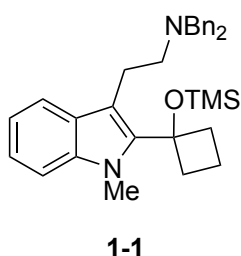


Problem Session (4)

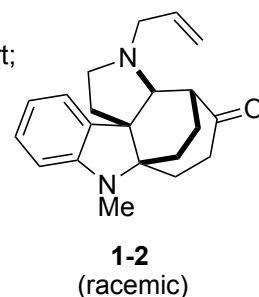
2021.6.12 Toshiya Nagai

Please explain each reaction mechanism and stereoselectivity.

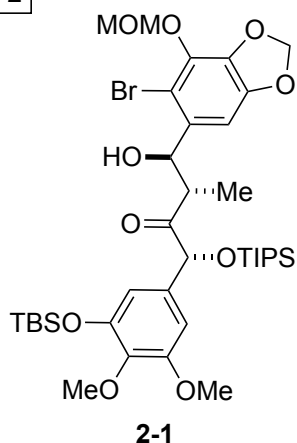
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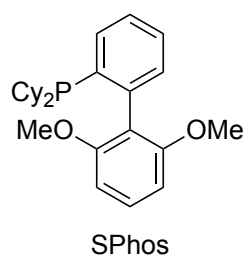
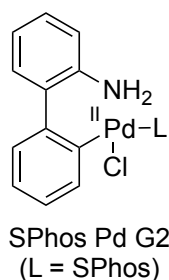
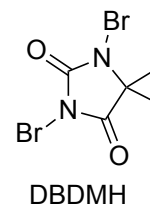
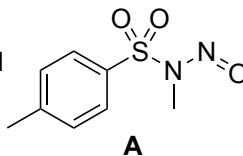
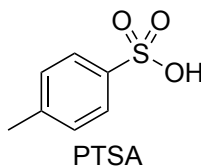
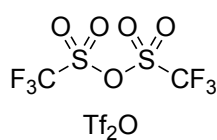
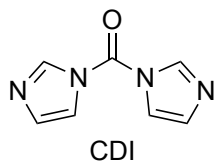
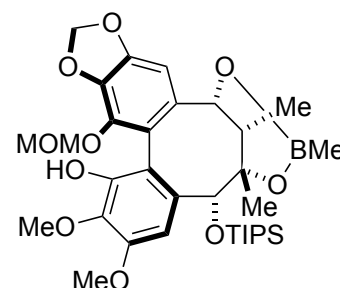
1. Pd(OH)₂/C, H₂, MeOH/THF (50/1), 35 °C
2. HCO₂H (1.0 eq.), CDI (1.2 eq.), CH₂Cl₂, 0 °C, 80% (2 steps)
3. NaH (3.0 eq.), allyl bromide (2.0 eq.)
THF/DMF (10/1), 0 °C to rt, 80%
4. Tf₂O (1.1 eq.), 2-Cl-pyridine (2.2 eq.), CH₂Cl₂, -78 °C to rt;
NaHCO₃ aq.; SiO₂ column, 67%
5. PTSA (0.05 eq.), toluene, reflux
6. **A** (1.1 eq.), KOH (15 eq.)
THF/MeOH/H₂O (10/3/3), 0 °C to rt, 69% (2 steps)
7. TMSCHN₂ (1.3 eq.), *n*-BuLi (1.3 eq.), THF, -78 °C;
MeOH (2.0 eq.), -78 °C;
SiO₂ column, 84%



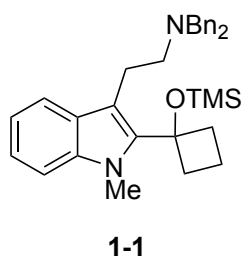
2



1. LiH (1.5 eq.), TiCl₄ (2.0 eq.), THF, -30 °C;
MeMgBr (4.0 eq.), -78 to -40 °C, 70% (dr = 3:1)
2. MeB(OH)₂ (1.2 eq.), MS 4A, CH₂Cl₂, rt, 97%
3. *t*-BuLi (2.0 eq.), THF, -78 °C to rt
4. KHF₂ (2.0 eq.), MeOH/THF (1/1), rt, 81% (2 steps)
5. DBDMH (0.5 eq.), CHCl₃, 0 °C, 97%
6. SPhos Pd G2 (20 mol%), SPhos (20 mol%)
K₃PO₄ (3.0 eq.), toluene
60 °C, 87% (single isomer)

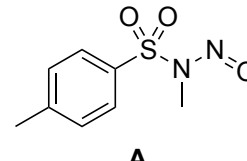
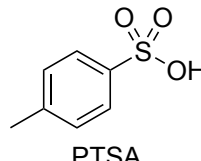
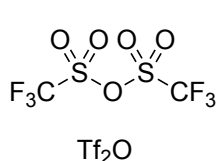
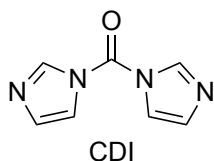
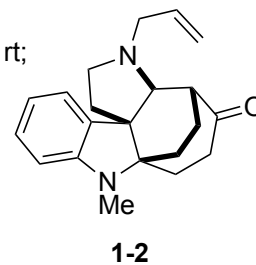


1



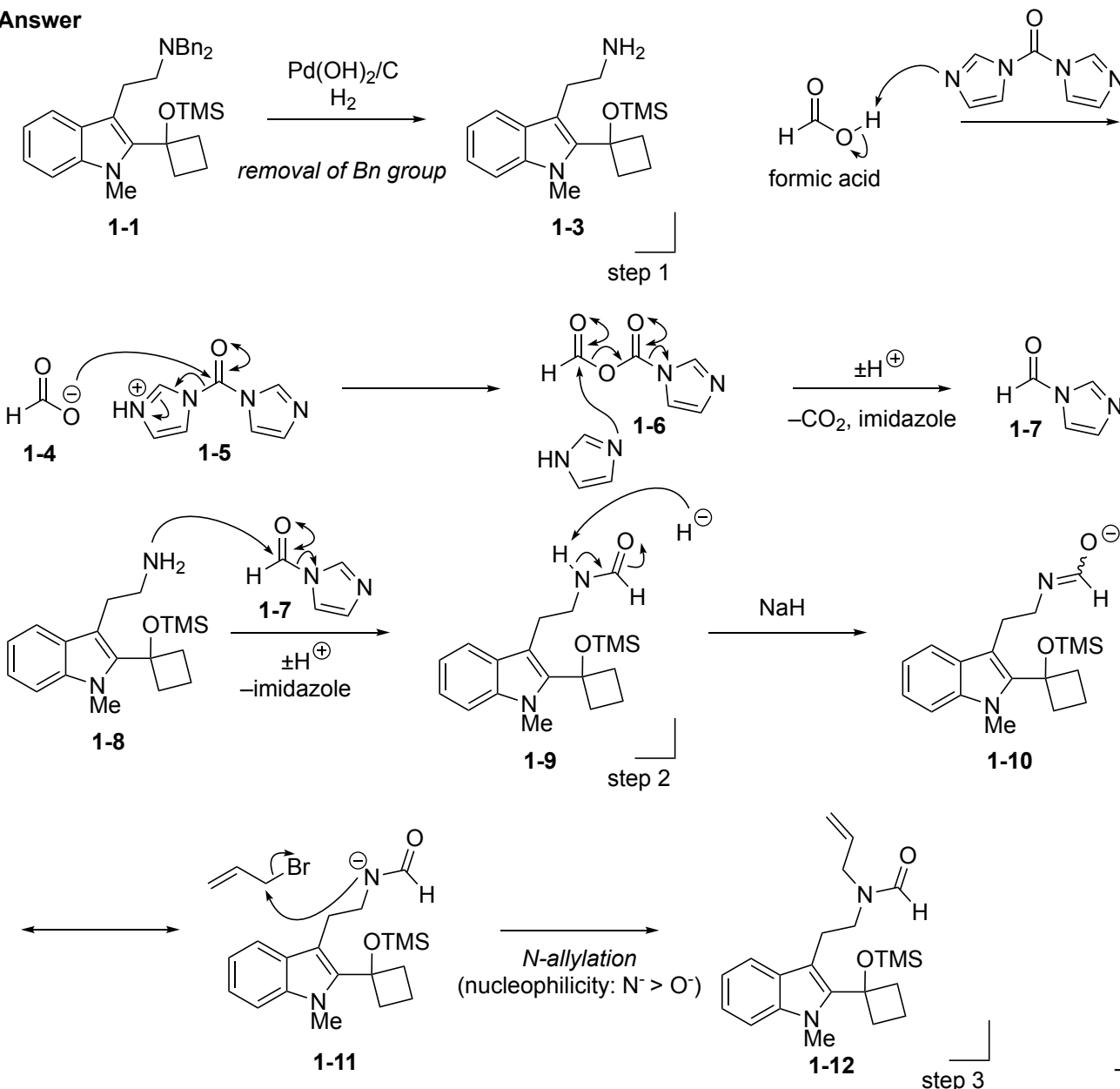
1. Pd(OH)₂/C, H₂, MeOH/THF (50/1), 35 °C
2. HCO₂H (1.0 eq.), CDI (1.2 eq.), CH₂Cl₂, 0 °C, 80% (2 steps)
3. NaH (3.0 eq.), allyl bromide (2.0 eq.)
THF/DMF (10/1), 0 °C to rt, 80%
4. Tf₂O (1.1 eq.), 2-Cl-pyridine (2.2 eq.), CH₂Cl₂, -78 °C to rt;
NaHCO₃ aq.; SiO₂ column, 67%

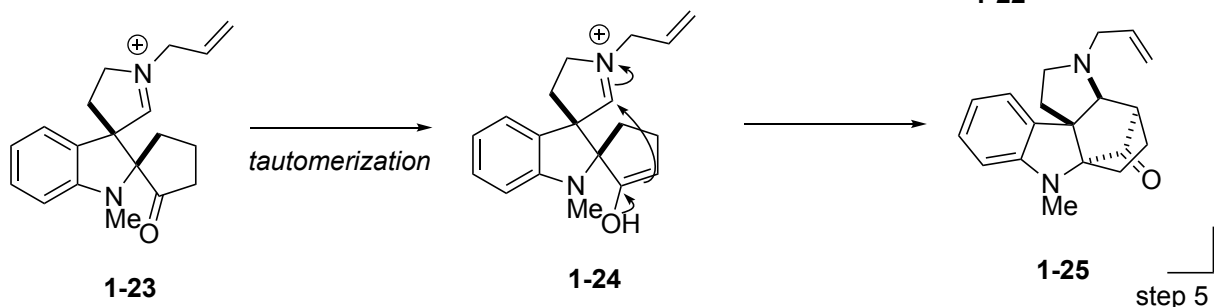
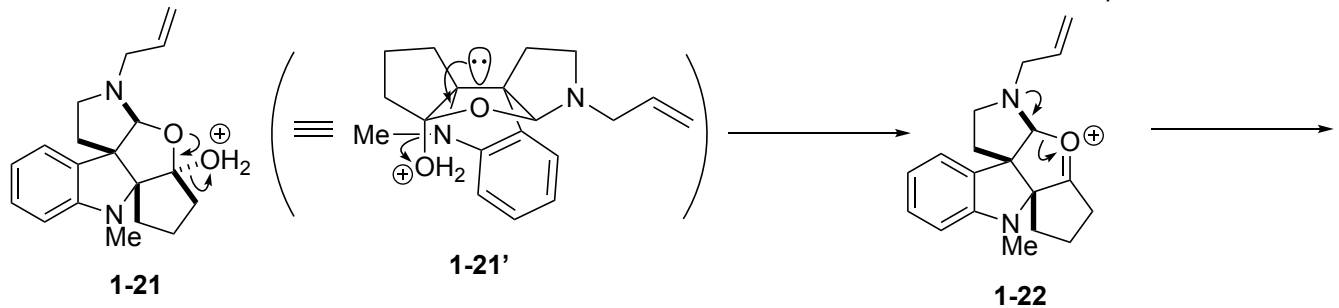
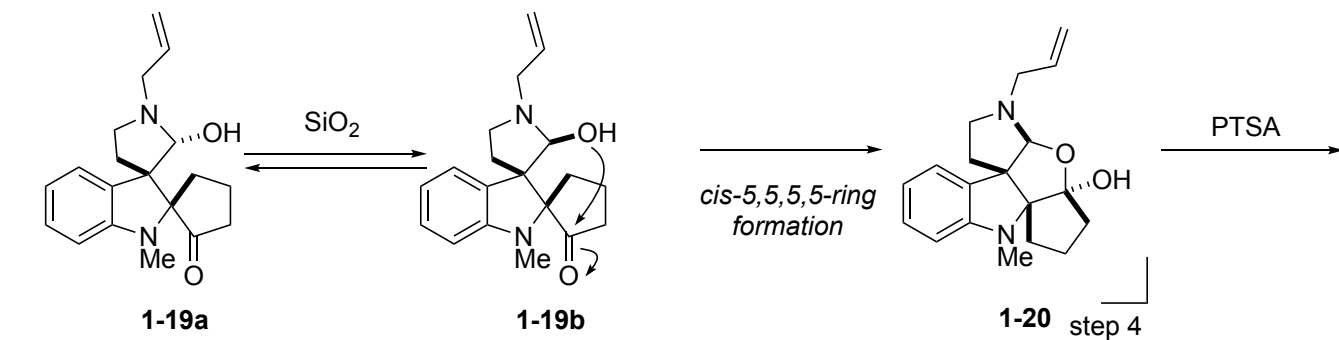
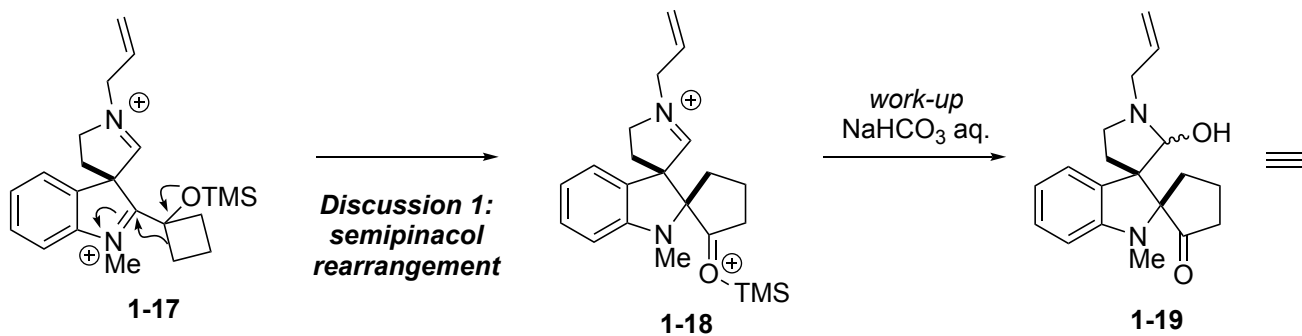
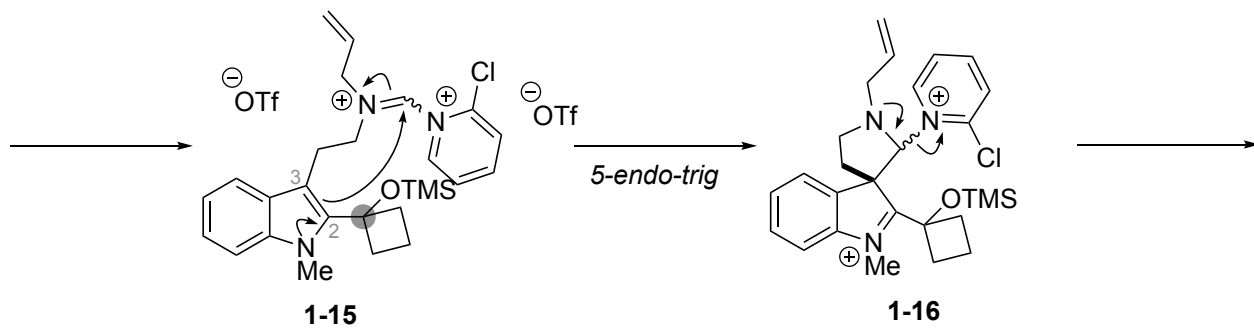
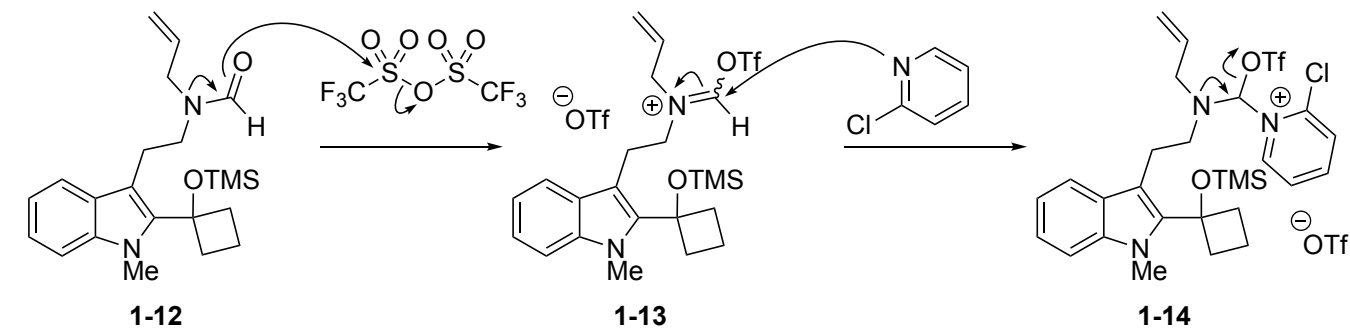
5. PTSA (0.05 eq.), toluene, reflux
6. **A** (1.1 eq.), KOH (15 eq.)
THF/MeOH/H₂O (10/3/3), 0 °C to rt, 69% (2 steps)
7. TMSCHN₂ (1.3 eq.), *n*-BuLi (1.3 eq.), THF, -78 °C;
MeOH (2.0 eq.), -78 °C;
silica gel column, 84%

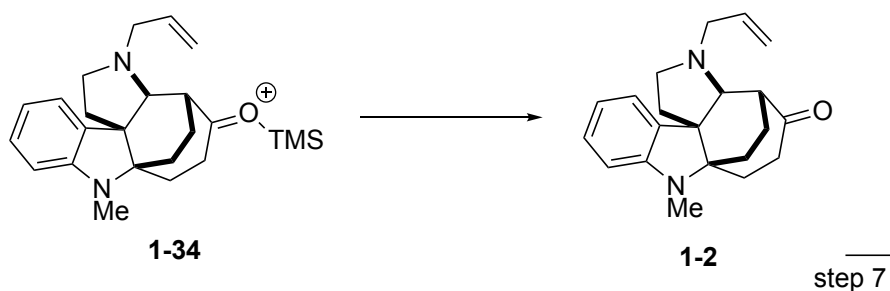
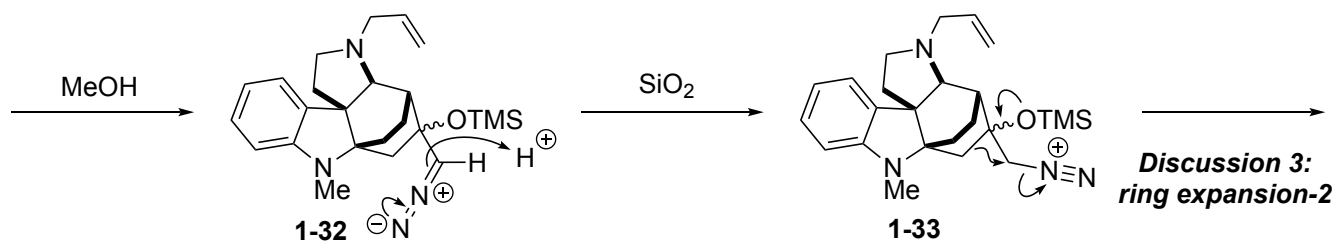
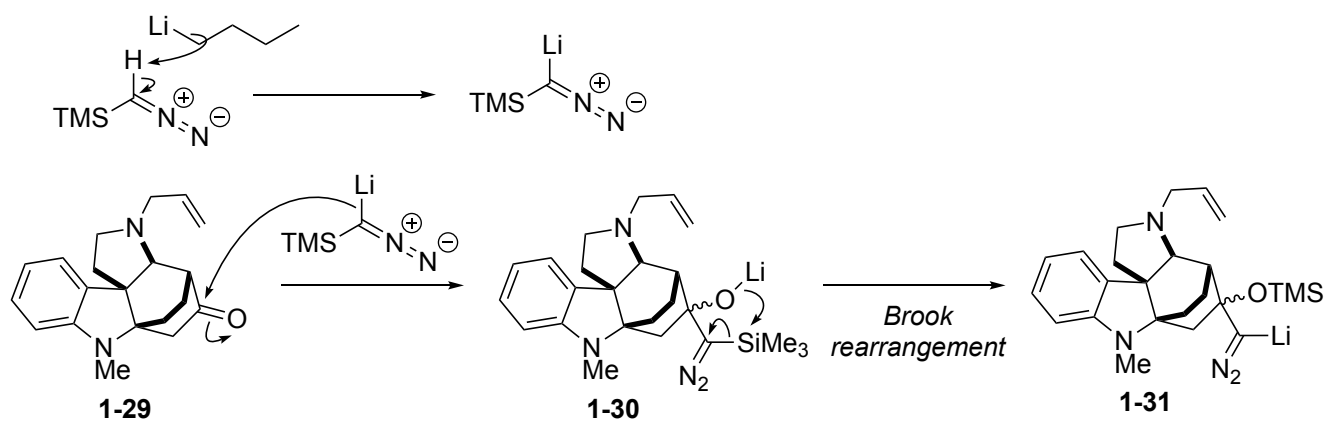
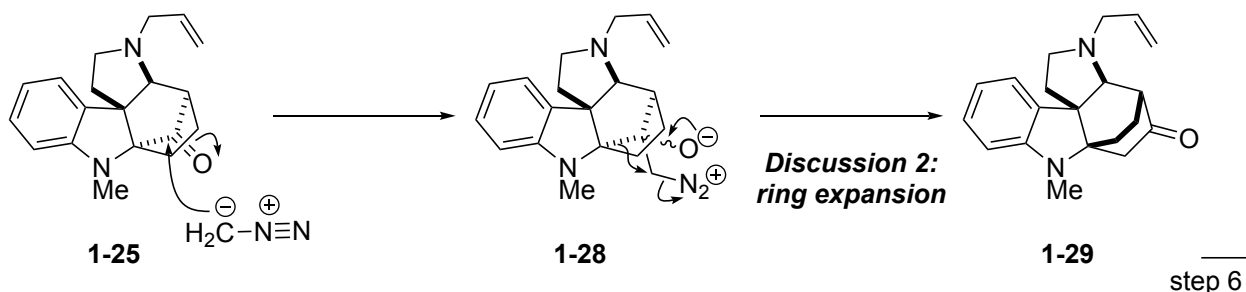
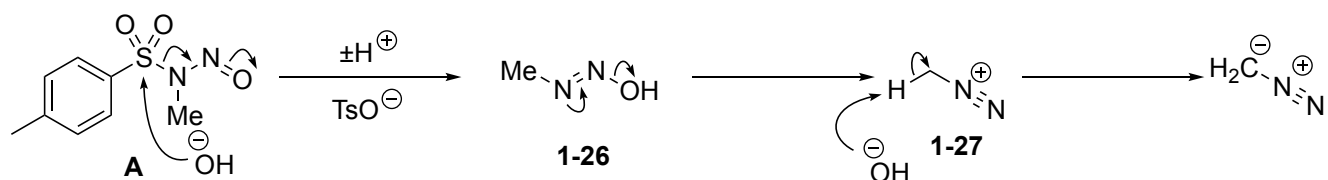


Wang, S.-H.; Si, R.-Q.; Zhuang, Q.-B.; Guo, X.; Ke, T.; Zhang, X.-M.; Zhang, F.-M.; Tu, Y.-Q. *Angew. Chem. Int. Ed.* **2020**, *59*, 21954.

Answer

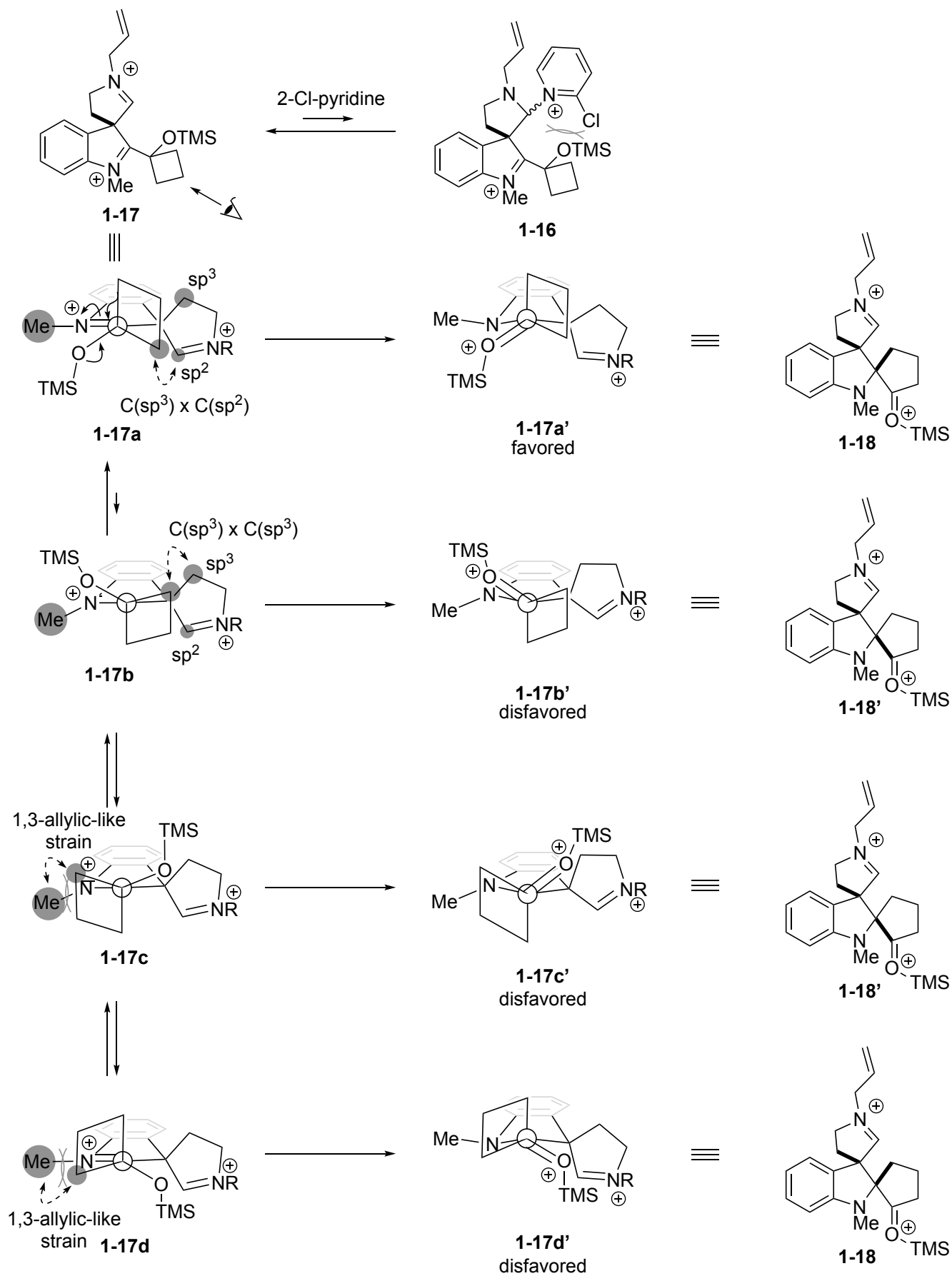




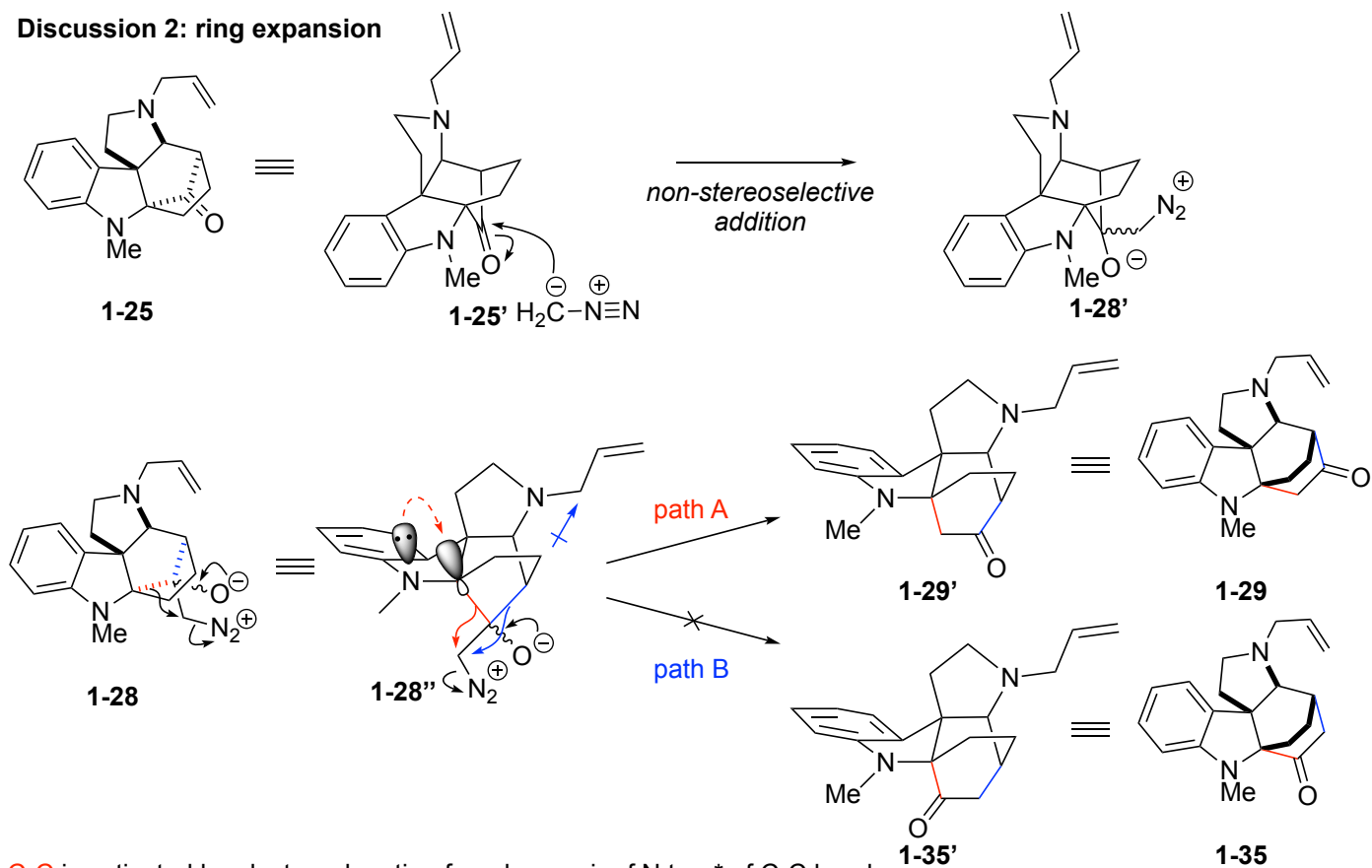


The ring expansion conditions¹⁾ in step 7 has the advantage to prevent over-reaction, compared with the conventional method.

Discussion 1: semipinacol rearrangement



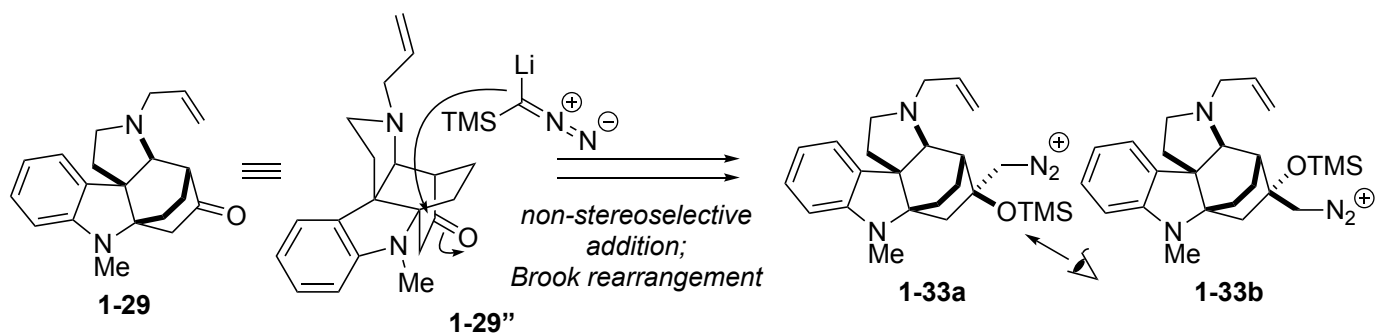
Discussion 2: ring expansion



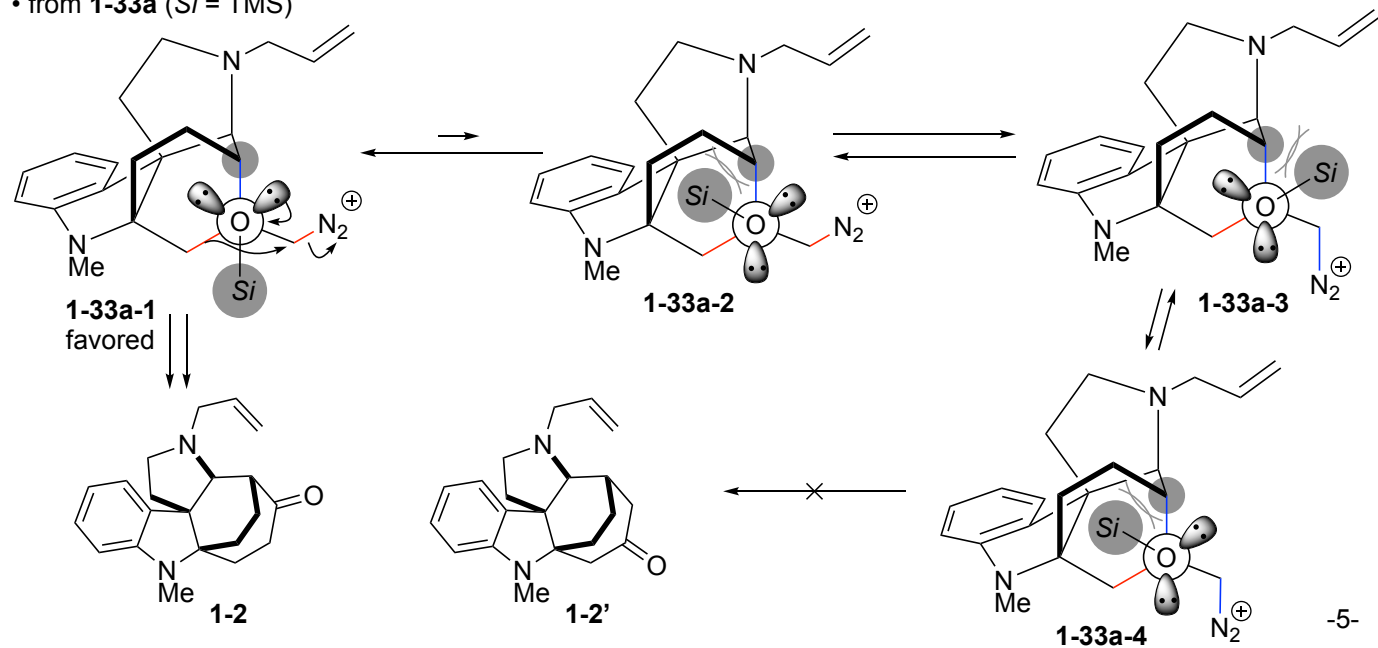
C-C is activated by electron donation from lone pair of N to σ^* of C-C bond.

C-C is deactivated by inductive effect of N.

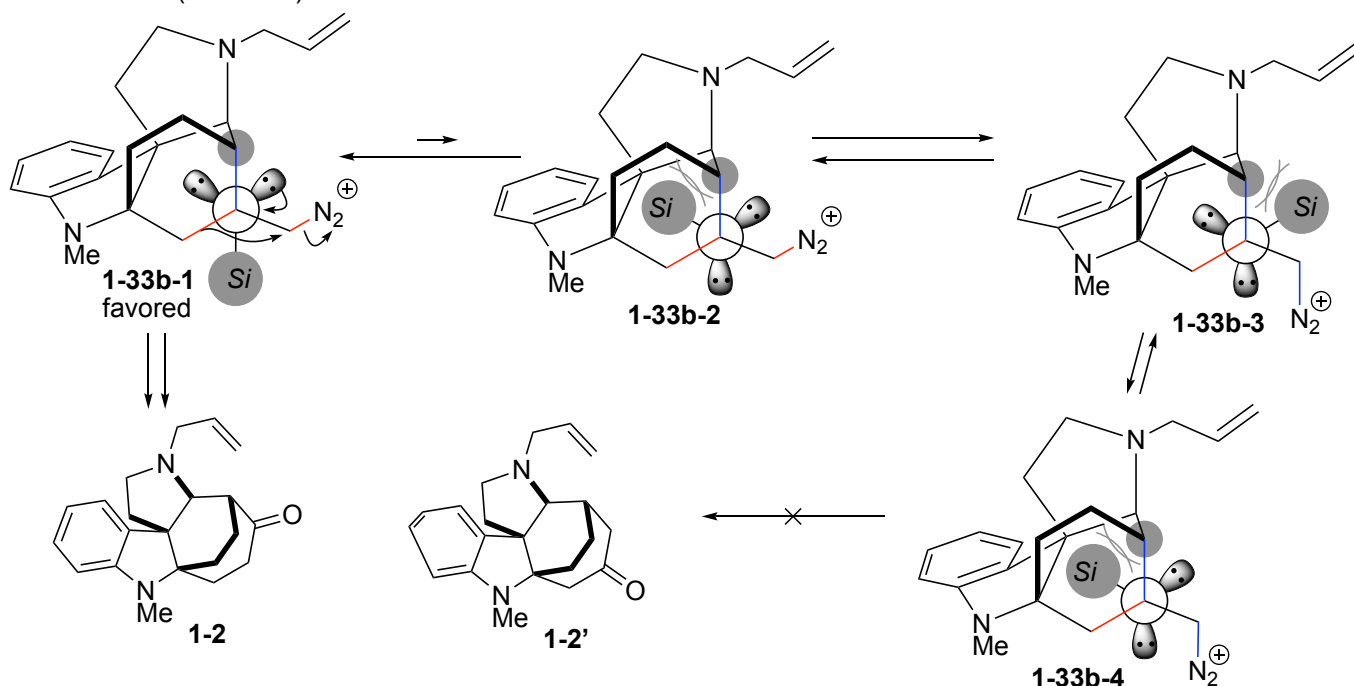
Discussion 3: ring expansion-2



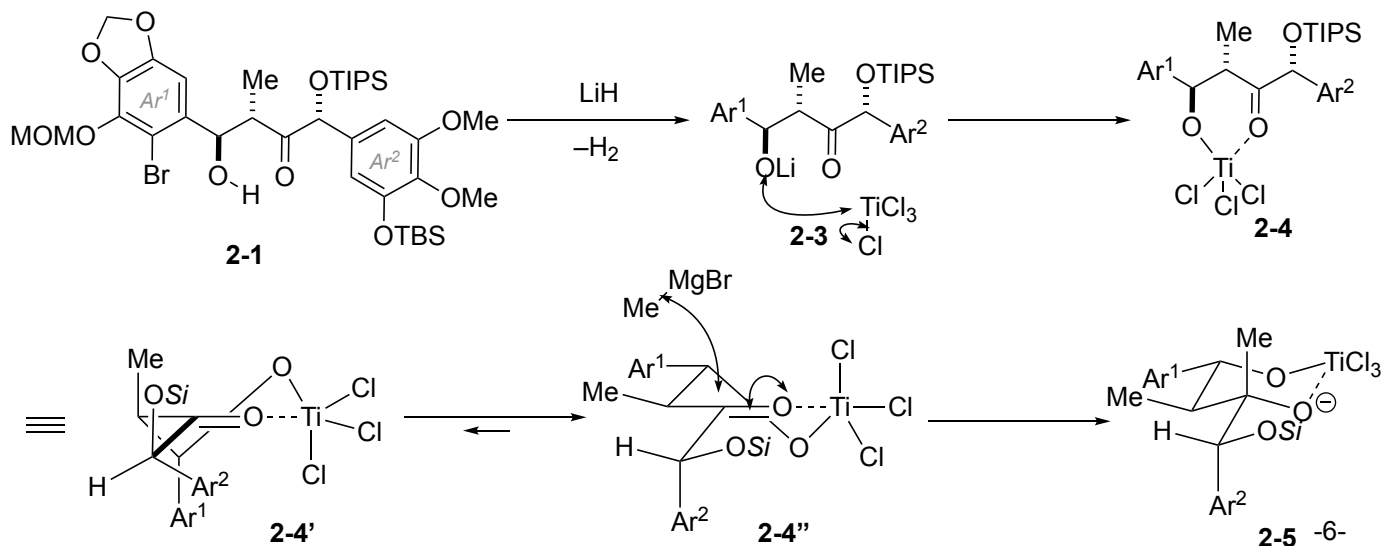
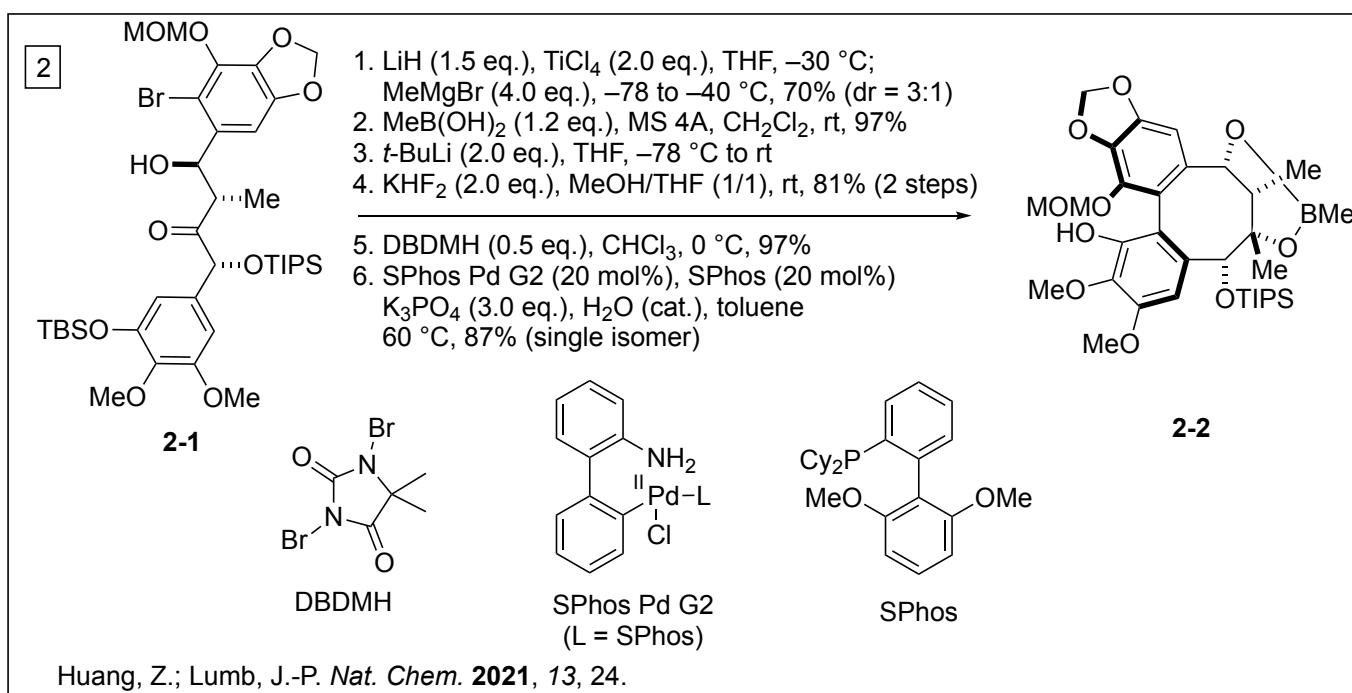
• from 1-33a (Si = TMS)

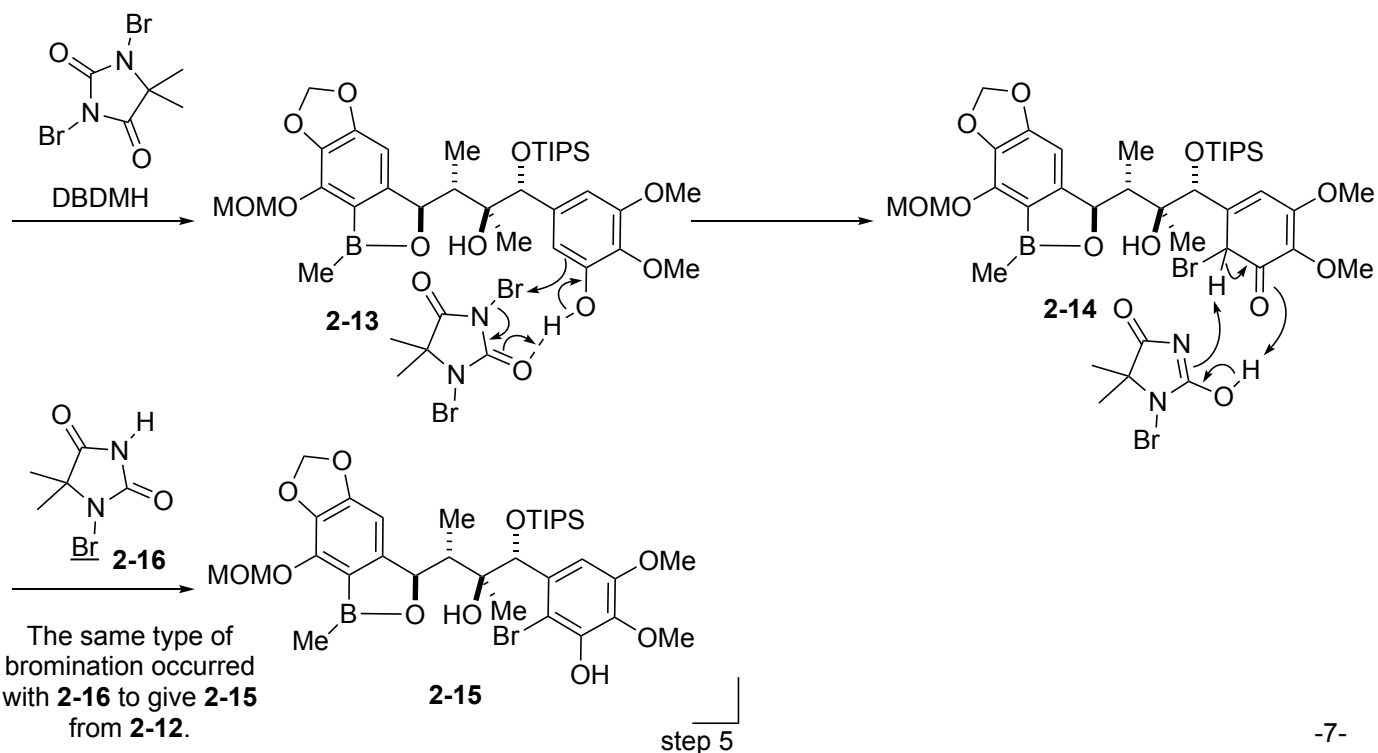
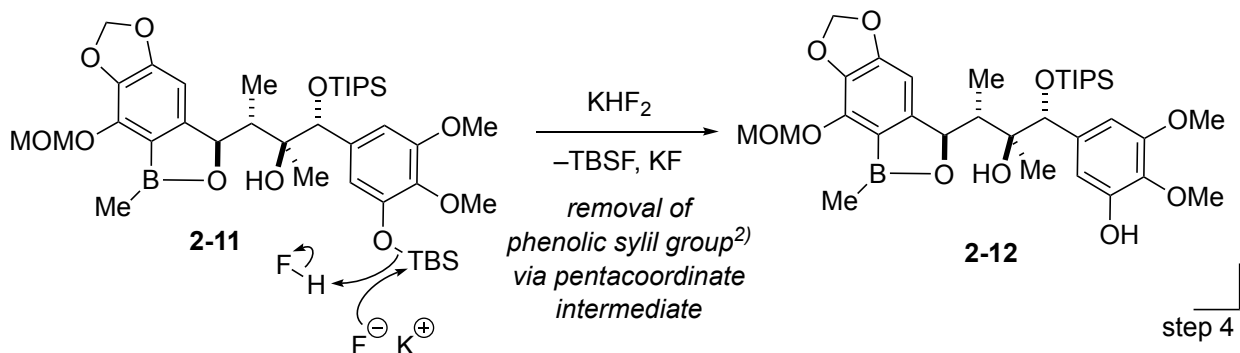
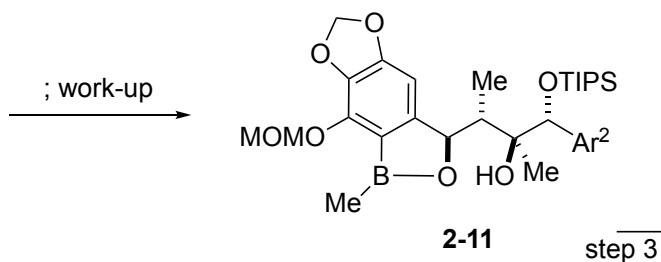
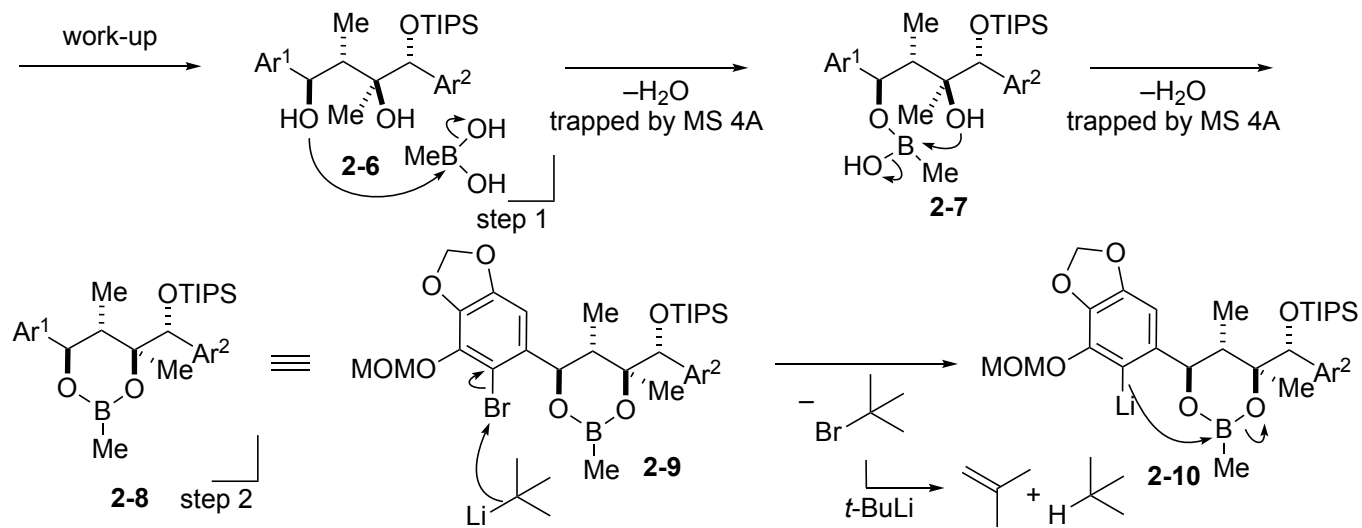


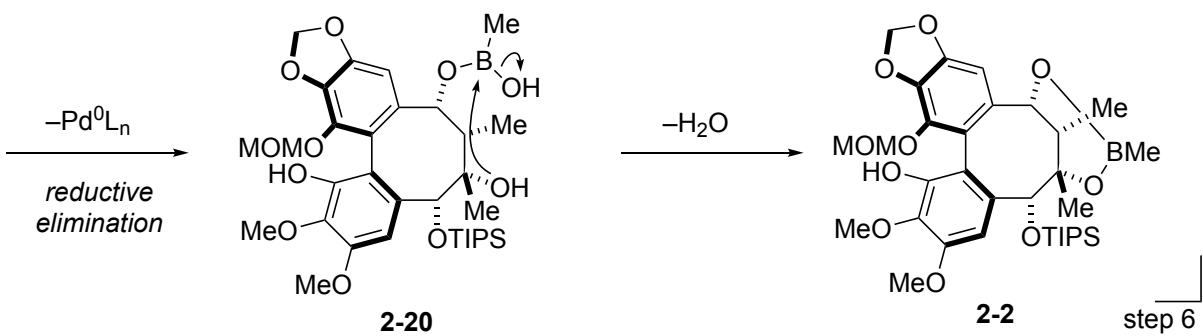
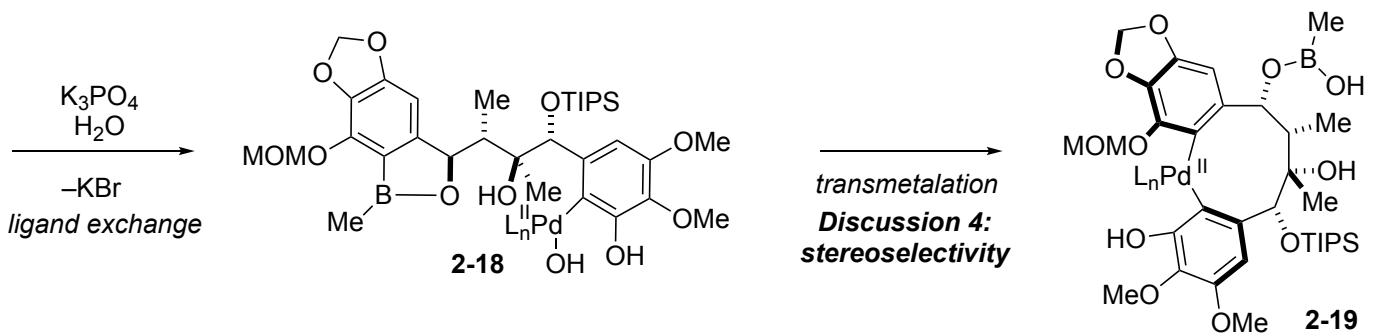
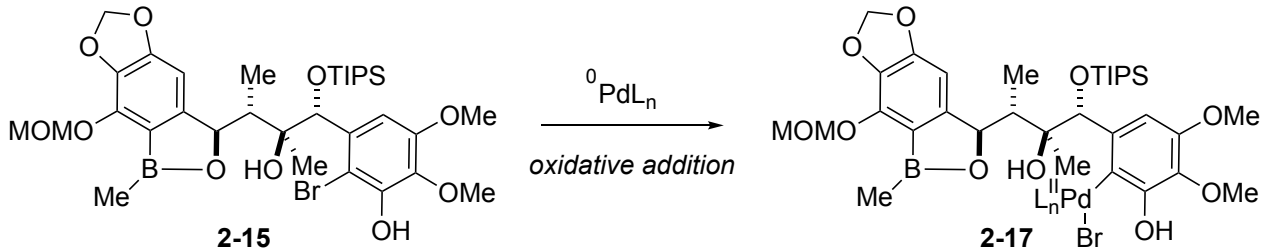
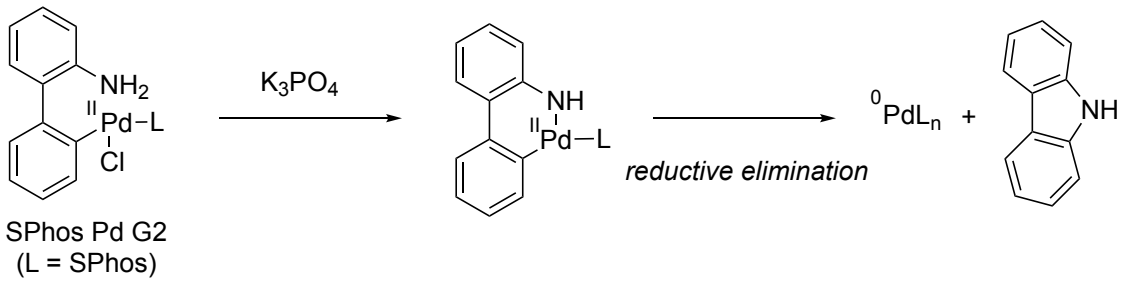
• from 1-33b (Si = TMS)



This regioselectivity should also be explained by least motion³⁾.

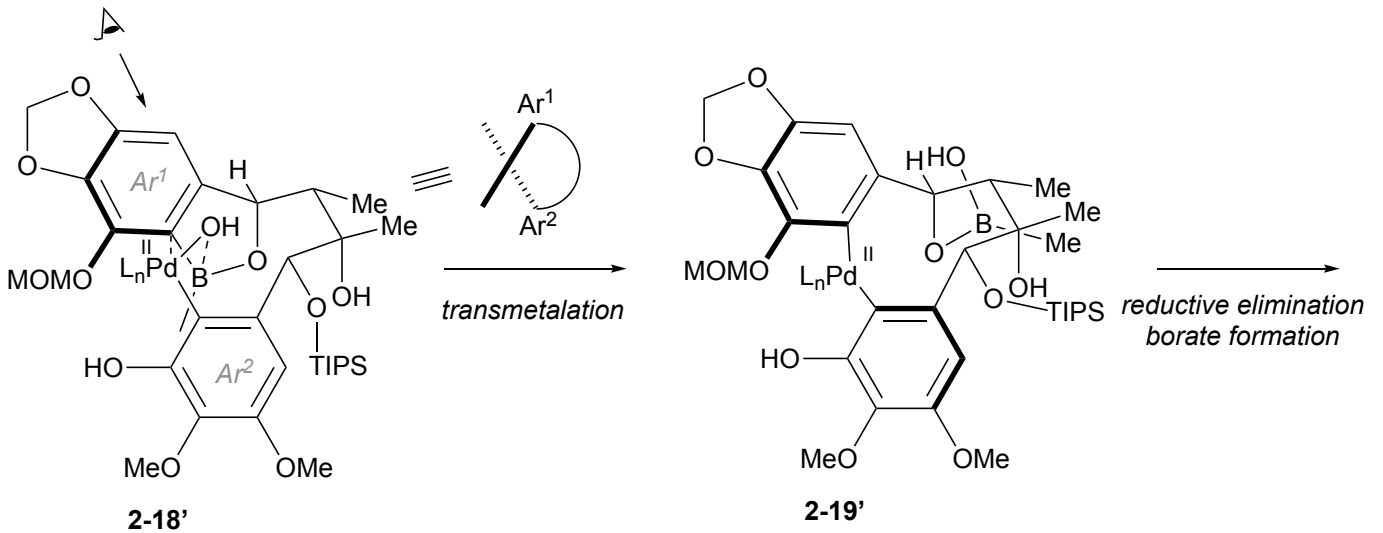


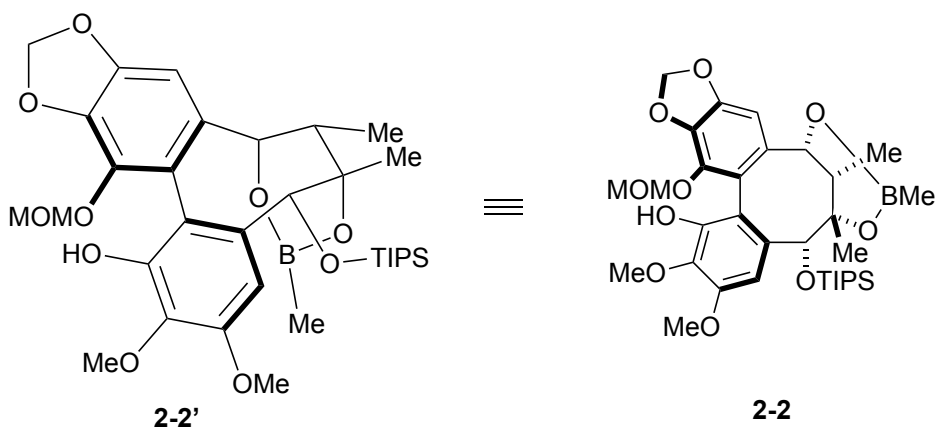




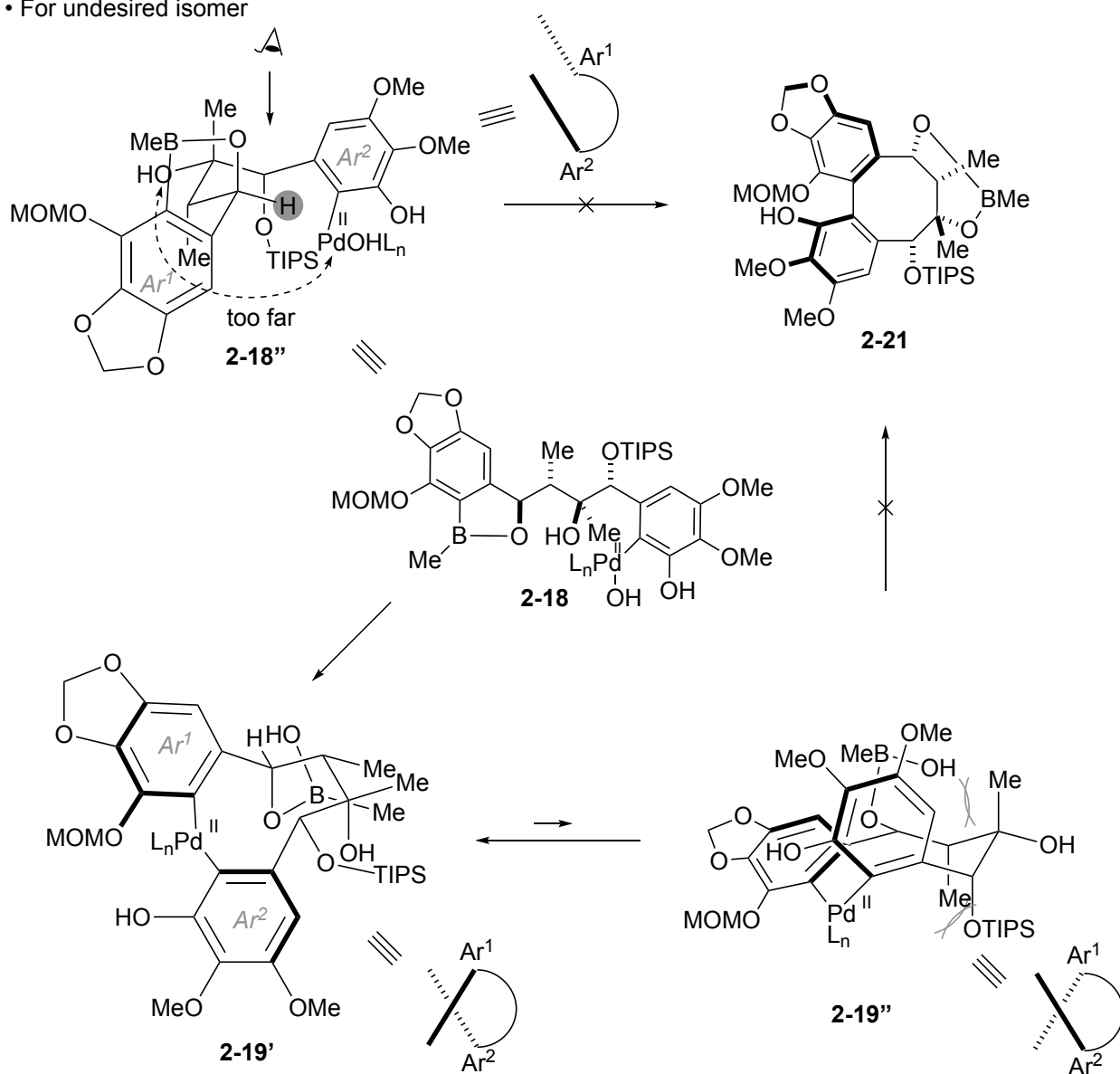
Discussion 4: stereoselectivity

- For desired isomer





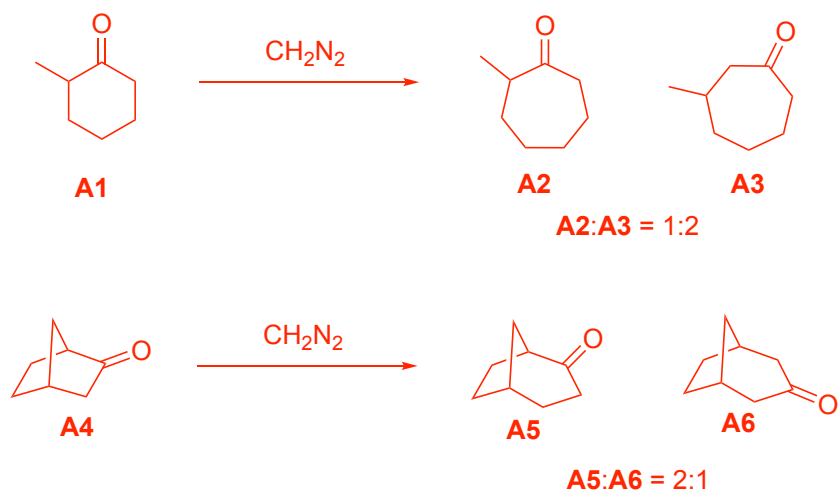
• For undesired isomer



Reference:

1. Liu, H.; Sun, C.; Lee, N. K.; Henry, R. F.; Lee, D. *Chem. Eur. J.* **2012**, *18*, 11889.
2. Lakshman, M.K.; Tine, F. A.; Khandaker, T. A.; Basava, V.; Agyemang, N. B.; Benavidez, M. S. A.; Gaši, M.; Guerrero, L.; Zajc, B. *Synlett* **2017**, *28*, 381.
3. McKinney, M. A.; Patel, P. P. *J. Org. Chem.* **1973**, *38*, 4059.

Krow, G. R. *Tetrahedron* **1987**, *43*, 3.



Sakai, T.; Ito, S.; Furuta, H.; Kawahara, Y.; Mori, Y. *Org. Lett.* **2012**, *14*, 4564.

