M. Kevin Brown

Larisa P. Pop

The Scripps Research Institute

Shenvi Laboratory

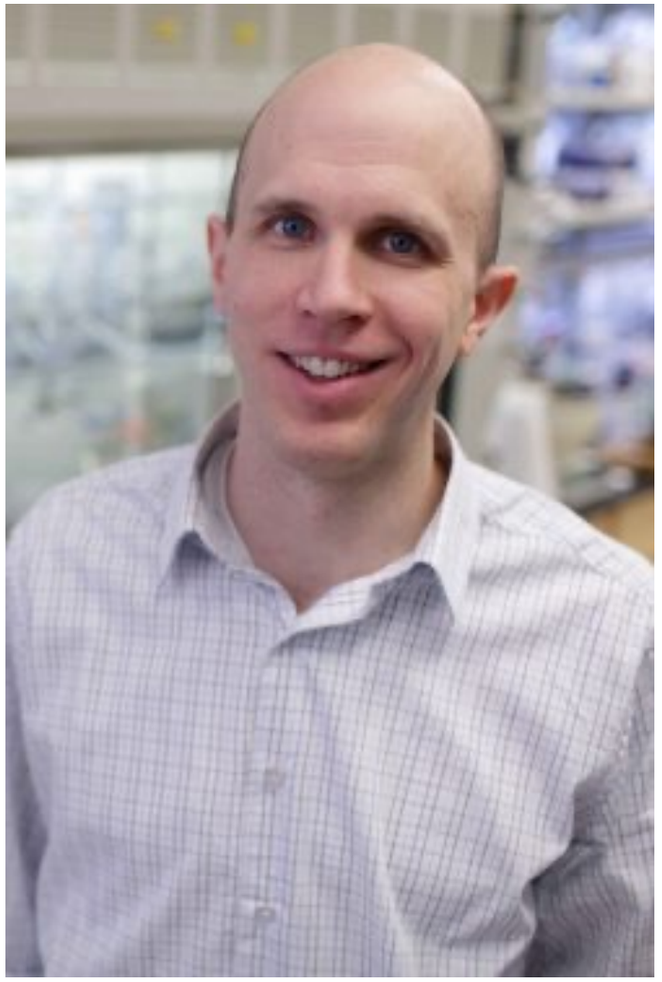
August 18th, 2024

Disclaimer

Out of 73 publications in his independent career, 29 papers are going to be discussed (+6 papers from PhD and +2 papers from Postdoc)

Author Profile

Date of Birth	May 28th, 1980
Education	1998–2002 Undergraduate studies, Hamilton College 2002–2008 PhD with Amir Hoveyda, Boston College 2008–2011 NIH Postdoctoral fellow with E. J. Corey, Harvard University
Career	2011-2017 Assistant Professor at Indiana University 2017-2021 Associate Professor at Indiana University 2021 Full Professor at Indiana University 2021-present James F. Jackson Professor of Chemistry
Awards	Sloan Research Fellow 2015 NSF CAREER Award 2016 Amgen Young Investigator Award 2016 Novartis Early Career Award 2016
Research	catalysis, synthesis, natural products
Hobbies	hiking, running, rock climbing, skiing

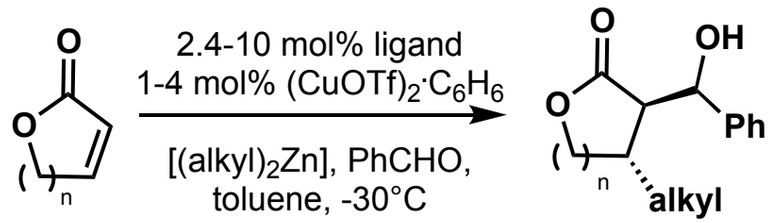


My favorite quote is “Simplicity is the ultimate sophistication” (Leonardo da Vinci).
The most amusing chemistry adventure in my career was driving 14 hours through the night to make my talk at an ACS meeting after my flight was cancelled.
If I were not a scientist, I would be a park ranger.
My favorite place on earth is Jackson Hole, Wyoming.

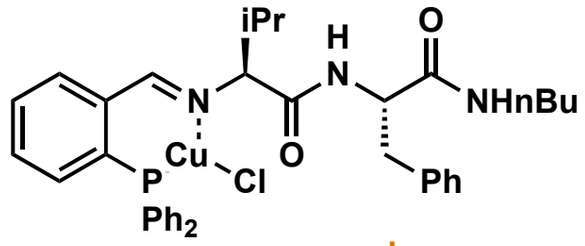
Jackson Hole, Wyoming

PhD work with Amir Hoveyda (1)

“Highly Enantioselective Cu-Catalyzed Conjugate Additions of Dialkylzinc Reagents to Unsaturated Furanones and Pyranones” *ACIE* **2005**, *44*, 5306-5310



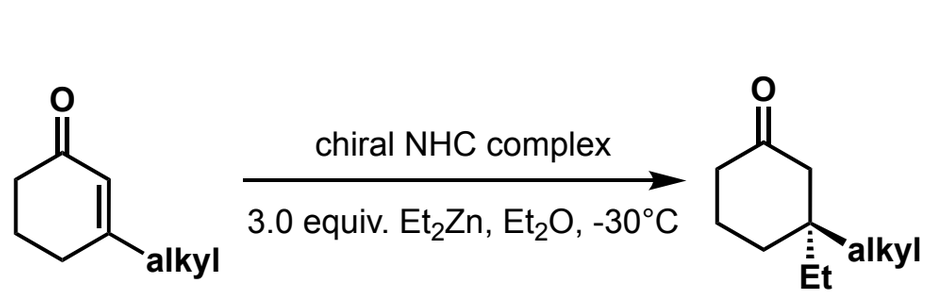
improved enantioselectivity using the prepared Cu-complex:



orange powder

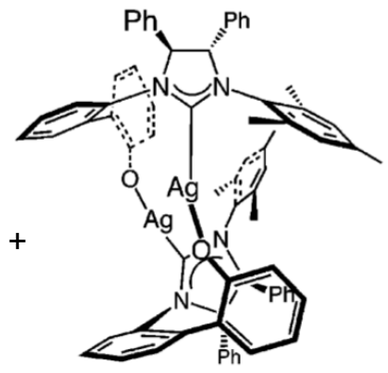
Amir Hoveyda, Boston College

“A Practical Method for Enantioselective Synthesis of All-Carbon Quaternary Stereocenters through NHC-Cu-Catalyzed Conjugate Additions” *JACS* **2006**, *128*, 7182-7184

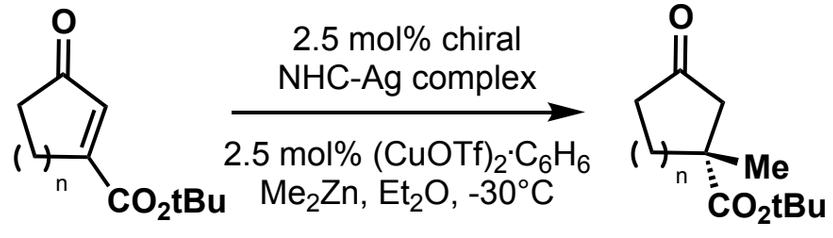


best combination

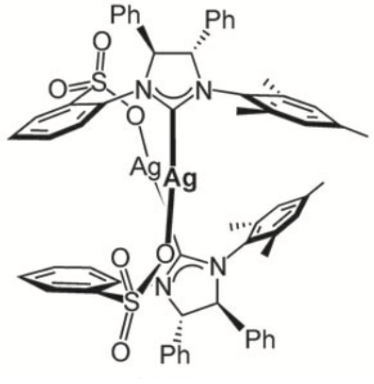
$(CuOTf)_2 \cdot C_6H_6$ +



“All-Carbon Quaternary Stereogenic Centers by Enantioselective Cu-Catalyzed Conjugate Additions Promoted by chiral NHC” *ACIE* **2007**, *46*, 1097-1100



where NHC-Ag complex:



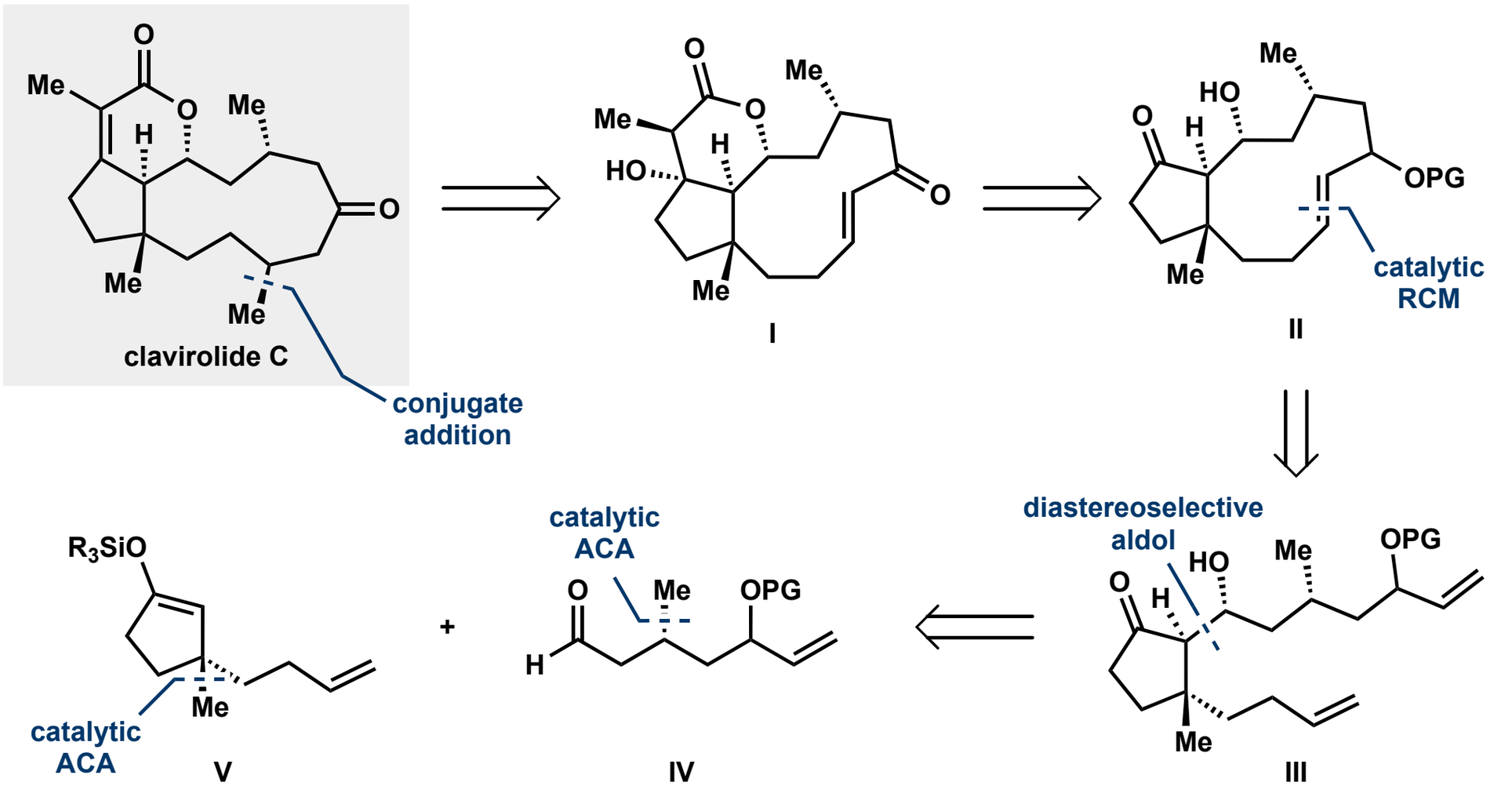
ACIE **2005**, *44*, 5306-5310; *JACS* **2006**, *128*, 7182-7184; *ACIE* **2007**, *46*, 1097-1100.

PhD work with Amir Hoveyda (2)

Amir Hoveyda, Boston College

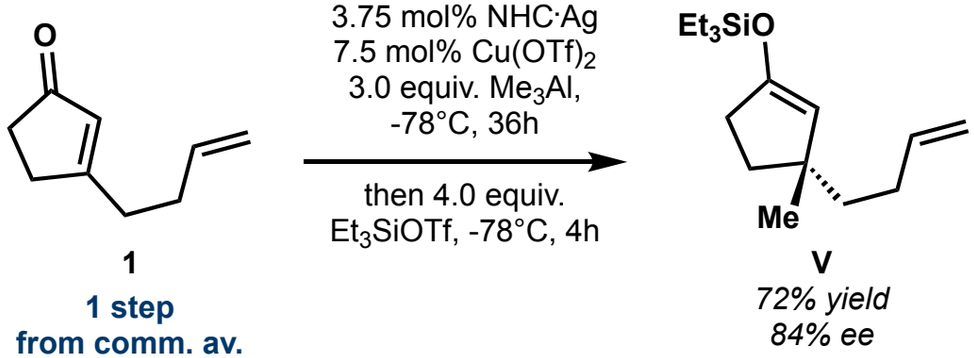
"Enantioselective Total Synthesis of Clavirolide C. Application of Cu-Catalyzed Asymmetric Conjugate Additions and Ru-Catalyzed Ring-Closing Metathesis"

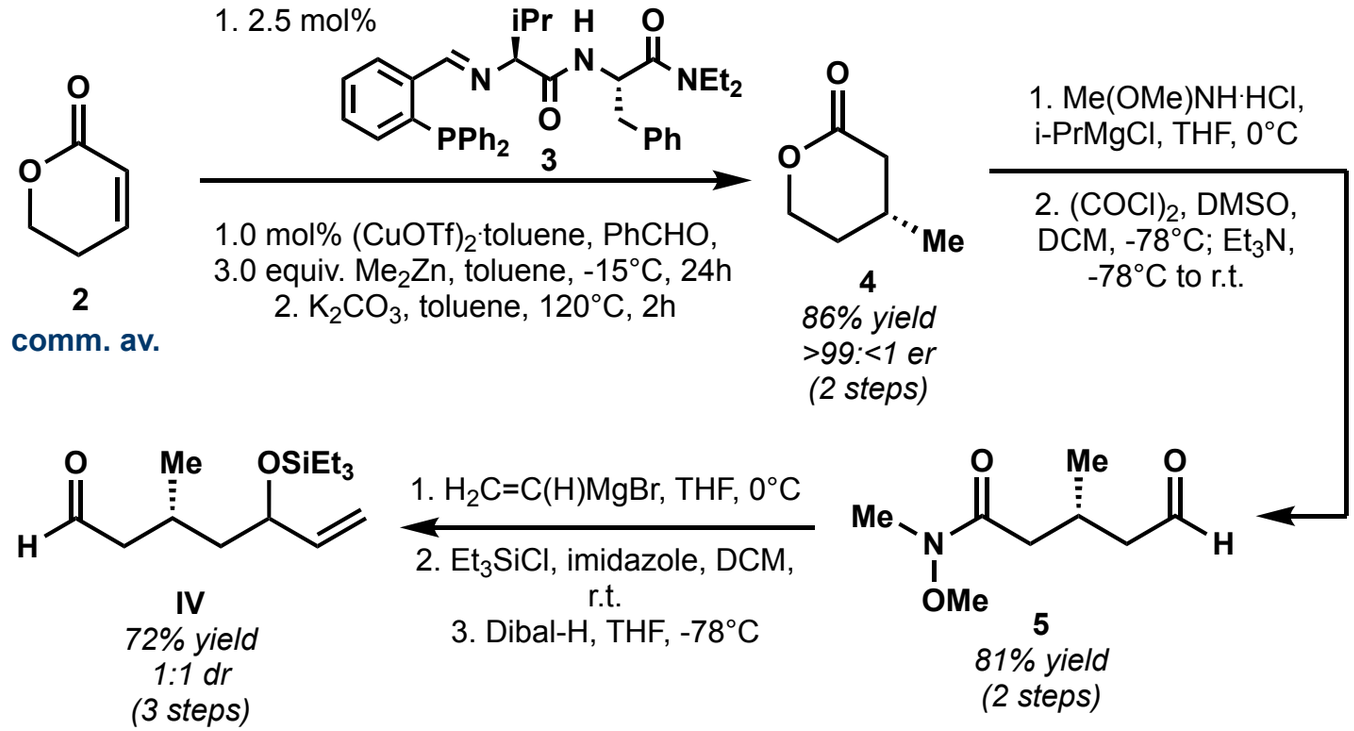
Retrosynthesis



JACS **2008**, *130*, 12904-12906.

PhD work with Amir Hoveyda (3)





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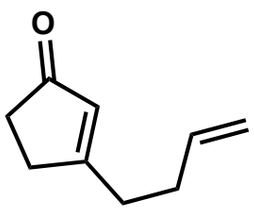
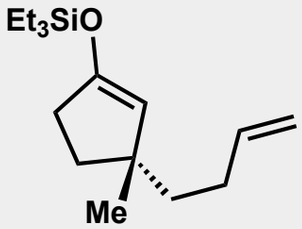


1

1 step from comm. av.

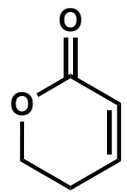
3.75 mol% NHC·Ag
7.5 mol% $Cu(OTf)_2$
3.0 equiv. Me_3Al,
-78°C, 36h

then 4.0 equiv.
Et_3SiOTf, -78°C, 4h



V

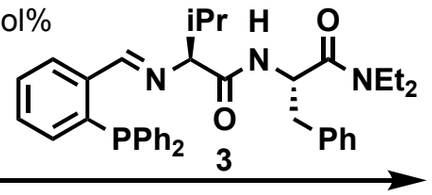
72% yield
84% ee



2

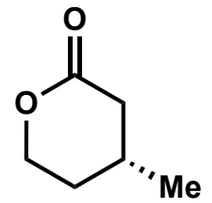
comm. av.

1. 2.5 mol%



3

1.0 mol% $(CuOTf)_2$·toluene, PhCHO,
3.0 equiv. Me_2Zn, toluene, -15°C, 24h
2. K_2CO_3, toluene, 120°C, 2h

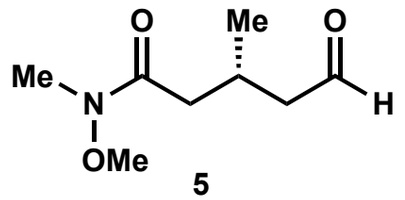


4

86% yield
>99:<1 er
(2 steps)

1. Me(OMe)NH·HCl,
i-PrMgCl, THF, 0°C

2. $(COCl)_2$, DMSO,
DCM, -78°C; Et_3N,
-78°C to r.t.

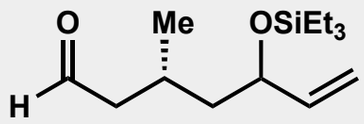


5

81% yield
(2 steps)

1. $H_2C{=}C(H)MgBr$, THF, 0°C

2. Et_3SiCl, imidazole, DCM,
r.t.
3. Dibal-H, THF, -78°C

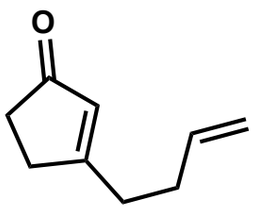


IV

72% yield
1:1 dr
(3 steps)

JACS **2008**, *130*, 12904-12906.

PhD work with Amir Hoveyda (3)



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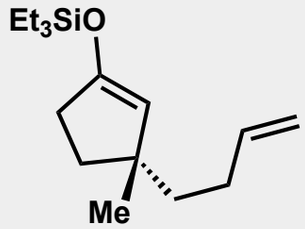
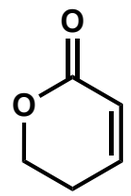


V

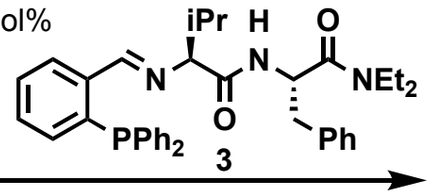
72% yield
84% ee



2

comm. av.

1. 2.5 mol%



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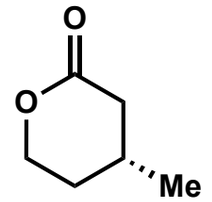
2. K_2CO_3, toluene, 120°C, 2h



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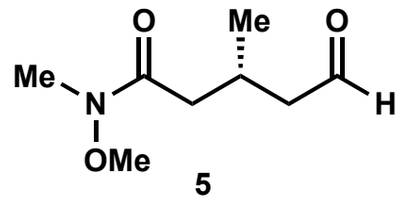

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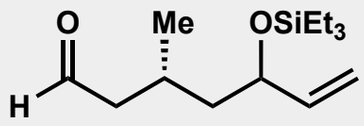
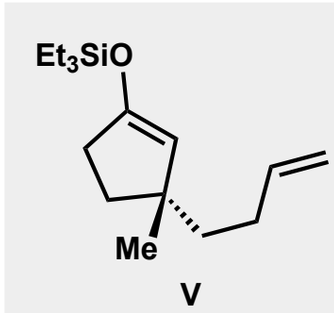


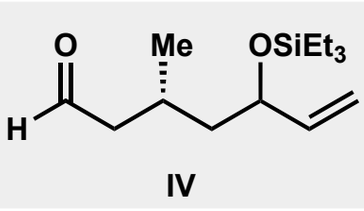
IV

72% yield
1:1 dr
(3 steps)



V

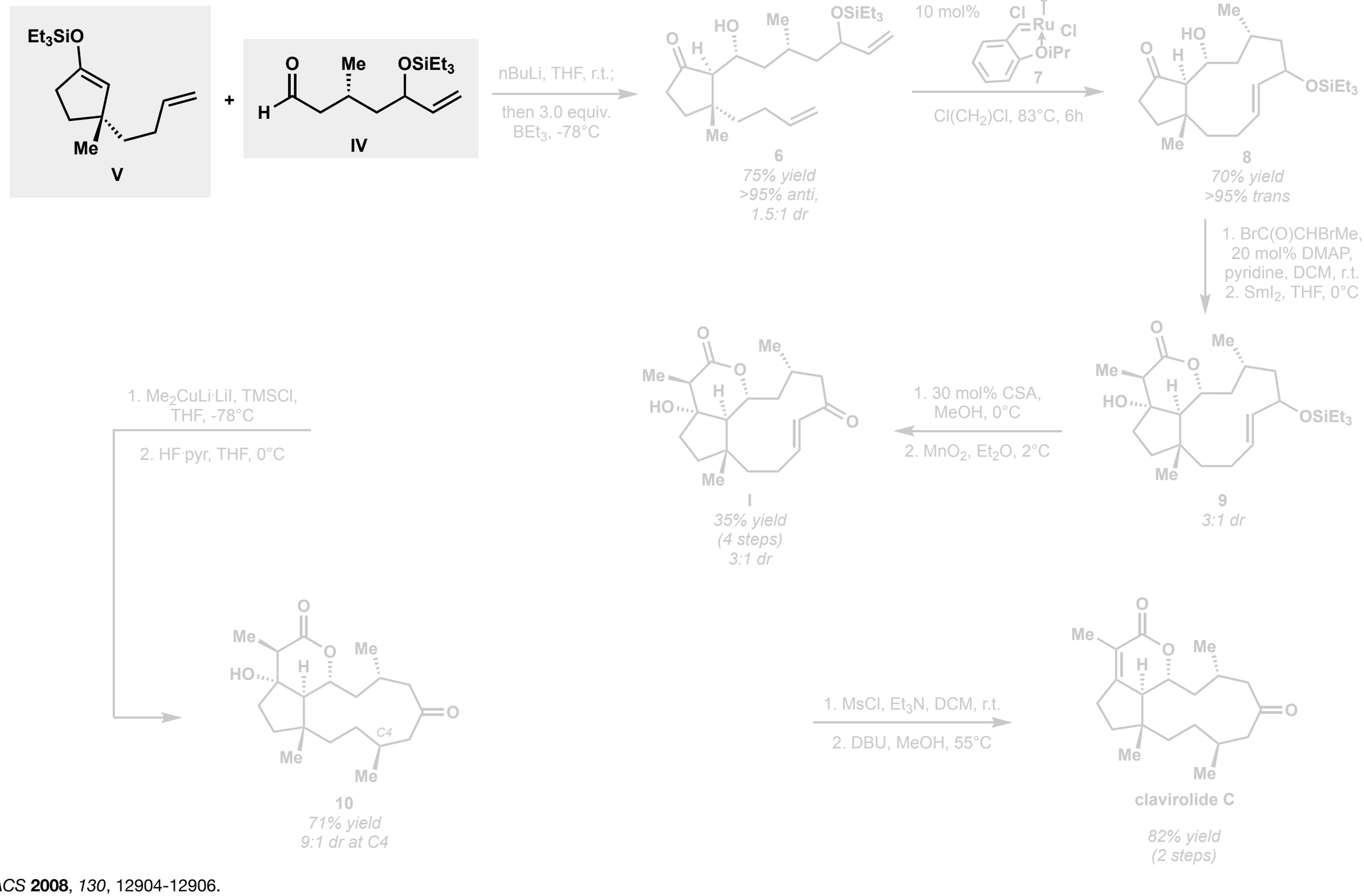
+



IV

JACS **2008**, *130*, 12904-12906.

PhD work with Amir Hoveyda (3)



JACS **2008**, *130*, 12904-12906.

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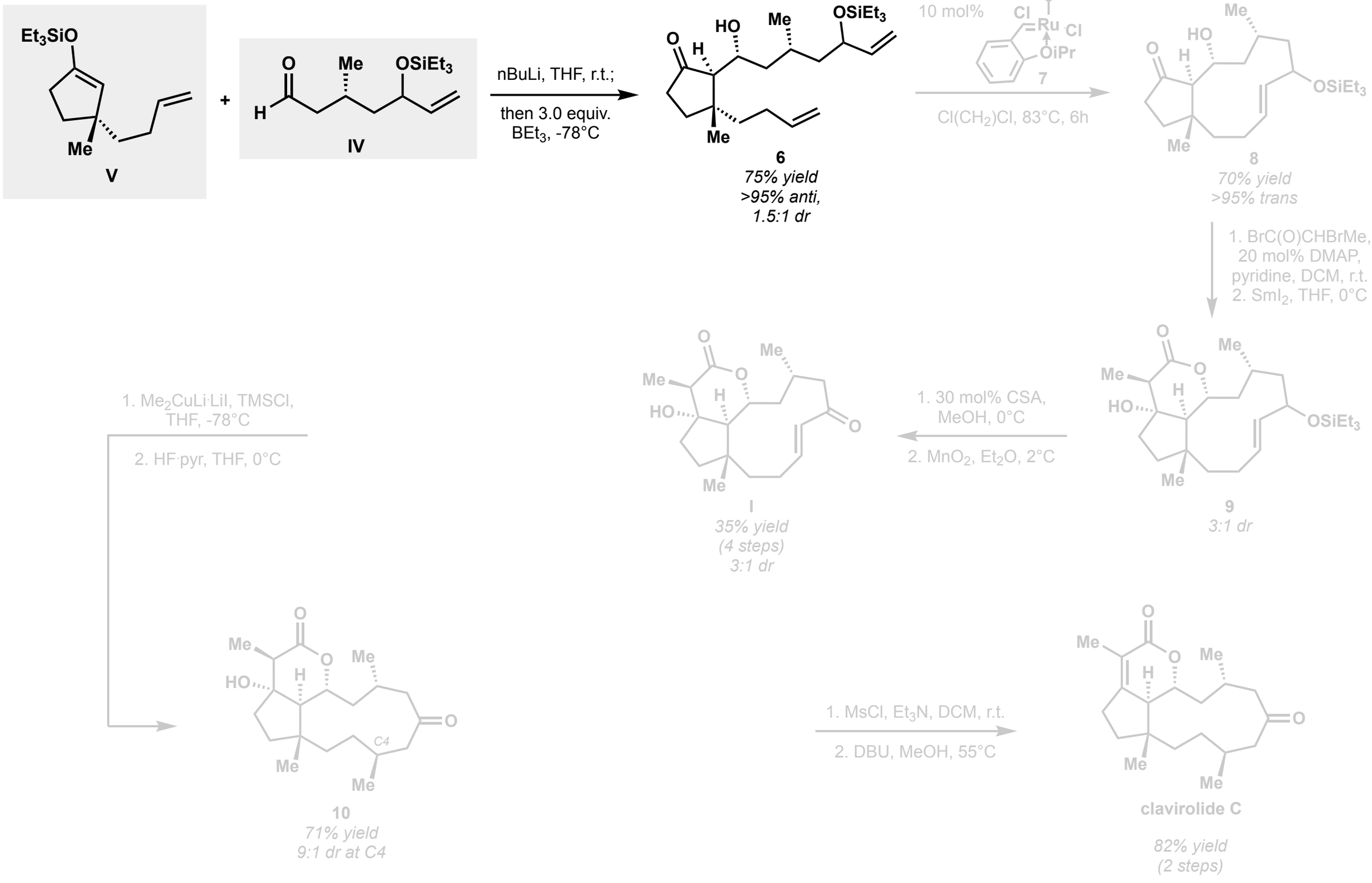
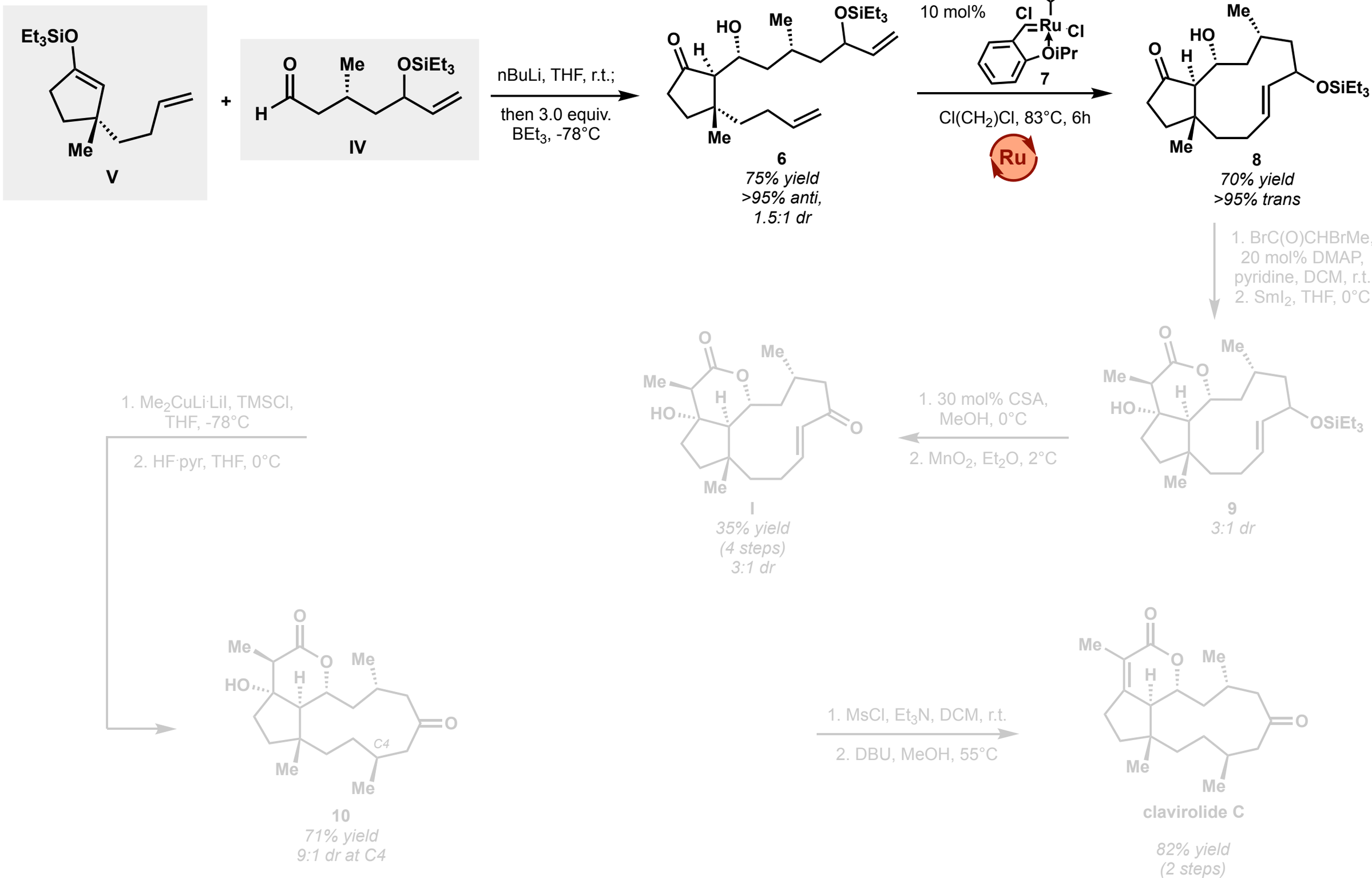


JACS **2008**, *130*, 12904-12906; *Tetrahedron* **1982**, *23*, 2387-2390.

PhD work with Amir Hoveyda (3)



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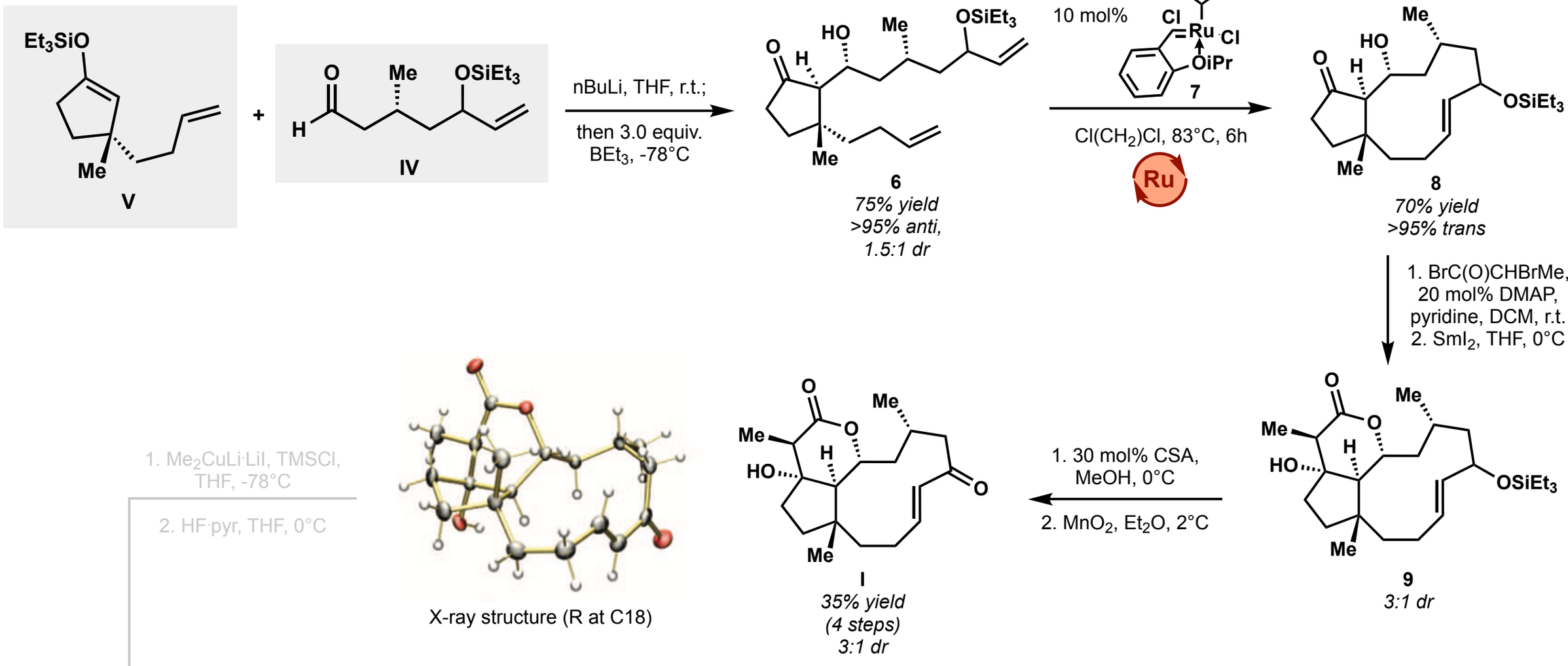
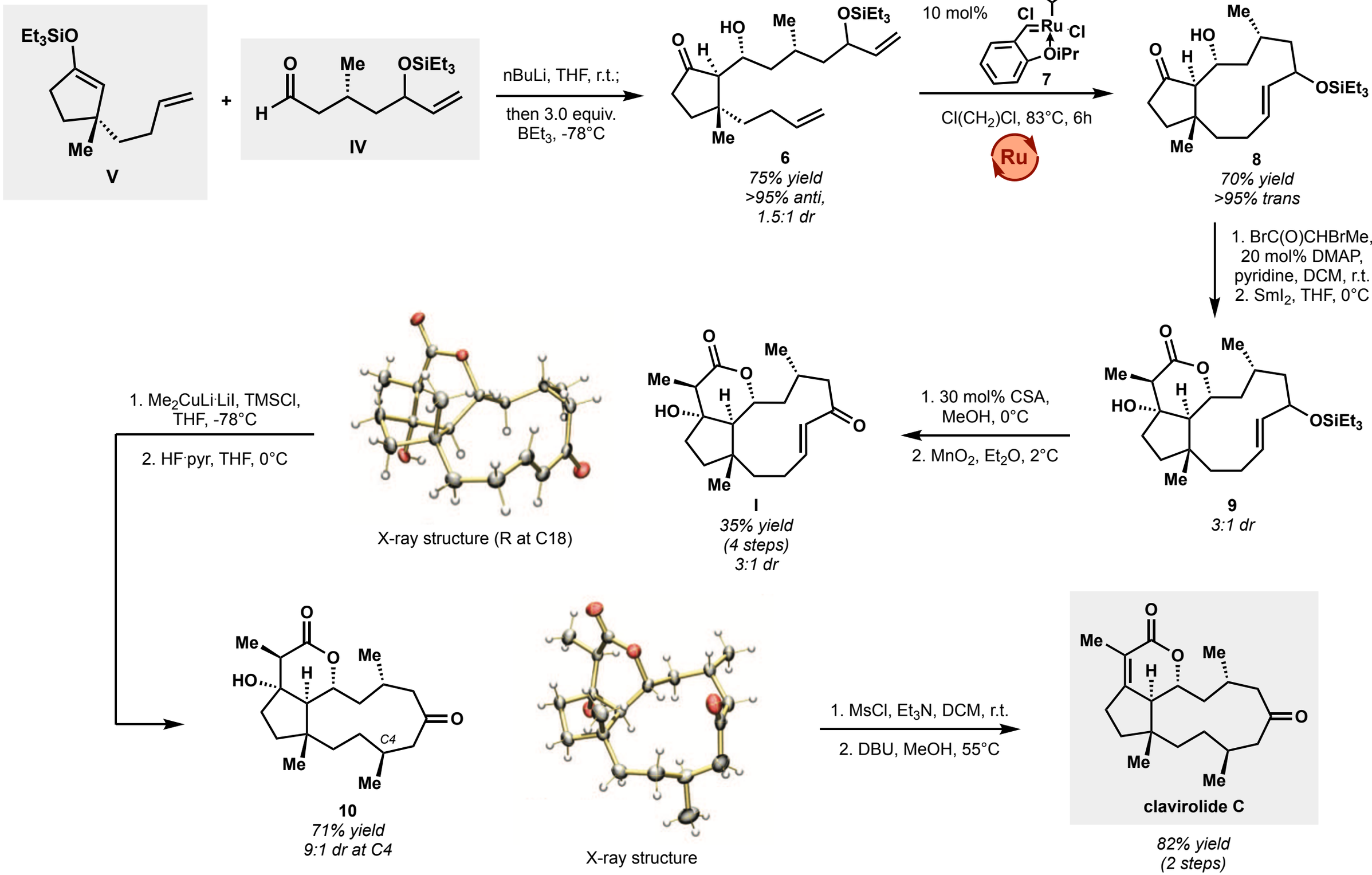


JACS **2008**, *130*, 12904-12906.

PhD work with Amir Hoveyda (3)

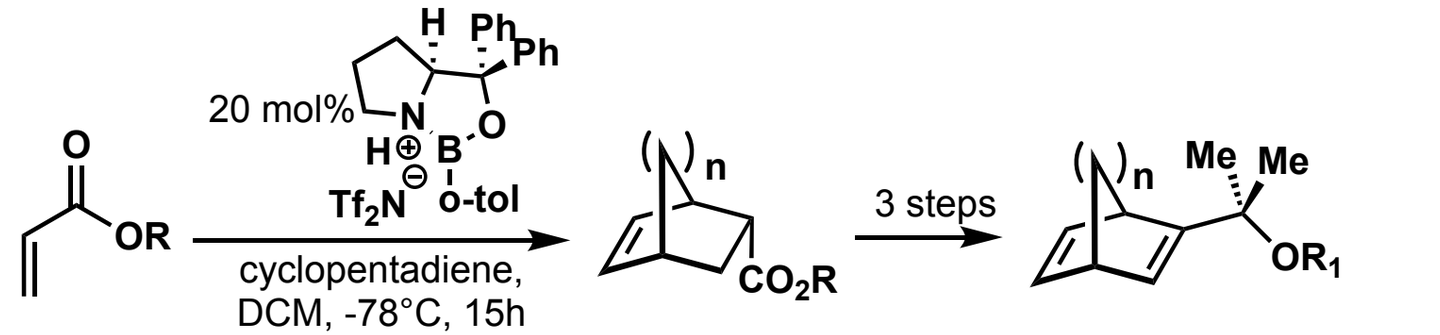


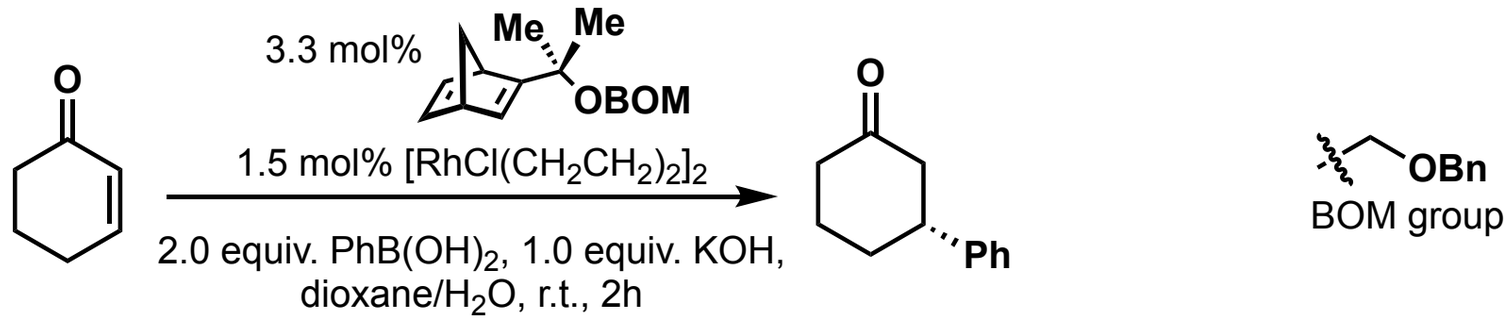
JACS **2008**, *130*, 12904-12906.

Postdoc work with E. J. Corey

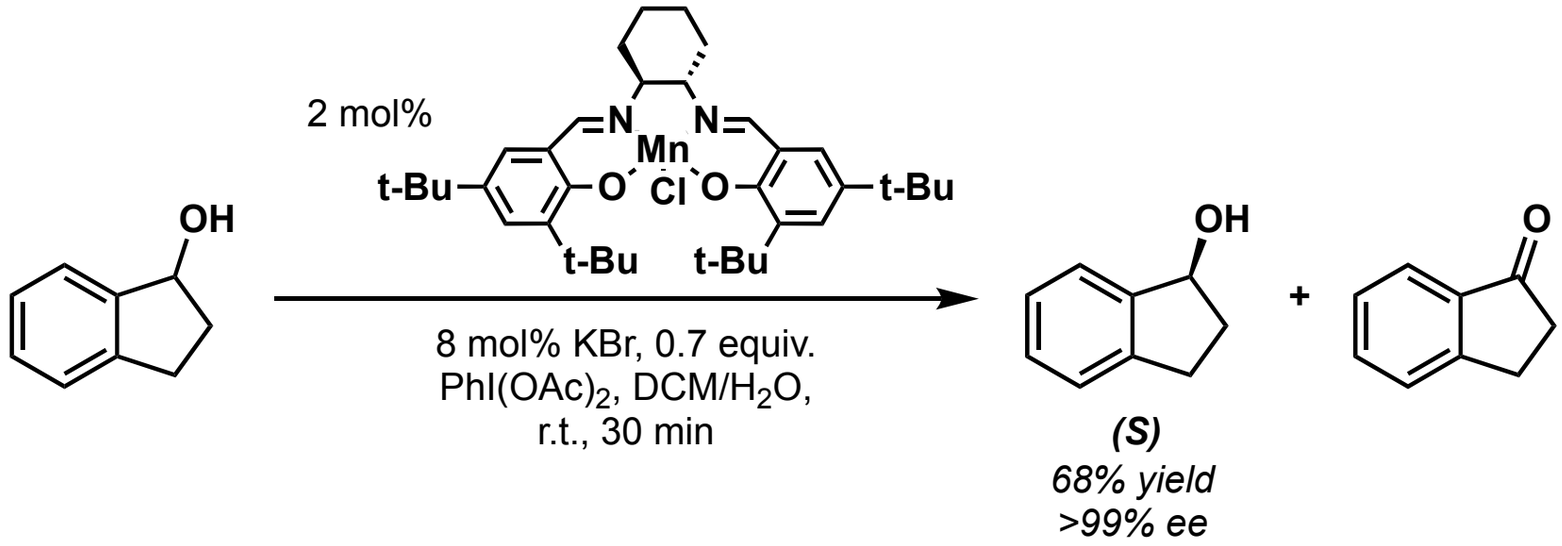
E. J. Corey, Harvard University

"Catalytic Enantioselective Formation of Chiral-Bridged Dienes Which Are Themselves Ligands for Enantioselective Catalysis" *Org. Lett.* **2010**, *12*, 172-175.





"Mechanism of the Enantioselective Oxidation of Racemic Secondary Alcohols Catalyzed by Chiral Mn(III)-Salen Complexes" *JACS* **2010**, *132*, 11165-11170.

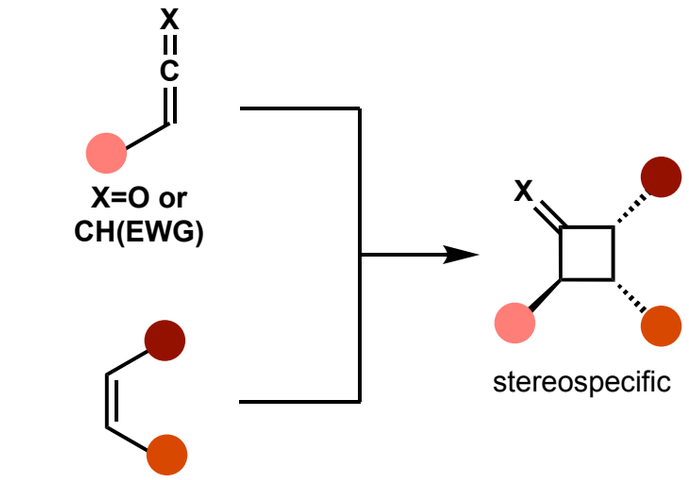


Org. Lett. **2010**, *12*, 172-175; *JACS* **2010**, *132*, 11165-11170.

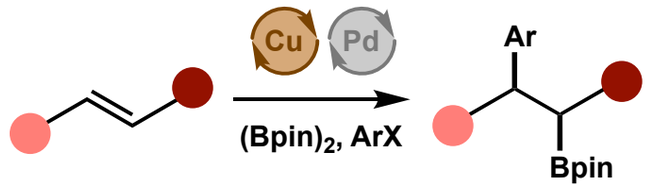
Independent Career

Independent Career

Lewis Acid Mediated [2+2] Cycloadditions

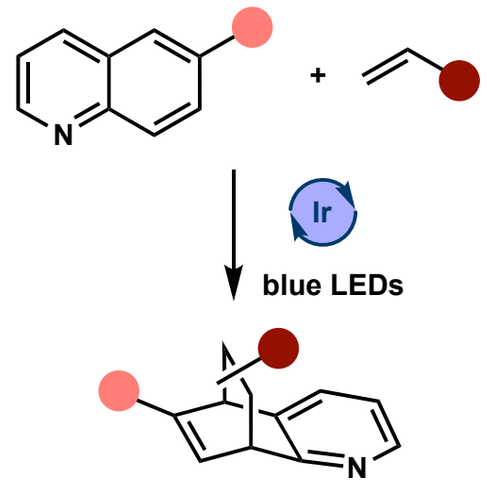


Cu/Pd Catalysis and Carboboration

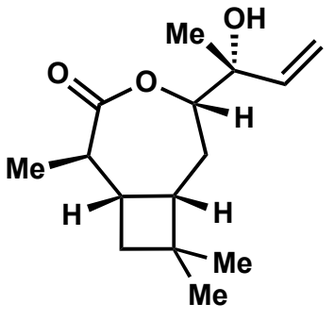


Catalyst controlled selectivity

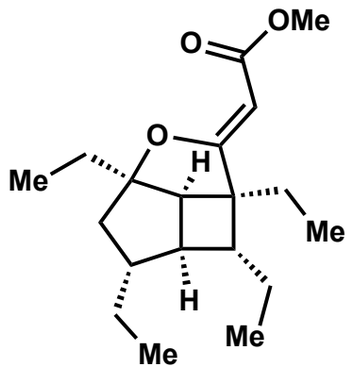
Photochemical Dearomative Cycloadditions



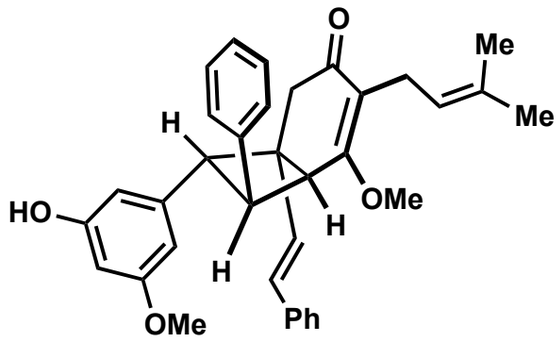
Total Synthesis



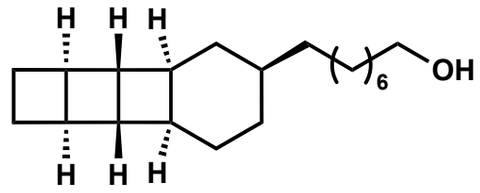
(-)-Hebelophyllene E



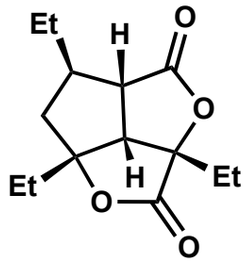
Hippolachnin A



(-)-Cajanusine



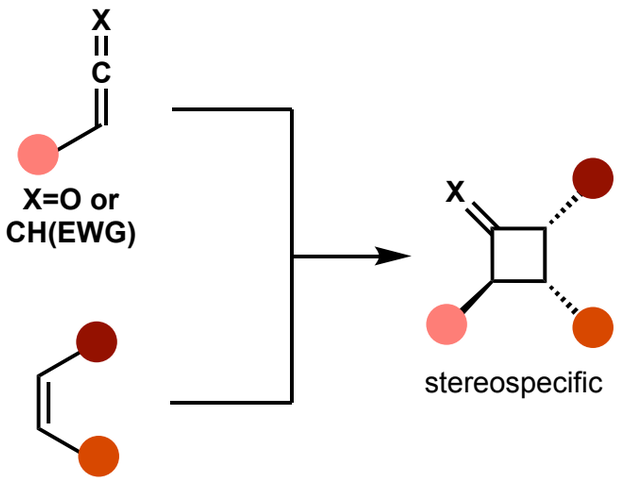
ent-[3]-Ladderanol



Gracilioether F

Independent Career

Lewis Acid Mediated [2+2] Cycloadditions



Cu/Pd Catalysis and Carboboration

Catalyst controlled selectivity

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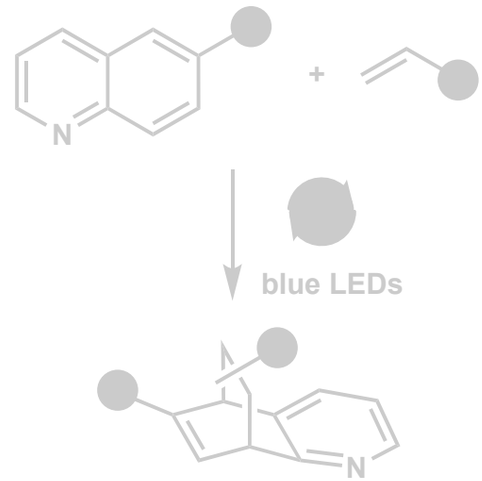
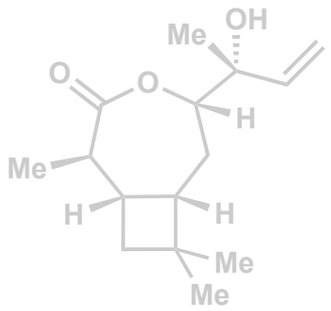
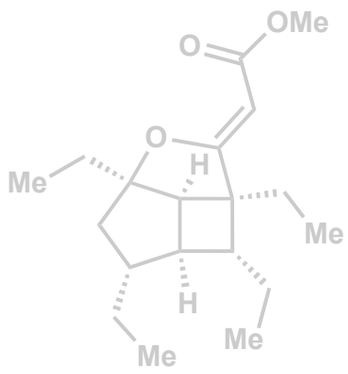


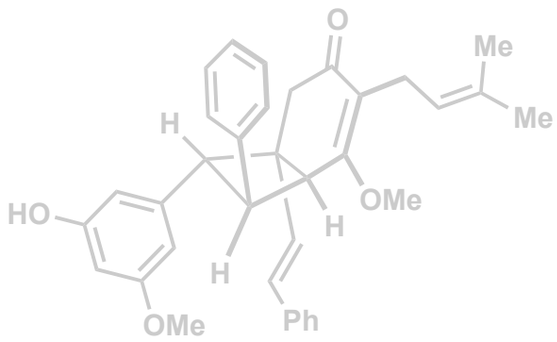
Total Synthesis



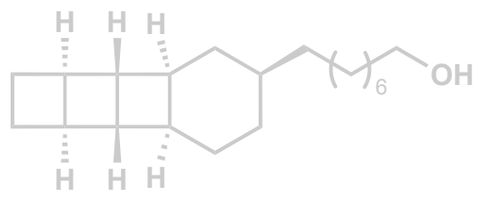
(-)-Hebelophyllene E



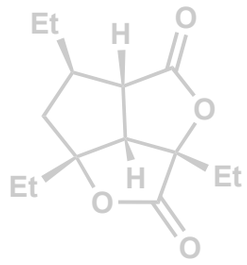
Hippolachnin A



(-)-Cajanusine

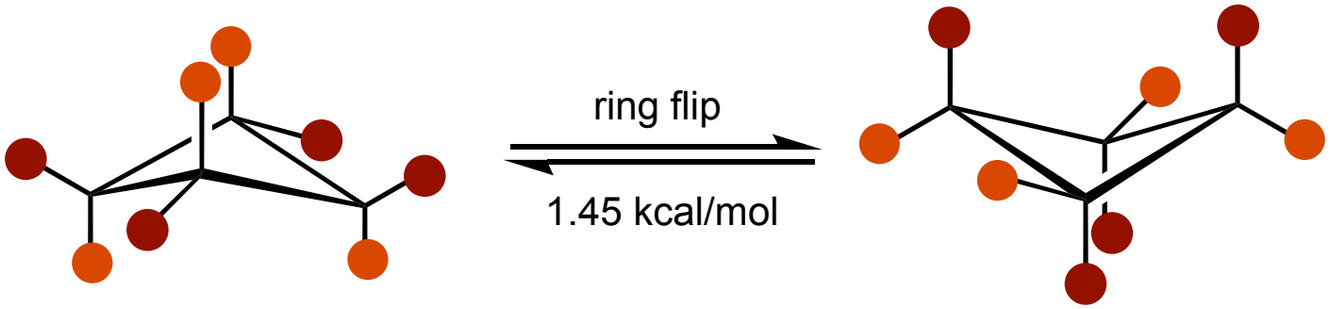


ent-[3]-Ladderanol



Gracilioether F

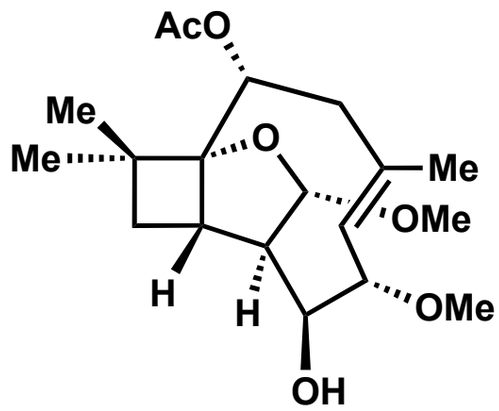
Cyclobutane as important scaffolds



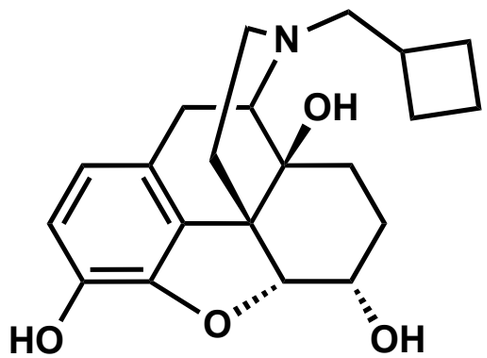
- Valuable intermediates in synthesis

- Favoured structures in drug candidates, introducing conformational restriction and reducing planarity, as aryl isostere

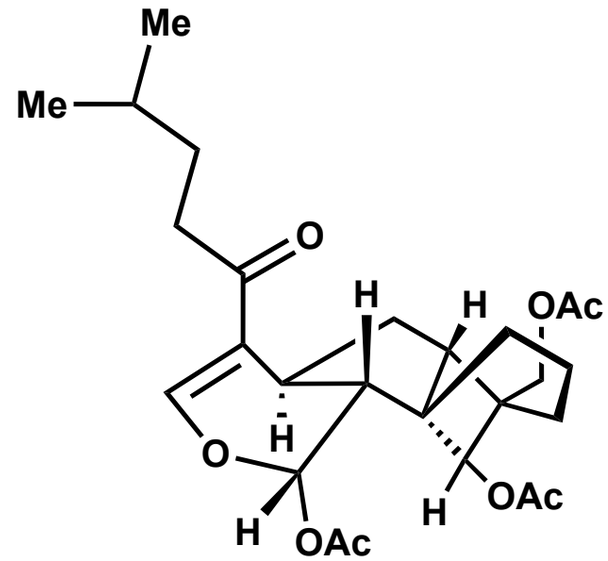
- Present in >2000 natural product



(-)-14-*O*-methyl-pestalotiopsin A
immunosuppressive



Nalbuphine
analgesic

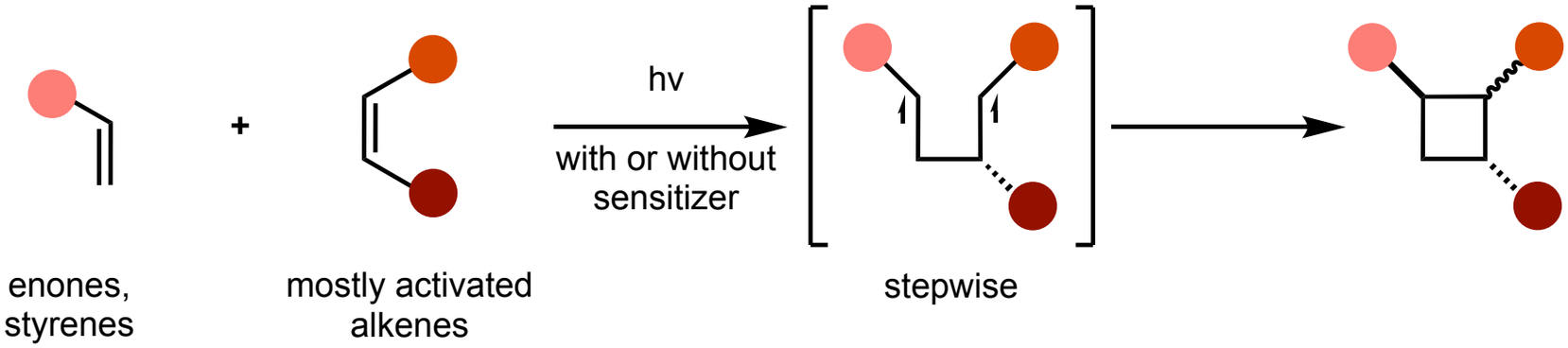


(+)-plumisclerin A
cytotoxic against multiple tumor cells

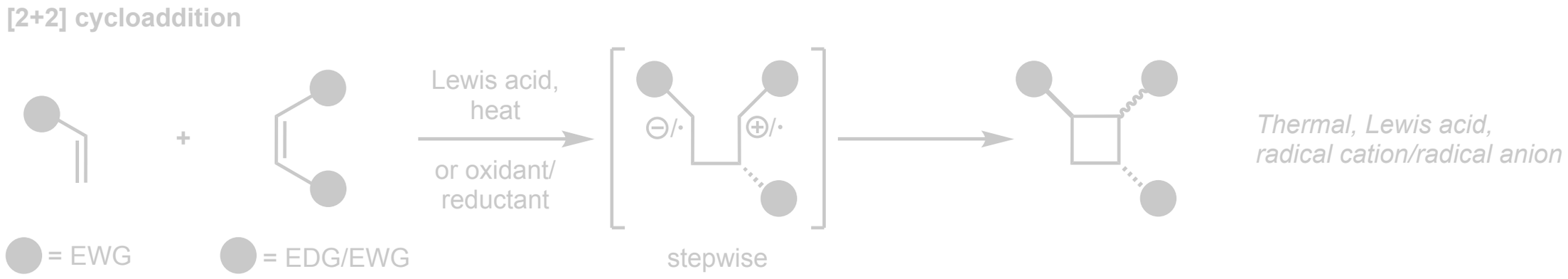
Acc. Chem. Res. **2023**, *56*, 2253-2264; *Org. Chem. Front*. **2020**, *7*, 136.

Cyclobutanes through [2+2] cycloaddition

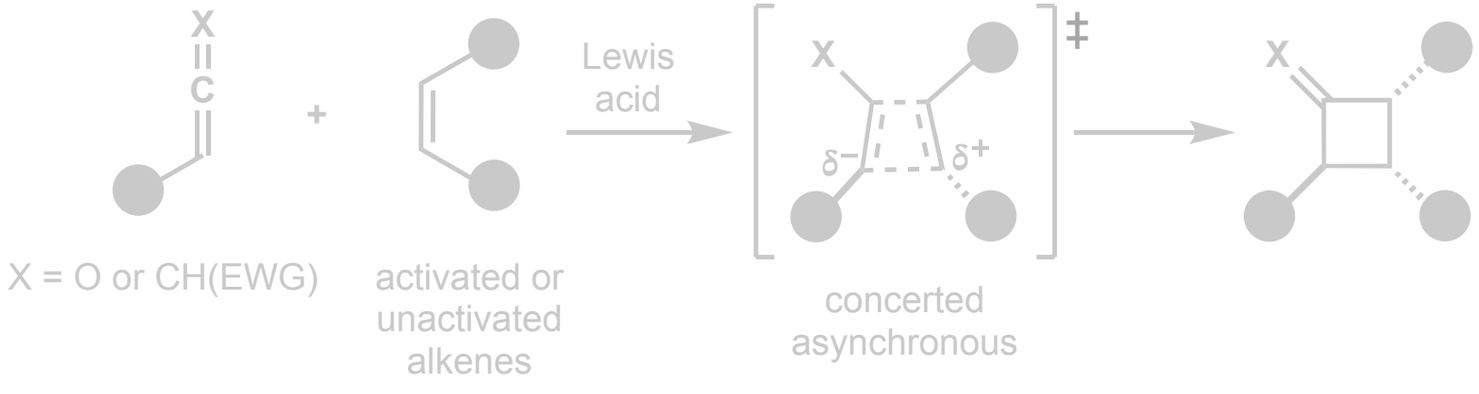
Diradical [2+2] cycloaddition



Polar [2+2] cycloaddition



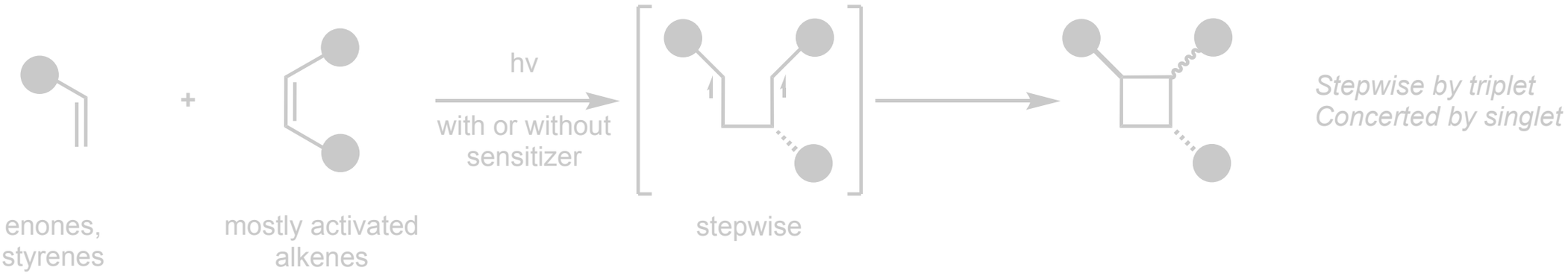
Lewis acid promoted [2+2] cycloaddition of ketenes and allenes



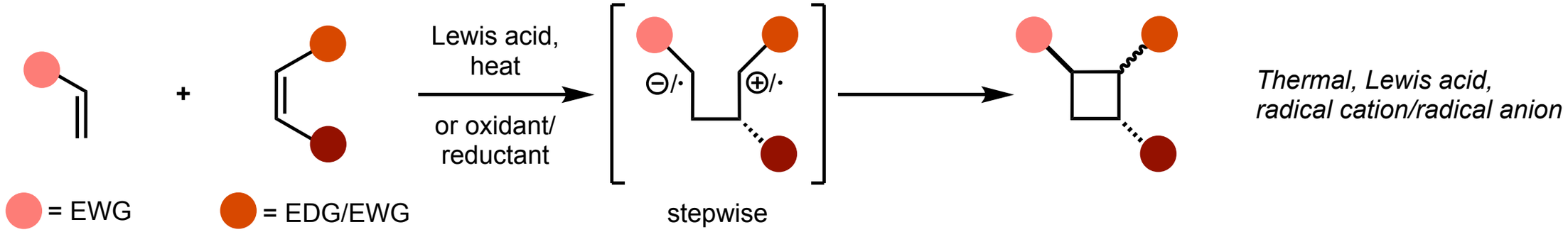
Acc. Chem. Res. **2023**, *56*, 2253-2264.

Cyclobutanes through [2+2] cycloaddition

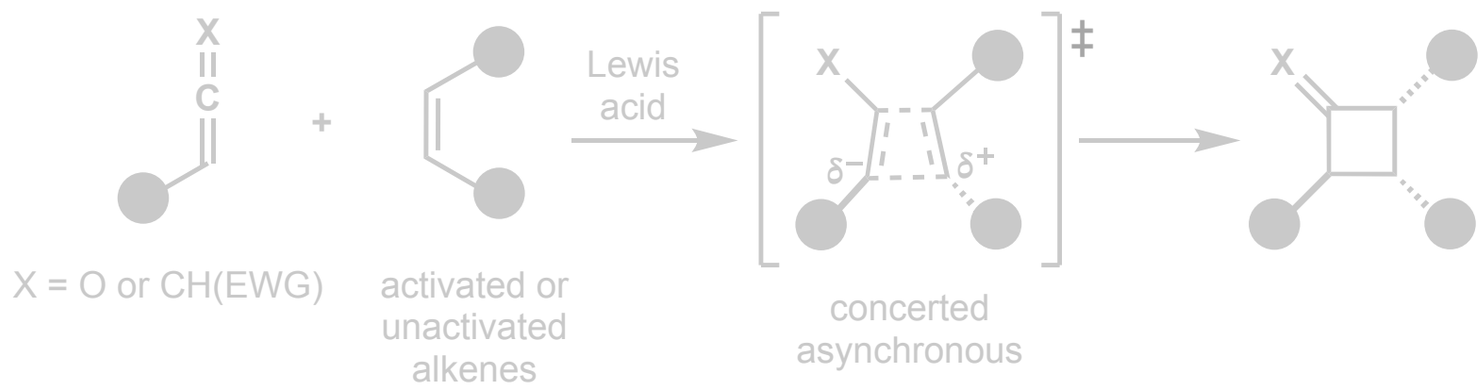
Diradical [2+2] cycloaddition



Polar [2+2] cycloaddition



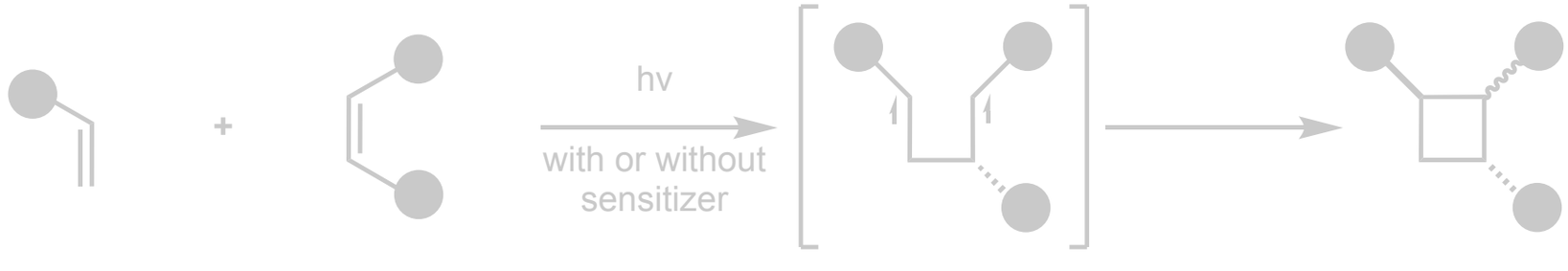
Lewis acid promoted [2+2] cycloaddition of ketenes and allenes



Acc. Chem. Res. **2023**, *56*, 2253-2264.

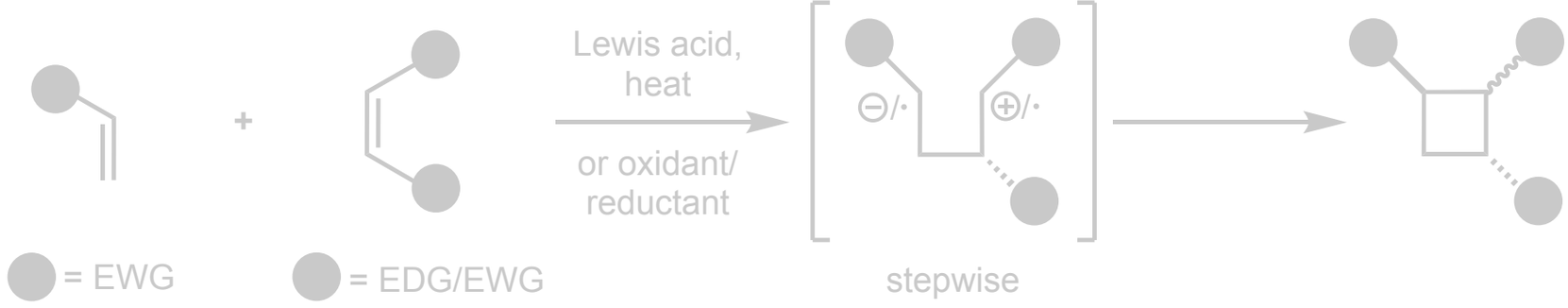
Cyclobutanes through [2+2] cycloaddition

Diradical [2+2] cycloaddition



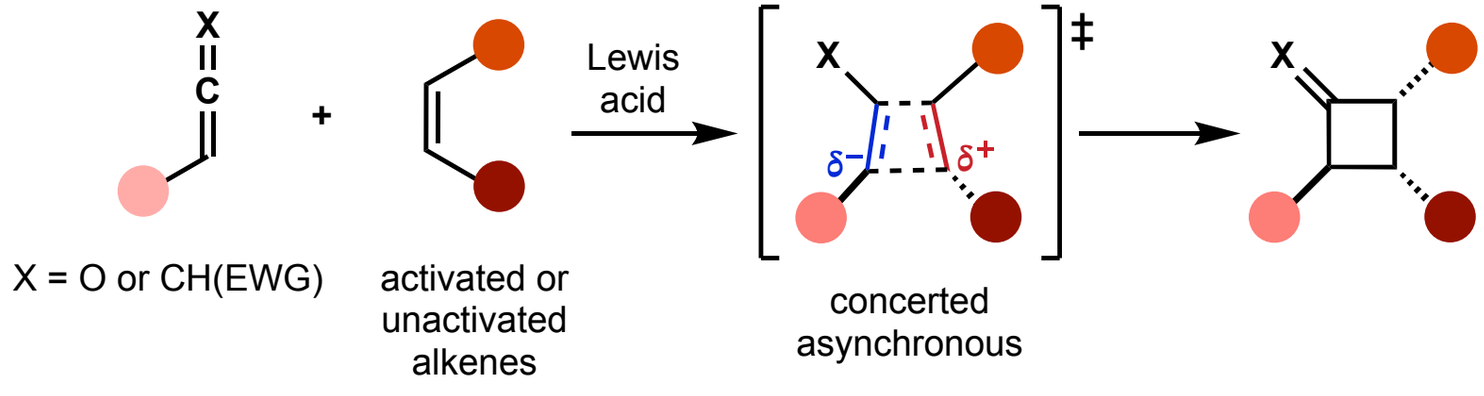
Stepwise by triplet
Concerted by singlet

Polar [2+2] cycloaddition



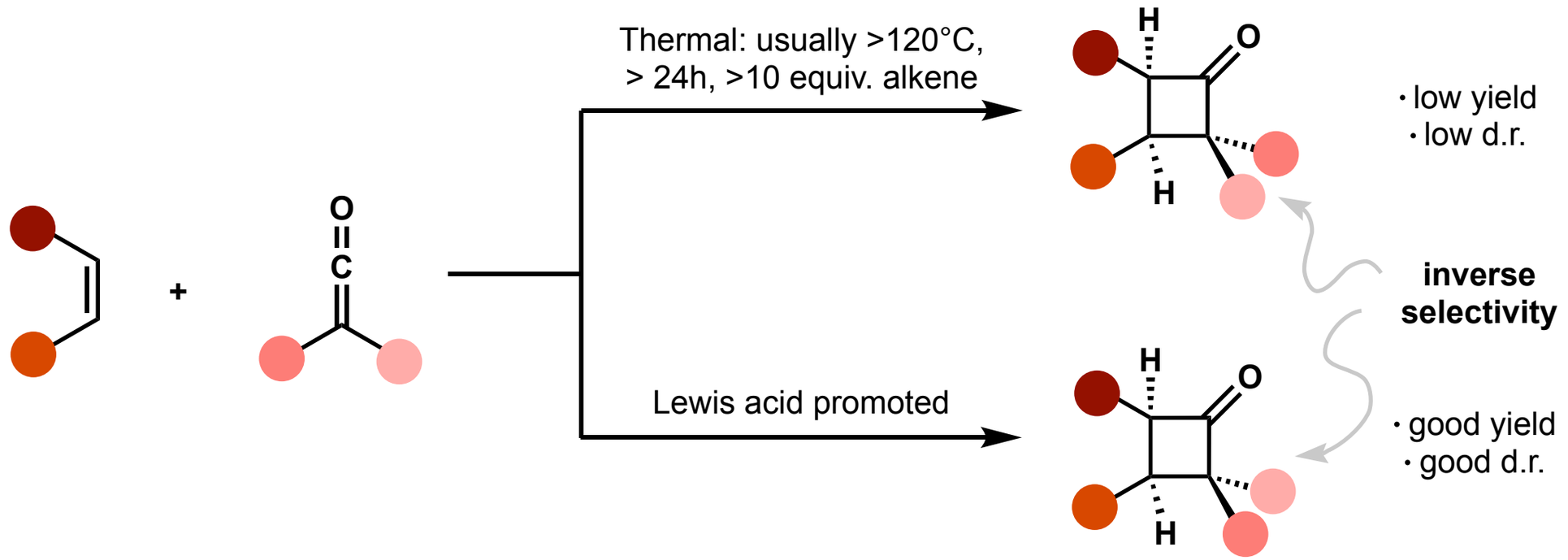
Thermal, Lewis acid,
radical cation/radical anion

Lewis acid promoted [2+2] cycloaddition of ketenes and allenes

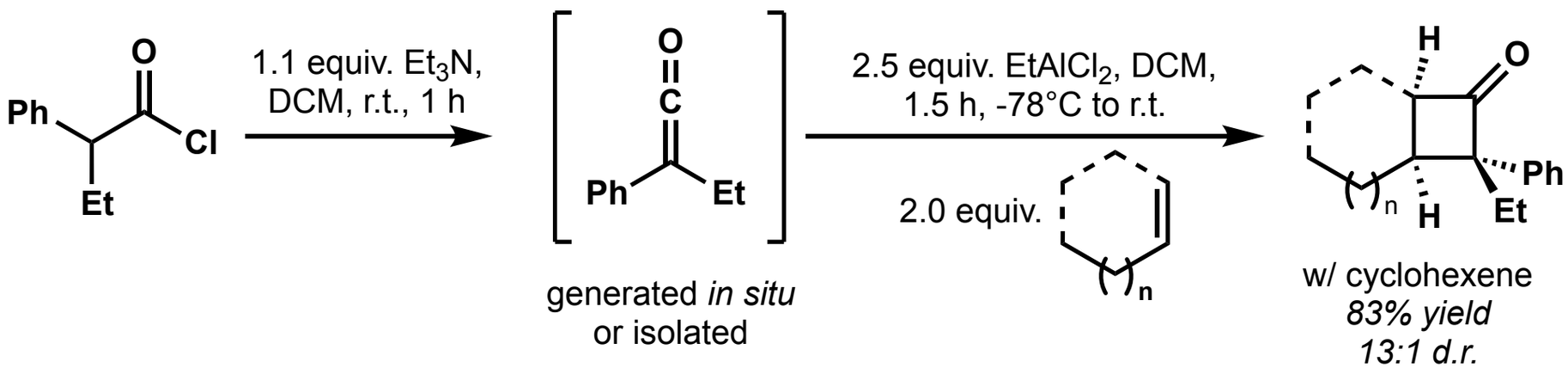


Acc. Chem. Res. **2023**, *56*, 2253-2264.

Lewis Acid Mediated [2+2] Cycloadditions



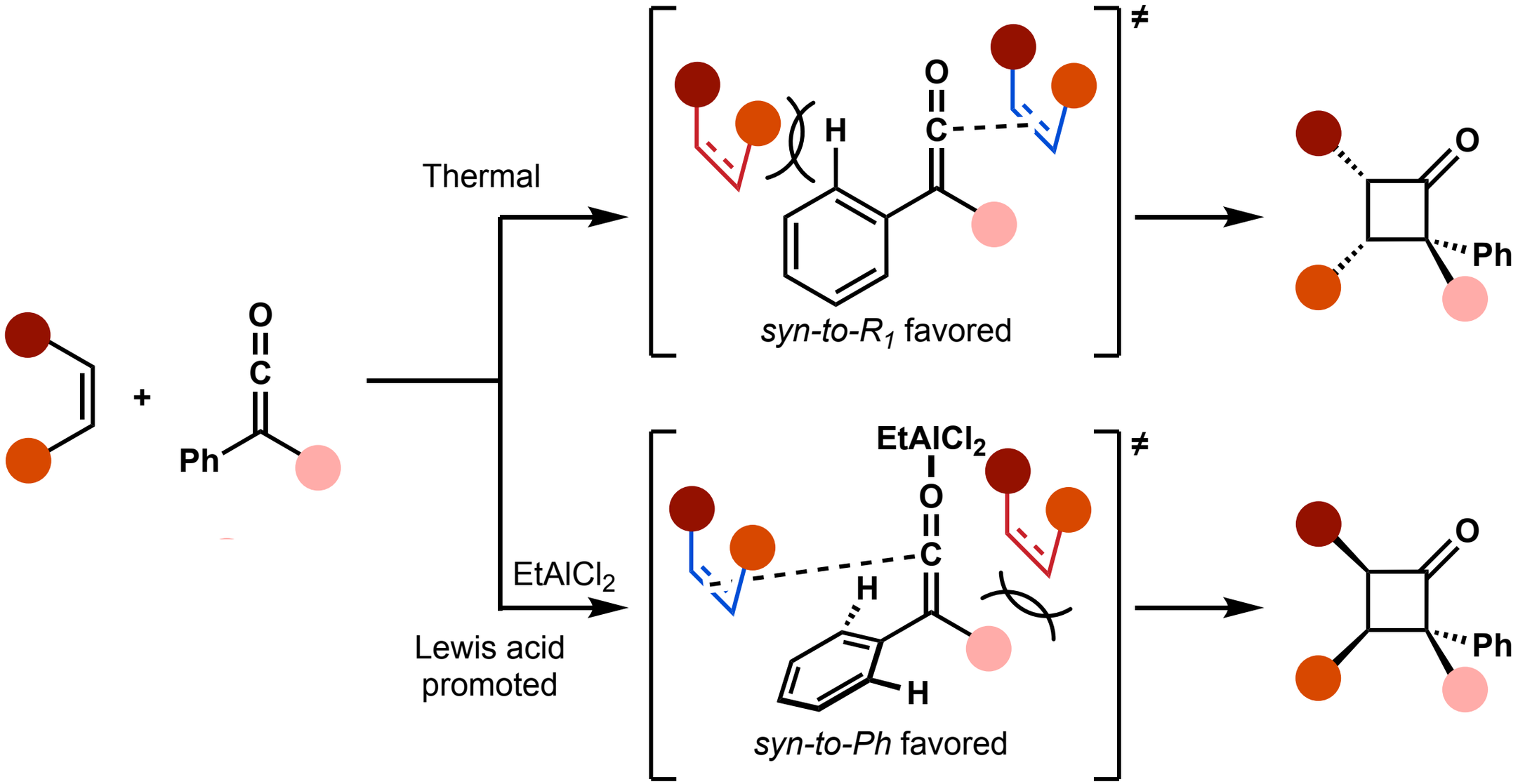
General reactivity explored:



Why does the use of a Lewis acid promote the opposite diastereoisomer compared to the thermal conditions?

JACS **2013**, *135*, 1673-1676.

Origin of Diastereoselectivity

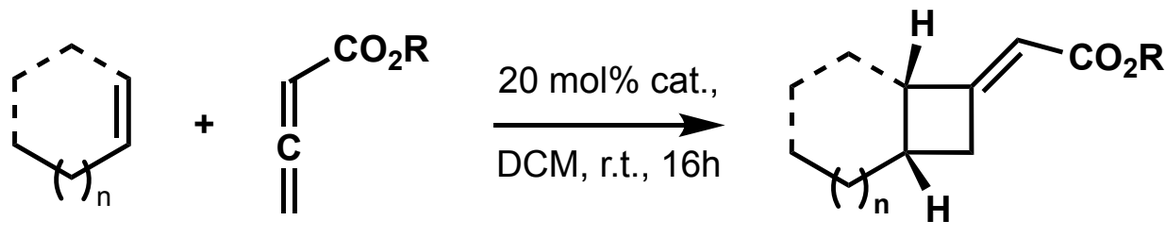


Phenyl group rotates out of conjugation in presence of the Lewis acid

JACS **2013**, *135*, 1673-1676; *Org. Lett.* **2014**, *16*, 5168-5171.

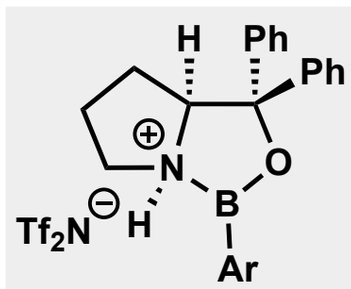
Further Developments of The Reaction

Catalytic Allenoate-Alkene [2+2] Cycloadditions



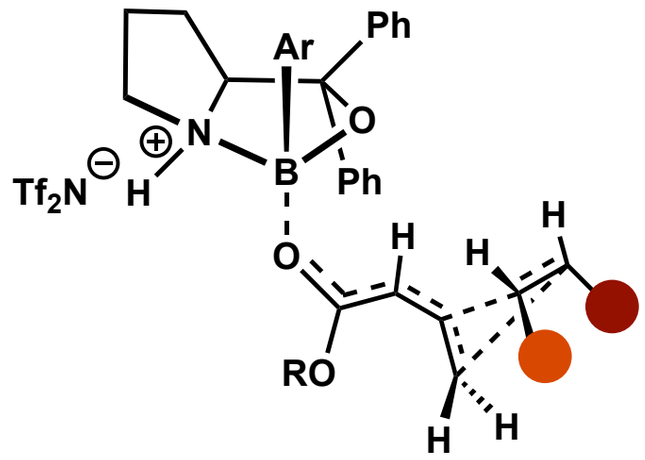
R = Bn or CH_2CF_3

catalyst:



Ar = 2-CF_3-4-Cl-C_6H_3

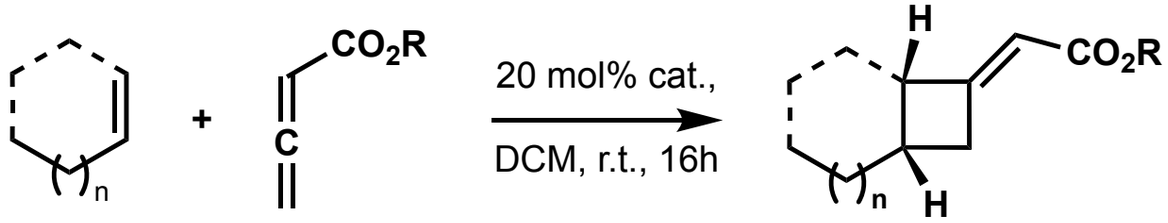
proposed model for selectivity



JACS **2015**, *137*, 3482-3485. *ACIE* **2015**, *54*, 11918-11928; *Tetrahedron* **2019**, *75*, 3265-3271; *JACS* **2018**, *140*, 15943-15949;

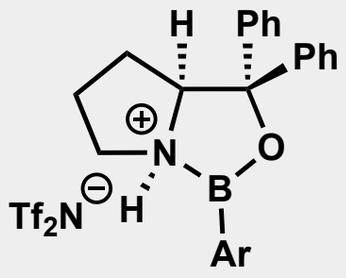
Further Developments of The Reaction

Catalytic Allenoate-Alkene [2+2] Cycloadditions



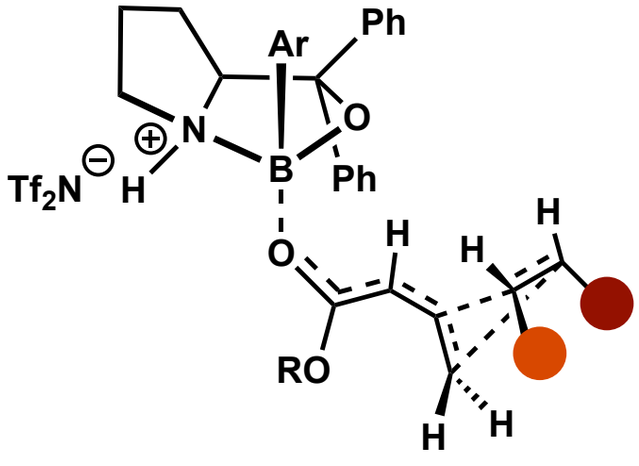
R = Bn or CH_2CF_3

catalyst:

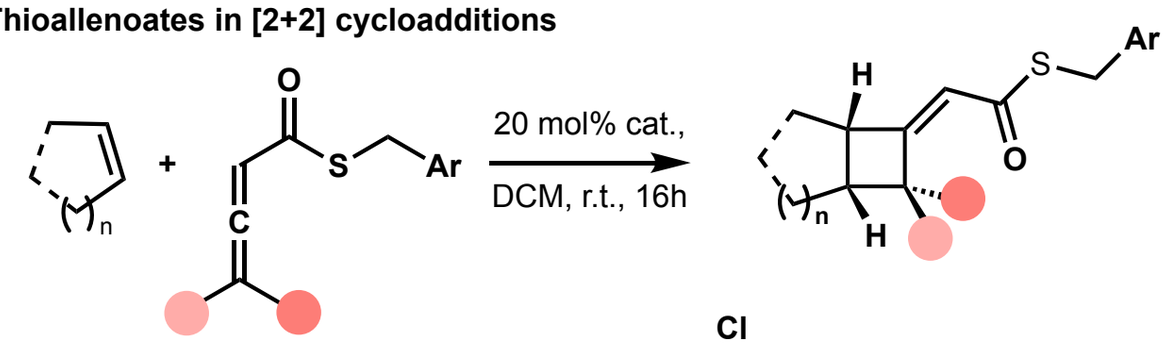


Ar = 2-CF_3-4-Cl-C_6H_3

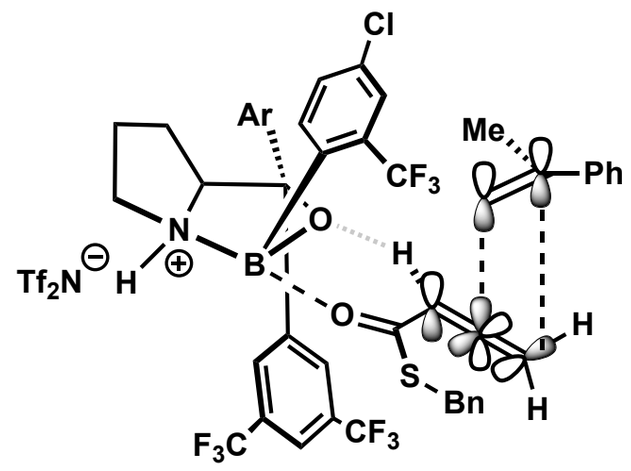
proposed model for selectivity



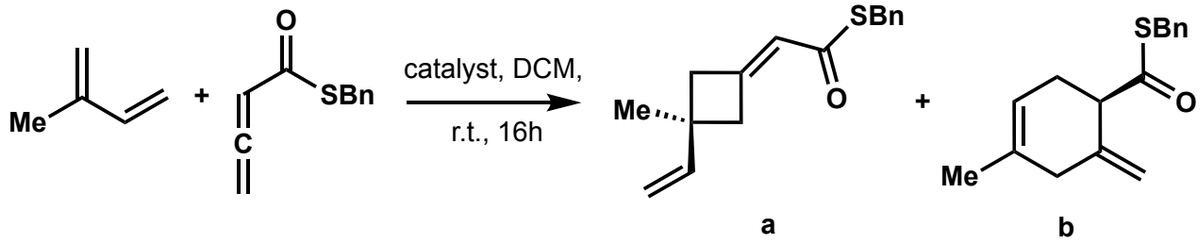
Thioallenoates in [2+2] cycloadditions



proposed model for selectivity



Periselectivity with isoprene

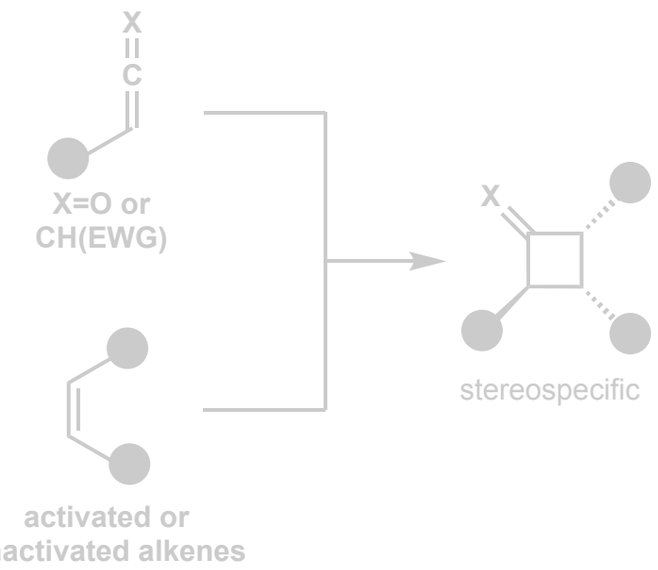


Catalyst	Yield	Selectivity (a:b)	e.r.
oxazaborolidine cat.	73%	>99:1	75:25
$EtAlCl_2$	83%	37:63	

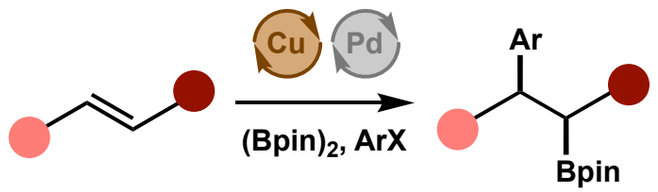
JACS **2015**, *137*, 3482-3485. *ACIE* **2015**, *54*, 11918-11928; *Tetrahedron* **2019**, *75*, 3265-3271; *JACS* **2018**, *140*, 15943-15949;

Independent Career

Lewis Acid Mediated [2+2] Cycloadditions

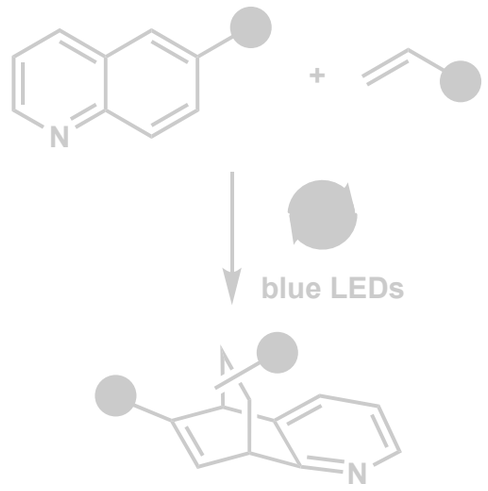


Cu/Pd Catalysis and Carboboration

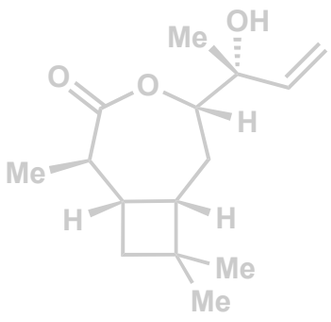


Catalyst controlled selectivity

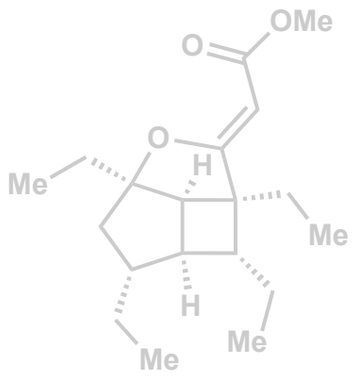
Photochemical Dearomative Cycloadditions



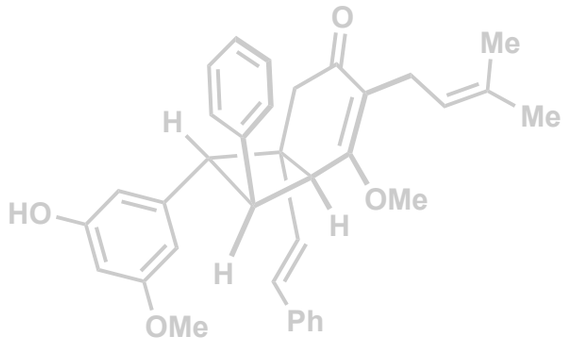
Total Synthesis



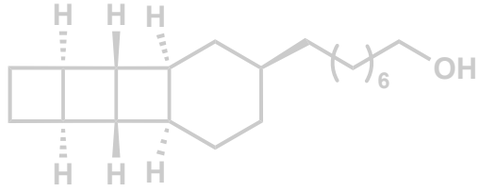
(-)-Hebelophyllene E



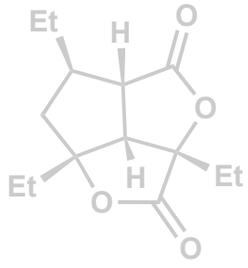
Hippolachnin A



(-)-Cajanusine

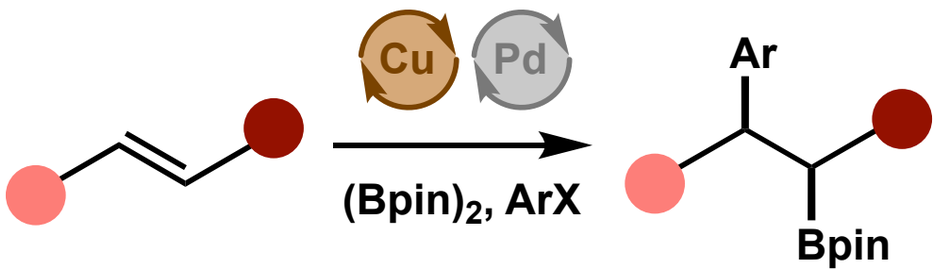


ent-[3]-Ladderanol



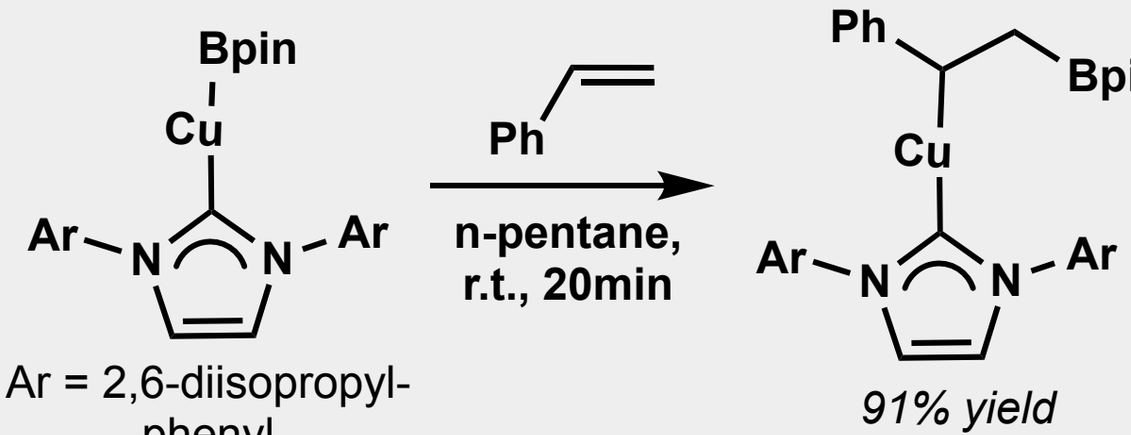
Gracilioether F

Cooperative Catalysis



Catalyst controlled selectivity

Key precedent:



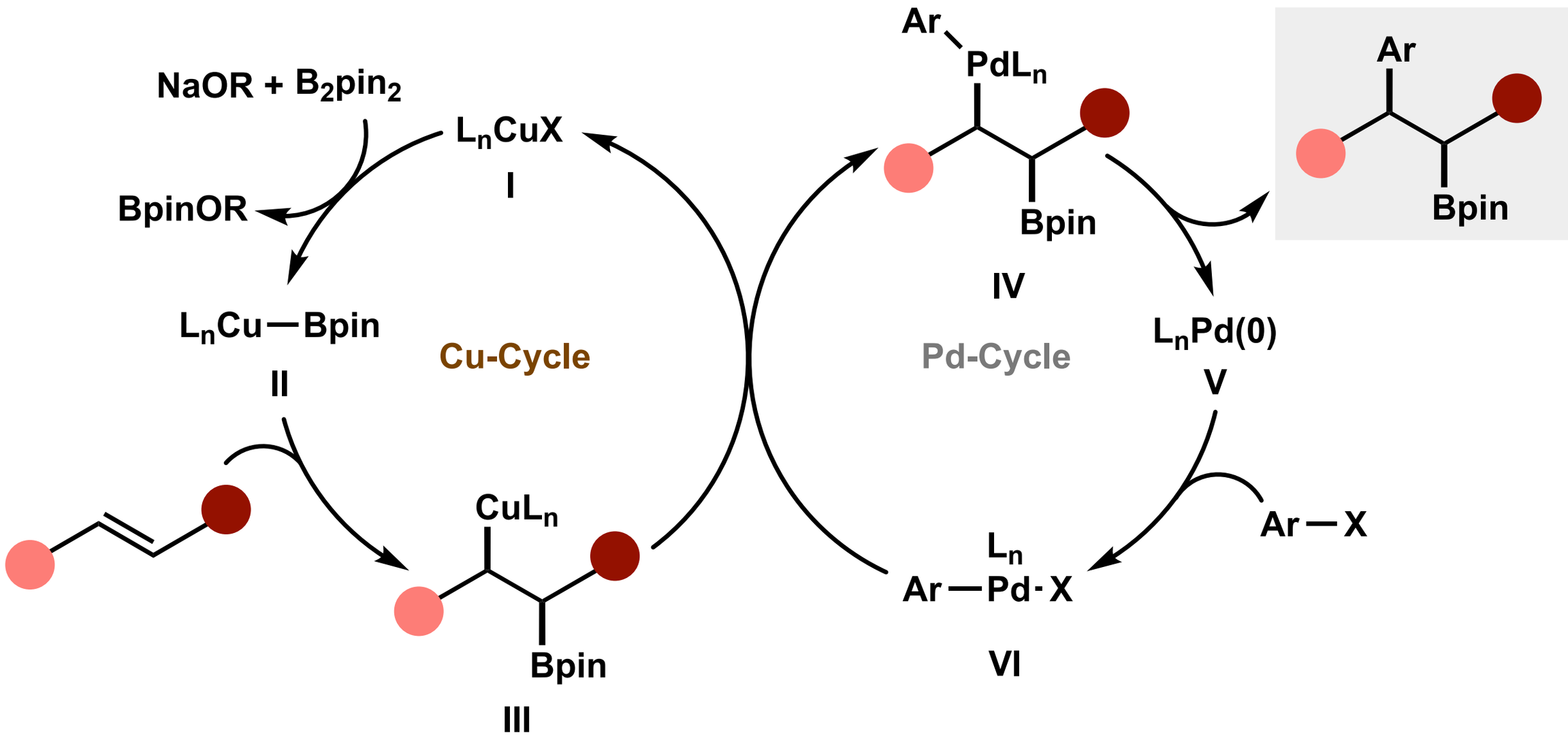
Ar = 2,6-diisopropyl-phenyl

91% yield

Sadighi, J. P. *Organometallics* **2006**, *25*, 2405-2408.

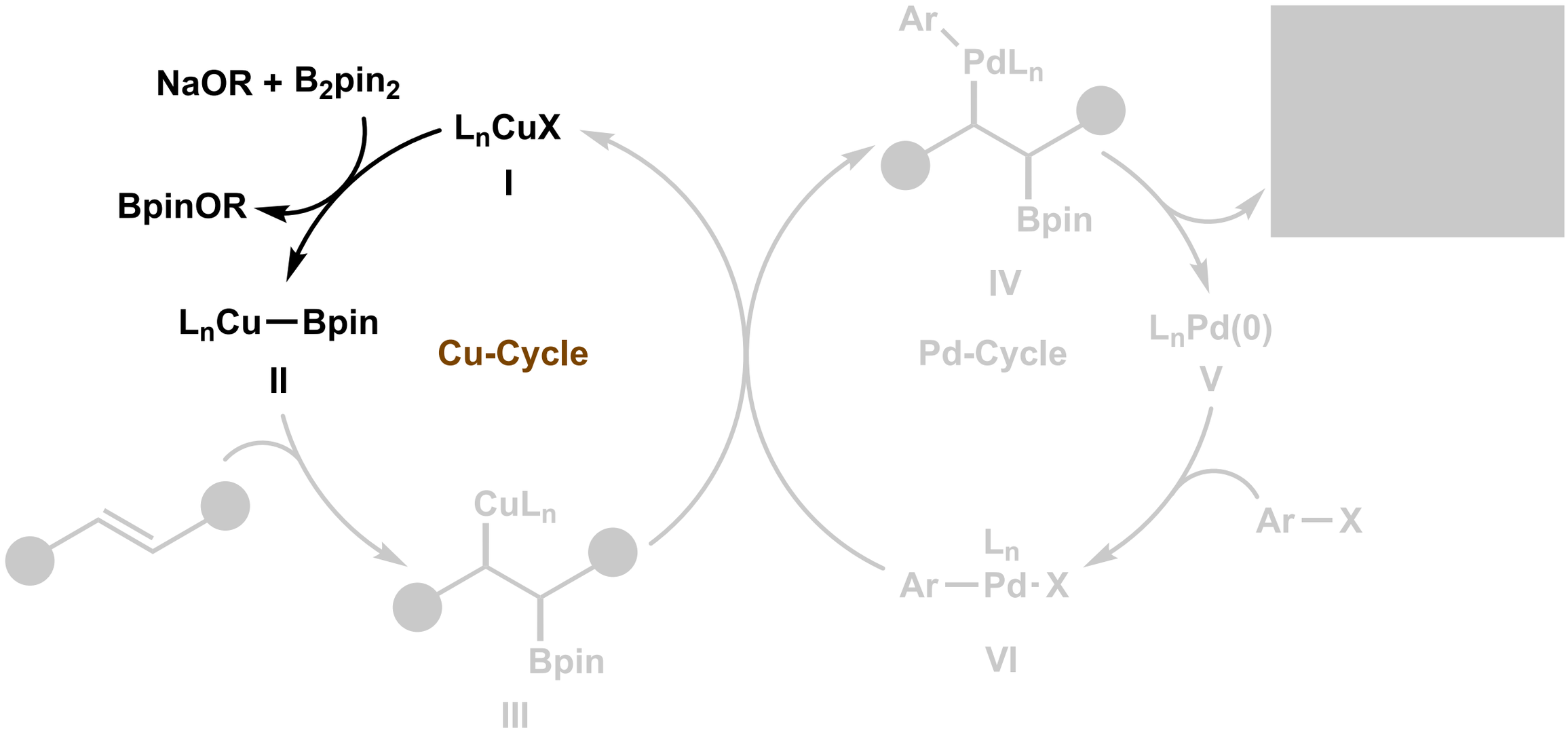
ACS Catal. **2022**, *12,* 2058-2063; *Organometallics* **2006**, *25*, 2405-2408.

Pd/Cu-Catalyzed Carboboration: Mechanism



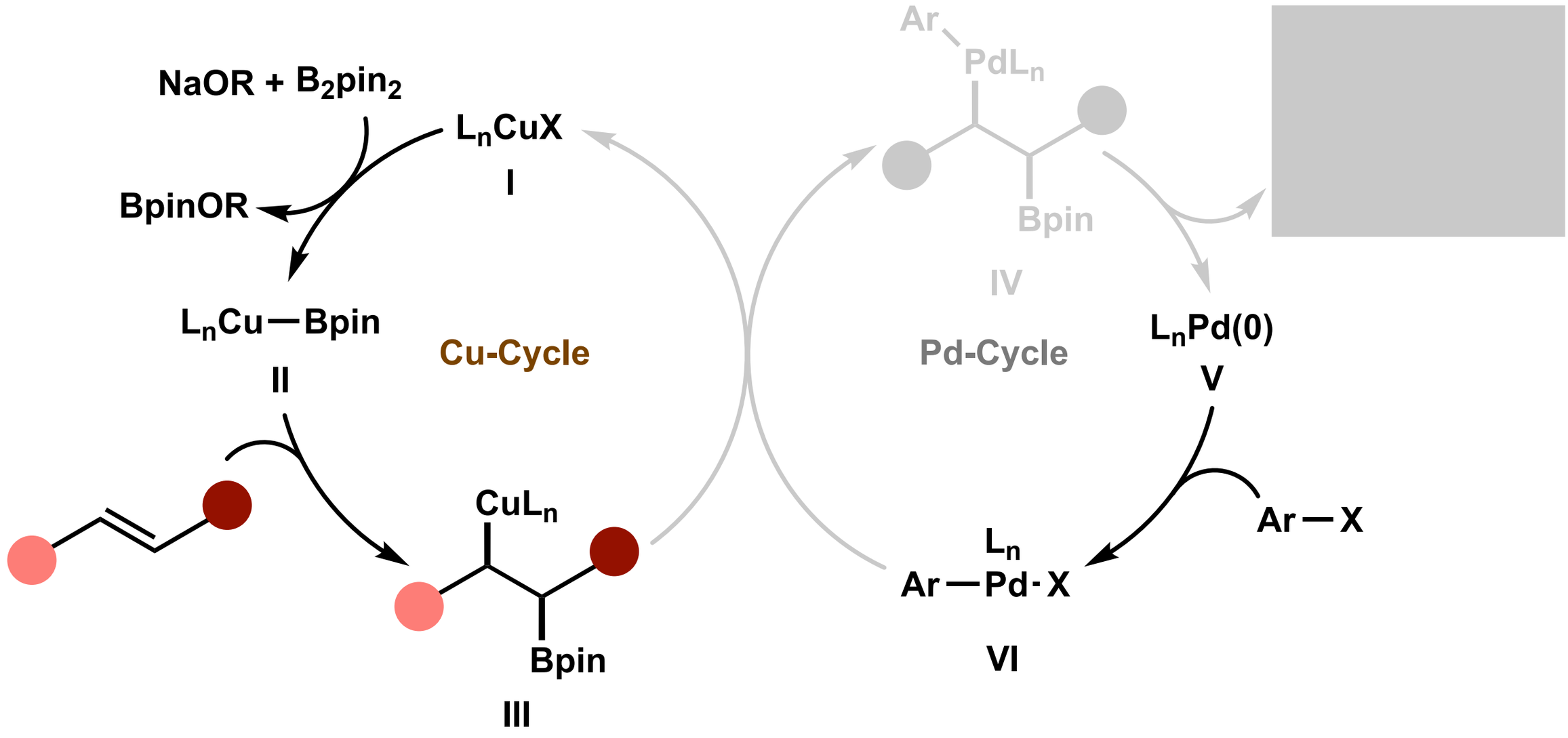
ACS Catal. **2022**, *12*, 2058-2063;

Pd/Cu-Catalyzed Carboboration: Mechanism



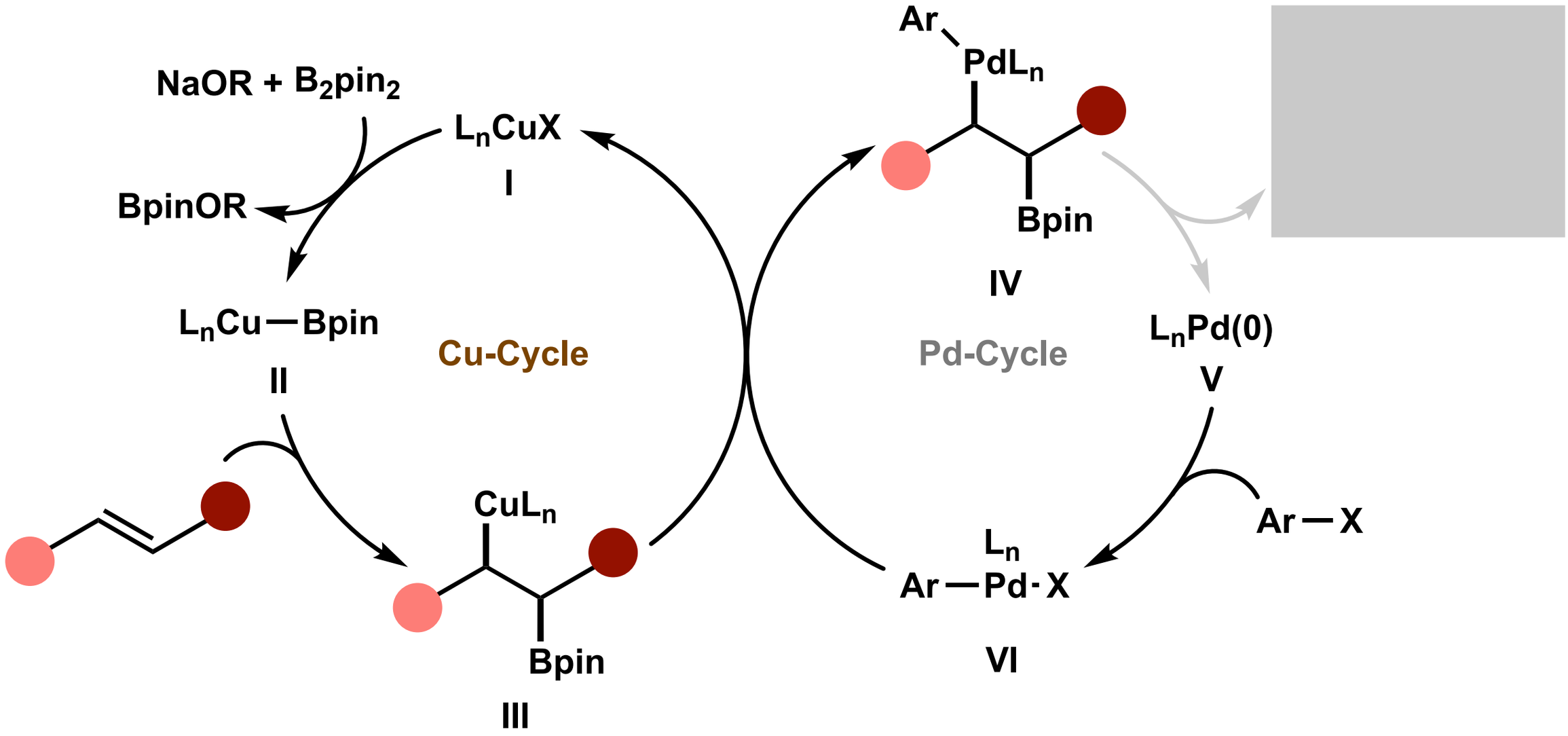
ACS Catal. **2022**, *12,* 2058-2063;

Pd/Cu-Catalyzed Carboboration: Mechanism



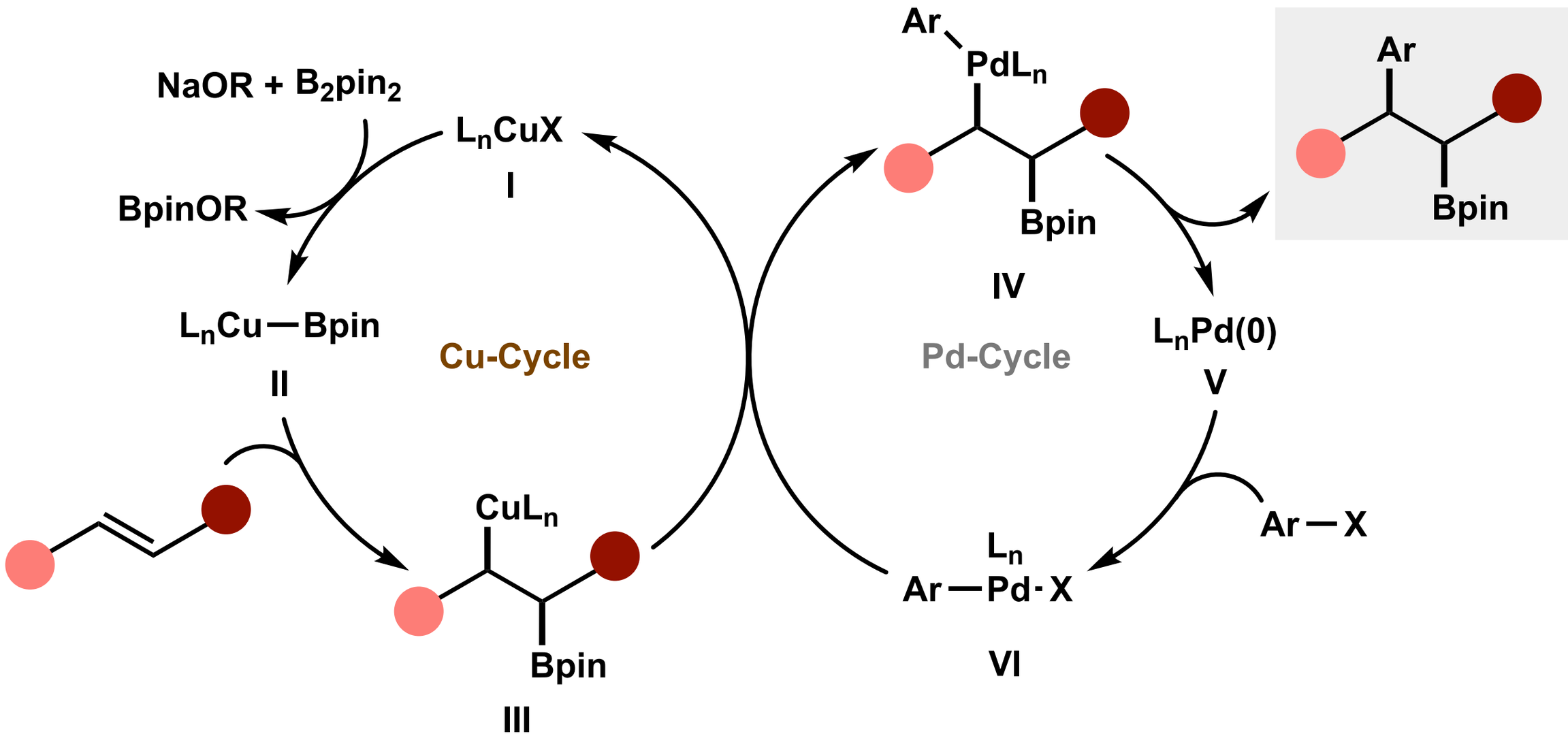
ACS Catal. **2022**, *12,* 2058-2063;

Pd/Cu-Catalyzed Carboboration: Mechanism



ACS Catal. **2022**, *12*, 2058-2063;

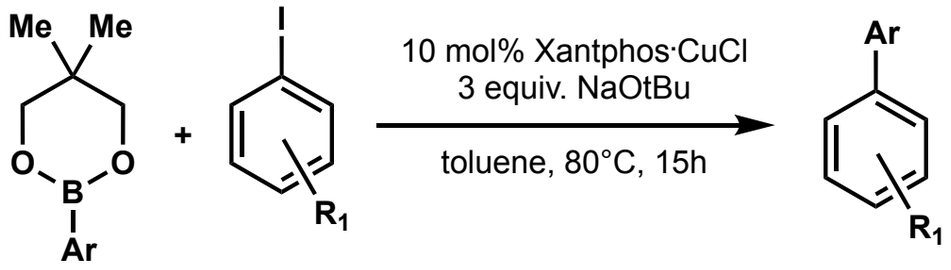
Pd/Cu-Catalyzed Carboboration: Mechanism

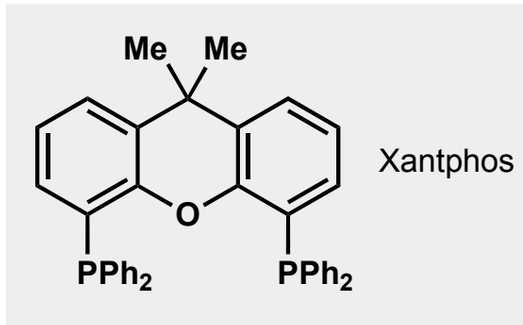


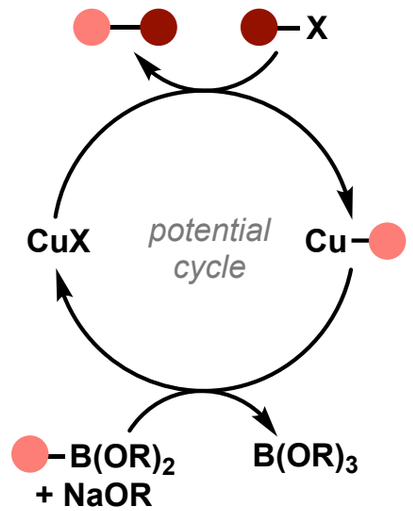
ACS Catal. **2022**, *12*, 2058-2063;

First Works on Carboboration

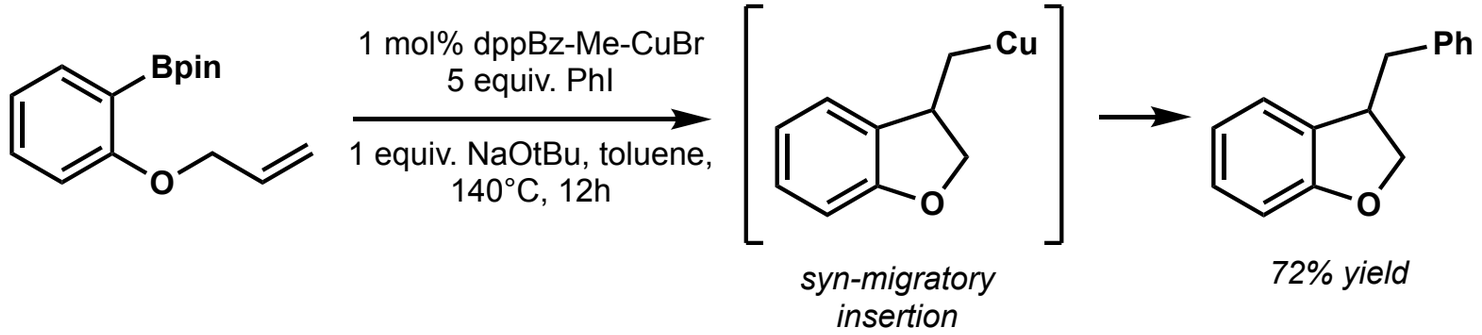
ACIE **2014**, *53*, 3475-3479.

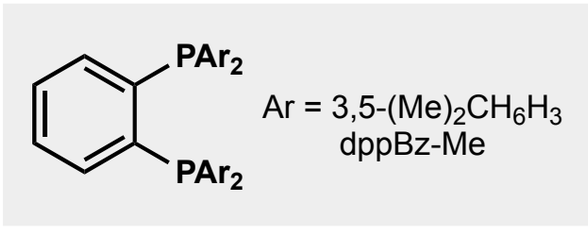




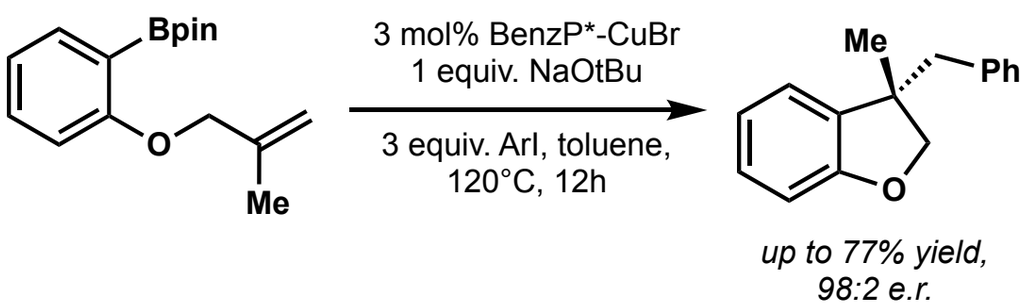


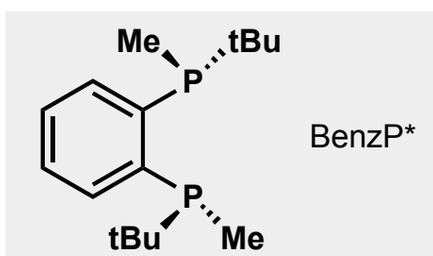
JACS **2014**, *136*, 14730-14733.





JACS **2015**, *137*, 14578-14581.

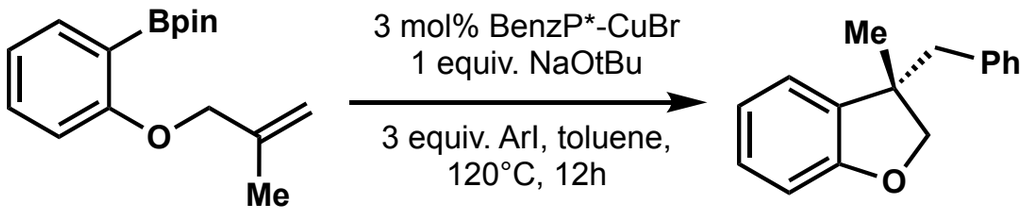




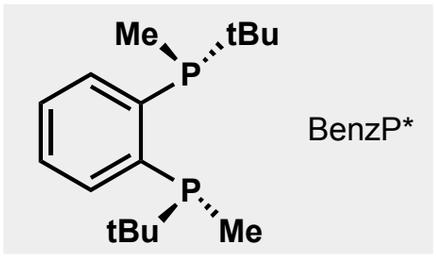
ACIE **2014**, *53*, 3475-3479; *JACS* **2014**, *136*, 14730-14733; *JACS* **2015**, *137*, 14578-14581.

First Works on Carboboration

JACS **2015**, *137*, 14578-14581.

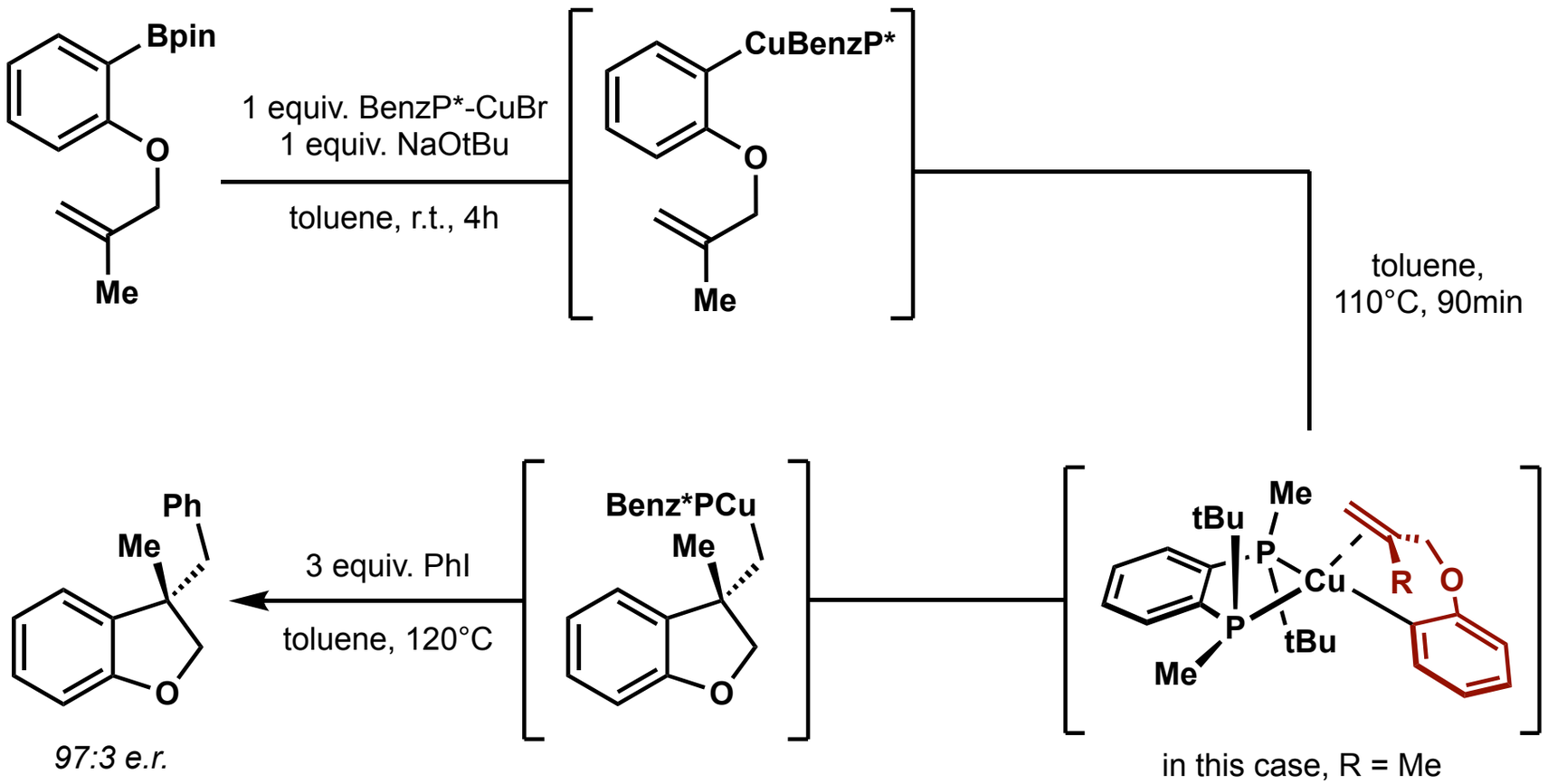


up to 77% yield,
98:2 e.r.



BenzP*

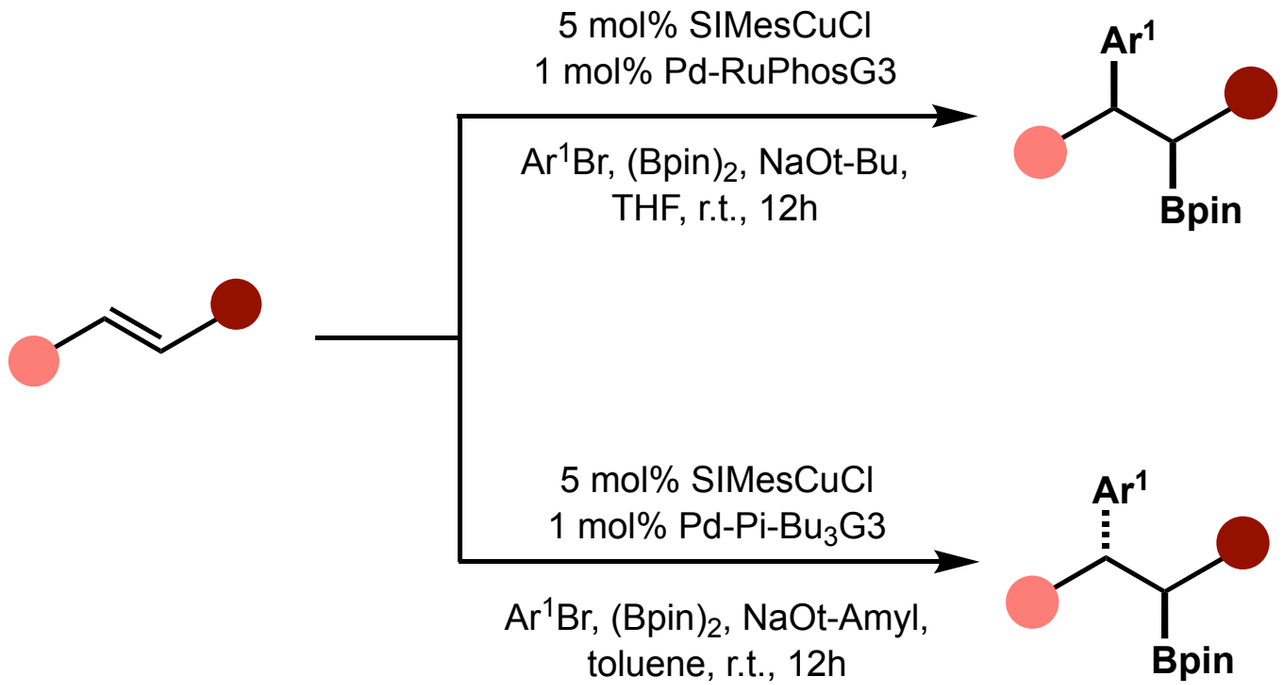
Hypothesized mechanism:



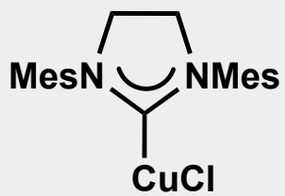
97:3 e.r.

ACIE **2014**, *53*, 3475-3479; *JACS* **2014**, *136*, 14730-14733; *JACS* **2015**, *137*, 14578-14581.

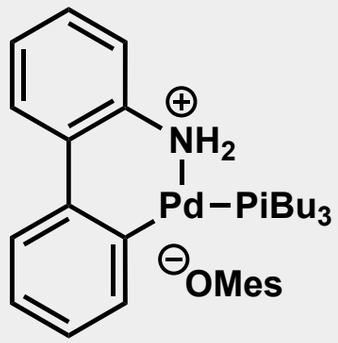
Diastereodivergence



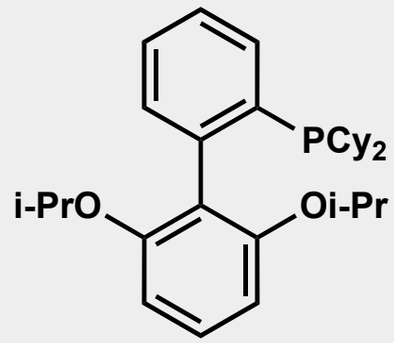
Catalysts:



SIMesCuCl



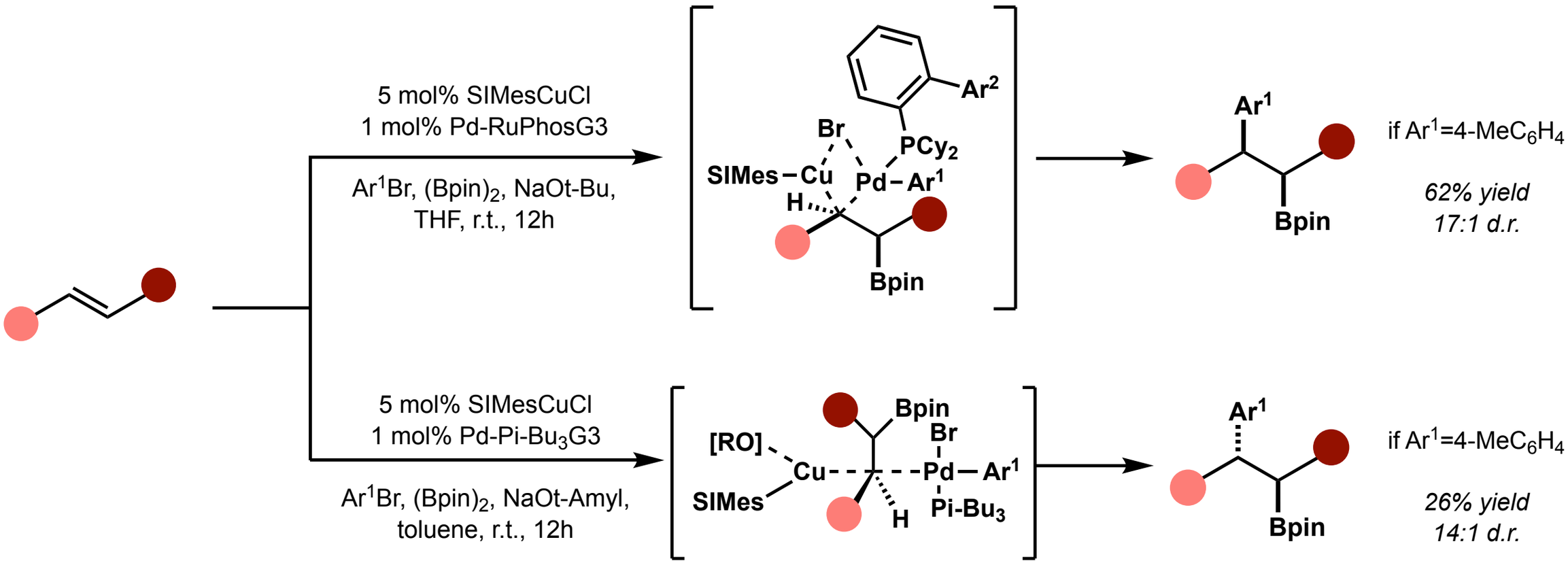
Pd-Pi-Bu$_3$G3



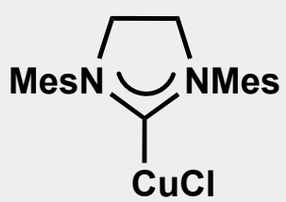
RuPhos

ACIE **2015**, *54*, 5228-5231.

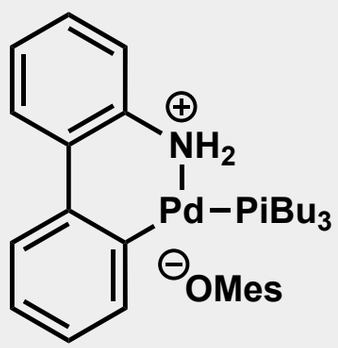
Diastereodivergence



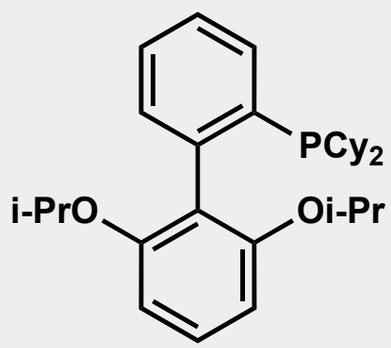
Catalysts:



SIMesCuCl



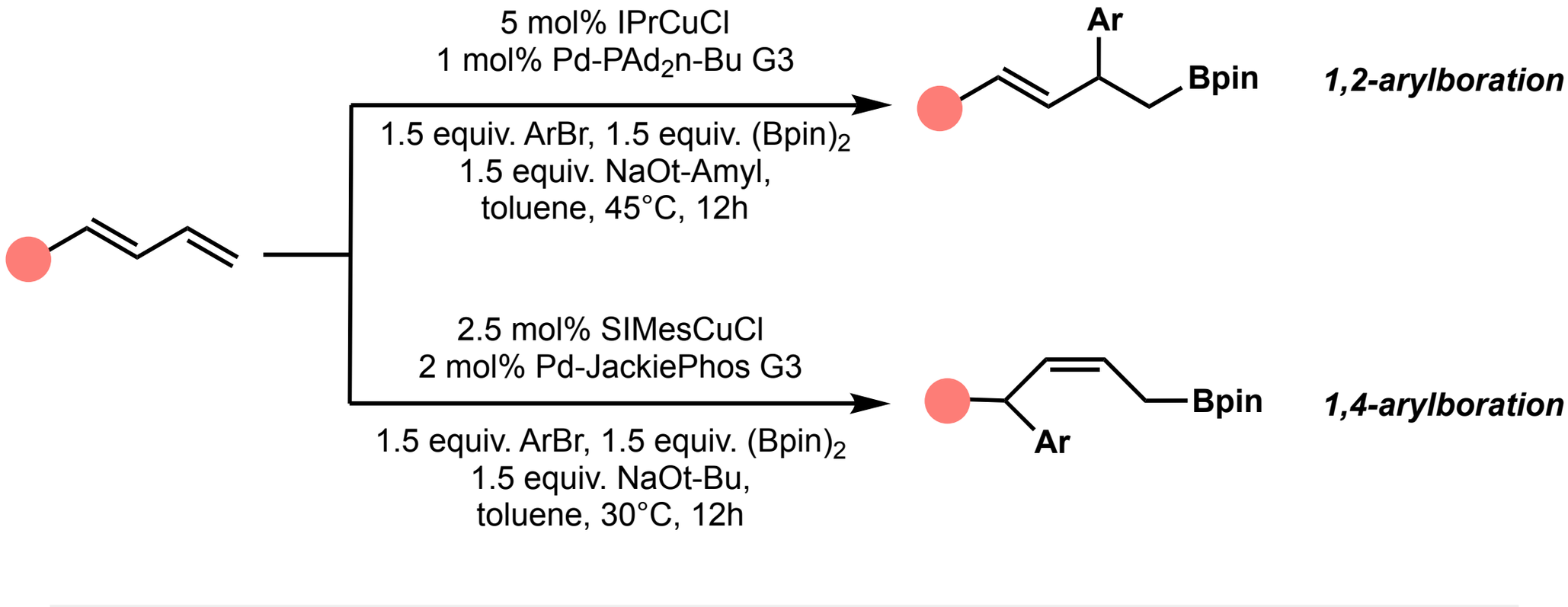
Pd-Pi-Bu$_3$G3

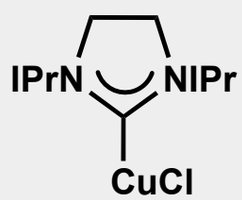


RuPhos

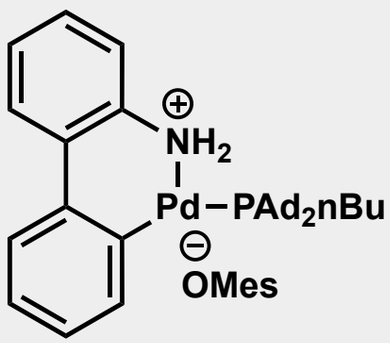
ACIE **2015**, *54*, 5228-5231.

Regiodivergence (1,2 vs 1,4)

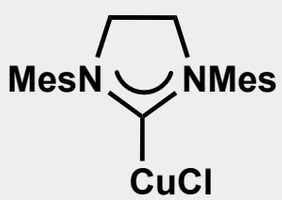




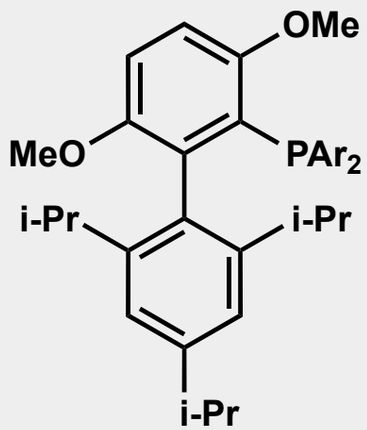
IPrCuCl



Pd-PAd$_2$nBuG3



SIMesCuCl

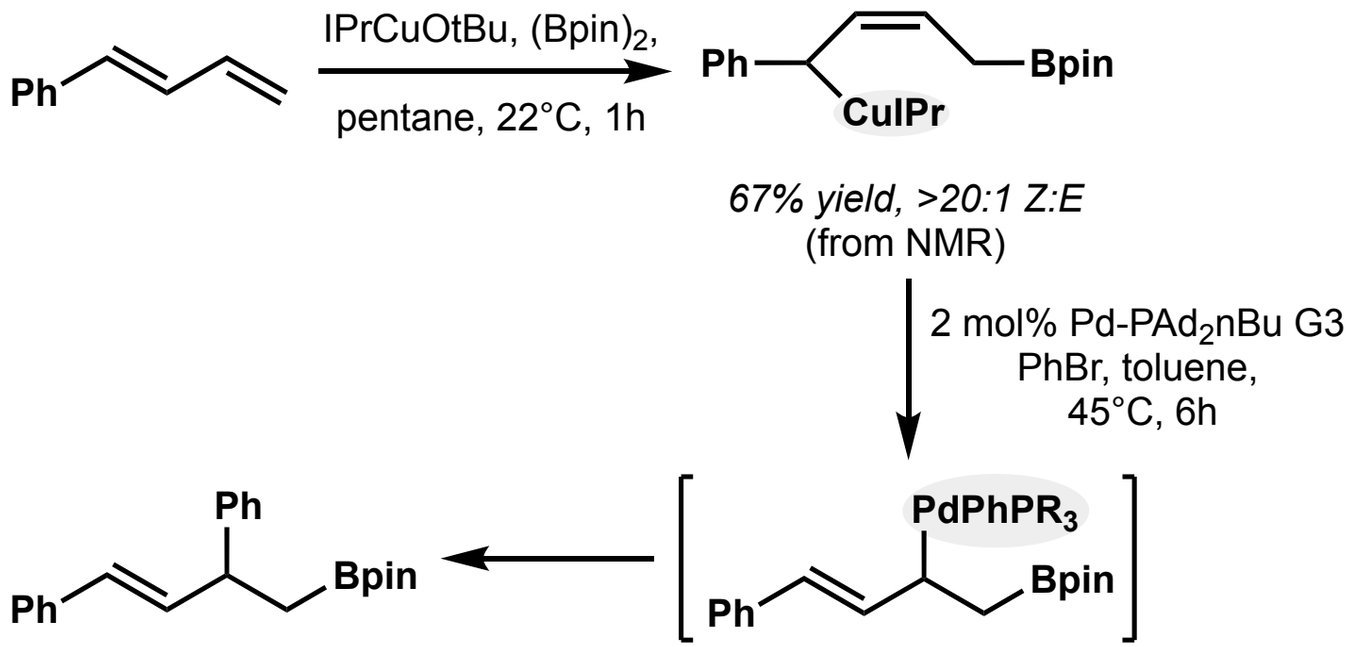


Ar = 3,5-(CF$_3$)C$_6$H$_3$
JackiePhos

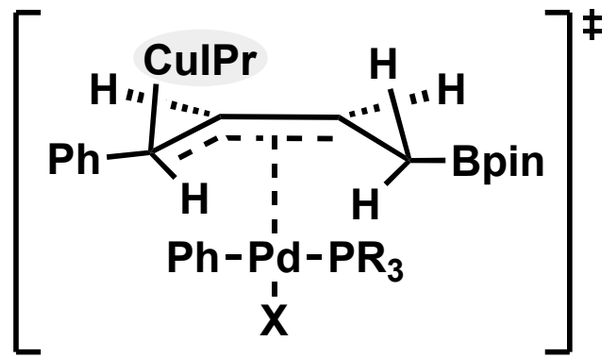
JACS **2017***; 139,* 9823-9826.

Regiodivergence (1,2 vs 1,4)

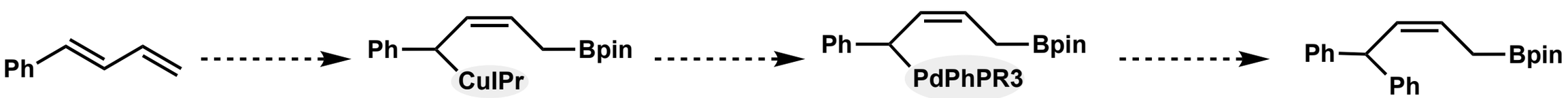
Mechanistic investigation on 1,2 addition:



proposed model for transmetallation:

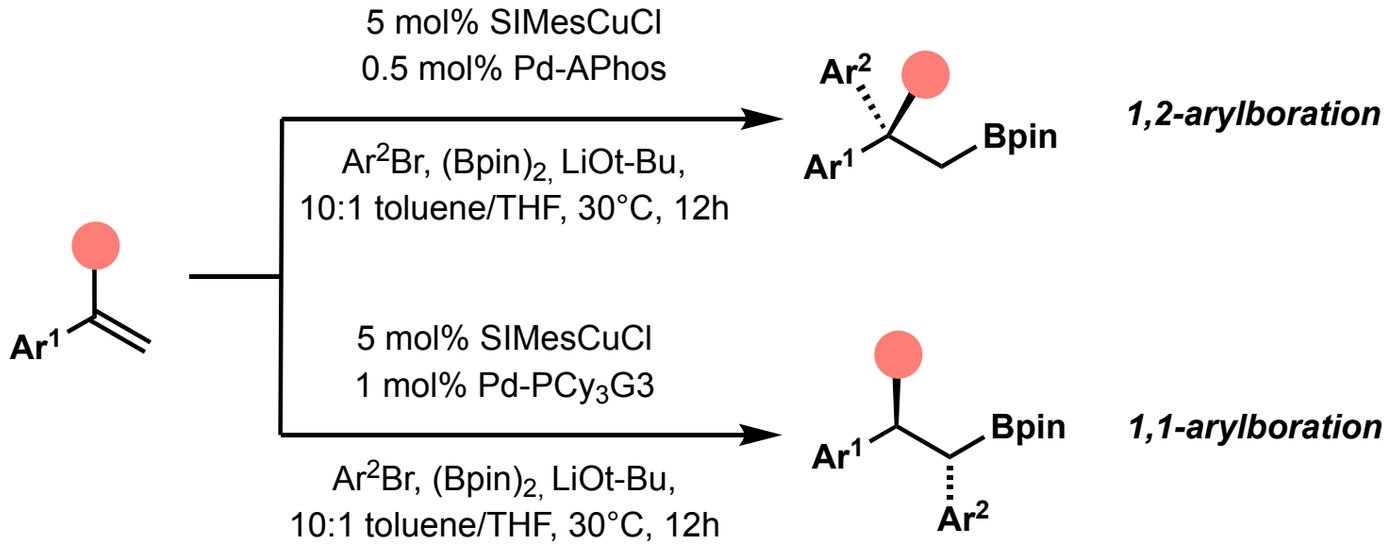


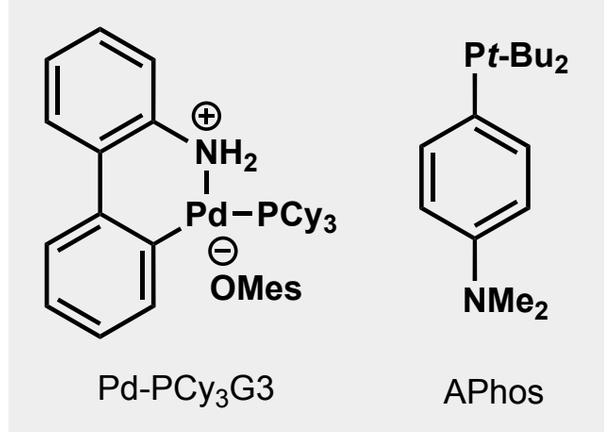
Mechanistic hypothesis for 1,4 addition:



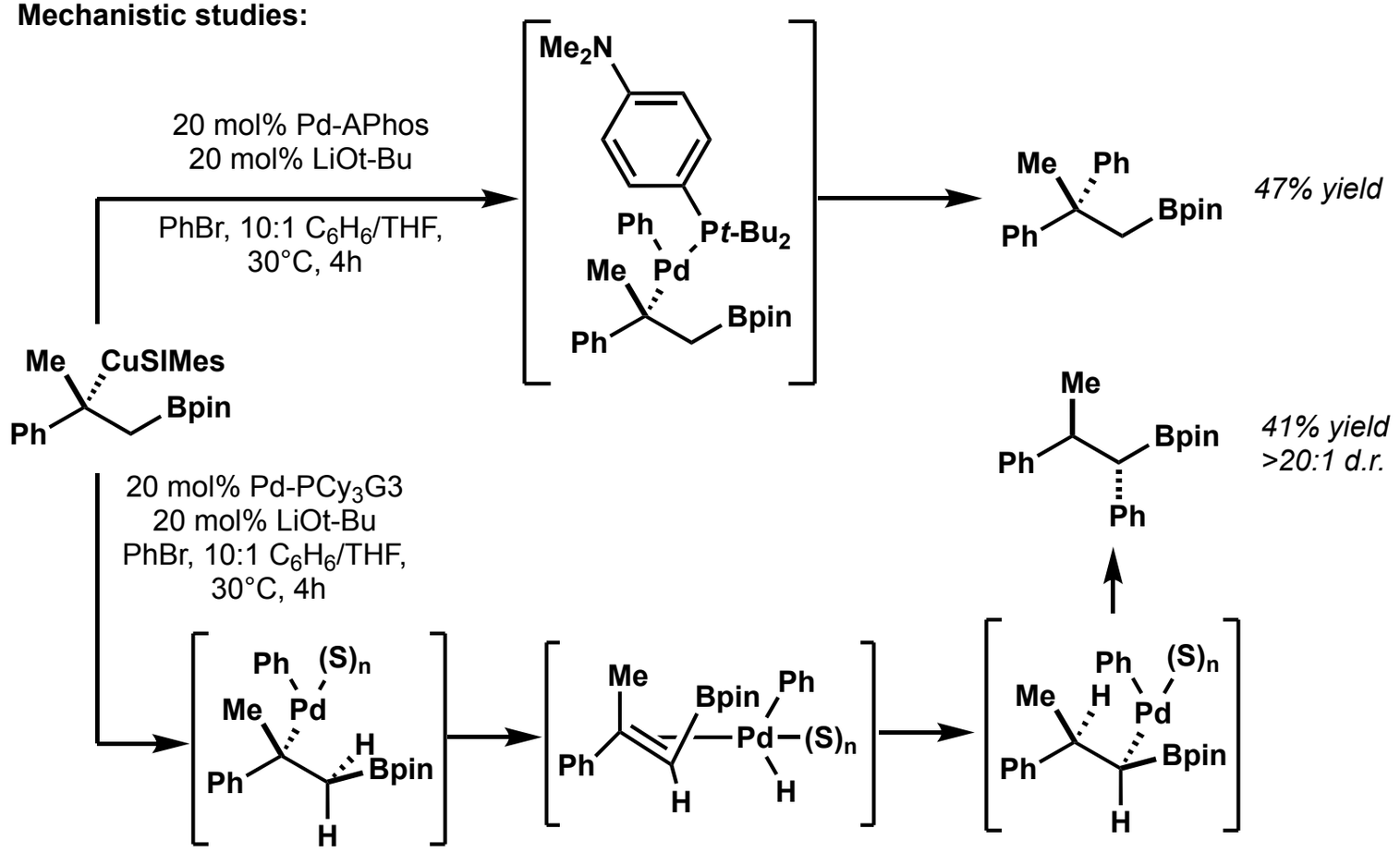
JACS **2017***; 139,* 9823-9826.

Regiodivergence (1,2 vs 1,1)





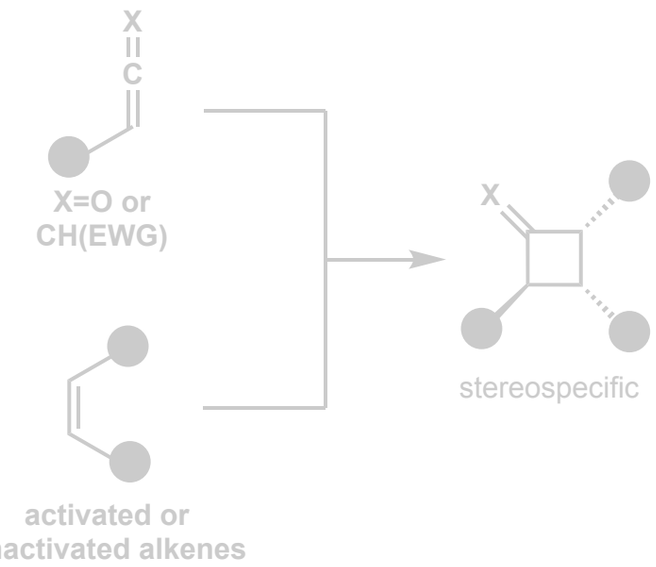
Mechanistic studies:



ACIE 2019, *58,* 1719-1723.

Independent Career

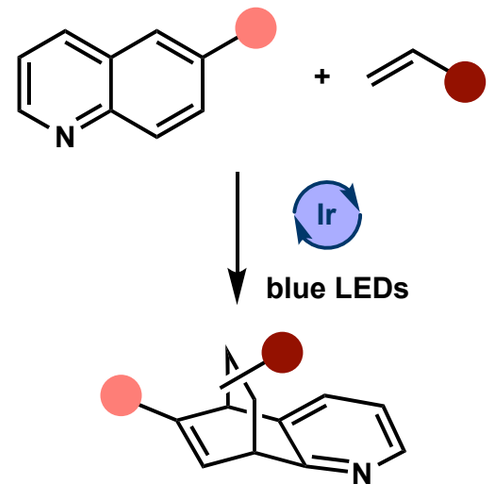
Lewis Acid Mediated [2+2] Cycloadditions



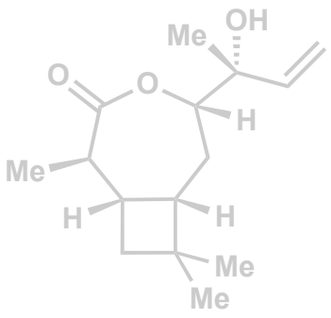
Cu/Pd Catalysis and Carboboration

Catalyst controlled selectivity

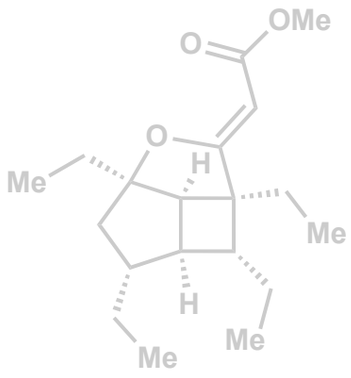
Photochemical Dearomative Cycloadditions



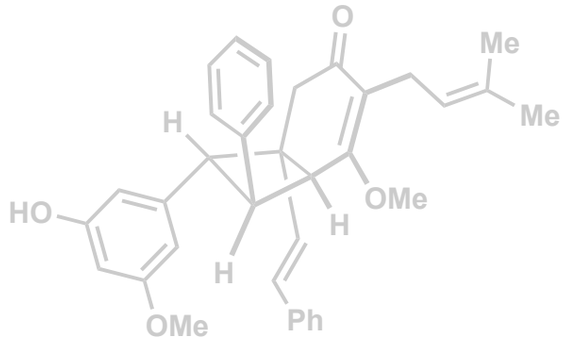
Total Synthesis



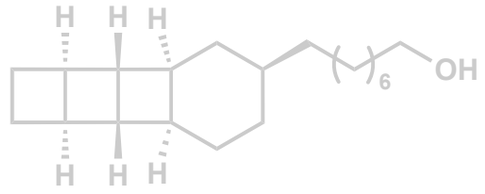
(-)-Hebelophyllene E



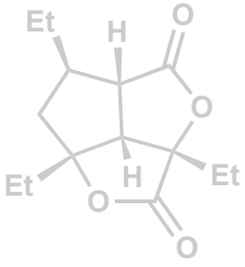
Hippolachnin A



(-)-Cajanusine

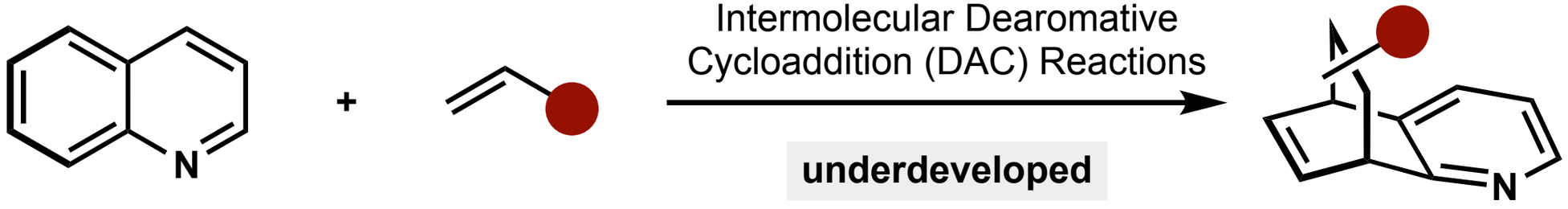


ent-[3]-Ladderanol



Gracilioether F

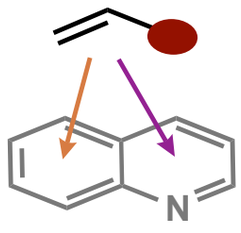
Dearomative Cycloaddition Reactions (DAC)



81.0 kcal/mol

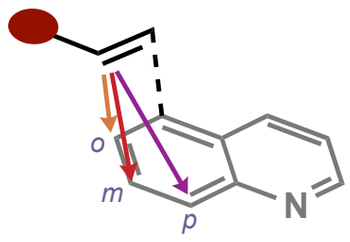
resonance stabilization energy

Selectivity challanges:



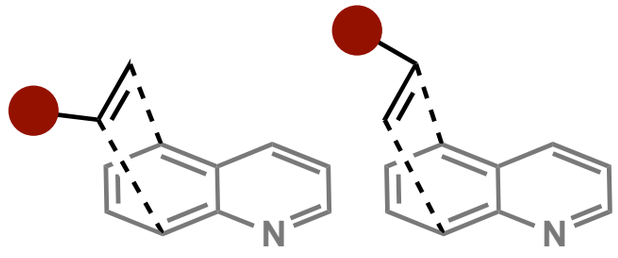
carbocycle vs heterocycle

Chemoselectivity



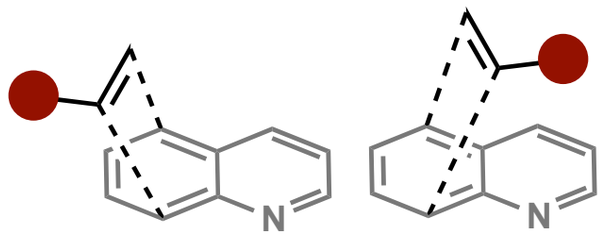
ortho vs meta vs para

Regioselectivity



syn vs anti

Regioselectivity

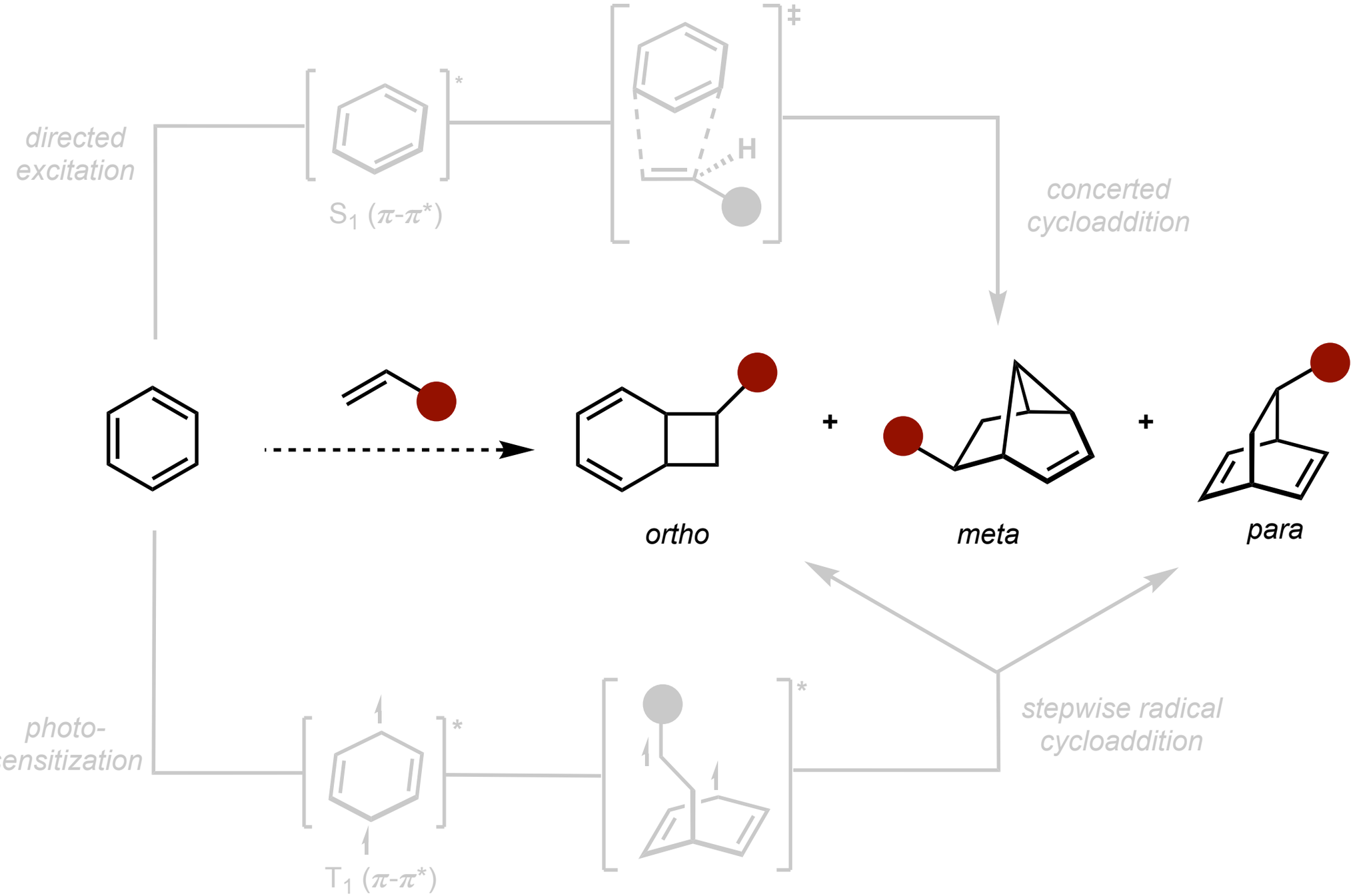


exo vs endo

Diastereoselectivity

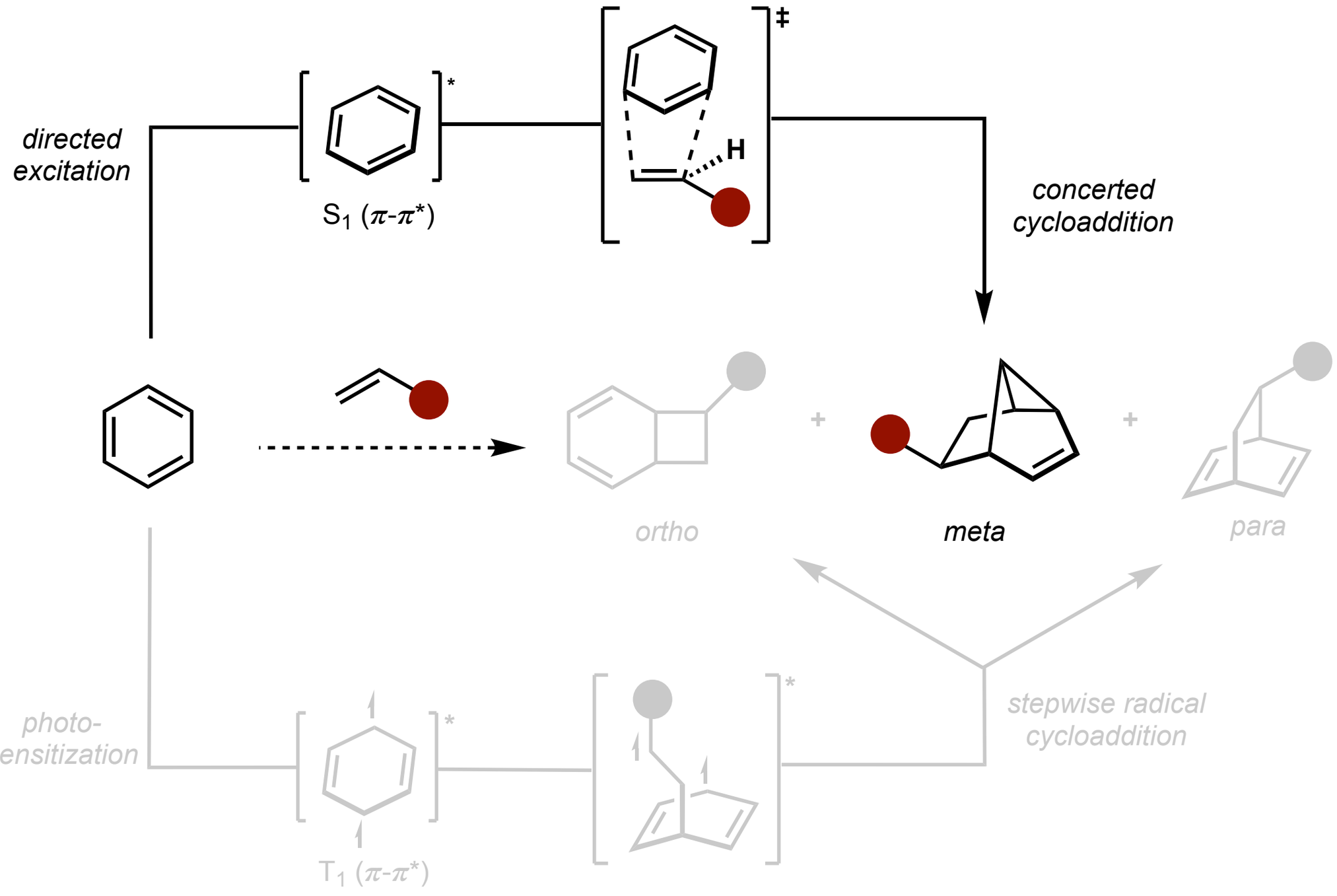
Science **2021**, *371*, 1338-1345;

Photochemical DAC



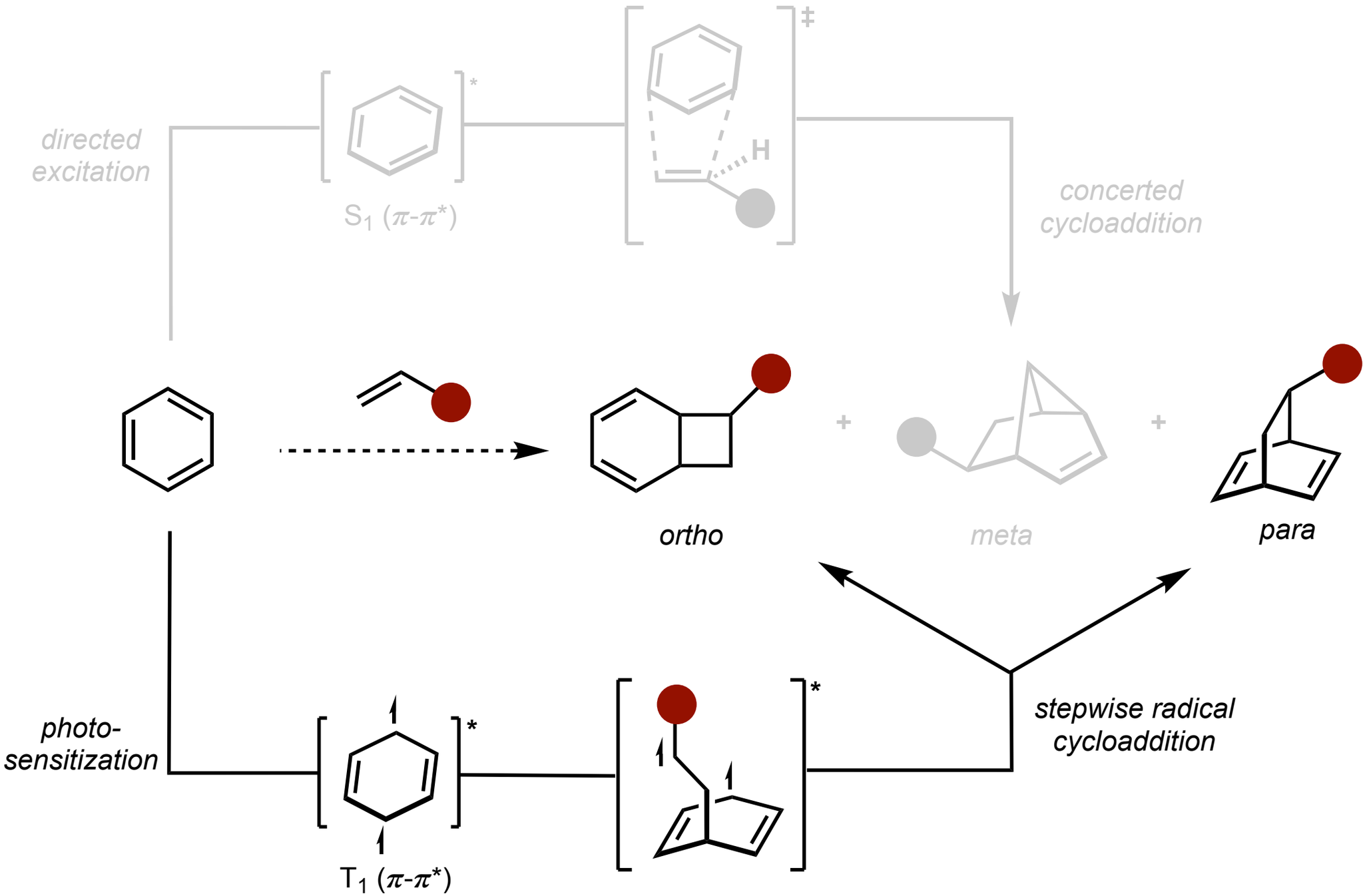
Science **2021**, *371,* 1338-1345; *JACS* **2022**, *144*, 17680-17691; *Pure and Applied Chemistry* **1982**, *54*(9), 1633-1650.

Photochemical DAC



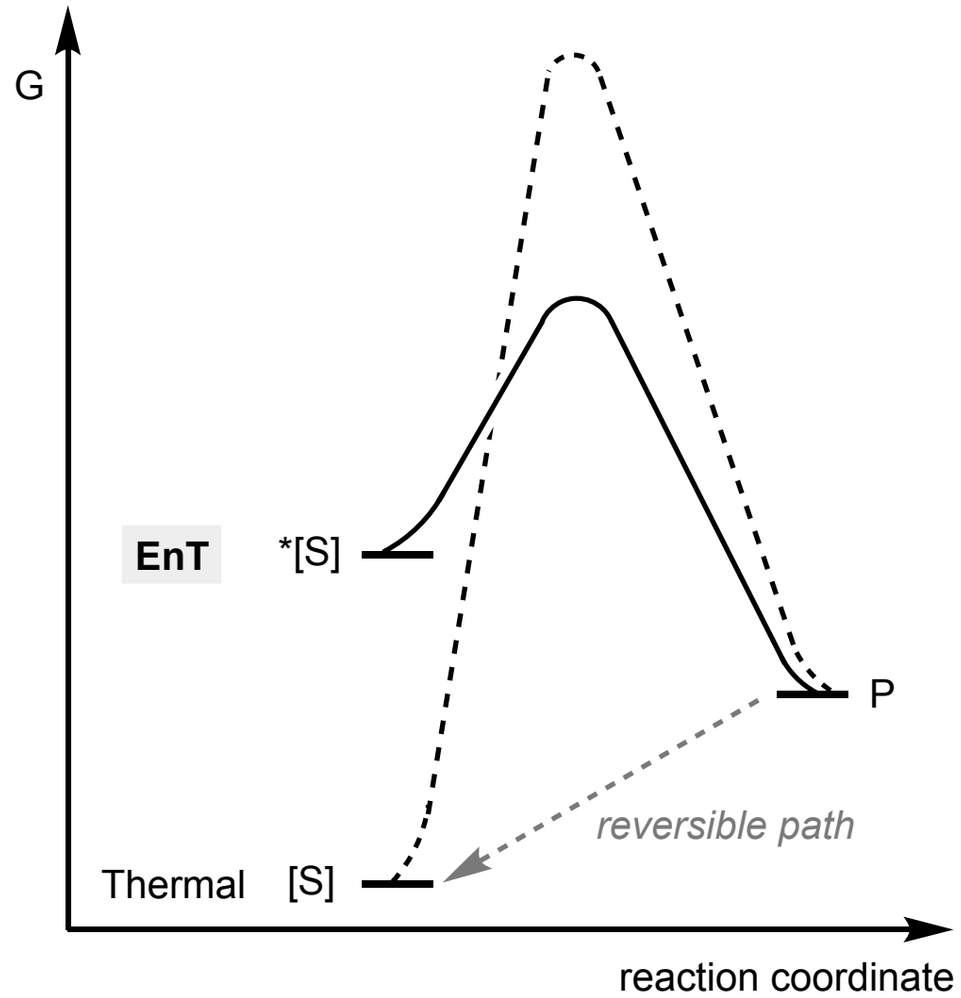
Science **2021**, *371,* 1338-1345; *JACS* **2022**, *144*, 17680-17691; *Pure and Applied Chemistry* **1982**, *54*(9), 1633-1650.

Photochemical DAC



Science **2021**, *371,* 1338-1345; *JACS* **2022**, *144*, 17680-17691; *Pure and Applied Chemistry* **1982**, *54*(9), 1633-1650.

EnT could help to solve the problems



Challanges:

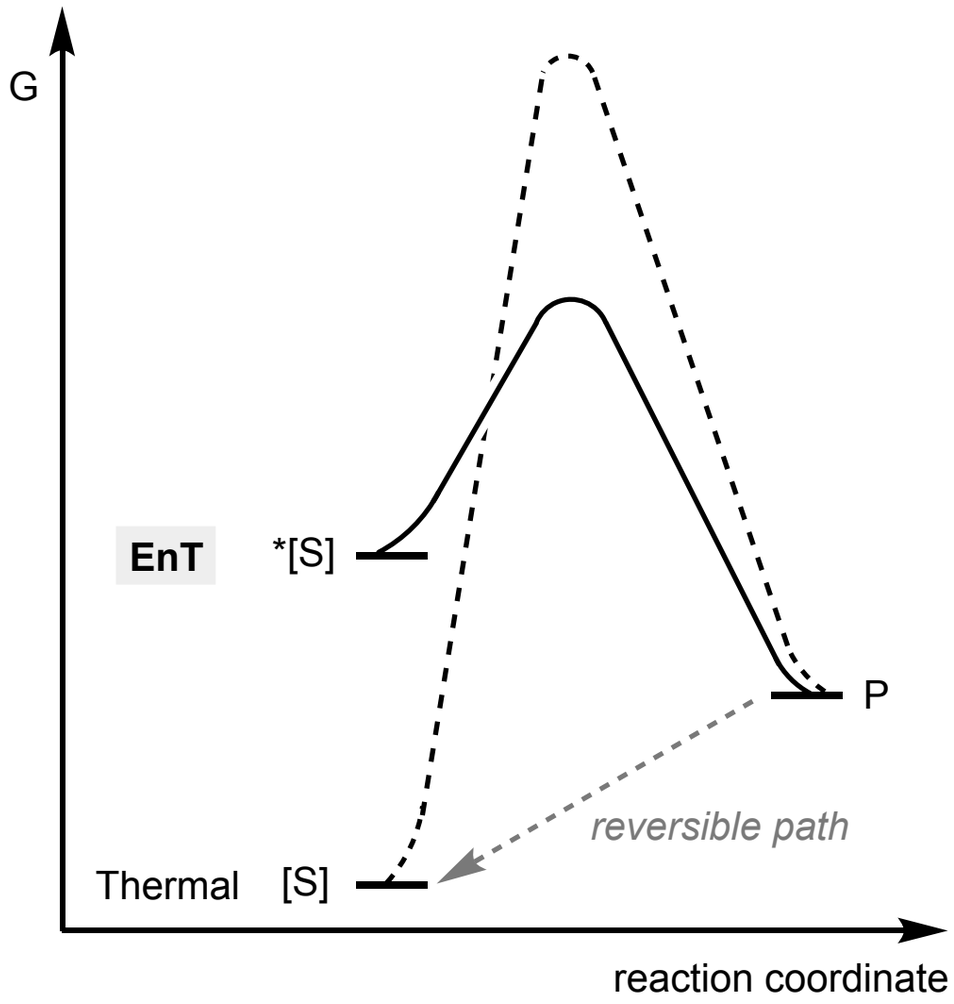
- High kinetic barrier
- Reverse reaction

Solution: EnT process

- Mild conditions
- Selective excitation
- Compressed kinetic barrier

Science **2021**, *371,* 1338-1345;

EnT could help to solve the problems



Challanges:

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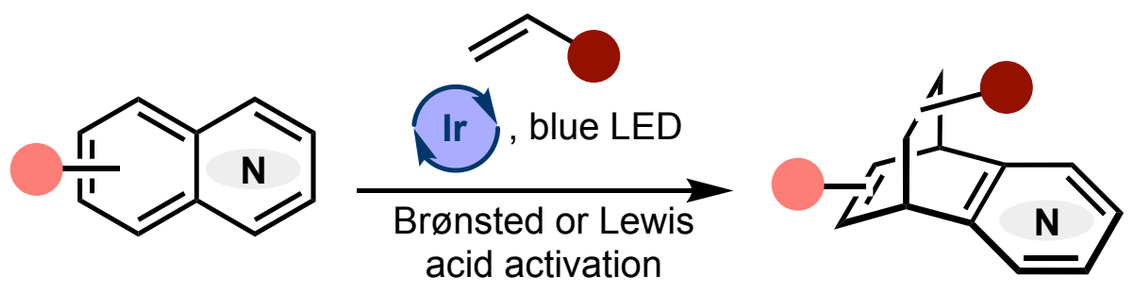


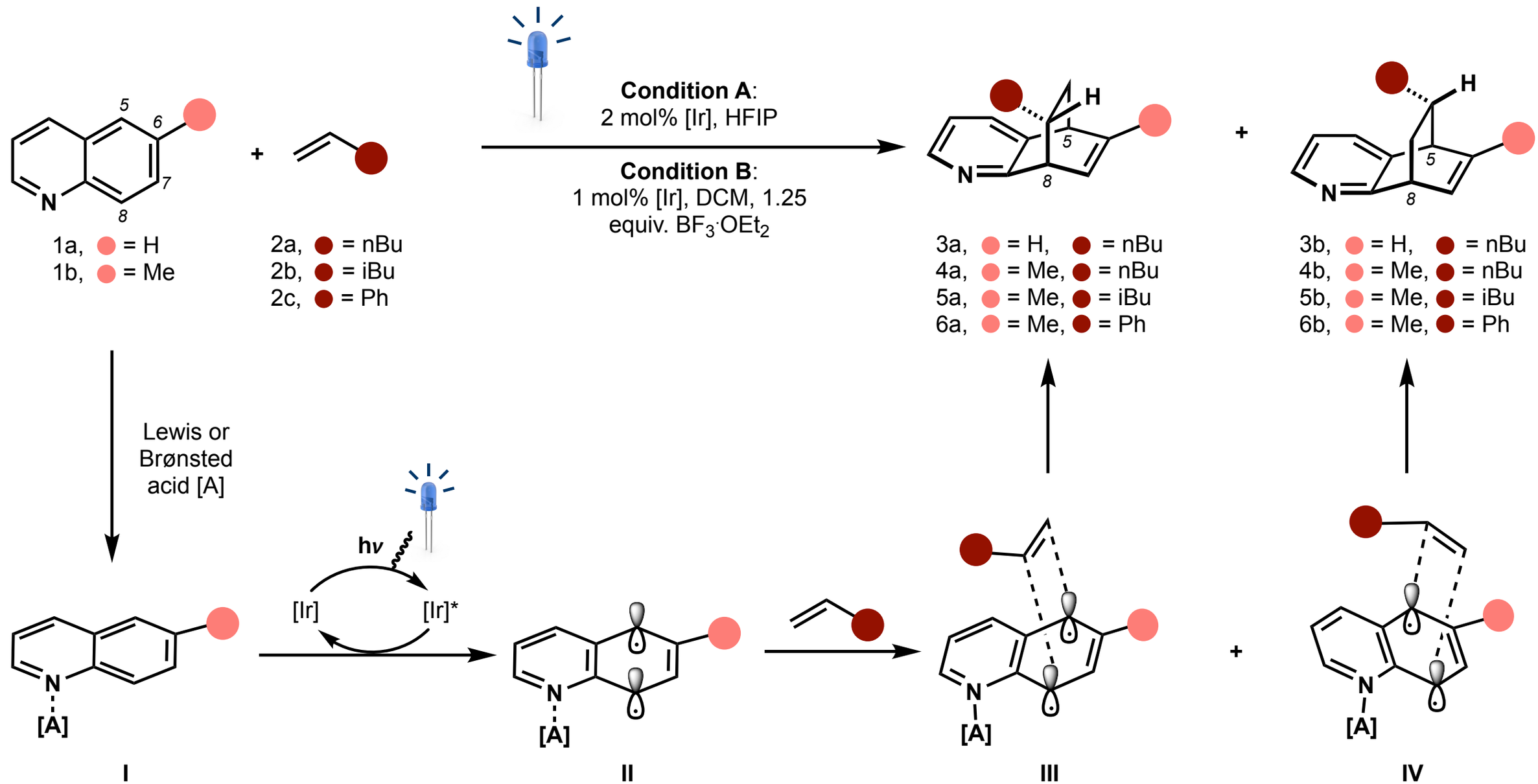
- Quinolines
- Isoquinolines
- Quinazolines

Ent

- Carbocycle selectivity
- Para selectivity
- Controlled regioselectivity
- Endo diastereoselectivity

Science **2021**, *371*, 1338-1345;

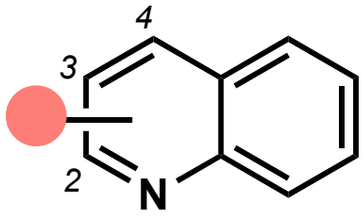
Initial evaluations



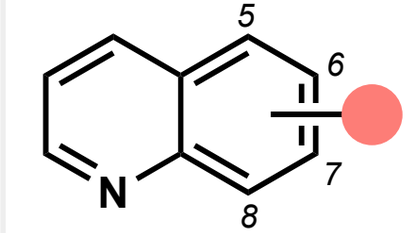
Science **2021**, *371*, 1338-1345;

Scope and next developments

Scope of quinolines:

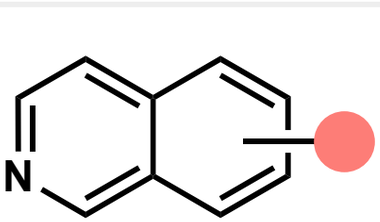


Condition **B** used

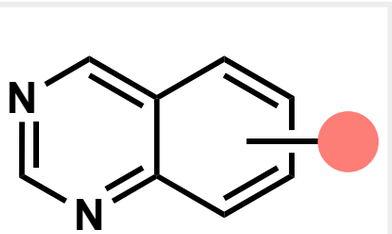


Condition **A** used

Scope of isoquinolines and quinazolines:



Condition **A** used



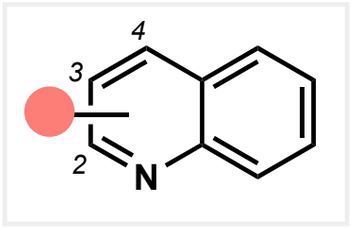
Condition **A** used

= activated or unactivated alkenes

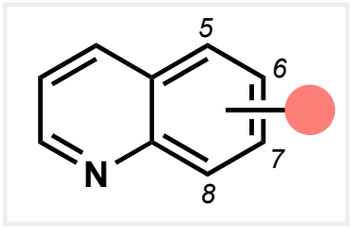
Science **2021**, *371,* 1338-1345; *JACS* **2022**; *144, 17680-17681*.

Scope and next developments

Scope of quinolines:

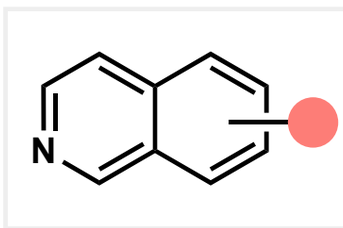


Condition **B** used

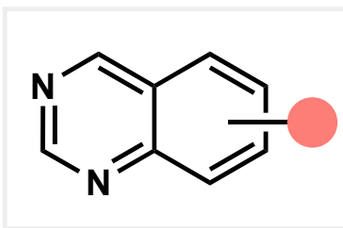


Condition **A** used

Scope of isoquinolines and quinazolines:



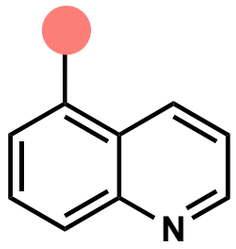
Condition **A** used

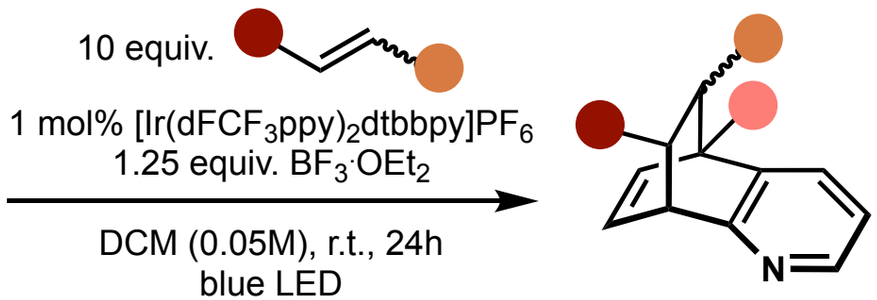


Condition **A** used

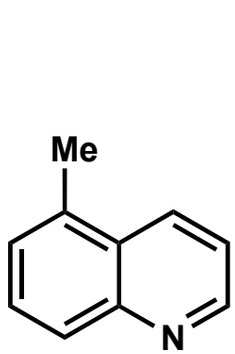
= activated or unactivated alkenes

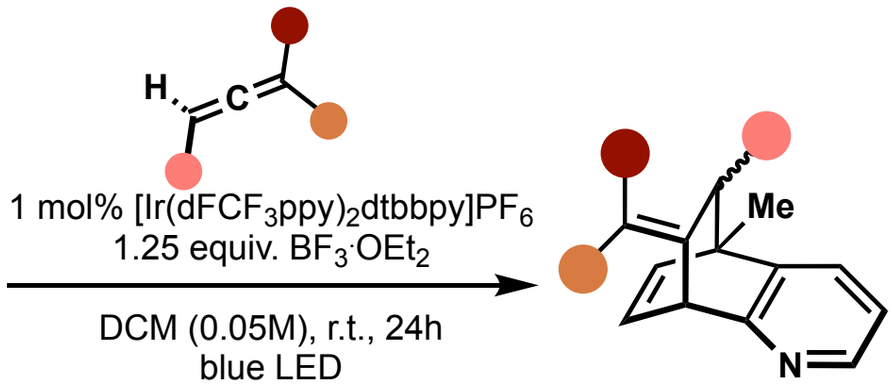
Scope expanded to disubstituted alkenes and allenes:





8-to-5 prdt, >20:1 dr

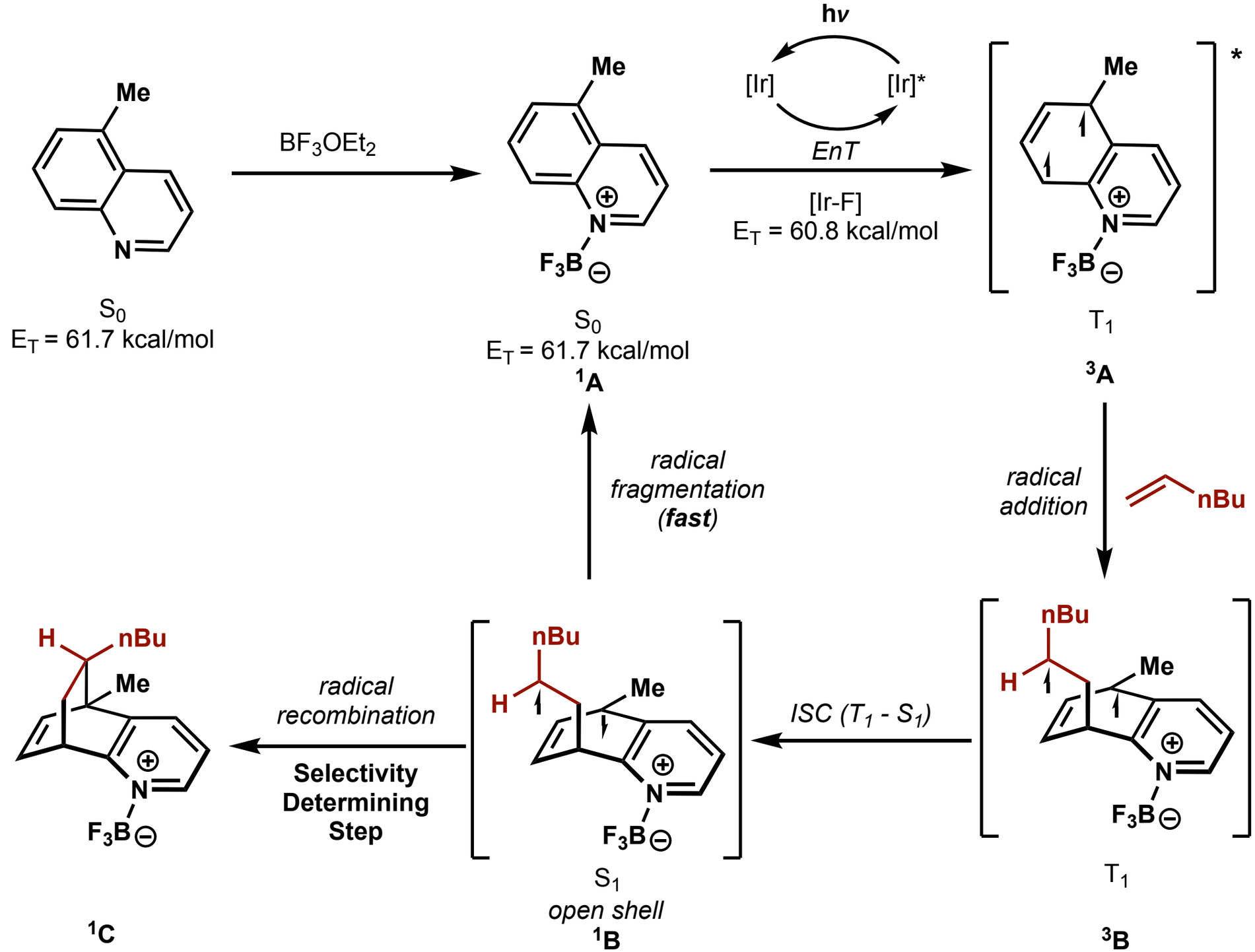




8-to-5 prdt, >20:1 dr

Science **2021**, *371,* 1338-1345; *JACS* **2022**; *144, 17680-17681*.

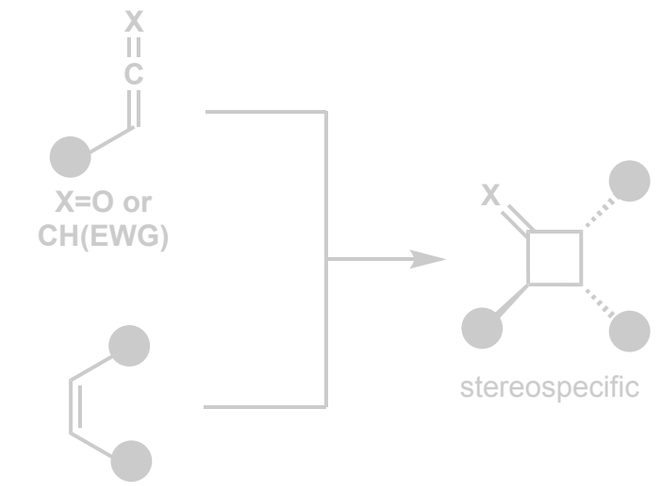
Proposed mechanism



JACS **2022**; *144, 17680-17681*.

Independent Career

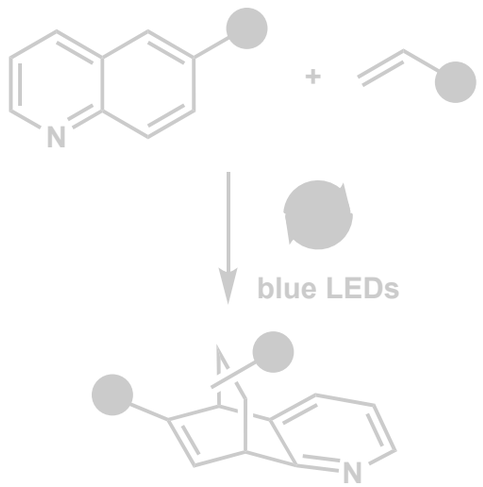
Lewis Acid Mediated [2+2] Cycloadditions



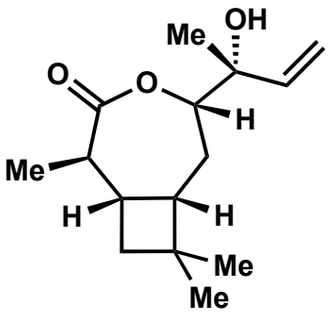
Cu/Pd Catalysis and Carboboration

Catalyst controlled selectivity

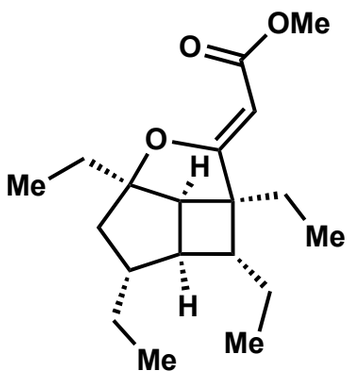
Photochemical Dearomative Cycloadditions



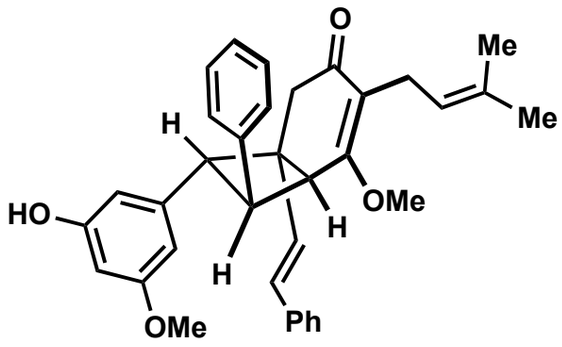
Total Synthesis



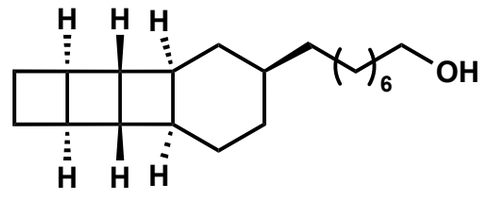
(-)-Hebelophyllene E



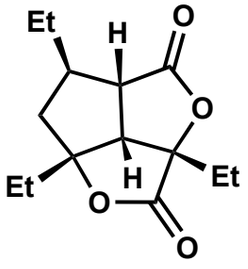
Hippolachnin A



(-)-Cajanusine



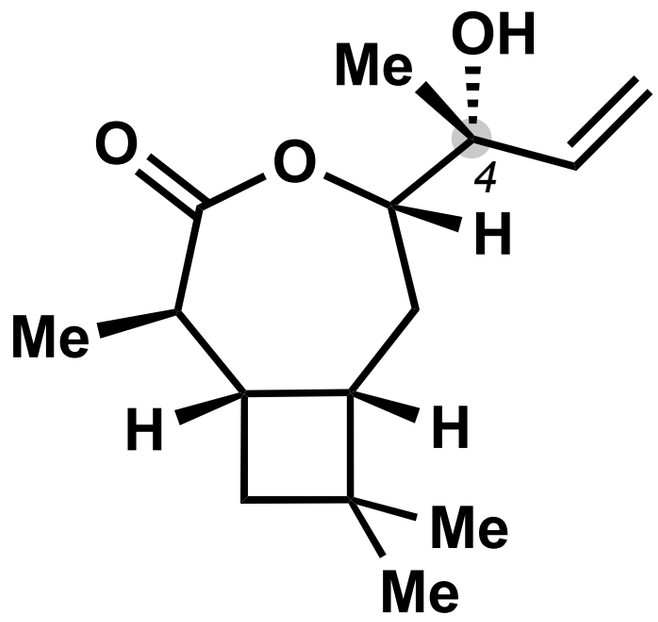
ent-[3]-Ladderanol



Gracilioether F

Hebelophyllene E

Fungus *Hebeloma longicaudum*

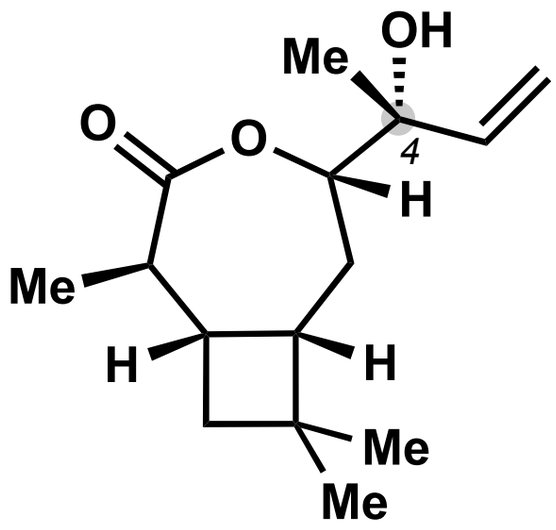


(-)-Hebelophyllene E

- *cis*-fused caryophyllene-type sesquiterpenes family
  - No previous synthesis reported
  - Unknown C4 stereochemistry

ACIE **2018***; 57,* 4647-4651; *Phytochemistry* **1999**, *51*, 873-877;. *J. Nat. Prod.* **1999**, *62*, 484-486.

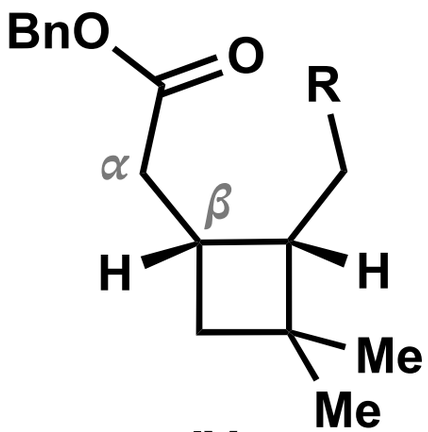
Hebelophyllene E: retrosynthesis



(-)-Hebelophyllene E

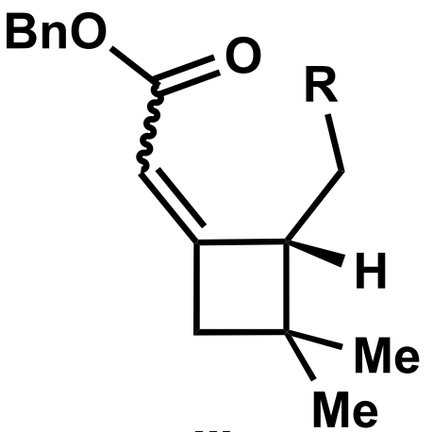
IV

FGI

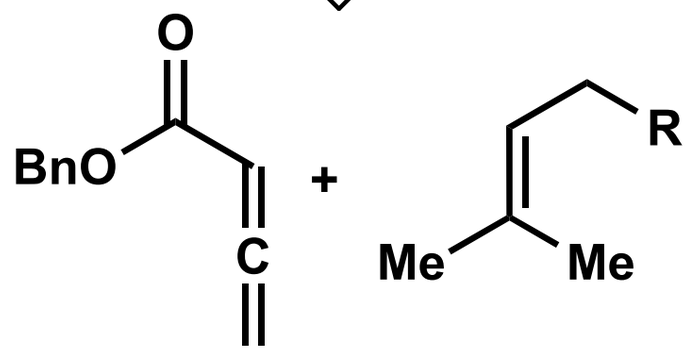


III

diastereo-selective reduction



Lewis acid mediated [2+2]

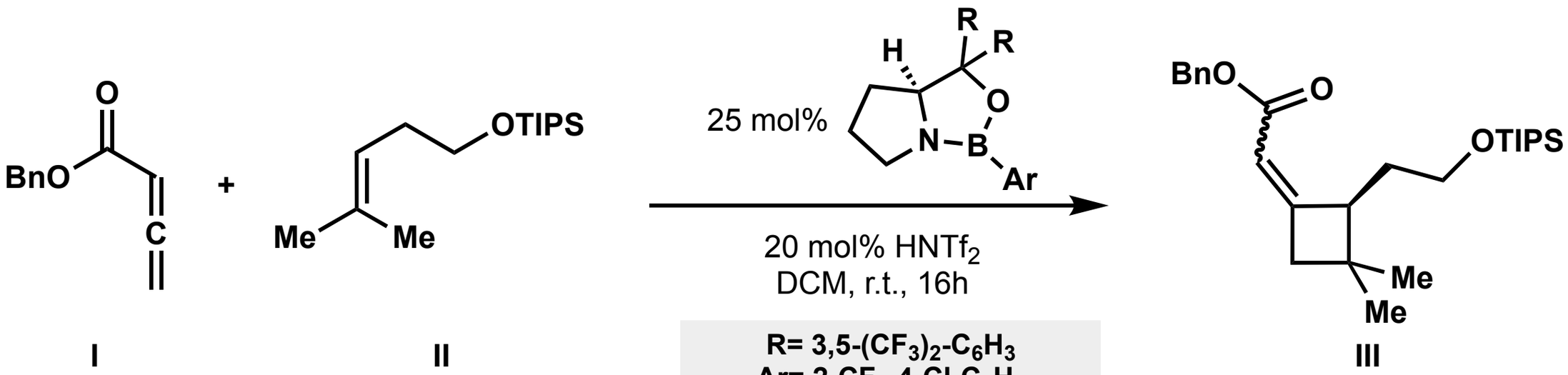


I **II**

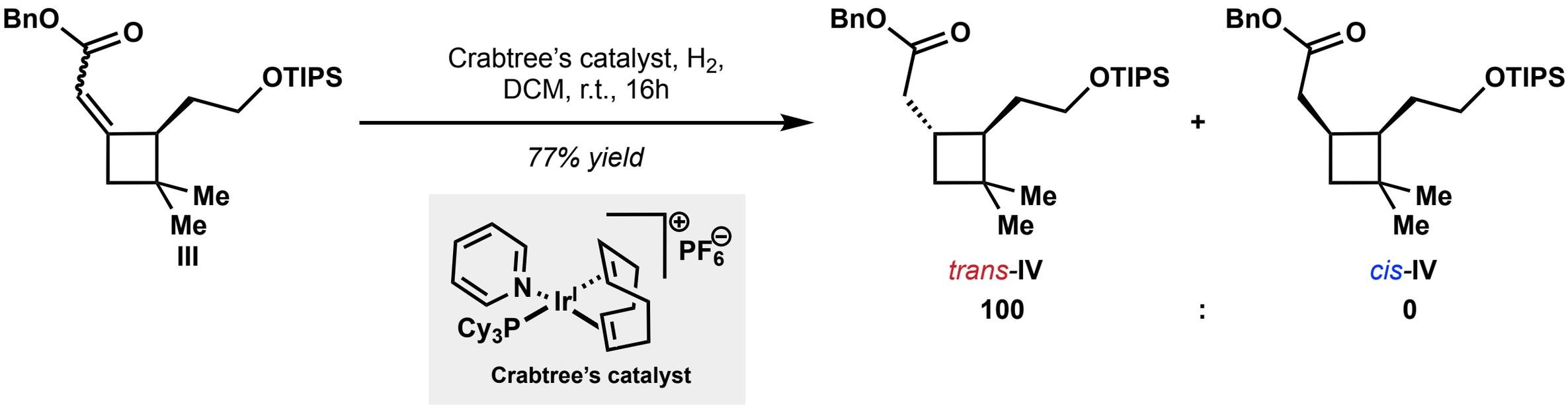
ACIE **2018**; *57,* 4647-4651.

Hebelophyllene E: model system

Lewis acid mediated [2+2] screening



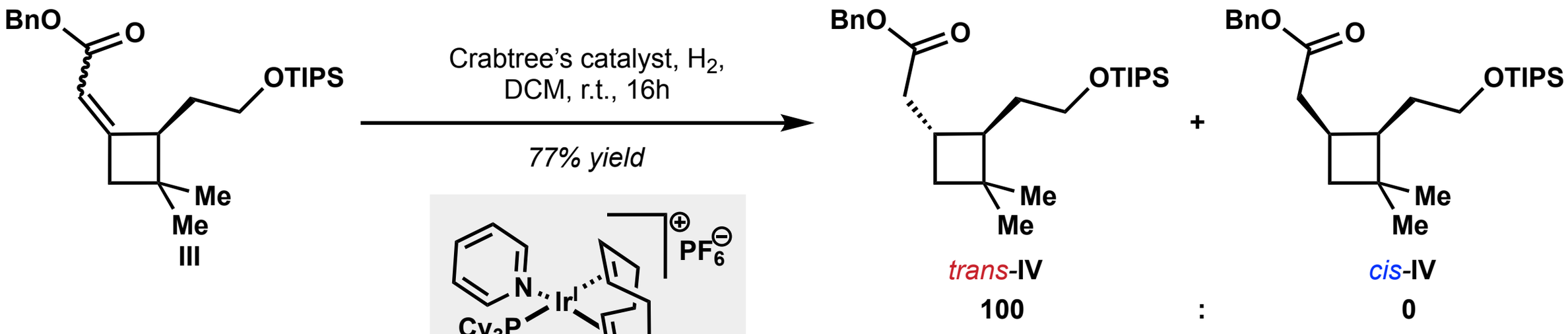
Conjugate reduction screening



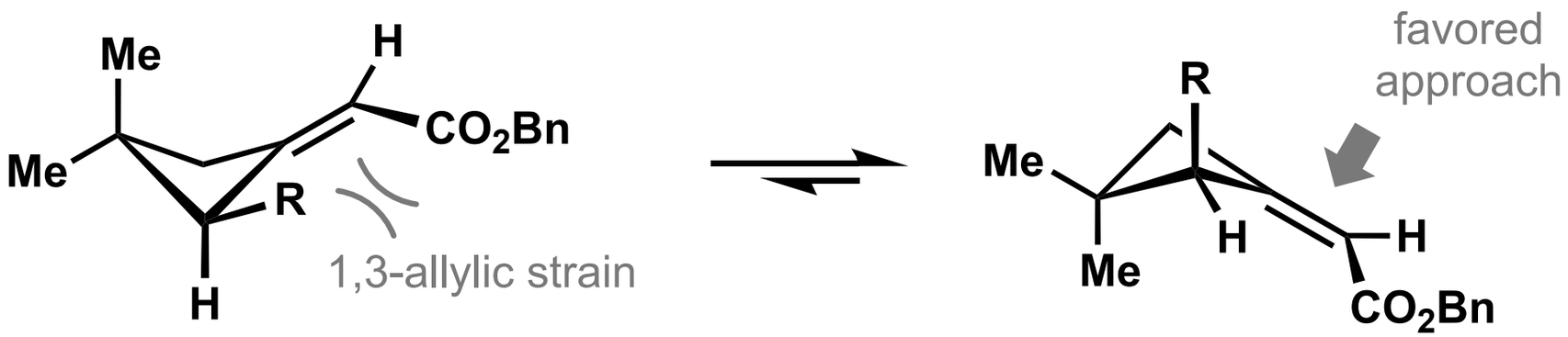
ACIE **2018**; *57,* 4647-4651.

Hebelophyllene E: model system

Conjugate reduction screening

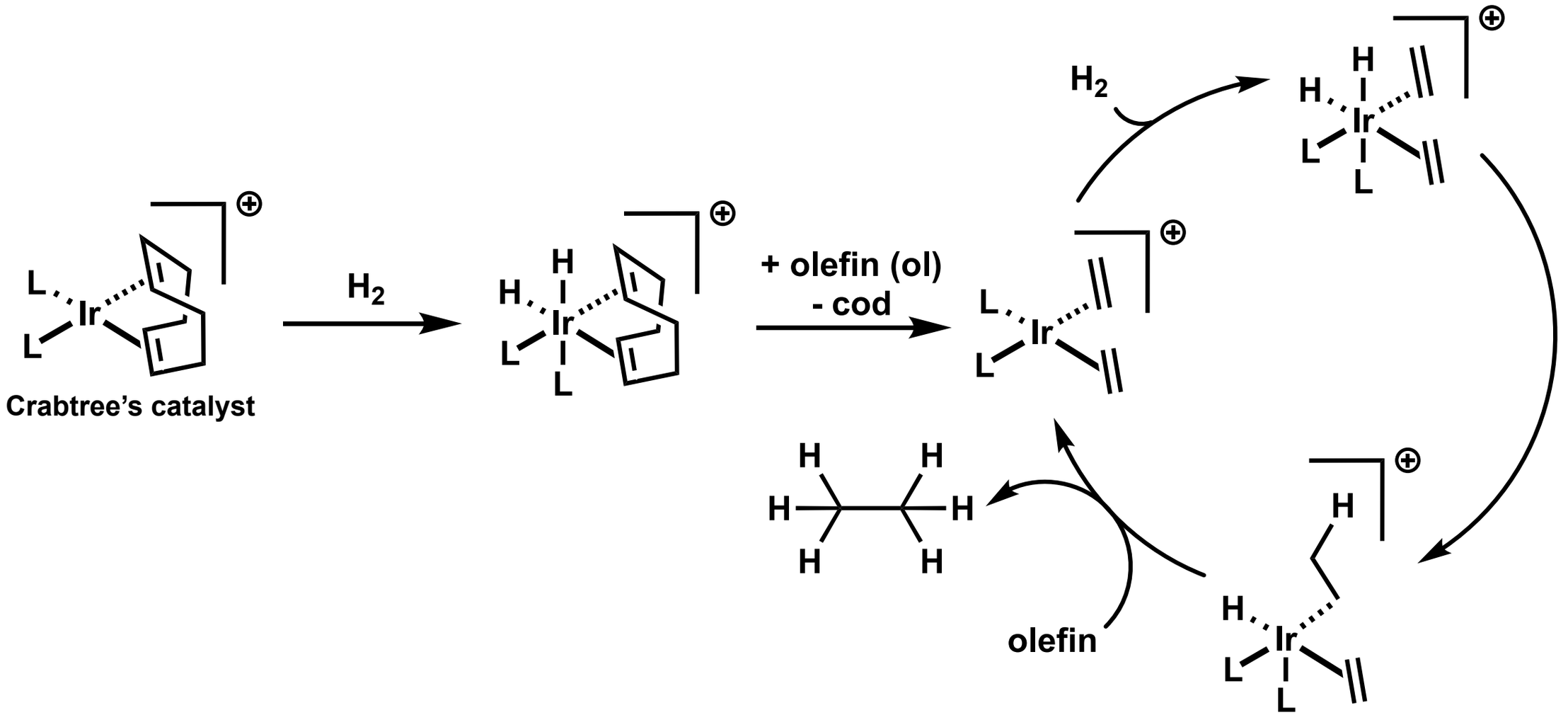


Crabtree's catalyst



ACIE **2018***; 57,* 4647-4651.

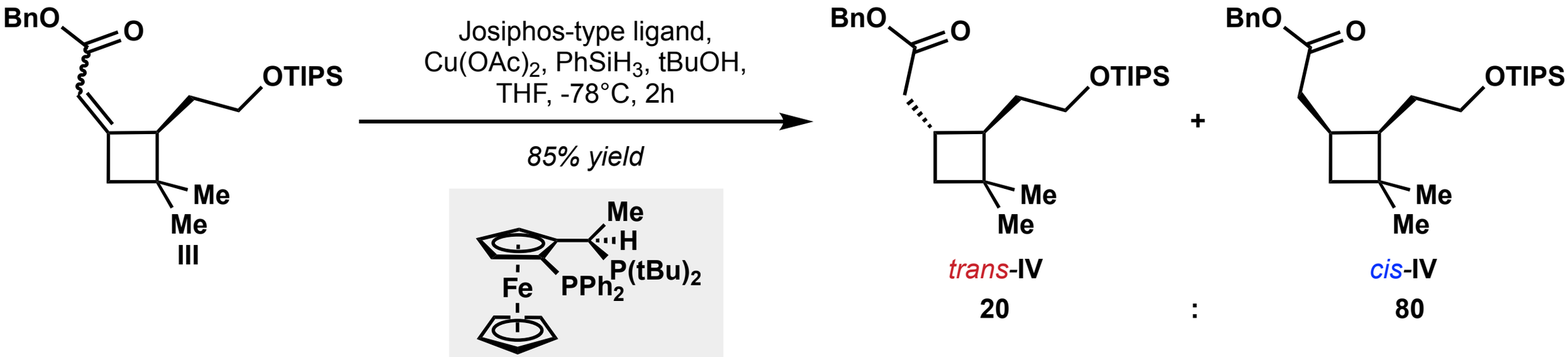
Crabtree’s catalyst mechanism



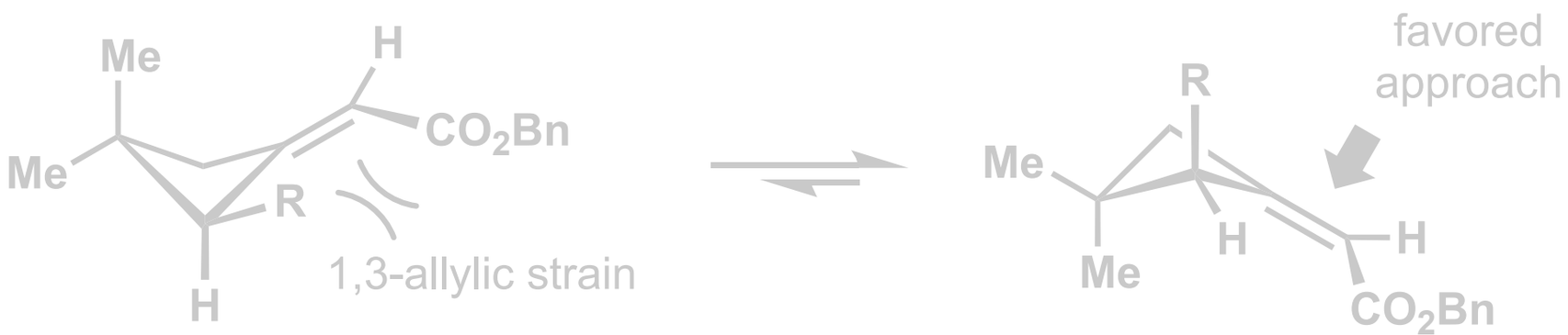
JACS ***1982****, 104* (25), 6994-7001.

Hebelophyllene E: model system

Conjugate reduction screening

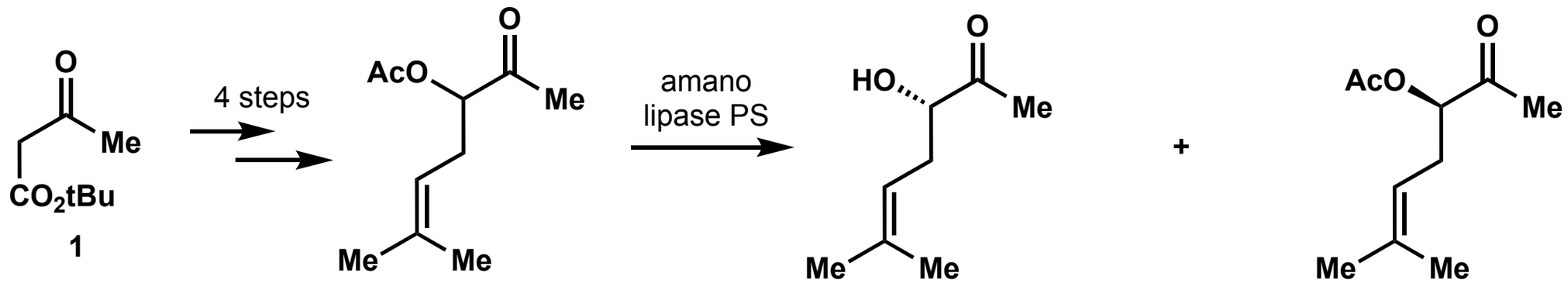


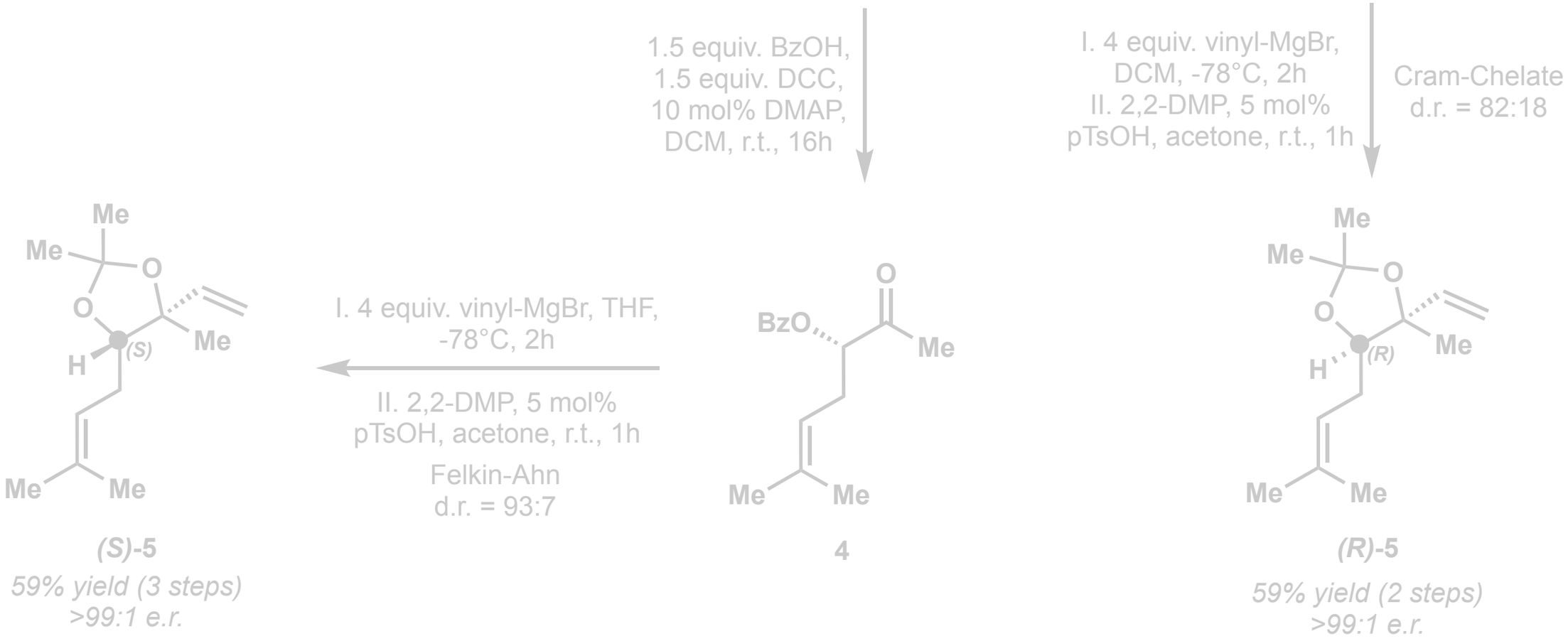
Josiphos-type ligand



ACIE **2018***; 57,* 4647-4651.

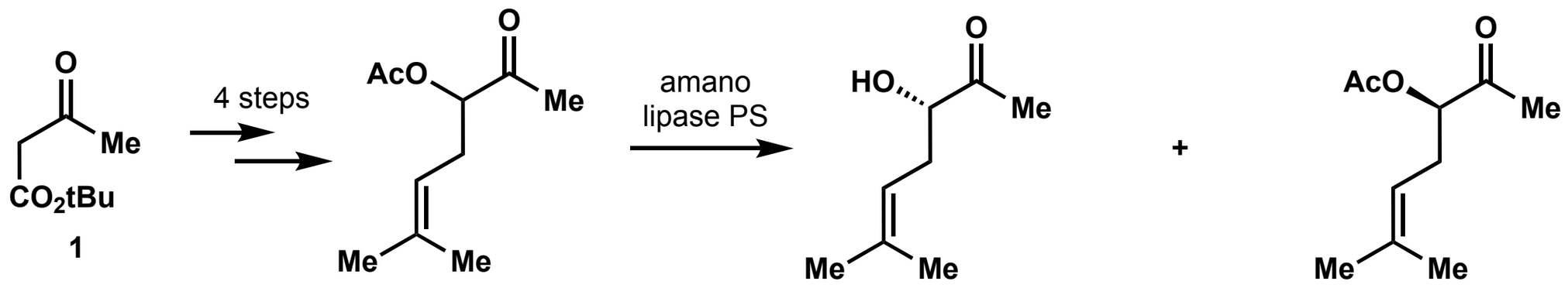
Hebelophyllene E: synthesis (1)

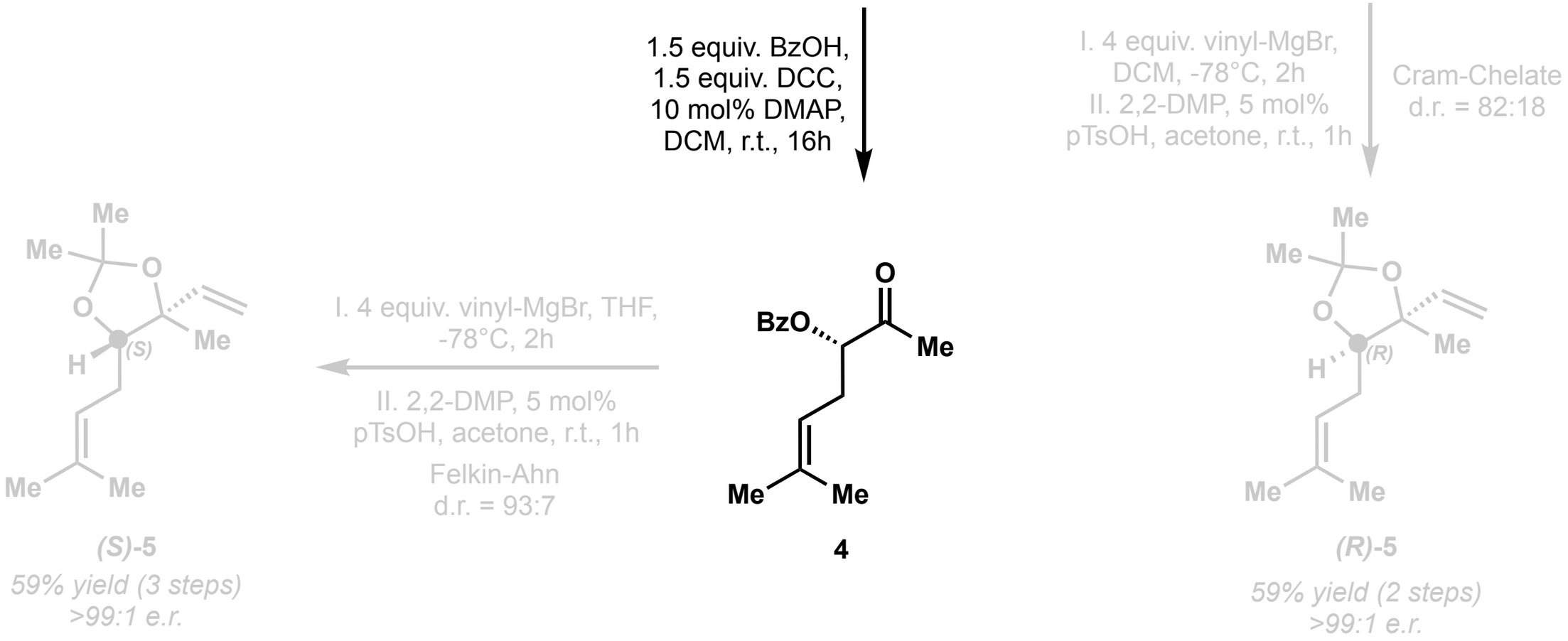




ACIE **2018***; 57,* 4647-4651; *JACS* **1963**, *85*, 1245-1249.

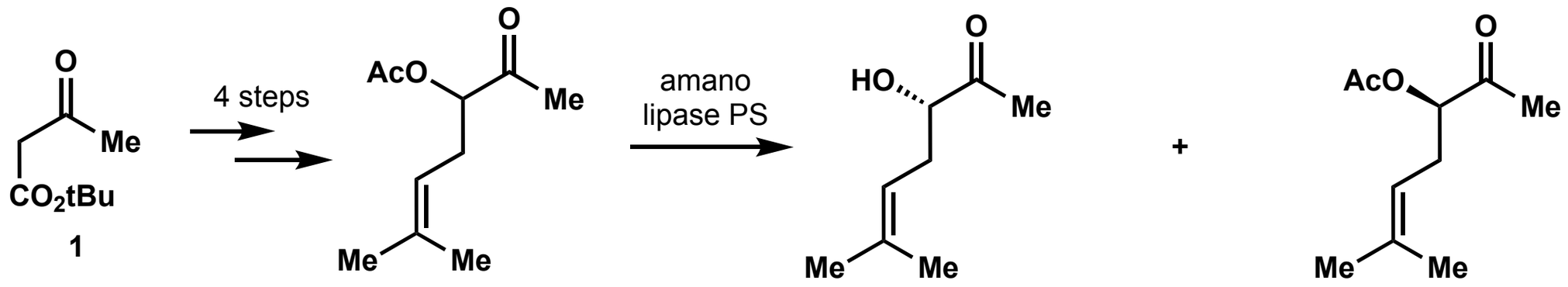
Hebelophyllene E: synthesis (1)

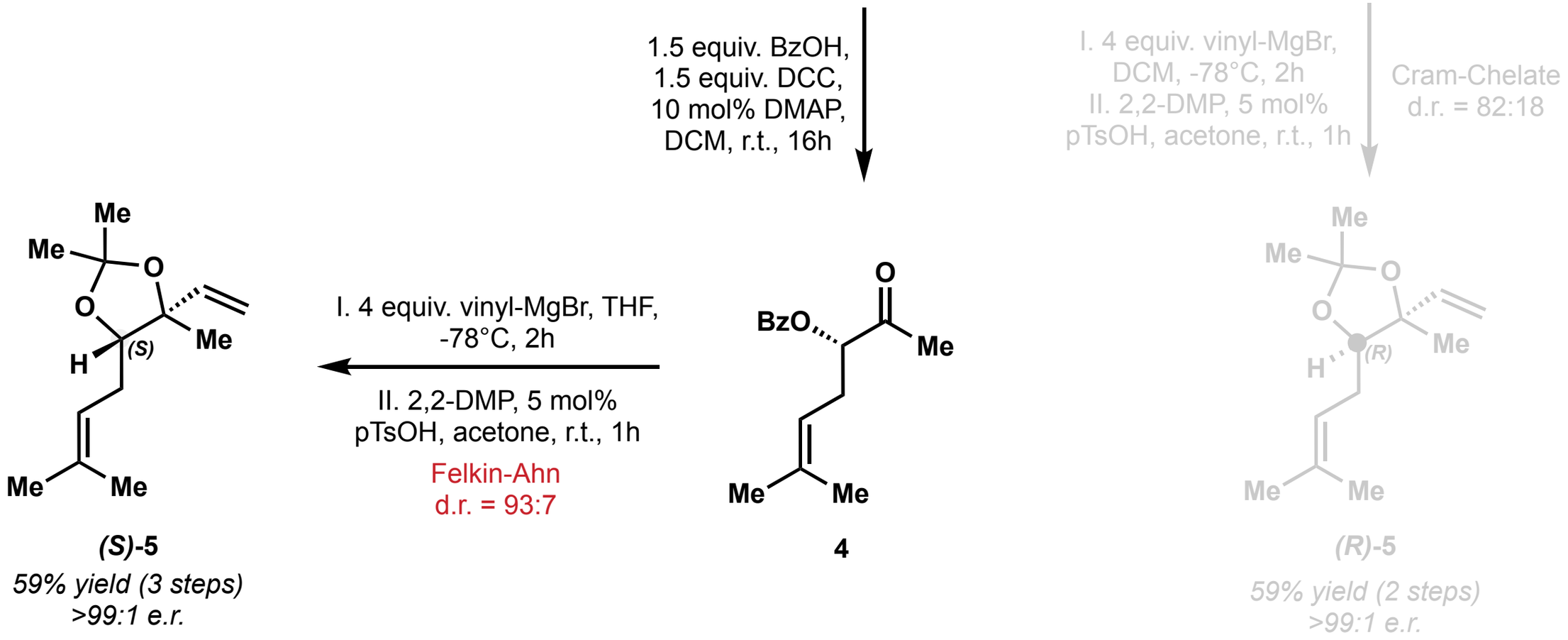




ACIE **2018***; 57,* 4647-4651; *JACS* **1963**, *85*, 1245-1249.

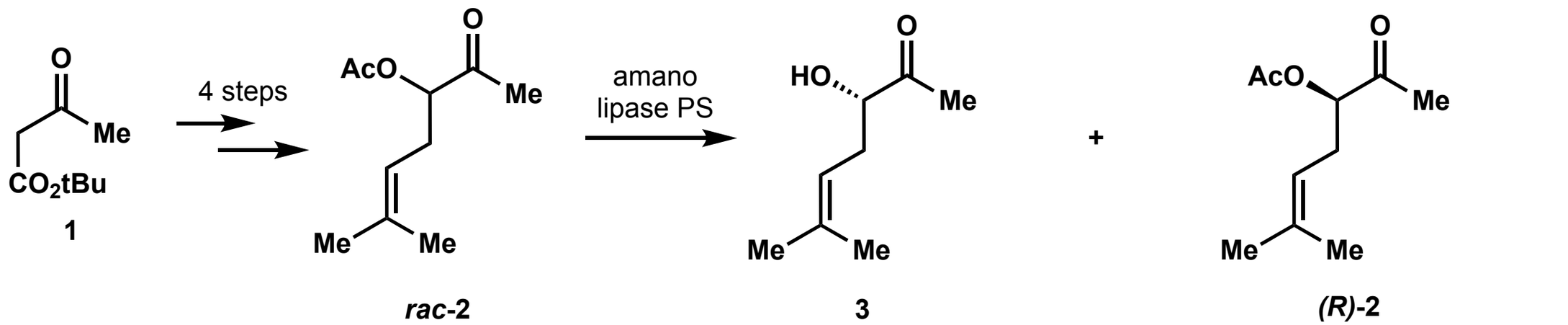
Hebelophyllene E: synthesis (1)





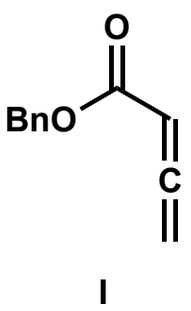
ACIE **2018***; 57,* 4647-4651; *JACS* **1963**, *85*, 1245-1249.

Hebelophyllene E: synthesis (1)



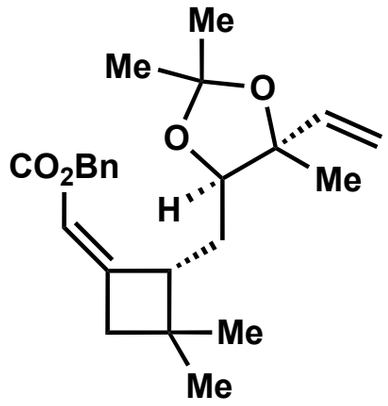
ACIE **2018***; 57,* 4647-4651; *JACS* **1963**, *85*, 1245-1249.

Hebelophyllene E: synthesis (2)



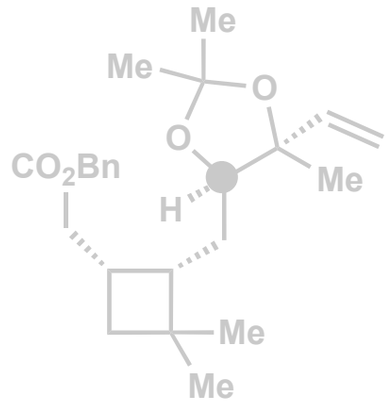
I

4 equiv. ***(R)*-5**,
0.5 equiv. oxazoborolidine *ent*-cat.,
0.4 equiv. $HNTf_2$, DCM, -17°C, 48h



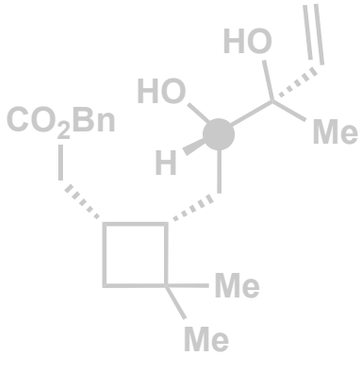
***(Z)*-6**
52% yield

11 mol% Josiphos *ent*-cat.,
10 mol% $Cu(OAc)_2$, $PhSiH_3$,
tBuOH, THF, -78°C, 2h



***cis*-7**
89% yield
89:11 d.r.

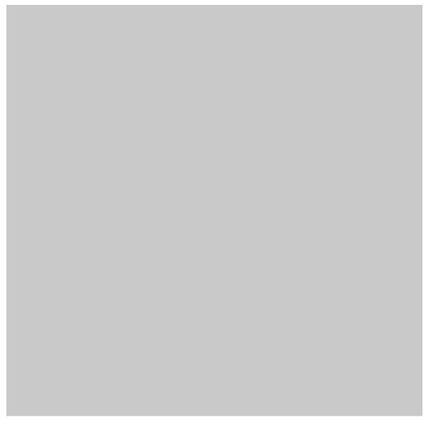
I. TFA, THF/H_2O, r.t., 3h
II. 5 equiv. pyr·SO_3, Et_3N,
DMSO, DCM, r.t., 19h
III. 9.4 equiv. $Zn(BH_4)_2$,
THF, -78°C, 2h



8
69% yield (3 steps)
71:29 d.r.

I. 10 equiv. LiOH, THF/H_2O, r.t., 2h
II. 2 equiv. DCC, 20 mol% DMAP,
DCM, r.t., 2h

III. 10 equiv. TMSCl, 12 equiv.
imidazole, DCM, r.t., 2h
IV. 5 equiv. LiHMDS, 5 equiv. MeI,
THF, -78°C, 0.5h, then HCl

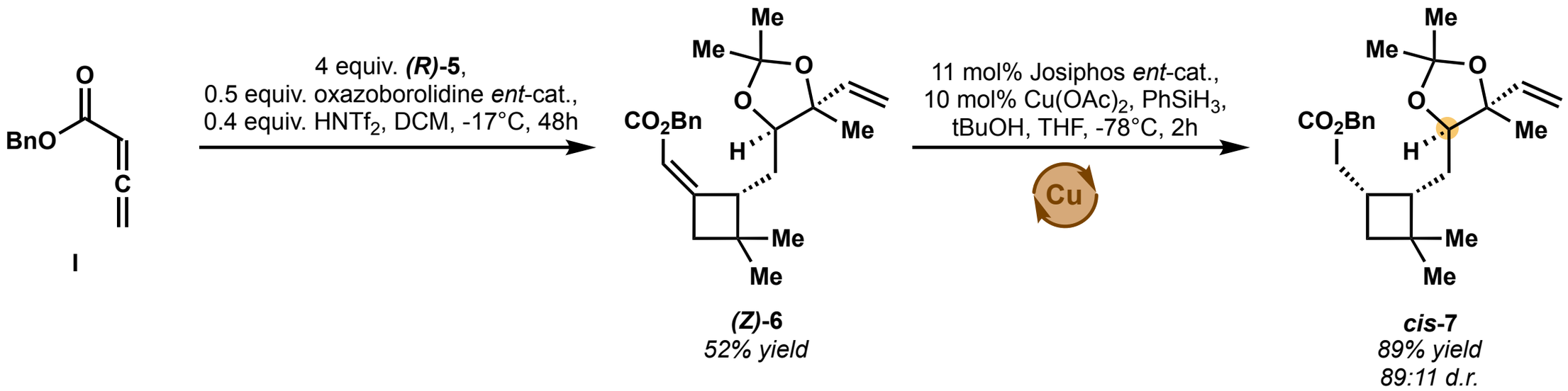


(-)-Hebelophyllene E

47% yield (4 steps)
99:1 e.r.
99:1 d.r.

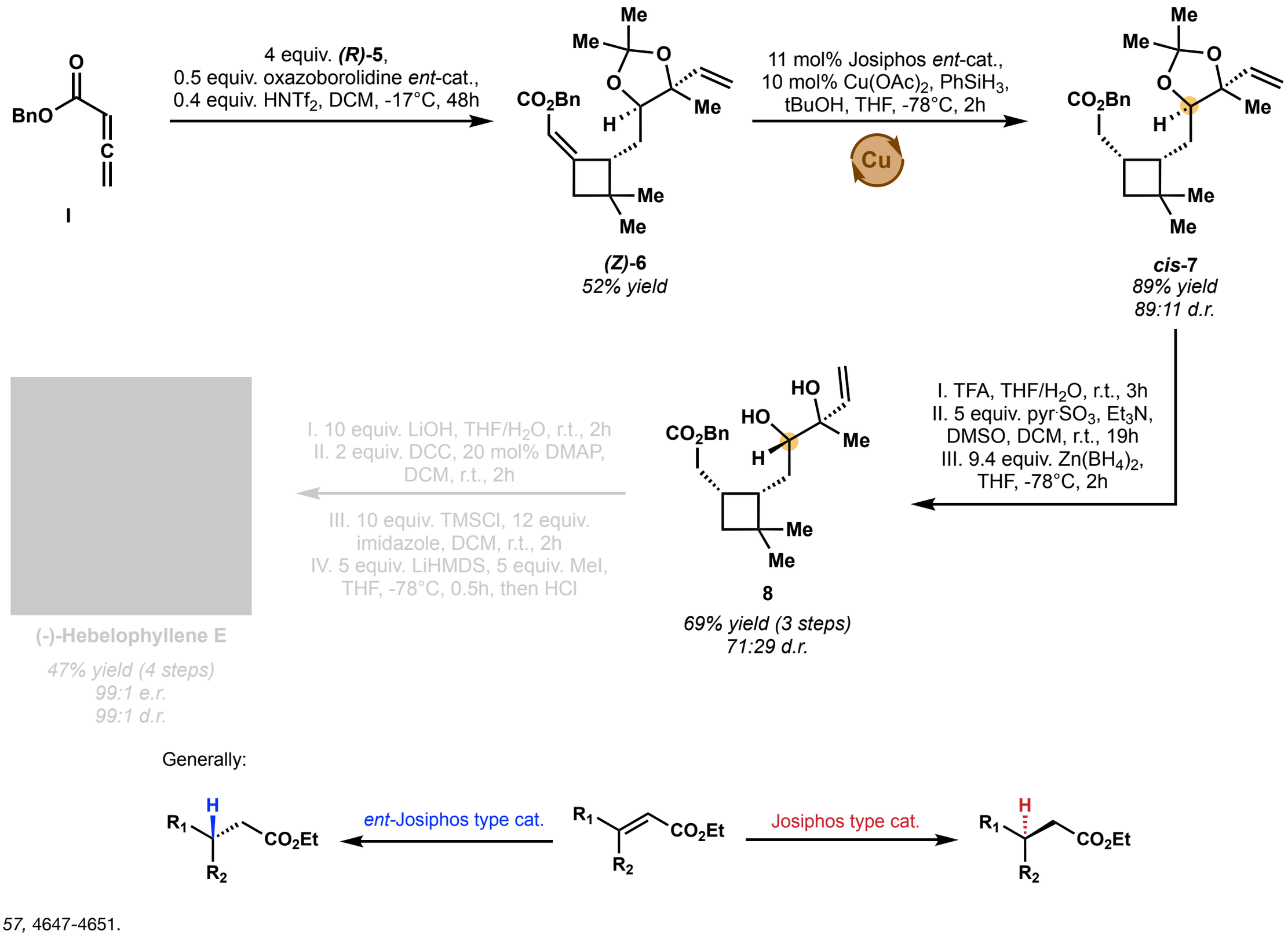
ACIE **2018***; 57,* 4647-4651.

Hebelophyllene E: synthesis (2)



ACIE **2018**; *57,* 4647-4651.

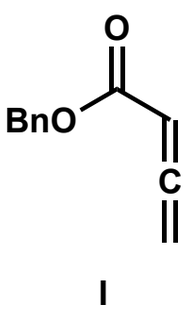
Hebelophyllene E: synthesis (2)



Generally:

ACIE **2018**; *57,* 4647-4651.

Hebelophyllene E: synthesis (2)



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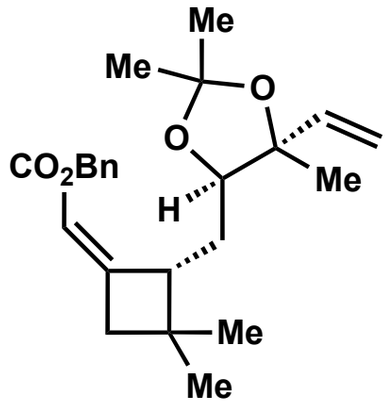
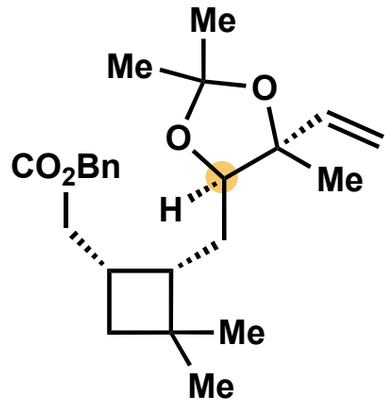


***(Z)*-6**
52% yield

11 mol% Josiphos *ent*-cat.,
10 mol% $Cu(OAc)_2$, $PhSiH_3$,
tBuOH, THF, -78°C, 2h

Cu



***cis*-7**
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89:11 d.r.

I. TFA, THF/H_2O, r.t., 3h
II. 5 equiv. pyr·SO_3, Et_3N,
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III. 9.4 equiv. $Zn(BH_4)_2$,
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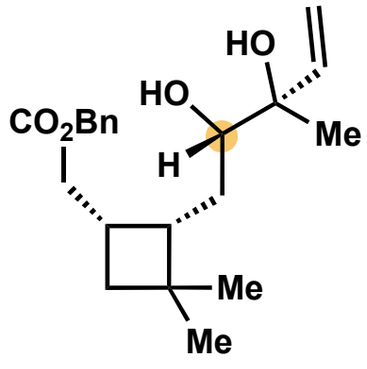

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69% yield (3 steps)
71:13 d.r.

I. 10 equiv. LiOH, THF/H_2O, r.t., 2h
II. 2 equiv. DCC, 20 mol% DMAP,
DCM, r.t., 2h

III. 10 equiv. TMSCl, 12 equiv.
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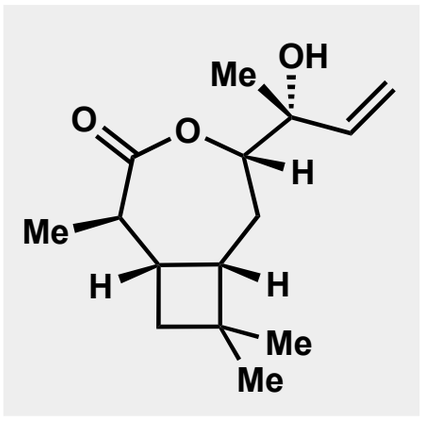
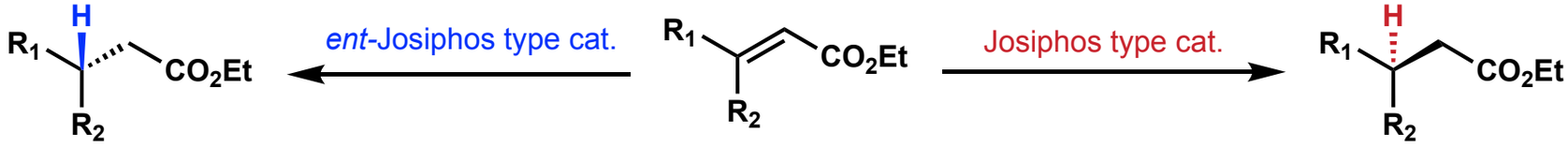
IV. 5 equiv. LiHMDS, 5 equiv. MeI,
THF, -78°C, 0.5h, then HCl



(-)-Hebelophyllene E

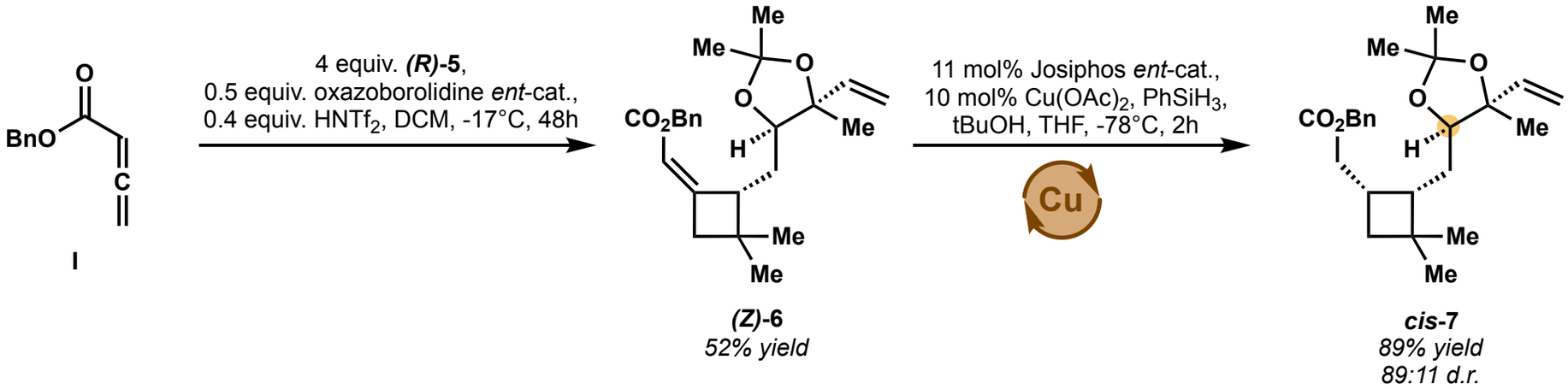
47% yield (4 steps)
99:1 e.r.
99:1 d.r.

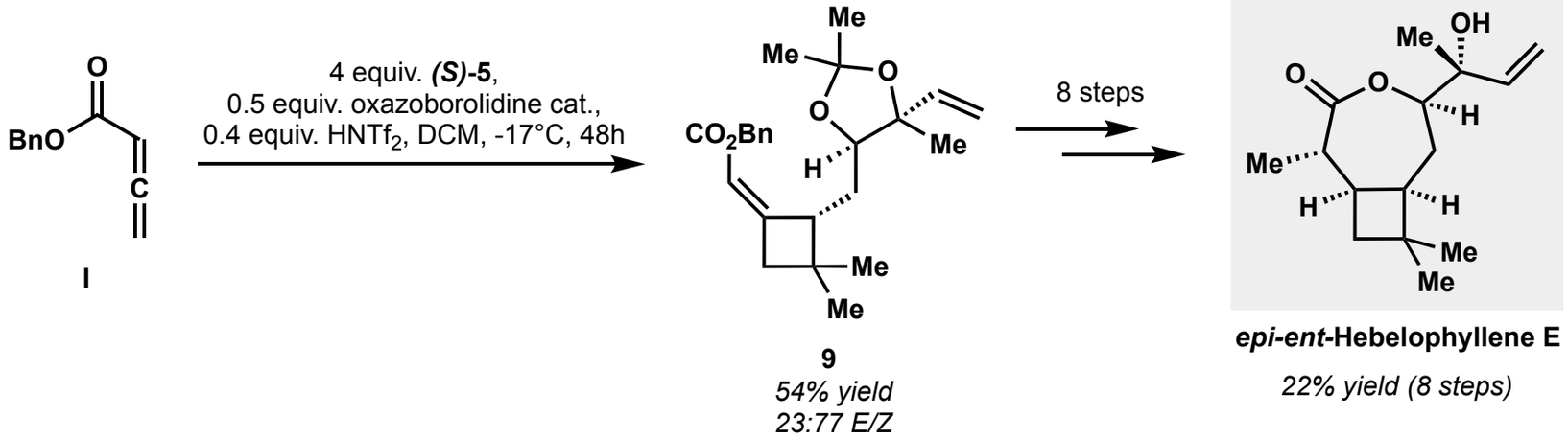
Generally:



ACIE **2018**; *57,* 4647-4651.

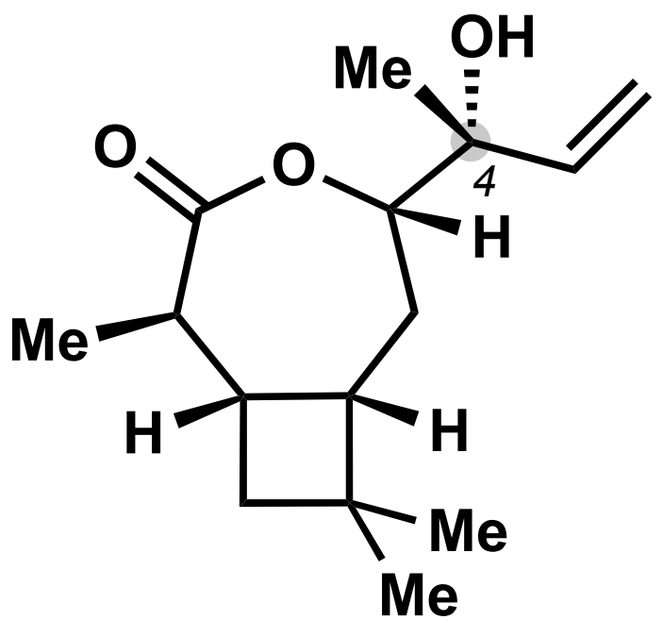
Hebelophyllene E: synthesis (2)





ACIE **2018***; 57,* 4647-4651.

Hebelophyllene E: summary



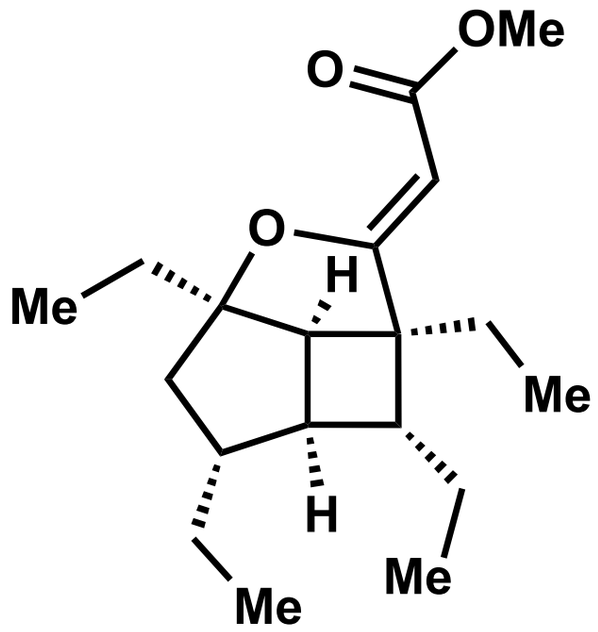
(-)-Hebelophyllene E

- First total synthesis of Hebelophyllene E in 16 steps (LLS)
- C4 configuration was assigned by synthesis of both isomers
- Development of a key [2+2] cycloaddition was crucial for the synthesis of the core

ACIE **2018***; 57,* 4647-4651.

Hippolachnin A

Marine sponge *Hippospongia lachne*

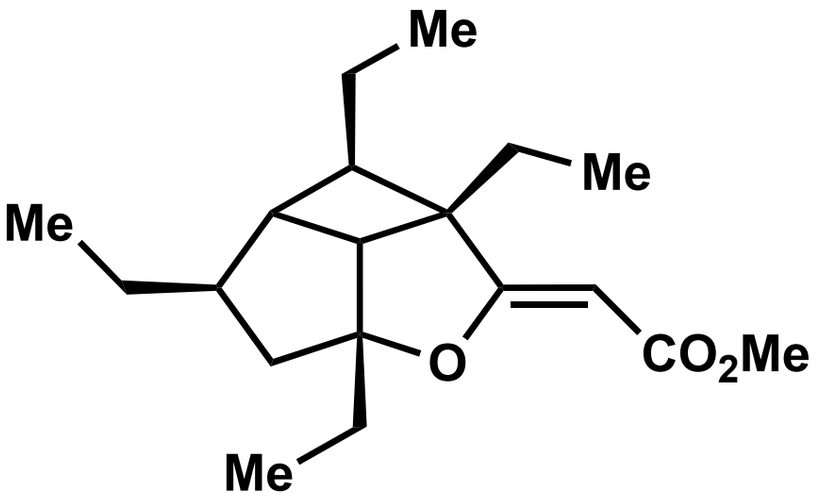


Hippolachnin A

- Very low isolation yield (0.00014% yield)
- Polyketide has an unprecedented carbon skeleton with six contiguous stereocenters
- Potent antifungal activity against several species (410nM for both *Cryptococcus neoformans* and *Trichophyton rubrum*)

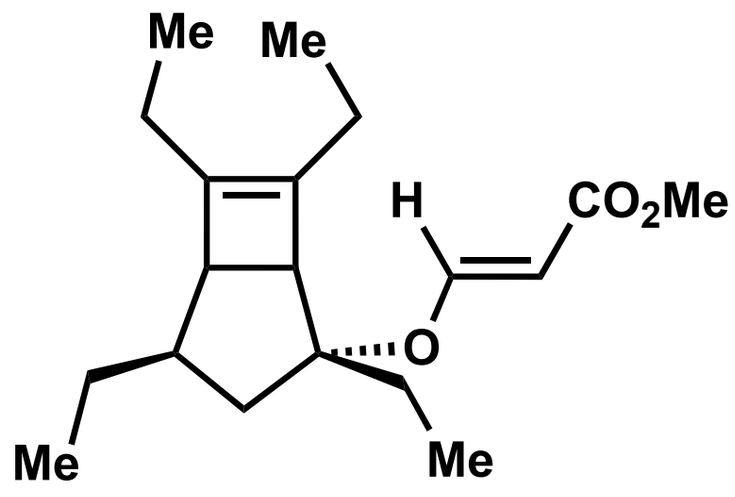
JACS **2016**, *138,* 2437-2442; *Org. Lett*. **2013**, *15*, 3526-3529.

Hippolachnin A: Carreira's approach



Hippolachnin A

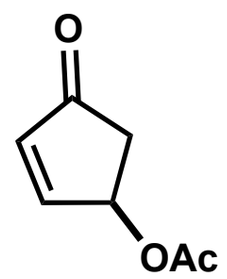
regio- and stereoselective hydroalkylation



I

JACS **2016***, 138,* 2437-2442; *ACIE* **2015**, *54*, 2378-2382.

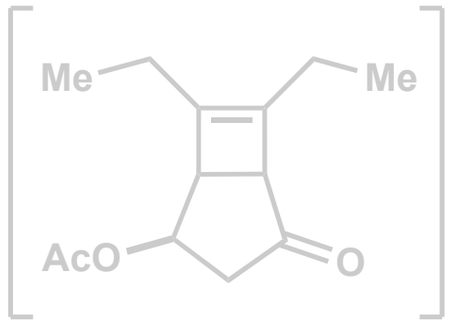
Hippolachnin A: Carreira's approach



1

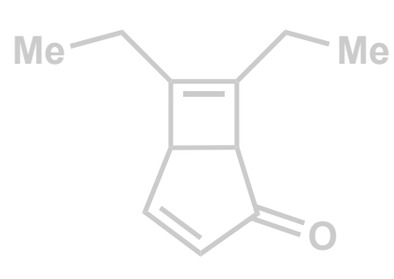
1 step from comm. avail.

h*ν* (270-600nm),
10 equiv. hex-3-yne,
acetone, r.t.



2

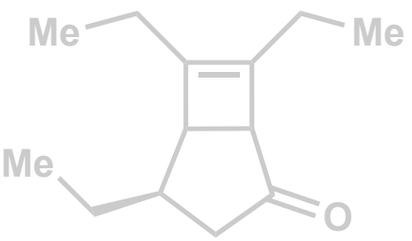
5 equiv. K_2CO_3,
basic Al_2O_3, DCM,
r.t.



3

54% yield (2 steps)

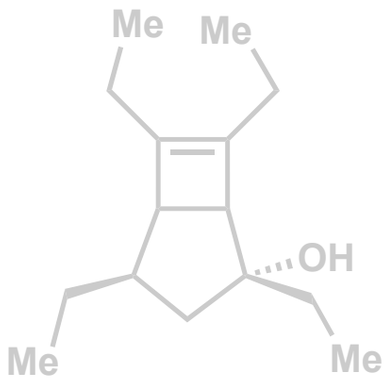
2.1 equiv. CuI,
4 equiv. EtMgBr,
-78°C to -20°C



4

73% yield

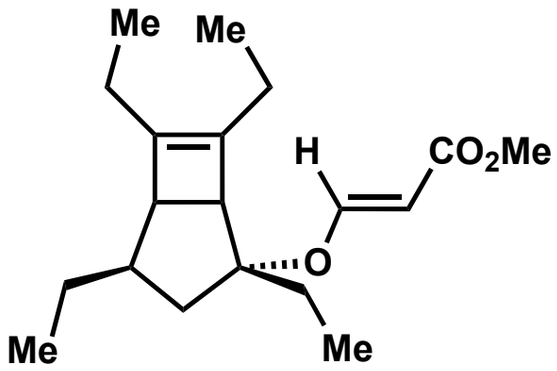
3 equiv. EtMgBr,
1.02 equiv. $LaCl_3{\cdot}LiCl$,
0°C



5

90% yield

40 equiv. (E)-methyl-3-methoxyacrylate,
0.1 equiv. PPTS, 80°C

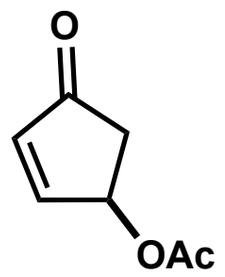


I

95% yield

JACS **2016**, *138,* 2437-2442; *ACIE* **2015**, *54*, 2378-2382.

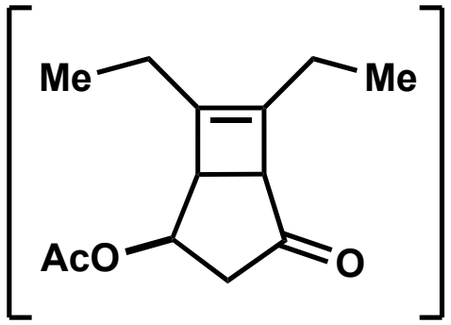
Hippolachnin A: Carreira's approach



1

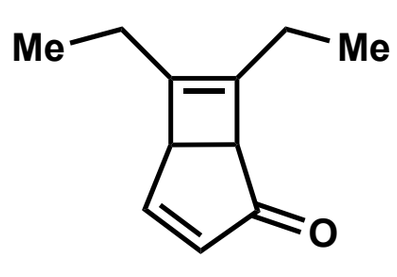
1 step from comm. avail.

h*ν* (270-600nm),
10 equiv. hex-3-yne,
acetone, r.t.



2

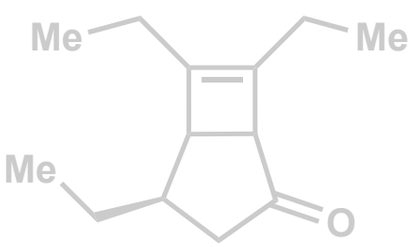
5 equiv. K_2CO_3,
basic Al_2O_3, DCM,
r.t.



3

54% yield (2 steps)

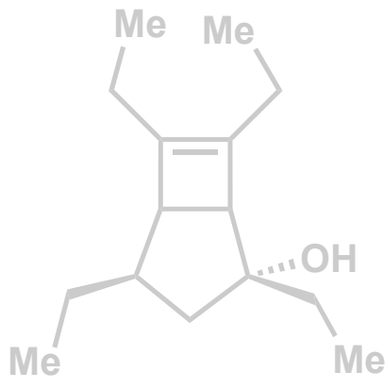
2.1 equiv. CuI,
4 equiv. EtMgBr,
-78°C to -20°C



4

73% yield

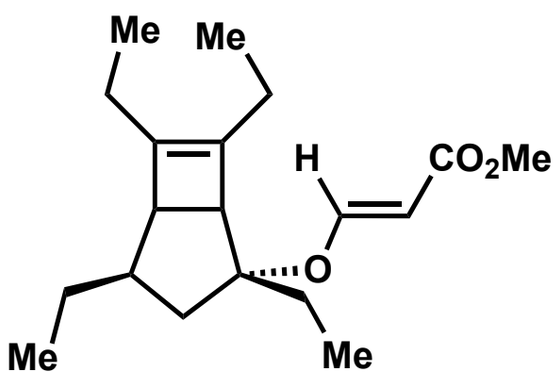
3 equiv. EtMgBr,
1.02 equiv. $LaCl_3{\cdot}LiCl$,
0°C



5

90% yield

40 equiv. (E)-methyl-3-methoxyacrylate,
0.1 equiv. PPTS, 80°C

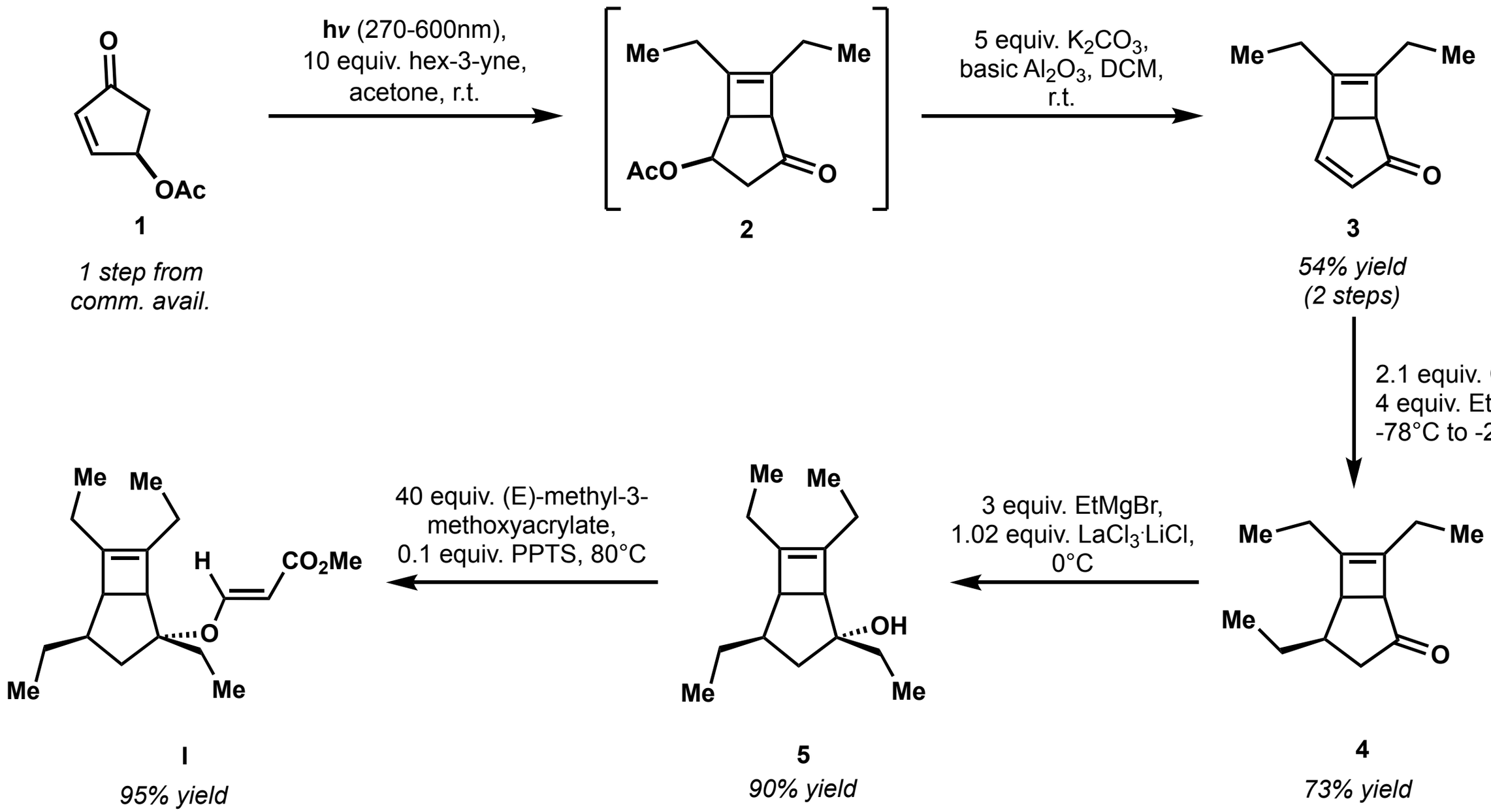


I

95% yield

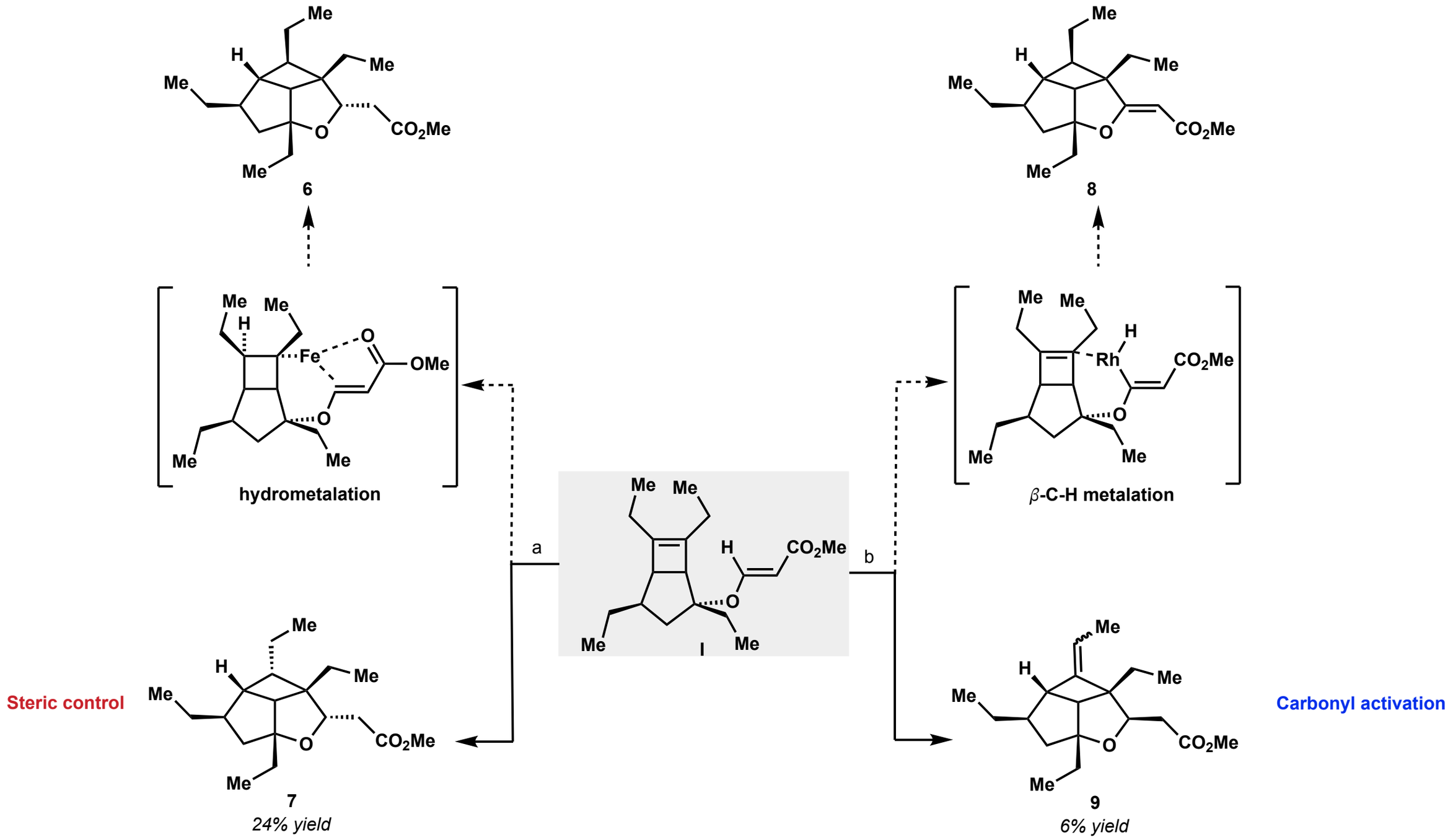
JACS **2016**, *138,* 2437-2442; *ACIE* **2015**, *54*, 2378-2382.

Hippolachnin A: Carreira's approach



JACS **2016**, *138,* 2437-2442; *ACIE* **2015**, *54*, 2378-2382.

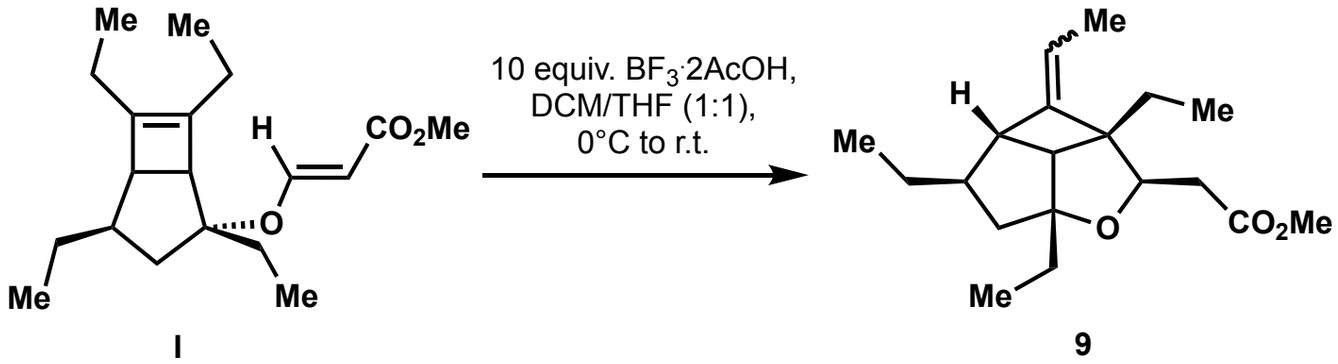
Hippolachnin A: Carreira's key step



a) 2 equiv. $[Fe(acac)_3]$, 4 equiv. $PhSiH_3$, DCE/ethylene glycol (5:1), 80°C
b) 5 mol% $[\{RhCl(cod)\}_2]$, 10 mol% $AgSbF_6$, DCE, r.t.

JACS **2016**, *138*, 2437-2442; *ACIE* **2015**, *54*, 2378-2382.

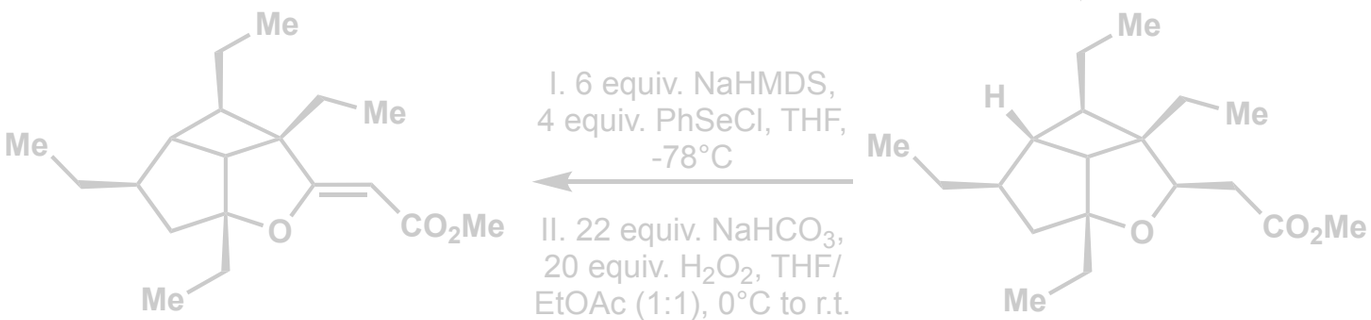
Hippolachnin A: Carreira's endgame



I

9

65% yield
6:1 d.r.



Hippolachnin A

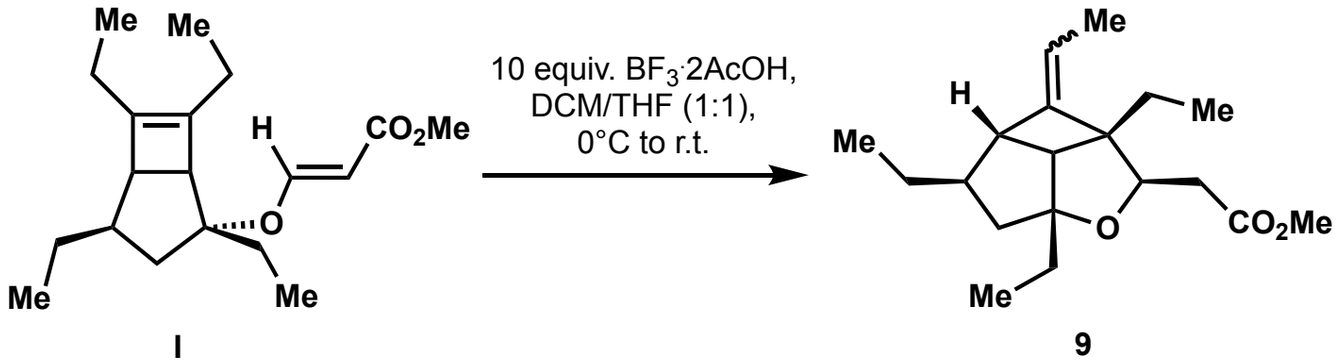
61% yield
(2 steps)

10

89% yield
25:75 endo/exo

JACS **2016***, 138,* 2437-2442; *ACIE* **2015**, *54*, 2378-2382.

Hippolachnin A: Carreira's endgame

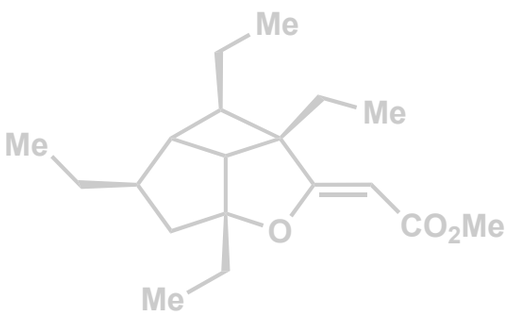


I **9**

65% yield
6:1 d.r.

Pd

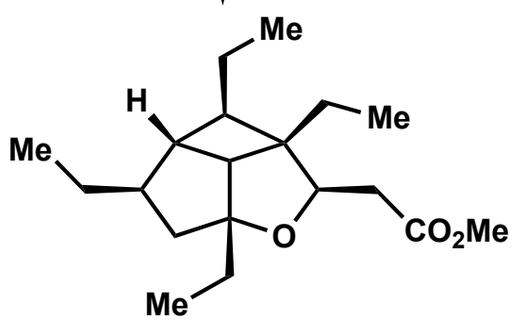
	Entry	Conditions[a]	Yield[b] [%]	endo/exo
	1	$[Mn(dpm)_3]$, $PhSiH_3$, TBHP, *i*PrOH	75	>99:1
radical	2	$[Co(acac)_2]$, $PhSiH_3$, TBHP, DCE	63	>99:1
	3	$[Fe(acac)_3]$, $PhSiH_3$, TBHP, MeOH	46	>99:1
homo-geneous	4	$[RhCl(PPh_3)_3]$, MeOH, H_2 (10 bar)	31	47:53
	5	$[Ir(PCy_3)(cod)(py)]PF_6$, CH_2Cl_2, H_2 (10 bar)	0	–
hetero-geneous	6	Pd/C, MeOH, H_2 (10 bar)	92	29:71
	7	$Pd(OAc)_2$, MeOH, H_2 (10 bar)	90	33:67
	8	$Pd(OH)_2/C$, MeOH, H_2 (10 bar)	89	25:75
	9	Raney Ni, MeOH, H_2 (10 bar)	68	37:63
	10	PtO_2, MeOH, H_2 (10 bar)	88	36:64



Hippolachnin A
61% yield
(2 steps)

I. 6 equiv. NaHMDS,
4 equiv. PhSeCl, THF,
-78°C

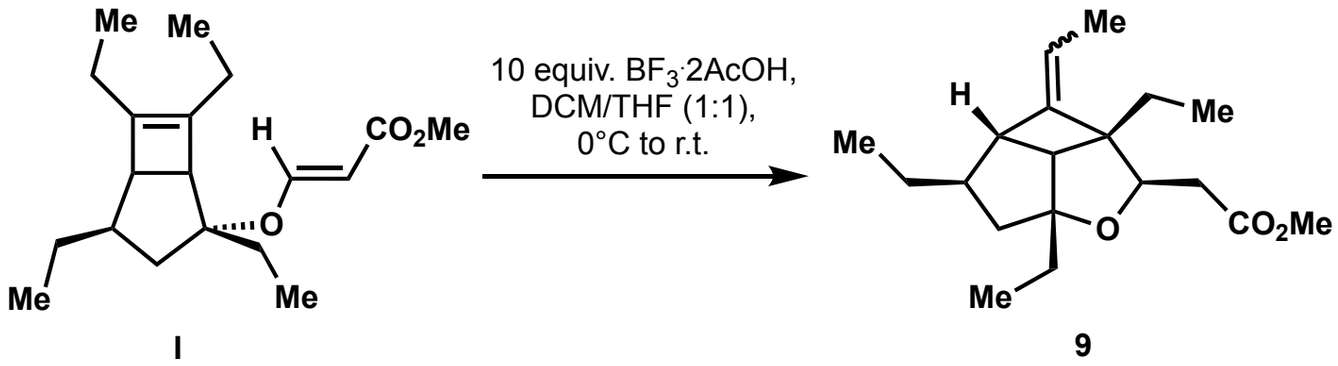
II. 22 equiv. $NaHCO_3$,
20 equiv. H_2O_2, THF/
EtOAc (1:1), 0°C to r.t.



10
89% yield
25:75 endo/exo

JACS **2016**, *138*, 2437-2442; *ACIE* **2015**, *54*, 2378-2382.

Hippolachnin A: Carreira's endgame



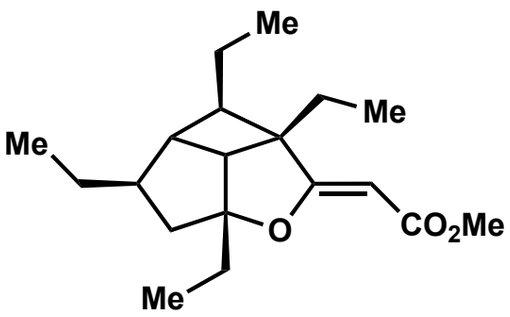
I **9**

65% yield
6:1 d.r.

- First total synthesis of Hippolachnin A (LLS of 9 steps)
- Overall 9% yield

Pd

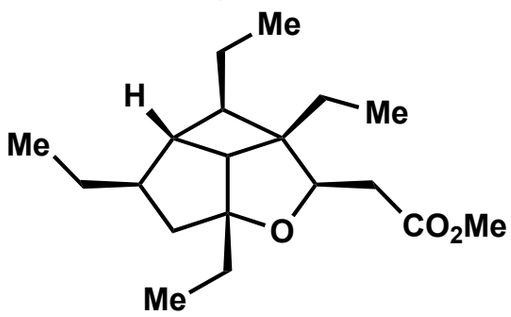
	Entry	Conditions[a]	Yield[b] [%]	endo/exo
	1	$[Mn(dpm)_3]$, $PhSiH_3$, TBHP, *i*PrOH	75	>99:1
radical	2	$[Co(acac)_2]$, $PhSiH_3$, TBHP, DCE	63	>99:1
	3	$[Fe(acac)_3]$, $PhSiH_3$, TBHP, MeOH	46	>99:1
homo-geneous	4	$[RhCl(PPh_3)_3]$, MeOH, H_2 (10 bar)	31	47:53
	5	$[Ir(PCy_3)(cod)(py)]PF_6$, CH_2Cl_2, H_2 (10 bar)	0	–
hetero-geneous	6	Pd/C, MeOH, H_2 (10 bar)	92	29:71
	7	$Pd(OAc)_2$, MeOH, H_2 (10 bar)	90	33:67
	8	$Pd(OH)_2/C$, MeOH, H_2 (10 bar)	89	25:75
	9	Raney Ni, MeOH, H_2 (10 bar)	68	37:63
	10	PtO_2, MeOH, H_2 (10 bar)	88	36:64



Hippolachnin A
61% yield
(2 steps)

I. 6 equiv. NaHMDS,
4 equiv. PhSeCl, THF,
-78°C

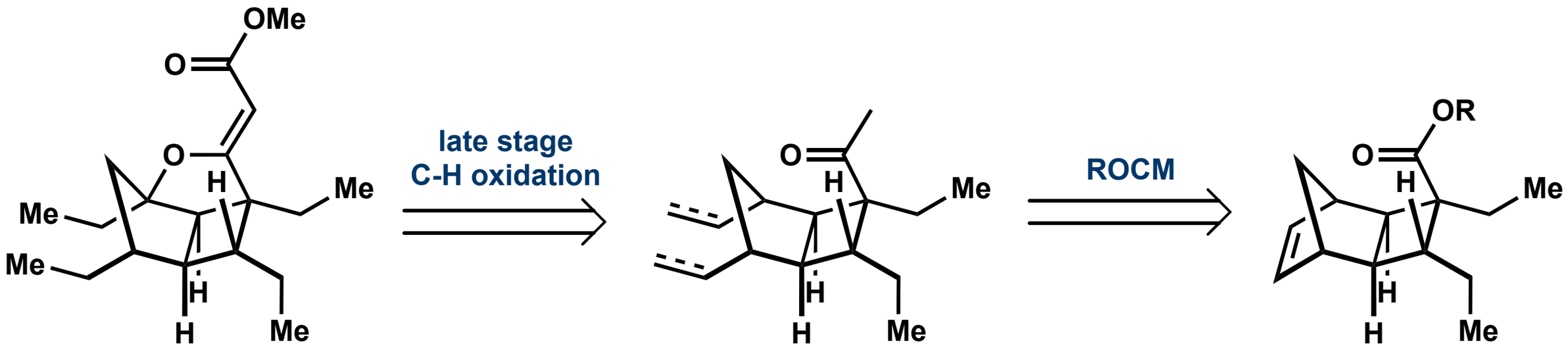
II. 22 equiv. $NaHCO_3$,
20 equiv. H_2O_2, THF/
EtOAc (1:1), 0°C to r.t.



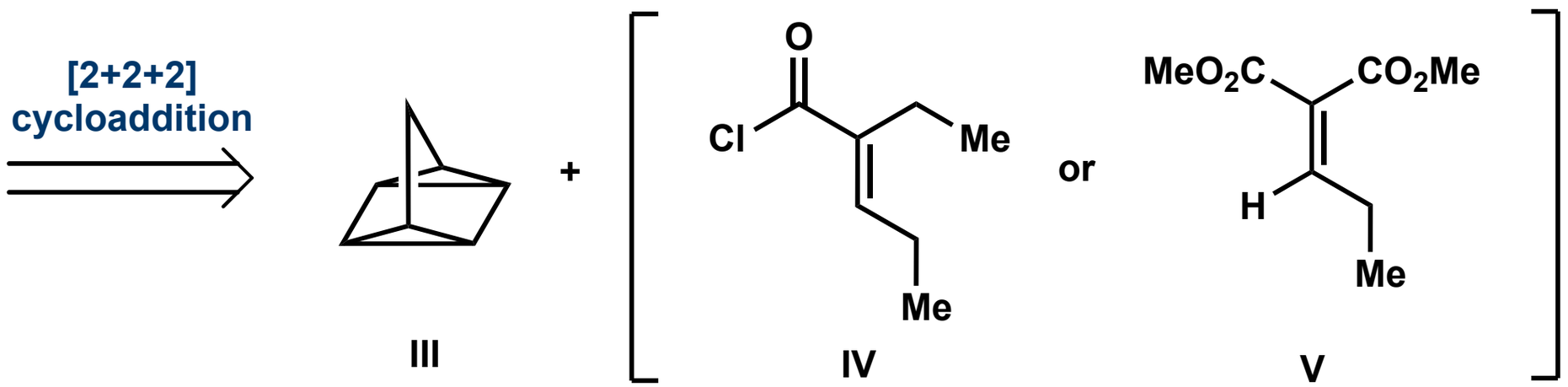
10
89% yield
25:75 endo/exo

JACS **2016**, *138*, 2437-2442; *ACIE* **2015**, *54*, 2378-2382.

Hippolachnin A: Brown vs Wood



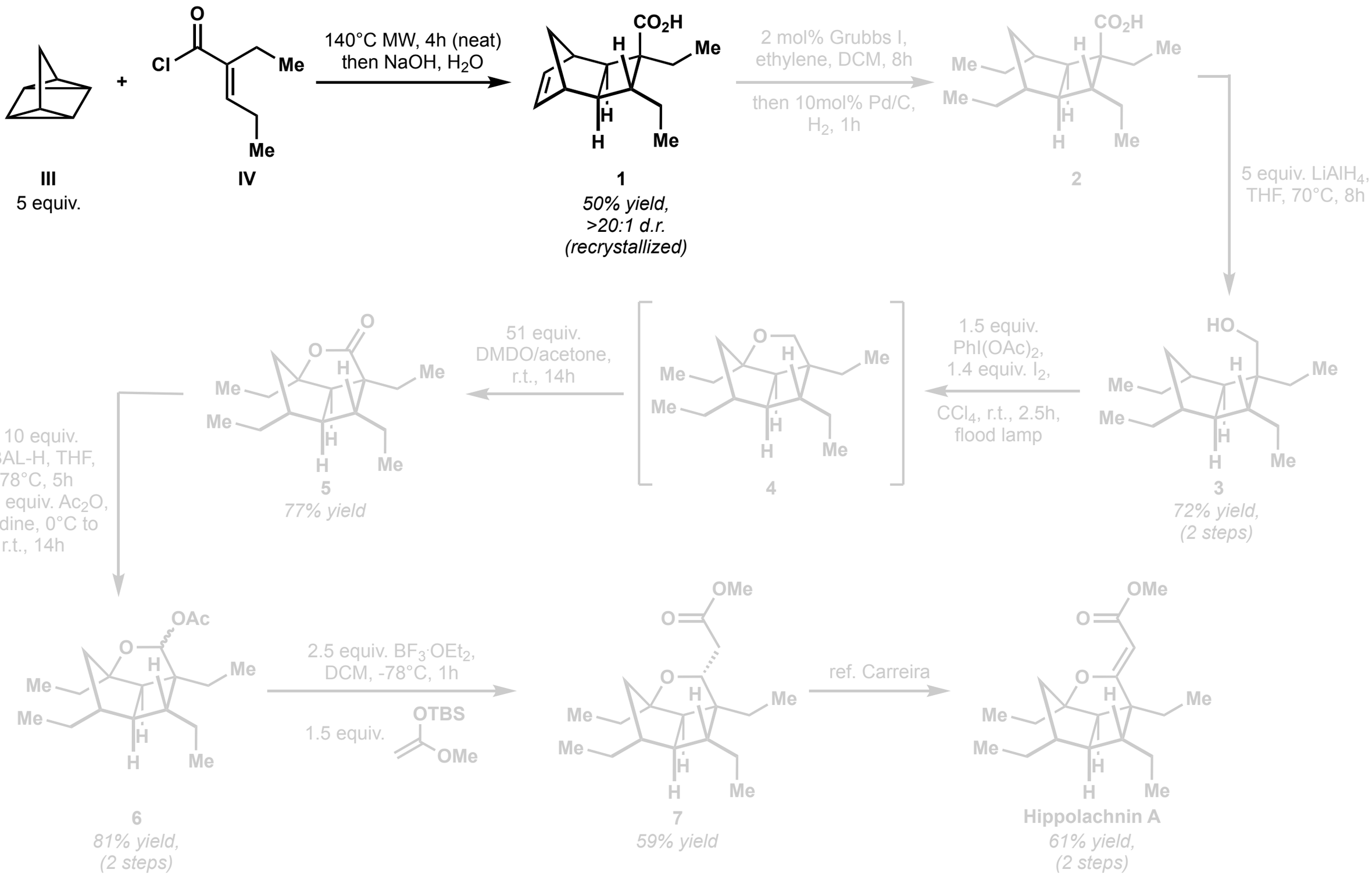
Hippolachnin A **I** **II**



III **IV** **V**

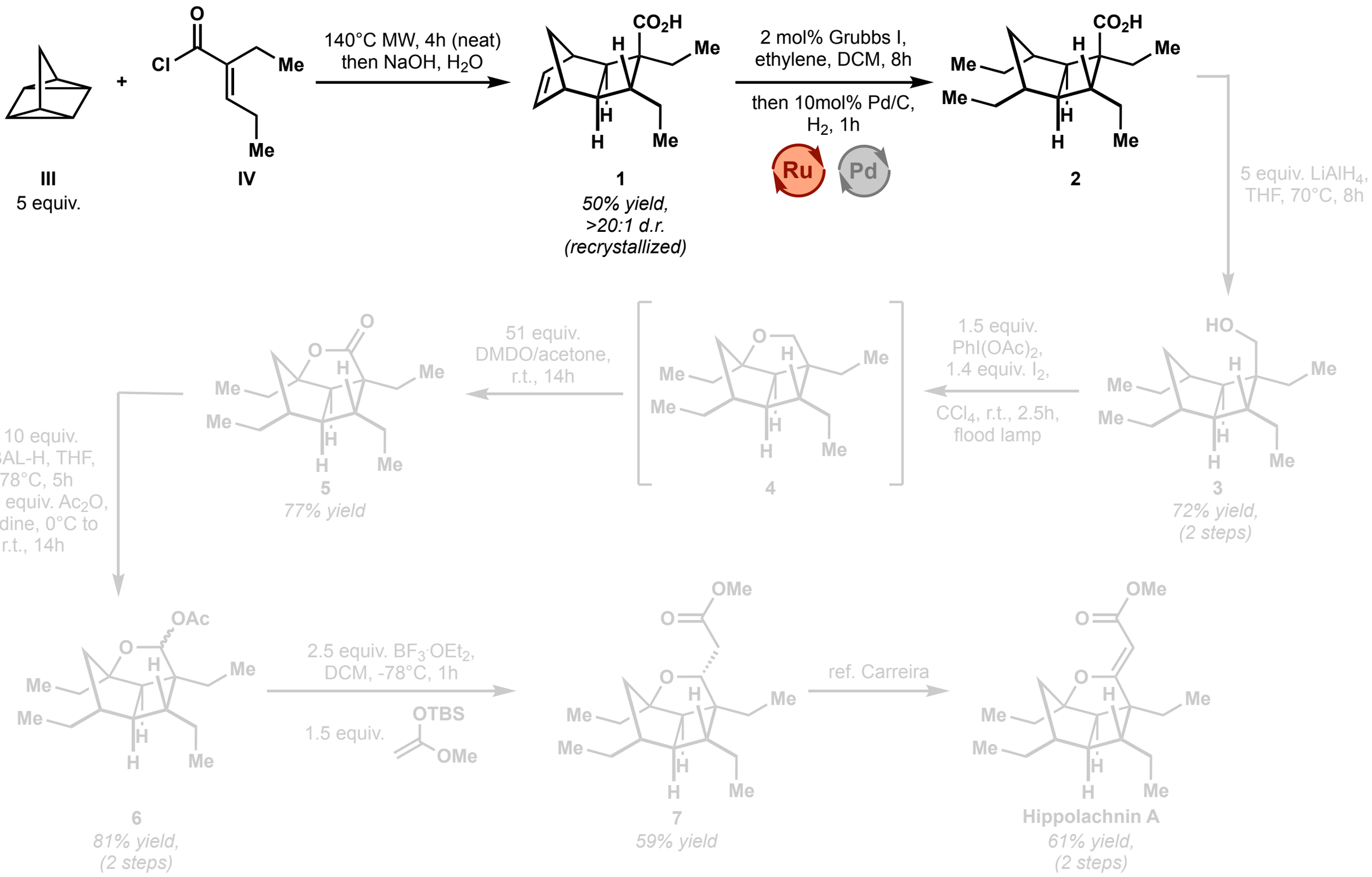
JACS **2016**, *138*, 2437-2442.

Hippolachnin A: Brown's strategy



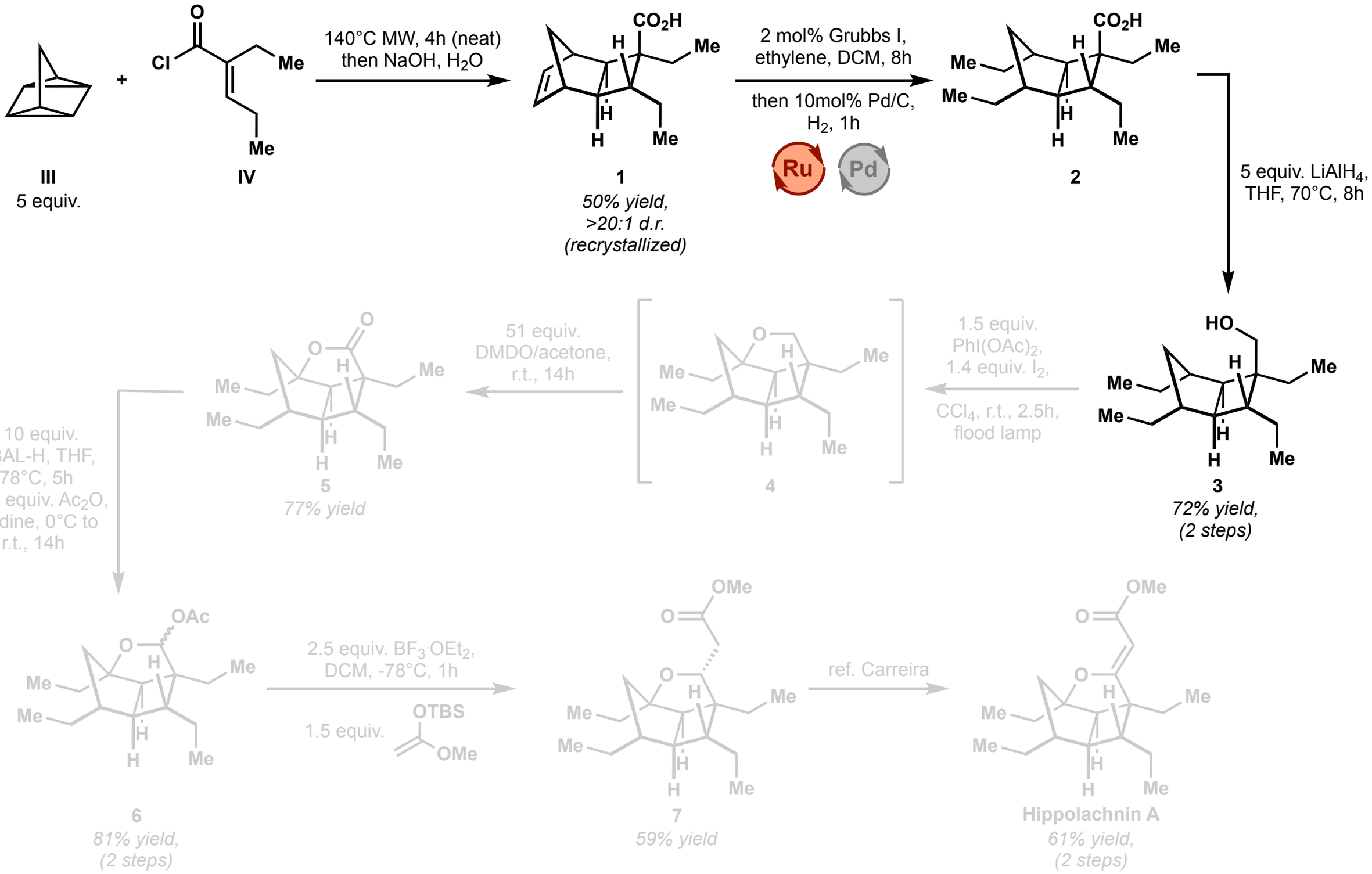
JACS **2016**, *138,* 2437-2442.

Hippolachnin A: Brown's strategy



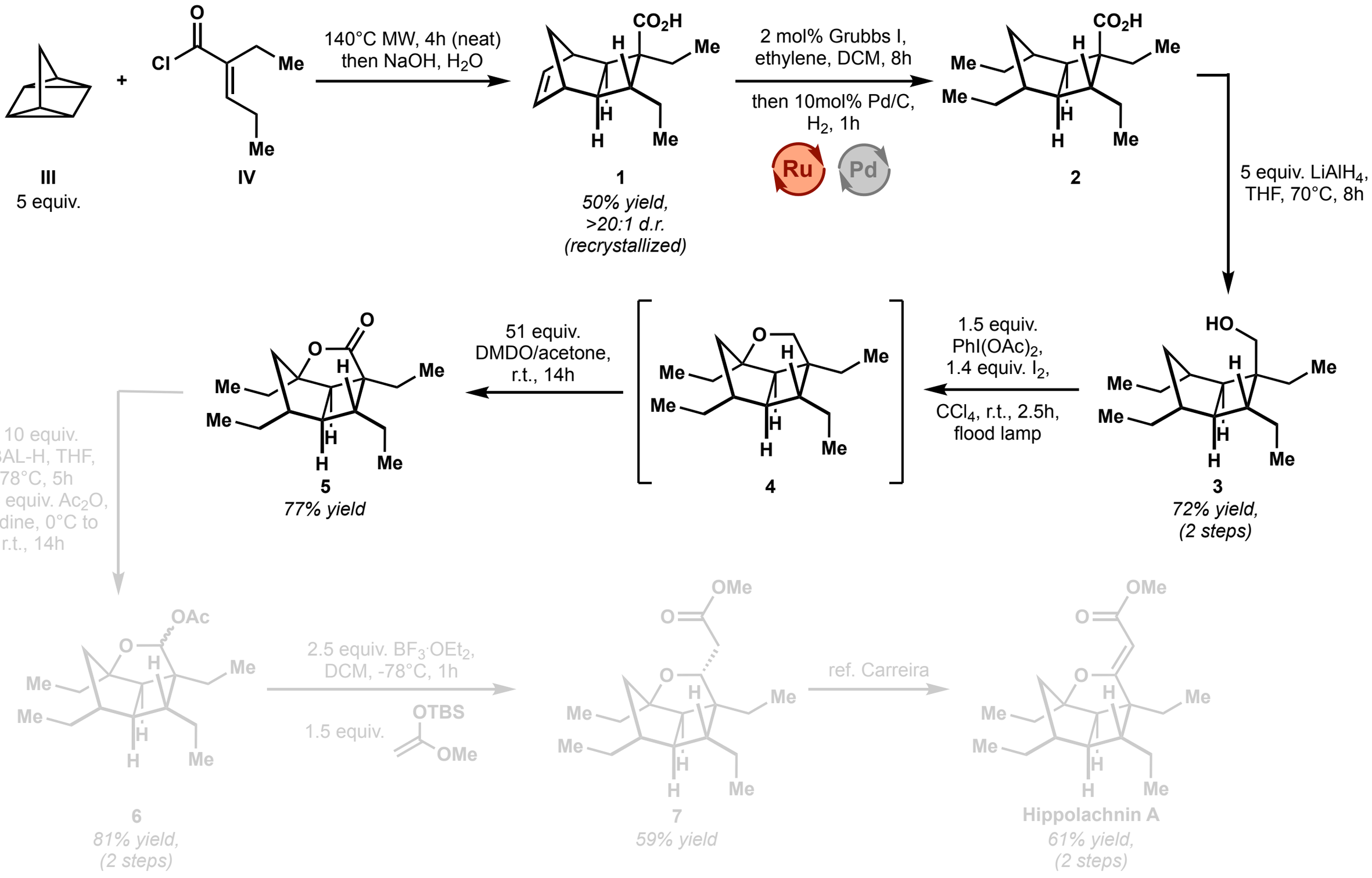
JACS **2016**, *138,* 2437-2442.

Hippolachnin A: Brown's strategy



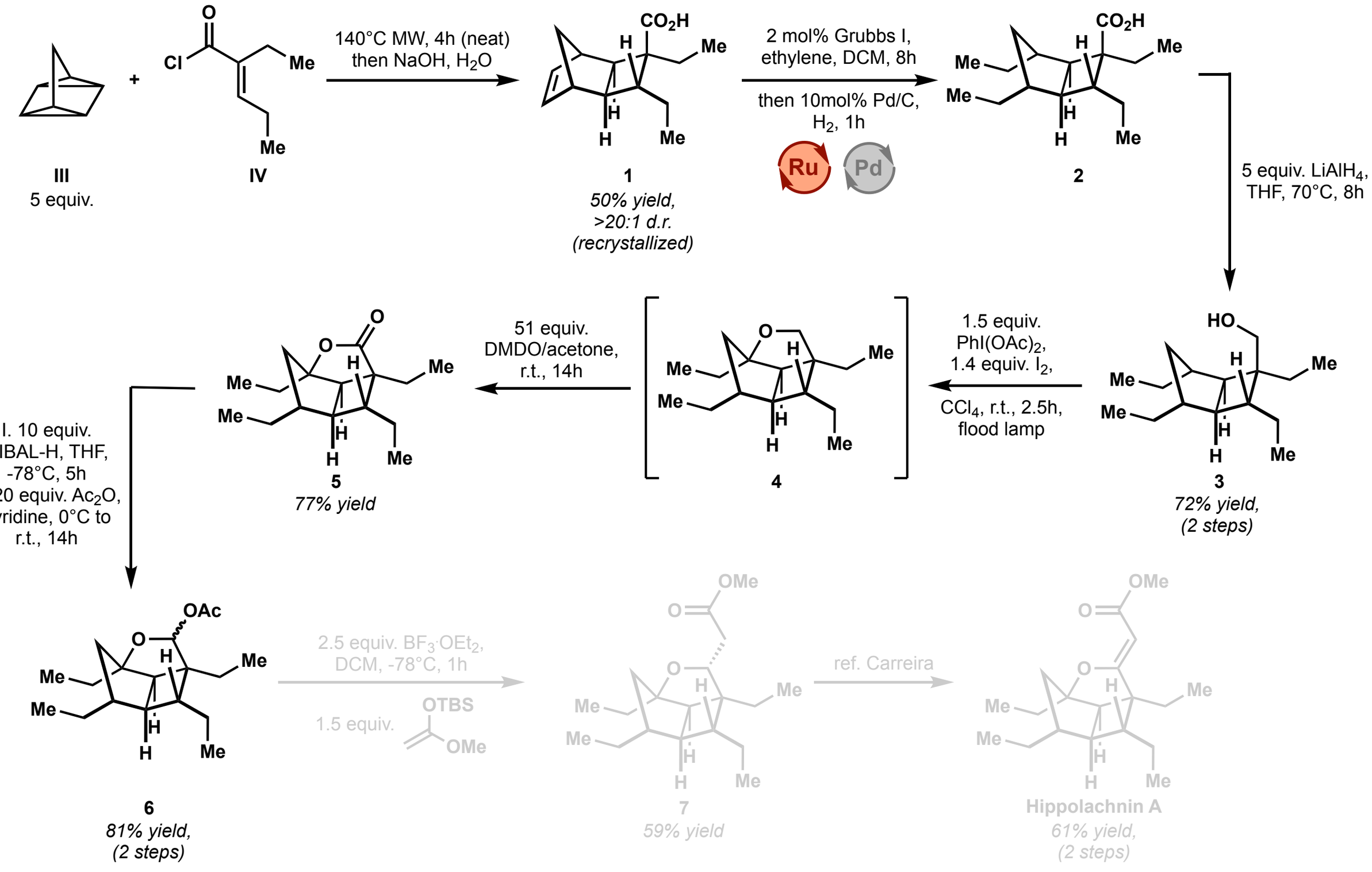
JACS **2016**, *138,* 2437-2442.

Hippolachnin A: Brown's strategy



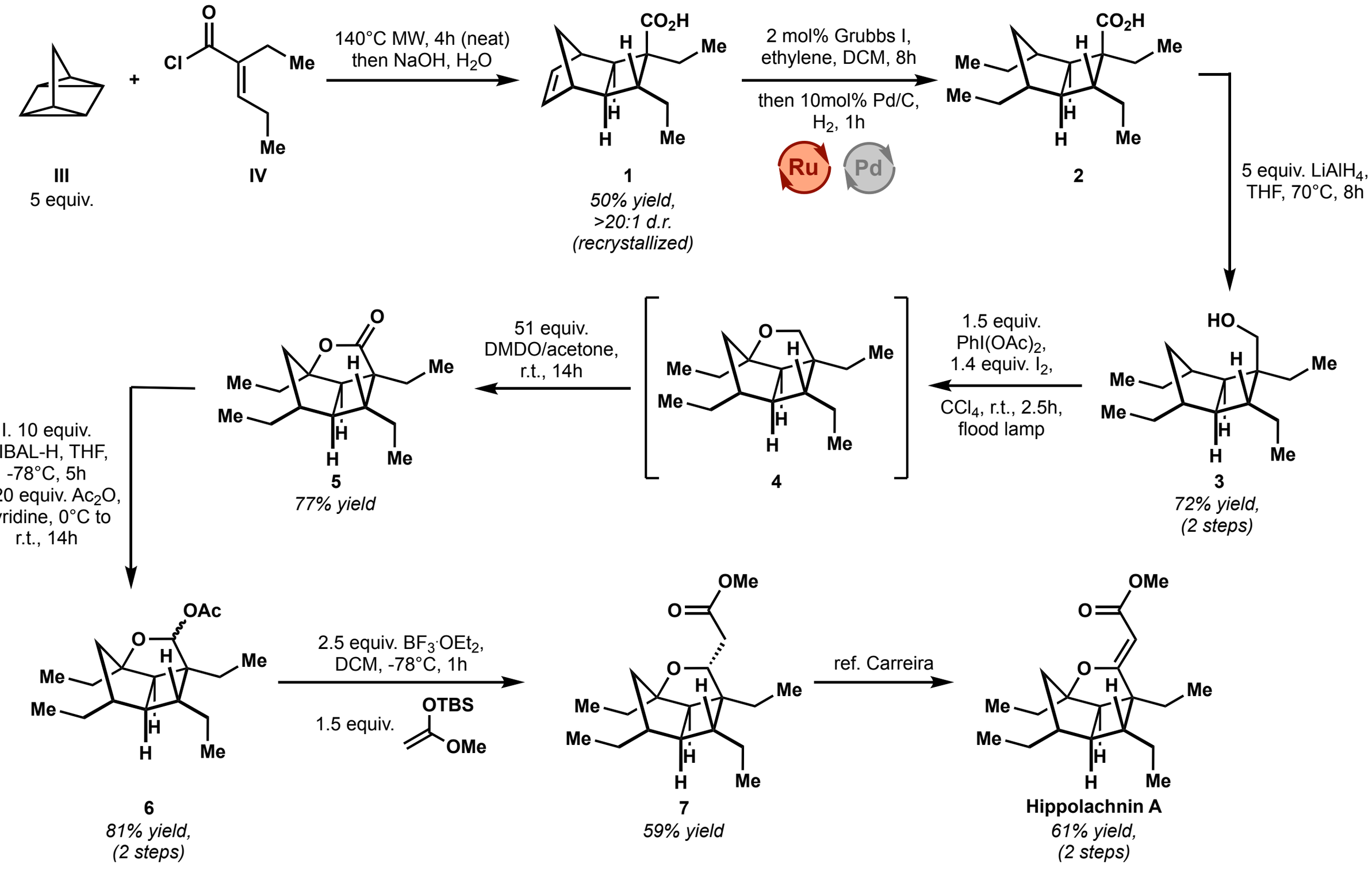
JACS **2016**, *138,* 2437-2442.

Hippolachnin A: Brown's strategy



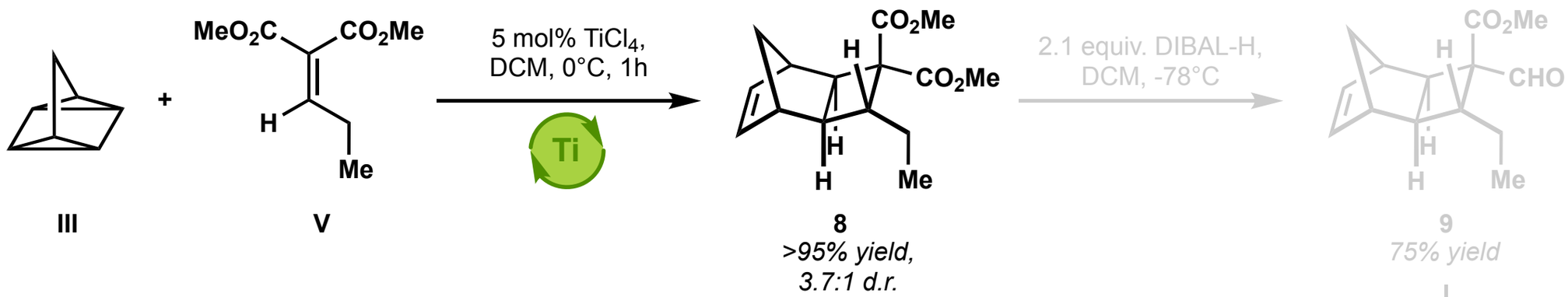
JACS **2016**, *138,* 2437-2442.

Hippolachnin A: Brown's strategy



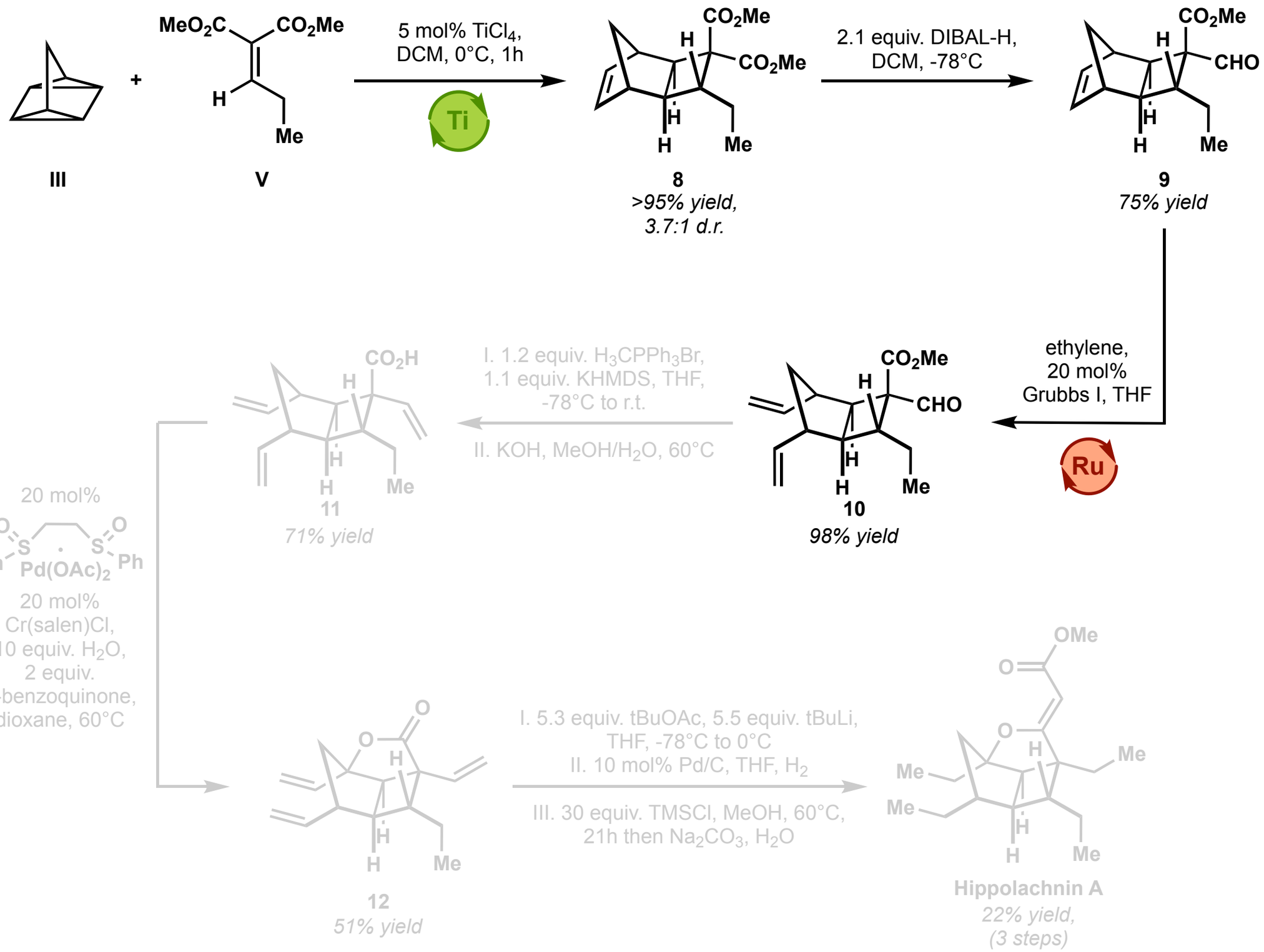
JACS **2016**, *138,* 2437-2442.

Hippolachnin A: Wood's approach



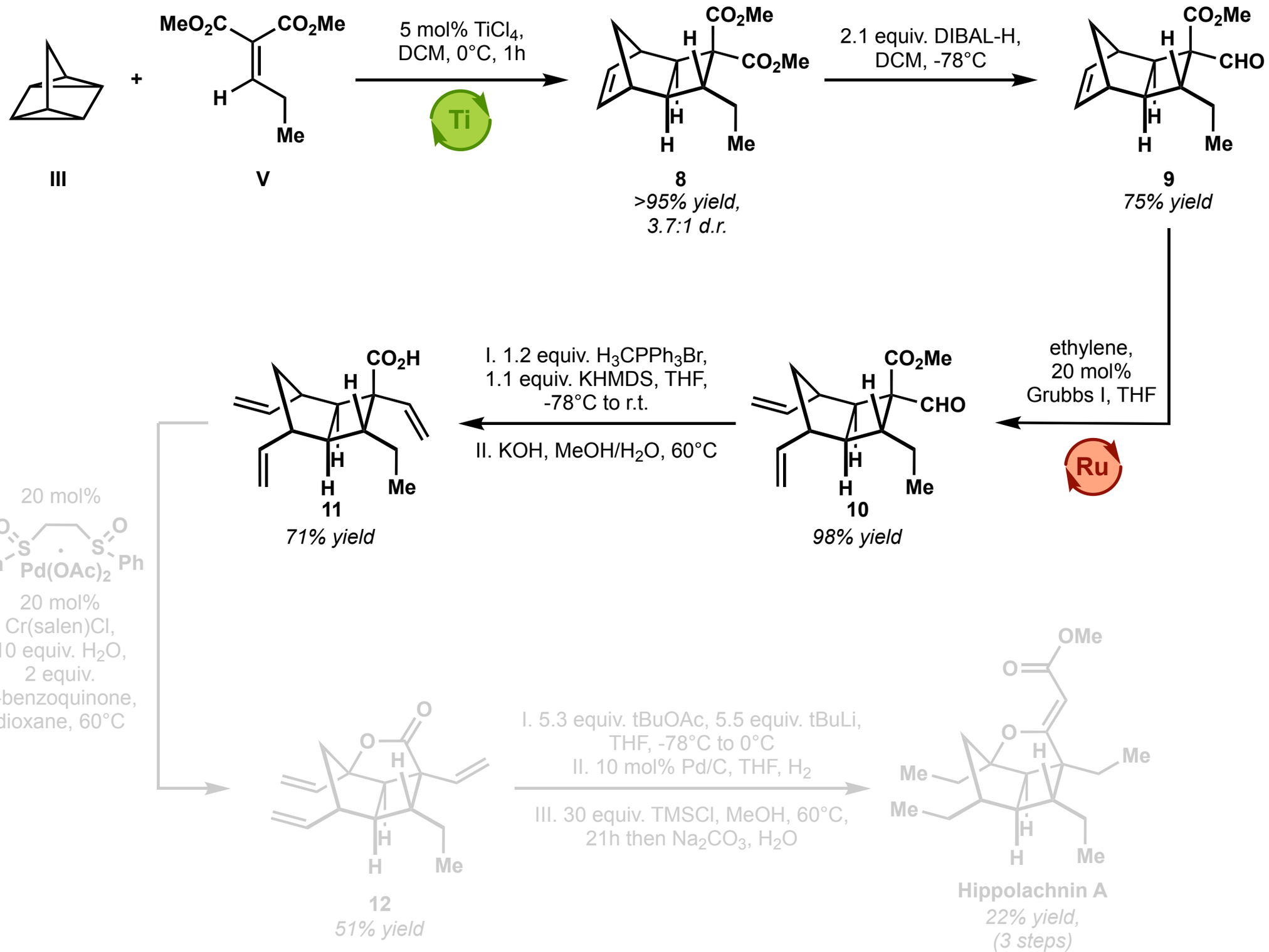
JACS **2016**, *138*, 2437-2442.

Hippolachnin A: Wood's approach



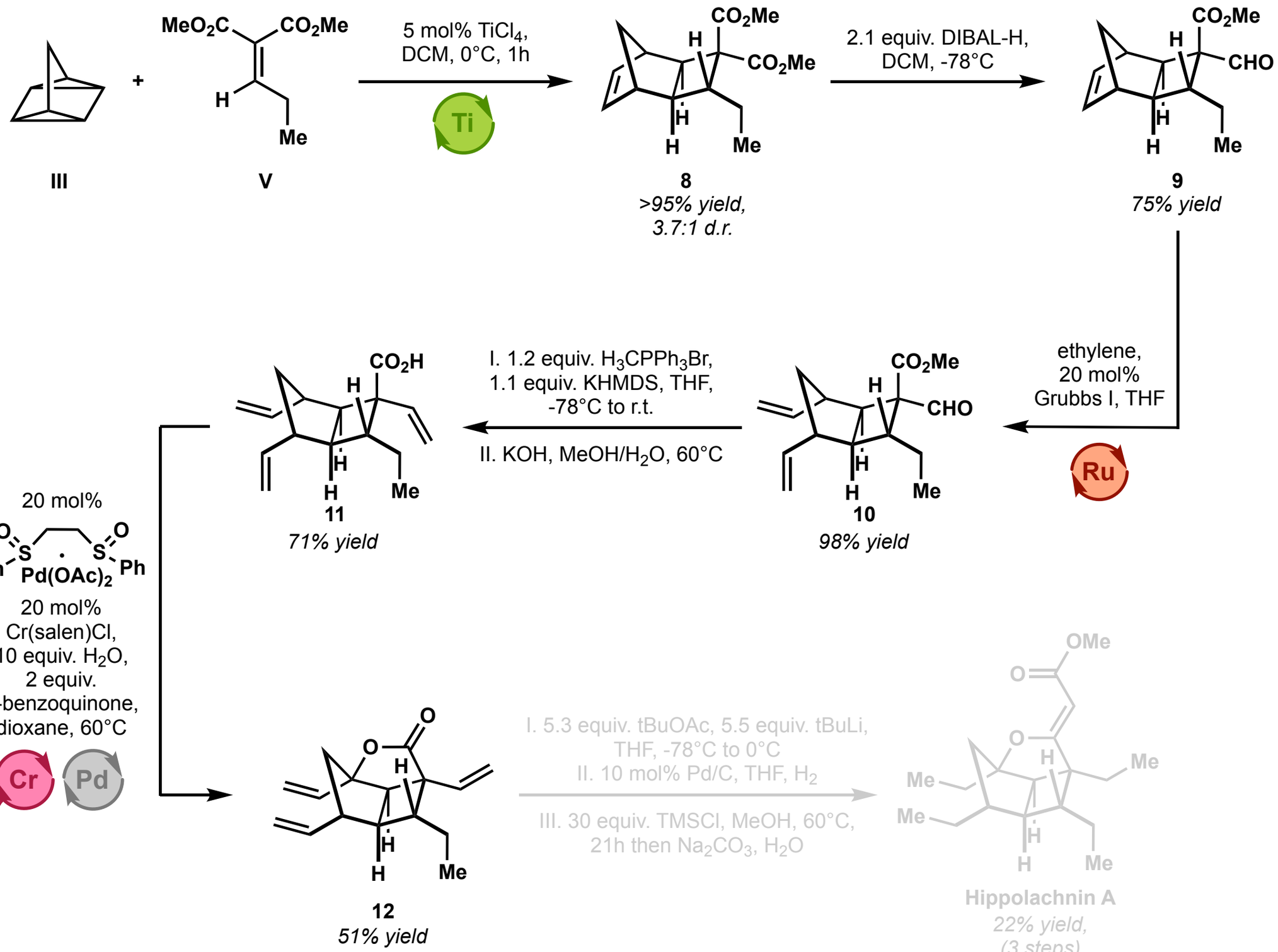
JACS **2016**, *138*, 2437-2442.

Hippolachnin A: Wood's approach



JACS **2016**, *138*, 2437-2442.

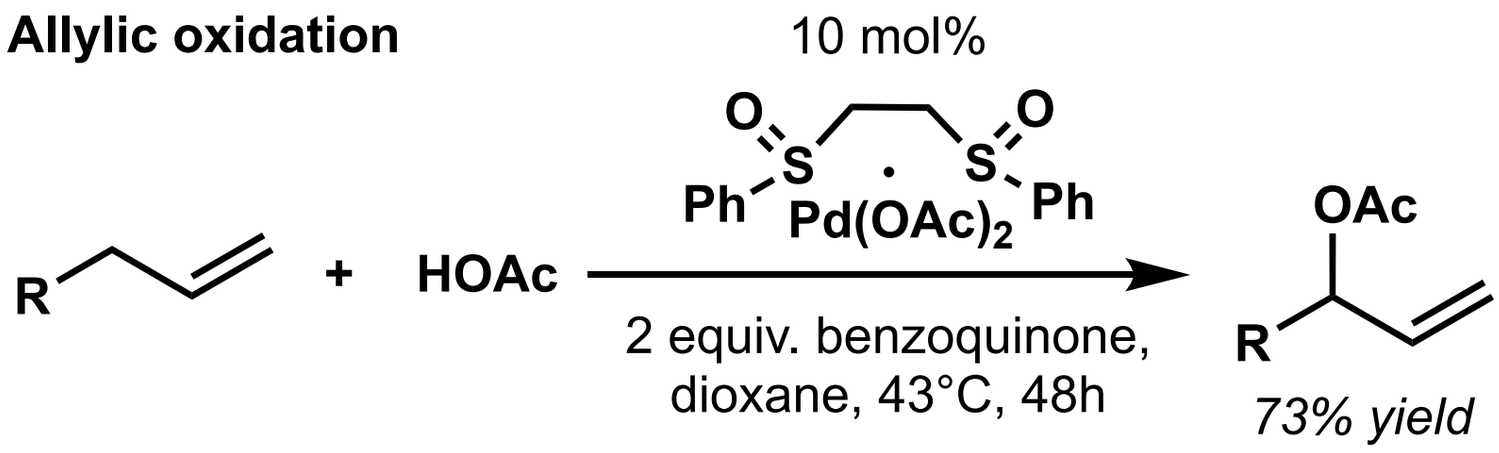
Hippolachnin A: Wood's approach



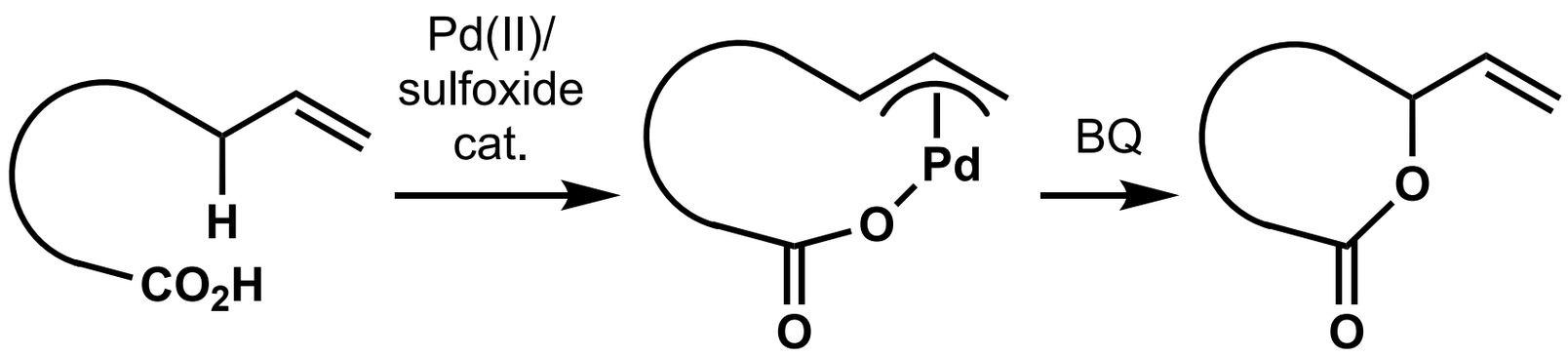
JACS **2016**, *138,* 2437-2442.

White's catalyst

Allylic oxidation

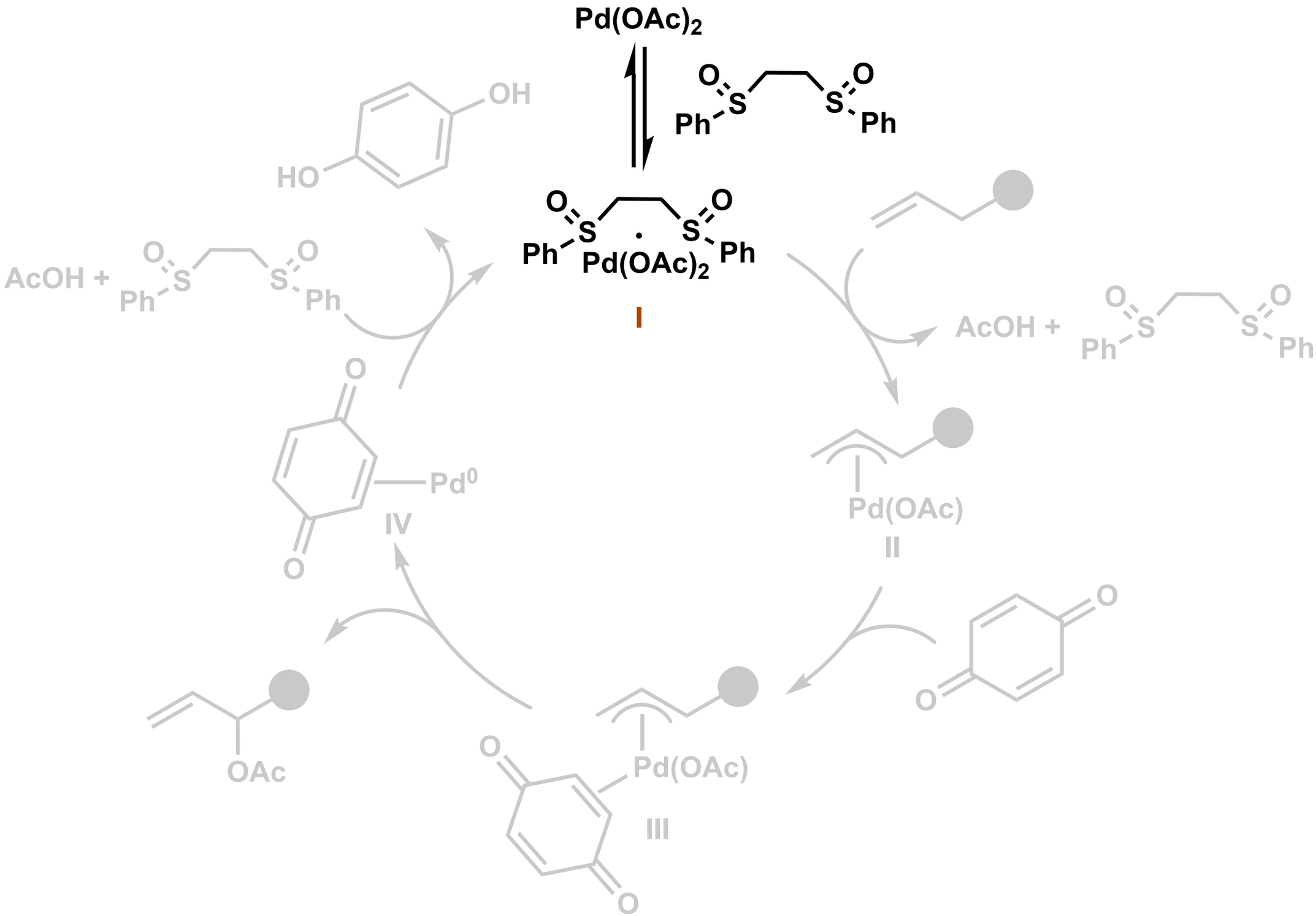


Macrolactonization strategy



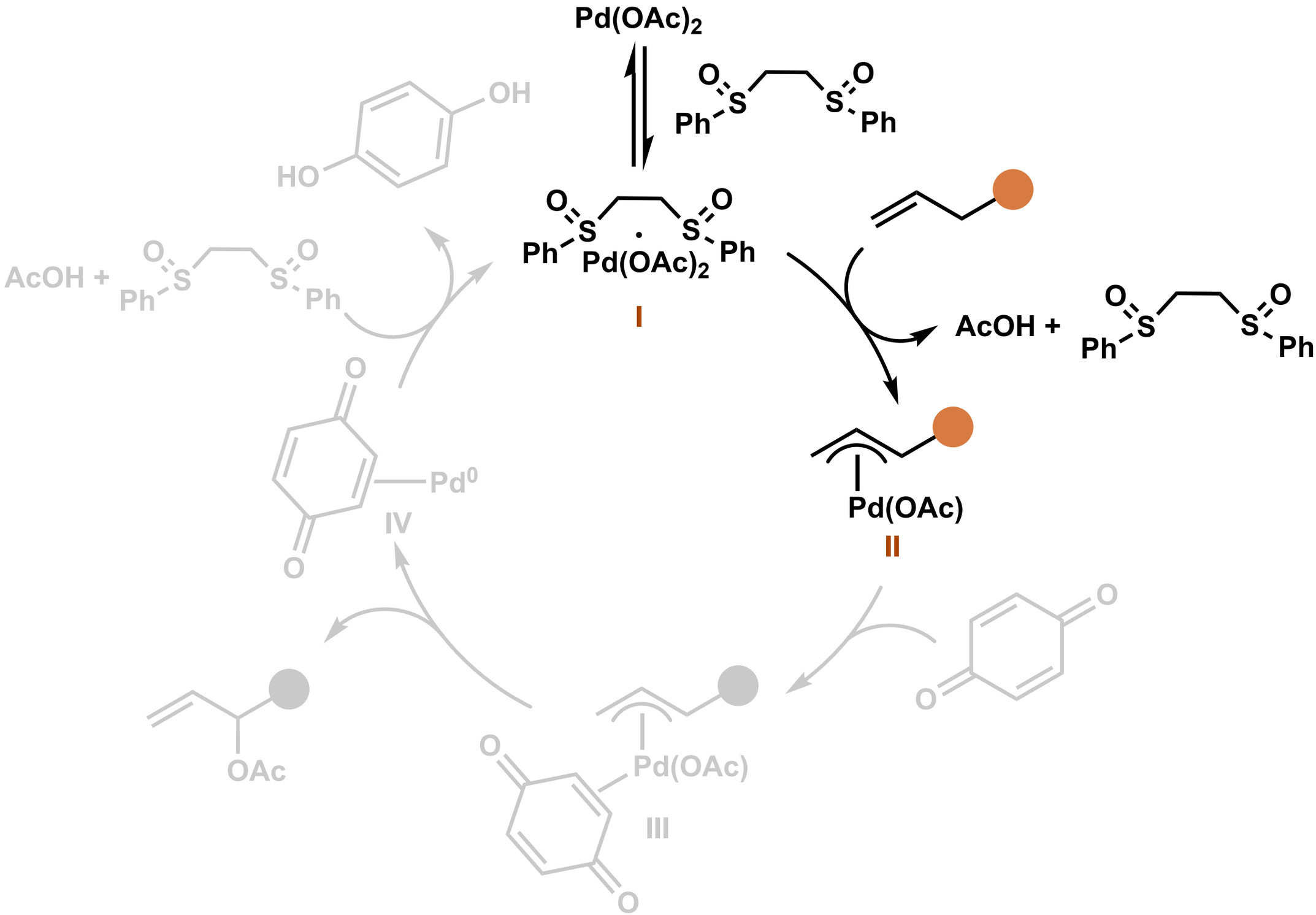
JACS **2004**, *126,* 1346; *JACS* **2006**, *128,* 9032-9033.

White’s catalyst



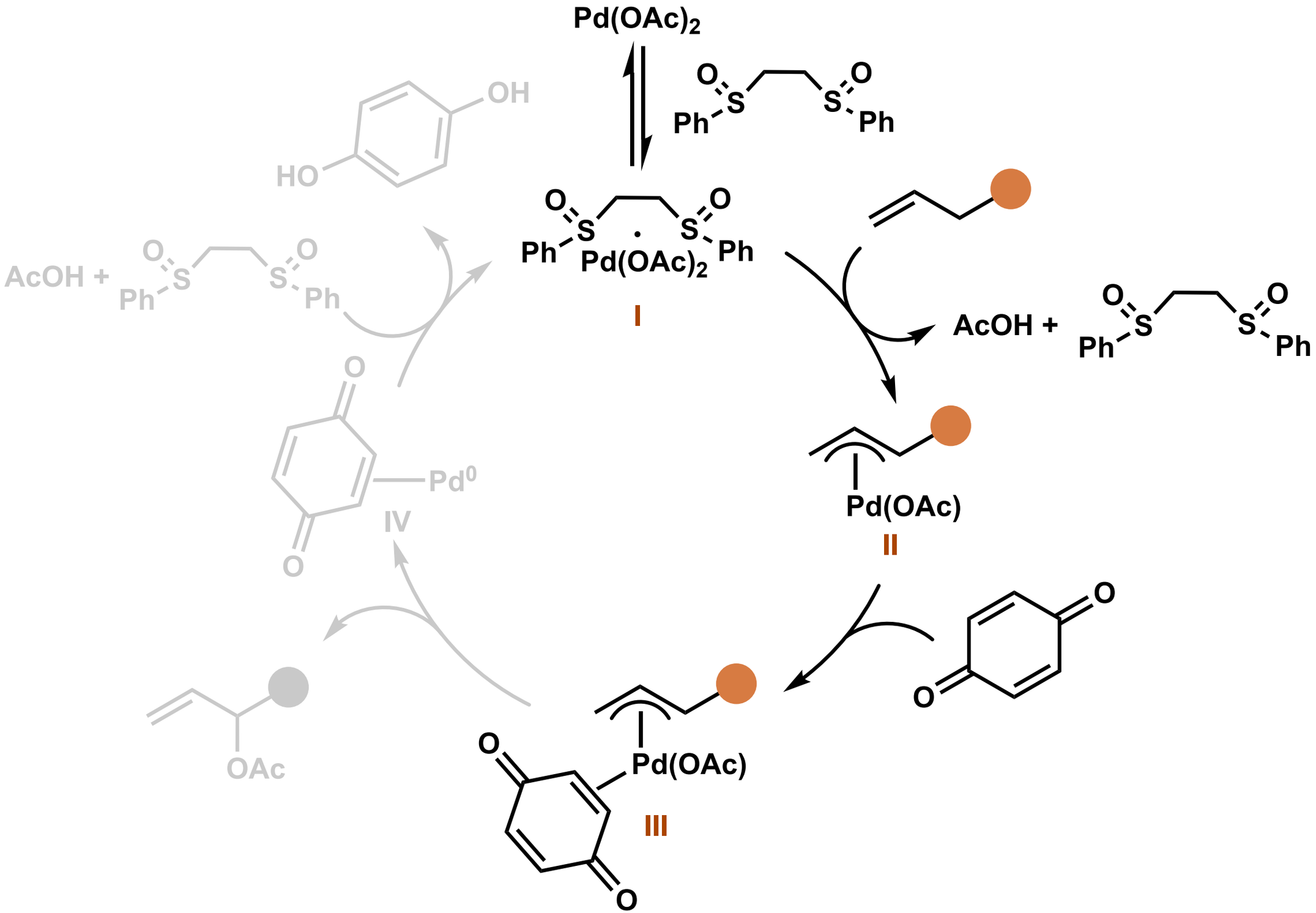
JACS **2004**, *126*, 1346; *JACS* **2006**, *128*, 9032-9033.

White’s catalyst



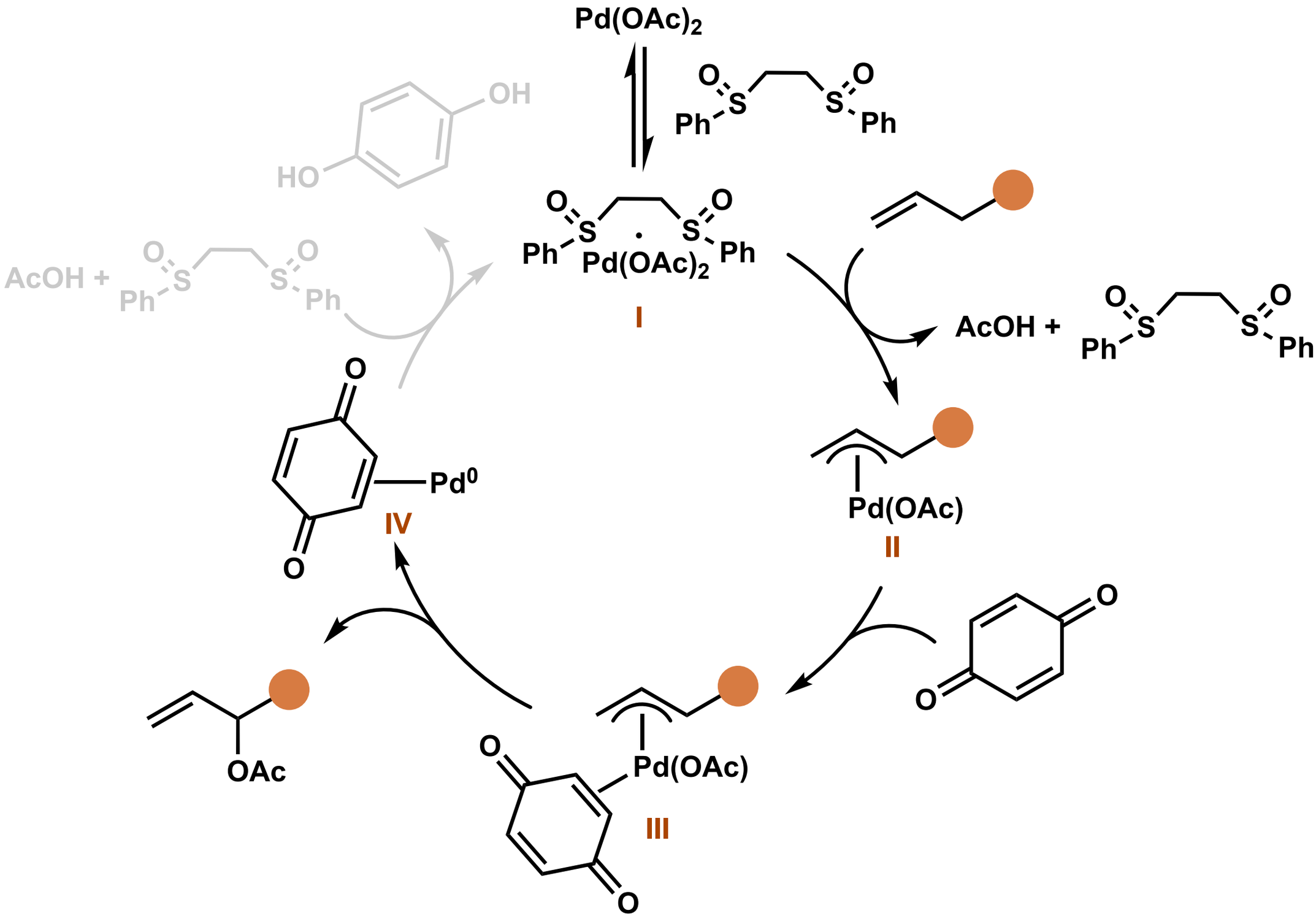
JACS **2004**, *126*, 1346; *JACS* **2006**, *128*, 9032-9033.

White’s catalyst



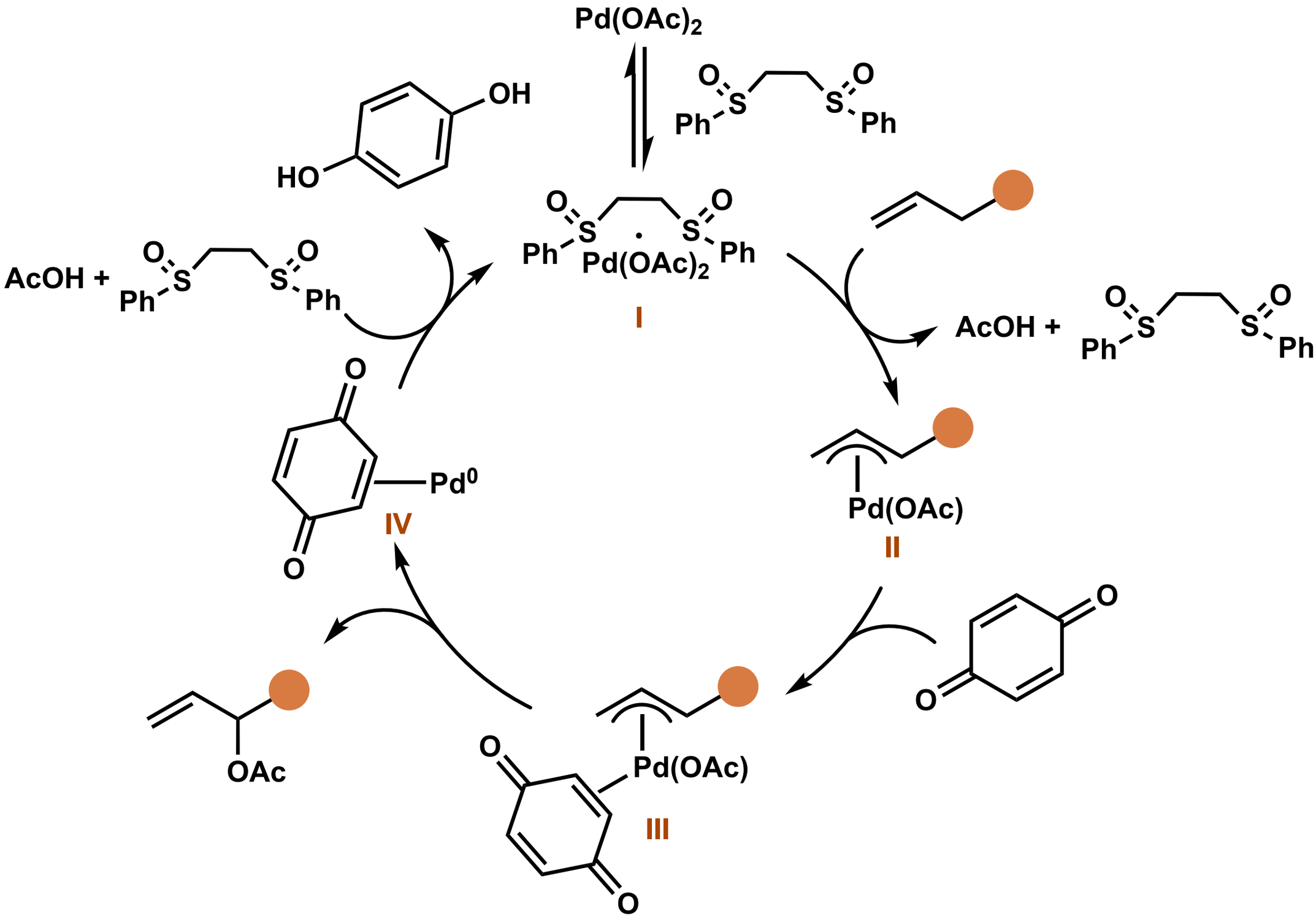
JACS **2004**, *126*, 1346; *JACS* **2006**, *128*, 9032-9033.

White’s catalyst



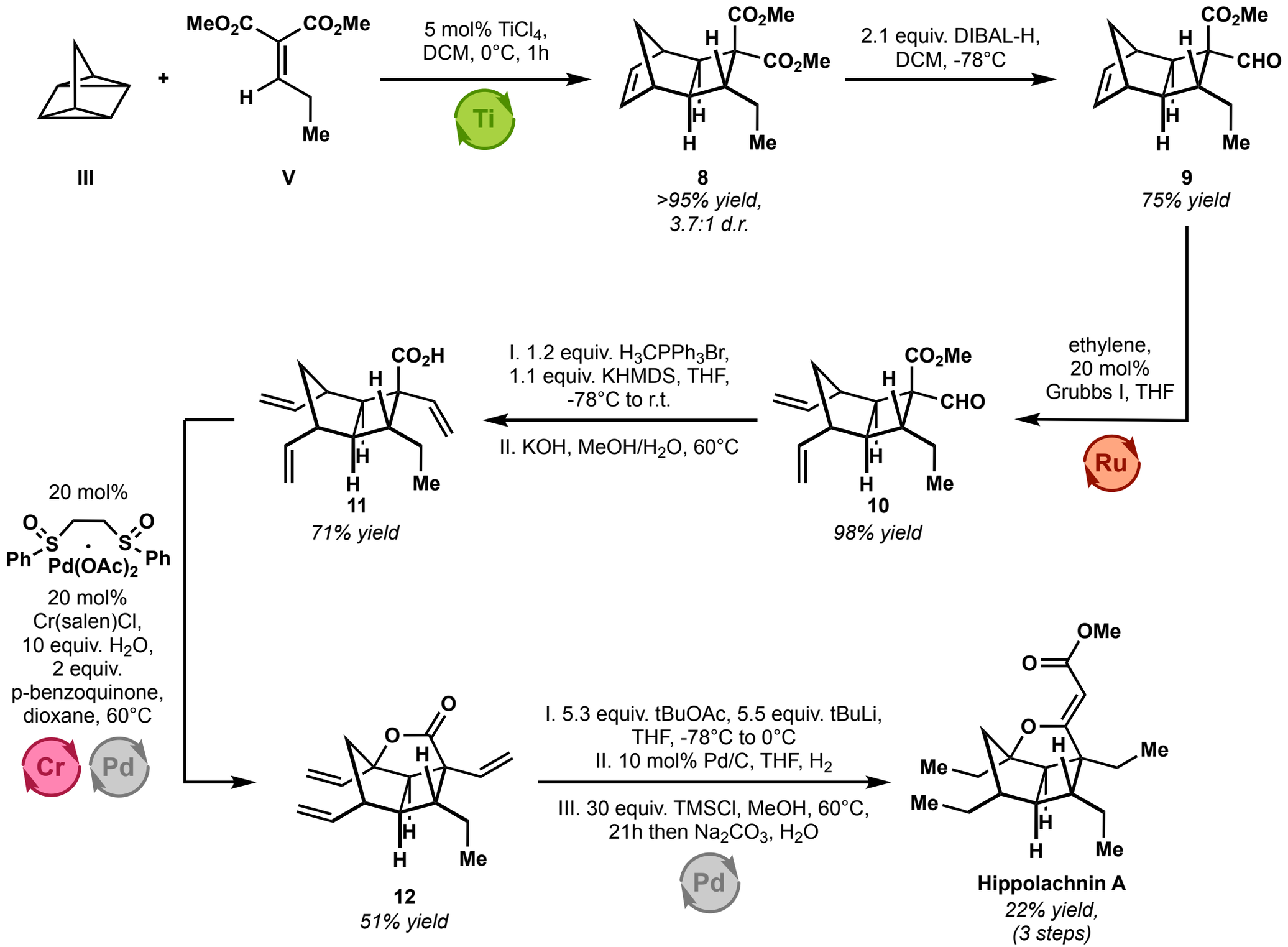
JACS **2004**, *126*, 1346; *JACS* **2006**, *128*, 9032-9033.

White’s catalyst



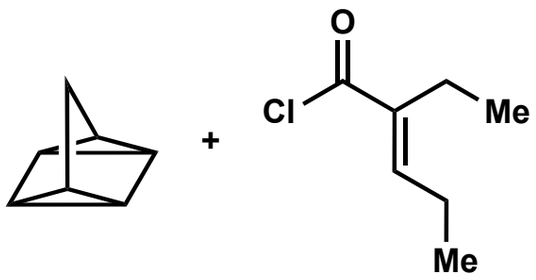
JACS **2004**, *126*, 1346; *JACS* **2006**, *128*, 9032-9033.

Hippolachnin A: Wood's approach



JACS **2016**, *138*, 2437-2442.

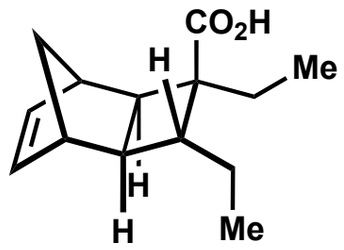
Hippolachnin A: collaborative route



III

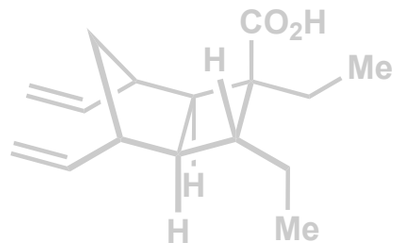
IV

140°C MW, 4h (neat)
then NaOH, H_2O



1
50% yield,
>20:1 d.r.
(recrystallized)

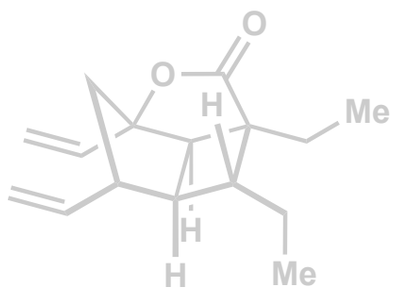
2 mol% Grubbs I,
ethylene, THF,



13
92% yield

20 mol%

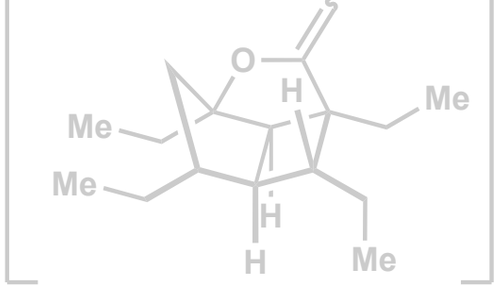
20 mol% Cr(salen)Cl,
10 equiv. H_2O,
2 equiv. p-benzoquinone,
dioxane, 60°C



14
70% yield

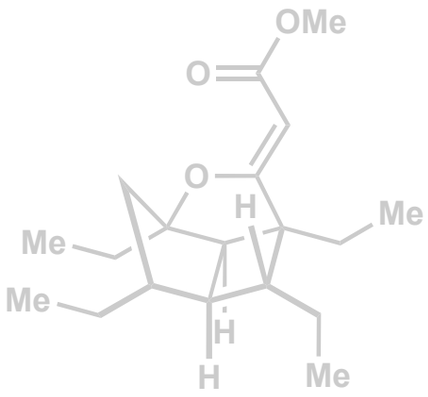
I. 5.3 equiv. tBuOAc,
5.5 equiv. tBuLi,
THF, -78°C to 0°C

then 6M HCl (aq.)
II. 10 mol% Pd/C, H_2, THF



15

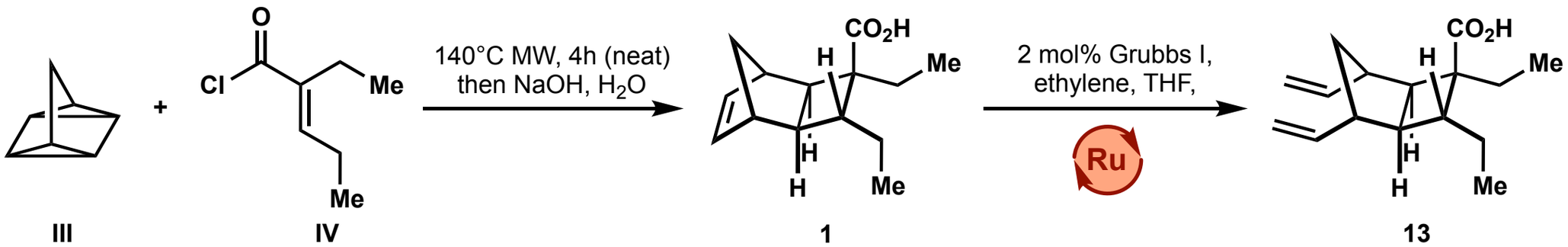
III. 30 equiv. TMSCl,
MeOH, 60°C, 21h

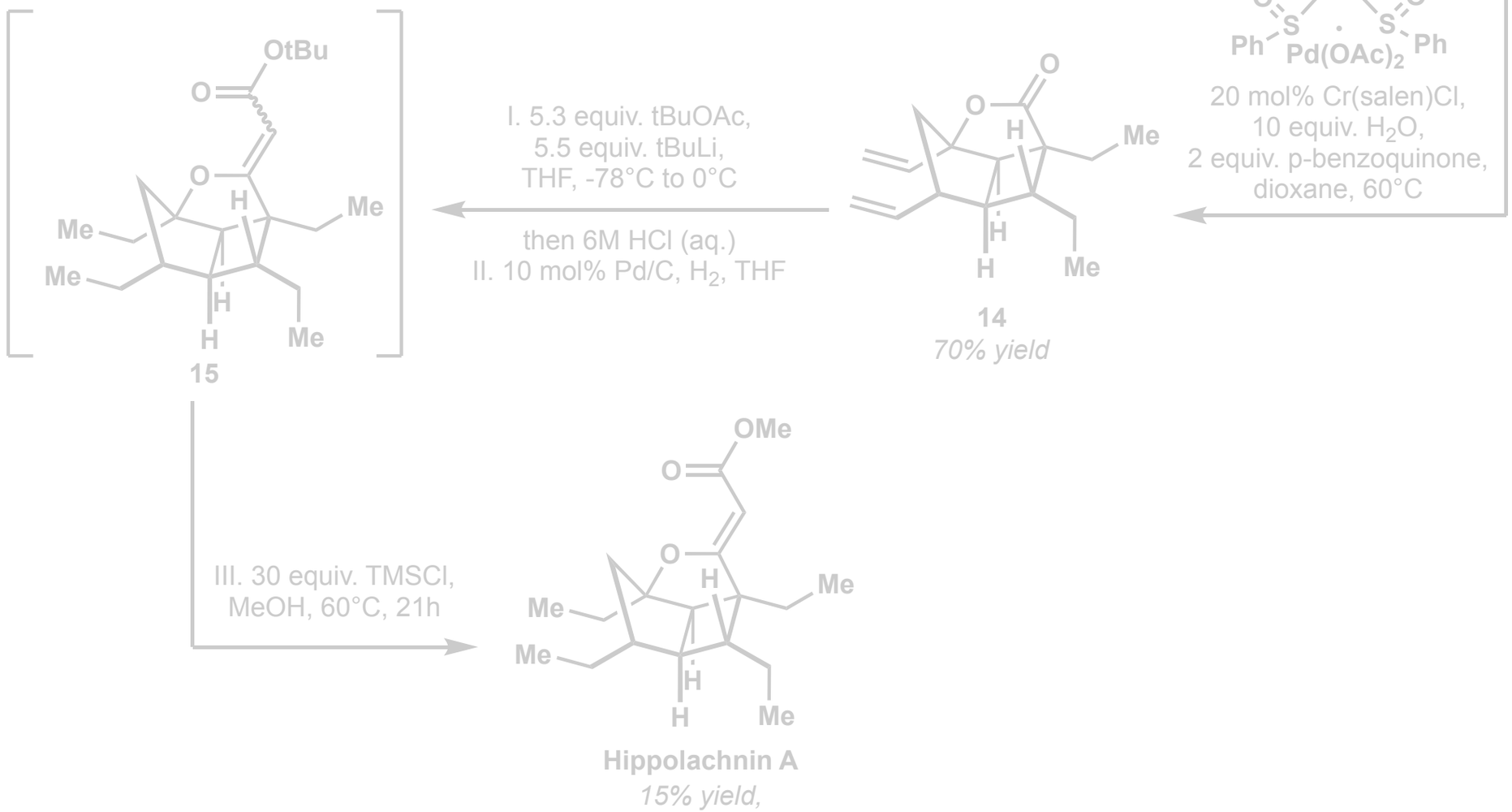


Hippolachnin A
15% yield,
(3 steps)

JACS **2016**, *138,* 2437-2442.

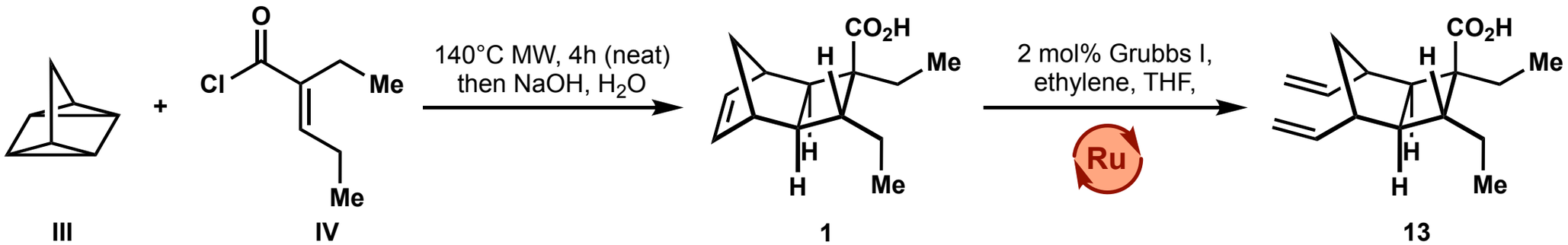
Hippolachnin A: collaborative route





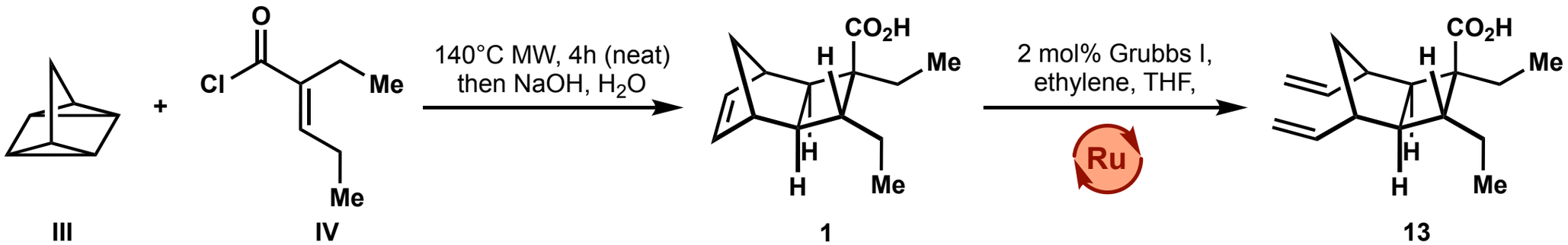
JACS **2016**, *138,* 2437-2442.

Hippolachnin A: collaborative route



JACS **2016**, *138,* 2437-2442.

Hippolachnin A: collaborative route

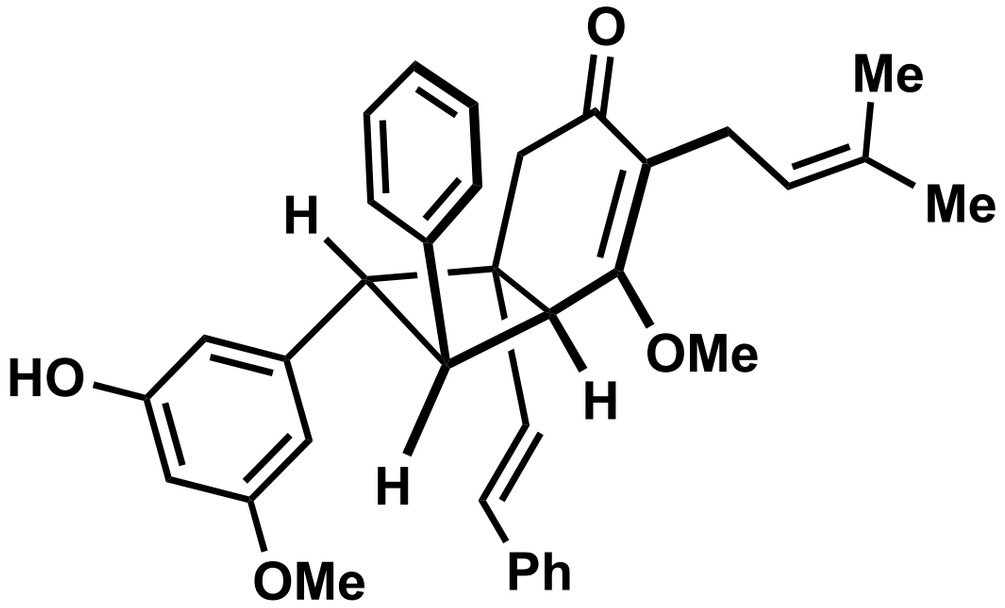


- 6 total steps
- [2+2+2] cycloaddition of quadricyclane
- Key directed C-H oxidation

JACS **2016**, *138*, 2437-2442.

(-)-Cajanusine

Plant *Cajanus cajan*

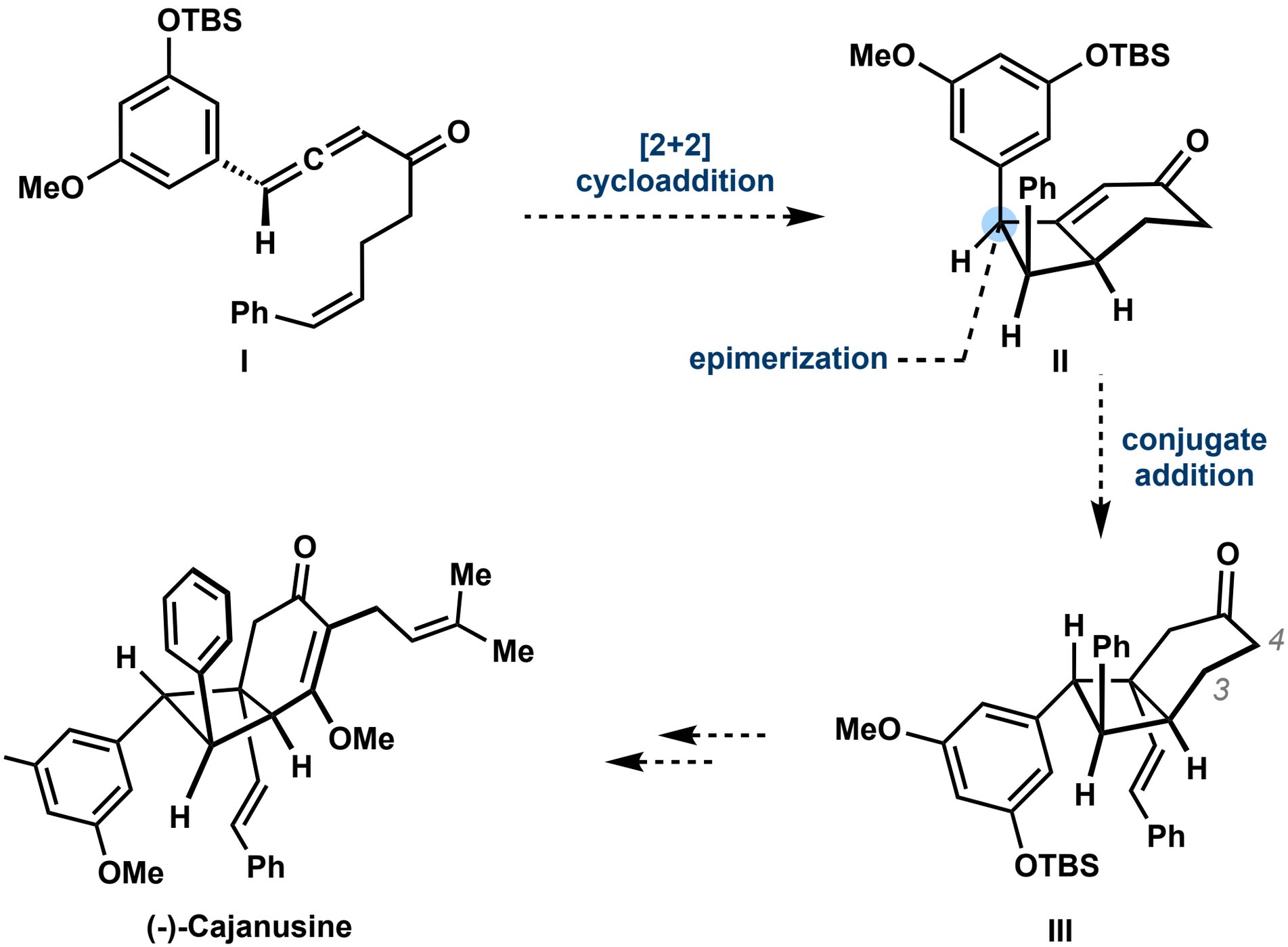


(-)-Cajanusine

- Dimer derived biosynthetically from a formal [2+2] cycloaddition of the alkene units
- Used in folk medicine for diabetes, anemia, hepatic disorders and many others
- Isolation paper describes inhibitory activities on the growth of human hepatocellular carcinoma cells

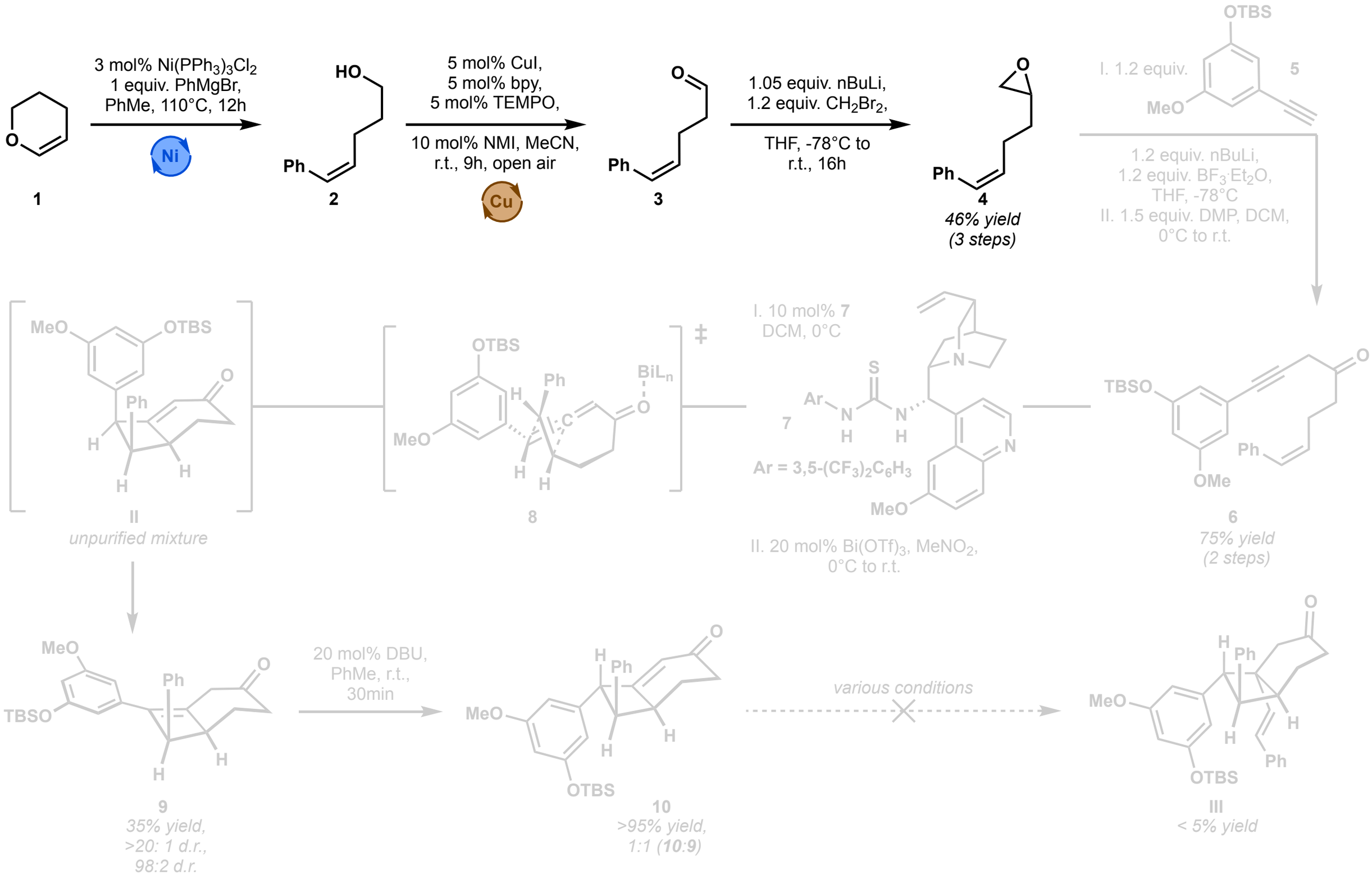
JACS **2020**, *142,* 5002-5006; *Org. Lett*. **2014**, *16*, 224.

(-)-Cajanusine: initial strategy (G1)



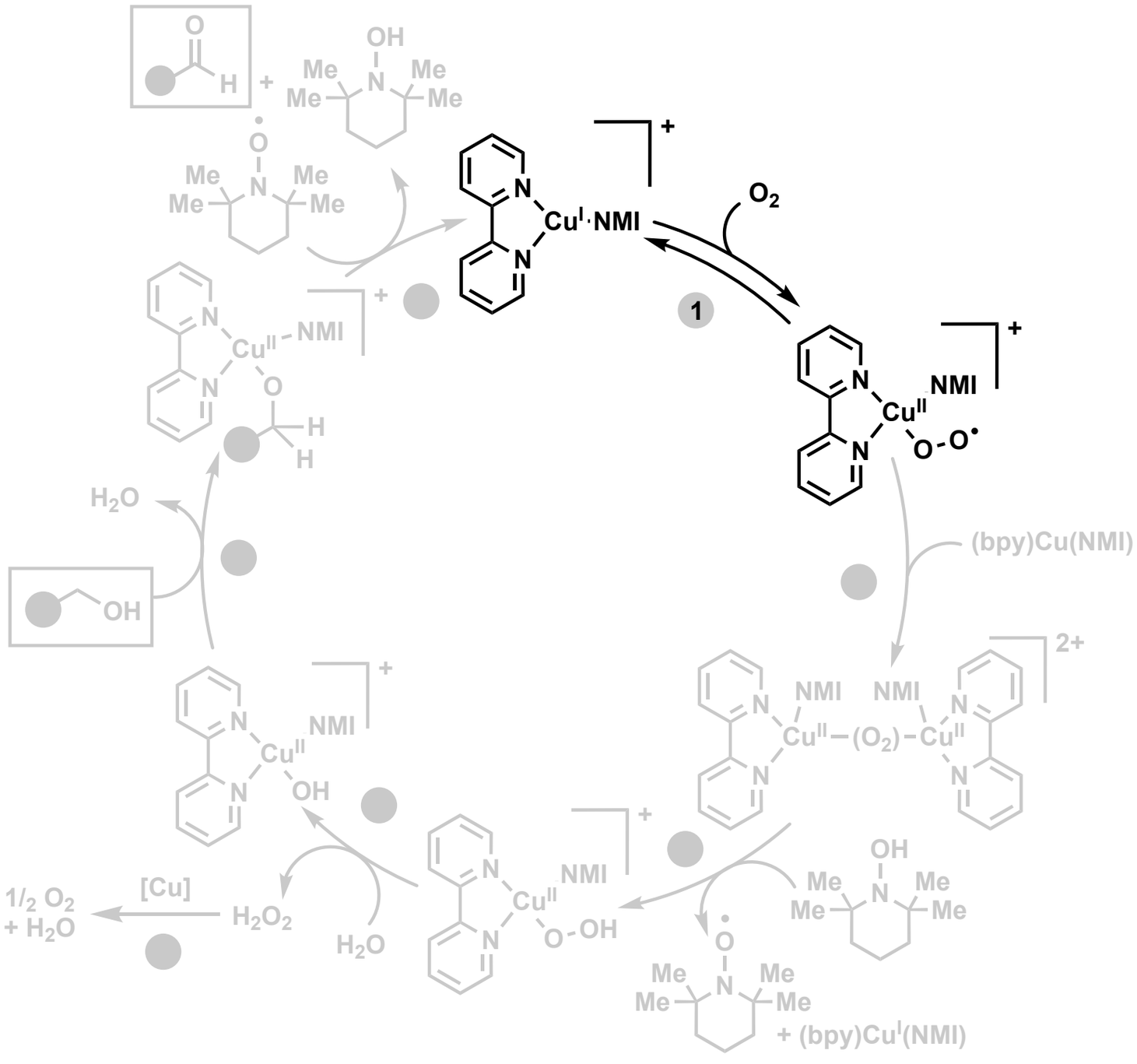
JACS **2020**, *142*, 5002-5006.

(-)-Cajanusine: first-generation approach



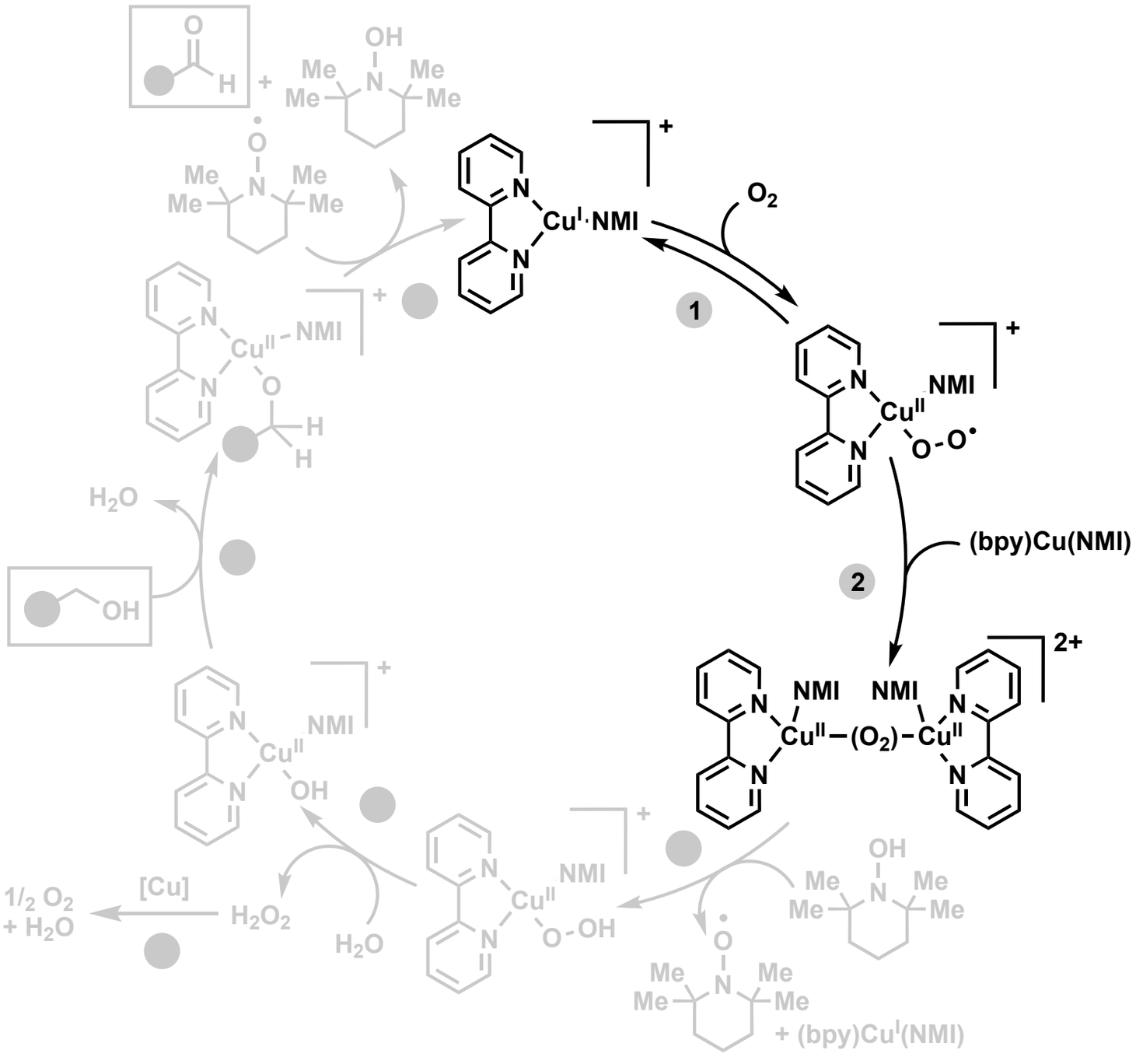
JACS **2020**, *142,* 5002-5006.

Stahl Oxidation



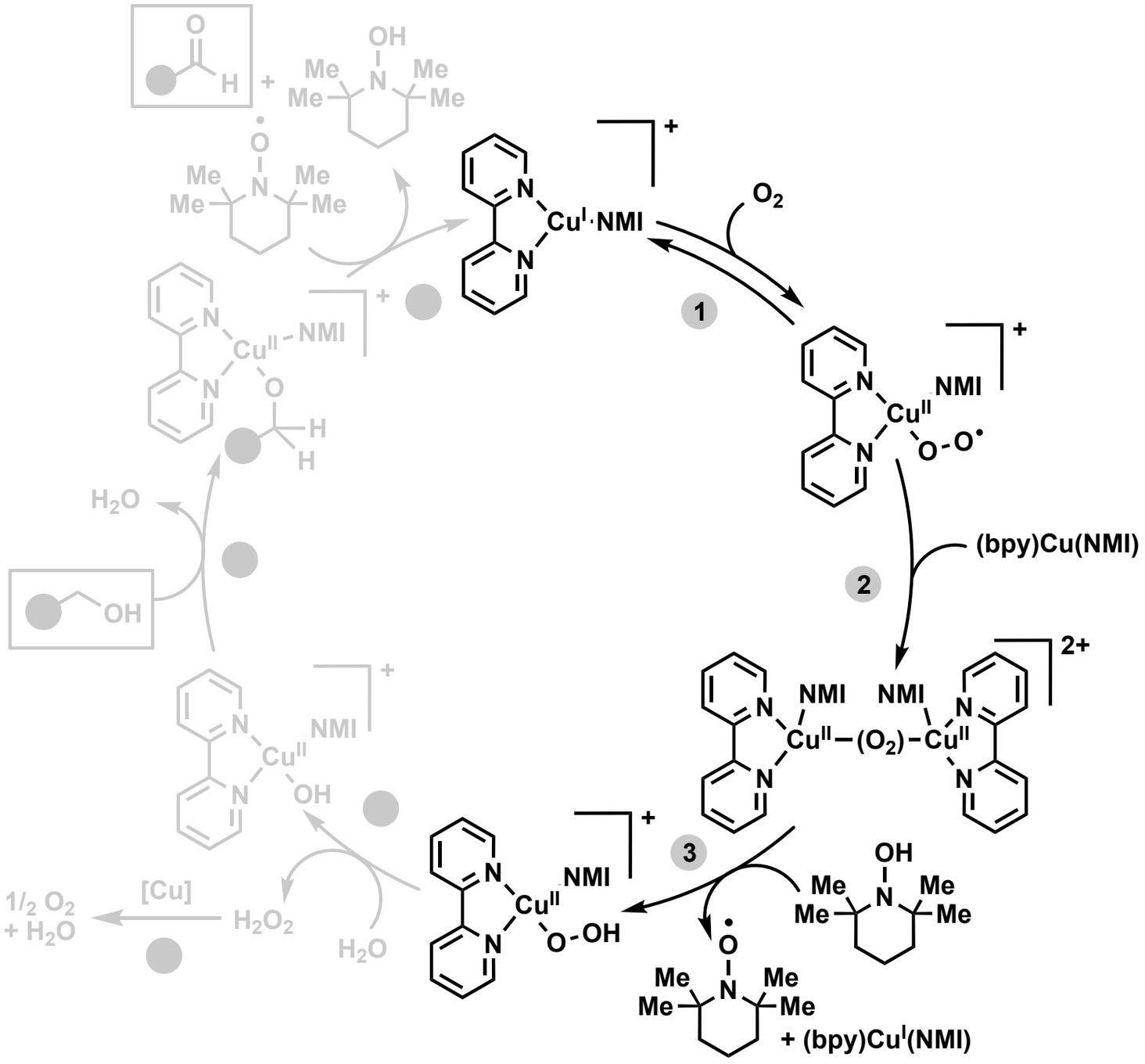
JACS **2013**, *135, 2357*-2367..

Stahl Oxidation

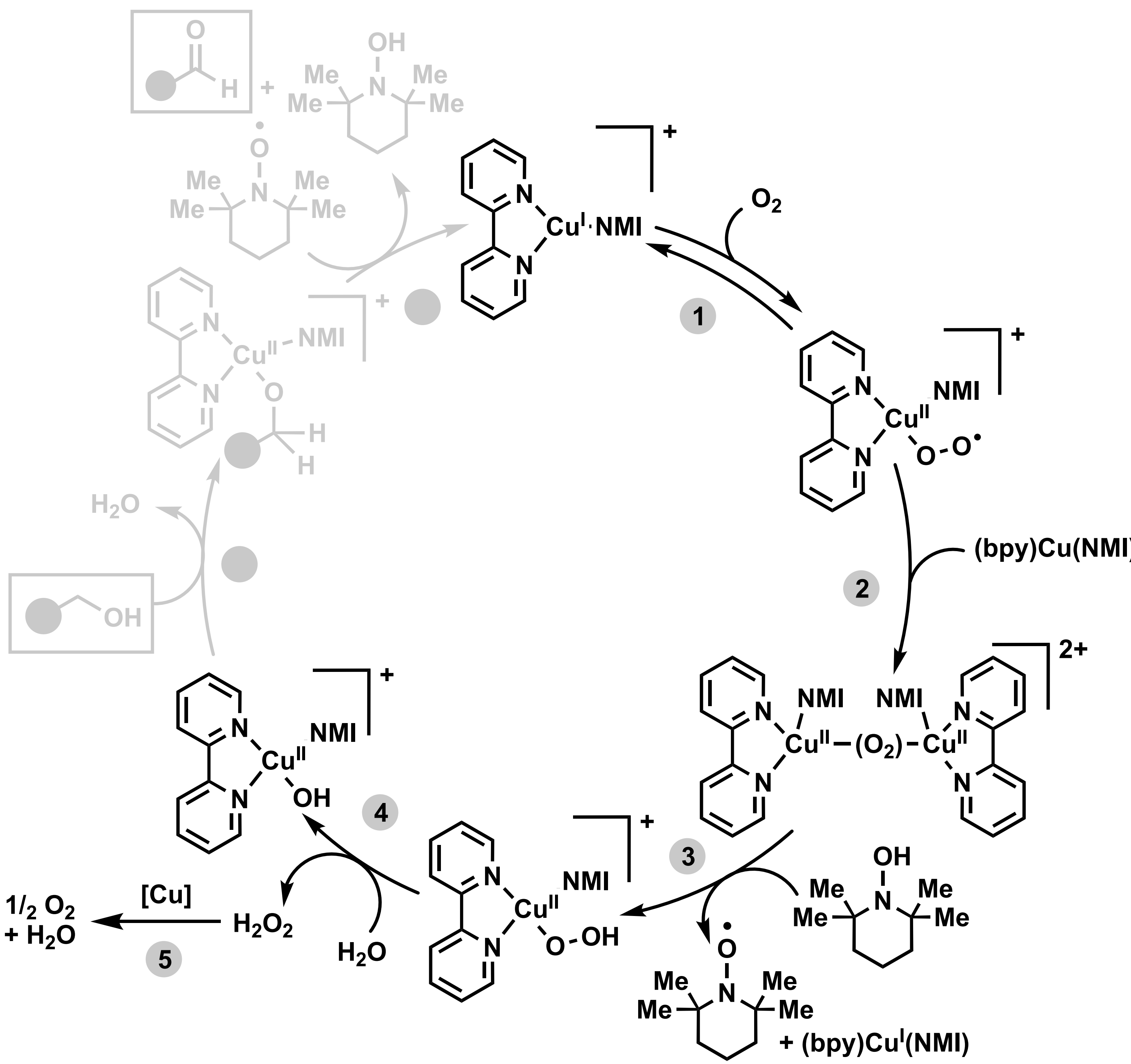


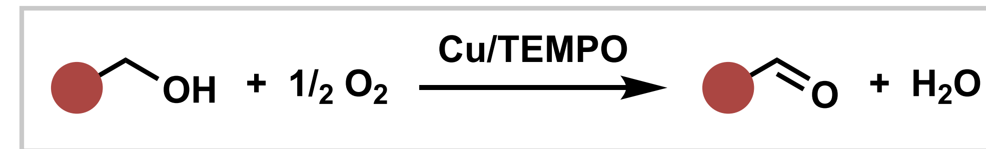
JACS **2013**, *135, 2357*-2367..

Stahl Oxidation



JACS **2013**, *135, 2357-2367*..





(1) $Cu^{I} + O_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Cu^{II}\text{-O-O}^{\bullet}$

(2) $Cu^{II}\text{-O-O}^{\bullet} + Cu^{I} \xrightarrow{k_2} Cu^{II}\text{-}(O_2)\text{-}Cu^{II}$

---

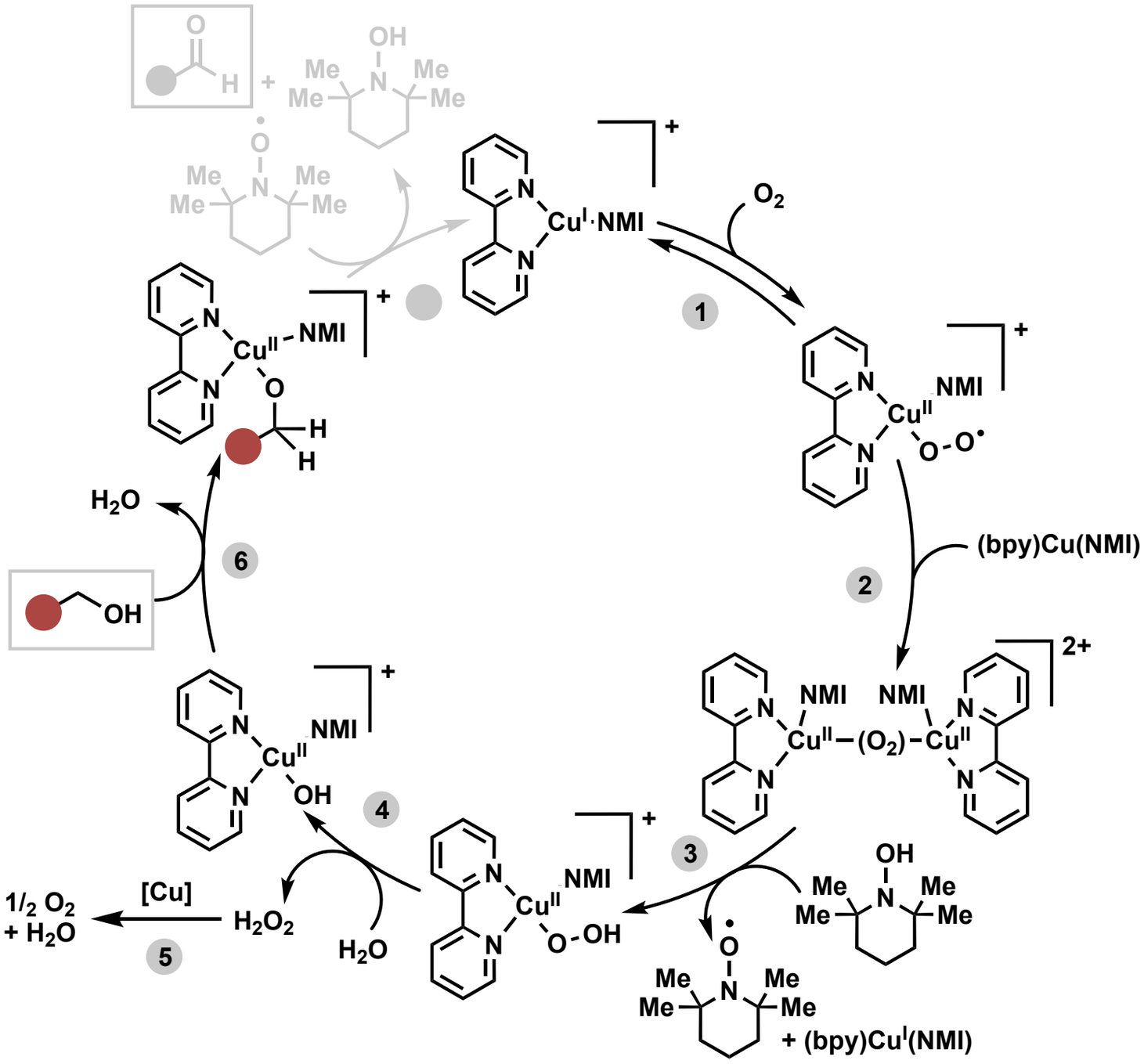
(3) $Cu^{II}\text{-}(O_2)\text{-}Cu^{II} + \text{TEMPOH} \xrightarrow{k_3} Cu^{I} + Cu^{II}\text{-O-OH} + \text{TEMPO}^{\bullet}$

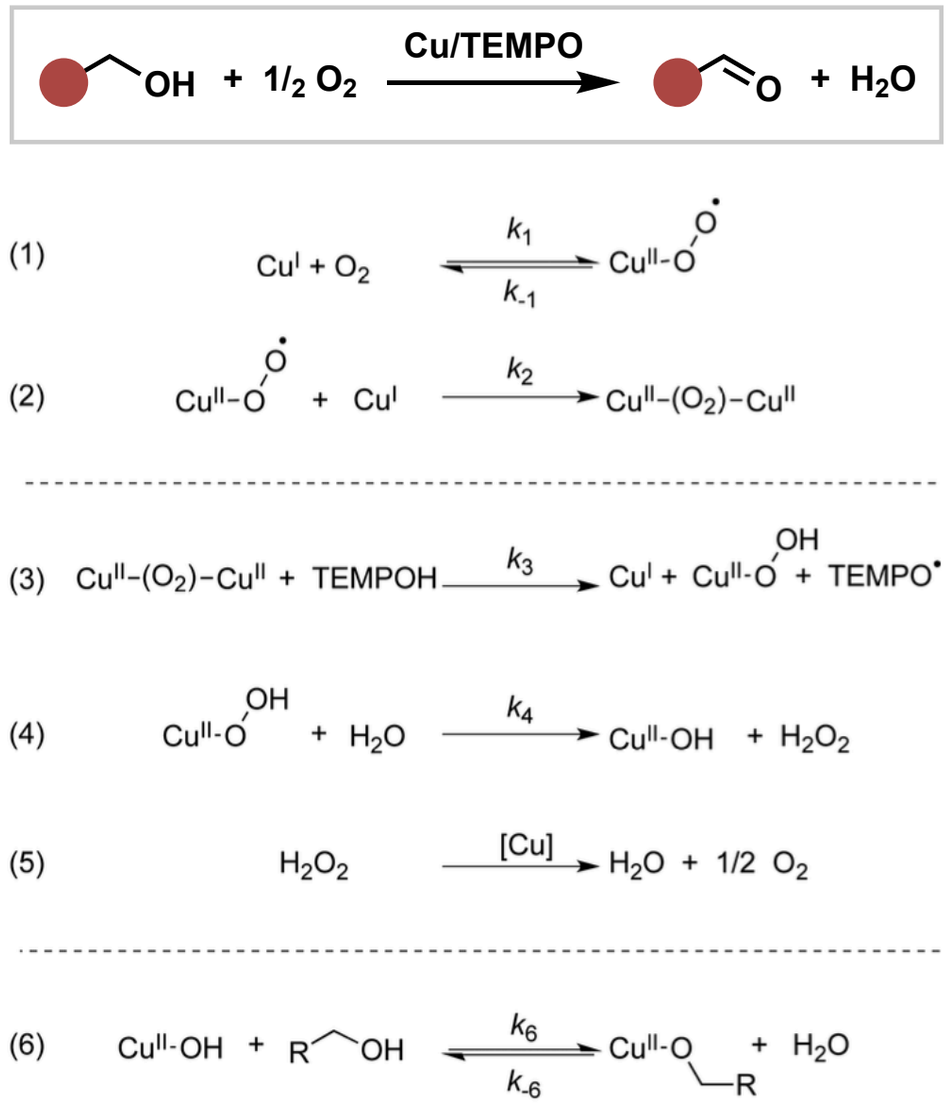
(4) $Cu^{II}\text{-O-OH} + H_2O \xrightarrow{k_4} Cu^{II}\text{-OH} + H_2O_2$

(5) $H_2O_2 \xrightarrow{[Cu]} H_2O + 1/2\ O_2$

JACS **2013**, *135*, 2357-2367..

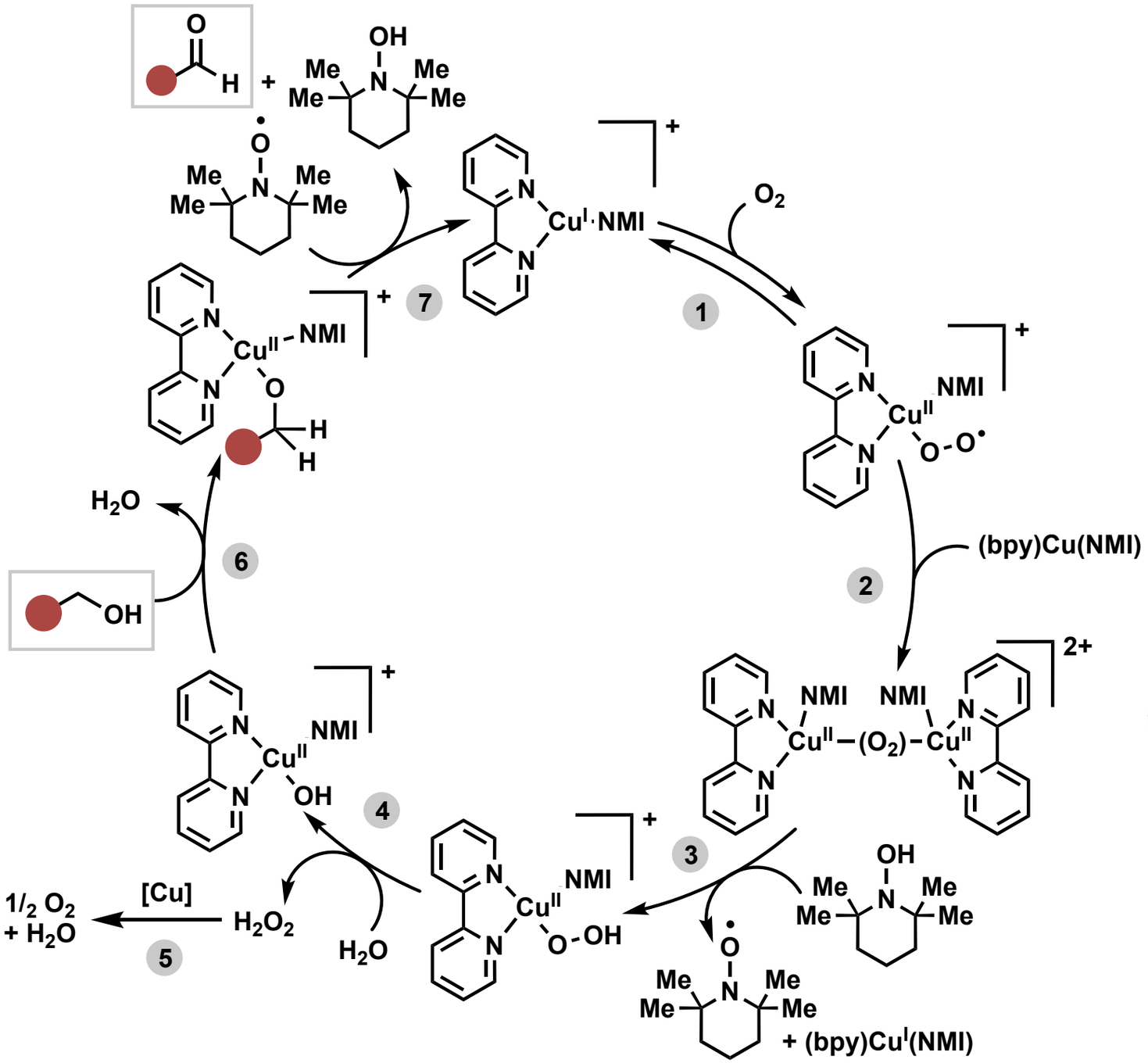
Stahl Oxidation

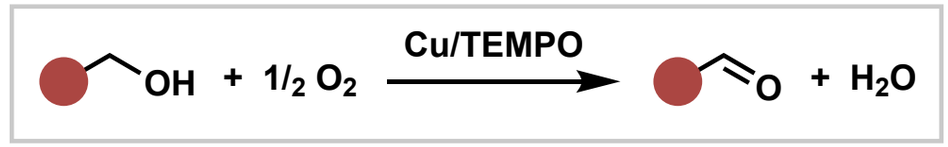




JACS **2013**, *135, 2357-2367*..

Stahl Oxidation





(1) $Cu^{I} + O_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Cu^{II}\text{-}O_2^{\bullet}$

(2) $Cu^{II}\text{-}O_2^{\bullet} + Cu^{I} \xrightarrow{k_2} Cu^{II}\text{-}(O_2)\text{-}Cu^{II}$

---

(3) $Cu^{II}\text{-}(O_2)\text{-}Cu^{II} + TEMPOH \xrightarrow{k_3} Cu^{I} + Cu^{II}\text{-}OOH + TEMPO^{\bullet}$

(4) $Cu^{II}\text{-}OOH + H_2O \xrightarrow{k_4} Cu^{II}\text{-}OH + H_2O_2$

(5) $H_2O_2 \xrightarrow{[Cu]} H_2O + 1/2\ O_2$

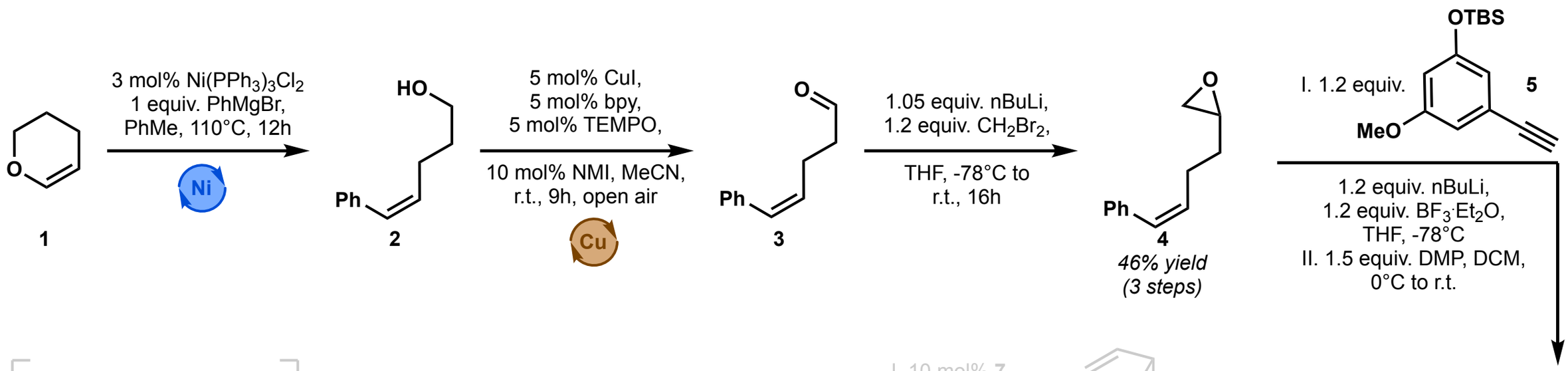
---

(6) $Cu^{II}\text{-}OH + R\text{-}OH \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} Cu^{II}\text{-}O\text{-}R + H_2O$

(7) $Cu^{II}\text{-}O\text{-}R + TEMPO^{\bullet} \xrightarrow{k_7} Cu^{I} + TEMPOH + R\text{=}O$

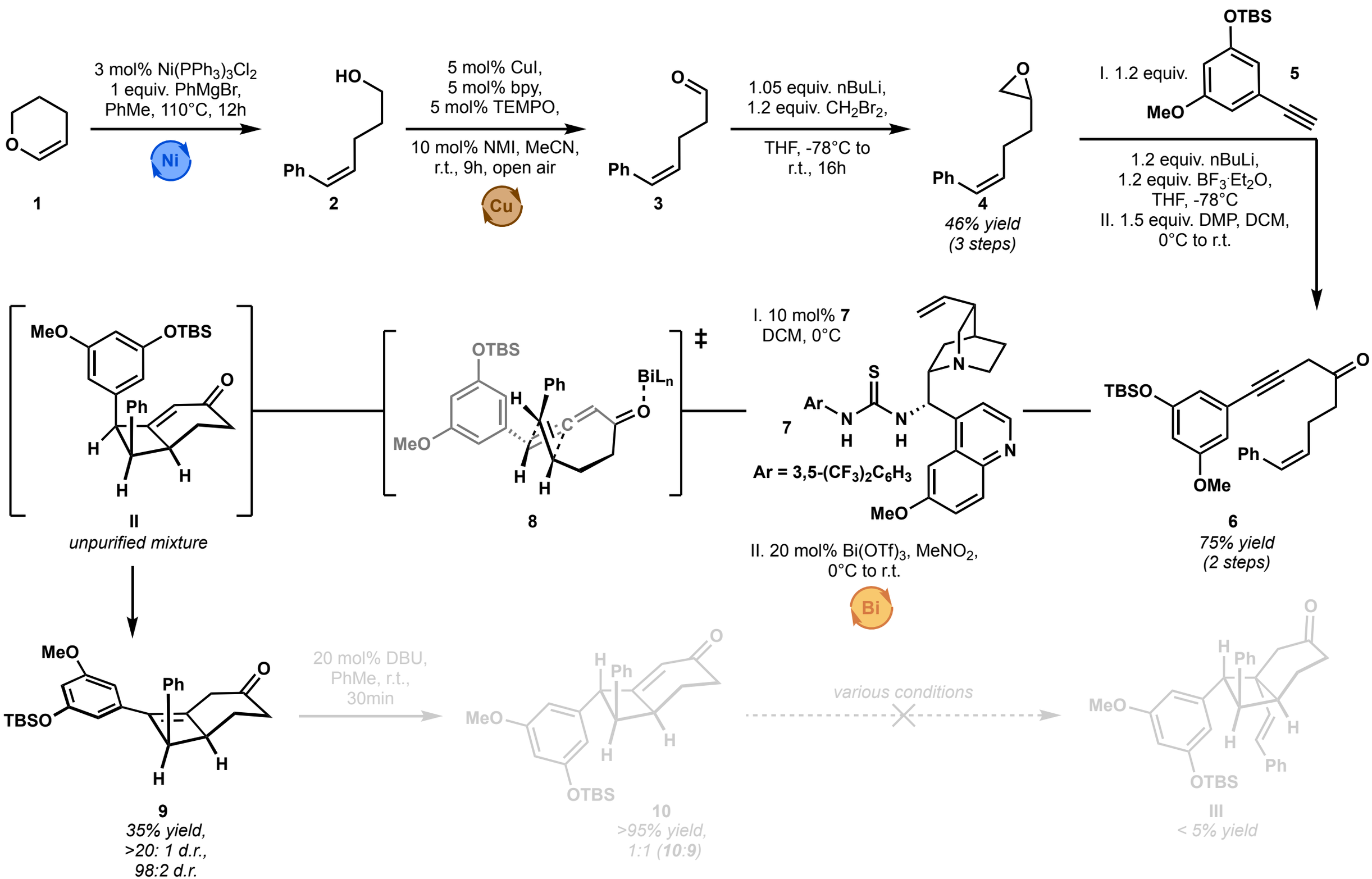
JACS **2013**, *135*, 2357-2367..

(-)-Cajanusine: first-generation approach



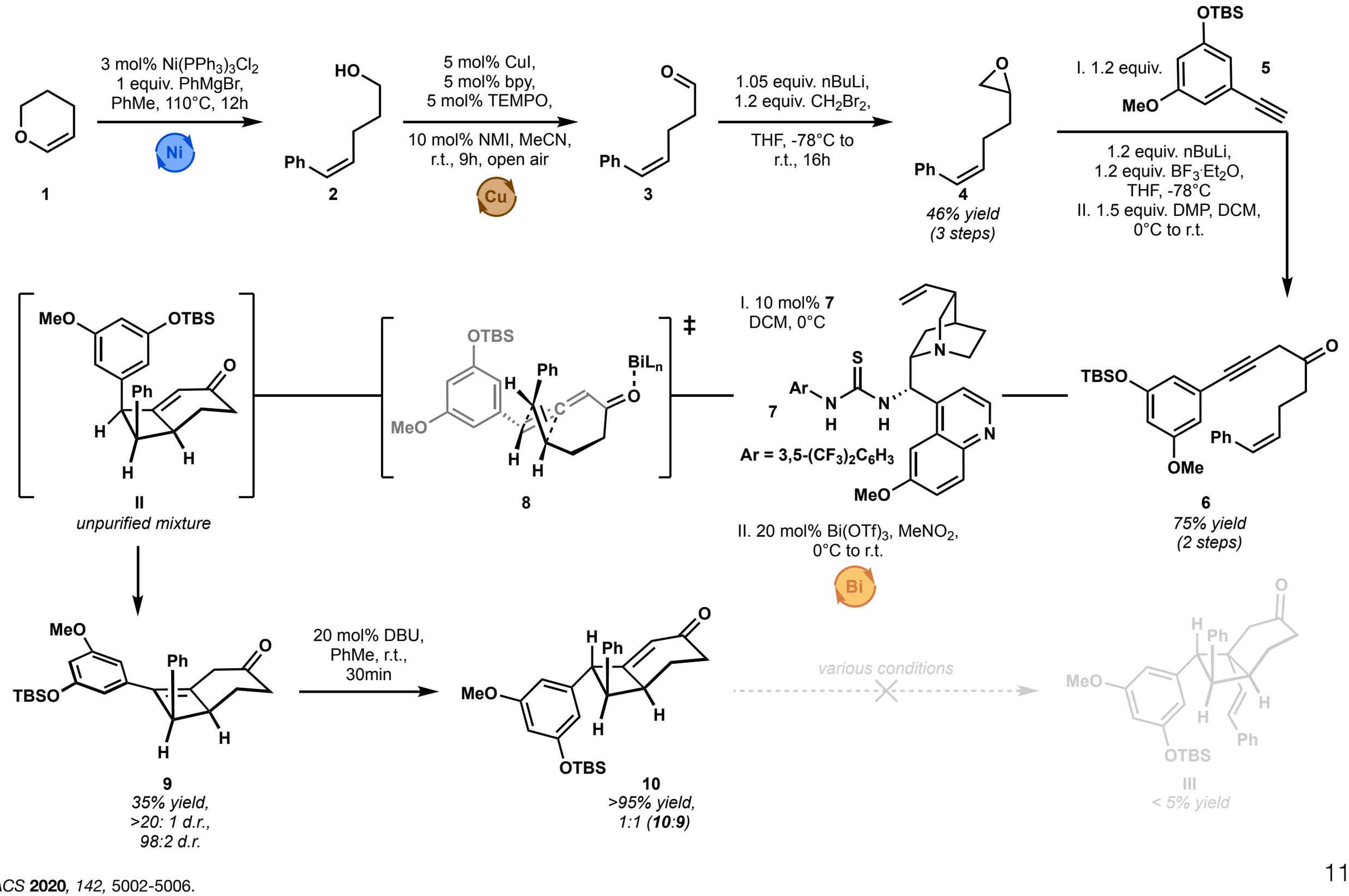
JACS **2020**, *142,* 5002-5006.

(-)-Cajanusine: first-generation approach



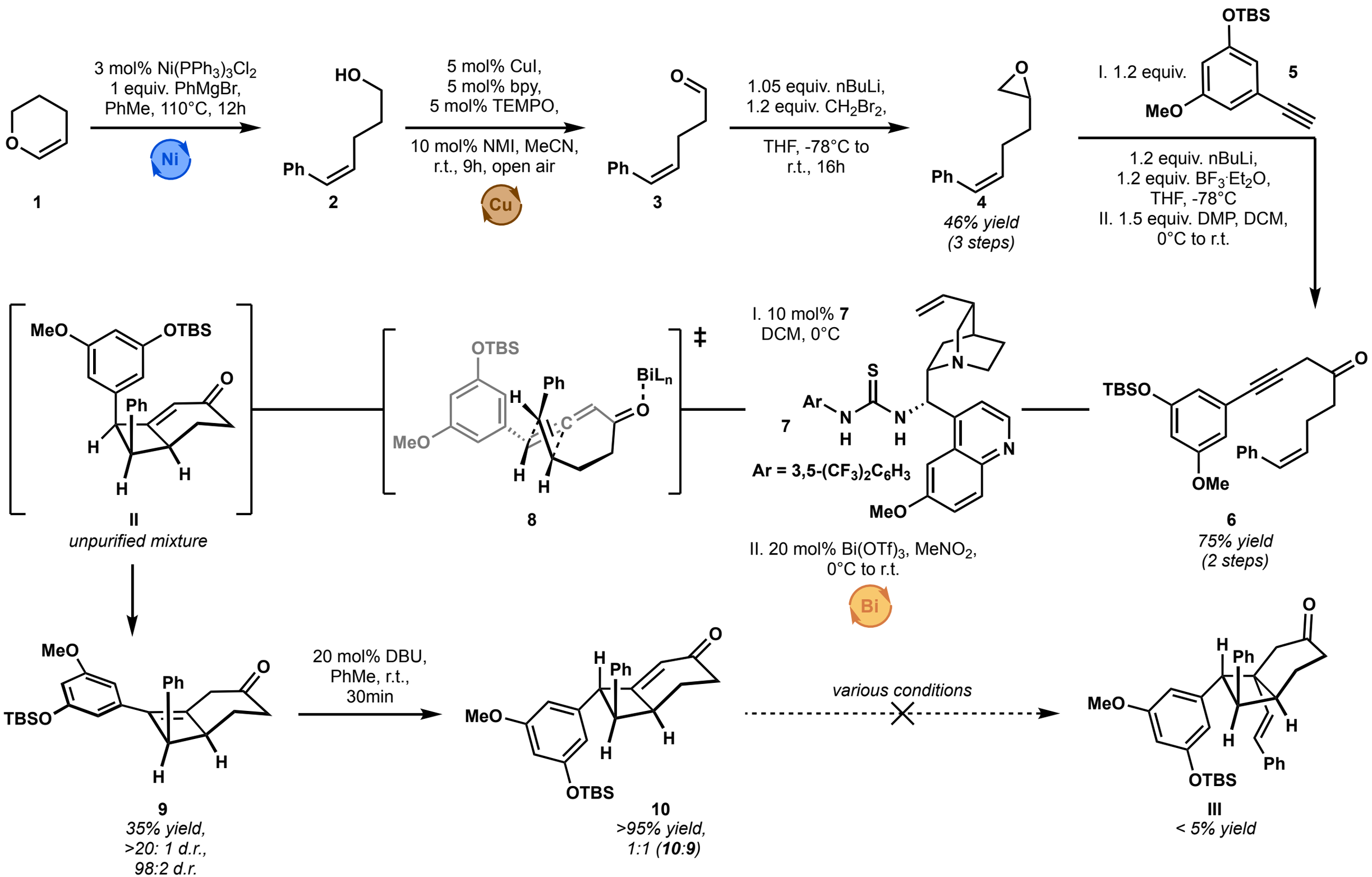
JACS **2020**, *142*, 5002-5006.

(-)-Cajanusine: first-generation approach



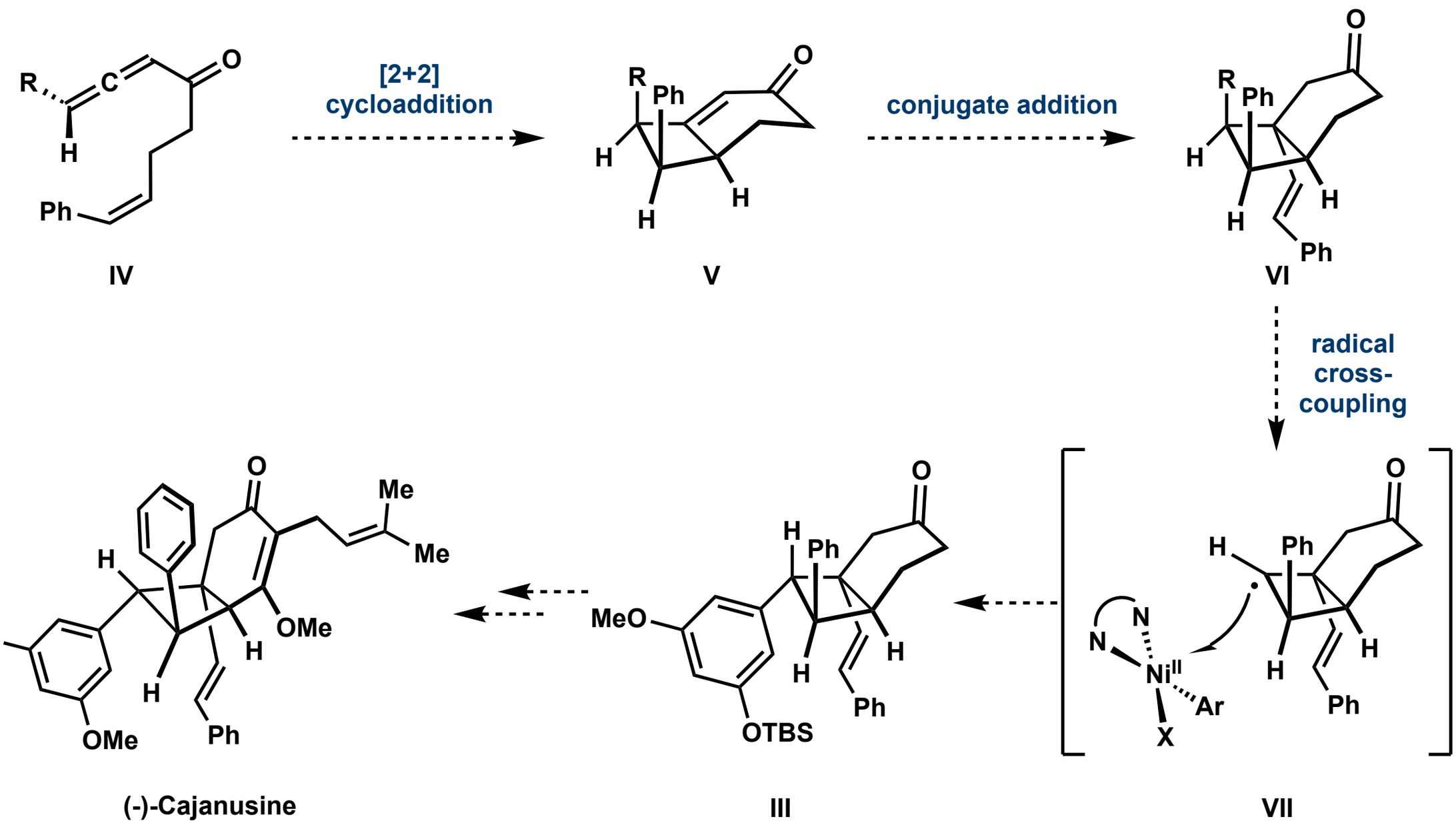
JACS **2020**, *142*, 5002-5006.

(-)-Cajanusine: first-generation approach



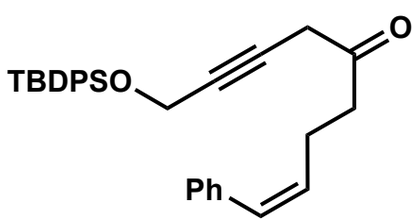
JACS **2020**, *142*, 5002-5006.

(-)-Cajanusine: second-generation approach



JACS **2020**, *142*, 5002-5006.

(-)-Cajanusine: synthesis (G2)

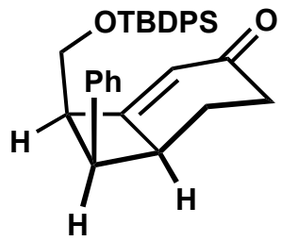


11
34% yield
(5 steps
*from **1**)*

I. 10 mol% **7**, DCM, 0°C

II. 20 mol% $Bi(OTf)_3$, $MeNO_2$, 0°C to r.t.

Bi

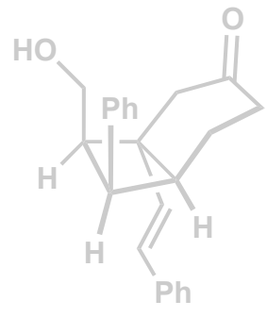


12
65% yield,
>20:1 d.r.,
96:4 e.r.

I. 5 mol% $[Rh(COD)Cl]_2$,

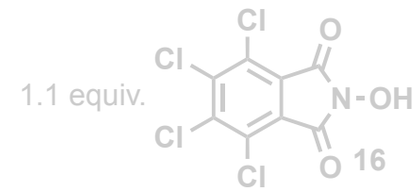
1.2 equiv. Ph⟋⟍$B(OH)_2$ **13**

LiOH, dioxane/H_2O, 60°C
II. 1.2 equiv. TBAF, THF,
0°C to r.t.



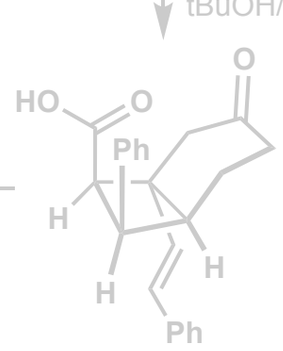
14
73% yield
(2 steps)
>20:1 d.r.

I. 1.25 equiv. DMP,
DCM, 0°C to r.t.
II. 5 equiv. $NaClO_2$,
5 equiv. NaH_2PO_4,
2-methyl-2-butene,
$tBuOH/H_2O$, 0°C to r.t.

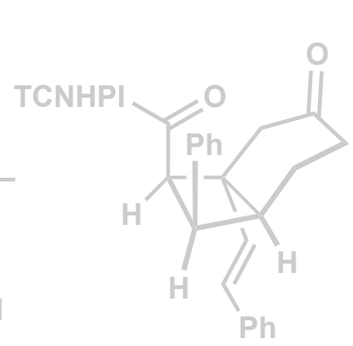


1.2 equiv. DCC,

10 mol% DMAP, DCM,
0°C to r.t., 12h



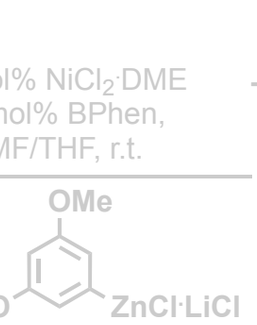
15

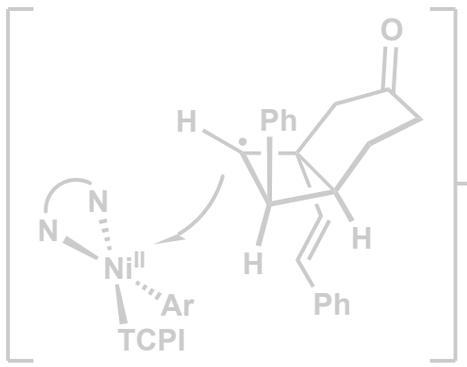


17
72% yield
(3 steps)

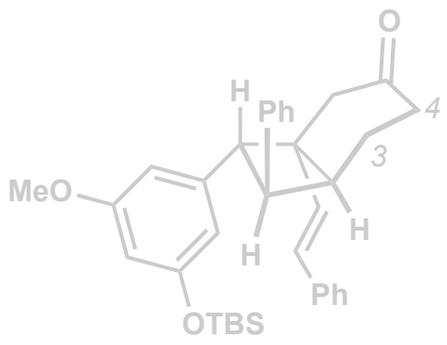
40 mol% $NiCl_2$·DME
80 mol% BPhen,
DMF/THF, r.t.

3.0 equiv.





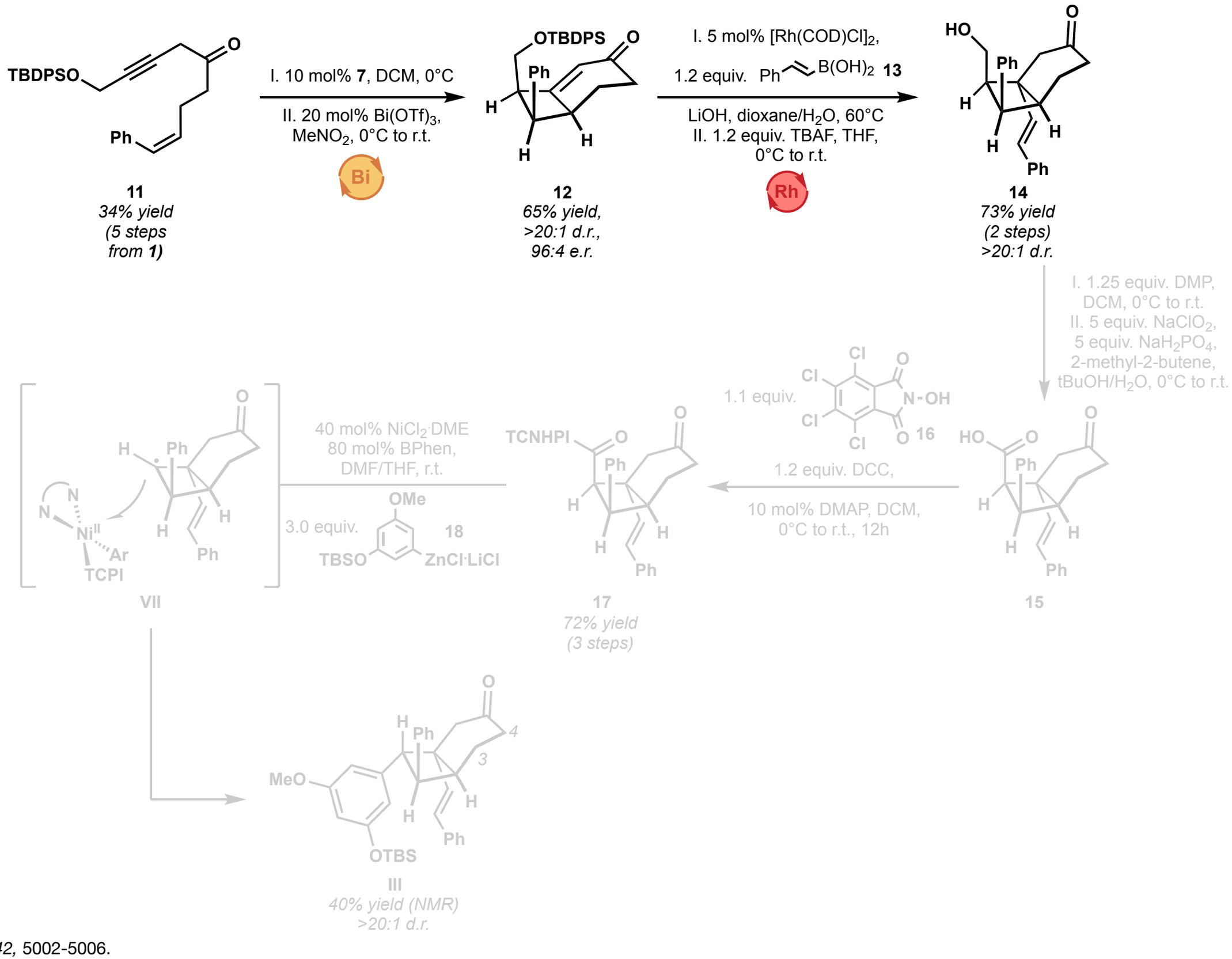
VII



III
40% yield (NMR)
>20:1 d.r.

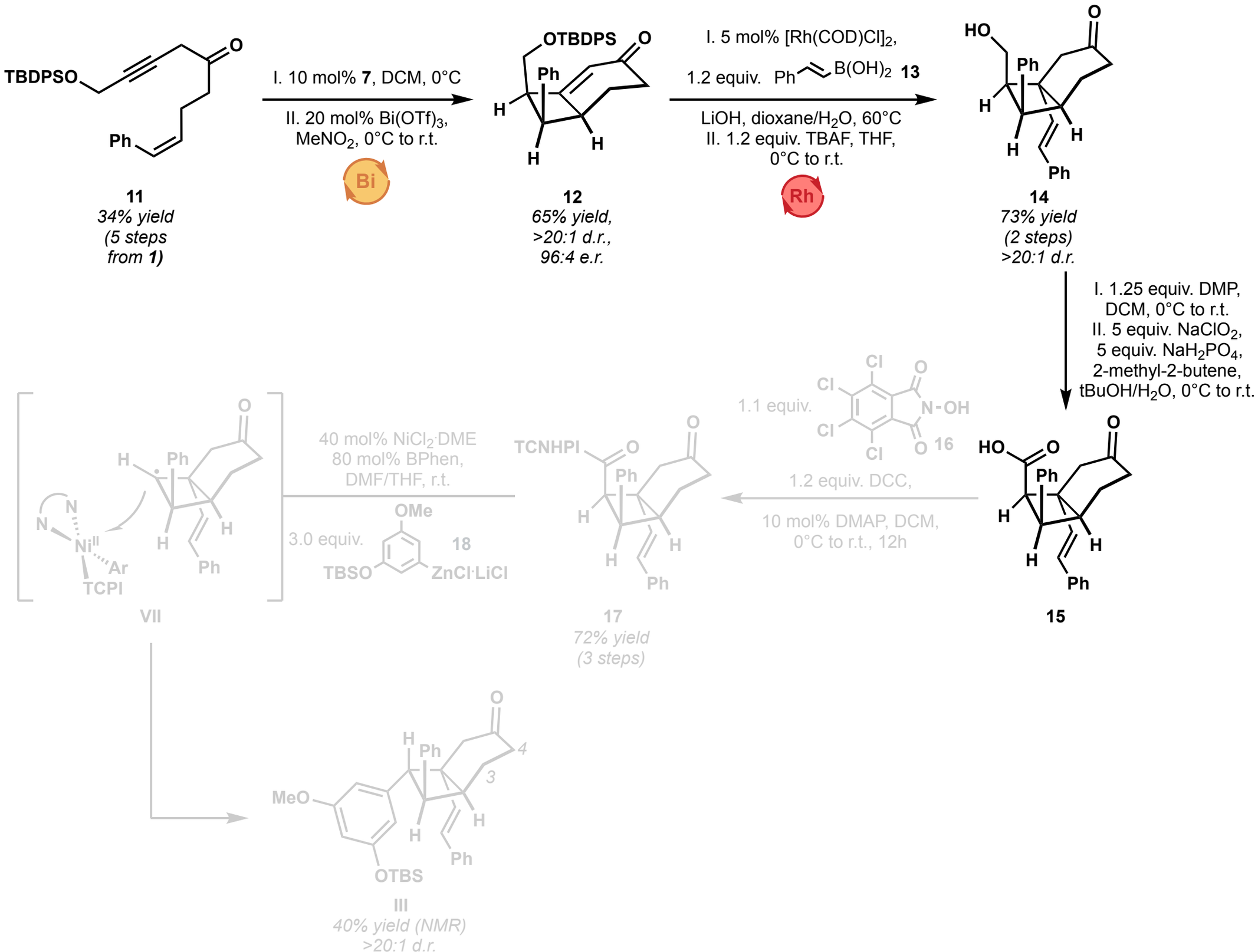
JACS **2020**, *142,* 5002-5006.

(-)-Cajanusine: synthesis (G2)



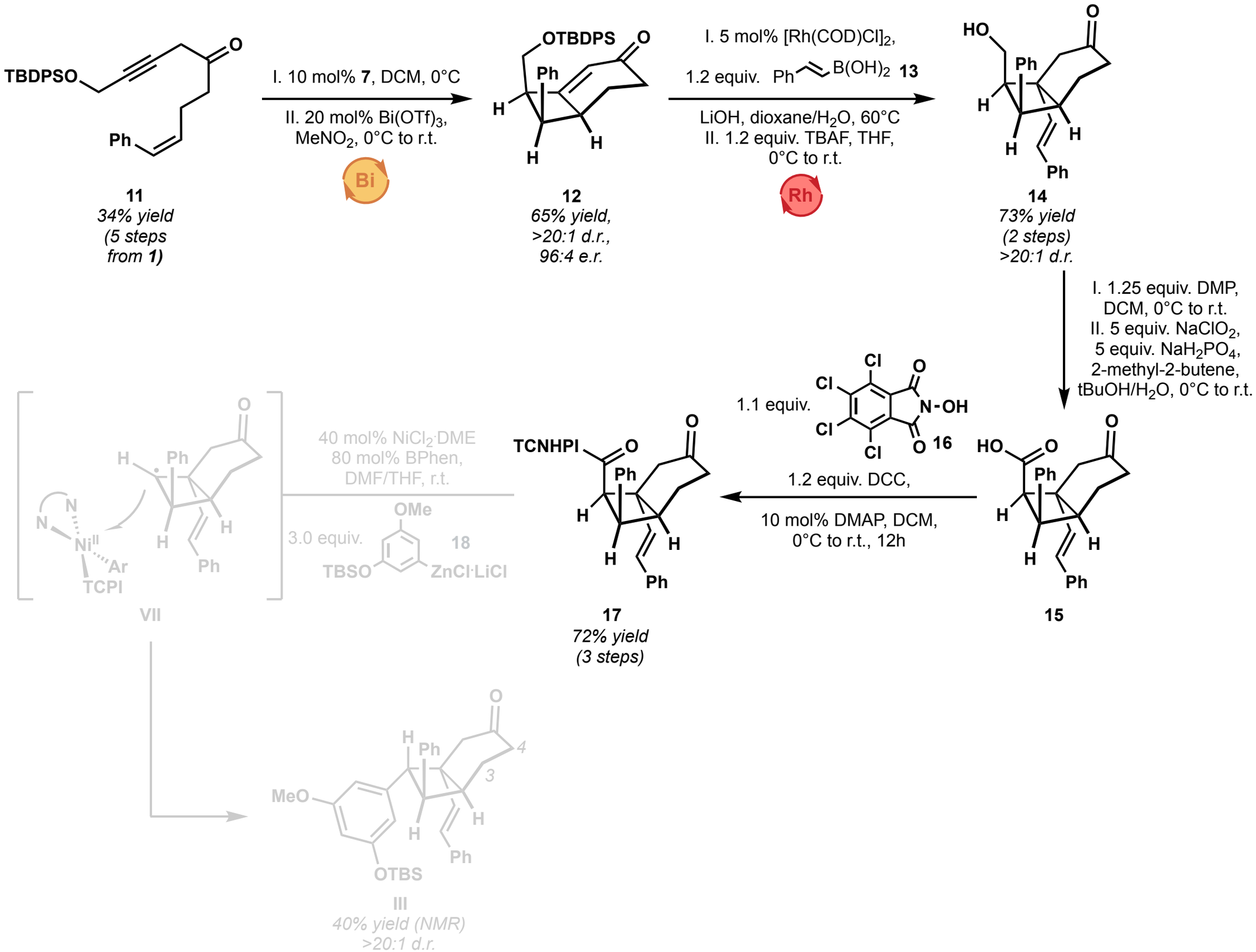
JACS **2020**, *142,* 5002-5006.

(-)-Cajanusine: synthesis (G2)



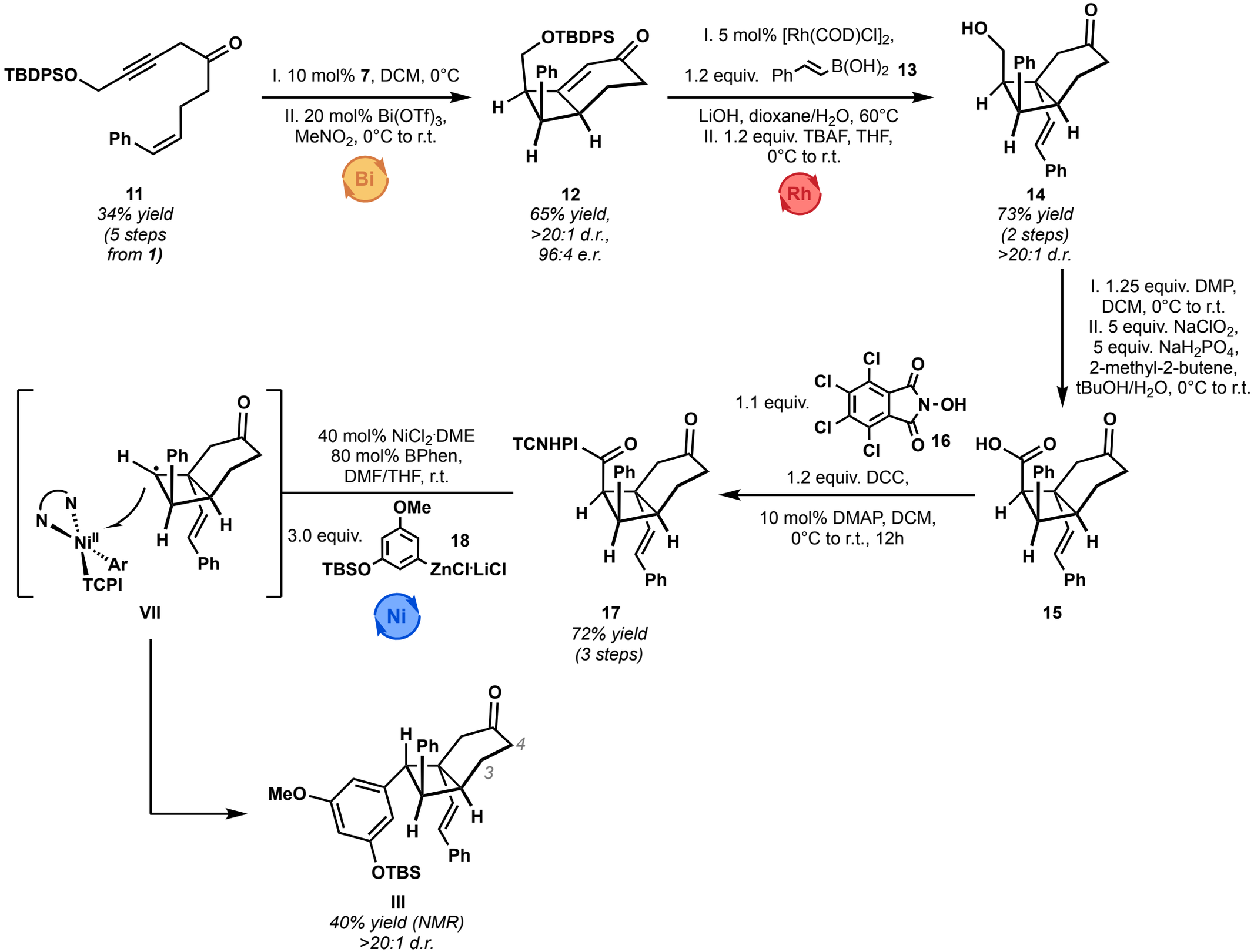
JACS **2020**, *142,* 5002-5006.

(-)-Cajanusine: synthesis (G2)



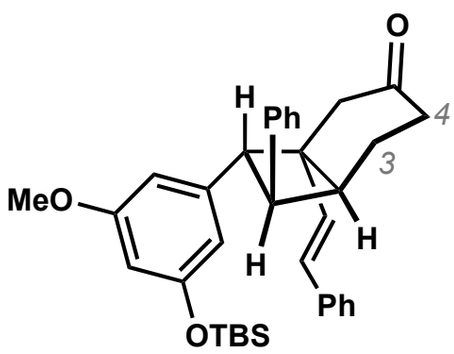
JACS **2020**, *142,* 5002-5006.

(-)-Cajanusine: synthesis (G2)



JACS **2020**, *142,* 5002-5006.

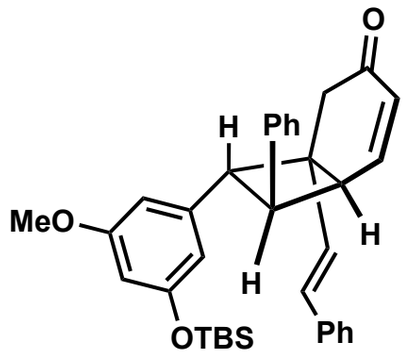
(-)-Cajanusine: synthesis (G2)



III
40% yield (NMR)
>20:1 d.r.

I. 2.0 equiv. *N*-MePMP, 1.5 equiv. Me_3SiOTf, DCM, -78°C, 3h

II. 3.0 equiv. IBX·MPO, DMSO, r.t., 12h

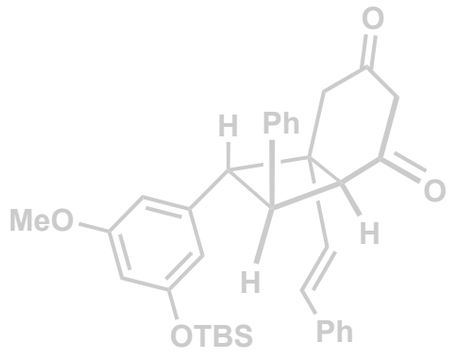


19
80% yield
(2 steps)

I. 3 mol% CuCl, 3 mol% DPEPhos, 10 mol% tBuONa, 1.5 equiv. B_2pin_2, MeOH, THF, 3h

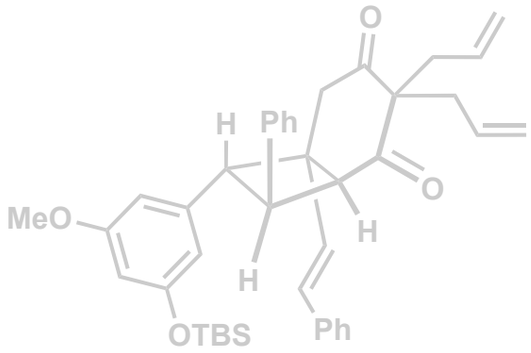
then 5.0 equiv. $NaBO_3 \cdot 4H_2O$, H_2O, r.t., 3h

II. 3.0 equiv. CrO_3, H_2SO_4, acetone, -20°C



20
61% yield
(2 steps)

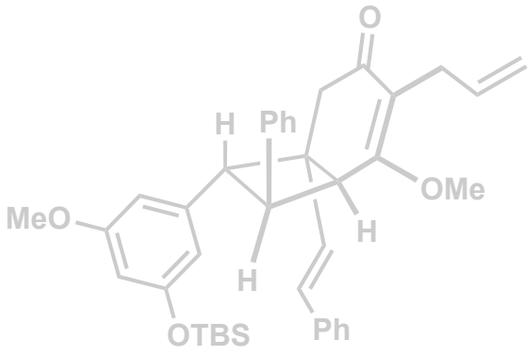
2.5 mol%. $[Pd(allyl)Cl_2]$, 10 mol% dppe, 3.0 equiv. allylacetate, 5.0 equiv. K_2CO_3, THF, 50°C



21
98% yield

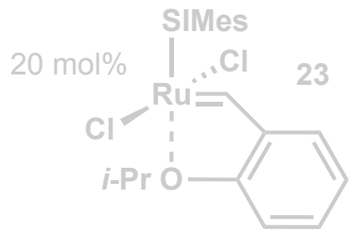
5 mol% $Ni(PPh_3)_2Br_2$, 2.0 equiv. Et_3Al, toluene, r.t.

then 1.5 equiv. $TMSCHN_2$, MeOH, r.t.



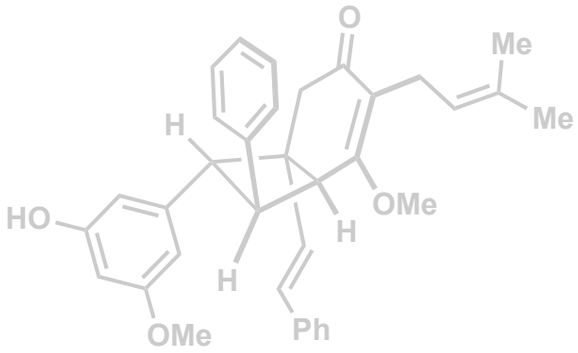
22
73% yield

20 mol%



23

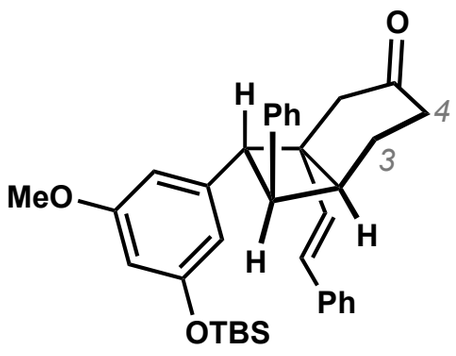
isobutene, 50°C, 48h
then 2.0 equiv. TBAF, THF, 0°C, 30min



(-)-Cajanusine
82% yield

JACS **2020**, *142,* 5002-5006.

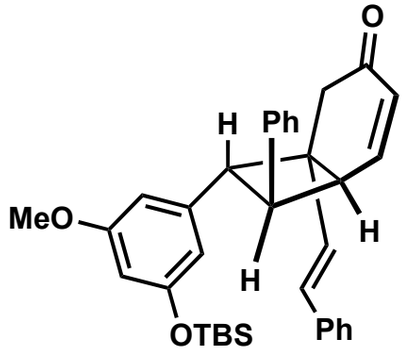
(-)-Cajanusine: synthesis (G2)



III
40% yield (NMR)
>20:1 d.r.

I. 2.0 equiv. *N*-MePMP, 1.5 equiv. Me_3SiOTf, DCM, -78°C, 3h

II. 3.0 equiv. IBX·MPO, DMSO, r.t., 12h



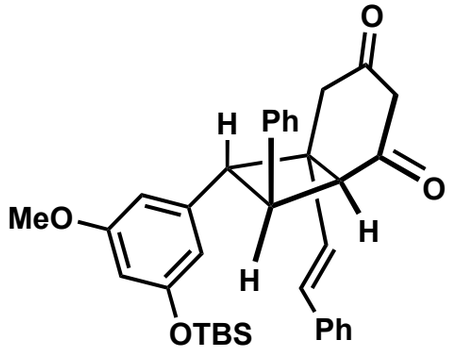
19
80% yield
(2 steps)

I. 3 mol% CuCl,
3 mol% DPEPhos,
10 mol% tBuONa,
1.5 equiv. B_2pin_2, MeOH, THF, 3h

then 5.0 equiv. $NaBO_3{\cdot}4H_2O$, H_2O, r.t., 3h

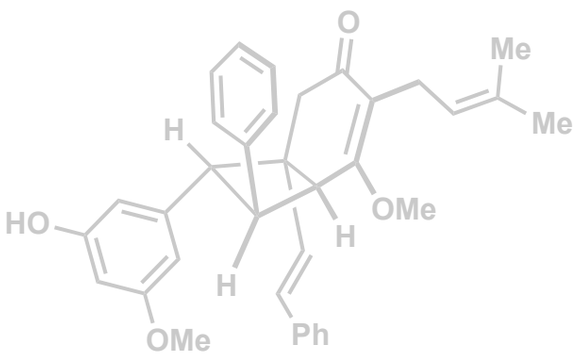
II. 3.0 equiv. CrO_3, H_2SO_4, acetone, -20°C

Cu



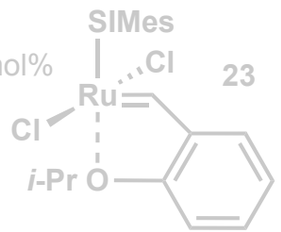
20
61% yield
(2 steps)

2.5 mol%. $[Pd(allyl)Cl_2]$,
10 mol% dppe,
3.0 equiv. allylacetate,
5.0 equiv. K_2CO_3, THF,
50°C



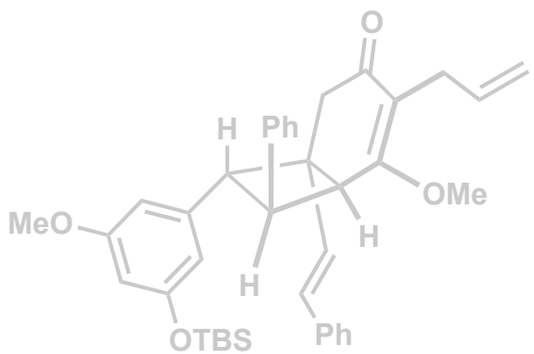
(-)-Cajanusine
82% yield

20 mol%



23

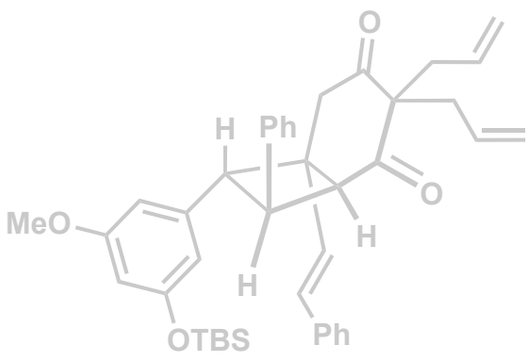
isobutene, 50°C, 48h
then 2.0 equiv. TBAF,
THF, 0°C, 30min



22
73% yield

5 mol% $Ni(PPh_3)_2Br_2$,
2.0 equiv. Et_3Al,
toluene, r.t.

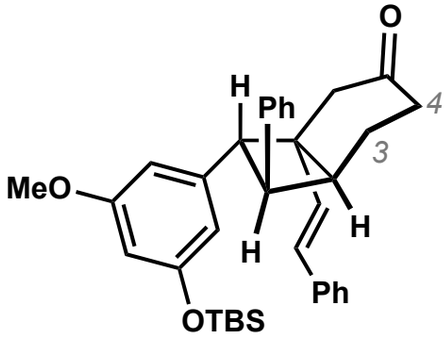
then
1.5 equiv. $TMSCHN_2$,
MeOH, r.t.



21
98% yield

JACS **2020**, *142,* 5002-5006.

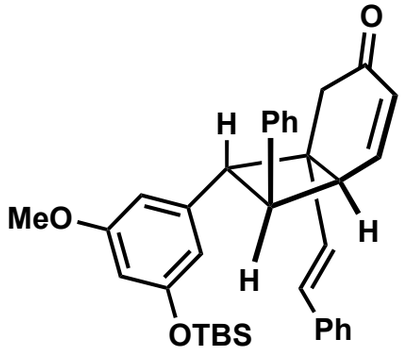
(-)-Cajanusine: synthesis (G2)



III
40% yield (NMR)
>20:1 d.r.

I. 2.0 equiv. *N*-MePMP, 1.5 equiv. Me_3SiOTf, DCM, -78°C, 3h

II. 3.0 equiv. IBX·MPO, DMSO, r.t., 12h



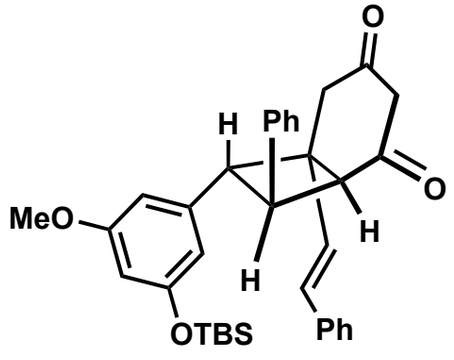
19
80% yield
(2 steps)

I. 3 mol% CuCl, 3 mol% DPEPhos, 10 mol% tBuONa, 1.5 equiv. B_2pin_2, MeOH, THF, 3h

then 5.0 equiv. $NaBO_3{\cdot}4H_2O$, H_2O, r.t., 3h

II. 3.0 equiv. CrO_3, H_2SO_4, acetone, -20°C

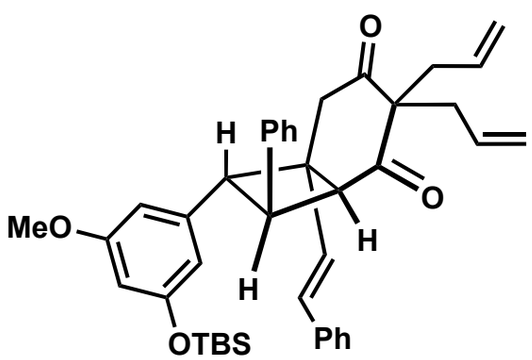
Cu



20
61% yield
(2 steps)

Pd

2.5 mol%. $[Pd(allyl)Cl_2]$, 10 mol% dppe, 3.0 equiv. allylacetate, 5.0 equiv. K_2CO_3, THF, 50°C

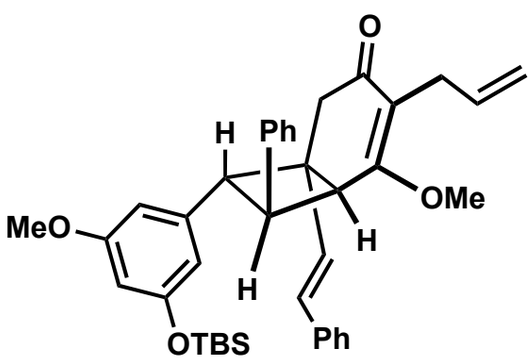


21
98% yield

5 mol% $Ni(PPh_3)_2Br_2$, 2.0 equiv. Et_3Al, toluene, r.t.

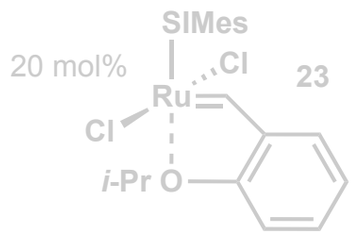
then 1.5 equiv. $TMSCHN_2$, MeOH, r.t.

Ni

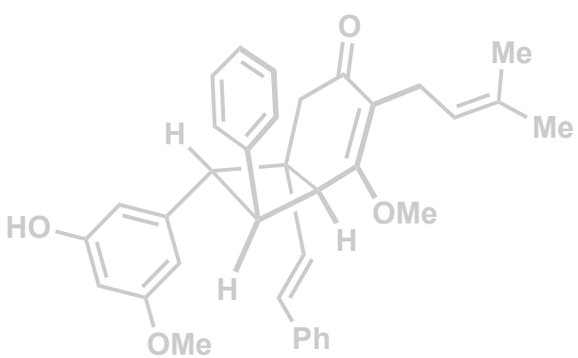


22
73% yield

20 mol%



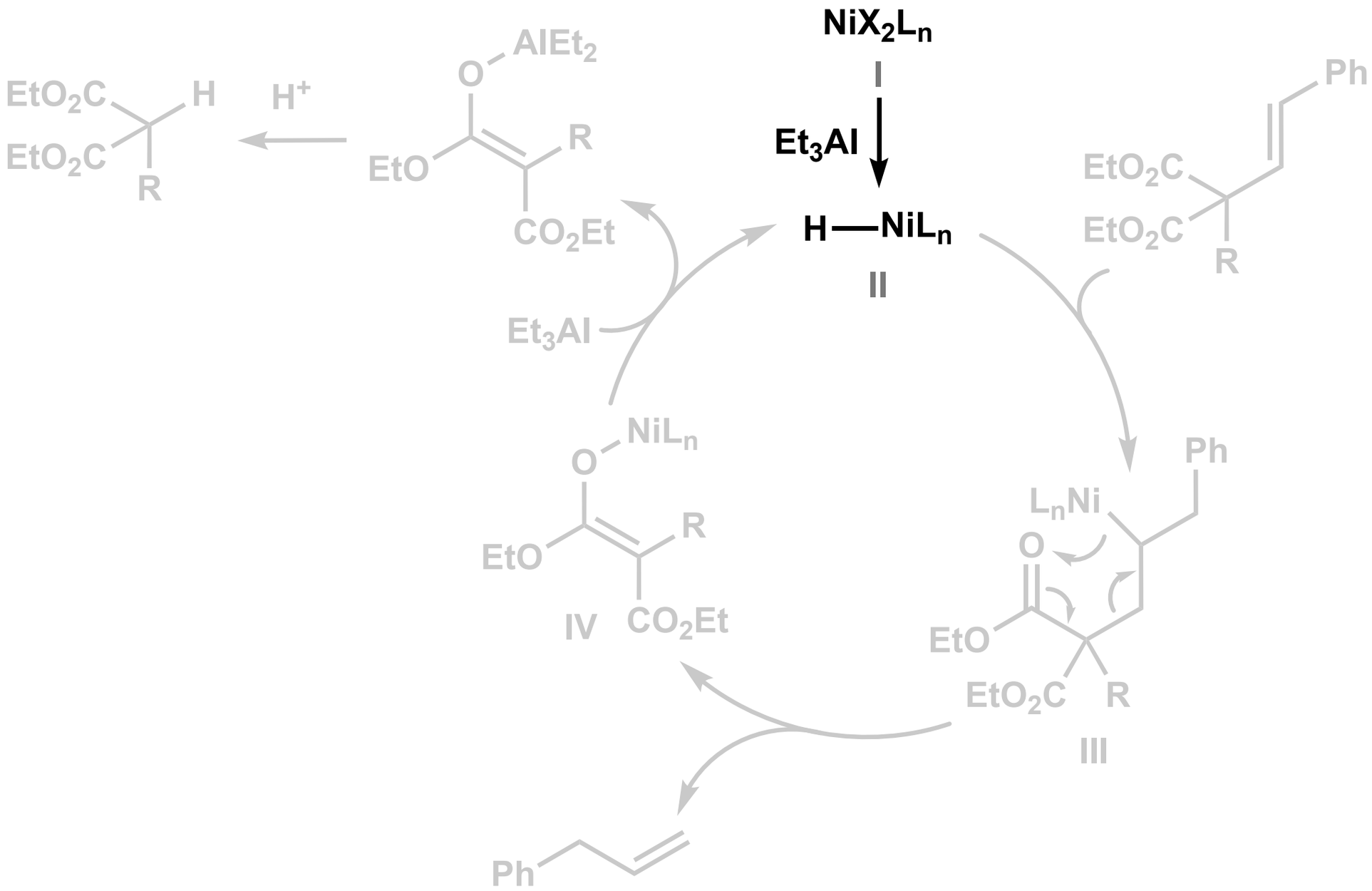
isobutene, 50°C, 48h
then 2.0 equiv. TBAF, THF, 0°C, 30min



(-)-Cajanusine
82% yield

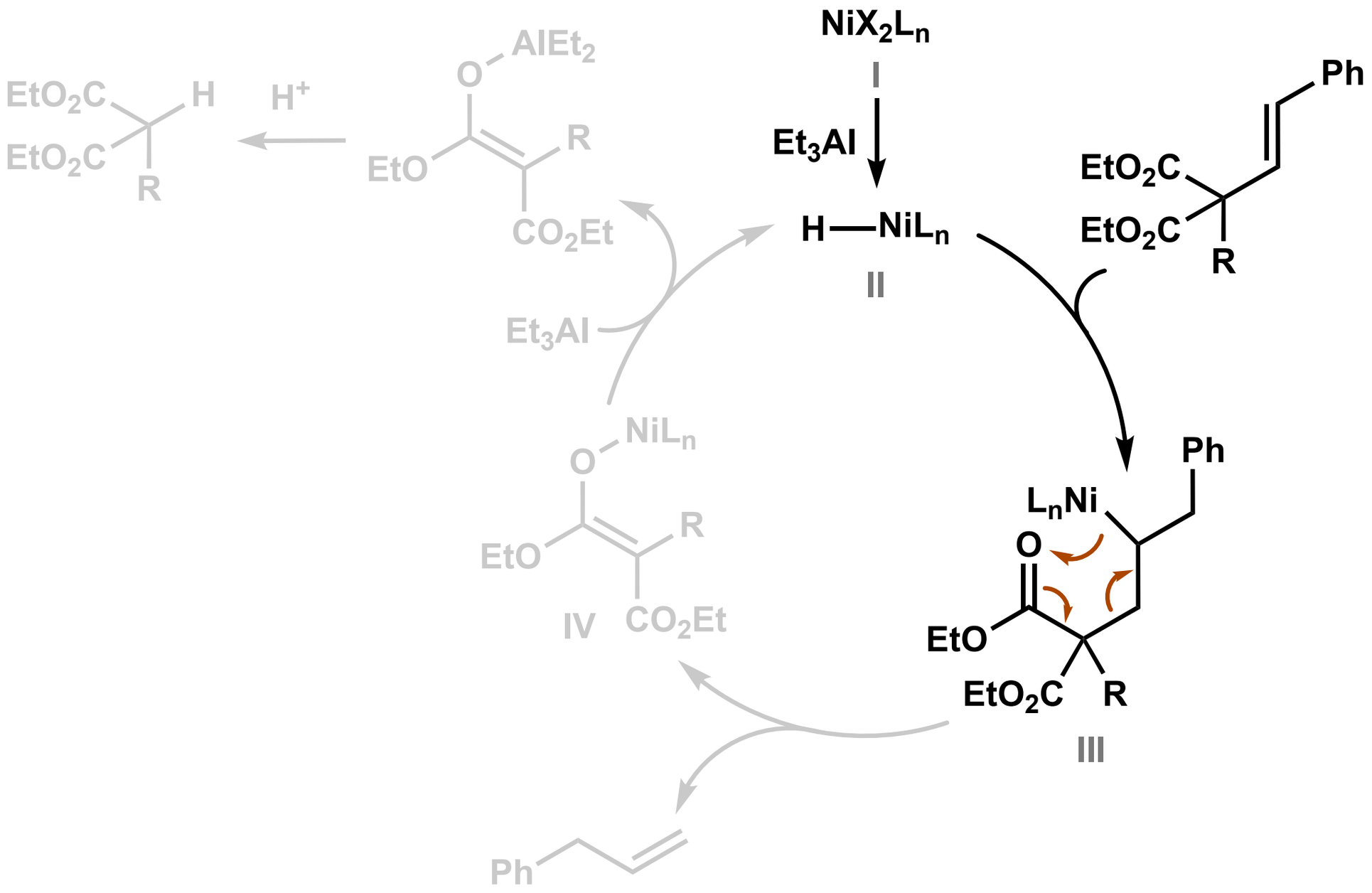
JACS **2020**, *142,* 5002-5006.

Ni-Catalyzed Deallylation



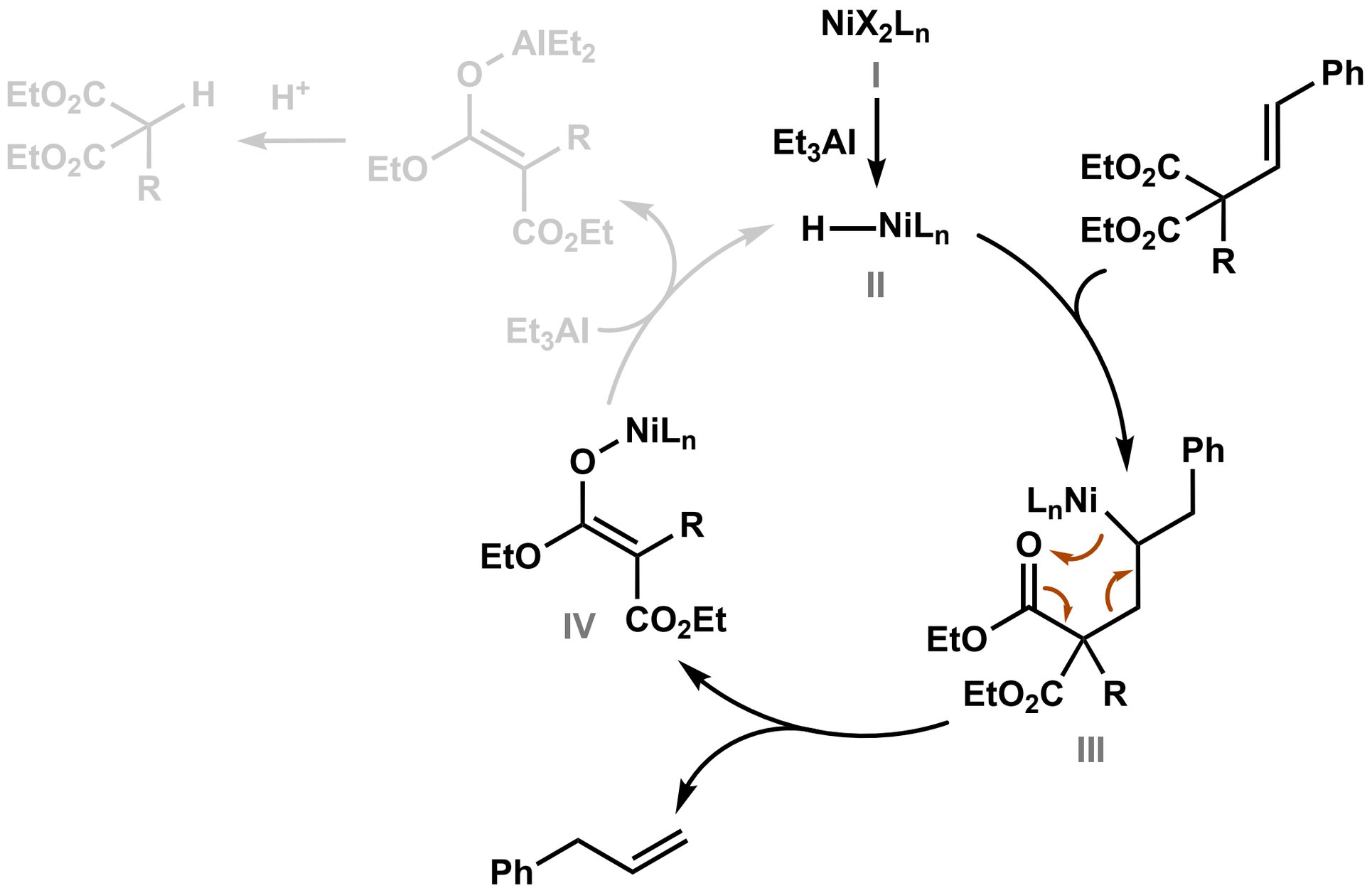
JACS **2004**, *126*, 10222-10223.

Ni-Catalyzed Deallylation



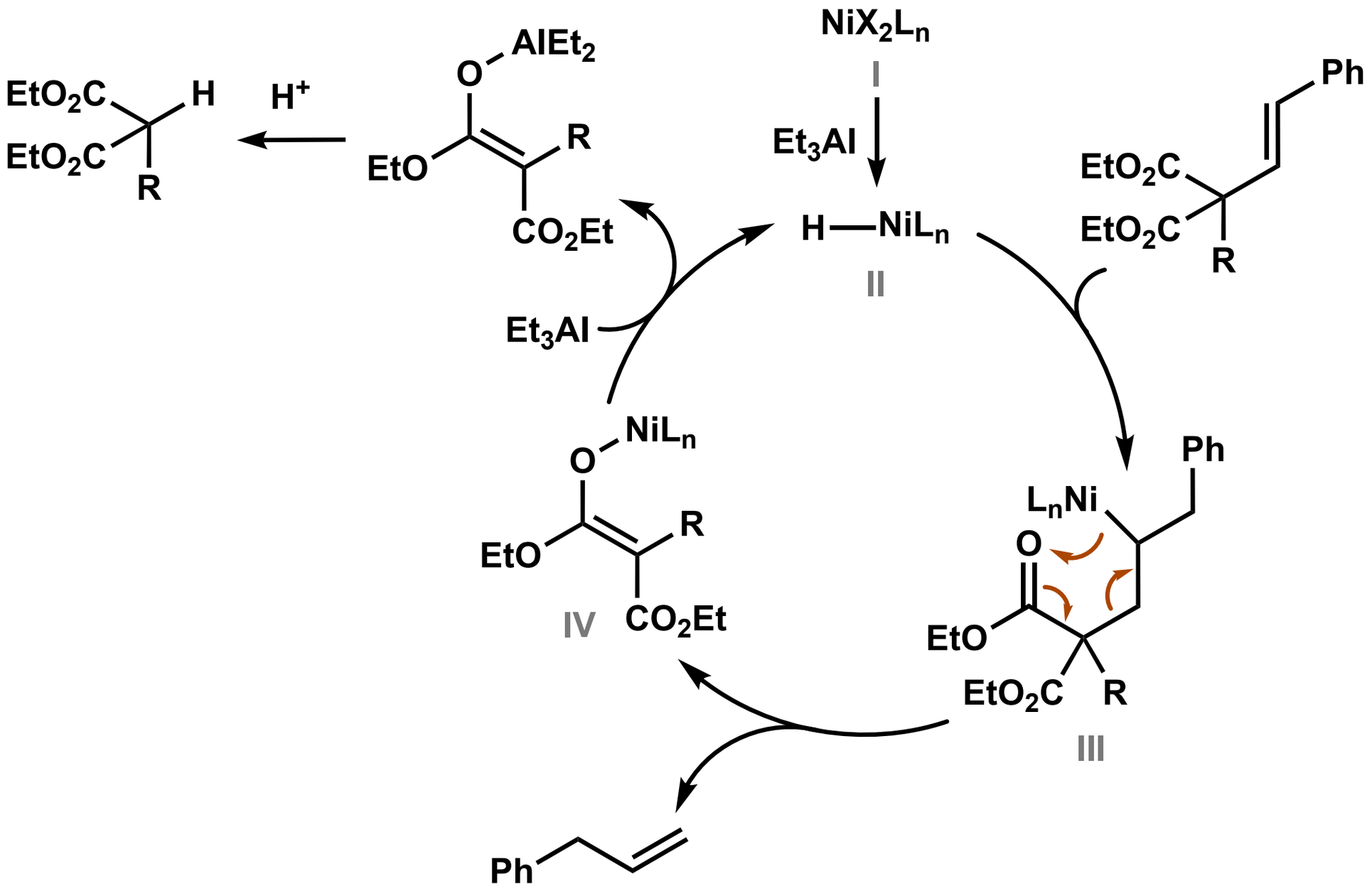
JACS **2004**, *126*, 10222-10223.

Ni-Catalyzed Deallylation



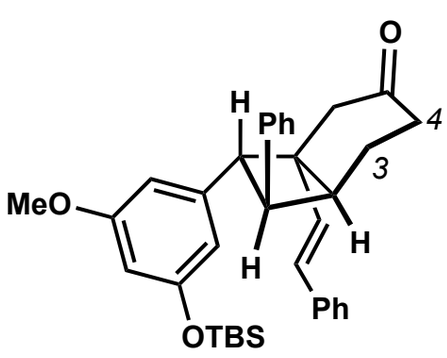
JACS **2004**, *126*, 10222-10223.

Ni-Catalyzed Deallylation



JACS **2004**, *126*, 10222-10223.

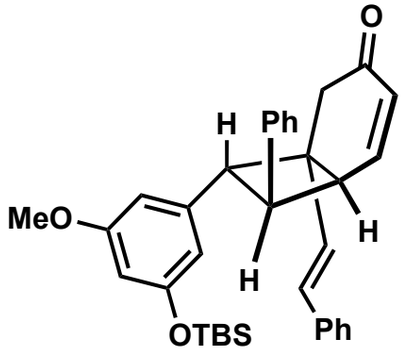
(-)-Cajanusine: synthesis (G2)



III
40% yield (NMR)
>20:1 d.r.

I. 2.0 equiv. *N*-MePMP, 1.5 equiv. Me_3SiOTf, DCM, -78°C, 3h

II. 3.0 equiv. IBX·MPO, DMSO, r.t., 12h



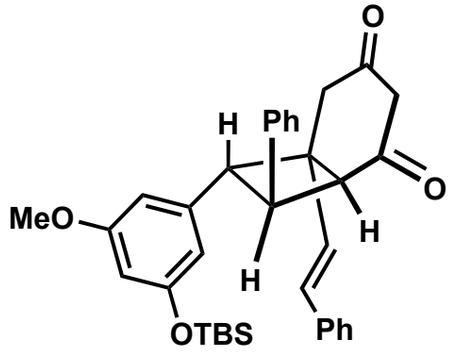
19
80% yield
(2 steps)

I. 3 mol% CuCl,
3 mol% DPEPhos,
10 mol% tBuONa,
1.5 equiv. B_2pin_2, MeOH, THF, 3h

then 5.0 equiv. $NaBO_3{\cdot}4H_2O$, H_2O, r.t., 3h

II. 3.0 equiv. CrO_3, H_2SO_4, acetone, -20°C

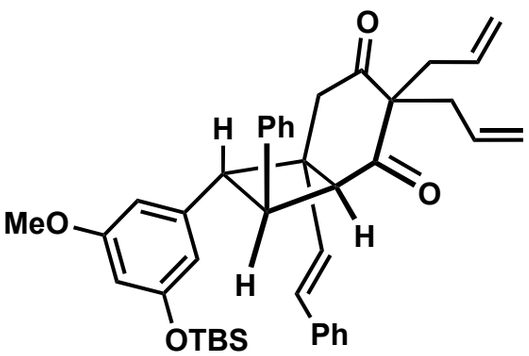
Cu



20
61% yield
(2 steps)

Pd

2.5 mol%. $[Pd(allyl)Cl_2]$,
10 mol% dppe,
3.0 equiv. allylacetate,
5.0 equiv. K_2CO_3, THF,
50°C

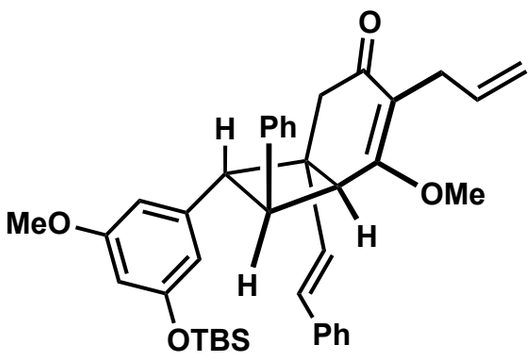


21
98% yield

5 mol% $Ni(PPh_3)_2Br_2$,
2.0 equiv. Et_3Al,
toluene, r.t.

then
1.5 equiv. $TMSCHN_2$,
MeOH, r.t.

Ni

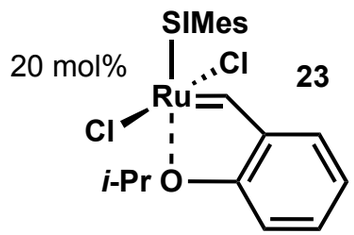


22
73% yield

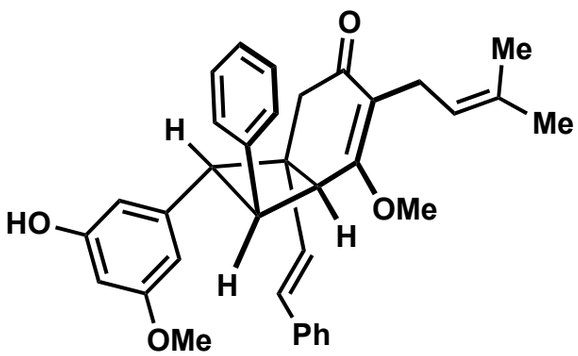
isobutene, 50°C, 48h
then 2.0 equiv. TBAF,
THF, 0°C, 30min

Ru

20 mol%



23

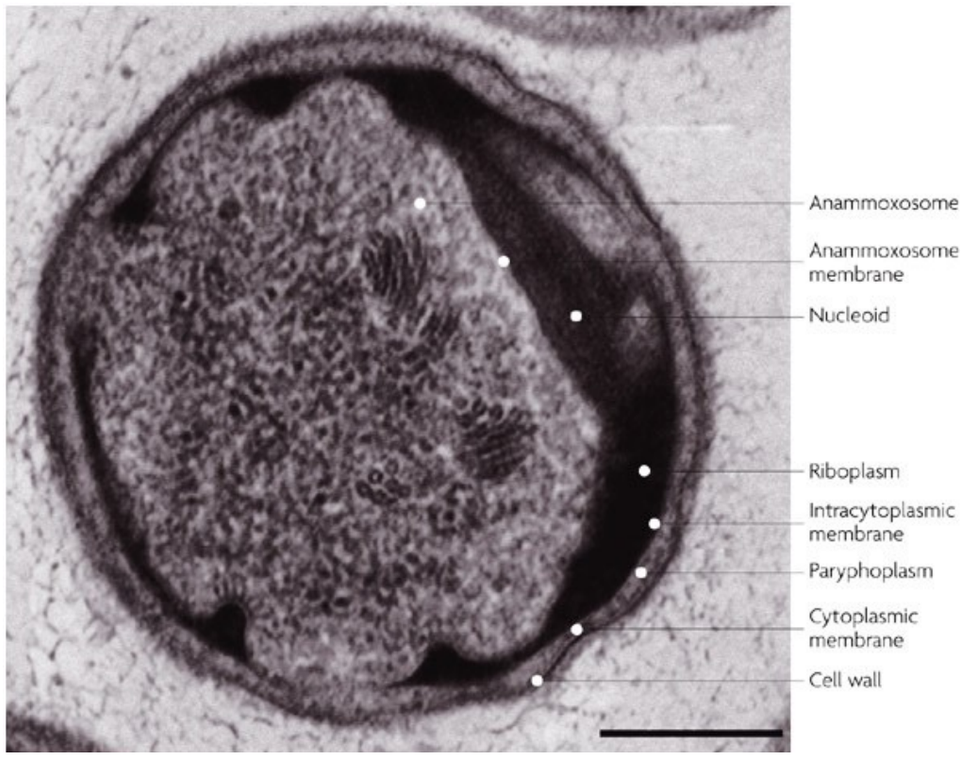


(-)-Cajanusine
82% yield

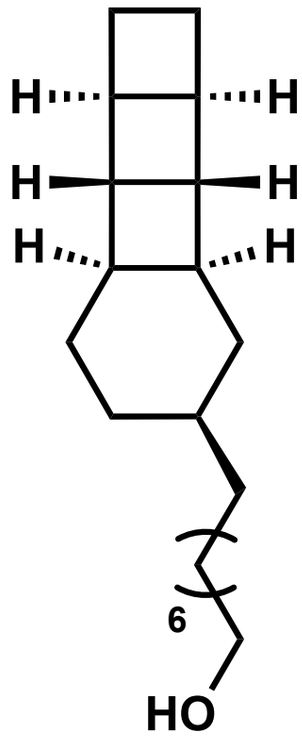
- First enantioselective synthesis of (-)-Cajanusine
- More than 100mg of natural product prepared

JACS **2020**, *142,* 5002-5006.

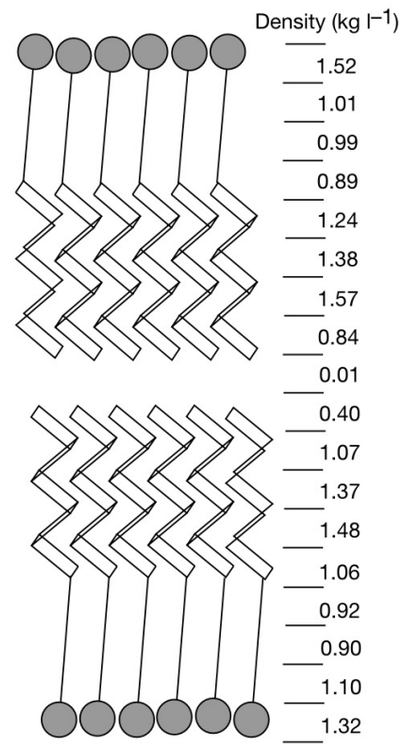
ent-(3)-Ladderanol



Anammox bacteria
Nature Reviews Microbiology **2008**, *6*, 320-326



ent-[3]-Ladderanol

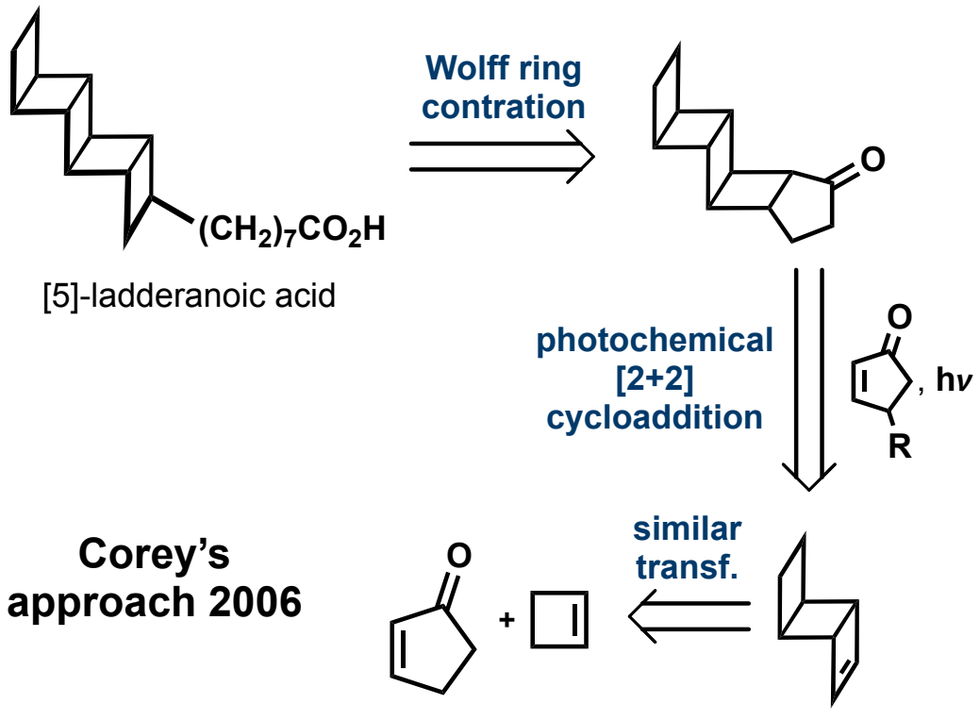


Conceptual stacking model of ladderane membrane lipids
Nature **2002**, *419*, 708.

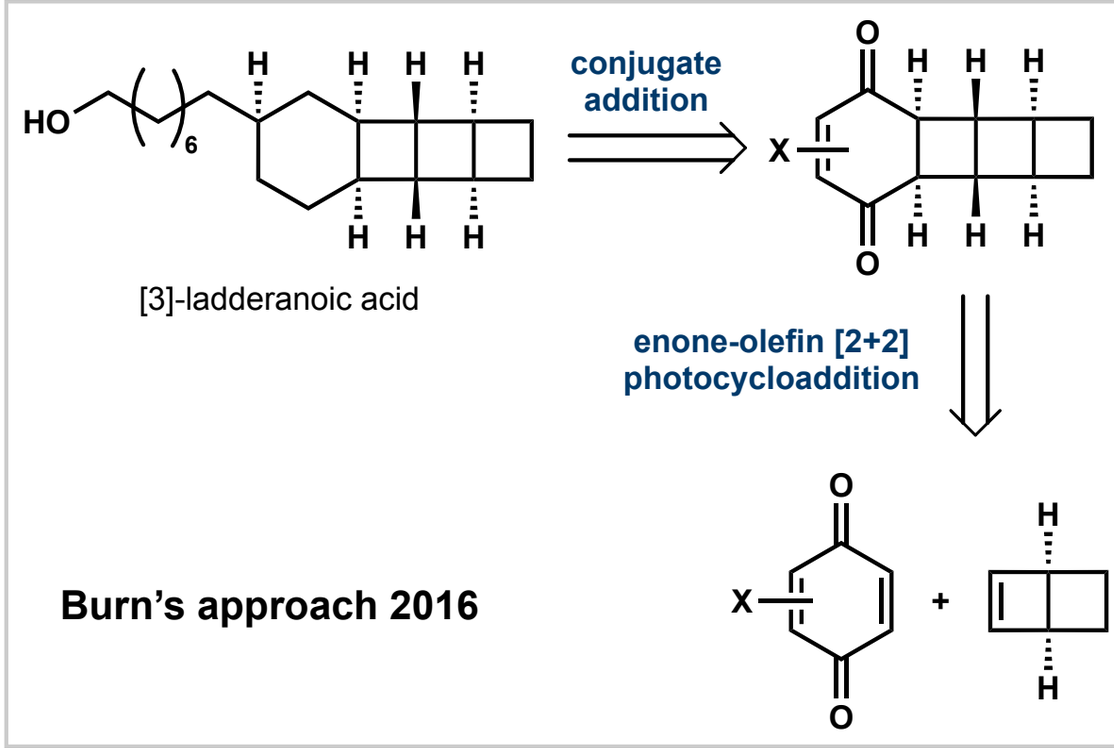
- Isolated in 2002 from annamox bacteria
- Biological function of organism protection
- Unique fused cyclobutane ring structure
- Previous synthesis of members of the family by Corey in 2006 and Burns in 2016.

JACS **2017**, *139,* 14392-14395; *Nature* **2002**, *419*, 708.

Ladderanol family: previous strategies



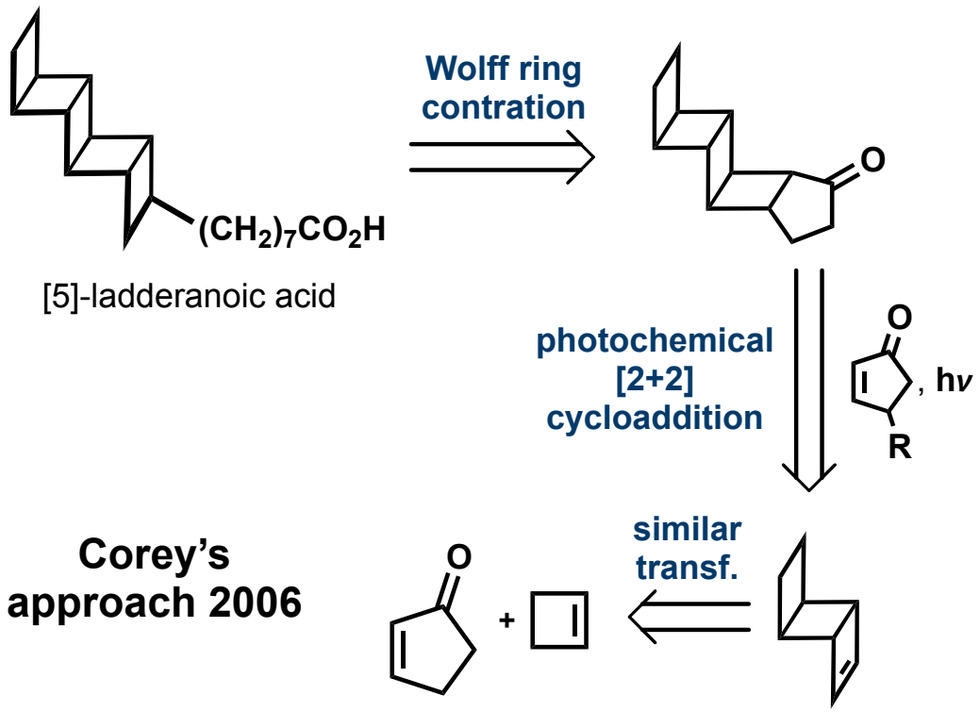
Corey's approach 2006



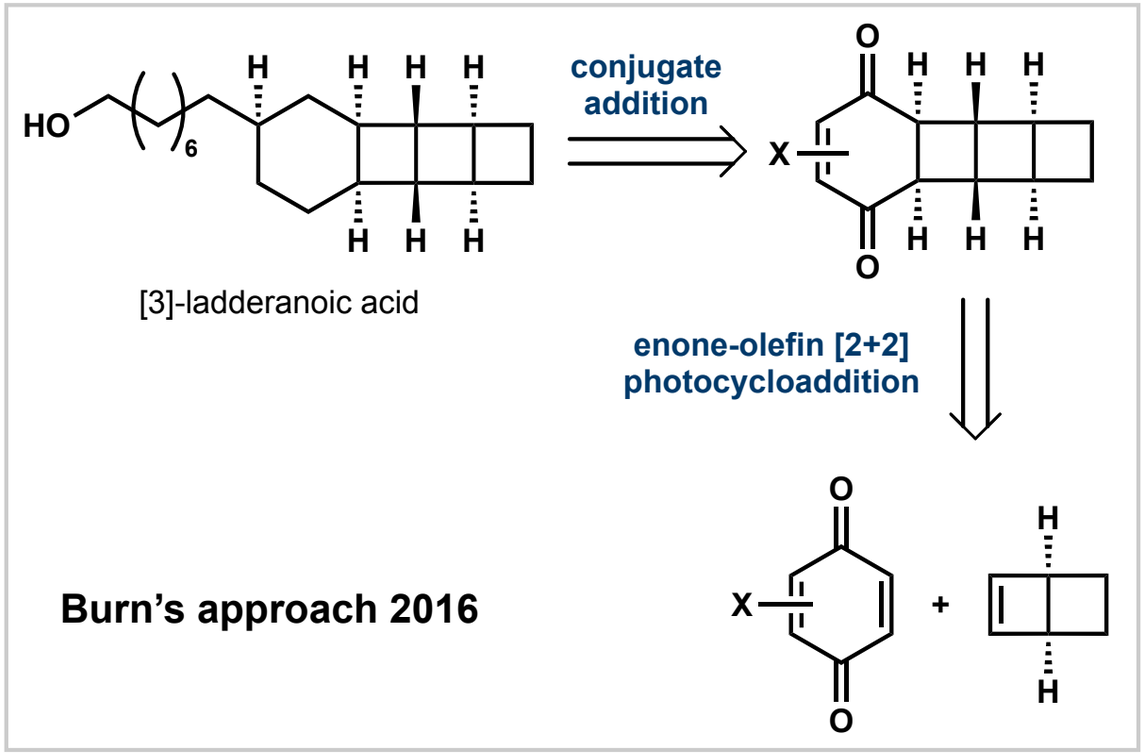
Burn's approach 2016

JACS **2017**, *139*, 14392-14395.

Ladderanol family: previous strategies



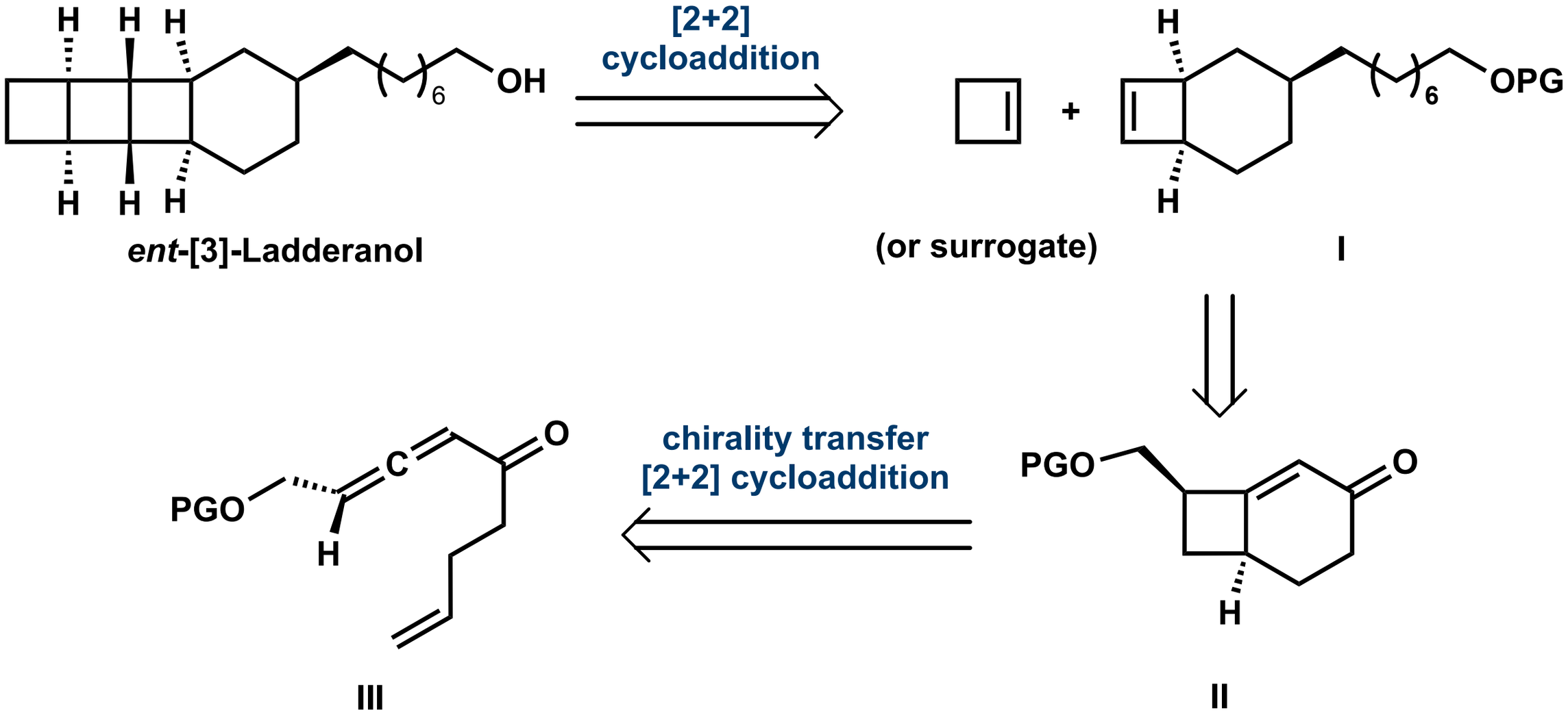
- 17 steps LLS
- Enantioselective synthesis
- Produced enough material for biological investigation, even though route not that scalable (23mg)



- 8 steps
- First synthesis of [3]-Ladderanol
- Highly scalable route (> 600mg)
- Synthesis of also ladderane phospholipids, to enable biophysical studies

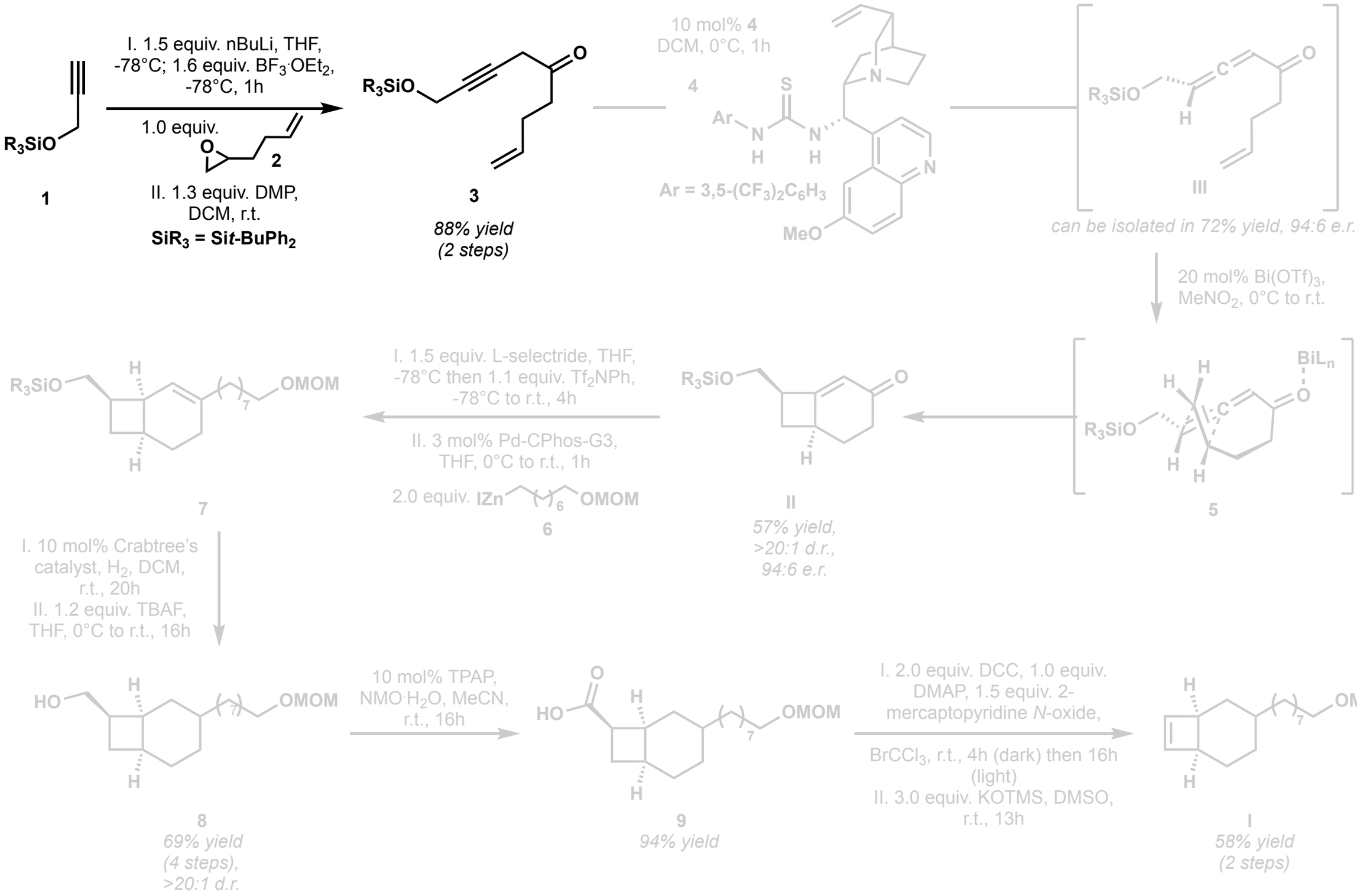
JACS **2017**, *139,* 14392-14395; *JACS* **2006**, *128*, 3118-3119; *JACS* **2016**, *138*, 15845-15848.

ent-(3)-Ladderanol: Brown's retrosynthesis



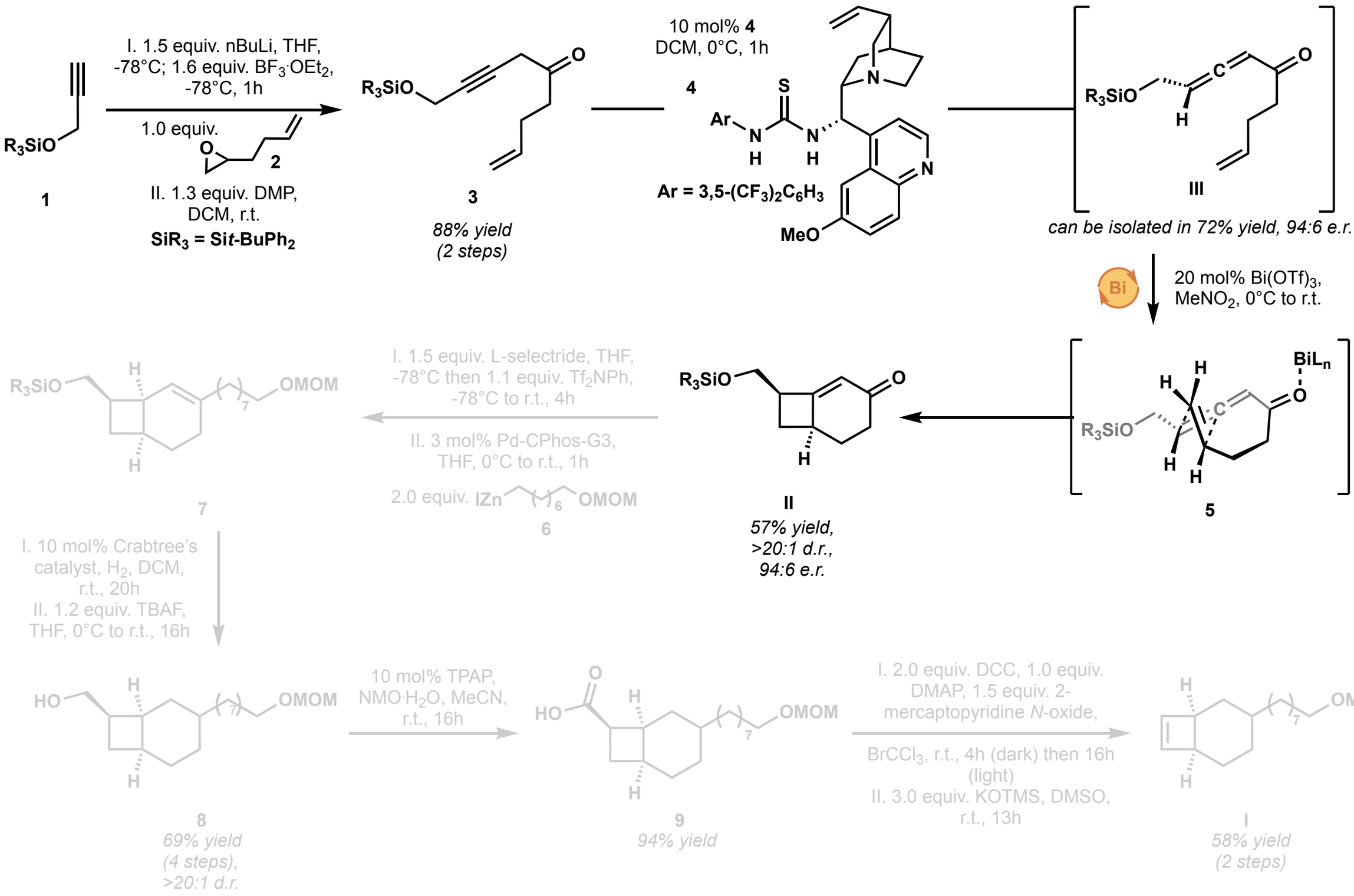
JACS **2017**, *139*, 14392-14395.

ent-(3)-Ladderanol: synthesis (1)



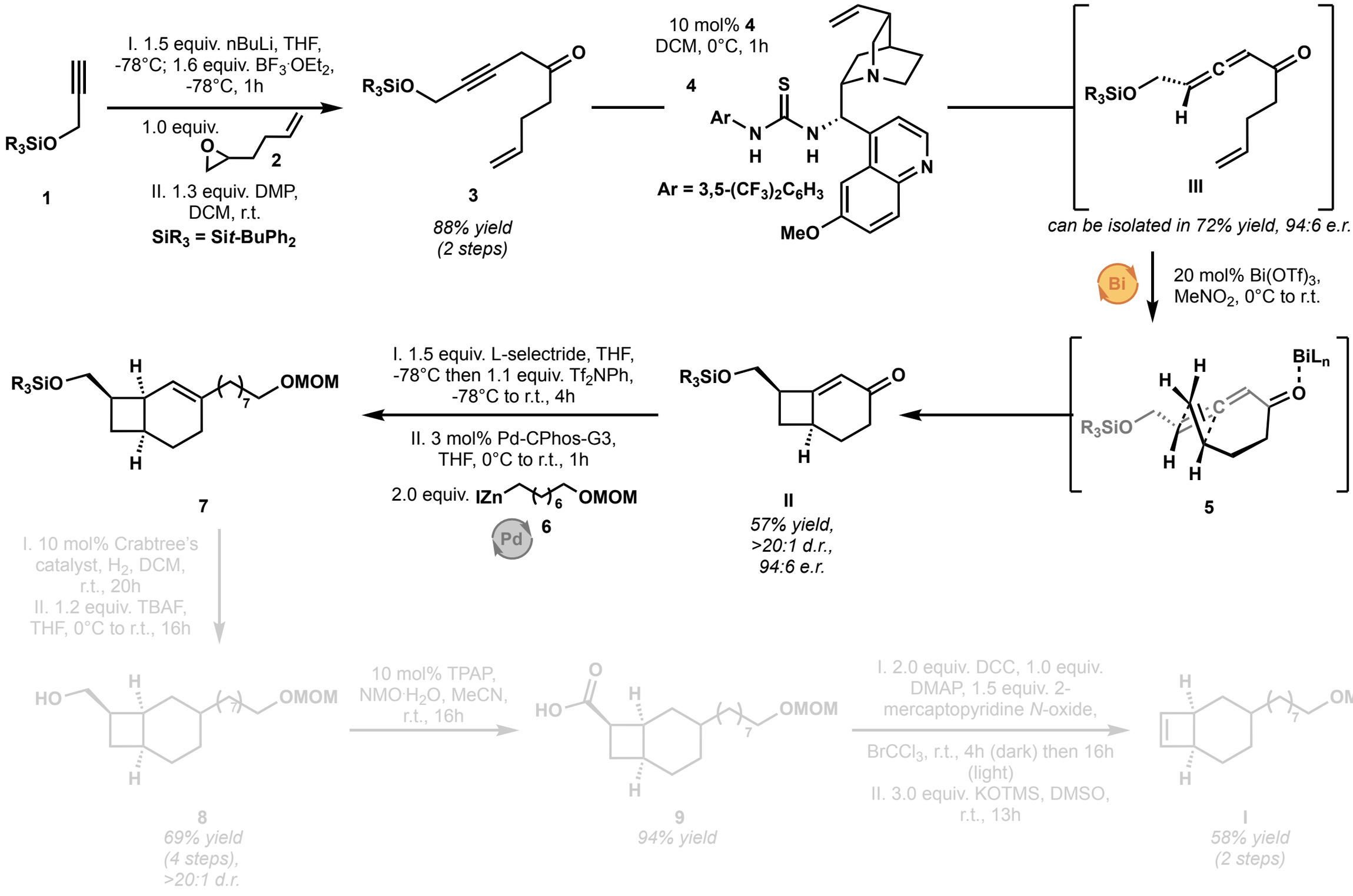
JACS **2017**, *139,* 14392-14395.

ent-(3)-Ladderanol: synthesis (1)



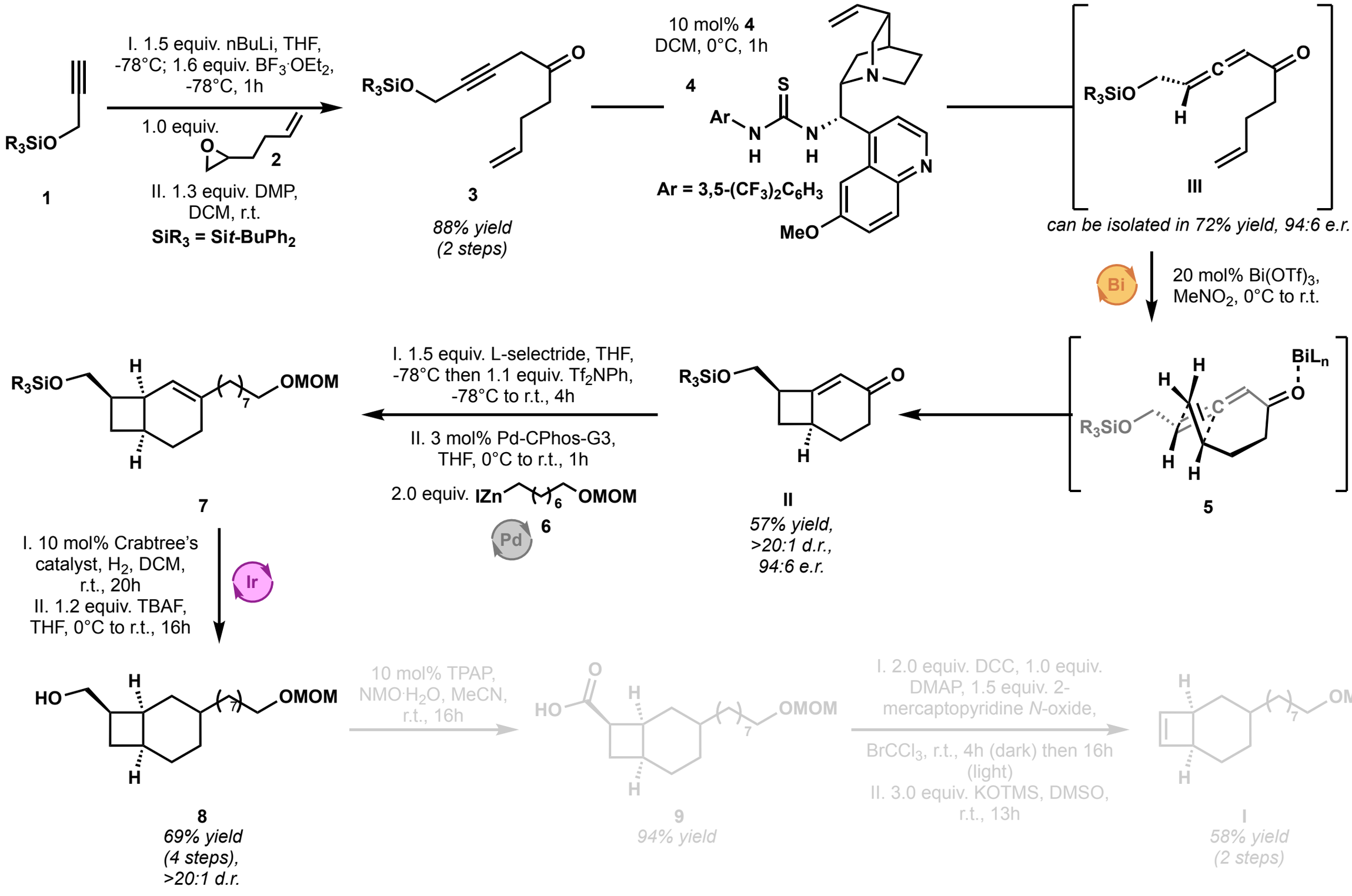
JACS **2017**, *139,* 14392-14395.

ent-(3)-Ladderanol: synthesis (1)



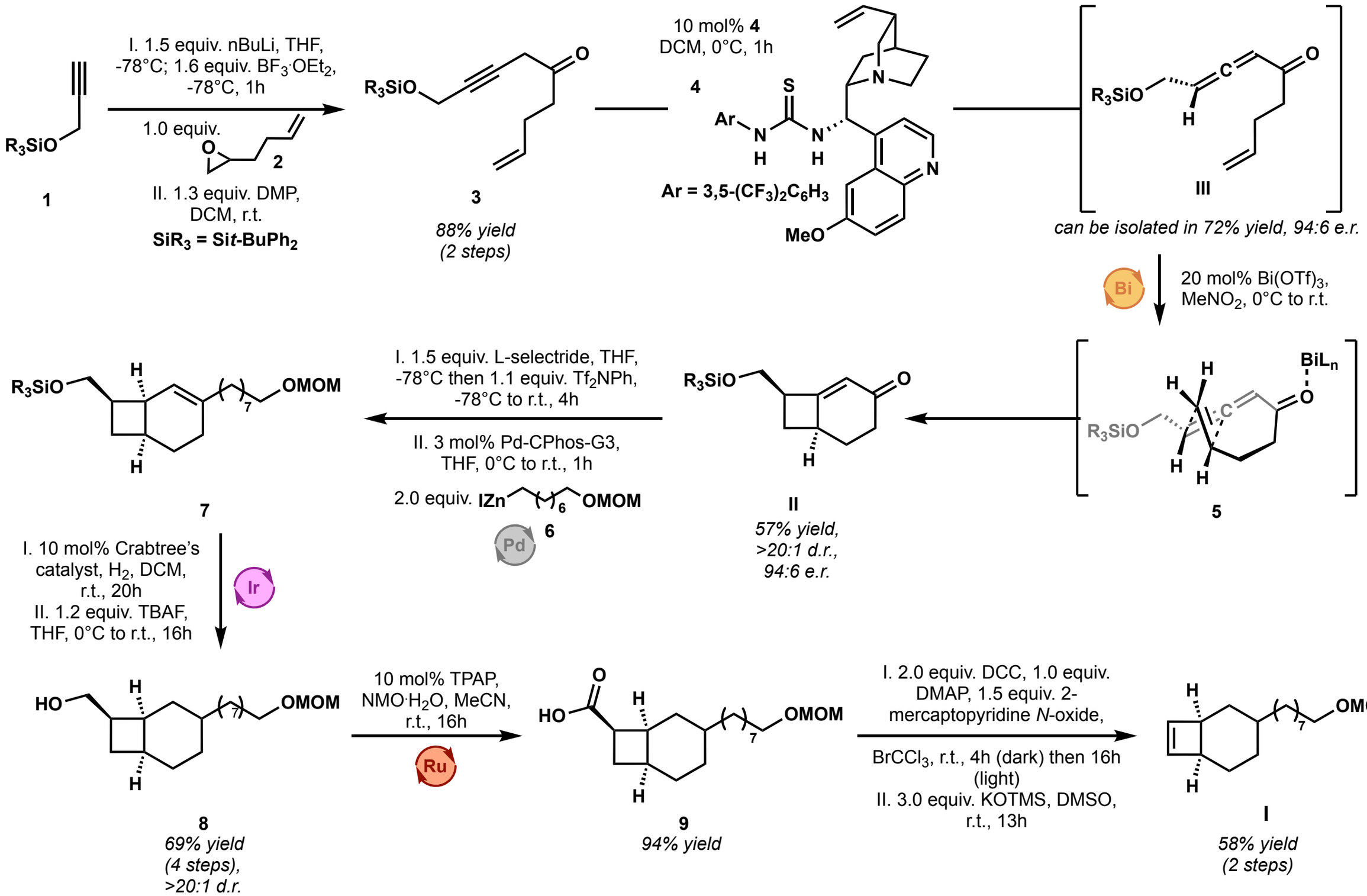
JACS **2017**, *139*, 14392-14395.

ent-(3)-Ladderanol: synthesis (1)



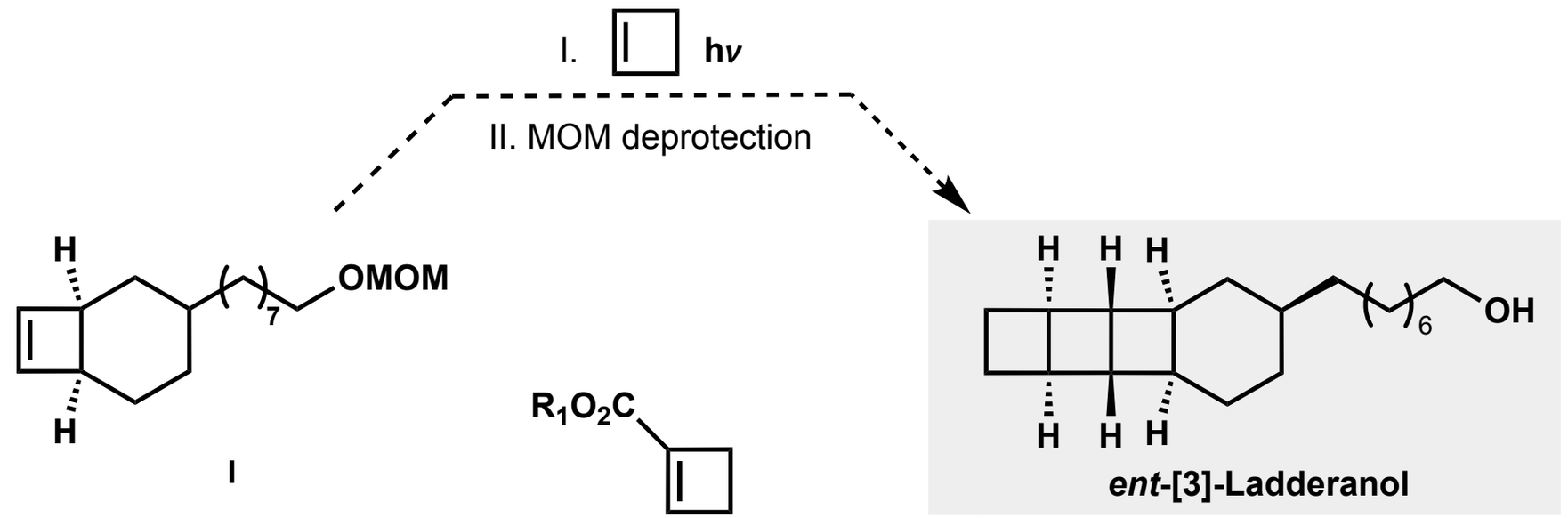
JACS **2017**, *139,* 14392-14395.

ent-(3)-Ladderanol: synthesis (1)



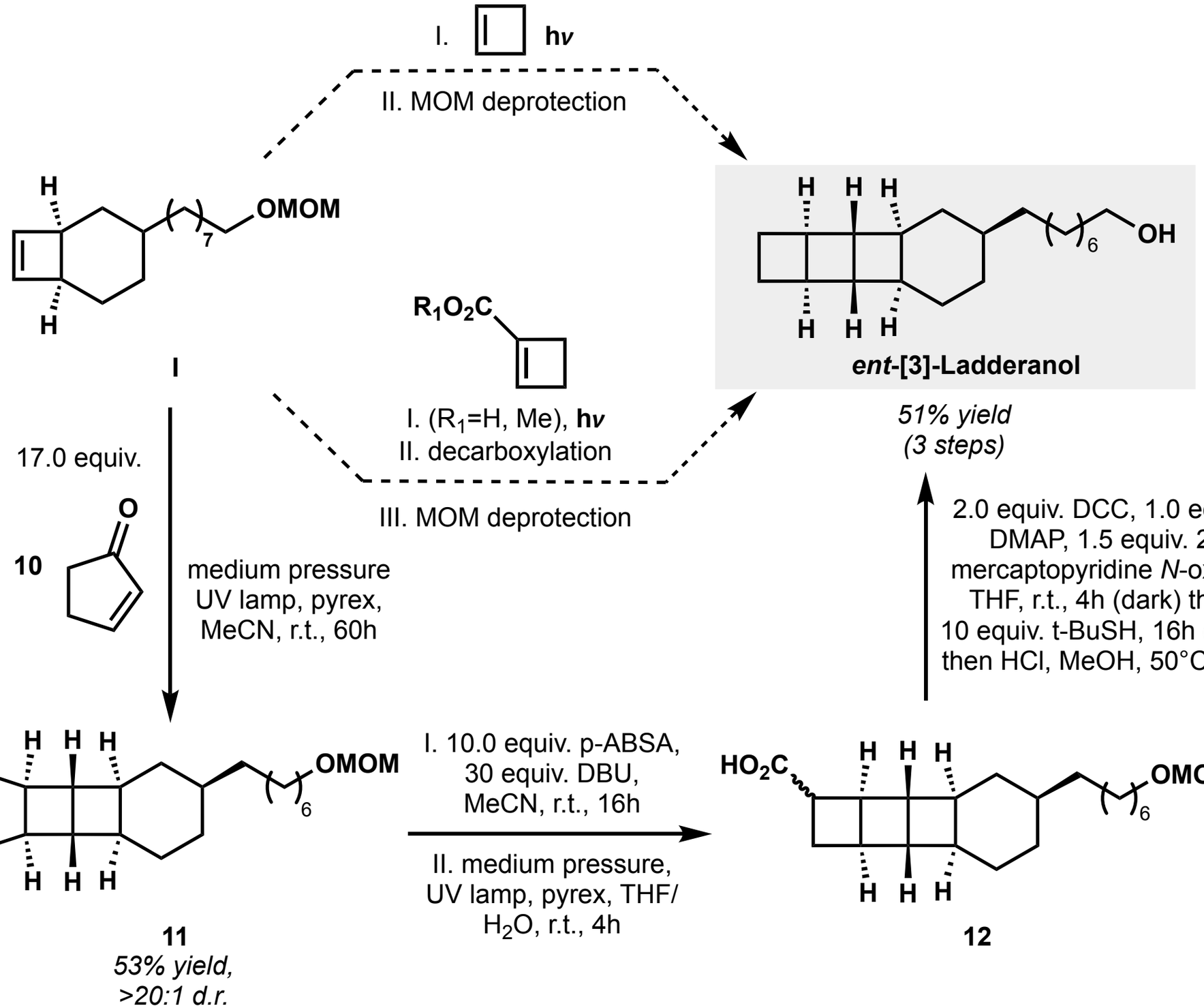
JACS **2017**, *139*, 14392-14395.

ent-(3)-Ladderanol: synthesis (2)



JACS **2017**, *139,* 14392-14395.

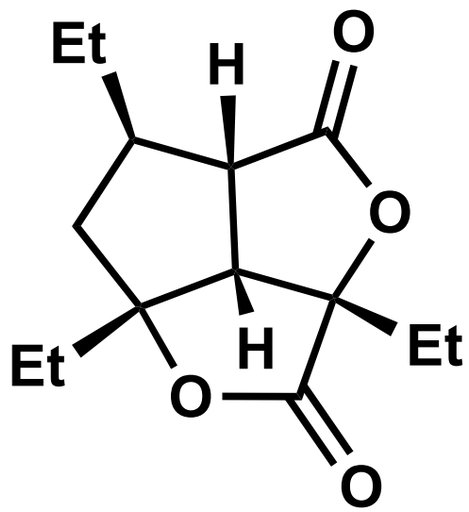
ent-(3)-Ladderanol: synthesis (2)



JACS **2017**, *139*, 14392-14395.

Gracilioether F

Marine sponge *Plakinastrella mammillaris*

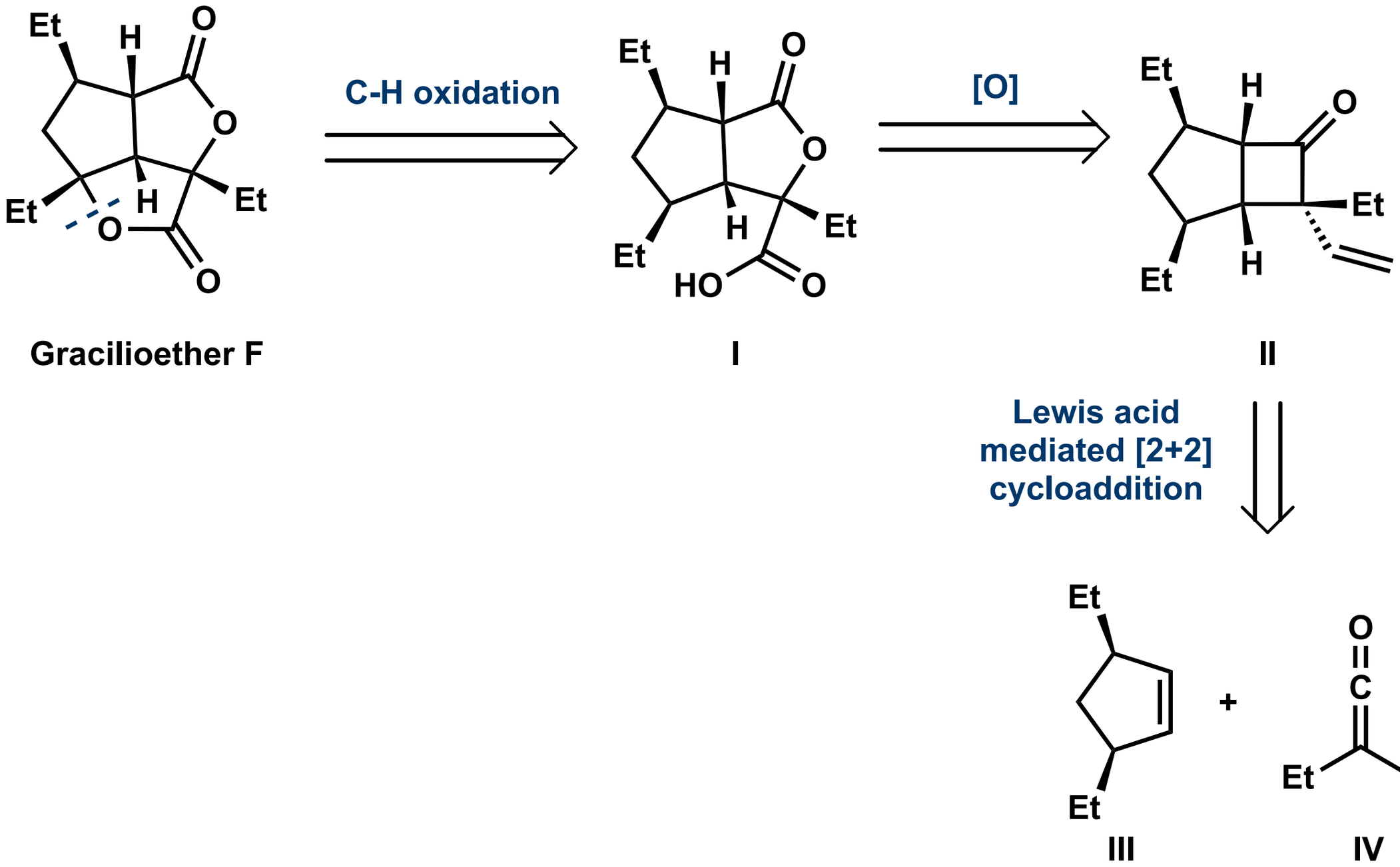


Gracilioether F

- Polyketide extracted from several families of marine sponges
- Members of the family have shown antimalarial activity against *Plasmodium falciparum* (IC_{50} < 10µg/mL)
- Tricyclic core skeleton with five contiguous stereocenters

ACIE **2014**, *53,* 14522-14526; *J. Org. Chem.* **2009**, *74*, 4203-4207; *Tetrahedron* **2012**, 68, 10157-10163.

Gracilioether F: retrosynthesis

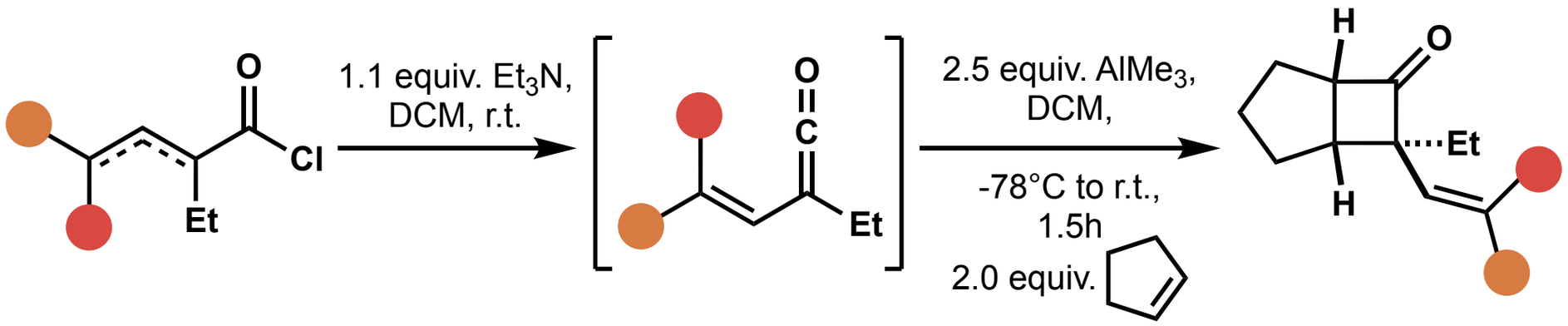


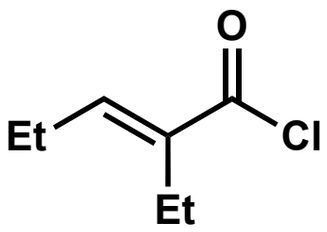
Gracilioether F **I** **II**

III **IV**

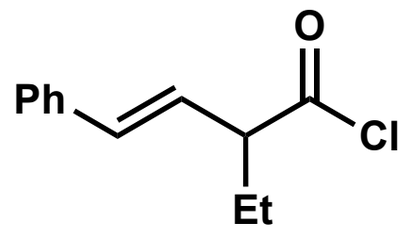
ACIE **2014**, *53,* 14522-14526.

Gracilioether F: model system

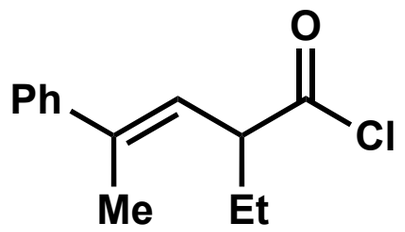




a
poor ketene generation
>2% yield of cycloaddition



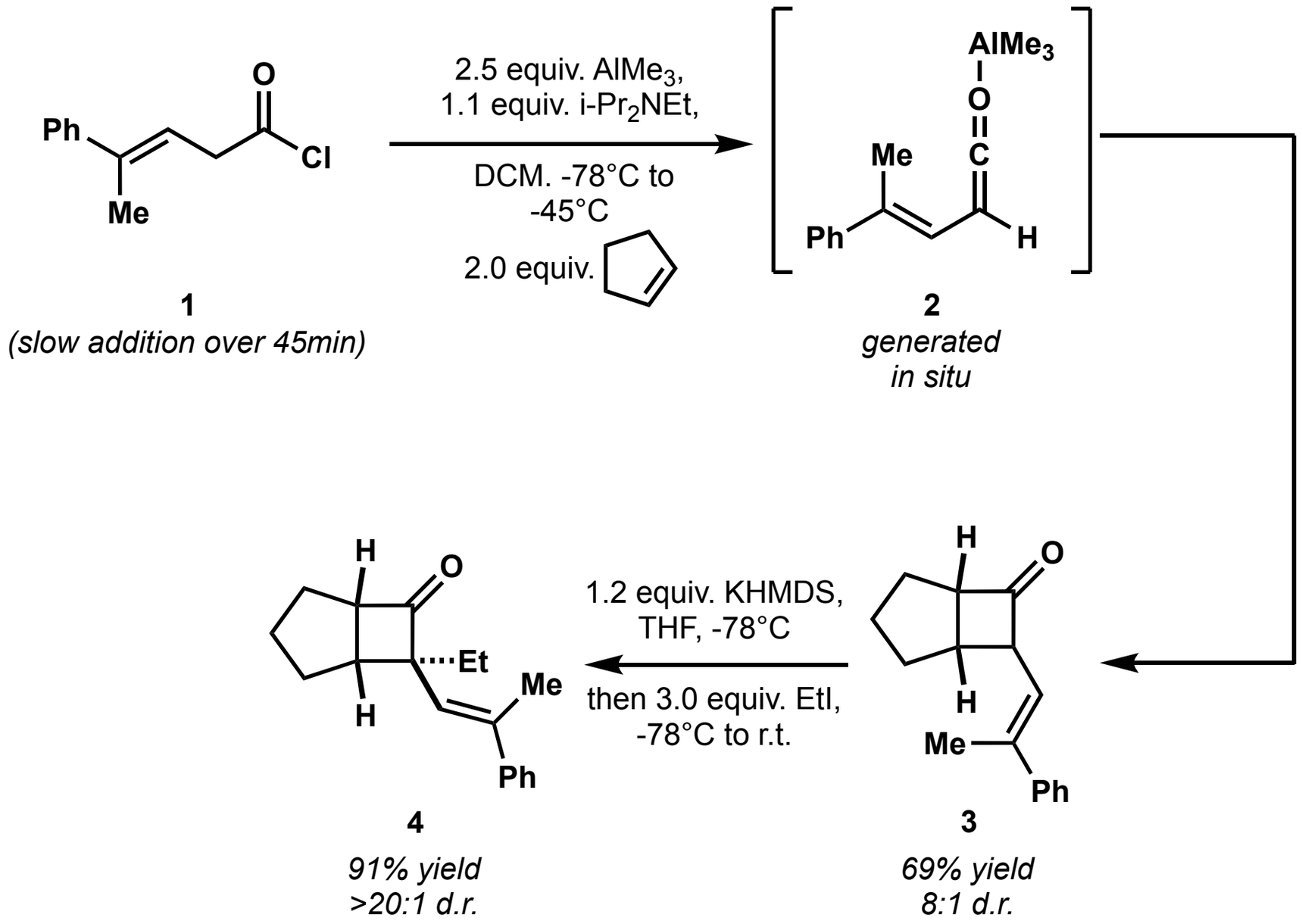
b
good ketene generation
42% yield of cycloaddition



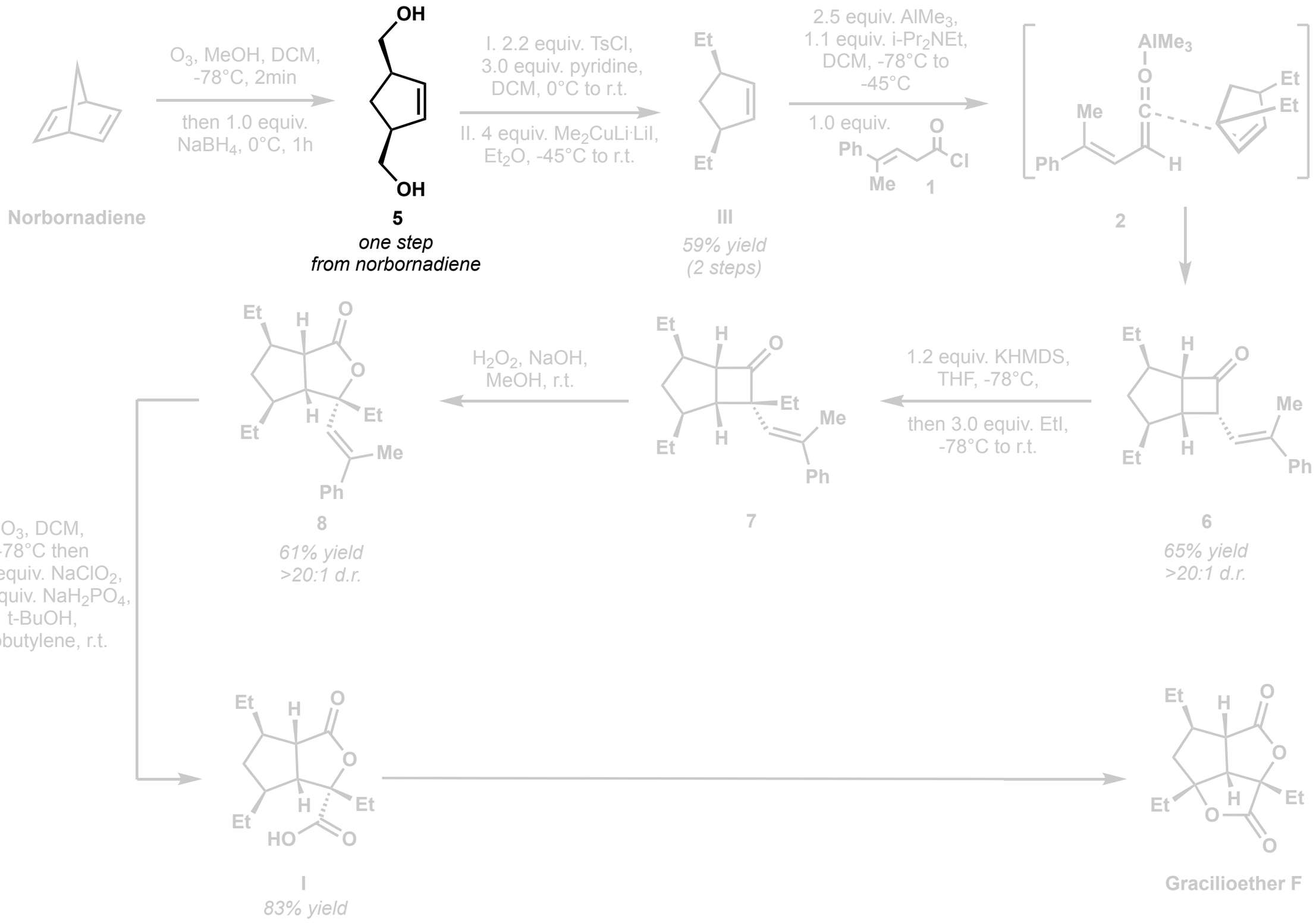
c
excellent ketene generation
61% yield of cycloaddition

ACIE **2014**, *53,* 14522-14526.

Gracilioether F: model system

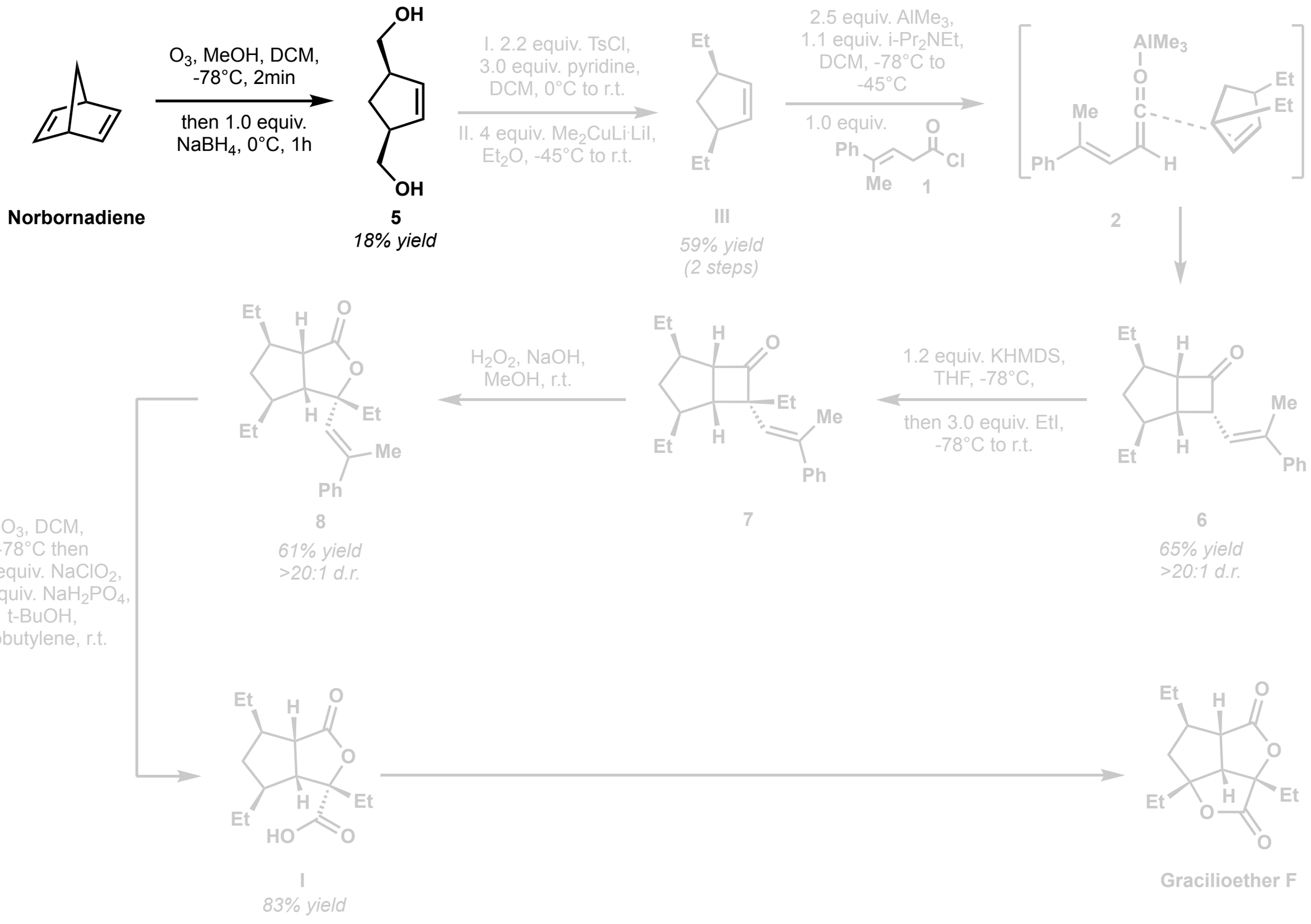


Gracilioether F: synthesis



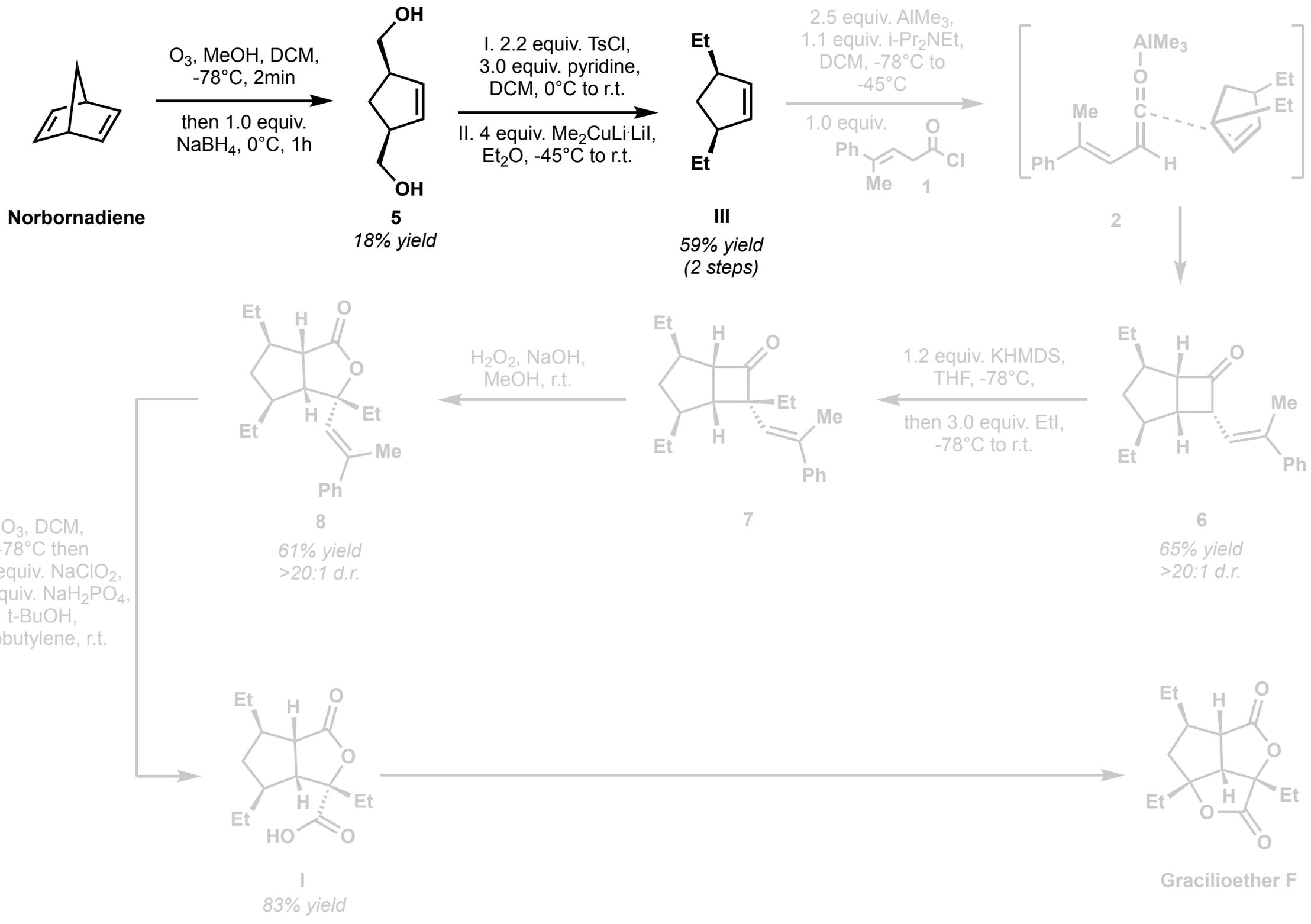
ACIE **2014**, *53,* 14522-14526.

Gracilioether F: synthesis



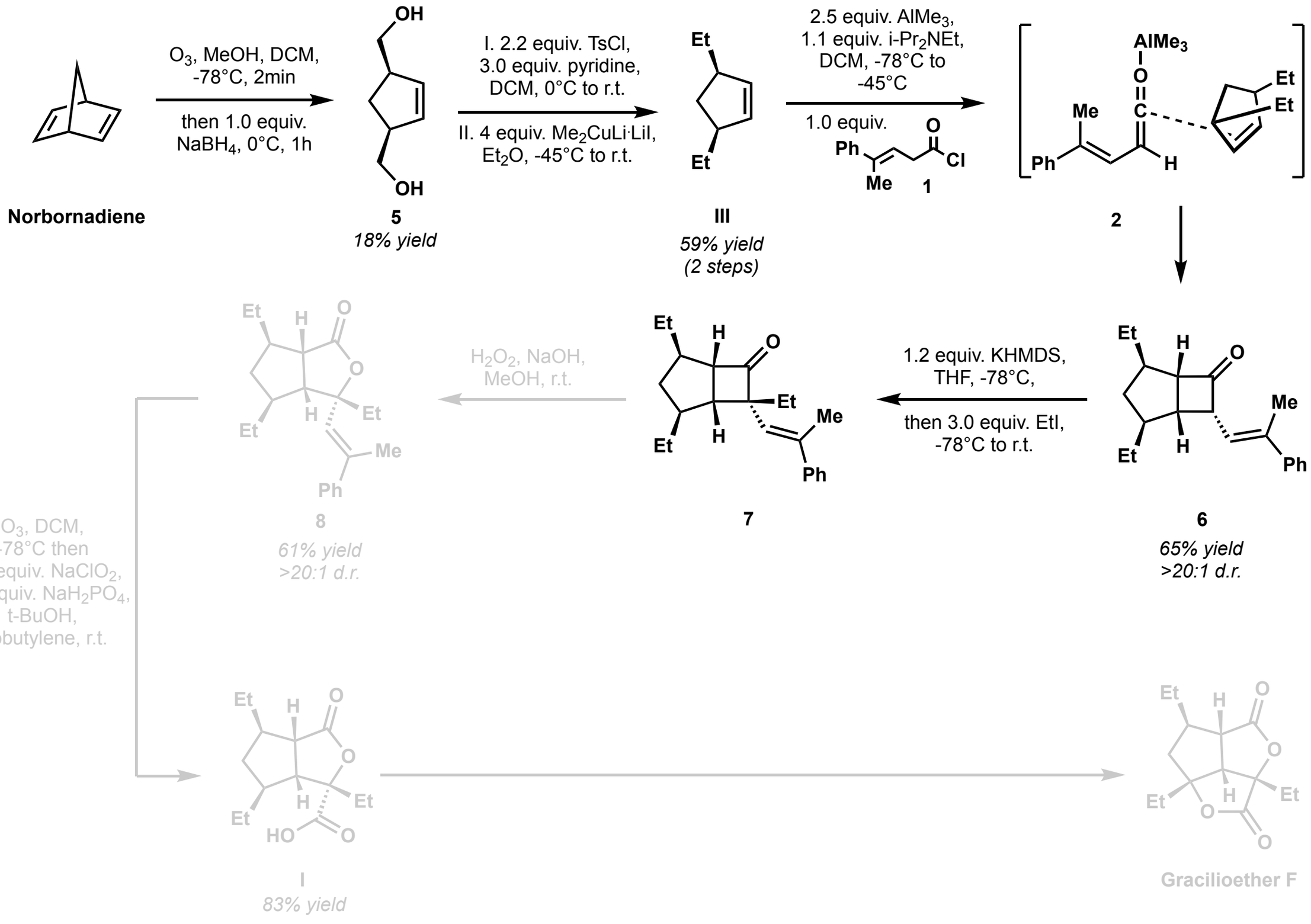
ACIE **2014**, *53,* 14522-14526.

Gracilioether F: synthesis



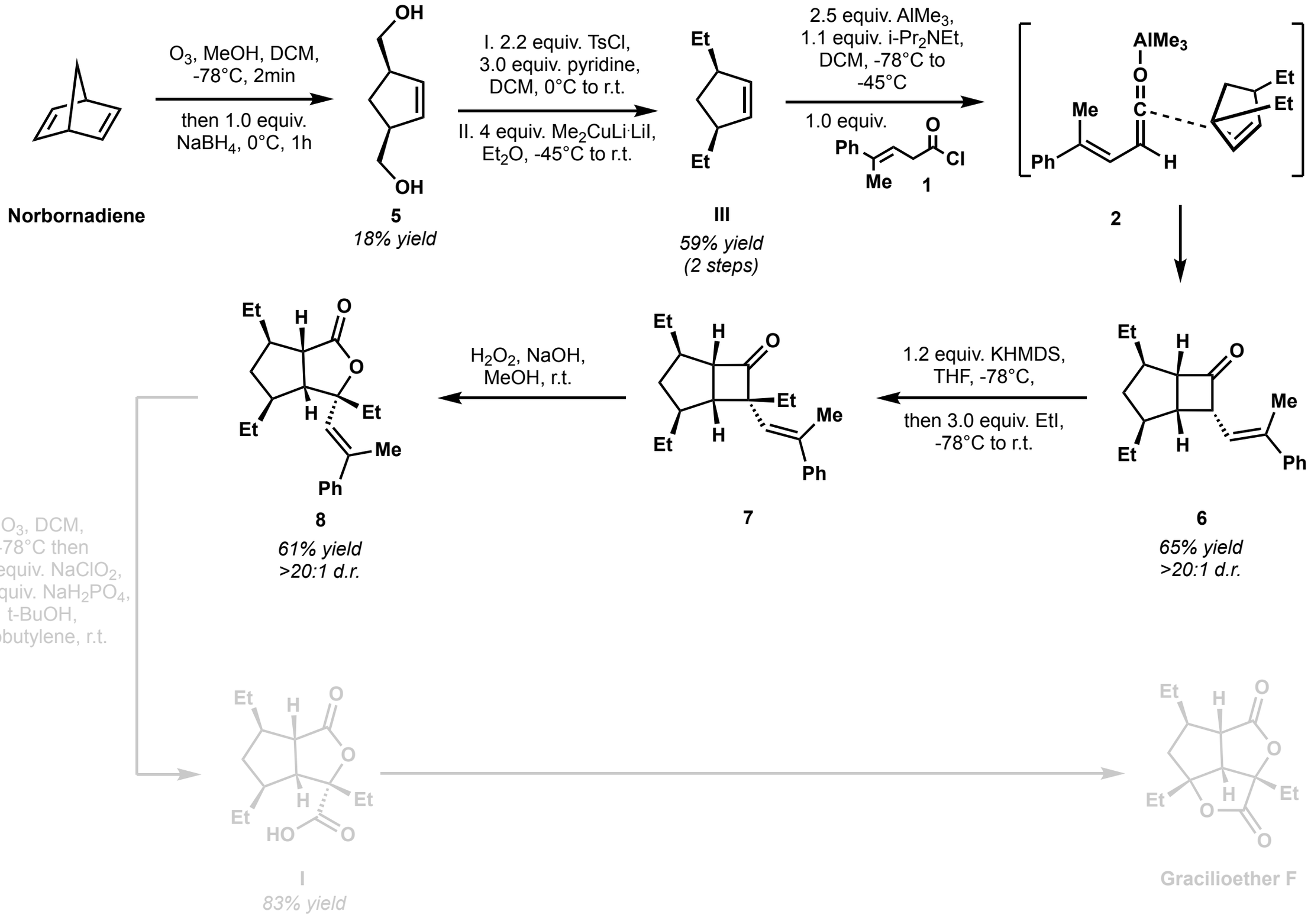
ACIE **2014**, *53,* 14522-14526.

Gracilioether F: synthesis



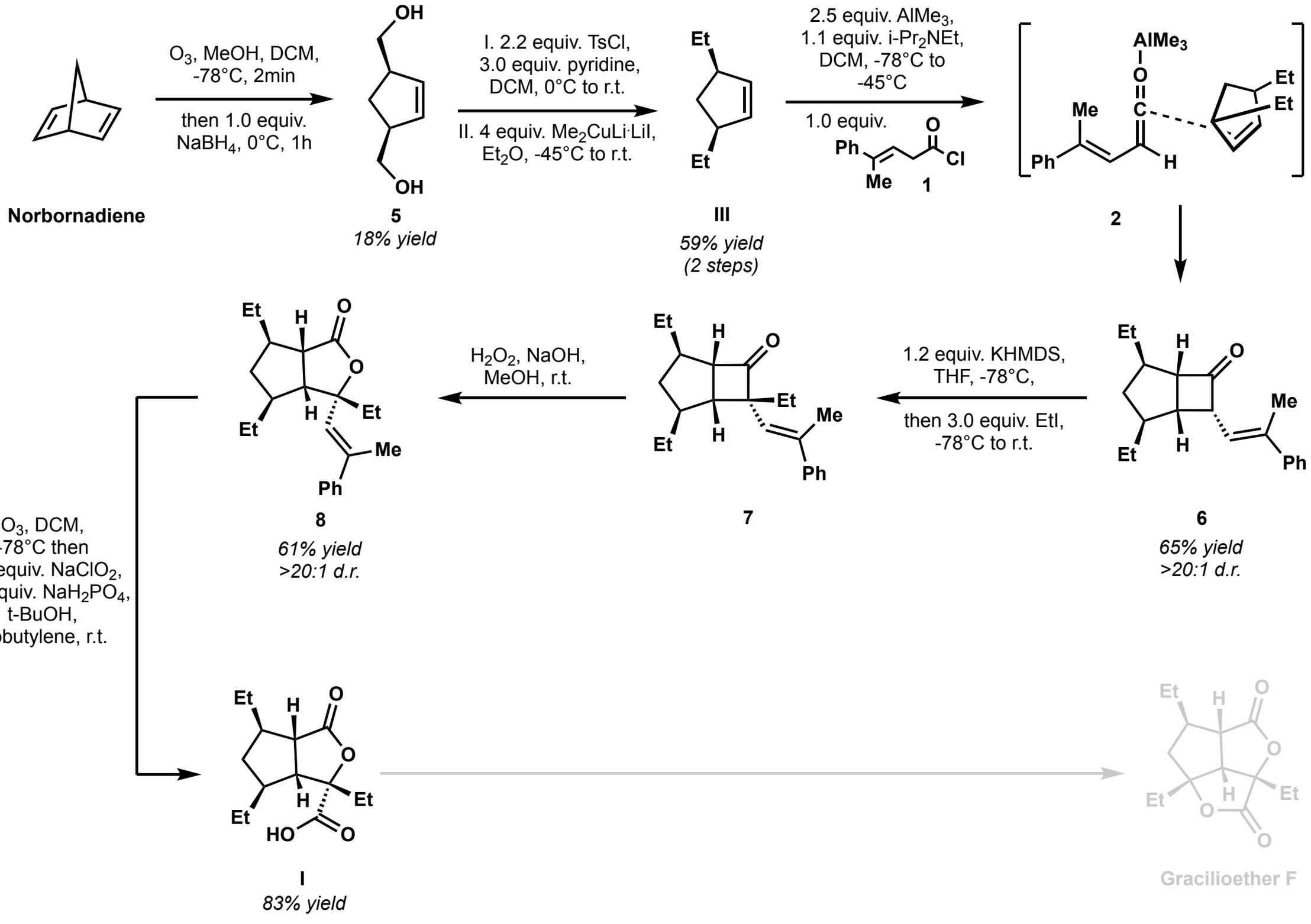
ACIE **2014**, *53,* 14522-14526.

Gracilioether F: synthesis



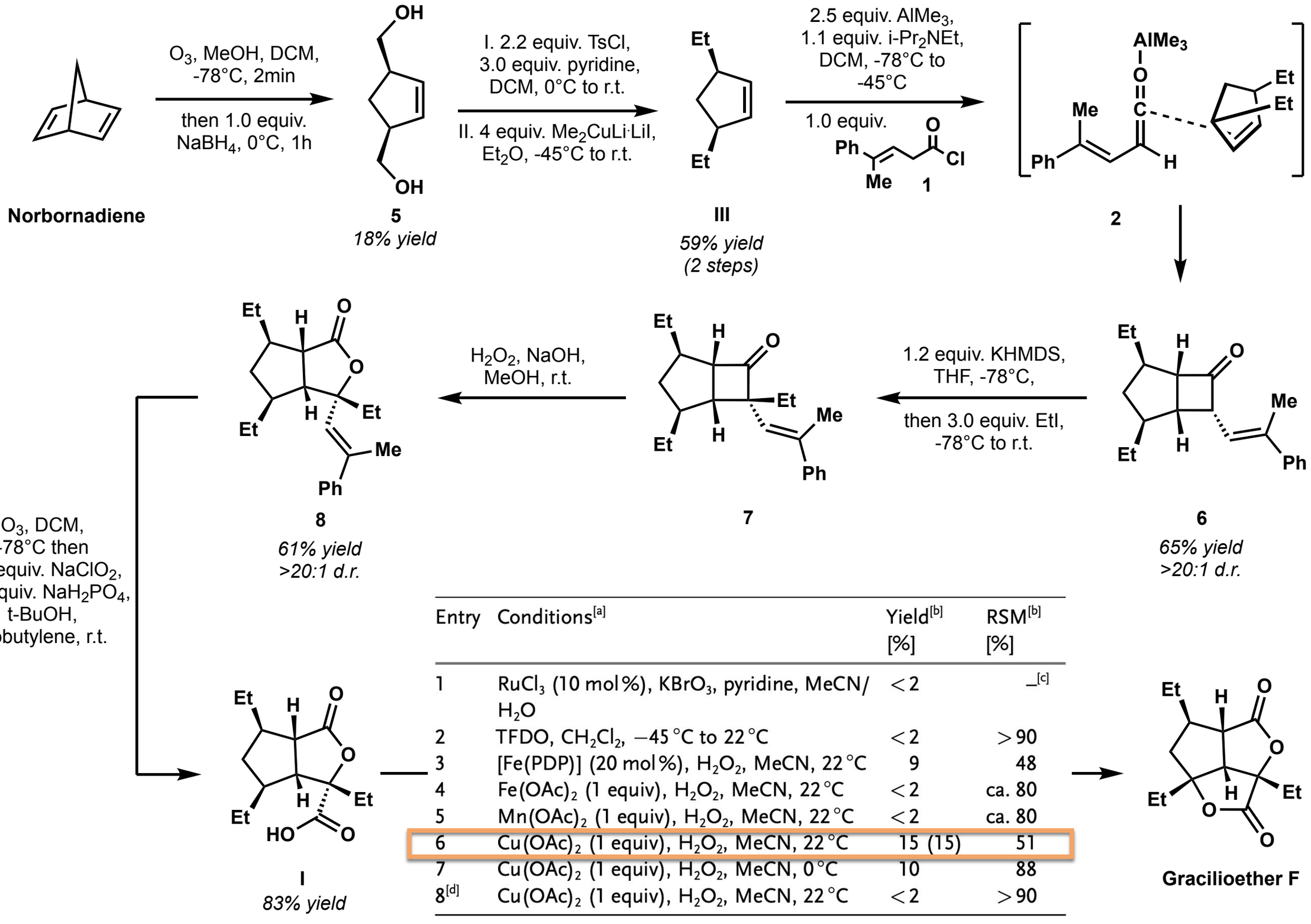
ACIE **2014**, *53,* 14522-14526.

Gracilioether F: synthesis



ACIE **2014**, *53,* 14522-14526.

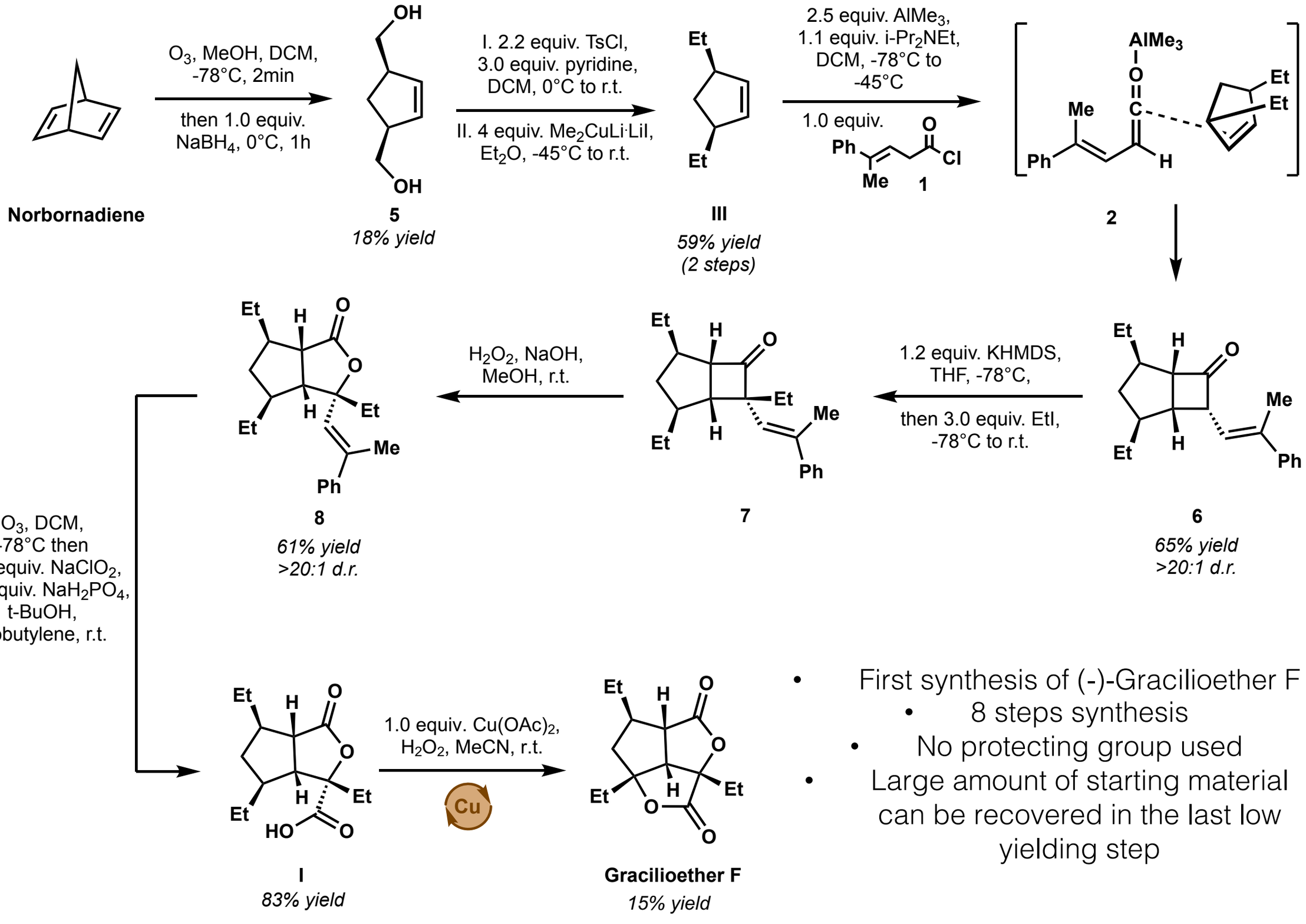
Gracilioether F: synthesis



Entry	Conditions[a]	Yield[b] [%]	RSM[b] [%]
1	$RuCl_3$ (10 mol%), $KBrO_3$, pyridine, MeCN/H_2O	<2	–[c]
2	TFDO, CH_2Cl_2, −45 °C to 22 °C	<2	>90
3	[Fe(PDP)] (20 mol%), H_2O_2, MeCN, 22 °C	9	48
4	$Fe(OAc)_2$ (1 equiv), H_2O_2, MeCN, 22 °C	<2	ca. 80
5	$Mn(OAc)_2$ (1 equiv), H_2O_2, MeCN, 22 °C	<2	ca. 80
6	$Cu(OAc)_2$ (1 equiv), H_2O_2, MeCN, 22 °C	15 (15)	51
7	$Cu(OAc)_2$ (1 equiv), H_2O_2, MeCN, 0 °C	10	88
8[d]	$Cu(OAc)_2$ (1 equiv), H_2O_2, MeCN, 22 °C	<2	>90

ACIE **2014**, *53*, 14522-14526.

Gracilioether F: synthesis

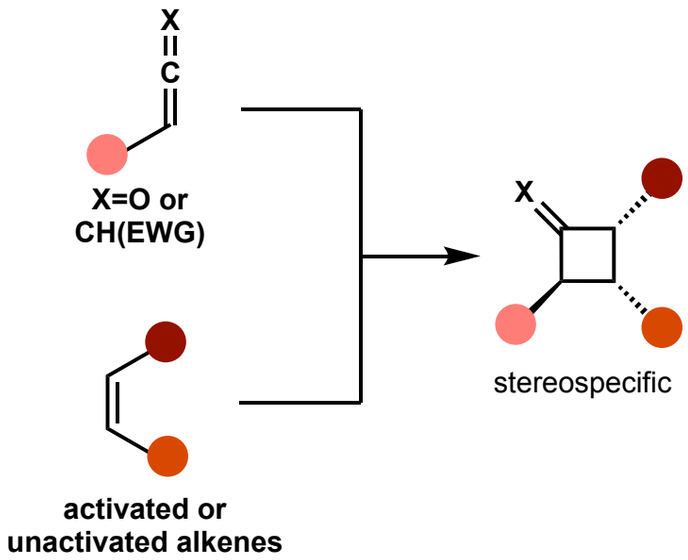


- First synthesis of (-)-Gracilioether F
  - 8 steps synthesis
  - No protecting group used
  - Large amount of starting material can be recovered in the last low yielding step

ACIE **2014**, *53,* 14522-14526.

Independent Career

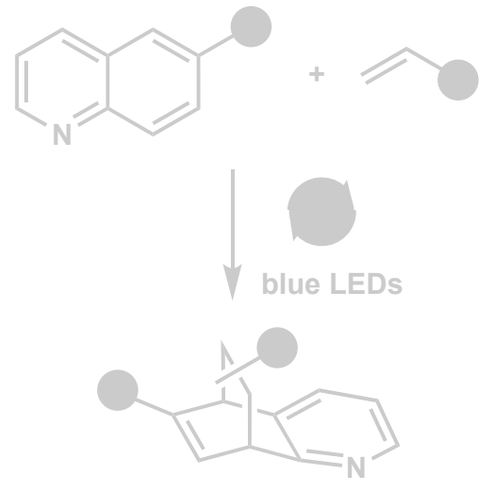
Lewis Acid Mediated [2+2] Cycloadditions



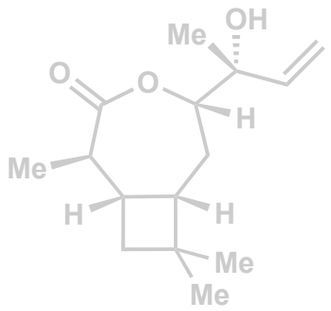
Cu/Pd Catalysis and Carboboration

Catalyst controlled selectivity

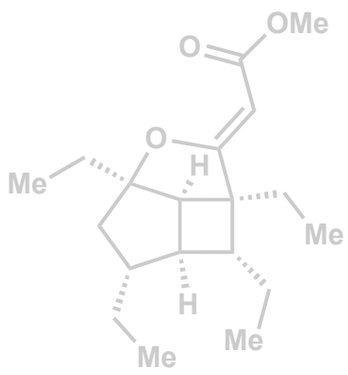
Photochemical Dearomative Cycloadditions



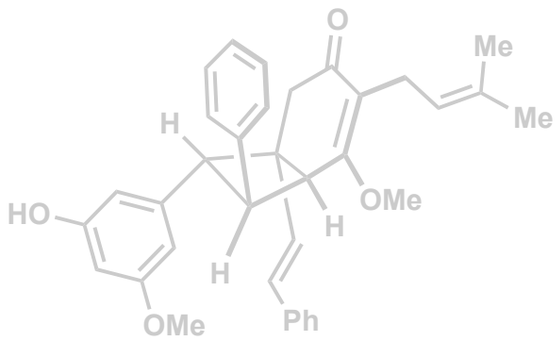
Total Synthesis



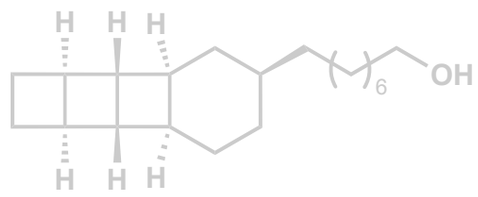
(-)-Hebelophyllene E



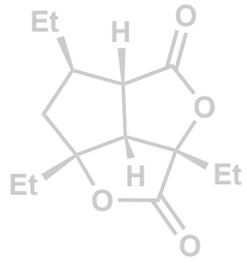
Hippolachnin A



(-)-Cajanusine



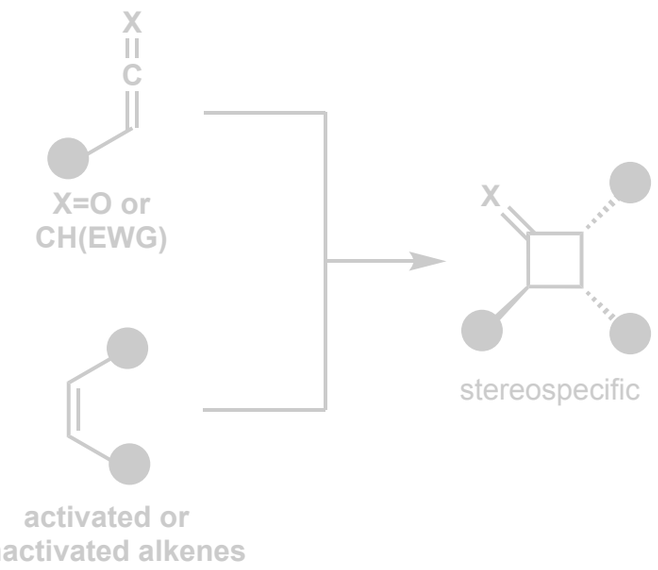
ent-[3]-Ladderanol



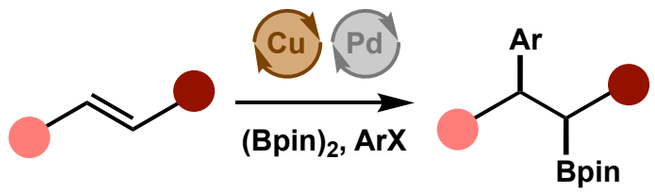
Gracilioether F

Independent Career

Lewis Acid Mediated [2+2] Cycloadditions

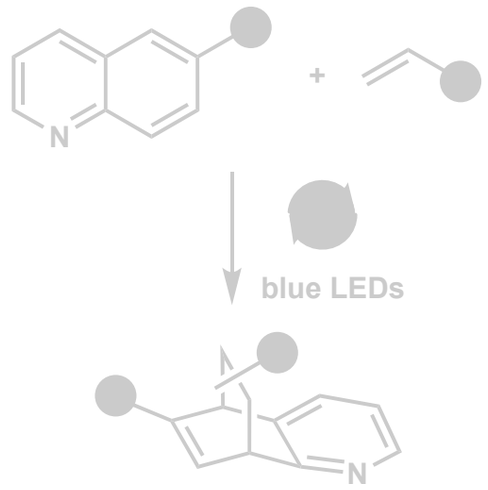


Cu/Pd Catalysis and Carboboration

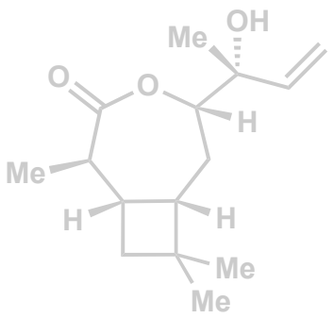


Catalyst controlled selectivity

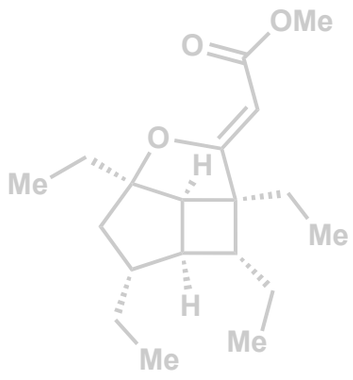
Photochemical Dearomative Cycloadditions



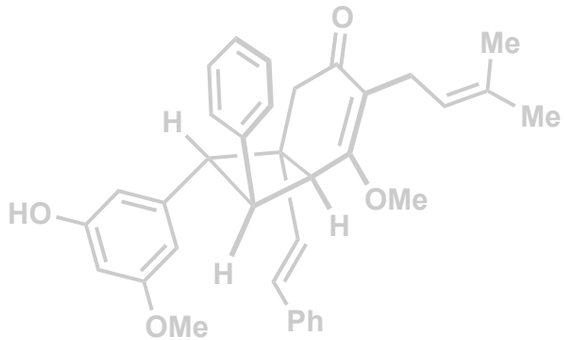
Total Synthesis



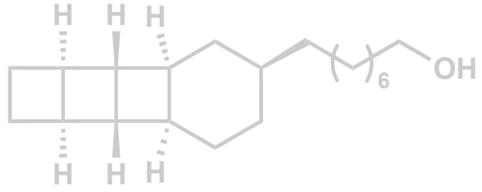
(-)-Hebelophyllene E



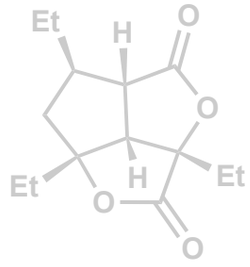
Hippolachnin A



(-)-Cajanusine



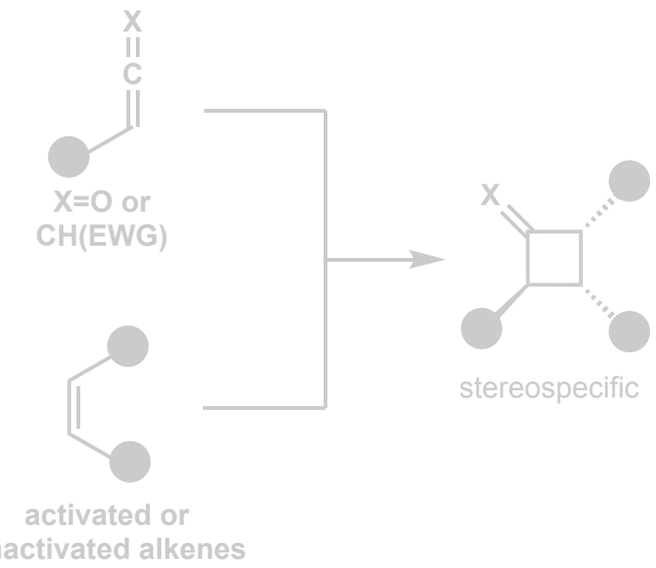
ent-[3]-Ladderanol



Gracilioether F

Independent Career

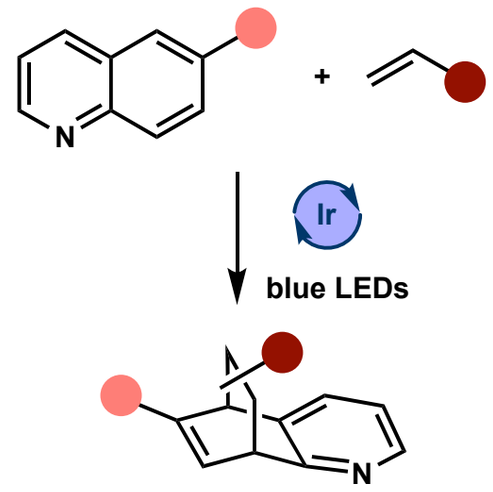
Lewis Acid Mediated [2+2] Cycloadditions



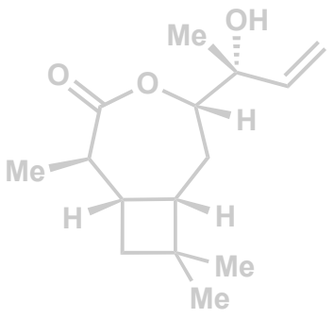
Cu/Pd Catalysis and Carboboration

Catalyst controlled selectivity

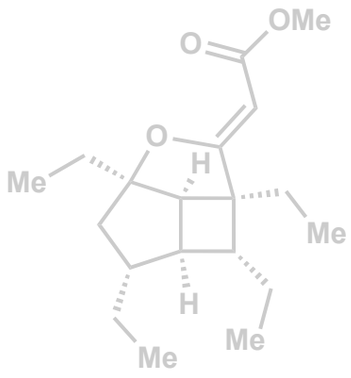
Photochemical Dearomative Cycloadditions



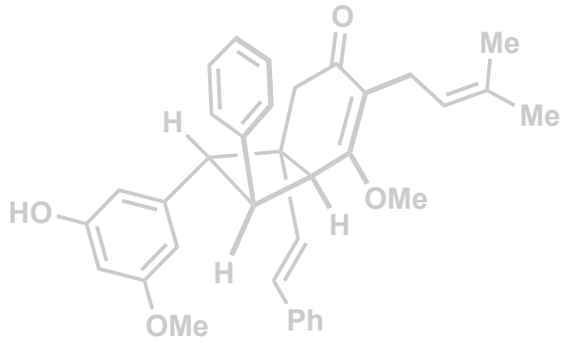
Total Synthesis



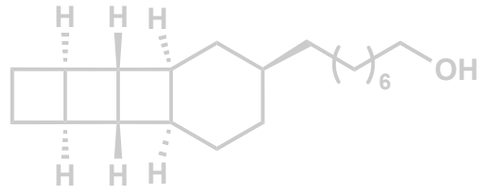
(-)-Hebelophyllene E



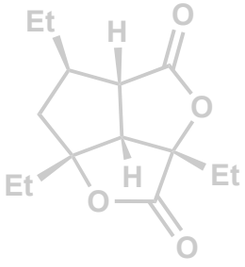
Hippolachnin A



(-)-Cajanusine



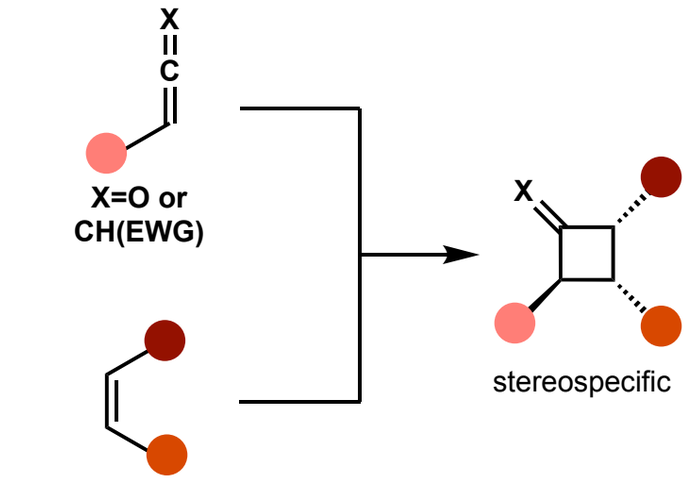
ent-[3]-Ladderanol



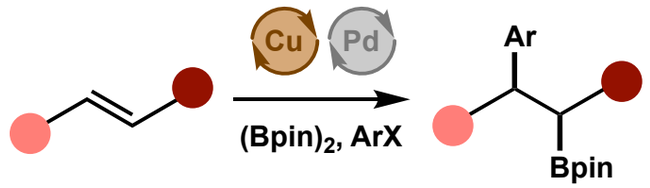
Gracilioether F

Independent Career

Lewis Acid Mediated [2+2] Cycloadditions

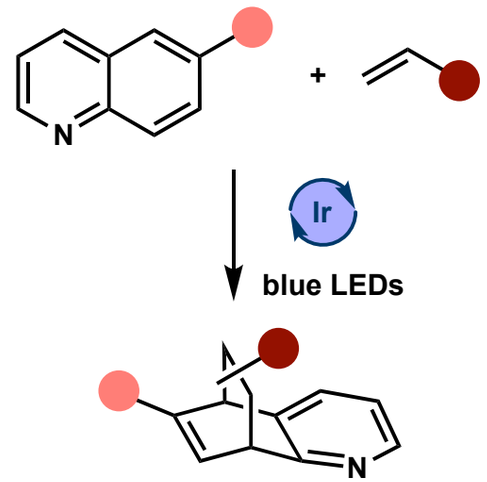


Cu/Pd Catalysis and Carboboration

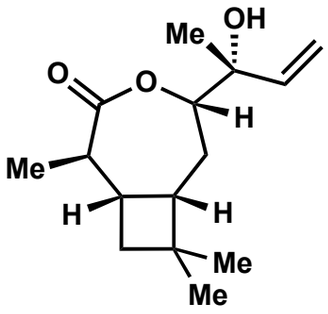


Catalyst controlled selectivity

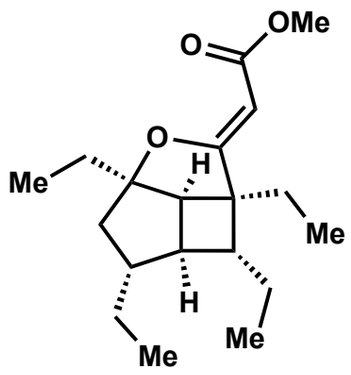
Photochemical Dearomative Cycloadditions



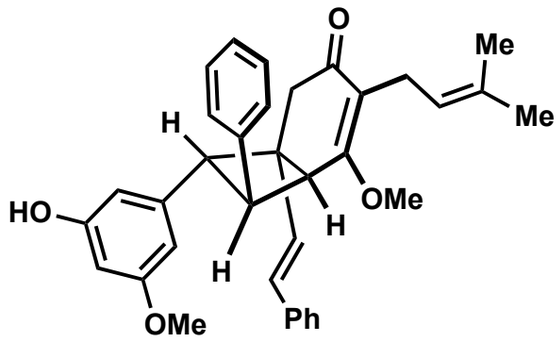
Total Synthesis



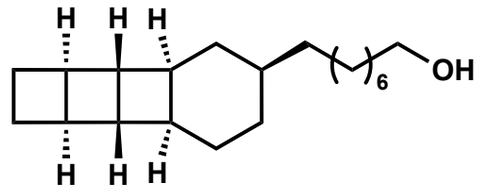
(-)-Hebelophyllene E



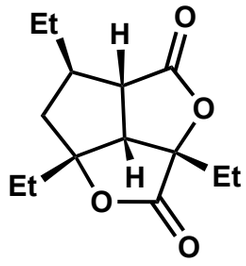
Hippolachnin A



(-)-Cajanusine

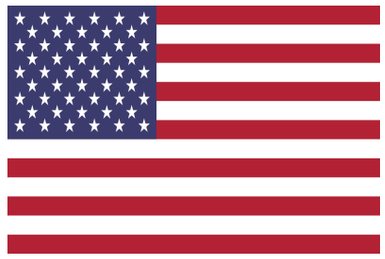


ent-[3]-Ladderanol



Gracilioether F

Thank you for the attention



Grazie dell’attenzione

Mulțumesc pentru atenția

Larisa P. Pop
The Shenvi Lab, The Scripps Research Institute