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

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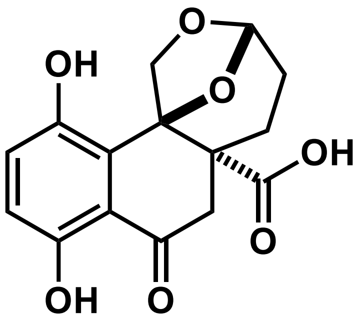
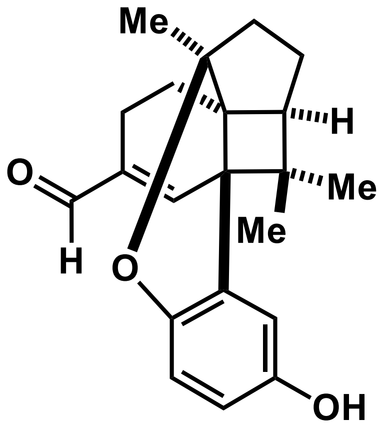
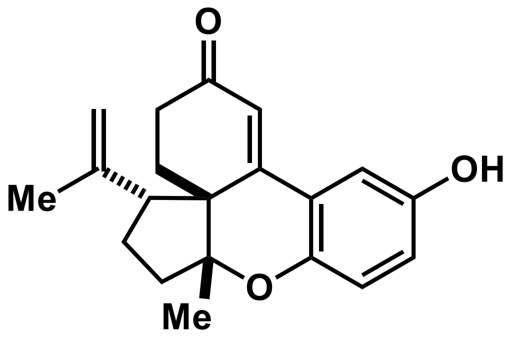
A. Selected Meroterpenoids Isolated from *Ganoderma cochlear*



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

***Ganoderma* meroterpenoids including cochlearol B (2).**

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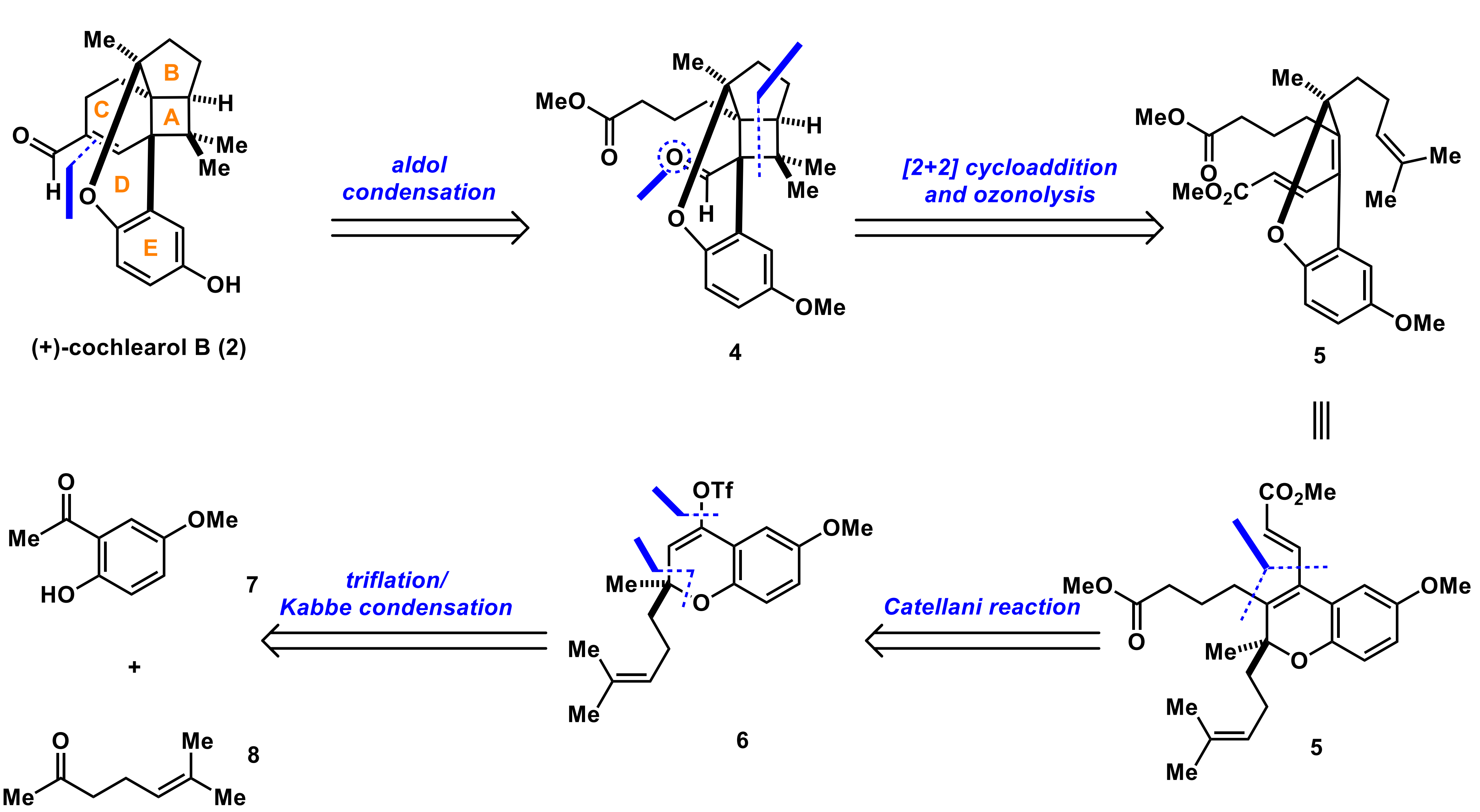
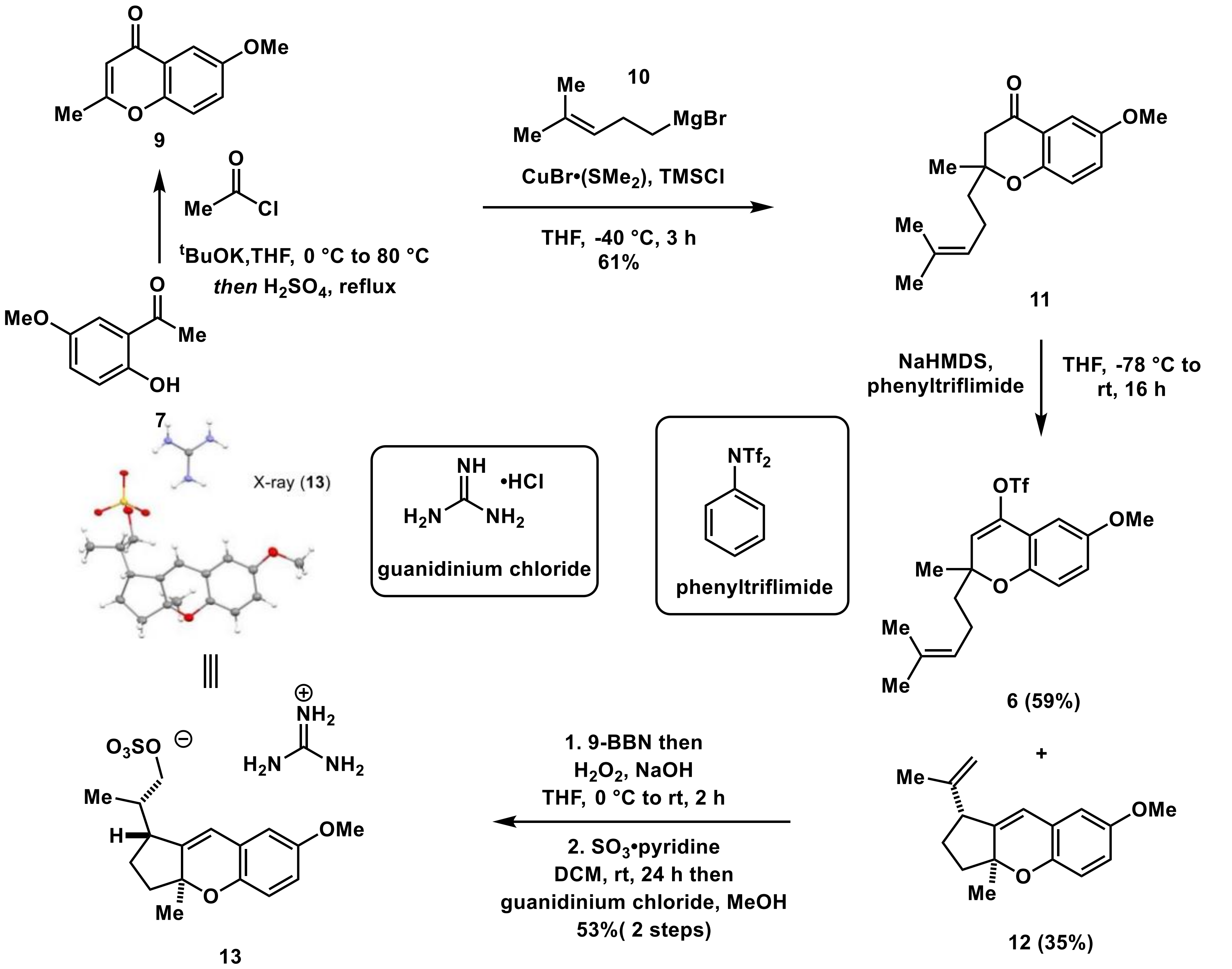
B. Retrosynthetic Strategy Towards Cochlearol B (2)



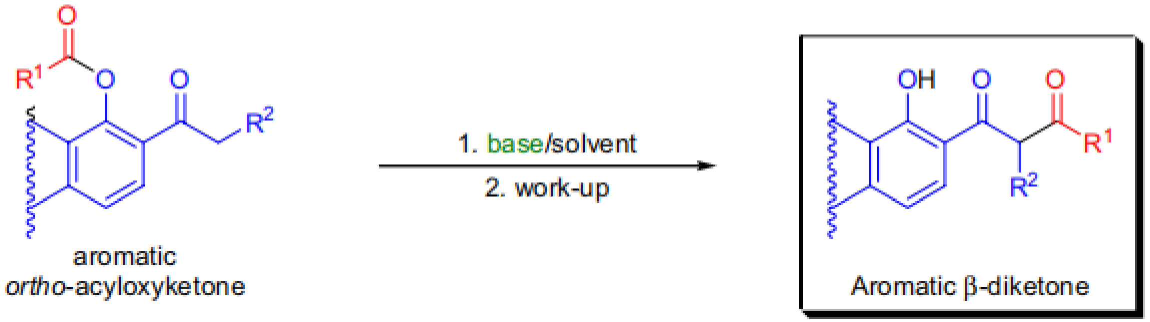
Retrosynthetic strategy towards cochlearol B (2) relying on Catellani and [2+2] cycloaddition reactions. Proceeds through an EDBAC ring formation sequence.



OMe
Me
9
O
Me
Cl
tBuOK,THF, 0 °C to 80 °C
then H2SO4, reflux
MeO
Me
OH
7
Me
10
MgBr
CuBr•(SMe2), TMSCl
THF, -40 °C, 3 h
61%
11
NaHMDS,
phenyltriflimide
THF, -78 °C to
rt, 16 h
OTf
6 (59%)
+
12 (35%)
X-ray (13)
NH
•HCl
H2N
NH2
guanidinium chloride
NTf2
phenyltriflimide
1. 9-BBN then
H2O2, NaOH
THF, 0 °C to rt, 2 h
2. SO3•pyridine
DCM, rt, 24 h then
guanidinium chloride, MeOH
53%(2 steps)
O3SO
H
13

BAKER-VENKATARAMAN REARRANGEMENT

(References are on page 542)



R^1 = alkyl, aryl, NH_2; R^2 = alkyl, aryl; base: KOH, KO*t*-Bu, NaH, Na metal, KH, C_5H_5N

Mechanism: [18-22]

In the first step of the mechanism, the aromatic ketone is deprotonated at the α-carbon and an enolate is formed. This nucleophile attacks the carbonyl group of the acyloxy moiety intramolecularly to form a tetrahedral intermediate that subsequently breaks down to form the aromatic β-diketone.

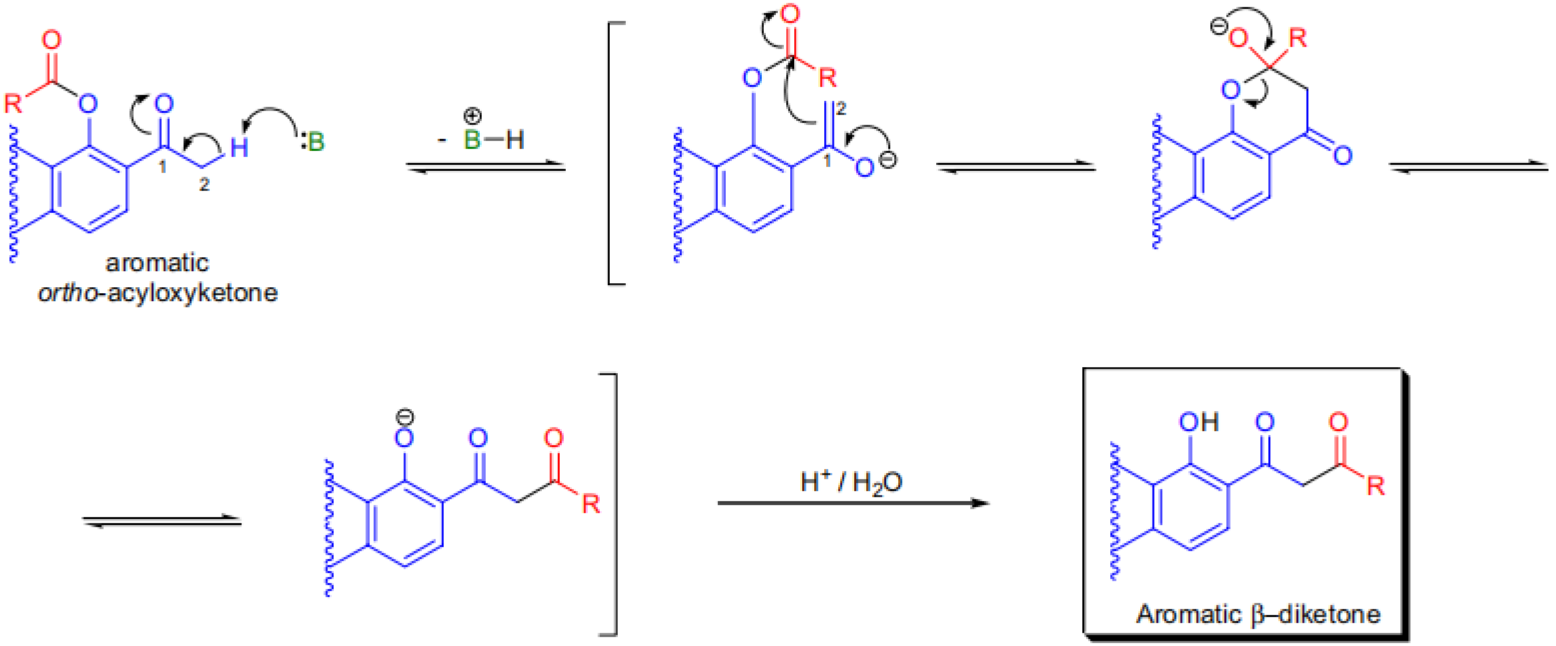
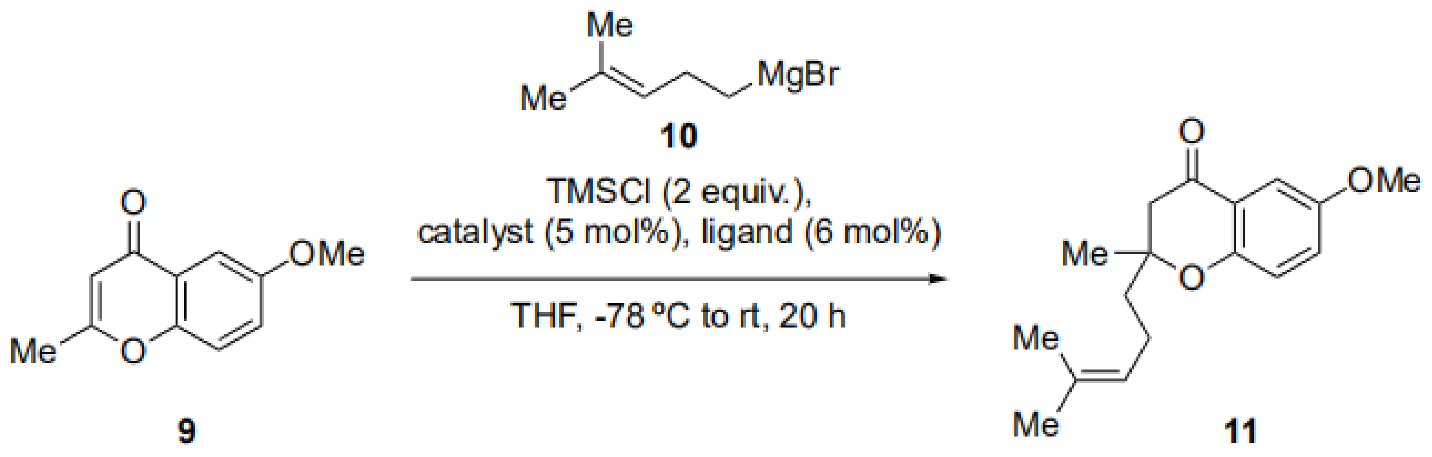
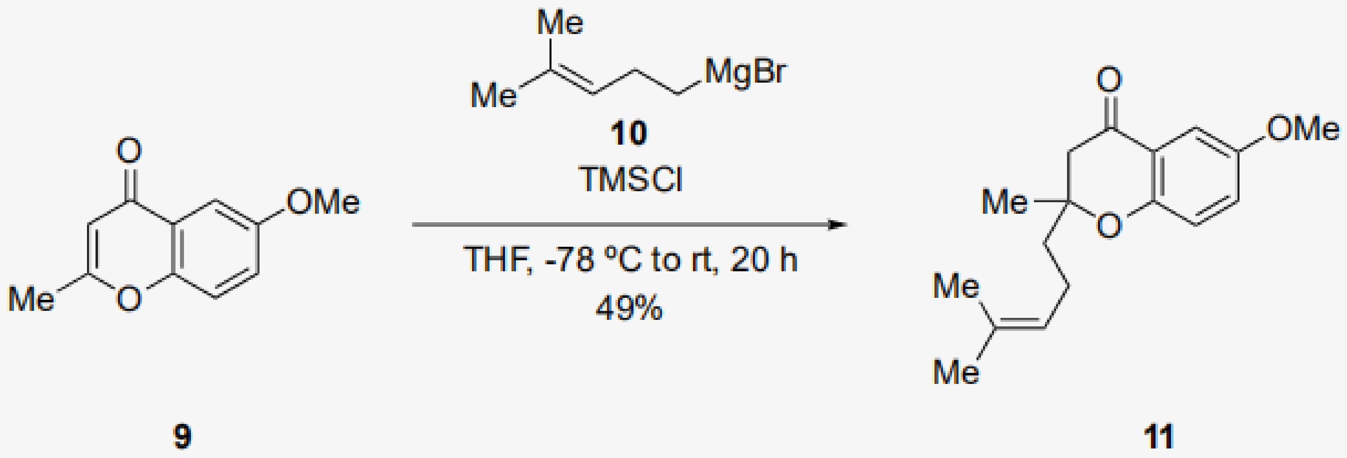


Table S1. (A) Evaluation of asymmetric conjugate addition conditions. (B) Control reaction without copper.

A. Conditions evaluated for an asymmetric copper-catalyzed conjugate addition



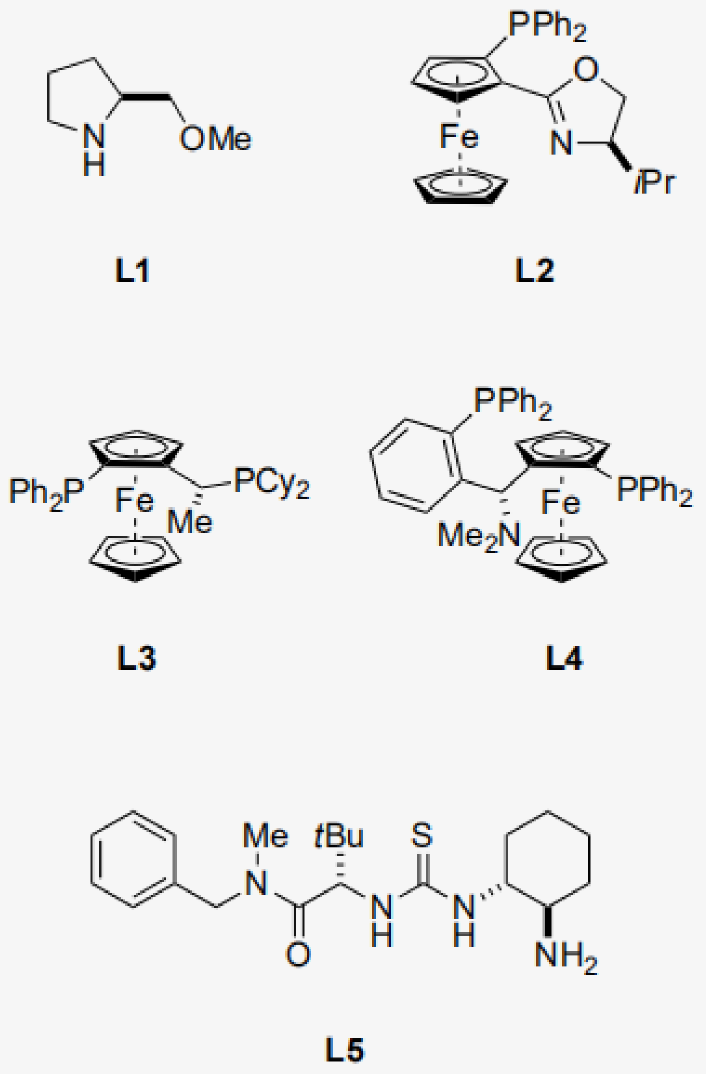
B. Background reactivity likely responsible for racemic product observed



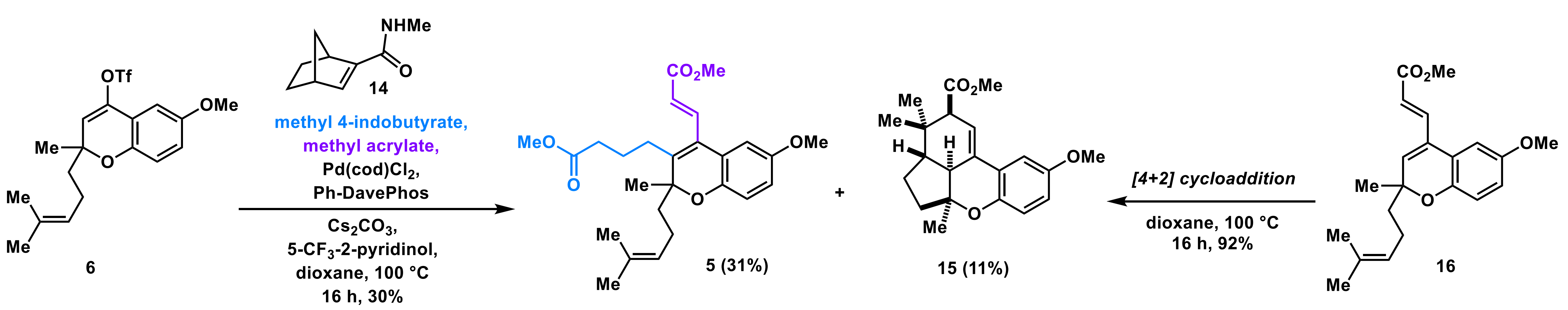
Entry	Catalyst	Ligand	ee (%)
1	CuBr·(SMe$_2$)	L1	0
2	CuI	L1	0
3	CuBr·(SMe$_2$)	L2	0
4	CuBr·(SMe$_2$)	L3	0
5	CuI	L4	0
6	CuBr·(SMe$_2$)	L5	0
7[a]	CuBr·(SMe$_2$)	L1	0
8[a]	CuI	L1	0
9[a]	CuBr·(SMe$_2$)	L2	0
10[a]	CuI	L2	0
11[a]	CuBr·(SMe$_2$)	L3	0
12[a]	CuI	L3	0
13[a]	CuBr·(SMe$_2$)	L4	0
14[a]	CuI	L4	0

[a] Reaction performed without TMSCl

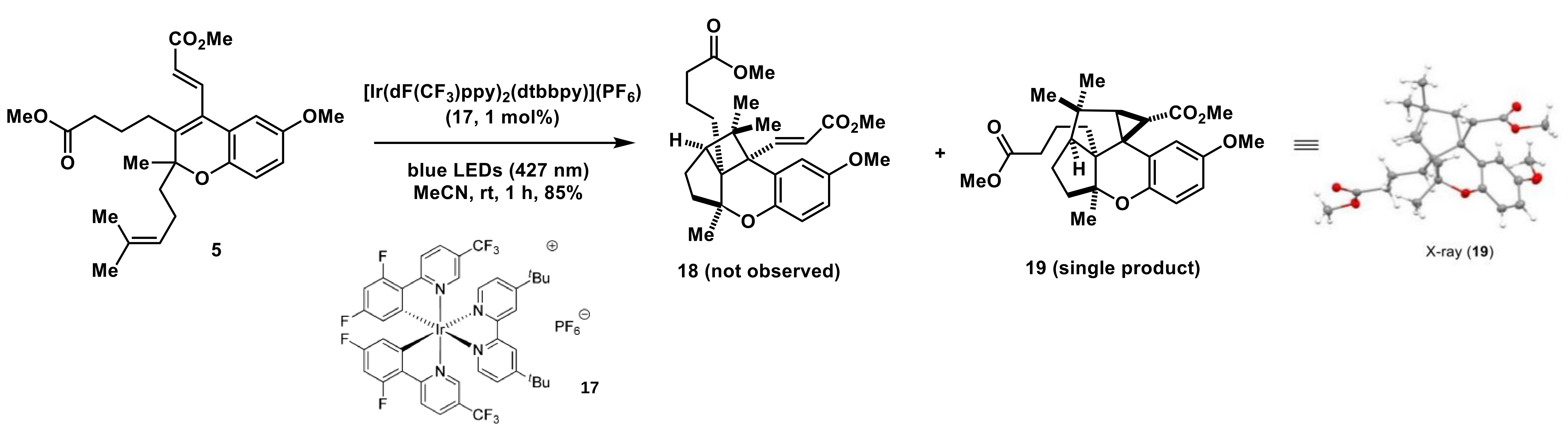
Ligands:



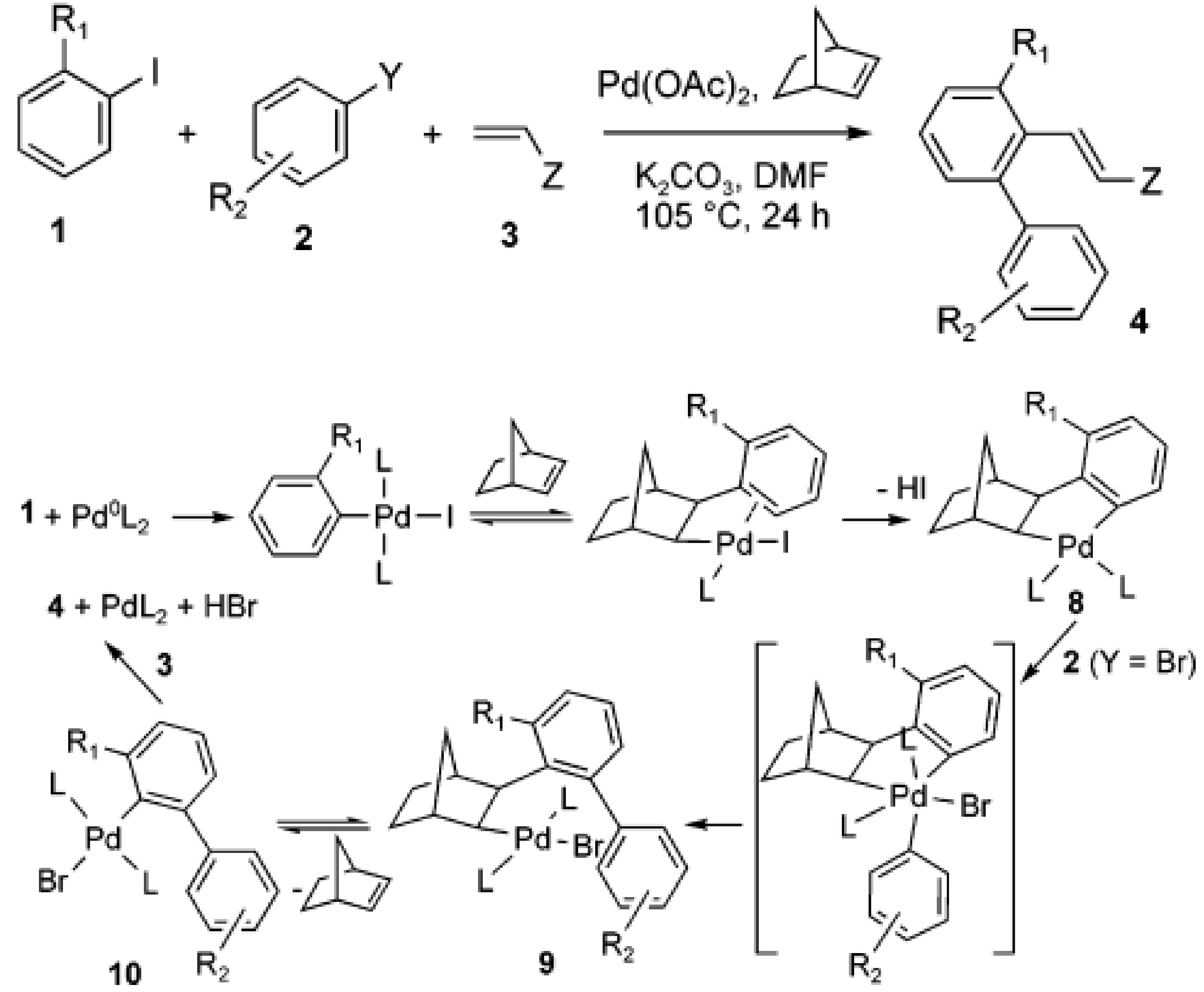
A. First Generation Catellani Approach: Challengens due to Competing [4+2] Cycloaddition



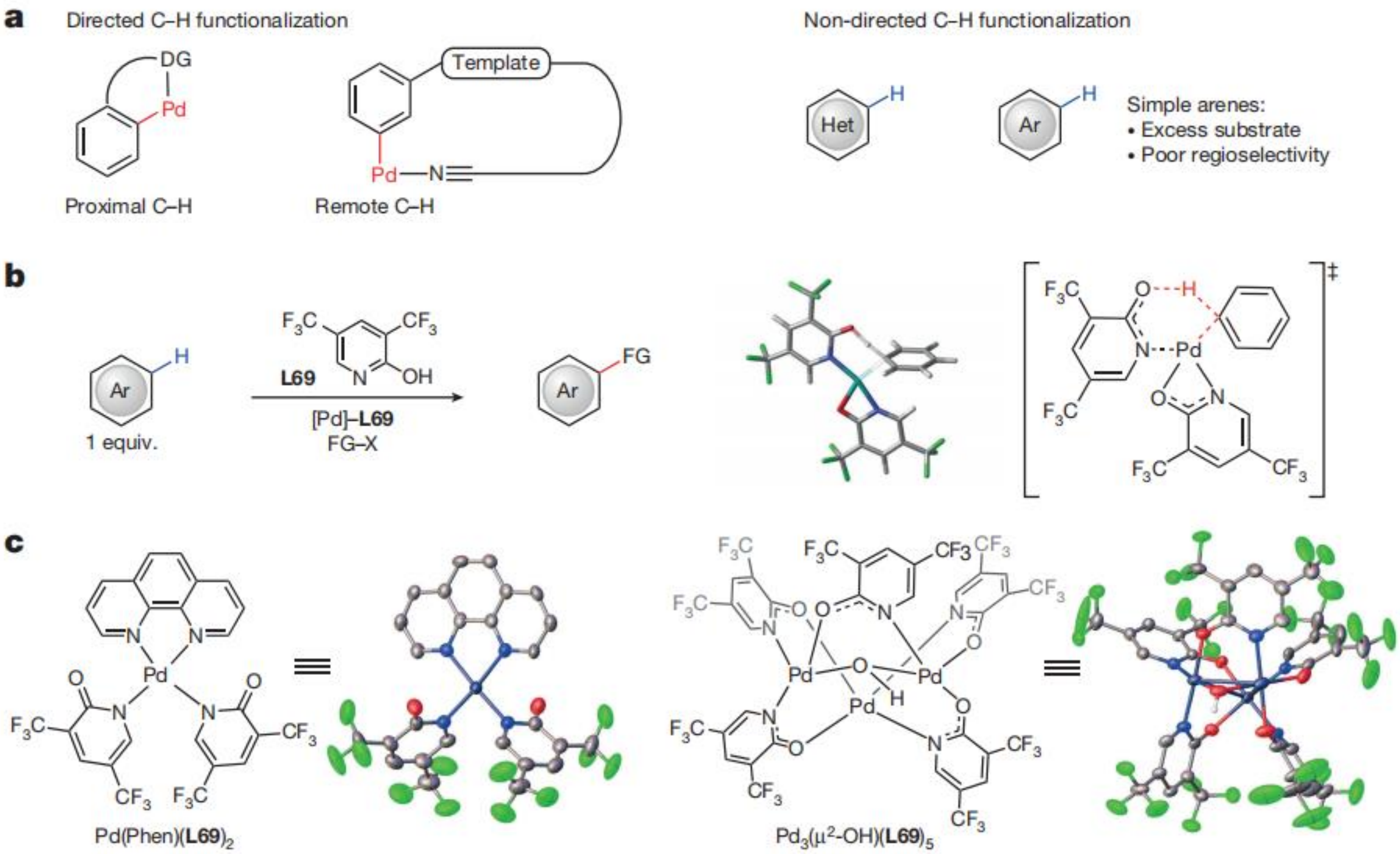
B. [2+2] Cycloaddition: Challenges due to Competing Cyclopropanation



Catellani Reaction

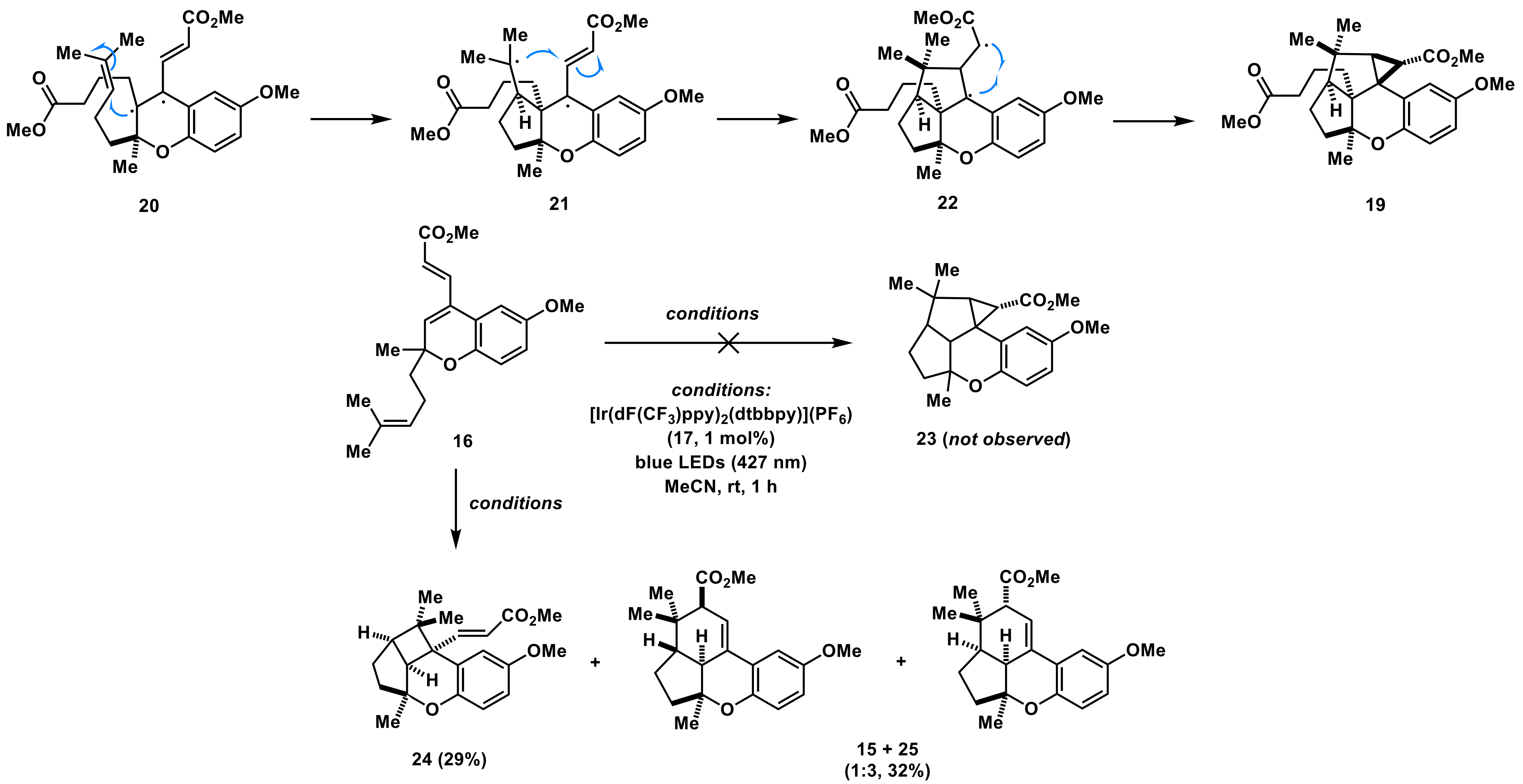


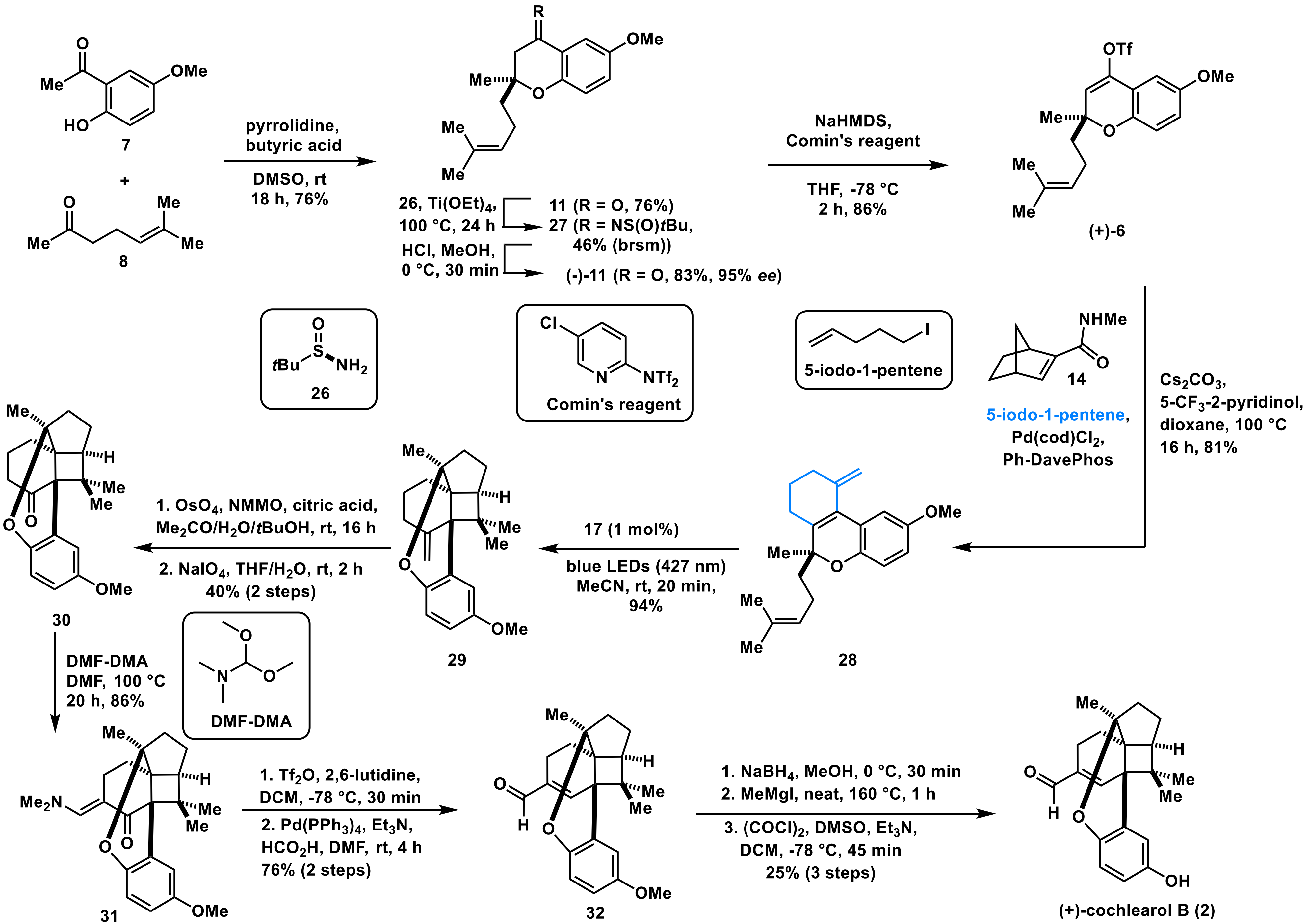
J. Am. Chem. Soc., **2004**, *126*, 78.



Nature, **2017**, *551*, 489.

C. Mechanistic Hypothesis for the Formation of 19:





7
8
pyrrolidine, butyric acid
DMSO, rt
18 h, 76%
26, Ti(OEt)4, 100 °C, 24 h
11 (R = O, 76%)
27 (R = NS(O)tBu, 46% (brsm))
HCl, MeOH, 0 °C, 30 min
(-)-11 (R = O, 83%, 95% ee)
NaHMDS, Comin's reagent
THF, -78 °C
2 h, 86%
(+)-6
26
Comin's reagent
5-iodo-1-pentene
14
5-iodo-1-pentene, Pd(cod)Cl2, Ph-DavePhos
Cs2CO3, 5-CF3-2-pyridinol, dioxane, 100 °C
16 h, 81%
28
17 (1 mol%)
blue LEDs (427 nm)
MeCN, rt, 20 min, 94%
29
1. OsO4, NMMO, citric acid, Me2CO/H2O/tBuOH, rt, 16 h
2. NaIO4, THF/H2O, rt, 2 h
40% (2 steps)
30
DMF-DMA
DMF, 100 °C
20 h, 86%
DMF-DMA
31
1. Tf2O, 2,6-lutidine, DCM, -78 °C, 30 min
2. Pd(PPh3)4, Et3N, HCO2H, DMF, rt, 4 h
76% (2 steps)
32
1. NaBH4, MeOH, 0 °C, 30 min
2. MeMgI, neat, 160 °C, 1 h
3. (COCl)2, DMSO, Et3N, DCM, -78 °C, 45 min
25% (3 steps)
(+)-cochlearol B (2)

Kabbe Condensation

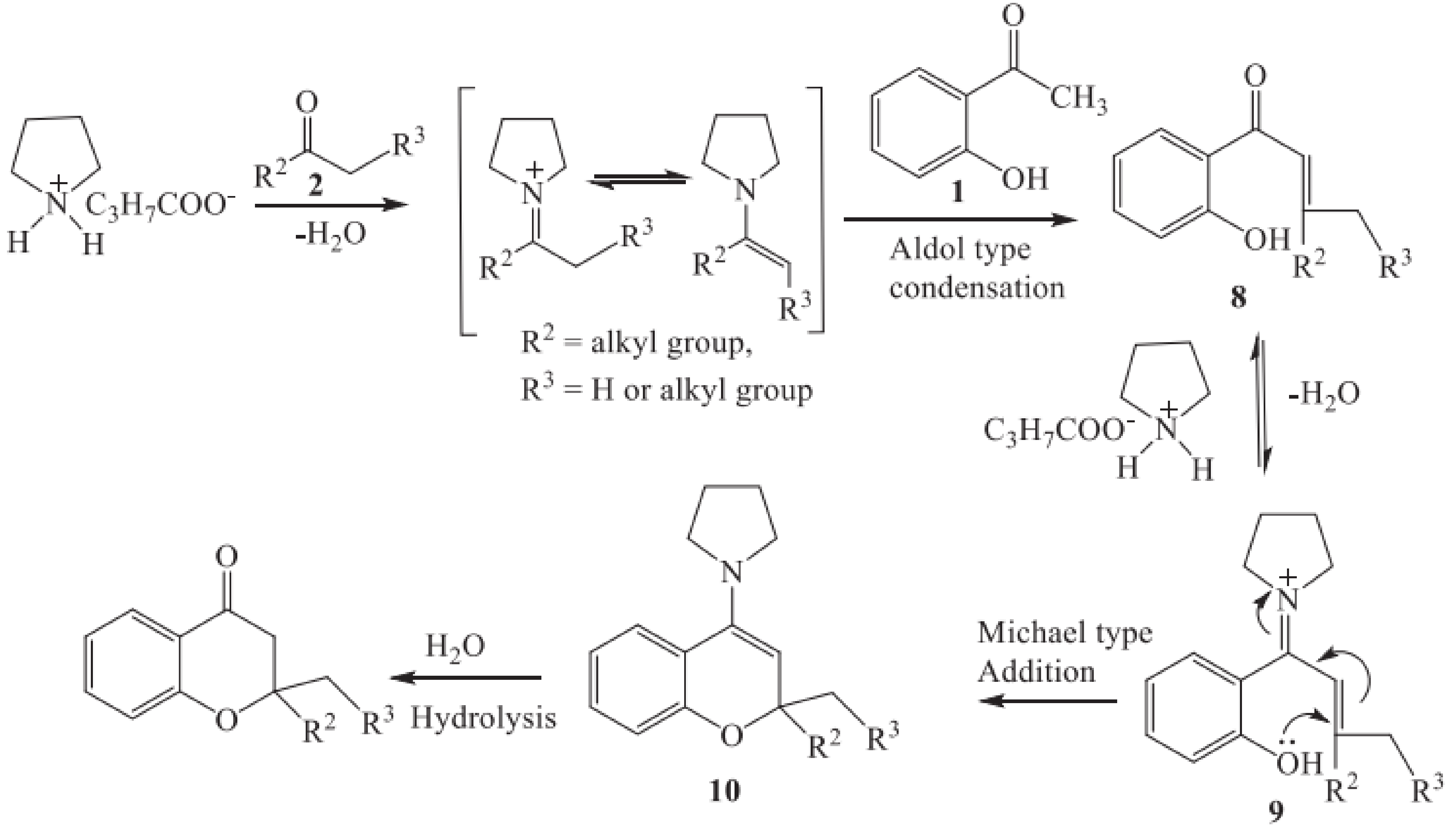
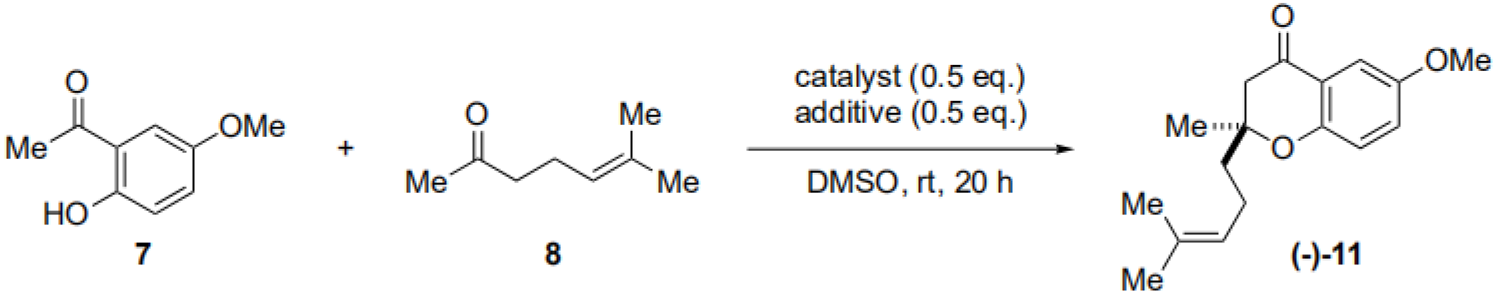


Table S2. Evaluation of asymmetric Kabbe condensation conditions.



Entry	Catalyst	Additive	Yield (%)	ee (%)
1	(R)-2-methylpyrrolidine (**C1**)	butyric acid	5	23
2	(S)-2-diphenylmethylpyrrolidine (**C2**)	butyric acid	NR	-
3	(S)-2-(methoxymethyl)pyrrolidine (**C3**)	butyric acid	NR	-
4	(R)-5-(hydroxylmethyl)-2-pyrrolidine (**C4**)	butyric acid	NR	-
5	(S)-5-(2-pyrrolidinyl)-1H-tetrazole (**C5**)	butyric acid	NR	-
6	(S)-1-boc-2-pyrrolidinecarbonitrile (**C6**)	butyric acid	NR	-
7	L-prolinamide (**C7**)	butyric acid	7	7
8	(3S,8aS)-3-methyloctahydropyrrolo[1,2-a]pyrazine] (**C8**)	butyric acid	NR	-
9	(2S,5R)-2,5-dimethylpyrrolidine (**C9**)	butyric acid	NR	-
10	(S)-5-benzyl-2,2,3-trimethylimidazolidin-4-one monohydrochloride (**C10**)	-	NR	-
11	(S)-5-benzyl-2,2,3-trimethylimidazolidin-4-one dichloroacetic acid (**C11**)	-	NR	-
12	(S)-2-(tertbutyl)-3-methylimidazolidin-4-one trifluoroacetic acid (**C12**)	-	NR	-

13	(2S,5S)-5-benzyl-2-(tertbutyl)-3-methylimidazolidin-4-one (**C13**)	butyric acid	NR	-
14[a]	(R)-2-methylpyrrolidine (**C1**)	butyric acid	19	0
15[b]	(S)-2-(methoxymethyl)pyrrolidine (**C3**)	butyric acid	26	12
16[b]	(R)-2-methylpyrrolidine (**C1**)	butyric acid	30	9
17[b]	(S)-2-diphenylmethylpyrrolidine (**C2**)	butyric acid	3	16

[a] Reaction performed at 50 ºC. [b] 3 eq. of the catalyst and 1 eq. of the additive were used. NR = no reaction.