Problem Session (2) -Answer-

2017/5/27 Takehiro Kato

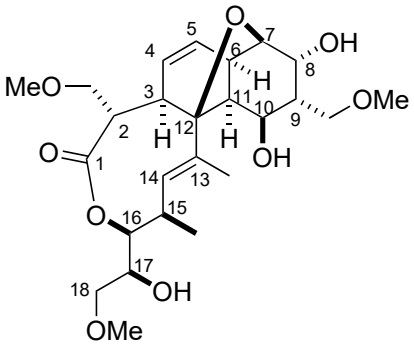
Topics: Total synthesis of branimycin

0. Introduction

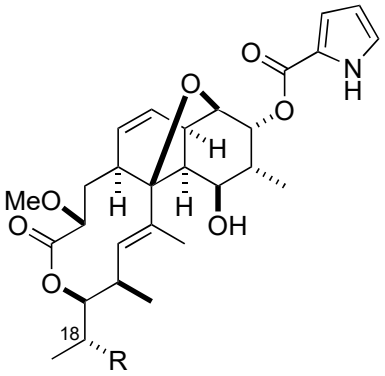
Isolation

Isolated from *Actinomycete GW 60/1571*

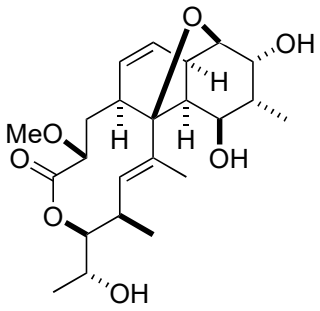
Speitling, M. Ph. D. Thesis. University of Göttingen, **1998**. (Laatsch group)



branimycin (**1-11**)



nargenicin A_1 (**0-1**): R = OH
18-deoxynargenicin A_1 (**0-2**): R = H



nodusmycin (**0-3**)

nargenicin family

Biological activity

active against *Escherichia Coli*, *Bacillus subtilis*, *Staphylococus aureus*, and in particular against *Streptomyces viridochromogenes*.

Structural feature

cis-dehydrodecalin core
transannular oxa-bridge
12 stereocenters
nine-membered lactone

Total synthesis

Branimycin

Marchart, S.; Gromov, A.; Mulzer, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 2050. (-> ***Problems***)

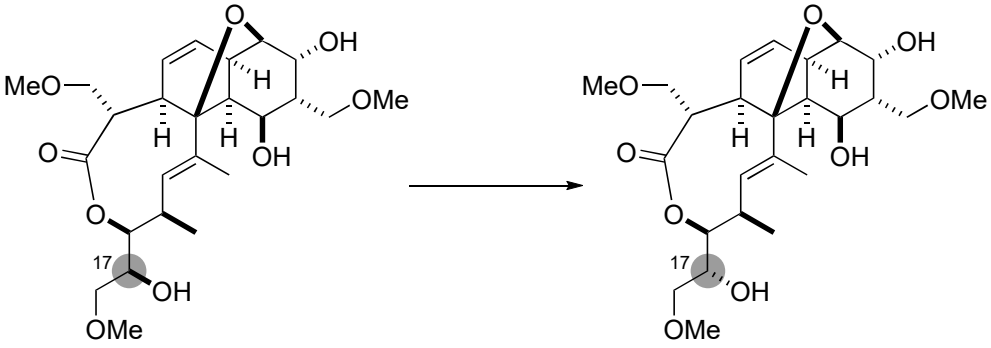
18-deoxynargenicin A_1

Plata, D. J.; Kallmerten, J. *J. Am. Chem. Soc.* **1988**, *110*, 4041.

Structural revision

Cikos, *et al*. proposed that the stereochemistry of C-17 should be *R* in 2016, after the total synthesis was achieved.
The proposal was based on X-ray diffraction, NMR spectra (NOESY, ROESY), and conformational calculation.

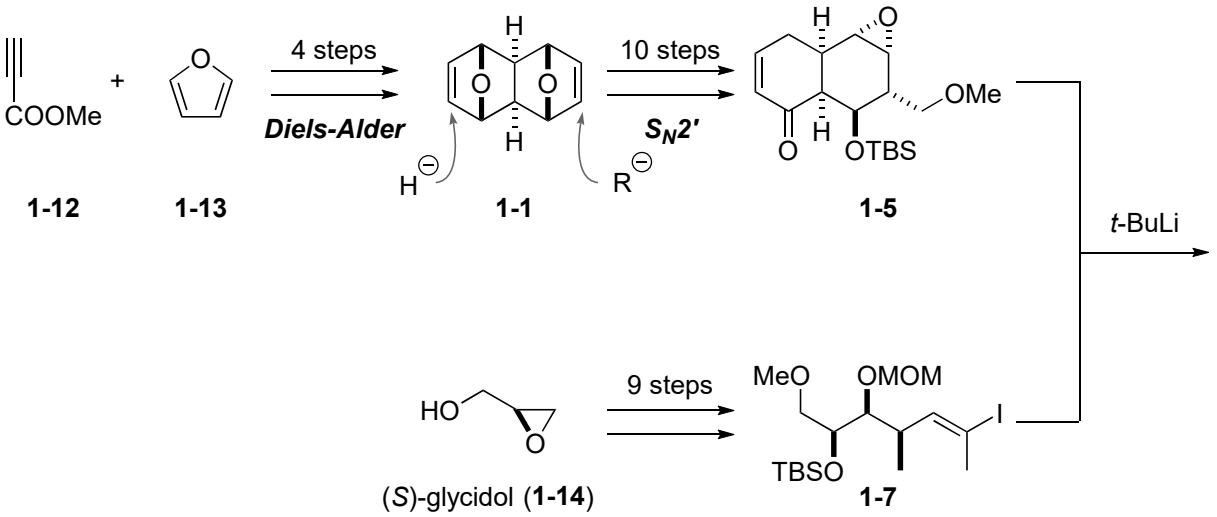
Cikos, A., *et al*. *Org. Lett.* **2016**, *18*, 780.

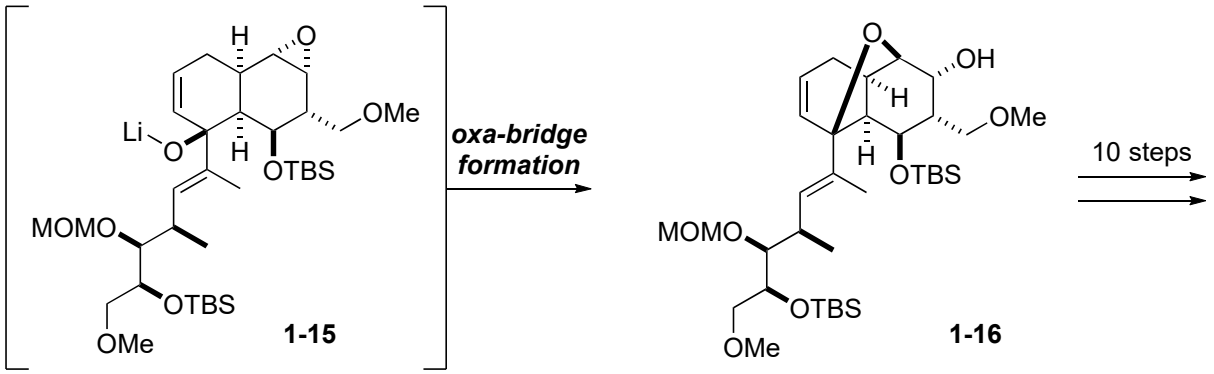


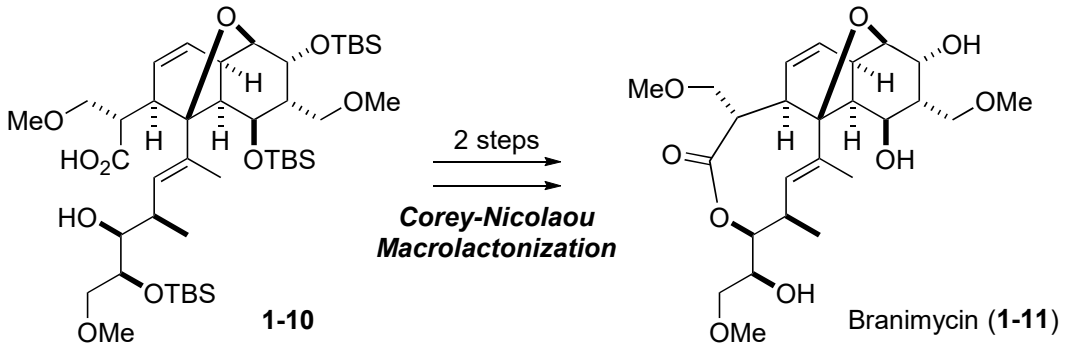
formerly proposed structure of branimycin (**1-11**)

revised structure of branimycin (**0-4**)

1. Short summary of Mulzer's route



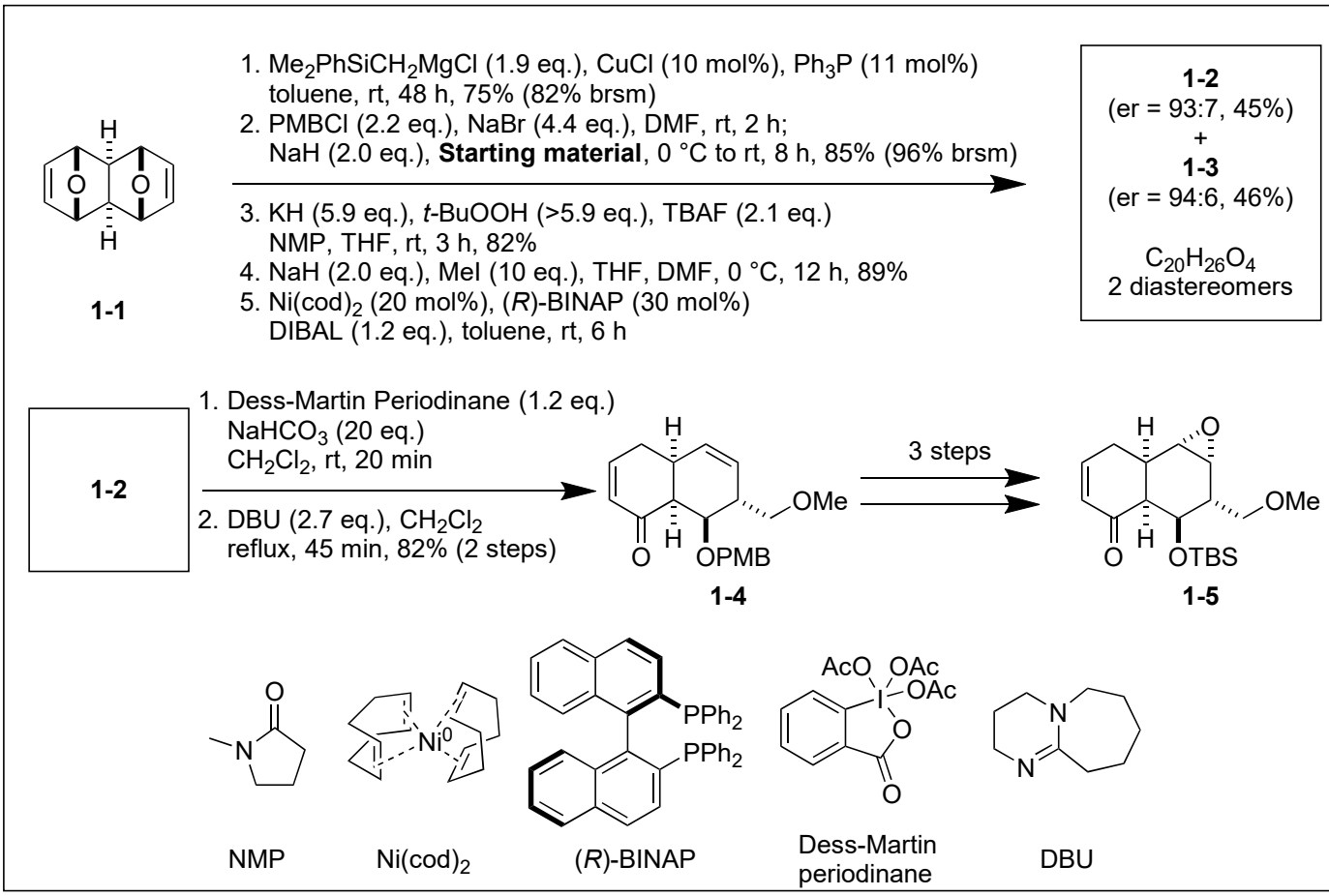




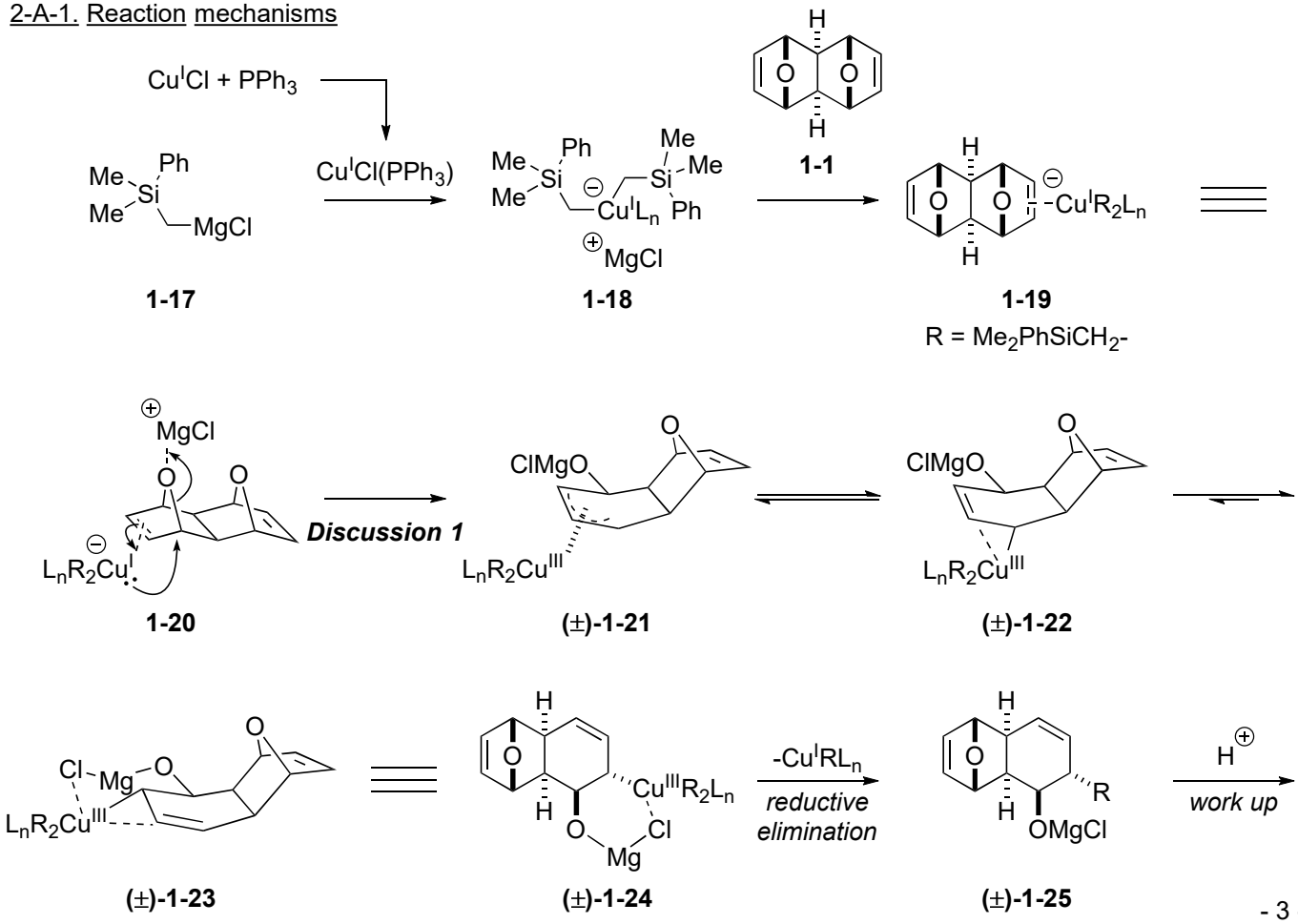
total 27 steps in longest linear
2% overall

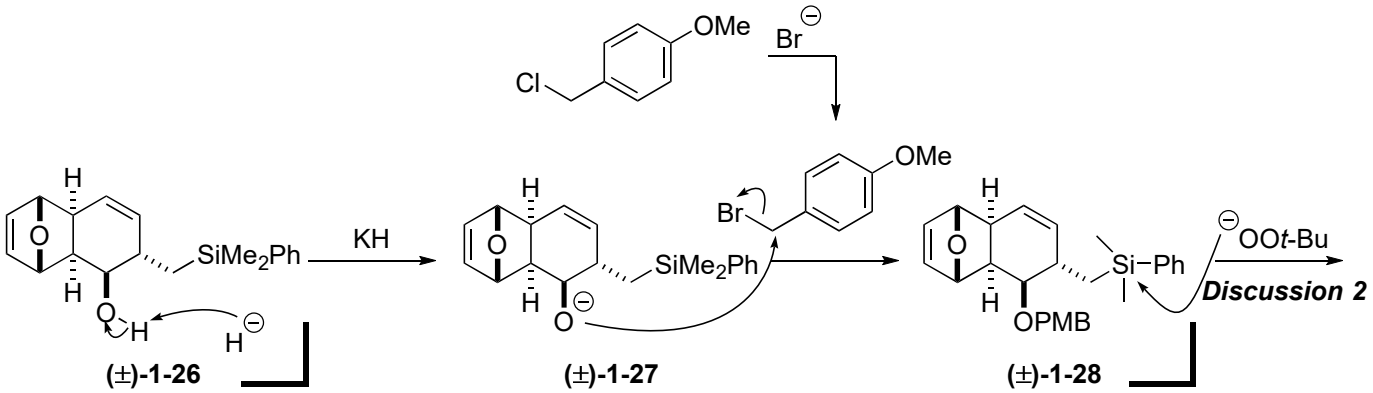
2. Answer

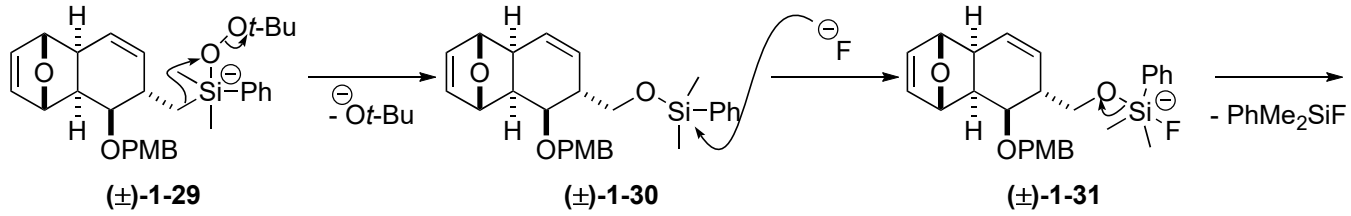
2-A. Synthesis of decaline core **1-5**

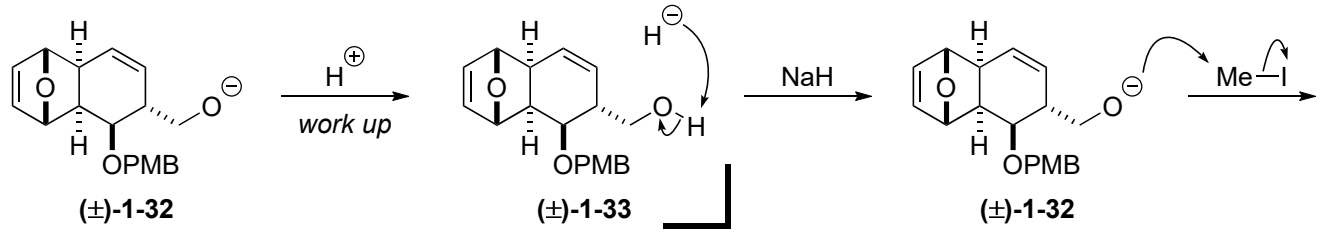


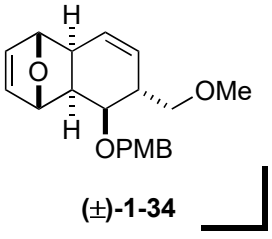
2-A-1. Reaction mechanisms



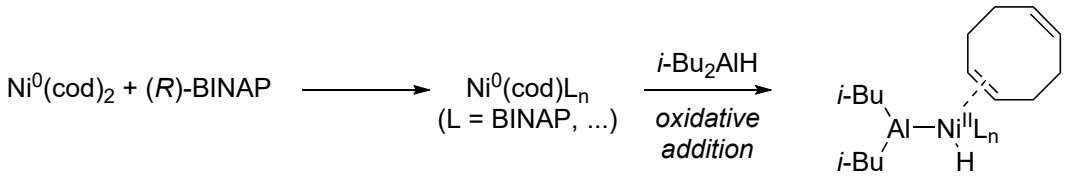








(±)-1-34

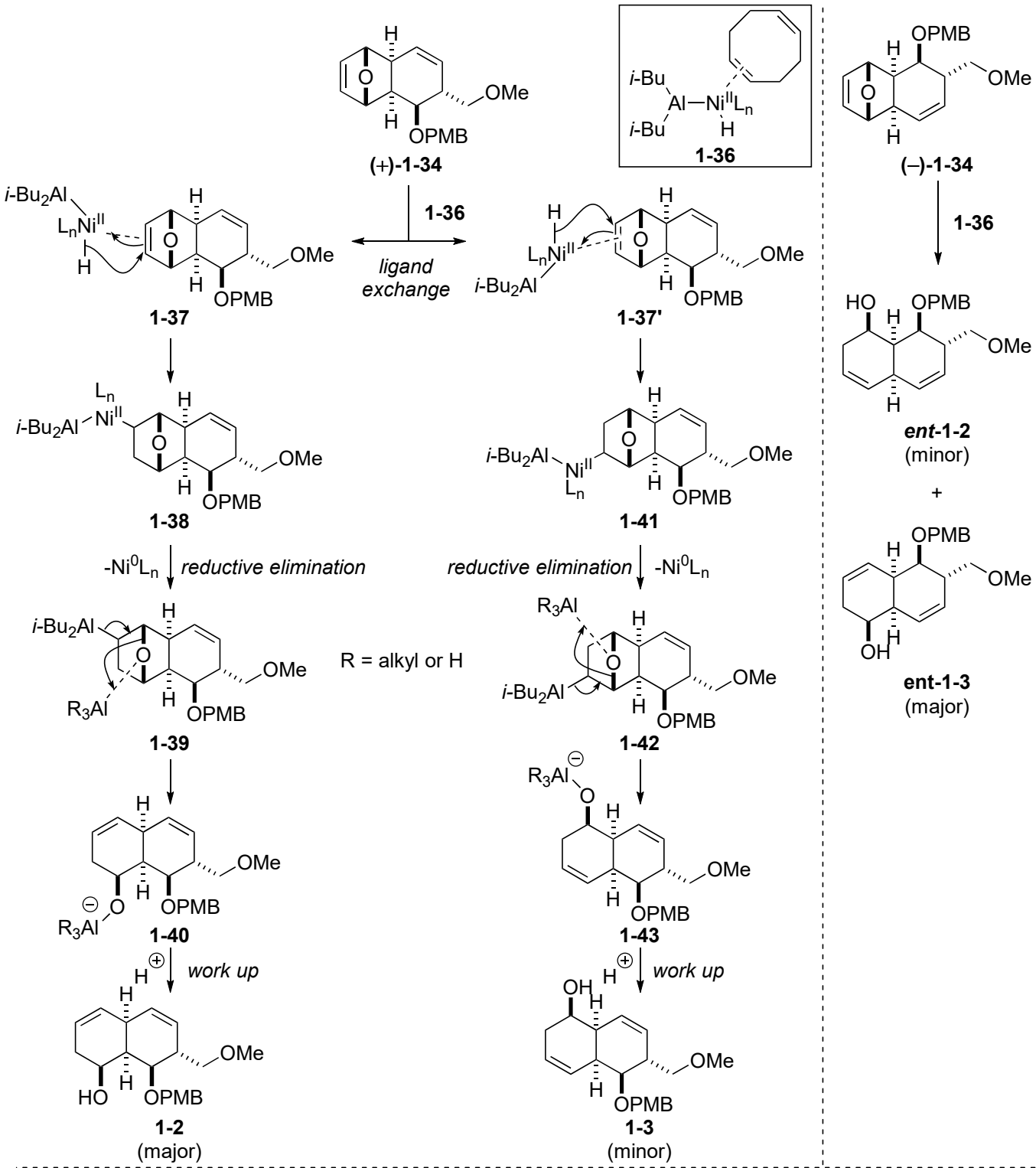


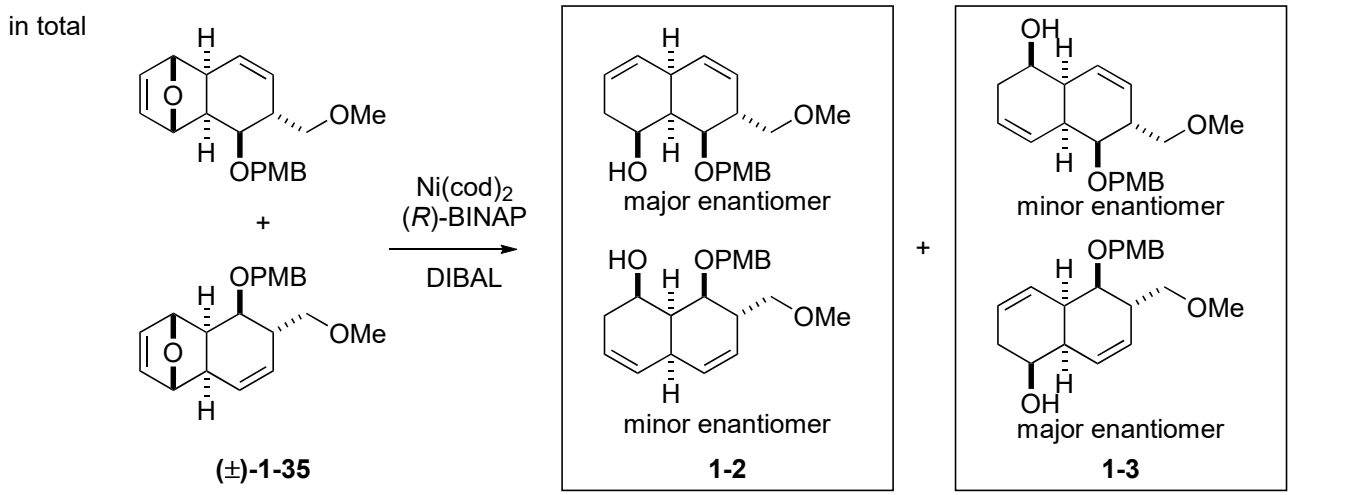
Discussion 3

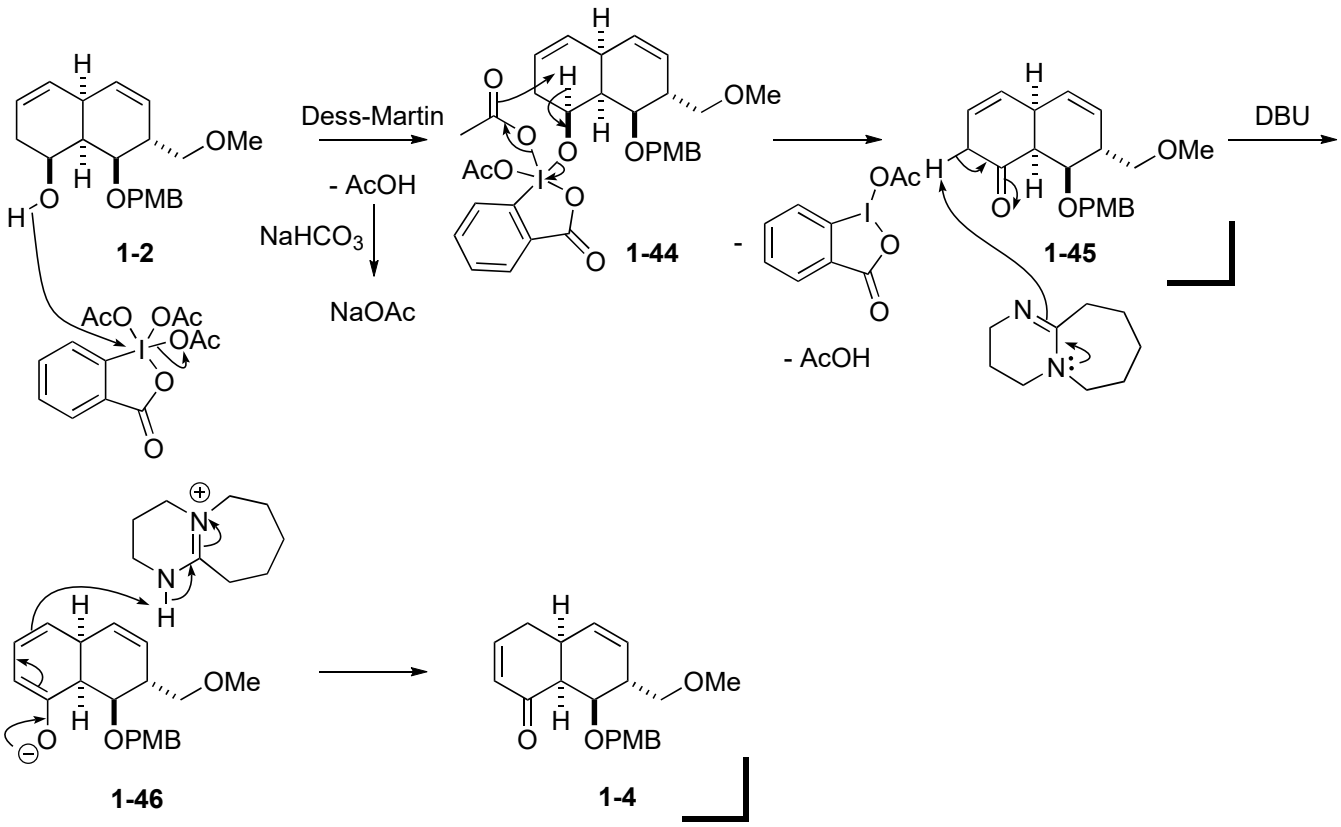
1-35 **1-36**

Ni: $[Ar]3d^8 4s^2$

Ni^{II}: $[Ar]3d^8$


(+)-1-34
1-36
(–)-1-34
1-36
ligand exchange
1-37
1-37'
1-38
1-41
-Ni0Ln
reductive elimination
reductive elimination
-Ni0Ln
R = alkyl or H
1-39
1-42
1-40
1-43
work up
work up
ent-1-2
(minor)
+
ent-1-3
(major)
1-2
(major)
1-3
(minor)

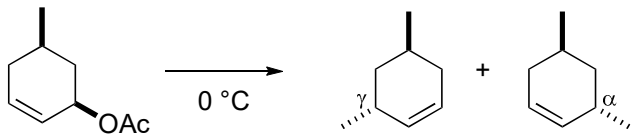

in total
(±)-1-35
+
Ni(cod)2
(R)-BINAP
DIBAL
major enantiomer
minor enantiomer
1-2
+
minor enantiomer
major enantiomer
1-3



2-A-2. Discussion

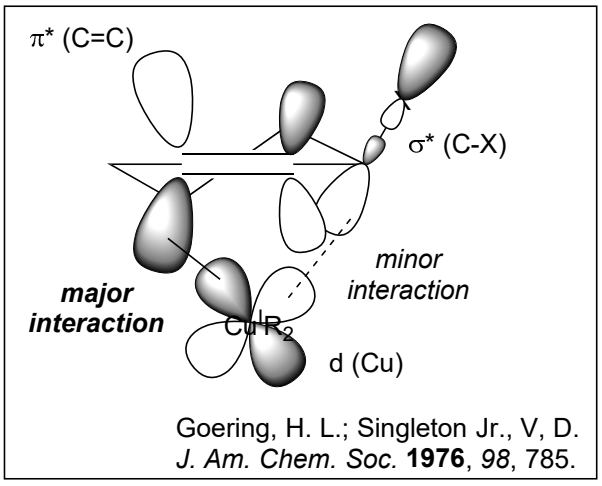
Discussion 1: Copper-catalyzed S_N2/S_N2' reaction

anti-selective substitution: in general



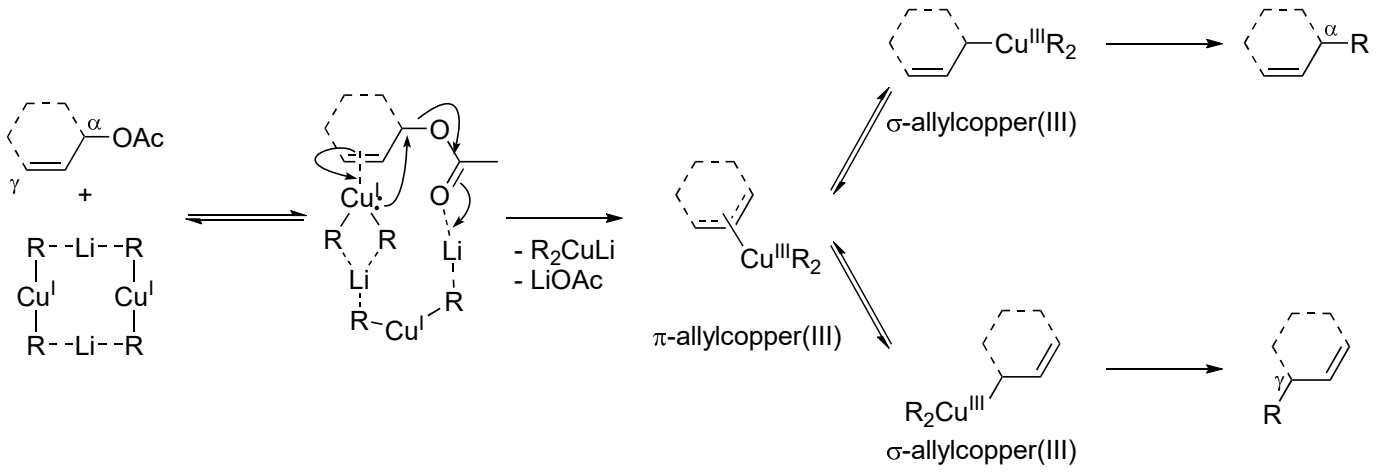
1-47 **1-48a** **1-48b**

Me_2CuLi	50	:	50
MeCu(CN)Li	96	:	4



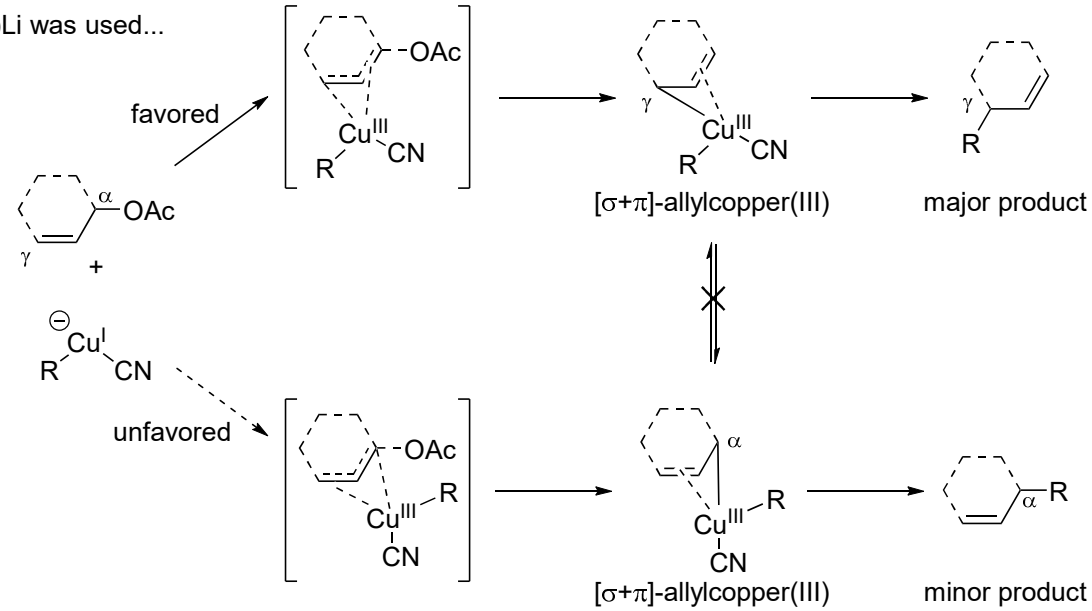
Goering, H. L.; Singleton Jr., V, D. *J. Am. Chem. Soc.* **1976**, *98*, 785.

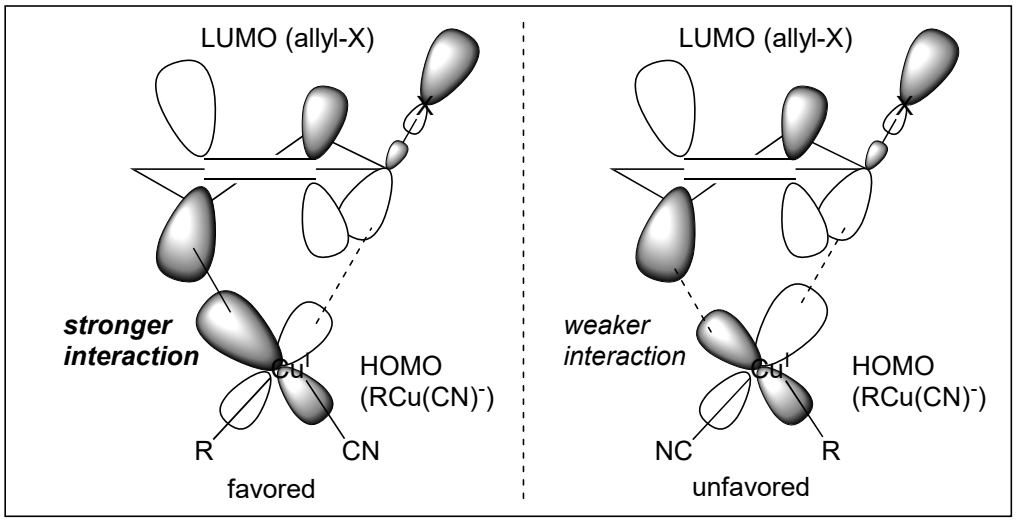
• If Me_2CuLi was used...



-> The reaction proceeds via π-allylcopper(III) complex, so there is no α/γ selectivity.

• If MeCu(CN)Li was used...

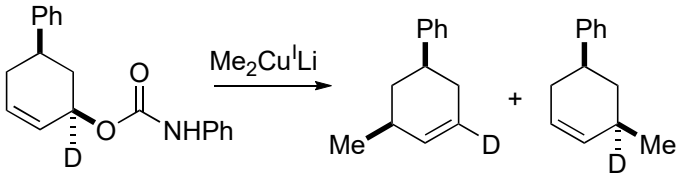




Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339.

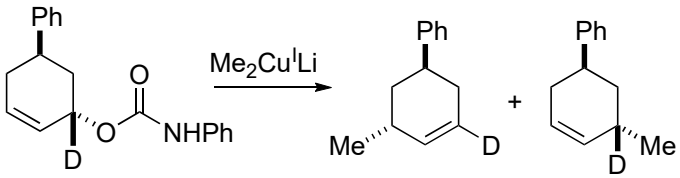
-> The HOMO of a bent $RCu(CN)^-$ fragment is more extended in the direction opposite to the CN ligand because of its lower σ-donor ability. Since the LUMO of allyl-X is more extended on the γ position, the HOMO of $RCu(CN)^-$ and γ side of π* orbital make better interaction and it leads to [σ+π]-allylcopper(III) complex. It is configurationally stable and there is no equillibrium between two types of [σ+π]-allylcopper(III), so reductive elimination occurs mainly at the γ position.

syn-selective substitution: with directing groups (carbamate, phosphine, ...)



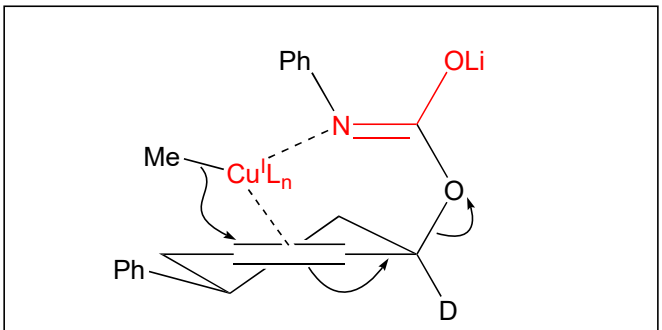
(±)-1-49α 80-90% **(±)-1-50α** **(±)-1-51α**

>98:2



(±)-1-49β 80-90% **(±)-1-50β** **(±)-1-51β**

>98:2



Breit, B.; Schmidt,Y. *Chem. Rev.* **2008**, *108*, 2928.

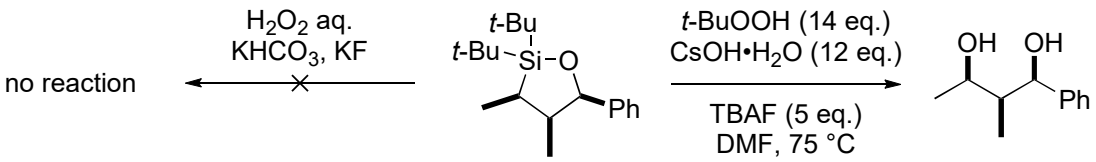
-> If the leaving group has a functional groups which can coordinates to the Cu atom, the substitution goes *syn*-selectively.

Gallina, C.; Ciattini, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035

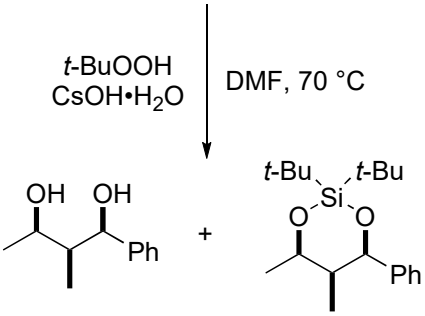
Discussion 2: Tamao-Fleming oxidation

Sterically hindered alkoxysilane is unreactive under standard condition.

Excess peroxide and strong base increase the reactivity.

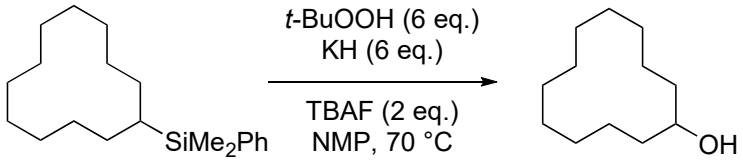


1-52 **1-53** 64%



1-53 **1-54**

In the developed condition, oxidation proceeded with no fluoride sources.
-> Fluoride ion is important for deprotection, not for the oxidation itself.



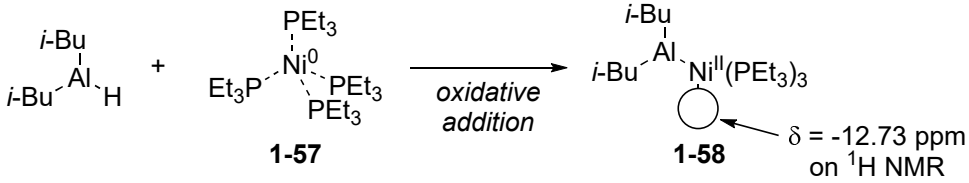
1-55 **1-56** 80%

-> The condition is also applicable to the oxidation of arylsilane with no hetero-substituents on Si atom.

Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044.

Discussion 3: Ni-catalyzed hydroalumination

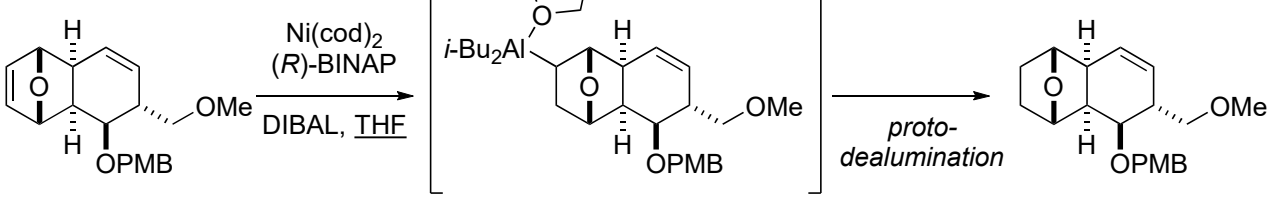
1. Evidence for the existence of nickel hydride



1-57 **1-58**

Strong shift to upfield on ^{1}H NMR is typical of Ni-H bond.
->Active species which has Ni-H is formed.

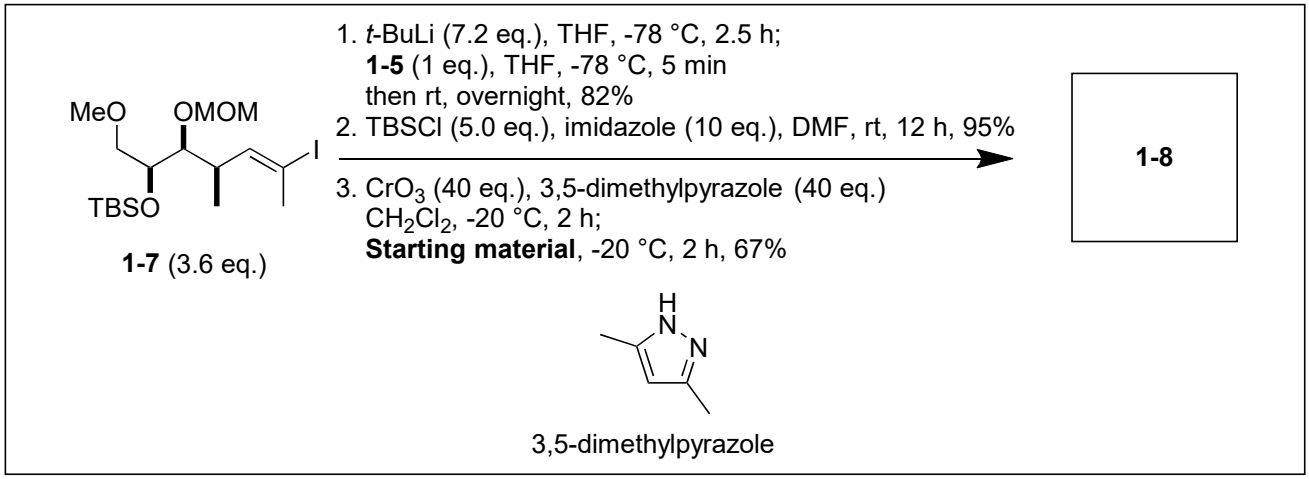
2. Solvent effect on ring opening



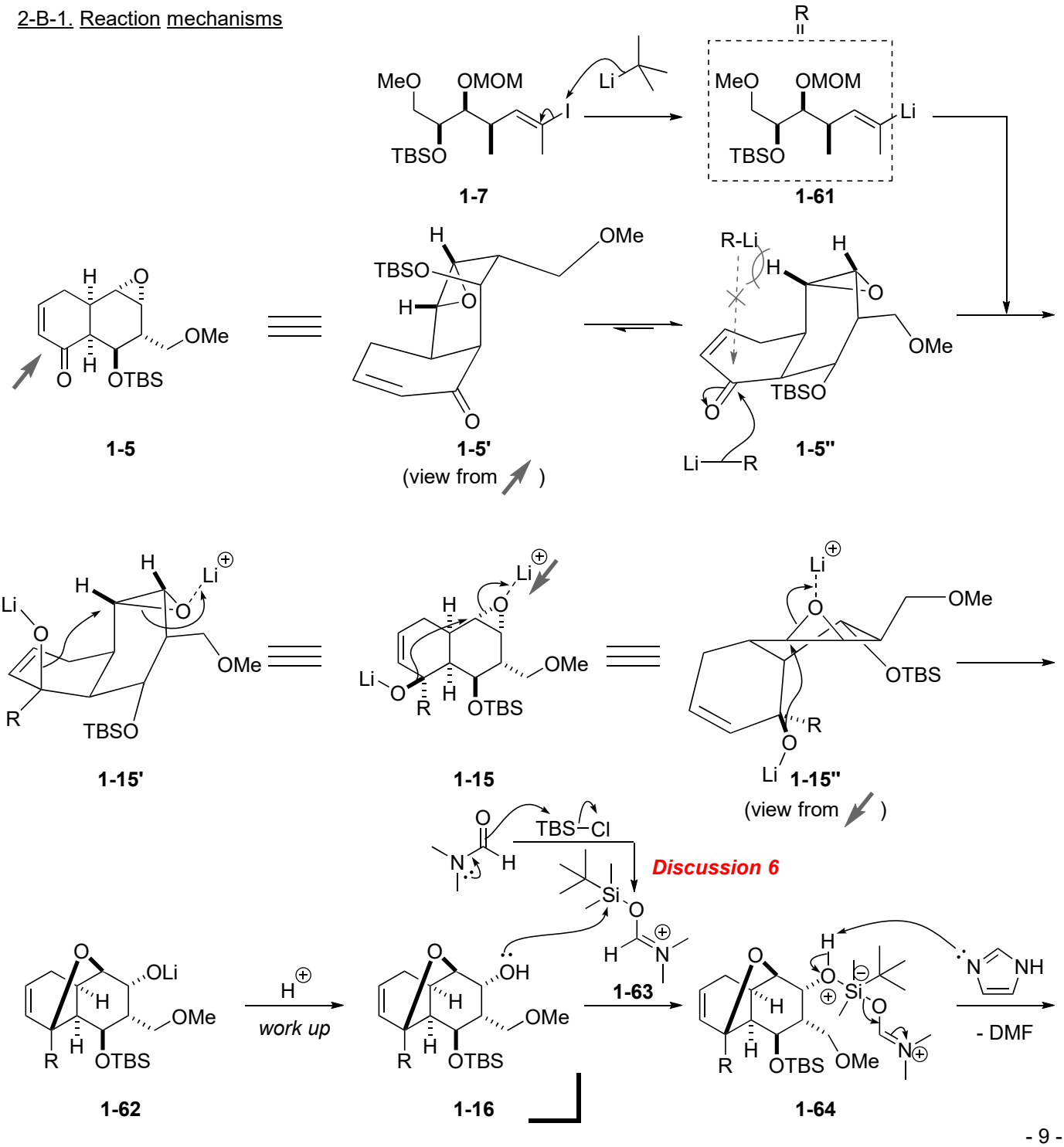
(±)-1-34 **(±)-1-59** **(±)-1-60**

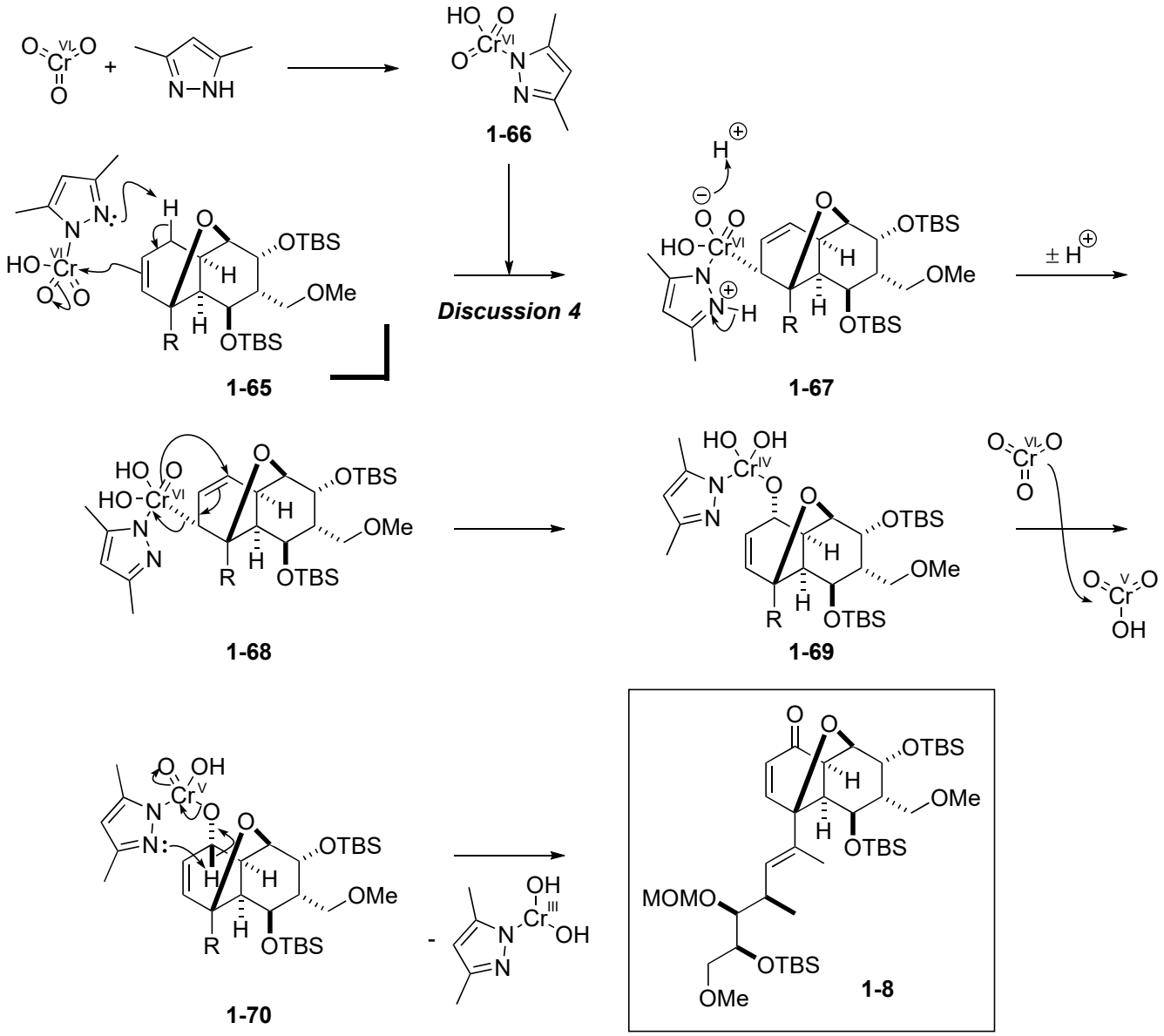
The oxa-bridge of **(±)-1-59** is not activated by any Lewis acids, so protodealumination proceeds before the ring opening.

2-B. Formation of oxa-bridge



2-B-1. Reaction mechanisms





2-B-2. Discussion

Discussion 4: Allylic oxidation with dimethylpyrazole(DMP)-CrO_3 complex

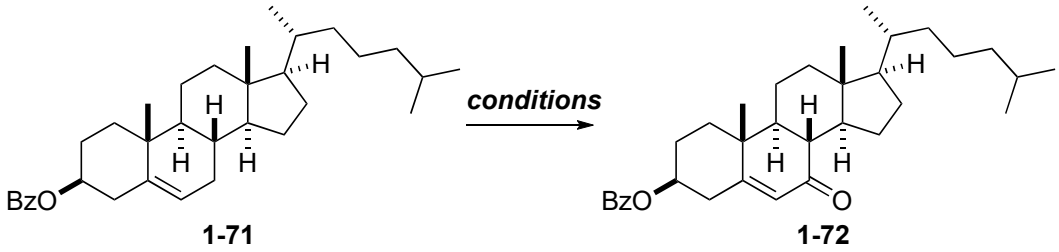


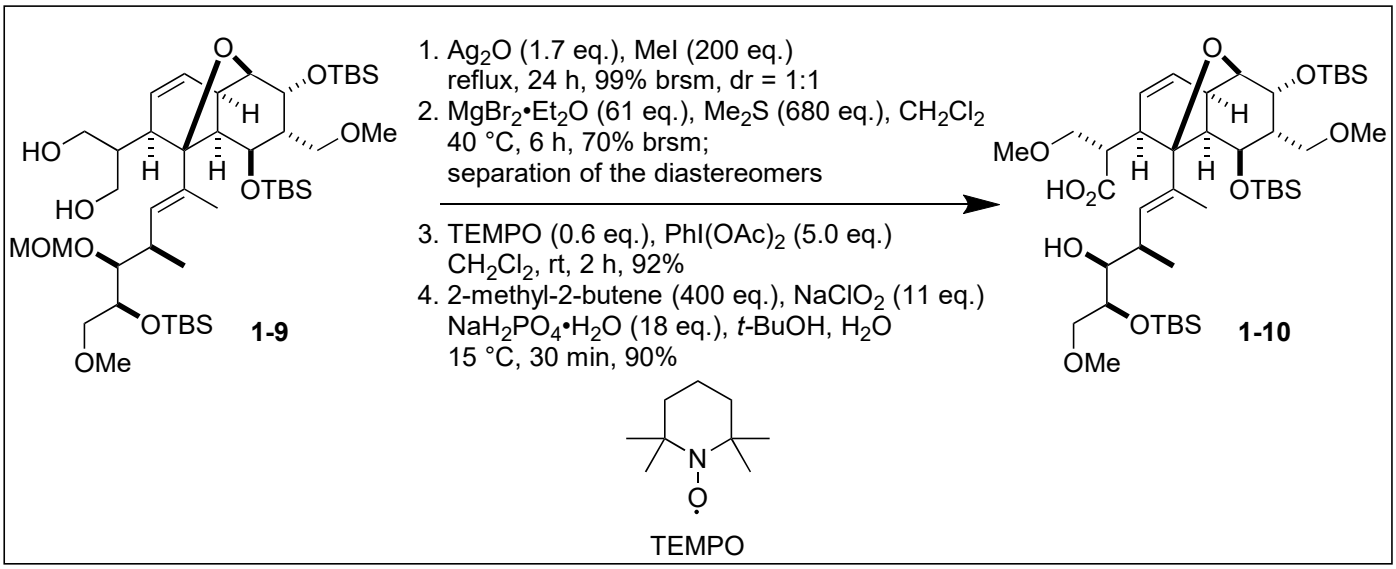
Table 1.

reagent	***time***	results
Na_2CrO_4 $AcOH/Ac_2O$	3-4 days	max 38%
CrO_3•py/CH_2Cl_2 (Collins' reagent)	50 h	68%
pyH^+•$ClCrO_3^-$ (PCC) CH_2Cl_2	-	not proceeded
DMP•CrO_3 CH_2Cl_2	<30 min	70-75%

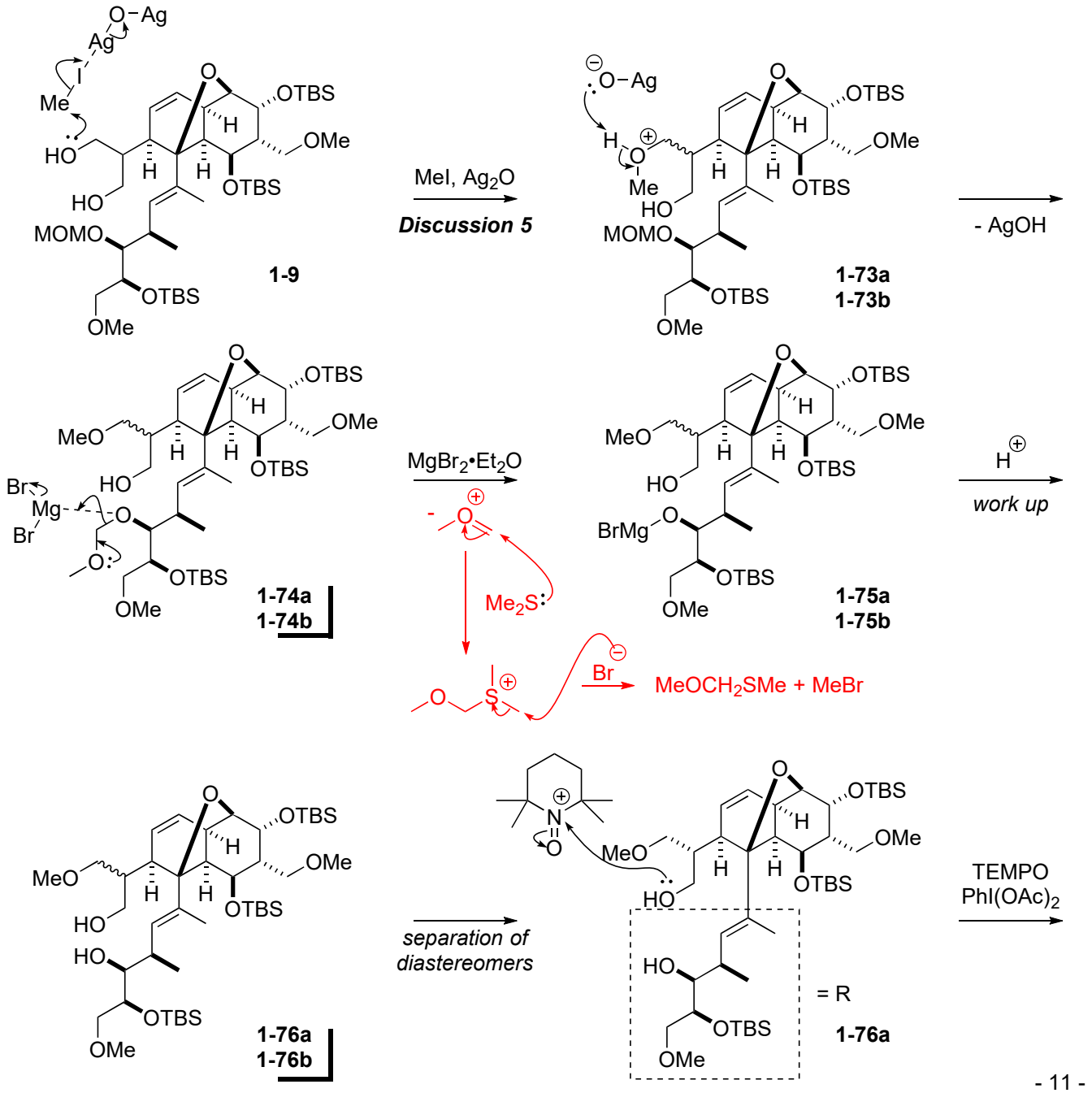
-> 3,5-Dimethylpyrazole as the ligand of chromium trioxide accelerates the oxidation by inter- and intramolecular deprotonation as shown in the scheme above.

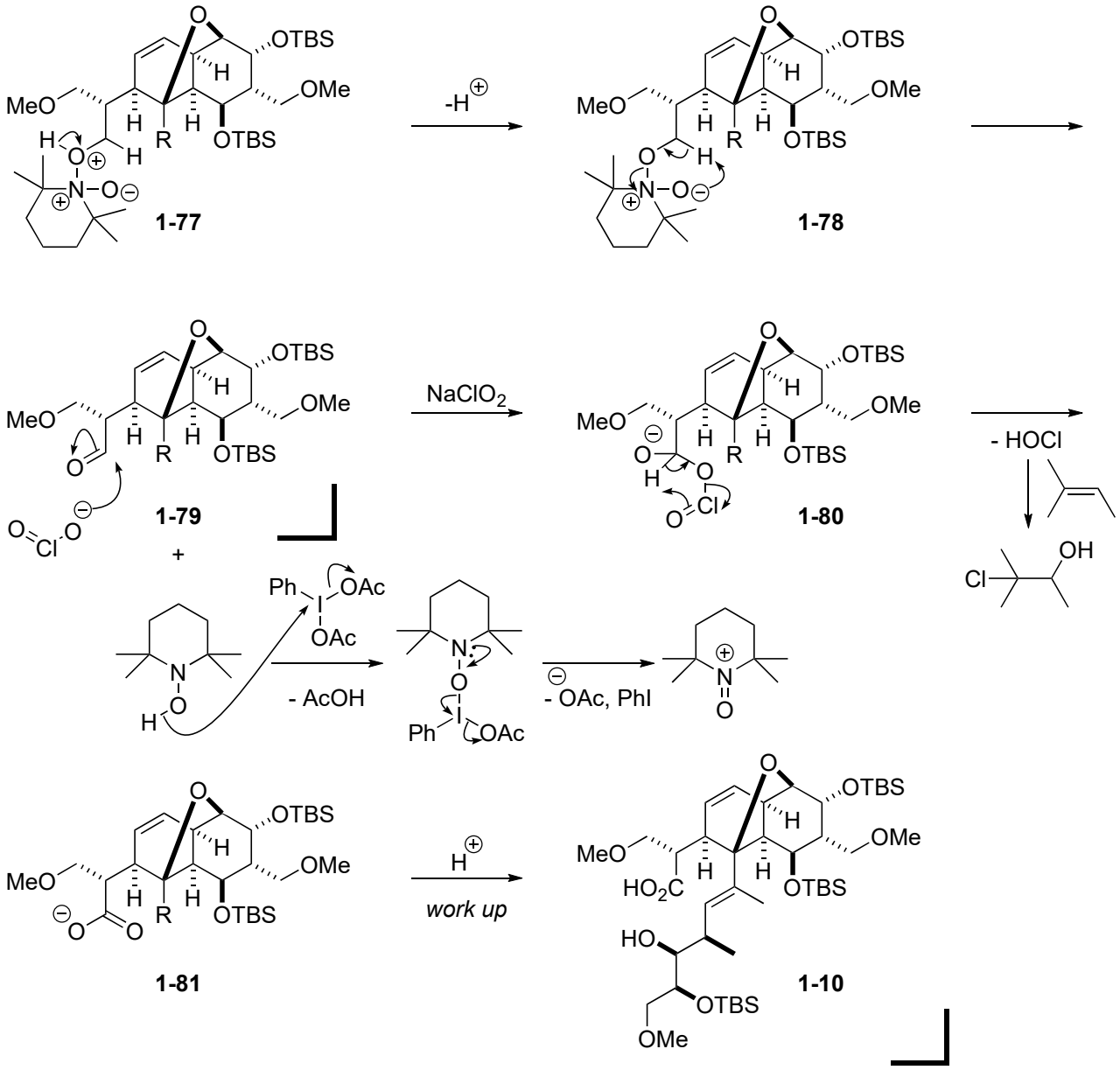
Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.

2-C. Synthesis of lactone precursor **1-10**



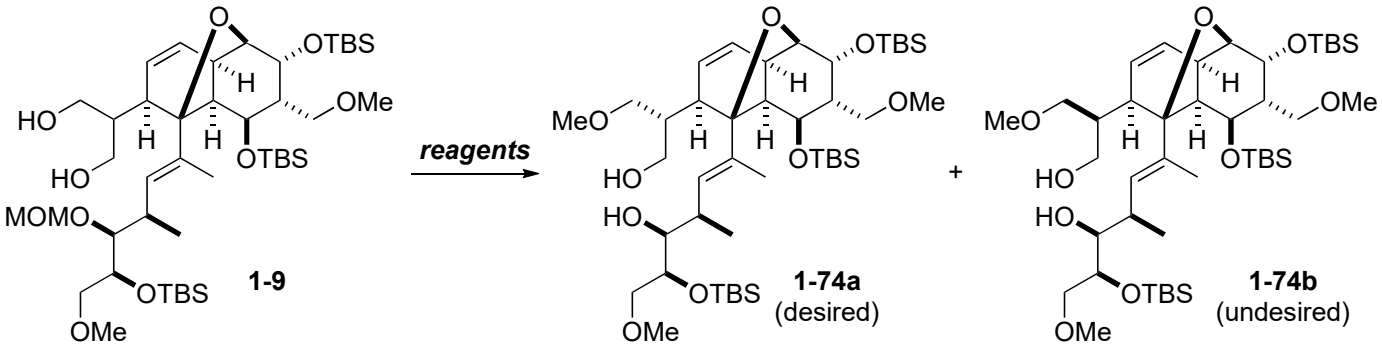
2-C-1. Reaction mechanisms





2-C-2. Discussion

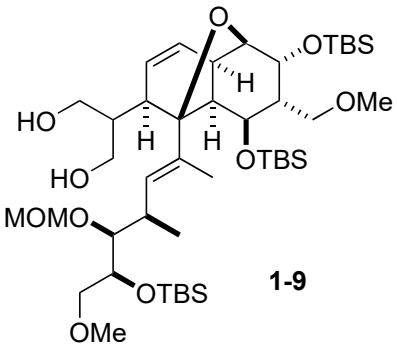
Discussion 5: Selectivity on monomethylation of diol **1-9**



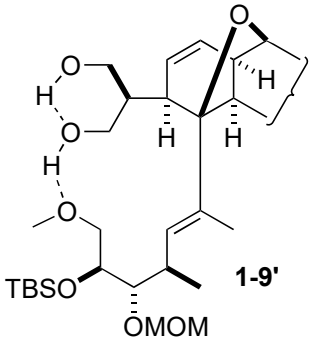
MeI, Ag_2O **1-74a**:**1-74b** = 1:1

MeI, $KN(TMS)_2$ **1-74a**:**1-74b** = 1:4

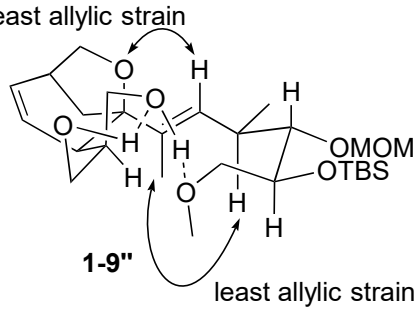
My proposal for the explanation of the selectivity



1-9



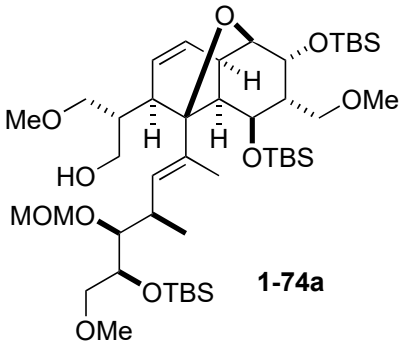
1-9'



1-9"

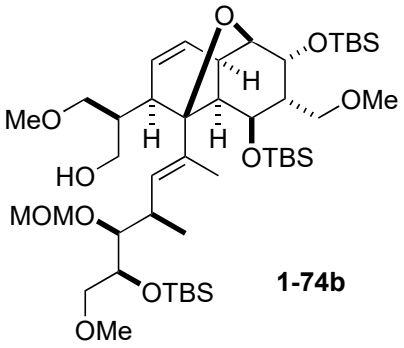
MeI, Ag_2O

Both of the hydroxy groups are moderately hindered.
-> Almost no selectivity was observed.



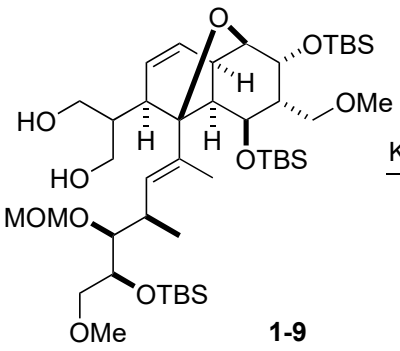
1-74a

+



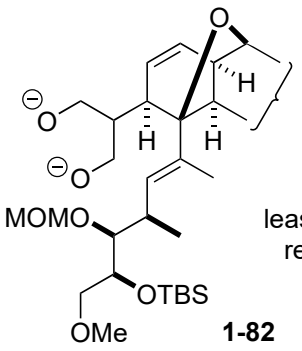
1-74b

1-74a:**1-74b** = 1:1

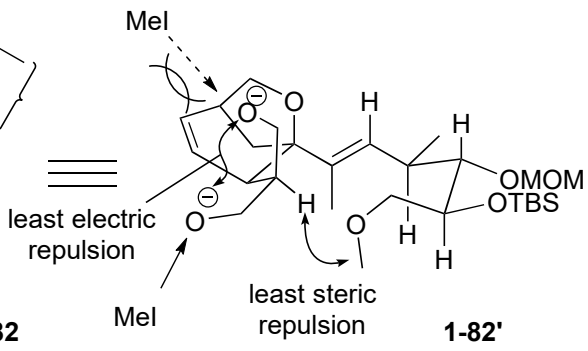


1-9

$KN(TMS)_2$



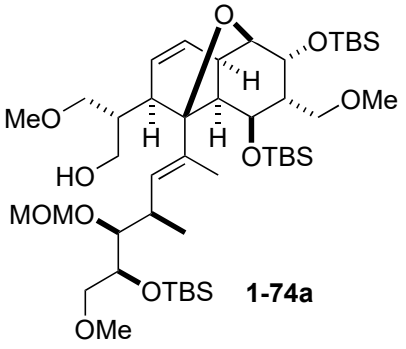
1-82



1-82'

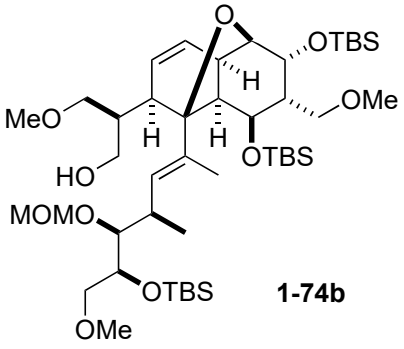
minor MeI

major MeI



1-74a

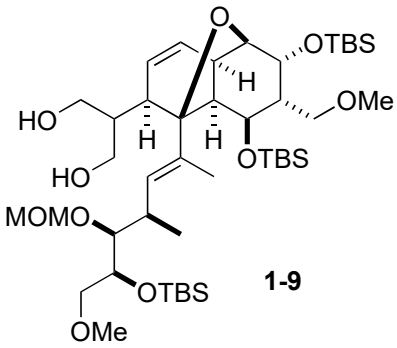
+



1-74b

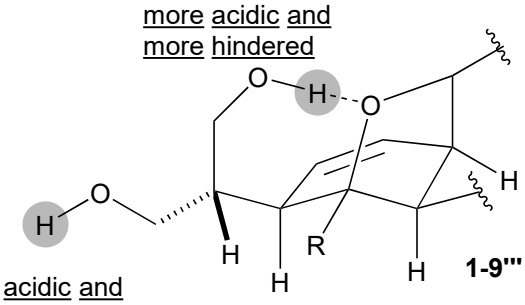
1-74a:**1-74b** = 1:4

Prof. Inoue's proposal



1-9

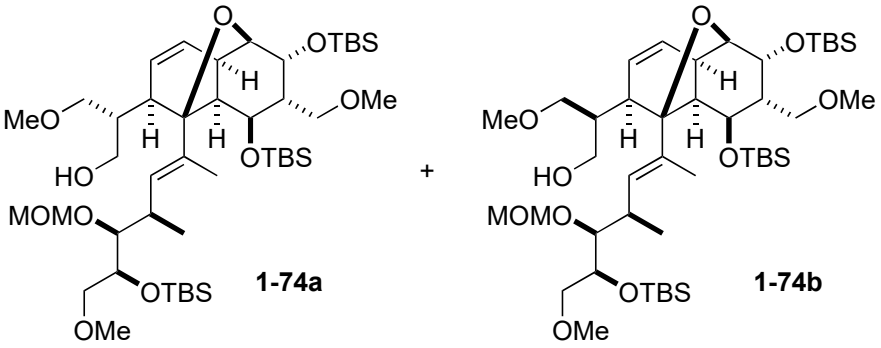
more acidic and more hindered



1-9'''

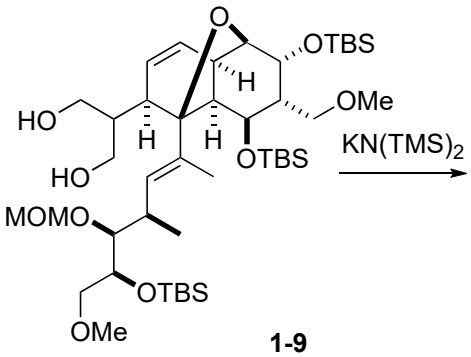
less acidic and less hindered

MeI, Ag_2O



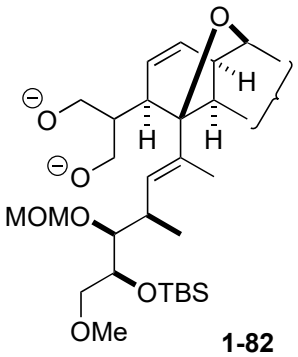
1-74a **1-74b**

1-74a:**1-74b** = 1:1



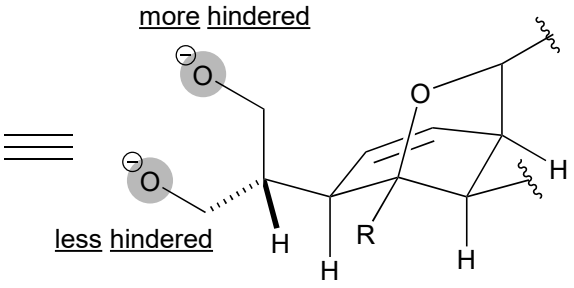
1-9

$KN(TMS)_2$



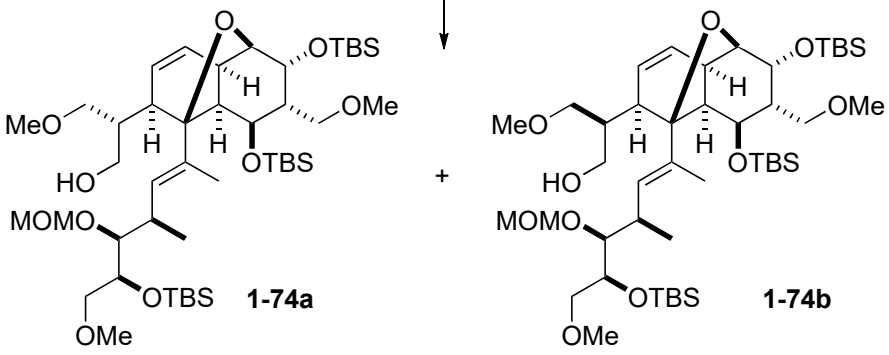
1-82

more hindered



less hindered

1-82"

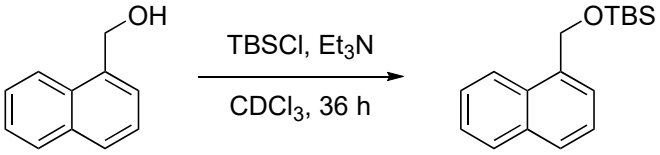


1-74a **1-74b**

1-74a:**1-74b** = 1:4

Discussion 6: Active reagent of silylation

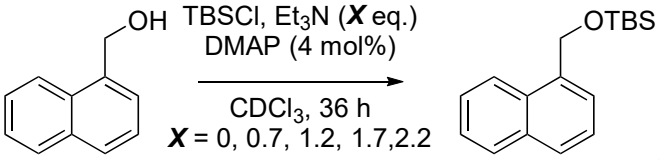
A. Silyation only with Et_3N



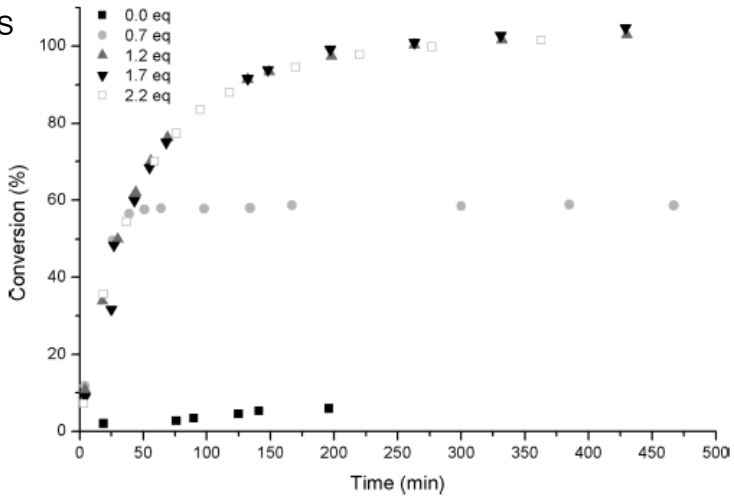
1-83 **1-84**

<1% -> Et_3N itself does not accelerate the reaction.

B. Silyation with variable amount of Et_3N



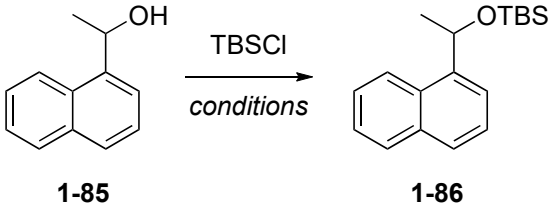
1-83 **1-84**



- The rates of silylation were practically identical for the reactions with 2.2, 1.7, and 1.2 equiv. of Et_3N.
- The reaction slowed down after a certain percentage of conversion with 0.7 equiv. of Et_3N.
- The reaction was extremely slow in absence of Et_3N.

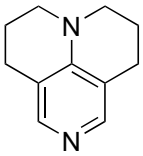
-> Et_3N is not directly involved in the catalytic cycle,
but is merely needed to regenerate the catalyst by removing proton from it.

C. Silylation in various solvents

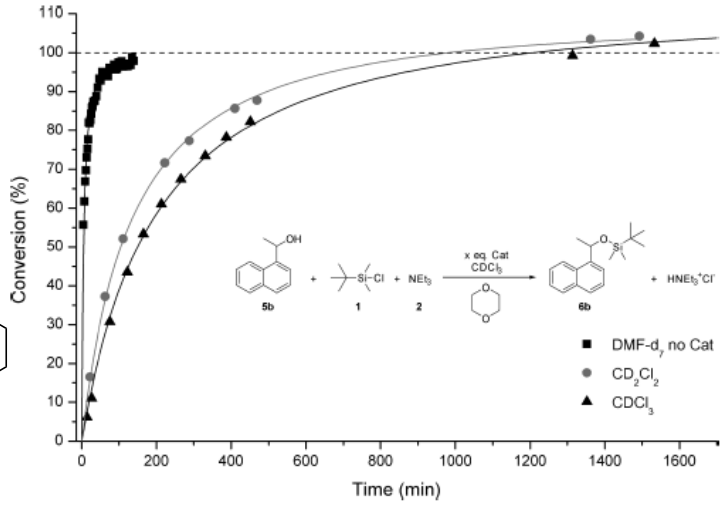


1-85 **1-86**

entry	*conditions*
1	$DMF\text{-}d_7$, Et_3N (1.2 eq.)
2	CD_2Cl_2, Et_3N (1.2 eq.) **cat A** (30 mol%)
3	$CDCl_3$, Et_3N (1.2 eq.) **cat A** (30 mol%)



cat A



In $DMF\text{-}d_7$, basic catalyst derived from DMAP was not needed. Even without the catalyst, the reaction rate of silylation in $DMF\text{-}d_7$ was significantly faster than that with the catalyst in CD_2Cl_2 and $CDCl_3$.
-> DMF itself could act as a catalyst of silylation.

The active species **1-63** had not been directly detected on ^{29}Si NMR,
but further analysis with calculational prediction was performed by authors.
Patschinski, P.; Zhang, C.; Zipse, H. *J. Org. Chem.* **2014**, *79*, 8348.