Chemistry of Homoenolates

Topic review
August 21st, 2014

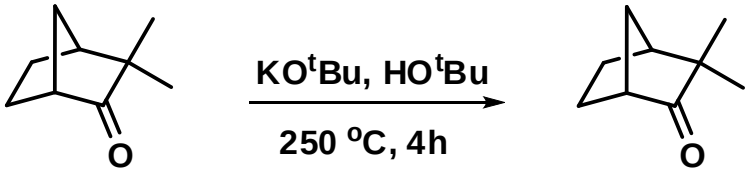
Sankar Rao Suravarapu

Prof. Dr. Philippe Renaud
University of Bern, Department of Chemistry and Biochemistry

Chemistry of Homoenolates

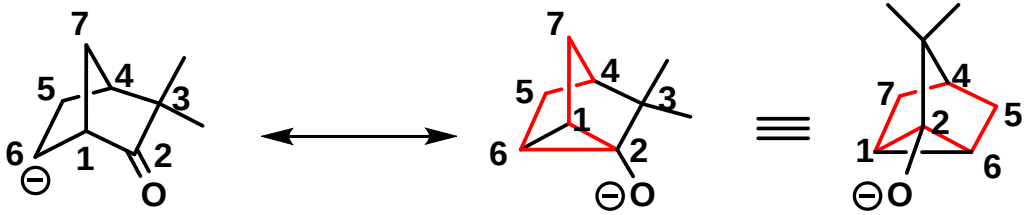
Introduction

The First "Homoenolate"



(+)-camphenilone

racemic camphenilone

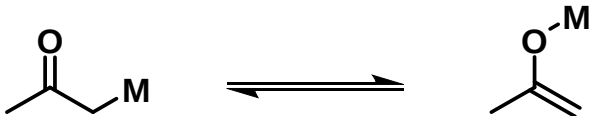


Formation of this ion provides an opportunity for the C.2-C.6 bond to become equivalent to C.2-C.1 and hence system looses its optical activity

Nickon, A.; Lambert, J. L. *J. Am Chem. Soc*. **1962**, *84*, 4604.

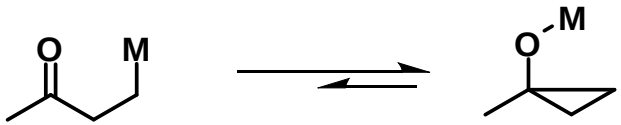
Problem of tautomerism

- enolate



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

- homoenolate



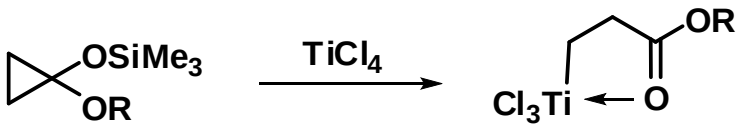
Rarely acts as a carbon centered nucleophile because it is irreversible

Definition: Species containing an anionic carbon β to a carbonyl moiety

Chemistry of Homoenolates

Metal homoenolates

Synthesis of Titanium homoenolate



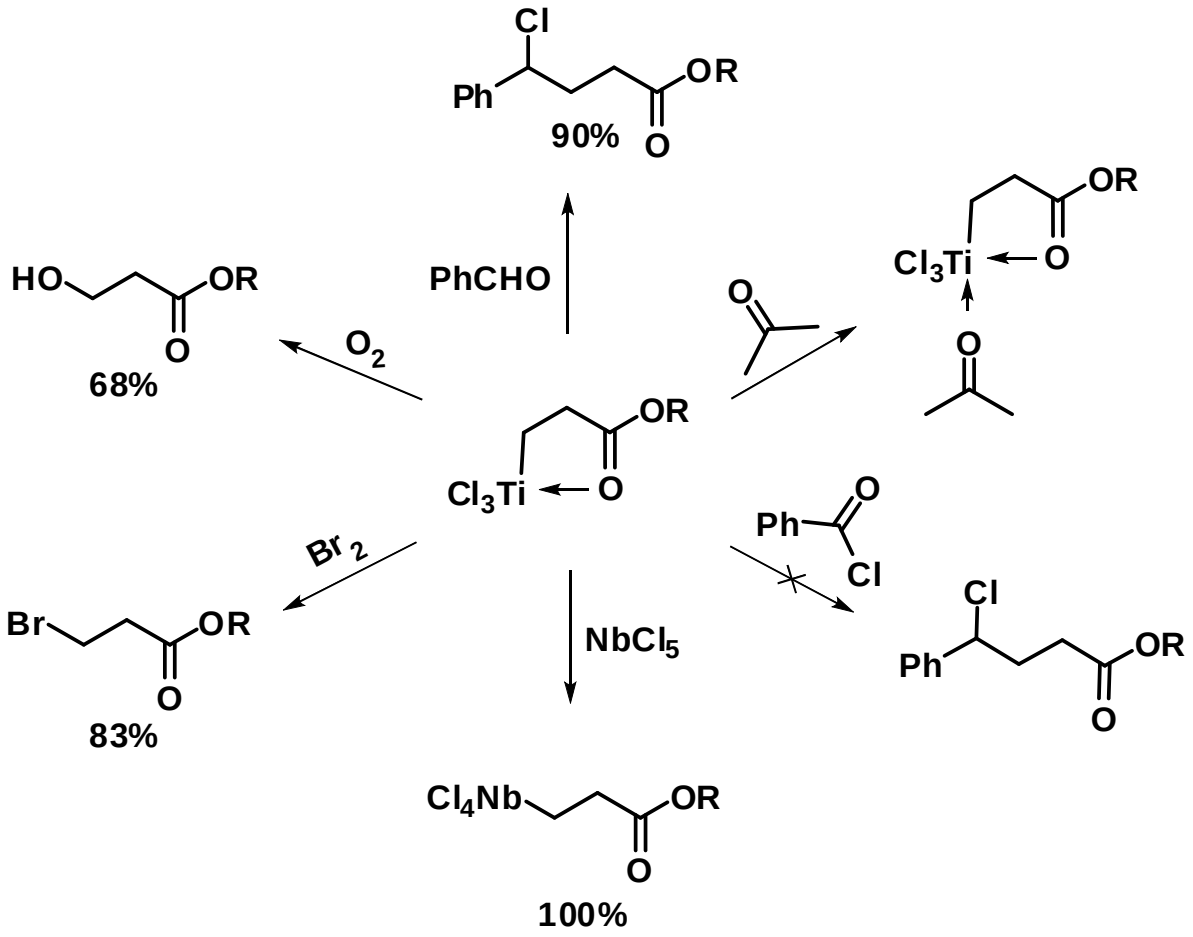
70-89%

R = Me, Et, *i*-Pr

- If the reaction is conducted in DCM, initially it forms yellow suspension soon it will turn in to deep wine-red color solution with evolution of heat
- Precipitates as microcrystalline powder with hexanes
- This complex structure was verified by Floriani

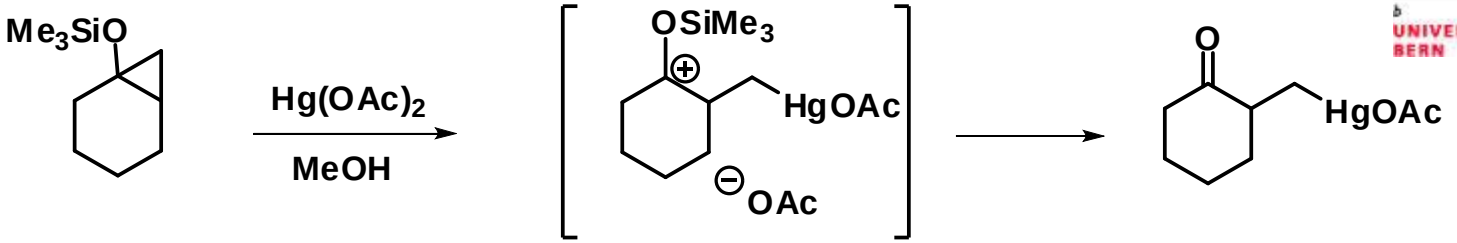
J. Am. Chem. Soc. **1983**, *105*, 651.

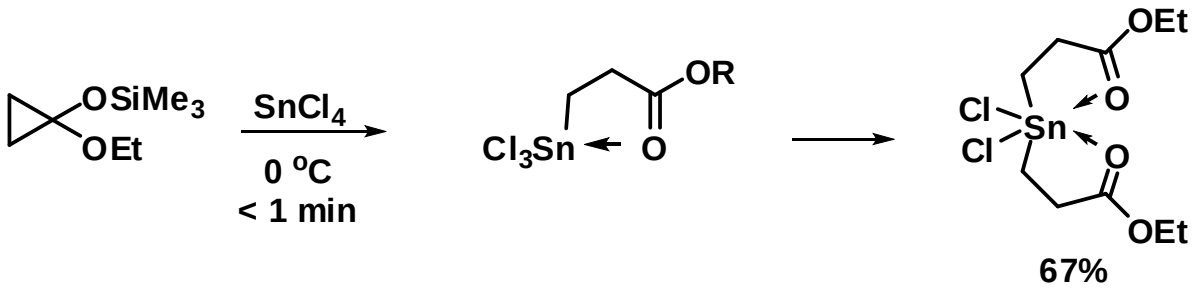
- Reactions of titanium homoenolates

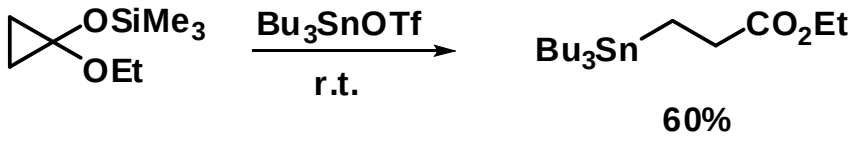


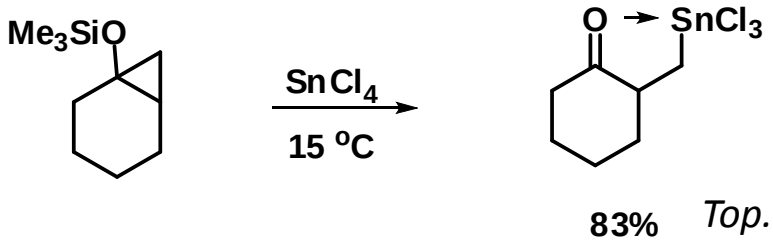
J. Am. Chem. Soc. **1986**, *108*, 3745.

• Synthesis of different metal homoenolates



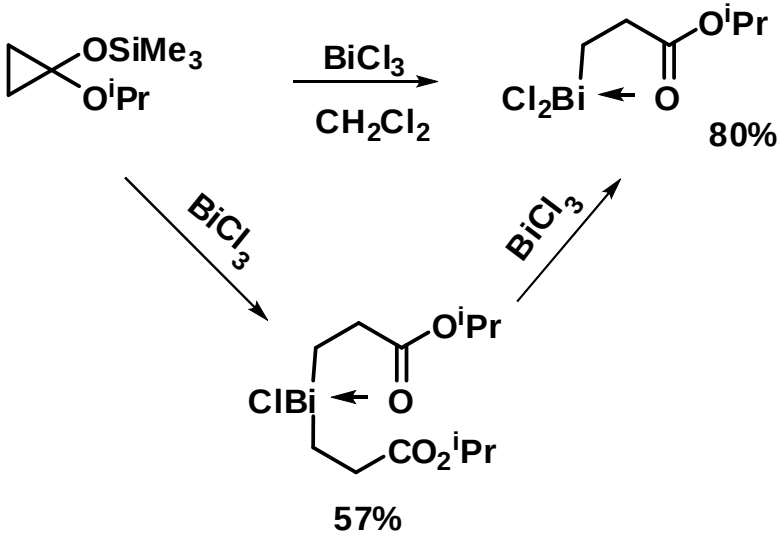


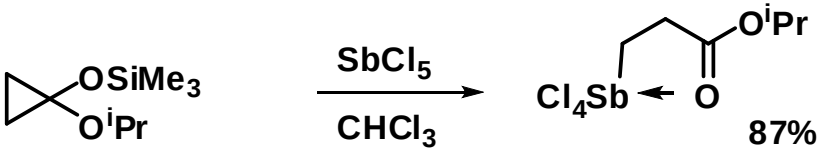




Top. Curr. chem. **1990**, *155*, 1

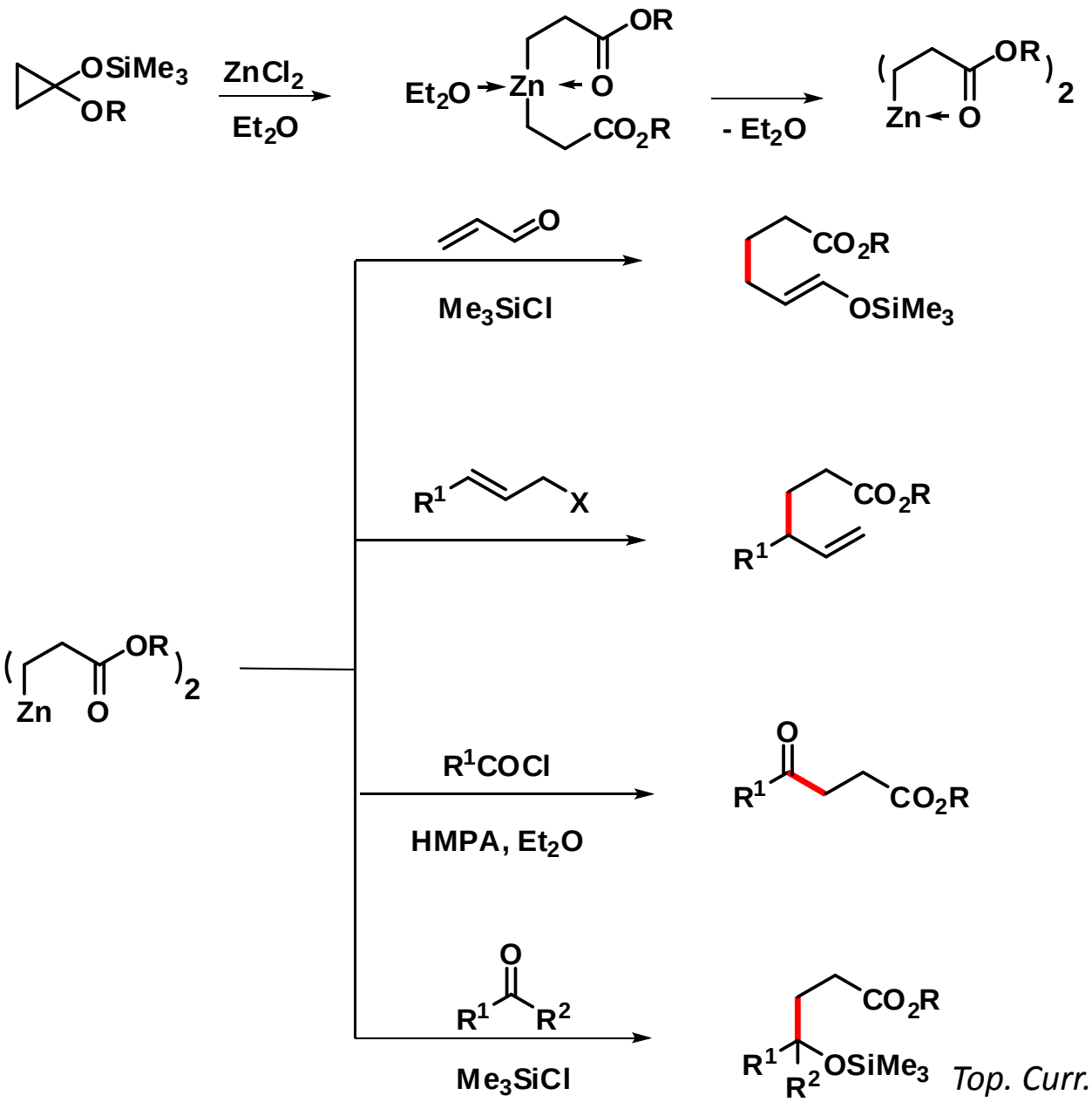
• Synthesis of different metal homoenolates





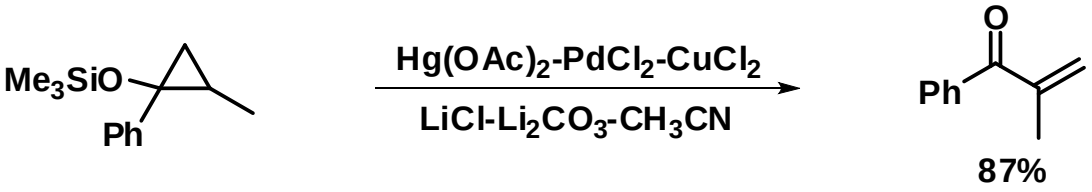
Top. Curr. chem. **1990**, *155*, 1

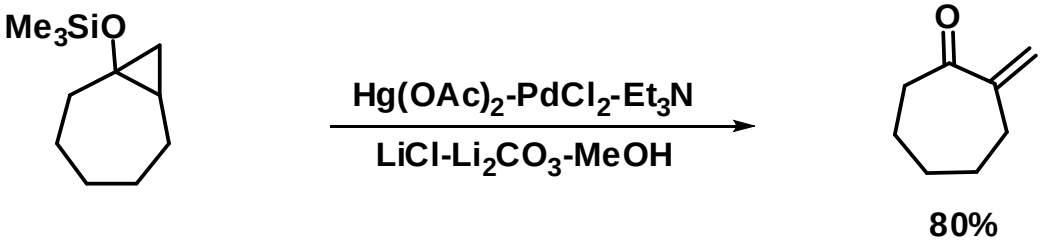
• Synthesis of zinc homoenolates and C-C bond formation reactions

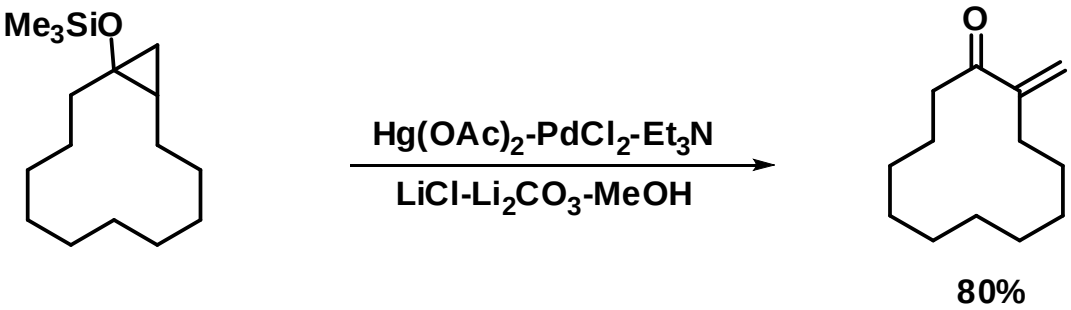


Top. Curr. chem. **1990**, *155*, 1

• Elemination reactions of mercury metal homoenolates

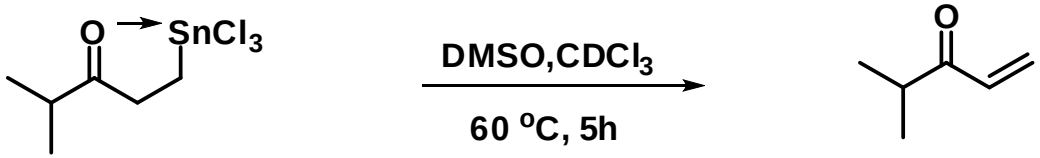


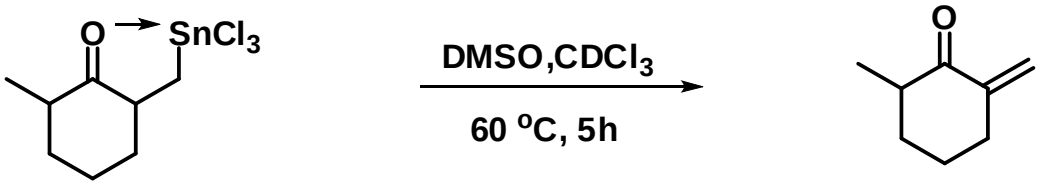


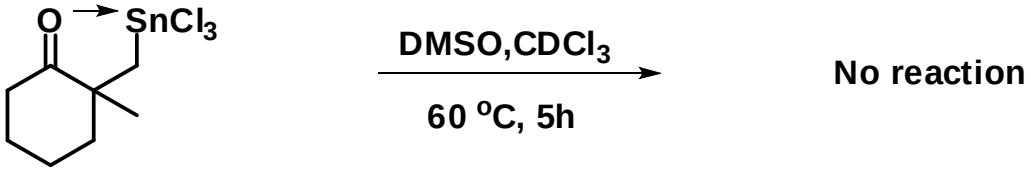


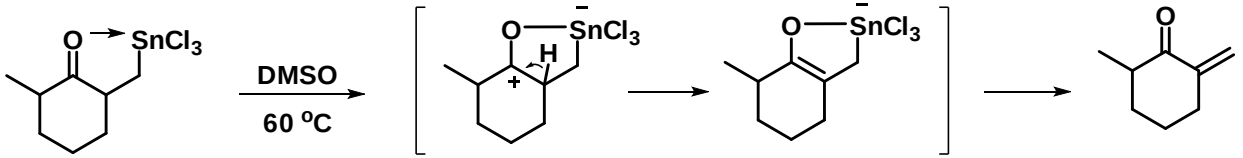
Top. Curr. chem. **1990**, *155*, 1

- Elemination reactions of tin metal homoenolates



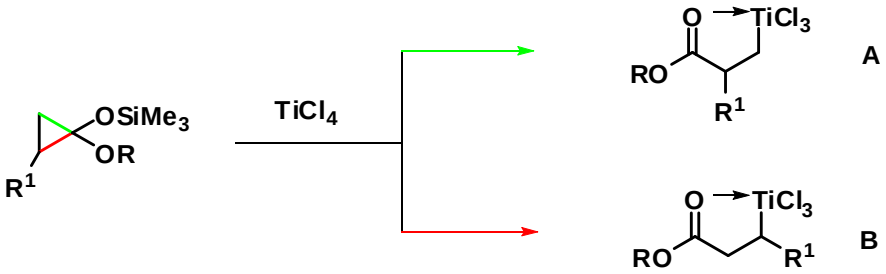






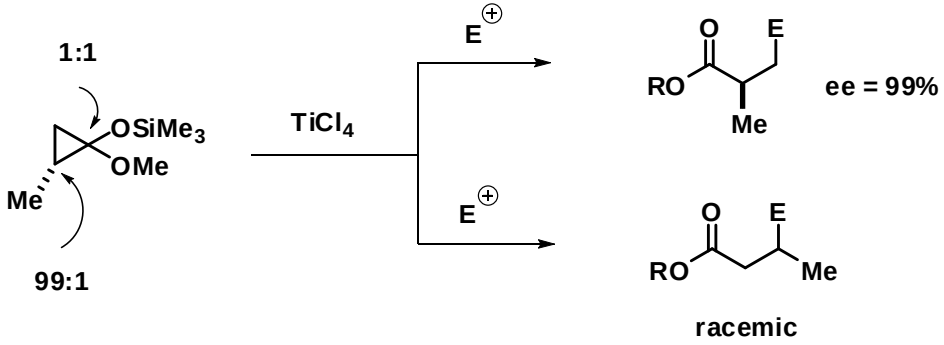
Top. Curr. chem. **1990**, *155*, 1

• Regioselectivity of ring cleavage



A can be isolated, **B** is too unstable and it can be seen by quenching with electrophiles

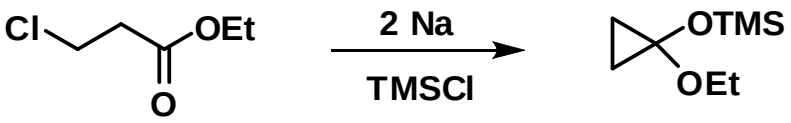
R	R1	A : B
iPr	Me	>95 : 5
Me	Me	60 : 40
Et	Ph	78 : 22



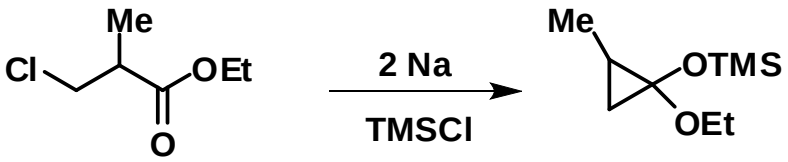
J. Am. Chem. Soc. **1986**, *108*, 3745.

• Cyclopropane synthesis

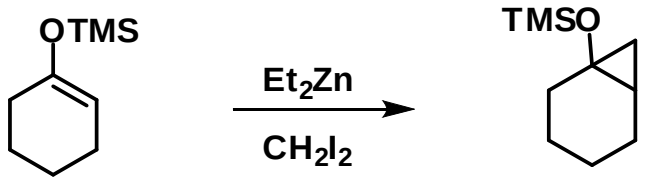
• General method



• Synthesis of substituted cyclopropanes

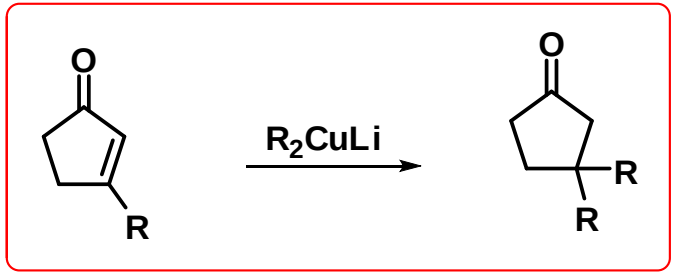


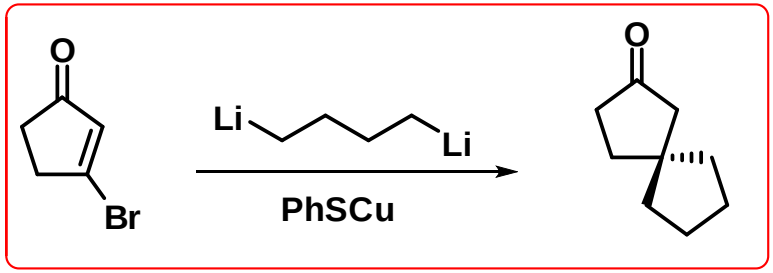
• Simon-smith reaction

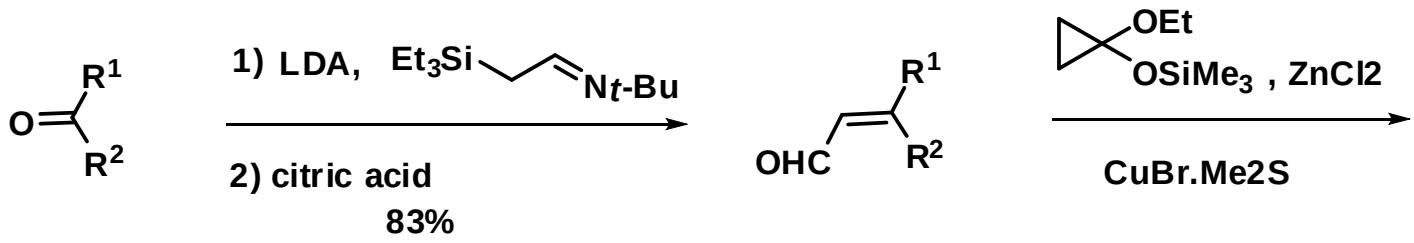


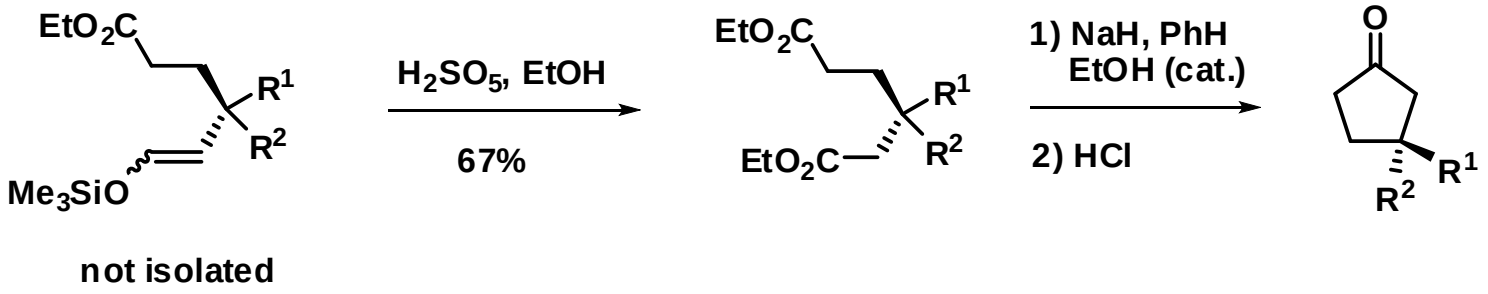
1. *Synthesis,* **1971**, 236.
2. *Org. Synthesis.*, **1985**, *63*, 147

Cyclopentannulation

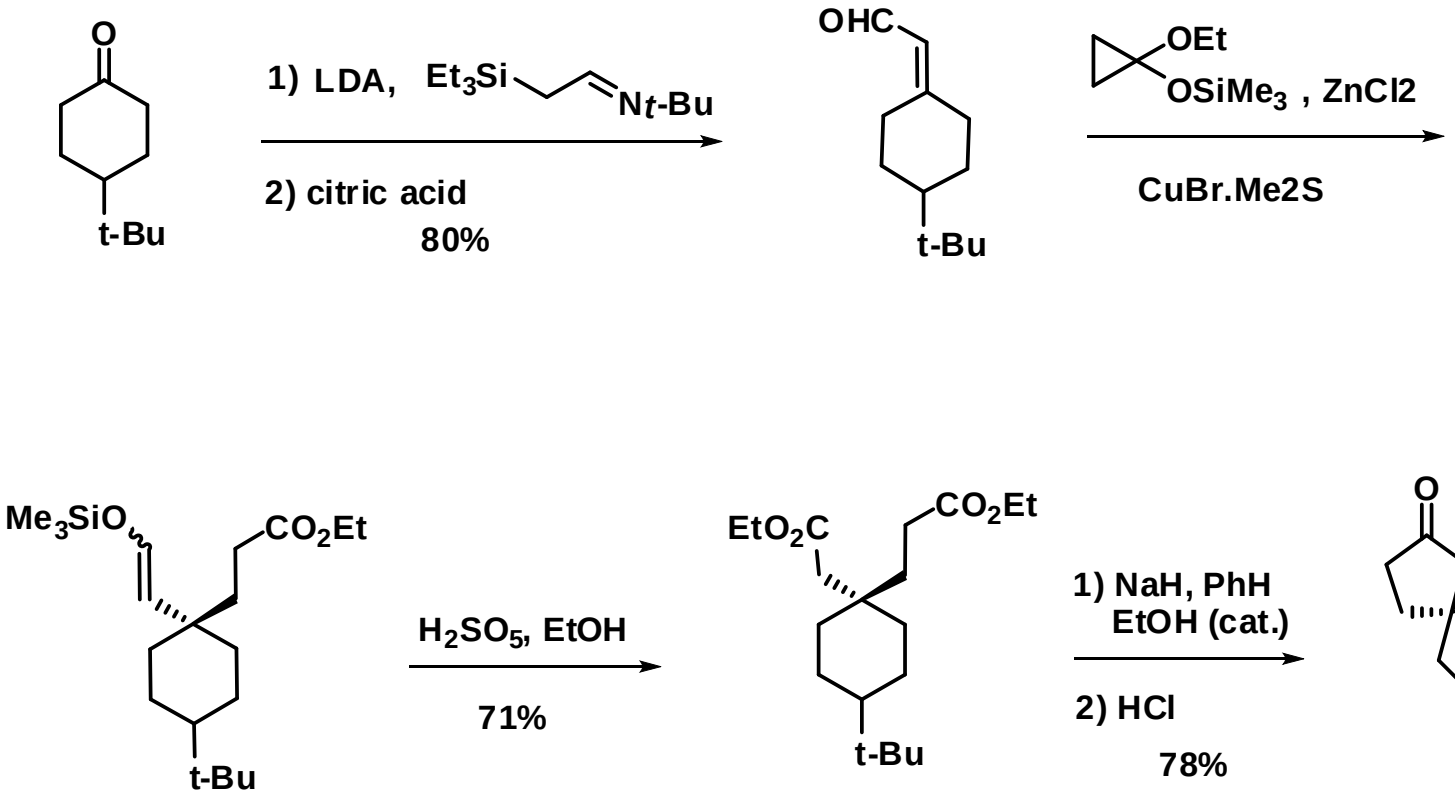






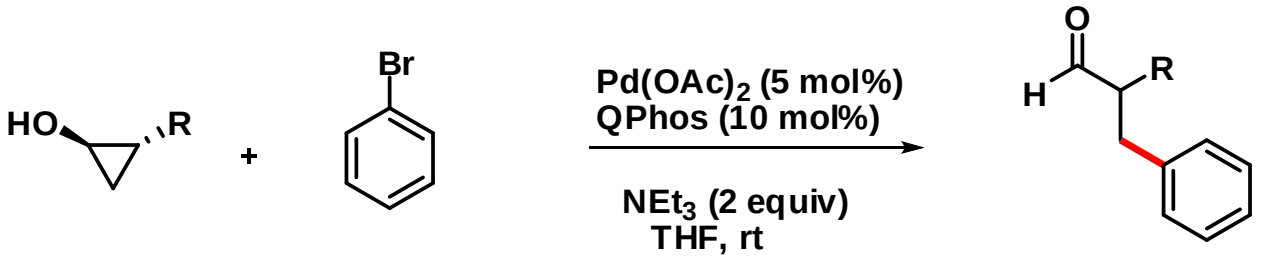


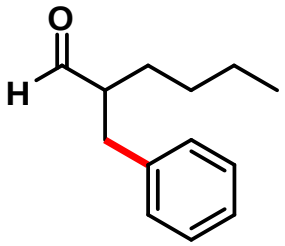
J. Org. Chem. **1994**, *59*, 5496.



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

• Arylation of Aldehyde Homoenolates





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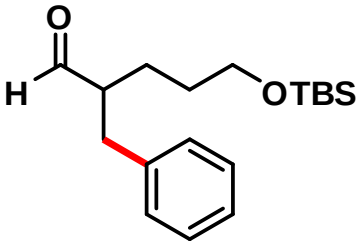
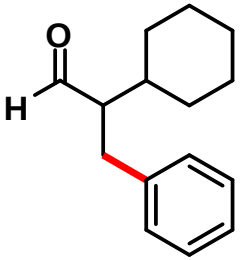
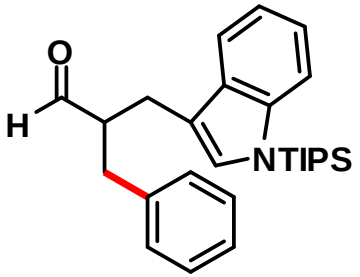


83%



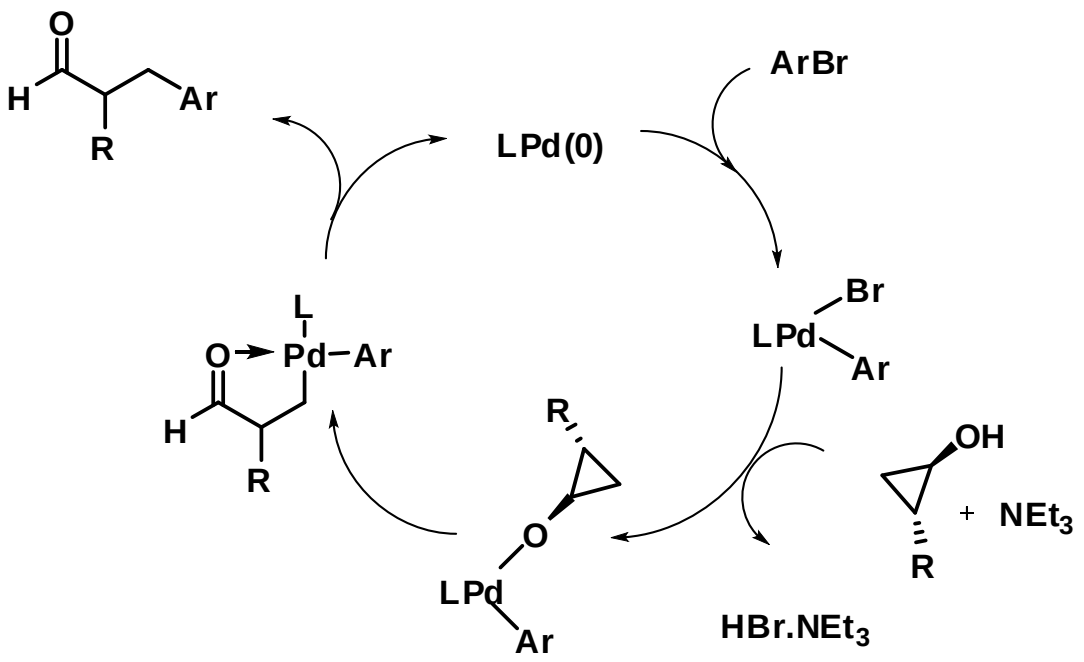
88%



61%

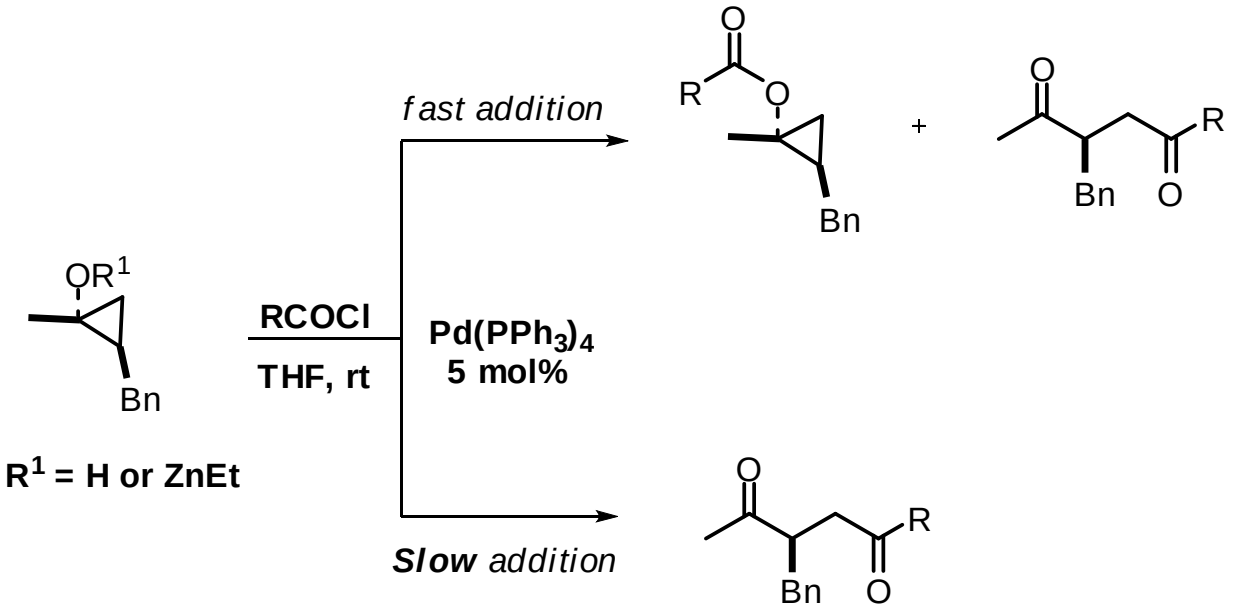
Org. Lett., **2013**, *15*, 2298.

• Plausible reaction pathway for arylation of aldehyde homoenolates



Org. Lett., **2013**, *15*, 2298.

• *C*-Acylation of Cyclopropanols: Preparation of functionalized 1,4-Diketones

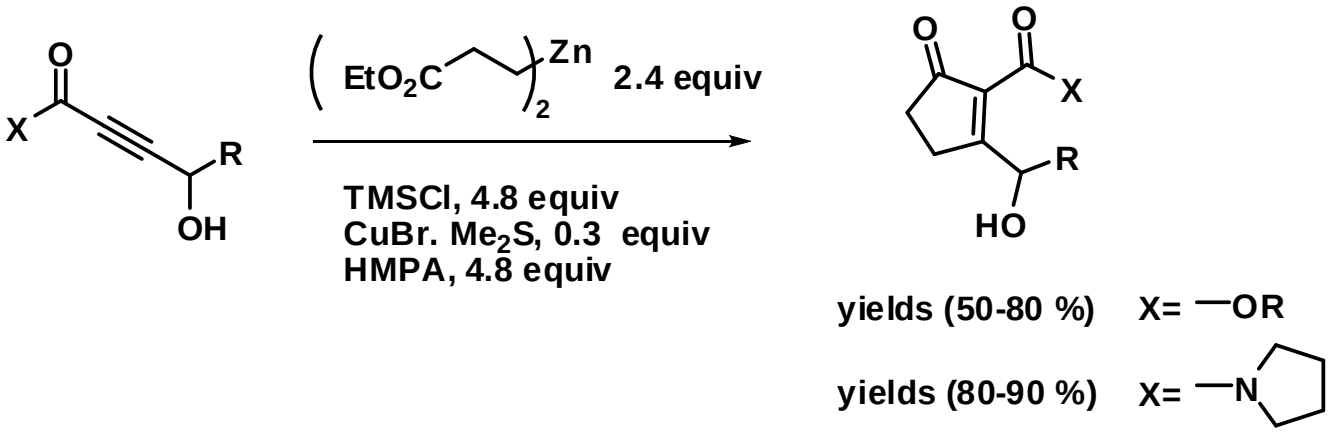


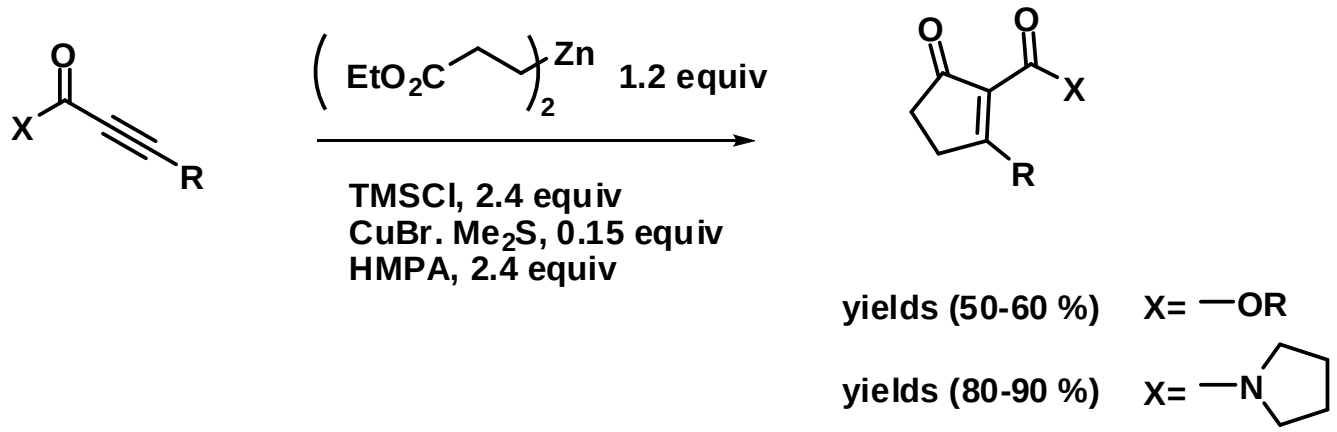
1. Fast addition leads to almost 1:1 of *O*-acylation and *C*-acylation products..!!!
2. Slow addition gives exclusively *C*-acylation product

Org. Lett., **2013**, *15*, 1780.

Addition of Zinc Homoenolates to acetylinic Esters and amides

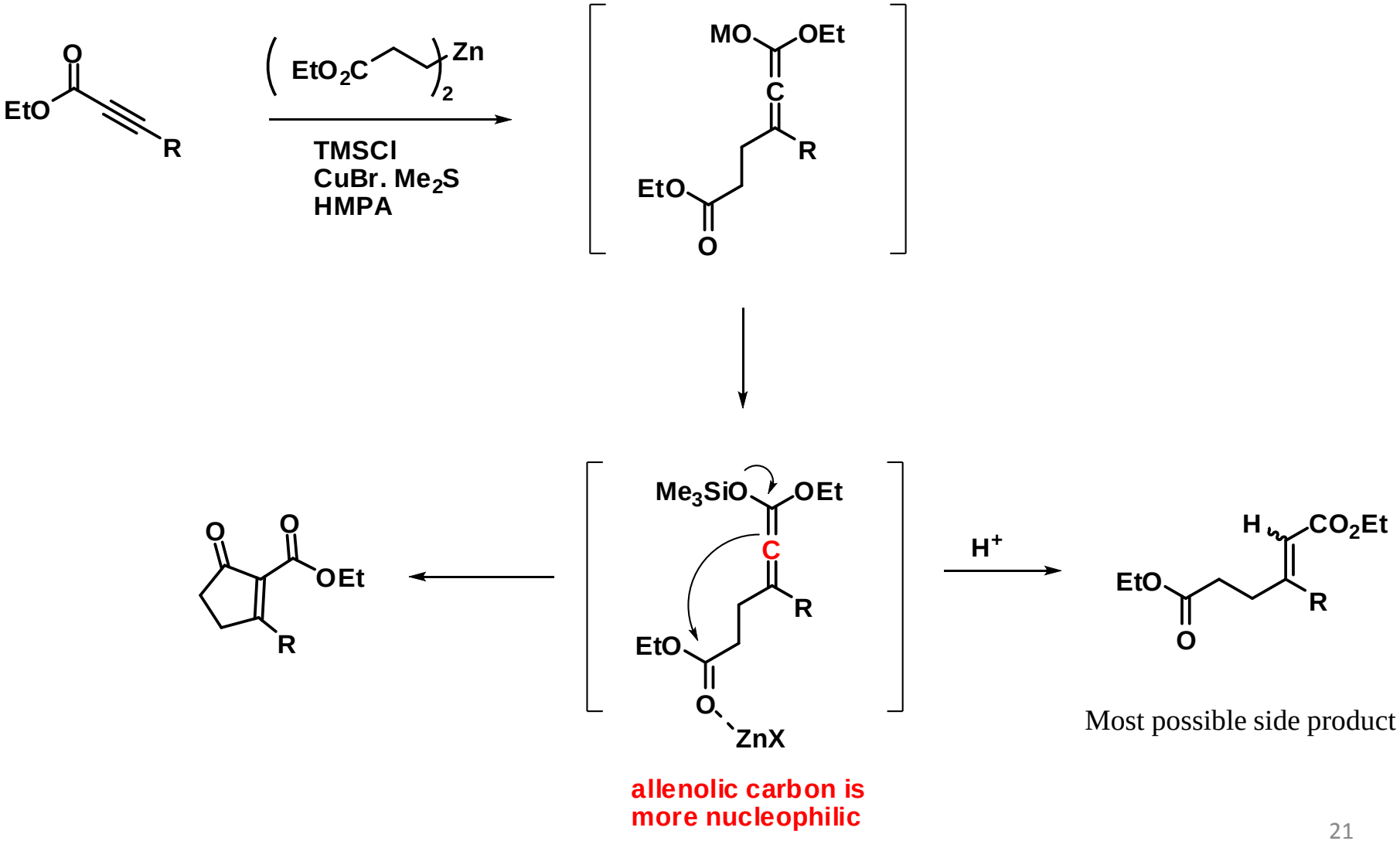
- Crimmin's Cyclopentenone synthesis

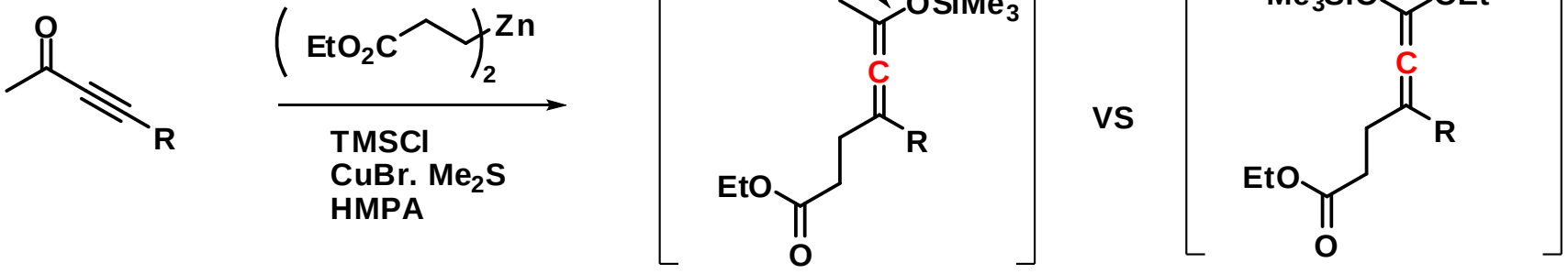




J. Org. Chem. **1993**, *58*, 1038.

• Crimmin's Cyclopentenone synthesis: Mechanistic considerations



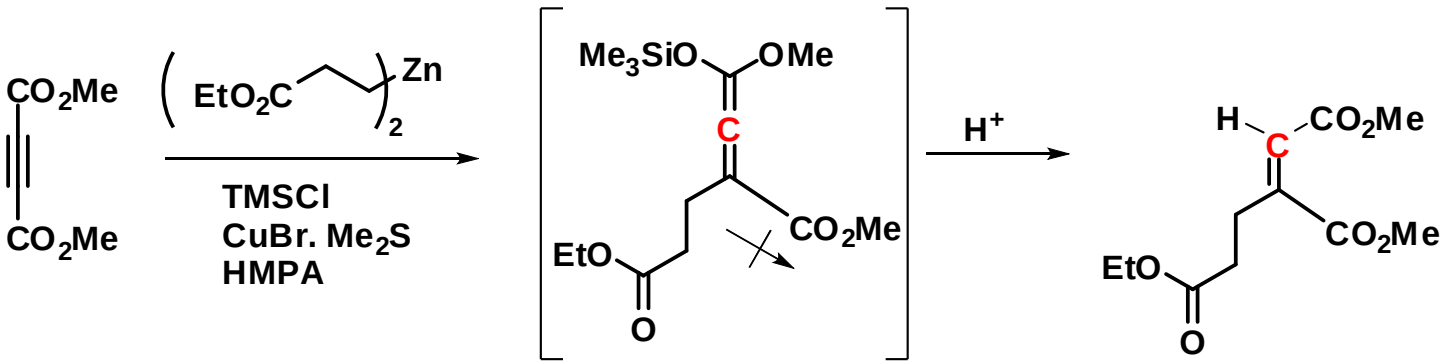


allenolic carbon is not very nucleophilic

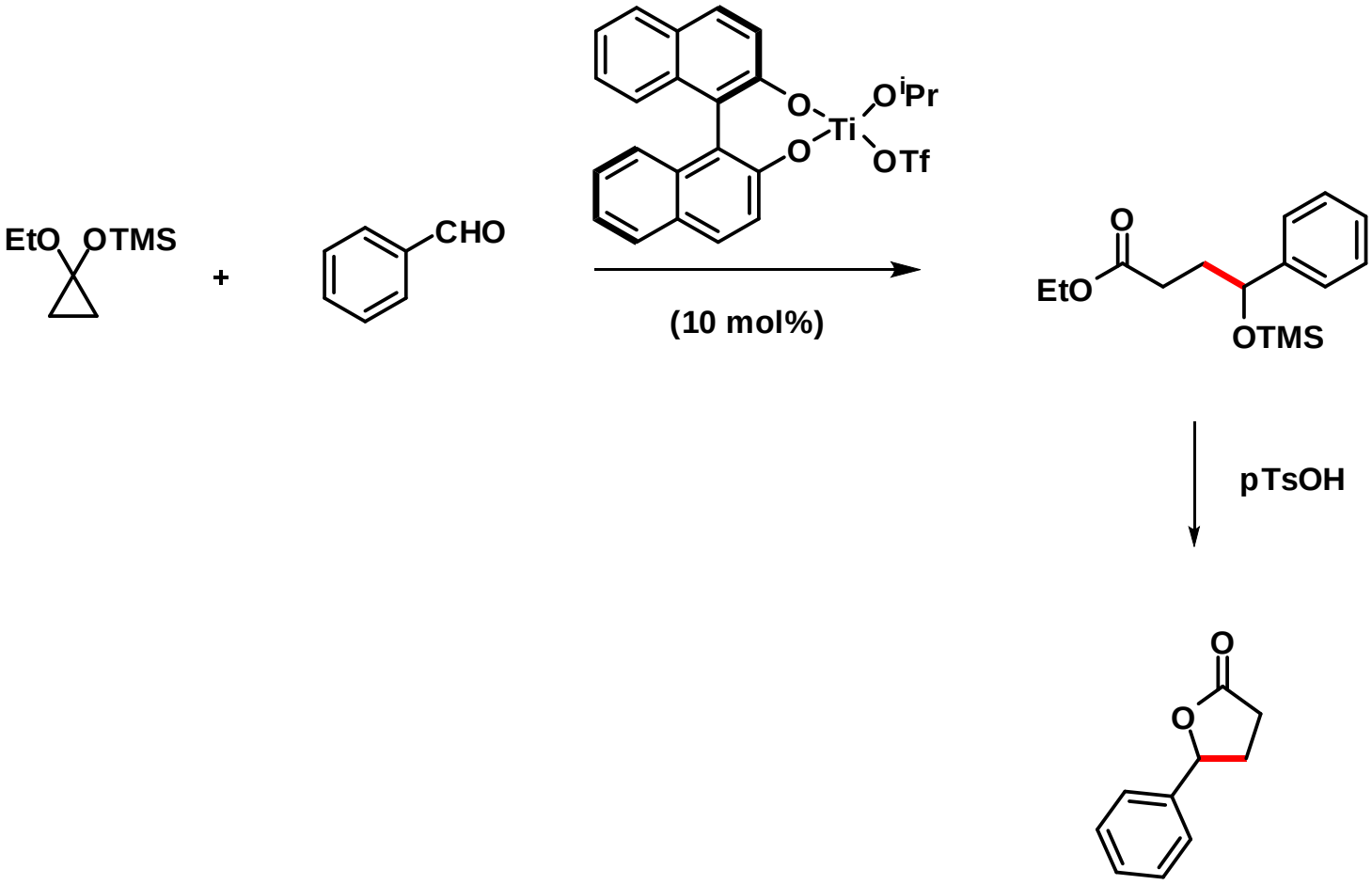
allenolic carbon is more nucleophilic

isolated in 80% yield

no cyclized product



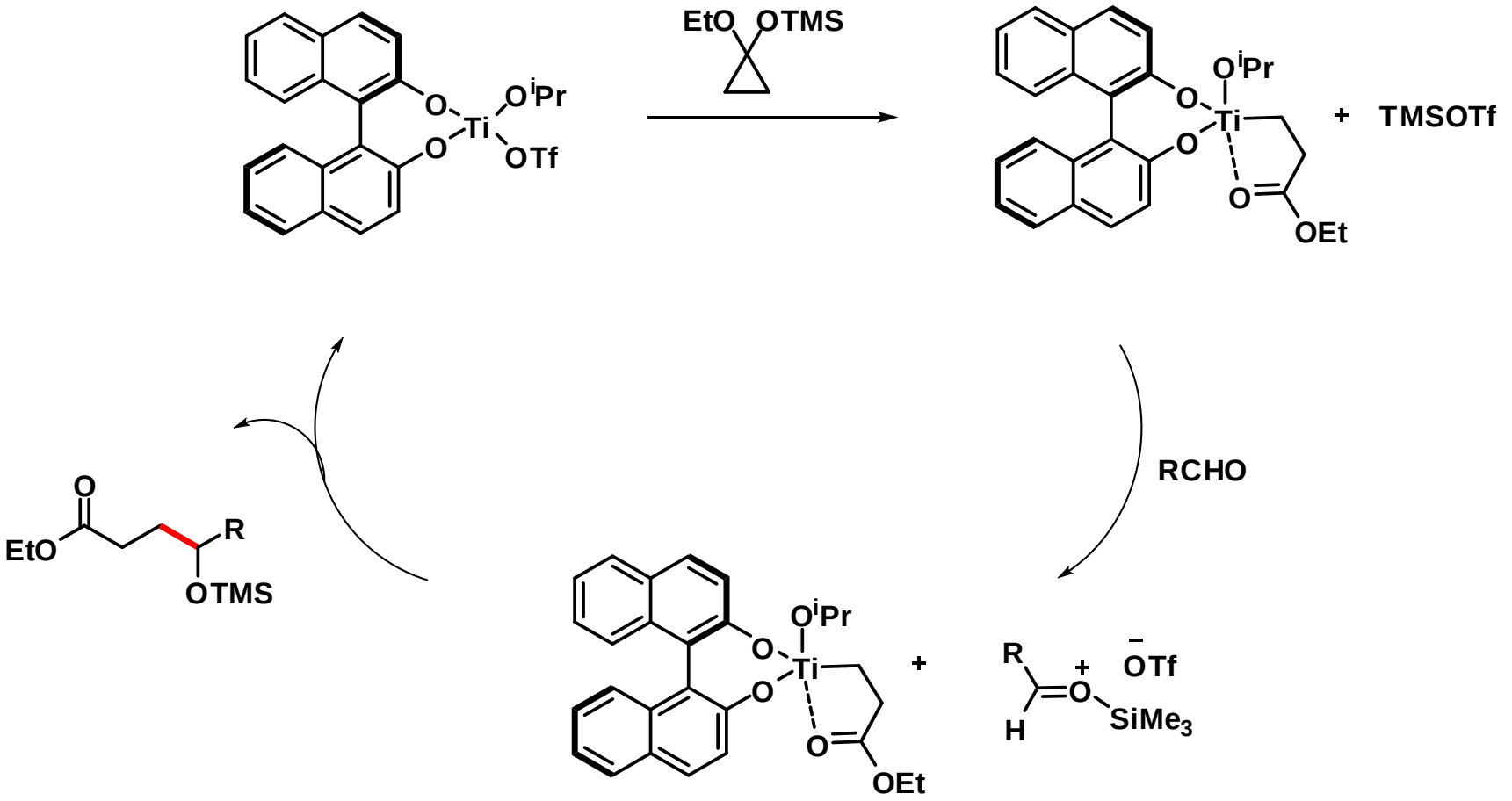
• Titanium(IV) Triflates Catalyzed Homoaldol Reaction



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

• Titanium(IV) Triflates Catalyzed Homoaldol Reaction

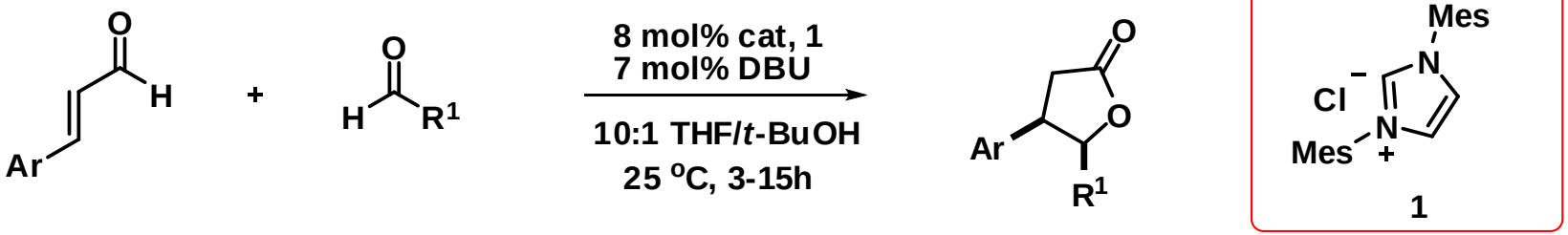
• Mechanism

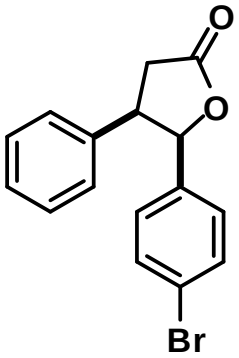


Chemistry of Homoenolates

NHC derived homoenolates

• Bode's Lactone synthesis





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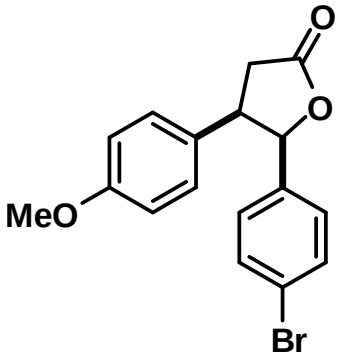
dr = 4:1



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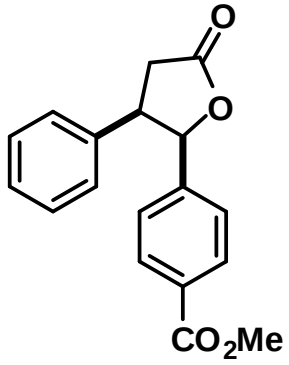
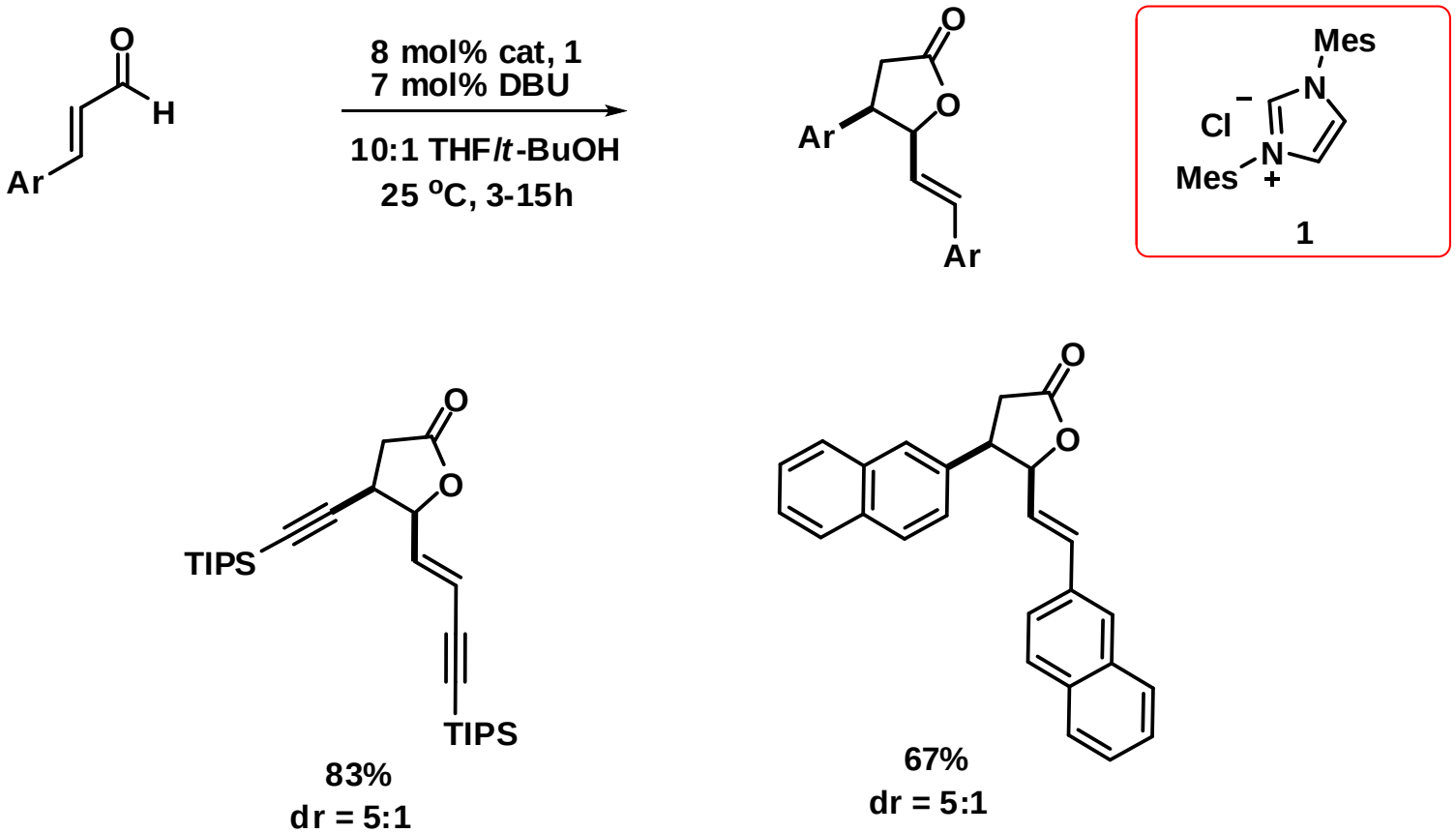


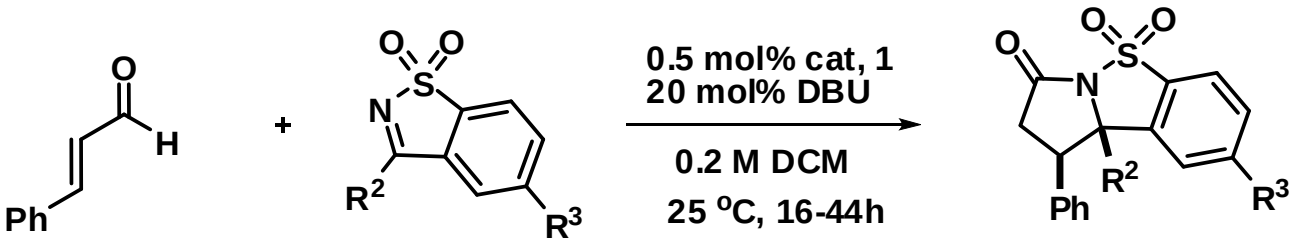
87%
dr = 5:1

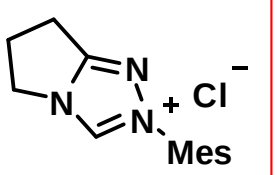
J. Am. Chem. Soc. **2004**, *126*, 14370.

- Catalytic dimerization of enals



J. Am. Chem. Soc. **2004**, *126*, 14370.





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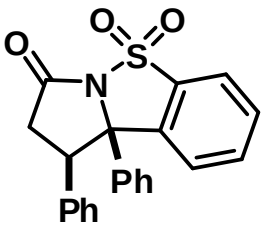

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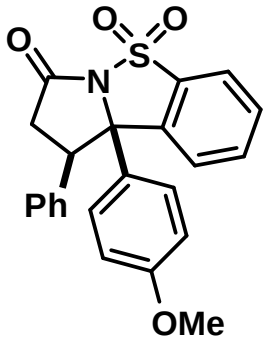

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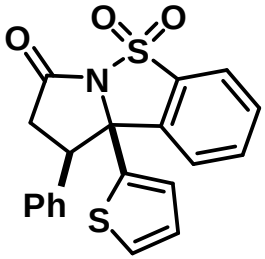
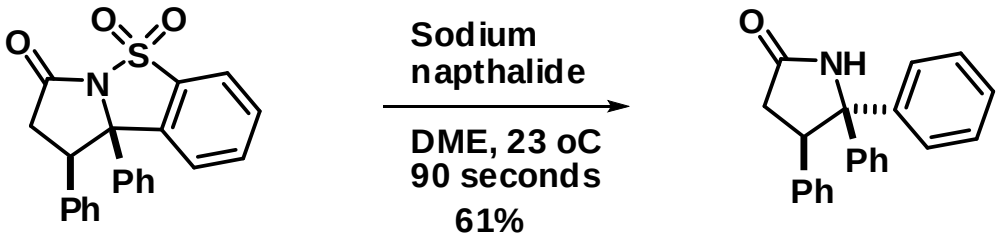


90%

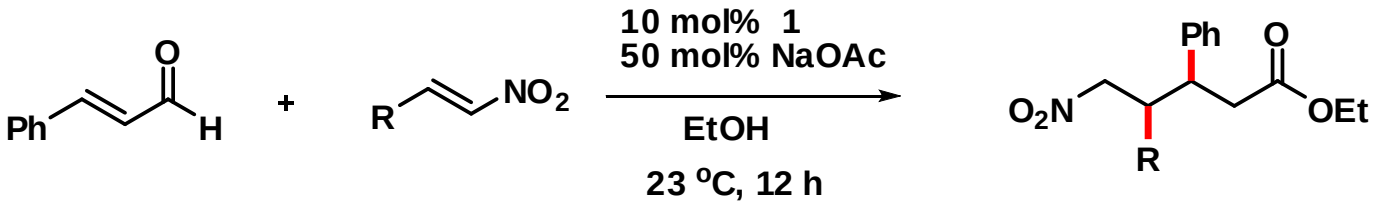
dr = 4:1

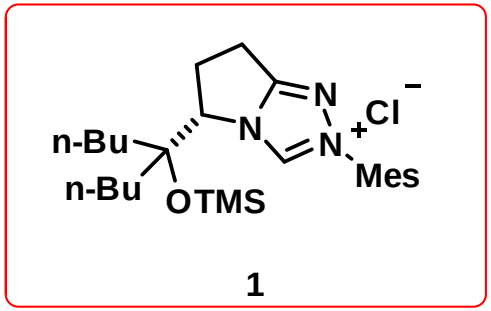
- Desufonylation of adduct leads to highly functionalized γ-lactams



J. Am. Chem. Soc. **2008**, *130*, 17266.

• Rovis addition of enals to nitroalkenes: Avoiding Stetter type reaction





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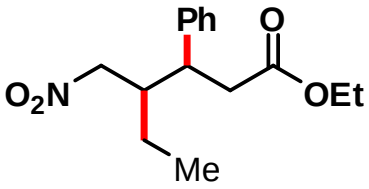
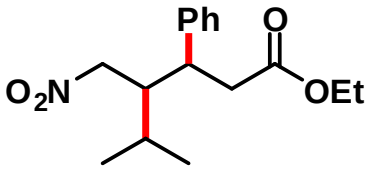


70%

17:1 dr

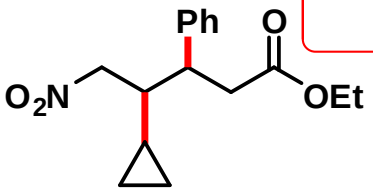
93% ee



57%

20:1 dr

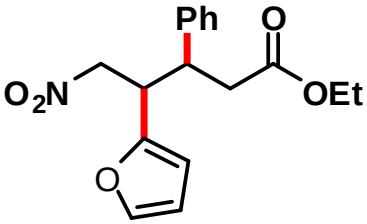
94% ee



68%

18:1 dr

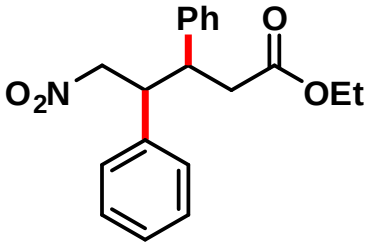
88% ee



90%

3:1 dr

81% ee



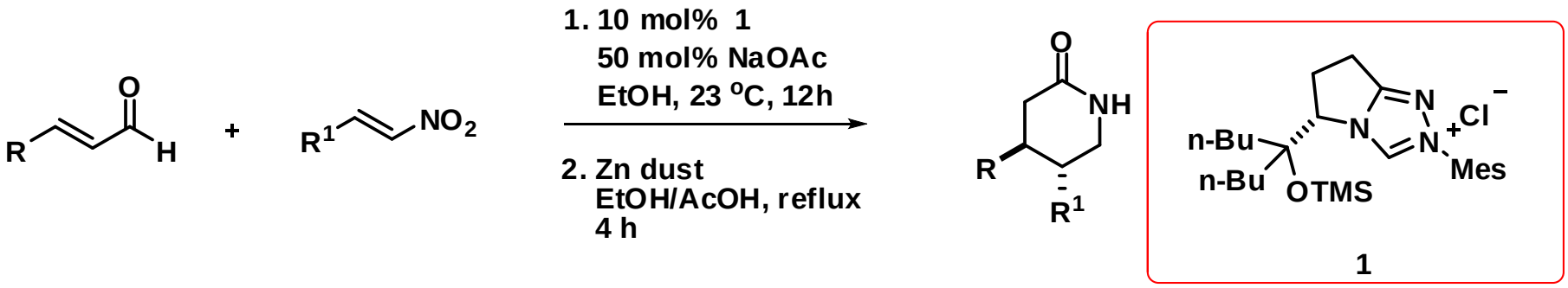
95%

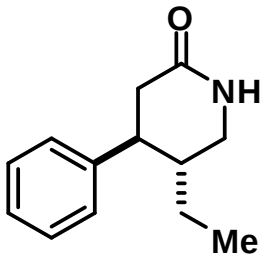
6:1 dr

87% ee

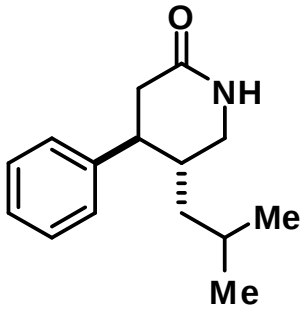
J. Am. Chem. Soc. **2013**, *135*, 8504.

• One pot synthesis of δ- lactams

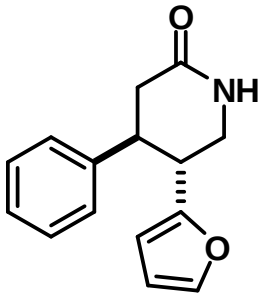




63%
17:1 dr
93% ee



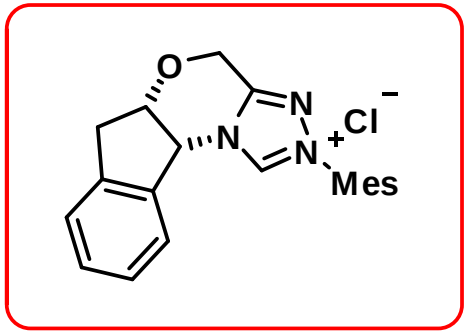
65%
19:1 dr
93% ee

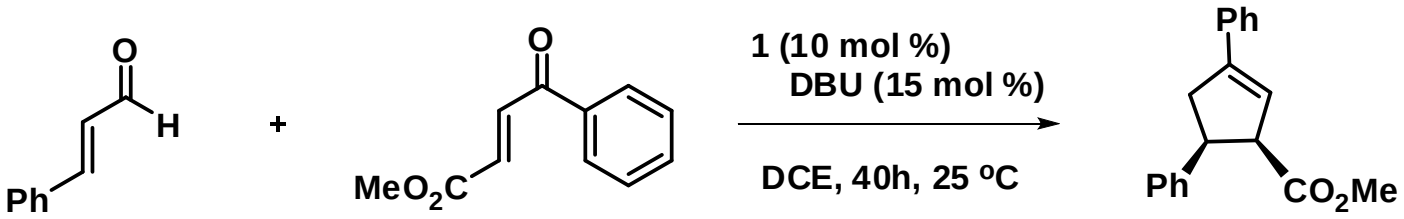


82%
3:1 dr
82% ee

J. Am. Chem. Soc. **2013**, *135*, 8504.

• Bode's enantioselective cyclopentene synthesis



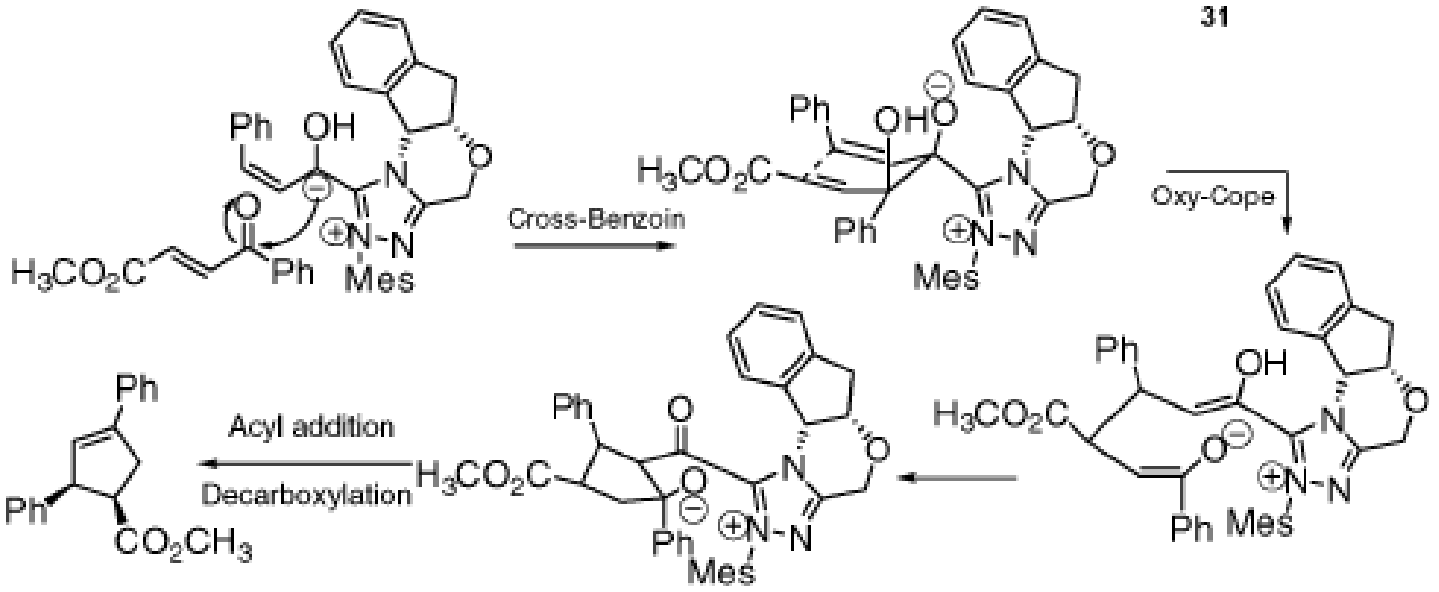


Cis : Trans = 11:1

***ee* = 99%**

J. Am. Chem. Soc. **2007**, *129*, 3520.

• proposed mechanism

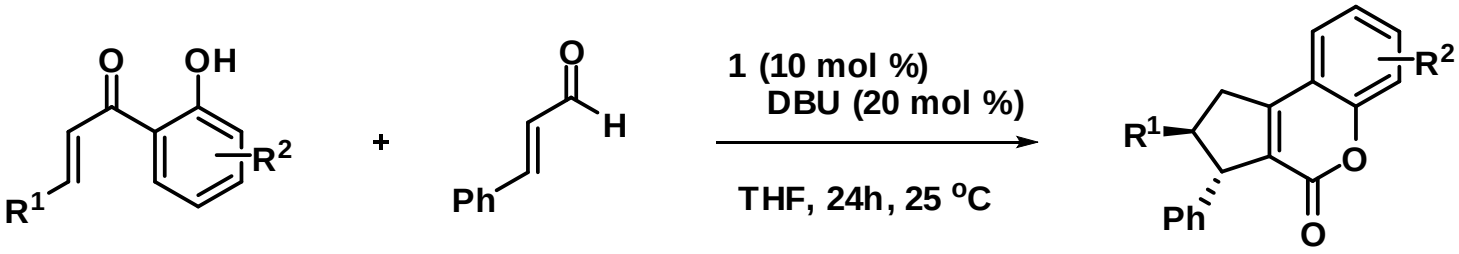


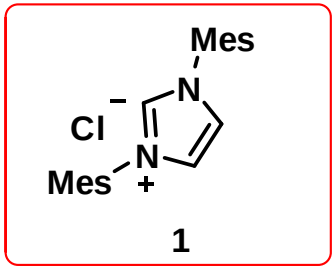
•There is theoretical support for the mechanism and recent DFT calculations showed that the energy requirement for crossed benzoin reaction is very high and hence Oxy –Cope path way is rejected as a possibility for cyclopentene synthesis

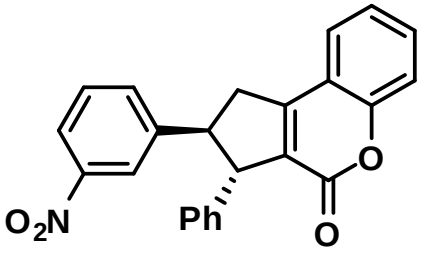
• Possible mechanism is homoenolate pathway !!!

J. Org. Chem. **2011**, *76*, 5606.

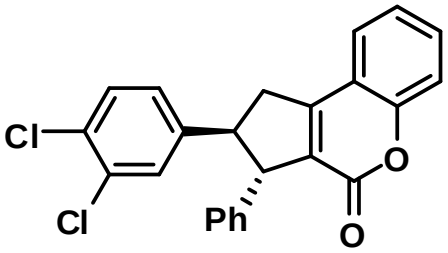
• Diastereoselective Synthesis of Functionalized Coumarins







84%



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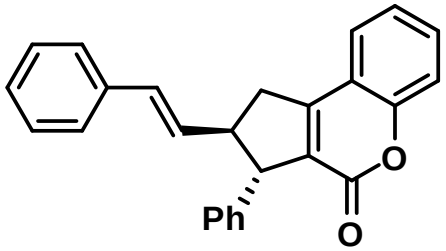
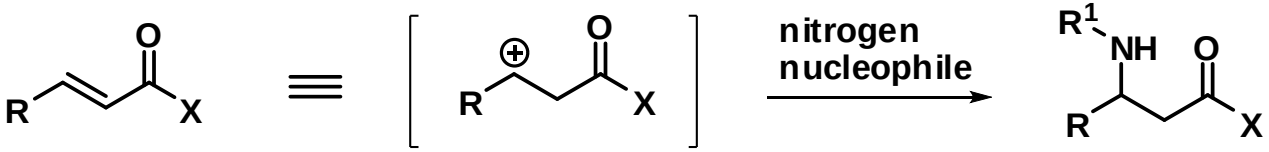


79%

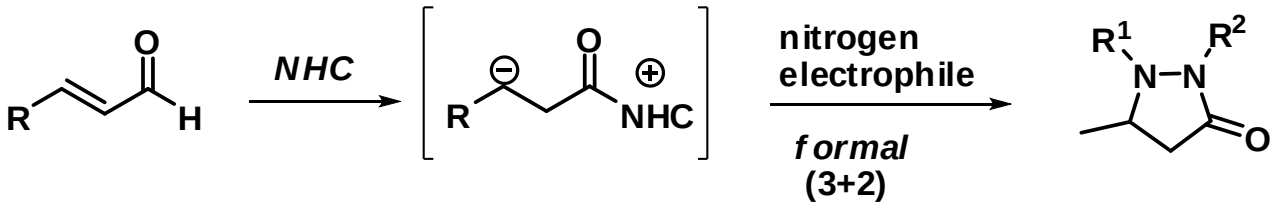
Org. Lett., **2013**, *15*, 1756.

• Direct Amination of Homoenolates

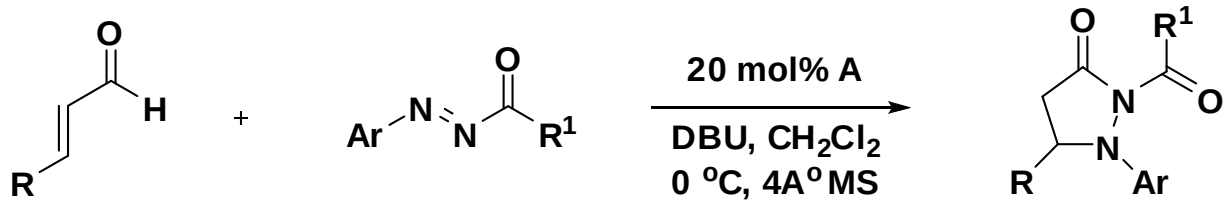
1. Conjugate addition

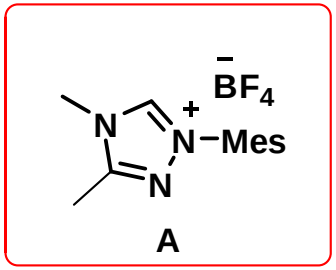


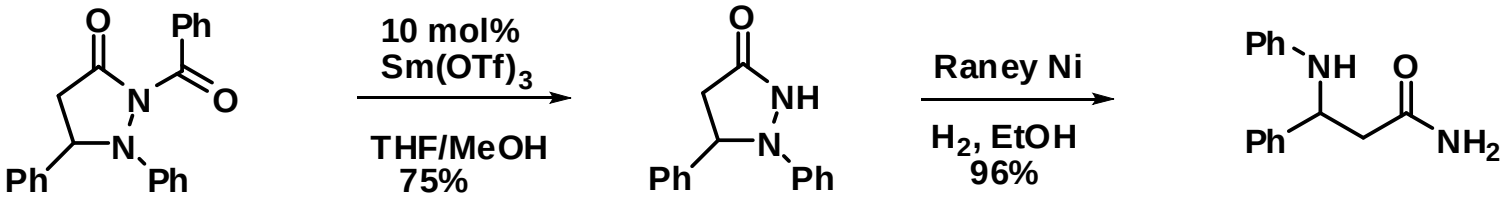
2. Homoenolate strategy



J. Am. Chem. Soc. **2008**, *130*, 2740.

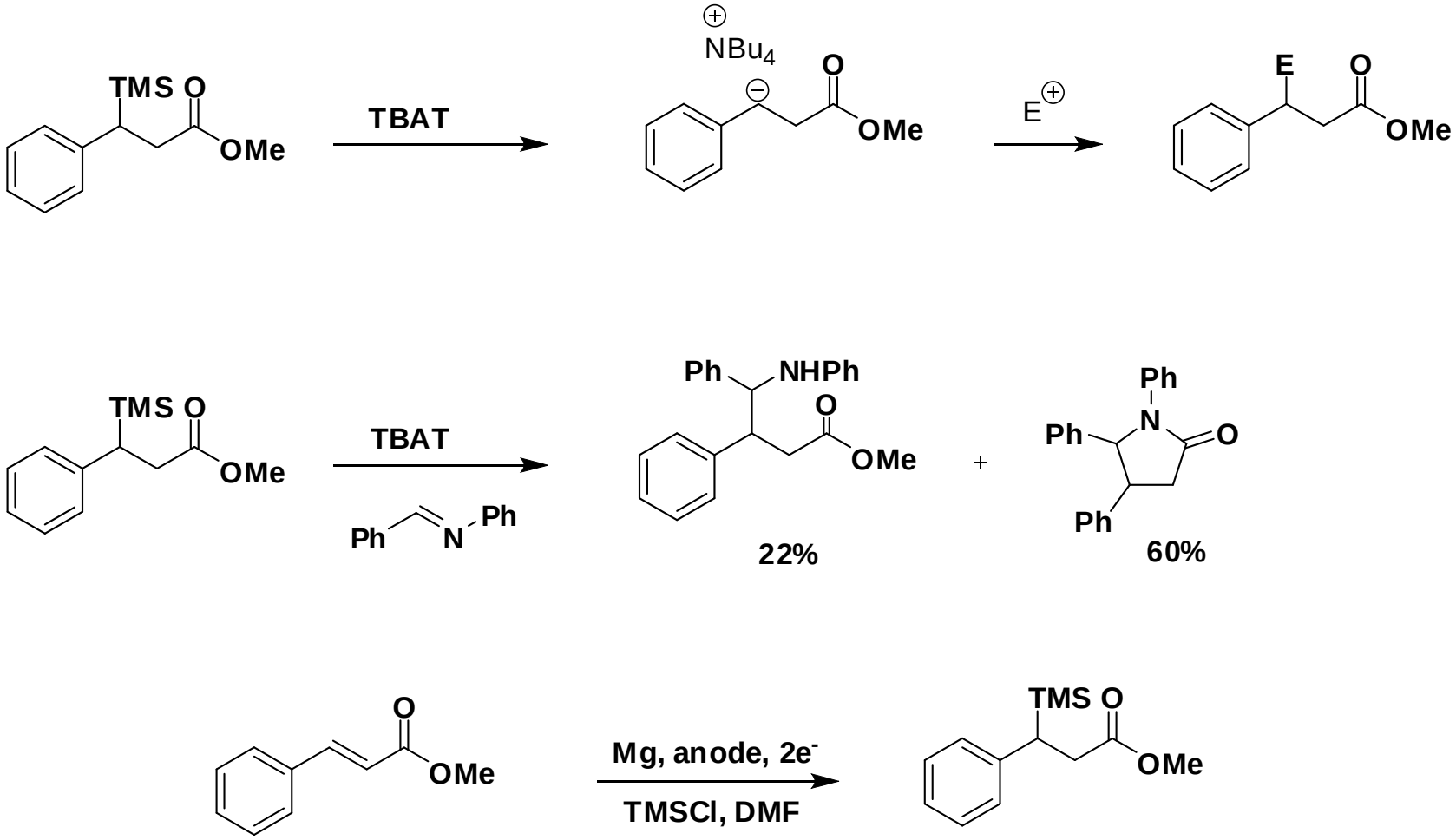






J. Am. Chem. Soc. **2008**, *130*, 2740.

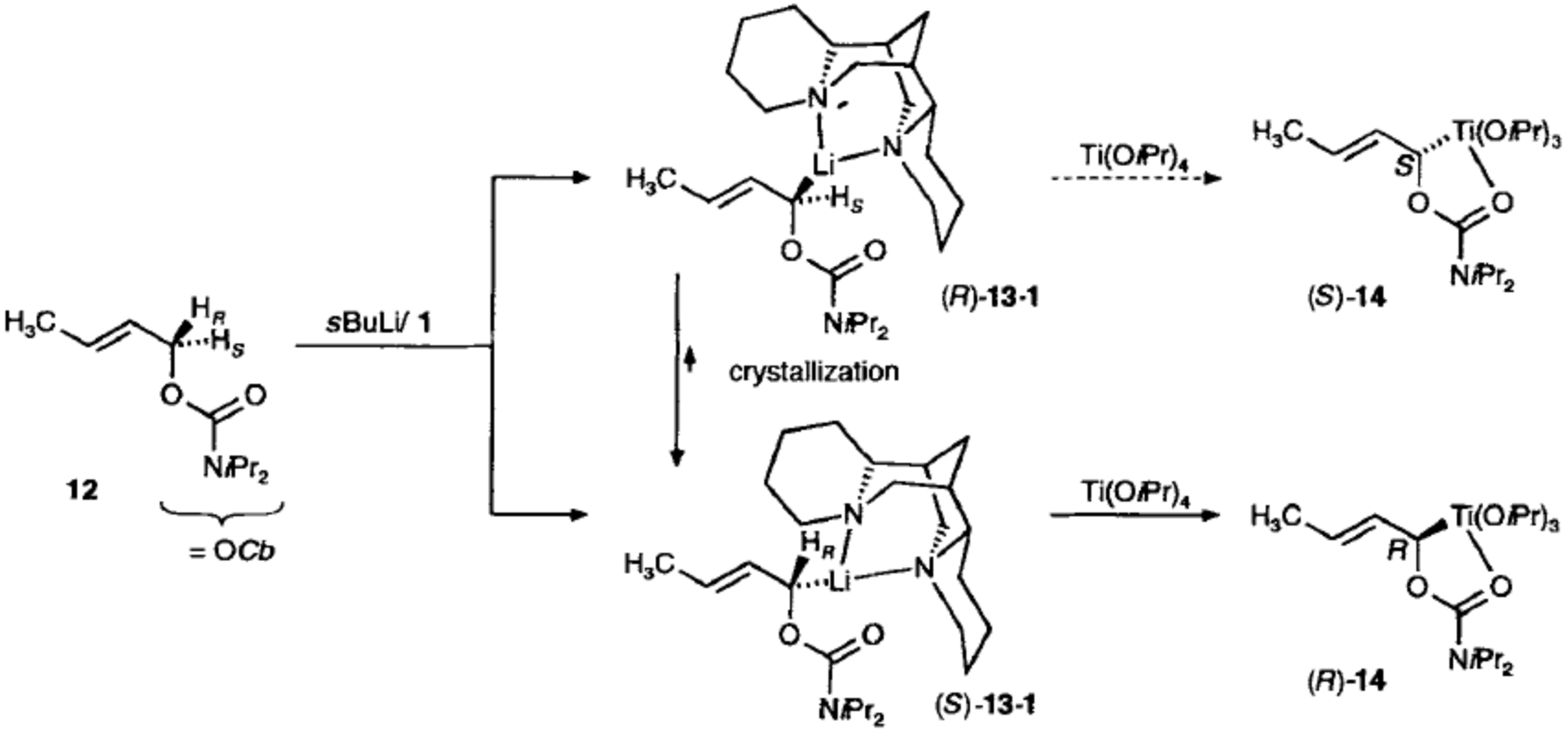
- Metal free homoenoates



Tetrahedron Lett., **1992**, *33*, 5515.

Tetrahedron Lett., **1999**, *40*, 7945.

• Hoppe's homoenolate equivalents

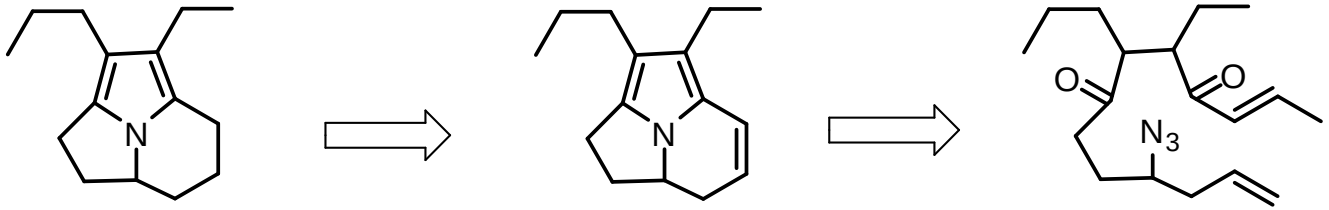


Angew. Chem. Int. Ed. Engl. **1997**, *36*, 2282.

Chemistry of Homoenolates

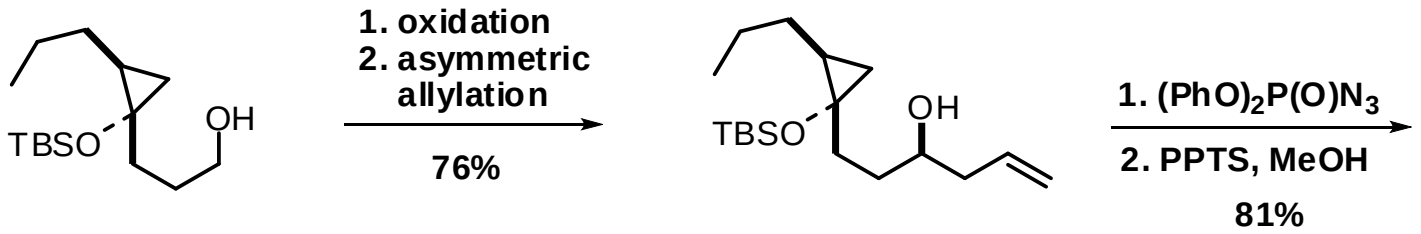
Homoenolates in total synthesis

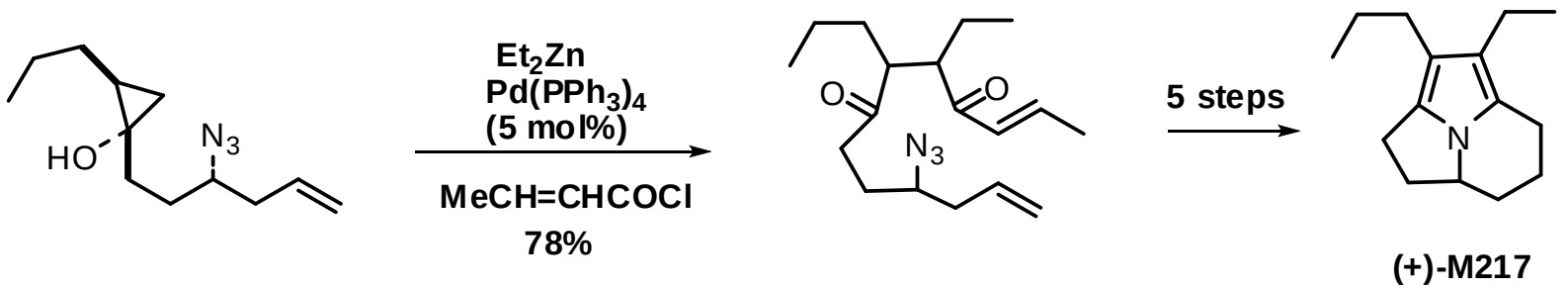
• Retro synthesis



(+)-M217

• Synthesis



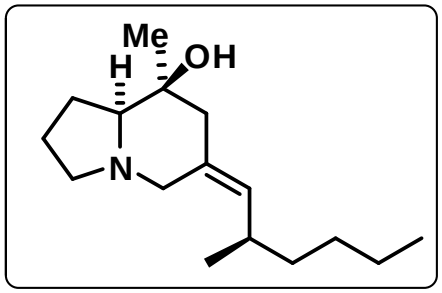


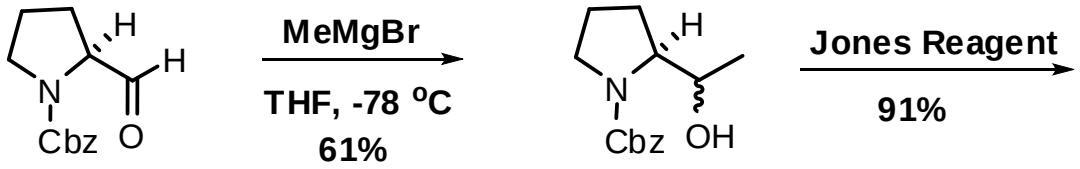
(+)-M217

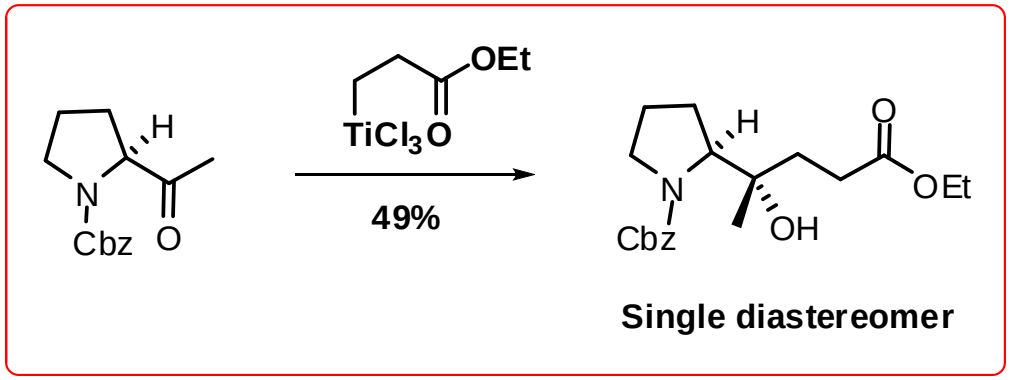
homoenolate strategy

Org. Lett., **2013**, *15*, 1780.

- Synthesis of pumiliotoxin 251 D



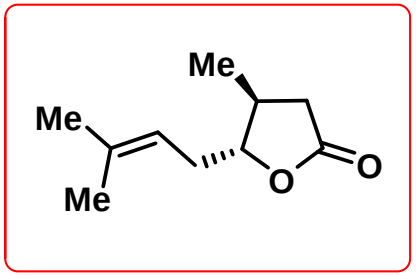


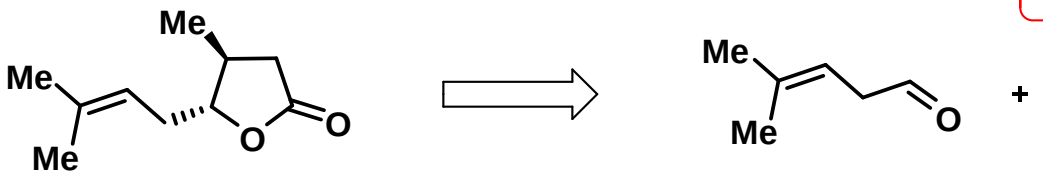


J. Org. Chem. **1999**, *64*, 1410.

• Synthesis of the insect phermone (+)-endanolide by enantioselective homoaldol reaction

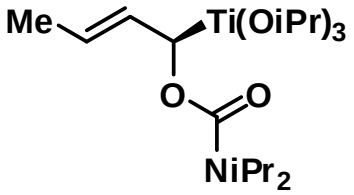
• Hoppe's Retro synthesis





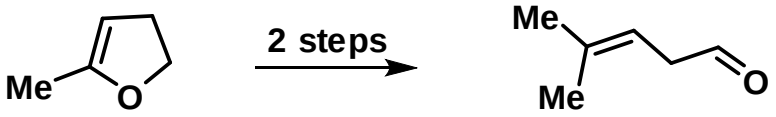
1

• Synthetic equivalent of homoenolate



Tetrahedron **1992**, *48*, 5667.

- Synthesis of aldehyde



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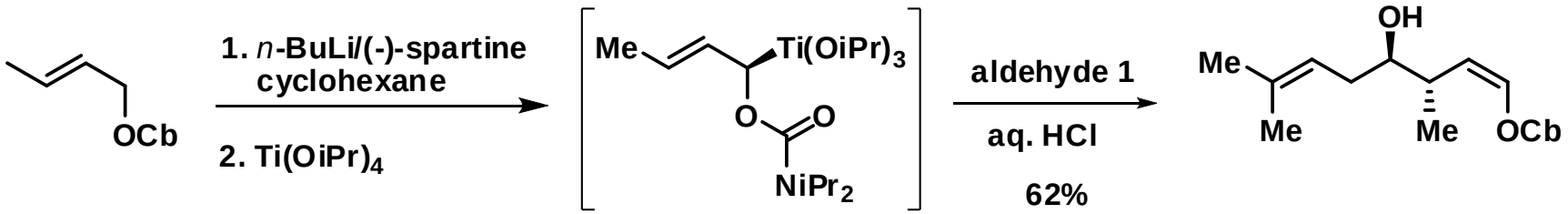
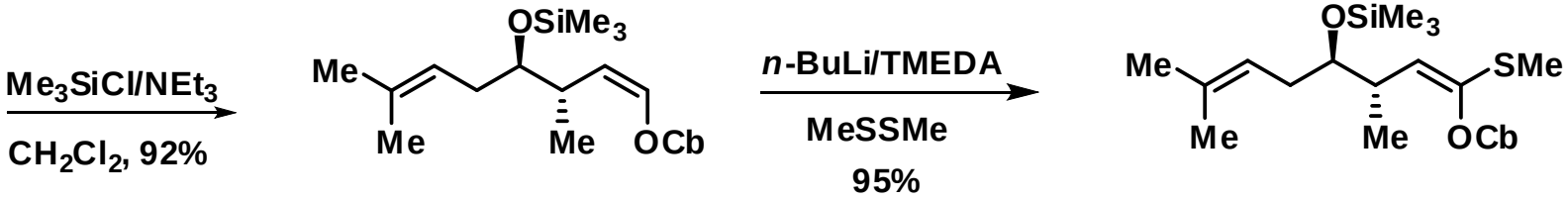
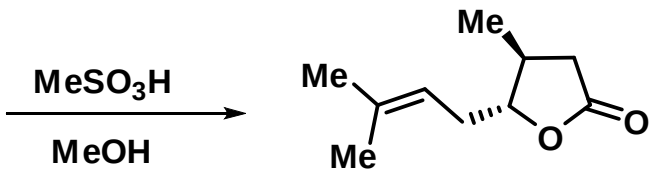
- Synthesis of (+)-endanolide

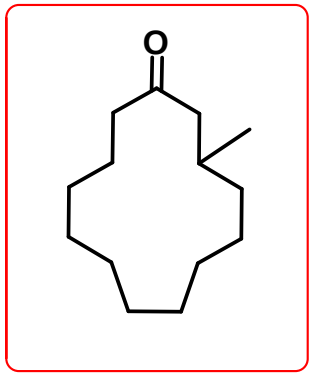


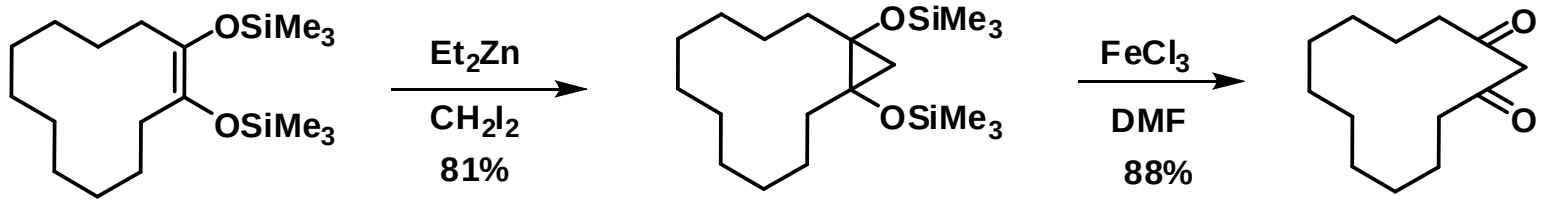


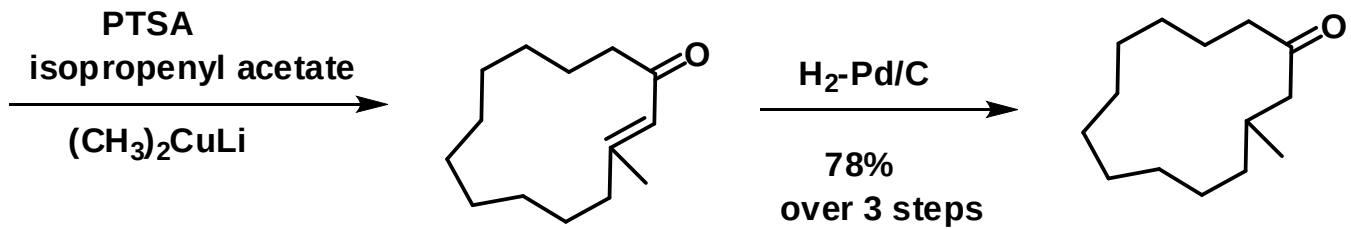


Tetrahedron **1992**, *48*, 5667.

• Synthesis of racemic Muscone

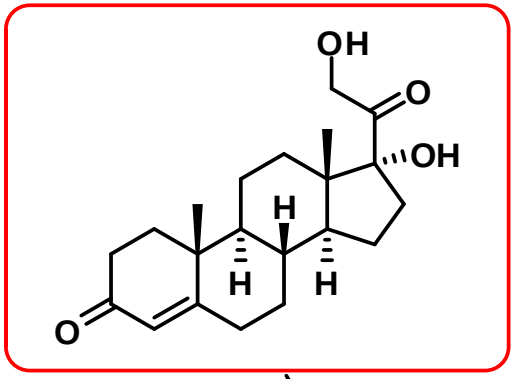


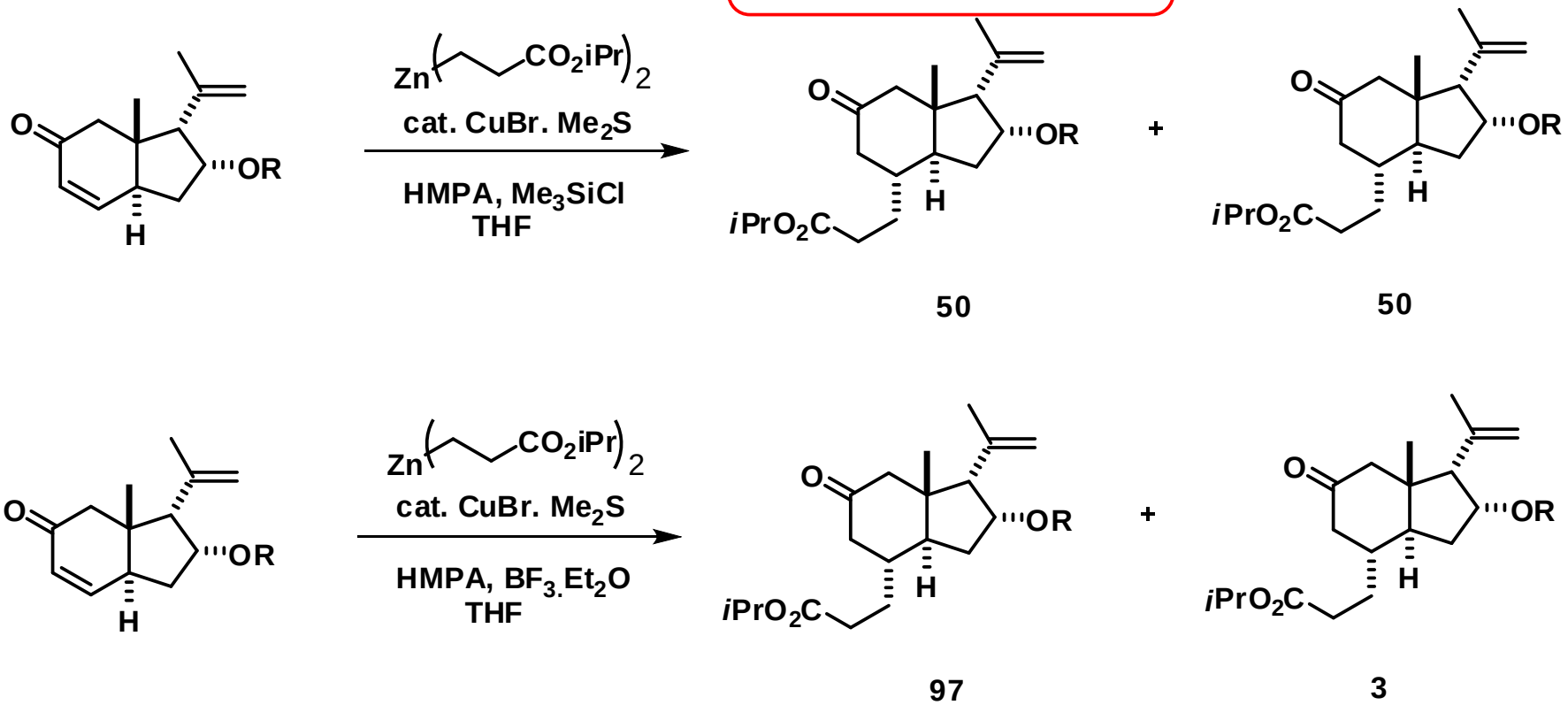




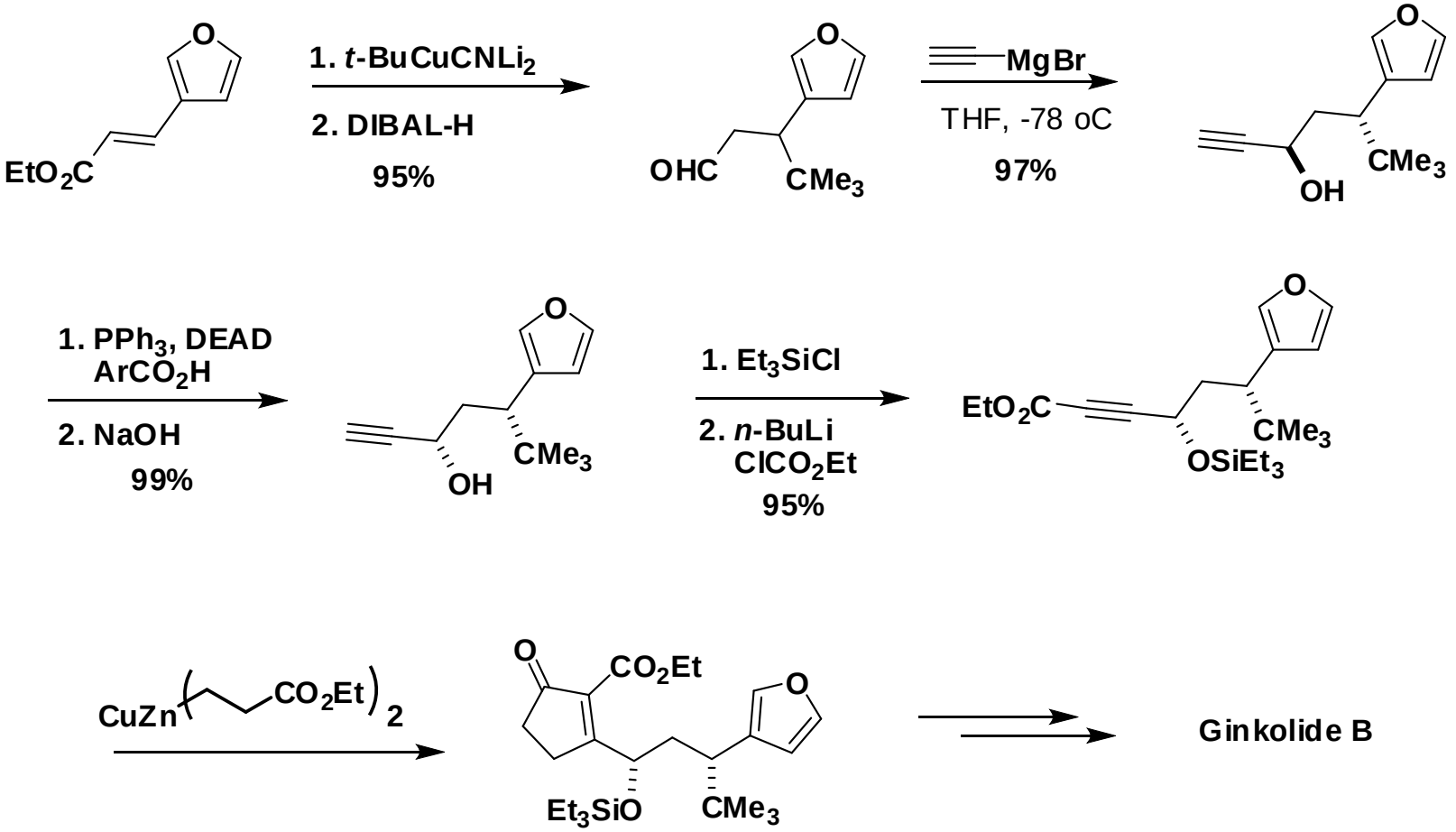
J. Org. Chem. **1977**, *42*, 2326.

• Synthesis of racemic cortisone





• Total Synthesis of Ginkolide B



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

Thank you !!!