Total Synthesis of (-)-Daphnezomines A and B

Chao Li's group *J. Am. Chem. Soc.* 2020, **142**, 15240

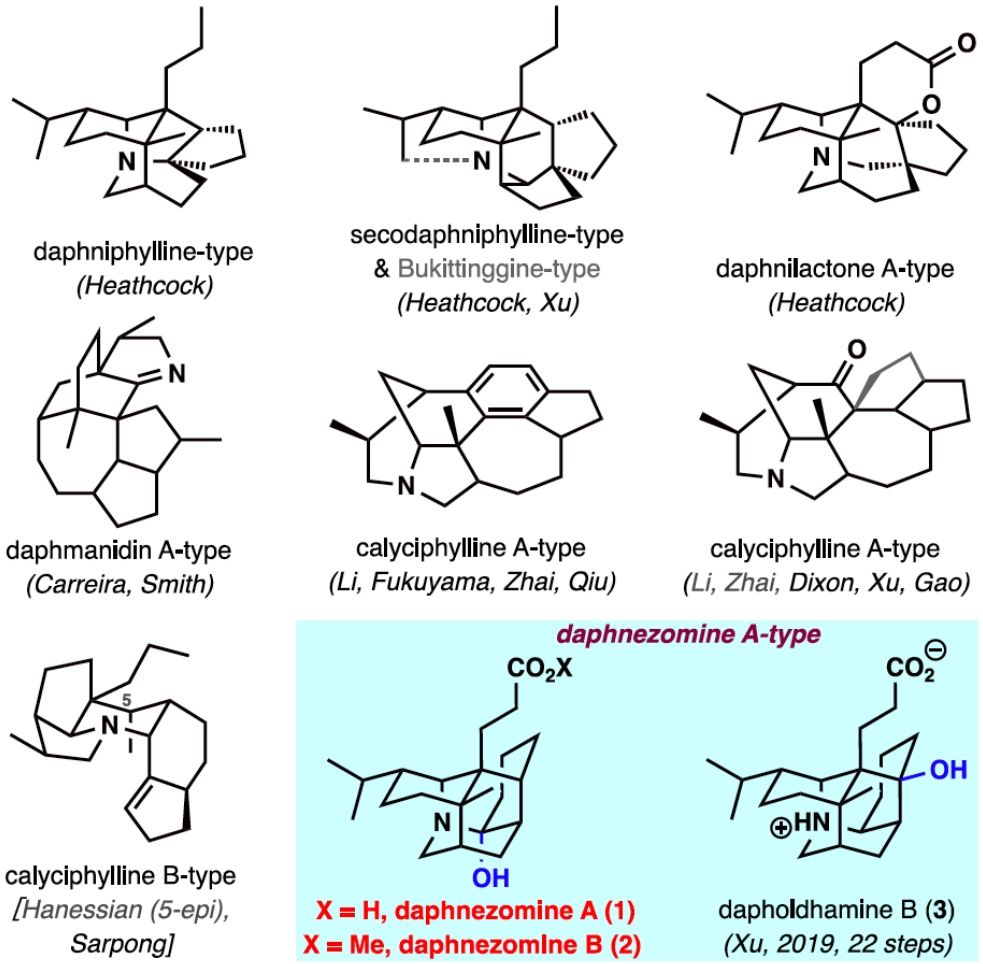
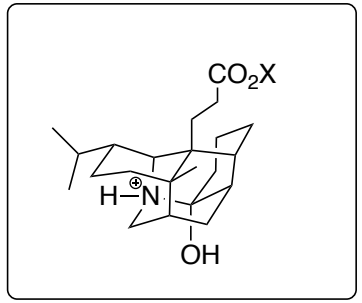


Figure 1. Frameworks of previously synthesized *Daphniphyllum* alkaloids, and the structures of daphnezomine A-type alkaloids.

- belong to the Daphniphyllum alkaloids family isolated from plants *Daphniphyllum*
- biological activities including anticancer, anti-HIV and anti-oxidant
- Daphnezomine A-type: aza-adamantane core bearing a carbinolamine bridge system.
- Xu reported the total synthesis of Dapholdhamine B, and here Chao Li's group reported the first total synthesis of (-)-Daphnezomines A and B

Xinyu Yang 12/16/2020
Liu's group total synthesis presentation

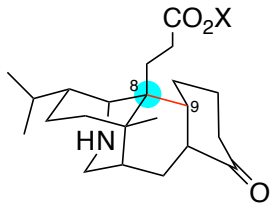
Retrosynthetic Analysis



X = H daphnezomine A (**1**)
X = Me daphnezomine B (**2**)

keto amine — carbinolamine tautomerization

H^+
tautomer—locked



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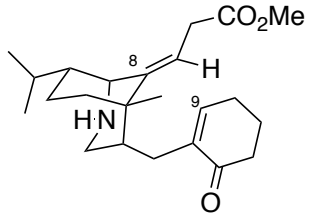
HAT-based radical cyclization



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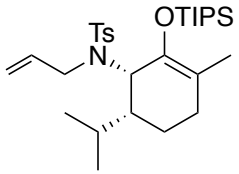
olefination



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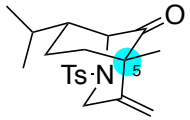
palladium-catalyzed oxidative cyclization



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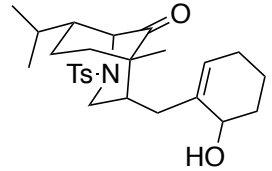
stereoselective
B-alkyl Suzuki-Miyaura Coupling



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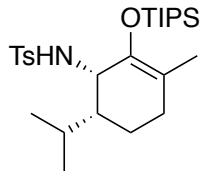

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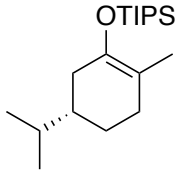
Sharpless allylic amination



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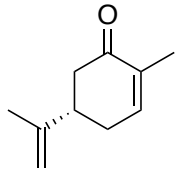
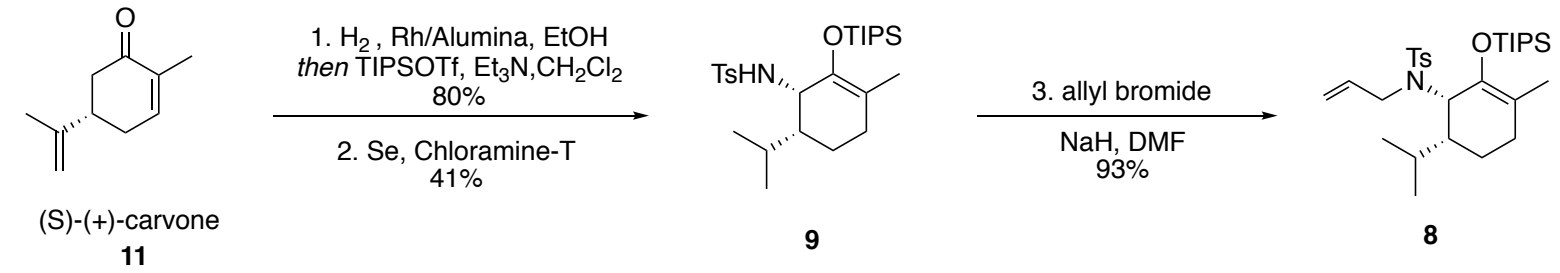


(S)-(+)-carvone
11

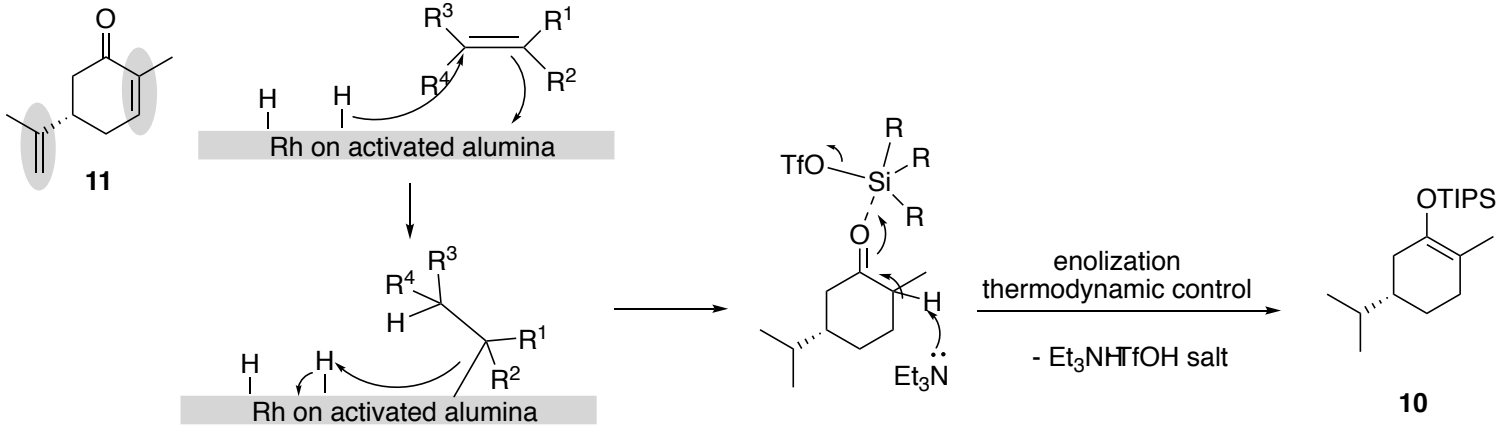


(S)-(+)-carvone
11

9

8

global alkene hydrogenation — enolization



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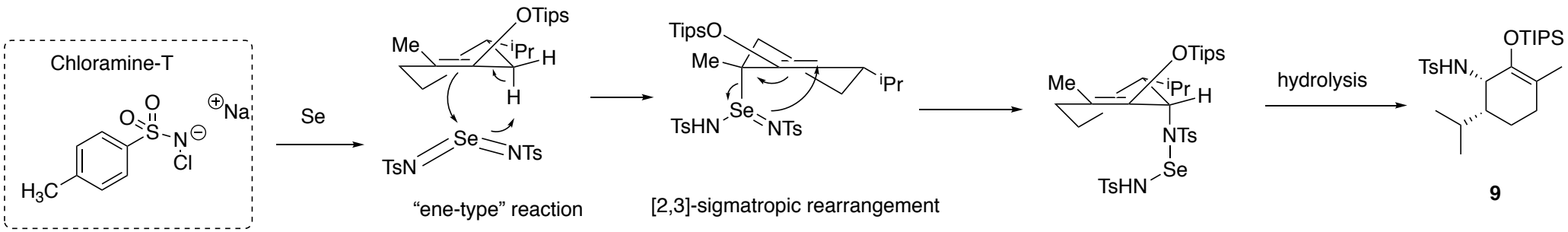
10

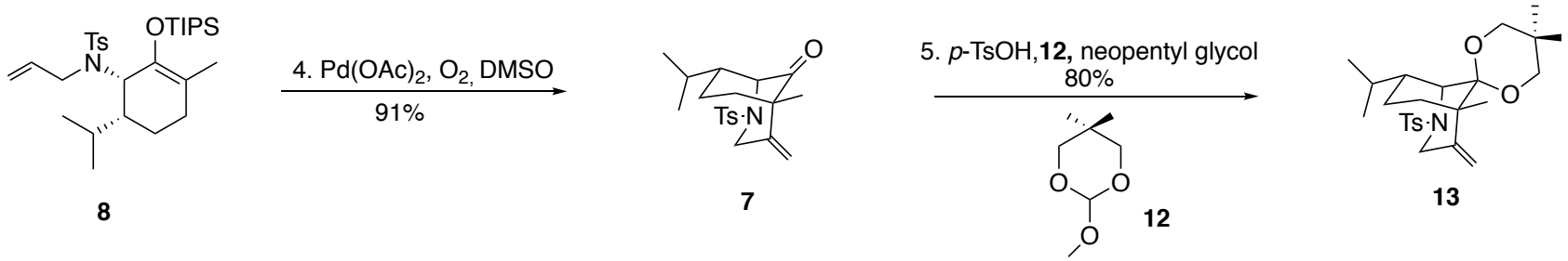
Sharpless allylic amination



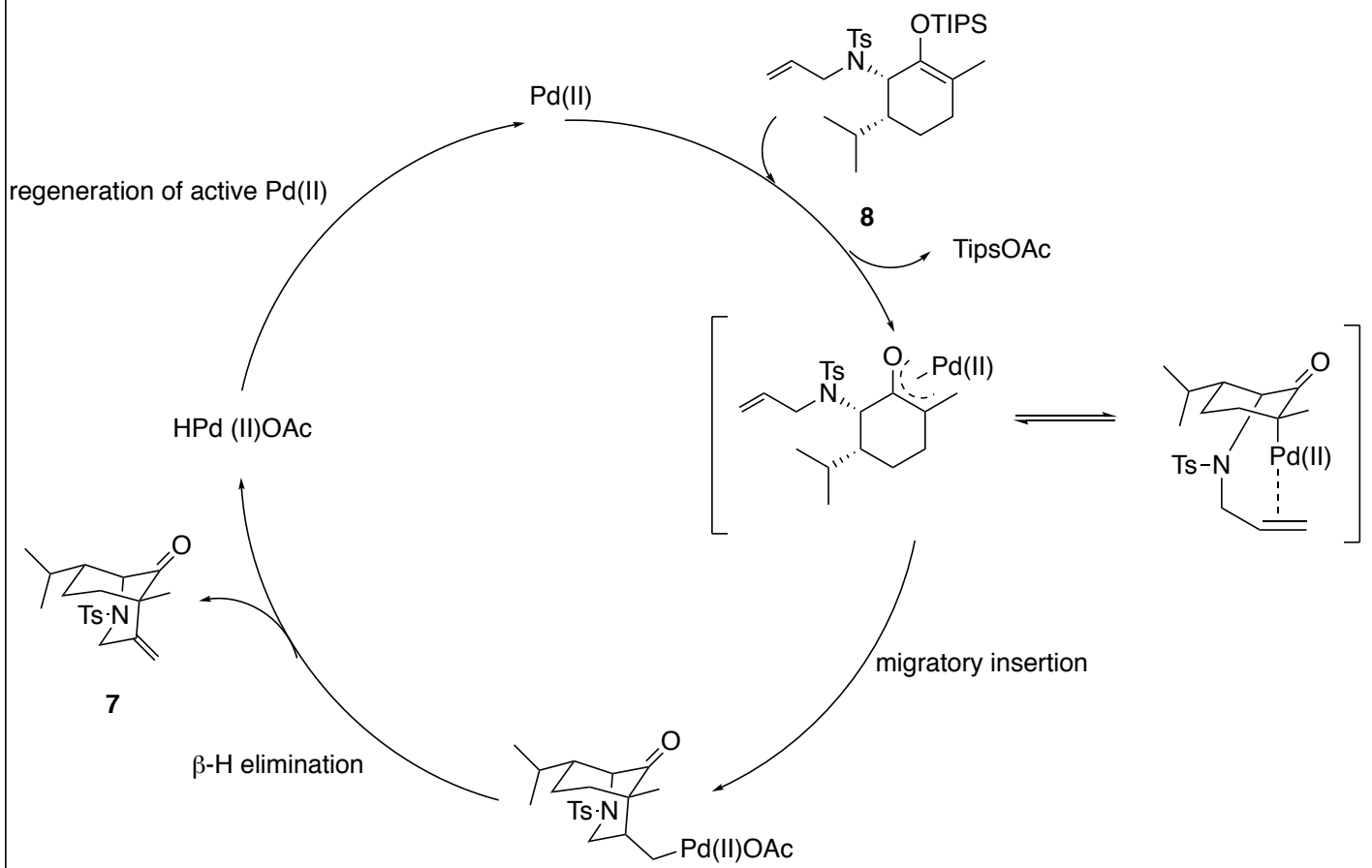
"ene-type" reaction

[2,3]-sigmatropic rearrangement

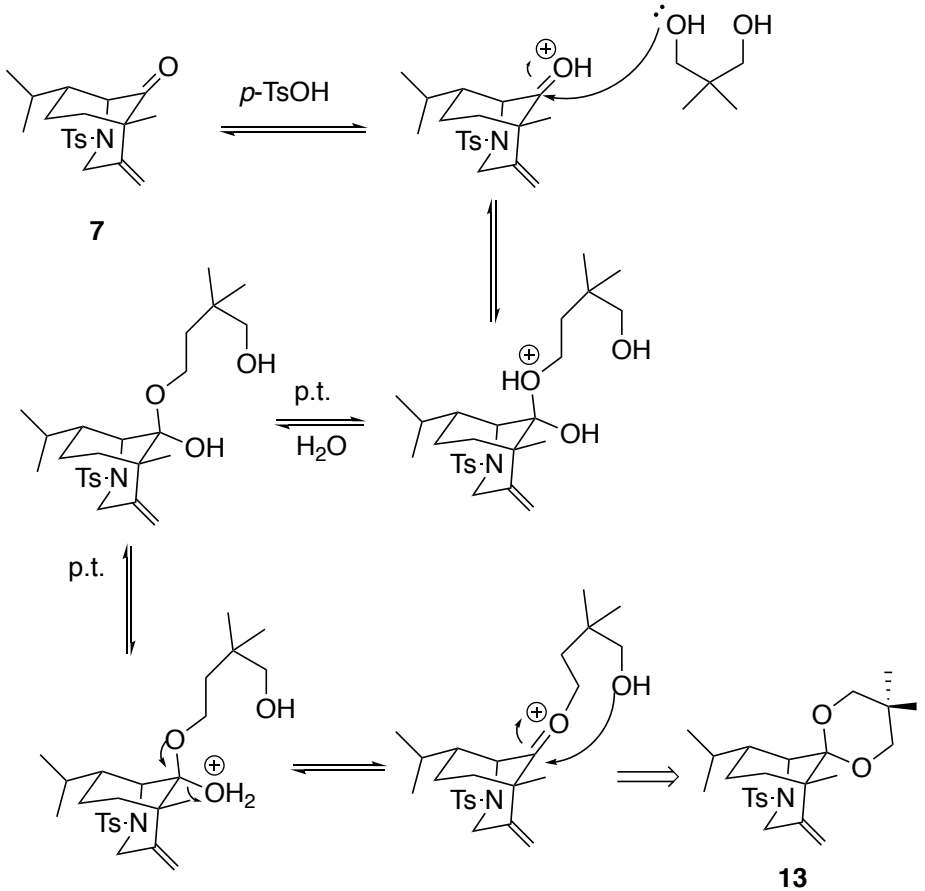
9

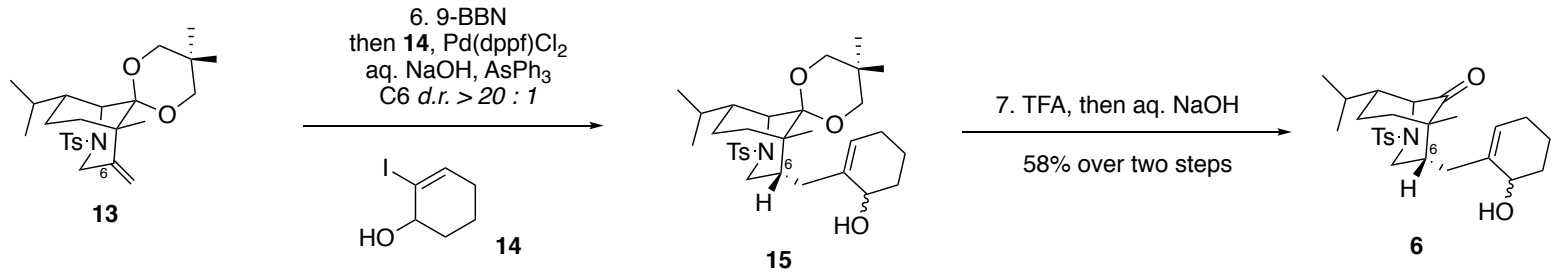


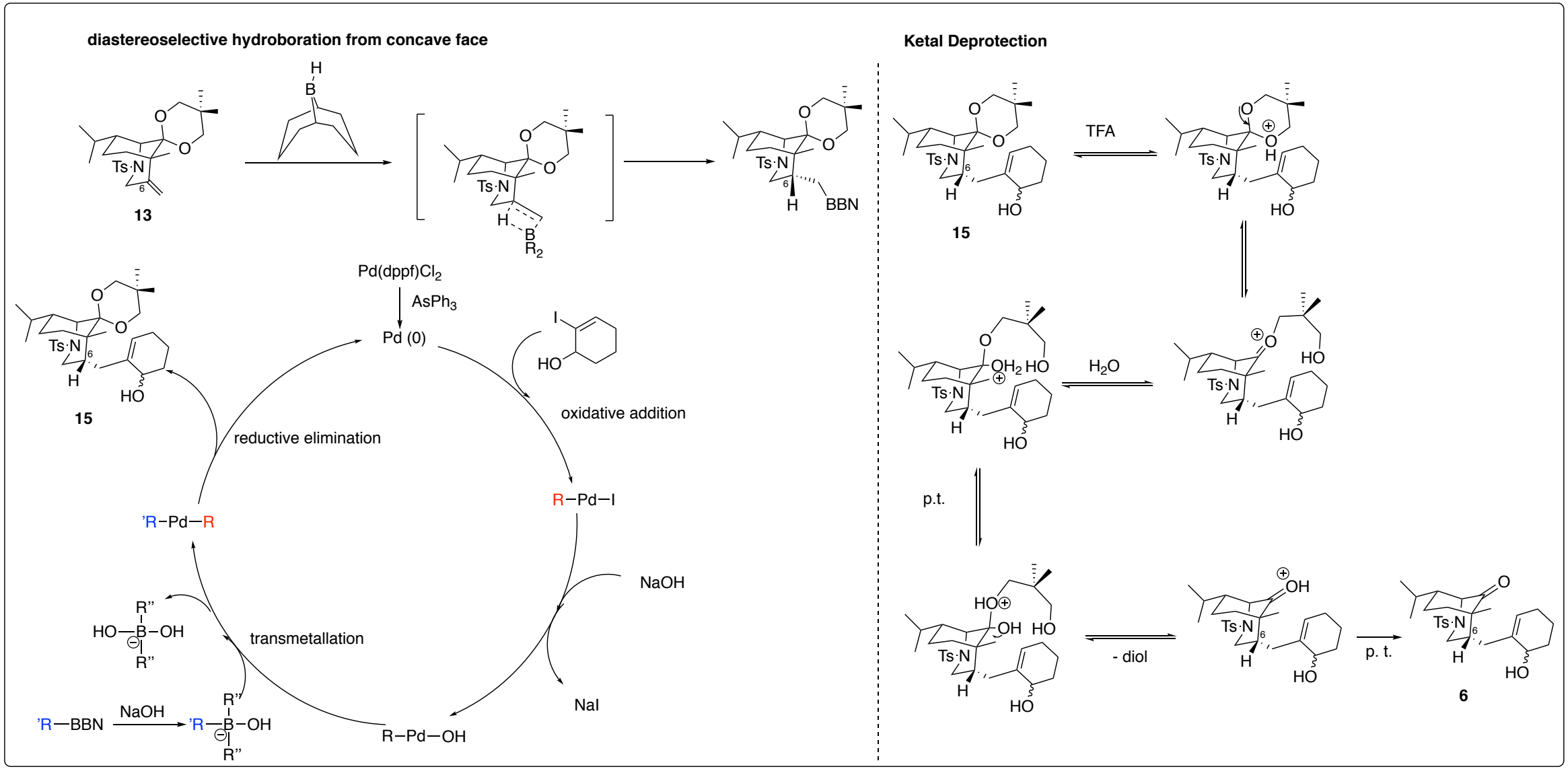
palladium-catalyzed oxidative cyclization

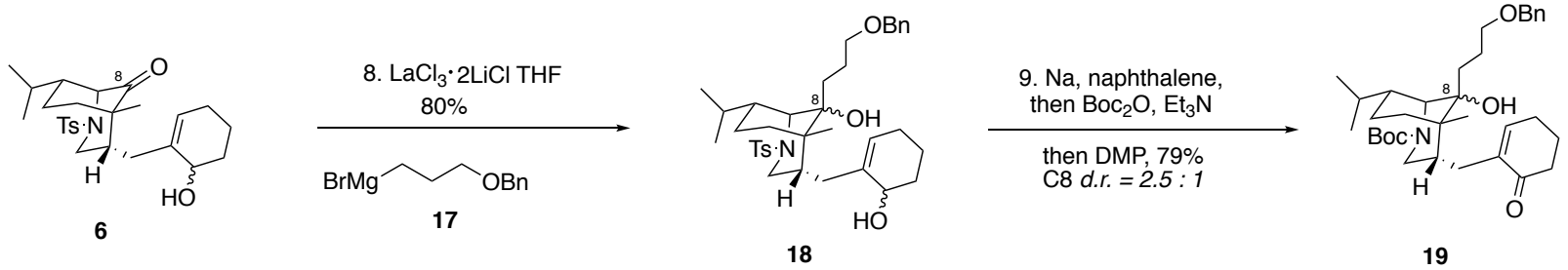


Ketal protection



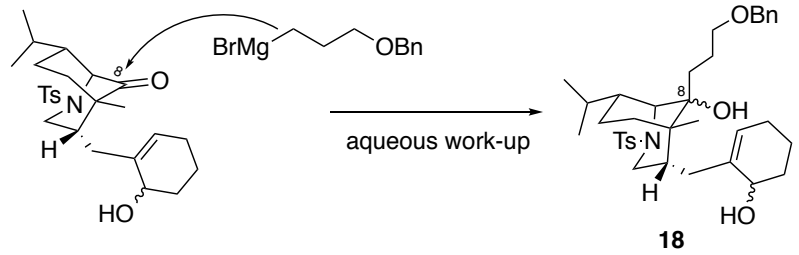

6. 9-BBN
then 14, Pd(dppf)Cl2
aq. NaOH, AsPh3
C6 d.r. > 20 : 1
7. TFA, then aq. NaOH
58% over two steps
13
14
15
6


diastereoselective hydroboration from concave face
Ketal Deprotection
13
15
BBN
Pd(dppf)Cl2
AsPh3
Pd (0)
oxidative addition
R–Pd–I
NaOH
NaI
R–Pd–OH
transmetallation
'R–Pd–R
reductive elimination
'R–BBN
NaOH
TFA
H2O
p.t.
- diol
p. t.
6

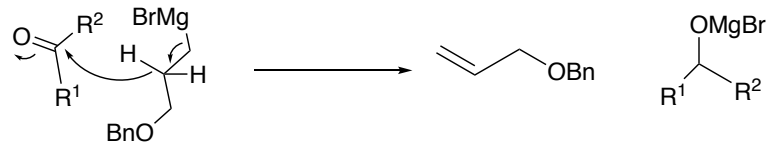


nucleophilic addition using grignard reagent: Knochel's Salt ($LaCl_3$ 2LiCl) is important

with Knochel's salt

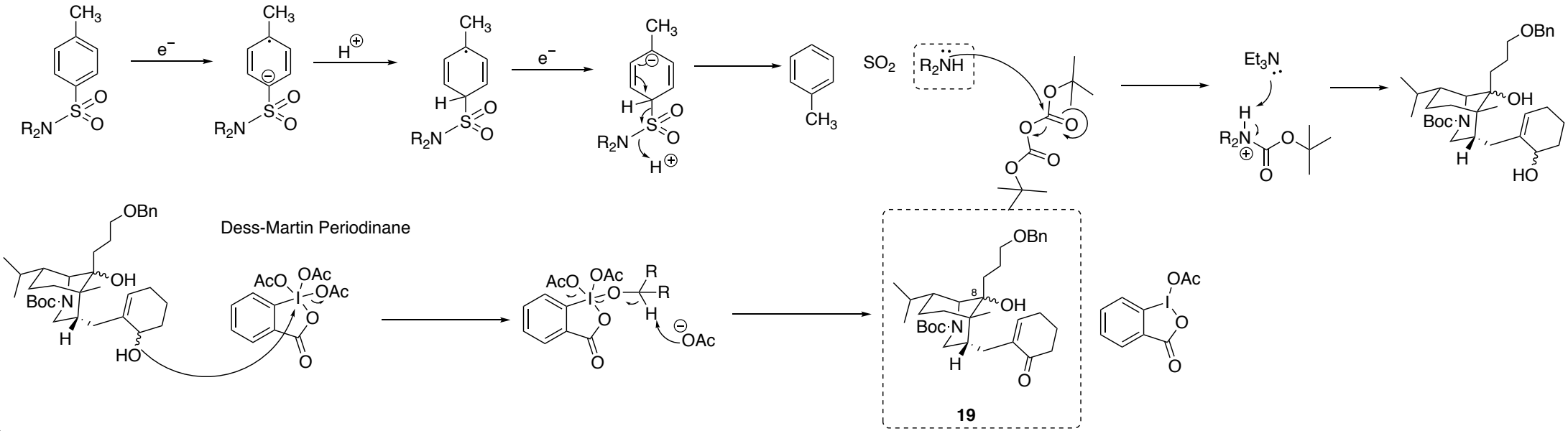


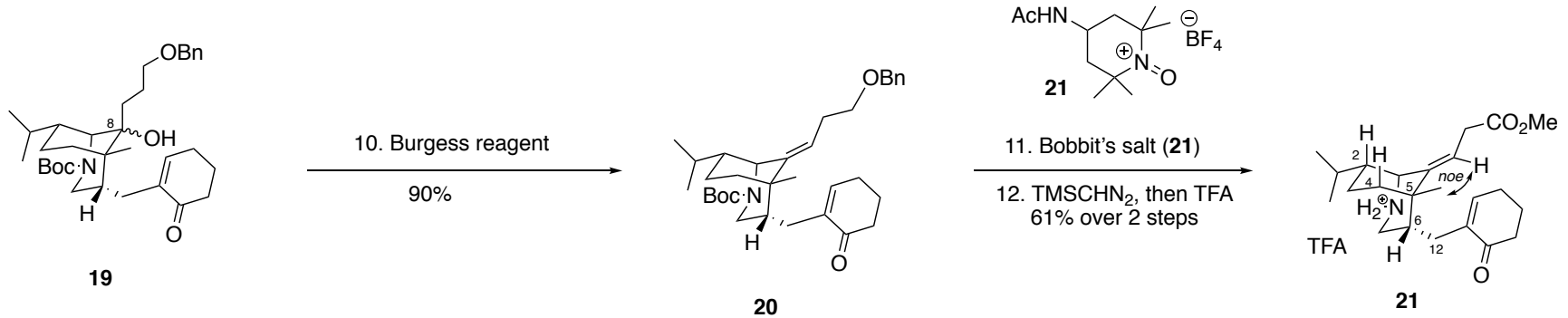
without Knochel's salt : Grignard reduction via β-H elimination



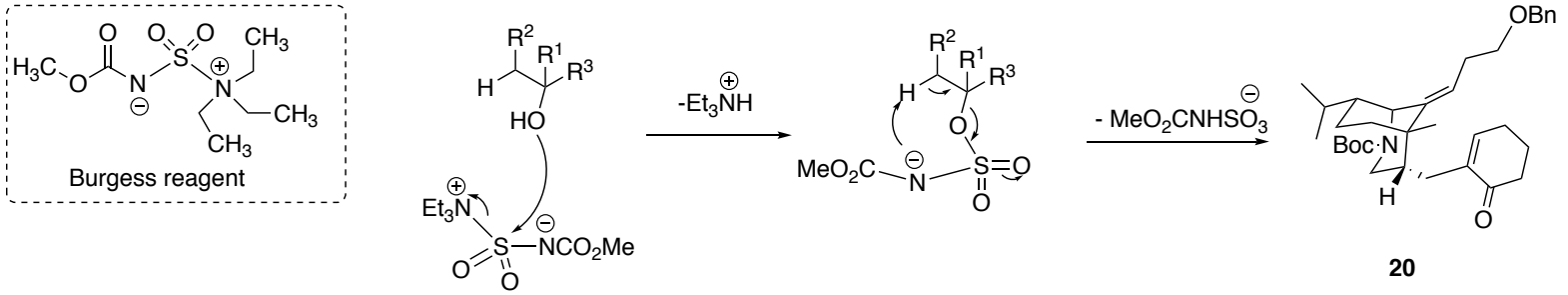
the role of lanthanum salt:
1. promote 1,2-addition;
2. prevent Grignard reduction;
3. attenuate basicity of Grignard

deprotection — reprotection —Dess Martin Oxidation

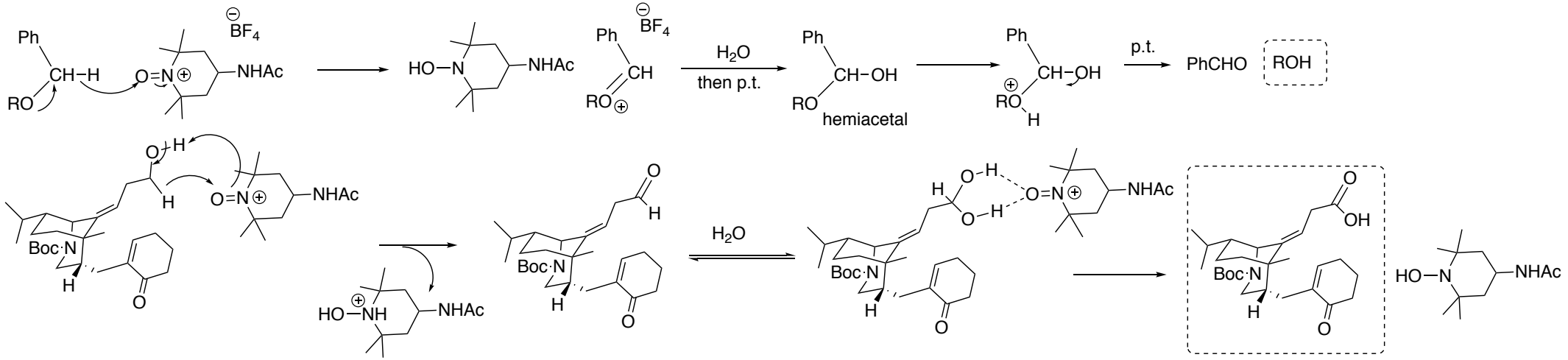


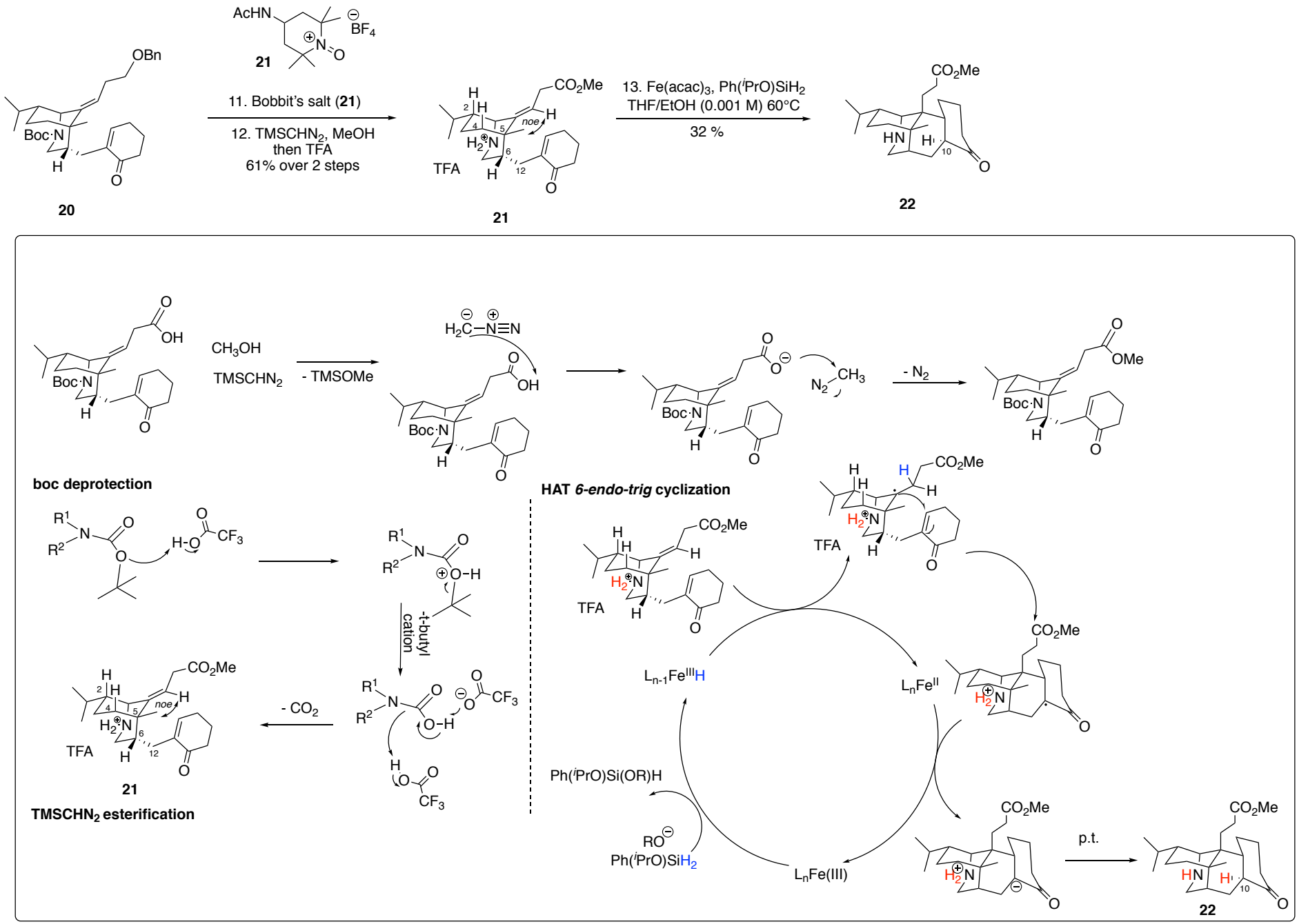


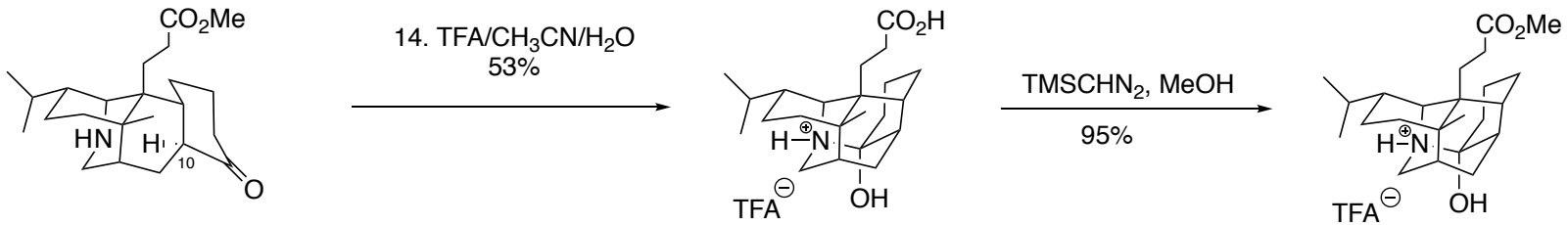
dehydration of tertiary alcohol by Burgess reagent



benzyl other cleavage and further oxidation by Bobbit's salt

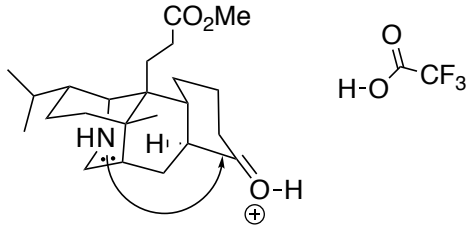


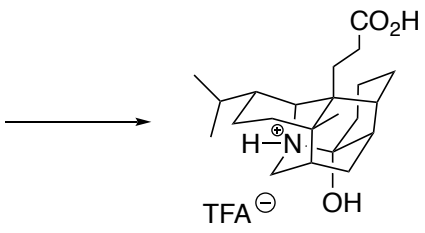

20
21
11. Bobbit's salt (21)
12. TMSCHN2, MeOH
then TFA
61% over 2 steps
13. Fe(acac)3, Ph(iPrO)SiH2
THF/EtOH (0.001 M) 60°C
32 %
22
boc deprotection
CH3OH
TMSCHN2
- TMSOMe
HAT 6-endo-trig cyclization
- N2
TMSCHN2 esterification
t-butyl cation
- CO2
TFA
Ln-1FeIIIH
LnFeII
LnFe(III)
Ph(iPrO)Si(OR)H
Ph(iPrO)SiH2
RO
p.t.



22 1 2

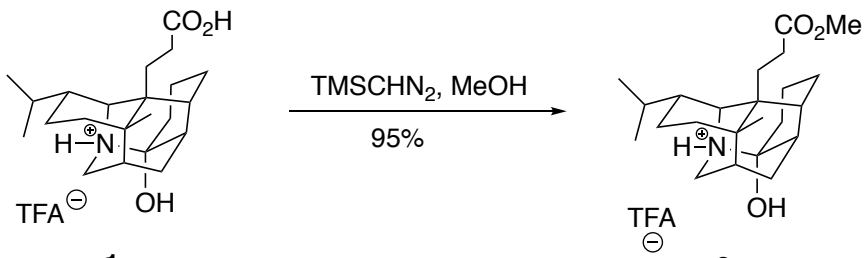
TFA promoted tautomerrization





1

$TMSCHN_2$ esterification



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