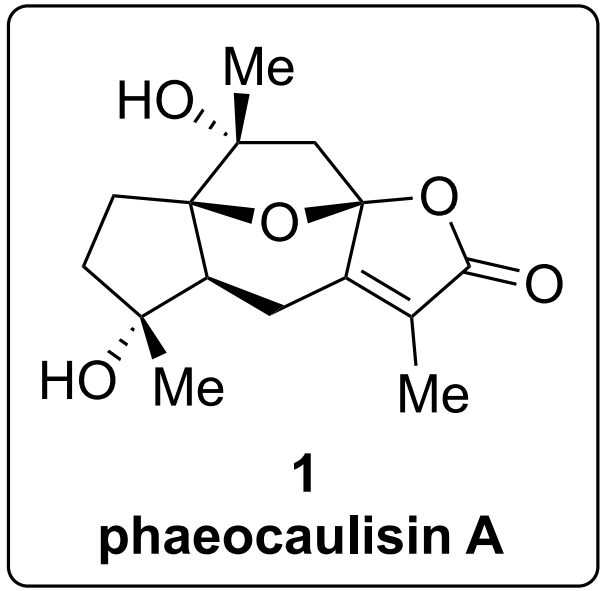
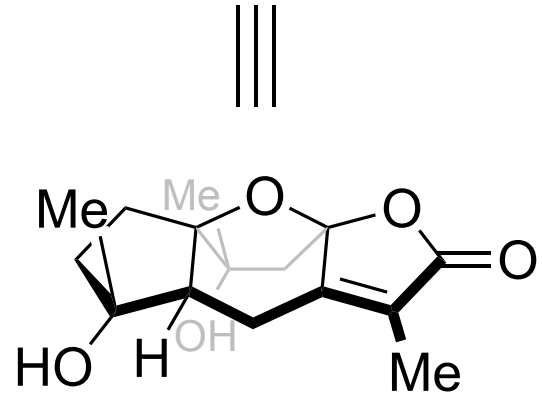
Asymmetric Total Synthesis of (–)-Phaeocaulisin A

D. J. Procter *et al. JACS,* **ASAP.**

- First asymmetric total synthesis of **phaeocaulisin A**, which was isolated in 2013 from *C. phaeocaulis* and has shown remarkable anti-inflammatory and anticancer activity.
- Preliminary structure-activity relationship studies indicated that its bioactive properties comes from its characteristic acetal oxygen bridge.
- **Phaeocaulisin A** contains four tetrasubstituted and four contiguous stereogenic centers.
- Three stereogenic centers were generated during the two key steps of diastereroselective SmI_2-mediated cyclizations.
- For Professor Procter's SmI_2-mediated reactions,
  See; *J. Am. Chem. Soc.* **2021**, *143*. 3655.
  Nat Catal. **2019**, *2,* 211.
  Organomet. Chem., **2016**, *40*. 1. (Review article)

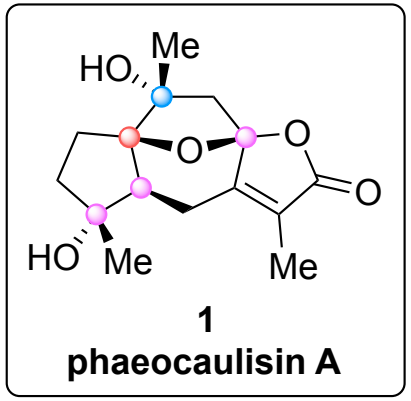


1
phaeocaulisin A



Tomoya Ozaki, Liu Group, Boston College
2022/04/22

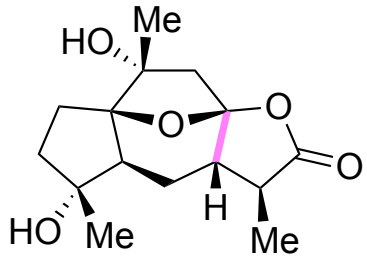
Retrosynthetic Analysis



1
phaeocaulisin A

[ox]

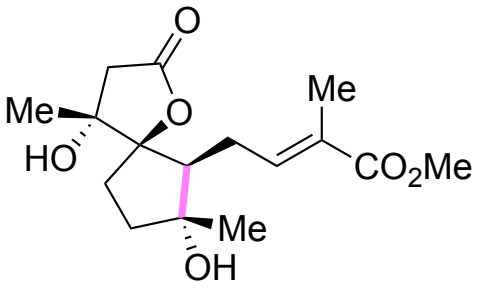
4 steps



17

SmI_2

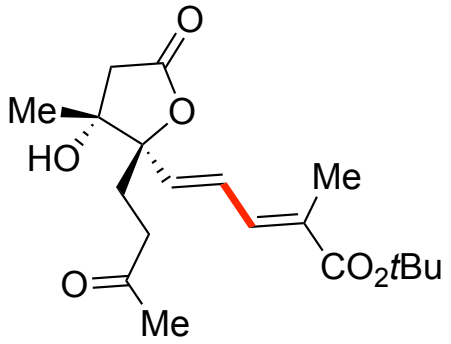
1 steps



16

SmI_2

4 steps



14

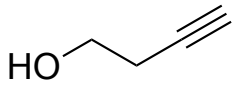
Mizoroki–Heck

1 steps

Sharpless asymmetric dihydrogenation

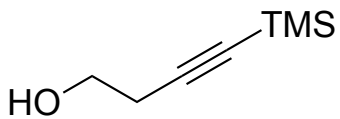
Chelate-controlled lewis acid-mediated Grignard addition

SmI_2-mediated cyclization



2
0.52 €/g

+



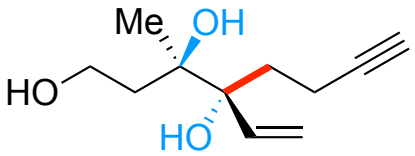
3

Negishi coupling

&

Sharpless asymmetric dihydroxylation

9 steps



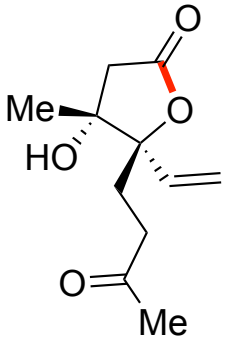
11

oxidative lactonization

&

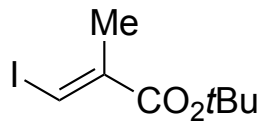
hydration of alkynes

2 steps

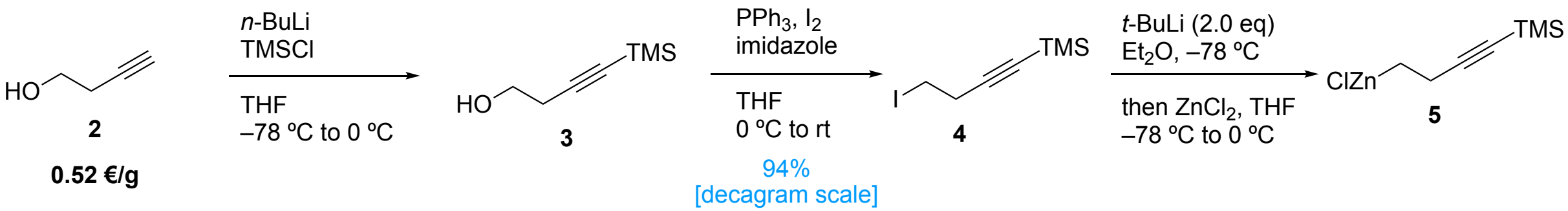


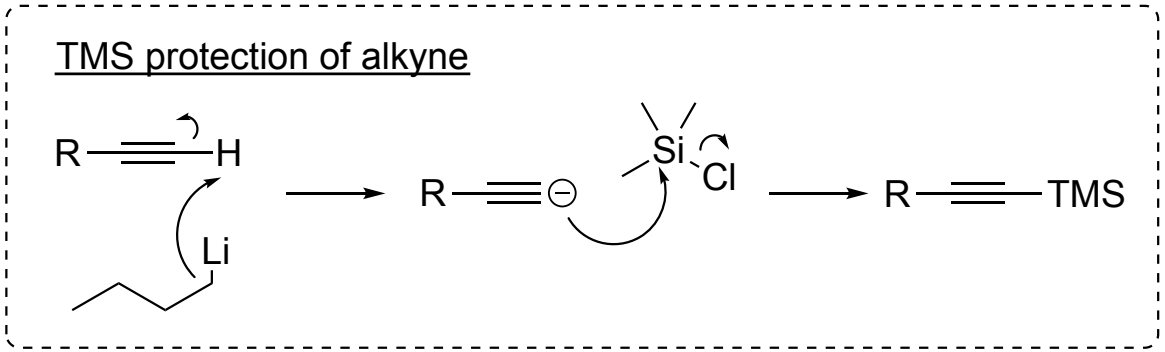
13

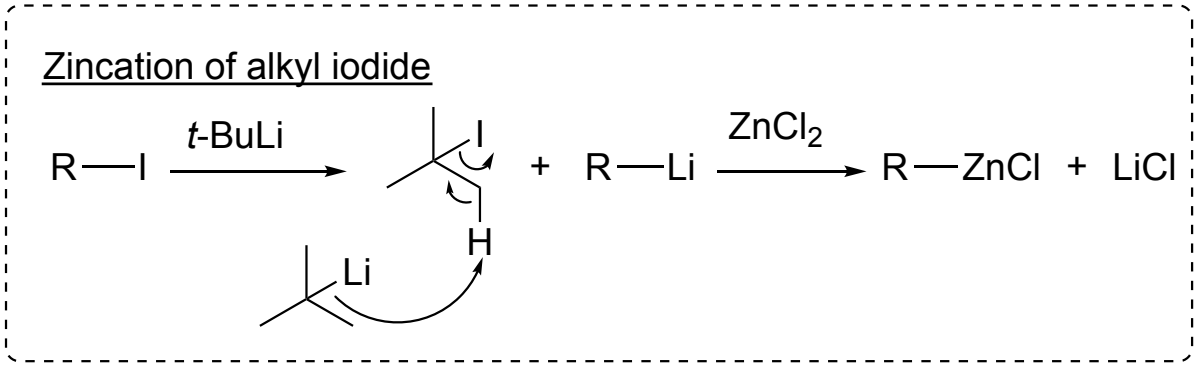
+

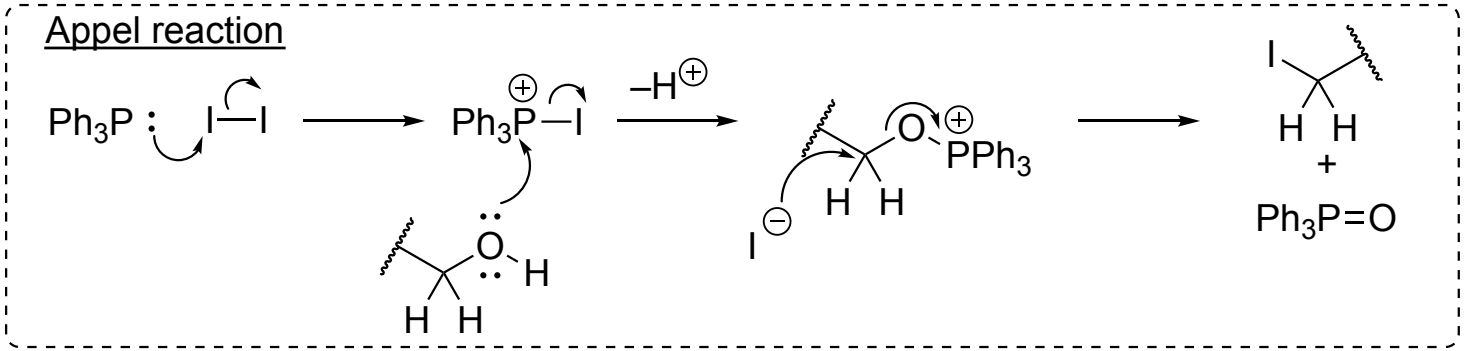


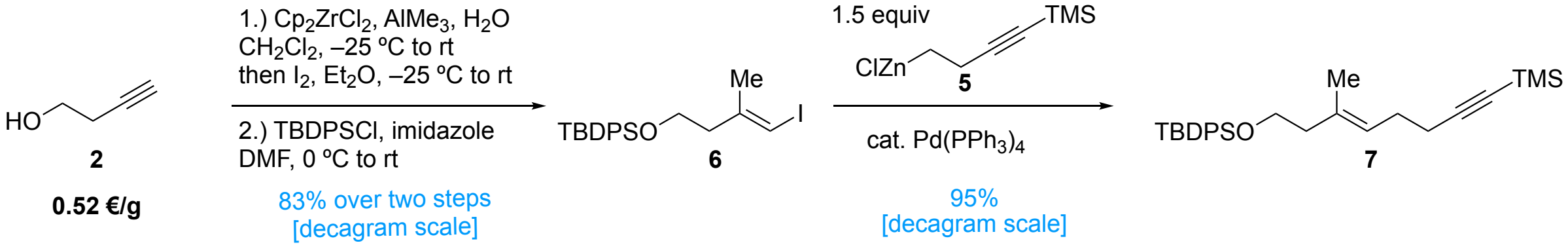
S1

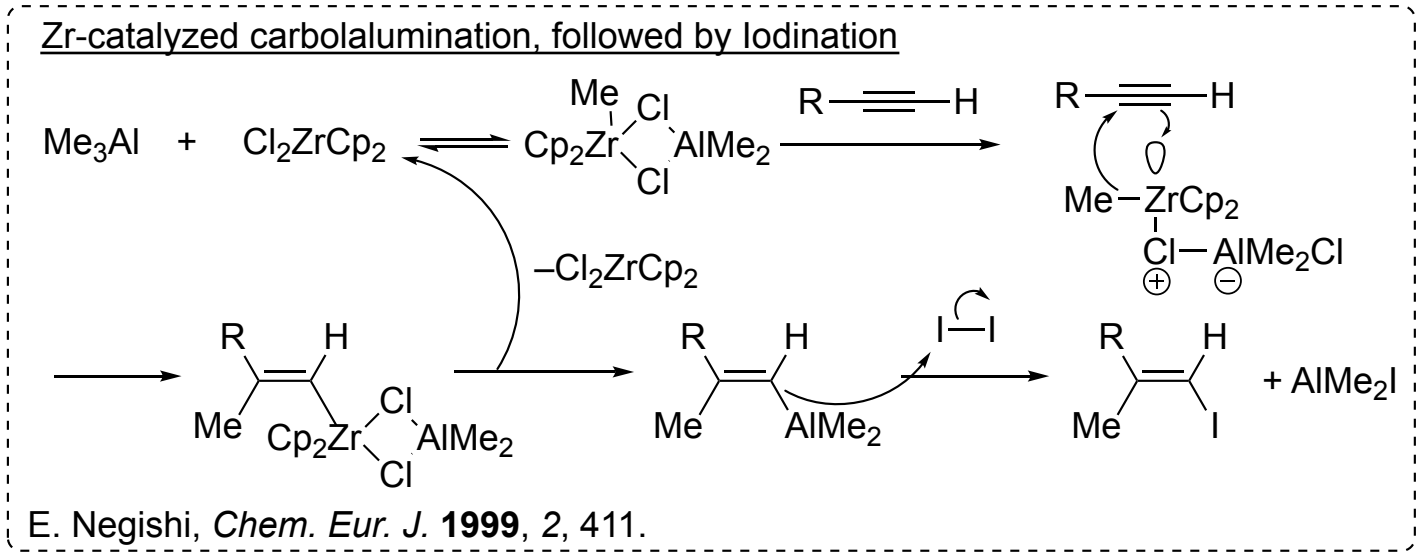

HO
2
0.52 €/g
n-BuLi
TMSCl
THF
–78 °C to 0 °C
HO
TMS
3
PPh3, I2
imidazole
THF
0 °C to rt
94%
[decagram scale]
I
TMS
4
t-BuLi (2.0 eq)
Et2O, –78 °C
then ZnCl2, THF
–78 °C to 0 °C
ClZn
TMS
5

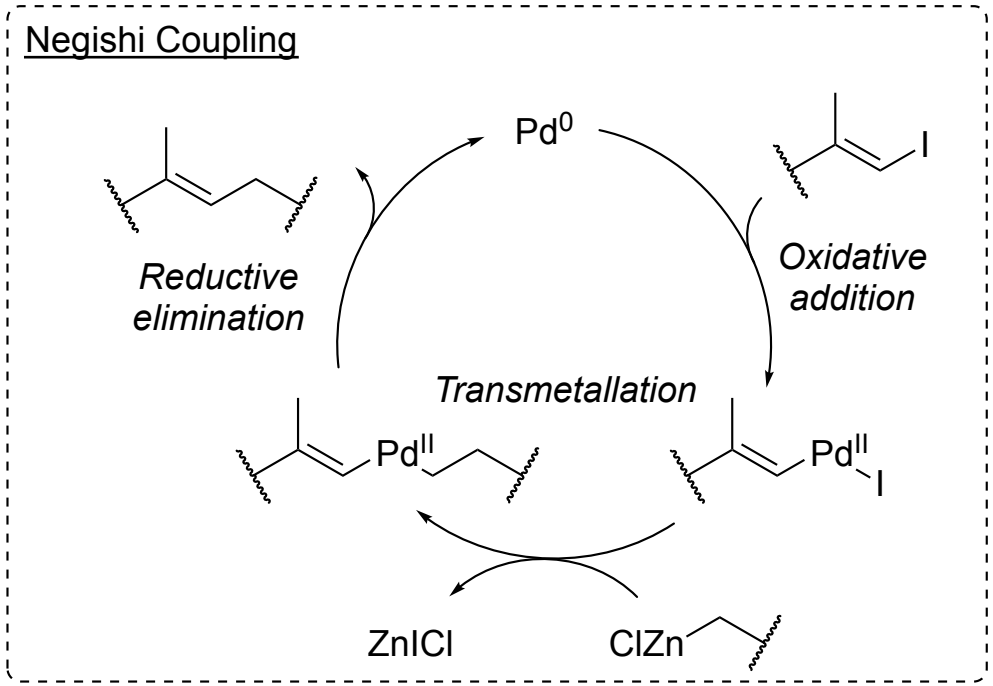

TMS protection of alkyne
R
H
Li
Si
Cl
TMS

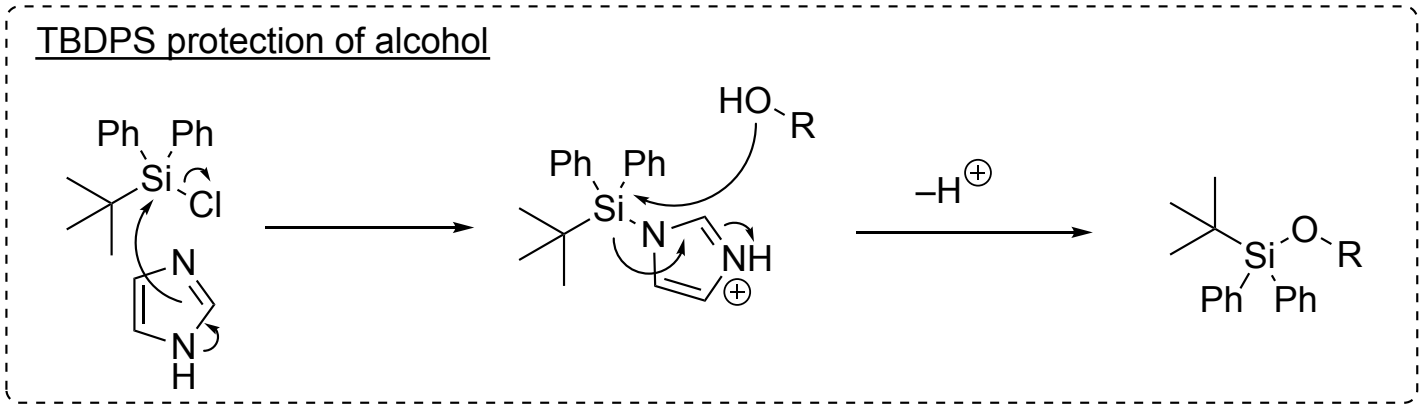

Zincation of alkyl iodide
R—I
t-BuLi
I
H
Li
+
R—Li
ZnCl2
R—ZnCl
+
LiCl

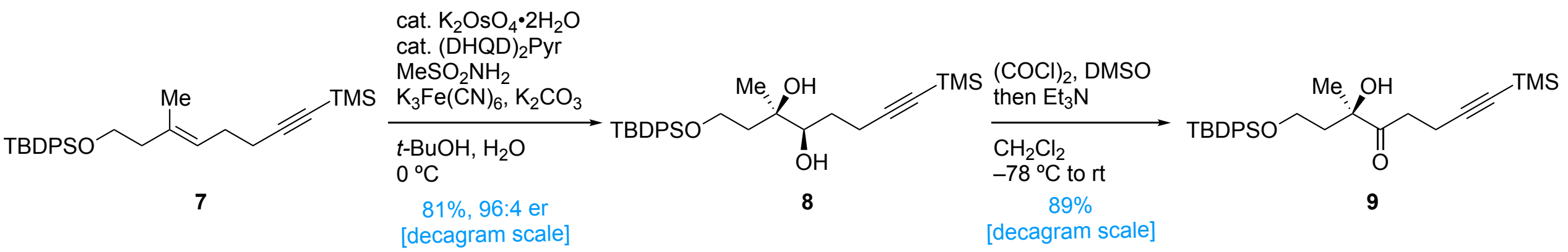

Appel reaction
Ph3P
I—I
Ph3P—I
–H
O
H
H
PPh3
I
I
H
H
+
Ph3P=O


HO
2
0.52 €/g
1.) Cp2ZrCl2, AlMe3, H2O
CH2Cl2, –25 °C to rt
then I2, Et2O, –25 °C to rt
2.) TBDPSCl, imidazole
DMF, 0 °C to rt
83% over two steps
[decagram scale]
TBDPSO
Me
I
6
1.5 equiv
ClZn
TMS
5
cat. Pd(PPh3)4
95%
[decagram scale]
TBDPSO
Me
TMS
7

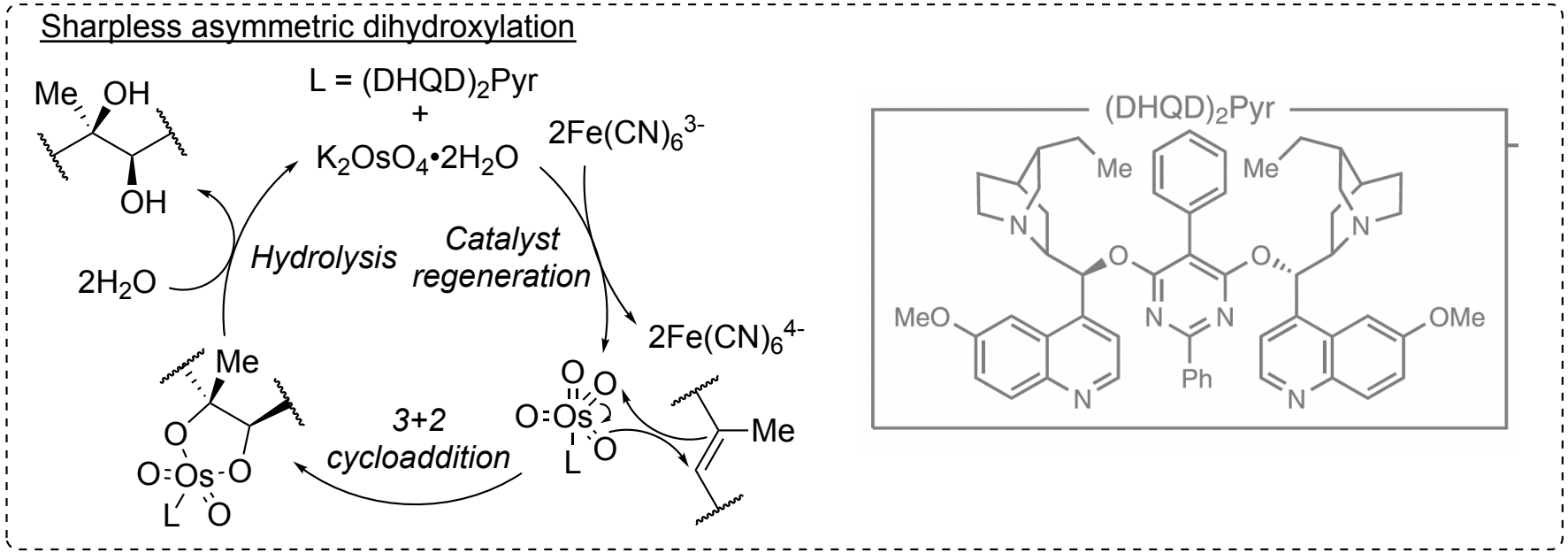

Zr-catalyzed carbolalumination, followed by Iodination
Me3Al + Cl2ZrCp2
Me
Cl
Cp2Zr
AlMe2
Cl
R—≡—H
R—≡—H
Me—ZrCp2
Cl—AlMe2Cl
–Cl2ZrCp2
R
H
Me
Cp2Zr
Cl
AlMe2
Cl
I—I
Me
AlMe2
Me
I
+ AlMe2I
E. Negishi, Chem. Eur. J. 1999, 2, 411.

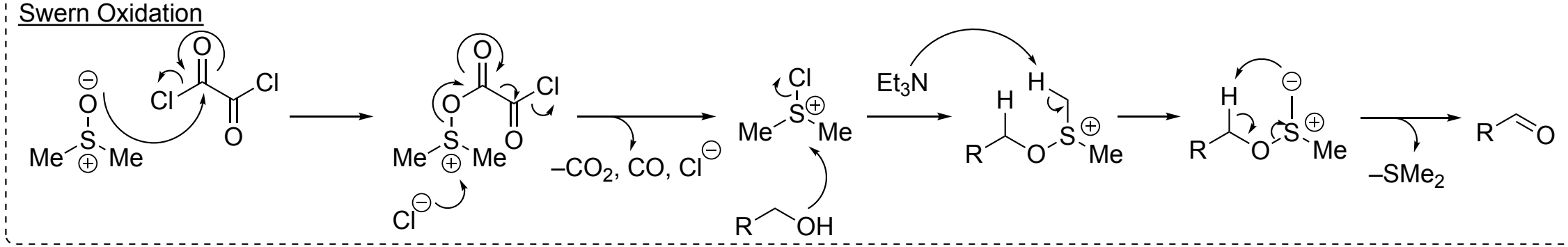

Negishi Coupling
Pd0
Reductive elimination
Oxidative addition
Transmetallation
PdII
PdII
I
ZnICl
ClZn

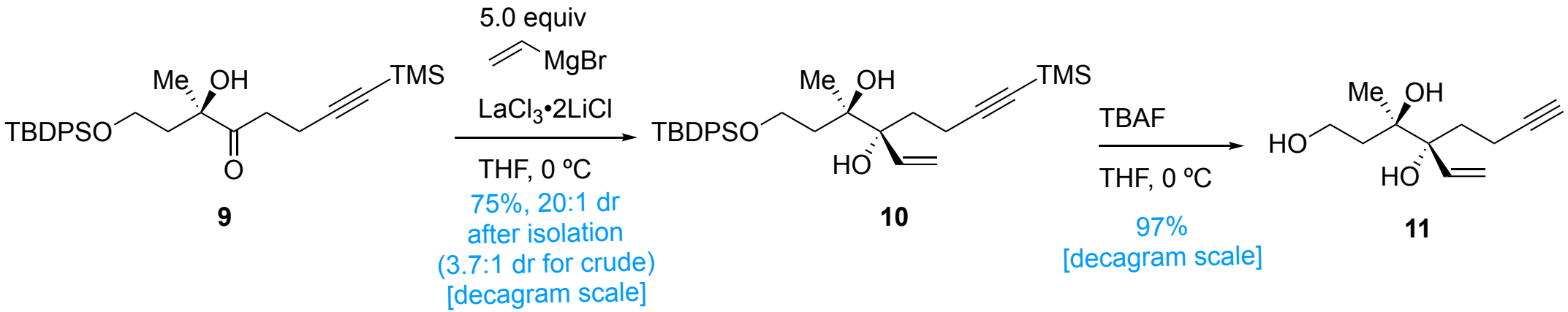

TBDPS protection of alcohol
Ph
Ph
Si
Cl
N
N
H
HO
R
Ph
Ph
Si
N
NH
–H⊕
Si
O
R
Ph
Ph


cat. K2OsO4•2H2O
cat. (DHQD)2Pyr
MeSO2NH2
K3Fe(CN)6, K2CO3
t-BuOH, H2O
0 °C
81%, 96:4 er
[decagram scale]
(COCl)2, DMSO
then Et3N
CH2Cl2
–78 °C to rt
89%
[decagram scale]
Me
OH
TMS
TBDPSO
O

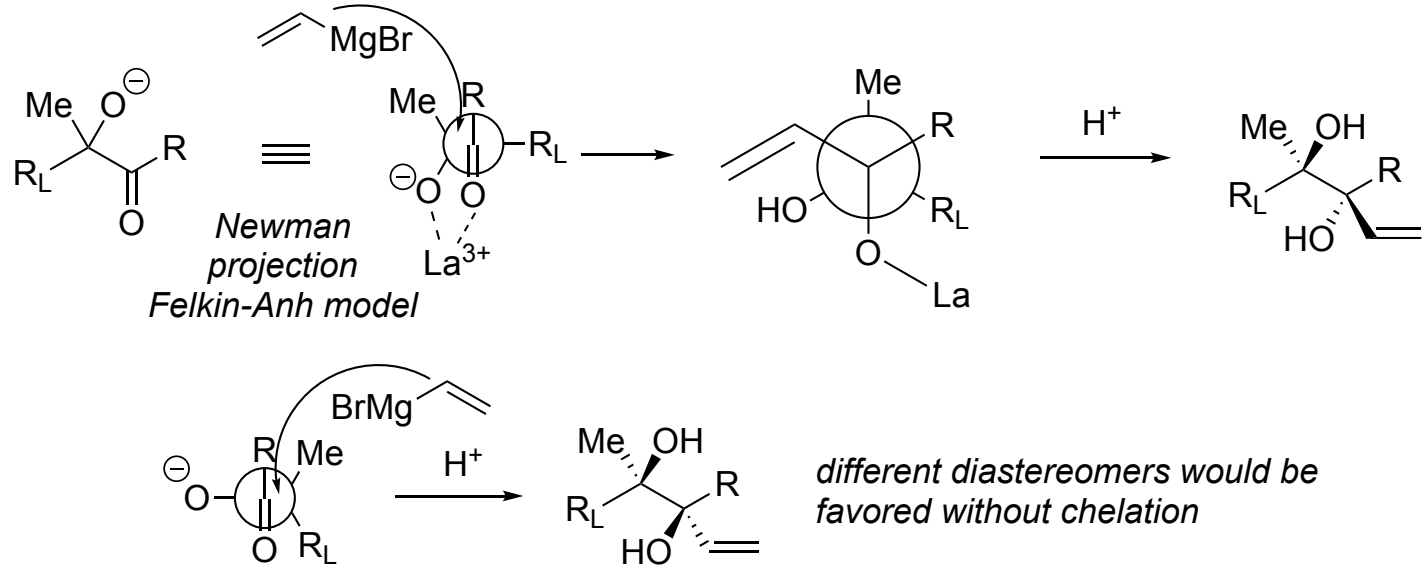
7 **8** **9**


Sharpless asymmetric dihydroxylation
L = (DHQD)2Pyr
+
K2OsO4•2H2O
2Fe(CN)6 3-
2Fe(CN)6 4-
Hydrolysis
Catalyst regeneration
2H2O
3+2 cycloaddition
(DHQD)2Pyr
MeO
OMe
Ph

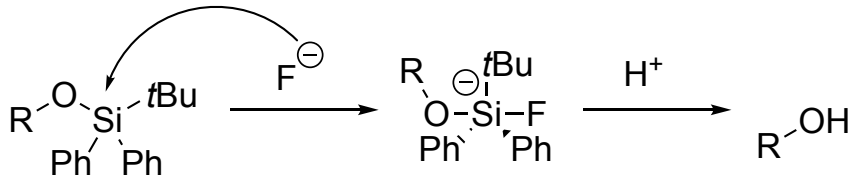

Swern Oxidation
Cl
Me
S
O
–CO2, CO, Cl
Et3N
R
OH
–SMe2

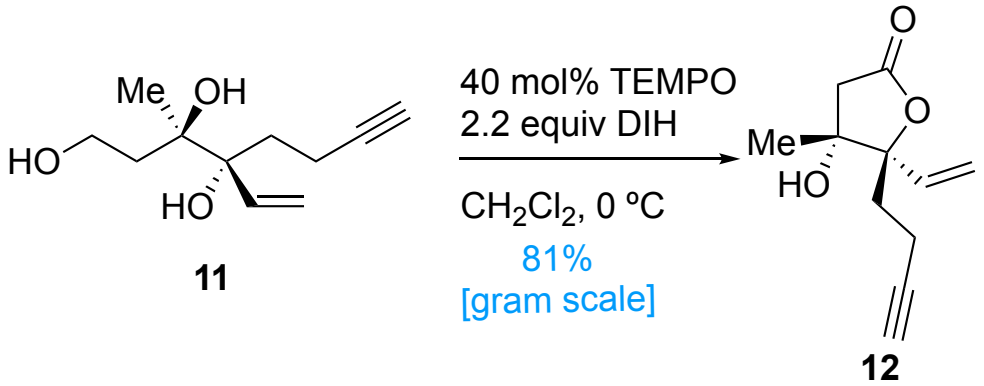


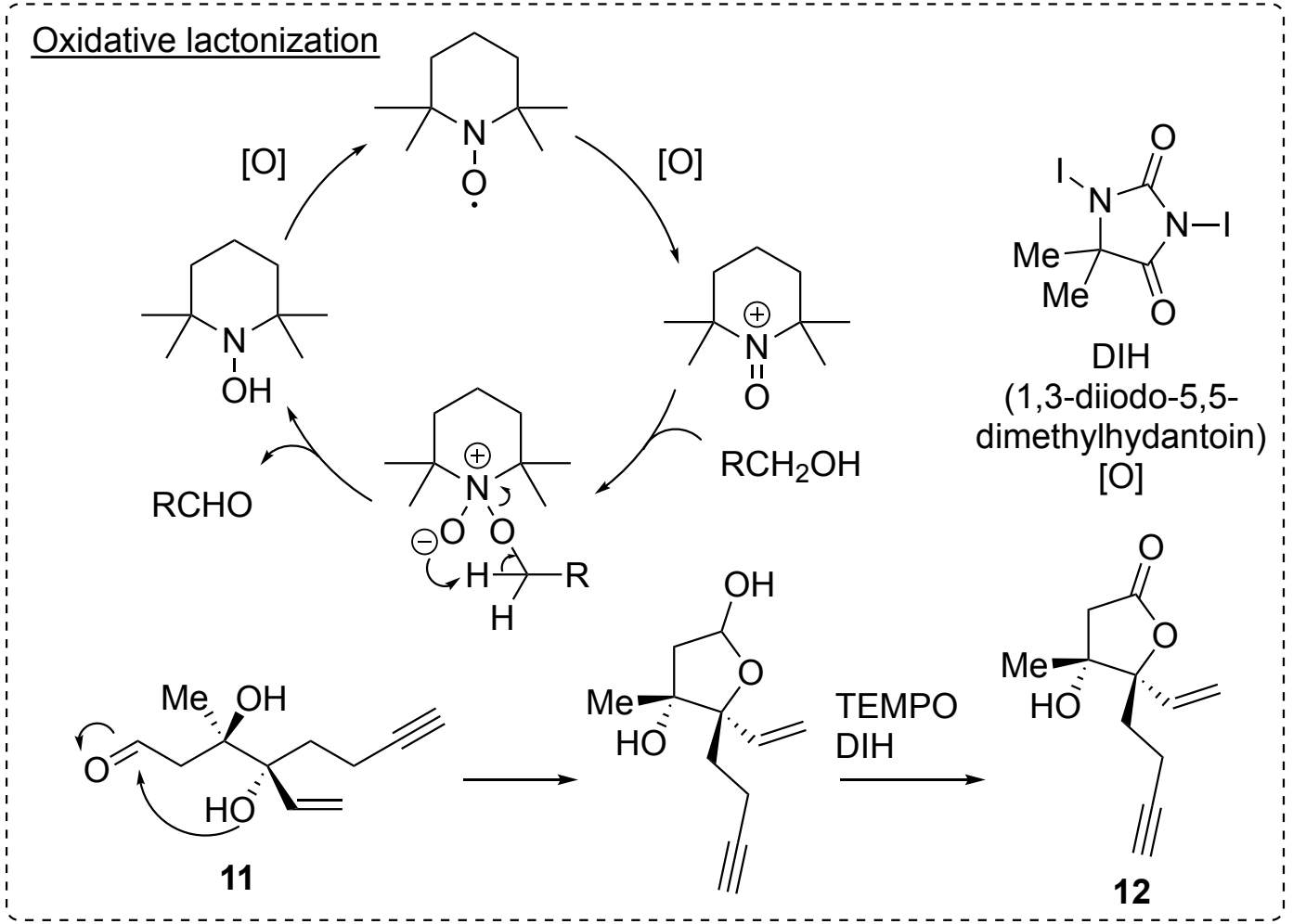
Chelate-controlled lewis acid-mediated Grignard addition

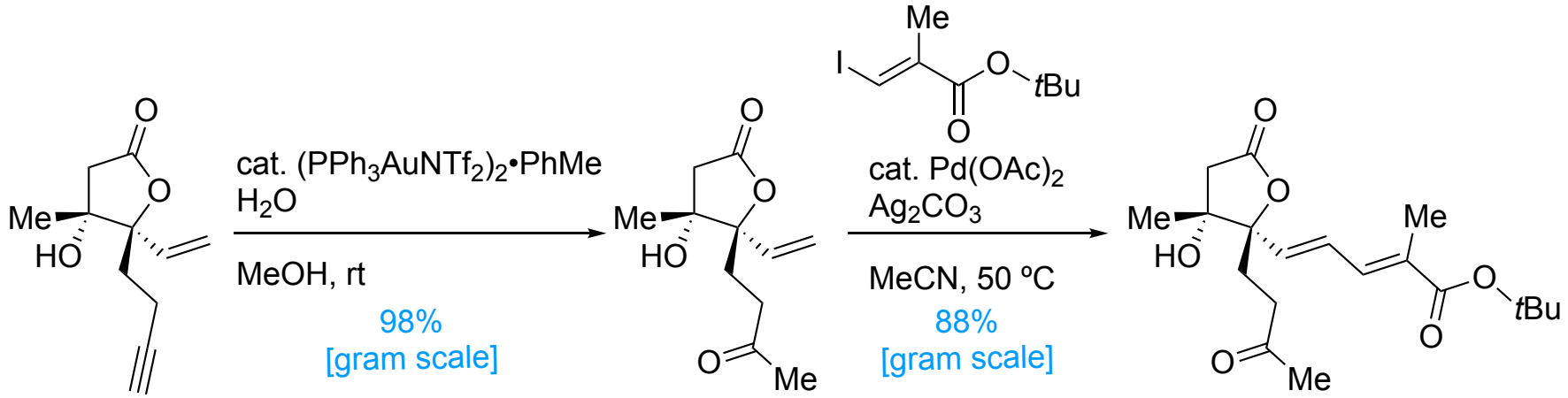


Deprotection of silyl protecting groups



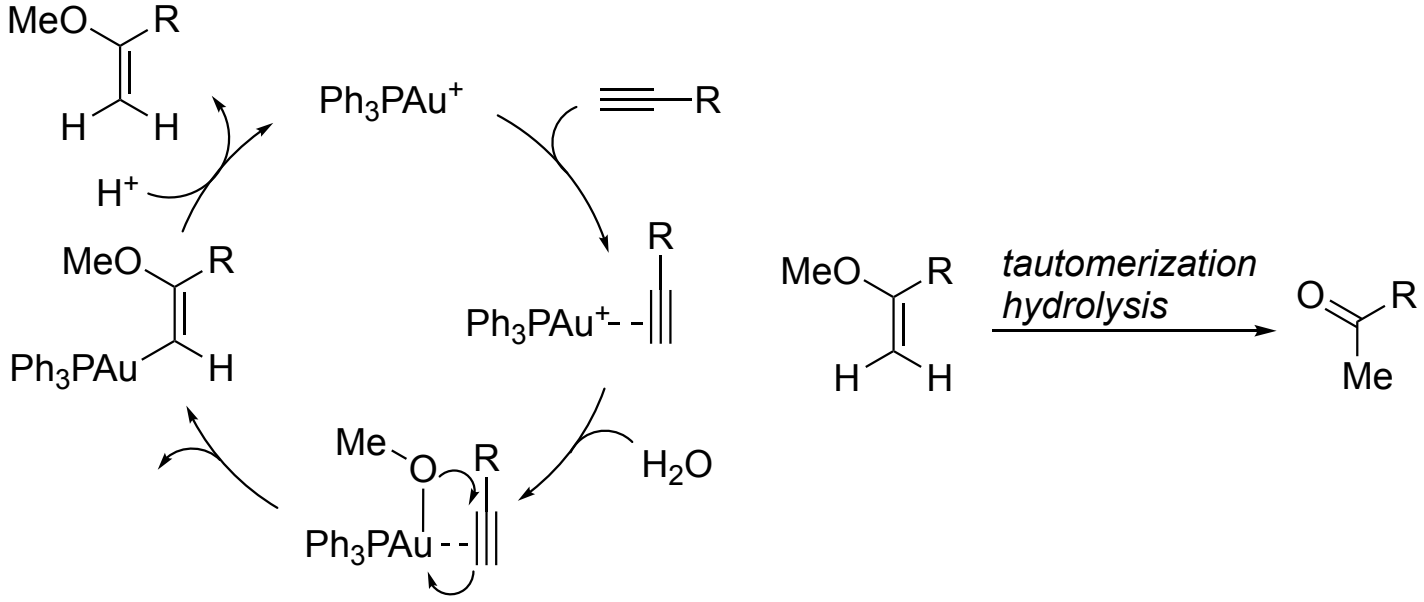

Me
OH
HO
HO
11
40 mol% TEMPO
2.2 equiv DIH
CH2Cl2, 0 ºC
81%
[gram scale]
O
O
Me
HO
12


Oxidative lactonization
[O]
[O]
N
O
N
OH
N
O
RCHO
RCH2OH
N
O
O
H
R
H
I
N
O
N—I
Me
Me
O
DIH
(1,3-diiodo-5,5-dimethylhydantoin)
[O]
Me
OH
O
HO
11
OH
O
Me
HO
TEMPO
DIH
O
O
Me
HO
12



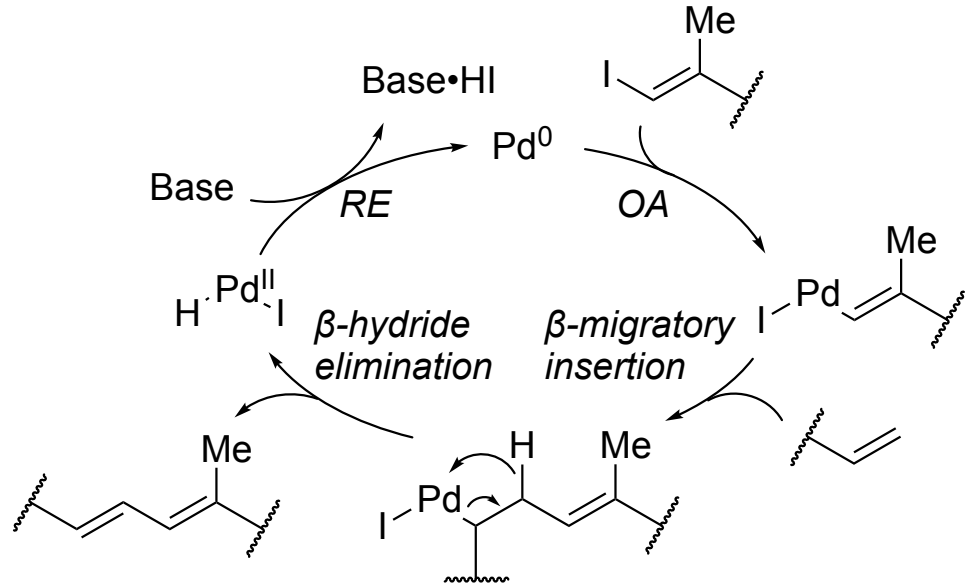
12 **13** **14**

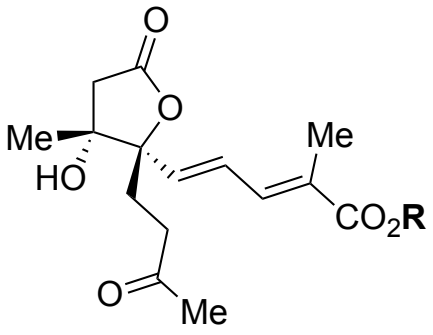
Au(I)-catalyzed hydration of alkynes



J. Org. Chem. **2009**, *74*, 2067.

Heck reaction

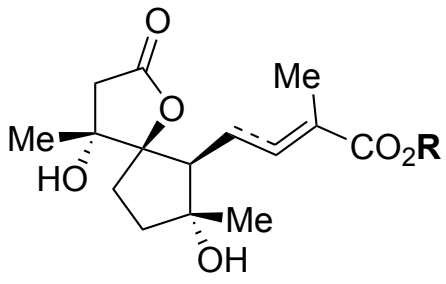




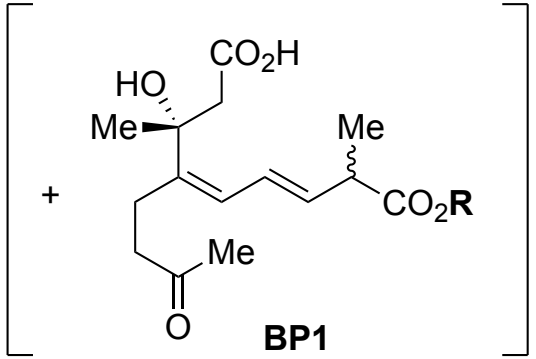
14

2.2 eq SmI_2
TPPA
2,4,6-TTBP

THF, –78 °C

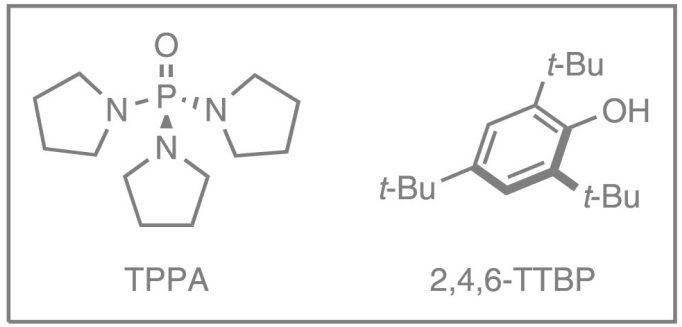


15



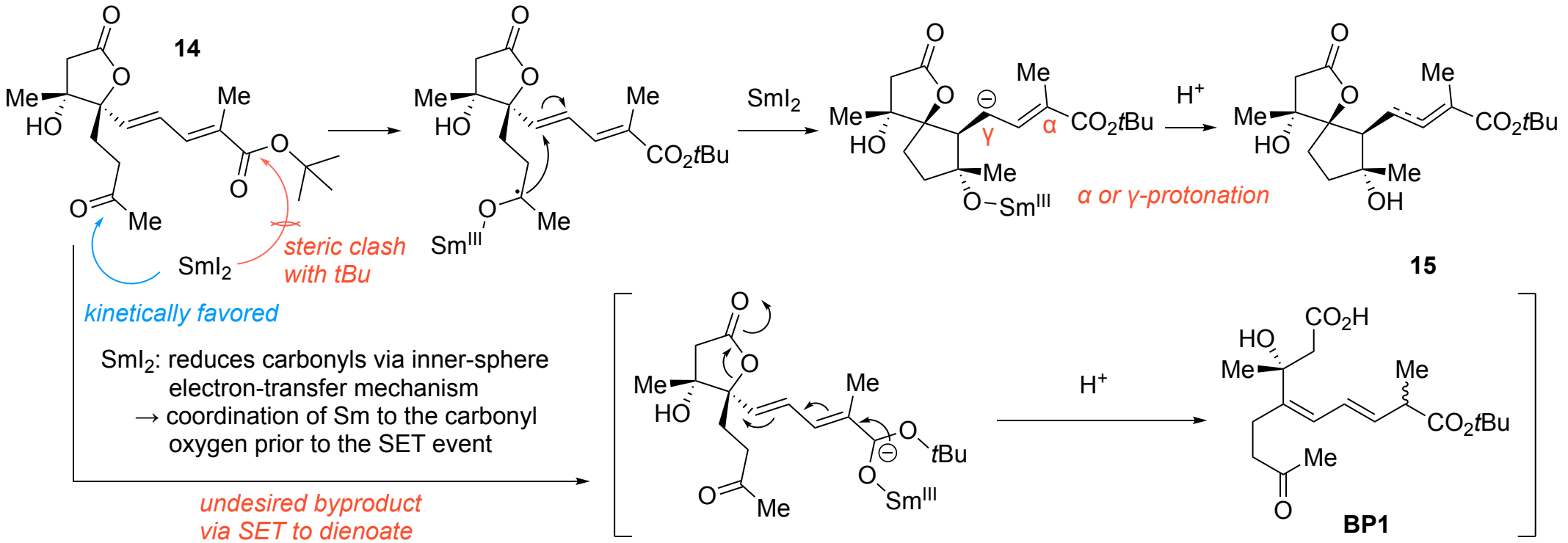
BP1

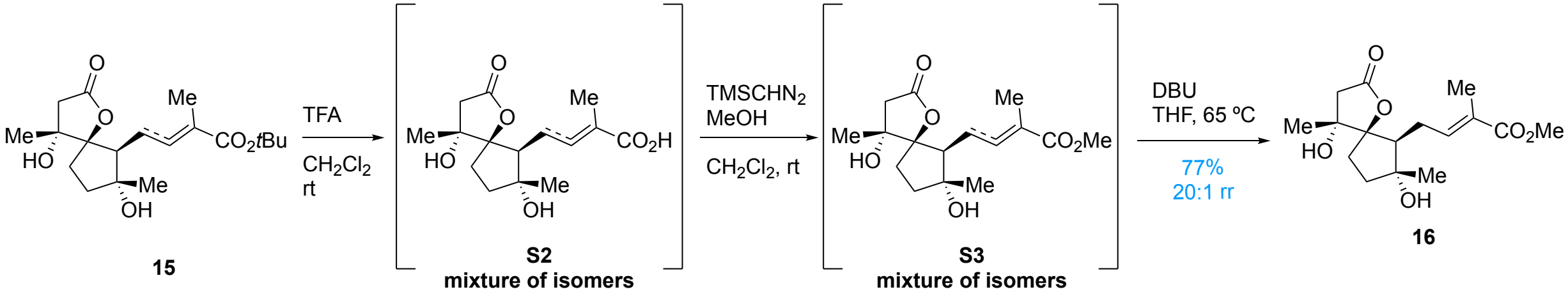
R = Me	16% 1:20 rr, >20:1 dr	45%
R = *t*Bu	58% 1.3:1 rr, >20:1 dr	11%



TPPA 2,4,6-TTBP

1st SmI_2-mediated cyclization





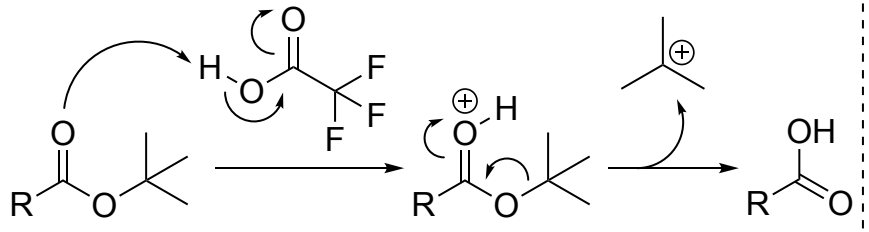
15

S2
mixture of isomers

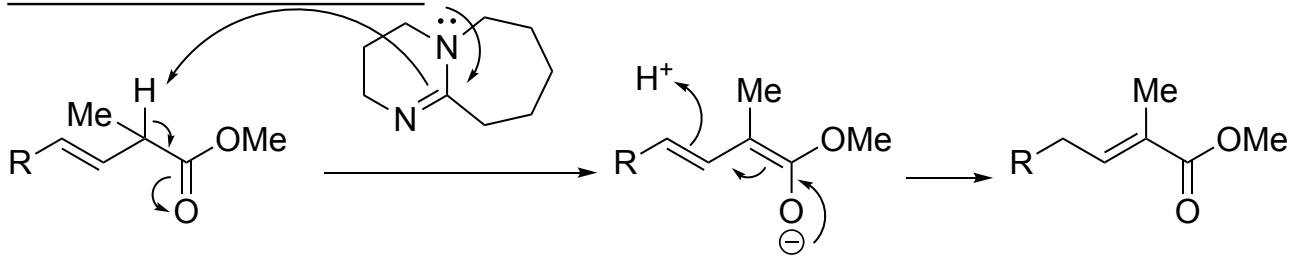
S3
mixture of isomers

16

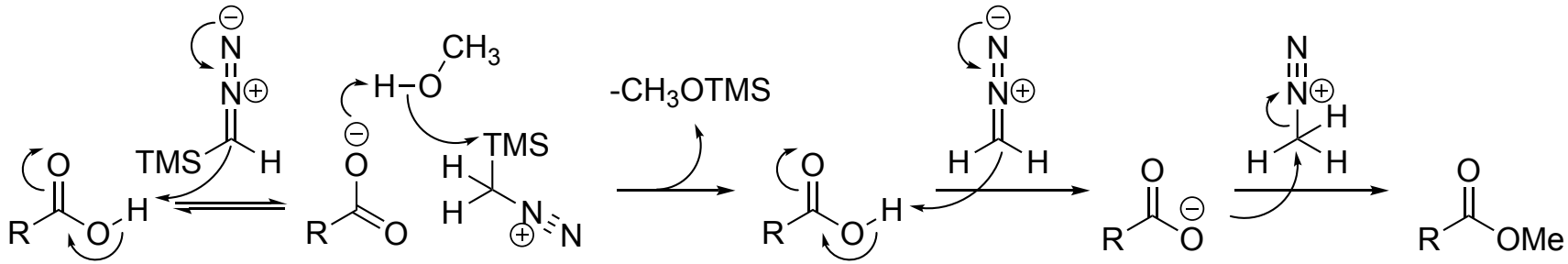
Deprotection of *t*Bu ester



Base-assisted isomerization



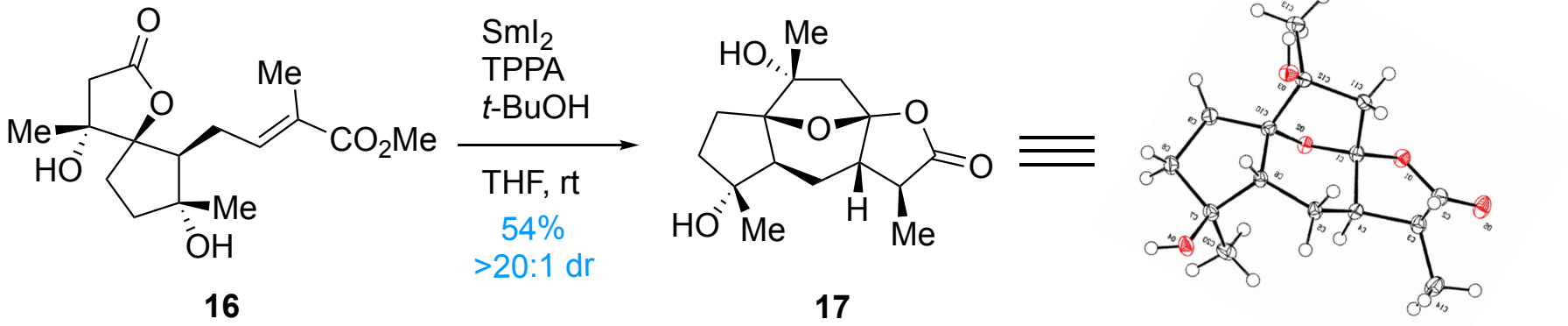
Methylation of carboxylic acid



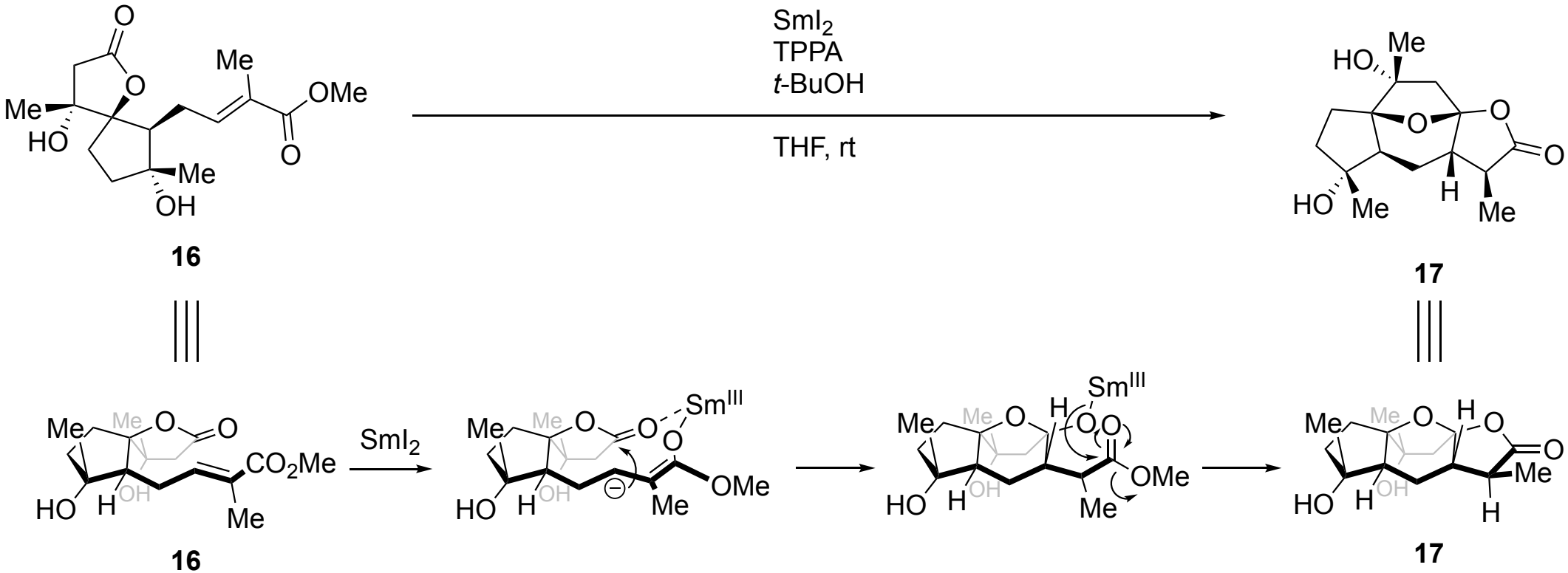
$TMSCHN_2$
less explosive
stable liquid (b.p. 96 °C)

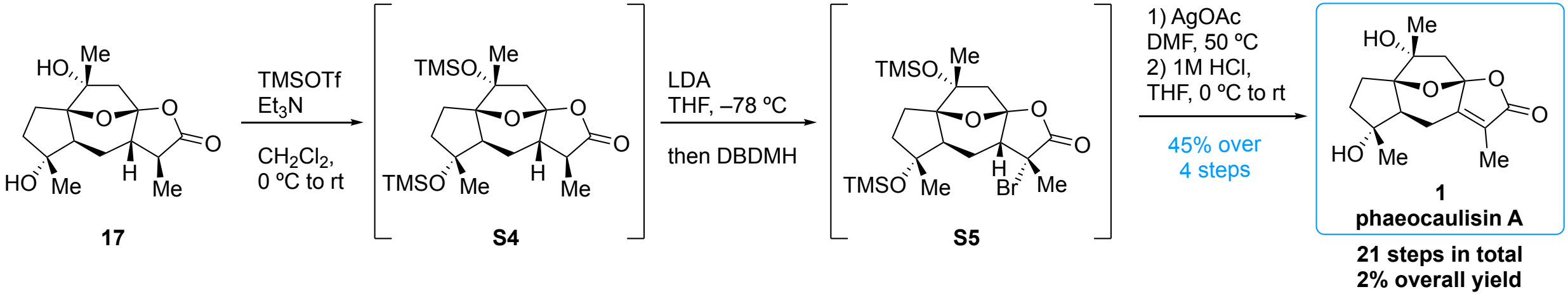
in situ generation of CH_2N_2
more explosive
gas (b.p. –23 °C)

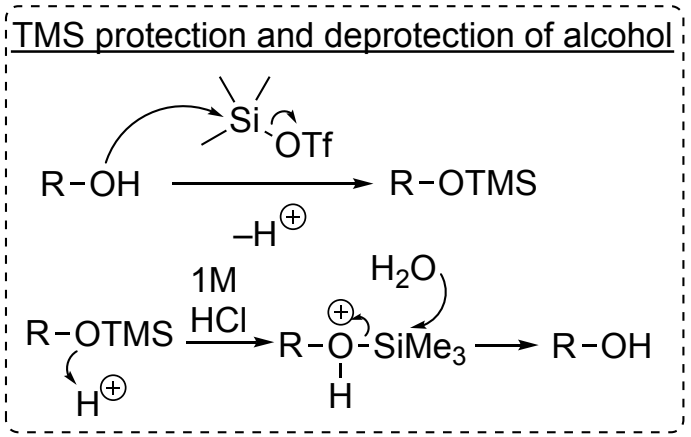
Angew. Chem. Int. Ed. **2007**, *46*, 7075.

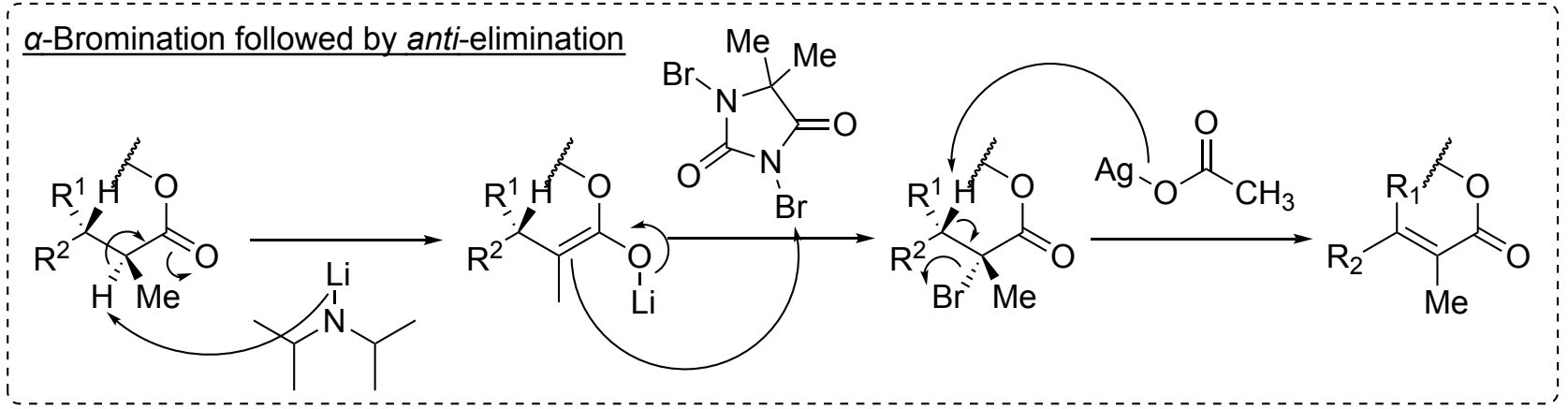


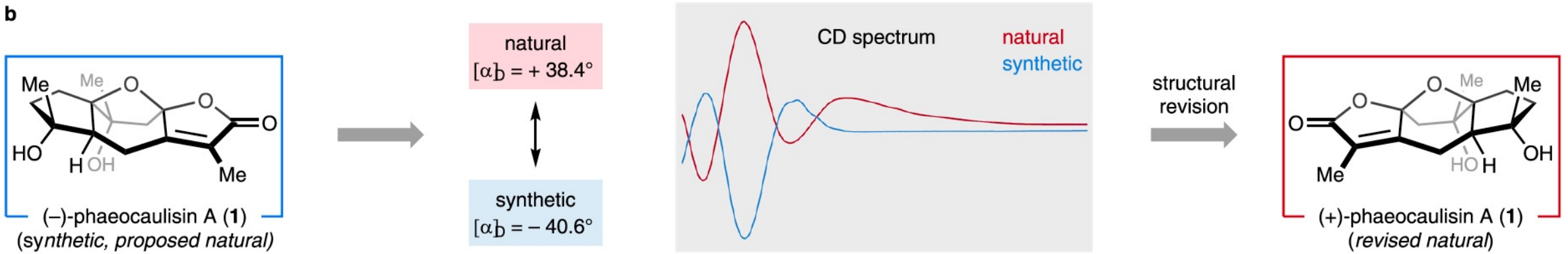
2nd SmI_2-mediated cyclization and lactonization




17
TMSOTf
Et3N
CH2Cl2,
0 °C to rt
S4
LDA
THF, –78 °C
then DBDMH
S5
1) AgOAc
DMF, 50 °C
2) 1M HCl,
THF, 0 °C to rt
45% over
4 steps
1
phaeocaulisin A
21 steps in total
2% overall yield


TMS protection and deprotection of alcohol
R–OH
R–OTMS
–H
1M
HCl
H2O
SiMe3


α-Bromination followed by anti-elimination
Li
N
Br
Ag
CH3


b
(–)-phaeocaulisin A (1)
(synthetic, proposed natural)
natural
[α]D = + 38.4°
synthetic
[α]D = – 40.6°
CD spectrum
natural
synthetic
structural
revision
(+)-phaeocaulisin A (1)
(revised natural)