

# *Synthetic Chemistry of Carbohydrates*

**Will Zhao**

*Literature Talk*

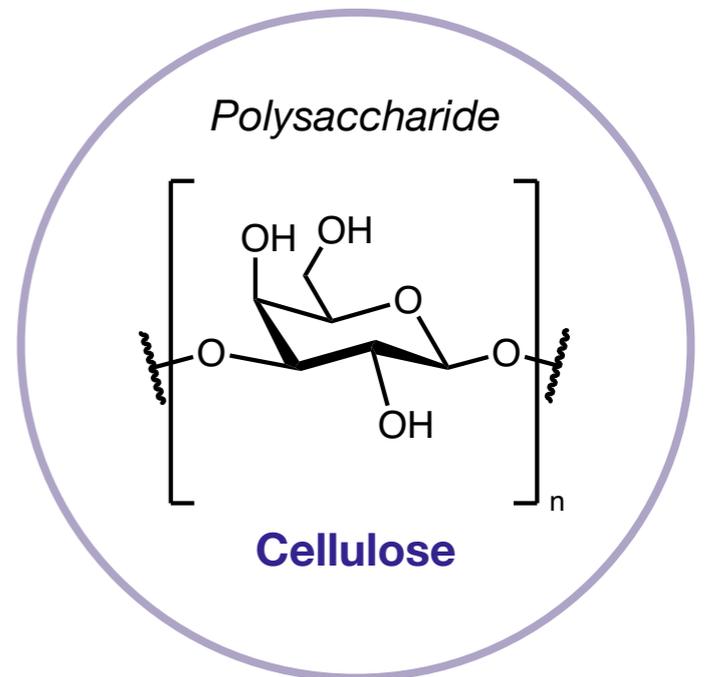
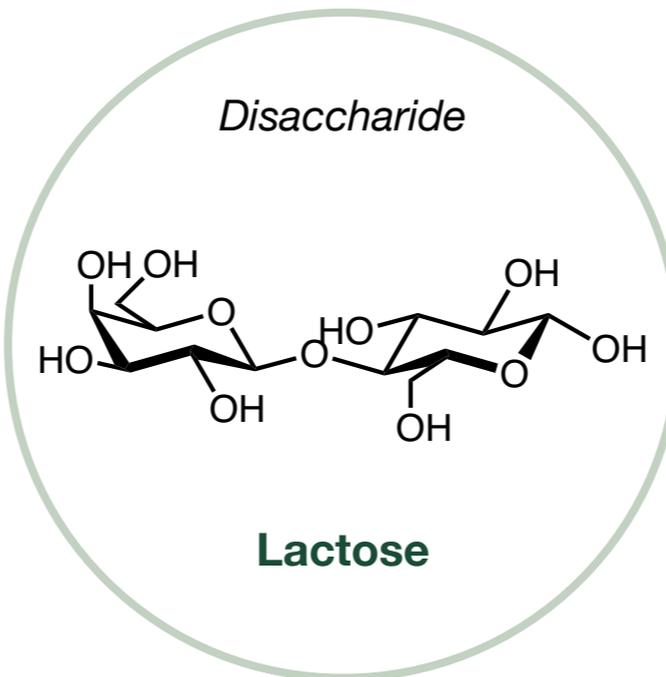
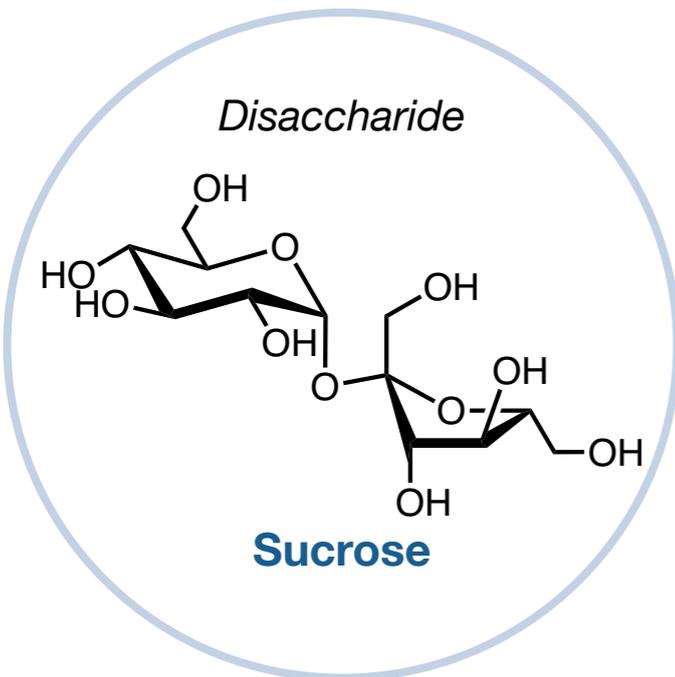
November 5th, 2025

MacMillan Group Meeting



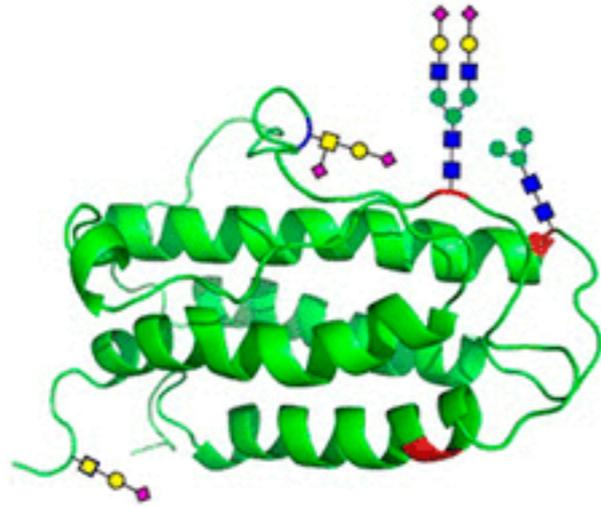
*Why do we care about carbohydrates?*

# Carbohydrates are Abundant in Nature

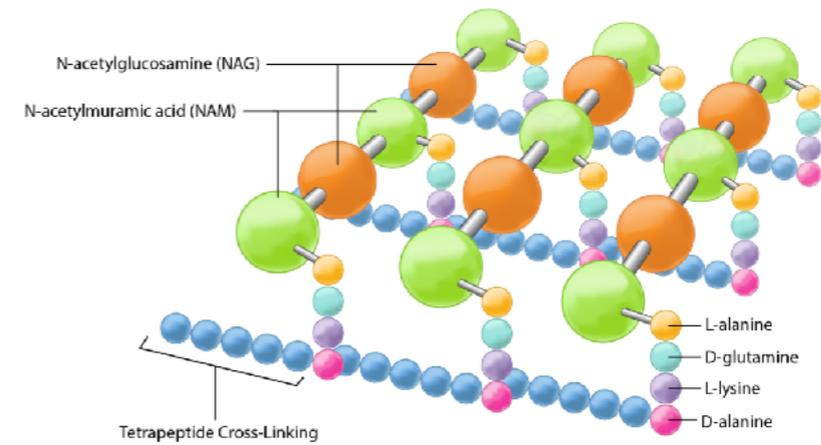


# Carbohydrates are Ubiquitous in Biological Systems

## Protein glycosylation



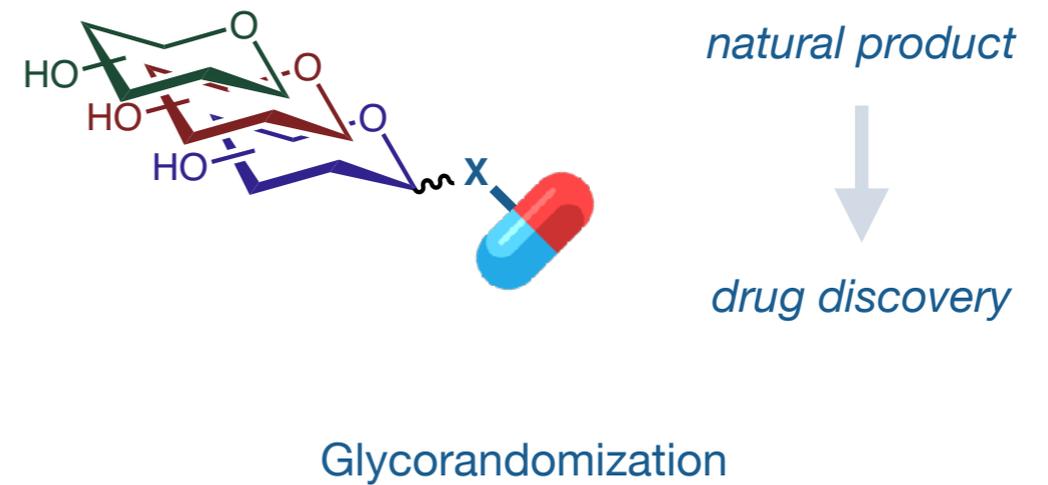
## Bacterial cell wall: peptidoglycan



## Drug design and discovery

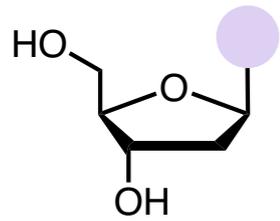


## Applications in library synthesis



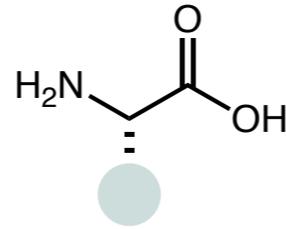
# Synthetic Potential of Carbohydrates

## Nucleosides



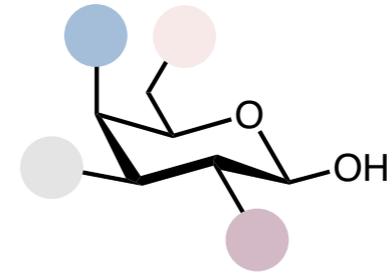
4 canonical nucleobases

## Amino acids

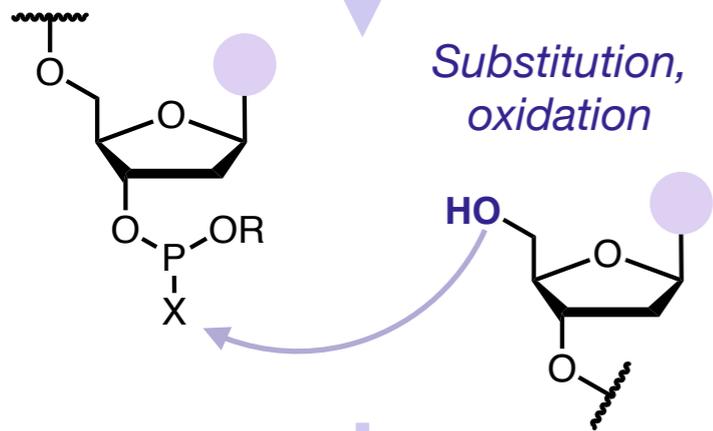


23 proteogenic amino acids

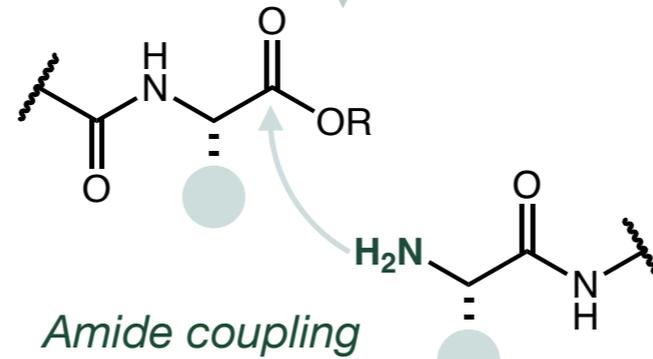
## Carbohydrates



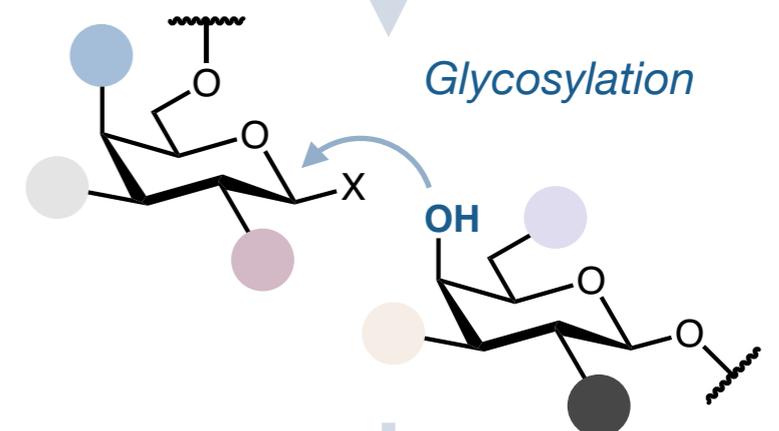
36 mono-saccharides\*



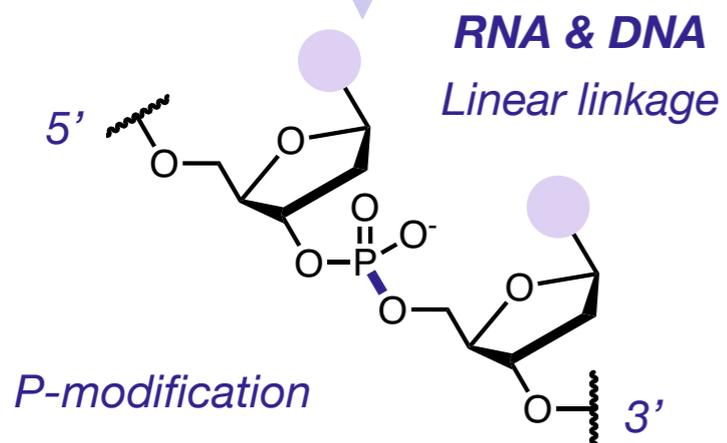
Substitution, oxidation



Amide coupling



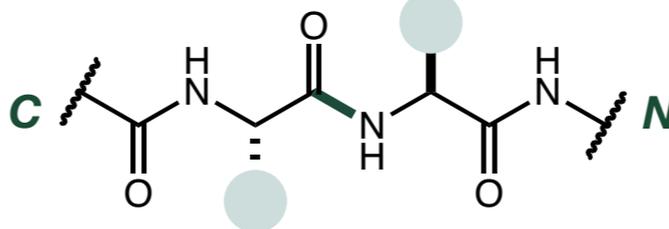
Glycosylation



RNA & DNA  
Linear linkage

P-modification

Peptide Achiral linkage



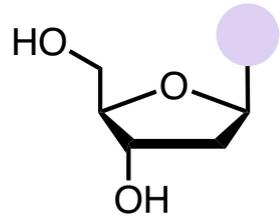
Termini functionalization

Polysaccharide  
Chiral linkage

5 chiral sites  
of reaction

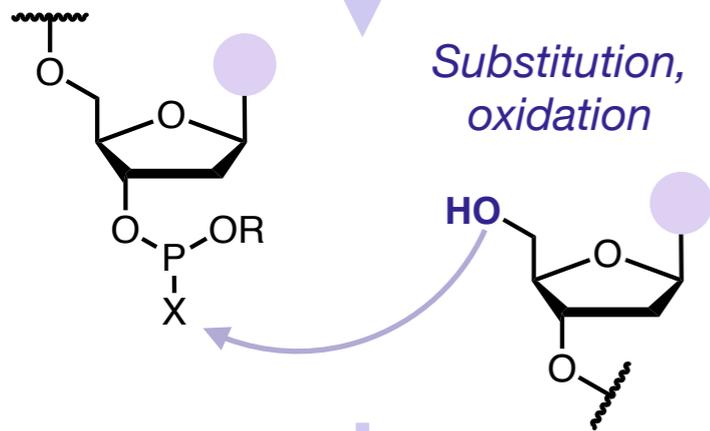
# Synthetic Potential of Carbohydrates

## Nucleosides

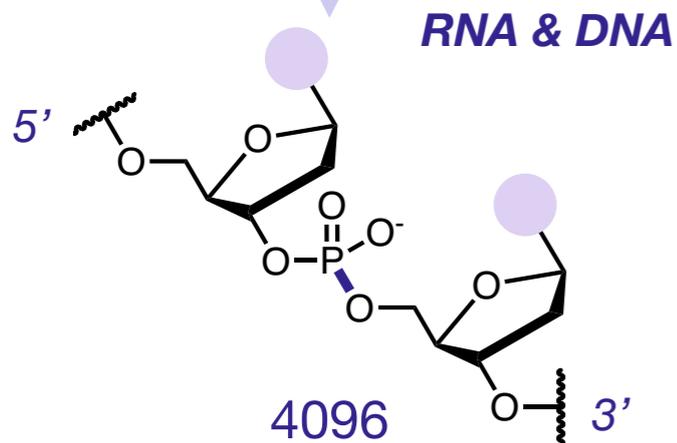


4 canonical nucleobases

× 6

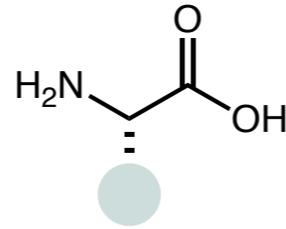


× 6



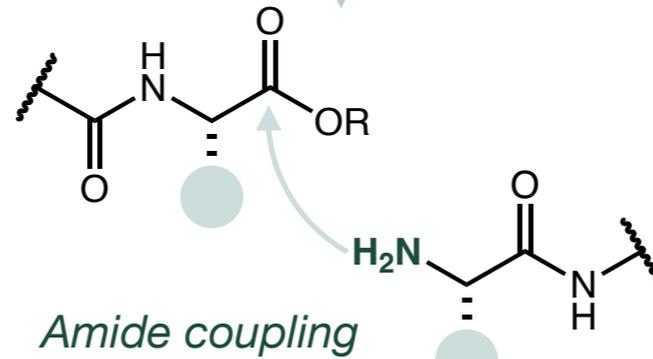
4096

## Amino acids



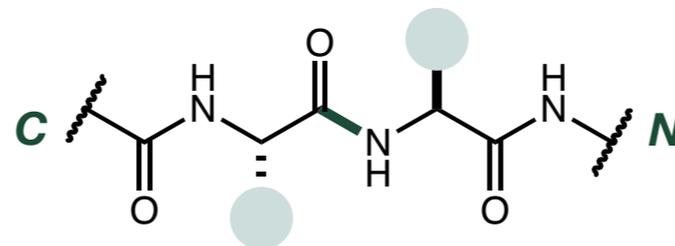
23 proteogenic amino acids

× 6



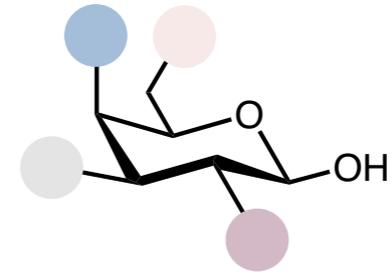
× 6

## Peptide



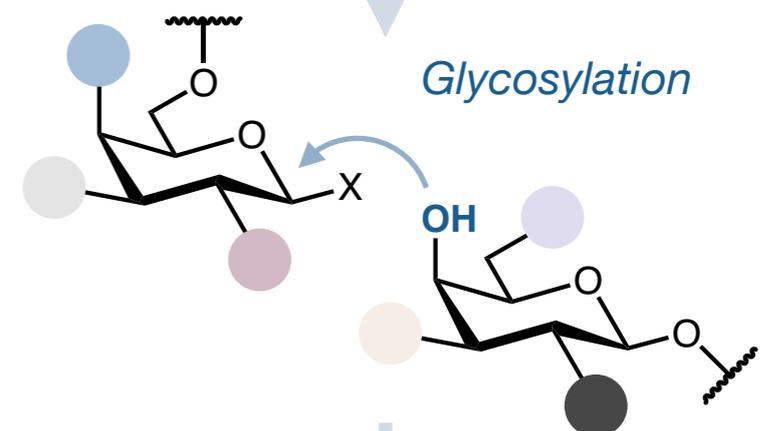
64 million

## Carbohydrates



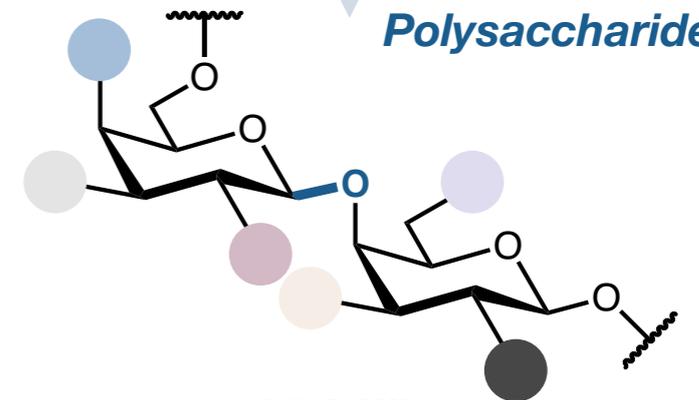
36 mono-saccharides\*

× 6



× 6

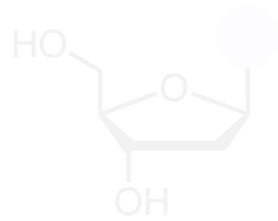
## Polysaccharide



192 billion

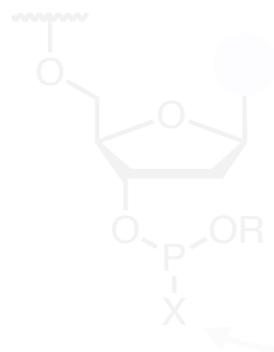
# Synthetic Potential of Carbohydrates

## Nucleosides



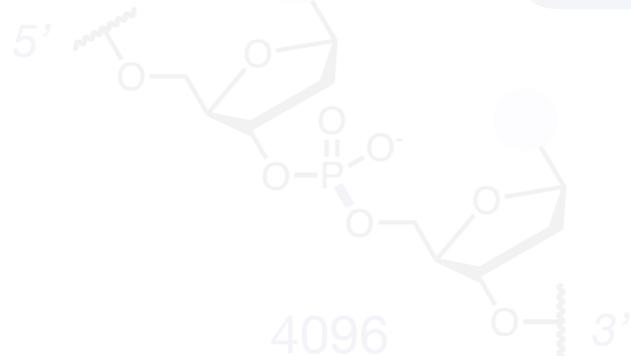
4 canonical nucleobases

× 6



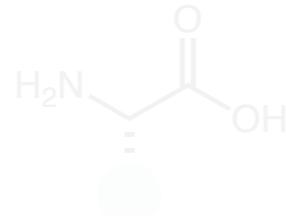
Substitution, oxidation

× 6



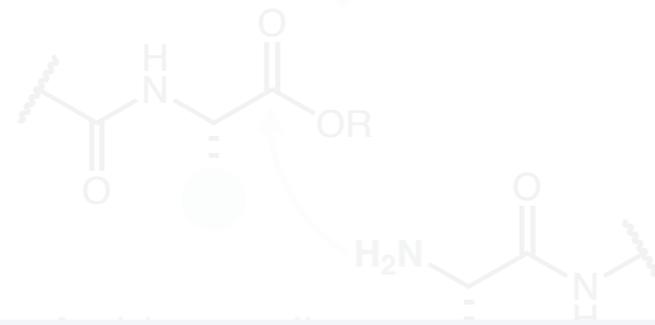
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## Amino acids

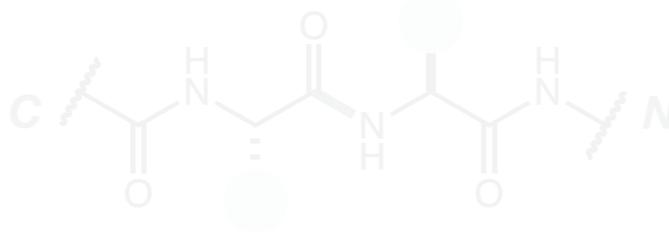


23 proteogenic amino acids

Why are synthetic chemists **reluctant** to work with carbohydrates?



“Difficult **chemistry**, difficult **biology**, difficult **analysis**, I don't want to see another **protecting group**, let's leave the sugar out.”



64 million

## Carbohydrates



36 mono-saccharides\*

× 6



Glycosylation

× 6

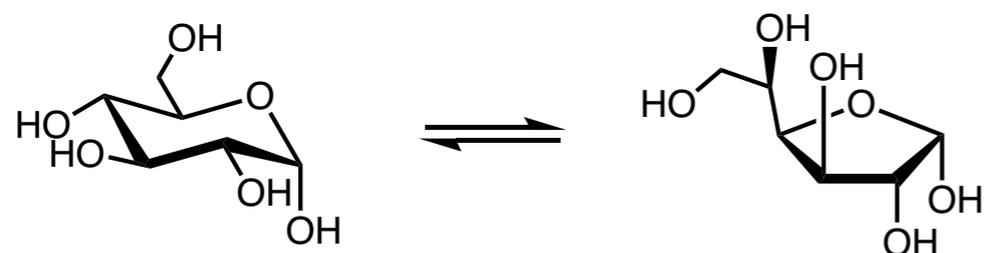


Polysaccharide

192 billion

# Synthetic Challenges in Carbohydrate Chemistry

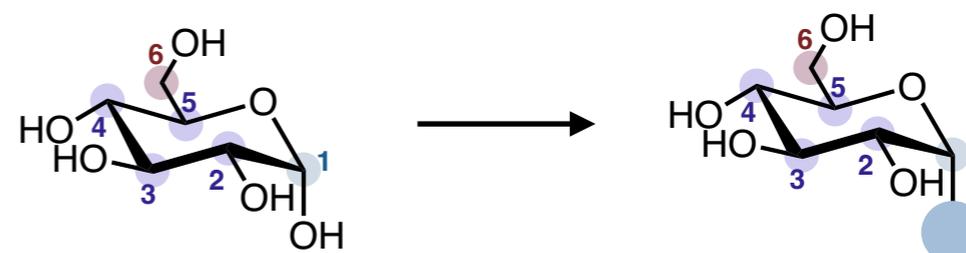
## Conformational fluidity



Pyranose

Furanose

## Regiochemical control



Steric & electronic properties

*"A hostile frontier"*

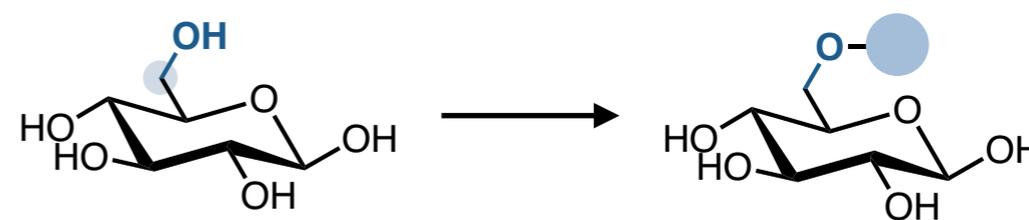
## Stereochemical control



$\alpha$ -glycoside

$\beta$ -glycoside

## Protecting group manipulations



Selective protection & deprotection

# *Outline*

***Discovery and Early History***

***Terminology***

***Monomer Functionalization & Chemical Glycosylation***

***Recent Advancements & Applications***

# *Outline*

***Discovery and Early History***

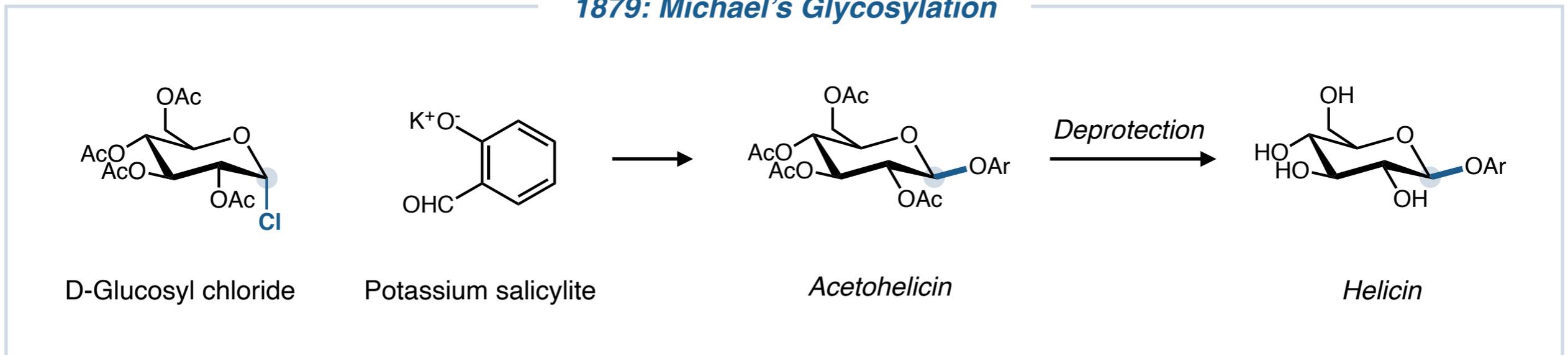
*Terminology*

***Monomer Functionalization & Chemical Glycosylation***

***Recent Advancements & Applications***

# World's First Chemical Glycosylation

## 1879: Michael's Glycosylation



**Arthur Michael**

(1853-1942)

### *Action of Acetochlorhydrose on an Alcoholic Solution of Potassium Salicylite.*

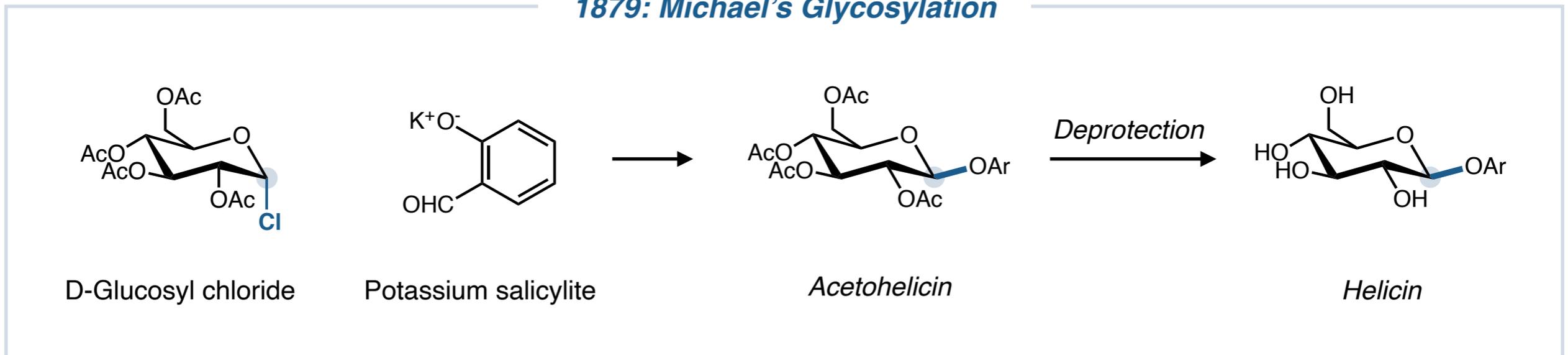
The properties of phenolglucoside indicate that this compound belongs to the group of natural glucosides, and made it probable that the glucosides obtained by synthesis would not prove isomeric, but identical with those occurring in nature. I have first undertaken the synthesis of helicin, by allowing acetochlorhydrose to act on potassium salicylite.

\*The action of absolute alcohol on the compounds obtained by dehydrating with acetic anhydride, as hexacetatidiglucose, presents considerable interest. I shall also return, in a future paper, to the action of acetylchloride on levulose, and other carbohydrates.

†Ann. Chem. Pharm. 154, 23.

# World's First Chemical Glycosylation

## 1879: Michael's Glycosylation



**Arthur Michael**  
(1853-1942)

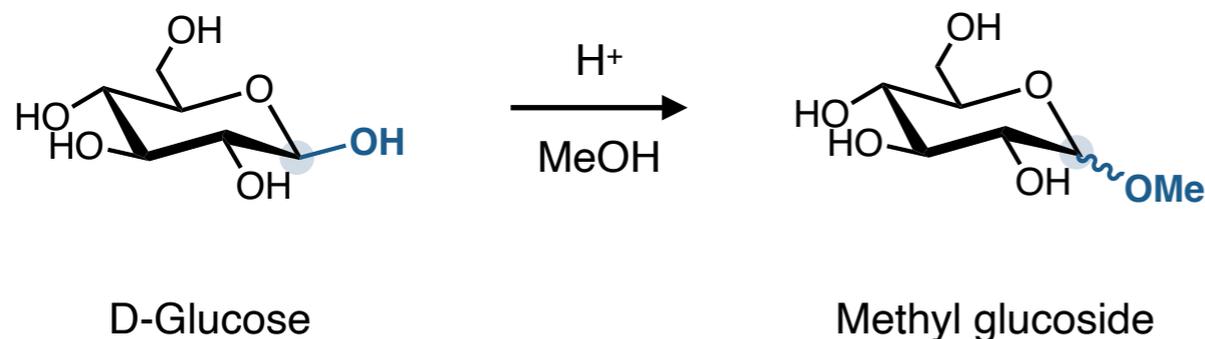
An analysis of the substance, dried at 100°, gave results which correspond well with the formula  $C_{13}H_{16}O_7$ . .2100 gr. of substance gave .4206 gr. of  $CO_2$  and .1124 gr. of  $H_2O$ .

		Calculated.	Found.
C	...	54.93	55.09
H	...	5.63	5.90
O	...	39.44	39.11

*"...small, white, odourless needles [that has] a **bitter** taste."*

## Structure Elucidation: Absolute Configuration

### 1893: Fischer Glycosylation



Other reactions named after Fischer:

- **Kiliani–Fischer synthesis**
- Fischer–Speier esterification
- Fischer indole synthesis
- Fischer oxazole synthesis

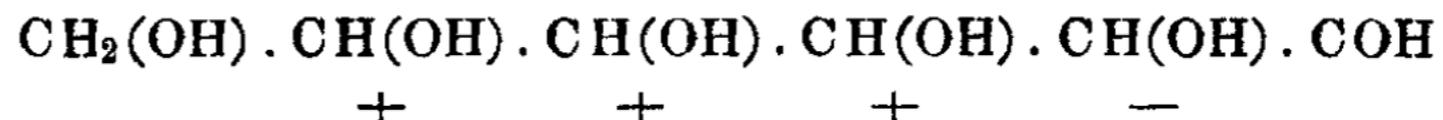


**Emil Fischer**  
(1852-1919)

### 432. Emil Fischer: Ueber die Configuration des Traubenzuckers und seiner Isomeren. II.

[Mittheilung aus dem chemischen Laboratorium der Universität Würzburg.]  
(Eingangen am 8. August.)

In der ersten Abhandlung<sup>1)</sup> habe ich für den Traubenzucker die Formel



First reported **stereoisomeric** assignment of D-glucose

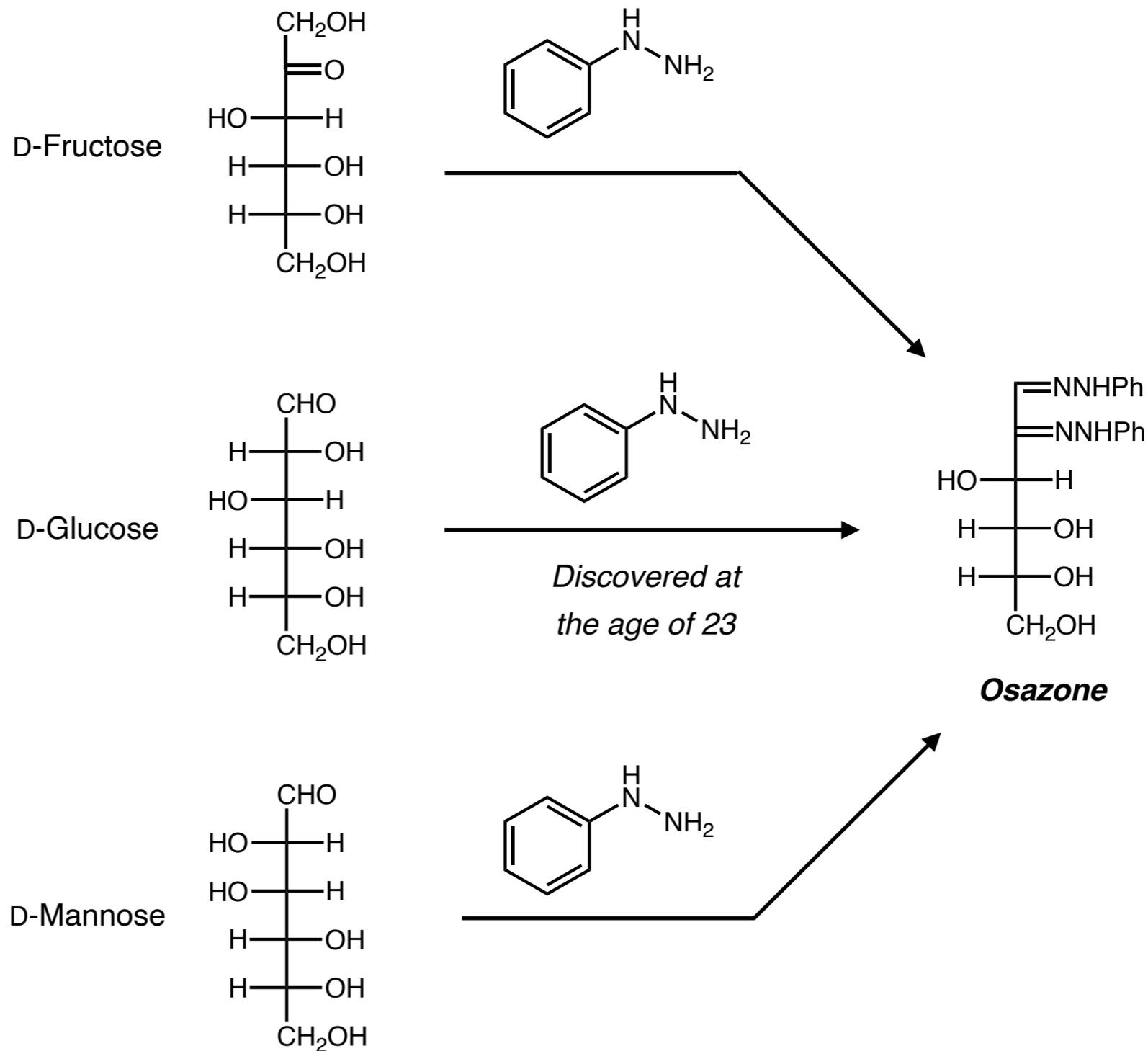
Fischer, E. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2683-2687.

Fischer, E. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 2400-2412.

# Structure Elucidation: Absolute Configuration

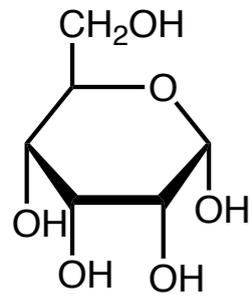


**Emil Fischer**  
(1852-1919)

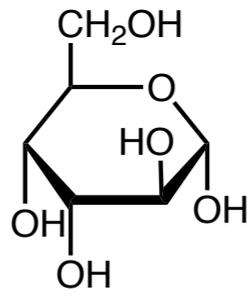




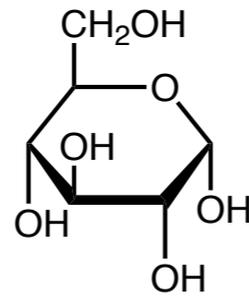
## Structural Elucidation: Conformational Analysis



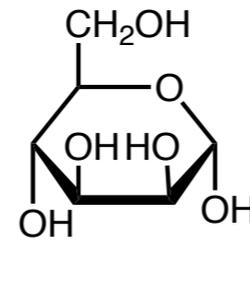
D-Allose



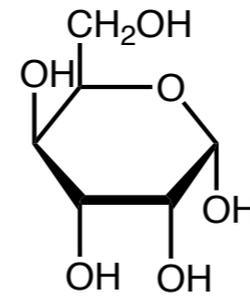
D-Altrose



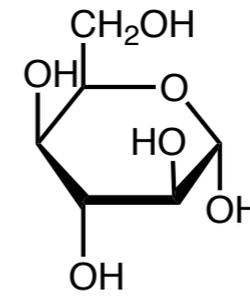
**D-Glucose**



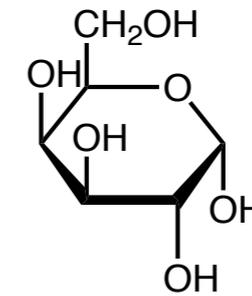
D-Mannose



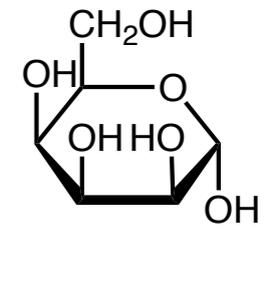
D-Gulose



D-Idose



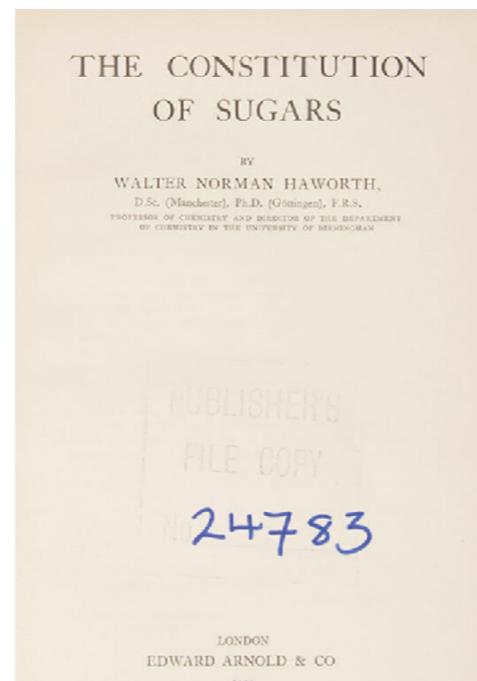
D-Galactose



D-Talose



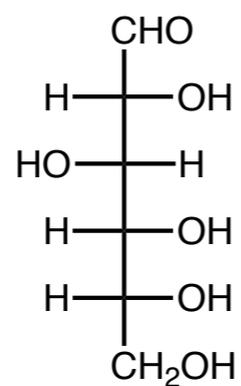
**Norman Haworth**  
(1883-1950)



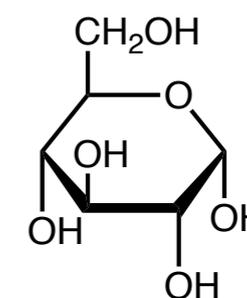
*The Constitution of Sugars* (1929)

- Cyclic structure of monosaccharides
- Structure elucidation of various disaccharides
- Synthesis of Vitamin C

## Structural Elucidation: Nobel Prize



Fischer projection



Haworth projection

 **Emil Fischer**  
(1852-1919)

 **Norman Haworth**  
(1883-1950)

## Structural Elucidation: Nobel Prize



 **Emil Fischer**  
(1852-1919)



Nobel Prize in  
Chemistry (1902)

“...for his work on  
sugar and purine  
syntheses”



 **Norman Haworth**  
(1883-1950)



Nobel Prize in  
Chemistry (1937)

“...for his investigations  
on carbohydrates and  
vitamin C”

# *Outline*

*Discovery and Early History*

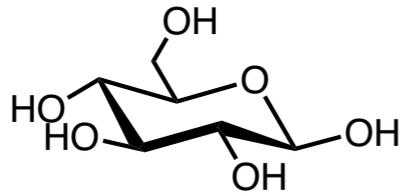
*Terminology*

*Monomer Functionalization & Chemical Glycosylation*

*Recent Advancements & Applications*

# The ABCs of Carbohydrate Chemistry: Nomenclature and Vocabulary

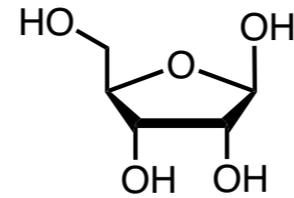
## Chain Length



D-Glucose

### Hexose

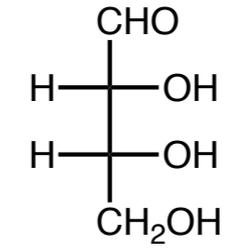
*Polysaccharide building blocks*



D-Ribose

### Pentose

*Nucleoside synthesis*



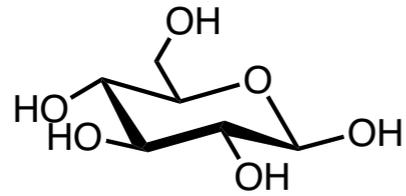
D-Erythrose

### Tetrose

*Pentose phosphate pathway*

# The ABCs of Carbohydrate Chemistry: Nomenclature and Vocabulary

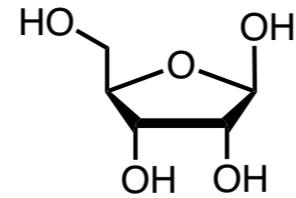
## Conformation



D-Glucose

### Pyranose

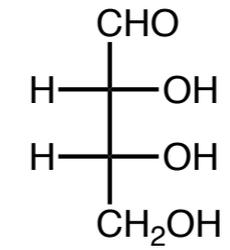
*Dominant form in solution*



D-Ribose

### Furanose

*24:76 furanose vs. pyranose*



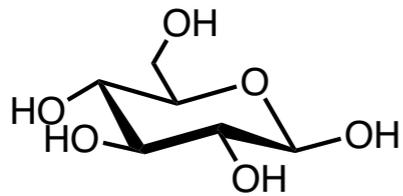
D-Erythrose

### Acyclic

*Least common for reducing sugars*

# The ABCs of Carbohydrate Chemistry: Nomenclature and Vocabulary

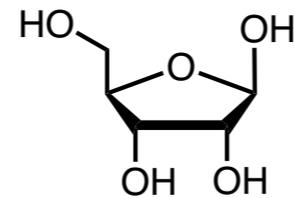
## Conformation



D-Glucose

### Pyranose

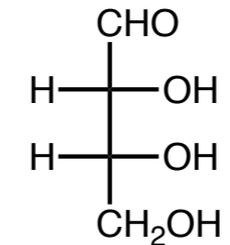
*Dominant form in solution*



D-Ribose

### Furanose

*24:76 furanose vs. pyranose*

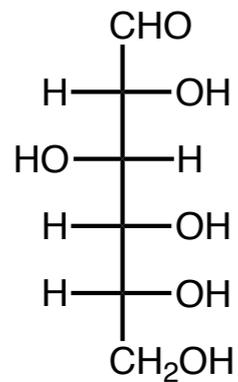


D-Erythrose

### Acyclic

*Least common for reducing sugars*

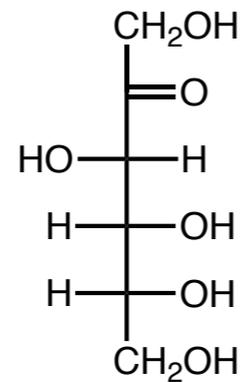
## Carbonyl reactivity



D-Glucose

### Aldose

*Aldohexose*



D-Fructose

### Ketose

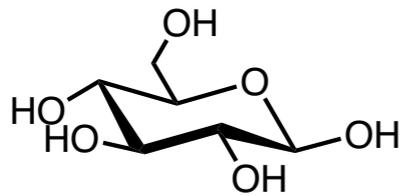
*Ketohexose*

Both aldoses and ketoses are **reducing sugars** due to the presence of the carbonyl group.

**All monosaccharides** are reducing sugars.

# The ABCs of Carbohydrate Chemistry: Nomenclature and Vocabulary

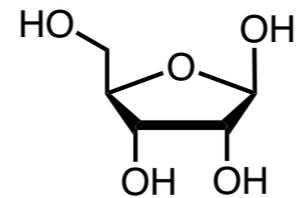
## Conformation



D-Glucose

### Pyranose

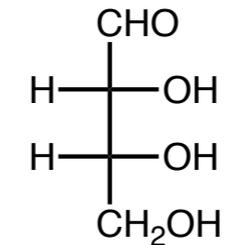
*Dominant form in solution*



D-Ribose

### Furanose

*24:76 furanose vs. pyranose*

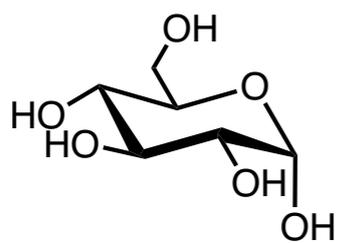


D-Erythrose

### Acyclic

*Least common for reducing sugars*

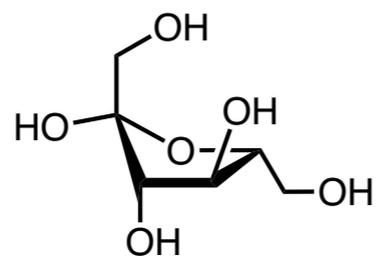
## Carbonyl reactivity



D-Glucose

### Aldose

*Aldohexose*



D-Fructose

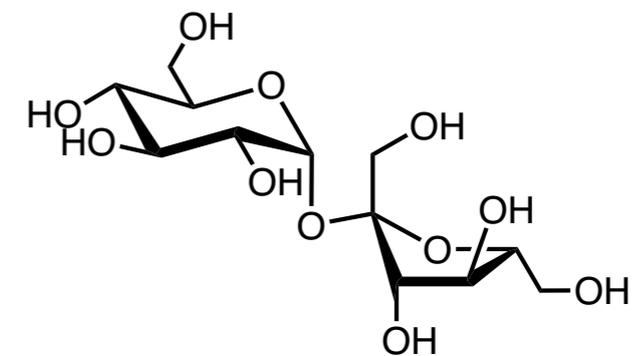
### Ketose

*Ketohexose*

*Glycosylation*



*“-H<sub>2</sub>O”*



Sucrose

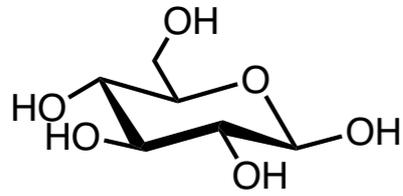
### Disaccharide

*A non-reducing sugar*

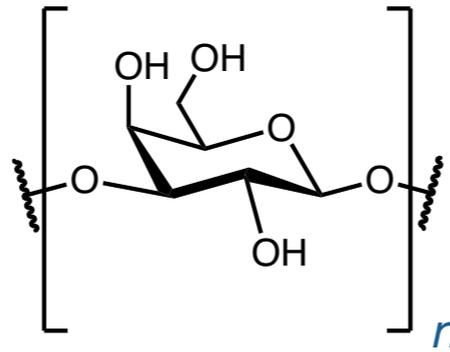
Loss of **carbonyl** reactivity

# The ABCs of Carbohydrate Chemistry: Nomenclature and Vocabulary

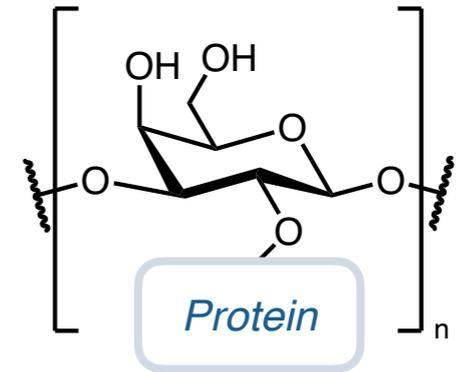
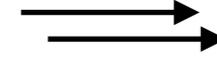
## Monomers and Polymers



Monosaccharide

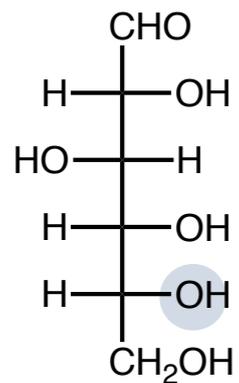


$n = 3-9$ : oligosaccharide  
 $n > 9$ : polysaccharide

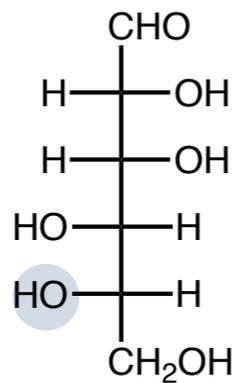


Glycoconjugate

## Enantiomeric Forms

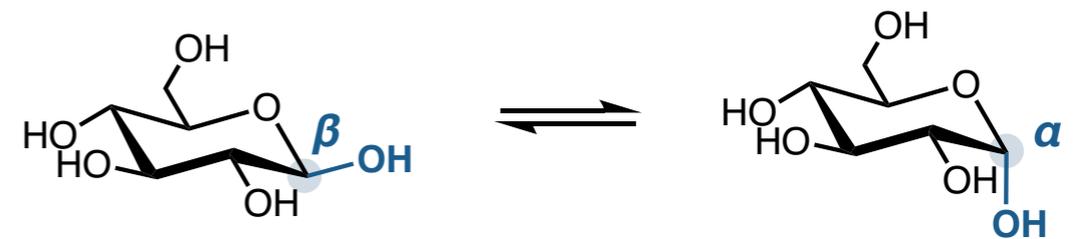


D-(+)-Glucose



L-(-)-Mannose

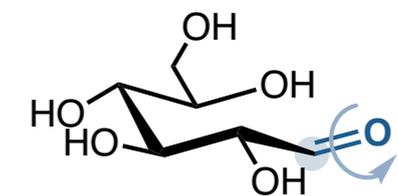
## Anomeric Forms



$\beta$ : up

$\alpha$ : down

via  
Mutarotation



# *Outline*

*Discovery and Early History*

*Terminology*

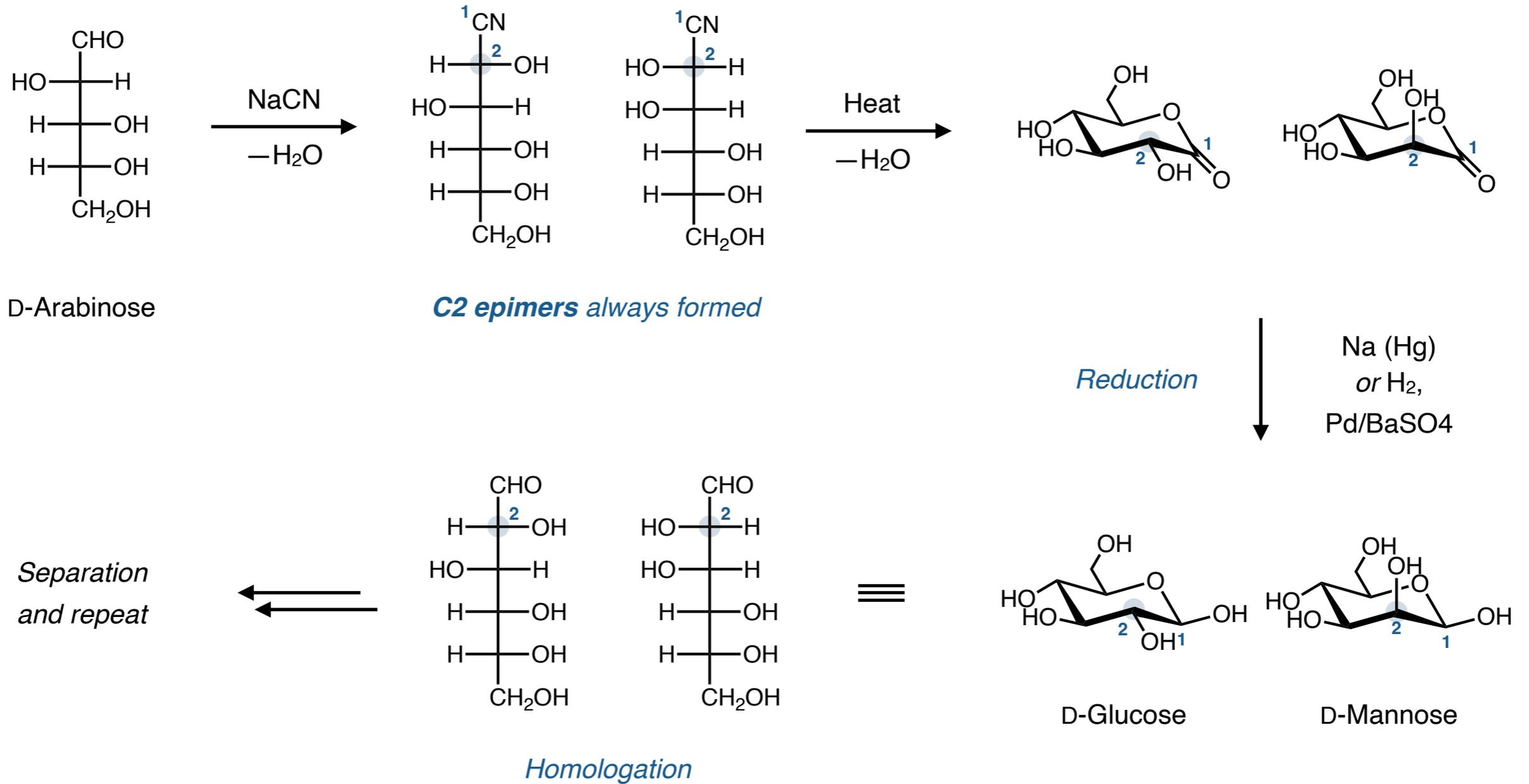
***Monomer Functionalization & Chemical Glycosylation***

*Recent Advancements & Applications*

# Synthesis of Monosaccharides

## Homologation

### Kiliani–Fischer Synthesis



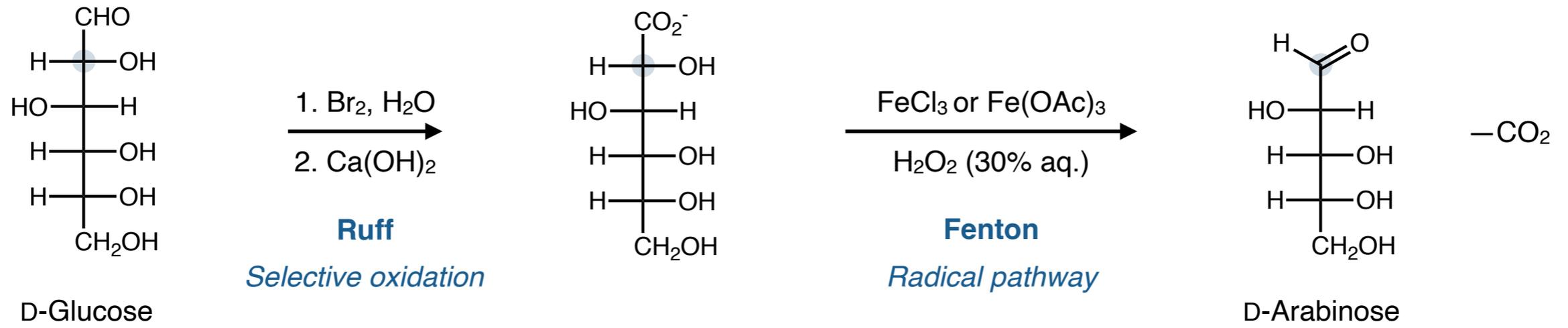
Fischer, E. *Ber. Dtsch. Chem. Ges.* **1889**, 22, 2204-2205.

Kiliani, H. *Ber. Dtsch. Chem. Ges.* **1885**, 18, 3066-3072.

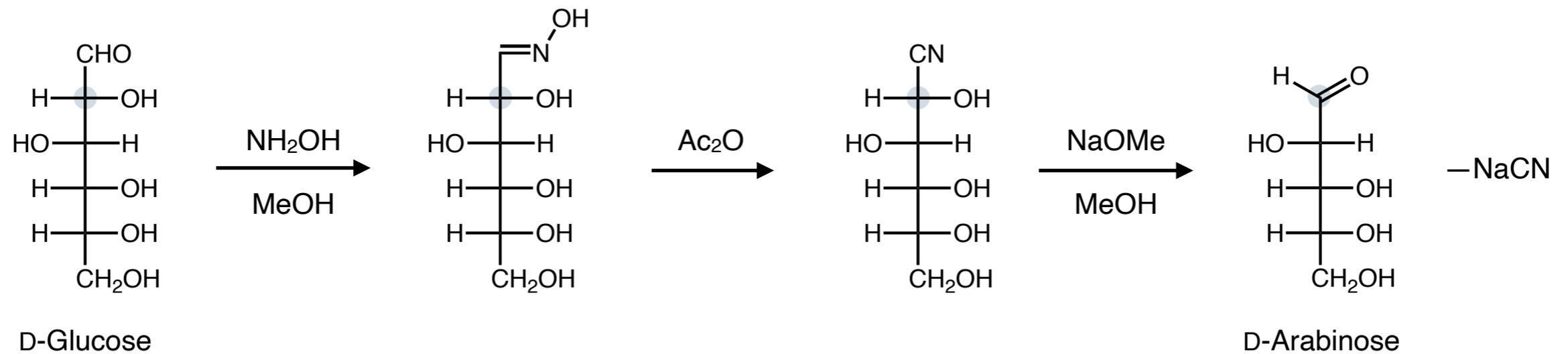
# Synthesis of Monosaccharides

## Degradation

### Ruff–Fenton Degradation



### Wohl Degradation



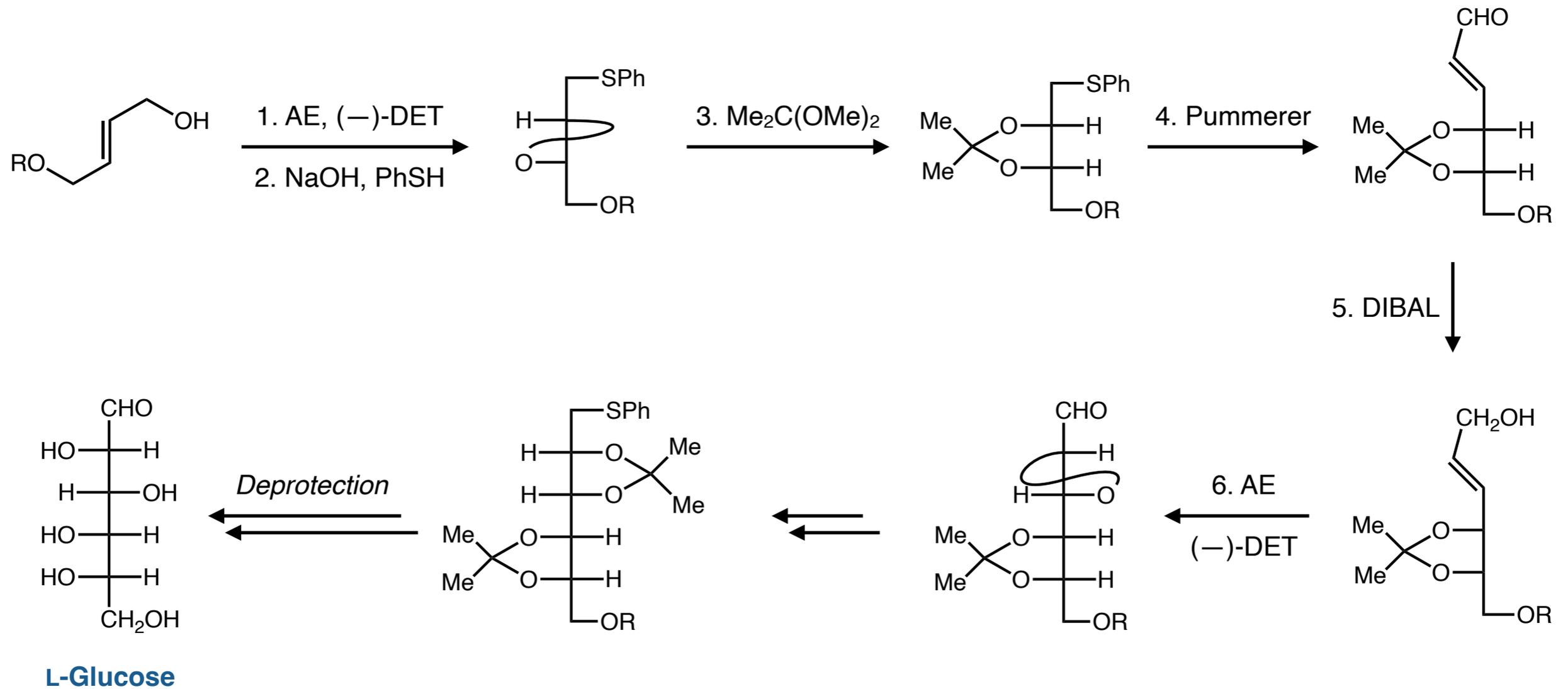
Ruff, O. *Ber. Dtsch. Chem. Ges.* **1898**, 31, 1573-1577.

Wohl, A. *Chem. Ber.* **1893**, 730-744.

# Synthesis of Monosaccharides

## Sharpless total synthesis

### The Sharpless Total Synthesis

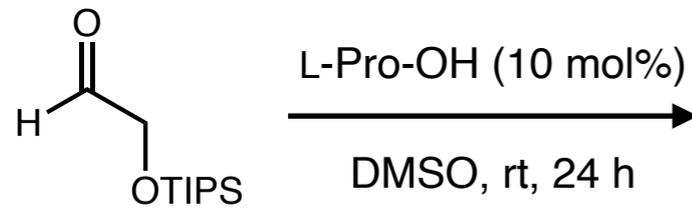


“Since the **mirror image** of every compound in Fig. 2 can be prepared by simple exchange of the chiral ligand in the **AE reaction**, the **formal synthesis** of the **D-hexoses** has also been achieved.”

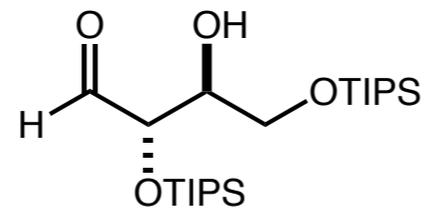
# Synthesis of Monosaccharides

## Organocatalytic Aldol

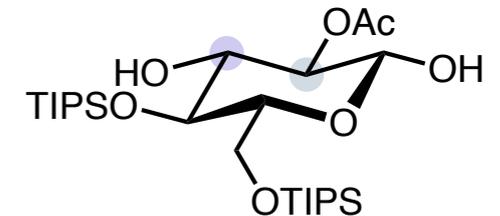
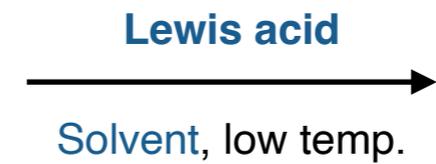
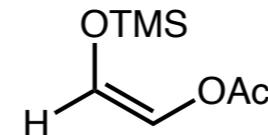
A. B. Northrup & D.W.C. MacMillan, 2004



Glyceraldehyde



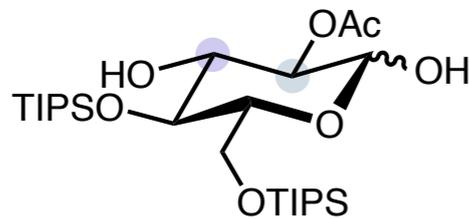
92% yield, 95% ee (anti)  
4:1 anti:syn



Stereoselective aldol

L-hexoses

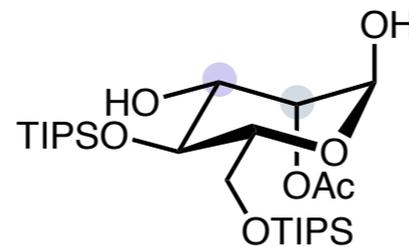
Divergent access to three L-hexoses



L-Glucose

79% yield, 10:1 dr  
95% ee

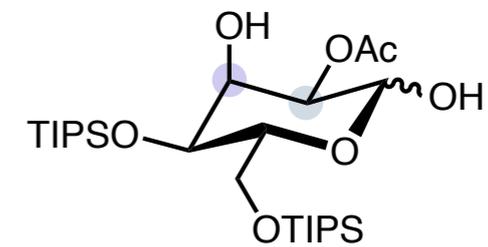
MgBr<sub>2</sub> Et<sub>2</sub>O  
Et<sub>2</sub>O, -20 °C to 4 °C



L-Mannose

87% yield, >19:1 dr  
95% ee

MgBr<sub>2</sub>, Et<sub>2</sub>O  
DCM, -20 °C to 4 °C



L-Allose

97% yield, >19:1 dr  
95% ee

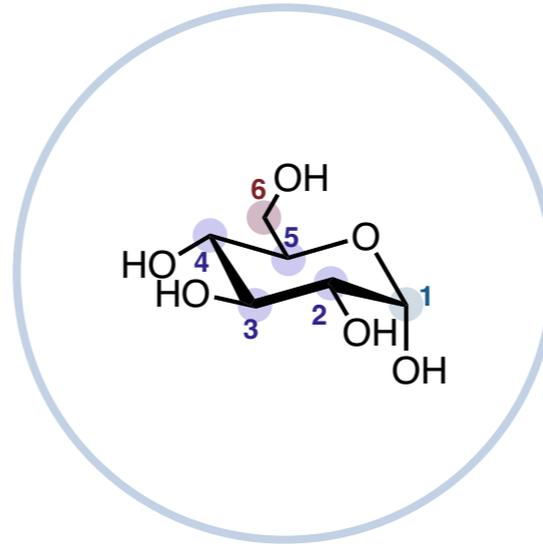
TiCl<sub>4</sub>  
DCM, -78 °C to -40 °C

# Protecting Group Strategies

## Site-Selective Functionalization

**Secondary C2-4**  
*Stereochemistry dependent*

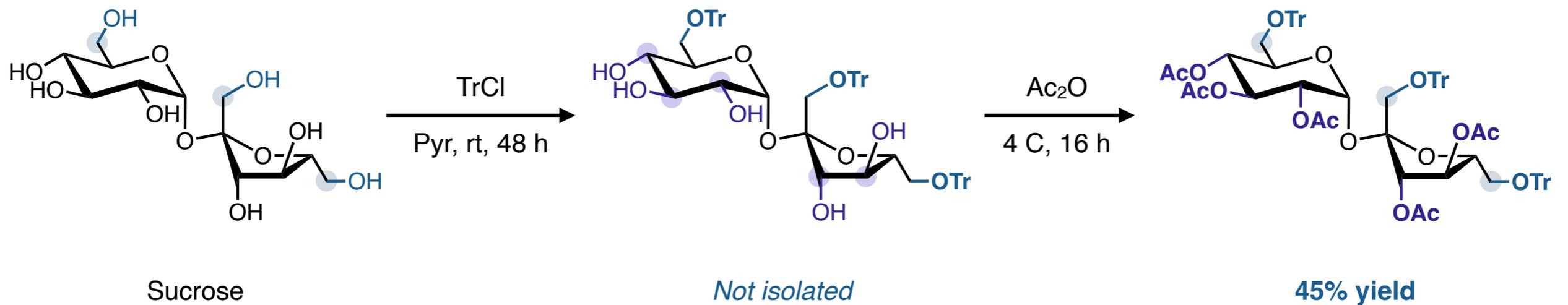
**Equatorial** > axial,  
acetonides, benzylidene, etc.



**Primary C6**  
*Steric hindrance*  
Limiting reagent, low temp., etc.

**Anomeric C1**  
*Hemiacetals*

### Example: **First** synthesis of **Sucralose**



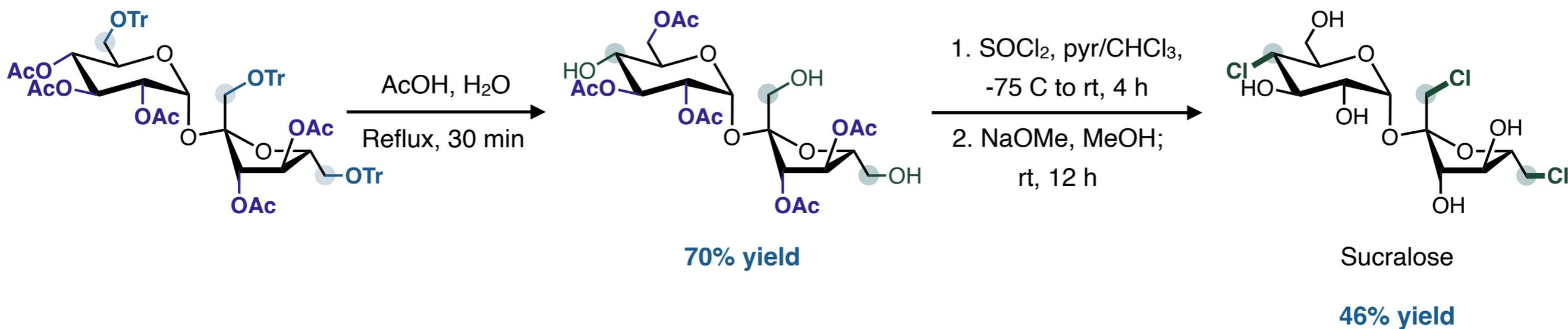
# Protecting Group Strategies

## Site-Selective Functionalization

Hough: “**Test** this compound”.

Phadnis: “I **tasted** it. It’s sweet!”

### Example: **First** synthesis of **Sucralose**

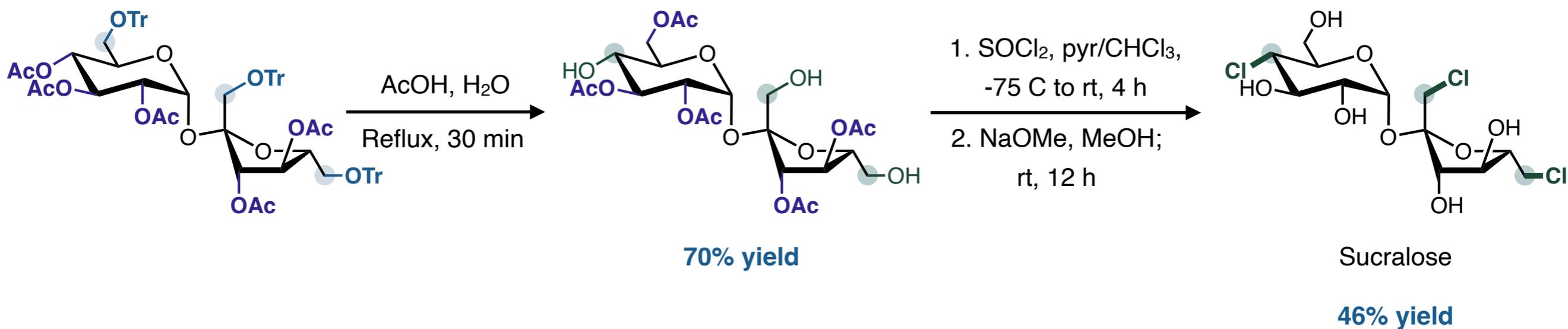


# Protecting Group Strategies

## Site-Selective Functionalization

However, PG manipulations are **not** always that straightforward...

### Example: **First** synthesis of **Sucralose**

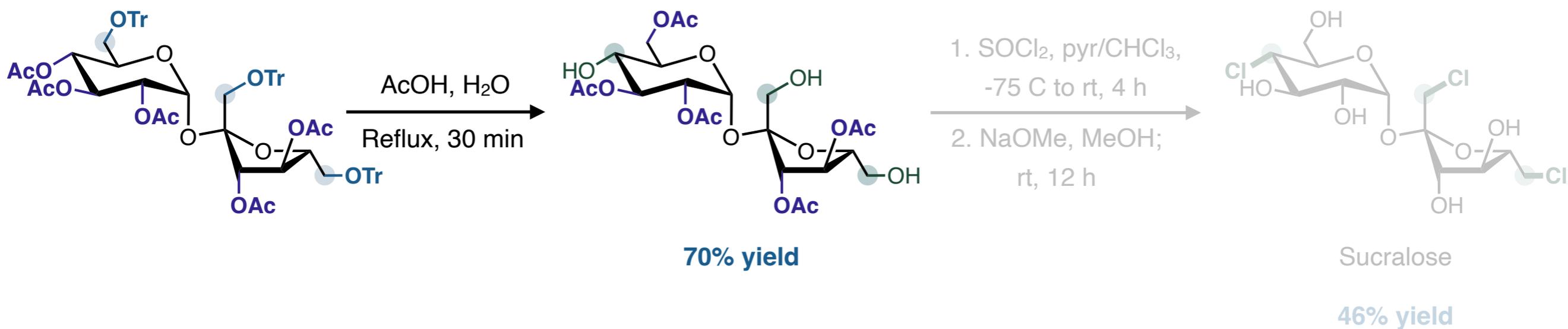


# Protecting Group Strategies

## Site-Selective Functionalization

However, PG manipulations are **not** always that straightforward...

### Example: **First** synthesis of **Sucralose**

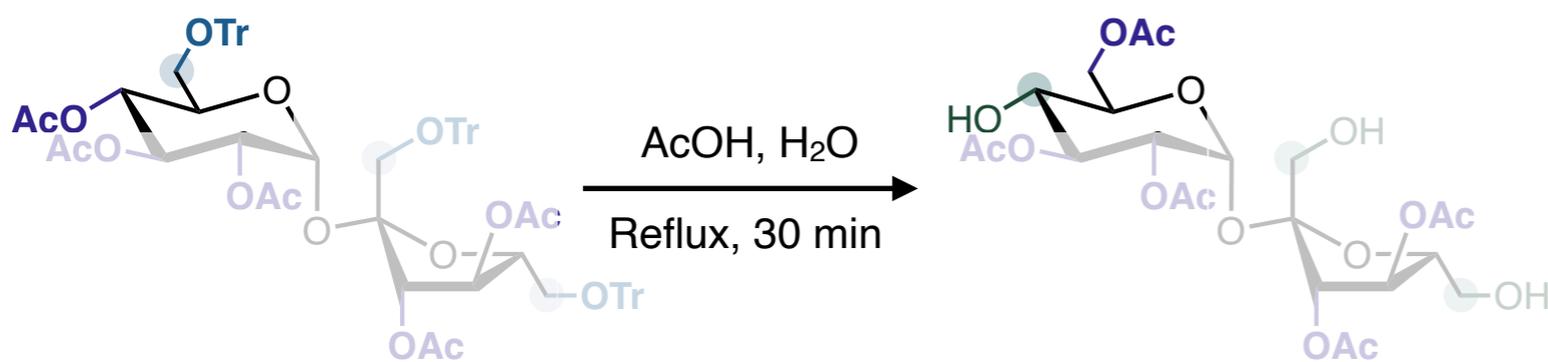


# Protecting Group Strategies

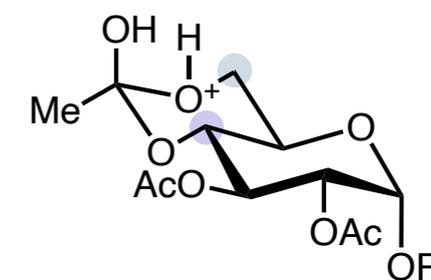
## Site-Selective Functionalization

However, PG manipulations are **not** always that straightforward...

Example: **First** synthesis of **Sucralose**



via

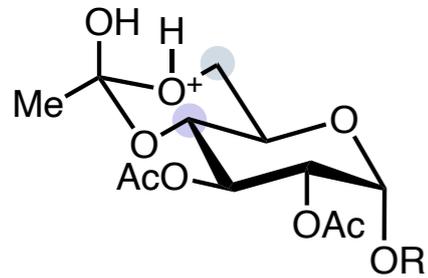


*Cyclic acetoxonium*

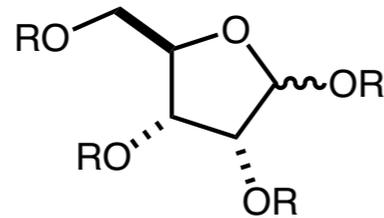
*Protecting group migration*

# Protecting Group Strategies

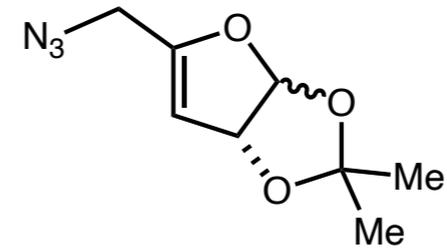
## Site-Selective Functionalization



Migration



Epimerization

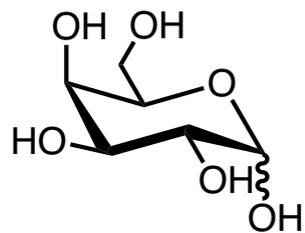


Elimination

*Rearrangements,  
transpositions...*

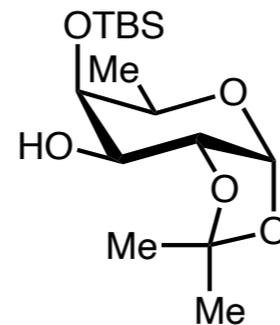
Other

*PG manipulations curtail synthetic efficiency*



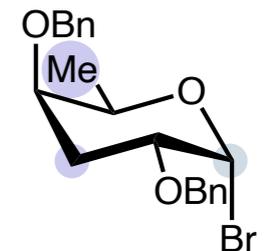
D-Galactose

1. Acetone, H<sub>2</sub>SO<sub>4</sub>
2. TsCl, pyr
3. NaBH<sub>4</sub>, DMSO
4. H<sup>+</sup>, DMSO
5. BuSnO
6. BnBr, NaH
7. TBSCl, pyr
8. H<sub>2</sub>, Pd/C



1 deoxygenation

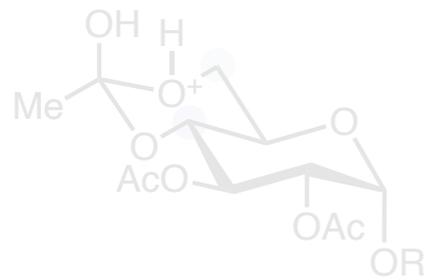
9. NaH, CS<sub>2</sub>, MeI
10. Bu<sub>3</sub>SnH, AIBN
11. H<sup>+</sup>
12. Ac<sub>2</sub>O, pyr
13. PhSH, BF<sub>3</sub> OEt<sub>2</sub>
14. NaOMe
15. BnBr, NaH
16. Br<sub>2</sub>



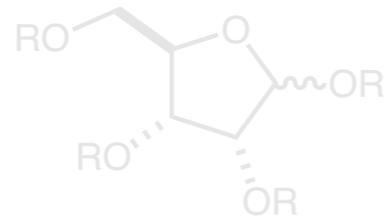
*1 deoxygenation  
1 functionalization*

# Protecting Group Strategies

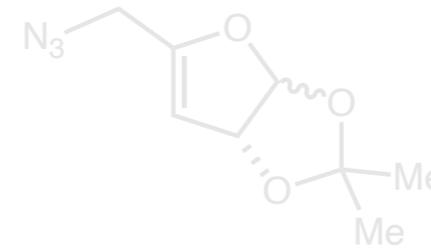
## Site-Selective Functionalization



Migration



Epimerization

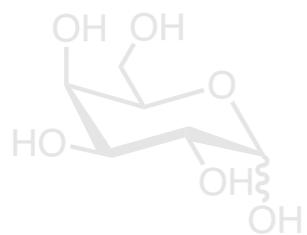


Elimination

Rearrangements,  
transpositions...

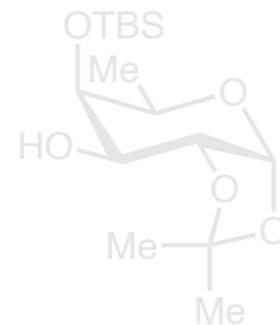
Other

Why do we still use protecting groups?



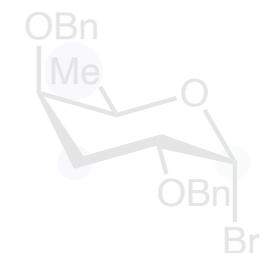
D-Galactose

1. Acetone, H<sub>2</sub>SO<sub>4</sub>
2. TsCl, pyr
3. NaBH<sub>4</sub>, DMSO
4. H<sup>+</sup>, DMSO
5. BuSnO
6. BnBr, NaH
7. TBSCl, pyr
8. H<sub>2</sub>, Pd/C



1 deoxygenation

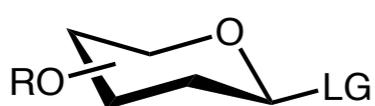
9. NaH, CS<sub>2</sub>, MeI
10. Bu<sub>3</sub>SnH, AIBN
11. H<sup>+</sup>
12. Ac<sub>2</sub>O, pyr
13. PhSH, BF<sub>3</sub> OEt<sub>2</sub>
14. NaOMe
15. BnBr, NaH
16. Br<sub>2</sub>



1 deoxygenation  
1 functionalization

# Introduction to Chemical Glycosylation

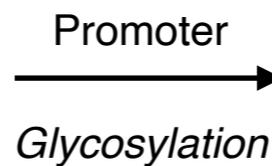
## Cationic Glycosylation



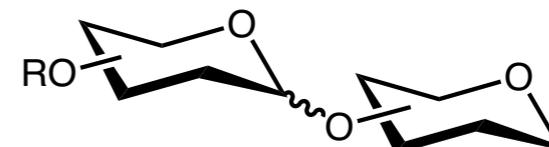
Glycosyl Donor  
*Electrophile*



Glycosyl Acceptor  
*Nucleophile*

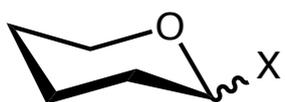


*Substitution*



*Glycoside*  
*Selective formation*

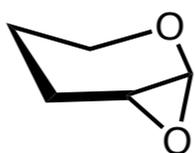
## Common Glycosyl Donors



Halide



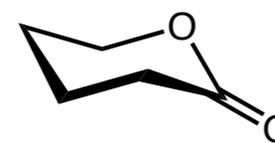
Glycal



1,2-anhydro



Lactol



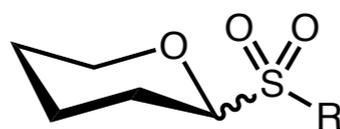
Lactone



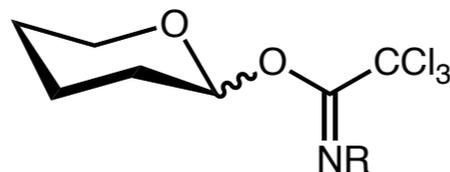
Sulfide



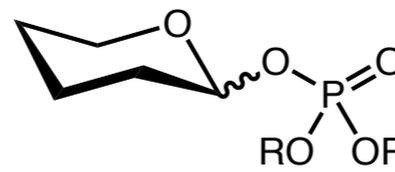
Sulfoxide



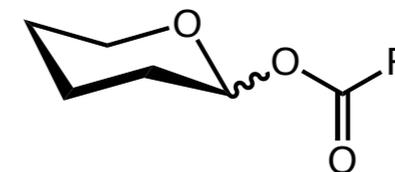
Sulfone



Imidate



Phosphate



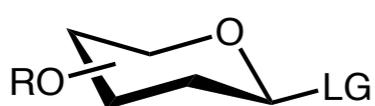
Carboxylate



Methyl glycoside

# Introduction to Chemical Glycosylation

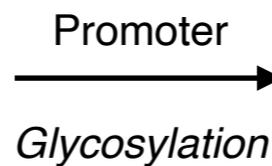
## Cationic Glycosylation



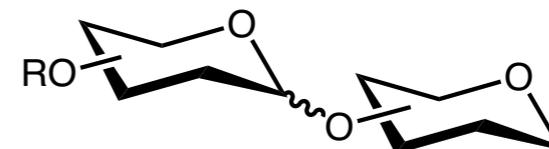
Glycosyl Donor  
*Electrophile*



Glycosyl Acceptor  
*Nucleophile*

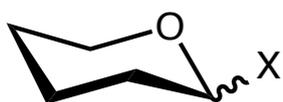


**Substitution**



Glycoside  
**Selective formation**

## Common Glycosyl Donors



**Halide**

*Koenigs—Knorr*



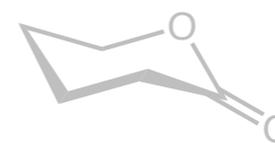
Glycal



1,2-anhydro



Lactol



Lactone



Sulfide

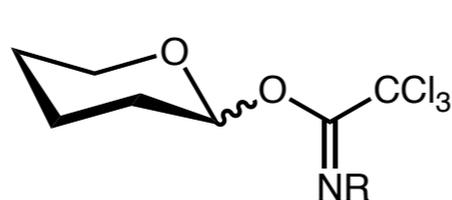


**Sulfoxide**

*Kahne—Crich*

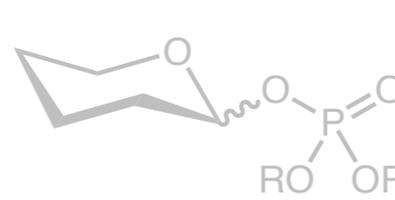


Sulfone

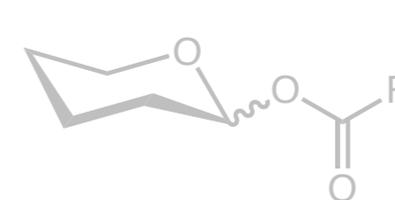


**Imidate**

*Trichloroacetimidate*



Phosphate



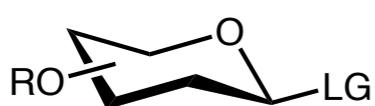
Carboxylate



Methyl glycoside

# Introduction to Chemical Glycosylation

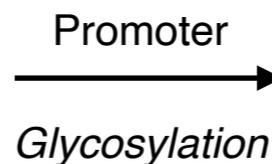
## Cationic Glycosylation



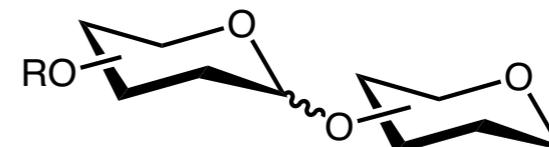
Glycosyl Donor  
*Electrophile*



Glycosyl Acceptor  
*Nucleophile*

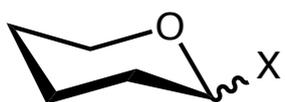


**Substitution**



Glycoside  
**Selective formation**

## Common Glycosyl Donors



**Halide**

*Koenigs—Knorr*



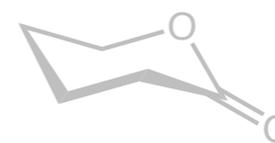
Glycal



1,2-anhydro



Lactol



Lactone



Sulfide



**Sulfoxide**

*Kahne—Crich*

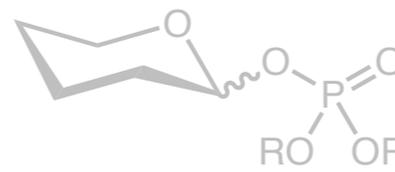


Sulfone

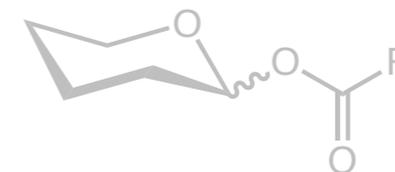


**Imidate**

*Trichloroacetimidate*



Phosphate



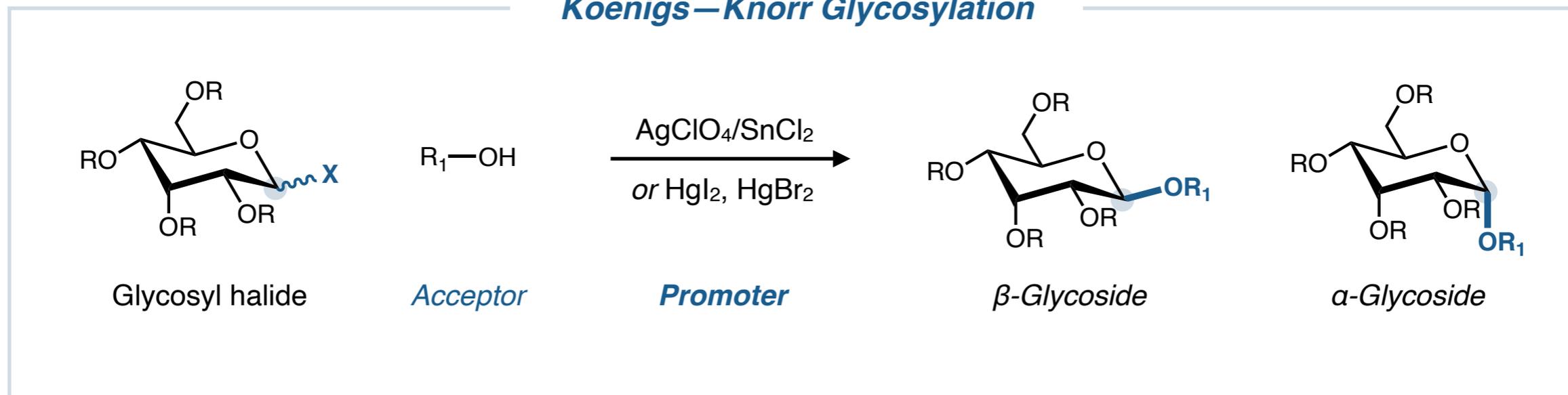
Carboxylate



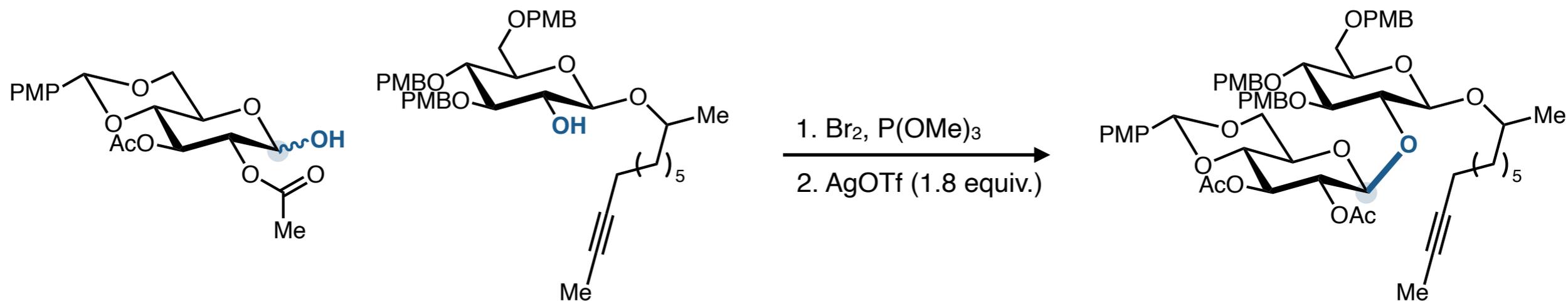
Methyl glycoside

# Koenigs–Knorr: Glycosyl Halides as Donors

## Koenigs–Knorr Glycosylation



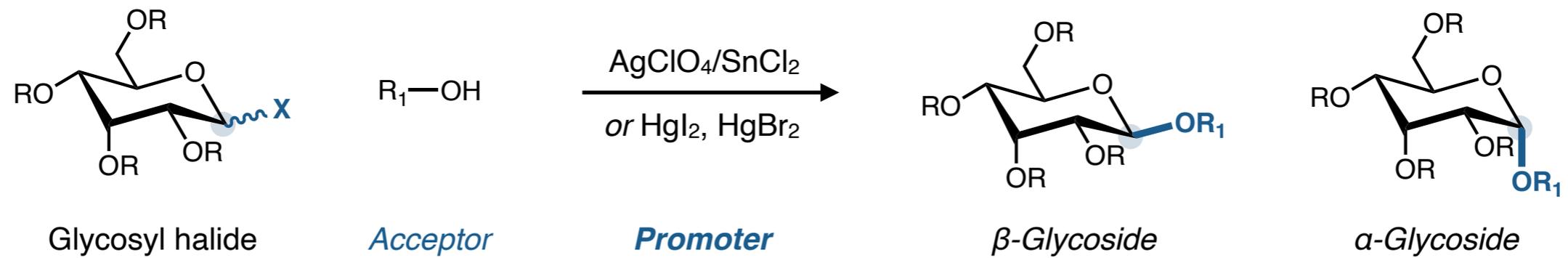
## Participating C2 protecting group



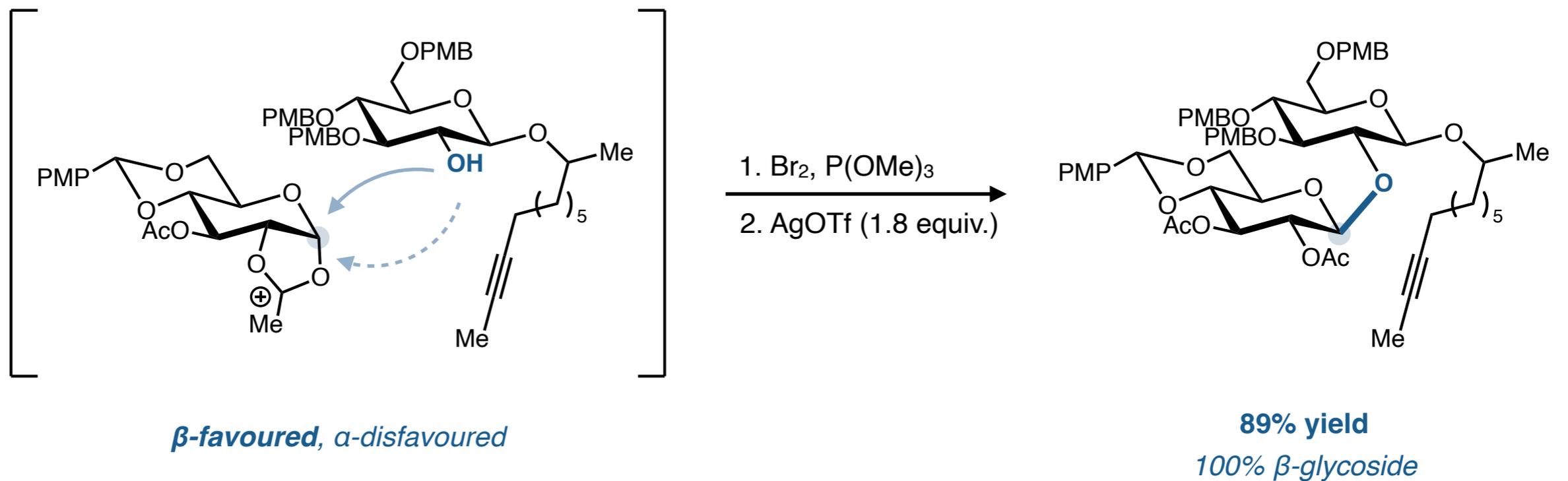
**89% yield**  
*100%  $\beta$ -glycoside*

# Koenigs–Knorr: Glycosyl Halides as Donors

## Koenigs–Knorr Glycosylation

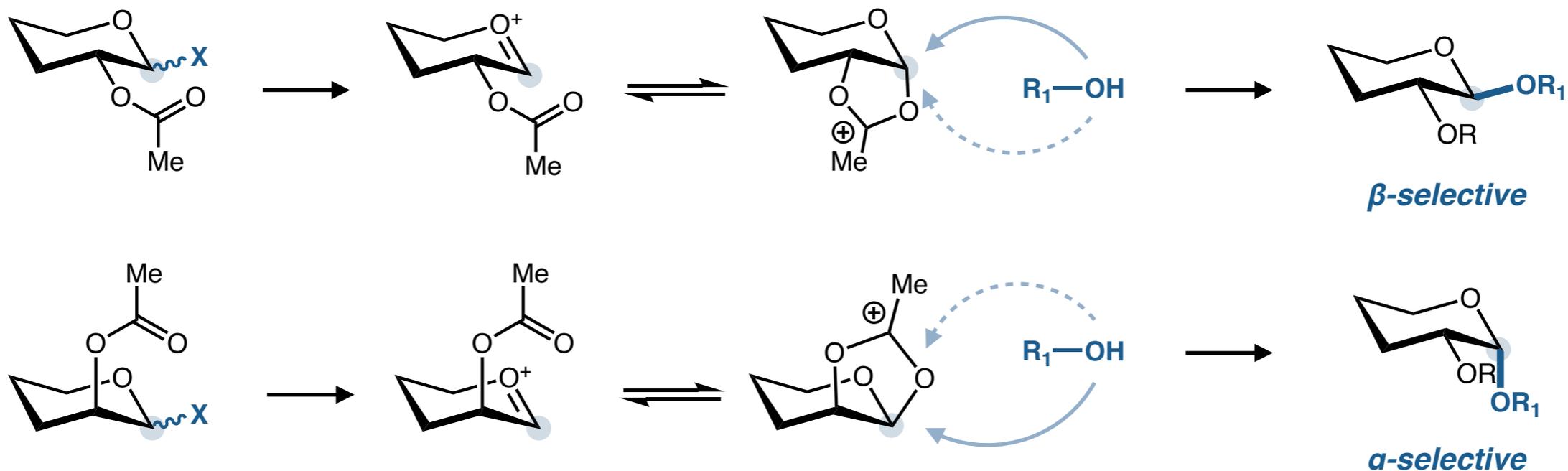


## Participating C2 protecting group

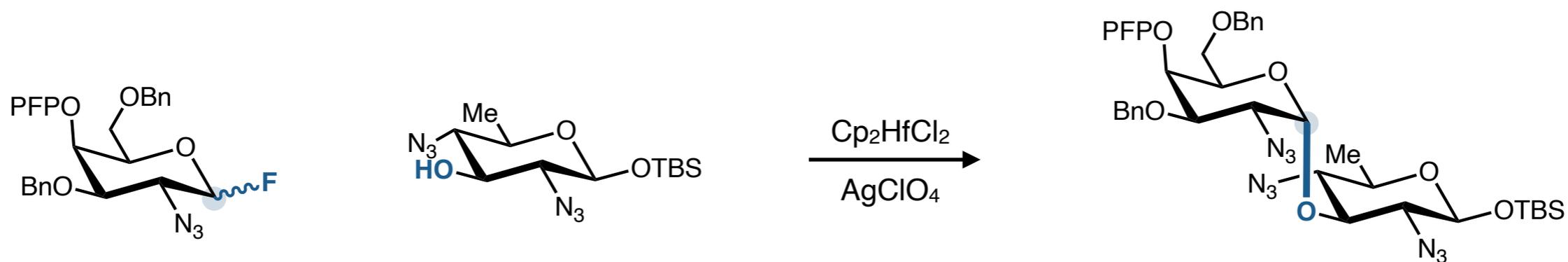


# Protecting Groups and Stereoselectivity

## The 1,2-trans Rule

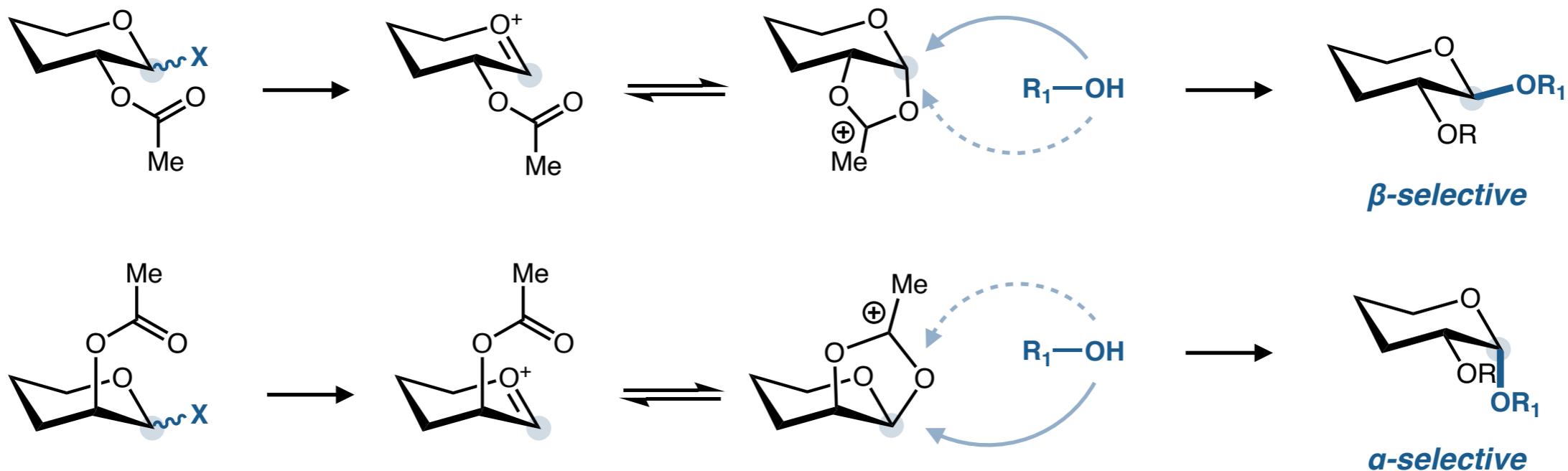


*Distal participating groups have a similar effect.*

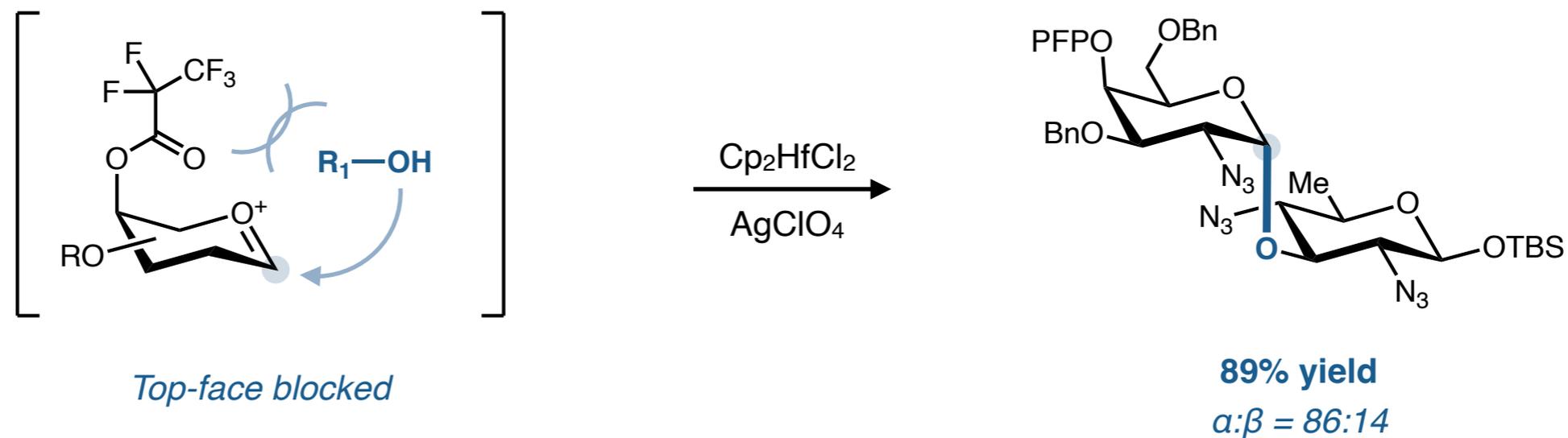


# Protecting Groups and Stereoselectivity

## The 1,2-trans Rule

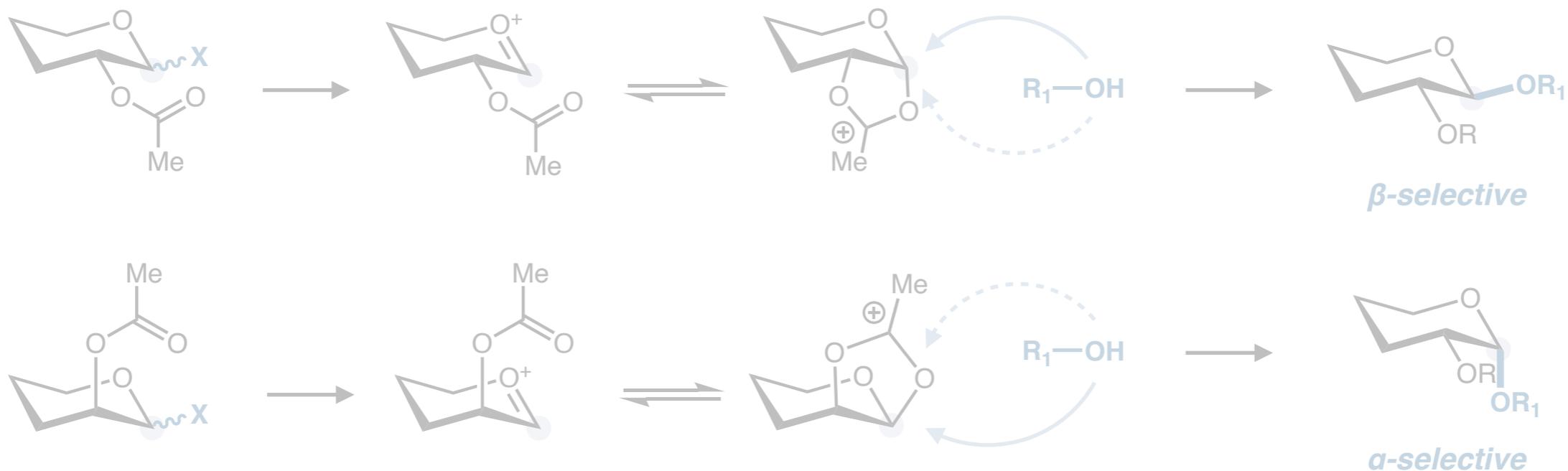


*Distal participating groups have a similar effect.*

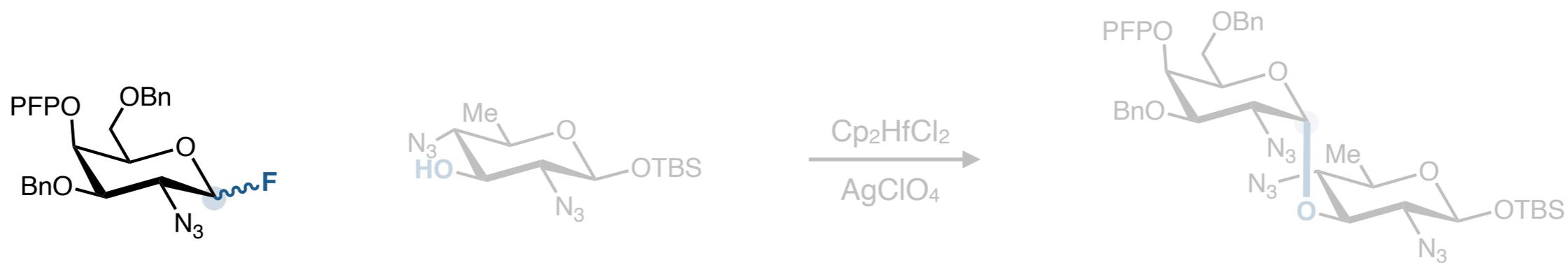


# Protecting Groups and Stereoselectivity

## The 1,2-trans Rule



*Distal participating groups have a similar effect.*

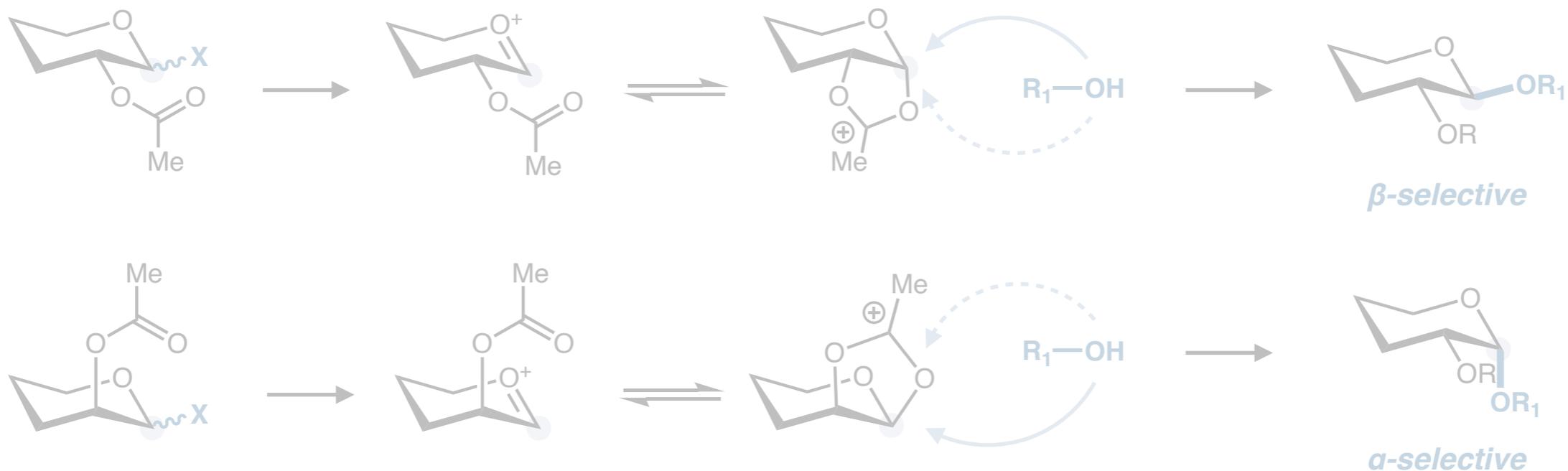


**Glycosyl fluoride**

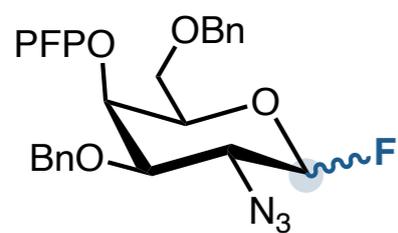
**89% yield**  
 *$\alpha$ : $\beta$  = 86:14*

# Protecting Groups and Stereoselectivity

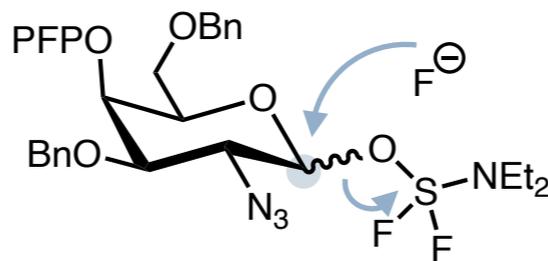
## The 1,2-trans Rule



*Distal participating groups have a similar effect.*



DAST  
 $\Rightarrow$

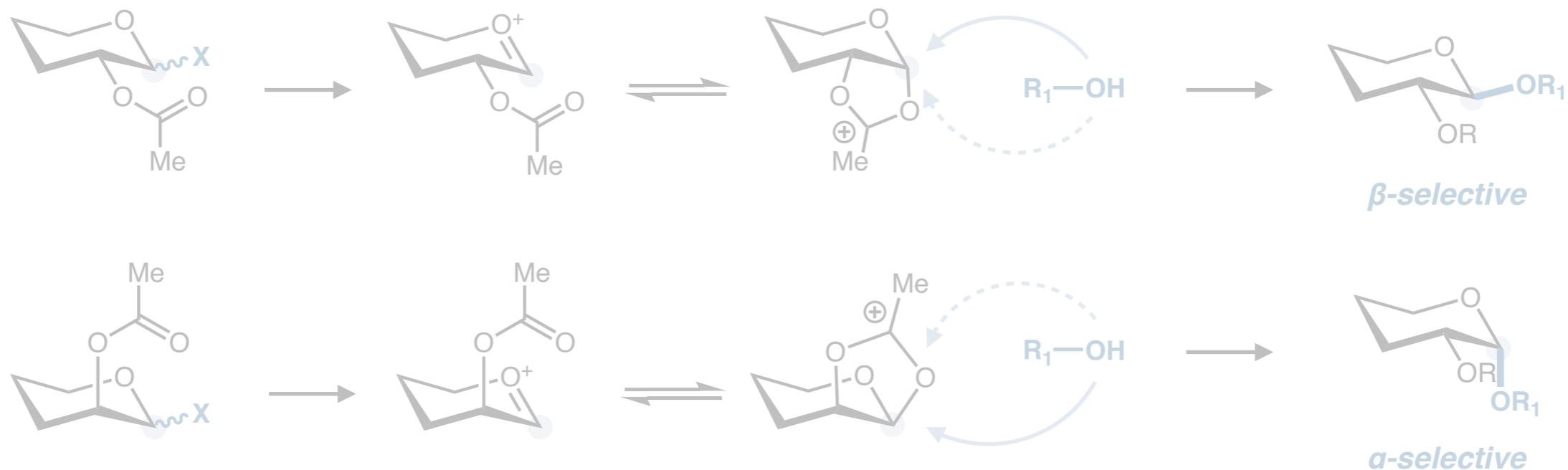


Highly  $\alpha$ -selective when C2 has a non-participating group

Glycosyl fluoride

# Protecting Groups and Stereoselectivity

## The 1,2-*trans* Rule

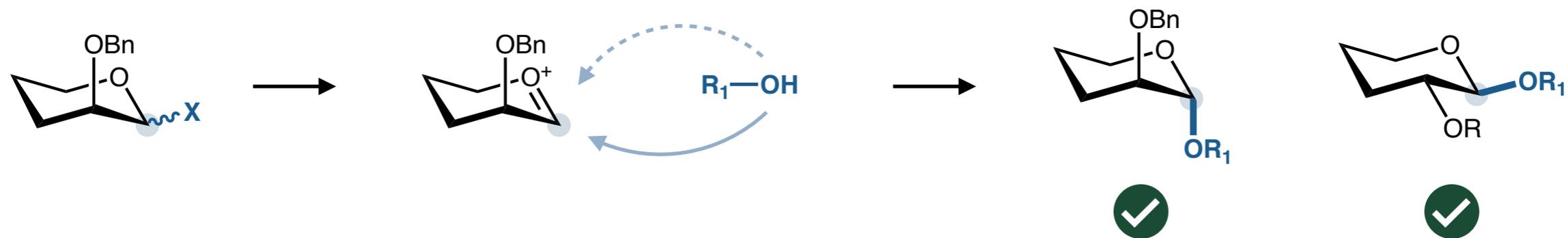


*Distal* participating groups have a similar effect.

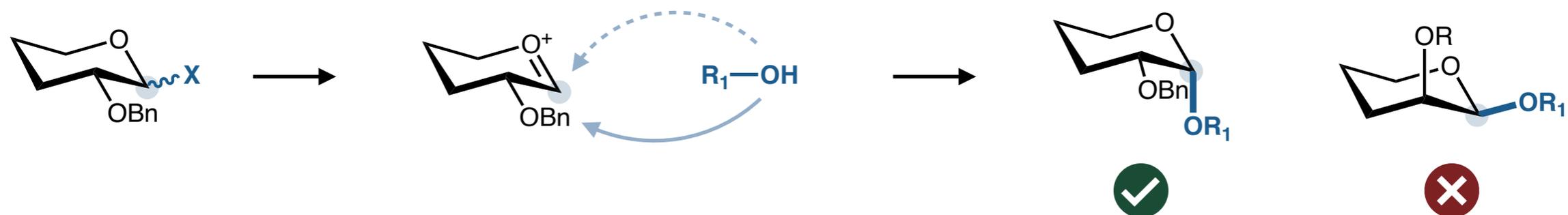
Does the 1,2-*trans* rule still apply when a **non-participating** group is located at C2?

# Protecting Groups and Stereoselectivity

*No longer the 1,2-trans Rule!*



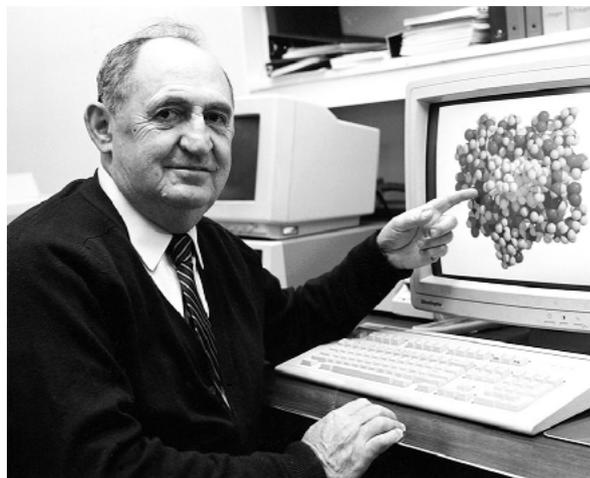
*Favoured due to anomeric effect*



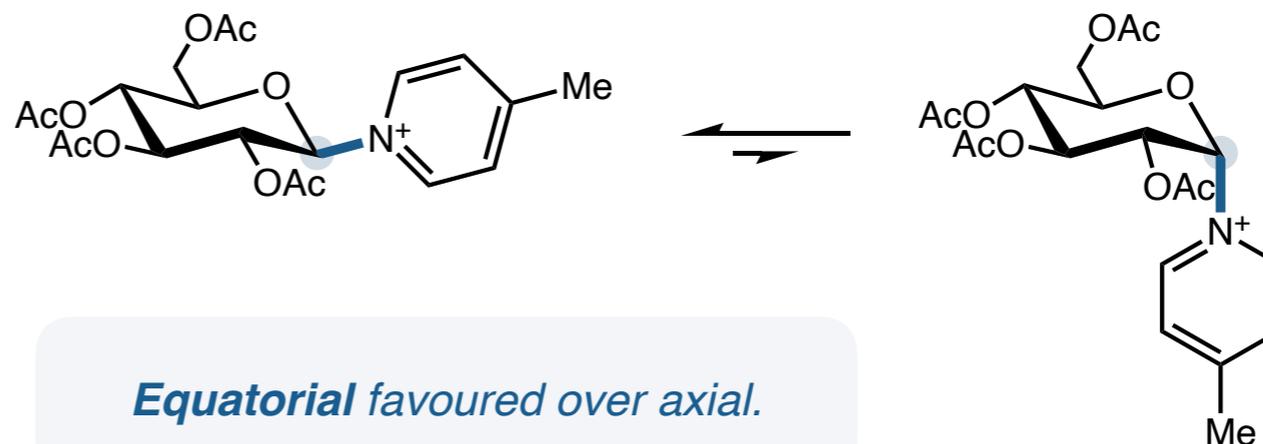
How do we fight the anomeric effect?

# Protecting Groups and Stereoselectivity

## The **Reverse** Anomeric Effect

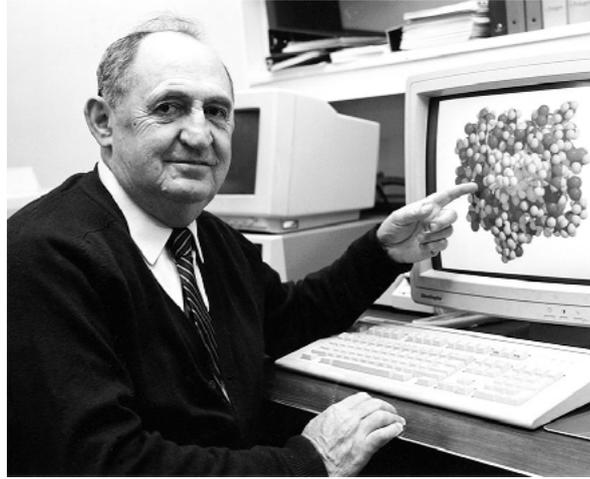


**Raymond Lemieux**  
(1920-2000)



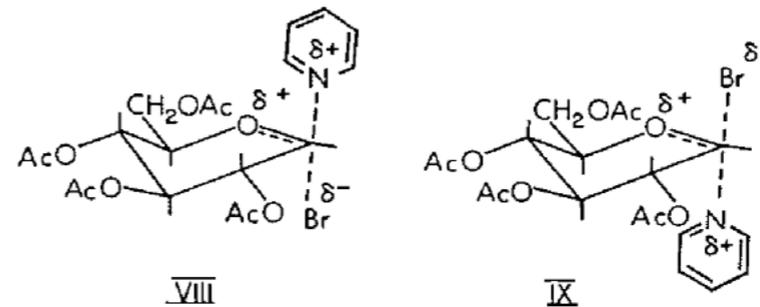
# Protecting Groups and Stereoselectivity

## The Reverse Anomeric Effect

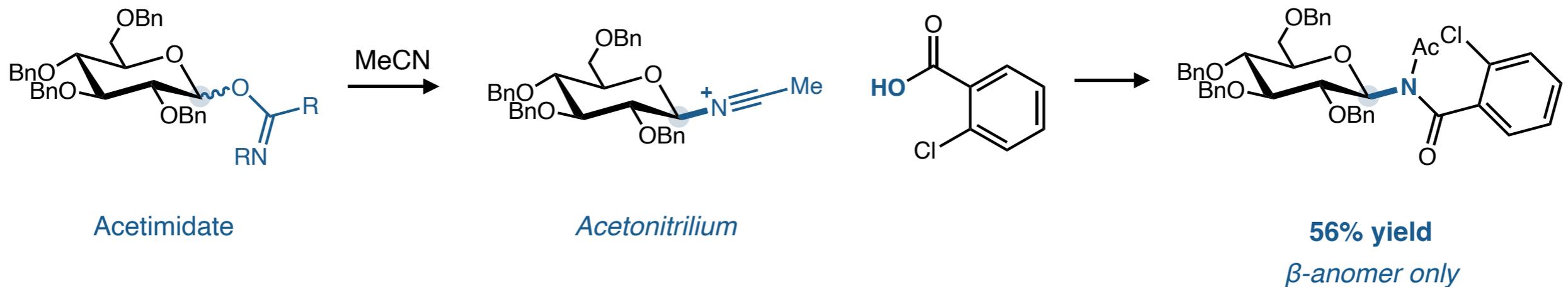


**Raymond Lemieux**  
(1920-2000)

Thirdly, an attack by a molecule at the anomeric center which leads to development of positive charge on the entering group must be expected to be much more favorable when the entering group leads to the equatorial product. For example, it would be expected on the basis of the reverse anomeric effect that the transition state VIII would be considerably more favorable than that represented by IX.

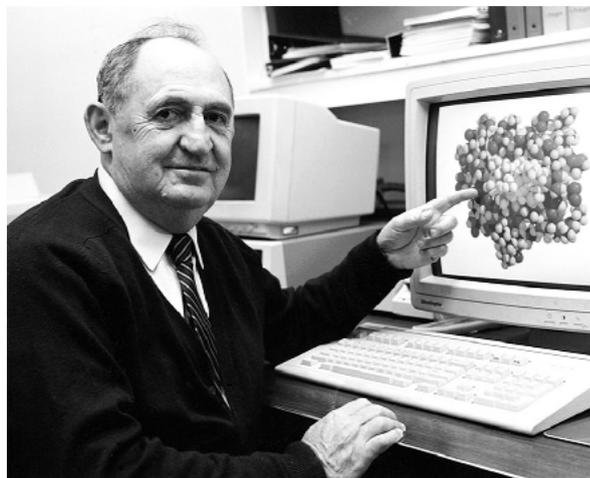


## Access to $\beta$ -Glycosides



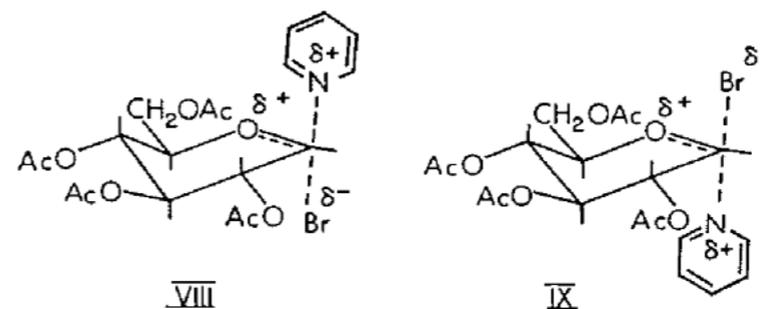
# Protecting Groups and Stereoselectivity

## The Reverse Anomeric Effect

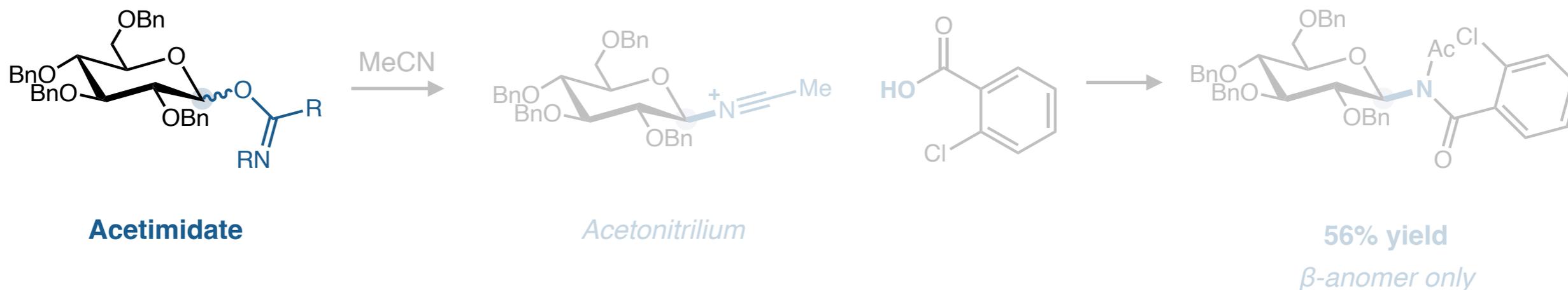


**Raymond Lemieux**  
(1920-2000)

Thirdly, an attack by a molecule at the anomeric center which leads to development of positive charge on the entering group must be expected to be much more favorable when the entering group leads to the equatorial product. For example, it would be expected on the basis of the reverse anomeric effect that the transition state VIII would be considerably more favorable than that represented by IX.

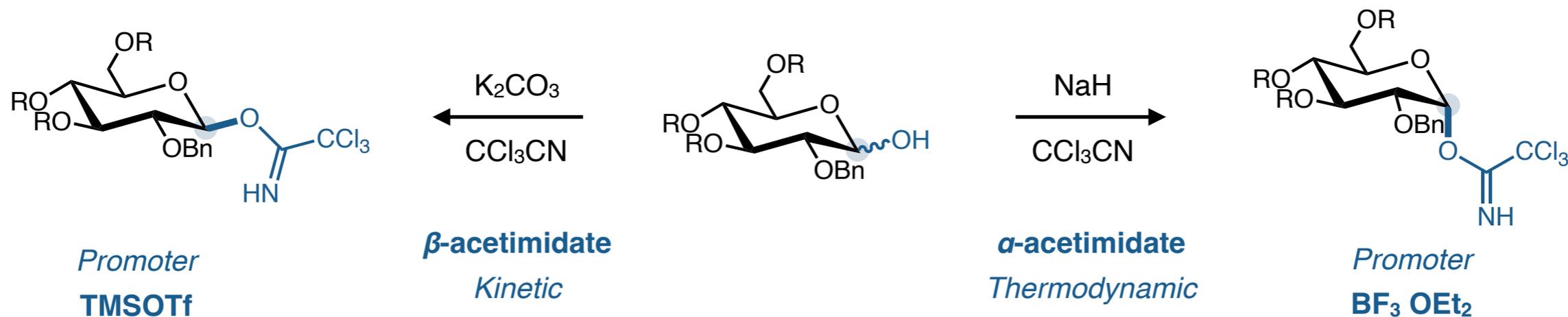


## Access to $\beta$ -Glycosides



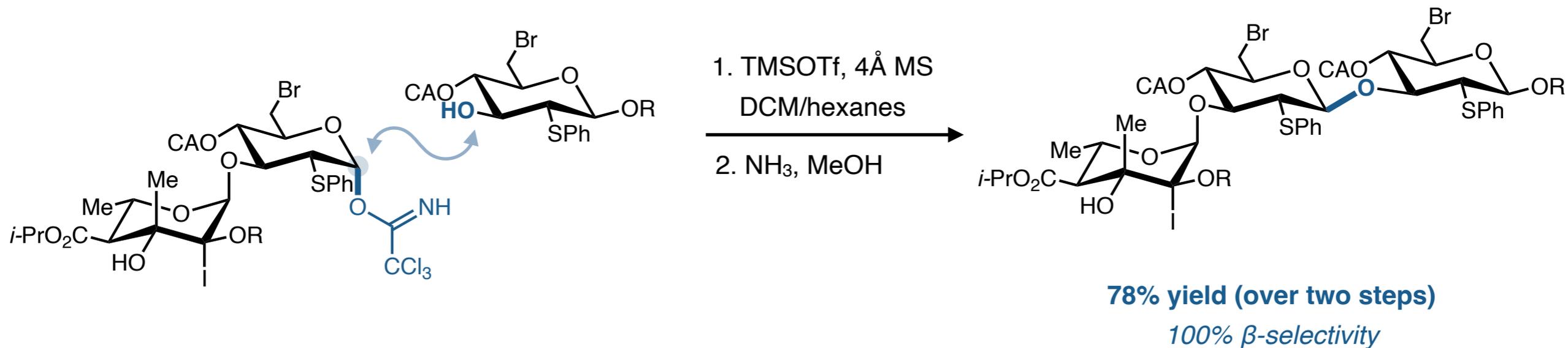
# Trichloroacetimidate as Glycol Donor

## Trichloroacetimidate: Formation and Selectivity



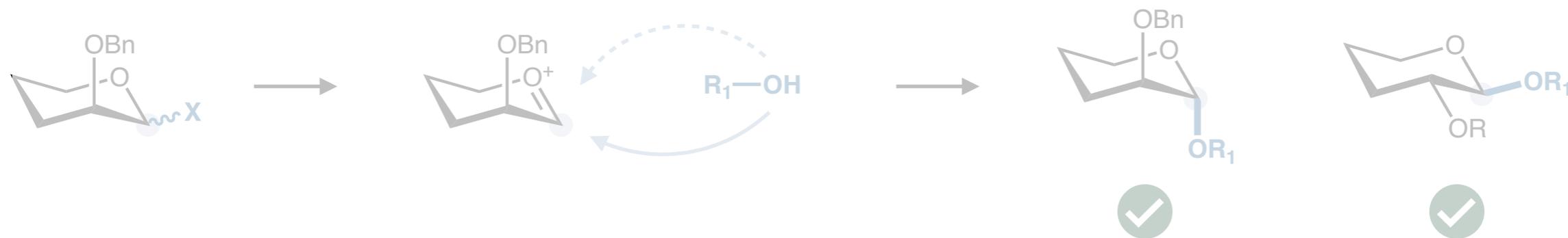
Glycosylations involving trichloroacetimidate proceed through an essentially  $\text{S}_{\text{N}}2$ -type mechanism.

## Access to $\beta$ -Glycosides

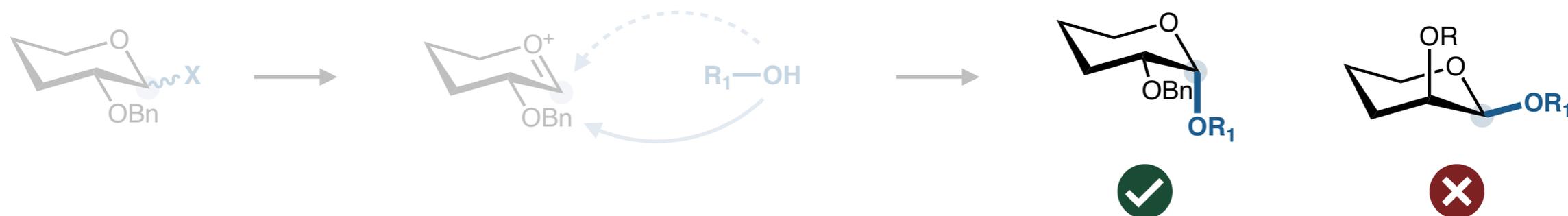


# Protecting Groups and Stereoselectivity

**No longer the 1,2-trans Rule!**



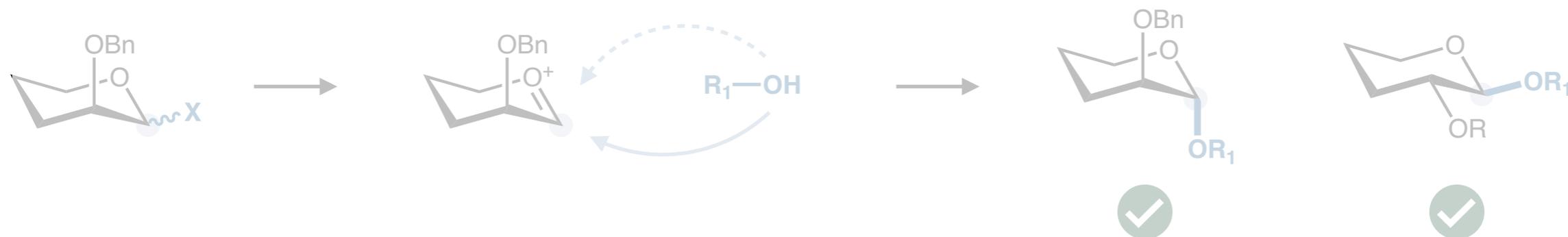
*Favoured due to anomeric effect*



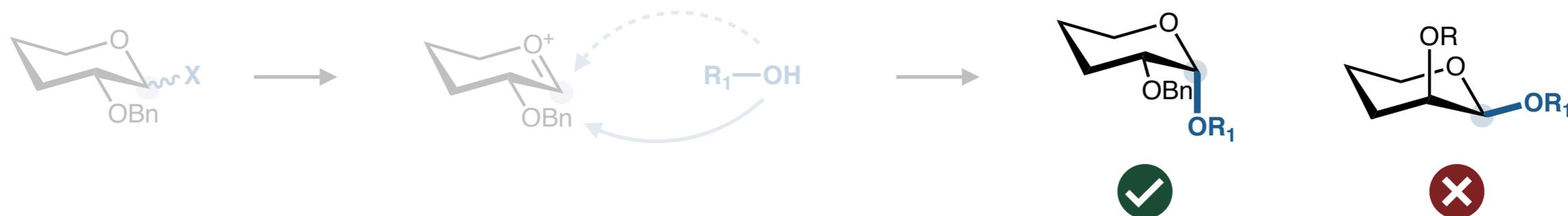
How do we **fight** the **anomeric effect**?

# Protecting Groups and Stereoselectivity

**No longer the 1,2-trans Rule!**



*Favoured due to anomeric effect*



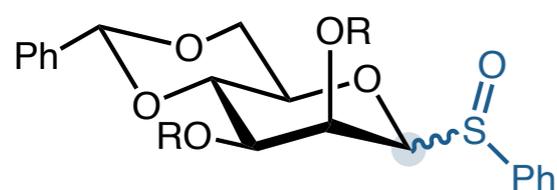
**$\beta$ -mannoside**

*Inaccessible by Koenigs-Knorr*

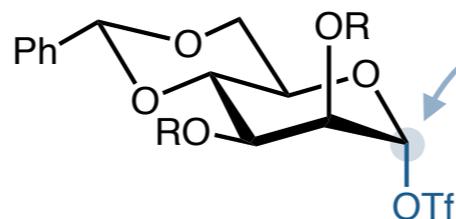
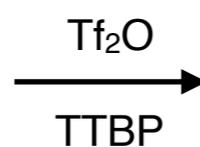
How do we prepare  **$\beta$ -mannosides**?

# Kahne—Crich: Glycol Sulfoxide as Donor

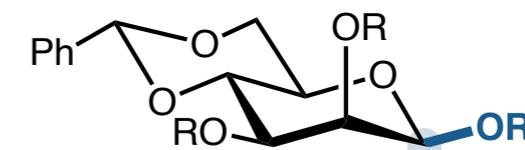
## Kahne—Crich: Glycosulfoxide



From sulfide + *m*-CPBA



*α*-anomer preferred

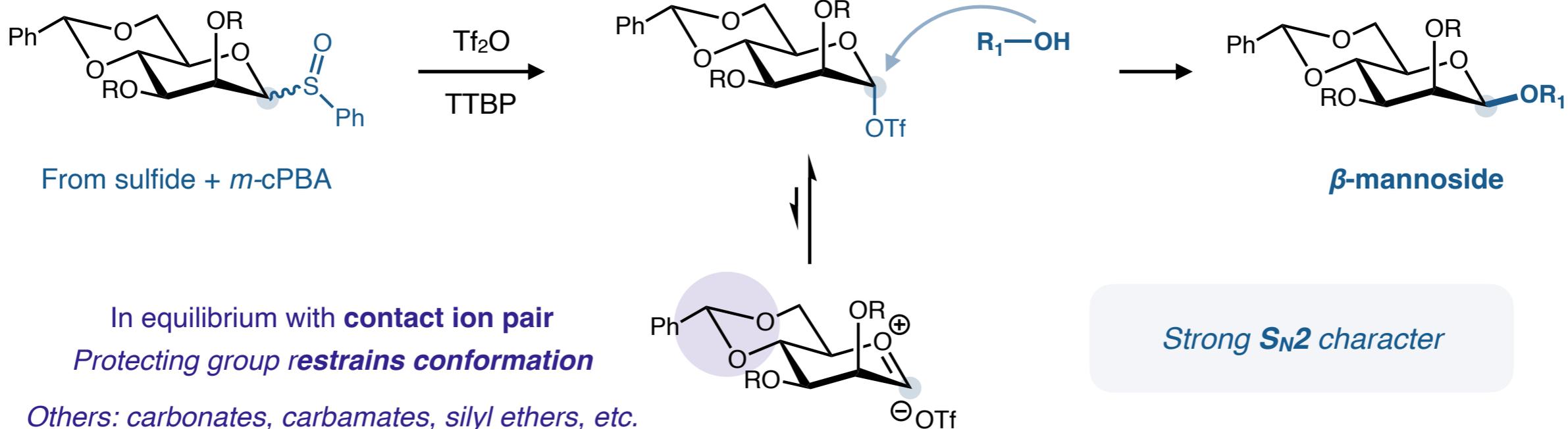


*β*-mannoside

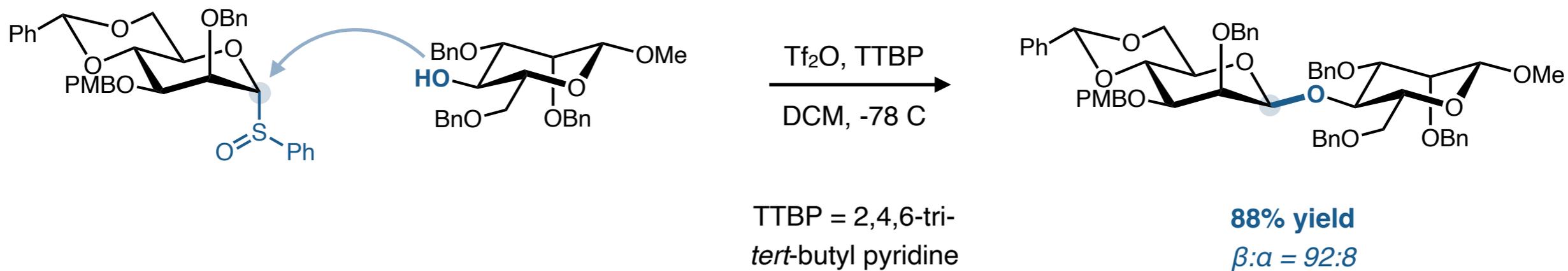
Strong S<sub>N</sub>2 character

# Kahne—Crich: Glycol Sulfoxide as Donor

## Kahne—Crich: Glycosulfoxide

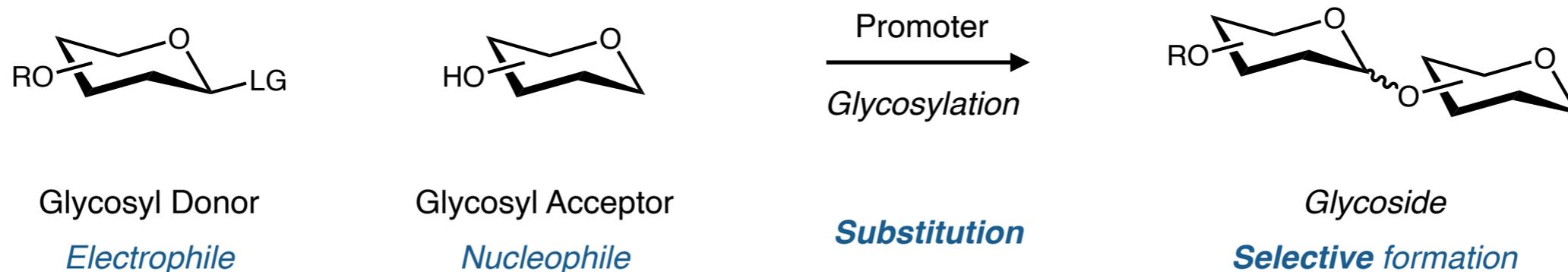


## Access to $\beta$ -Mannosides

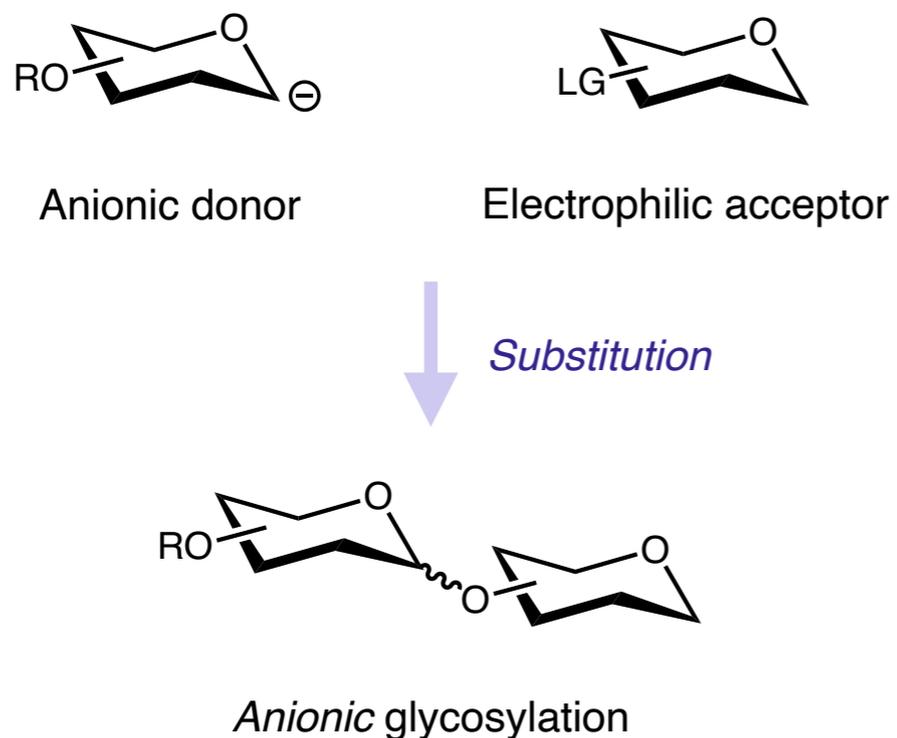


# Introduction to Chemical Glycosylation

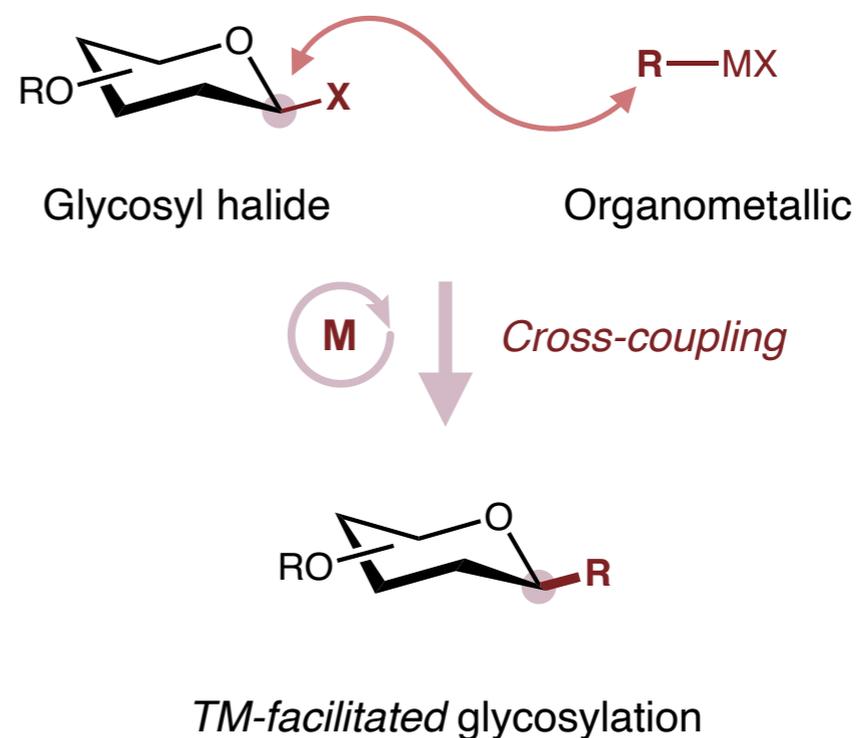
## Cationic Glycosylation



## Anionic Glycosylation

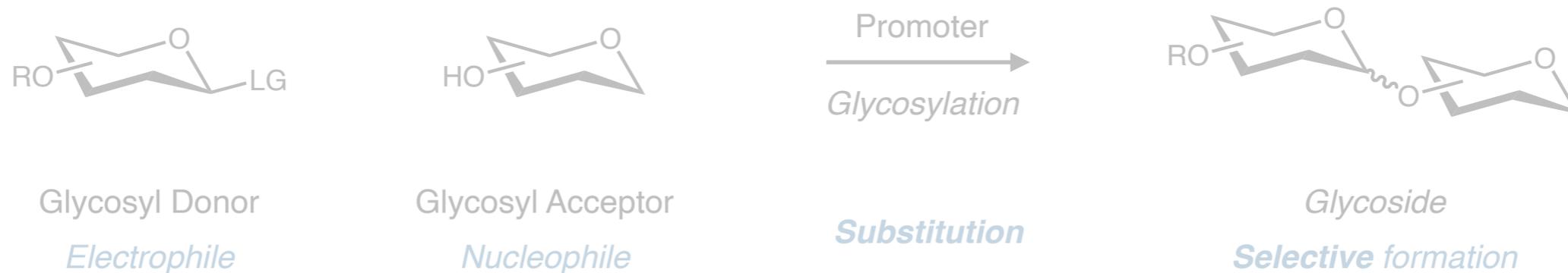


## Transition-metal Mediated

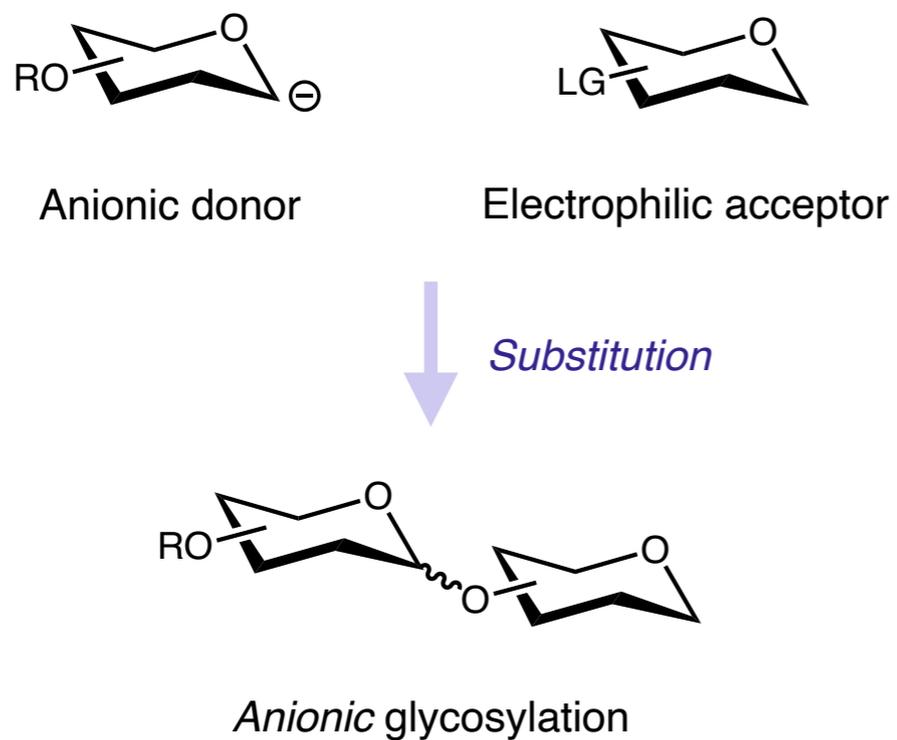


# Introduction to Chemical Glycosylation

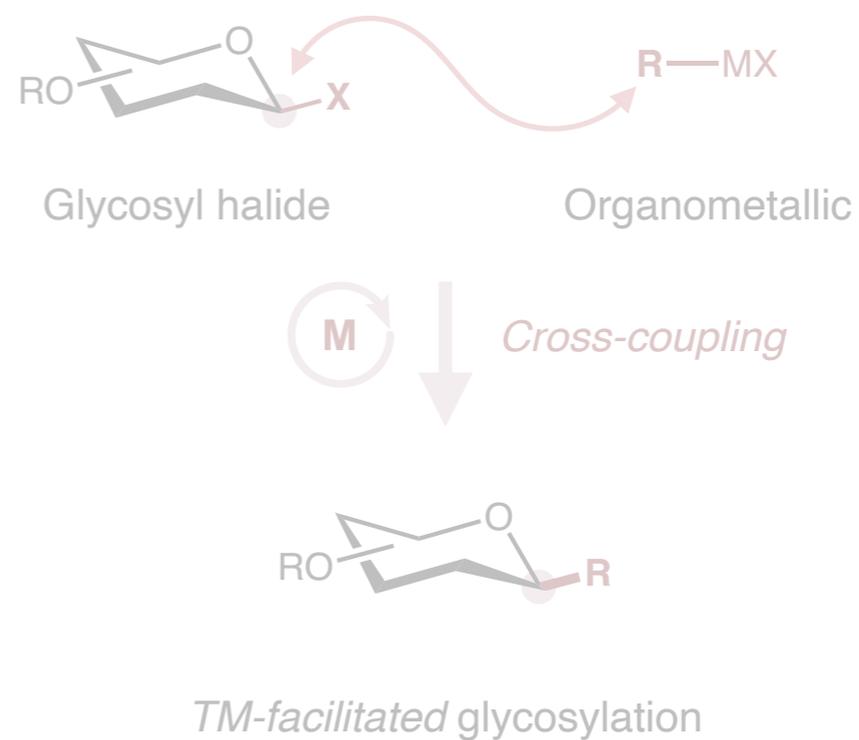
## Cationic Glycosylation



## Anionic Glycosylation

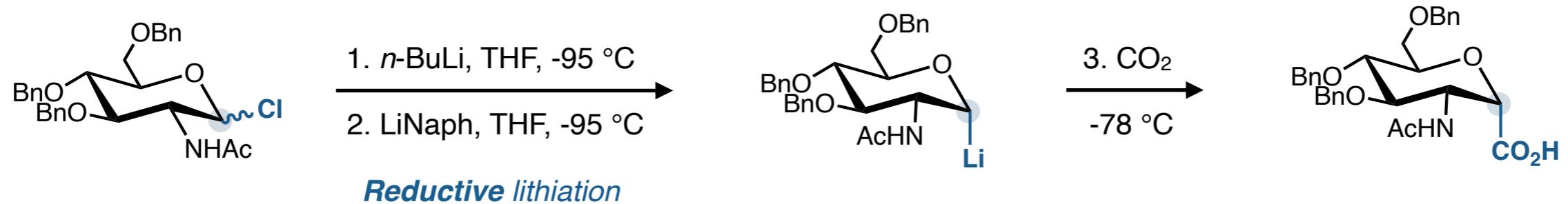


## Transition-metal Mediated



# Anionic Glycosylation: Precursors & Reagents

## Glycosyl Halide: Lithium-halogen exchange



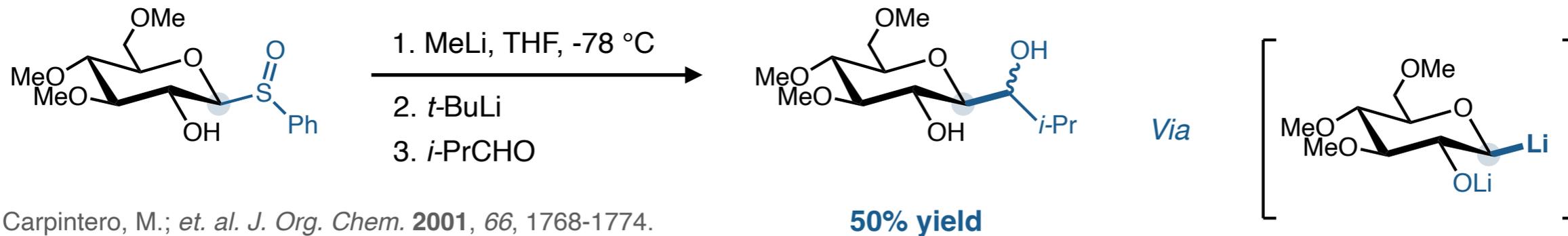
Glycosyl chloride

Schäfer, A.; Theim, J. *J. Org. Chem.* **2000**, *65*, 24-29.

**66% yield**

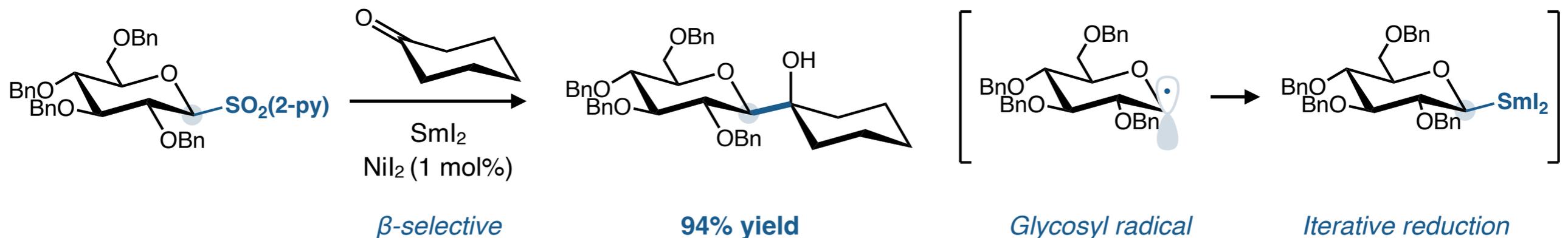
Over three steps

## Glycosulfoxides may also serve as precursors.



Carpintero, M.; et. al. *J. Org. Chem.* **2001**, *66*, 1768-1774.

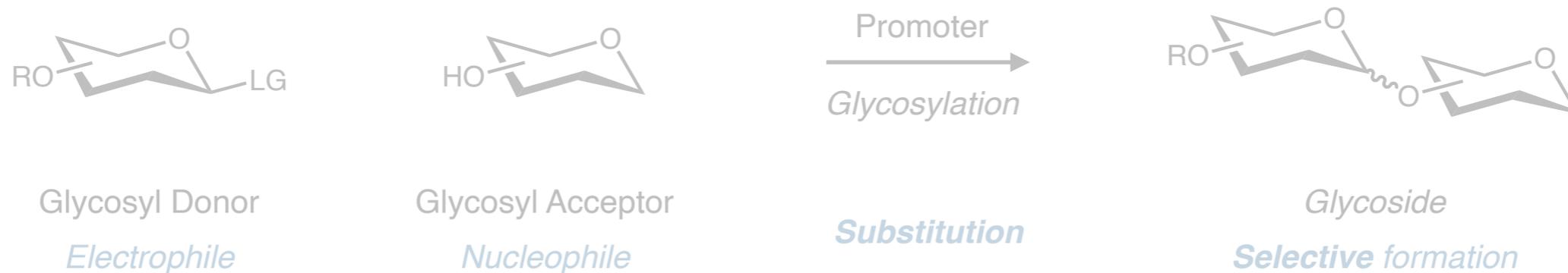
## $\text{SmI}_2$ can facilitate glycosylation.



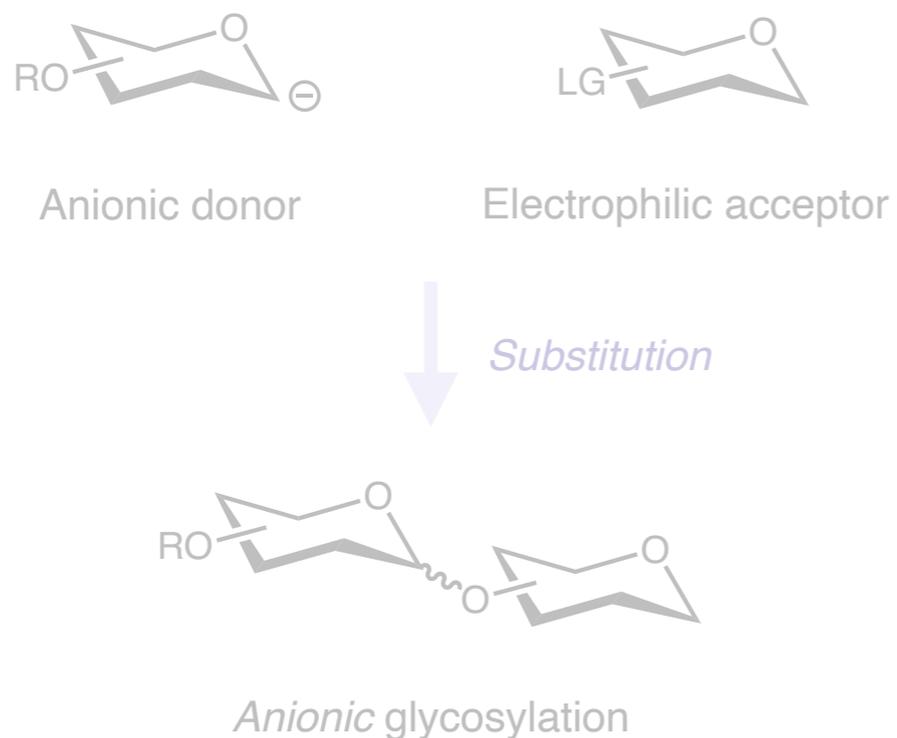
Miquel, N.; Doisneau, G.; Beau, J.-M. *Angew. Chem. Intl. Ed.* **2000**, *39*, 4111-4114.

# Introduction to Chemical Glycosylation

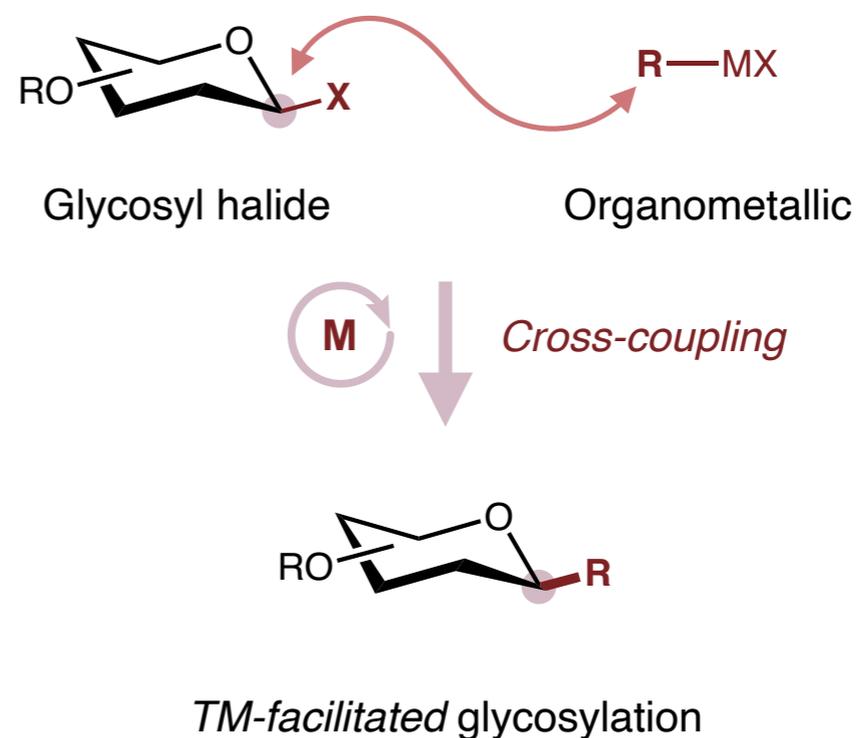
## Cationic Glycosylation



## Anionic Glycosylation

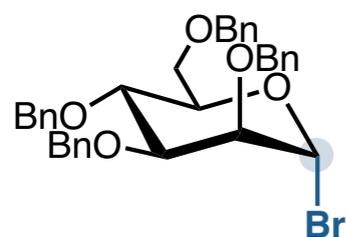


## Transition-metal Mediated



## Example: Negishi Coupling via a Glycosyl Radical Intermediate

### Ni-catalyzed Negishi Coupling



Glycosyl halide



Or

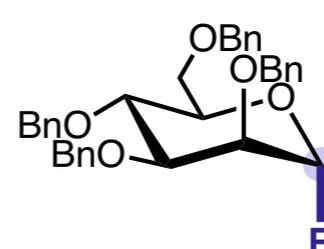


Zincate

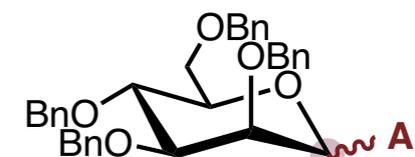
Ni(II) (10 mol%)

Ligand

Divergent  
stereoselectivity

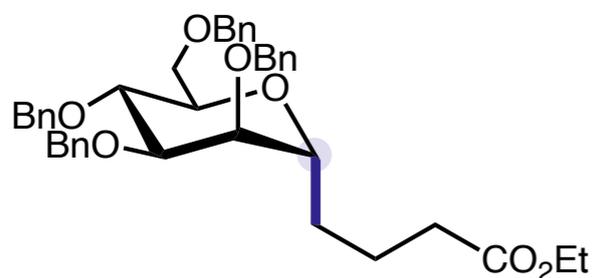


C-alkyl-glycosylation



C-aryl-glycosylation

### Ligand and C2 configuration dictate stereoselectivity

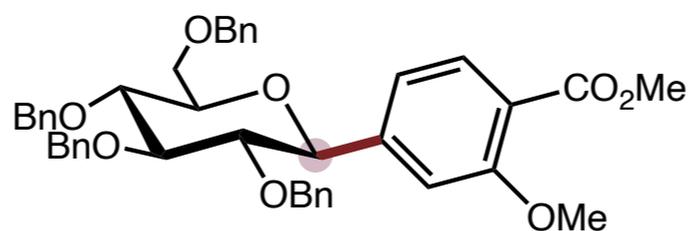


$\alpha$ -Manno

76% yield

$\alpha$ -only

NiCl<sub>2</sub>, PyBox, DMI

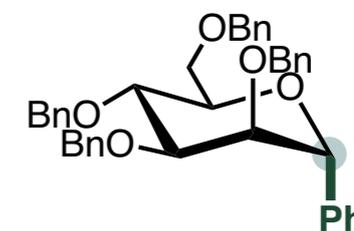


$\beta$ -Gluco

82% yield

$\beta$ : $\alpha$  = 93:7

Ni(COD)<sub>2</sub>, <sup>t</sup>Bu-Terpy, DMF



$\alpha$ -Manno

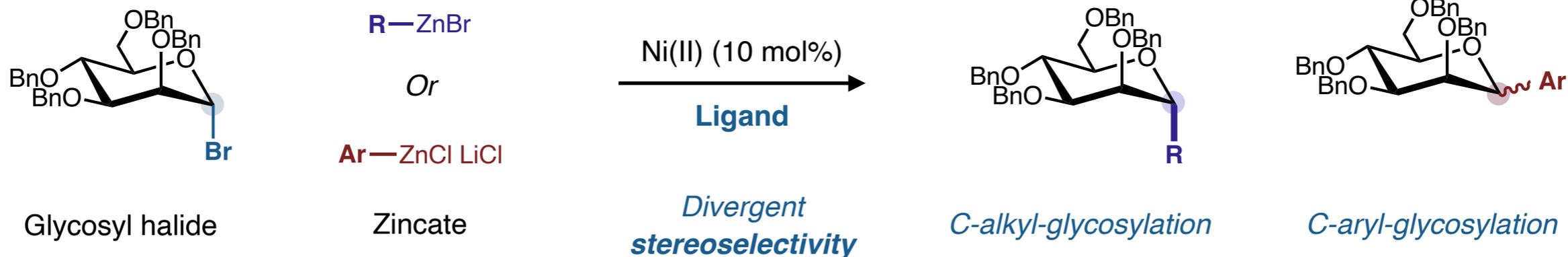
80% yield

$\alpha$ : $\beta$  = 95:5

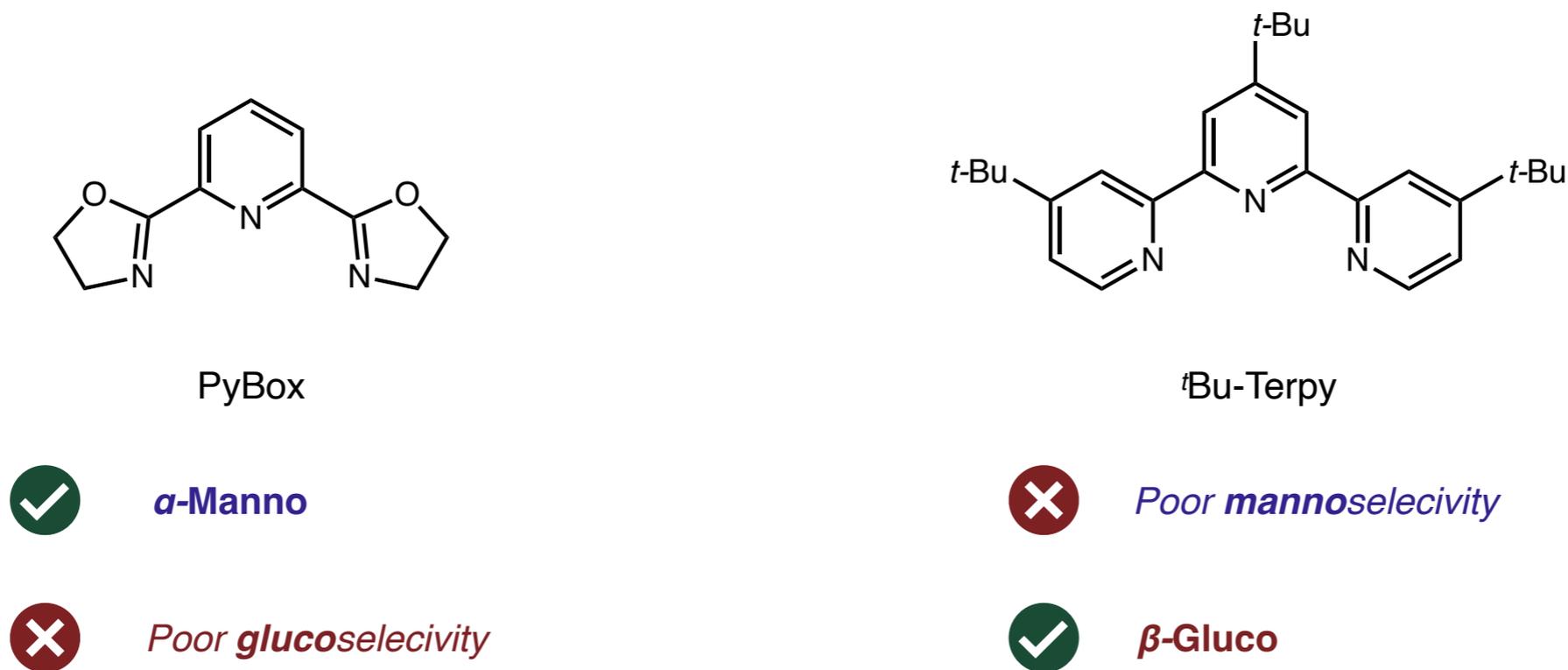
Ni(COD)<sub>2</sub>, PyBox, DMF

## Example: Negishi Coupling via a Glycosyl Radical Intermediate

### Ni-catalyzed Negishi Coupling

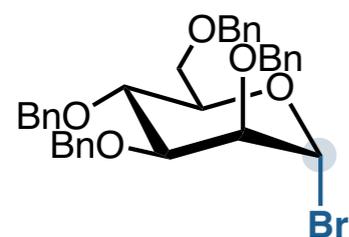


### Ligand and C2 configuration dictate stereoselectivity



## Example: Negishi Coupling via a Glycosyl Radical Intermediate

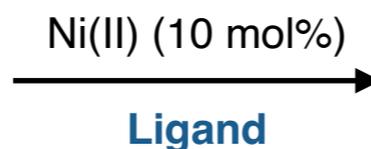
### Ni-catalyzed Negishi Coupling



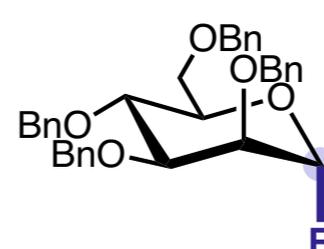
Glycosyl halide



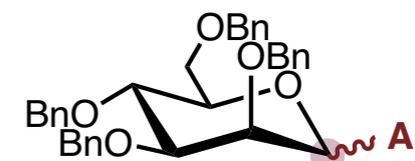
Zincate



Divergent  
stereoselectivity

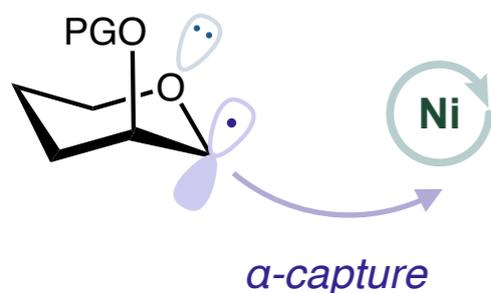


C-alkyl-glycosylation



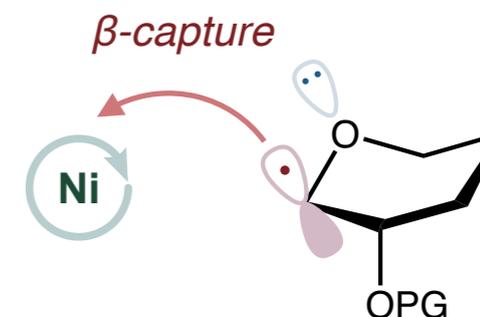
C-aryl-glycosylation

### Possibility of a Glycosyl Radical Intermediate



Mannosyl radical  
**Chair**

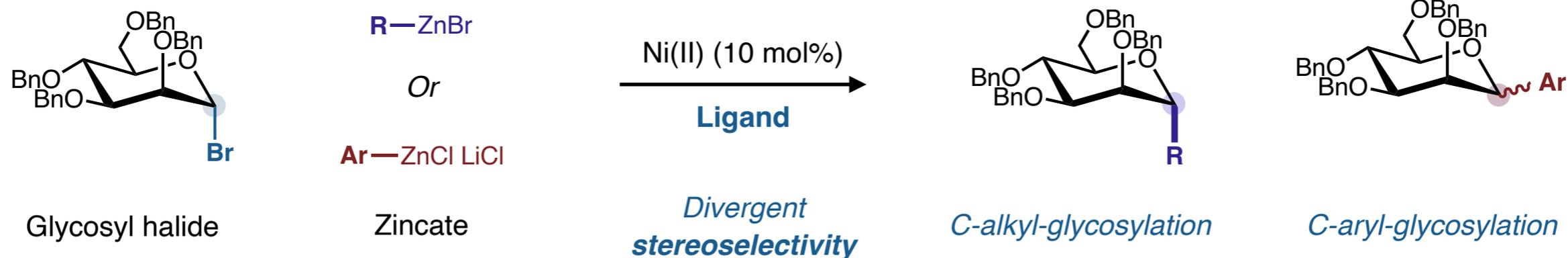
However, the **stereoselectivity**  
suggests a more **nuanced** mechanism  
than simple radical attack...



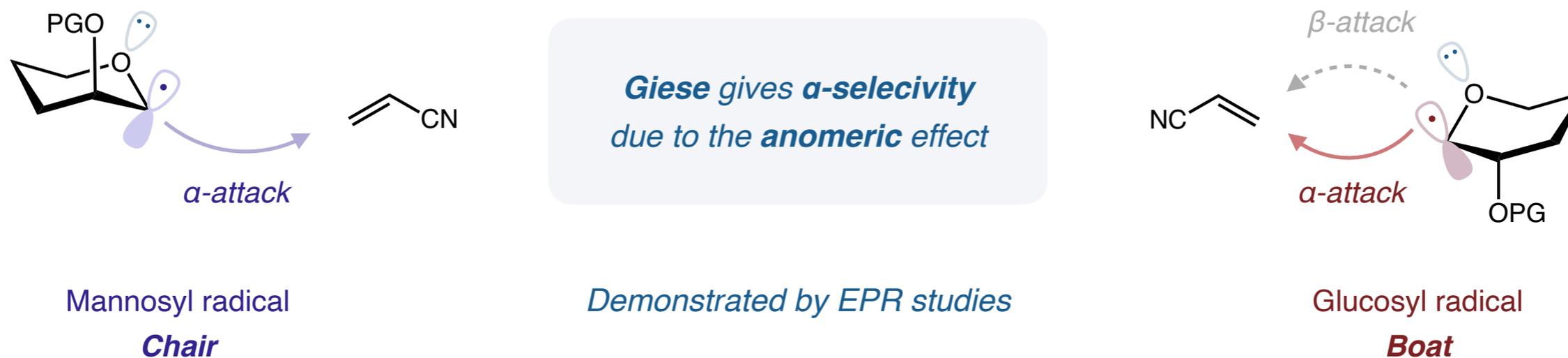
Glucosyl radical  
**Boat**

## Example: Negishi Coupling via a Glycosyl Radical Intermediate

### Ni-catalyzed Negishi Coupling



### Possibility of a Glycosyl Radical Intermediate



# *Outline*

*Discovery and Early History*

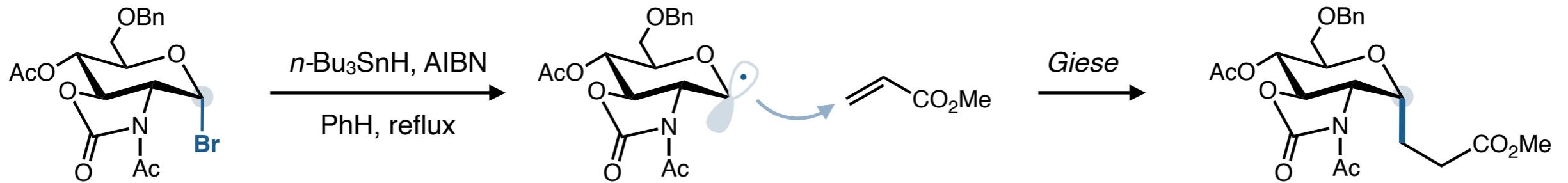
*Terminology*

*Monomer Functionalization & Chemical Glycosylation*

***Recent Advancements & Applications***

# Introduction to Radical Glycosylation

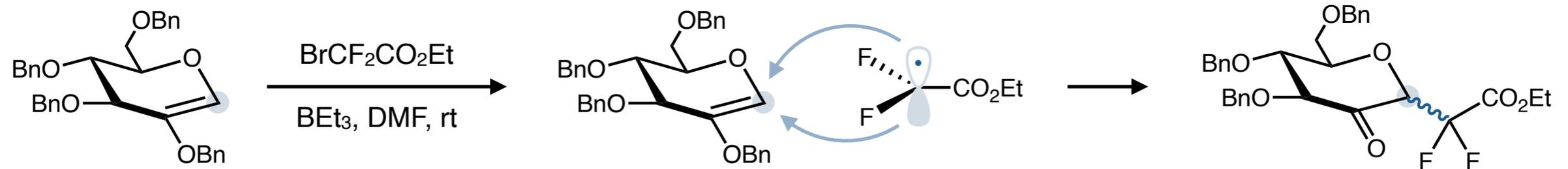
## Glycosyl radical: dehalogenative formation



Manabe, S.; Aihara, Y.; Ito, Y. *Chem. Comm.* **2011**, 34, 9720–9722.

**74% yield,  $\alpha$ -only**

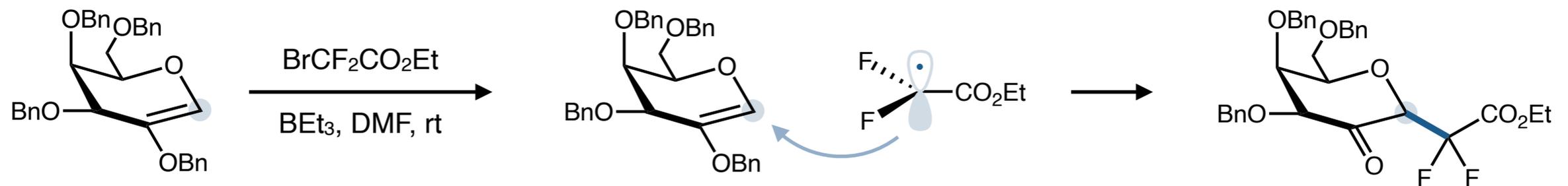
## Glycols as radical acceptors



Glycol

Distal **C4** steric hindrance

**51% yield,  $\alpha:\beta = 3:1$**



**58% yield,  $\alpha$ -only**

Moreno, B. *et. al. Org. Lett.* **2007**, 9, 2477-2480.

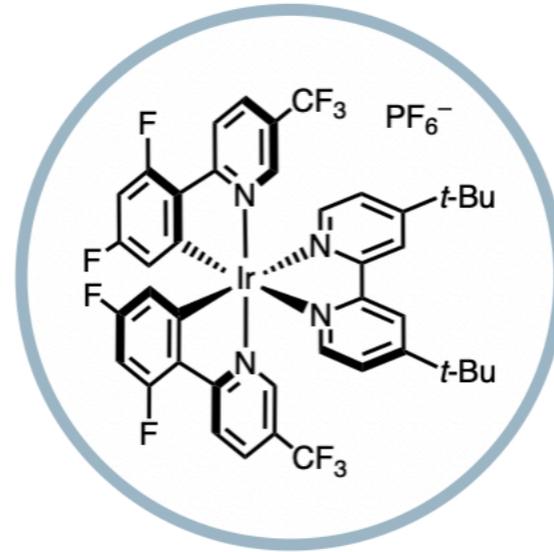
# Introduction to Radical Glycosylation

## Glycosyl radical: dehalogenative formation

**photoredox  
catalysis**



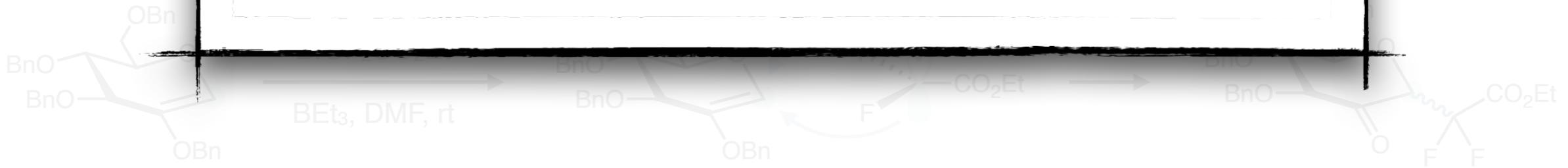
oxidation  
reduction  
energy transfer



**visible light  
irradiation**

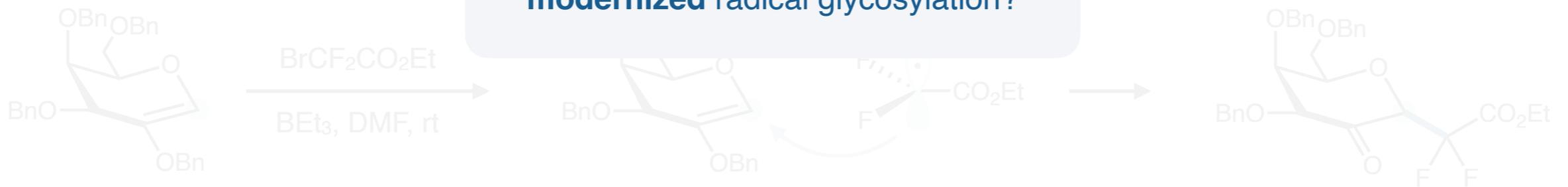


photonic to  
chemical energy  
(60 kcal/mol)



51% yield,  $\alpha:\beta = 3:1$

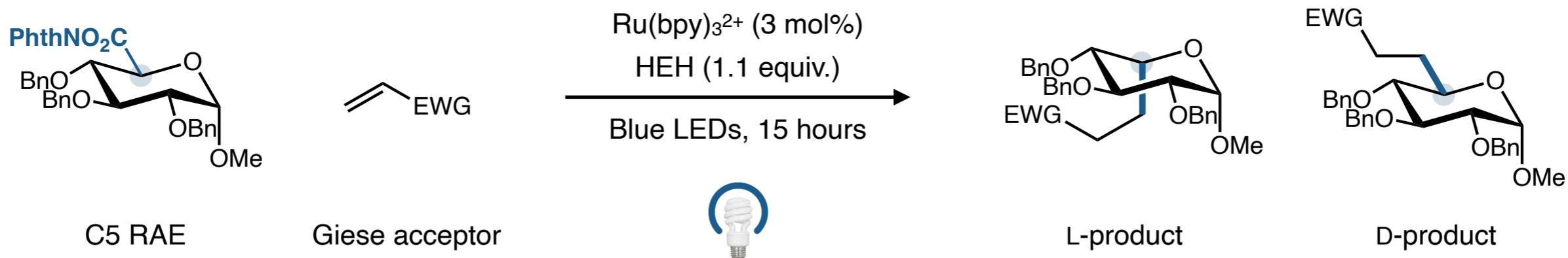
How has **photoredox** catalysis  
**modernized** radical glycosylation?



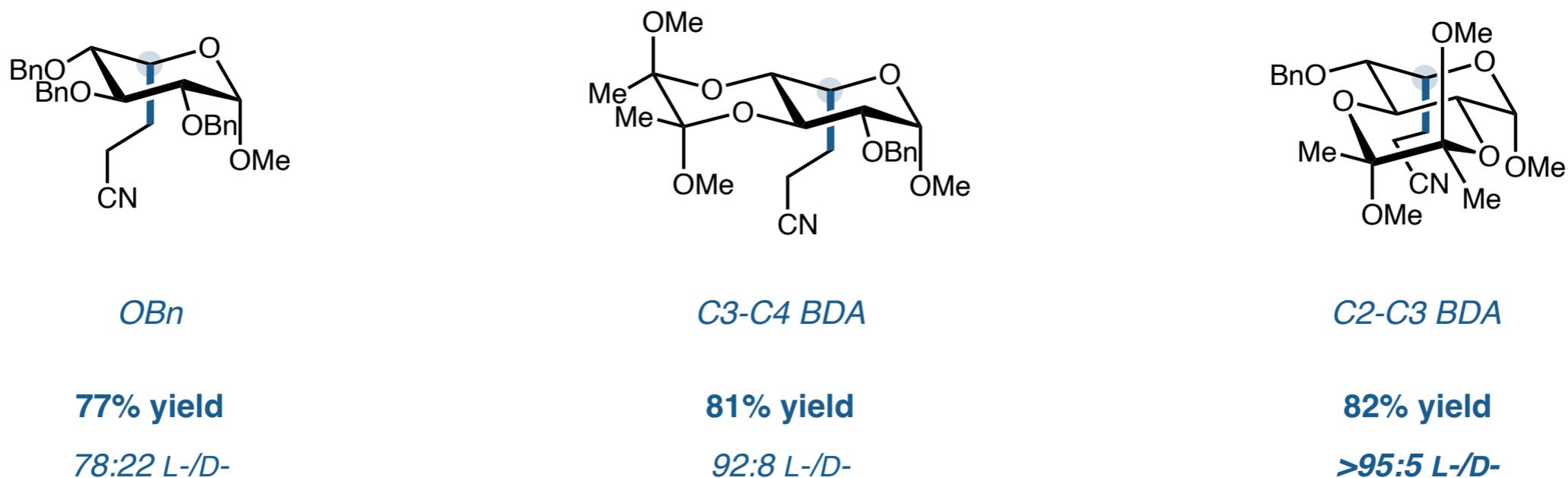
58% yield,  $\alpha$ -only

# Radical Glycosylation via Photoredox Catalysis

## C5 Decarboxylative Giese



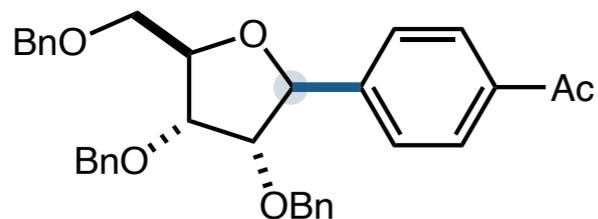
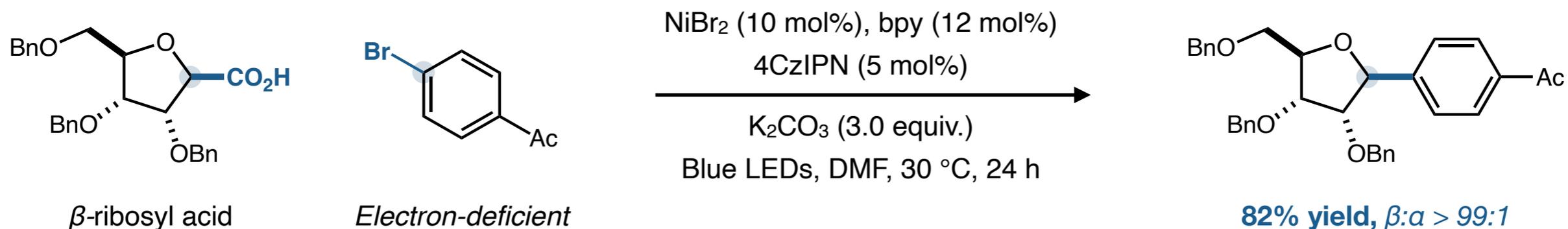
## Protecting group still relevant: *conformational restraints*



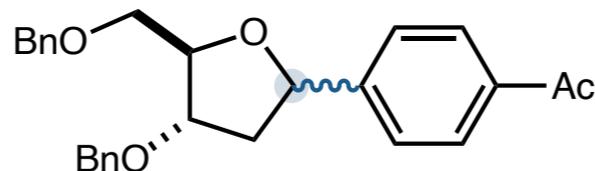
**Conformational rigidity**

# Aryl C–Glycosylation via Metallophotoredox Catalysis

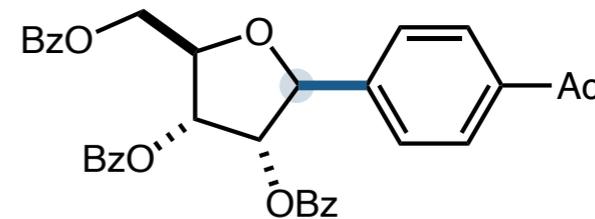
## C1 Decarboxylative Arylation



**80% yield,  $\beta:\alpha > 99:1$**   
*From  $\alpha$ -ribose acid*



**61% yield**  
 $\beta:\alpha = 20:80$

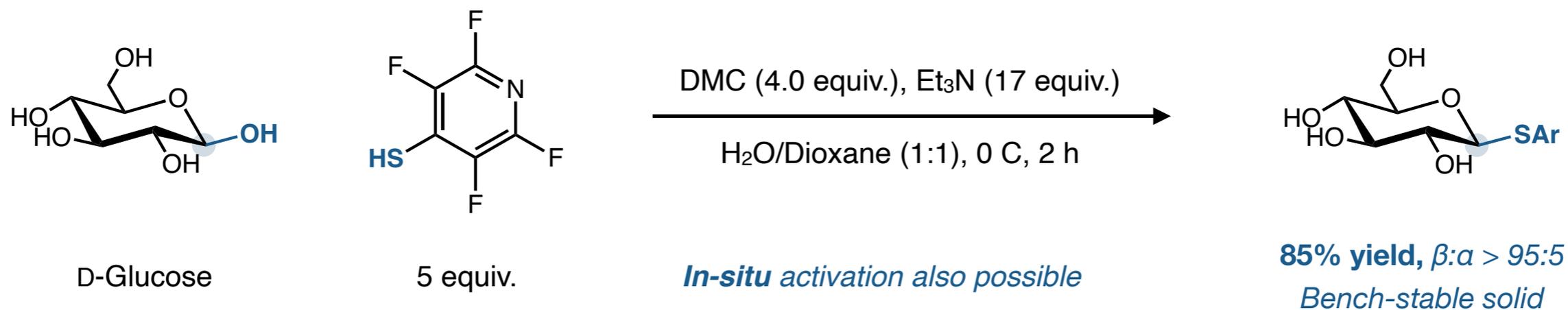


**No reaction**  
*Disarmed donor*

Various **scope limitations**; non-trivial **pre-functionalization** of glycosyl donor required

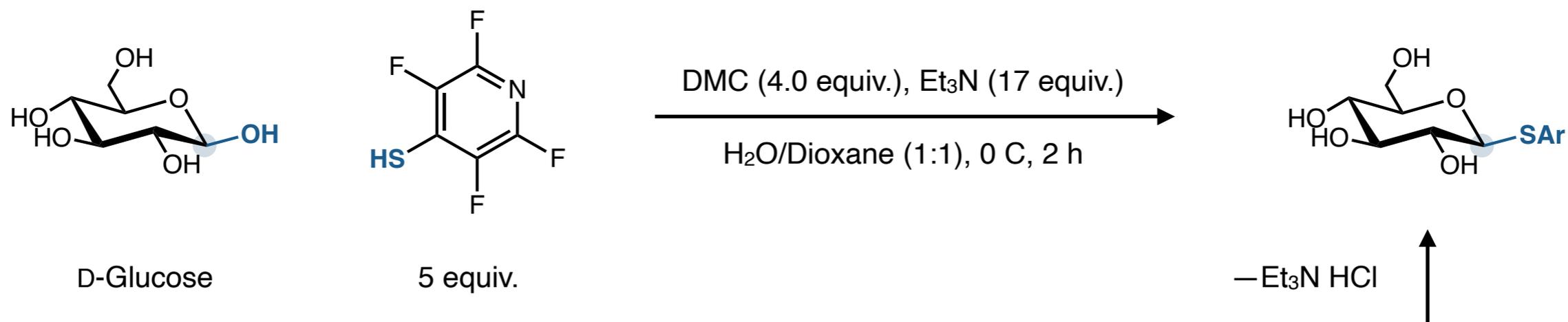
# Protecting-group Free Light-mediated Radical Glycosylation

PG-free, selective C1 activation (*Nature* 2024)

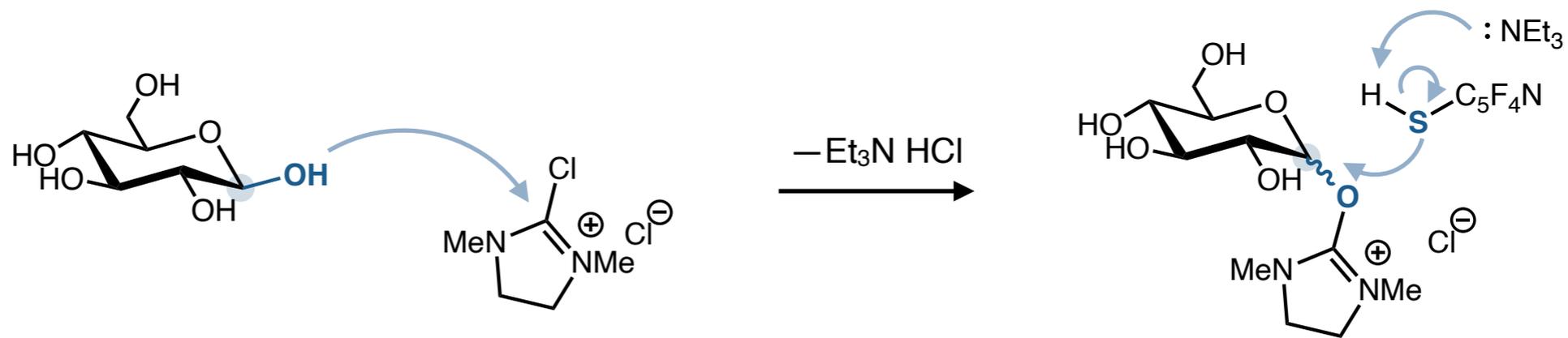


# Protecting-group Free Light-mediated Radical Glycosylation

PG-free, selective C1 activation (*Nature* 2024)

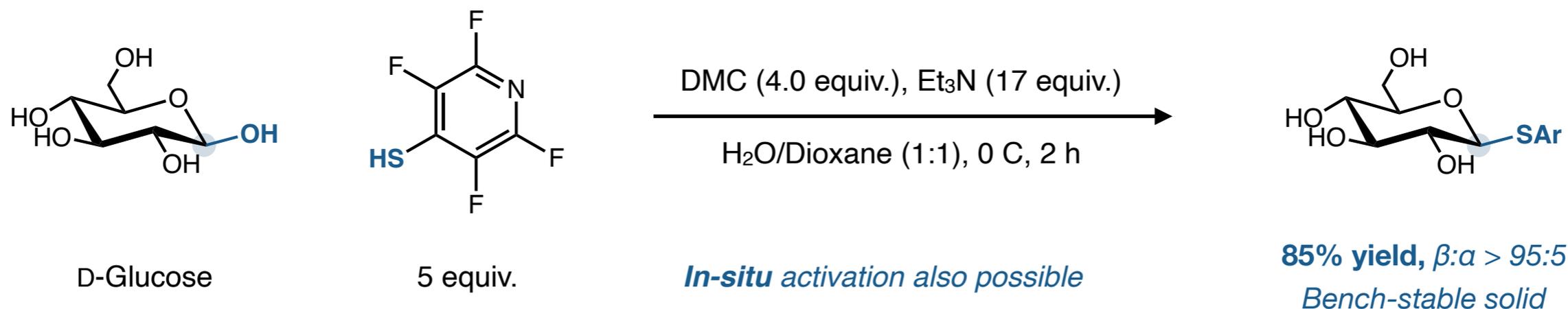


via

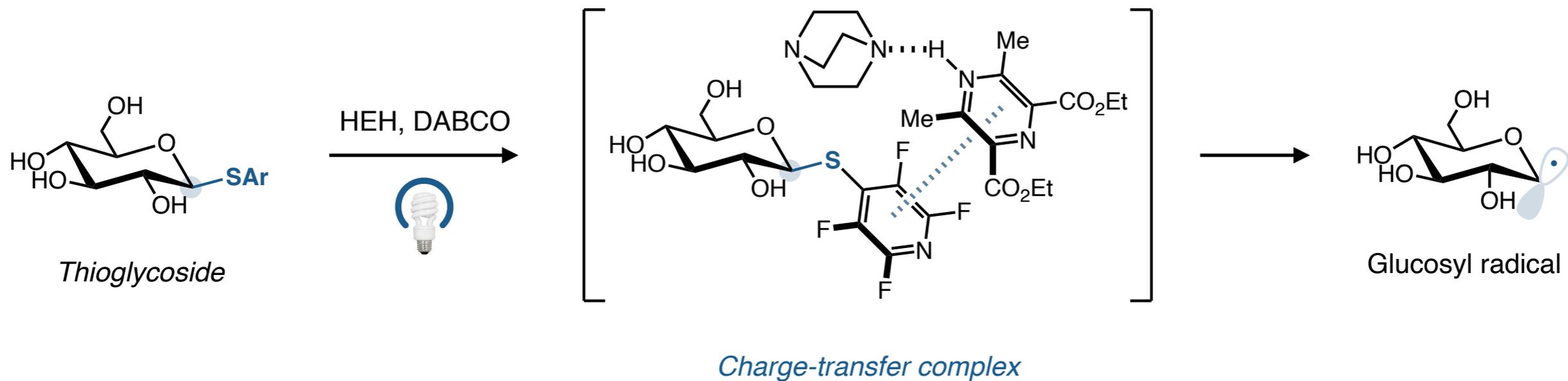


# Protecting-group Free Light-mediated Radical Glycosylation

## PG-free, selective C1 activation (*Nature* 2024)

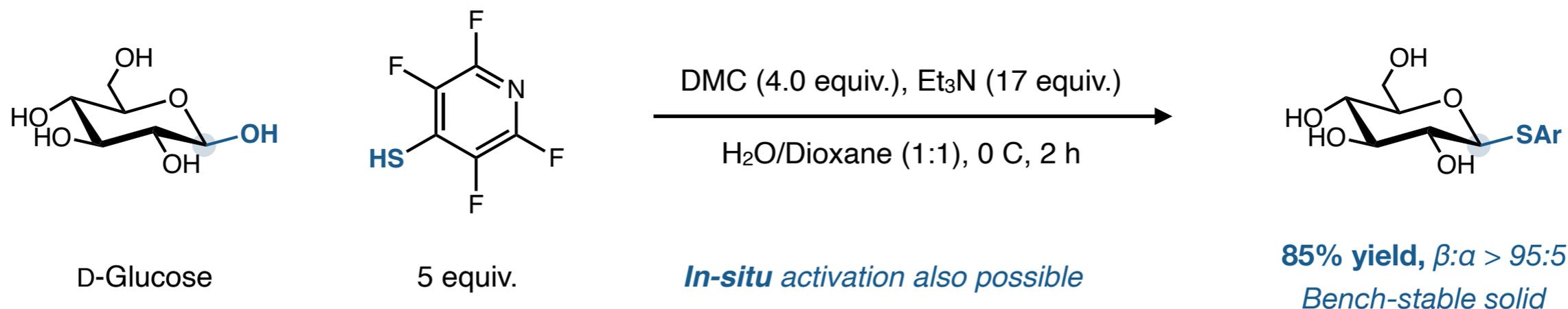


## Radical formation: mechanism

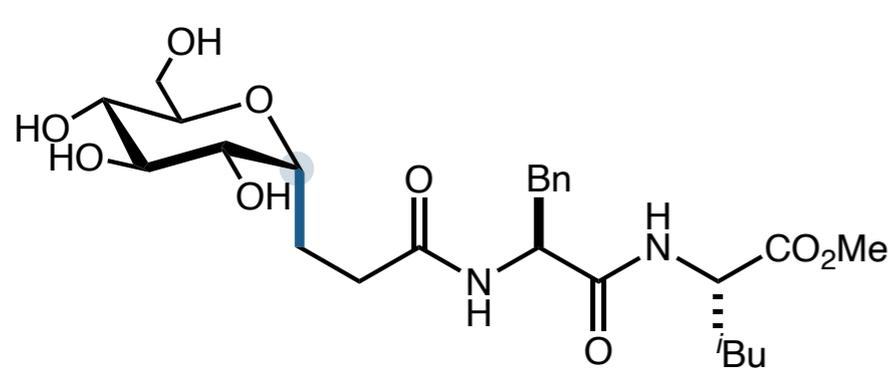


# Protecting-group Free Light-mediated Radical Glycosylation

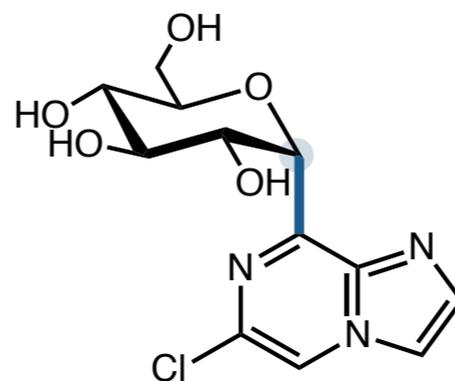
## PG-free, selective C1 activation (*Nature* 2024)



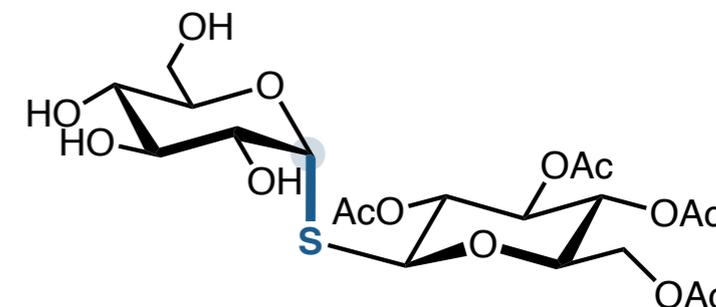
## Access to diverse $\alpha$ -glycosides



**73% yield,  $\alpha:\beta > 95:5$**   
C-glycosylation via Giese



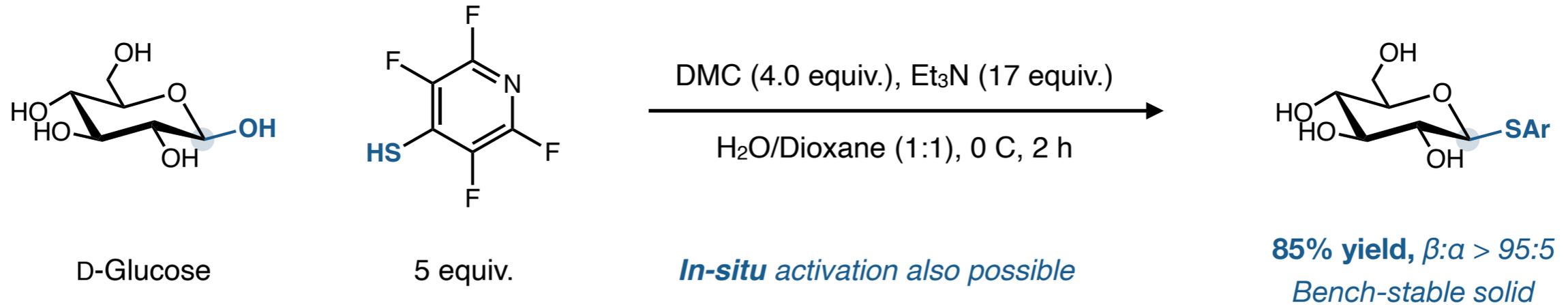
**44% yield,  $\alpha:\beta > 95:5$**   
C-glycosylation via Minisci



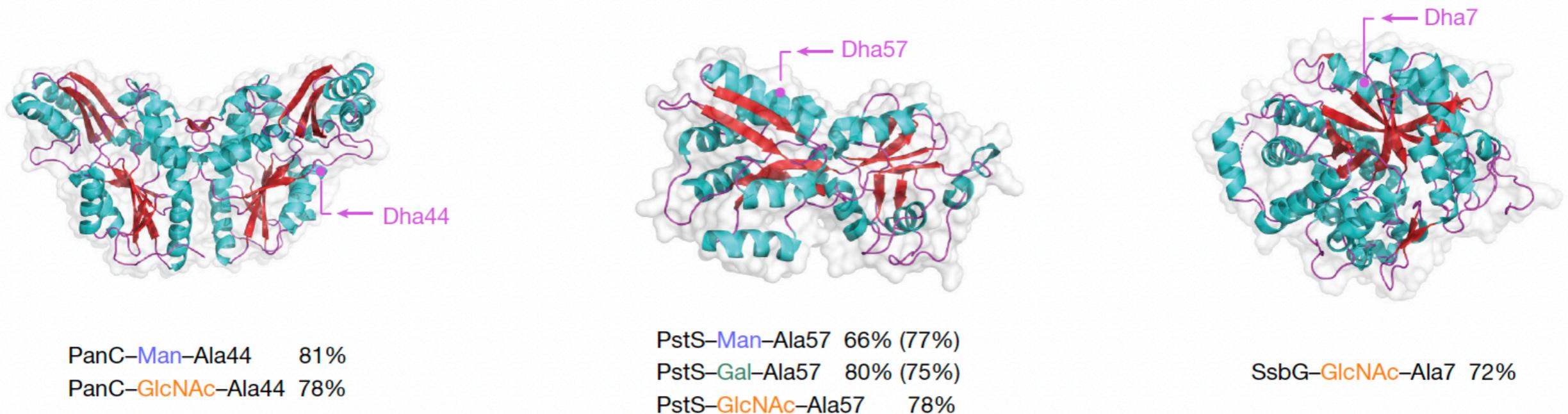
**34% yield,  $\alpha:\beta > 95:5$**   
S-glycosylation

# Protecting-group Free Light-mediated Radical Glycosylation

## PG-free, selective C1 activation (*Nature* 2024)

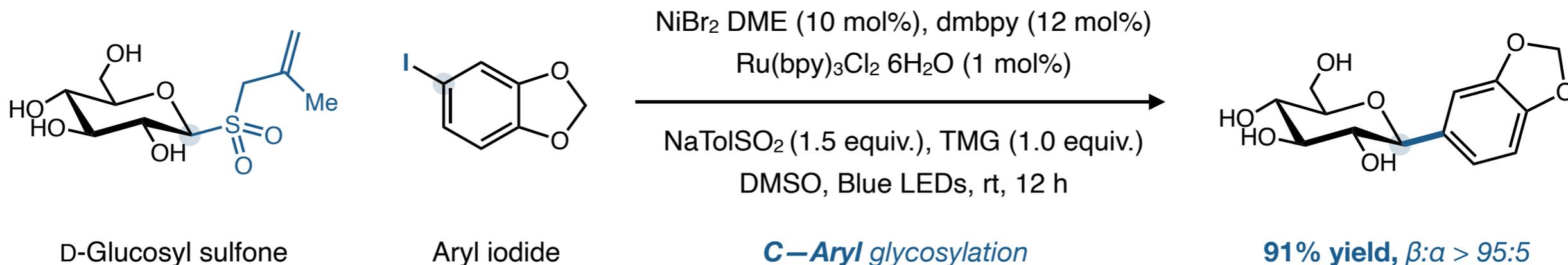


## Post-translational *protein glycosylation*

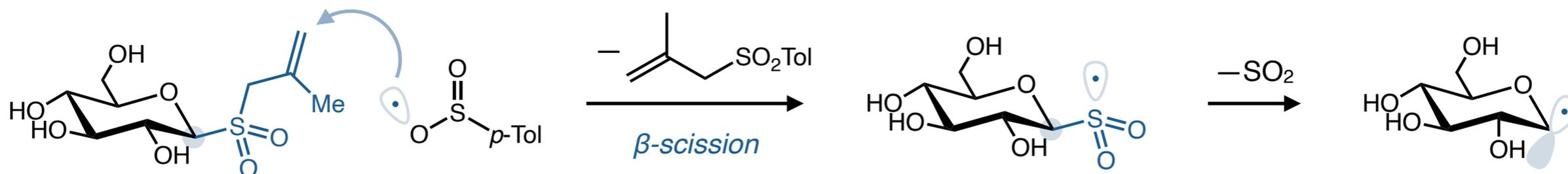


# The Frontier: Protecting-group Free Metallophotoredox Glycosylation

From two-electron to **one-electron** donors: glycosyl **sulfones**

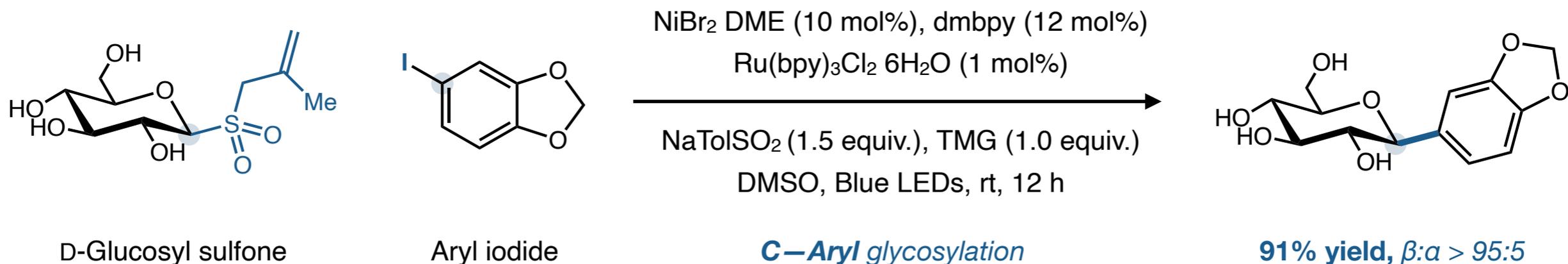


*Activation mechanism: sulfone as radical acceptor*

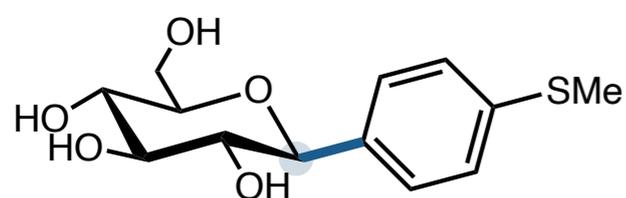


# The Frontier: Protecting-group Free Metallophotoredox Glycosylation

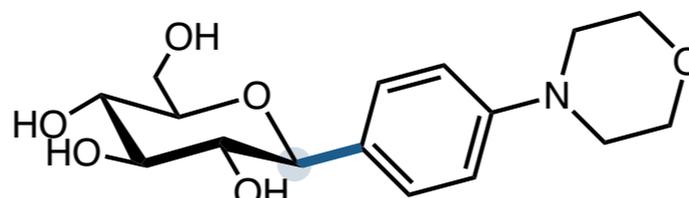
From two-electron to **one-electron** donors: glycosyl **sulfones**



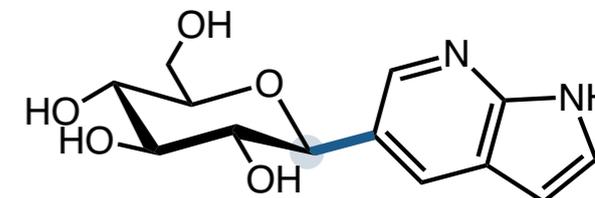
Scope: **broad functional group tolerance**



**52% yield**  
β:a > 95:5



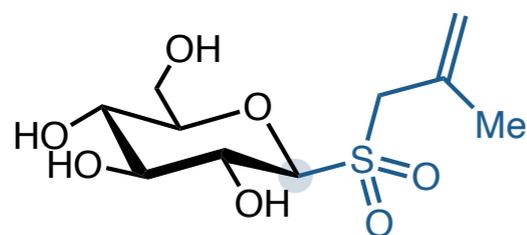
**65% yield**  
β:a > 95:5



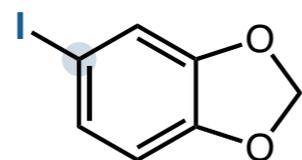
**91% yield**  
β:a = 89:11

# The Frontier: Protecting-group Free Metallophotoredox Glycosylation

From two-electron to **one-electron** donors: glycosyl **sulfones**



D-Glucosyl sulfone

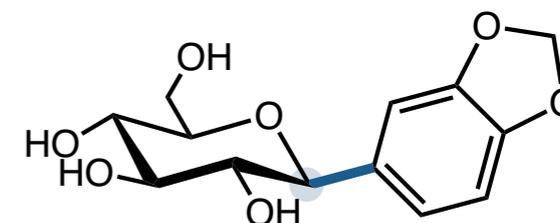


Aryl iodide

NiBr<sub>2</sub> DME (10 mol%), dmbpy (12 mol%)  
Ru(bpy)<sub>3</sub>Cl<sub>2</sub> 6H<sub>2</sub>O (1 mol%)

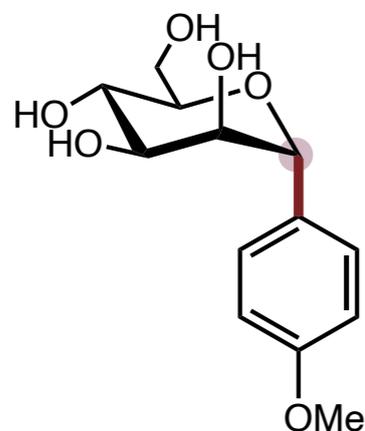
NaTolSO<sub>2</sub> (1.5 equiv.), TMG (1.0 equiv.)  
DMSO, Blue LEDs, rt, 12 h

**C–Aryl glycosylation**



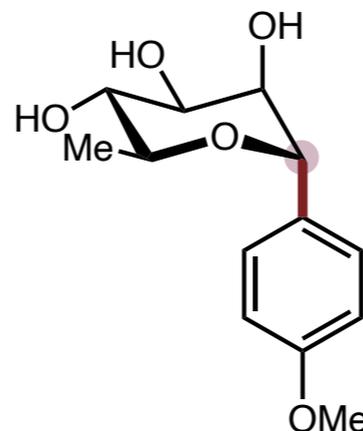
**91% yield,  $\beta$ : $\alpha$  > 95:5**

## Stereoselectivity: Inversions and Limitations



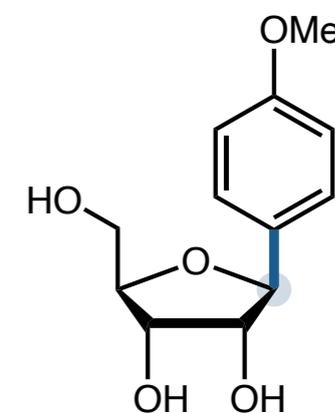
D-Mannose

**52% yield**  
 $\alpha$ : $\beta$  = 86:14



D-Rhamnose

**87% yield**  
 $\alpha$ : $\beta$  = 71:29

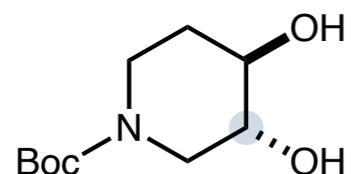


D-Ribose

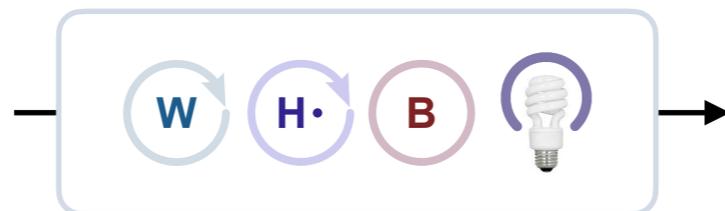
**76% yield**  
 $\beta$ : $\alpha$  = 83:17

# Monosaccharide Stereochemical Editing Enabled by Radicals

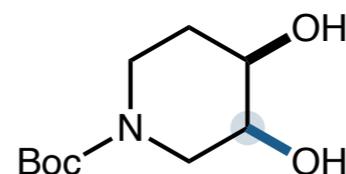
Christian: Diol **Epimerization** (*JACS* 2022)



*trans*-diol

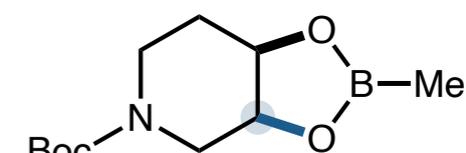


**Contrathermodynamic**



*cis*-diol

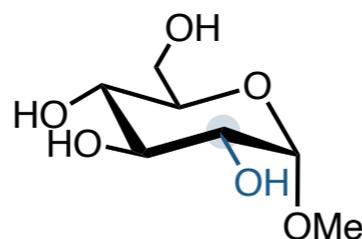
Via



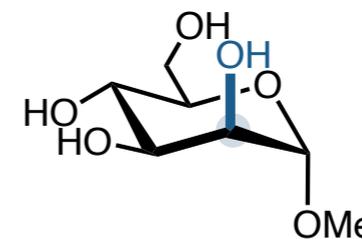
Borate ester



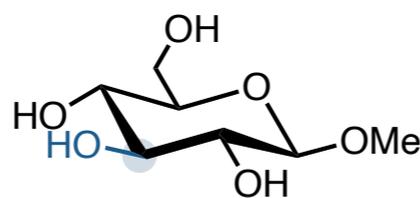
Dr. Christian Oswood



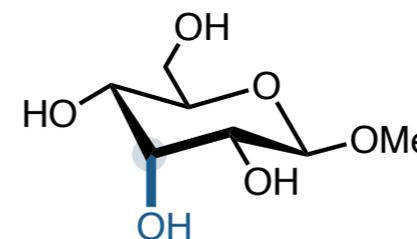
*α*-glucose



**47% yield**  
*α*-mannose



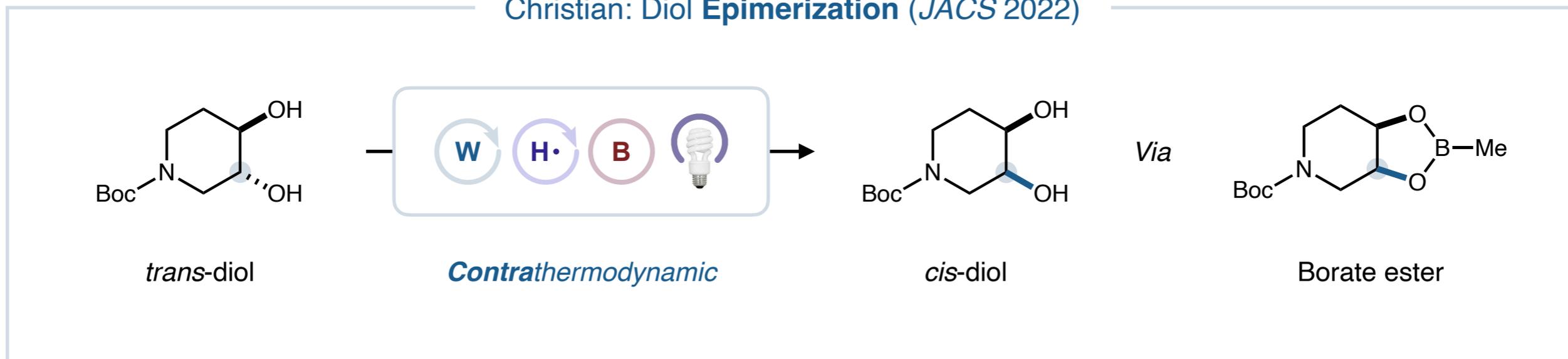
*β*-glucose



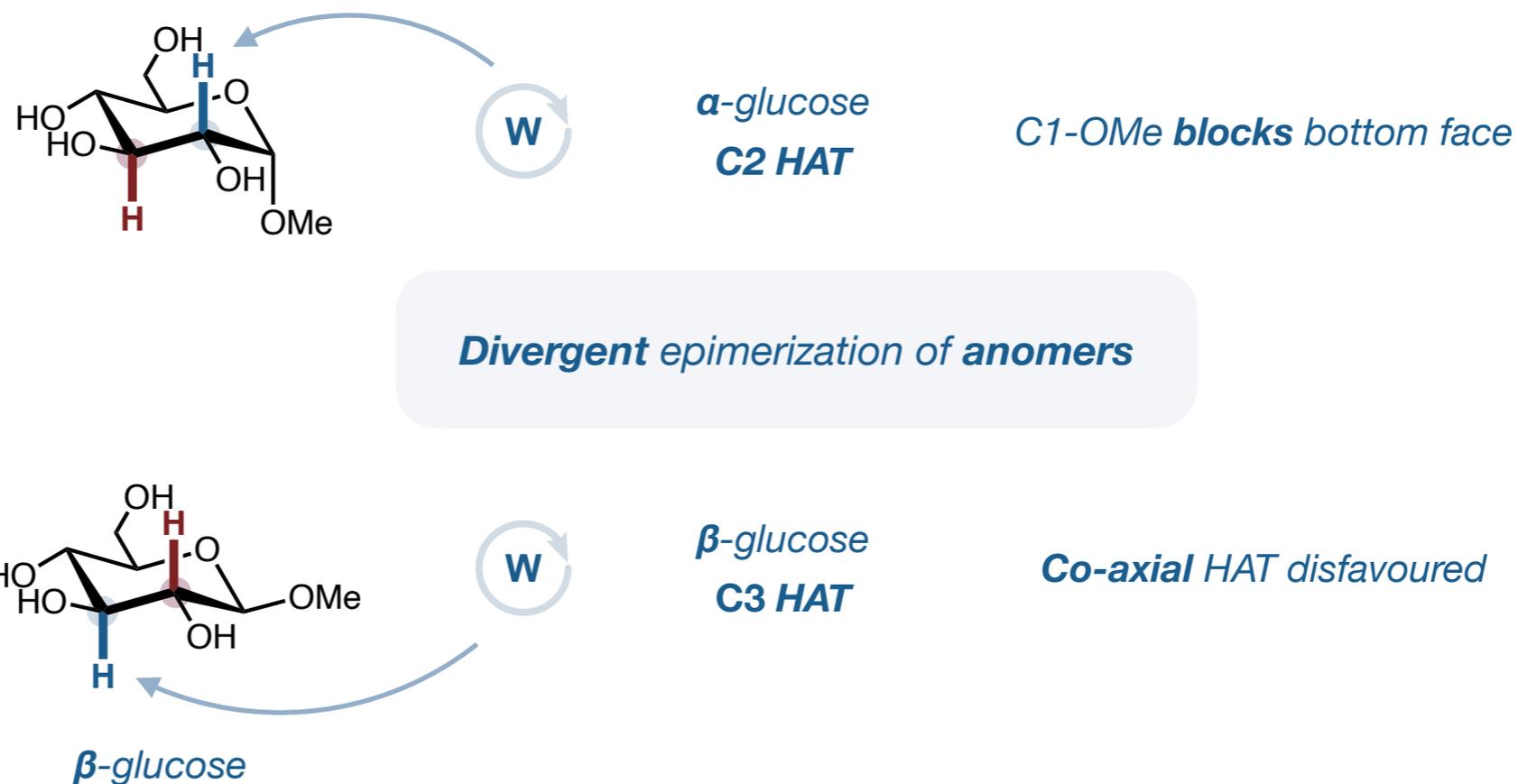
**47% yield**  
*β*-allose

# Monosaccharide Stereochemical Editing Enabled by Radicals

Christian: Diol **Epimerization** (*JACS* 2022)

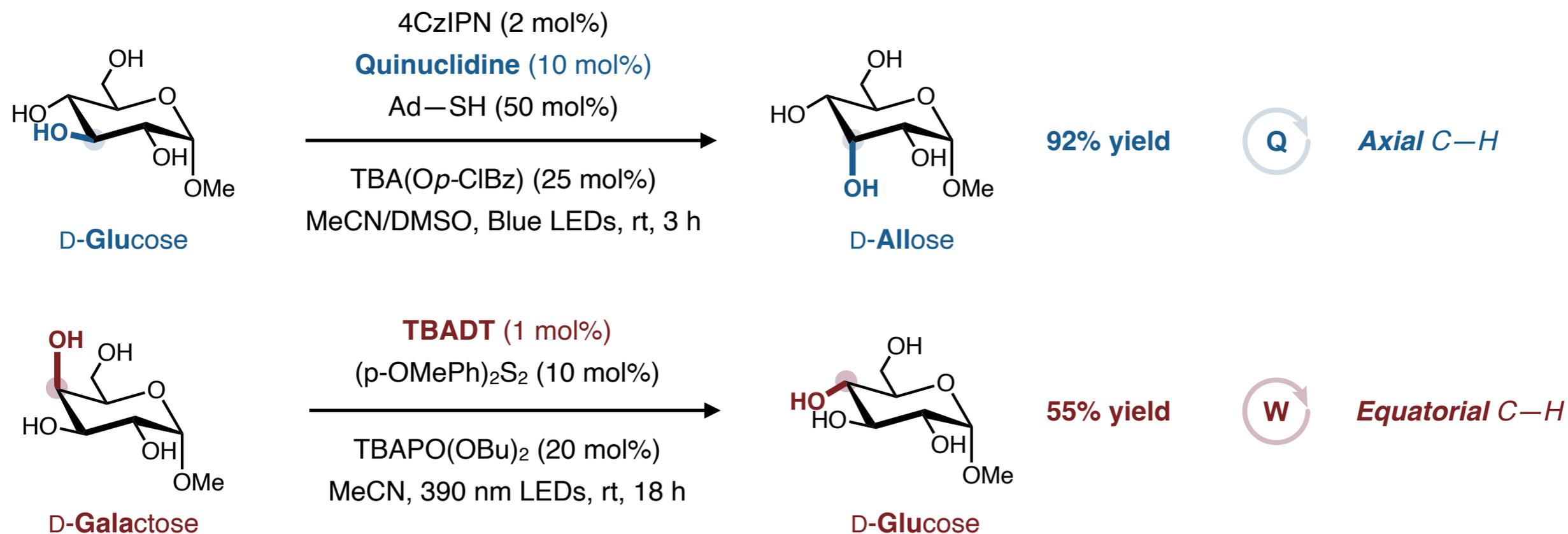
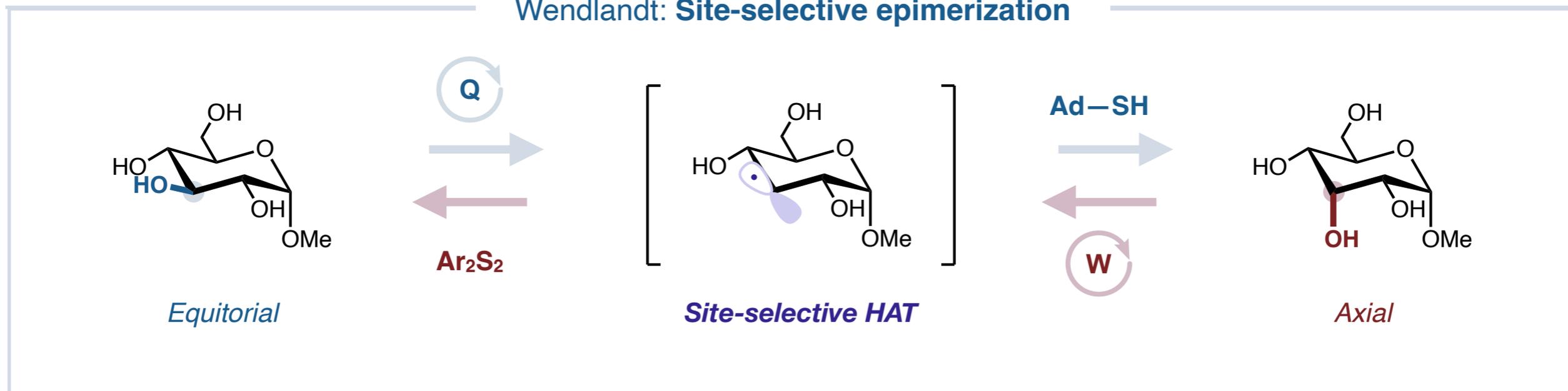


Dr. Christian Oswood



# Monosaccharide Stereochemical Editing Enabled by Radicals

## Wendlandt: Site-selective epimerization

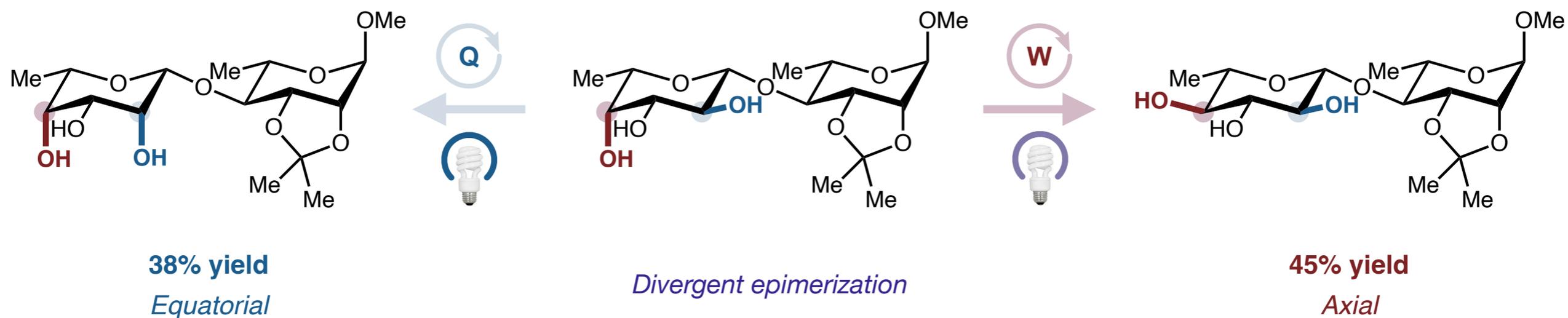
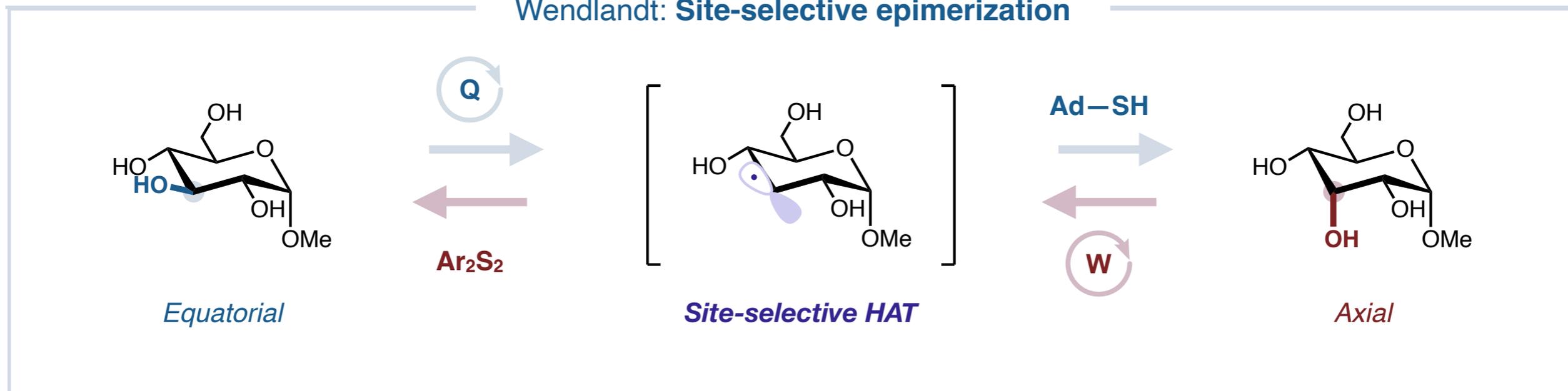


Wang, Y.; Carder, H. M.; Wendlandt, A. E. *Nature* **2020**, *578*, 403-408.

Carder, H. M.; Wang, Y.; Wendlandt, A. E. *J. Am. Chem. Soc.* **2022**, *144*, 11870-11877.

# Monosaccharide Stereochemical Editing Enabled by Radicals

## Wendlandt: Site-selective epimerization

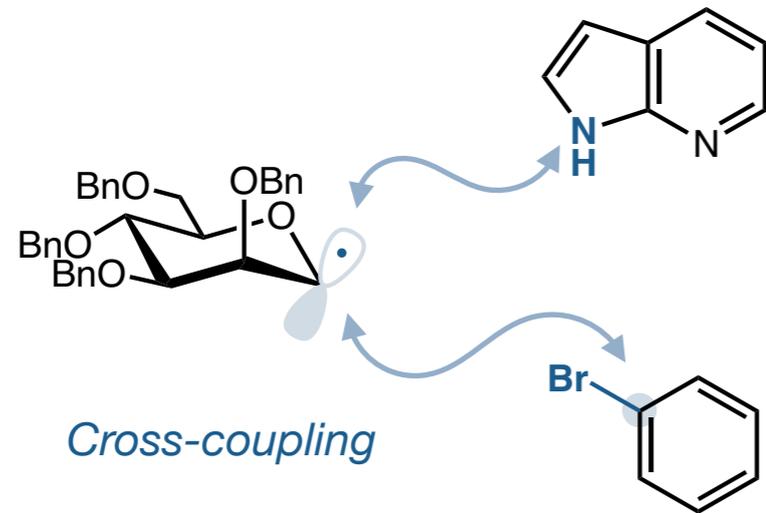


Wang, Y.; Carder, H. M.; Wendlandt, A. E. *Nature* **2020**, *578*, 403-408.

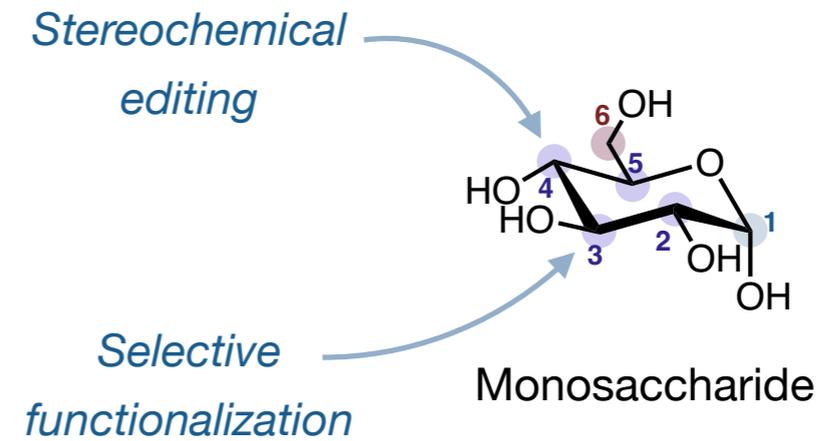
Carder, H. M.; Wang, Y.; Wendlandt, A. E. *J. Am. Chem. Soc.* **2022**, *144*, 11870-11877.

# Modern Carbohydrate Chemistry: Applications and Outlook

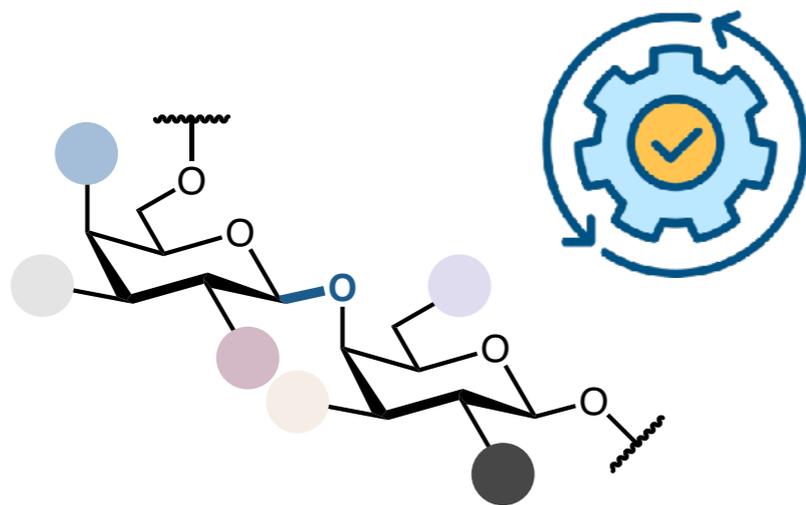
## Radical Glycosylation



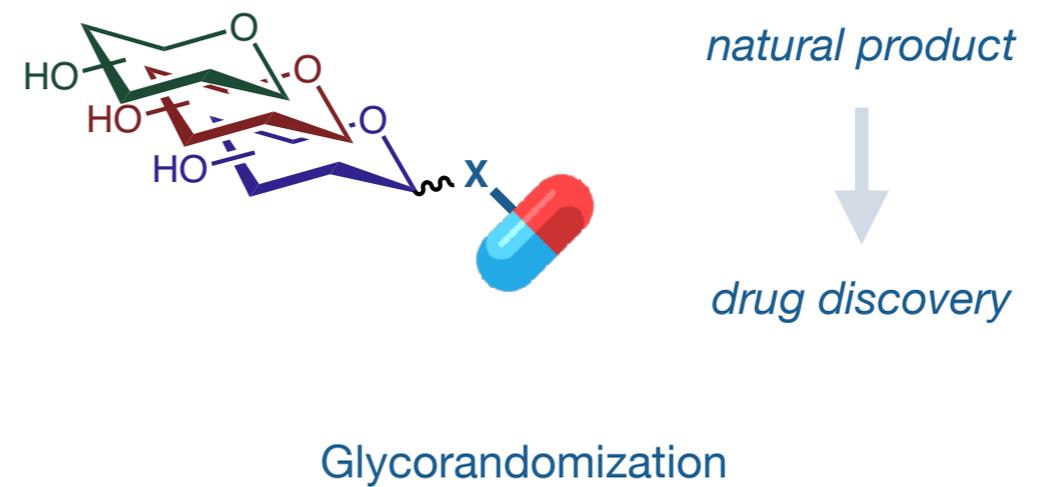
## Monomer Functionalization



## Automated Polysaccharide Synthesis



## Beyond Synthetic Chemistry

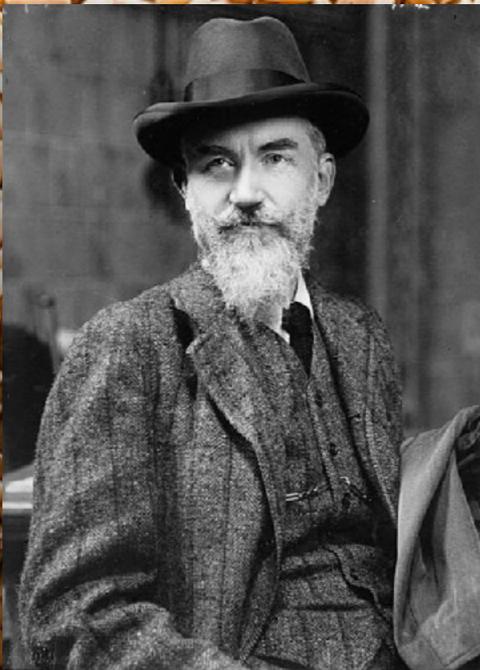


Questions?

Q: "Did you know that 'sugar' is the only word in the English language where 'su' is pronounced 'sh'?"

A: "Sure."

—George Bernard Shaw,  
1925 Nobel laureate of Literature



**Bernard Shaw**  
(1856-1950)