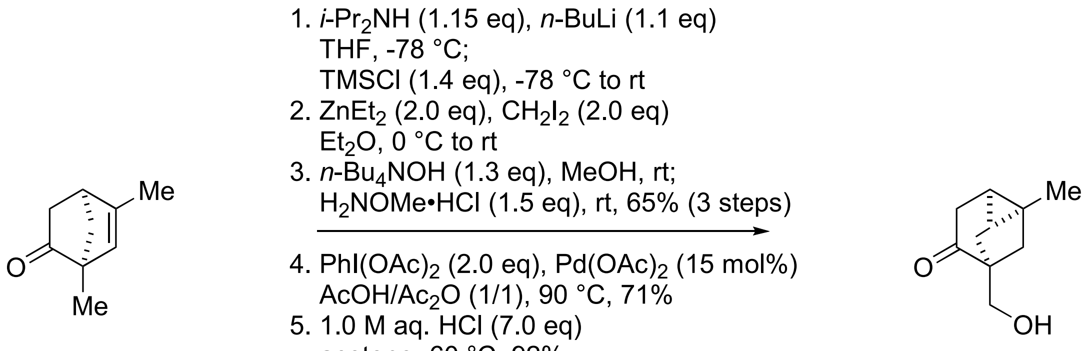
Problem Session (6)

2021/5/15 Takumi Fukuda

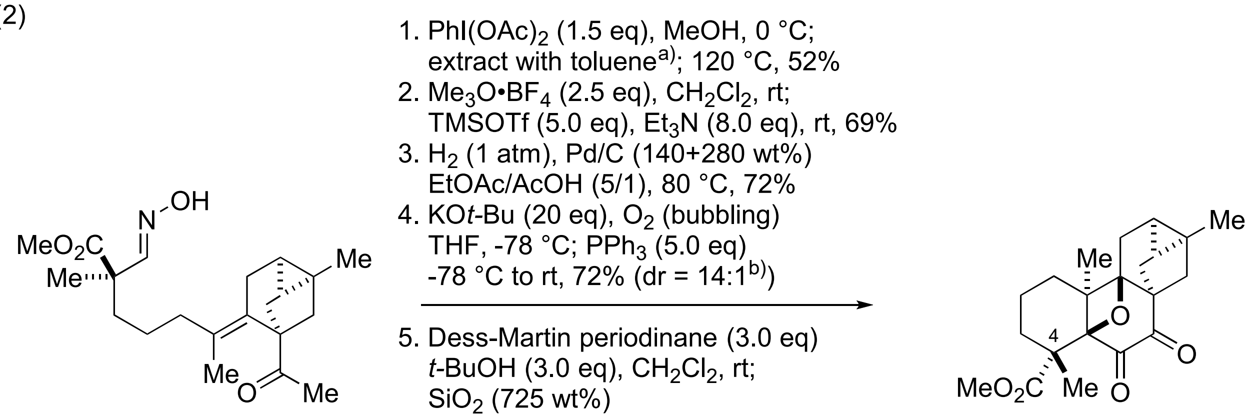
Please provide the reasonable reaction mechanisms and explain the stereoselectivities.

(1)



1-1 → **1-2**

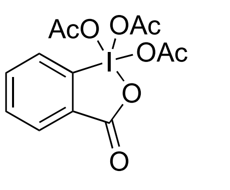
(2)



2-1 → (–)-Mitrephorone A (**2-2**)

a) After addition of saturated aq. $Na_2S_2O_3$/saturated aq. $NaHCO_3$/H_2O (1/1/2), the resultant mixture was extracted with toluene (x2). Combined organic layers were washed with brine/H_2O (1/1) and dried over Na_2SO_4. The filtrate was heated to 120 °C.

b) The configuration of the newly formed stereogenic center was not assigned.



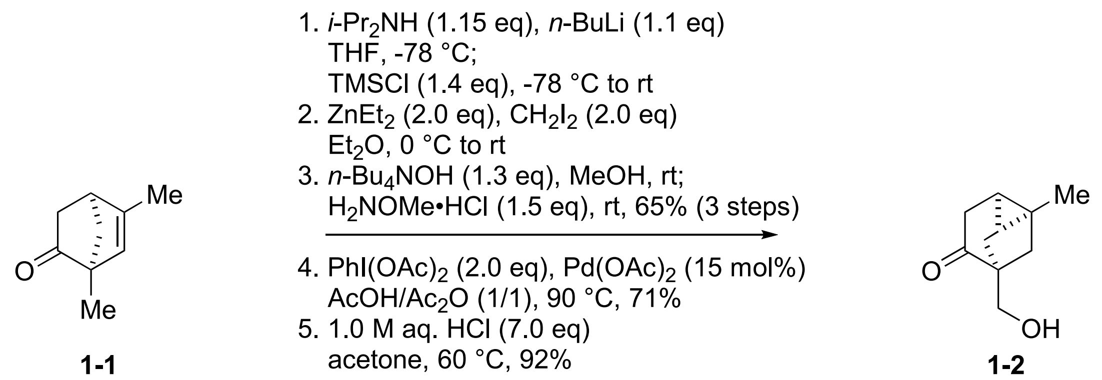
Dess-Martin periodinane

Problem Session (6) Answer 2020/5/15 Takumi Fukuda

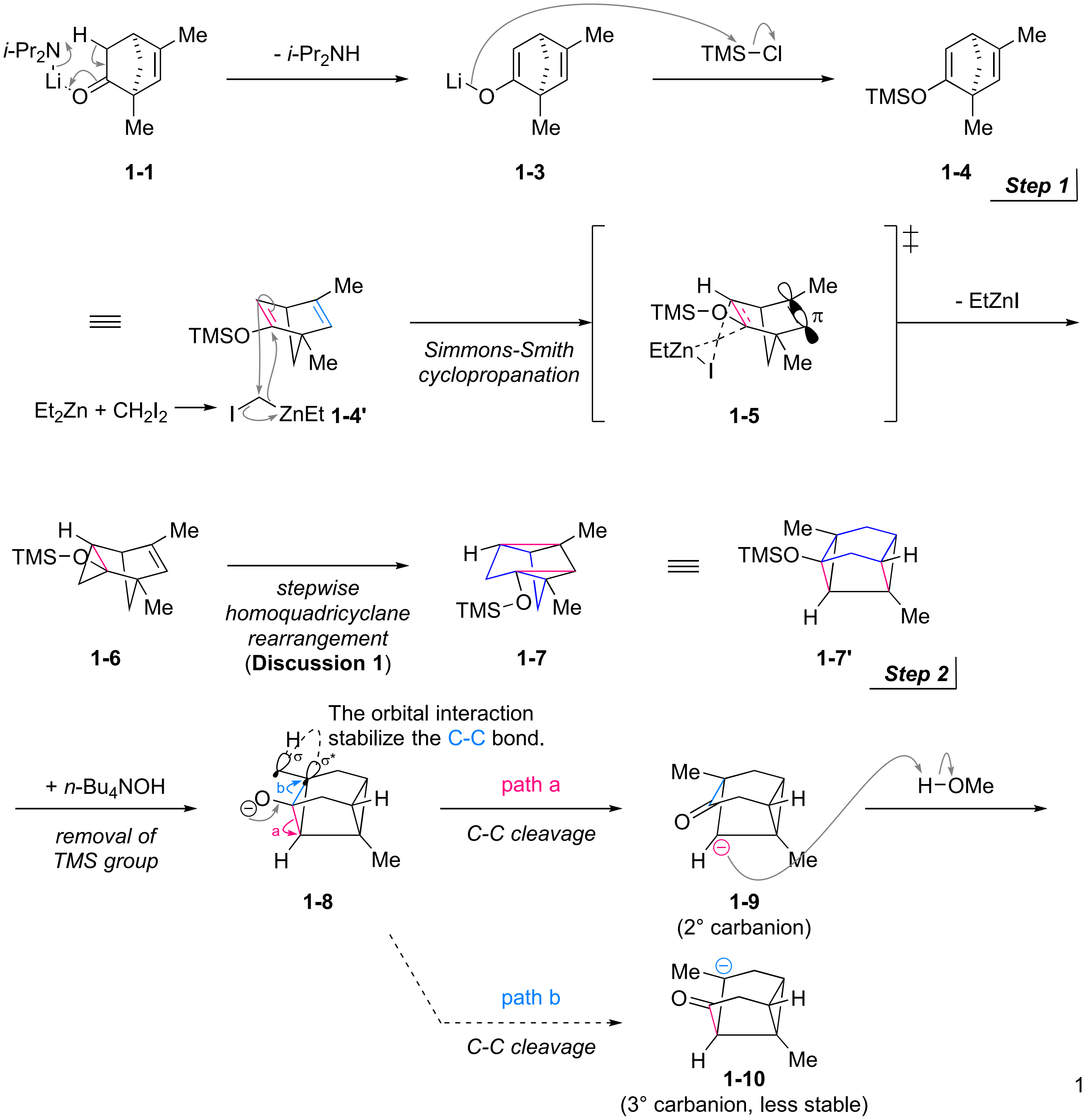
Topic: Total synthesis of (–)-Mitrephorone A by Carreira's group

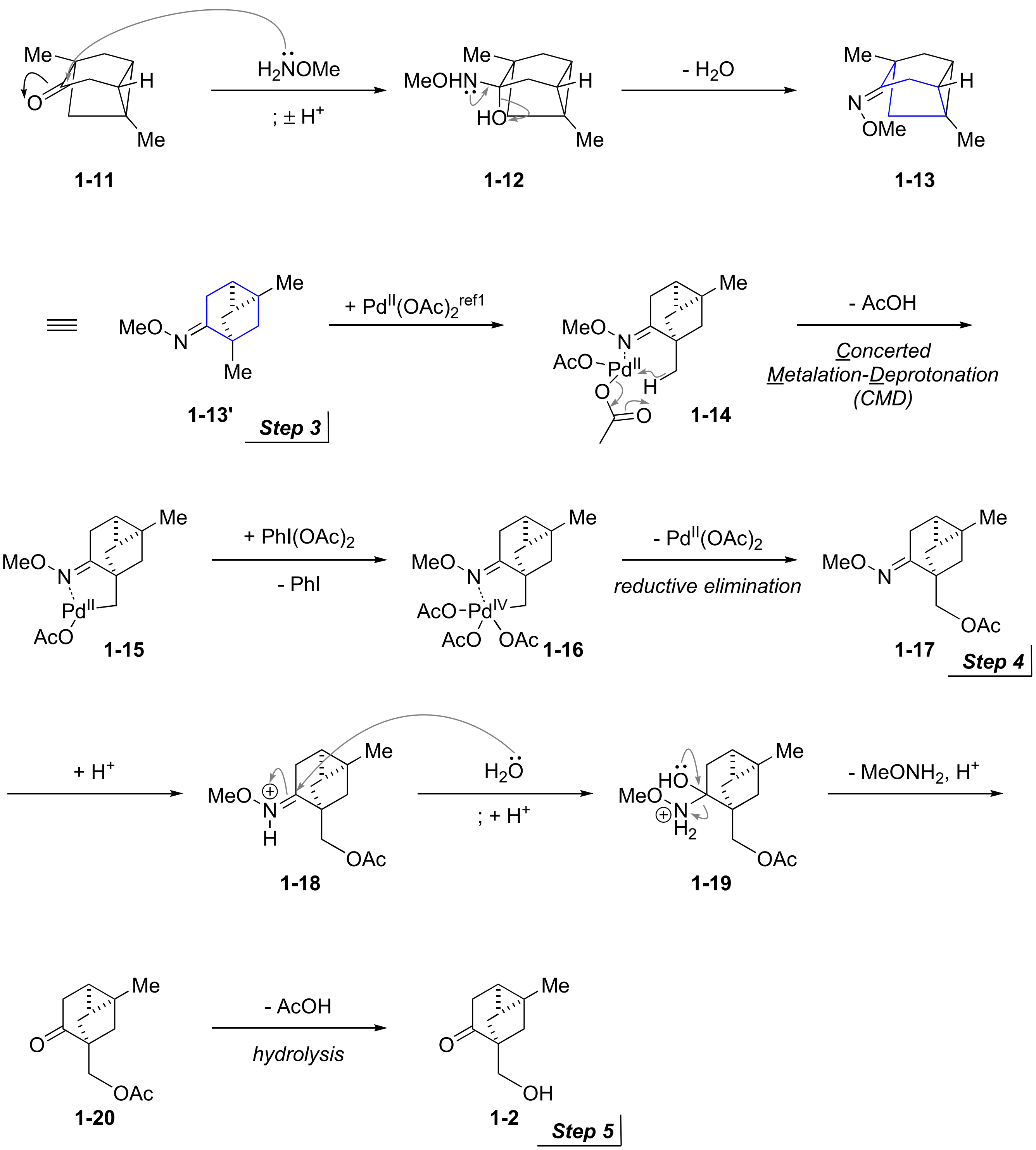
1-1. Reaction mechanism

(1)



Schneider, M.; Richter, M. J. R.; Krautwald, S.; Carreira, E. M. *Org. Lett.* **2019**, *21*, 8705.

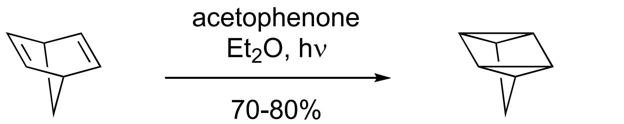




1-2. Discussion
1-2-1. Homoquadricyclane rearrangement
1-2-1-1. Synthesis and reactivity of quadricyclane

♦ Synthesis of quadricyclane

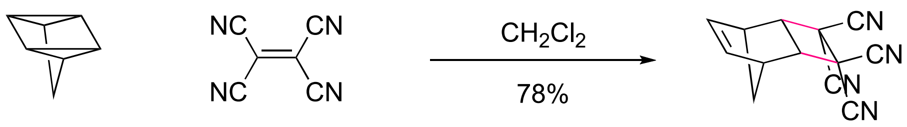
Smith, C. D. *Org. Synth.* **1971**, *51*, 133.



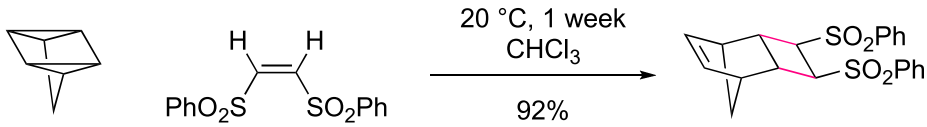
norbornadiene (**1-21**) quadricyclane (**1-22**)

♦ Reactivity of quadricyclane

Petrov, V. A.; Vasil'ev, N. V. *Current. Org. Syn.* **2006**, *3*, 215.

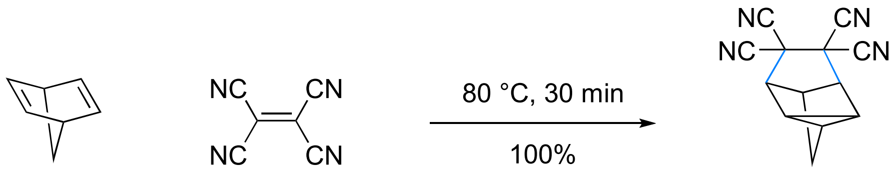


quadricyclane (**1-22**) **1-23a** **1-24a**

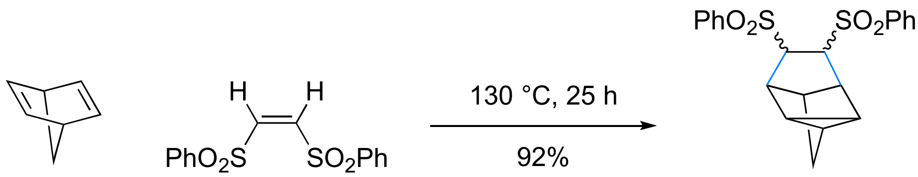


quadricyclane (**1-22**) **1-23b** **1-24b**

Quadricyclane (**1-22**) reacts with variety of electron deficient olefins stereoselectively with the formation of *exo*-tricyclonoenes.



norbornadiene (**1-21**) **1-23a** **1-25a**



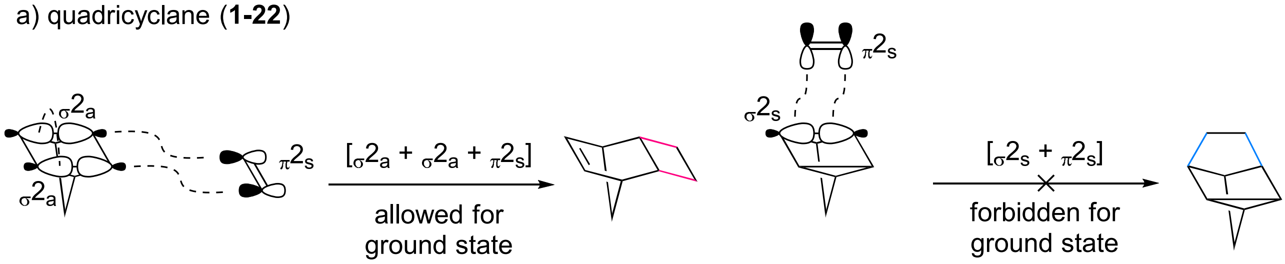
norbornadiene (**1-21**) **1-23b** **1-25b**

On the otherhand, the cycloaddition reactions of norbornadiene (**1-21**) and electron dificient olefins usually proceed at higher temperature and result in selective formation of tetracyclononanes (Also see 150509_PS_Shunichiroh_KATOH_Woodward_Hoffmann_rules).

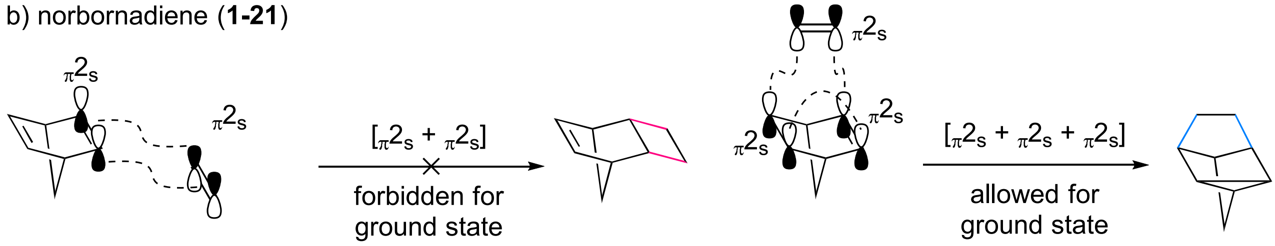
♦ Rationale for reactivity

These reacitivity can be explained by Woodward-Hoffmann rules.

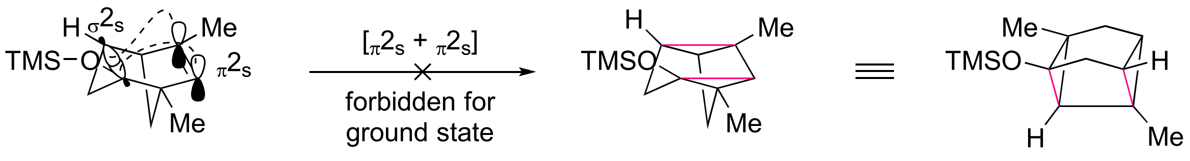
a) quadricyclane (**1-22**)



b) norbornadiene (**1-21**)

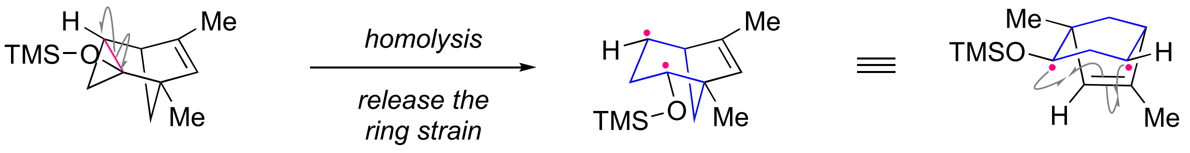


1-2-1. Homoquadricyclane rearrangement
1-2-2. Stepwise vs concerted

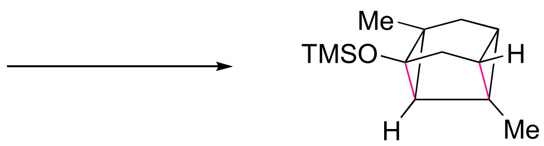


1-5 **1-7** **1-7'**

The reaction proceeds through a stepwise mechanism.



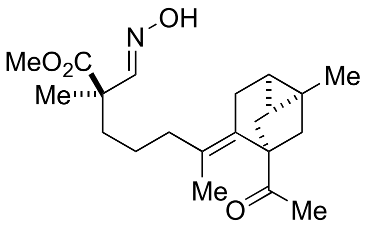
1-6 **1-26** **1-26'**



1-7'

2-1. Reaction mechanism

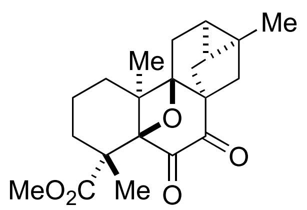
(2)



2-1

1. $PhI(OAc)_2$ (1.5 eq), MeOH, 0 °C; extract with toluene[a)]; 120 °C, 52%
2. $Me_3O•BF_4$ (2.5 eq), CH_2Cl_2, rt; TMSOTf (5.0 eq), Et_3N (8.0 eq), rt, 69%
3. H_2 (1 atm), Pd/C (140+280 wt%) EtOAc/AcOH (5/1), 80 °C, 72%
4. KO*t*-Bu (20 eq), O_2 (bubbling) THF, -78 °C; PPh_3 (5.0 eq) -78 °C to rt, 72% (dr = 14:1[b)])

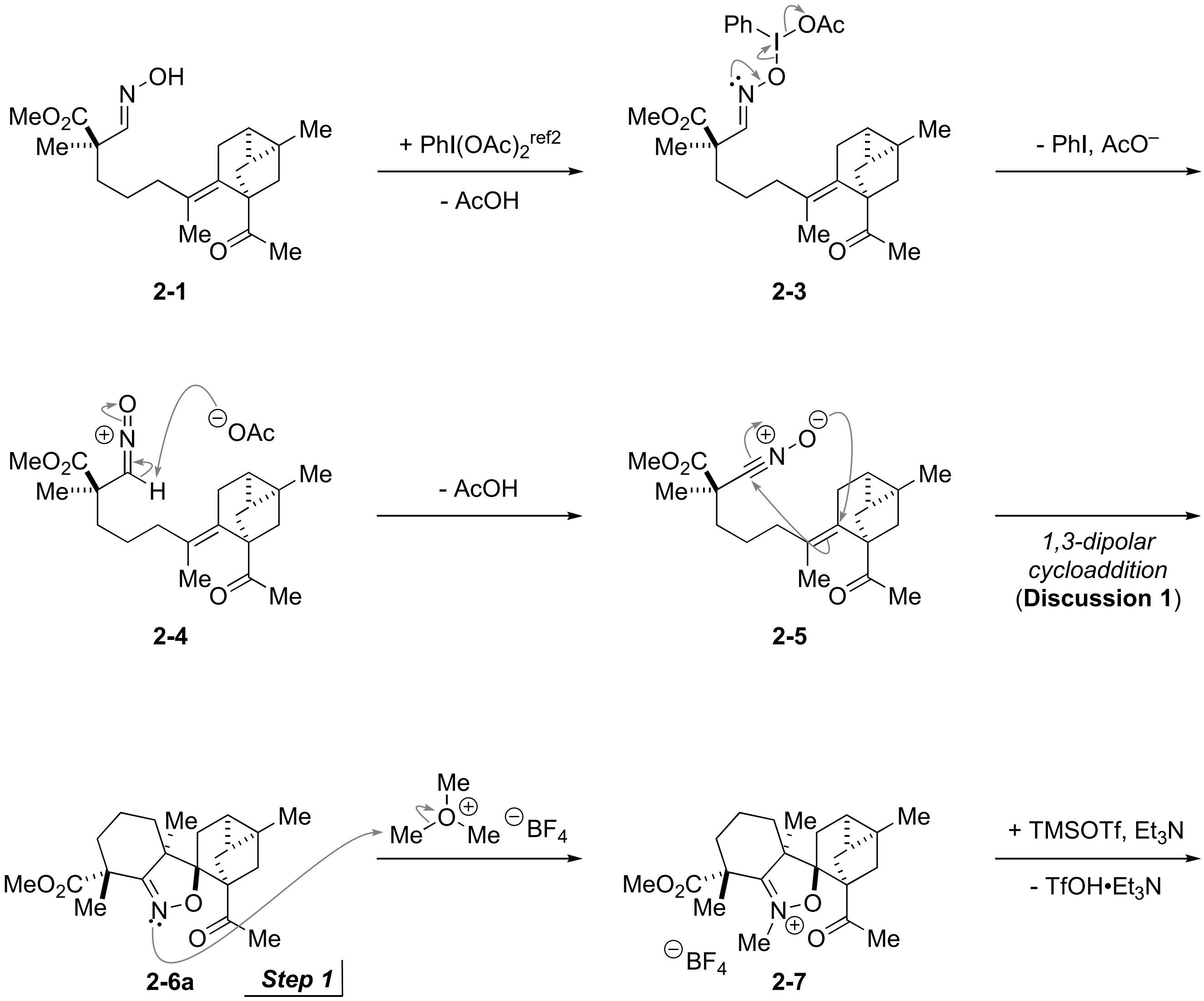
5. Dess-Martin periodinane (3.0 eq) *t*-BuOH (3.0 eq), CH_2Cl_2, rt; SiO_2 (725 wt%) hexane/EtOAc (3/1), rt, 74%
6. PhI(OH)OTs (10 eq) $NaHCO_3$ (10 eq), CH_2Cl_2, rt, 72%

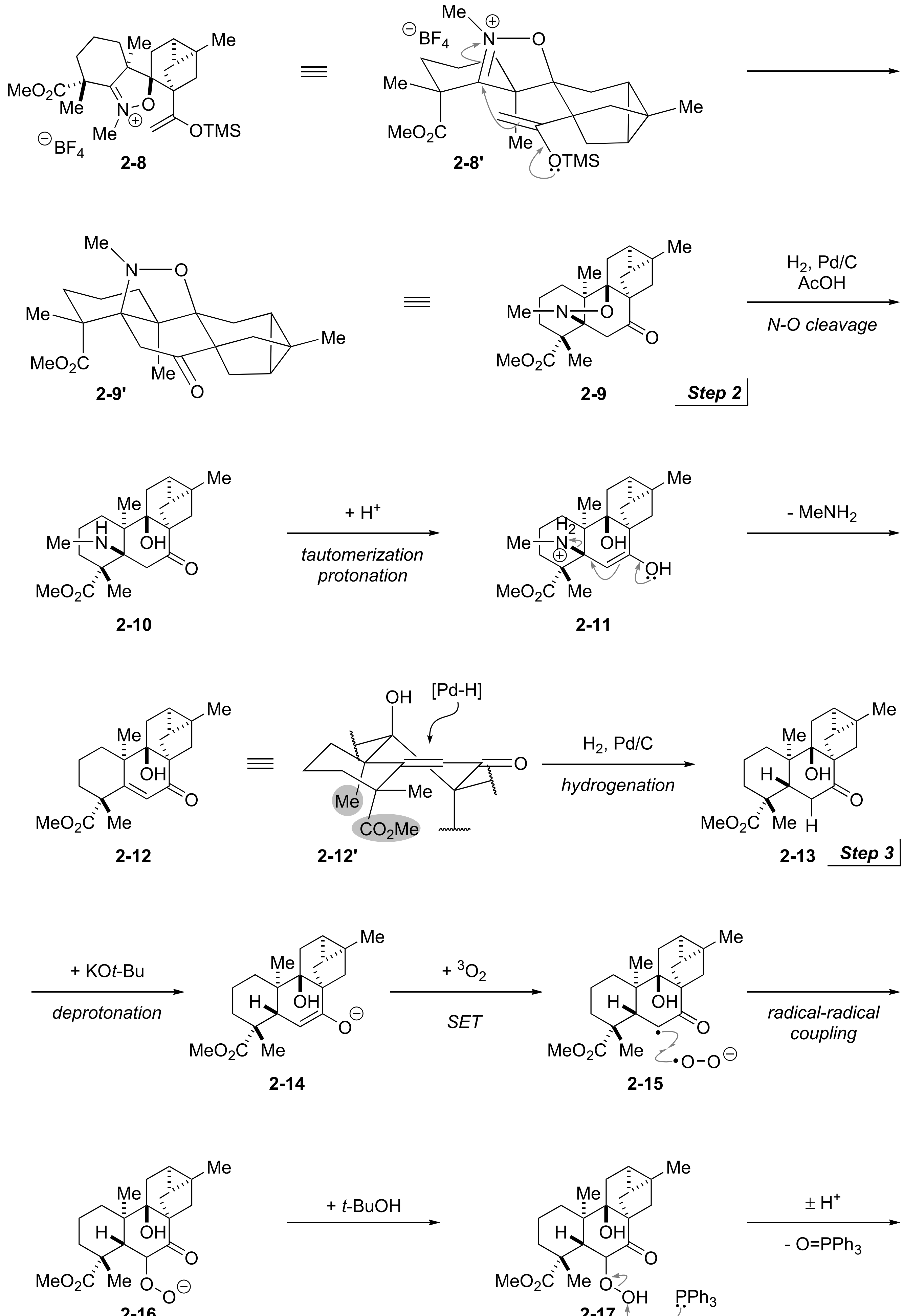


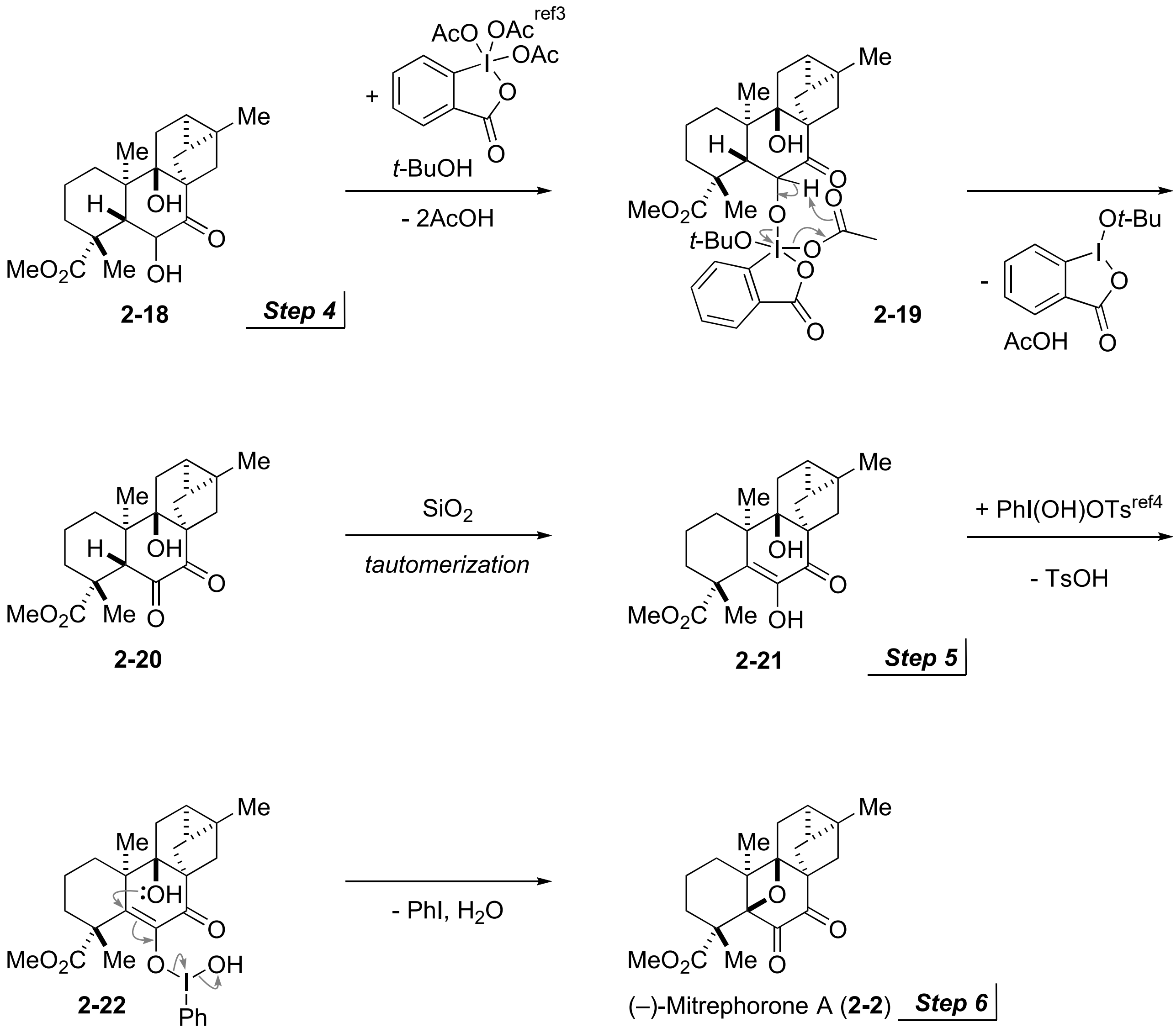
(–)-Mitrephorone A (**2-2**)

a) After addition of saturated aq. $Na_2S_2O_3$/saturated aq. $NaHCO_3/H_2O$ (1/1/2), the resultant mixture was extracted with toluene (x2). Combined organic layers were washed with brine/H_2O (1/1) and dried over Na_2SO_4. The filtrate was heated to 120 °C.
b) The configuration of the newly formed stereogenic center was not assigned.

Schneider, M.; Richter, M. J. R.; Carreira, E. M. *J. Am. Chem. Soc.* **2020**, *142*, 17802.



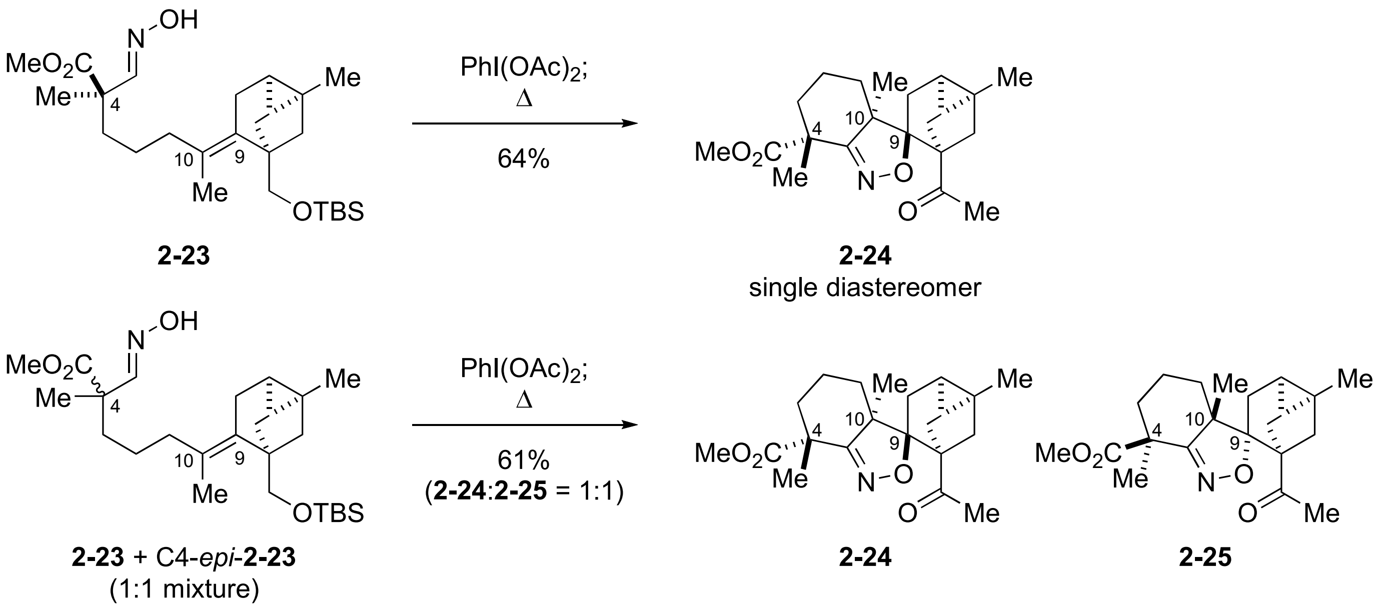

2-8
2-8'
2-9'
2-9
H2, Pd/C
AcOH
N-O cleavage
Step 2
2-10
+ H+
tautomerization
protonation
2-11
- MeNH2
2-12
2-12'
[Pd-H]
H2, Pd/C
hydrogenation
2-13
Step 3
+ KOt-Bu
deprotonation
2-14
+ 3O2
SET
2-15
radical-radical
coupling
2-16
+ t-BuOH
2-17
± H+
- O=PPh3



2-2. Discussion

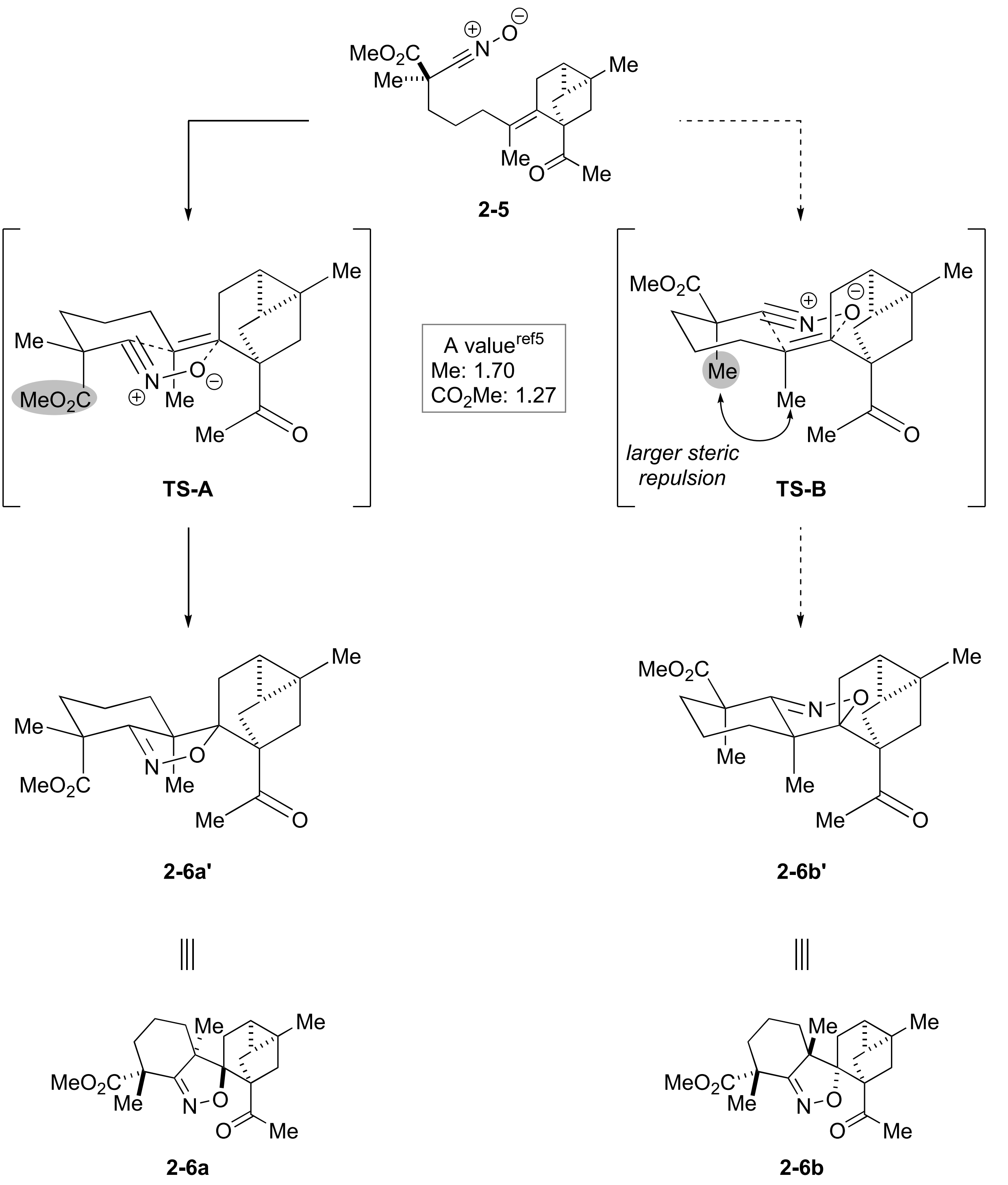
2-2-1. 1,3-Dipolar cycloaddition

2-2-1-1. Experimental results



Two diastereomers **2-24** and **2-25** have the same relative configuration at C4, C9, and C10 positions. This result shows that the facial selectivity in the 1,3-dipolar cycloaddition is fully controlled by the α stereocenter of the nitrile oxide (C4 position).

2-2-1-2. Rationale for the stereoselectivity of 1,3-dipolar cycloaddition



Reference

1. a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542.
   b) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790.
2. Das, B.; Holla, H.; Mahender, G.; Banerjee J.; Reddy, M. R. *Tetrahedron Lett.* **2004**, *45*, 7347.
3. a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
   b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 24, 7549.
4. Arava, S.; Kumar, J. N.; Maksymenko, S.; Iron, M. A.; Parida, K. N.; Fristrup, P.; Szpilman, A. M. *Angew. Chem. Int. Ed.* **2017**, *56*, 2599.
5. Hirsch, J. A. *Topics in Stereochemistry* **1967**, *3*, 199.