2022.7.9

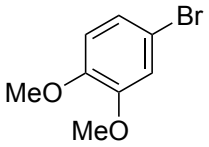
Problem Session (3)

Topic: N-O bond

Please provide the reaction mechanisms.

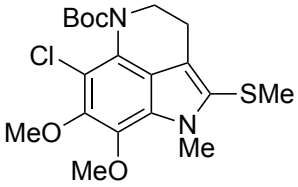
Hibiki Asai

1



1-1

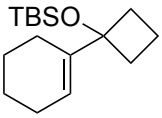
1. **1-3** (2 equiv), LiTMP (5 equiv), THF, −78 ºC then HF (46% H_2O solution, 5 equiv), rt, 84%
2. NsNHBoc (1 equiv), PPh_3 (1 equiv), DMEAD (1 equiv) THF, rt, 78%
3. NBS (1.5 equiv), MeCN, rt, 96%
4. NH_2OH•HCl (2.5 equiv), pyridine, 130 ºC*
5. *p*-$ClC_6H_4SO_2Cl$ (2.5 equiv), Et_3N (6 equiv) CH_2Cl_2, −78 ºC, 99% (2 steps)
6. Boc_2O (2 equiv), DMAP (0.1 equiv), MeCN, rt, 100%
7. NaSMe (5 equiv), MeCN, rt, 86%
8. NaH (1.2 equiv), MeI (1.2 equiv), THF, rt, 74%
9. LiTMP (10 equiv), THF, −78 ºC then **1-4** (15 equiv), −78 ºC, 76% (recovery of SM: 17%)



1-2

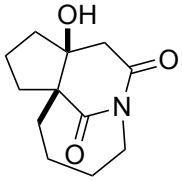
* Unexpected removal of Boc group occurred.

2



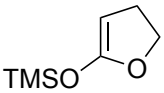
2-1

1. $NOBF_4$ (1.25 equiv), DTBP (0.15 equiv) MeCN, −30 ºC, 91%
2. CF_3CO_2H/CH_2Cl_2 (1/4), 90 ºC, 87%
3. $ClCOCH_2Cl$ (5 equiv), toluene, reflux, 83%
4. Zn* (5 equiv), THF, 95 ºC, 53%

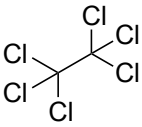


2-2

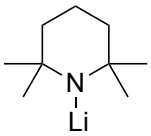
* freshly prepared from $ZnCl_2$ (5 equiv), Li (10 equiv), naphthalene (10.5 equiv), and benzothiophene (0.23 equiv) in THF.



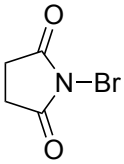
1-3



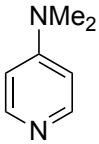
1-4



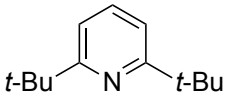
LiTMP



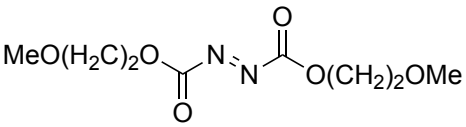
NBS



DMAP



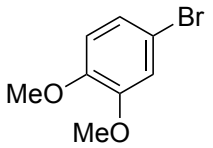
DTBP



DMEAD

Ns: 2-nitrobenzenesulfonyl
Boc: *tert*-butoxycarbonyl

1



1-1

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   then HF (46% H_2O solution, 5 equiv), rt, 84%
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→

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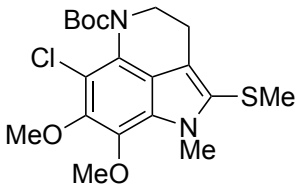
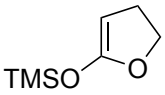
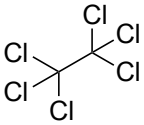


1-2



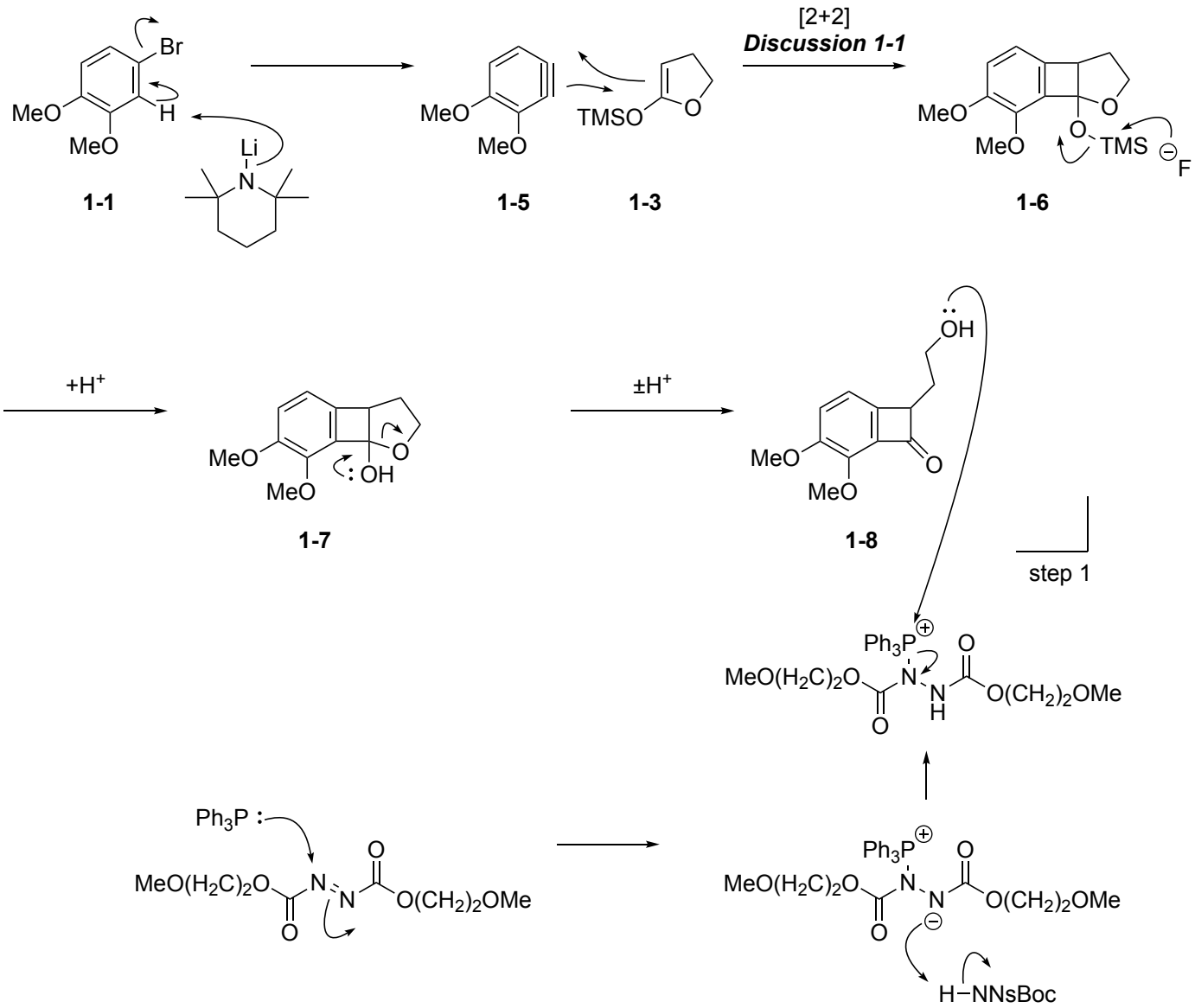
1-3

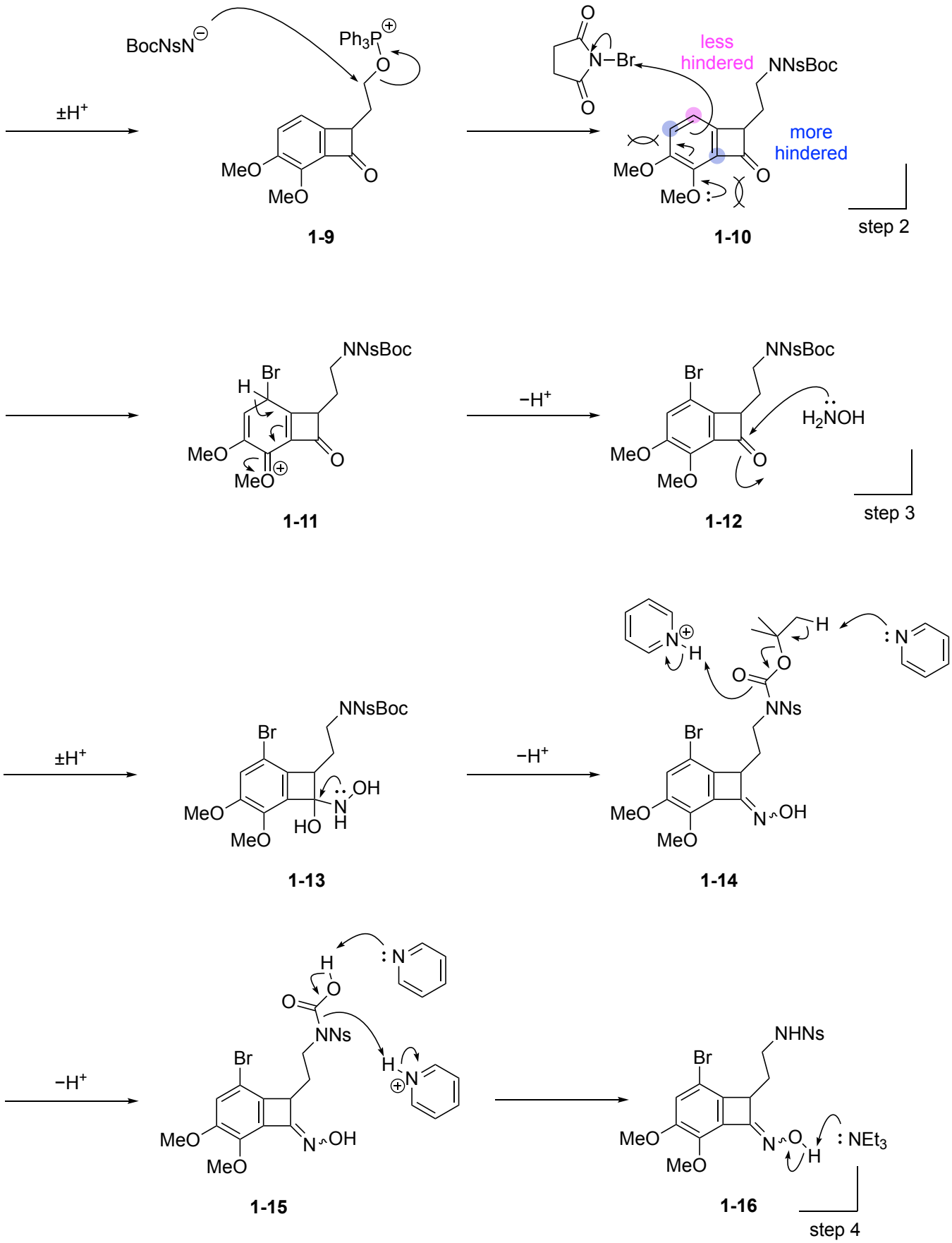


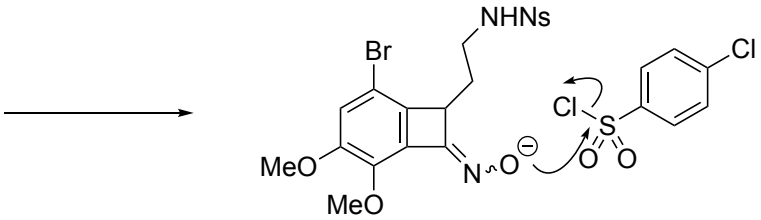
1-4

Yamashita, Y.; Poignant, L.; Sakata, J.; Tokuyama, H. *Org. Lett.* **2020**, *22*, 6239.

Answer:




BocNsN
Ph3P
±H+
MeO
MeO
O
1-9
N–Br
less hindered
NNsBoc
more hindered
1-10
step 2
Br
H
1-11
−H+
H2NOH
1-12
step 3
OH
HO
1-13
1-14
NNs
1-15
NHNs
NEt3
1-16
step 4



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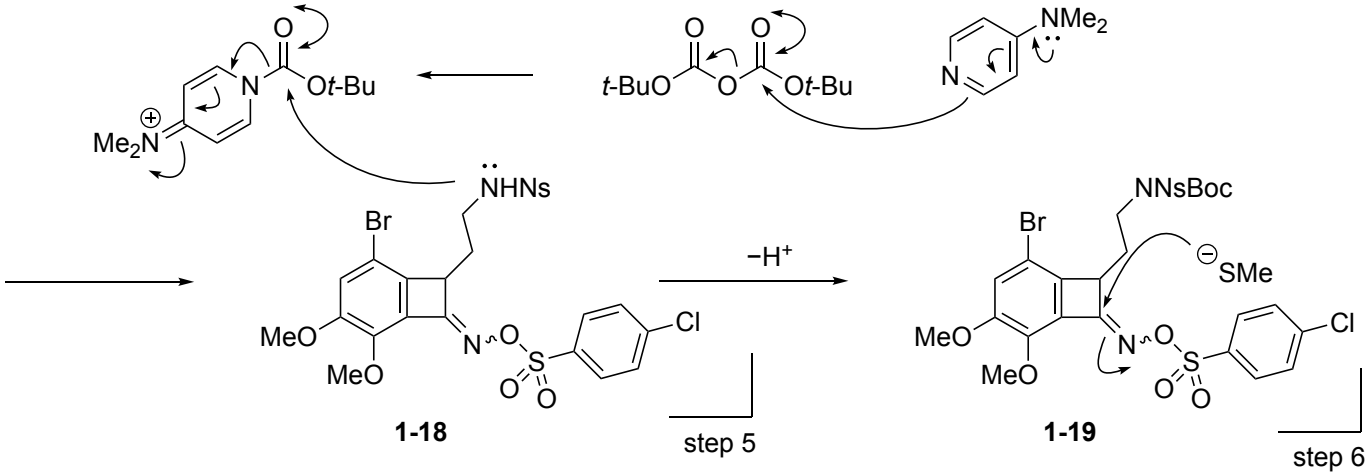
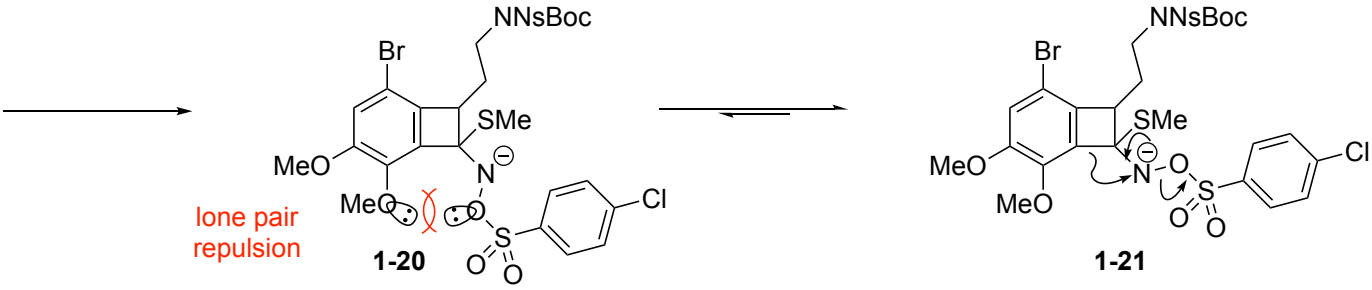
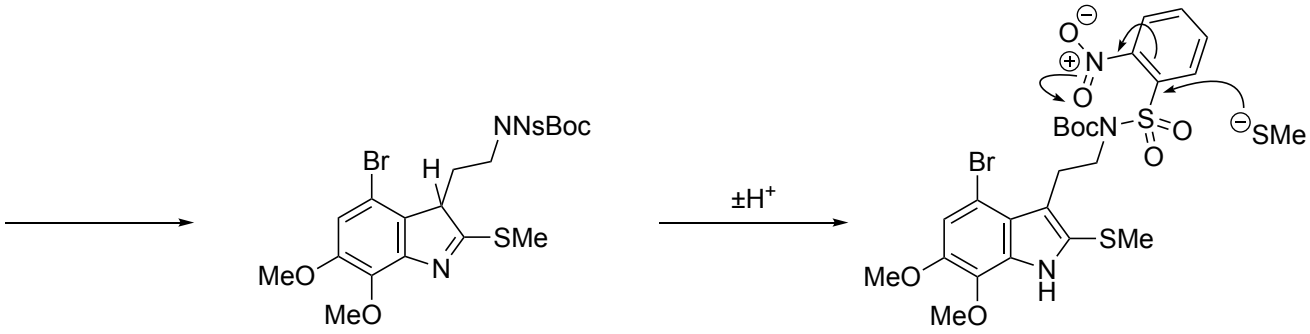


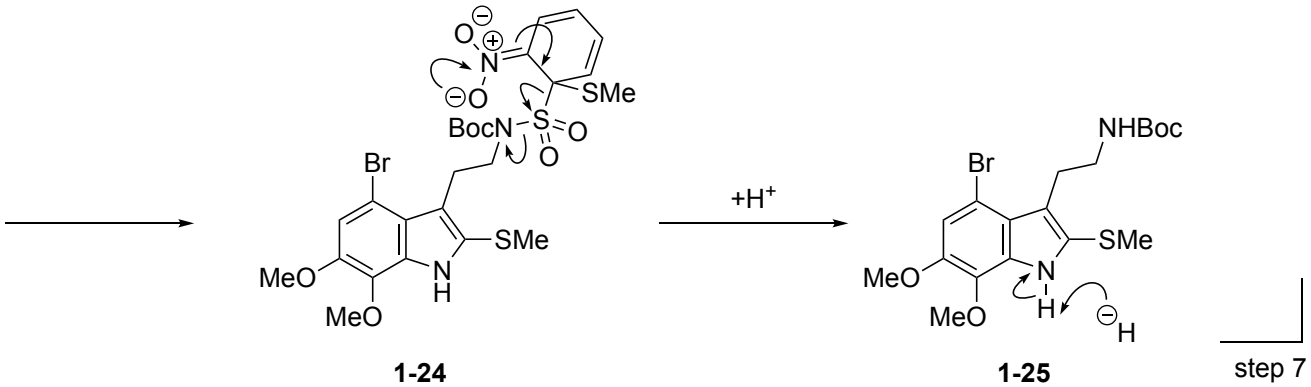
1-18 **1-19**

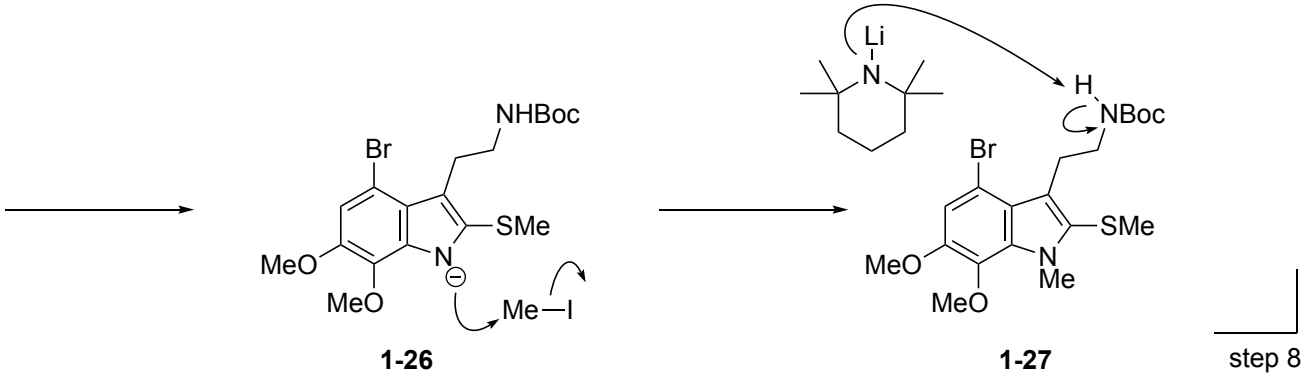


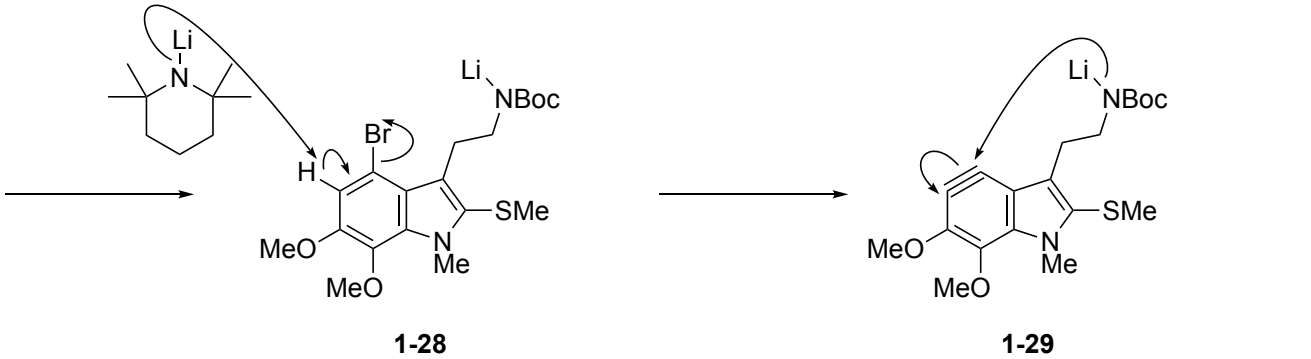
1-20 **1-21**

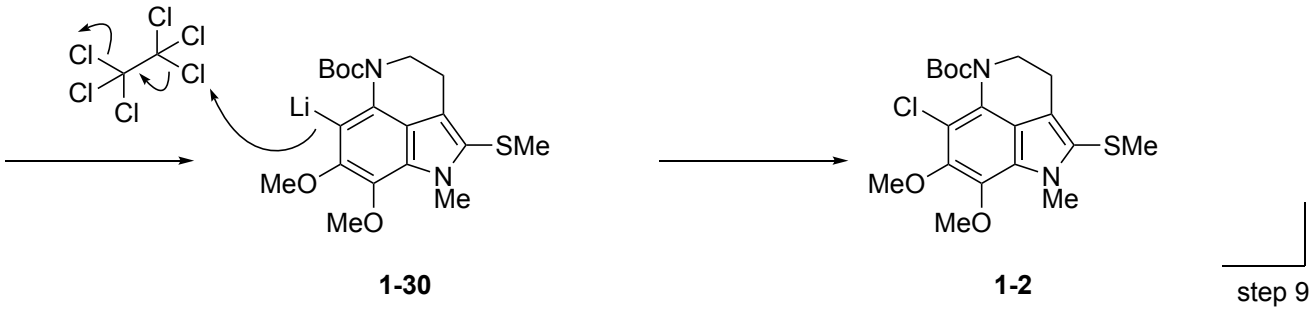


1-22 **1-23**


+H+
1-24
1-25
step 7

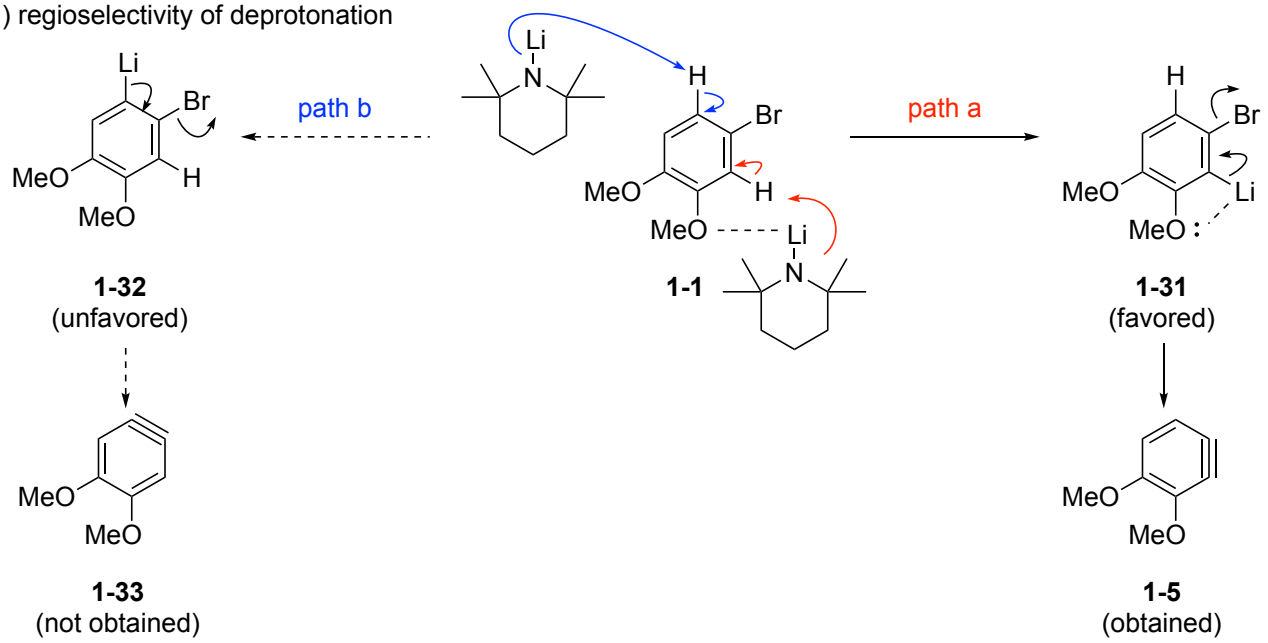

1-26
1-27
step 8


1-28
1-29

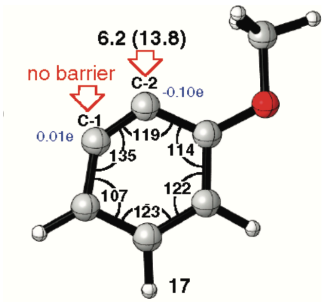

1-30
1-2
step 9

Discussion 1-1: [2+2]

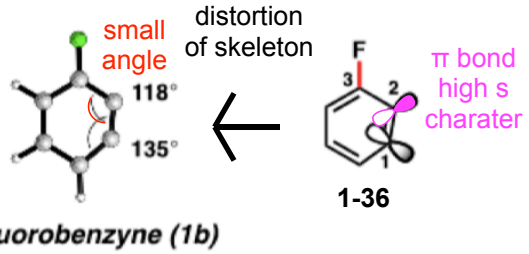
1) regioselectivity of deprotonation

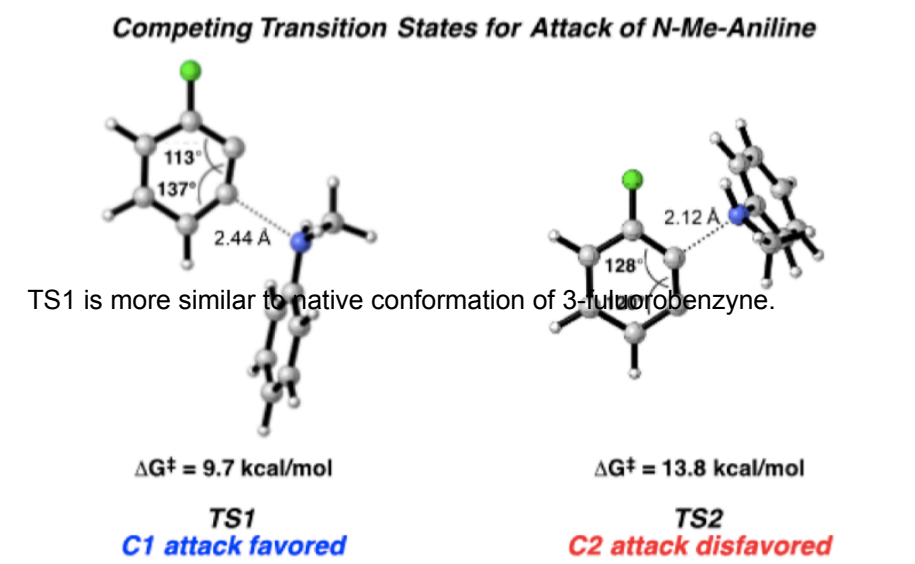


2) regioselectivity of cycloaddition



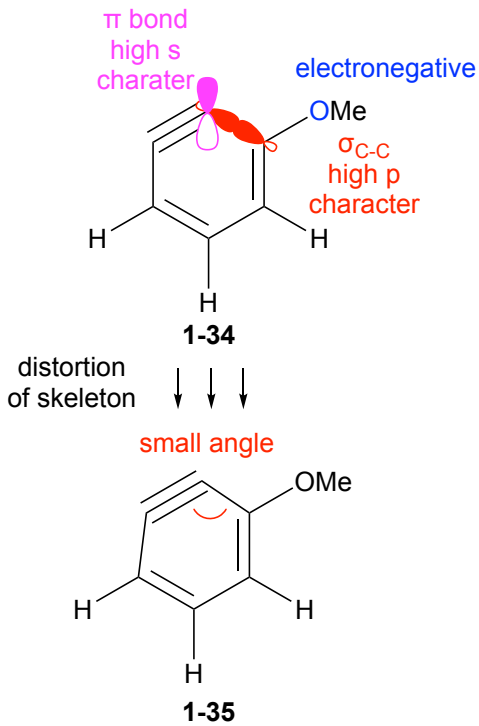
B3LYP/6-31G(d)





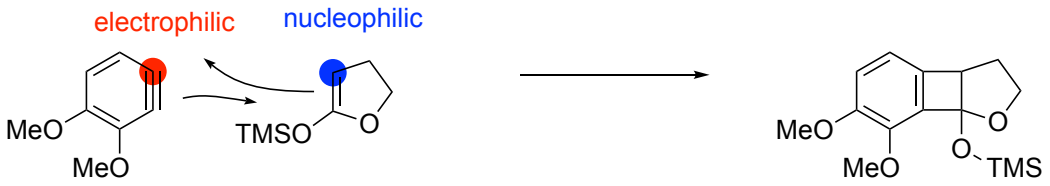
TS1 is more similar to native conformation of 3-fluorobenzyne.

B3LYP/6-311+G(d)



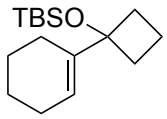
a) Cheng, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 1267.

b) Medina, J. M.; Mackey, J. L. Garg, N. K. Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 15798.



1-5 **1-3** **1-6**

2



2-1

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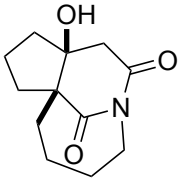
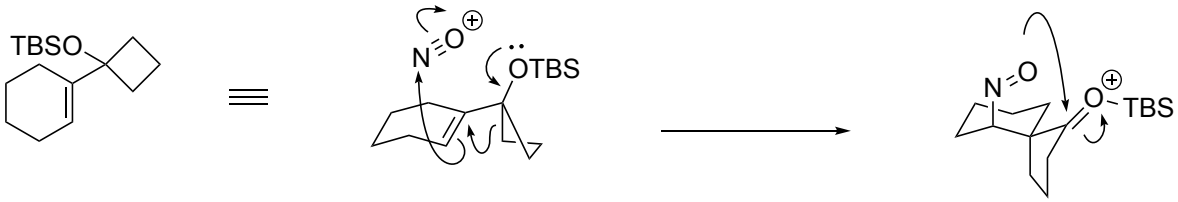


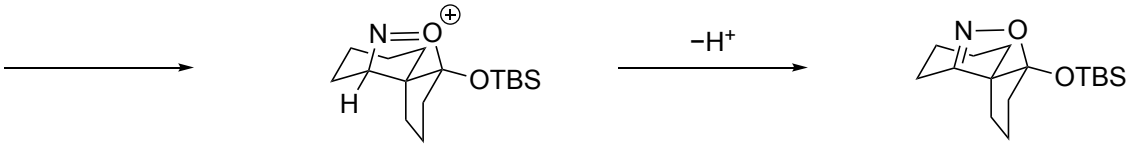
2-2

Dong, J.-W.; Ding, T.; Zhang, S.-Y.; Chen, Z.-M.; Tu, Y.-Q. *Angew. Chem. Int. Ed.* **2018**, *57*, 13192.

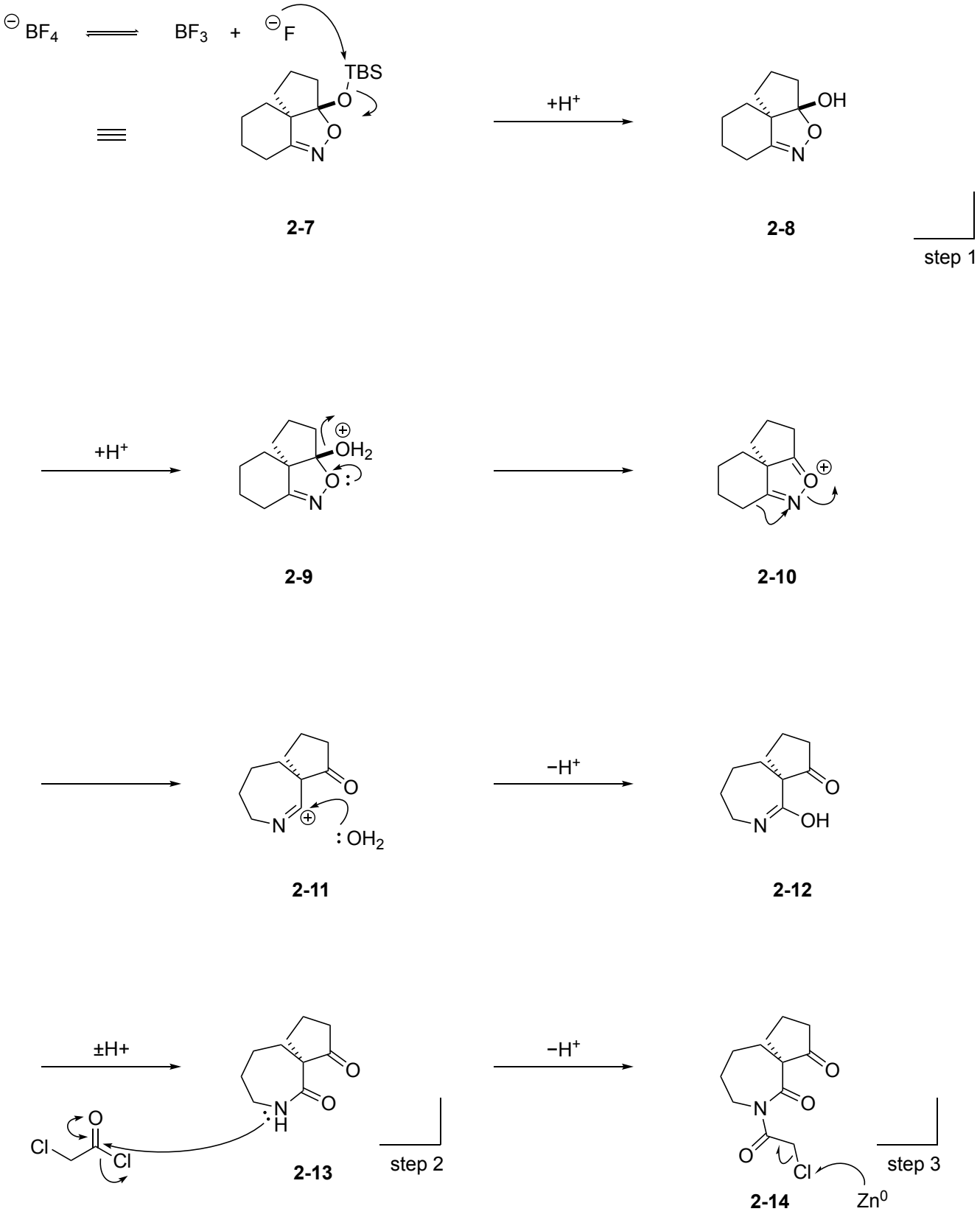
Answer:

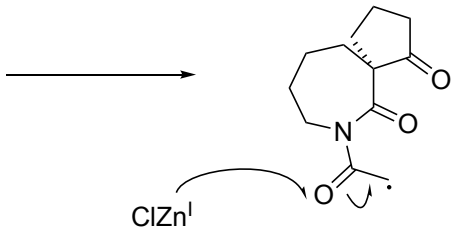


2-1 **2-3** **2-4**

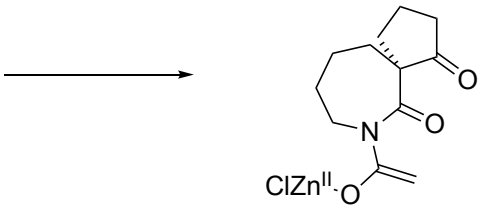


2-5 **2-6**


BF4
BF3
F
TBS
O
N
2-7
+H+
OH
2-8
step 1
+H+
OH2
2-9
2-10
2-11
: OH2
−H+
2-12
±H+
Cl
2-13
step 2
2-14
Zn0
step 3

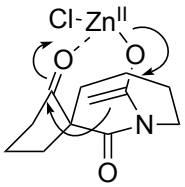


2-15



2-16

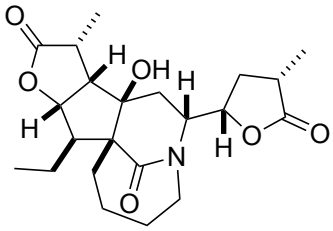
≡



2-17

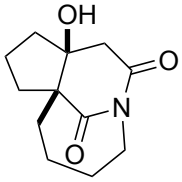
2-18

2-19



tuberostemoninol B

≡



2-2

step 4