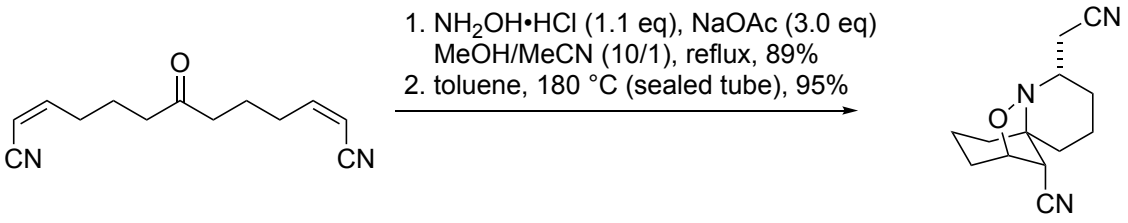
Problem Session (2) Answer

2022/05/21 Hisahiro Morozumi

Topic: [3+2] cycloaddition with nitrones

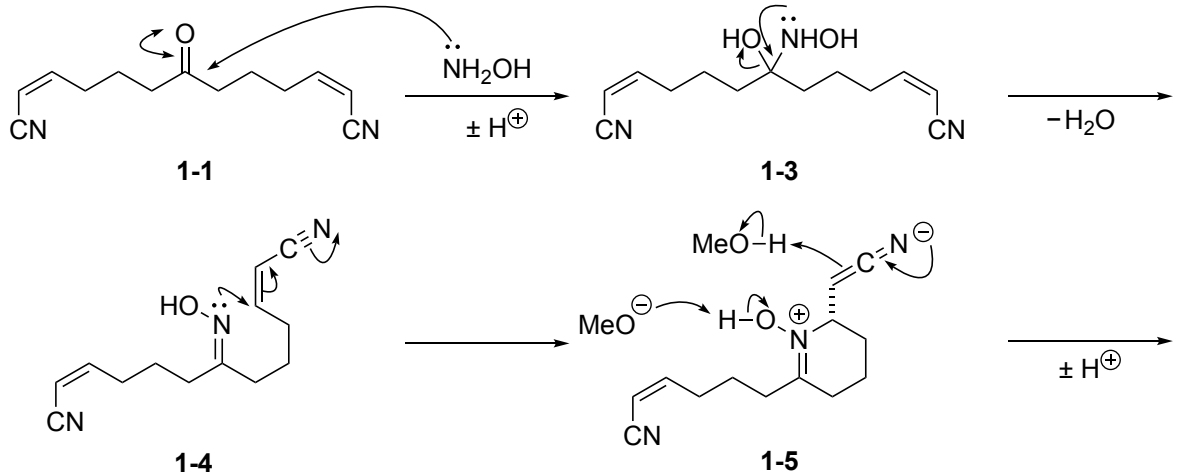
(1)

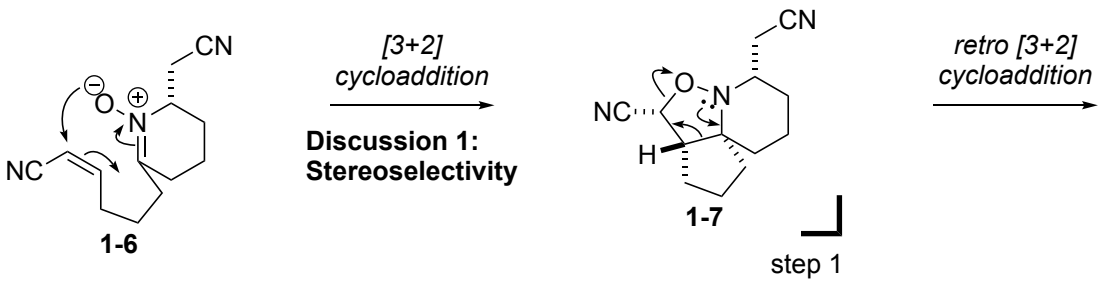


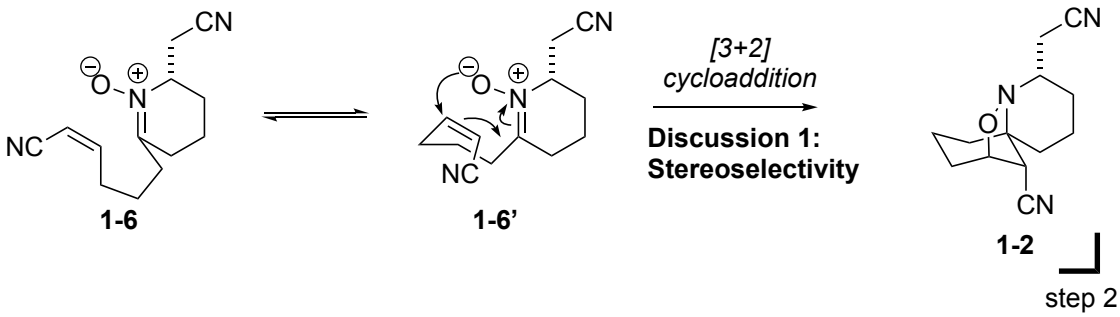
1-1 **1-2**

1) Karatholuvhu, M. S.; Sinclair, A.; Newton, A. F.; Alcaraz, M. L.; Stockman, R. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **2012**, *134*, 15237-15240

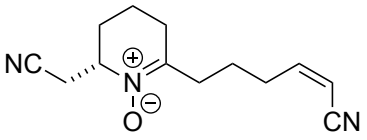
1-1. Reaction mechanism[1)]



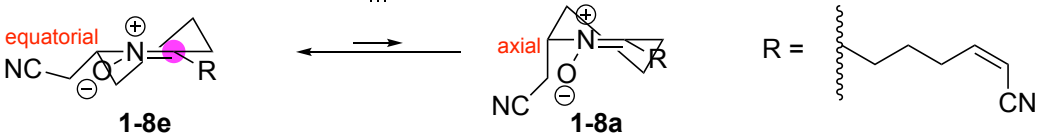




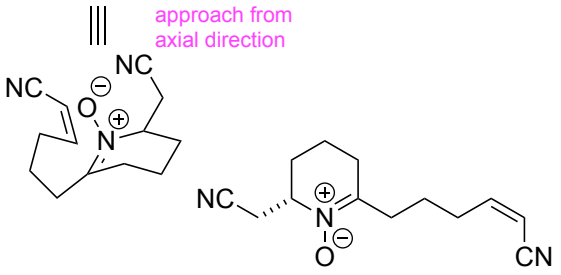
1-2. **Discussion 1**: Stereoselectivity of [3+2] cycloaddition



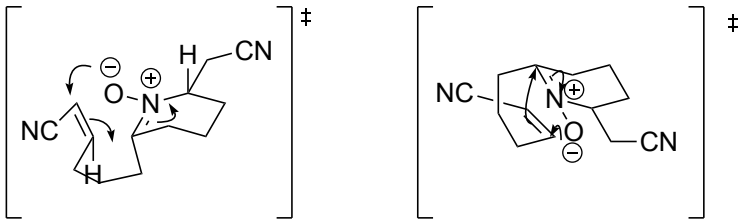
1-8



1-8e **1-8a**

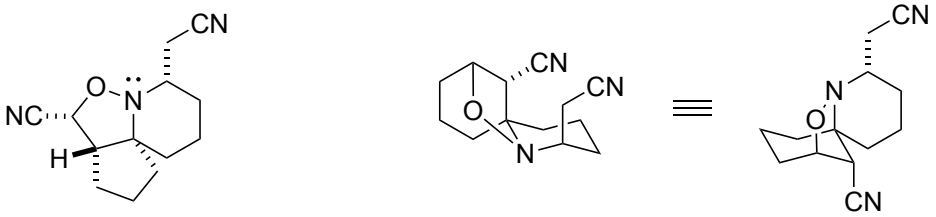


1-8



1-6 **1-6'**

Gibbs free energy relative to nitrone **1-8**[a] 21.0 (kcal/mol) 23.2 (kcal/mol)



1-7 **1-2** **1-2**

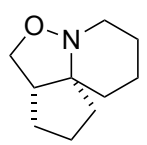
Gibbs free energy relative to nitrone **1-8**[a] − 7.0 (kcal/mol) − 18.1 (kcal/mol)

[a]calculation at the B3LYP/6-31 G(d) level[2)]

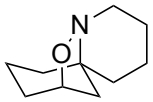
It is thought that…

1-7 (kinetic product) **1-2** (Thermodynamic product)

(i) Thermodynamic control



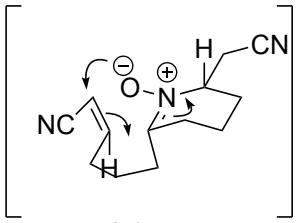
A
[6,5,5-tricyclic core]



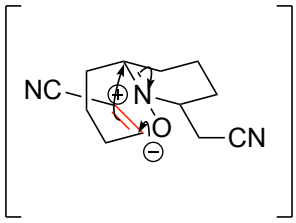
B
[6,6,5-tricyclic core]

It is calculated that **B** is 4 kcal/mol more stable than **A**.[2)]

(ii) kinetic control



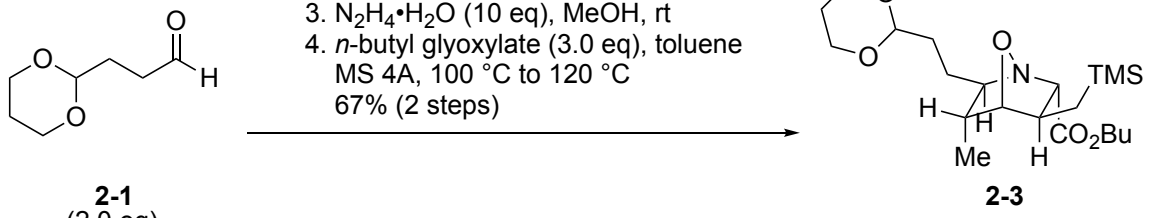
1-6



1-6'

It is thought that In the **1-6'** state, alkene fragment is more distorted and is oriented less ideally for bonding to the nitrone.

(2)

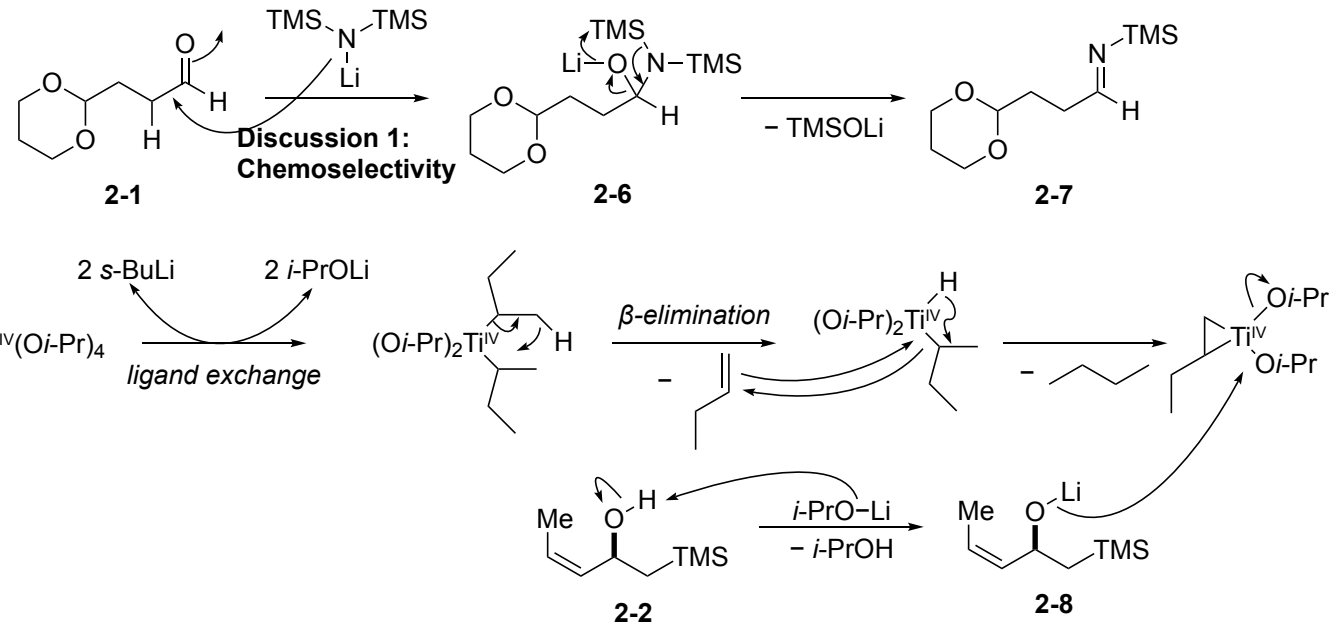


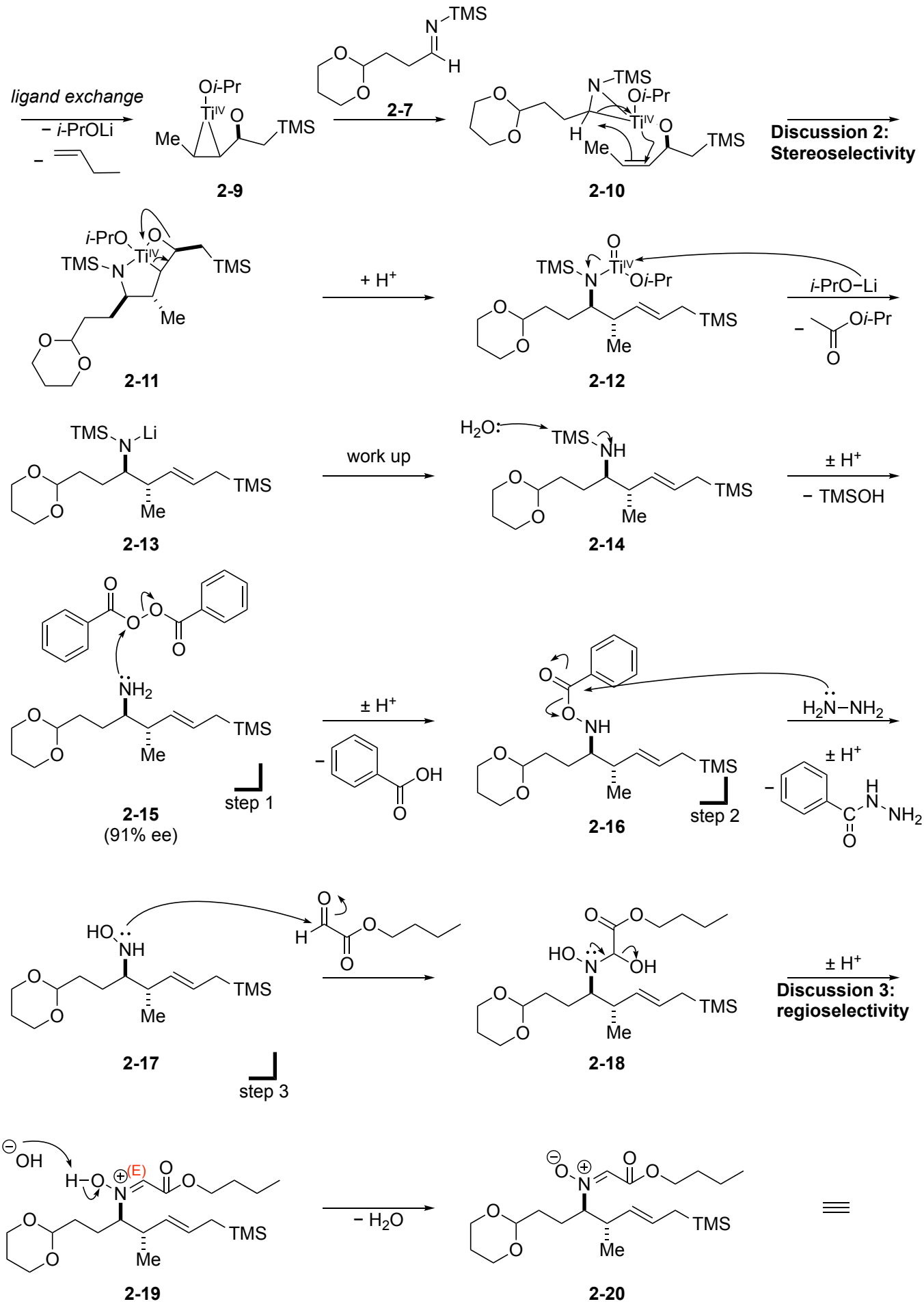
2-1
(2.0 eq)

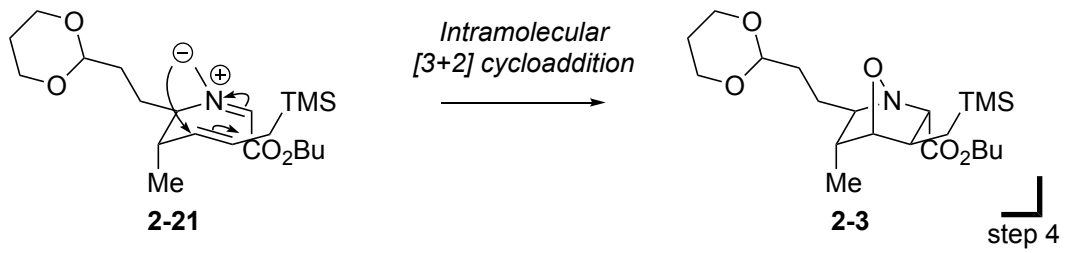
2-3

3) Yang, D.; Micalizio, G. C. J. Am. Chem. Soc. 2012, 134, 15237-15240

2-1. Reaction mechanism[3)]

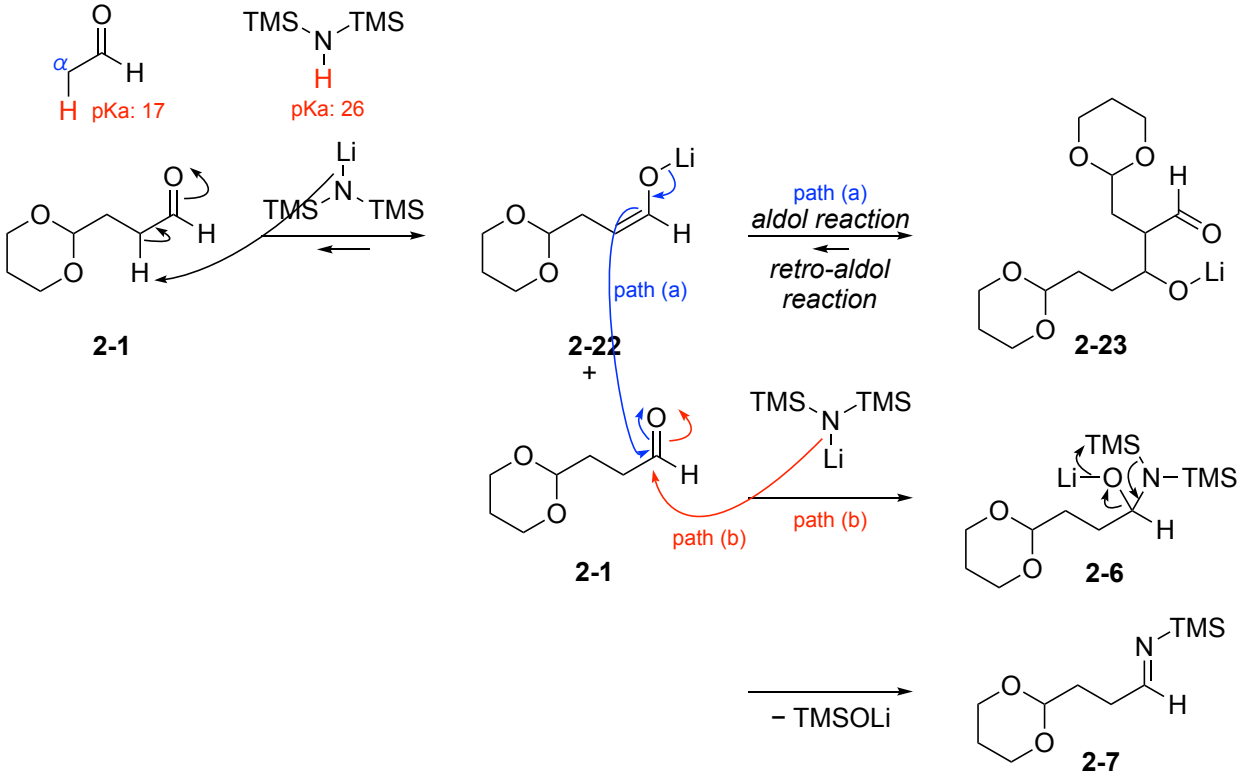



ligand exchange
− i-PrOLi
2-9
2-7
2-10
Discussion 2:
Stereoselectivity
2-11
+ H+
2-12
i-PrO−Li
2-13
work up
2-14
± H+
− TMSOH
2-15
(91% ee)
step 1
± H+
2-16
step 2
H2N−NH2
± H+
2-17
step 3
2-18
± H+
Discussion 3:
regioselectivity
2-19
− H2O
2-20

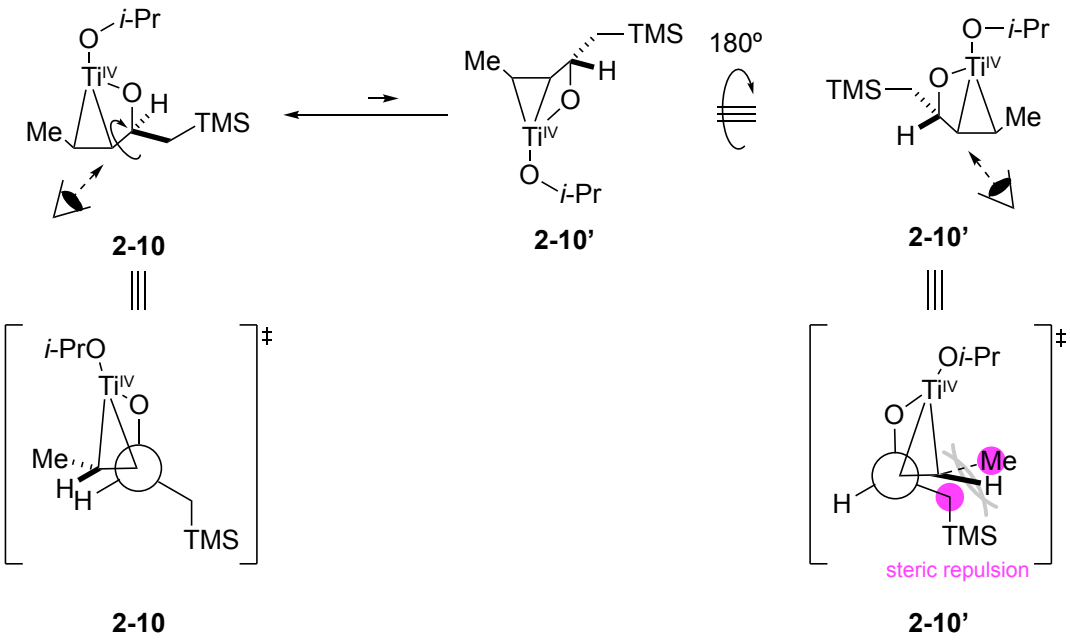


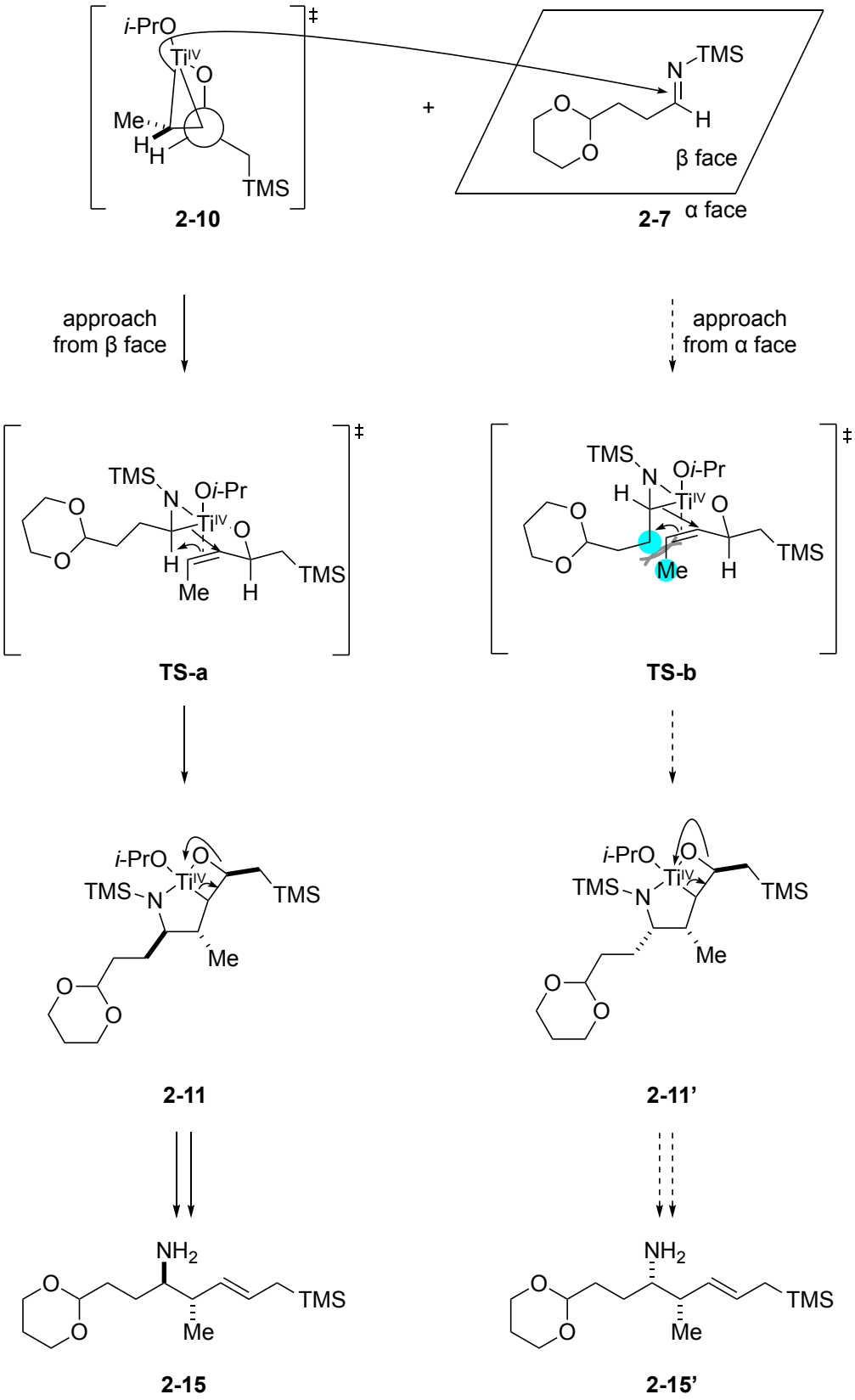
2-2. Discussion

2-2-1. **Discussion 1**: chemoselectivity of $LiN(TMS)_2$



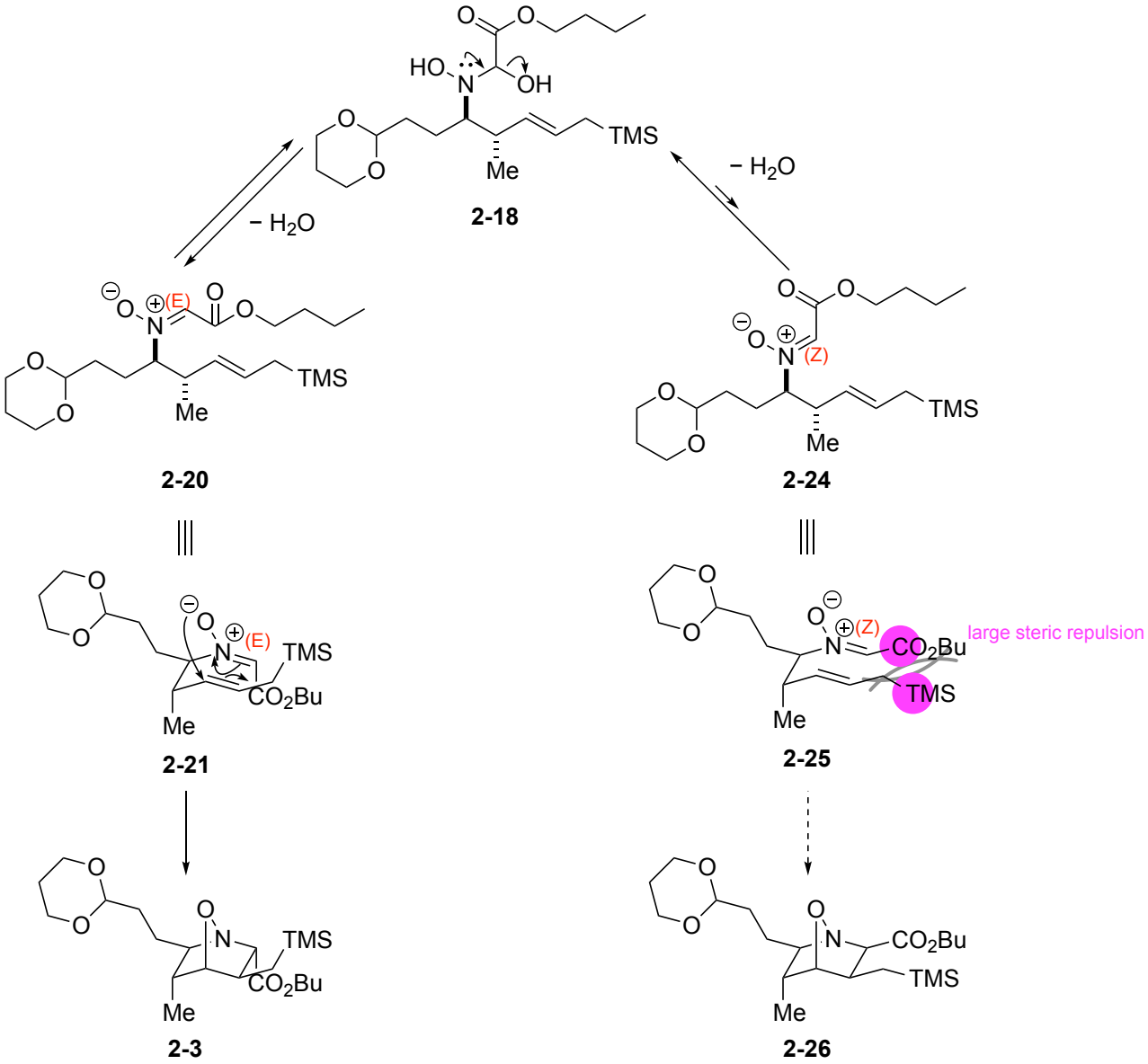
2-2-2. **Discussion 2**: stereoselectivity of cross-coupling between **2-10** and **2-7**

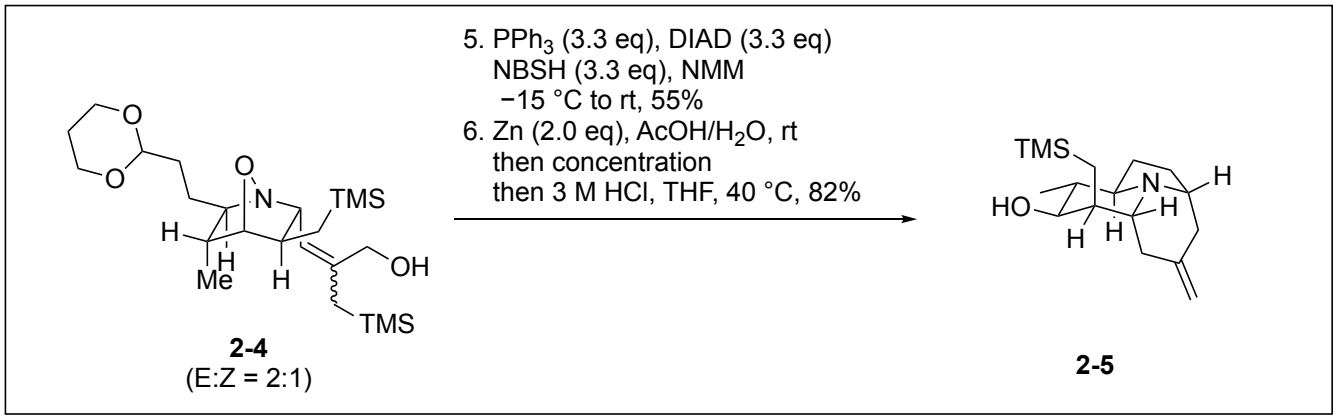




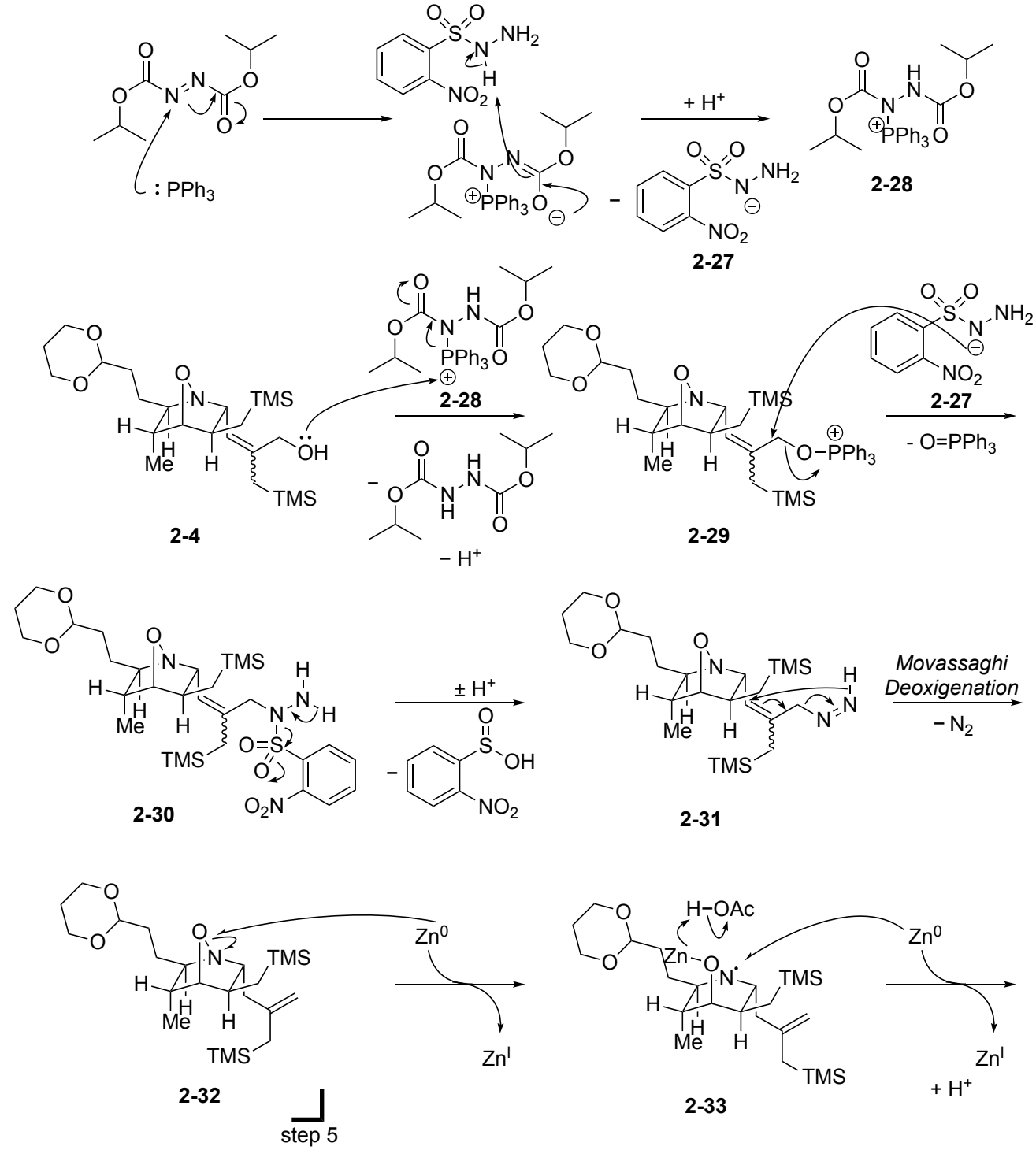
2-10 is considered to be in two states, **2-10** and **2-10'**. However, there is a large steric repulsion (Me group and CH_2TMS group) so **2-10'** is an unfavorable state and the reaction is considered to proceed at the **2-10** conformation. Two transition states are possible, depending on the approach to the plane that imine has; **Ts-a** and **Ts-b**. **TS-b** is considered an unfavorable conformation due to steric hindrance.
The enantiomer of **2-10** is also considered to be coupled with **2-7** from a single transition state as well so **2-15** was produced with complete transfer of absolute stereochemical information.

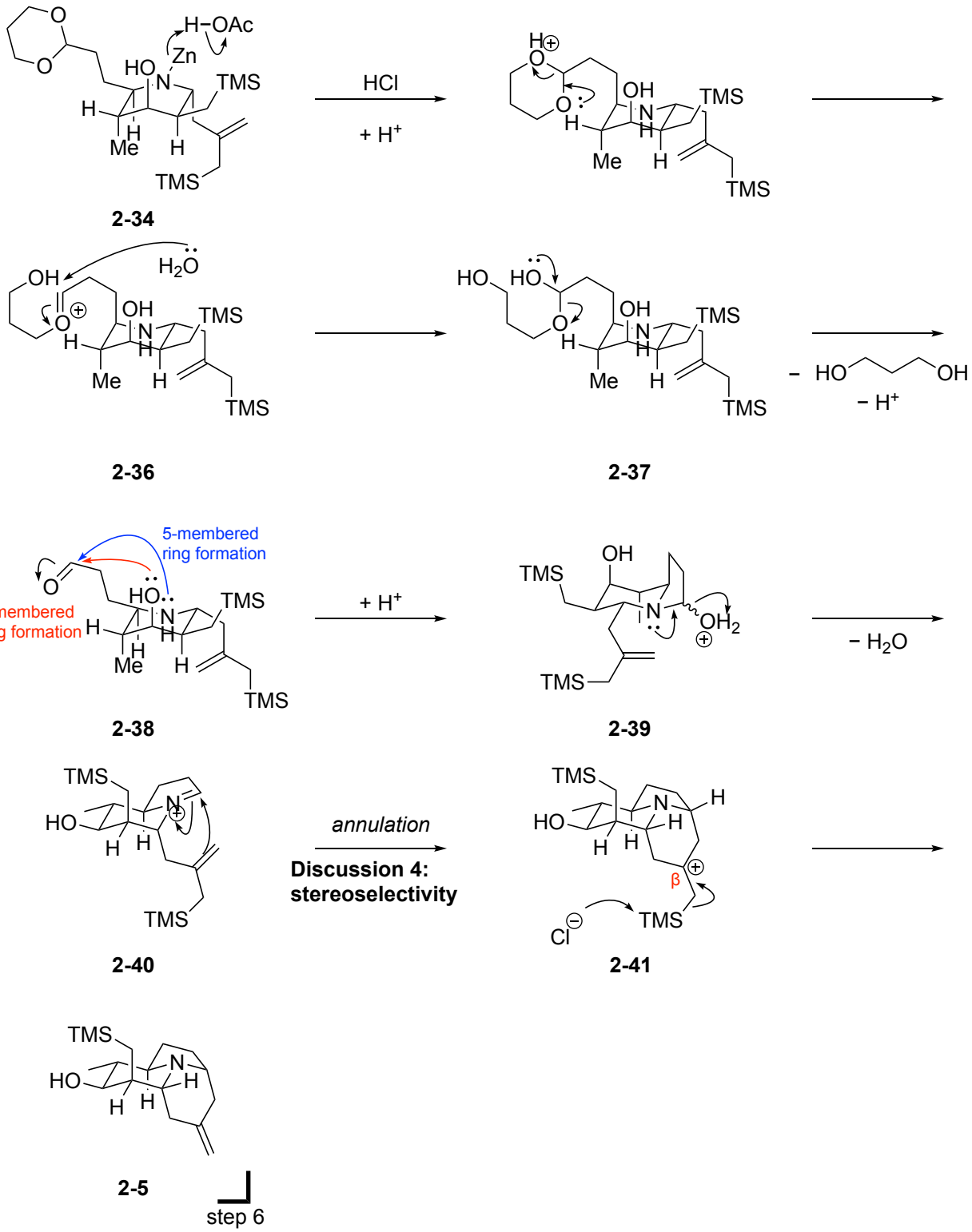
2-2-3. **Discussion 3**: regioselective elimination



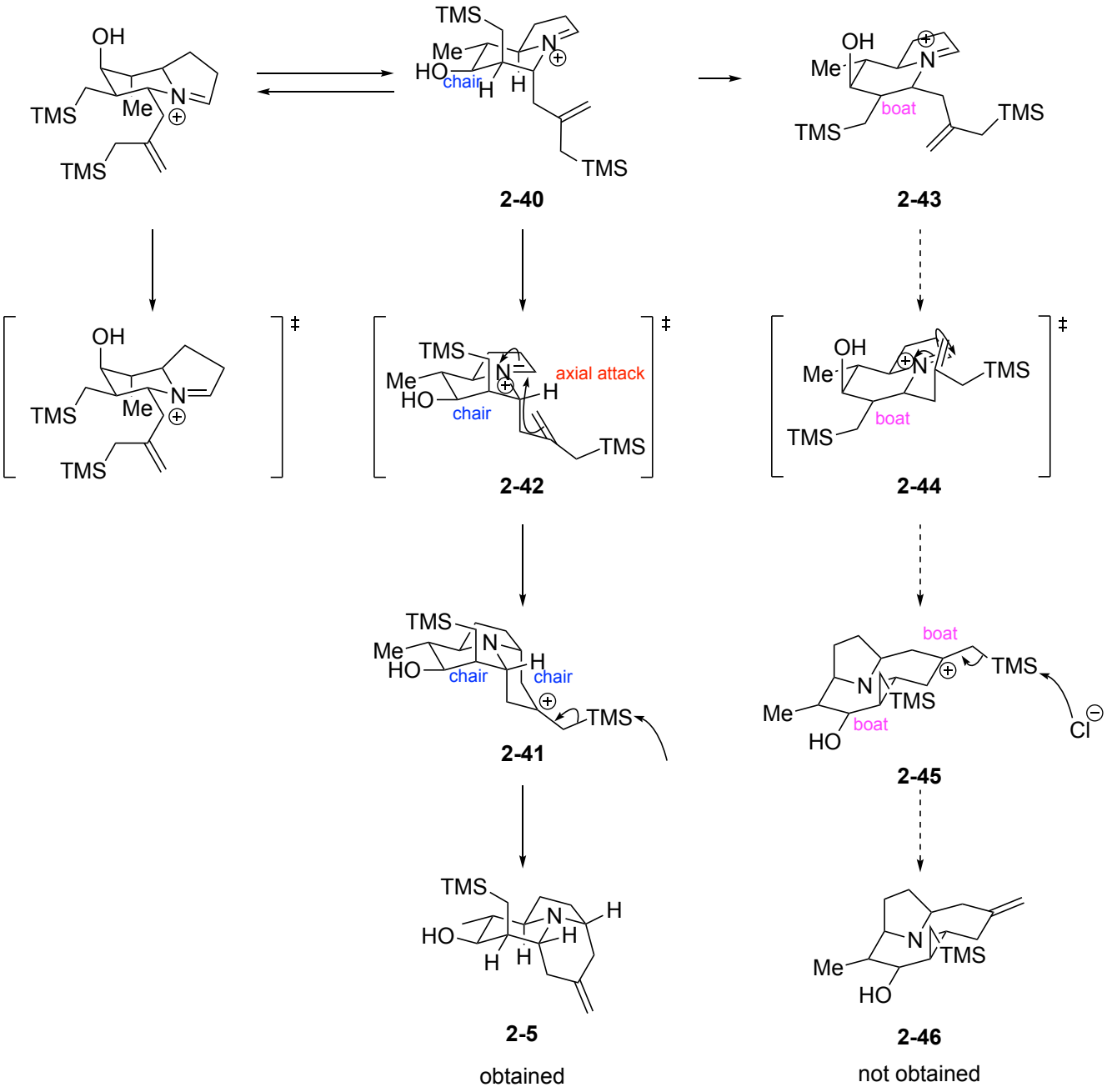


2-3. Reaction mechanism[3)]




H–OAc
Zn
HO
N
TMS
H
H
Me
H
TMS
HCl
+ H+
H
O
OH
TMS
O
H
N
H
Me
H
TMS
2-34
H2O
OH
O
H
OH
N
H
TMS
Me
H
TMS
HO
HO
OH
TMS
O
H
N
H
Me
H
TMS
– HO
OH
– H+
2-36
2-37
5-membered
ring formation
7-membered
ring formation
O
HO
N
H
H
TMS
Me
H
TMS
+ H+
OH
TMS
N
OH2
TMS
– H2O
2-38
2-39
TMS
HO
N
H
H
TMS
annulation
Discussion 4:
stereoselectivity
TMS
HO
N
H
H
H
β
Cl
TMS
2-40
2-41
TMS
HO
N
H
H
H
2-5
step 6

2-4. **Discussion 4**: stereoselectivity of annulation



Reference

1) Karatholuvhu, M. S.; Sinclair, A.; Newton, A. F.; Alcaraz, M. L.; Stockman, R. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **2012**,*134*, 15237-15240
2) Krenske, E. H.; Agopcan, S.; Aviyente, V.; Houk, K. N.; Johnson, B. A.; Holmes, A. B. *J. Am. Chem. Soc.* **2012**, *134*, 12010-12015
3) Yang, D.; Micalizio, G. C. J. Am. Chem. Soc. 2012, 134, 15237-15240