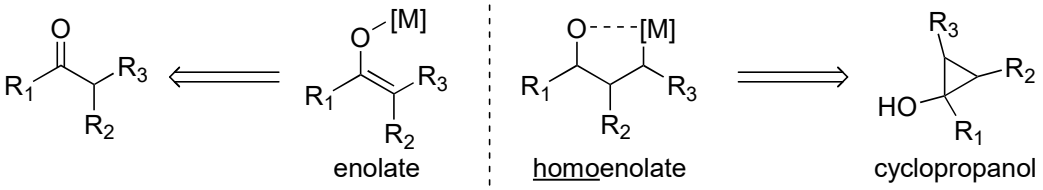
Problem Session (5)

2020. 5. 13. Tsukasa Shimakawa

Topic: Homoenolate and its equivalent in total synthesis

Introduction:



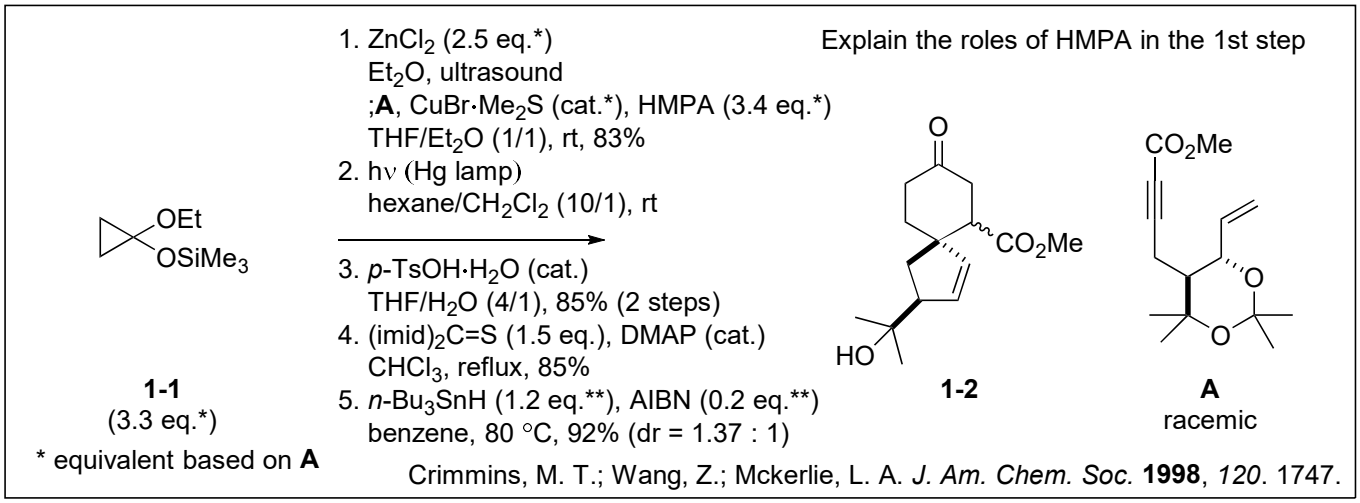
1. use as nucleophile = polarity exchange (***Problem 1***)
2. transition metal chemistry ([M] = Pd→cross-coupling, etc...) (***Problem 2***)
3. use as β-keto alkylradical equivalent (***Problem 3***)

Recent Review: "Cyclopropanol in total synthesis" Cai, X.; Liang, W.; Dai, M. *Tetrahedron* **2019**, *75*, 193.

Answer:

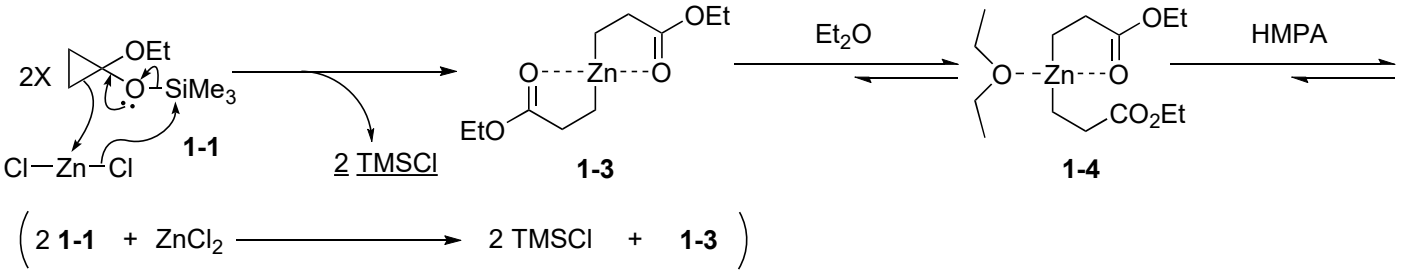
1. Total synthesis of (±)-lubiminol by Crimmins's group

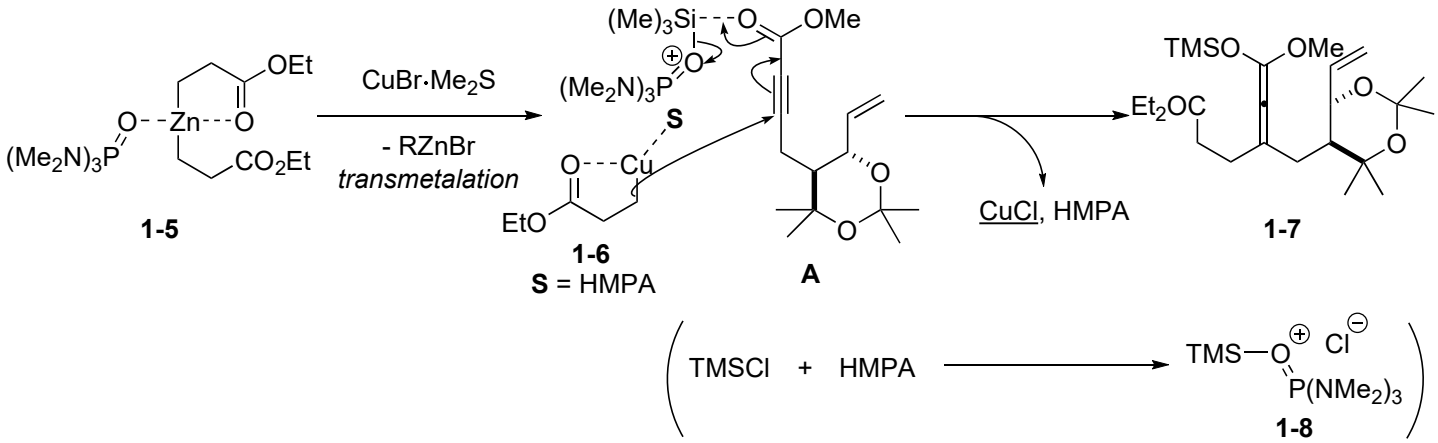
1-1. Reaction mechanism



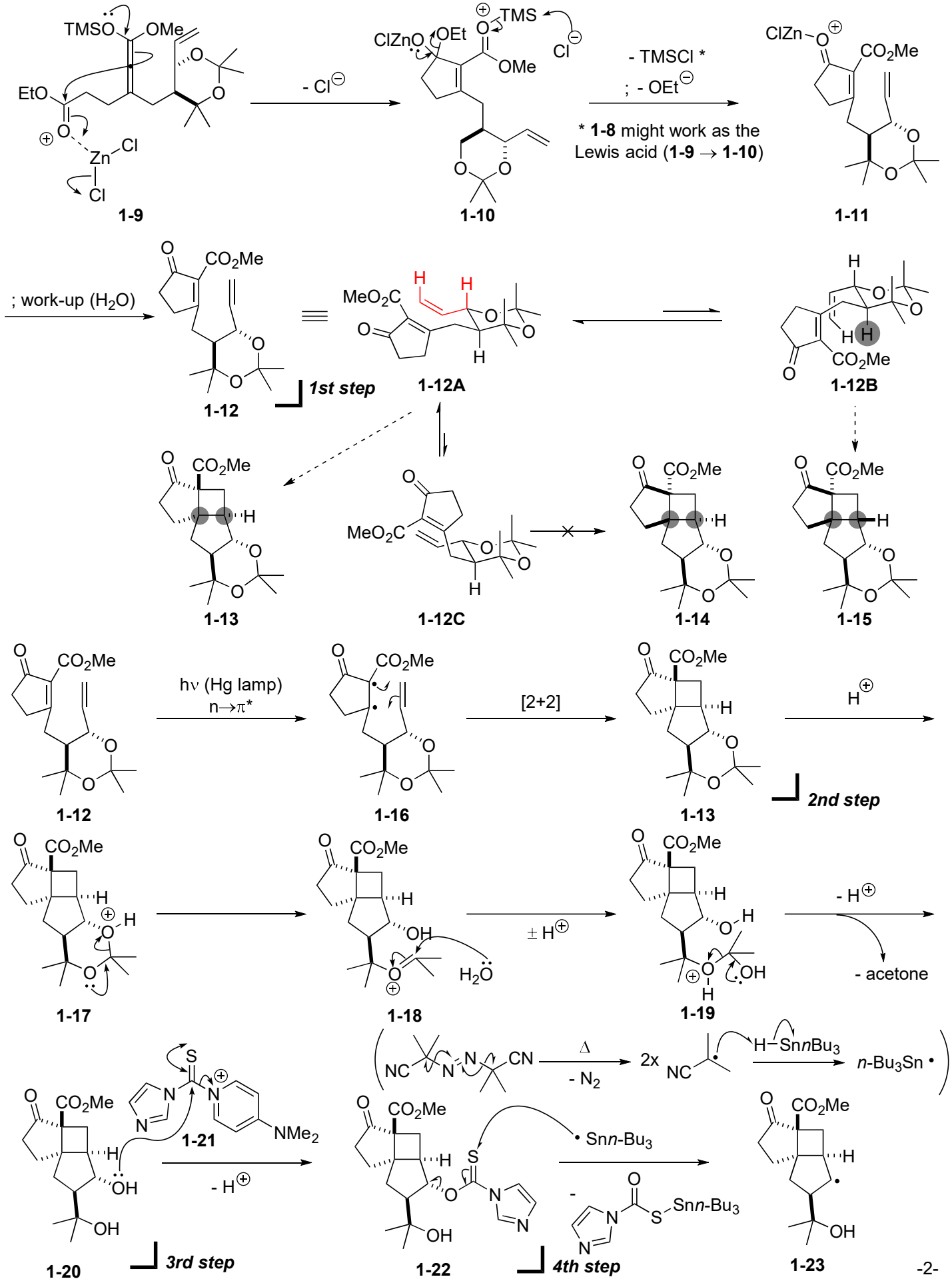
Crimmins, M. T.; Wang, Z.; Mckerlie, L. A. *J. Am. Chem. Soc.* **1998**, *120*. 1747.

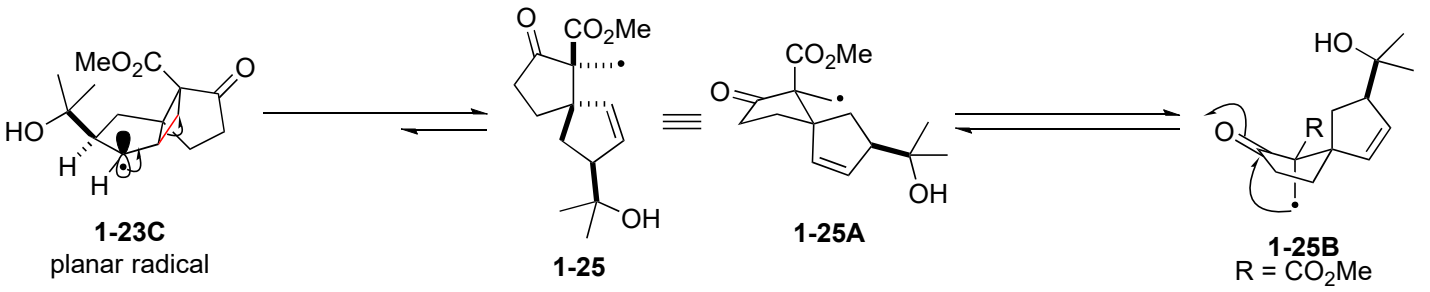
Key point: 1. Crimmins's cyclopentenone annulation 2. Dowd-Beckwith ring expansion





Bassindale, A. R. and Stout, T. *Tetrahedron Lett*. **1985**, *26*, 3403.


TMSO
OMe
EtO
Zn
Cl
1-9
- Cl⊖
ClZnO
OEt
TMS
Cl
OMe
1-10
- TMSCl *
; - OEt⊖
* 1-8 might work as the
Lewis acid (1-9 → 1-10)
ClZn
CO2Me
1-11
; work-up (H2O)
CO2Me
1-12
1st step
MeO2C
H
1-12A
1-12B
CO2Me
1-13
MeO2C
1-12C
1-14
1-15
hν (Hg lamp)
n→π*
1-16
[2+2]
H⊕
2nd step
OH
H2O
± H⊕
- H⊕
- acetone
1-17
1-18
1-19
NC
CN
N2
Δ
- N2
2x
H–SnnBu3
n-Bu3Sn•
S
NMe2
1-21
1-20
3rd step
Snn-Bu3
1-22
4th step
1-23



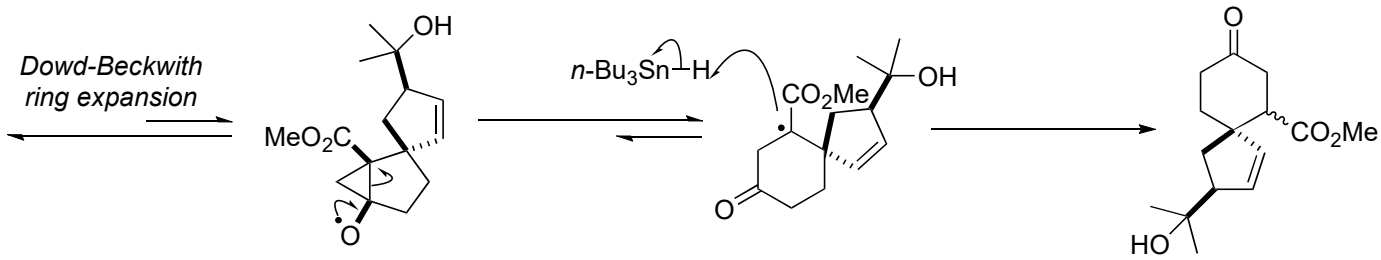
1-23C
planar radical

1-25

1-25A

1-25B
R = CO_2Me

radical **1-23C** has the π-radical character, not the σ-radical



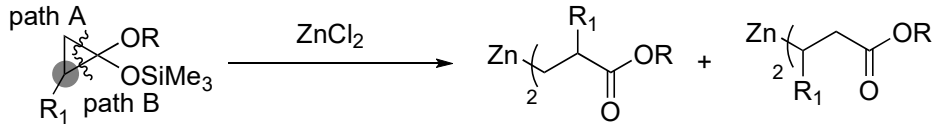
1-26

1-27

1-2

1-2. Crimmins's cyclopentenone annulation (See: Crimmins, M. T. et al. *J. Org. Chem*. **1993**, *58*, 1038.)

1-2-1. Mechanism of zinc-homoenolate formation



1-28

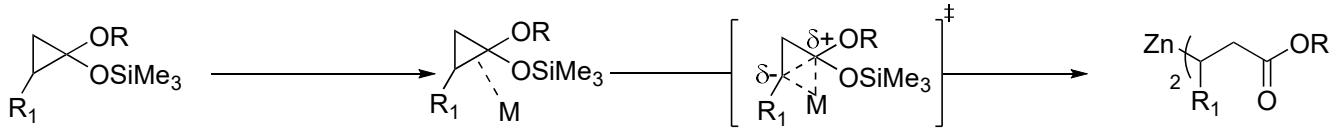
1-29 (path A)

1-30 (path B)

	1-29 (path A)	**1-30** (path B)
R_1 = Me	>98%	2%
R_1 = Ph	2%	>98%

anionically more stable Zn homoenolate is mainly formed

Kuwajima, I. *et al. J. Am. Chem. Soc*. **1987**, *109*, 8056.



1-28

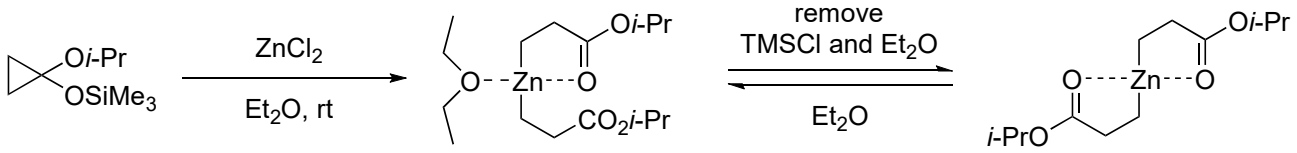
1-31

TS1

1-30

δ- stabilized TS is favored

1-2-2. The character of Zn-homoenolate



1-32

1-33

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

4 inequivalent methylene proton

(without considering methylene proton of Et_2O)

1-34

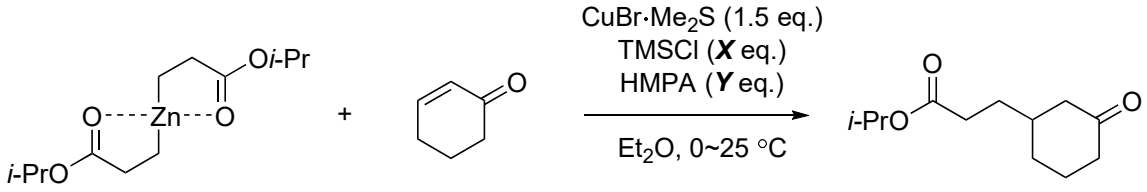
$\nu_{C=O}$ = 1645 cm^{-1}

2 inequivalent methylene proton

Nakamura, E.; Shimada, J.; Kuwajima, I. *Organometallics*. **1985**, *4*, 641.

1-2-3. The role of TMSCl and HMPA

a) Activation of carbonyl group by TMSCl and HMPA



1-34 **1-35** (3.6 eq.) **1-36**

Table

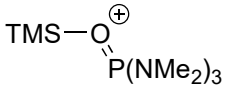
entry	***X***	***Y***	yield after 20 min	yield after 8 h
1	0	0	<5%	<5%
2	0	3.6	<5%	ca. 5%
3	3.6	0	<5%	ca. 5%
4	1.1	3.6	80%	—

Kuwajima, I. *et al. J. Am. Chem. Soc*. **1987**, *109*, 8056.

♣ Both TMSCl and HMPA are necessary to facilitate the 1,4-addition of copper homoenolate

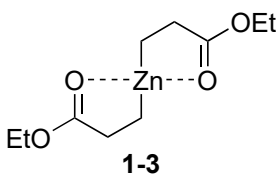
⇓

Specie **1-8** works as the strong Lewis acid for the activation of enone



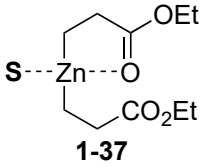
1-8

b) IR spectrum of Zn homoenolate - The nucleophilicity of homoenolate-

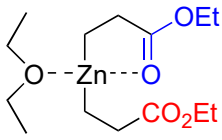


1-3

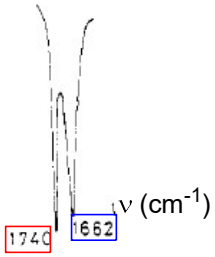
Solvent



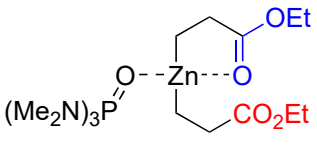
1-37



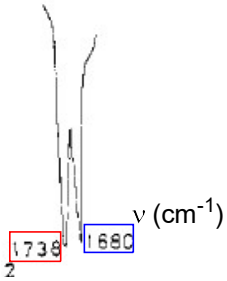
1-4



(a) 0.06 M in Et_2O



1-5

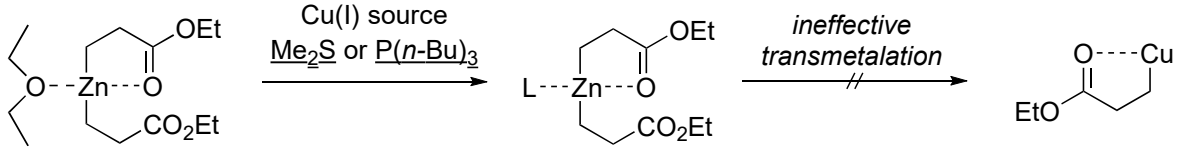


(b) 0.06 M in Et_2O + HMPA (2 eq.)

Kuwajima, I. *et al. J. Am. Chem. Soc*. **1987**, *109*, 8056.

The effects of electron donating solvent (Et_2O or HMPA) are
1. displacement of the equibirium to specie **1-37**
2. weaker Lewis acidity of the metal center = Increase the carbanion character of homoenolate

c) The role of HMPA in transmetalation

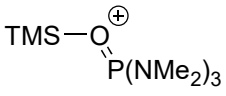


1-4 **1-38** **1-39**

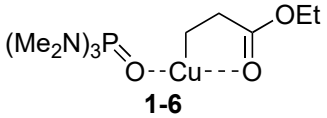
L = Me_2S or P(*n*-Bu)$_3$

Nakamura, E. and Kuwajima, I. *J. Am. Chem. Soc*. **1984**, *106*, 3368.

The roles of HMPA are
1. facilitate the transmetalation (from Zn to Cu)
2. Increase the nucleophilicity of copper-homoenolate (form **1-6**)
3. Formation of the more Lewis acidic specie **1-8** from *in situ* generated TMSCl



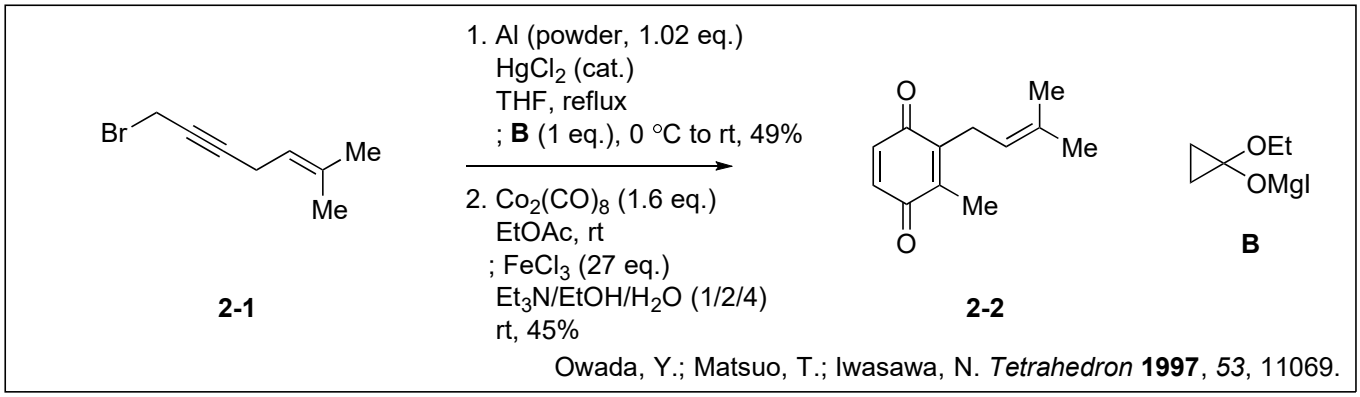
1-8



1-6

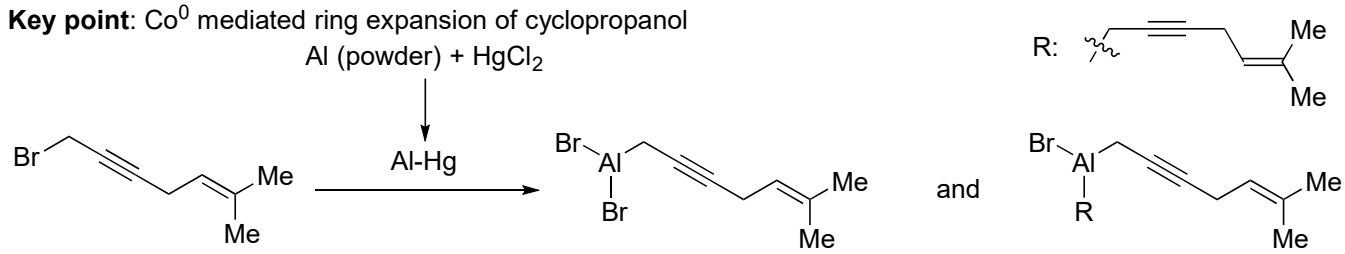
2. Synthesis of vitamin E analogues by Iwasawa's group

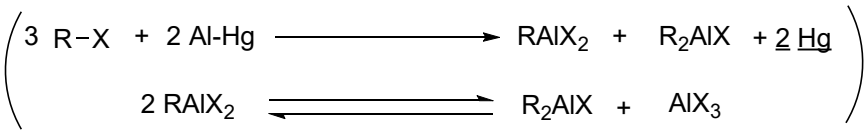
2-1. Reaction mechanism

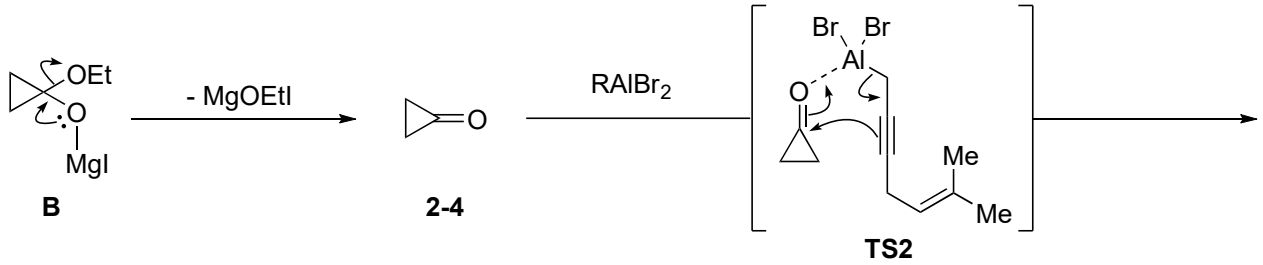


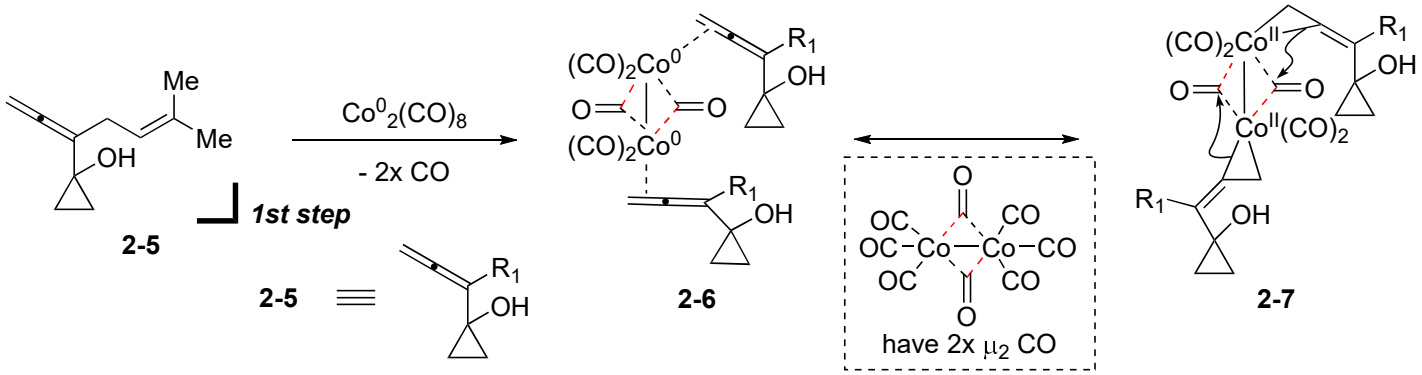
Owada, Y.; Matsuo, T.; Iwasawa, N. *Tetrahedron* **1997**, *53*, 11069.

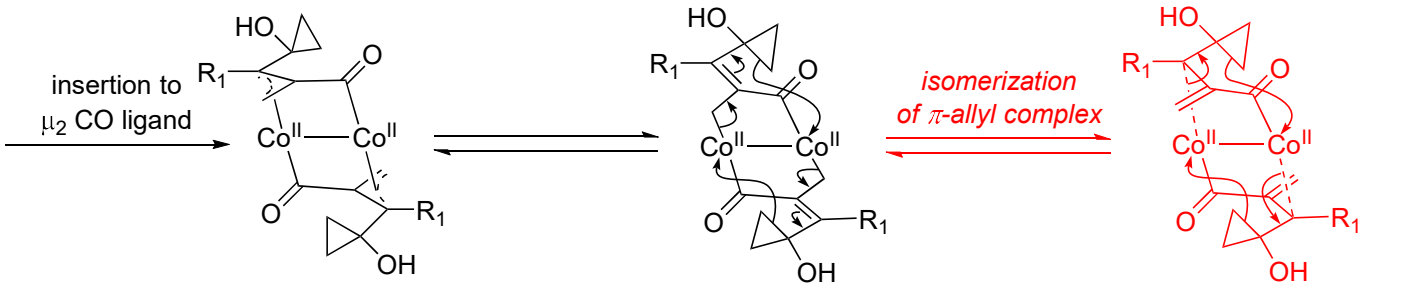
Key point: Co^0 mediated ring expansion of cyclopropanol

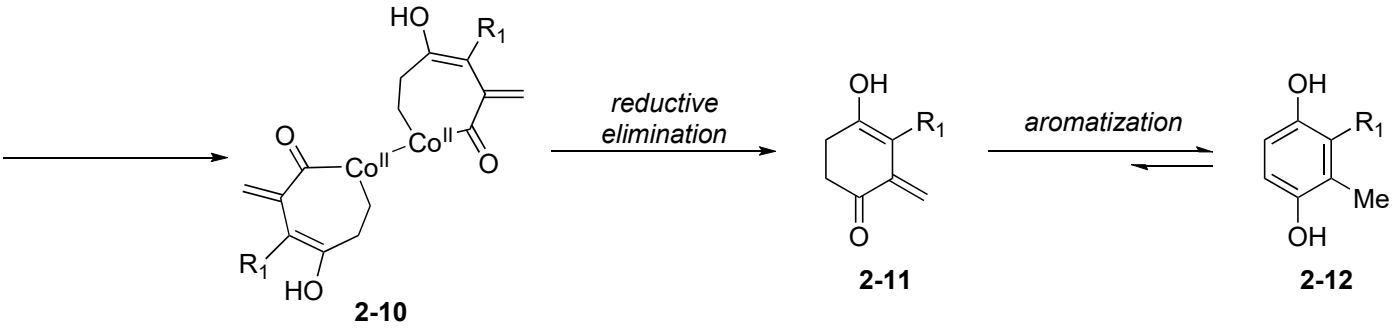








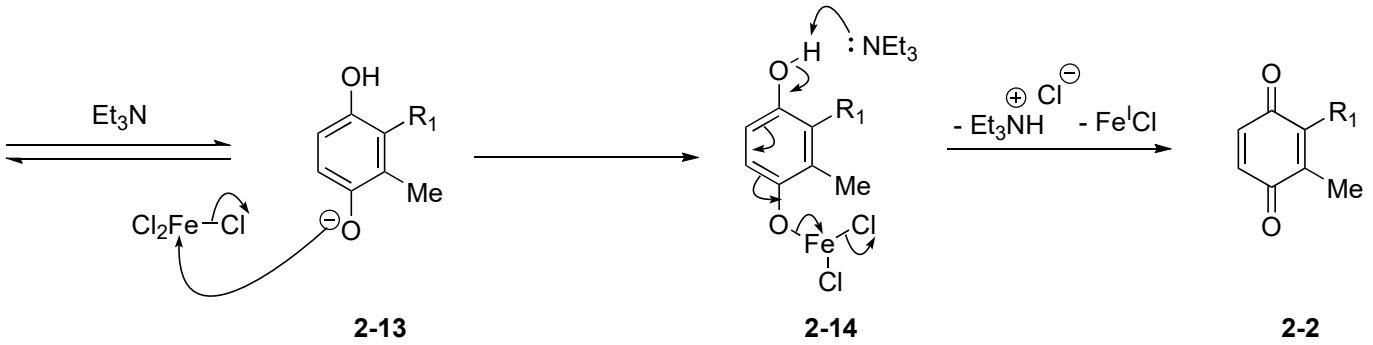




2-10

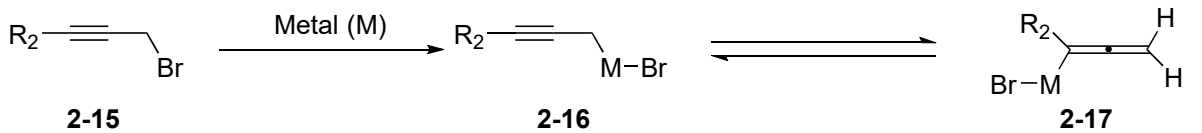
(CO ligand omitted. n= 1 or 2)

2-11 **2-12**

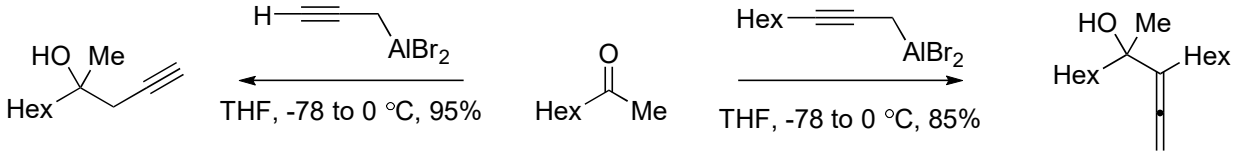


2-13 **2-14** **2-2**

2-2. allene-propargyl equibirium



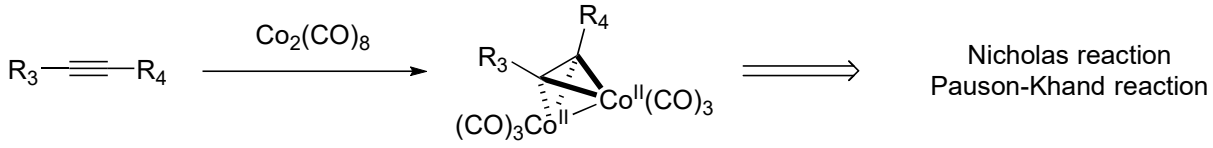
2-15 **2-16** **2-17**



2-18 **2-19** **2-20**

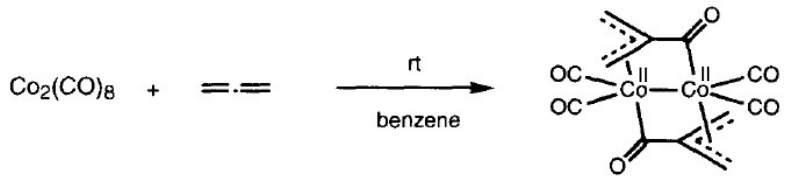
Guo, L-N.; Gao, H.; Mayer, P.; Knochel, P. *Chem. Eur. J*. **2010**, *16*, 9829.

2-3. Example of allene-$Co_2(CO)_8$ complex



2-23 **2-24**

Nicholas reaction
Pauson-Khand reaction



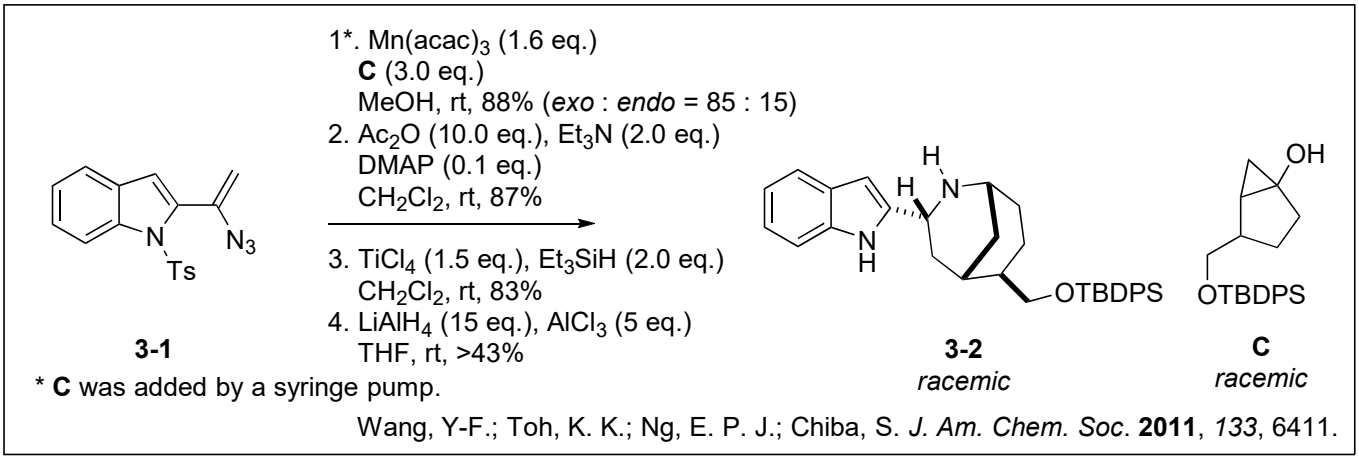
2-25

1. η^3-allyl ligand
2. CO inserted complex

Nakamura, A. *Bull. Chem. Soc. Jpn*. **1966**, *39*, 543.

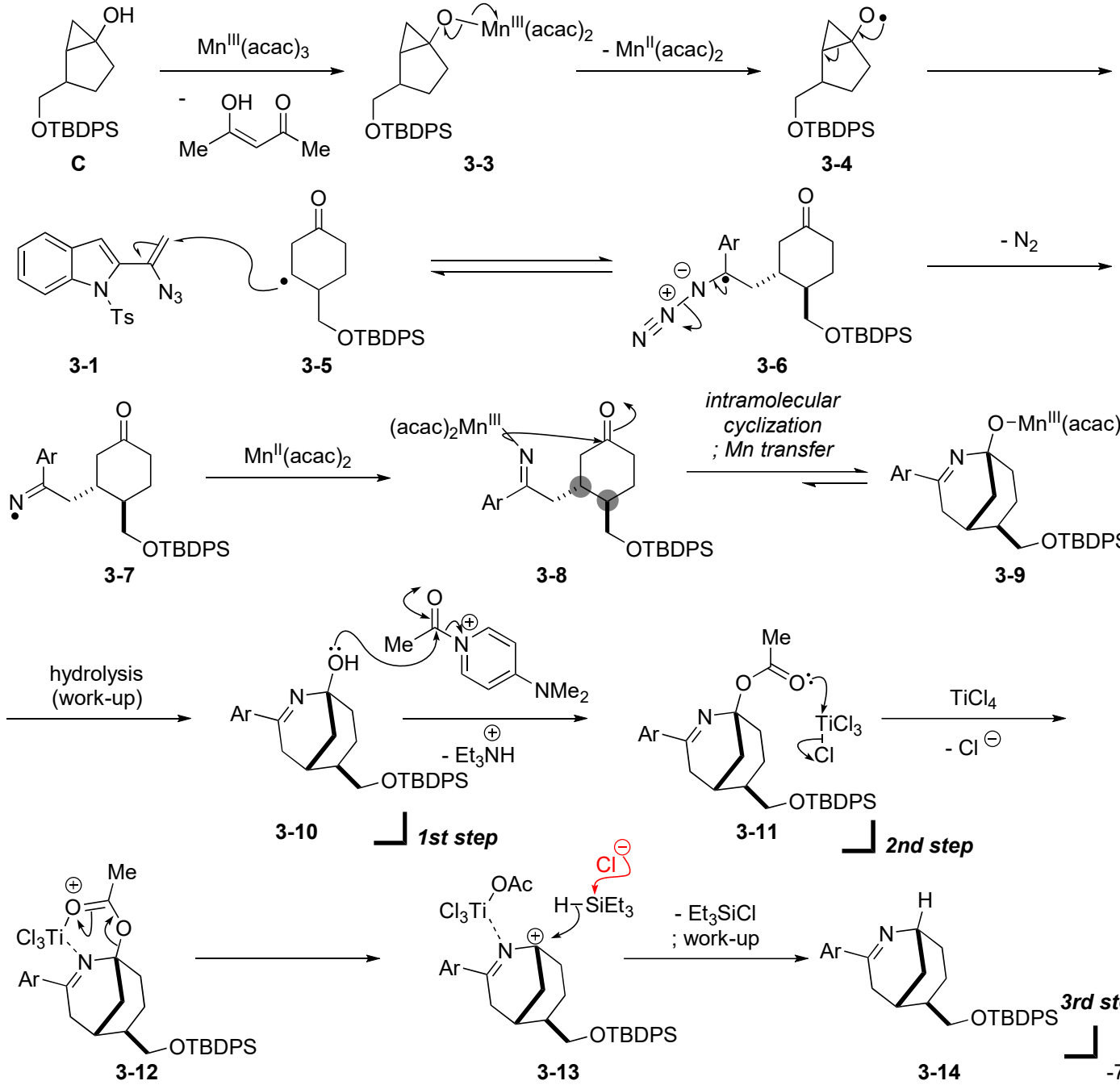
3. Total synthesis of (±)-melinonine E by Chiba's group

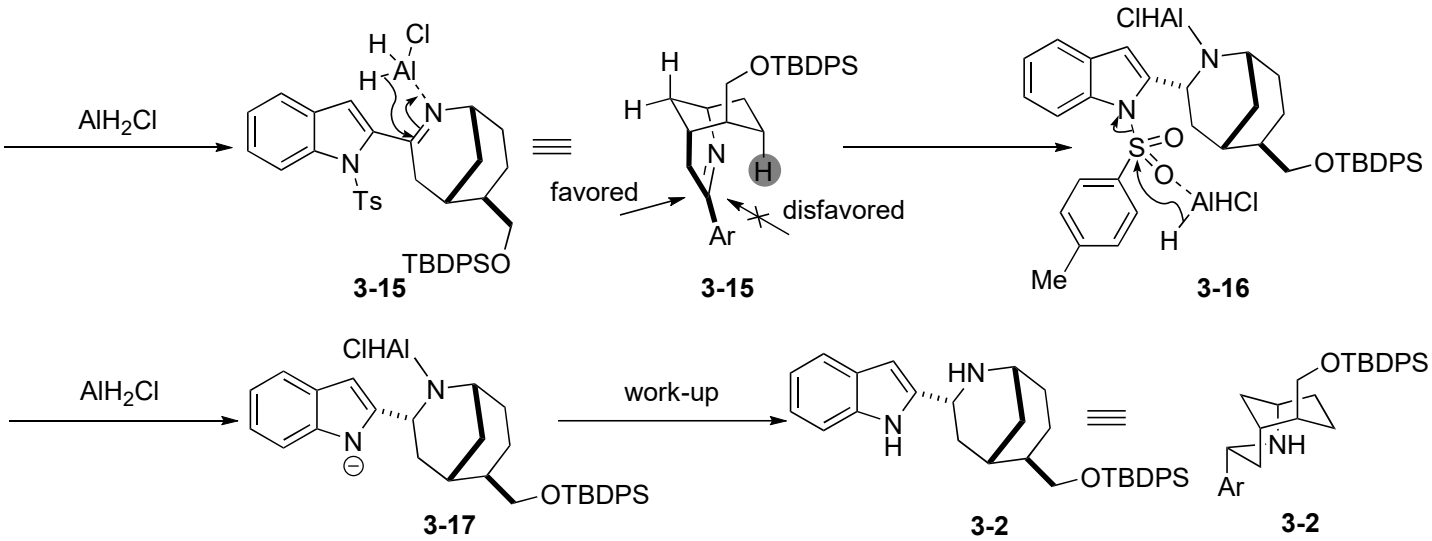
3-1. Reaction mechanism

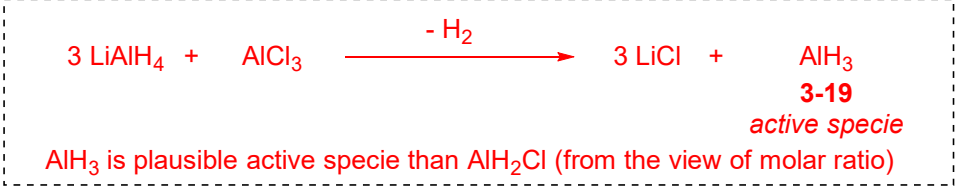


Wang, Y-F.; Toh, K. K.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 6411.

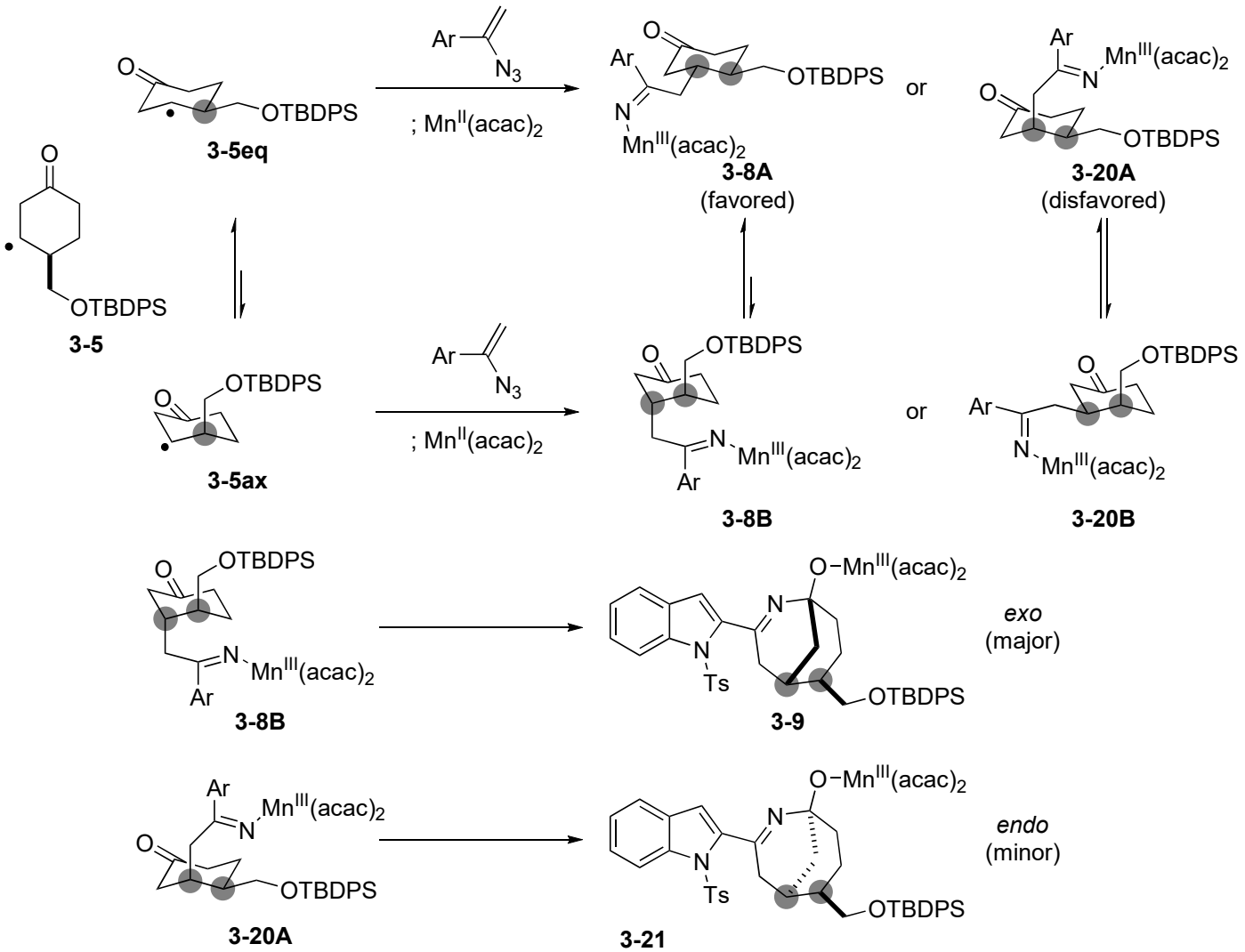
Key point: Mn(III)-mediated formal [3+3] cycloaddition





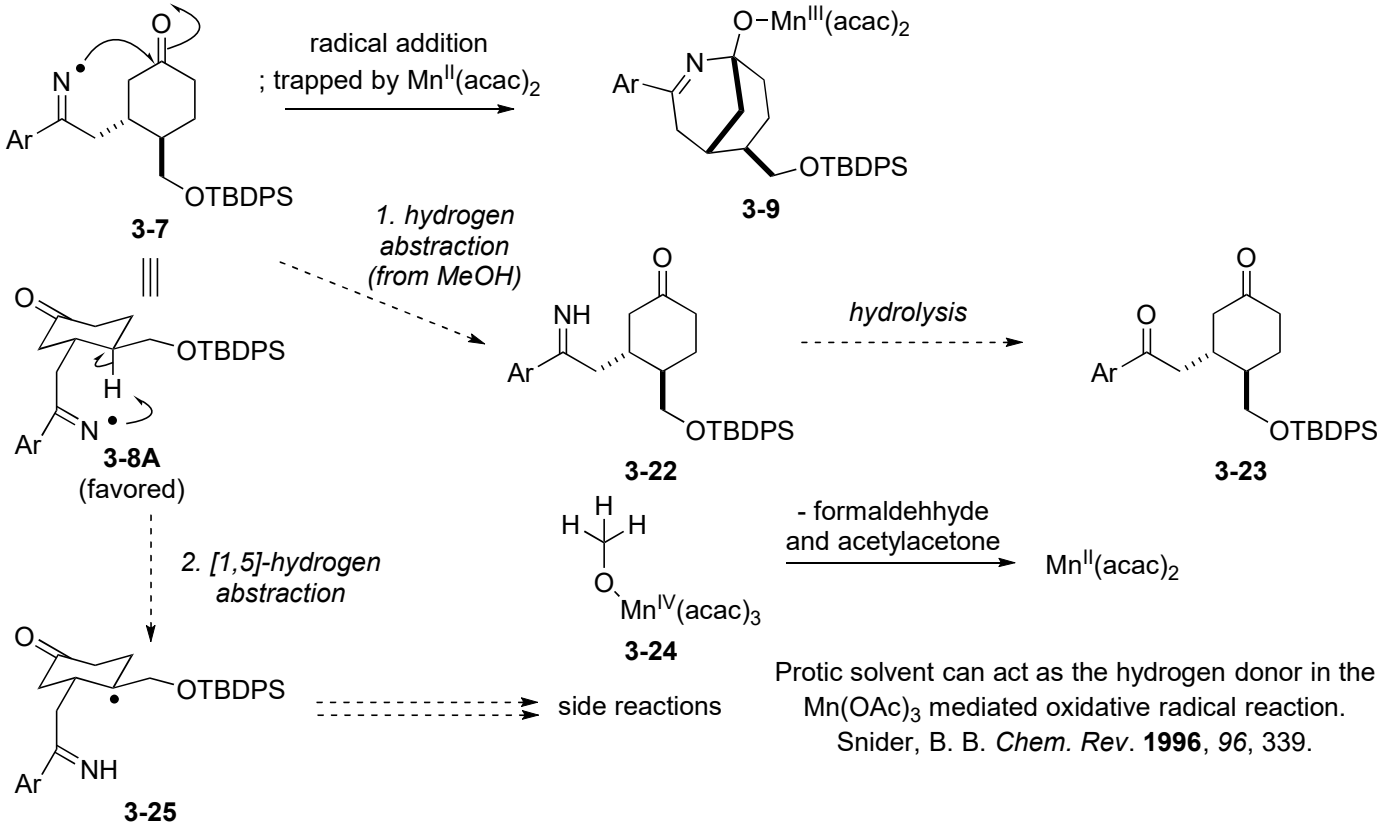


3-2. Diastereoselectivity in [3+3] cycloaddition



From the enantiomer of **3-5**, the enantiomer of **3-9** and **3-21** are also obtained (The detail is omitted).

3-3. Another path of intramolecular cyclization proposed by author



Protic solvent can act as the hydrogen donor in the $Mn(OAc)_3$ mediated oxidative radical reaction.
Snider, B. B. *Chem. Rev*. **1996**, *96*, 339.