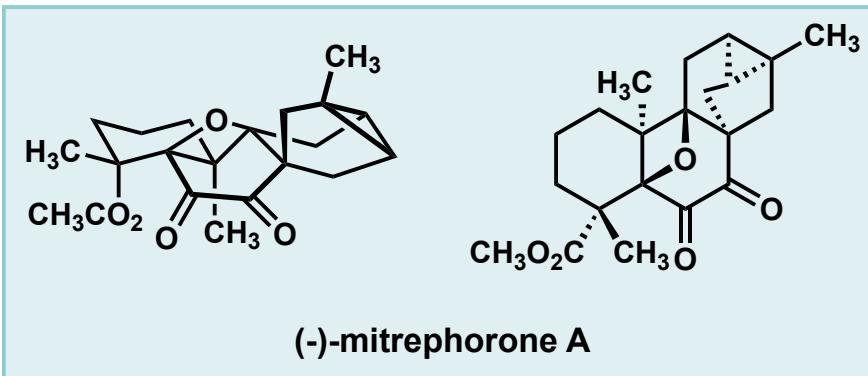


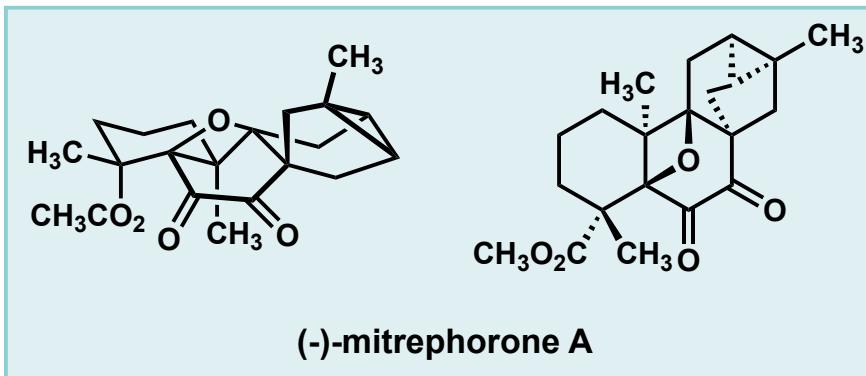
Mitrephorone 2: Electric Boogaloo



Nicholas A. Falcone
Literature Group Meeting
Spooktober 30th, 2020

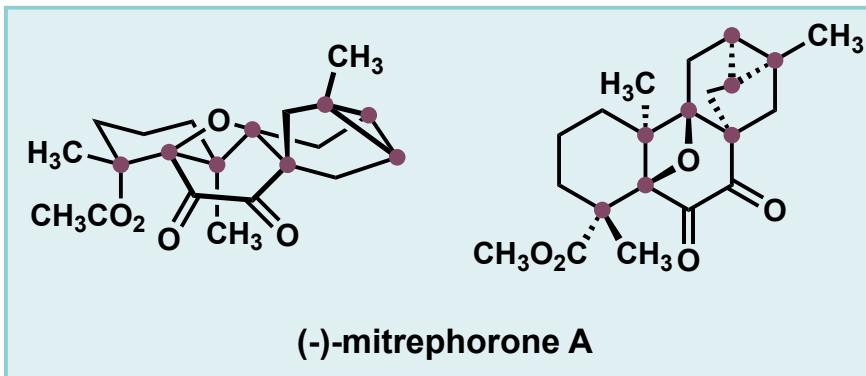
Carreira, E. M. et al. J. Am. Chem. Soc. **2020**, 142, 17802.

(-)-Mitrephorone A: A Structurally Unique Terpenoid



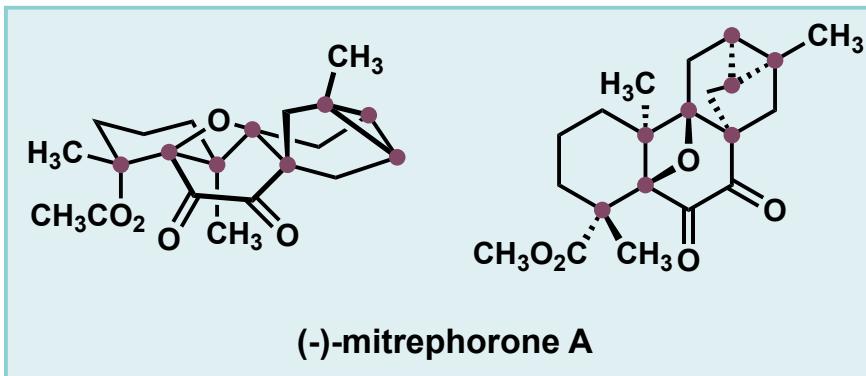
- trachylobane diterpenoid
- anticancer & antimicrobial properties
- tricyclo[3.2.1.0^{2,7}]octane
- Eight stereocenters

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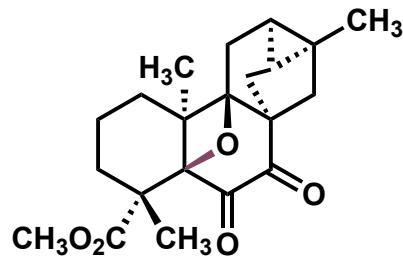
Total Syntheses:

Carreira, E. M. et al. *J. Am. Chem. Soc.* **2018**, *140*, 16704.
Magauer, T. et al. *J. Am. Chem. Soc.* **2019**, *141*, 19589.

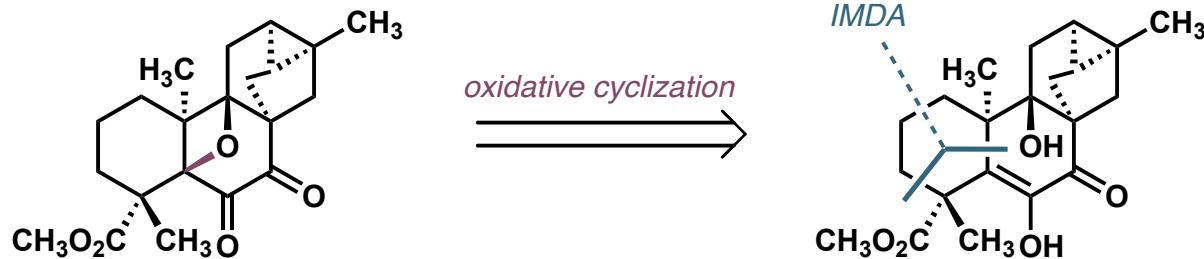
Semi-synthesis:

Renata, H. *Science*, **2020**, *369*, 799.

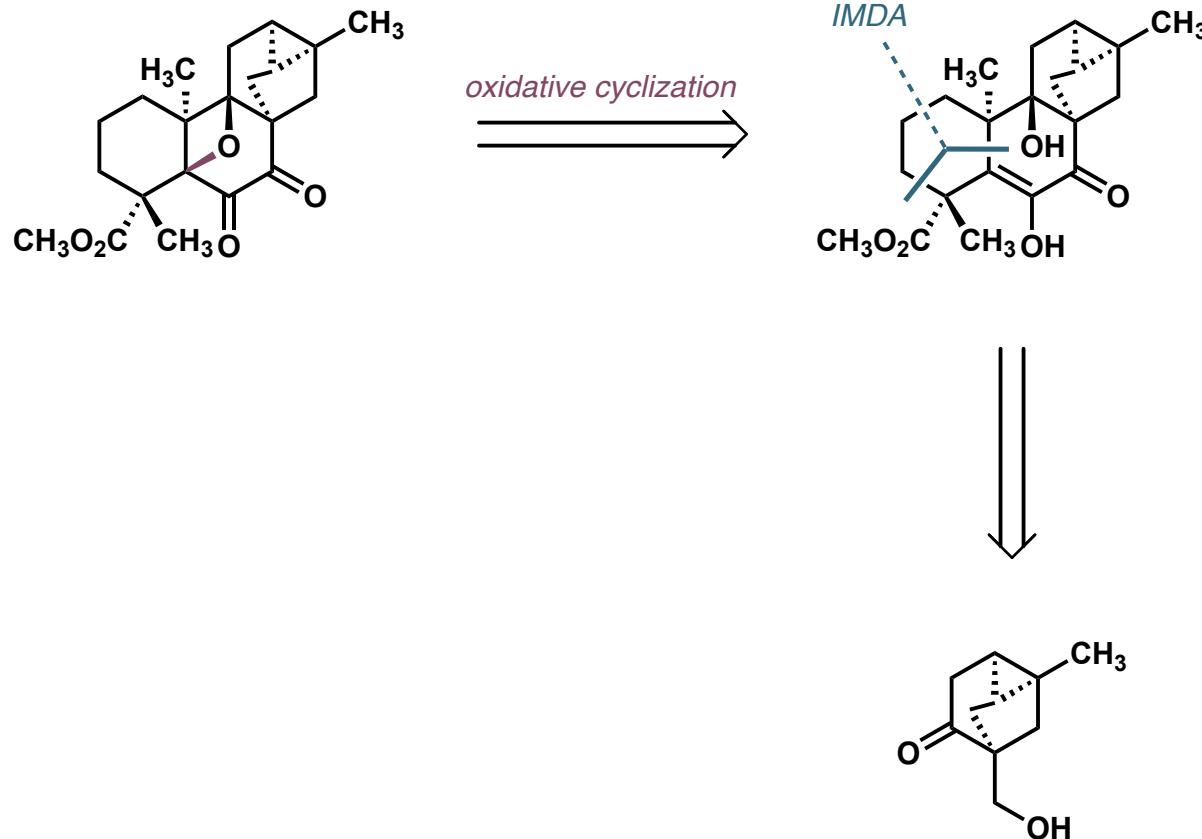
Carreira's 2018 Strategy



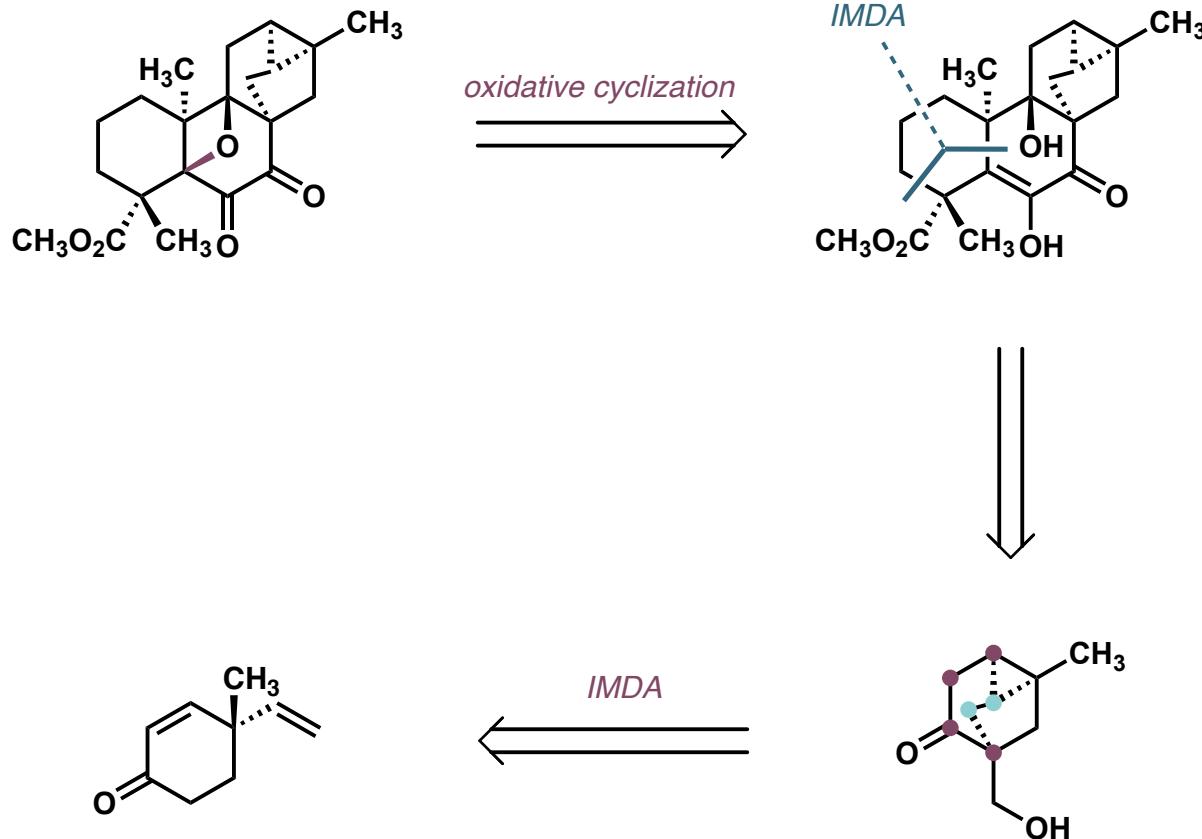
Carreira's 2018 Strategy



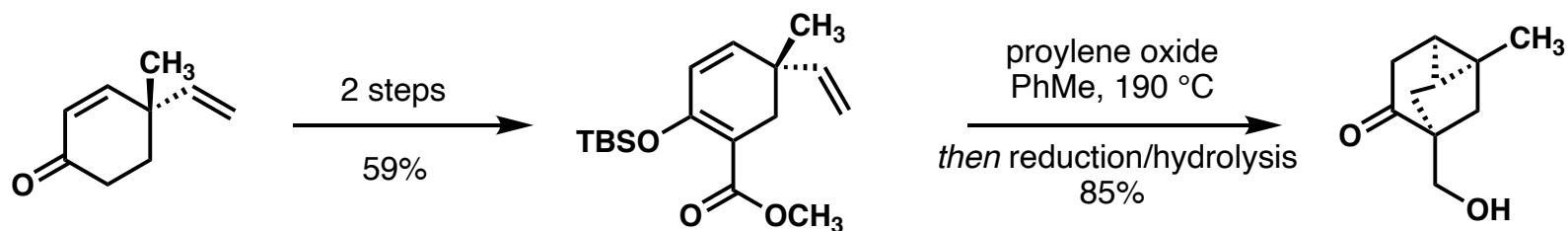
Carreira's 2018 Strategy



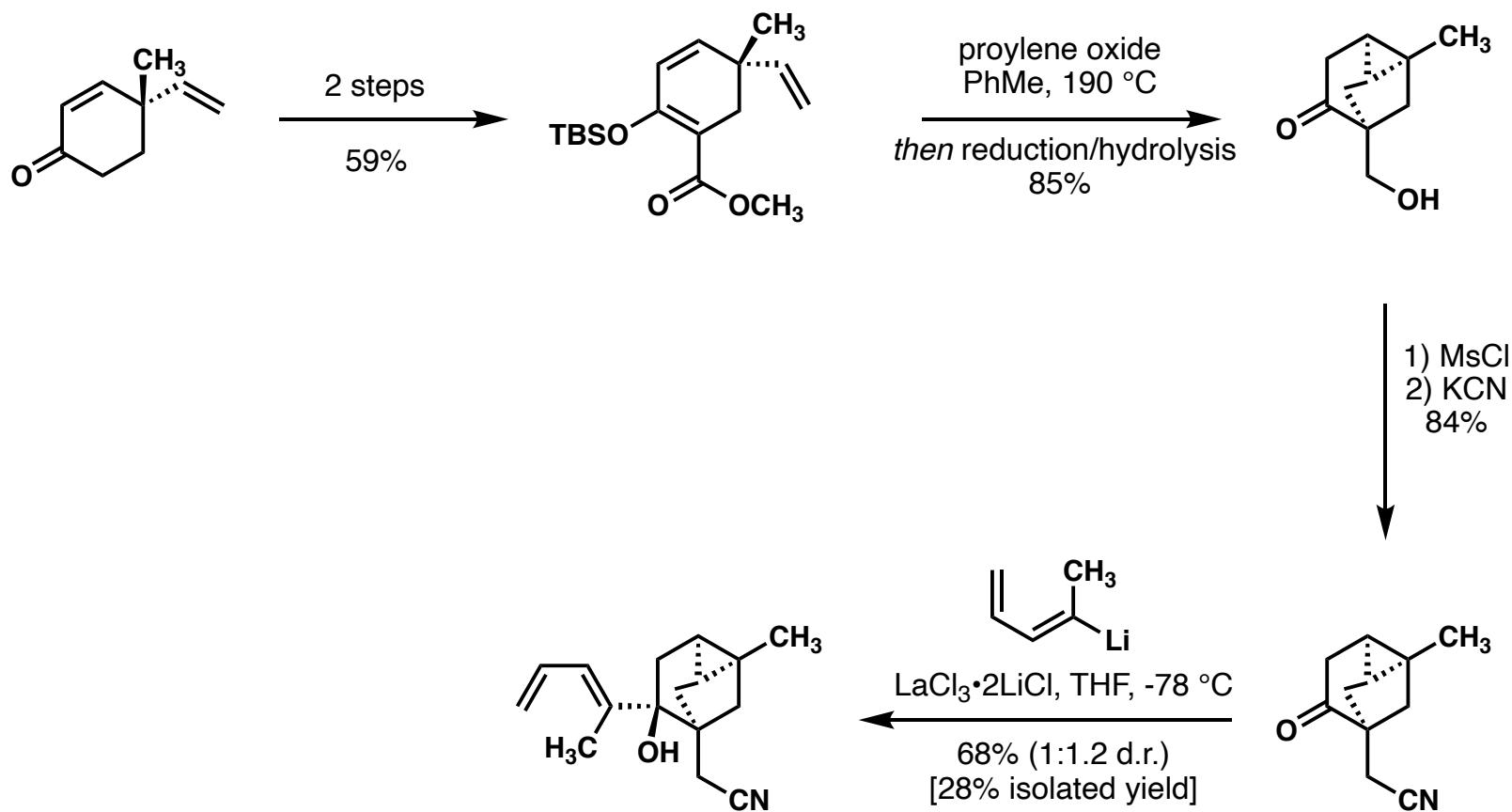
Carreira's 2018 Strategy



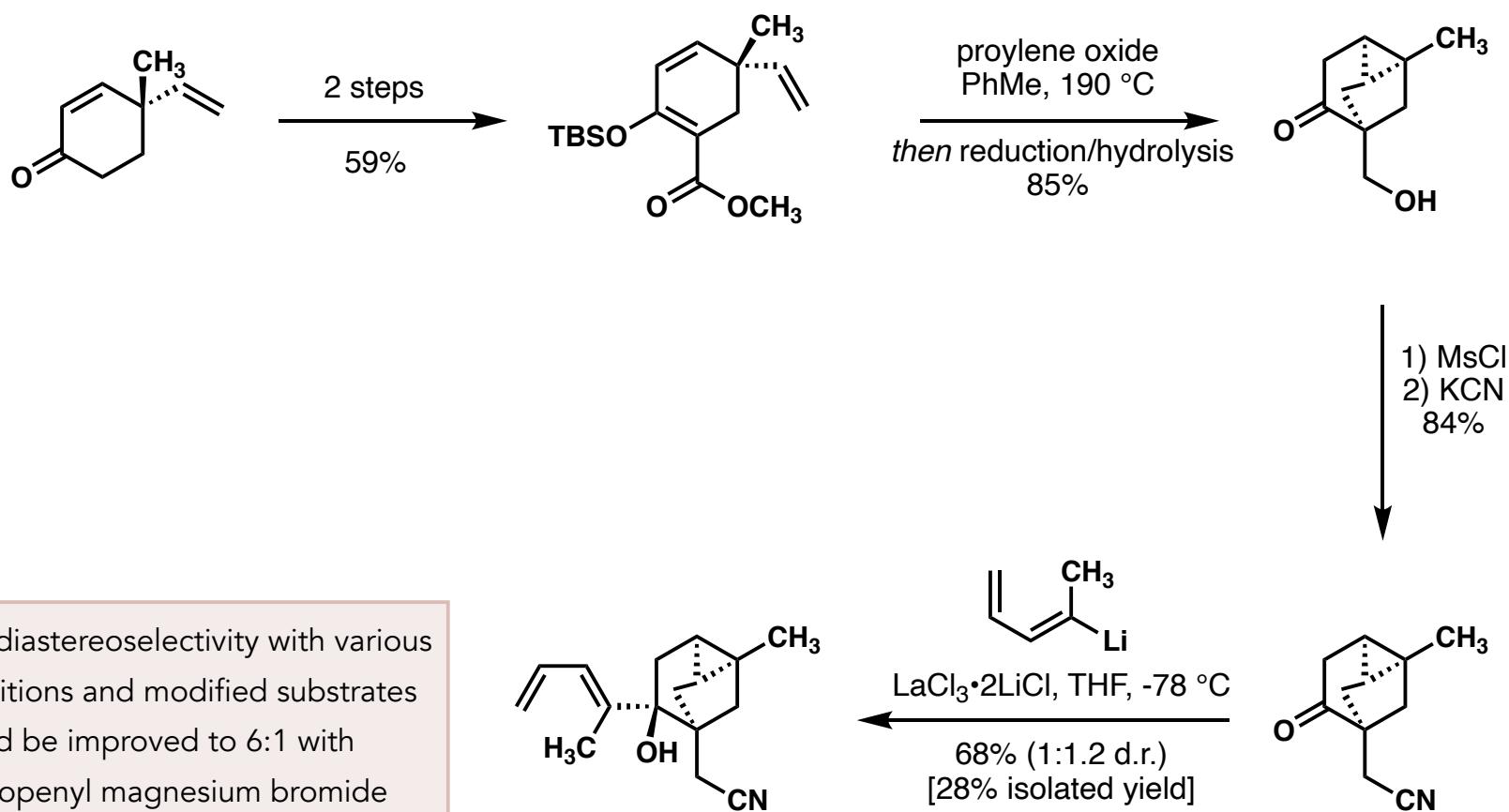
Carreira's 2018 Strategy



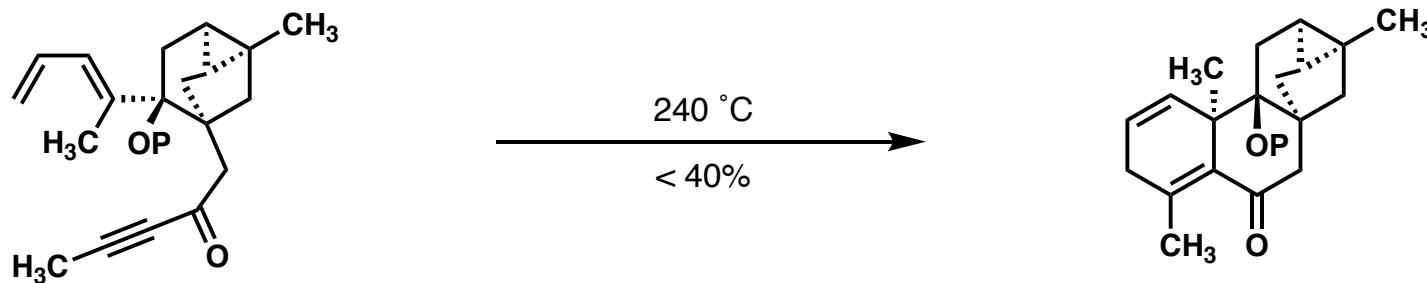
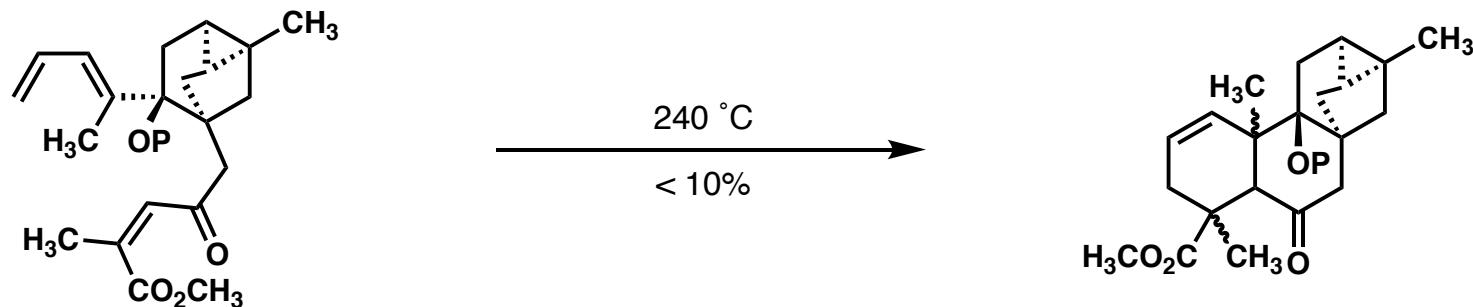
Carreira's 2018 Strategy



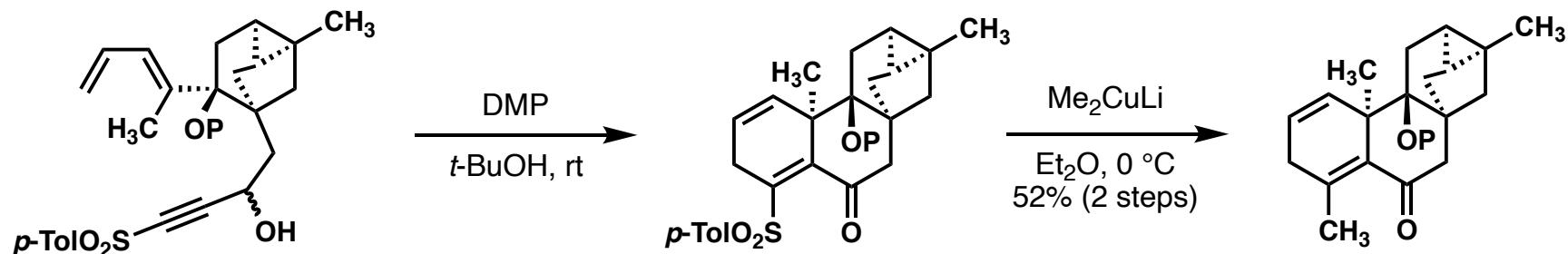
Carreira's 2018 Strategy



Exploring the Key Intramolecular Diels-Alder



Completing Mitrephorone A



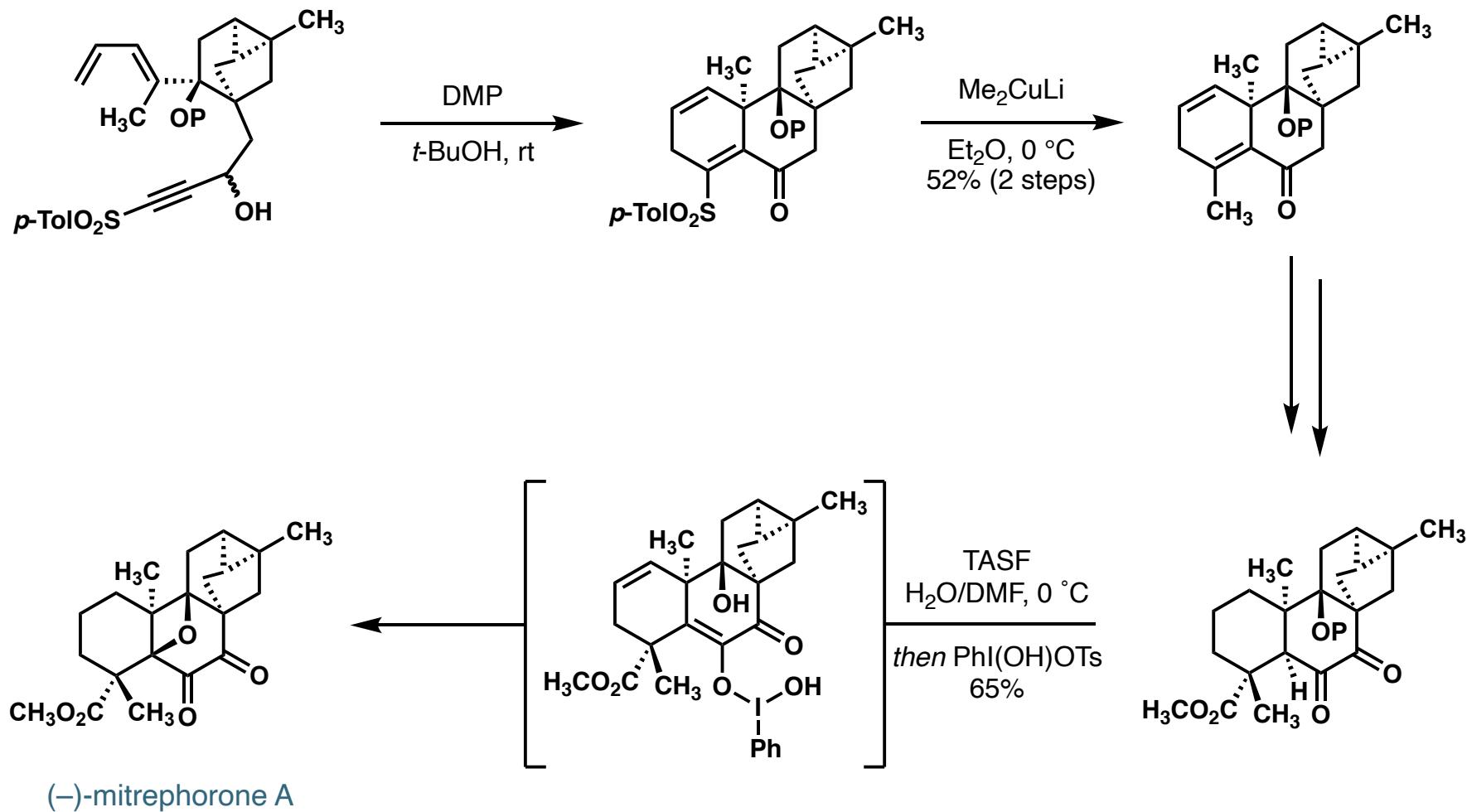
Shen, M.; Schultz, A. G. *Tetrahedron Lett.* **1981**, 22, 3347.

Fuchs, P. L. et al. *J. Am. Chem. Soc.* **2002**, 124, 11093.

Review on I(III) chemistry: Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, 517.

Carreira, E. M. et al. *J. Am. Chem. Soc.* **2018**, 140, 16704.

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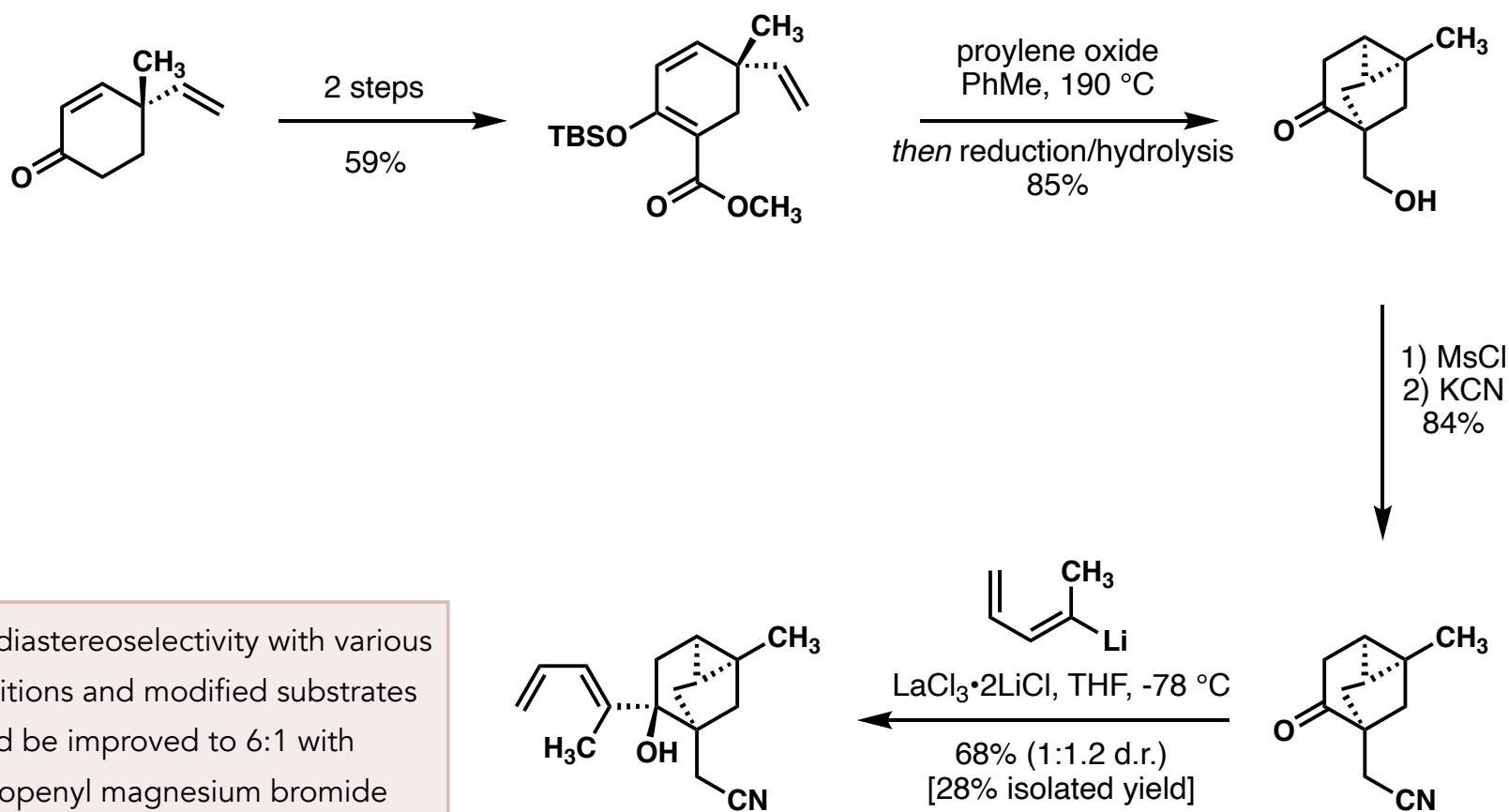
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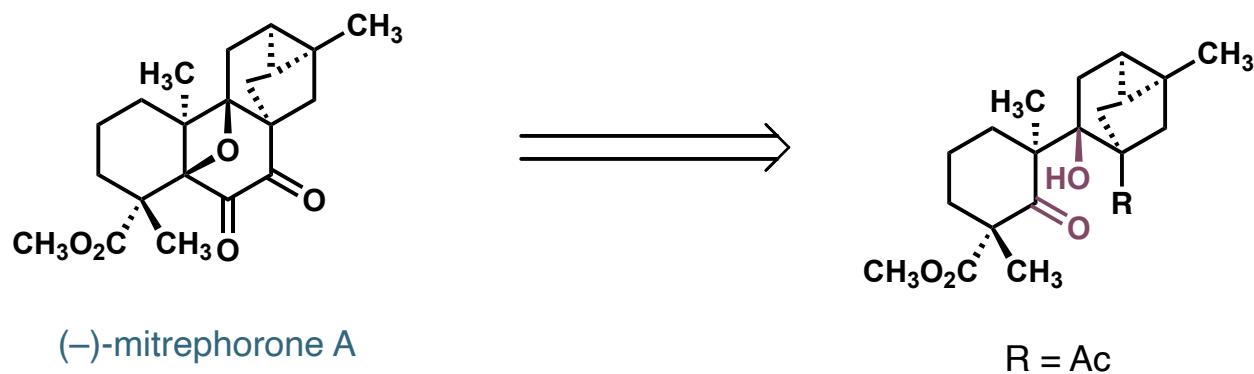
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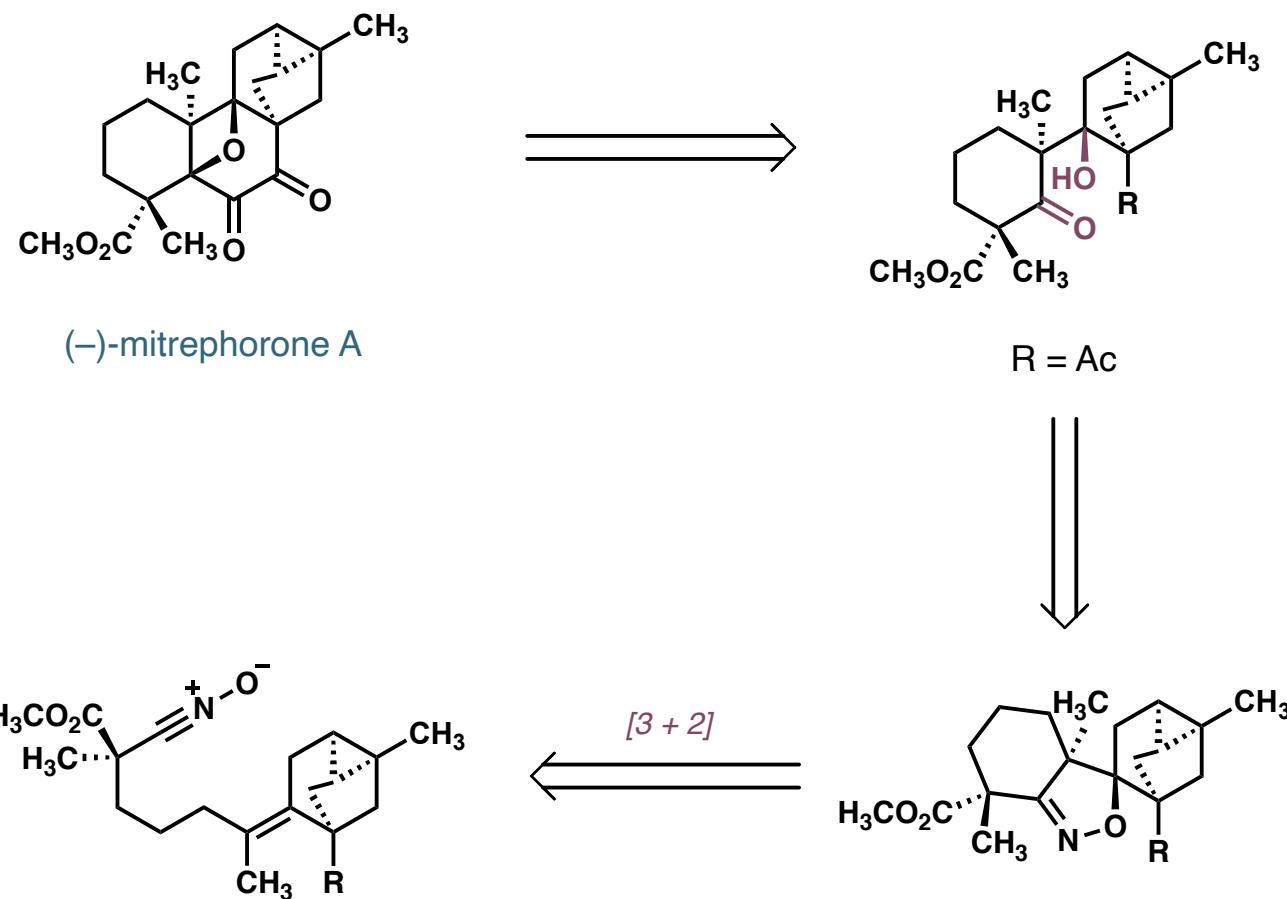
Carreira's 2018 Strategy



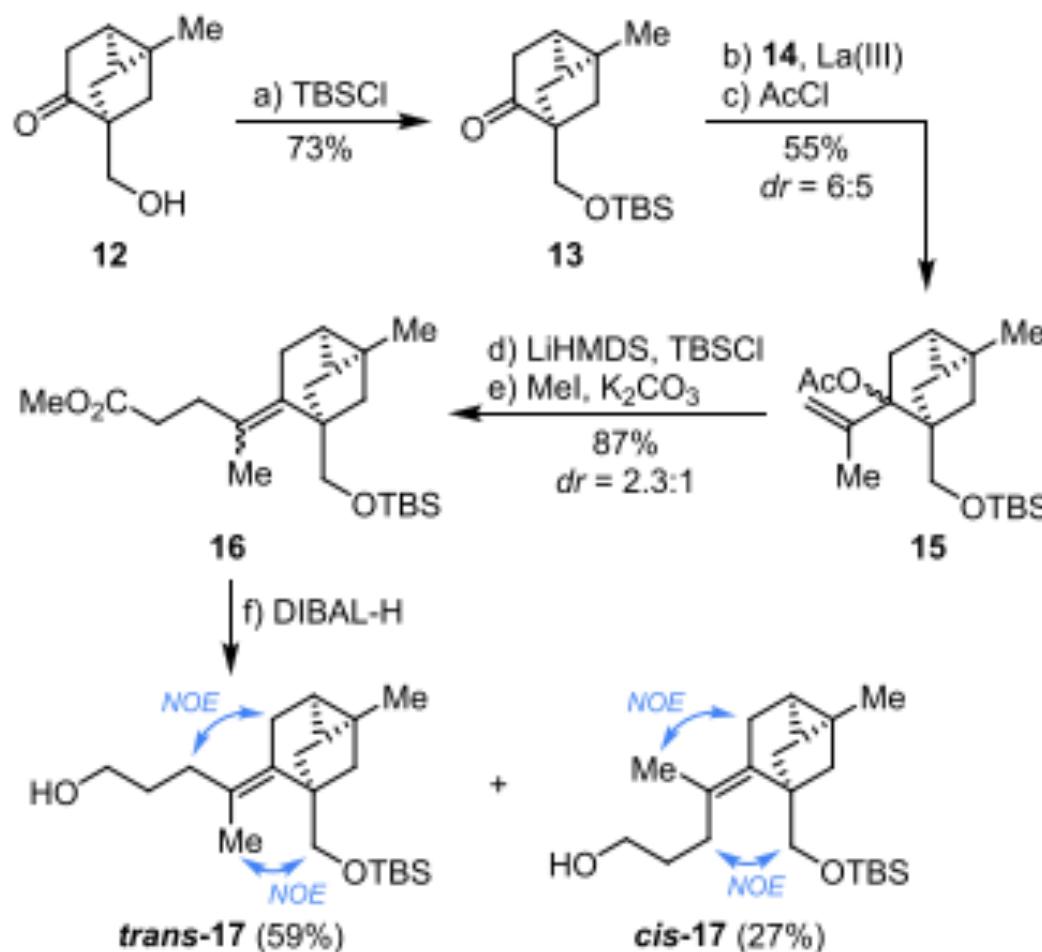
Revised Strategy



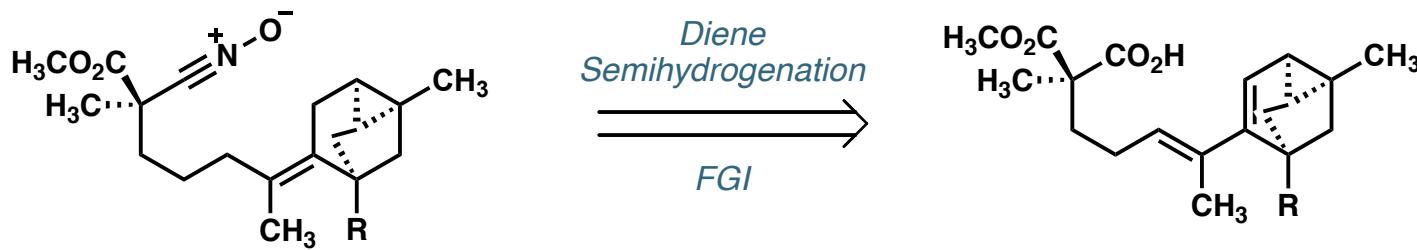
Revised Strategy



Initial Attempts to Prepare the Tetrasubstituted Olefin

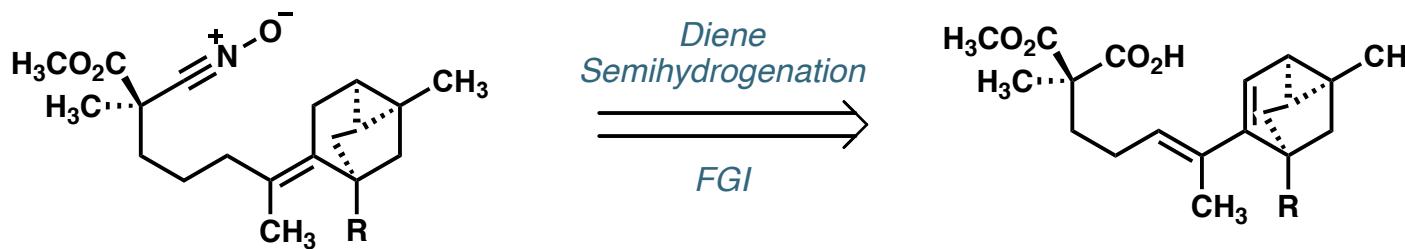


Revised Strategy

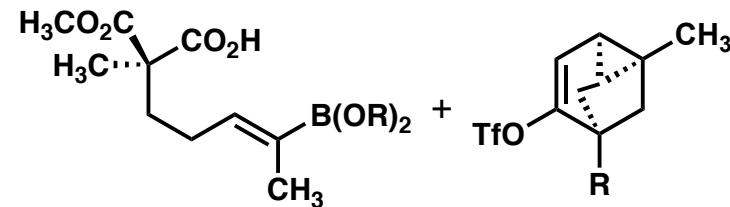


Major Challenge
Stereocontrolled synthesis of
a tetrasubstituted olefin

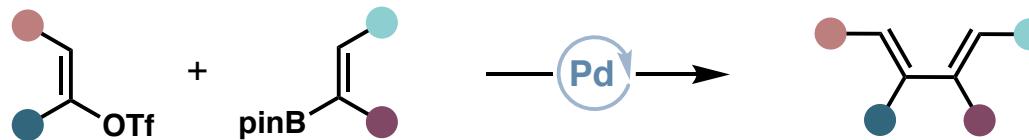
Revised Strategy



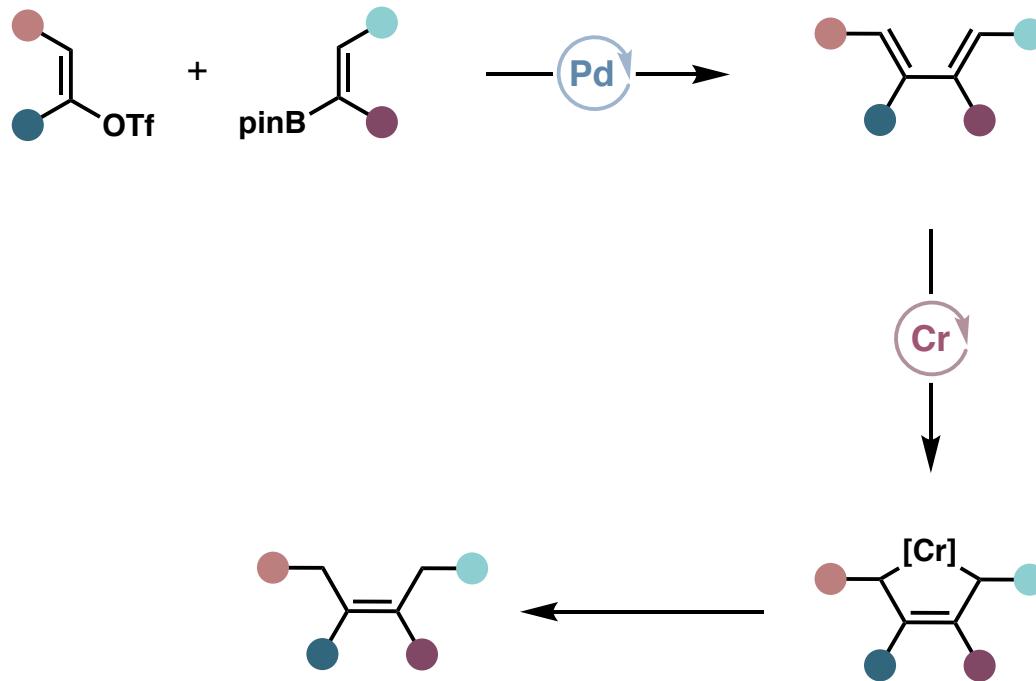
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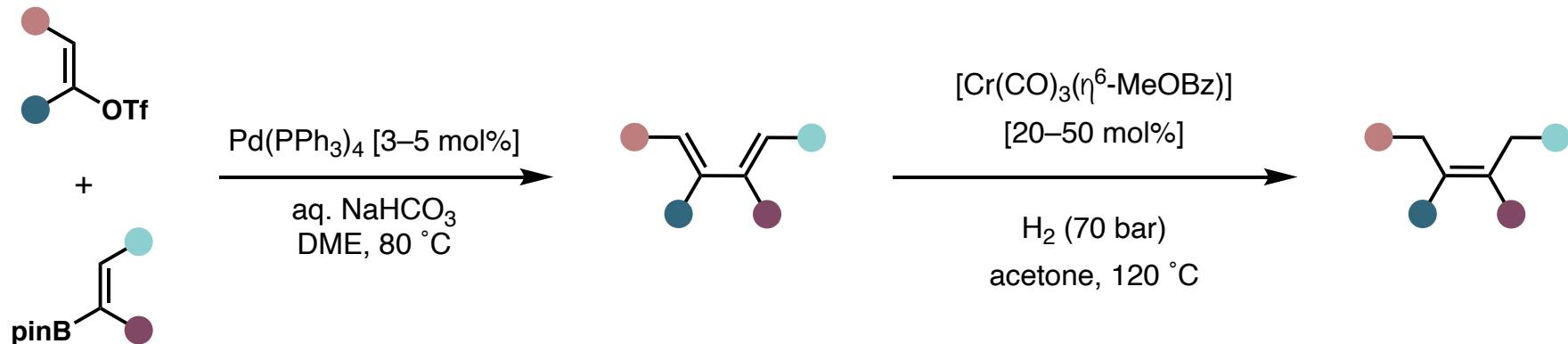
Concept Towards Tetrasubstituted Olefin Synthesis



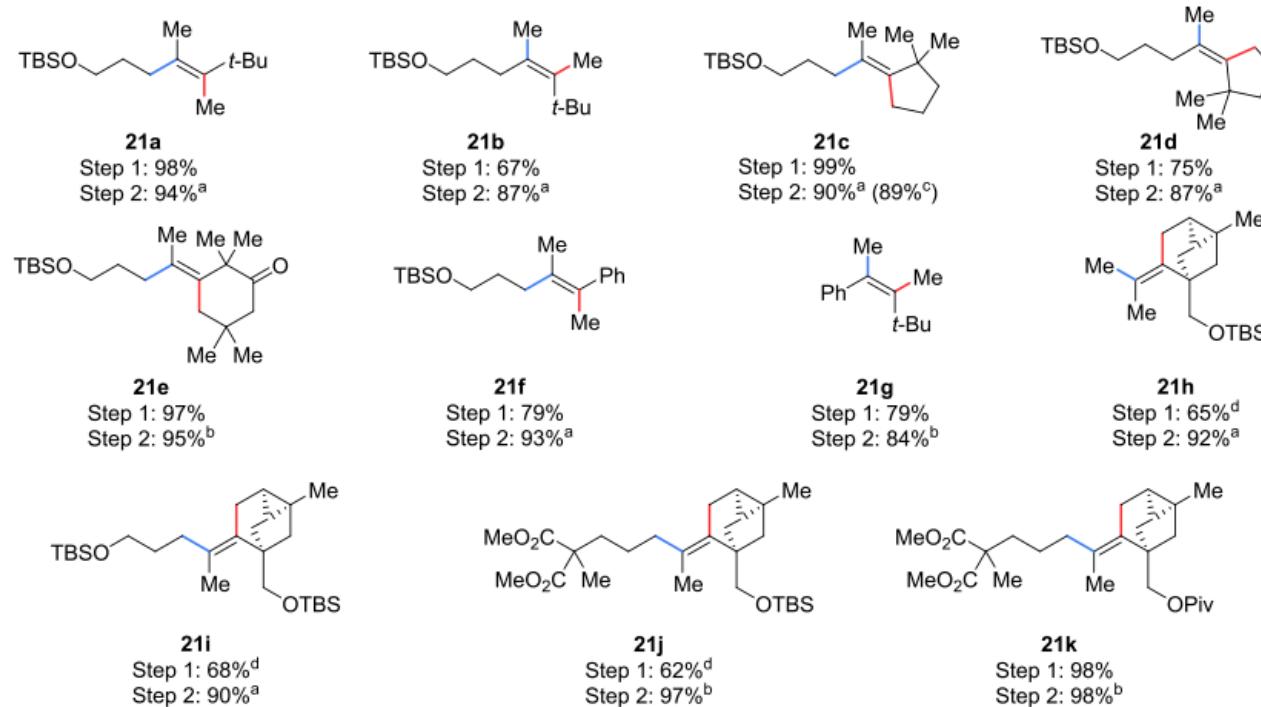
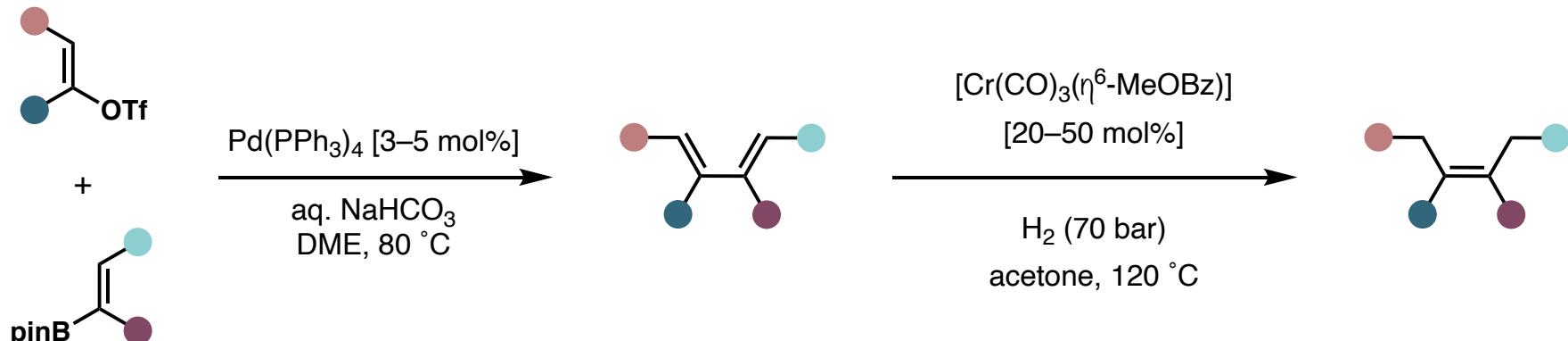
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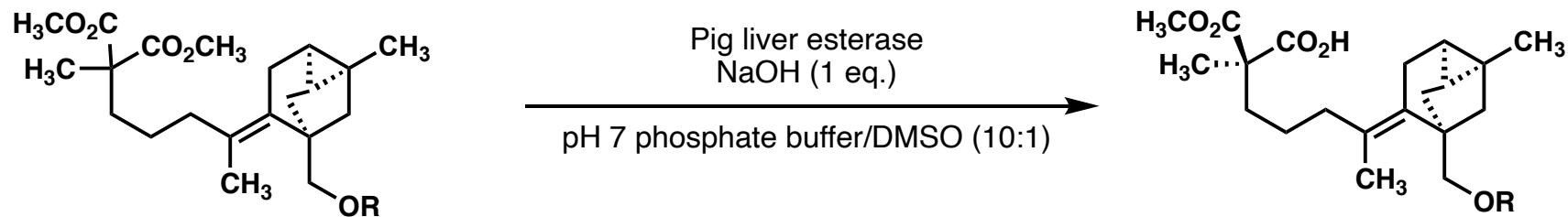
Concept Towards Tetrasubstituted Olefin Synthesis



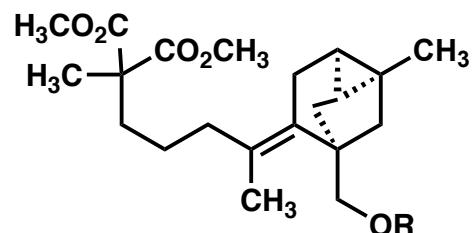
Concept Towards Tetrasubstituted Olefin Synthesis



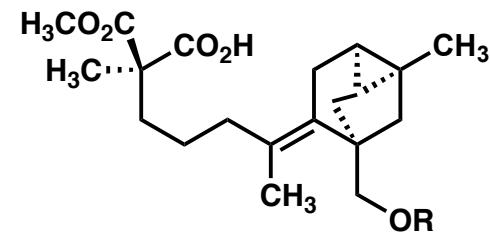
Stereoselective Monohydrolysis of the Diester



Stereoselective Monohydrolysis of the Diester



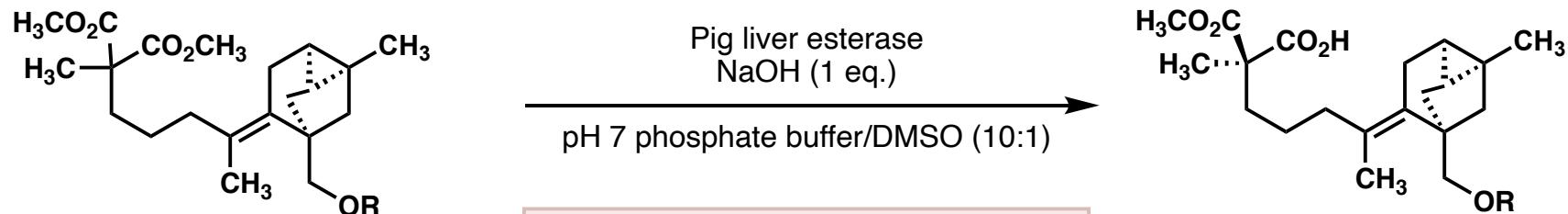
Pig liver esterase
NaOH (1 eq.)
pH 7 phosphate buffer/DMSO (10:1)



R = TBS : no conversion

R = H : full conversion, > 20:1 d.r.

Stereoselective Monohydrolysis of the Diester

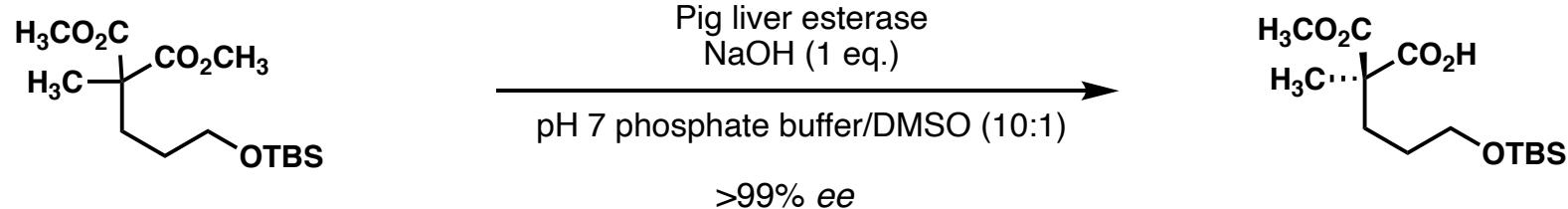


R = TBS : no conversion

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Solution: Install C-4 stereocenter directly with enantiopure cross-coupling partner

Preparation of an Enantiopure Coupling Partner

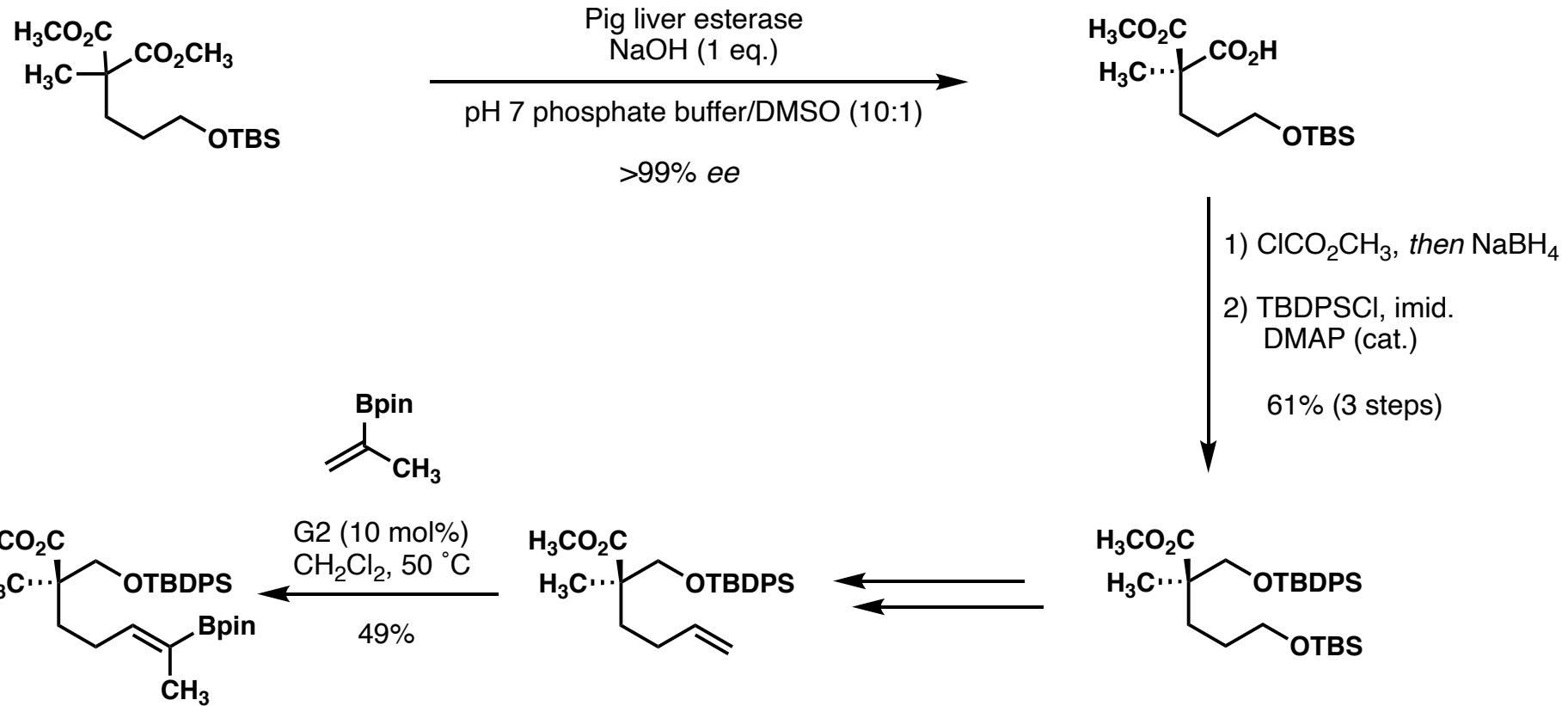


Prantz, K.; Mulzer, J. *Angew. Chem. Int. Ed.* **2009**, 48, 5030.

Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, 41, 3171.

Carreira, E. M. et al. *J. Am. Chem. Soc.* **2020**, 142, 17802.

Preparation of an Enantiopure Coupling Partner

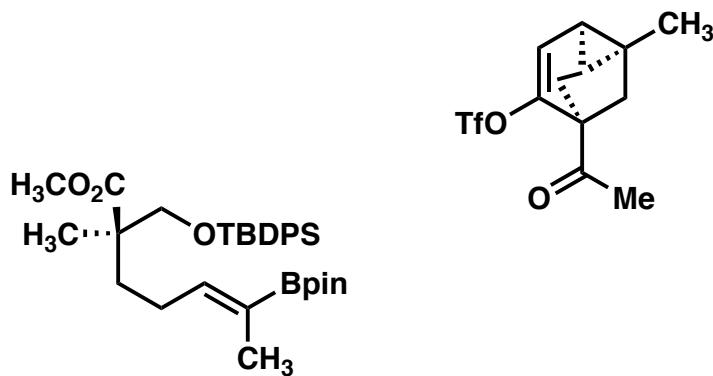


Prantz, K.; Mulzer, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5030.

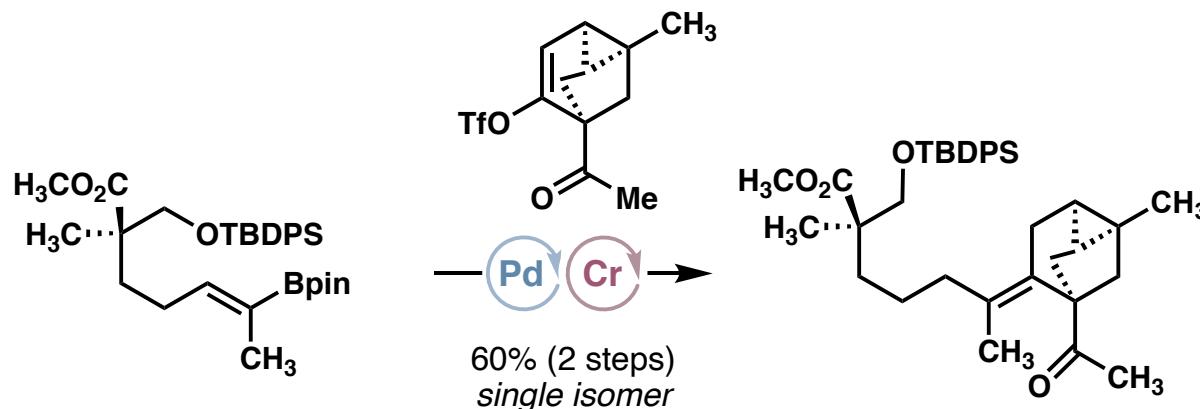
Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3171.

Carreira, E. M. et al. *J. Am. Chem. Soc.* **2020**, *142*, 17802.

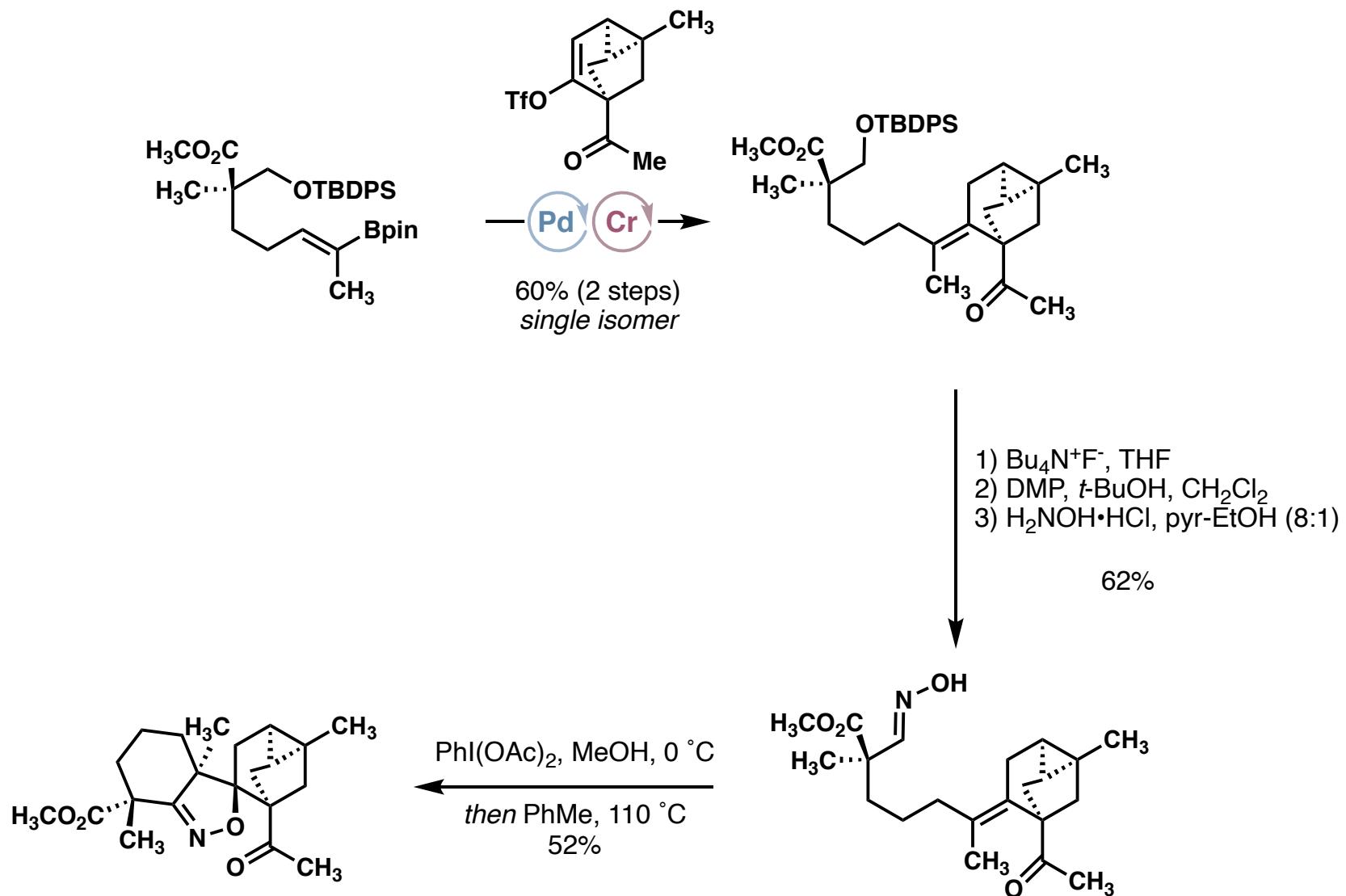
Advancing to the Key [3 + 2] Cycloaddition



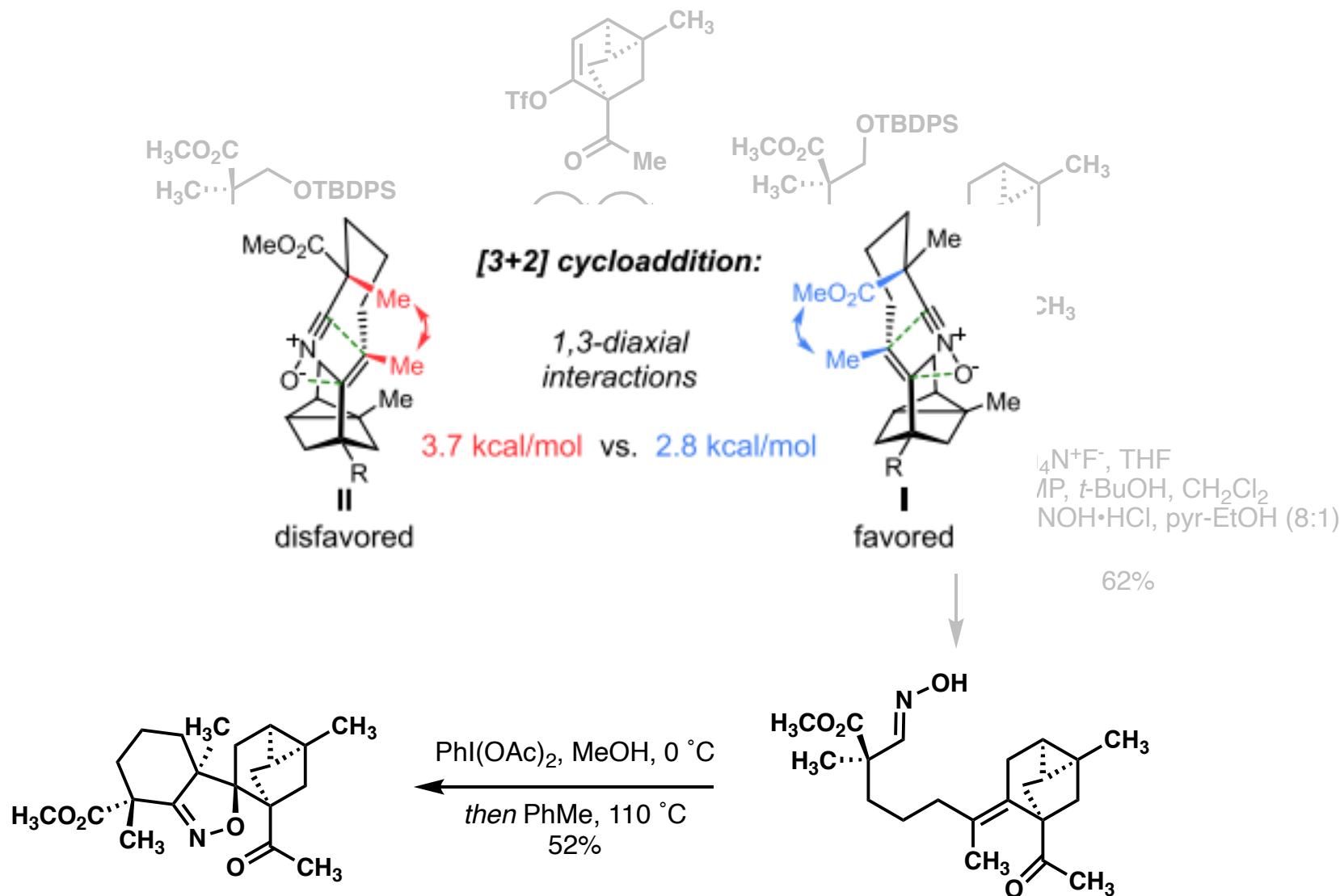
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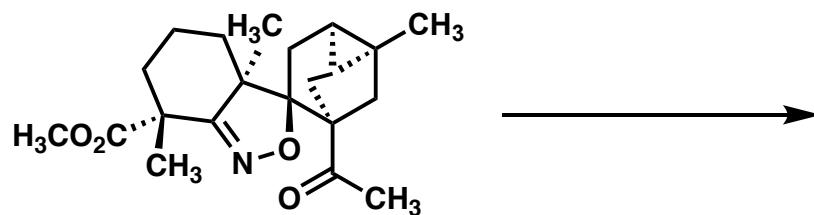
Advancing to the Key [3 + 2] Cycloaddition



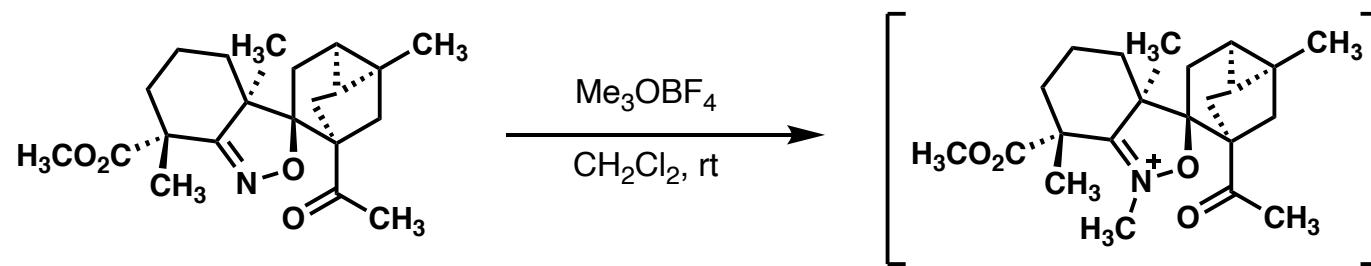
Advancing to the Key [3 + 2] Cycloaddition



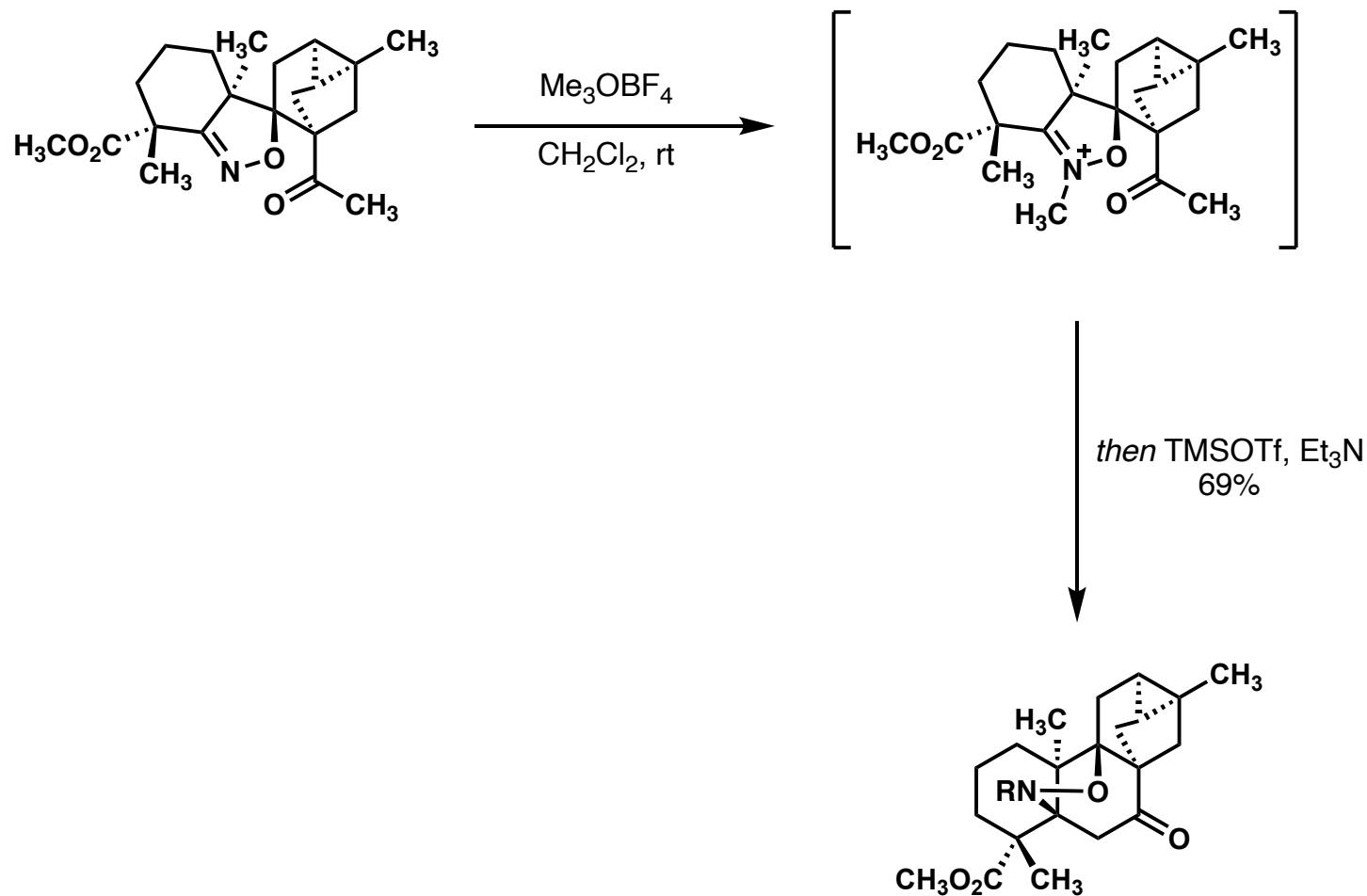
Mannich-Type Cyclization



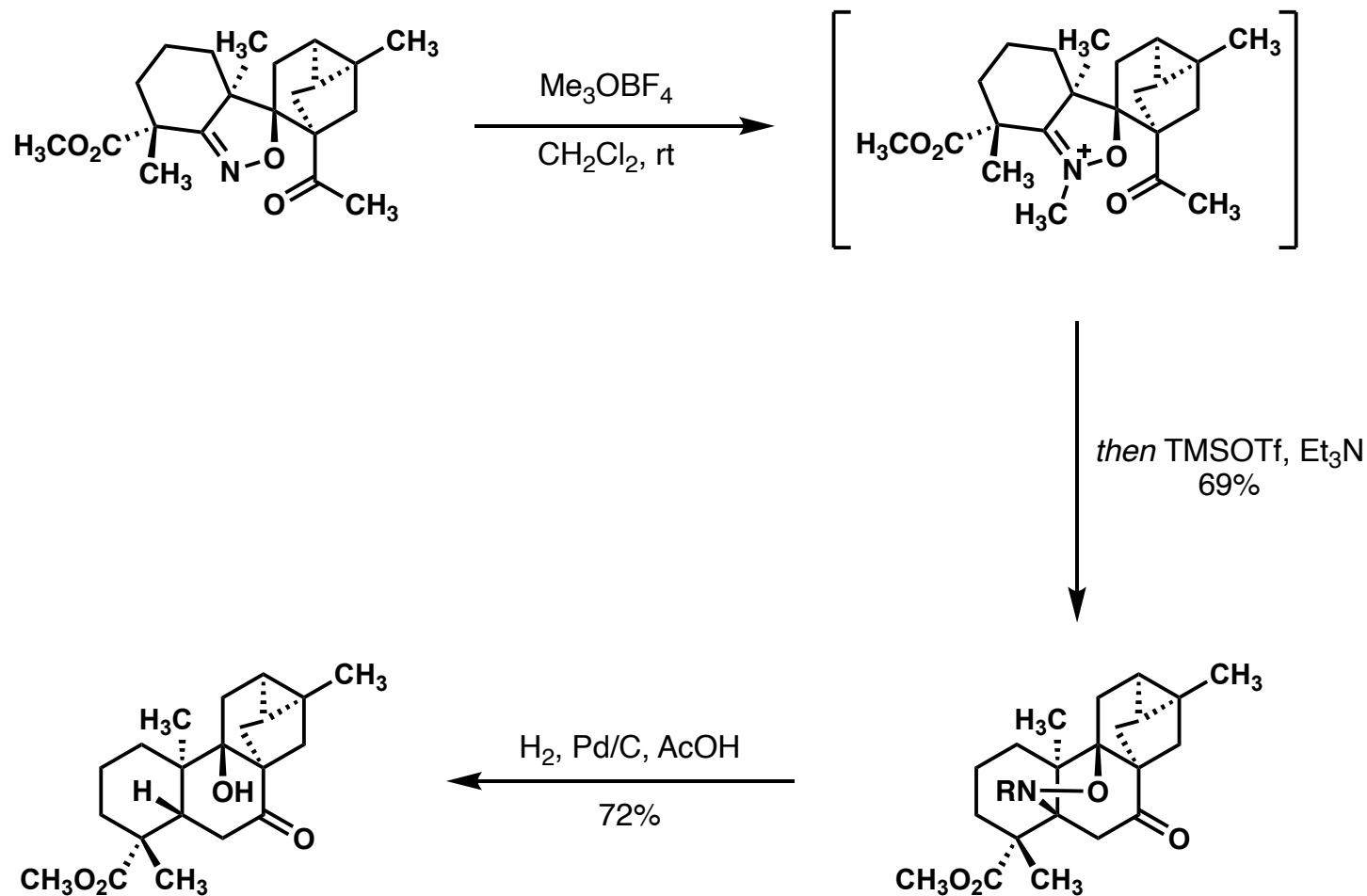
Mannich-Type Cyclization



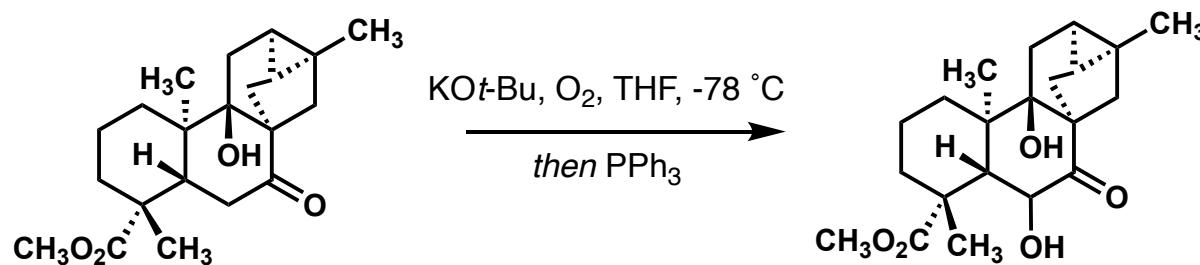
Mannich-Type Cyclization



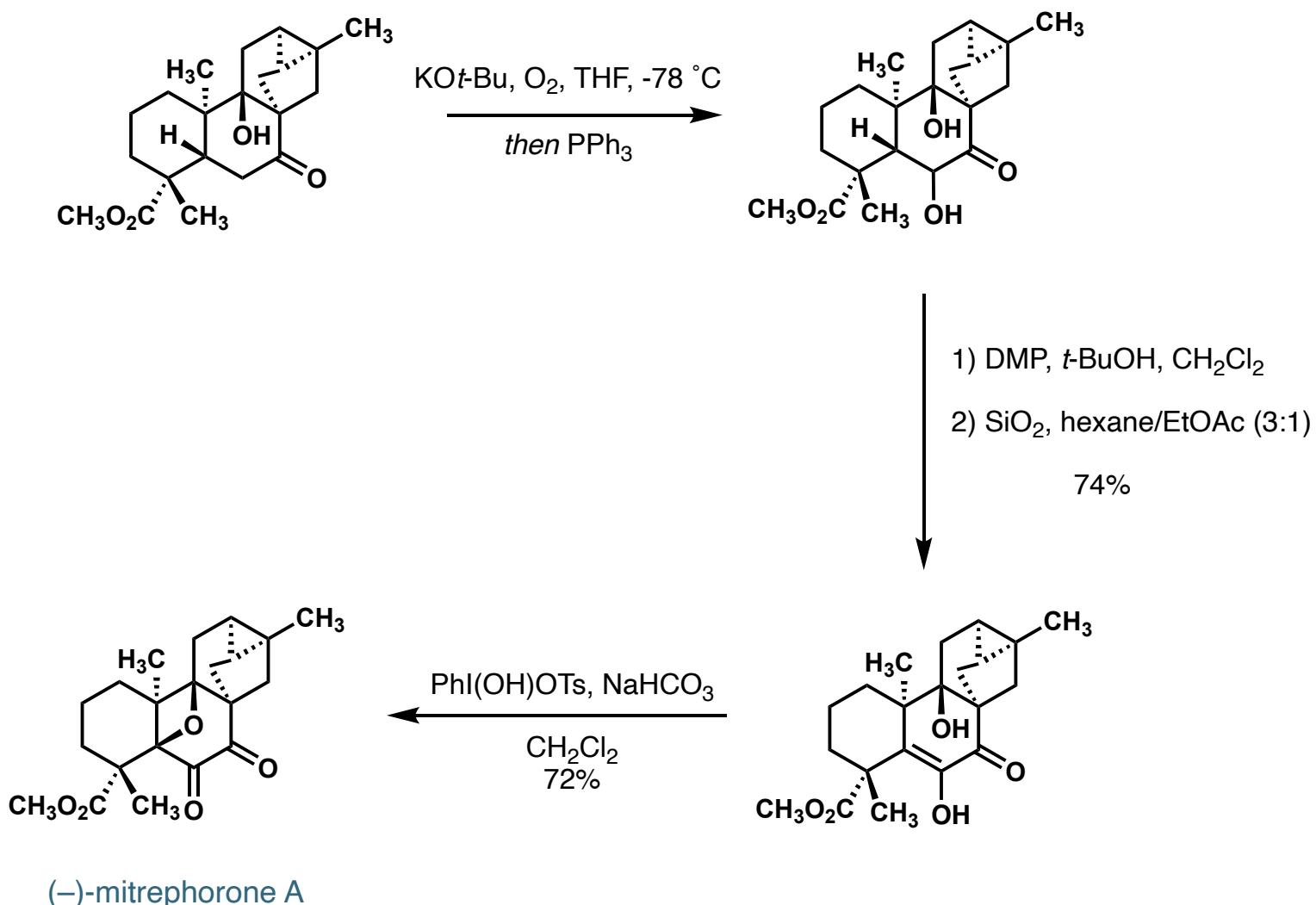
Mannich-Type Cyclization



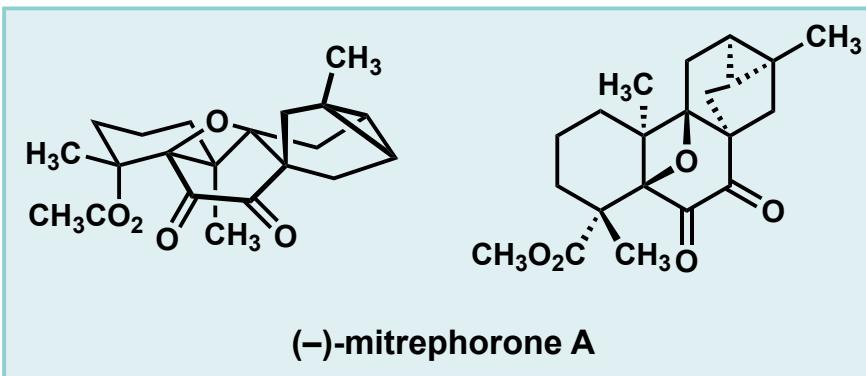
Completing (–)-Mitrephorone A



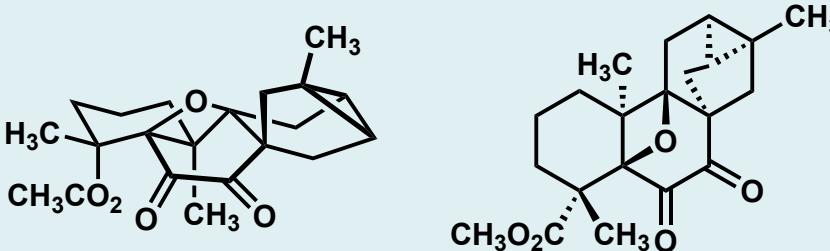
Completing (-)-Mitrephorone A



Comparing the Routes



Comparing the Routes

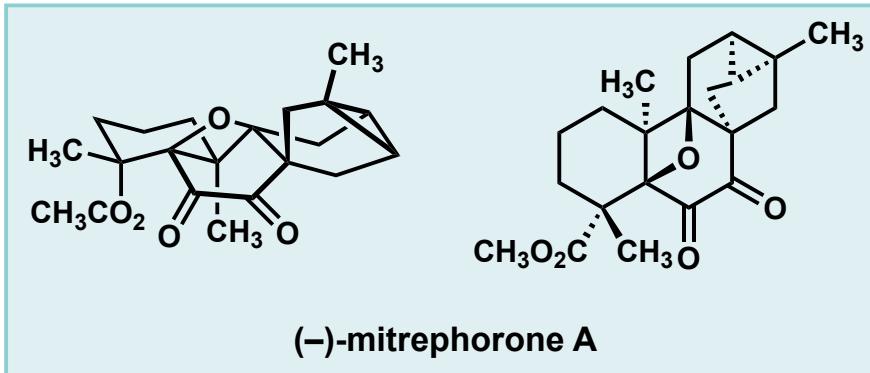


(*-*)-mitrephorone A

2018

- 14 steps LLS
- IMDA with sulfonyl ynone
- C-9 stereoschemistry set via unselective addition to hindered ketone
- Oxidative cyclization to form oxetane
- Modest enantioselectivity (88% ee)

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2020

- 20 steps LLS
- Stereoselective generation of tetrasubstituted olefin via diene semireduction
 - Highly diastereoselective [3 + 2]
- Oxidative cyclization to form oxetane
- Improved enantioselectivity (>99% ee)