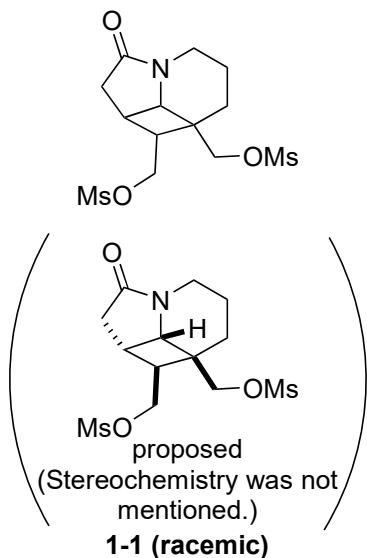


Problem Session (2)

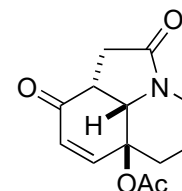
2020.11.7 Shu Nakamura

Please explain the reaction mechanism.

1.

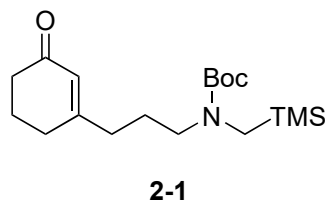


1. Na₂S (2.5 eq.), DMF, 50 °C, 75%
2. *m*-CPBA (1 eq.), CH₂Cl₂, -78 °C, 76% (dr = 5:1*)
3. SO₂Cl₂ (1.05 eq.), pyridine (2.1 eq.), CH₂Cl₂, -78 to -40 °C, 90% (complex mixture of diastereomers*)
4. *t*-BuOK (5 eq.), THF, 23 °C, 43%
5. benzene, 110 °C, 82% (85%, brsm)
6. O₂, TPP (1 mol%), hν (white), CH₂Cl₂, 0 °C; Et₃N (2 eq.), 23 °C; Et₃N (2 eq.), Ac₂O (3 eq.), DMAP (0.1 eq.), 23 °C, 90%

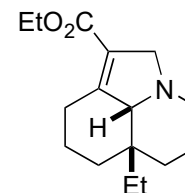


* It is unknown which diastereomer was major.

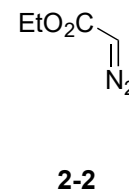
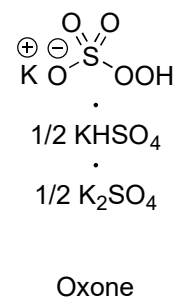
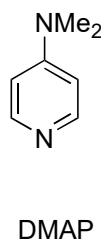
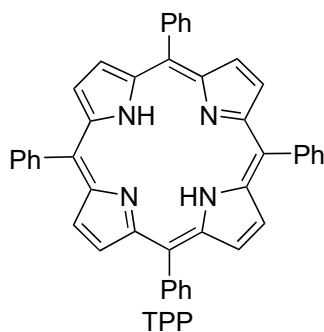
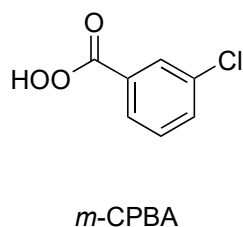
2.



1. CuI (15 mol%), LiCl (25 mol%), TMSCl (1.1 eq.), Et₃N (1.2 eq.), EtMgBr (1.2 eq.), THF, 0 °C, 89%
2. Oxone (4 eq.), CH₂Cl₂/acetone/sat. NaHCO₃ aq., 0 °C, 79%*
3. TMSCl (3 eq.), DMAP (0.3 eq.), imidazole (3 eq.), CH₂Cl₂, rt, 82%*
4. LiN(*i*-Pr)₂ (1.5 eq.), **2-2** (1.7 eq.), THF, -78 °C, 73%*
5. In(OTf)₃ (1 eq.) MS4A, CH₂Cl₂, rt, 90%
6. CsF (2.4 eq.), MeCN, reflux, 60% (single diastereomer)



* as a mixture of diastereomers

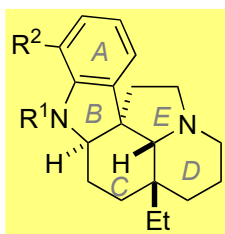


Problem Session (2) -Answer-

2020.11.7 Shu Nakamura

Topic: Construction of C,D,E ring system of *Aspidosperma* alkaloids
- via ring opening -

Introduction:



aspidospermine
($R^1 = \text{Ac}$, $R^2 = \text{OMe}$)
aspidospermidine
($R^1 = \text{H}$, $R^2 = \text{H}$)

***Aspidosperma* alkaloids:** over 250 members

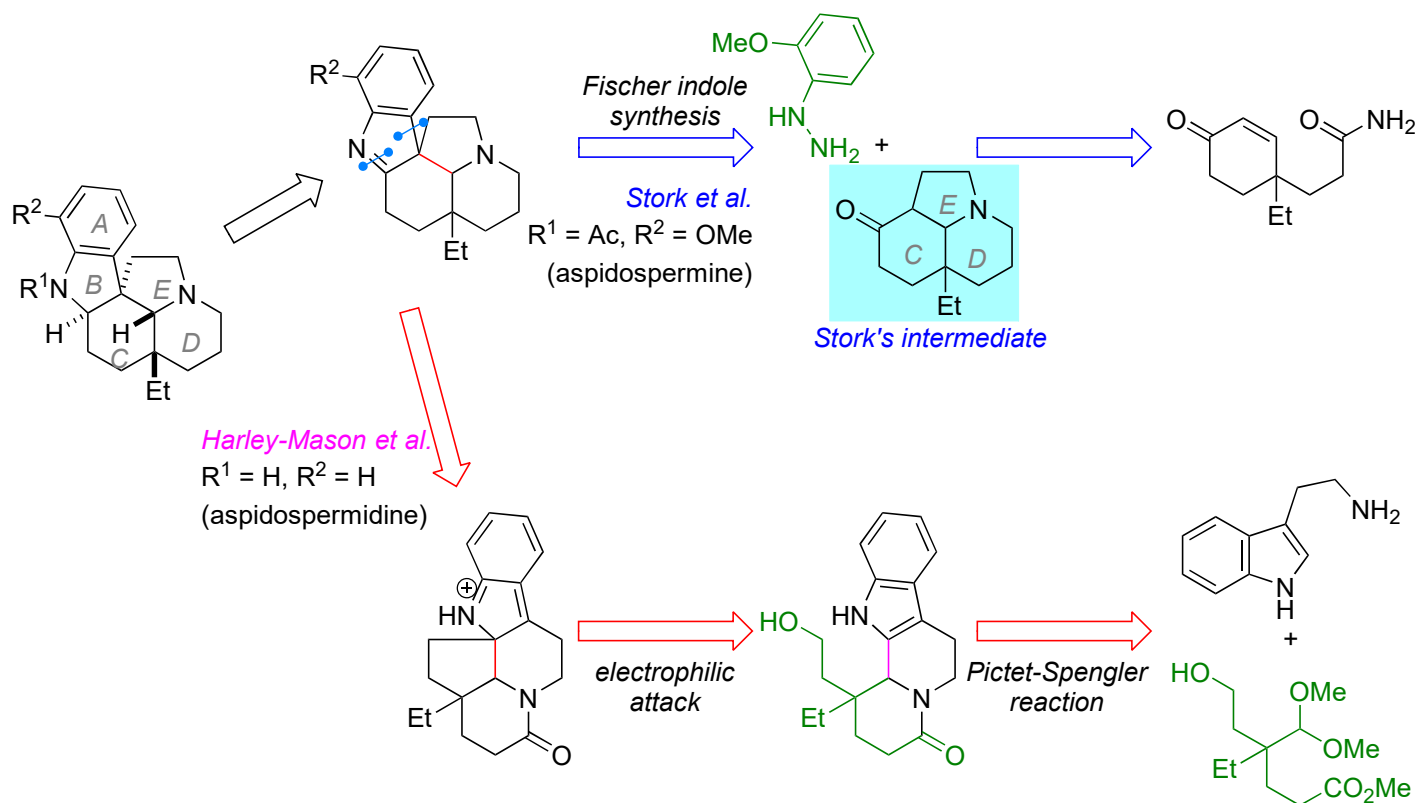
isolation

aspidospermine: from *Aspidosperma quebracho blanco* (1878)
(Fraude, G. *Berichte der deutschen chemischen Gesellschaft* **1878**, 11, 2189.)

structural features:

pentacyclic ABCDE ring system

Example strategies to *Aspidosperma* alkaloids



Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, 85, 2872.

Harley-Mason, J.; Kaplan, M. *Chem. Commun. (London)* **1967**, 915.

For more information, see:

Saya, J. M.; Ruijter, E.; Orru, R. V. A. *Chem. Eur. J.* **2019**, 25, 8916.

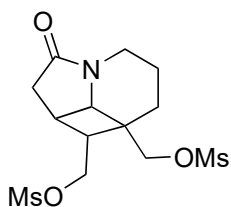
also:

160625_PS_Eiji_Yoshida

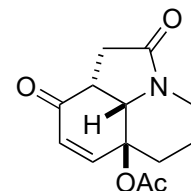
161024_PS_Tsukasa_Shimakawa

1.

1. Na₂S (2.5 eq.), DMF, 50 °C, 75%
2. *m*-CPBA (1 eq.), CH₂Cl₂, -78 °C, 76% (dr = 5:1*)
3. SO₂Cl₂ (1.05 eq.), pyridine (2.1 eq.), CH₂Cl₂, -78 to -40 °C, 90% (complex mixture of diastereomers*)
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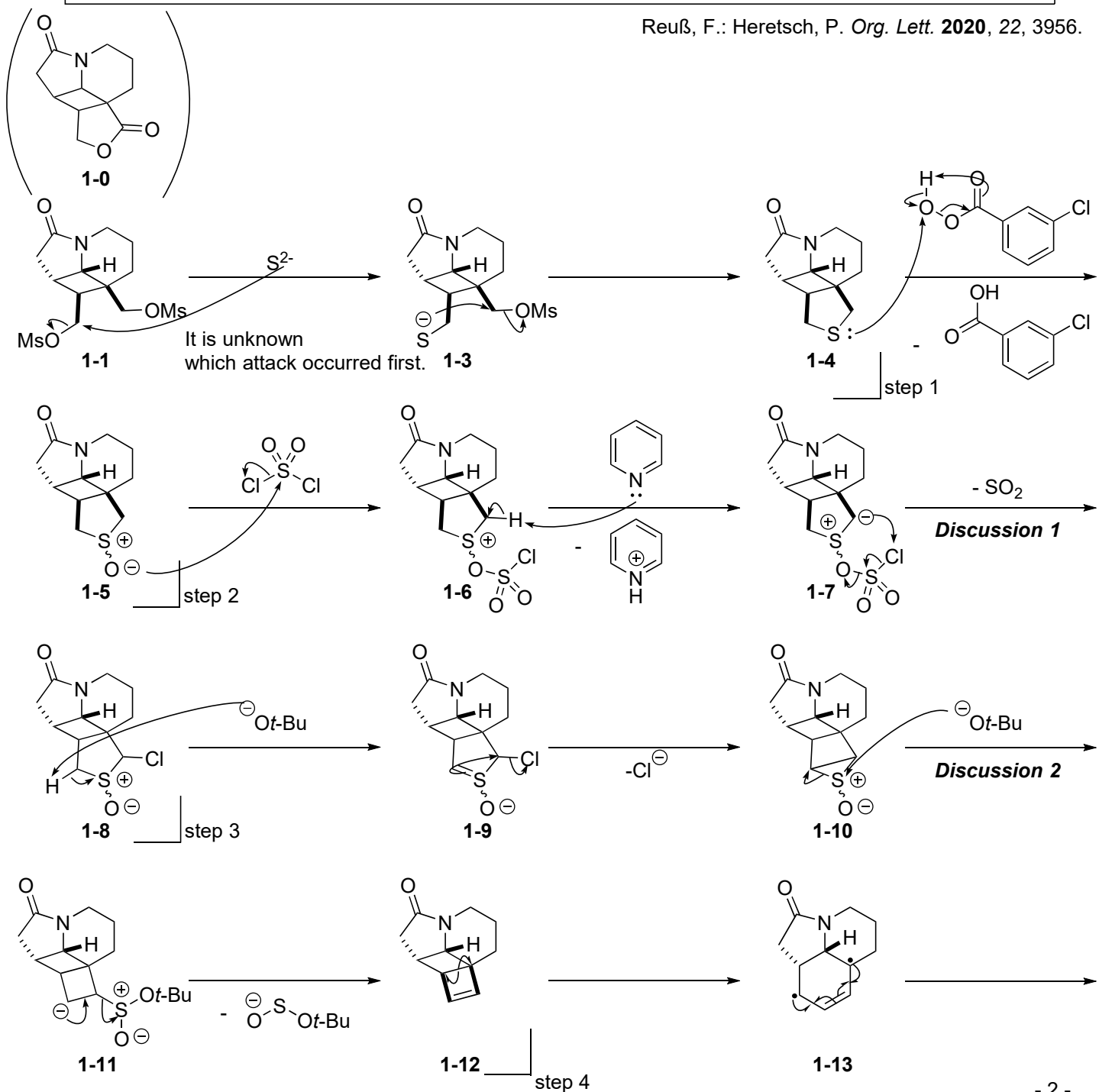


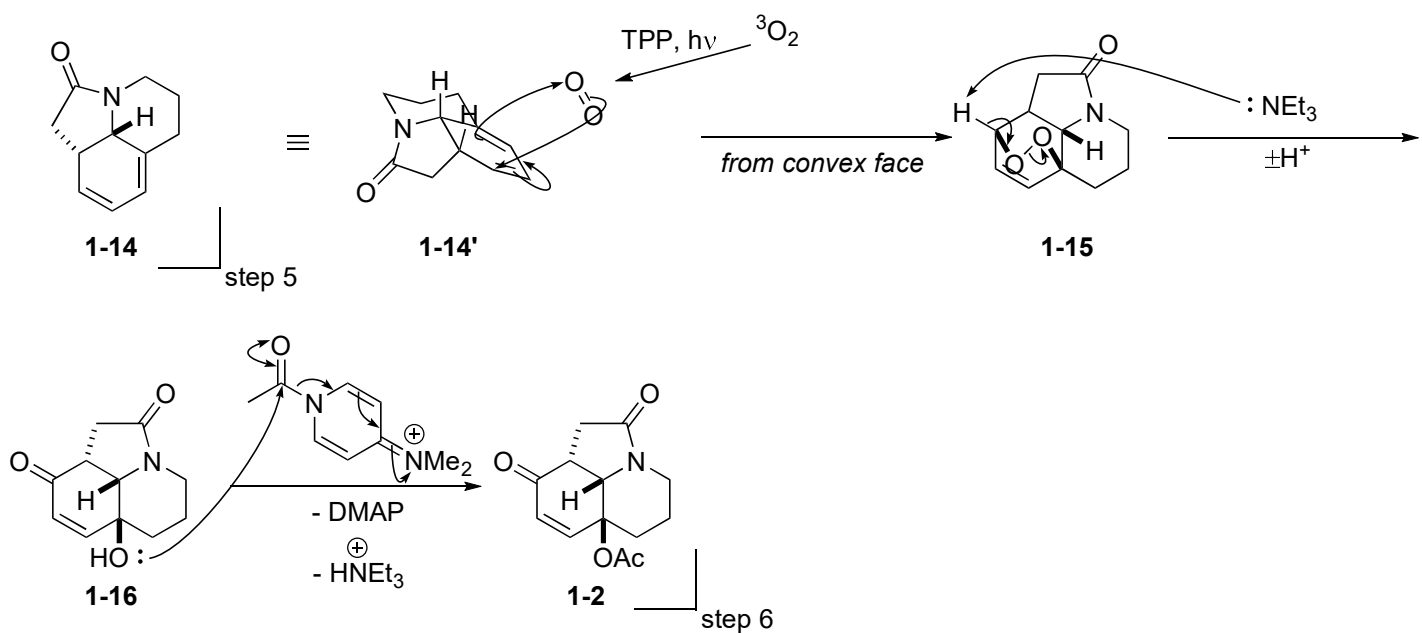
1-1 (racemic)



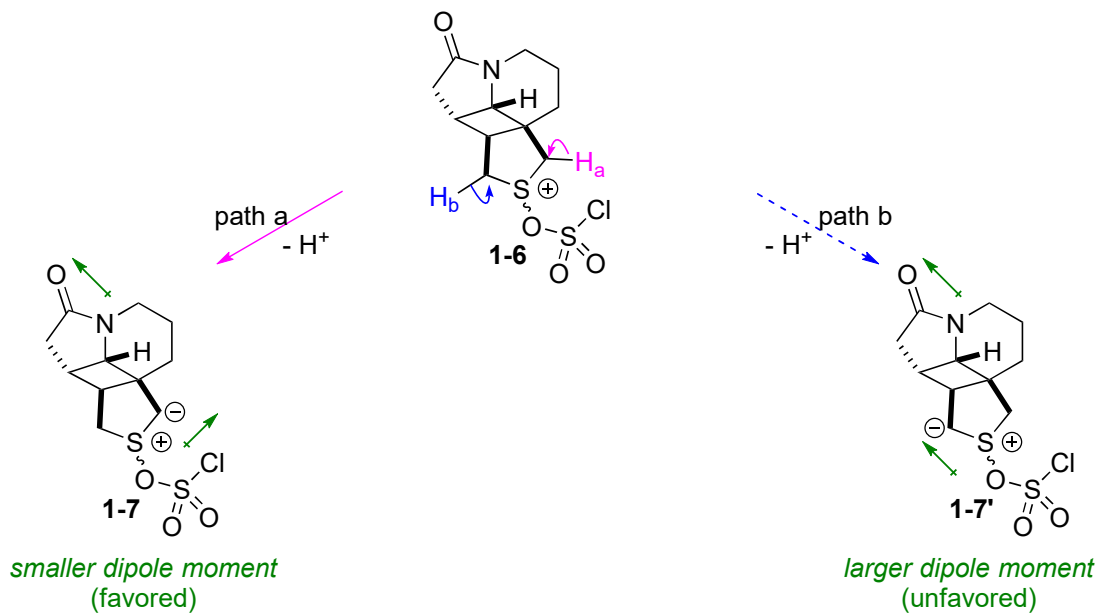
1-2 (racemic)

* It is unknown which diastereomer was major.

Reuß, F.; Heretsch, P. *Org. Lett.* **2020**, *22*, 3956.

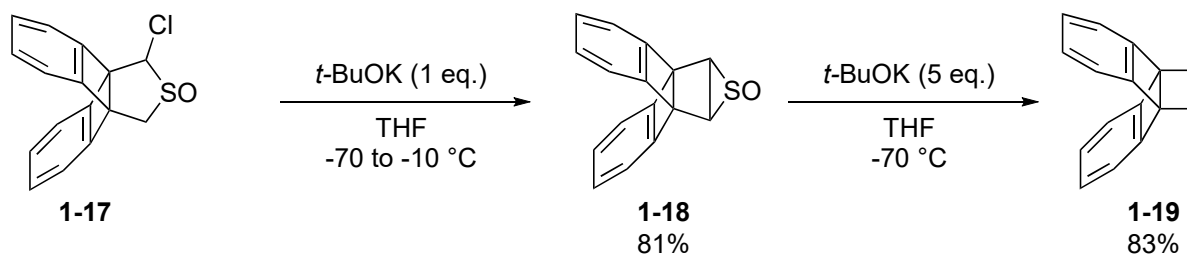


Discussion 1: regioselectivity



Discussion 2: mechanism of the ring contraction

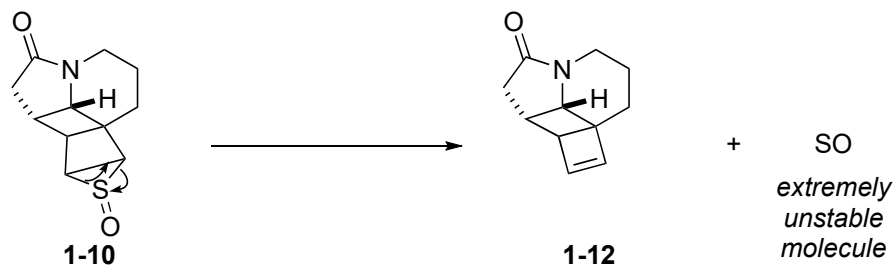
2-1. Intermediate



Weinges, K.; Sipos, W.; Klein, J.; Deuter, J.; Irgartinger, H. *Chem. Ber.* **1987**, *120*, 5.

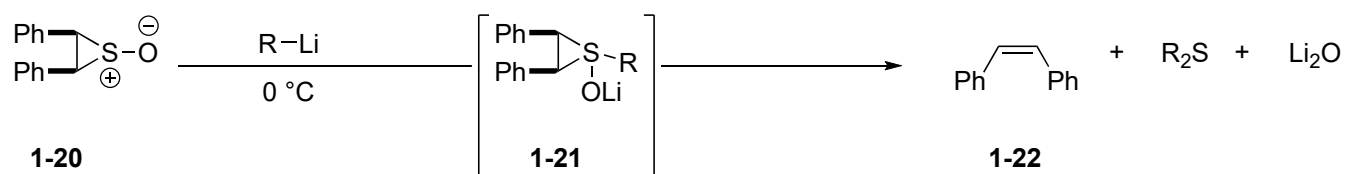
Episulfoxide (**1-10**) should be the intermediate of the reaction.

2-2. Another possible mechanism (like Ramberg-Bäcklund rearrangement) proposed by author

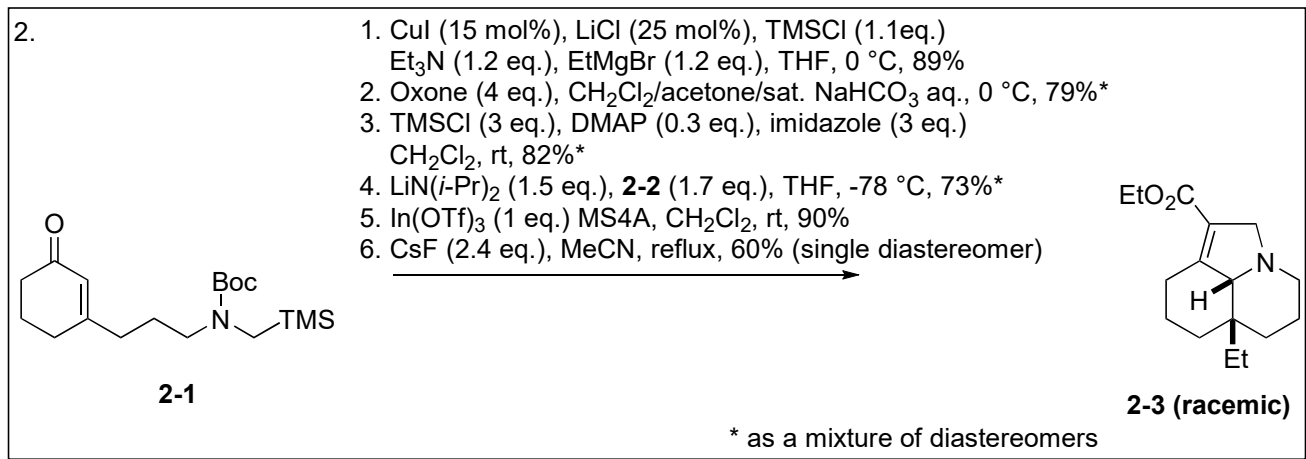


Although emission of SO from episulfide is known, it requires high temperature (100~ °C; and SO is trapped by olefin or polyene).

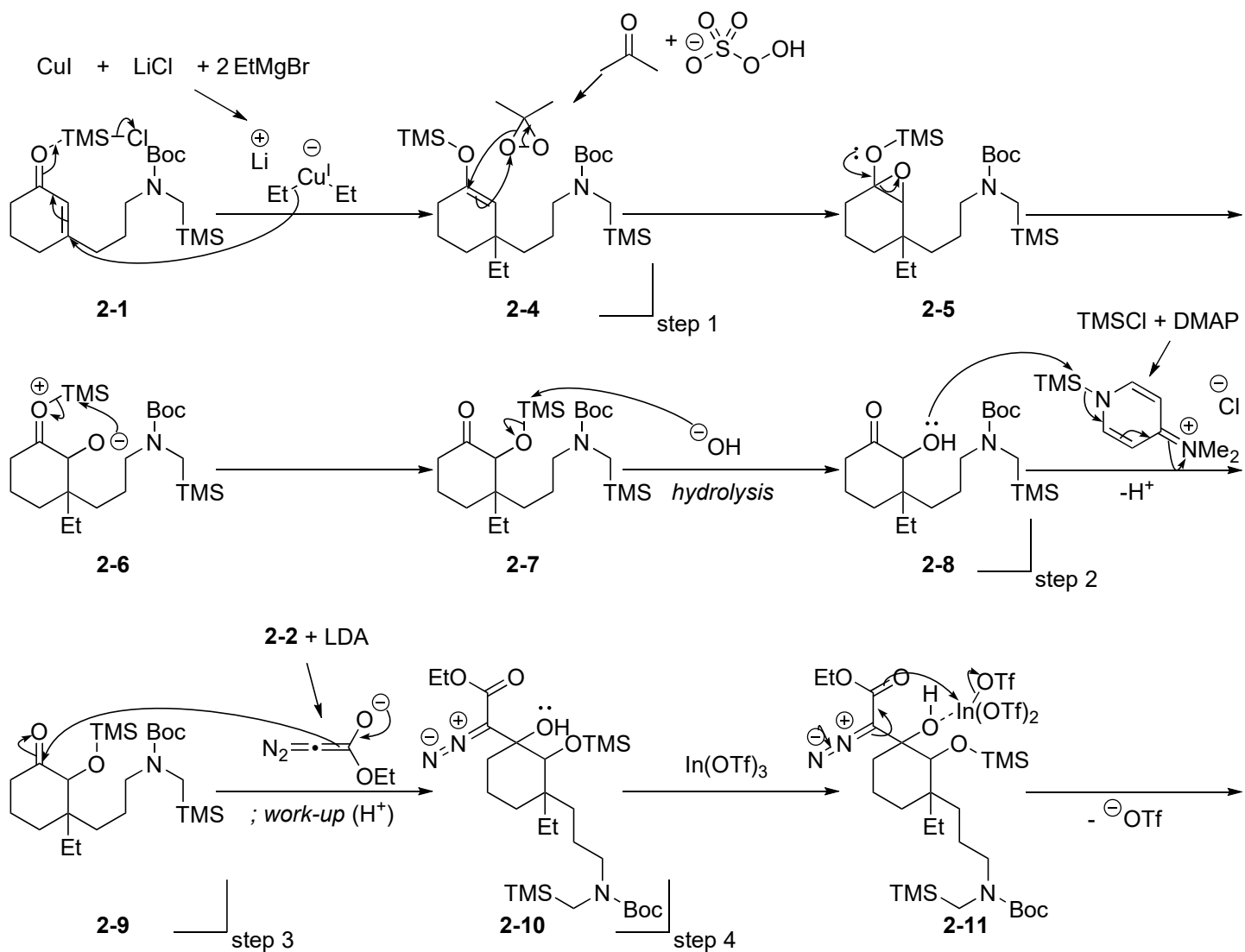
Also, it is reported that strong base (such as *n*-BuLi, LDA) accelerates this olefination (see below).

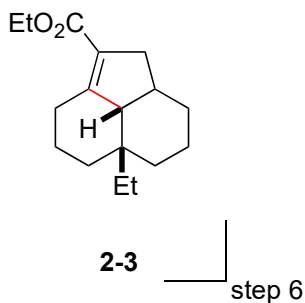
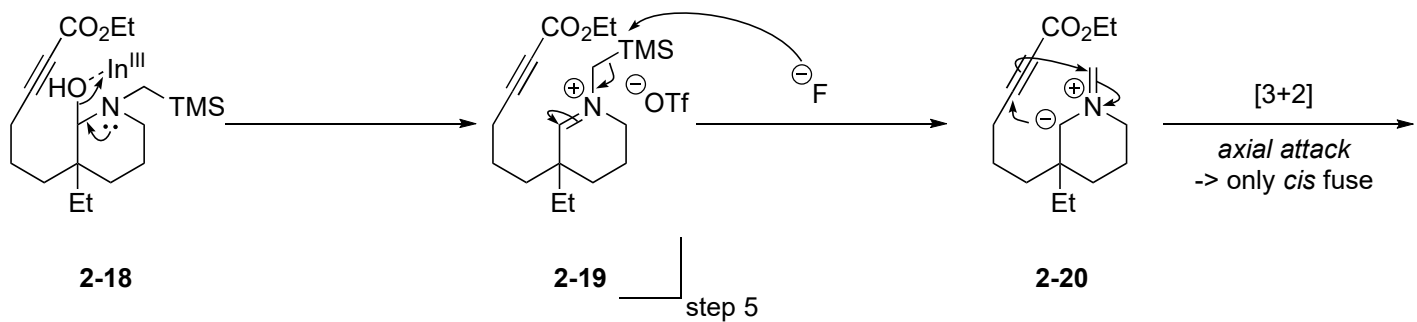
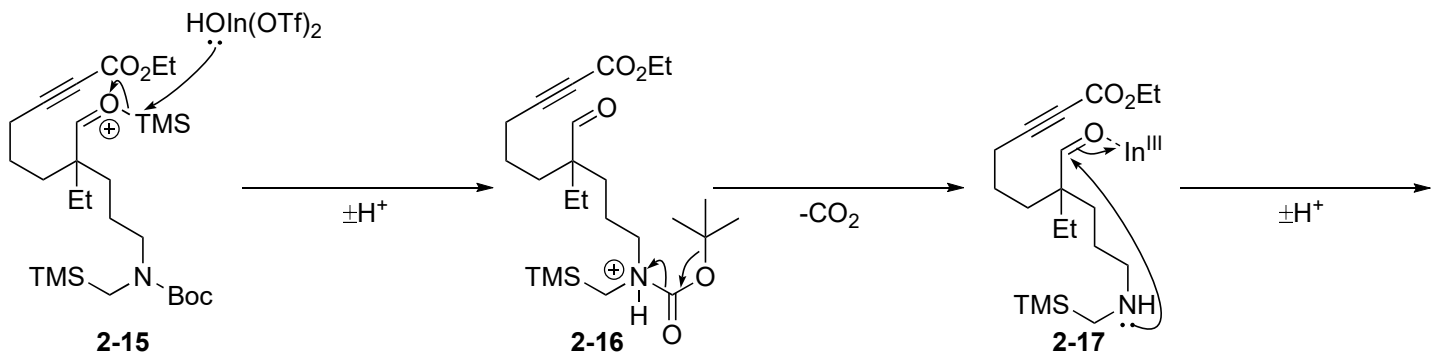
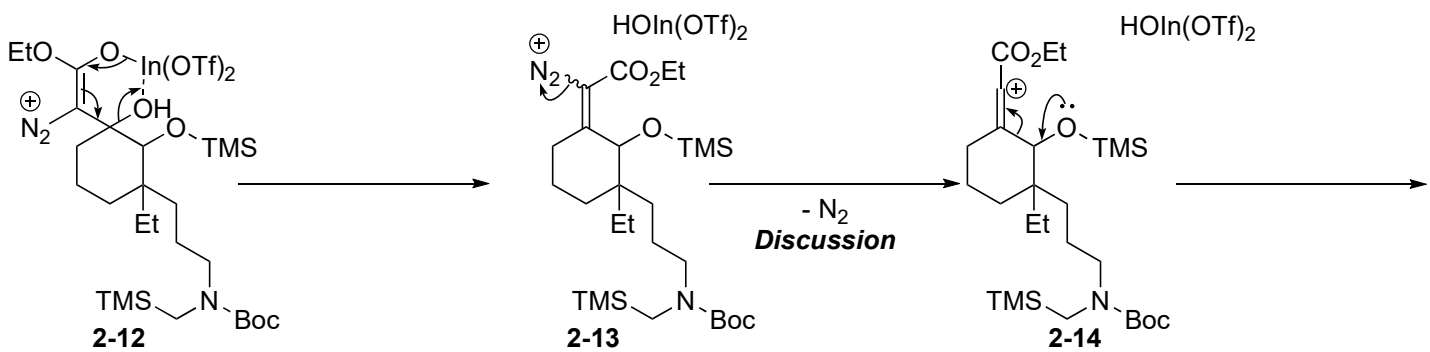


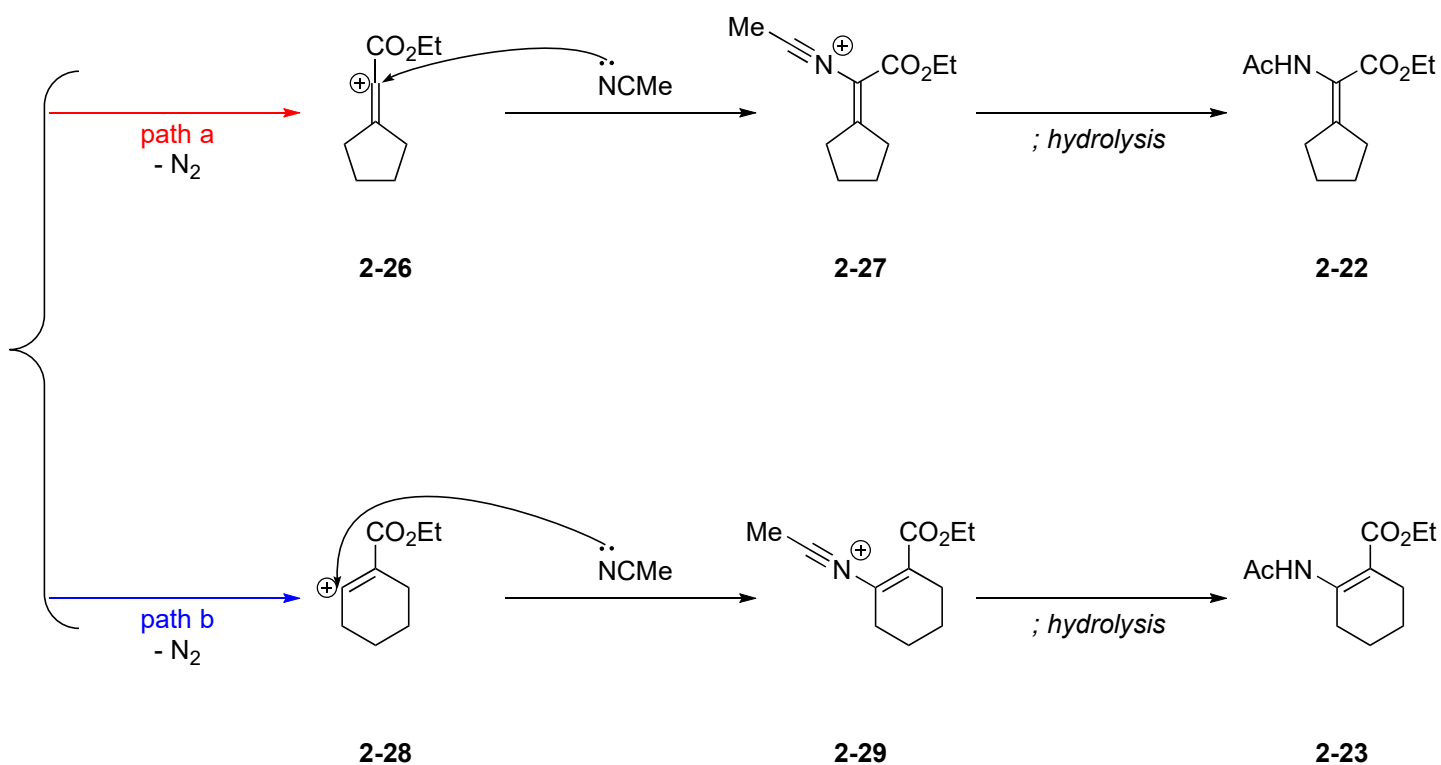
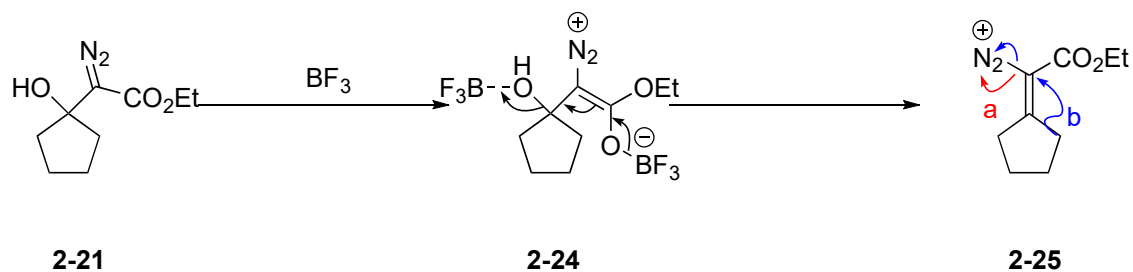
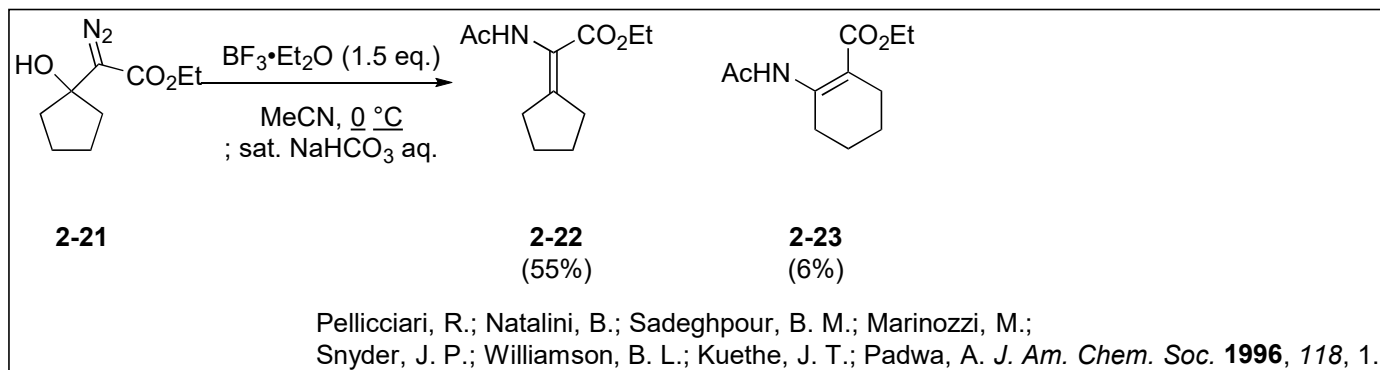
Bonini, B. F.; Maccagnani, G.; Mazzanti, G.; Piccinelli, P. *Tet. Lett.* **1979**, *41*, 3987.



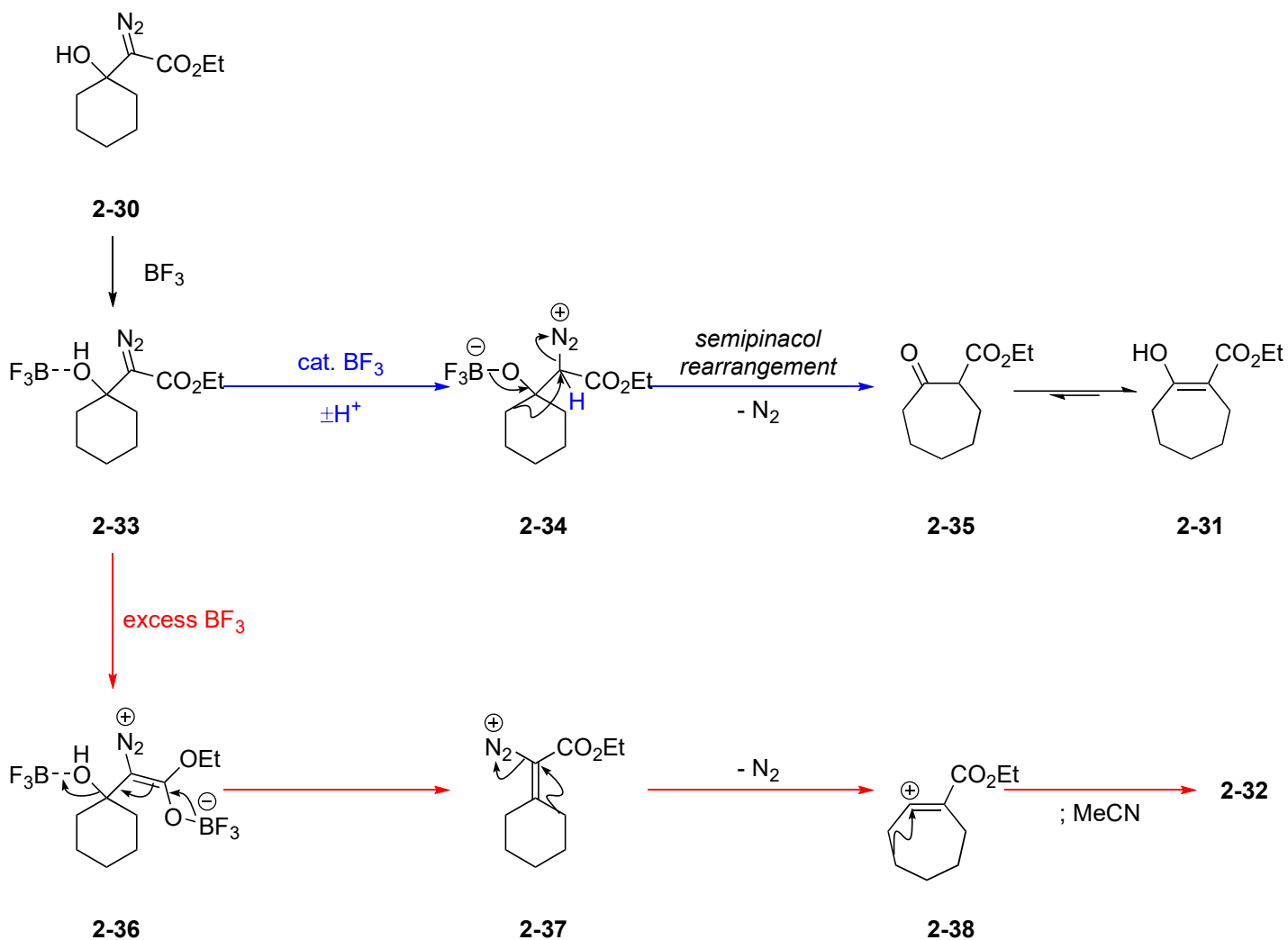
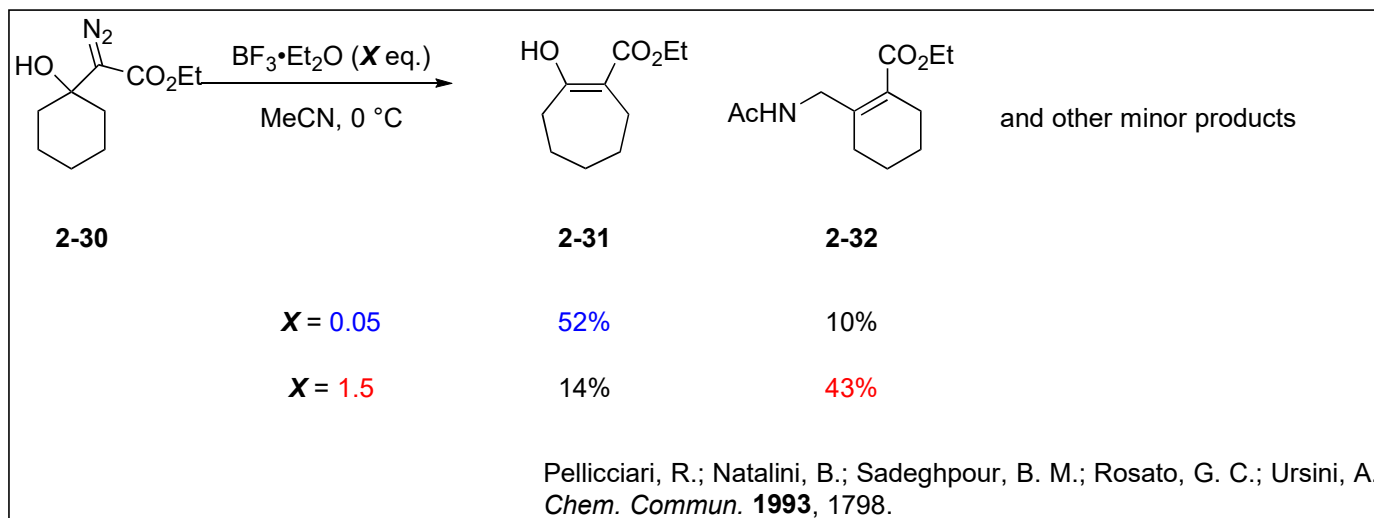
Giampa, G. M.; Fang, J.; Brewer, M. *Org. Lett.* **2016**, *18*, 3952.





Discussion:**1-1. Generation of electron-deficient vinyl cation**

1-2. Necessity for carbonyl group to coordinate



To inhibit the semipinacol rearrangement, carbonyl group should coordinate to Lewis acid.