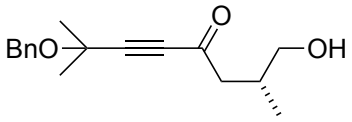
Problem Session (2)

21/10/23 Junhao Fu

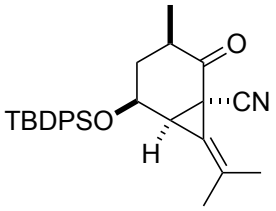
Please provide the mechanisms of the following reactions:

Problem 1

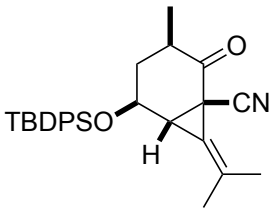


1-1

1. (*S*,*S*)-**A** (10 mol%), *t*-BuONa (0.10 eq.), acetone (1.2 eq.) *i*-PrOH (3.0 eq.), EtOAc, rt, 68% (*d.r.* = 18:1);
2. **B** (2 mol%), $CDCl_3$, rt, 81%;
3. LiHMDS (0.32 eq.), CH_3CN (0.34 eq.) THF, –78 °C, 93%;
4. TBDPSCl (3.0 eq.), imidazole (4.0 eq.), DMF, rt;
5. 1.0 M aq. NaOH, MeOH, rt, 86% (2 steps);
6. *p*-ABSA (1.1 eq.), Et_3N (1.5 eq.), CH_3CN, 0 °C, 65%;
7. $Rh_2(esp)_2$ (1 mol%), CH_2Cl_2, rt, 77%



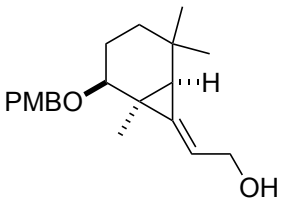
1-2



1-2'

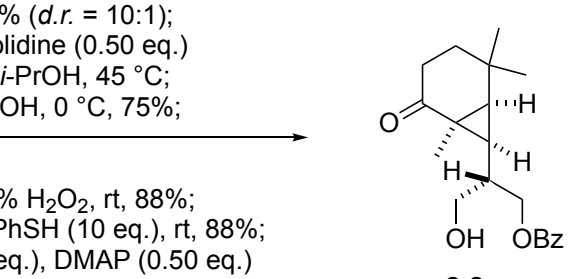
d.r. = 13:1

Problem 2

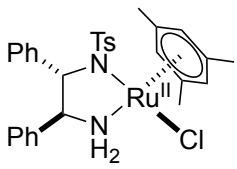


2-1

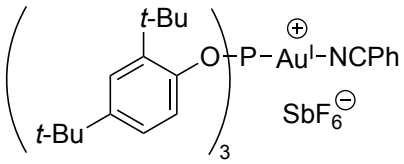
1. $[Ir(cod)(pyr)(PCy_3)]BAr_F$ (5 mol%) CH_2Cl_2, H_2 (1 atm), rt, 68% (*d.r.* = 10:1);
2. aq. HCHO (1.1 eq.), pyrrolidine (0.50 eq.) propionic acid (0.50 eq.), *i*-PrOH, 45 °C; then $NaBH_4$ (1.5 eq.), MeOH, 0 °C, 75%;
3. $BH_3 \cdot THF$ (2.0 eq.), rt; then 3.0 M aq. NaOH, 30% H_2O_2, rt, 88%;
4. *p*-$TsOH \cdot H_2O$ (0.32 eq.), PhSH (10 eq.), rt, 88%;
5. BzCl (2.0 eq.), Et_3N (4.0 eq.), DMAP (0.50 eq.) CH_2Cl_2, rt, 86%;
6. *ca.* 0.5 M TFDO, CH_2Cl_2, -78 °C, 96%



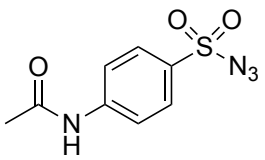
2-2



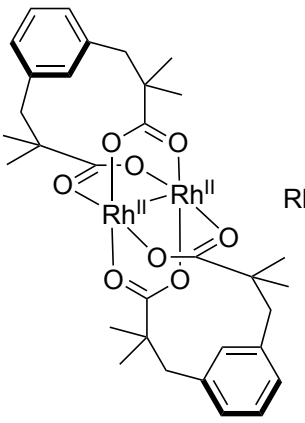
(*S*,*S*)-**A**



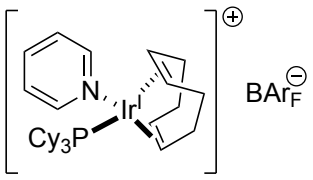
B



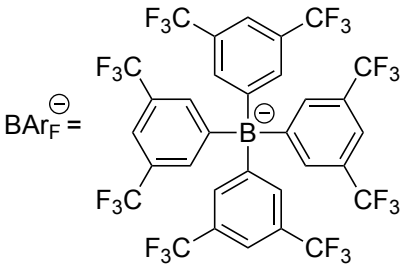
p-ABSA



$Rh_2(esp)_2$



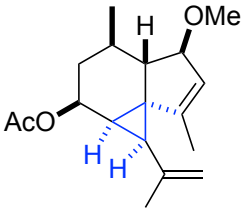
$[Ir(cod)(pyr)(PCy_3)]BAr_F$



Problem Session (2) – Answer

21/10/23 Junhao Fu

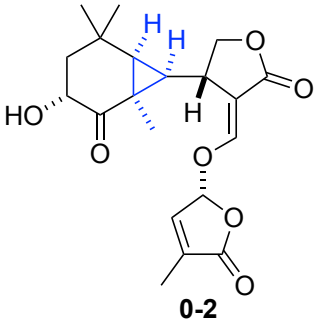
Topic: Total synthesis of non-cage-shaped natural products containing all-*cis*-substituted cyclopropanes



Shagenes A
Problem 1

- isolated from a soft coral in the Scotia Sea
- toxicity against *L. donovani* (IC_{50} = 5 μM)

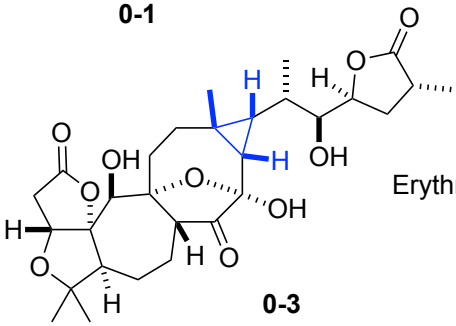
0-1



Avenaol
Problem 2

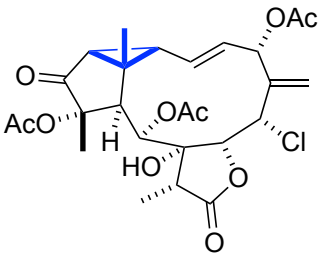
- isolated from the allelopathic plant balck oat
- germination-stimulating activity

0-2



Erythrolide A

0-3

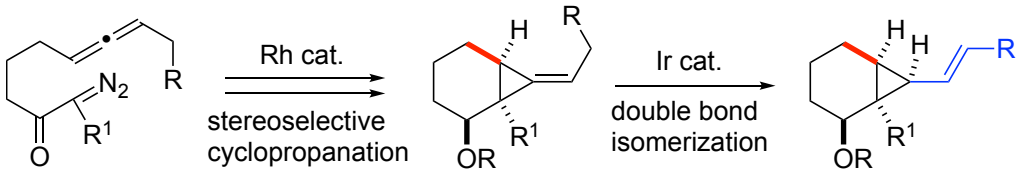


Arisanlactone C

0-4

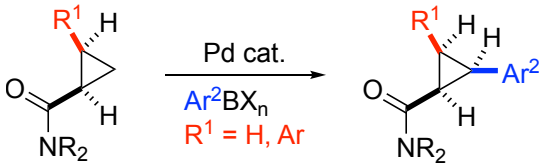
Construction of all-*cis*-cyclopropane:

(a) double bond isomerization of alkylidenecyclopropane



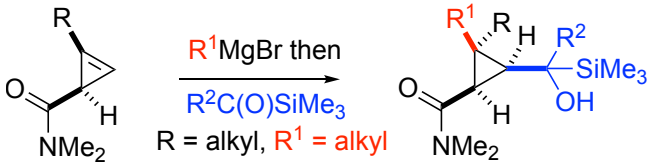
0-5 **0-6** **0-7**

(b) C-H functionalization



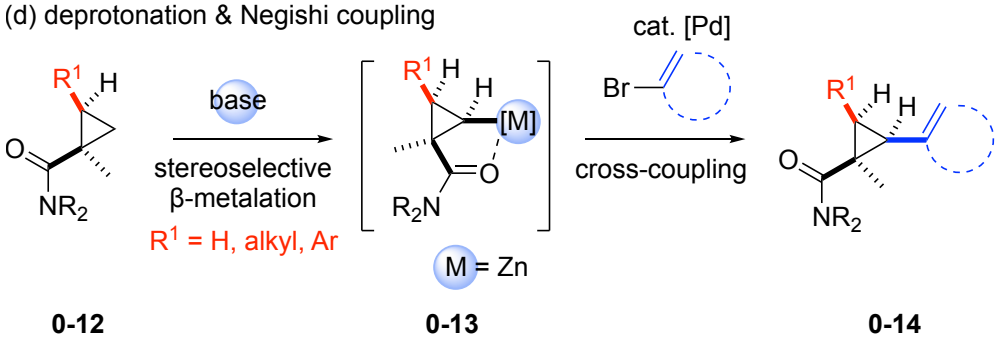
0-8 **0-9**

(c) carbometalation & addition of acyl silane



0-10 **0-11**

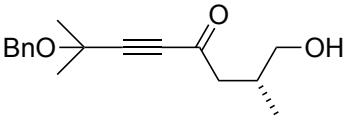
(d) deprotonation & Negishi coupling



0-12 **0-13** **0-14**

Yasui, M.; Ota, R.; Tsukano, C.; Takemoto, Y. *Org. Lett.* **2018**, *20*, 7656.

Problem 1



1-1

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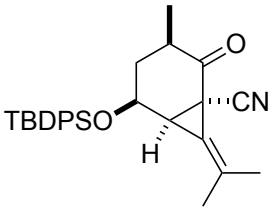
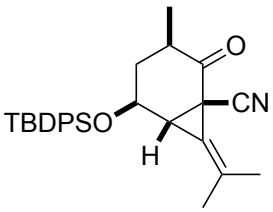


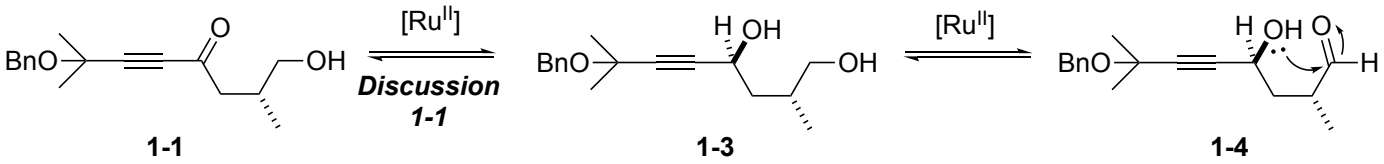
1-2

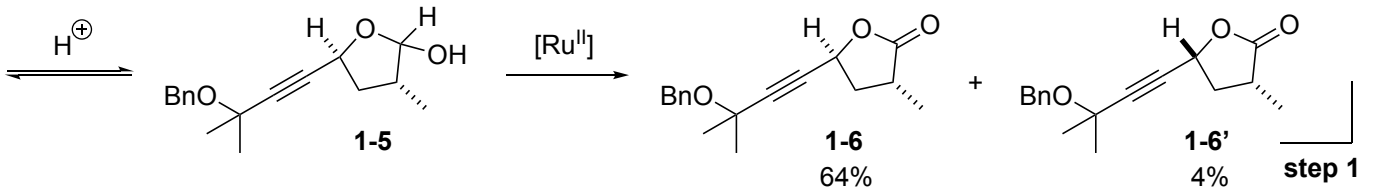


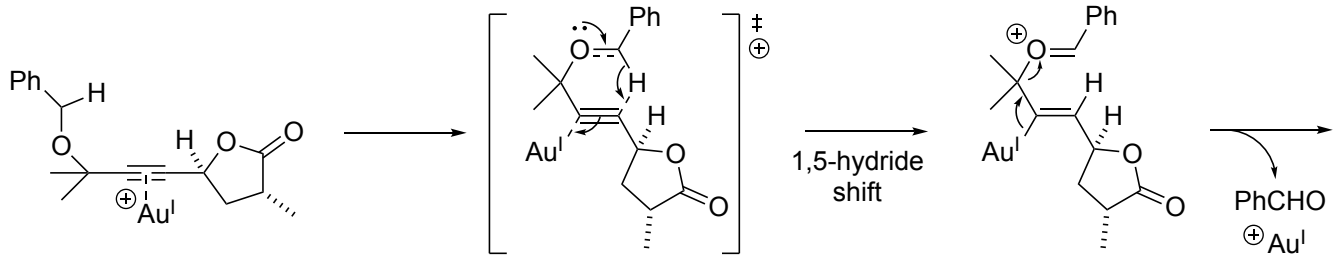
1-2'

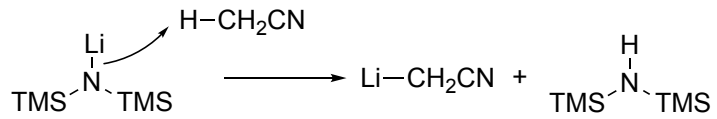
d.r. = 13:1

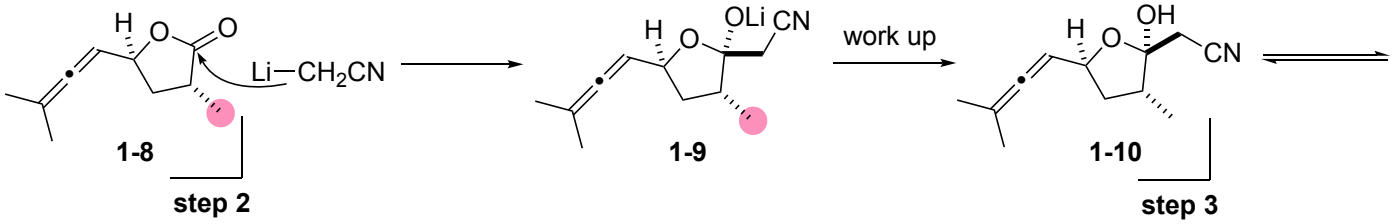
Tsukano, C.; Yagita, R.; Heike, T.; Mohammed, T. A.; Nishibayashi, K.; Irie, K.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2021**, *60*, 23106.



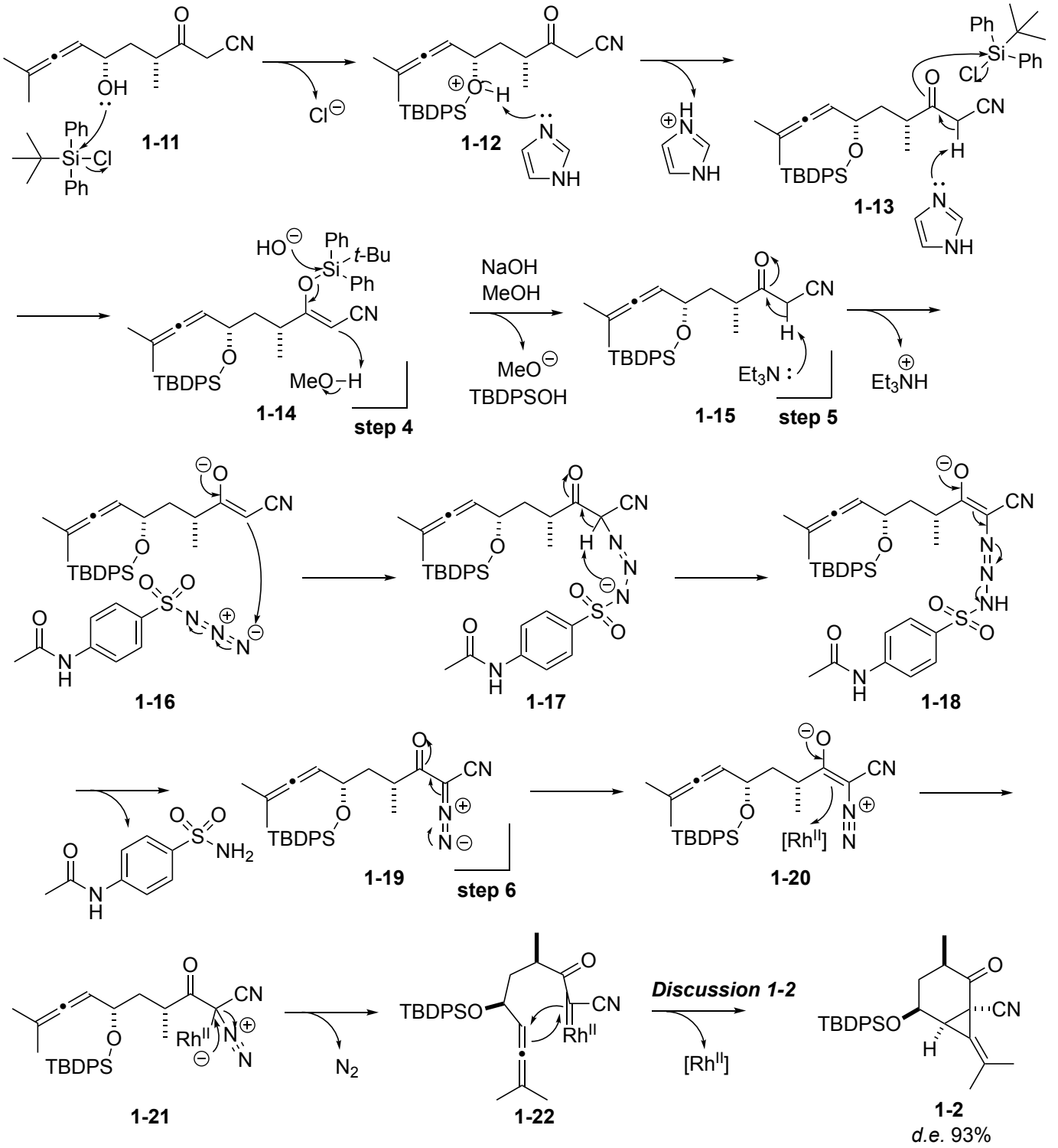






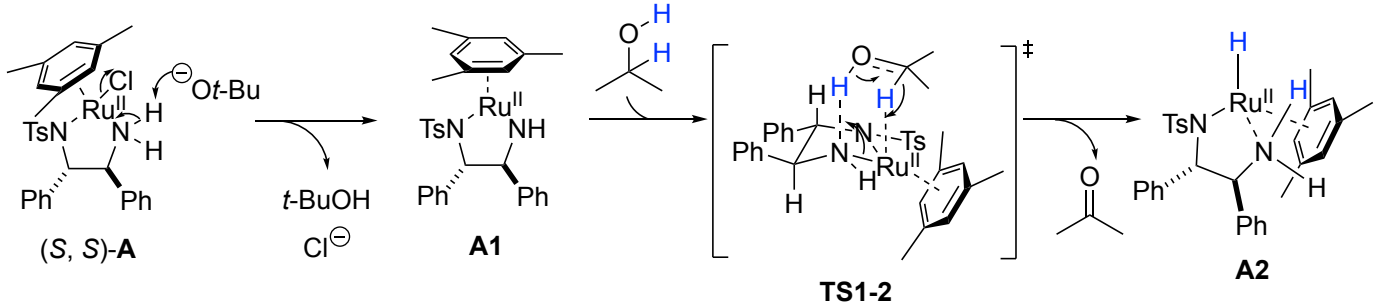


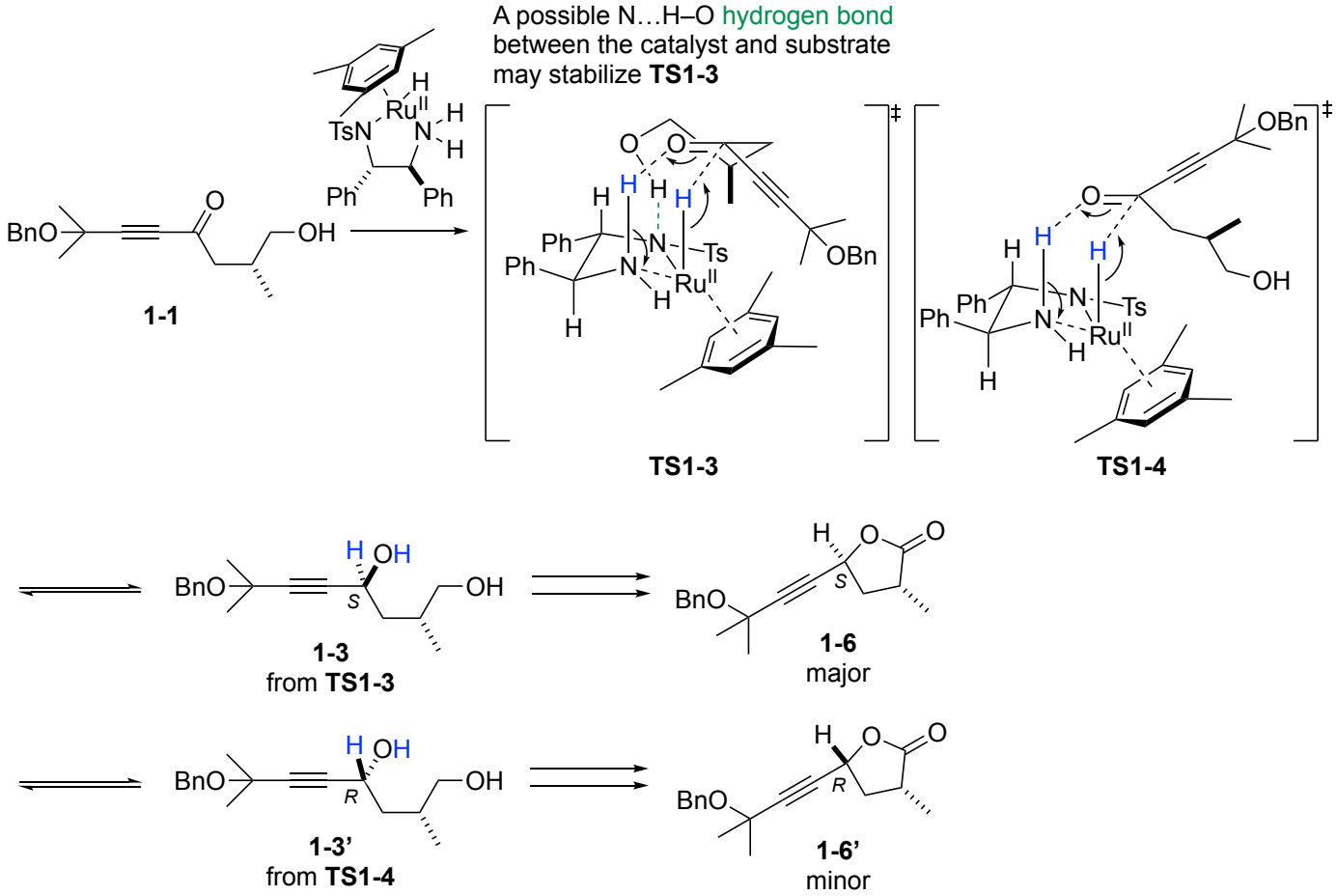
attack from the opposite side of methyl group to avoid stereo hindrance



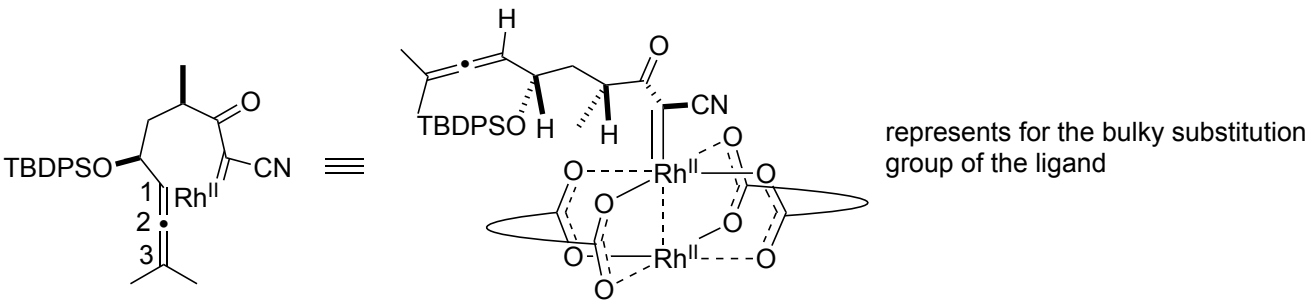
Discussion 1-1: Asymmetric hydroacylation of ketone using Noyori's transfer hydrogenation catalyst

Stereo control of ruthenium hydride by tuning the stereo chemistry of ligand:

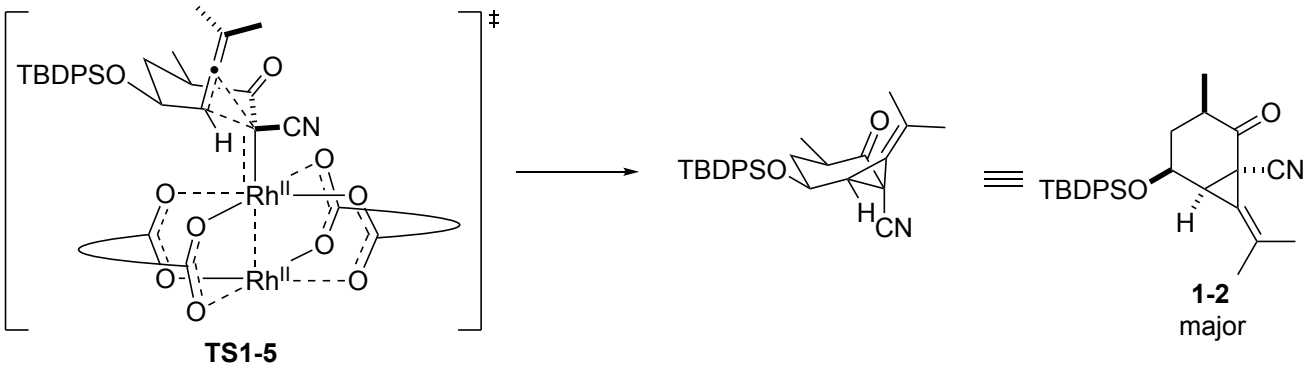




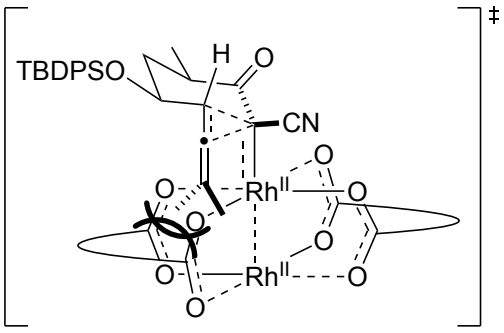
Discussion 1-2: Enantioselective cyclopropanation of allene



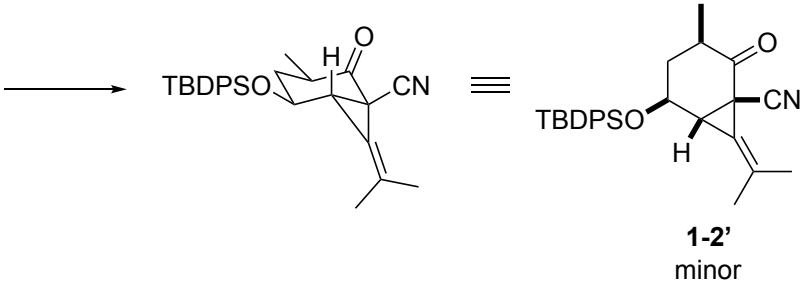
(1) cyclopropanation with C1, C2: front side



(2) cyclopropanation with C1, C2: back side



TS1-6

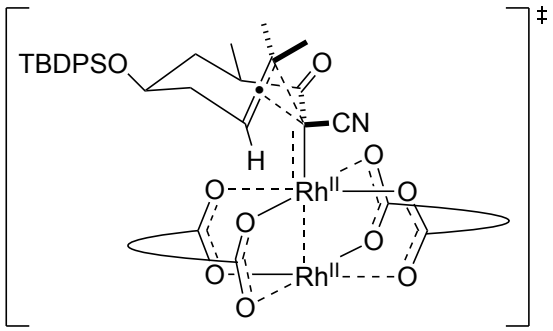


1-2'
minor

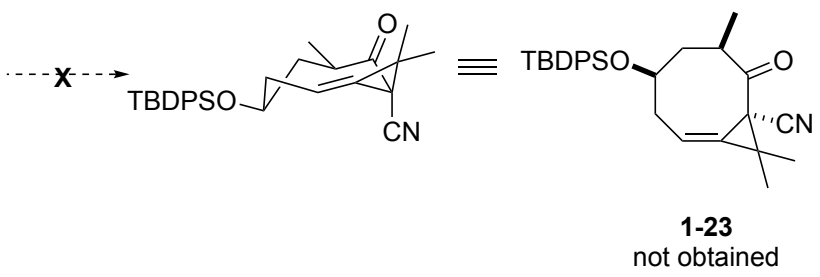
Stereo repulsion of the methyl groups with the bulky liagnds makes this transition state less stable.

(3) cyclopropanation with C2, C3

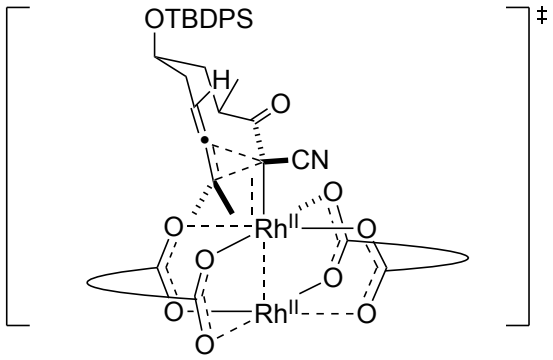
1.The olefin suffers from extreme angle strain according to Bredt's rule thus cannot be obtained.
2. The reaction sites are spatially far away.



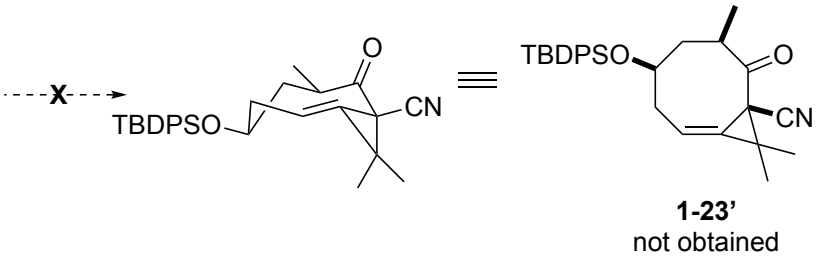
TS1-7



1-23
not obtained

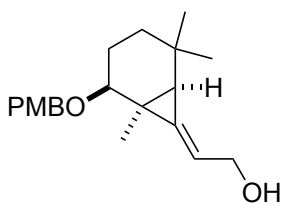


TS1-8



1-23'
not obtained

Problem 2



2-1

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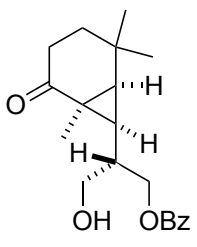
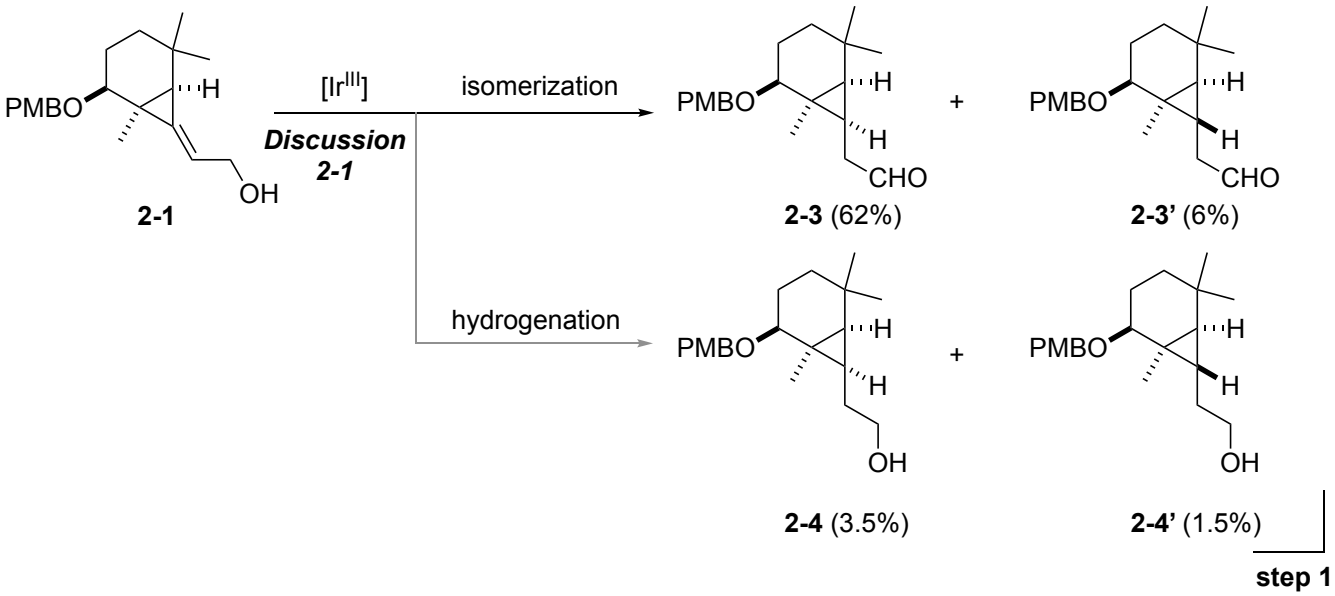
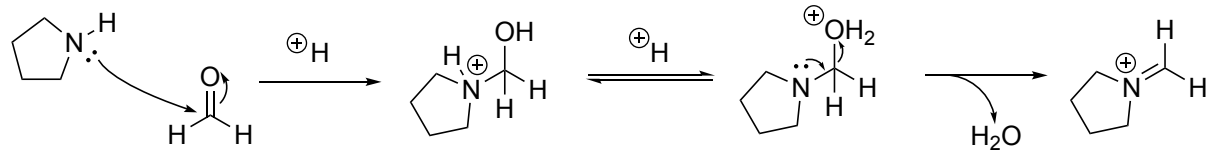
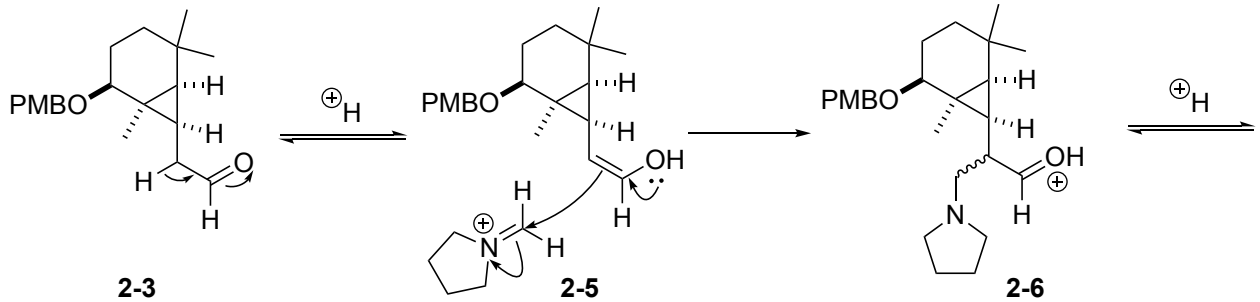


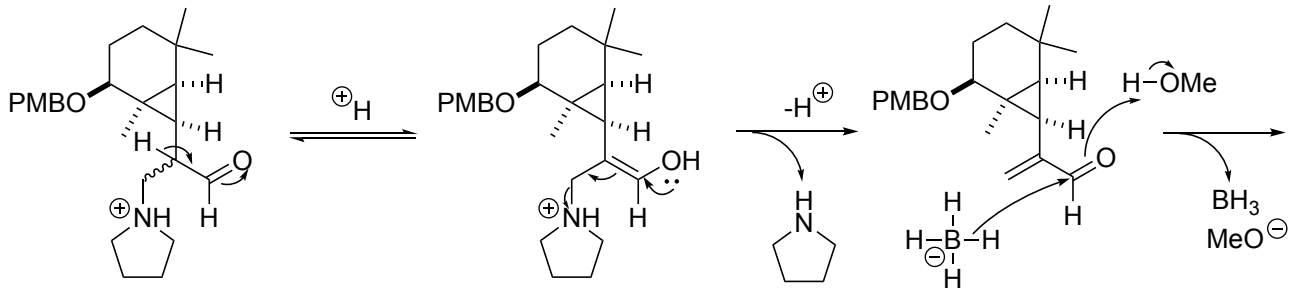
2-2

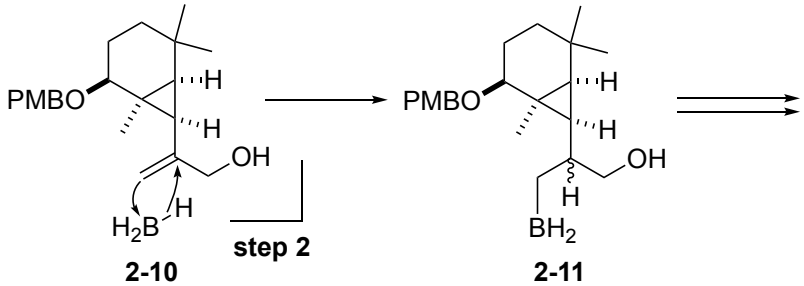
Yasui, M.; Ota, R.; Tsukano, C.; Takemoto, Y. *Nat. Commun.* **2017**, *8*, 674

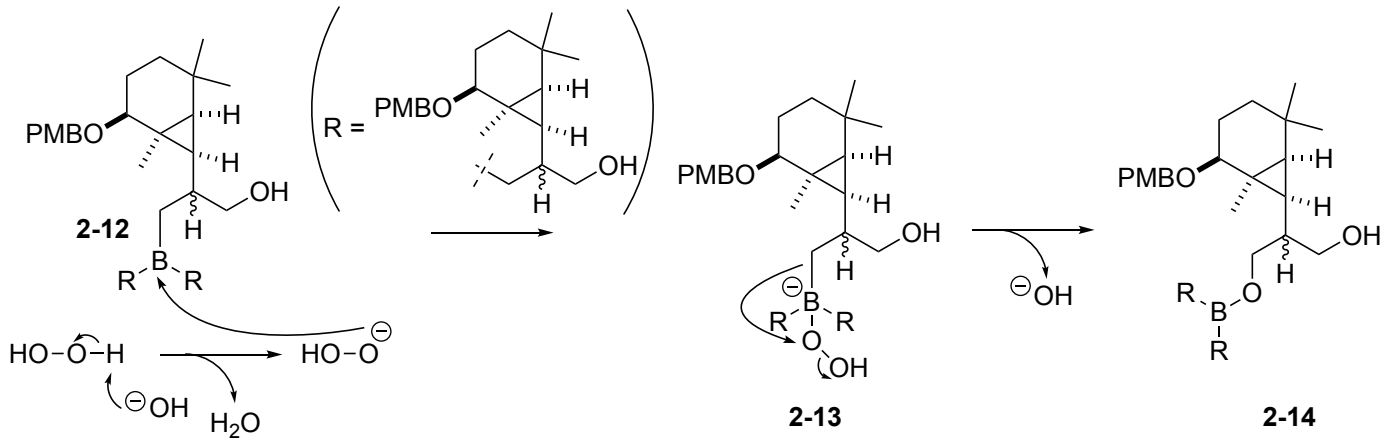

PMBO
H
OH
2-1
[Ir^III]
Discussion 2-1
isomerization
hydrogenation
CHO
2-3 (62%)
2-3' (6%)
OH
2-4 (3.5%)
2-4' (1.5%)
step 1

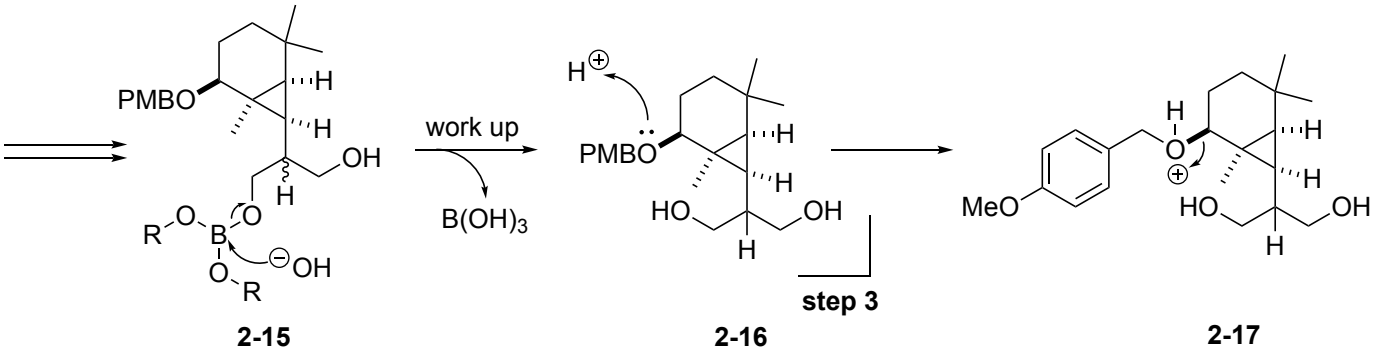

N
H
O
OH
OH2
H2O

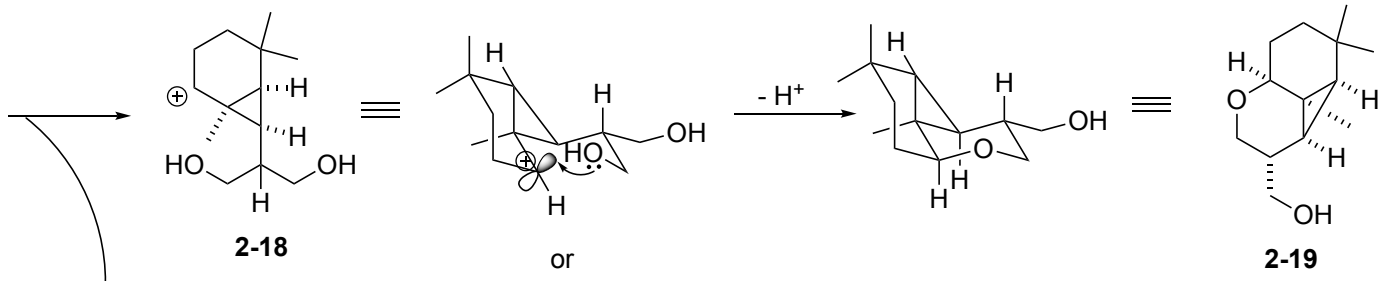

PMBO
OH
2-3
2-5
2-6

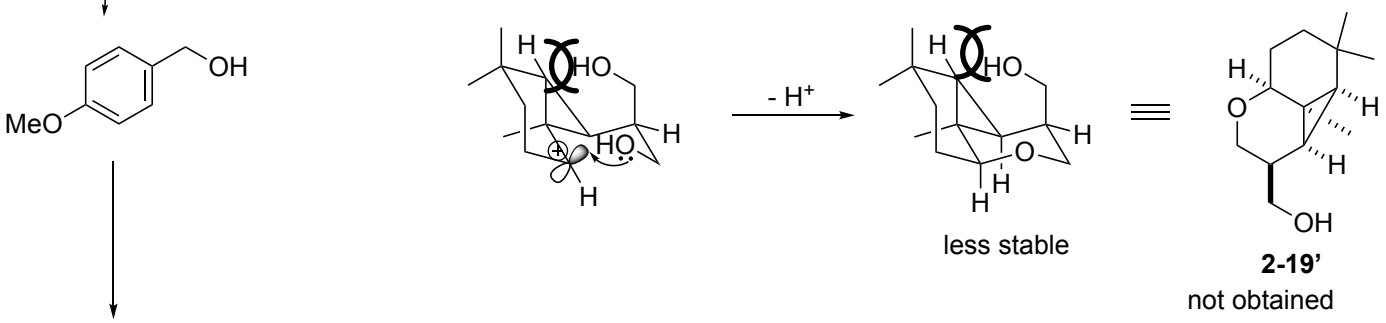

PMBO
NH
OH
-H
H–OMe
BH3
MeO
2-7
2-8
2-9

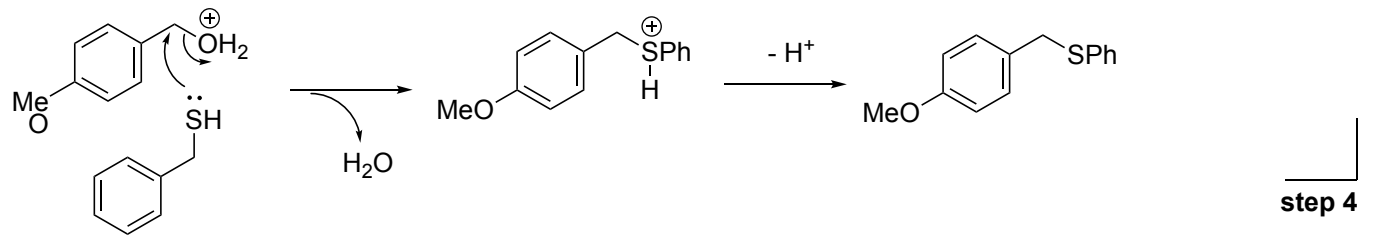

PMBO
OH
H2B
BH2
step 2
2-10
2-11

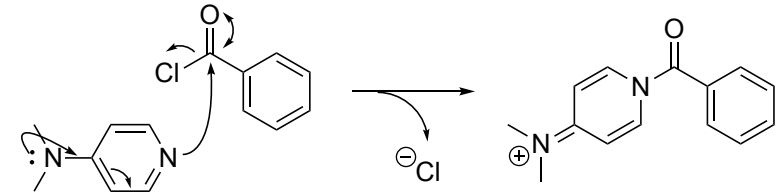

PMBO
R =
OH
2-12
HO–O–H
H_2O
2-13
2-14

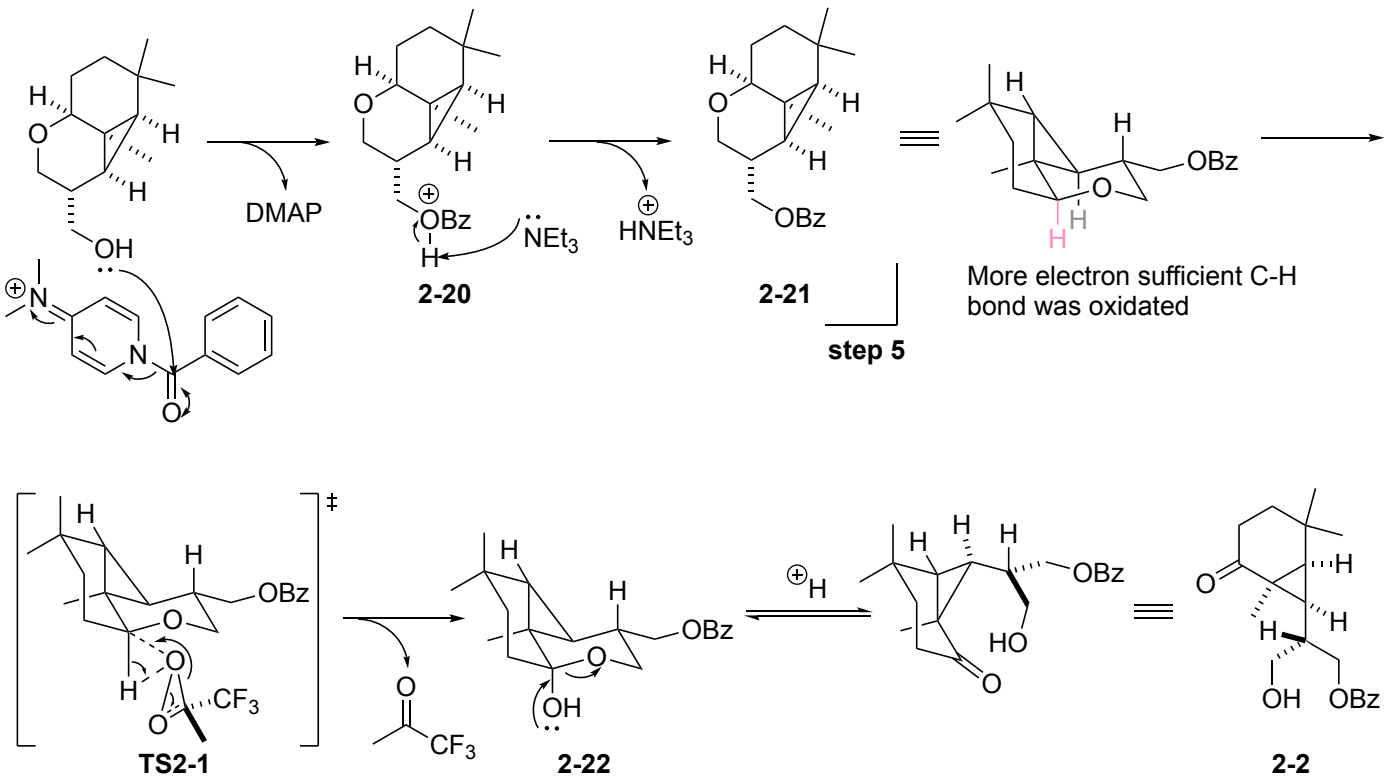

work up
$B(OH)_3$
2-15
2-16
step 3
2-17
MeO


2-18
or
- H^+
2-19

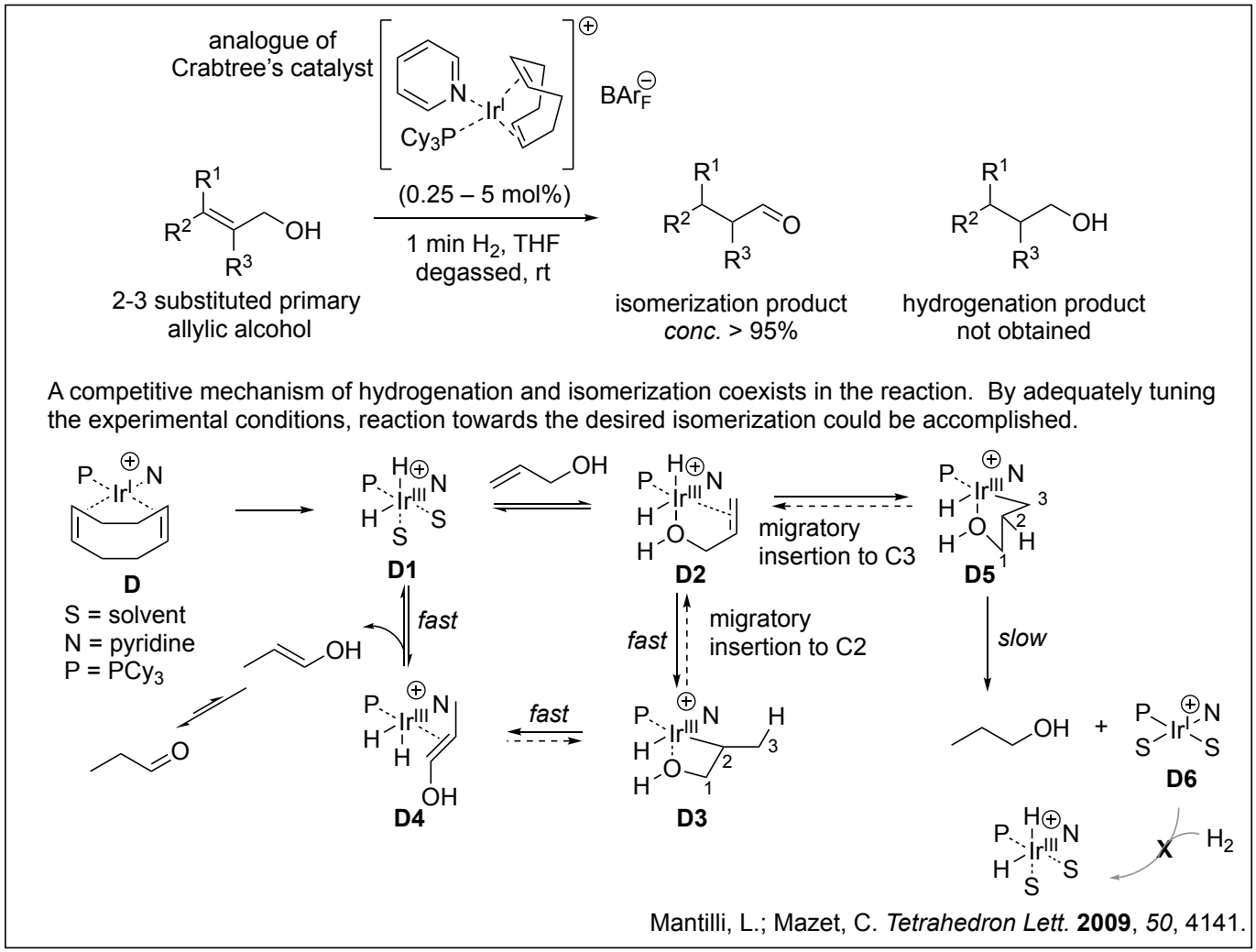

MeO
- H^+
less stable
2-19'
not obtained


Me
O
OH_2
SH
H_2O
SPh
- H^+
step 4

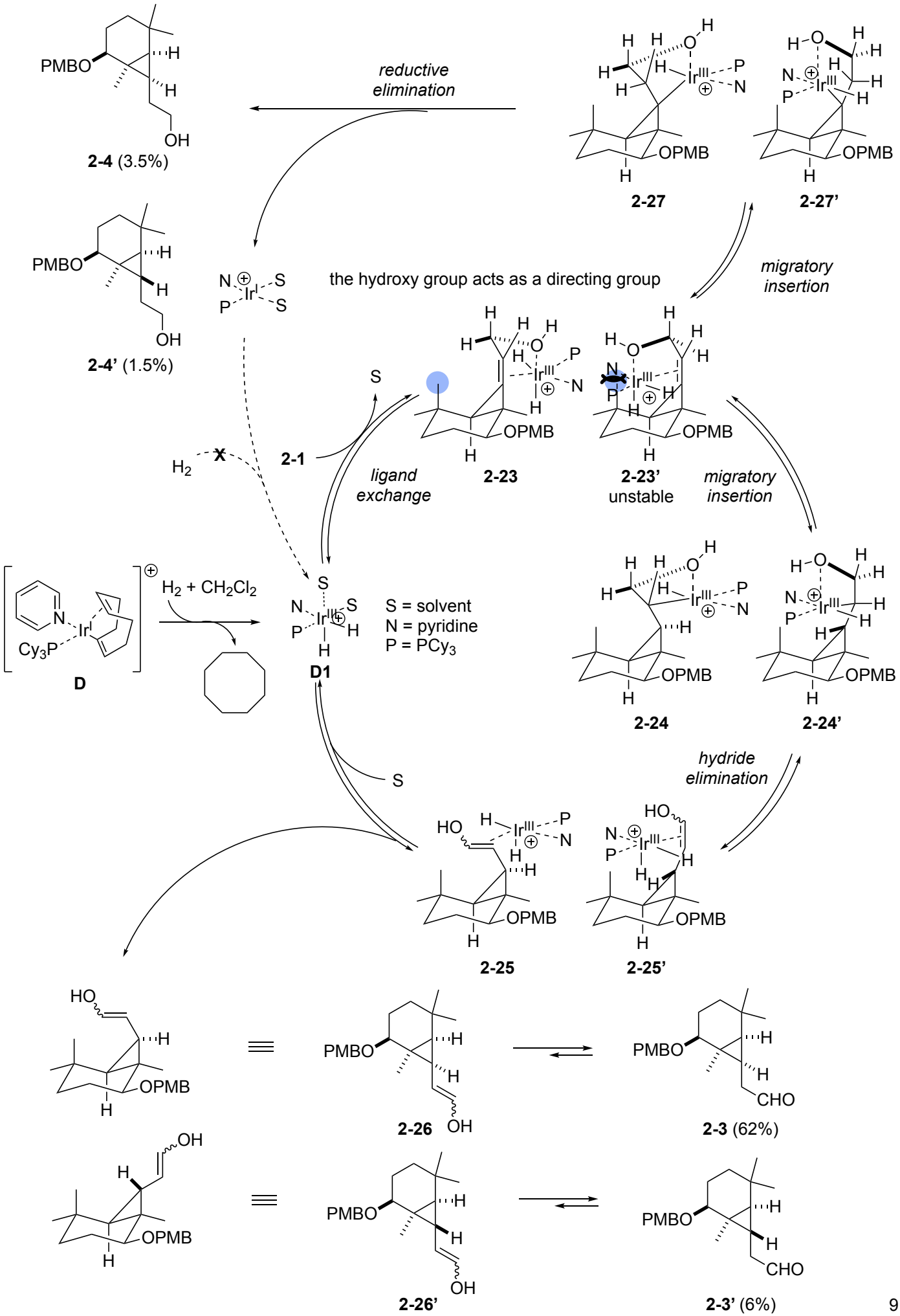

Cl
N
$^{\ominus}$Cl



Discussion 2-1: Iridium-catalyzed asymmetric isomerization of primary allylic alcohol



Mantilli, L.; Mazet, C. *Tetrahedron Lett.* **2009**, *50*, 4141.


2-4 (3.5%)
reductive elimination
2-27
2-27'
2-4' (1.5%)
the hydroxy group acts as a directing group
migratory insertion
2-1
ligand exchange
2-23
2-23'
unstable
migratory insertion
D
H2 + CH2Cl2
D1
S = solvent
N = pyridine
P = PCy3
2-24
2-24'
hydride elimination
2-25
2-25'
2-26
2-3 (62%)
2-26'
2-3' (6%)