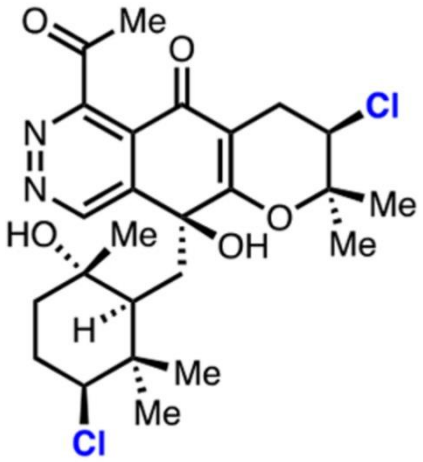
Enantioselective Synthesis of Azamerone

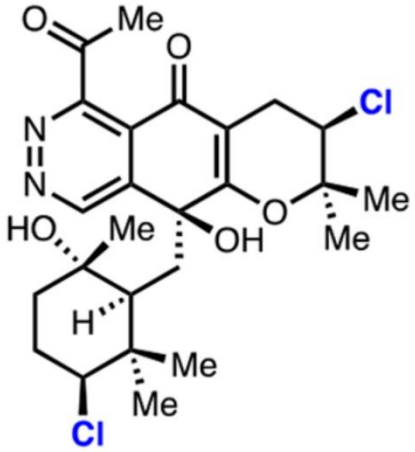
Matthew L. Landry, Grace M. McKenna, and Noah Z. Burns*



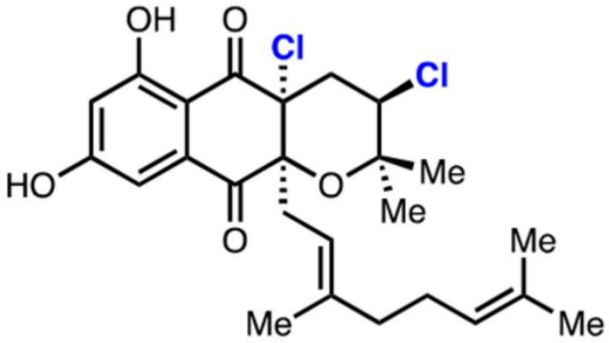
1: azamerone

J. Am. Chem. Soc. **2019**, 141, 2867−2871

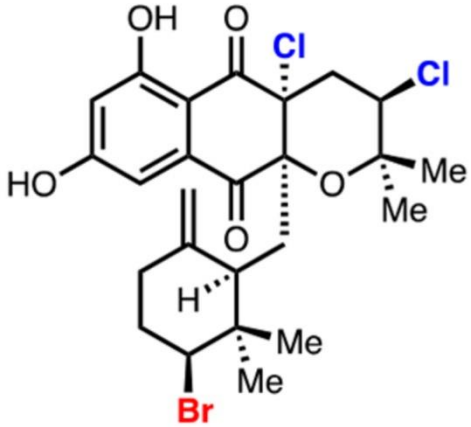
A. Napyradiomycin meroterpenoids



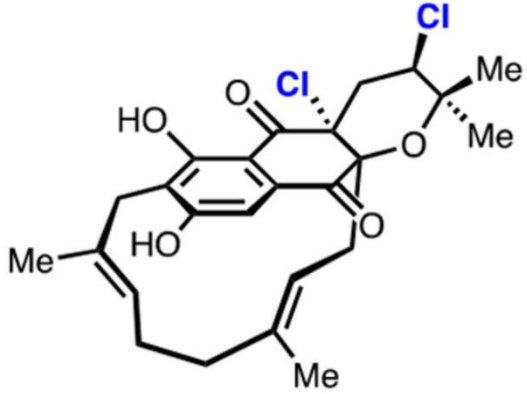
1: azamerone



2: napyradiomycin A1

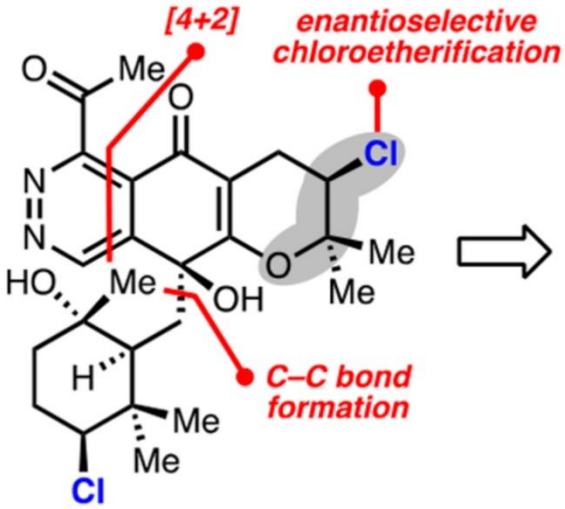


3: napyradiomycin B3

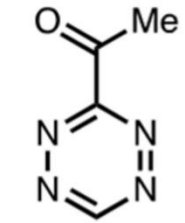


4: napyradiomycin C1

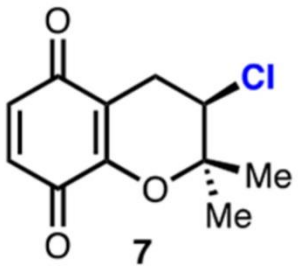
C. Azamerone retrosynthesis



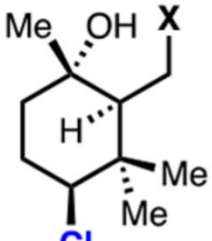
1: azamerone



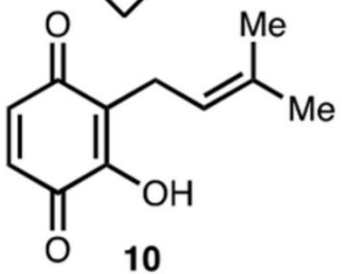
8



7

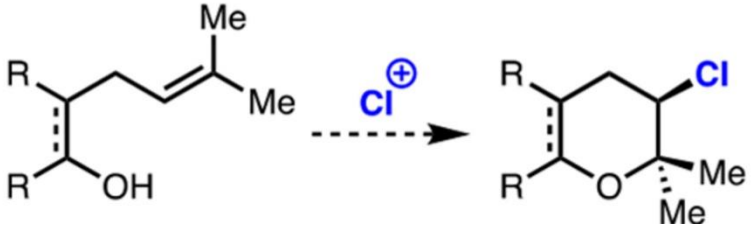


9

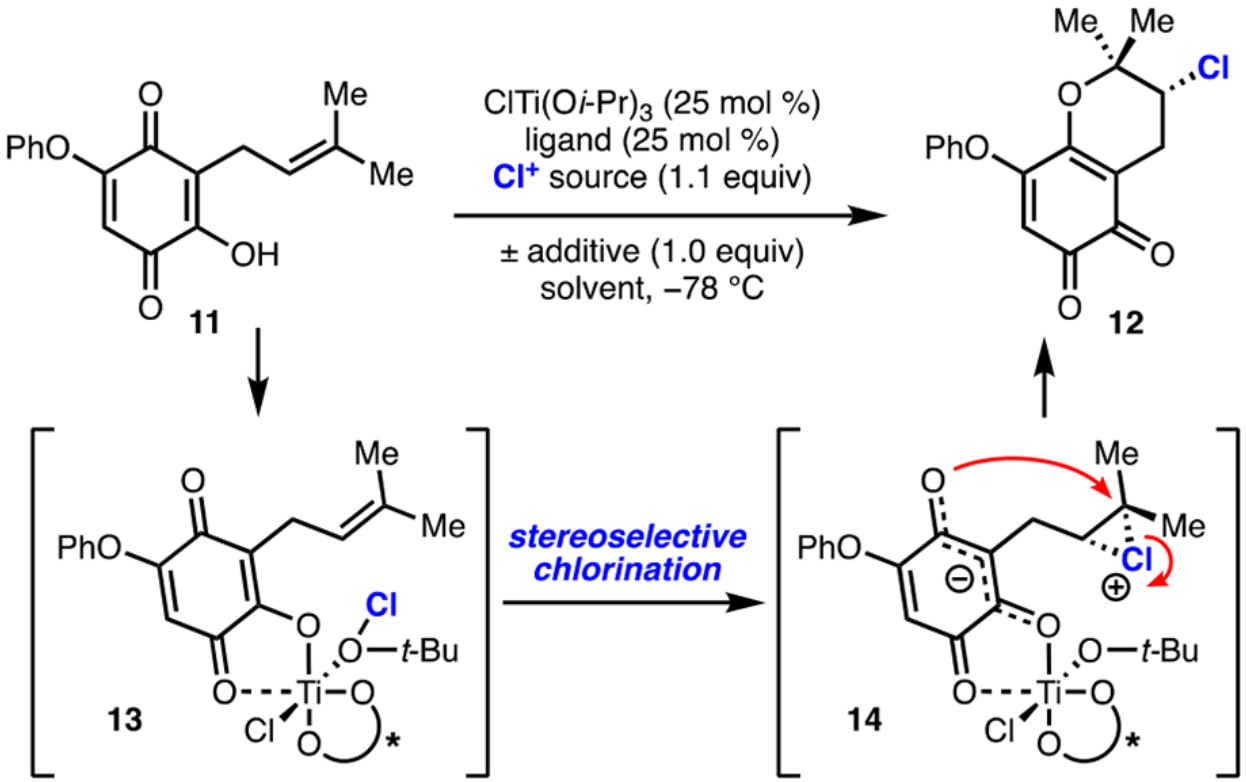


10

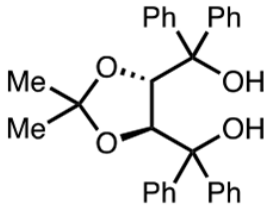
D. Methodological gap: enantioselective prenyl chloroetherification



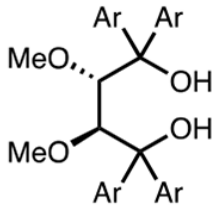
- *natural product motif*
- *no enantioselective variants*


PhO
Me
Me
OH
11
ClTi(O*i*-Pr)$_3$ (25 mol %)
ligand (25 mol %)
Cl$^+$ source (1.1 equiv)
± additive (1.0 equiv)
solvent, –78 °C
Me
Me
Cl
12
13
stereoselective chlorination
14
t-Bu

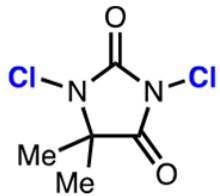
entry[a]	conditions	yield (%)	ee (%)
1	**A**, *t*-BuO**Cl**, DCM	29	10
2	**B**, *t*-BuO**Cl**, DCM	39	7
3	**B**, *t*-BuO**Cl**, hexanes	11	<1
4	**B**, *t*-BuO**Cl**, PhMe	38	16
5	**B**, *t*-BuO**Cl**, Et_2O	36	14
6	**B**, *t*-BuO**Cl**, *t*-BuOMe	25	16
7	**B**, *t*-BuO**Cl**, THF	18	22
8	**B**, *t*-BuO**Cl**, 2-Me-THF	33	57
9	**B**, N**C**S, 2-Me-THF	<5	–
10	**B**, D**C**DMH, 2-Me-THF	42	33
11	**B**, Palau'**Chlor**, 2-Me-THF	28	29
12	**B**, *t*-BuO**Cl**, 2-Me-THF, pyridine	20	78
13	**B**, *t*-BuO**Cl**, 2-Me-THF, quinoline	24	81
14[b]	**B**, *t*-BuO**Cl**, 2-Me-THF, quinoline	68	84
15[c]	**B**, *t*-BuO**Cl**, 2-Me-THF, quinoline	45	79
16[c,d]	**B**, *t*-BuO**Cl**, 2-Me-THF, quinoline	40[e]	84



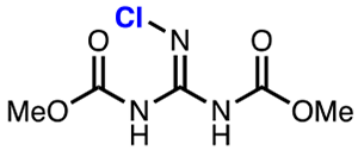
A



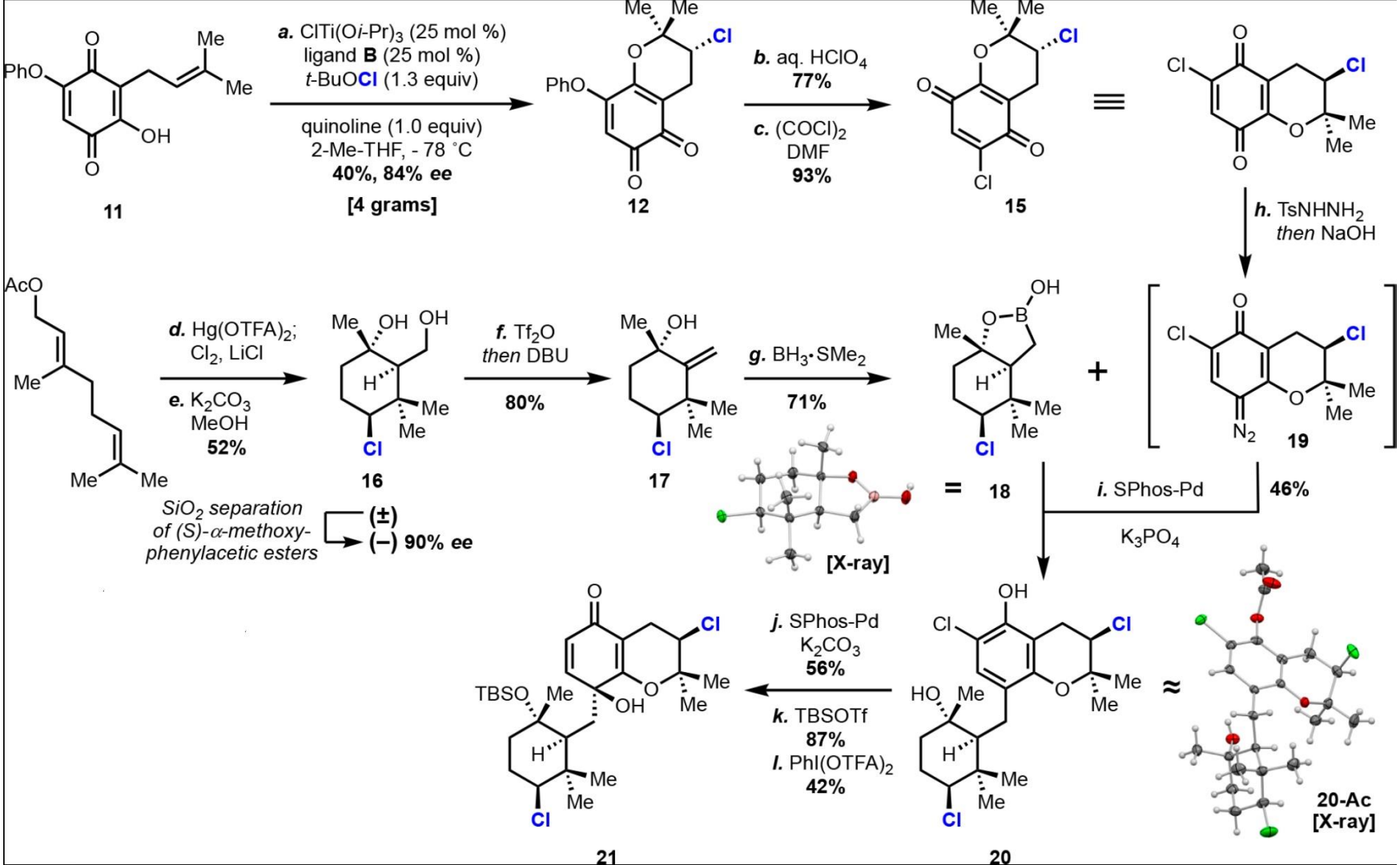
B: Ar = 2-naphthyl

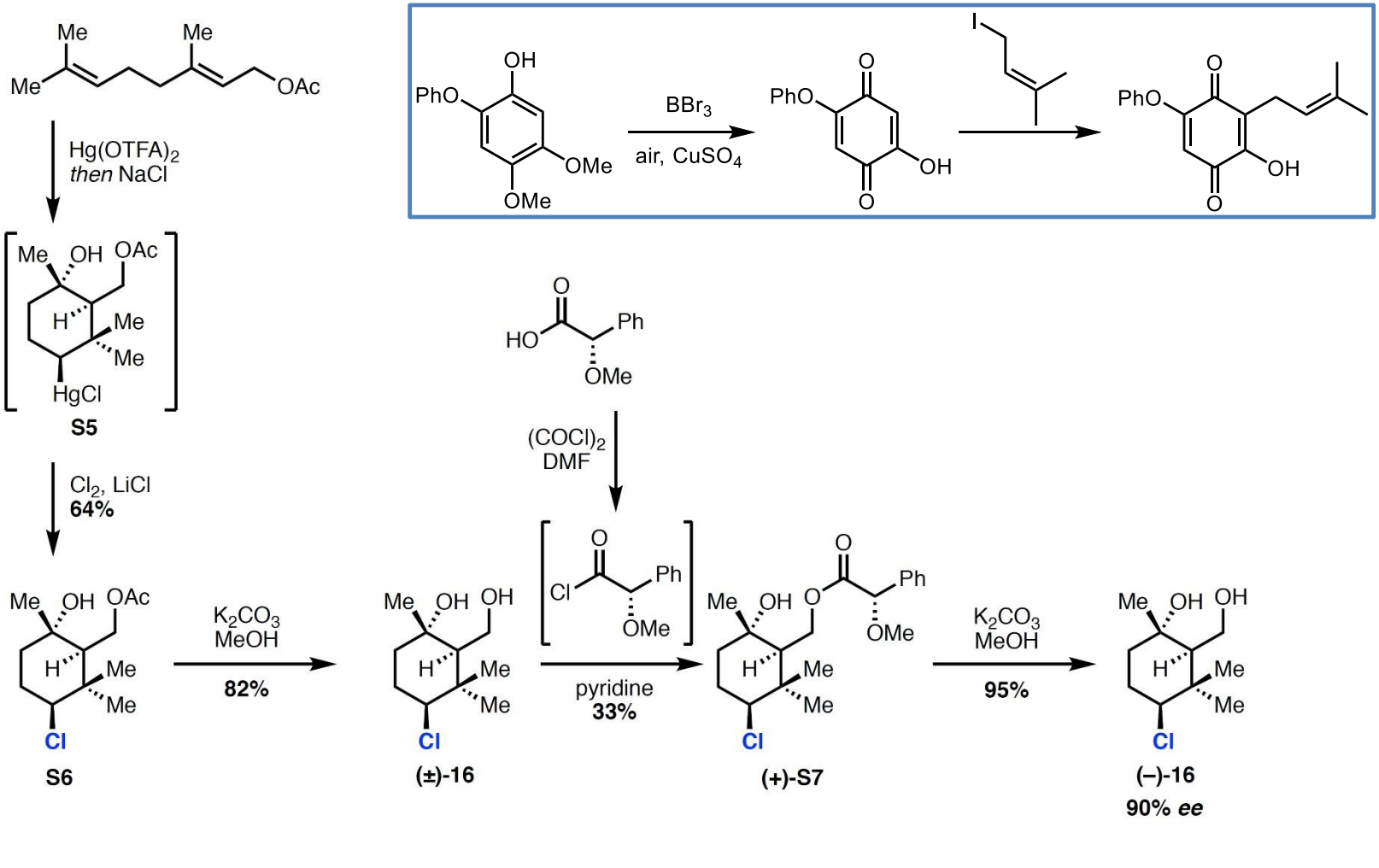


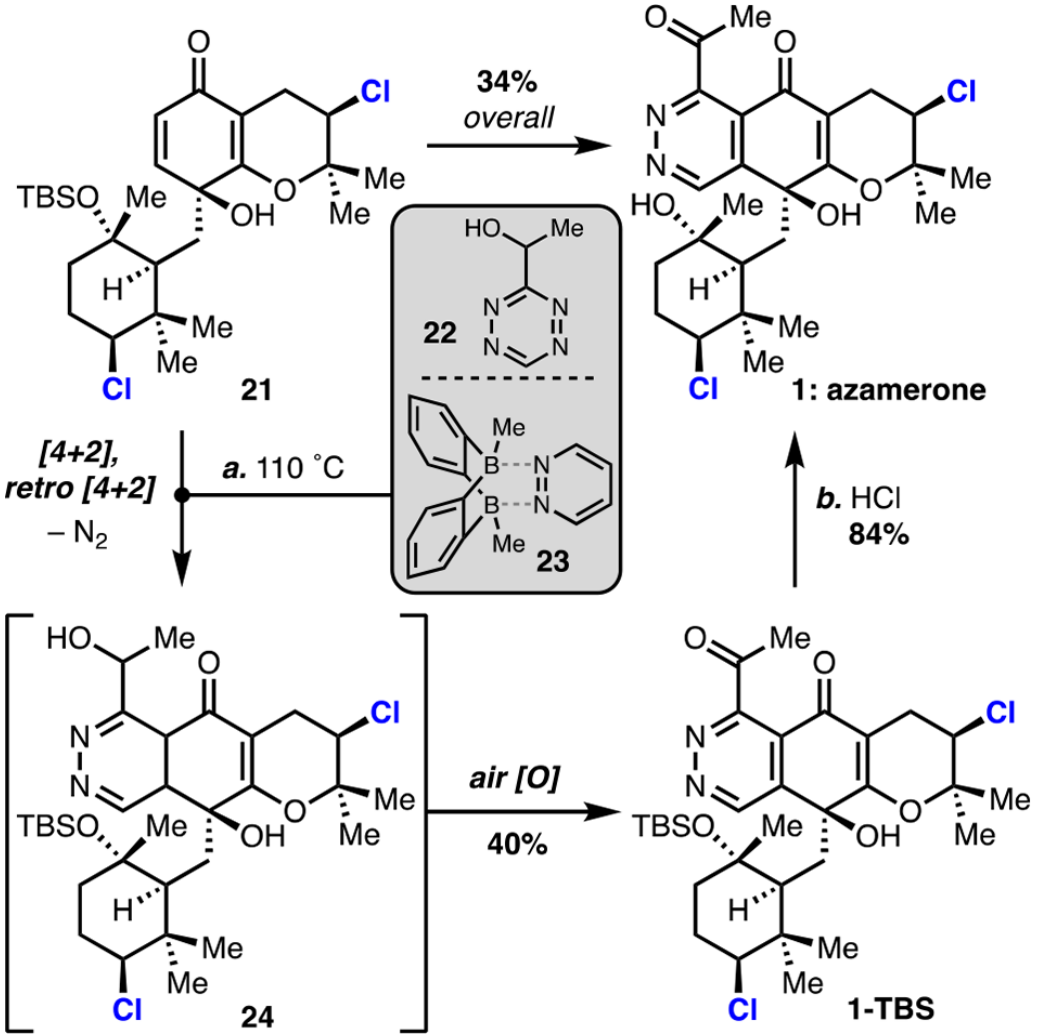
DCDMH

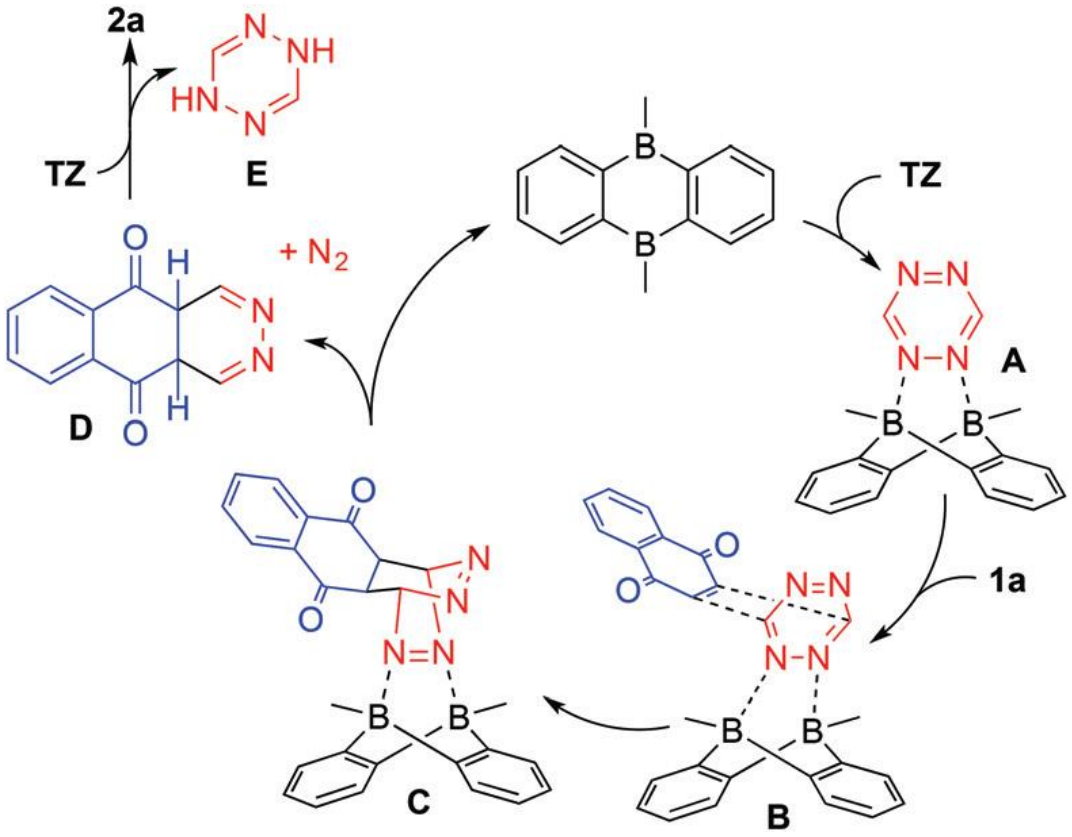


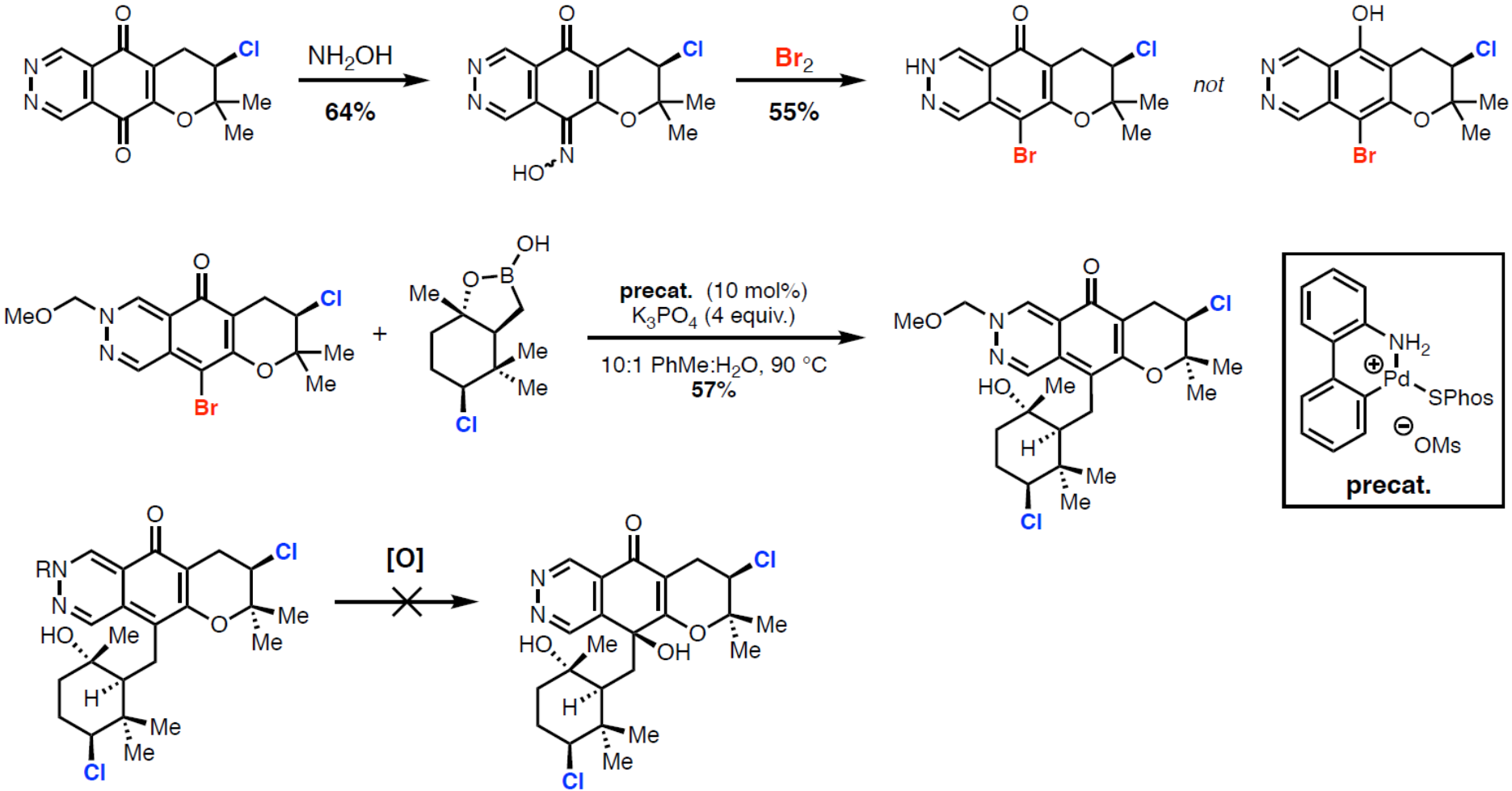
Palau'Chlor

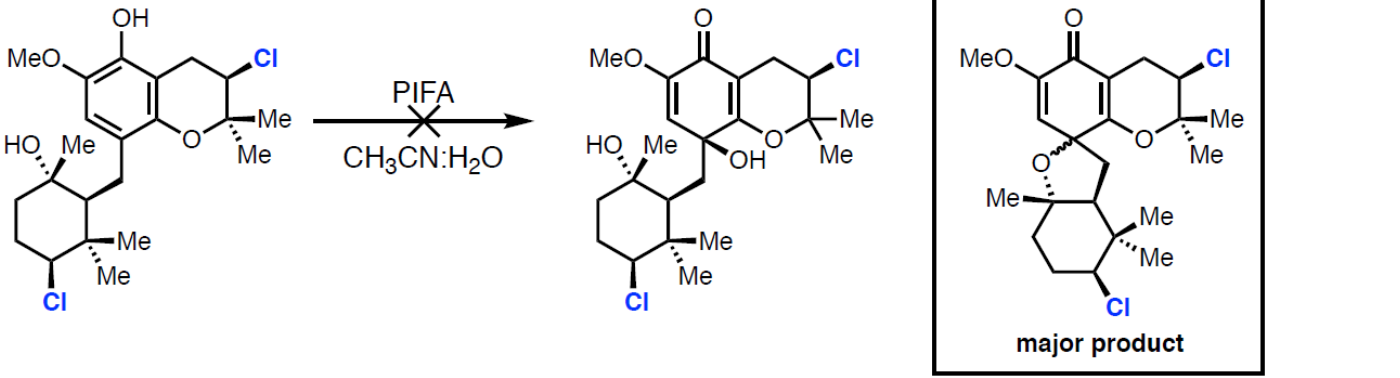

11
a. ClTi(O*i*-Pr)$_3$ (25 mol %)
ligand **B** (25 mol %)
t-BuO**Cl** (1.3 equiv)
quinoline (1.0 equiv)
2-Me-THF, - 78 °C
40%, 84% *ee*
[4 grams]
12
b. aq. $HClO_4$
77%
c. $(COCl)_2$
DMF
93%
15
h. $TsNHNH_2$
then NaOH
19
d. $Hg(OTFA)_2$;
Cl_2, LiCl
e. K_2CO_3
MeOH
52%
16
f. Tf_2O
then DBU
80%
17
g. $BH_3{\cdot}SMe_2$
71%
18
i. SPhos-Pd
K_3PO_4
46%
SiO$_2$ separation of (S)-α-methoxy-phenylacetic esters
(±)
(–) 90% *ee*
[X-ray]
j. SPhos-Pd
K_2CO_3
56%
k. TBSOTf
87%
l. $PhI(OTFA)_2$
42%
21
20
20-Ac
[X-ray]

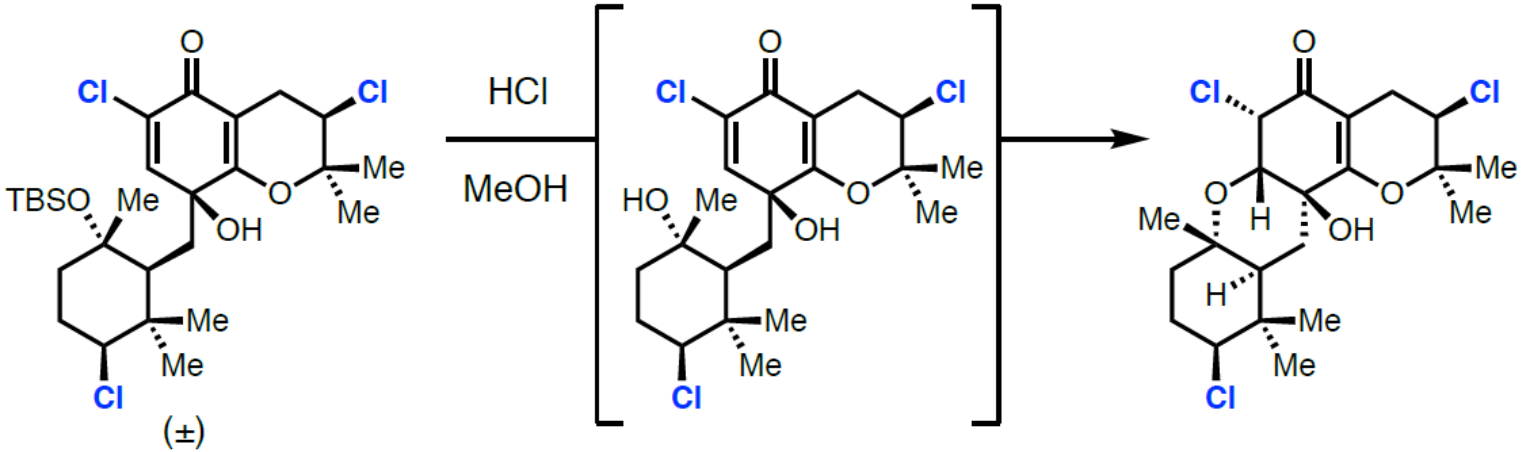

Me
Me
Me
OAc
Hg(OTFA)2
then NaCl
Me
OH
OAc
H
Me
Me
HgCl
S5
Cl2, LiCl
64%
Me
OH
OAc
H
Me
Me
Cl
S6
K2CO3
MeOH
82%
Me
OH
OH
H
Me
Me
Cl
(±)-16
HO
O
Ph
OMe
(COCl)2
DMF
Cl
O
Ph
OMe
pyridine
33%
Me
OH
O
O
Ph
OMe
H
Me
Me
Cl
(+)-S7
K2CO3
MeOH
95%
Me
OH
OH
H
Me
Me
Cl
(–)-16
90% ee
PhO
OH
OMe
OMe
BBr3
air, CuSO4
PhO
O
OH
O
I
PhO
O
OH
O

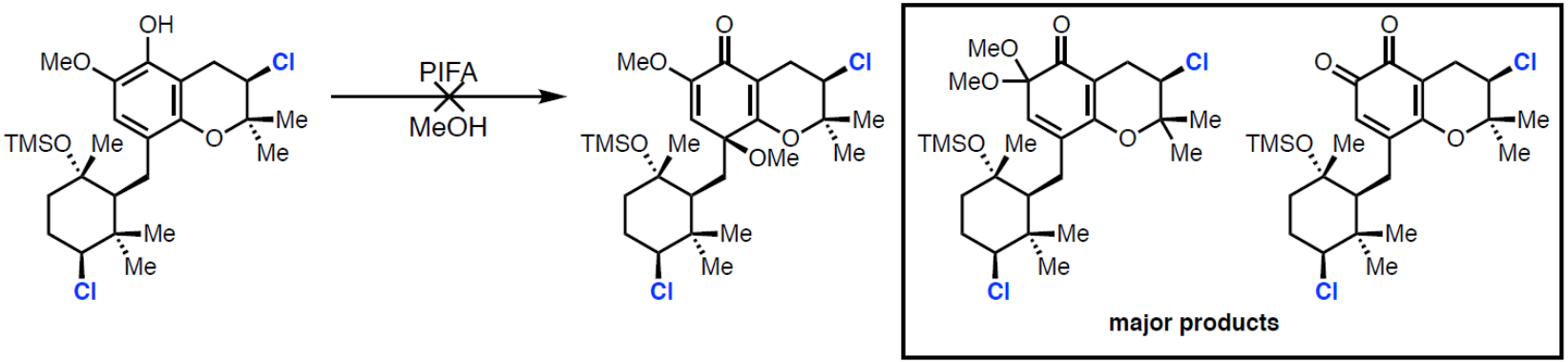

34%
overall
21
22
23
1: azamerone
[4+2],
retro [4+2]
– N2
a. 110 °C
b. HCl
84%
air [O]
40%
24
1-TBS

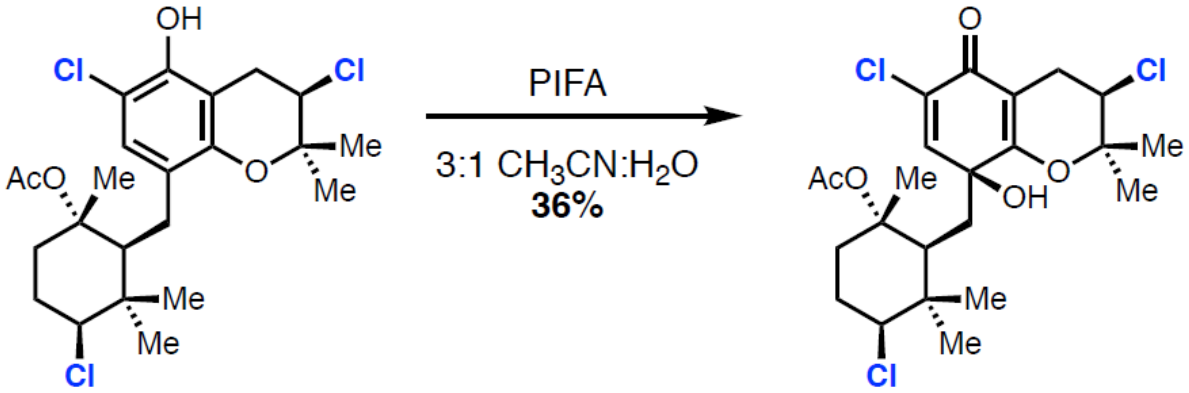

2a
TZ
E
D
+ N2
TZ
A
1a
B
C


NH2OH
64%
Br2
55%
not
precat. (10 mol%)
K3PO4 (4 equiv.)
10:1 PhMe:H2O, 90 °C
57%
[O]
precat.


OH
MeO
Cl
Me
HO
Me
O
Me
Me
Me
Cl
PIFA
$CH_3CN:H_2O$
O
MeO
Cl
Me
HO
Me
O
OH
Me
Me
Me
Cl
O
MeO
Cl
Me
O
O
Me
Me
Me
Me
Cl
major product


O
Cl
Cl
Me
TBSO
Me
O
OH
Me
Me
Cl
(±)
HCl
MeOH
O
Cl
Cl
Me
HO
Me
O
OH
Me
Me
Me
Cl
O
Cl
Cl
Me
O
H
O
Me
OH
Me
H
Me
Me
Cl


OH
MeO
Cl
TMSO
Me
O
Me
Me
Me
Me
Cl
PIFA
MeOH
O
MeO
Cl
TMSO
Me
O
OMe
Me
Me
Me
Cl
MeO
MeO
Cl
TMSO
Me
O
Me
Me
Me
Me
Cl
major products
O
O
Cl
TMSO
Me
O
Me
Me
Me
Me
Cl


OH
Cl
Cl
AcO
Me
O
Me
Me
Me
Me
Cl
PIFA
3:1 CH3CN:H2O
36%
O
Cl
Cl
AcO
Me
OH
O
Me
Me
Me
Me
Cl