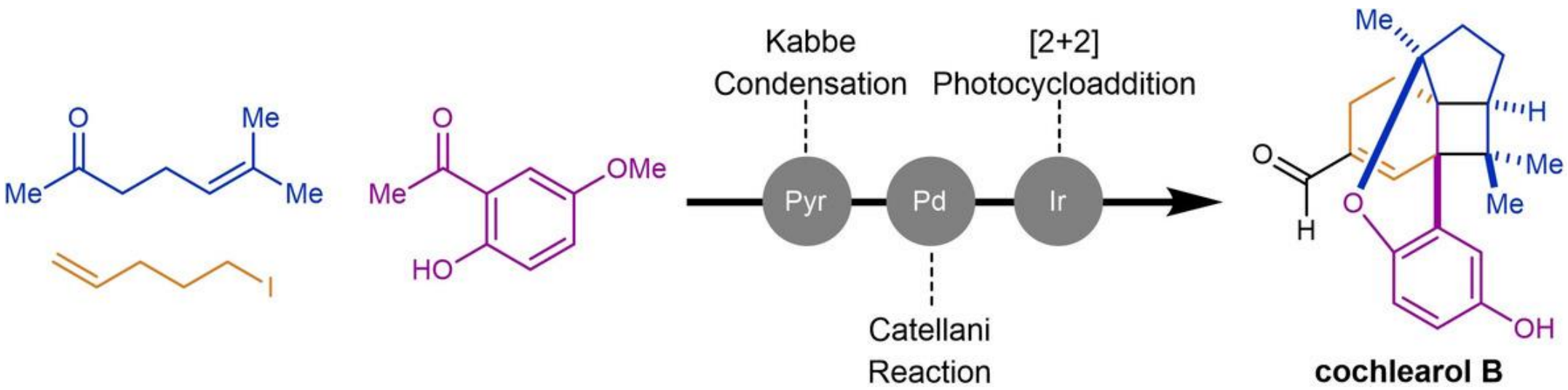
GDCh Zuschriften Angewandte Chemie www.angewandte.org

Natural Products Synthesis

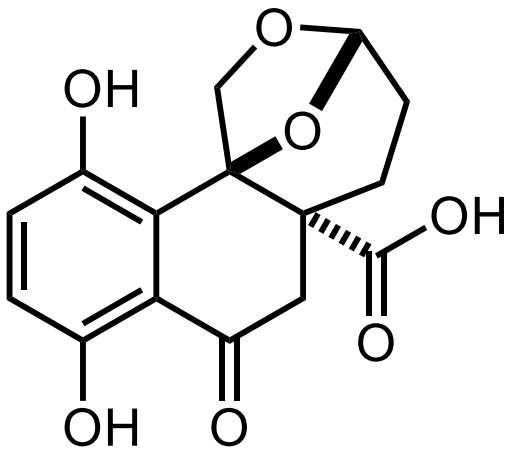
Zitierweise: *Angew. Chem. Int. Ed.* **2022,** *61,* e202201213
Internationale Ausgabe: doi.org/10.1002/anie.202201213
Deutsche Ausgabe: doi.org/10.1002/ange.202201213

Total Synthesis of (+)-Cochlearol B by an Approach Based on a Catellani Reaction and Visible-Light-Enabled [2+2] Cycloaddition**

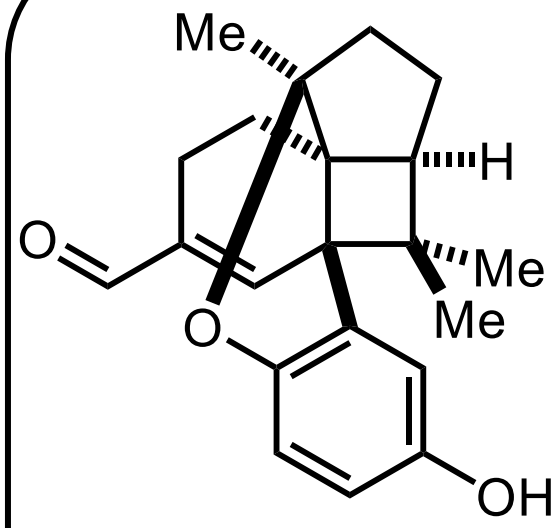
*Alistair D. Richardson, Trenton R. Vogel, Emily F. Traficante, Kason J. Glover, and Corinna S. Schindler**



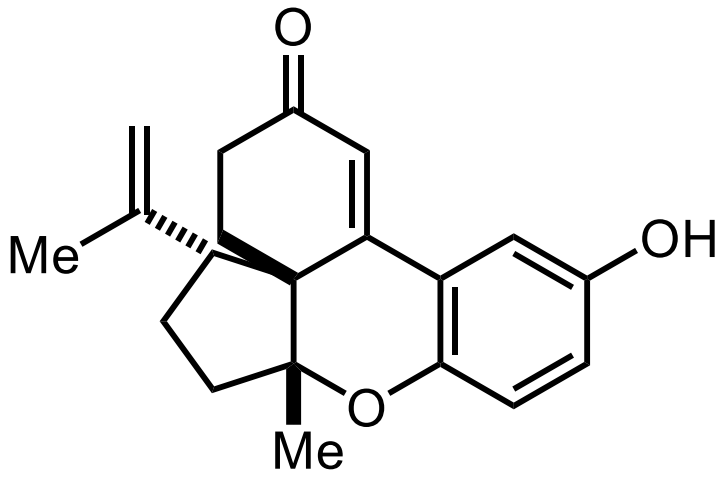
Background



cochlearol A (1)
from Ganoderma cochlear
renoprotective effects

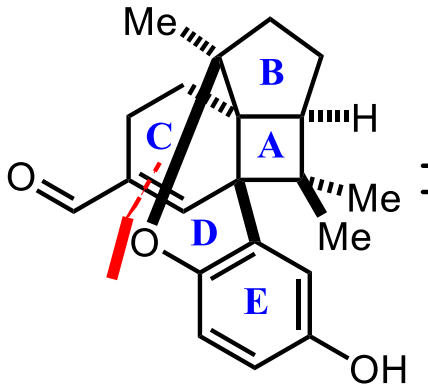


cochlearol B (2)
from Ganoderma cochlear
renoprotective effects
(-)-cochlearol B (2) only



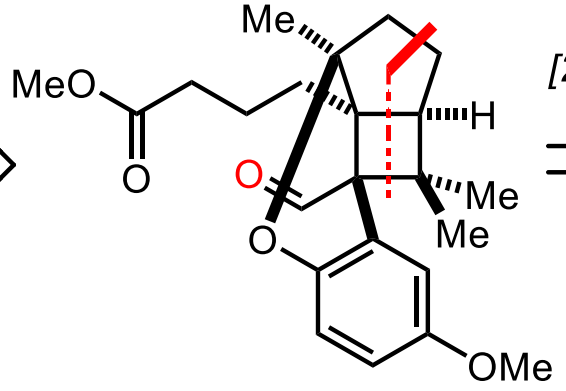
ganocin B (3)
from Ganoderma cochlear
structurally related to
AChE inhibitors

Rretrosynthetic Analysis



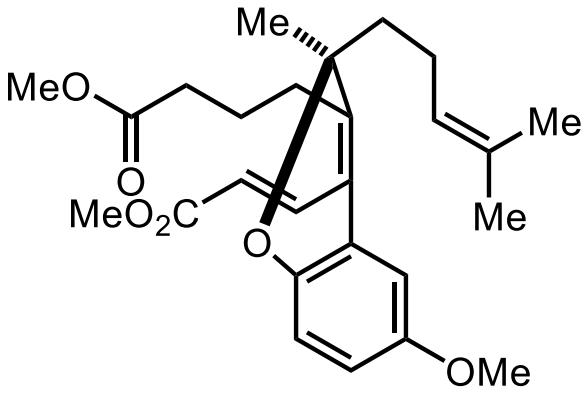
cochlearol B (2)

aldol condensation

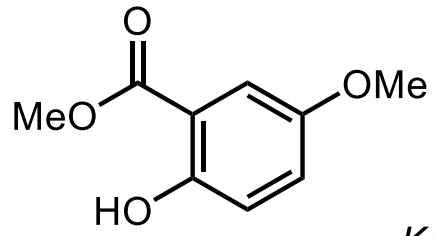


4

[2+2]-cycloaddition and ozonolysis

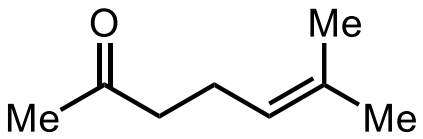


5



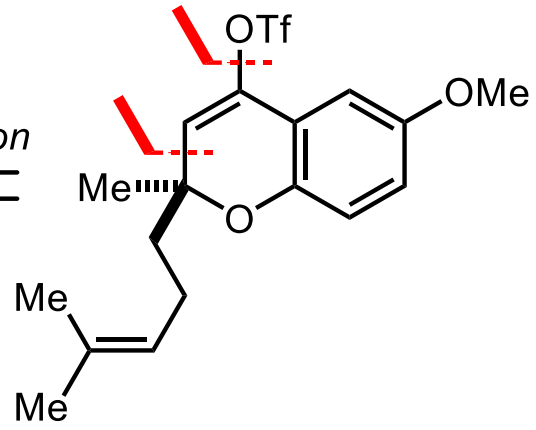
7

+



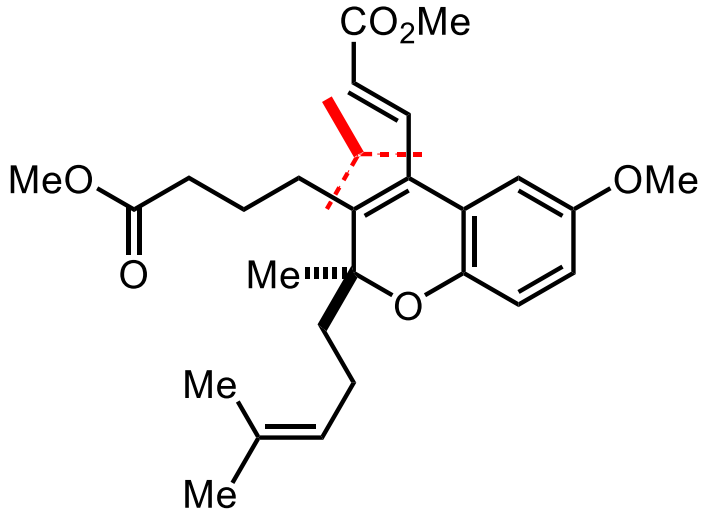
8

triflation/ Kabbe condensation



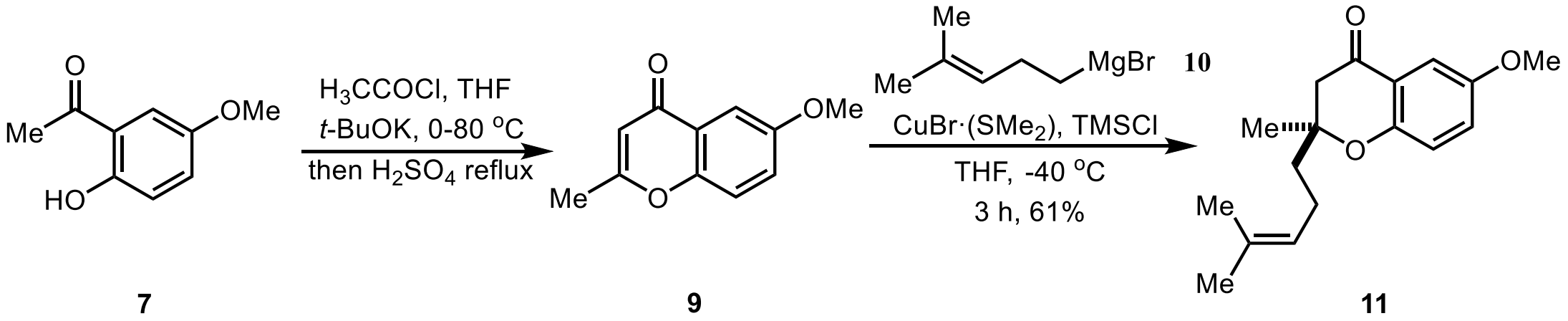
6

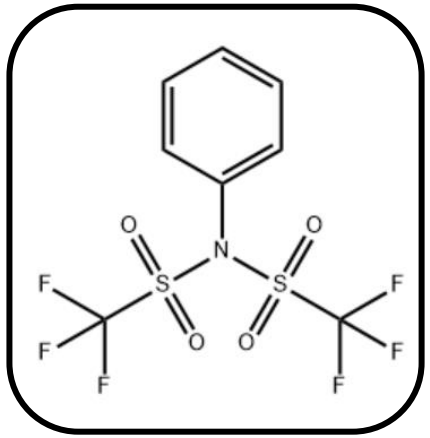
Catellani reaction



5

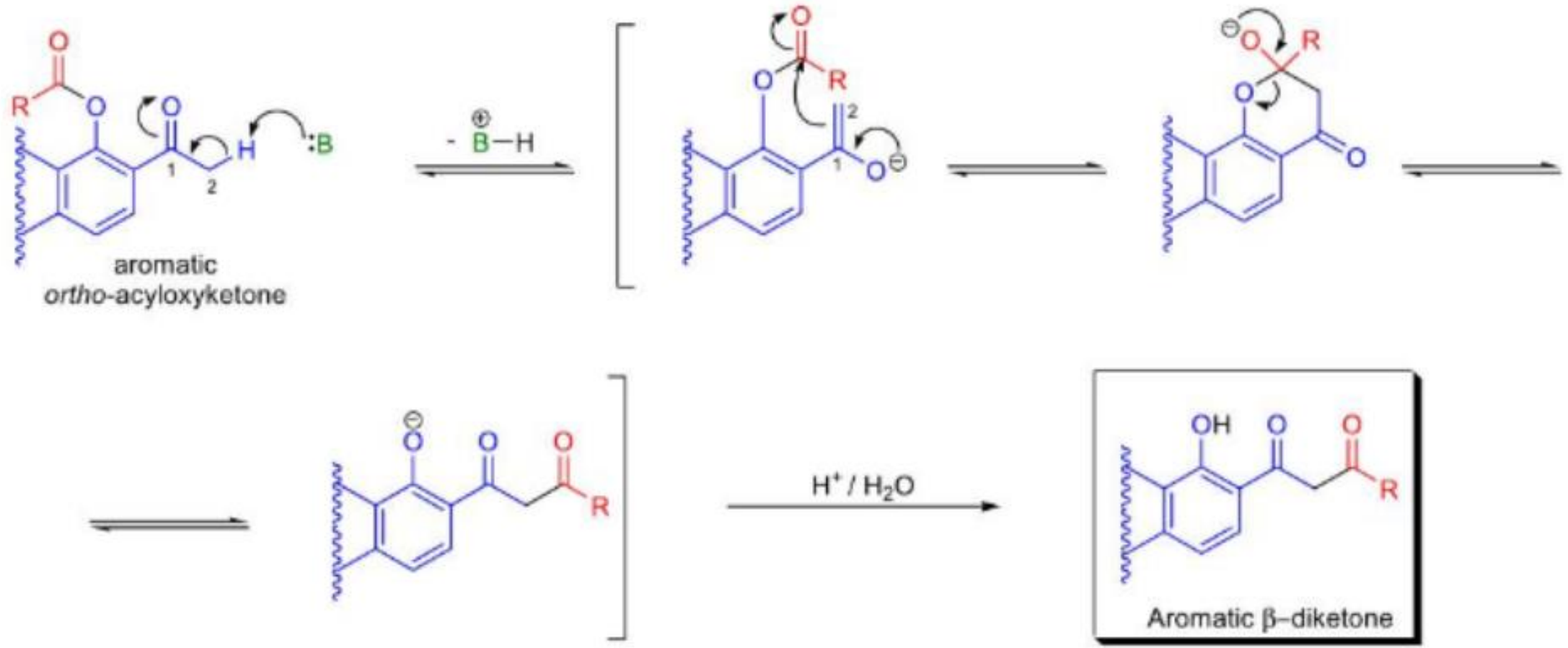
Initial Synthesis Strategy

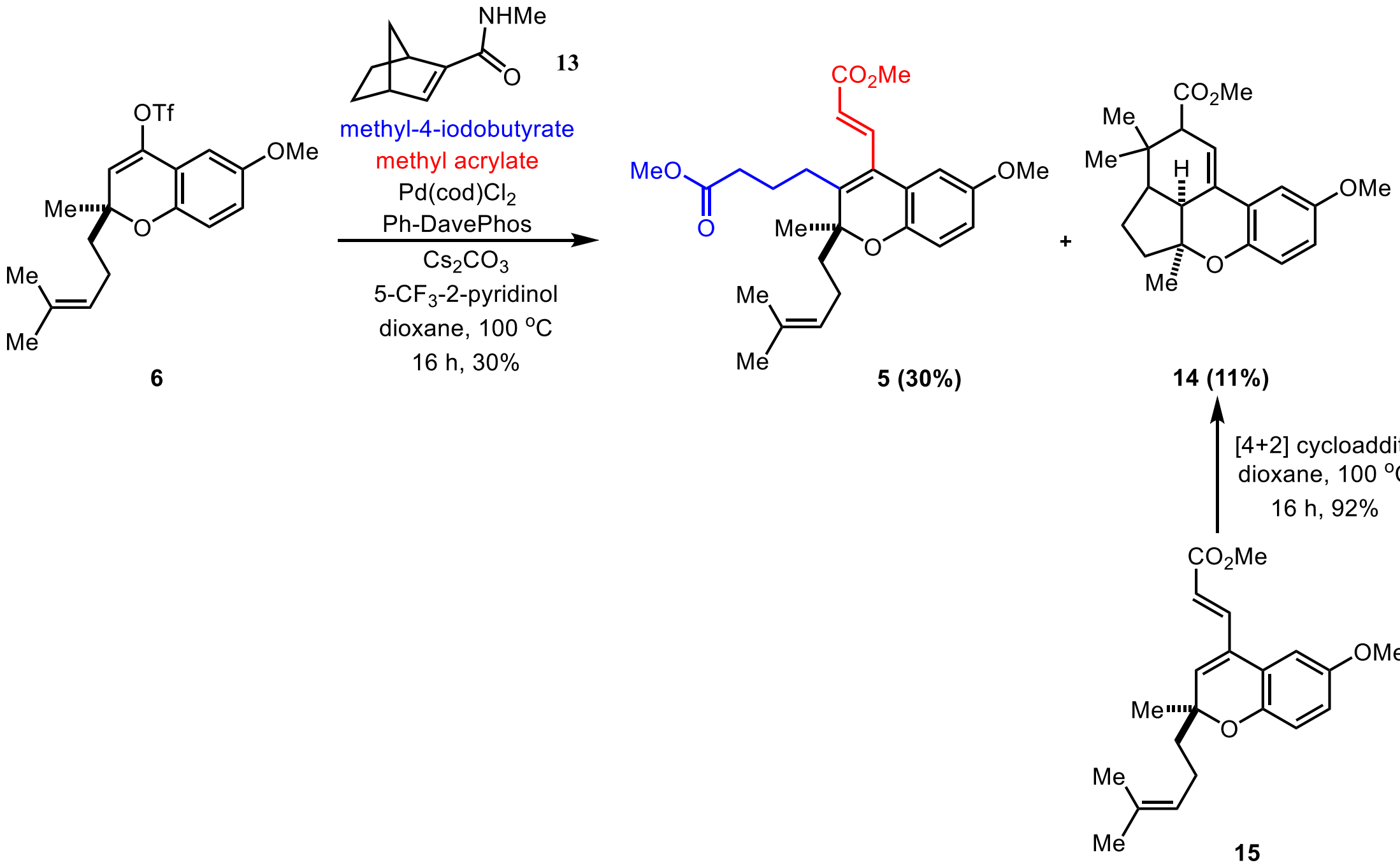




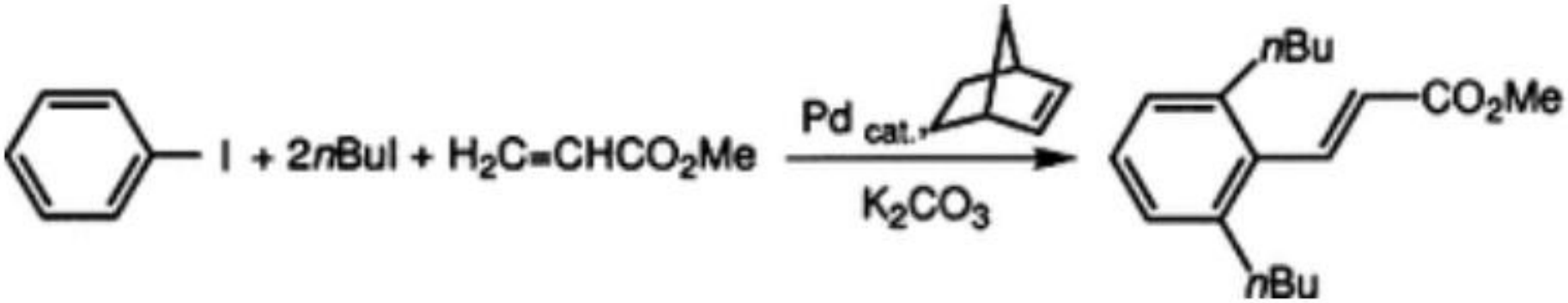
phenyltriflimide

Baker-Venkataraman Rearrangement

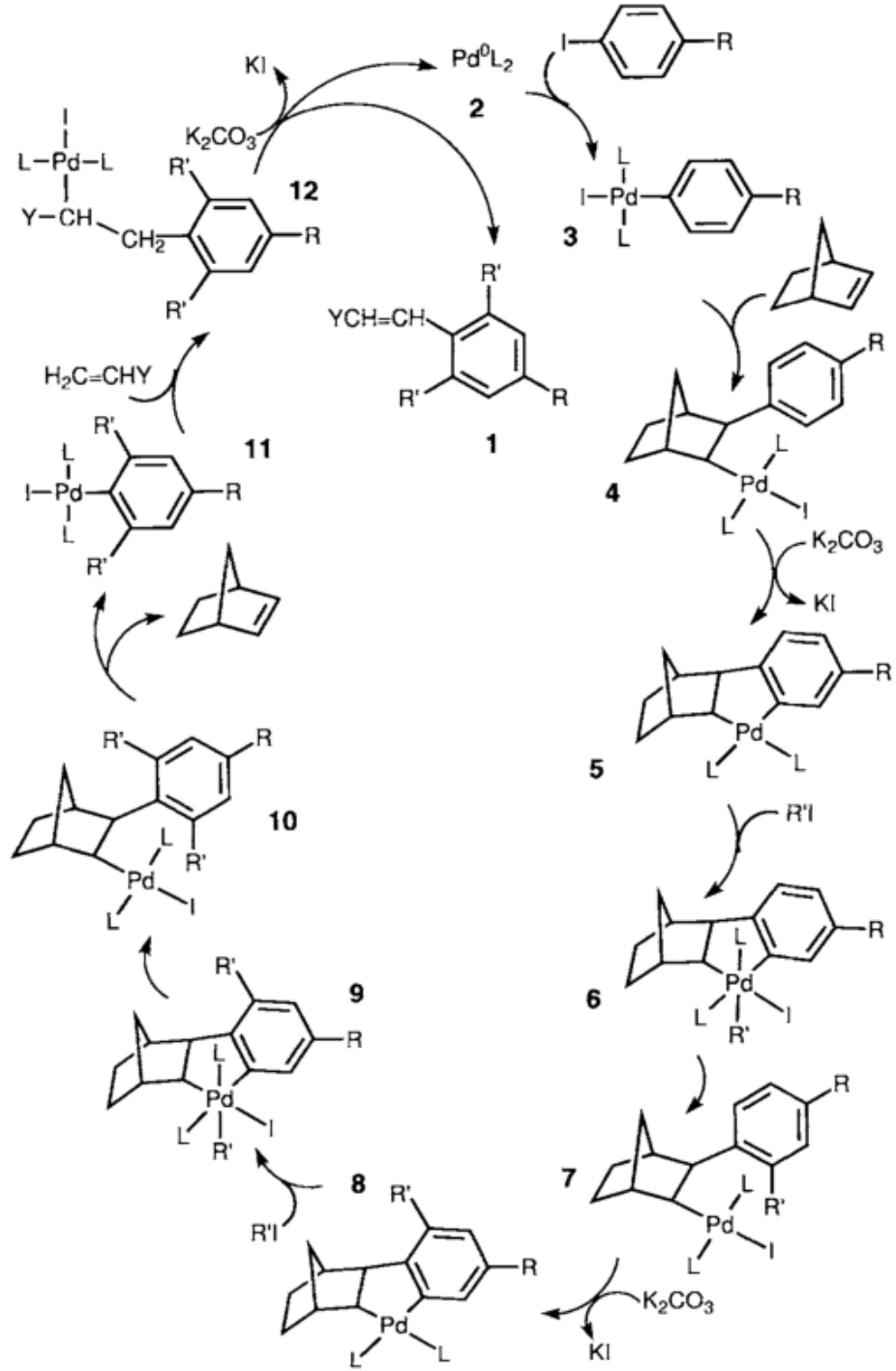


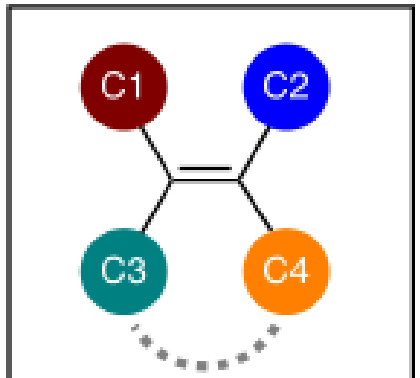

NHMe
O
13
OTf
OMe
Me
O
Me
Me
6
methyl-4-iodobutyrate
methyl acrylate
Pd(cod)Cl2
Ph-DavePhos
Cs2CO3
5-CF3-2-pyridinol
dioxane, 100 °C
16 h, 30%
CO2Me
MeO
O
OMe
Me
O
Me
Me
5 (30%)
+
CO2Me
Me
Me
H
OMe
O
Me
14 (11%)
[4+2] cycloaddition
dioxane, 100 °C
16 h, 92%
CO2Me
OMe
Me
O
Me
Me
15

Catellani Reaction

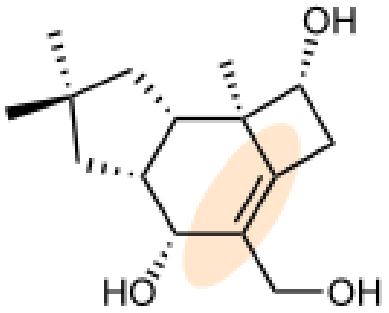


Angew. Chem. Int. Ed., **1997**, *36*, 119.

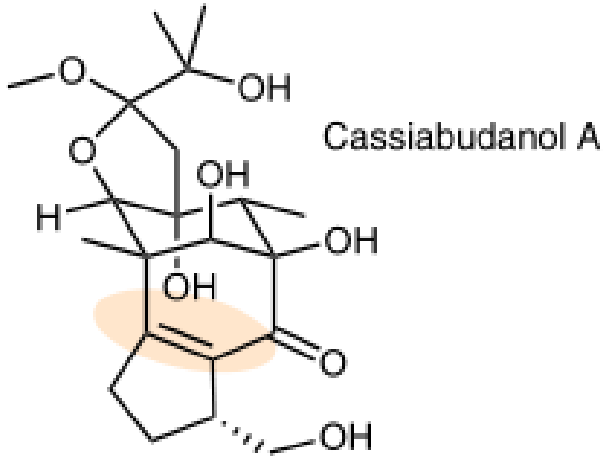

Pd0L2
2
I
R
L
I–Pd
L
R
3
R'
YCH=CH
R'
R
1
R
L
Pd
I
L
4
K2CO3
KI
R
Pd
L
L
5
R'I
R
L
Pd
L
R'
6
R
L
Pd
R'
L
I
7
R'
L
Pd
L
I
8
R'I
R'
L
Pd
L
I
9
R'
R
L
Pd
L
I
10
R'
R
L
Pd
L
R'
L
I
11
R'
L
I–Pd
L
R
R'
H2C=CHY
KI
K2CO3
12
I
L–Pd–L
Y–CH
CH2
R'
R
R'



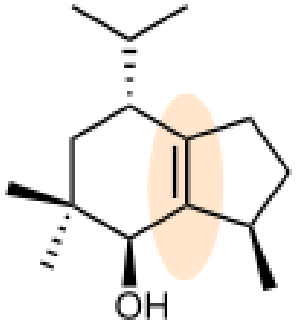
Unsymmetrical all-carbon tetrasubstituted alkene



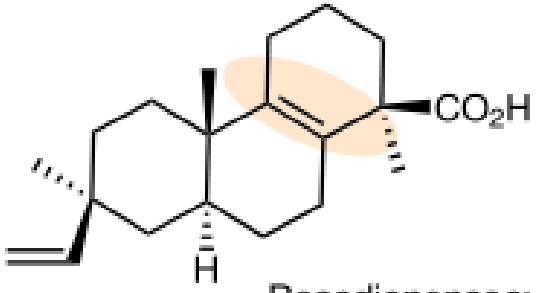
Illudol



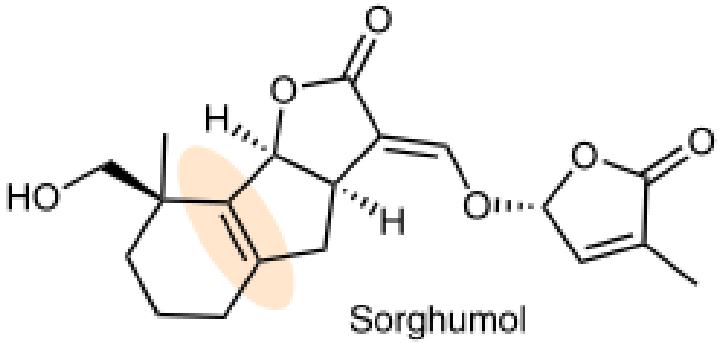
Cassiabudanol A



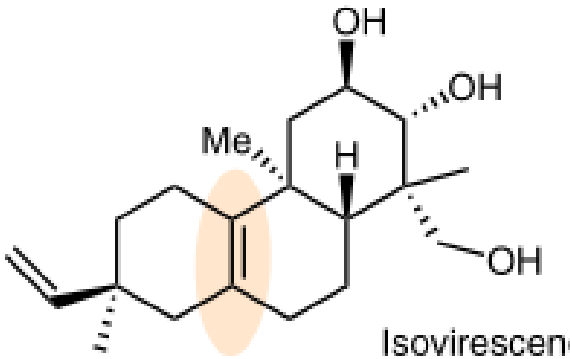
Brasilenol



Rosadienonsaeure

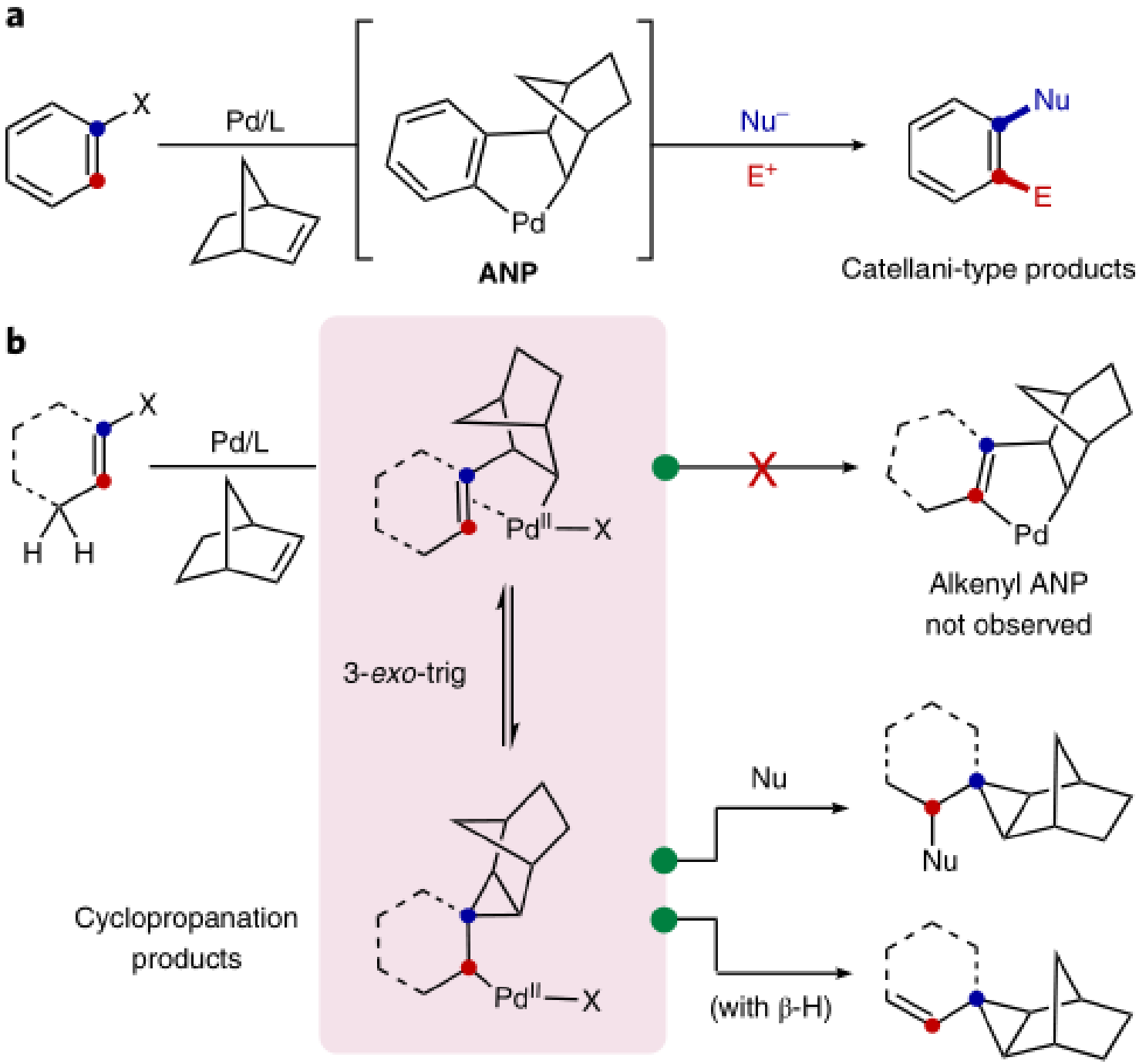


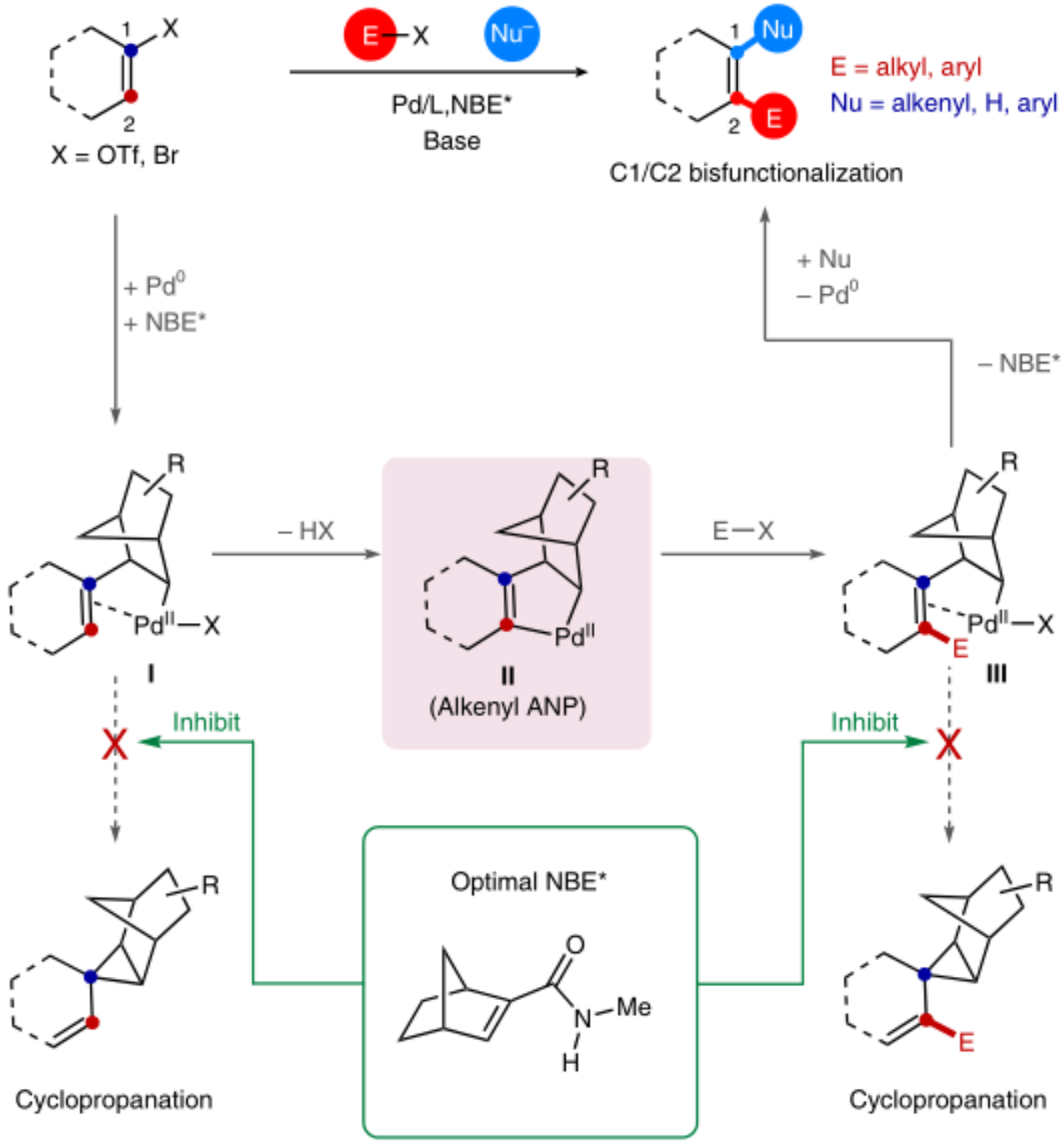
Sorghumol

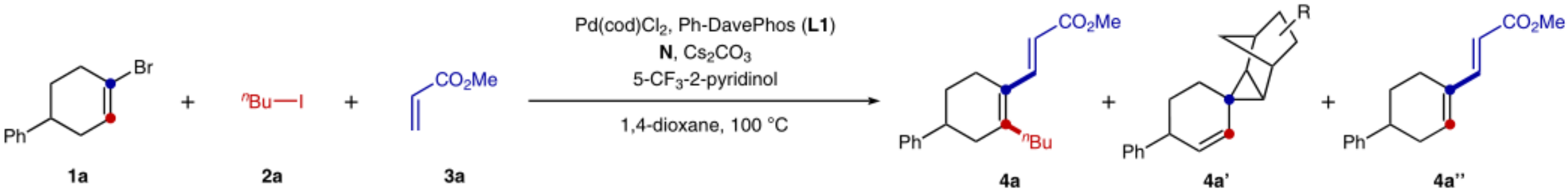


Isovirescenol A

Nat. Chem., **2019**, *11*, 1106.


a
X
Pd/L
Pd
ANP
Nu⁻
E⁺
Nu
E
Catellani-type products
b
X
H
H
Pd/L
Pd^II—X
3-exo-trig
Pd^II—X
Cyclopropanation
products
X
Pd
Alkenyl ANP
not observed
Nu
Nu
(with β-H)

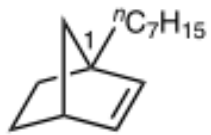

X = OTf, Br
E—X
Nu⁻
Pd/L,NBE*
Base
E = alkyl, aryl
Nu = alkenyl, H, aryl
C1/C2 bisfunctionalization
+ Pd⁰
+ NBE*
+ Nu
– Pd⁰
– NBE*
– HX
E—X
Pdᴵᴵ—X
I
II
(Alkenyl ANP)
III
Inhibit
Inhibit
Optimal NBE*
Me
N
H
O
Cyclopropanation
Cyclopropanation



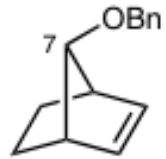
1a **2a** **3a** **4a** **4a'** **4a''**

N1

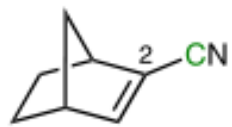
N2



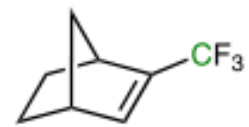
N3



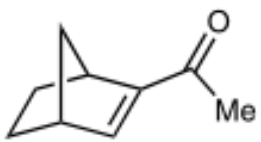
N4



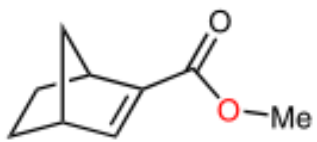
N5



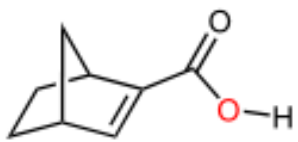
N6



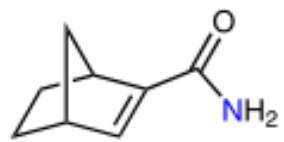
N7



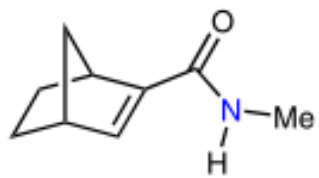
N8



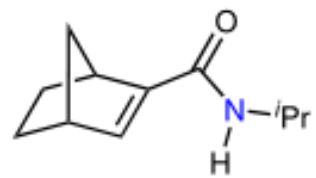
N9



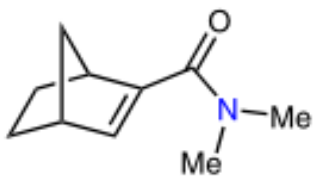
N10



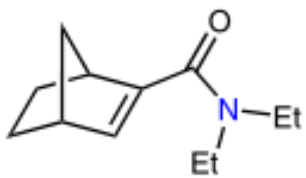
N11



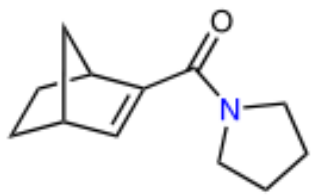
N12



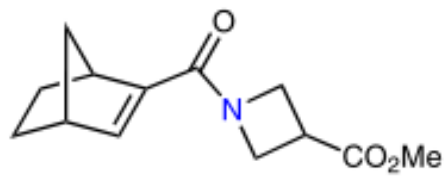
N13



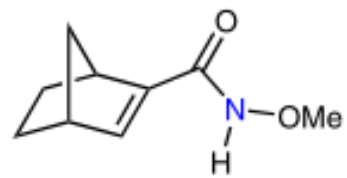
N14



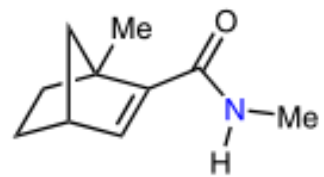
N15



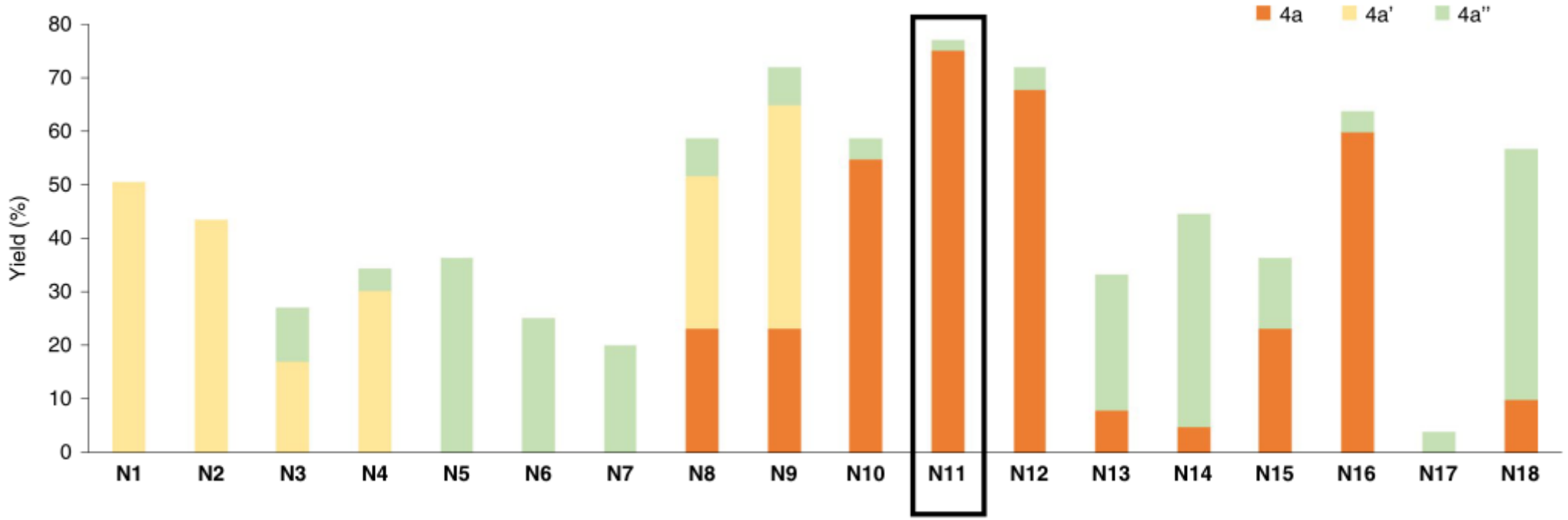
N16



N17[a]

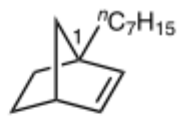


N18



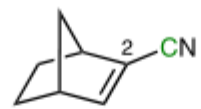

N1

N2

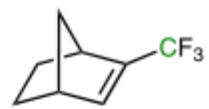


N3

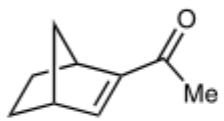
N4



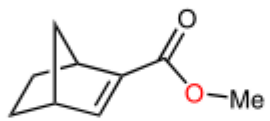
N5



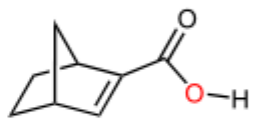
N6



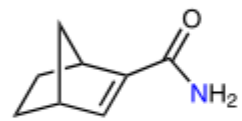
N7



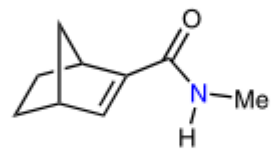
N8



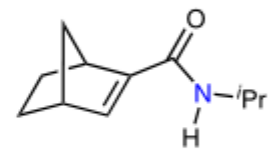
N9



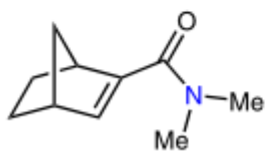
N10



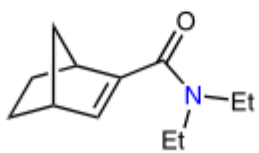
N11



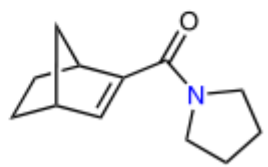
N12



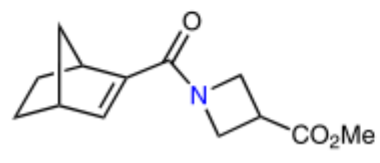
N13



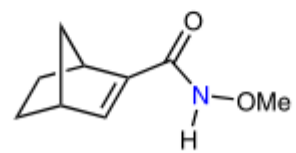
N14



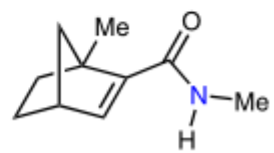
N15



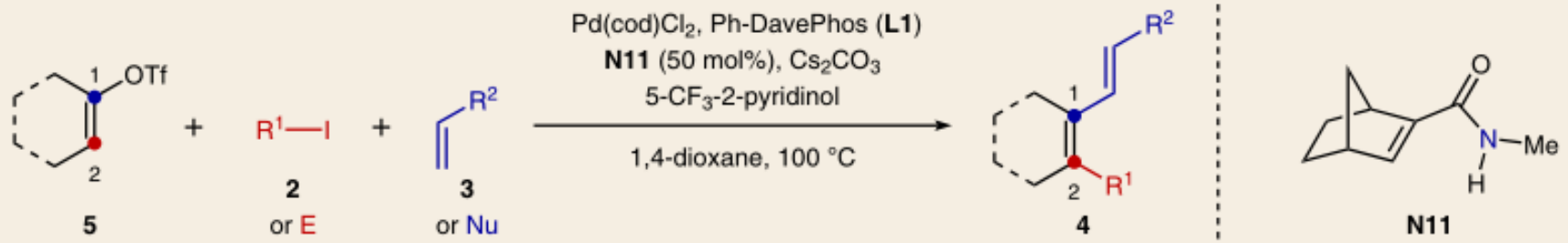
N16



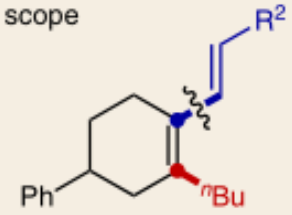
N17[a]



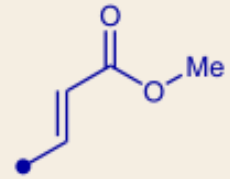
N18



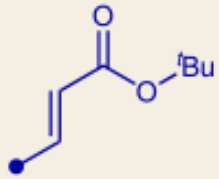
Olefin scope



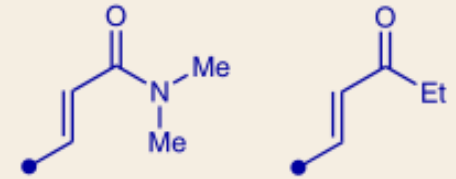
4a, 74%
71%[a]



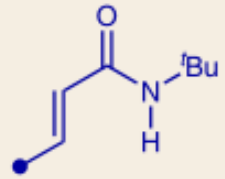
4b, 73%



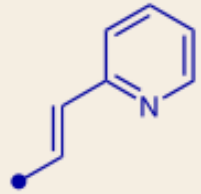
4c, 76%



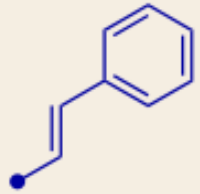
4d, 45%



4e, 75%
(X-ray obtained)

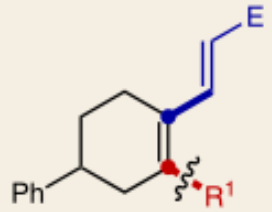


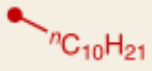
4f, 70%



4g, 48%

Alkyl iodide scope
E: CO_2Me





4h, 76%

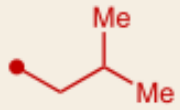
4i, 73%

4j, 68%

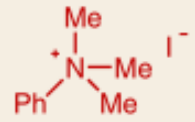
4k, 56%

4l, 76%

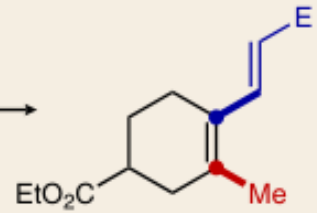
4m, 69%



4n, 40%

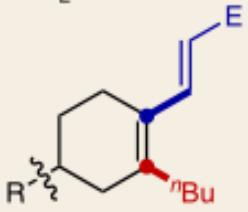


2o'

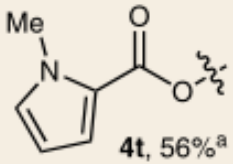


4o, 50%

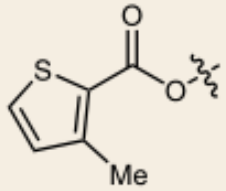
Alkenyl triflate scope
E: CO_2Me



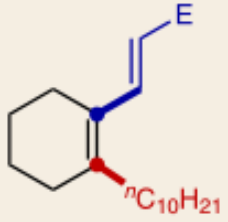
4p (R = ^{t}Bu), 65%
4q (R = CO_2Et), 64%
4r (R = CF_3), 77%
4s (R = OBz), 58%



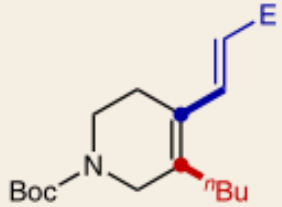
4t, 56%[a]



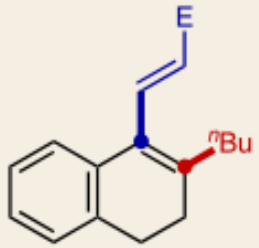
4u, 52%[a]



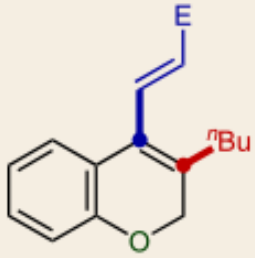
4v, 73%



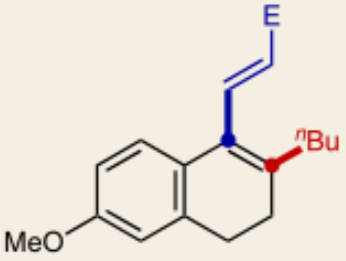
4w, 62%



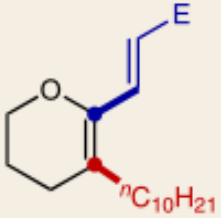
4x, 88%



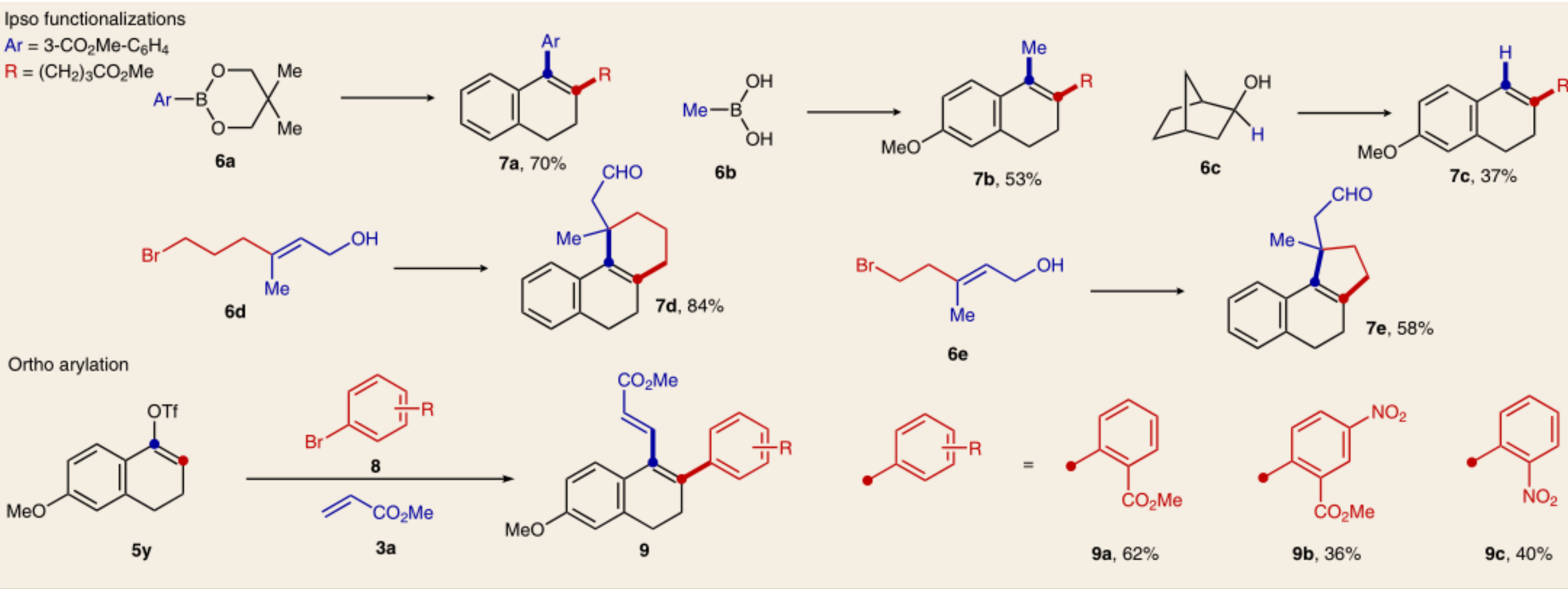
4y, 72%

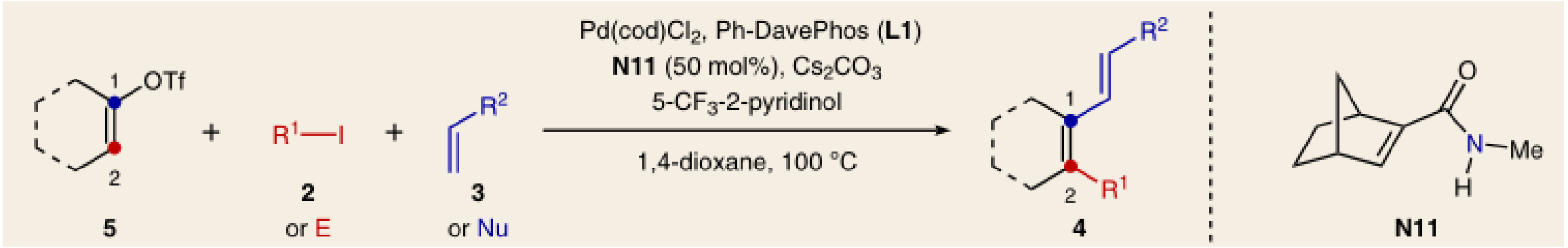


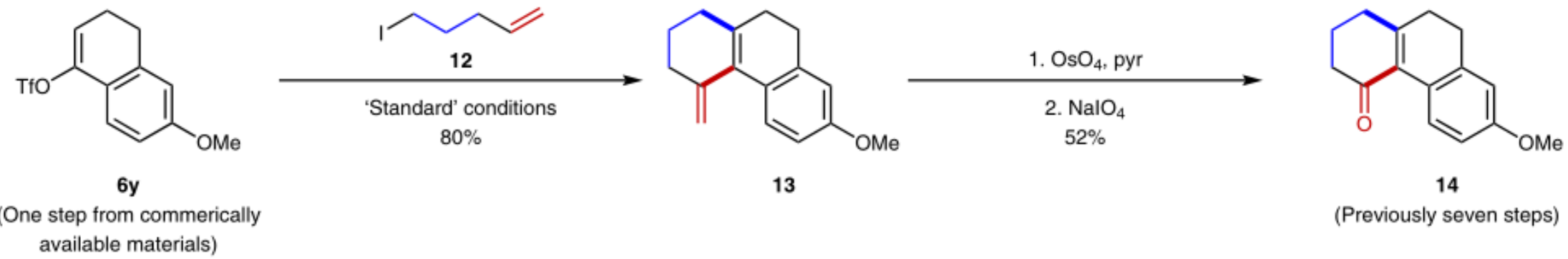
4z, 78%

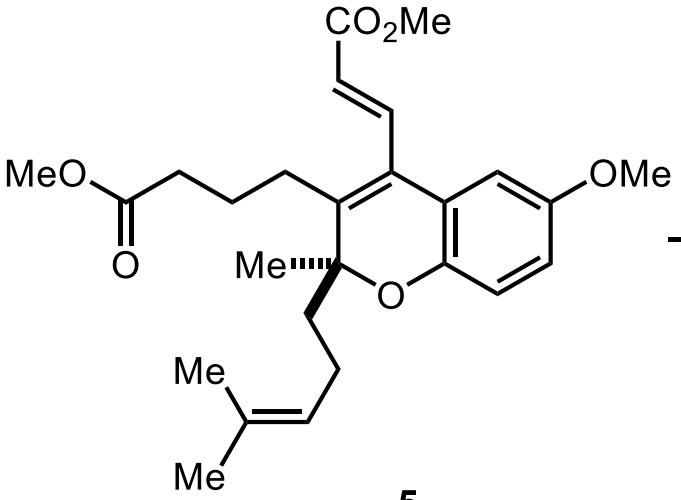


4aa, 55%


Ipso functionalizations
Ar = 3-CO2Me-C6H4
R = (CH2)3CO2Me
6a
7a, 70%
6b
7b, 53%
6c
7c, 37%
6d
7d, 84%
6e
7e, 58%
Ortho arylation
5y
8
3a
9
9a, 62%
9b, 36%
9c, 40%


1
OTf
2
5
+
R1—I
2
or E
+
R2
3
or Nu
Pd(cod)Cl2, Ph-DavePhos (L1)
N11 (50 mol%), Cs2CO3
5-CF3-2-pyridinol
1,4-dioxane, 100 °C
R2
1
2
R1
4
O
N
Me
H
N11

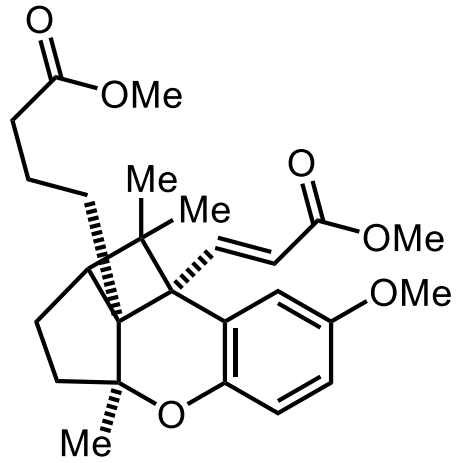

TfO
OMe
6y
(One step from commerically available materials)
I
12
'Standard' conditions
80%
OMe
13
1. OsO4, pyr
2. NaIO4
52%
O
OMe
14
(Previously seven steps)



5

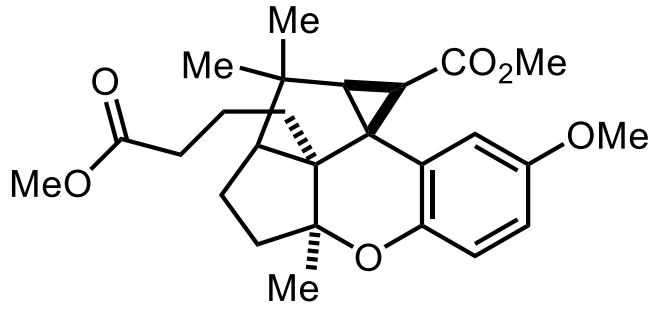
[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)](PF$_6$)

blue LEDs (427 nm)
MeCN, rt, 1 h, 85%

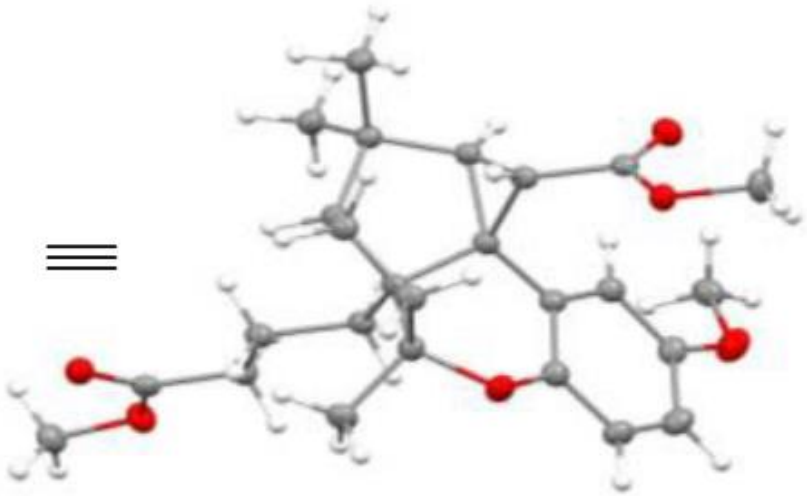


16 (not observed)

+

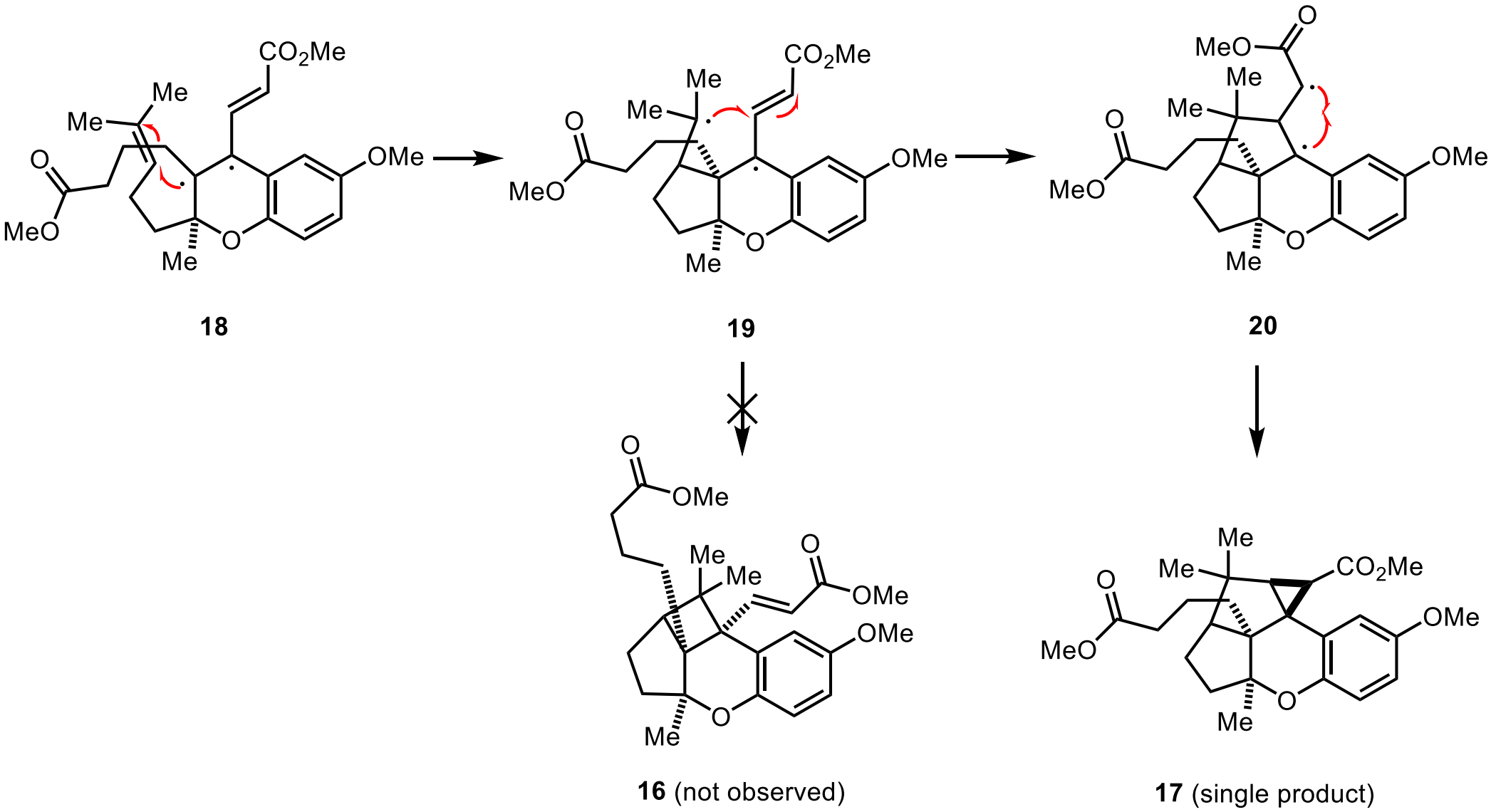


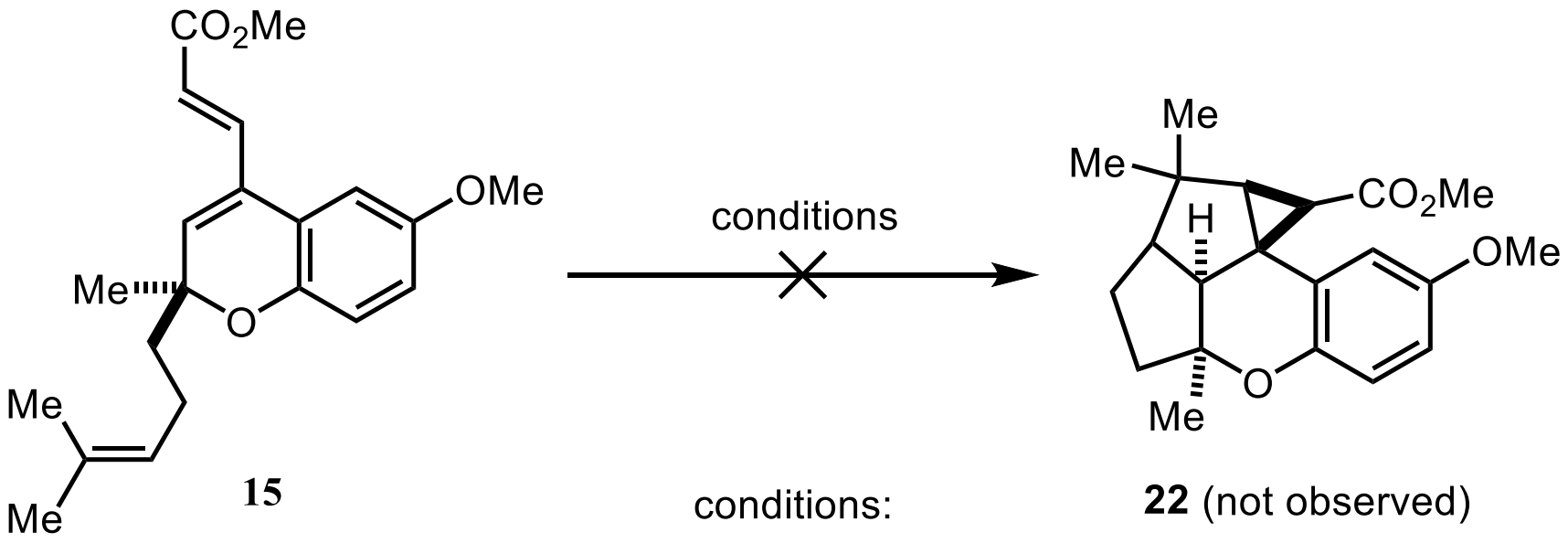
17 (single product)



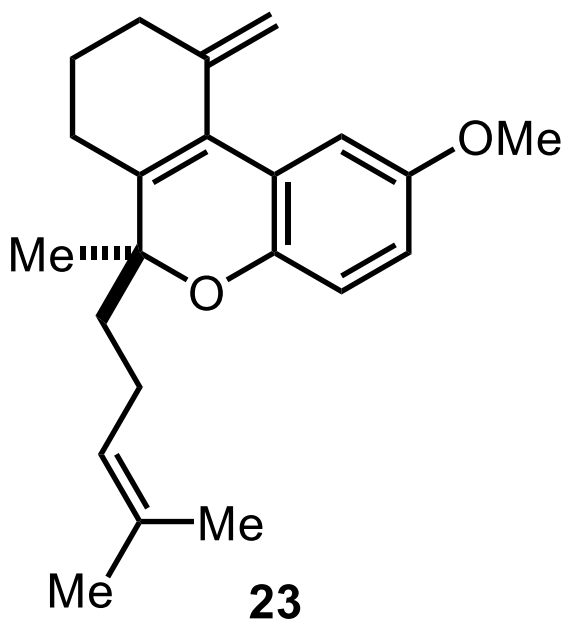
X-ray (**17**)

Mechanistic Hypothesis for the Formation of **17**




CO2Me
OMe
Me
O
Me
Me
15
conditions
Me
Me
H
CO2Me
OMe
O
Me
22 (not observed)
conditions:
[Ir(dF(CF3)ppy)2(dtbbpy)](PF6)
blue LEDs (427 nm)
MeCN, rt, 1 h
conditions
Me
Me
O
OMe
OMe
O
Me
21 (19%)
+
CO2Me
Me
Me
H
OMe
O
Me
14 (32%)

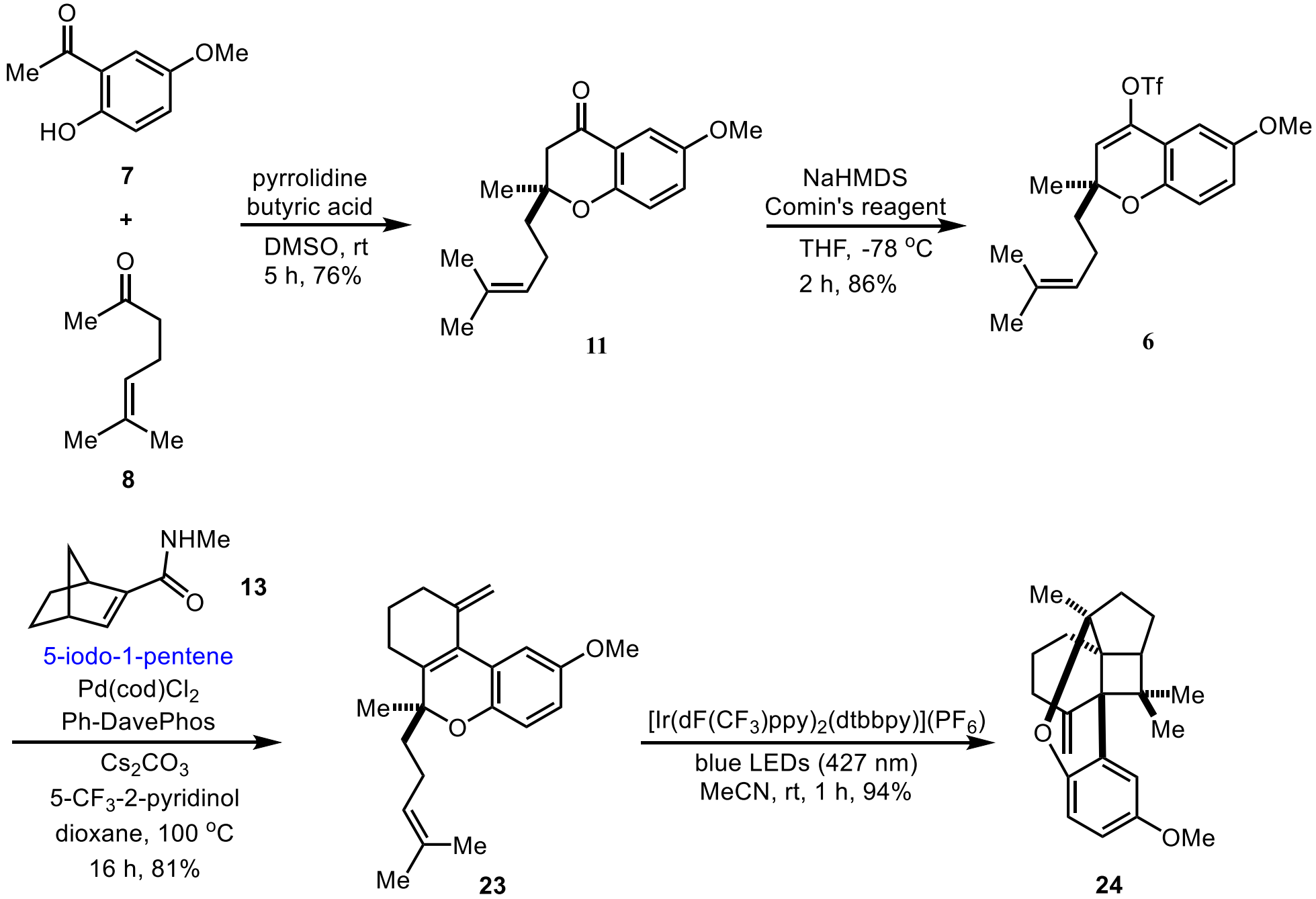
设计出新的中间体



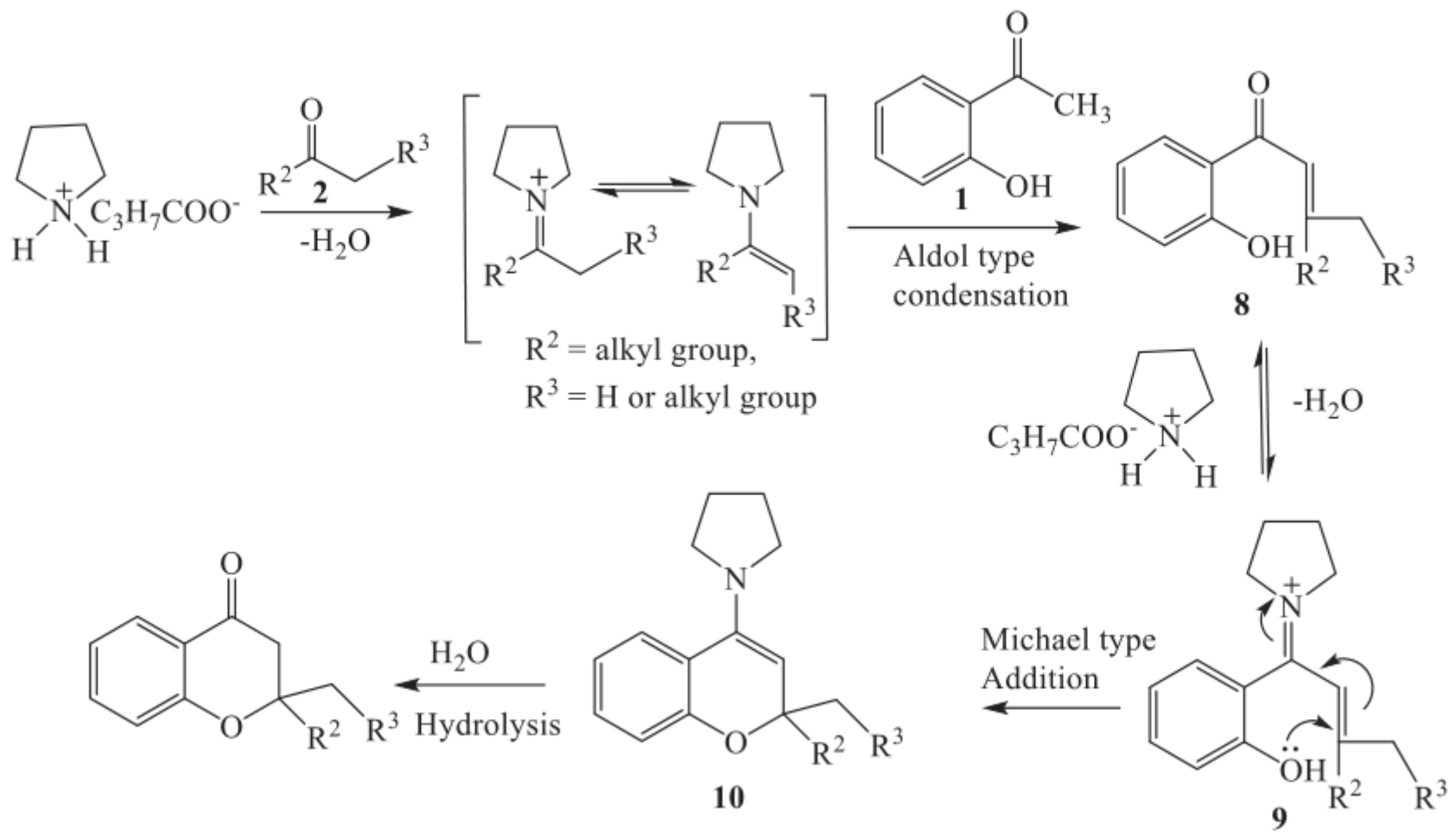
23

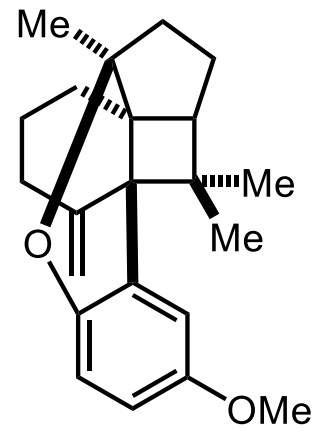
- 反式二烯避免了[4+2]环加成；
- 烯烃亲电性降低，避免了环丙烷中间体的生成；
- C环在[2+2]环加成前形成，避免了空间位阻影响环丁烷的生成。

EDBAC → **EDCBA**


O
Me
OMe
HO
7
+
O
Me
Me
Me
8
pyrrolidine
butyric acid
DMSO, rt
5 h, 76%
O
OMe
Me
O
Me
Me
11
NaHMDS
Comin's reagent
THF, -78 °C
2 h, 86%
OTf
OMe
Me
O
Me
Me
6
NHMe
O
13
5-iodo-1-pentene
Pd(cod)Cl2
Ph-DavePhos
Cs2CO3
5-CF3-2-pyridinol
dioxane, 100 °C
16 h, 81%
OMe
Me
O
Me
Me
23
[Ir(dF(CF3)ppy)2(dtbbpy)](PF6)
blue LEDs (427 nm)
MeCN, rt, 1 h, 94%
Me
Me
O
OMe
24

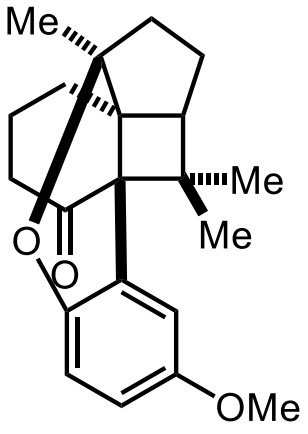
Kabbe Condensation





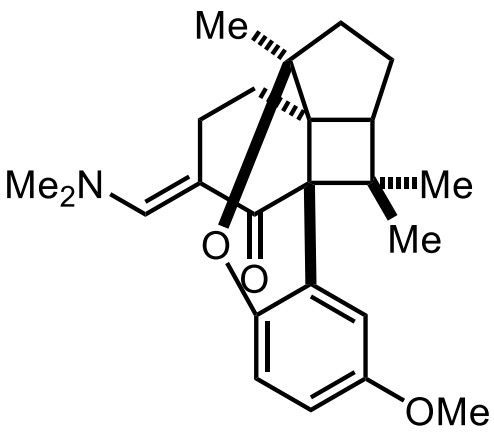
24

1. OsO_4, NMMO, citric acid
$Me_2CO/H_2O/tBuOH$, rt, 16 h
2. $NaIO_4$, THF/H_2O, rt, 2 h
40% (2 steps)



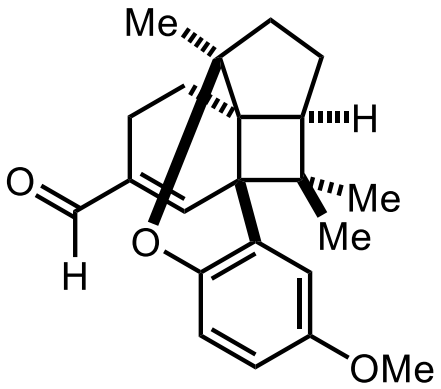
25

DMF-DMA
DMF, 100 °C
20 h, 86%



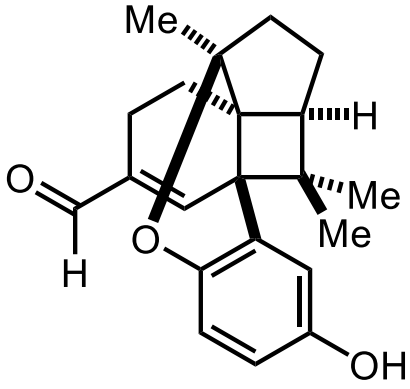
26

1. Tf_2O, 2,6-lutidine
DCM, -78 °C
30 min
2. $Pd(PPh_3)_4$, Et_3N
HCO_2H, DMF, rt, 4 h
76% (2 steps)

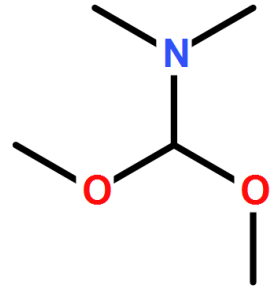


27

1. $NaBH_4$, MeOH
0 °C, 30 min
2. MeMgBr, neat
160 °C, 1 h
3. $(COCl)_2$, DMSO
Et_3N
25% (3 steps)



cochlearol B (2)



DMF-DMA