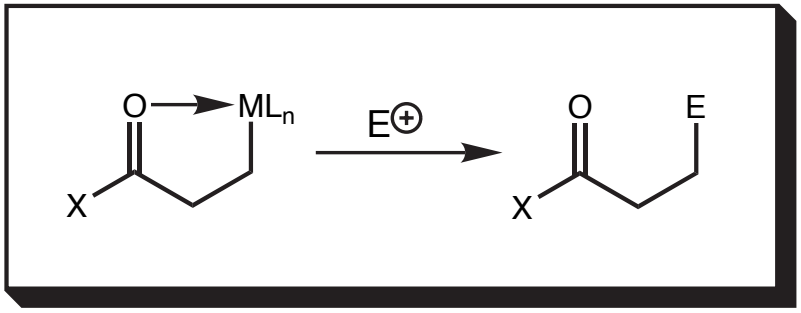
Homoenolates

Synthesis and Applications

Evans Group Seminar

March 24, 2000

Jason Burch



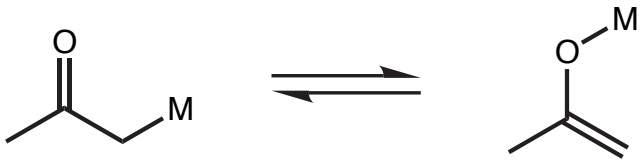
I. Enolates, Homoenolates and Homoenolate Equivalents
II. Synthesis of Homoenolates
III. The Homoaldol Reaction
IV. Coupling Reactions
V. Other Reactions
VI. Synthetic Applications

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

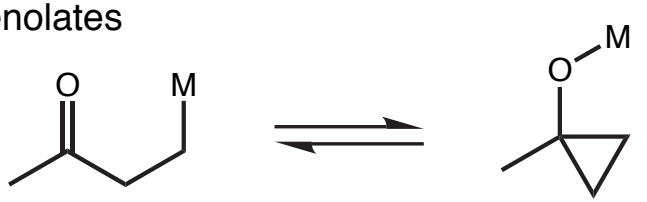
The Tautomerism Problem

• Enolates



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

• Homoenolates



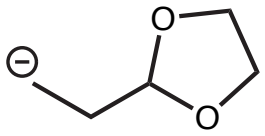
• tautomerism is a much larger problem because it is often irreversible and oxyanioic tautomer rarely acts as a carbon nucleophile

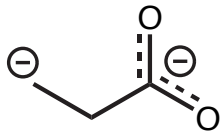
Nakamura in *Comp.Org.Synth.,* **1991***, 2*, 441

Homoenolate Equivalents

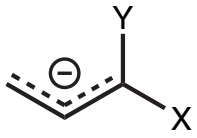
Definition: species containing an ionic carbon β to a moeity which can be converted into a carbonyl group

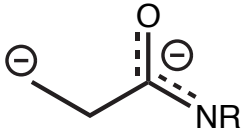
Examples:





in situ protection

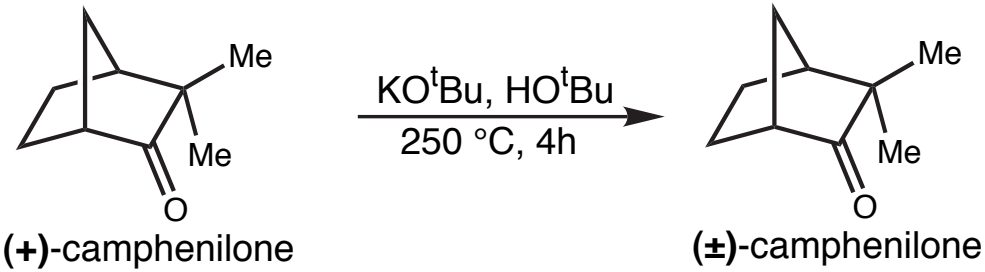




X = OR, NR_2, etc.
Y = H, R, OR, NR_2, etc.

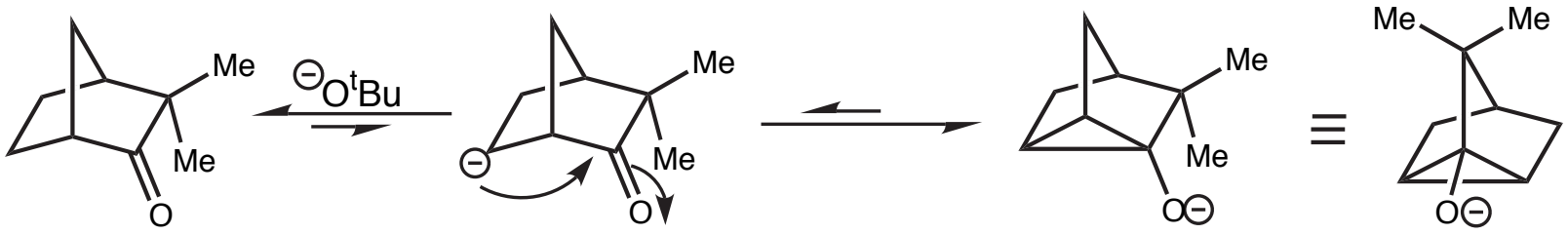
Werstiuk in "Umpoled Synthons", Hase, Ed.;
Wiley: New York, **1987**, Chap. 6
Ahlbrecht, *Synthesis,* **1999**, 365 (chiral examples)

The First "Homoenolate"



(+)-camphenilone **(±)**-camphenilone

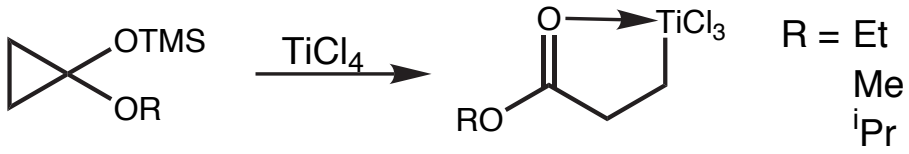
- no racemization occurred in >4 days at 250 °C in the absence of base
- proposed to proceed via a "homoenolate anion"



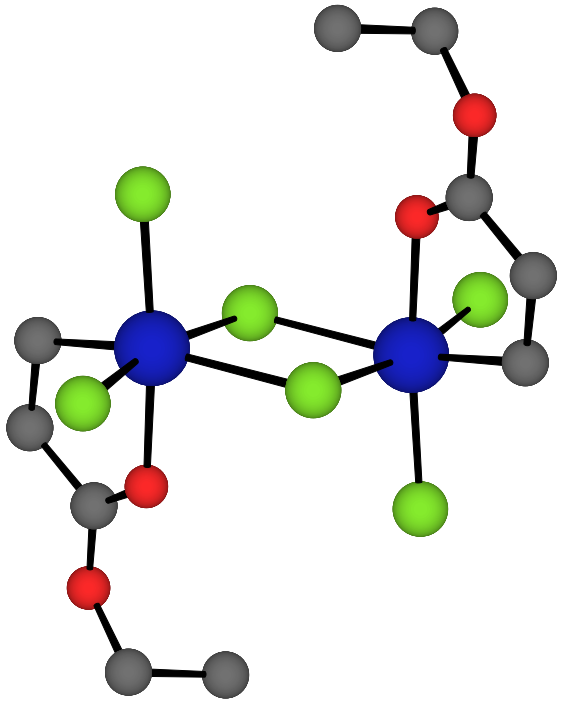
Nickon, *J.Am.Chem.Soc.*, **1962**, *84*, 4604

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 ($\nu_{C=O}$ = 1603 for R = ^{i}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 (Å):

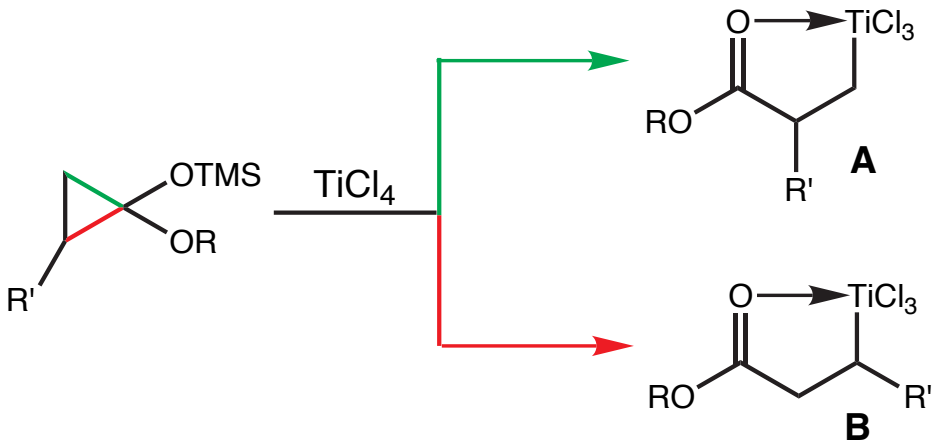
Ti-C	2.081
Ti-O	2.072
C=O	1.235

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

Cyclopropane Ring Opening

Regioselectivity of Ring Cleavage - Titanium

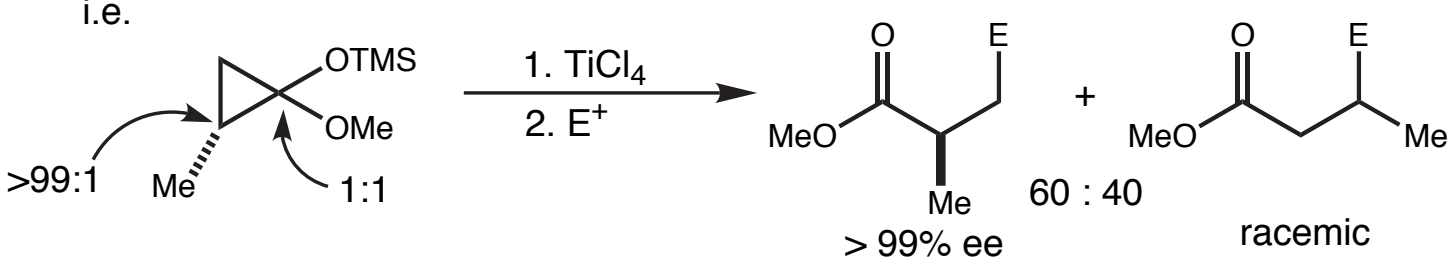
- in general, cleavage occurs selectively at the least substituted cyclopropane bond



R	R'	A : B
^{i}Pr	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_2, RCHO)
- if non-racemic starting material is used, quench with electrophiles indicates non-racemized **A** and totally racemic **B**

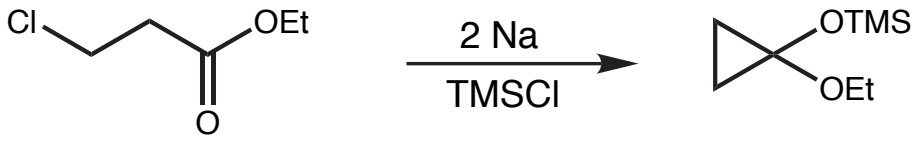
i.e.



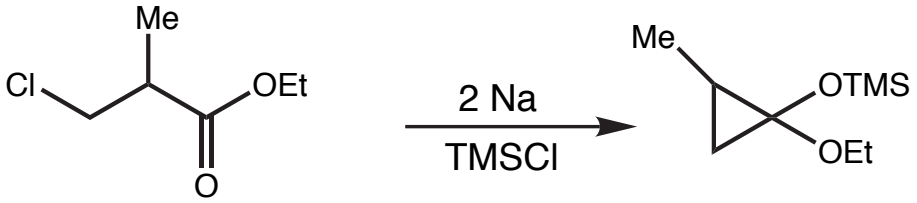
Nakamura, *J.Am.Chem.Soc.*, **1986**, *108*, 3749

Cyclopropane Synthesis

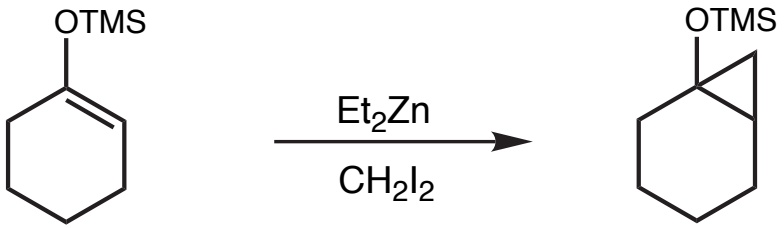
• most common method



- used to prepare substituted cyclopropanes



• use Simmons-Smith for ketone-derived substrates

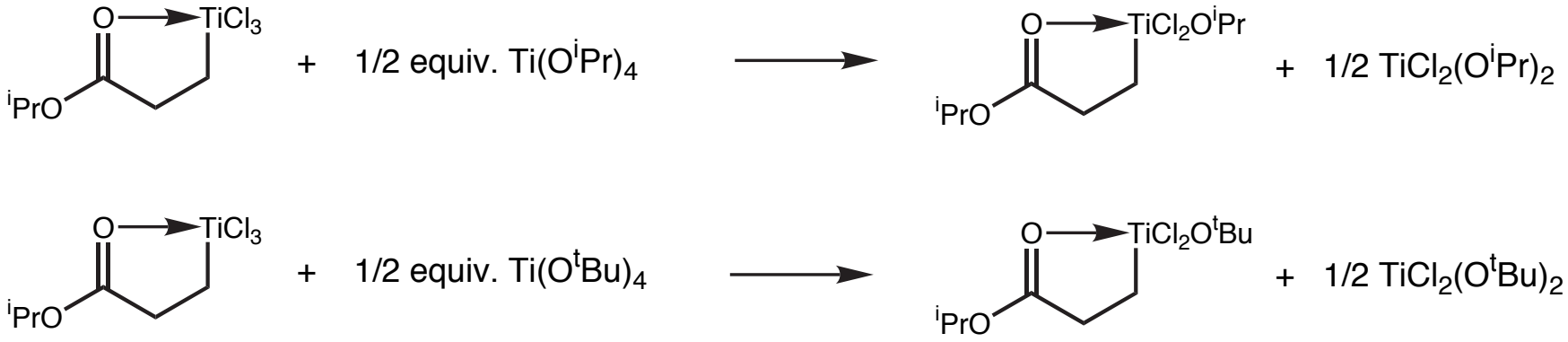


Ruhlmann, *Synthesis* , **1971**, 236.
Salaun, *Org. Synth.,* **1985**, *63*, 147
Murai, *J.Org.Chem.*, **1973**, *38*, 4354

Alkoxide-Modified Homoenolates

Tuning Titanium Homoenolate Reactivity

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



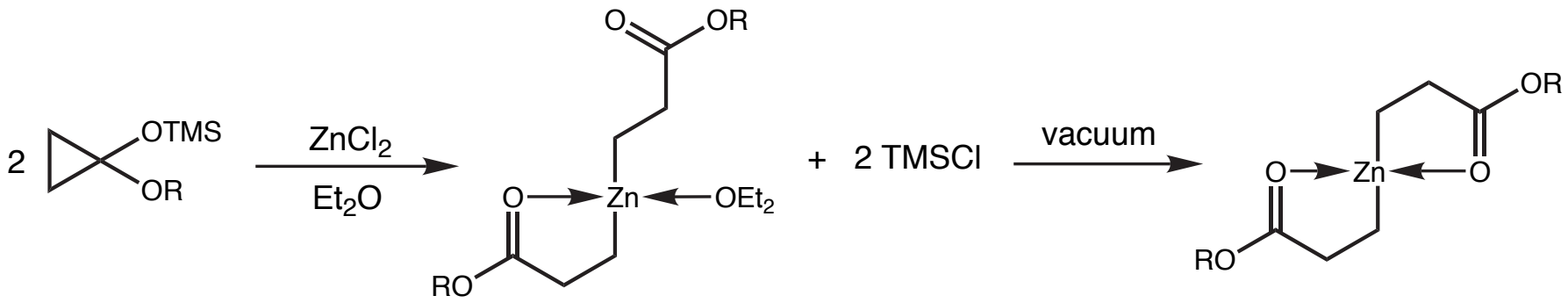
- Have not been characterized to the detail of the trichlorohomoenolates
- Appear to have "significant contribution from monomeric forms" (from molecular weight data)
- Are more reactive than trichloro homoenolates towards homoaldolisation

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

Cyclopropane Ring Opening

Zinc Homoenolates

• Zinc homoenolates can be prepared in a similar method to titanium



$\nu_{C=O}$ = 1662 cm^{-1}
1740 cm^{-1}

4 inequivalent methylene groups in ^{1}H-NMR

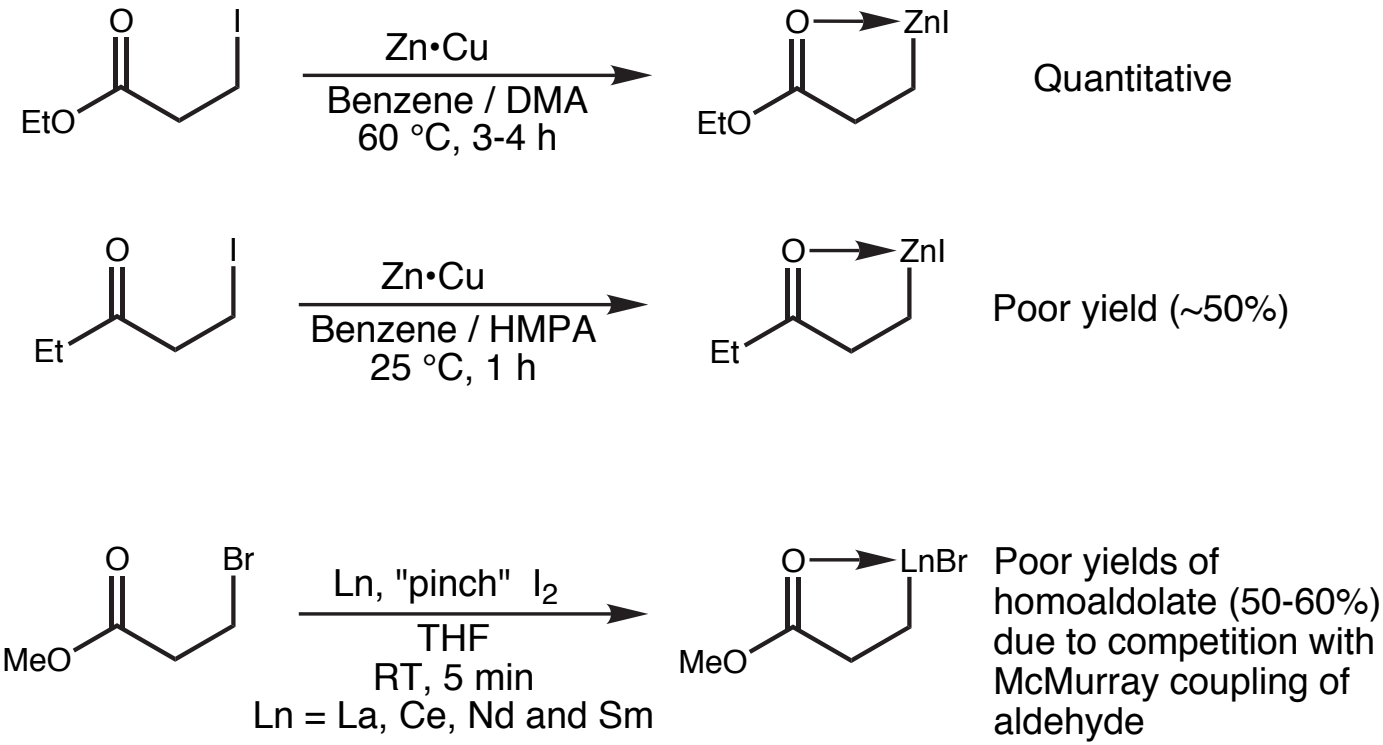
$\nu_{C=O}$ = 1645 cm^{-1}

2 inequivalent methylene groups in ^{1}H-NMR

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

Direct Oxidative Addition

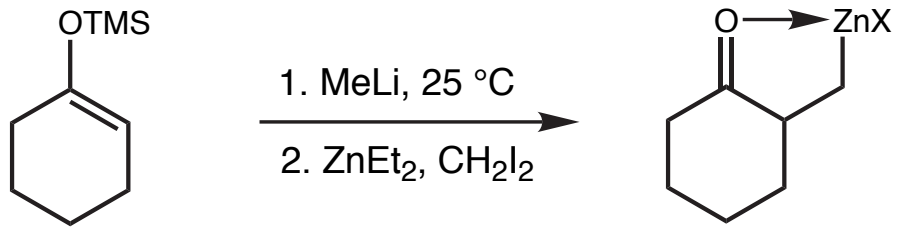
Zinc and Lanthanide Homoenolates



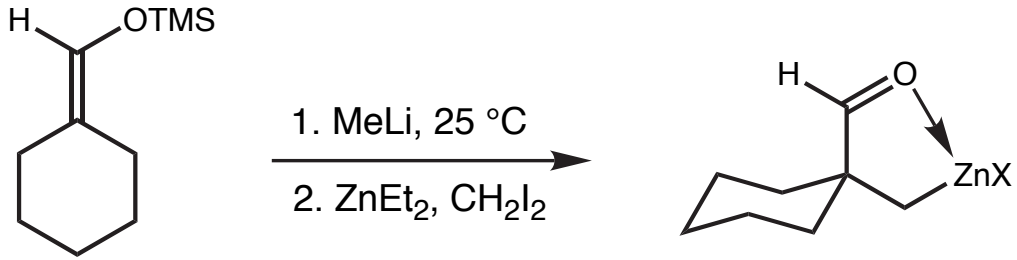
Yoshida, *Tetrahedron Lett.*, **1985**, *26*, 5559
Yoshida, *Angew.Chem.,Int.Ed.Engl.*, **1987**, *26*, 1157
Fukuzawa, *Chem. Commun.*, **1986**, 475

Enolate Homologation

Synthesis of Zinc Homoenolates



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

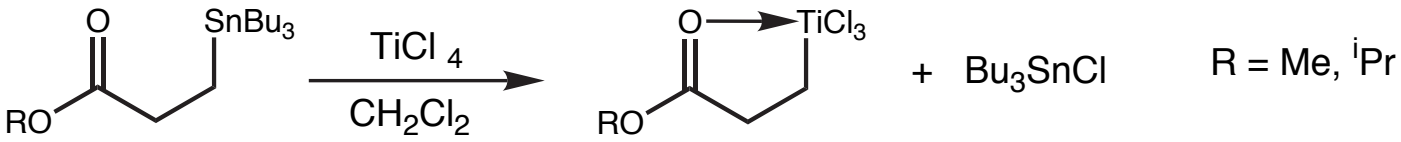


Knochel, *J.Org.Chem.*, **1993**, *58*, 2694

Direct Tin-Titanium Exchange

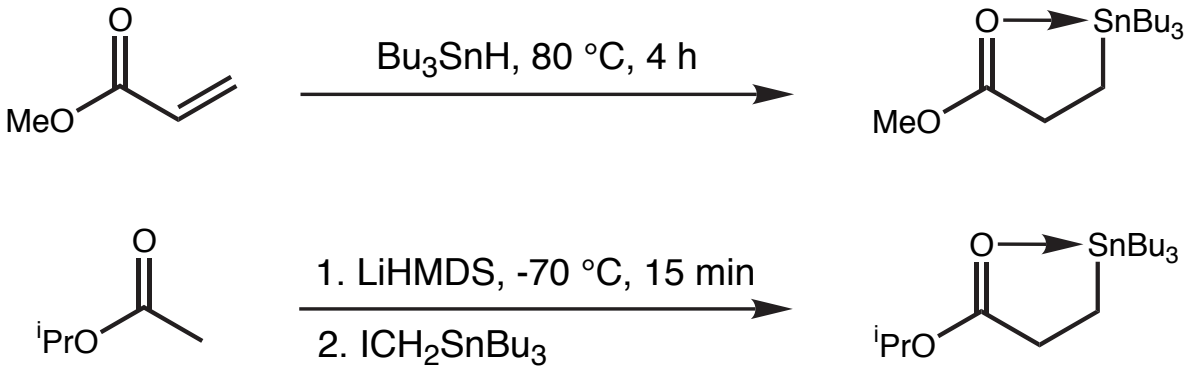
New Route to Titanium Homoenolates

- Treatment of β–tri-n-butylstannyl esters with $TiCl_4$ directly forms titanium homoenolate



- Isotope labelling studies showed rxn does not proceed via cyclopropane

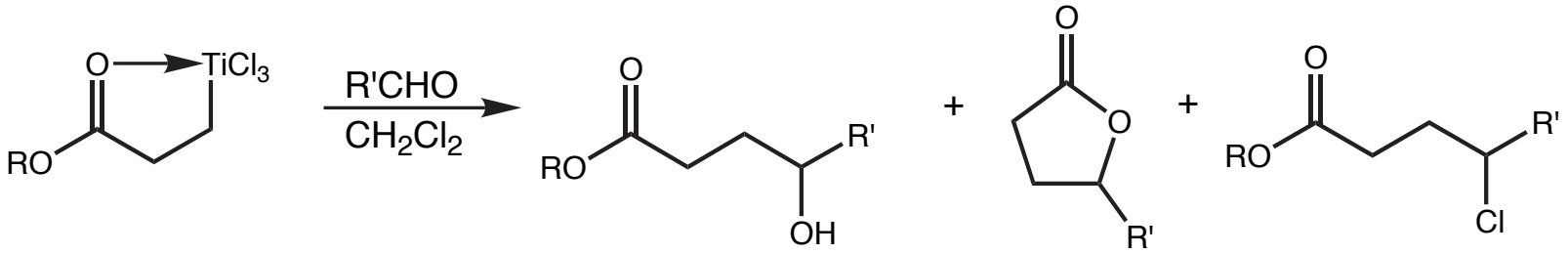
- Substrates can easily be prepared by two methods:

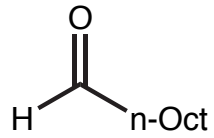
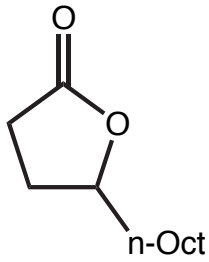
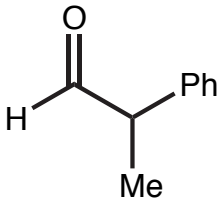
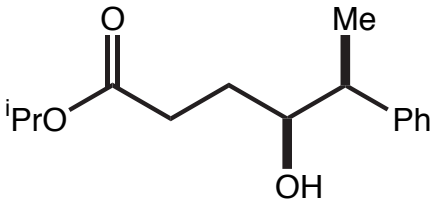
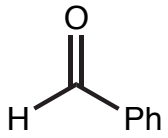
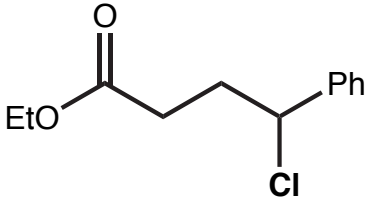


Goswami, *J.Org.Chem.*, **1985**, *50*, 5907
van der Kirk, *J. Appl. Chem.*, **1957**, *7*, 356
Still, *J.Am.Chem.Soc.*, **1978**, *100*, 1481

The First Homoaldol Reaction

Synthesis of γ-hydroxyesters and γ-lactones

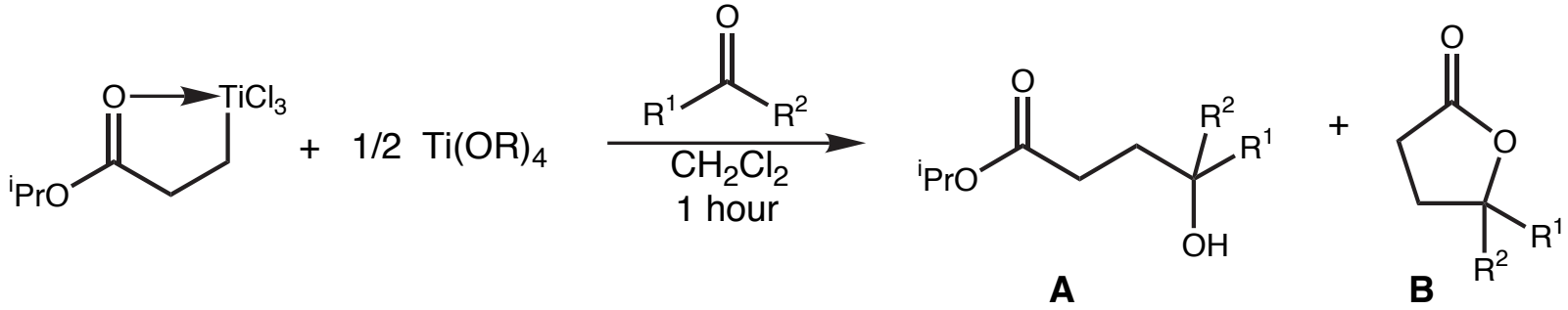


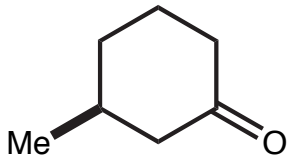
Aldehyde	R	Temp (°C)	Time (h)	Workup	Product	Yield
	Et	0	1	Acidic		81
	^{i}Pr	0	2.5	Neutral		67 (85:15)
	Et	0	1.5	Neutral		90

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

Homoaldol Reactions with Alkoxide-modified Homoenolates

Homoaldol Reactions with Aromatic Aldehydes and Ketones

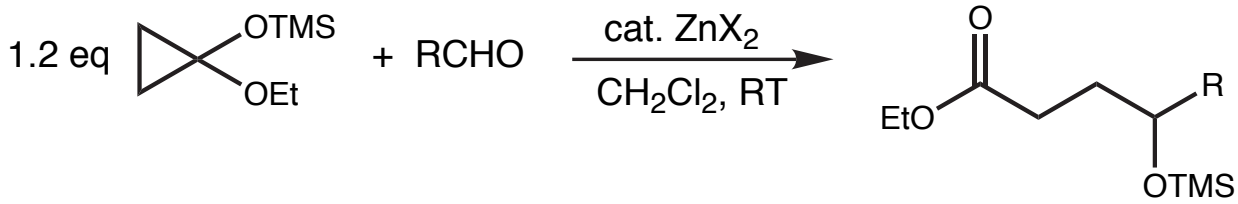


Electrophile	R	Temp(°C)	Yield (**A** or **B**)
Benzaldehyde	^{i}Pr	0	90(**A**)
Crotonaldehyde	^{i}Pr	0	88(**A**)
Acetophenone	^{i}Pr	20	66(**A**), 12(**B**)
	^{t}Bu	20	93(**B**)
Cyclohexanone	^{i}Pr	20	62(**B**)
	^{t}Bu	20	91(**B**)
	^{t}Bu	20	91(**B**) dr = 88 : 12 equatorial attack

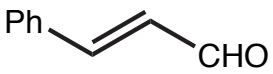
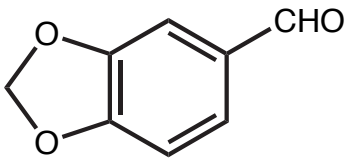
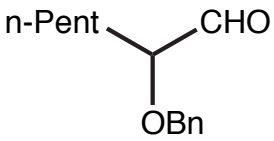
Nakamura, *J.Am.Chem.Soc.*, **1986**, *108*, 3745

Homoaldol Reactions of Zinc Homoenolates

First Catalytic Homoaldol Reactions



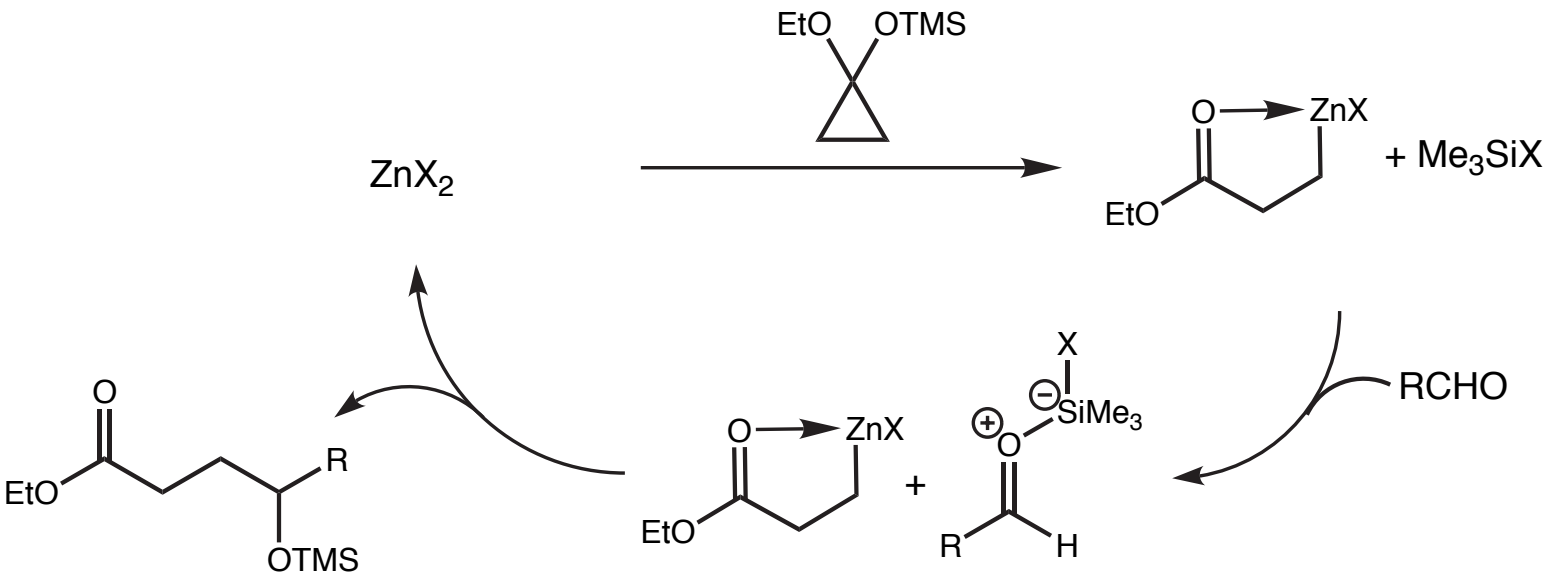
• TMSCl generated is essential (i.e. no reaction if removed *in vacuo* for stoichiometric case)

Aldehyde	Catalyst, yield $ZnCl_2$ (30-50 mol%)	ZnI_2 (0.1-1 mol%)
PhCHO	84	89
	94	84
	91	95
	--	84
	79 93:7 *syn : anti* chelation product	--

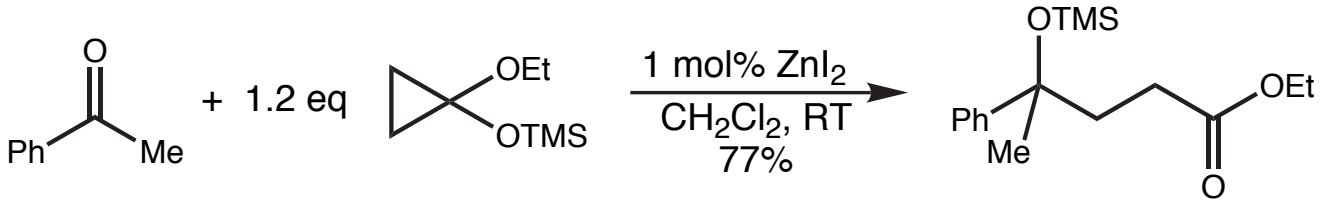
Nakamura, *J.Am.Chem.Soc.*, **1987**, *109*, 8056

Homoaldol Reactions of Zinc Homoenolates

Proposed Catalytic Cycle



• with ZnI_2, the homoenolate is reactive enough to add to ketones:

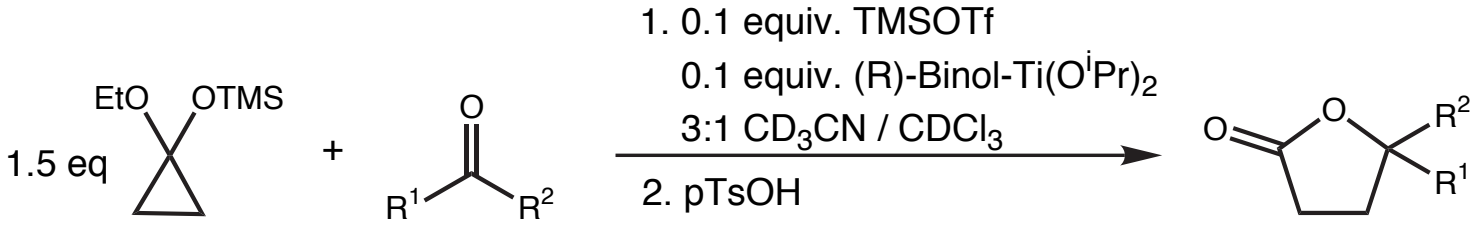


- no reaction even with stoichiometric $ZnCl_2$

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
Ph–	H	0 °C, 36 h	76
TMS–	H	0 °C, 36 h	82
Cl–	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

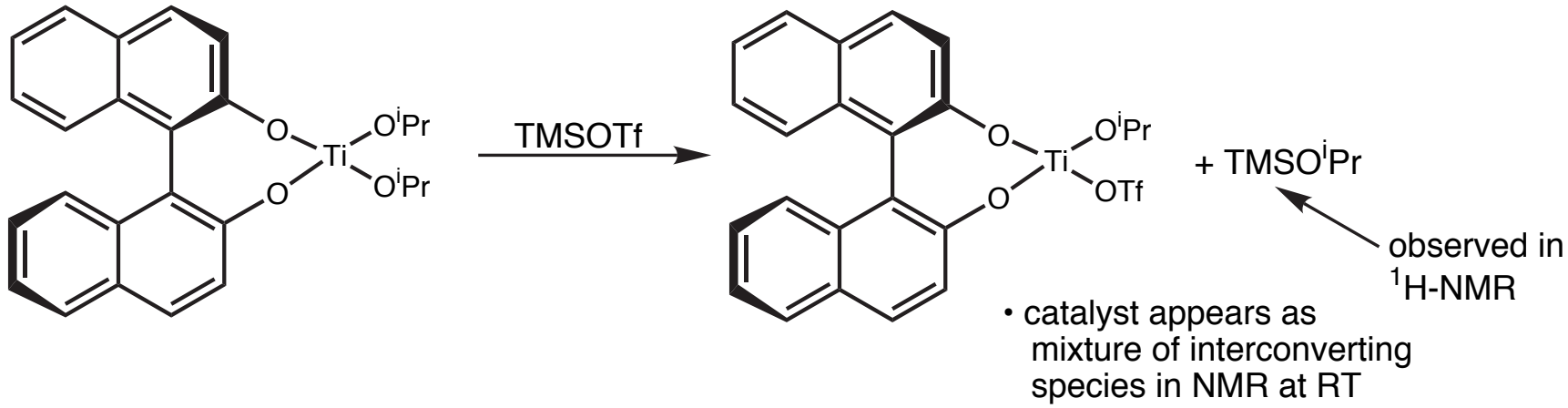
[a] 2 equiv. of cyclopropane used

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

Gleason's Homoaldol reaction

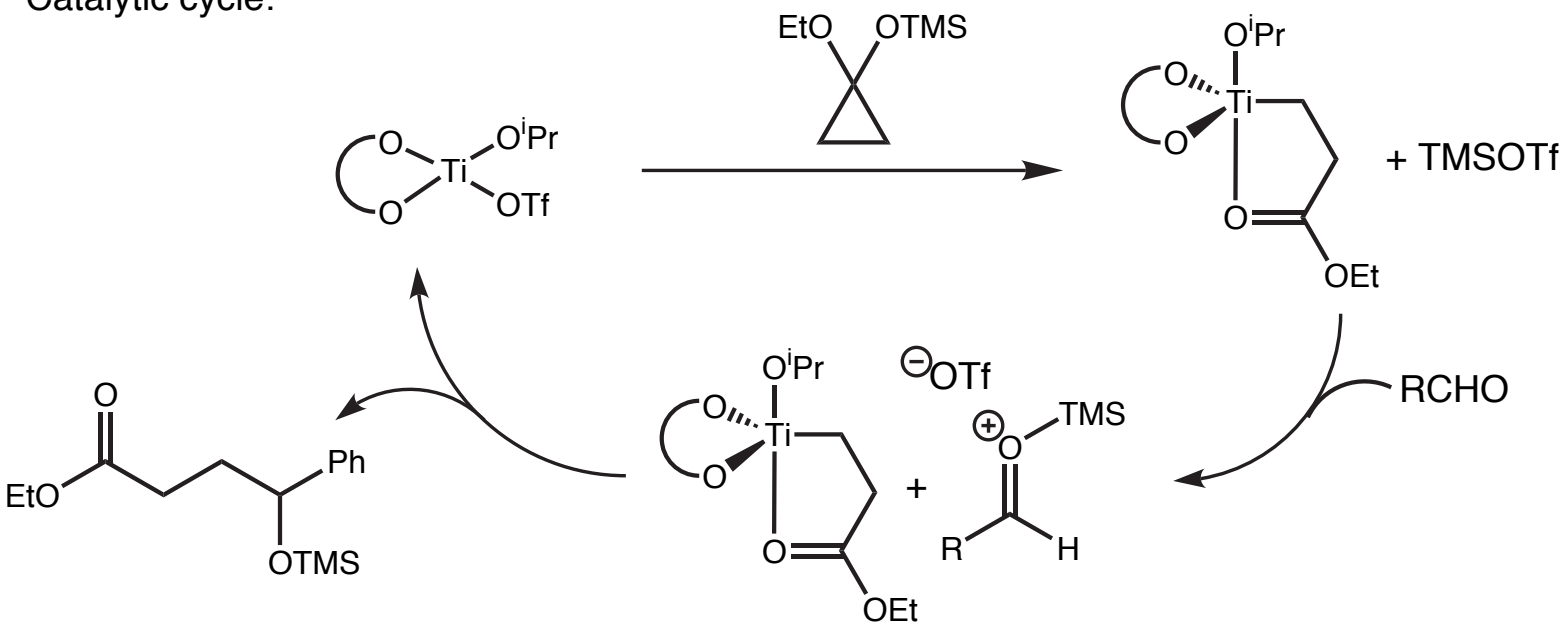
Proposed Catalyst and Catalytic Cycle

Catalyst:



- catalyst appears as mixture of interconverting species in NMR at RT

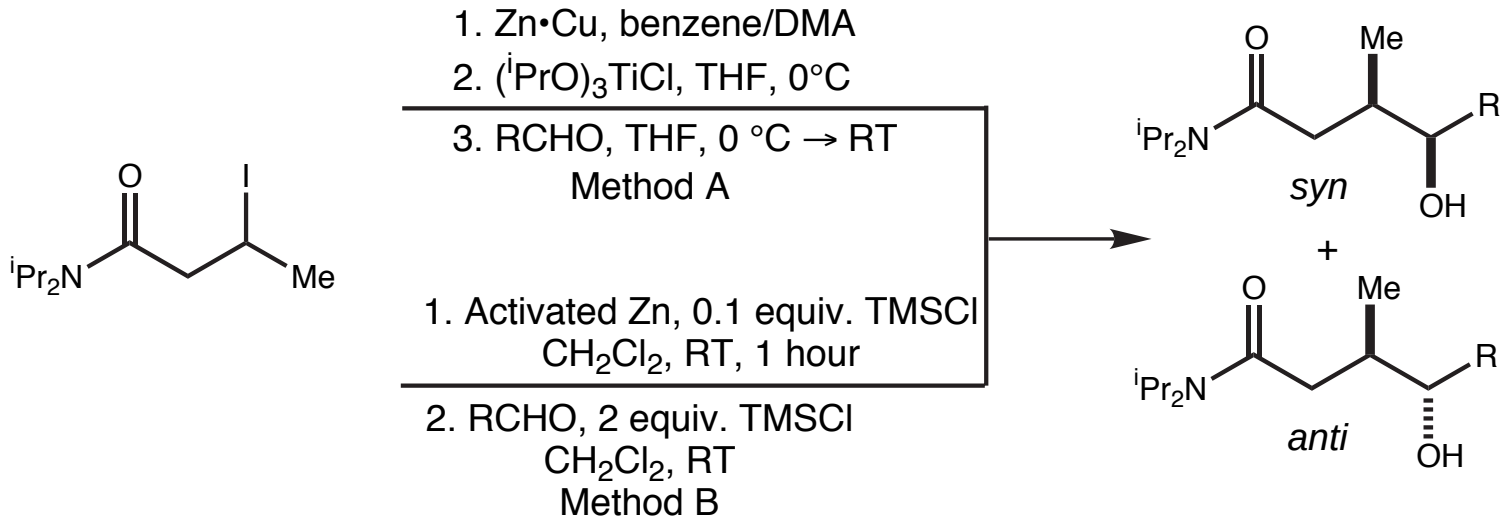
Catalytic cycle:



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

Diastereoselective Homoaldol Reactions of Amide-homoenolates

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



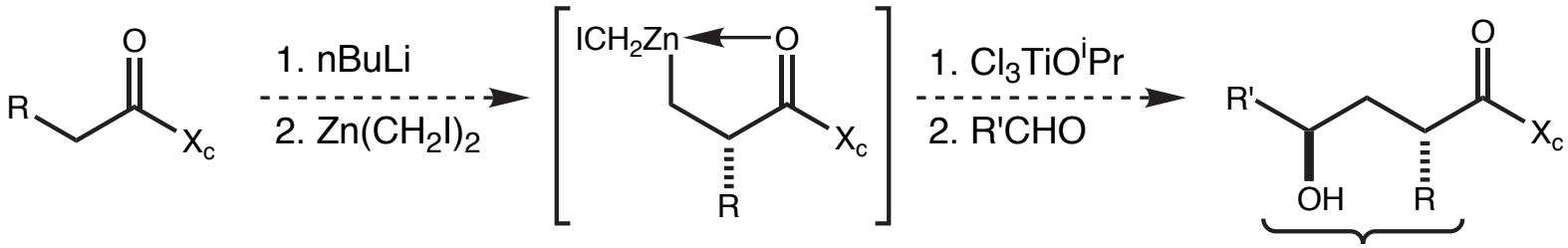
R	Method	Time (h)	Yield	*syn:anti*
Ph	A	3	79	94 : 6
	B	2.5	82	13 : 87
o-MeOPh	A	3	87	85 : 15
	B	0.6	95	25 : 75
2-furyl	A	0.5	61	96 : 4
	B	0.6	60	38 : 62

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

Tandem Asymmetric Enolate Homologation - Homoaldol Reaction

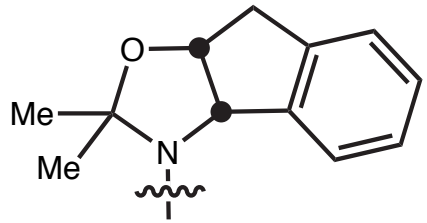
Asymmetric Synthesis of α-alkyl, γ-hydroxy Carbonyl Compounds

• idea:

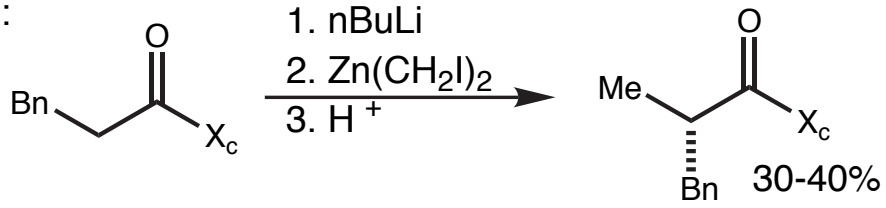


2 new stereocenters generated

X_c =



• initial results:



30-40%

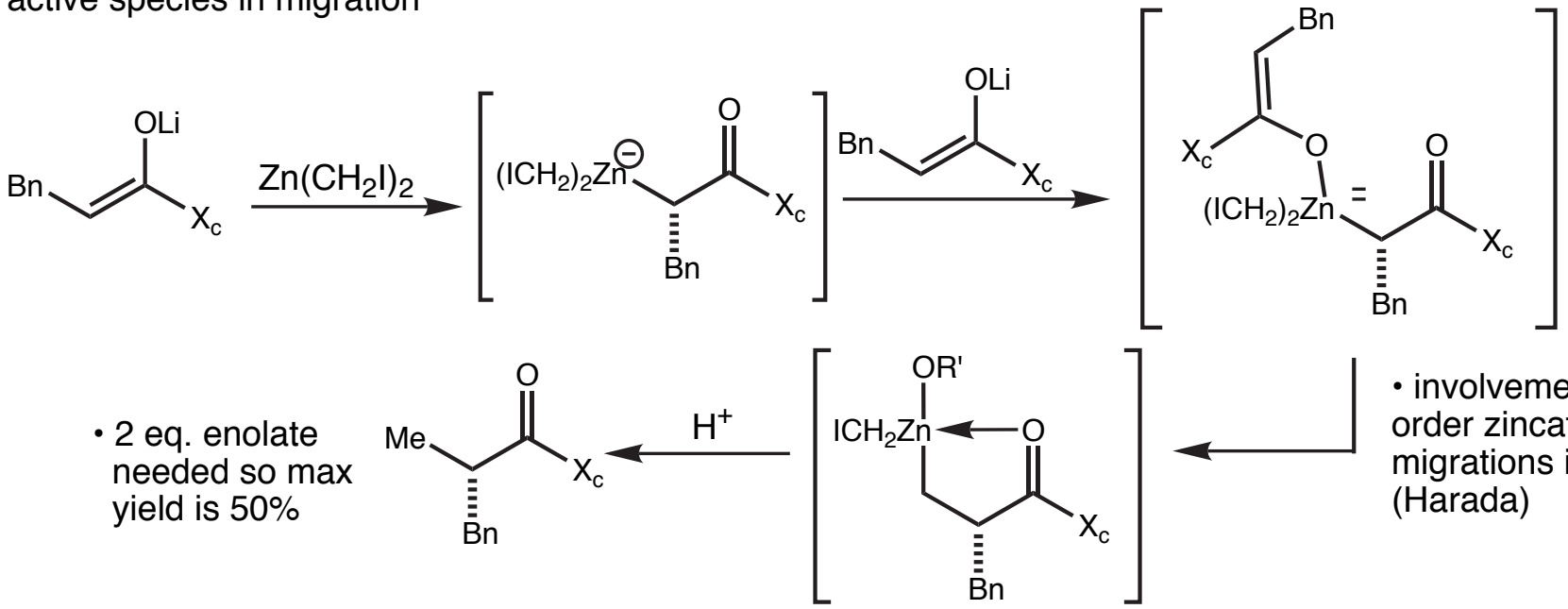
But ReactIR showed disappearance of enolate and appearence of new species

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

Tandem Asymmetric Enolate Homologation - Homoaldol Reaction

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

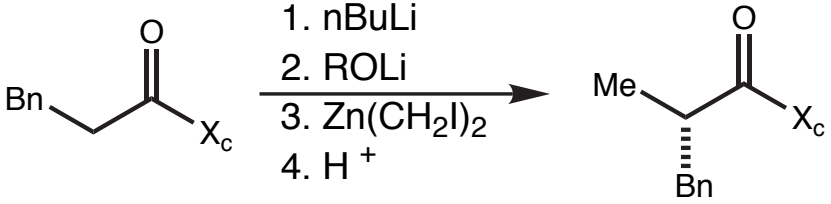
• proposal: zinc enolate unreactive towards homolagation; higher order zincate (zincate + extra enolate) active species in migration



• 2 eq. enolate needed so max yield is 50%

• involvement of higher order zincates in 1,2-migrations is known (Harada)

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



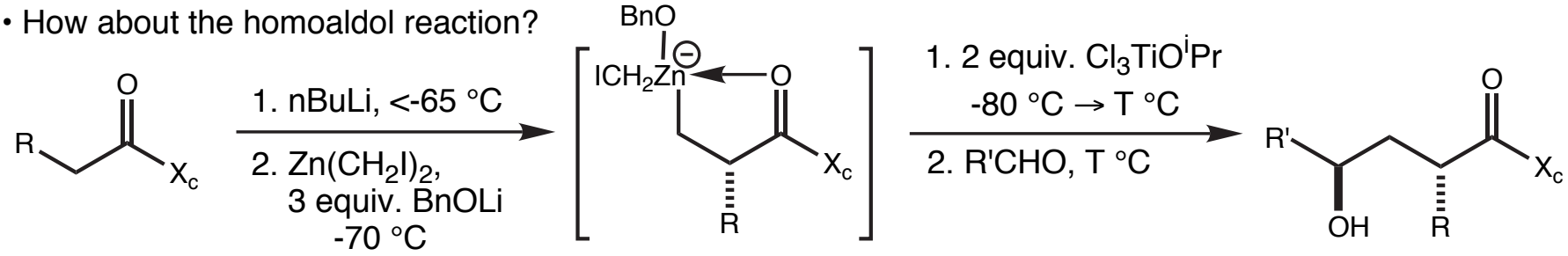
ROLi	Conversion
EtOLi	35
nPrOLi	74
BnOLi	82 (78% isolated)
$LiO(CH_2)_2OLi$	31

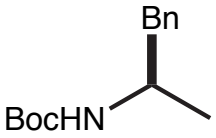
McWilliams, *J.Am.Chem.Soc.*, **1996**, *118*, 11970
Harada, *J.Org.Chem.*, **1993**, *113*, 2958

Tandem Asymmetric Enolate Homologation - Homoaldol Reaction

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

- How about the homoaldol reaction?

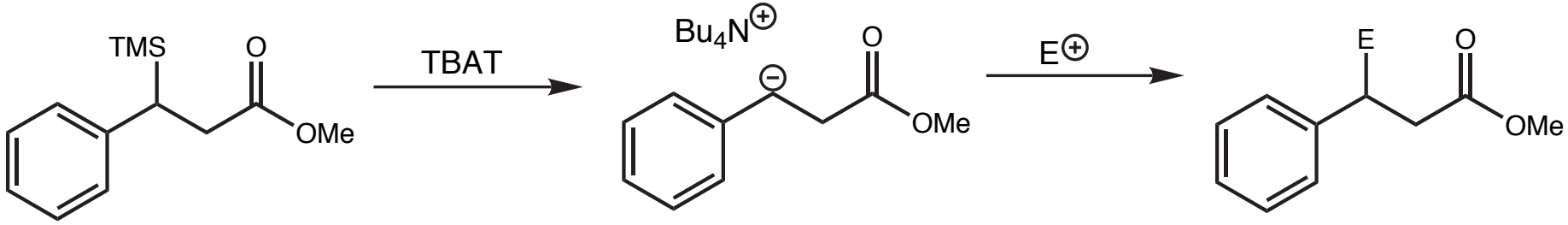


Aldehyde (R')	R	T (°C)	de (%)	Yield
	Bn	-20	≥99	59
	Me	-20	82	58
phenyl	Bn	-40	82	50
phenyl	Me	-40	80	44
iso-propyl	Bn	-50	76	53
n-butyl	Bn	-20	64	53

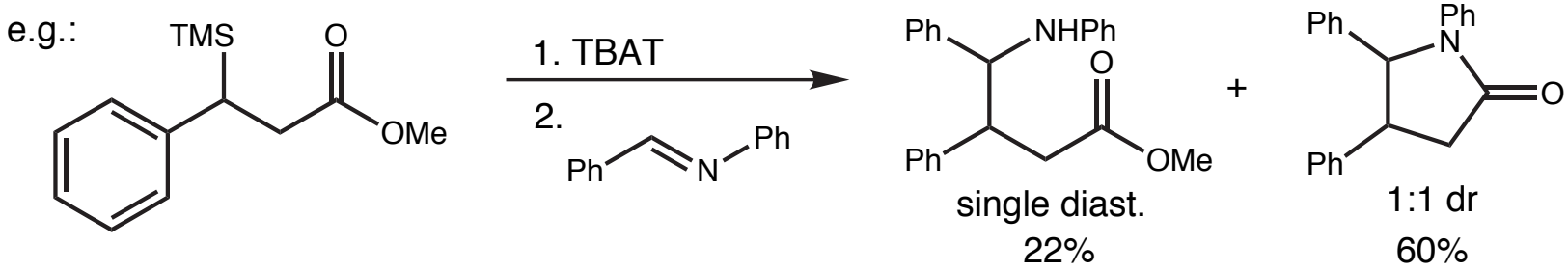
McWilliams, *J.Am.Chem.Soc.*, **1996**, *118*, 11970

Reactive Homoenolates

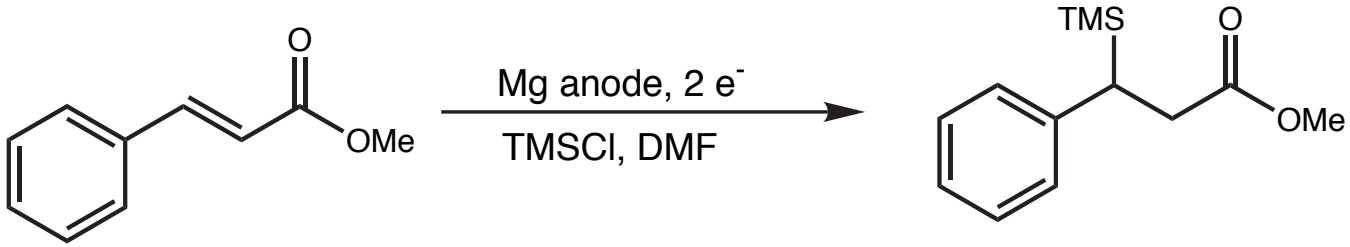
First Synthesis of a Metal-free Homoenolate



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



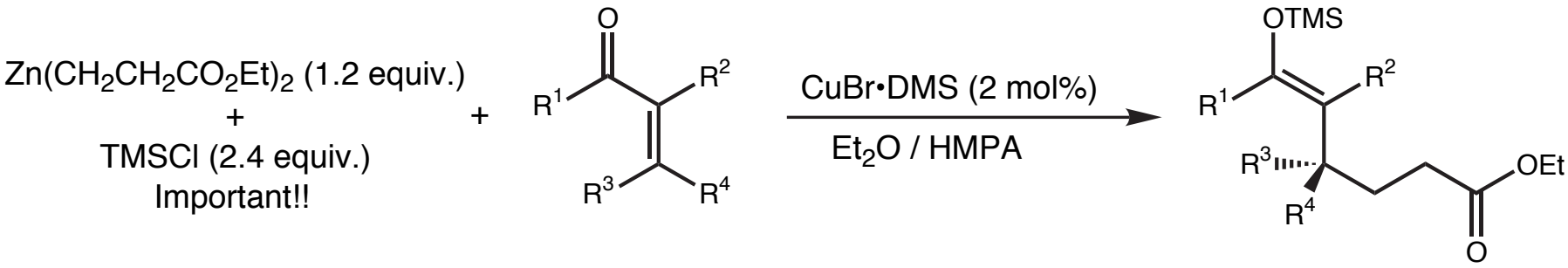
- substrate made easily using Nishiguchi method

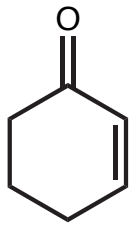
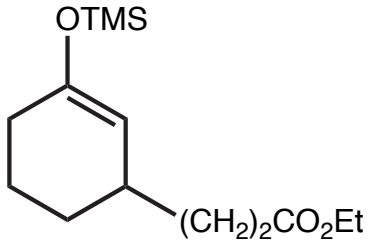
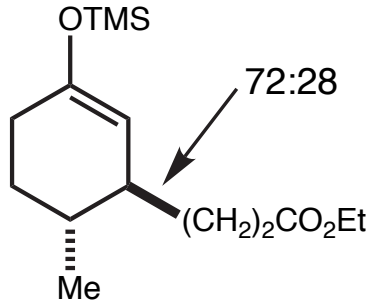


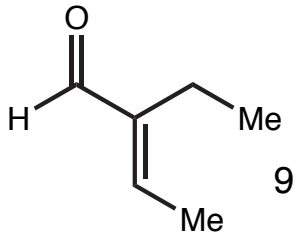
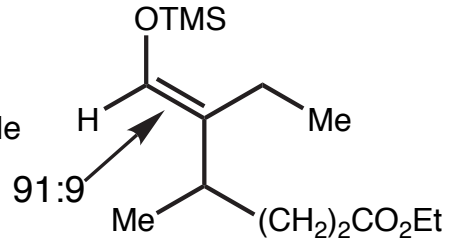
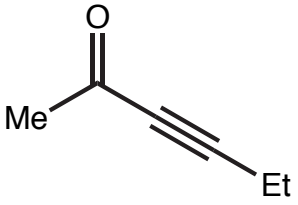
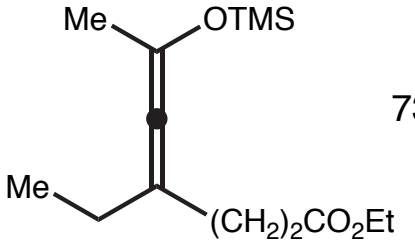
Fry, *Tetrahedron Lett.*, **1999**, *40*, 7945
Nishiguchi, *Tetrahedron Lett.*, **1992**, *33*, 5515

Conjugate Addition of Zinc Homoenolates

Synthesis of δ,ε-(silylenolether)-esters



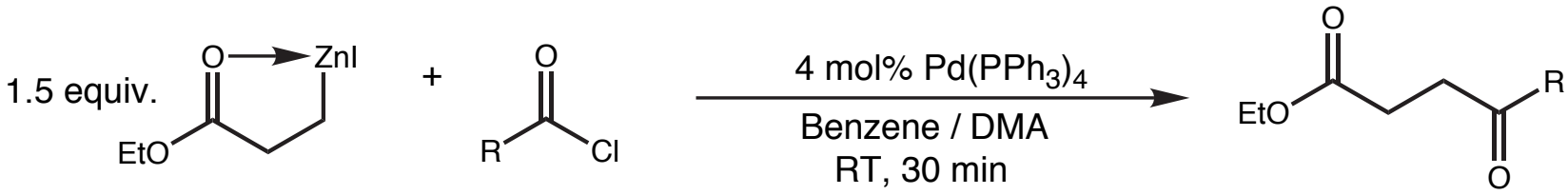
Enone	Product	Yield
		93
		78

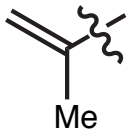
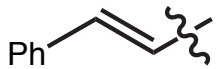
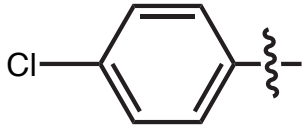
Enone	Product	Yield
		75
		73

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

Acylation of Zinc Homoenolates

Synthesis of γ-ketoesters - Yoshida

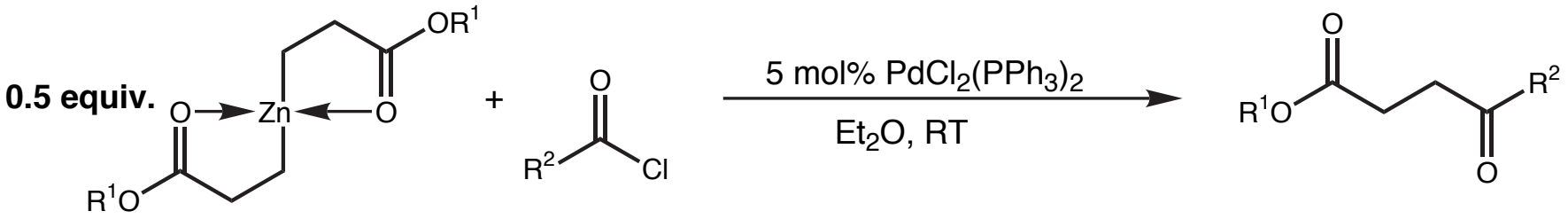


R	Yield
Ph	100
	90
	92
	100

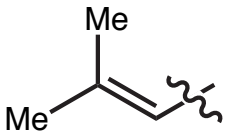
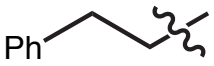
Yoshida, *Tetrahedron Lett.*, **1985**, *26*, 5559

Acylation of Zinc Homoenolates

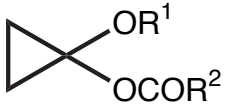
Synthesis of γ-ketoesters - Nakamura



• note: only 0.5 equiv. of Zn species needed so both homoenolates are transferred

R^1	R^2	Yield
Et	Ph	93
^{i}Pr		81
Et		83
^{i}Pr	^{t}Bu	50

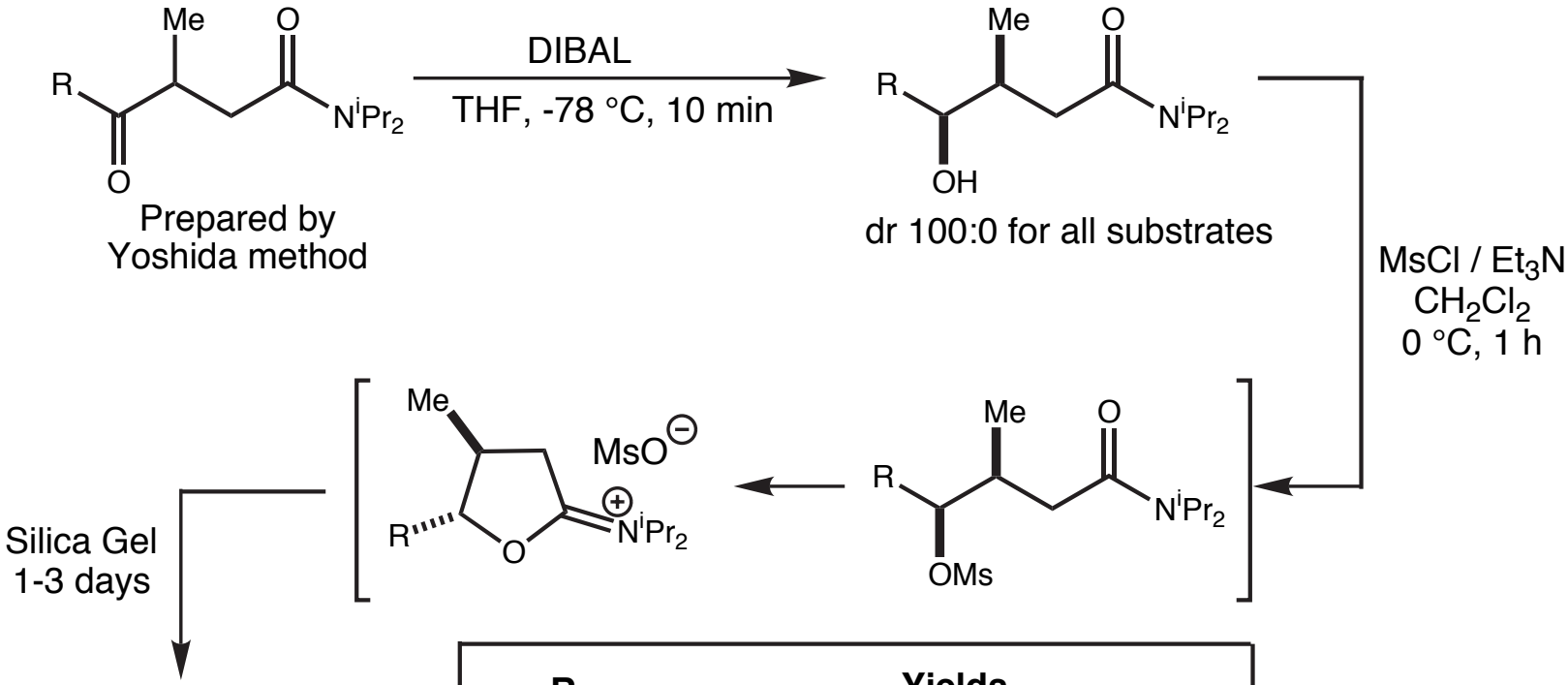
• when carried out in $CDCl_3$ got quantitative O-acylation (with or without Pd)

i.e. 

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

Application of Homoenolate Acylation

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

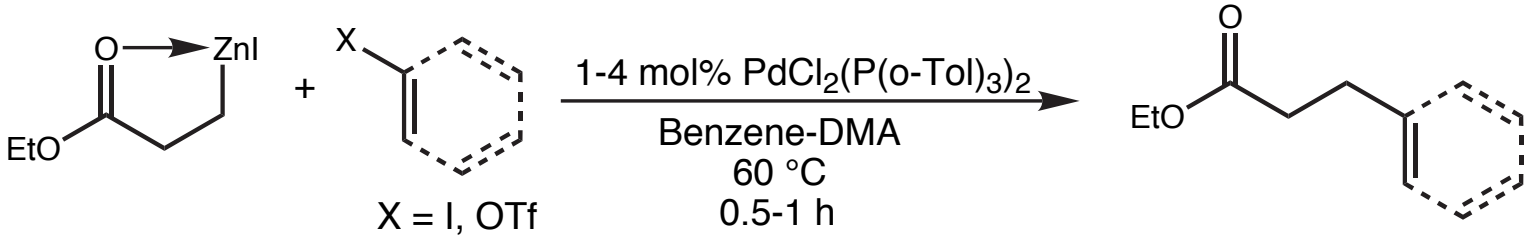


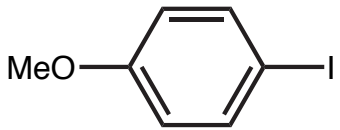
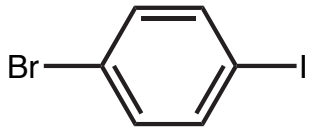
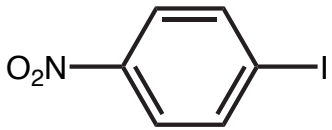
R	Yields	
	Reduction	Cyclization
Ph	87	82
p-ClPh	93	95
p-MeOPh	90	92
Bn	62	83

Asaoka, *Heterocycles*, **2000**, *52*, 227

Arylation and Vinylation of Zinc Homoenolates

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



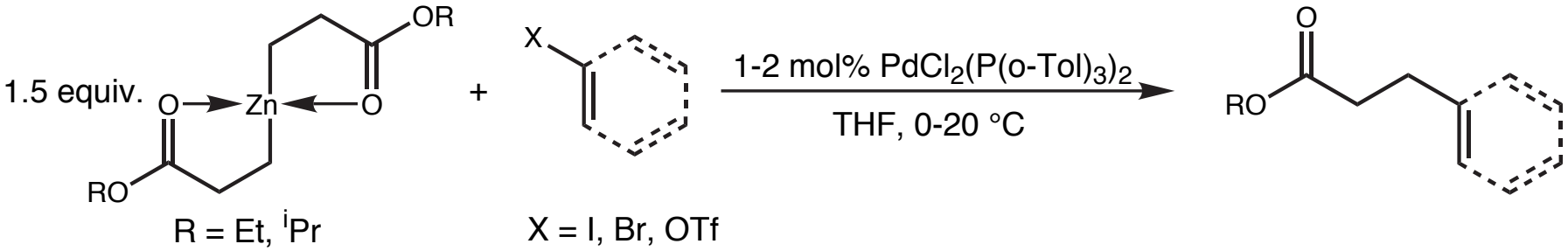
Coupling Partner	Yield
	74
	96
	67
	80

← Only vinylation example given

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

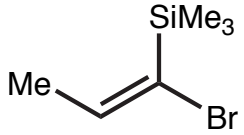
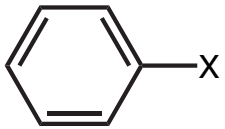
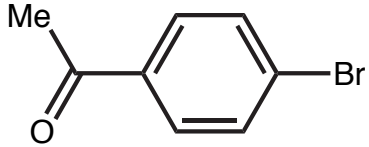
Arylation and Vinylation of Zinc Homoenolates

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



R = Et, ^{i}Pr

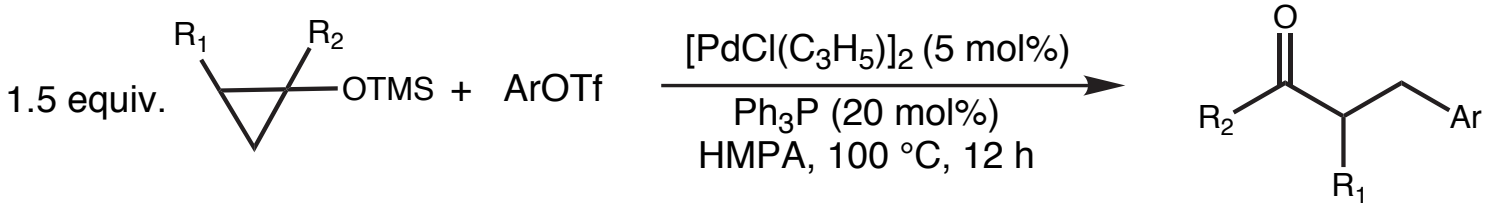
X = I, Br, OTf

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

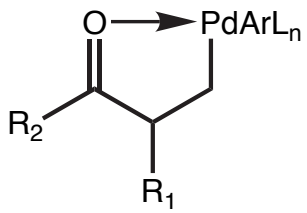
Nakamura, *J.Org.Chem.*, **1987**, *26*, 8056

Arylation of Palladium Homoenolates

Catalytic Formation of β–aryl Ketones



• proposed to proceed via

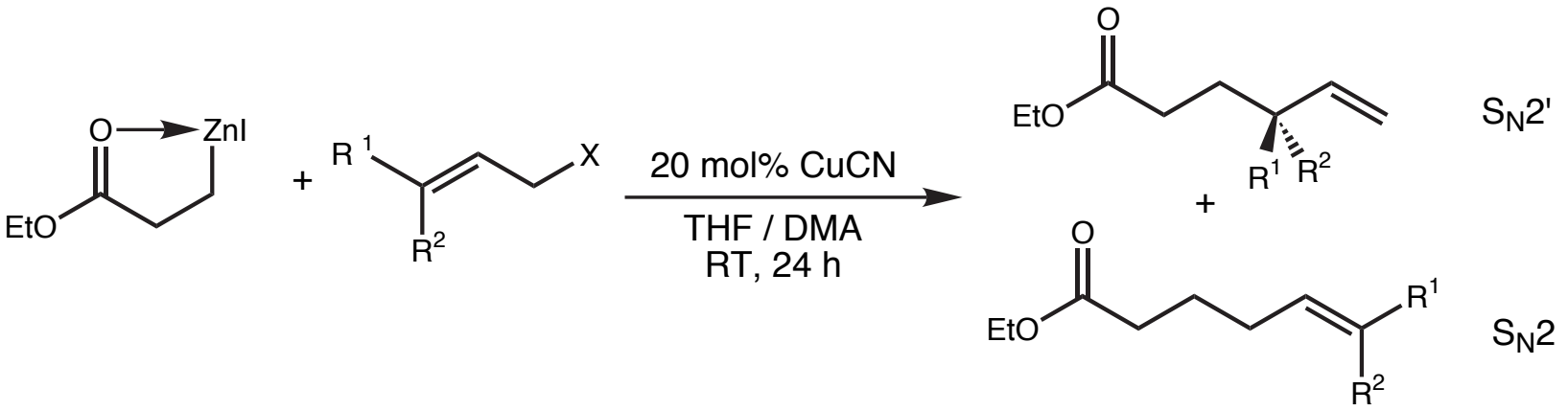


R_1	R_2	Ar	Yield
$-CH_2CH_2CH_2CH_2-$		1-napthyl	84
$-CH_2CH_2CH_2CH_2-$		p-NO_2Ph	68
H	p-OMePh	Phenyl	65
n-Heptyl	H	1-napthyl	58

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

Allylation of Zinc Homoenolates

Synthesis of δ,ε-unsaturated Esters - Yoshida

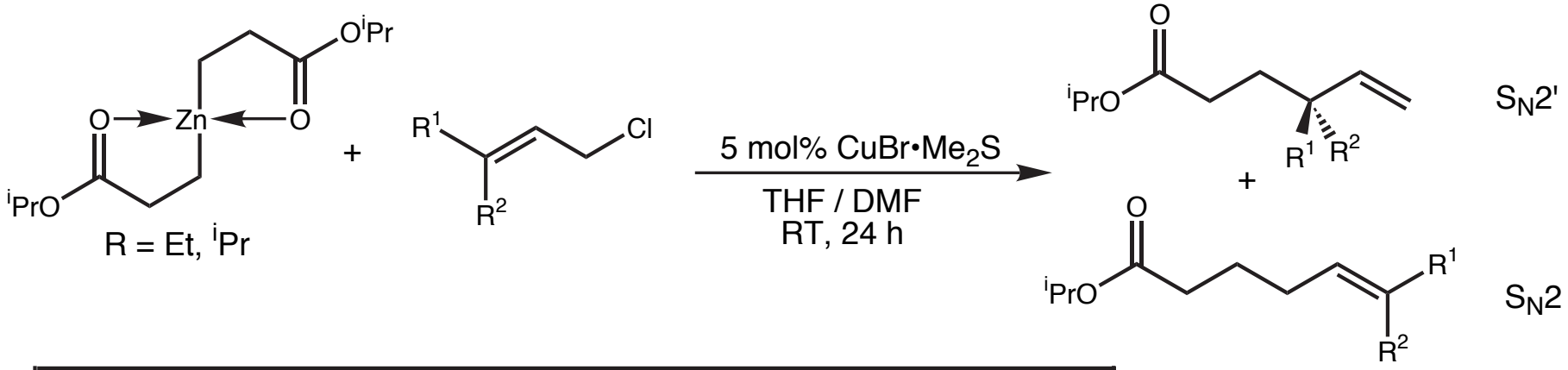


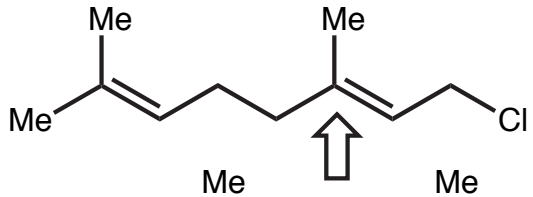
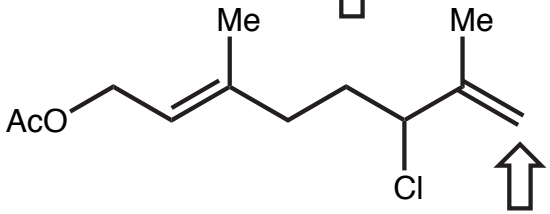
R^1	R^2	X	Yield	S_N2' : S_N2
H	H	OTs	89	--
Ph	H	OTs	80	87 : 13
		Br	93	88 : 12
		Cl	99	87 : 13
CO_2Me	H	Br	80	100 : 0

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

Allylation of Zinc Homoenolates

Synthesis of δ,ε-unsaturated Esters - Nakamura



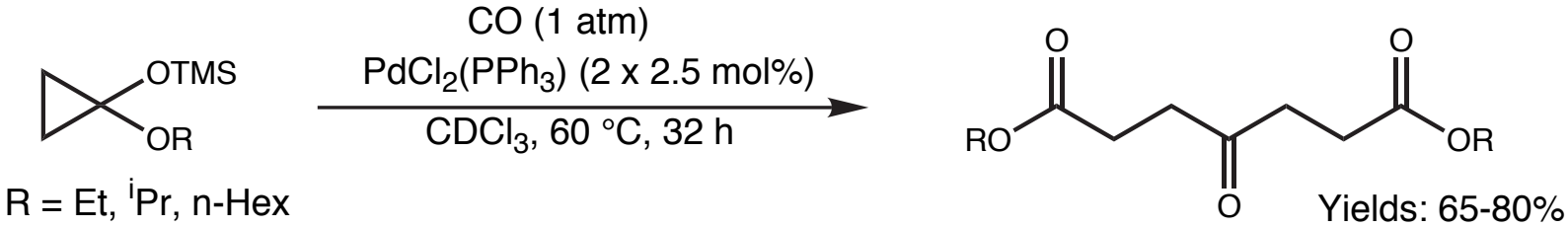
Allyl chloride	Yield	$S_N2' : S_N2$
	97	96 : 4
	65	1 : 99
	81	88 : 12
	72	100 : 0

← Catalyst changed to 5 mol% $NiCl_2$•dppe

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

Carbonylative Symmetrical Coupling of Palladium Homoenolates

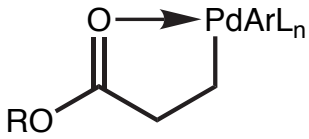
Catalytic Synthesis of 4-keto Pimelates



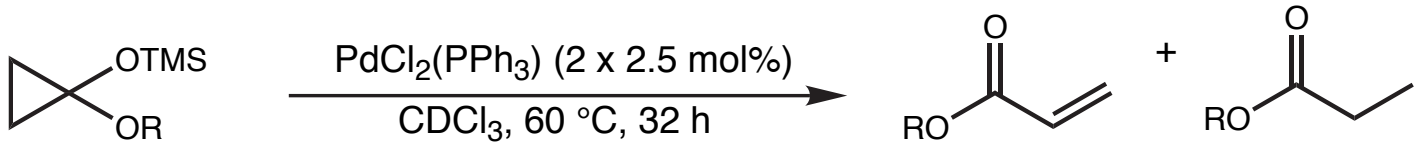
R = Et, ^{i}Pr, n-Hex

Yields: 65-80%

- proposed to proceed via



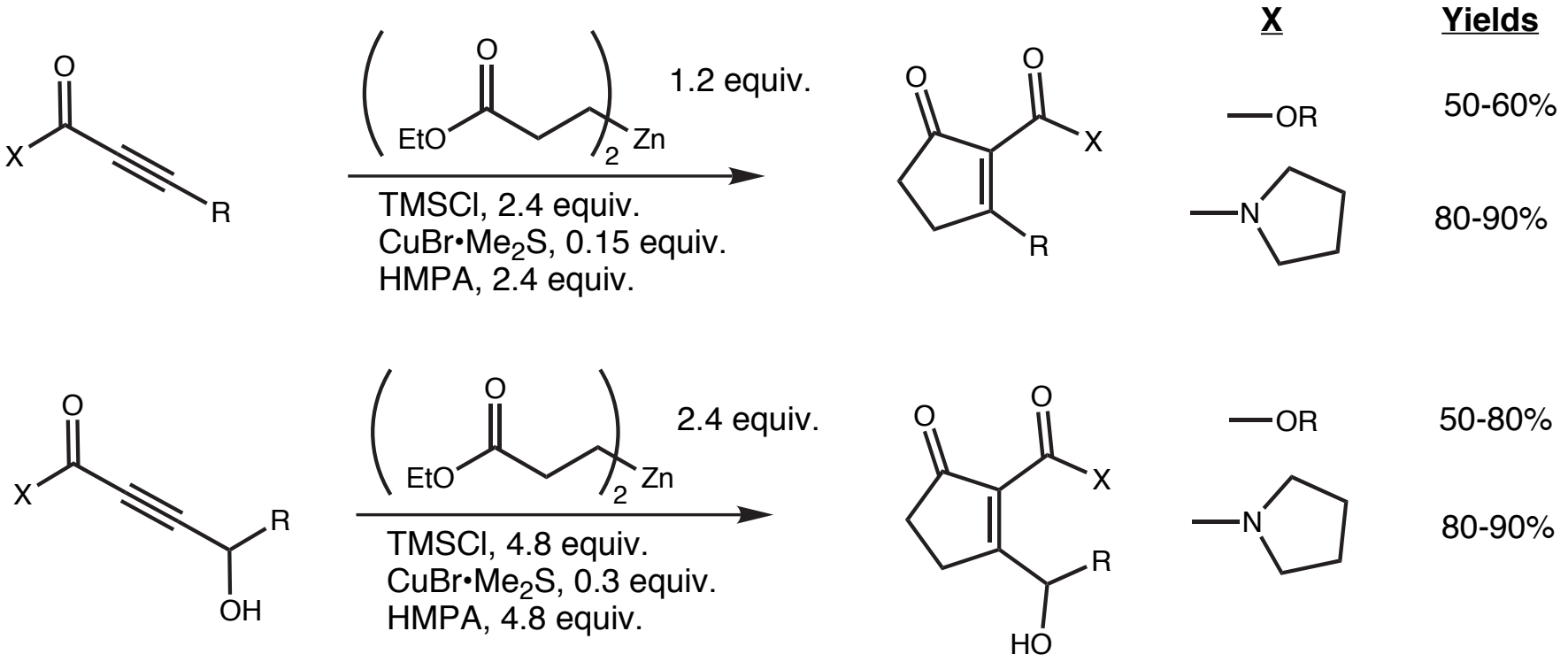
- evidence



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

Crimmins' Cyclopentenone Synthesis

Introduction and Generality

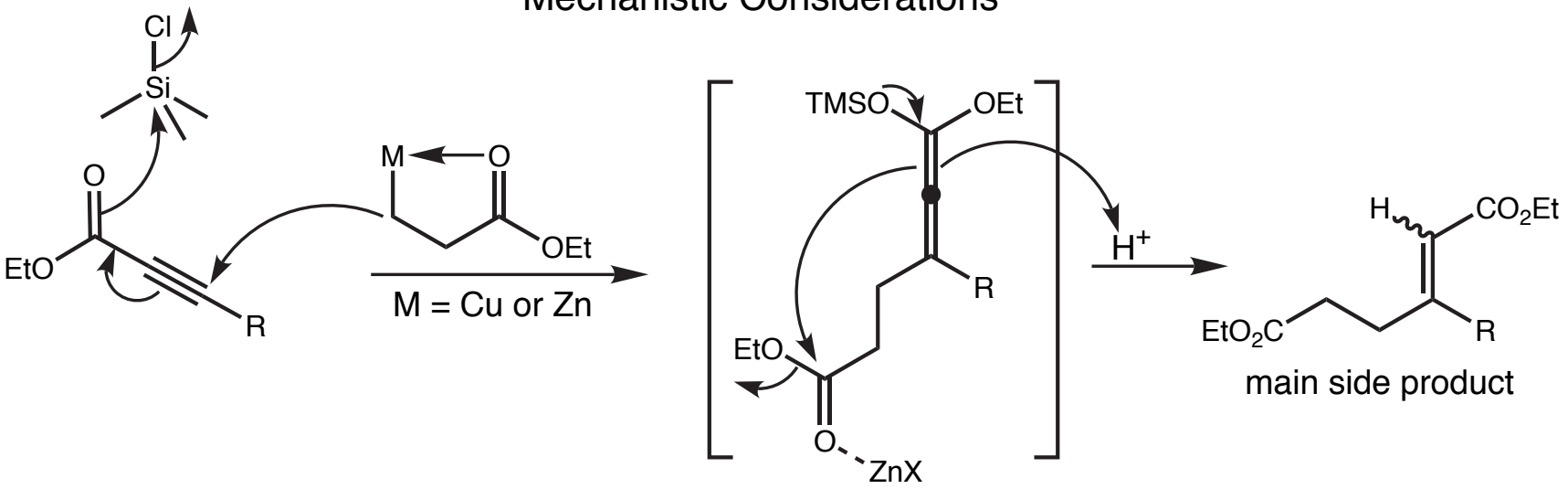


Functionality supported in R: ethers, epoxides, furans, α,β unsaturated esters

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

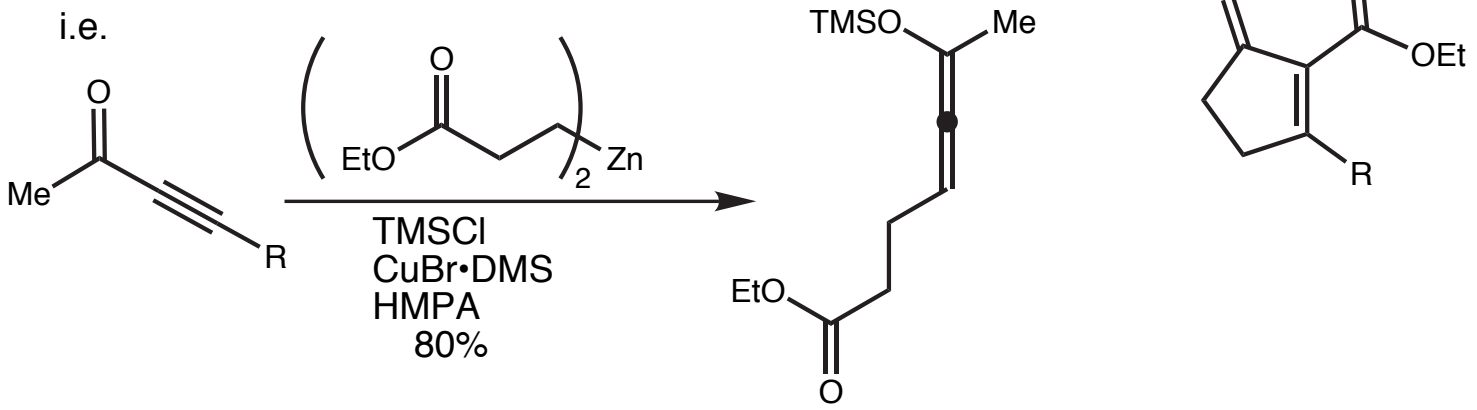
Crimmins' Cyclopentenone Synthesis

Mechanistic Considerations



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

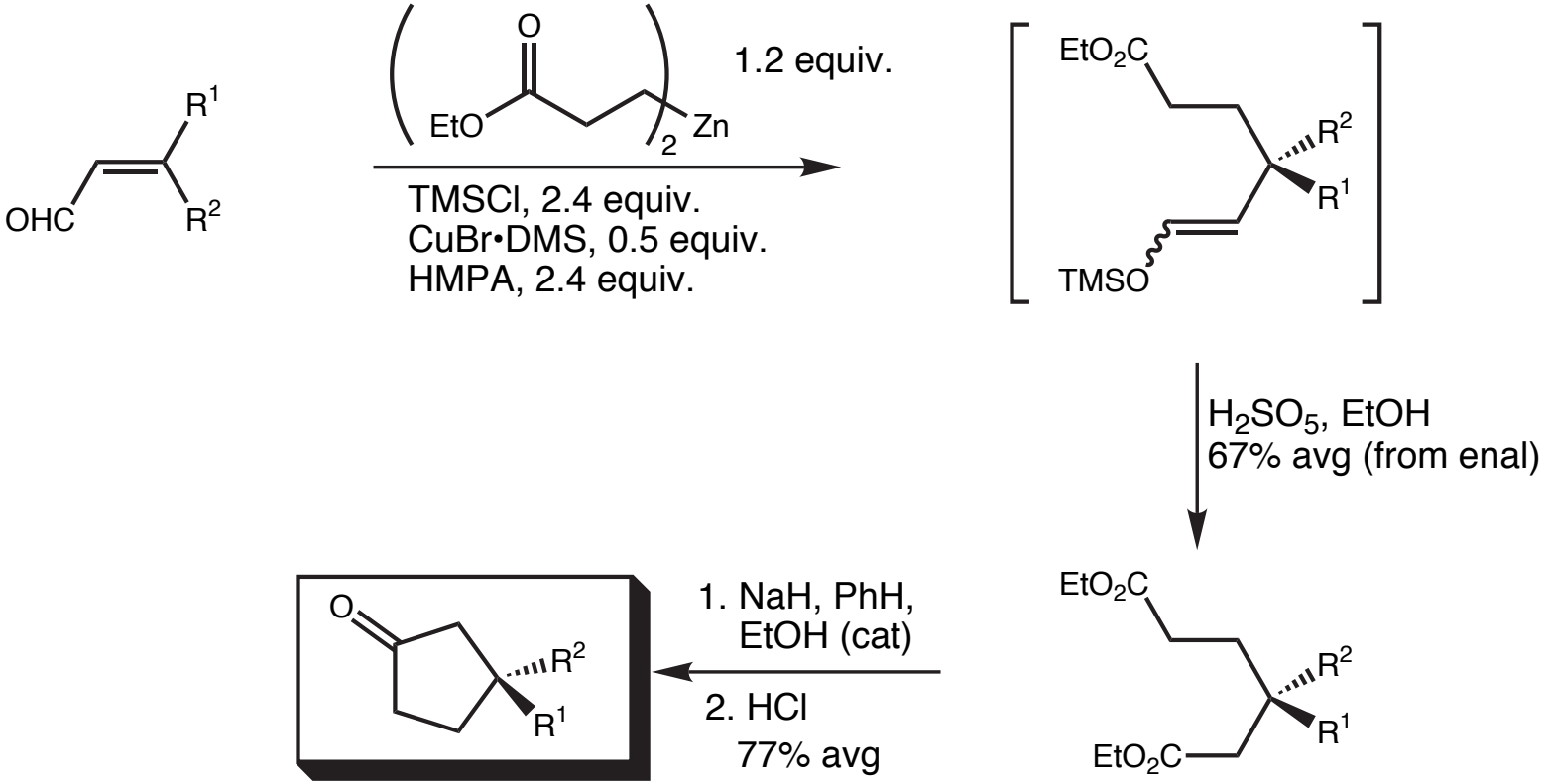
i.e.



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

Leahy Cyclopentannulation

Synthesis of 3,3-disubstituted cyclopentanones



Substrates studied:

$R^1 = R^2 = n$-Bu

$R^1 = R^2$= Ph

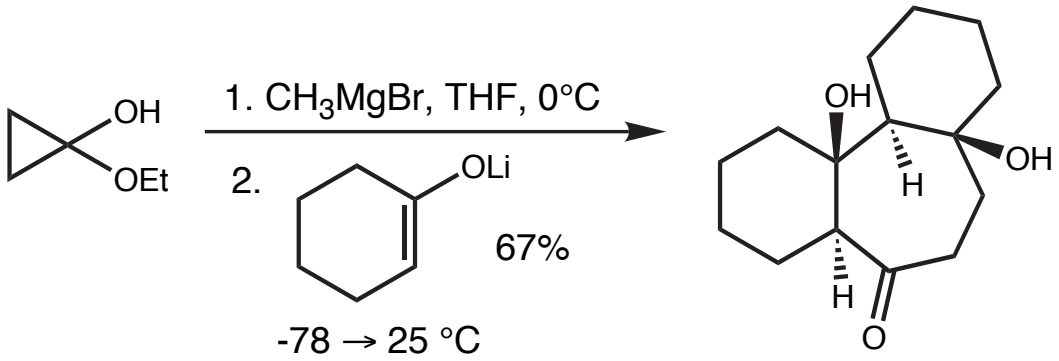
R^1 = Ph, R^2 = Me

R^1 = Ph, R^2 = H

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

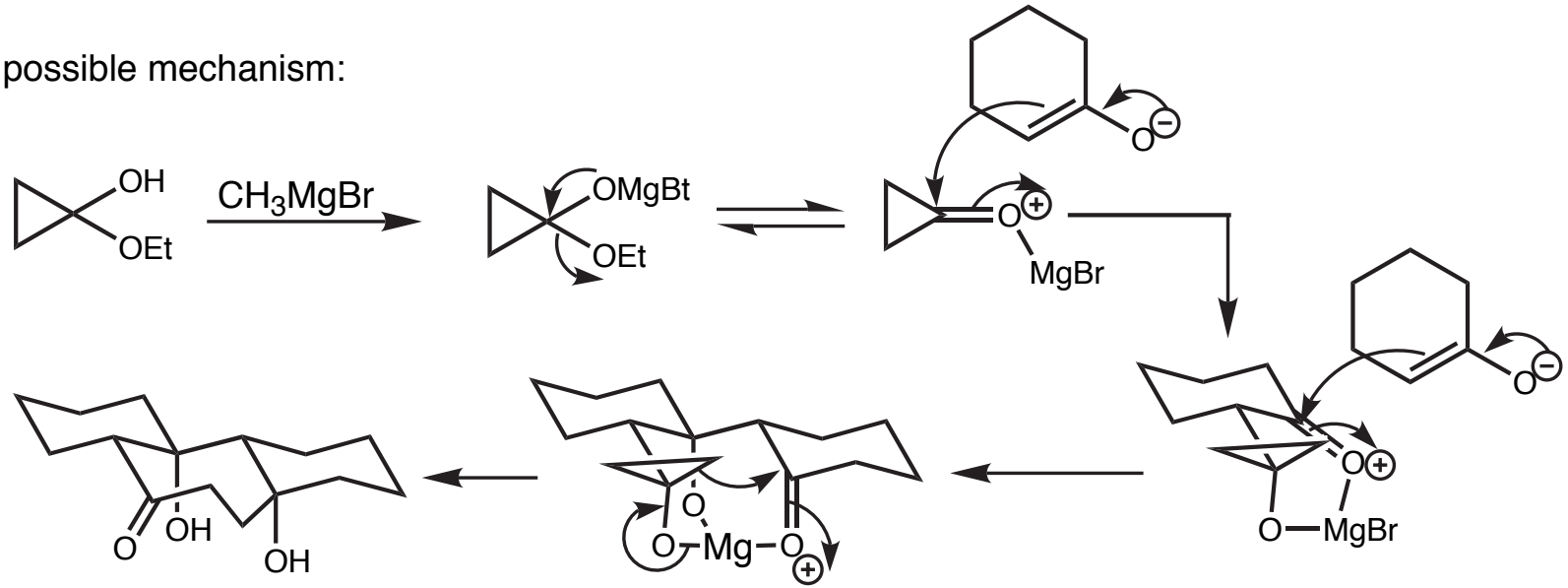
Tandem Aldol / Aldol / Homoaldol Reaction

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



Relative stereochemistry verified by x-ray crystallography

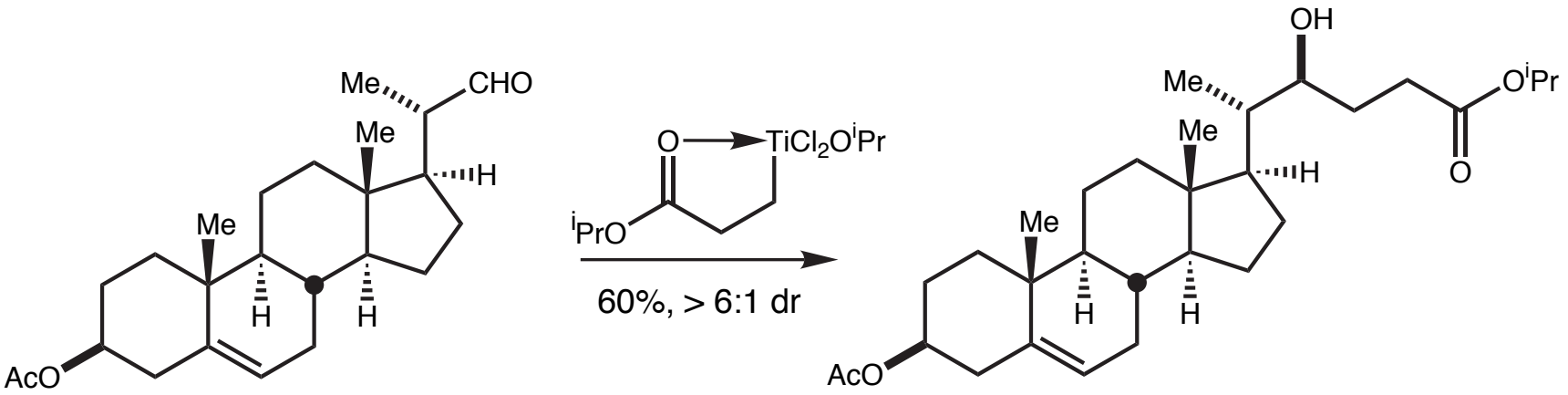
A possible mechanism:



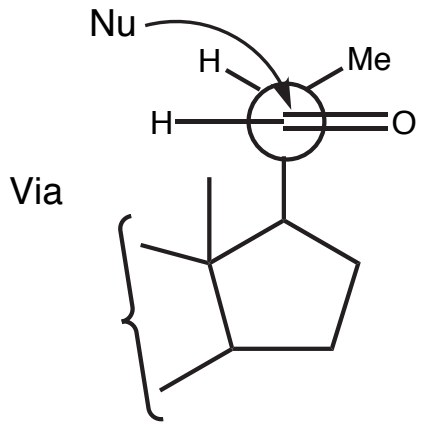
Helquist, *J.Am.Chem.Soc.*, **1986**, *108*, 8313

Synthetic Examples

Depresosterol



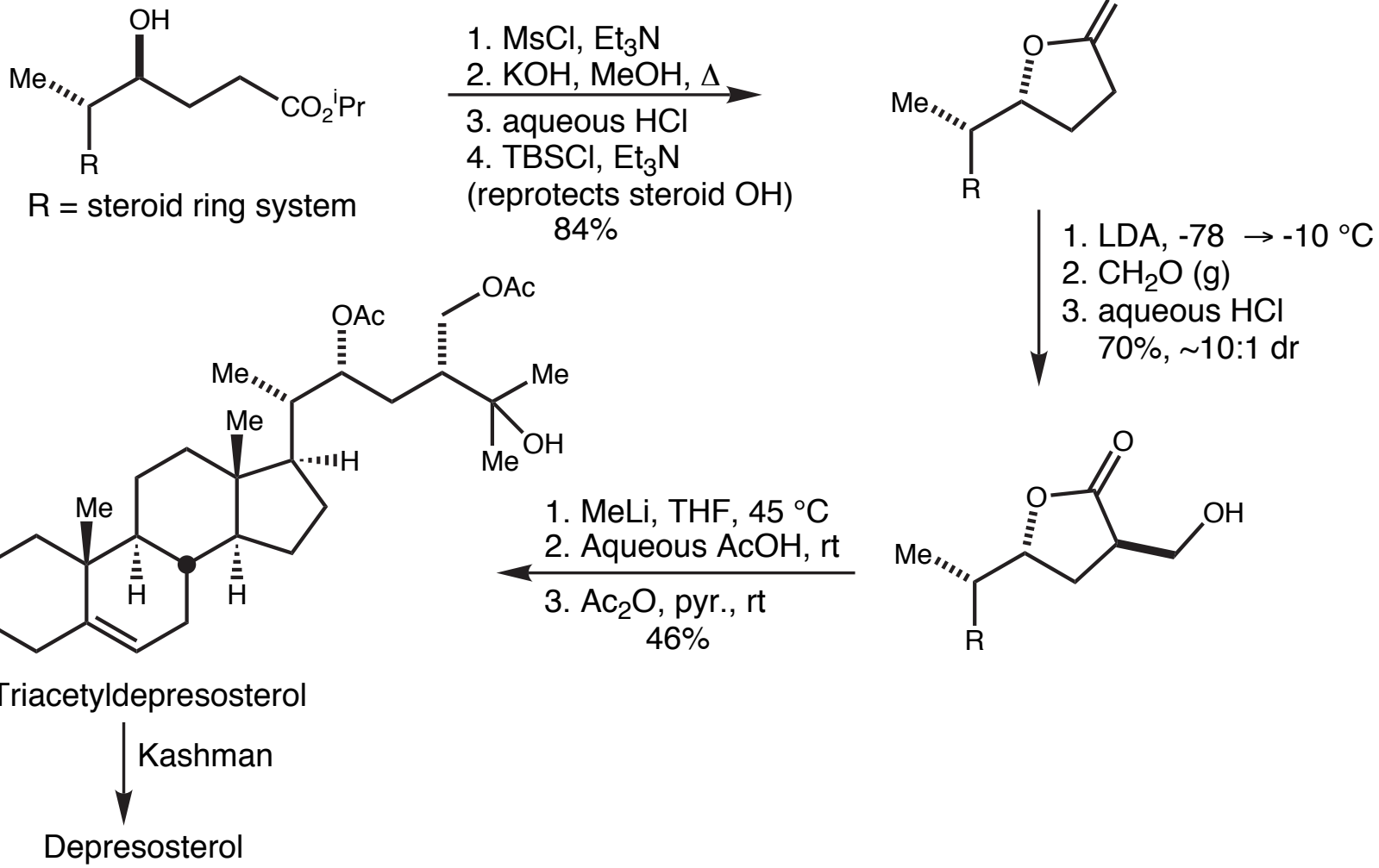
- trichlorotitanium homoenolate is not reactive enough to add to hindered aldehyde



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

Synthetic Examples

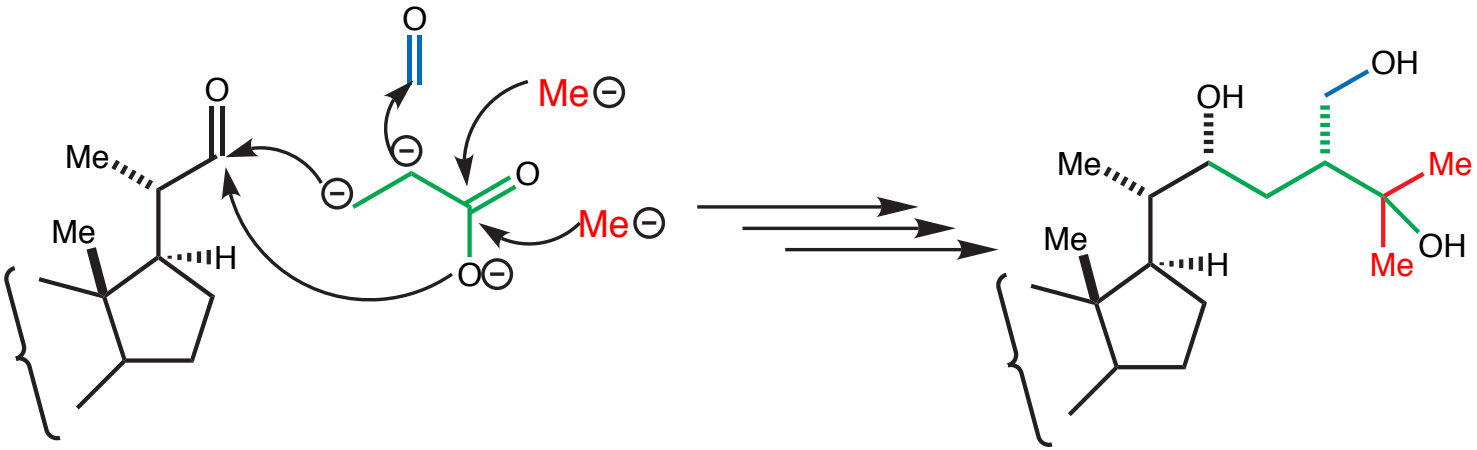
Depresosterol - completion of the formal synthesis



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

Synthetic Examples

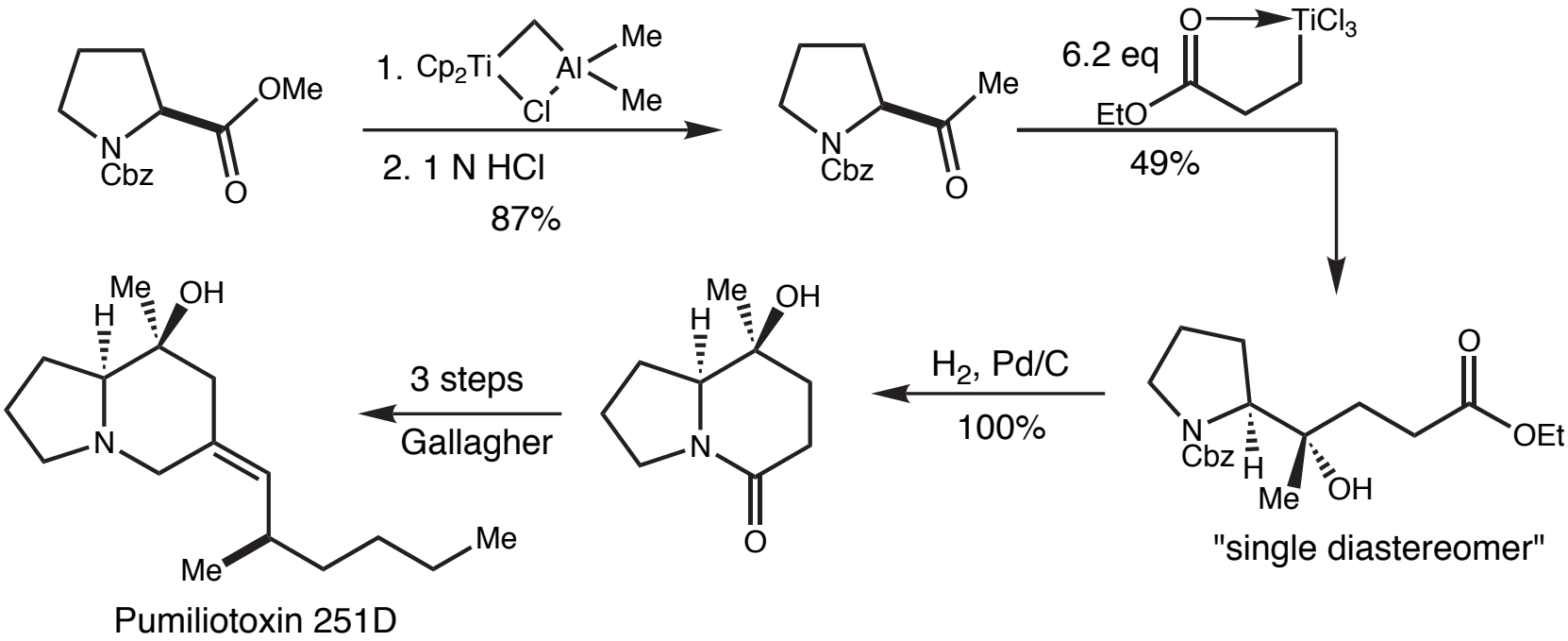
Depresosterol - Maximizing Homoenolate Functionality



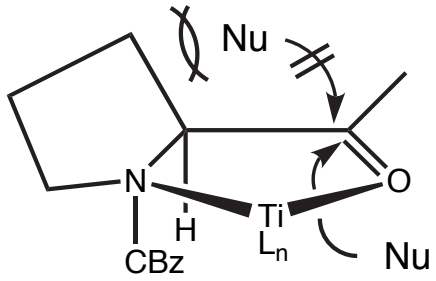
Nakamura, *J.Am.Chem.Soc.*, **1985**, *107*, 2138

Synthetic Examples

Pumiliotoxin 251D



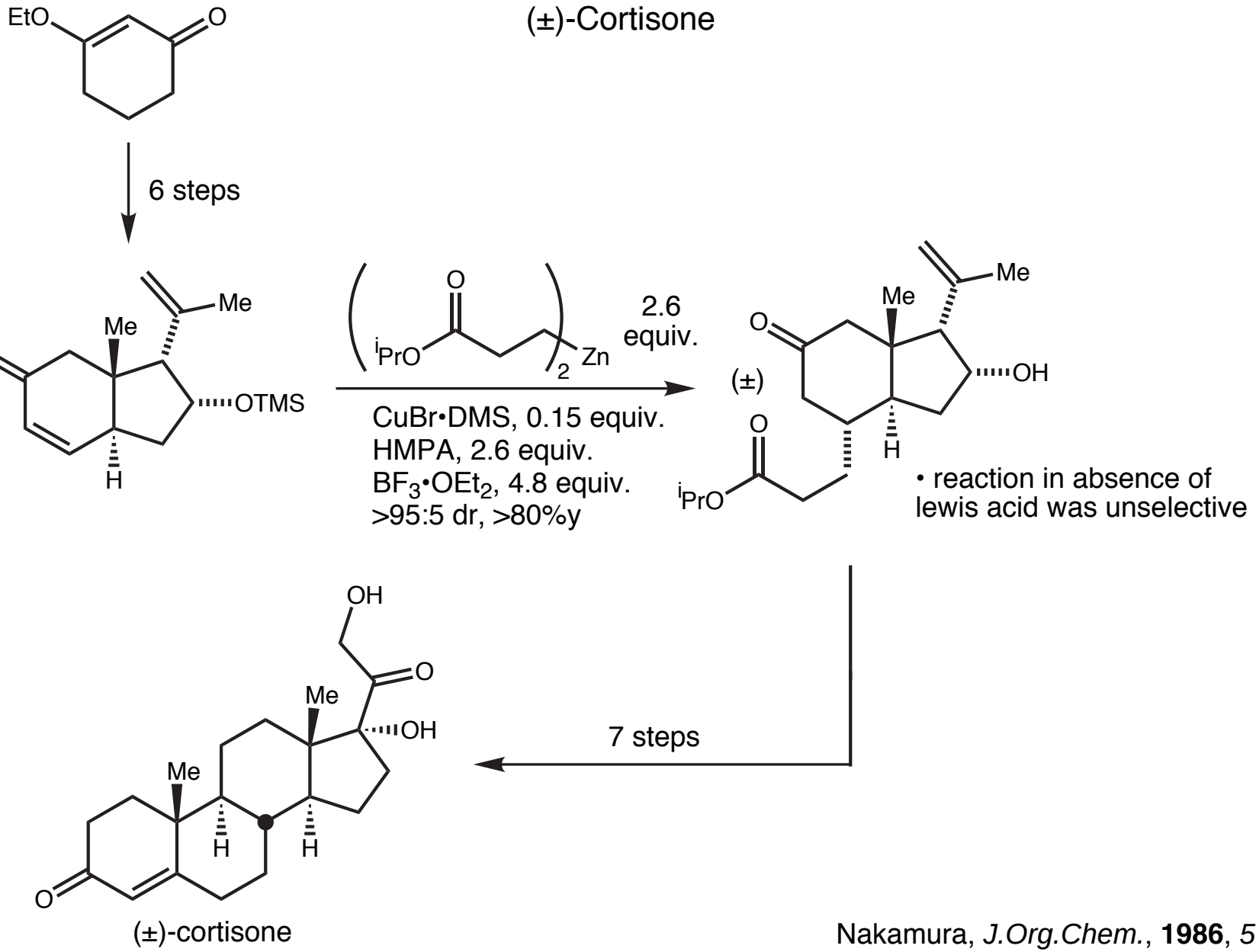
via:



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

Synthetic Examples

(±)-Cortisone

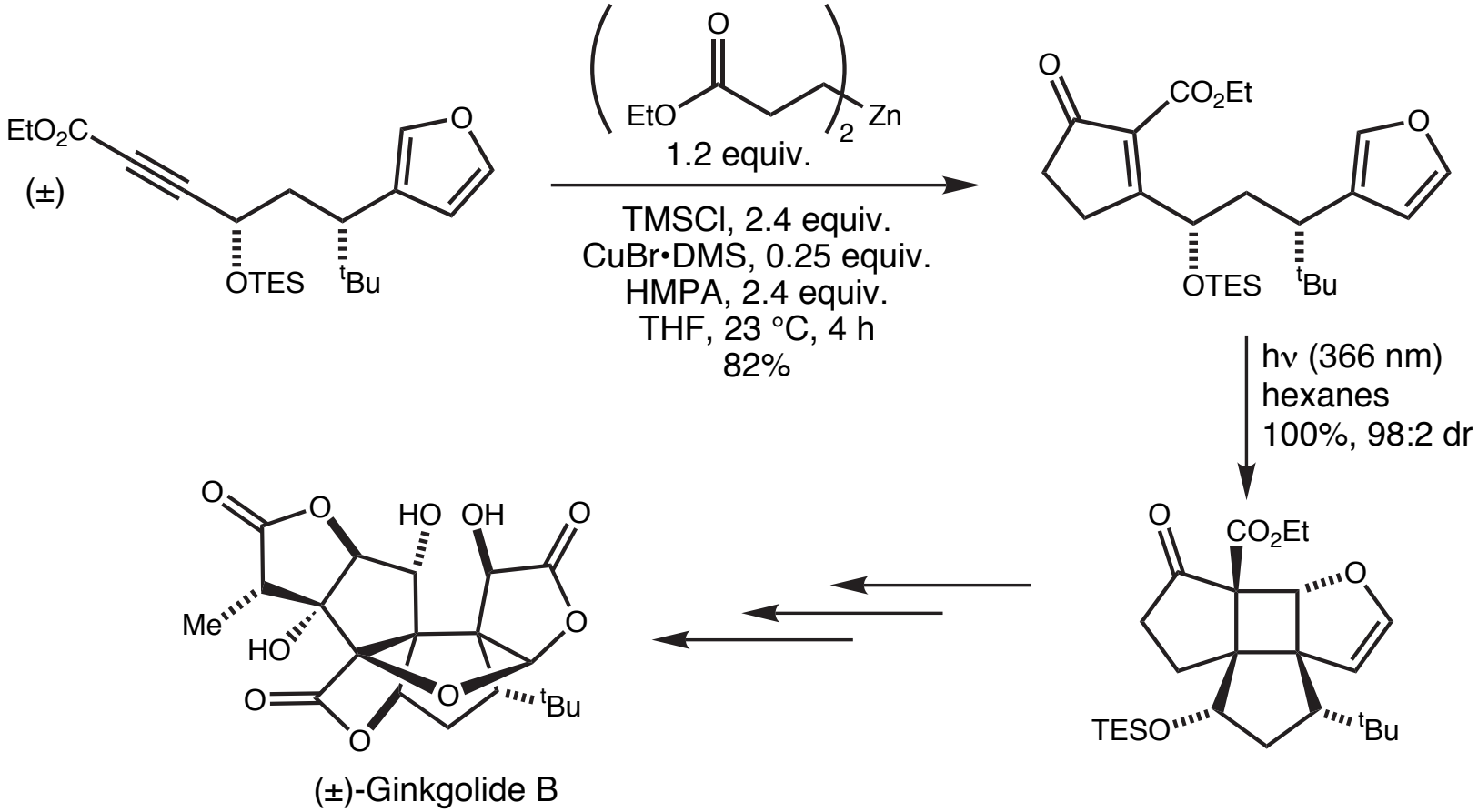


(±)-cortisone

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

Synthetic Examples

(±)-Ginkgolide B

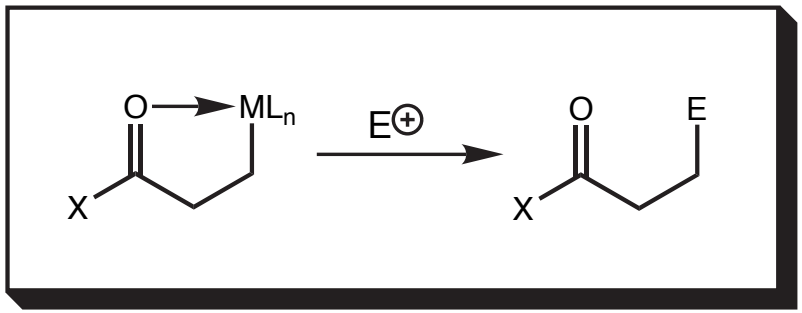


(±)-Ginkgolide B

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) → enantioselective varients on the horizon?
- synthetic applications, while limited thus far, illustrate functional diversity of homoenolate adducts