Problem Session -answer- (4)

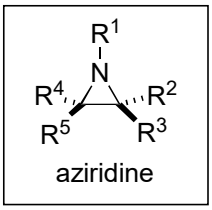
2024.5.24 Yuya Shiga

Topic : Aziridine in total synthesis

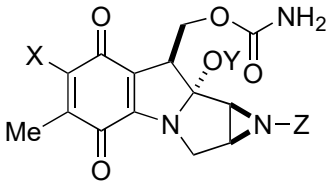
Main review : Botuha, C.; Chemla, F.; Ferreira, F. ; Pérez-Luna, A. *Heterocycles in Natural Product Synthesis,* Wiley, **2011**, 1.

Brief introduction :

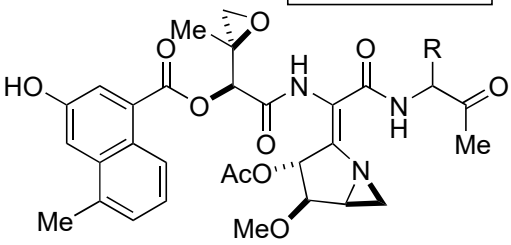
Aziridines, the smallest nitrogen-containing heterocycles,
are useful building blocks in synthesis, as well as important synthetic targets.



0-1. Aziridine-bearing natural product and reported total synthesis

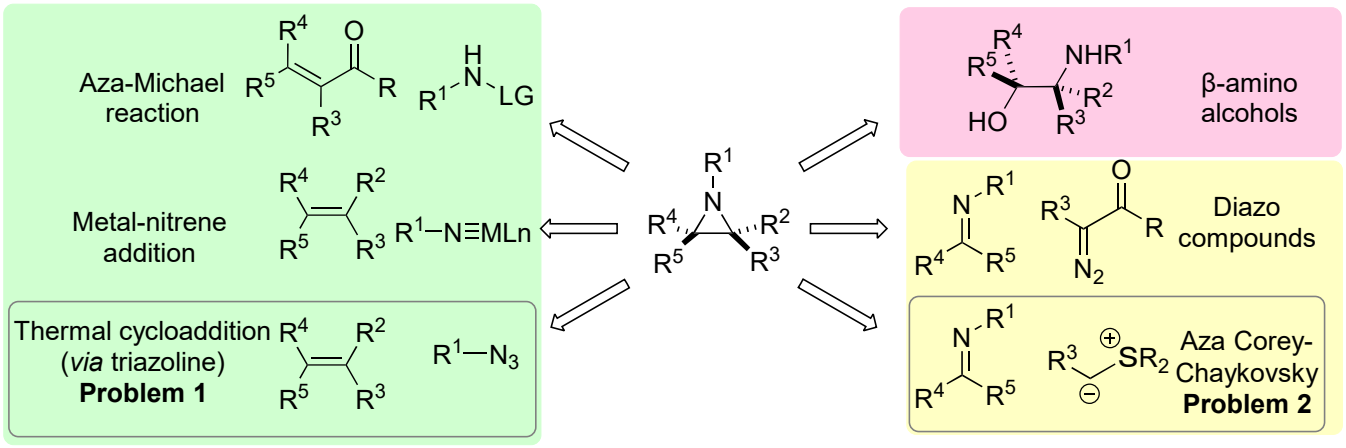


Mitomycin A : X=OMe, Y=Me, Z=H (Kishi, Fukuyama[ref1])
Mitomycin B : X=OMe, Y=H, Z=Me (Kishi[ref2])
Mitomycin C : X=NH_2, Y=Me, Z=H (Fukuyama[ref3], **Problem 1**)
Porfiromycin : X=NH_2, Y=Me, Z=Me (Kishi[ref4])

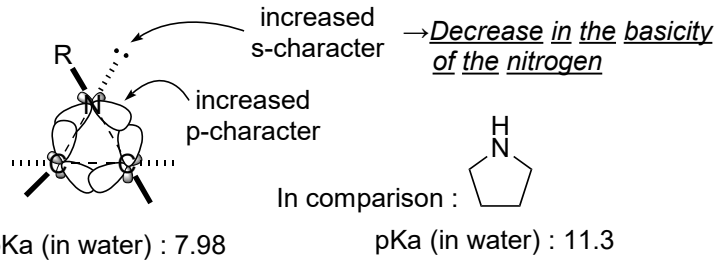


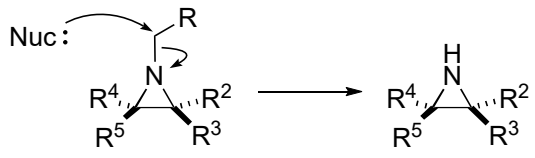
Azinomycin A : R=H (Coleman[ref5])
Azinomycin B : R=CHO

0-2. Synthesis of aziridine[ref6]



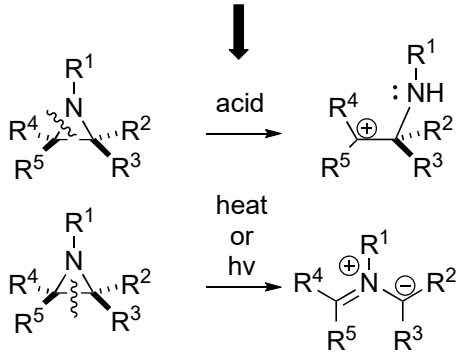
0-3. Reactivity of Aziridine





Aziridine works as a good leaving group due to the high s-character of nitrogen lonepair.
(**Problem 1**)

Highly strained 3-membered ring
(ca. 27.3 kcal/mol)
→*easy ring cleavage*

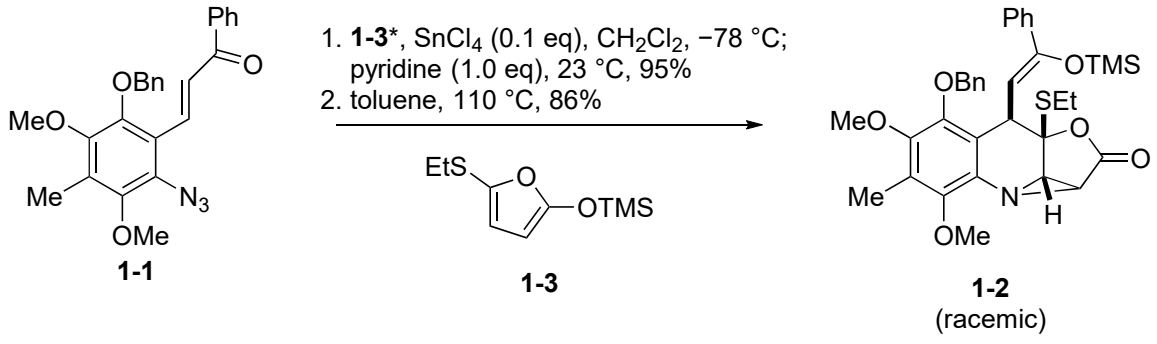


Ring cleavage (**Problem 2**)

1

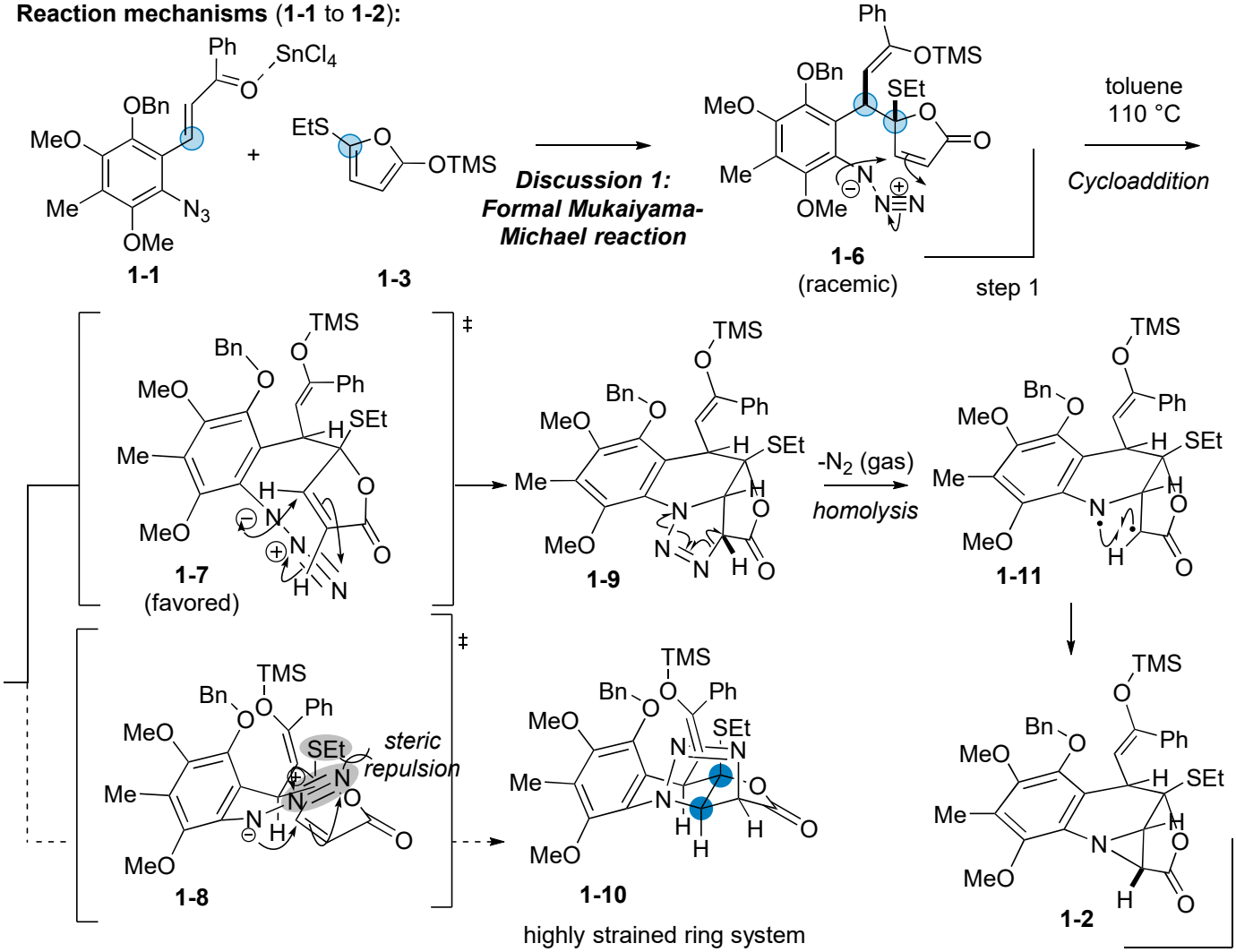
Practical Total Synthesis of (±)-Mitomycin C
a) Fukuyama, T.; Yang, L.-H. *J. Am. Chem. Soc.* **1987**, *109*, 7881. b) Fukuyama, T.,; Yang, L.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8303.

(1) Synthesis of aziridine from azide via thermal cycloaddition reactions.



1-1 **1-3** **1-2** (racemic)

Reaction mechanisms (**1-1** to **1-2**):



1-1 **1-3** **1-6** (racemic) **1-7** (favored) **1-8** **1-9** **1-10** **1-11** **1-2**

Discussion 1: Formal Mukaiyama-Michael reaction

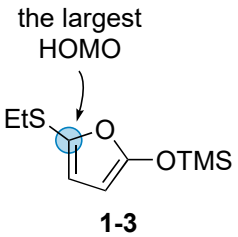
1-1. Reactivity of furan **1-3**

Table 1: Hammet's substituent constants[ref7]

X	σ_p
OTMS	−0.27
SMe	0.00

σ_p : substituent constant
(how the substituent is electro-withdrawing or -donating)

positive → EWG negative → EDG

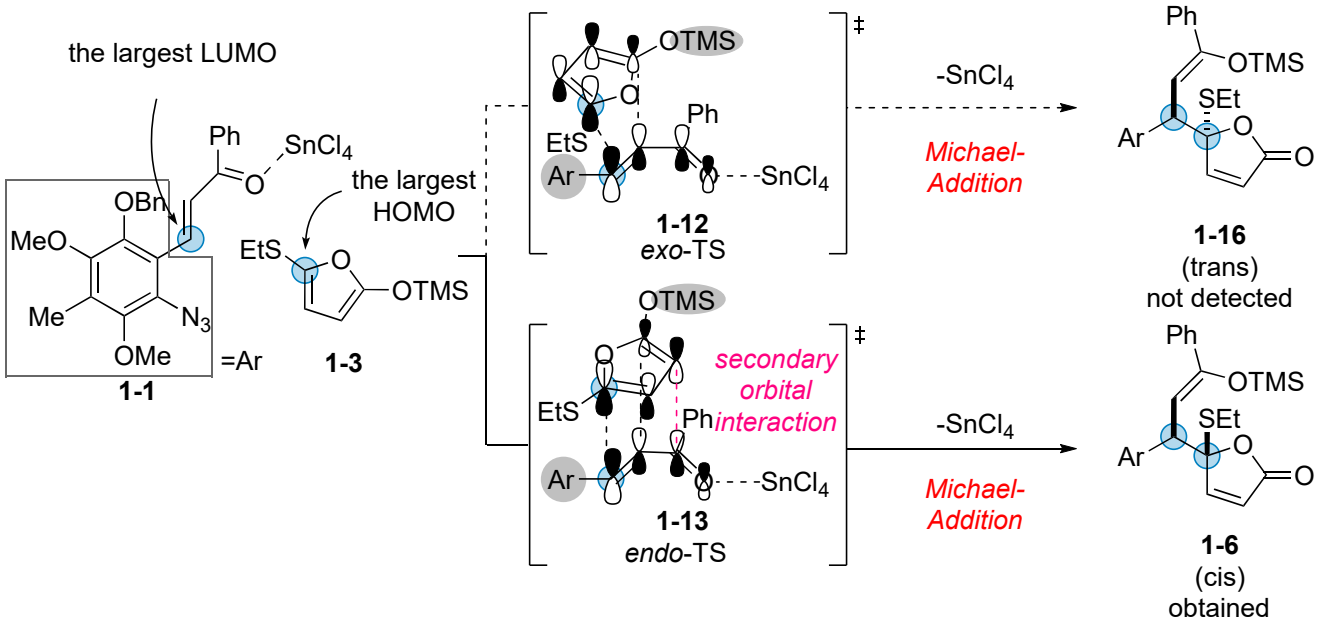


1-3

In this case, OTMS group is assumed to be a better electron donating group.

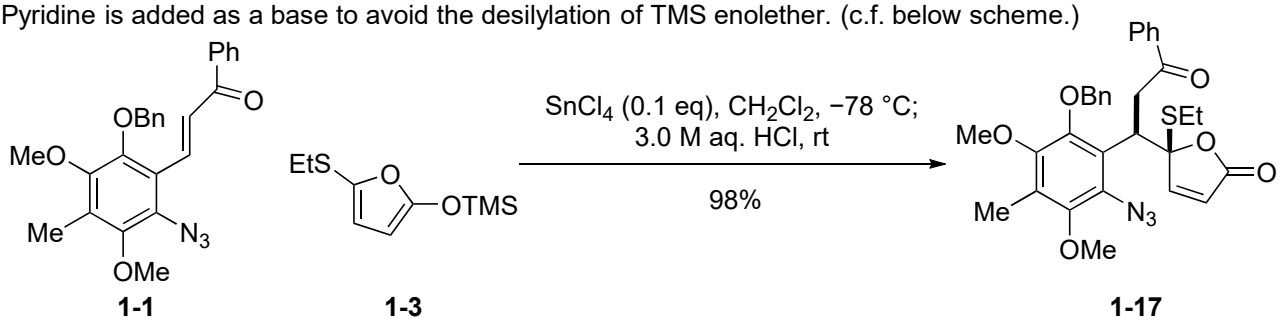
1-2. Reaction mechanism and stereoselectivity

This high stereoselectivity might be attributable to the Lewis acid-promoted Diels-Alder reaction through endo cyclization.

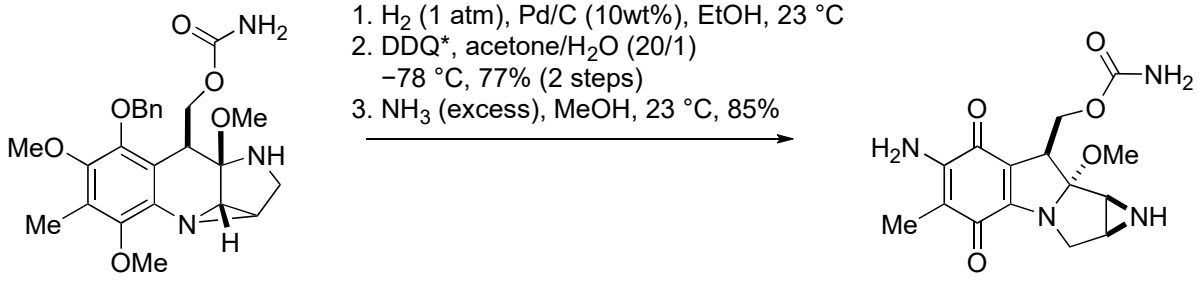


Two bulky substituents (OTMS and Ar) are located in opposite directions from each other.

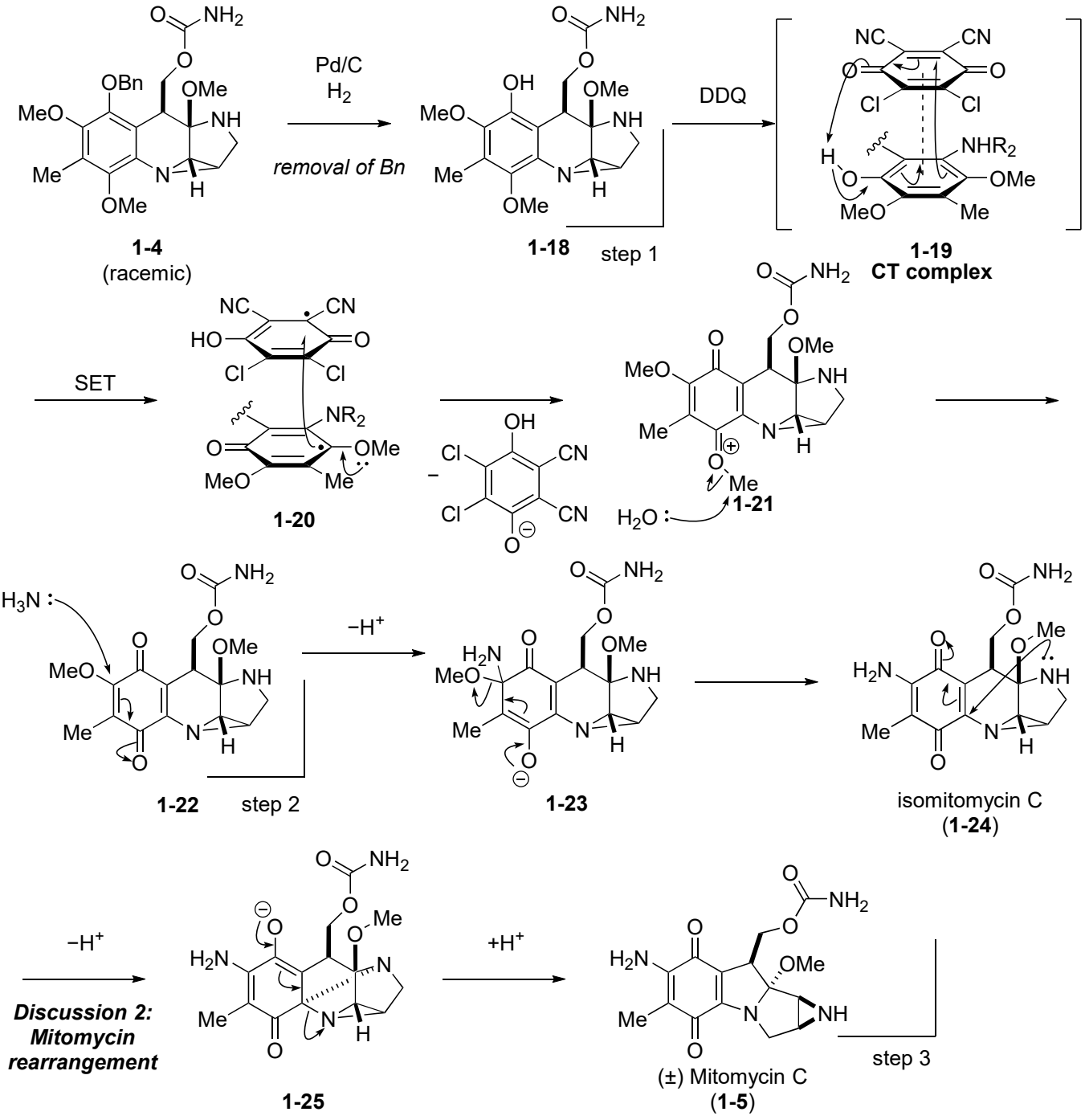
Pyridine is added as a base to avoid the desilylation of TMS enolether. (c.f. below scheme.)



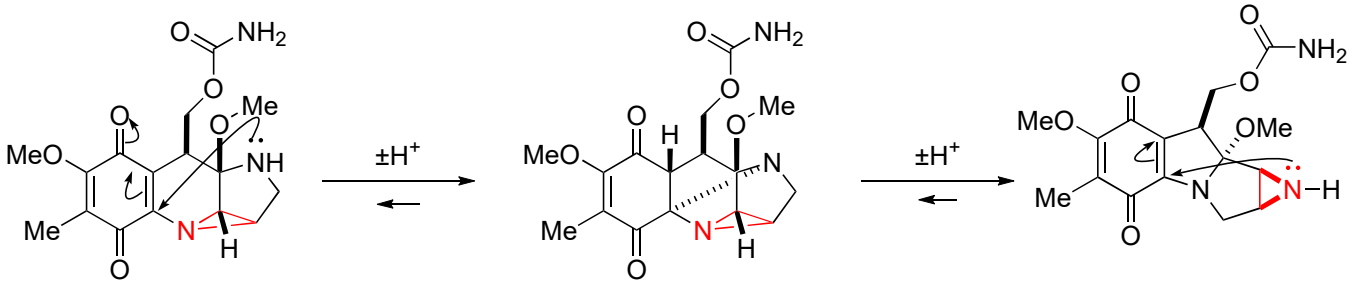
(2) Aziridine as a leaving groups.



Reaction mechanisms (**1-4** to **1-5**):



Discussion 2 : Mitomycin rearrangement



isomitomycin A
(**1-26**)

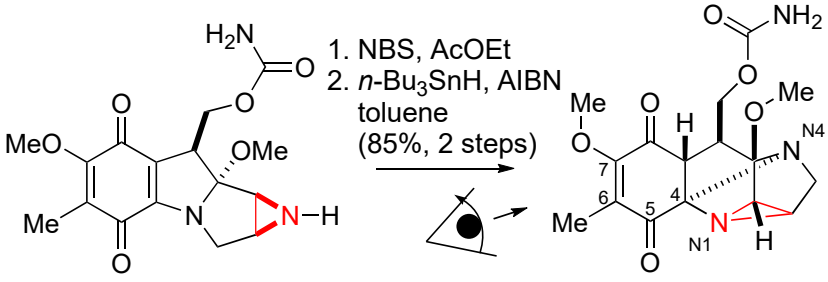
Albomitomycin A
(**1-27**)
Isolated

Mitomycin A
(**1-28**)

Mitomycin rearrangement, which is the equilibrium betwen **1-26**, **1-27** and **1-28** was reported by Kyowa Hakko research groups at 1985[ref8].

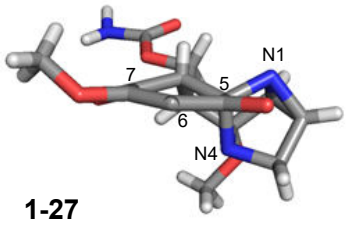
Under basic or acidic conditions with protic solvent, **1-28** is the heavily favored, because aziridine works better leaving group than pyrrolidine ring. (c.f. 0-3)

Reductive conversion of Mitomycin A to isomitomycin A[ref 8]



Mitomycin A
(**1-28**)

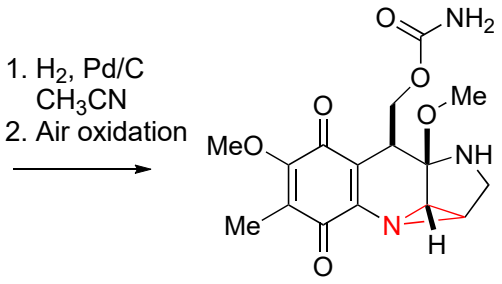
Albomitomycin A
(**1-27**)



1-27

reported X-ray structure[ref9]

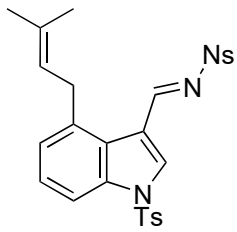
C4-N4 σ* orbital has a good interaction with C5-O5 π* orbital
→C4-N4 bond is more easily hydrogenated than C4-N1.



isomitomycin A
(**1-26**)

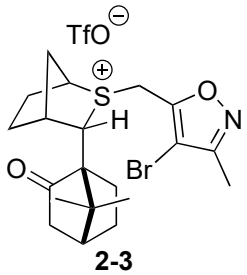
2 Enantioselective Synthesis of the Cyclopiazonic Acid Family Using Sulfur Ylides
Shurakovskyi, O.; Turkmen, Y.E.; Loffler, L. E.; Moorthie, V. A.; Chen, C. C.;Shaw, M. A.; Crimmin, M. R.; Ferrara, M.; Ahmad, M.; Ostovar, M.; Matlock, J. V.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2018**, *57*, 1346.

- Enantioselective aza Corey-Chaykovsky reaction with a chiral sulfur ylide
- Acid mediated formal [3+2] cycloaddition

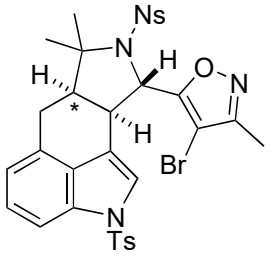


2-1

1. **2-3** (1.2 eq), K_2CO_3 (2.0 eq), MeCN
   −20 °C, 56% (d.r. = 9:1, e.r = 98:2)
2. TfOH (1.0 eq), CH_2Cl_2
   −55 °C to 10 °C, 50% (*d.r. =3.5 :1)

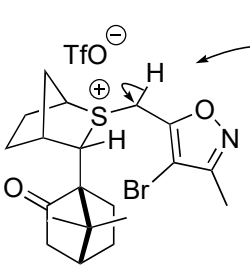


2-3



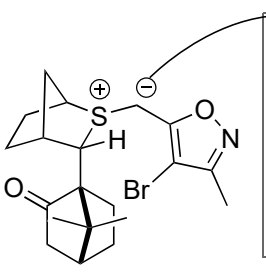
2-2

Reaction mechanisms (**2-1** to **2-2**):

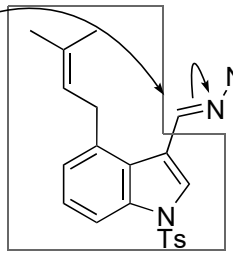


2-3

−$KHCO_3$
−KOTf



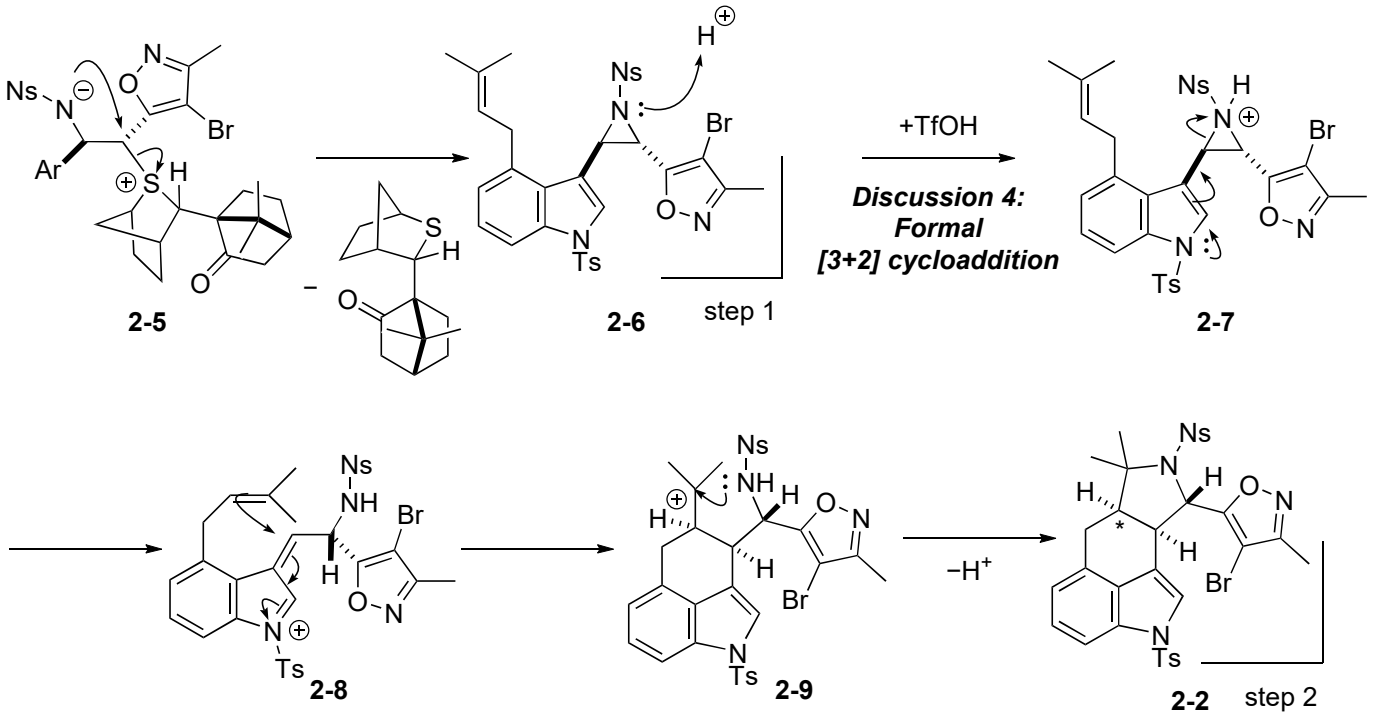
2-4



2-1

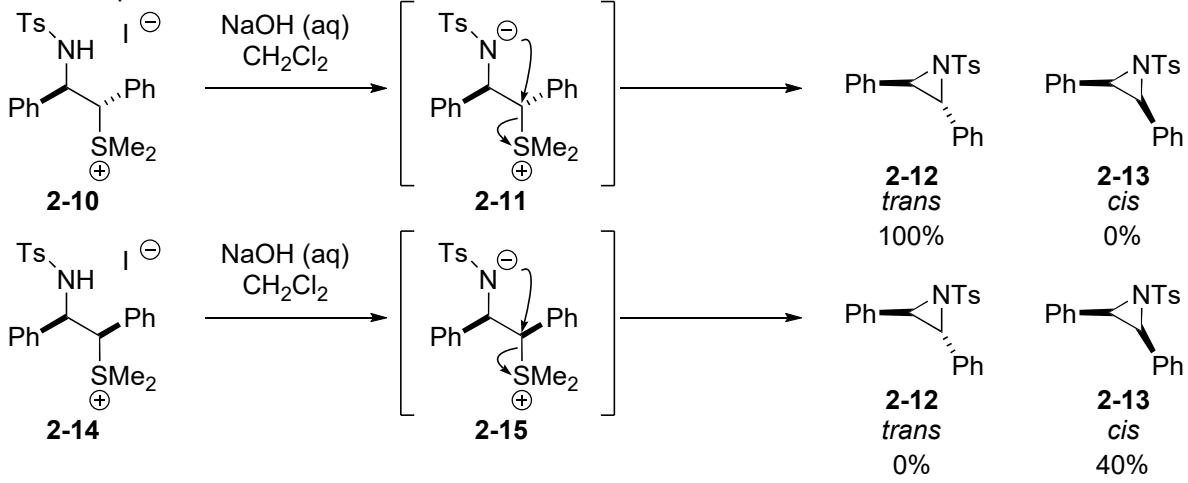
=Ar

Discussion 3: Enantioselective aza Corey-Chaykovsky reaction



Discussion 3: Enantioselective aza Corey-Chaykovsky reaction

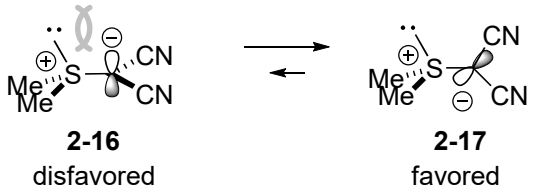
3-1. Cross over experiment[ref10]

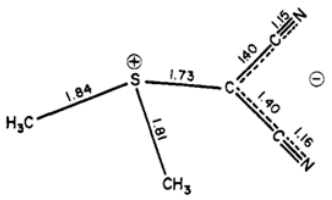


No scrambling of stereochemistry is observed.
→no base-catalysed epimerisation occurred and that the intermediate betaines do not revert back to the corresponiding ylide and imine.
→The addition of ylide to imine is the stereocontrolling step.

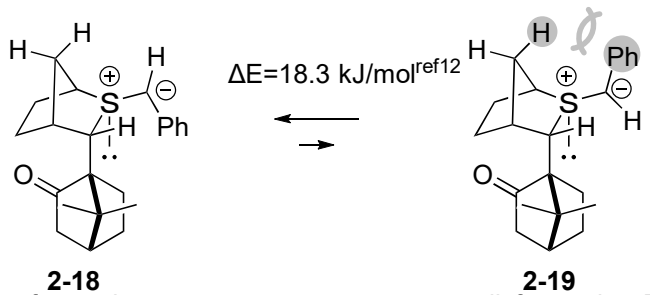
3-2. Face selectivity of sulfonium ylide.

sulfur lone-pair : carbon π-electron repulsion





The orientation of sulfur lone-pair and carbon π-electron is confirmed by the X-ray annalysis.[ref11]

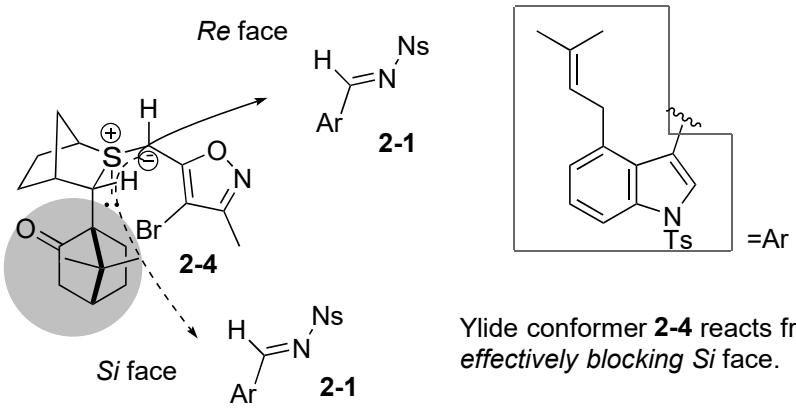


2-18
favored

2-19
disfavored

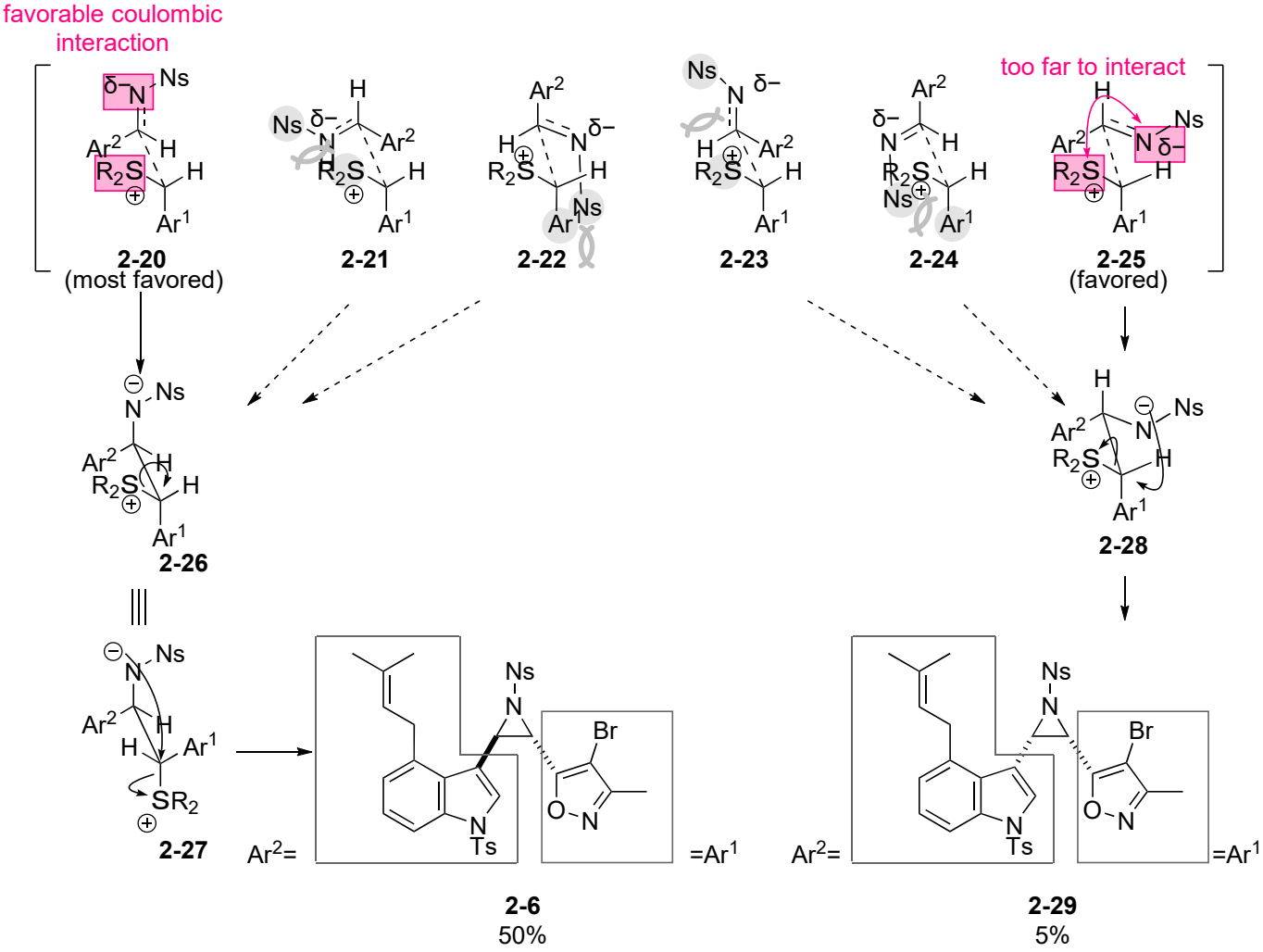
B3LYP/6-311G**+(CH_3CN)//6-31G*(CH_3CN)

2-18 is strongly favored over **2-19** because of steric interactions between the ylide substituent and methylene unit of the [2.2.1] bycycle.



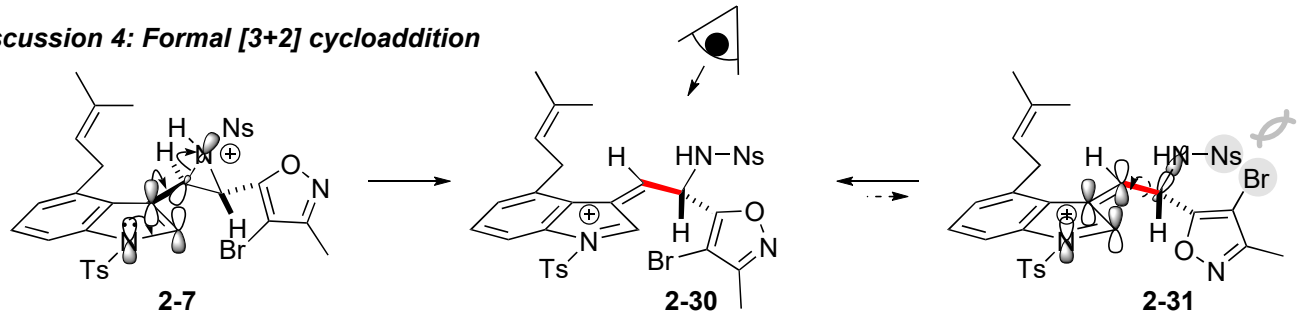
Ylide conformer **2-4** reacts from *Re face due to camphor moiety effectively blocking Si* face.

3-3. Face selectivity of imine



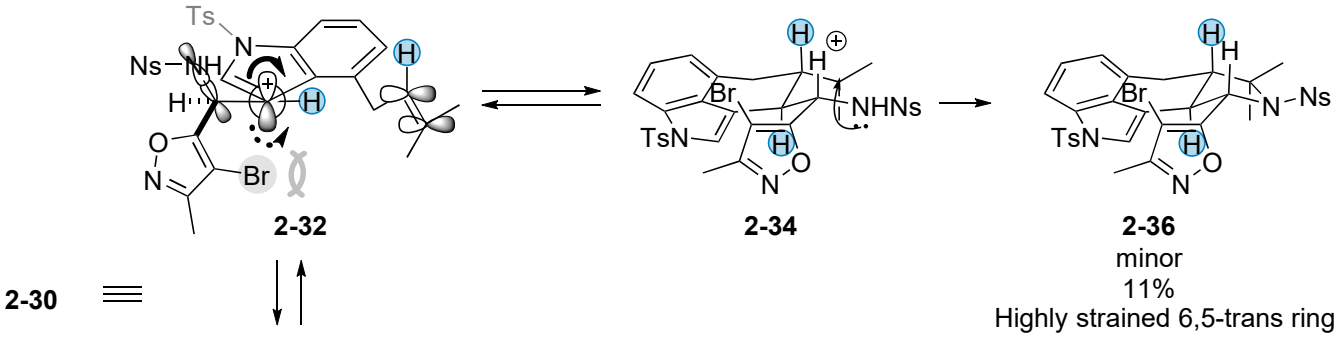
2-21, 2-22, 2-23, 2-24 ... (unfavored TS) the steric repulsion between Bulky Ns and SR_2 or Ar^1 or Ar^2
2-20...(most favored TS) no large steric repulsion and favored coulombic interaction
2-25...(favored TS) no large steric repulsion

Discussion 4: Formal [3+2] cycloaddition



2-7 **2-30** **2-31**

The direction of oxazole is fixed like **2-30** to avoid the steric repulsion between Ns and Br.



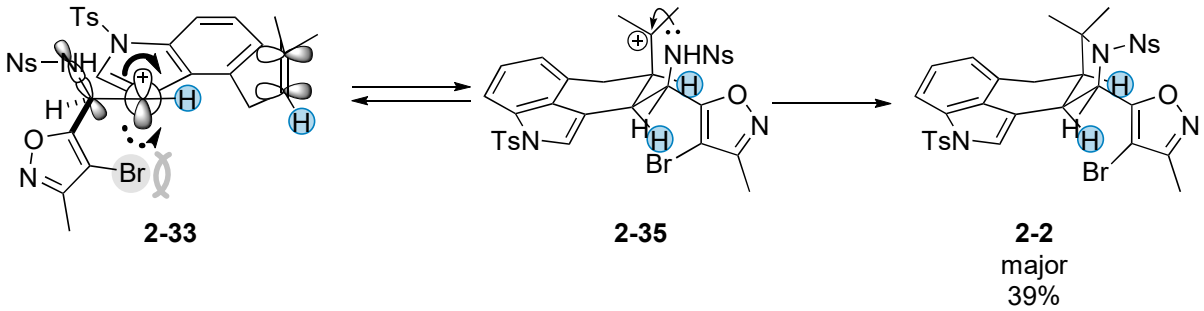
2-32 **2-34** **2-36**

minor

11%

Highly strained 6,5-trans ring system.

2-30



2-33 **2-35** **2-2**

major

39%

References

1a) Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron. Lett.* **1977**, *49*, 4295.
1b) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7881.
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