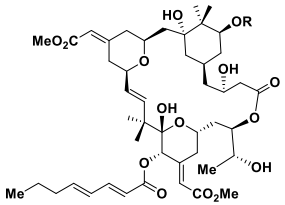
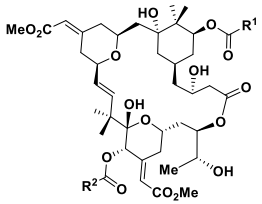
Total synthesis of Bryostatin 3

Trost *et al.*, *Science* **368**, 1007–1011 (2020)



Bryostatin 1: R = Ac, PKC K_i = 1.35 nM
Keck 2011, 31 steps (LLS), 58 steps (TS)
Wender 2017, 19 steps (LLS), 29 steps (TS)

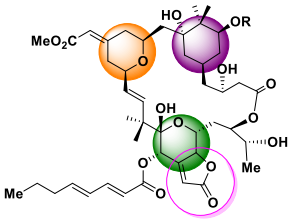
Bryostatin 2: R = H, PKC K_i = 5.86 nM
Evans 1999, 42 steps (LLS), 72 steps (TS)



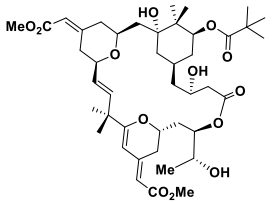
Bryostatin 7: R^1 = Me, R^2 = Me, PKC K_i = 0.84 nM
Masamune 1990, 41 steps (LLS), 79 steps (TS)
Krische 2011, 20 steps (LLS), 36 steps (TS)

Bryostatin 8: R^1 = ^{n}Pr, R^2 = ^{n}Pr, PKC K_i = 1.72 nM
Song 2018, 29 steps (LLS), 51 steps (TS)

Bryostatin 9: R^1 = Me, R^2 = ^{n}Pr, PKC K_i = 1.31 nM
Wender 2011, 25 steps (LLS), 43 steps (TS)



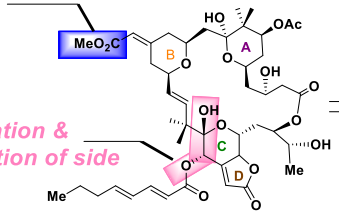
Bryostatin 3, PKC K_i = 2.75 nM
Yamamura 2000, 43 steps (LLS), 88 steps (TS)
This work, 22 steps (LLS), 31 steps (TS)



Bryostatin 16, PKC K_i = 118 nM
Trost 2008, 28 steps (LLS), 42 steps (TS)

[Pd] carbonylative esterification

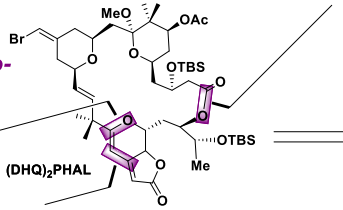
epoxidation & installation of side chain



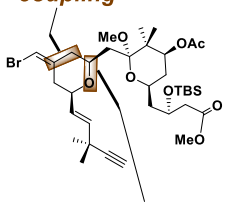
[Au] 6-Endo-Dig Cyclization

Yamaguchi Macrolactonization

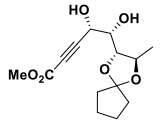
[Pd] Alkyne/Alkyne Coupling

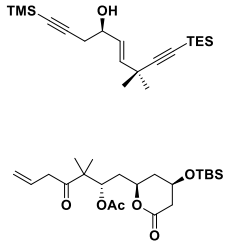


[Ru] Alkene/Alkyne coupling



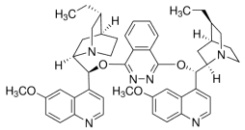
Michael addition



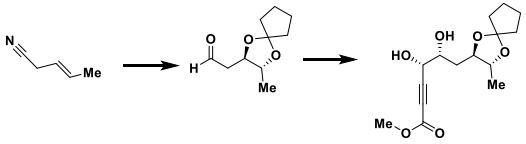


Bryostation 3

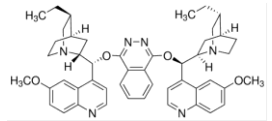
$(DHQD)_2PHAL$



[redacted]



$(DHQ)_2PHAL$



^{n}BuLi (2 equiv)
TMEDA (1 equiv)
Et_2O, 55°C, 16h

then DMF (1 equiv), -78°C
then TESCl (2.5 equiv),
-78°C - rt
67%

[redacted]

^{t}BuLi, Me_2Zn
Et_2O, -78°C, 6h

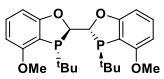
[redacted]

aq. $NaHSO_4$, 5 d
72%

[redacted]

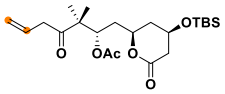
Cu(II) Isobutyrate (7 mol%)
LiO^tBu (7 mol%)

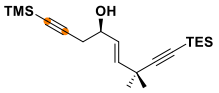
THF, -30°C, 20h, 86%, 98% ee



9 mol%

[redacted]





$[CpRu(MeCN)_3]PF_6$
10 mol%
Acetone, rt, 22h

[redacted]

Comment on the nature
of Transition state
No drawing needed

[redacted]

NBS

DMF, 0°C, 2h
88%

[redacted]

PPTS
MeOH

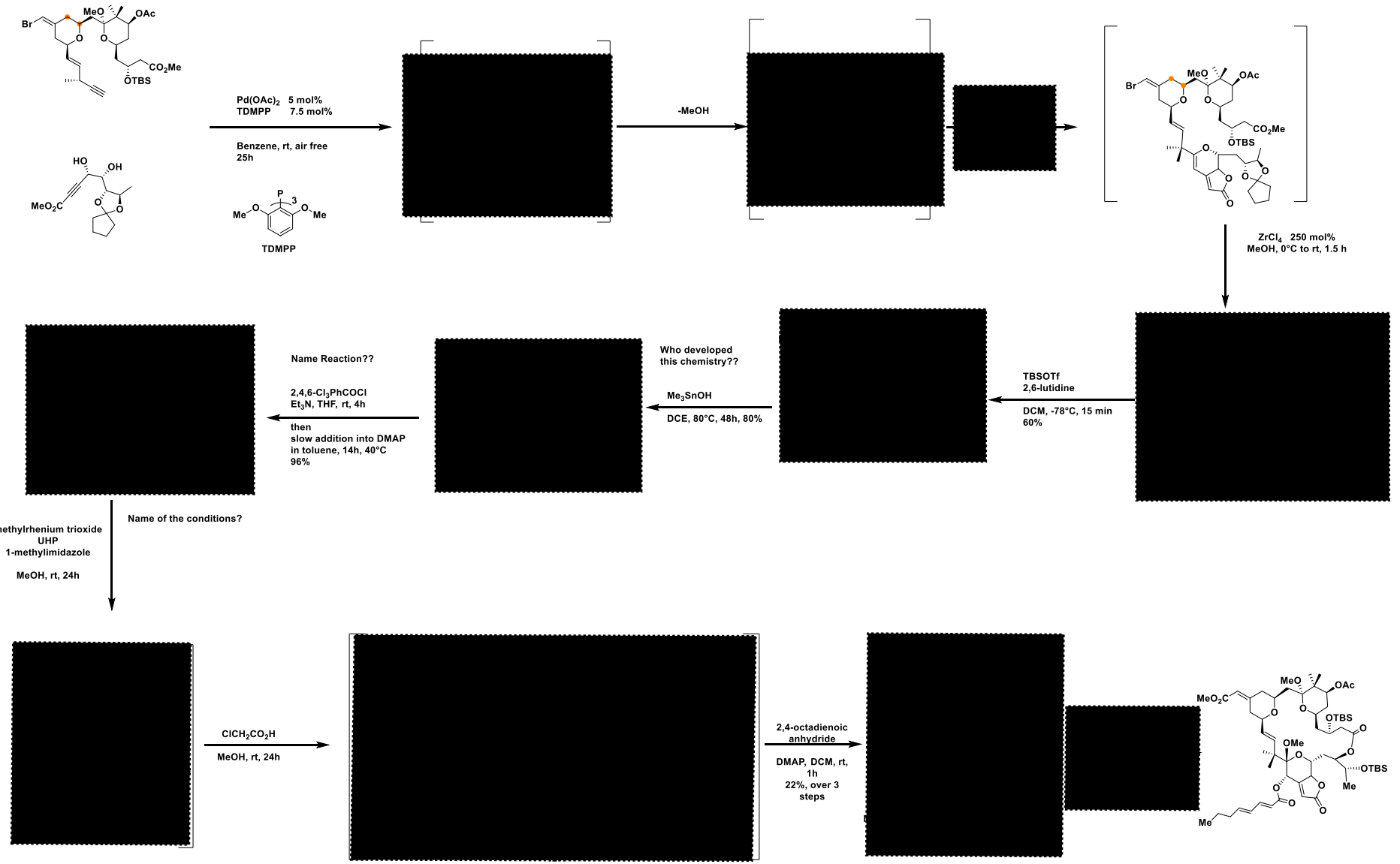
0°C to rt, 6h
80%

[redacted]

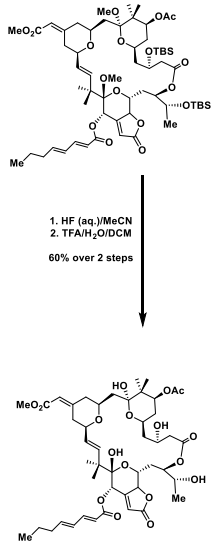
$AgNO_3$
THF/H_2O

0°C to rt, 45 min
87%

[redacted]


Pd(OAc)2 5 mol%
TDMPP 7.5 mol%
Benzene, rt, air free
25h
TDMPP
-MeOH
ZrCl4 250 mol%
MeOH, 0°C to rt, 1.5 h
TBSOTf
2,6-lutidine
DCM, -78°C, 15 min
60%
Who developed this chemistry??
Me3SnOH
DCE, 80°C, 48h, 80%
Name Reaction??
2,4,6-Cl3PhCOCl
Et3N, THF, rt, 4h
then
slow addition into DMAP
in toluene, 14h, 40°C
96%
Name of the conditions?
methylrhenium trioxide
UHP
1-methylimidazole
MeOH, rt, 24h
ClCH2CO2H
MeOH, rt, 24h
2,4-octadienoic anhydride
DMAP, DCM, rt, 1h
22%, over 3 steps

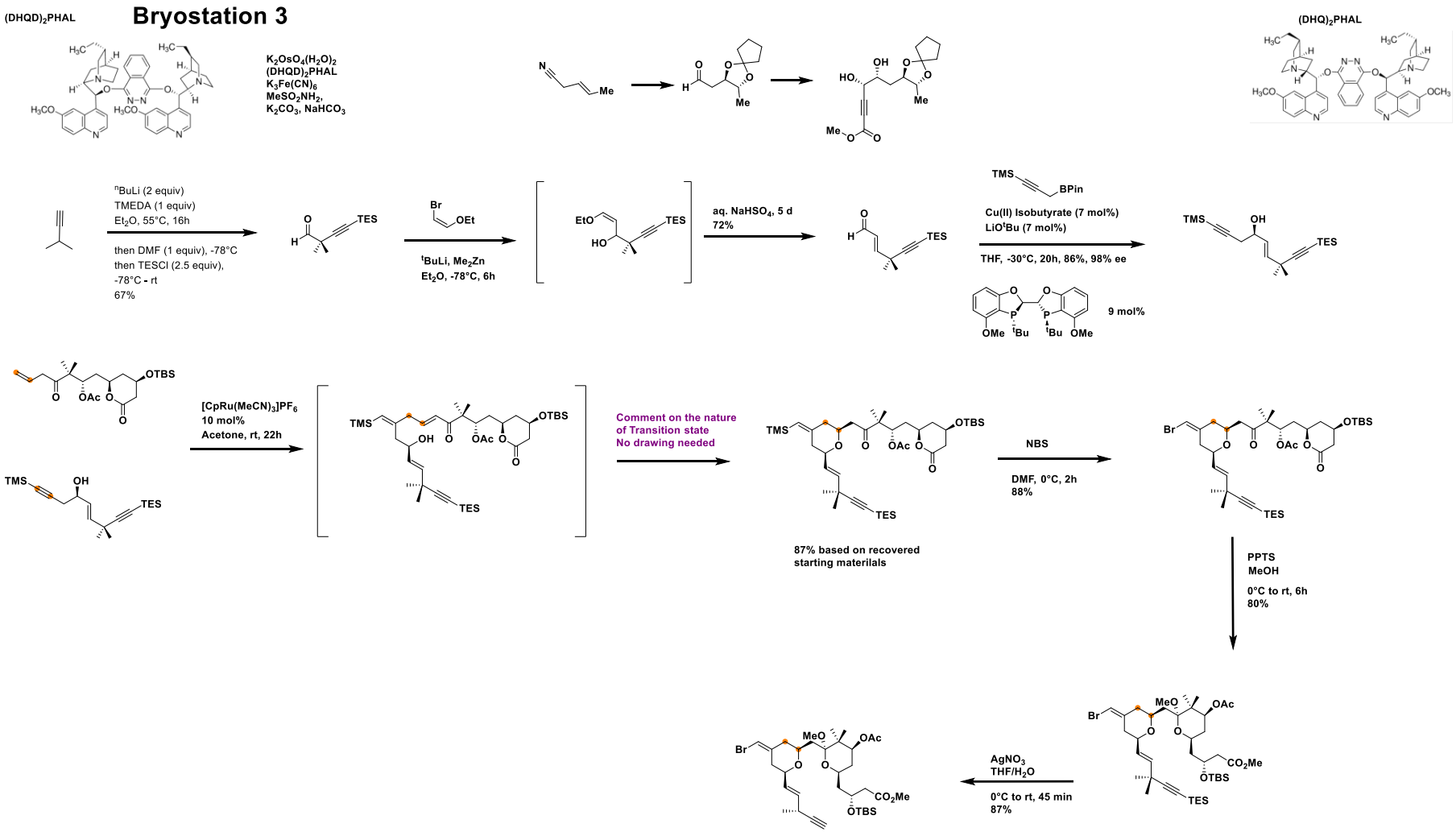
[redacted]

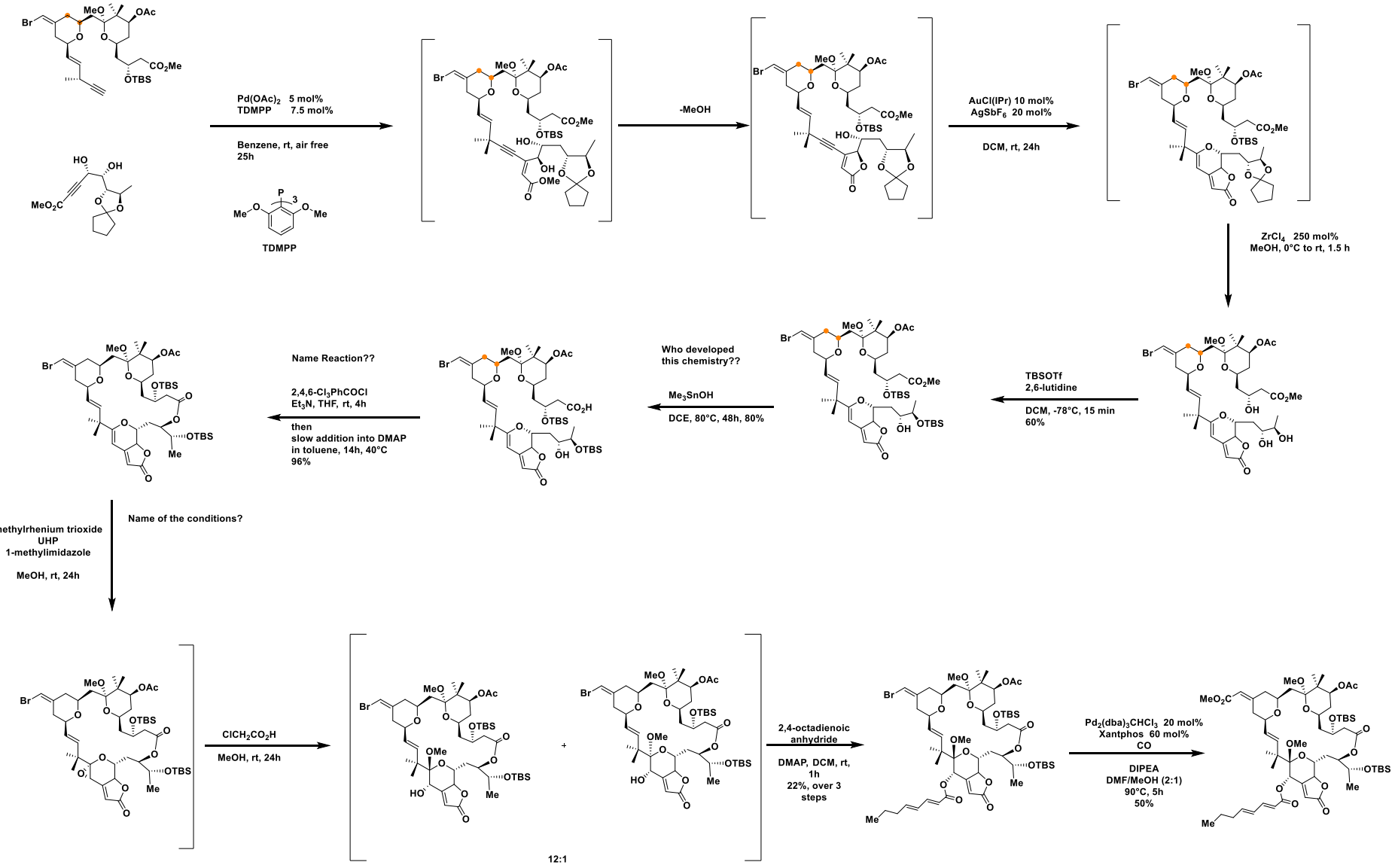


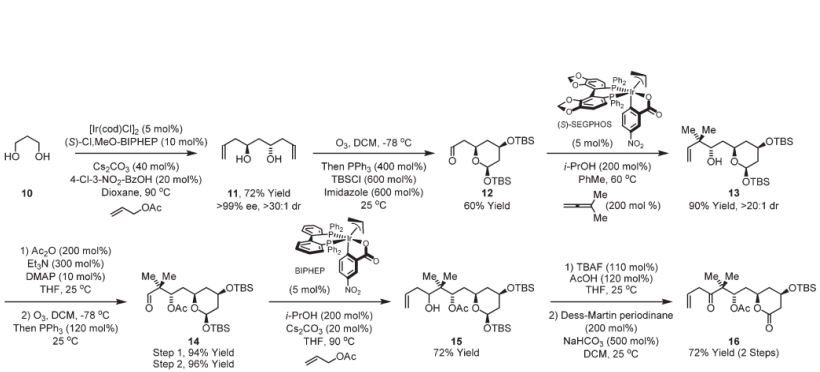
[redacted]

[redacted]

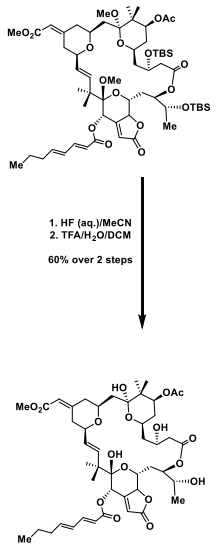
Solution


(DHQD)2PHAL
Bryostation 3
K2OsO4(H2O)2
(DHQD)2PHAL
K3Fe(CN)6
MeSO2NH2,
K2CO3, NaHCO3
(DHQ)2PHAL
nBuLi (2 equiv)
TMEDA (1 equiv)
Et2O, 55°C, 16h
then DMF (1 equiv), -78°C
then TESCl (2.5 equiv),
-78°C - rt
67%
tBuLi, Me2Zn
Et2O, -78°C, 6h
aq. NaHSO4, 5 d
72%
Cu(II) Isobutyrate (7 mol%)
LiOtBu (7 mol%)
THF, -30°C, 20h, 86%, 98% ee
9 mol%
[CpRu(MeCN)3]PF6
10 mol%
Acetone, rt, 22h
Comment on the nature
of Transition state
No drawing needed
87% based on recovered
starting materilals
NBS
DMF, 0°C, 2h
88%
PPTS
MeOH
0°C to rt, 6h
80%
AgNO3
THF/H2O
0°C to rt, 45 min
87%

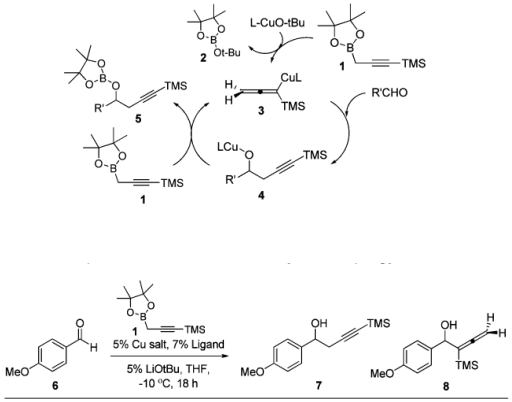

Pd(OAc)2 5 mol%
TDMPP 7.5 mol%
Benzene, rt, air free
25h
TDMPP
-MeOH
AuCl(IPr) 10 mol%
AgSbF6 20 mol%
DCM, rt, 24h
ZrCl4 250 mol%
MeOH, 0°C to rt, 1.5 h
TBSOTf
2,6-lutidine
DCM, -78°C, 15 min
60%
Who developed
this chemistry??
Me3SnOH
DCE, 80°C, 48h, 80%
Name Reaction??
2,4,6-Cl3PhCOCl
Et3N, THF, rt, 4h
then
slow addition into DMAP
in toluene, 14h, 40°C
96%
methylrhenium trioxide
UHP
1-methylimidazole
MeOH, rt, 24h
Name of the conditions?
ClCH2CO2H
MeOH, rt, 24h
12:1
2,4-octadienoic
anhydride
DMAP, DCM, rt,
1h
22%, over 3
steps
Pd2(dba)3CHCl3 20 mol%
Xantphos 60 mol%
CO
DIPEA
DMF/MeOH (2:1)
90°C, 5h
50%



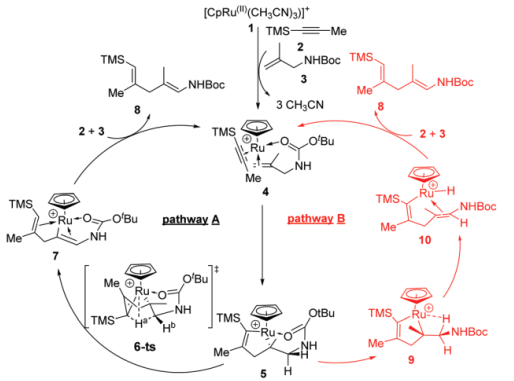
dx.doi.org/10.1021/ja205673e | *J. Am. Chem. Soc.* 2011, 133, 13876–13879



Scheme 1. Proposed Mechanism for a Cu Catalyzed Propargylation of Aldehydes with a Propargyl Borolane



J. AM. CHEM. SOC. 2010, *132*, 7600–7601



Scheme 4 Plausible mechanism for Ru-catalyzed Alder-ene reaction with acetylene **2** and propene **3**.

Org. Chem. Front., 2018, **5**, 3178–3185