

Anomeric Modification of Saccharides

Literature Seminar, 24/12/12,
B4, Haruki Kobori

Today's content

1. Introduction

2. Main

- **Ti-catalyzed C-glycosylation of glycosyl chlorides**
- **Two step functionalization of unprotected saccharides**
- **Ti-catalyzed direct anomeric activation of unprotected saccharides**

3. Summary

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1. Introduction

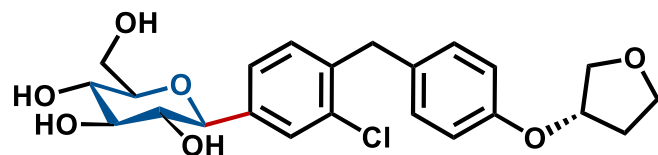
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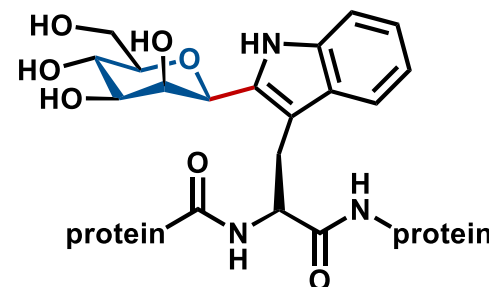
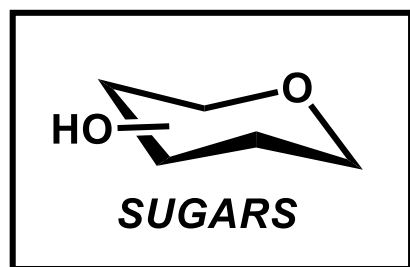
3. Summary

C-Glycosides

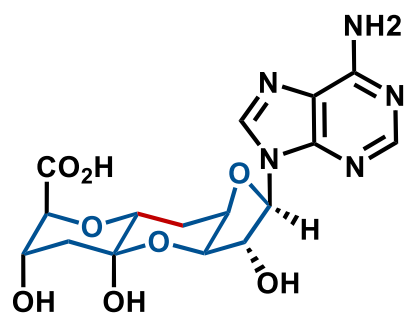
- C-glycosides are important structures in various compounds: natural products, bioactive compounds and marketed drugs.
- Substitution of C-O acetal with C-C bond increases stability in vivo.
→ **In demand as potential therapeutic agents and biological probes**



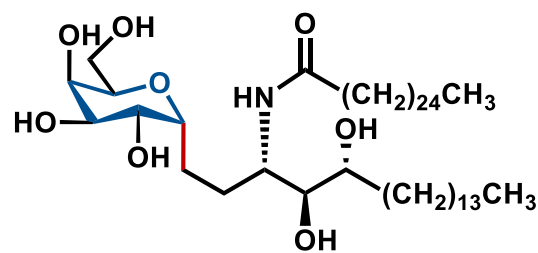
Empagliflozin
(antidiabetic)



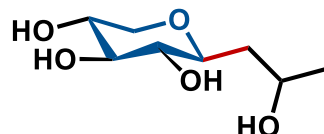
C-Mannosyl-Trp
(PTM of proteins)



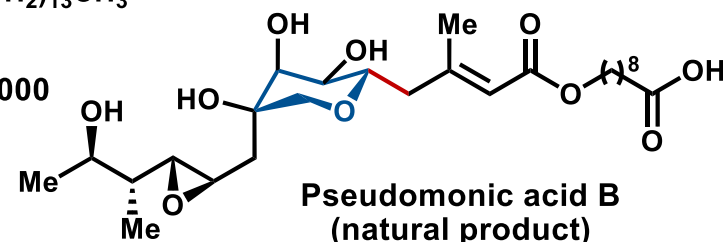
Aureonuclemycin
(natural product)



C-analogue of KRN7000
(anticancer)



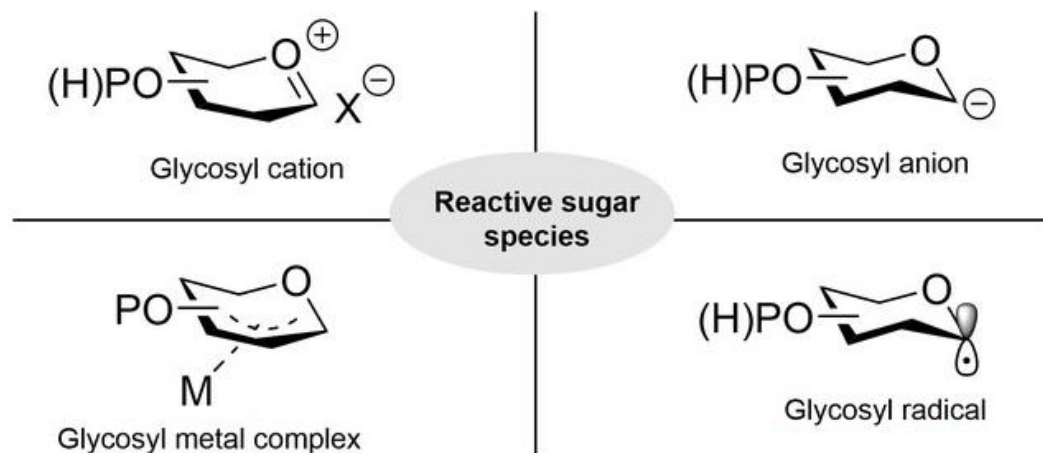
Pro-Xylane™
(skin care)



Pseudomonic acid B
(natural product)

Synthesis of C-Glycosides via Glycosyl Radicals

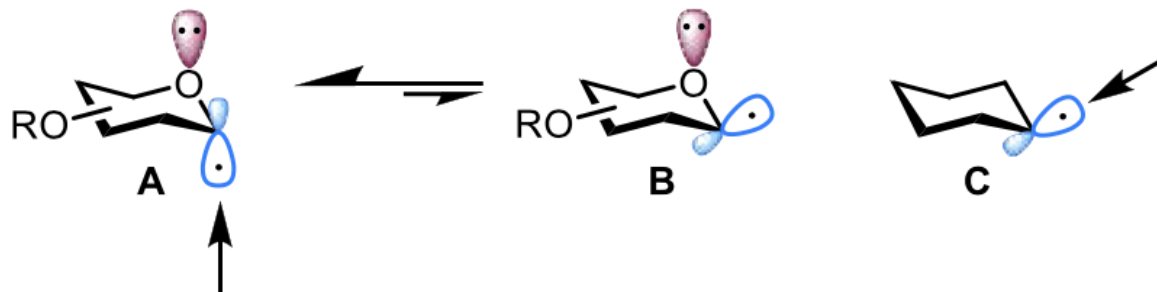
Anomeric activation



- Mild conditions
- High functional group tolerance
- High anomeric stereoselectivity
- Compatible with water

Reviews on glycosyl radical-mediated C-glycosylation: Koh, M. J. *Angew. Chem. Int. Ed.* **2023**, e202305138.; Hu, X.-G. *et al. Org. Biomol. Chem.* **2020**, 18, 5095.; Nokami, T. *et al. Carbohydr. Res.* **2022**, 522, 108677.

Anomeric stereoselectivity



- Anomeric radical is likely to be axial position.
- ← Interaction with lone pair of adjacent O atom.

Nokami, T. *et al. Carbohydr. Res.* **2022**, 522, 108677.

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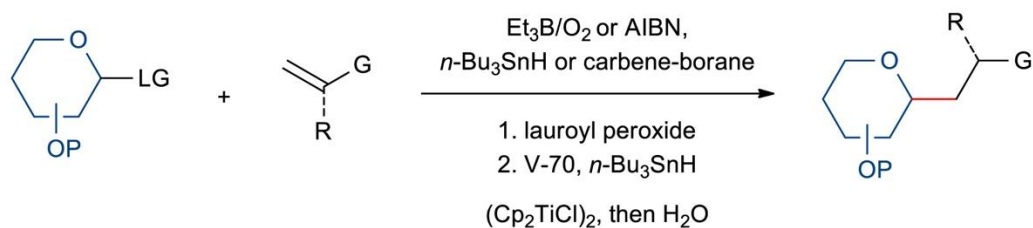
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- **Ti-catalyzed C-glycosylation of glycosyl chlorides**
- Two step functionalization of unprotected saccharides
- Ti-catalyzed direct anomeric activation of unprotected saccharides

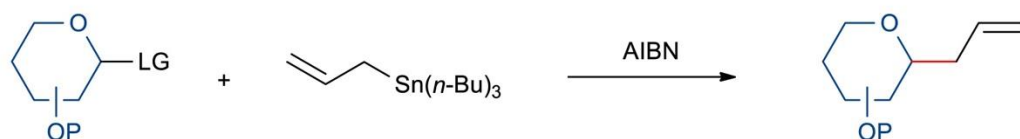
3. Summary

Background

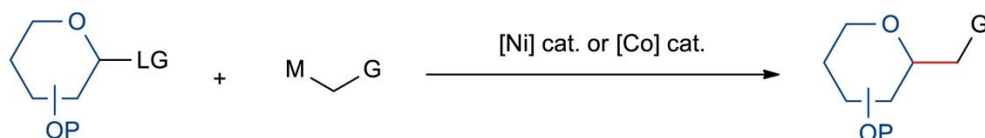
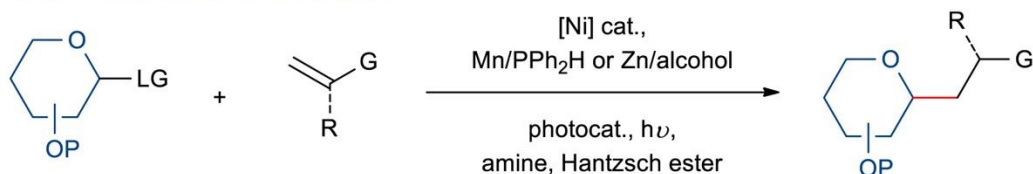
Non-catalytic



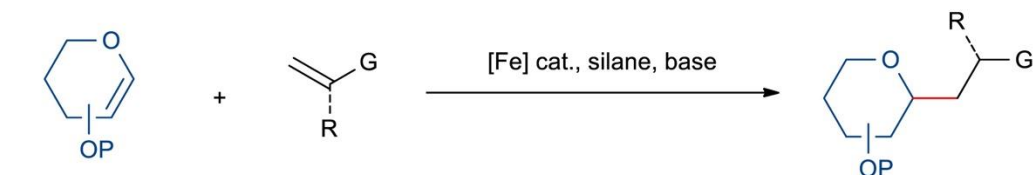
- **Stoichiometric or excess amount of reagent.**
- **Toxic or pyrophoric reagent.**
- **Ti(III) was used super-stoichiometrically.**



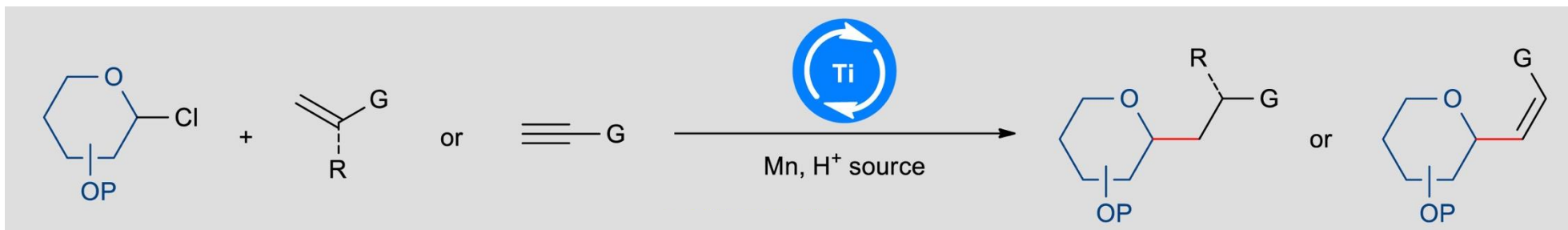
Metal- or photoredox-catalyzed



- **Limited scope.**
 - **Use of air- and moisture-sensitive alkylmetal reagent.**
 - **Addition of less electron-deficient acrylamide is inefficient.**
- **Synthesis of glycopeptide is difficult.**



Strategy

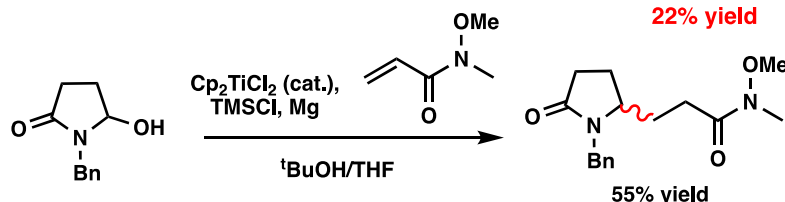
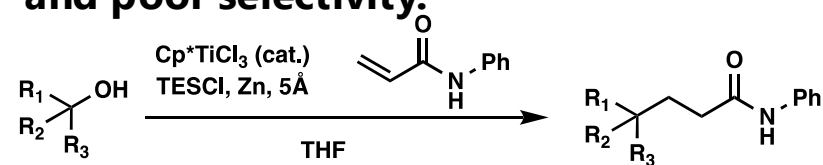


Ti catalyst

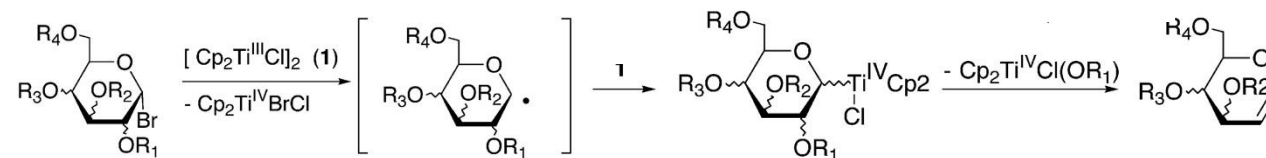
- Nonprecious and non-toxic reagent.
 - High affinity with halogen atoms.
- Radical generation from glycosyl halides.

Challenges

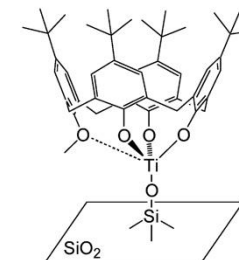
- Addition to acrylamides is low yield and poor selectivity.



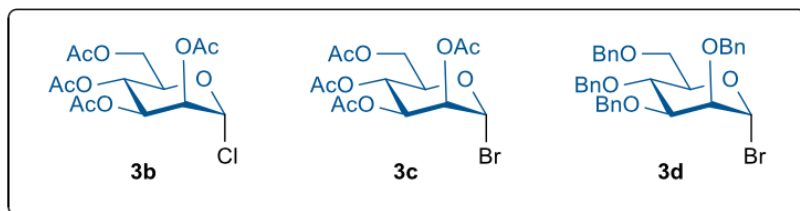
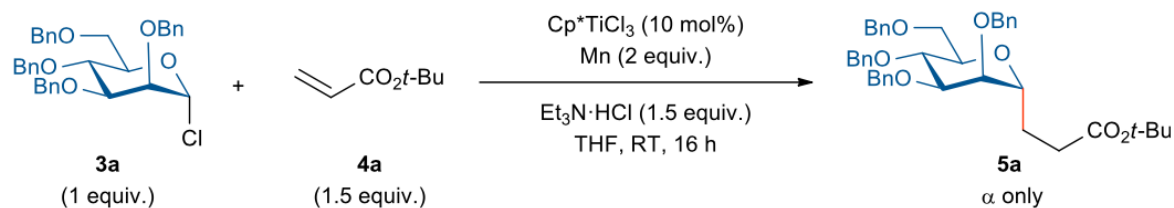
- Alkyltitanium formation followed by β-elimination.



- Oxygen coordination to Ti, inhibiting catalytic reaction.



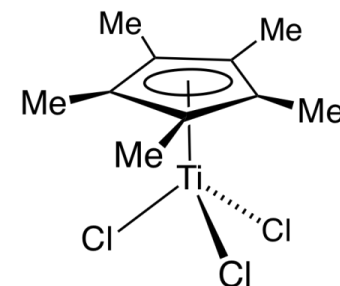
Optimization



| Entry | Deviation from standard conditions | Yield (%) ^a |
|-----------------|--|------------------------|
| 1 | none | 93 (78) ^b |
| 2 | Zn instead of Mn | 47 |
| 3 | CpTiCl_3 instead of Cp^*TiCl_3 | Trace |
| 4 | Cp_2TiCl_2 instead of Cp^*TiCl_3 | 80 |
| 5 | DCM instead of THF | 52 |
| 6 | Toluene, DME, DMSO, or MeCN instead of THF | <10 |
| 7 | 2,4,6-Collidine·HCl instead of $\text{Et}_3\text{N}\cdot\text{HCl}$ | 28 |
| 8 | HCl (dioxane) instead of $\text{Et}_3\text{N}\cdot\text{HCl}$ | <10 |
| 9 | <i>i</i> -PrOH, <i>t</i> -BuOH or Ph_2CHOH instead of $\text{Et}_3\text{N}\cdot\text{HCl}$ | Trace |
| 10 | H_2O instead of $\text{Et}_3\text{N}\cdot\text{HCl}$ | <2 |
| 11 | 3b instead of 3a | <2 |
| 12 ^c | 3c instead of 3a | 40 |
| 13 | 3d instead of 3a | 48 |

• Mn or Zn to reduce Ti(IV) to Ti (III).
(entry 2)

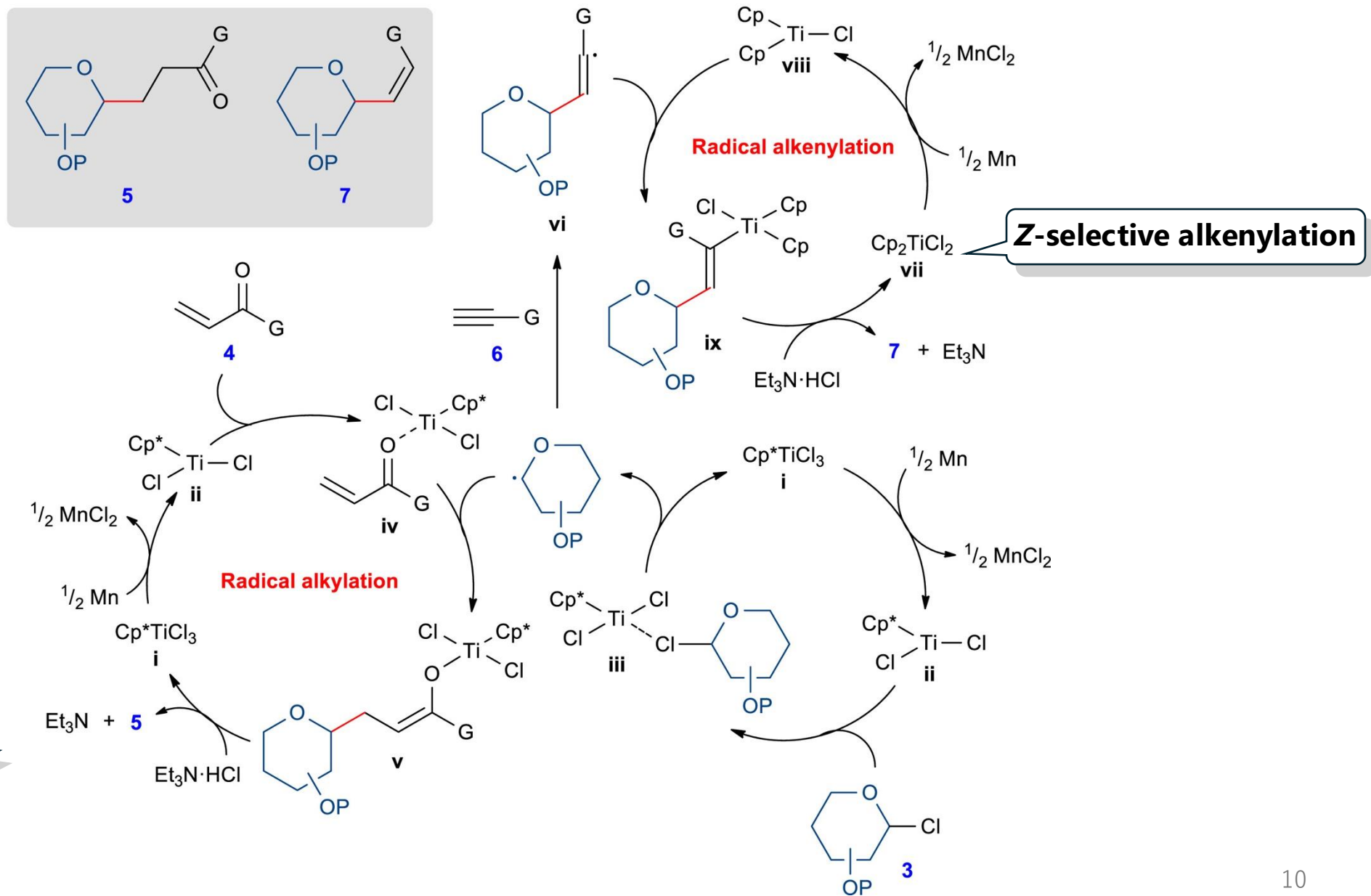
• Cp^*TiCl_3 was the best catalyst. (entry 3,4)



• Appropriate acidity of proton source.
→ Protonolysis of Ti-O bond in enolate intermediate.
(entry 7-10)

• 30% of glucal by β -elimination was observed.
(entry 12)

Reaction Mechanism

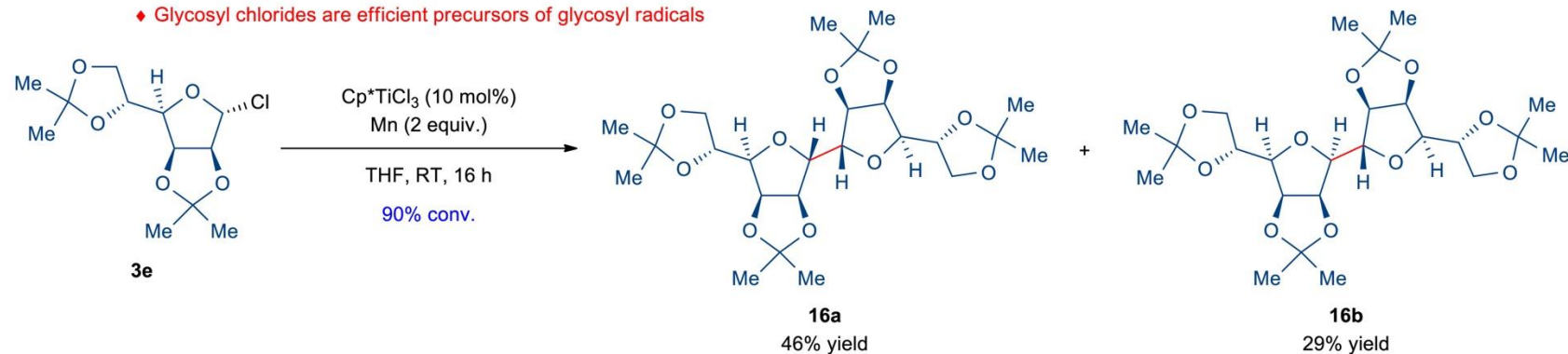


Appropriate acidity
for protonolysis

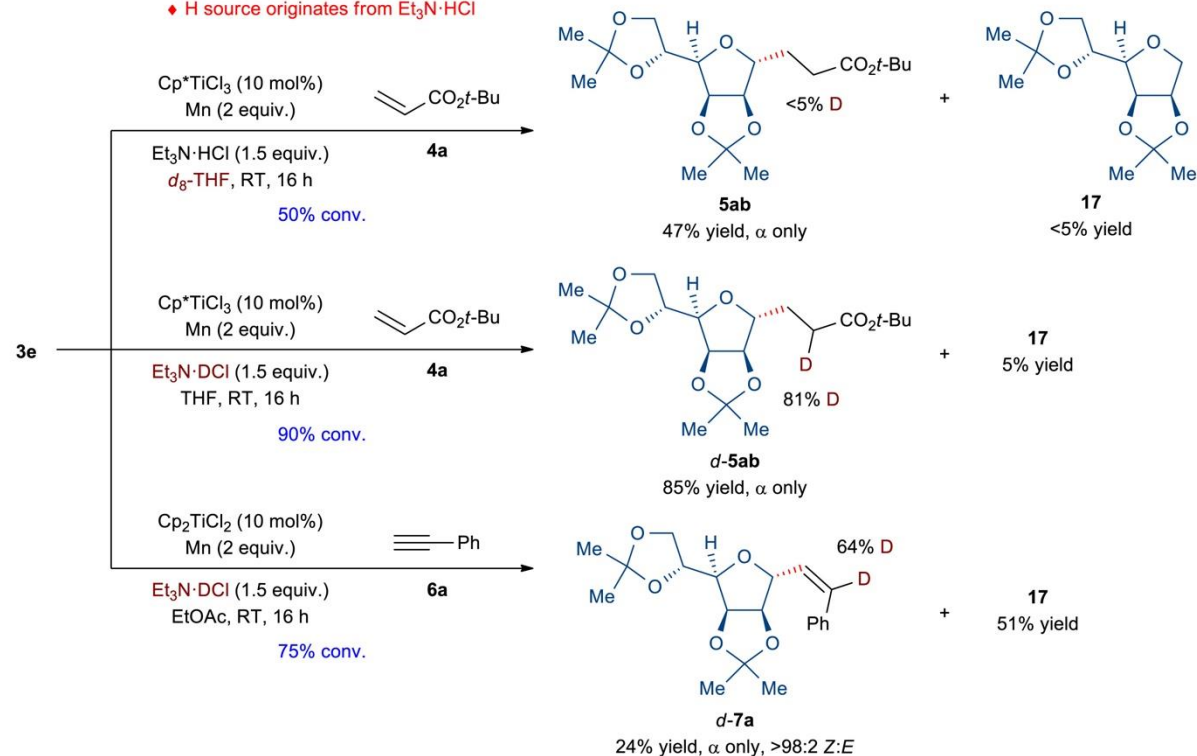
Z-selective alkenylation

Mechanistic Investigation

♦ Glycosyl chlorides are efficient precursors of glycosyl radicals



♦ H source originates from $\text{Et}_3\text{N}\cdot\text{HCl}$



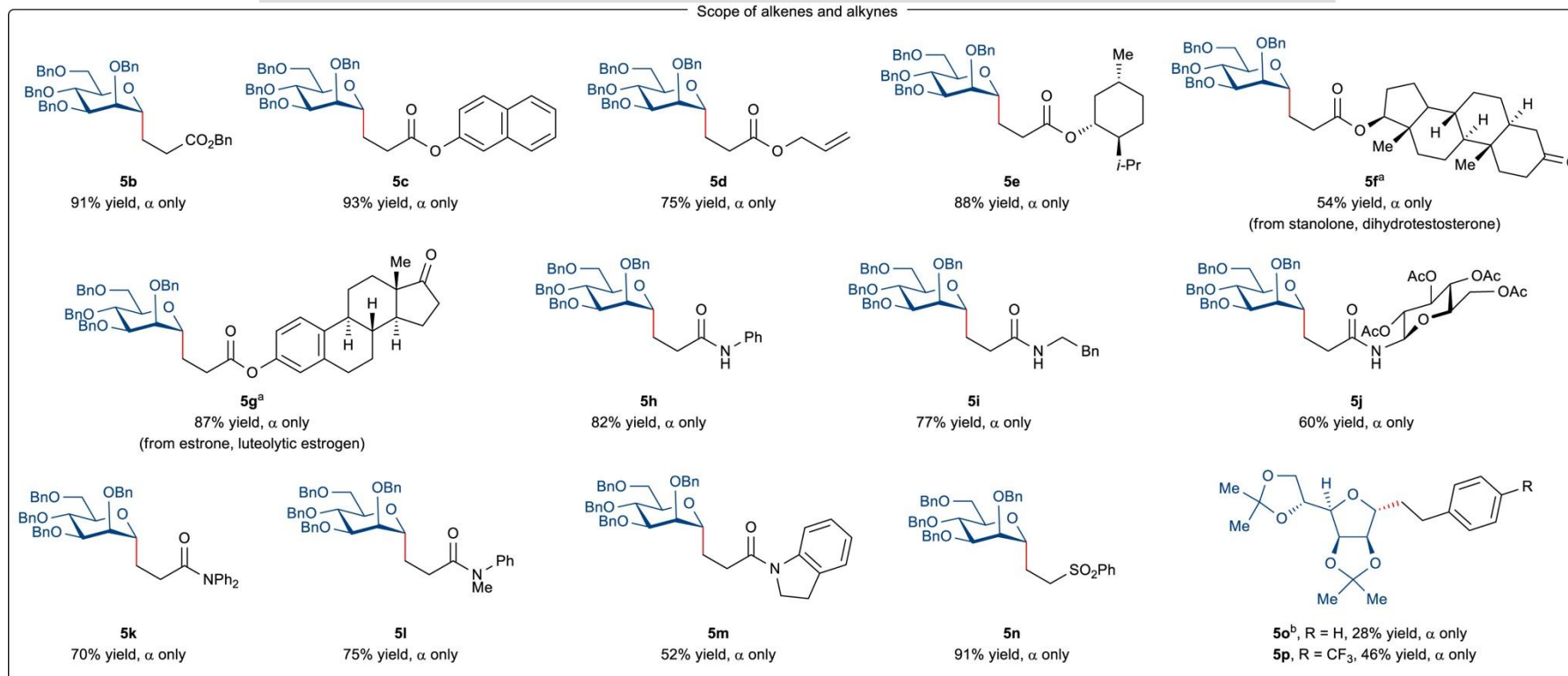
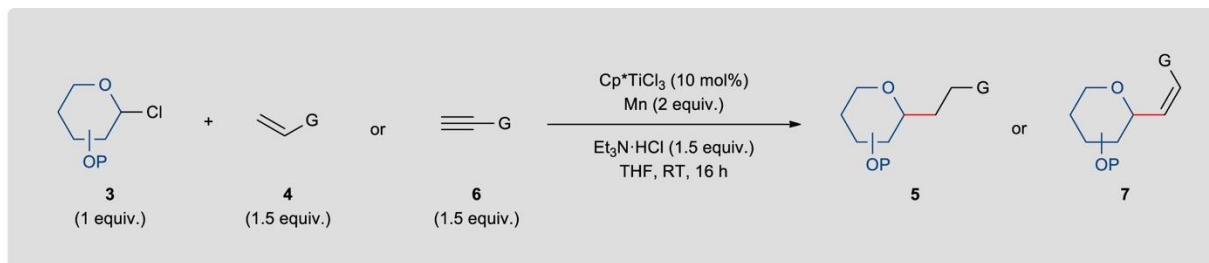
Radical generation

- Homo-coupling is observed w/o radical acceptor.
- Generation of glycosyl radicals

H source

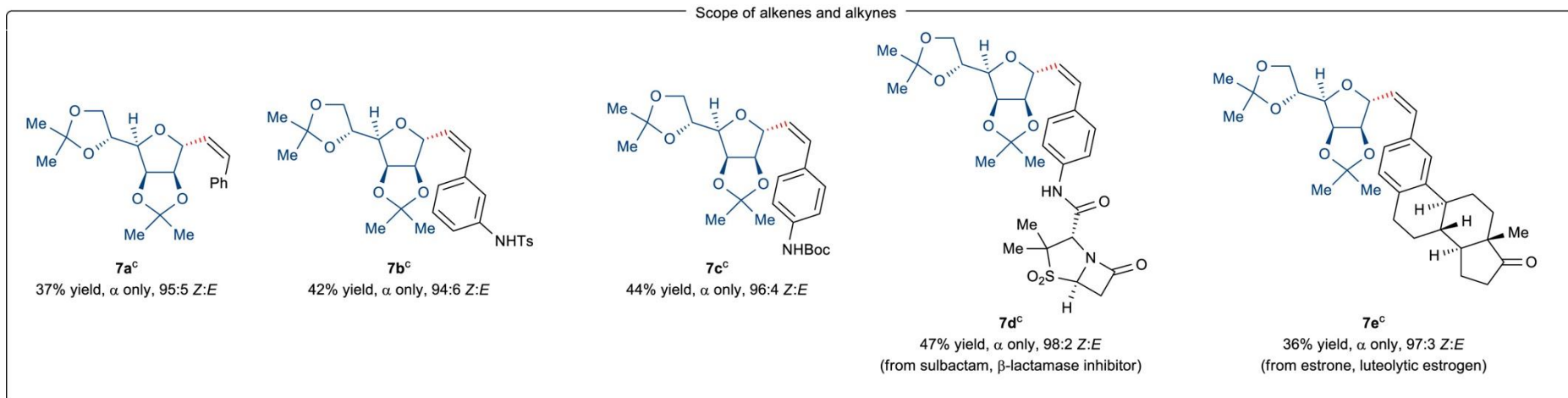
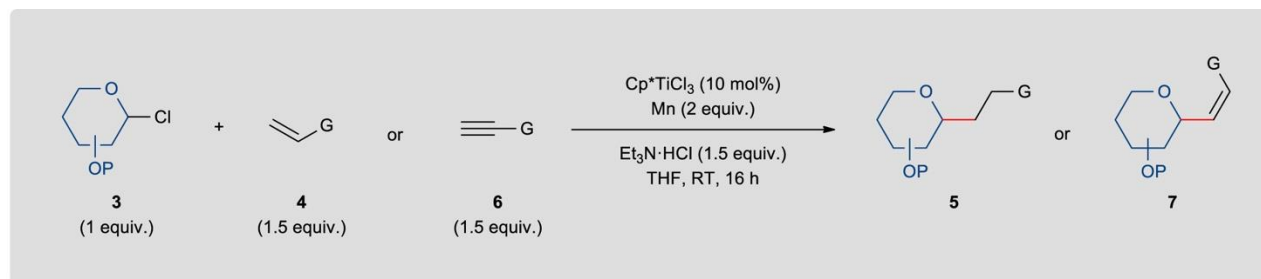
- D was incorporated when using $\text{Et}_3\text{N}\cdot\text{DCl}$
- H source is $\text{Et}_3\text{N}\cdot\text{HCl}$, not solvent.

Substrate Scope (alkene)



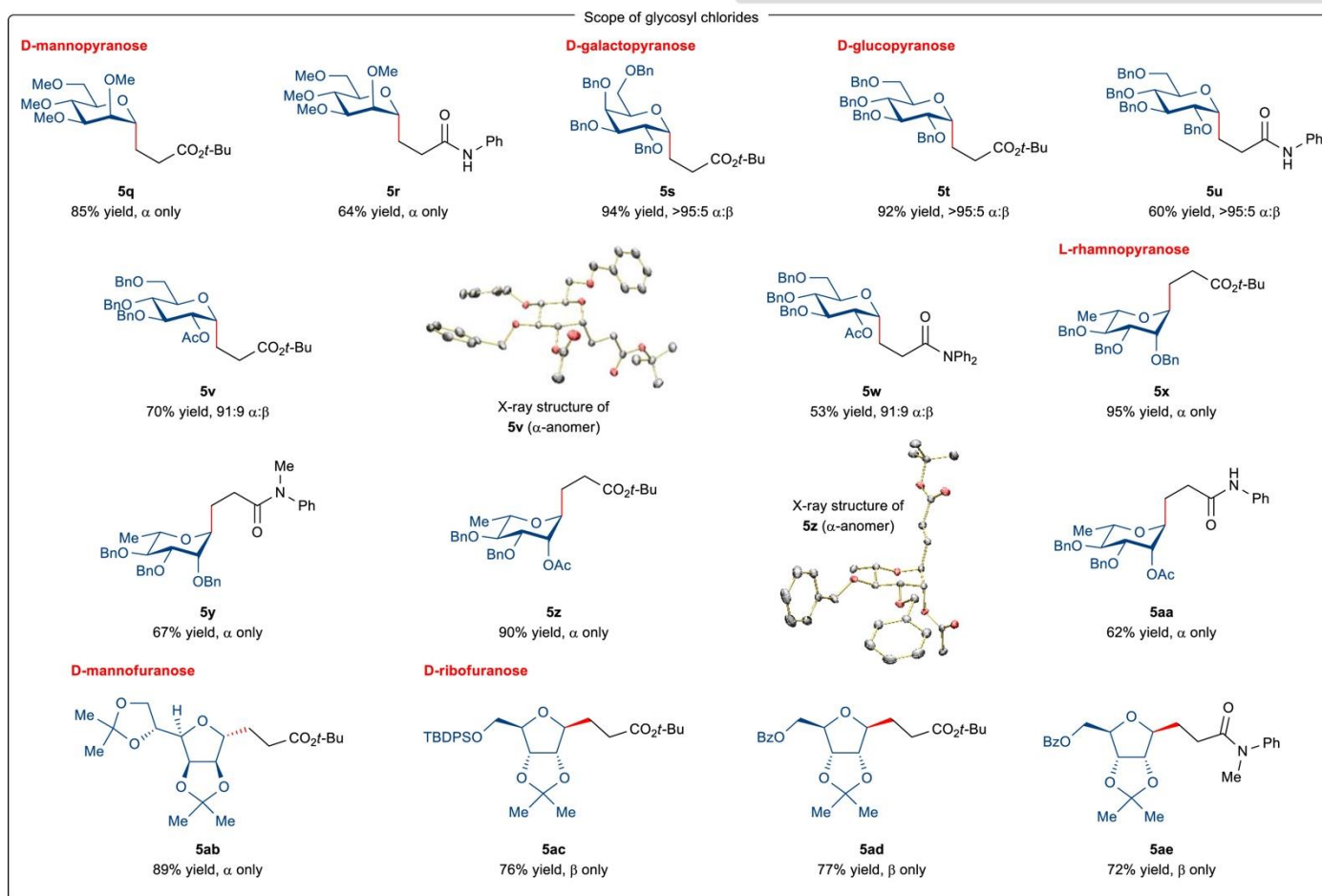
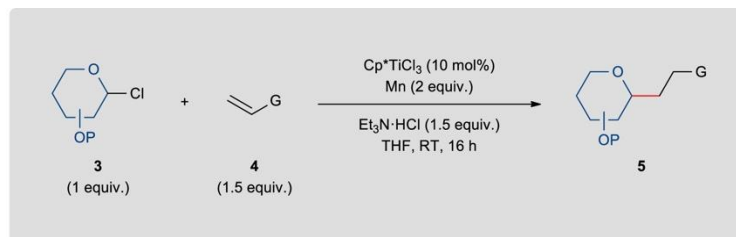
- All products were α -selective.
- Applicable to acrylamides. (5h-5m)
- Non-activated alkene was not productive.

Substrate Scope (alkyne)



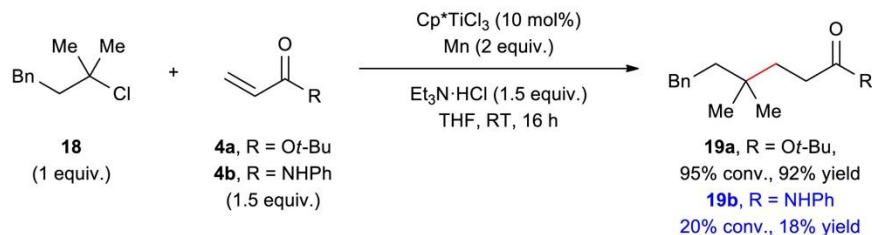
- Aryl alkyne yielded Z olefin selectively.
- Cp_2TiCl_2 was used instead of Cp^*TiCl_3 for more Z selectivity.
- ← Anti-configuration of C-glycosyl bond and the adjacent C-Ti bond by steric repulsion.

Substrate Scope (saccharide)

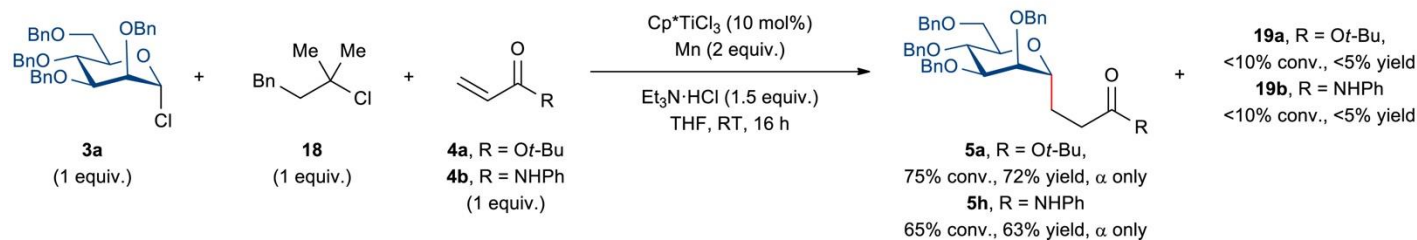


- Various saccharides.
(mannose, galactose, glucose, rhamnose, ribose)
- Pyranose was α -selective.
- Furanose was α - or β -selective (**5ab-5ae**)

Reactivity of Glycosylchlorides



♦ Glycosyl chlorides are unexpectedly more reactive than simple tertiary alkyl chlorides

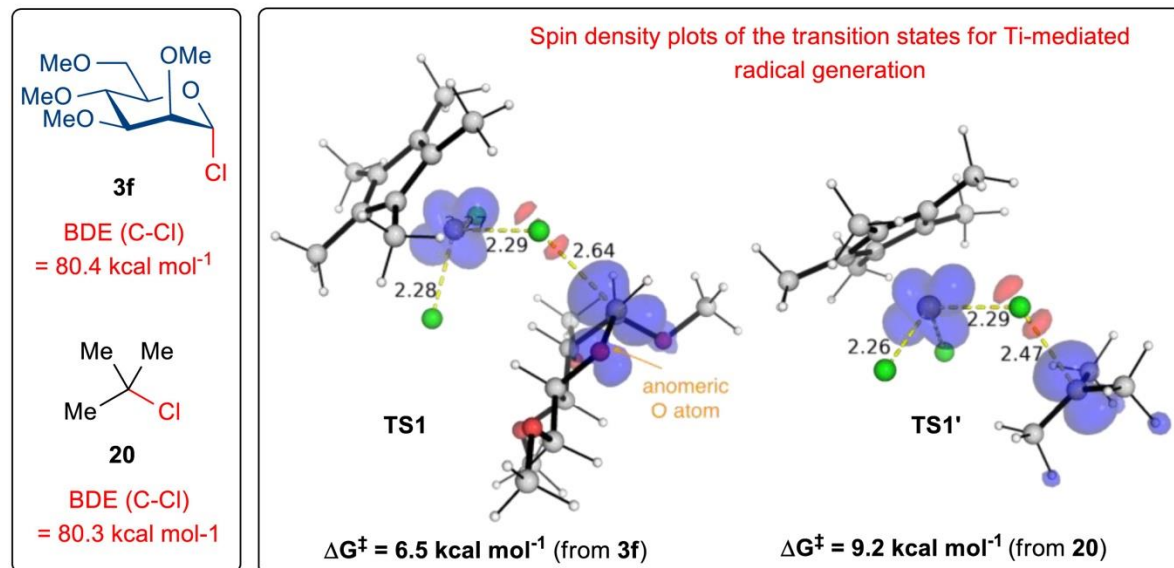


• **Reactivity :**
***tert*-alkylchloride < glycosylchloride**

• **Energy barrier for radical formation :**
glycosylchloride < *tert*-alkylchloride
→ **Kinetically favorable by ~95 times.**

• **Delocalization of spin density stabilizes TS1.**

• **Glycosylchlorides well coordinate to Ti(III) in the presence of acrylamides.**



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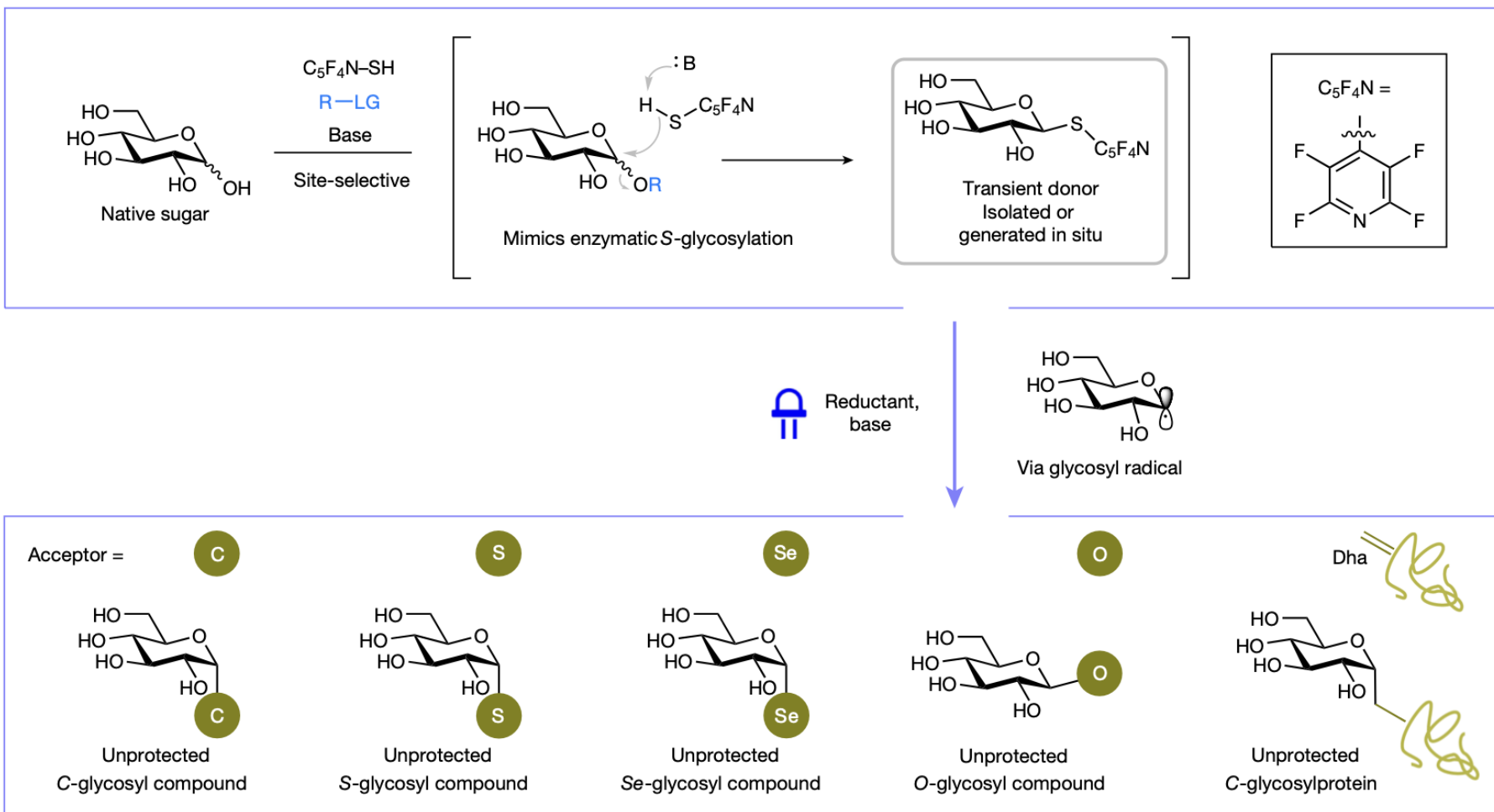
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Two Step functionalization of Unprotected Saccharides

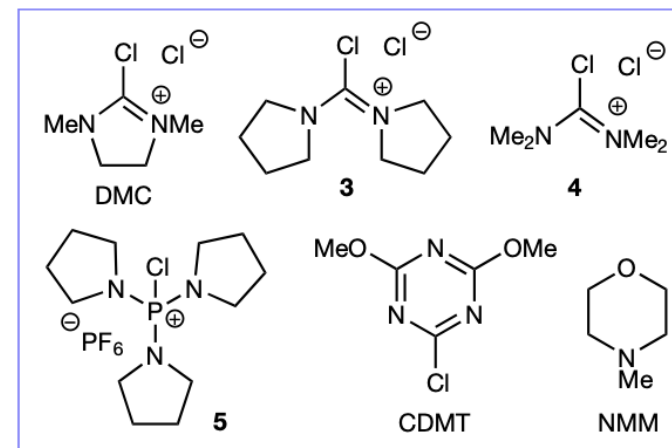
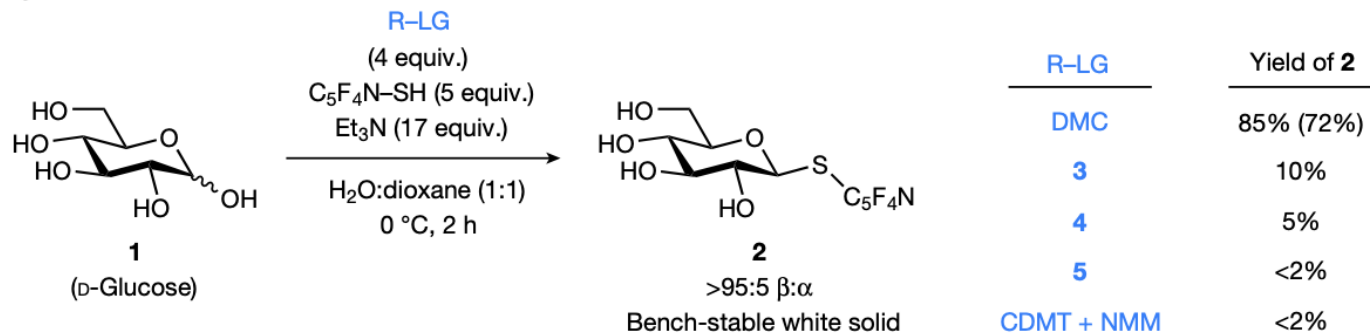


- Radical generation from unprotected sugar.
- C-, S-, Se-, O-glycosylation
- Require thioglycoside for radical generation.
- Non-catalytic reaction

Optimization

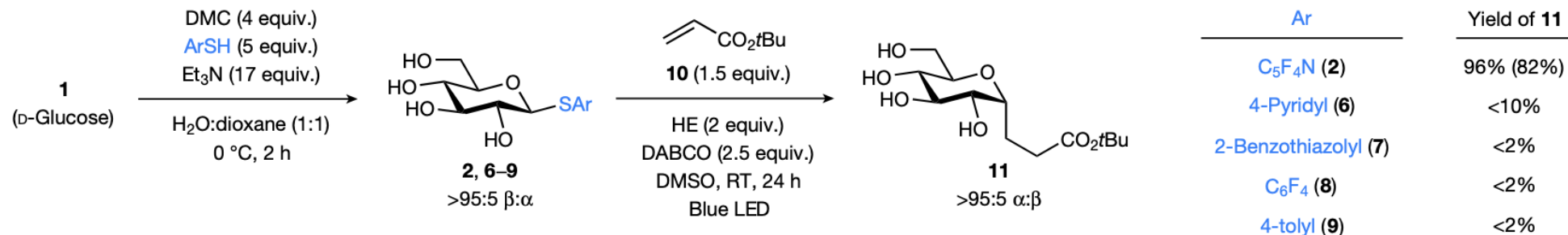
Thioglycosylation of unprotected sugar

a



- DMC : highly electrophilic, soluble in aqueous solution, high leaving ability

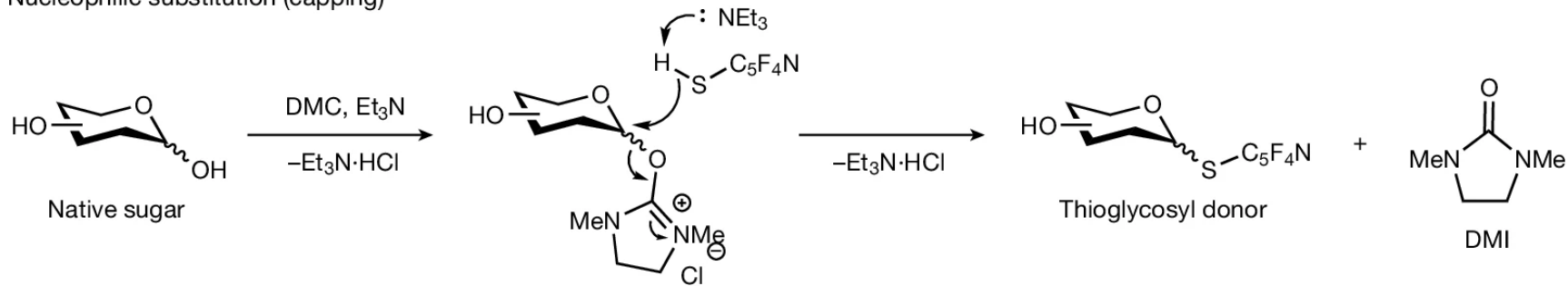
b



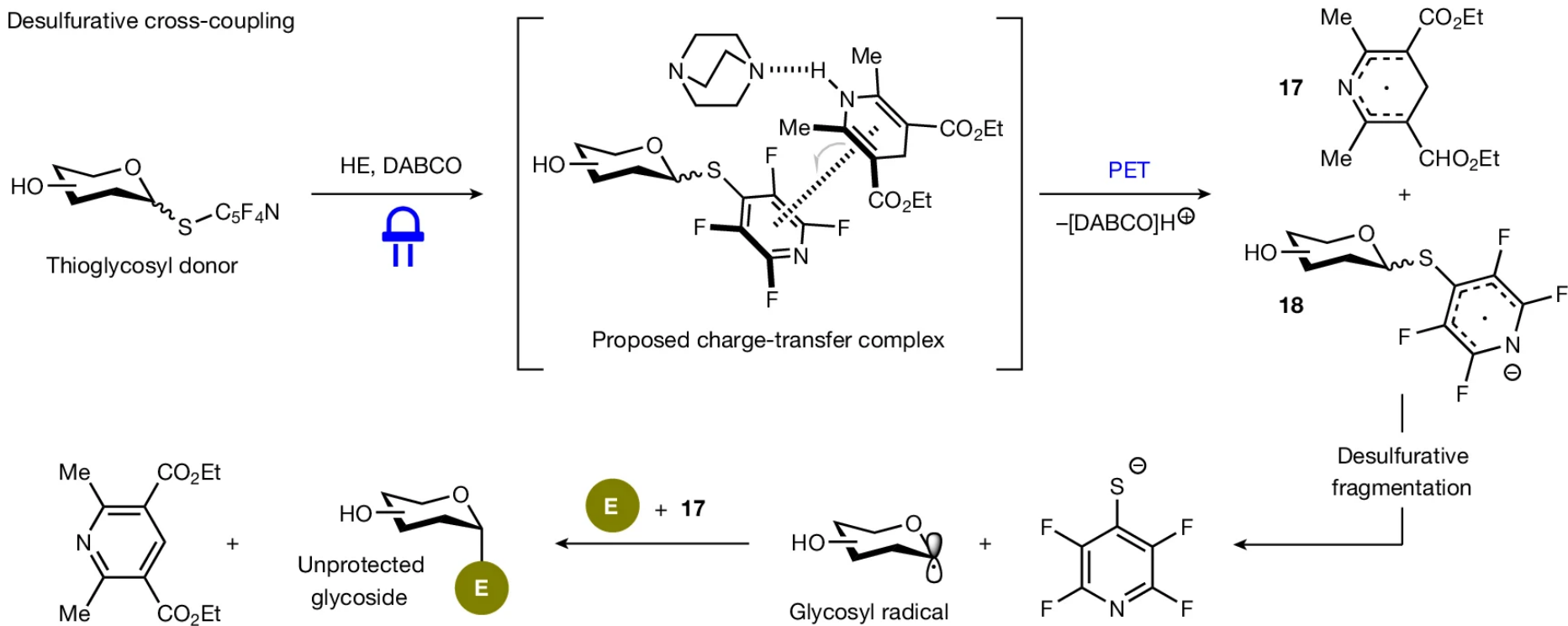
- E_{red} of 2 is comparable to that of redox-active glycosyl sulfone.

Reaction Mechanism

d Nucleophilic substitution (capping)

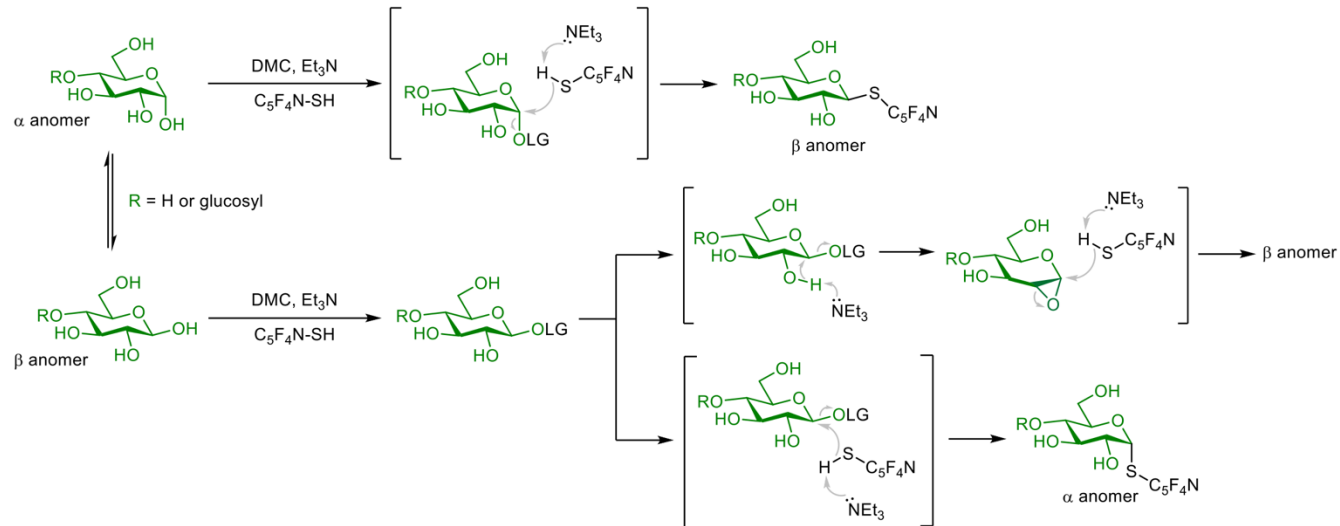


Desulfurative cross-coupling



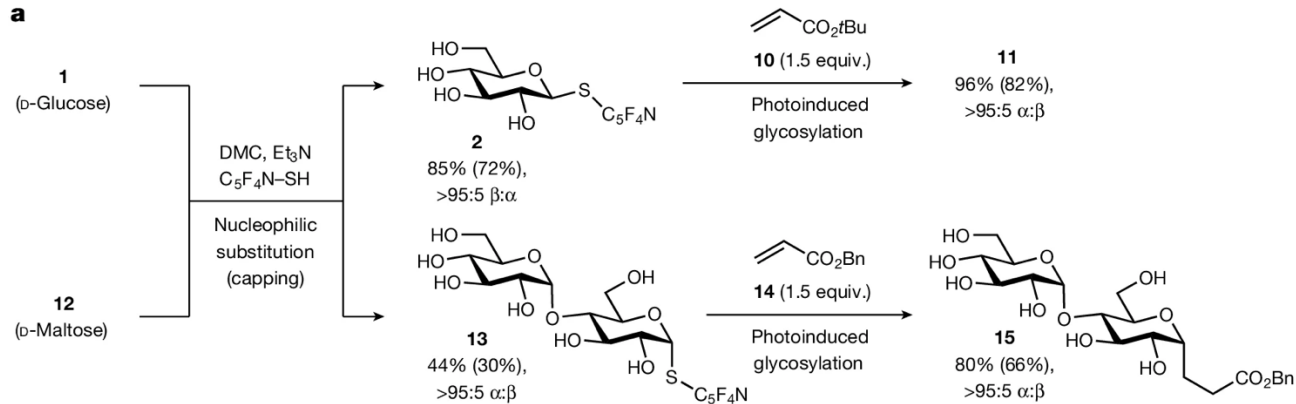
Mechanistic Investigation

Stereoselectivity



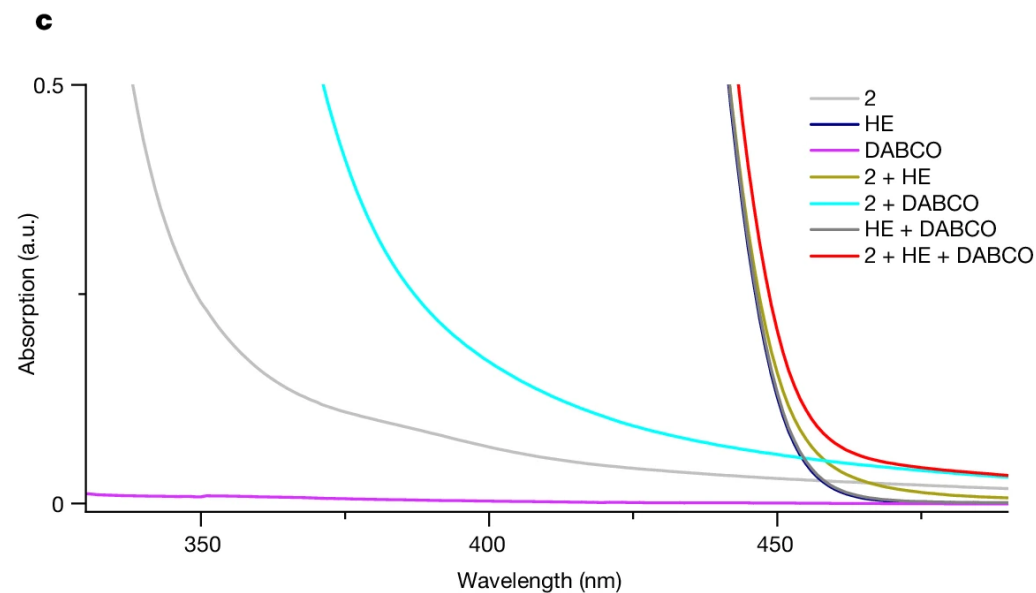
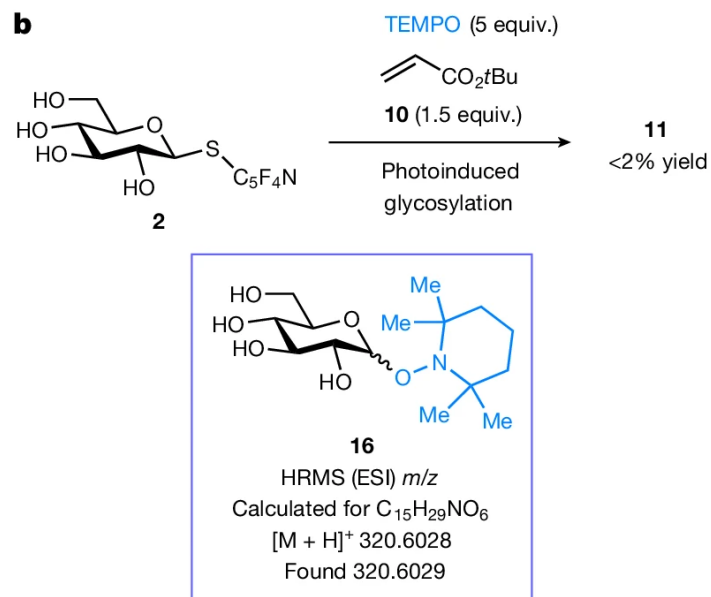
- Both α - and β -anomer are possible for DMC adduct.
- Each adduct undergoes stereo inversion once or twice. (via 1,2-anhydrosugar)

a



- Both α - and β -thioglycosides (**2**, **13**) yields α -C-glycosides selectively (**11**, **15**).
- Stereochemistry of thioglycosides is insignificant for that of C-glycosides.

Mechanistic Investigation



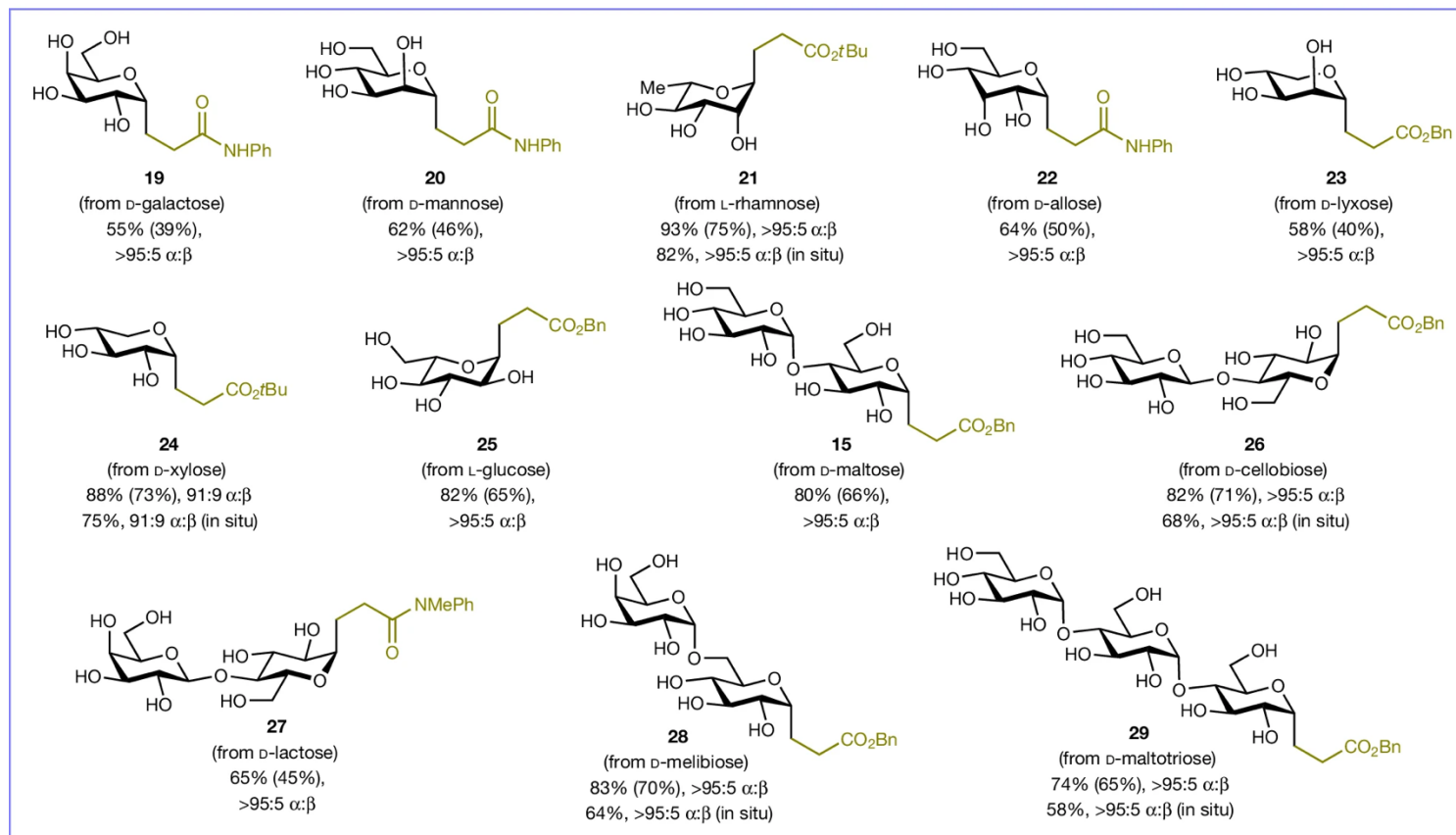
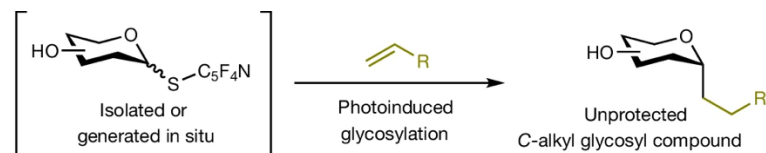
Radical generation

- TEMPO inhibited C-glycosylation.
- Evidence of sufficiently long-lived glycosyl radical generation.

Ternary complex

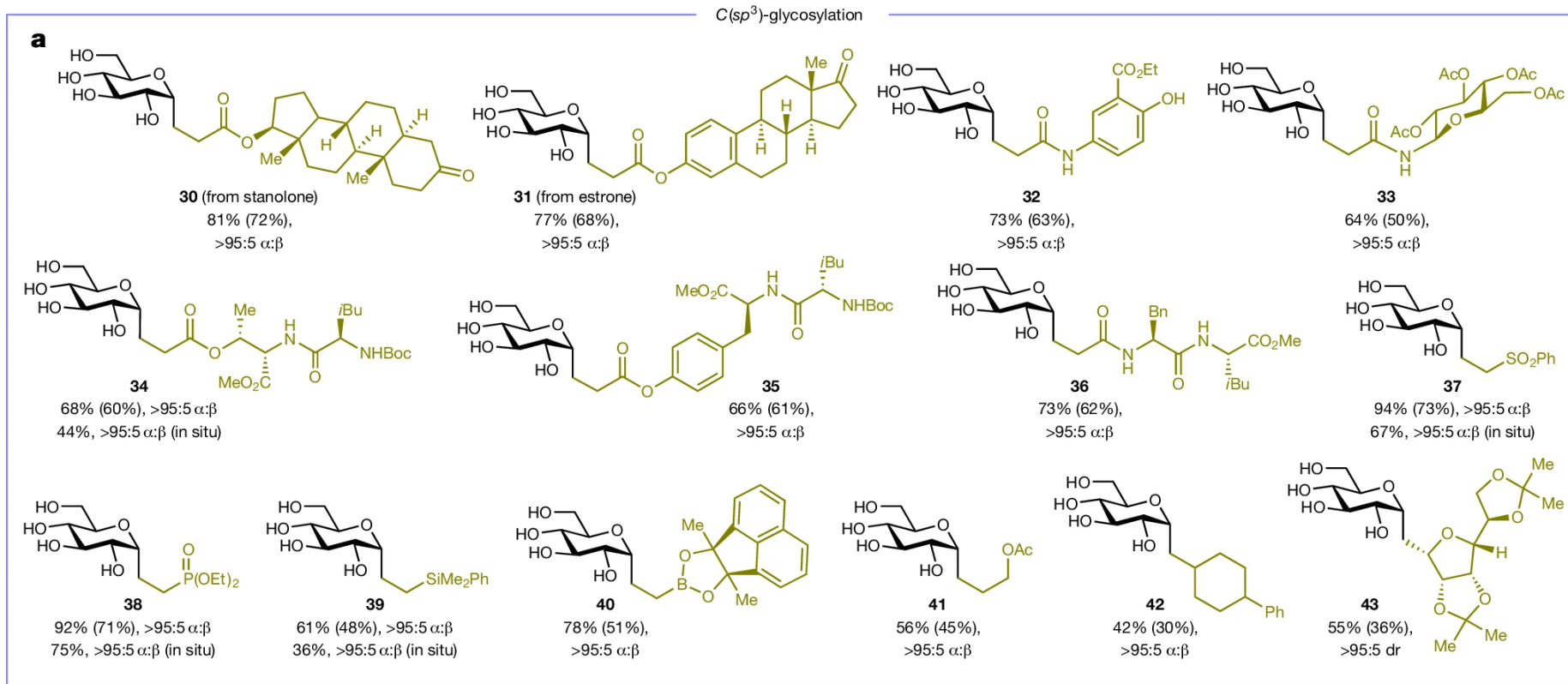
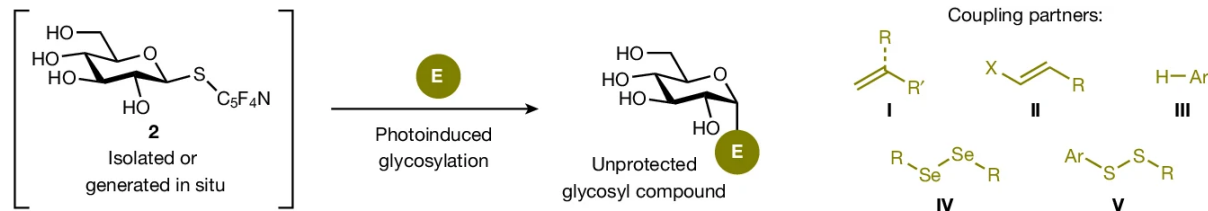
- Mixture of 2, Hantzsch ester, DABCO showed slight red shift.
- These three make putative complex in situ.

Substrate Scope (saccharide)



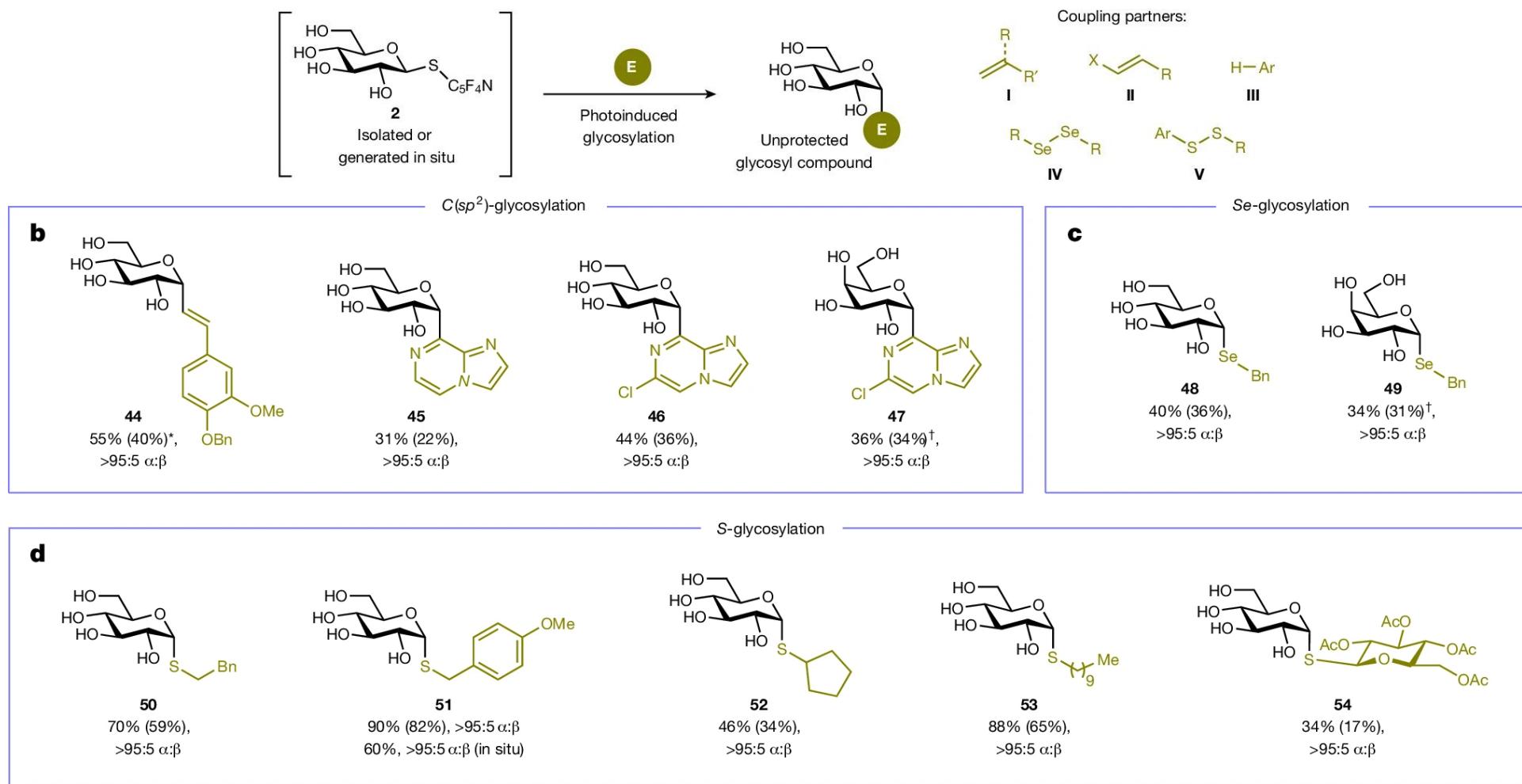
- Biomass-derived monosaccharides (19-21,24)
- Rare sugar (22,23)
- Non-natural sugar (25)
- Oligosaccharides (15,26-29)

Substrate Scope (radical acceptor)



- Bioactive molecules (30-31), peptides (34-36)
- Other Michael acceptors (37-38,40)
- Less electrophilic or less activated alkene (39,41-42)

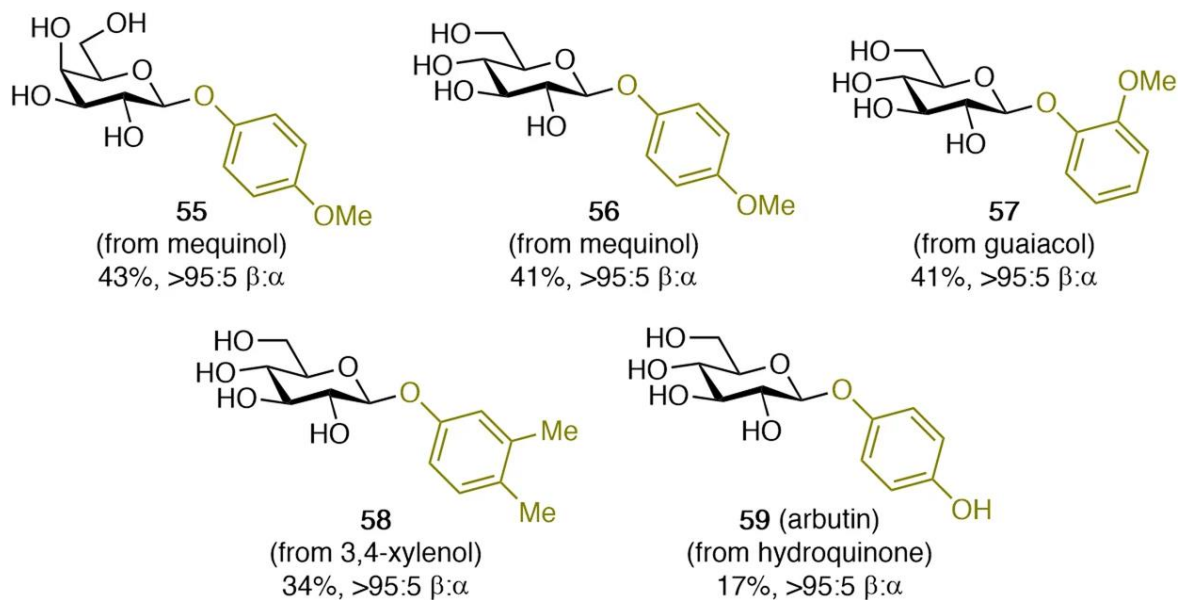
Substrate Scope (radical acceptor)



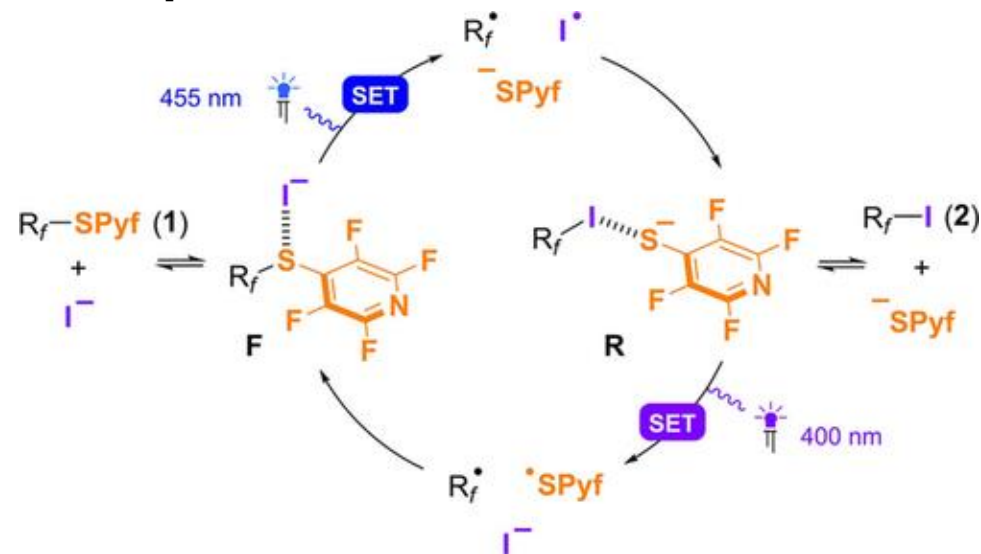
- **C(sp²)-glycosides, Se-glycosides, S-glycosides are accessible.**
- **Accessible to α -S-glycosides (\leftrightarrow DMC mediated thioglycosylation)**

O-glycosylation

Condition and Scope

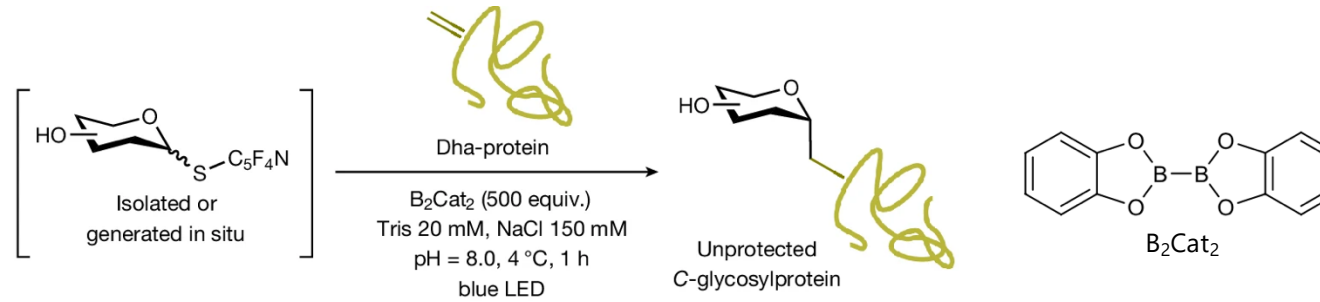


Proposed mechanism (other substrate)

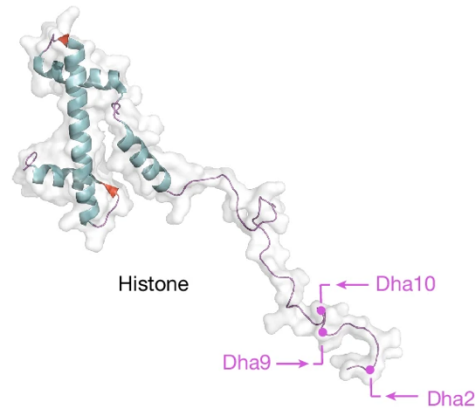


- O-glycosides are obtained by different reaction condition.
- β -selective glycosylation.
- ← Stereo inversion of α -glycosyl iodide.

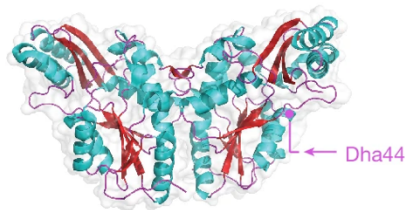
Glycoprotein



- Modified coupling condition
- Conjugate with Dha-tagged protein (Dha: dehydroalanine)
- α -selective

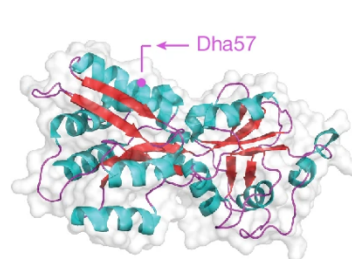


| | eH3-Dha9 | H3-Dha10 | TEV-H3-Dha2 |
|-----------------|-----------|---------------------|------------------------|
| eH3-Man-Ala9 | 83% (82%) | H3-Man-Ala10 80% | TEV-H3-Man-Ala2 52% |
| eH3-Gal-Ala9 | 88% (90%) | H3-Gal-Ala10 83% | TEV-H3-Gal-Ala2 56% |
| eH3-GlcNAc-Ala9 | 70% | H3-GlcNAc-Ala10 77% | TEV-H3-GlcNAc-Ala2 64% |



PanC-Man-Ala44 81%

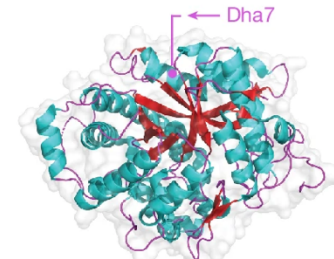
PanC-GlcNAc-Ala44 78%



PstS-Man-Ala57 66% (77%)

PstS-Gal-Ala57 80% (75%)

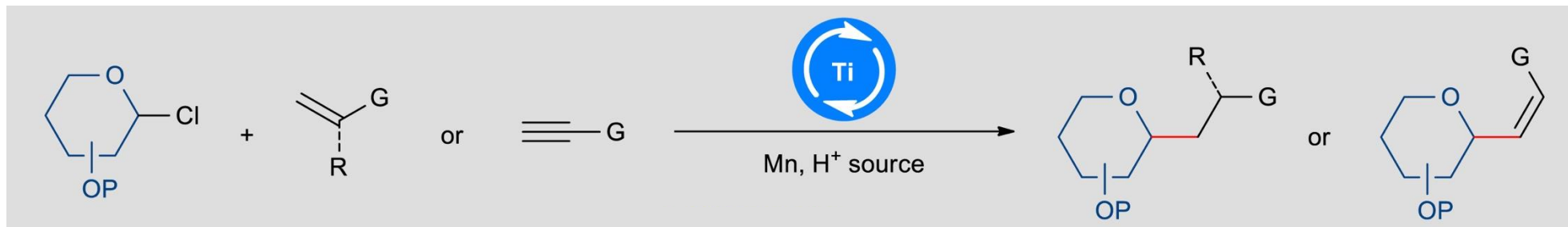
PstS-GlcNAc-Ala57 78%



SsbG-GlcNAc-Ala7 72%

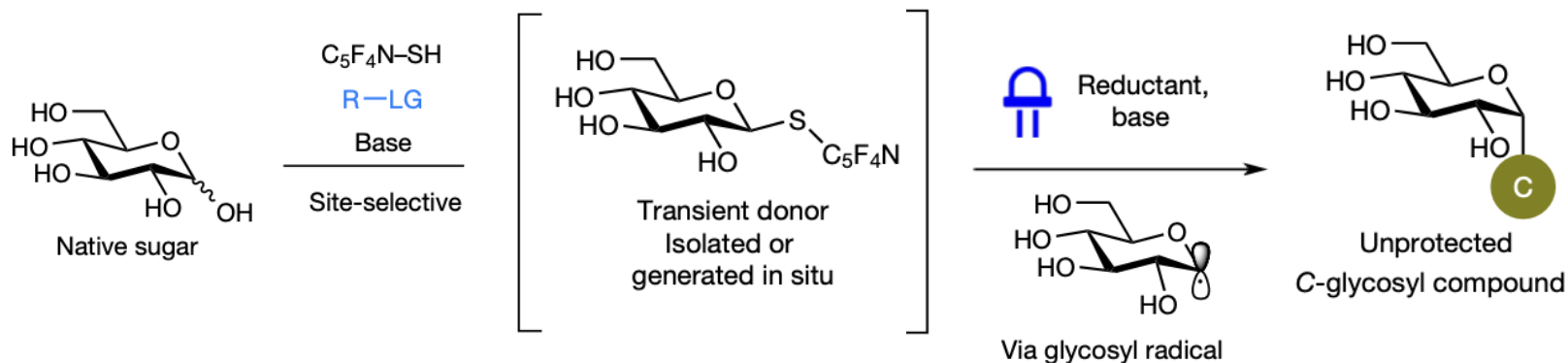
Short Summary

Ti-catalyzed C-glycosylation of glycosyl chlorides



- ✓ Use of nonprecious and non-toxic Ti catalyst
- ✓ Wide range of scope
- ✗ Require protected glycosyl chlorides

Two step functionalization of unprotected saccharides



- ✓ Unprotected saccharides
- ✓ Wide range of scope
- ✗ Multi steps
- ✗ Non-catalytic

Today's content

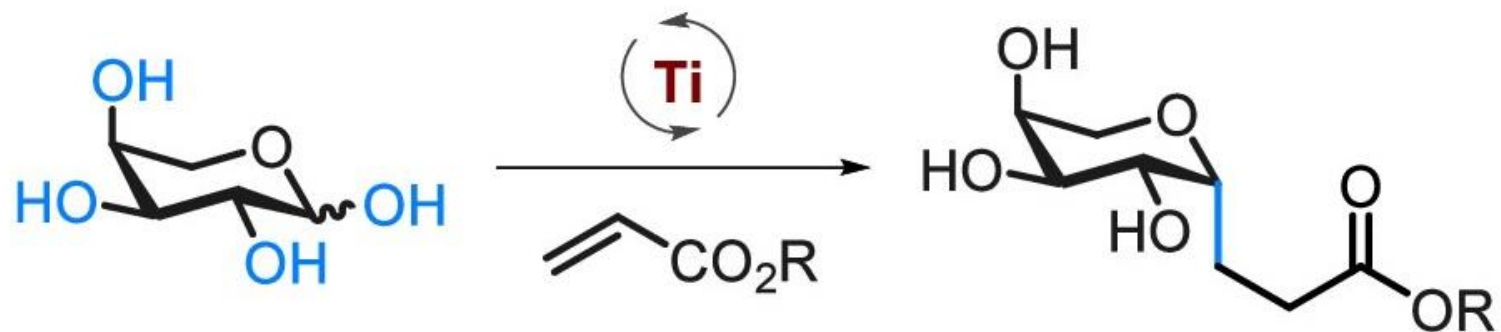
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- Two step functionalization of unprotected saccharides
- **Ti-catalyzed direct anomeric activation of unprotected saccharides**

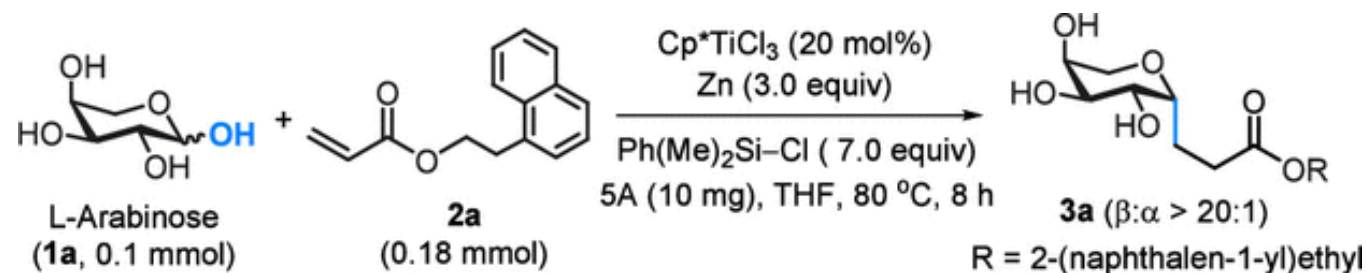
3. Summary

Ti-Catalyzed Direct Anomeric Activation of Unprotected Sugar



- High oxophilicity and one-electron reductive capability of low-valent Ti catalyst.
→ Direct activation of anomeric –OH by Ti cat.
- High stereoselectivity.
- Applicable to various mono- and oligosaccharides.

Optimization



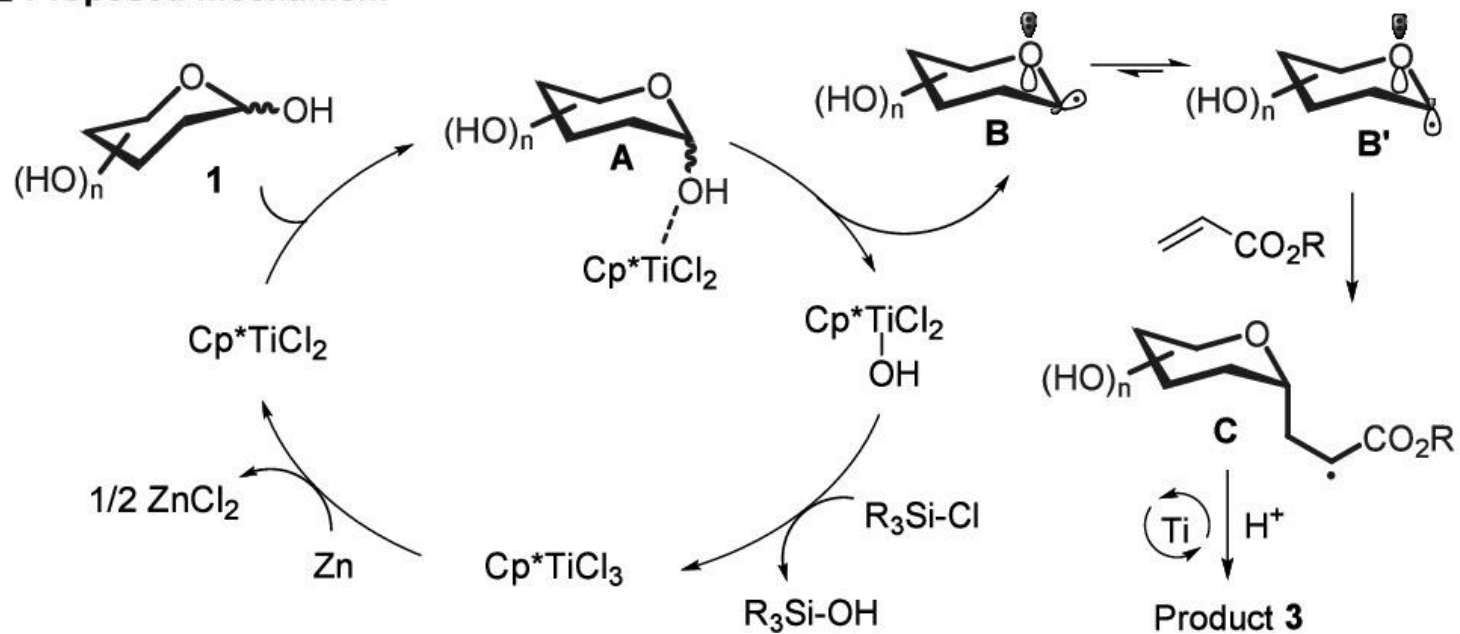
| entry | change of conditions | 3a (%) |
|-------|---|--------|
| 1 | none | 62 |
| 2 | $\text{Cp}^*_2\text{TiCl}_2$ | 33 |
| 3 | CpTiCl_3 | 12 |
| 4 | at 30 °C | 28 |
| 5 | Mn instead of Zn | 0 |
| 6 | no 5 Å molecular sieves | 50 |
| 7 | no $\text{R}_3\text{Si}-\text{Cl}$ | trace |
| 8 | $\text{Et}_3\text{Si}-\text{Cl}$ instead of $\text{Ph}(\text{Me})_2\text{Si}-\text{Cl}$ | 30 |
| 9 | TBSCl instead of $\text{Ph}(\text{Me})_2\text{Si}-\text{Cl}$ | 0 |
| 10 | $\text{Et}_3\text{N}\cdot\text{HCl}$ instead of $\text{Ph}(\text{Me})_2\text{Si}-\text{Cl}$ | 0 |
| 11 | $\text{Coll}\cdot\text{HCl}$ instead of $\text{Ph}(\text{Me})_2\text{Si}-\text{Cl}$ | 0 |
| 12 | no Ti or Zn | 0 |

^a**1a** (0.1 mmol) and **2a** (1.8 equiv) were used; the reaction at 80 °C for 8 h and isolated yield is given.

- Zn to reduce Ti(IV) to Ti(III).
- MS 5Å to remove H₂O, HCl
- Suitable Cl source. (entry 7-11)

Reaction Mechanism

G Proposed mechanism

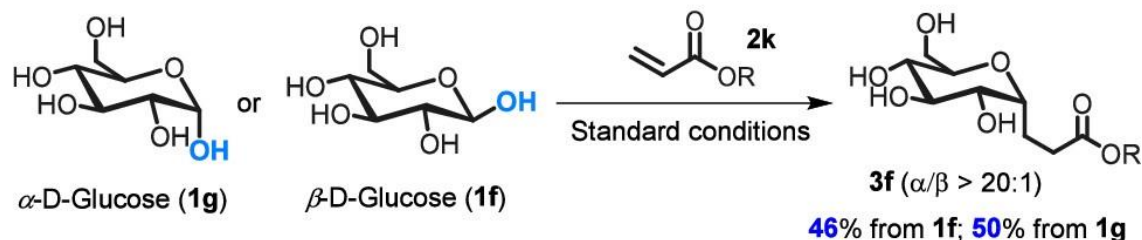


- Activation of Ti(IV) to Ti(III) by Zn.
- Anomeric C-O bond cleavage by Cp^*TiCl_2 .
- OH-Cl exchange with chlorosilane.

Mechanistic Investigation

Homolysis of anomeric C-O bond

a Experiments agree with a radical process^a



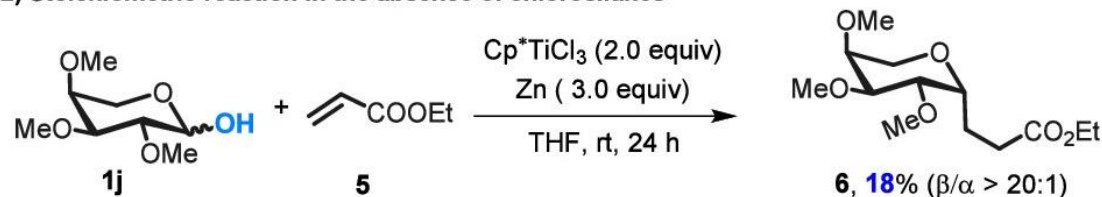
- Both α - and β - glucose reacted to same product with high stereoselectivity.
- Suggesting radical pathway.

b Experiments agree with C-O homolysis

(1) Inconsistent with the intermediacy of glycosyl chlorides^b



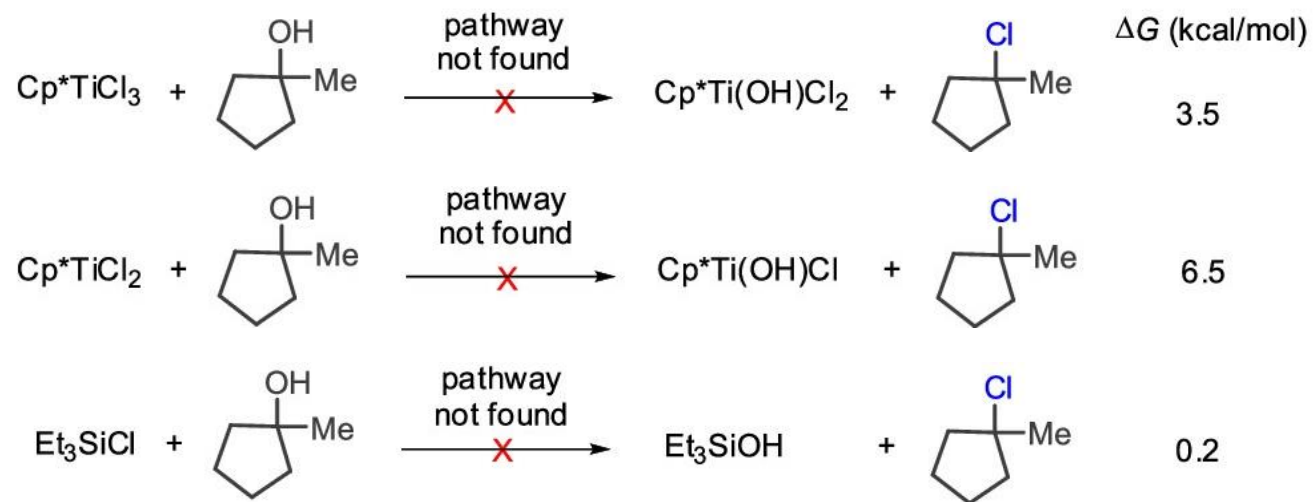
(2) Stoichiometric reaction in the absence of chlorosilanes^c



- Mixture of chlorosilane and Cp^*TiCl_3 doesn't generate glycosyl chlorides.
 - Reaction proceeds without chlorosilane.
- Denying halogen exchange between chlorosilane and saccharides.

Mechanistic Investigation

Homolysis of anomeric C-O bond

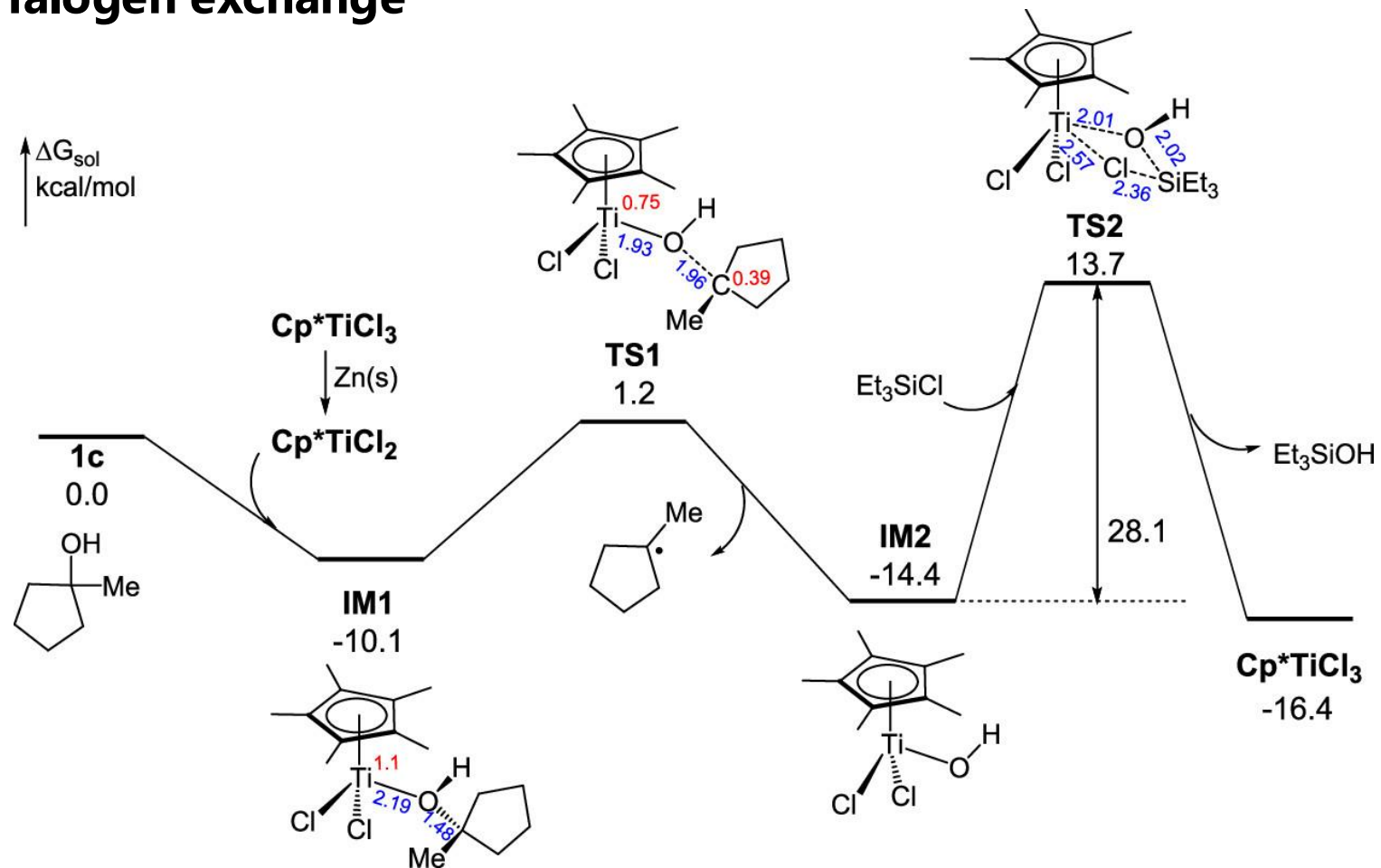


• Chlorination of alcohol with Cp^*TiCl_3 , Cp^*TiCl_2 , R_3SiCl is thermodynamically and kinetically unfavorable.

→ Saccharides may directly generate glycosyl radical.

Mechanistic Investigation

Halogen exchange



- Halogen exchange with chlorosilane could occur.
- This process was rate determining in the past reaction.

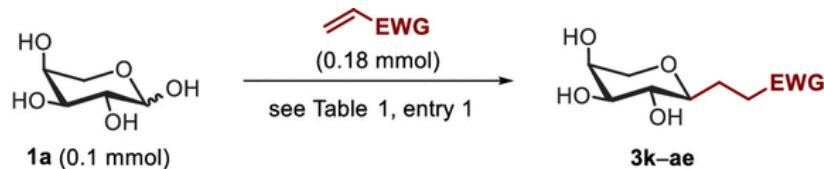
Substrate Scope (saccharide)



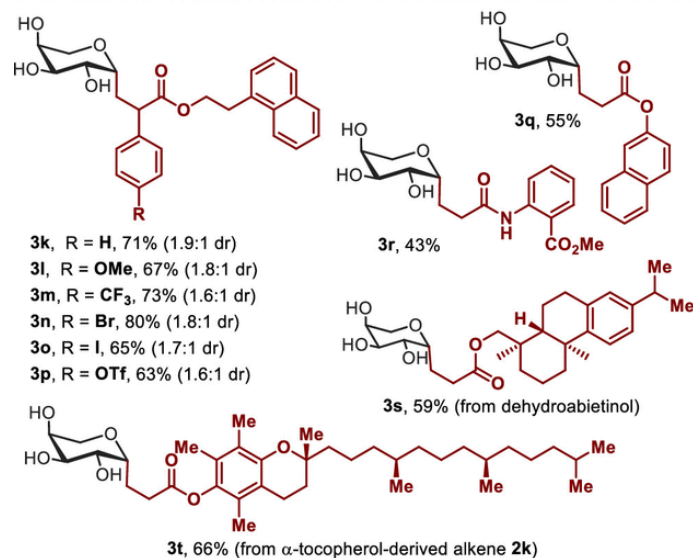
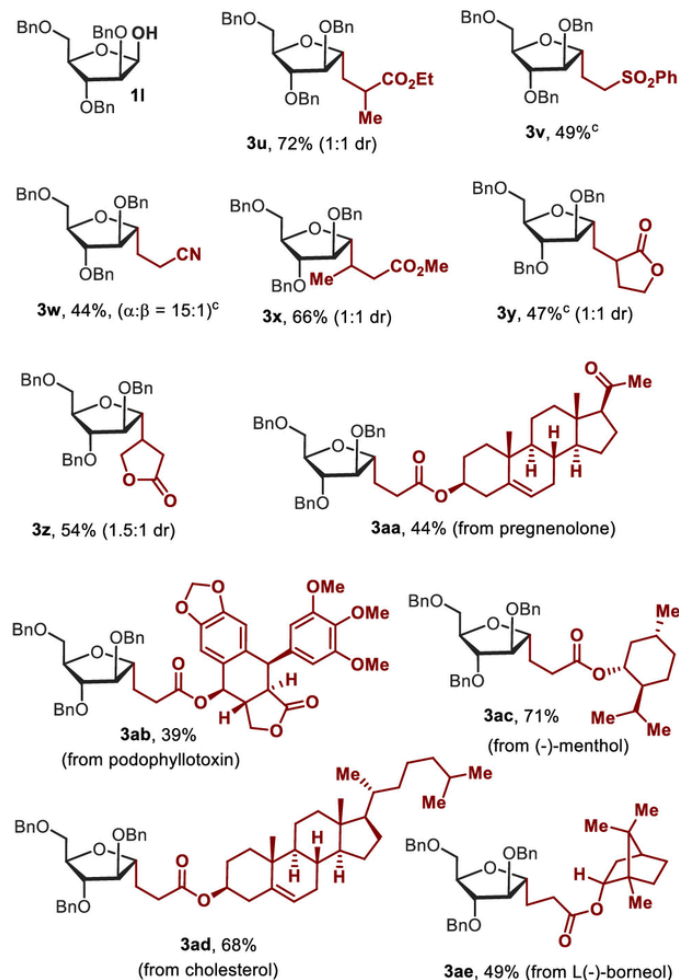
| entry | saccharide | product | entry | saccharide | product |
|-------|----------------------------------|---|-------|-----------------------------------|---|
| 1 | D-Arabinose (1b) | 3b , 60% ($\beta:\alpha > 20:1$) | 6 | α -D-Glucose (1g) | 3f , 50%, ^b ($\alpha:\beta > 20:1$) |
| 2 | D-Xylose (1c) | 3c , 46%, ($\alpha:\beta > 20:1$) | 7 | D-Mannose (1h) | 3g , N.D. ^b |
| 3 | L-Xylose (1d) | 3d , 55%, ($\alpha:\beta > 20:1$) | 8 | L-Ribose (1i) | 3h , 43%, ($\beta:\alpha > 20:1$) |
| 4 | D-Galactose (1e) | 3e , 61%, ^b ($\alpha:\beta > 20:1$) | 9 | (Me)-L-Arabinose (1j) | 3i , 50%, ($\beta:\alpha > 20:1$) |
| 5 | β -D-Glucose (1f) | 3f , 46%, ^b ($\alpha:\beta > 20:1$) | 10 | (Ac)-L-Arabinose (1k) | 3j , N.D. |

- Various saccharides (except entry 7)
- Protecting groups lower yields.
- Stereoselective

Substrate Scope (alkene)



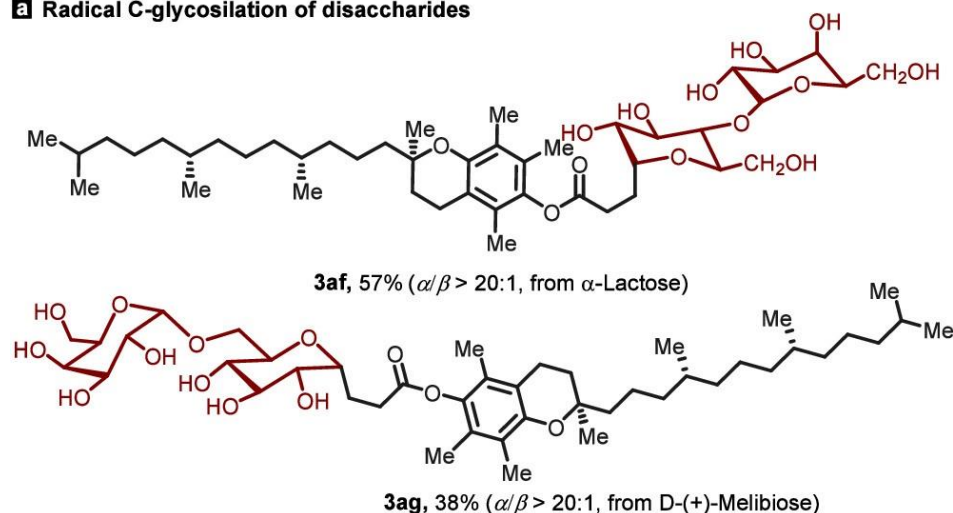
■ Bn Protection 1m for Easy Detection and Isolation^p



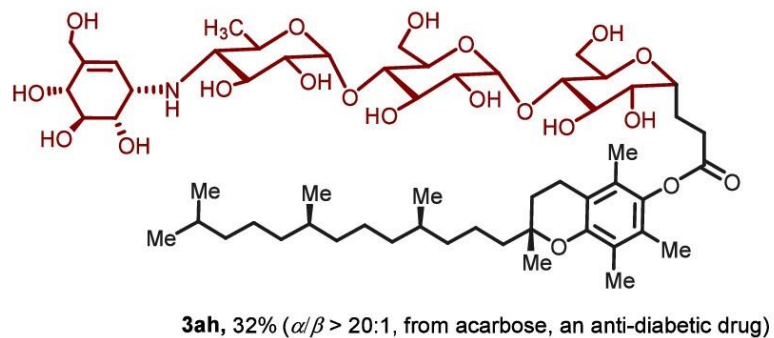
- Acrylates, acrylamides, vinyl sulfone, acrylonitrile
- Cyclic acceptor
- Acrylates derived from natural products

Synthetic Application

a Radical C-glycosylation of disaccharides

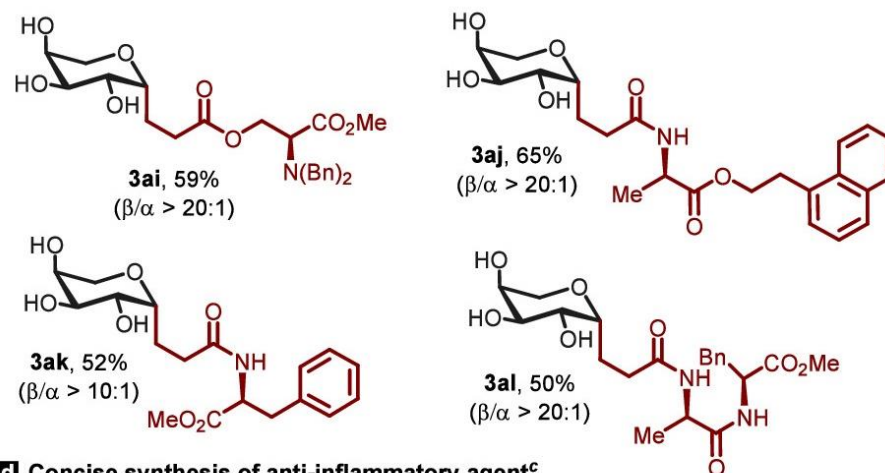


b Derivatization of pharmaceuticals

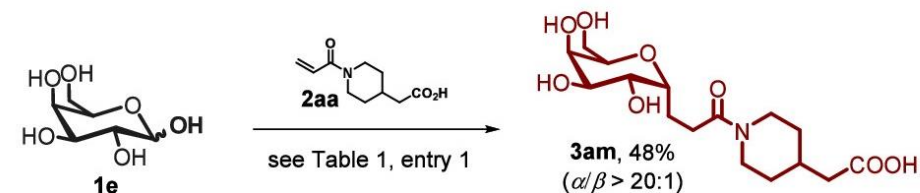


- Applicable to disaccharides
- Late-stage modification of bioactive molecules

c Modification of amino acid and peptide^b



d Concise synthesis of anti-inflammatory agent^c



- Glycopeptide
- Reduce synthetic steps (five step to single step)

Today's content

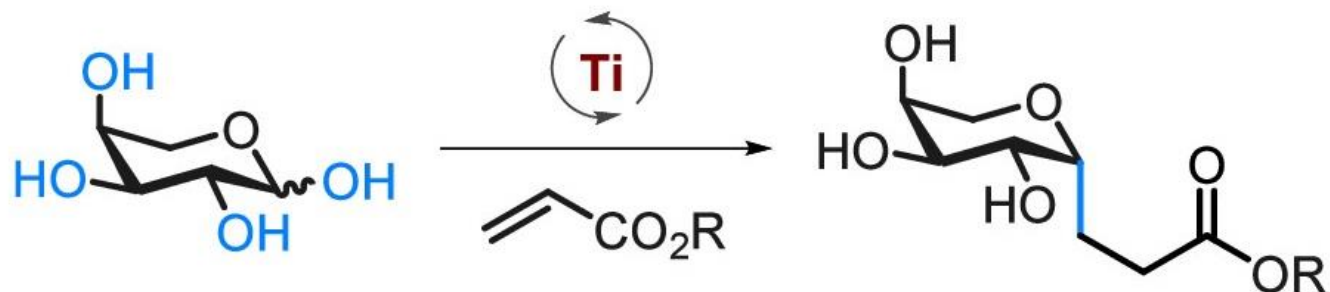
1. Introduction

2. Main

- Ti-catalyzed C-glycosylation of glycosyl chlorides
- Two step functionalization of unprotected saccharides
- Ti-catalyzed direct anomeric activation of unprotected saccharides

3. Summary

Summary



- ✓ Direct -OH activation of native saccharides.
- ✓ Applicable to various saccharides.
- ✓ Highly stereoselective.
- ✗ Generally moderate yield.

Perspective

- Other metal or metal-free method.
- Catalytic anomeric activation and C-X cleavage. (e.g. catalyst with thioglycosyldonor)