

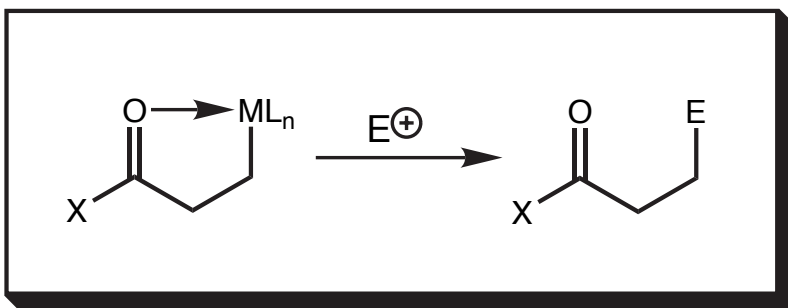
Homoenolates

Synthesis and Applications

Evans Group Seminar

March 24, 2000

Jason Burch



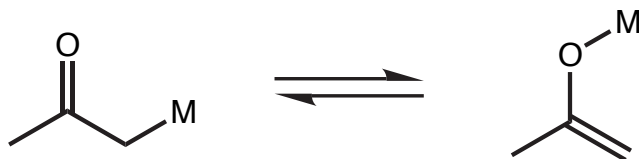
- I. Enolates, Homoenolates and Homoenolate Equivalents
- II. Synthesis of Homoenolates
- III. The Homoaldol Reaction
- IV. Coupling Reactions
- V. Other Reactions
- VI. Synthetic Applications

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

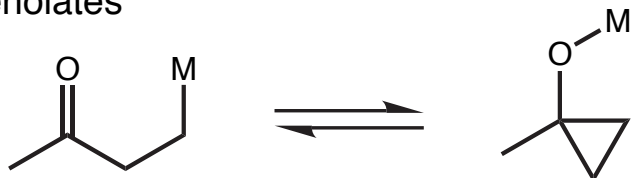
The Tautomerism Problem

- Enolates



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

- Homoenolates

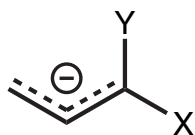
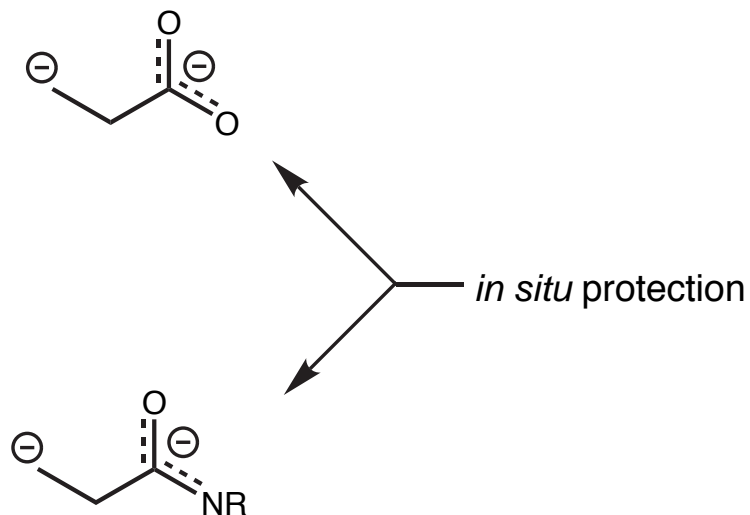
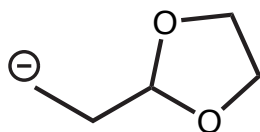


- tautomerism is a much larger problem because it is often irreversible and oxyanionic tautomer rarely acts as a carbon nucleophile

Homoenolate Equivalents

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

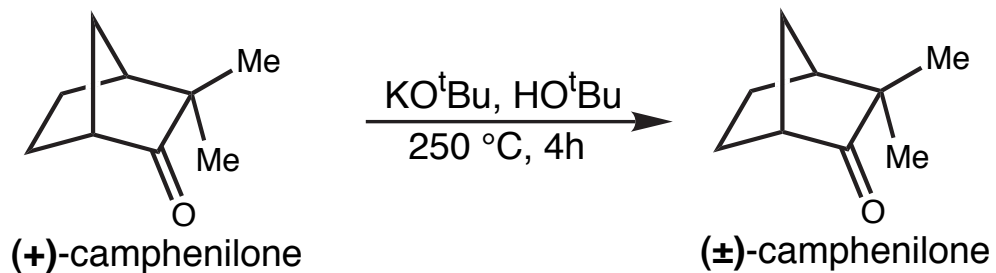
Examples:



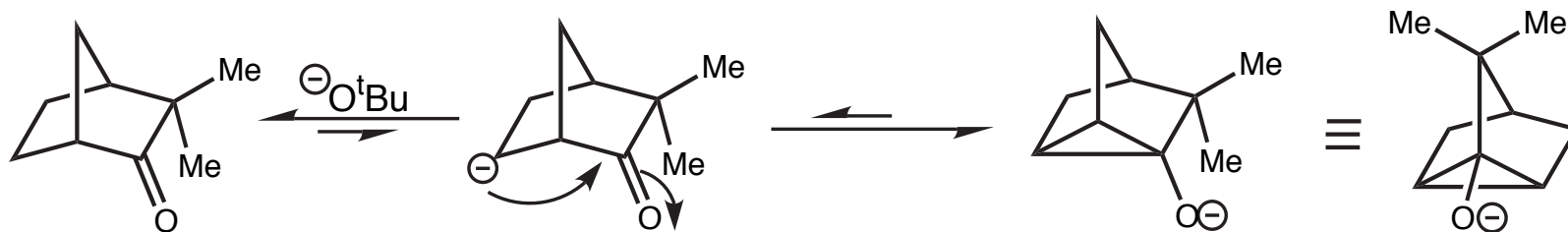
X = OR, NR₂, etc.
Y = H, R, OR, NR₂, etc.

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

The First "Homoenolate"



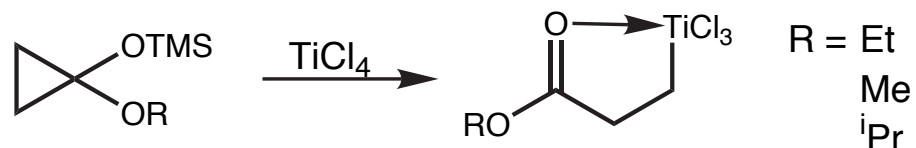
- no racemization occurred in >4 days at 250 °C in the absence of base
- proposed to proceed via a "homoenolate anion"



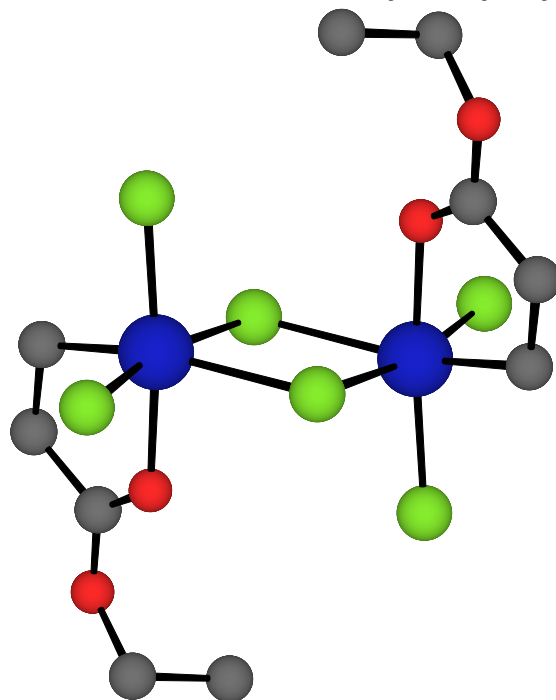
Nickon, *J.Am.Chem.Soc.*, **1962**, *84*, 4604

Cyclopropane Ring Opening

Synthesis of Titanium Homoenolates



- if conducted in 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 (\AA):

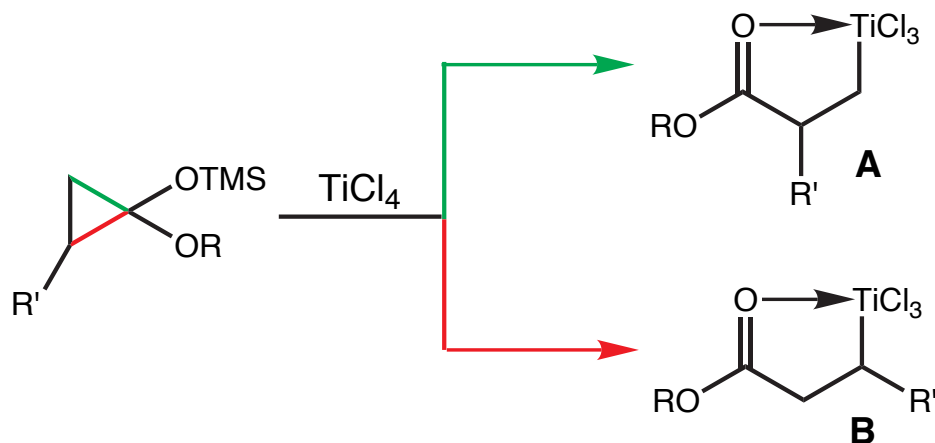
Ti-C	2.081
Ti-O	2.072
C=O	1.235

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

Cyclopropane Ring Opening

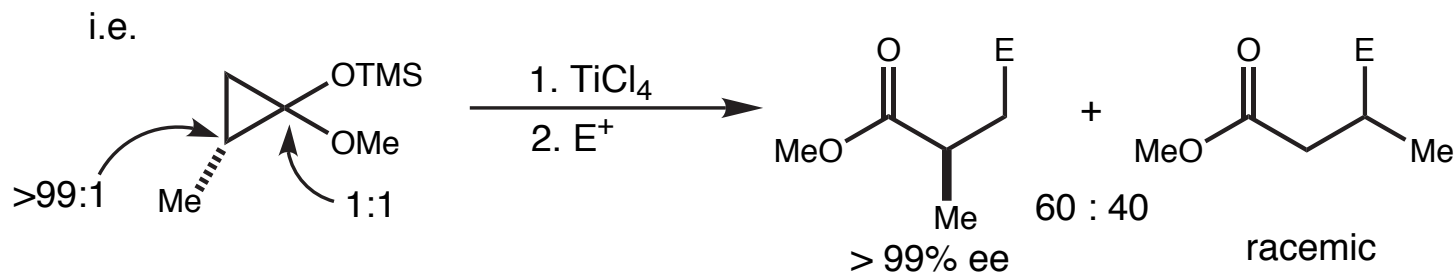
Regioselectivity of Ring Cleavage - Titanium

- 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

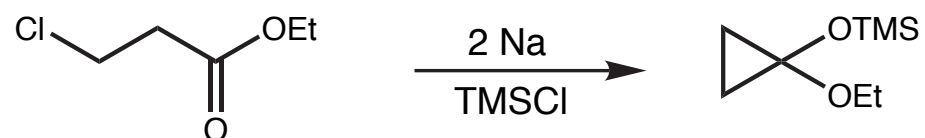
- A** can be isolated, but **B** is too unstable; only detected by *in situ* quench with electrophiles (i.e. Br₂, RCHO)
- if non-racemic starting material is used, quench with electrophiles indicates non-racemized **A** and totally racemic **B**



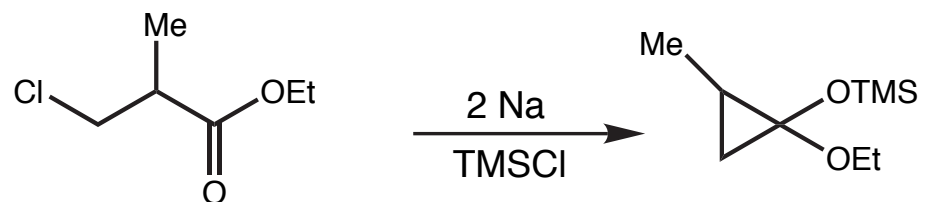
Nakamura, *J. Am. Chem. Soc.*, **1986**, 108, 3749

Cyclopropane Synthesis

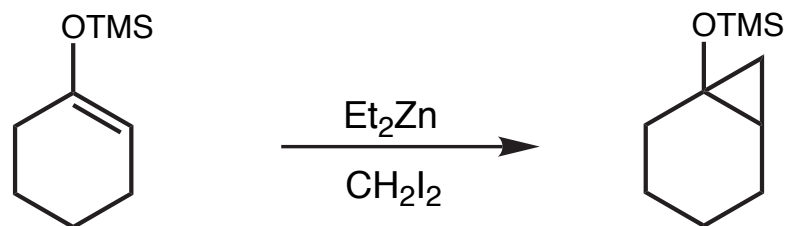
- most common method



- used to prepare substituted cyclopropanes



- use Simmons-Smith for ketone-derived substrates

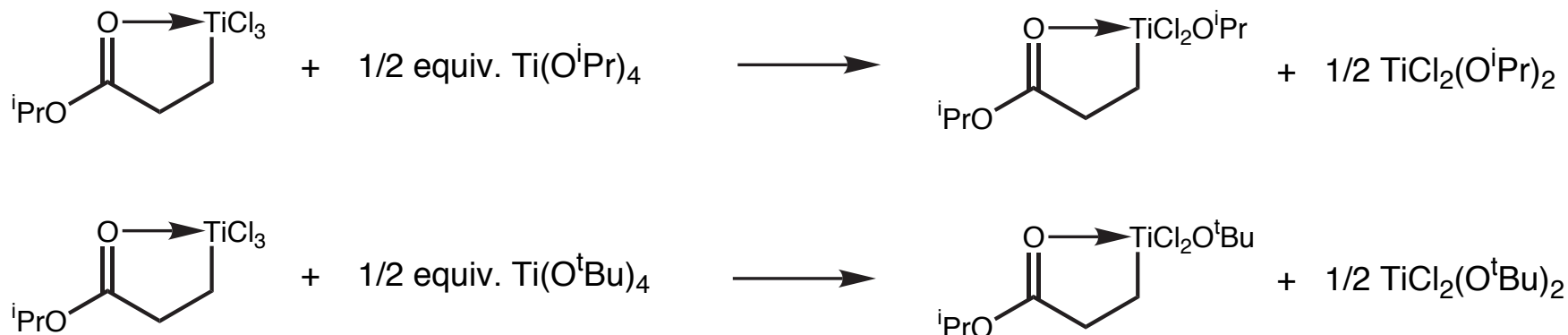


Ruhlmann, *Synthesis*, **1971**, 236.
Salaun, *Org. Synth.*, **1985**, 63, 147
Murai, *J.Org.Chem.*, **1973**, 38, 4354

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



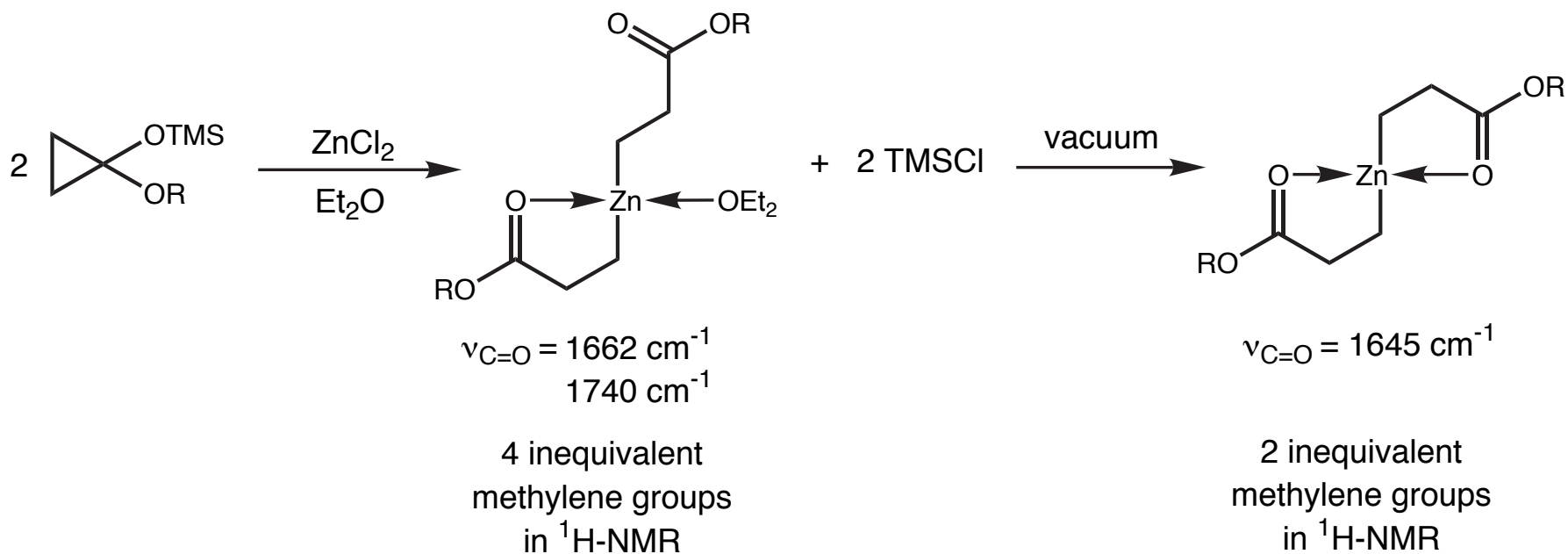
- Have not been characterized to the detail of the trichlorohomoenoates
- Appear to have "significant contribution from monomeric forms" (from molecular weight data)
- Are more reactive than trichloro homoenoates towards homoaldolisation

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

Cyclopropane Ring Opening

Zinc Homoenoates

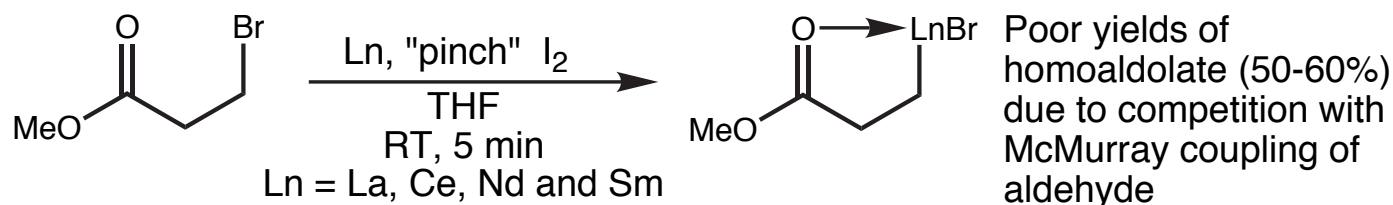
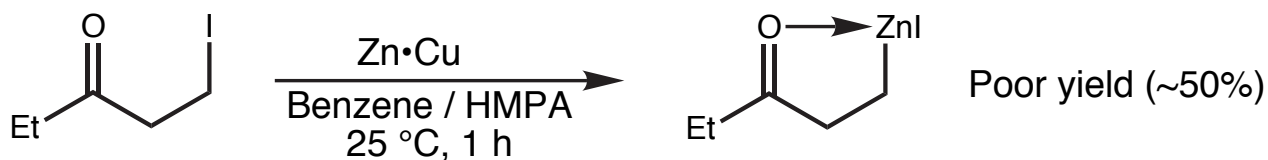
- Zinc homoenoates can be prepared in a similar method to titanium



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

Direct Oxidative Addition

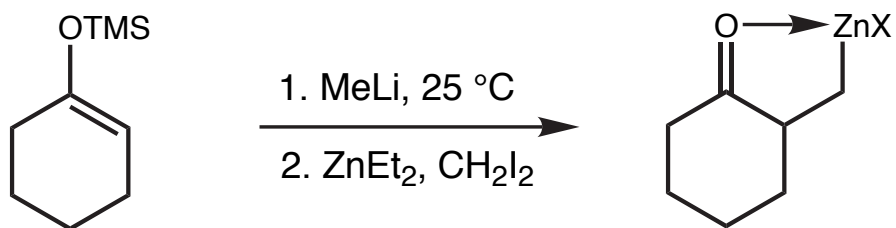
Zinc and Lanthanide Homoenoates



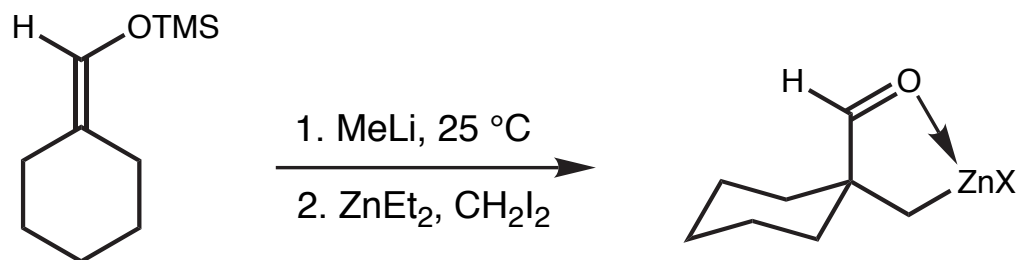
Yoshida, *Tetrahedron Lett.*, **1985**, 26, 5559
Yoshida, *Angew.Chem.,Int.Ed.Engl.*, **1987**, 26, 1157
Fukuzawa, *Chem. Commun.*, **1986**, 475

Enolate Homologation

Synthesis of Zinc Homo-enolates



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

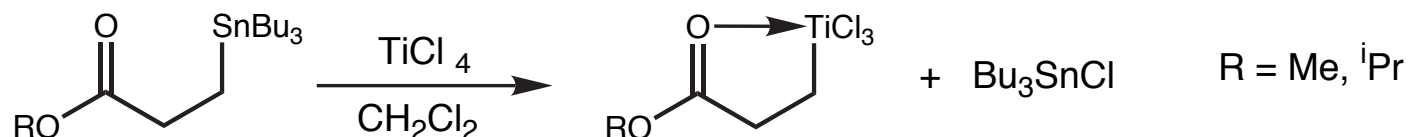


Knochel, *J.Org.Chem.*, **1993**, 58, 2694

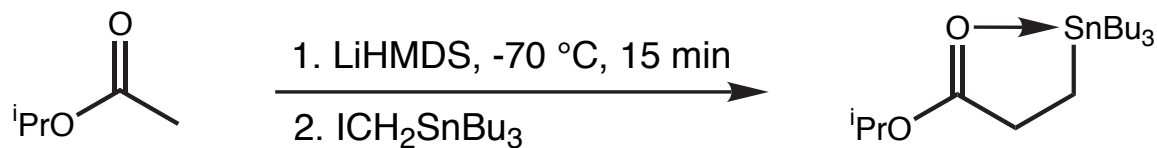
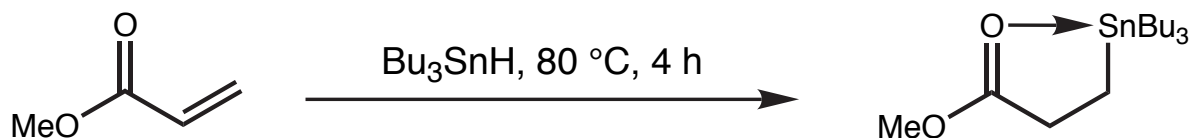
Direct Tin-Titanium Exchange

New Route to Titanium Homoenoates

- Treatment of β -tri-n-butylstannyl esters with TiCl_4 directly forms titanium homoenoate



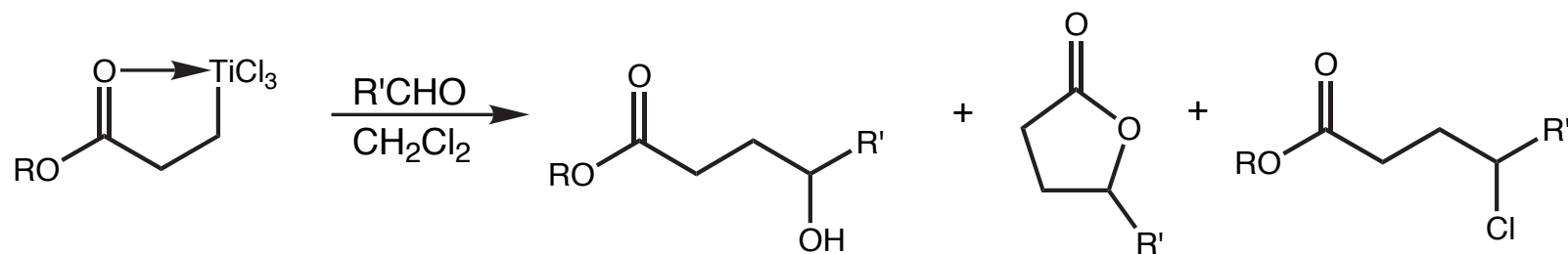
- Isotope labelling studies showed rxn does not proceed via cyclopropane
- Substrates can easily be prepared by two methods:



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 γ -hydroxyesters and γ -lactones

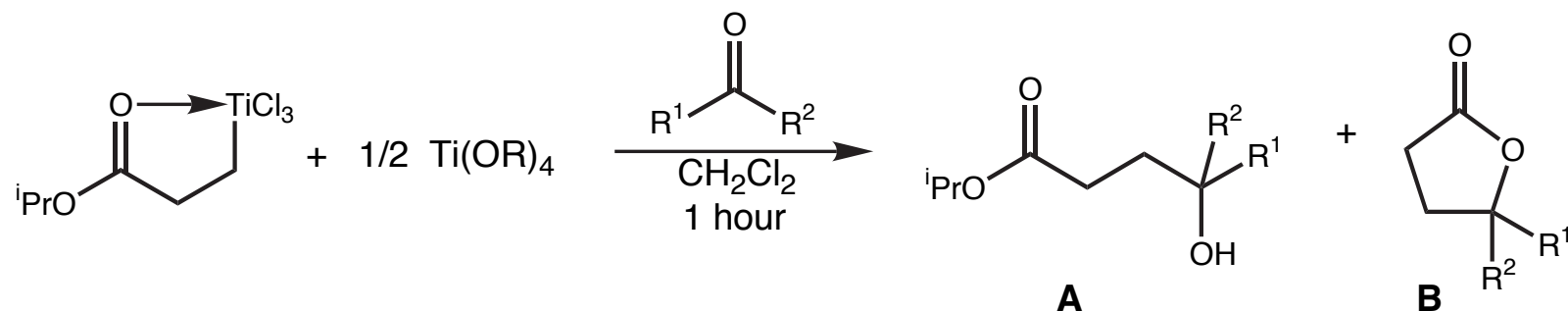


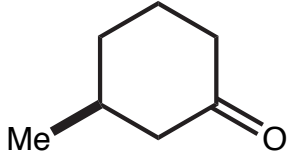
Aldehyde	R	Temp ($^{\circ}C$)	Time (h)	Workup	Product	Yield
	Et	0	1	Acidic		81
	iPr	0	2.5	Neutral		67 (85:15)
	Et	0	1.5	Neutral		90

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

Homoaldol Reactions with Alkoxide-modified Homoenolates

Homoaldol Reactions with Aromatic Aldehydes and Ketones

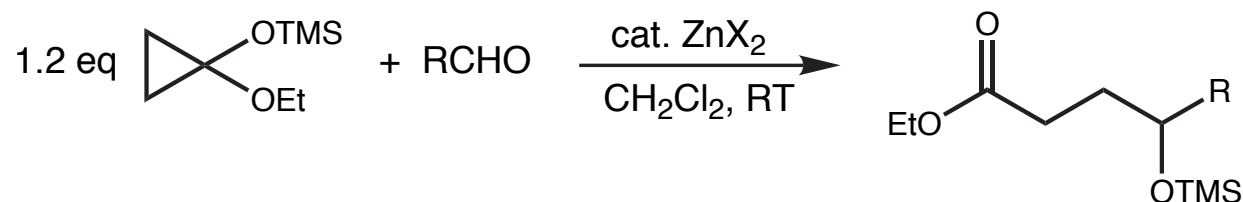


Electrophile	R	Temp(°C)	Yield (A or B)
Benzaldehyde	iPr	0	90(A)
Crotonaldehyde	iPr	0	88(A)
Acetophenone	iPr	20	66(A), 12(B)
	tBu	20	93(B)
Cyclohexanone	iPr	20	62(B)
	tBu	20	91(B)
	tBu	20	91(B)
			dr = 88 : 12 equatorial attack

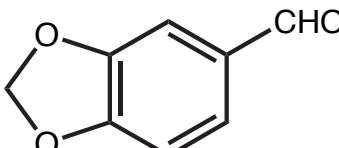

Nakamura, *J. Am. Chem. Soc.*, **1986**, 108, 3745

Homoaldol Reactions of Zinc Homoenolates

First Catalytic Homoaldol Reactions

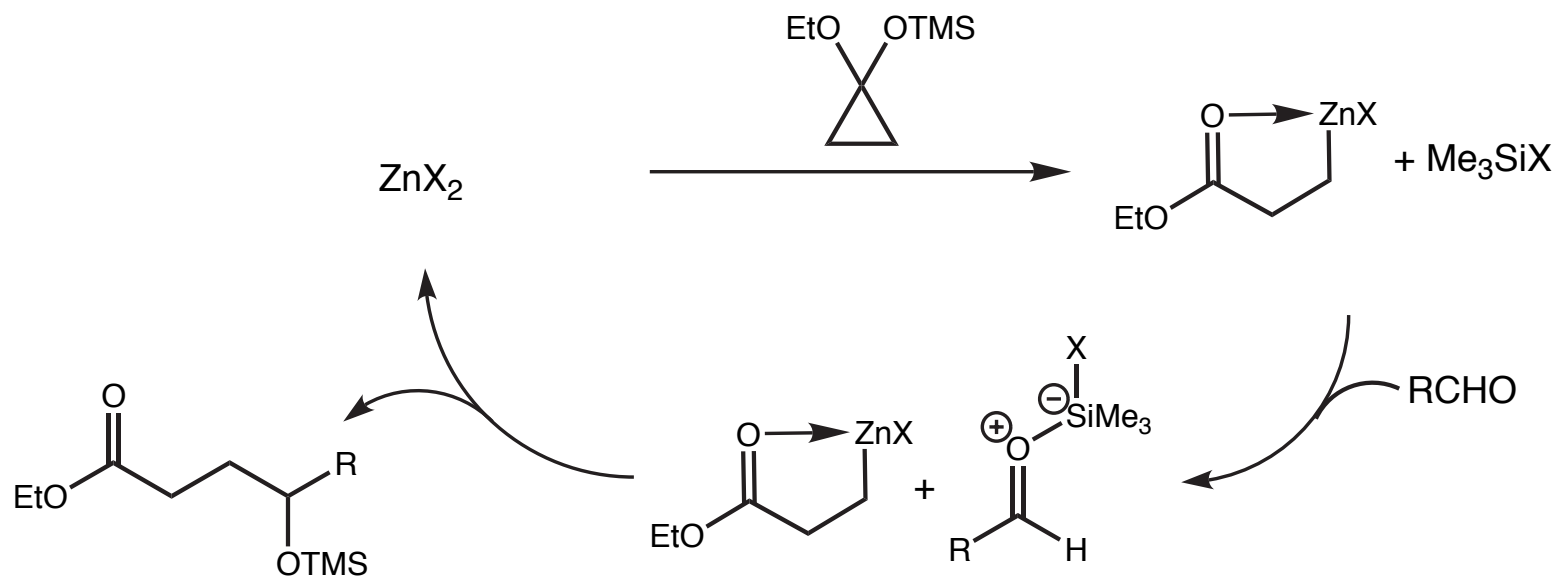


- TMSCl generated is essential (i.e. no reaction if removed *in vacuo* for stoichiometric case)

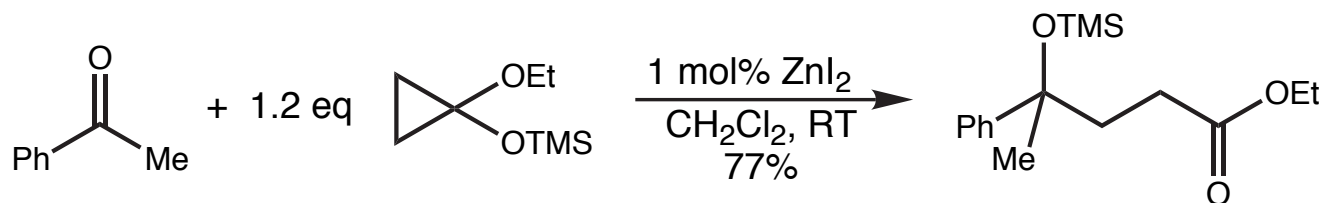
Aldehyde	Catalyst, yield	
	ZnCl ₂ (30-50 mol%)	ZnI ₂ (0.1-1 mol%)
PhCHO	84	89
Ph-CH=CH-CHO	94	84
	91	95
	--	84
n-Pent-CH(OBn)-CHO	79 93:7 <i>syn</i> : <i>anti</i> chelation product	--

Homoaldol Reactions of Zinc Homoenoates

Proposed Catalytic Cycle



- with ZnI_2 , the homoenoate is reactive enough to add to ketones:

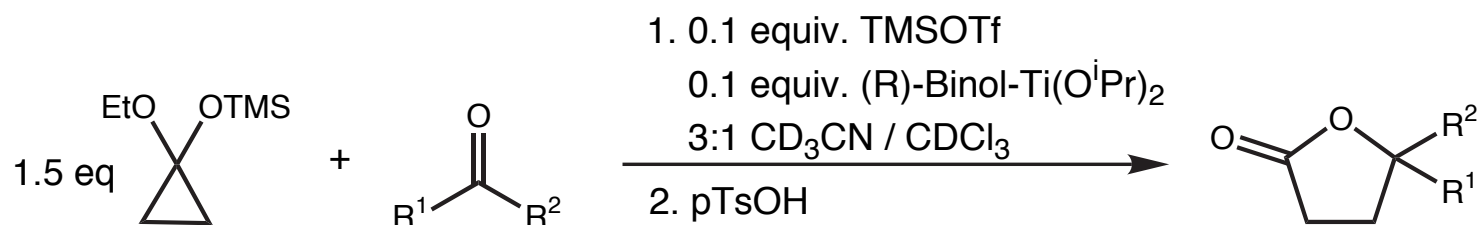




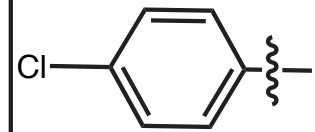
- no reaction even with stoichiometric ZnCl_2

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

Gleason's Homoaldol reaction

First Catalytic Titanium Homoaldol Reaction



R ¹	R ²	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
^t Bu	H	45-50 °C, 54 h ^a	52
Ph	Me	45-50 °C, 60 h ^a	78

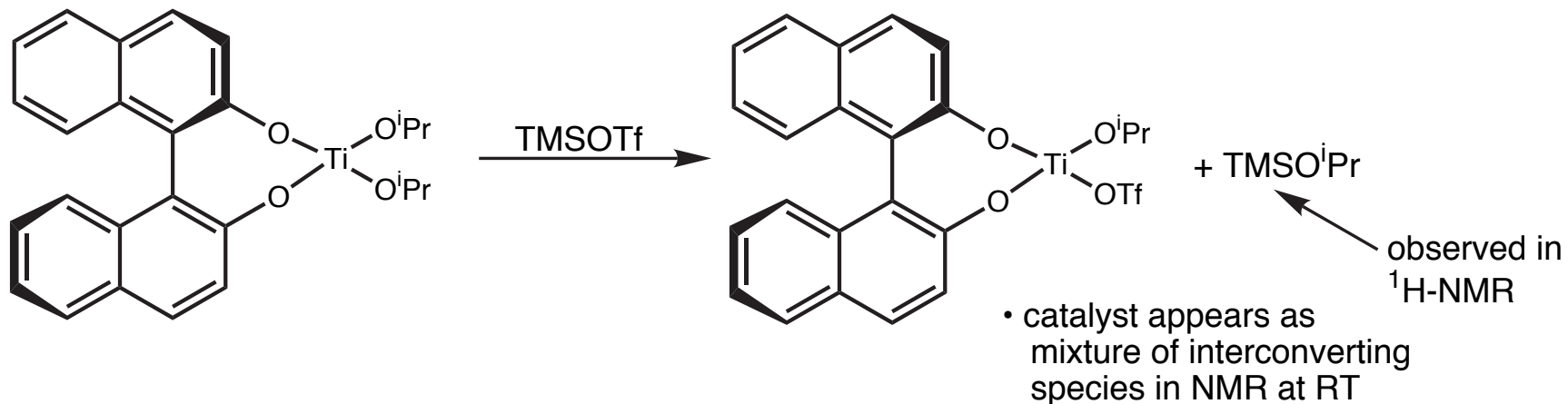
^a2 equiv. of cyclopropane used

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

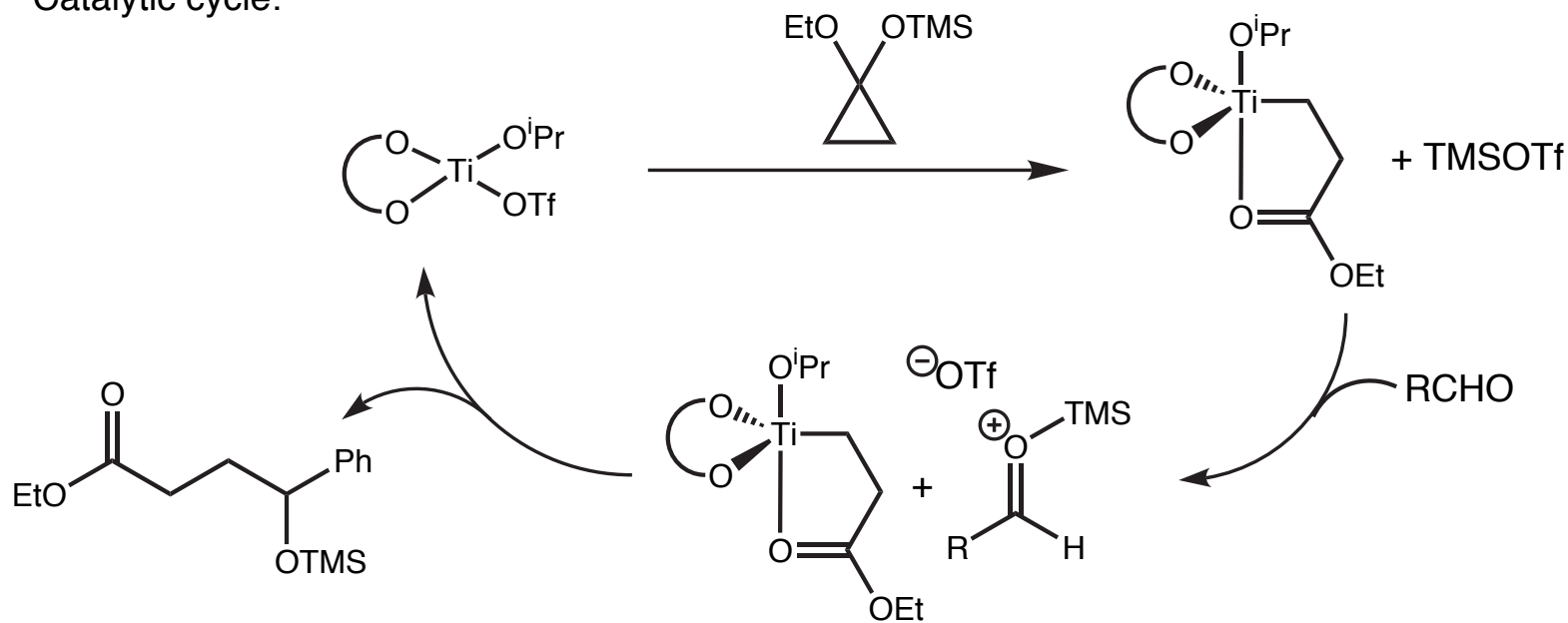
Gleason's Homoaldol reaction

Proposed Catalyst and Catalytic Cycle

Catalyst:



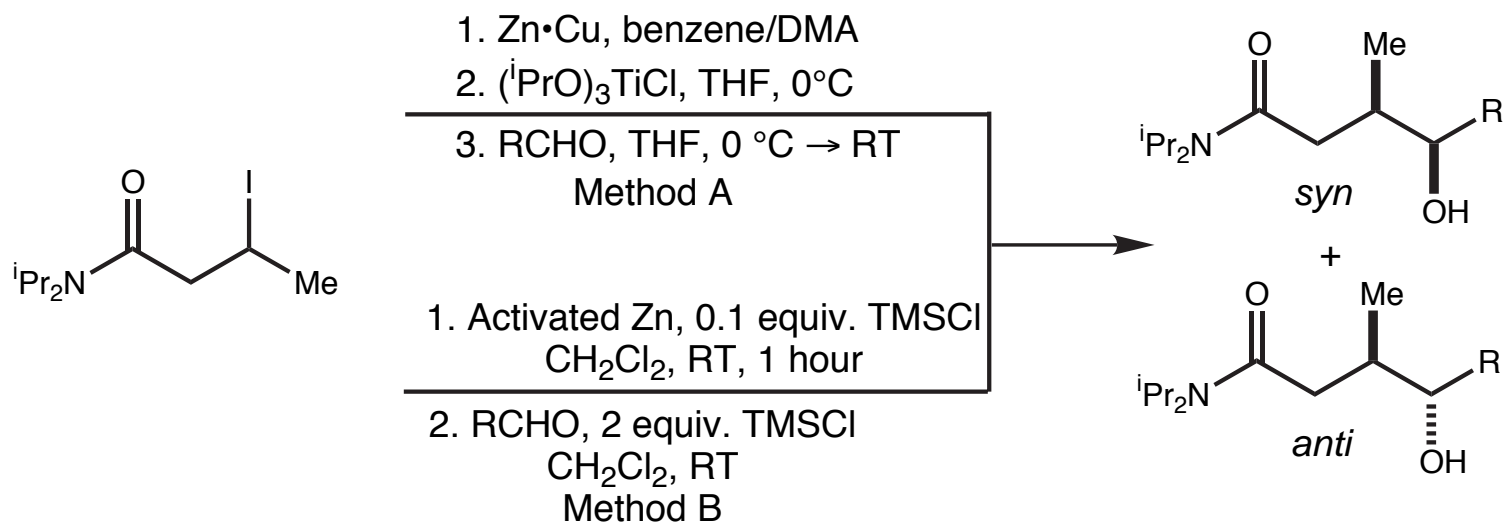
Catalytic cycle:



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

Diastereoselective Homoaldol Reactions of Amide-homoenolates

Synthesis of *syn*- or *anti*- β -methyl- γ -hydroxyamides



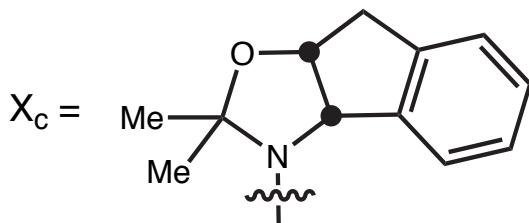
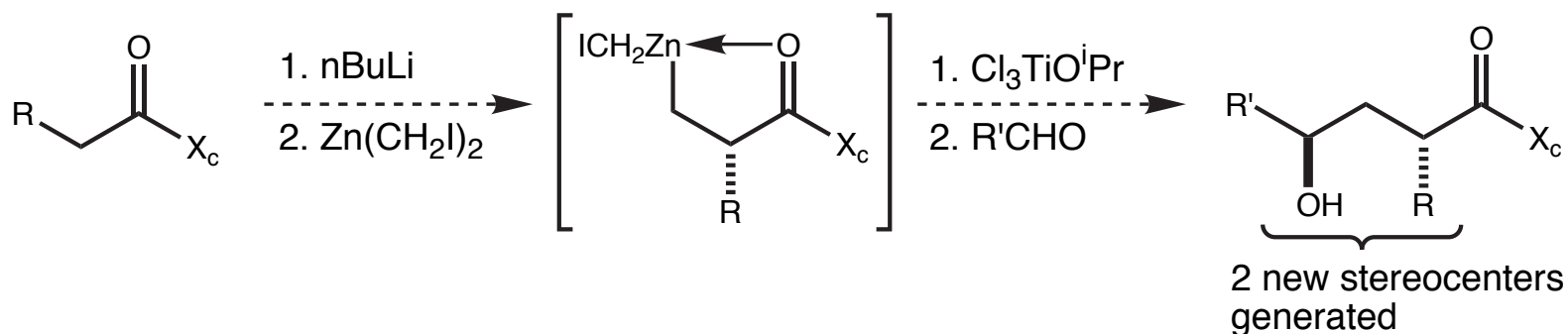
R	Method	Time (h)	Yield	<i>syn:anti</i>
Ph	A	3	79	94 : 6
	B	2.5	82	13 : 87
o-MeOPh	A	3	87	85 : 15
	B	0.6	95	25 : 75
2-furyl	A	0.5	61	96 : 4
	B	0.6	60	38 : 62

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

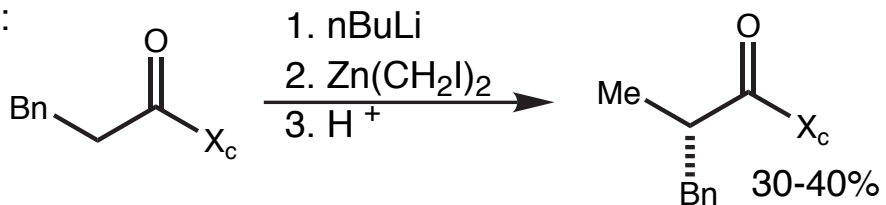
Tandem Asymmetric Enolate Homologation - Homoaldol Reaction

Asymmetric Synthesis of α -alkyl, γ -hydroxy Carbonyl Compounds

• idea:



• initial results:



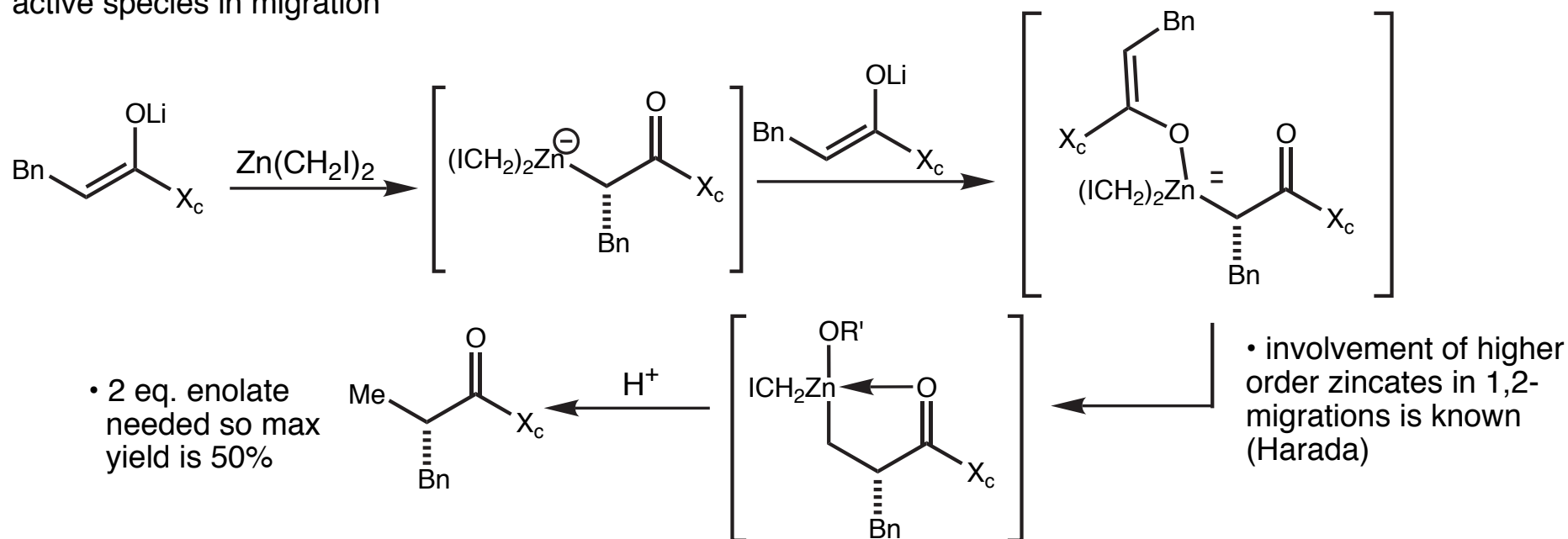
But ReactIR showed disappearance of enolate and appearance of new species

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

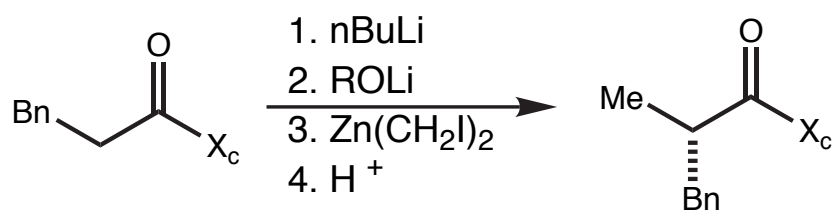
Tandem Asymmetric Enolate Homologation - Homoaldol Reaction

Asymmetric Synthesis of α -alkyl, γ -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



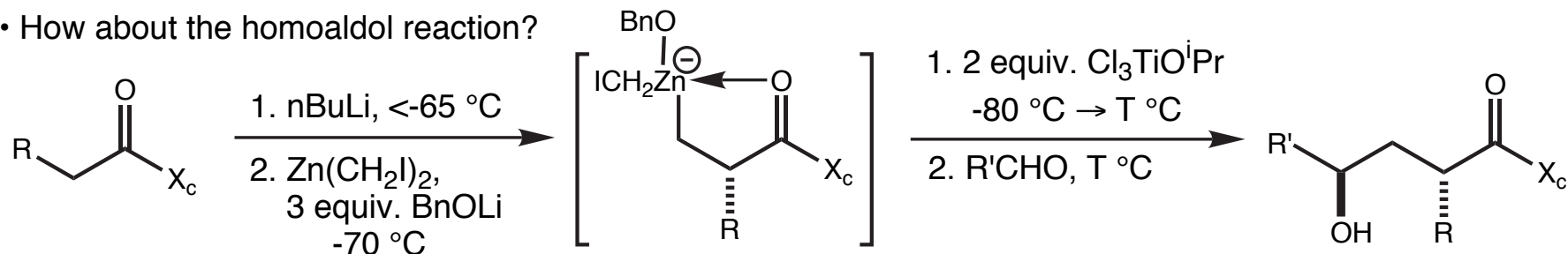
ROLi	Conversion
EtOLi	35
nPrOLi	74
BnOLi	82 (78% isolated)
LiO(CH ₂) ₂ OLi	31

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

Tandem Asymmetric Enolate Homologation - Homoaldol Reaction

Asymmetric Synthesis of α -alkyl, γ -hydroxy Carbonyl Compounds

- How about the homoaldol reaction?

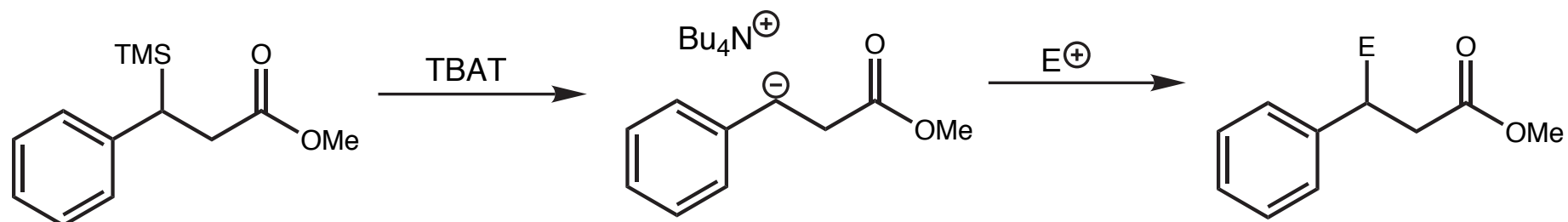


Aldehyde (R')	R	T (°C)	de (%)	Yield
	Bn	-20	≥ 99	59
	Me	-20	82	58
phenyl	Bn	-40	82	50
phenyl	Me	-40	80	44
iso-propyl	Bn	-50	76	53
n-butyl	Bn	-20	64	53

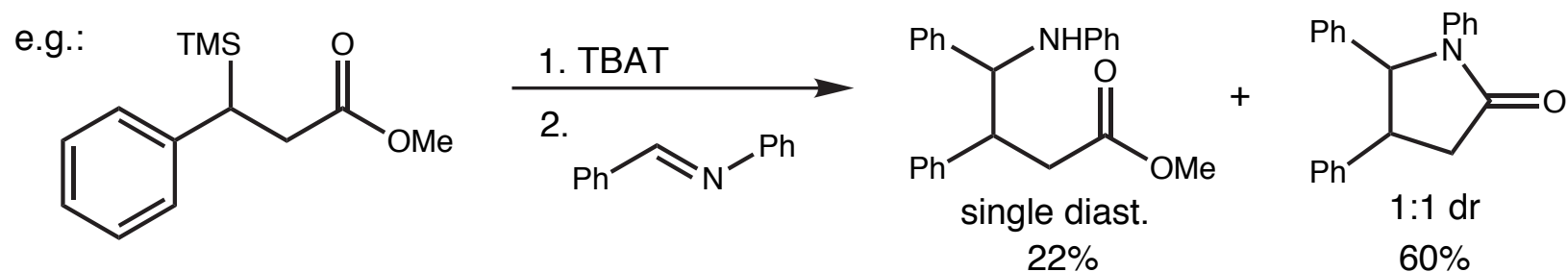
McWilliams, *J. Am. Chem. Soc.*, **1996**, 118, 11970

Reactive Homo-enolates

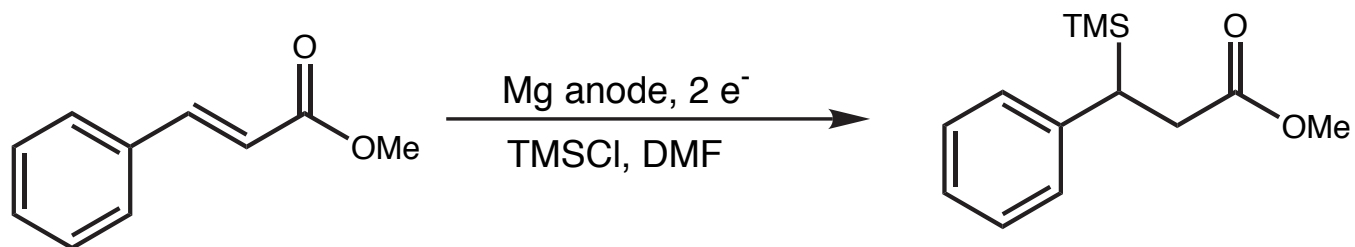
First Synthesis of a Metal-free Homo-enolate



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



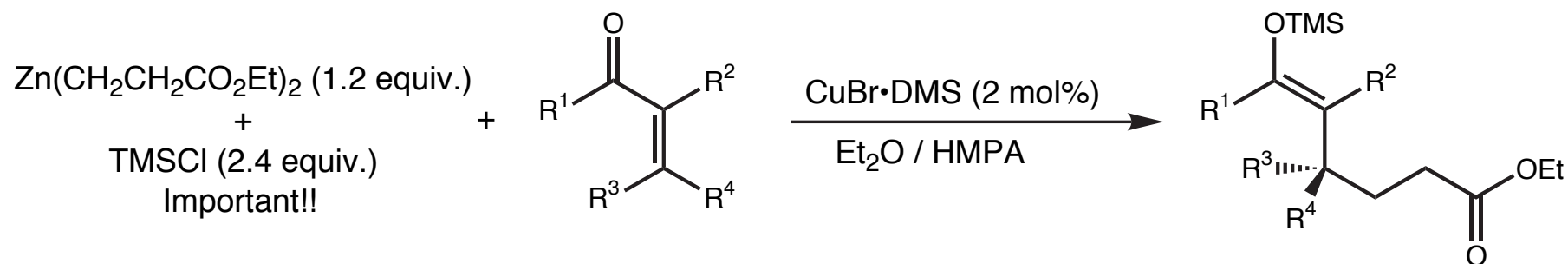
- substrate made easily using Nishiguchi method

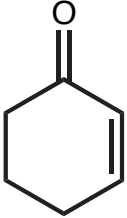
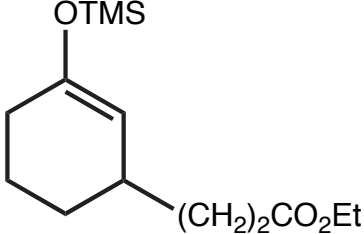
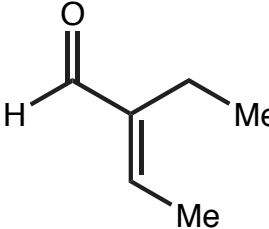
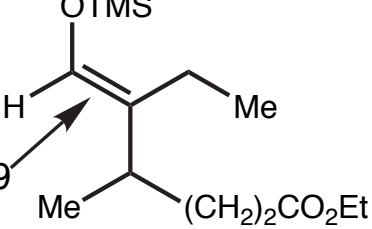

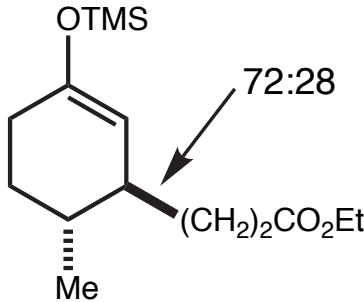
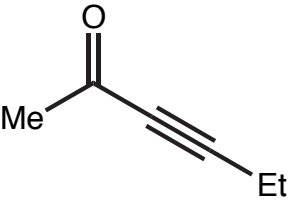
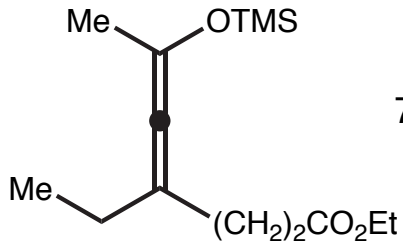


Fry, *Tetrahedron Lett.*, **1999**, 40, 7945
Nishiguchi, *Tetrahedron Lett.*, **1992**, 33, 5515

Conjugate Addition of Zinc Homoenoletes

Synthesis of δ,ϵ -(silylenoether)-esters

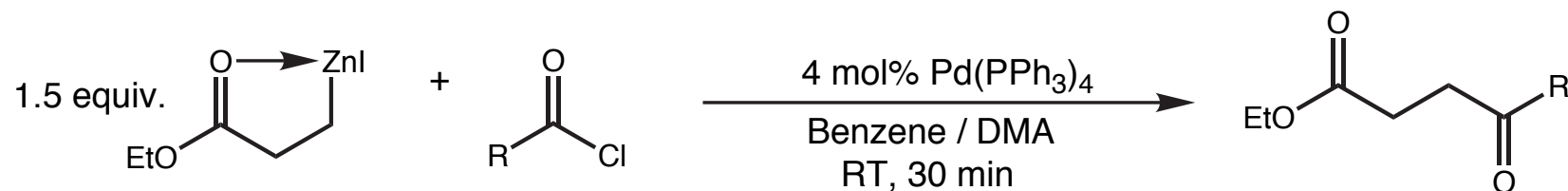


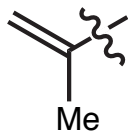
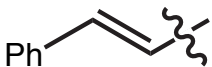
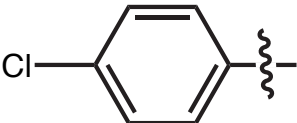
Enone	Product	Yield	Enone	Product	Yield
		93			75
		78			73

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

Acylation of Zinc Homoenoates

Synthesis of γ -ketoesters - Yoshida

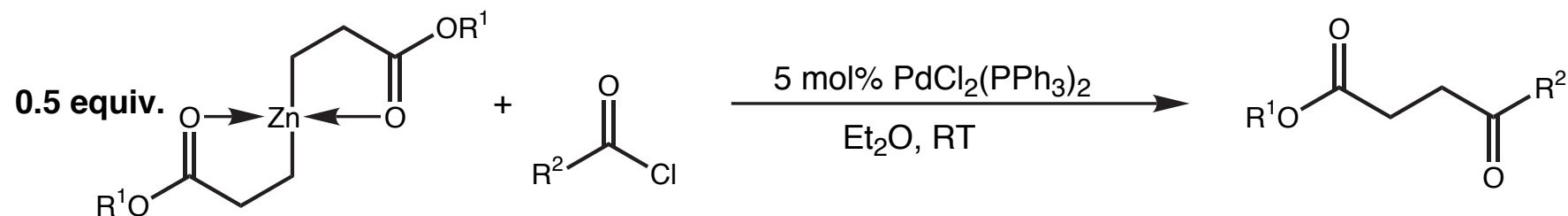


R	Yield
Ph	100
	90
	92
	100

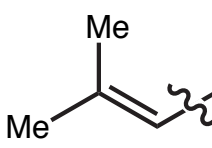
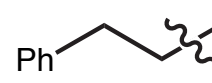
Yoshida, *Tetrahedron Lett.*, **1985**, 26, 5559

Acylation of Zinc Homoenoates

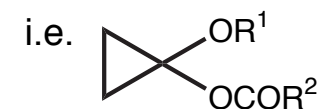
Synthesis of γ -ketoesters - Nakamura



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

R ¹	R ²	Yield
Et	Ph	93
iPr		81
Et		83
iPr	tBu	50

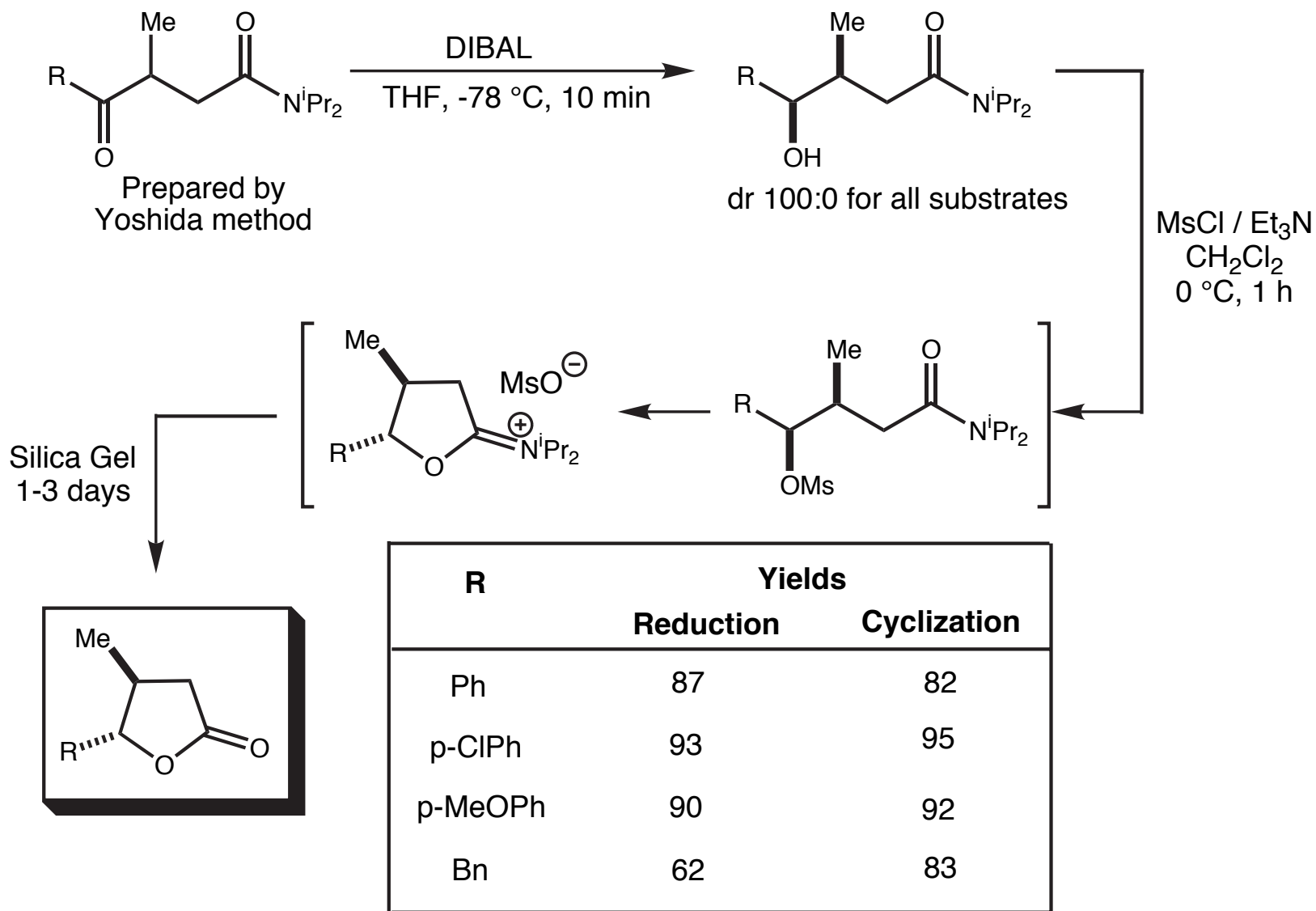
- when carried out in CDCl₃ got quantitative O-acylation (with or without Pd)



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

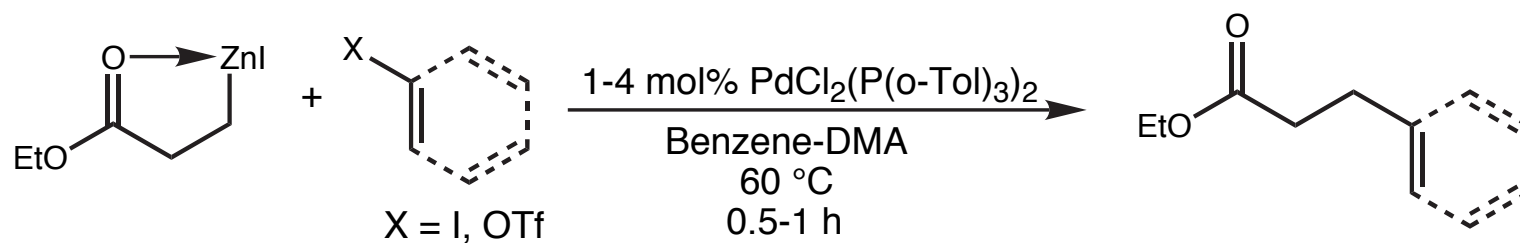
Application of Homoenoate Acylation

Synthesis of α,β -disubstituted γ -butyrolactones by Diastereoselective Reduction



Arylation and Vinylation of Zinc Homoenoates

Synthesis of β -vinyl and β -aryl esters - Yoshida



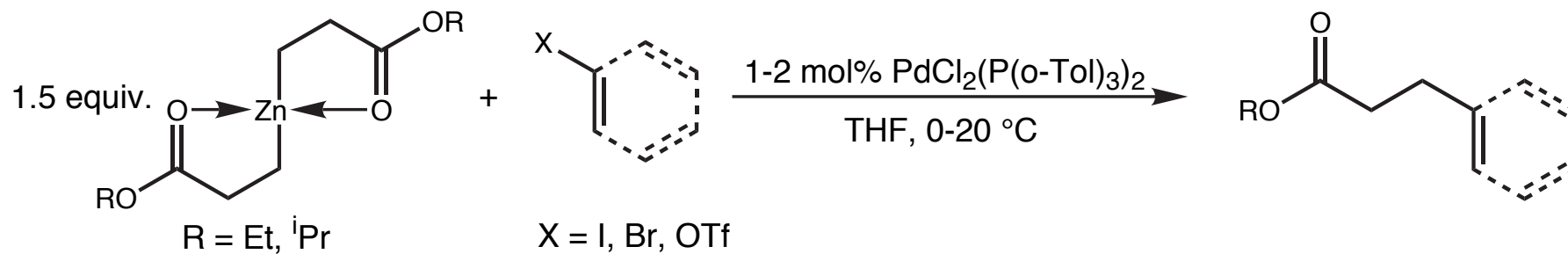
Coupling Partner	Yield
	74
	96
	67
	80


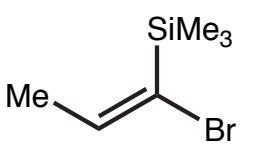
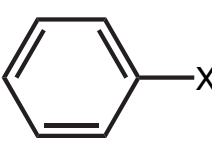
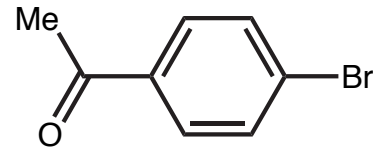
← Only vinylation example given

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

Arylation and Vinylation of Zinc Homoenoates

Synthesis of β -vinyl and β -aryl esters - Nakamura

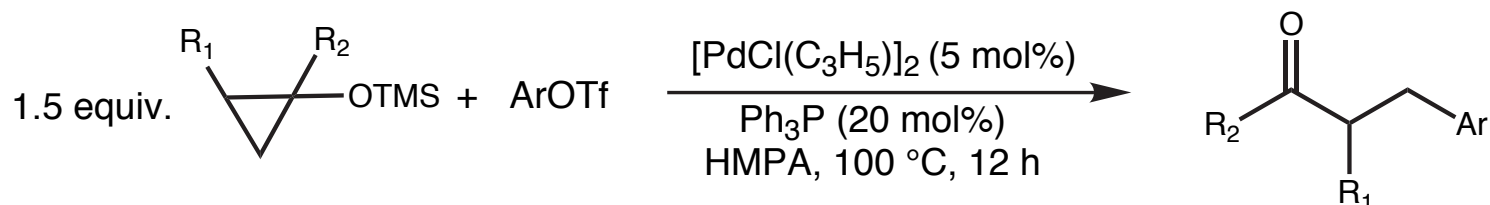


Coupling Partner	Yield
	90
	87
 X = OTf Br I	0 67 79
	49

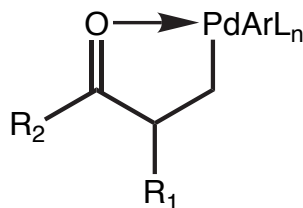
Nakamura, *J.Org.Chem.*, **1987**, 26, 8056

Arylation of Palladium Homoenolates

Catalytic Formation of β -aryl Ketones



• proposed to proceed via

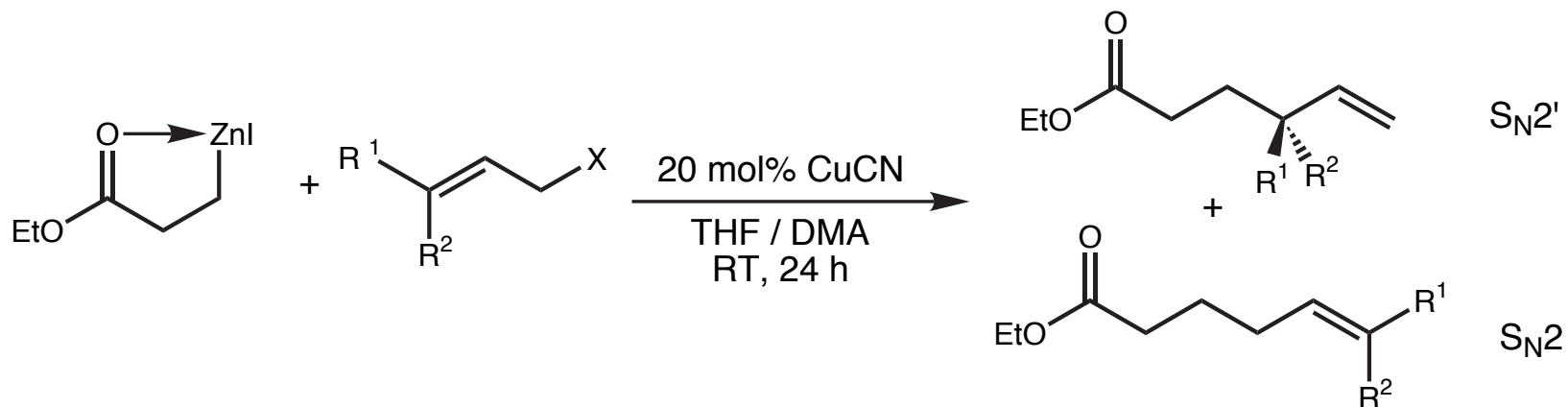


R_1	R_2	Ar	Yield
-CH ₂ CH ₂ CH ₂ CH ₂ -	-CH ₂ CH ₂ CH ₂ CH ₂ -	1-naphthyl	84
-CH ₂ CH ₂ CH ₂ CH ₂ -	-CH ₂ CH ₂ CH ₂ CH ₂ -	p-NO ₂ Ph	68
H	p-OMePh	Phenyl	65
n-Heptyl	H	1-naphthyl	58

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

Allylation of Zinc Homoenolates

Synthesis of δ,ϵ -unsaturated Esters - Yoshida

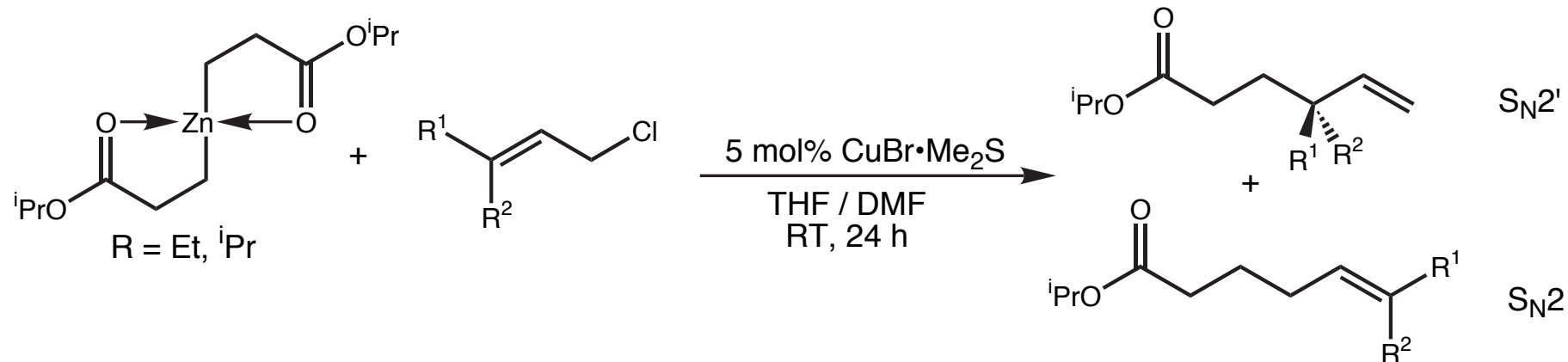


R^1	R^2	X	Yield	$S_N2' : S_N2$
H	H	OTs	89	--
Ph	H	OTs	80	87 : 13
		Br	93	88 : 12
		Cl	99	87 : 13
CO ₂ Me	H	Br	80	100 : 0

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

Allylation of Zinc Homoenoates

Synthesis of δ,ϵ -unsaturated Esters - Nakamura

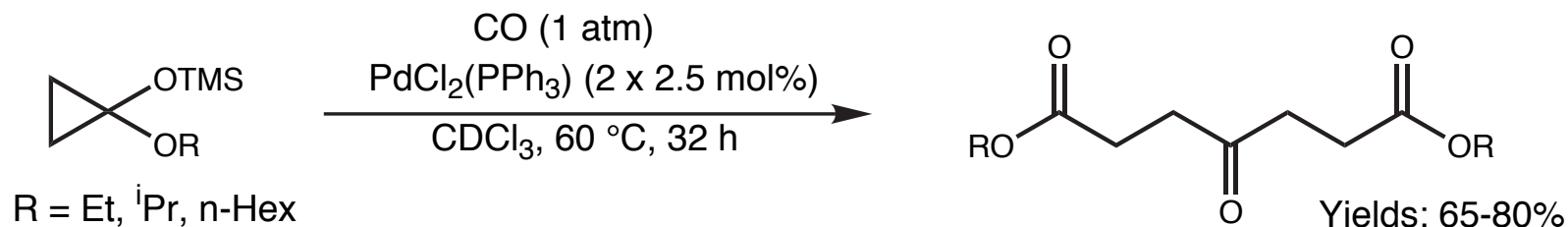


Allyl chloride	Yield	S_N2' : S_N2
	97	96 : 4
	65	1 : 99
	81	88 : 12
	72	100 : 0

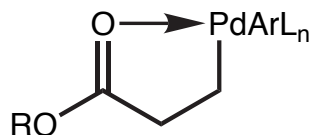
← Catalyst changed to 5 mol% NiCl₂·dppe

Carbonylative Symmetrical Coupling of Palladium Homoenoates

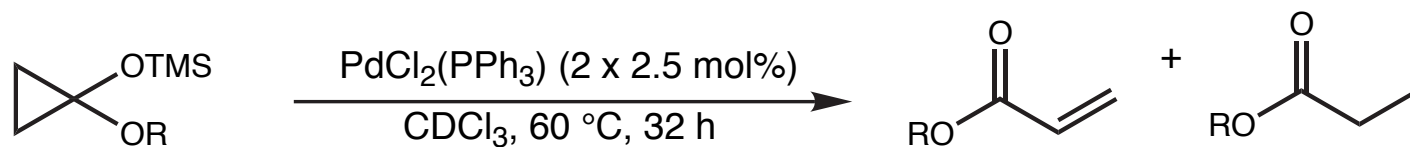
Catalytic Synthesis of 4-keto Pimelates



- proposed to proceed via



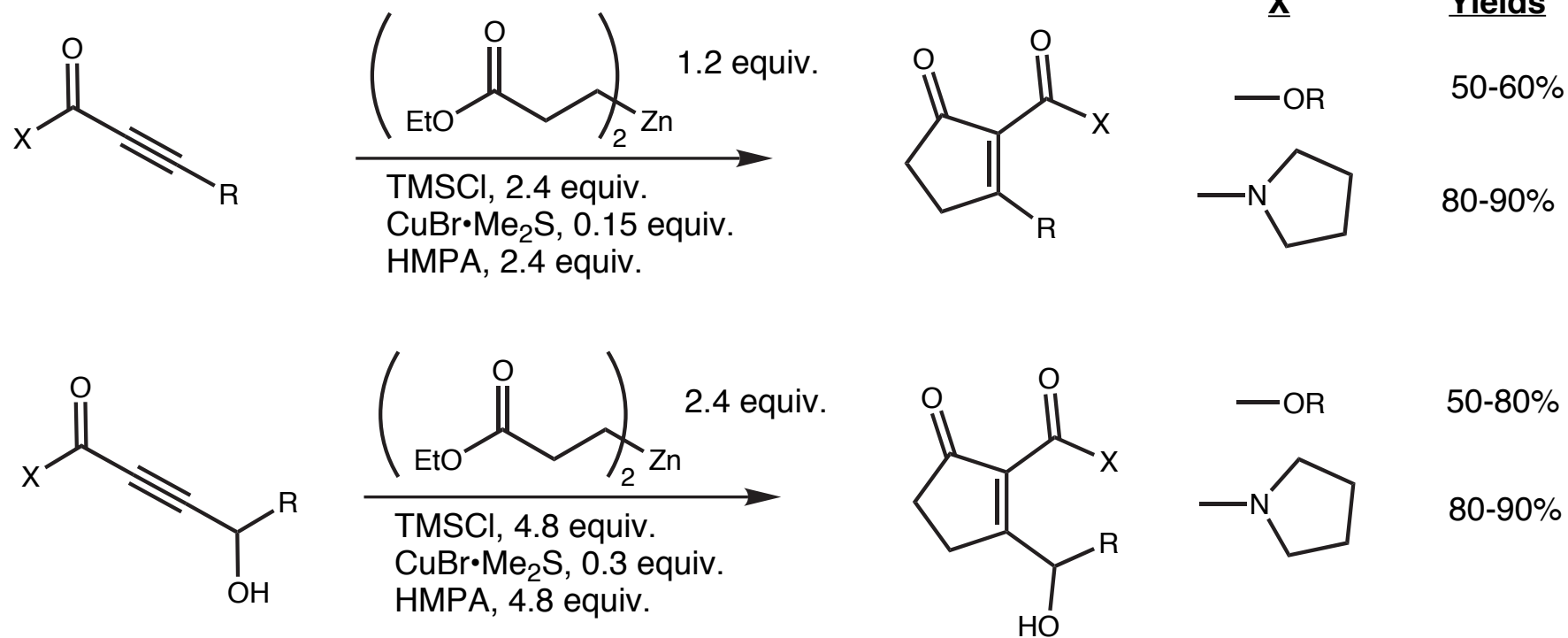
- evidence



Nakamura, *Tetrahedron Lett.*, **1988**, 29, 1541

Crimmins' Cyclopentenone Synthesis

Introduction and Generality

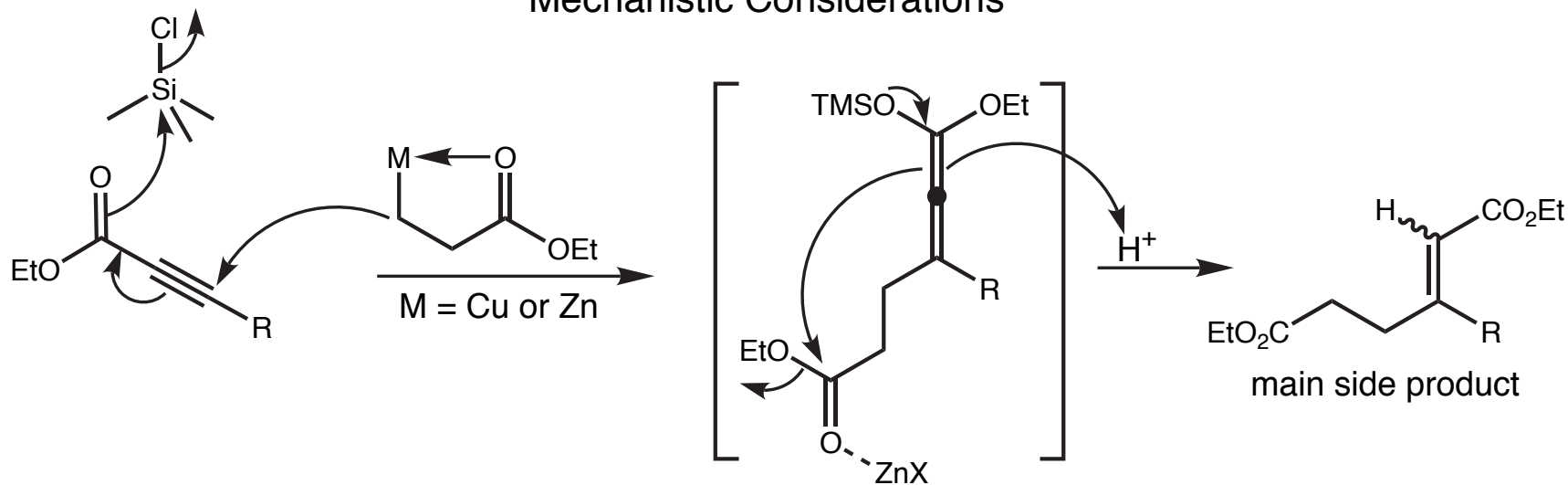


Functionality supported in R: ethers, epoxides, furans, α,β unsaturated esters

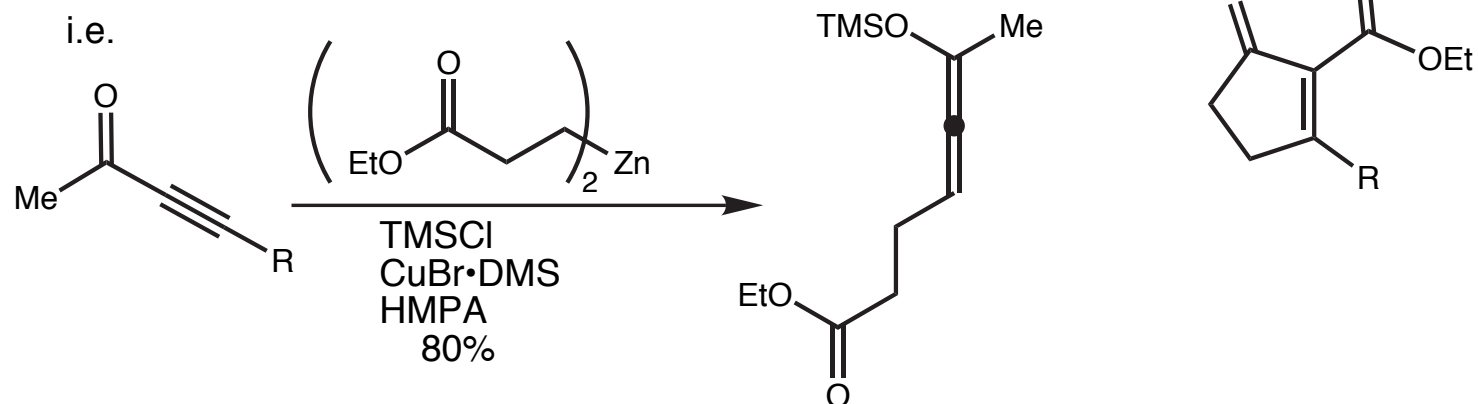
Crimmins, *J.Org.Chem.*, **1993**, 58, 1038

Crimmins' Cyclopentenone Synthesis

Mechanistic Considerations



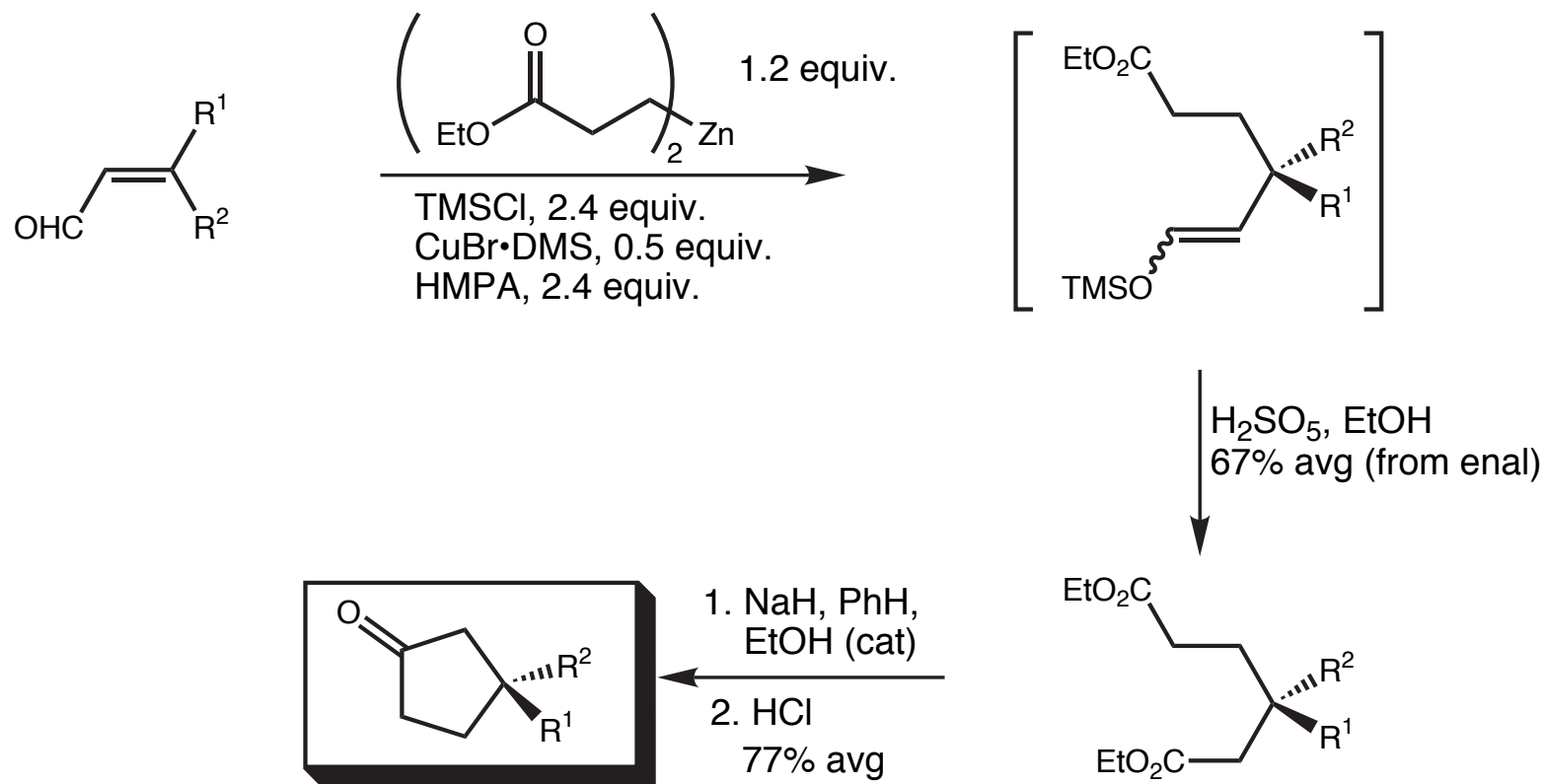
- problem: two steps have opposite electronic requirements
- appears amide and ester have right balance; ketone too electron poor to cyclize



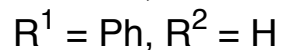
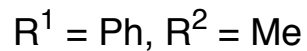
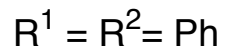
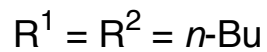
Crimmins, *J.Org.Chem.*, **1993**, 58, 1038

Leahy Cyclopentannulation

Synthesis of 3,3-disubstituted cyclopentanones



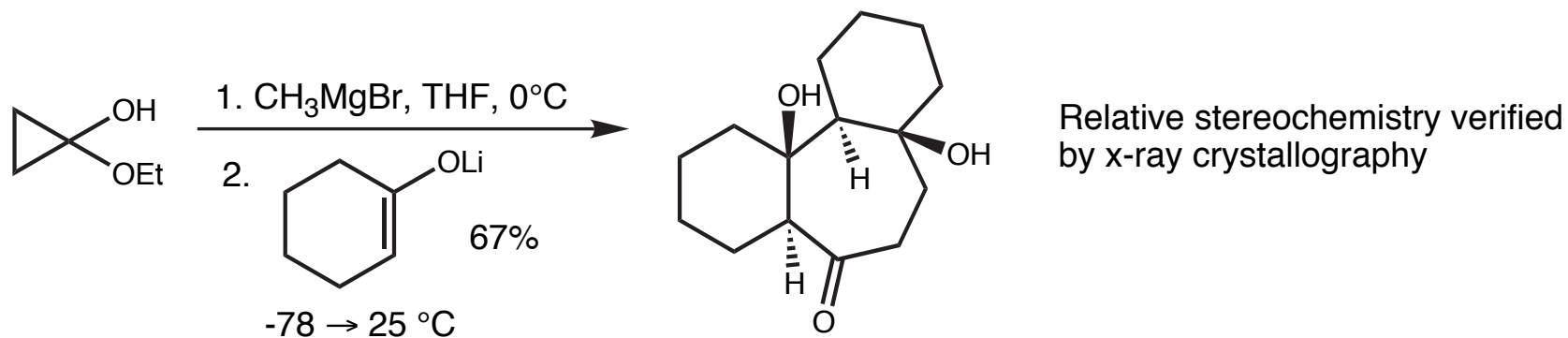
Substrates studied:



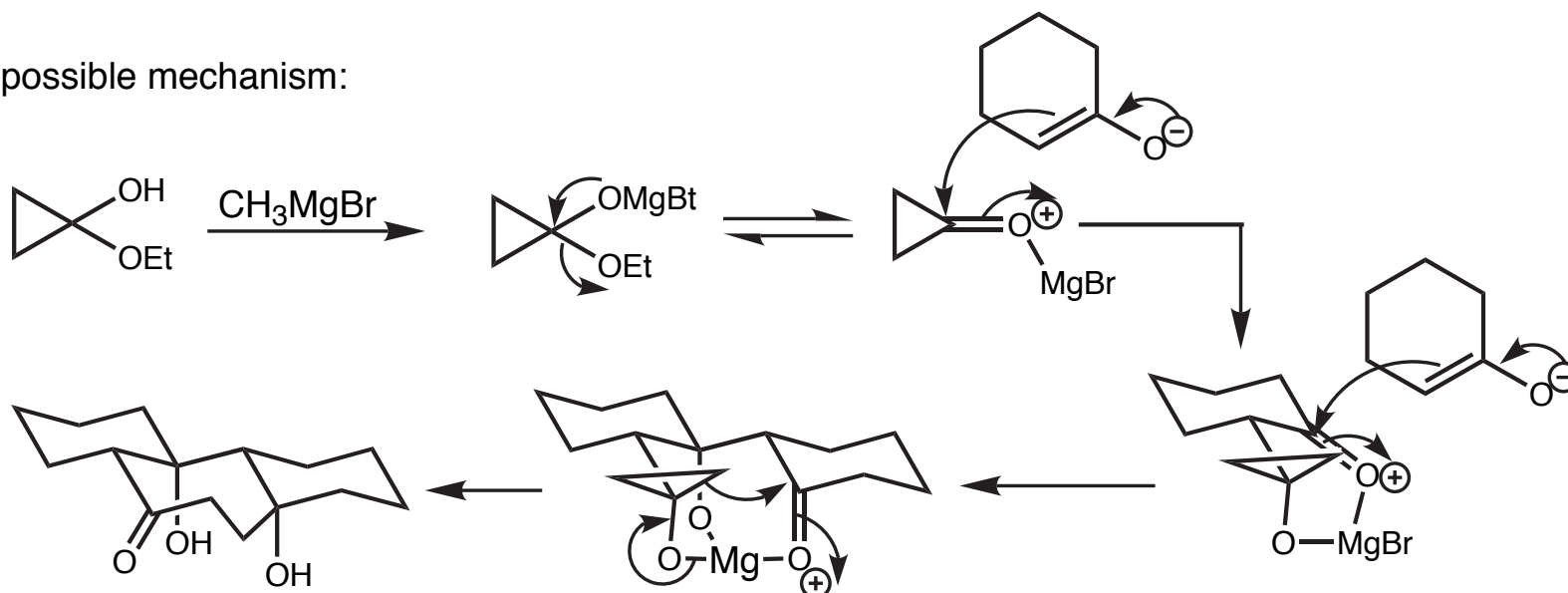
Leahy, *J.Org.Chem.*, **1994**, 59, 5496

Tandem Aldol / Aldol / Homoaldol Reaction

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



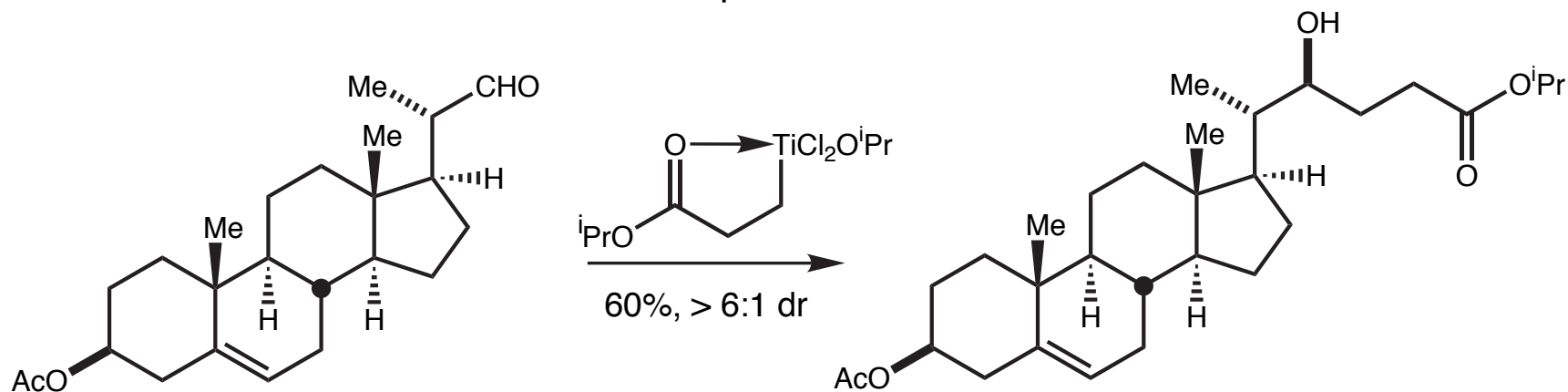
A possible mechanism:



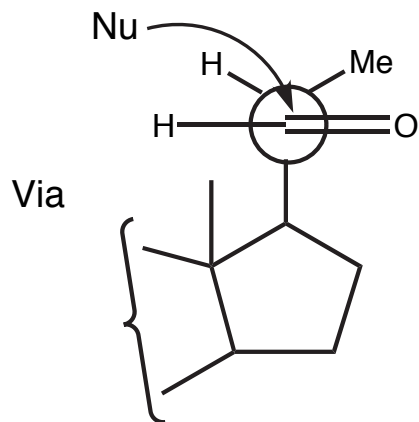
Helquist, *J. Am. Chem. Soc.*, **1986**, *108*, 8313

Synthetic Examples

Deprososterol

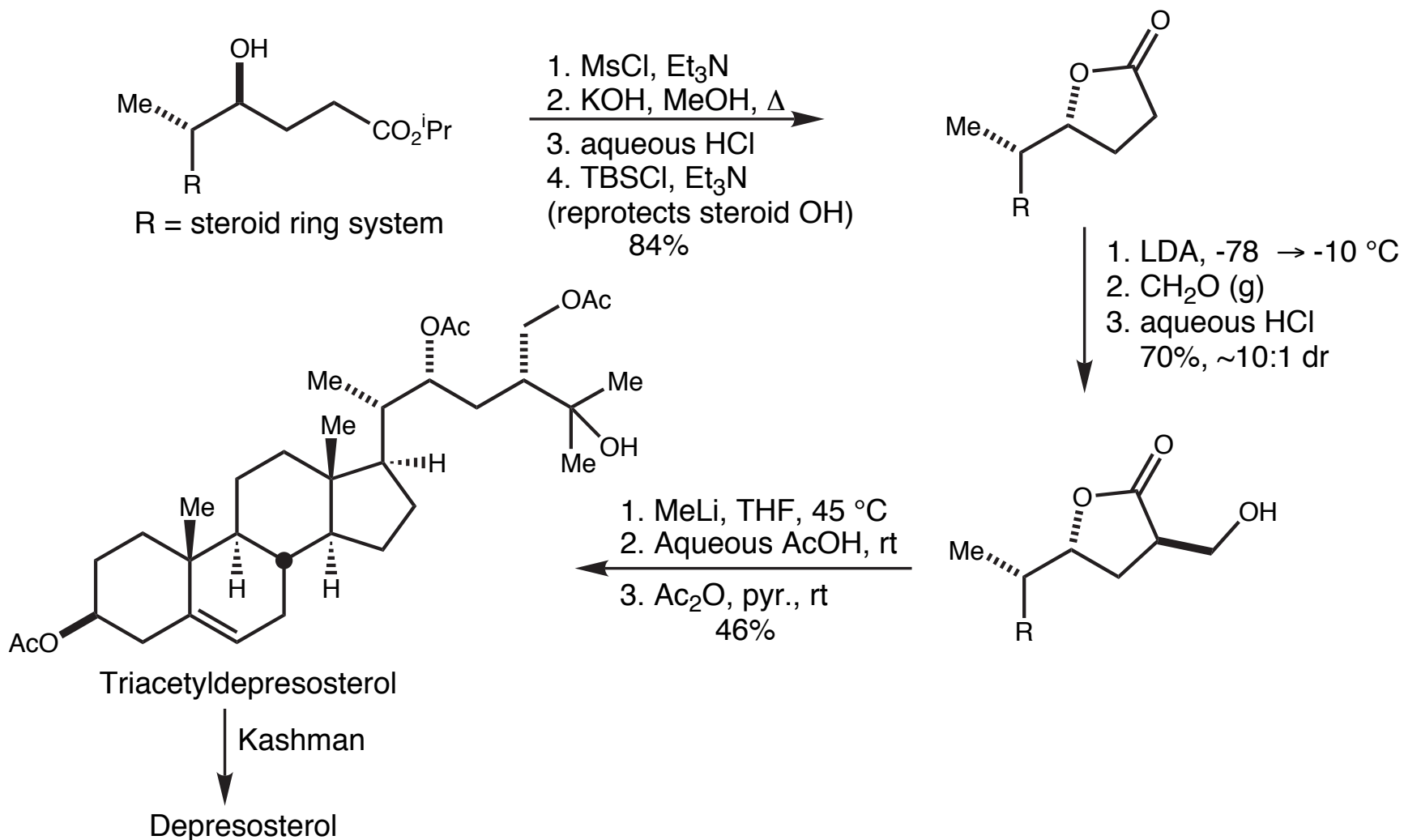


- trichlorotitanium homoenolate is not reactive enough to add to hindered aldehyde



Synthetic Examples

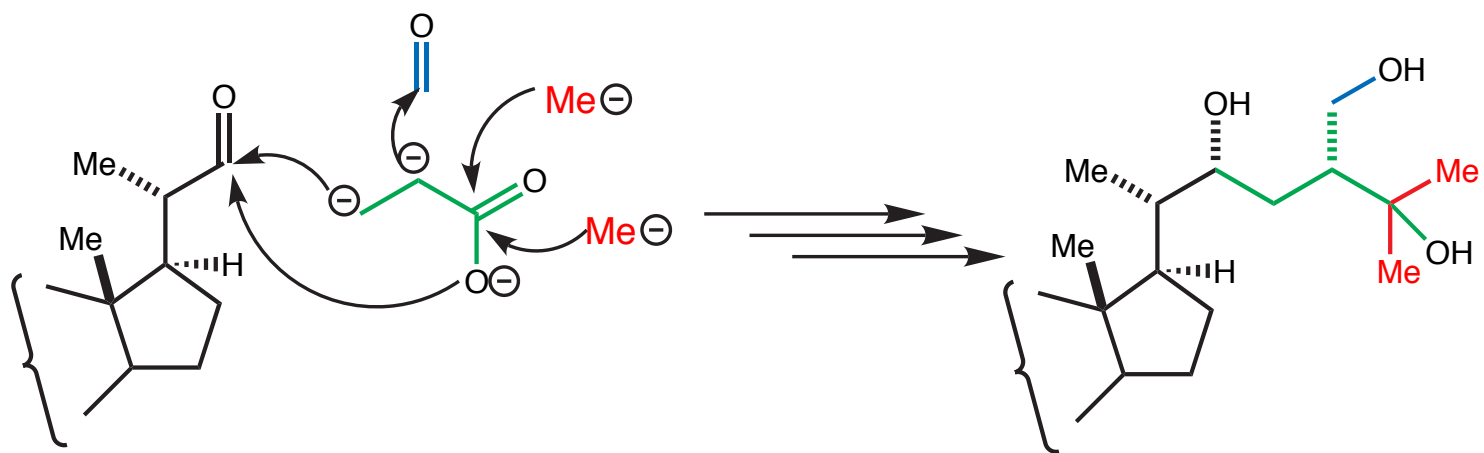
Deprososterol - completion of the formal synthesis



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

Synthetic Examples

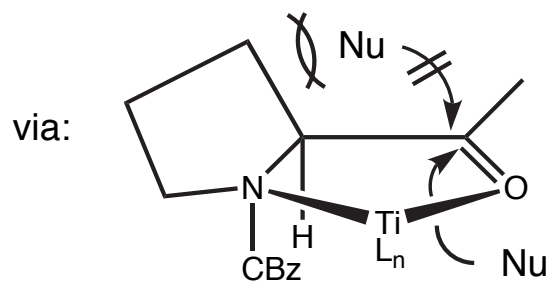
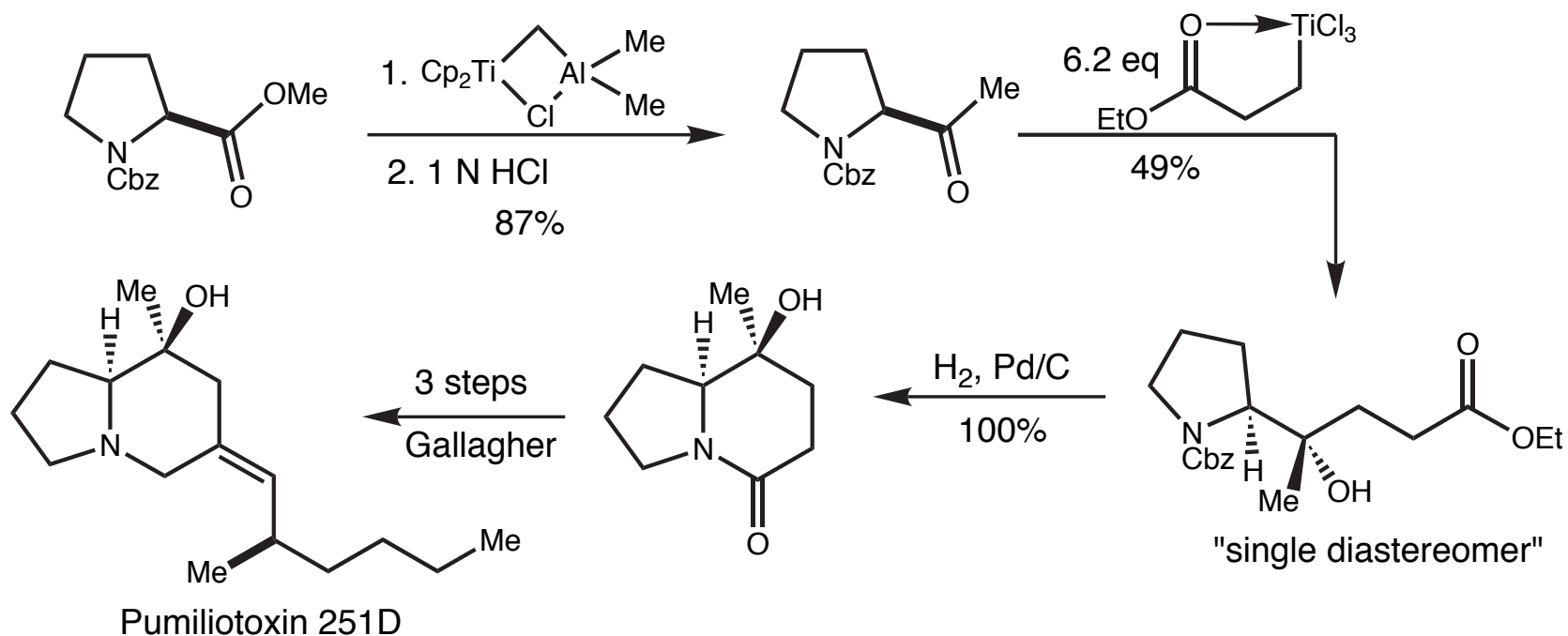
Deprososterol - Maximizing Homoenolate Functionality



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

Synthetic Examples

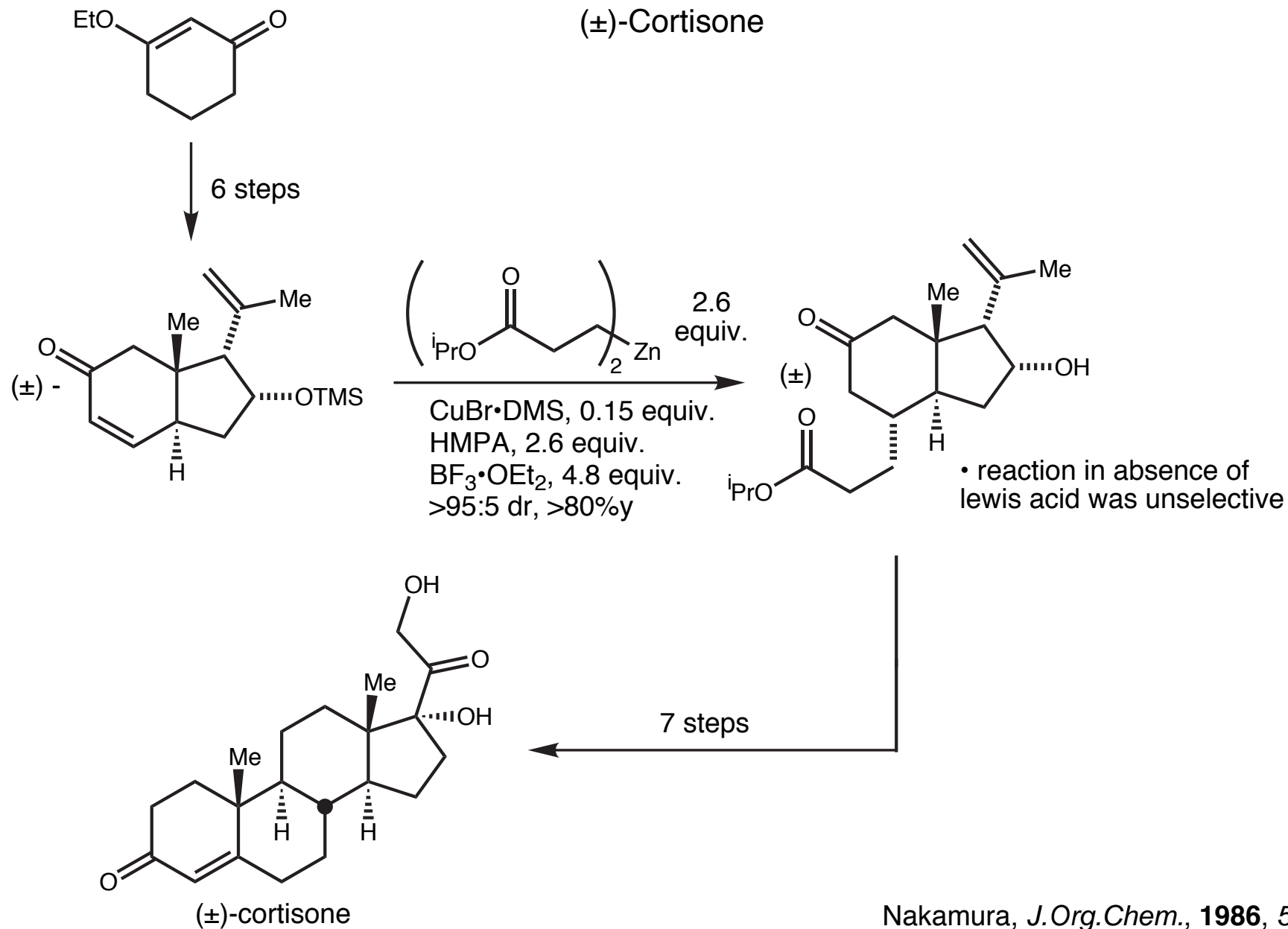
Pumiliotoxin 251D



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

Synthetic Examples

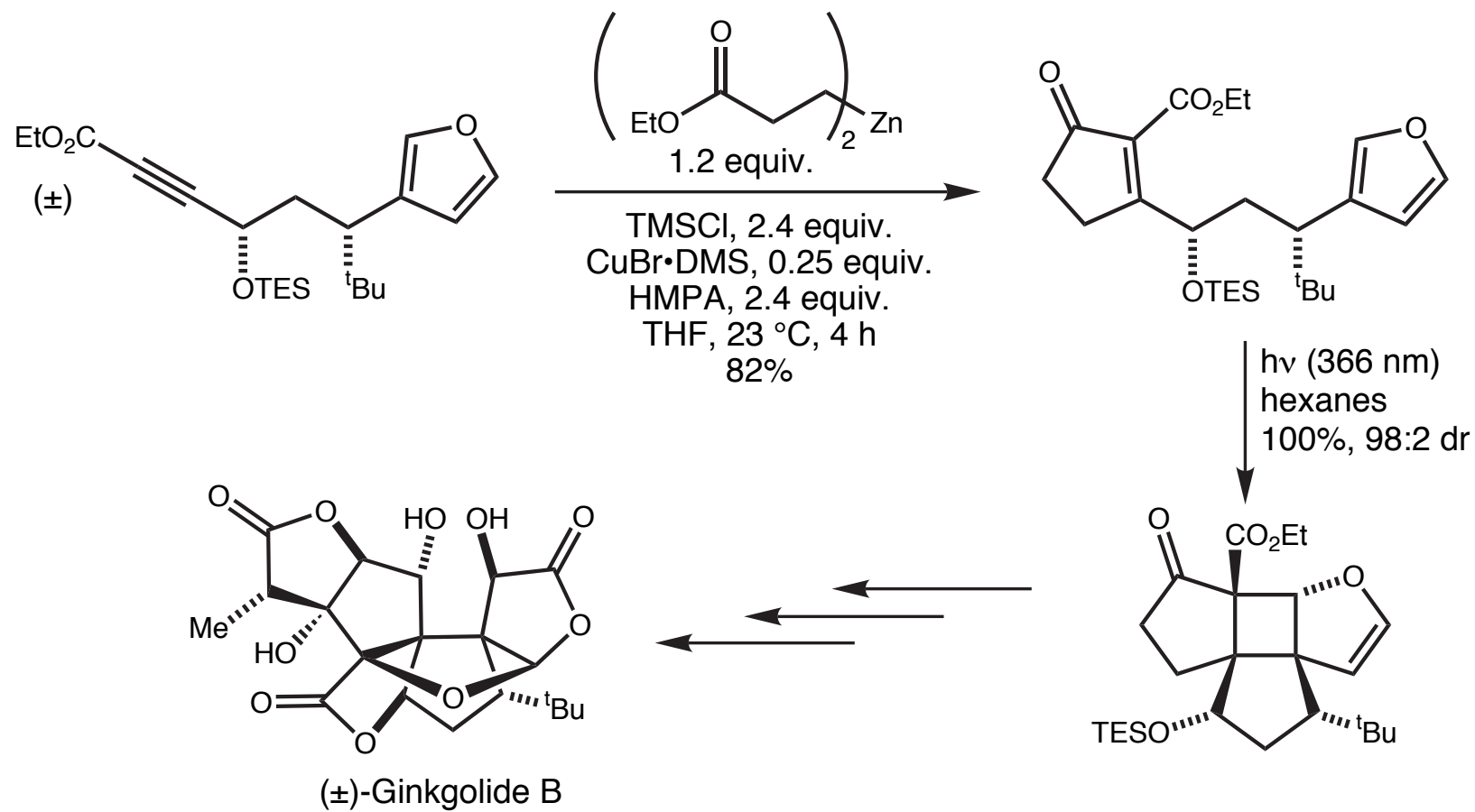
(±)-Cortisone



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

Synthetic Examples

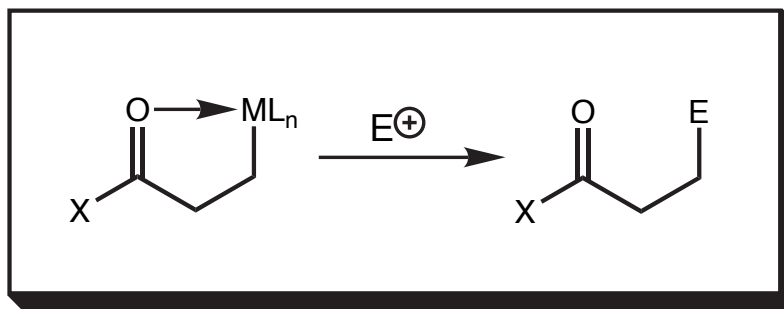
(±)-Ginkgolide B



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

Homoenolate Chemistry

A Summary



- homoenolates are synthesized by cyclopropane ring-opening or oxidative addition of β -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