Total Synthesis of Soraphen A

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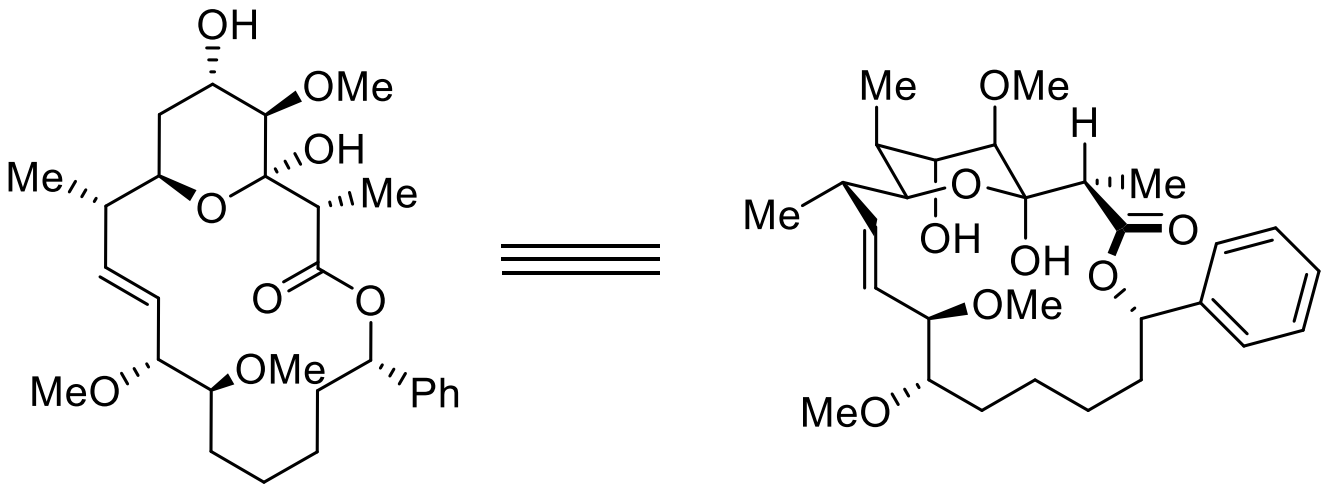
Article

Total Synthesis of the Acetyl CoA Carboxylase Inhibitor Soraphen A: Asymmetric Tsuji Reduction Enables Successive Olefin Metathesis

Tabitha T. Schempp and Michael J. Krische*

- Type I polyketide secondary metabolite produced from the myxobacteria *Sorangium cellulosum*
- Interacts with eukaryotic acetyl coenzyme A carboxylase (ACC) w/ K_d = 1.1 nM
- Modulates the biosynthesis and metabolism of fatty acids
- 3 previous syntheses – 25, 25, and 36 steps LLS
- This synthesis – 11 steps LLS



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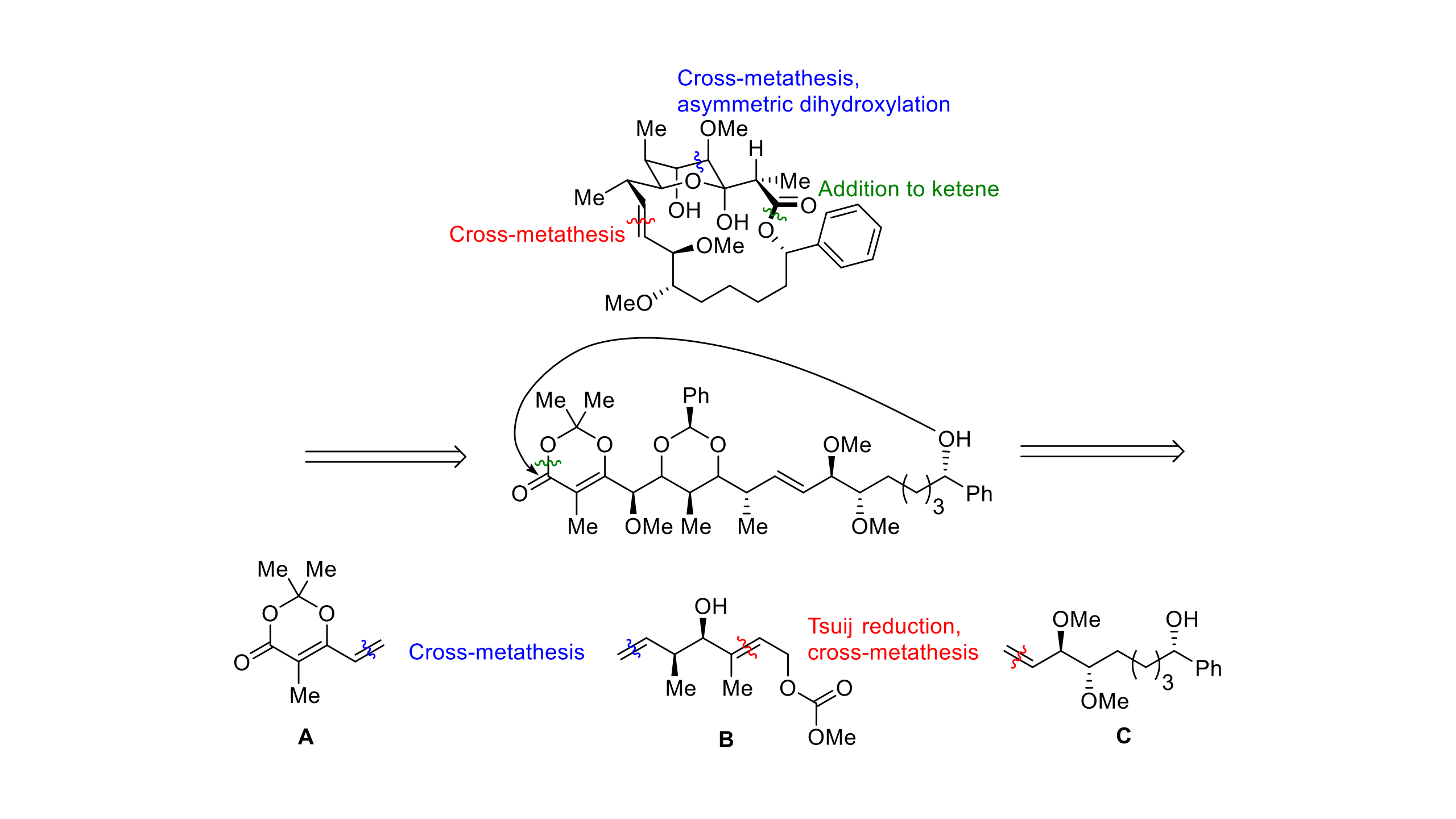
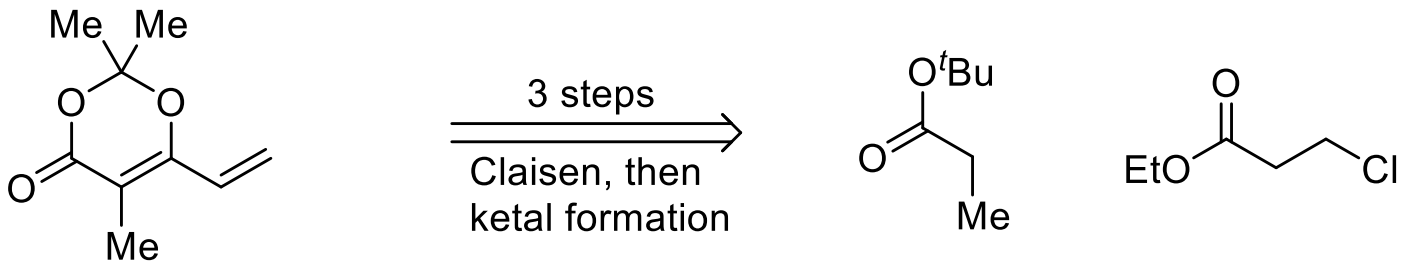
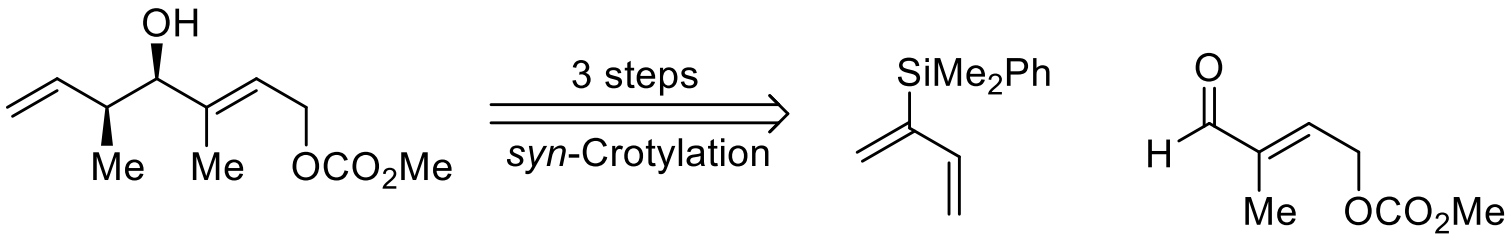

Cross-metathesis,
asymmetric dihydroxylation
Addition to ketene
Cross-metathesis
Cross-metathesis
Tsuij reduction,
cross-metathesis
A
B
C

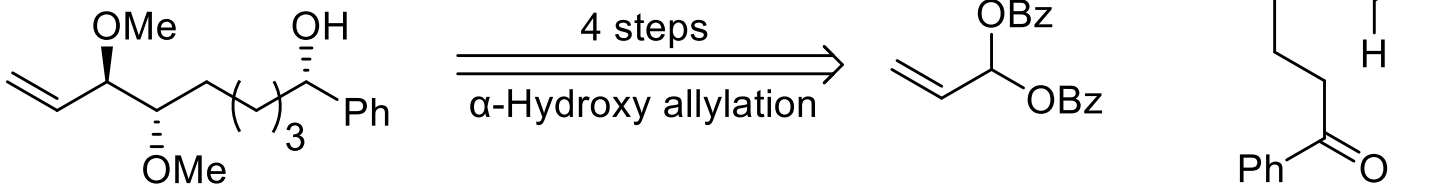
A

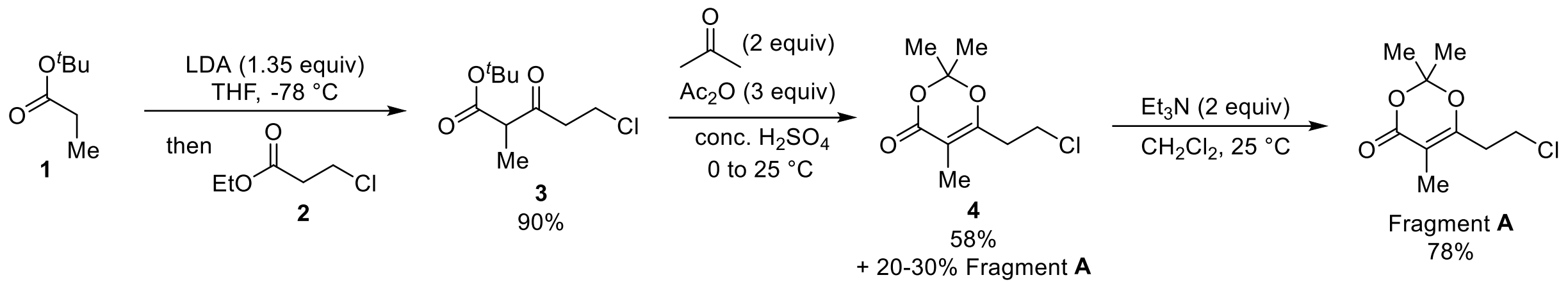

Me
Me
O
O
O
Me
3 steps
Claisen, then
ketal formation
O^{t}Bu
O
Me
O
EtO
Cl

B

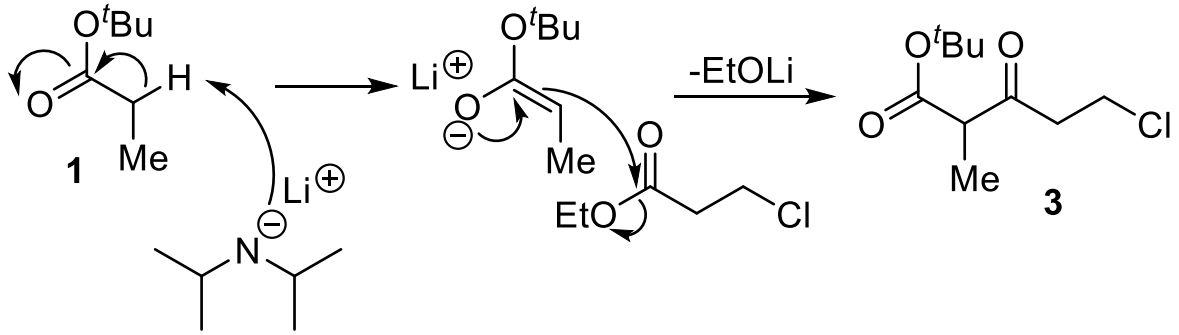

OH
Me
Me
OCO$_2$Me
3 steps
syn-Crotylation
SiMe$_2$Ph
O
H
Me
OCO$_2$Me

C

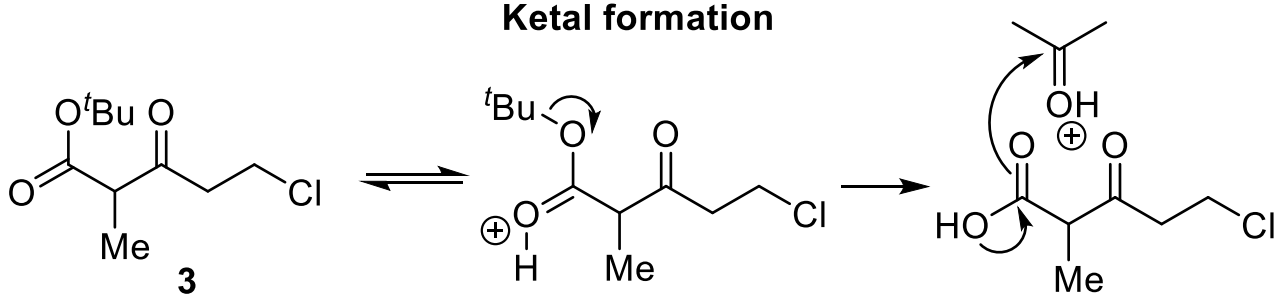

OMe
OH
Ph
3
OMe
4 steps
α-Hydroxy allylation
OBz
OBz
O
H
Ph
O



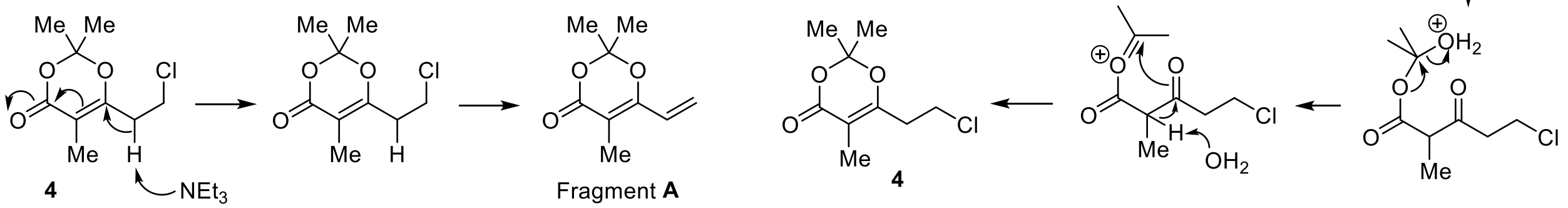
Claisen Condensation

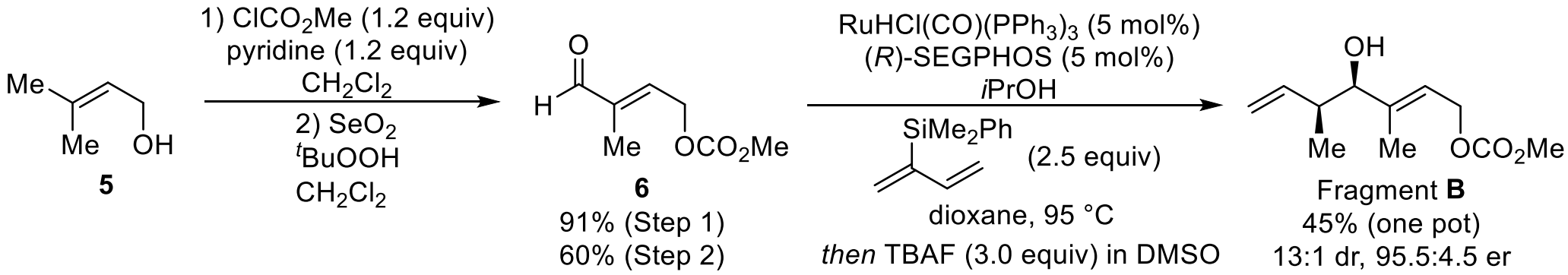


Ketal formation

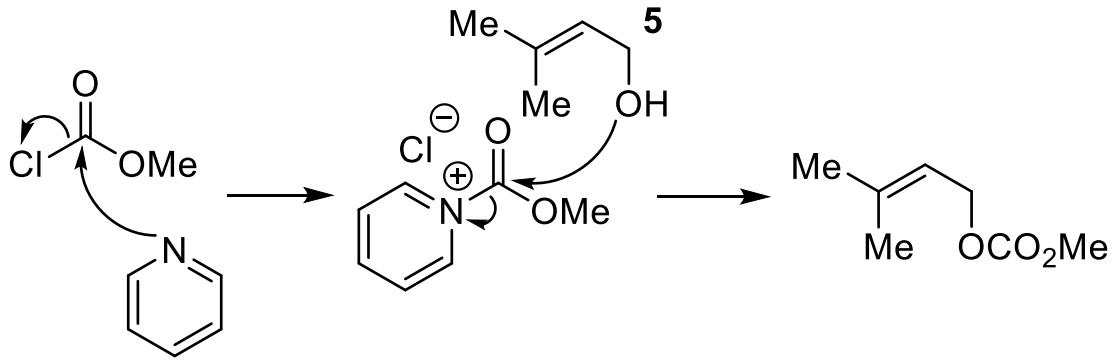


E_{1cb} Elimination

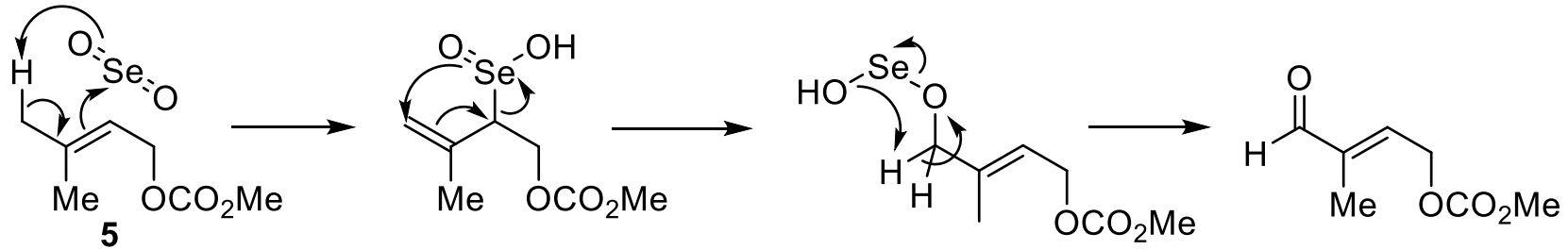


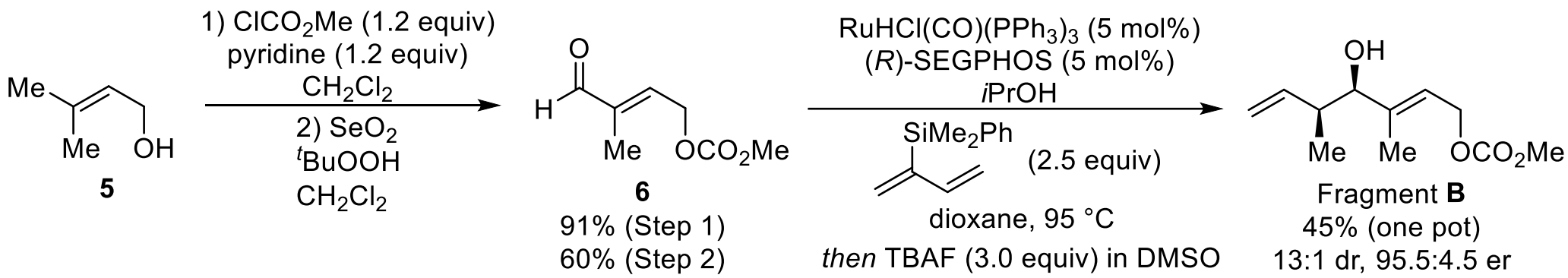


Acyl substitution

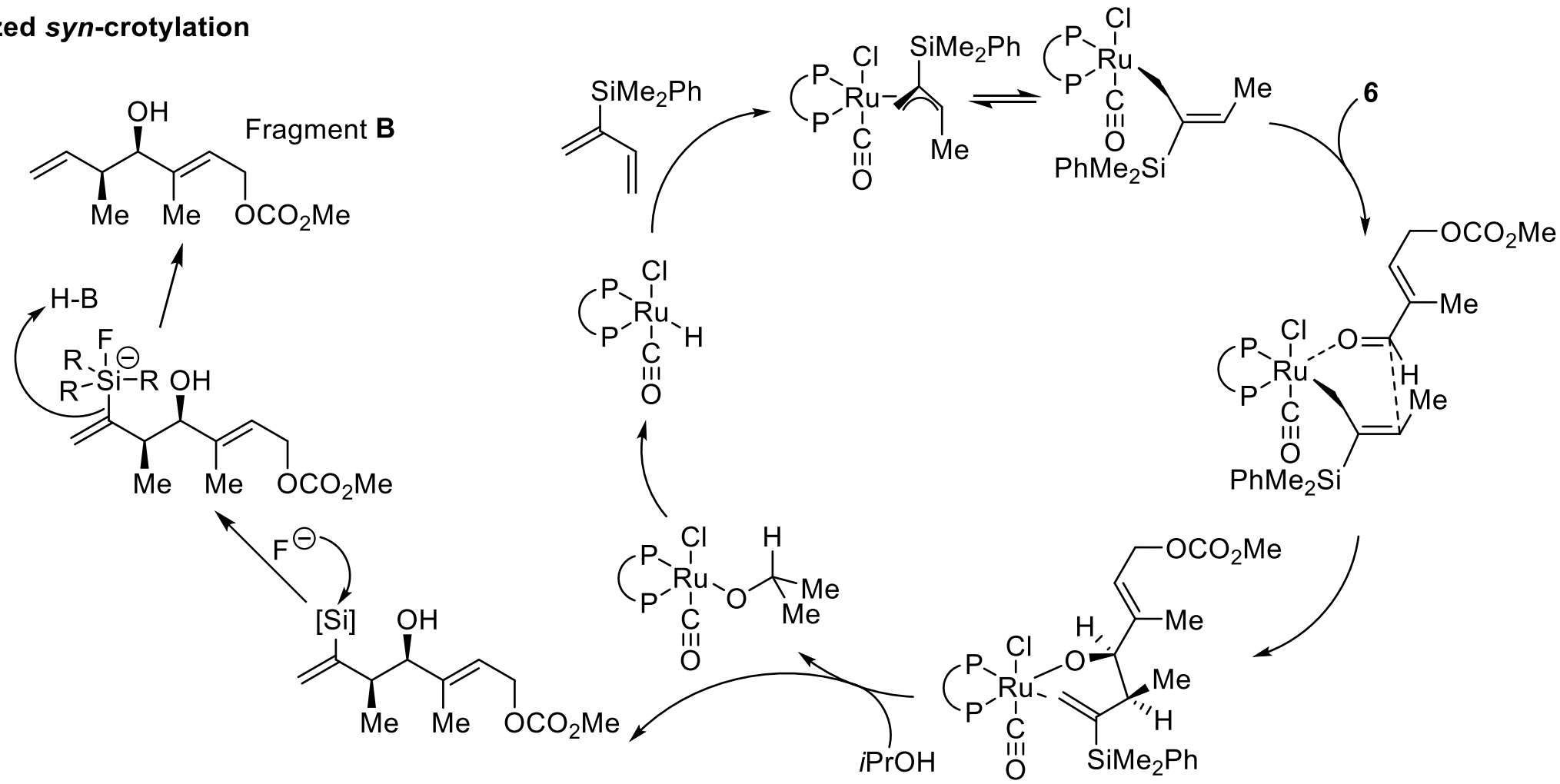


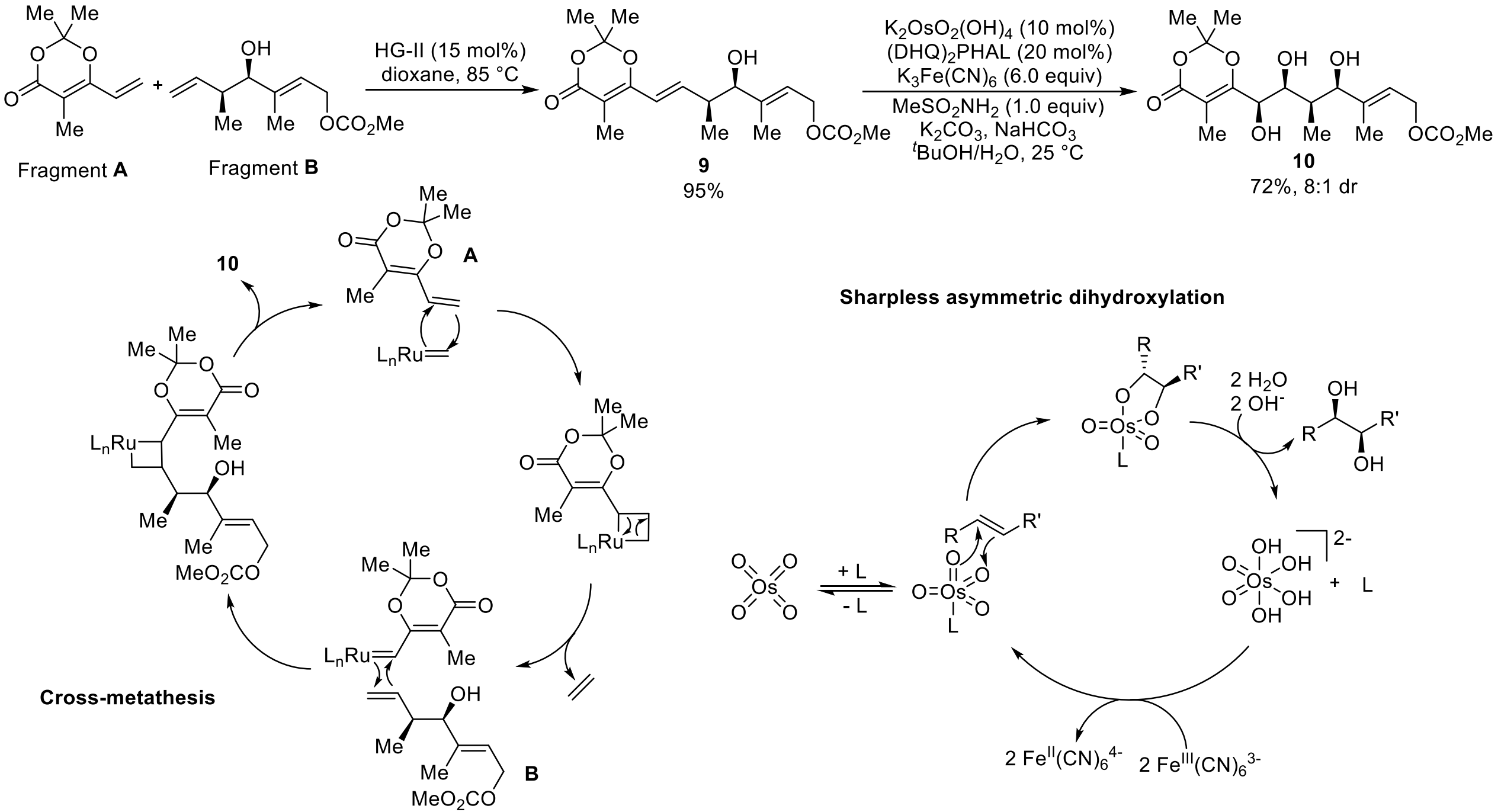
SeO_2-mediated allylic oxidation

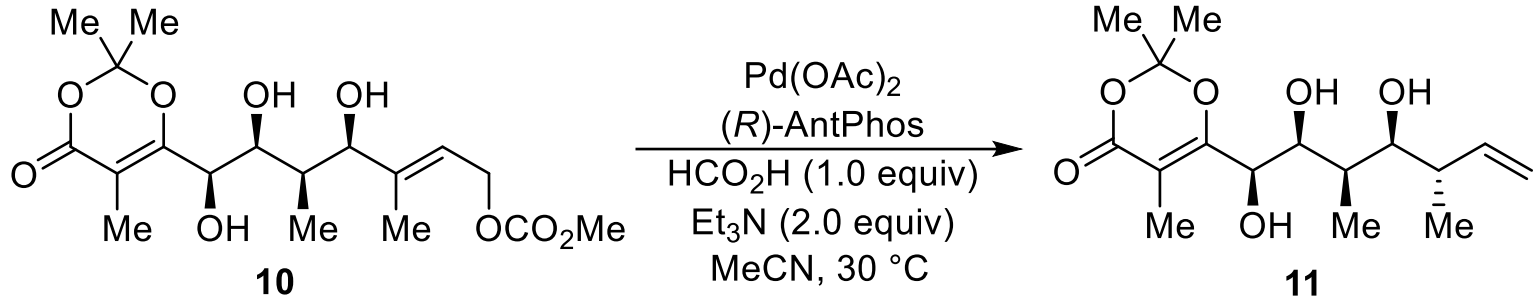




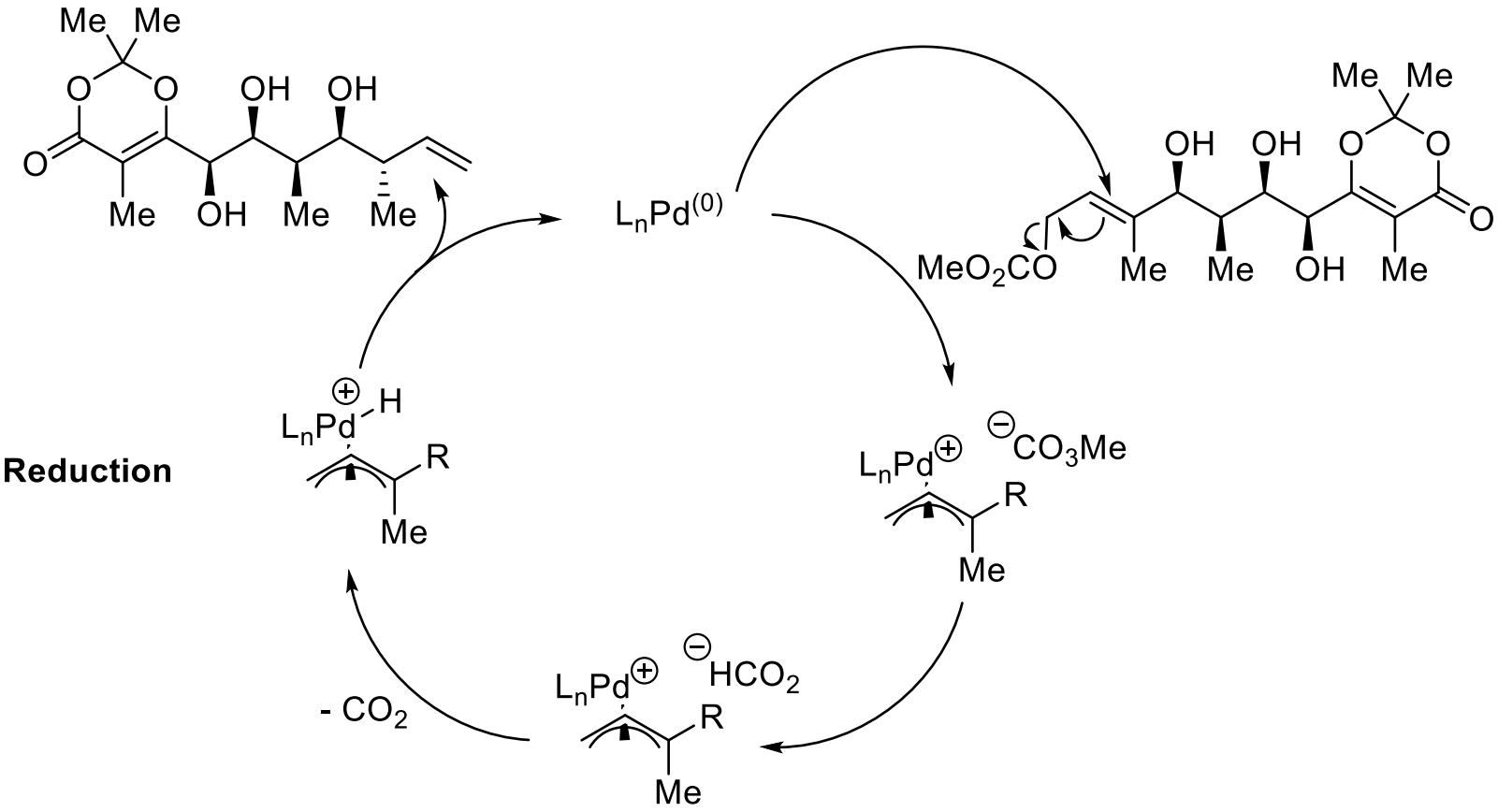
Ru-catalyzed *syn*-crotylation

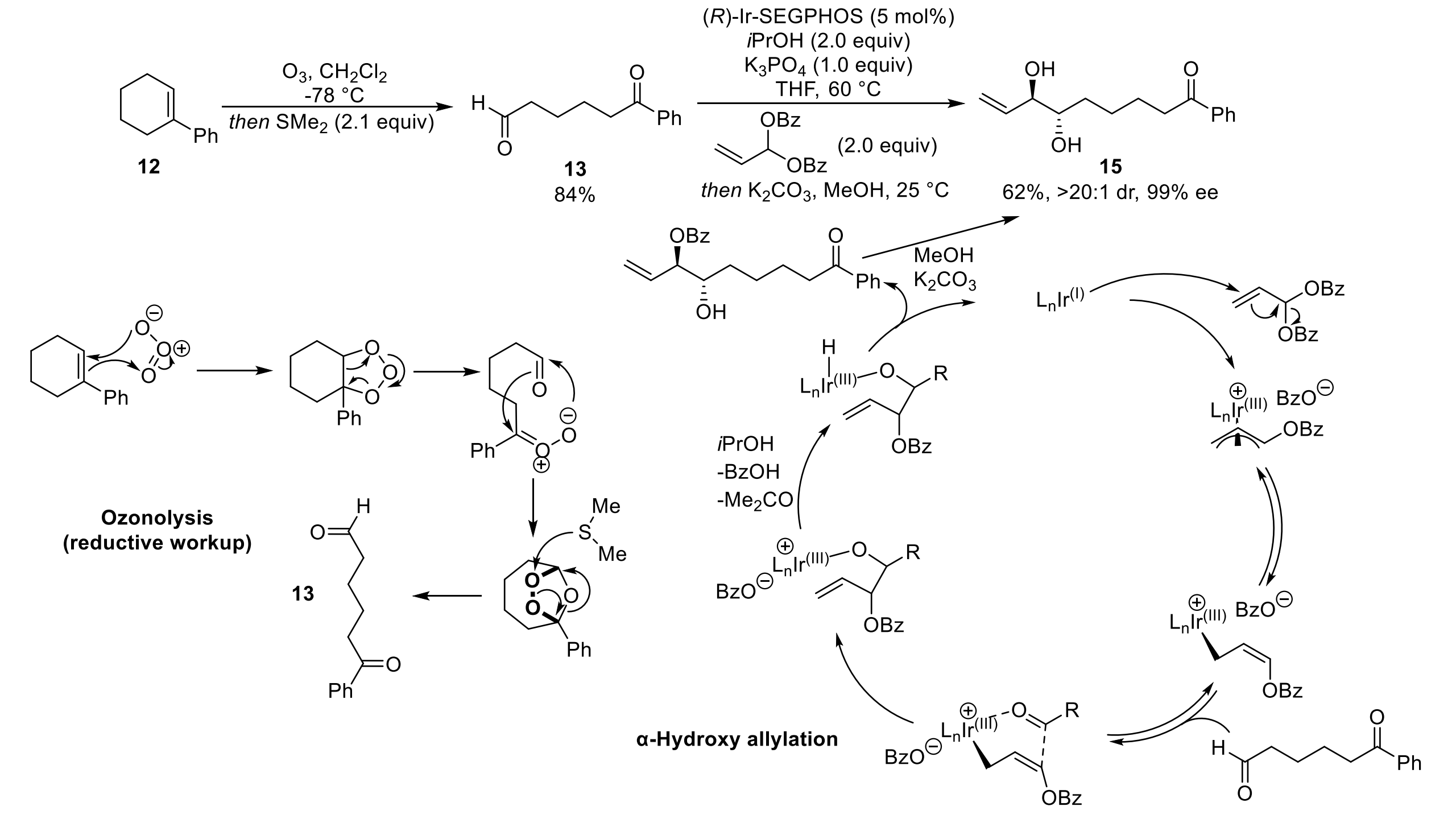


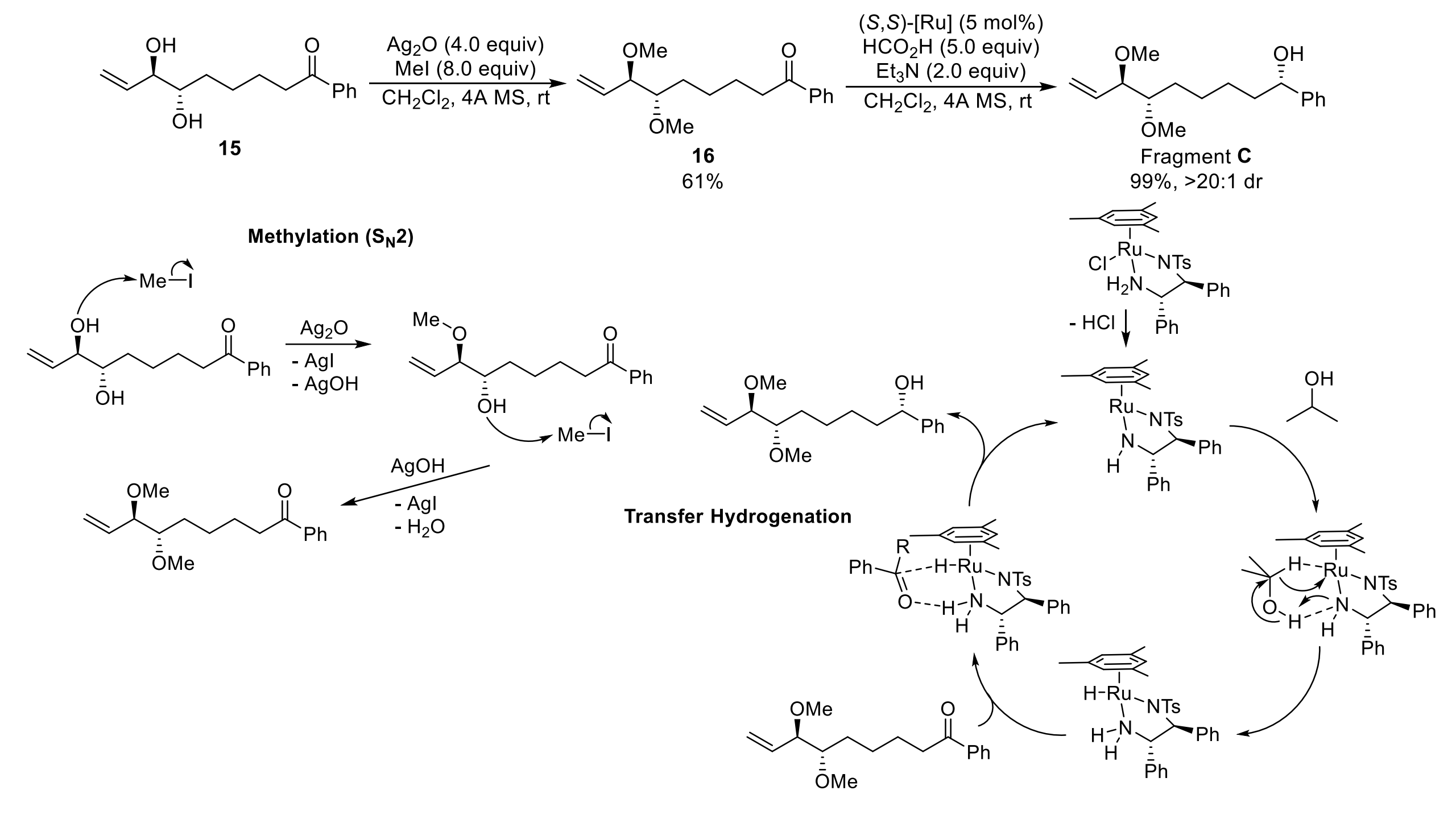

Fragment A
Fragment B
HG-II (15 mol%)
dioxane, 85 °C
9
95%
$K_2OsO_2(OH)_4$ (10 mol%)
$(DHQ)_2PHAL$ (20 mol%)
$K_3Fe(CN)_6$ (6.0 equiv)
$MeSO_2NH_2$ (1.0 equiv)
K_2CO_3, $NaHCO_3$
$^tBuOH/H_2O$, 25 °C
10
72%, 8:1 dr
Cross-metathesis
Sharpless asymmetric dihydroxylation
+ L
- L
2 H_2O
2 OH^-
2 $Fe^{II}(CN)_6^{4-}$
2 $Fe^{III}(CN)_6^{3-}$

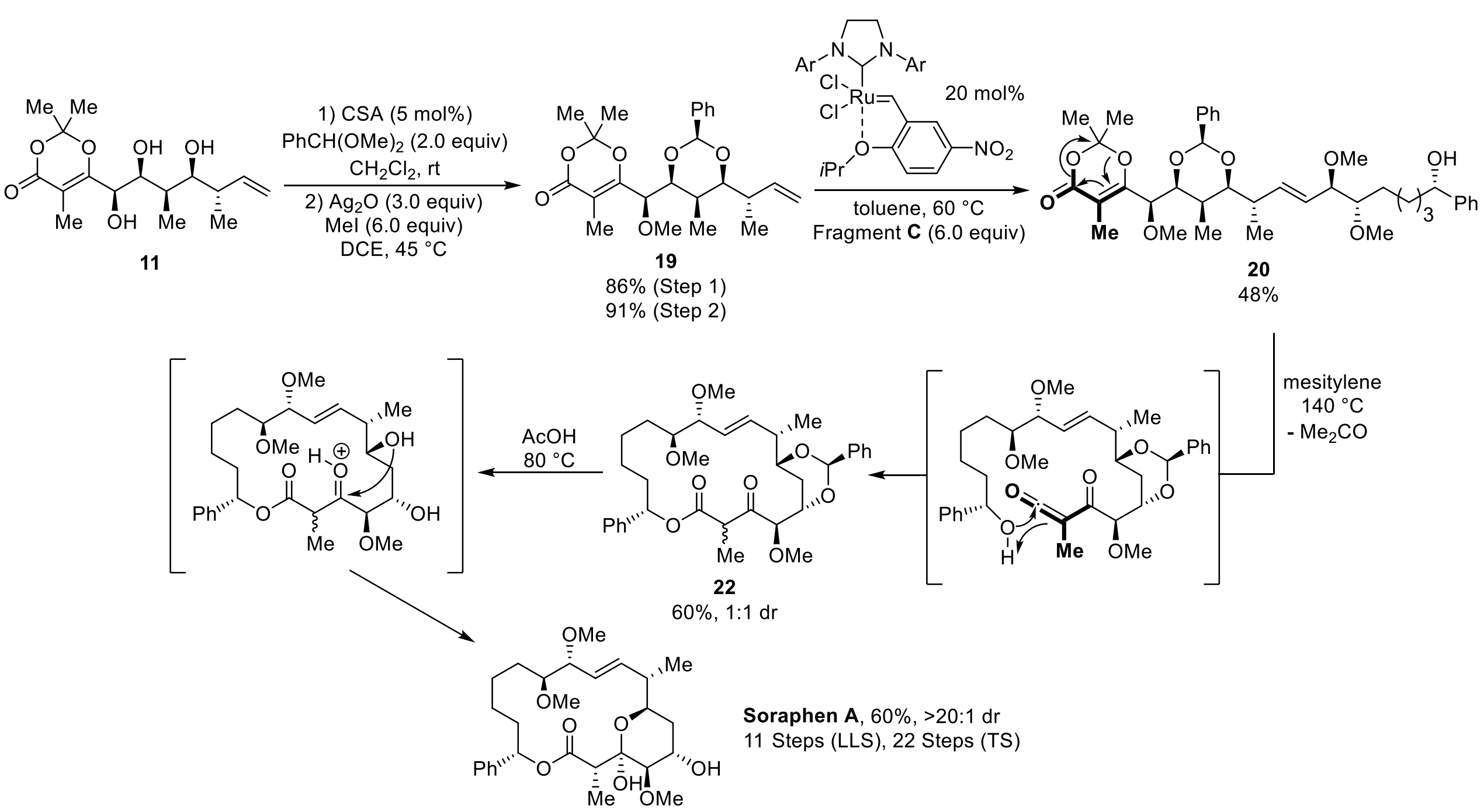


Tsuji Reduction




12
O3, CH2Cl2
-78 °C
then SMe2 (2.1 equiv)
13
84%
(R)-Ir-SEGPHOS (5 mol%)
iPrOH (2.0 equiv)
K3PO4 (1.0 equiv)
THF, 60 °C
(2.0 equiv)
then K2CO3, MeOH, 25 °C
15
62%, >20:1 dr, 99% ee
Ozonolysis
(reductive workup)
MeOH
K2CO3
iPrOH
-BzOH
-Me2CO
α-Hydroxy allylation


Ag2O (4.0 equiv)
MeI (8.0 equiv)
CH2Cl2, 4A MS, rt
(S,S)-[Ru] (5 mol%)
HCO2H (5.0 equiv)
Et3N (2.0 equiv)
CH2Cl2, 4A MS, rt
15
16
61%
Fragment C
99%, >20:1 dr
Methylation (SN2)
Ag2O
- AgI
- AgOH
AgOH
- AgI
- H2O
- HCl
Transfer Hydrogenation


11
1) CSA (5 mol%)
PhCH(OMe)2 (2.0 equiv)
CH2Cl2, rt
2) Ag2O (3.0 equiv)
MeI (6.0 equiv)
DCE, 45 °C
19
86% (Step 1)
91% (Step 2)
20 mol%
toluene, 60 °C
Fragment C (6.0 equiv)
20
48%
mesitylene
140 °C
- Me2CO
AcOH
80 °C
22
60%, 1:1 dr
Soraphen A, 60%, >20:1 dr
11 Steps (LLS), 22 Steps (TS)