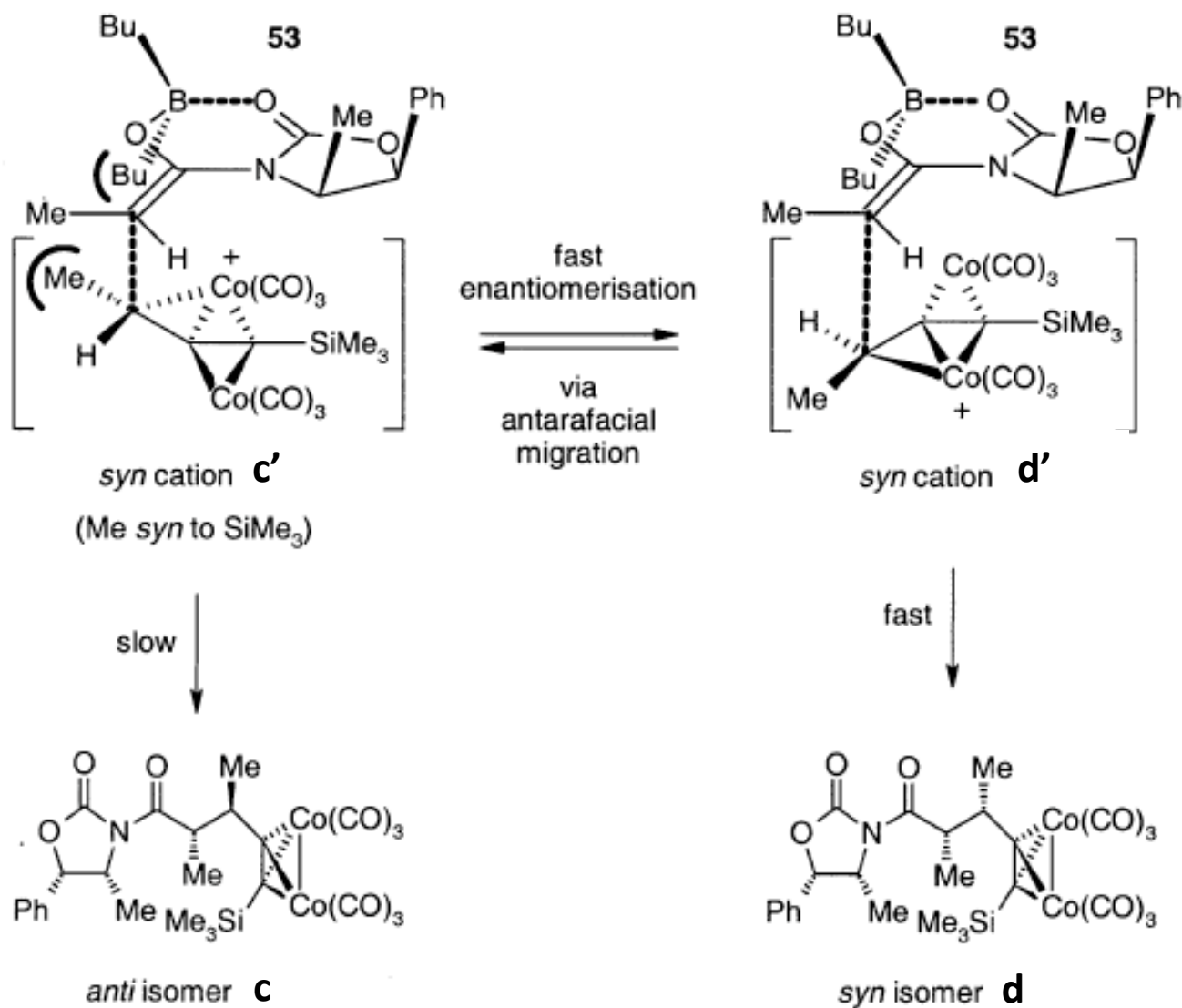
Caffyn, A. J. M.; Nicholas, K. M. J. *Am. Chem. Soc.* **1993**, *115*, 6438.

Reaction with Chiral Nucleophiles



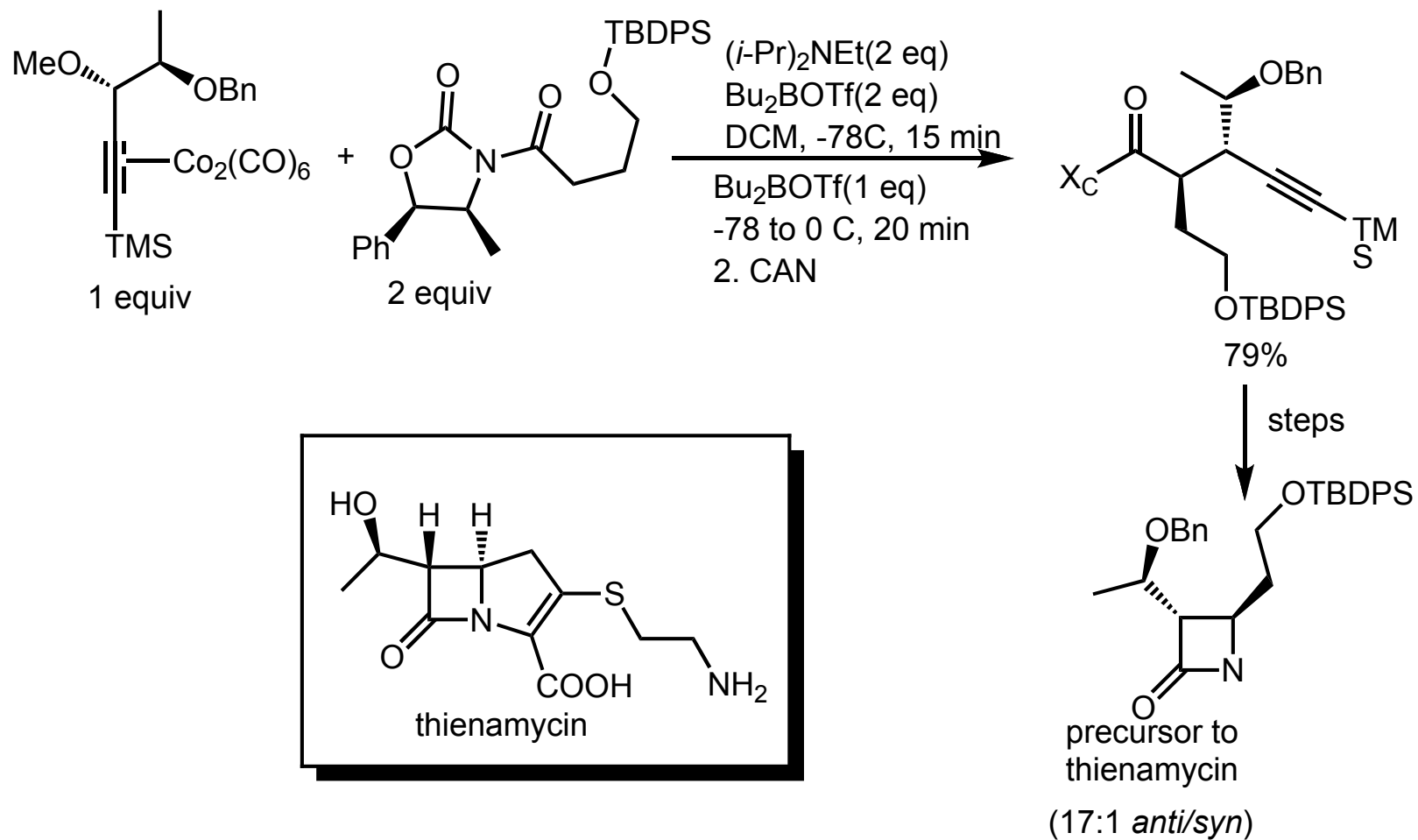
Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749–5759.

Transition States

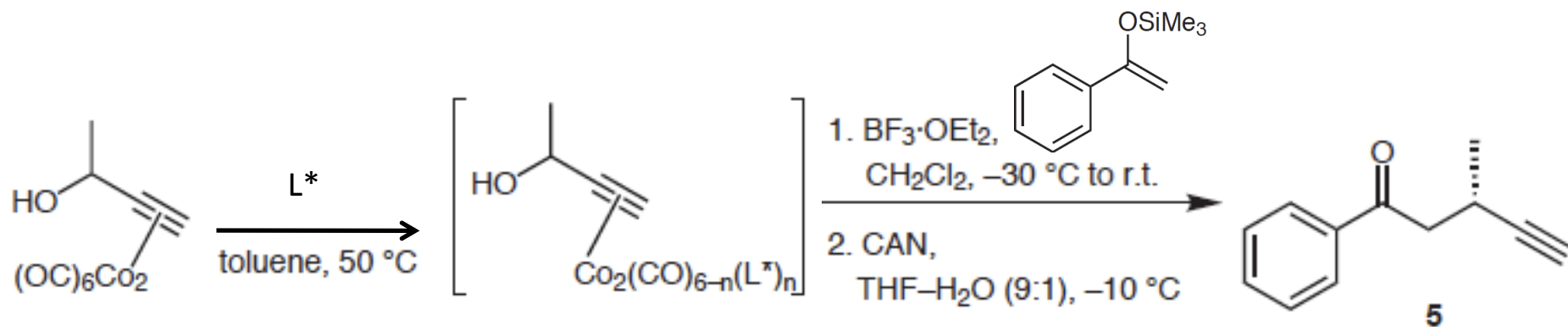


Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749–5759.

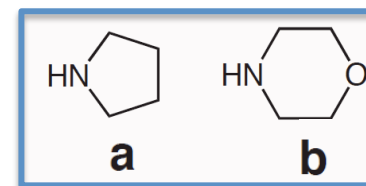
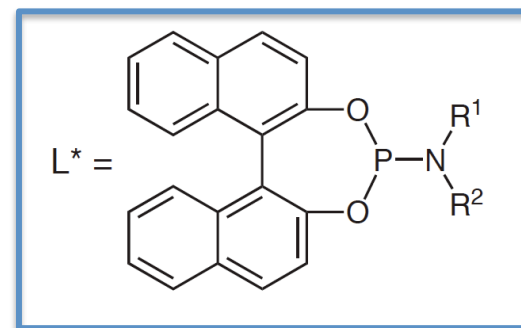
Total Synthesis of Thienamycin



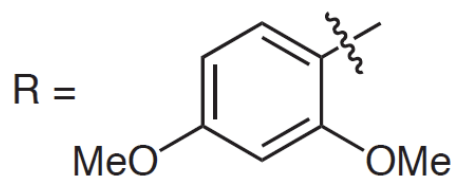
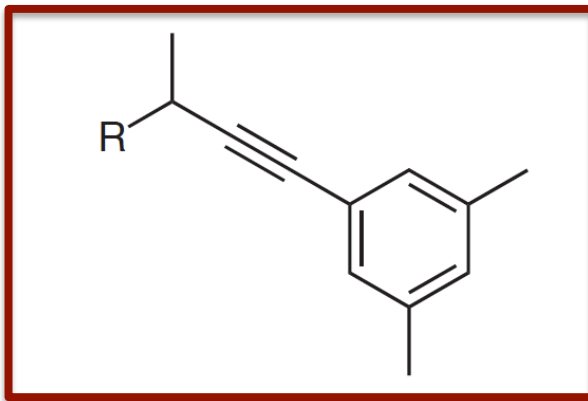
Chiral Phosphoramidite Ligands



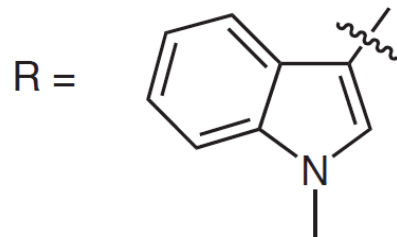
Entry	Ligand ^a (<i>R</i>)	Amount (equiv) ^b	Yield (%)	ee ^{d,e}
1	a	1	26	16 (<i>S</i>)
2	a	2	33	24 (<i>S</i>)
3	b	1	12	20 (<i>S</i>)
4	b	2	10	26 (<i>S</i>)



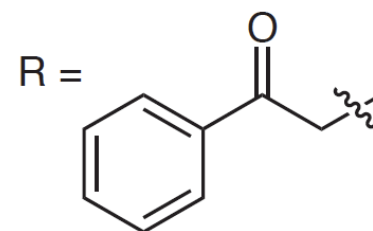
Substrate Scope



Ligand **a**, yield :74 %
%ee :12

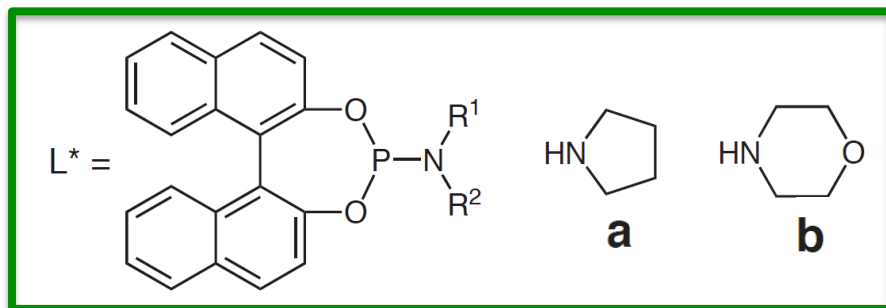


Ligand **a**, yield :90 %
%ee :22

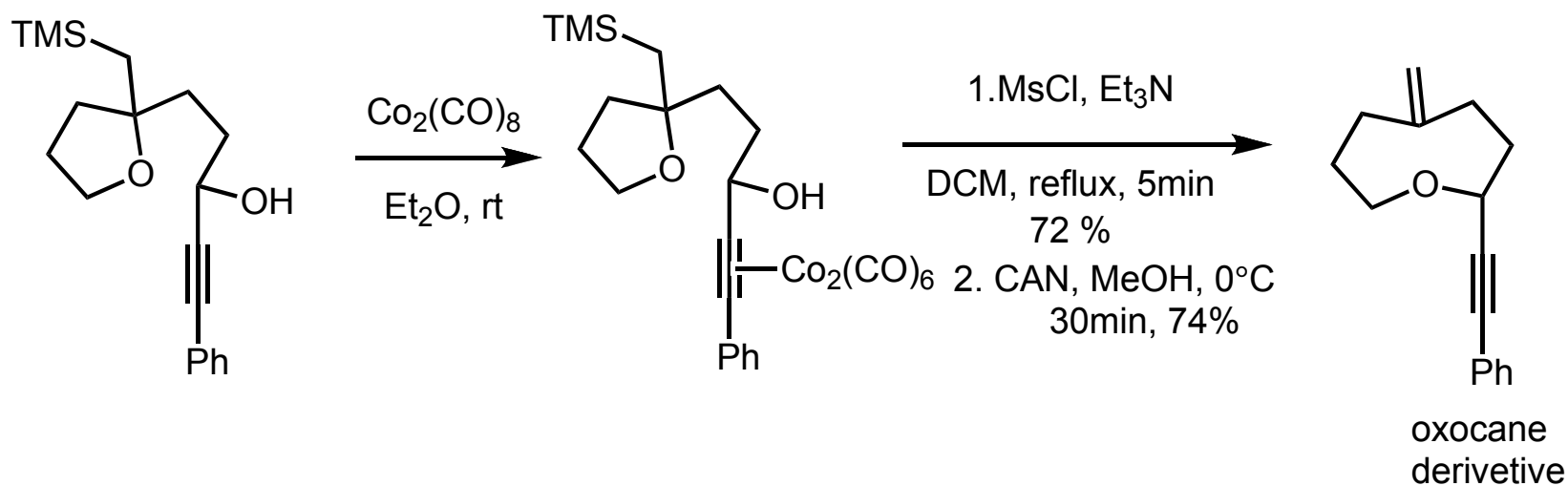


Ligand **a**, yield :30 %
%ee :66

Ligand **b**, yield :17 %
%ee :74

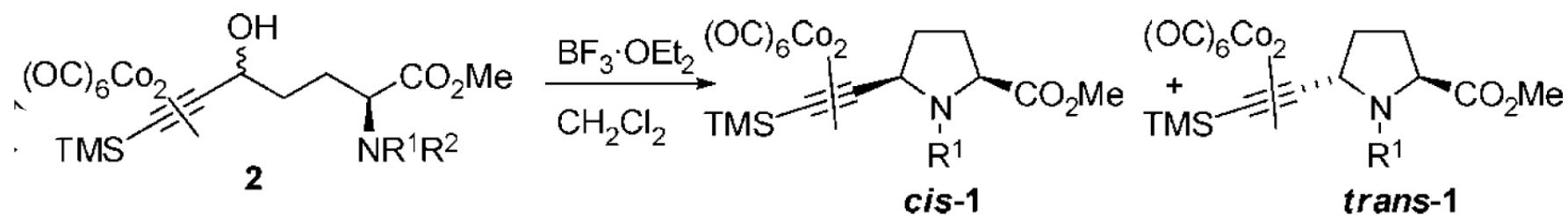


Intramolecular Nicholas Reaction



Mukai, C.; Yamashita, H.; Ichiryu, T.; Hanaoka, M. *Tetrahedron* **2000**, *56*, 2203

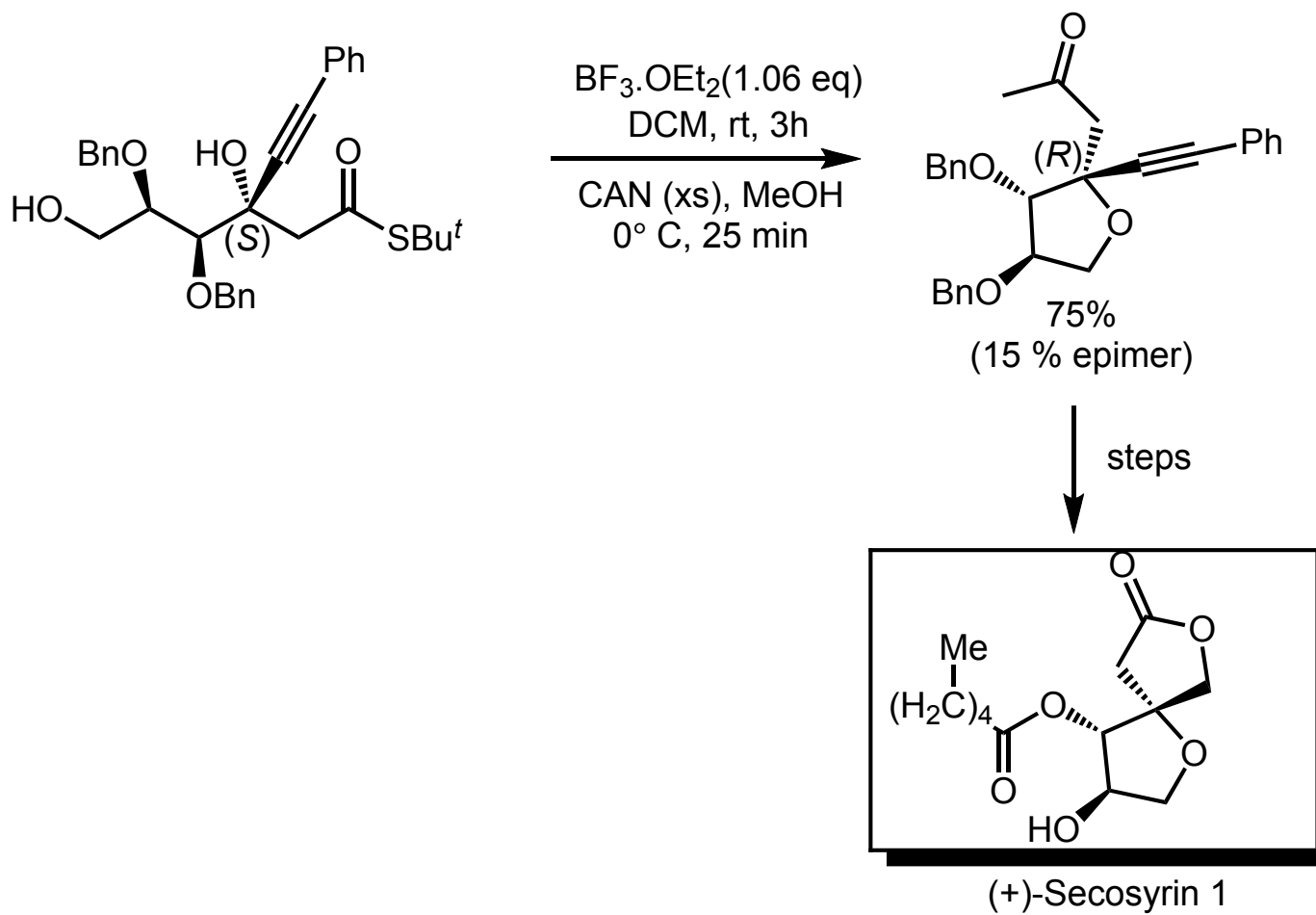
Intramolecular Nicholas Reaction



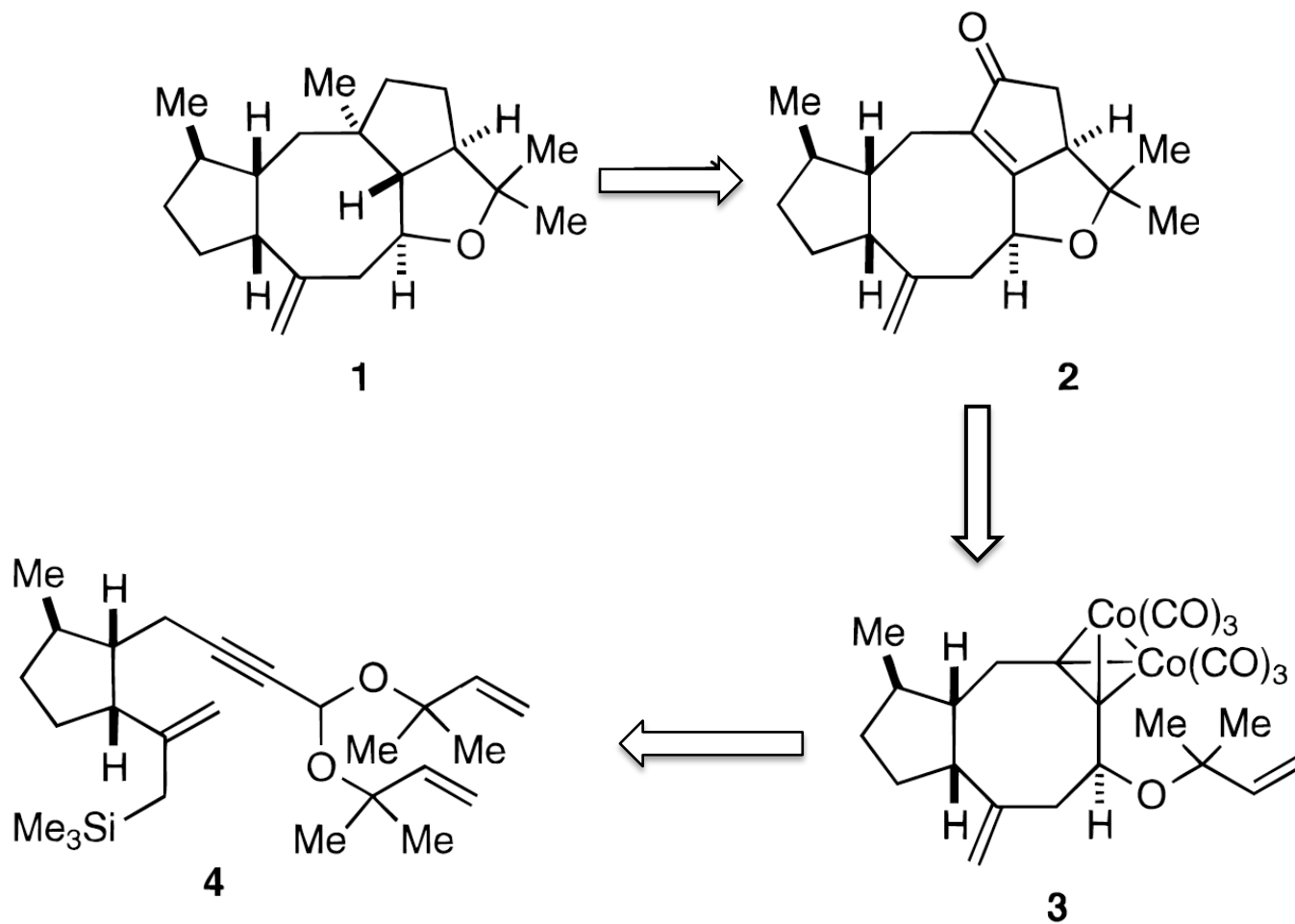
entry	2	T ($^{\circ}\text{C}$)	time (h)	yield	product <i>cis:trans</i>
1	2c , $\text{R}^1 = \text{Ts}$, $\text{R}^2 = \text{H}$	rt	0.25	88	^{1.2} >99:1
2		0	2	85	>99:1
3		-20	2	84	>99:1
4	2d , $\text{R}^1 = \text{Bz}$, $\text{R}^2 = \text{H}$	rt	2	86	1:10
5		0	2	85	1:10
6		-20	2	82	1:10
7	2e , $\text{R}^1 = \text{Ts}$, $\text{R}^2 = \text{Boc}$	rt	1	87	>99:1
8		0	20	- ^a	
9	2f , $\text{R}^1 = \text{Bz}$, $\text{R}^2 = \text{Boc}$	rt	17	88	1:10
10		0	30	- ^a	

^a Almost all of the starting material was recovered.

Total Synthesis of (+)-Secosyrin 1

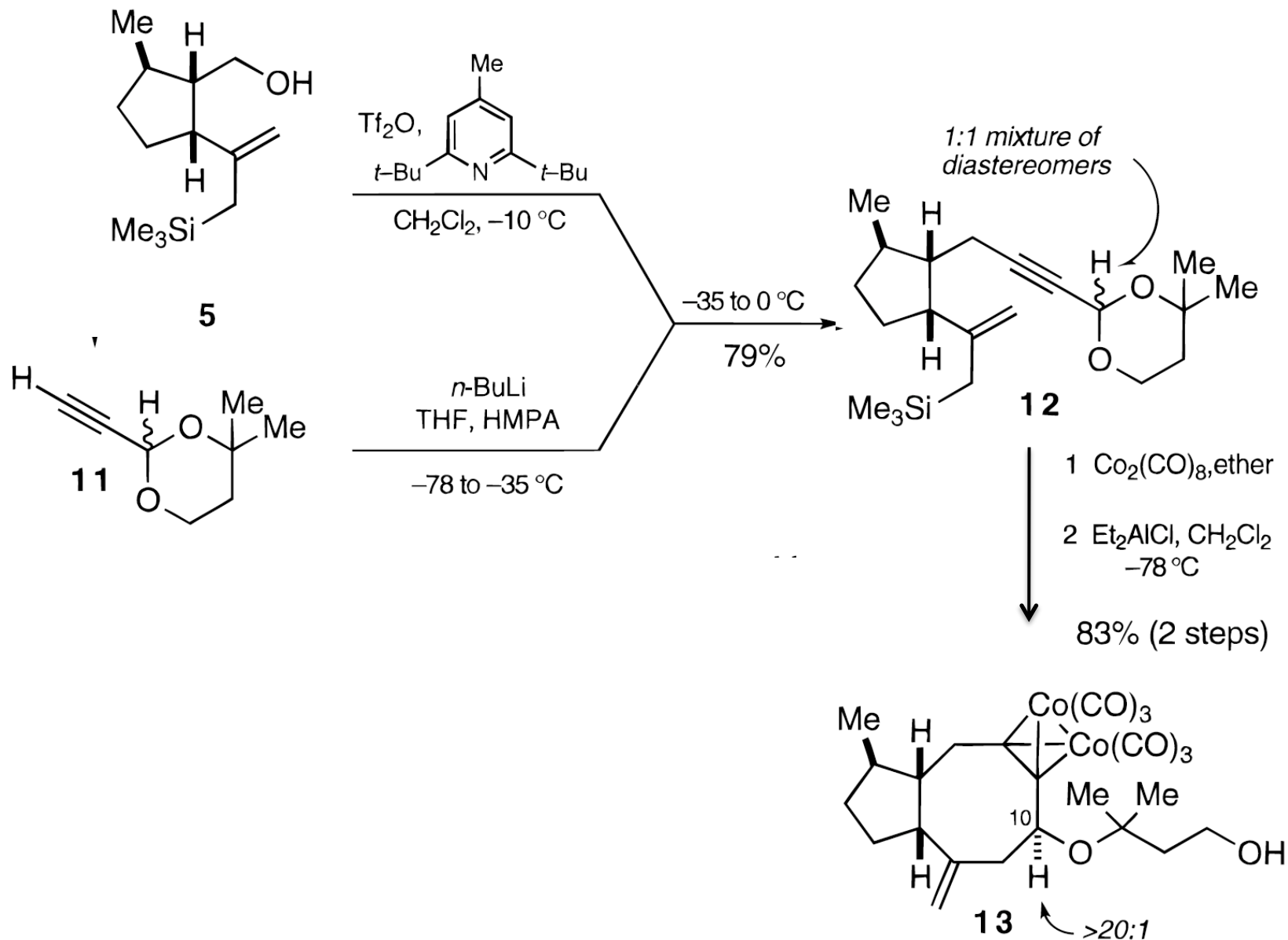


Total Synthesis of (+)-Epoxydictymene



Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.*, **1997**, *119*, 4353

Total Synthesis of (+)-Epoxydictymene



Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.*, **1997**, *119*, 4353

Some features of Nicholas Reaction

- The alkyne complexes are obtained in almost quantitative yields and can be purified by column chromatography
- A wide range of nucleophiles reacts with the resulting propargylic cations including S-, C-, O-, N-nucleophiles.
- Oxidative decomplexation regenerates triple bond, reductive decomplexation yields corresponding alkene.
- When cobalt complex is not removed can be used in subsequent Pausan-Khand reaction
- It can be both inter- and intra molecular and macrocyclisation can be achieved
- there are no allene side products that often complicates the reaction of uncomplexed substrates