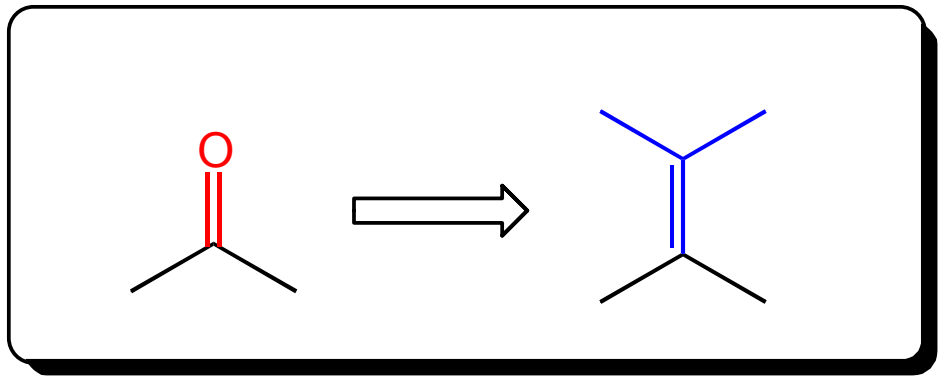
Reagents for Alkylidenations



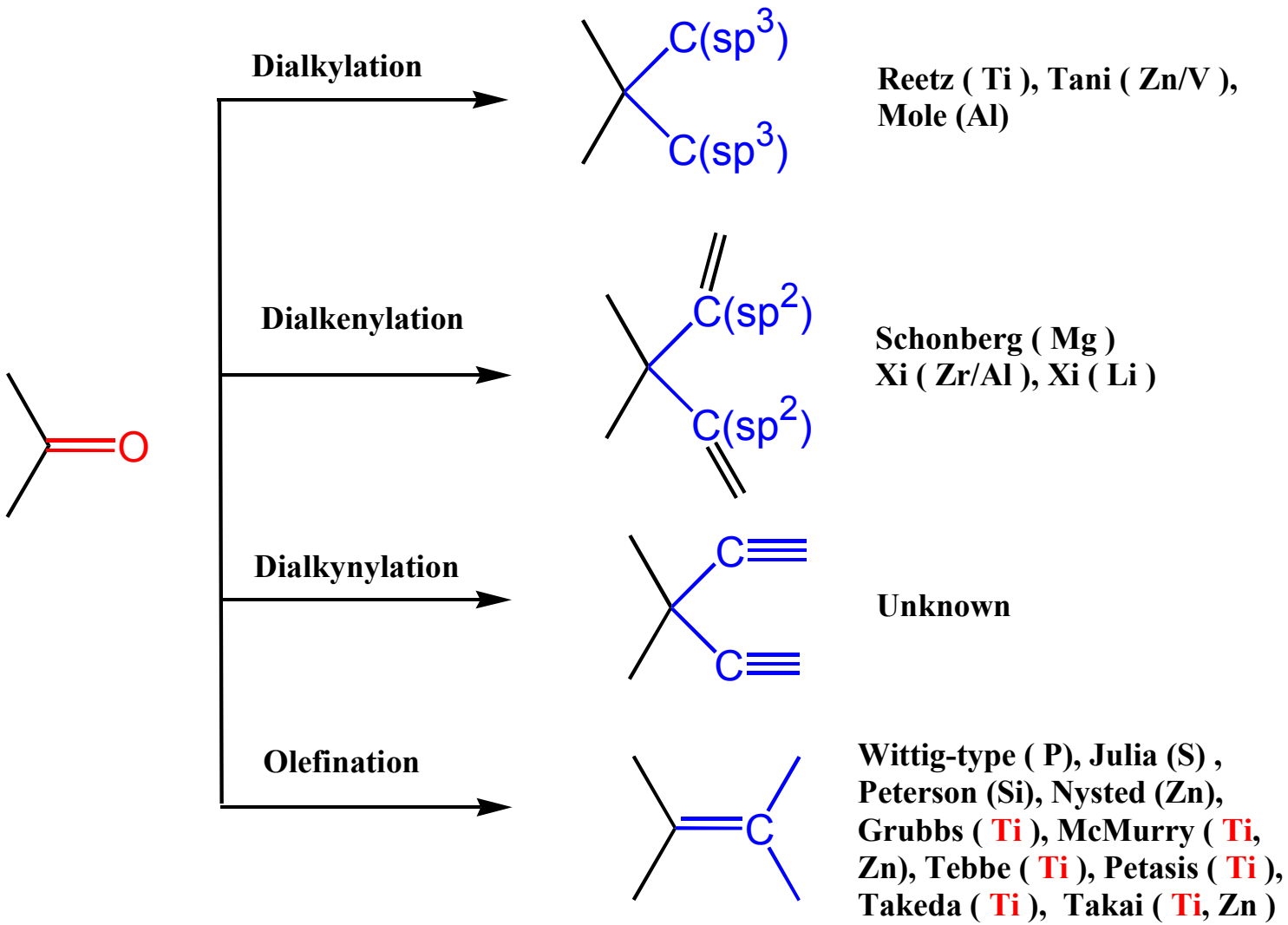
Jinglong Chen

Feb. 2, 2005

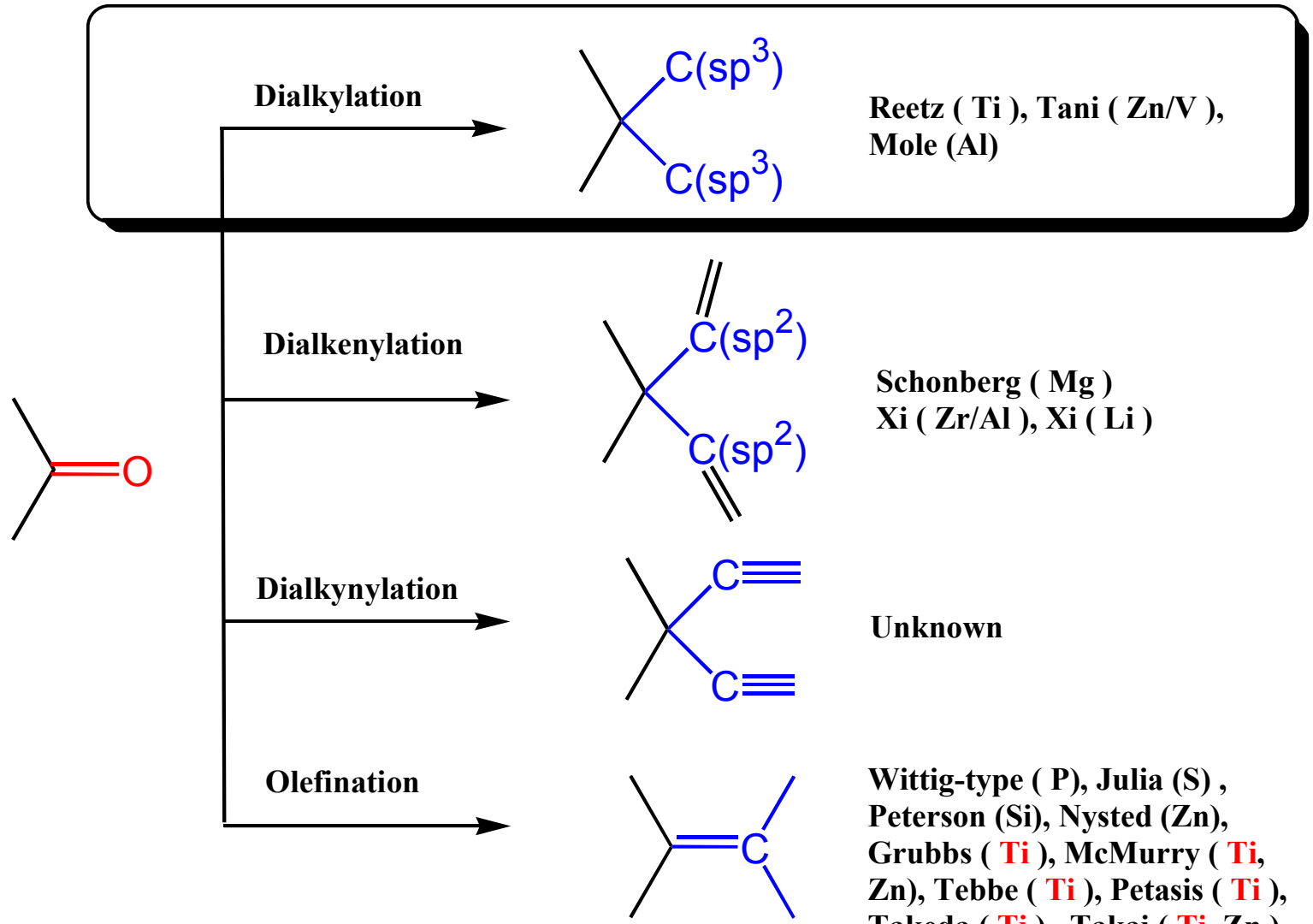
Farewell the Monkey Year

Welcome the Rooster Year

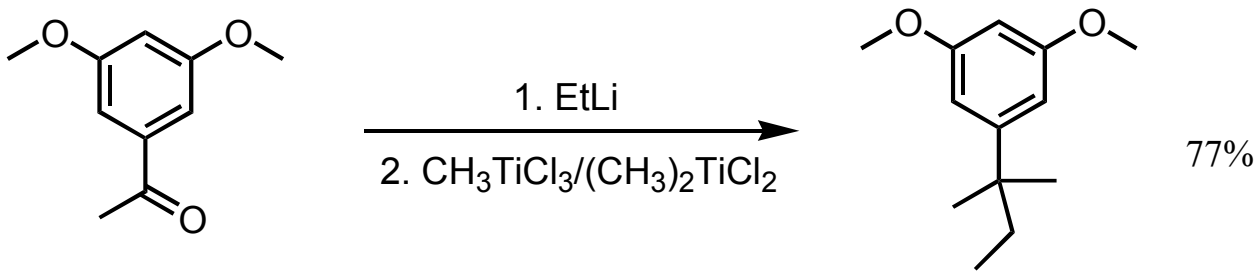
C=O Bond Cleavage Reactions



Dialkylation

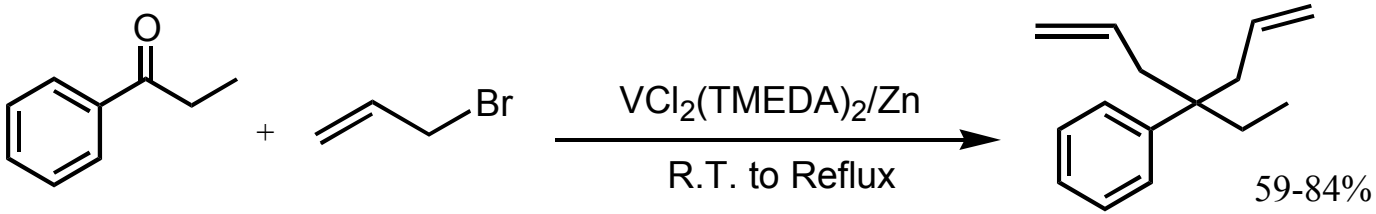


Dialkylation



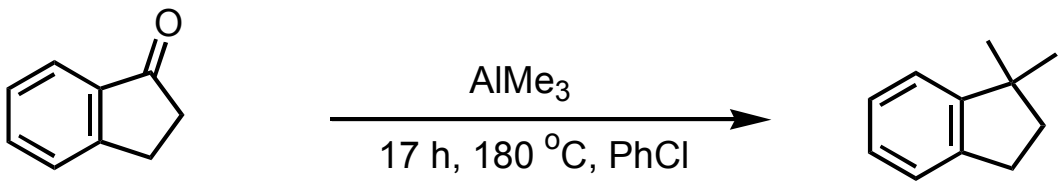
77%

Reetz, M. T. et. al. *J. Org. Chem*. **1983**, *48*, 254



59-84%

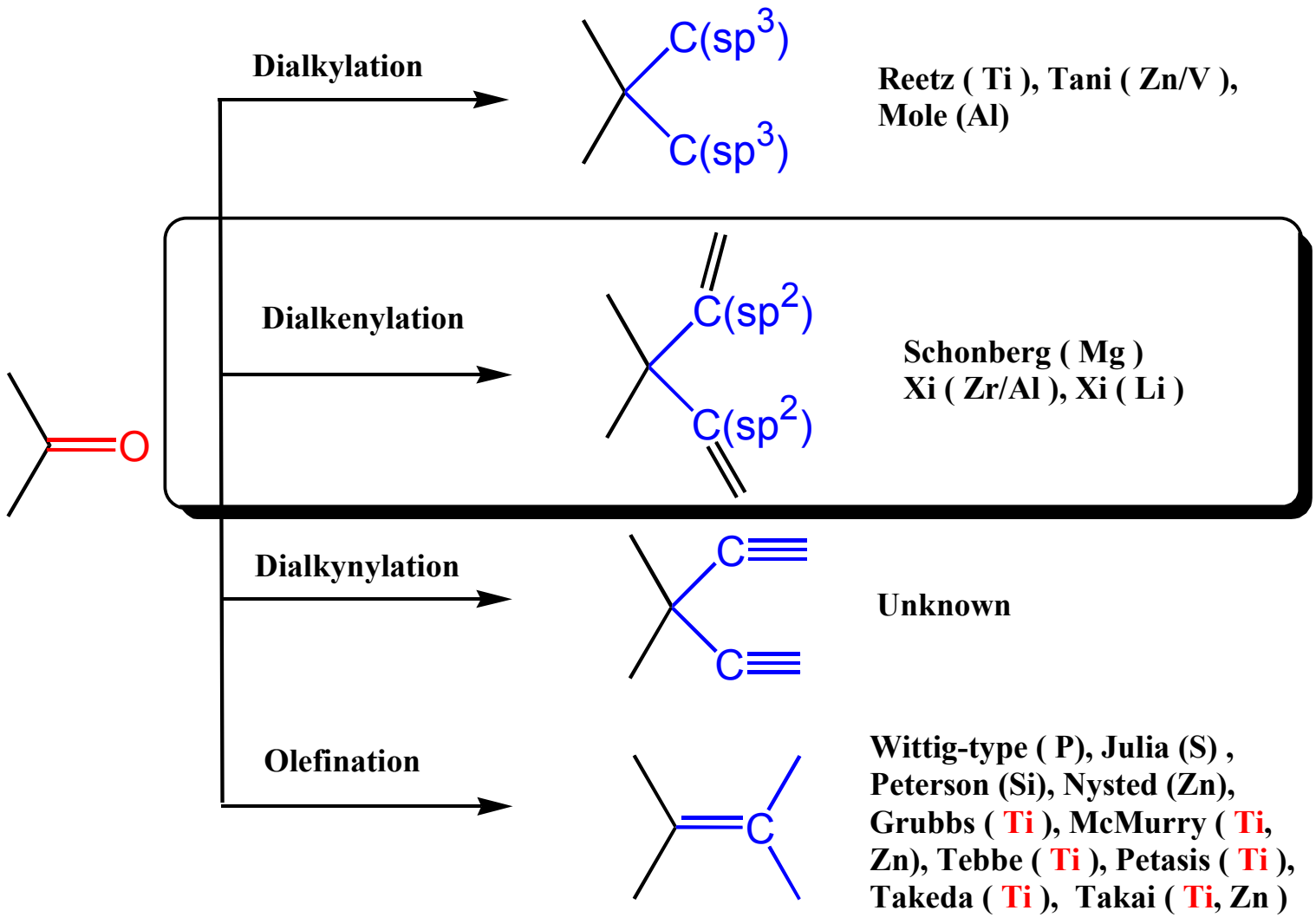
Tani, K. et. al. *J. Org. Chem*. **199**7, *62*, 8109



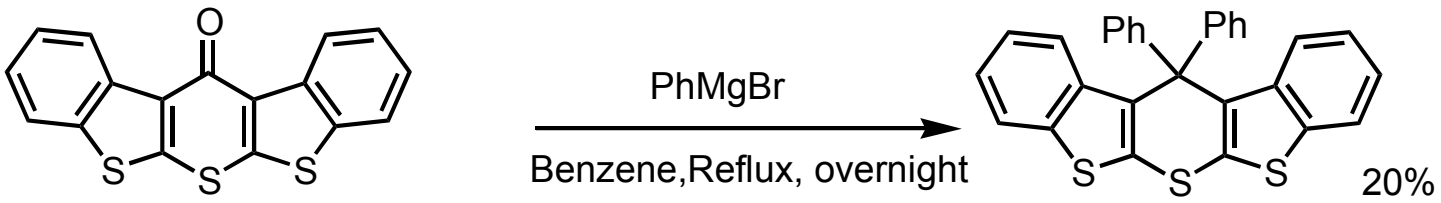
50%

Mole, T. et. al. *JCS. Chem. Comm.* **1972**, 595

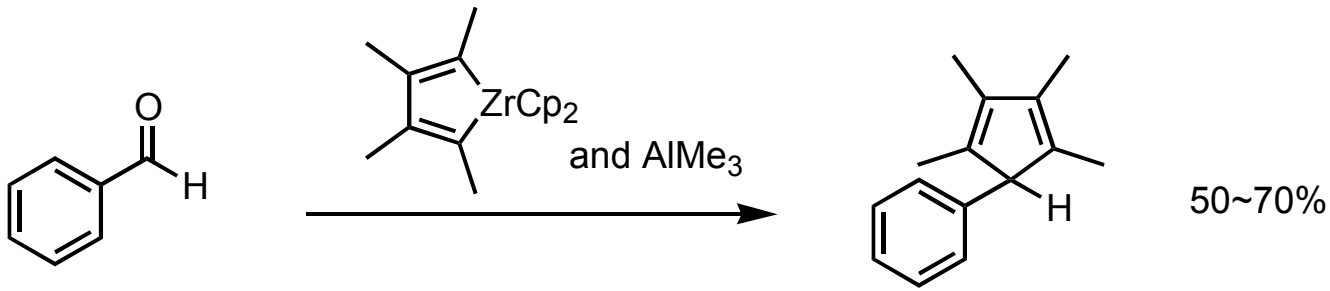
Dialkenylation



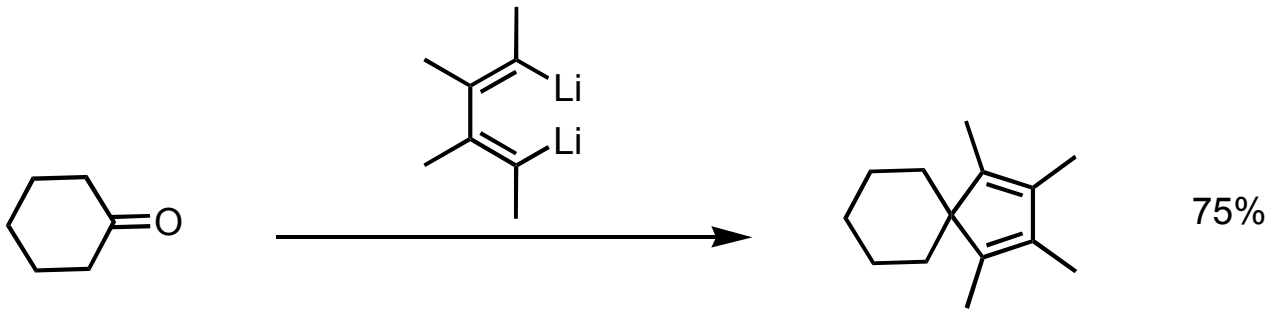
Dialkenylation



Schonberg, A. et. al. *J. Am. Chem. Soc*. **1946**, 609

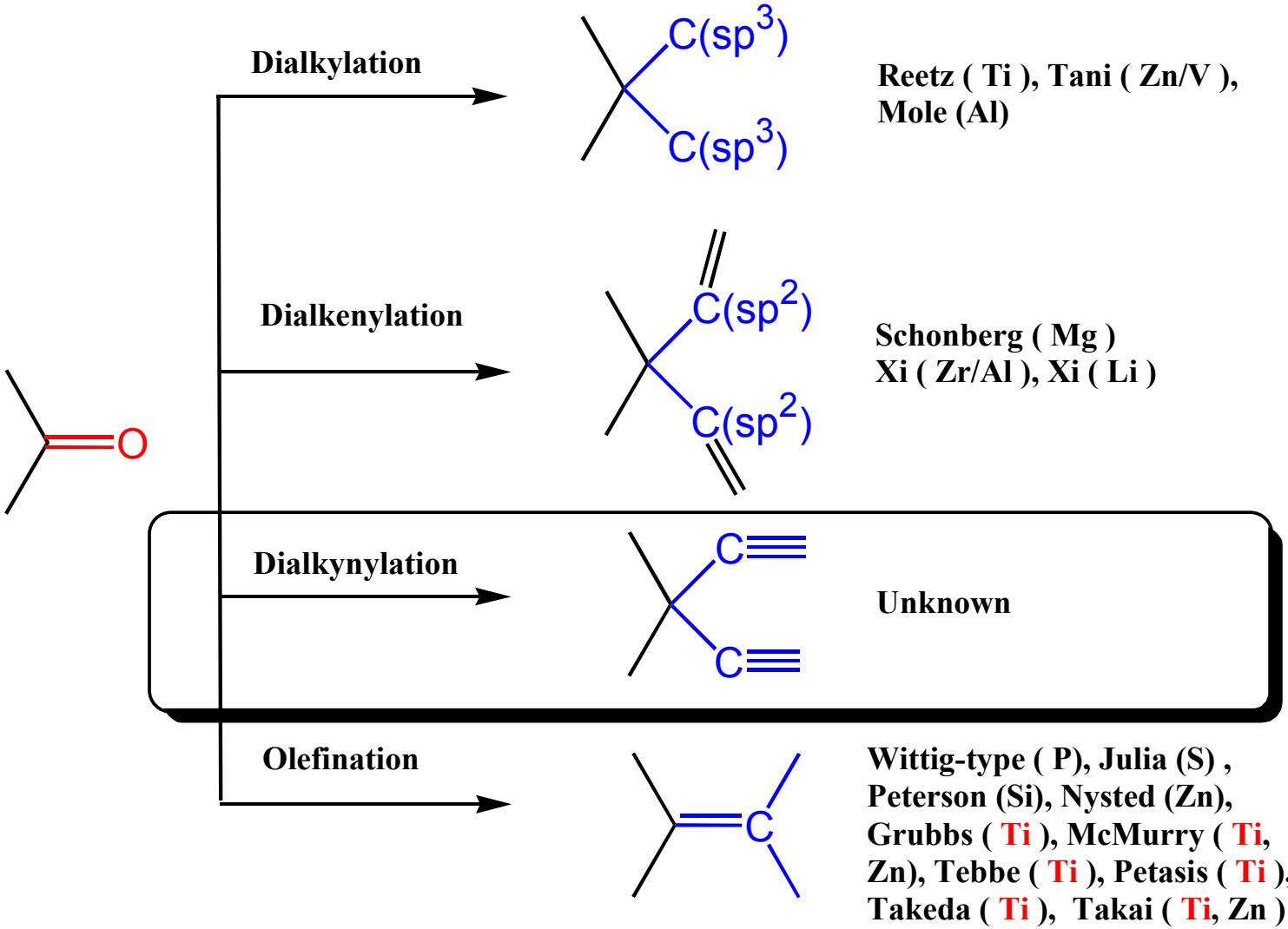


Xi, Z. et. al. *Angew.Chem. Int. Ed*. **2000**, *39*, 2950

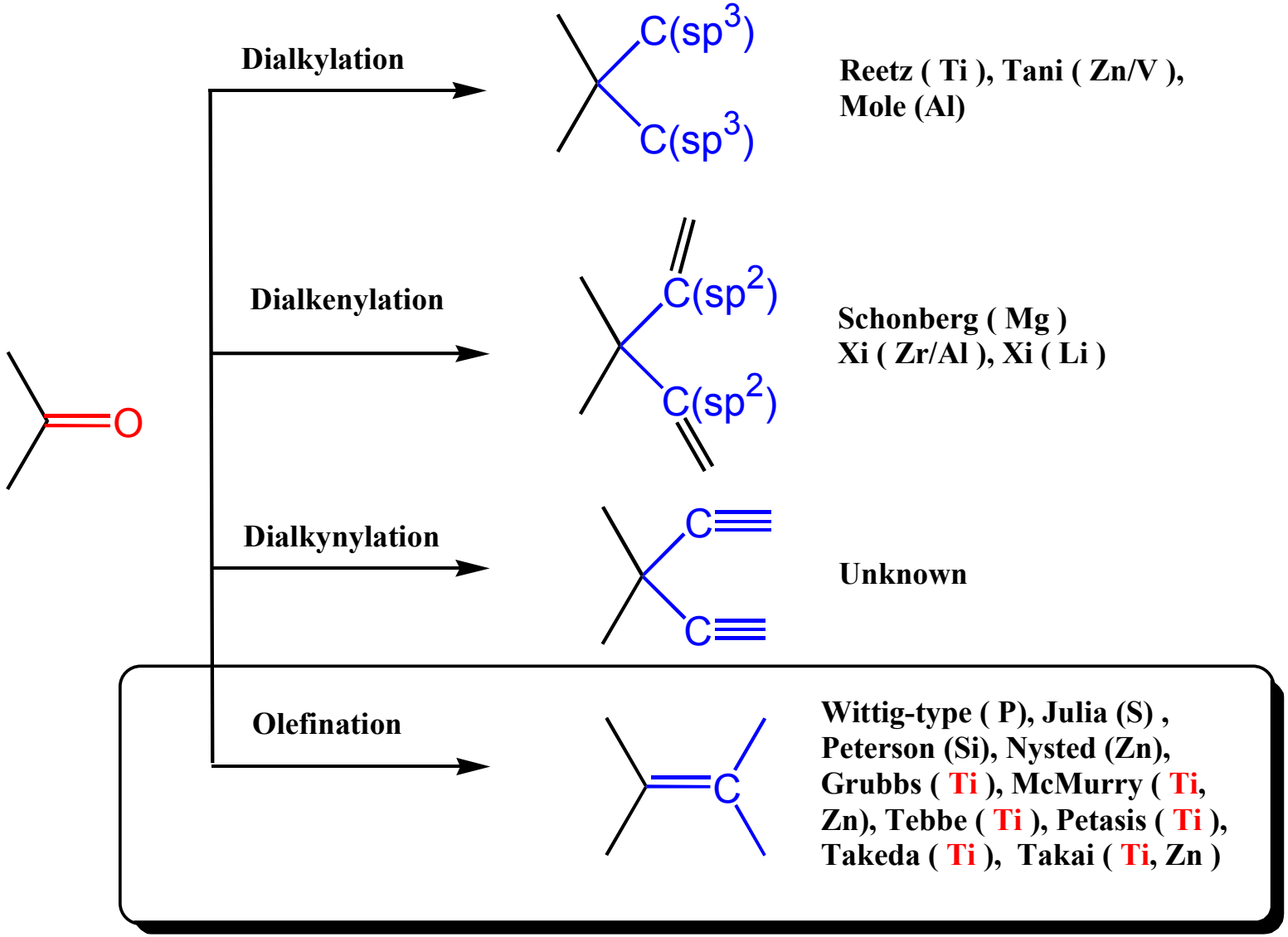


Xi, Z. et. al. *Angew.Chem. Int. Ed*. **2001**, *40*, 1913

Dialkynylation—Opportunity

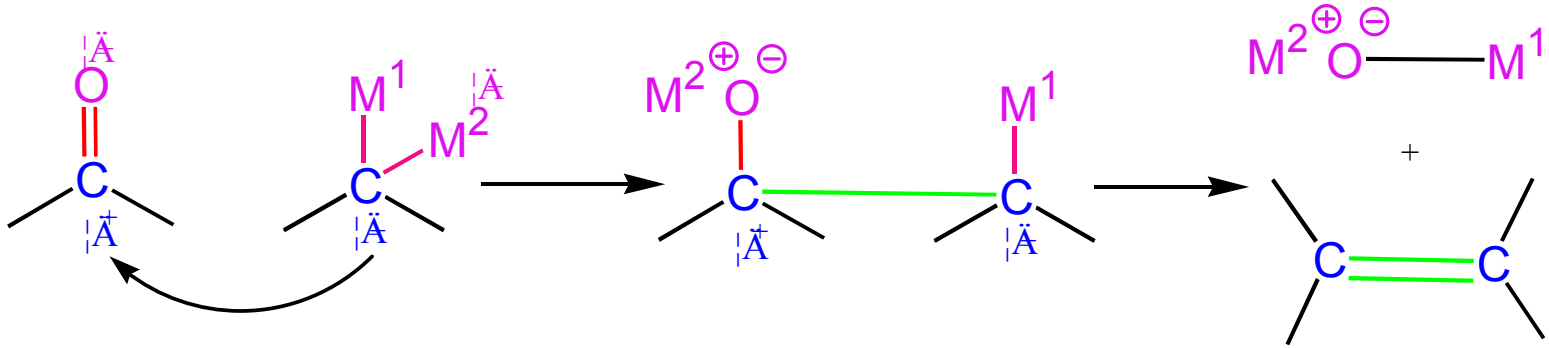


Olefination

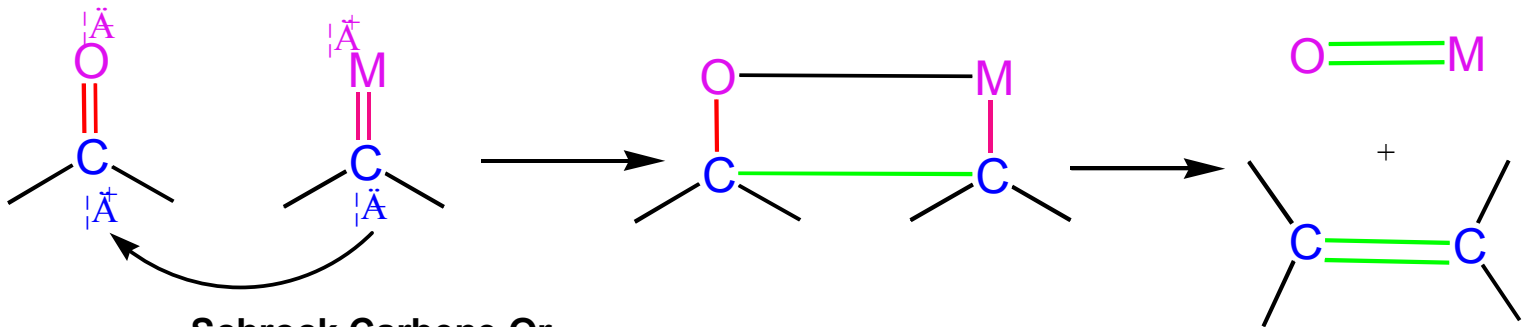


Olefination (Alkylidenation)—Hot Field

1. sp^3-Geminated Organodimetallic Reagents:



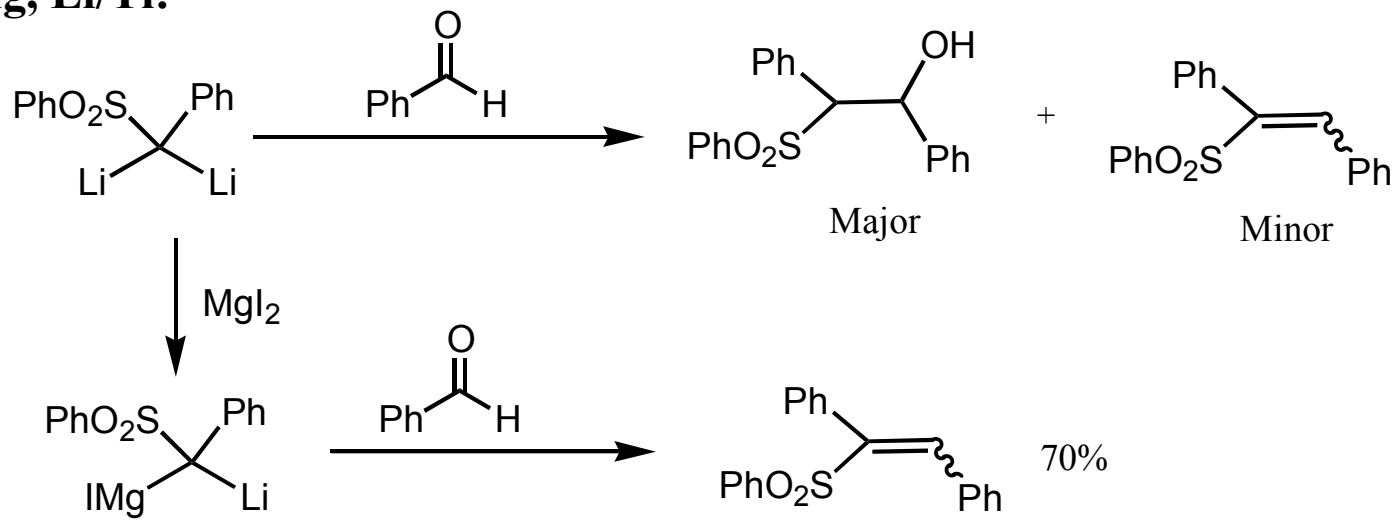
2. Metallacarbene or Carbene-like Species:



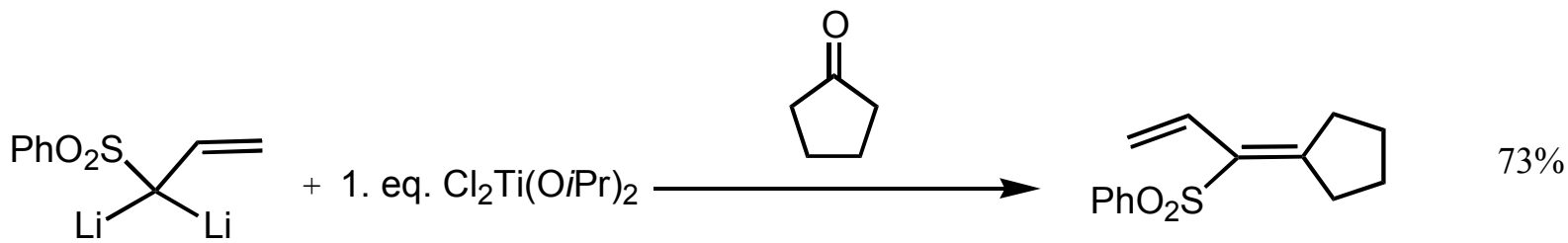
Schrock Carbene Or
Carbene-like Species

sp^3-Geminated Organodimetallic Reagents

1. Li/Mg, Li/Ti:



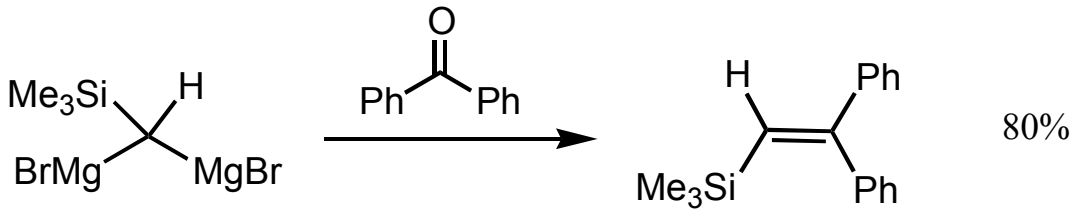
Umani-Ronchi, A. et. al. *J. Chem. Soc. Perkin Trans. I* **1973**, 1166



Gais, H. J. et. al. *Angew. Chem. Int. Ed.* **1985**, *24*, 610

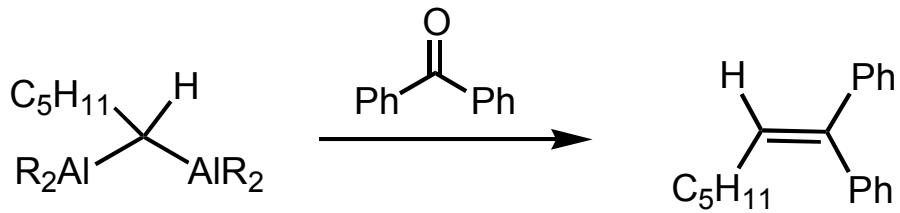
sp^3-Geminated Organodimetallic Reagents

2. Mg:



Bertini. F. et. al. *Tetrahedron* **1970**, *26*, 1281

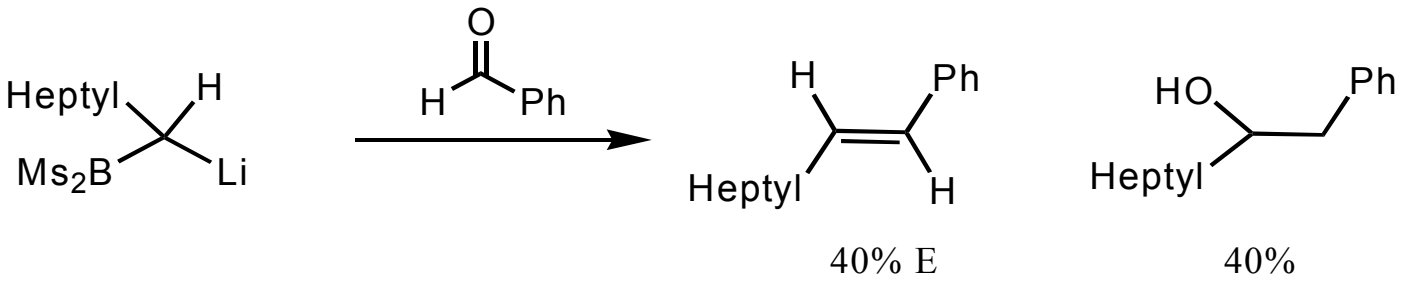
3. Al:



Eisch, J. J. et. al. *J. Org. Chem.* **1988**, *53*, 2829

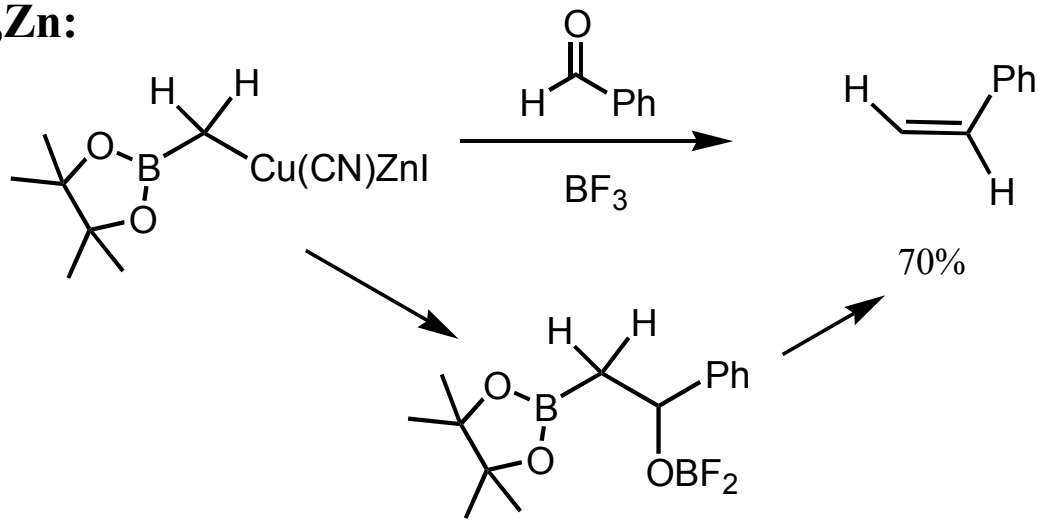
sp^3-Geminated Organodimetallic Reagents

4. B/Li:



Pelter, A. et. al. *Tetrahedron Lett.* **1983**, *24*, 635

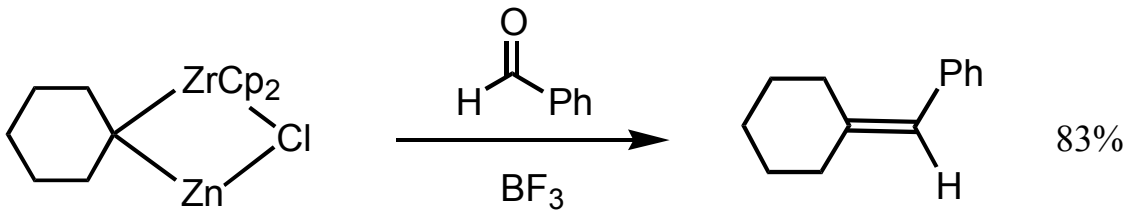
5. B/Cu,Zn:



Miyarua, N. et. al. *Tetrahedron* **1996**, *52*, 915

sp^3-Geminated Organodimetallic Reagents

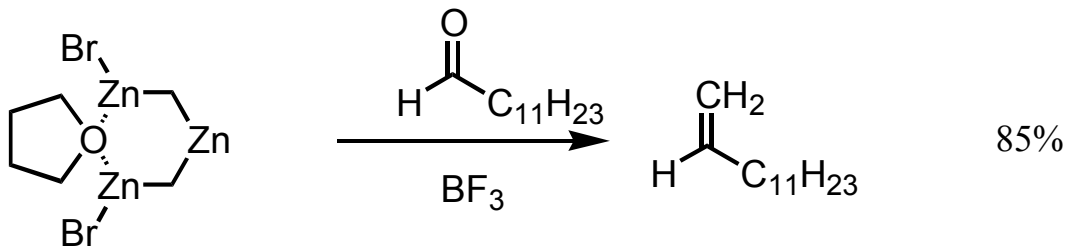
6. Zr/Zn:



83%

Knochel, P. et. al. *J. Am. Chem.Soc.* **1991**, *113*, 9888

7. Zn:



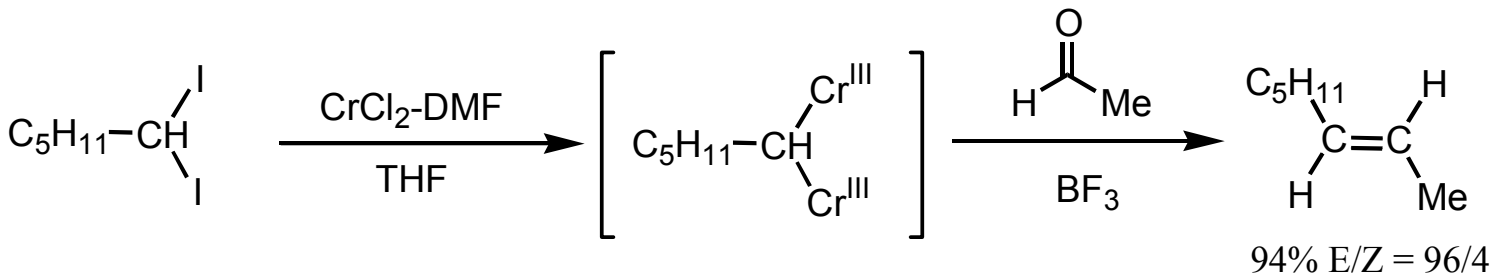
85%

Matsubara, S. et. al. *Synlett* **1998**, 313

Nysted Reagent ***US Pat.*** **(1975)**

sp^3-Geminated Organodimetallic Reagents

8. Cr:

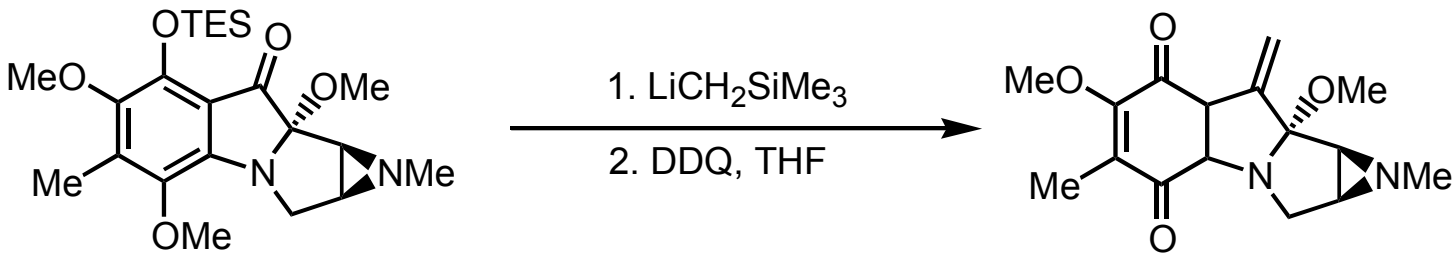


Takai, K.; Utimoto, K. et. al. *JACS.* **1987**, *109*, 951

Takai-Utimoto Reaction

sp^3-Geminated Organodimetallic Reagents

9. Li/Si:

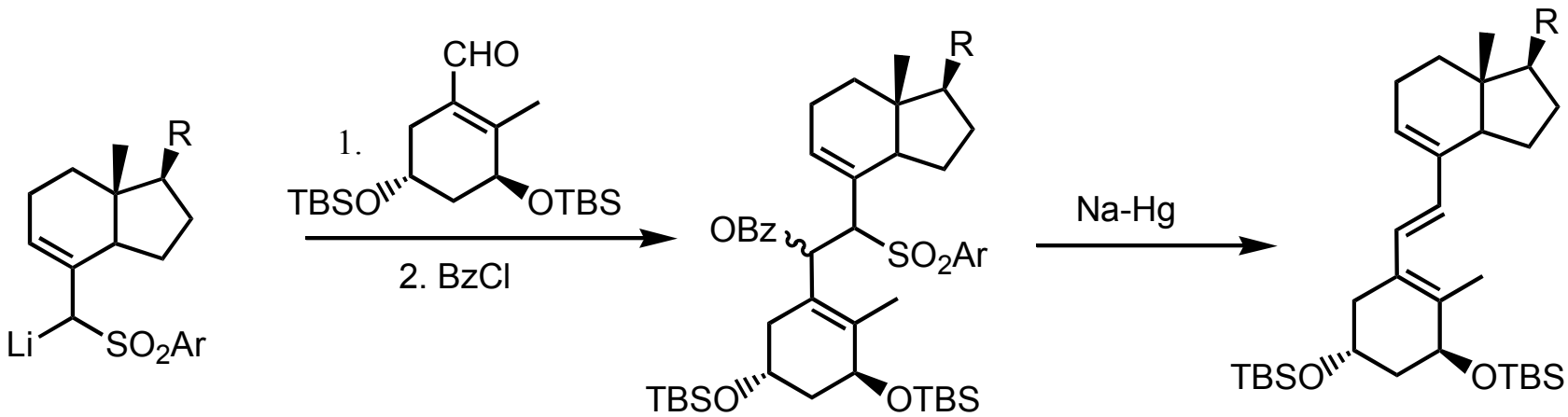


Mitomycin Congeners Danishefsky, S.J. et. al. *J. Org. Chem.* **1988**, *53*, 3391.

Peterson Olefination *JOC* (1968)

sp^3-Geminated Organodimetallic Reagents

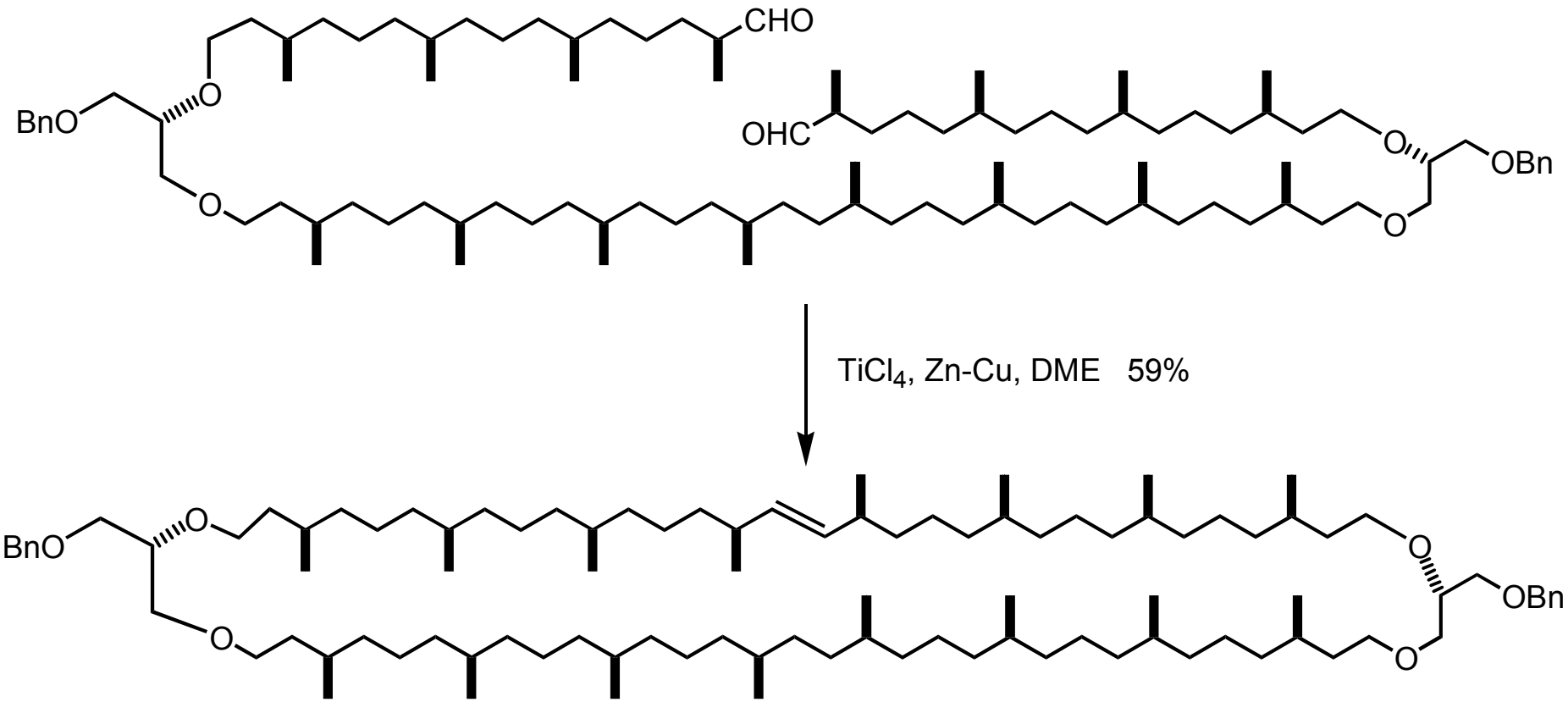
10. Li/S:



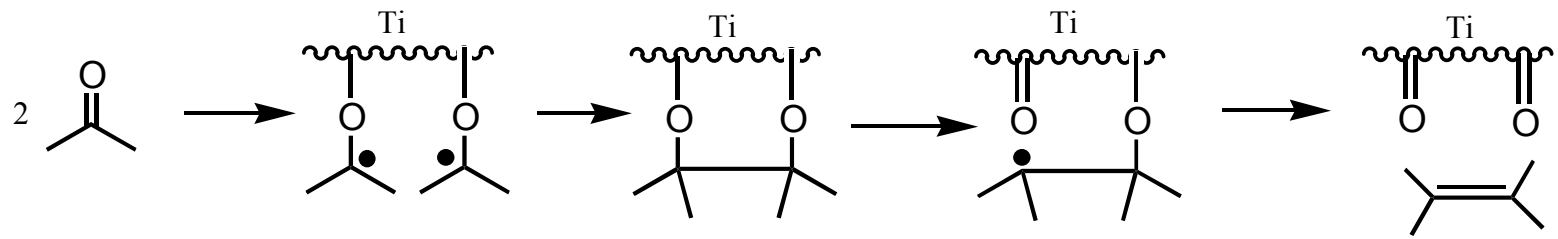
(+)-Himbacin Hart, D. and Kozikowski A.P. et. al. *JOC*, **1997**, *62*, 5023

Julia Olefination *TL* (1973)

11. Ti:

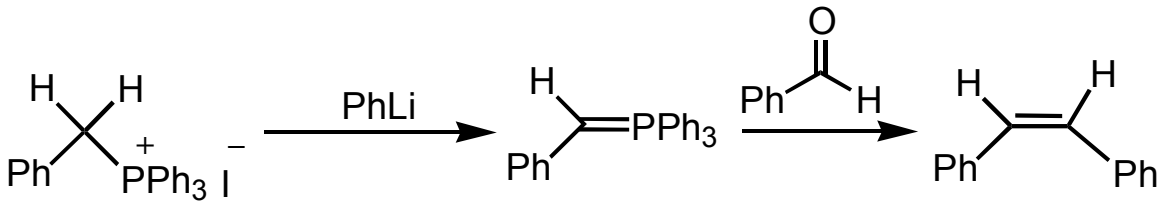


Archaeal 72-Membered Macrocyclic Tetraether Lipids Kakinuma, K. et. al. *J. Org. Chem*. **1998**, *63*, 2689



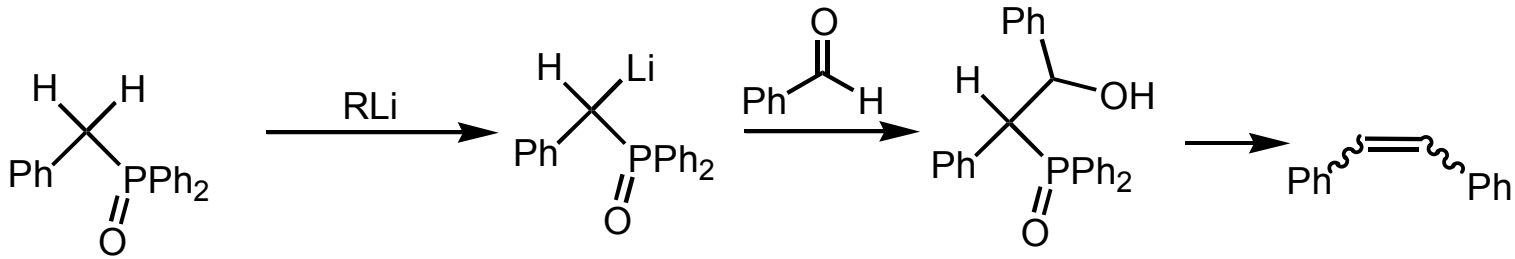
Wittig and Horner-Wittig Reactions

12. P:



82%, 70% Z

Wittig, G. et. al. *Chem. Ber.* **1954**, *87*, 1318



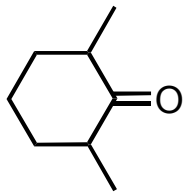
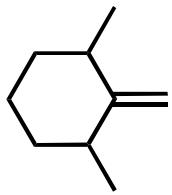
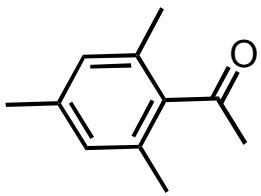
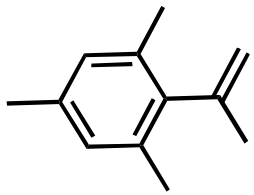
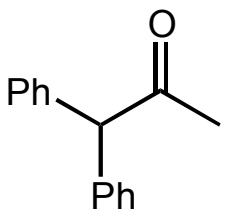
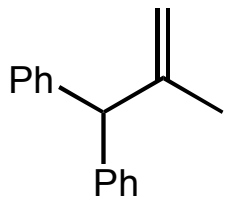
Clayden, J. et. al. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 241

Why use Titanium-based Reagents?

1. **Non-basic, reactive reagent**

2. **More reactive to the sterically hindered carbonyl group**

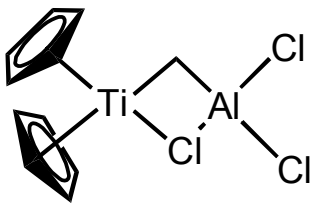
Comparison of Tebbe and Wittig Reagents

		Tebbe	Wittig
		97%	89%
		77%	4%
		63%	38%

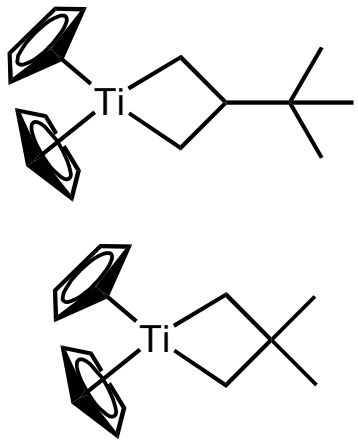
Pine, S. H.; Shen, G. S., Hoang, H. *Synthesis,* **1991**, 165

Why use Titanium-based Reagents ?

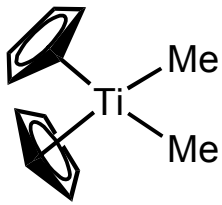
1. **Non-basic, reactive reagent**
2. **More reactive to the sterically hindered carbonyl group**
3. **Alkylidenate carboxylic acid and carboxylic acid derivatives**



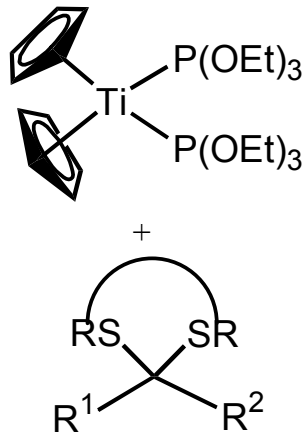
Tebbe Reagent



Grubbs Reagent



Petasis Reagent



Takeda Reagent

Zn, $TiCl_4$, TMEDA, $PbCl_2$(cat), $RCHBr_2$

Takai Reagent

Citing Articles--Summary

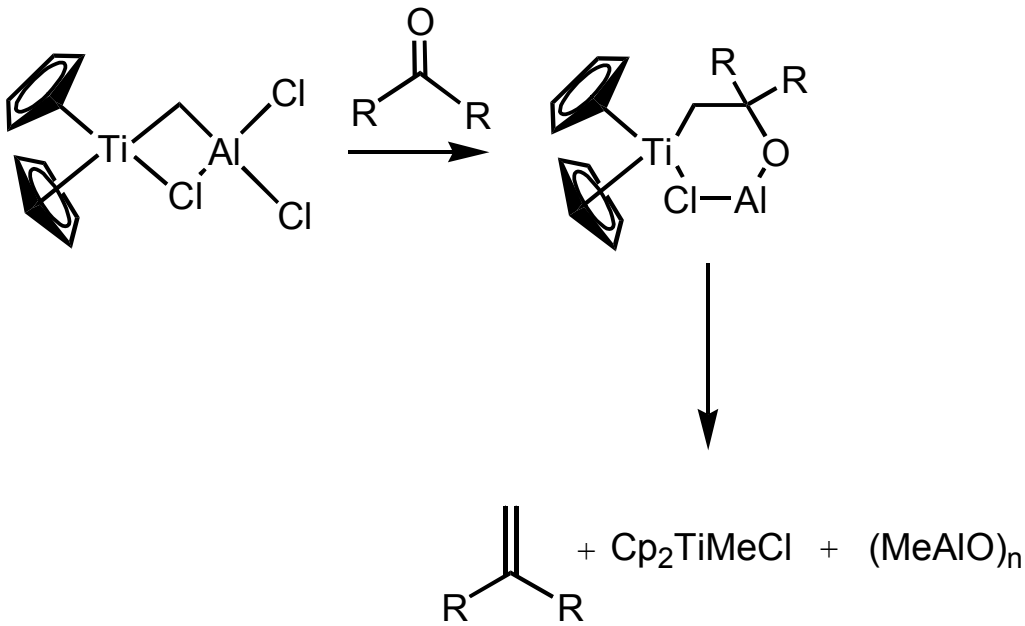
OLEFIN HOMOLOGATION WITH TITANIUM METHYLENE-COMPOUNDS
TEBBE FN, PARSHALL GW, REDDY GS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY100: 3611-3613 1978 These documents in the database cite the above record: 623 results found
Go to Page: of 63 Records 1 -- 10
[*1* | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10]
***Use the checkboxes to select individual records for marking, then click Submit to add them to the Marked List.* 1.**
Eyrisch KK, Muller BKM, Herzig C, et al.
Ethenolysis of functionalized cycloolefins
DESIGNED MONOMERS AND POLYMERS 7 (6): 661-676 2004
Times Cited: 0

2.
Korotchenko VN, Nenajdenko VG, Balenkova ES, et al.
Olefination of carbonyl compounds. Modern and classical methods
USPEKHI KHIMII 73 (10): 1039-1074 2004
Times Cited: 0

3.
Yan TH, Tsai CC, Chien CT, et al.
Dichloromethane activation. Direct methylenation of ketones and aldehydes with CH2Cl2 promoted by Mg/TiCl4/THF
ORGANIC LETTERS 6 (26): 4961-4963 DEC 23 2004
Times Cited: 1

Tebbe Reagent

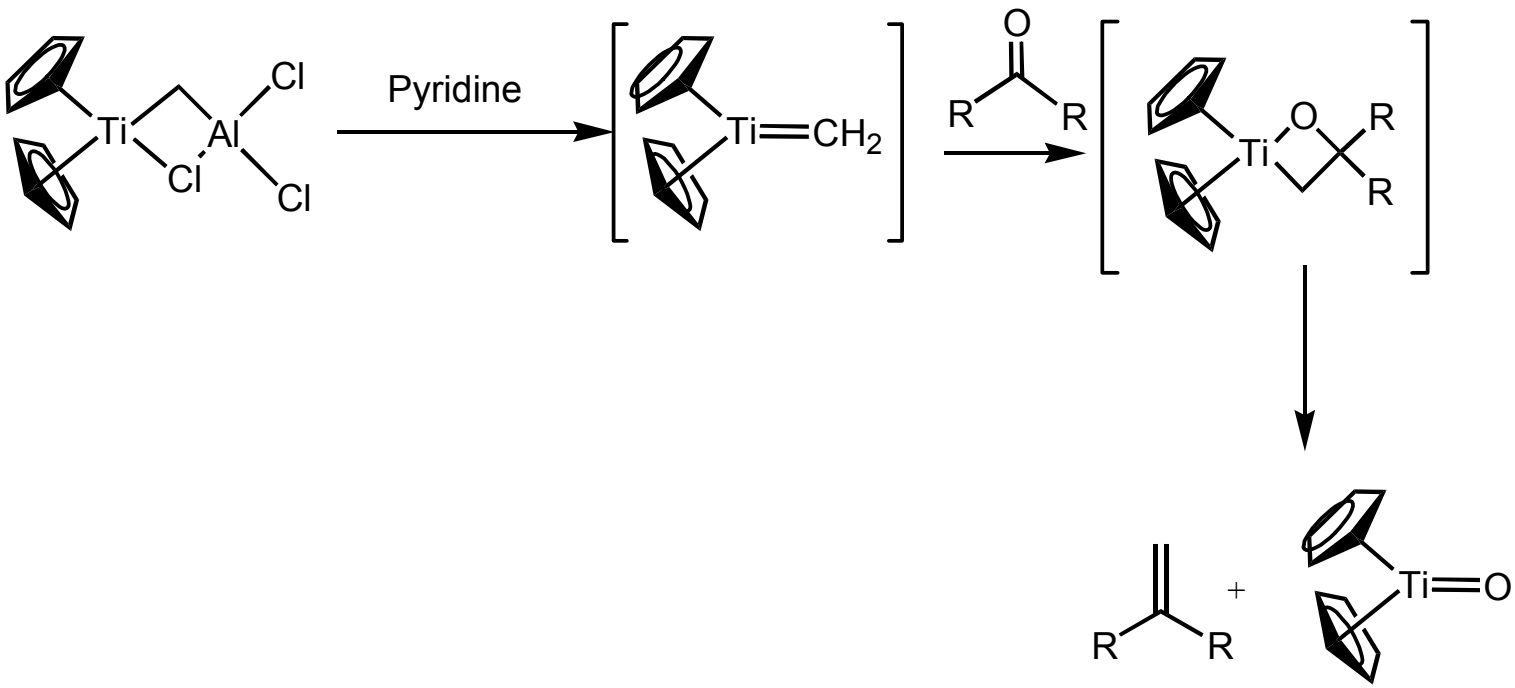
Without Base



Hughes, D. L. et. al. *Organometallics* **1996**, *63*, 2689

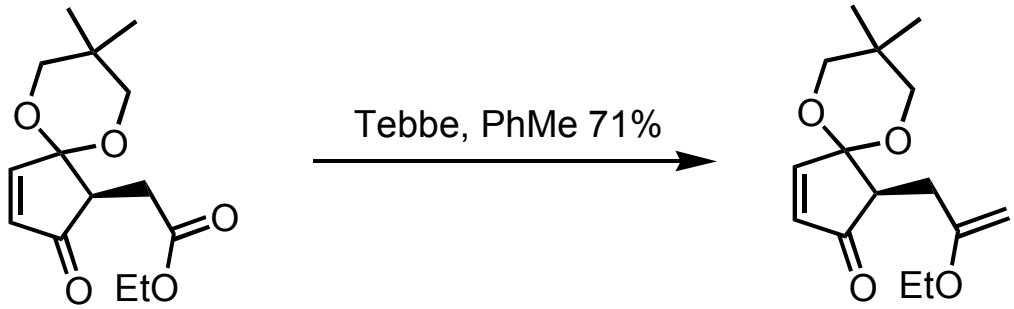
Tebbe Reagent

In the presence of base

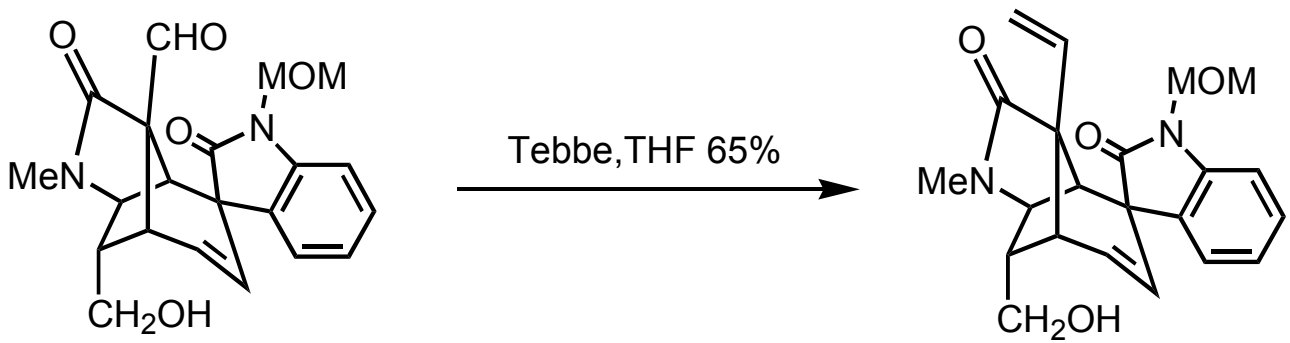


Hughes, D. L. et. al. *Organometallics* **1996**, *63*, 2689

Tebbe Reagent with Ketone and aldehyde

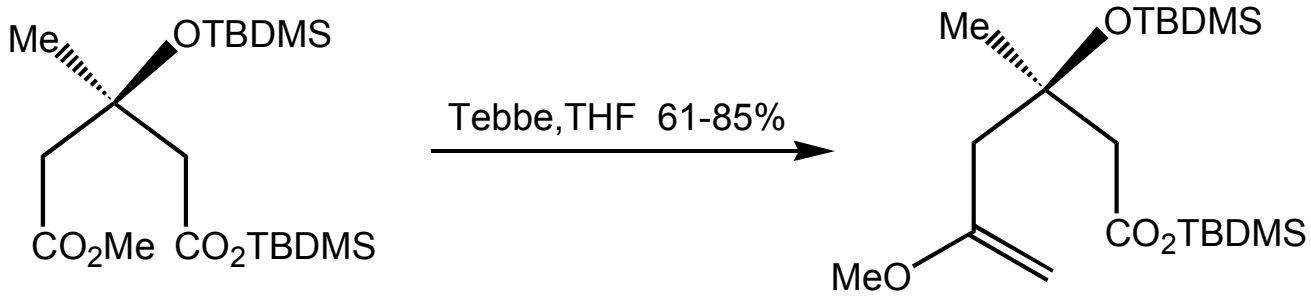


Didemnenones Winterfeldt, E. et. al. *JCS. Pekin Trans I* **1994**, 3525

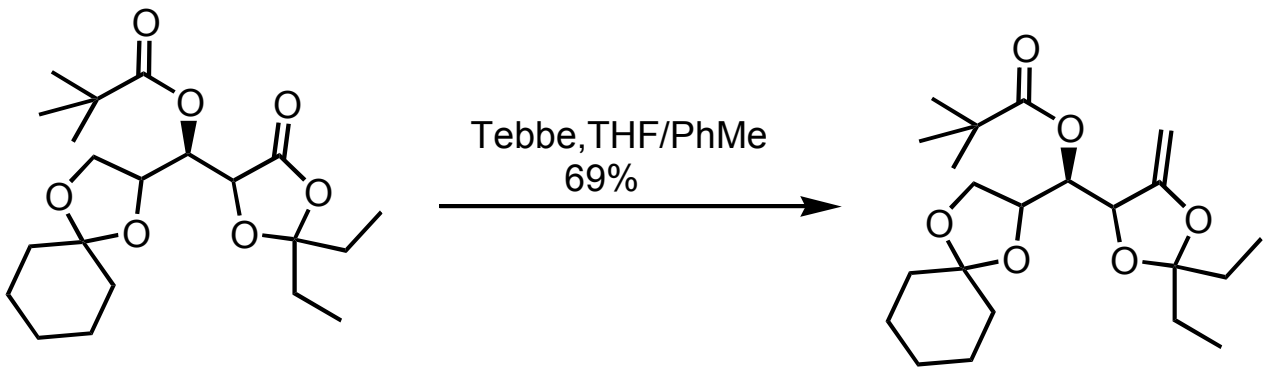


Fukuyama, T. et. al. *Pure Appl. Chem.* **1997**, *69*, 501

Tebbe Reagent: Esters and Lactones

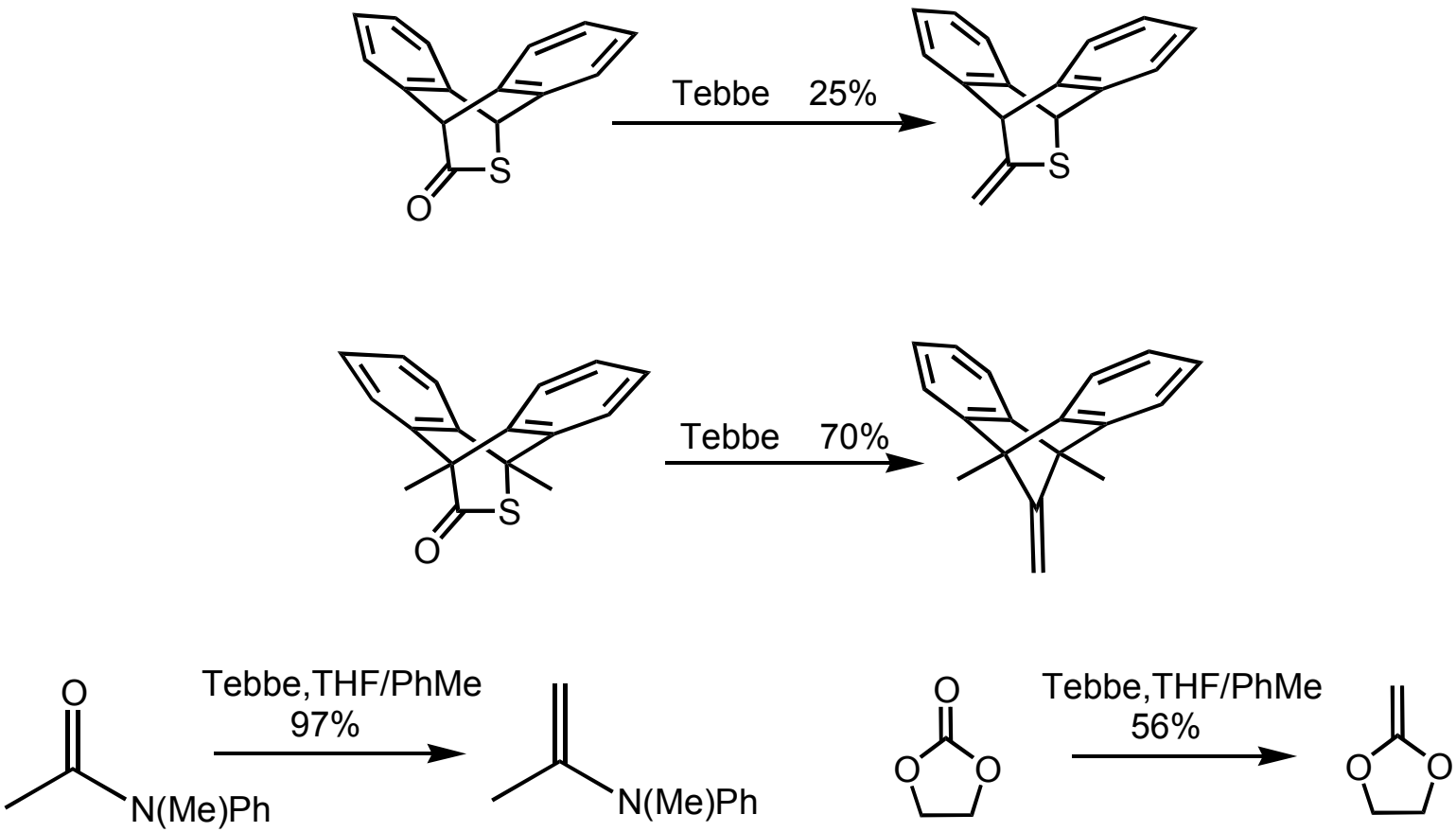


Atrochrysone Steglich, W. et. al. *JCS. Pekin Trans I* **2000**, 2483



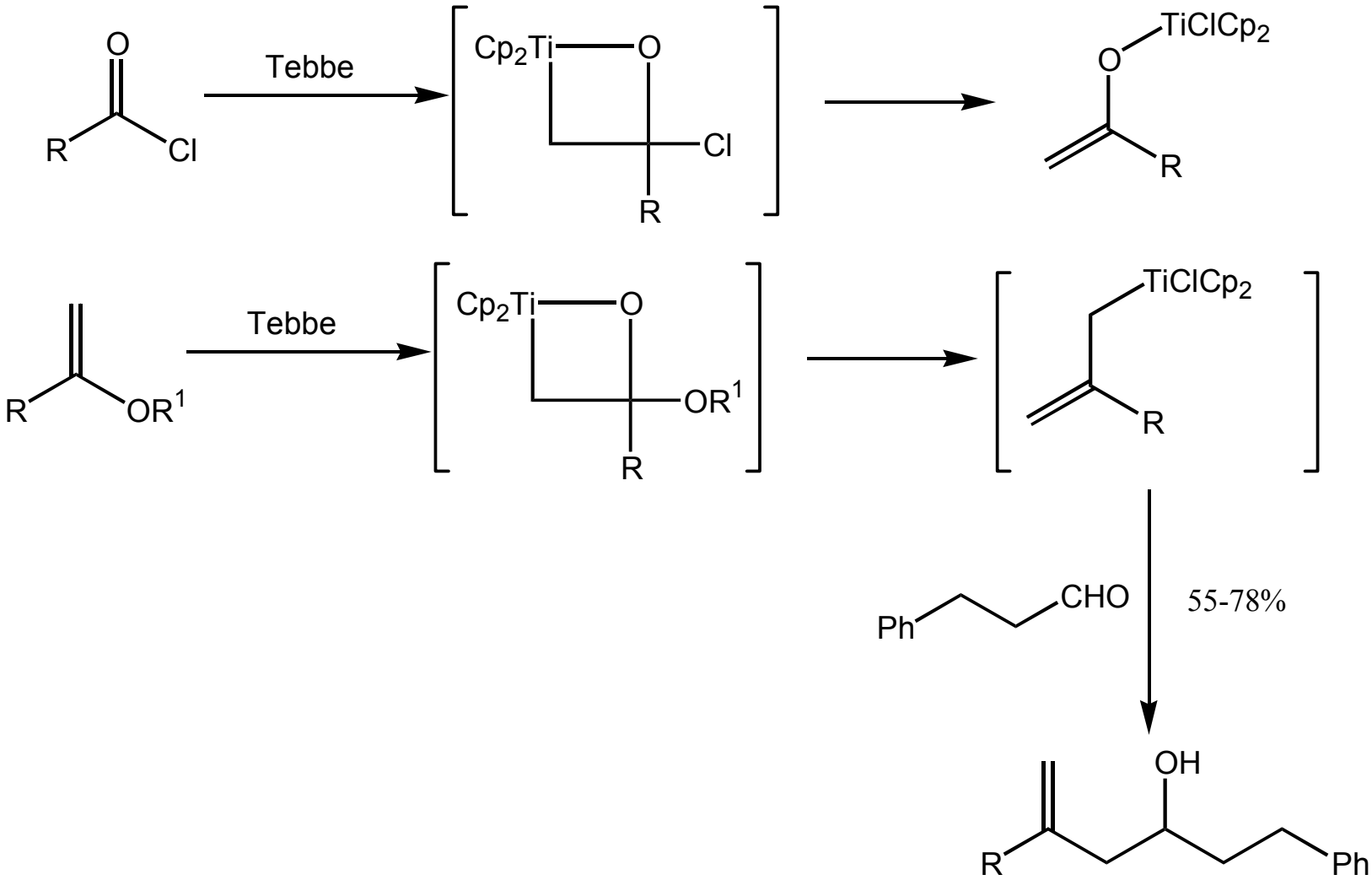
Polyhydroxylated Molecules Sinay, P. et. al. *TL* **1994**, 2537

Tebbe Reagent: Thioesters, Amids and Carbonates



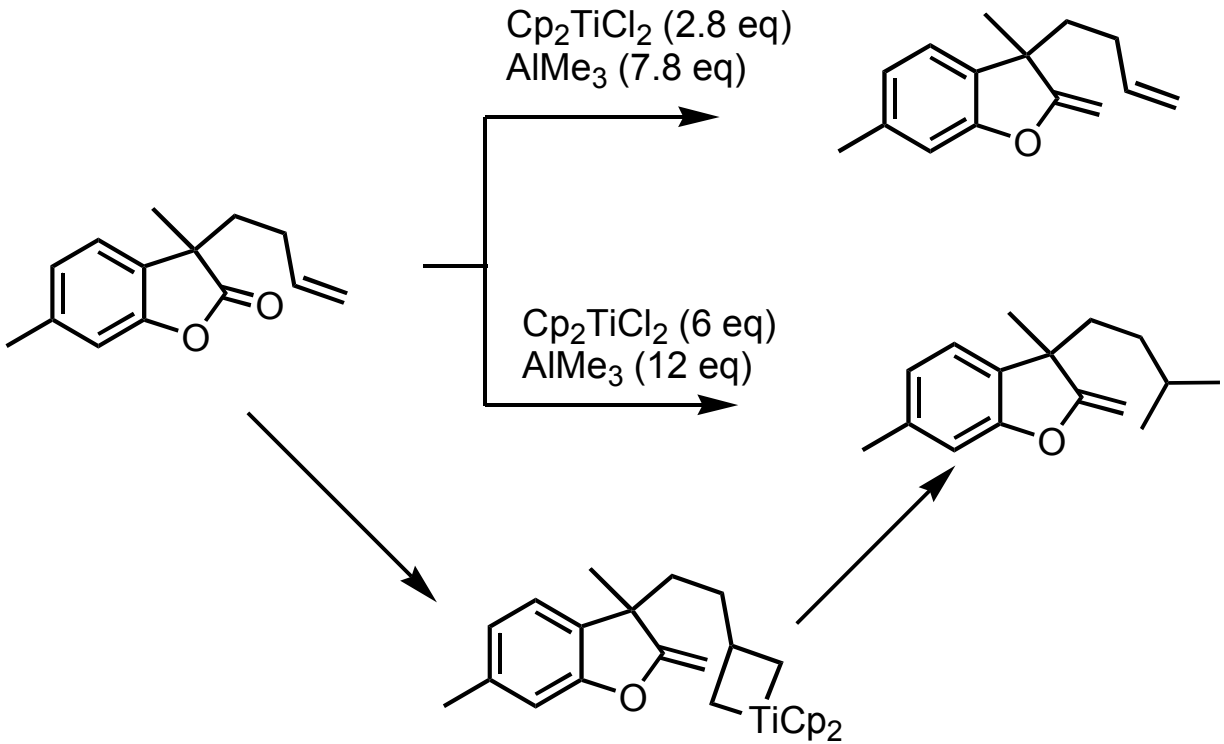
Hartley, R. C. et. al. *JCS, Perkin Trans. I* **2002**, 2763 and references therein.

Tebbe Reagent: Acid Chlorides and Enol ethers



Hanzawa, Y.; and Taguchi, T. et. al. *Tetrahedron* **1998**, 1138728

Tebbe Reagent: Alkenes



Aplysins Harrowven, D. C. et. al. *Tetrahedron* **2001**, 791

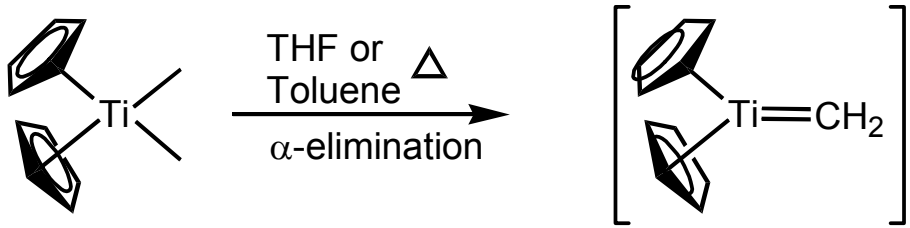
Summary of the Tebbe Reagent

Tebbe methylenation of esters has been accomplished in the presence of many functional groups.
Alkenes including dienes,
Vinyl fluorides, vinyl chlorides, aryl bromides, and aryl iodides
Ethers including benzyl,and trityl ethers,
Silyl ethers including TMS,TBDMS,and di-*tert*butylsilylene,
Acetals including benzylidene acetal,MOM, and acetonides
Selenoglycosides and thioglycosides
Carbamates including NHBoc,and sulfonamides

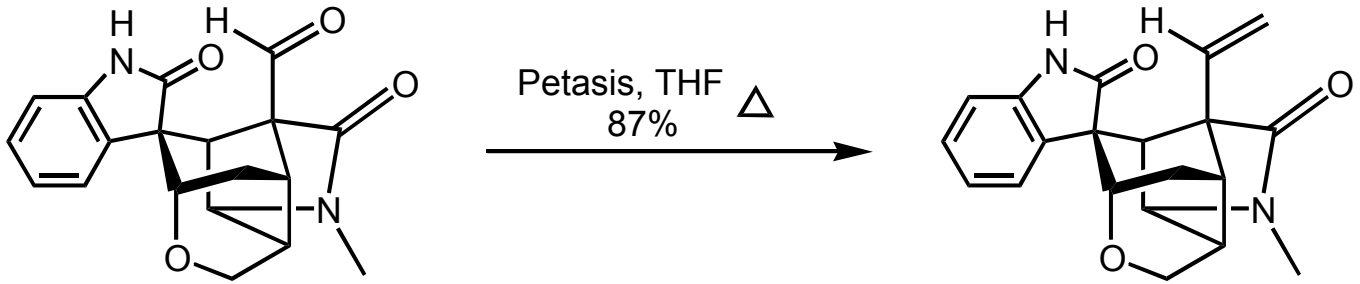
The key advantage of the Tebbe reagent over other titanium reagents used in alkylidenations is that the reactive titanium methylidene is generated and reacted at low temperature.

Its disadvantages are its high sensitivity to both moisture and air, its Lewis acidic character, and the fact that it is limited to methylenation.

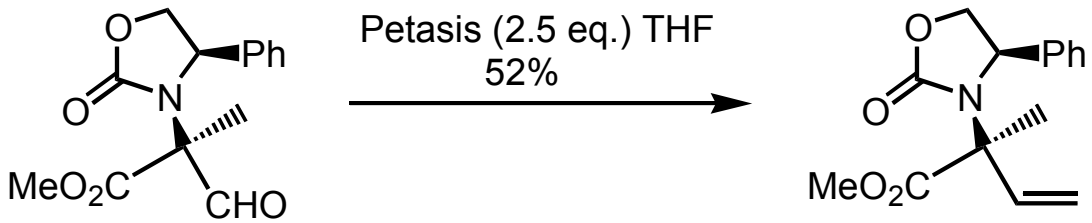
Petasis Reagent: Aldehydes



Petasis, N. A. et. al. *J. Am. Chem. Soc.***1990**, 6392

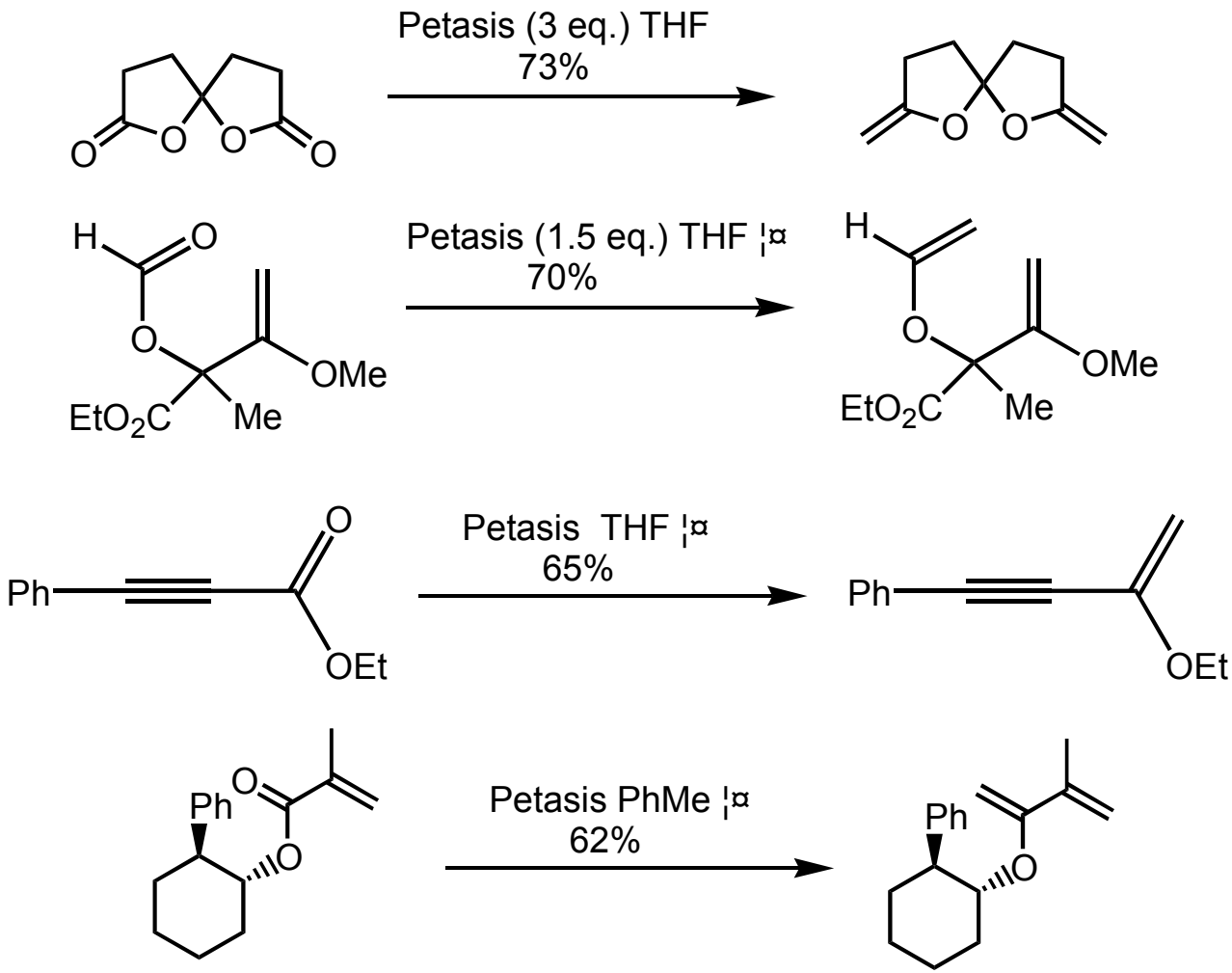


21-oxogelsemine Hart, D. J. et. al. *J. Am. Chem. Soc.***1990**, 6392



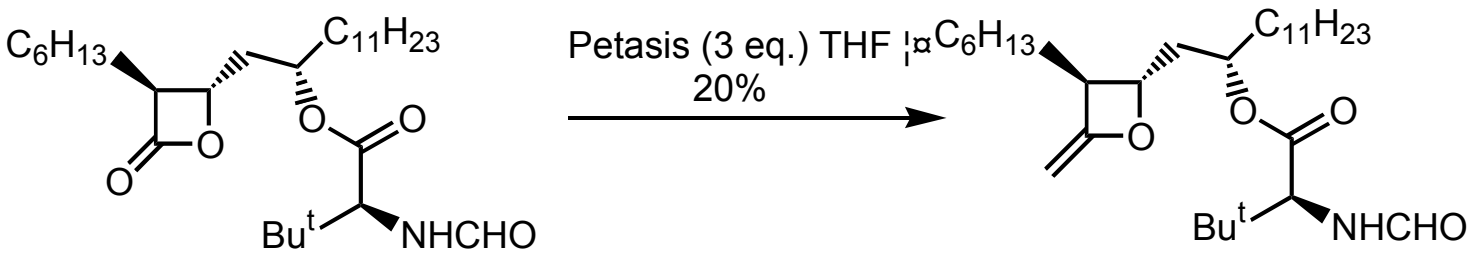
α-Alkyl-α-amino Acids Hegedus, L. S. *JOC* **1993**, 5918

Petasis Reagent: Ester and Lactones



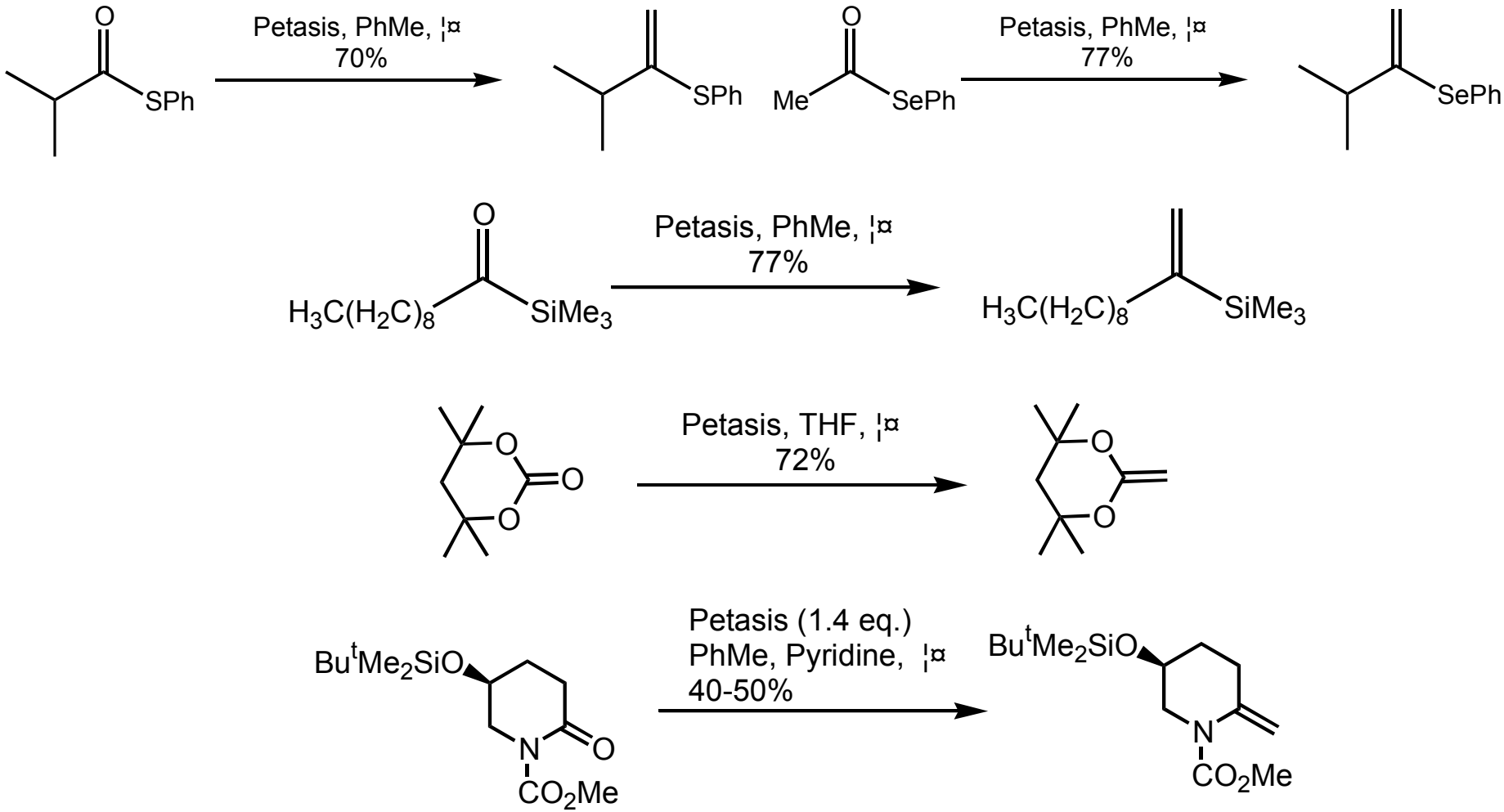
Hartley, R. C. et. al. *JCS, Perkin Trans. I* **2002**, 2763 and references therein.

Petasis Reagent: β-Lactones



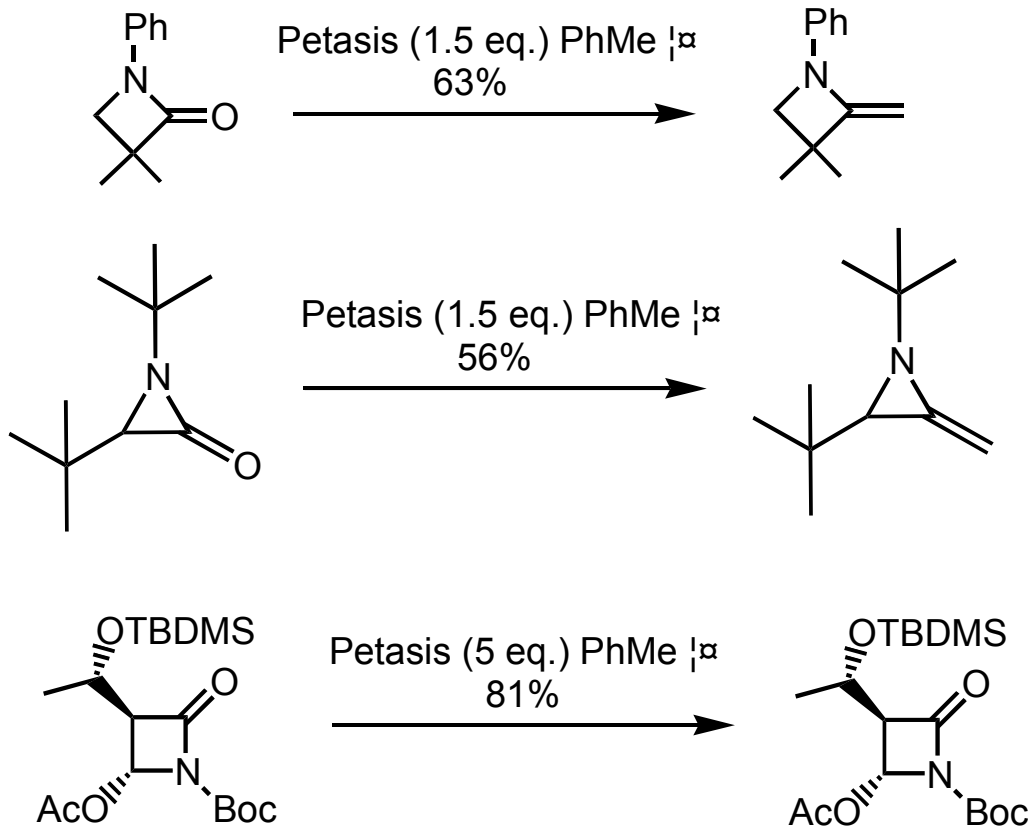
Orlistat Howell, A. R. et. al. *Bioorg. Mol. Chem. Lett*. **1998**, 977

Petasis Reagent: Thioesters, Selenoesters, Acylsilanes, Carbonates, and Lactams



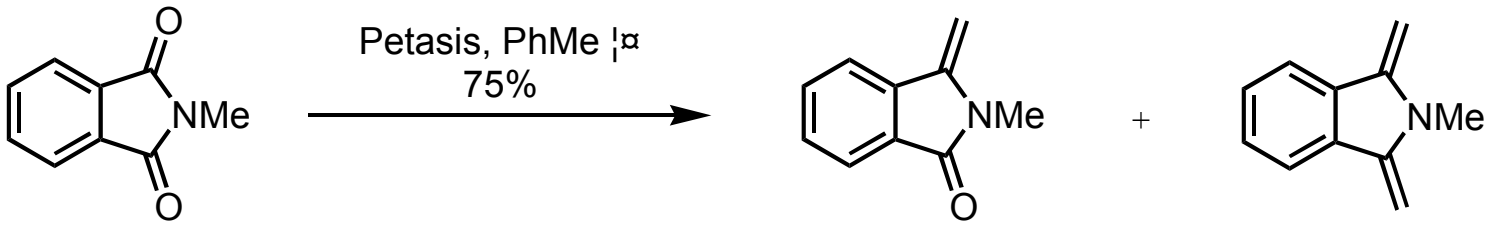
Hartley, R. C. et. al. *JCS, Perkin Trans. I* **2002**, 2763 and references therein

Petasis Reagent: β-Lactams and α-Lactams

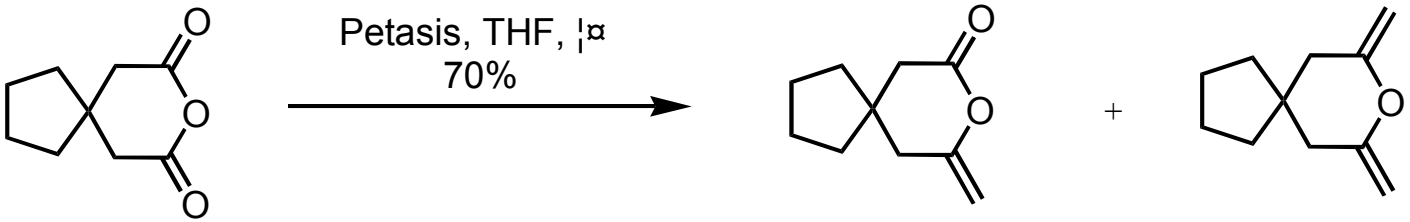


Hartley, R. C. et. al. *JCS, Perkin Trans. I* **2002**, 2763 and references therein.

Petasis Reagent: Imides, and Acid anhydrides



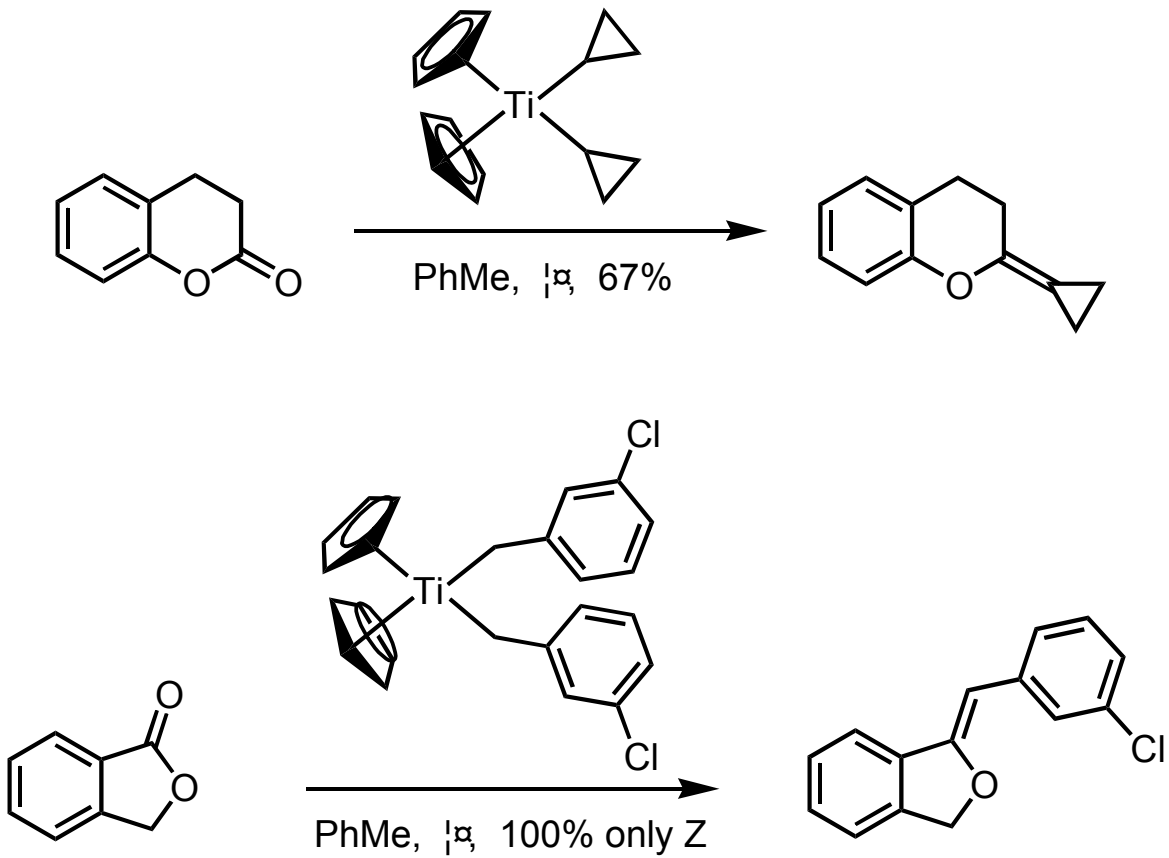
1.5 eq. Petasis	1 : 0
4.0 eq. Petasis	1 : 20



1 eq. Petasis	10 : 1
2 eq. Petasis	2 : 1
4 eq. Petasis	0 : 1

Hartley, R. C. et. al. *JCS, Perkin Trans. I* **2002**, 2763 and references therein.

Petasis' Method for Alkylidenation



Hartley, R. C. et. al. *JCS, Perkin Trans. I* **2002**, 2763 and references therein.

Summary of the Petasis Reagent

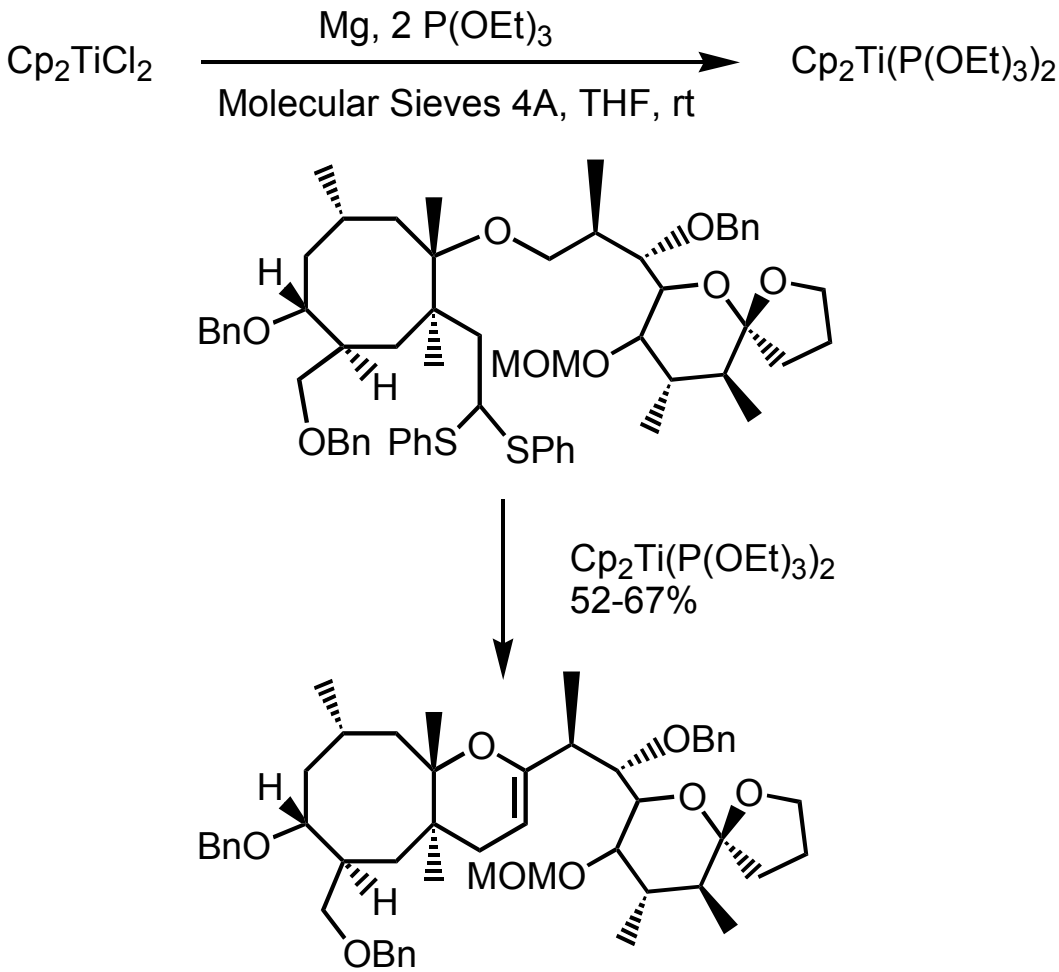
The advantages of Petasis methylenation of carbonyl groups:

1. The stability to air and moisture of dimethyltitanocene,
2. The absence of Lewis acid from these reactions and
3. The ease of purification following reaction
Titanium-containing impurities can often be precipitated and removed by simple filtration

The disadvantages

The high temperature (65°C) needed to induce elimination

Takeda Reaction



Takeda, T. et. al. *JACS*. **1997**, 1127
Hirama, M. et. al. *Chem. Comm.* **2001**, 381

Summary of the Takeda Reation

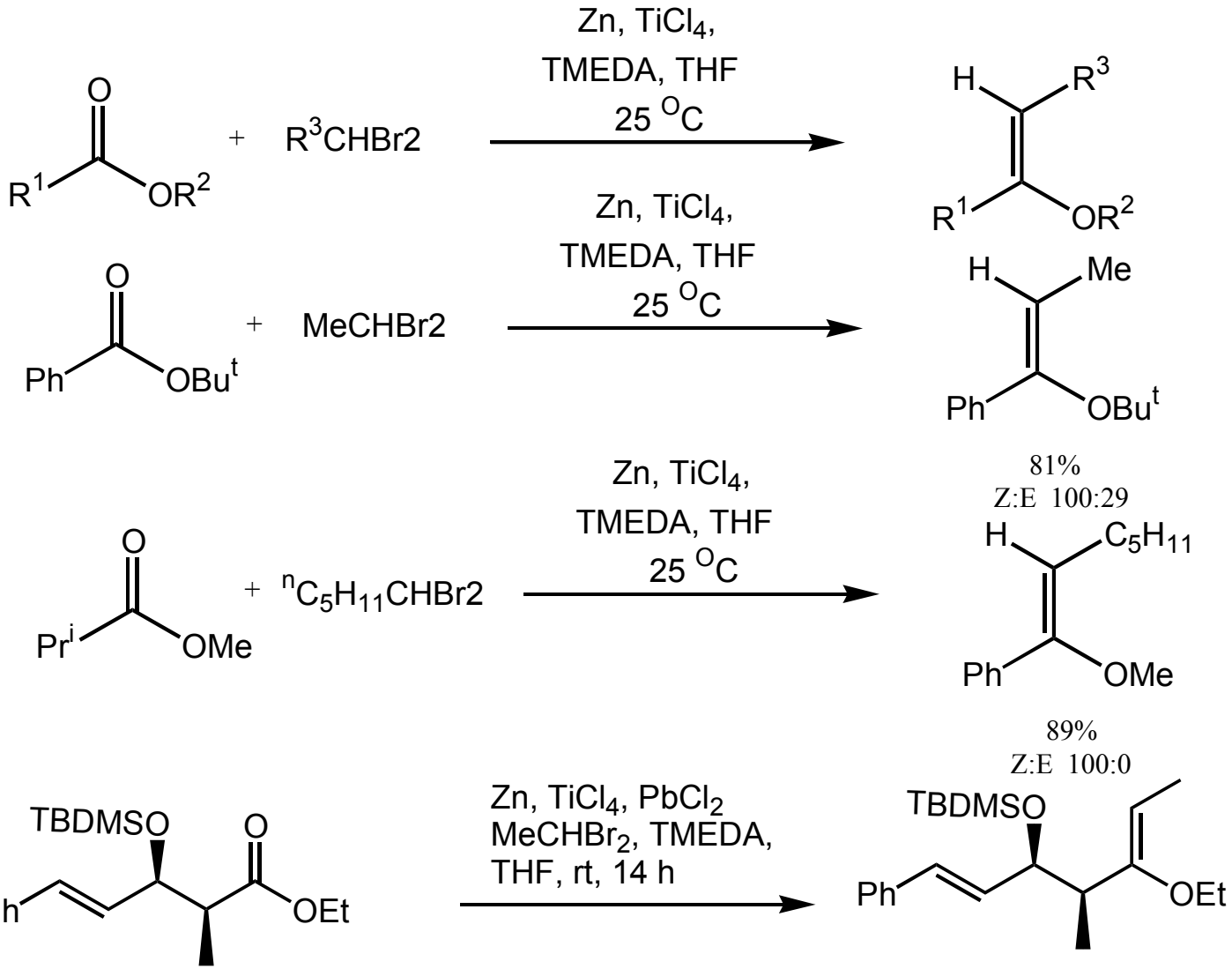
Advantages:

A range of alkylidenating agents that can be produced
The mildness of the conditions
The ease of synthesis of thioacetal substrates

Disadvantages:

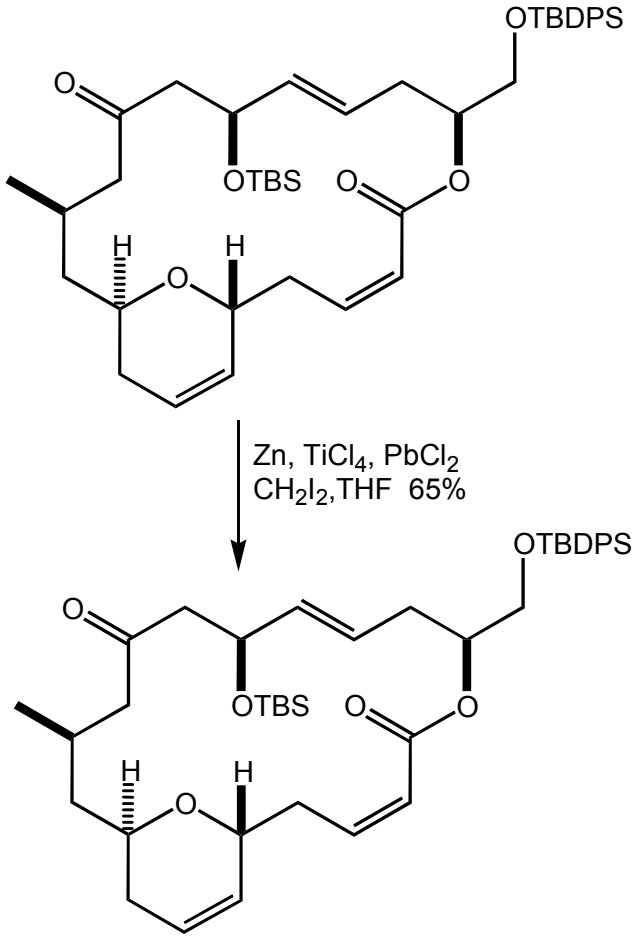
The use of excess titanocene (at least 3 equiv.)
and triethylphosphite (at least 6 equiv.).

Takai Reagent



Hartley, R. C. et. al. *JCS, Perkin Trans. I* **2002**, 2763 and references therein.

Applications of the Takai Reagent



Laulimalide Paterson, I. et. al. *OL* **2001**, 213

Summary of the Takai Reagent

The advantage:

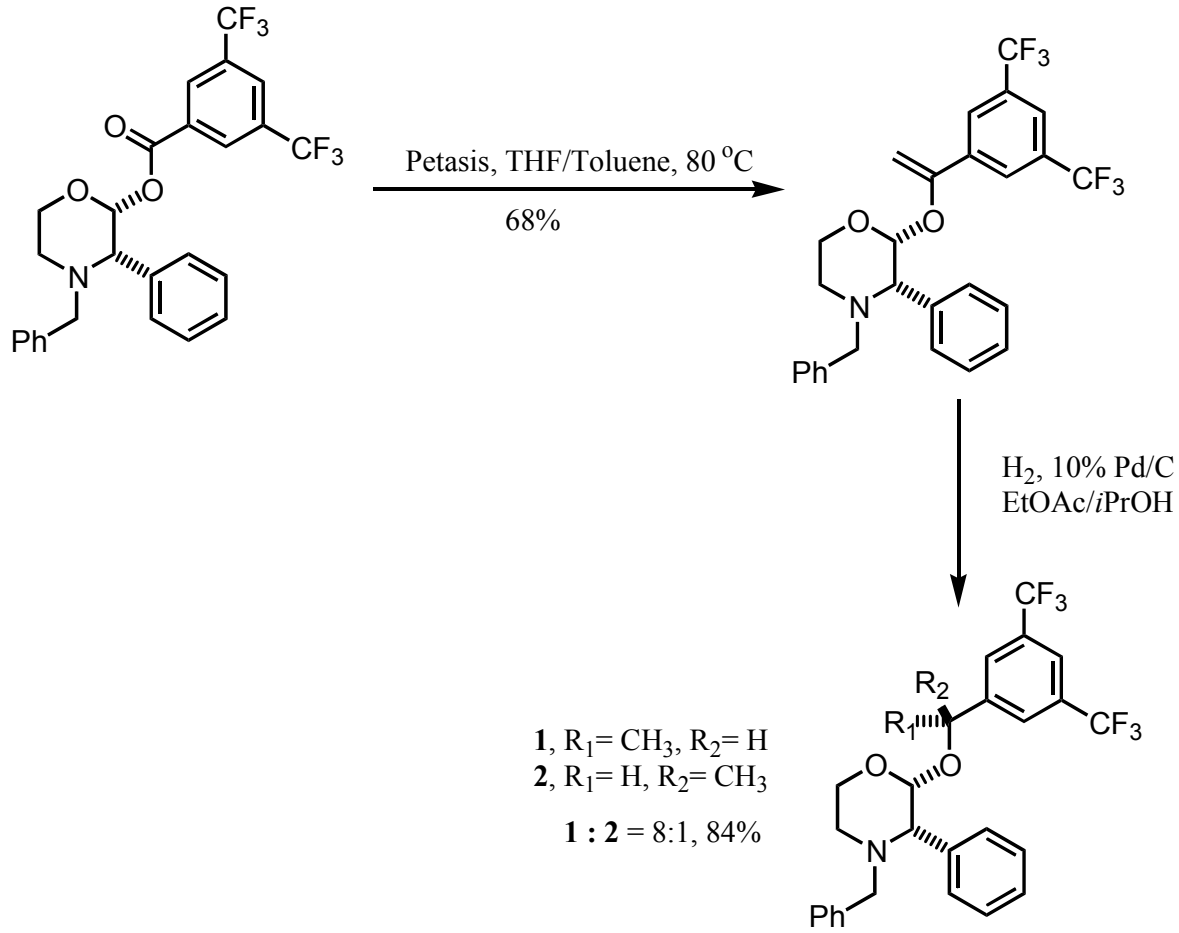
A mild one-pot procedure that allows the alkylidenation of a range of carboxylic acid and carbonic acid derivatives with good stereoselectivity.

The disadvantage:

1,1-dibromoalkanes

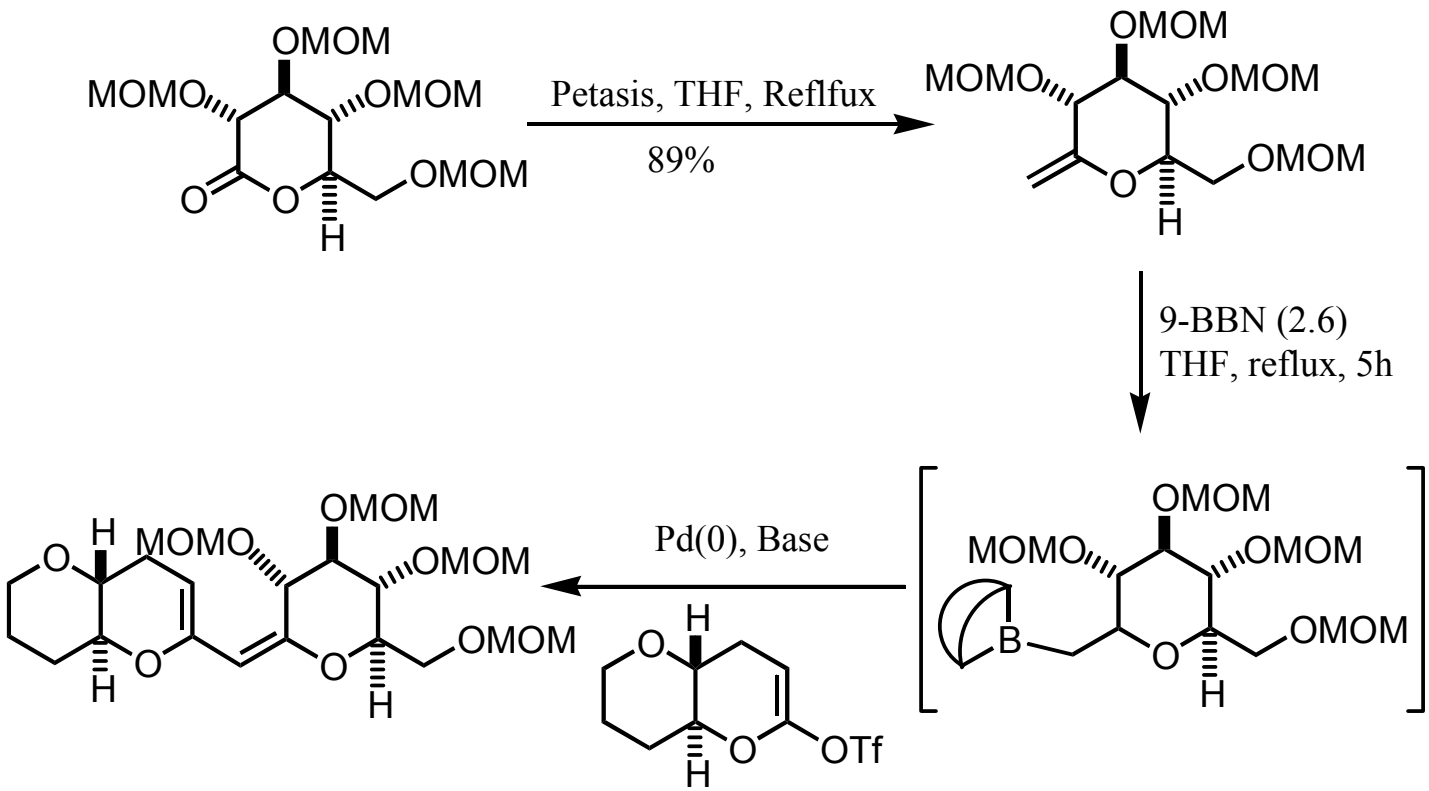
Methylenation is not good

Applications of Alkylidenation Reactions
Alkylidenation-Hydrogenation



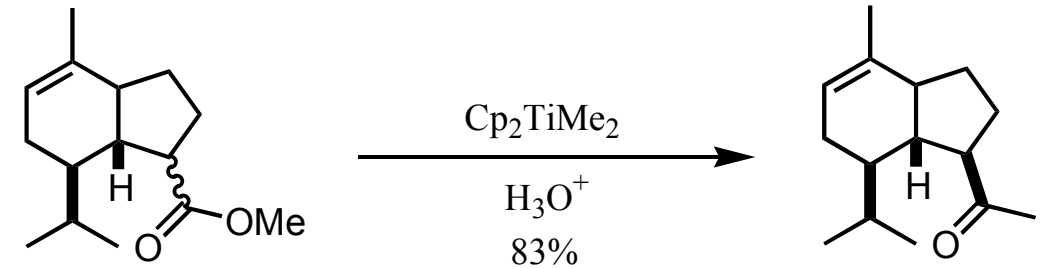
Human NK-1 Receptor Antagonist Hale, J. J. et. al. *JMC* **1998**, *41,* 4607

Methylenation-Hydroboration

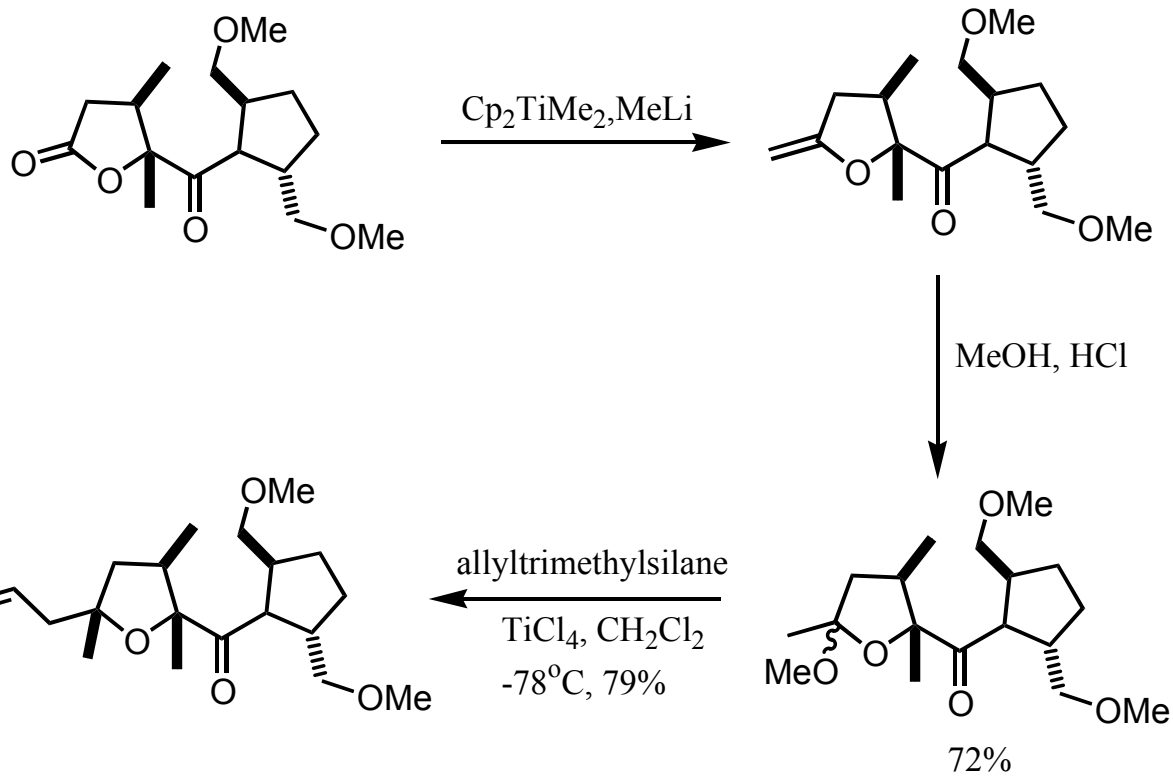


Polycyclic ether Sasaki, M. et. al. *TL* **1998**, *39,* 9027

Methylenation-Hydrolysis and Alkoxylation

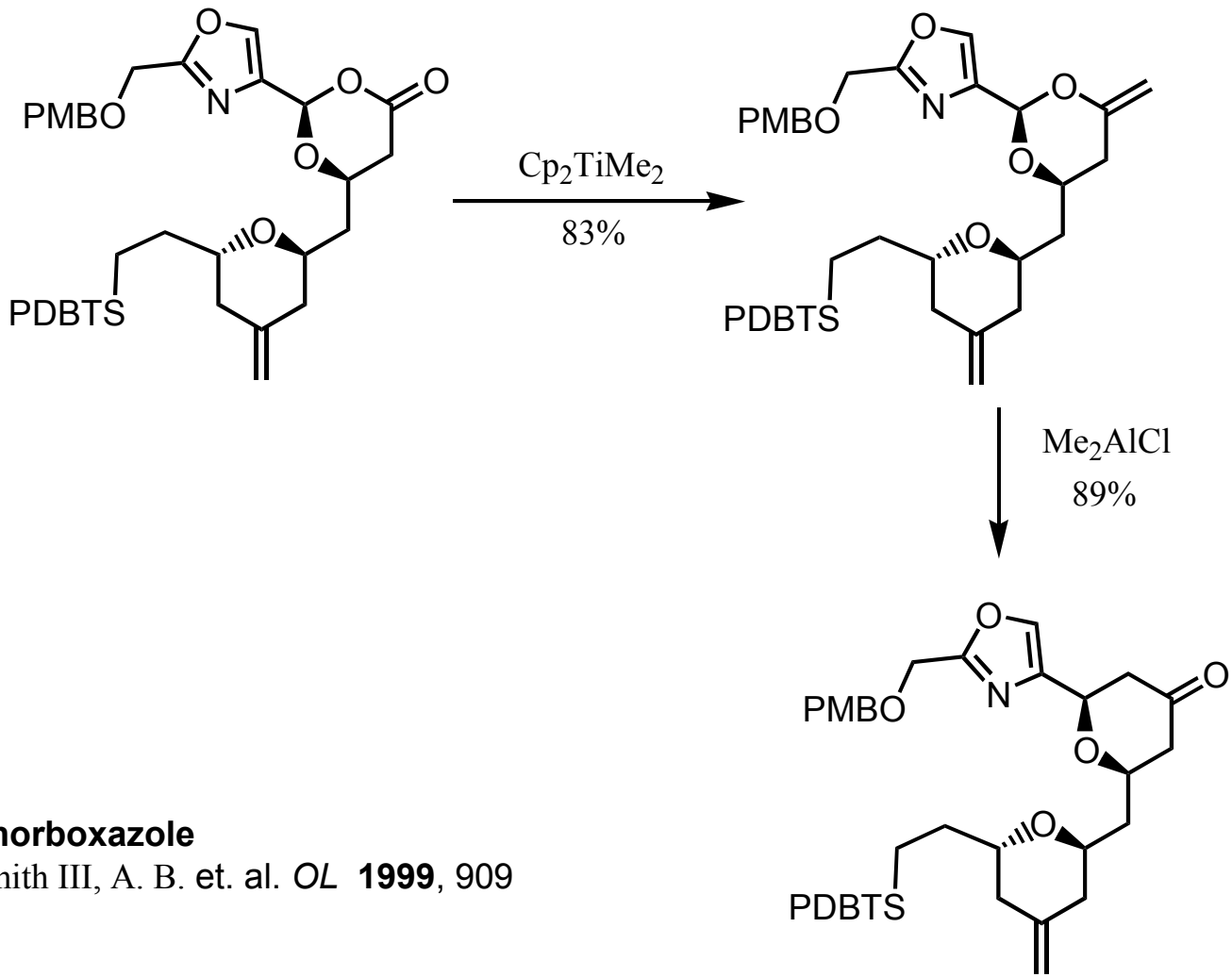


α-Oplopenone Taber, D. F. et. al. *JOC* **1998**, *63,* 7953



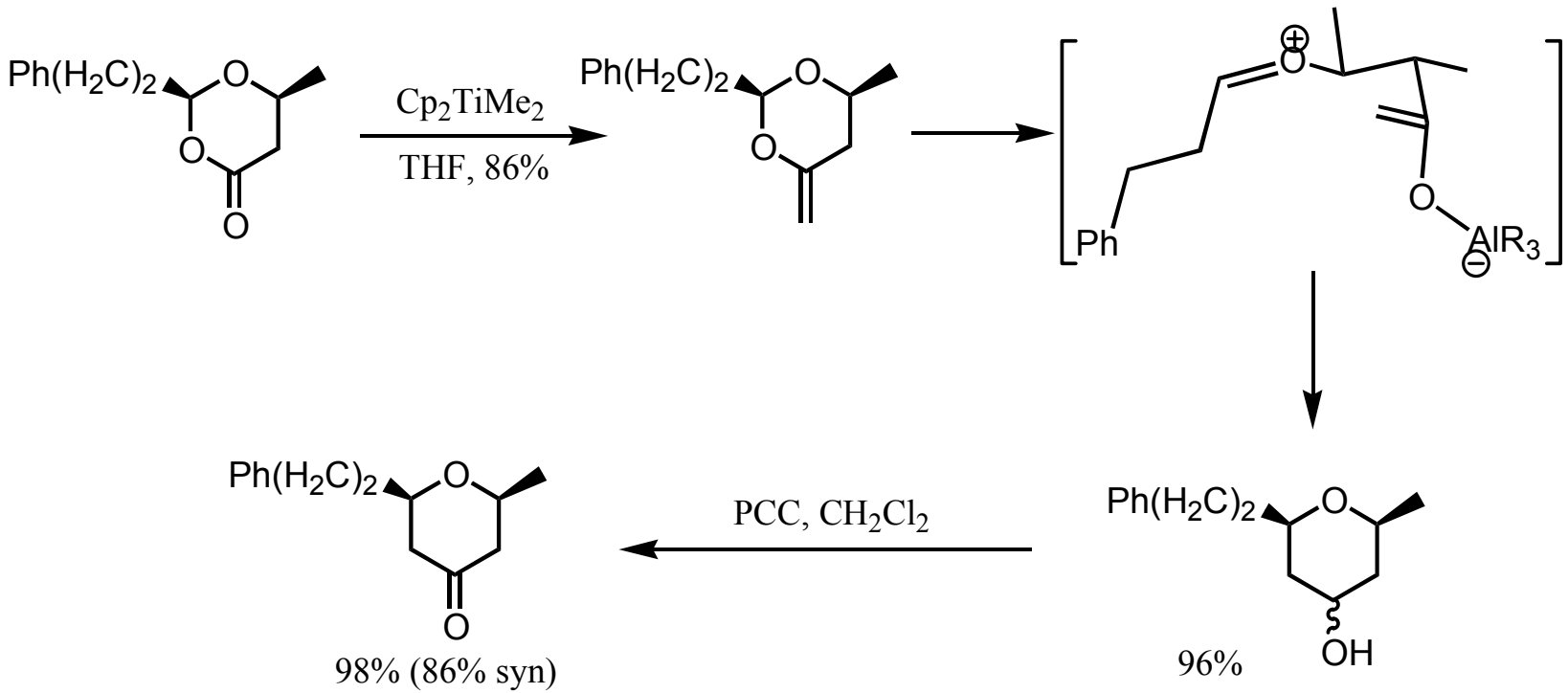
(+)-nemorensic acid Donohoe, T. J. et. al. *CC* **2000**, 465

Petasis-Ferrier Reaction



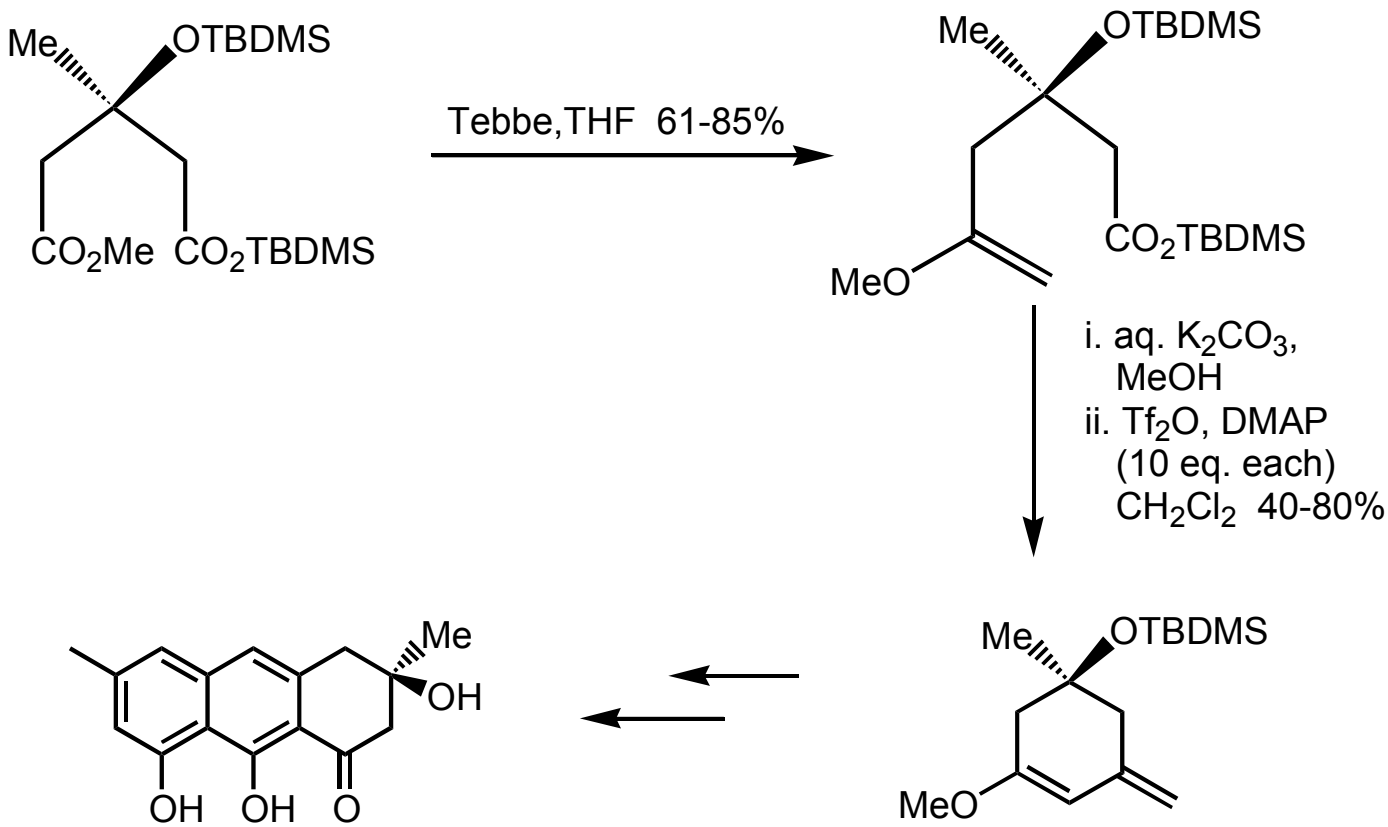
Phorboxazole
Smith III, A. B. et. al. *OL* **1999**, 909

Petasis-Ferrier Reaction



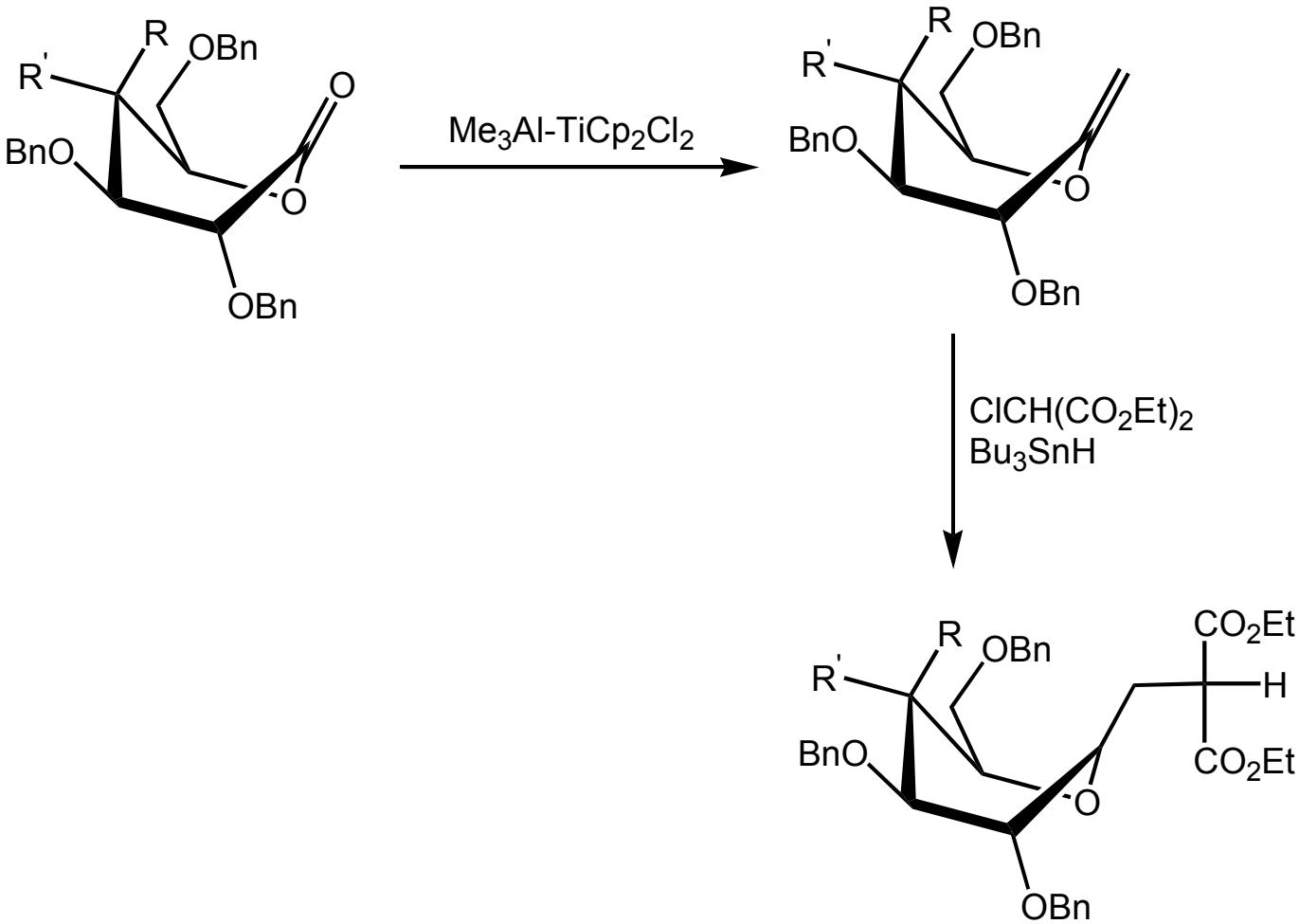
Petasis, N. A. et. al. *TL* **1996**, 141

Petasis-Ferrier-like Reaction



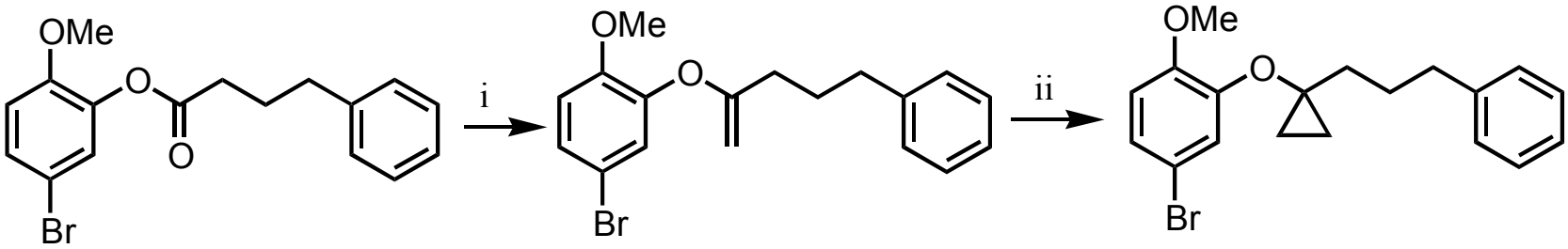
Atrochrysone Steglich, W. et. al. *JCS. Pekin Trans I* **2000**, 2483

Tebbe-Radical Reaction



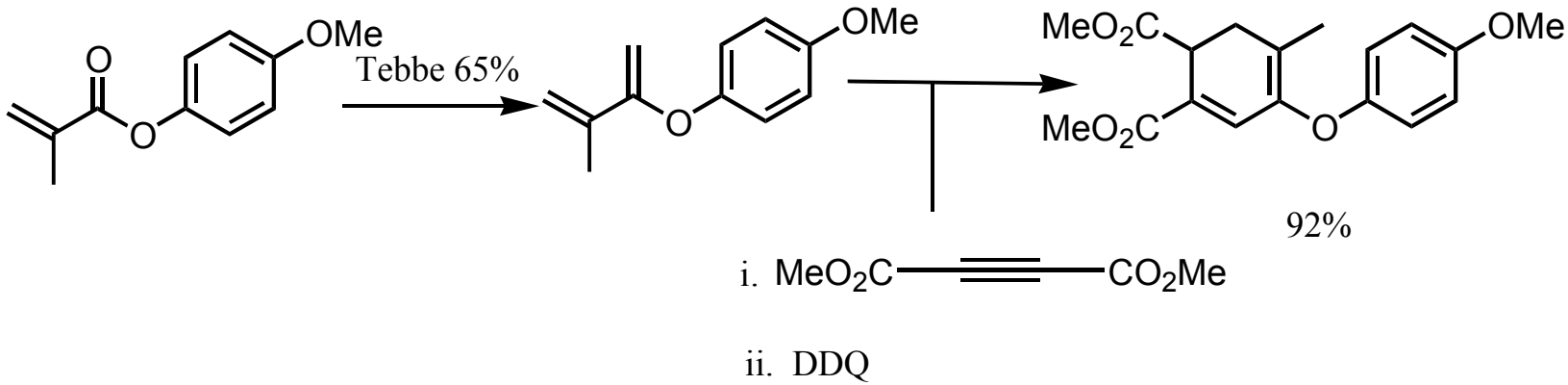
Analogues of Glyceroglycolipids Nicotra, F. et. al. *Tetrahedron* **1997**, 6163

Tebbe-Simmons-Smith and Tebbe-D-A Reaction



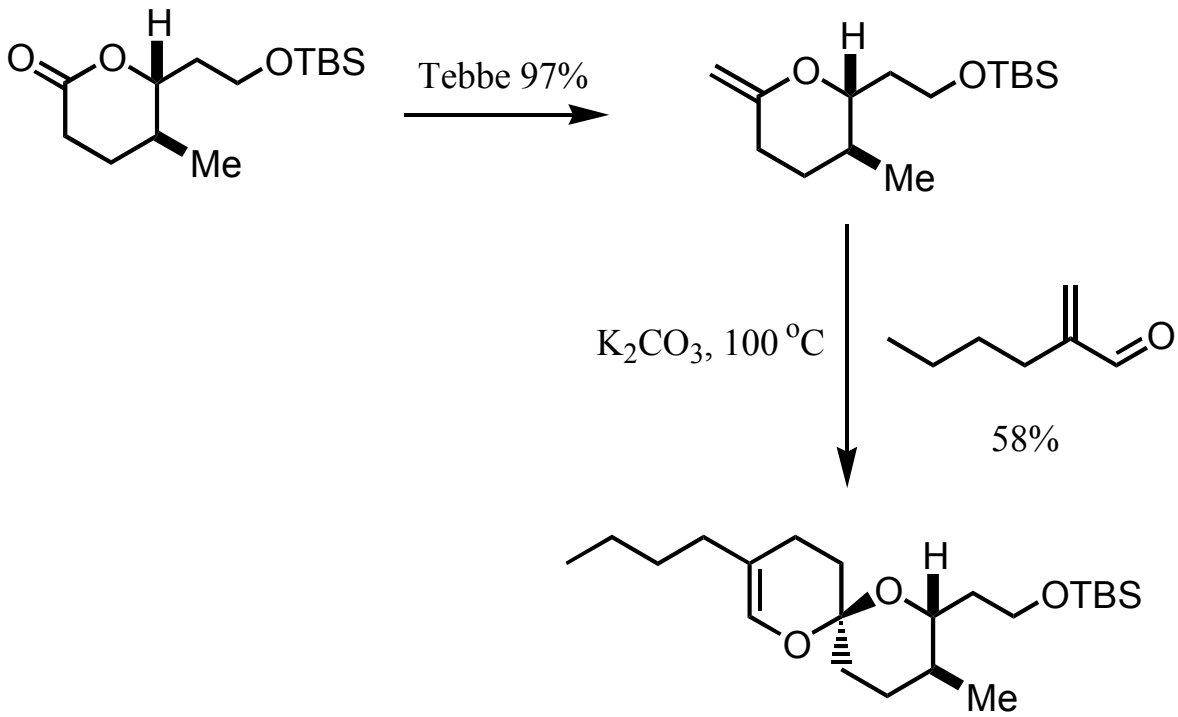
i. Tebbe Reagent, pyridine, 1:3 THF/toluene. ii. CH_2I_2, Zn-Cu couple, I_2, ether, reflux

A potential antiinflamatory Duplantier, A. J. J. et. al. *JMC* **1996**, *39,* 120



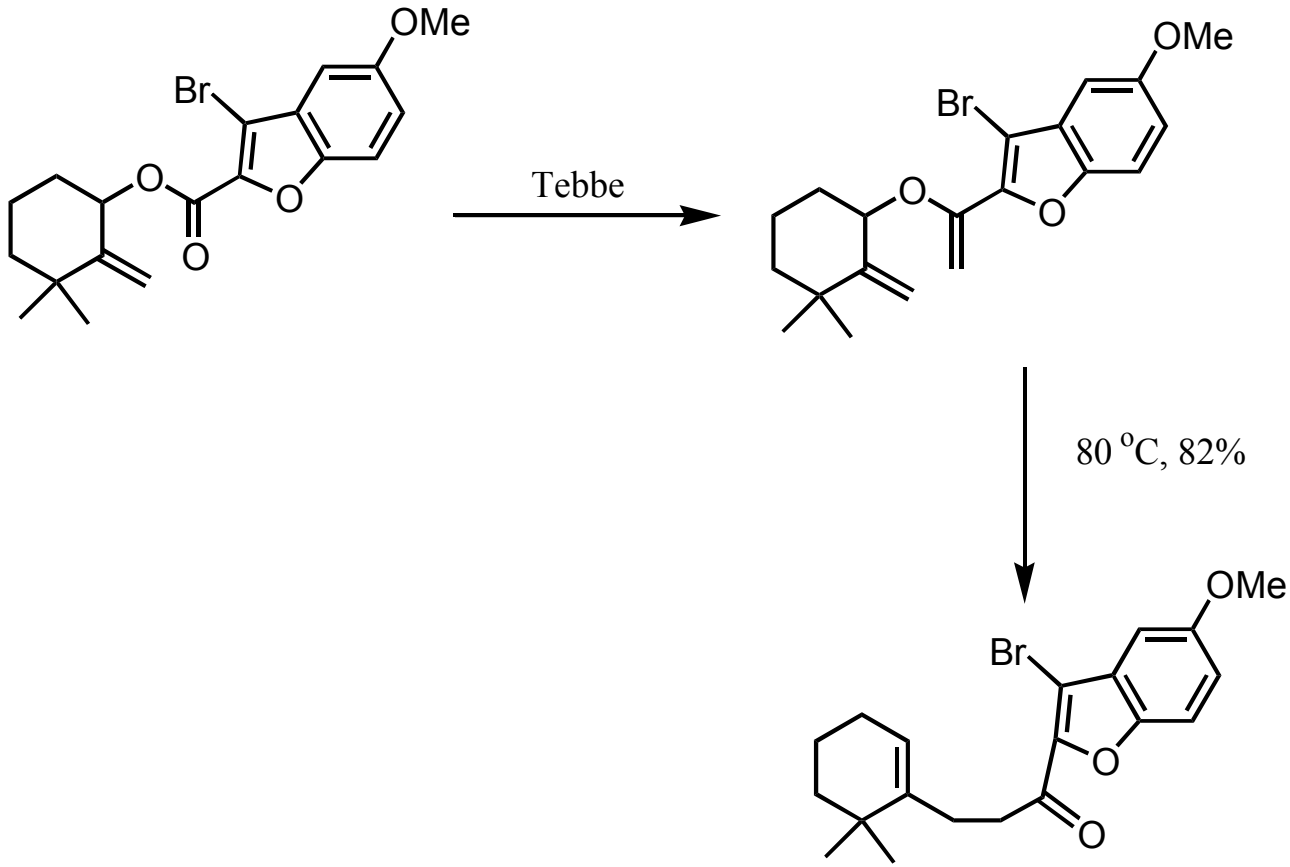
Diaryl ethers Olsen, R. K. et. al. *JOC* **1995**, 6025

Petasis-Diels-Alder Reaction



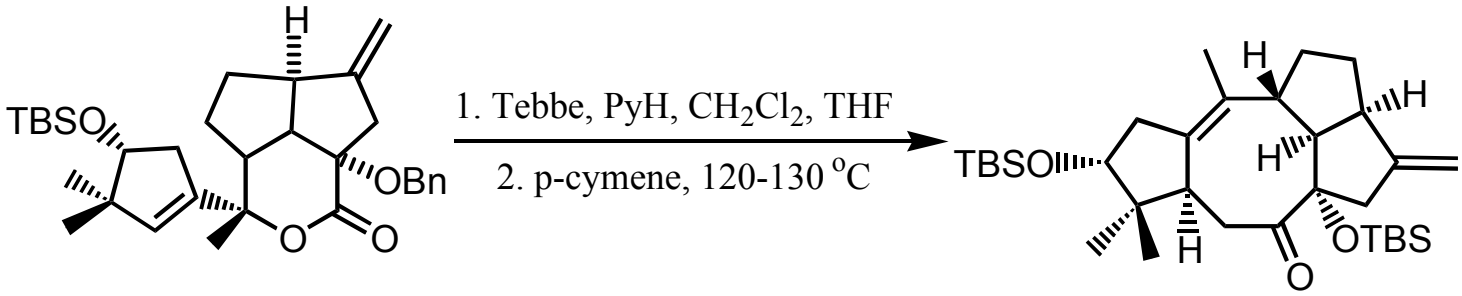
Reveromycin B Rizzacasa, M. A. et. al. *JOC* **1997**, 1196

Tebbe-Claisen Reaction

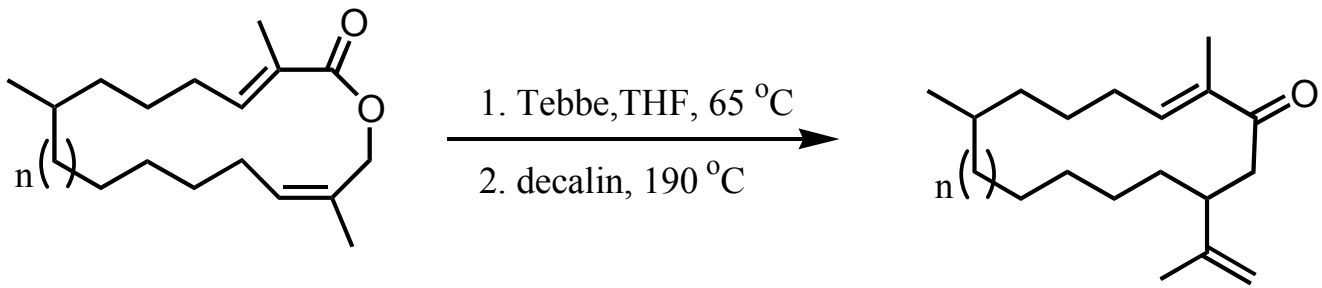


Frondosin B Danishefsky, S. G. et. al. *Angew. Chem.Int. Ed.* **2000**, *39,* 761

Tebbe-Claisen Reaction

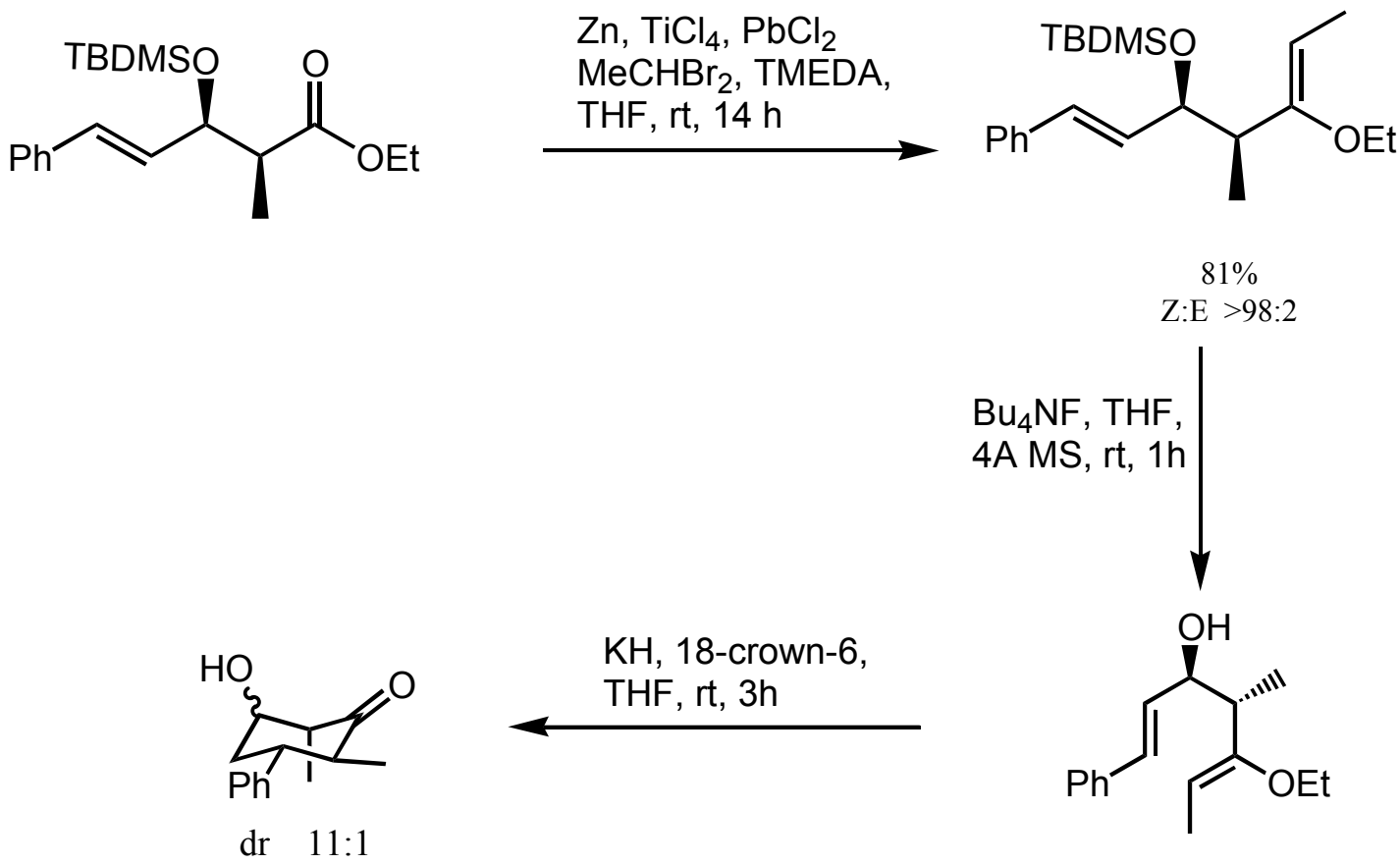


Kalmanol Paquette, L. A. et. al. *JACS* **1996**, *118,* 727



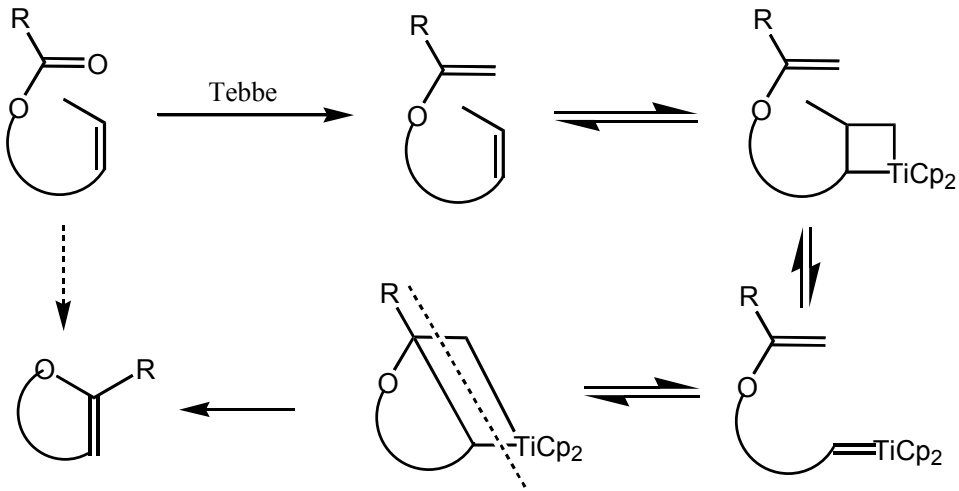
Petasis, N. A. et. al. *TL* **1993**, *34,* 1721

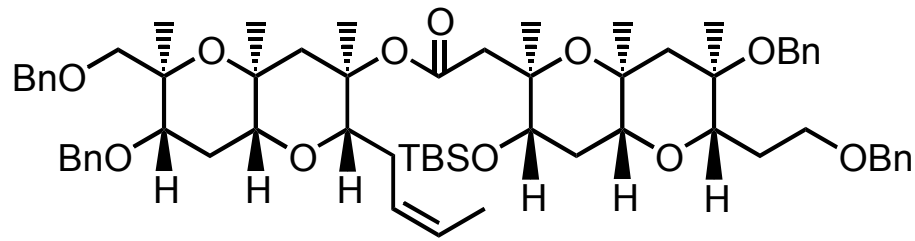
Takai-Cope Reaction



Hartley, R. C. et. al. *TL* **1998**, *39,* 685

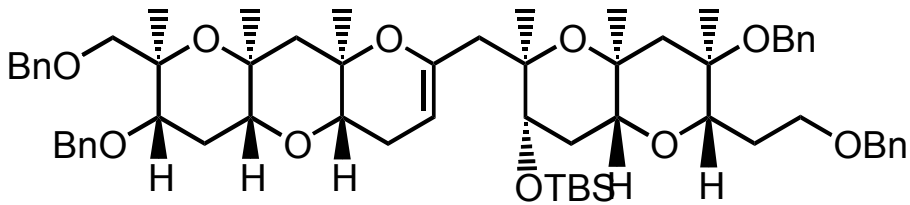
Tebbe-RCM Reaction





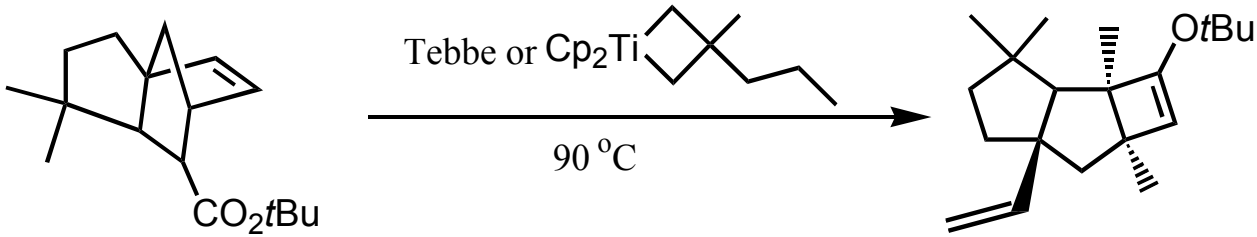
Tebbe (4 eq.), THF, 25°C,0.5h,then, reflux

71%

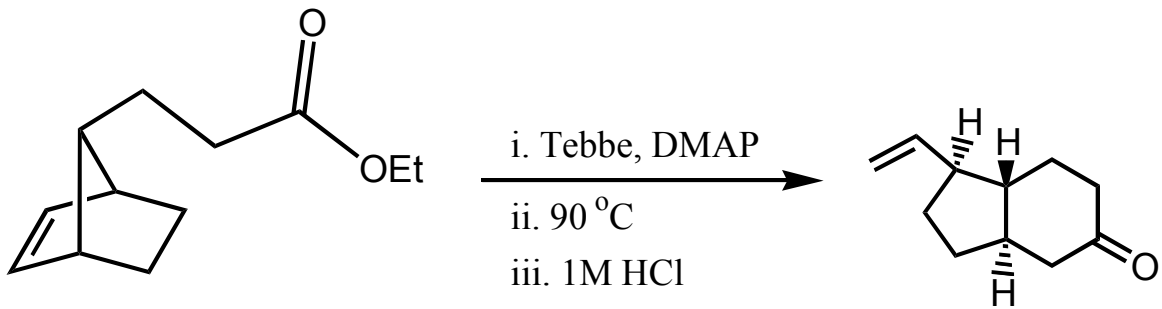


Nicolaou, K. C. et. al. *JACS* **1996**, *118,* 1565

Tebbe-ROM Reaction



Capnellene Grubbs, R. H. et. al. *JOC* **1990**, *55,* 843



Hydroindanone Harlterman, R. L. et. al. *JOMC* **1997**, *547,* 41

Summary

Hurry up! Please Use Tebbe and Petasis!

The End!