

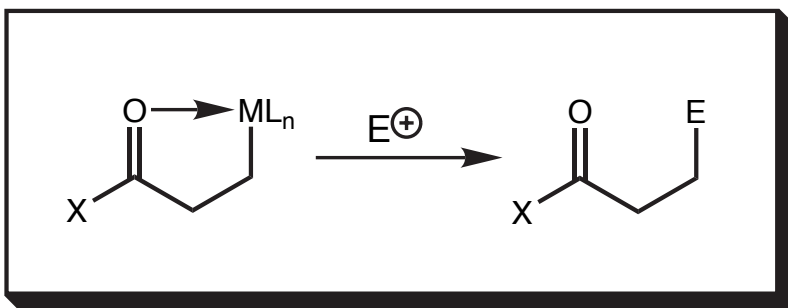
# Homoenolates

## Synthesis and Applications

Evans Group Seminar

March 24, 2000

Jason Burch



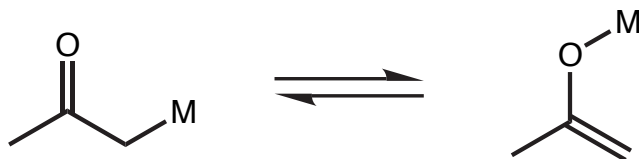
- I. Enolates, Homoenolates and Homoenolate Equivalents
- II. Synthesis of Homoenolates
- III. The Homoaldol Reaction
- IV. Coupling Reactions
- V. Other Reactions
- VI. Synthetic Applications

Leading References: Kuwajima and Nakamura in *Comp. Org. Synth.*, Trost and Fleming, Eds.; Pergammon: Oxford, **1991**, 2, 441  
Crimmins and Nantermet, *Org. Prep. Proc.*, **1993**, 25, 43

# Enolates and Homoenolates

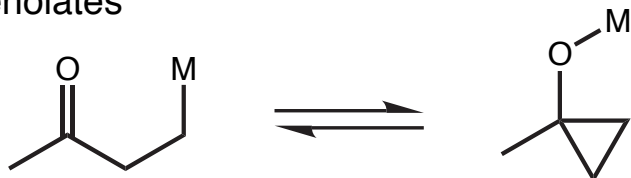
## The Tautomerism Problem

- Enolates



- tautomerism is generally not a problem because oxyanionic tautomer still acts as carbon nucleophile

- Homoenolates

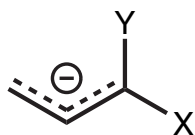
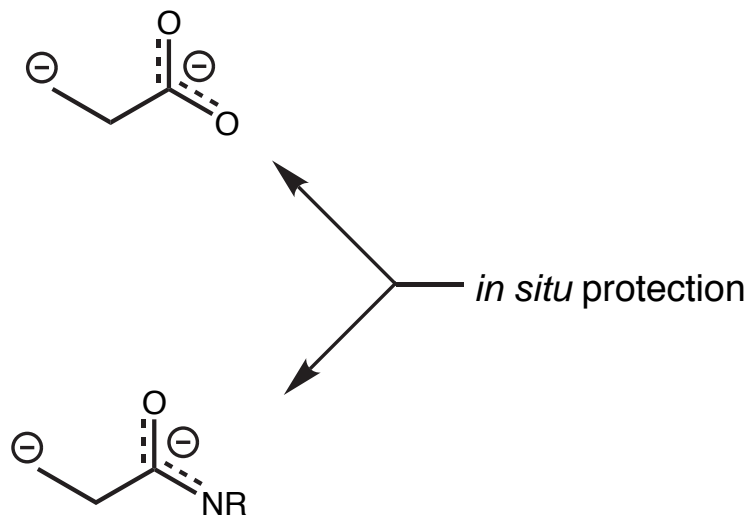
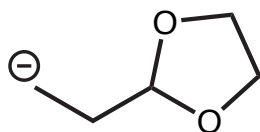


- tautomerism is a much larger problem because it is often irreversible and oxyanionic tautomer rarely acts as a carbon nucleophile

# Homoenolate Equivalents

Definition: species containing an ionic carbon  $\beta$  to a moiety which can be converted into a carbonyl group

Examples:

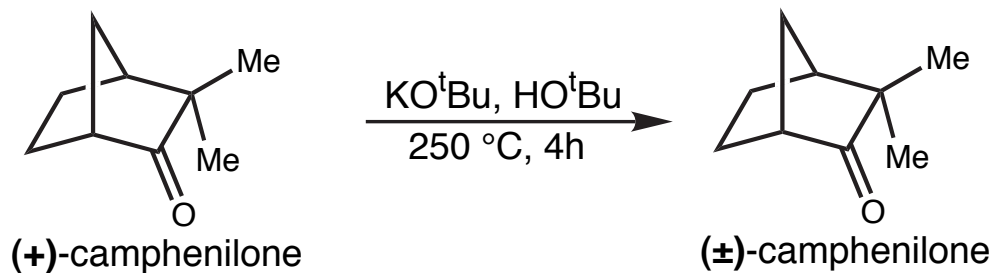


X = OR, NR<sub>2</sub>, etc.

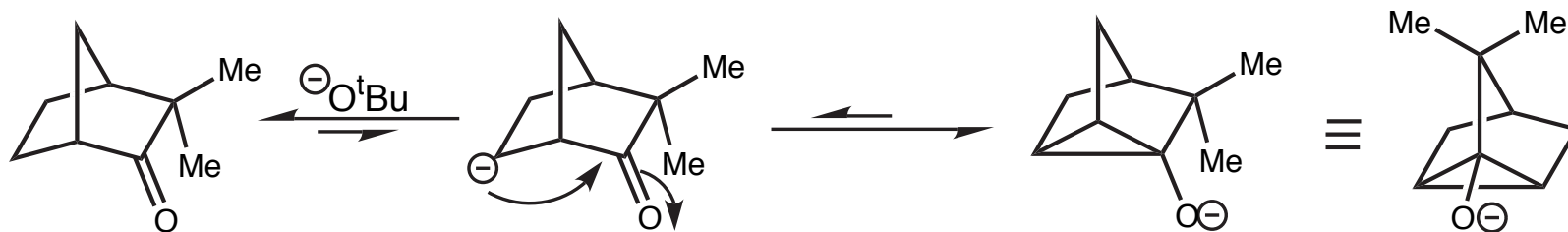
Y = H, R, OR, NR<sub>2</sub>, etc.

Werstiuk in "Umpoled Synthons", Hase, Ed.;  
Wiley: New York, **1987**, Chap. 6  
Ahlbrecht, *Synthesis*, **1999**, 365 (chiral examples)

# The First "Homoenolate"



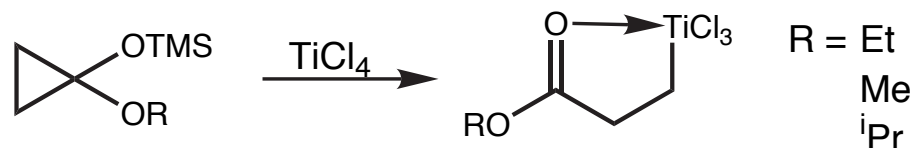
- no racemization occurred in >4 days at 250 °C in the absence of base
- proposed to proceed via a "homoenolate anion"



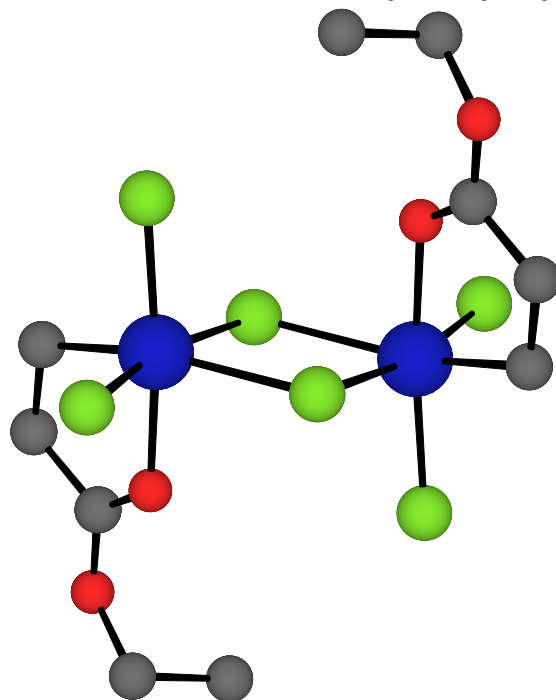
Nickon, *J.Am.Chem.Soc.*, **1962**, *84*, 4604

# Cyclopropane Ring Opening

## Synthesis of Titanium Homoenolates



- if conducted in  $\text{CDCl}_3$  leads to a deep wine-red color; precipitates as purple needles in hexanes
- IR spectrum strongly supports coordinated carbonyl ( $\nu_{\text{C}=\text{O}} = 1603$  for R =  $i\text{Pr}$  in benzene)
- molecular weight by cryoscopy is 560-620 indicating dimeric structure  
→ later verified in solid state by x-ray crystal structure (Floriani)



Relevant bond lengths ( $\text{\AA}$ ):

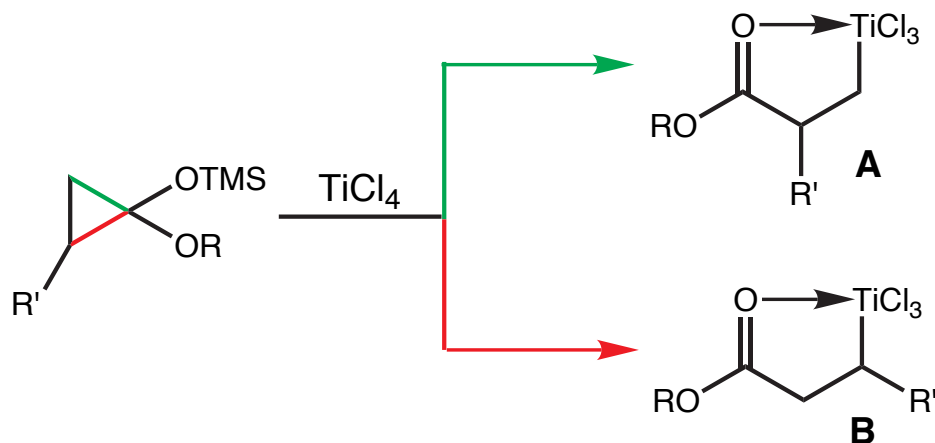
Ti-C	2.081
Ti-O	2.072
C=O	1.235

Nakamura, *J. Am. Chem. Soc.* **1983**, *105*, 651  
Floriani, *Organometallics*, **1993**, *12*, 2845

# Cyclopropane Ring Opening

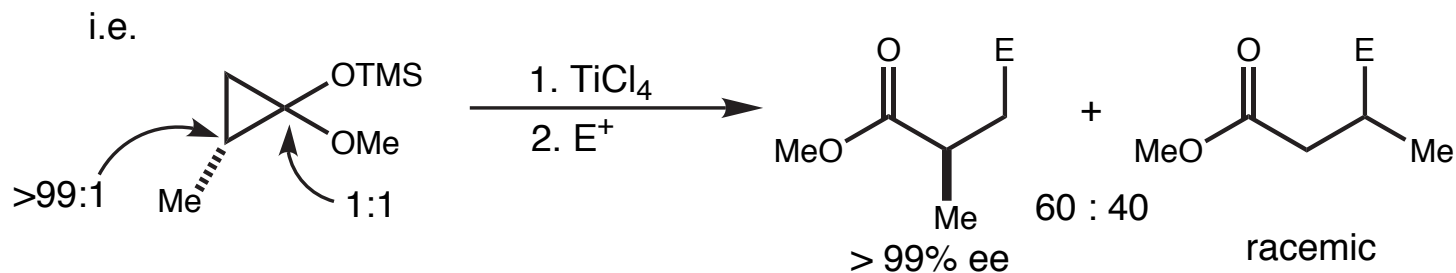
## Regioselectivity of Ring Cleavage - Titanium

- in general, cleavage occurs selectively at the least substituted cyclopropane bond



R	R'	A : B
iPr	Me	>95 : 5
Me	Me	60 : 40
Et	Ph	78 : 22

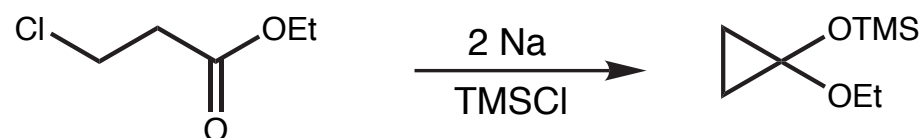
- A** can be isolated, but **B** is too unstable; only detected by *in situ* quench with electrophiles (i.e. Br<sub>2</sub>, RCHO)
- if non-racemic starting material is used, quench with electrophiles indicates non-racemized **A** and totally racemic **B**



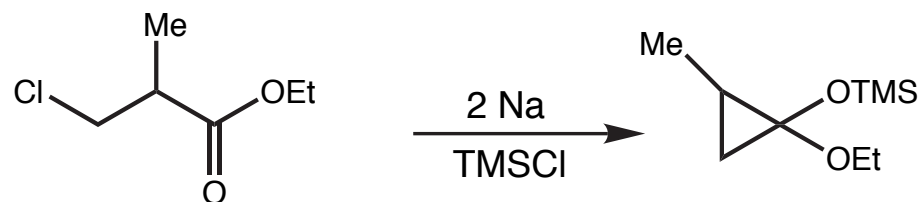
Nakamura, *J.Am.Chem.Soc.*, **1986**, 108, 3749

# Cyclopropane Synthesis

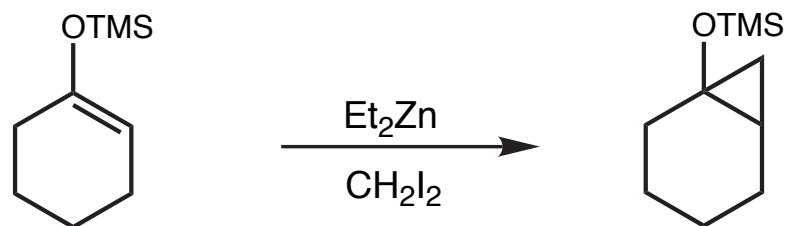
- most common method



- used to prepare substituted cyclopropanes



- use Simmons-Smith for ketone-derived substrates

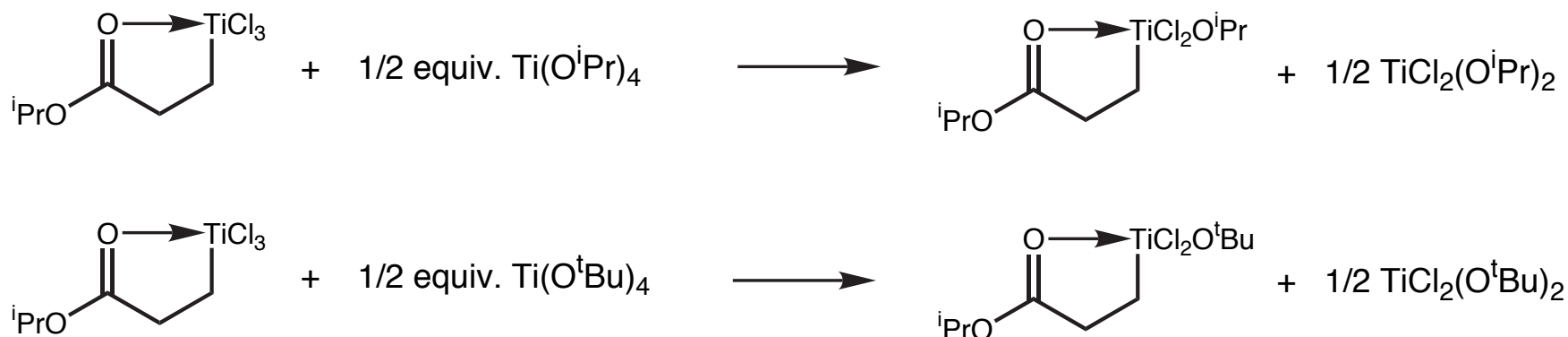


Ruhlmann, *Synthesis*, **1971**, 236.  
Salaun, *Org. Synth.*, **1985**, 63, 147  
Murai, *J. Org. Chem.*, **1973**, 38, 4354

# Alkoxide-Modified Homoenoates

## Tuning Titanium Homoenoate Reactivity

- Problem: trichlorotitanium homoenoates are not reactive enough for some applications  
can also lead to chlorinated byproducts
- Idea: replace 1 or more chlorides with alkoxides to increase nucleophilicity



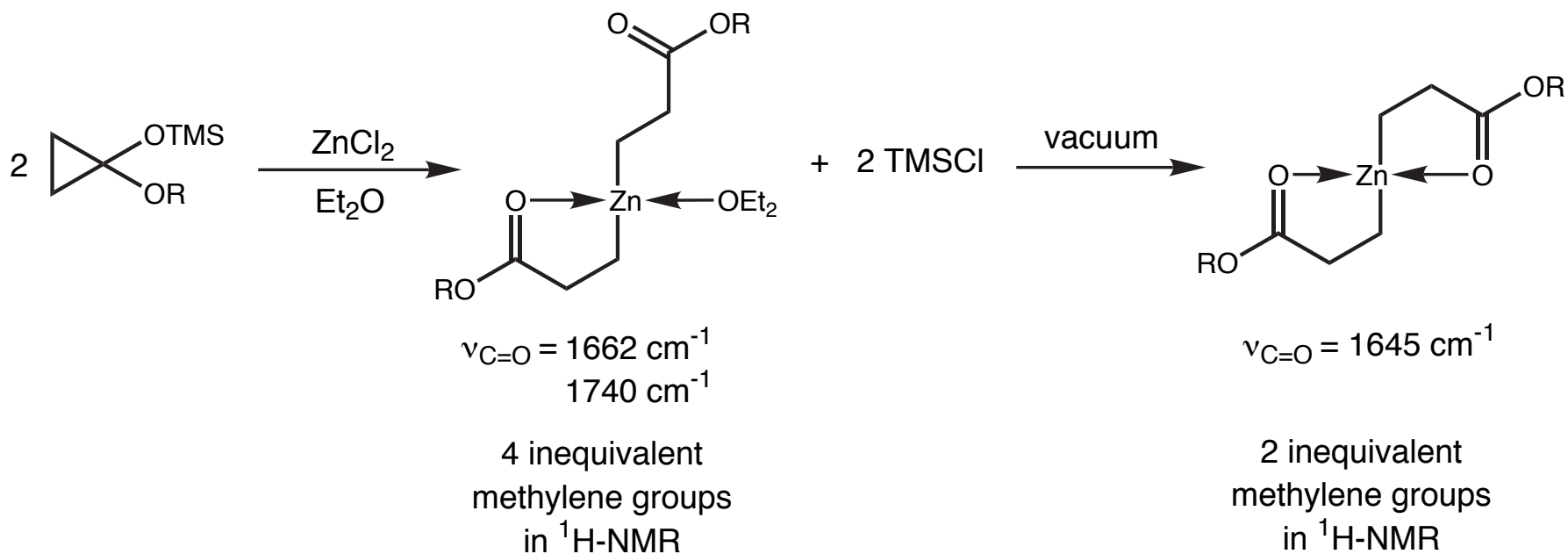
- Have not been characterized to the detail of the trichlorohomoenoates
- Appear to have "significant contribution from monomeric forms" (from molecular weight data)
- Are more reactive than trichloro homoenoates towards homoaldolisation

Nakamura, *J.Am.Chem.Soc.*, **1986**, 108, 3745

# Cyclopropane Ring Opening

## Zinc Homoenoates

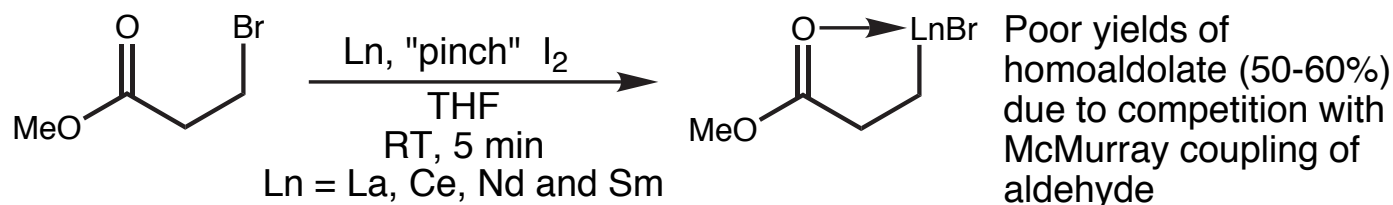
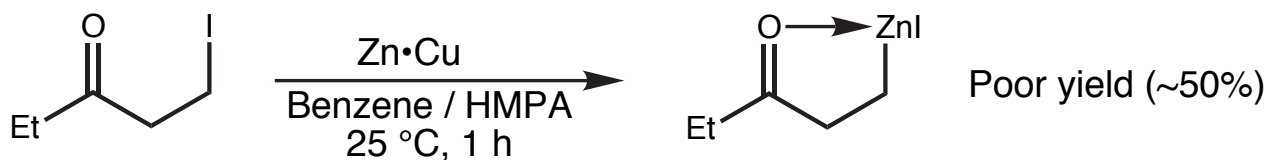
- Zinc homoenoates can be prepared in a similar method to titanium



Nakamura, *Organometallics*, **1985**, *4*, 641

# Direct Oxidative Addition

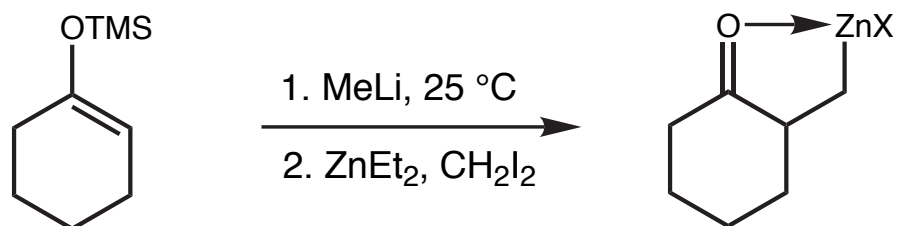
## Zinc and Lanthanide Homoenoates



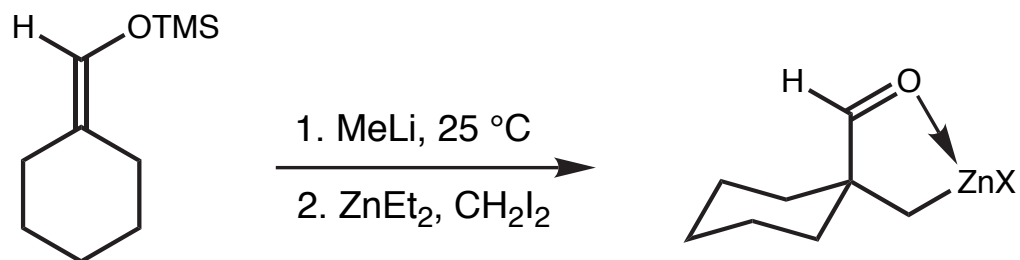
Yoshida, *Tetrahedron Lett.*, **1985**, 26, 5559  
Yoshida, *Angew.Chem.,Int.Ed.Engl.*, **1987**, 26, 1157  
Fukuzawa, *Chem. Commun.*, **1986**, 475

# Enolate Homologation

## Synthesis of Zinc Homo-enolates



- less reactive than most zinc homo-enolates
- can also be used to form aldehyde homo-enolates

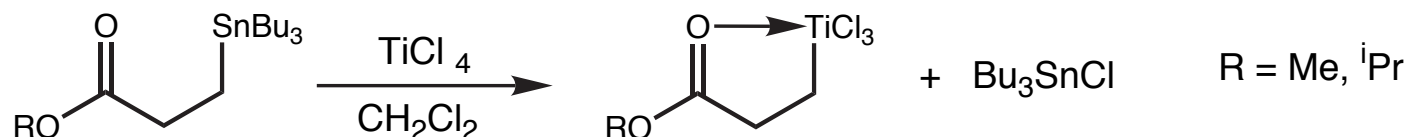


Knochel, *J.Org.Chem.*, **1993**, 58, 2694

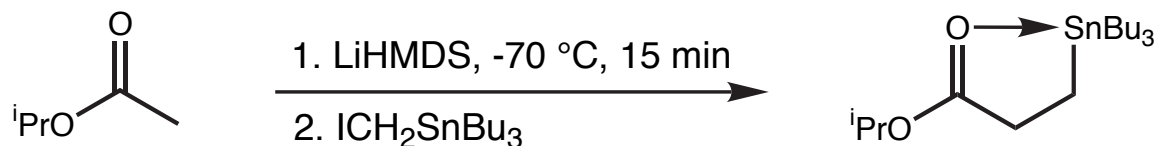
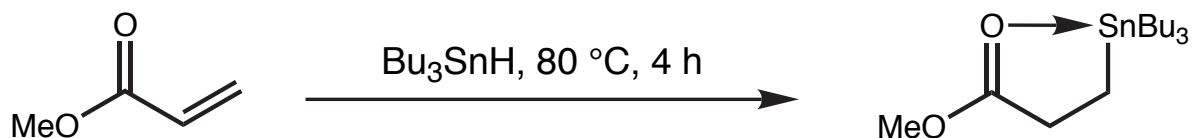
# Direct Tin-Titanium Exchange

## New Route to Titanium Homoenoates

- Treatment of  $\beta$ -tri-n-butylstannyl esters with  $\text{TiCl}_4$  directly forms titanium homoenoate



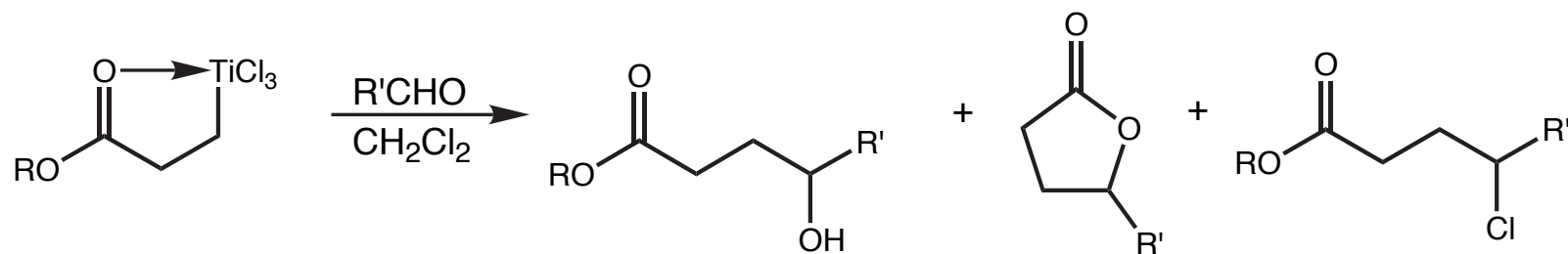
- Isotope labelling studies showed rxn does not proceed via cyclopropane
- Substrates can easily be prepared by two methods:



Goswami, *J.Org.Chem.*, **1985**, *50*, 5907  
van der Kirk, *J. Appl. Chem.*, **1957**, *7*, 356  
Still, *J.Am.Chem.Soc.*, **1978**, *100*, 1481

# The First Homoaldol Reaction

Synthesis of  $\gamma$ -hydroxyesters and  $\gamma$ -lactones

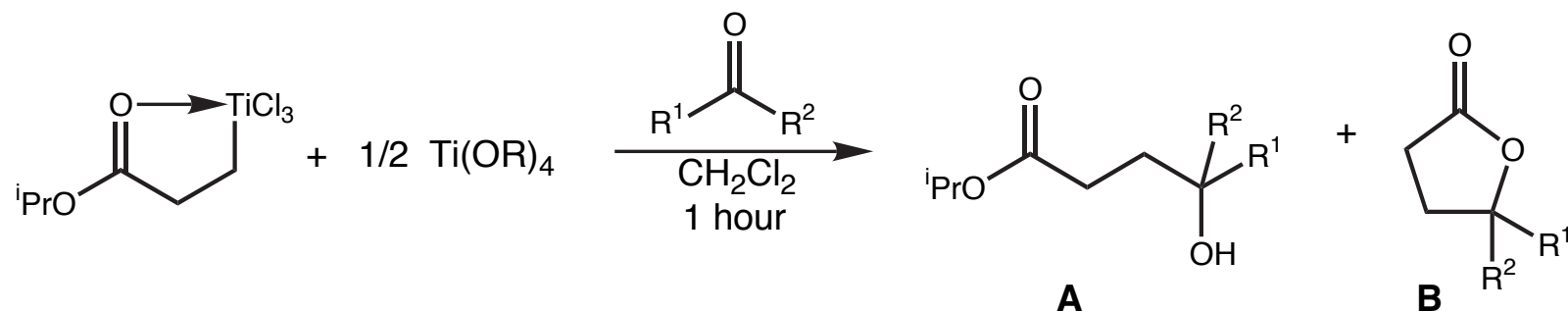


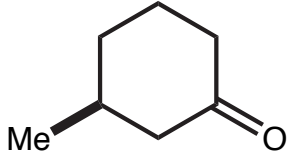
Aldehyde	R	Temp (°C)	Time (h)	Workup	Product	Yield
	Et	0	1	Acidic		81
	iPr	0	2.5	Neutral		67 (85:15)
	Et	0	1.5	Neutral		90

Nakamura, *J. Am. Chem. Soc.*, **1977**, *99*, 7360

# Homoaldol Reactions with Alkoxide-modified Homoenolates

## Homoaldol Reactions with Aromatic Aldehydes and Ketones

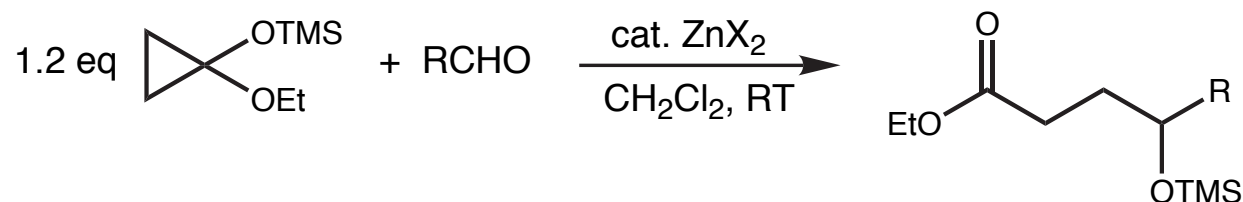


Electrophile	R	Temp(°C)	Yield ( <b>A</b> or <b>B</b> )
Benzaldehyde	iPr	0	90( <b>A</b> )
Crotonaldehyde	iPr	0	88( <b>A</b> )
Acetophenone	iPr	20	66( <b>A</b> ), 12( <b>B</b> )
	tBu	20	93( <b>B</b> )
Cyclohexanone	iPr	20	62( <b>B</b> )
	tBu	20	91( <b>B</b> )
	tBu	20	91( <b>B</b> )
			dr = 88 : 12 equatorial attack

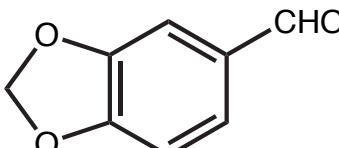

Nakamura, *J. Am. Chem. Soc.*, **1986**, 108, 3745

# Homoaldol Reactions of Zinc Homoenolates

## First Catalytic Homoaldol Reactions

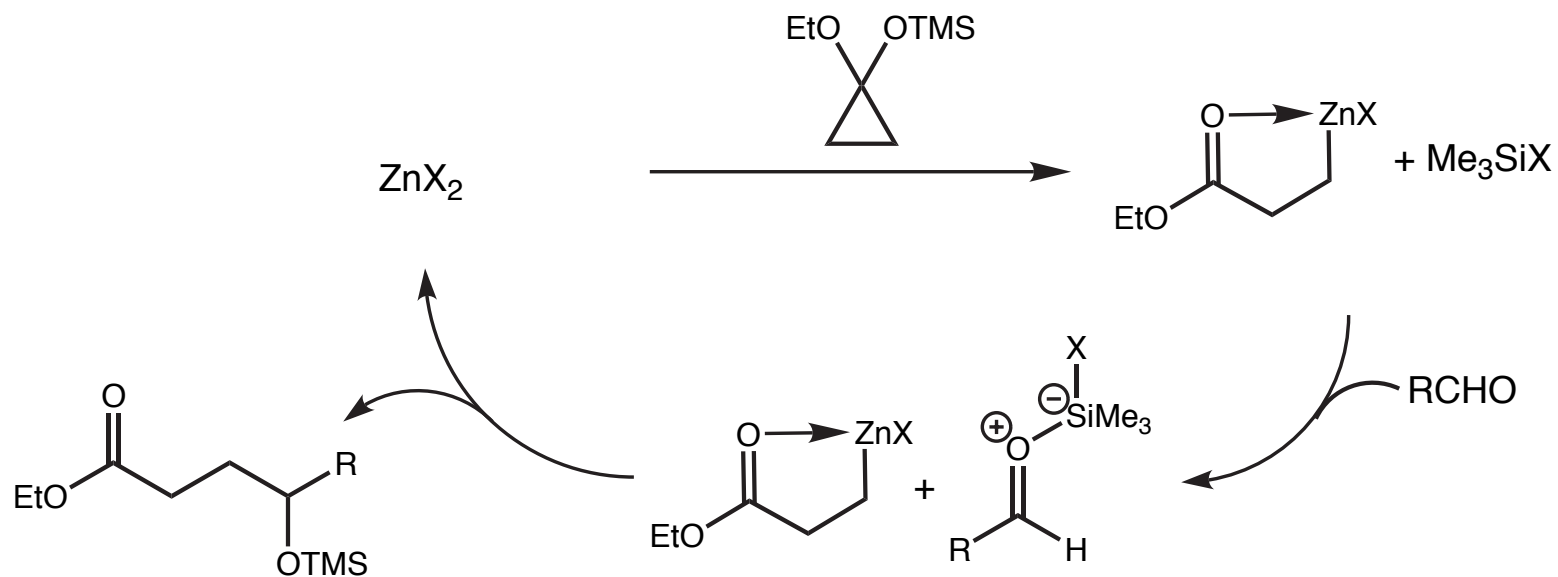


- TMSCl generated is essential (i.e. no reaction if removed *in vacuo* for stoichiometric case)

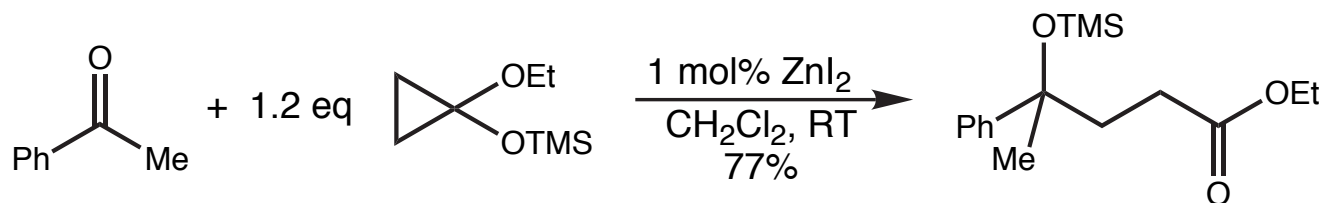
Aldehyde	Catalyst, yield	
	ZnCl <sub>2</sub> (30-50 mol%)	ZnI <sub>2</sub> (0.1-1 mol%)
PhCHO	84	89
Ph-CH=CH-CHO	94	84
	91	95
	--	84
n-Pent-CH(OBn)-CHO	79 93:7 <i>syn</i> : <i>anti</i> chelation product	--

# Homoaldol Reactions of Zinc Homoenoates

## Proposed Catalytic Cycle



- with  $\text{ZnI}_2$ , the homoenoate is reactive enough to add to ketones:

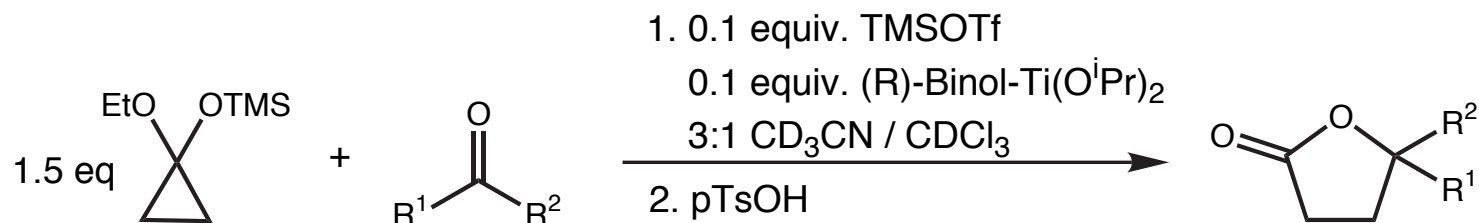




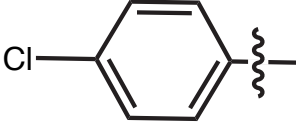
- no reaction even with stoichiometric  $\text{ZnCl}_2$

Nakamura, *J. Am. Chem. Soc.*, **1987**, *109*, 8056

# Gleason's Homoaldol reaction

## First Catalytic Titanium Homoaldol Reaction



R <sup>1</sup>	R <sup>2</sup>	Conditions	Yield
Ph	H	0 °C, 24 h	99
	H	0 °C, 36 h	76
	H	0 °C, 36 h	82
	H	0 °C, 80 h	84
<sup>t</sup> Bu	H	45-50 °C, 54 h <sup>a</sup>	52
Ph	Me	45-50 °C, 60 h <sup>a</sup>	78

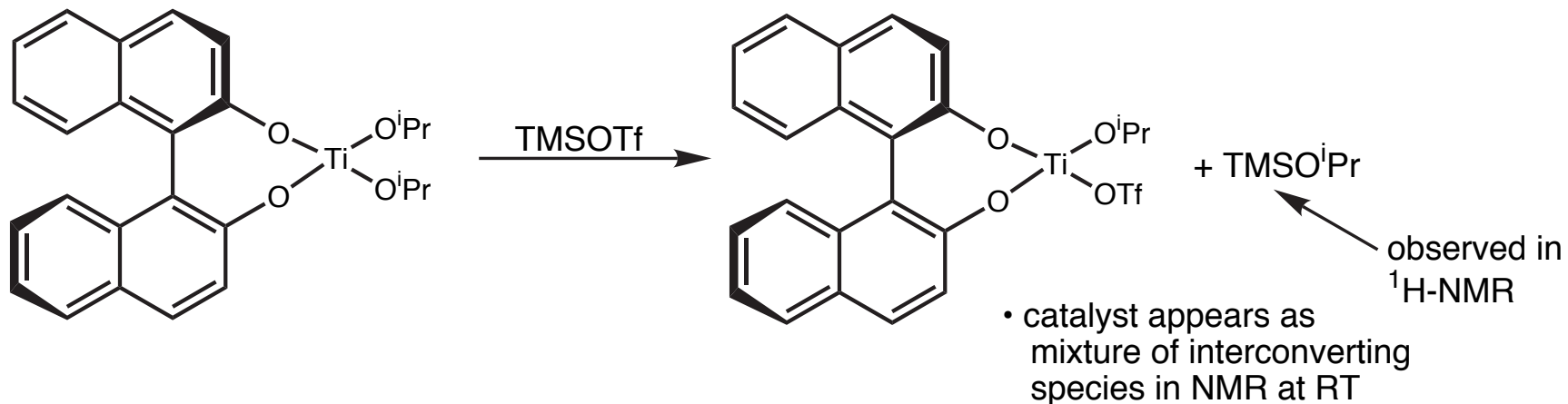
<sup>a</sup>2 equiv. of cyclopropane used

Gleason, *Org. Lett.*, **1999**, *1*, 1643

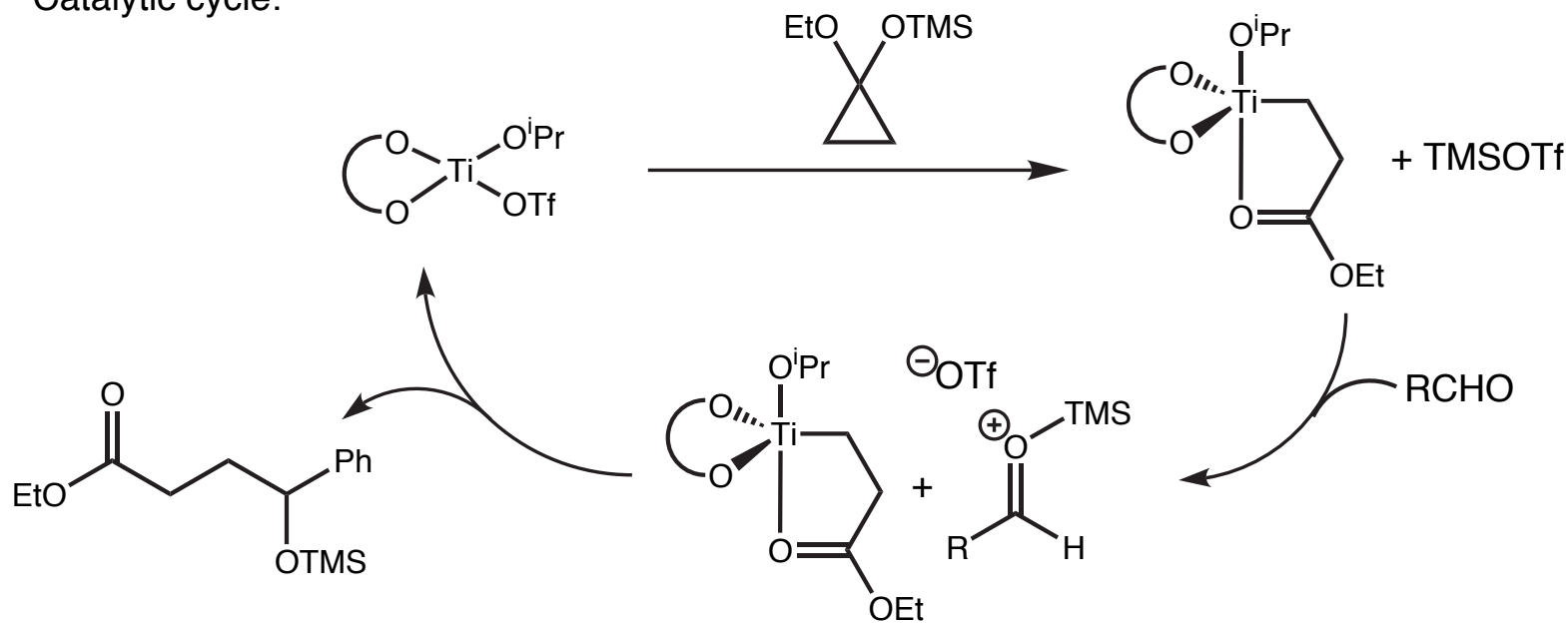
# Gleason's Homoaldol reaction

## Proposed Catalyst and Catalytic Cycle

Catalyst:



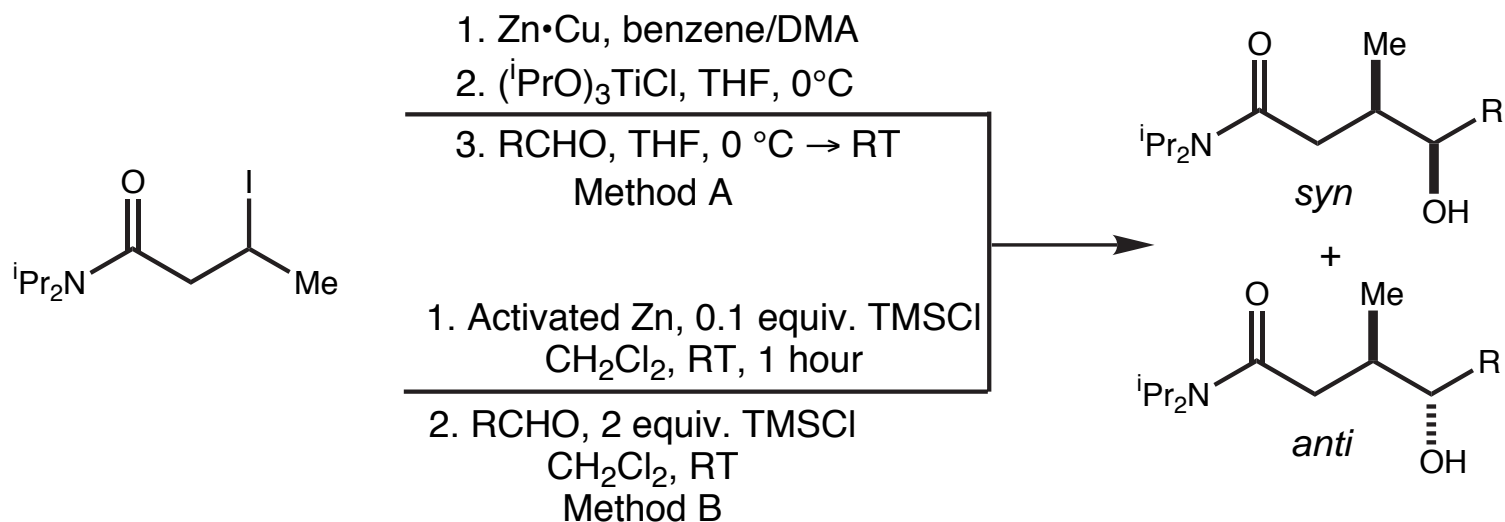
Catalytic cycle:



Gleason, *Org. Lett.*, **1999**, *1*, 1643

# Diastereoselective Homoaldol Reactions of Amide-homoenolates

Synthesis of *syn*- or *anti*- $\beta$ -methyl- $\gamma$ -hydroxyamides



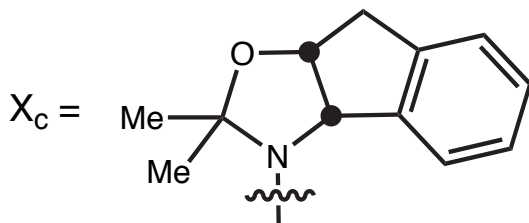
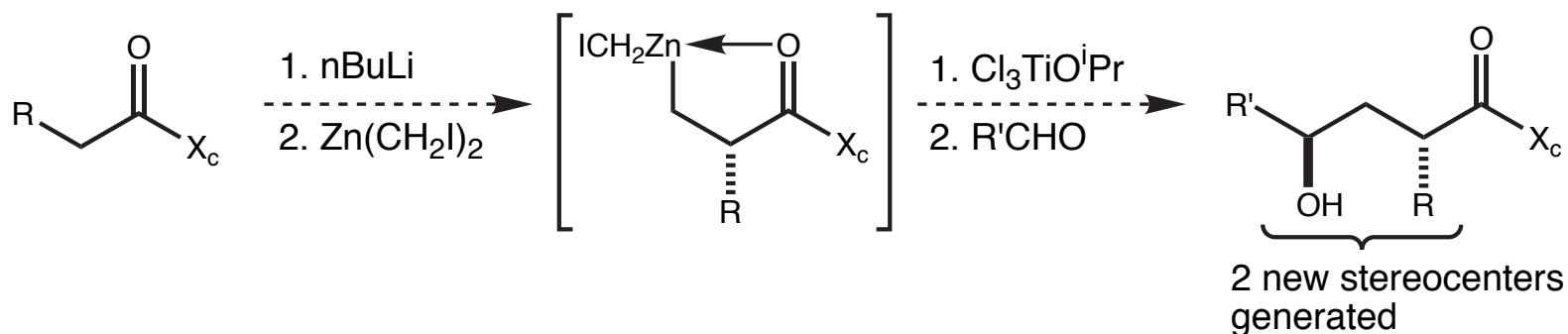
R	Method	Time (h)	Yield	<i>syn:anti</i>
Ph	A	3	79	94 : 6
	B	2.5	82	13 : 87
o-MeOPh	A	3	87	85 : 15
	B	0.6	95	25 : 75
2-furyl	A	0.5	61	96 : 4
	B	0.6	60	38 : 62

Asaoka, *J.Chem.Soc. Perkin Trans. 1*, **1995**, 285

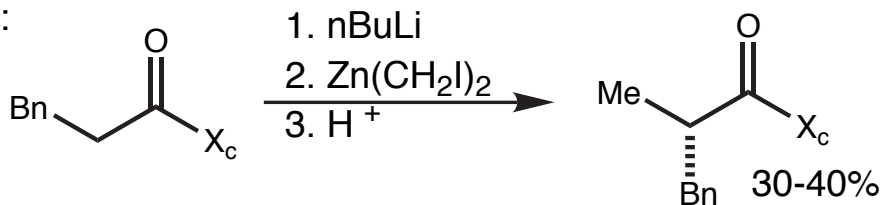
# Tandem Asymmetric Enolate Homologation - Homoaldol Reaction

Asymmetric Synthesis of  $\alpha$ -alkyl,  $\gamma$ -hydroxy Carbonyl Compounds

• idea:



• initial results:



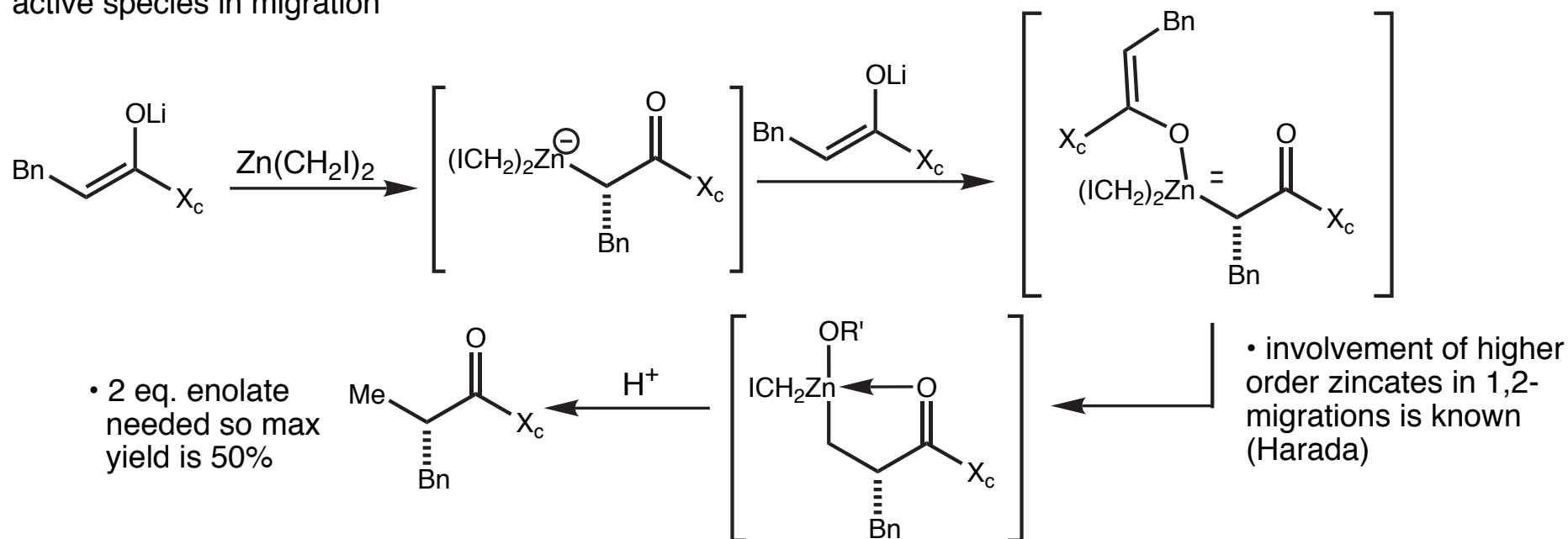
But ReactIR showed disappearance of enolate and appearance of new species

McWilliams, *J. Am. Chem. Soc.*, **1996**, 118, 11970

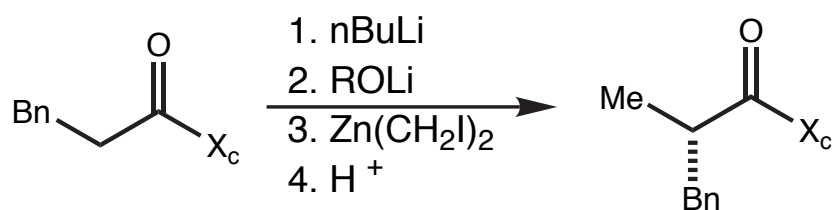
# Tandem Asymmetric Enolate Homologation - Homoaldol Reaction

## Asymmetric Synthesis of $\alpha$ -alkyl, $\gamma$ -hydroxy Carbonyl Compounds

- proposal: zinc enolate unreactive towards homologation; higher order zincate (zincate + extra enolate) active species in migration



- idea: add an equivalent of alkoxide to take the place of the enolate in the higher order zincate



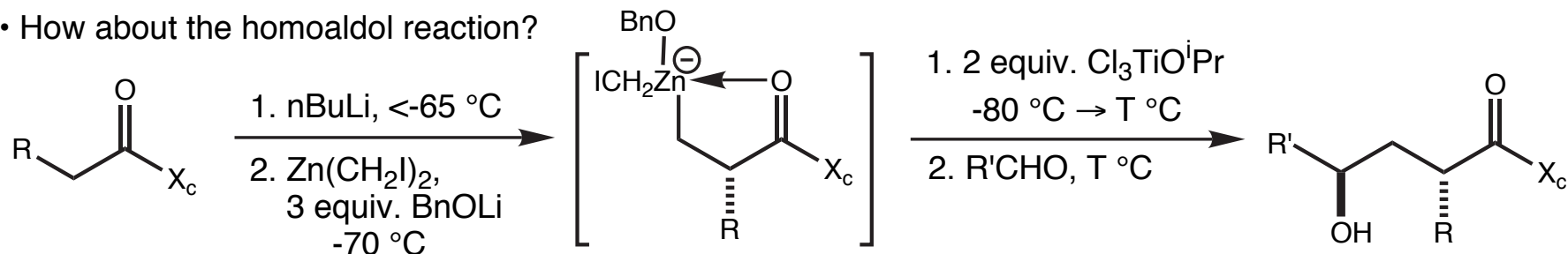
ROLi	Conversion
EtOLi	35
nPrOLi	74
BnOLi	82 (78% isolated)
LiO(CH <sub>2</sub> ) <sub>2</sub> OLi	31

McWilliams, *J. Am. Chem. Soc.*, **1996**, *118*, 11970  
 Harada, *J. Org. Chem.*, **1993**, *113*, 2958

# Tandem Asymmetric Enolate Homologation - Homoaldol Reaction

## Asymmetric Synthesis of $\alpha$ -alkyl, $\gamma$ -hydroxy Carbonyl Compounds

- How about the homoaldol reaction?

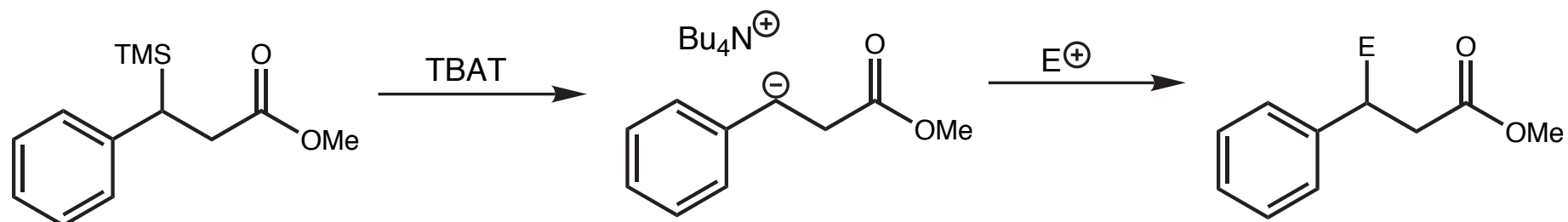


Aldehyde (R')	R	T (°C)	de (%)	Yield
	Bn	-20	$\geq 99$	59
	Me	-20	82	58
phenyl	Bn	-40	82	50
phenyl	Me	-40	80	44
iso-propyl	Bn	-50	76	53
n-butyl	Bn	-20	64	53

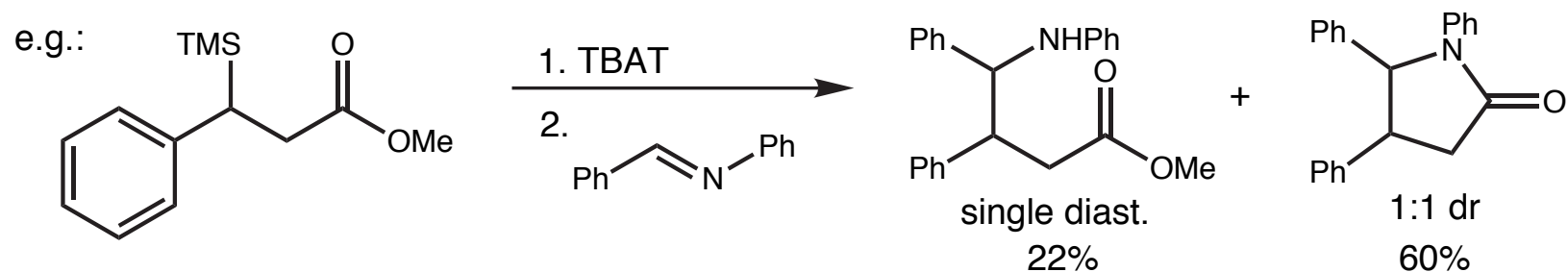
McWilliams, *J. Am. Chem. Soc.*, **1996**, 118, 11970

# Reactive Homoenolates

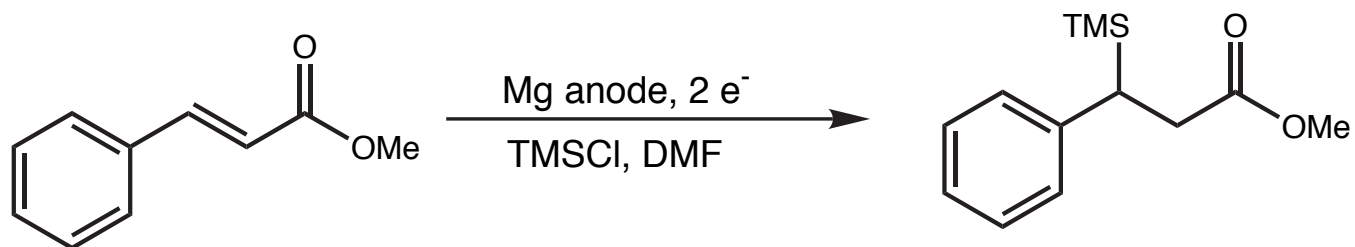
## First Synthesis of a Metal-free Homoenolate



- reactive enough to add to imines, as well as aldehydes and ketones



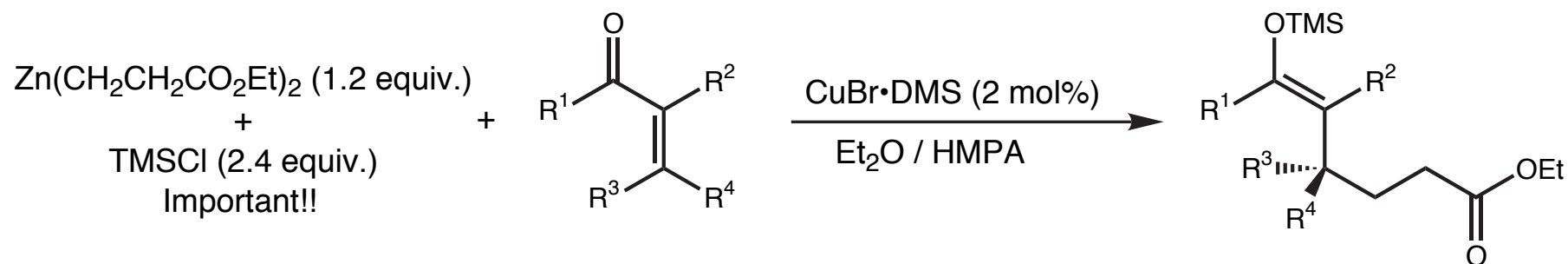
- substrate made easily using Nishiguchi method

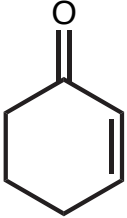
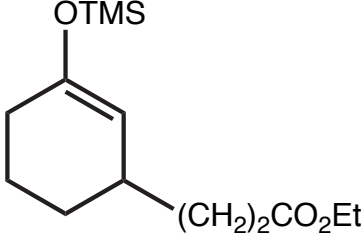
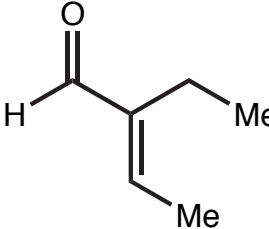
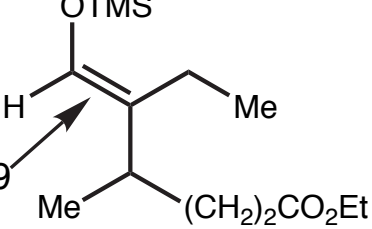

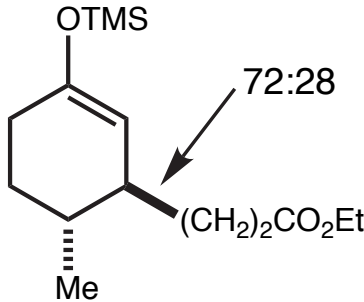
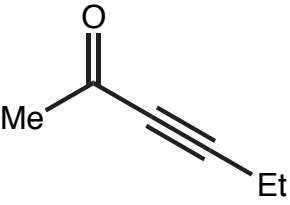
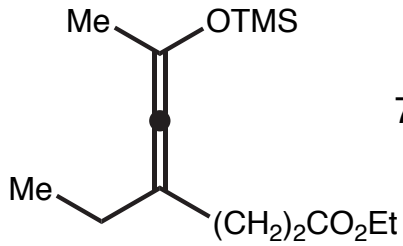


Fry, *Tetrahedron Lett.*, **1999**, 40, 7945  
Nishiguchi, *Tetrahedron Lett.*, **1992**, 33, 5515

# Conjugate Addition of Zinc Homoenoletes

Synthesis of  $\delta,\epsilon$ -(silylenoether)-esters

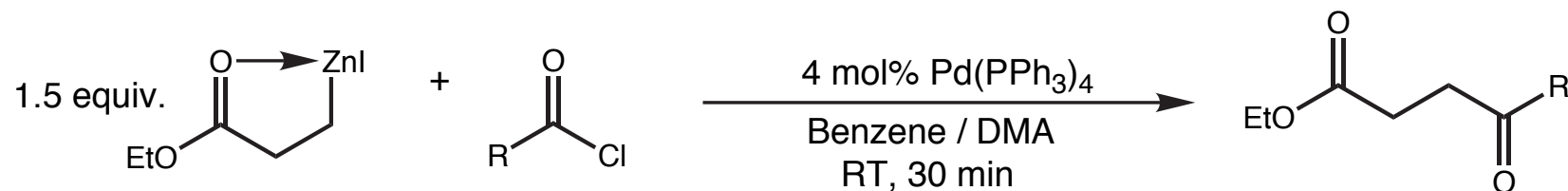


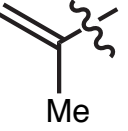
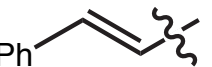
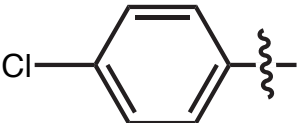
Enone	Product	Yield	Enone	Product	Yield
		93			75
		78			73

Nakamura, *J. Am. Chem. Soc.*, **1987**, *109*, 8056  
 Nakamura, *Org. Synth.*, **1987**, *66*, 43

# Acylation of Zinc Homoenoates

Synthesis of  $\gamma$ -ketoesters - Yoshida

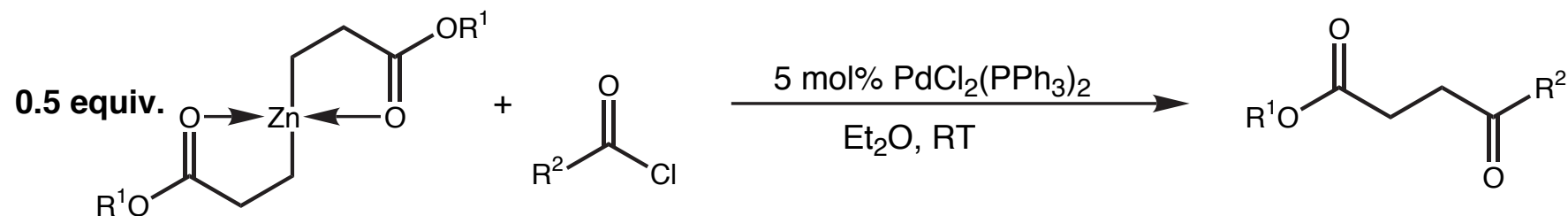


R	Yield
Ph	100
	90
	92
	100

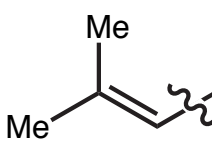
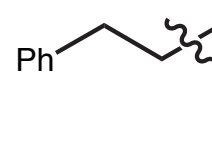
Yoshida, *Tetrahedron Lett.*, **1985**, 26, 5559

# Acylation of Zinc Homoenoates

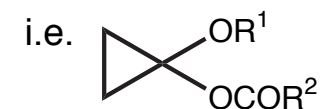
Synthesis of  $\gamma$ -ketoesters - Nakamura



- note: only 0.5 equiv. of Zn species needed so both homoenoates are transferred

R <sup>1</sup>	R <sup>2</sup>	Yield
Et	Ph	93
iPr		81
Et		83
iPr	tBu	50

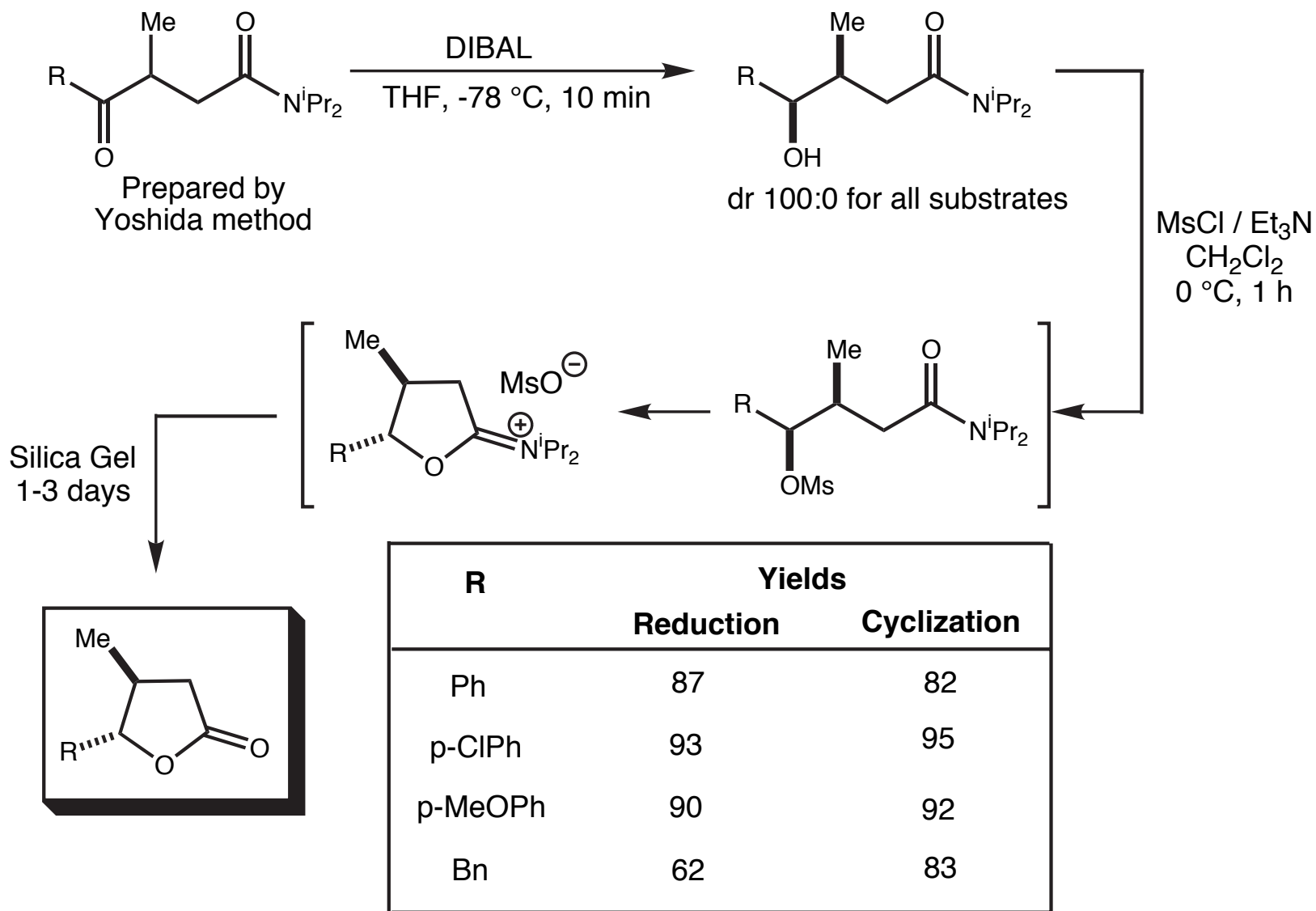
- when carried out in CDCl<sub>3</sub> got quantitative O-acylation (with or without Pd)



Nakamura, *J.Org.Chem.*, **1987**, 26, 8056

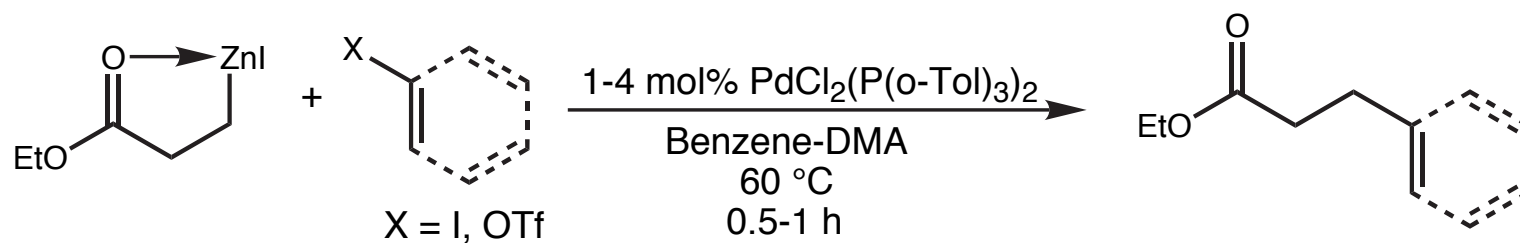
# Application of Homoenate Acylation

Synthesis of  $\alpha,\beta$ -disubstituted  $\gamma$ -butyrolactones by Diastereoselective Reduction



# Arylation and Vinylation of Zinc Homoenoates

Synthesis of  $\beta$ -vinyl and  $\beta$ -aryl esters - Yoshida



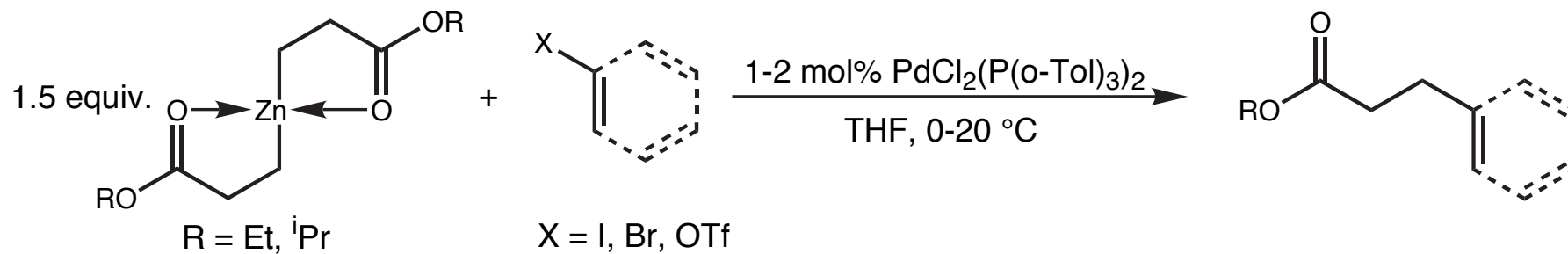
Coupling Partner	Yield
	74
	96
	67
	80


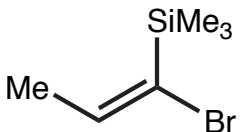
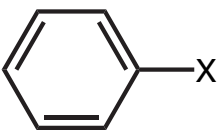
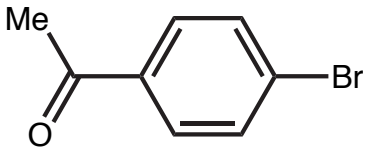
← Only vinylation example given

Yoshida, *Tetrahedron Lett.*, **1986**, 27, 955

# Arylation and Vinylation of Zinc Homoenoates

Synthesis of  $\beta$ -vinyl and  $\beta$ -aryl esters - Nakamura

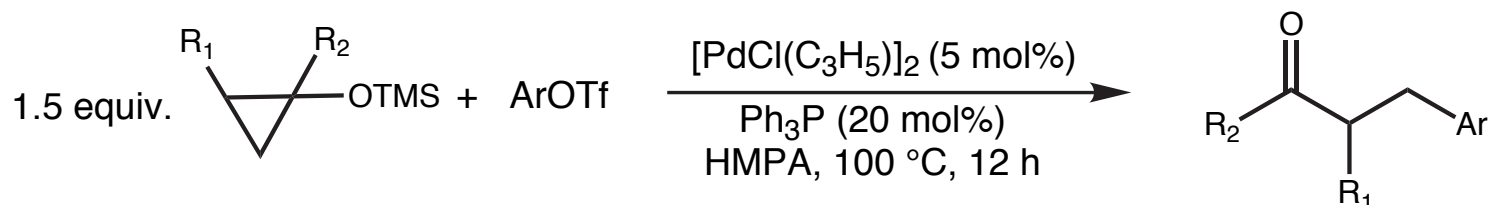


Coupling Partner	Yield
	90
	87
 X = OTf Br I	0 67 79
	49

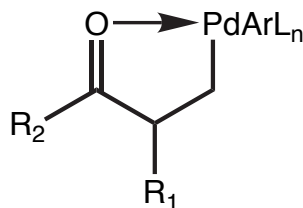
Nakamura, *J.Org.Chem.*, **1987**, 26, 8056

# Arylation of Palladium Homoenoletes

Catalytic Formation of  $\beta$ -aryl Ketones



• proposed to proceed via

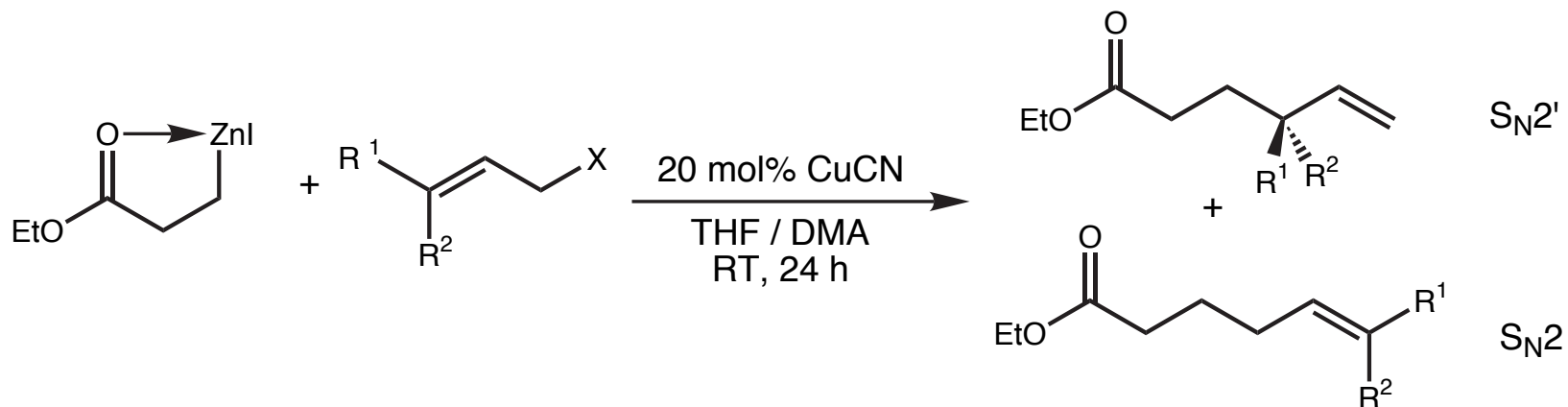


$R_1$	$R_2$	Ar	Yield
-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -	1-naphthyl	84
-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -	p-NO <sub>2</sub> Ph	68
H	p-OMePh	Phenyl	65
n-Heptyl	H	1-naphthyl	58

Nakamura, *J. Am. Chem. Soc.*, **1988**, 110, 3296

# Allylation of Zinc Homoenoates

Synthesis of  $\delta,\epsilon$ -unsaturated Esters - Yoshida

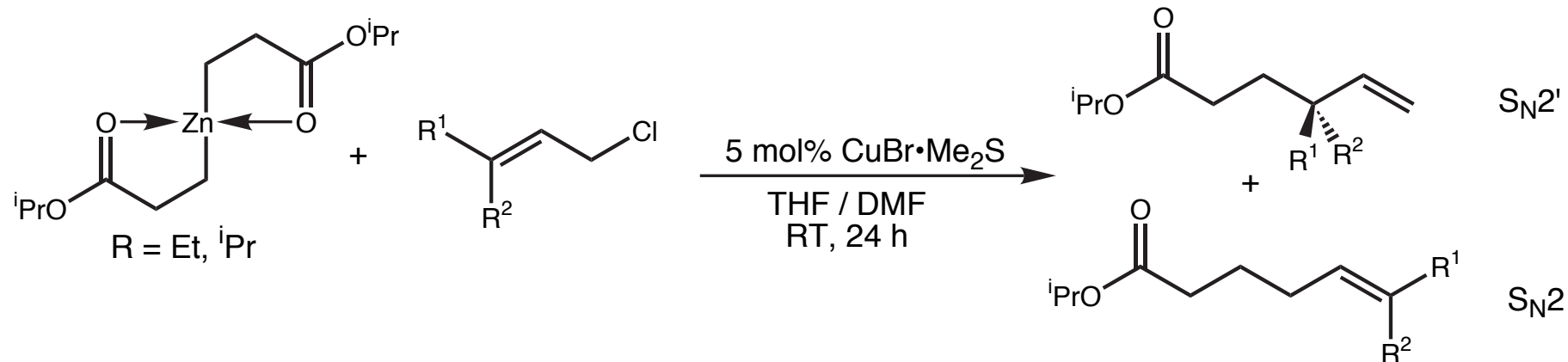


$R^1$	$R^2$	X	Yield	$S_N2' : S_N2$
H	H	OTs	89	--
Ph	H	OTs	80	87 : 13
		Br	93	88 : 12
		Cl	99	87 : 13
CO <sub>2</sub> Me	H	Br	80	100 : 0

Yoshida, *J.Org.Chem.*, **1987**, *52*, 4418

# Allylation of Zinc Homoenoates

Synthesis of  $\delta,\epsilon$ -unsaturated Esters - Nakamura

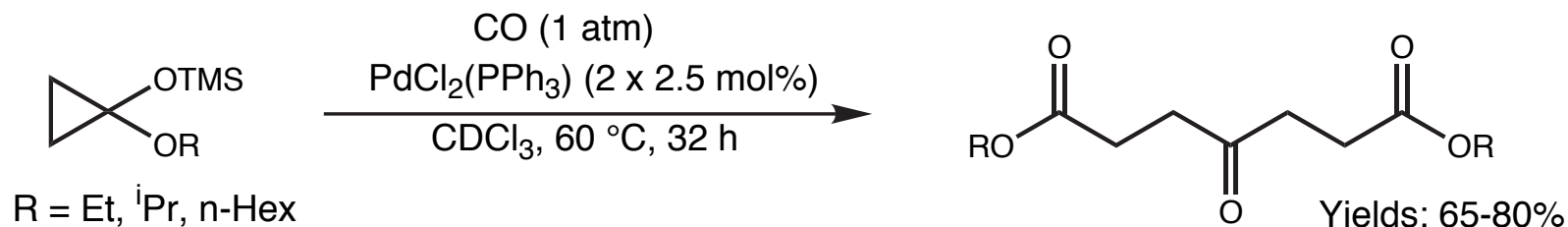


Allyl chloride	Yield	$S_N2'$ : $S_N2$
	97	96 : 4
	65	1 : 99
	81	88 : 12
	72	100 : 0

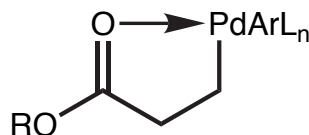
← Catalyst changed to 5 mol% NiCl<sub>2</sub>·dppe

# Carbonylative Symmetrical Coupling of Palladium Homoenoates

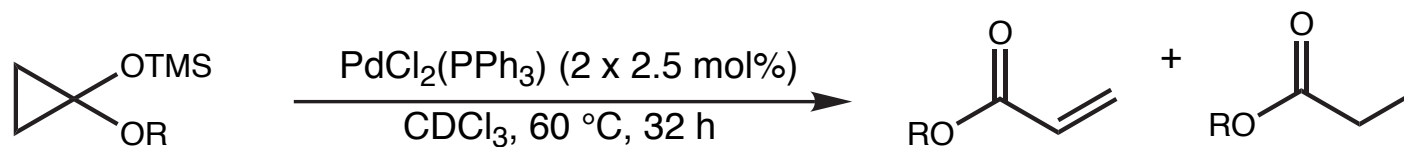
## Catalytic Synthesis of 4-keto Pimelates



- proposed to proceed via

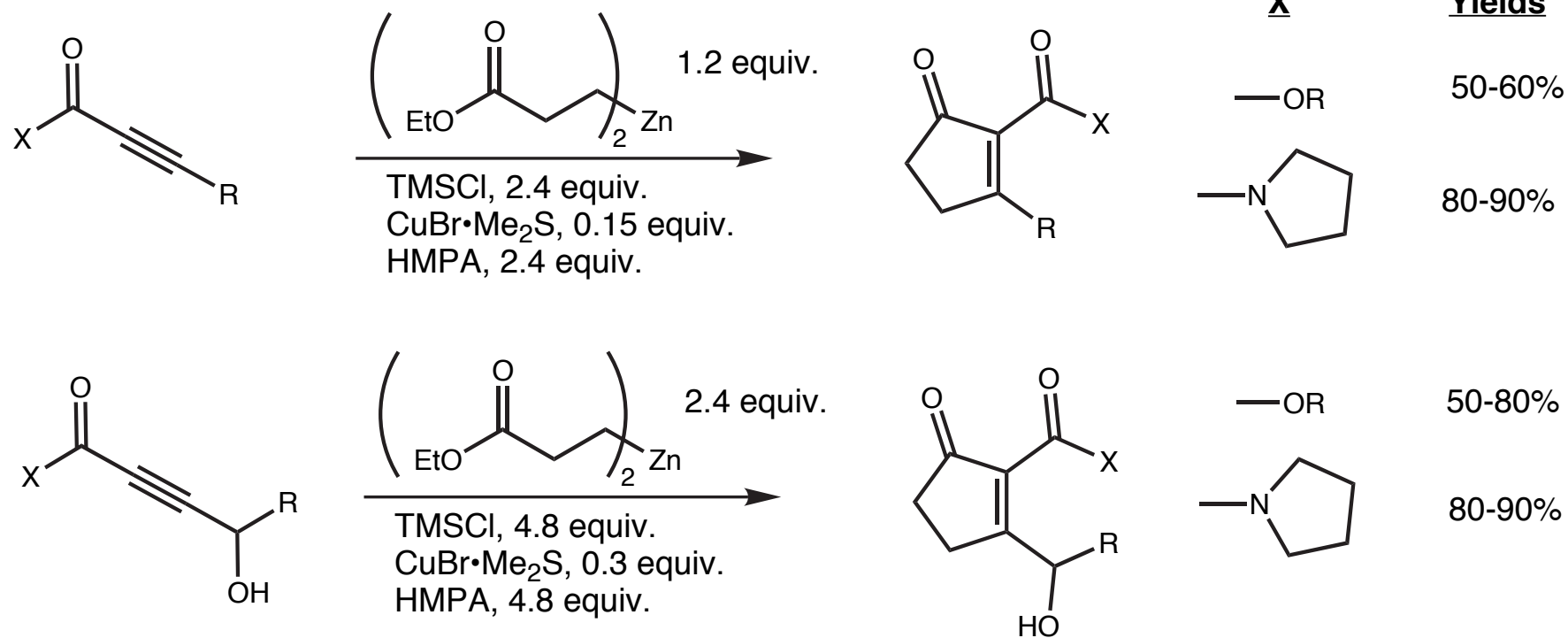


- evidence



# Crimmins' Cyclopentenone Synthesis

## Introduction and Generality

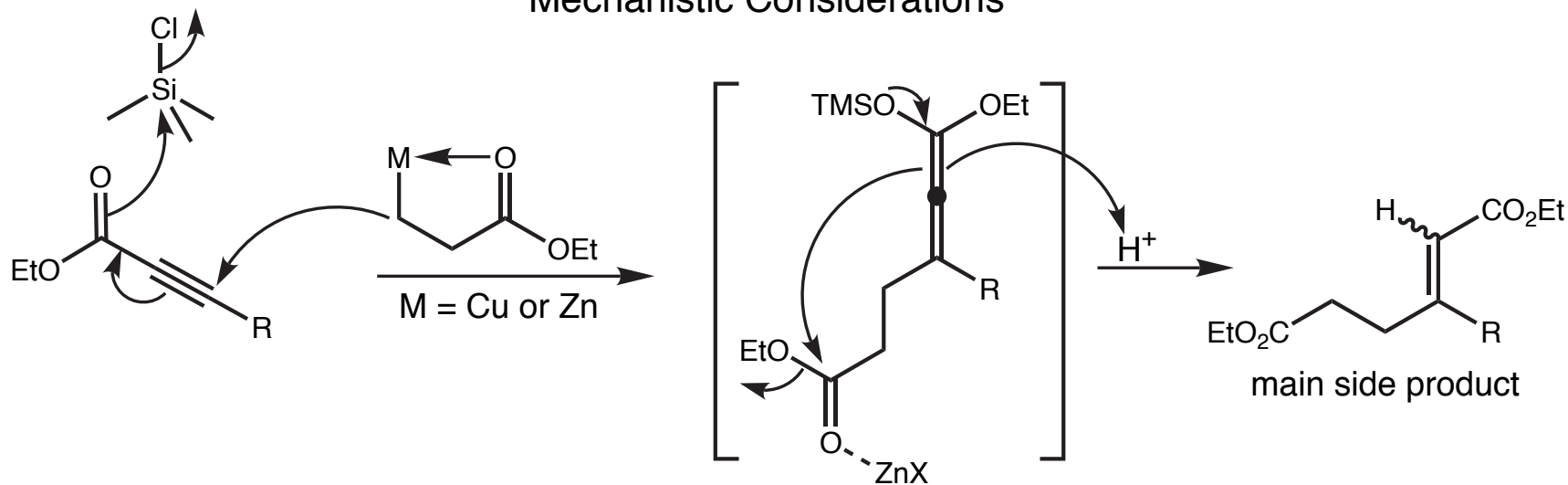


Functionality supported in R: ethers, epoxides, furans,  $\alpha,\beta$  unsaturated esters

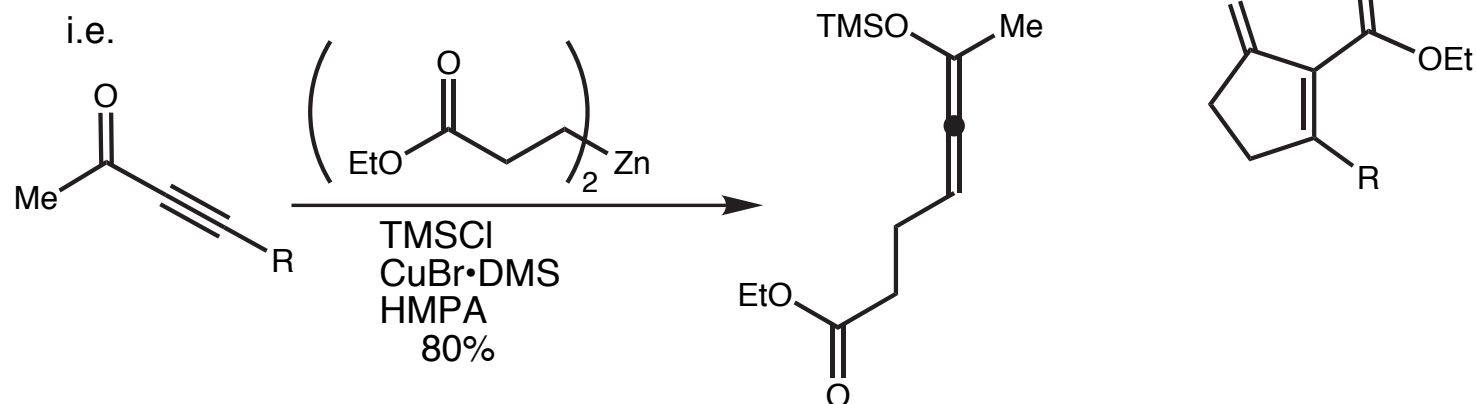
Crimmins, *J.Org.Chem.*, **1993**, 58, 1038

# Crimmins' Cyclopentenone Synthesis

## Mechanistic Considerations



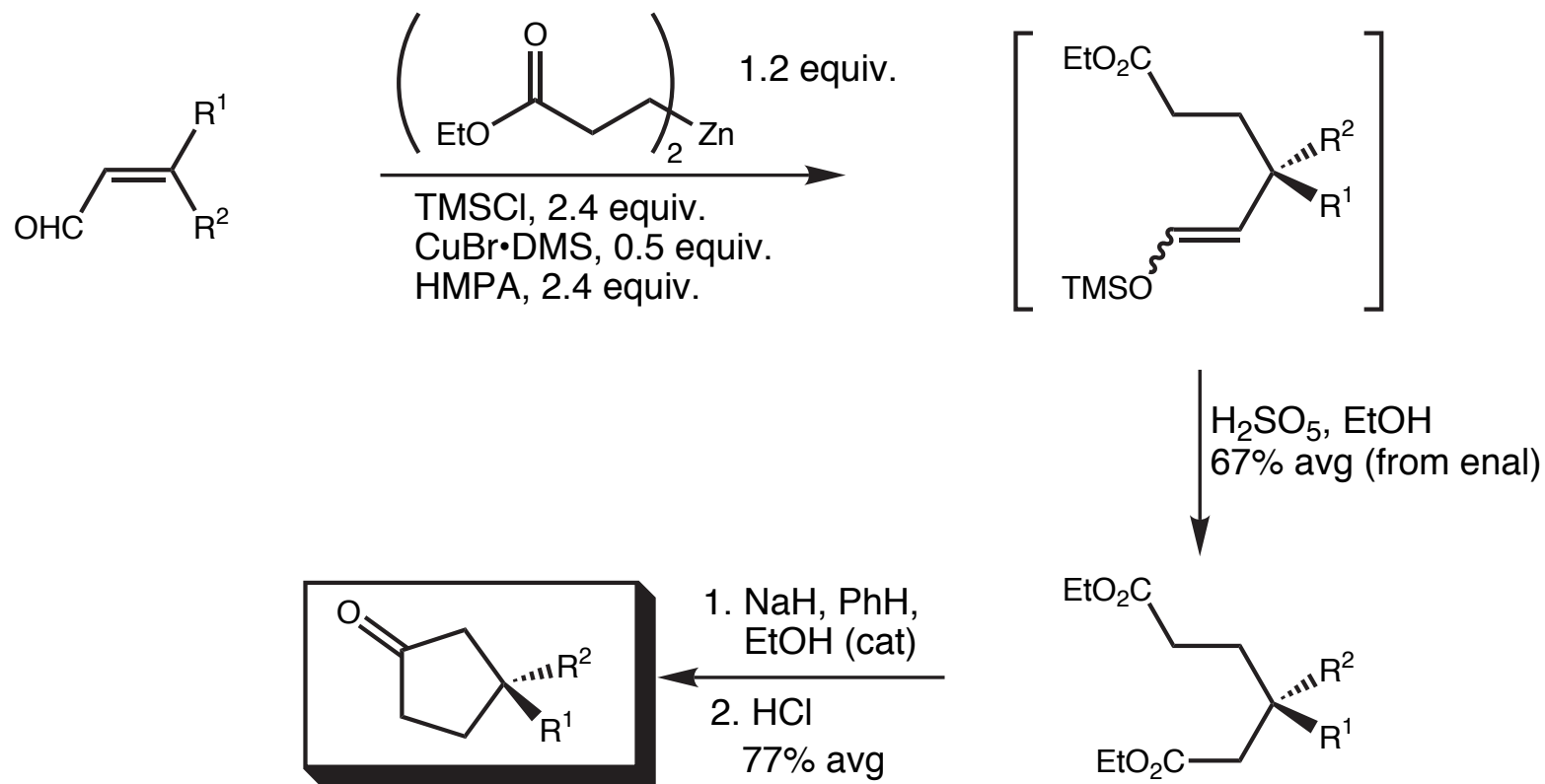
- problem: two steps have opposite electronic requirements
- appears amide and ester have right balance; ketone too electron poor to cyclize



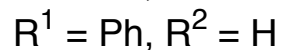
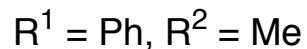
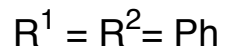
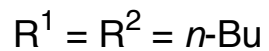
Crimmins, *J.Org.Chem.*, **1993**, *58*, 1038

# Leahy Cyclopentannulation

Synthesis of 3,3-disubstituted cyclopentanones



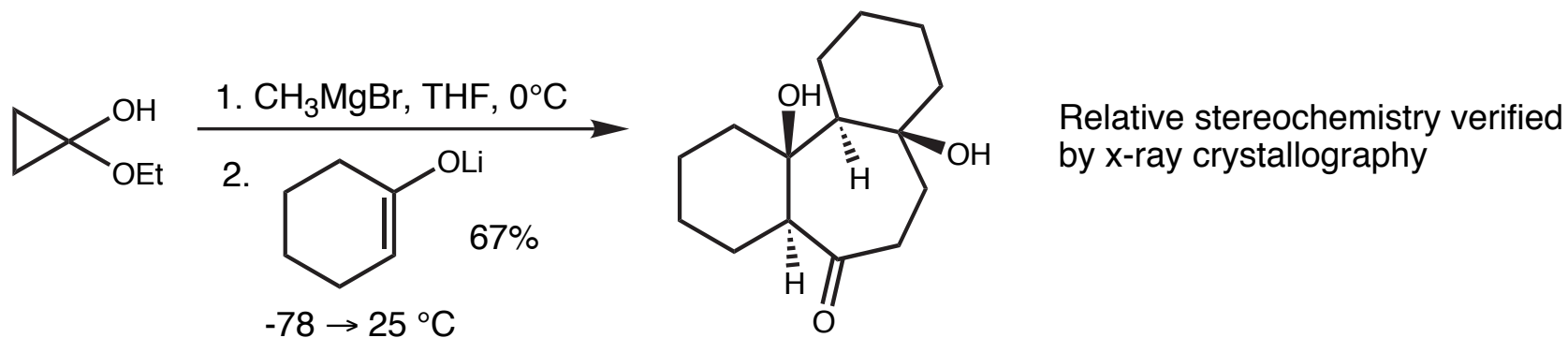
Substrates studied:



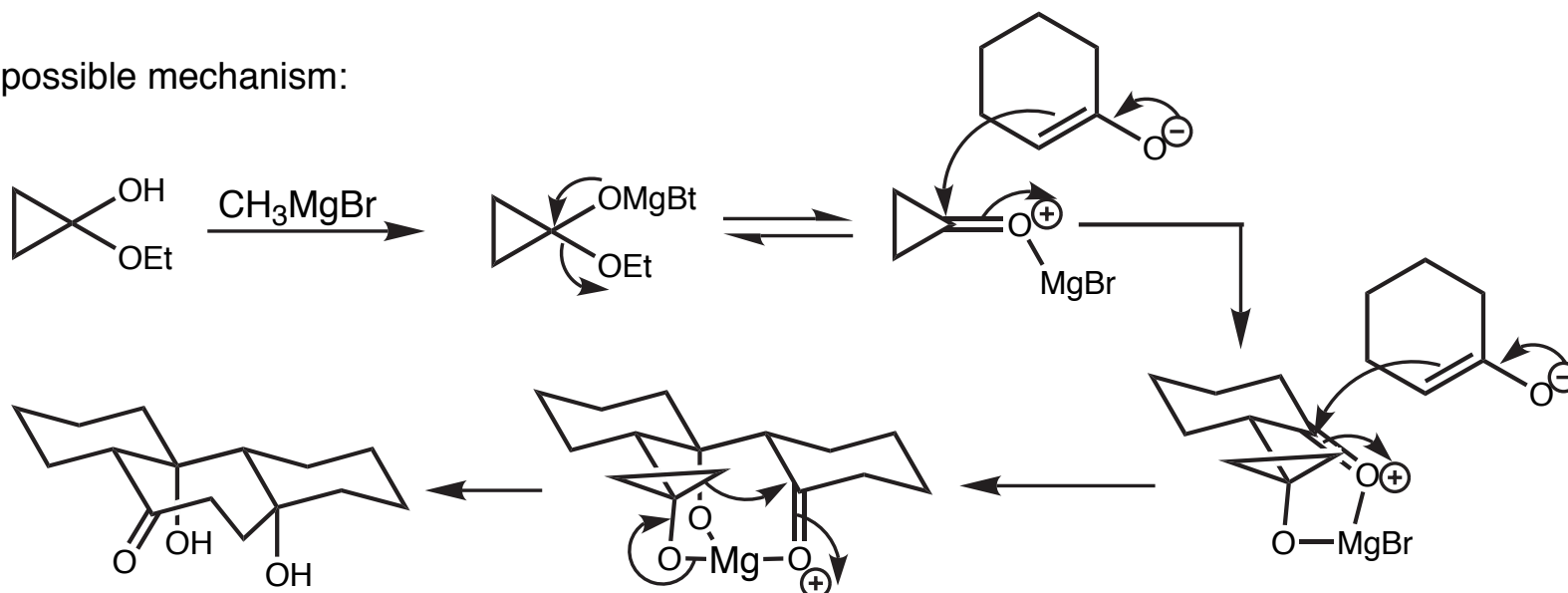
Leahy, *J.Org.Chem.*, **1994**, 59, 5496

# Tandem Aldol / Aldol / Homoaldol Reaction

One-pot synthesis of a 6,7,6-tricycle



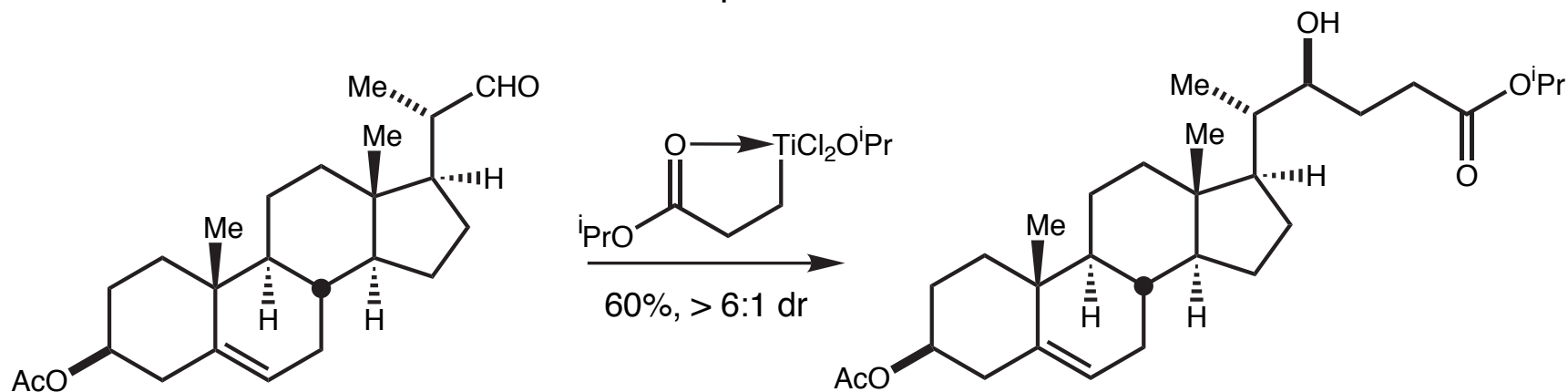
A possible mechanism:



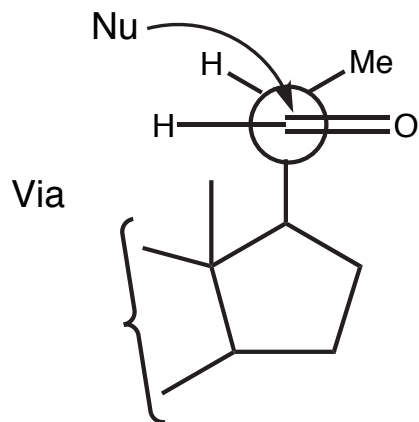
Helquist, *J.Am.Chem.Soc.*, **1986**, *108*, 8313

# Synthetic Examples

## Deprososterol



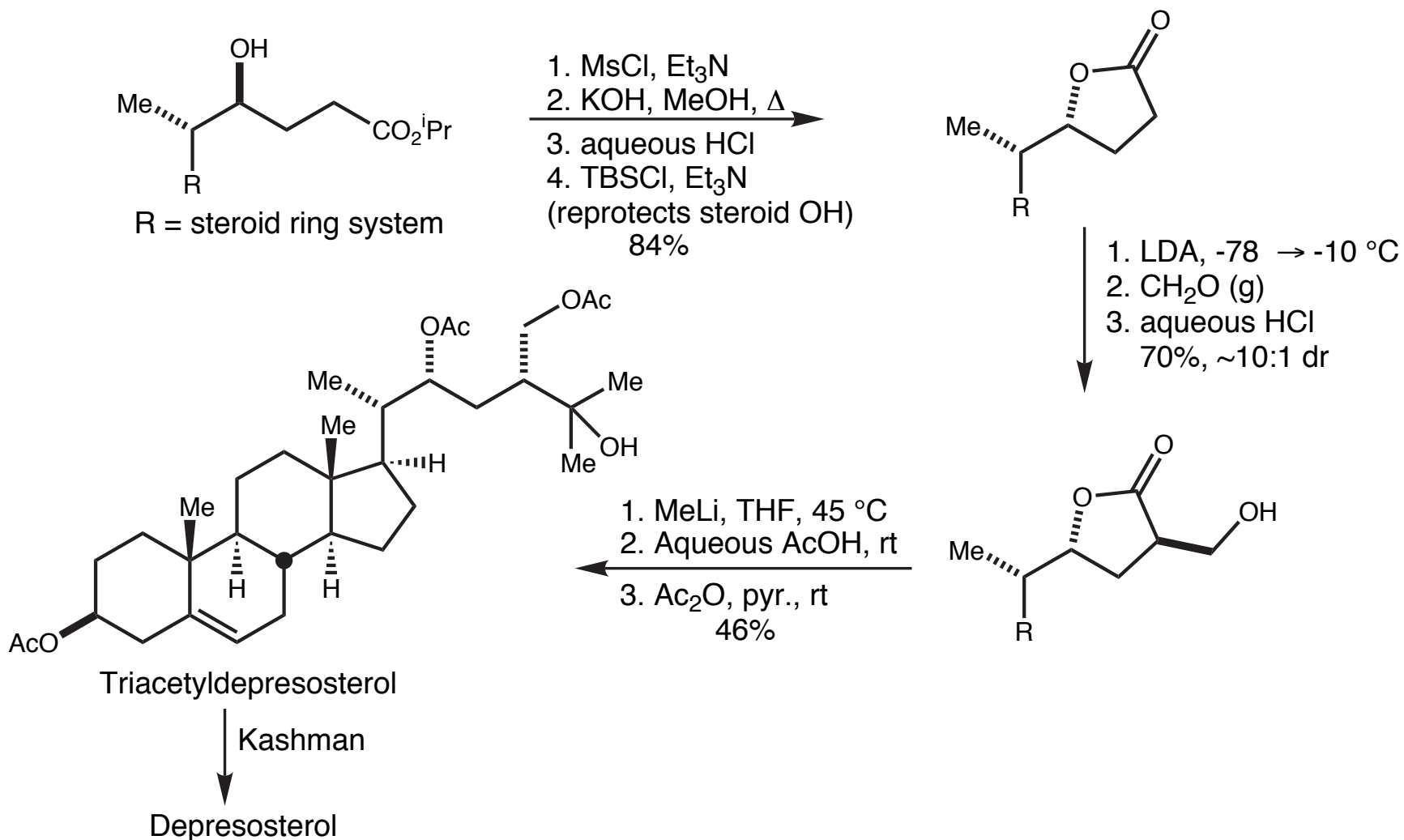
- trichlorotitanium homoenolate is not reactive enough to add to hindered aldehyde



Nakamura, *J. Am. Chem. Soc.*, **1985**, *107*, 2138

# Synthetic Examples

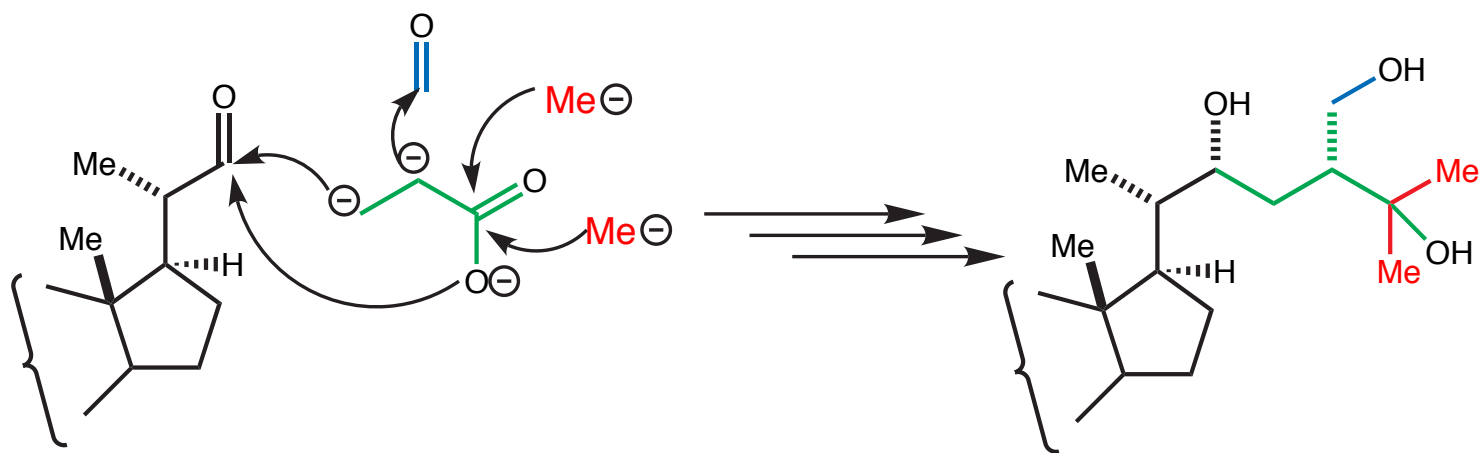
Deprososterol - completion of the formal synthesis



Nakamura, *J. Am. Chem. Soc.*, **1985**, 107, 2138  
Kashman, *Tetrahedron*, **1981**, 37, 2397

# Synthetic Examples

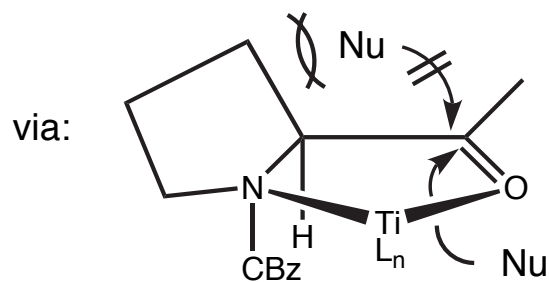
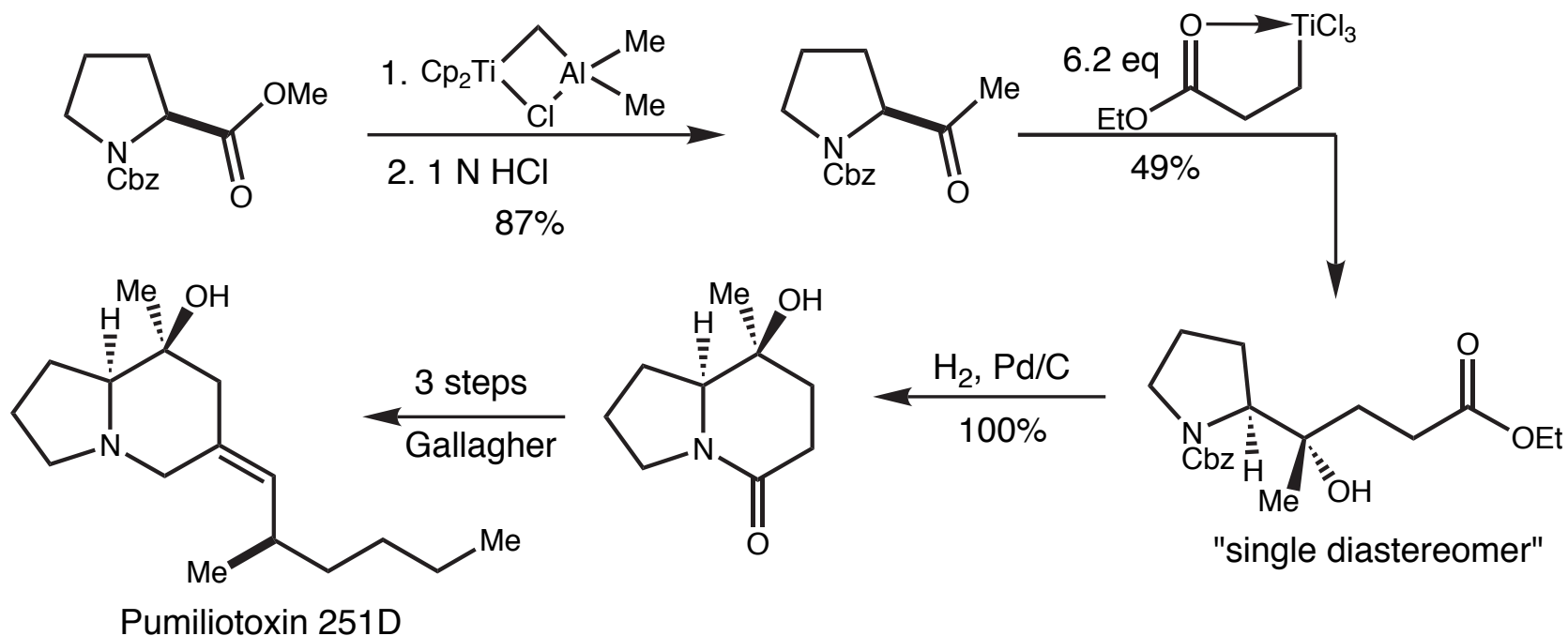
## Deprososterol - Maximizing Homoenolate Functionality



Nakamura, *J.Am.Chem.Soc.*, **1985**, 107, 2138

# Synthetic Examples

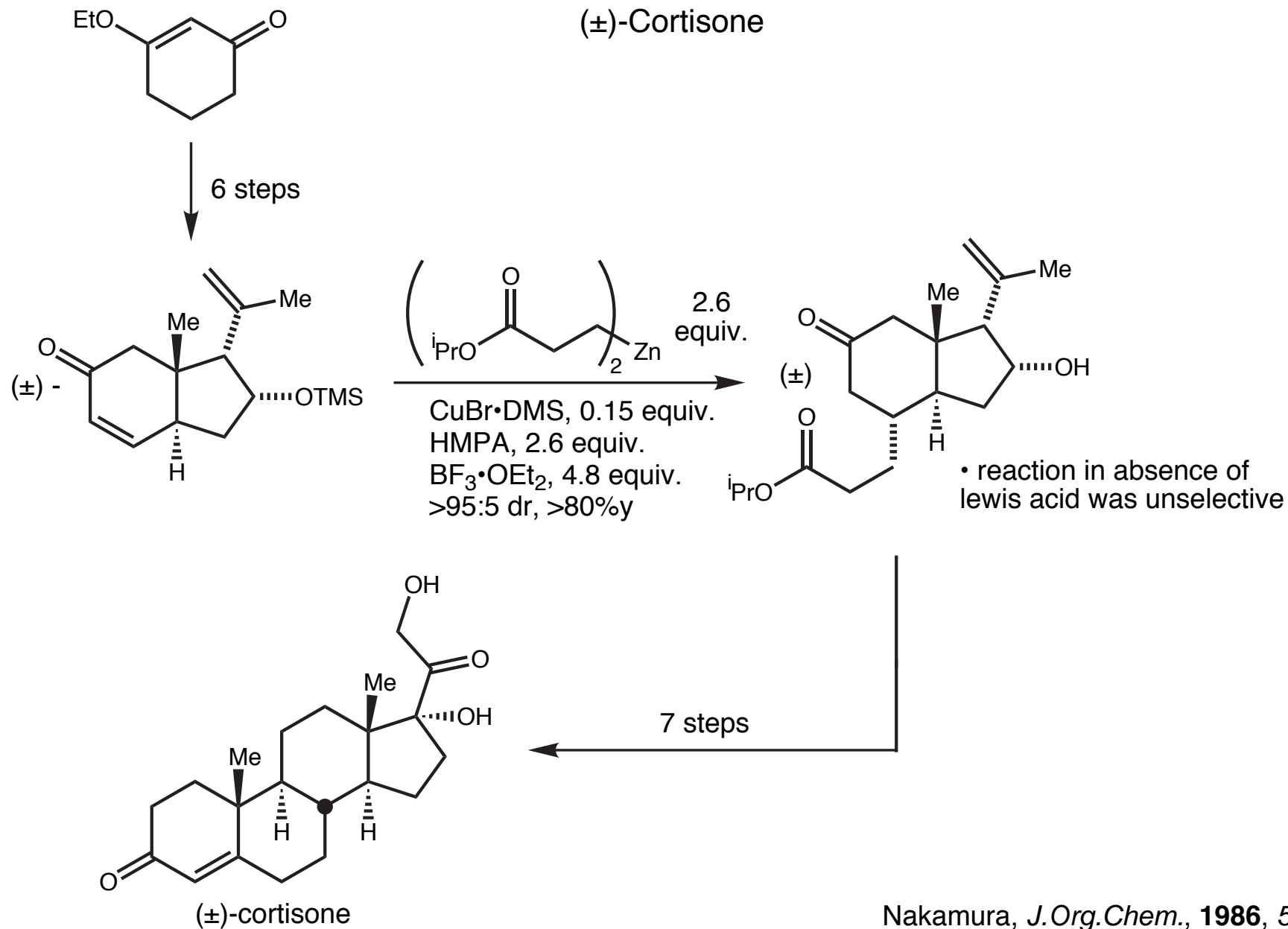
## Pumiliotoxin 251D



Barrett, *J.Org.Chem.*, **1999**, *64*, 1410  
Gallagher, *J.Am.Chem.Soc.*, **1991**, *113*, 2652

# Synthetic Examples

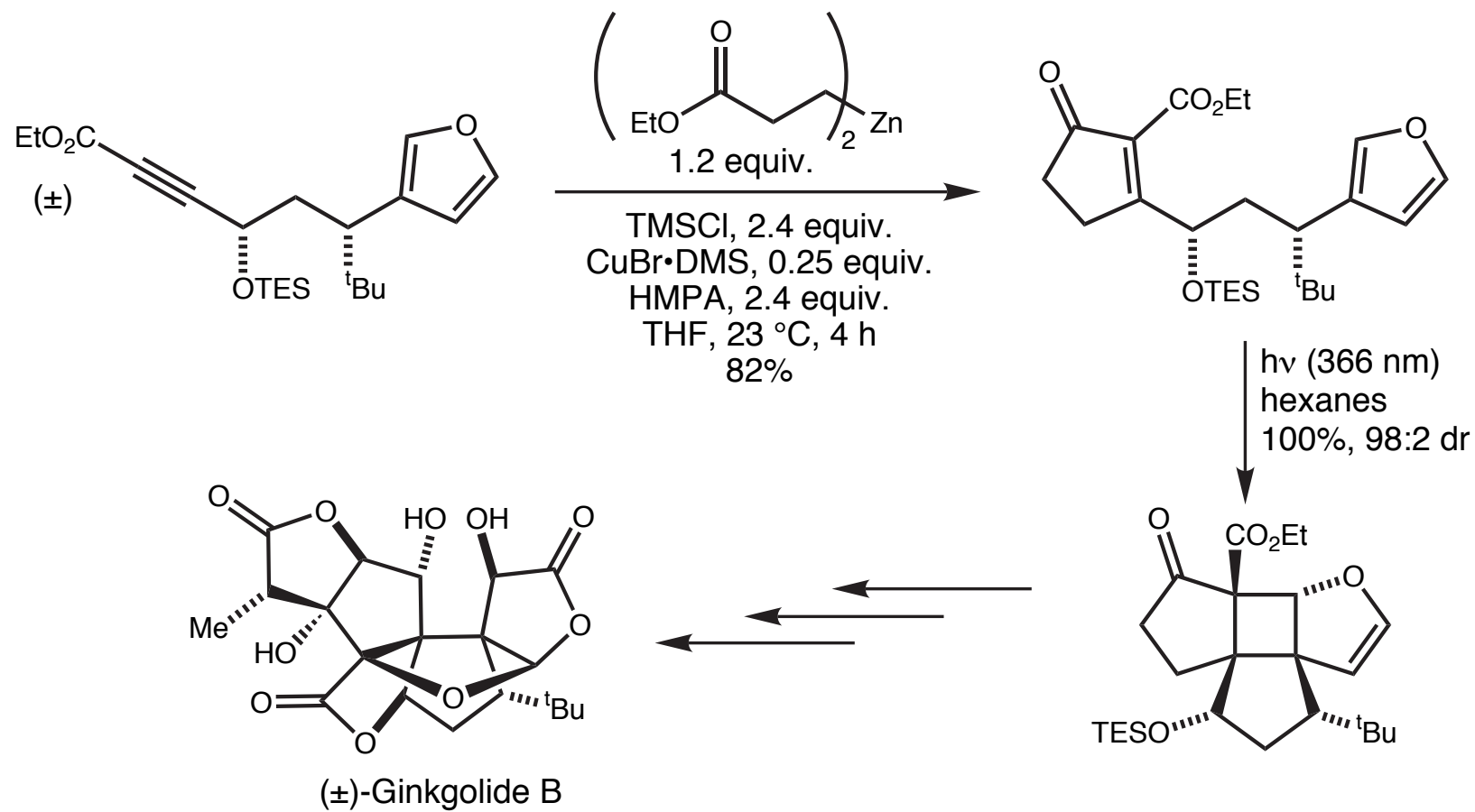
(±)-Cortisone



Nakamura, *J.Org.Chem.*, **1986**, 51, 4324

# Synthetic Examples

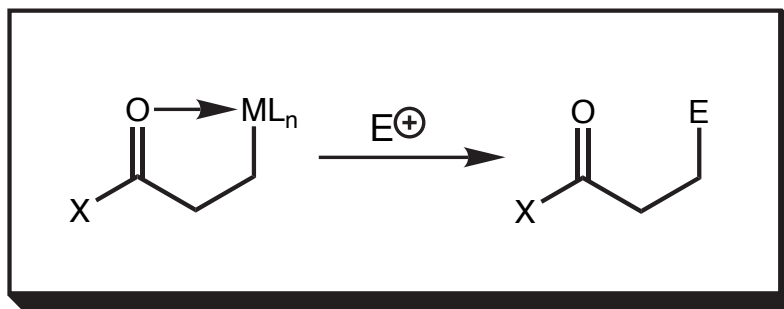
## (±)-Ginkgolide B



Crimmins, *J.Am.Chem.Soc.*, **1999**, 121, 10249

# Homoenolate Chemistry

## A Summary



- homoenolates are synthesized by cyclopropane ring-opening or oxidative addition of  $\beta$ -iodoesters
- titanium homoenolates useful for homoaldol reactions; reactivity can be tuned by  $Ti(OR)_4$  additives
- zinc homoenolates far more useful: can undergo Pd coupling reactions and conjugate additions as well as homoaldol reactions, although latter two require TMSX due to lower reactivity when compared to Ti
- catalytic homoaldol reactions now possible (for Ti and Zn)  $\rightarrow$  enantioselective variants on the horizon?
- synthetic applications, while limited thus far, illustrate functional diversity of homoenolate adducts