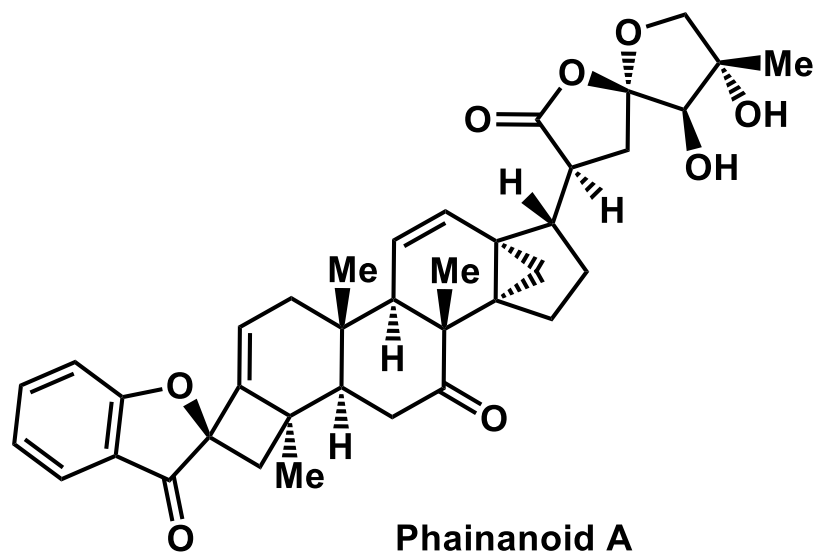
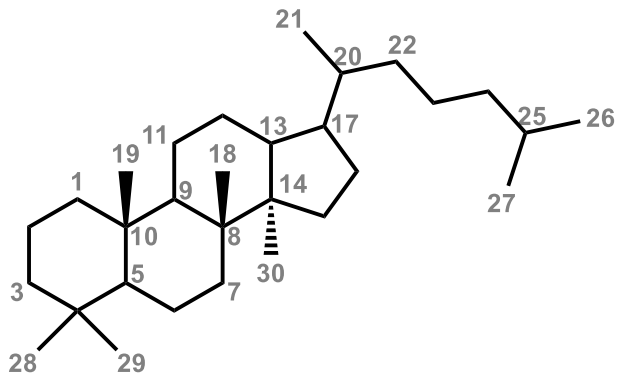


Bidirectional Total Synthesis of Phainanoid A via Strategic Use of Ketones

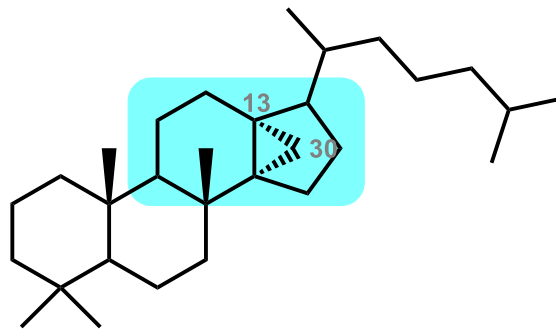
Jiaxin Xie, Xin Liu, Nan Zhang, Shinyoung Choi, and Guangbin Dong*



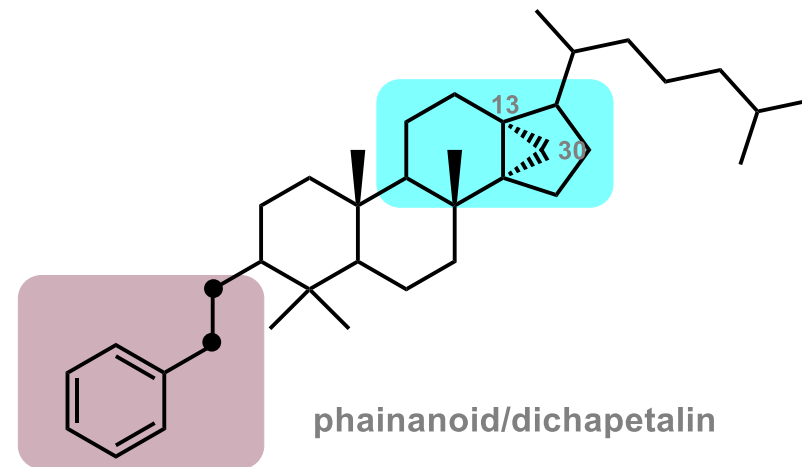
- isolated from *Phyllanthus hainanensis*
- cytotoxicity against various cancer cell lines
- nanomolar immunosuppressive activity



dammarane-type
triterpenoids (DTTs)

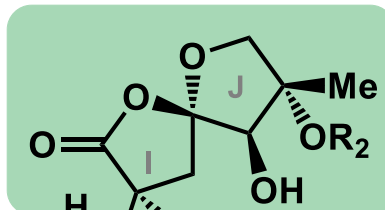


13, 30-cyclodammarane-type
triterpenoids (CDTTs)



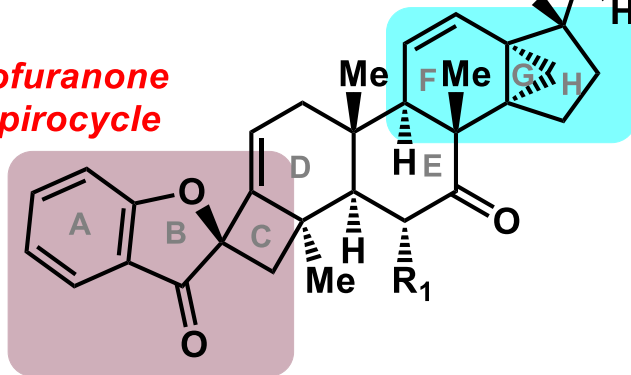
phainanoid/dichapetalin

5,5-oxaspirolactone

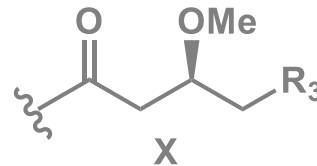


[4.3.1]propellane

*benzofuranone
4,5-spirocycle*



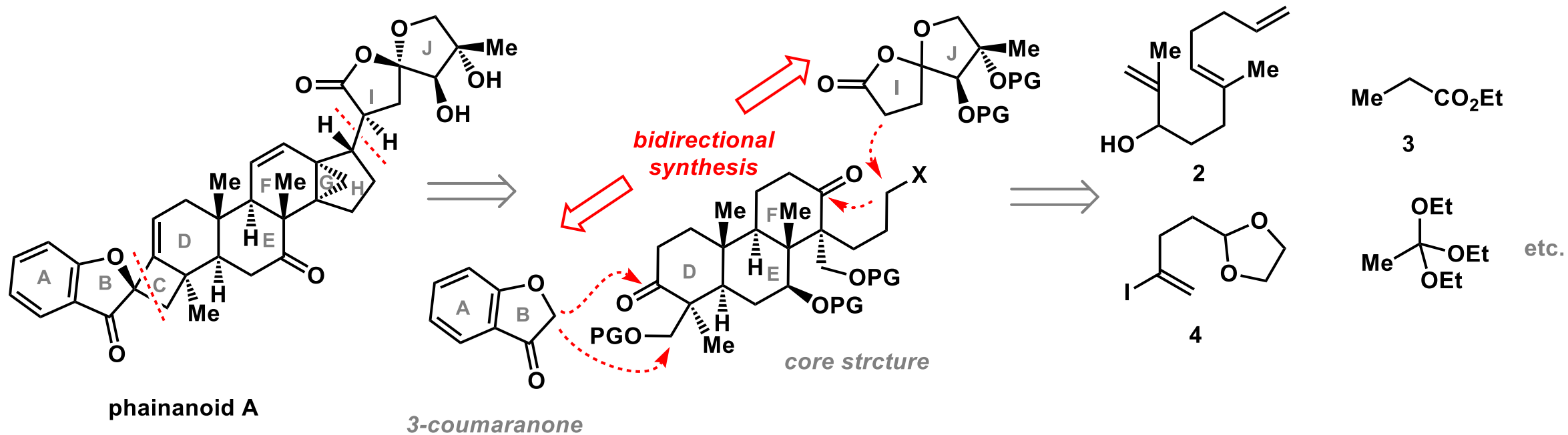
23R: A-H
23S: I



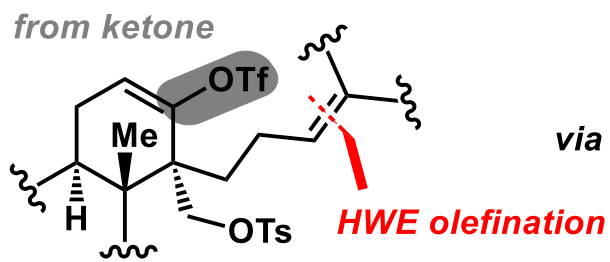
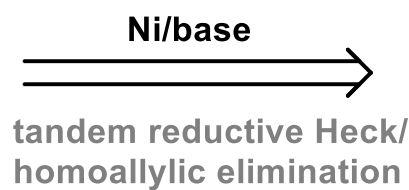
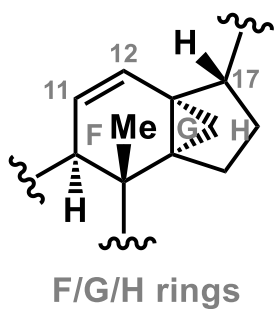
- A $R_1 = H, R_2 = H$ (1)
- B $R_1 = OH, R_2 = H$
- C $R_1 = OH, R_2 = Me$
- D $R_1 = OH, R_2 = CO(CH_2)_5OH$
- E $R_1 = OH, R_2 = X, R_3 = OH$
- F $R_1 = OH, R_2 = X, R_3 = OMe$
- G $R_1 = OAc, R_2 = H$
- H $R_1 = OH, R_2 = X, R_3 = H$
- I $R_1 = OH, R_2 = H$

phainanoid A-I

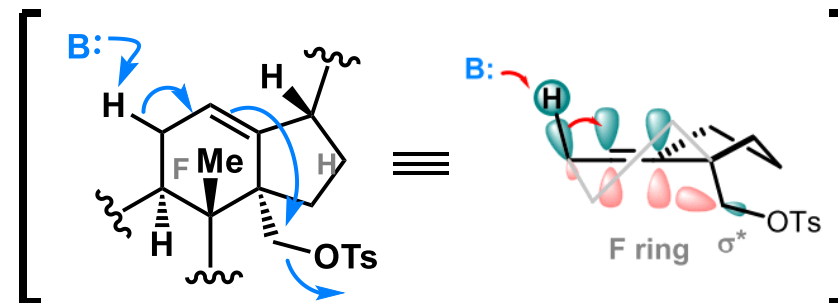
Bidirectional synthetic strategy enabled by ketone-mediated transformations



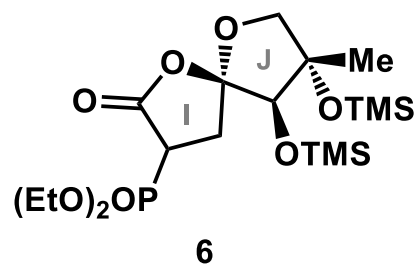
F/G/H propellane



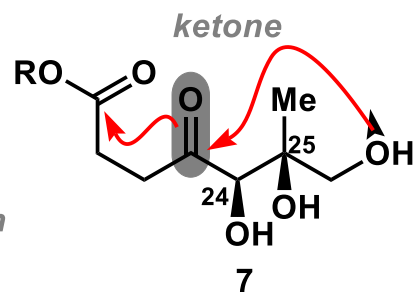
via



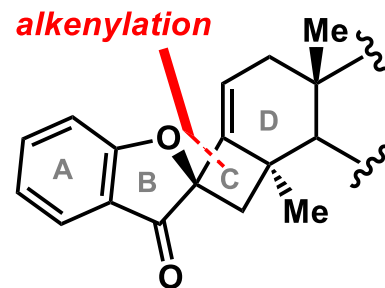
I/J spiroketal



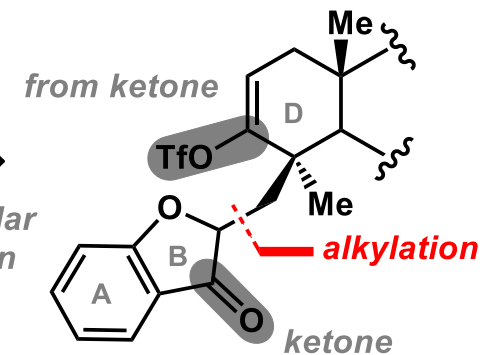
acid-promoted
spiroketalization



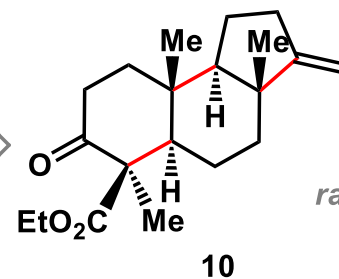
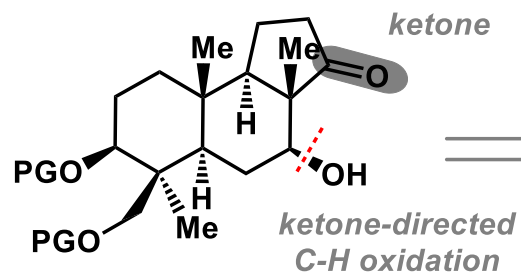
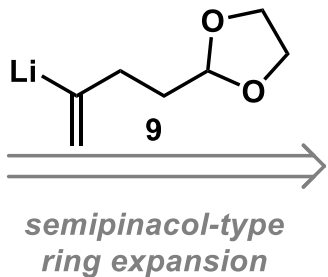
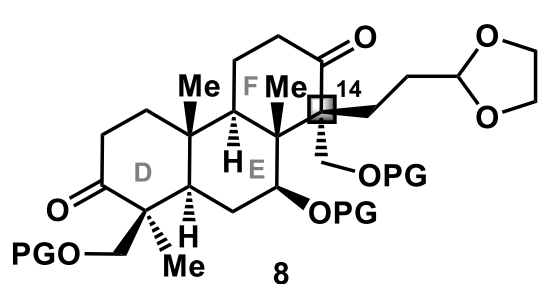
A/B/C spirocycle



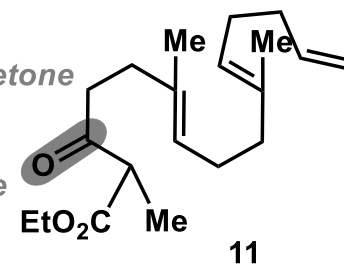
Pd cat.
intramolecular
alkenylation

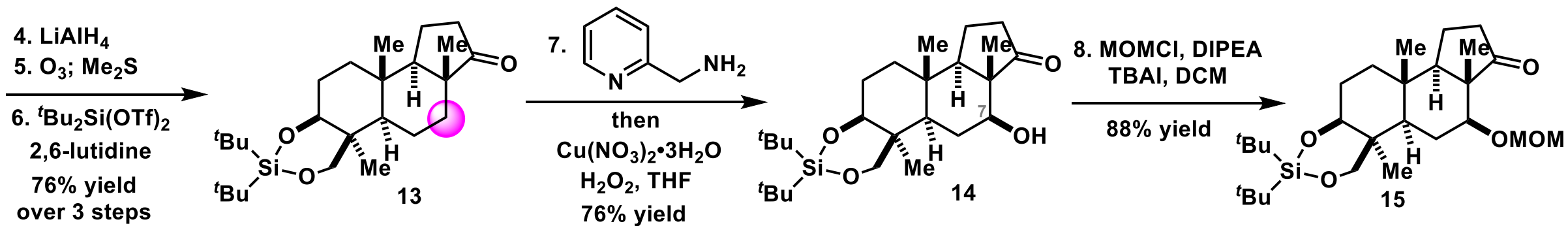
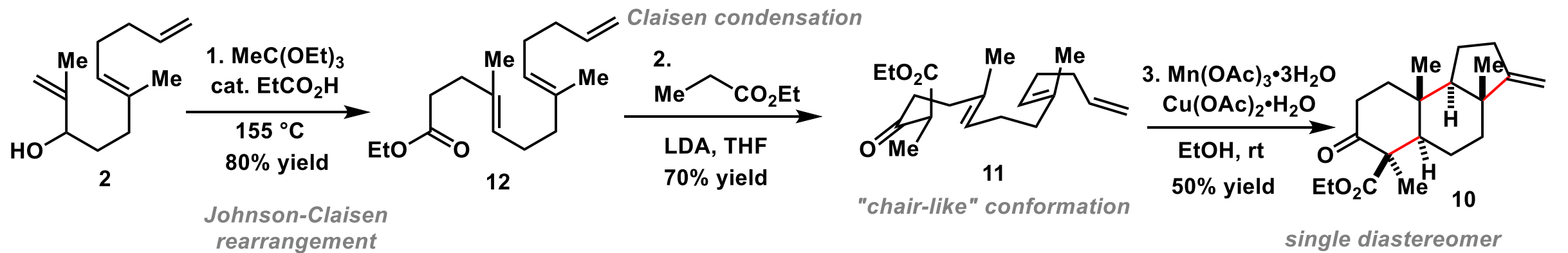


D/E/F core

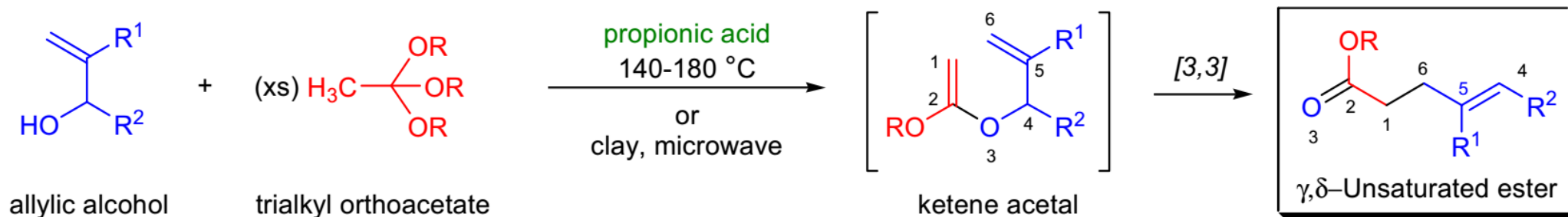


Mn/Cu
radical polyene
cyclization

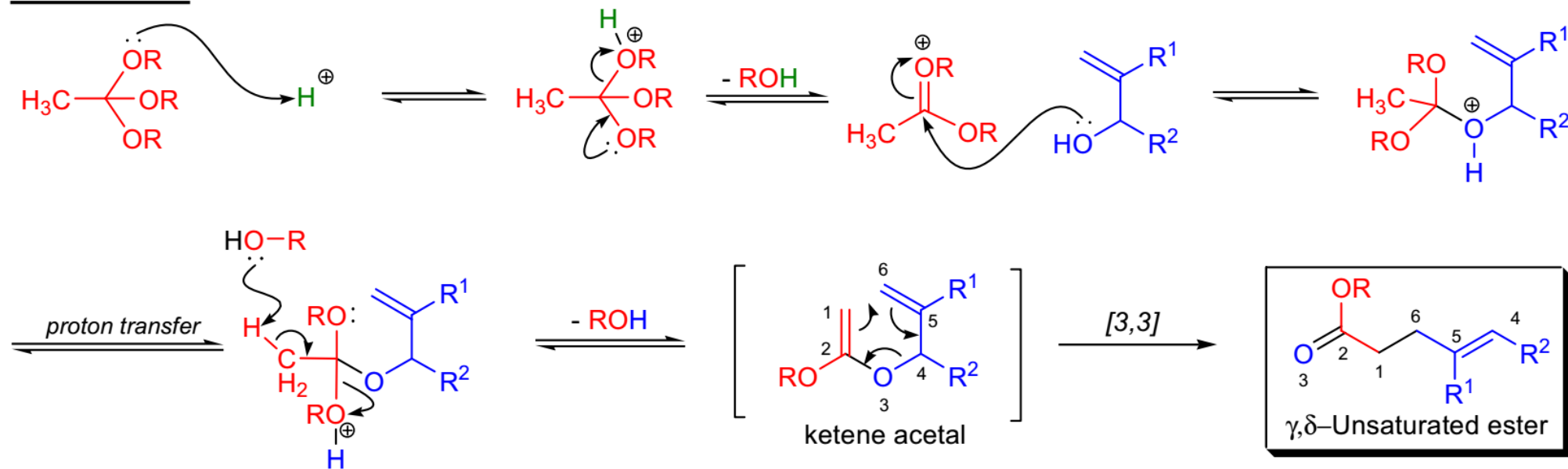




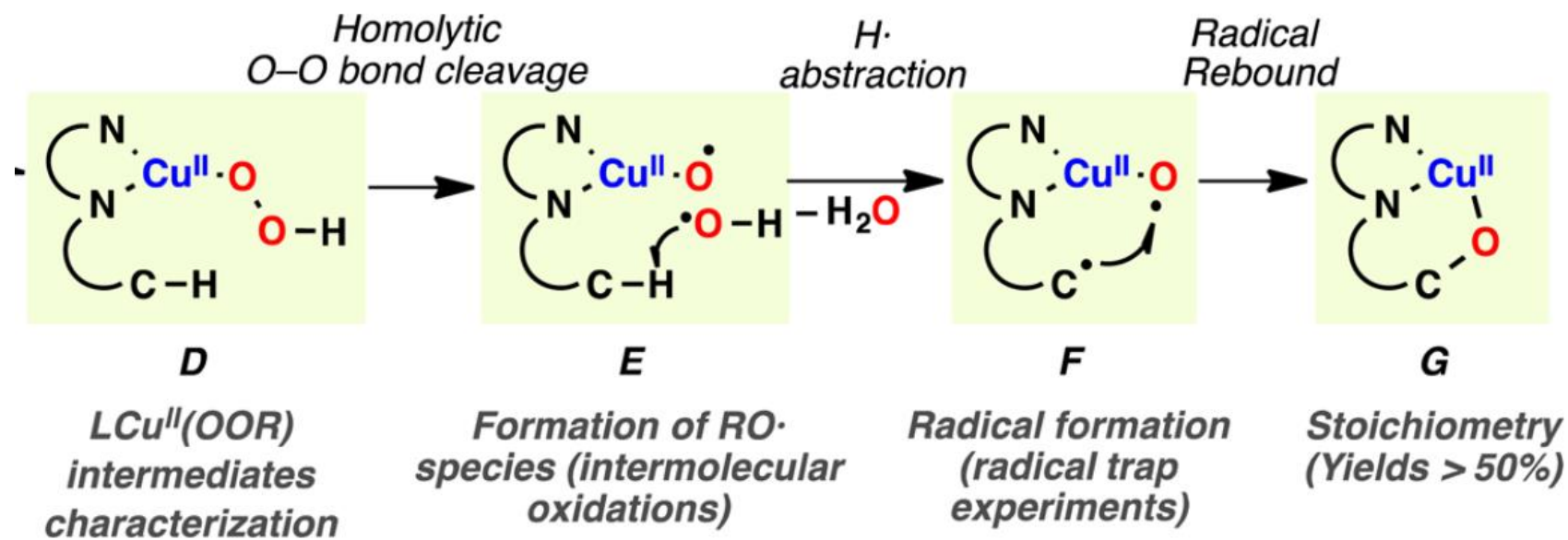
Johnson-Claisen rearrangement



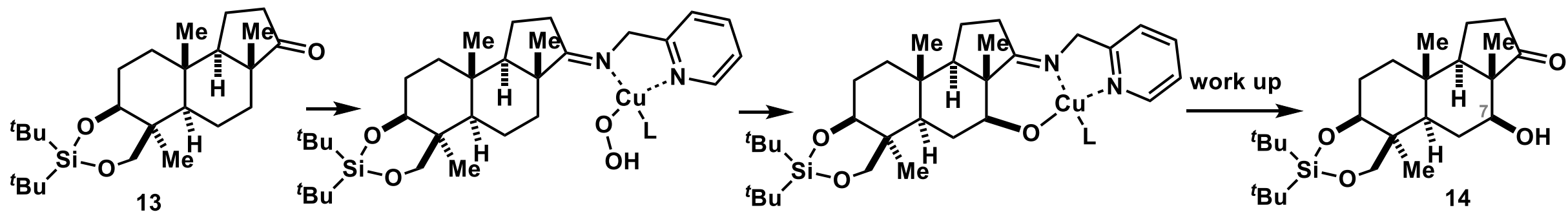
Mechanism:

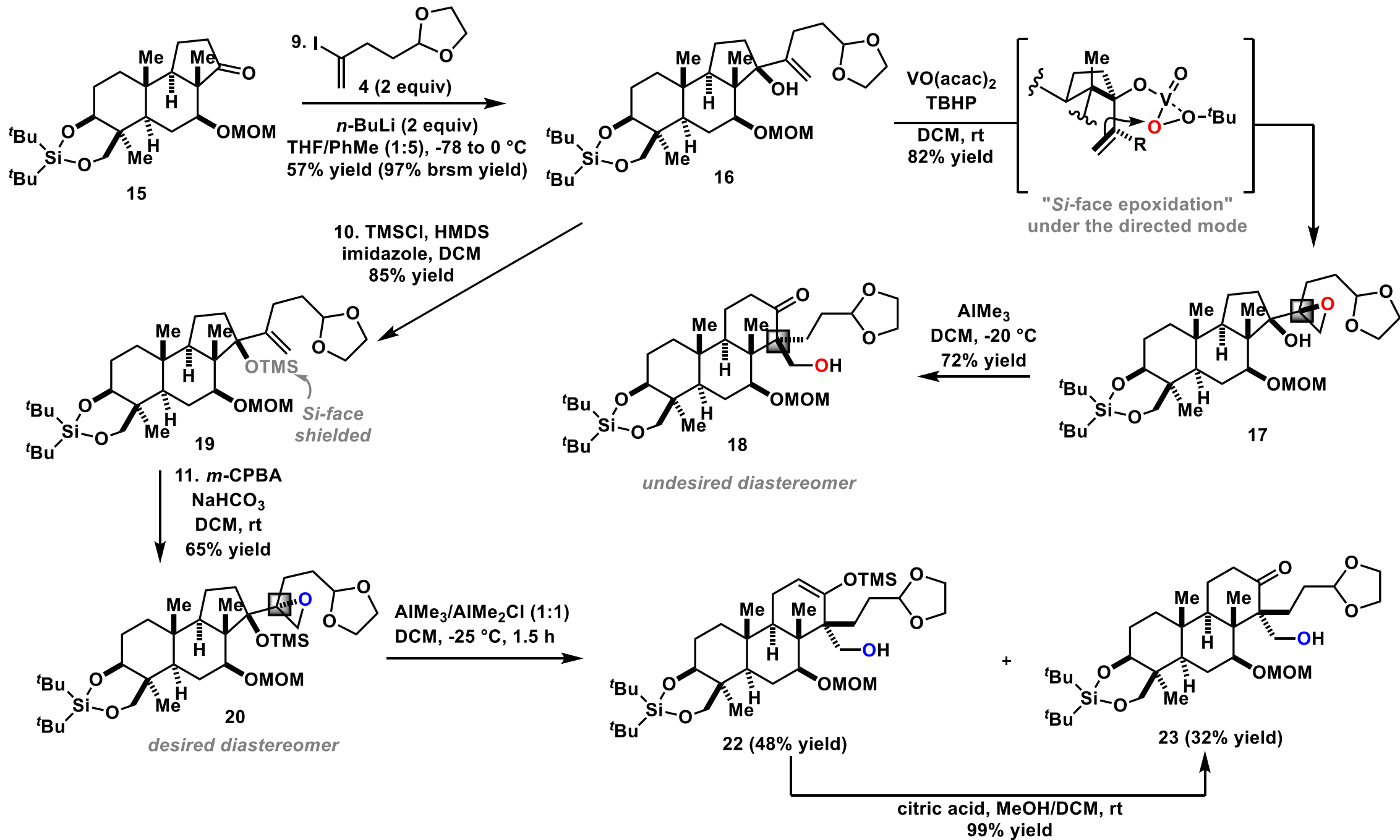


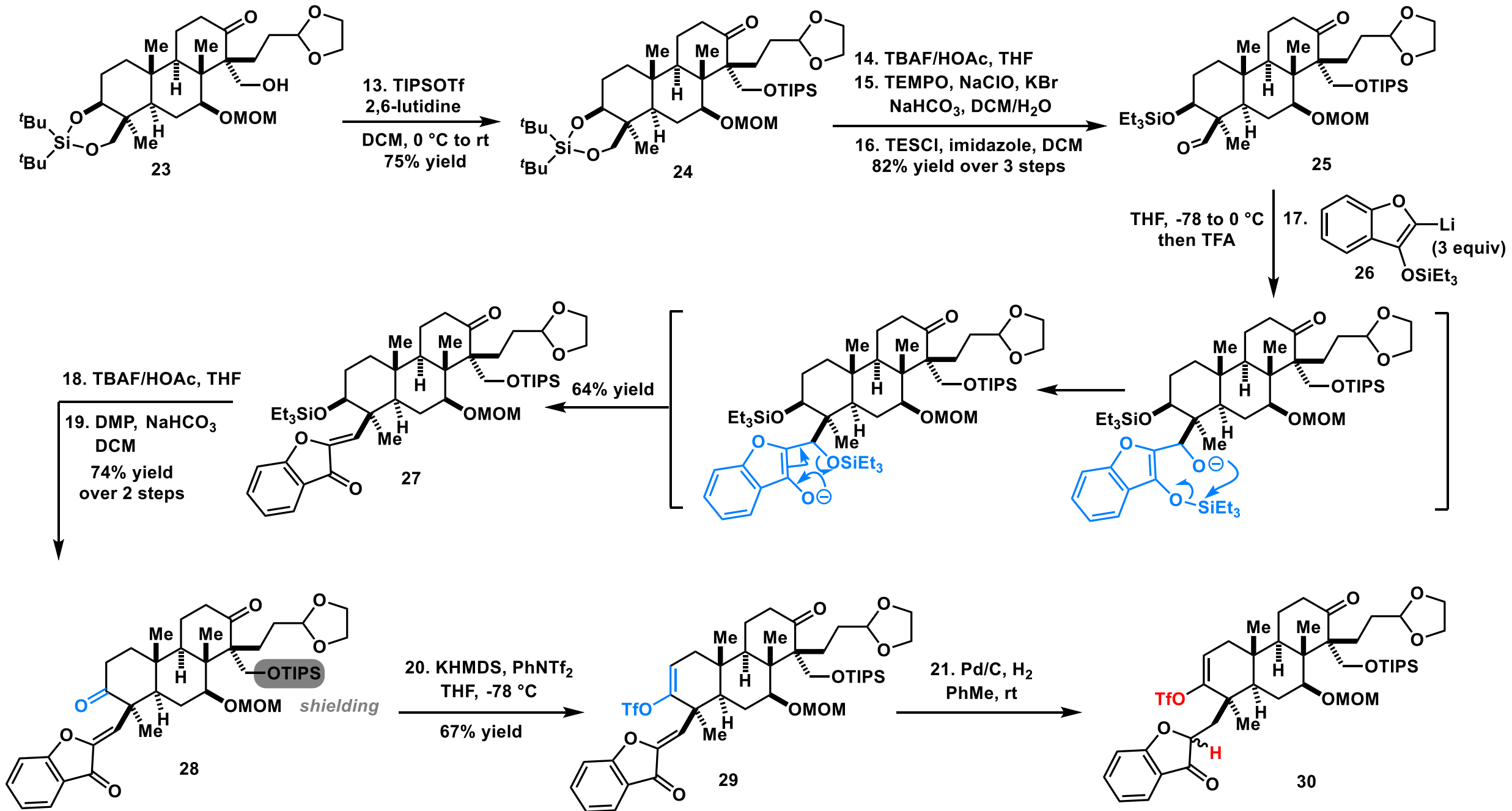
ketone-directed C-H oxidation

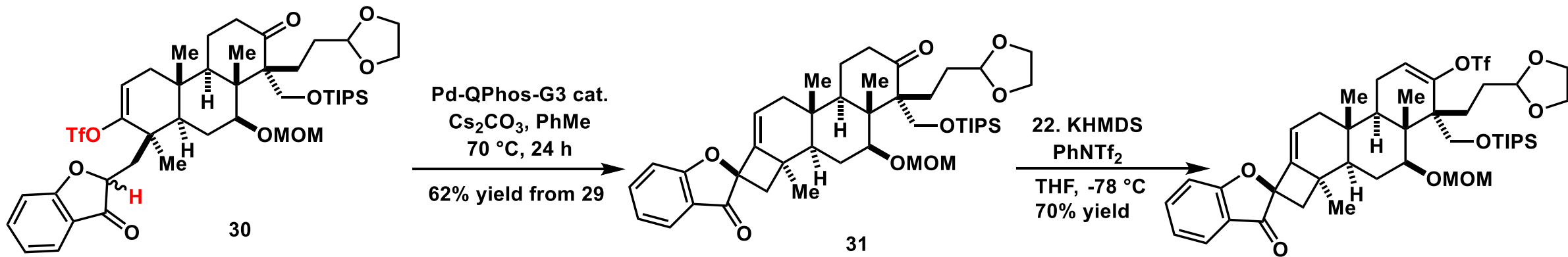


J. Org. Chem. **2017**, *82*, 7887.



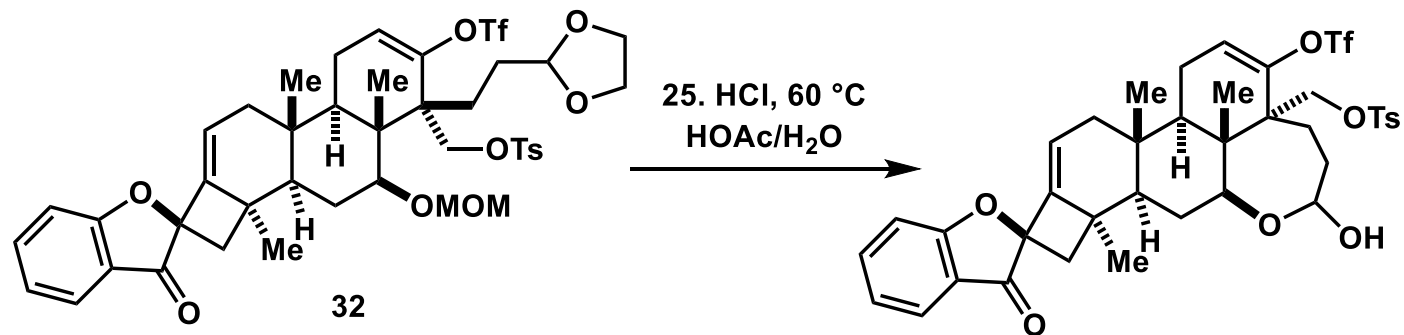


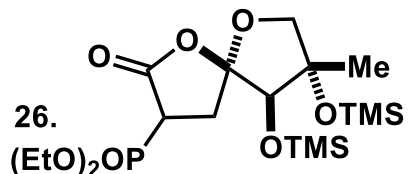




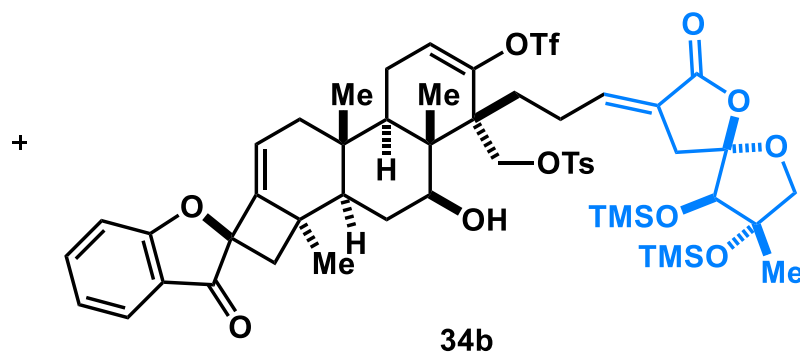
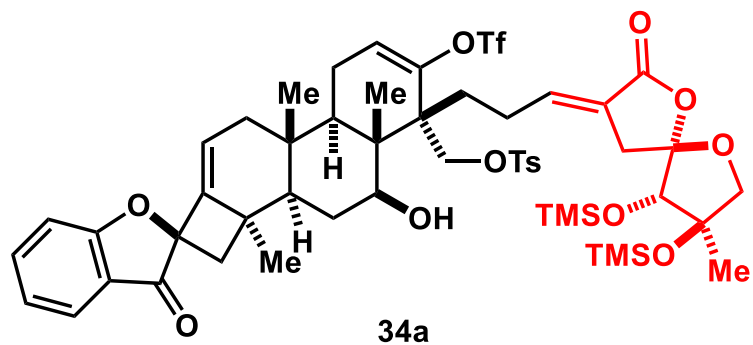
23. TBAF/HOAc, THF

24. TsCl, Et₃N, DMAP, DCM
65% yield over 2 steps

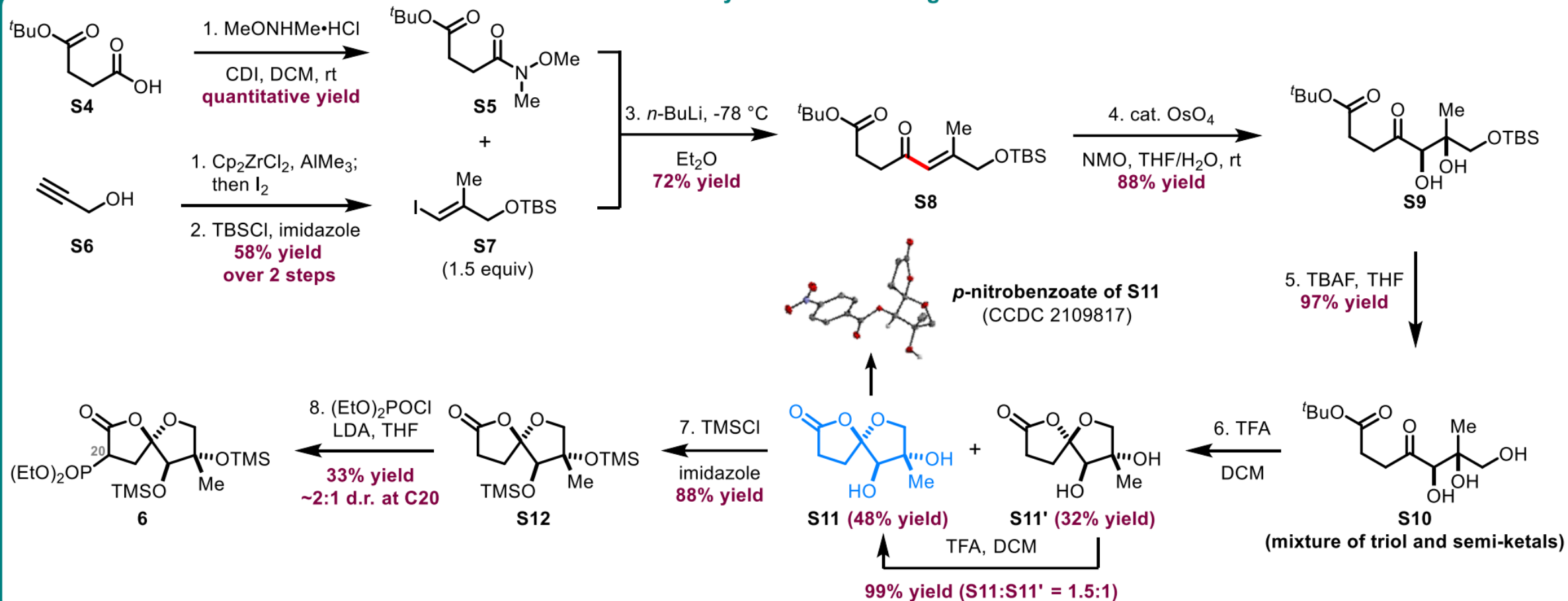


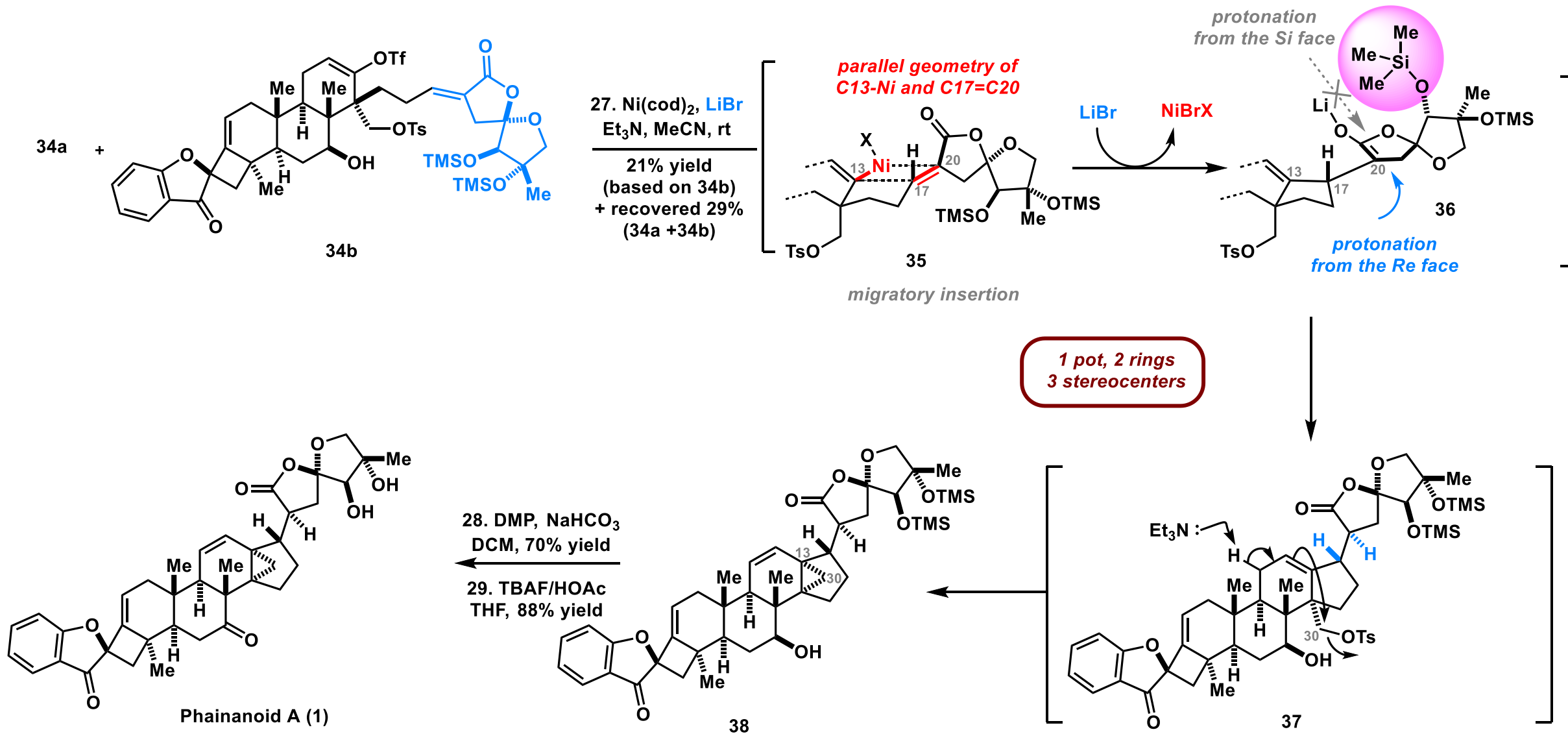
26. 
 (EtO)₂OP (racemate)
 6 (3 equiv)

DIPEA, LiCl, MeCN, 36 °C
 57% yield, 63% brsm
 (34a:34b = 1:1)

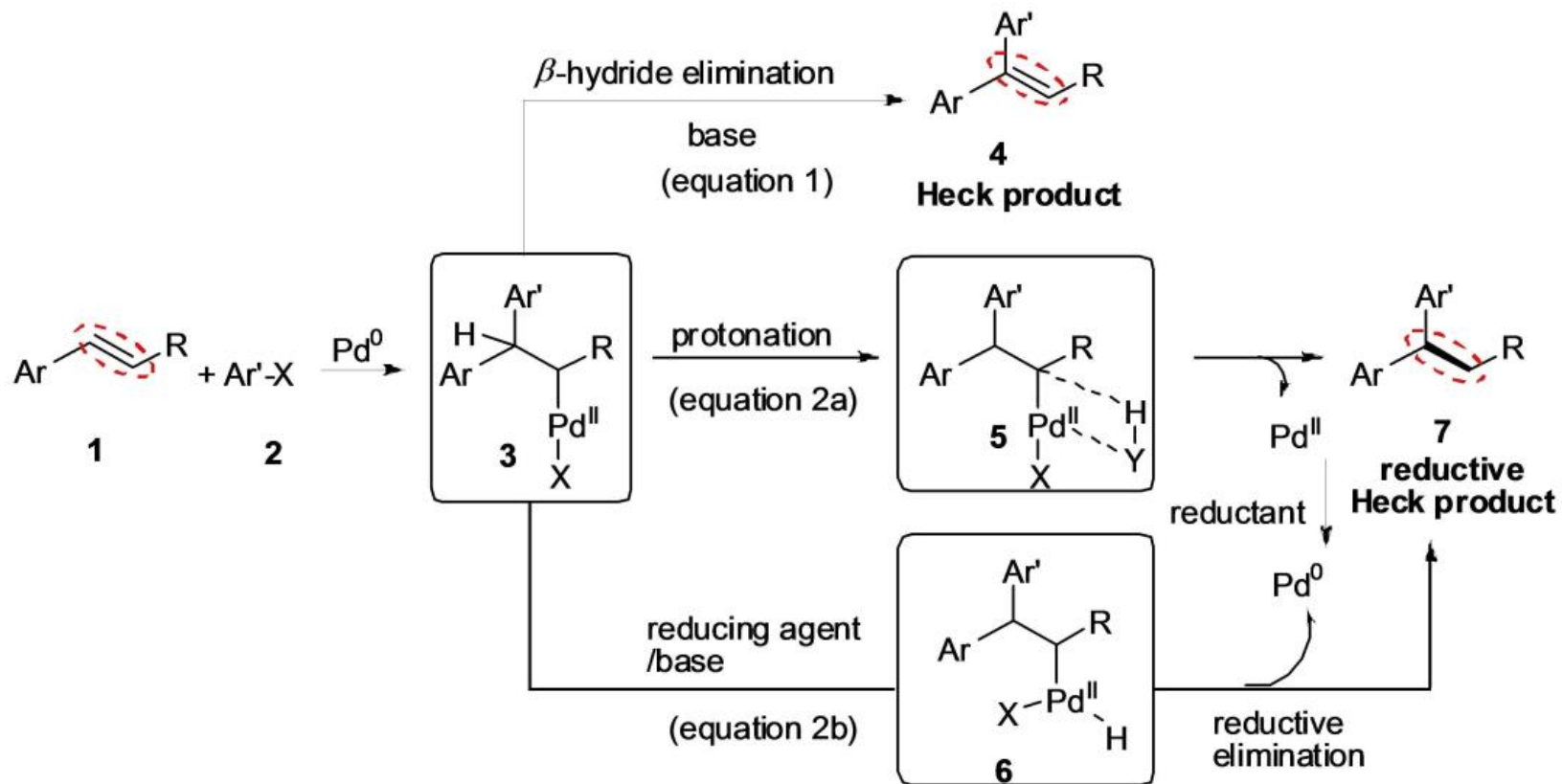


Synthesis of HWE agent 6

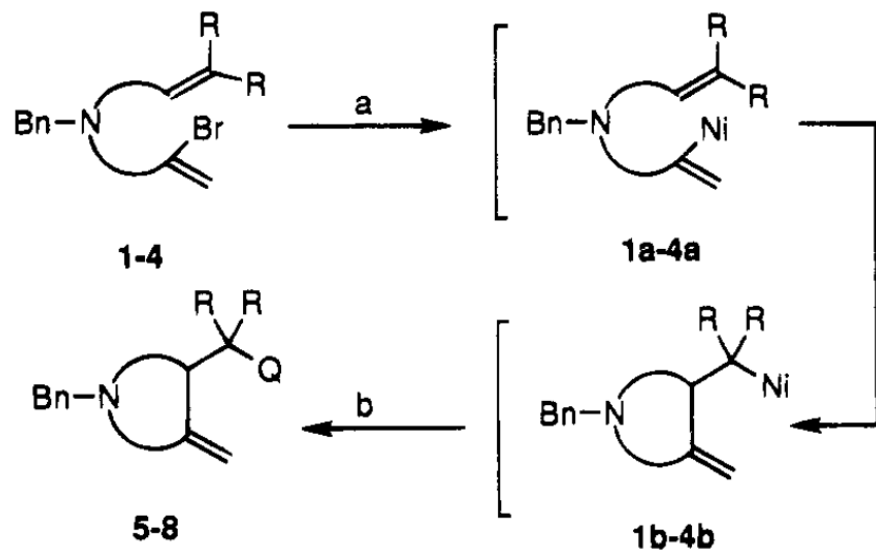




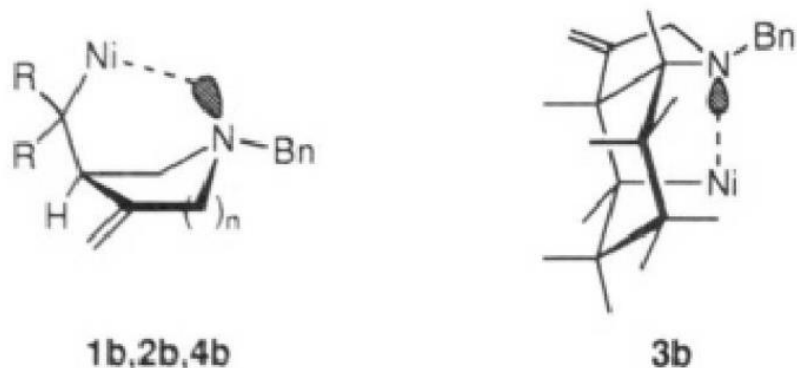
reductive Heck reaction



Scheme 1. Plausible mechanistic pathways; Heck product versus reductive Heck product.



^a (a) Ni(COD)₂, (1–2 equiv), CH₃CN, 3–10 min; (b) quencher (Q); R: H, alkyl.



entry	substrate	quencher ^(a)	product	R	% isolated yield
1 2 3		A B C		5a COOCH ₃ 5b CN 5c H	70 99 45
4 5		A B		6a COOCH ₃ 6b CN	50 61
6 7 8 9 10		A B C D E		7a COOCH ₃ 7b CN 7c H 7c H 7d OH	95 ^(b) 99 ^(b) 70 ^(b) 77 ^(b) 45 ^(b,c)
11 12 13		A B C		8a COOCH ₃ 8b CN 8c H	40 60 ^(d) 41 ^(e)

^a A: addition of MeOH (3 equiv) and bubbling of CO through the reaction mixture. B: TMS-CN (neat, 2.5 equiv). C: NaBH₄ (16 equiv) in MeOH (6 equiv). D: Et₃SiH (neat, 2.5 equiv). E: O₂ bubbling through the reaction mixture. ^b Stereochemistry based on ¹H and ¹³C

homoallylic elimination

