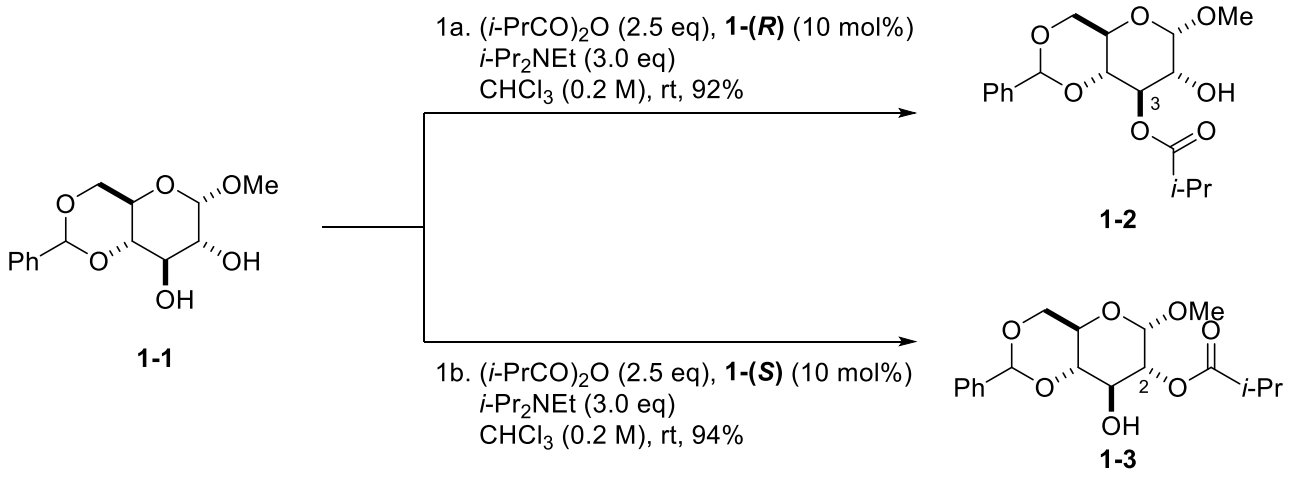
Problem Session (3)

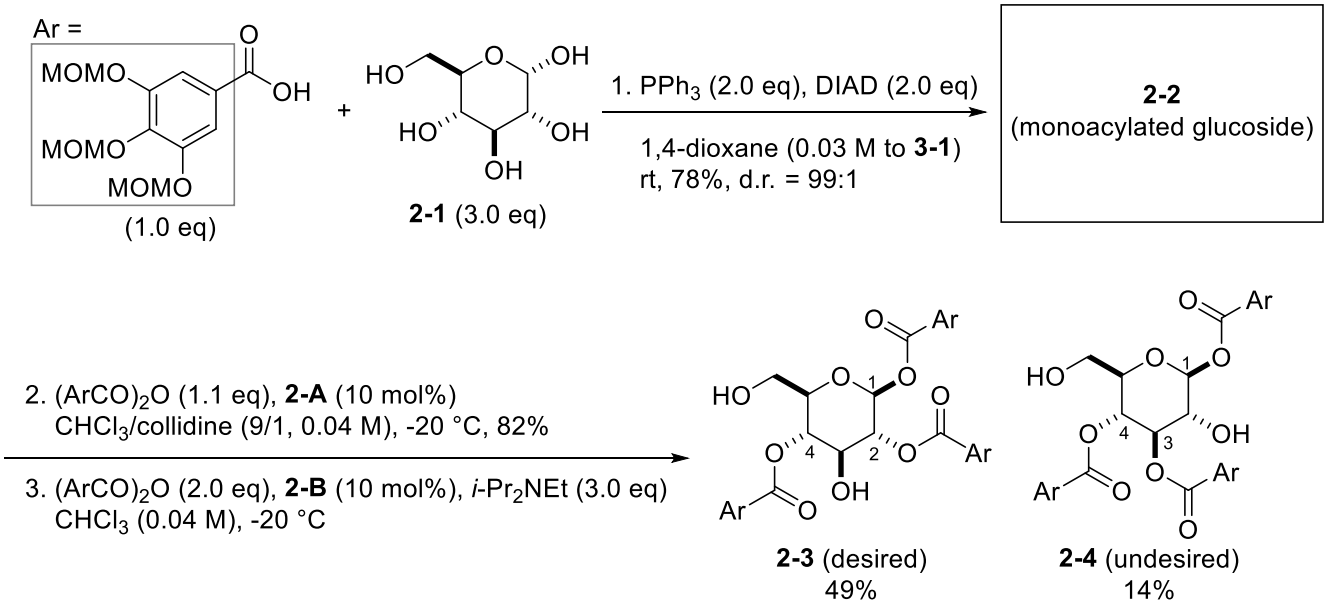
2022/8/27 Yosuke Nakata

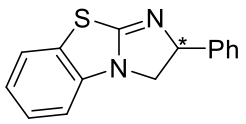
Please provide the structure of **2-2** and explain the reaction mechanisms and the selectivities

1.

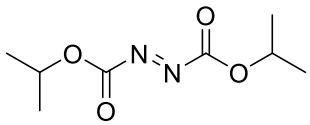


2.

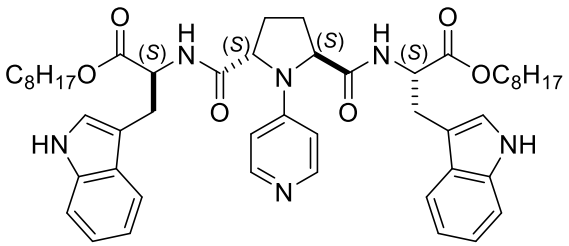




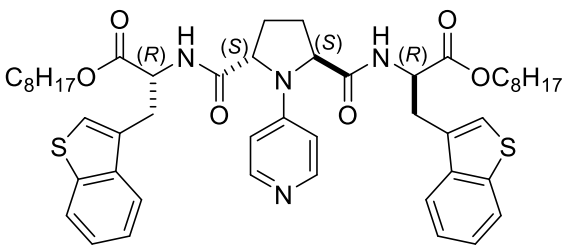
1-(*R*)
1-(*S*)



DIAD



2-A



2-B

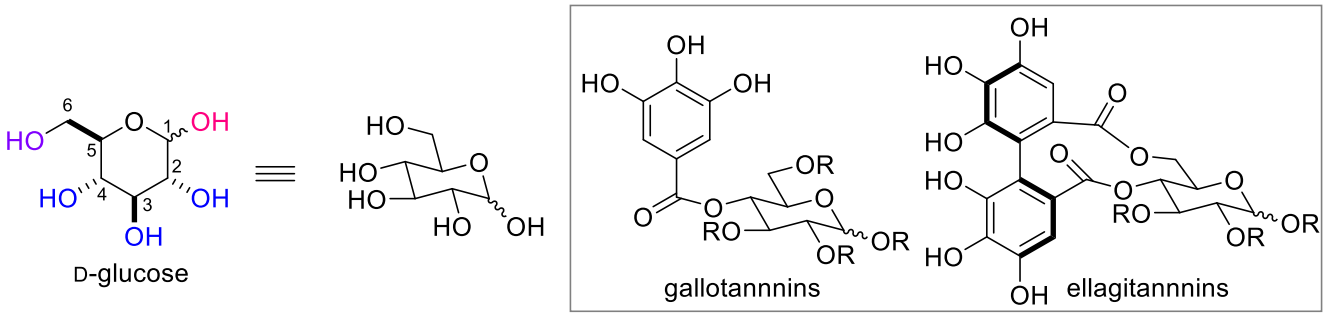
Problem Session (3) -Answer-

2022/8/27 Yosuke Nakata

Topic: site-selective acylation of glucose by organocatalysts

0. Introduction

0-1. glucose

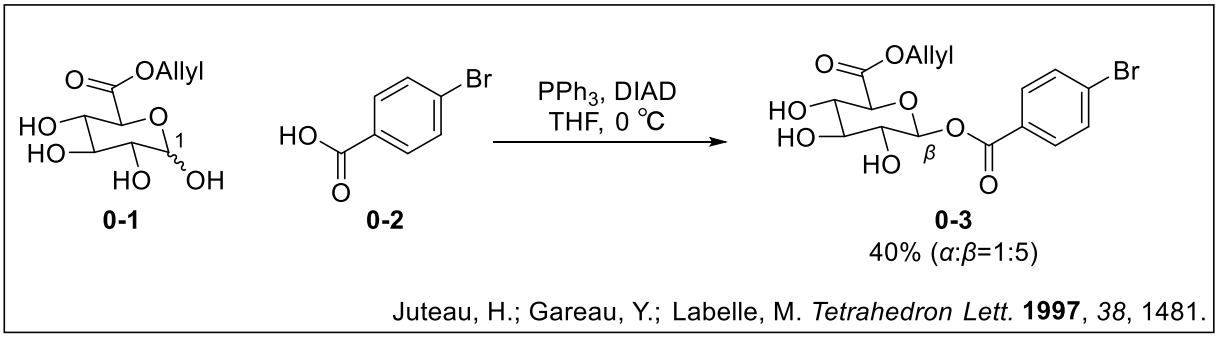


- 5 hydroxy groups: hemiacetal (1-OH), 1° OH (6-OH) and trans-positioned 2° OH (2, 3, 4-OH)
- Site-selective acylation of OH groups is a major task for synthesis of glucose derivatives (e.g. tannins).

0-2. Site-selective acylation

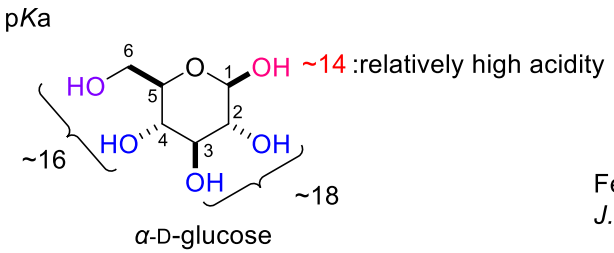
0-2-1. Reactivity of OH groups

(i) hemiacetal (1-OH) vs alcohol (2, 3, 4 ,6-OH)



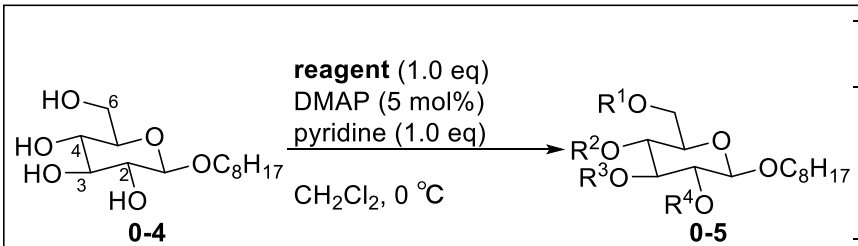
Juteau, H.; Gareau, Y.; Labelle, M. *Tetrahedron Lett.* **1997**, *38*, 1481.

- Selective acylation at 1-OH is generally conducted by Mistunobu conditions (problem 2, step 1).
- Site-selectivity was explained by relatively high acidity of 1-OH.



Feng, S.; Bagia, C.; Mpourmpakis, G. *J. Phys. Chem. A* **2013**, *117*, 5211.

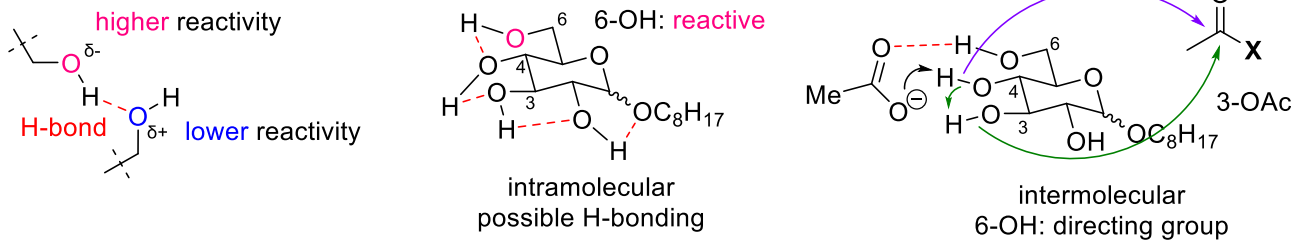
(ii) 1° OH (6-OH) vs 2° OH (2, 3, 4-OH)



	reagent	
	AcCl	Ac_2O
6-OAc: R^1 = Ac, R^2-R^4 = H	62%	12%
4-OAc: R^2 = Ac, R^1,R^3,R^4 = H	2%	13%
3-OAc: R^3 = Ac, R^1,R^2,R^4 = H	9%	34%
2-OAc: R^4 = Ac, R^1-R^3 = H	0%	0%

Kattnig, E.; Albert, M. *Org. Lett.* **2004**, *6*, 945.

- Acetylation with Ac_2O and DMAP proceeds with inverted reactivity of 1° OH (6-OH) and 2° OH (3, 4-OH).

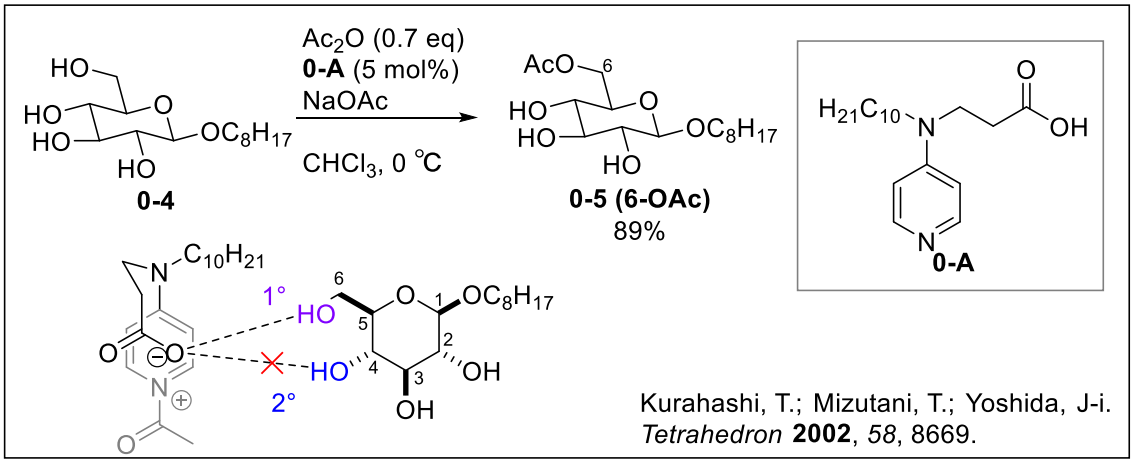


- It was proposed that intra- or intermolecular hydrogen bonding between OH groups affect the reactivity.

0-2-2. Site-selective acylation by organocatalysts

- For highly site-selective acylation of 2, 3, 4, 6-OH, organocatalysts have been developed.

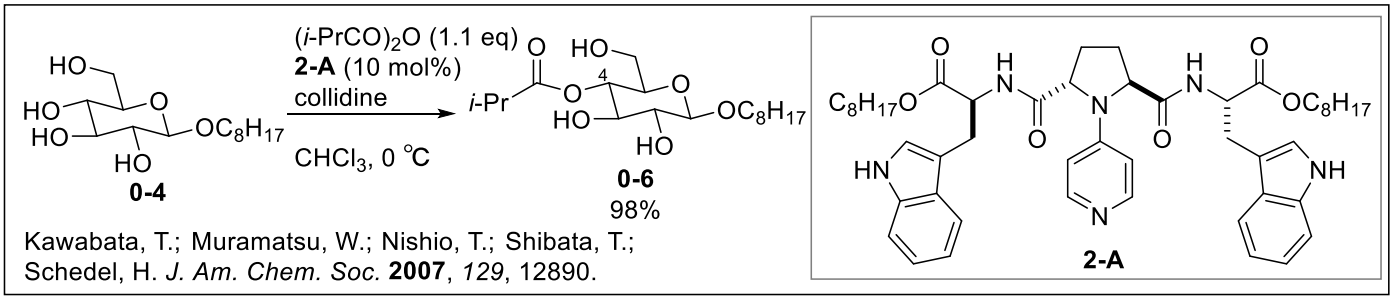
(i) 6-OH selective (vs 2, 3, 4-OH)



Kurahashi, T.; Mizutani, T.; Yoshida, J-i. *Tetrahedron* **2002**, *58*, 8669.

- Steric repulsion against **0-A**, which acts both acylation reagent and base, is dominant.

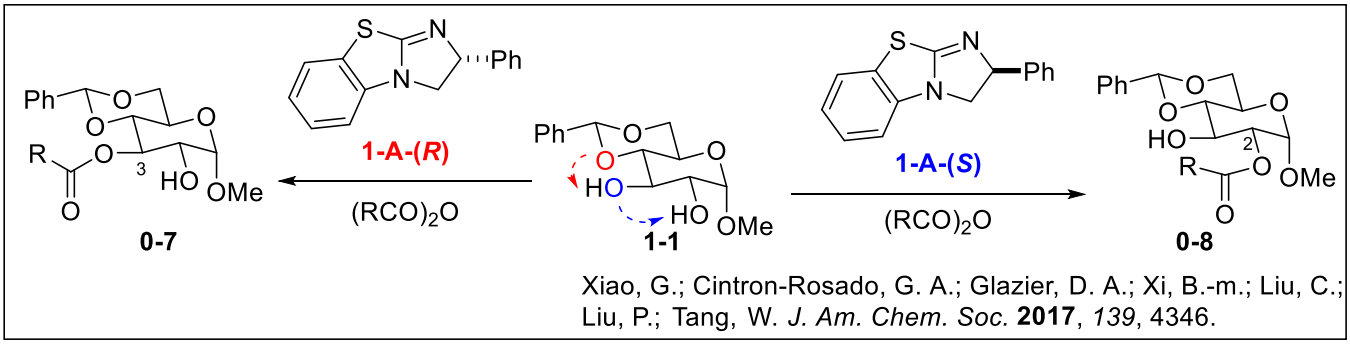
(ii) 4-OH selective (vs 2, 3, 6-OH)



Kawabata, T.; Muramatsu, W.; Nishio, T.; Shibata, T.; Schedel, H. *J. Am. Chem. Soc.* **2007**, *129*, 12890.

- H-bonding between 6-OH of **0-4** and amide C=O of **2-A** is important for catalyst-substrate recognition (problem 2, step 2)

(iii) 2-OH vs 3-OH

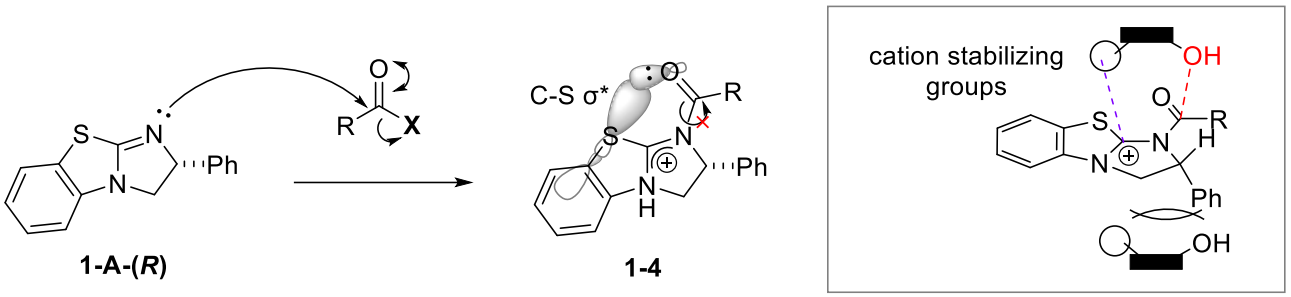


Xiao, G.; Cintron-Rosado, G. A.; Glazier, D. A.; Xi, B.-m.; Liu, C.; Liu, P.; Tang, W. *J. Am. Chem. Soc.* **2017**, *139*, 4346.

- Interaction between the neighbor O-atom and the catalysts is important for the selectivity (problem 1).

1. Problem 1

1-0. Benzotetramisole **1-A**

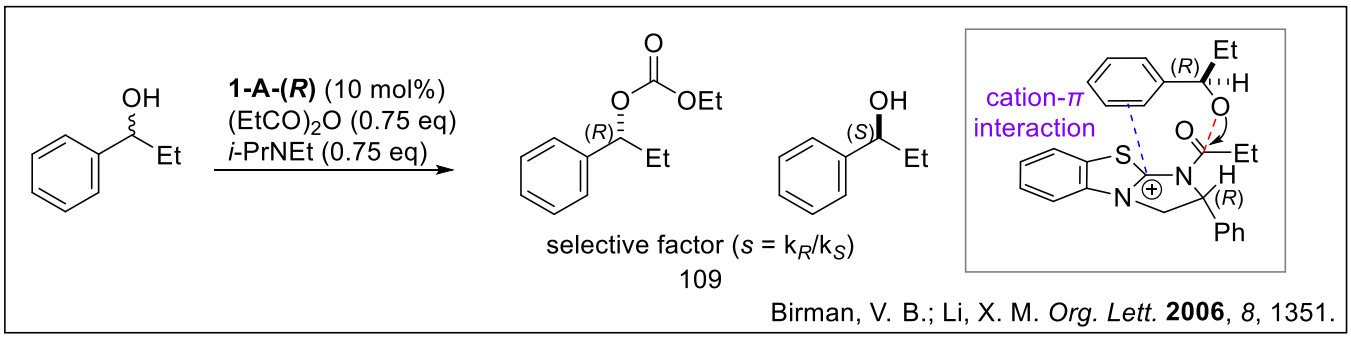


- The direction of carbonyl C=O bond is restricted by chalcogen bonding.

  (a) Yang, X.; Liu, P.; Houk, K. N.; Birman, V. B. *Angew. Chem., Int. Ed.* **2012**, 51, 9638.

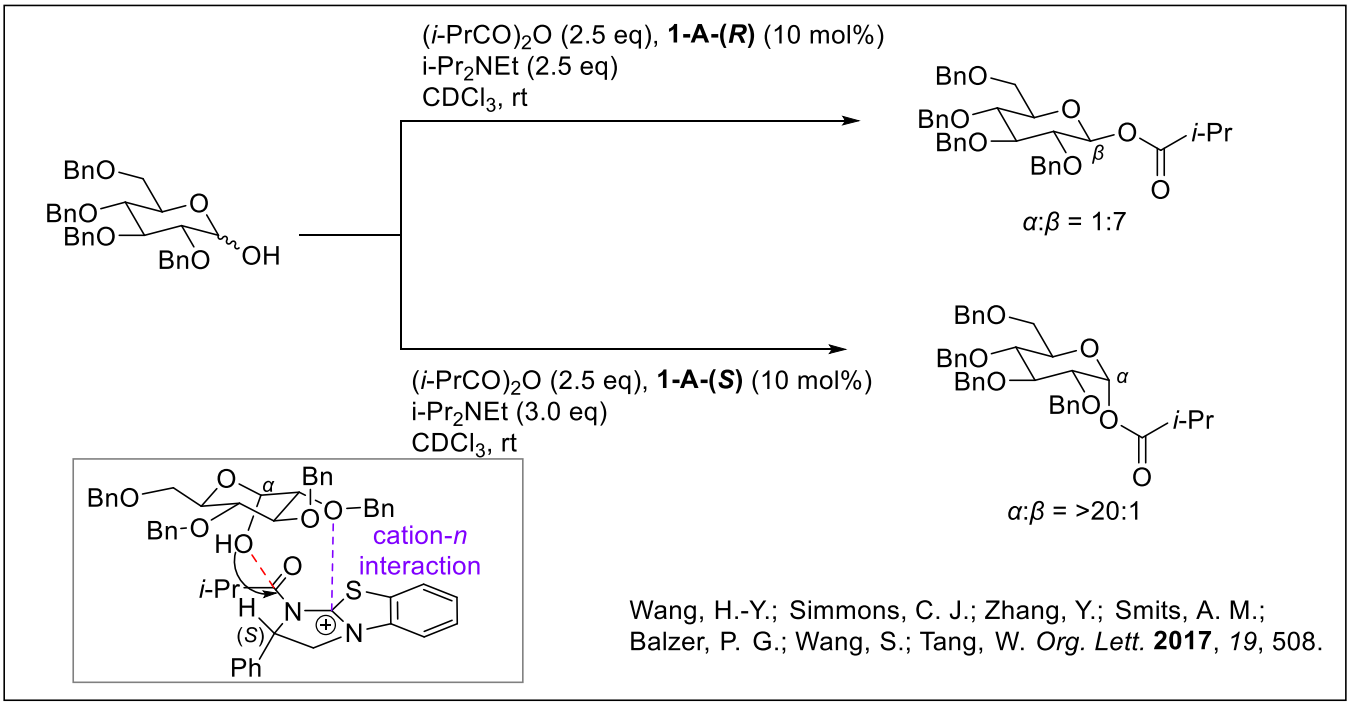
  (b) Abbasov, M. E.; Hudson, B. M.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2014**, 136, 4492.
- Substrate can approach from the opposite site to Ph group.
- The interaction between positively charged catalyst and cation stabilizing group enhances the selectivity.

example 1. kinetic resolution by selective acylation of racemic alcohol



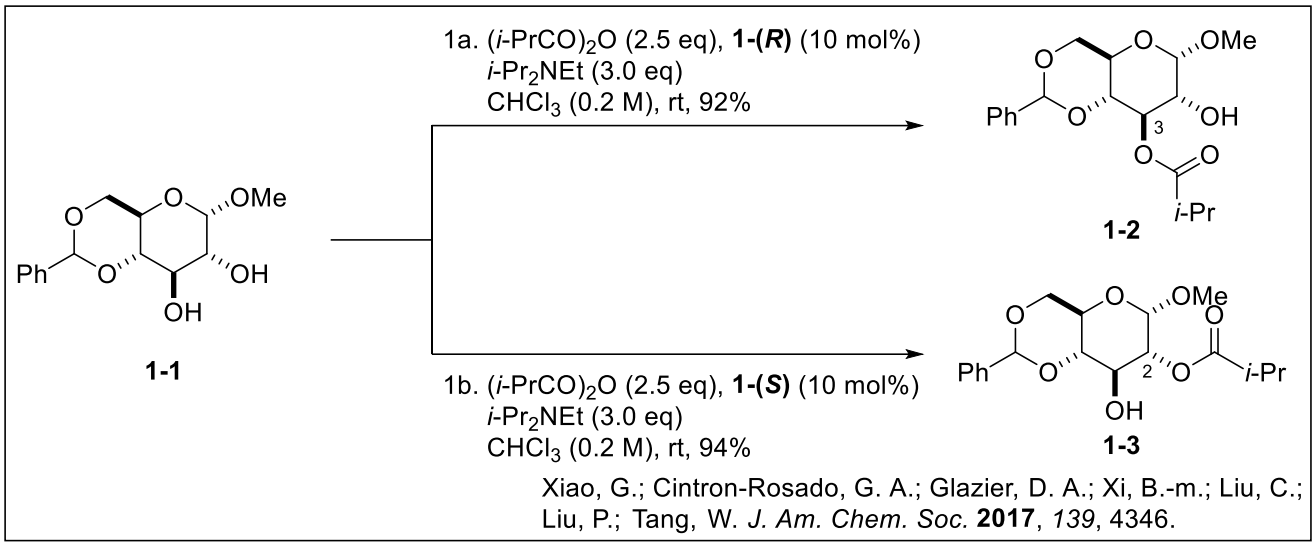
Birman, V. B.; Li, X. M. *Org. Lett.* **2006**, *8*, 1351.

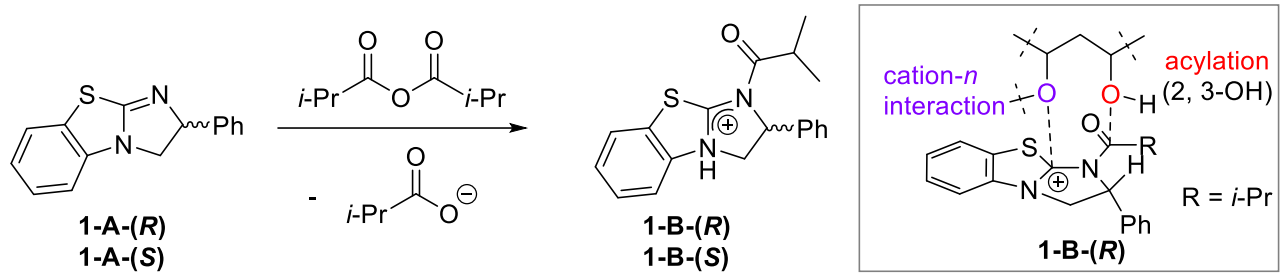
example 2. Selective acylation of 1-OH of glucosides



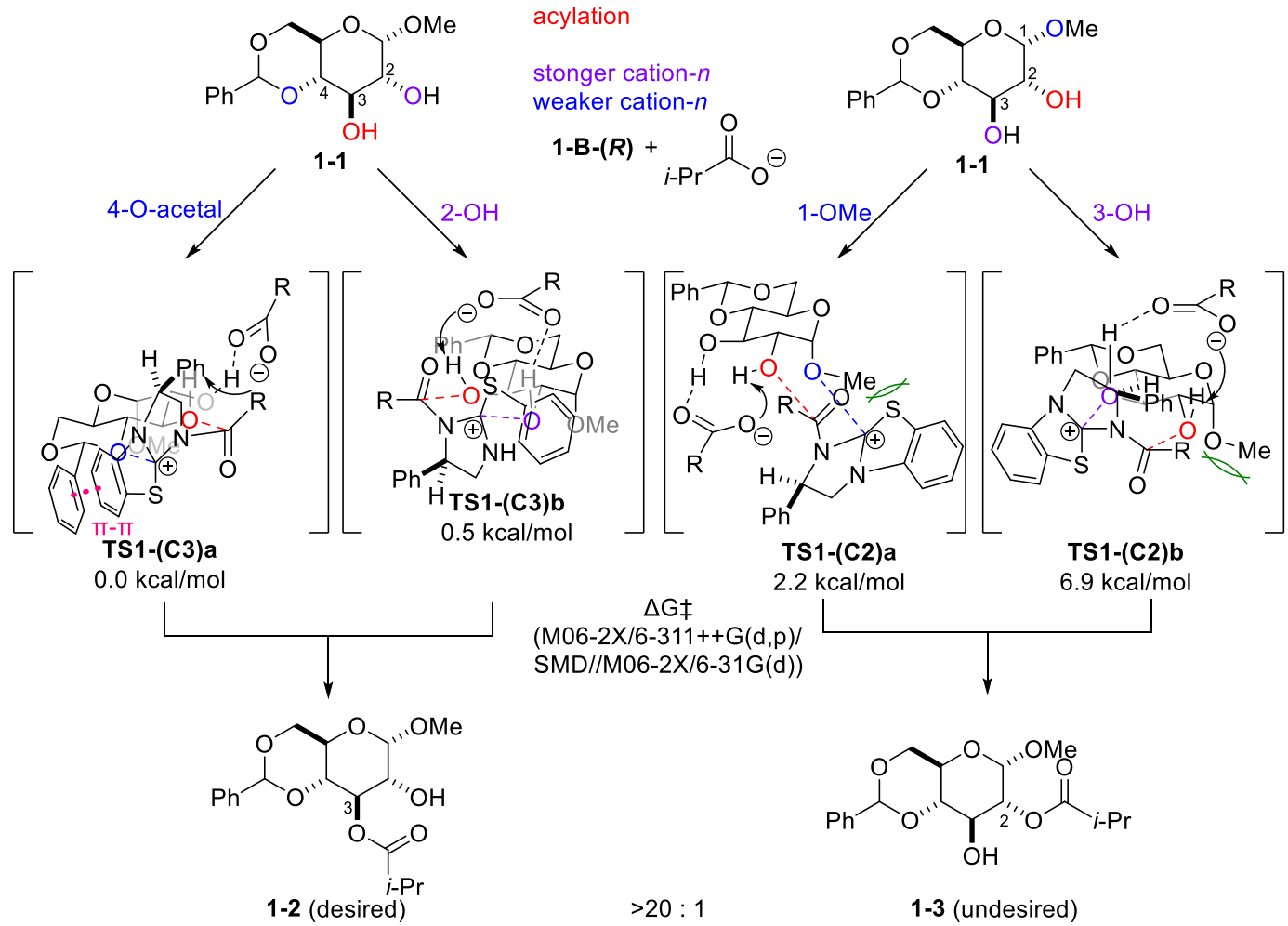
Wang, H.-Y.; Simmons, C. J.; Zhang, Y.; Smits, A. M.; Balzer, P. G.; Wang, S.; Tang, W. *Org. Lett.* **2017**, *19*, 508.

1-1. answer for problem 1



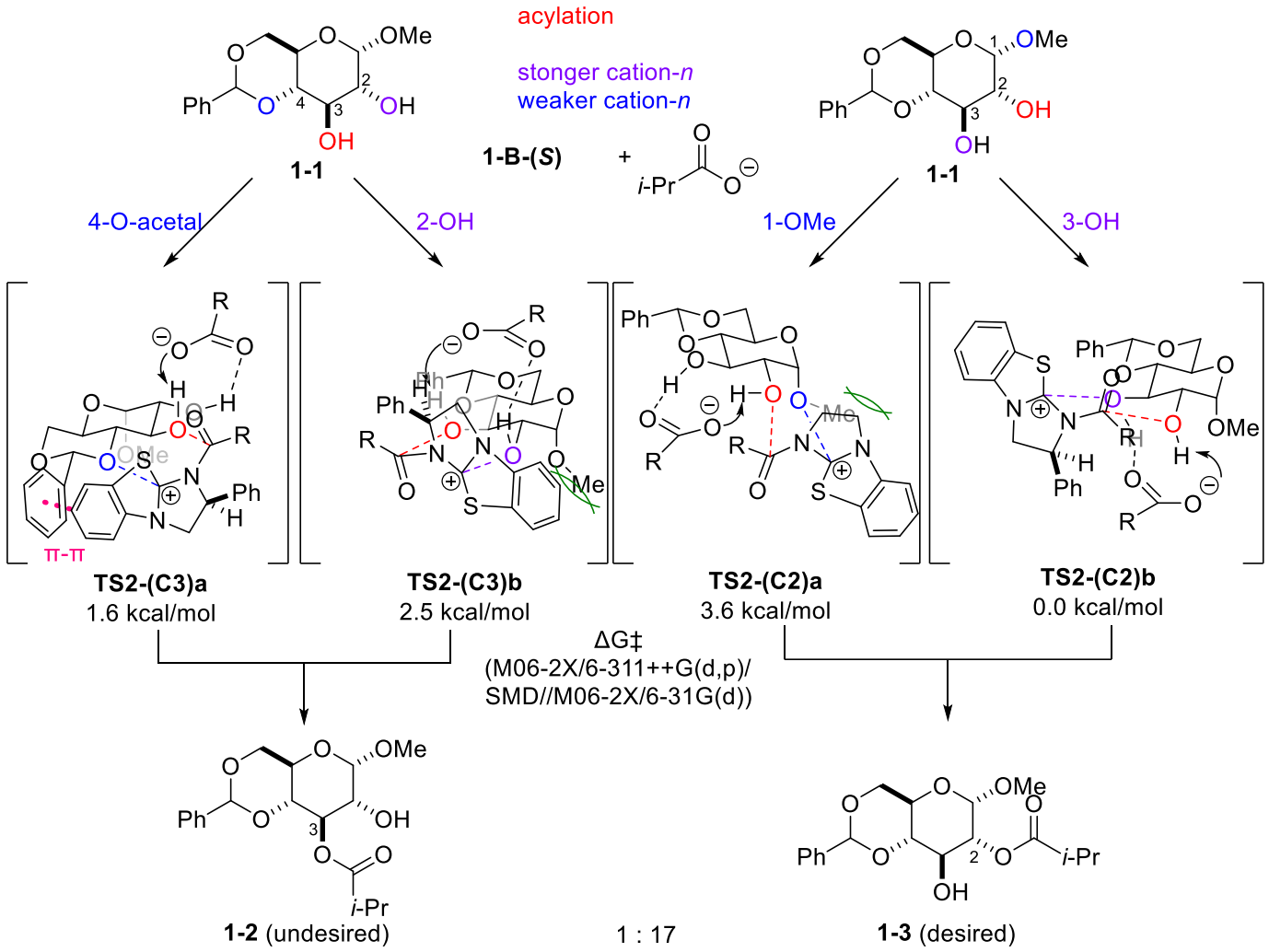


1-1-1. Acylation by **1-B-(*R*)**



- It is assumed that cation-*n* interaction of OH (2-OH and 3-OH) is stronger than that of O-alkyl (4-O-acetal and 1-OMe) due to its electron richness derived from H-bonding with carboxylate.
- **TS1-(C3)a** (weaker cation-*n*) is more stable than **TS1-(C3)b** (stronger cation-*n*) due to the π-π interaction between Ph of benzylidene acetal and the catalyst.
- **TS1-(C3)a** and **TS1-(C3)b** is destabilized by steric repulsion between 1-OMe and the catalyst, yielding to suppression of 2-OH acylation.

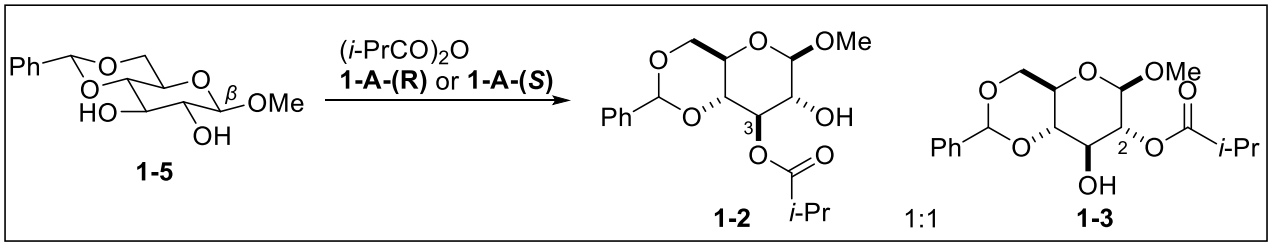
1-1-2. Acylation by **1-B-(*S*)**



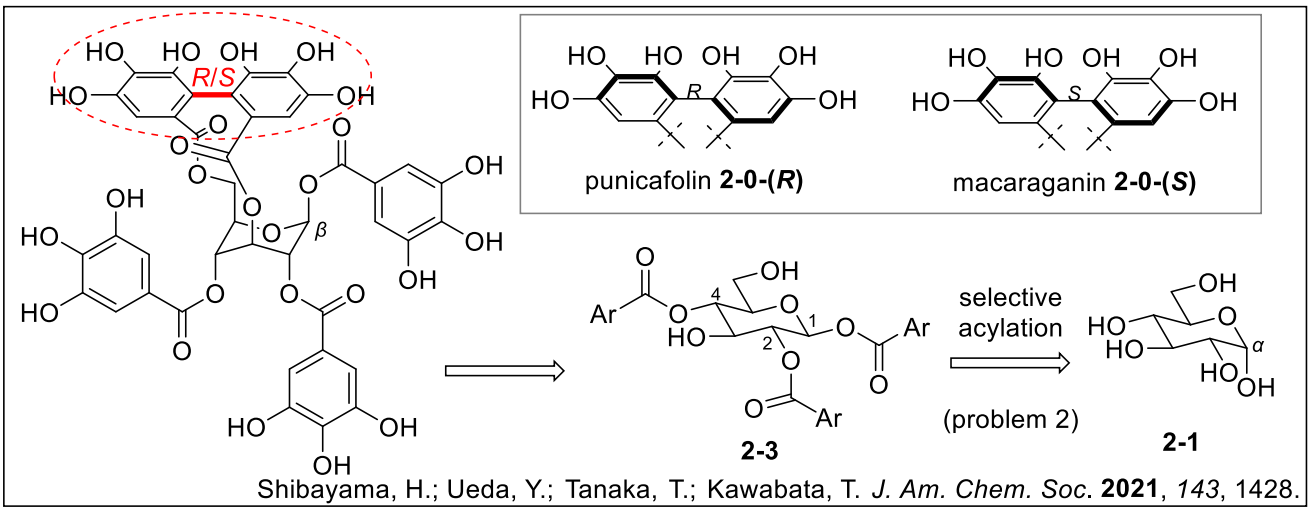
- **TS2-(C2)b** is most stable, yielding the high selectivity of 2-OH acylation.
- **TS2-(C3)b** and **TS2-(C2)a** is destabilized by steric repulsion between 1-OMe and the catalyst.
- As is the case with acylation by **1-B-(*R*)**, **TS2-(C3)a** (weaker cation-*n*) is stabilized by π-π interaction but still less stable than **TS2-(C2)a**.
- Probably, the order of the factor for stabilizing the TS of acylation by **1-A** is

  steric repulsion (1-OMe) > cation-*n* interaction ≥ π-π interaction

  In fact, the site-selectivity was completely lost in the acylation of β-anomer **1-5**.

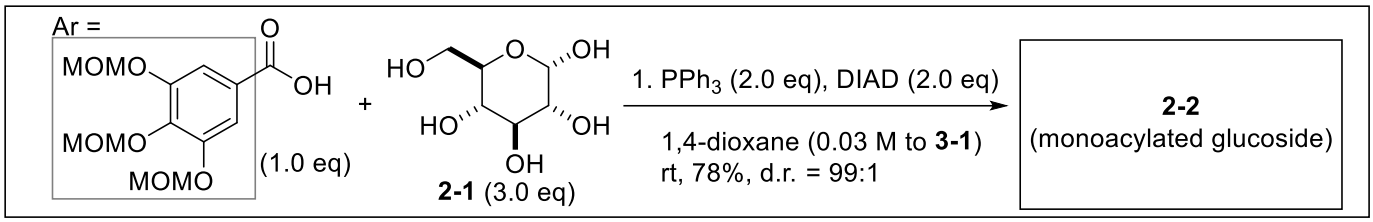


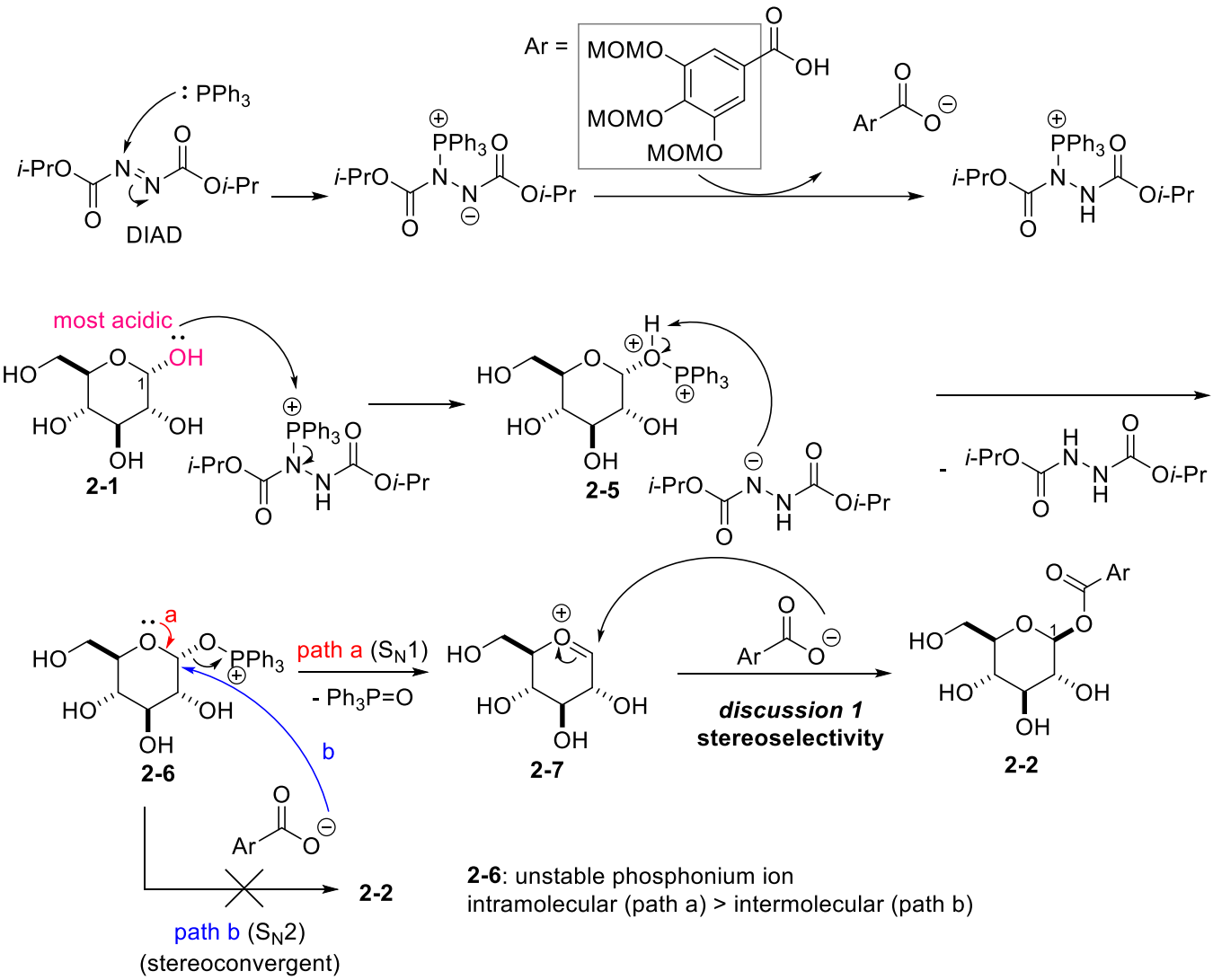
2. Problem 2



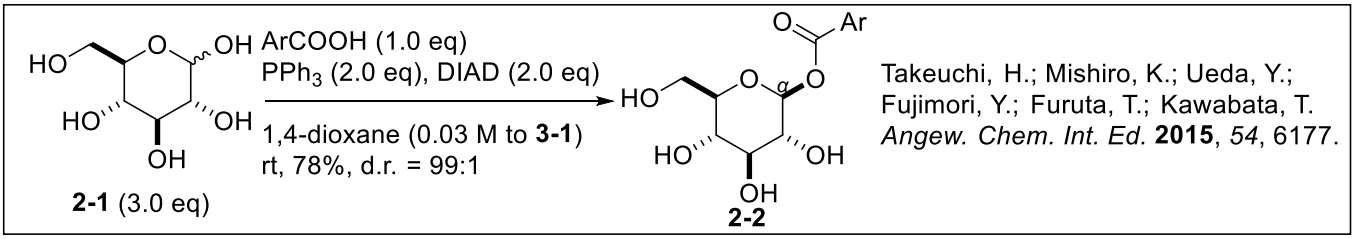
Shibayama, H.; Ueda, Y.; Tanaka, T.; Kawabata, T. *J. Am. Chem. Soc.* **2021**, *143*, 1428.

2-1. answer for step 1

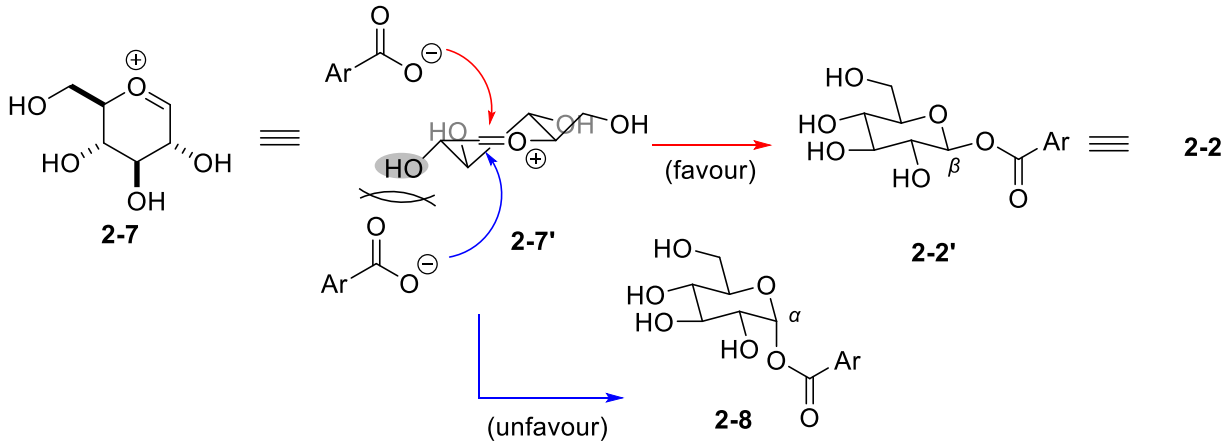




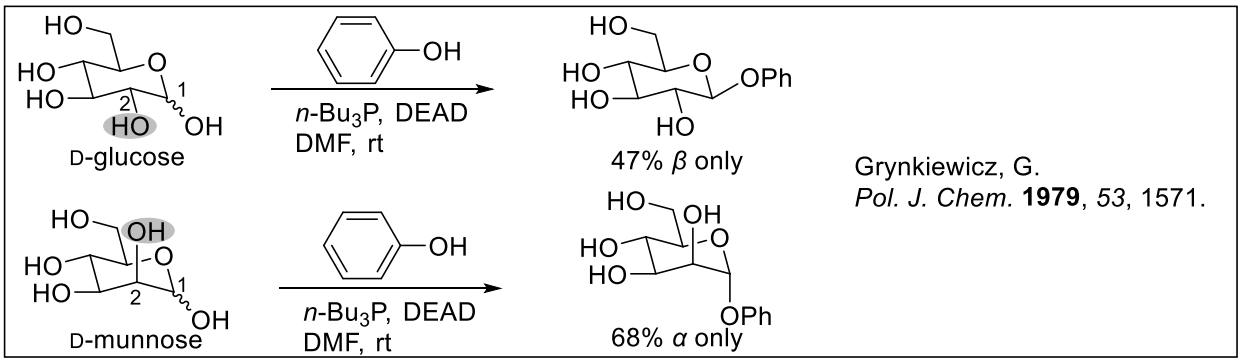
e.g. The yield and stereoselectivity was not affected when mixture of *α*- and *β*-D-glucose was used.



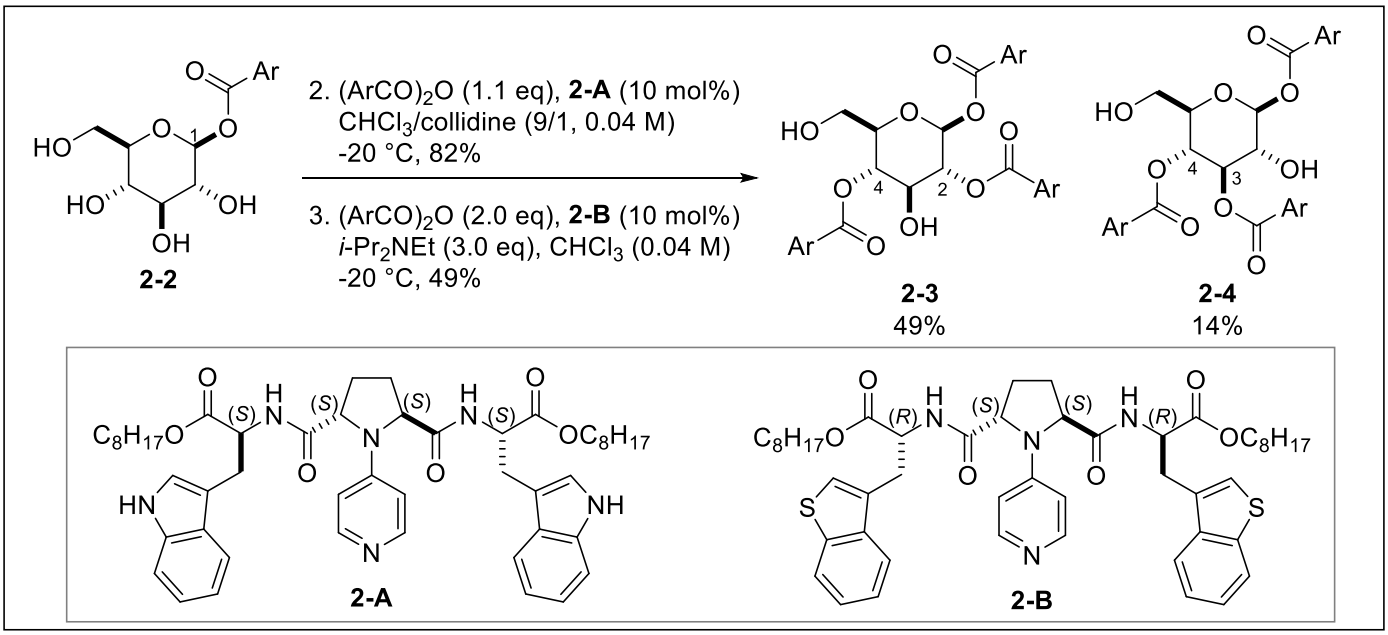
discussion 1. Stereoselectivity

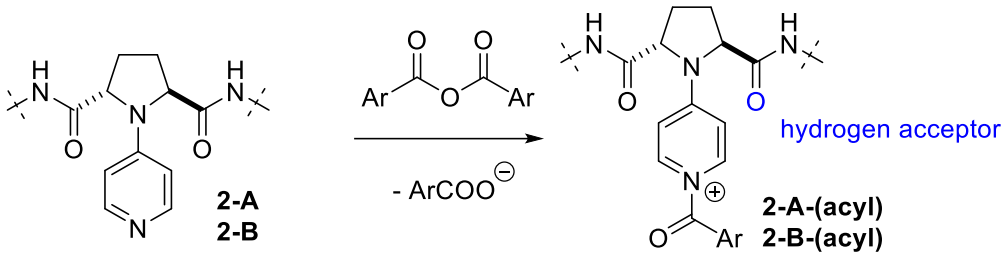


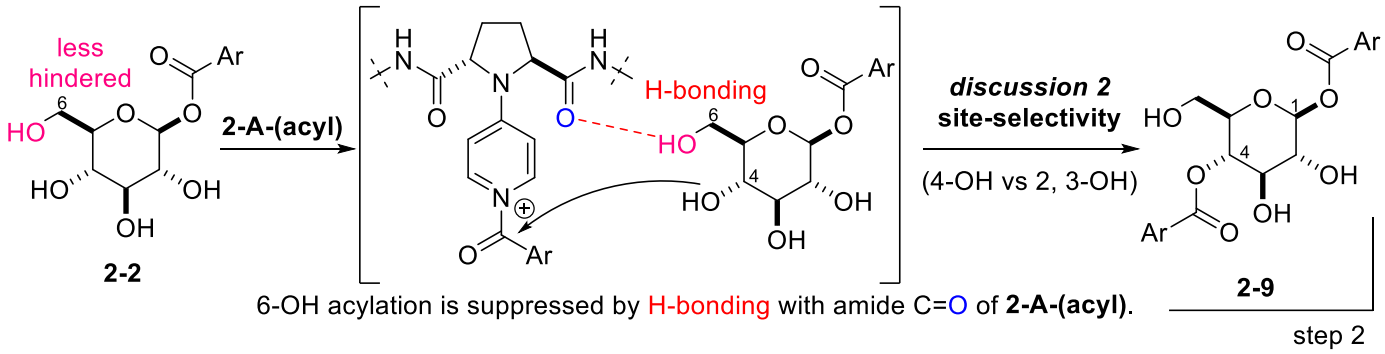
- The stereoselectivity was significantly affected by the stereochemistry of 2-OH.

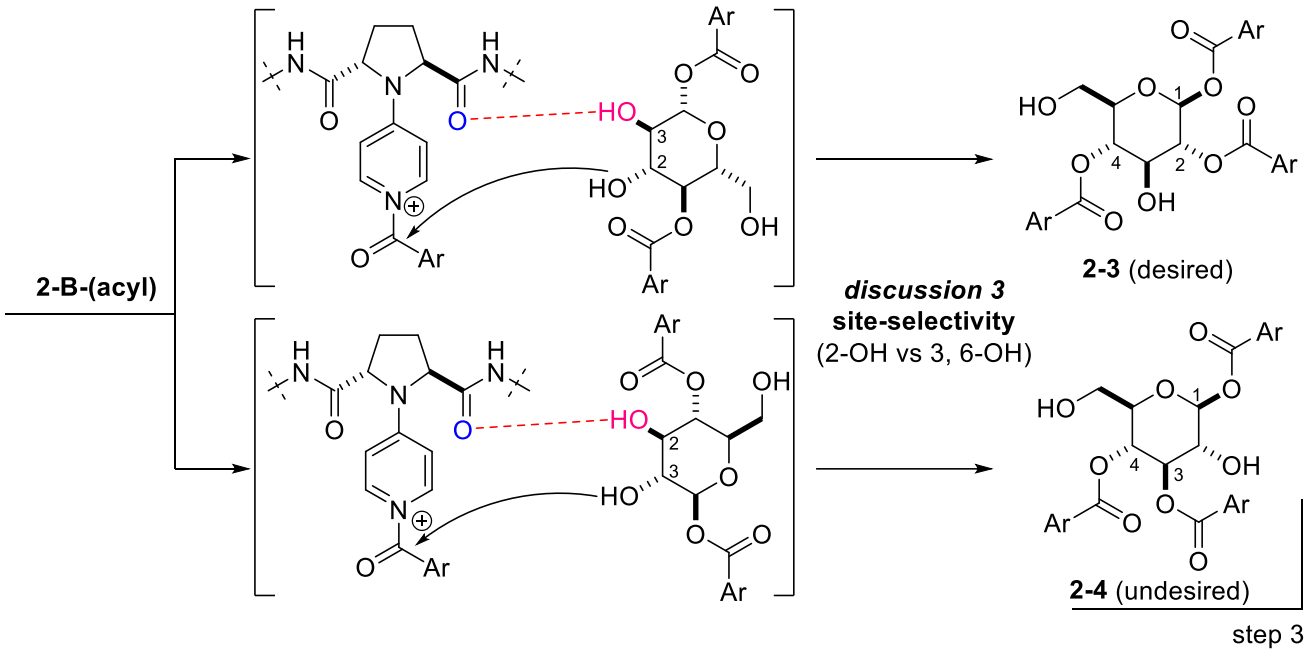


2-2. answer for step 2 and 3



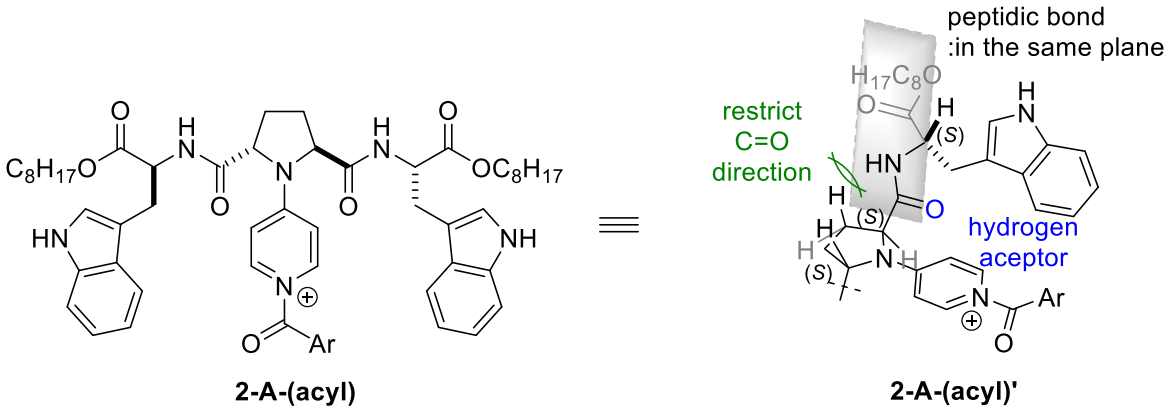


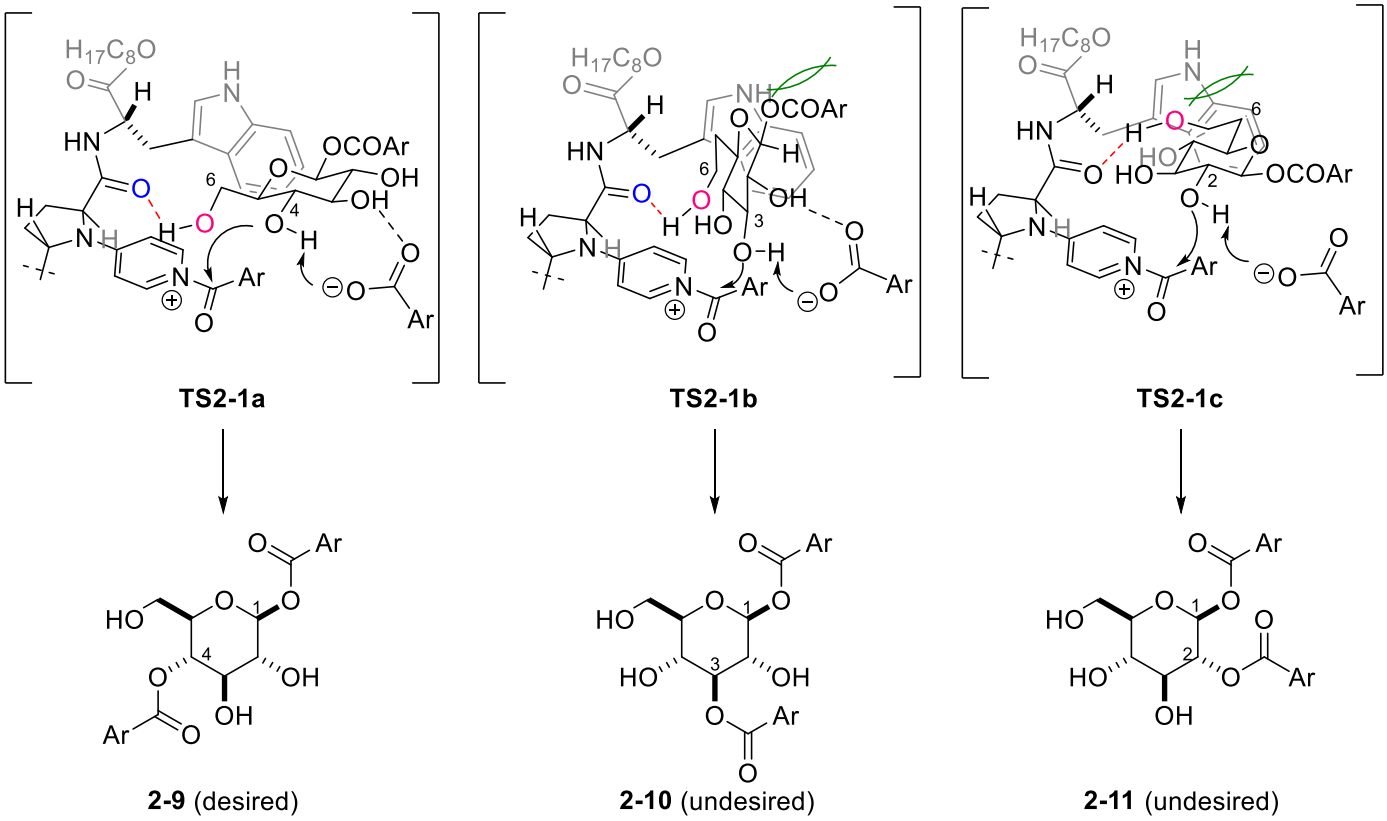




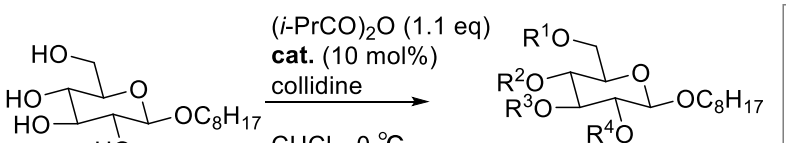
Discussion 2. 4-OH selective acylation by **2-A**

2-1. Transition states for the products

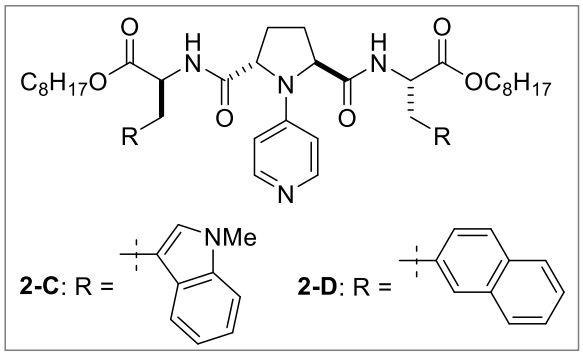




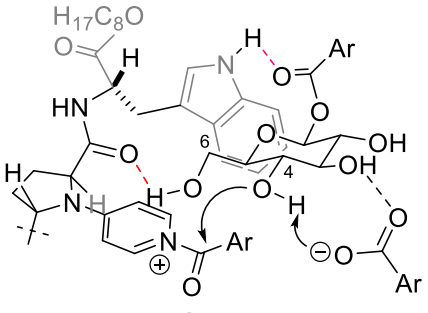
2-2. Effect of indole at the side chain of **2-A**



cat.	6-O	4-O	3-O	2-O
DMAP	20%	15%	26%	0%
2-A	0%	95%	2%	0%
2-C	10%	41%	18%	0%
2-D	5%	48%	21%	0%



Kawabata, T.; Muramatsu, W.; Nishio, T.; Shibata, T.; Schedel, H. *J. Am. Chem. Soc.* **2007**, *129*, 12890.

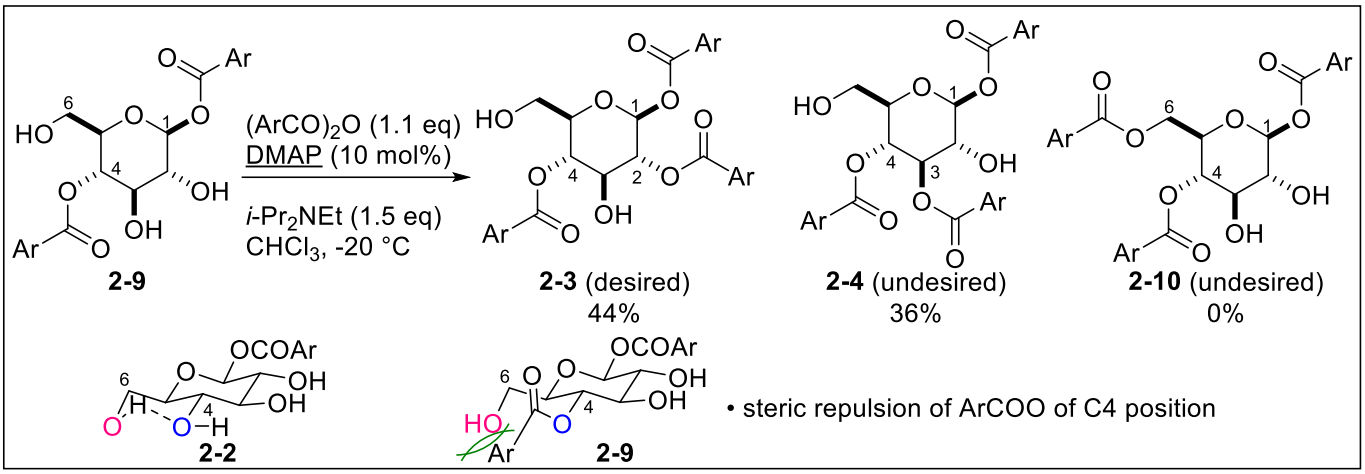


role of indole
○ H-donar (vs **2-C**)
× CH-π interaction (vs **2-D**)

possible H-bonding between indole NH and O atom of **2-2** probably contributes to stabilization of TS.

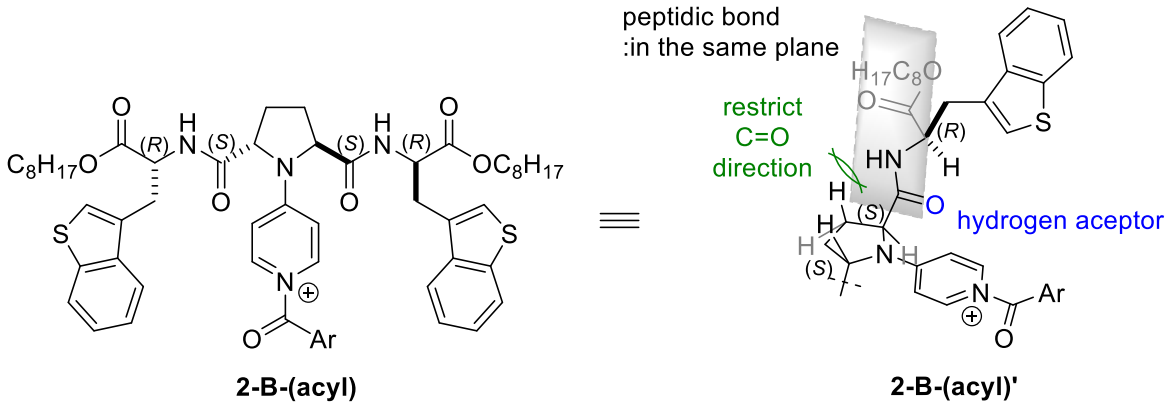
Discussion 3. 2-OH selective acylation by **2-B**

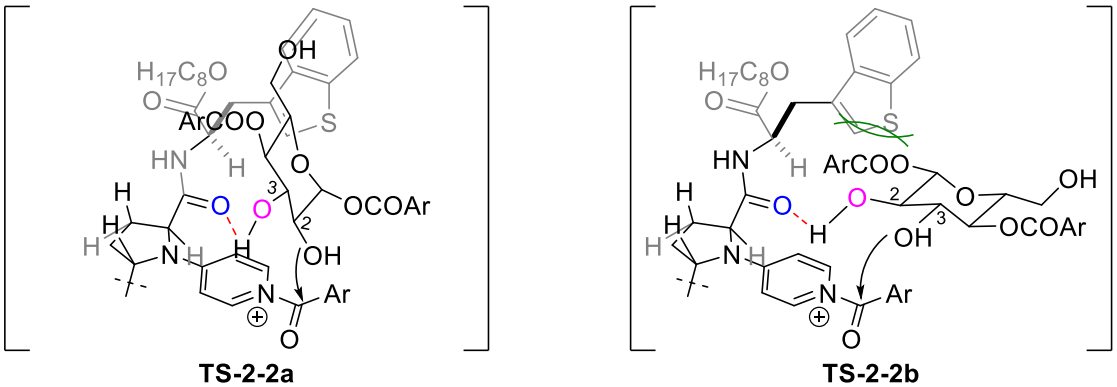
3-1. decreasing reactivity of 6-OH



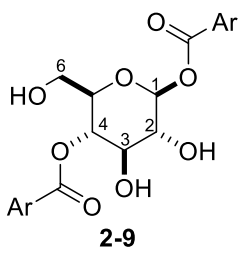
- The reactivity of 6-OH is decreased by modification of 4-OH, indicating that 6-OH of **2-9** is less likely to form H-bond with amide carbonyl O atom the catalyst **2-B-(acyl)**.

3-2. Transition states for the products





3-3. Optimization of catalysts derived from **2-A**

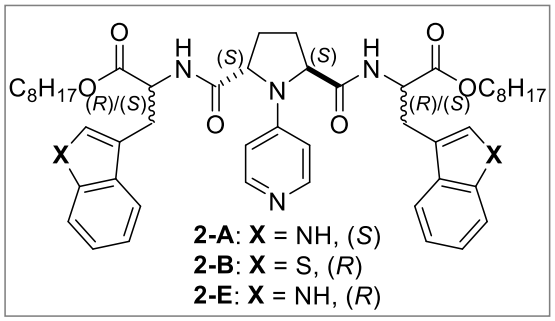


2-9

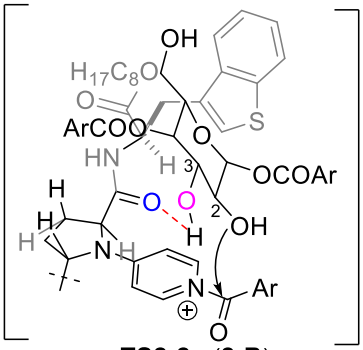
$(ArCO)_2O$ (1.1 eq)
cat. (10 mol%)
i-Pr_2NEt (1.5 eq)
$CHCl_3$, -20 °C

→ **2-3** (2-O-acyl) + **2-4** (2-O-acyl)

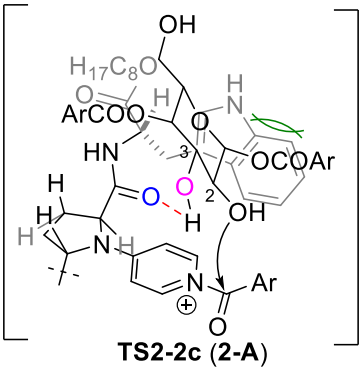
cat.	**2-3** (2-O-acyl)	**2-4** (2-O-acyl)
DMAP	44%	36%
2-A	32%	23%
2-E	23%	9%
2-B	42%	10%



2-A: **X** = NH, (*S*)
2-B: **X** = S, (*R*)
2-E: **X** = NH, (*R*)

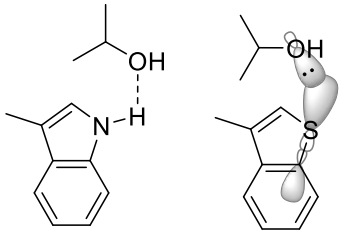


TS2-2a (**2-B**)



TS2-2c (**2-A**)

steric repulsion of indole and 2-O-acyl probably destabilizes the **TS2-2c**.



H-bond chalcogen bond

Recognition of substrates may be affected the slight difference of the angle.