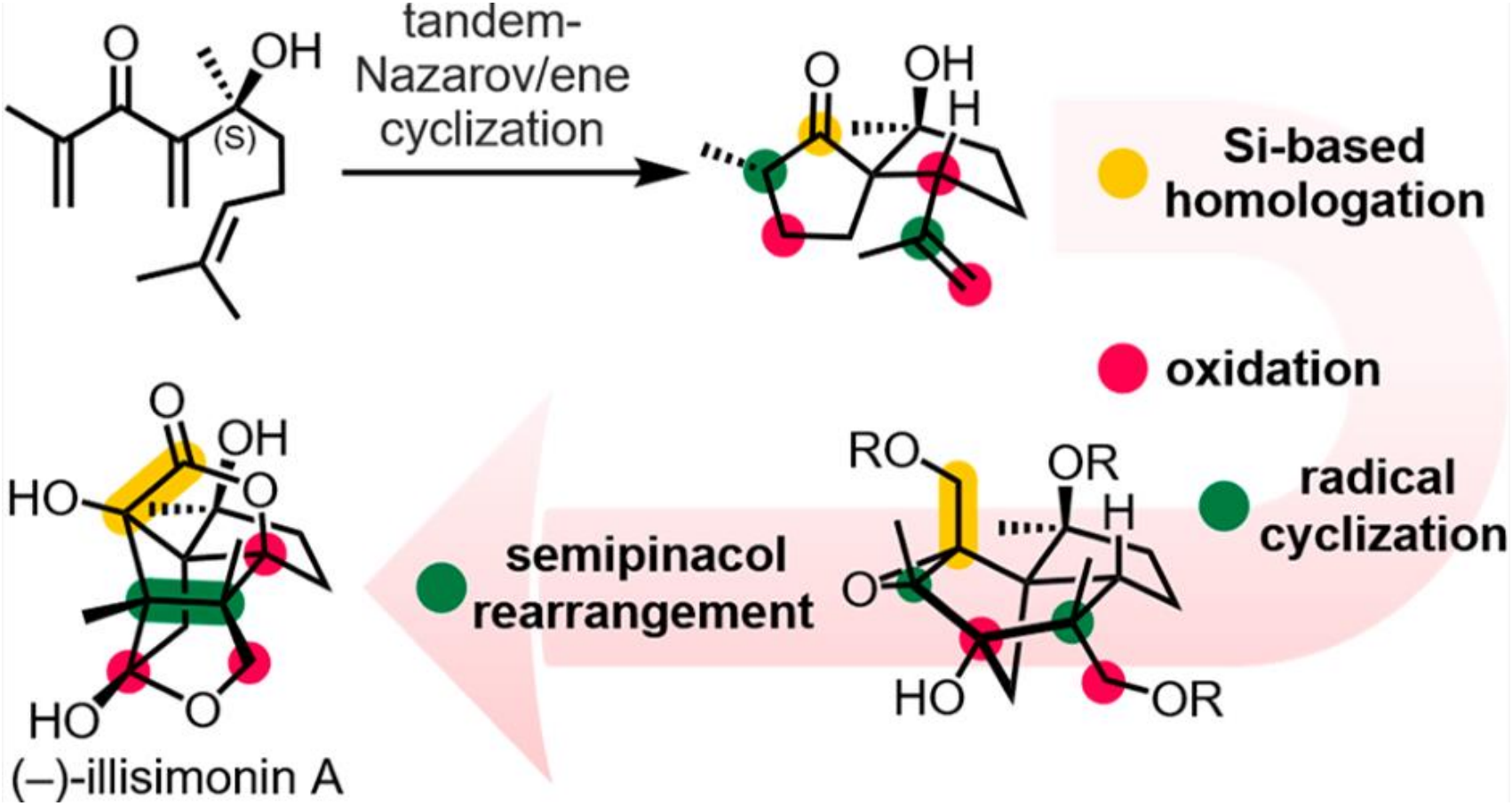
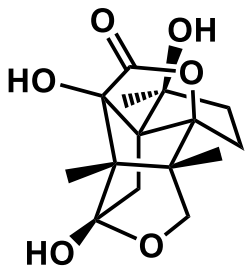
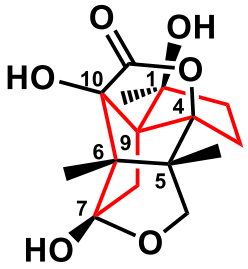
Asymmetric Total Synthesis of Illisimonin A

Christoph Etling, Giada Tedesco,
Anna Di Marco, and Markus Kalesse*
J. Am. Chem. Soc., **2023**, *145*, 12.



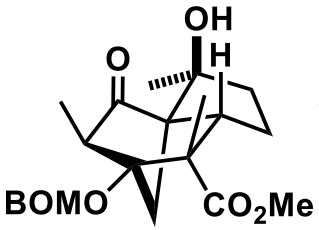


(-)-illisimonin A (1)

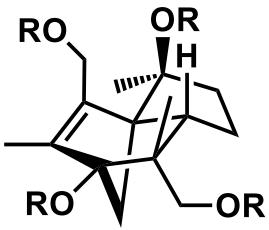


spiro substructure and stereocenters

Rychnovsky and Burns (2019)

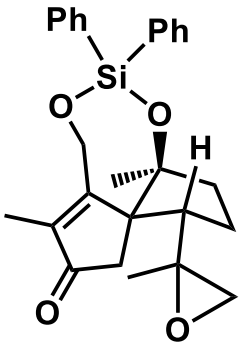


(±)-3



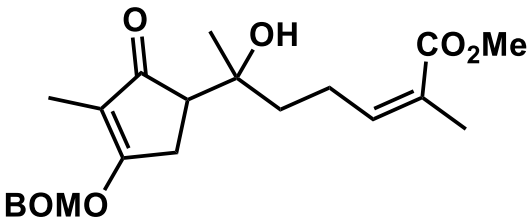
2

This work



5

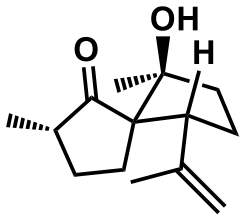
intramolecular Diels-Alder



(±)-4

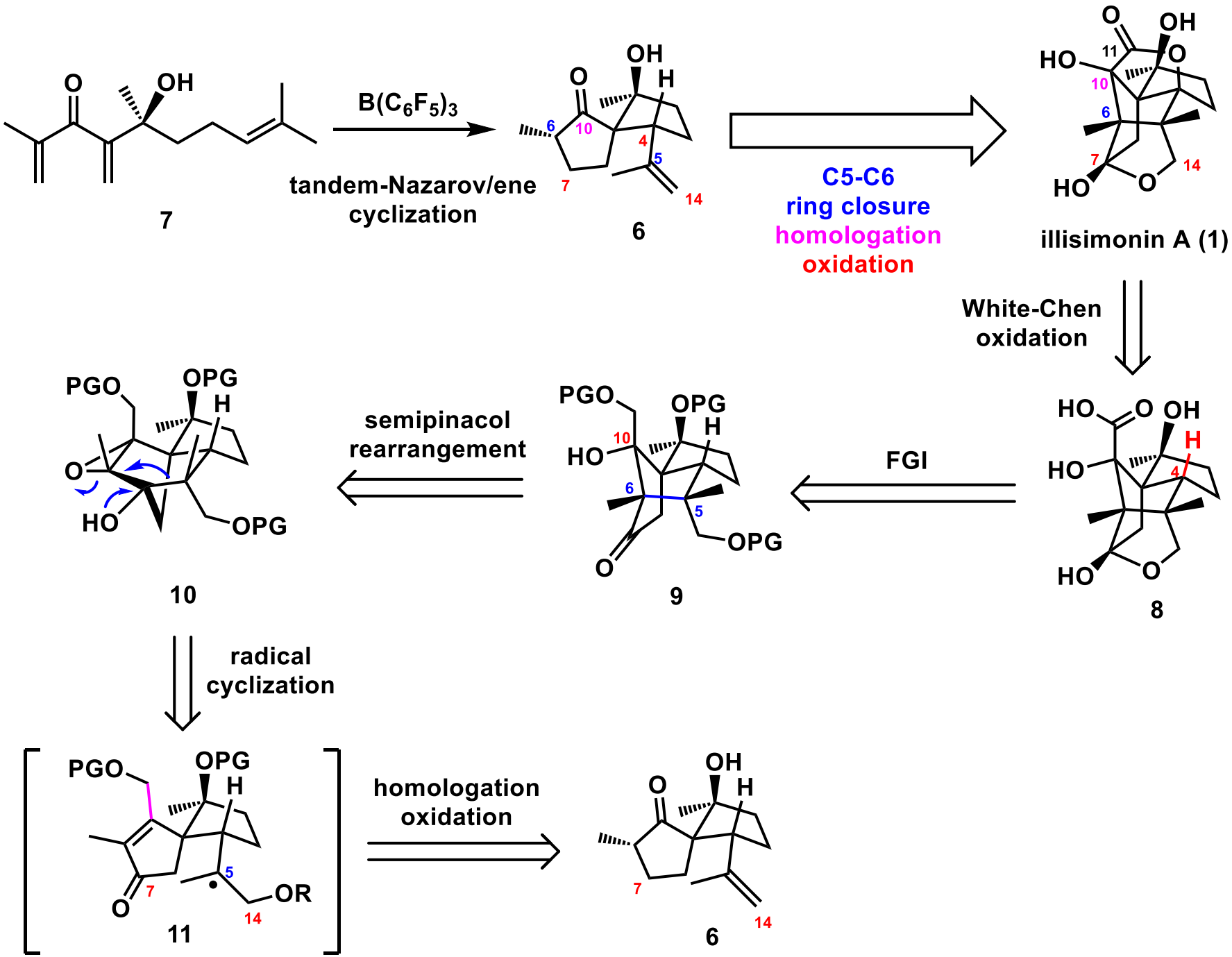
late-stage seperation of enantiomers

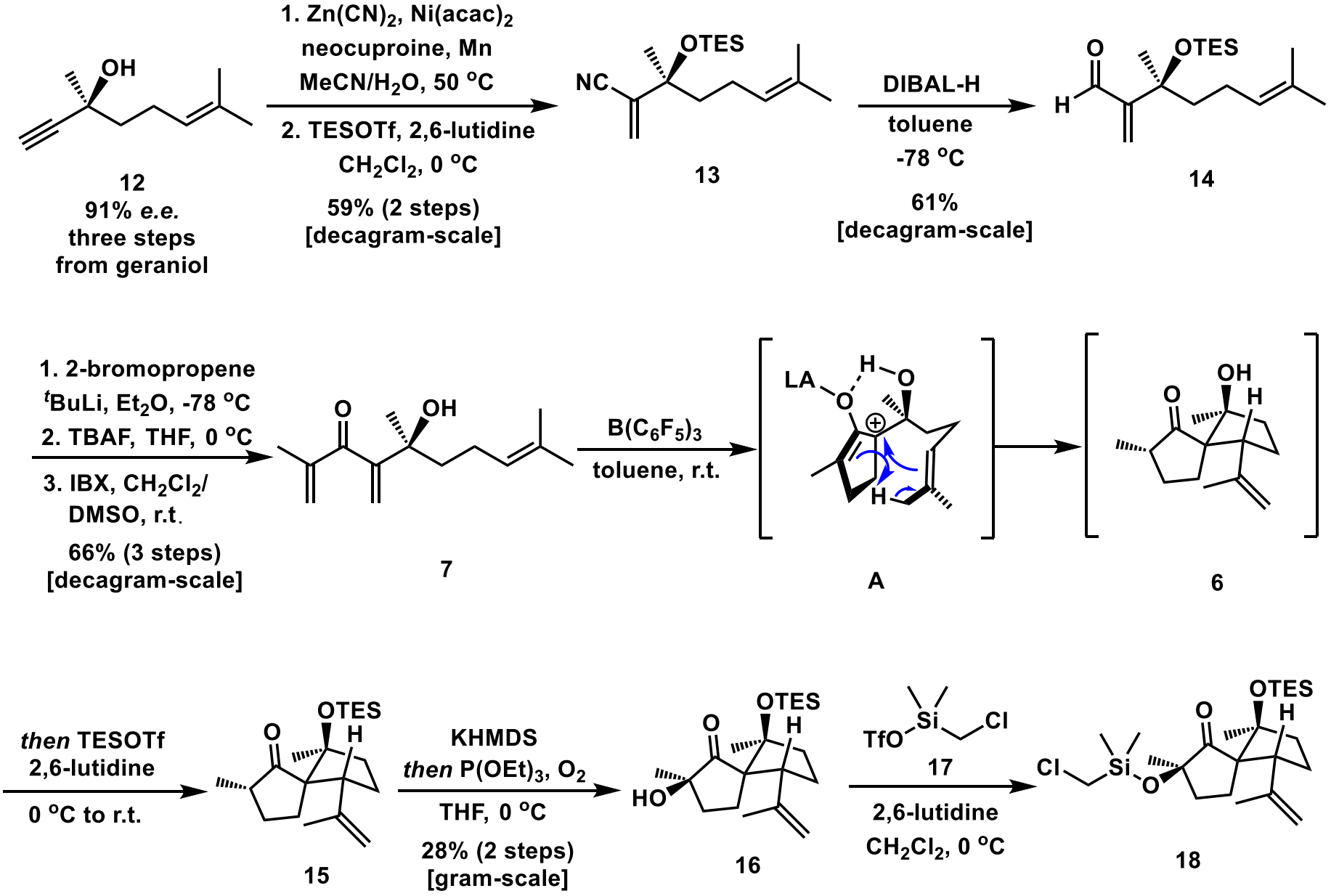
homologation oxidation

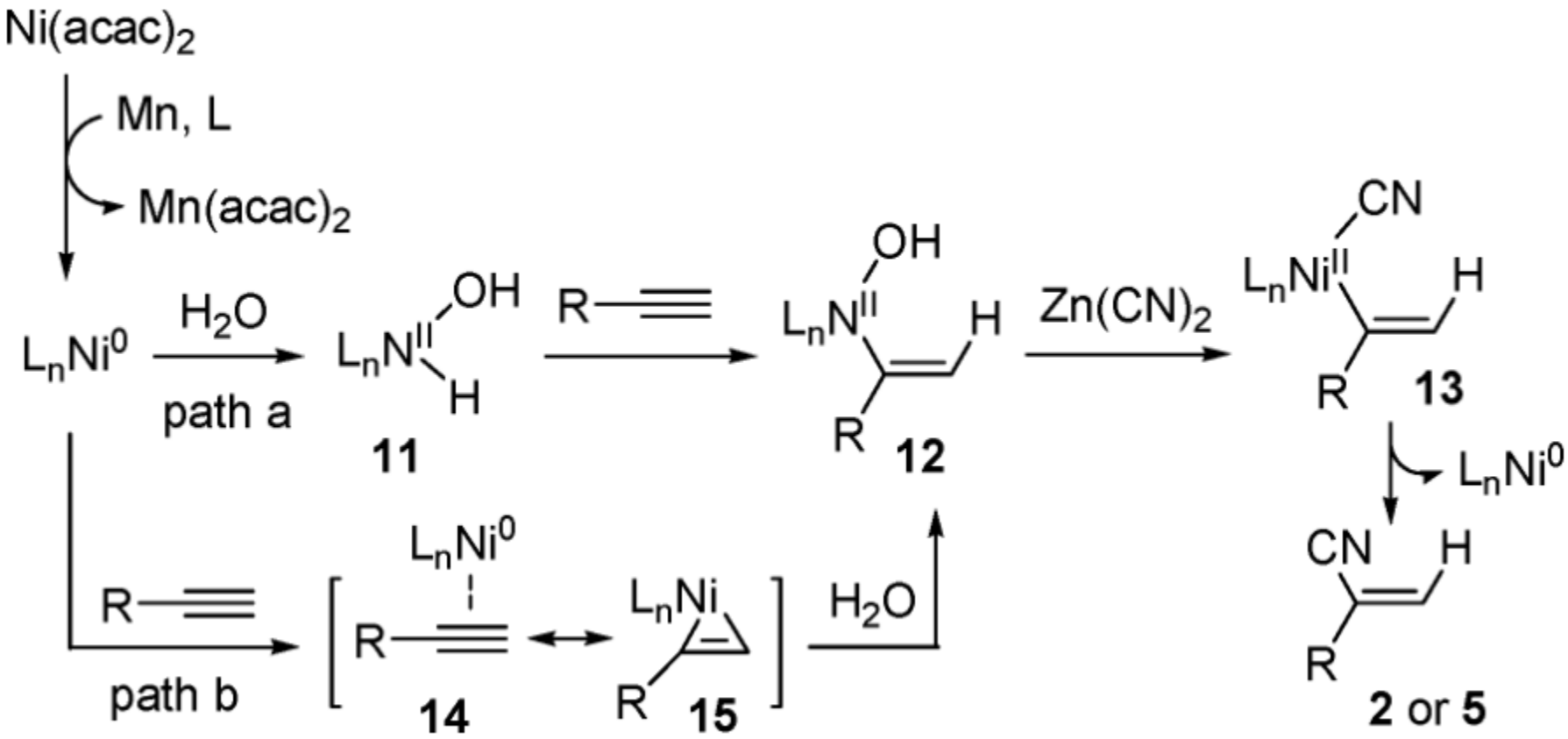


(±)-6

enantioenriched intermediate

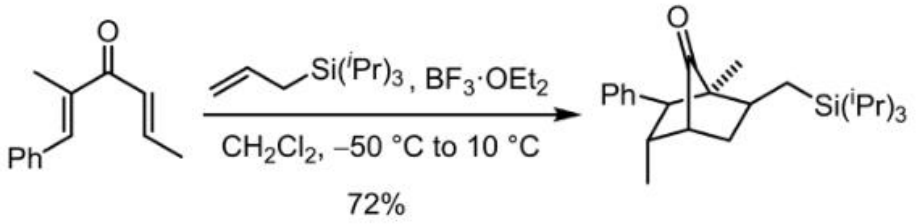

7
B(C6F5)3
tandem-Nazarov/ene
cyclization
6
C5-C6
ring closure
homologation
oxidation
illisimonin A (1)
White-Chen
oxidation
8
FGI
9
semipinacol
rearrangement
10
radical
cyclization
11
homologation
oxidation
6


OH
12
91% e.e.
three steps
from geraniol
1. Zn(CN)2, Ni(acac)2
neocuproine, Mn
MeCN/H2O, 50 °C
2. TESOTf, 2,6-lutidine
CH2Cl2, 0 °C
59% (2 steps)
[decagram-scale]
NC
OTES
13
DIBAL-H
toluene
-78 °C
61%
[decagram-scale]
O
H
OTES
14
1. 2-bromopropene
tBuLi, Et2O, -78 °C
2. TBAF, THF, 0 °C
3. IBX, CH2Cl2/
DMSO, r.t.
66% (3 steps)
[decagram-scale]
O
OH
7
B(C6F5)3
toluene, r.t.
LA
O
H
O
H
A
OH
O
H
6
then TESOTf
2,6-lutidine
0 °C to r.t.
OTES
O
H
15
KHMDS
then P(OEt)3, O2
THF, 0 °C
28% (2 steps)
[gram-scale]
HO
OTES
O
H
16
TfO
Si
Cl
17
2,6-lutidine
CH2Cl2, 0 °C
Cl
Si
O
OTES
O
H
18

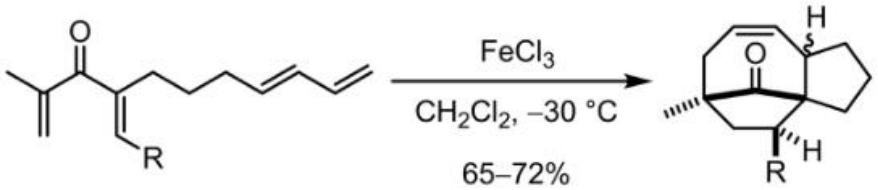


J. Am. Chem. Soc., **2018**, *140*, 7385.

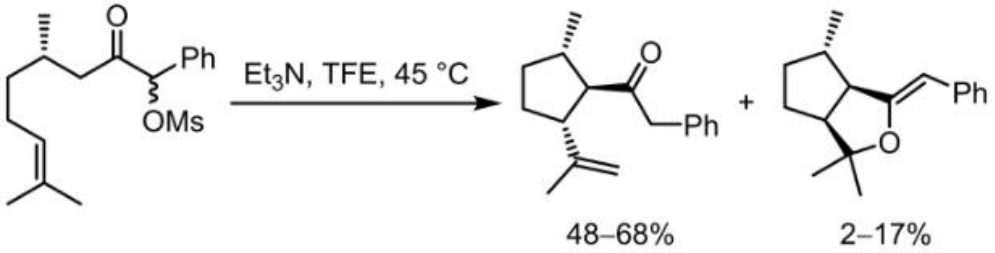
Nazarov cyclization/formal [3+2] cycloaddition (West 2000)[6]



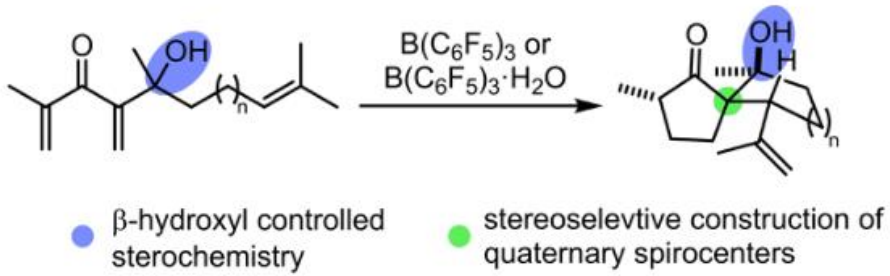
Nazarov cyclization/intramolecular [4+3] (West 1999)[7a]



Cyclopentane synthesis *via* intramolecular cyclization of oxyallyl cations (Saicic 2019)[12]

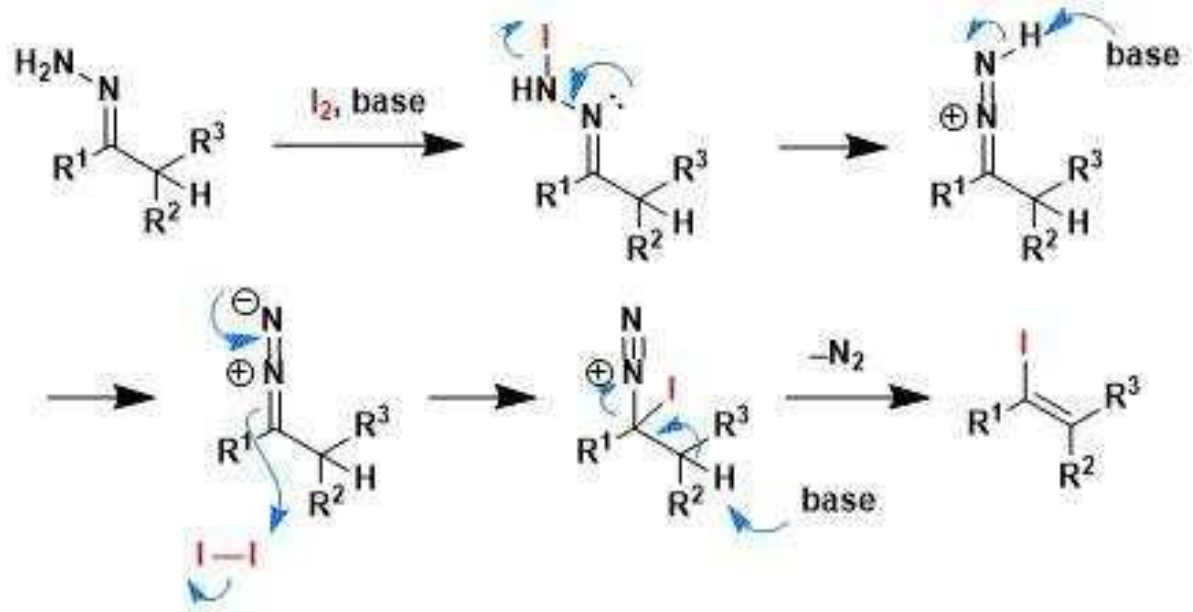


This work: Novel Nazarov/ene cyclization tandem reaction

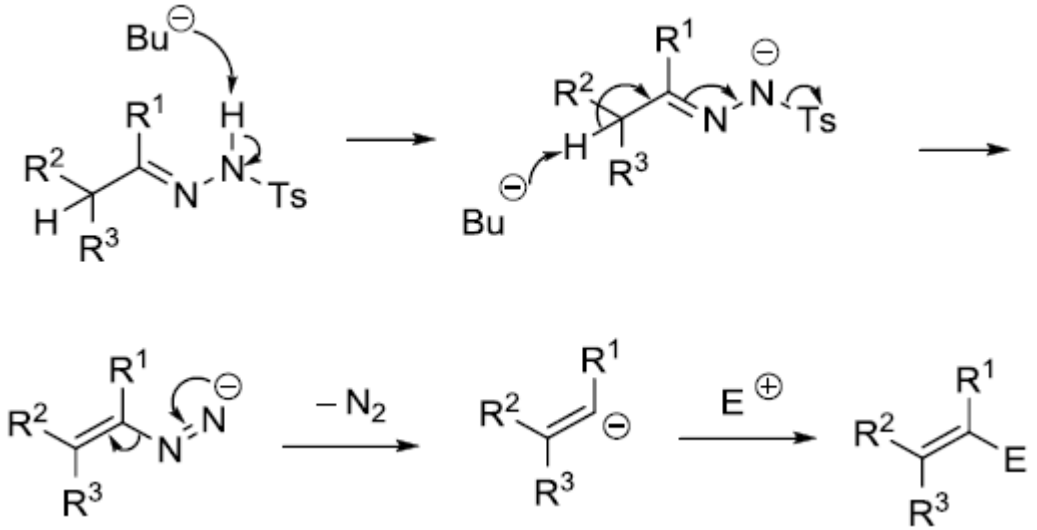


Chem. Eur. J., **2021**, *27*, 9257.

Barton Vinyl Iodide Synthesis:



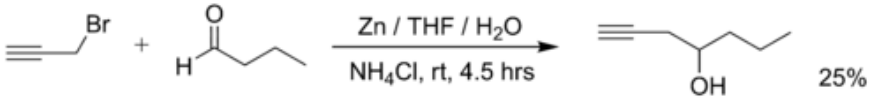
Shapiro Reaction:



Barbier reaction:

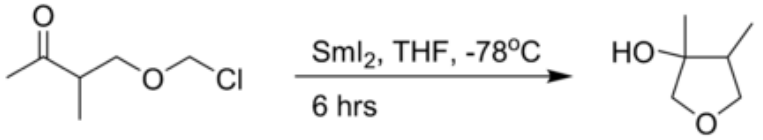
Scope [edit]

Examples of Barbier reactions are the reaction of propargylic bromide with butanal with zinc metal (the reaction is carried out in THF, the saturated aqueous ammonium chloride solution added later to quench the reaction):[2]

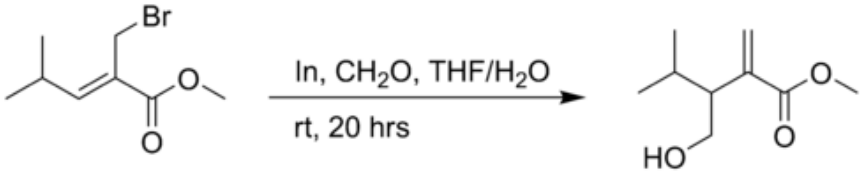


With a substituted alkyne instead of a terminal alkyne the allene product is favoured

the intramolecular Barbier reaction with samarium(II) iodide:[3]

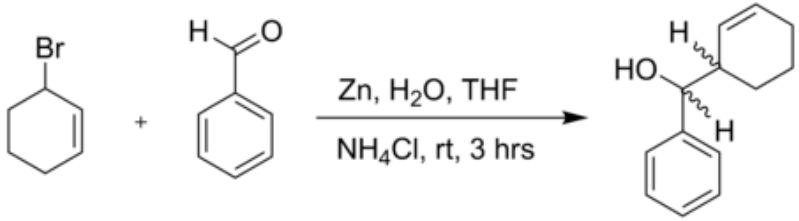


the reaction of an allyl bromide with formaldehyde in THF with indium powder:[4]

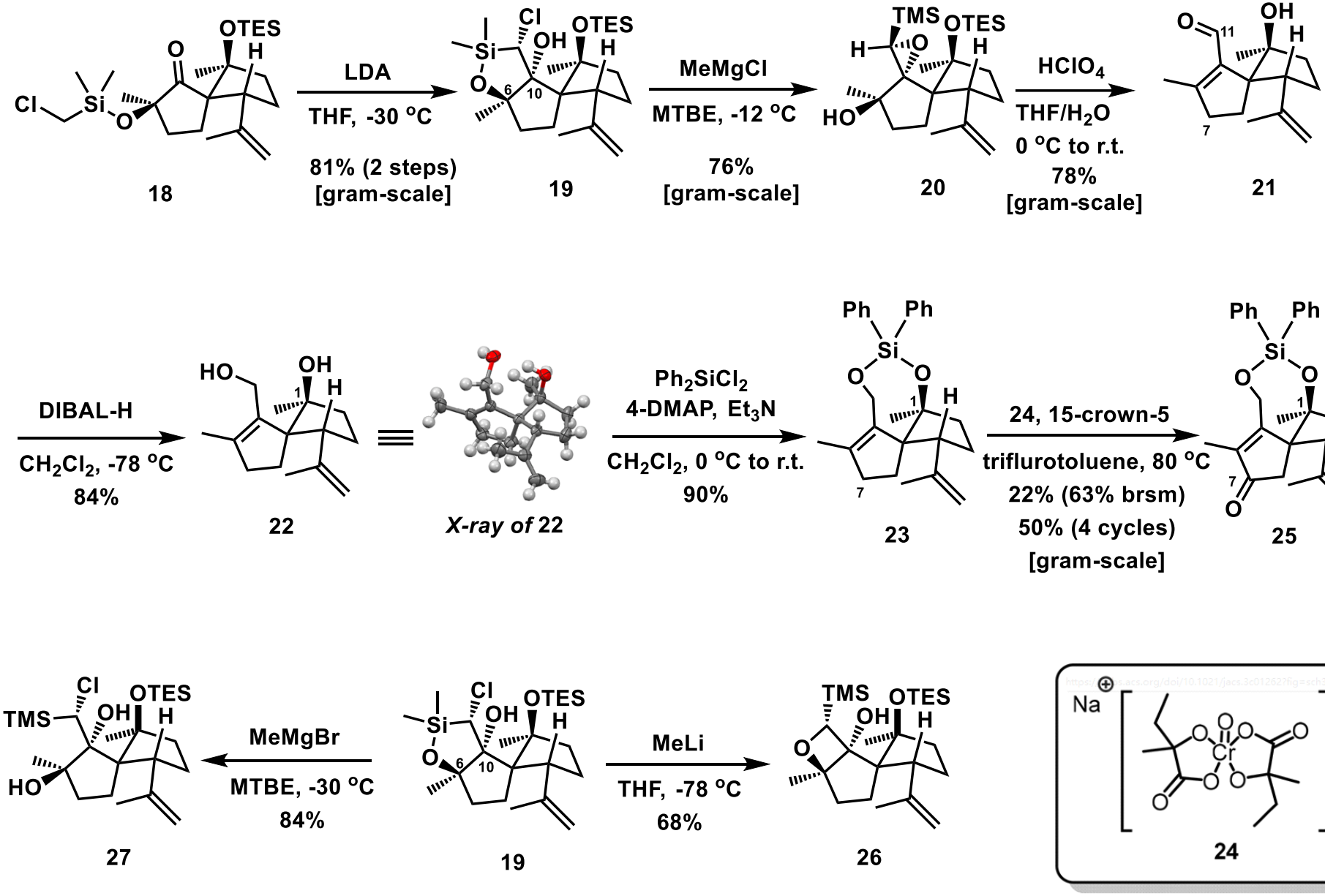


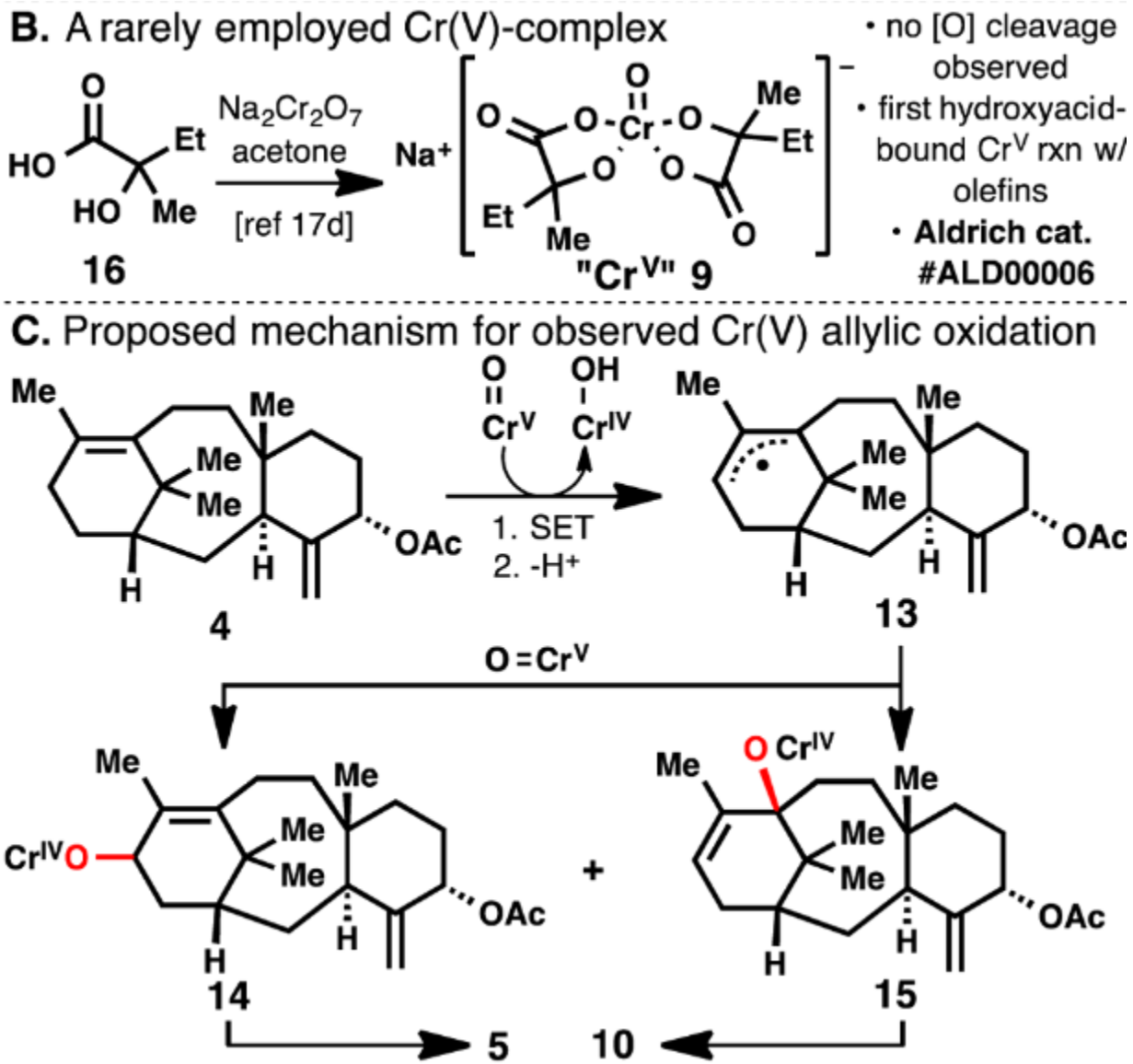
The Barbier reaction is accompanied by an allylic rearrangement to a terminal alkene

The reaction of 3-Bromocyclohexene with benzaldehyde and zinc powder in water:[5]

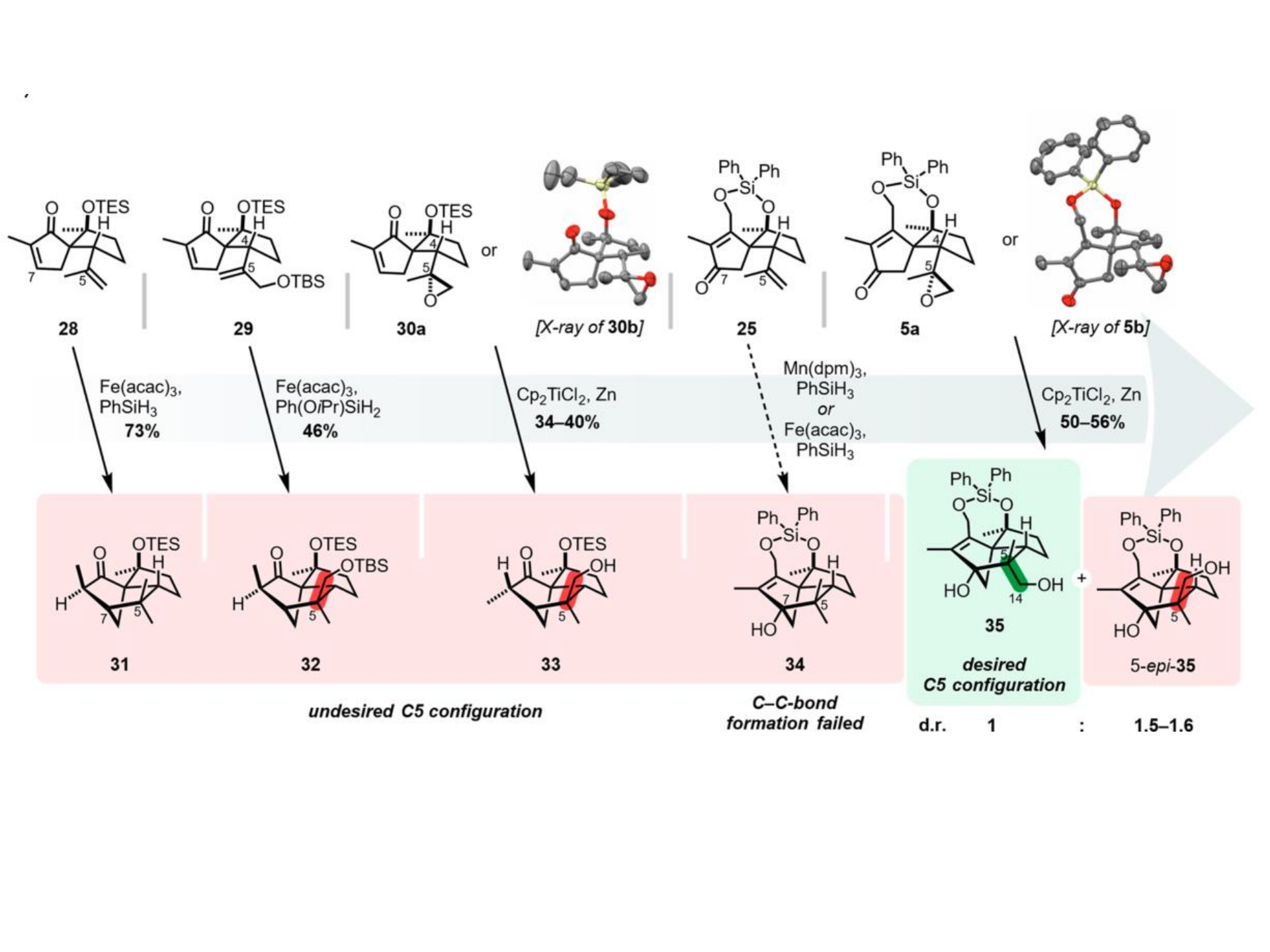


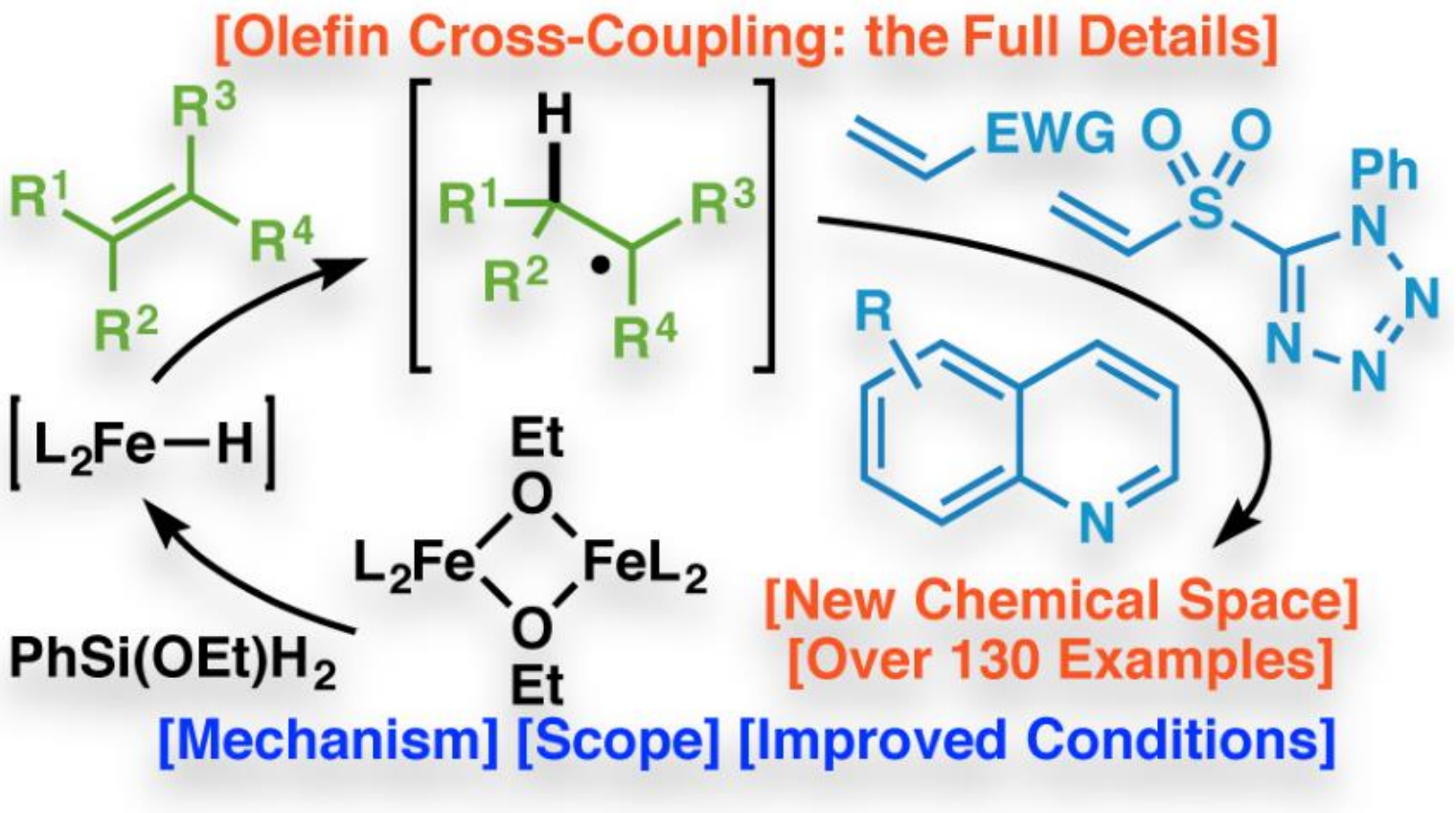
The observed diastereoselectivity for this reaction is erythro : threo = 83 : 17


OTES
H
O
Cl
Si
O
18
LDA
THF, -30 °C
81% (2 steps)
[gram-scale]
Cl
OH
OTES
H
Si
O
6
10
19
MeMgCl
MTBE, -12 °C
76%
[gram-scale]
TMS
OTES
H
O
H
HO
20
HClO4
THF/H2O
0 °C to r.t.
78%
[gram-scale]
O
11
OH
H
7
21
DIBAL-H
CH2Cl2, -78 °C
84%
HO
OH
1
H
22
X-ray of 22
Ph2SiCl2
4-DMAP, Et3N
CH2Cl2, 0 °C to r.t.
90%
Ph
Ph
Si
O
O
1
H
7
23
24, 15-crown-5
triflurotoluene, 80 °C
22% (63% brsm)
50% (4 cycles)
[gram-scale]
Ph
Ph
Si
O
O
1
H
7
O
25
Cl
TMS
OH
OTES
H
HO
27
MeMgBr
MTBE, -30 °C
84%
Cl
OH
OTES
H
Si
O
6
10
19
MeLi
THF, -78 °C
68%
TMS
OTES
OH
H
O
26
Na
O
O
O
O
Cr
O
O
O
24

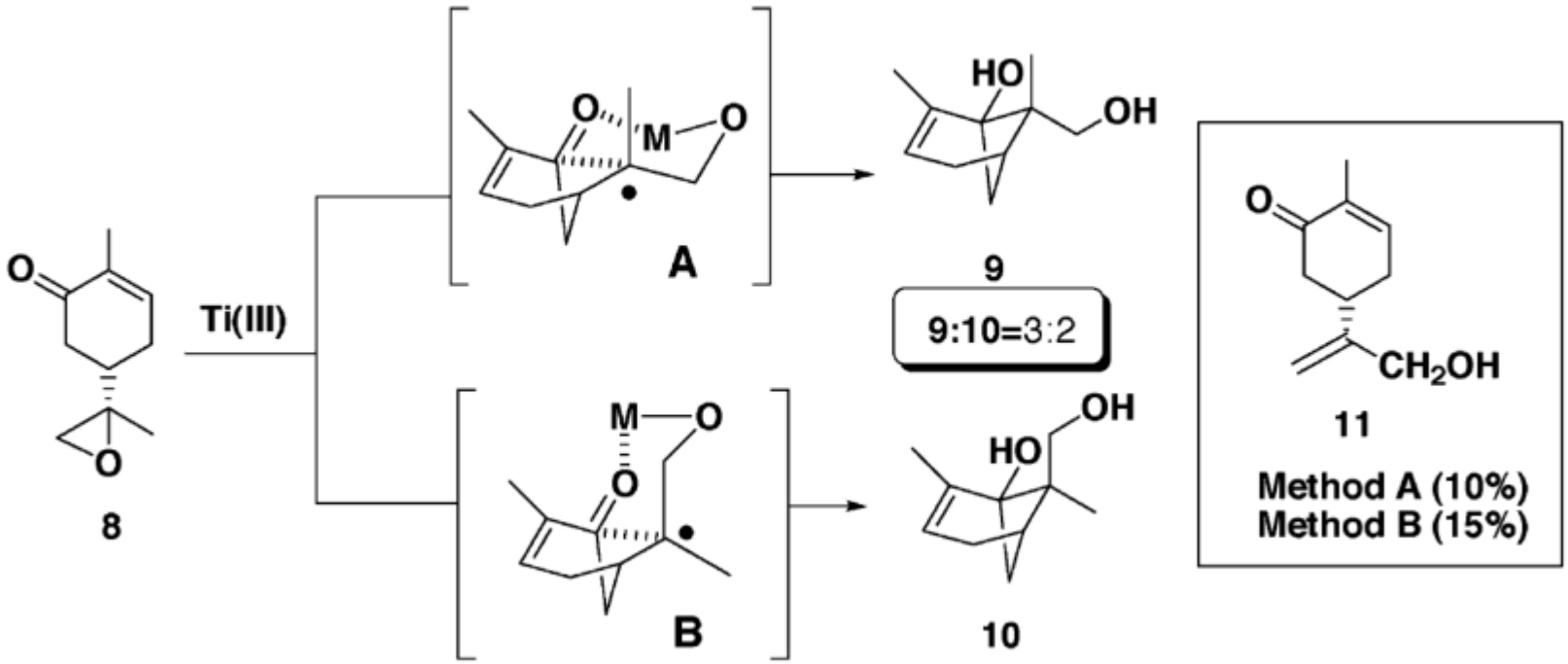


J. Am. Chem. Soc., **2014**, *136*, 4909.

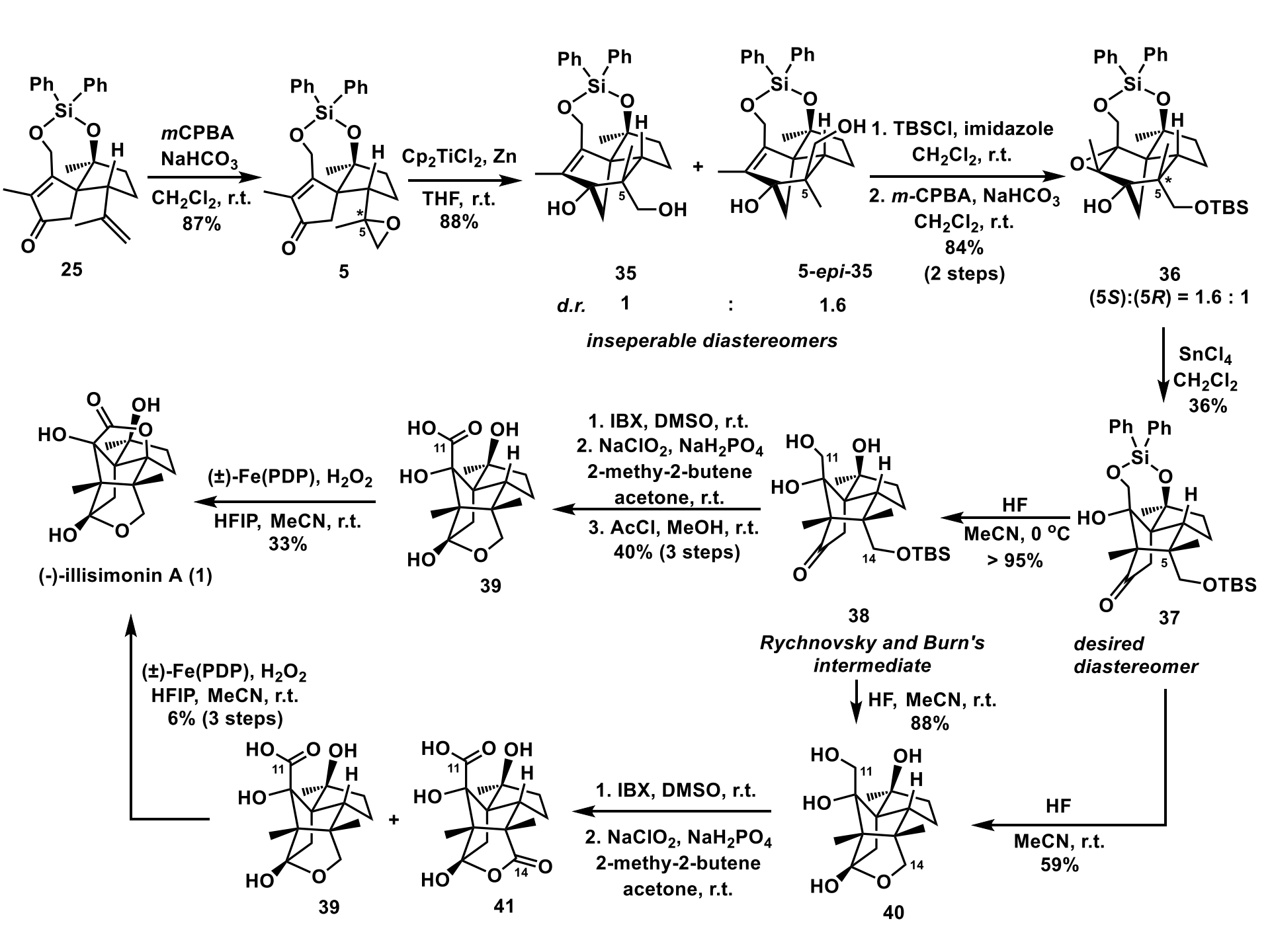

28
29
30a
or
[X-ray of 30b]
25
5a
or
[X-ray of 5b]
Fe(acac)3, PhSiH3
73%
Fe(acac)3, Ph(OiPr)SiH2
46%
Cp2TiCl2, Zn
34–40%
Mn(dpm)3, PhSiH3
or
Fe(acac)3, PhSiH3
Cp2TiCl2, Zn
50–56%
31
32
33
34
35
5-epi-35
undesired C5 configuration
C–C-bond formation failed
desired C5 configuration
d.r. 1 : 1.5–1.6

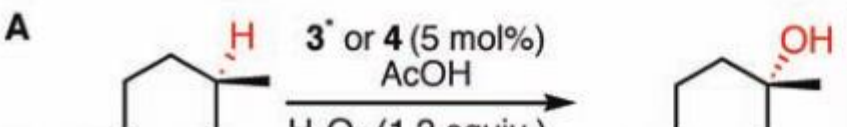


J. Am. Chem. Soc., **2017**, *139*, 2484.



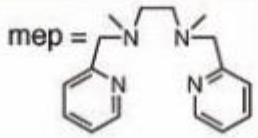
Tetrahedron, **2006,** *62*, 8933.

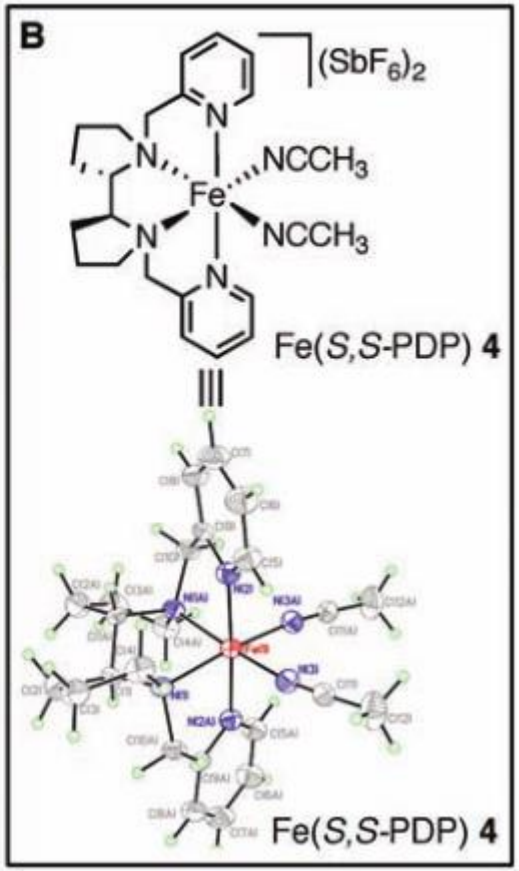

25
mCPBA
NaHCO3
CH2Cl2, r.t.
87%
5
Cp2TiCl2, Zn
THF, r.t.
88%
35
+
5-epi-35
d.r. 1 : 1.6
inseperable diastereomers
1. TBSCl, imidazole
CH2Cl2, r.t.
2. m-CPBA, NaHCO3
CH2Cl2, r.t.
84%
(2 steps)
36
(5S):(5R) = 1.6 : 1
SnCl4
CH2Cl2
36%
37
desired diastereomer
HF
MeCN, 0 °C
> 95%
38
Rychnovsky and Burn's intermediate
1. IBX, DMSO, r.t.
2. NaClO2, NaH2PO4
2-methy-2-butene
acetone, r.t.
3. AcCl, MeOH, r.t.
40% (3 steps)
39
(±)-Fe(PDP), H2O2
HFIP, MeCN, r.t.
33%
(-)-illisimonin A (1)
HF, MeCN, r.t.
88%
40
HF
MeCN, r.t.
59%
1. IBX, DMSO, r.t.
2. NaClO2, NaH2PO4
2-methy-2-butene
acetone, r.t.
39
+
41
(±)-Fe(PDP), H2O2
HFIP, MeCN, r.t.
6% (3 steps)



Entry	Catalyst	AcOH (equiv.)	Yield (%)	Conv.† (%)	Select.‡ (%)
1	**3**•	0	7	12	56
2	**4**	0	14	15	92
3	**3**•	0.5	26	41	62
4	**4**	0.5	38	42	90
5§	**4**	0.5	51	-	-

•[Fe(mep)(CH_3CN)$_2$](SbF_6)$_2$ (**3**). †Conversion of starting material. ‡Selectivity for desired product (yield/conversion). §Iterative addition protocol (isolated yield).





Science, **2007**, *318*, 784.