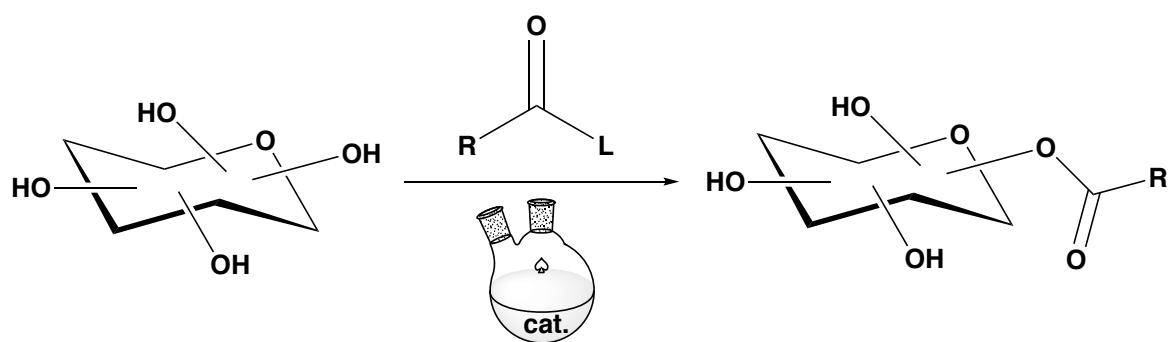


Site-selective Acylation of Carbohydrates



2024/10/11(Fri.)
Shan Chengyi

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5.	Migrations of Acyl in Carbohydrate Chemistry
6.	Acylation Agents with Variation of Leaving Group
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12.	Organic catalysts in site-selective acylation: Organotin and Organoboron Catalysts
13-14.	Organic catalysts in site-selective acylation: Transition Metal Salt
15.	Representative Enzyme-Catalyzed Esterifications of Carbohydrate Derivatives
16-17.	Proposals

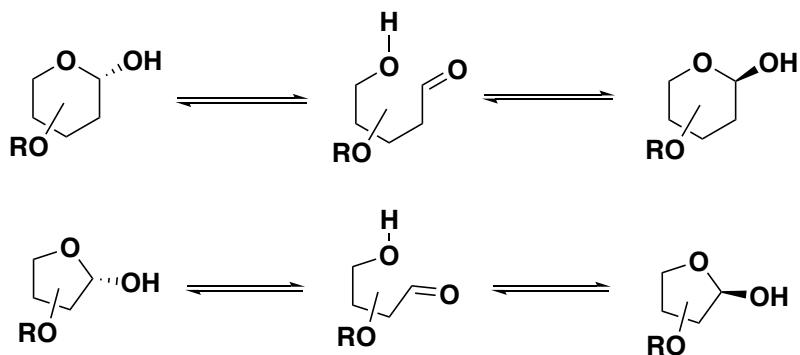
1 Overview of Carbohydrates

1) Basic Types of Carbohydrates

n = 0 Monosaccharides
n = 1 Disaccharides
2 < n ≤ 10 Oligosaccharides
n > 10 Polysaccharides

• Consist of carbon, hydrogen, and oxygen
• The ratio hydrogen and oxygen is 2:1

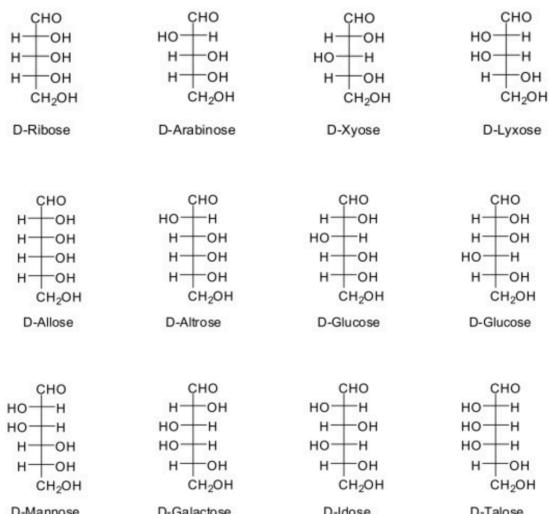
2) Forms of Sugars: Chain and Ring Structures (Mutarotation)



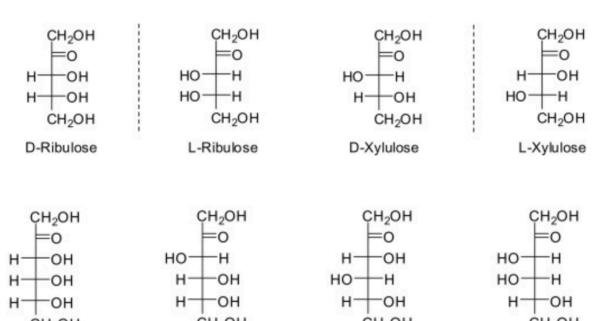
3) Monosaccharides Classification

- a. Based on Number of Carbon Atoms: Triose, Tetrose, Pentose, Hexose, Heptose...
- b. Based on Functional Groups: Aldose(-CHO), Ketose(-C=O)

examples of naturally aldose¹



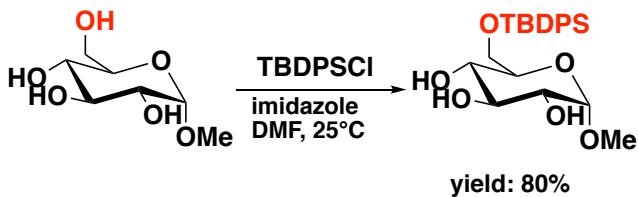
examples of naturally ketose¹



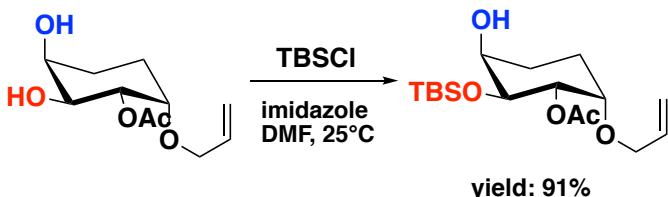
¹ Organic Chemistry (Second Edition), 2018

2 Reactivity of Hydroxyl Groups in Carbohydrates: steric effect

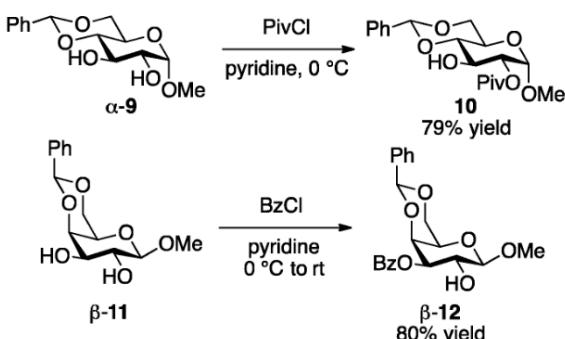
1) primary(6-OH) vs. secondary¹



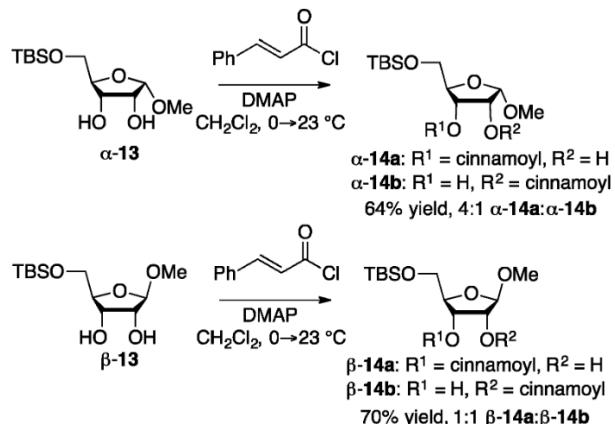
2) axial vs. equatorial²



3) Equatorial OH with flanking equatorial substituents^{3,4}



4) Effect of Anomeric Configuration⁵



Overview of Steric effects in Carbohydrates:

- secondary OH group > primary OH group
- axial OH group > equatorial OH group
- flanked substituent(same configuration) ↑
steric effect ↑

¹ Lavallée. et. al. Can. J. Chem. 1975, 53, 2975–2977. ³ Chan. et. al. J. Org. Chem. 1998, 63, 6035–6038.

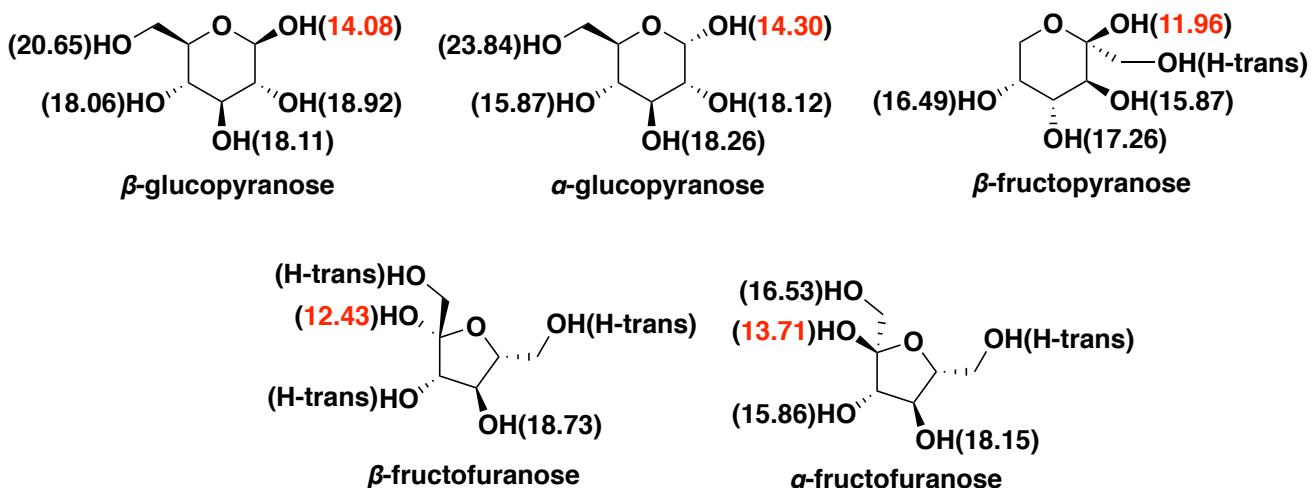
² Du, Y. et. al. J. Chem. Soc., Perkin Trans. 1 2002, 2075–2079.

⁴ Magnusson. et. al Carbohydr. Res. 1986, 152, 113–130.

⁵ Camarasa. et. al. Tetrahedron: Asymmetry 1994, 5, 2141–2154.

3 Reactivity of Hydroxyl Groups in Carbohydrates: Relative Acidities of OH

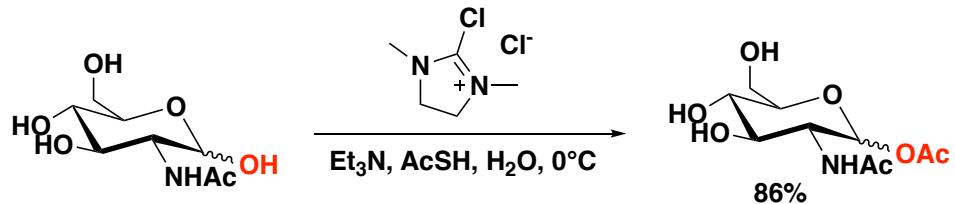
1) Calculated pKa Values of OH in carbohydrate¹



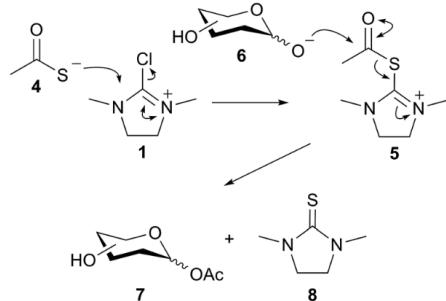
H-trans: proton transfer from a neighboring OH group to the deprotonated site.

2) Examples of Selective Functionalization of the Most Acidic OH Group of a Carbohydrate Substrate under Basic Conditions

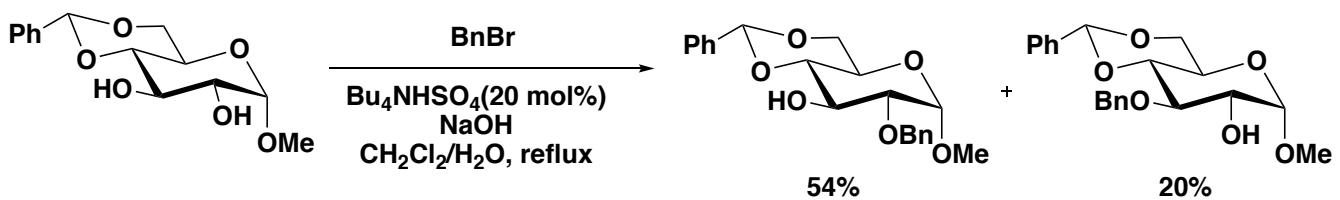
a) Selective anomeric acetylation of unprotected sugars²:



Plausible reaction mechanism:



b) Selective benzylation at 2-position of protected sugars³:

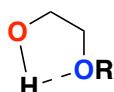


¹ Giannis. et. al. *J. Phys. Chem. A.* 2013, 117, 5211–521.

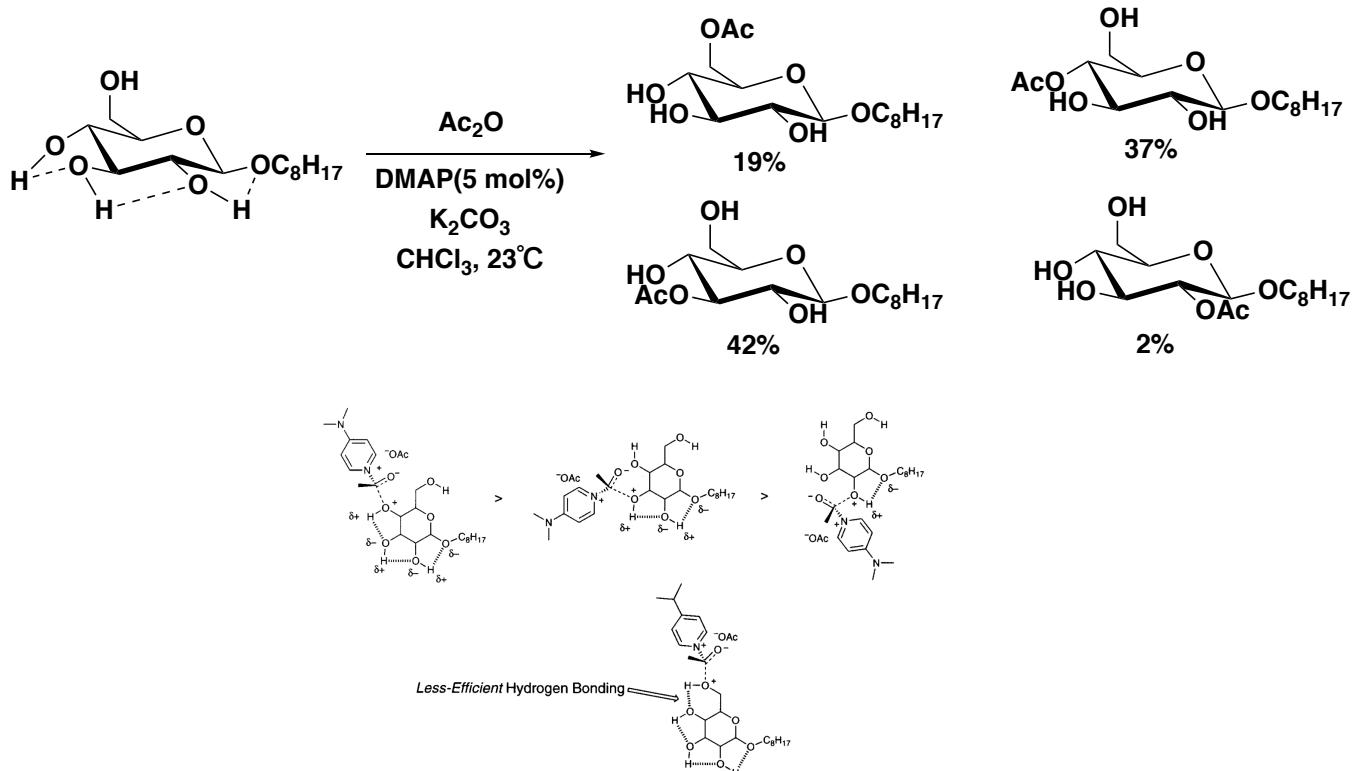
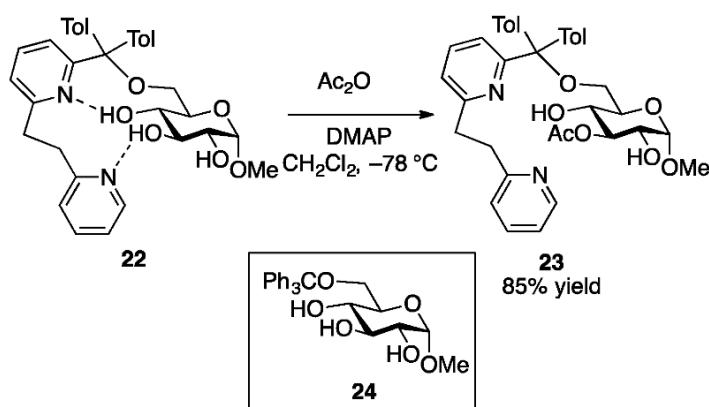
² Antony. et. al. *Chem. Sci.*, 2017, 8, 1896–1900.

³ Willi. et. al. *J. Org. Chem.* 1984, 49, 1, 51–56.

1) Effect of hydrogen bonding interactions in carbohydrates



Blue circle: O as acceptor of hydrogen bonds, nucleophilic ↓
 Red circle: O as donor of hydrogen bonds, nucleophilic ↑

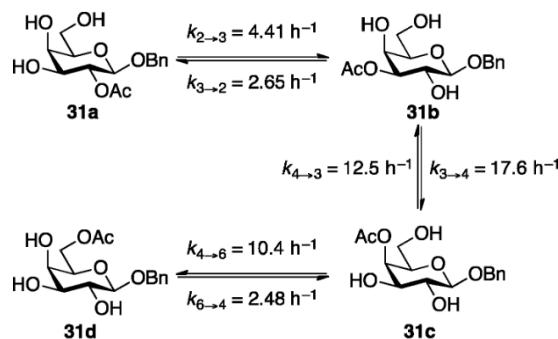
2) Example: Selective acylation attributed to intramolecular hydrogen-bonding network¹3) Example: Selective acylation attributed to directing group's effect²

¹ Yoshida. et. al. J. Chem. Soc., Perkin Trans. 1, 1999, 465–473.

² Chapleur. et. al. Tetrahedron 2005, 61, 6839–6853.

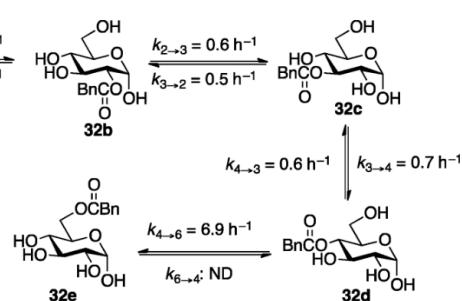
5 Migrations of Acyl in Carbohydrate Chemistry(intramolecular transesterification)

a) Rate Constants for Acetyl Group Migration in Benzyl β-D-Galactopyranoside Derivatives¹



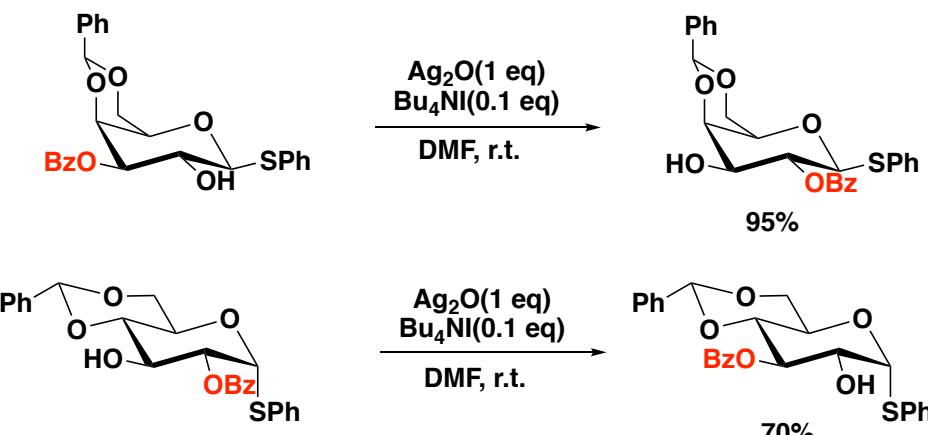
D_2O , pD= 8.0, Sodium Phosphate Buffer

b) Rate Constants for Phenacyl Group Migration in α-D-Glucopyranoside Derivatives²

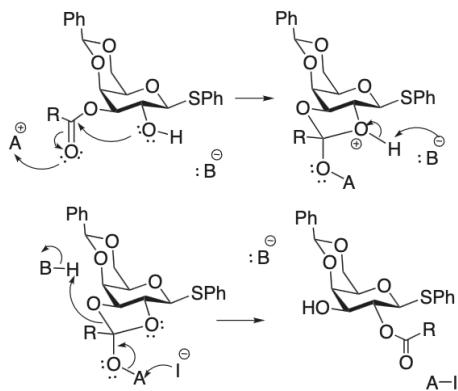


D_2O , pD= 8.0, Phosphate Buffer

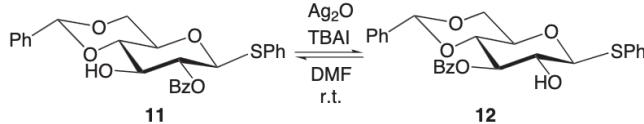
Example: Migrations Promoted by Ag_2O /Tetrabutylammonium Iodide³



Proposed mechanism:



without steric preference:



ratio of 11 and 12 = 1:1

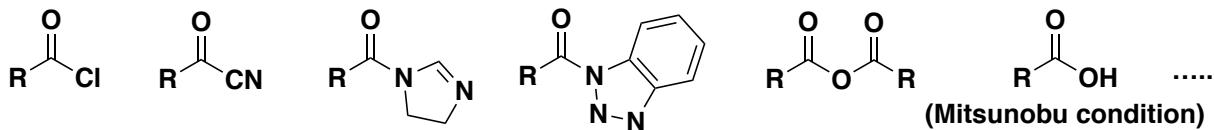
¹ Leino. et. al. *J. Am. Chem. Soc.* 2008, 130, 8769–8772.

² Stachulski. et. al. *Org. Biomol. Chem.*, 2011, 9, 926–934

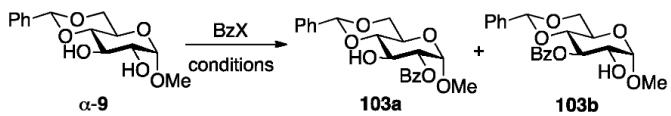
³ Chang. et. al. *Synlett.*, 2006, 5, 756–760

6 Acylating Agents with Variation of Leaving Group

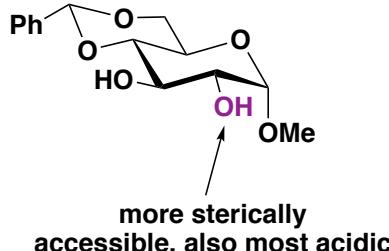
1) Acylating Agents:



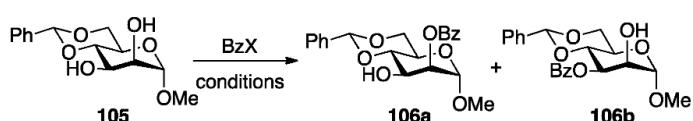
2) Reactions of Glucopyranoside-Derived Diol with Various Benzoylating Reagents^{1,2,3,4,5}



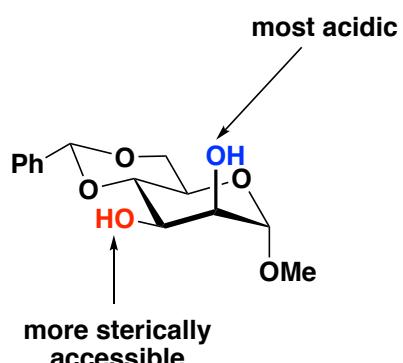
Acylating agent:	Conditions:	Result:
BzCl	pyridine, 0 °C	24% 103a, 6% 103b, 35% diester
Bz-NHC(=O)-imidazole	CHCl ₃ , reflux	78% 103a
BzCN	Et ₃ N, MeCN, 23 °C	62% 103a
BzO-NHC(=O)-1,2-dihydro-1,2-diazepine (BzOBt)	Et ₃ N, CH ₂ Cl ₂ , 23 °C	90% 103a, 4% 103b, 2% diester
EtO-C(=O)-NHC(=O)-CN 104	Et ₃ N, CH ₂ Cl ₂ , 0 to 23 °C	103a 83%
Bz ₂ O	pyridine, 20–30 °C	25% 103b, 12% 103a, 9% diester
Bz ₂ O	Et ₃ N, CH ₂ Cl ₂ , rt	93% 103a



3) Reactions of α-Mannopyranoside-Derived Diol with Various Benzoylating Reagents^{1,2,3}



Acylating agent:	Conditions:	Result:
BzCl	pyridine, –45 °C to rt	90% 106b
BzCN	Et ₃ N, MeCN, 23 °C	2.3:1 106a:106b
BzOBt	Et ₃ N, CH ₂ Cl ₂ , 23 °C	90% 106a
Bz-NHC(=O)-imidazole	CHCl ₃ , reflux	~1:1 106a:106b



¹ Williams. et. al. Org. Biomol. Chem., 2016, 14, 97.

² Jeanloz. et. al. J. Am. Chem. Soc. 1957, 79, 2579–2583.

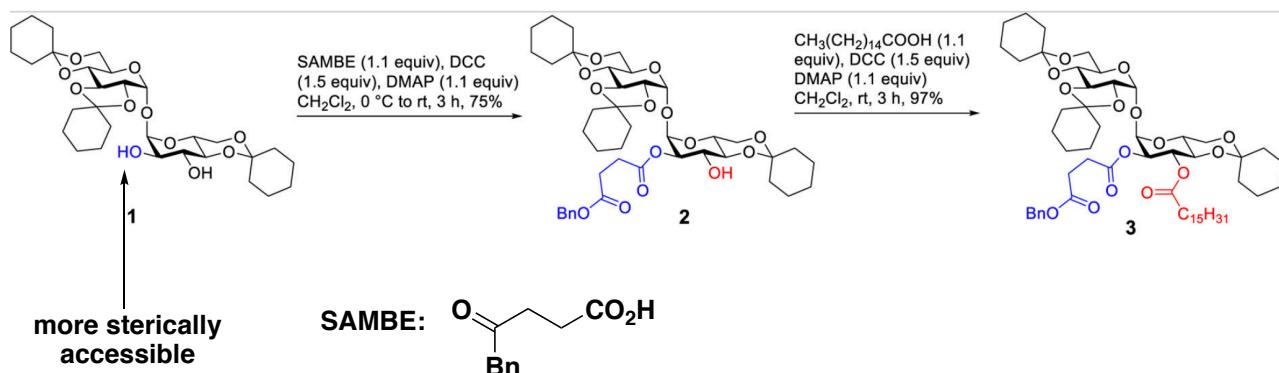
³ Hodgson. et. al. Carbohydr. Res. 1970, 12, 463–465.

⁴ Haines. et. al. Carbohydr. Res. 1975, 39, 358–363.

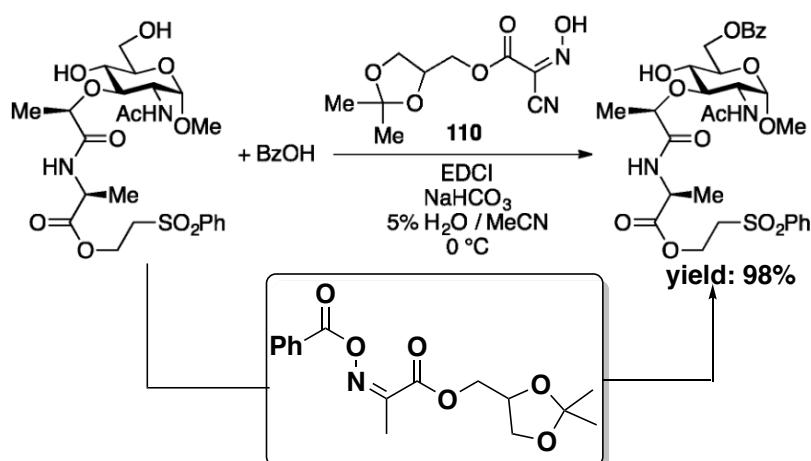
⁵ Kim. et. al. J. Org. Chem. 1985, 50, 1751–1752.

7 Carbodiimide- and Uronium Salt-Mediated Esterification

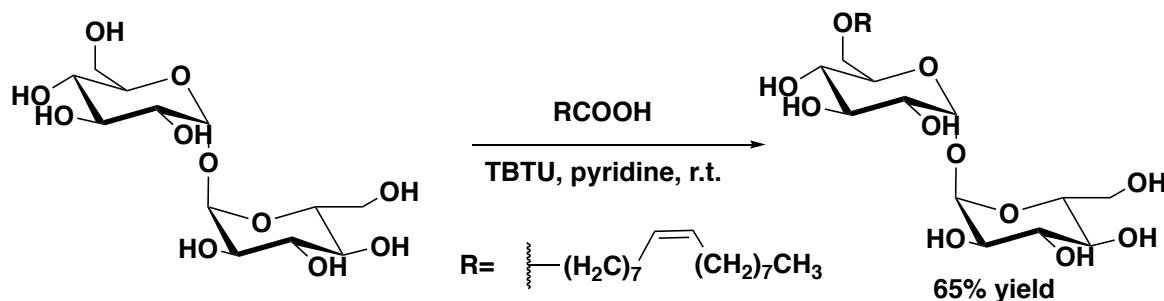
1) Site-Selective DCC-Mediated Esterification¹



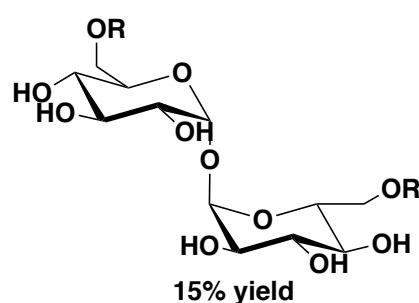
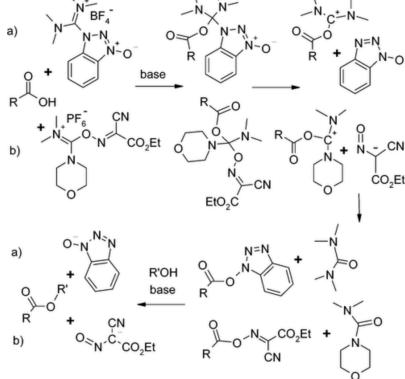
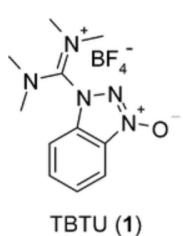
2) Site-Selective EDCI/Oxyma-Mediated Esterification²



3) Site-Selective Esterification of Trehalose with Oleic Acid in the Presence of TBTU³



Proposed mechanism:

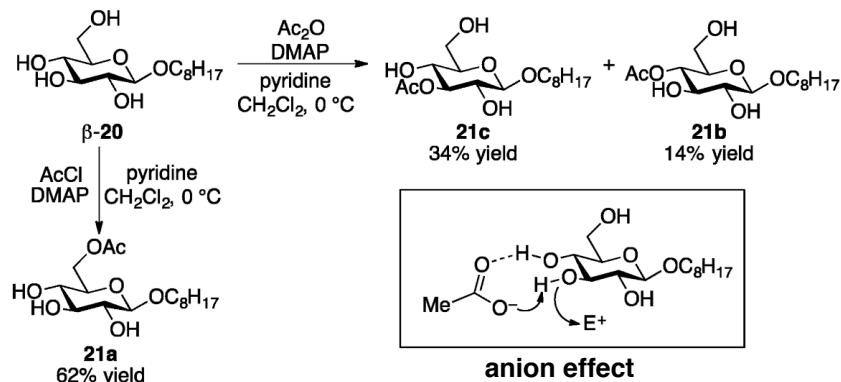


¹ Kulkarni. et. al. Org. Lett. 2017, 19, 7, 1784–1787. ² Kurosu. et. al. Org. Lett. 2012, 14, 18, 4910–4913.

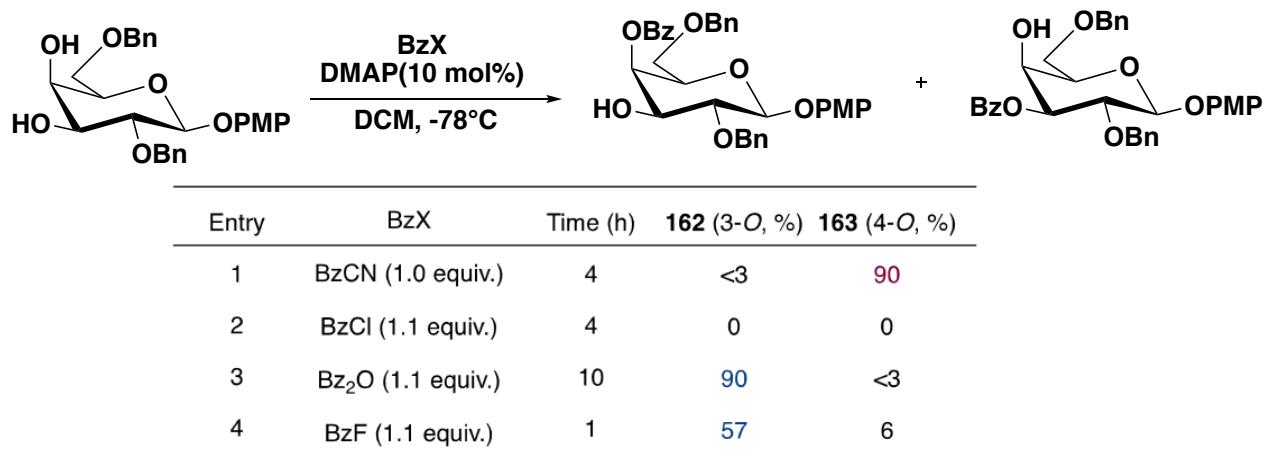
³ Griendley. et. al. J. Org. Chem. 2013, 78, 2, 363–369.

8 Organic catalysts in site-selective acylation: DMAP

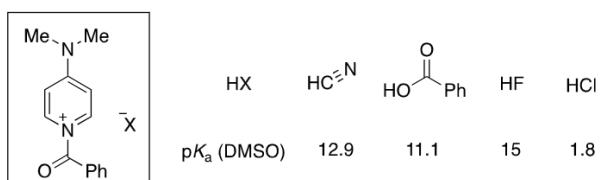
1) DMAP-Catalyzed Acetylation on the Identity of the Leaving Group(anion effect)¹



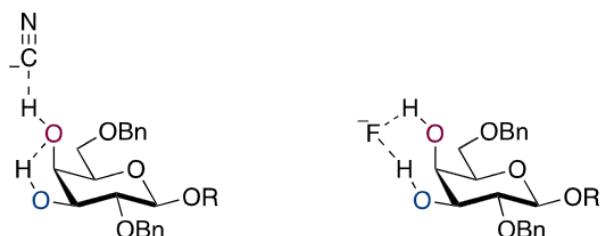
2) DMAP-Catalyzed Acylation when CN as the Leaving Group(Cyanide Effect)²



pKa of conjugate acids of various counterion:



A rationale for the axial-selectivity mediated by cyanide ion:

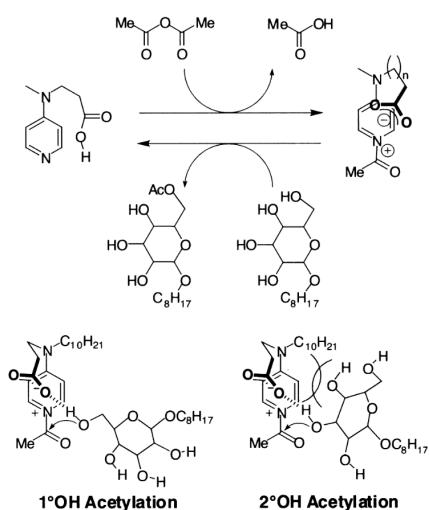
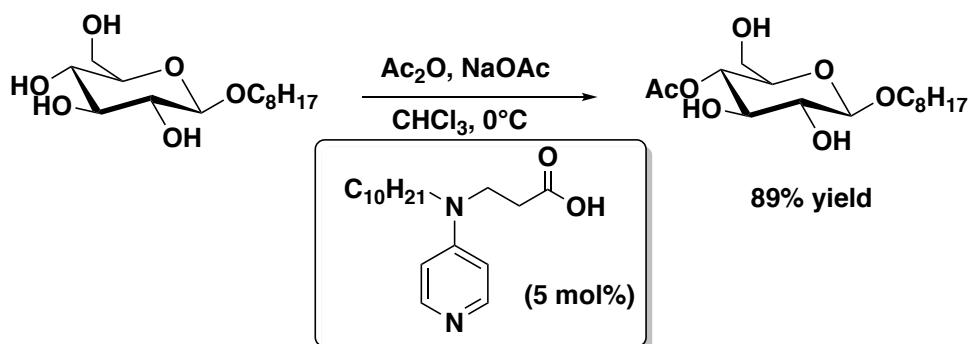


¹ Albert. et. al. Org. Lett. 2004, 6, 6, 945–948.

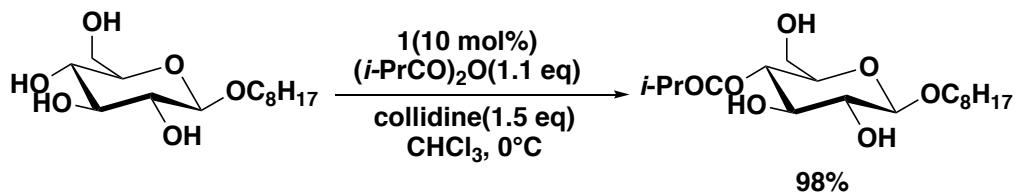
² Schmidt. et. al. J. Am. Chem. Soc. 2016, 138, 18, 6002–6009.

9 Organic catalysts in site-selective acylation: DMAP derivatives

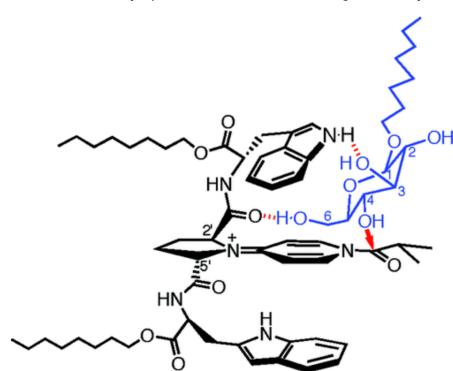
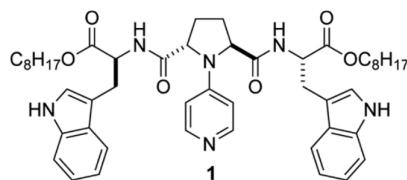
1) Selective Esterification Catalyzed by a Functionalized DMAP Derivative¹



2) PPY-Derived Chiral Catalyst for Site-selective Acylation of Pyranosides²



Proposed mechanism:

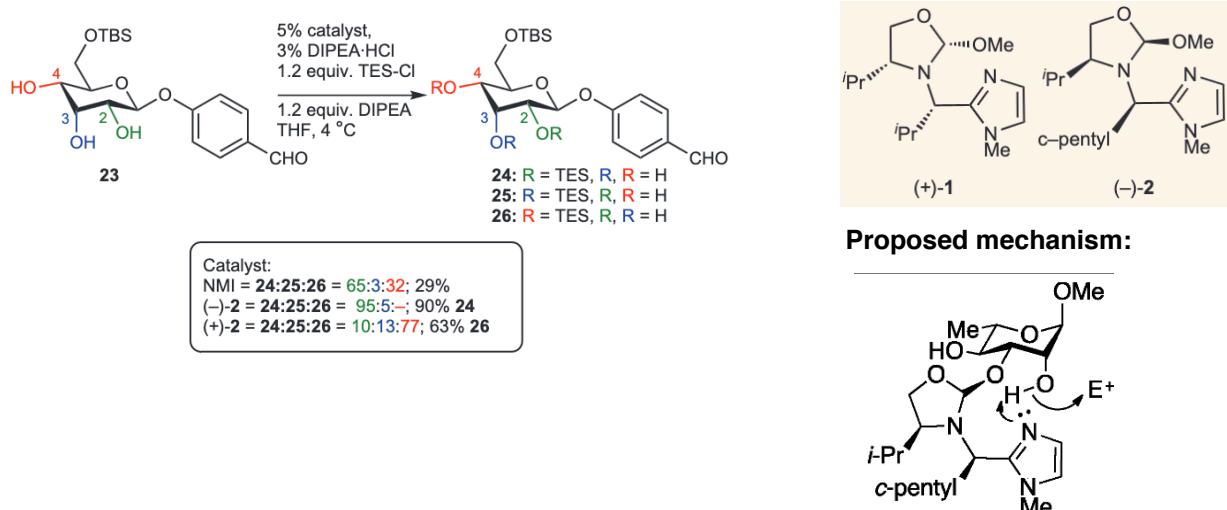


¹ Yoshida. et. al. Tetrahedron 2002, 58, 8669–8677.

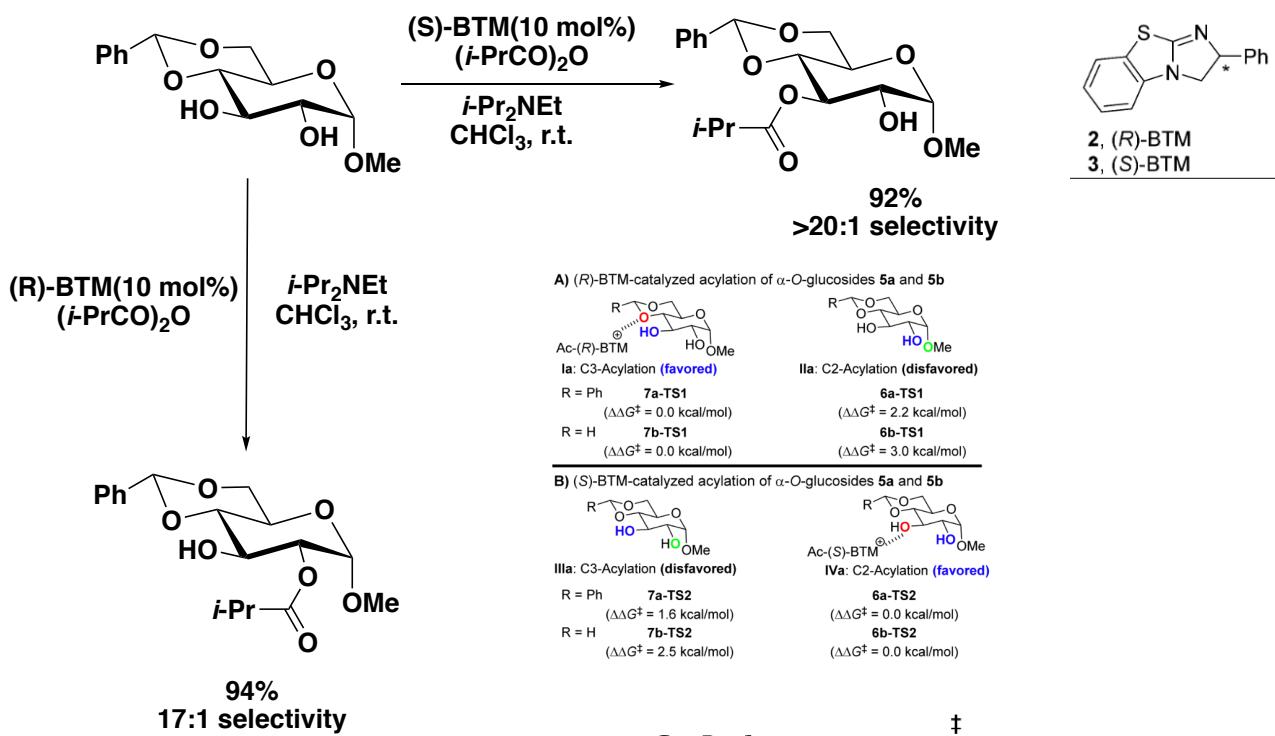
² Ding. et. al. J. Am. Chem. Soc. 2007, 129, 42, 12890–12895

10 Organic catalysts in site-selective acylation: Imidazole derivatives¹

1) Catalyst-Controlled Acetylation of the Cis-1,2-Diol Group in Methyl α-L-Rhamnopyranoside¹



2) Selective Acylation of Glucopyranoside Derivative Using Enantiomeric Benzotetramisole Catalysts²

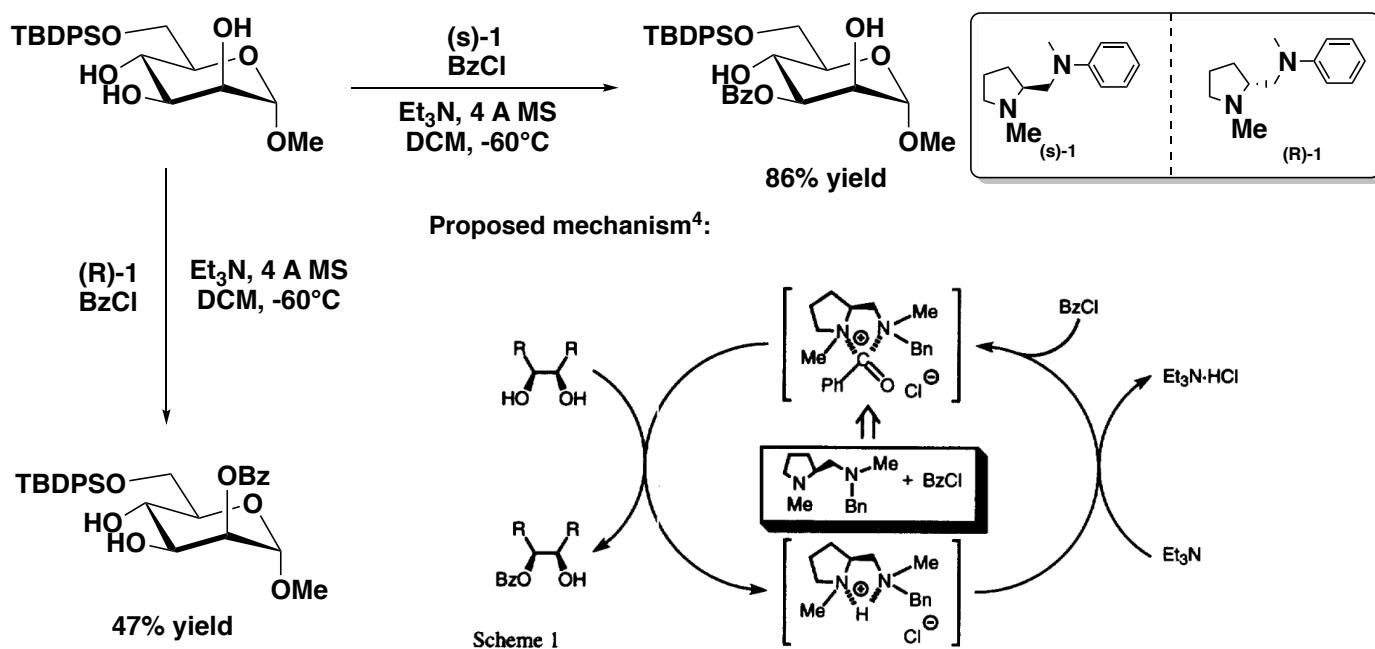


¹ Tan. et. al. Nat. Chem. 2013, 5, 790–795.

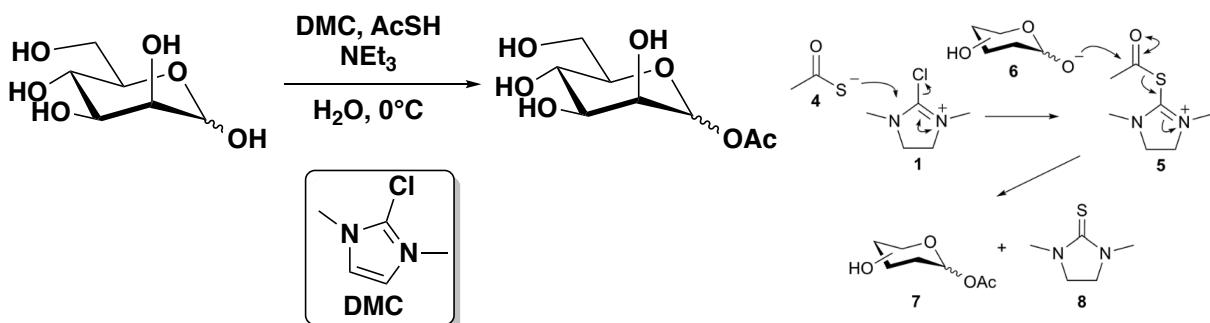
² Tang. et. al. J. Am. Chem. Soc. 2017, 139, 12, 4346–4349.

11 Organic catalysts in site-selective acylation: Amine Catalysts

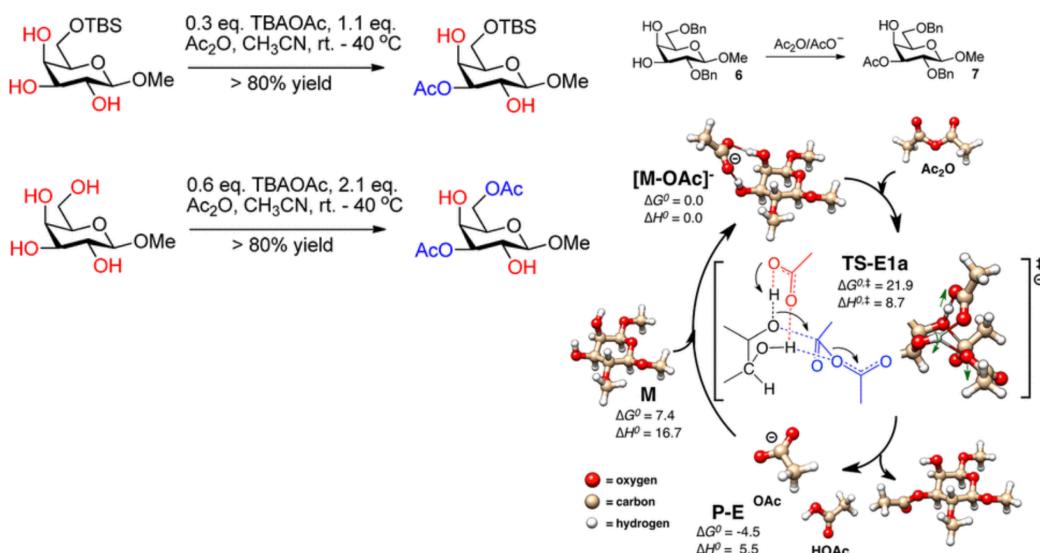
1) Selective Benzoylation of α -Mannopyranoside Derivative Using Enantiomeric Diamine Catalyst¹



2) Base-Promoted Selective Acetylation of the Anomeric OH Group of D-Mannose²

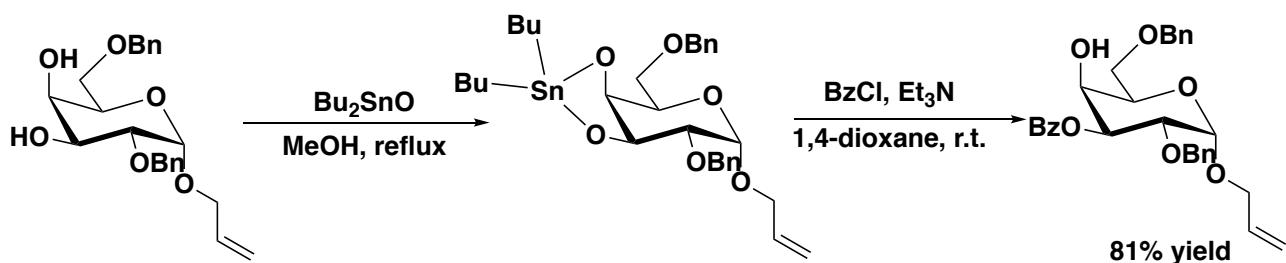


3) Selective Esterification under Conditions of Phase Transfer Catalysis³

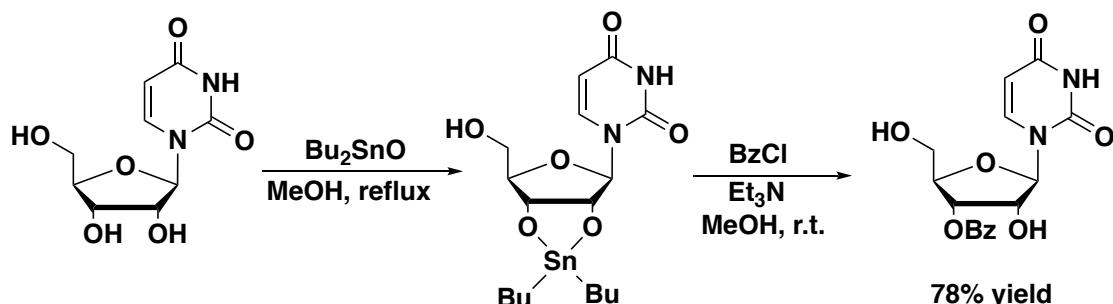


12 Organic catalysts in site-selective acylation: Organotin and Organoboron Catalysts

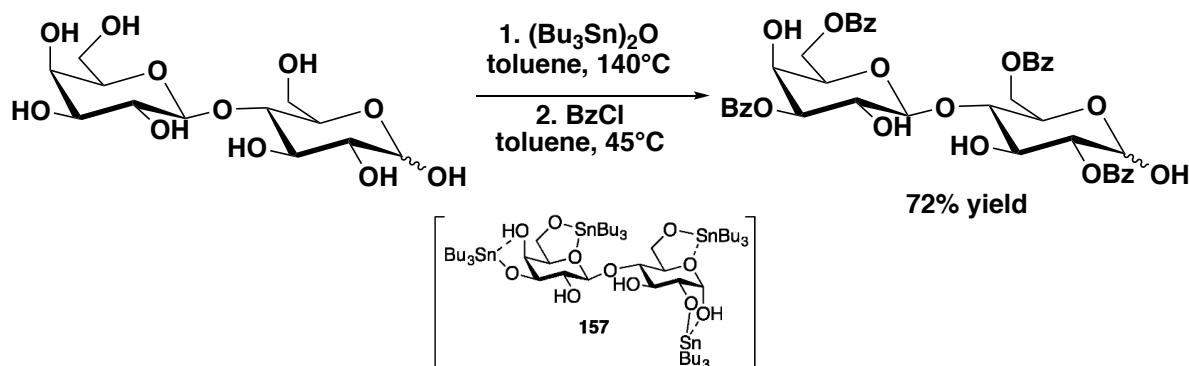
1) Selective Acylations of Secondary OH Groups via Stannylene Acetal¹



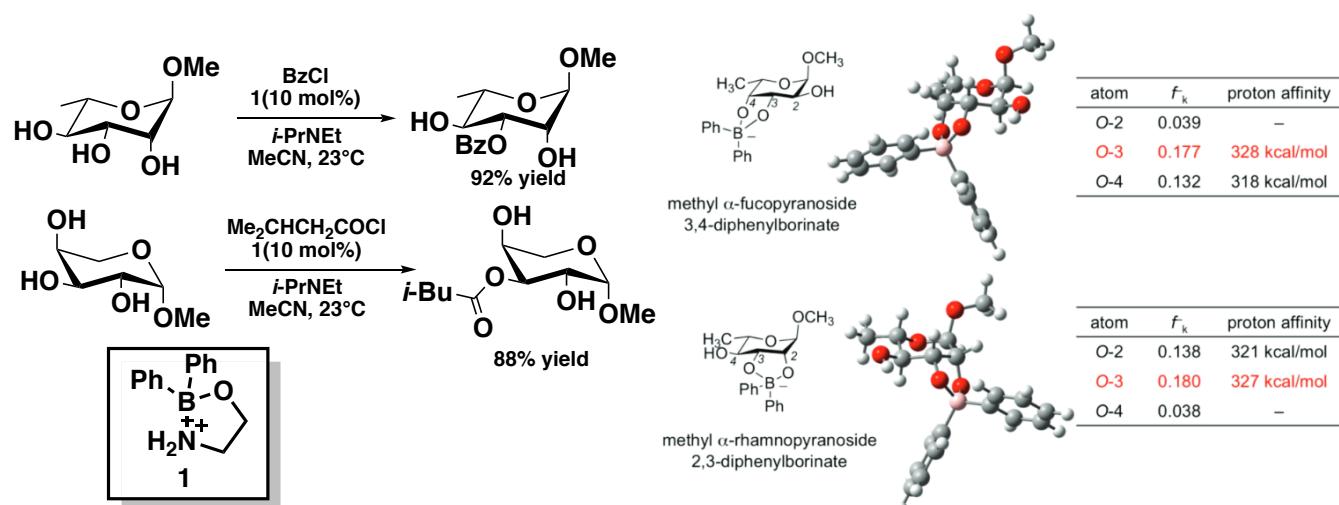
2) Selective Benzoylation of Uridine through Formation of a Cyclic Stannylene Acetal²



3) Selective Benzoylation of Lactose by Trialkystannyly Ether Formation³



4) Selective Monoacylations of Pyranosides Catalyzed by Borinic Ester⁴

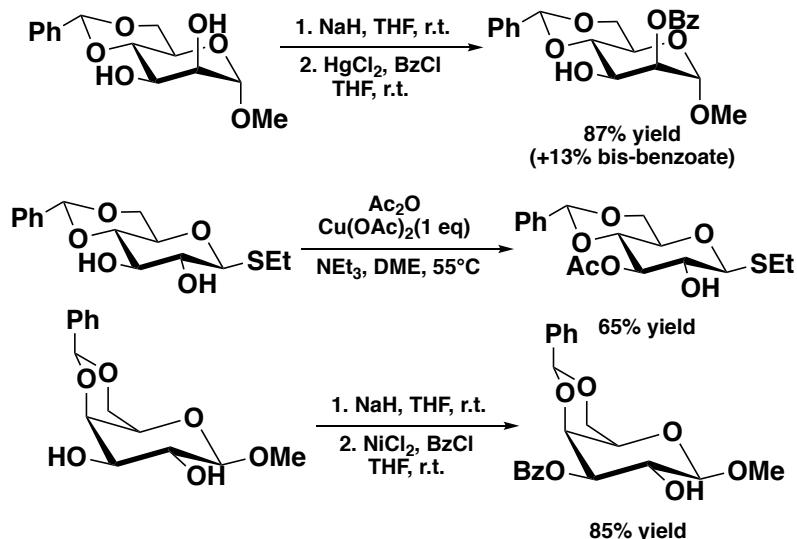


¹ Moffatt. et. al. J. Org. Chem. 1974, 39, 24–30. ² Anderson. et. al. Tetrahedron Lett. 1976, 17, 3503–3506.

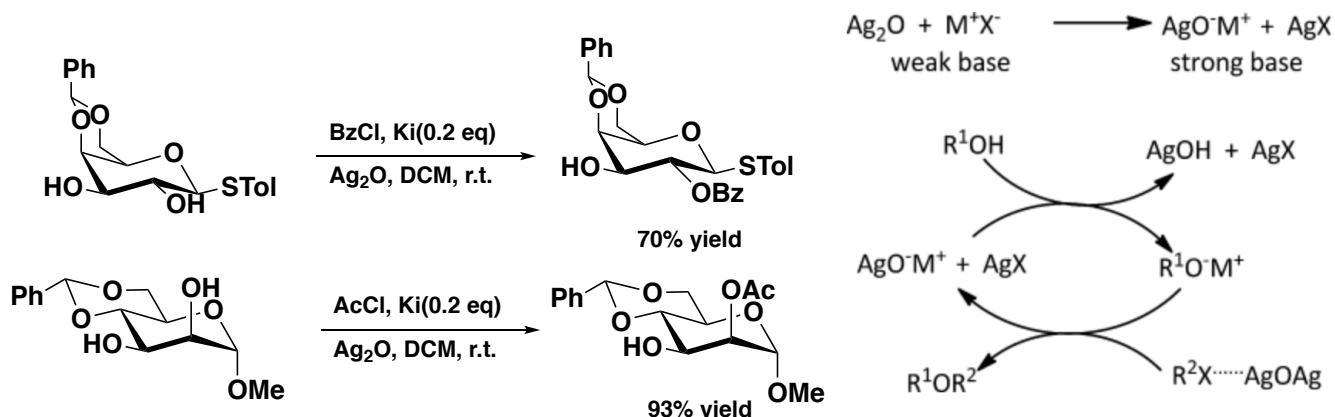
³ Matsui. et. al. Tetrahedron 1981, 37, 2363–2369. ⁴ Mark. et. al. J. Am. Chem. Soc. 2011, 133, 11, 3724–3727.

13 Organic catalysts in site-selective acylation: Transition Metal Salt

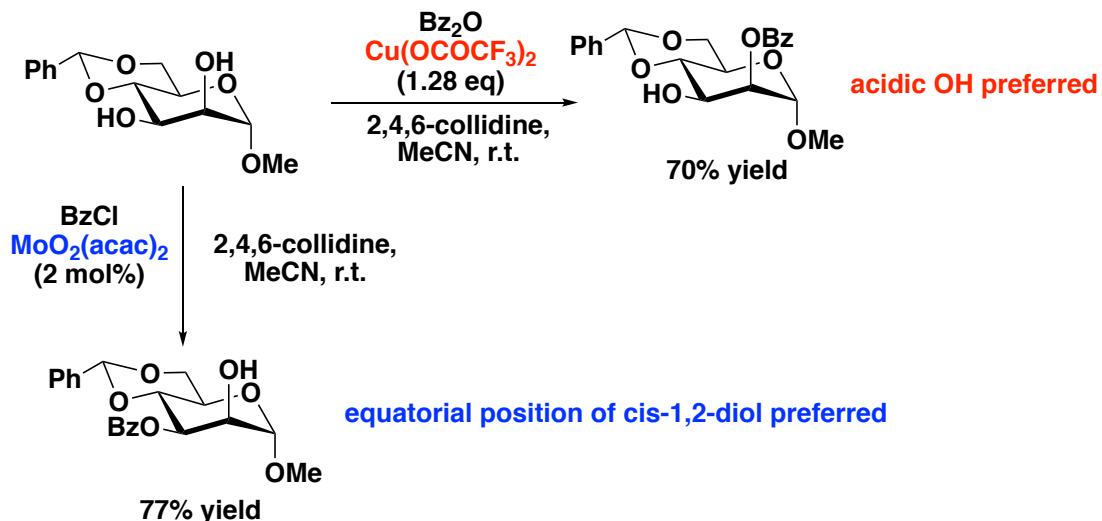
1) Hg(II)- and Cu(II)- and Ni(II)-Mediated Monobenzoylation^{1,2}



2) Ag(I) and KI Mediated Monoesterification^{3,4}



3) Different Regiochemical Outcomes Obtained Using Cu(II) and Mo(VI) Complexes as Catalysts⁵



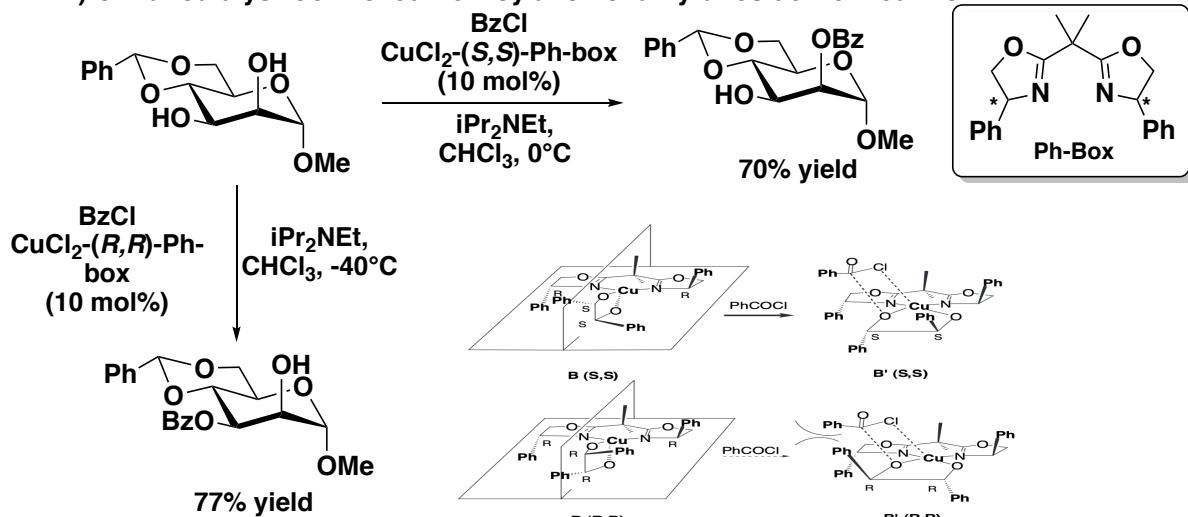
¹ Avela. et. al. Sucr. Belge 1973, 92, 337–344. ² Suthers. et. al. Tetrahedron Lett. 1999, 40, 6991–6994.

³ Ye. et. al. J. Org. Chem. 2004, 69, 5774–5777. ⁴ Dong. et. al. ChemCatChem. 2015, 7, 761–765.

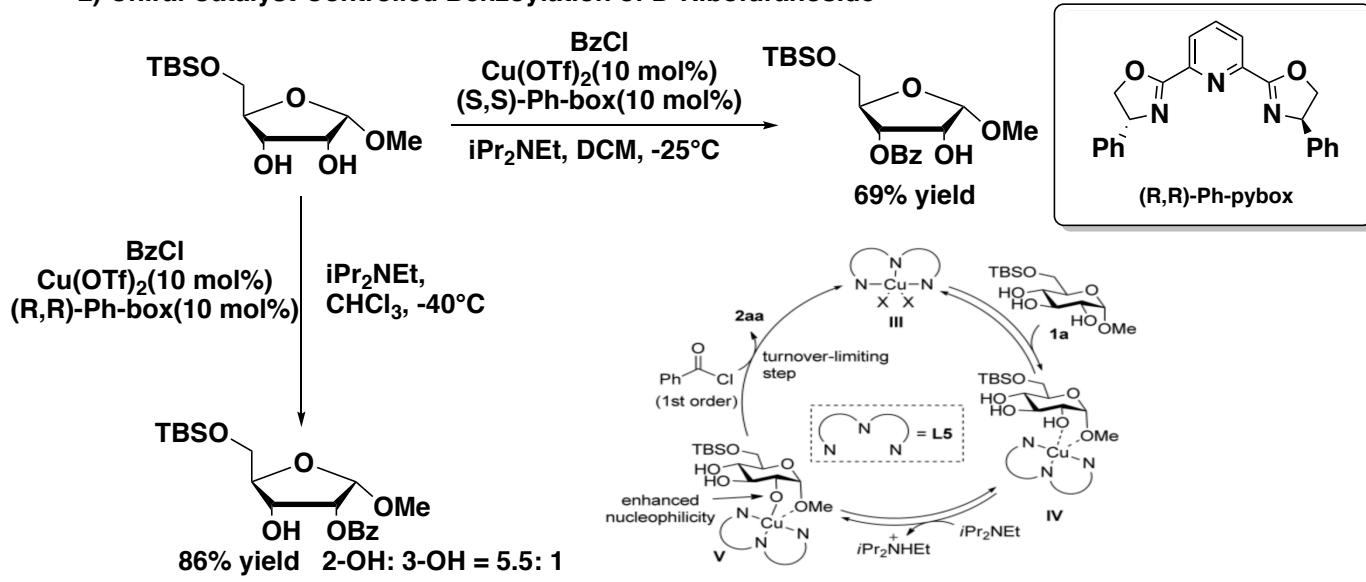
⁵ Evtushenko. et. al. J. Carbohydr. Chem. 2015, 34, 41–54

14 Organic catalysts in site-selective acylation: Transition Metal Salt

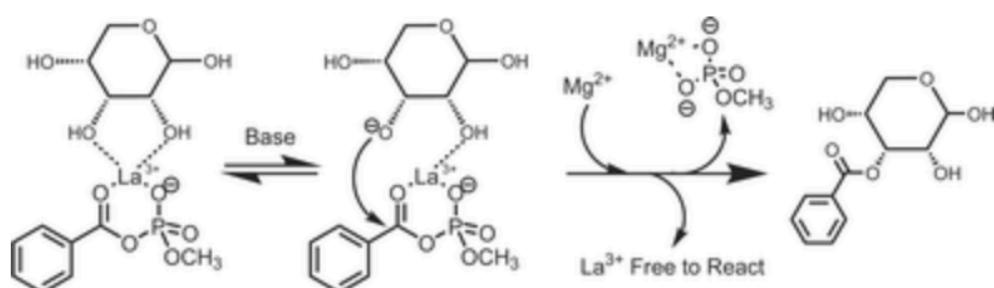
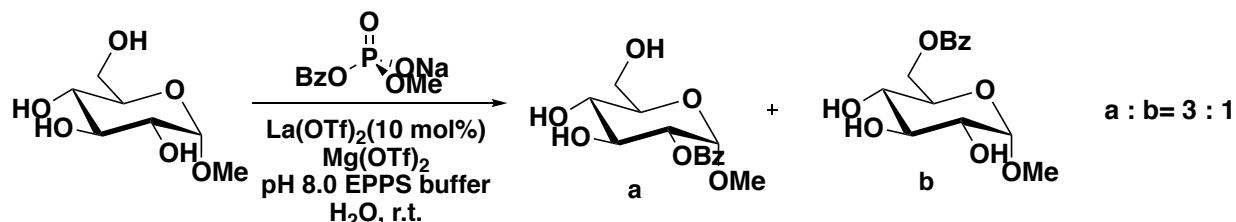
1) Chiral Catalyst-Controlled Benzoylation of a Pyranoside-Derived Diol¹



2) Chiral Catalyst-Controlled Benzoylation of D-Ribofuranoside²



3) Lanthanum(III)-Catalyzed Esterification of Glucopyranoside with Benzoyl Methyl Phosphate



¹ Miller. et. al. Org. Lett. 2013, 15, 6178–6181. ² Dong. et. al. Chem. Eur. J. 2014, 20, 5013–5018.

³ Kluger. et. al. Org. Biomol. Chem., 2010, 8, 2006–2008.

15 Representative Enzyme-Catalyzed Esterifications of Carbohydrate Derivatives

1) Lipase as catalysts of site-selective transesterification¹

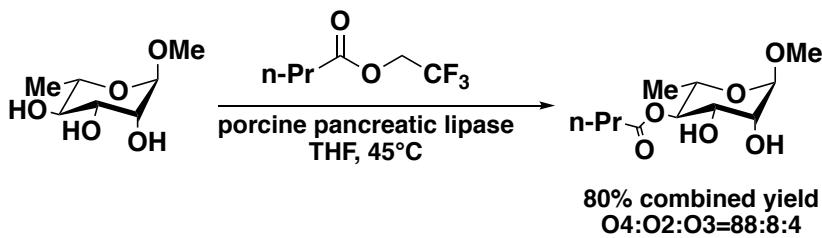


Table I. Enzymatic Butylation of Compounds 1a–4a

entry	substrate	enzyme	T, °C	time, days	overall yield, %	% monoesters		
						b (C-2)	c (C-3)	d (C-4)
1	1a	PPL ^a	45	12	80	8	4	88
2	2a	PPL ^b	45	12	66	4	28	68
3	3a	PPL ^a	45	12	8	41	27	32
4	4a	PPL ^b	45	4	83	94	d	6
5	1a	CCL ^c	45	3	89	d	35	65
6	2a	CCL ^c	45	7	66	4	89	7
7	3a	CCL ^c	45	7	65	63	34	3
8	4a	CCL ^c	45	3	90	78	15	7
9	1a	PFL ^a	25	12	63	1	3	96
10	2a	PFL ^b	25	12	45	2	1	97
11	3a	PFL ^a	25	12	42	96	1	3
12	4a	PFL ^b	25	4	88	96	d	4

^aSolvent: tetrahydrofuran. ^bSolvent: tetrahydrofuran–pyridine, 4:1. ^cSolvent: methylene chloride–acetone, 4:1. ^dTraces (by NMR).

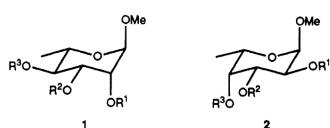


Figure 1.

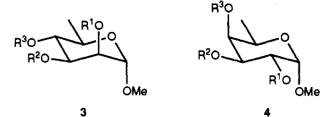


Figure 2.

a: R¹=R²=R³=H; b: R¹=COPr, R²=R³=H;
c: R¹=R³=H, R²=COPr; d: R¹=R²=H, R³=COPr.

2) CMP-Sialic acid as catalyst of site-selective transesterification²

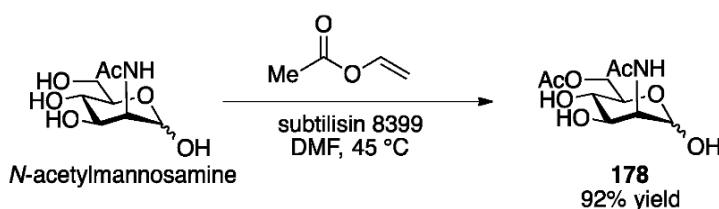


Table I. Kinetic Parameters for the Native and Tagged CMP-NeuAc Synthetase

	k_{cat} , s ⁻¹	K_m , mM		V_{max} , units/mg
		NeuAc	CTP	
native enzyme	1.8	4	0.31	2.1
tagged enzyme	1.9	4.8	1.99	2.3

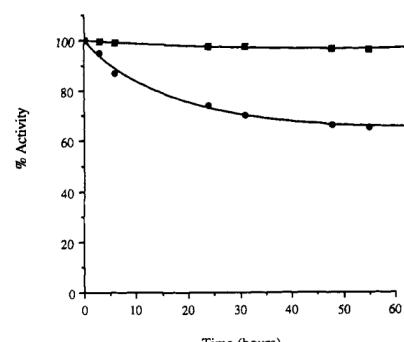


Figure 2. Stability study of both the native (■) and the tagged (○) CMP-sialic acid synthetase.

¹Toma. et. al. J. Org. Chem. 1990, 55, 13, 4187–4190.

²Wong. et. al. J. Am. Chem. Soc. 1992, 114, 3901–3910.