Phenanthroline-Catalyzed 1,2-Cis Glycosylation: Scope And Mechanism

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Wayne State University

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PHENANTHROLINE-CATALYZED 1,2-CIS GLYCOSYLATION: SCOPE AND MECHANISM

by

JIAYI LI

DISSERTATION

Submitted to the Graduate School

of Wayne State University,

Detroit, Michigan

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

2022

MAJOR: CHEMISTRY (Organic)

Approved By:

______________________________________________  ______________________________
Advisor                        Date

______________________________________________

______________________________________________

______________________________________________
DEDICATION

To the coin that stayed on my side.
ACKNOWLEDGMENTS

It was a summer night in 2010, a coin decided my journey in America. Firstly, I would like to acknowledge my elder brother who flipped the coin, and my twin sister who chose the other side of the coin (journey to the U.K.). Without them, my path in life would be completely different. Next, I would like to acknowledge my younger brother, who kept me accompanied during my college time. Last but not least, I would like to acknowledge my parents, who gave unconditional love and support to all four of us.

My interest in chemistry began in 2012, the second year after I arrived in America. Here, I would like to thank my parents again for supporting me on a path that was different from their expectations. I quickly adjusted my path and started to look for a new university with a chemical engineering major. Understood the family’s financial situation, I covered both coasts on the American map and picked the University of Iowa with my eyes closed.

During my first year at the University of Iowa, I encountered my current advisor, Prof. Hien M. Nguyen, who inspired my interest in organic chemistry, and encouraged me to pursue a higher degree in organic chemistry. In my junior year, I joined Hien’s research lab, where I met my fellow mentors Dr. Eric Sletten, Dr. Ravi Loka, and Dr. Fei Yu. Thank you for all the guidance and for being extremely patient with me.

With great enthusiasm for carbohydrate chemistry, I decided to continue my study in Hien’s lab, which led me to Wayne State University. I would like to thank all the labmates throughout the years when I stayed in the Nguyen lab. I would also like to acknowledge all the faculties and staffs in the department of chemistry for providing a stable and efficient research environment.

I would also like to acknowledge my committee member: Prof. Jeremy Kodanko, Prof. David Crich, Prof. Long Luo, Prof. Stanislav Groysman, and Prof. Pavel Nagorny, for giving me suggestions on the projects. Special thanks to Prof. H. Bernhard Schlegel for all the guidance on computational chemistry.

In the end, I would like to thank all my family, friends, and acquaintances who have participated in my journey. It has been a wonderful journey with your participation.
# TABLE OF CONTENTS

**DEDICATION** ........................................................................................................................................... ii

**ACKNOWLEDGMENTS** ................................................................................................................................. iii

**LIST OF ABBREVIATIONS** ......................................................................................................................... viii

**LIST OF FIGURES** ....................................................................................................................................... xiii

**LIST OF SCHEMES** ..................................................................................................................................... xvi

**LIST OF TABLES** ......................................................................................................................................... xviii

**CHAPTER 1: INTRODUCTION** ................................................................................................................... 1

1.1 The Significance of Carbohydrates in Biological Systems ......................................................................... 1

1.1.1 Metabolism: carbohydrates as an energy source .................................................................................. 1

1.1.2 Structural building blocks .................................................................................................................... 3

1.1.3 Cellular communication and recognition: glycocode and the decoders ............................................. 7

1.2 Carbohydrates and their mimics in drug discovery .................................................................................. 11

1.2.1 Carbohydrate vaccines ...................................................................................................................... 11

1.2.2 Carbohydrate drugs targeting the central dogma of biology ............................................................. 12

1.2.3 Glycosidase and glycosyltransferase inhibitors .................................................................................. 13

1.2.4 Glycosaminoglycans and their therapeutic applications ....................................................................... 14

1.3 Chemical Methods of Carbohydrates Synthesis ..................................................................................... 15

1.3.1 General pathways of chemical glycosylation ..................................................................................... 16

1.3.2 Substrate-control of stereochemistry .................................................................................................. 18

1.3.3 Reagent-control of stereochemistry .................................................................................................. 21

1.4 Catalytic Glycosylation ........................................................................................................................... 24
1.4.1 Beginning of catalytic glycosylation ................................................................. 24
1.4.2 Design of stereoselective catalytic glycosylation ............................................. 25
1.4.3 Catalyst development in stereoselective glycosylation ..................................... 26
1.5 Main objectives ................................................................................................... 40
1.5.1 Inspiration and hypothesis ............................................................................. 40
1.5.2 Preliminary results and continuation ............................................................... 42
1.5.3 Major Goals .................................................................................................. 43

CHAPTER 2: SCOPE OF PHENANTHROLINE-CATALYZED 1,2-CIS PYRANOSYLATION .... 44

2.1 First generation phenanthroline catalysis ......................................................... 44
2.2 Second generation phenanthroline catalyst ...................................................... 45
  2.2.1 Development of a new class of phenanthroline catalyst ............................... 45
  2.2.2 Influence of phenanthroline catalyst ............................................................ 49
2.3 Reaction scope with phenanthroline catalysis .................................................. 51
  2.3.1 Stereoselective glycosylation and limitation ................................................. 51
  2.3.2 Site-selective glycosylation ........................................................................ 53
  2.3.3 Chemoselective glycosylation ..................................................................... 54
  2.3.4 Orthogonal glycosylation .......................................................................... 57
2.4 Summary ........................................................................................................... 58

CHAPTER 3: MECHANISM OF PHENANTHROLINE-CATALYZED 1,2-CIS PYRANOSYLATION ................................................................. 59

3.1 β-Glycosyl bromide driven glycosylation? ....................................................... 59
3.2 Double S_{N}2 mechanism? (Kinetic study) ....................................................... 60
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3.1.</td>
<td>Kinetic study</td>
<td>114</td>
</tr>
<tr>
<td>5.3.2.</td>
<td>Mechanistic study</td>
<td>120</td>
</tr>
<tr>
<td>5.3.3.</td>
<td>Density Functional Theory (DFT) Calculations</td>
<td>128</td>
</tr>
<tr>
<td>5.4.</td>
<td>Chapter 4 experimental section</td>
<td>129</td>
</tr>
<tr>
<td>5.4.1.</td>
<td>Preparation of 2-deoxy-2-fluro-3,5-di-O-benzyl-D-furanosyl bromide donors</td>
<td>129</td>
</tr>
<tr>
<td>5.4.2.</td>
<td>NMR study with 2-fluoro xylofuranosyl donor</td>
<td>130</td>
</tr>
<tr>
<td>5.4.3.</td>
<td>NMR study with 2-fluoro arabinofuranosyl donor</td>
<td>135</td>
</tr>
<tr>
<td>APPENDIX A</td>
<td>SYMBOL NOMENCLATURE FOR GLYCANS</td>
<td>140</td>
</tr>
<tr>
<td>APPENDIX B</td>
<td>$^1$H, $^{13}$C AND $^{19}$F NMR SPECTRA</td>
<td>141</td>
</tr>
<tr>
<td>APPENDIX C</td>
<td>LICENSES FROM PUBLISHERS</td>
<td>172</td>
</tr>
<tr>
<td>REFERENCES</td>
<td></td>
<td>175</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td></td>
<td>197</td>
</tr>
<tr>
<td>AUTOBIOGRAPHICAL STATEMENT</td>
<td></td>
<td>199</td>
</tr>
</tbody>
</table>
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>ADP</td>
<td>Adenosine diphosphate</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>AZT</td>
<td>Azidothymidine</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-Bi-2-naphthol</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>BPhen</td>
<td>Bathophenanthroline</td>
</tr>
<tr>
<td>bs</td>
<td>broad singlet</td>
</tr>
<tr>
<td>Bu4NBr</td>
<td>Tetrabutylammonium bromide</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>C6D6</td>
<td>Deuterated benzene</td>
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<td>Citric acid cycle</td>
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<tr>
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<td>Catalyst</td>
</tr>
<tr>
<td>CD2Cl2</td>
<td>Deuterated dichloromethane</td>
</tr>
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<td>Deuterated chloroform</td>
</tr>
<tr>
<td>CH2Cl2</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>CoA</td>
<td>Coenzyme A</td>
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<tr>
<td>COSY</td>
<td>COrelated SpectroscopY</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus disease 2019</td>
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<td>CRD</td>
<td>Carbohydrate recognition domain</td>
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<td>Description</td>
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<tr>
<td>d</td>
<td>Doublet</td>
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<tr>
<td>D$_2$O</td>
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<td>DFT</td>
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<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
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<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<td>Deoxyribonucleic acid</td>
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<td>DTBMP</td>
<td>2,6-di-tert-butyl-4-methylypyridine</td>
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<td>equiv.</td>
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<td>ESI</td>
<td>Electrospray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
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<tr>
<td>FADH$_2$</td>
<td>Flavin adenine dinucleotide</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GAG</td>
<td>Glycosaminoglycan</td>
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<td>GalNac</td>
<td>N-acetylgalactosamine</td>
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<tr>
<td>GBPs</td>
<td>Glycan-binding proteins</td>
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<tr>
<td>Glc</td>
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<td>Glycoprotein 120</td>
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<td>GTs</td>
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<td>h</td>
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<tr>
<td>H-bonding</td>
<td>Hydrogen bonding</td>
</tr>
<tr>
<td>HBr</td>
<td>Hydrobromic acid</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Human immunodeficiency virus and acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>HRMS</td>
<td>High-Resolution Mass spectrometry</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>IBO</td>
<td>Isobutylene oxide</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>KDO</td>
<td>3-Deoxy-d-manno-octulosonic acid</td>
</tr>
<tr>
<td>LG</td>
<td>Leaving group</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low molecular weight heparin</td>
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<tr>
<td>LPS</td>
<td>Lipopolysaccharide</td>
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<td>Molar</td>
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<tr>
<td>m</td>
<td>Multiplet</td>
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<td>Me</td>
<td>Methyl</td>
</tr>
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<td>min</td>
<td>Minute</td>
</tr>
<tr>
<td>mL</td>
<td>milliliter</td>
</tr>
<tr>
<td>mmol</td>
<td>millimoles</td>
</tr>
<tr>
<td>mol%</td>
<td>mole percent</td>
</tr>
<tr>
<td>MTBE</td>
<td>tert-butyl methyl ether</td>
</tr>
<tr>
<td>NADH</td>
<td>Nicotinamide adenine dinucleotide</td>
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<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
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<tr>
<td>NMR</td>
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<tr>
<td>NOESY</td>
<td>Nuclear Overhauser Effect Spectroscopy</td>
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<tr>
<td>Nu</td>
<td>Nucleophile</td>
</tr>
<tr>
<td>°C</td>
<td>Degree Celsius</td>
</tr>
<tr>
<td>PG</td>
<td>Protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
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</table>
Phen  Phenanthroline
POCl₃  phosphorus oxychloride
q  quartet
RNA  Ribonucleic acid
ROESY  Rotating frame Overhauser Enhancement Spectroscopy
s  Singlet
SARS-CoV-2  Severe acute respiratory syndrome coronavirus 2
SARS-CoV-2  Severe acute respiratory syndrome coronavirus 2
SMD  solvation model based on density
SN₁  Nucleophilic substitution unimolecular
SN₂  Nucleophilic substitution bimolecular
SNFG  Symbol nomenclature for glycans
SPINOL  1,1’-Spirobiindane-7,7’-diol
t  Triplet
TAB  (ortho-tosylamido)benzyl
TAC  Tricarboxylic acid cycle
TBS  tert-Butyldimethylsilyl
TCA  Trichloroacetimidate
Tf  Triflate
TfOH  Trifluoromethanesulfonate acid
THF  Tetrahydrofuran
TLC  Thin-layer chromatography
TMEDA  N,N,N’,N’-tetramethylethylenediamine
TMSOTf  Trimethylsilyl triflate
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>TMSOTf</td>
<td>Trimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>TS2</td>
<td>Second transition state</td>
</tr>
<tr>
<td>TsOH</td>
<td>p-Toluenesulfonic acid</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>XyG</td>
<td>Xyloglucan</td>
</tr>
<tr>
<td>Xyl</td>
<td>Xylose</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

Figure 1. Examples of carbohydrates in nature ................................................................................................................................. 1

Figure 2. The structures of starch and cellulose ................................................................................................................................. 3

Figure 3. Constitution of plant cell wall .............................................................................................................................................. 4

Figure 4. Constitution of bacterial cell wall ......................................................................................................................................... 6

Figure 5. Structure of pyranose ............................................................................................................................................................. 7

Figure 6. Symbolic representation of monosaccharides and an example of lipopolysaccharide ................................................................. 8

Figure 7. Glycoconjugates on the cell surface: glycoprotein, glycolipid, and glycoRNA .......................................................................... 9

Figure 8. Structure of a galactose-specific C-type lectin. PDB: 1JZN ........................................................................................................ 10

Figure 9. The design concept of carbohydrate vaccine .................................................................................................................... 12

Figure 10. Nucleoside/nucleotide mimetics as carbohydrate-based drugs ............................................................................................... 13

Figure 11. Examples of glycosidase and glycosyltransferase inhibitors ............................................................................................... 14

Figure 12. Structures of heparin and fondaparinux ........................................................................................................................... 15

Figure 13. Category of glycosides ......................................................................................................................................................... 16

Figure 14. Design concepts for stereoselective catalytic glycosylation ............................................................................................... 26

Figure 15. Kinetics of the reaction of 2-propanol with glucosyl bromide 1 in C6D6 at 50 °C ........................................................................ 62

Figure 16. Kinetic study in respect to donor concentration .................................................................................................................. 63

Figure 17. Product concentration versus time for the phenanthroline-catalyzed glycosylation with three different phenanthroline catalysts .................................................................................................................... 64

Figure 18. Detection of phenanthrolinium intermediate by 1H NMR ........................................................................................................ 65

Figure 19. Mixture of nucleophile 3 and 10 mol% C14 with DTBMP in CD2Cl2 ....................................................................................... 66

Figure 20. Conformation of the glycosyl phenanthrolinium ion intermediates ....................................................................................... 67

Figure 21. Conformation of glycosyl phenanthrolinium intermediates and NMR evidence ................................................................ 68

Figure 22. Variable-temperature 1H NMR spectra and proposed intermediates internal hydrogen bondings ........................................... 70

Figure 23. Possible mechanism of phenanthroline-catalyzed glycosylation ....................................................................................... 72
Figure 24. Conformation of the 2-deoxy-2-fluoro glycosyl phenanthroline ion ........................................... 72

Figure 25. Hexasaccharide motifs found in the cell wall complex of mycobacterial arabinogalactan (AG) and lipoarabinomannan (LAM). .......................................................................................................................... 74

Figure 26. Detection of xylofuranosyl phenanthroline intermediates ................................................................. 81

Figure 27. Detection of arabinofuranosyl phenanthroline intermediates.............................................................. 82

Figure 28. Reaction progress for phenanthroline-catalyzed xylofuranosylation of alcohol acceptor 3 .... 84

Figure 29. Reaction progress for phenanthroline-catalyzed arabinofuranosylation of alcohol acceptor 3. 85

Figure 30. Energy diagram of phenanthroline-catalyzed furanosylation for the second nucleophilic substitution.............................................................................................................................. 86

Figure 31. Possible mechanism for phenanthroline-catalyzed xylofuranosylation.............................................. 87

Figure 32. Possible mechanism for phenanthroline-catalyzed arabinofuranosylation................................. 88

Figure 33. Example spectra array for a kinetic experiment with 1 as donor........................................... 116

Figure 34. Example rate plot: product concentration versus time for a kinetic experiment .................. 116

Figure 35. Product formation versus time at different equivalent of IBO .................................................. 117

Figure 36. Product formation versus time at 0 mol% catalyst ................................................................. 117

Figure 37. Example spectra array for a kinetic experiment with 2* as donor........................................... 119

Figure 38. $^1$H NMR of deuterated tetrabenzyl glucosyl bromide 2*......................................................... 122

Figure 39. $^1$H NMR of deuterated tetrabenzyl glucosyl bromide 2* and C14 at 0 min.................. 122

Figure 40. $^1$H NMR of deuterated tetrabenzyl glucosyl bromide 2* and C14 at 30 min............. 123

Figure 41. $^1$H NMR of deuterated tetrabenzyl glucosyl bromide 2* and C14 with acceptor 3 at 30 min 123

Figure 42. $^1$H NMR of deuterated tetrabenzyl glucosyl bromide 2* and C14 with acceptor 3 at 300 min ........................................................................................................................................ 124

Figure 43. $^1$H NMR of glucosyl phenanthroline intermediates (Int$_1$ and Int$_2$) ........................................... 125

Figure 44. $^1$H-$^1$H 2D COSY NMR of glucosyl phenanthroline intermediates (Int$_1$ and Int$_2$) ........... 125

Figure 45. $^1$H-$^1$H 2D ROESY NMR of glucosyl phenanthroline intermediates (Int$_1$ and Int$_2$) ........ 126

Figure 46. Mass spectrum detection of glucosyl phenanthroline intermediates (Int$_1$ and Int$_2$)....... 126

Figure 47. $^1$H NMR of 2-deoxy-2-fluoro glucosyl phenanthroline intermediate (Int$_3$) ......................... 127
Figure 48. $^1$H-$^1$H 2D COSY NMR of 2-deoxy-2-fluoro glucosyl phenanthroline intermediate (Int$_3$) 127

Figure 49. $^1$H-$^1$H 2D ROESY NMR of 2-deoxy-2-fluoro glucosyl phenanthroline intermediate (Int$_3$) .......................................................................................................................... 128

Figure 50. Optimized structures of $\beta$- and possible $\alpha$-glycosyl phenanthroline intermediates .......... 129

Figure 51. $^1$H NMR course of furanosylation with 2-fluoro xylofuranosyl bromide 50 ......................... 130

Figure 52. $^{19}$F NMR course of furanosylation with 2-fluoro xylofuranosyl bromide 50 ......................... 131

Figure 53. $^1$H NMR detection of xylofuranosyl phenanthroline intermediates (Int$_4$ and Int$_5$) .......... 132

Figure 54. $^{19}$F NMR detection of xylofuranosyl phenanthroline intermediates (Int$_4$ and Int$_5$) .......... 132

Figure 55. $^1$H NMR of xylofuranosyl phenanthroline intermediates (Int$_4$ and Int$_5$) ....................... 133

Figure 56. $^1$H-$^1$H COSY NMR of xylofuranosyl phenanthroline intermediates (Int$_4$ and Int$_5$) ....... 133

Figure 57. $^1$H-$^1$H ROESY NMR of xylofuranosyl phenanthroline intermediates (Int$_4$ and Int$_5$) ...... 134

Figure 58. Mass Spectrum of xylofuranosyl phenanthroline intermediates (Int$_4$ and Int$_5$) ............... 134

Figure 59. $^1$H NMR course of furanosylation with 2-fluoro arabinofuranosyl bromide 48 ..................... 135

Figure 60. $^{19}$F NMR course of furanosylation with 2-fluoro arabinofuranosyl bromide 48 ..................... 136

Figure 61. $^1$H NMR detection of arabinofuranosyl phenanthroline intermediates (Int$_6$ and Int$_7$) ....... 137

Figure 62. $^{19}$F NMR detection of arabinofuranosyl phenanthroline intermediates (Int$_6$ and Int$_7$) ..... 137

Figure 63. $^1$H NMR of arabinofuranosyl phenanthroline intermediates (Int$_6$ and Int$_7$) ..................... 138

Figure 64. $^1$H-$^1$H COSY NMR of arabinofuranosyl phenanthroline intermediates (Int$_6$ and Int$_7$) ..... 138

Figure 65. $^1$H-$^1$H NOESY NMR of arabinofuranosyl phenanthroline intermediates (Int$_6$ and Int$_7$) 139

Figure 66. Mass Spectrum of xylofuranosyl phenanthroline intermediates (Int$_6$ and Int$_7$) ............... 139
LIST OF SCHEMES

**Scheme 1.** ATP as a rapid source of energy ................................................................. 2

**Scheme 2.** Glucose as a source of energy in the biological system .......................... 3

**Scheme 3.** The central dogma of biology ........................................................................ 12

**Scheme 4.** Concept of glycosylation ............................................................................ 16

**Scheme 5.** General pathways of glycosylation ......................................................... 17

**Scheme 6.** Neighboring group participation .............................................................. 18

**Scheme 7.** Bimodal anchimeric assistance ................................................................. 19

**Scheme 8.** Hydrogen bonding mediated aglycone delivery ...................................... 20

**Scheme 9.** Use of bicyclic protecting group in stereoselective glycosylation .......... 20

**Scheme 10.** Koenigs-Knorr glycosylation and its development toward 1,2-cis glycosylation .............................. 22

**Scheme 11.** Halide ion catalyzed 1,2-cis glycosylation .................................................. 22

**Scheme 12.** Glycosylation through in situ anomerization ..................................... 23

**Scheme 13.** Glycosylation through direct \( S_N 2 \) substitution with alkoxide ................. 23

**Scheme 14.** The first catalytic glycosylation by Emil Fischer ........................................ 24

**Scheme 15.** First catalytic glycosylation with TCA donors .......................................... 25

**Scheme 16.** Glycal as glycosyl donor in catalytic glycosylation ........................................... 26

**Scheme 17.** Boron trifluoride activation of TCA donor ................................................ 27

**Scheme 18.** Synthesis of glycosyl phosphate and inspiration ........................................ 27

**Scheme 19.** Development of acid-base catalysis ...................................................... 28

**Scheme 20.** Regioselective activation of glycosyl acceptor .......................................... 29

**Scheme 21.** Regioselective glycosylation using acid-base catalysis .............................. 30

**Scheme 22.** Cationic palladium(II)-catalyzed stereoselective glycosylation ................. 31

**Scheme 23.** Brønsted acid-catalyzed glycosylation ...................................................... 32

**Scheme 24.** Kinetic resolution in stereoselective glycosylation using chiral Brønsted acid .......................... 33
Scheme 25. Site-selective glycosylation by the selection of chiral phosphoric acid.......................... 34
Scheme 26. Schreiner's thiourea catalyzed 2-deoxy galactoside synthesis ........................................... 36
Scheme 27. Schreiner's thiourea catalyst as an organo photoacid in catalytic glycosylation ............... 37
Scheme 28. Macrocyclic bis-thiourea catalyzed stereospecific glycosylation .................................. 39
Scheme 29. Bis-thiourea activation of glycosyl phosphate .................................................................. 39
Scheme 30. Retaining glycosyltransferases-catalyzed stereoretentive glycosylation ......................... 40
Scheme 31. Phenanthroline-catalyzed α-1,2-cis-glycosylation .......................................................... 41
Scheme 32. C14-catalyzed site-selective coupling of functionally diverse substrates ......................... 54
Scheme 33. C14-catalyzed orthogonal glycosylation ............................................................................ 58
Scheme 34. Effect of the configuration of glycosyl bromide ............................................................ 60
Scheme 35. Catalytic stereoselective xylofuranosylation ................................................................. 76
Scheme 36. Overview of reaction outcome of phenanthroline catalysis in furanosylation system ...... 77
Scheme 37. Catalytic stereoselective arabinofuranosylation ............................................................. 78
Scheme 38. Effect of donor anomeric composition in C1-catalyzed furanosylation ............................ 79
LIST OF TABLES

Table 1. Chiral Brønsted acid-catalyzed glycosylation ................................................................. 32
Table 2. Hidden Brønsted acids catalyzed glycosylation ................................................................. 35
Table 3. Urea-catalyzed stereoselective glycosylation ................................................................ 38
Table 4. Bathophenanthroline-catalyzed 1,2-cis glycosylation[a] ...................................................... 42
Table 5. Bathophenanthroline-catalyzed 1,2-cis glycosylation with electron-rich substrates[a] ........ 45
Table 6. Catalyst screening with electron-rich electrophile [a] ............................................................ 47
Table 7. Catalyst development in phenanthroline framework[a] ....................................................... 48
Table 8. Influence of phenanthroline catalyst[a] ............................................................................. 50
Table 9. Stereoselective glycosylation using C1 and C14 catalyst [a] ............................................... 52
Table 10. C14-catalyzed chemoselective glycosylation[a] ............................................................... 56
CHAPTER 1: INTRODUCTION

1.1 The Significance of Carbohydrates in Biological Systems

Carbohydrates, also known as glycans, saccharides, or simply sugars, represent a family of compounds with empirical formula \( C_m (H_2O)_n \). The term carbohydrate was derived from the French (hydrate de carbone) in the nineteenth century, which later extended to polyhydroxylated aldehydes or ketone containing carbons varying between 3 and 9.\(^1\) Carbohydrates as one of the primary constituents of cells, are the most abundant organic molecules on earth. For example, starch and cellulose are polymers of glucose (1), a sugar that contains 6 carbon atoms. DNA (deoxyribonucleic acid) and RNA (ribonucleic acid), the molecules that are responsible for the storage and reading of genetic information, are also built with carbohydrates such as deoxyribose or ribose (2), which contain 5 carbon atoms. Sialic acid (3), an alpha-keto acid sugar contains 9 carbon backbone that is typically found attached to the outermost ends of N-glycans, O-glycans, and glycosphingolipid.

![Figure 1. Examples of carbohydrates in nature](image)

Carbohydrates play many central roles in the biological system. It has been long recognized that sugars are an important energy source and structural building blocks for many living organisms. In addition to their participation in metabolism and other intracellular events, carbohydrates also play important roles in intercellular communication or recognition by conjugation to lipids and integral membrane proteins. This section highlights the essential roles of carbohydrates play in the biological system.

1.1.1 Metabolism: carbohydrates as an energy source

Adenosine triphosphate (ATP) 4, a molecule containing a core of ribose, is a rapidly available energy source in biological systems. ATP is also referred to as the cell’s energy currency due to its property of storing and transferring energy in cells. This energy is stored in the phosphodiester bond. Through cleavage
of a phosphodiester bond of ATP, 30.6 kJ/mol of free energy is released in the biological system, and adenosine diphosphate (ADP) \( \text{5} \) is generated (Scheme 1). Similarly, when a phosphate is removed from ADP, energy is also released and leading to the formation of adenosine monophosphate (AMP), which can be recycled into ADP or ATP by regeneration of the phosphodiester bond to restore the energy. ATP, ADP, and AMP are constantly interconverted in the cell to participate in the biochemical processes. In these events, sugars act as carriers during energy storing and transferring.

![Scheme 1. ATP as a rapid source of energy](image)

The regeneration of ADP from AMP requires ATP; therefore, regeneration of ATP becomes necessary. The major method to regenerate ATP is through phosphorylation of ADP, in which the energy is supplied by the oxidation of glucose. The breakdown of glucose to yield energy-rich ATP involved four stages as shown in Scheme 2.

Firstly, glucose \( \text{1} \) undergoes a ten-step sequential process to generate two pyruvates \( \text{6} \) in stage (i). This process is known as glycolysis, where a 6-carbon sugar is dissected into two 3-carbon fragments. During the process of glycolysis, two ATP are generated. In stage (ii), the pyruvates undergo oxidative decarboxylation to form a thioester of acetic acid with coenzyme A (CoA), whose product is known as acetyl-CoA \( \text{7} \). Similar to acetyl chloride or acetic anhydride, the S-CoA portion of acetyl-CoA is a good leaving group. Therefore, hydrolysis of the thioester bond is favorable, allowing the acetyl group to enter the stage (iii) – the citric acid cycle (CAC), also known as tricarboxylic acid cycle (TAC) or Krebs’ cycle. Through a series of chemical reactions in CAC, the energy stored in the thioester bond is released into 2 ATP and the reduced compounds nicotinamide adenine dinucleotide (NADH) and flavin adenine
dinucleotide (FADH$_2$). Due to their high reductive potential, NADH and FADH$_2$ are also strong electron donors. As such, in the oxidative phosphorylation stage (iv), ten NADH and two FADH$_2$ that are generated in stages (i)-(iii) are fed into the electron transport chain and produce 34 ATP. In total, one glucose molecule produces 36 ATP in the biological system.

![Scheme 2](image)

**Scheme 2.** Glucose as a source of energy in the biological system

### 1.1.2 Structural building blocks

Nature utilizes sugars as building blocks in a polymeric fashion, where the sugars are joining each other covalently through glycosidic linkages.$^{1,2}$ For example, starch (8) and cellulose (9) are both polymers of D-glucose (Figure 2). Yet, the structural properties of these two polysaccharides are different, where starch is an easily digestible material with no significant structural utility. Cellulose, on the other hand, provides strong structural support to the plant cells, which further developed into materials such as wood and cotton.$^2$

The difference in the structural properties between starch and cellulose simply arises from the anomeric configuration of the glycosidic linkages between the glucose. While starch possesses glycosidic bonds with axial ($\alpha$) stereochemistry from the C1 anomeric carbon to the C4 oxygen ($\alpha$-$(1\rightarrow4)$ linkage), cellulose

![Figure 2](image)

**Figure 2.** The structures of starch and cellulose
holds equatorial (β) glycosidic bonds (β-(1→4) linkage). The difference in the anomeric configuration causes variations in the glycosidic torsion angles, where cellulose is less helical compared to starch. As a result, the cellulose strands can pack and interact with each other to form layers, which further turn into fibrils.² As such, while starch develops into the energy storage for plants, cellulose exists as the main construction of cell walls.

The cell wall (Figure 3) is a complex and heterogeneous matrix of polysaccharides that surrounds the plasma membrane of the plant cell, which is the major difference between plant and animal cells (animal cells do not have cell walls).²⁻³ A plant cell wall is a load-bearing network where layers of cellulose are cross-linked by hemicellulose and pectins.⁴⁻⁵ Hemicelluloses are polysaccharides that cross-link between cellulose layers to primarily increase wall strength. Xyloglucan (XyG, 10) is the most common hemicellulose on earth and has been found in almost every land plant species.⁶ The basic structure of XyG includes a backbone of cellulose, with a branch of D-xylose (Xyl) connecting at the C6 oxygen position of...
the glucose (Glc) with α anomic configuration (D-Xyl-α-(1→6)-Glc). The branching patterns of XyG variate their function such as solubility, which is significant in taxonomy. The remaining matrix of polysaccharides are pectins, the most structurally and functionally complex polysaccharides in plant cell wall. The structure and chemical composition of pectins are diverse, yet contain a high degree of galacturonic acid, in which common structures include homogalacturonan (11), rhamnogalacturonan I and II, and xylogalacturonan. Galacturonic acid is a sugar acid derived from galactose, which the carboxyl group is often methylesterified in nature. The partially methylesterified pectins can form complex hydrated gels, which contribute strength and flexibility to the cell wall and provide connections to the adjacent cells in the middle lamellae (Figure 3).

Unlike plant cell walls, bacterial cell walls are constituted of conjugated polysaccharides. In general, there are two types of bacteria: Gram-positive and Gram-negative bacteria. Their difference can be determined by Gram staining, where Gram-positive bacteria adopt the crystal violet color, and Gram-negative bacteria appear pink or red after treatment with alcohol. These staining results are based on the difference in the cell wall structures, whereas Gram-positive bacteria have a thick layer of peptidoglycan in the cell wall, while Gram-negative bacteria surround the peptidoglycan with an outer membrane (Figure 4). Peptidoglycan (12) is a polysaccharide cross-linked by peptides, consisting of repeating disaccharides of N-acetylglucosamine (blue) and N-acetylglucosamine acid (green) carrying short peptides. In Gram-positive bacteria, peptidoglycan provides mechanical strength through the construction of tens of nanometers thick architecture. On the other hand, Gram-negative bacteria have a thin layer of peptidoglycan surrounded by the plasma membrane and the outer membrane. This double-membrane cellular envelop enables the Gram-negative bacteria to colonize harsh environments. Lipopolysaccharide (LPS) is the main component of most outer membranes, a macromolecule containing up to hundreds of sugars. Figure 4 demonstrates LPS of E. coli, where the molecule is categorized in three main components: lipid A, core, and O-antigen. Lipid A is the hydrophobic phospholipid anchor of
Figure 4. Constitution of bacterial cell wall
LPS containing a β-(1→6) linked glucosamine disaccharide, which is also known as endotoxin. The 6’ position of lipid A is glycosylated with a core containing nonrepeating oligosaccharides: a trisaccharide consisting of eight-carbon sugar 3-deoxy-D-manno-octulosonic acid (KDO), a trisaccharide involving seven-carbon sugar L-glycero-D-manno-heptose, and a pentasaccharide comprising of glucose, galactose, and N-acetylglicosamine, whereas the KDO region and the heptose region compose the inner core, and the pentasaccharide make up the outer core. At the end, a repetitive glycan is attached to the outer core oligosaccharide designated as O-antigen. The O-antigens are highly variable in different strains of bacteria, which are targets for recognition by host antibodies in the immune system.

1.1.3 Cellular communication and recognition: glycocode and the decoders

In the first half of the 20th century, research on carbohydrates in biological systems is primarily focused on metabolism and structural function. Until the 1970s, the studies of glycans lagged far behind other major classes of biomolecules such as nucleotides and peptides. This was due to the inherent complications in the structure of carbohydrates. For example, Figure 5 demonstrates the structure of a pyranose, a six-carbon monosaccharide where the six-membered ring consists of five carbon atoms and one oxygen atom. The first complication arises from the ring size, where the six-membered ring can be contracted into a five-membered ring, which is known as a furanose. Secondly, each carbon on the ring can have an R or S configuration. In addition, each hydroxyl group can react with another sugar through glycosylation. Therefore, glycans exist in both linear and branch forms, in contrast to the linear nature of nucleotides and peptides. A calculation was performed to show $1.05 \times 10^{12}$ possible oligosaccharides structures for a reducing hexasaccharide, whereas a hexamer of DNA (a basis set of 4) may form 4096 different combinations, and a hexapeptide (a basis set of 20) may have $6.4 \times 10^7$ isomers. Asides, each hydroxyl group can be decorated with sulfates,

![Figure 5. Structure of pyranose](image-url)
phosphates, methyls, or acyls, and more than one hydroxyl group can be modified on the same sugar.\textsuperscript{1} As such, the information that the glycans can convey is enormous. Glycomics, a systematic and comprehensive study of the total glycan structures (glycome) in the biological system, emerged. The molecular messages cracked from this study are called glycocode, also known as sugar code.\textsuperscript{20}

Given the complexity of many glycans, a schematic glycan representation is necessary. In the late 1970s, Kornfeld and colleagues first presented a symbolic representation of vertebrate glycans, which quickly gained popularity and was adopted by the community of glycoscience.\textsuperscript{21-22} Figure 6 demonstrates some monosaccharides symbols (the full universal symbol nomenclature for glycans (SNFG) can be found in Appendix A),\textsuperscript{22} where both shapes and colors are utilized to overcome the diversity of carbohydrates. Utilizing this SNFG, the structure of lipopolysaccharides in Figure 4 can be simplified (Figure 6).

\textbf{Figure 6}. Symbolic representation of monosaccharides and an example of lipopolysaccharide

The cell surface was first observed as a polysaccharide coat by electron microscopy.\textsuperscript{18} These glycans on the cell surface exist in the conjugated form, in which the glycans are covalently bonded to non-carbohydrate molecules (aglycone). Increasing research has shown that these glycoconjugates play crucial roles in cellular function, especially in the events on the cell surface.\textsuperscript{18} Three classes of glycoconjugates were found on the cell surface (Figure 7): glycoprotein, glycolipid, and glycoRNA (a new class of glycoconjugate discovered recently by Flynn and colleagues\textsuperscript{23}).
Figure 7. Glycoconjugates on the cell surface: glycoprotein, glycolipid, and glycoRNA

A glycoprotein is a glycoconjugate in which a protein covalently carries one or more glycans, usually through the side chain of the amino acids such as asparagine (N-linkage) or serine/threonine (O-linkage). Similar to O-glycans (O-linked oligosaccharides), glycosaminoglycans (GAG) attached to the core protein through glycosylation to the hydroxyl group of a serine residue, and these glycoconjugates are also known as proteoglycans. The main difference between an O-linked glycoprotein and a proteoglycan is at the core region, where an O-linked glycoprotein links to the glycan via N-acetylgalactosamine (GalNAc), while a proteoglycan connects to the protein through a xylose residue. These glycans decorated proteins also change in their properties such as increasing solubility, altering the antigenicity, and preventing the proteins from degradation. Unlike nucleotides and proteins, the biosynthesis of glycans is non-templated. Therefore, glycoproteins naturally occur in forms with different glycosylation, and these various forms are known as glycoforms.

Glycolipid, also known as glycosphingolipid, consists of a glycan (polar) attached to a nonpolar moiety. The nonpolar moiety is ceramide, which is composed of sphingosine (a long chain base) and fatty acid. The glucose or galactose from the glycan connects to the terminal primary hydroxyl group of the ceramide through a glycosidic linkage. Typically, the hydrophobic lipid positions itself at the outer lipid layer to allow the hydrophilic glycans to face outside of the cell. Consequently, glycolipids can play essential roles in cellular recognition, such as mediating cell-cell interactions or modulating activities of proteins in the same membrane.
GlycoRNA is a class of glycoconjugate that only appeared in discussion in the past decade. RNA as an essential biopolymer participates in many events in the biological system, including coding, decoding, regulation, and expression of genes. Until 2011, the first membrane-bound non-coding RNAs were discovered in bacteria,\textsuperscript{27-28} declaring their essential membrane function. As such, associations of membrane RNA with glycans seem possible. In 2021, Flynn and colleagues first reported glycoRNA on living cell surface,\textsuperscript{23} opening a new chapter on cell surface glycoconjugates.

The aforementioned glycoconjugates on the cell surface encrypt an enormous amount of information. To crack these encrypted codes on the cell surface, nature has designed specific decoders: the glycan-binding proteins (GBPs). Two main categories are included in the GBPs: lectins (Figure 8) and sulfated GAG-binding proteins.\textsuperscript{29} Lectins typically recognized the terminal sugar on a glycan by fitting the sugar molecule into its shallow but highly specific binding pockets through hydrogen bonding, while sulfated GAG-binding proteins bind to sulfated GAGs (negatively charged) through ionic interaction with clusters of positively charged residues in the binding pocket.\textsuperscript{1, 29} To overcome the weak hydrogen bonding interaction, many lectins have multiple carbohydrate recognition domains (CRDs). For example, Figure 8 demonstrates a galactose specific C-type lectin (PDB: 1JZN),\textsuperscript{30} in which the protein resembles a pentamer

\textbf{Figure 8.} Structure of a galactose-specific C-type lectin.\textsuperscript{30} PDB: 1JZN
with five CRDs (red boxed). This setting increases the chance of binding and allows multiple glycans binding at the same time, consequently increasing its specificity. This avidity effect is also known as the multivalent effect.\textsuperscript{1,29}

1.2 Carbohydrates and their mimics in drug discovery

1.2.1 Carbohydrate vaccines

Vaccines are preparations to stimulate the body’s immune response against one or several diseases, typically containing agents that resemble the pathogen such as a deactivated microbe, or its toxins or surface proteins.\textsuperscript{31} The pathogens’ and malignant cells’ surfaces often consist of unique glycan structures, which makes carbohydrates an attractive vaccine target.\textsuperscript{32} The history of carbohydrate vaccines dates back to 1930 when oligosaccharides decorated proteins were used as a vaccine against pneumonia.\textsuperscript{1,33-34} Unfortunately, this research was limited due to the complicated process to isolate natural oligosaccharides and the lack of synthetic methods.\textsuperscript{1} Until the 1970s, advances in glycan analysis, synthesis, and structure determination contribute significantly to carbohydrate vaccine development, which promoted the first commercialized polysaccharide vaccine PNEUMOVAX launching in 1983.\textsuperscript{1,32} This vaccine contains capsular polysaccharides isolated from 14 pneumonia serotypes, which protect people against approximately 90% of infections caused by these pathogens.\textsuperscript{32} Unfortunately, this unconjugated capsular polysaccharide vaccine did not induce sufficient protection to the high-risk group (children under 2-year-old, and immunocompromised elderly),\textsuperscript{35} which is now well understood that these polysaccharides need to be conjugated to immunogenic proteins to induce long-lasting protection for the high-risk group.\textsuperscript{32,36-37}

The modern design of carbohydrate-based glycoconjugate vaccine consists of four parts: the antigen (poly-/oligo saccharide), the linker, the carrier (protein, glycolipids, or nanoparticles), and the adjuvant (alum or self-adjuvanting) (Figure 9).\textsuperscript{38} Traditionally, carbohydrate vaccines are naturally derived. However, due to the economic challenges of meeting quality control and safety standards required by the U.S. Food and Drug Administration (FDA), movements toward synthetic carbohydrate vaccines are in progress.\textsuperscript{32,38}
1.2.2 Carbohydrate drugs targeting the central dogma of biology

The central dogma of biology explains the flow of genetic information within a biological system, which is demonstrated in Scheme 3. Therefore, nucleoside/nucleotide mimetics that interrupt the replication of pathogens gained lots of spotlight in the antiviral battle. However, it is easy to forget that nucleosides/nucleotides are made of carbohydrates, where the core molecule contains the pentose D-ribose (Section 1.1). As such, these nucleoside/nucleotide analogs contain carbohydrate moiety in the structures.

Scheme 3. The central dogma of biology

Human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) is an ongoing epidemic spread to the U.S. between 1966 and 1972. Azidothymidine (AZT, Figure 10) is the first antiretroviral drug for the treatment of AIDS approved by the FDA in March of 1987. AZT is a reverse transcriptase inhibitor, which stops retroviruses such as HIV from replication. After treatment of AZT, the reverse transcriptase incorporates the nucleoside analogs into its DNA during the reverse transcription process, which causes termination of the DNA elongation due to the lack of 3'-hydroxyl group (it is azide group in AZT).

In December 2019, coronavirus disease 2019 (COVID-19), an acute respiratory disease emerged and quickly spread globally, which was declared as a pandemic in March 2020 by the World Health Organization (WHO). This pandemic was caused by a new strain of coronavirus: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Remdesivir (Figure 10), a nucleotide analog was authorized
for emergency use as a post-infection treatment for COVID-19.\textsuperscript{45} Coronaviruses contain a large family of single-stranded RNA viruses that are characterized by their spherical shapes.\textsuperscript{46} Remdesivir as an RNA-dependent RNA polymerase inhibitor, causes a decrease in viral RNA production. As such, prior to treatment for COVID-19, Remdesivir was used in the investigation of other viral diseases such as Ebola virus disease and showed promising therapeutic efficacy.\textsuperscript{47} In December 2021, the first orally available COVID-19 antiviral medication Molnupiravir (22, Figure 10) was approved by the U.S. FDA.\textsuperscript{48} Unlike AZT and Remdesivir, Molnupiravir inhibits viral reproduction by promoting mutation during viral RNA replication.\textsuperscript{49}

\textbf{Figure 10.} Nucleoside/nucleotide mimetics as carbohydrate-based drugs

\subsection*{1.2.3 Glycosidase and glycosyltransferase inhibitors}

Glycosidases and glycosyltransferases are two types of carbohydrate processing enzymes utilized by nature to construct all the carbohydrate structures in all biological systems. Through inhibition of these enzymes, the biosynthesis or degradation of some carbohydrate structures can be controlled.\textsuperscript{1} For example, Miglustat (23, Figure 11) is a ceramide glucosyltransferase inhibitor that is used to treat Gaucher disease, a genetic disorder of glucosylceramide accumulation in cells and organs.\textsuperscript{50-51} Inhibition of ceramide glucosyltransferase might also alter the membrane surface glycoconjugate. Therefore, Miglustat was also studied for HIV/AIDS treatment and found reduced infection of white blood cells by HIV due to the inefficient binding to gp120 (glycoprotein found on virus surface).\textsuperscript{52-53} Unfortunately, Miglustat showed limited efficacy in phase II clinical trial for HIV/AIDS due to low potency and difficulty to achieve steady-state therapeutic concentration.\textsuperscript{54-55}
Figure 11. Examples of glycosidase and glycosyltransferase inhibitors

On the other hand, Acarbose (24, Figure 11) is a pseudo-tetrasaccharide consisting of multiple α-(1→4) linkages that acts as an α-glucosidase inhibitor. α-Glucosidase is an intestinal enzyme that releases glucose from breaking down the large carbohydrates with α-(1→4) linkage. Therefore, Acarbose is used as a treatment for Type 2 diabetes and showed great efficacy in Asian patients, in which the efficacy is likely due to the high carbohydrate diet.56-58

1.2.4 Glycosaminoglycans and their therapeutic applications

Today, one of the most widely prescribed drugs is the anticoagulant heparin (25, Figure 12), a highly sulfated glycosaminoglycan containing repeating units of glucuronic acid/iduronic acid and glucosamine. Antithrombin is a protease inhibitor of the coagulation cascade, which is triggered by tissue trauma or vascular injury.59 Activation of antithrombin leads to rapid inhibition of thrombin and factor Xa, shutting down the production of fibrin clots, eventually limits the blood’s ability to clot.60 Heparin binds and activates antithrombin, therefore, it is often prescribed for patients after surgeries to prevent and treat thrombosis (blood clotting).59 Low molecular weight heparin (LMWH) is a fractionated heparin derived by chemical or enzymatic cleavage of heparin, which has replaced unfractionated heparin in developed countries as a therapeutic of choice due to its fewer secondary complication (thrombocytopenia induced by heparin and antibodies).60 To further eliminate the secondary complication, a synthetic heparin mimic pentasaccharide fondaparinux (26, Figure 12) was developed. Fondaparinux specifically and irreversibly binds to antithrombin and is used to prevent deep-vein thrombosis and pulmonary embolism. Nevertheless, the high cost of production has prevented fondaparinux from larger success therapeutic.60
Figure 12. Structures of heparin and fondaparinux

1.3 Chemical Methods of Carbohydrates Synthesis

Although impressive progress has been achieved in the field of glycoscience, the major bottleneck is the lack of homogeneous forms of oligosaccharide as well as scalable methods of oligosaccharide synthesis. Unlike nucleic acids and proteins, the biosynthesis of carbohydrates is not templated, which leads to a variety of complicated carbohydrates products. As most bioactive carbohydrates used in clinics are isolated from natural sources, the inconsistency of natural products becomes problematic. In 2008, heparin was contaminated by a heparin-like compound, oversulfated chondroitin sulfate, which caused nearly 100 deaths. As such, a scalable method that allows us to produce well-defined glycans is currently demanded.

Glycosylation is the fundamental method for constructing complex glycans, in which a glycosyl donor (sugar that donates the anomeric carbon) reacts with a glycosyl acceptor (the molecule that accepts the anomeric carbon) to form a glycoside through the newly formed glycosidic linkage. Scheme 4 demonstrates the glycosylation of pyranosyl donor and acceptor as well as the formation of two possible glycosides, where the glycosidic linkage can be either axial or equatorial.
There are two general methods of glycosylation: chemical and chemoenzymatic glycosylation. It is envisioned that the combination of chemical and chemoenzymatic tools is a promising solution to the construction of complex natural or designed glycans. This section will focus on chemical glycosylation.

1.3.1 General pathways of chemical glycosylation

Glycosylation is a substitution reaction at the anomeric (C1) position. Although the concept of glycosylation is extremely simple, the operation has been frustrating. The challenges arise from carbohydrate molecules' inherent poly-hydroxyl nature, which leads to problems with regioselectivity and stereoselectivity. To avoid problems with regioselectivity, protecting groups are often used on the sugar molecules. The other main challenge is the stereochemical outcome at the anomeric center, which is considered the most challenging in carbohydrate synthesis. The stereoselectivity at the anomeric center can be viewed in respect to the C2 position (Figure 13), where 1,2-\textit{cis} and 1,2-\textit{trans} glycosides could be possibly formed in glycosylation. In the case of 2-deoxy glycoside, an \(\alpha\) and \(\beta\) mixture of glycosides is often found after glycosylation.

![Diagram of glycosylation](image)

**Scheme 4.** Concept of glycosylation

**Figure 13.** Category of glycosides
To solve the stereoselectivity problem of glycosylation, it is necessary to consider the possible mechanisms, which generally include three pathways: the $S_N1$, $S_N2$, and free radical pathways (Scheme 5). Chemical glycosylation is commonly seen as a nucleophilic substitution reaction, where the glycosyl donor is an electrophile, and the glycosyl acceptor is a nucleophile. As such, $S_N1$ and $S_N2$ pathways are often processed in chemical glycosylation. Yet, the complication of glycosylation rises from the ring oxygen, which facilitates the $S_N1$ pathway.\(^1\) As demonstrated in Scheme 5a, upon the departure of the leaving group, the lone pair on the ring oxygen can stabilize the carbocation through resonance, and generate an oxocarbenium ion. A nucleophile can approach the anomeric center from either $\alpha$ or $\beta$ face, which leads to two possible products. On the other hand, glycosylation undergoing the $S_N2$ pathway gives a clean inversion of configuration at the anomeric center (Scheme 5b).

Another less mentioned pathway in glycosylation is the radical pathway (Scheme 5c). Propagation of anomeric glycosyl radicals followed by termination with glycosyl acceptor radicals, the radical pathway in glycosylation allows efficient access to $C$-glycosides, sugars with a carbon substituent at the anomeric center.

![Scheme 5. General pathways of glycosylation](image-url)
1.3.2 **Substrate-control of stereochemistry**

The ability to forge glycosidic bonds in a stereoselective fashion is not easily predictable due to the reaction’s high degree of variables and shifting $S_N1-S_N2$ mechanistic paradigm (Scheme 5a-b).\textsuperscript{63-65} Many factors influence the stereochemical outcome of glycosylation, such as the substrate itself, additives to the reaction, the temperature, and even the solvents and the concentration of the reaction.\textsuperscript{1,66} Most established methods to achieve stereoselective glycosylation reactions have focused on tuning the steric and electronic nature of the protecting group on the electrophilic partners\textsuperscript{67-73}. The most reliable approach is based on the $O$-acyl participatory protecting group at C2 of the glycosyl electrophile for construction of the 1,2-\textit{trans} glycosidic linkage (Scheme 6).\textsuperscript{67,74} Upon the formation of oxocarbenium ion 27, the C2-$O$-acyl protecting group leads to a more stable 1,2-\textit{cis} acyloxonium bridged intermediate 28. Subsequent nucleophilic attack at the anomeric center leads to 1,2-\textit{trans} glycoside 29. To achieve 1,2-\textit{cis} glycoside, Boons and coworkers have developed (1S)-phenyl-2-(phenylsulfanyl)ethyl chiral auxiliary as a C2 participatory protecting group.\textsuperscript{68-69} To minimize the steric and electronic interference, a 1,2-\textit{trans} decalin sulfonium intermediate 30 is formed. Following the displacement of the sulfonium ion by a nucleophile at the anomeric center leads to 1,2-\textit{cis} glycoside 31.

**Scheme 6.** Neighboring group participation

Besides participation in constructing a stable intermediate, the C2-neighboring group is also capable of bimodal assistance in stereoselective glycosylation. In 2018, Ding, Ishiwata, and Ito discovered that the C2-$O$-(\textit{ortho}-tosylamido)benzyl (TAB) protecting group enables access to $\alpha$- or $\beta$-anomeric product under specific reaction conditions (Scheme 7).\textsuperscript{75} TAB group is a functional group designed for anchimeric assistance in glycosylation. With a catalytic amount of triflimide in the reaction, and propionitrile as the solvent, the TAB protecting group proceeds intramolecular hydrogen bonding between the tosylamido
proton and C2-oxygen resembles a phthalimide moiety. Following anchimeric assistance of the sulfonyl oxygen leads to the formation of a stable 1,2-cis cyclic intermediate 33. A final nucleophilic substitution by the alcohol glycosyl acceptor at the anomeric center on 33 eventually yields 1,2-trans glycoside 34\(\beta\). On the other hand, when diethyl ether is used as the solvent, the intramolecular hydrogen bonding that resembles the phthalimide moiety is disrupted. After activation by a catalytic amount of triflic acid, an oxocarbenium ion 35 is formed, leading to the thermodynamically favored \(\alpha\)-product 34\(\alpha\).

**Scheme 7.** Bimodal anchimeric assistance

Apart from functionalization on the C2 position, the remote positions on the sugar molecule could also participate in glycosylation. In 2012, Yasomane and Demchenko utilized O-picolinyl and O-picoloyl groups at remote positions to control facial selectivity for the nucleophilic attack of the alcohol glycosyl acceptor, which is known as hydrogen bond-mediated aglycone delivery (Scheme 8).\(^{70}\) When a picolinyl group is functionalized at the C3 or the C6 position, the formation of the oxocarbenium ion 37 or 39 shifts the picolinyl group to the \(\beta\)-face. Hydrogen bonding between the picolinyl group and the alcohol delivers the glycosyl acceptor to the \(\beta\)-face eventually generates the \(\beta\)-glycosides 38 or 40. Conversely, functionalization of the picolinyl group at the C4 position directs the alcohol glycosyl acceptor to the \(\alpha\)-face, leading to \(\alpha\)-glycoside 42 as the major product.
Scheme 8. Hydrogen bonding mediated aglycone delivery

The utilization of conformationally constraining bicyclic protecting groups is another effective method to control the diastereoselectivity of glycosylation. For example, the Crich group demonstrated the use of the 4,6-\(O\)-benzylidene group on mannosyl sulfoxides (43) give superior \(\beta\)-selectivity compared to the conformationally mobile donor (46, Scheme 9).\(^{76-77}\) Extensive mechanistic study showed that an \(\alpha\)-mannosyl triflate (44) is formed upon activation with triflic anhydride.\(^{78}\) Subsequent displacement by the nucleophile leads to the \(\beta\)-mannoside product (45). On the other hand, the minor \(\alpha\)-mannoside product arises from an oxocarbenium-like intermediate, which is destabilized due to the conformationally constrained 4,6-\(O\)-benzylidene protecting group.

Scheme 9. Use of bicyclic protecting group in stereoselective glycosylation

These substrate-controlled methods, however, are highly specialized for each electrophilic partner. In addition, some technical issues are particularly difficult to avoid. For example, low temperature is typically required to achieve the desired selectivity. Besides, a dilute concentration of reaction is preferred to allow proper hydrogen bonding denoting that more solvent is required in the reaction. Additionally, sterically hindered nucleophiles are less effective in the hydrogen bonding mediated aglycone delivery methods.\(^{79}\)
Furthermore, the undesired byproduct is hard to avoid in some cases. For instance, in C2-O-acyl neighboring group participation, the carbocation is competing with the anomeric center leading orthoester as a byproduct when a weak nucleophile is used. Alternatively, reagent-controlled glycosylation has emerged as a way to eliminate the need for specific protecting groups.

1.3.3 Reagent-control of stereochemistry

Since the first glycosylation was reported in 1879, C2-O-acyl neighboring group participation has been utilized to access 1,2-trans glycosides. It was until 2005 that the Boons group have developed the sulfanyl chiral auxiliary as a C2-participatory group which allowed access to 1,2-cis glycosides through the substrate-controlled method (Scheme 8a). Aiming to stereoselectively synthesize 1,2-cis glycosides, chemists had diversified their focus in controlling the stereochemical outcome of glycosylation.

The first step to access 1,2-cis glycosides was to eliminate the C2-O-acyl anchimeric assistance. In 1901, Koenigs and Knorr reported glycosylation through the displacement of glycosyl halide 47 with alcohol under excess Ag2CO3 to achieve β-1,2-trans glycoside 48 (Scheme 10a). The Koenigs-Knorr glycosylation has then developed into one of the most common methods to synthesize oligosaccharides and glycoconjugates. It was later understood that the silver assisted the bromide to leave and concerted nucleophilic substitution of alcohol led to the glycoside product with inversion of configuration at the anomeric center. In 1926, Brigl and Keppler demonstrated the first 1,2-cis glycosylation using the Koenig-Knorr method (Scheme 10b). In this reaction, a β-glycosyl chloride (49) was used as the glycosyl donor. To eliminate the C2-O-acyl anchimeric competition, a trichloroacetyl protecting group, in which the carbonyl oxygen is less nucleophilic, was installed at the C2 position. Under the excess amount of Ag2CO3, the alcohol successfully displaced β-glycosyl chloride 49 resulting in the desired α-1,2-cis glycoside 50.
a. Koenigs-Knorr glycosylation, 1901

\[
\begin{align*}
\text{Ac}_2\text{O} & \quad \text{R-OH} && \text{Ag}_2\text{CO}_3 \\
\text{47} & \quad \text{Ac}_2\text{O} & \quad \text{Ac}_2\text{O} & \quad \text{Br} & \quad \text{CH}_3 \\
\text{48} & \quad \text{Ac}_2\text{O} & \quad \text{Ac}_2\text{O} & \quad \text{OR} \\
\end{align*}
\]

b. Bríg-Keppler 1,2-cis glycosylation, 1926

\[
\begin{align*}
\text{Ac}_2\text{O} & \quad \text{R-OH} && \text{Ag}_2\text{CO}_3 \\
\text{49} & \quad \text{Ac}_2\text{O} & \quad \text{Ac}_2\text{O} & \quad \text{Cl} & \quad \text{CCl}_3 \\
\text{50} & \quad \text{Ac}_2\text{O} & \quad \text{Ac}_2\text{O} & \quad \text{OR} \\
\end{align*}
\]

**Scheme 10.** Koenigs-Knorr glycosylation and its development toward 1,2-cis glycosylation

Breakthrough toward 1,2-cis glycosylation was made in 1975 by Lemieux and coworkers, where tetraethylammonium bromide was added to control the diastereoselectivity of glycosylation (Scheme 11). This extraordinary work allowed efficient, and more importantly, reproducible stereoselective synthesis of 1,2-cis glycoside for the first time. The central concept of this work is to anomerize the α-glycosyl bromide 51 to the more reactive β-glycosyl bromide 51β *in situ* with excess bromide ion, subsequent S_N_2-like displacement with alcohol leads to the desired 1,2-cis glycoside 52.

\[
\begin{align*}
\text{51} & \quad \text{Et}_3\text{N}^+\text{Br}^{-} \\
\text{51β} & \quad \text{R-OH} \\
\text{52} & \quad \text{OR} \\
\end{align*}
\]

**Scheme 11.** Halide ion catalyzed 1,2-cis glycosylation

The concept of *in situ* anomerization has a strong impact on the chemical synthesis of α-1,2-cis glycosylation, and it is not limited to glycosyl halide as starting material. For example, Demchenko and coworkers employed bromine to activate the inert thioglycoside 53, and the formation of the reactive β-glycosyl bromide 54 leads to α-1,2-cis glycoside 55 as the major product (Scheme 12a). Lemieux’s concept is also applicable to 2-deoxy sugars, which neighboring groups are inherently null. For example, Bennett and coworkers generated β-2-deoxy glycosyl iodide 57 *in situ* through activation of the inert 2-
deoxy glycosyl hemiacetal 56, followed by the addition of tetrabutylammonium iodide (TBAI). Subsequent reaction of 57 with alcohol eventually leads to a majority of α-selective products 58α (Scheme 12).\textsuperscript{87}

\textbf{a. Demchenko, 2012}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=0.4\textwidth]{demchenko.png}};
\end{tikzpicture}
\end{center}

\textbf{b. Bennett, 2011}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=0.4\textwidth]{bennett.png}};
\end{tikzpicture}
\end{center}

**Scheme 12. Glycosylation through \textit{in situ} anomerization**

Direct S\textsubscript{N}2 substitution is an efficient way of controlling the stereochemical outcome of glycosylation, as an inversion of configuration is expected at the reaction center. As demonstrated by Arthur Michael in 1879 (Scheme 13a),\textsuperscript{81} a phenoxide anion (60) substituted the α-glycosyl chloride (59) from the β-face, resulting in β-glycoside 61 as the product. Although the acetyl protecting groups were removed under the reaction condition, it was the first successful glycosylation in history.

\textbf{a. First glycosylation in history by Michael, 1879}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=0.4\textwidth]{michael.png}};
\end{tikzpicture}
\end{center}

\textbf{b. β-specific dehydrative glycosylation, 2013}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=0.4\textwidth]{2013.png}};
\end{tikzpicture}
\end{center}

**Scheme 13. Glycosylation through direct S\textsubscript{N}2 substitution with alkoxide**
This direct SN2 substitution method at the anomeric center with alkoxide is convenient for 2-deoxy sugars, in which the C2 position is free of manipulation. In 2013, the Bennett group developed a dehydrative method to access β-linked 2-deoxy-sugars (Scheme 13b).88 Firstly, the inert 2-deoxy glycosyl hemiacetal 56 is converted into α-glycosyl tosylate 62 in situ. Subsequent addition of alkoxide or thiolate displaces the tosylate leaving group, leading to β-2-deoxy glycoside 58β as the glycosylated product. These dehydrative protocols together with the in situ anomerization method (Scheme 12b) and the direct SN2 method (Scheme 13b) allow stereocontrol in the direct synthesis of 2-deoxy glycosides using bench stable glycosyl hemiacetals.

Reagent-controlled glycosylation is an effective method to bias the stereochemical outcome in the absence of anchimeric assistance. However, these reagent-controlled methods that require the addition of excess reagents are not efficient from the environmental and industrial perspectives. Therefore, catalytic glycosylation has emerged to meet the demand for the environment and economy.

1.4 Catalytic Glycosylation

1.4.1 Beginning of catalytic glycosylation

The first catalytic glycosylation was reported in 1893 by Emil Fischer, in which glycosylation was carried out through the reaction of aldose (1’) and alcohol (MeOH) in the presence of a catalytic amount of acid (Scheme 14).89 This is also known as Fischer glycosylation. Nevertheless, the Fischer glycosylation undergoes an equilibrium process which leads to a mixture of ring size isomers such as 63 and 64.

![Scheme 14](image)

**Scheme 14.** The first catalytic glycosylation by Emil Fischer

Although Fischer glycosylation is still the preferred method to make simple glycoside nowadays, it is not practical for oligosaccharide synthesis.90 Until 1980, Michel and Schmidt demonstrated catalytic activation of the trichloroacetimidate (TCA) in glycosyl donors with either Lewis acid or Brønsted acid
(Scheme 15), leading to the blooming of catalytic glycosylation. One problem at a time, the early stage of catalytic glycosylation focuses on the ability of coupling. For instance, Michel and Schmidt employed anchimeric assistance from the C2 acyl protecting group to achieve β-glycoside 67 in a practical yield with absolute stereocontrol. However, when a non-participatory protecting group was used in donor 68, the diastereoselectivity of coupled glycoside 70 reduced to 1:2 (α:β). Since then, chemists began to take the challenge in stereocontrol of glycosylation through the development of catalysts. Nowadays, in addition to the coupling ability, the focus on catalyst design in glycosylation has extended into stereocontrol and regiocontrol.

Scheme 15. First catalytic glycosylation with TCA donors

1.4.2 Design of stereoselective catalytic glycosylation

Despite reaction conditions and substituent effects, three components are considered in catalytic glycosylation: the glycosyl donor that donates the anomeric carbon, the glycosyl acceptor that accepts the anomeric center, and the catalyst. Aiming at successful glycosylation, the catalyst must interact with either the glycosyl donor or the glycosyl acceptor, or both. Considering catalytic O-glycosylation through the coupling of alcohol with glycosyl donor bearing a leaving group, it can be simplified as alcohol substitution at one reaction center. There are five possible interactions between the catalyst and the glycosyl donor or the glycosyl acceptor (Figure 14). Interactions between the catalyst and the glycosyl donor include direct displacement, insertion, and induced departure. On the other hand, the catalyst interacts with the glycosyl
acceptor through hydrogen bonding or insertion in the OH group. For the outcome of catalytic glycosylation to be selective, chemists have elaborated these aforementioned interactions and designed catalysts that allow collaboration with both the glycosyl donor and acceptor.

**Figure 14.** Design concepts for stereoselective catalytic glycosylation

Another common method of glycosylation is through the coupling of glycal with alcohol (Scheme 16). Unlike glycosyl donors with leaving groups, the glycal contains a double bond between the anomeric carbon and C2. In other words, there are two reaction centers upon activation of the glycal. This type of glycosyl donor is preferred in the synthesis of 2-deoxy glycosides as the ring oxygen bias regioselectivity, and the stereochemistry at C2 can be neglected.

**Scheme 16.** Glycal as glycosyl donor in catalytic glycosylation

1.4.3 Catalyst development in stereoselective glycosylation

1.4.3.1 From Lewis acid to acid-base catalysis (complexation with nucleophilic acceptor)

The early approach in catalytic glycosylation began with the activation of glycosyl donors. For example, in Schmidt’s first reported catalytic glycosylation (Scheme 17), boron trifluoride diethyl etherate (BF₃·OEt₂) acted as a Lewis acid accepting electrons from the imidate nitrogen, which promoted the departure of the TCA leaving group, leading to the formation of a carbocation. With the assistance of the
C2-acyl protecting group, β-glycoside was obtained as the product. Although glycosyl fluorides have been detected in this glycosylation, the mechanism of BF₃ activation of TCA donor is still debatable.

Scheme 17. Boron trifluoride activation of TCA donor

An interesting phenomenon was observed by the Schmidt group in 1982 when mixing perbenzylated glucosyl TCA donor and phosphoric acid mono- or di-esters, where α-glucosyl TCA 68 led to β-glucosyl phosphate 74 with absolute stereocontrol in the absence of a catalyst (Scheme 18a). In 1990, a cyclohexane-like eight-membered cyclic transition state (73) was proposed for this stereospecific glycosylation leading to a new concept of catalysis. The Schmidt group proposed that a catalyst \(B = C\) would generate an \(A - B - C - H\) intermediate in situ with an alcohol acceptor \(A - H\), which would resemble the 6-membered ring-like transition state (75) and lead to stereospecific glycosylation (Scheme 18b).

Scheme 18. Synthesis of glycosyl phosphate and inspiration
After testing a series of carbonyl compounds, chloral (78, Scheme 19) was able to catalyze glycosylation with TCA donor and alcohol acceptor.\textsuperscript{93} Although the temperature, solvent, and catalyst concentration affect the rate, yield, and diastereoselectivity of the glycosylation dramatically, the concept of acid-base catalysis through complexation with acceptor in stereoselective glycosylation was first established. Twenty years later, the Schmidt group reinvestigated the complexation concept and demonstrated boron-centered catalysts (79, Scheme 19)\textsuperscript{94} for stereospecific glycosylation.

Several key criteria were listed for the activation through precomplexation: (1) A fast equilibrium between the alcohol acceptor and the $A - B - C - H$ intermediate; (2). Increased acidity of alcohol acceptor after complexation; (3). The catalyst cannot react with glycosyl TCA in the absence of the acceptor; (4). Increased nucleophilicity of the alcohol after complexation.

In 2011, the Taylor group demonstrated the utility of commercially available diarylborinic acid derivatives in catalyzing regioselective Koenigs-Knorr glycosylation (Scheme 20), in which the regioselectivity was accomplished through complexation of acceptor and catalyst.\textsuperscript{95} The borinate ester 81 is a precatalyst, as the ethanolamine ligand is replaced by the diol during the reaction. Coordination of a 1,2-\textit{cis} diol (80) to the boron catalyst leads to a tetracoordinate boron-acceptor adduct (83), which alternates the nucleophilicity of the alcohols. Eventually, the most nucleophilic complexed equatorial alcohol (C3
alcohol) leads to the final product 82. This method is a big step forward in chemical glycosylation as it allows regioselective glycosylation with the catalytic addition of a simple small molecule. Yet, this glycosylation still relies on an equivalent amount of silver oxide to activate the glycosyl bromide 47.

![Scheme](image)

**Scheme 20.** Regioselective activation of glycosyl acceptor

Since then, Schmidt and coworkers exercised their acid-based catalysis system on regioselective glycosylation (Scheme 21). In 2012, the Schmidt group successfully coupled the complexed equatorial alcohol in a 1,2-\textit{cis} diol to the TCA donor with a catalytic amount of PhSiF₃. Similar to the boron-centered catalysts 79, silicon has a higher affinity to fluorine and oxygen than nitrogen. However, unlike the boron-centered catalyst 77, the silicon-center allows penta- or hexacoordination. In other words, the PhSiF₃ catalyst can coordinate to more than one alcohol. Elaborating on this concept, Peng and Schmidt later reported gold(III)⁹⁷ and platinum(IV)⁹⁸ catalyzed glycosylation allowing regioselective coupling of the complexed equatorial alcohol in 1,2-\textit{cis} diols and 1,2-\textit{trans} diols (PtCl₄ only).
Regioselective glycosylation using acid-base catalysis

Transition metals are frequently Lewis acid. Previous to Peng and Schmidt’s work on gold(III) and platinum(IV), the Nguyen group has reported activation of TCA donors utilizing commercially available cationic palladium(II) as the catalyst (Scheme 22). More importantly, this cationic palladium(II) catalyzed glycosylation expressed great stereocontrol, as 1,2-trans glycosides are expected even without anchimeric assistance. Furthermore, this chemistry has effectively coupled a wide scope of donors including glucose (68), mannose (90), and galactose to a variety of acceptors including primary and secondary alcohols, as well as phenols. Although the mechanism of this palladium(II)-catalyzed glycosylation is still unclear, it is believed that the catalyst interacts with both the donor and acceptor.
31

Scheme 22. Cationic palladium(II)-catalyzed stereoselective glycosylation

**Summary**: Begin with BF$_3$·OEt$^{91}$, Lewis acids catalyzed glycosylation has elaborated beyond simple activation of TCA donor. Through observation from the synthesis of glycosyl phosphates$^{92}$, the Schmidt group hypothesized acid-base catalysis and developed several organo-catalysts allowing stereoselective glycosylation.$^{93-94}$ The stereocontrol arises from the formation of a six-membered ring-like complex during the transition state, where the catalyst inserts in the alcohol acceptor leading to simultaneously increased acidity and nucleophilicity of the complexed alcohol. Later, the Nguyen group demonstrated stereocontrol in glycosylation using TCA donors and transition metal catalyst$^{100-102}$, along with the Taylor group presented regiocontrol in glycosylation using a small molecule catalyst.$^{95}$ These successful studies have eventually led to stereocontrol and regiocontrol in glycosylation through the use of one catalyst.$^{96-98}$

1.4.3.2 **From Brønsted acid to chiral acid catalysis (cooperative catalysis)**

Dated back in 1980, Schmidt and coworkers also reported activation of the TCA donor using 20 mol% $p$-toluenesulfonic acid (TsOH).$^{91}$ In this glycosylation, TsOH acts as a Brønsted acid donating a proton to the imidate nitrogen, which promotes the departure of the TCA leaving group, leading to the formation of an oxocarbenium ion (Scheme 23). Due to the lack of C2-neighboring group participation, the stereochemical outcome of the glycosylation was uncontrollable and led to $\alpha:\beta$ at 1:2.
Scheme 23. Brønsted acid-catalyzed glycosylation

Fast forward to thirty years later, the Fairbanks group revisited the Brønsted acid-catalyzed glycosylation and added chirality as an element of diastereocontrol in catalytic glycosylation. Inspired by asymmetric synthesis and activation of TCA leaving group on a non-carbohydrate compound using chiral Brønsted acids as catalysts, the Fairbanks group sought solutions for stereoselective glycosylation in BINOL-derived phosphoric acid catalysis (Table 1). In the glycosylation of galactosyl TCA donor with alcohol acceptor, the chiral BINOL-derived phosphoric acids (entry 2 and 3) catalyzed glycosylation with superior diastereocontrol than TMSOTf (entry 1) and better yield than the achiral diphenyl phosphate (entry 4). In addition, the catalyst configuration significantly affects the diastereoselectivity of the glycosylation, as (S)-catalyzed the glycosylation with \( \beta:\alpha \) ratio of 7:1, while reduced anomeric selectivity was observed with the (R)-enantiomer (\( \beta:\alpha = 2:1 \)).

Table 1. Chiral Brønsted acid-catalyzed glycosylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>( \alpha:\beta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSOTf</td>
<td>98</td>
<td>1.2:1</td>
</tr>
<tr>
<td>2</td>
<td>(S)-94</td>
<td>80</td>
<td>1:7</td>
</tr>
<tr>
<td>3</td>
<td>(R)-94</td>
<td>88</td>
<td>1:2</td>
</tr>
<tr>
<td>4</td>
<td>(PhO)(_2)P(O)OH</td>
<td>19</td>
<td>1:1.9</td>
</tr>
</tbody>
</table>

In 2013, Toshima and coworkers extended the work on chiral phosphoric acid-catalyzed glycosylation further to kinetic resolution of racemic alcohol acceptors (Scheme 24). Taking advantage of the chirality...
on the catalyst, only the alcohol with $R$-configuration was recognized by $(S)$-94. In the glycosylation catalyzed by $(S)$-94, the glucosyl TCA donor 68 and racemic alcohol acceptors 95 lead to coupled glycoconjugate 96 with ($\beta$-$R$)-selectivity. Based on this observation, the Toshima group proposed a cooperative mechanism: while the chiral BINOL-derived phosphoric acid $(S)$-94 plays its role as a Brønsted acid to activate the TCA donor, it also acts as a hydrogen bond acceptor to guide the alcohol acceptor to the anomeric carbon (97). Overall, an $S_N$2 mechanism was proposed to explain the high $\beta$-selective, although the mechanism on the diastereoselectivity remains unknown.

**Scheme 24.** Kinetic resolution in stereoselective glycosylation using chiral Brønsted acid

In 2017, the Nagorny group reported site-selective glycosylation of 6-deoxyerythronolide B acceptor 99 through the selection of chiral phosphoric acids as catalysts (Scheme 25). While SPINOL-based phosphoric acid 100 catalyzes the glycosylation at the C3 position of macrolactone 99, the BINOL-based phosphoric acid 94 prefers to catalyze at the C5 position of 99. In the mechanistic study, covalent glycosyl phosphate intermediates were observed through NMR. While $\beta$-glycosyl phosphate 103 was detected in the 6-deoxy glucosyl substrate 98, $\alpha$-intermediates were found in the D- and L- fucose cases, indicating the formation of glycosyl phosphate intermediate may not always be $S_N$2-like (contrasting Scheme 18a). In addition, the same stereochemical outcomes of glycosylation were observed despite the anomeric compositions of the TCA donor. As the $\beta$-glycosyl phosphate intermediate led to the $\alpha$-glycoside product (vice versa in fucose substrates), it was proposed that the anomeric composition of the glycosyl phosphate intermediate was responsible for the stereochemical outcome of the glycosylation.
Scheme 25. Site-selective glycosylation by the selection of chiral phosphoric acid

Although transition metals are often Lewis acid, some of which could be “hidden Brønsted acids”. In 2019, the Nguyen group conducted a thorough mechanism investigation on nickel(II) triflate (Ni(OTf)$_2$) catalyzed 1,2-cis glycosylation of $N$-phenyl trifluoroacetimidate donor (104), in which experimental evidence pointed toward triflate acid (TfOH) as the active catalyst in the system (Table 2). A correlation was found between the catalytic activity of the metal triflates and their hydrolysis constant ($pK_h$). For metal salts with $pK_h$ less than 10.1, the cationic metals are generally easy to hydrolyze when the anion is weakly coordinating. As such, the catalytic glycosylation proceeded with similar yield and selectivity when Ni(OTf)$_2$ ($pK_h = 9.86$), Zn(OTf)$_2$ ($pK_h = 8.96$), and In(OTf)$_3$ ($pK_h = 4.00$) were used as the catalyst (entry 1-3). On the other hand, AgOTf cannot catalyze glycosylation since the $pK_h$ of Ag(I) is 12 (entry 4). $^{19}$F NMR observation on the mixture of glycosyl donor 104 and Ni(OTf)$_2$ confirmed and quantified the formation of TfOH. In the end, the glycosylation was successfully repeated with only 1 mol% TfOH added to the reaction (entry 5). In the variable temperature NMR study, glycosyl triflate 106 was identified leading to a Curtin-Hammett scenario to explain the high diastereoselectivity of the catalytic glycosylation.
Table 2. Hidden Brønsted acids catalyzed glycosylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>α:β</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni(OTf)₂</td>
<td>90</td>
<td>10:1</td>
</tr>
<tr>
<td>2</td>
<td>Zn(OTf)₂</td>
<td>91</td>
<td>10:1</td>
</tr>
<tr>
<td>3</td>
<td>In(OTf)₂</td>
<td>95</td>
<td>9:1</td>
</tr>
<tr>
<td>4</td>
<td>AgOTf (30 mol%)</td>
<td>&lt;6</td>
<td>n/a</td>
</tr>
<tr>
<td>5</td>
<td>TfOH (1 mol%)</td>
<td>78</td>
<td>10:1</td>
</tr>
</tbody>
</table>

Summary: The ability of Brønsted acid-catalyzed glycosylation has first been shown in 1980, albeit with poor stereoselectivity. Until recently, improved stereoselectivity was observed with chiral Brønsted acid. Although the role of chirality in stereocontrol remains unclear, the ability of kinetic resolution during glycosylation is presented. Further NMR observation of glycosyl phosphate intermediate suggested the stereocontrol of the chiral Brønsted acid-catalyzed glycosylation arises from the anomeric composition of the intermediate. Besides the aforementioned chiral Brønsted acids, some metal triflates are considered “hidden Brønsted acid”, where TfOH is the active catalyst in the metal-catalyzed glycosylation system. Although the mechanism of diastereocontrol with TfOH in catalyzing glycosylation remains unresolved, a Curtin-Hammett scenario is generally accepted.

1.4.3.3 From thiourea to bis-thiourea catalysis (cooperative catalysis)

Similar to phosphoric acid, thiourea is also an important class of small molecule that has successfully catalyzed a variety of asymmetric chemical transformations. The utilization of thiourea as a catalyst in glycosylation was first reported by McGarrigle and coworkers in 2012 (Scheme 26). Inspired by Kotke and Schreiner’s acetalization, McGarrigle and coworkers applied the Schreiner’s thiourea catalyst to the synthesis of 2-deoxy galactoside through the coupling of galactal and alcohol. Under the influence of 1 mol% thiourea, the alkyl and silyl ether protected galactals react with a variety of primary and
secondary glycosyl alcohols in *syn* fashion, leading to the formation of α-2-deoxygalactosides as the products. The originally proposed mechanism involved the formation of an alcohol-thiourea complex (110) through double hydrogen bonding, where the thiourea catalyst 108 acted as the hydrogen bond donor. Yet, the subsequent mechanistic study in 2019 revealed that the thiourea catalyst played a role as Brønsted acid in glycosylation of galactal donor and alcohol acceptor (111).  

![Scheme 26. Schreiner's thiourea catalyzed 2-deoxy galactoside synthesis](image)

Using thiourea derivative as a Brønsted acid in catalyzing glycosylation was reported before 2019. In 2016, Toshima and coworkers envisioned the conjugate base of aryl thiourea (nitrogen anion) should be rather stable due to the resonance effect, which translated into increased acidity of aryl thiourea upon photoirradiation. As such, the group demonstrated the use of Schreiner’s thiourea catalyst 108 as an organo photoacid in catalyzing glycosylation with glycosyl TCA donor (Scheme 27). Upon irradiation at 365 nm, a proton (H⁺) was released from the excited thiourea 108⁺ and activated the glycosyl TCA donor. Additionally, the Toshima group discovered that this photoinduced catalytic glycosylation proceeded with β-selectivity at high reaction concentration (1-2 M), indicating the reaction underwent an *S*₂*₅*-type mechanism. Conversely, an *S*₁*-type mechanism was expected at low reaction concentration, which led to
α-selectivity in the stereochemical outcome. As expected, the photoinduced catalytic glycosylation proceeded with α-selectivity at 0.005-0.1 M.

Scheme 27. Schreiner's thiourea catalyst as an organo photoacid in catalytic glycosylation

On the other hand, thiourea derivatives as hydrogen bond donors have proven to activate halogenated compounds. In 2016, Ye and coworkers attempted to activate perbenzylated glucosyl chloride utilizing thiourea as a catalyst (Table 3). However, a diminished yield was collected when using a catalytic amount of thiourea, where 10 mol% catalyst loading led to an 11% yield (entry 1). In addition, the S-glycosylated byproduct was isolated in all reactions with thiourea. The urea-derived catalyst was used to avoid this side reaction and led to an excellent yield (95%), albeit poor stereoselective (α:β = 1:1, entry 2). However, this catalytic reaction with galactosyl, mannosyl, rhamnosyl, and glucosaminyl donor proceeded with high α-selectivity. To solve the stereoselectivity issue with the glucose substrate, a phosphine additive was added to the catalytic reaction, and the anomeric selectivity improved to 12.6:1 α/β (entry 3). NMR mechanistic study revealed that the glycosyl chloride was activated by urea through a dual hydrogen bonding as the chemical shift of the urea protons shifted upfield upon mixing with glycosyl chloride. Although the function of phosphine additive is still unclear, a complex of glycosyl chloride with both catalyst and additive was indicated based on the NMR study.
In 2017, the Jacobsen group designed a dimeric, macrocyclic thiourea catalyst to promote stereospecific glycosylation with glycosyl chlorides (Scheme 28).\textsuperscript{120} Aiming to catalyze glycosylation in an S$_{N}$2 pathway, cooperative activation of both glycosyl donor and acceptor through a catalyst was pursued. The cyclic design of bis-thiourea 116 weakens the C-Cl bond through quadruple hydrogen bonding. Meanwhile, the Lewis base interaction between the alcohol acceptors and the indoline amides adjacent to the thiourea increases the acceptors’ nucleophilicity (117). More importantly, the C$_2$ symmetric design of 116 not only simplifies the catalyst synthesis but also allows the alcohol nucleophile to approach the anomeric carbon at a broader angle. As such, both enantiomers of 116 expressed similar reactivity and diastereoselectivity in glycosylation. Through simultaneous activation of $\alpha$-glycosyl chloride and alcohol acceptors, the Jacobsen group has successfully demonstrated the synthesis of trans-1,2-$\alpha$, cis-1,2-$\alpha$, and 2-deoxy-$\beta$-glycosides in good yield and high stereoselectivity using bis-thiourea catalyst 116.

Table 3. Urea-catalyzed stereoselective glycosylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>108</td>
<td>-</td>
<td>11-85%</td>
</tr>
<tr>
<td></td>
<td>(10-100 mol%)</td>
<td></td>
<td>$\alpha:\beta = 1:1$</td>
</tr>
<tr>
<td>2</td>
<td>113</td>
<td>-</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>(20 mol%)</td>
<td></td>
<td>$\alpha:\beta = 1:1$</td>
</tr>
<tr>
<td>3</td>
<td>113</td>
<td>114</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td>(20 mol%)</td>
<td>(1.5 equiv.)</td>
<td>$\alpha:\beta = 12.6:1$</td>
</tr>
</tbody>
</table>
Besides glycosyl chlorides, the Jacobsen group later designed another bis-thiourea catalyst enabling the activation of glycosyl phosphates (Scheme 29).[121-122] Since the phosphate leaving group exhibited a stronger Lewis basic character than the chloride, a quadruple hydrogen bonding is no longer needed. As such, the new catalyst 118 adopted a linear design to accommodate the spatial need of the phosphate leaving group. Kinetic study showed a 16-fold improvement in catalytic efficiency when using glycosyl phosphate as the donor compare to that of glycosyl chloride. In addition, since the thiourea catalyst 118 binds stronger to the phosphate leaving group, a larger scope of nucleophiles, including thiol and phenol, can be used in the reaction.

**Scheme 28.** Macrocyclic bis-thiourea catalyzed stereospecific glycosylation

**Summary:** While thiourea derivatives are commonly known as dual hydrogen bond donors, they can serve a role as Brønsted acids, such as activation of galactal using Schreiner’s thiourea catalyst.[114] Upon
photo-irradiation, the Schreiner’s thiourea catalyst becomes more acidic, which is capable of activating the TCA donor. Certainly, the Schreiner’s thiourea/urea catalysts serving as dual hydrogen bond donors enable activation of glycosyl chlorides, although the diastereoselective depends on the nature of substrates or additives in the reaction. In the end, Jacobsen’s bis-thiourea catalyst demonstrated simultaneous activation of glycosyl donor and nucleophilic displacement, leading to stereospecific glycosylation.

1.5 Main objectives

1.5.1. Inspiration and hypothesis

It has been reported that enzymatic glycosylation undergoes an S_N2 pathway. While inverting glycosyltransferases (GTs) proceed a direct S_N2 displacement to provide the products with inversion of anomeric configuration, the retaining GTs proceed a double S_N2 mechanism to generate the products with net retention of anomeric stereochemistry (Scheme 30). The nucleophilic residue of the retaining glycosyltransferase reacts with \( \alpha \)-glycosyl phosphate to generate a covalent \( \beta \)-glycosyl-enzyme intermediate with inversion of stereochemistry. Inverted substitution by a nucleophile affords the corresponding \( \alpha \)-glycoside product with net retention of anomeric stereochemistry.

**Scheme 30.** Retaining glycosyltransferases-catalyzed stereoretentive glycosylation

Hypothesis: Inspired by the effectiveness of retaining GTs, it is envisioned that a small molecule catalyst capable of acting like GTs to provide 1,2-cis glycosides, via a double S_N2 displacement with predictable \( \alpha \)-selectivity and in high yields, would likely find broad applications.

It was first reported by Lemieux and Morgan that pyridine could serve as a nucleophile to displace the anomeric leaving group to afford a glycosyl pyridinium complex. To minimize the steric and electrostatic interactions, the pyridinium ion intermediate prefers to position at the equatorial face on the
glycosyl electrophile. The nucleophilic attack is more likely to take place at the axial position of the pyridinium ion complex to provide an axial (α) glycosidic bond. However, pyridine is not bulky enough to form an exclusively equatorial intermediate. As an axial glycosyl pyridinium intermediate could also be generated in the reaction, the stereoselectivity of the coupling product would be detrimentally affected. To overcome this inherent problem, we sought to identify a catalyst that would be able to form an exclusively equatorial intermediate.

The commercially available pyridine-like compound, phenanthroline, appealed to us with great interest. As demonstrated in Scheme 31, it is hypothesized that the first nitrogen atom of phenanthroline (Phen) could serve as the nucleophile to displace the anomeric bromide leaving group, generating a covalent β-glycosyl phenanthrolinium intermediate. Meanwhile, the two fused pyridine rings of phenanthroline could sterically prevent the formation of α-glycosyl phenanthrolinium intermediate. In addition, the second nitrogen could cooperate to promote glycosylation, either by directing the alcohol nucleophile to α-face or non-covalently interacting with the carbohydrate moiety. All these advantages of phenanthroline have driven us to explore its ability as the catalyst to promote the reactions that afford high-yielding 1,2-cis products with predictable stereoselectivity.

**Scheme 31.** Phenanthroline-catalyzed α-1,2-cis-glycosylation
1.5.2. Preliminary results and continuation

The initial investigation was performed by Dr. Fei Yu utilizing α-glycosyl bromide 1 as the model electrophile and 1,2:3,4-di-O-isoprolyiene-α-D-galactopyranose (3) as the nucleophile to afford the disaccharide 4. After a series of catalyst screening and reaction optimization, use of 15 mol% bathophenanthroline (BPhen) and 2 equivalent of isobutylene oxide (IBO) as an acid scavenger of hydrogen bromide (HBr) in tert-butyl methyl ether (MTBE) at 50 °C for 24 h were found to be the most effective at promoting the reaction (Table 4, entry 1, 4: 73% yield, α:β > 20:1)[126]. However, when the reaction temperature decreased to 25 °C (room temperature), the glycosylation did not proceed (Table 4, entry 2). It has been determined that the protecting groups on glycosyl electrophile and nucleophiles could affect the efficiency and selectivity of the coupling product[64, 73]. As such, 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl bromide (2, entries 3 and 4), which is to promote glycosylation via the S_N1 pathway, was then explored as part of my Ph.D. work. As expected, under standard conditions at 50 °C, the glycosylation proceeded to provide 82% yield of the disaccharide 5 with reduced α-selectivity (α:β = 6:1, entry 3). This result suggested that the S_N1-S_N2 reaction paradigm was slightly shifted. On the other hand, when the reaction was conducted at room temperature (entry 4), the coupling product was obtained with excellent

| Table 4. Bathophenanthroline-catalyzed 1,2-cis glycosylation[^a] |
|---|---|---|
| entry | R | Temp. (°C) | yield[^b] (α:β)[^c] |
| 1* | Ac | 50 | 73% (>20:1) |
| 2* | Ac | 25 | - |
| 3 | Bn | 50 | 82% (6:1) |
| 4 | Bn | 25 | 55% (16:1) |

[^a] All reactions were conducted with 0.1 mmol glycosyl bromide and 0.2 mmol glycosyl accepter.[^b] Yield of isolated products.[^c] Diastereoselectivity (α:β) was determined by 1H NMR.[^d] Result from Dr. Fei Yu.
selectivity ($\alpha$:$\beta = 16:1$) albeit in lower yield (55%). The high selectivity with tetrabenzyglycosyl substrate indicates that the ability of the catalyst overrides the inherent substrate’s selectivity preference. The coupling of glycosyl nucleophile 3 with electrophilic partner 2 to yield the disaccharide 5 was later optimized to 95% yield by using 20 mol% of BPhen catalyst.\textsuperscript{126}

1.5.3. Major Goals

My graduate works have mainly focused on exploring the phenanthroline catalysis system. The first part was to investigate the utility of BPhen on electron-rich glycosyl donors. As the $S_N1$-$S_N2$ reaction paradigm shifts toward the $S_N1$ direction with the electron-rich substrates, a more practical catalyst was highly desirable. This has led to the second part of the study: identify an efficient catalyst within and beyond the phenanthroline framework allowing stereoselective glycosylation in a shorter time with the electron-rich electrophilic donors. The successful identification of an efficient catalyst led to the expansion of substrate scope. Chapter 2 of this dissertation contains substrate scope and catalyst screening. Another main focus of the exploration was to investigate the mechanism of the phenanthroline catalytic system (Chapter 3), which includes kinetic studies, NMR studies, and computational studies.

Furanoses are more prone to proceed at the $S_N1$-$S_N2$ boundary than their pyranose counterparts due to their conformational flexibility and electronic properties.\textsuperscript{127} As Dr. Hengfu Xu explored the stereoselective 1,2-cis furanosylation method promoted by phenanthroline catalyst, the mechanism was unclear. The last part of my dissertation is focused on the mechanistic study of phenanthroline-catalyzed stereoselective 1,2-cis furanosylation (Chapter 4).
CHAPTER 2: SCOPE OF PHENANTHROLINE-CATALYZED 1,2-CIS PYRANOSYLATION

2.1 First generation phenanthroline catalysis

Several underlying factors potentially influence the efficiency and the selectivity of the glycosylated products, including the protecting group nature of glycosyl electrophiles, the reactivity of nucleophiles, and the reaction conditions. To explore the utility of this phenanthroline catalysis system on electron-rich donor substrates, a series of glycosylation were performed to prepare a variety of disaccharides and glycoconjugate (Table 5). For example, while AgBF$_4$ promoted glycosylation provided the disaccharide 6 with $\alpha$:$\beta$ ratio of 2.4:1$^{129}$, or TMSOTf-mediated coupling with trichloroacetimidate electrophiles provided 6 with marginal a selectivity ($\alpha$:$\beta$ = 1:1.2-4:1)$^{130}$, our catalysis system generated the coupling product 6 with $\alpha$:$\beta$ = 14:1. Extremely hindered secondary alcohol nucleophile is also amendable to provide the disaccharide 7 with good selectivity ($\alpha$:$\beta$ = 7:1), for which the $S_N1$-$S_N2$ reaction paradigm was slightly shifted.

In addition to glucosyl electrophile 2, a number of different sugar substrates were adapted into glycosyl bromide electrophiles to prepare disaccharides 8 – 11 and glycoconjugate 12. It has been reported that D-galactose favors $\beta$-product compared to D-glucose.$^{131}$ Nevertheless, phenanthroline-catalyzed glycosylation with galactosyl bromide produced disaccharide 8 with excellent $\alpha$-selectivity ($\alpha$:$\beta$ = 10:1). In contrast, the amide-promoted reaction provided 8 with $\alpha$:$\beta$ = 3:1.$^{132}$ In addition, the phenanthroline catalysis system produces disaccharide 9 with excellent diastereoselectivity ($\alpha$ only).

Arabinose is a more challenging substrate due to its lability with electron-rich protecting groups. Use of D- or L-tribenzyl arabinosyl bromide in the phenanthroline catalyzed glycosylation reaction provides disaccharide 10 or 11 with excellent diastereoselectivity ($\alpha$:$\beta$ = 9:1 and $\alpha$ only, respectively), albeit with low yield (<50%) due to decomposition of the arabinosyl bromide during the reaction. The yield could be improved with the use of acetyl protecting groups (10$: 83\%$, 11$: 84\%). Similarly, while tribenzyl L-
fucosyl bromide afforded 12 with $\alpha:\beta = 6:1$, the use of triacetyl L-fucosyl bromide provided exclusively $\alpha$-isomer 12'. Both 12 and 12' are key units of a thrombospondin type 1 compound associated with an autosomal recessive disorder.\textsuperscript{133}

Table 5. Bathophenanthroline-catalyzed 1,2-cis glycosylation with electron-rich substrates\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Glycosyl Donor</th>
<th>Nucleophile</th>
<th>Catalyst</th>
<th>Yields</th>
<th>Diastereoselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Glucose</td>
<td>R-OH</td>
<td>BPhen (20 mol%)</td>
<td>63%\textsuperscript{b}</td>
<td>$\alpha:\beta = 14:1$</td>
</tr>
<tr>
<td>D-Arabinose</td>
<td>RO</td>
<td>BPhen (20 mol%)</td>
<td>49%\textsuperscript{b}</td>
<td>$\alpha:\beta = 9:1$</td>
</tr>
<tr>
<td>L-Arabinose</td>
<td>RO</td>
<td>BPhen (20 mol%)</td>
<td>47%\textsuperscript{b}</td>
<td>$\alpha:\beta = 9:1$</td>
</tr>
<tr>
<td>L-Fucose</td>
<td>RO</td>
<td>BPhen (20 mol%)</td>
<td>80%\textsuperscript{b}</td>
<td>$\alpha:\beta = 6:1$</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} All reactions were conducted with 0.1-0.3 mmol glycosyl bromide. Yields of isolated products. Diastereoselectivity ($\alpha:\beta$) was determined by $^1$H NMR analysis. \textsuperscript{[b]} 20 mol% BPhen at 25 °C. \textsuperscript{[c]} 20 mol% BPhen at 50 °C. * Result from Dr. Fei Yu, 15-30 mol% BPhen at 50 °C for 24-48 h.

2.2 Second generation phenanthroline catalyst

2.2.1. Development of a new class of phenanthroline catalyst

To improve the practicality of this glycosylation on electron-rich substrates, we sought to re-screen the commercially available catalyst with the reactive donors. (Table 6). We selected 2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranosyl bromide (2) as an electrophilic donor and 1,2:3,4-di-O-isopropyldiene-$\alpha$-D-galactopyranoside (3) as the nucleophilic model coupling partners in catalyst screening because they are the most reactive coupling partners.\textsuperscript{126} Previously, we reported the reaction of glycosyl bromide 2 and hydroxyl nucleophile 2 with 20 mol% 4,7-diphenyl-1,10-phenanthroline (C1 or BPhen) catalyst in the
presence of IBO as an acid scavenger in MTBE at 25 °C for 24 h yielded disaccharide 5 (95%) with outstanding diastereoselectivity ($\alpha:\beta = 15:1$). This effective glycosylation model was adapted in this investigation. To distinguish the reactivity of different catalysts, we decreased the catalyst loading to 15 mol% and kept the reaction time at 24 h.

In the absence of the catalyst, only a trace amount of the product was detected (entry 1), and 98% of starting material 3 was recovered. As for the phenanthroline derivatives (C₁ – C₅), we first investigated how the electronic nature of the substituents on the catalyst would vary the reaction outcome. Interestingly, use of the non-substituted 1,10-phenanthroline (C₂, entry 3) delivered comparable yield (54% vs 55%) and selectivity ($\alpha:\beta = 18:1$ vs $16:1$) as 4,7-diphenyl-1,10-phenanthroline (C₁, entry 2). However, with Dr. Yu’s triacetate substrate, the yields of the coupling product with the use of catalysts C₁ and C₂ differed by 20% (73% and 53% yield respectively), while the selectivity was comparable ($\alpha:\beta > 20:1$). This is probably due to the electron-rich nature of the tetrabenzyl glycosyl electrophile overcomes the marginal difference in nucleophilicity of the catalyst. Therefore, when we utilized bromine as a substituent on the para-position of the catalyst C₃ (entry 4), the yield was not affected. The methoxy group is known as an electron-donating substituent; however, the use of 4,7-dimethoxy-1,10-phenanthroline (C₄, entry 5) did not further improve the yield of the disaccharide 5. This might be due to the inductive effect of the oxygen atom that decreases the nucleophilicity of the catalyst. As such, the electron-rich tetramethyl substituted phenanthroline was used (C₅, entry 6), and the glycosylation proceeded with a significantly higher yield (76%) than those with other phenanthroline derivatives (54 – 58%).

Furthermore, we investigated the necessity of the phenanthroline framework on coupling efficiency and selectivity (Table 6, entry 7-13). The performance with the non-phenanthroline-based catalysts varied in the glycosylation. For example, when we free the two nitrogen from the planar configuration by using 2,2’-bipyridine type catalyst (C₆ and C₇), the yield and selectivity reduced significantly (entries 7 and 8) compared to C₁ (entry 2). Similarly, increasing the number of pyridines on the catalyst (C₈, entry 9) did not improve the yield or selectivity (23% yield, $\alpha:\beta = 8:1$). Meanwhile, maintaining the planar structure of
the catalyst preserved the glycosylation outcome. In the case of 4,5-diazafluoren-9-one as the catalyst (C9, entry 10), the yield of the glycosylation is similar to that of C2, albeit with lower α-selectivity, which is likely due to the change in the distance and angle between the two nitrogen on the catalyst.

**Table 6.** Catalyst screening with electron-rich electrophile

<table>
<thead>
<tr>
<th>entry</th>
<th>Catalyst</th>
<th>yield (%)</th>
<th>α:β</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>Trace</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>C1</td>
<td>55</td>
<td>16:1</td>
</tr>
<tr>
<td>3</td>
<td>C2</td>
<td>54</td>
<td>18:1</td>
</tr>
<tr>
<td>4</td>
<td>C3</td>
<td>58</td>
<td>10:1</td>
</tr>
<tr>
<td>5</td>
<td>C4</td>
<td>56</td>
<td>10:1</td>
</tr>
<tr>
<td>6</td>
<td>C5</td>
<td>76</td>
<td>10:1</td>
</tr>
<tr>
<td>7</td>
<td>C6</td>
<td>24</td>
<td>10:1</td>
</tr>
<tr>
<td>8</td>
<td>C7</td>
<td>33</td>
<td>9:1</td>
</tr>
<tr>
<td>9</td>
<td>C8</td>
<td>23</td>
<td>8:1</td>
</tr>
<tr>
<td>10</td>
<td>C9</td>
<td>50</td>
<td>13:1</td>
</tr>
<tr>
<td>11</td>
<td>C10</td>
<td>43</td>
<td>12:1</td>
</tr>
<tr>
<td>12</td>
<td>C11</td>
<td>73</td>
<td>14:1</td>
</tr>
<tr>
<td>13</td>
<td>C12</td>
<td>93</td>
<td>11:1</td>
</tr>
</tbody>
</table>

[a] All reactions were conducted with 0.2 mmol glycosyl bromide 2 and 0.1 mmol glycosyl acceptor 3. [b] Yields of isolated products. [c] Diastereoselectivity (α:β) was determined by 1H NMR analysis.

In addition, 5-membered fused rings were also of interest. Similar to the bi- or tri-pyridine catalysts, the imidazole substituted pyridine catalyst (C10, entry 11) did not proceed to completion. Since the tertiary amine is more nucleophilic than pyridine, we attempted N,N,N',N'-tetramethylethylenediamine (TMEDA, C11) bearing two tertiary amine groups (entry 12). The yield of TMEDA-catalyzed glycosylation increased as expected; however, the reaction did not proceed to completion after 24 hours. In the end, we anticipated that dimethylamino substituents on the para-position would drastically improve the glycosylation outcome.
As expected, the use of 4-(dimethylamino)pyridine (DMAP, **C12**) provided the desired disaccharide **5** in 93% yield (entry 13) with good α-selectivity (α:β = 11:1) in 24 h. This result led to further design on the phenanthroline catalyst.

To further improve the catalyst performance, the dimethylamino substituents were installed onto the phenanthroline framework (**C13**, Table 7). Catalyst **C13** was prepared over 2 steps from commercially available 4,7-dihydroxy-1,10-phenanthroline. First, treatment of dihydroxyl phenanthroline with phosphorus oxychloride (POCl₃) at 60 °C for 2 h allowed functional group interconversion to produce the 4,7-dichloro-1,10-phenanthroline. After removal of excess POCl₃, the dichlorophenanthroline was then treated with N,N-dimethylformamide (DMF) at 160 °C for 60 h to afford catalyst **C13**.

**Table 7. Catalyst development in phenanthroline framework**[a]

<table>
<thead>
<tr>
<th>entry</th>
<th>Catalyst</th>
<th>yield (%)[^b]</th>
<th>α:β[^c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>C1</strong></td>
<td>40</td>
<td>13:1</td>
</tr>
<tr>
<td>2</td>
<td><strong>C12</strong></td>
<td>63</td>
<td>11:1</td>
</tr>
<tr>
<td>3</td>
<td><strong>C13</strong></td>
<td>61</td>
<td>15:1</td>
</tr>
<tr>
<td>4</td>
<td><strong>C14</strong></td>
<td>67</td>
<td>12:1</td>
</tr>
</tbody>
</table>

[^a]: All reactions were conducted with 0.2 mmol glycosyl bromide **2** and 0.1 mmol glycosyl acceptor **3**.  
[^b]: Yields of isolated products.  
[^c]: Diastereoselectivity (α:β) was determined by ¹H NMR analysis.
To distinguish the efficiency of the catalysts, the reaction time was reduced to 5 h. As illustrated in Table 7, the glycosylation catalyzed by BPhen (C1) only proceeded with a 40% yield of disaccharide 5 at 5 h, while DMAP (C12) catalyzed the glycosylation with 63% yield. Expectedly, the glycosylation catalyzed by catalyst C13 (entry 3) is more efficient than C1 (BPhen, entry 1) and C12 (DMAP, entry 2), as the yield of glycosylation with C13 is higher than that with BPhen (61% vs 40%), and the diastereoccontrol is better than DMAP (15:1 vs 11:1). However, catalyst C13 is not suitable in the synthesis of 2-deoxy-2-fluoro glycoside, as only a trace amount of disaccharide was observed in the reaction. This is likely due to competition of the dimethylamine in the reaction leading to many side products. As such, the sterically hindered piperidine substituents (C14) were installed to replace the dimethylamino substituents (C13). Gratifyingly, catalyst C14 promoted glycosylation of 2-deoxy-2-fluoro-glycosyl electrophile with high yield and excellent levels of diastereoselectivity, and the effectiveness of C14 with the electron-rich glycosyl electrophile remains remarkable (entry 4, 67% yield, α:β = 12:1).

2.2.2. Influence of phenanthroline catalyst

Next, we evaluated the electronic and structural effects of phenanthroline (Table 8). Use of C1 provided disaccharide 3 in 40% yield with α:β = 13:1 (entry 1). Meanwhile, the use of C14 provided 3 in higher high yield due to the electron-donating para-piperidine substituents increasing the nucleophilicity of the catalyst (67%, entry 3). In contrast, electron-withdrawing para-bromide substituted phenanthroline C3 reduced glycosylation reactivity, providing 9% of the desired disaccharide 3 (entry 6). Predictably, the non-substituted phenanthroline C2 yielded slightly less product compared to C1 (35% vs. 40%, entry 5 vs. 1). We next evaluated the mono-piperidine substituted phenanthroline C15, and a reduced yield (24%, entry 7) was obtained in comparison to the symmetrical catalysts C14 (entry 3) and C2 (entry 5), confirming the C2-symmetry of phenanthroline plays a critical role in glycosylation reactivity. Benzo[h]quinoline (C16, entry 8) catalyst containing only one pyridine ring is less reactive and α-selective compared with the two fused pyridine C2 catalyst (entry 5), suggesting the importance of the second nitrogen atom on the phenanthroline framework. Further exploration revealed that replacement of IBO with 2,6-di-tert-butyl-4-
methyldipyridine (DTBMP) as acid scavenger resulted in improved $\alpha$-selectivity while maintaining comparable yield (entries 2 and 4 vs 1 and 3). We rationalized that utilizing DTBMP as an acid scavenger would preserve bromide ion in the reaction, which further facilitates the equilibrium between the glycosyl phenanthroline ion intermediate and the $\alpha$-glycosyl bromide (Scheme 31).\textsuperscript{134}

**Table 8. Influence of phenanthroline catalyst\textsuperscript{[a]}**

<table>
<thead>
<tr>
<th>entry</th>
<th>Catalyst</th>
<th>Scavenger</th>
<th>yield\textsuperscript{[b]} ($\alpha$:\textsuperscript{[c]}$\beta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C1</td>
<td>IBO</td>
<td>40% (13:1)</td>
</tr>
<tr>
<td>2</td>
<td>C1</td>
<td>DTBMP</td>
<td>31% (19:1)</td>
</tr>
<tr>
<td>3</td>
<td>C14</td>
<td>IBO</td>
<td>67% (12:1)</td>
</tr>
<tr>
<td>4</td>
<td>C14</td>
<td>DTBMP</td>
<td>63% (14:1)</td>
</tr>
<tr>
<td>5</td>
<td>C2</td>
<td>IBO</td>
<td>35% (14:1)</td>
</tr>
<tr>
<td>6</td>
<td>C3</td>
<td>IBO</td>
<td>9% (10:1)</td>
</tr>
<tr>
<td>7</td>
<td>C15</td>
<td>IBO</td>
<td>24% (13:1)</td>
</tr>
<tr>
<td>8</td>
<td>C16</td>
<td>IBO</td>
<td>6% (5:1)</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} All reactions were conducted with 0.2 mmol glycosyl bromide 2 and 0.1 mmol glycosyl acceptor 3. \textsuperscript{[b]} Yields of isolated products. \textsuperscript{[c]} Diastereoselectivity ($\alpha$:\textsuperscript{[c]}$\beta$) was determined by $^1$H NMR analysis.
Overall, we have identified that increasing nucleophilicity on phenanthroline facilitates the glycosylation reaction, as well as the critical role of the symmetrical phenanthroline framework in catalyzing glycosylation.

2.3. Reaction scope with phenanthroline catalysis

2.3.1. Stereoselective glycosylation and limitation

Previously, we focused on 4,7-diphenyl-1,10-phenanthroline (C1)-catalyzed glycosylation reactions with electron-withdrawing glycosyl bromides, providing \( \alpha-1,2-cis \) products in good yield with high levels of \( \alpha \)-selectivity (Section 2.1).\(^{126} \) This C1 catalyst, however, is not effective at promoting the glycosylation of the highly hindered C4-hydroxyls of D-glucoside and L-rhamnoside acceptors \( 16 - 18 \) (Table 9) with electron-donating glycosyl bromide donors. For instance, coupling of \( 16 \) with 2,3,4,6-tetra-O-benzyl-\( \alpha \)-D-glucosyl bromide 2, under the influence of C1, provided disaccharide 7 in 55% yield with moderate \( \alpha \)-selectivity (\( \alpha:\beta = 7:1 \), entry 1).\(^{126} \) This result suggests that the \( S_N1-S_N2 \) reaction paradigm is slightly shifted in the presence of the hindered alcohol 16. The use of DTBMP as an acid scavenger led to a slight increase in yield (55%→71%) and \( \alpha \)-selectivity (7:1→10:1) in favor of \( \alpha-1,2-cis \) glycoside 7. The use of C14 as the catalyst maintained the yield and diastereoselectivity (entry 1). Although the \( \alpha/\beta \) selectivity of the resulting disaccharide 7 was determined by the standard \( ^1H \) NMR analysis, it can be challenging due to the overlap of the anomeric protons with the benzyl protons. This issue was overcome by introducing the 4-fluorobenzyl group onto C6 of glucoside acceptor 17, wherein the \( \alpha/\beta \) selectivity of the resulting disaccharide 22 was determined using \( ^{19}F \) NMR (entry 2).\(^{135} \) The ArF-resonance of \( \alpha \)-isomer 22 appeared at \( \delta_F = -115.07 \) ppm while \( \beta \)-isomer counterpart appeared at \( \delta_F = -114.49 \) ppm. The diastereoselectivity of product 22 through coupling of 17 with glucosyl bromide 2 was significantly improved using C14 catalyst (10:1→20:1, entry 2). Notably, when we coupled galactosyl bromide 13 to C4-hydroxyl nucleophile 17 under the influence of both C1 and C14 catalysts, the yield of the coupling product 23 increased while \( \alpha \)-selectivity remained excellent compared to glucosyl bromide 2 (entry 3). Again, the C14 catalyst is more \( \alpha \)-selective than the C1 catalyst.
Table 9. Stereoselective glycosylation using C1 and C14 catalyst \[^{[a]}\]

<table>
<thead>
<tr>
<th>entry</th>
<th>Donors</th>
<th>Acceptors</th>
<th>Products</th>
<th>C1 Catalyst</th>
<th>C14 Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IBO, 50 °C[^{[b]}]</td>
<td>DTBMP, 50 °C[^{[b]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55% (α:β = 7:1)</td>
<td>54% (α:β = 10:1)</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>16: R = Bn; 17: R = 4-F-Bn</td>
<td>7: R = Bn</td>
<td>DTBMP, 50 °C[^{[b]}]</td>
<td>DTBMP, 50 °C[^{[b]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>71% (α:β = 10:1)</td>
<td>72% (α:β = 20:1)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>17</td>
<td>22: R = 4-F-Bn</td>
<td>DTBMP, 50 °C[^{[b]}]</td>
<td>DTBMP, 50 °C[^{[b]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>79% (α:β = 10:1)</td>
<td>72% (α:β = 20:1)</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>17</td>
<td>23: R = 4-F-Bn</td>
<td>IBO, 50 °C[^{[c]}]</td>
<td>DTBMP, 50 °C[^{[c]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92% (α:β = 11:1)</td>
<td>90% (α:β = 13:1)</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>16</td>
<td>18</td>
<td>DTBMP, 25 °C[^{[d]}]</td>
<td>DTBMP, 25 °C[^{[d]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>37% (α:β = 5:1)</td>
<td>46% (α:β = 12:1)</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>19</td>
<td>12</td>
<td>IBO, 25 °C[^{[e]}]</td>
<td>DTBMP, 25 °C[^{[e]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80% (α:β = 6:1)</td>
<td>99% (α:β = 11:1)</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>20 (R = Bn)</td>
<td>6 (R = Bn)</td>
<td>DTBMP, 25 °C[^{[f]}]</td>
<td>DTBMP, 25 °C[^{[f]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90% (α:β = 8:1)</td>
<td>98% (α:β = 16:1)</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>21 (R = Bz)</td>
<td>25 (R = Bz)</td>
<td>DTBMP, 25 °C[^{[f]}]</td>
<td>DTBMP, 25 °C[^{[f]}]</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>16</td>
<td>26</td>
<td>IBO, 50 °C[^{[g]}]</td>
<td>DTBMP, 50 °C[^{[g]}]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11% (α:β = 5:1)</td>
<td>27% (α:β &gt; 20:1)</td>
</tr>
</tbody>
</table>

\[^{[a]}\] All reactions were conducted with glycosyl bromide (0.2 mmol) and glycosyl acceptor (0.1 mmol) in MTBE (0.5 M). \[^{[b]}\] Reaction complete at 24 h. \[^{[c]}\] Reaction was allowed to stir for 48 h. \[^{[d]}\] Yields of isolated products. \[^{[e]}\] Diastereoselectivity (α:β) was determined either by \(^1\)H or \(^19\)F NMR analysis. \[^{[f]}\] Reaction was run in CH\(_2\)Cl\(_2\).
Next, we examined the glycosylation of challenging C4-hydroxyl rhamnose acceptor 18 with L-fucosyl bromide 14 (Table 9, entry 4). Under the influence of C1 catalysts, the coupling product 24 (entry 4) was obtained in moderate α-selectivity (α:β = 5:1). The diastereoselectivity of disaccharide 24 significantly improved (5:1 → 12:1) with the use of C14 catalyst. An important consequence of C14 catalyst is its effectiveness with many different coupling partners. For example, C1-catalyzed glycosylation of serine residue 19 with fucosyl bromide 14 provided glycoconjugate 12 with moderate α-selectivity (α:β = 6:1, entry 5). In contrast, the use of C14 in the analogous reaction substantially increased in selectivity from 6:1 to 11:1 in favor of α-1,2-cis glycoside 12. We also noted that C14 catalyst is more selective with electron-withdrawing acceptor 21 (α:β = 16:1, entry 7) than with electron-donating acceptor 20 (α:β = 8:1, entry 6). We rationalized that the less reactive nucleophile 21 allows the equilibrium of the reactive glycosyl intermediates shifts toward β-glycosyl phenanthrolinium ion, further enhancing the diastereoselectivity of the final product 25. Unfortunately, the phenanthroline system proved to be less robust with the combination of highly unreactive donor 15 and highly hindered C4-hydroxyl acceptor 16 (entry 8). Although C14 was found more efficient to promote the coupling of 16 with 15 than that of C1, the glycosylated product 26 was isolated in only 27% yield, albeit with excellent levels of α-selectivity (α:β > 20:1).

2.3.2. Site-selective glycosylation

Next, we sought to evaluate the performance of functionally complex nucleophiles under C14-catalyzed site-selective reaction (Scheme 32). Dexamethasone 26, bearing a variety of functional groups and three hydroxyls, is an anti-inflammatory and immunosuppressive corticosteroid that has been used as the drug to treat severe COVID-19 patients.136-137 Although there are three potential coupling sites in dexamethasone 26, we hypothesized that a primary hydroxyl would be the preferred site. As expected, a 58% yield of the coupling product 27 was obtained with high α-diastereoselectivity (α:β = 10:1) and complete site-selectivity (Scheme 32A) when C14 was applied to the glycosylation of 26 with glucosyl bromide 2. Estriol 28, bearing three hydroxyl groups at the C3, C16, and C17 positions, was then evaluated to furnish a 6:1 mixture of regioisomers 29 and 30 (Scheme 32B) in 60% yield with almost
exclusive \( \alpha \)-selectivity. In this reaction, the C16-hydroxyl is the preferred site for glycosylation forming 29 as a major product while the more hindered C17-hydroxyl site afforded minor product 30. Importantly, the glycosylation at the C3-phenol site was not observed in the reaction, suggesting that an alkyl hydroxyl can be site-selectively coupled in the presence of a phenol nucleophile. These results demonstrate the applicability of C14 catalyst in the site-selective \( \alpha \)-1,2-\textit{cis} glycosylation to afford synthetically useful yields of complex carbohydrates.

![Scheme 32. C14-catalyzed site-selective coupling of functionally diverse substrates](image)

**2.3.3. Chemoselective glycosylation**

In typical approaches to the synthesis of oligosaccharides, a glycosyl electrophile is glycosylated with a nucleophile in the presence of external reagents or catalysts, and the resulting disaccharide then undergoes additional steps for selective anomeric deprotection followed by installation of an anomeric latent leaving group after each glycosylation. In principle, the C14-controlled approach could streamline the needs for anomeric deprotection and protecting group manipulations. We envisioned that a glycosyl bromide is activated by C14 catalyst and subsequently coupled to a carbohydrate acceptor incorporated with an alkyl hydroxyl as well as an unprotected C1-hemiacetal functionality. Ideally, the primary or secondary alkyl
hydroxyl is chemoselectively glycosylated in the presence of the C1-hydroxyl to generate the hemiacetal-terminated disaccharide, which can be directly converted into a glycosyl donor or is directly used as a glycosyl donor for another coupling iteration to selectively furnish the corresponding oligosaccharide. The key issue of glycosylation chemoselectivity relies on the nucleophilic difference between the alkyl hydroxyls and the C1-hydroxyl within the carbohydrate acceptor itself. Due to the inductive effect of the pyranose ring oxygen, we hypothesized that an alkyl hydroxyl is likely to be more nucleophilic than a C1-hydroxyl functionality. The influence of donor reactivity in chemoselective glycosylation reactions has been well-documented. In contrast, our chemoselective strategy focuses on the effect of acceptor nucleophilicity, which has been underdeveloped. Although the chemoselective coupling of an alkyl hydroxyl in the presence of a free C1-hydroxyl within a carbohydrate acceptor has been reported using dehydrative glycosylation method, the process is neither catalytic nor diastereoselective.

We aimed to address these limitations by examining the efficacy of the C14 catalyst to promote both stereo- and chemoselective coupling of carbohydrate diol acceptors. Furthermore, the concept of chemoselectivity can only be realized under conditions that do not promote oligomerization of the carbohydrate diol acceptor. To validate the critical questions of stereo- and chemoselectivity, a coupling of 1,6-diol acceptor 32 with glycosyl bromide 2 was examined under the influence of C14 catalyst (Table 10, entry 1). We selected diol 32 to test the feasibility of the chemoselective concept because it incorporates a relatively unhindered C6-hydroxyl as the preferred site for glycosylation. In addition, the aryl fluorine helps to determine the chemoselectivity and diastereoselectivity of the final product via 19F NMR. Under optimal C14-catalyzed conditions, the desired hemiacetal-terminated disaccharide 34 was obtained in 63% yield with excellent diastereoselectivity (α:β = 11:1) and complete chemoselectivity (entry 1). Importantly, self-coupling of diol acceptor 32 to form 1,1’-linked disaccharide was not observed in the reaction. We next examined fluorinated diol acceptor 32 in glycosylation with glycosyl bromide donors 31 and 14 (entries 2 and 3), the yields and α-diastereoselectivities of these reactions were excellent (80%, α:β ≥ 20:1). Notably, these reactions proceeded with complete chemoselectivity.
Having demonstrated that the C14-catalyzed stereo- and chemoselective couplings of primary alcohols within carbohydrate acceptors in the presence of free C1-hydroxyls, this chemistry was further explored with secondary alcohol within carbohydrate acceptor 33 (Table 10, entries 4). The diol 33 incorporates a highly hindered C4-hydroxyl as the preferred site for the coupling to take place. To our excitement, coupling of diol acceptor 33 with electron-withdrawing glycosyl bromide 1 (entry 4) also proceeded with complete chemoselectivity to afford the corresponding 1,4-linked disaccharide 37 in 70% yield with high levels of...
diastereoselectivity (α:β = 11:1). More importantly, self-coupling of 1,4-diol acceptor 33 to form 1,1-linked disaccharide was also not observed in the reactions. Overall, these results demonstrate that the C14 catalyst effectively promotes the stereo- and chemoselective coupling of an alkyl hydroxyl in the presence of a free C1-hydroxyl functionality within a carbohydrate acceptor.

2.3.4. Orthogonal glycosylation

The concept of orthogonal glycosylation reaction focuses on the relative reactivities of glycosyl donors, which can be modulated by protecting groups and anomeric latent leaving groups. Successful glycosylation requires the anomeric leaving group of each carbohydrate coupling partner to be chemically distinct and activated by different reagents.\textsuperscript{141-143} The orthogonal glycosylation strategy streamlines the need for anomeric derivatization steps as the coupling products are directly used as glycosyl donors for subsequent glycosylation. In addition, it has been illustrated to provide solutions for the synthesis of complex oligosaccharides.\textsuperscript{141-143} However, subtle changes to the structures of carbohydrate coupling partners and protecting groups could impact glycosylation selectivity and reactivity. In addition, the process is not catalytic. We sought to assess the efficiency of C14 catalyst to promote the couplings of carbohydrate coupling partners possessing chemically distinct anomeric leaving groups. Thioglycoside 38 and glycosyl bromide 2 was used in the first combination (Scheme 33A) as their anomeric leaving groups can be activated by different sets of external reagent and catalyst. The C14 catalyzed orthogonal reaction was evaluated under optimized standard conditions with the use of dichloromethane as a solvent because thioglycoside 38 was partially soluble in MTBE. The disaccharide product 39 (Scheme 33A) was obtained in 89% yield with good α-selectivity (α:β = 8:1). Similarly, the combination of glycosyl fluoride 40 and glycosyl bromide 2 under the influence of C14 catalyst provided disaccharide 41 (Scheme 33B) in good yield and diastereoselectivity.
Scheme 33. C14-catalyzed orthogonal glycosylation

2.4. Summary

Several trends were obtained from this phenanthroline catalysis: (1) while reactions with α-glycosyl bromide donors containing the electron-withdrawing groups require to be conducted at 50 ºC, their electron-donating counterparts can proceed at 25 ºC; (2) reactions with primary alcohols proceeds faster than sterically hindered secondary alcohols. Furthermore, while primary alcohols could couple to reactive glycosyl donors at 25 ºC, the sterically hindered secondary alcohol needs to proceed at 50 ºC for the coupling to occur; (3) phenanthroline derived catalysts are more efficient compared to pyridine derived catalysts, and (4) C4- and C7-heterocyclic nitrogen substituted phenanthroline catalysts increase the reaction reactivity and improve diastereomeric outcome.

Limitations of the phenanthroline catalysis on coupling of highly unreactive glycosyl bromide and sterically hindered C4-hydroxyl acceptors was overcome by introducing piperidine substituents on the C4- and C7 position on the phenanthroline. The utility of this phenanthroline catalysis is expanded to sterically hindered hydroxyl nucleophiles and chemoselective coupling of an alkyl hydroxyl group in the presence of free C1-hemiacetal functionality. The phenanthroline-based catalyst also has a pronounced effect on site-selective couplings of triol motifs and orthogonally activates the anomeric bromide leaving group over the fluoride and sulfide counterparts.
CHAPTER 3: MECHANISM OF PHENANTHROLINE-CATALYZED 1,2-CIS PYRANOSYLATION

Phenanthroline has been utilized extensively as a powerful ligand for metals and a binding agent for DNA/RNA. However, there was no report on the use of phenanthroline as a nucleophilic catalyst in organic reactions or stereoselective glycosylation until our recent discovery. Our initial proposed mechanism evolved from a basic principle: two pyridine nitrogen atoms are positioned to act cooperatively (Scheme 31, Chapter 2). The first nitrogen atom acts as a catalytic nucleophile to displace the C1-anomeric bromide leaving group of a glycosyl donor, via an S_N2-like pathway, to generate an equatorial (β) phenanthrolium ion intermediate preferentially to avoid the steric interactions associated with positioning that group in the axial (α) orientation. The second nitrogen atom could interact with carbohydrate moiety to further stabilize the phenanthrolium ion intermediate. Subsequent S_N2-like substitution by a hydroxyl nucleophile leads to the formation of α-1,2-cis glycosides.

3.1. β-Glycosyl bromide driven glycosylation?

The preferential formation of α-glucosides from α-glucosyl bromide in the presence of added bromide ion (Bu4NBr) was first described by Lemieux and attributed to the enhanced reactivity of the higher energy β-glycosyl bromide. As such, we evaluated if the stereochemistry of the α-1,2-cis product would be dictated by the configuration of glycosyl bromide at the anomeric carbon. Because it is difficult to obtain β-isomer of glycosyl bromide in a pure form, a 5:1 mixture of β- and α-isomers of glycosyl bromide 1β/α with β-isomer being a major diastereomer was used as a model substrate (Scheme 34). We observed that a 5:1 β/α mixture of starting material 1β/α slowly anomerized to the corresponding a 2:1 α/β mixture in the absence of the phenanthroline catalyst after 24 h. However, a 5:1 β/α mixture 1β/α converted exclusively to the corresponding α-isomer 1α in the presence of 15 mol% of C1 catalyst within 1 h at 25 °C (Scheme 34A). We also performed the reaction of a 5:1 β/α mixture 1β/α with galactoside acceptor 3 under the influence of C1 catalyst at 25 °C. We observed isomerization of this 5:1 β/α mixture to α-isomer
**1α** is faster than formation of the coupling product **4** at 25 °C (Scheme 34B). On the other hand, coupling of **3** with this 5:1 β/α mixture **1β/α** under standard C1-catalyzed conditions provided **4** (Scheme 34C) in comparable yield and α-selectivity to that obtained with α-isomer **1α** (Scheme 34D). Collectively, these results suggest that β-isomer of glycosyl bromide is not the reacting partner in the phenanthroline-catalyzed reaction. This catalysis, which derives its α-stereoselectivity from the highly reactive β-covalent phenanthrolinium ion intermediate, is different from the Lemieux system. 

**Scheme 34.** Effect of the configuration of glycosyl bromide

**3.2. Double S$_{N}2$ mechanism? (Kinetic study)**

To further verify the glycosylation reaction undergoes double S$_{N}2$-like mechanism, we conducted kinetic investigation based on the mechanism outlined for phenanthroline-catalyzed glycosylation in Scheme 31 (Chapter 2), the overall reaction can be described as equation (1), wherein $k_1$ and $k_2$ defined the pre-equilibrium in the first nucleophilic substitution between the reactants, glycosyl bromide donor (D) and catalyst (C), and the intermediate (I). An irreversible nucleophilic attack ($k_2$) by a hydroxyl acceptor (A) then leads to formation of the coupling product (P) and regeneration of catalyst.
\[
D + C \xrightleftharpoons[k_{-1}]{k_1} 1 \xrightarrow{k_2[A]} P + C
\] (1)

Applying steady-state approximation, the rate of product formation can be derived as equation (2).

\[
\frac{d[P]}{dt} = \frac{k_1k_2[D][A][C_0]}{k_{-1} + k_1[D] + k_2[A]}
\] (2)

For fixed donor and acceptor concentration, the rate of product formation in respect to catalyst concentration is simplified in equation (3):

\[
\frac{d[P]}{dt} = k'[C]_0
\] (3)

where \( k' = \frac{k_1k_2[D][A]}{k_{-1} + k_1[D] + k_2[A]} \).

For fixed donor and catalyst concentration, the rate of product formation in respect to acceptor concentration is illustrated in equation (4):

\[
\frac{d[P]}{dt} = \frac{k_2[A]}{k_b + k_2[A]}
\] (4)

where \( k_a = k_1k_2[D][C]_0 \), and \( k_b = k_{-1} + k_1[D] \).

In the end, for fixed acceptor and catalyst concentration, the rate of product formation in respect to donor concentration is shown in equation (5):

\[
\frac{d[P]}{dt} = \frac{k_2[D]}{k_d + k_1[D]}
\] (5)

where \( k_c = k_1k_2[A][C]_0 \), and \( k_d = k_{-1} + k_2[A] \).

The kinetic studies were conducted at 50 °C, using C\textsubscript{6}D\textsubscript{6} as the reaction solvent and toluene as a quantitative internal standard, with 3,4,6-tri-acetyl-2-O-benzyl-\( \alpha \)-glucopyranosyl bromide (1) and 2-propanol (1A) as coupling partners in the presence of IBO and C1. The product (1P) formation was monitored by \(^1\text{H} \) NMR over the course of 60 h. The rates of reaction were then plotted as functions of the concentration of C1 (Figure 15a) and 2-propanol (Figure 15b).
Overall, the rate of the reaction is both catalyst- and acceptor-dependent. At fixed donor and acceptor concentration (Figure 15a), a linear correlation was observed in the plot of rate vs catalyst concentration, which was predicted by equation (3). On the other hand, a biphasic kinetic was observed from the plot of rate vs acceptor concentration (Figure 15b). This biphasic kinetic suggests a shift in the rate-determining step (RDS) at different concentrations of 2-propanol. At high concentration of 2-propanol, the RDS is formation of the phenanthrolinium ion (first step in Scheme 31), and is further supported by the linear dependence of rate on catalyst concentration (Figure 15a). At low concentration of 2-propanol, nucleophilic attack (second step in Scheme 31) is the RDS. The biphasic kinetic is also predicted by equation (4).

![Scheme 31](image)

**Figure 15.** Kinetics of the reaction of 2-propanol with glucosyl bromide 1 in C₆D₆ at 50 °C: (a) Initial rate of reaction vs C1; reaction condition: glucosyl bromide 1 (0.5 M), 2-propanol (1.5 M), IBO (1 M), catalyst C1 (0-20 mol%); (b) Initial rate of reaction vs 2-propanol; reaction condition: glucosyl bromide 1 (0.5 M), 2-propanol (0.25 – 3.5 M), IBO (1 M), catalyst C1 (15 mol%).

However, due to solubility issue, we were not able to conduct the kinetic study with high concentration of glycosyl bromide 1. In addition, we were not able to lower the glycosyl bromide concentration as the experiment required 60 h to obtain sufficient data under standard C1-catalyzed conditions.

To verify the glycosylation is first-order dependent in the concentration of glycosyl bromide, we adapted the optimal reagent system in Table 8, and conducted kinetic experiment at varying glycosyl bromide concentration. To obtain a clear view on the product anomeric region (4.5 – 5.0 ppm) in ¹H NMR,
2,3,4,6-tetra-benzyl-d-\textsubscript{7}-glucopyranosyl bromide \(2^*\) was used as the model electrophile. The kinetic experiments were carried at 25 °C in CD\(_2\)Cl\(_2\), with glucosyl bromide \(2^*\) and glycosyl nucleophile \(3\) as the coupling partners, using phenanthroline \(\text{C14}\) as the catalyst, DTBMP as acid scavenger, and mesitylene as internal standard. As illustrated in Figure 16a, the coupling product concentration appeared linear relationship to time (apparent zero-order kinetics in substrates), and induction period was not observed. In addition, the rate of product formation increases as the concentration of glucosyl bromide \(2^*\) increases. The initial rate of reaction in Figure 16b showed first-order dependence on glycosyl bromide \(2^*\). Unfortunately, due to limiting amount of \(2^*\), we were not able to observe the saturation behavior in glucosyl bromide concentration. However, the collective kinetic studies suggest that the phenanthroline catalyzed \(\alpha\)-selective glycosylation undergoes associative mechanisms (likely double S\(_\text{N}\)2).

Figure 16. Kinetic study in respect to donor concentration: (a) Product concentration versus time for phenanthroline-catalyzed (\(\text{C14}, 0.02\text{M}\)) glycosylation with varying donor concentration: 0.2 M \(2^*\) (●, green), 0.4 M \(2^*\) (▲, red) and 0.6 M \(2^*\) (♦, blue). Reaction conditions: donor \(2^*\) (0.2 – 0.6 M), acceptor \(3\) (0.2 M), \(\text{C14}\) (0.02 M), DTBMP (0.4 M), CD\(_2\)Cl\(_2\) (0.5 mL), 25 °C; (b) the initial rate of reaction is dependent on the concentration of \(2^*\).
The rates of phenanthroline-catalyzed reactions with different substituents on the phenanthroline framework were also investigated. As illustrated in Figure 17, all three phenanthroline catalysts provide similar rate profile, where the overall rates are apparent zero-order kinetics in substrates and showing no induction period. Due to the electron donating effect of the piperidine substituents, the rate of C14-catalyzed glycosylation should be faster than that of C1 and C2. As predicted, the C14-catalyzed reaction is more rapid than both C1- and C2-catalyzed reaction. On the other hand, both C1 and C2 showed similar rate, complementary to the observation in Table 8 (Chapter 2).

![Figure 17. Product concentration versus time for the phenanthroline-catalyzed glycosylation with three different phenanthroline catalysts: C1 (●, orange), C2 (◇, dark blue) and C14 (▲, red). Reaction condition: 2* (0.4 M), 3 (0.2 M), catalyst (0.02 M), DTBMP (0.4 M), CD2Cl2 (0.5 mL), 25 °C](image)

3.3. Detection of pyranosyl phenanthrolinium ion intermediates

For the phenanthroline-catalyzed glycosylation to yield α-1,2-cis product, the catalyst must associate with either or both substrates in the reaction. In our proposed mechanism (Scheme 31), phenanthroline displaces the bromide leaving group to form a glycosyl phenanthrolinium ion intermediate. Unlike sugars, phenanthroline is a rigid and planar organic compound with a C2 symmetry. However, if phenanthroline is coupled with a sugar molecule, the symmetry will be destroyed. As a result, our first objective was to perform 1H NMR study to observe the symmetry on phenanthroline (Figure 18). To obtain a clear view on the aromatic region in 1H NMR, 2,3,4,6-tetra-benzyl-d-glucopyranosyl bromide 2* was used as an
electrophile, wherein the chemical shift of anomeric proton (H1) resonance appeared at $\delta_H = 6.55$ ppm in CD$_2$Cl$_2$ (Figure 18a). Piperidine substituted phenanthroline C14 was chosen for our NMR study because it is the most effective catalyst$^{134}$ compared to other catalysts,$^{126}$ implying formation of the reactive glycosyl intermediates is more favorable. In addition, the chemical shift of the piperidyl substituents would not appear in the aromatic region. To avoid any possible side reaction with by-product of isobutyl oxide (IBO),$^{134}$ di-tert-butylmethylpyridine (DTBMP) was chosen as the acid scavenger in the later NMR experiment (Figure 18).

![Chemical structure and NMR spectra](image)

**Figure 18.** Detection of phenanthrolinium intermediate by $^1$H NMR: (a) Deuterated tetra-benzyl glucosyl bromide 2' in CD$_2$Cl$_2$; (b) 2' and 10 mol% C14 at 0 min; (c) 2' and C14 at 30 min, new signals emerging around phenanthroline aromatic region; (d) 2', 3, C14 at 30 min, disaccharide 5' emerging; and (e) 2', 3, C14 at 300 min, more disaccharide 5' formed in the reaction. See Section 5.3.2 for full spectrum.
Upon addition of 10 mol% of C14 to the deuterated glycosyl bromide 2*, three new signals appeared at δ_H = 8.88 ppm (H_a, d, J = 5.0 Hz) and δ_H = 7.07 ppm (H_b, d, J = 5.1 Hz) and the singlet at δ_H = 7.98 ppm (H_c) represented the symmetry of C14 catalyst (Figure 18b). Within 30 min, new signals emerged around the phenanthroline region (Figure 18c). These new signals were not detected in the mixture of nucleophile 3 and C14 (Figure 19). An aliquot of the reaction mixture was subjected to electrospray ionization (ESI) mass spectrometry and returned m/z ratio of 897.6393 (Figure 46), confirming the presence of the intermediate Int* (Figure 18) which resembled a phenanthrolinium ion. Hydroxyl nucleophile 3 was subsequently added to the reaction mixture along with DTBMP and mesitylene (internal standard). After 30 min, new signals still surrounded the aromatic region (Figure 18d) along with the appearance of the disaccharide product whose anomeric proton appeared at δ_H = 5.03 ppm (d, J = 3.6 Hz, Figure 18d). At 5 h, more product was formed and the new peaks remained at the aromatic region (Figure 18e). The reaction mixture was allowed to stir overnight at 25 °C. The product 5* was isolated in comparable yield (80%) and selectivity (α:β = 10:1) to that of disaccharide 5 (Table 8, entry 4). Several key observations were obtained.
from this NMR experiment: (1) the new signals appeared to be doublets, indicating the newly-formed phenanthroline species did not maintain their symmetry; (2) the number of signals suggests that there are two possible phenanthroline species (Int$_1$ and Int$_2$) present in the solution (Figure 20); (3) the population of unbound phenanthroline C14 and the two phenanthroline species (Int$_1$ and Int$_2$) shifted from 76:14:10 (C14: Int$_1$: Int$_2$) to 81:12:7 upon addition of alcohol 2, suggesting the equilibrium of the catalyst states had shifted toward regeneration of C14, likely through formation of the coupling product; and (4) the integration of the signals suggested that an extra hydrogen atom appeared on the phenanthroline aromatic region for each newly-formed species, which was subsequently identified as a C1-proton of the sugar unit (Figure 20).

To further identify the presence of the two newly-formed species upon mixing deuterated glycosyl bromide 2* with C14, a 1:1 stoichiometry ratio of 2* and C14 catalyst was employed. As the concentration of C14 increased, the equilibrium shifted toward the two new intermediates, wherein the population of unbound C14 catalyst, Int$_1$ and Int$_2$ became 55%, 30%, and 15%, respectively (see Section 5.3.2 for $^1$H

\[\text{Figure 20. Conformation of the glycosyl phenanthrolinium ion intermediates: 1H-1H 2D COSY (red) and ROESY (blue) NMR evidence as well as DFT calculation structures.}\]
NMR spectra). Variable temperature $^1$H, $^1$H-$^1$H 2D COSY and ROESY NMR spectra at 0 °C were subsequently obtained. Density functional theory (DFT) calculations were employed to assist the deconvolution of these intermediates. The geometries of possible intermediates’ structures were optimized and vibrational frequencies were calculated at the B3LYP/6-31+G(d,p) level\textsuperscript{146-156} with the SMD implicit solvent model\textsuperscript{157} and the GD3BJ empirical dispersion correction\textsuperscript{158-159}. All calculations were carried out with Gaussian 09.\textsuperscript{160} In our DFT calculations, tetramethyl glucosyl bromide was used as a model electrophile to reduce computational cost (Figure 20). The DFT calculation results are consistent with our NMR data.

Employing 2D COSY NMR, the newly formed protons in the phenanthroline aromatic region resided at $\delta_H = 8.68$ ppm (d, $J = 8.1$ Hz) and $\delta_H = 8.36$ ppm (d, $J = 3.6$ Hz) were identified to be the C1 protons of the anomeric mixture of Int\textsubscript{1} ($\beta$) and Int\textsubscript{2} ($\alpha$), in a ratio of 2:1 ($\beta$:$\alpha$) (Figure 20 and Figure 21c). Suggested

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure21.png}
\caption{Conformation of glycosyl phenanthrolinium intermediates and NMR evidence: (a) Conformation of $\beta$- and $\alpha$-phenanthrolinium intermediates; (b) $^1$H-$^1$H 2D ROESY NMR spectrum; (c) $^1$H-$^1$H 2D COSY NMR spectrum.}
\end{figure}
by DFT calculations (Figure 20), while H₃ proton on the phenanthroline is spatially closed to the C2 proton for the β-isomer Int₁ (2.646 Å), the H₄ proton for the α-isomer Int₂ is closed to the C5 proton (2.700 Å) on the sugar ring. These spatial interactions were also observed through 2D ROESY NMR (Figure 21b), which consolidate the anomeric configurations for the two detected intermediates. Similar to the glycosyl pyridinium ion,¹⁶¹-¹⁶³ the major phenanthrolinium ion intermediate is a β-configured isomer (Int₁) and exists in the ⁴C₁ chair conformation while the minor α-isomer (Int₂) exists in the B₂,₅ boat conformation to avoid stereo- and electronic effect from the ring.

3.4. Hydrogen bonding in the pyranosyl phenanthrolinium ion intermediates

Several NMR evidences were found below to support hydrogen bonding (H-bonding) interaction between the second nitrogen of phenanthroline and the C1 anomeric proton. In general, for H-bonding involving an electronegative acceptor such as oxygen or nitrogen, the donor nucleus experiences a deshielding effect.¹⁶⁴ Conversely, if the C1 anomeric proton is hydrogen bonding to the second nitrogen of phenanthroline, the chemical shift should appear more downfield in the ¹H NMR. It has been reported that the anomeric proton of β-glucosyl pyridinium bromide resonances at δ_H = 6.10 ppm in D₂O.¹⁶⁵ In addition, Gin and coworker established anomeric mixture of glycosyl pyridinium species, wherein the anomeric protons resonance at δ_H = 6.63 and 6.49 ppm in CD₂Cl₂ at -60 °C.¹⁶⁶ However, the ¹H NMR spectra of a 1:1 mixture of glycosyl bromide 2* and C14 taken at -60 °C (Figure 22) showed the anomeric protons of the intermediates, Int₁ (β) and Int₂ (α), resonance at δ_H = 8.44 and 8.18 ppm, respectively. The downfield shift of the anomeric protons of glycosyl phenanthrolinium ion intermediates compare to that of the reported glycosyl pyridinium species is likely due to an intramolecular hydrogen bonding between the anomeric proton and second nitrogen on phenanthroline.

A more direct hydrogen bonding observation is through hydrogen bond scalar coupling.¹⁶⁴ The scalar interaction arises from electron cloud between nuclei, such as covalent bonds. Upon formation of H-bonding, the redistribution of electron density of the nuclei associate with H-bonding allows us to observe
Figure 22. Variable-temperature $^1$H NMR spectra and proposed intermediates internal hydrogen bondings: (a) VT-NMR spectra of glucosyl bromide $2^*$ and C14 (1 equiv.) in CD$_2$Cl$_2$ with mesitylene as internal standard; (b). Zoomed-in spectra of anomeric protons for Int$_1$ and (c) Int$_2$.

The scalar coupling using COSY experiment.$^{164}$ As shown in Figure 21, scalar couplings ($^3J_{	ext{HH}}$) between the anomeric proton and H$_a$ on the phenanthroline were observed for both intermediates Int$_1$ and Int$_2$.

These scalar interactions mediated by the lone pair electrons on the second pyridine nitrogen of phenanthroline and the conjugated system are evidential for H-bonding between the anomeric proton and the second nitrogen of phenanthroline. In order to obtain a clear view of the hydrogen bond coupling in $^1$H NMR, a rigid H-bonding network is required.$^{167-168}$ As hydrogen bond formation is highly dependent on
temperature,\textsuperscript{169} we cooled the 1:1 mixture of glucosyl bromide 2* and C14 in CD$_2$Cl$_2$ to -60 °C and gradually warm to room temperature. The $^1$H NMR spectra were taken at 10 °C interval and combined (Figure 22a). The $^1$H NMR spectrum was at highest resolution at -10 °C. The C1-anomeric proton of Int$_1$ (β) showed a defined allylic splitting at -10 °C (Figure 22b). Further, DFT optimized structures (Figure 20) for anomeric mixtures of the phenanthroline intermediates are consistent with the NMR observation: for Int$_1$ (β) the H1–N’ distance is 1.958 Å and the C1–H1---N angle is 133°, while those for Int$_2$ (α) are 2.089 Å and 117°.

**3.5. Proposed mechanism**

Based on the NMR study and DFT calculations,\textsuperscript{134} a proposed mechanism for the phenanthroline-catalyzed α-1,2-cis glycosylation is illustrated in Figure 3. We hypothesize that the first pyridine nitrogen atom of the phenanthroline catalyst C14 displaces the anomeric α-bromide leaving group of glycosyl donor to form the β-phenanthroline ion intermediate. This phenanthroline ion positions equatorially to avoid the steric and electrostatic interactions. Our recent DFT calculations suggest that formation of the β-covalent phenanthroline ion intermediate is reversible.\textsuperscript{134} The β-covalent glycosyl intermediate adopts the $^4$C$_1$ chair conformation and is in equilibrium with the α-glycosyl intermediate whose exists in the B$_{2,5}$ boat conformation. Our NMR study showed that these two key intermediates, a major $^4$C$_1$ β-phenanthroline ion conformer (Int$_1$) and a minor B$_{2,5}$ α-phenanthroline ion conformer (Int$_2$) were formed in the reaction (Figure 20). To obtain high levels of diastereoselectivity, a Curtin-Hammett situation must be established: interconversion of the $^4$C$_1$ chair-like β-conformer and B$_{2,5}$ boat-like α-conformer via an oxocarbenium ion intermediate is rapid and much faster than the subsequent nucleophilic attack (Figure 23). In the NMR study, these two intermediates were formed and equilibrated within 30 min while the product formation typically required more than 1 h to be observable. To rationalize the diastereoselectivity for the major α-1,2-cis product, hydroxyl acceptor preferentially approaches to the α-face of the $^4$C$_1$ chair conformation of the β-glycosyl phenanthroline ion intermediate via an $S_N$2 pathway. This would the
reaction proceeding through a disfavored B$_{2,5}$ boat conformation of the $\alpha$ intermediate, which leads to the minor $\beta$-1,2-trans product. preclude

**Figure 23.** Possible mechanism of phenanthroline-catalyzed glycosylation

To further verify that the $^4$C$_1$ chair-like $\beta$-glycosyl phenanthroline is indeed the reactive intermediate, we sought to detect the intermediates for 2-deoxy-2-fluoro glycosyl bromide donor. The highly reactive tribenzyl 2-fluoro galactosyl bromide 31 was chosen as a model electrophile (Figure 24). The transient glycosyl phenanthroline ion intermediate (Int$_3$) was detected by $^1$H NMR within several minutes using

**Figure 24.** Conformation of the 2-deoxy-2-fluoro glycosyl phenanthroline ion and ROESY (blue) NMR evidence (see Section 5.3.2 for full spectrum).
a 1:1 mixture of 2-fluoro glycosyl bromide 31 and C14 catalyst at 25 °C. Importantly, only the β-glycosyl phenanthrolinium ion intermediate Int3 (Figure 24) existing in the 4C1 chair conformation was observed. In addition, more than 90% of 31 were converted to the Int3 intermediate within 2 h. Unlike the tetrabenzyl glycosyl bromide donor 2*, which produces highly interconvertible intermediates (Int1 and Int2, Figure 20), the 2-fluoro galactosyl bromide 31 generates a more stable intermediate (Int3), which results in either formation of the products or reverts to the reactant 31. This observation was further supported by DFT calculations.134

3.6. Conclusion

A systematic mechanistic investigation of the 4,7-dipiperidine substituted phenanthroline C14 catalyzed-stereoselective α-1,2-cis glycosylation reaction with α-glycosyl bromide donor was performed employing variable temperature NMR (1H, COSY, and ROESY) experiments. In this respect, NMR studies have showed that activation of deuterated tetrabenzyl glucosyl bromide with C14 catalyst can readily form the two phenanthrolinium ion intermediates: the β-isomer adopts a 4C1 chair conformation while the α-isomer adopts a B2,5 boat conformation. These two glycosyl intermediates exist in a ratio of 2:1 favoring the 4C1 chair-like β-phenanthroline ion. The 1H and COSY NMR studies indicate that there is an intramolecular hydrogen bonding between the anomeric C1- proton of the carbohydrate moiety and the second pyridine nitrogen of phenanthroline framework for the two glycosyl phenanthrolinium ion intermediates. The coupling is governed by Curtin-Hammett principles and proceeds through the more reactive 4C1 chair-like β-phenanthroline ion. The α-anomeric selectivity is rationalized by a model in which nucleophilic attack takes place from the α-face of the β-covalent glycosyl phenanthrolinium ion intermediate. Kinetic study suggested that the phenanthroline-catalyzed reaction operates by associative mechanisms.
CHAPTER 4: EXPLORATION OF PHENANTHROLINE-CATALYZED

1,2-CIS FURANOSYLATION

4.1. Introduction

The interest in the stereoselective synthesis of furanose-containing glycans has been growing rapidly over the past decade\textsuperscript{170-175} as furanoses are key constituents of many pathogenic microorganisms and plants.\textsuperscript{176-179} Oligosaccharides and polysaccharides containing 1,2-\textit{trans} and 1,2-\textit{cis} furanosidic linkages (Figure 25) are generally present in the cell walls of the microorganisms and play critical roles in disease progression and interaction with the host immune system.\textsuperscript{176-179} As a result, they are targets for therapeutic intervention.\textsuperscript{180-181} The 1,2-\textit{trans} furanosides are obtained through neighboring group participation of the C2-\textit{O}-acyl protecting group. On the other hand, the ability to access 1,2-\textit{cis} furanosides requires furanosyl donors with a non-assisting functionality at C2. The use of these electrophilic donors often leads to the formation of a mixture of two stereoisomers that differ in the configuration of the anomeric center.\textsuperscript{170-175}

![Mycobacterial AG fragment](image1.png)
![Mycobacterial LAM fragment](image2.png)

Figure 25. Hexasaccharide motifs found in the cell wall complex of mycobacterial arabinogalactan (AG) and lipoarabinomannan (LAM).

The furanosides react closer to the S\textsubscript{N}1 end of the S\textsubscript{N}1-S\textsubscript{N}2 boundary than their pyranoside counterparts due to their conformational flexibility and electronic properties.\textsuperscript{127} To overcome these inherent challenges,
several groups have employed conformationally blocked furanosyl donors that provide 1,2-\textit{cis} furanosides with high levels of selectivity. The introduction of 1,2-\textit{cis}-furanosidic, remote participation of the acyl protecting group at C3 or C5, hydrogen bonding-assisted coupling, and regioselective opening of the 2,3-anhydrofuransoyl donor. While these substrate-controlled methods have been successful to provide solutions to a number of 1,2-\textit{cis} furanosylation challenges in the oligosaccharide synthesis, achieving the desired stereoselectivity remains system-dependent. Subtle changes to the structure of carbohydrate coupling partners have pronounced effects on the furanosylation selectivity and reactivity.

Methods that enable catalytic stereoselective glycosylation are a powerful means of rapidly introducing 1,2-\textit{cis} furanosidic linkages into biologically relevant oligosaccharides, obviating the need to rely on substrate control. The catalysis with small organic molecules to expand the chemical space of stereoselective 1,2-\textit{cis} furanosylation reaction is of interest. The area of organocatalysis has become a highly dynamic area of research as small organic molecules are capable of catalyzing a wide range of organic reactions. Recently, Jacobsen and coworkers reported the use of small molecule catalysts, bis-thiourea hydrogen-bond donors, to mediate the formation of 1,2-\textit{cis} furanosides in high yields and diastereoselectivities. In their investigation, 1,2-\textit{trans} furanosyl phosphate donors undergo substitution with a variety of hydroxyl acceptors to provide access to 1,2-\textit{cis} products. However, when \( \beta \)-1,2-\textit{trans} xylofuranosyl phosphate donor (42, \textit{cis:trans} = 1:11) was employed in the reaction (Scheme 35A), the \( \beta \)-1,2-\textit{trans} product 44\( \beta \) was obtained as the major product with the net retention of anomeric configuration (\textit{cis:trans} = 1:13). This is a unique case when compared to other furanosyl phosphates under bis-thiourea-catalyzed selective furanosylation conditions.

Our group recently discovered that phenanthroline, a rigid and planar organic compound with two pyridine rings fused to a benzene ring, effectively acts as a nucleophilic catalyst to promote the stereoselective glycosylation with \( \alpha \)-pyranosyl bromide donors providing \( \alpha \)-1,2-\textit{cis} pyranosides with net retention of anomeric configuration. The reaction is governed by Curtin-Hammett principles and
proceeds through the more reactive β-pyranosyl phenanthroline ion intermediate. The α-1,2-cis selectivity is rationalized by a model in which nucleophilic attack takes place from the α-face of the β-glycosyl phenanthroline ion.\textsuperscript{216} Given the paucity of catalytic stereoselective 1,2-cis furanosylation reports, we saw an opportunity to demonstrate the utility of our catalytic strategy toward furanose substrates. Dr. Hengfu Xu has investigated the commercially available phenanthroline-catalyzed stereoselective glycosylation of a variety of hydroxyl nucleophiles with furanosyl bromide donors to provide access to the challenging 1,2-cis furanoside products with high levels of anomeric selectivity. Unlike the pyranose substrates, the reaction with furanose substrates proceeds with inversion of stereochemistry.

Scheme 35. Catalytic stereoselective xylofuranosylation

As illustrated in Scheme 35B, reaction of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside 3 with β-1,2-trans xylofuranosyl bromide donor (43, cis:trans = 1:10) using 15 mol% 4,7-diphenyl-1,10-phenanthroline (C\textsubscript{1}) provided the α-1,2-cis product 44\textsubscript{α} with excellent selectivity (cis:trans = 15:1). This result is the opposite of Jacobsen’s observation (Scheme 35A).\textsuperscript{215} This catalysis system has also been extended to a number of furanosyl bromide donors. While arabinofuranosyl bromide provides β-1,2-cis products as the major stereoisomers, xylo- and ribofuranosyl donors favor α-1,2-cis products (Scheme 36).
To understand the behavior of phenanthroline in the furanosylation system, an extensive mechanistic investigation was initiated.

**Scheme 36. Overview of reaction outcome of phenanthroline catalysis in furanosylation system**

**4.2. Effects of donor anomic composition**

Jacobsen and coworkers have reported that the anomic composition of the furanosyl phosphate donors had a pronounced effect on the reaction outcome under bis-thiourea-catalyzed furanosylation conditions. For example, the coupling of alcohol acceptor 3 with α-arabinofuranosyl phosphate 45 provided disaccharide 47 with $\alpha:\beta = 1:25$ (Scheme 37A). In contrast, the use of an 8:1 α/β mixture of arabinofuranosyl phosphate donor led to a decrease in selectivity, affording 47 with $\alpha:\beta = 1:10$ which is comparable with our C1 catalysis conditions ($\alpha:\beta = 1:7$, Scheme 37B).
Scheme 37. Catalytic stereoselective arabinofuranosylation

Since we were unable to obtain α-D-arabinofuranosyl bromide 46 in a high α-form, it is unclear how the anomeric composition of this donor could impact the stereochemical outcome under phenanthroline-catalyzed furanosylation conditions and whether the furanosylation operates by associative mechanisms. To determine if the stereochemical outcome of the reaction is dependent on the anomeric configuration of the electrophilic partner, we proposed to replace the C2-oxygen of arabinose with a fluorine atom to generate 2-fluoro-arabinofuranosyl bromide since this donor has been obtained with high α-selectivity. As anticipated, 2-fluoro arabinosyl bromide 48 (Scheme 38A) was primarily isolated as the α-furanosyl donor (α:β = 20:1). Although the reaction of donor 48 with primary alcohol acceptor 3 provided disaccharide 49 in 71% yield (Scheme 38A), a decrease in β-1,2-cis selectivity (α:β = 1:5) was observed in comparison to the result obtained for a 7:1 α/β mixture of arabinofuranosyl bromide donor 46 (α:β = 1:7, Scheme 37B). Interestingly, similar anomic selectivity (α:β = 1:5) was also obtained for 1,2-cis product 49 in the coupling of alcohol 3 with 2-fluoro arabinosyl phosphate mediated by the bis-thiourea catalyst. Next, we replace C2-oxygen of xylose with a fluorine atom to form 2-fluoro xylofuranosyl bromide donor 50 (Scheme 38B). Interestingly, while donor 50 was primarily isolated as a 1:1 α/β mixture, the coupling product 51 was obtained with excellent levels of cis/trans diastereoselectivity (α:β = 17:1).
Taken together, the data obtained in Scheme 38 suggest that furanosyl donor anomeric composition is not responsible for the reaction anomeric selectivity.

Scheme 38. Effect of donor anomeric composition in C1-catalyzed furanosylation

The use of 2-fluorofuranosyl bromide donors 48 and 50 (Scheme 38) also allows to study the effect of C2-fluorine atom on the reaction selectivity as the directing role of fluorine at C2 on 1,2-trans glycosylation with pyranosyl donors has been reported. Two mechanistic S<sub>N</sub>1 and S<sub>N</sub>2 scenarios have been proposed. For the S<sub>N</sub>1 pathway, the C2-F bond of pyranosyl donor adopts a quasi-axial arrangement to allow maximum orbital overlap for σ<sub>C-F</sub> and the incoming alcohol nucleophile in the transition state. As such, if the C2-fluorine directs furanosylation, 1,2-trans products should be obtained as the major products. However, in both the phenanthroline system and the bis-thiourea system, 1,2-cis products 49 and 51 (Scheme 38) were observed as the major products, suggesting either the reaction did not undergo S<sub>N</sub>1 pathway or the catalyst overrides the C2-fluorine directing effect. For the S<sub>N</sub>2 pathway, it has been proposed that the C2-fluorine may induce an electrostatic attraction between the pyranosyl donors and alcohol nucleophiles. If the reaction proceeds through S<sub>N</sub>2 pathway, the final coupling product should be in the opposite stereochemistry of the glycosyl electrophile. In the 2-fluoro-arabinofuranosylation case, we used furanosyl bromide 48 with 20:1 of α:β ratio, but only obtained 1:5 of α:β ratio for the coupling products.
49 (Scheme 38A). On the other hand, in the 2-fluoro-xylofuranosylation case, although a 1:1 anomic mixture of furanosyl bromide 50 was used in the reaction, a high α:β ratio (17:1) of the coupling product 51 (Scheme 38B) was obtained. These results suggest that the furanosylation does not undergo direct S_N2 pathway. The data are also consistent with our recent report on the phenanthroline-catalyzed stereoselective construction of 2-fluoroglycosides, in which phenanthroline catalyst overrides the C2-fluorine directing effect and gives access to the corresponding 1,2-cis-2-fluoro glycosides.134

4.3. Detection of furanosyl phenanthrolinium ion intermediates

With the possibility that the reaction goes through covalent phenanthrolinium ion intermediates, NMR spectroscopy was employed to detect the putative intermediates. To minimize the proton signals on the aromatic region, C14 was chosen as a catalyst of choice. In addition, both 2-fluoro xylosyl 50 and arabinosyl 48 bromides were chosen as model donors in our NMR study as we have established their anomic composition (see Scheme 38).

With the previous knowledge that the covalent phenanthrolinium ion intermediates form within 30 min upon combining the pyranosyl donor with C14,216 the first step in our study was to add C14 (0.13 mmol) to the 1:1.25 α/β mixture of 2-fluoro xylofuranosyl bromide 50 (0.10 mmol) at 25 °C. Within 1 h, new signals appeared around the phenanthroline region (7.0 – 9.1 ppm) and the sugar region (5.4 – 6.0 ppm) (Figure 26). An aliquot of the reaction mixture was then analyzed by electrospray ionization (ESI) mass spectrometry with an m/z ratio of 661.3548 (Figure 26 and Figure 58), confirming the formation of the phenanthrolinium ion. Furthermore, the number of new signals in both 1H and 19F NMR indicates that there are two possible intermediates, Int4 and Int5, present in a ratio of 2:1 in the reaction (Figure 26, Figure 53 and Figure 54). In 1H-1H COSY (Figure 56) and ROESY (Figure 57) NMR analysis, the C1 protons of the anomic mixture of Int4 and Int5 were identified to reside at δH = 7.63 ppm and δH = 8.02 ppm, respectively. On the other hand, the C2-fluorine of Int4 and Int5 resides at δF = -188.01 ppm (ddd, J = 45.7, 16.1, 8.4 Hz) and δF = -189.64 ppm (ddd, J = 52.2, 17.9, 14.0 Hz), respectively, in the 19F NMR (Figure 54). Through 2D
ROESY NMR analysis, the major \textbf{Int}_4 was identified as a $\beta$-phenanthrolinium ion and exists in the $^3E$ envelop conformation while the minor \textbf{Int}_5 was an $\alpha$-phenanthrolinium ion and adopts the $E_3$ envelop conformation (Figure 26, Figure 55 and Figure 57).

\begin{figure}[h!]
\centering
\includegraphics[width=\textwidth]{figure26}
\caption{Detection of xylofuranosyl phenanthrolinium intermediates}
\end{figure}

In the case of 2-fluoro arabinofuranosyl bromide \textbf{48} ($\alpha$:$\beta$ = 20:1, Figure 27), our NMR study of the 1:1 stoichiometry ratio of donor \textbf{48} and \textbf{C14} mixture shows that two key intermediates, a major $^3E$ $\beta$-phenanthrolinium ion conformer (\textbf{Int}_6) and a minor $E_3$ $\alpha$-phenanthrolinium ion conformer (\textbf{Int}_7), were also formed in a ratio of 2:1 $\beta$/$\alpha$ mixture (Figure 27, Figure 59 and Figure 60). The formation of the arabinosyl
phenanthrolinium ion intermediate was also confirmed using electrospray ionization (ESI) with an m/z ratio of 661.3541 (Figure 27 and Figure 66). From the 2D NMR study (Figure 64 and Figure 65), the C1 protons of the anomeric mixture of \textbf{Int}_6 and \textbf{Int}_7 were identified to reside at $\delta_H = 7.99$ ppm and $\delta_H = 8.05$ ppm, whereas the C2-fluorine resides at $\delta_F = -192.53$ ppm (ddd, $J = 51.3$, 20.5, 11.8 Hz) and $\delta_F = -186.34$ ppm (dt, $J = 46.0$, 13.3 Hz), respectively (Figure 62).

\textbf{Figure 27.} Detection of arabinofuranosyl phenanthrolinium intermediates

Collectively, the discovery of both $\alpha/\beta$ intermediates in the NMR study further illustrated that the phenanthroline-catalyzed furanosylation does not proceed through a stereospecific substitution. However,
to obtain high levels of 1,2-cis selectivity, the reaction is likely to proceed through a Curtin-Hammett scenario, wherein interconversion of the β-phenanthrolinium intermediate and its corresponding α-conformer must be more rapid than nucleophilic addition of alcohol acceptor. To further investigate this potential mechanism, we next performed reaction progress analysis using NMR spectroscopy.

### 4.4. Reaction progress analysis of phenanthroline-catalyzed furanosylation

In the reaction progress analysis, both 2-fluoro xylose 50 and arabinose 48 were again chosen as furanosyl bromide donors (0.3 M), and primary alcohol 3 (0.1 M) was chosen as the acceptor since we have established the α/β selectivity of the resulting products 51 and 49 (Scheme 38). The reactions were carried in deuterated chloroform (CDCl₃) with 15 mol% C14 and 1.5 equivalent of DTBMP as the acid scavenger. Taking advantage of the C2-fluorine, the reaction progress was monitored using ¹⁹F NMR for 20 – 24 h, and the relative concentrations of furanosyl bromide, covalent phenanthrolinium intermediates, and the disaccharide products were then determined (Figure 28 and Figure 29).

Firstly, we monitored the reaction progress for 2-fluoro xylofuranosyl bromide donor 50 (α:β = 1:1.25) 30 minutes after mixing 50 with 5 mol% C14 using both ¹H (Figure 51) and ¹⁹F (Figure 52) NMR. Interestingly, Int$_β$ and Int$_α$ appeared with a ratio of 1:8 (Figure 52). After alcohol acceptor 3 had been added to the reaction mixture for 1 h, a new sharp fluorine signal resided at $δ_F = -204.18$ ppm (dd, $J = 52.9$, 16.2 Hz) was verified to be the disaccharide 51$_α$ (α-isomer, Figure 52). Meanwhile, an indistinct fluorine peak located at $δ_F = -193.02$ ppm (ddd, $J = 50.2$, 17.5, 14.3 Hz) was later confirmed to be the β-isomer of 51$_β$ (Figure 52). Overall, the α/β selectivity of the disaccharides 51 was determined to be 21:1 after 24 h. The reaction progress analysis of xylofuranosyl donor 51 and alcohol acceptor 3 was also quantified as a kinetic profile in a concentration vs time graph (Figure 28). The linear relationship in Figure 28a between the concentrations and time in the kinetic profile revealed that the xylofuranosylation was in apparent zero-order kinetics in the first 7 h. Interestingly, although the anomeric mixture of xylofuranosyl bromides disappeared at similar rates, the two products appeared at significantly different rates – the rate of 51$_α$ formation was 16 times faster than that of 51$_β$ (Figure 28a). Meanwhile, increasing concentration
of \textbf{Ints(\(\alpha\))} was also observed in the kinetic profile of the xylofuranosyl phenanthrolinium intermediates (Figure 28b) while \textbf{Int(\(\beta\))} concentration maintained at a low level. These kinetic profiles suggested that the consumption rate of \textbf{Int(\(\beta\))}, which led to the major product 51\(\alpha\), was much faster than that of \textbf{Ints(\(\alpha\))}. As more products were formed in the reaction, the consumption rate of \textbf{Int(\(\beta\))} decreased, and a slight downward slope of product formation was observed at 7 h. This ratio of \textbf{Int(\(\beta\))} and \textbf{Ints(\(\alpha\))} maintained at 1:16 until the end of the reaction course (24 h), likely due to hydrolysis in the reaction.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure28.png}
\caption{Reaction progress for phenanthroline-catalyzed xylofuranosylation of alcohol acceptor 3 using \(^{19}\text{F}\) NMR: (a) xylofuranosyl bromide 50 and products 51; (b) xylofuranosyl-phenanthrolinium intermediates \textbf{Int(\(\beta\))} and \textbf{Ints(\(\alpha\))}}
\end{figure}

On the other hand, in the reaction progress of 2-fluoro arabinofuranosyl bromide 48 (Figure 29), the ratio of intermediates \textbf{Int(\(\beta\))} and \textbf{Ints(\(\alpha\))} only increased to 3:1 upon addition of primary alcohol 3 (Figure 60). Meanwhile, the \(\alpha/\beta\) selectivity of the disaccharides 49 slowly decreased from 1:7 at 1 h to 1:5 at 6 h.
(Figure 29a, Figure 59 and Figure 60). This 1:5 α/β ratio maintained until the end of the course of the reaction (20 h). Like the 2-fluoro-xylofuranosylation reaction, the kinetic profile of the 2-fluoro arabinofuranosylation also expressed apparent zero-order kinetics in the first 6 h. The disappearance rate of 48α was 24 times faster than that of 48β (Figure 29a), likely due to the higher concentration of starting material 48α, which further resulted in the higher concentration of Int6(β). However, unlike xylofuranosylation, the consumption rates of the two intermediates (Int6(β) and Int7(α), Figure 29b) in the arabinofuranosylation were similar, which eventually led to a lower selectivity in the coupling products 49.

Figure 29. Reaction progress for phenanthroline-catalyzed arabinofuranosylation of alcohol acceptor 3 using 19F NMR: (a) arabinofuranosyl bromide 48 and coupling products 49; (b) arabinofuranosyl-phenanthrolinium intermediates Int6(β) and Int7(α).
4.5. Proposed mechanism of phenanthroline-catalyzed furanosylation

To obtain high levels of 1,2-cis selectivity, a Curtin-Hammett situation must be established such that equilibration of \( \text{Int}(\beta) \) and \( \text{Int}(\alpha) \) is rapid and much faster than the subsequent nucleophilic attack. The hypothesis, that the rate-determining step takes place after the phenanthrolinium intermediates are formed, was confirmed by kinetic analysis (Figure 28b and Figure 29b), as the kinetic profiles for both xylose and arabinose showed an accumulation (positive slope) of the intermediates.

To provide further insight into the mechanism and selectivity, Dr. Richard N. Schaugaard performed density functional theory (DFT) calculations to examine the key transition states and intermediates along the reaction pathway. DFT calculations indicate that the second transition state (Figure 30) – the nucleophilic attack of alcohol onto the faster reacting phenanthrolinium ion intermediate – determines the stereochemistry of the product. As illustrated in Figure 30, TS2 indicates the second transition state that leads to the major product, while TS2’ represents the route to the minor product. The difference between TS2 and TS2’ (\( \Delta \Delta G^\ddagger \)) of xylofuranosylation was calculated as 4.0 kcal/mol, which results in a high product ratio (51\( \alpha \):51\( \beta \) = 21:1, Figure 30a). Meanwhile, the \( \Delta \Delta G^\ddagger \) of arabinofuranosylation was only 1.6 kcal/mol, which leads to a moderate product ratio as 49\( \alpha \):49\( \beta \) = 1:5 (Figure 30b).

**Figure 30.** Energy diagram of phenanthroline-catalyzed furanosylation for the second nucleophilic substitution: (a) xylofuranosylation (b) arabinofuranosylation
Based on the NMR data, kinetic profile (Figure 28), and computational results (Figure 30a) for xylofuranosyl bromide donor 50, we propose the following mechanistic rationale for the observed α-1,2-cis stereochemistry (Figure 31). Since α- and β-isomers of xylofuranosyl bromide 50 exist as a 1:1.25 mixture, displacement of their anomeric bromide leaving group with NPhen via an Sn2-like pathway would generate 3E β-phenanthroline ion conformer Int4(β) and E3 α-phenanthroline ion conformer Int5(α), respectively, with the preference of the Int4(β) intermediate. Calculations predict that Int5(α) is 0.4 kcal/mol less stable than Int4(β), likely due to eclipsing interaction between C2-F and C1-N in Int5(α). Nucleophilic attack of alcohol acceptor 3 onto Int4(β), via an Sn2-like pathway, would provide the α-xylofuranoside product 51α. To obtain high levels of 1,2-cis selectivity, a Curtin-Hammett situation must be established such that equilibration of Int4(β) and Int5(α) is rapid and much faster than the subsequent nucleophilic attack. The hypothesis, that the rate-determining step takes place after the phenanthroline

Figure 31. Possible mechanism for phenanthroline-catalyzed xylofuranosylation
intermediates are formed, was confirmed by kinetic analysis (Figure 28b) and computational observation (Figure 30a). It is also observed that \textbf{Int}_d(\beta)\) is not only the more stable intermediate than \textbf{Int}_5(\alpha)\) by 0.4 kcal/mol, but also is the faster-reacting conformer (Figure 30a). Indeed, the calculated TS2 transition state for the formation of the \(\alpha\)-xyloside product resulted from \textbf{Int}_d(\beta)\) is 4.0 kcal/mol more favorable than the analogous formation of the \(\beta\)-xyloside product (Figure 30a). Collectively, the \(\alpha\)-1,2-cis xyloside product 51\(\alpha\) resulted from the nucleophilic attack of alcohol 3 onto the major intermediate \textbf{Int}_d(\beta)\) should prevail and will not reflect the equilibrium distribution of \textbf{Int}_d(\beta)\) and \textbf{Int}_5(\alpha)\).

In the case of arabinose (Figure 32), the kinetic profile (Figure 29), and DFT calculations (Figure 30b) for arabinofuranosyl bromide suggest that (1) the donor anomic composition would not reflect the intermediate distribution; and (2) although \textbf{Int}_7(\alpha)\) is the minor intermediate observed by both NMR study (Figure 29b) and DFT calculation (Figure 30b), it is the fast-reacting conformer that reacts with alcohol.

\[\text{Figure 32. Possible mechanism for phenanthroline-catalyzed arabinofuranosylation}\]
acceptor to form the major \( \beta-1,2\text{-cis-arabinoside} \) product (see the proposed mechanism in Figure 32). Kinetic analysis (Figure 29b) shows that the rate of the nucleophilic substitution of \( \text{Int}_7(\alpha) \) is also faster than that of the more stable one \( \text{Int}_6(\beta) \). As a result, as soon as \( \text{Int}_7(\alpha) \) is consumed, it is replenished from \( \text{Int}_6(\beta) \) as the energy barrier for interconversion of \( \text{Int}_6 \) and \( \text{Int}_7 \) is low. The difference of the energy barrier for the two transition states (\( \Delta \Delta G^\ddagger \)) is about 1.6 kcal/mol (Figure 30b), further supporting the experimental result that a mixture of 1,2-\text{-cis-} and 1,2-\text{-trans-arabinoside} products (5:1) was obtained in the reaction.

4.5. Conclusion

A phenanthroline-catalyzed stereoselective furanosylation is developed to achieve access to the challenging 1,2-\text{-cis-furanosidic} linkages. Substitution of xylofuranosyl bromide donor with a variety of primary and secondary hydroxyl acceptors affords \( \alpha-1,2\text{-cis} \) linked products in high yields and with excellent levels of \( \text{cis/trans} \) diastereoselectivity. This phenanthroline catalysis method is also applicable to other furanosyl donors. Experiments with 2-fluoro-xylofuranosyl and -arabinofuranosyl bromide donors indicate that furanosyl donor anomeric composition is not responsible for the reaction selectivity. Importantly, the furanosylation reaction is unlikely to proceed through a stereospecific substitution. NMR experiments, kinetic profile, and DFT calculations indicate that the second transition state – the nucleophilic attack of alcohol onto the faster reacting phenanthrolinium ion intermediate – determines the stereochemistry of the product. Collectively, the results obtained highlight the unique features of phenanthroline to catalyze the highly stereoselective furanosylation reactions. The utility of this new method is currently extending to other carbohydrate electrophiles as well as nitrogen and sulfur carbohydrate nucleophiles.
CHAPTER 5: EXPERIMENTAL SECTION

5.1. General Information

Methods and Reagents. All reactions were performed in oven-dried flasks fitted with septa under a positive pressure of nitrogen atmosphere. Organic solutions were concentrated using a Buchi rotary evaporator below 40 °C at 25 torr. Analytical thin-layer chromatography was routinely utilized to monitor the progress of the reactions and performed using pre-coated glass plates with 230-400 mesh silica gel impregnated with a fluorescent indicator (250 nm). Visualization was then achieved using UV light, iodine, or ceric ammonium molybdate. Flash column chromatography was performed using 40-63 μm silica gel (SiliaFlash F60 from Silicycle) or a Biotage Isolera One system using normal phase pre-column cartridges and SNAP Ultra 10g column. Purifications were performed using ethyl acetate/n-hexanes eluting with a step gradient method starting from 0% ethyl acetate and ending at 30% ethyl acetate. Dry solvents were obtained from a SG Waters solvent system utilizing activated alumina columns under an argon pressure. All other commercial reagents were used as received from Sigma Aldrich, Alfa Aesar, Acros Organics, TCI, and Combi-Blocks, unless otherwise noted.

Instrumentation. All new compounds were characterized by Nuclear Magnetic Resonance (NMR) spectroscopy and High-Resolution Mass spectrometry (HRMS). All ¹H NMR spectra were recorded on either Agilent 400 or 600 MHz spectrometers. All ¹³C NMR spectra were recorded on either Agilent 100 or 150 MHz spectrometer. All ¹⁹F NMR spectra were recorded on either Agilent 376 or 564 MHz spectrometer. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent (CDCl₃: δ 7.26 ppm, δ 77.00 ppm; CD₂Cl₂: δ 5.20 ppm, δ 54.00 ppm). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and bs = broad singlet), integration, and coupling constant in hertz (Hz).

High resolution (ESI-TOF) mass spectrometry was performed at Wayne State University Chemistry Lumigen Center.
5.2. Chapter 2 experimental section

5.2.1. General procedure and condition in Table 5

Condition A: A 10 mL Schlenk flask was charged with glycosyl bromide (0.4 mmol, 2.0 equiv), alcohol (0.2 mmol, 1.0 equiv), catalyst C1 (0.06 mmol, 30 mol%), IBO (0.4 mmol, 2.0 equiv.) and MTBE (0.4 mL). The resulting solution was stirred at 50 °C for 24 h, diluted with toluene, and purified by silica gel flash chromatography (toluene/ethyl acetate: 9/1→4/1) to give the desired product.

Condition B: A 10 mL Schlenk flask was charged with glycosyl bromide (0.2 mmol, 2.0 equiv), alcohol (0.1 mmol, 1.0 equiv), catalyst C1 (0.02 mmol, 20 mol%), IBO (0.2 mmol, 2.0 equiv.) and MTBE (0.2 mL). The resulting solution was stirred at 25 °C for 24 h, diluted with toluene, and purified by silica gel flash chromatography (toluene/ethyl acetate: 9/1→4/1) to give the desired product.

Condition C: A 10 mL Schlenk flask was charged with glycosyl bromide (0.2 mmol, 2.0 equiv), alcohol (0.1 mmol, 1.0 equiv), catalyst C1 (0.02 mmol, 20 mol%), IBO (0.2 mmol, 2.0 equiv.) and MTBE (0.2 mL). The resulting solution was stirred at 25 °C for 48 h, diluted with toluene, and purified by silica gel flash chromatography (toluene/ethyl acetate: 9/1→4/1) to give the desired product.

Condition D: A 10 mL Schlenk flask was charged with glycosyl bromide (0.2 mmol, 1.0 equiv), alcohol (0.6 mmol, 3.0 equiv), catalyst C1 (0.04 mmol, 20 mol%), IBO (0.4 mmol, 2.0 equiv.) and MTBE (0.4 mL). The resulting solution was stirred at 25 °C for 24 h, diluted with toluene, and purified by silica gel flash chromatography (toluene/ethyl acetate: 9/1→4/1) to give the desired product.

Condition E: A 10 mL Schlenk flask was charged with glycosyl bromide (0.2 mmol, 1.0 equiv), alcohol (0.6 mmol, 3.0 equiv), catalyst C1 (0.04 mmol, 20 mol%), IBO (0.4 mmol, 2.0 equiv.) and MTBE (0.4 mL). The resulting solution was stirred at 50 °C for 24 h, diluted with toluene, and purified by silica gel flash chromatography (toluene/ethyl acetate: 9/1→4/1) to give the desired product.
Note: The $\alpha/\beta$ ratio of the desired products were determined by $^1$H NMR analysis based on the ratio of the anomeric protons of both $\alpha$- and $\beta$-anomers. When the anomeric protons are overlapped, other protons of both anomers were analyzed. In some cases, we utilized prep-TLC to separate the $\alpha$-anomer from the $\beta$-anomer so that we can accurately determine the $\alpha/\beta$ ratio of the mixture.

Conditions D: 63% (124.2 mg), $\alpha:\beta = 14:1$

$^1$H and $^{13}$C NMR of disaccharide 6 has been reported.$^{219}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.44 – 7.16 (m, 35H), 5.08 – 4.97 (m, 4H), 4.93 – 4.83 (m, 3H), 4.81 – 4.70 (m, 4H), 4.67 – 4.61 (m, 3H), 4.56 – 4.46 (m, 2H), 4.10 – 4.01 (m, 2H), 3.93 – 3.83 (m, 3H), 3.82 – 3.66 (m, 4H), 3.65 – 3.58 (m, 2H), 3.52 (dd, $J = 9.6$, 3.6 Hz, 1H), 3.43 (s, 3H). $^1$H NMR matches with the literature report.$^{219}$

Conditions A: 55% (54.3mg), $\alpha:\beta = 7:1$

$^1$H and $^{13}$C NMR of disaccharide 7 has been reported.$^{219}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.37 – 7.05 (m, 35H), 5.69 (d, $J = 3.5$ Hz, 1H), 5.03 (d, $J = 11.6$ Hz, 1H), 4.91 – 4.39 (m, 13H), 4.27 (d, $J = 12.2$ Hz, 1H), 4.11 – 4.01 (m, 2H), 3.93 – 3.80 (m, 3H), 3.74 – 3.69 (m, 1H), 3.67 – 3.56 (m, 3H), 3.51 – 3.46 (m, 2H), 3.41 – 3.39 (m, 1H), 3.37 (s, 3H). $^1$H NMR matches with the literature report.$^{219}$
Conditions D: 77% (120.4mg), \( \alpha: \beta = 10:1 \)

\(^1\)H and \(^{13}\)C NMR of disaccharide 8 has been reported.\(^{220}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.43 – 7.10 (m, 20H), 5.53 (d, \( J = 5.0 \) Hz, 1H), 5.03 (d, \( J = 3.6 \) Hz, 1H), 4.95 (d, \( J = 11.4 \) Hz, 1H), 4.85 (d, \( J = 11.7 \) Hz, 1H), 4.78 – 4.72 (m, 3H), 4.62 – 4.56 (m, 2H), 4.52 – 4.40 (m, 2H), 4.35 – 4.29 (m, 2H), 4.10 – 3.95 (m, 5H), 3.84 – 3.73 (m, 2H), 3.62 – 3.51 (m, 2H), 1.54 (s, 3H), 1.45 (s, 3H), 1.35 – 1.29 (m, 6H). \(^1\)H NMR matches with the literature report.\(^{220}\)

Conditions E: 58% (86.4mg), \( \alpha \) only

\(^1\)H and \(^{13}\)C NMR of disaccharide 9 has been reported.\(^{219}\)

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.39 – 7.21 (m, 20H), 4.98 – 4.92 (m, 2H), 4.87 – 4.81 (m, 2H), 4.75 – 4.68 (m, 3H), 4.59 (d, \( J = 11.3 \) Hz, 1H), 4.48 (d, \( J = 11.9 \) Hz, 1H), 4.39 (d, \( J = 11.9 \) Hz, 1H), 4.24 (dd, \( J = 9.2, 4.5 \) Hz, 1H), 4.16 – 4.04 (m, 4H), 3.96 (dd, \( J = 10.2, 2.7 \) Hz, 1H), 3.77 – 3.60 (m, 2H), 3.50 (dd, \( J = 8.3, 4.6 \) Hz, 1H), 3.36 – 3.27 (m, 4H), 1.37 (s, 3H), 1.30 (d, \( J = 6.3 \) Hz, 3H), 1.25 (s, 3H). \(^1\)H NMR matches with the literature report.\(^{219}\)
Conditions C: 48% (62mg), α:β = 9:1

\[ ^1H \text{NMR} \quad (\text{CDCl}_3, 400 \text{ MHz}) \]: \( \delta = 7.42-7.22 \text{ (m, 30 H)}, 5.00-4.60 \text{ (m, 14 H)}, 4.03-3.56 \text{ (m, 10 H)}, 3.50 \text{ (dd,} \ J = 8.0, 4.0 \text{ Hz, 1 H)}, 3.32 \text{ (s, 3 H).} \]

\[ ^{13}C \text{NMR} \quad (\text{CDCl}_3, 100 \text{ MHz}) \]: \( \delta = 138.7, 138.62, 138.58, 138.4, 138.3, 138.2, 128.4, 128.31, 128.28, 128.2, 128.1, 1287.94, 127.90, 127.83, 127.75, 127.7, 127.6, 127.5, 98.3, 97.9, 82.0, 80.0, 77.7, 76.2, 75.7, 74.9, 73.7, 73.4, 73.2, 72.3, 71.7, 70.0, 66.4, 60.4, 55.0. \]

**HRMS (ESI):** calc. for C_{54}H_{58}O_{10}Na (M+Na): 889.3922; found: 889.3959.

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Conditions C: 47% (61mg), α only

\[ ^1H \text{NMR} \quad (\text{CDCl}_3, 400 \text{ MHz}) \]: \( \delta = 7.42-7.22 \text{ (m, 30 H)}, 5.00-4.60 \text{ (m, 14 H)}, 4.03-3.96 \text{ (m, 2 H)}, 3.88-3.58 \text{ (m, 8 H)}, 3.46 \text{ (dd,} \ J = 12.0, 4.0 \text{ Hz, 1 H)}, 3.32 \text{ (s, 3 H).} \]

\[ ^{13}C \text{NMR} \quad (\text{CDCl}_3, 100 \text{ MHz}) \]: \( \delta = 138.82, 138.76, 138.4, 138.3, 138.1, 128.32, 128.26, 128.24, 128.18, 127.91, 127.89, 127.8, 127.6, 127.4, 98.3, 97.8, 82.0, 80.0, 77.9, 76.3, 76.2, 75.6, 74.9, 73.9, 73.3, 72.8, 72.4, 71.6, 70.2, 66.4, 60.5, 54.9. \]

**HRMS (ESI):** calc. for C_{54}H_{58}O_{10}Na (M+Na): 889.3922; found: 889.3943.
Conditions B: 80% (55.7 mg), α:β = 6:1

**1H NMR** (400 MHz, CDCl₃): δ = 7.42 – 7.19 (m, 20H), 6.08 (d, J = 9.0 Hz, 1H), 5.90 – 5.80 (m, 1H), 5.29 (d, J = 17.2 Hz, 1H), 5.21 – 5.12 (m, 3H), 4.97 (d, J = 11.6 Hz, 1H), 4.85 – 4.77 (m, 2H), 4.73 – 4.53 (m, 7H), 4.20 (dd, J = 9.9, 2.2 Hz, 1H), 4.01 (dd, J = 10.1, 3.6 Hz, 1H), 3.80 (dd, J = 10.1, 2.7 Hz, 1H), 3.73 (q, J = 6.4 Hz, 1H), 3.60 – 3.52 (m, 2H), 1.07 (d, J = 6.4 Hz, 3H).

**13C NMR** (CDCl₃, 100 MHz): δ = 170.0, 156.2, 138.8, 138.5, 138.4, 136.3, 131.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.6, 127.5, 118.6, 98.9, 79.0, 77.6, 76.4, 74.8, 73.3, 73.2, 69.0, 67.0, 66.8, 66.0, 54.4, 16.5.

### 5.2.2. Standard procedure for catalyst screening

To a 10 mL oven-dried Schlenk flask, added alcohol 3 (0.1 mmol, 1.0 equiv.), catalyst (0.015 mmol, 15 mol%), acid scavenger (IBO or DTBMP, 0.2 mmol, 2.0 equiv.), then transferred glycosyl bromide 2 (0.2 mmol, 2 equiv.) with MTBE (0.2 mL). The resulting solution was stirred at 25 °C for 5 - 24 h, then directly subjected to Biotage Isolera One purification system to give 5 as a colorless syrup.

**1H and 13C NMR** of disaccharide 5 has been reported.²¹⁹

**1H NMR** (600 MHz, CDCl₃) δ 7.38 – 7.23 (m, 18H), 7.15 – 7.11 (m, 2H), 5.51 (d, J = 5.0 Hz, 1H), 4.99 (d, J = 3.5 Hz, 1H), 4.97 (d, J = 10.9 Hz, 1H), 4.80 (dd, J = 12.5, 11.1 Hz, 2H), 4.74 (d, J = 11.9 Hz, 1H), 4.68 (d, J = 11.9 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.59 (dd, J = 7.9, 2.2 Hz, 1H), 4.48 (d, J = 7.9 Hz, 1H),
4.46 (d, J = 9.3 Hz, 1H), 4.35 (dd, J = 7.9, 1.6 Hz, 1H), 4.30 (dd, J = 5.0, 2.3 Hz, 1H), 4.05 – 4.01 (m, 1H),
3.98 (t, J = 9.3 Hz, 1H), 3.84 – 3.80 (m, 1H), 3.80 – 3.72 (m, 3H), 3.69 – 3.62 (m, 2H), 3.58 (dd, J = 9.6,
3.6 Hz, 1H), 1.53 (s, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H).

1H NMR matches with the literature report.\(^\text{219}\)

5.2.3. Preparation of monosaccharide

**Preparation of Methyl 6-O-(4-Fluorobenzyl)-2,3-bis-O-Benzyl-\(\alpha\)-D-Glucopyranoside (17)**

\[
\begin{align*}
\text{F} & \quad \text{+} \\
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} \\
\end{align*}
\]

4-Fluorobenzaldehyde dimethyl acetal (S1) was prepared according to literature procedure.\(^\text{221}\)

To a 250 mL round-bottom flask, added CH₂Cl₂ (40mL), 4-fluorobenzaldehyde (2.2 mL, 21 mmol) and
trimethyl orthoformate (4.6 mL, 42 mmol), then stirred the mixture at room temperature. 5 minutes later,
indium triflate (59 mg, 0.105 mmol) was added to the flask, and stirred for 10 minutes. Upon completion
(monitored by TLC), the mixture was passed through a short plug of neutral alumina which was washed
with additional CH₂Cl₂ (2 x 50 mL). The combined solution was concentrated \textit{in vacuo}, and the resulting
residue (S1) was directly used in the next step.

1H NMR (400 MHz, CDCl₃): \(\delta\) 7.38 (dd, J = 8.5, 5.6 Hz, 2H), 7.00 (t, J = 8.7 Hz, 1H), 5.32 (s, 1H), 3.26
(s, 3H).

19F NMR (376 MHz, CDCl₃): \(\delta\) -114.11 (tt, J = 8.8, 5.5 Hz).

1H NMR matches with the literature report.\(^\text{222}\)
To a 250 mL round-bottom flask with S1 residue (21 mmol) in it, added methyl α-D-glucopyranoside (2g, 10.3 mmol), DMF (50 mL) and p-toluenesulfonic acid monohydrate (1 g, 5.15 mmol). The mixture was stirred at room temperature overnight, and then put on rotary evaporators to remove byproduct (MeOH) and excess solvent. Upon completion (monitored by TLC), the mixture was diluted with 300 mL ethyl acetate, and then washed with 100 mL deionized water, followed by 100 mL saturated sodium bicarbonate solution twice, and 100 mL brine. The organic solution was then dried over sodium sulfate, and concentrated in vacuo overnight to give S2 as a white solid. The resulting residue (S2) was directly used in the next step.

\[ {^1}H \text{ NMR} \ (400 \text{ MHz, CDCl}_3): \ δ \text{ of crude } 4.81 \ (d, J = 3.9 \text{ Hz, } 1\text{H-α}). \]

The white residue S2 was charged to a 500 mL round-bottom flask, and then DMF (75 mL) and benzyl bromide (3.7 mL, 31 mmol) were added to the flask. The solution was then cooled to 0 °C in an ice bath and sodium hydride (60% in mineral oil) (1.24 g, 31 mmol) was added in 3 portions. The mixture was stirred in ice bath overnight. The resulting solution was poured into chipped ice (~ 200 mL), and extracted with 300 mL ethyl acetate. The organic solution was washed with brine, dried over sodium sulfate, and then concentrated in vacuo. The residue was then subjected to Biotage Isolera One purification system to give 3.56 g (72% over two steps) of S3 as a white solid.

\[ {^1}H \text{ NMR} \ (600 \text{ MHz, CDCl}_3): \ δ \ 7.44 \ (dd, J = 8.4, 5.6 \text{ Hz, } 2\text{H}), \ 7.38 – 7.24 \ (m, 10\text{H}), \ 7.04 \ (t, J = 8.6 \text{ Hz, } 2\text{H}), \ 5.50 \ (s, 1\text{H}), \ 4.89 – 4.81 \ (m, 3\text{H}), \ 4.69 \ (d, J = 12.1 \text{ Hz, } 1\text{H}), \ 4.58 \ (d, J = 3.6 \text{ Hz, } 1\text{H}), \ 4.24 \ (dd, J = 10.2, 4.8 \text{ Hz, } 1\text{H}), \ 4.02 \ (t, J = 9.3 \text{ Hz, } 1\text{H}), \ 3.80 \ (td, J = 10.0, 4.8 \text{ Hz, } 1\text{H}), \ 3.68 \ (t, J = 10.3 \text{ Hz, } 1\text{H}), \ 3.57 \ (d, J = 9.6 \text{ Hz, } 1\text{H}), \ 3.54 \ (dd, J = 9.5, 3.9 \text{ Hz, } 1\text{H}), \ 3.39 \ (s, 3\text{H}). \]
Methyl 6-O-(4-Fluorobenzyl)-2,3-bis-O-Benzyl-α-D-Glucopyranoside (17) was prepared according to literature procedure.²²³

To a 100 mL round-bottom flask, added S3 (1 g, 2.08 mmol), THF (15 mL), and 4Å molecular sieves (1.5 g), stirred at room temperature for 30 minutes. Then sodium cyanoborohydride (1.3 g, 20.8 mmol) was added to the solution. Upon all solid dissolved (~15 min), hydrogen chloride solution (2.0 M in diethyl ether) was added dropwise until the evolution of gas ceased (~10 mL). Upon completion (~5 min, monitored by TLC), the mixture was diluted with 150 mL ethyl acetate, and then washed with 50 mL saturated sodium bicarbonate solution three times. The organic solution was dried over sodium sulfate, and concentrated in vacuo. The residue was then subjected to Biotage Isolera One purification system to give 17 as a colorless syrup.

¹H NMR (600 MHz, CDCl₃):  δ 7.37 – 7.24 (m, 12H), 6.99 (t, J = 8.7 Hz, 2H), 5.00 (d, J = 11.5 Hz, 1H), 4.76 (d, J = 12.1 Hz, 1H), 4.72 (d, J = 11.5 Hz, 1H), 4.65 (d, J = 12.1 Hz, 1H), 4.63 (d, J = 3.5 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 3.77 (t, J = 9.2 Hz, 1H), 3.69 (dt, J = 9.6, 3.7 Hz, 1H), 3.65 (d, J = 3.8 Hz, 2H), 3.57 (t, J = 9.3 Hz, 1H), 3.52 (dd, J = 9.6, 3.5 Hz, 1H), 3.37 (s, 3H).

¹³C NMR (151 MHz, CDCl₃): δ 163.23, 161.60, 138.87, 138.13, 133.90, 133.88, 129.45, 129.40, 128.71, 128.58, 128.22, 128.10, 128.07, 127.98, 115.36, 115.22, 98.29, 81.54, 79.74, 75.52, 73.24, 72.96, 70.63, 70.03, 69.52.

¹⁹F NMR (564 MHz, CDCl₃): δ -114.91 – -114.97 (m).

Preparation of 2,3-bis-O-Benzyl-4-O-(4-Fluorobenzyl)-D-Glucopyranose (32)

Methyl 2,3-bis-O-Benzyl-4-(4-Fluorobenzyl)-α-D-Glucopyranoside (S4) was prepared according to literature procedure.\textsuperscript{224}

To a 25 mL Schlenk flask, under nitrogen, added S3 (500 mg, 1.04 mmol) and borane tetrahydrofuran complex solution (1 M in THF), and then stirred at room temperature for 10 minutes. Next, copper(II) trifluoromethanesulfonate (18 mg, 0.05mmol) was added to the flask. Upon completion (monitored by TLC), the reaction was cooled to 0 °C, and sequentially quenched with triethylamine and methanol (\textit{Caution: hydrogen gas evolved!}). The solution was then concentrated \textit{in vacuo} and subjected to Biotage Isolera One purification system to give 483.4 mg (96%) of S4 as a colorless syrup.

\textbf{1H NMR} (400 MHz, CDCl\textsubscript{3}) δ 7.39 – 7.19 (m, 12H), 6.99 (t, J = 8.7 Hz, 2H), 5.00 (d, J = 11.0 Hz, 1H), 4.85 – 4.76 (m, 3H), 4.66 (d, J = 12.1 Hz, 1H), 4.59 (d, J = 12.8 Hz, 1H), 4.57 (d, J = 3.7 Hz, 1H, H-1α), 3.99 (t, J = 9.3 Hz, 1H), 3.78 (d, J = 11.4 Hz, 1H), 3.72 – 3.62 (m, 2H), 3.54 – 3.47 (m, 2H), 3.37 (s, 3H), 1.70 (brs, 1H, -OH).

\textbf{13C NMR} (101 MHz, CDCl\textsubscript{3}) δ 138.70, 138.05, 129.73, 129.65, 128.47, 128.40, 128.11, 127.95, 127.85, 127.62, 115.38, 115.17, 98.14, 81.86, 79.99, 77.39, 75.70, 74.26, 73.40, 70.58, 61.85, 55.20.

\textbf{19F NMR} (376 MHz, CDCl\textsubscript{3}) δ -114.26 – -114.77 (m).

To a 50 mL round-bottom flask, added S4 (483.4 mg, 1 mmol), acetic acid (2.5 mL), and acetic anhydride (2.5 mL). The mixture was cooled to 0 °C in an ice bath, and then concentrated sulfuric acid...
(0.11 mL, 2 mmol) was added to the reaction. Upon completion (~15 min, monitored by TLC), the mixture was diluted with 150 mL ethyl acetate, and then washed with 50 mL saturated sodium bicarbonate solution three times, followed by 50 mL brine. The organic solution was dried over sodium sulfate, and concentrated in vacuo overnight to give S5 a colorless syrup. The resulting residue (S5) was directly used in the next step.

$^1$H NMR (499 MHz, CDCl$_3$) of $\alpha/\beta$ (5/1) mixture (crude) $\delta$ 6.32 (d, $J = 3.5$ Hz, 1H-$\alpha$), 5.61 (d, $J = 8.2$ Hz, 1H-$\beta$).

To a 50 mL round-bottom flask with S5 inside, added dry methanol (5 mL) and sodium methoxide (27 mg, 0.5 mmol). The mixture was stirred at room temperature overnight. Upon completion (monitored by TLC), the reaction was neutralized with Amberlyst® 15 hydrogen form, then filtered. The resulting solution was then concentrated in vacuo and subjected to Biotage Isolera One purification system to give 320.1 mg (66% over two steps) of 32 as a white solid.

$^1$H NMR (600 MHz, CDCl$_3$) of $\alpha:\beta = 2:1$ mixture $\delta$ 7.37 – 7.26 (m, 28H), 7.24 – 7.18 (m, 6H), 7.02 – 6.95 (m, 6H), 5.18 (d, $J = 3.5$ Hz, 2H, H-1$\alpha$), 4.96 – 4.90 (m, 4H), 4.84 – 4.73 (m, 10H), 4.68 (d, $J = 11.7$ Hz, 2H), 4.63 – 4.57 (m, 3H), 3.95 (t, $J = 9.2$ Hz, 2H), 3.93 – 3.89 (m, 2H), 3.85 (dd, $J = 12.0$, 2.4 Hz, 1H), 3.79 (dd, $J = 11.9$, 2.5 Hz, 2H), 3.73 – 3.64 (m, $J = 18.2$, 14.1, 6.4 Hz, 4H), 3.58 – 3.50 (m, 5H), 3.42 – 3.38 (m, 1H), 3.36 (dd, $J = 9.1$, 7.8 Hz, 1H), 3.32 (brs, 1H, $\beta$-OH, hemiacetal), 3.00 (brs, 2H, $\alpha$-OH, hemiacetal), 2.02 (brs, 1H, $\beta$-OH), 1.74 (brs, 2H, $\alpha$-OH).

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 138.52, 138.36, 138.13, 137.63, 133.89, 133.87, 129.75, 129.70, 129.65, 128.54, 128.44, 128.41, 128.10, 128.07, 128.02, 127.82, 127.77, 127.72, 127.68, 127.67, 115.38, 115.35, 115.24, 115.21, 97.38, 91.24, 84.36, 83.14, 81.47, 80.15, 77.35, 75.63, 75.29, 74.82, 74.25, 73.34, 70.97, 61.88, 61.75.

$^{19}$F NMR (376 MHz, CDCl$_3$, $^1$H decoupled) $\delta$ -114.32 (s, $\beta$), -114.44 (s, $\alpha$).

HRMS (ESI): calc. for C$_{27}$H$_{29}$O$_6$FNa (M+Na): 491.1840; found: 491.1846
Preparation of 6-Deoxy-2,3-O-(4-Fluorobenzylidene)-L-Mannopyranose (33)

Procedures of S6 → S7 refer to synthesis of S2.

$^1$H NMR (400 MHz, CDCl$_3$) of diastereomer mixture (~1:1.5) δ 7.53 – 7.39 (m, 11H), 7.36 – 7.28 (m, 8H), 6.14 (s, 2H), 5.93 (s, 1H), 5.87 (s, 1H), 5.78 (s, 2H), 4.43 (dd, $J = 7.0$, 4.8 Hz, 3H), 4.33 (d, $J = 5.3$ Hz, 2H), 4.29 – 4.24 (m, 1H), 4.22 – 4.09 (m, 3H), 3.62 (dd, $J = 9.8$, 7.6 Hz, 3H), 3.45 (dd, $J = 9.7$, 7.3 Hz, 1H), 2.24 (s, 2H), 1.30 (d, $J = 6.2$ Hz, 5H), 1.24 (d, $J = 6.2$ Hz, 3H).

$^{19}$F NMR (376 MHz, CDCl$_3$) δ -111.94 (tt, $J = 8.5$, 5.4 Hz), -112.34 (tt, $J = 8.7$, 5.4 Hz).

To a 100 mL round-bottom flask with S7 (2.07 g, 5.7 mmol) inside, added acetone (50 mL), deionized water (7 mL), N-bromosuccinimide (2.03 g, 11.4 mmol) and potassium carbonate (3.93 g, 28.5 mmol). The mixture was stirred at room temperature overnight. Upon completion (monitored by TLC), the mixture was diluted with 250 mL ethyl acetate, and then washed with 100 mL saturated sodium bicarbonate solution three times. The organic solution was dried over sodium sulfate, and concentrated in vacuo. The residue was then subjected to Biotage Isolera One purification system to give 33 as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.44 (dd, $J = 8.6$, 5.4 Hz, 2H), 7.07 (t, $J = 8.6$ Hz, 2H), 5.93 (s, 1H), 5.57 (s, 1H), 5.00 (dd, $J = 5.4$, 3.9 Hz, 1H), 4.77 (d, $J = 5.6$ Hz, 1H), 4.13 (td, $J = 12.6$, 6.3 Hz, 1H), 4.00 (dd, $J = 8.0$, 3.7 Hz, 1H), 2.45 (s, 1H), 2.35 (s, 1H), 1.39 (d, $J = 6.3$ Hz, 3H).
**13C NMR** (151 MHz, CDCl₃) δ 128.65, 128.59, 115.51, 115.36, 105.02, 101.28, 85.05, 84.15, 80.03, 66.22, 20.32.

**19F NMR** (376 MHz, CDCl₃) δ -111.46 (tt, J = 8.7, 5.4 Hz).

**HRMS (ESI):** calc. for C₁₃H₁₆O₅F (M+H): 271.0976; found: 271.0975.

### 5.2.4. Standard procedures for C1 or C14-catalyzed glycosylation (Table 9 and Scheme 33)

To a 10 mL oven-dried Schlenk flask, added alcohol 2 (0.1 mmol, 1.0 equiv.), catalyst (C1 or C14, 0.015 – 0.03 mmol, 15 – 30 mol%), acid scavenger (IBO or DTBMP, 0.2 mmol, 2.0 equiv.), then transferred glycosyl bromide (0.2 mmol, 2 equiv.) with MTBE or CH₂Cl₂ (0.2 mL). The resulting solution was stirred at 25 - 50 °C for 24 - 48 h, then directly subjected to Biotage Isolera One purification system to give desired products.

Reaction was conducted with 30 mol% catalyst at 50 °C.

**1H and 13C NMR of disaccharide 7 has been reported.**

**1H NMR** (600 MHz, CDCl₃) δ 7.35 – 7.25 (m, 33H), 7.17 – 7.13 (m, 2H), 5.74 (d, J = 3.6 Hz, 1H), 5.08 (d, J = 11.6 Hz, 1H), 4.93 (d, J = 10.8 Hz, 1H), 4.87 – 4.80 (m, 3H), 4.74 (d, J = 12.1 Hz, 1H), 4.66 – 4.53 (m, 7H), 4.47 (d, J = 10.9 Hz, 1H), 4.33 (d, J = 12.2 Hz, 1H), 4.14 (t, J = 9.0 Hz, 1H), 4.10 (t, J = 9.0 Hz, 1H), 3.96 (t, J = 9.3 Hz, 1H), 3.92 – 3.87 (m, 2H), 3.79 – 3.75 (m, 1H), 3.73 – 3.67 (m, 2H), 3.64 (dd, J = 9.3, 3.5 Hz, 2H), 3.56 – 3.53 (m, 2H), 3.46 – 3.43 (m, 1H), 3.42 (s, 3H).

**1H NMR matches with the literature report.**

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**Note:** The text contains chemical structures and reactions that are not rendered as images in this text format. For a complete understanding, please refer to the original document or a chemistry-specific rendering tool.
Reaction was conducted with 30 mol% catalyst at 50 °C.

\*\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) \(\delta\) 7.31 – 7.15 (m, 30H), 7.11 – 7.08 (m, 2H), 6.90 (t, \(J = 8.6\) Hz, 2H), 5.67 (d, \(J = 3.5\) Hz, 1H), 5.02 (d, \(J = 11.6\) Hz, 1H), 4.88 (d, \(J = 10.8\) Hz, 1H), 4.80 (d, \(J = 3.4\) Hz, 1H), 4.77 (d, \(J = 10.6\) Hz, 2H), 4.69 (d, \(J = 12.1\) Hz, 1H), 4.60 – 4.50 (m, 5H), 4.43 – 4.41 (m, 3H), 4.31 (d, \(J = 12.2\) Hz, 1H), 4.07 (t, \(J = 9.1\) Hz, 1H), 4.01 (t, \(J = 9.2\) Hz, 1H), 3.89 (t, \(J = 9.3\) Hz, 1H), 3.85 – 3.79 (m, 2H), 3.70 (d, \(J = 10.0\) Hz, 1H), 3.66 – 3.60 (m, 2H), 3.58 (dd, \(J = 9.5, 3.5\) Hz, 1H), 3.50 – 3.45 (m, 2H), 3.39 – 3.37 (m, 1H), 3.37 (s, 3H).

\*\textsuperscript{13}C NMR (151 MHz, CDCl\textsubscript{3}) \(\delta\) 162.92, 161.29, 138.92, 138.72, 138.43, 137.95, 137.88, 133.86, 128.96, 128.91, 128.40, 128.30, 128.27, 128.25, 128.20, 128.17, 127.95, 127.90, 127.85, 127.76, 127.69, 127.64, 127.60, 127.56, 127.47, 127.07, 126.73, 115.08, 114.94, 97.76, 96.59, 82.01, 81.97, 80.19, 79.46, 77.64, 75.50, 74.97, 74.41, 73.47, 73.35, 73.22, 72.43, 72.29, 70.98, 69.47, 69.04, 68.19, 55.13.

\*\textsuperscript{19}F NMR (564 MHz, CDCl\textsubscript{3}) \(\delta\) -115.15 – -115.24 (m).

HRMS (ESI): calc. for C\textsubscript{62}H\textsubscript{65}O\textsubscript{11}F\textsubscript{N}Na (M+Na): 1027.4403; found: 1027.4436.

Reaction was conducted with 30 mol% catalyst at 50 °C.

\*\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) \(\delta\) 7.35 – 7.18 (m, 32H), 6.95 (t, \(J = 8.6\) Hz, 2H), 5.76 (d, \(J = 3.8\) Hz, 1H), 4.98 (d, \(J = 11.5\) Hz, 1H), 4.89 (d, \(J = 11.4\) Hz, 1H), 4.84 (d, \(J = 11.4\) Hz, 1H), 4.73 (d, \(J = 11.7\) Hz, 1H), 4.71 – 4.66 (m, 3H), 4.59 – 4.53 (m, 5H), 4.38 (d, \(J = 12.1\) Hz, 1H), 4.30 (dd, \(J = 27.2, 11.6\) Hz, 3H), 4.08 (t, \(J = 9.1\) Hz, 1H), 4.02 (dd, \(J = 10.3, 3.8\) Hz, 1H), 3.98 – 3.93 (m, 2H), 3.89 – 3.82 (m, 3H), 3.71 (dd, \(J = 10.6\),
4.7 Hz, 1H), 3.63 (dd, \( J = 10.6, 1.9 \) Hz, 1H), 3.56 (dd, \( J = 9.6, 3.5 \) Hz, 1H), 3.51 (t, \( J = 8.2 \) Hz, 1H), 3.44 (dd, \( J = 8.8, 5.5 \) Hz, 1H), 3.39 (s, 3H).

\(^{13}\text{C NMR}\) (151 MHz, CDCl\(_3\)) \( \delta \) 162.95, 161.33, 138.97, 138.56, 138.27, 137.99, 137.95, 134.11, 134.09, 129.26, 129.20, 128.40, 128.36, 128.32, 128.30, 128.23, 128.23, 128.18, 128.17, 127.89, 127.84, 127.77, 127.73, 127.61, 127.46, 127.38, 127.04, 115.09, 114.95, 97.75, 97.57, 81.97, 80.16, 79.18, 75.61, 74.77, 74.53, 74.37, 73.84, 73.46, 73.37, 72.92, 72.71, 72.36, 69.93, 69.47, 69.39, 68.75, 55.11.

\(^{19}\text{F NMR}\) (564 MHz, CDCl\(_3\)) \( \delta \) -115.03 – -115.11 (m).

\(\text{HRMS (ESI)}\): calc. for C\(_{62}\)H\(_{65}\)O\(_{11}\)FNa (M+Na): 1027.4403; found: 1027.4434.

Reaction was conducted with 30 mol% catalyst at 25 °C.

\(^{1}\text{H NMR}\) (600 MHz, CDCl\(_3\)) \( \delta \) 7.43 – 7.23 (m, 15H), 5.66 (d, \( J = 3.9 \) Hz, 1H), 4.97 (d, \( J = 11.6 \) Hz, 1H), 4.89 (d, \( J = 11.7 \) Hz, 1H), 4.85 (s, 1H), 4.81 (d, \( J = 11.5 \) Hz, 1H), 4.76 – 4.70 (m, 2H), 4.66 (d, \( J = 11.6 \) Hz, 1H), 4.31 (dd, \( J = 7.2, 5.9 \) Hz, 1H), 4.11 – 4.03 (m, 2H), 3.91 (q, \( J = 6.5 \) Hz, 1H), 3.86 (dd, \( J = 10.2, 2.8 \) Hz, 1H), 3.74 (dq, \( J = 12.4, 6.2 \) Hz, 1H), 3.69 – 3.65 (m, 1H), 3.56 (dd, \( J = 9.9, 7.4 \) Hz, 1H), 3.34 (s, 3H), 1.51 (s, 3H), 1.35 (s, 3H), 1.24 (d, \( J = 6.2 \) Hz, 4H), 1.10 (d, \( J = 6.5 \) Hz, 3H).

\(^{13}\text{C NMR}\) (151 MHz, CDCl\(_3\)) \( \delta \) 139.01, 138.55, 138.48, 128.51, 128.31, 128.23, 128.13, 127.54, 127.54, 127.41, 127.39, 109.26, 98.02, 95.92, 79.27, 78.68, 77.55, 77.38, 76.13, 76.06, 74.69, 73.39, 72.91, 66.56, 63.82, 54.63, 27.96, 26.42, 18.03, 16.60.
Reaction was conducted with 20 mol% catalyst at 25 °C.

$^1$H and $^{13}$C NMR of 20 has been reported.\textsuperscript{225}

$^1$H NMR (600 MHz, CDCl\textsubscript{3}) $\delta$ 7.42 – 7.19 (m, 20H), 6.05 (d, $J = 9.0$ Hz, 1H), 5.85 (dq, $J = 10.9$, 5.7 Hz, 1H), 5.28 (d, $J = 17.2$ Hz, 1H), 5.18 (d, $J = 10.4$ Hz, 1H), 5.16 – 5.11 (m, 2H), 4.96 (d, $J = 11.6$ Hz, 1H), 4.80 (t, $J = 12.2$ Hz, 2H), 4.70 (d, $J = 11.8$ Hz, 1H), 4.68 (d, $J = 3.4$ Hz, 1H), 4.64 – 4.59 (m, 4H), 4.58 – 4.54 (m, 1H), 4.19 (dd, $J = 9.9$, 2.0 Hz, 1H), 4.00 (dd, $J = 10.1$, 3.6 Hz, 1H), 3.80 (dd, $J = 10.1$, 2.7 Hz, 1H), 3.72 (q, $J = 6.3$ Hz, 1H), 3.58 – 3.54 (m, 2H), 1.07 (d, $J = 6.5$ Hz, 3H).

$^1$H NMR matches with the literature report.\textsuperscript{225}

Reaction was conducted with 20 mol% catalyst at 25 °C.

$^1$H and $^{13}$C NMR of disaccharide 6 has been reported.\textsuperscript{219}

$^1$H NMR (600 MHz, CDCl\textsubscript{3}) $\delta$ 7.40 – 7.24 (m, 33H), 7.19 – 7.16 (m, 2H), 5.04 (d, $J = 3.4$ Hz, 1H), 5.02 (d, $J = 10.9$ Hz, 1H), 4.99 (t, $J = 6.7$ Hz, 1H), 4.97 (d, $J = 11.1$ Hz, 1H), 4.87 (dd, $J = 10.8$, 8.4 Hz, 2H), 4.83 (d, $J = 10.9$ Hz, 1H), 4.76 (d, $J = 12.0$ Hz, 1H), 4.72 – 4.68 (m, 3H), 4.64 – 4.60 (m, 3H), 4.51 (d, $J = 11.0$ Hz, 1H), 4.47 (d, $J = 12.1$ Hz, 1H), 4.04 (t, $J = 7.2$ Hz, 1H), 4.01 (t, $J = 7.2$ Hz, 1H), 3.88 (dd, $J = 11.6$, 4.5 Hz, 1H), 3.85 – 3.81 (m, 2H), 3.79 – 3.75 (m, 1H), 3.73 – 3.66 (m, 3H), 3.62 – 3.58 (m, 2H), 3.49 (dd, $J = 9.6$, 3.5 Hz, 1H), 3.40 (s, 3H).

$^1$H NMR matches with the literature report.\textsuperscript{219}
Reaction was conducted with 20 mol% catalyst at 25 °C.

$^1$H and $^{13}$C NMR of disaccharide 25 has been reported.\textsuperscript{226}

$^1$H NMR (600 MHz, CDCl\textsubscript{3}) $\delta$ 8.03 – 8.00 (m, 2H), 7.99 – 7.97 (m, 2H), 7.91 – 7.88 (m, 2H), 7.71 (d, $J = 7.6$ Hz, 2H), 7.45 – 7.21 (m, 25H), 7.17 (d, $J = 6.6$ Hz, 2H), 6.19 (t, $J = 9.7$ Hz, 1H), 5.58 (t, $J = 9.9$ Hz, 1H), 5.28 – 5.32 (m, 2H), 4.95 (d, $J = 10.9$ Hz, 1H), 4.86 (d, $J = 11.0$ Hz, 1H), 4.83 – 4.77 (m, 3H), 4.66 (d, $J = 12.2$ Hz, 1H), 4.58 (d, $J = 12.1$ Hz, 1H), 4.49 (d, $J = 11.0$ Hz, 1H), 4.41 (d, $J = 12.1$ Hz, 1H), 4.38 – 4.33 (m, 1H), 4.01 (t, $J = 9.3$ Hz, 1H), 3.92 – 3.86 (m, 2H), 3.70 – 3.65 (m, 2H), 3.63 (dd, $J = 11.0$, 1.9 Hz, 1H), 3.58 (dd, $J = 9.7$, 3.5 Hz, 1H), 3.54 (dd, $J = 10.6$, 1.7 Hz, 1H), 3.47 (s, 3H).

$^1$H NMR matches with the literature report.\textsuperscript{226}

Reaction was conducted with 30 mol% catalyst at 50 °C.

$^1$H NMR (600 MHz, CDCl\textsubscript{3}) $\delta$ 7.34 – 7.15 (m, 30H), 5.75 (d, $J = 3.6$ Hz, 1H), 5.02 (d, $J = 11.7$ Hz, 1H), 4.85 (d, $J = 10.9$ Hz, 1H), 4.80 – 4.75 (m, 3H), 4.68 (d, $J = 12.1$ Hz, 1H), 4.65 (d, $J = 12.3$ Hz, 1H), 4.61 (d, $J = 3.4$ Hz, 1H), 4.60 (d, $J = 8.6$ Hz, 1H), 4.57 – 4.54 (m, 2H), 4.52 (d, $J = 9.1$ Hz, 1H), 4.50 (d, $J = 8.8$ Hz, 1H), 4.30 (d, $J = 9.9$ Hz, 1H), 4.11 – 4.05 (m, 2H), 3.94 (t, $J = 9.3$ Hz, 1H), 3.89 – 3.83 (m, 2H), 3.72 (t, $J = 9.5$ Hz, 2H), 3.59 (dd, $J = 8.7$, 2.9 Hz, 1H), 3.52 (dd, $J = 9.7$, 3.6 Hz, 1H), 3.46 (s, 3H), 3.39 (s, 3H).

$^{13}$C NMR (151 MHz, CDCl\textsubscript{3}) $\delta$ 170.31, 139.06, 138.55, 138.44, 138.11, 138.03, 137.89, 128.54, 128.46, 128.44, 128.42, 128.34, 128.32, 128.30, 128.04, 127.91, 127.88, 127.74, 127.73, 127.72, 127.41, 127.35,
127.18, 126.72, 97.87, 97.29, 81.87, 81.26, 80.30, 79.89, 78.88, 77.37, 77.16, 76.95, 75.71, 75.19, 74.42, 73.55, 73.45, 73.31, 71.24, 69.44, 69.09, 55.33, 52.29.

Reaction was conducted with 15 mol% catalyst at 25 °C.

$^1$H and $^{13}$C NMR of disaccharide 39 has been reported.\textsuperscript{227}

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.63 – 7.60 (m, 2H), 7.48 (d, $J = 7.2$ Hz, 2H), 7.44 – 7.27 (m, 32H), 7.25 – 7.18 (m, 4H), 5.11 (d, $J = 3.5$ Hz, 1H), 5.06 (d, $J = 10.9$ Hz, 1H), 4.95 (dd, $J = 11.1$, 3.7 Hz, 2H), 4.93 – 4.85 (m, 5H), 4.81 (d, $J = 12.1$ Hz, 1H), 4.75 (d, $J = 11.1$ Hz, 1H), 4.71 (d, $J = 9.9$ Hz, 1H), 4.68 (d, $J = 5.3$ Hz, 1H), 4.67 (d, $J = 7.2$ Hz, 1H), 4.55 (d, $J = 11.0$ Hz, 1H), 4.51 (d, $J = 12.1$ Hz, 1H), 4.06 (t, $J = 9.3$ Hz, 1H), 3.96 – 3.90 (m, 2H), 3.87 – 3.84 (m, 1H), 3.80 – 3.71 (m, 4H), 3.70 – 3.65 (m, 2H), 3.57 (ddd, $J = 9.8$, 4.7, 1.5 Hz, 1H), 3.34 (dd, $J = 9.7$, 8.8 Hz, 1H).

$^1$H NMR matches with the literature report.\textsuperscript{227}

Reaction was conducted with 15 mol% catalyst at 25 °C.

$^1$H and $^{13}$C NMR of disaccharide 41 has been reported.\textsuperscript{228}

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.54 – 7.09 (m, 35H), 5.28 (dd, $J = 52.9$, 6.8 Hz, 1H), 5.08 (d, $J = 3.5$ Hz, 1H), 5.04 (d, $J = 10.9$ Hz, 1H), 4.93 (dd, $J = 11.1$, 4.7 Hz, 2H), 4.90 (d, $J = 10.9$ Hz, 1H), 4.86 (d, $J = 10.9$ Hz, 1H), 4.82 (d, $J = 11.1$ Hz, 2H), 4.82 (d, $J = 11.1$ Hz, 2H), 4.79 (d, $J = 7.6$ Hz, 2H), 4.72 (d, $J = 11.2$ Hz, 1H), 4.65 (d, $J = 12.3$ Hz, 2H), 4.54 (d, $J = 10.9$ Hz, 1H), 4.50 (d, $J = 12.1$ Hz, 1H), 4.05 (t, $J = 9.3$ Hz,
1H NMR (600 MHz, CDCl₃) δ 7.45 (d, J = 7.5 Hz, 2H), 7.35 (d, J = 7.4 Hz, 2H), 7.30 (d, J = 7.5 Hz, 2H), 7.23 (d, J = 7.4 Hz, 2H), 7.21 – 7.13 (m, 7H), 7.12 – 7.06 (m, 5H), 6.91 (d, J = 10.1 Hz, 1H), 6.48 (dd, J = 10.1, 1.6 Hz, 1H), 6.23 (s, 1H), 5.27 (d, J = 3.4 Hz, 1H, H-1), 5.05 (d, J = 11.4 Hz, 1H), 4.95 (d, J = 11.3 Hz, 1H), 4.86 (d, J = 11.4 Hz, 1H), 4.82 (d, J = 11.4 Hz, 1H), 4.79 (d, J = 17.1 Hz, 1H), 4.63 (d, J = 11.5 Hz, 1H), 4.60 (d, J = 11.3 Hz, 1H), 4.54 (d, J = 17.0 Hz, 1H), 4.42 (d, J = 12.2 Hz, 1H), 4.38 (d, J = 12.2 Hz, 1H), 4.34 (t, J = 9.3 Hz, 1H), 4.21 – 4.16 (m, 1H), 4.00 – 9.98 (m, 1H), 3.75 – 3.67 (m, 3H), 3.65 (dd,
$J = 9.6, 3.5 \text{ Hz, 1H}$, 3.21 – 3.10 (m, 2H), 2.41 – 2.39 (m, 1H), 2.25 – 2.15 (m, 1H), 2.11 – 1.92 (m, 2H), 1.91 – 1.84 (m, 2H), 1.46 – 1.30 (m, 4H), 1.28 (s, 3H), 1.27 – 1.20 (m, 1H), 1.06 (s, 3H), 1.03 – 0.94 (m, 2H), 0.83 (d, $J = 7.2 \text{ Hz, 3H}$).

$^{13}C$ NMR (151 MHz, $C_6D_6$) $\delta$ 207.62, 186.09, 165.50, 151.88, 139.72, 139.20, 138.99, 138.86, 130.28, 128.70, 128.65, 128.57, 128.56, 128.53, 128.14, 127.98, 127.76, 127.61, 101.00, 99.83, 97.31, 91.57, 88.88, 82.19, 80.73, 78.39, 75.61, 75.17, 73.70, 72.89, 72.34, 72.08, 71.84, 71.07, 69.93, 48.68, 48.44, 48.28, 44.12, 37.03, 36.28, 34.99, 34.48, 34.35, 32.45, 31.02, 30.49, 30.23, 29.43, 27.58, 25.65, 23.07, 18.96, 17.32, 14.91, 11.67.

$^{19}F$ NMR (564 MHz, $C_6D_6$) $\delta$ -165.18 (dd, $J = 28.9, 10.1 \text{ Hz}$).

HRMS (ESI): calc. for $C_{38}H_{66}O_{10}FNa (M+Na)$: 937.4297; found: 937.4327.

Reaction was conducted at 50 °C for 48 h.

29: $^1H$ NMR (600 MHz, CDCl$_3$) $\delta$ 7.42 – 7.26 (m, 18H), 7.17 – 7.13 (m, 2H), 7.10 (d, $J = 8.6 \text{ Hz, 1H}$), 6.59 (dd, $J = 8.3, 2.4 \text{ Hz, 1H}$), 6.53 (d, $J = 2.4 \text{ Hz, 1H}$), 5.71 (brs, 1H, phenol-OH), 5.11 (d, $J = 3.6 \text{ Hz, 1H}$), 5.02 (d, $J = 10.9 \text{ Hz, 1H, H-1}$), 4.85 (d, $J = 11.4 \text{ Hz, 2H}$), 4.81 (d, $J = 11.9 \text{ Hz, 1H}$), 4.72 (d, $J = 11.9 \text{ Hz, 1H}$), 4.62 (d, $J = 12.1 \text{ Hz, 1H}$), 4.50 (dd, $J = 11.3, 9.0 \text{ Hz, 2H}$), 4.08 (dd, $J = 11.9, 6.0 \text{ Hz, 1H, H-16}$), 4.03 (t, $J = 9.3 \text{ Hz, 1H}$), 3.92 – 3.89 (m, 1H), 3.74 (d, $J = 5.9 \text{ Hz, 1H, H-17}$), 3.71 (dd, $J = 10.5, 4.3 \text{ Hz, 1H}$), 3.67 (dd, $J = 10.4, 1.8 \text{ Hz, 1H}$), 3.64 – 3.59 (m, 2H), 2.77 – 2.73 (m, 2H), 2.29 – 2.23 (m, 1H), 2.18 – 2.12 (m, 1H), 1.91 – 1.87 (m, 1H), 1.79 – 1.71 (m, 3H), 1.50 – 1.40 (m, 2H), 1.37 – 1.22 (m, 4H), 0.76 (s, 3H).
\[ ^{13} \text{C NMR} \ (151 \text{ MHz, CDCl}_3) \ \delta \ 153.41, 138.85, 138.13, 138.10, 137.88, 137.84, 132.39, 129.01, 128.52, 128.39, 128.38, 128.34, 128.22, 128.20, 127.98, 127.96, 127.88, 127.86, 127.74, 127.67, 127.56, 126.34, 125.27, 115.25, 112.69, 96.79, 87.84, 84.40, 82.00, 80.12, 77.96, 75.67, 75.16, 73.46, 73.18, 70.45, 68.69, 47.90, 43.79, 43.33, 38.24, 36.38, 31.25, 29.53, 27.06, 25.84, 21.43, 12.13. \]

Distinguished peak for \( \text{30} \): \( ^{1} \text{H NMR} \ (600 \text{ MHz, CDCl}_3) \ \delta \ 4.31 - 4.27 \ (\text{m, 1H, H-16}), \ 3.98 - 3.95 \ (\text{m, 1H, H-5}), \ 3.51 \ (\text{d, J = 5.6 Hz, 1H, H-17}), \ 0.79 \ (\text{s, 3H}). \)

### 5.2.5. Standard procedures for C14-catalyzed chemoselective glycosylation (Table 10)

To a 10 mL oven-dried Schlenk flask, added Steroid-triol (0.15 – 0.3 mmol, 1.5 - 3 equiv.), catalyst (C14, 0.015 – 0.02 mmol, 15 - 20 mol%), DTBMP (0.2 mmol, 2.0 equiv.), then transferred glycosyl bromide (0.1 mmol, 1 equiv.) with MTBE (0.2 mL). The resulting solution was stirred at 25 - 50 °C for 24 h, then directly subjected to Biotage Isolera One purification system to give desired products.

![Chemical structure](image)

Reaction was conducted with 15 mol% catalyst at 25 °C.

\( ^{1} \text{H NMR} \ (499 \text{ MHz, CDCl}_3) \ \delta \ 7.44 - 7.18 \ (\text{m, 45H}), 7.17 - 7.11 \ (\text{m, 3H}), 7.00 - 6.91 \ (\text{m, 3H}), 5.17 \ (\text{d, J = 3.4 Hz, 1H}), 5.06 - 4.93 \ (\text{m, 4H}), 4.93 - 4.79 \ (\text{m, 6H}), 4.79 - 4.66 \ (\text{m, 6H}), 4.65 - 4.56 \ (\text{m, J = 18.8, 6.7 Hz, 4H}), 4.52 - 4.44 \ (\text{m, 3H}), 4.08 \ (\text{dd, J = 9.8, 2.6 Hz, 1H}), 3.99 \ (\text{t, J = 9.0 Hz, 2H}), 3.87 - 3.76 \ (\text{m, 4H}), 3.70 - 3.52 \ (\text{m, 9H}), 3.46 \ (\text{dd, J = 9.4, 3.5 Hz, 1H}), 3.33 \ (\text{t, J = 7.8 Hz, 1H}). \)
$^{13}$C NMR (126 MHz, CDCl$_3$) δ 138.79, 138.76, 138.71, 138.58, 138.36, 138.25, 138.16, 137.89, 137.79, 137.77, 134.15, 134.12, 134.06, 134.03, 129.57, 129.53, 129.51, 129.47, 128.50, 128.49, 128.43, 128.39, 128.36, 128.34, 128.09, 127.99, 127.98, 127.97, 127.95, 127.91, 127.84, 127.82, 127.78, 127.74, 127.69, 127.66, 127.62, 127.59, 127.55, 115.29, 115.27, 115.12, 115.10, 97.56, 97.30, 91.05, 84.48, 83.33, 81.74, 81.69, 80.34, 80.08, 77.79, 77.70, 77.47, 75.63, 75.58, 75.55, 75.40, 75.14, 75.06, 74.65, 74.52, 74.16, 74.11, 73.46, 73.43, 73.19, 72.74, 72.45, 70.55, 70.34, 68.68, 67.04, 66.87.

$^{19}$F NMR (376 MHz, CDCl$_3$, $^1$H decoupled) δ -114.60, -114.74.

HRMS (ESI): calc. for C$_{51}$H$_{63}$O$_{11}$FNa (M+Na): 1013.4247; found: 1013.4277.

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.39 – 7.21 (m, 60H), 7.17 (dd, $J = 13.9$, 6.9 Hz, 5H), 6.95 (td, $J = 8.6$, 3.8 Hz, 4H), 5.17 – 5.12 (m, 4H), 5.01 – 4.87 (m, 8H), 4.81 – 4.71 (m, 9H), 4.68 (dd, $J = 14.0$, 6.0 Hz, 5H), 4.55 – 4.48 (m, 4H), 4.46 (d, $J = 12.8$ Hz, 1H), 4.44 (d, $J = 11.9$ Hz, 2H), 4.37 (d, $J = 11.9$ Hz, 2H), 4.34 (d, $J = 11.7$ Hz, 1H), 4.07 (t, $J = 6.1$ Hz, 1H), 4.01 (dd, $J = 10.3$, 4.4 Hz, 2H), 3.99 – 3.85 (m, 11H), 3.79 – 3.71 (m, 3H), 3.63 (t, $J = 8.9$ Hz, 1H), 3.58 – 3.43 (m, 10H), 3.37 – 3.32 (m, 1H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 163.10, 161.47, 138.64, 138.50, 138.36, 138.29, 138.26, 138.24, 138.20, 137.87, 137.59, 137.45, 134.06, 134.04, 133.86, 133.83, 129.61, 129.56, 129.51, 128.49, 128.44, 128.42, 128.40, 128.37, 128.33, 128.28, 128.24, 128.11, 128.07, 127.95, 127.93, 127.89, 127.86, 127.84, 127.76, 127.72, 127.69, 127.67, 127.65, 127.53, 127.49, 115.30, 115.27, 115.16, 115.13, 97.62, 97.48, 97.40, 90.95, 89.91, 89.86, 88.61, 88.60, 84.49, 83.47, 81.75, 80.36, 77.73, 77.68, 76.58, 76.48, 75.69, 75.57, 75.55, 75.51, 75.44, 75.39, 74.89, 74.86, 74.82, 74.53, 74.16, 74.11, 73.57, 73.48, 73.21, 72.89, 72.88, 72.77, 72.75, 70.83, 69.67, 68.91, 68.88, 67.65, 67.45.
\[^{19}F\] NMR (564 MHz, CDCl\(_3\)) \(\delta -114.47 - -114.54 \text{ (m),} -114.62 - -114.69 \text{ (m),} -207.04 \text{ (ddd, } J = 50.4, 10.0, 4.1 \text{ Hz),} -207.25 \text{ (ddd, } J = 50.3, 10.2, 4.1 \text{ Hz).}

HRMS (ESI): calc. for C\(_{54}\)H\(_{56}\)O\(_{10}\)F\(_2\)Na (M+Na): 925.3734; found: 925.3761.

\[^{1}\text{H}\] NMR (600 MHz, CDCl\(_3\)) \(\delta 7.45 - 7.26 \text{ (m, 36H),} 7.25 - 7.18 \text{ (m, 5H),} 7.17 - 7.12 \text{ (m, 3H),} 6.96 \text{ (t, } J = 8.6 \text{ Hz, 3H),} 5.22 \text{ (d, } J = 3.2 \text{ Hz, 1H),} 5.00 \text{ (t, } J = 9.9 \text{ Hz, 2H),} 4.95 \text{ (d, } J = 11.5 \text{ Hz, 1H),} 4.91 \text{ (dd, } J = 8.5, 3.2 \text{ Hz, 2H),} 4.89 - 4.61 \text{ (m, 17H),} 4.11 - 4.05 \text{ (m, 3H),} 4.05 - 3.93 \text{ (m, 4H),} 3.89 \text{ (dd, } J = 26.3, 10.9 \text{ Hz, 2H),} 3.72 - 3.60 \text{ (m, 6H),} 3.55 \text{ (dd, } J = 9.4, 3.3 \text{ Hz, 1H),} 3.53 - 3.47 \text{ (m, 1H),} 3.40 \text{ (t, } J = 8.1 \text{ Hz, 1H),} 1.14 \text{ (d, } J = 7.2 \text{ Hz, 3H),} 1.13 \text{ (d, } J = 6.8 \text{ Hz, 3H).}

\[^{13}\text{C}\] NMR (151 MHz, CDCl\(_3\)) \(\delta 163.11, 163.06, 161.48, 161.44, 138.86, 138.84, 138.70, 138.67, 138.65, 138.63, 138.61, 138.56, 138.41, 138.00, 134.31, 134.29, 134.14, 134.12, 129.59, 129.53, 129.49, 129.44, 128.52, 128.42, 128.39, 128.27, 128.24, 128.22, 128.21, 128.09, 127.95, 127.91, 127.88, 127.81, 127.67, 127.61, 127.60, 127.49, 127.48, 115.26, 115.22, 115.12, 115.08, 98.04, 97.90, 97.47, 91.11, 84.50, 83.26, 81.72, 80.34, 79.32, 77.76, 77.72, 77.54, 76.42, 76.35, 75.75, 75.68, 74.89, 74.86, 74.73, 74.53, 74.15, 73.32, 73.25, 73.13, 72.93, 72.91, 70.20, 66.68, 66.49, 66.41, 66.30, 16.65, 16.63.

\[^{19}F\] NMR (564 MHz, CDCl\(_3\)) \(\delta -114.62 - -114.69 \text{ (m),} -114.80 - -114.88 \text{ (m).}

HRMS (ESI): calc. for C\(_{54}\)H\(_{57}\)O\(_{10}\)F\(_2\)Na (M+Na): 907.3828; found: 907.3853.

Reaction was conducted with 15 mol% catalyst at 50 °C.
\textbf{1H NMR} (500 MHz, CDCl₃) δ 7.45 – 7.37 (m, 2H), 7.36 – 7.25 (m, 6H), 7.10 – 7.01 (m, 2H), 5.85 (s, 1H), 5.49 (s, 1H), 5.39 (t, $J = 9.7$ Hz, 1H), 5.03 (d, $J = 3.6$ Hz, 1H), 5.00 (dd, $J = 5.2$, 2.4 Hz, 1H), 4.93 (t, $J = 9.9$ Hz, 1H), 4.75 (d, $J = 5.5$ Hz, 1H), 4.59 (dd, $J = 23.2$, 12.3 Hz, 2H), 4.31 – 4.25 (m, 1H), 4.20 – 4.11 (m, 2H), 3.97 (dd, $J = 12.5$, 3.2 Hz, 1H), 3.63 (dd, $J = 12.5$, 1.9 Hz, 1H), 3.58 (dd, $J = 10.0$, 3.7 Hz, 1H), 3.04 (brs, 1H), 2.01 (s, 3H), 1.97 – 1.95 (m, 6H), 1.31 (d, $J = 5.0$ Hz, 2H).

\textbf{13C NMR} (126 MHz, CDCl₃) δ 170.48, 170.13, 169.76, 164.48, 162.50, 137.50, 132.41, 132.39, 128.52, 128.45, 128.11, 127.92, 115.48, 115.30, 104.65, 100.98, 92.77, 85.22, 82.44, 79.36, 76.49, 72.98, 72.04, 69.02, 68.36, 67.27, 61.44, 20.83, 20.63, 20.61, 15.89.

\textbf{19F NMR} (376 MHz, CDCl₃, \textsuperscript{1}H decoupled) δ -111.53.

\textbf{HRMS (ESI)}: calc. for C₃₂H₃₇O₁₃FNa (M+Na): 671.2110; found: 671.2124.
5.3. Chapter 3 experimental section

5.3.1. Kinetic study

Rate equation derivation

Based on the mechanism outlined for phenanthroline-catalyzed glycosylation in Scheme 31, the overall reaction can be described as equation (1), wherein $k_i$ and $k_j$ defined the pre-equilibrium in the first nucleophilic substitution between the reactants, glycosyl bromide donor (D) and catalyst (C), and the intermediate (I). An irreversible nucleophilic attack ($k_2$) by a hydroxyl acceptor (A) then leads to formation of the coupling product (P) and regeneration of catalyst. Based on the assumption of steady-state approximation, the complete rate law can be derived as equation (2).

$$D + C \xrightarrow{\kappa_{1 \to 1}} P + C \quad (1)$$

Therefore,

$$\frac{d[P]}{dt} = k_2[I][A] \quad (S1)$$

$$\frac{d[I]}{dt} = k_1[D][C] - k_{-1}[I] - k_2[I][A] \quad (S2)$$

In addition,

$$[C] = [C_0] - [I] \quad (S3)$$

Applying steady-state approximation,

$$\frac{d[I]}{dt} = 0 \quad (S4)$$

After incorporation of equation (S3):

$$[I] = \frac{k_1[D][C_0]}{k_{-1} + k_2[D] + k_2[A]} \quad (S5)$$

Substitute $[I]$ into rate equation (S1), the rate of product formation can be derived as:

$$\frac{d[P]}{dt} = \frac{k_1 k_2[D][A][C_0]}{k_{-1} + k_1[D] + k_2[A]} \quad (2)$$
General experimental procedure for kinetic study with 1 as donor

A 10 mL scintillation vial was charged with glycosyl bromide 1 (fixed amount, 0.25 mmol, 1.0 equiv), isopropanol acceptor 1A (vary amount from 0.5 to 5 equiv), catalyst C1 (vary amount from 2 to 20 mol%), IBO (vary amount from 1.5 to 3 equiv), toluene (internal standard, 0.083 mmol, 0.33 equiv), and C6D6 (0.5 mL). The resulting solution was then transferred to a 5 mm NMR tube. 1H NMR spectrum was acquired on a 400 MHz instrument before heating. Then the mixture in NMR tube was then consistently shaken and heated in a 50 °C water bath. Between 3 and 60 hours, spectra were obtained depending on the experiment. Example spectra and example rate plot were based on standard condition: 0.25 mmol glycosyl bromide 1 (1.0 equiv), 0.75 mmol acceptor (3.0 equiv), 15 mol% catalyst C1, 0.5 mmol IBO (2 equiv), 0.083 mmol toluene (0.33 equiv) as an internal standard, and 0.5 mL C6D6 (0.5 M).

Spectra processing

The spectra for each kinetic experiment were processed using MestReNova (v. 6.0.2, Mestrelab Research S.L.). The concentrations of product were measured by integration of its H-1 proton against the toluene internal standard, \( \delta = 2.1 \) ppm. Peak fitting or deconvolution algorithms were not used for integration. An example of 1H NMR spectra array is shown in Figure 33.
Graphing

For each kinetic experiment, the concentration of product versus time were plotted on Excel 2016. Linear regression was obtained by best fitting with all points (Figure 34). Slope of the best-fit line represents the initial rate of reaction for each kinetic experiment. The initial rate was then graphed against catalyst concentration for fixed acceptor concentration (Figure 15a), and against acceptor concentration for fixed catalyst concentration (Figure 15b).

Figure 33. Example spectra array for a kinetic experiment with 1 as donor

Figure 34. Example rate plot: product concentration versus time for a kinetic experiment
The product formation versus time was also compared at different equivalent of IBO (Figure 35). As shown in Figure 35, the rate of reactions does not change significantly with varying amounts of IBO.

![Figure 35. Product formation versus time at different equivalent of IBO](image)

A control kinetic experiment was performed in the absence of catalyst (Figure 36). As shown in Figure 36, the desired product was not observed even after 24 h in the absence of catalyst. This result is consistent with our control experiment. After 24 h, the desired product was slowly formed in the reaction. Until 60 h, only 3% conversion was observed. Collectively, these results suggest that the background reaction only takes place after a long period, and it would not affect the aforementioned kinetic experiment.

![Figure 36. Product formation versus time at 0 mol% catalyst](image)
General experimental procedure for kinetic study with $2^\ast$ as donor

All reagents were prepared into three stock solutions:

**Solution A**: 1 M donor $2^\ast$ stock solution. (1.2 mmol $2^\ast$ in 1.2 mL CDCl$_2$)

**Solution B**: 0.1 M Catalyst stock solution. (20.8 mg (0.06 mmol) C14 in 0.6 mL CDCl$_2$)

**Solution C**: 1 M acceptor $3$ solution. (156 mg (0.6 mmol) $3$, 246.4 mg (1.2 mmol) DTBMP, and 27.8 µL (0.2 mmol) mesitylene in 0.6 mL CDCl$_2$)

0.1 mL of solution B and 0.1 mL of solution C were charged to a 1-dram scintillation, then added 0.1-0.3 mL solution A (vary amount of donor from 1 to 3 equiv.). CD$_2$Cl$_2$ was then added to the vial to bring the final volume to 0.5 mL. The reaction mixture was then transferred to an NMR tube, and immediately subjected to $^1$H NMR to obtain spectrum at $t = 0$. Then a $^1$H NMR spectrum was recorded every 30 minutes until 300 minutes.

For kinetic experiment with different catalyst, solution B was switched to 0.1 M stock solution with corresponding catalyst.

**Spectra processing**

The spectra for each kinetic experiment were processed using MestReNova (v. 6.0.2, Mestrelab Research S.L.). The concentrations of product were measured by integration of its H-1 proton against the mesitylene internal standard, $\delta = 6.85$ ppm. Peak fitting or deconvolution algorithms were not used for integration. An example of $^1$H NMR spectra array is shown in Figure 37.
Figure 37. Example spectra array for a kinetic experiment with 2* as donor
5.3.2. Mechanistic study

Preparation of 2,3,4,6-Tera-O-Benzyl-d7-α-D-Glucopyranosyl Bromide (1*).

Ethyl 1-thio-β-D-Glucopyranoside (1.14 g, 5.08 mmol) was dissolved in 25 mL dry DMF in a 100 mL round-bottom flask, then benzyl bromide-d7 (2.66 mL, 22.35 mmol, 4.4 equiv.) was added to the flask. The solution was then cooled to 0 °C in an ice bath and sodium hydride (60% in mineral oil) (894 mg, 22.35 mmol, 4.4 equiv.) was added in 2 portions. The mixture was stirred in ice bath overnight. The resulting solution was poured into chipped ice (~ 100 mL), and extracted with 200 mL ethyl acetate. The organic solution was washed with brine, dried over sodium sulfate, and then concentrated in vacuo. The residue was then subjected to Biotage Isolera One purification system to give 1.37 g (46%) of S2* as a white solid.

1H NMR (600 MHz, CDCl3) δ 4.45 (d, J = 9.8 Hz, 1H, H-1β), 3.73 (dd, J = 10.9, 1.8 Hz, 1H), 3.69 – 3.63 (m, 2H), 3.59 (t, J = 9.4 Hz, 1H), 3.49 – 3.39 (m, 2H), 2.83 – 2.68 (m, 2H), 1.32 (t, J = 7.4 Hz, 3H).

S2* (711.4 mg, 1.2 mmol) was charged to a 50 mL round-bottom flask equipped with nitrogen balloon, then 12 mL dry CH2Cl2 was added. The solution was cooled to 0 °C in an ice bath, and Br2 (0.12 mL, 2.4 mmol, 2 equiv.) was added. The reaction was stirred in ice bath, and monitored by TLC. Upon completion (~ 15 minutes), the reaction was quenched with cyclohexene. The resulting residue was concentrated in vacuo, and yielded 2* as pale-yellow syrup. This crude product was directly used for NMR study without further purification.

1H NMR (600 MHz, CD2Cl2) δ 6.53 (d, J = 3.7 Hz, 1H, H-1α), 4.05 – 4.01 (m, 1H), 3.97 (t, J = 9.1 Hz, 1H), 3.76 (dd, J = 11.0, 3.6 Hz, 1H), 3.72 (t, J = 9.6 Hz, 1H), 3.65 (dd, J = 11.0, 1.5 Hz, 1H), 3.53 (dd, J = 9.2, 3.7 Hz, 1H). HR ESI-TOF MS (m/z): calcd for C34H7D28BrO5Na [M + Na]+, 653.3333; found, 653.3325.
Preparation of NMR samples.

All reagents were prepared into three stock solutions:

**Solution A**: 1 M donor **2** stock solution. (1.2 mmol **2** in 1.2 mL CDCl$_2$)

**Solution B**: 0.1 M Catalyst stock solution. (20.8 mg (0.06 mmol) C14 in 0.6 mL CDCl$_2$)

**Solution C**: 1 M acceptor **3** solution. (156 mg (0.6 mmol) **3**, 246.4 mg (1.2 mmol) DTBMP, and 27.8 µL (0.2 mmol) mesitylene in 0.6 mL CDCl$_2$)

Detection of Glycosyl Phenanthroline Intermediate. 0.1 mL solution A, 0.1 mL solution B and 0.3 mL CD$_2$Cl$_2$ was mixed in a 1-dram scintillation vial, then transferred to an oven-dried NMR tube, and sealed with a septum. The NMR tube was then purged with nitrogen. The tube was immediately placed into the NMR probe and the sample was locked and shimmed properly. $^1$H NMR was taken at t = 0, then every 5 minutes. At t = 30 minutes, after the $^1$H NMR was taken, 1 mL solution C was added to the NMR tube through the septum, and then purged with nitrogen. The solution was carefully mixed in the NMR tube by tightening the NMR tube to a stir bar retriever and stirred on a stir plate. $^1$H NMR was then taken at t = 30 minutes and 300 minutes upon the addition of solution C. The full $^1$H NMR spectra are shown in Figure 38 - Figure 42.
Figure 38. $^1$H NMR of deuterated tetrabenzyl glucosyl bromide 2\textsuperscript{*}

Figure 39. $^1$H NMR of deuterated tetrabenzyl glucosyl bromide 2\textsuperscript{*} and C14 at 0 min
Figure 40. $^1$H NMR of deuterated tetrabenzy glucosyl bromide 2* and C14 at 30 min

Figure 41. $^1$H NMR of deuterated tetrabenzy glucosyl bromide 2* and C14 with acceptor 3 at 30 min
Figure 42. $^1$H NMR of deuterated tetrabenzyl glucosyl bromide $2^*$ and C14 with acceptor 3 at 300 min.

**Conformation of glycosyl phenanthrolinium intermediates.** 0.15 mmol of $2^*$ was prepared freshly from S2*, then dissolved in 0.75 mL CD$_2$Cl$_2$ to make 0.2 M donor solution. C14 (41.5 mg, 0.12 mmol) and mesitylene (5.6 µL, 0.04 mmol) was charged to a 1-dram scintillation vial, then 0.6 mL of the 0.2 M donor solution was added to the vial. After mixing, the solution was transferred to an oven-dried NMR tube, and purged with nitrogen. The tube was immediately placed into the NMR probe and the sample was locked and shimmed properly. Control $^1$H NMR was taken every 5 minutes to ensure the intermediates was formed. Upon formation of intermediates (30 minutes), the NMR probe was cooled to -60 °C using liquid nitrogen and the sample was reshimmed, retuned, and the $^1$H NMR spectrum was then recorded. The sample was warmed at intervals of 10 °C and allowed to equilibrate for 10 minutes. A $^1$H NMR spectrum was recorded at every interval. The collected spectra array was then combined using MestReNova 6.0.2 (Figure 22). As hydrogen bond scalar coupling were observable at 0 °C, $^1$H-$^1$H 2D COSY and ROESY spectra were recorded at 0 °C. The full spectra are shown in Figure 43 - Figure 49.
Figure 43. $^1$H NMR of glucosyl phenanthrolinium intermediates (Int$_1$ and Int$_2$)

Figure 44. $^1$H-$^1$H 2D COSY NMR of glucosyl phenanthrolinium intermediates (Int$_1$ and Int$_2$)
Figure 45. 1H-1H 2D ROESY NMR of glucosyl phenanthroline intermediates (Int₁ and Int₂)

Figure 46. Mass spectrum detection of glucosyl phenanthroline intermediates (Int₁ and Int₂)
Figure 47. $^1$H NMR of 2-deoxy-2-fluoro glucosyl phenanthroline intermediate (Int3)

Figure 48. $^1$H-$^1$H 2D COSY NMR of 2-deoxy-2-fluoro glucosyl phenanthroline intermediate (Int3)
Figure 49. 1H-1H 2D ROESY NMR of 2-deoxy-2-fluoro glucosyl phenanthrolinium intermediate (Ints)

5.3.3. Density Functional Theory (DFT) Calculations

Based on the observation from NMR studies, the β-glycosyl phenanthrolinium ion was at $^4C_1$ chair conformation. However, both B$_{2,5}$ and B$_{1,4}$ boat conformations were fitted with the NMR observation for α-glycosyl phenanthrolinium ion. As such, DFT calculations were performed to compare their energy level. All calculations were carried out with Gaussian 09.$^{160}$ Geometry optimization and vibrational frequency for these intermediates was computed at the B3LYP/6-31+G(d,p) level of theory$^{146-156}$ with the SMD implicit solvation model$^{157}$ in diethyl ether and the GD3BJ empirical dispersion correction$^{229-230}$. There is no imaginary frequency for these intermediates. The free energy of each optimized structure was in comparison with the β-glycosyl phenanthrolinium ion. As shown in Figure 50, α-glycosyl phenanthrolinium ion is more likely to be at B$_{2,5}$ boat conformation since its free energy is 7.9 kcal/mol lower than that of the B$_{1,4}$ boat conformation.
Figure 50. Optimized structures of β- and possible α-glycosyl phenanthroline intermediates

The cartesian coordinates of these three structures was reported in the literature.\(^{216}\)

5.4. Chapter 4 experimental section

5.4.1. Preparation of 2-deoxy-2-fluoro-3,5-di-O-benzyl-D-furanosyl bromide donors

A solution of 1-acetate-2-deoxy-2-fluoro-3,5-bis-O-benzyl-D-furanose (1.0 equiv.) in dry CH\(_2\)Cl\(_2\) (2.0 ml.) was placed in an ice bath to cool to 0°C and HBr (33% in acetic acid, 5.0 equiv.) was added in a dropwise manner. Then, the ice was removed and the mixture was allowed to warm up to ambient temperature while stirring, and continued reacting at this temperature for 1 h. The reaction mixture was then diluted with cold CH\(_2\)Cl\(_2\) (50 mL) and washed with cold water (1 x 50 ml), cold saturated NaHCO\(_3\) solution (2 x 50 ml), dried over Na\(_2\)SO\(_4\), filtered, and evaporated to yield the product as a brown oil. The product was immediately used without additional purification or characterization.
5.4.2. NMR study with 2-fluoro xylofuranosyl donor

NMR course of glycosylation with 2-fluoro xylofuranosyl bromide 50

A 5 mm NMR tube was charged with 2-fluoro xylofuranosyl bromide 50 (3.0 equiv) and CDCl$_3$ (0.6 mL) ($^1$H and $^{19}$F NMR were acquired). Then 5 mol% (according to donor) phenanthroline C14 was added, $^1$H and $^{19}$F NMR were acquired after mixing for 30 min. After the NMR was taken, then the mixture in the NMR tube was added with acceptor 3 (1.0 equiv.) and DTBMP (1.5 equiv.). $^1$H (Figure 51) and $^{19}$F (Figure 52) NMR spectra were obtained at the given time (10 min -24 h) depending on the experiment.

Figure 51. $^1$H NMR course of furanosylation with 2-fluoro xylofuranosyl bromide 50
Figure 52. $^{19}$F NMR course of furanosylation with 2-fluoro xylofuranosyl bromide 50

NMR detection of xylofuranosyl phenanthroline intermediates

A 5 mm NMR tube was charged with 2-fluoro xylofuranosyl bromide 50 (1.5 equiv.) and CDCl$_3$ (0.6 mL), $^1$H and $^{19}$F NMR were acquired. Then phenanthroline C14 (1.0 equiv.) was added to the NMR tube. $^1$H (Figure 53) and $^{19}$F (Figure 54) NMR spectra were obtained at the given time (10 min -16 h) depending on the experiment. The full spectra of $^1$H, $^1$H-$^1$H 2D COSY and ROESY NMR and mass spectrum are shown in Figure 55 - Figure 58.
Figure 53. $^1$H NMR detection of xylofuranosyl phenanthroline intermediates (Int$_4$ and Int$_5$)

Figure 54. $^{19}$F NMR detection of xylofuranosyl phenanthroline intermediates (Int$_4$ and Int$_5$)
Figure 55. $^1$H NMR of xylofuranosyl phenanthrolinium intermediates (Int$_4$ and Int$_5$)

Figure 56. $^1$H-$^1$H COSY NMR of xylofuranosyl phenanthrolinium intermediates (Int$_4$ and Int$_5$)
Figure 57. $^1\text{H}^-^1\text{H}$ ROESY NMR of xylofuranosyl phenanthrolinium intermediates (Int$_4$ and Int$_5$)

Figure 58. Mass Spectrum of xylofuranosyl phenanthrolinium intermediates (Int$_4$ and Int$_5$)
5.4.3. NMR study with 2-fluoro arabinofuranosyl donor

NMR course of glycosylation with 2-fluoro arabinofuranosyl bromide 48

A 5 mm NMR tube was charged with 2-fluoro arabinosyl bromide 48 (3.0 equiv) and CDCl₃ (0.6 mL) (¹H and ¹⁹F NMR were acquired). Then 5 mol% phenanthroline C14 (with respect to donor) was added, ¹H and ¹⁹F NMR were acquired after 30 min. After the NMR was taken, then the mixture in the NMR tube was added with acceptor 3 (1.0 equiv.) and DTBMP (1.5 equiv.). ¹H (Figure 59) and ¹⁹F (Figure 60) NMR spectra were obtained at the given time (10 min -20 h) depending on the experiment.

Figure 59. ¹H NMR course of furanosylation with 2-fluoro arabinofuranosyl bromide 48
Figure 60. $^{19}$F NMR course of furanosylation with 2-fluoro arabinofuranosyl bromide 48

NMR detection of arabinofuranosyl phenanthroline intermediates

A 5 mm NMR tube was charged with 2-fluoro arabinosyl bromide 48 (1.5 equiv.) and CDCl$_3$ (0.6 mL), $^1$H and $^{19}$F NMR were acquired. Then phenanthroline C14 (1.0 equiv.) was added to the NMR tube. $^1$H (Figure 61) and $^{19}$F (Figure 62) NMR spectra were obtained at the given time (10 min -16 h) depending on the experiment. The full spectra of $^1$H, $^1$H-$^1$H 2D COSY and NOESY NMR and mass spectrum are shown in Figure 63 - Figure 66.
Figure 61. $^1$H NMR detection of arabinofuranosyl phenanthrolinium intermediates ($\text{Int}_6$ and $\text{Int}_7$)

Figure 62. $^{19}$F NMR detection of arabinofuranosyl phenanthrolinium intermediates ($\text{Int}_6$ and $\text{Int}_7$)
Figure 63. $^1$H NMR of arabinofuranosyl phenanthrolinium intermediates (Int$_6$ and Int$_7$)

Figure 64. $^1$H-$^1$H COSY NMR of arabinofuranosyl phenanthrolinium intermediates (Int$_6$ and Int$_7$)
Figure 65. $^1$H-$^1$H NOESY NMR of arabinofuranosyl phenanthrolinium intermediates (Int$_6$ and Int$_7$)

Figure 66. Mass Spectrum of xylofuranosyl phenanthrolinium intermediates (Int$_6$ and Int$_7$)
APPENDIX A: SYMBOL NOMENCLATURE FOR GLYCANS

<table>
<thead>
<tr>
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Symbols:
- Glc: Glucose
- Man: Mannose
- Gal: Galactose
- Qul: Quinate
- All: Allenose
- Tia: Tiaose
- GlcNAc: N-acetylglucosamine
- ManNAc: N-acetylmannosamine
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- TiaNAc: N-acetyltiaose
APPENDIX B: $^1$H, $^{13}$C AND $^{19}$F NMR SPECTRA

$^1$H NMR, 600 MHz, CDCl$_3$

$^1$H NMR, 600 MHz, CD$_2$Cl$_2$
$^{1}H$ NMR, 400 MHz, CDCl$_3$

$^{19}$F NMR, 376 MHz, CDCl$_3$
$^1$H NMR, 600 MHz, CDCl$_3$

$^{13}$C NMR, 151 MHz, CDCl$_3$
$^{19}$F NMR, 376 MHz, CDCl$_3$

$^1$H NMR, 600 MHz, CDCl$_3$
$^{13}$C NMR, 151 MHz, CDCl$_3$

$^{19}$F NMR, 564 MHz, CDCl$_3$
S4

$^1$H NMR, 400 MHz, CDCl$_3$

S4

$^{13}$C NMR, 101 MHz, CDCl$_3$
$^{19}$F NMR, 376 MHz, CDCl$_3$

$^1$H NMR, 600 MHz, CDCl$_3$
$^{13}\text{C NMR, 151 MHz, CDCl}_3$

$^{19}\text{F NMR, 376 MHz, CDCl}_3$
1H NMR, 400 MHz, CDCl$_3$

19F NMR, 376 MHz, CDCl$_3$
$^1$H NMR, 400 MHz, CDCl$_3$

$^{13}$C NMR, 151 MHz, CDCl$_3$
$^{19}$F NMR, 376 MHz, CDCl$_3$

$^1$H NMR, 600 MHz, CDCl$_3$
$^1$H NMR, 600 MHz, CDCl$_3$
\[ \text{1H NMR, 600 MHz, CDCl}_3 \]

Diagram of chemical structures 12 and 22.
$^{13}$C NMR, 151 MHz, CDCl$_3$

$^{19}$F NMR, 564 MHz, CDCl$_3$
\[ ^1H \text{ NMR, 600 MHz, CDCl}_3 \]

\[ ^{13}C \text{ NMR, 151 MHz, CDCl}_3 \]
$^{19}$F NMR, 564 MHz, CDCl$_3$

$^1$H NMR, 600 MHz, CDCl$_3$
$^{13}$C NMR, 151 MHz, CDCl$_3$

$^1$H NMR, 600 MHz, CDCl$_3$
$^1$H NMR, 600 MHz, CDCl$_3$

$^{13}$C NMR, 151 MHz, CDCl$_3$
$^1$H NMR, 600 MHz, CDCl$_3$

$^{13}$C NMR, 151 MHz, C$_6$D$_6$
$^{13}$C NMR, 151 MHz, CDCl$_3$

$^{19}$F NMR, 564 MHz, CDCl$_3$
$^1$H NMR, 600 MHz, CDCl$_3$

$^{13}$C NMR, 151 MHz, CDCl$_3$
$^{19}$F NMR, 564 MHz, CDCl$_3$

$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 126 MHz, CDCl$_3$

$^{19}$F NMR, 376 MHz, CDCl$_3$
$^1$H NMR, 600 MHz, CDCl$_3$
$^{19}$F NMR, 564 MHz, CDCl$_3$
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ABSTRACT

PHENANTHROLINE-CATALYZED 1,2-CIS GLYCOSYLATION: SCOPE AND MECHANISM

by

JIAYI LI

August 2022

Advisor: Dr. Hien M. Nguyen

Major: Organic Chemistry

Degree: Doctor of Philosophy

Phenanthroline, a rigid and planar organic compound with two fused pyridine rings, has been used as a powerful ligand for metals and a binding agent for DNA/RNA. We recently discovered that phenanthroline could be used as a nucleophilic catalyst to access high yielding and diastereoselective α-1,2-cis glycosides through the coupling of hydroxyl acceptors with α-glycosyl bromide donors. The utility of the phenanthroline catalysis is expanded to sterically hindered hydroxyl nucleophiles and chemoselective coupling of an alkyl hydroxyl group in the presence of a free C1-hemiacetal functionality. In addition, the phenanthroline-based catalyst has a pronounced effect on site-selective couplings of triol motifs and orthogonally activates the anomeric bromide leaving group over the anomeric fluoride and sulfide counterparts.

An extensive mechanistic investigation showed two glycosyl phenanthrolinium ion intermediates, a $^4C_1$ chair-like β-conformer and a $B_{2,5}$ boat-like α-conformer, in a ratio of 2:1 (β:α). Further, NMR studies show that a hydrogen bonding is formed between the second nitrogen atom of phenanthroline and the C1-anomeric hydrogen of sugar moiety to stabilize the phenanthrolinium ion intermediates. To obtain high levels of α-1,2-cis stereoselectivity, a Curtin-Hammett scenario was proposed wherein interconversion of the $^4C_1$ β-conformer and $B_{2,5}$ α-conformer is more rapid than nucleophilic addition. Hydroxyl attack takes
place from the $\alpha$-face of the more reactive $^4C_1$ chair-like $\beta$-phenanthrolinium intermediate to give an $\alpha$-anomeric product.

The phenanthroline catalysis system is applicable to a number of furanosyl bromide donors to provide the challenging $1,2$-$cis$ substitution products in good yield with high anomeric selectivity. While arabinofuranosyl bromide provides $\beta$-$1,2$-$cis$ products, xylo- and ribofuranosyl bromides favor $\alpha$-$1,2$-$cis$ products. NMR experiments and density-functional theory calculations support an associative mechanism in which the rate-determining step occurs from an invertive displacement of the faster reacting phenanthrolinium ion intermediate with alcohol nucleophile.
AUTOBIOGRAPHICAL STATEMENT

JIAYI LI

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08/2021 AbbVie Scholars Symposium, Online

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