Using C–C Activation as the Key Step in Total Synthesis

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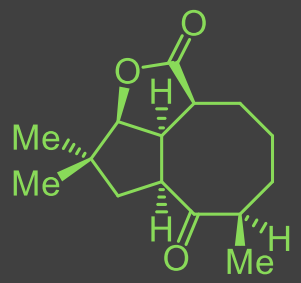
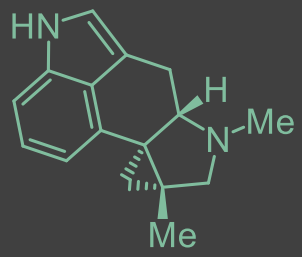
U of U Synthesis Club

August 28th, 2018



(+)-asteriscanolide



(–)-cycloclavine

Introduction to Organometallics

Types of Ligands:

Anionic Ligands:

M–Cl M–H M–alkyl

Neutral Ligands:

M---:PR_3 M---:CO M---‖

π–Allyl Complex:

Ligand Association/Dissociation

Example:

Migratory Insertion/Deinsertion

Oxidative Addition/Reductive Elimination

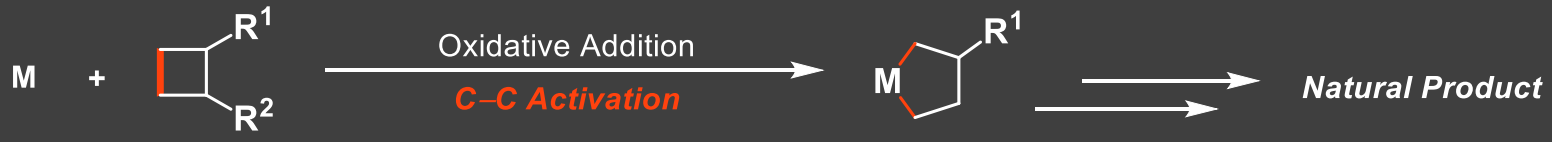
Oxidative Addition Example:

weak bond

Reductive Elimination Example:

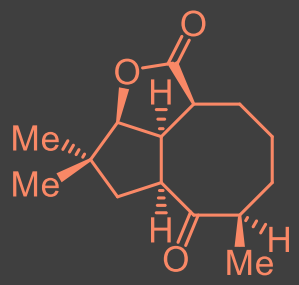
strong bond

C—C Activation in Total Synthesis



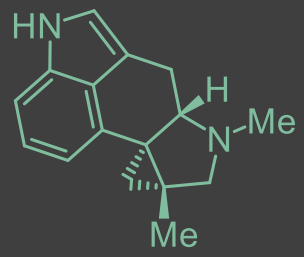
- Transition metal "M" is involved in the C–C cleavage process
- Small ring systems play an important role: release of ring strain facilitates the metal insertion
- The organometallic intermediate can undergo subsequent reactions to produce a functionalized product
- *Oxidative Addition* is one mechanism that is classified as a C–C Activation

- The cleavage and reorganization of C–C bonds in C–C Activation as a synthetic strategy for complex molecule synthesis
- Few examples of C–C Activation as the key step in total synthesis
- Even fewer examples in asymmetric synthesis of products



(+)-asteriscanolide

Liang, Y; Jiang, X; Yu, Z.–X.
Chem. Commun., **2011**, *47*, 6659

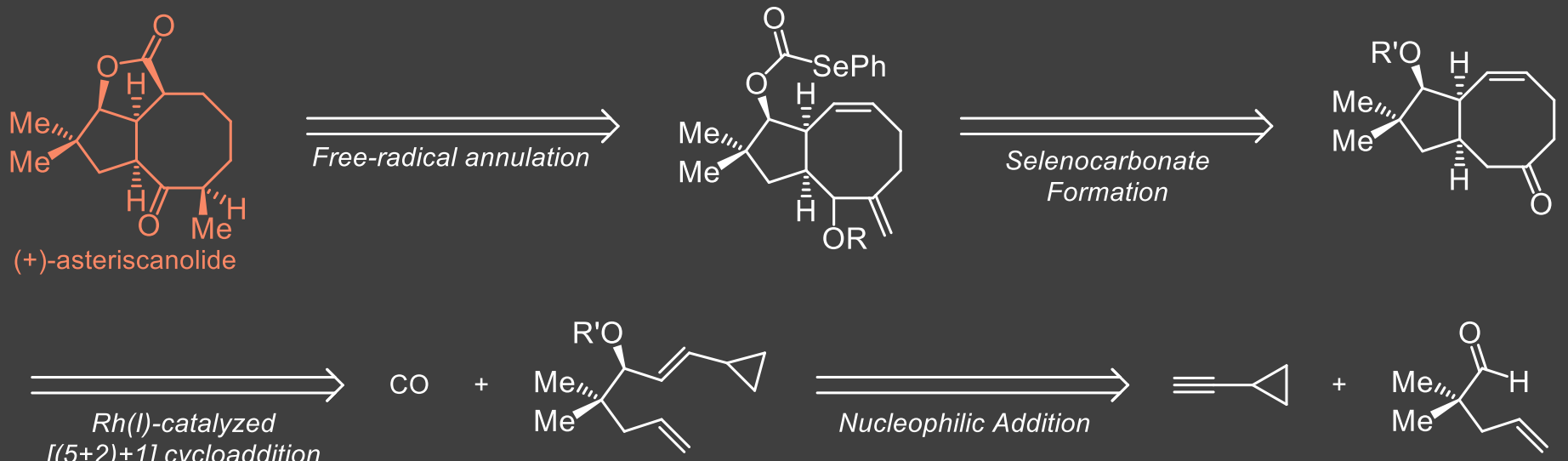


(–)-cycloclavine

Deng, L; Chen, M.; Dong, G.
J. Am. Chem. Soc., **2018**, *140* (30), 9652

Souillart, L; Cramer, N. *Chem. Rev.*, **2015**, *115*, 9410

(+)-Asteriscanolide



Characteristics:

- Isolated from *Asteriscus aquaticus L* by *San Feliciano* in 1985
- First total synthesis was reported in 1988 by Carlos Correia
- As a sesquiterpene, it has the potential for the treatment of cardiovascular disease and cancer

Synthetic Challenges:

- uncommon [6.3.0] carbocyclic system
- 5 *cis* stereocenters
- Construction of 8-membered carbocycle is the most challenging (based on previous synthesis)

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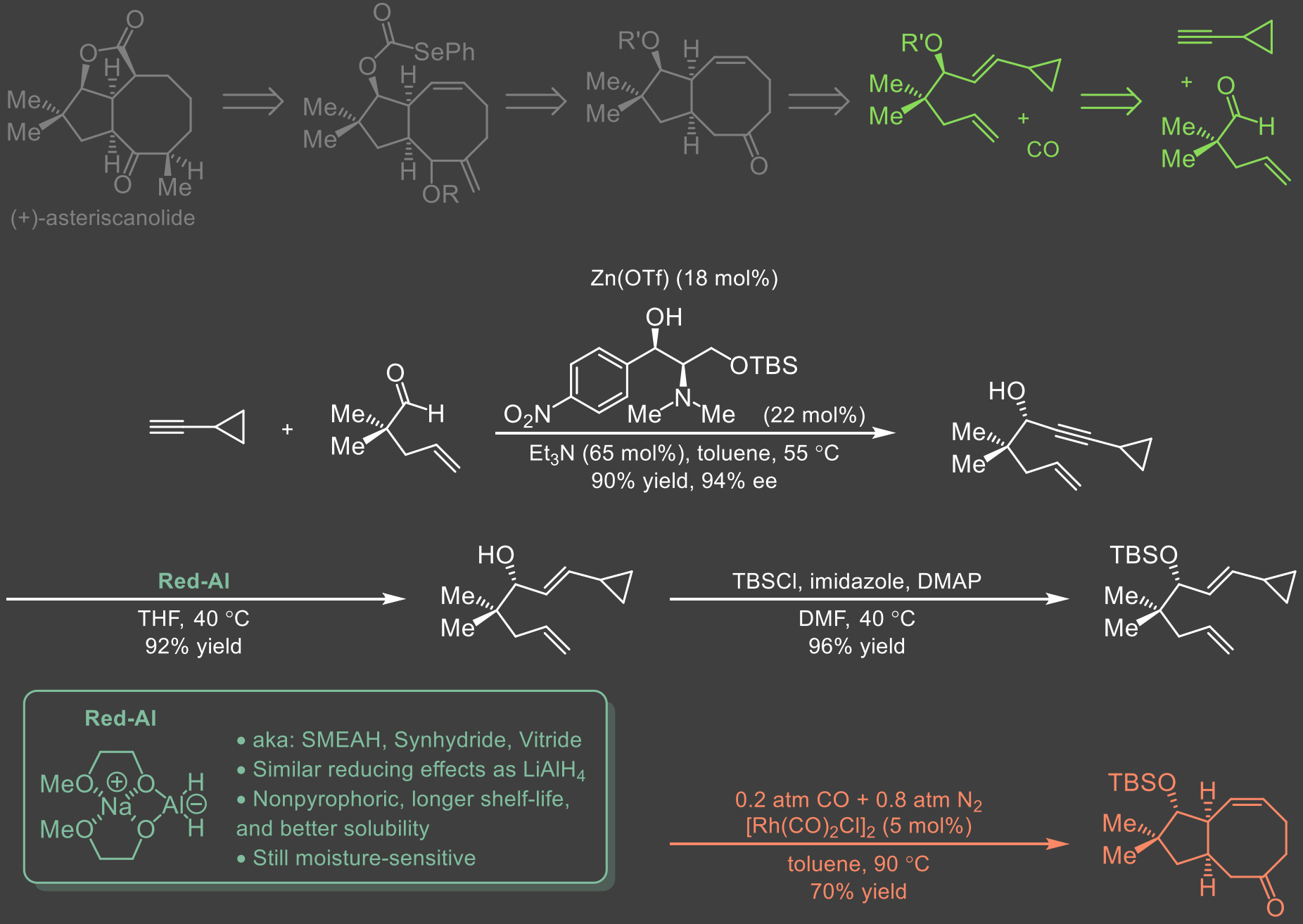

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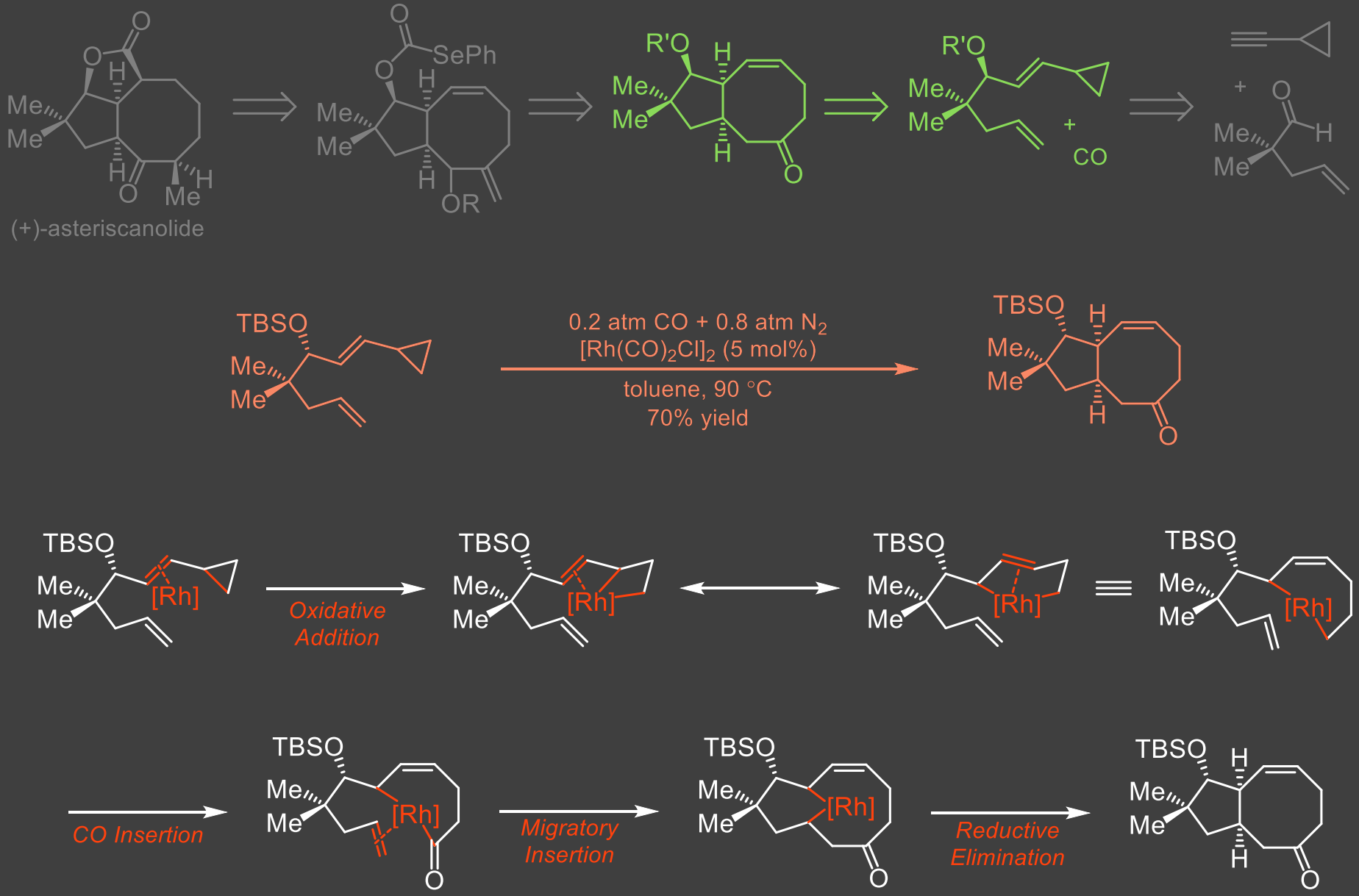

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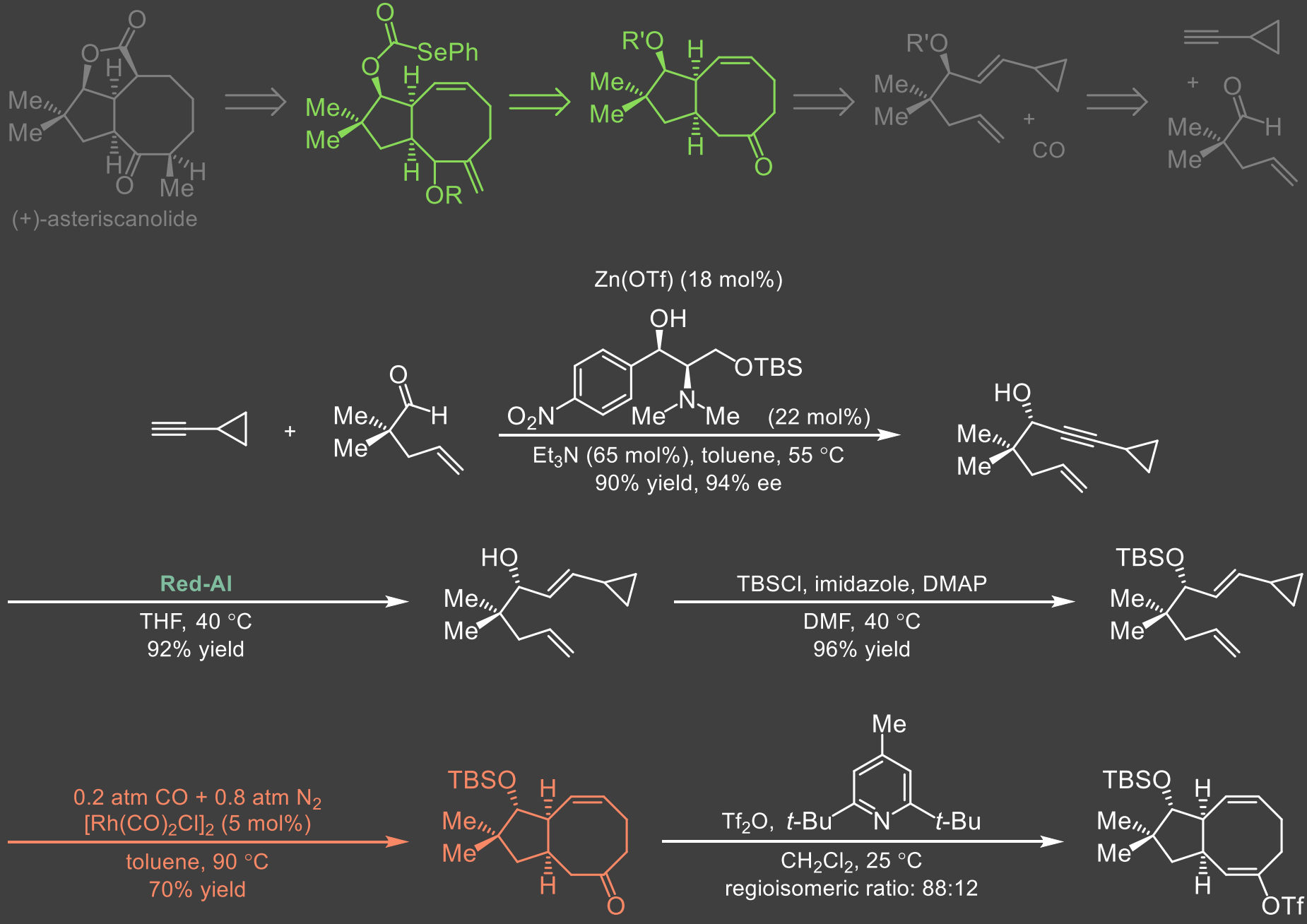

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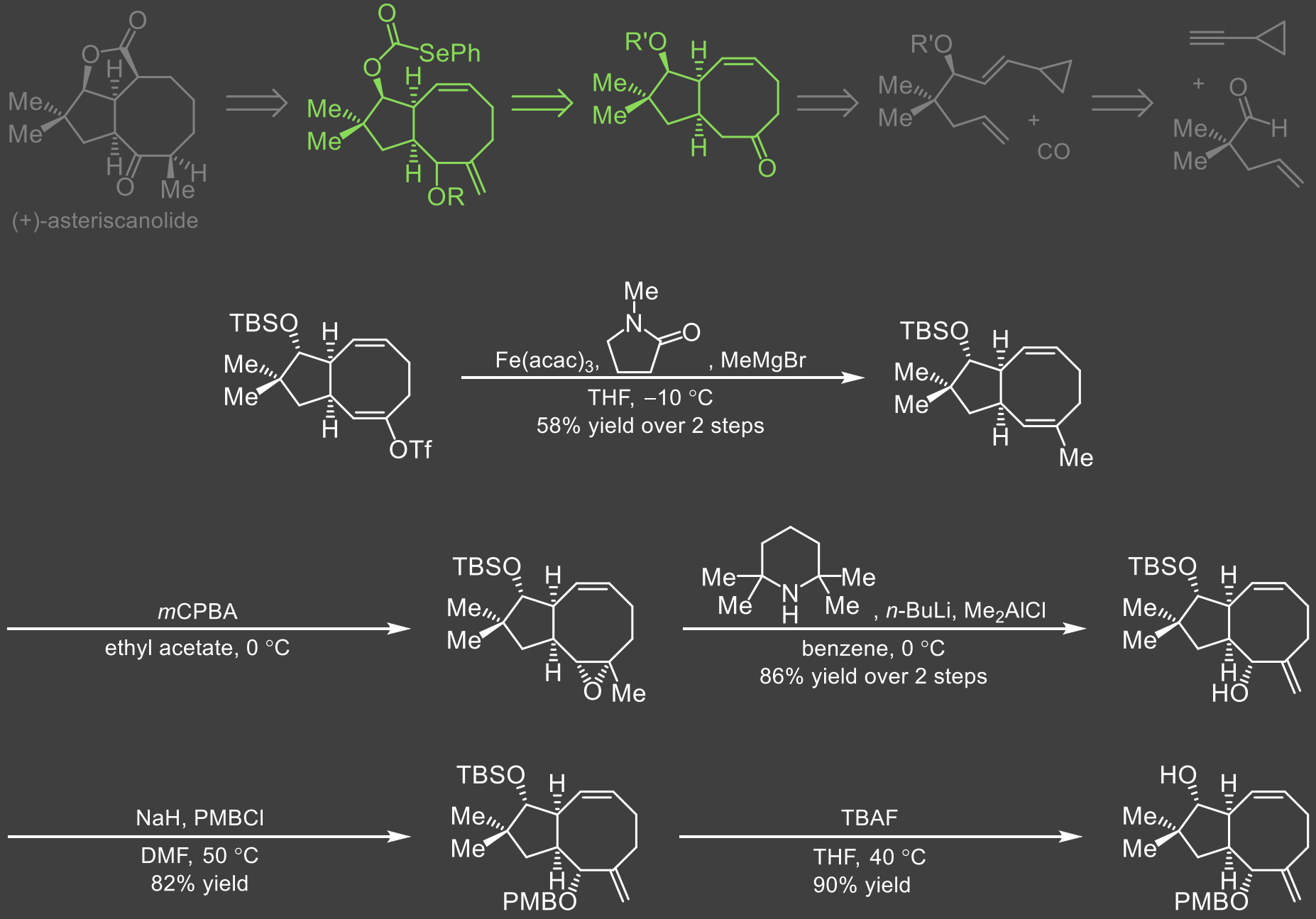

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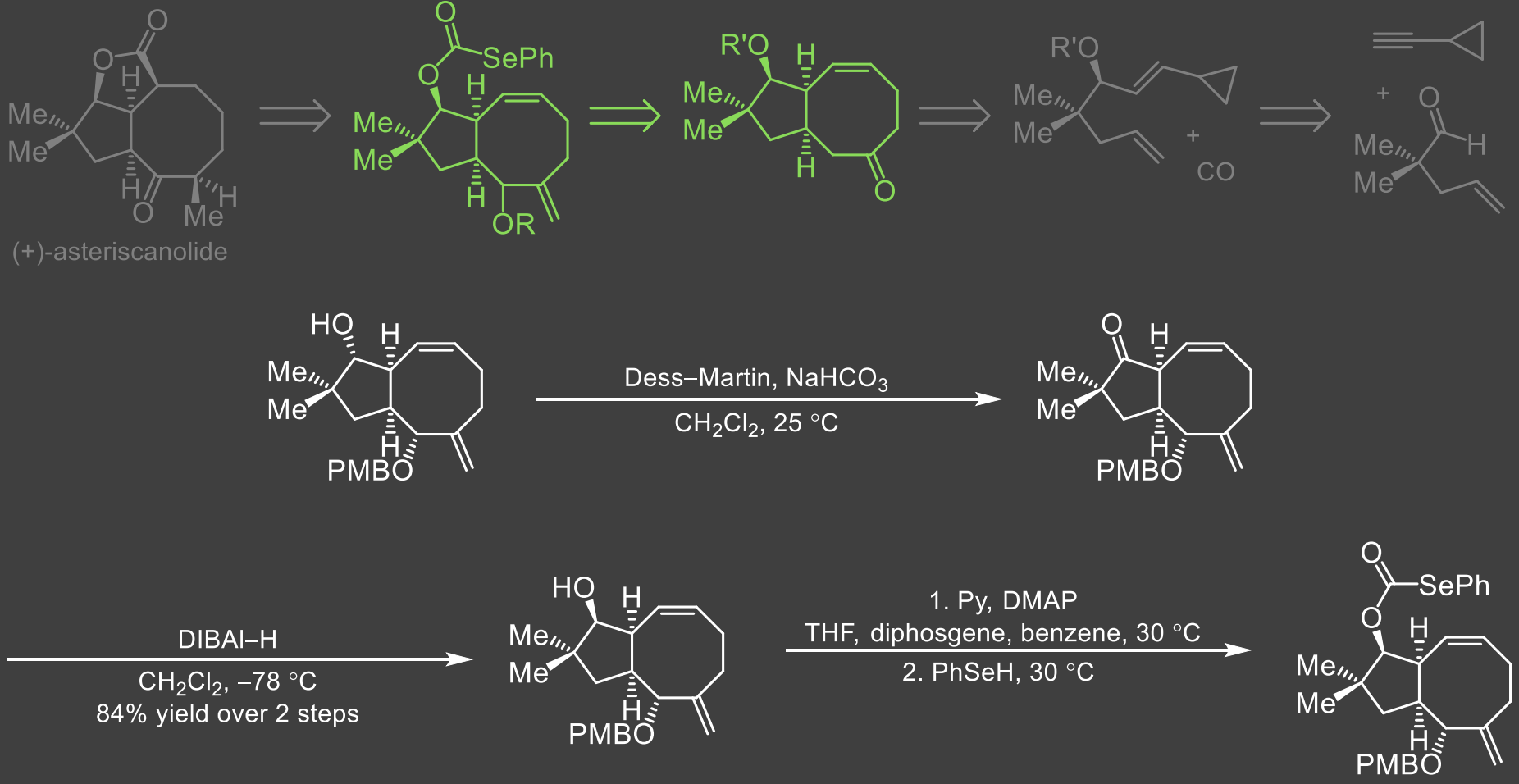

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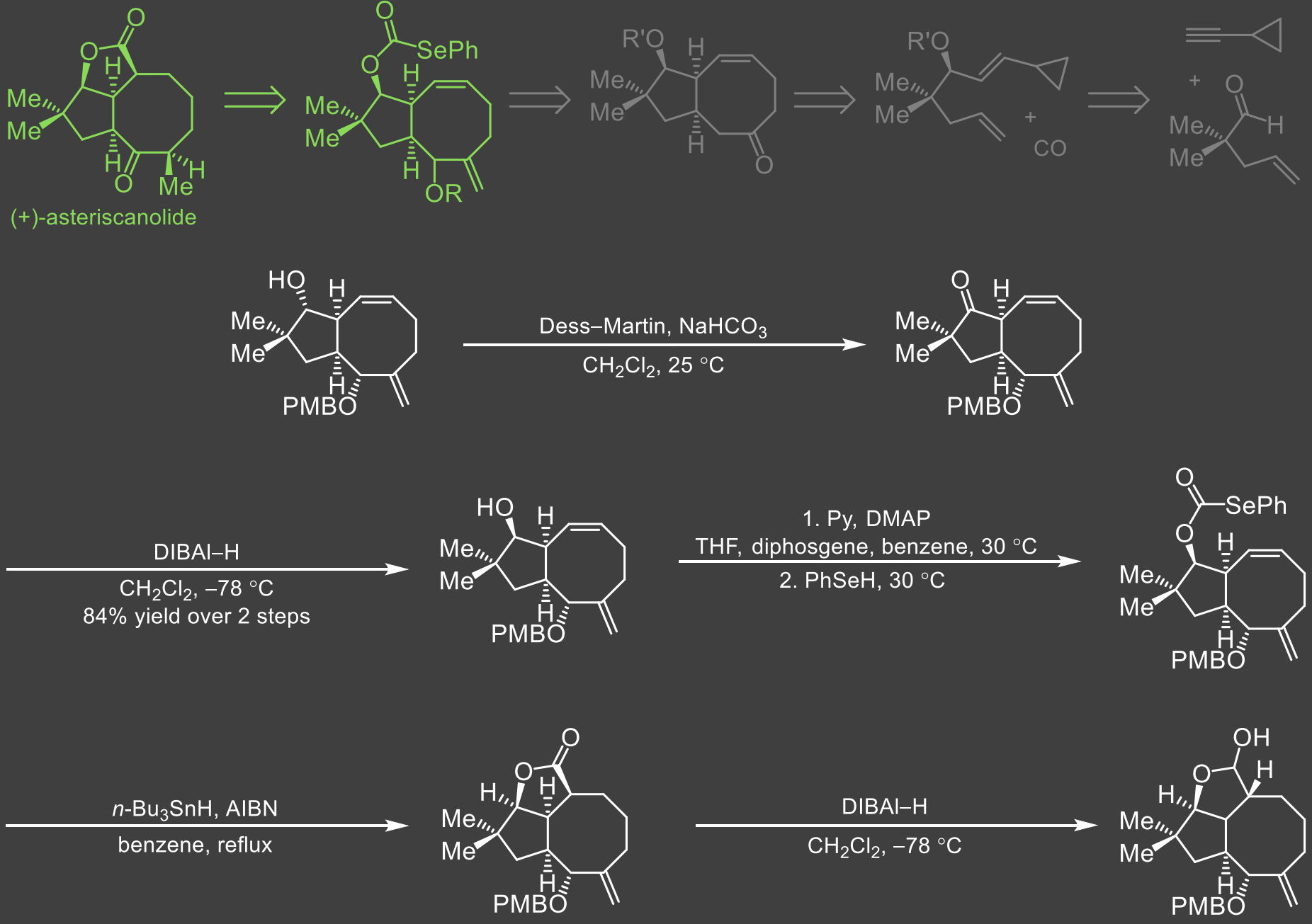

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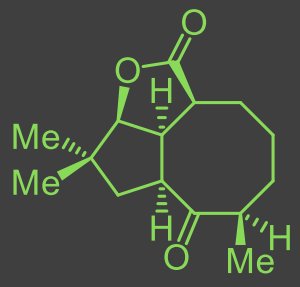
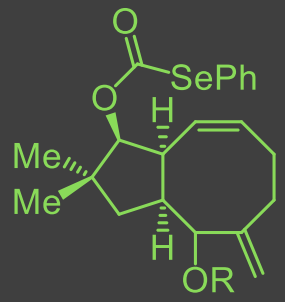
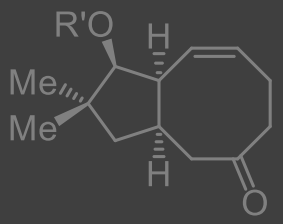
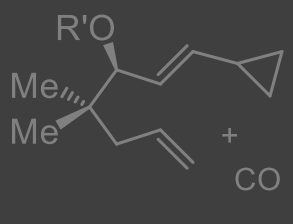
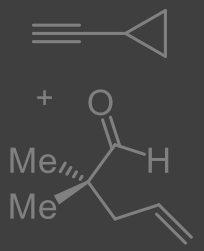


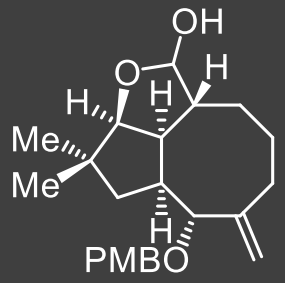
(+)-asteriscanolide







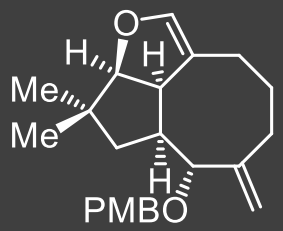




CH_3SO_2Cl, Et_3N

CH_2Cl_2, 25 °C

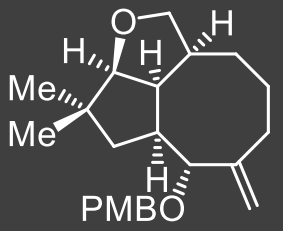
85% over two steps



H_2, Pd/C

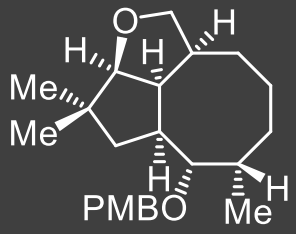
EtOH, 60 °C

dr = 66:34



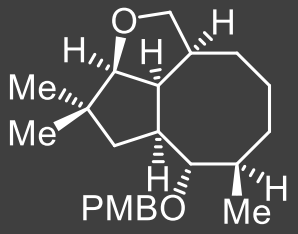
DMP, $NaHCO_3$

CH_2Cl_2, 25 °C



46% yield

+



24% yield

1. TMSOTf, 2,6-lutidine

CH_2Cl_2, 25 °C

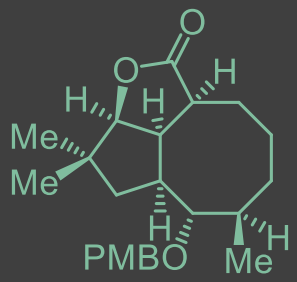
2. 1 M HCl, Et_2O, 25 °C

48% brsm

$RuCl_3$, $NaIO_4$

$CH_3CN/CCl_4/H_2O$ (1:1:1), 25 °C

59% yield



(+)-asteriscanolide

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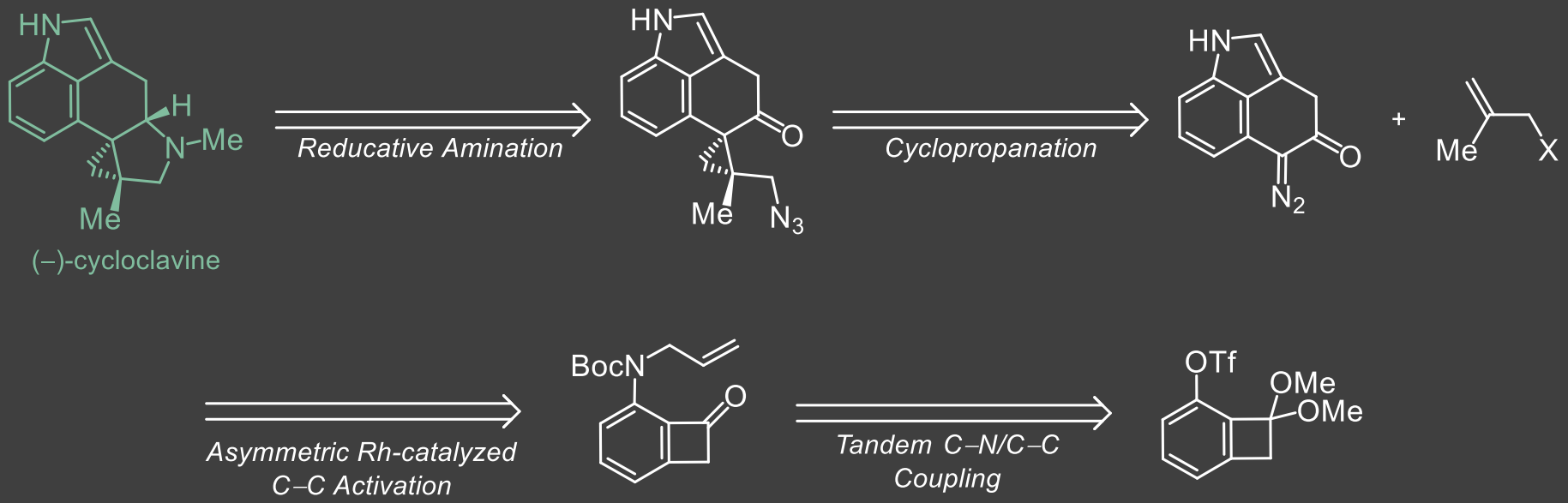
(–)-Cycloclavine



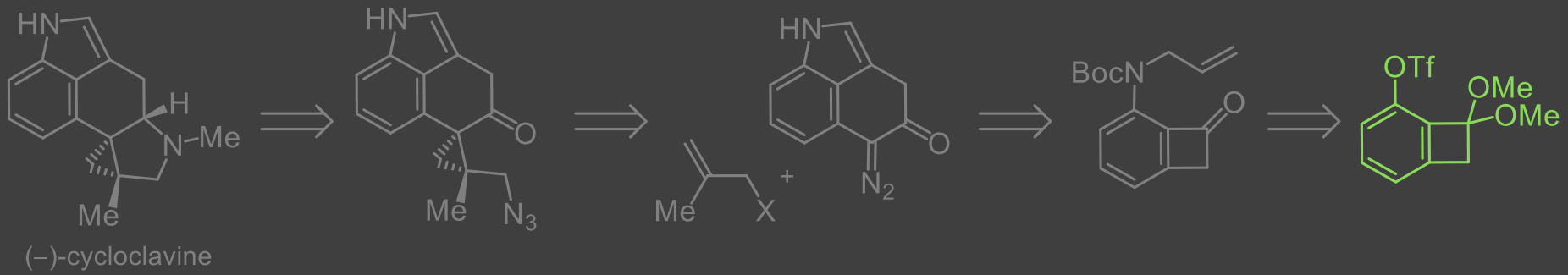
Characteristics:

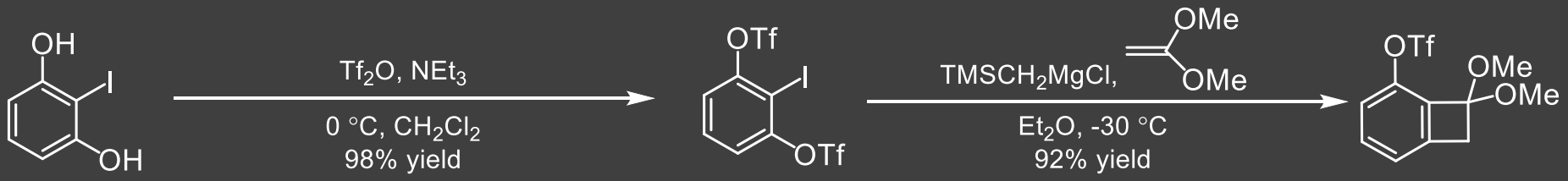
- Isolated from *seeds of Ipomoea hildebrantii vatke* in 1969, and later from *Aspergillus japonicas* in 1982
- First enantioselective total synthesis was accomplished in 2017 by the Wipf Group.
- Exhibits promising insecticidal and antiparasitic properties

Synthetic Challenges:

- penta-cyclic core with a unique [3.1.0] structural motif
- Sterically congested cyclopropane ring
- 3 contiguous stereogenic centers; 2 adjacent quaternary carbons

Deng, L; Chen, M.; Dong, G. *J. Am. Chem. Soc.*, **2018**, *140* (30), 9652





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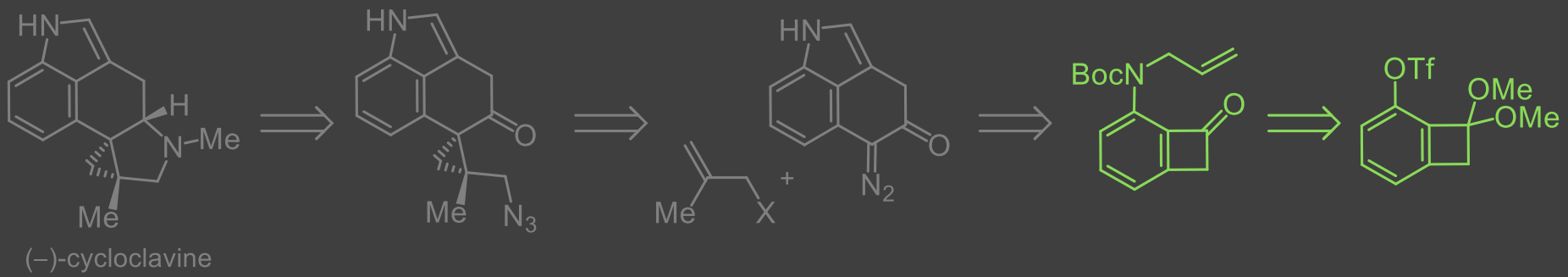

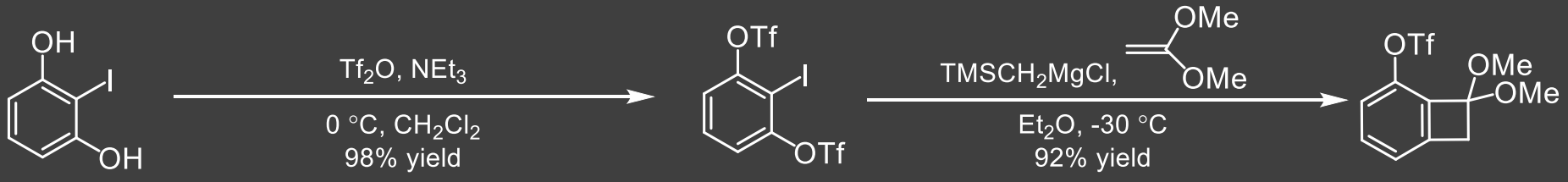

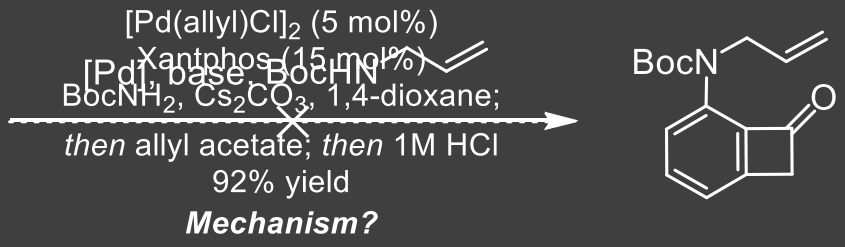

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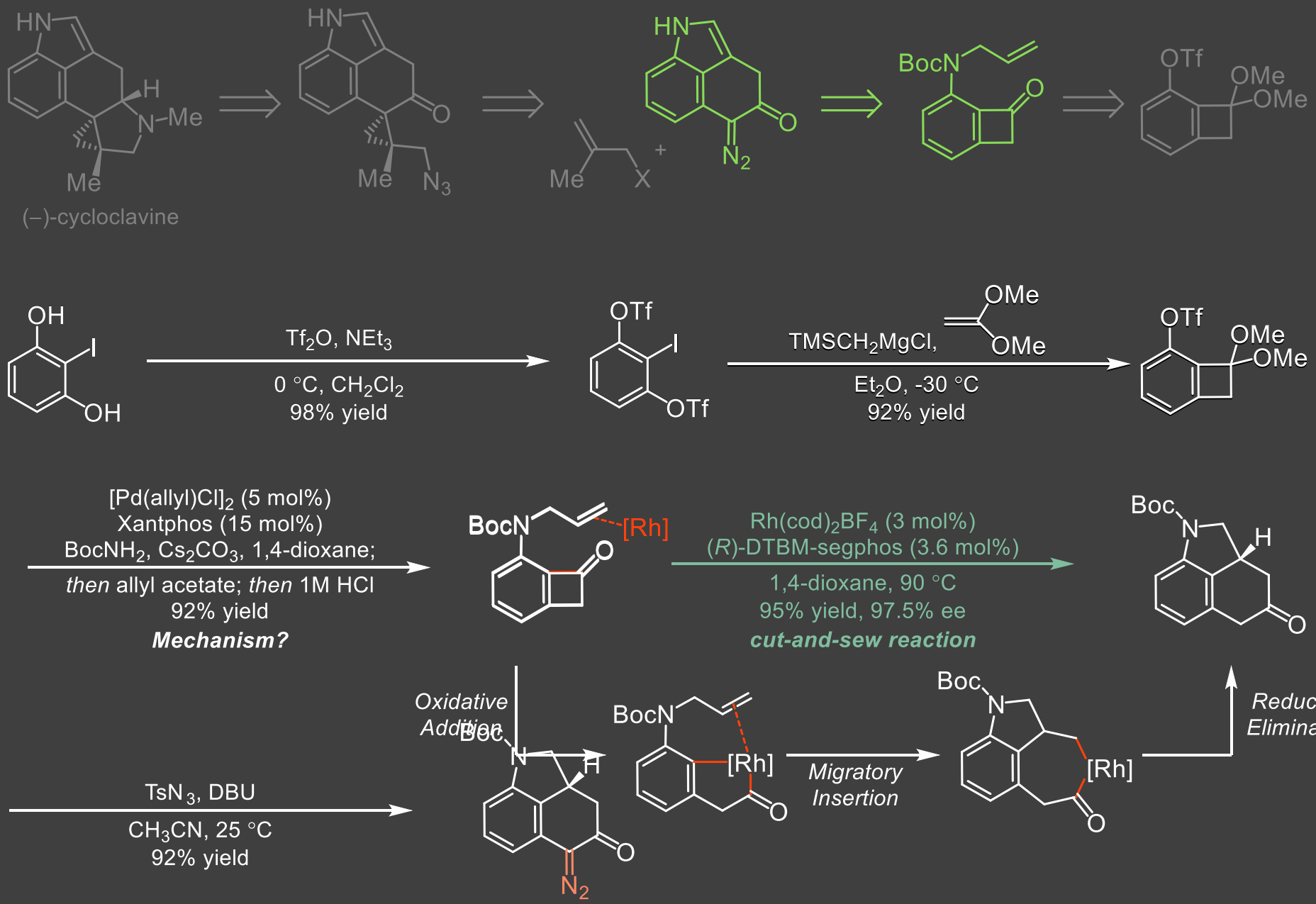

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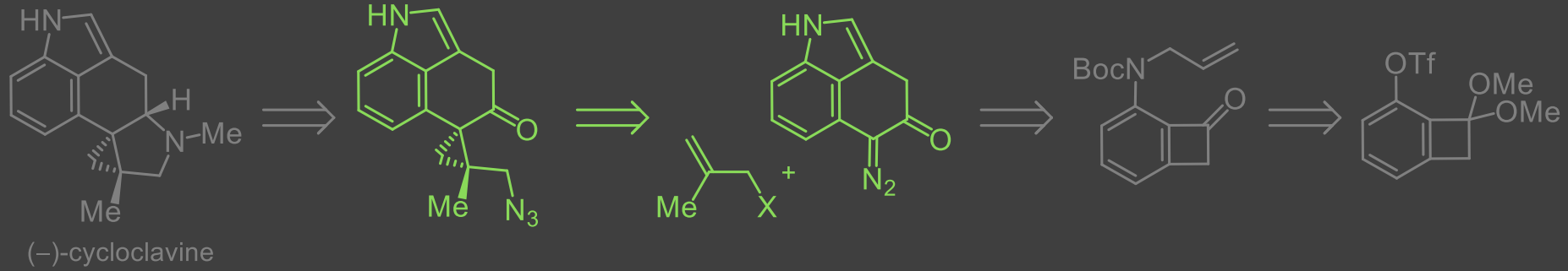

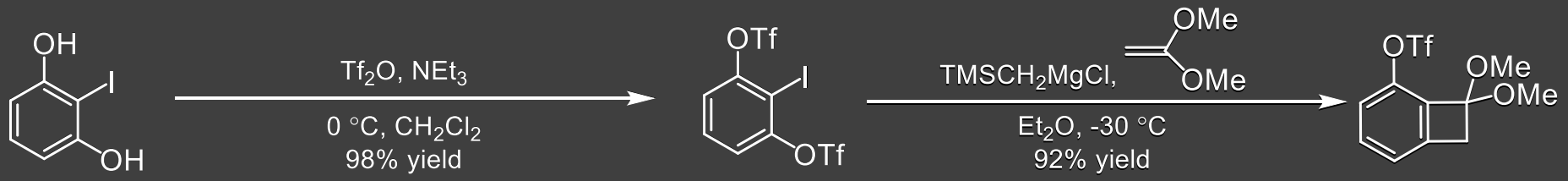

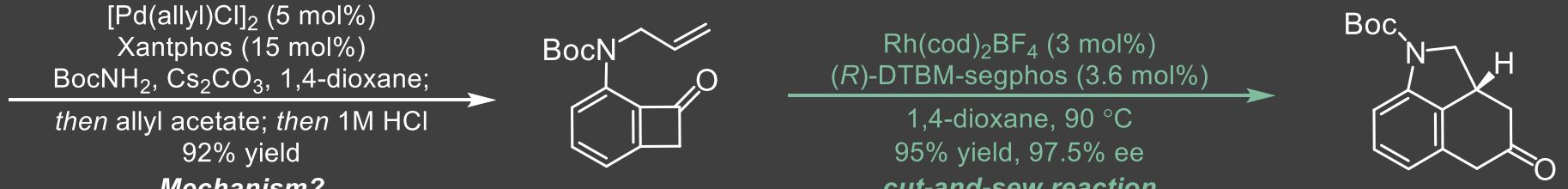

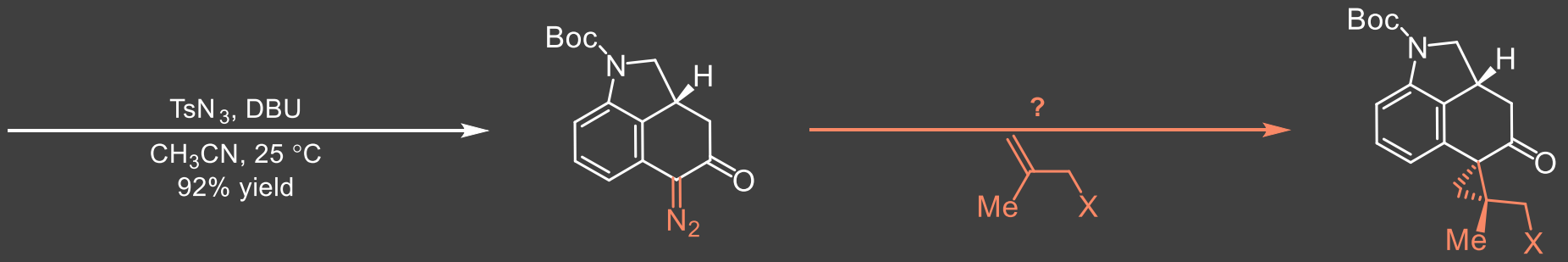

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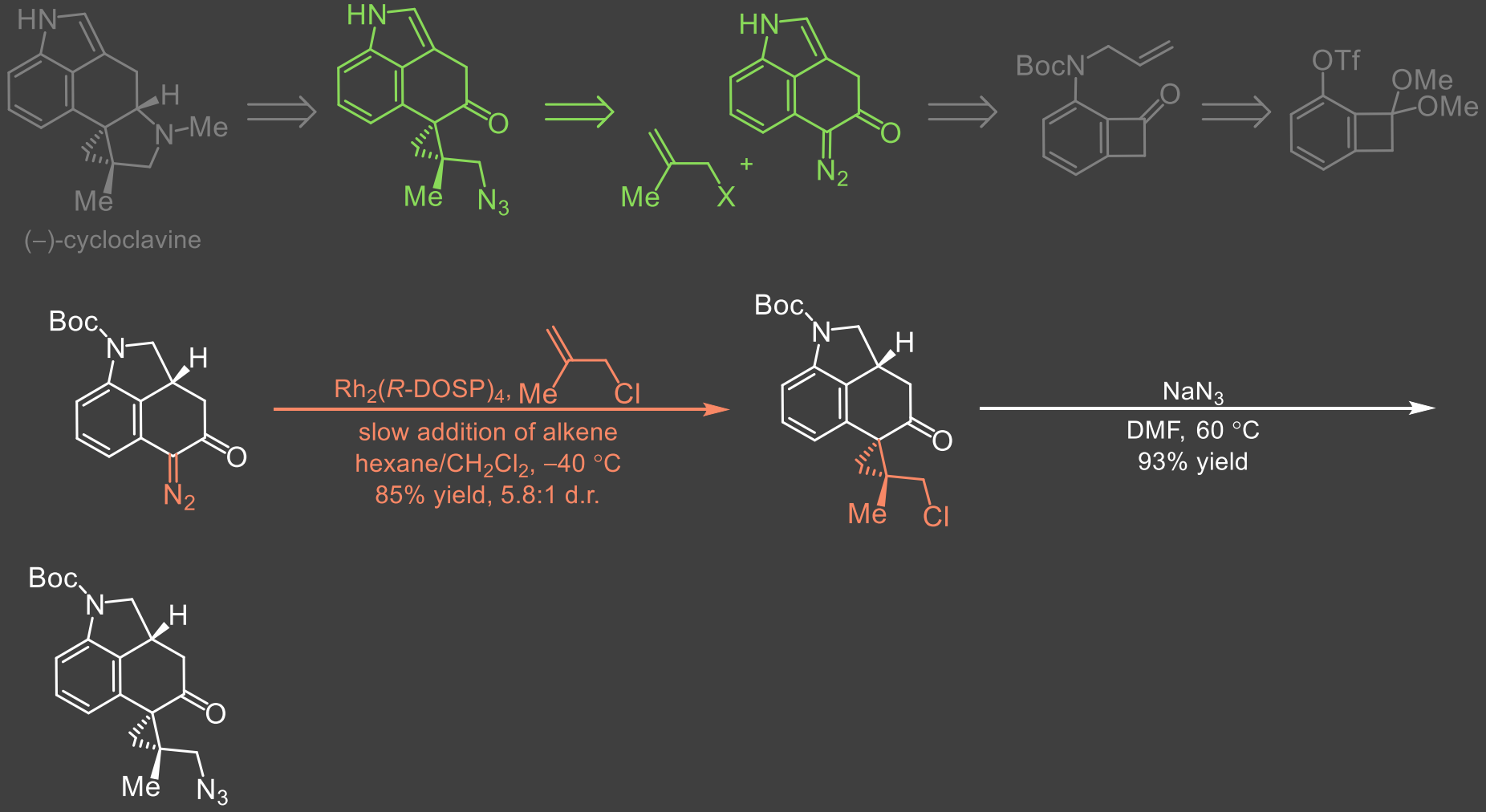

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(–)-cycloclavine

Rh_2(*R*-D

slow a

hexan

85%

NaN_3

DMF, 60 °C

93% yield

1. PPh_3, Na

BH_3CN

TFA

2 steps

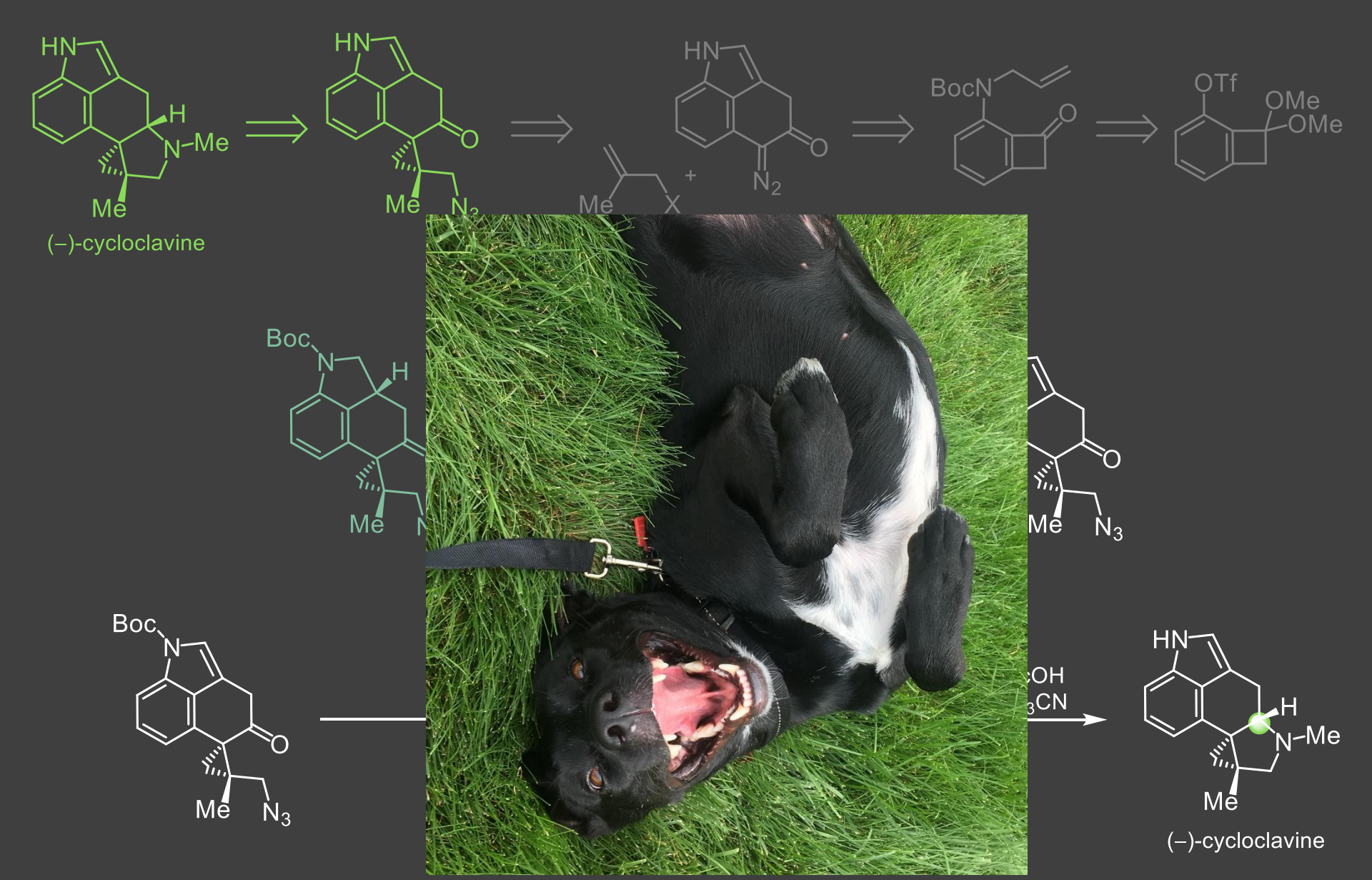
1

$(PhSeO)_2O$

THF, 55 °C

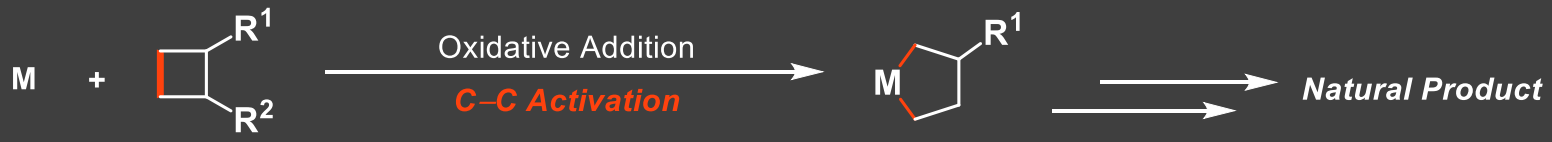
indole

Deng, L; Chen, M.; Dong, G. *J. Am. Chem. Soc.*, **2018**, *140* (30), 9652

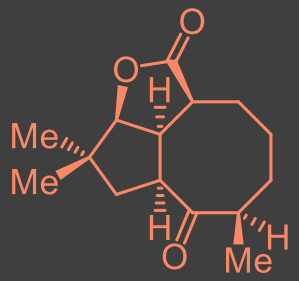


Deng, L; Chen, M.; Dong, G. *J. Am. Chem. Soc.*, **2018**, *140* (30), 9652

C—C Activation in Total Synthesis



19 steps
3.8% overall yield



(+)-asteriscanolide

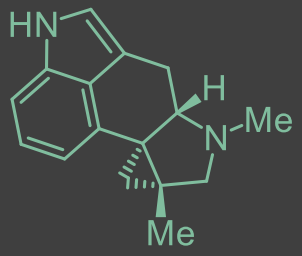
Liang, Y; Jiang, X; Yu, Z.–X.
Chem. Commun., **2011**, *47*, 6659

Previously

11 steps
1.3% overall yield

Limanto, J; Snapper, M. L.
J. Am. Chem Soc., **2000**, *122*, 8071

10 steps
30% overall yield



(–)-cycloclavine

Deng, L; Chen, M.; Dong, G.
J. Am. Chem. Soc., **2018**, *140* (30), 9652

Previously

8 steps
7.1% overall yield

McCabe, S. R.; Wipf, P. *Angew. Chem., Int. Ed.* **2017**, *56*, 324

Is C—C Activation always necessary?
Let's take a look at some other ways to synthesize these molecules….