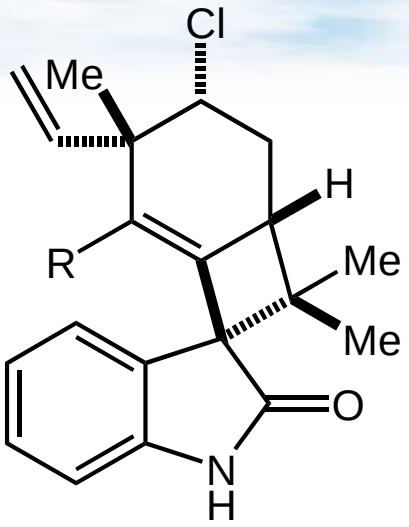
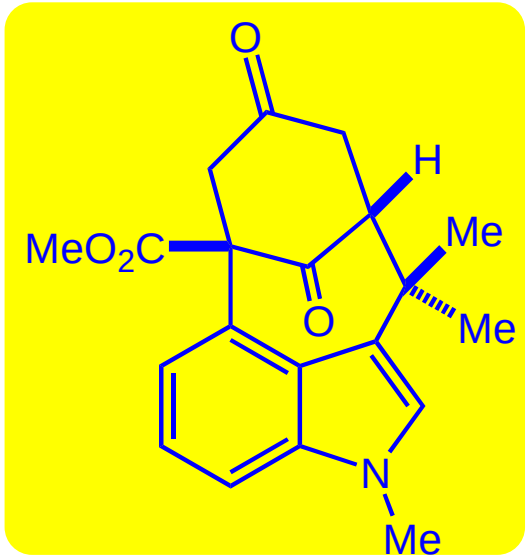
Approaches to *N*-Methylwelwitindolinone C Isothiocyanate: Facile Synthesis of the Tetracyclic Core

Kai Gao Checker: Changbin Yu

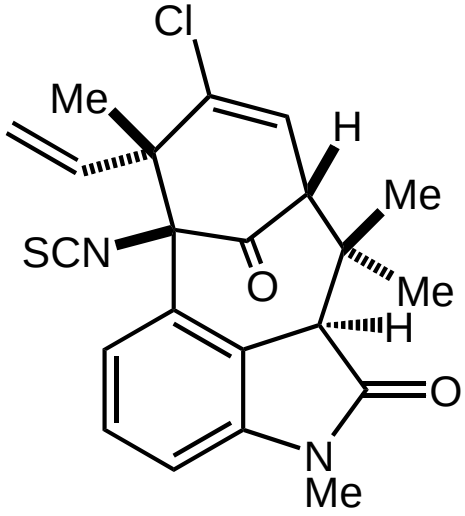
Martin, S. F.* *et al Org. Lett.* **2010**, *ASAP*



welwitindolinone A isocyanate **1** (R = NC)
welwitindolinone A isothiocyanate **2** (R = NCS)

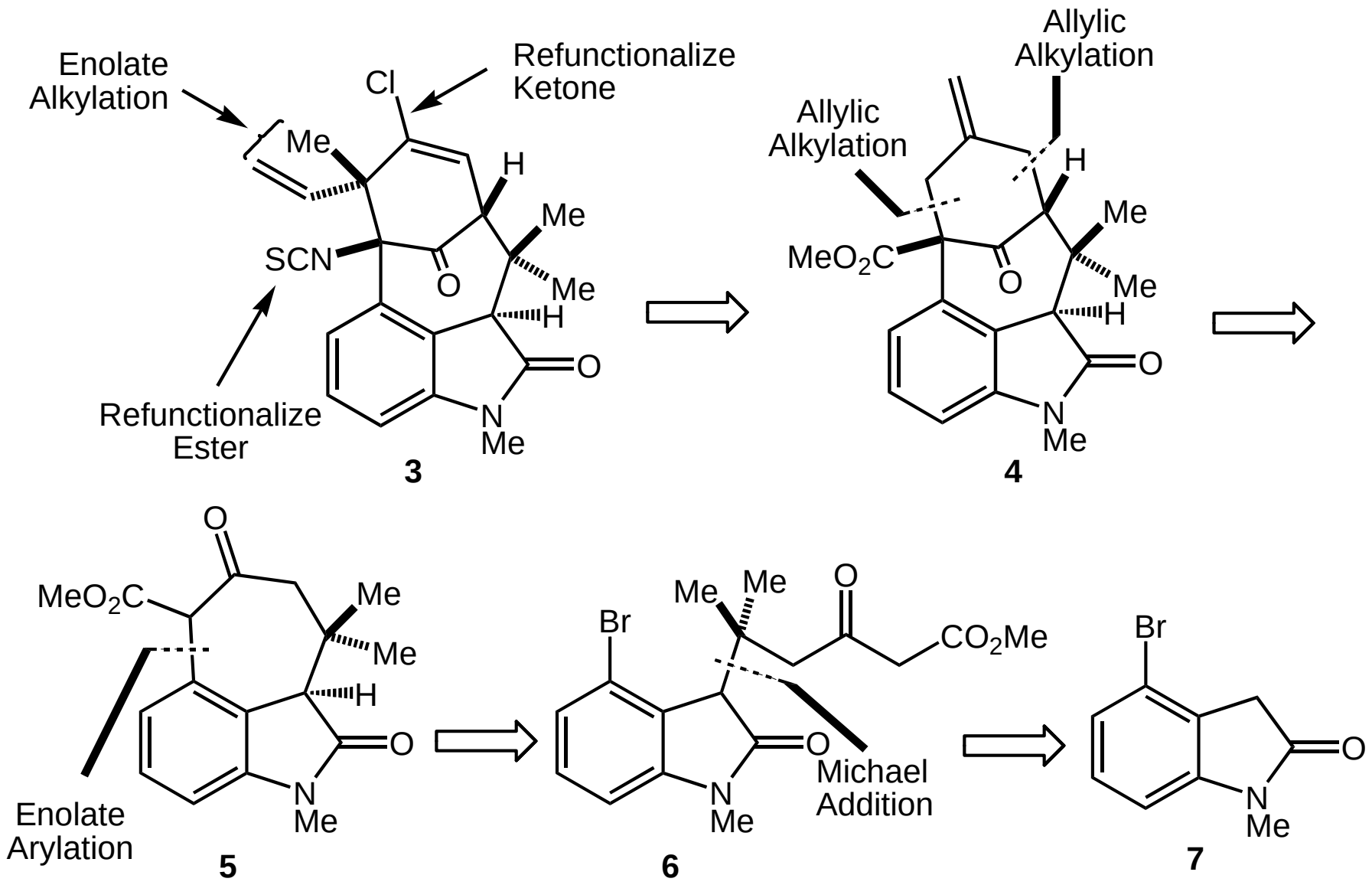


This Work

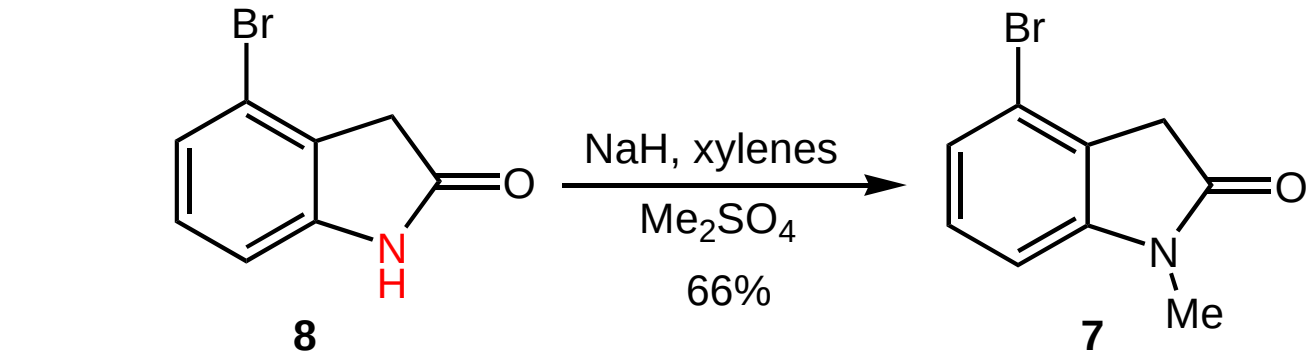


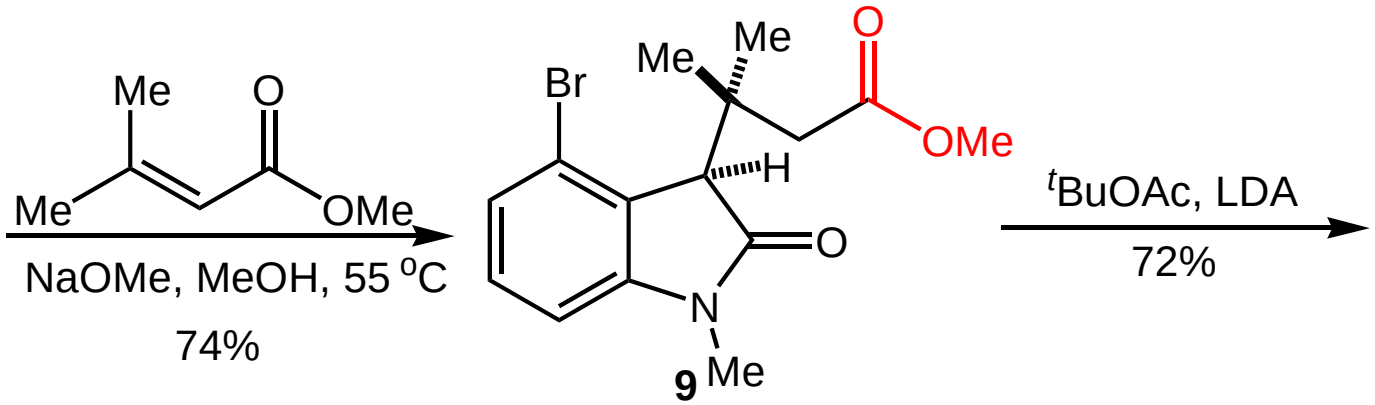
N-methylwelwitindolinone C isothiocyanate **3**

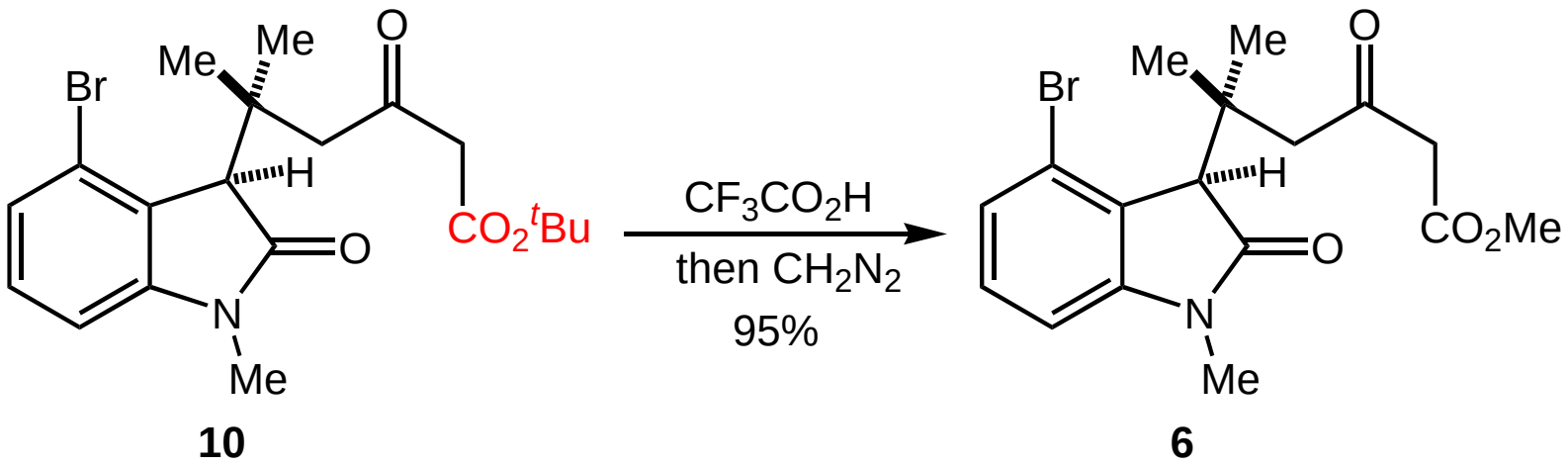
Initial Retrosynthetic Proposal



Preparation of Ketoester **6**

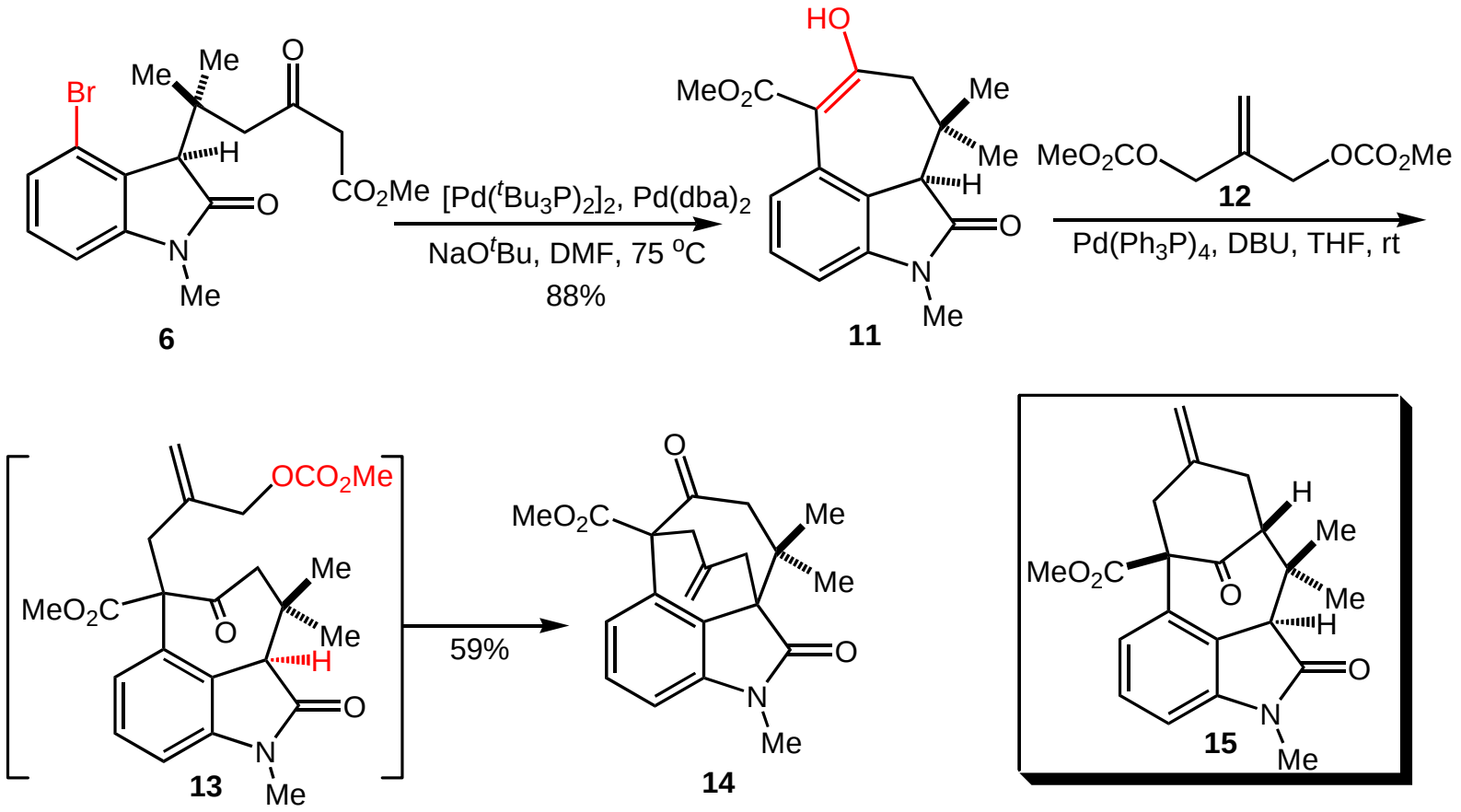




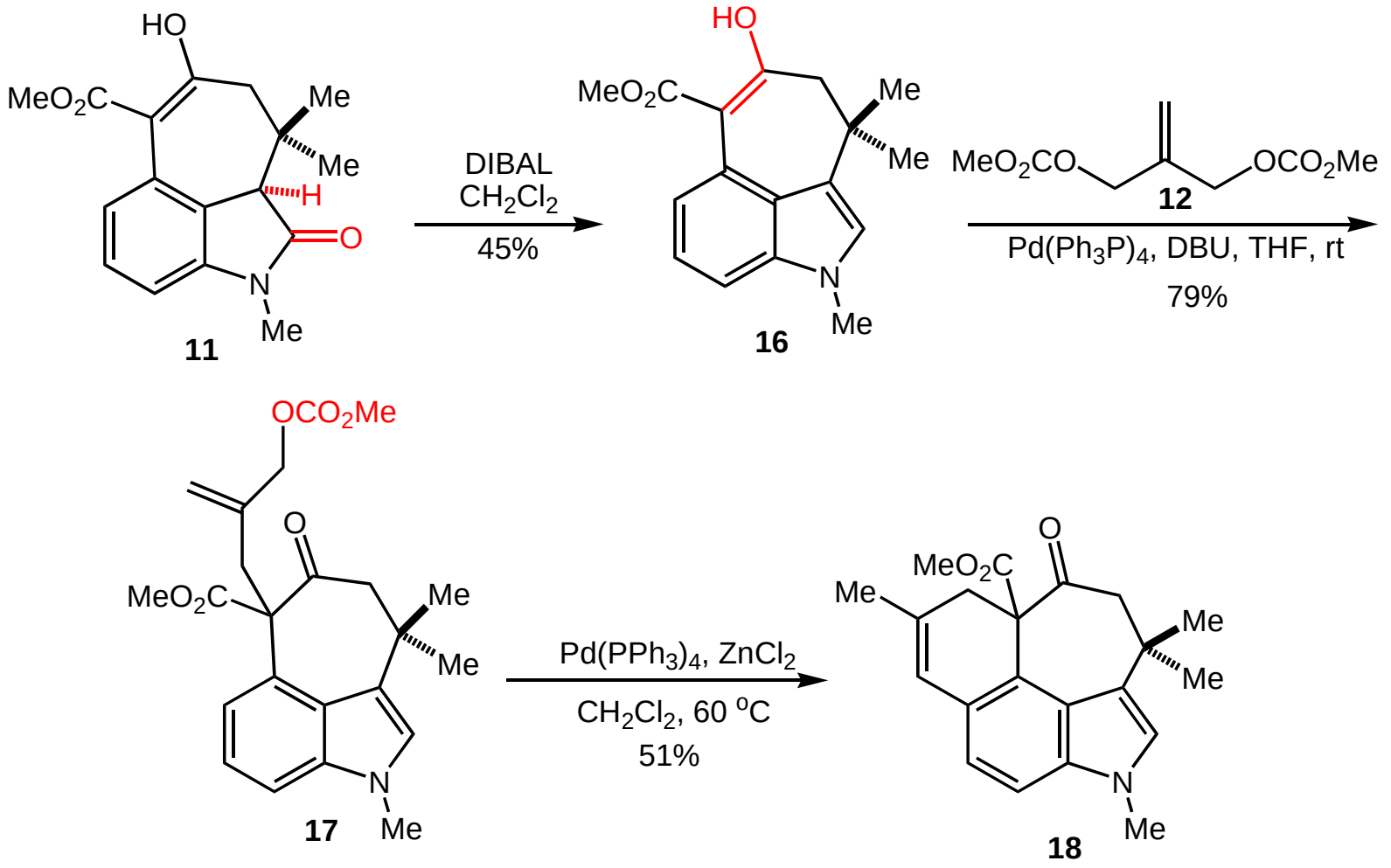

Br
Me
Me
O
H
O
N
Me
CO2tBu
CF3CO2H
then CH2N2
95%
Br
Me
Me
O
H
O
N
Me
CO2Me

10 **6**

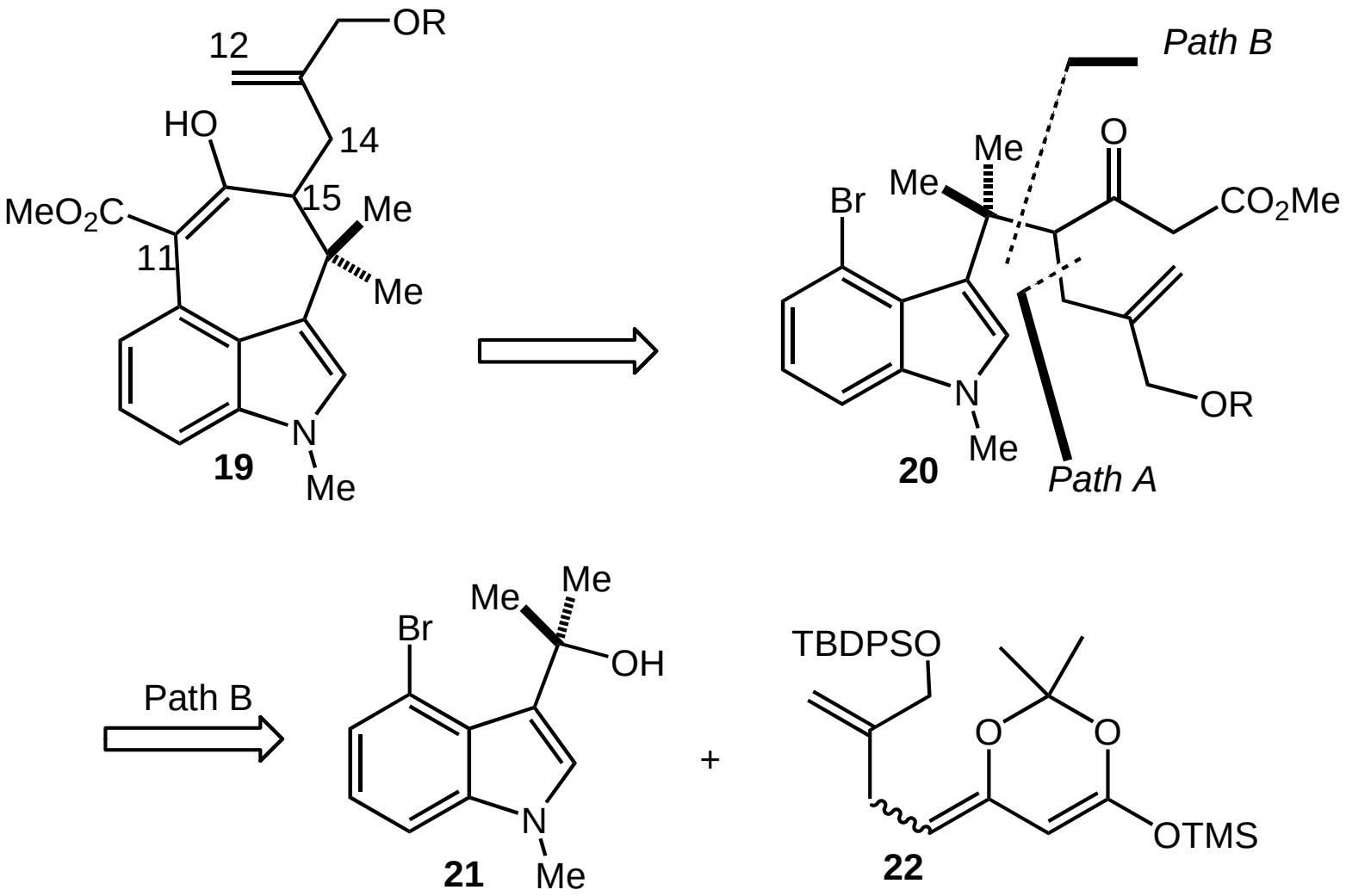
Attempted Preparation of Tetracycle **15**



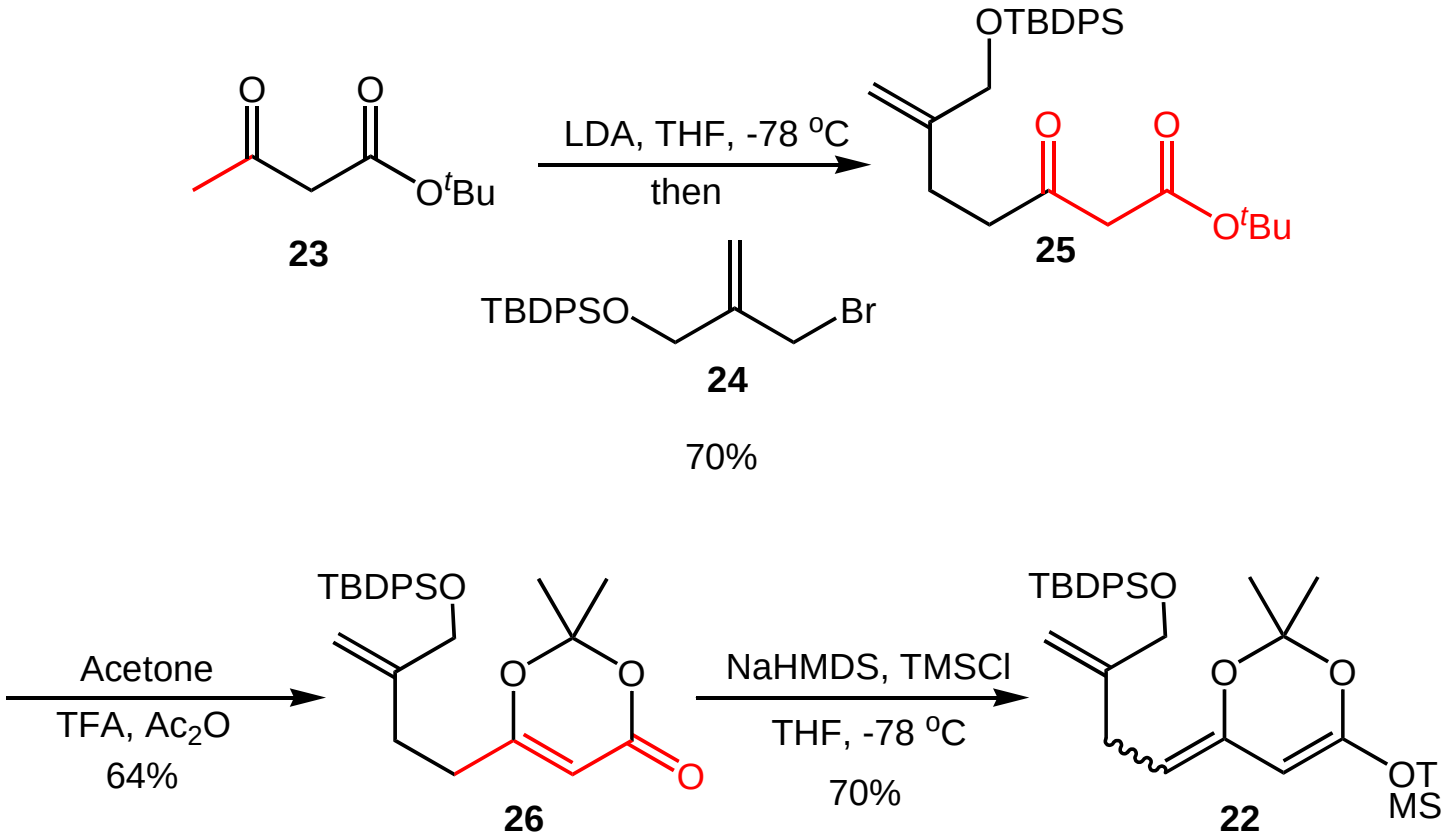
Attempted Preparation of an Indolic Tetracycle



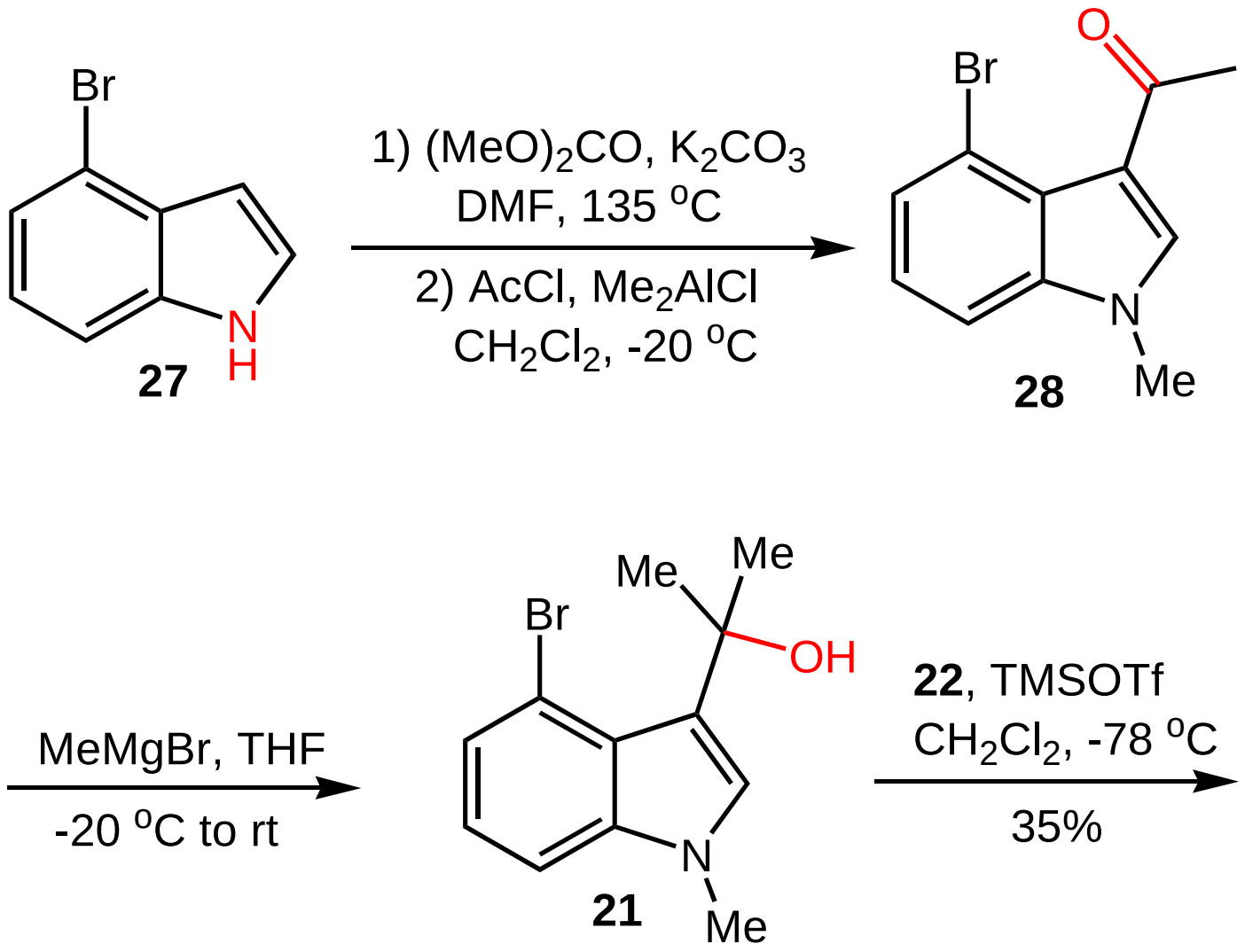
Revised Retrosynthetic Analysis

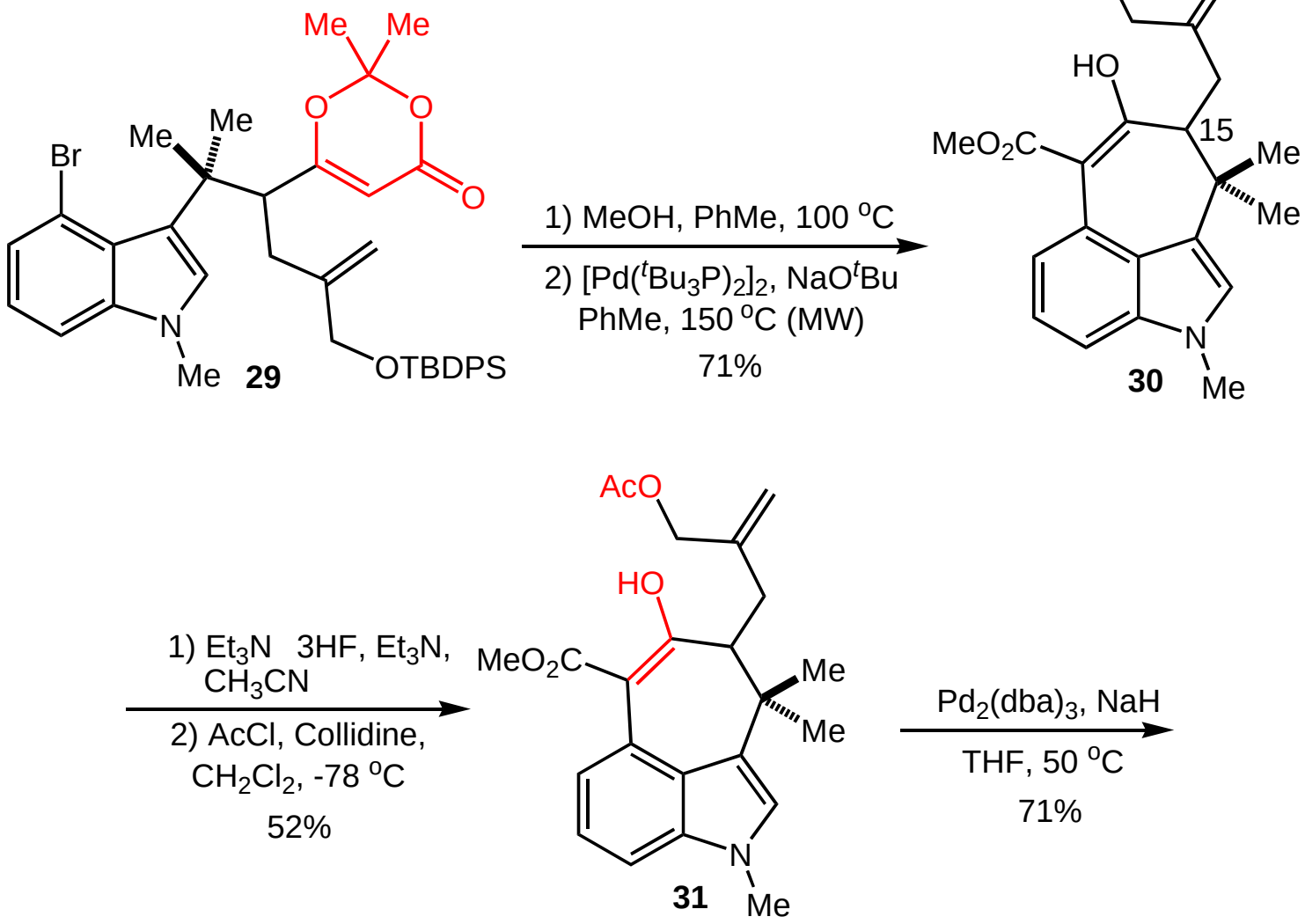


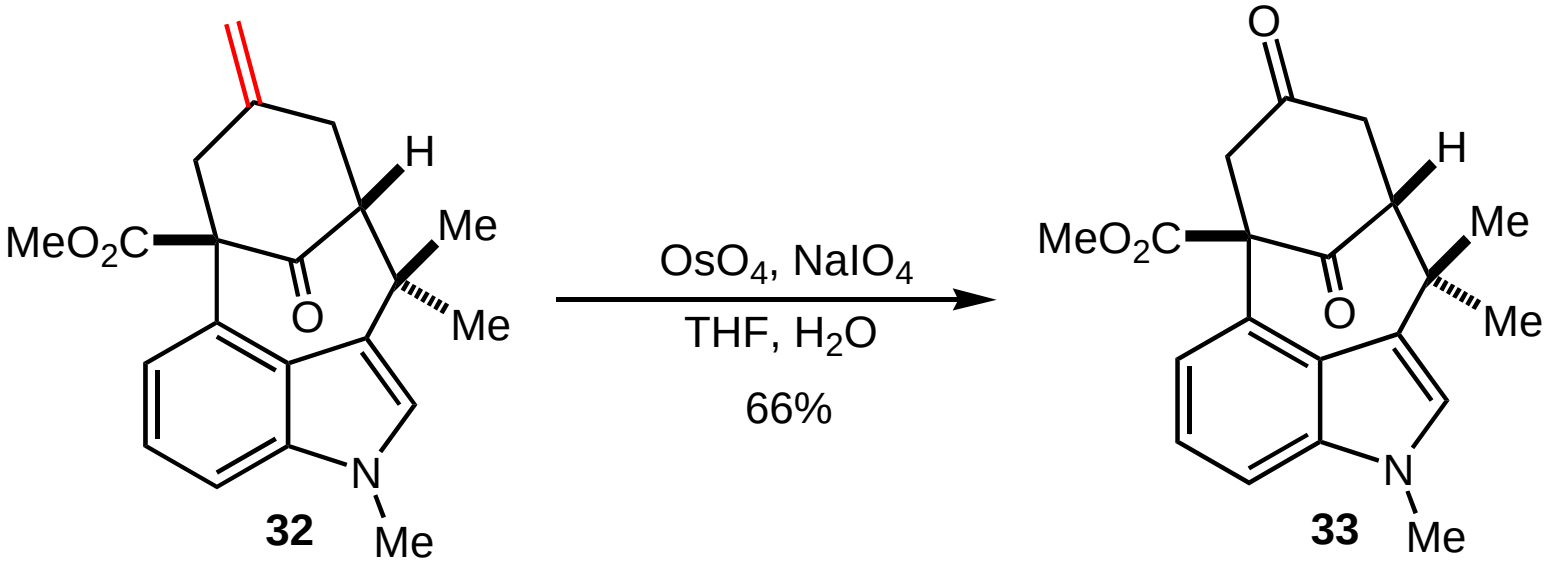
Preparation of Vinylogous Silyl Ketene Acetal 22



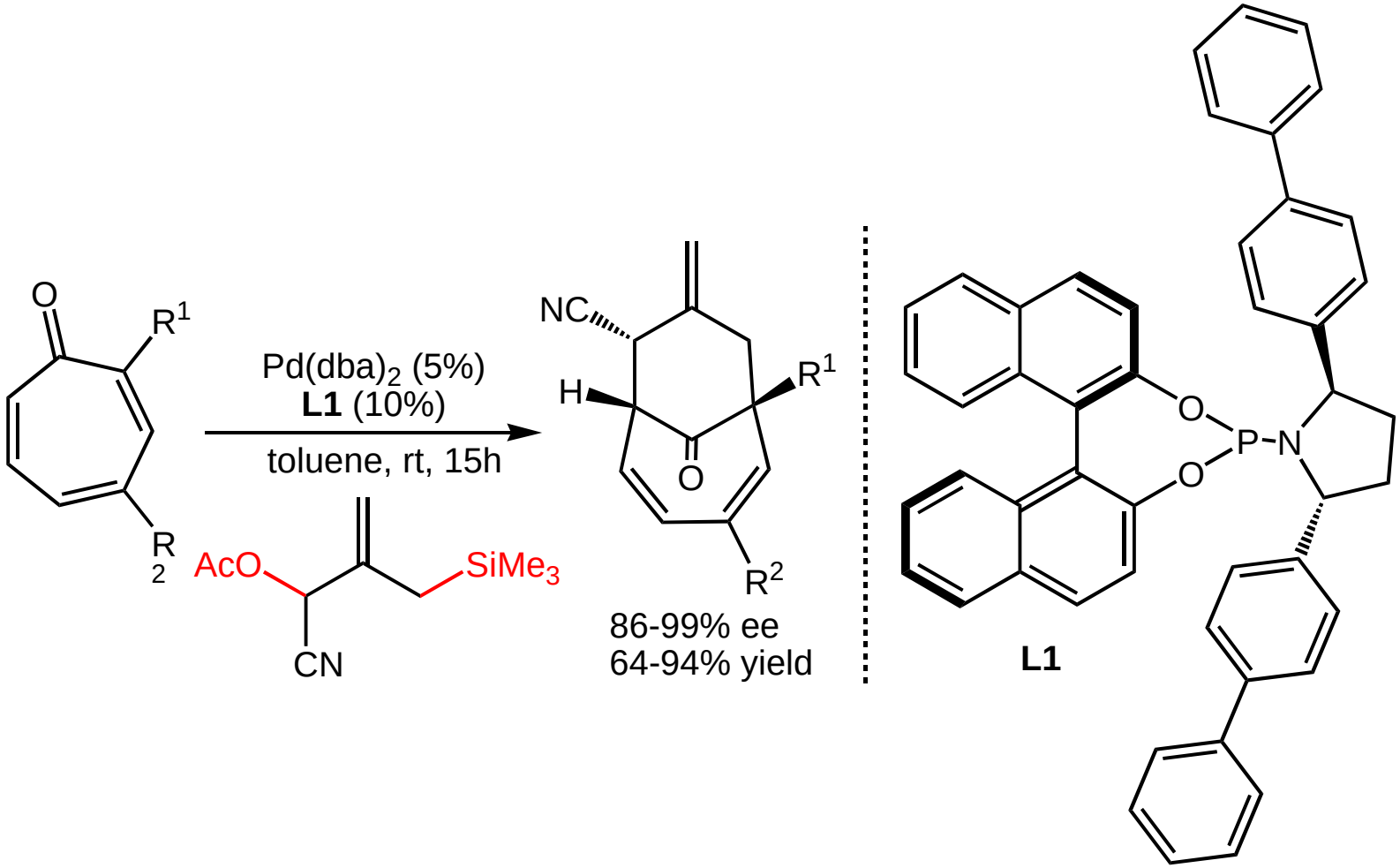
Preparation of the Welwitindolinone C Skeleton




Me
Me
O
O
O
Me
Me
Br
N
Me
29
OTBDPS
1) MeOH, PhMe, 100 °C
2) [Pd(tBu3P)2]2, NaOtBu
PhMe, 150 °C (MW)
71%
TBDPSO
HO
MeO2C
15
Me
Me
N
Me
30
1) Et3N 3HF, Et3N,
CH3CN
2) AcCl, Collidine,
CH2Cl2, -78 °C
52%
AcO
HO
MeO2C
Me
Me
N
Me
31
Pd2(dba)3, NaH
THF, 50 °C
71%

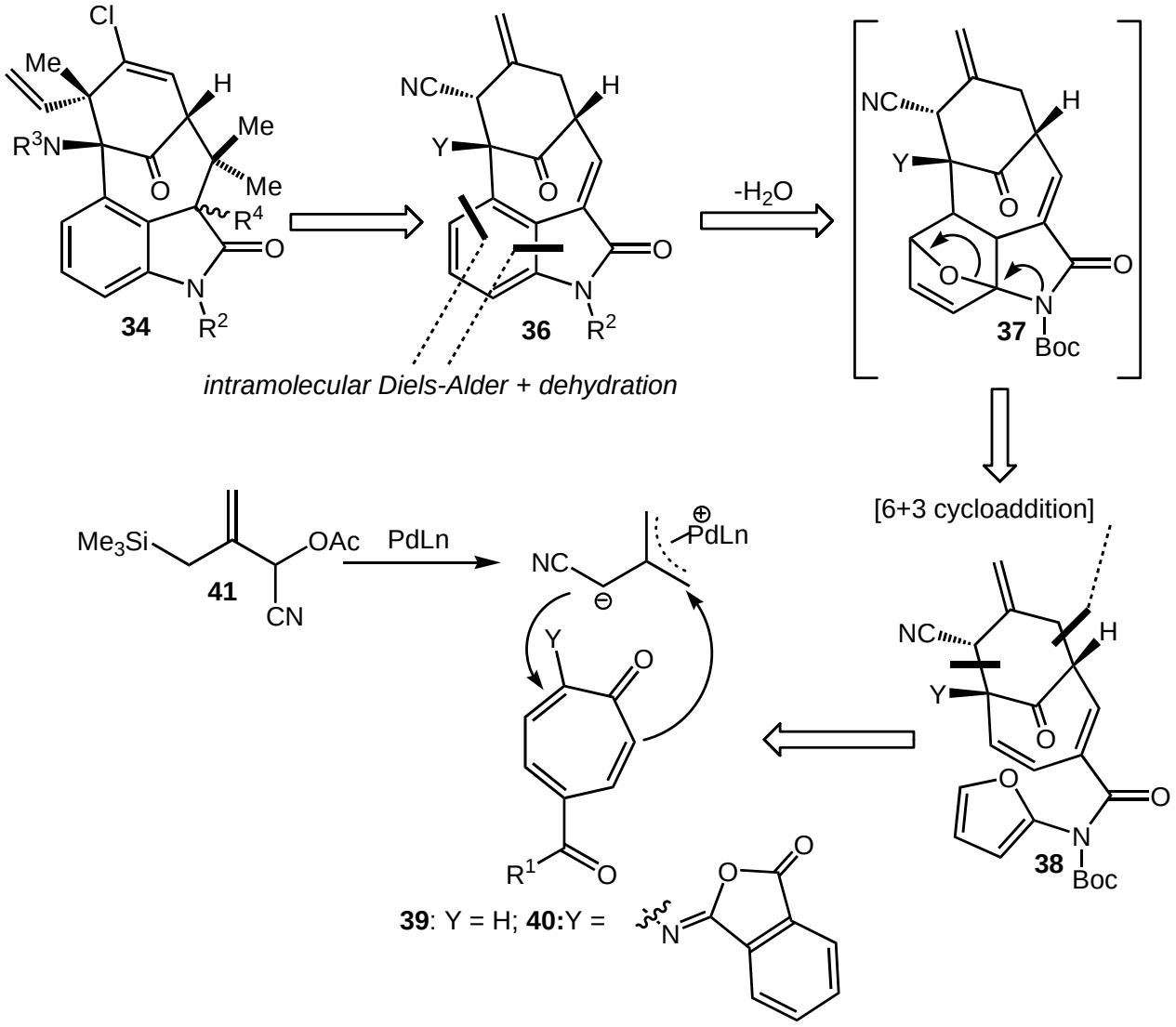

MeO2C
H
Me
Me
O
N
Me
32
OsO4, NaIO4
THF, H2O
66%
O
MeO2C
H
Me
Me
O
N
Me
33

Enantioselective Pd-TMM [6 + 3] Cycloadditions

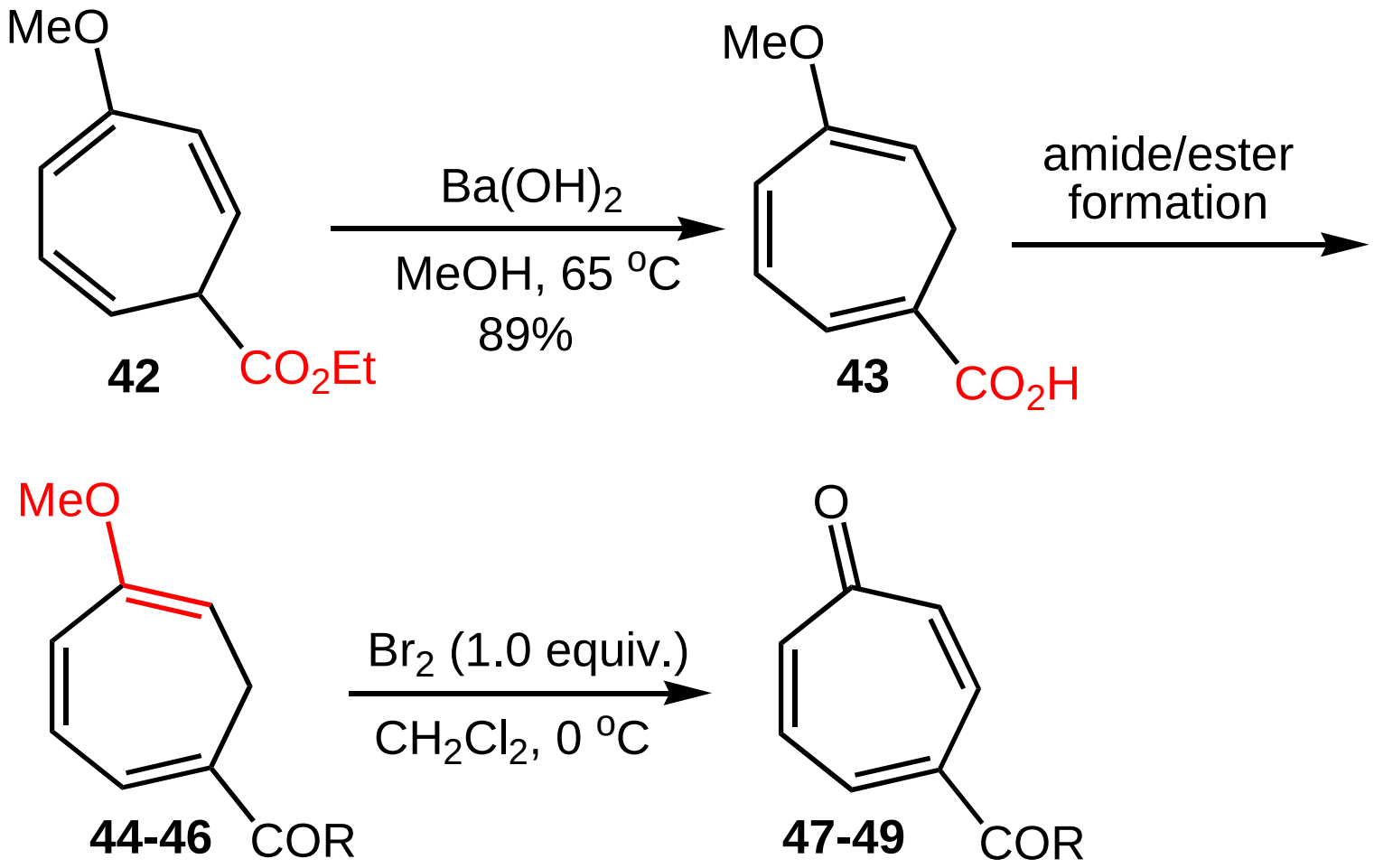


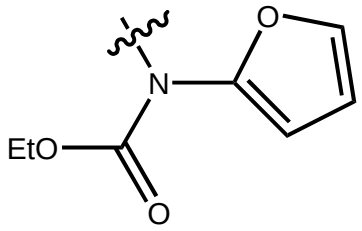
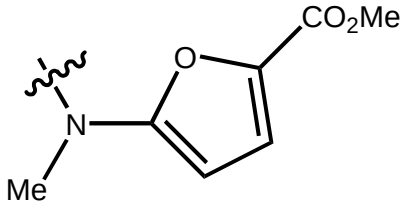
Trost, B. M. et al *J. Am. Chem. Soc.* **2008**, *130*, 14960-14961.

Retrosynthetic Analysis

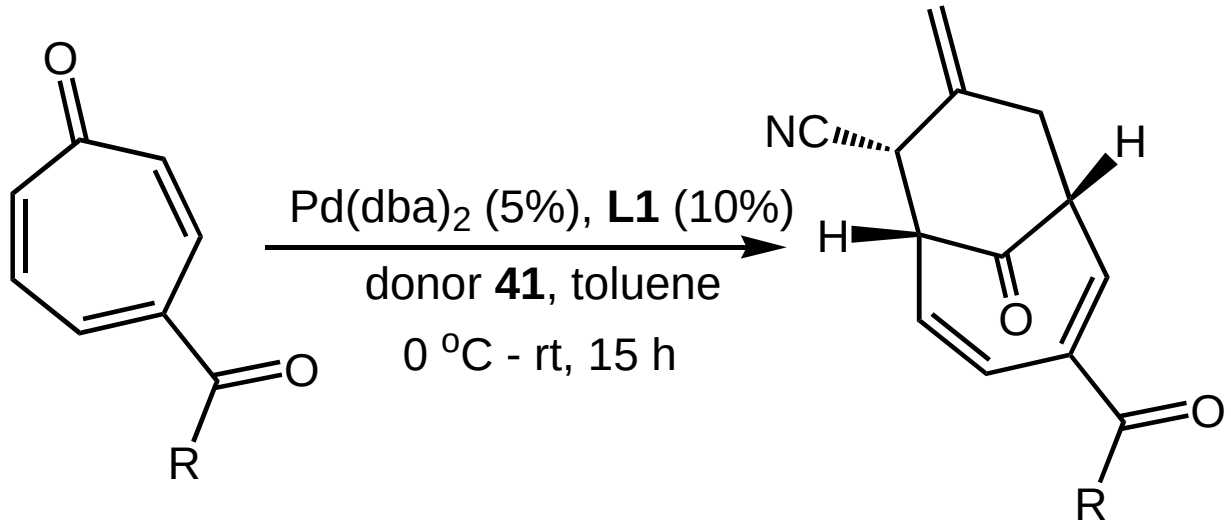


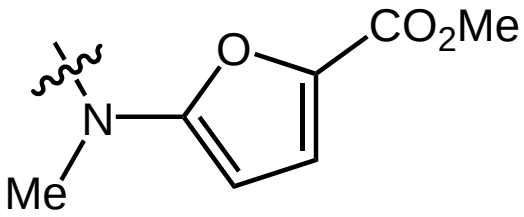
Preparation of the Tropone Intermediates



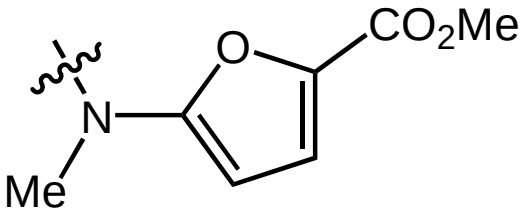
cycloheptatriene	R	tropone	yield
44		**47**	0%
45		**48**	54% (three steps)
46	OPMB	**49**	58% (two steps)

Asymmetric [6 + 3] Cycloadditions



50: R = 

51: R = OPMB

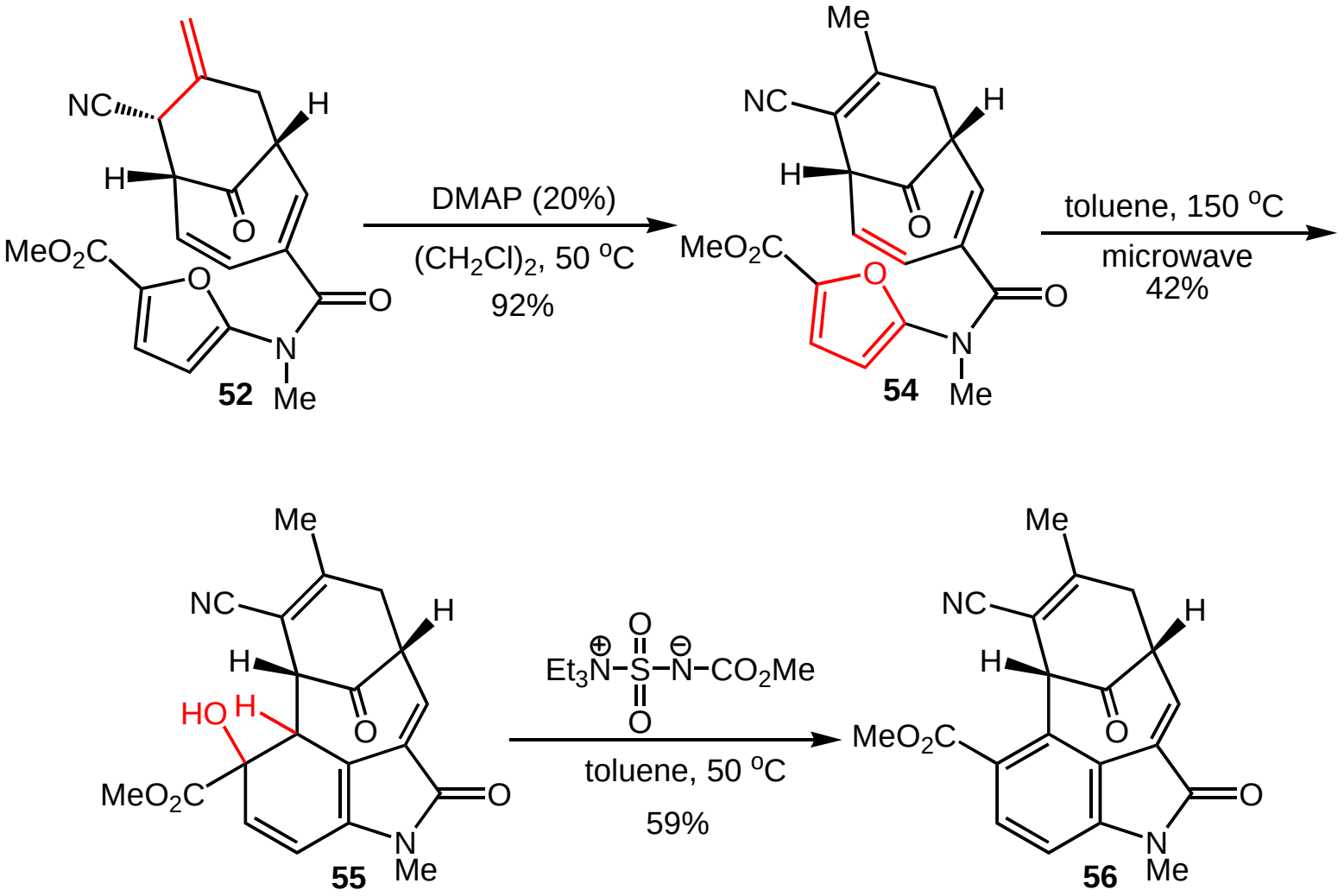
52: R = 

(60%, 94% ee)

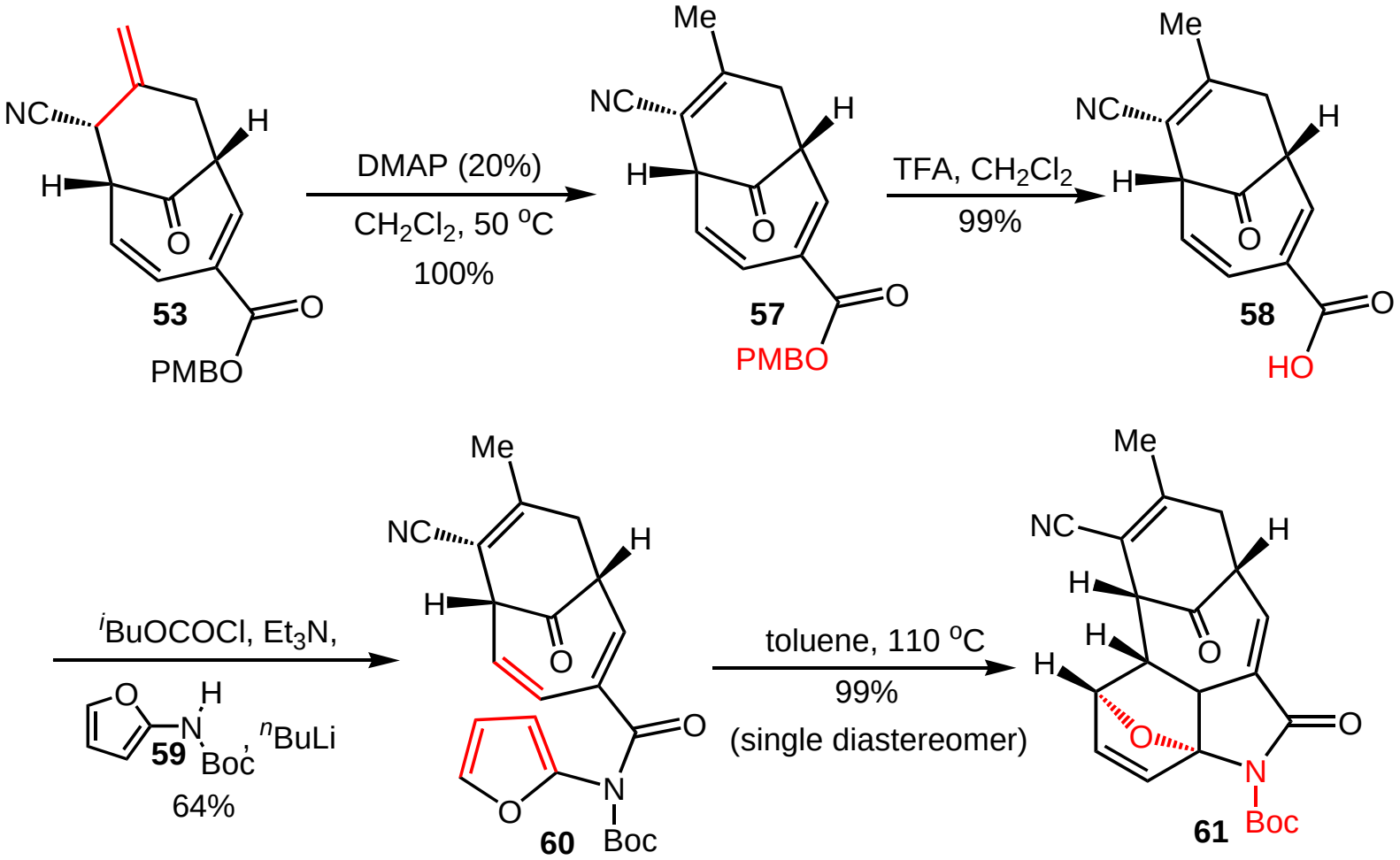
53: R = OPMB

(80%, 94% ee)

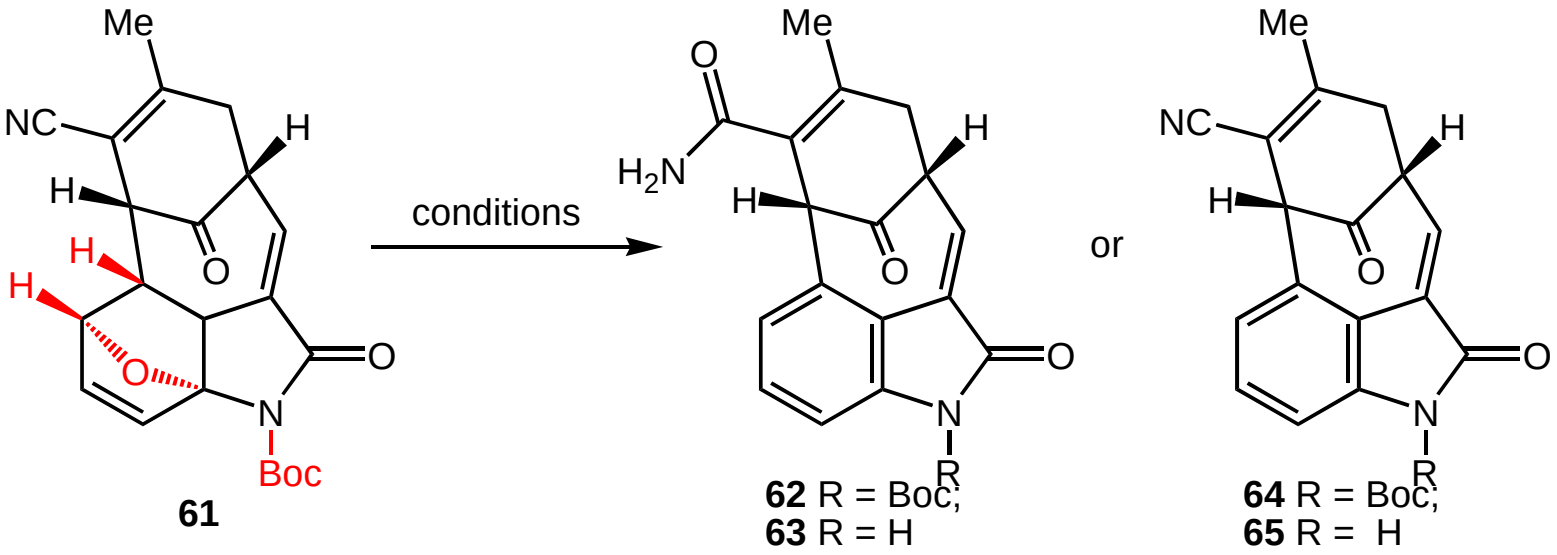
Elaboration of Adduct 22



Elaboration of Adduct 23



Completion of Oxindole Core



61

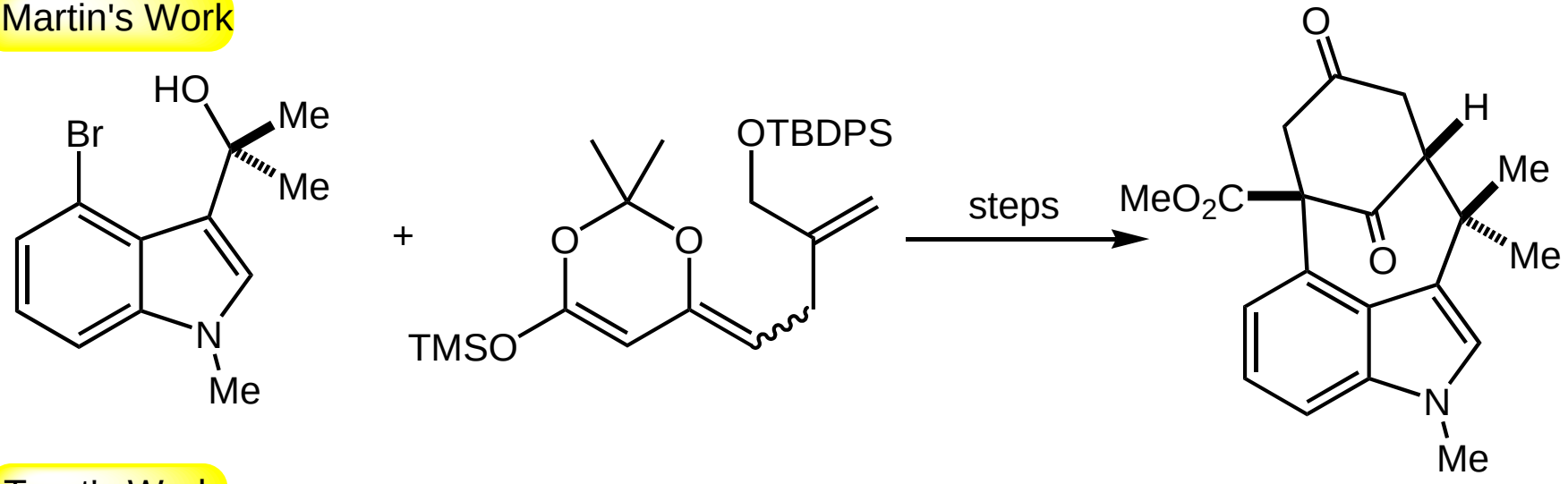
62 R = Boc;
63 R = H

64 R = Boc;
65 R = H

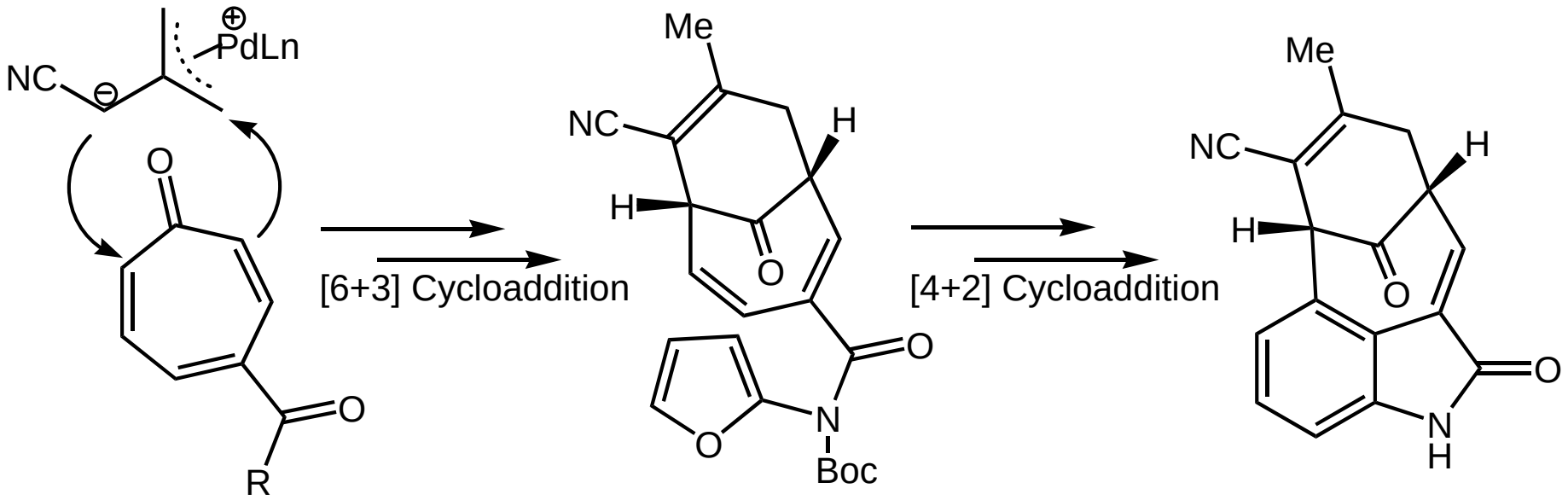
reagents	compd	yield (%)
TFA	**62** and**63**	not determined
BF_3•OEt_2	**64** and **65**	determined
Burgess reagent	**64**	**48**
$Yb(OTf)_3$	**65**	**50**

Summary

Martin's Work



Trost's Work



A series of novel indole alkaloids were isolated in 1994 by Moore and co-workers from the extracts of blue-green cyanobacteria *Hapalosiphon wetwitschii* and *Westiella intracta*. These compounds, which were collectively named welwitindolinones, possess a unique skeletal framework and were isolated along with the structurally related fischerindoles and hapalindoles. A putative biogenetic relationship among these alkaloids has been proposed. These natural products exhibit diverse biological activities, perhaps the most exciting of which is the ability of some to reverse multiple drug resistance (MDR) during chemotherapeutic treatment of cancer.

In preparing **33**, we have thus developed a facile entry to the tetracyclic scaffold found in *N*-methylwelwitindolinone C isothiocyanate (**3**). The synthesis features the coupling of an indole-stabilized carbocation with a vinylogous silyl ketene acetal as a π-nucleophile together with a palladium-catalyzed enolate arylation and a palladium-catalyzed allylic alkylation. Efforts toward the application of this approach and variants thereof to the total synthesis of **3** are in progress and will be reported in due course.