Gold(I) Catalyzed β-Selective Glycosylation via 1,2-Sulfur Migration

2025.06.21. Literature Seminar

D3 Wataru Shigematsu

Contents

1. Introduction

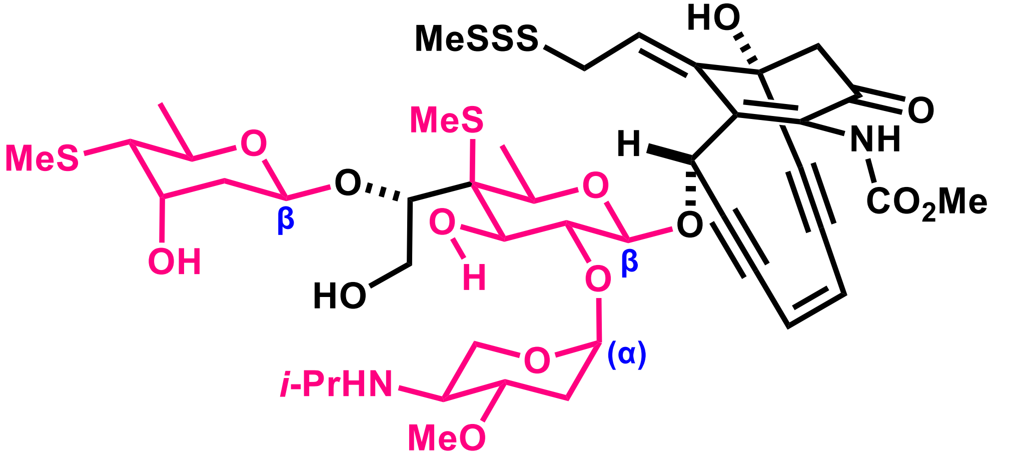
2. Gold(I)-Catalyzed 2-Deoxy-*β*-glycosylation

Contents

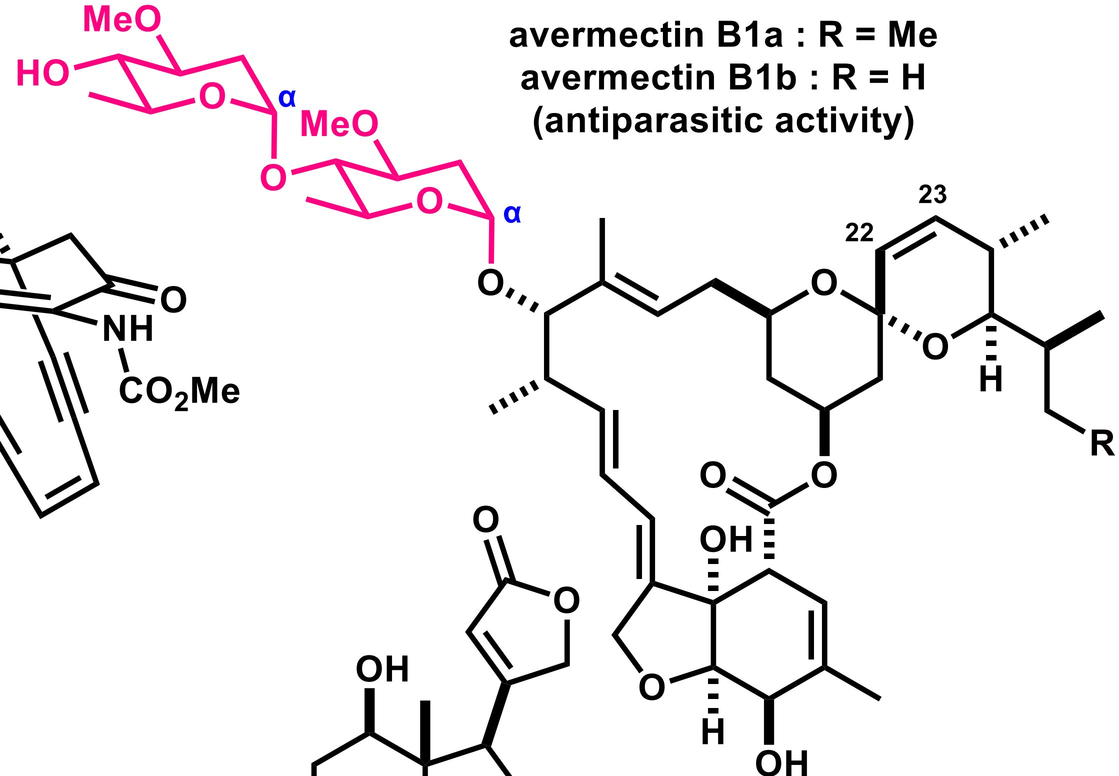
1. Introduction

2. Gold(I)-Catalyzed 2-Deoxy-*β*-glycosylation

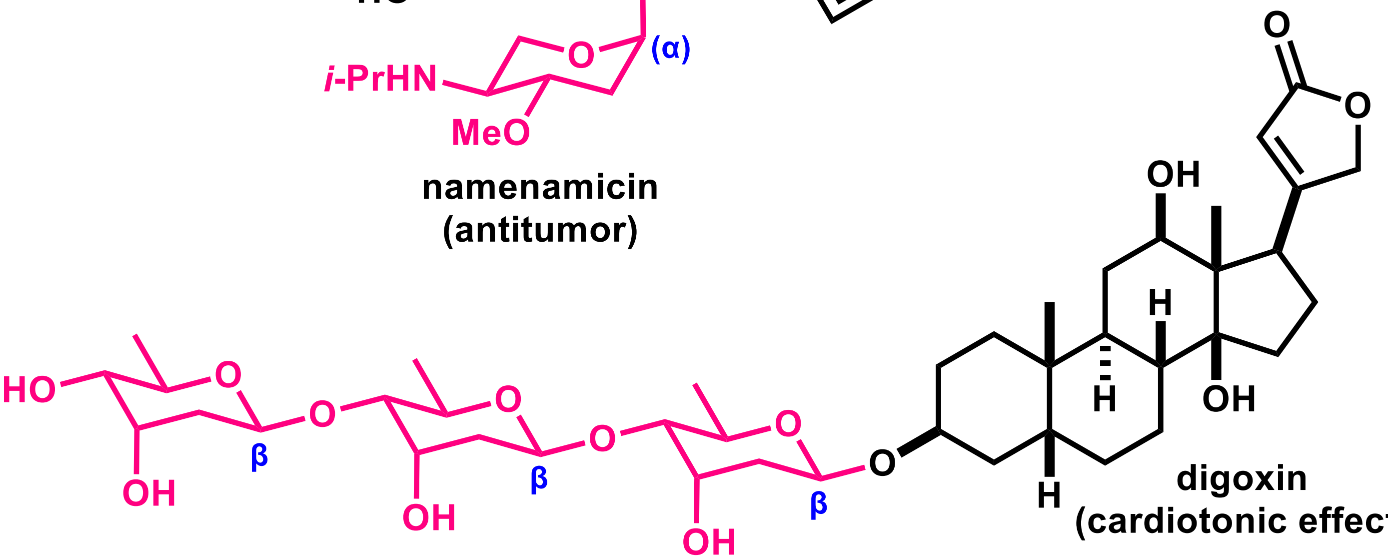
Glycosides in Natural Products



namenamicin
(antitumor)



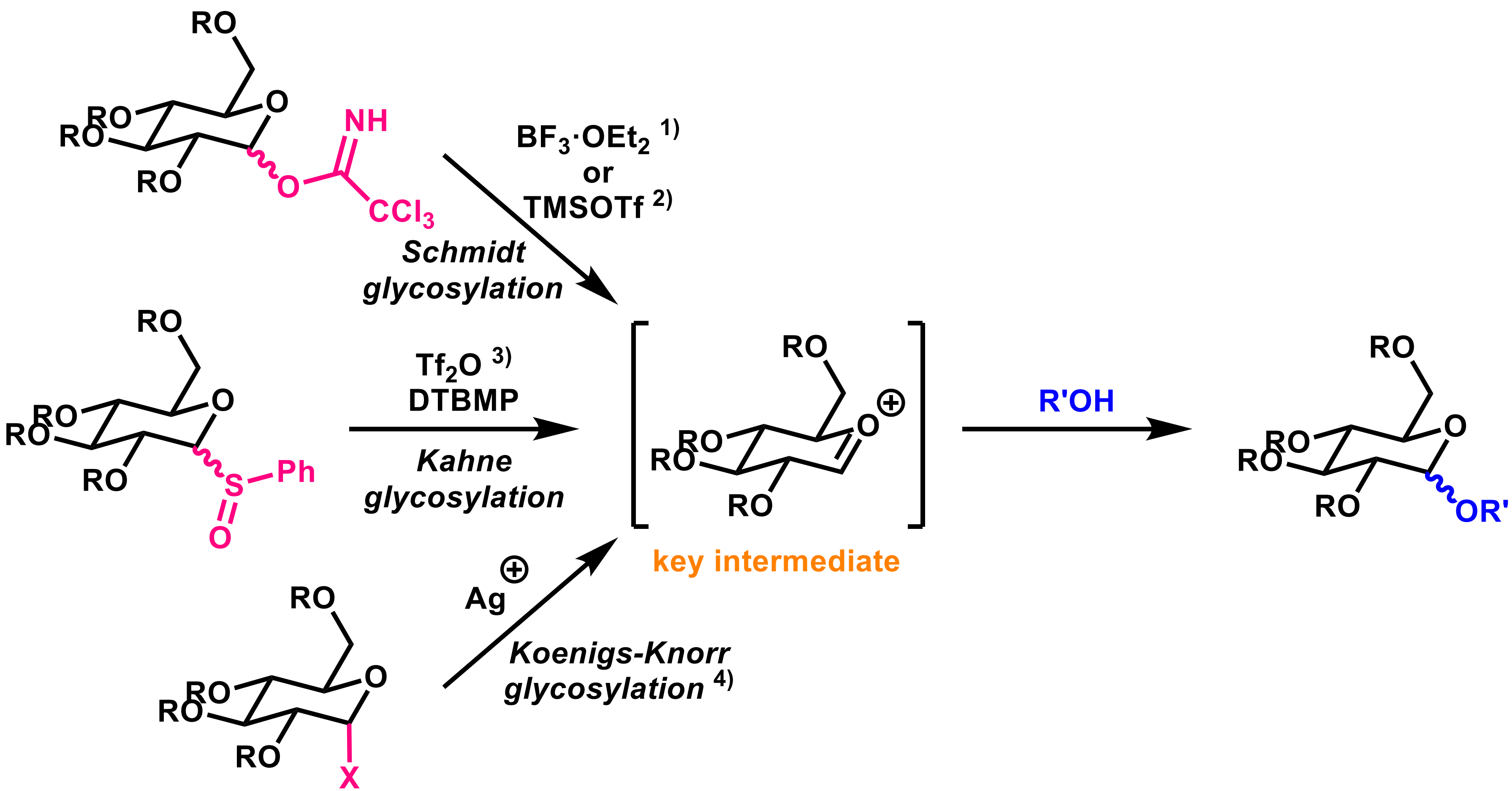
avermectin B1a : R = Me
avermectin B1b : R = H
(antiparasitic activity)



digoxin
(cardiotonic effect)

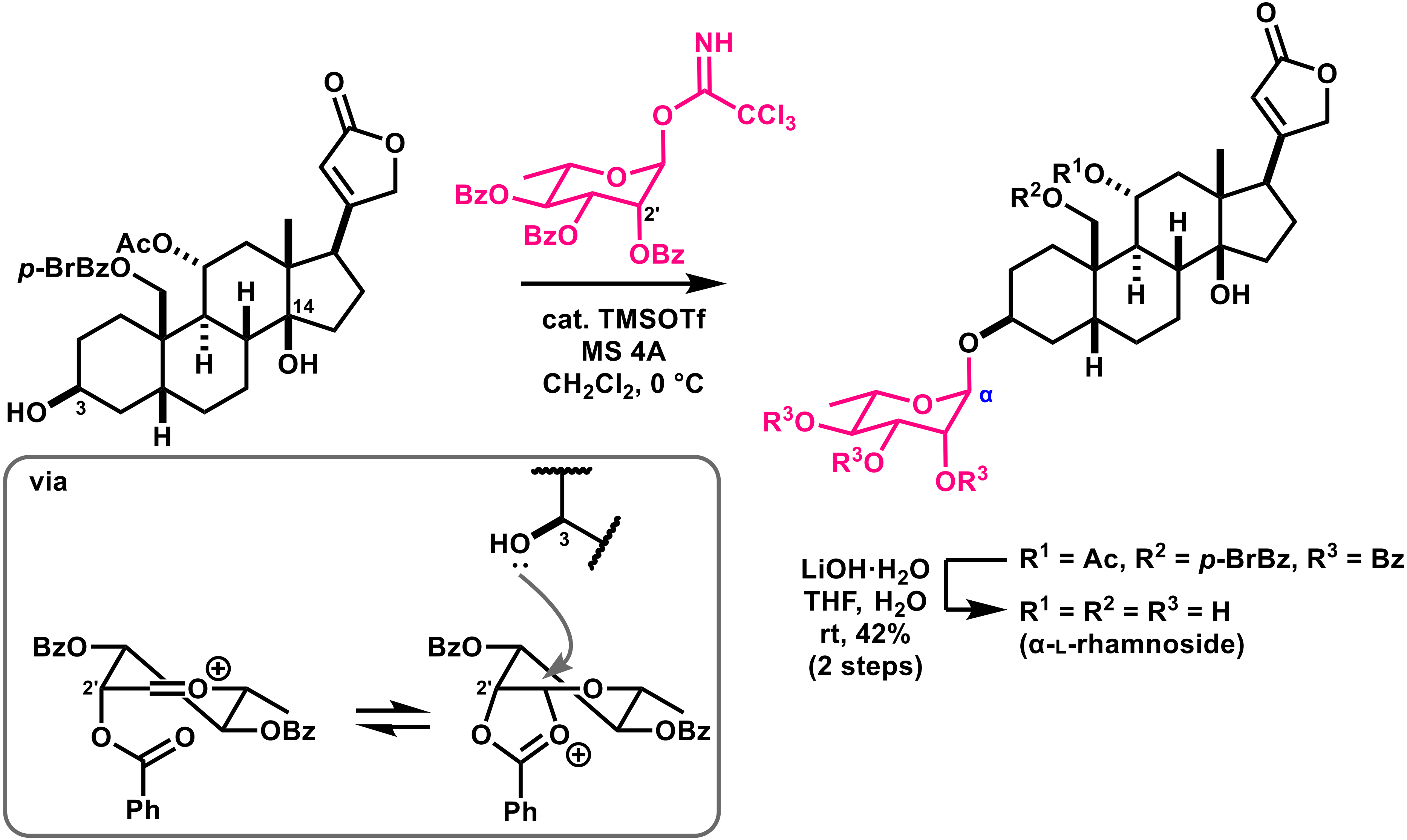
Total synthesis of avermectins : 1) Hanessian, S. et al. *Pure Appl. Chem.* **1987**, *59*, 299. 2) Ley, S. V. et al. *J. Chem. Soc., Perkin Trans.* **1991**, *1*, 667. 3) White, J. D. et al. *J. Am. Chem. Soc.* ***1995***, *117*, 1908. 4) Hirama, M. et al. *J. Antibiot.* **2016**, *69*, 31. 5) Danishefsky, S. J. et al. *J. Am. Chem. Soc.* ***1989***, *111*, 2967.
Total synthesis of namenamicin : 1) Nicolaou, K. C. et al. *J. Am. Chem. Soc.* **2018**, *140*, 8091.

Classical Glycosylation



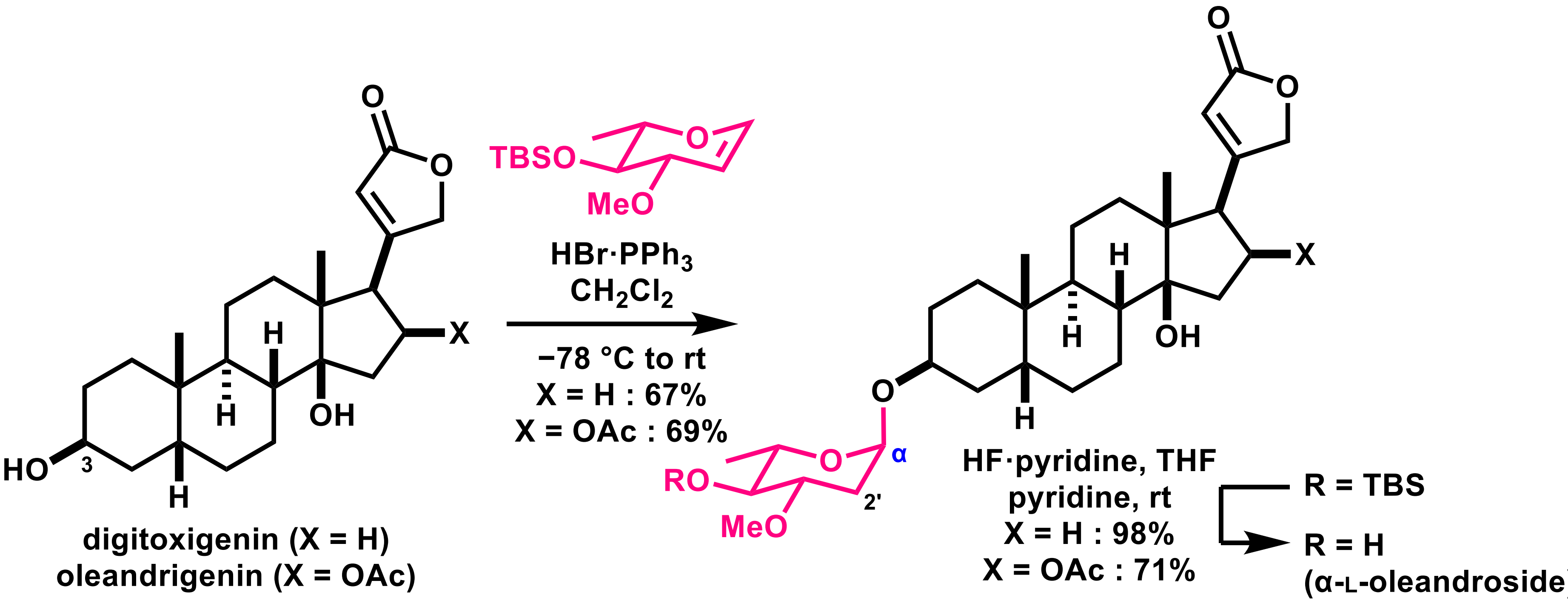
1) Schmidt, R. R., Michel, J. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 731.
2) Urabe, D.; Nakagawa, Y.; Mukai, K.; Fukushima, K.; Aoki, N.; Itoh, H.; Nagatomo, M.; Inoue, M. *J. Org. Chem.* **2018**, *83*, 13888.
3) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.
4) Koenigs, W.; Knorr, E. *Ber.* **1901**, *34*, 957.

α-Selective Glycosylation in Total Synthesis

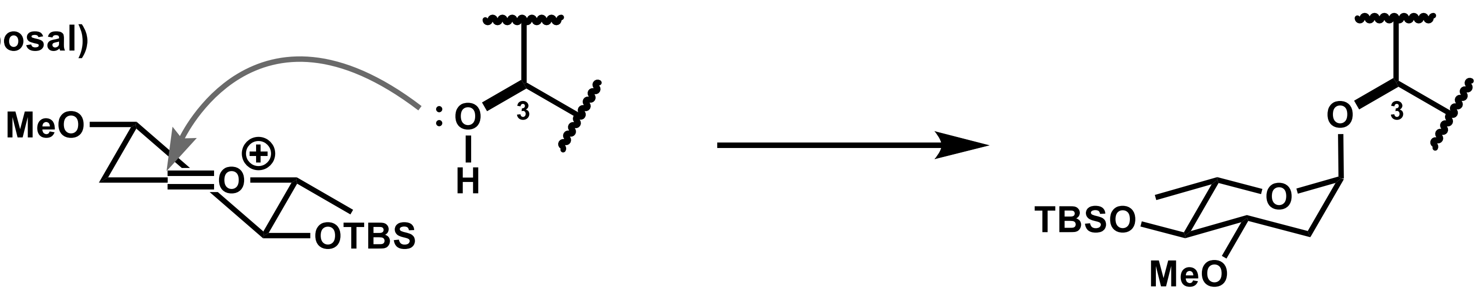


1) Urabe, D.; Nakagawa, Y.; Mukai, K.; Fukushima, K.; Aoki, N.; Itoh, H.; Nagatomo, M.; Inoue, M. *J. Org. Chem.* **2018**, *83*, 13888.

α-Selective Glycosylation in Total Synthesis

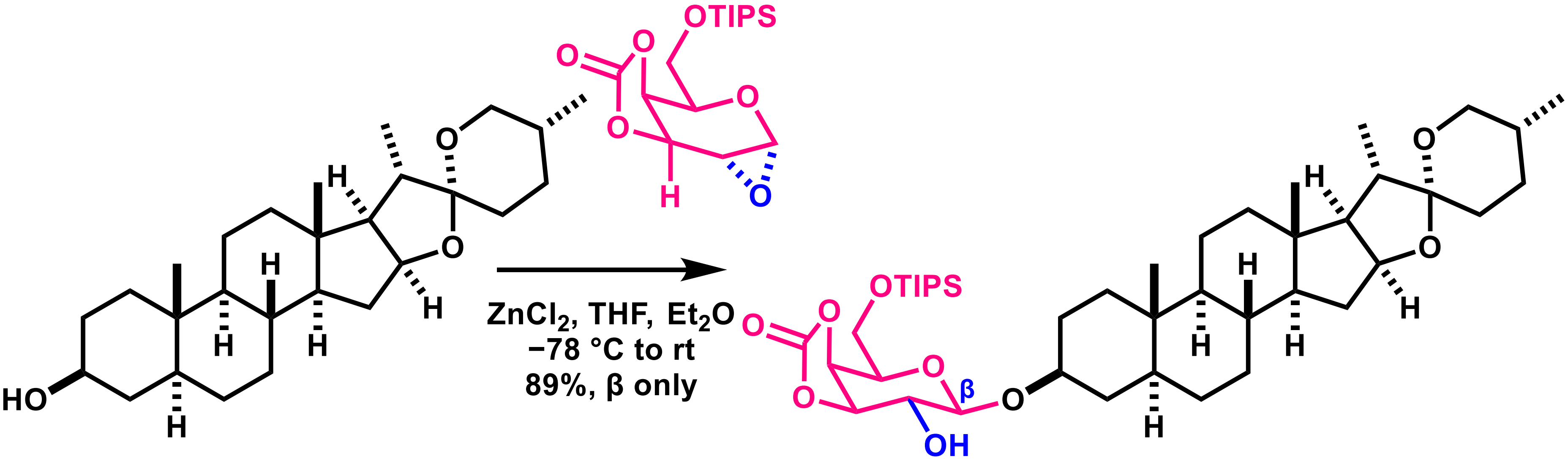


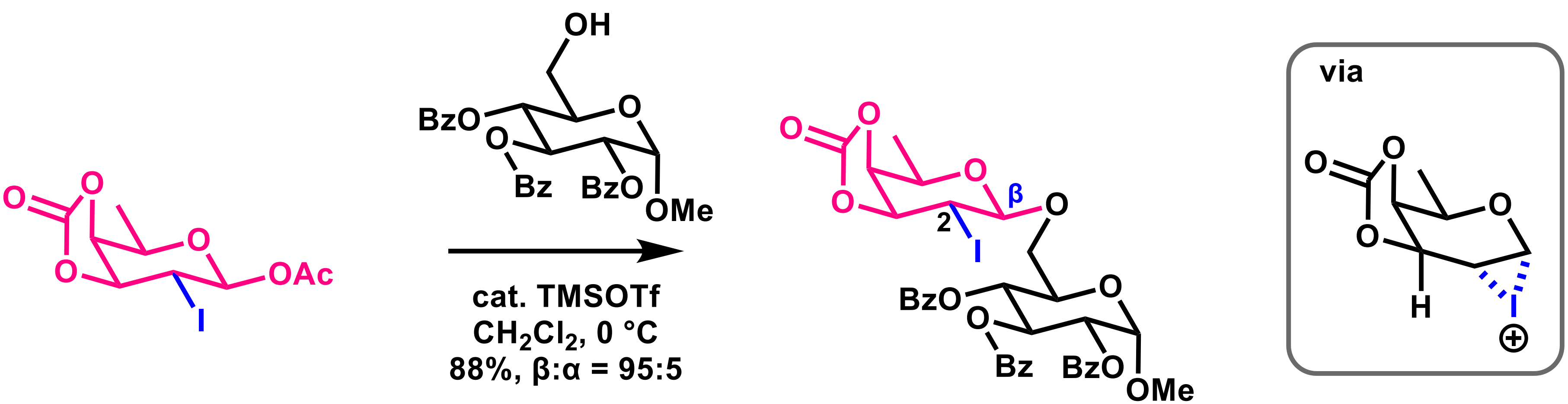
via (my proposal)



1) Carney, N.; Perry, N.; Garabedian, J.; Nagorny, P. *Org. Lett.* **2023**, *25*, 966.

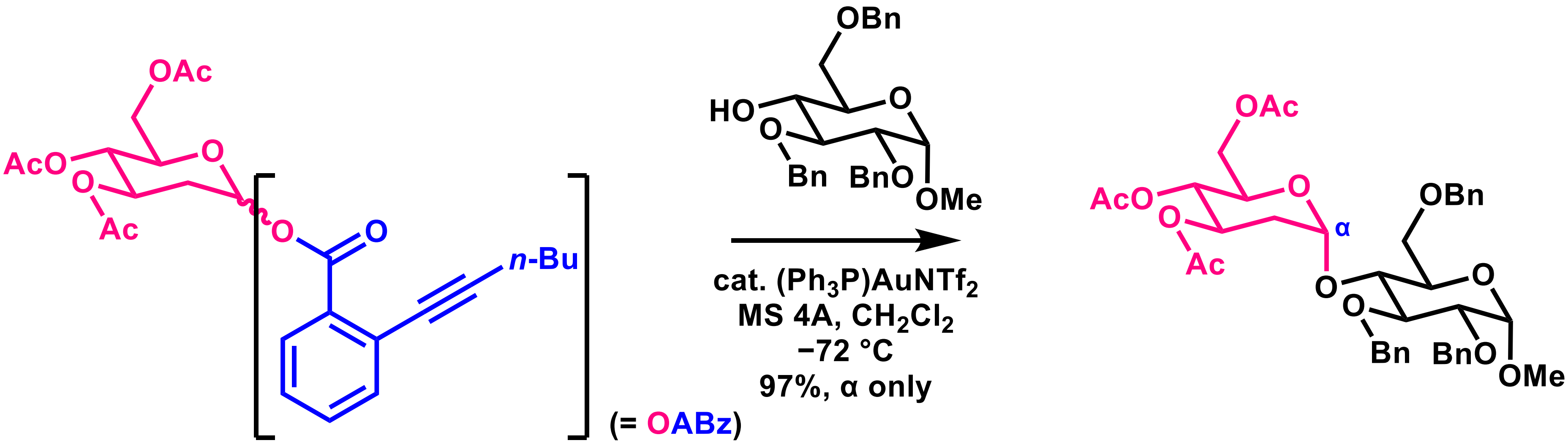
β-Selective Glycosylation

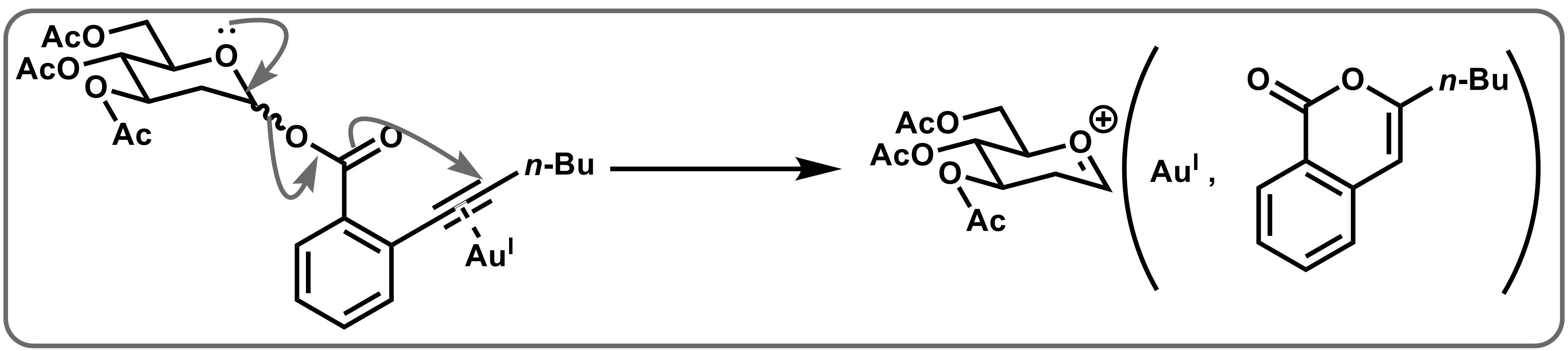




1) Randolph, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5693.
2) a) Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **1999**, *121*, 3541.
b) Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1871.

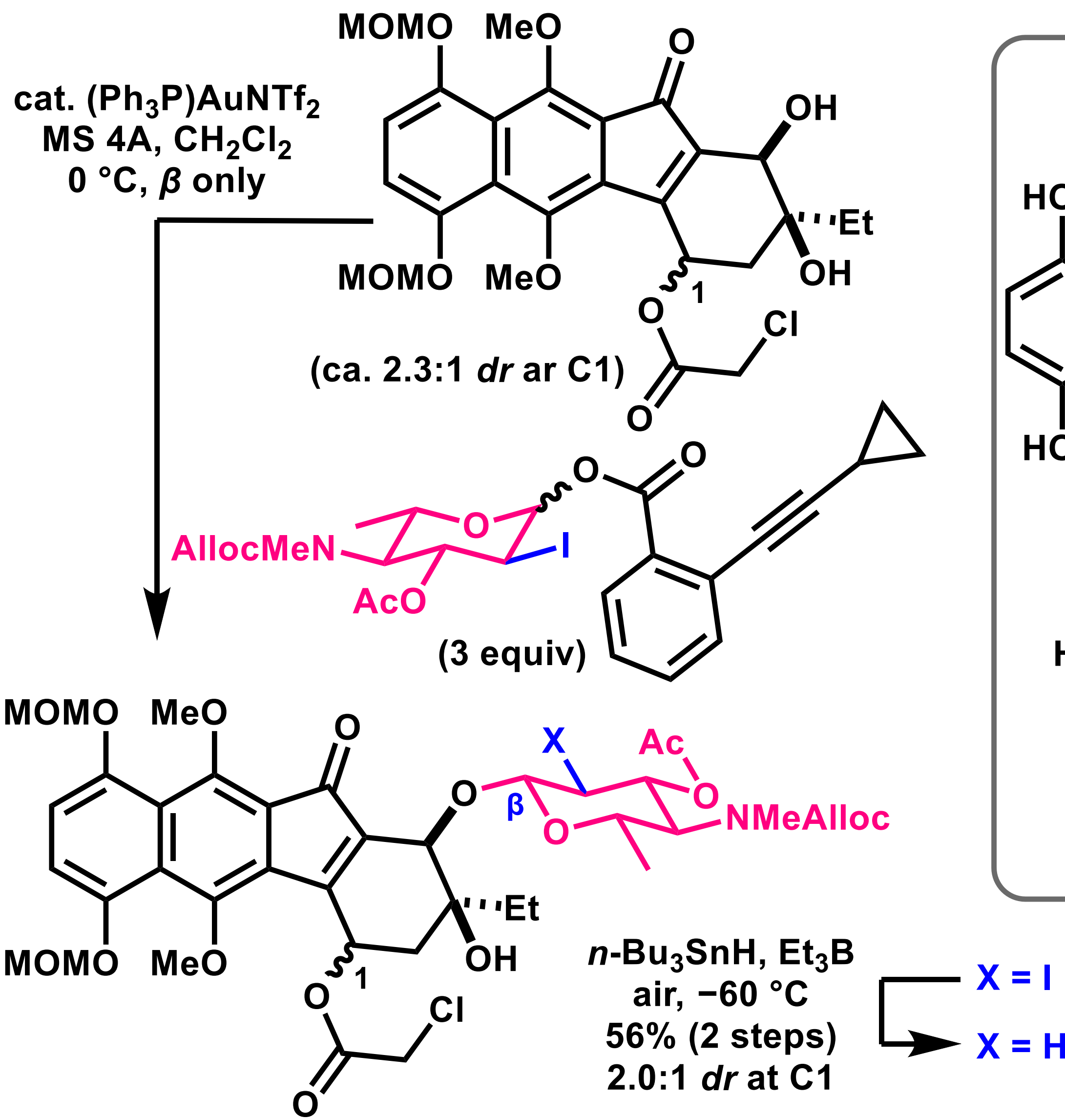
Au(I)-Catalyzed Glycosylation

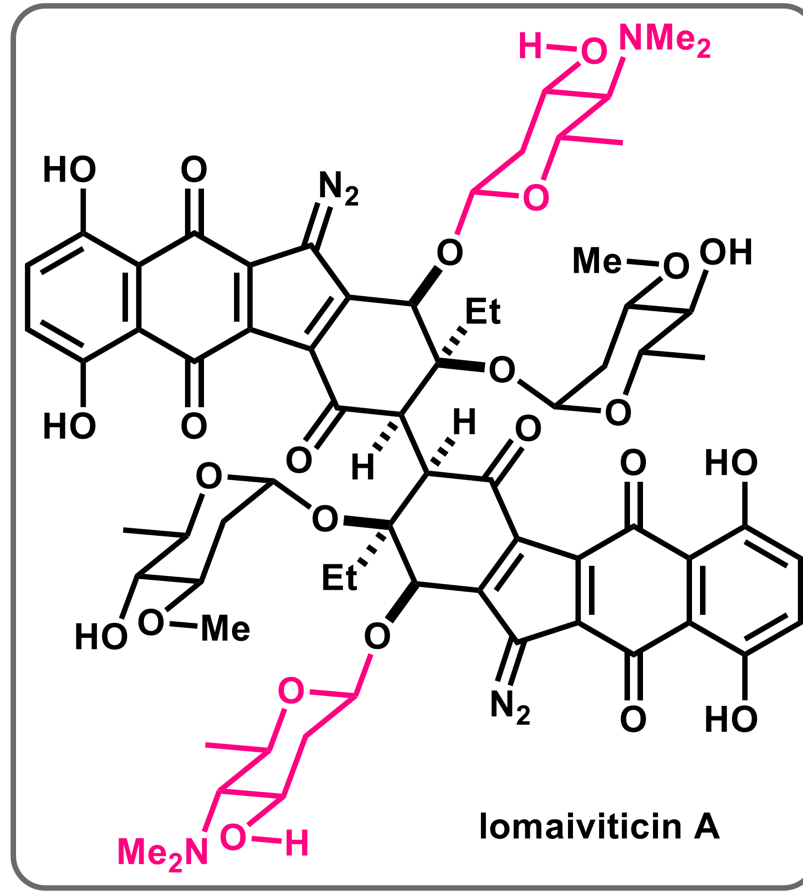




1) Li, Y.; Yang, X.; Liu, Y.; Zhu, C.; Yang, Y.; Yu, B. *Chem. Eur. J.* **2010**, *16*, 1871.

Au(I)-Catalyzed β-Glycosylation





1) Nicolaou, K. C.; Chen, Q.; Li, R.; Anami, Y.; Tsuchikawa, K. *J. Am. Chem. Soc.* **2020**, *142*, 20201.

Contents

1. Introduction

2. Gold(I)-Catalyzed 2-Deoxy-*β*-glycosylation

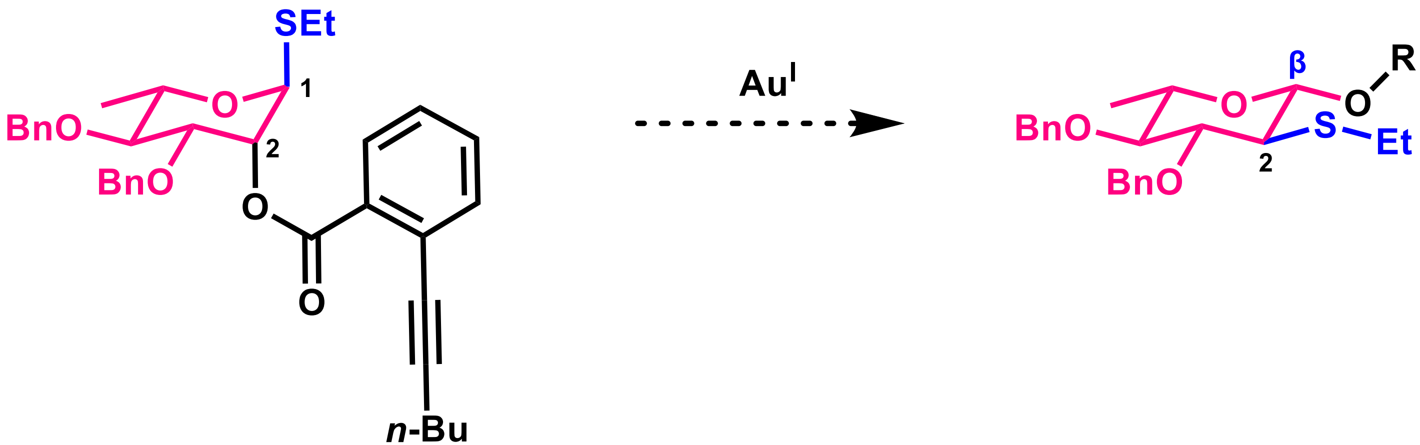
Prof. Liu Xue-wei

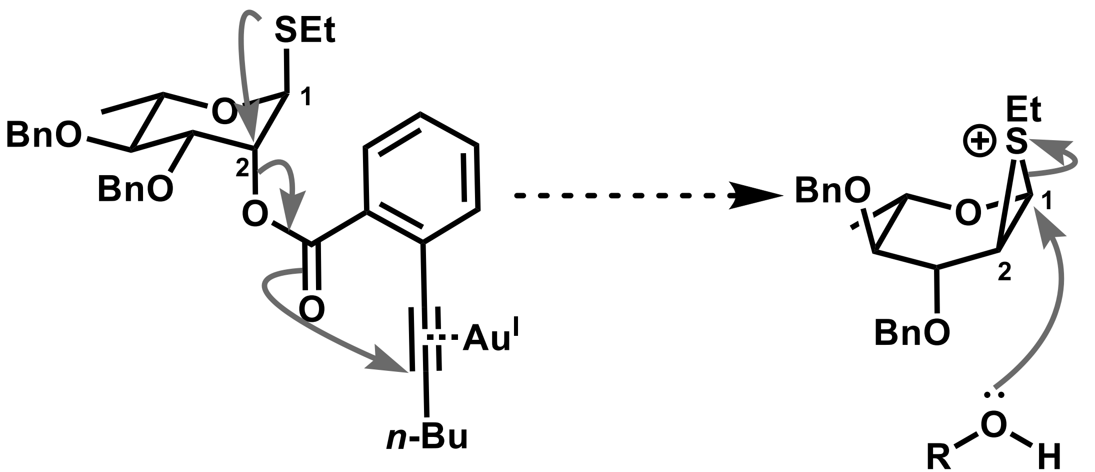
-1996 B.S. and M.S. @China Agricultural University
-2000 Ph.D. @University of Southern California
(Prof. Charles E. McKenna)
-2002 research scientist
@Proctor & Gamble Pharmaceuticals
-2003 senior research scientist
@Chugai Pharma USA
2003-2005
postdoc @California Institute of Technology
(Prof. Linda C. Hsieh–Wilson)
2005- assistant professor @Nanyang Technology University
2012- associate professor @Nanyang Technology University
2018- professor @Nanyang Technology University

Research Topics
- Carbohydrate Chemistry
- Chemical Glycobiology
- Natural Products, Food Chemistry, and Medicinal Chemistry

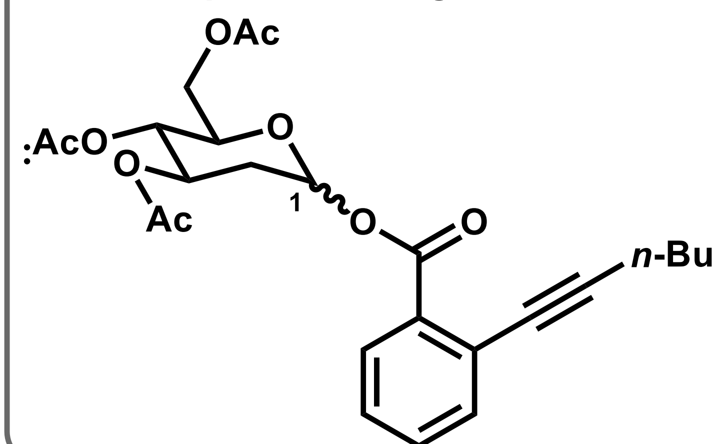
https://liuxuewei.wixsite.com/glycoscience

Hypothesis





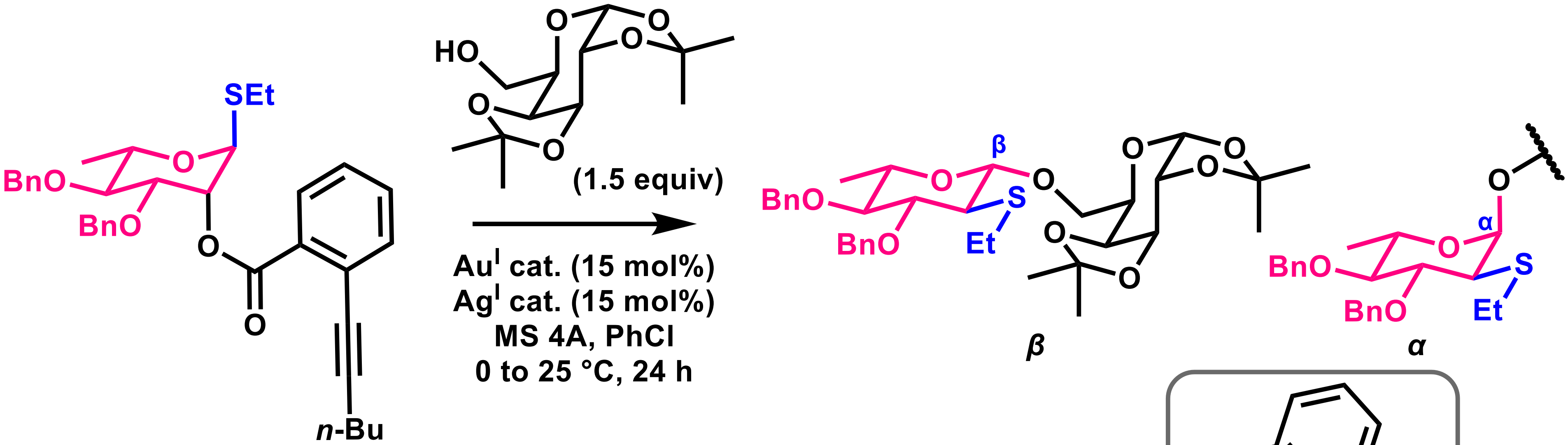
cf. Yu's previoius fragment [2)]



1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

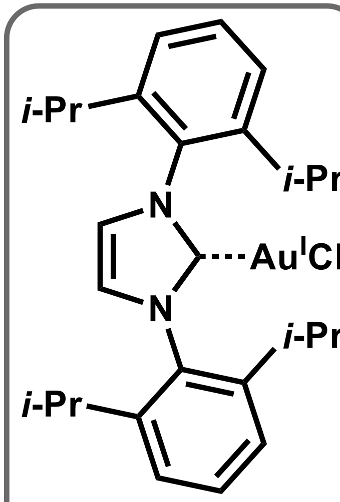
2) Li, Y.; Yang, X.; Liu, Y.; Zhu, C.; Yang, Y.; Yu, B. *Chem. Eur. J.* **2010**, *16*, 1871.

Glycosylation Using *o*-Alkynylbenzoate (ABz)



entry	Au^I cat.	Ag^I cat.	yields	*β* : *α*
1	$(Ph_3P)Au^ICl$	Ag^IOTf	trace	n.d.
2	$[(PhO)_3P]Au^ICl$	$Ag^IB(C_6F_5)_4$	82%	7.7 : 1
3[a)]	$[(PhO)_3P]Au^ICl$	Ag^INTf_2	90%	8.2 : 1
4	$IPrAu^ICl$	Ag^INTf_2	51%	9.1 : 1

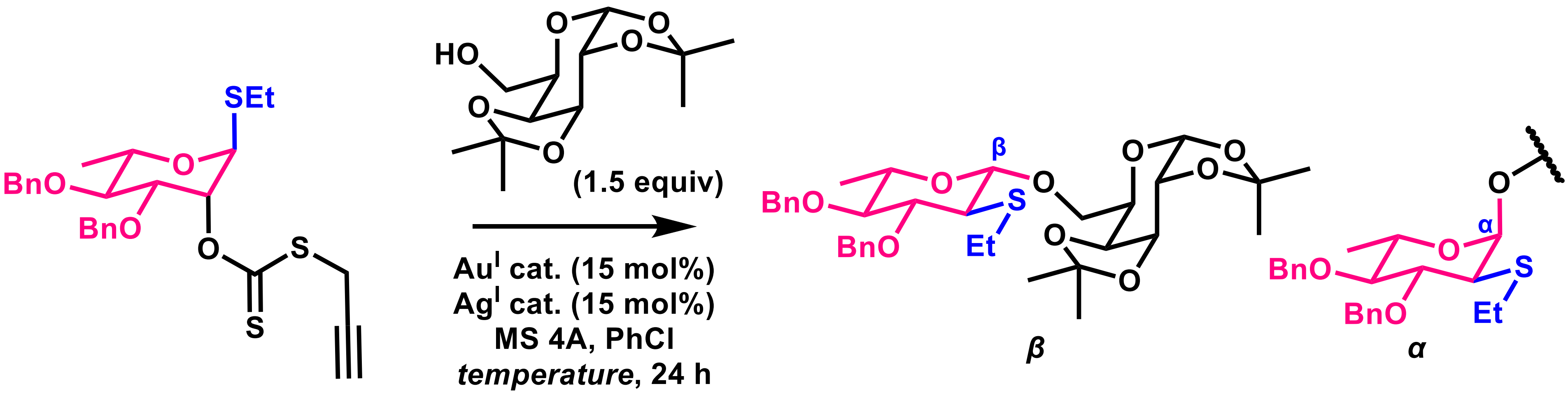
[a)] 2 h.



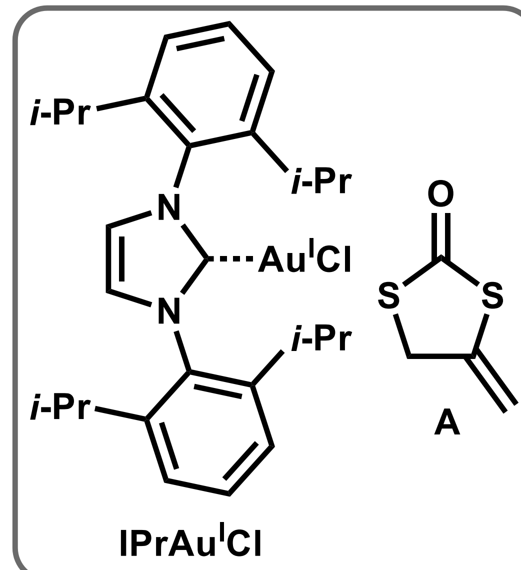
$IPrAu^ICl$

1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

Glycosylation Using *S*-Propargyl Xanthate (SPX)



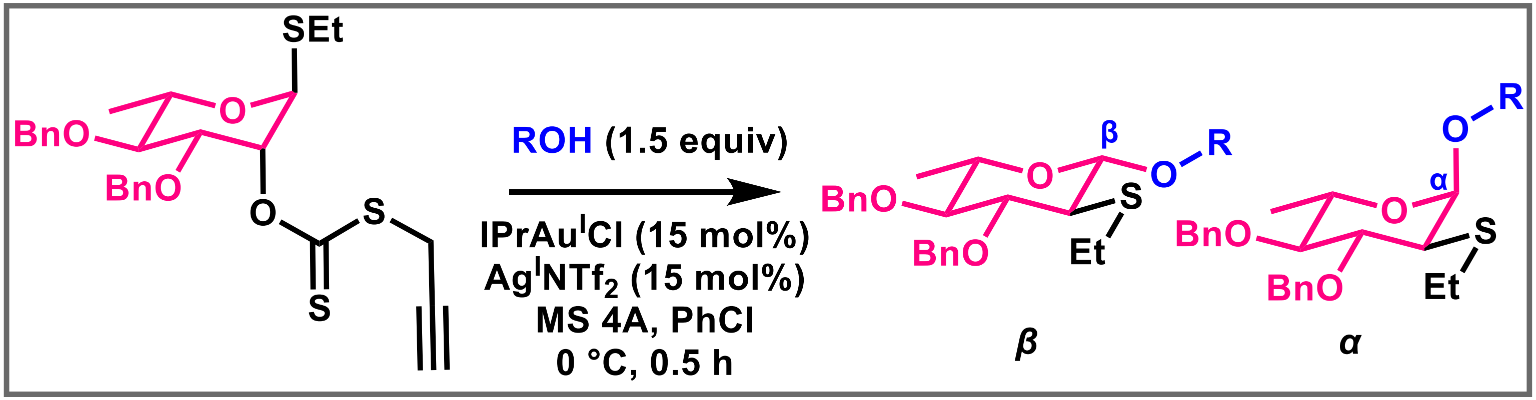
entry	Au[I] cat.	Ag[I] cat.	*temperature*	yields	β : α
1[a)]	$[(PhO)_3P]Au^ICl$	$Ag^IB(C_6F_5)_4$	0 to 25 °C	59%	6.7 : 1
2	$IPrAu^ICl$	Ag^INTf_2	25 °C	96%	6.3 : 1
3	$IPrAu^ICl$	Ag^INTf_2	16 °C	94%	10.0 : 1
4[a)]	$IPrAu^ICl$	Ag^INTf_2	0 °C	98%	14.3 : 1
5[b)]	$IPrAu^ICl$	Ag^INTf_2	−40 °C	80%	16.7 : 1
6[c)]	none	Ag^INTf_2	0 to 25 °C	12%	6.0 : 1

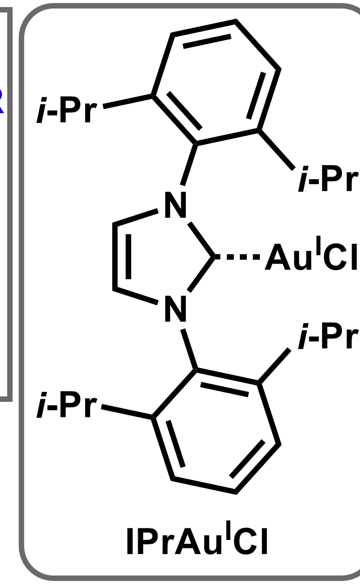


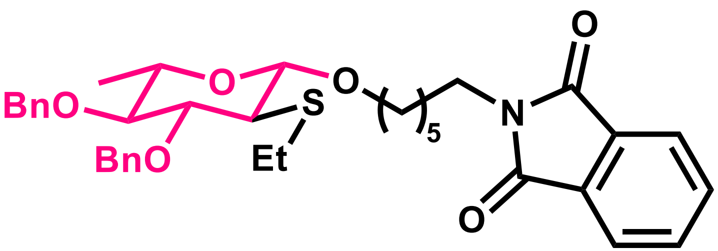
a) A : 92%. b) 24 h. c) 18 h.

1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

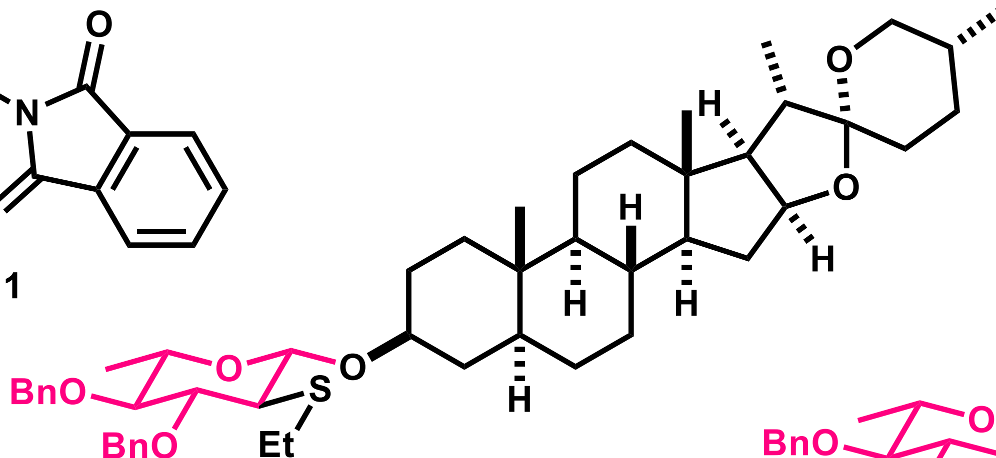
Acceptor Scope



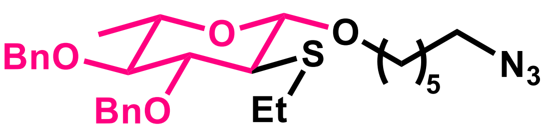




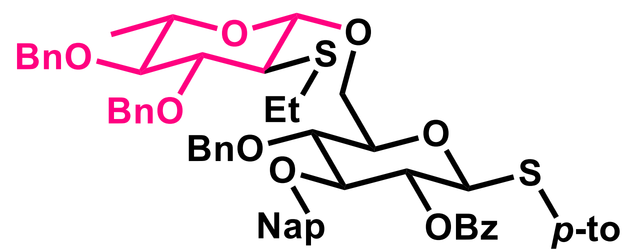
94%, β:α = 10.0:1



89%, β:α = 16.7:1



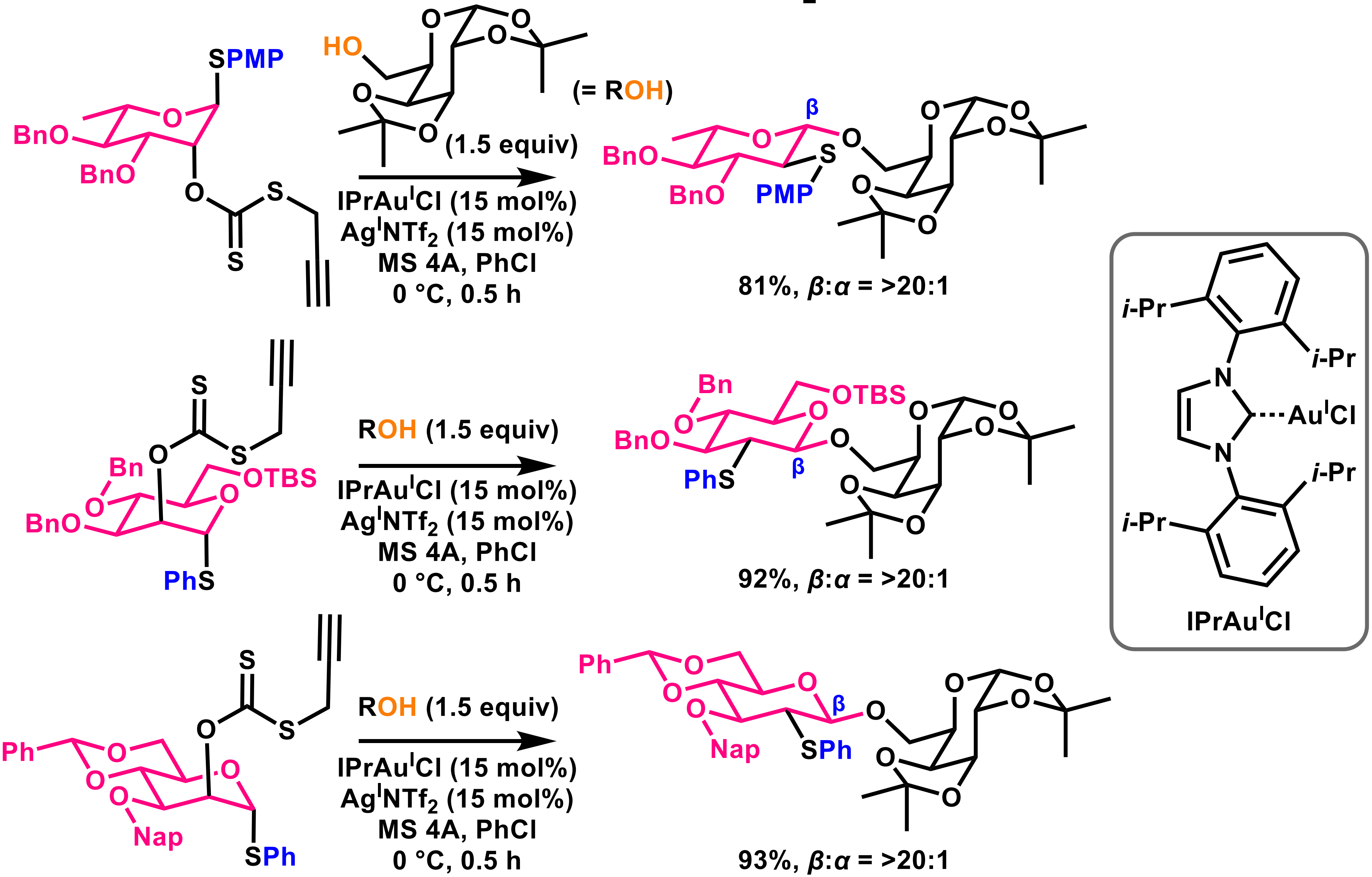
95%, β:α = 14.3:1



88%, β only

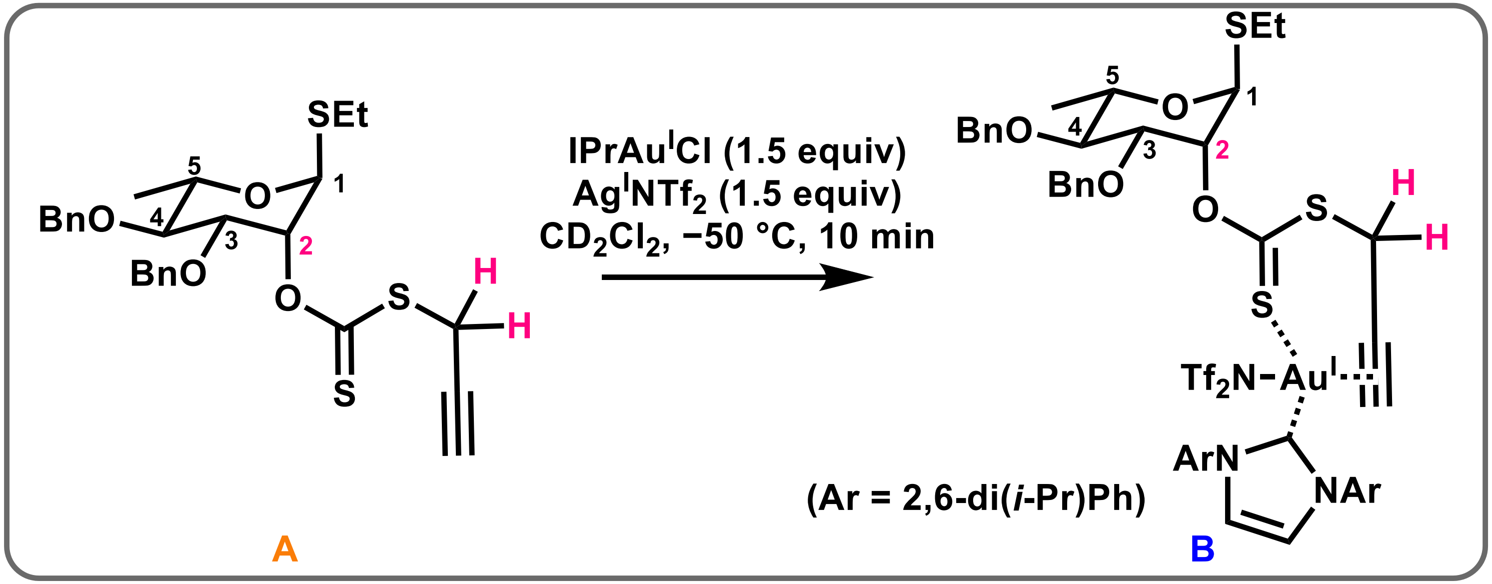
1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

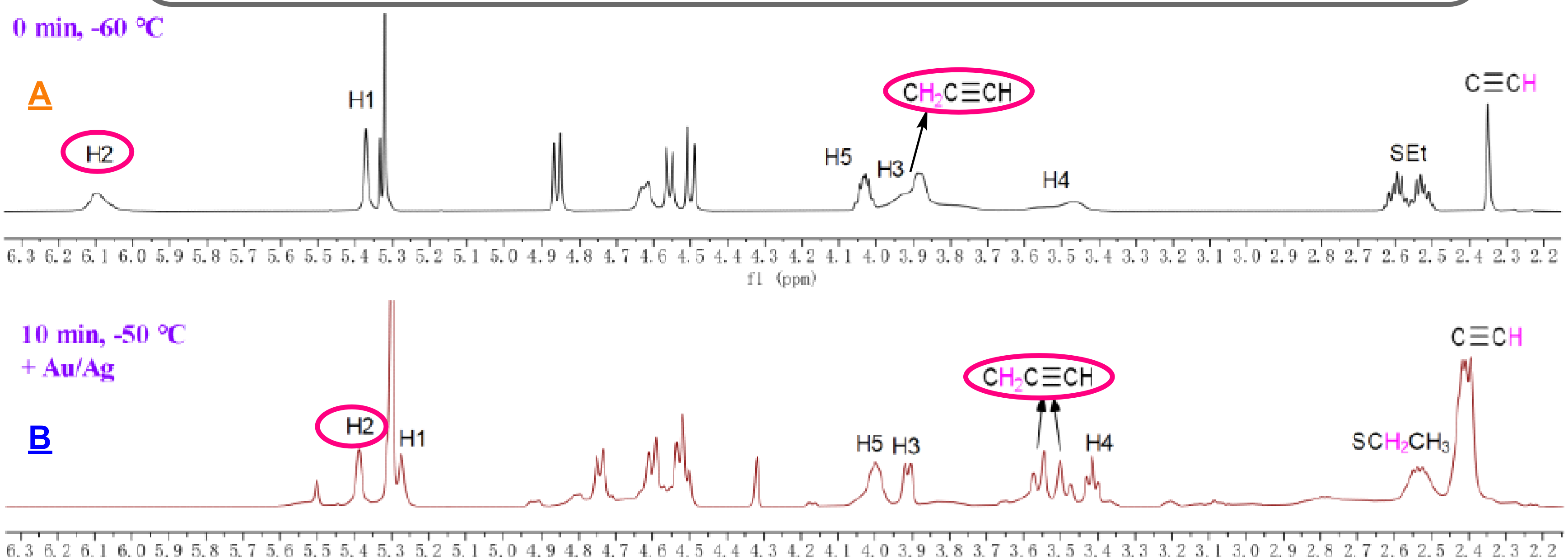
Donor Scope



1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

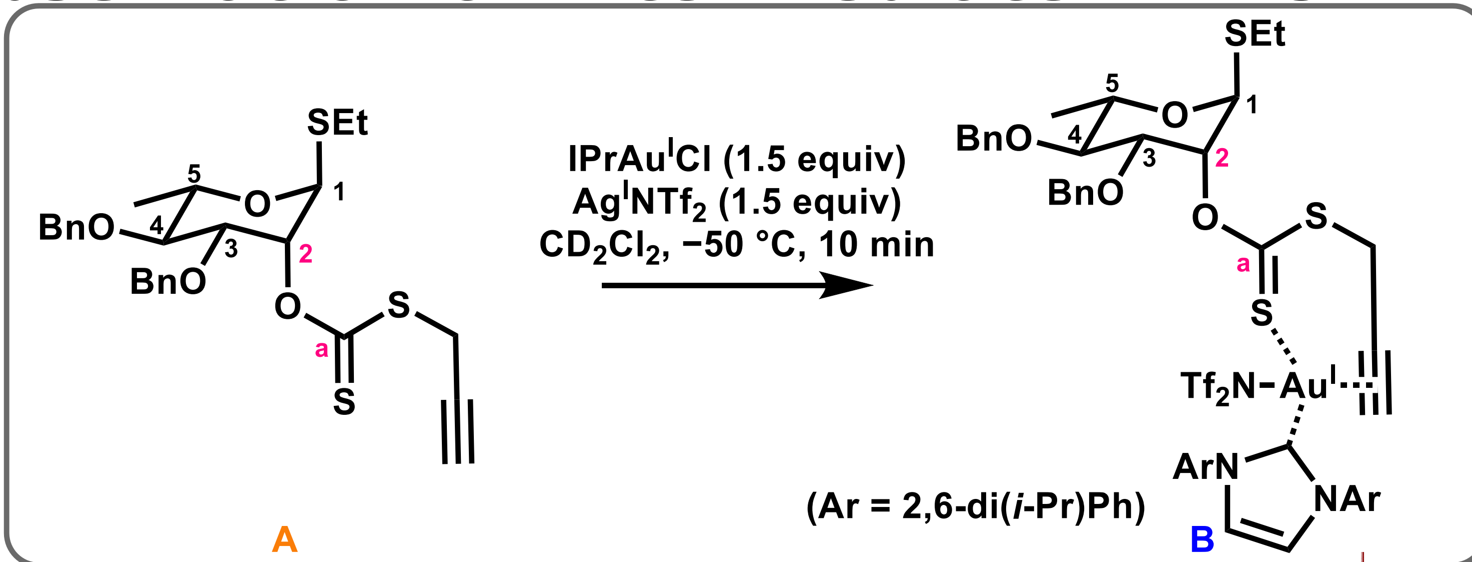
Observation of Intermediate in ^{1}H NMR

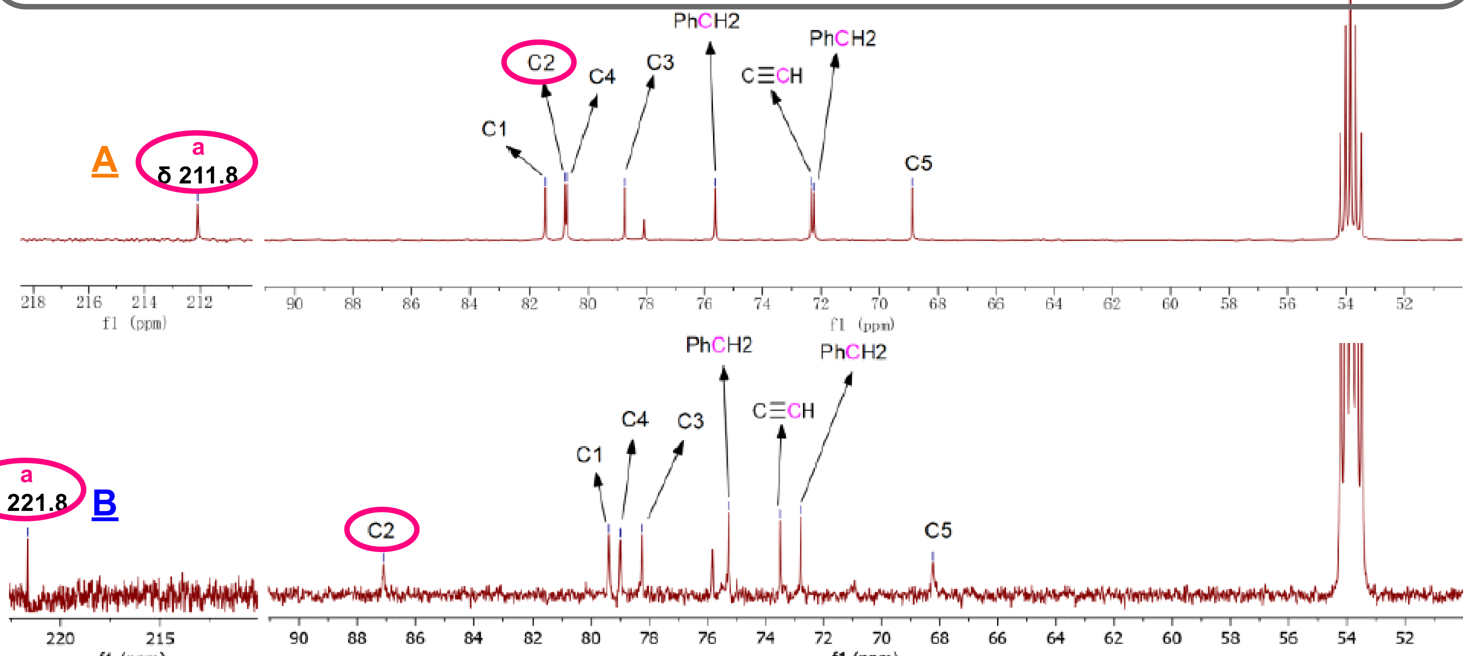




1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

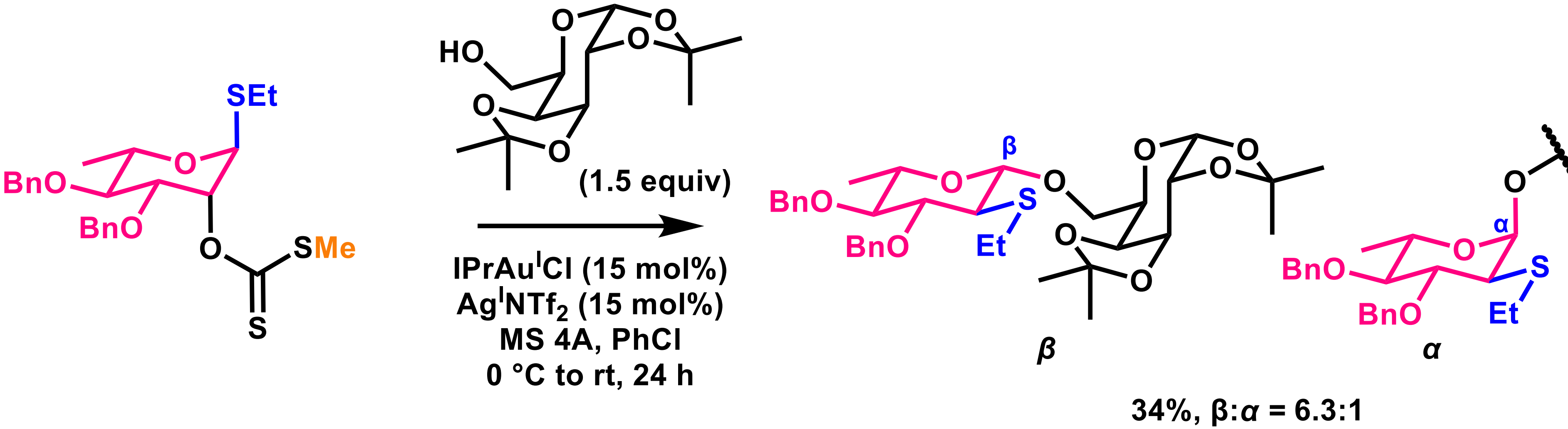
Observation of Intermediate in ^{13}C NMR

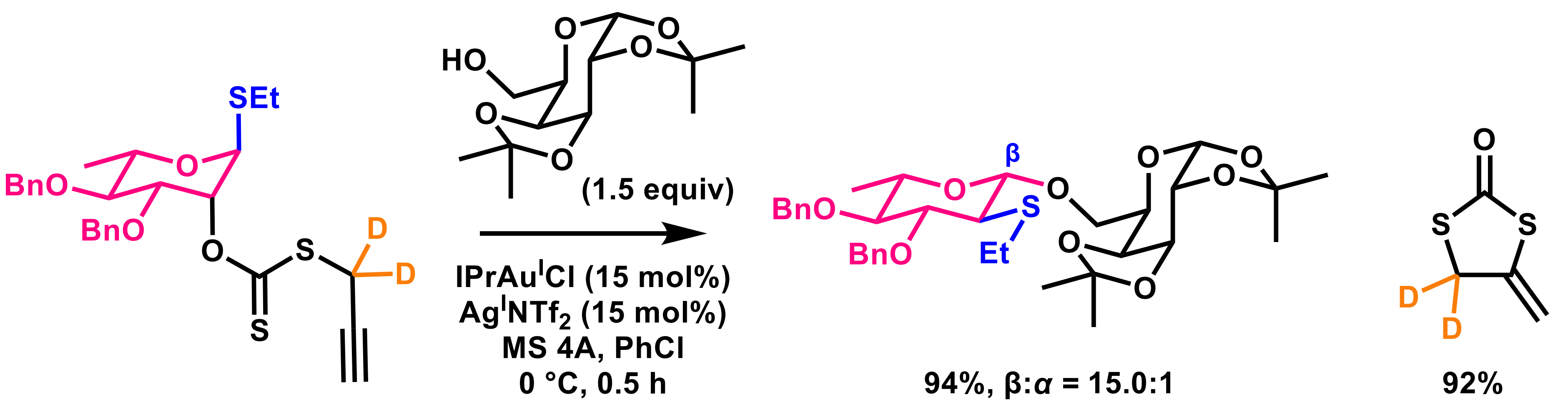




1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

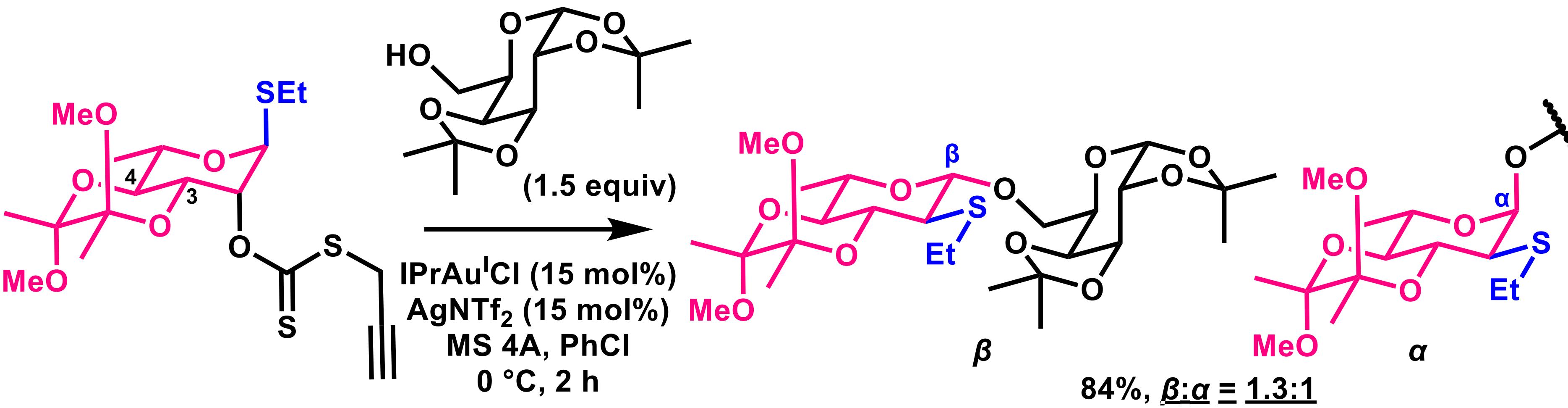
Control Experiments

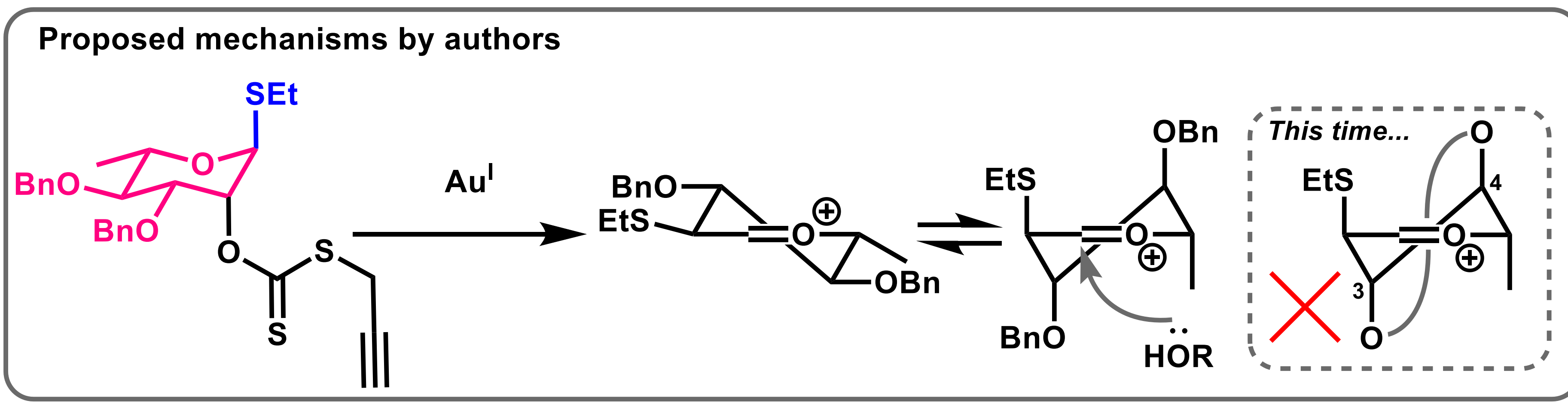




1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

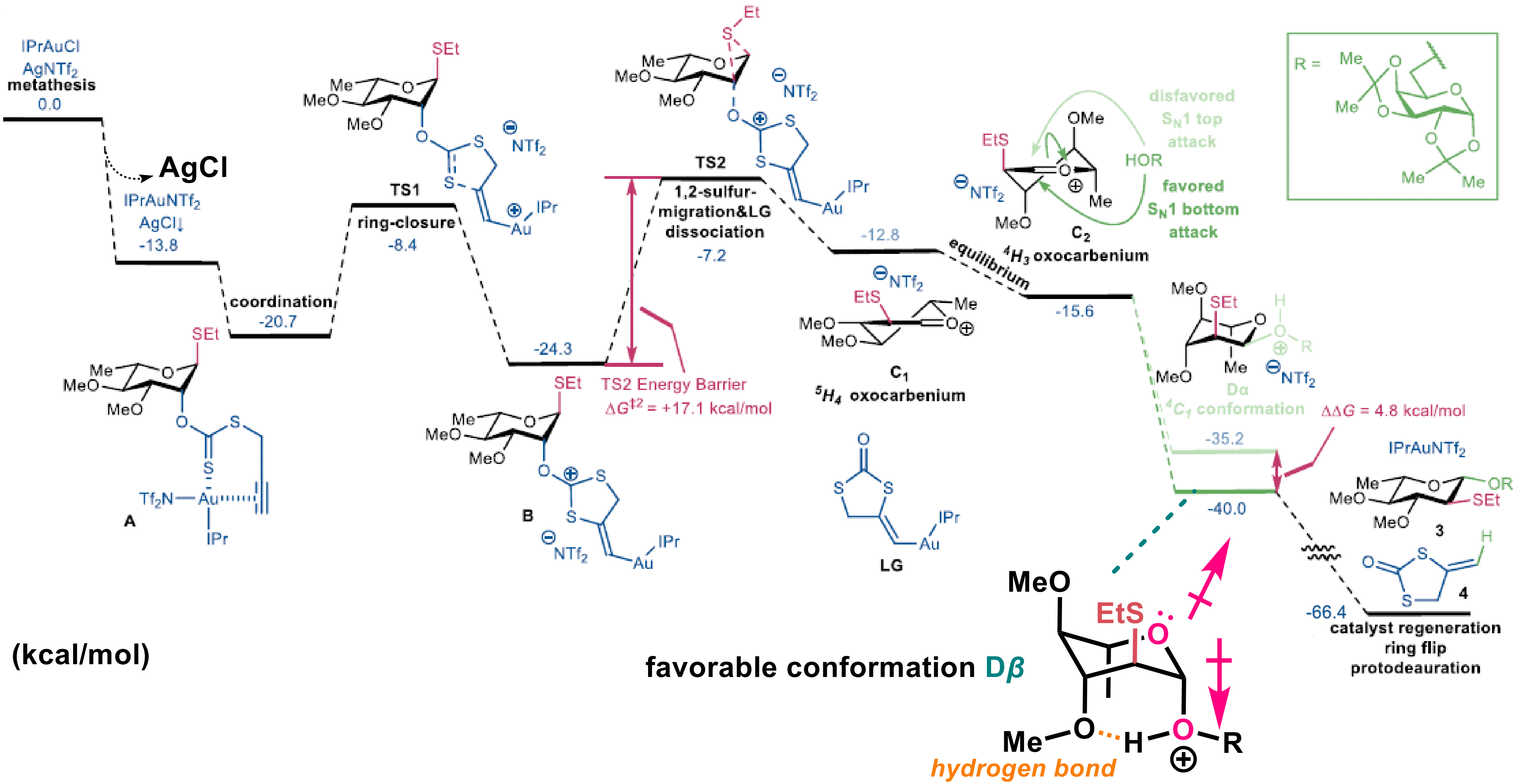
Glycosylation for 3,4-Tethered Doner





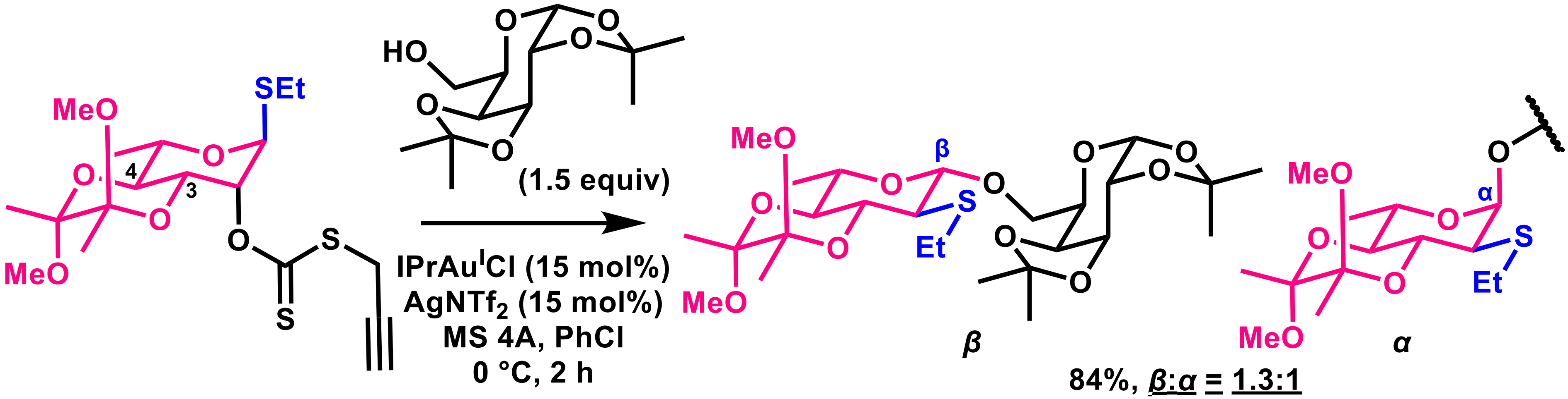
1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

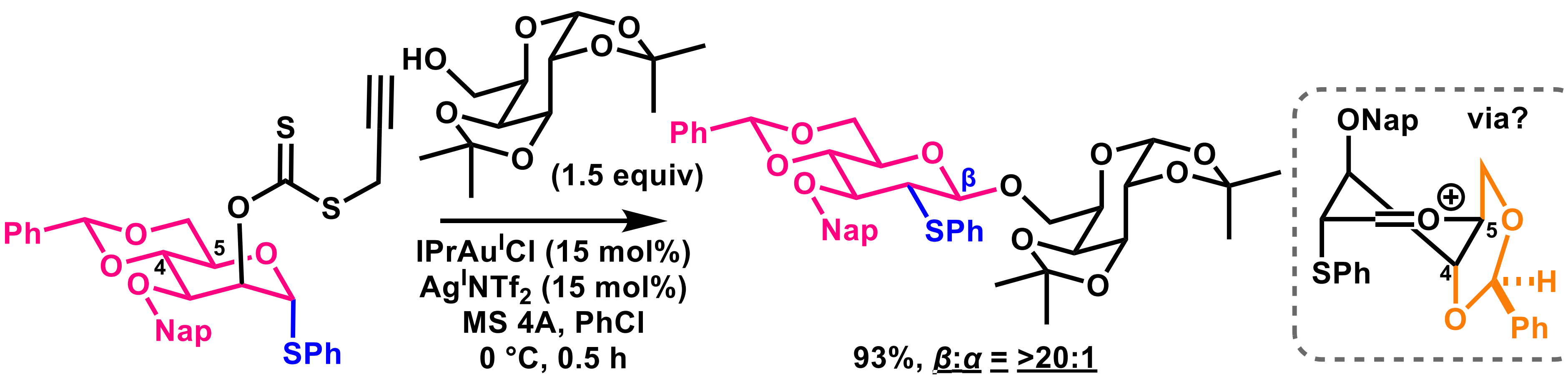
DFT Calculations



1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

Inconsistency in Author's Mechanism

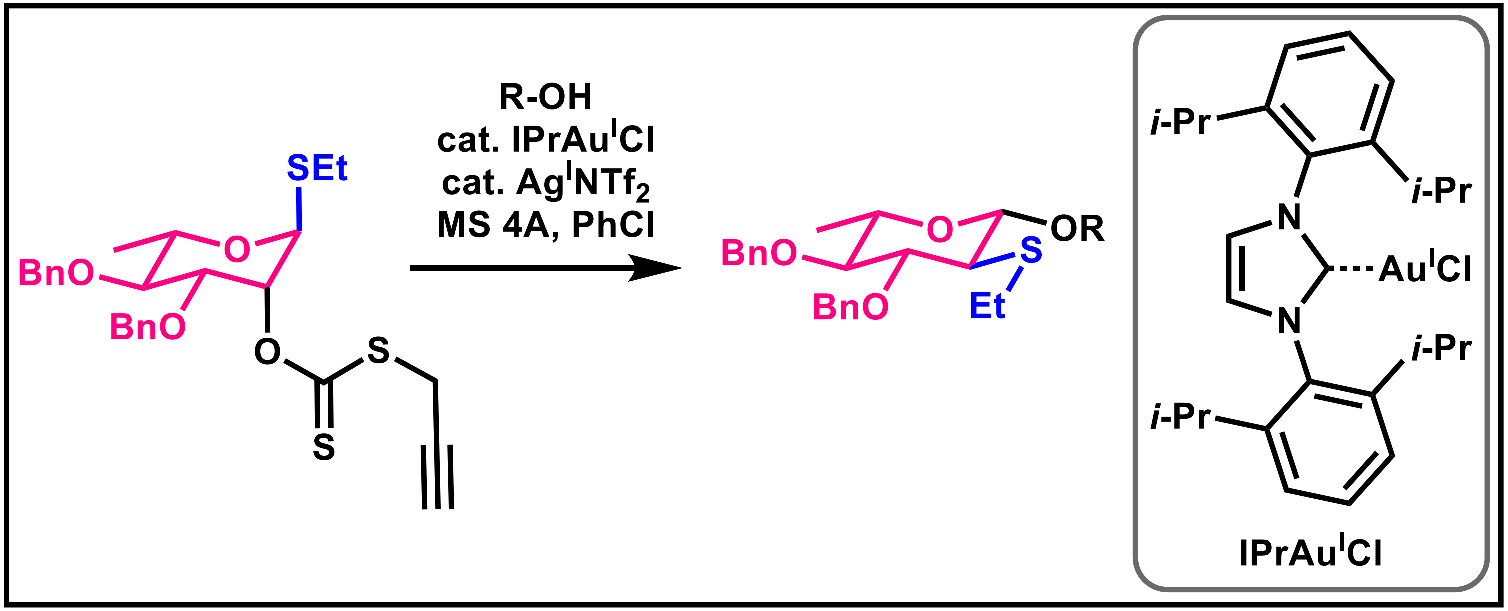


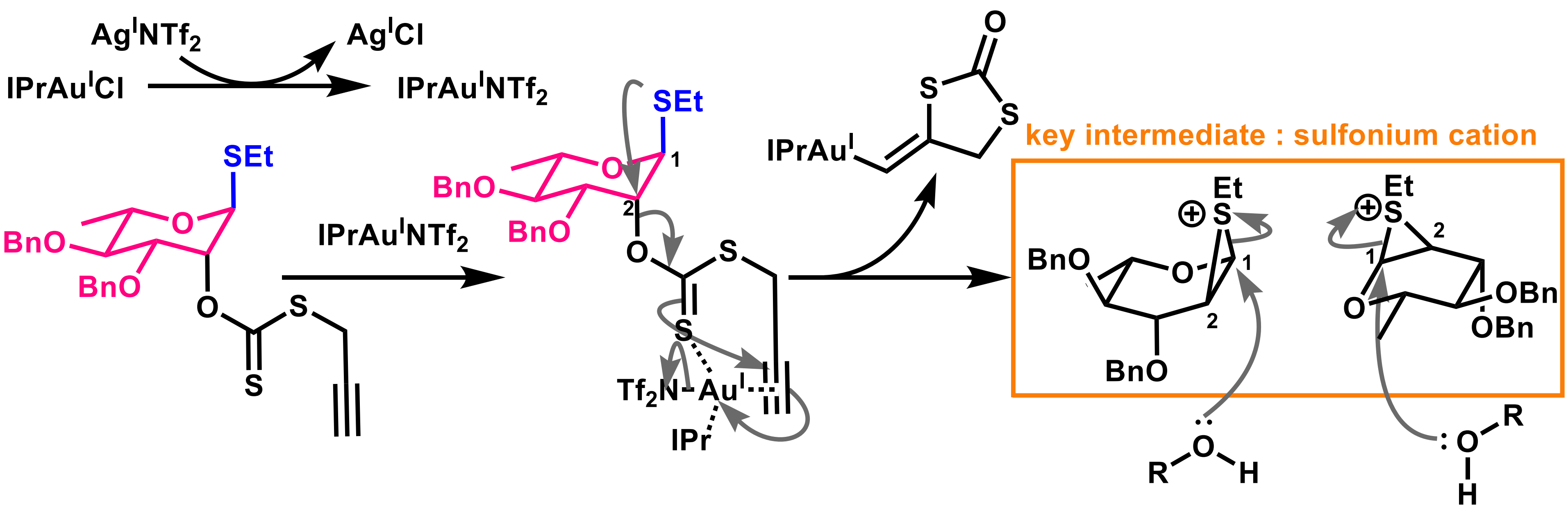


good β-selectivity!!

1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

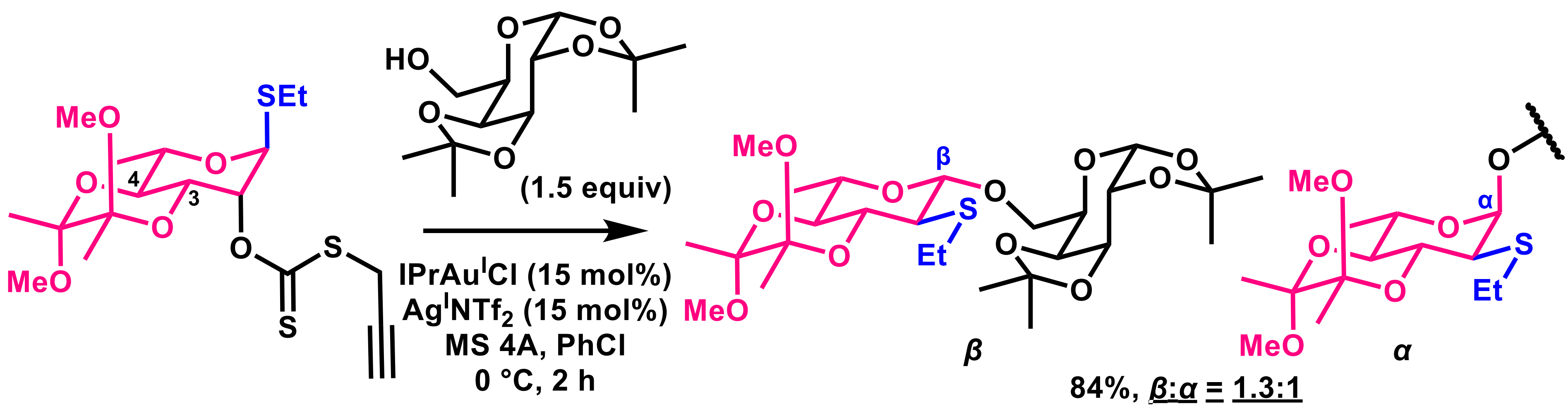
My Proposal for Reaction Mechanism

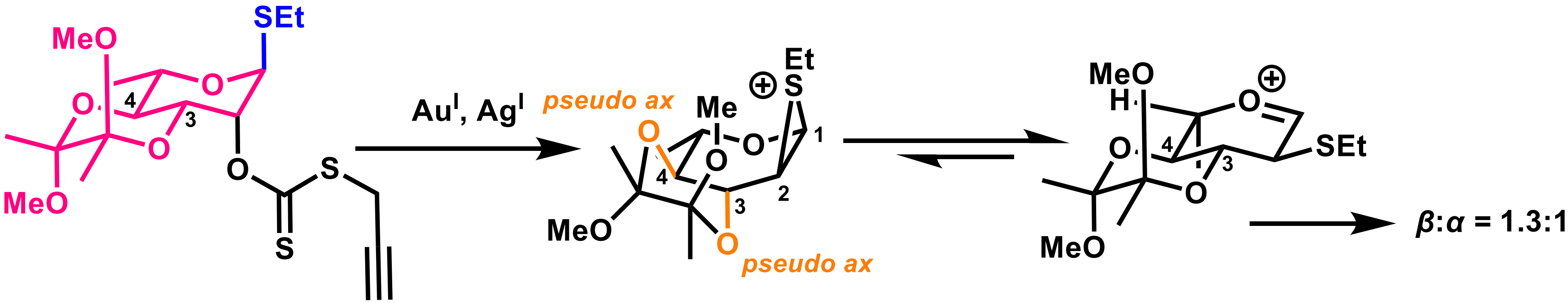




1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

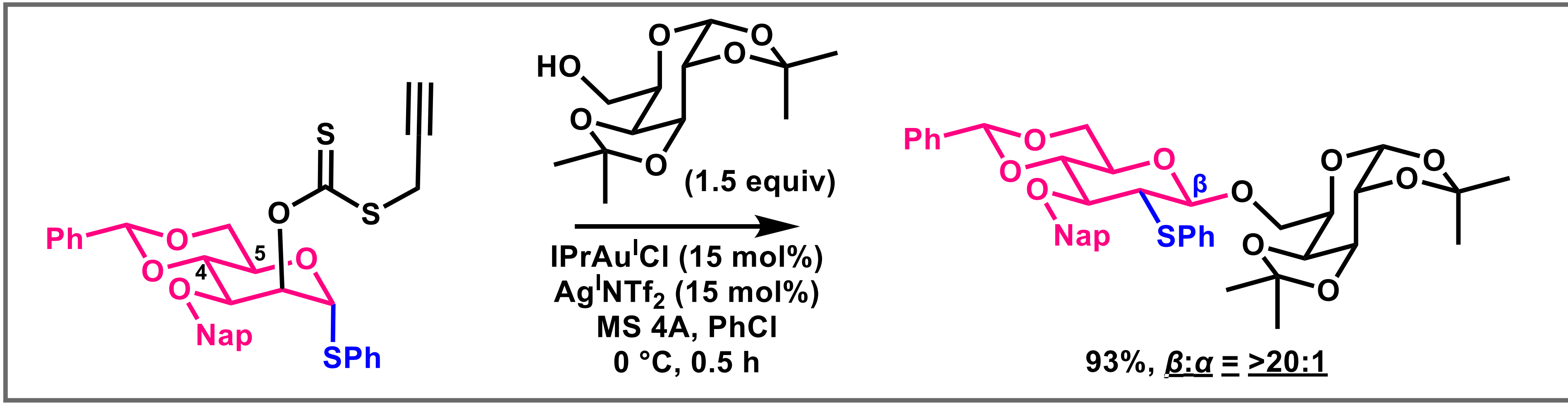
Explanation for Low *β*-selectivity for 3,4-Tethered Doner

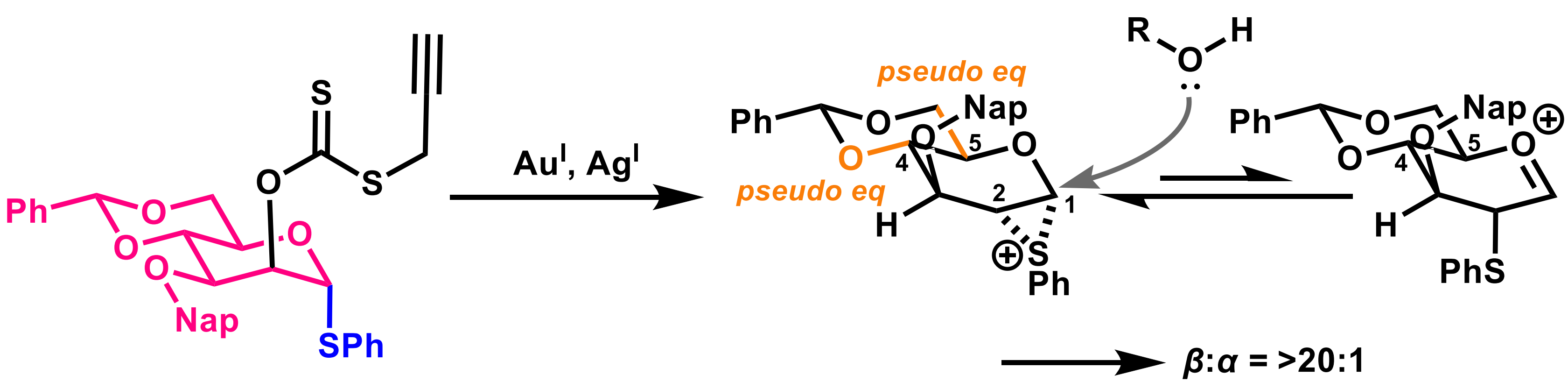




1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

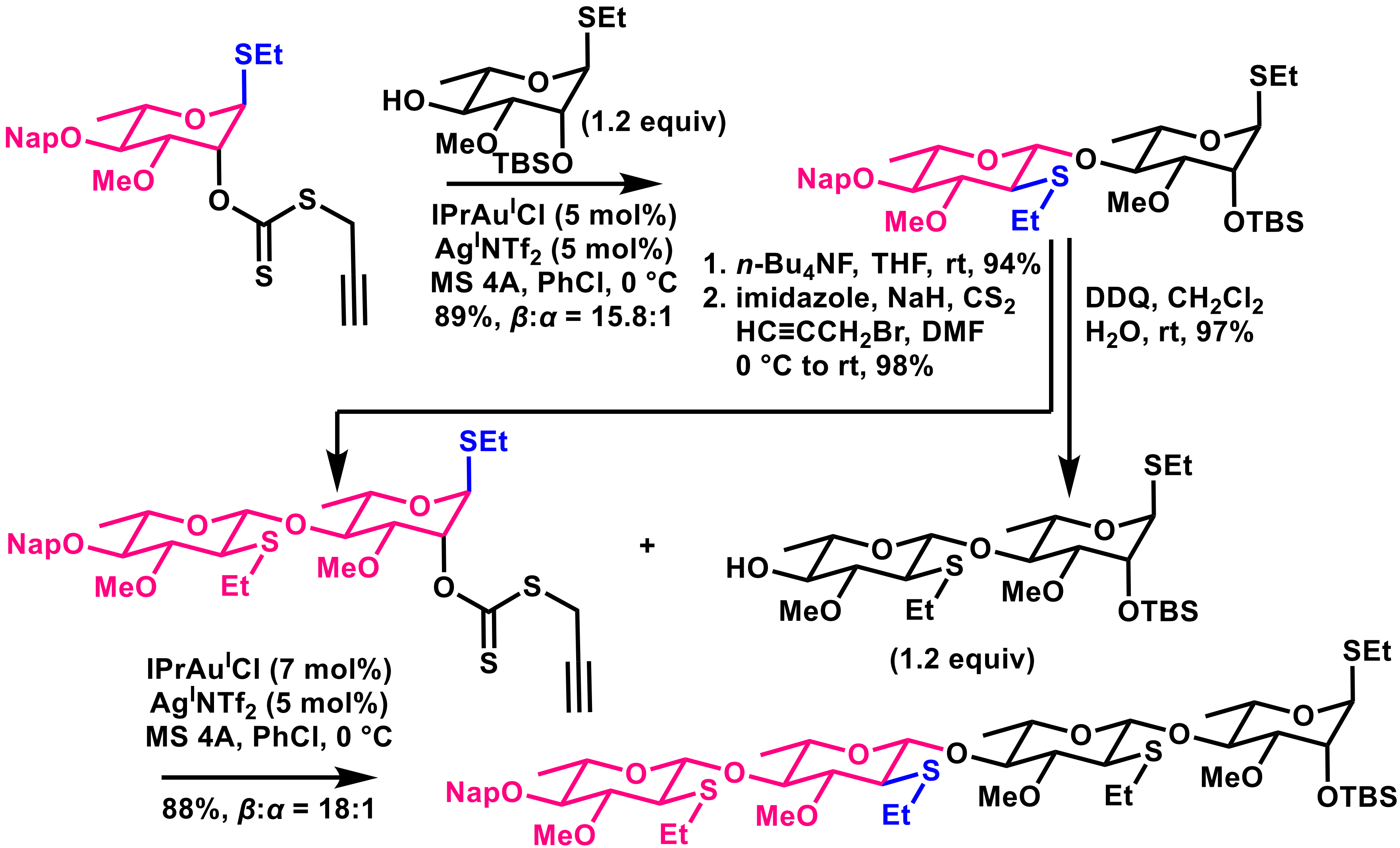
Explanation for Good *β*-selectivity for 4,5-Tethered Doner





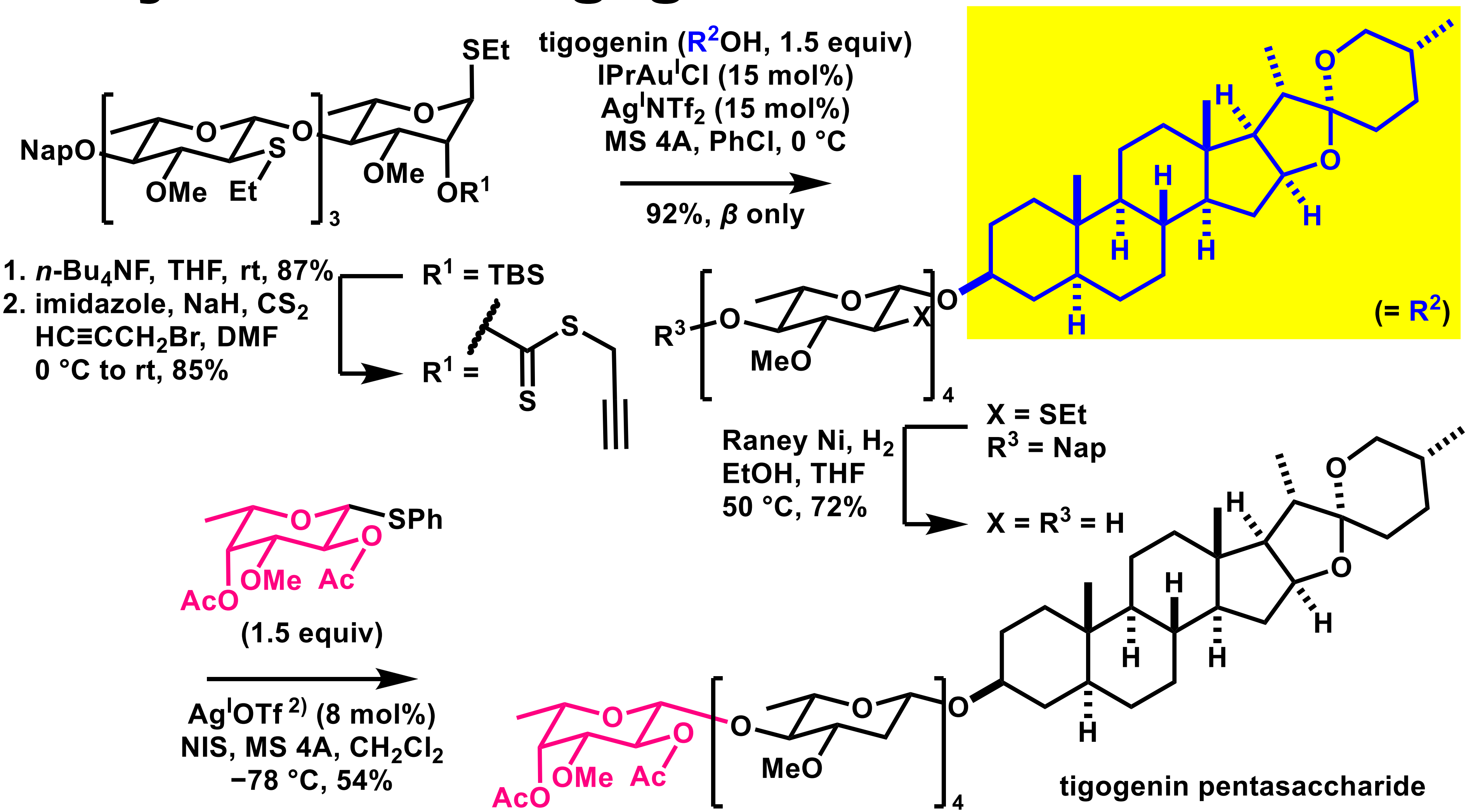
1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

Application for Total Synthesis : Synthesis of Tetramer



1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

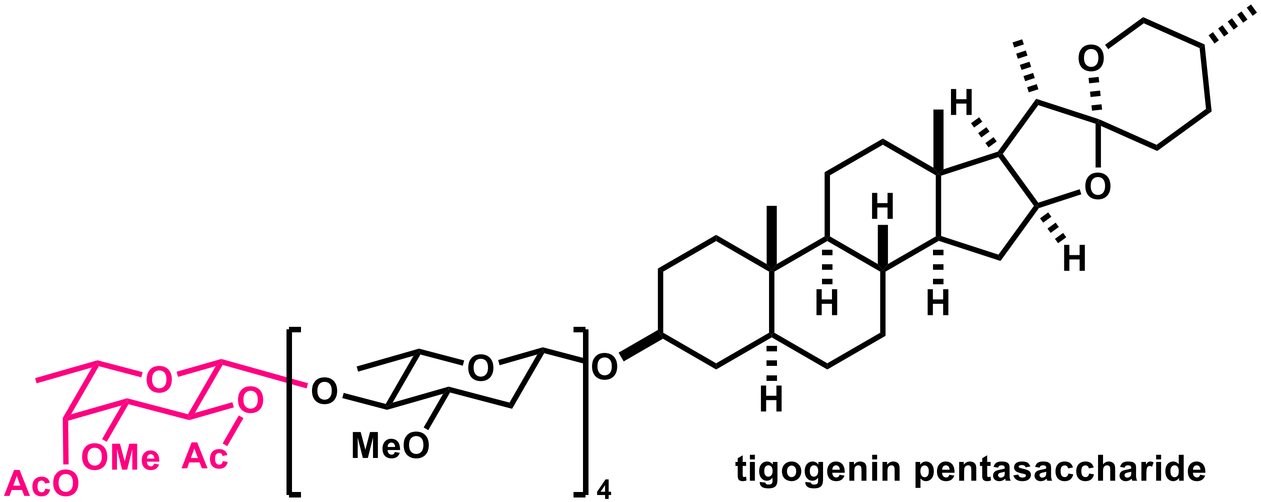
Application for Total Synthesis : Synthesis of Tigogenin Pentasaccharide



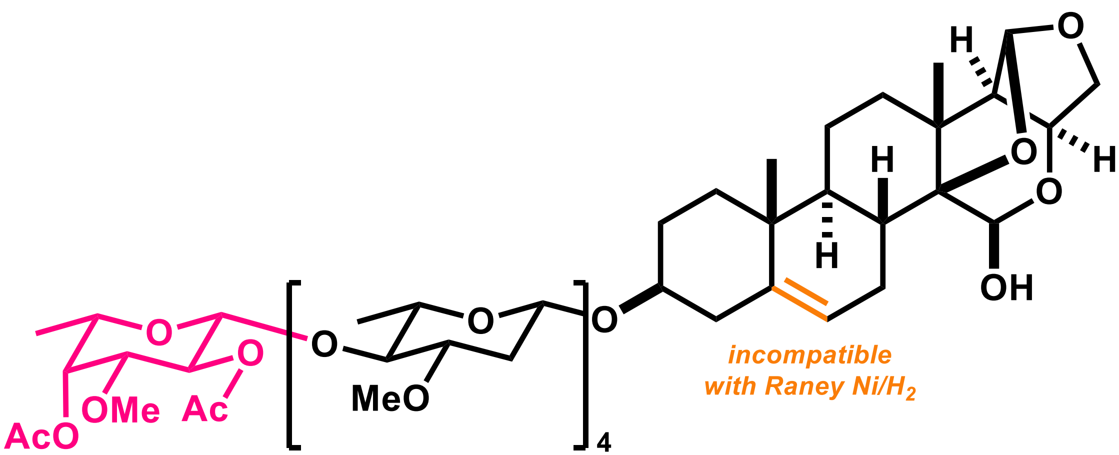
1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

2) Olsson, J. D. M.; Eriksson, L.; Lahmann, M.; Oscarson, S. *J. Org. Chem.* **2008**, *73*, 7181.

Application for Total Synthesis : The Remaining Problem



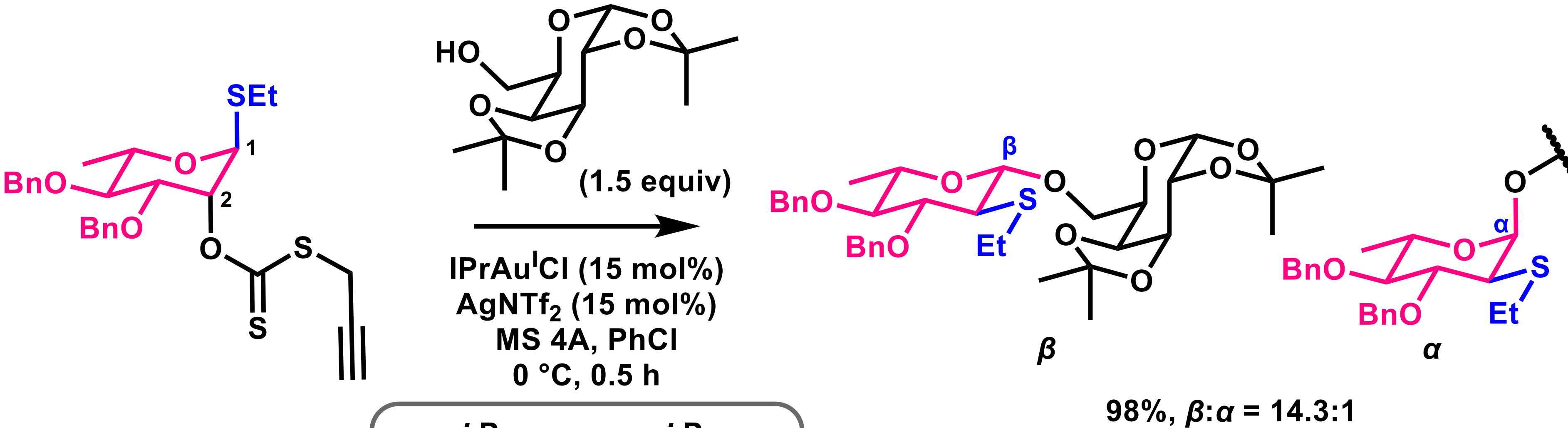
tigogenin pentasaccharide

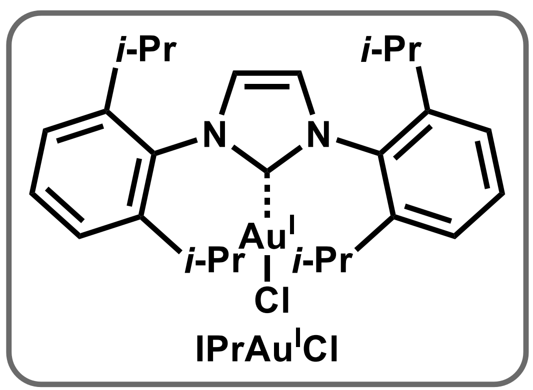


velutinoside A

1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

Summary

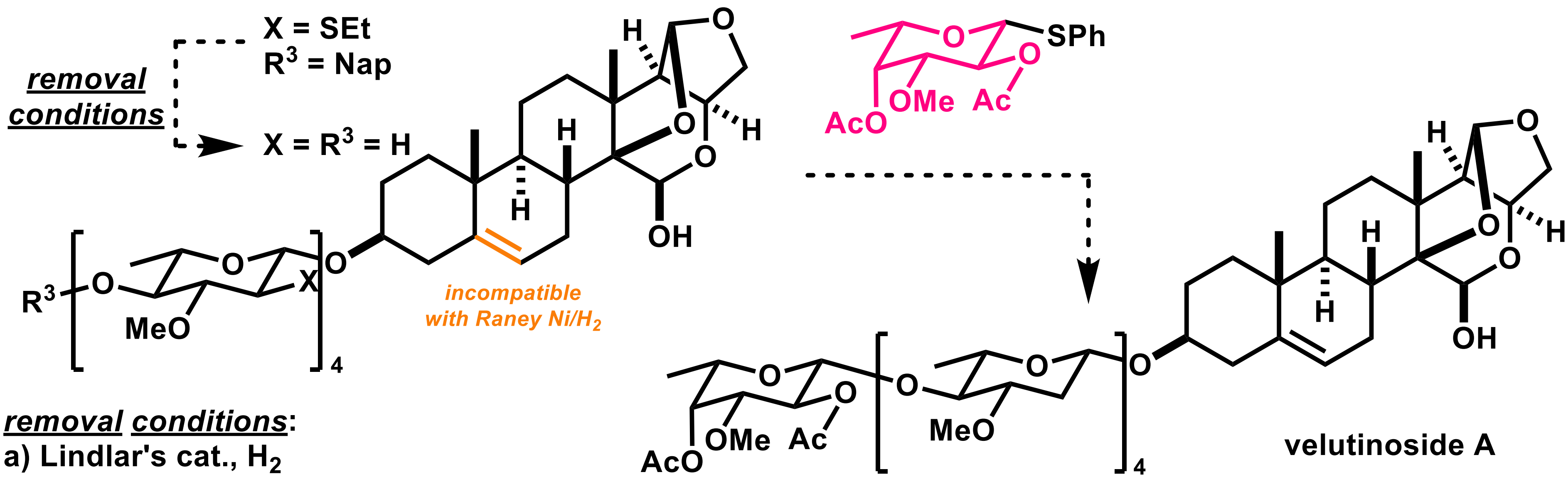




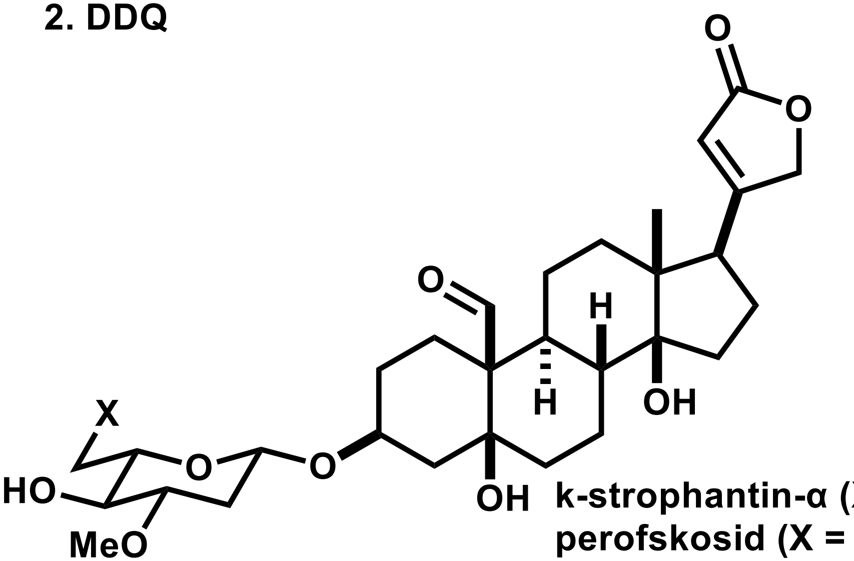
-Leaving group at C2 position
-High β-selectivity
-Removal of EtS by Raney Ni

1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

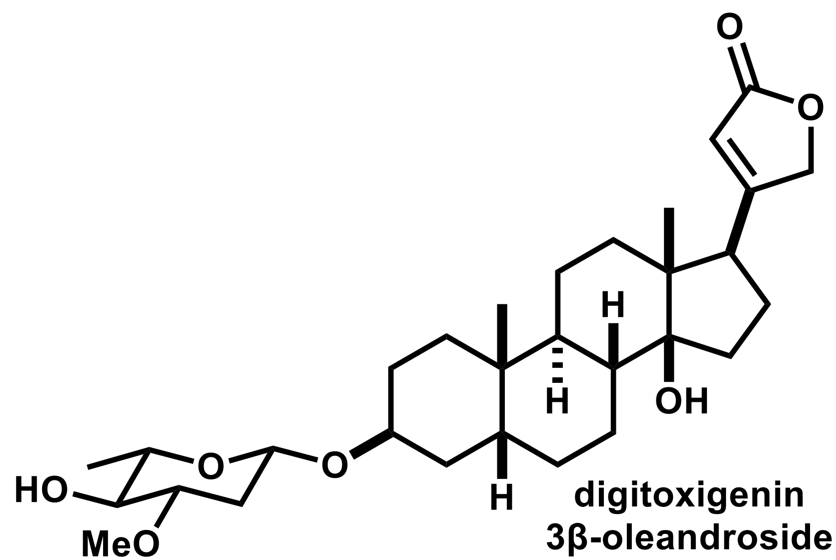
Future Prospect



removal conditions:
a) Lindlar's cat., H_2
b) 1. *n*-Bu_3SnH, cat. AIBN
 2. DDQ



k-strophantin-α (X = H)
perofskosid (X = OH)

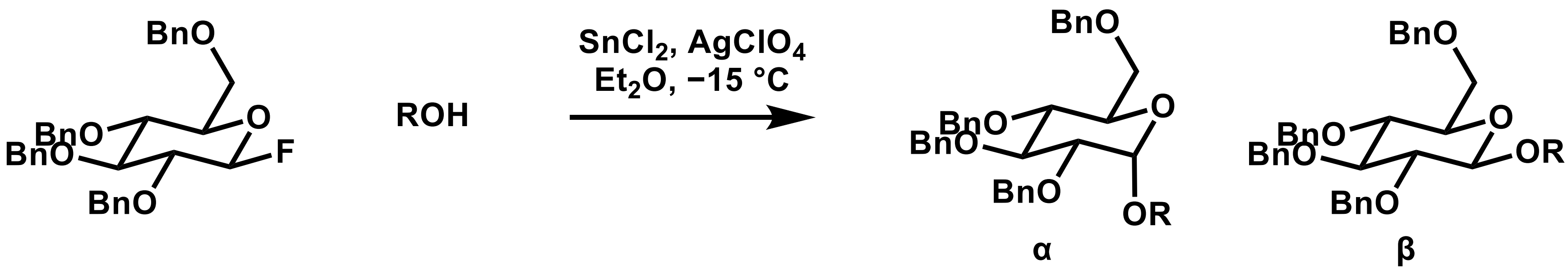


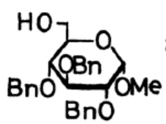
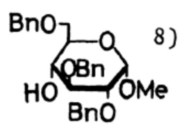
digitoxigenin 3β-oleandroside

1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

Appendix

Mukaiyama Glycosylation

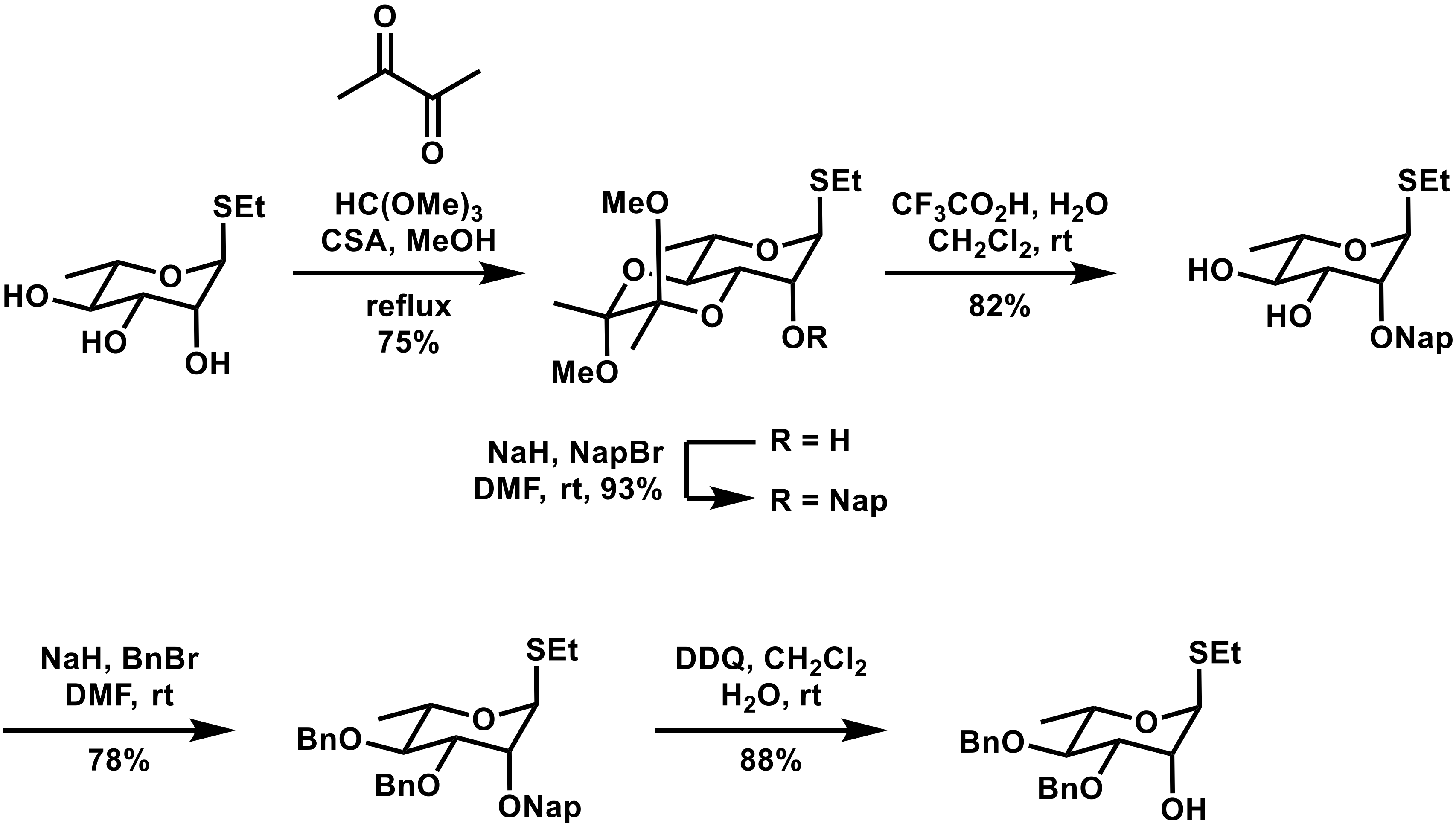


Alcohol	Yield(%)	α / β [c]
MeOH [a]	82 [b]	86 / 14
(H)-OH	88	83 / 17
t-BuOH	87	81[9] / 19[10]
Cholesterol	76	89 / 11
3β-Cholestanol	96	92 / 8
 8)	84	84 / 16 [11]
 8)	91	80 / 20 [11]

a) 2eq. of methanol was used.
b) Yield based on 1
c) These compounds were purified by TLC and were identified by ^{1}H-NMR spectra.

1) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431.

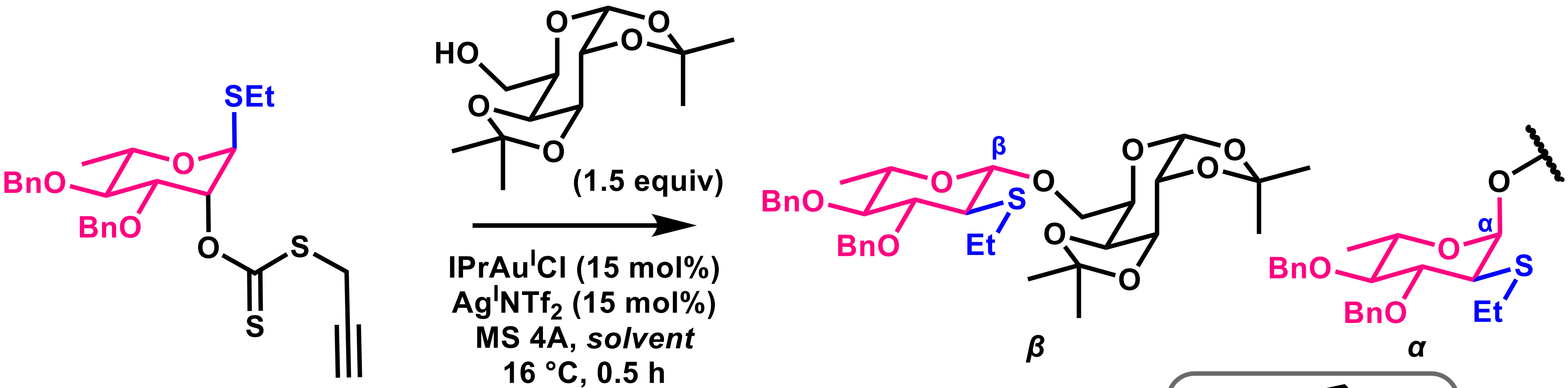
Synthesis of Intermediate A
(Ethyl-3,4-di-*O*-Bn-1-thio-α-L-rhamnoside)



A

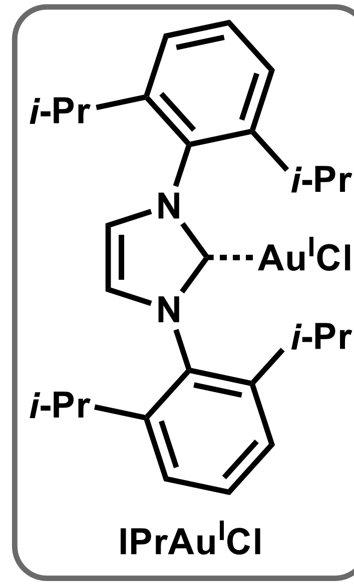
1) Schleyer, P. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N. J. R. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317.

Screening of the Solvent



entry	*solvent*	yields	*β* : *α*
2	**PhCl**	**94%**	**10.0 : 1**
6	$PhCF_3$	90%	10.0 : 1
7	*o*-dichlorobenzene	91%	8.3 : 1
8[a)]	$ClCH_2CH_2Cl$	92%	4.3 : 1

a) 2.5 h.



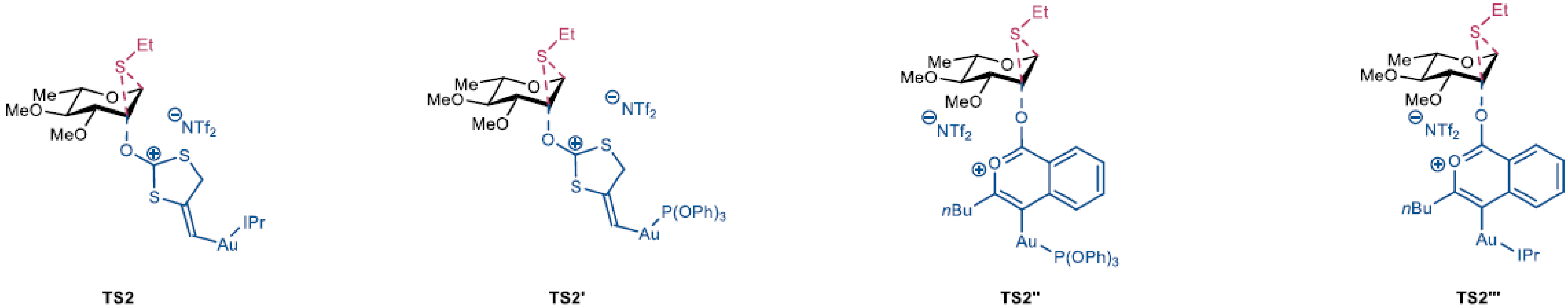
1) Wang, X.; Ding, H.; Guo, A.; Song, X.; Wang, P.; Song, N.; Yu, B.; Xu, P.; Liu, X.-W.; Li, M. *J. Am. Chem. Soc.* **2025**, *147*, 4469.

TS Analysis

Table 2. Calculated Physical Organic Parameters of the Transition States TS2, TS2′, TS2″, and TS2‴[a]

entry	TS[b]	energy barrier of the TS (kcal/mol)	electron contribution percentage from the C atom of the alkene C–Au bond (%)	electron contribution percentage from the Au atom in Au–ligand bond[c] (%)	ρ_{BCP}[d] of the Au–ligand bond[c] (a.u.)
1	TS2	+17.1	55.0	26.5	0.1322
2	TS2′	+20.4	51.9	23.1	0.1057
3	TS2″	+18.0	53.4	23.8	0.1101
4	TS2‴	+24.2	50.3	19.6	0.1248

[a]



[b]Transition state (TS). [c]The Au–ligand bond denotes the Au–C bond jointing Au with the ligand IPr and the Au–P bond jointing Au with the ligand $(PhO)_3P$. [d]Total electron density at the bond critical point (BCP).

1) Zhang, Z.; Zhu, H.; Gu, J.; Shi, H.; Hirose, T.; Jiang, L.; Zhu, Y.; Zhong, D.; Wang, J. *J. Am. Chem. Soc.* **2024**, *146*, 24681.