Chiral Phosphoric Acid Catalyzed Regioselective Functionalization of Carbohydrates

by

Jeonghyo Lee

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Medicinal Chemistry)
in the University of Michigan
2019

Doctoral Committee:

Associate Professor Pavel Nagorny, Chair
Professor John Montgomery
Professor Nouri Neamati
Professor David Sherman
Professor John P. Wolfe

Jeonghyo Lee

jnghlee@umich.edu

ORCID iD: 0000-0002-7985-7503

Dedication

To God and my family

Acknowledgements

I would like to express special appreciation to my advisor, Dr. Pavel Nagorny, for allowing me to be a part of his group and being a great mentor for me. When I started my graduate program in Michigan, I was inexperienced in the field of organic chemistry as I was from different background. Under his supervision, I learned how to perceive chemistry, communicate in chemistry, and perform chemistry. I am truly thankful for his guidance and all the support to help me grow and become the independent chemist I am today. Without his patience and support, I wouldn't be as successful as I am now, and wouldn't be able to complete this thesis.

I would also like to thank to my dissertation committee members, Dr. John Montgomery, Dr. David Sherman, Dr. John Wolfe, and Dr. Nouri Neamati for giving me valuable opportunity to share my chemistry with them. Special thanks should go to Dr. John Montgomery for the valuable feedback and advice from the monthly glyco meeting.

I want to thank my undergraduate research advisor Dr. Kimberley Cousins and Dr. Yujung Kim for their guidance and all the support for me to pursue the graduate degree.

I am also greatly thankful to Nagorny lab members. Firstly, I want to thank to our postdoctoral fellows, Dr. Iaroslav Khomutnyk and Dr. Hem Khatri for their valuable advice on my chemistry problems, teaching the practical techniques of experiments, and being good friends to me. I am also thankful to Dr. Bijay Bhattarai, Dr. Tay Rosenthal, Alonso Argüelles, Siyuan Sun, Zachary Fejedelem, Sibin Wang, Nicolas Diaz, Rami Hourani, Nolan Carney, and Sungjin Kim for conversations about chemistry as well as life in general, lunches, coffee, watching movies, and

playing soccer and basketball together. It was a truly privilege to have you all in my life. All the moment in the last 5 years together with you guys will be remembered forever in my life.

During my graduate studies, I was very fortunate to work with talented people for my research projects. Aminoglycoside project wouldn't be possible without the huge contribution of Dr. Alina Borovika and Dr. Iaroslav Khomutnyk. Especially, special credit should go to Dr. Alina Borovika as she established all the fundamental work for this project. I am thankful to Sibin Wang and Miranda Callahan for their contribution on the Cu(II)-decarboxylative Michael project. I would also like to give thanks to Alonoso Argüelles and Rami Hourani on their huge contribution on single-pot carbohydrate functionalization project.

I thank to National Science Foundation CAREER Award (CHE-1350060) and National Institute of Health (grants R01GM111476 and U01GM1252740) for the financial support of the described in this thesis studies.

I would also like to thank YoungJae Kim, Jaeho Im, Yunsu Na, Sangyeop Kim, Jukyung Kang, Sechang Oh, Kwangwoo Jeong, and Seonghoon Hur for all the good memories together in Ann Arbor. I can't imagine my 5 years of stay in Ann Arbor without these incredible people around me. I am very thankful to Christine Feak, Nicolas Diaz, and Nolan Carney for helping me with the proofreading of this thesis.

I express deepest appreciation to Da Yeon Kim, Seungheon Lee, and my family. Thanks to Da Yeon Kim for being always there for me and being the most special person to me. Thanks to Seungheon Lee for being my best friend. Thanks to my parents and my brother for their love, support, and all the prayers for me. I am deeply thankful to be part of my family.

Finally, but foremost, I want to thank God, who is the way, the truth, and the life for me. I am truly grateful for your exceptional love and grace during this entire journey.

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List of Abbreviations

DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DPPA	diphenylphosphoric acid
ee	enantiomeric excess
equiv	equivalent
Et	ethyl
Me	Methyl
EtOAc	ethyl acetate
Hex	Hexanes
g	gram
mg	milligram
HPLC	high-performance liquid chromatography
HSQC	heteronuclear single quantum correlation
Ac	Acetyl
i-Pr	iso-propyl
Ar	Aryl
Bn	Benzyl
Ad	adamantyl
LAH	lithium aluminum hydride
Boc	tert-Butyloxycarbonyl
t-Bu t	ert-Butyl
MeCN	acetonitrile
Bz	Benzoyl

Cat.	Catalyst
n-BuLi	butyl lithium
PG	protecting group
BINOL	1,1'-bi-2-naphthol
SPINOL	1,1’-spirobiindane-7,7’-diol
TFA	Trifluoroacetic acid
CPA	Chiral phosphoric acid
CSA	Camphorsulphonic acid
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMF	Dimethylformamide
n-Bu	*n*-Butyl
MS	Molecular sieves
NBS	*N*-Bromosuccinimide
Nu	Nucleophile
PG	Protecting Group
Ph	Phenyl
PMB	*para*-Methoxybenzyl
Pr	Propyl
i-Pr	iso-Propyl
μg	microgram
μmol	micromole
TCCA	Trichloroisocyanuric acid
TBAF	Tetrabutylammonium Fluoride
TBS	tert-Butyldimethylsilyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
THF	tetrahydrofuran
TMS	trimethylsilyl

TMSOTf	trimethylsilyl trifluoromethanesulfonate
TfOH	Trifluoromethanesulfonic acid
Ts	*para*-Toluenesulfonyl

Abstract

Polyols, such as carbohydrates and other compounds containing multiple hydroxyl groups, represent an important class of molecules. The selective transformations of polyol-containing compounds are of great importance as relatively easily accessible polyol building blocks can be transformed into more synthetic useful compounds. Accomplishing selective transformations of polyols is challenging due to intrinsic complexity of these molecules and unpredictable inherent selectivity of primary and secondary alcohols in the structure. These challenges can be addressed by employing asymmetric catalysis. This dissertation describes the use of chiral phosphoric acids (CPAs) to address the challenges associated with polyol functionalization in carbohydrate system. The described in this dissertation methods, hence, streamline the selective modification of carbohydrates and the carbohydrate synthesis. In addition to the selective functionalization of carbohydrates, this thesis describes the development and use of asymmetric catalysis to address other existing synthetic challenges such as biomimetic Michael reactions.

Chapter 1 describes the development of a new single-pot copper(II)-catalyzed decarboxylative Michael reaction between β-ketoacids and enones, followed by *in situ* aldol condensation. This reaction results in highly functionalized chiral and achiral cyclohexenones containing all carbon quaternary stereocenter.

Chapter 2 provides an overview of regioselective functionalization of polyols by chiral Brønsted acids and other catalysts. The utility of these transformations as well as the discussion of the various catalyst-controlled regioselective reactions of polyols including acylation, silylation, acetalization and glycosylation reactions is provided.

Chapter 3 describes CPA-catalyzed desymmetrizative glycosylation of a functionalized *meso*-diol derived from 2-deoxystreptamine. The chirality of CPA dictates the outcome of the glycosylation reactions, and the use of enantiomeric CPAs results in either C4-glycosylated or C6-glycosylated 2-deoxystreptamines. These glycosylated products can be converted to aminoglycosides, and the application of this strategy to the synthesis of protected *iso*-neamine and *iso*-kanamycin B with inverted connection at the C4 and C6 positions is described.

Chapter 4 summarizes CPA-catalyzed regioselective and stereoselective glycosylation reactions in carbohydrate-derived 2,3-diols. These studies describe evaluation and optimization of CPA-catalyzed glycosylation reactions that helped to identify the most promising catalysts in terms of their ability to control regio- and stereoselectivity. In addition to the structure of the CPA-based catalysts, other factors that can affect stereoselectivity and regioselectivity of glycosylation were investigated. These studies included evaluating the effect of the stereochemistry of the anomeric position of the donor, type and chirality of the sugar donors as well as acidity in the reaction mixture.

Chapter 5 illustrates the development of a regioselective single-pot functionalization of monosaccharides. A single-pot regioselective functionalization of the C2- and C3- hydroxyl groups in monosaccharides (e.g. D-glucose, D-galactose, and D-mannose) was accomplished using CPA-catalyzed regioselective acetalization as the initial step to differentiate the diol moieties in monosaccharides. From this, a single-pot regioselective protection and regioselective glycosylation of monosaccharide were developed with a wide range of protecting groups and sugars.

Chapter 1

Copper(II)-Catalyzed Tandem Decarboxylative Michael/Aldol Reactions Leading to the Formation of Functionalized Cyclohexenones

(This chapter was partially published in: Lee, J.; Wang, S.; Callahan, M.; Nagorny, P., *Org. Lett.* **2018,** *20* (7), 2067.)

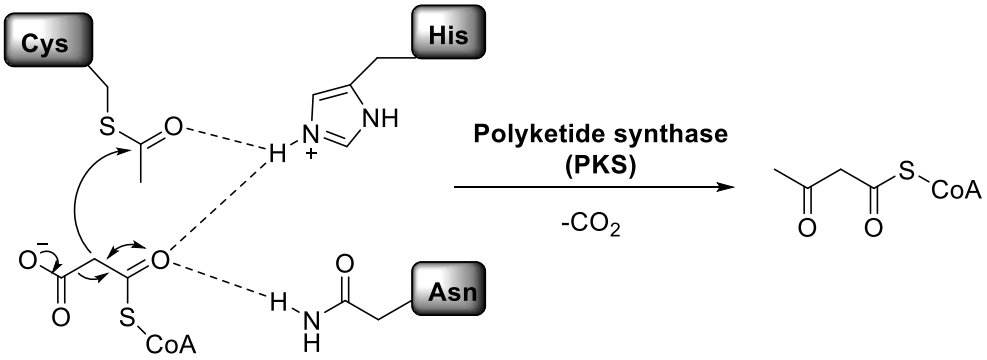
1.1 Introduction of biomimetic decarboxylative addition reactions

In recent years, carbon-carbon (C-C) bond formation from carbon−hydrogen (C-H) bond functionalization has flourished as a front-line research theme in the field of catalysis. Among many methods, a decarboxylative coupling reaction has attracted considerable attention as a way to construct new C-C bond. Compared to conventional C-C bonding methods, the decarboxylative coupling reaction has four major benefits[1]: 1) carboxylic acid derivatives are inexpensive and abundant in different forms, 2) the decarboxylation reaction uses mild conditions to generate the reactive intermediates, 3) the only byproduct of the decarboxylation reaction is CO_2, which is non-hazardous, non-flammable, and is easily removed from the reaction mixture, 4) the decarboxylation reaction results in selective functionalization of the site next to the carboxylate, whereas more traditional enolyzation methods are often not as selective..[2]

By elucidating the polyketides synthase, an essential enzyme for biosynthesis of fatty acids and polyketides, enzymatic mechanism, researchers found that nature already performs decarboxylative coupling reactions under mild conditions (Scheme 1.1). Polyketides synthases utilize malonic acid half-thioesters (MAHTs) as a thioester enolate[3] to carry out biosynthesis of polyketides under physiological conditions without need of strong bases.[4] Polyketides synthases,

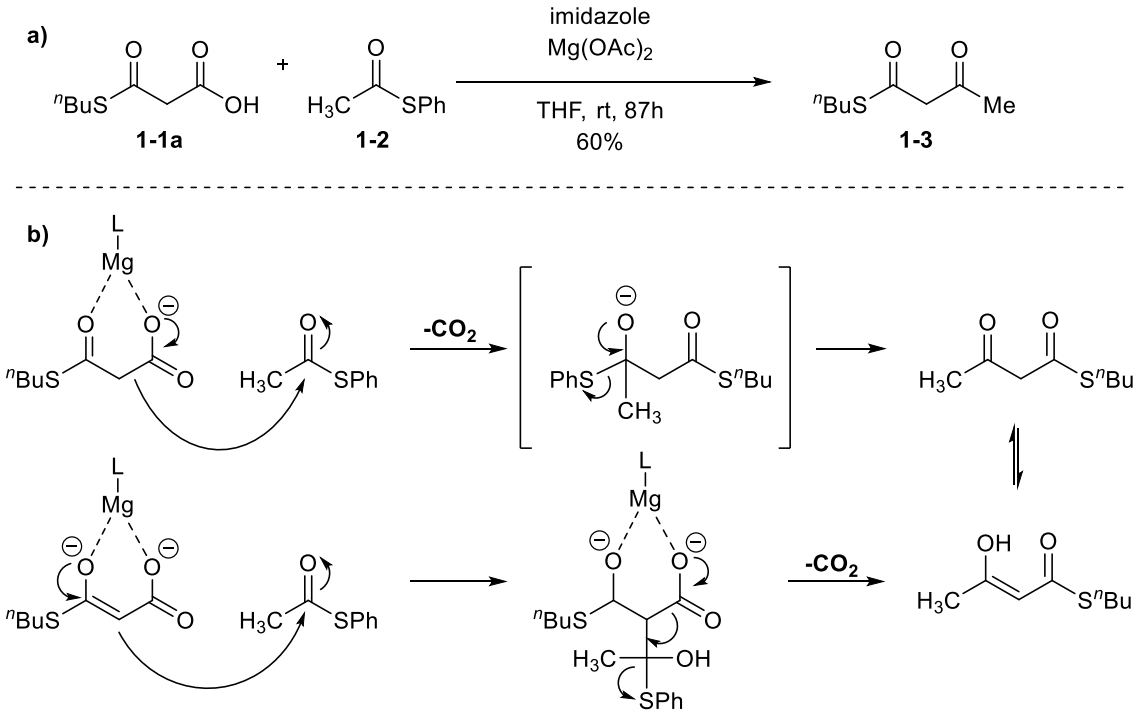
firstly, promote decarboxylation of MAHT through hydrogen bonding with asparagine (Asn) and histidine (His) to convert MAHT to a thioester enolate. The resulting thioester enolate performs a nucleophilic attack to the acyl group of cysteine (Cys) to afford the Claisen condensation product.[5] Decarboxylation enhances the nucleophilicity of the carbon, which is the driving force of the Claisen condensation reaction.

Scheme 1. 1. Claisen condensation in polyketide biosynthesis by the enzyme polyketide synthase.



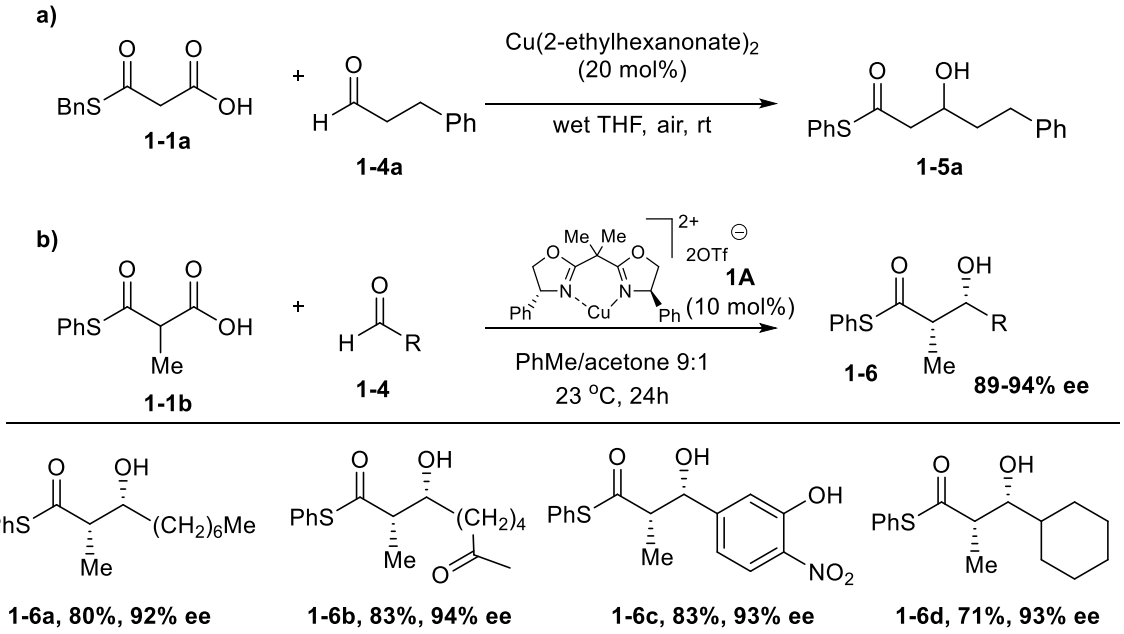
Inspired by polyketides synthases, several groups utilized MAHTs and their derivatives as coupling donors for decarboxylative addition reactions. The very first example of decarboxylative addition of MAHTs was reported by the Kobuke group.[6] The decarboxylative Claisen condensation of MAHT **1-1a** was successfully catalyzed by $Mg(OAc)_2$ to provide synthetically useful products (Scheme 1.2a). The authors proposed two possible mechanisms for the decarboxylative Claisen condensation reactions, (Scheme 1.2b) the first mechanism is based on decarboxylation followed by the enolate addition, while second mechanism is based on nucleophilic addition of enolate followed by decarboxylation. From the subsequent mechanistic study of MeMAHT by the Shair group, the second mechanism was supported by the kinetic and isotope-labeling studies.[7]

Scheme 1. 2. a) Kobuke's first example of decarboxylative addition of MAHTs to thioestates. b) Two potential mechanisms for decarboxylative acylation reactions.



Following Kobuke's pioneering biomimetic Claisen condensation reaction with MAHT, the Shair group illustrated the first example of a biomimetic decarboxylative aldol reaction in 2003 (Scheme 1.3a).[8] This reaction was performed by a Cu(2-ethylhexanoate)$_2$ under remarkably mild conditions (i.e. open air condition with wet solvent at room temperature). Due to its mild reaction condition, both aromatic and aliphatic aldehydes such as **1-4a** were converted to the corresponding aldol adducts such as **1-5a** without any enolization or self-condensation side reactions. Subsequently, Shair group described an enantioselective version of decarboxylative aldol reaction of MAHT **1-1b** to aldehydes **1-4** (Scheme 1.3b).[9] In this work, the authors employed chiral copper(II)/ *bis*(oxazoline) catalyst **1A** to carry out decarboxylative aldol reactions, which resulted in the desired aldol adducts **1-6** in high enantioselectivities and good yields (Scheme 1.3). Like their racemic examples, both aliphatic and aromatic aldehydes were well compatible with this reaction condition.

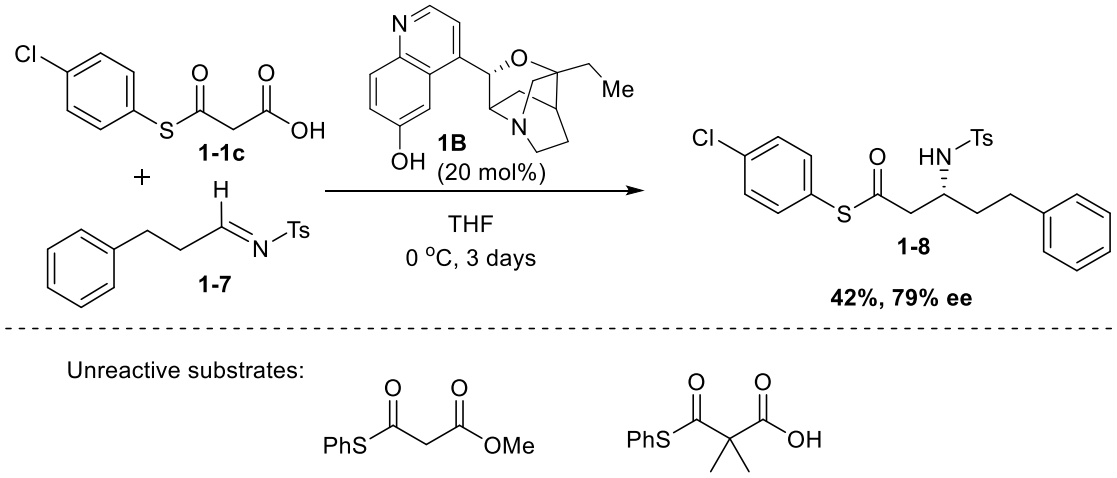
Scheme 1. 3. Shair's decarboxylative aldol reaction of MAHTs to aldehydes. a) Racemic Cu(II)-catalyzed decarboxylative aldol reactions. b) Enantioselective Cu(II)-catalyzed decarboxylative aldol reactions.



After the Shair group's pioneering work on Cu(II)-catalyzed enantioselective decarboxylative aldol reactions, numerous research groups have developed different metal-based catalyst-controlled decarboxylative addition of MAHTs to various electrophiles.[10] However, the decarboxylative addition reactions have been catalyzed not only by the metal-catalysts, but also by the metal-free organocatalysts. In 2007, the Ricci group demonstrated the first example of organocatalyst-controlled asymmetric decarboxylative Mannich reactions of MAHT **1-1c** to imine **1-7**. [11] They used a *Cinchona*-derived organocatalyst **1B** to catalyze the decarboxylative reaction affording the β-amino thioester **1-8** which can be converted to chiral β-amino acids. From this study, *O*-methylthioester maolnate and the α-dimethyl substituted diketone of MAHT were also subjected to the same condition. The reaction of the ester was sluggish, and the reaction of the substituted acid did not afford the desired product, but only unreactive decarboxylation happened. This result suggested first that the decarboxylation is vital for the reactivity of the reaction, and

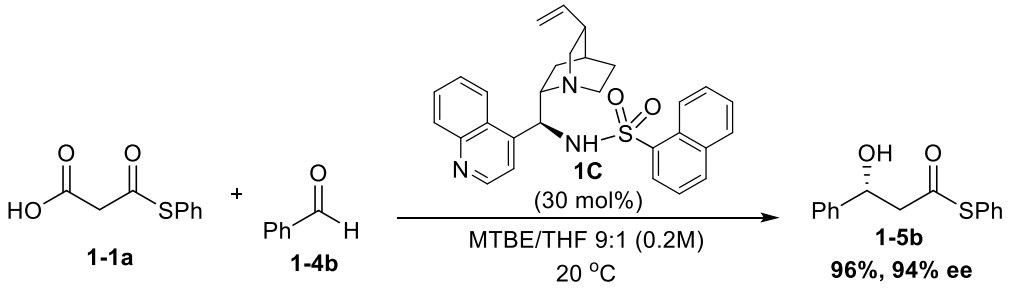
second that there is a severe limitation by the high sensitivity of the decarboxylative reaction due to steric effects exhibited by the substitution pattern.

Scheme 1. 4. Ricci's first example of organocatalyzed enantioselective decarboxylative Mannich reaction of MAHTs to imines.



Subsequently, the Song group developed an organocatalyzed enantioselective aldol reaction with a variety of aromatic and α,β-unsaturated aldehydes,[12] which were not previously described by the Shair group. The Song group demonstrated that the metal-free sulfonamide-based organocatalyst **1C** could catalyze the enantioselective decarboxylative aldol reaction of MAHT **1-1a** with aldehyde **1-4b**. The resulting aldol products such as **1-5b** were valuable as they could be utilized as the synthetic precursors to valuable drugs, such as paroxetine, duloxetine, tomoxetine.

Scheme 1. 5. Song's organocatalyzed enantioselective decarboxylative aldol reactions.



In addition to MAHTs, malonic acid half oxyester (MAHO)[13], β-ketoesters[14], β-ketoacids[15], and regular aliphatic[16] and aromatic carboxylic acids[16] can also be involved in the decarboxylative coupling reactions. This means that the decarboxylative coupling reactions could be used for carboxylic acid derivatives in general. The carboxylic acid functionality acts as a traceless activating groups (similar to cuprates, boronic acids, halides, and Grignards reagents in cross-coupling reactions).[17] Unlike many related transformations that are based on metal activation, decarboxylative reactions produce primarily CO_2 as the nontoxic side-product. Upon decarboxylation, the reactive nucleophilic carbon is generated, and then trapped with carbon-based electrophiles to form C-C bonds efficiently. For these and many other beneficial features, decarboxylative methods have been widely employed in various asymmetric transformations.

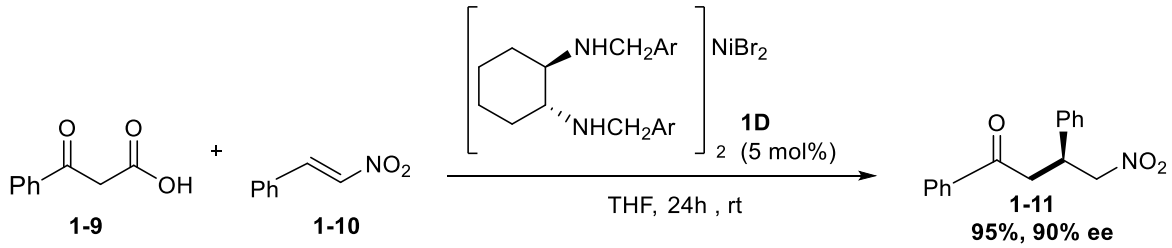
1.2 Overview of decarboxylative Michael reactions

From the discovery of the Michael reaction in 1887[18], 1,4-conjugated additions have been indispensable for C-C bond formation in organic synthesis.[17] In Michael reactions, either nucleophiles or SOMO-activated donors are added to the electrophilic olefin acceptors in a regioselective1,4-addition manner.[17] Among various ways of performing Michael reactions, the decarboxylative strategy was applied to Michael reaction substrates. Due to carboxylate acting as a traceless activating group, such reactions can be promoted under very mild conditions using catalysts that otherwise would not be compatible with strongly basic nucleophilic Michael donors.

In 2007, the Evans group reported the first enantioselective decarboxylative Michael reaction (Scheme 1.6).[15d] In this study, they used a Ni(II) complex **1D** to perform the Michael reaction of 1,3-dicarbonyl compounds, such as β-ketoacid **1-9**, to nitroalkene acceptor **1-10** in a good yields with high enantioselectivities. Similar to Shair's decarboxylative aldol reaction, [8-9] the conditions of Evans' Michael reaction were very mild, and a wide range of Michael acceptors and

donors were tolerated. The chiral diamine ligands did not only provide the chiral environment for the asymmetric transformation, but also promoted the substrate enolization as a base.

Scheme 1. 6. Evan's enantioselective decarboxylative Michael reaction.

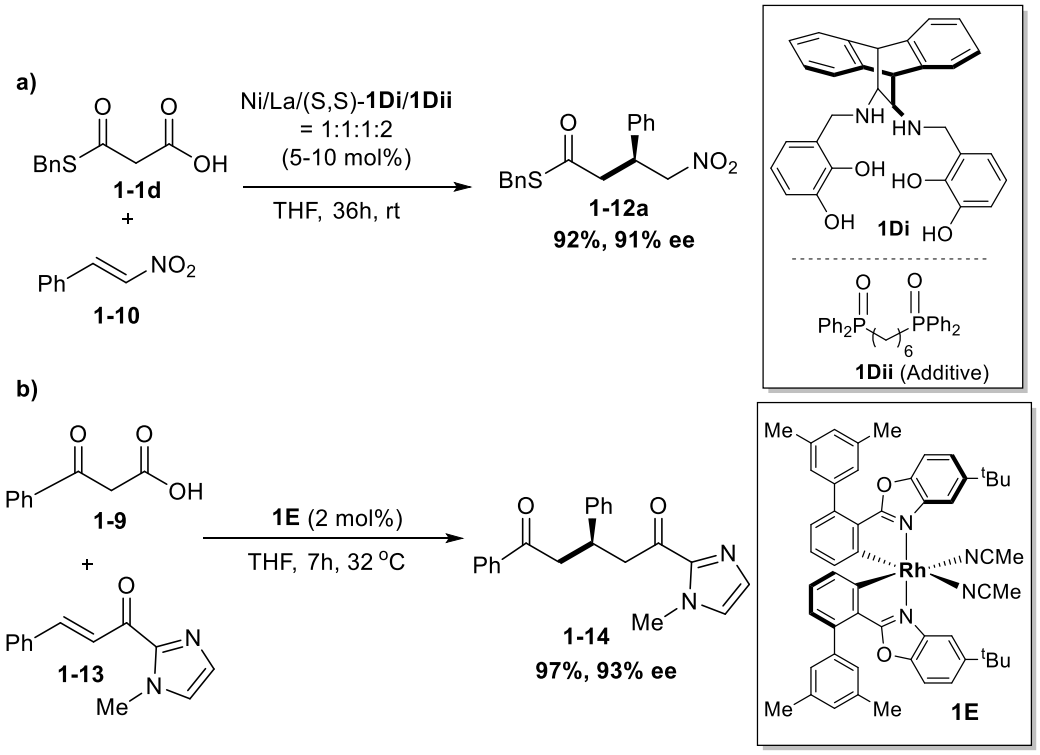


Following the Evans' pioneering work of the chiral Lewis acid complex-catalyzed enantioselective decarboxylative Michael reactions, the potential of enantioselective decarboxylative Michael additions has been unraveled over past decades. Up to date, three different categories of catalysts have been employed to accomplish enantioselective decarboxylative Michael reactions.

First, the asymmetric decarboxylative Michael addition has been accomplished by using Lewis acid catalysts, including Evans' example.[15d, 19] Subsequent to Evans' study, the Shibasaki group reported a Ni/La complex (Ni/La/**1Di**/**1Dii**) catalyzed decarboxylative Michael reaction of MAHT **1-1d** to nitroolefin **1-10** (Scheme 1.7a).[19a] To achieve the enantioselectivity, the dinucleating salan-type ligand **1Di** was used to coordinate to both nickel and lanthanum. As a result, high yields and enantioselectivities were obtained with aryl nitroolefins, but the Michael reaction with alkyl nitroolefins provided moderated yields and enantioselectivities. The Shibasaki group was able to convert the Michael adduct to the optically active antidepressant (*S*)-rolipram in 2 steps in 83% yield. In addition to the nickel and lanthanum complex, rhodium complexes have been employed in the decarboxylative Michael reactions. For instance, the Kang group demonstrated rhodium(III)-complex **1E** catalyzed 1,4-additions of β-ketoacid **1-9** to α,β-

unsaturated 2-acyl imidazole **1-13** (Scheme 1.7b). [19b,19c] Unlike the previous examples where asymmetric induction relied on the chiral ligand in the Lewis acid catalyst, this work achieved the enantioselectivity through the chirality at the actual metal rhodium. The concept of chiral-at-metal complexes was firstly introduced by the Meggers group,[20] and the Kang group successfully employed the chiral-at-metal Rh(III) complex **1E** in an asymmetric decarboxylative addition reaction. The reaction was very efficient with only 1 mol% of Rh(III)-catalysts **1E** to generate the desired Michael adduct **1-4** in 97% yield with 93% enantioselectivity.

Scheme 1. 7. Lewis-acid catalyzed enantioselective decarboxylative Michael addition. a) Shibasaki's example of Ni/La complex catalyzed MAHT to nitroolefins. b) Kang's example of Rh complex catalyzed β-ketoacid to α,β-unsaturated imidazoles or pyridines.



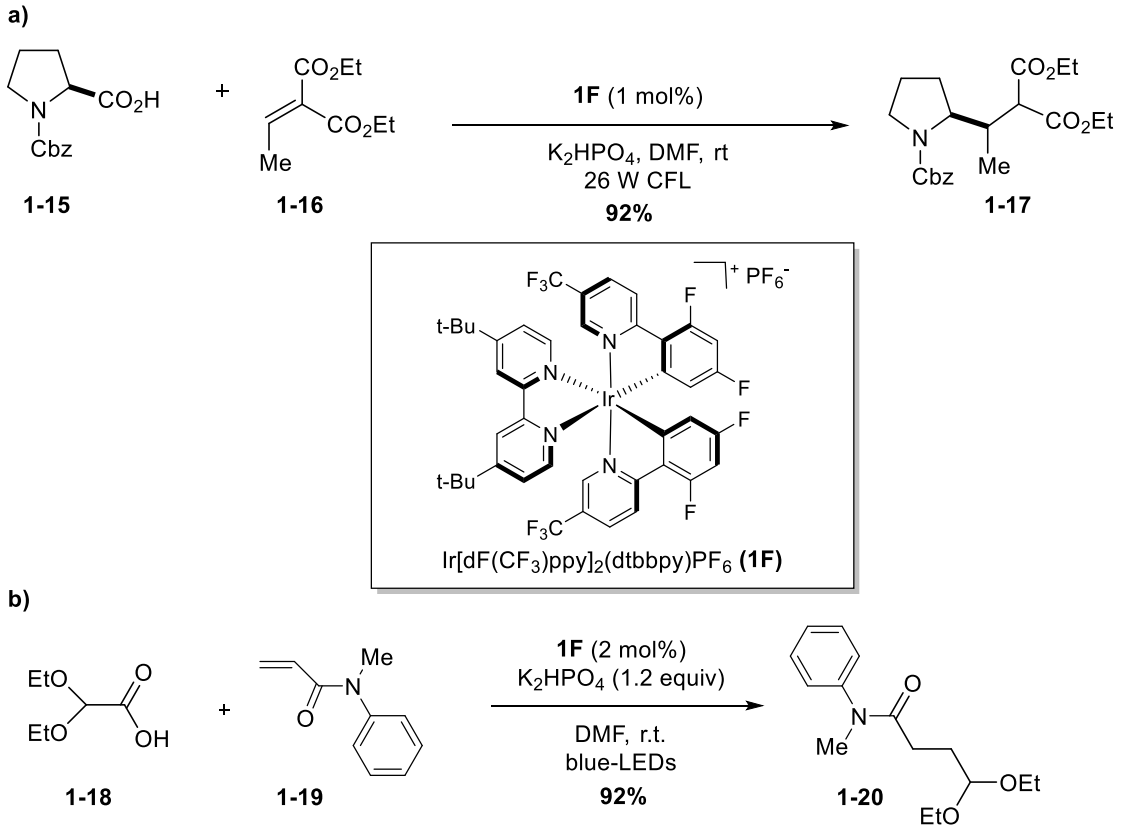
Next, the decarboxylative Michael reactions have been achieved using photoredox catalysis.[21] The representative example of photo-catalyzed Michael reaction was carried out by the MacMillan group by using a Ir(III)-catalyst **1F** as the photoredox catalyst (Scheme 1.8a).[17] The

authors proposed that the acidic proton gets deprotonated by the base and the subsequent single-electron oxidation of formed carboxylates is promoted by the visible-light excited photocatalyst. The resulting carboxyl radical fragments to lose CO_2 to provide active SOMO species, which readily undergo conjugate addition with an electron-deficient olefin to form a new C-C bond. Inspired by these decarboxylative radical conjugate addition reactions, a carboxylic acid **1-15** and Michael acceptor **1-16** were coupled together to afford desired Michael products **1-17** in high yields. By utilizing the Michael adduct from these studies, MacMillan group was able to synthesize optically active pregabalin (Lyrica), an anticonvulsant discovered by Pfizer, in three steps.

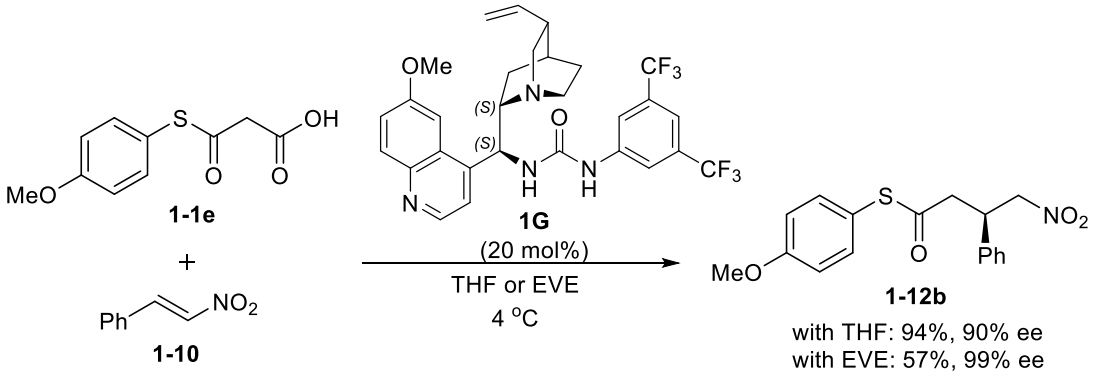
Inspired by Mariano's and Wang's work of photoredox catalyzed decarboxylative coupling of glyoxylic acid acetal to aryl and alkenyl electrophiles,[21a] Xu and coworkers developed another example of iridium-catalyzed photoredox decarboxylative Michael reaction.[21b] The Xu group employed the same Ir(III)-catalyst **1F** as the MacMillan group, [17] and demonstrated that the catalyst was able to catalyze decarboxylative 1,4-additions of glyoxylic acid acetal **1-18** to the Michael acceptor **1-19** with irradiation to afford Michael adduct **1-20** in high yields (Scheme 1.8b).

Lastly, a decarboxylative Michael reaction can also be carried out by chiral organocatalysts,[3a, 22]which resemble polyketide synthases. The organocatalysts have key diamine functionality in their structure, which mimics the active sites of a polyketide synthase. Among the examples of such organocatalyzed decarboxylative Michael reactions, the representative work is exemplified by the Wennemers group who developed the first chiral organocatalyzed enantioselective decarboxylative 1,4-addition of MAHT **1-1e** to nitroalkene **1-10** (Scheme 1.9). [3a] Wennemers employed the chiral *Cinchona* alkaloid-derived urea **1G** as the catalyst to improve the reactivity and selectivity of these reactions. The bifunctional catalyst **1G** can hydrogen-bond nitroolefin and deprotonated MAHT by the tertiary amine at the same time.

Scheme 1. 8. Photoredox Ir(III)-catalyst catalyzed decarboxylative Michael reaction. a) MacMillan's decarboxylative radical conjugate addition. b) Xu's decarboxylative 1,4 additions of glyoxylic acid acetals.

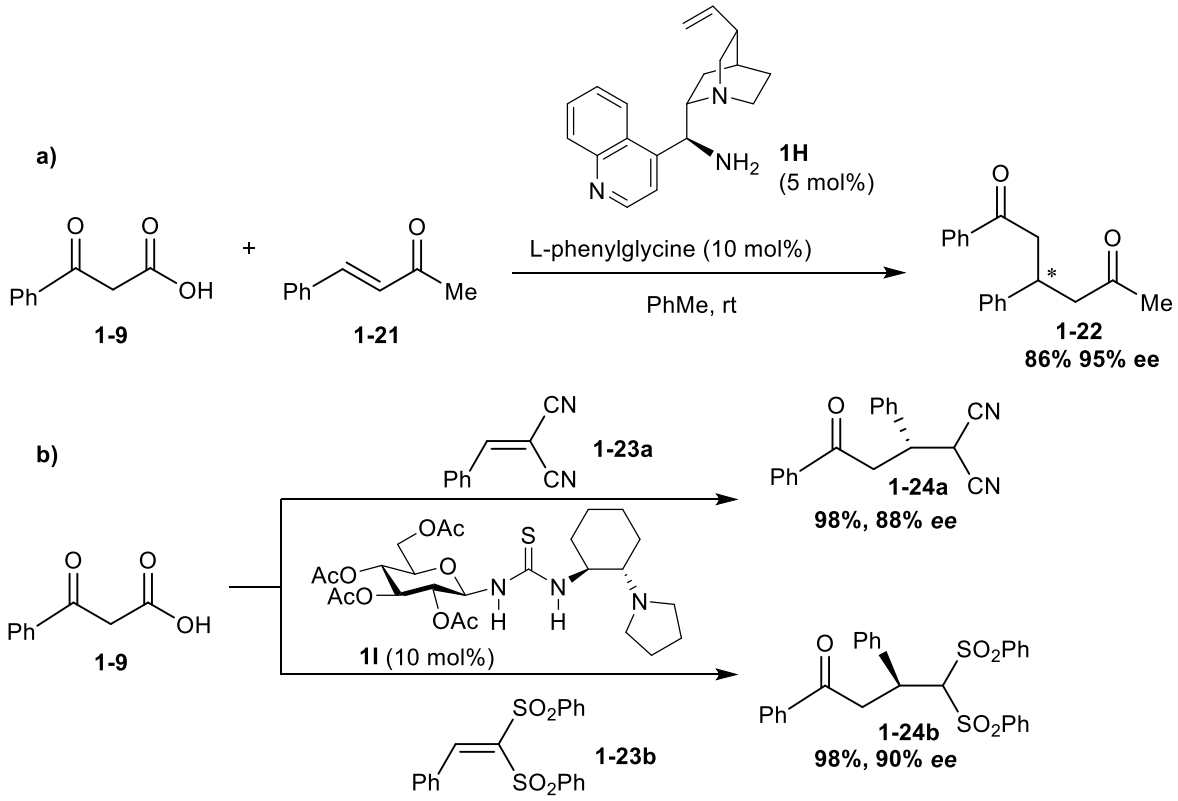


Scheme 1. 9. Wennemers' example of enantioselective decarboxylative 1,4-addition of MAHTs to nitroolefins.



Following the Wennemers' pioneering work, various chiral organocatalysts were designed for the enantioselective decarboxylative Michael reaction. For example, Kim group developed cinchonidine-derived chiral primary amine organocatalysts **1H**, to promote enantioselective 1,4-addition of β-ketoacid **1-9** to α,β-unsaturated ketones **1-21** (Scheme 1.10a).[22a] As a result, corresponding chiral 6-aryl-2,6-hexanedione **1-22** was generated efficiently. Subsequently, the Ma group described a glucose-derived chiral thiourea catalyst **1I** catalyzed decarboxylative Michael addition of β-ketoacid **1-9** to dicyanoolefins **1-23a** and disulfonylolefins **1-23b** (Scheme 1.10b).[22f] The reaction featured wide substrate scope, and afforded the Michael adducts with high yields and enantioselectivities for both the dicyano substrates and the disufonyl substrates. One chiral adduct was converted to a synthetically valuable optically active fluorine-containing building blocks in 4 steps (68% yield with 85% *ee*).

Scheme 1. 10. Example of organocatalyzed enantioselective decarboxylative Michael reaction. a) Kim's example. b) Ma's example.

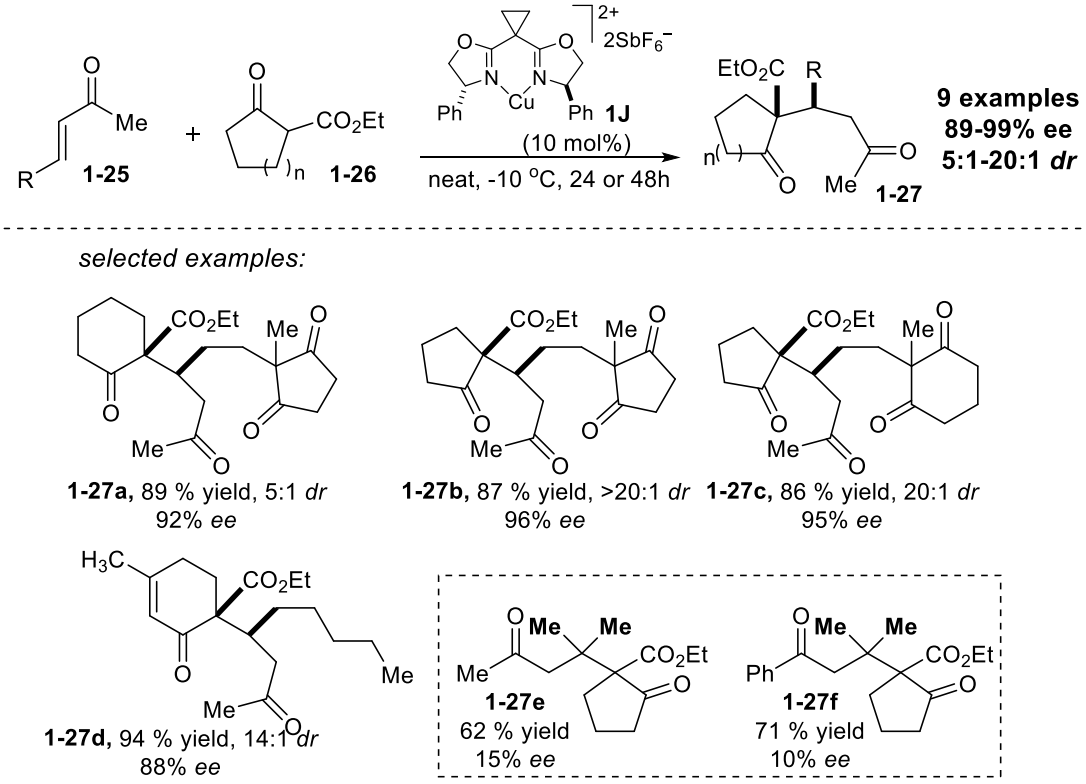


These studies demonstrated the synthetic utility of decarboxylative Michael reactions. Different kinds of catalysts were successfully employed to perform 1,4-addition of carboxylic acid-containing compounds to various electrophilic olefin containing substrates. These reactions do, however, suffer from severe limitations posed by the high sensitivity of Michael reactions to the steric effects exhibited by the substituents on the enones and β-ketoacids. For example, the studies discussed above do not include examples of sterically hindered substrates, such as β,β′-substituted Michael acceptors, due to their low reactivity. Intermolecular addition to β,β′-substituted Michael acceptors is extremely rare[23] and encountered mostly for the Mukaiyama Michael reactions.[24] To address this problem, a new, more powerful, catalyst for the decarboxylative Michael reactions is needed.

1.3 Cu(II)-catalyzed Michael reaction of β-ketoesters and enones

Recently, our group demonstrated that Cu(II) complexes are among the most active catalysts for the Michael reaction of β-ketoesters and enones under solvent-free conditions. [25] This catalytic Cu(II) protocol[26, 27, 28] enabled the unprecedented formation of highly strained Michael addition products containing vicinal quaternary/tertiary and quaternary /quaternary stereocenters[23] under atmospheric pressure (Scheme 1.11).[25b] A Cu(II)/ *bis*-oxazoline complex **1J** efficiently promoted 1,4-additions of β-ketoesters **1-26** to mono-β-substituted enone substrates **1-25** to afford the desired Michael adducts **1-27** with high yields, diastereoselectivies and enantioselectivities. The reaction was general in that different ring sizes of β-ketoesters and the wide range of substituents of β-position of enones were tolerated. Interestingly, Cu(II)-catalyst allowed successful addition of a β-ketoester to sterically hindered β,β′-substituted enones **1-27e** and **1-27f** in decent yield. Although low enantioselectivities were observed for these reactions (10 to 15% ee), this result was still remarkable considering how difficulty is the intermolecular addition to

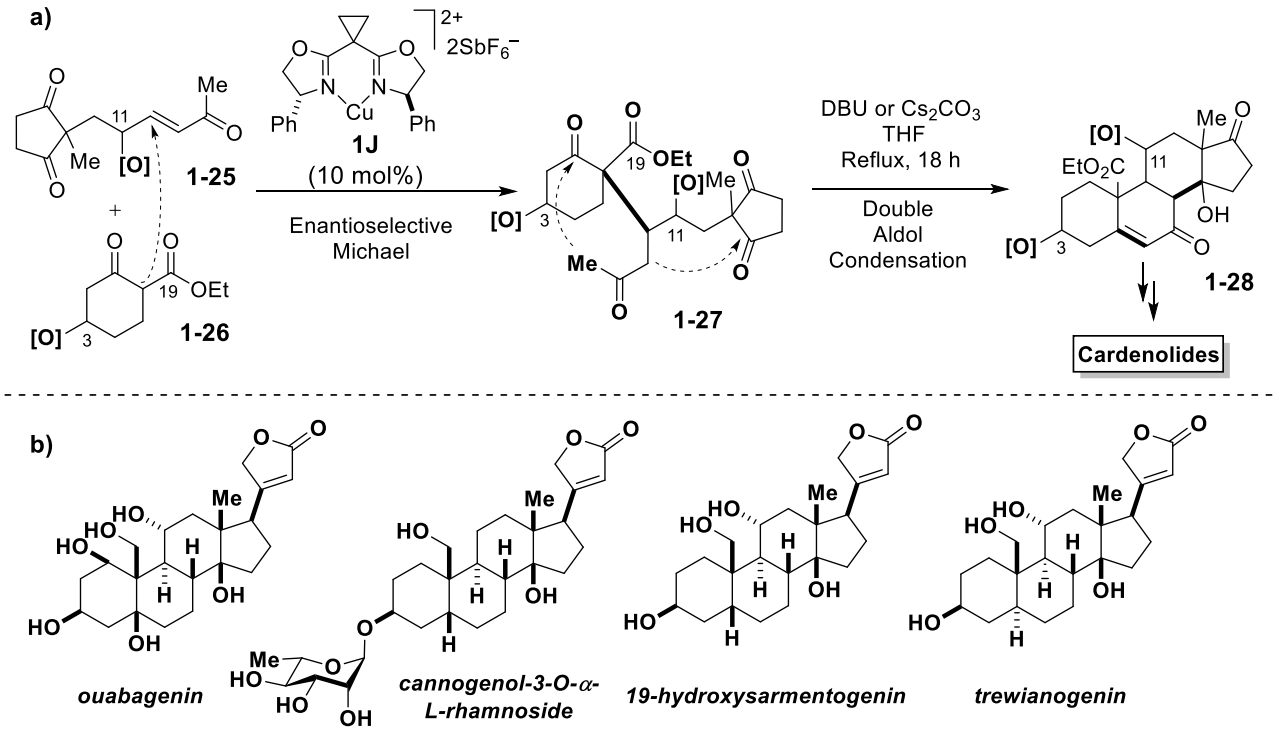
Scheme 1. 11. Nagorny's Cu(II)-complexes-catalyzed enantioselective Michael reaction.



β,β′-enones. This indicated that Cu(II)-catalysts are exceptional promoters of the Michael reactions, and therefore, further development of Cu(II)-catalysts may improve the Michael reactions of sterically hindered substrates.

Based on the enantioselective Cu(II)-catalyzed Michael reactions of β-ketoesters **1-26** and enones **1-25**, the total synthesis of a cardiatonic steroid was carried out (Scheme 1.12). The Michael adducts **1-27** underwent intramolecular aldol reactions to form the cardiotonic steroid cores **1-28**. The oxygenated steroid core **1-28** was further functionalized to afford several natural cardenolides including ouabagenin[25e], cannogenol[25a] 19-hydroxysarmentogenin, and trewianin.[25c]

Scheme 1. 12. Nagorny's enantioselective synthesis of oxygenated steroids via sequential copper(II)-catalyzed Michael addition/intramolecular aldol cyclization reactions.

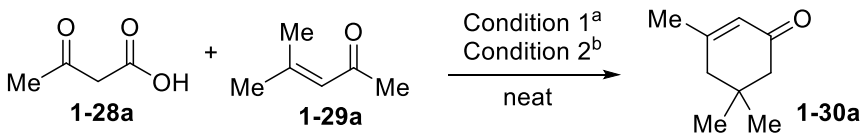


Based on these prior results, we envisioned that Cu(II) salts could promote decarboxylative Michael reactions of unreactive substrates to provide products that are typically inaccessible through the previously reported reactions of β-ketoacids. This chapter summarizes out studies that demonstrates for the first time that Cu(II) salts are unique catalysts for promoting the decarboxylative Michael reactions between β-ketoacids and enones, and the Michael adducts are directly cyclized to form functionalized cyclohexenones *in situ*. The enantioselective variant of this Robinson annulation reaction may also provide chiral cyclohexenones with vicinal tertiary centers. These aforementioned motifs are frequently present in natural products, but are challenging to construct as only few existing Robinson annulation methods could be used to efficiently and selectively install quaternary stereocenters.[29] The utility of this protocol in natural product synthesis has been successfully demonstrated by accomplishing an expedient synthesis of the oxygenated 10-nor cardiotonic steroid skeleton in excellent yield and selectivity.

1.4 Initial optimization for decarboxylative Robinson annulation

Our studies commenced with an investigation of the reaction between β-ketoacid **1-28a** and mesityl oxide **1-29a** (Table 1.1). Considering that the intermolecular addition to β,β′-enones such as **1-29a** is not typical,[23] we investigated various catalytic and stoichiometric promoters.[26c] Monitoring these reactions represents a challenge as multiple products are often observed. Interestingly, the preliminary screen identified that the Robinson annulation product **1-30a** rather than the direct Michael addition product prevailed in the cases when productive reactions were observed. The $Cu(OTf)_2$-catalyzed reaction resulted in the cleanest formation of **1-30a** in 45% yield (entry 1). This yield was further improved by adding a solution of *p*-TSA in THF at the end of the reaction to facilitate the cyclization and dehydration of cyclic and acyclic products arising from the Michael reaction of **1-28a** and **1-29a**. Re-evaluation of the Lewis acid-catalyzed reactions under these modified conditions (entries 1-3, 7-13, Table 1.1) further allowed us to conclude that $Cu(OTf)_2$ is an excellent and unique catalyst for the formation of **1-30a** (entry 1, 83% yield). In addition, $Fe(OTf)_2$ and $Yb(OTf)_3$ were found to possess some activity, but this was significantly lower than for the $Cu(OTf)_2$-catalyzed case (entries 10 and 11). The catalytic activity of $Cu(OTf)_2$ cannot be attributed solely to the *in situ* generation of triflic acid as it alone did not promote the formation of **1-30a** to the same extend (entry 6).

Table 1. 1. Evaluation of the Catalysts for Decarboxylative Robinson Annulation.



Entry	Catalyst	Condition 1 yield (%)	Condition 2 yield (%)
1	$Cu(OTf)_2$	45	83
2	$CuCl_2$	No Rxn[c]	20
3	$Cu(OAc)_2$	No Rxn[d]	N/A
4	Et_3N	No Rxn[c]	N/A
5	DBU	No Rxn[c]	N/A
6	TfOH	15	15
7	$BF_3{\cdot}OEt_2$	No Rxn[d]	N/A
8	$Ni(OTf)_2$	No Rxn[c]	N/A
9	$Fe(OTf)_2$	No Rxn[c]	16
10	$Fe(OTf)_3$	5	9
11	$Yb(OTf)_3$	5	17
12	$Zn(OTf)_2$	No Rxn[c]	N/A
13	$Mn(OTf)_2$	No Rxn[c]	N/A
14	pTSA	15	15

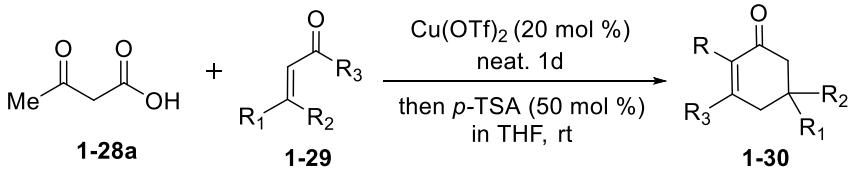
[a]**Condition 1**: **1-28a** (1.6 eq), **1-29a** (1 eq), Catalyst (0.2 eq), neat 12h (without p-TSA)
[b]**Condition 2**: **1-28a** (1.6 eq), **1-29a** (1 eq), Catalyst (0.2 eq), neat 12h, then add *p*-TSA (0.5 eq) in THF, 12h
[c]Consumption of both **1-28a** and **1-29a** leading to multiple products is observed
[d]Consumpition of **1-28a** leading to multiple products is observed

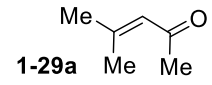
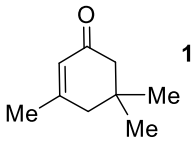
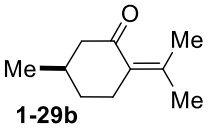
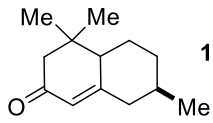
1.5 Decarboxylative Michael/aldol reaction with β,β′-enones to generate cyclohexenones with quaternary stereocenters

With the catalyst and conditions developed, the scope of the decarboxylative Robinson annulation of β,β′-disubstituted enones to give cyclohexenones with quaternary stereocenters was next explored (Table 1.2, 1.3, and Scheme 1.4). Consistent with the observations made for the

reaction of **1-28a** and **1-29a** (*vide supra*), all of the reactions with β,β′-disubstituted enones provided mixtures of Michael adducts and cyclized products when treated with $Cu(OTf)_2$ (20 mol%) alone. However, clean formation of the cyclohexenones was observed if the Cu(II)-catalyzed reactions were followed by *in situ* treatment with *p*-TSA (50 mol %) in THF. Thus, in accord with the results.

Table 1. 2. Substrate scope 1 for the decarboxylative Michael reaction leading to formation of cyclohexenones with quaternary carbon.[a]

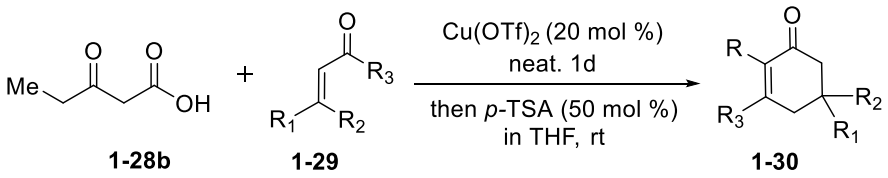


entry	vinyl ketone	time	yield[b] (%)	product
1	 **1-29a**	12 h	83	 **1-30a**
2	 **1-29b**	12 h	57	 **1-30b**

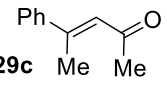
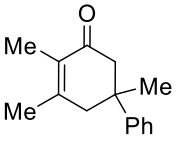
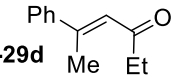
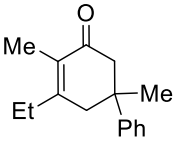
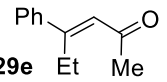
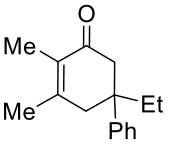
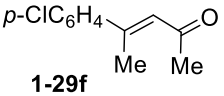
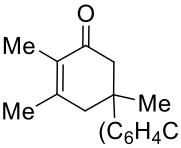
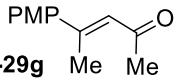
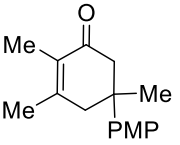
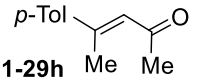
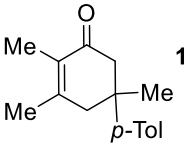
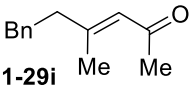
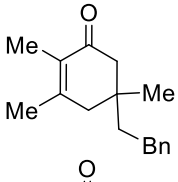
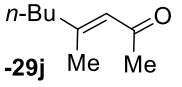
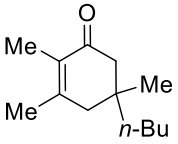
[a]β-Keto acid **1-28a** (1.6 equiv), vinyl ketone **1-29** (1 equiv), then add p-TSA (0.5 equiv).
[b]Isolated yield (average of 3 trials).

obtained for mesityl oxide **1-29a**, the reaction of (*R*)-(+)-pulegone **1-29b** and **1-28a** resulted in the unsaturated 2-decalone **1-30b** in 57% yield (Table 1.2, entry 2). This transformation could tolerate modifications in the β-ketoacid, and in addition to **1-28a**, β-ketoacids **1-28b** (Table 1.3) and **1-28c** (Scheme 1.3) were successfully employed to provide cyclohexenes **1-30c**–**1-30k** in good to excellent yields. Finally, the reactions of **1-28b** with a variety of β,β′-disubstituted enones (**1-29c**–**1-29j**) indicated that this method tolerated changes in the β,β′-substitution pattern without a significant drop in the overall yield. In addition to β,β′-substitution pattern, this method also

Table 1. 3. Substrate scope 2 for the decarboxylative Michael reaction leading to formation of cyclohexenones with quaternary carbon.[a]



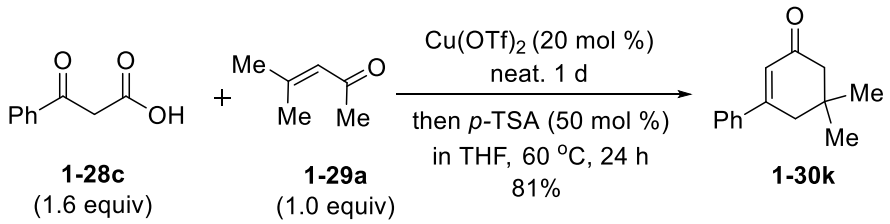
1-28b **1-29** **1-30**

entry	vinyl ketone	time	yield[b] (%)	product
1[c]	 **1-29c**	36 h	52	 **1-30c**
2[c]	 **1-29d**	36 h	43	 **1-30d**
3[c]	 **1-29e**	36 h	60	 **1-30e**
4[c]	 **1-29f**	36 h	53	 **1-30f**
5[c]	 **1-29g**	36 h	52	 **1-30g**
6[c]	 **1-29h**	36 h	59	 **1-30h**
7	 **1-29i**	12 h	62	 **1-30i**
8	 **1-29j**	12 h	70	 **1-30j**

[a]β-Keto acid **1-28b** (1.6 equiv), vinyl ketone **1-29** (1 equiv), then add p-TSA (0.5 equiv). [b]Isolated yield (average of 3 trials). [c]Additional β-keto acid **1-28b** (0.5 equiv) was added every 24 h due to decarboxylation.

tolerated the steric hinderance for alpha to the ketone as 3-oxo-3-phenylpropanoic acid **1-28c** gave the desired cyclohexene **1-30k** (Scheme1.3). Importantly, this method provides quick, straightforward, and selective access to highly functionalized cyclohexenones that are not always readily accessible through other transformations such as metal-catalyzed alkyne insertion into cyclobutanones.[30]

Scheme 1. 13. Decarboxylative Robinson annulation reaction of **1-28c** and **1-29a**.

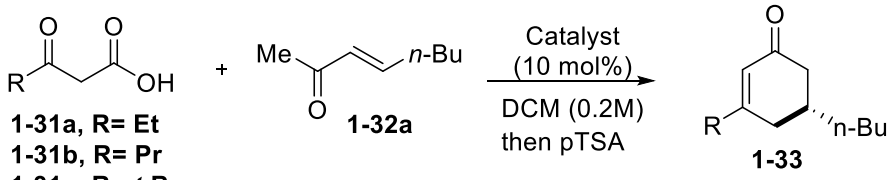


1.6 Enantioselective formation of cyclohexenones

Our initial attempts to accomplish the enantioselective formation of cyclohexenones **1-30** containing quaternary stereocenters by using the chiral *bis*(oxazoline)-based Cu(II) complexes such as **1J**[25a-d, 27, 28] (Scheme 1.4) were met with limited success as the reactions of β,β′-substituted 2-en-1-ones **1-29** suffered from low conversion and enantioselectivity. However, the reactions of β-monosubstituted enones such as **1-32a** proceeded with excellent yields and enantioselectivities (Table 1.4). Both racemic and enantioselective reactions of decarboxylative Robinson annulation of β-ketoacid **1-31** and enone **1-32a** successfully carried out with $Cu(OTf)_2$ and *bis*(oxazoline)-based Cu(II) complexes **1J** (Table 1.4a) Thus, the annulation of **1-32a** with reactive β-ketoacids **1-31** lacking the C2-substitution resulted in the formation of chiral cyclohexenones **1-33a**−**1-33c** in good yields and excellent enantioselectivities. In addition, the reaction of C2-substituted β-ketoester **1-31d** and **1-32a** led to the formation of the synthetically valuable functionalized decalin **1-33d** (Table 1.4b). From the optimization studies, we found that the catalyst **1J** at -10 °C provided

Table 1. 4. Reaction optimization of Cu(II)-catalyzed enantioselective decarboxylative Robinson annulation reactions of a) **1-31a-1-31c** and **1-32a** and b) **1-31d** and **1-32a**. c) List of chiral *bis*(oxazoline)-copper(II)-catalyst.

a)



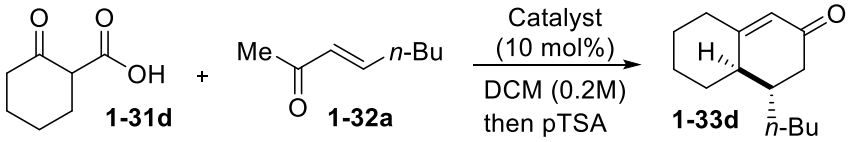
1-31a, R= Et
1-31b, R= Pr
1-31c, R= *t*-Bu

1-32a

1-33

Entry	β-ketoacid	Catalyst	T (°C)	Time (h)	product	Conv (Yield[b])	ee (%)	*d.r.*
1	**1-31a**	$Cu(OTf)_2$[a]	rt	5h	**1-33a**	>95 (58)	N/A	N/A
2	**1-31a**	**1J**	-10	1d	**1-33a**	>95 (65)	92	N/A
3	**1-31b**	$Cu(OTf)_2$[a]	rt	5h	**1-33b**	>95 (63)	N/A	N/A
4	**1-31b**	**1J**	-10	1d	**1-33b**	>95 (67)	91	N/A
5	**1-31c**	$Cu(OTf)_2$[a]	rt	5h	**1-33c**	>95 (69)	N/A	N/A
6	**1-31c**	**1J**	-10	1d	**1-33c**	>95 (73)	84	N/A

b)



1-31d

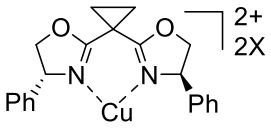
1-32a

1-33d

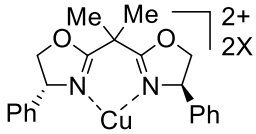
Entry	Catalyst	T (°C)	Time (h)	Conv (Yield[b])	ee (%)	*d.r.*
1	$Cu(OTf)_2$[a]	rt	5h	>95 (85)	N/A	7:1
2	**1L**	rt	5h	>95 (89)	81	4:1
3	**1L**	-10	1d	>95 (83)	89	3:1
4	**1J**	rt	5h	>95 (85)	81	3:1
5	**1J**	-10	1d	>95 (75)	94	4:1

[a] 20 mol %. [b] isolated yield. ee (enantiomeric excess). *dr* (diastereomeric ratio). ee was measured by a chiral HPLC. Reproted ee is from the major diastereomer. *dr* was mesured by crude NMR or HPLC.

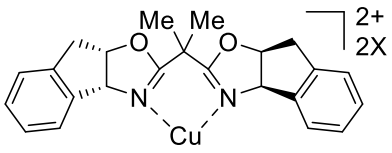
c)



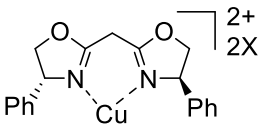
1J, X= $SbF6^-$
1K, X= OTf^-



1L, X= $SbF6^-$
1A, X= OTf^-



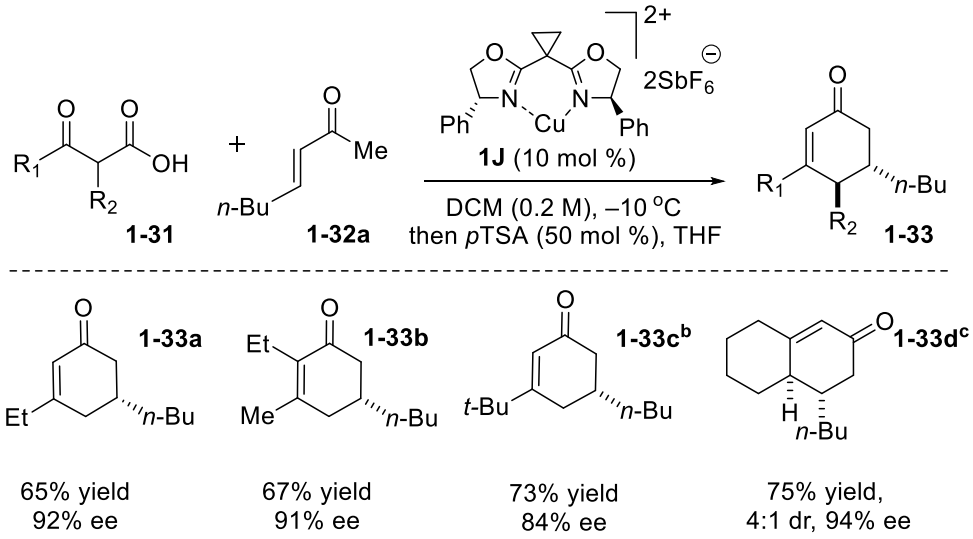
1M, X= OTf^-



1N, X= $SbF6^-$

the best result of a 4:1 mixture of diastereomers at C4 in 75% yield and 94% *ee* for both diastereomers (entry 5). The formed diastereomers were found to be epimeric at the C4 position as a result of decarboxylation followed by a moderately selective protonation of the resultant enol. The summarized result of enantioselective copper-catalyzed decarboxylative robinson annulation of β-ketoacid **1-31** and enone **1-32a** was described in scheme 1.14.

Scheme 1. 14. Enantioselective copper-catalyzed decarboxylative Robinson annulation.[a]



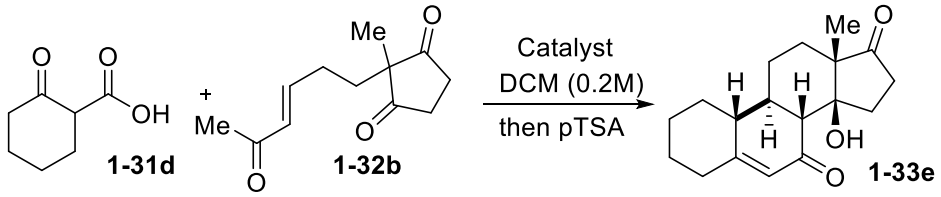
[a]β-Keto acid **1-31** (1.6 equiv), enone **1-32a** (1 equiv), then add *p*-TSA (50 mol %). Isolated yield (average of 2 trials). [b]*p*-TSA cyclization at 60 °C for 24 h. [c]Diastereomers of **1-33d** were found to have the same *ee* values.

1.7 Synthesis of 10-*nor*-steroid core

To further demonstrate the utility of this chemistry, the enantioselective decarboxylative Robinson annulation method was also successfully applied to the synthesis of 10-*nor*-steroid **1-33e** (Table 1.5). Based on our previous study,[25a-d] enone **1-32b** was generated in two steps from the readily available starting materials. The achiral catalyst $Cu(OTf)_2$ efficiently catalyze decarboxylative Robinson annulation of **1-32b** with β-ketoacids **1-31d**, resulting in formation of

10-*nor*-steroid **1-33e** in 80% yield with 7:1 *d.r* (entry 1). After the screening of various conditions of enantioselective decarboxylative Robinson annulation, catalyst **1J** at -10 ^{o}C again was found to be the best condition for this reaction (entry 8). With this condition, upon decarboxylative Robinson annulation of **1-32b** with β-ketoacids **1-31d**, 10-*nor*-steroid **1-33e** was directly obtained in 85% yield with 93% *ee* and 8:1 *dr* (1 g scale). The diastereomers arise at the C10 position as a result of decarboxylation/enol protonation, and the stereochemistry of the major diastereomer **1-33e** was assigned via X-ray crystallographic analysis. (Scheme 1.15) It is noteworthy that the skeleton present in **1-33e** is commonly found in various natural 10-*nor*-cardiotonic steroids. [31]

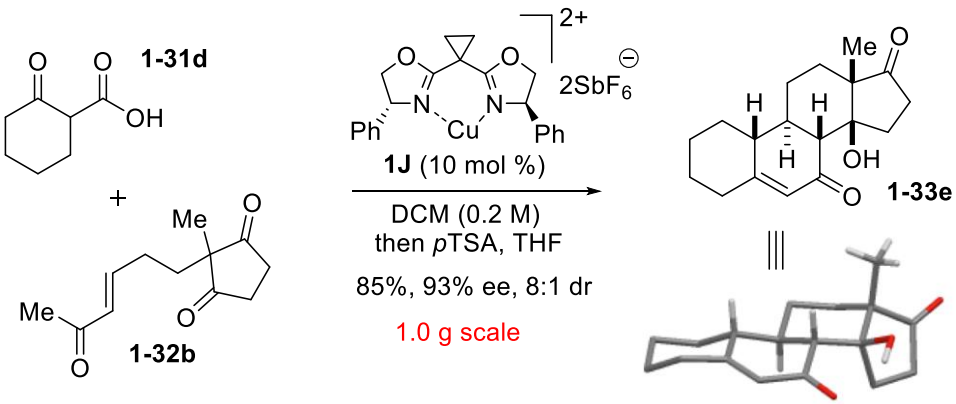
Table 1. 5. Reaction optimization of Cu(II)-catalyzed enantioselective decarboxylative Robinson annulation reactions of **1-31d** and **1-32b**.



Entry	Catalyst	T (°C)	Time (h)	Conv (Yield[b])	ee (%)	*d.r.*
1	$Cu(OTf)_2$[a]	rt	5h	>95 (80)	N/A	7:1
2	**1M**	rt	5h	~20	10	-
3	**1N**	rt	5h	-	50	-
4	**1A**	rt	5h	-	20	-
5	**1L**	rt	5h	>95 (78)	80	7:1
6	**1L**	-10	2d	>95 (80)	89	6:1
7	**1J**	rt	5h	>95 (83)	85	6:1
8	**1J**	**-10**	**3d**	**>95 (85)**	**93**	**8:1**

[a] 20 mol %. [b] isolated yield. ee (enantiomeric excess). dr (diastereomeric ratio).
ee was measured by a chiral HPLC. Reproted ee is from the major diastereomer.
dr was mesured by crude NMR or HPLC.

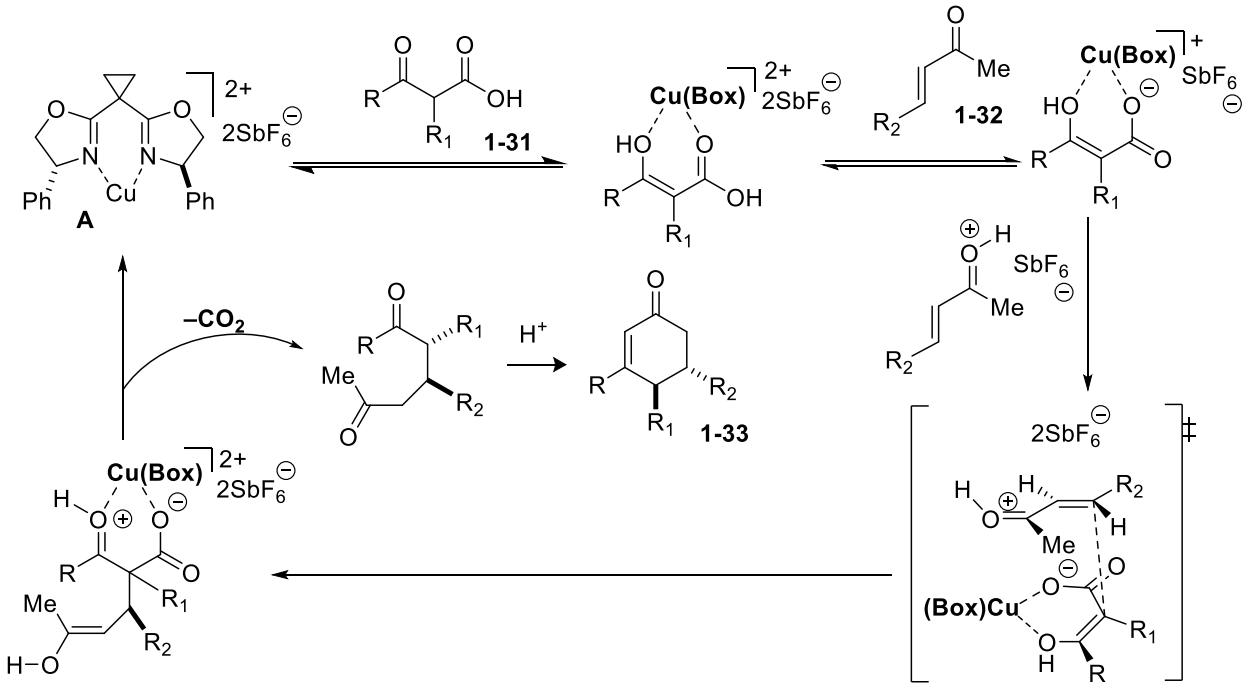
Scheme 1. 15. Synthesis of 10-*nor*-steroid core **1-33e**.



1.8 Plausible mechanism

The plausible mechanism for the copper(II)-catalyzed decarboxylative Michael reaction is proposed in Figure 1.1. The enol form of β-ketoacids **1-31** is proposed to undergo chelation with Cu(II) complex **1J**. The complexation to Cu(II) results in enhanced acidity of carboxylate, which is important for the activation of the enones **1-33** either by protonation or through hydrogen bonding. The activated enone **1-33** then undergoes a Michael reaction followed by a proton transfer with the enolized β-ketoacid. The Michael reaction is then followed by decarboxylation and aldol condensation leading to **1-33**. This proposal is consistent with the mechanism for decarboxylative aldol addition by Shair and co-workers who proposed that the decarboxylation takes place after the reaction with electrophile.[8-9] In the absence of enone, β-ketoacids were found to be stable when exposed to Cu(II) salts. This observation further confirms that decarboxylation takes place after the Michael addition step. It is also consistent with the observation that both diastereomers of **1-33d** are formed with identical enantiopurity, which implies that the enantiodetermining step precedes decarboxylation.

Figure 1. 1. Proposed mechanisms of Cu(II)-catalyzed enantioselective decarboxylative Robinson annulation reactions



1.9 Conclusions

In summary, a new single-pot protocol involving copper(II)-catalyzed decarboxylative Michael reaction between β-ketoacids and enones followed by *in situ* aldolization has been developed to achieve an expedient formation of highly functionalized chiral and achiral cyclohexenones. The achiral version of this Robinson annulation protocol features a previously unprecedented Michael reaction of β-ketoacids with sterically hindered β,β′-substituted enones and provides access to all carbon quaternary stereocenter-containing cyclohexenones (11 examples, 43−83% yield). Copper(II) salts were discovered to be unique catalysts for these Michael reactions as the other Lewis and Brønsted acids evaluated in these studies were inferior to Cu(II) catalysts. A similar protocol could be applied to achieve the formation of cyclohexenes with vicinal tertiary centers. The later substrates were also formed asymmetrically using chiral *bis*(oxazoline) copper(II) complexes as the catalysts. This single-pot enantioselective Robinson annulation was used to

generate chiral cyclohexenones containing vicinal stereocenters (4 examples, 65− 85% yield, 84−94% *ee*). In addition, this latter protocol was successfully applied to accomplish a single-pot enantioselective formation of an oxygenated 10-*nor*-steroid core from readily available starting materials in excellent yield and selectivity (85% yield, 93% *ee*, 8:1 *dr*).

1.10 Experimental Information

Methods and Reagents :

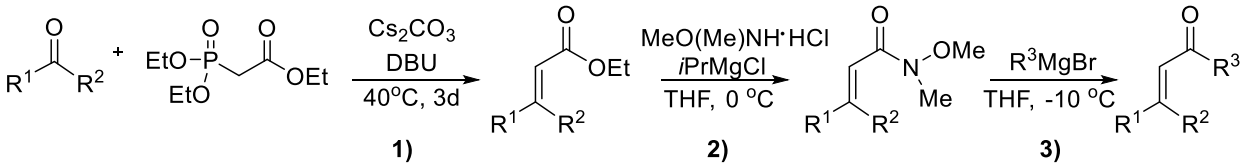
Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Tetrahyrofuran (THF), dichloromethane (DCM) and diethyl ether (Et_2O) were filtered through a column (Innovative Technology PS-MD-5) of activated alumina under nitrogen atmosphere. All reactions were carried out under an atmosphere of nitrogen in flame-or oven-dried glassware with magnetic stirring. Reactions were cooled using Neslab Cryocool CB-80 immersion cooler (0 to -60 °C) and Neslab Cryocool immersion cooler CC-100 II, or via external cooling baths: ice water (0 °C), sodium chloride/ ice water (-10 °C), or dry ice/acetone (-78°C). Heating was achieved by use of a silicone bath with heating controlled by electronic contact thermometer. Deionized water was used in the preparation of all aqueous solutions and for all aqueous extractions. Solvents used for extraction and chromatography were ACS or HPLC grade. Purification of reactions mixtures was performed by flash column chromatography on SiO_2 using SiliCycle SiliaFlash P60 (230-400 mesh). Diastereomeric ratios were determined by 1 H NMR analysis. Enantiomeric excess was determined by HPLC analysis using a Waters e2695 Separations Module with a Waters 2998 photodiode array detector.

Instrumentation :

All spectra were recorded on Varian vnmrs 700 (700 MHz), Varian vnmrs 500 (500 MHz), Varian MR400 (400 MHz), Varian Inova 500 (500 MHz) spectrometers and chemical shifts (δ) are reported in parts per million (ppm) and referenced to the ^{1}H signal of the internal tetramethylsilane according to IUPAC recommendations. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, m = multiplet; coupling constant(*S*) in Hz; integration). High resolution mass spectra (HRMS) were recorded on MicromassAutoSpecUltima or VG (Micromass) 70-250-S Magnetic sector mass spectrometers in the University of Michigan mass spectrometry laboratory. Infrared (IR) spectra were recorded as thin films on NaCl plates on a Perkin Elmer Spectrum BX FT-IR spectrometer. Absorption peaks were reported in wavenumbers (cm^{-1}).

Synthesis of Michael Acceptors (β,β'-disubstituted vinyl ketones)

Method A. ((*E*)-selective HWE reaction[32], Weinreb amide synthesis,[33] Grignard[33])



General Procedure:

1) (*E*)-selective Horner–Wadsworth–Emmons reaction[32]

Triethyl phosphonoacetate (1.0 eq), cesium carbonate (1.2 eq), and DBU (0.2 eq) were added and stirred in the flame dried reaction flask. After 10 min, a corresponding ketone (1.0 eq) was added to the reaction mixture. Then the reaction mixture was stirred in neat condition at 40 °C for 3 days under N_2. After reaction complete, the reaction was quenched with water and the crude product was extracted with EtOAc two times. The organic extract was washed with brine, and

combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by a flash column chromatography on SiO_2 (100% hexanes) to afford mixture of (*E*) and (*Z*) isomers of vinyl ester. ((*E*)-isomer is the major isomer)

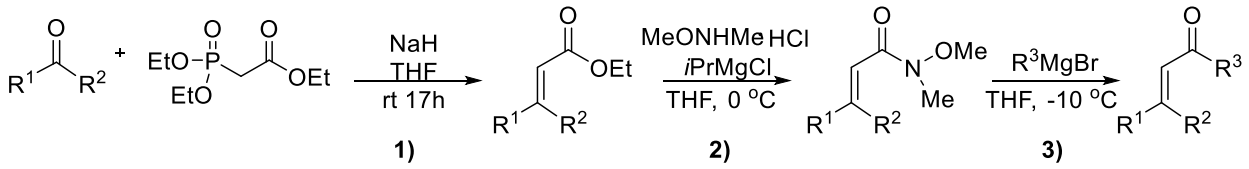
2) Weinreb amide synthesis

The (*E*)- and (*Z*)- mixtures of vinyl ester (1.0 eq), *N*,*O*-dimethylhydroxylamine hydrochloride (2.0 eq), and THF (0.4 M) were added in a flame dried flask. Then a solution of *i*PrMgCl (4.3 eq) in THF (0.1 M) was slowly added at 0 ^oC. The reaction mixture was stirred for 30 mins at 0 ^oC, and after that, the reaction was quenched with NH_4Cl. The crude product was extracted with EtOAc three times, and combined organic layers were washed with brine, and dried over $MgSO_4$. After the crude mixture was concentrated *in vacuo*, it was purified by a column chromatography on SiO_2 (6 : 1 / Hex : EtOAc). At this gradient, the (*E*)- and (*Z*)-isomers of Weinreb amides could be well separated, and (*E*) isomer was selectively moved forward.

3) Grignard reaction

At -30 ^oC, a solution of corresponding Grignard (R^3MgBr) (1.3 eq) in THF was slowly added to a solution of Weinreb amide (1.0 eq) in THF (0.35 M). The reaction mixture was stirred at -10 ^oC for 30 min. After reaction completion, the reaction was quenched with the NH_4Cl, and the crude mixture was extracted with EtOAc three times. The combined organic layers were washed with brined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude mixture was purified by column chromatography on SiO_2 on SiO_2 (4 : 1 / Hex : EtOAc) to afford vinyl ketone. (Generally, the vinyl ketone is volatile. Applying vacuum for more than 20 min is not recommended.)

Method B. (HWE reaction, Weinreb amide ketone synthesis, Grignard)[33]



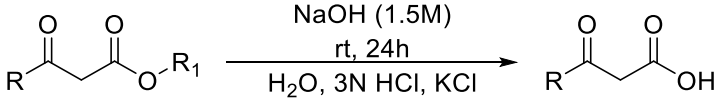
1) Horner–Wadsworth–Emmons reaction

To a suspension of NaH (1.4 eq) in THF (1.3 M), a solution of ketone (1.0 eq) in THF (0.1 M) was slowly added. The reaction mixture was stirred at room temp for 30 min, and corresponding ketone was added at 0 °C. Then the reaction mixture was stirred at room temp for 17 h. After the reaction is completed, a solution of saturated $NaHCO_3$ was added to the mixture, then the crude product was extracted with EtOAc three times and combined organic layers were washed with brine. The resulting crude mixture was concentrated *in vacuo*, and purified by column (100% hexanes) to afford (*E*) and (*Z*) isomeric mixture of vinyl ester.

2) Weinreb amide synthesis : exactly same as the **method A, 2).** The (*E*) and (*Z*) isomers of Weinreb amide could be separated by the column chromatography on SiO_2.

3) Grignard recation : exactly same as the **method A, 3).** Reaction was performed only with (*E*)-isomer.

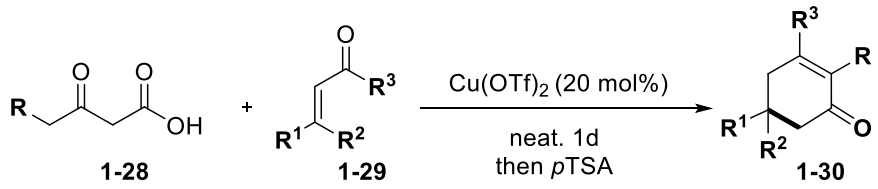
<u>Synthesis of Michael donor (β-ketoacids)</u>



General Procedure:

A corresponding β-ketoester (1.0 eq) was added to 1.5 M NaOH (1.2 eq) solution, and the reaction mixture was stirred at room temp for 24 h. The reaction mixture was diluted with ice water, and acidified with 3N HCl to pH 2. Then solid KCl was added to the reaction mixture to saturation. The reaction mixture was extracted with EtOAc five times, and the combined organic layers were dried with Na_2SO_4. The resulting crude mixture was then concentrated *in vacuo* to afford β-ketoacids without further separation (Caution! β-ketoacids could be subjected to self-decarboxylation. Store them in a freezer).

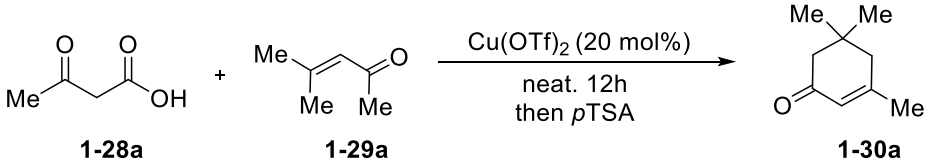
Decarboxylative Michael reaction leading to formation of cyclohexenones with quaternary carbon



General Procedure:

To a flame dried, N_2 flushed 1 dram vial, a stir bar and β-ketoacids **1-28** (1.6 eq) was placed, and the reaction vial was taken to a glove box to add CuOTf (20 mol%). The closed vial was taken out from the glove box, and vinyl ketone **1-29** (1.0 eq) was added to the reaction mixture under N_2 flow. The reaction was left to stir at room temp for 12 h (or 3 days). After the reaction completed, *p*TSA (0.50 eq) and THF (0.1 M) was added to the reaction mixture. The reaction was stirred at room temp for overnight, and the reaction was quenched with $NaHCO_3$. The crude mixture was extracted with DCM three times and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Crude material was purified by a flash column chromatography on SiO_2 to afford **1-30.**

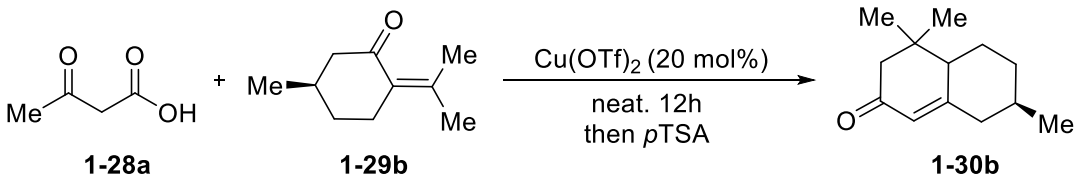
(FYI: Since the reaction is performed under neat condition, the stirring might not be efficient. All of the used vinyl ketones were liquid, which is not always the case for β-ketoacids. For solid β-ketoacids, stirring might be problematic. However, the problem goes away as the reaction proceeds because β-ketoacids partially decarboxylate to provide liquid ketones, which would solubilize solid residue and thus improve the stirring.)



3,5,5-trimethylcyclohex-2-en-1-one (1-30a)

(Following the general procedure): β-ketoacids **1-28a** (60 µL, 0.70 mmol, 1.6 eq), $Cu(OTf)_2$ (31 mg, 0.09 mmol, 20 mol%), vinyl ketone **1-29a** (50 µL, 0.43 mmol, 1.0 eq), *p*TSA (37 mg, 0.22 mmol, 0.50 eq), THF (4.3 mL, 0.1 M). The purification by the flash column chromatography on SiO_2 (9 : 1 / Hex : EtOAc) afforded **1-30a** (49 mg, 83 %) as a colorless oil.

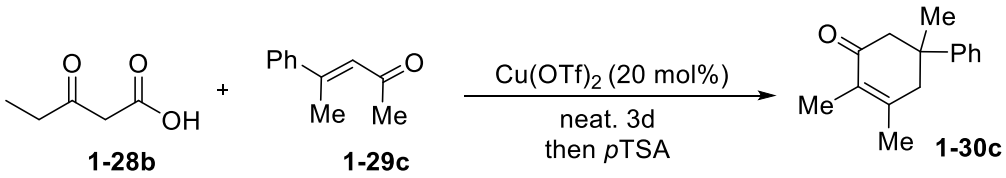
^{1}H NMR (700 MHz, Chloroform-*d*) δ 5.85 (s, 1H), 2.16 (s, 2H), 2.14 (s, 2H), 1.91 (s, 3H), 1.00 (s, 6H). **^{13}C NMR** (175 MHz, Chloroform-*d*) δ 200.0, 160.5, 125.6, 50.8, 45.4, 33.6, 28.4, 24.6. **IR** (thin film, cm^{-1}):2956, 2923, 2850, 1721, 1462. **HRMS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_9H_{14}O$ 139.1117, found 139.1123



(7R)-4,4,7-trimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (1-30b)

(Following the general procedure): β-ketoacids **1-28a** (60 µL, 0.69 mmol, 1.6 eq), $Cu(OTf)_2$ (31 mg, 0.086 mmol, 20 mol%), vinyl ketone **1-29b** (70 µL, 0.43 mmol, 1.0 eq), *p*TSA (37mg, 0.22 mmol, 0.50 eq), THF (4.3 mL, 0.1 M). The purification by the flash column chromatography on SiO_2 (100% hexanes) afforded **1-30b** (50 mg, 57 %) as a clear yellow oil.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.78 (s, 1H), 2.42 (m, 1H), 2.19 (q, 2H), 2.02 – 1.95 (m, 2H), 1.89 – 1.81 (m, 2H), 1.60 – 1.50 (m, 1H), 1.30 (dd, *J* = 13.3, 3.5 Hz, 1H), 1.17 – 1.12 (m, 1H), 1.03 (s, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.93 (s, 3H).**^{13}C NMR** (175 MHz, Chloroform-*d*). δ 200.2, 166.1, 122.7, 50.3, 49.2, 45.2, 35.6, 34.8, 34.8, 28.8, 28.2, 24.8, 22.5. **IR** (thin film, cm^{-1}): 2951, 2925, 2869, 1714, 1681, 1627, 1254, 730. **HRMS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{20}O$ 193.1592, found 193.1591.

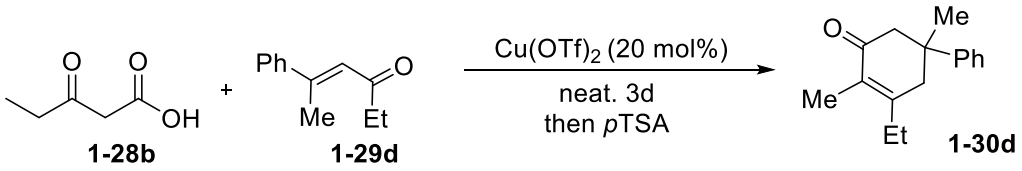


1,4,5-trimethyl-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (1-30c)

(Following the general procedure): β-ketoacids **1-28b** (46.4 mg, 0.40 mmol, 1.6 eq), $Cu(OTf)_2$ (18 mg, 0.05 mmol, 20 mol%), vinyl ketone **1-29c** (40 µL, 0.25 mmol, 1.0 eq), *p*TSA (21.5 mg, 0.12 mmol, 0.50 eq), THF (2.5 mL, 0.1 M). a flash column chromatography on SiO_2 (9 : 1 / Hex : EtOAc) to afford **1-30c** (28 mg, 53 %) as a colorless oil**.**

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.34 – 7.27 (m, 4H), 7.20 (tt, *J* = 5.4, 2.1 Hz, 1H), 2.86 (m, 2H), 2.66 – 2.55 (m, 2H), 1.94 (s, 3H), 1.73 (s, 3H), 1.33 (s, 3H). **^{13}C NMR** (175 MHz, Chloroform-*d*) δ 198.6, 152.5, 147.4, 130.8, 128.6, 126.4, 125.3, 49.8, 46.2, 39.8, 29.5, 21.8, 10.7.

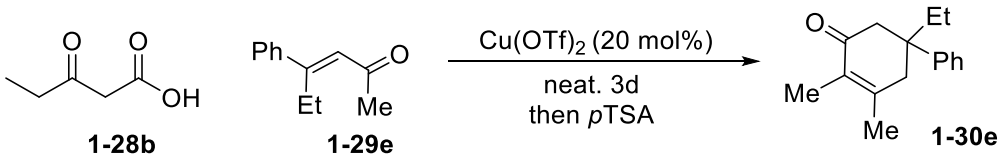
IR (thin film, cm^{-1}): 2947, 2924, 2868, 1711, 1660, 1639, 1444, 1072,1029, 763, 697 **HRMS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{18}O$ 215.1436, found 215.1432.



4-ethyl-1,5-dimethyl-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (1-30d)

(Following the general procedure): β-ketoacids **1-28a** (70 µL, 0.70 mmol, 1.6 eq), $Cu(OTf)_2$ (31 mg, 0.086 mmol, 20 mol%), vinyl ketone **1-29a** (50 µL, 0.43 mmol, 1.0 eq), *p*TSA (37 mg, 2.15 mmol, 5 eq), THF (4.3 mL, 0.1 M). The purification by the flash column chromatography on SiO_2 (9 : 1 / Hex : EtOAc) afforded **1-30d** (42 mg, 43 %) as a colorless oil.

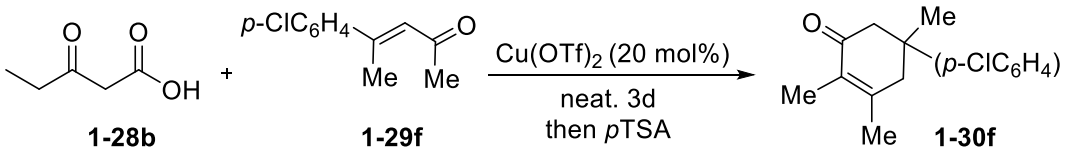
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.33 – 7.28 (m, 4H), 7.22 – 7.18 (m, 1H), 2.90 (d, *J* = 15.9 Hz, 1H), 2.82 (d, *J* = 17.7 Hz, 1H), 2.61 (dd, *J* = 16.4, 13.3 Hz, 2H), 2.32 – 2.17 (m, 2H), 1.74 (s, 3H), 1.33 (s, 3H), 1.02 (t, *J* = 7.6 Hz, 3H) **^{13}C NMR** (175 MHz, Chloroform-*d*) δ 199.2, 157.6, 147.5, 130.0, 128.6, 126.4, 125.3, 49.8, 44.0, 39.8, 29.2, 28.4, 11.4, 10.2. **IR** (thin film, cm^{-1}): 2965, 2927, 2873, 1713, 1659, 1638, 1496, 1444, 763, 698 **HRMS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{20}O$ 229.1592, found 229.1586.



1-ethyl-4,5-dimethyl-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (1-30e)

(Following the general procedure): β-ketoacids **1-28b** (64 mg, 0.55 mmol, 1.6 eq), $Cu(OTf)_2$ (25 mg, 0.069 mmol, 20 mol%), vinyl ketone **1-29e** (60 µL, 0.34 mmol, 1.0 eq), *p*TSA (30 mg, 0.17 mmol, 0.50 eq), THF (3.4 mL, 0.1 M). The purification by the flash column chromatography on SiO_2 (9 : 1 / Hex : EtOAc) afforded **1-30e** (46.3 mg, 59 %) as a colorless oil.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.31 – 7.27 (m, 2H), 7.22 – 7.17 (m, 3H), 2.93 (dd, *J* = 15.9, 1.8 Hz, 1H), 2.79 (d, *J* = 17.6 Hz, 1H), 2.67 – 2.61 (m, 2H), 1.93 (s, 3H), 1.73 – 1.70 (m, 2H), 1.69 (s, 3H), 0.59 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (175 MHz, Chloroform-*d*) δ 198.6, 152.4, 144.9, 131.2, 128.4, 126.2, 126.2, 47.7, 44.5, 43.5, 35.1, 21.9, 10.7, 8.3. **IR** (thin film, cm^{-1}): 2963, 2924, 2870, 1714, 1661, 1637, 1496, 1457, 759, 695. **HRMS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{20}O$ 229.1592, found 229.1587.

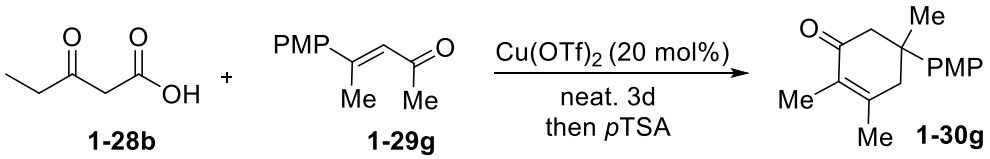


4'-chloro-1,4,5-trimethyl-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (1-30f)

(Following the general procedure): β-ketoacids **1-28b** (48.5 mg, 0.41 mmol, 1.6 eq), $Cu(OTf)_2$ (20 mg, 0.048 mmol, 20 mol%), vinyl ketone **1-29f** (50 µL, 0.26 mmol, 1.0 eq), *p*TSA (22.4 mg, 0.13 mmol, 0.50 eq), THF (2.6 mL, 0.1 M). The purification by the flash column chromatography on SiO_2 (9 : 1 / Hex : EtOAc) afforded **1-30f** (35 mg, 55 %) as a colorless oil.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.27 (m, 2H), 7.21 – 7.18 (m, 2H), 2.86 (dd, *J* = 15.9, 1.5 Hz, 1H), 2.77 (d, *J* = 17.9 Hz, 1H), 2.63 – 2.56 (m, 2H), 1.93 (s, 3H), 1.72 (s, 3H), 1.31 (s, 3H).

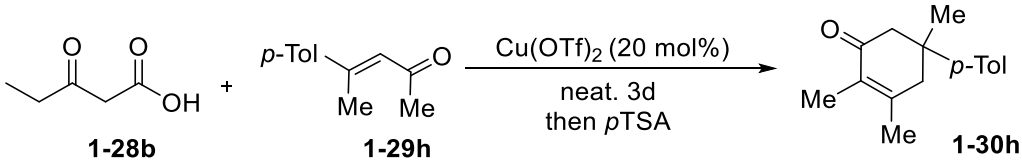
^{13}C NMR (175 MHz, Chloroform-*d*) δ 198.17, 152.17, 145.77, 132.19, 131.07, 128.71, 126.86, 49.81, 46.13, 39.71, 29.70, 21.83, 10.72. **IR** (thin film, cm^{-1}): 2956, 2921, 2852, 1712, 1660, 1634, 1492, 1449, 1092, 1009, 821, 760, 711, 666, 626. **HRMS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{17}OCl$ 249.1049, found 249.1043.



4'-methoxy-1,4,5-trimethyl-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (1-30g)

(Following the general procedure): β-ketoacids **1-28b** (49 µL, 0.42 mmol, 1.6 eq), $Cu(OTf)_2$ (19 mg, 0.053 mmol, 20 mol%), vinyl ketone **1-29g** (50 µL, 0.26 mmol, 1.0 eq), *p*TSA (22.6 mg, 0.13 mmol, 0.50 eq), THF (2.6 mL, 0.1 M). The purification by the flash column chromatography on SiO_2 (9 : 1 / Hex : EtOAc) afforded **1-30g** (33 mg, 51 %) as a colorless oil.

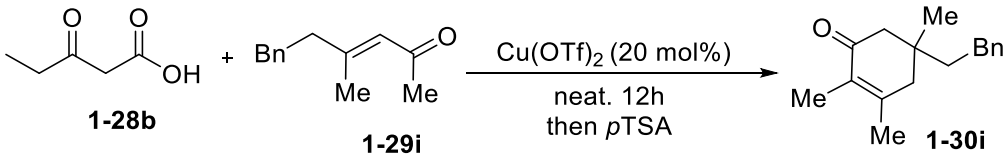
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.23 (t, *J* = 8.0 Hz, 1H), 6.89 – 6.85 (m, 1H), 6.82 (t, *J* = 2.2 Hz, 1H), 6.76 – 6.73 (m, 1H), 3.79 (s, 3H), 2.88 (d, *J* = 15.8 Hz, 1H), 2.81 (d, *J* = 17.9 Hz, 1H), 2.63 – 2.56 (m, 2H), 1.94 (s, 3H), 1.74 (s, 3H), 1.32 (s, 3H). **^{13}C NMR** (175 MHz, Chloroform-*d*) δ 198.5, 159.8, 152.4, 149.3, 130.8, 129.6, 117.8, 112.0, 111.0, 55.3, 49.9, 46.2, 39.9, 29.3, 21.8, 10.7. **IR** (thin film, cm^{-1}): 2959, 2926, 2833, 1708, 1661, 1601, 1582, 1429, 1376, 1285, 1243, 1214, 1174, 1070, 868, 699. **HRMS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{20}O_2$ 245.1542, found 245.1534.



1,4,4',5-tetramethyl-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (1-30h)

(Following the general procedure): β-ketoacids **1-28b** (75 mg, 0.64 mmol, 1.6 eq), $Cu(OTf)_2$ (30 mg, 0.08 mmol, 20 mol%), vinyl ketone **1-29h** (70 µL, 0.40 mmol, 1.0 eq), *p*TSA (34mg, 0.20 mmol, 0.50 eq), THF (4.3 mL, 0.1 M). The purification by the flash column chromatography on SiO_2 (9 : 1 / Hex : EtOAc) afforded **1-30h** (35 mg, 60 %) as a colorless oil.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.18 – 7.16 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 2.88 (d, *J* = 15.9 Hz, 1H), 2.80 (d, *J* = 17.9 Hz, 1H), 2.59 (m, 2H), 2.31 (s, 3H), 1.93 (s, 3H), 1.73 (s, 3H), 1.31 (s, 3H). **^{13}C NMR** (175 MHz, Chloroform-*d*). δ 198.7, 152.5, 144.4, 135.9, 130.8, 129.3, 125.2, 49.9, 46.3, 39.5, 29.6, 21.9, 21.0, 10.7. **IR** (thin film, cm^{-1}):): 2948, 2923, 2865, 1731, 1662, 1514, 1453, 1376, 954, 840, 699. **HRMS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{20}O$ 229.1592, found 229.1589.

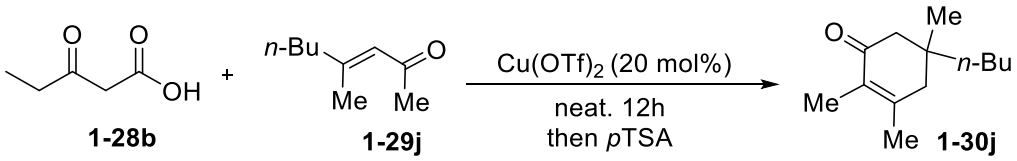


2,3,5-trimethyl-5-phenethylcyclohex-2-en-1-one (1-30i)

(Following the general procedure): β-ketoacids **1-28b** (50 mg, 0.43 mmol, 1.6 eq), $Cu(OTf)_2$ (20 mg, 0.054 mmol, 20 mol%), vinyl ketone **1-29i** (50 µL, 0.27 mmol, 1.0 eq), *p*TSA (23.2 mg, 0.14 mmol, 0.50 eq), THF (2.7 mL, 0.1 M). The purification by the flash column chromatography on SiO_2 (9 : 1 / Hex : EtOAc) afforded **1-30i** (40 mg, 62 %) as a colorless oil.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 7.6 Hz, 2H), 7.17 (dd, *J* = 20.1, 7.2 Hz, 3H), 2.63 – 2.52 (m, 2H), 2.38 – 2.34 (m, 2H), 2.30 (d, *J* = 15.2 Hz, 1H) 2.21 (d, *J* = 18.0 Hz, 1H), 1.90 (s, 3H), 1.78 (s, 3H), 1.65 – 1.60 (m, 2H), 1.06 (s, 3H). **^{13}C NMR** (175 MHz, Chloroform-*d*).

δ 199.20, 152.32, 142.54, 130.20, 128.56, 128.40, 125.96, 49.62, 45.50, 43.77, 35.65, 30.41, 24.99, 21.79, 10.73. **IR** (thin film, cm^{-1}): 2952, 2926, 2871, 1737, 1662, 1636, 1454, 721, 680. **HRMS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{22}O$ 243.1749, found 243.1745.

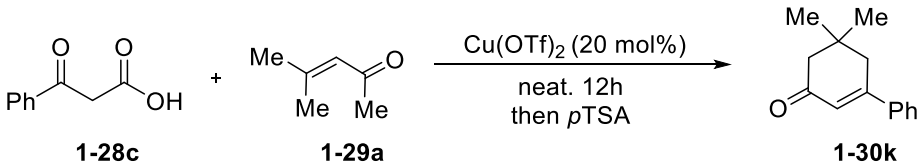


5-butyl-2,3,5-trimethylcyclohex-2-en-1-one (1-30j)

(**Large scale** reaction. N_2 filled balloon is needed in the system for storage of generated CO_2.)

(Following the general procedure): β-ketoacids **1-28b** (1.06 g, 9.13 mmol, 1.6 eq), $Cu(OTf)_2$ (412 mg, 1.142 mmol, 20 mol%), vinyl ketone **1-29j** (0.8 mL, 5.71 mmol, 1.0 eq), *p*TSA (491.6 mg, 2.86 mmol, 0.50 eq), THF (10 mL, 0.57 M). The purification by the flash column chromatography on SiO_2 (9 : 1 / Hex : EtOAc) afforded **1-30j** (770 mg, 70 %) as a colorless oil.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 2.31 – 2.26 (m, 2H), 2.21 (dd, *J* = 15.7, 1.3 Hz, 1H), 2.12 (d, *J* = 18.0 Hz, 1H), 1.90 (s, 3H), 1.76 (s, 3H), 1.31 – 1.20 (m, 6H), 0.94 (s, 3H), 0.89 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (175 MHz, Chloroform-*d*) δ 199.7, 152.5, 130.1, 49.8, 45.5, 41.5, 35.4, 26.1, 25.1, 23.5, 21.8, 14.2, 10.7. **IR** (thin film, cm^{-1}): 2955, 2928, 2860, 1710, 1638, 1376, 1081, 720. **HRMS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{22}O$ 195.1749, found 195.1746.

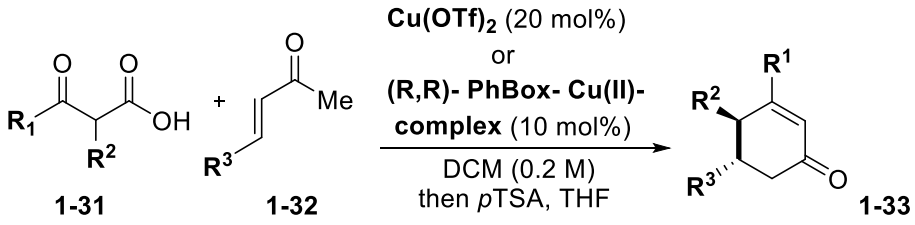


5,5-dimethyl-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (1-30k)

(Following the general procedure): β-ketoacids **1-28c** (115 mg, 0.70 mmol, 1.6 eq), $Cu(OTf)_2$ (31 mg, 0.086 mmol, 20 mol%), vinyl ketone **1-29a** (50 µL, 0.43 mmol, 1.0 eq), *p*TSA (0.37 mg, 0.22 mmol, 0.50 eq), THF (4.3 mL, 0.1 M). The reaction was heated at 60 ºC for 1d for the cyclization. The purification by the flash column chromatography on SiO_2 (9 : 1 / Hex : EtOAc) afforded **1-30k** (70 mg, 82 %) as a colorless oil.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.56 – 7.51 (m, 2H), 7.41 (m, 3H), 6.42 (s, 1H), 2.65 (s, 2H), 2.35 (s, 2H), 1.13 (s, 6H). **^{13}C NMR** (175 MHz, Chloroform-*d*) 200.3, 157.7, 139.2, 130.1, 128.9, 126.3, 124.5, 51.1, 42.5, 33.9, 28.6. **IR** (thin film, cm^{-1}): 2956, 2868, 1657, 1606, 1467, 1361, 902, 754, 690. **MS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{16}O$ 201.1279, found 201.1272.

Copper(II)-catalyzed decarboxylative Robinson annulation resulting in vicinal tertiary stereocenters

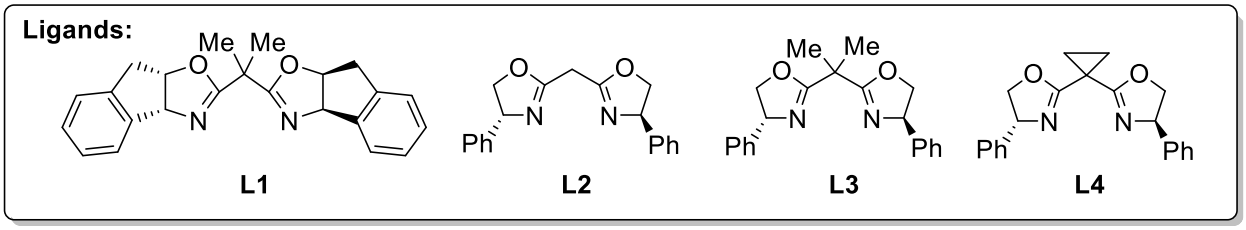


General Procedure:

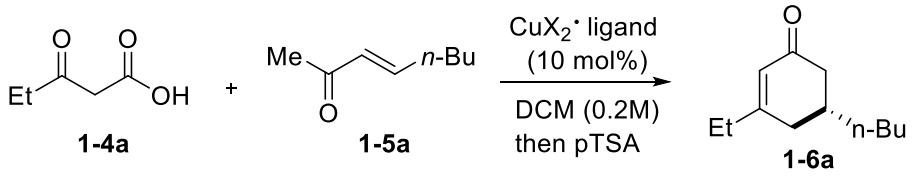
Racemic reaction: To a flame dried, N_2 flushed 1 dram vial, a stir bar and β-ketoacids **1-31** (1.6 eq) was placed, and the reaction vial was taken to a glove box to add $Cu(OTf)_2$ (20 mol%). The closed vial was taken out from the glove box, and vinyl ketone **1-32** (1.0 eq) and DCM (0.2 M) were added to the reaction mixture under N_2 flow. The reaction was left to stir at rt for 5 h. After the reaction completed, *p*TSA (0.50 eq) and THF (0.1 M) was added to the reaction mixture. The reaction was stirred at rt for overnight, and the reaction was quenched with $NaHCO_3$. The crude

mixture was extracted with DCM three times and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Crude material was purified by a flash column chromatography on SiO_2 to afford **1-33.**

Enantioselective reaction: To a flame dried, N_2 flushed 1 dram vial, a stir bar and β-ketoacids **1-31** (1.6 eq) was placed, and the reaction vial was taken to a glove box to add (*R,R*) copper(II)-(Box) catalyst (10 mol%). The closed vial was taken out from the glove box, and vinyl ketone **1-32** (1.0 eq) and DCM (0.2M) were added to the reaction mixture at -10 ^oC under N_2 flow. The reaction was placed in the cryocool, which was set to -10 ^oC, and stirred at -10 ^oC for 1 (or 3) days. After the reaction completed, *p*TSA (0.50 eq) and THF (0.1 M) was added to the reaction mixture. The reaction was stirred at rt for overnight, and the reaction was quenched with $NaHCO_3$. The crude mixture was extracted with DCM three times and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Crude material was purified by a flash column chromatography on SiO_2 to afford **1-33.**

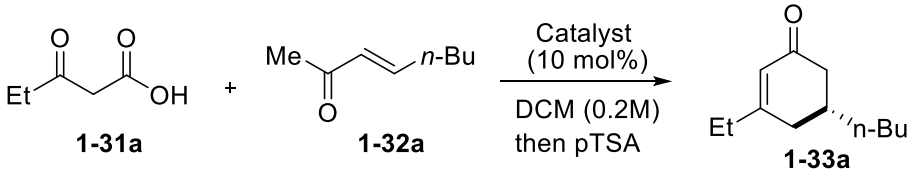


N1-((*1R,2R*)-2-hydroxy-2,3-dihydro-*1H*-inden-1-yl)-*N3*-((*1S,2R*)-2-hydroxy-2,3-dihydro-*1H*-inden-1-yl)-2,2-dimethylmalonamide **L1** and (*4S,4'S*)-2,2'-(propane-2,2-diyl)*bis*(4-phenyl-4,5-dihydrooxazole) **L3** were synthesized based on the known procedure.[34] *Bis*((*R*)-4-phenyl-4,5-dihydrooxazol-2-yl)methane **L2** and (*4R,4'R*)-2,2'-(cyclopropane-1,1-diyl)*bis*(4-phenyl-4,5-dihydrooxazole) **L4** were produced according to literature procedure.[35, 25b]



Entry	Ligand	CuX_2	T, °C	Time, h	Conv (Yield[b])	ee, %	d.r.
1	-	$Cu(OTf)_2$[a]	rt	5h	>95 (58)	N/A	N/A
2	**4**	**$Cu(SbF_6)_2$**	**-10**	**1d**	**>95 (65)**	**92**	**N/A**

[a] 20 mol %. [b] isolated yield. ee (enantiomeric excess). dr (diastereomeric ratio).
ee was measured by a chiral HPLC. Reproted ee is from the major diastereomer.
dr was mesured by crude NMR or HPLC.

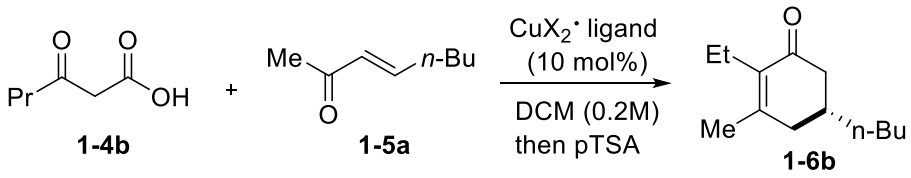


(*R*)-5-butyl-3-ethylcyclohex-2-en-1-one (1-33a)

Racemic reaction (entry 1) (following the general procedure): β-ketoacids **1-31a** (88.3 mg, 0.76 mmol, 1.6 eq), $Cu(OTf)_2$ (35 mg, 0.095 mmol, 20 mol%), vinyl ketone **1-32a** (60 µL, 0.48 mmol, 1.0 eq), DCM (2.3 mL, 0.2M), *p*TSA (41mg, 0.24 mmol, 0.50 eq), THF (4.7 mL, 0.1 M). Purified by a flash column chromatography on SiO_2 (9 : 1 / Hex : EtOAc to 5 : 1 / Hex : EtOAc) to afford **1-33a** (49 mg, 58 %) as a colorless oil

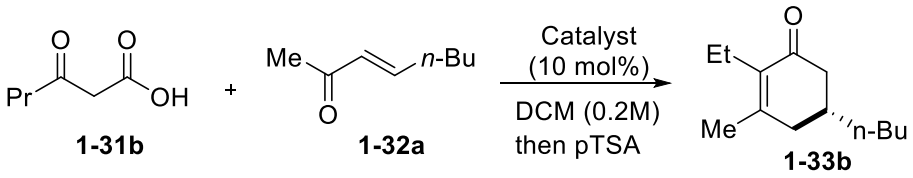
Enantioselective reaction (entry 2) (following the general procedure): β-ketoacids **1-31a** (88.3 mg, 0.761 mmol, 1.6 eq), (*R*,*R*) cyclopropane-substituted diphenyl *bis*-(oxazoline)-copper(II) catalyst (41.2 mg, 0.0476 mmol, 10 mol%), vinyl ketone **1-32a** (60 µL, 0.476 mmol, 1.0 eq), DCM (2.3 mL, 0.2 M), reaction for 1 day, *p*TSA (41 mg, 0.238 mmol, 0.50 eq), THF (4.7 mL, 0.1 M), Purified by a flash column chromatography on SiO_2 (9 : 1 / Hex : EtOAc to 5 : 1 / Hex : EtOAc) to afford **1-33a** (55 mg, 65 %) as a colorless oil.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 5.86 (s, 1H), 2.47 (d, *J* = 12.1 Hz, 1H), 2.35 – 2.29 (m, 1H), 2.23 (q, *J* = 7.5 Hz, 2H), 2.06 – 2.00 (m, 3H), 1.41 – 1.34 (m, 2H), 1.33 – 1.28 (m, *J* = 5.6, 4.6 Hz, 4H), 1.10 (t, *J* = 7.4 Hz, 3H), 0.90 (t, 3H). **^{13}C NMR** (175 MHz, Chloroform-*d*) δ 200.6, 167.3, 124.5, 44.0, 36.6, 35.6, 35.2, 31.0, 28.9, 22.9, 14.2, 11.4. **IR** (thin film, cm^{-1}): 2955, 2922, 2857, 1664, 1636, 1429, 1378, 1131, 1083, 714. **HRMS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{20}O$ 181.1592, found 181.1586 **$[\alpha]_D$** = -36.3 (*c* 0.9, $CHCl_3$) Enantiopurity was determined to be 92% ee by chiral HPLC (DAICEL CHIRALPAK IA, 4.6 X 250 mm, hexanes/2-proponal = 99.5/0.5, flow rate = 1 mL/min, λ = 242.0 nm, RT(minor) = 30.3 min, RT(major) = 32.6 min).



Entry	Ligand	CuX_2	T, °C	Time, h	Conv (Yield[b])	ee, %	d.r.
1	-	$Cu(OTf)_2$[a]	rt	5h	>95 (63)	N/A	N/A
2	**4**	**$Cu(SbF_6)_2$**	**-10**	**1d**	**>95 (67)**	**91**	**N/A**

[a] 20 mol %. [b] isolated yield. ee (enantiomeric excess). dr (diastereomeric ratio).
ee was measured by a chiral HPLC. Reproted ee is from the major diastereomer.
dr was mesured by crude NMR or HPLC.



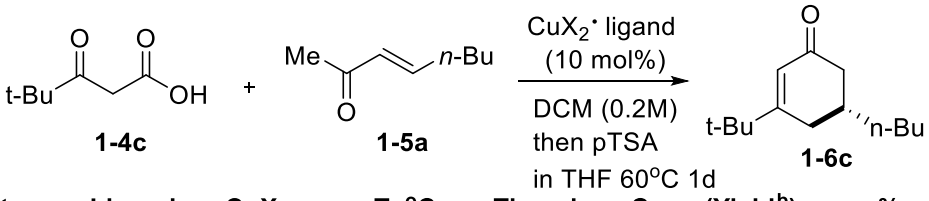
(*R*)-5-butyl-2-ethyl-3-methylcyclohex-2-en-1-one (1-33b)

Racemic reaction (entry 1) (following the general procedure): β-ketoacids **1-31b** (66 mg, 0.507 mmol, 1.6 eq), $Cu(OTf)_2$ (23 mg, 0.0634 mmol, 20 mol%), vinyl ketone **1-32a** (40 µL, 0.317 mmol,

1.0 eq), DCM (1.6 mL, 0.2M), *p*TSA (27mg, 0.159 mmol, 0.50 eq), THF (3.1 mL, 0.1 M). Purified by a flash column chromatography on SiO_2 (10 : 1 / Hex : EtOAc to 5 : 1 / Hex : EtOAc) to afford **1-33b** (38 mg, 63 %) as a colorless oil

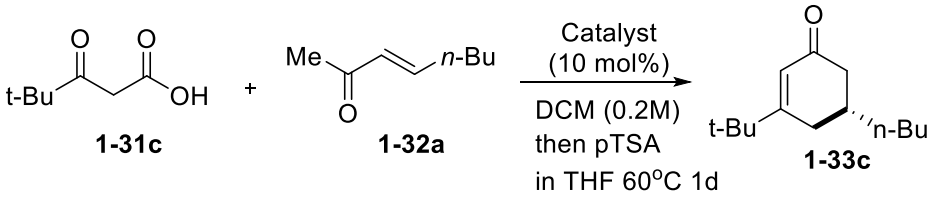
Enantioselective reaction (entry 2) (following the general procedure): β-ketoacids **1-31b** (66 mg, 0.507 mmol, 1.6 eq), (*R*,*R*) cyclopropane-substituted diphenyl *bis*-(oxazoline)-copper(II) catalyst (27.5 mg, 0.032 mmol, 10 mol%), vinyl ketone **1-32a** (40 µL, 0.317 mmol, 1.0 eq), DCM (1.6 mL, 0.2M), reaction for 1 day, *p*TSA (27 mg, 0.16 mmol, 0.50 eq), THF (3.1 mL, 0.1 M), Purified by a flash column chromatography on SiO_2 (10 : 1 / Hex : EtOAc to 5 : 1 / Hex : EtOAc) to afford **1-33b** (41 mg, 67 %) as a colorless oil.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 2.51 – 2.46 (m, 1H), 2.34 – 2.23 (m, 3H), 2.11 – 1.95 (m, 3H), 1.93 (s, 3H), 1.30 (m, 6H), 0.90 (m, 6H). **^{13}C NMR** (175 MHz, Chloroform-*d*) δ 199.3, 154.2, 137.0, 44.4, 39.7, 35.7, 34.5, 28.8, 22.9, 21.1, 18.5, 14.2, 13.6. **IR** (thin film, cm^{-1}): 2957, 2926, 2871, 2854, 1687, 1630, 1460, 1380, 980, 728, 650. **HRMS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{22}O$ 195.1749, found 195.1743 **$[\alpha]_D$** = 50.1 (*c* 0.7, $CHCl_3$) Enantiopurity was determined to be 91% ee by chiral HPLC (DAICEL CHIRALPAK IA, 4.6 X 250 mm, hexanes/2-proponal = 99.5/0.5, flow rate = 1 mL/min, λ = 242.0 nm, RT(major) = 7.7 min, RT(minor) = 8.4 min).



Entry	Ligand	CuX_2	T, °C	Time, h	Conv (Yield[b])	ee, %	d.r.
1	-	$Cu(OTf)_2$[a]	rt	5h	>95 (69)	N/A	N/A
2	**4**	**$Cu(SbF_6)_2$**	**-10**	**1d**	**>95 (73)**	**84**	**N/A**

[a] 20 mol %. [b] isolated yield. ee (enantiomeric excess). dr (diastereomeric ratio).
ee was measured by a chiral HPLC. Reproted ee is from the major diastereomer.
dr was mesured by crude NMR or HPLC.



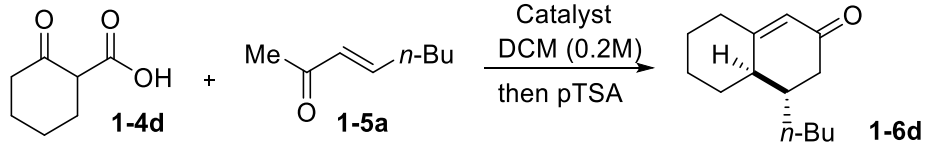
3-(tert-butyl)-5-butylcyclohex-2-en-1-one (1-33c)

Racemic reaction (entry 1) (following the general procedure): β-ketoacids **1-31c** (110 mg, 0.76 mmol, 1.6 eq), $Cu(OTf)_2$ (35 mg, 0.095 mmol, 20 mol%), vinyl ketone **1-32a** (60 µL, 0.48 mmol, 1.0 eq), DCM (2.3 mL, 0.2M), *p*TSA (41mg, 0.238 mmol, 0.50 eq), THF (4.7 mL, 0.1 M). The reaction was heated at 60 °C for 1 day for the cyclization. Purified by a flash column chromatography on SiO_2 (10 : 1 / Hex : EtOAc to 5 : 1 / Hex : EtOAc) to afford **1-33c** (62 mg, 69 %) as a colorless oil

Enantioselective reaction (entry 2) (following the general procedure): β-ketoacids **1-31c** (110 mg, 0.761 mmol, 1.6 eq), (*R*,*R*) cyclopropane-substituted diphenyl *bis*-(oxazoline)-copper(II) catalyst (41.2 mg, 0.048 mmol, 10 mol%), vinyl ketone **1-32a** (60 µL, 0.48 mmol, 1.0 eq), DCM (2.3 mL, 0.2 M), reaction for 1 day, *p*TSA (41 mg, 0.24 mmol, 0.50 eq), THF (4.7 mL, 0.1 M). The reaction was heated at 60 °C for 1 day for the cyclization. Purified by a flash column

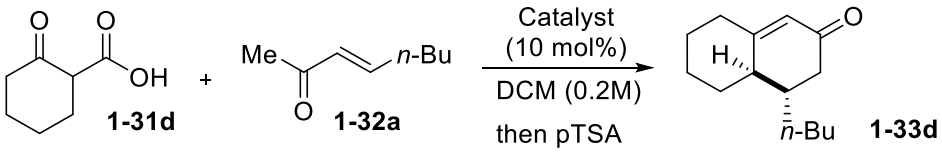
chromatography on SiO_2 (10 : 1 / Hex : EtOAc to 5 : 1 / Hex : EtOAc) to afford **1-33c** (66 mg, 73 %) as a colorless oil.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 5.94 (s, 1H), 2.51 – 2.46 (m, 2H), 2.05 – 1.94 (m, 3H), 1.41 – 1.27 (m, 6H), 1.12 (s, 9H), 0.91 (t, *J* = 6.4 Hz, 3H).**^{13}C NMR** (175 MHz, Chloroform-*d*) δ 201.33, 173.1, 123.0, 44.0, 36.9, 35.7, 35.6, 32.8, 29.0, 28.4, 22.9, 14.2. **IR** (thin film, cm^{-1}): 2956, 2928, 2871, 1706, 1666, 1614, 1466, 1364, 890, 728. **HRMS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{24}O$ 209.1905, found 209.1902 **[α]$_D$** = -6.87 (*c* 0.7, $CHCl_3$) Enantiopurity was determined to be 84% ee by chiral HPLC (DAICEL CHIRALPAK IA, 4.6 X 250 mm, hexanes/2-proponal = 99/1, flow rate = 1 mL/min, λ = 242.0 nm, RT(major) = 8.2 min, RT(minor) = 8.7 min).



Entry	Ligand	CuX_2	T, °C	Time, h	Conv (Yield[b])	ee, %	d.r.
1	-	$Cu(OTf)_2$[a]	rt	5h	>95 (85)	N/A	7:1
2	3	$Cu(SbF_6)_2$	rt	5h	>95 (89)	81	4:1
3	3	$Cu(SbF_6)_2$	-10	1d	>95 (83)	89	3:1
4	4	$Cu(SbF_6)_2$	rt	5h	>95 (85)	81	3:1
5	**4**	**$Cu(SbF_6)_2$**	**-10**	**1d**	**>95 (75)**	**94**	**4:1**

[a] 20 mol %. [b] isolated yield. ee (enantiomeric excess). dr (diastereomeric ratio).
ee was measured by a chiral HPLC. Reproted ee is from the major diastereomer.
dr was mesured by crude NMR or HPLC.



4-butyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (1-33d)

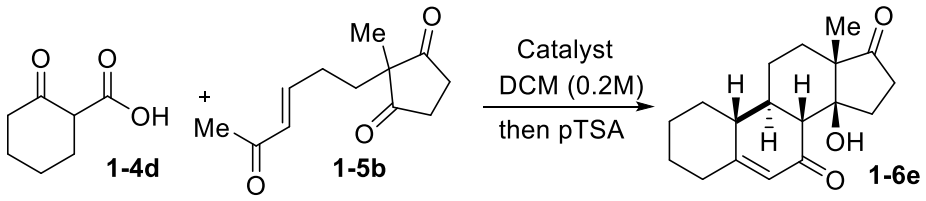
Racemic reaction (entry 1) (following the general procedure): β-ketoacids **1-31d** (65 mg, 0.46 mmol, 1.6 eq), $Cu(OTf)_2$ (21 mg, 0.058 mmol, 20 mol%), vinyl ketone **1-32a** (37 µL, 0.29 mmol, 1.0 eq), DCM (1.45 mL, 0.2 M), *p*TSA (24.8 mg, 0.14 mmol, 0.50 eq), THF (2.9 mL, 0.1 M). Purified by a flash column chromatography on SiO_2 (8 : 1 to 3 : 1 / Hex : EtOAc) to afford **1-33d** (50 mg, 85%) as a colorless oil.

The most optimized enantioselective reaction (entry 5) (following the general procedure): β-ketoacids **1-31d** (65 mg, 0.460 mmol, 1.6 eq), (*R*,*R*) cyclopropane-substituted diphenyl *bis*-(oxazoline)-copper(II) catalyst (24 mg, 0.029 mmol, 10 mol%), vinyl ketone **1-32a** (37 µL, 0.29 mmol, 1.0 eq), DCM (1.45 mL, 0.2 M), reaction for 1 day, *p*TSA (24.8mg, 0.14 mmol, 0.50 eq), THF (2.9 mL, 0.1 M). Purified by a flash column chromatography on SiO_2 (8 : 1 to 3 : 1 / Hex : EtOAc) to afford **1-33d** (44 mg, 75 %) as a colorless oil.

Major diastereomer (*Trans* stereochemistry was assigned based on ^3J (H_4-H_5) = 12 Hz)

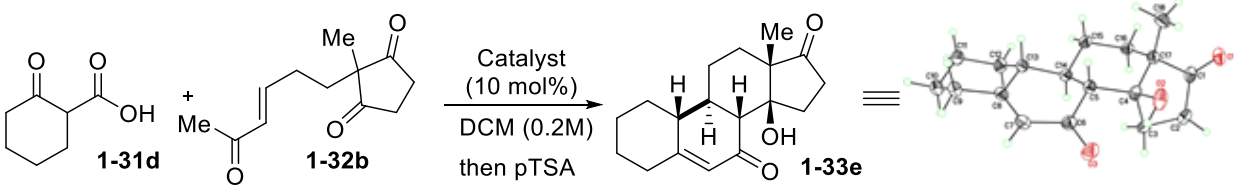
^{1}H NMR (700 MHz, Chloroform-*d*) δ 5.80 (s, 1H), 2.49 – 2.43 (m, 2H), 2.21 – 2.15 (m, 2H), 2.09 (dd, *J* = 15.8, 11.6 Hz, 1H), 2.02 (dt, *J* = 12.4, 6.4 Hz, 1H), 1.91 (ddt, *J* = 12.6, 4.9, 2.4 Hz, 1H), 1.89 – 1.85 (m, 1H), 1.74 – 1.69 (ddp, *J* = 12.0, 8.2, 4.1 Hz, 1H), 1.47 (dt, *J* = 13.1, 3.4 Hz, 1H), 1.42 – 1.32 (m, 3H), 1.32 – 1.25 (m, 3H), 1.23 – 1.17 (m, 1H), 1.13 (qd, *J* = 12.9, 3.6 Hz, 1H), 0.89 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (175 MHz, Chloroform-*d*) δ 200.38, 166.98, 123.98, 43.63, 41.83, 39.82, 36.33, 32.98, 32.86, 28.73, 27.39, 26.00, 22.96, 14.16. **IR** (thin film, cm^{-1}): 2951, 2924, 2868, 1768, 1715, 1673, 1453, 943, 861, 736 **HRMS (ESI+)** (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{22}O$ 207.1749, found 207.1741. Enantiopurity was determined to be 94% ee by chiral HPLC (DAICEL CHIRALPAK IA, 4.6 X 250 mm, hexanes/2-proponal = 99/1, flow rate = 1 mL/min, λ = 242.0 nm, RT(minor) = 18.3 min, RT(major) = 12.4 min).

(Separation of the minor diastereomer from the major isomer was not possible due to close R_f values)



Entry	Ligand	CuX_2	T, °C	Time, h	Conv (Yield[b])	ee, %	d.r.
1	-	$Cu(OTf)_2$[a]	rt	5h	>95 (80)	N/A	7:1
2	1	$Cu(OTf)_2$	rt	5h	~20	10	-
3	2	$Cu(SbF_6)_2$	rt	5h	-	50	-
4	3	$Cu(OTf)_2$	rt	5h	-	20	-
5	3	$Cu(SbF_6)_2$	rt	5h	>95 (78)	80	7:1
6	3	$Cu(SbF_6)_2$	-10	2d	>95 (80)	89	6:1
7	4	$Cu(SbF_6)_2$	rt	5h	>95 (83)	85	6:1
8	**4**	**$Cu(SbF_6)_2$**	**-10**	**3d**	**>95 (85)**	**93**	**8:1**

[a] 20 mol %. [b] isolated yield. ee (enantiomeric excess). dr (diastereomeric ratio).
ee was measured by a chiral HPLC. Reproted ee is from the major diastereomer.
dr was mesured by crude NMR or HPLC.



14-hydroxy-13-methyl-1,3,4,8,9,10,11,12,13,14,15,16-dodecahydro-7H-cyclopenta[a]phenanthrene-7,17(2H)-dione (1-33e)

Racemic reaction (entry 1): To a flame dried, N_2 flushed 1 dram vial, a stir bar, β-ketoacids **1-31d** (65.5 mg, 0.46 mmol, 1.6 eq), and vinyl ketone **1-32b**[25b] (60 mg, 0.29 mmol, 1.0 eq) were placed, and the reaction vial was taken to a glove box to add $Cu(OTf)_2$ (21 mg, 0.058 mmol, 20 mol%). The closed vial was taken out from the glove box, and DCM (1.4 mL, 0.2 M) were added

to the reaction mixture at room temp under N_2 flow. The reaction was left stirring at rt for 5 h. After the reaction completed, *p*TSA (24.8 mg, 0.14 mmol, 0.50 eq) and THF (2.9 mL, 0.1 M) was added to the reaction mixture. The reaction was stirred at 40 ^oC for overnight, and the reaction was quenched with $NaHCO_3$. The crude mixture was extracted with DCM three times and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Crude material was purified by a flash column chromatography on SiO_2 (5 : 1 to 3 : 1 / Hex : EtOAc) to afford **1-33e** (66 mg, 80 %) as a white solid.

The most optimized enantioselective reaction (entry 8) To a flame dried, N_2 flushed 1 dram vial, a stir bar, β-ketoacids **1-31d** (956 mg, 6.73 mmol, 1.6 eq), and vinyl ketone **1-32b** (1.0 g, 4.81 mmol, 1.0 eq) were placed, and the reaction vial was taken to a glove box to add (*R,R*) cyclopropane-substituted diphenyl *bis*-(oxazoline)-copper(II) catalyst (416 mg, 0.48 mmol, 10 mol%). The closed vial was taken out from the glove box, and DCM (24 mL, 0.2 M) were added to the reaction mixture at -10 ^oC under N_2 flow. The reaction was placed in the cryocool, which was set to -10 ^oC, and stirred at -10 ^oC for 3 days. After the reaction completed, *p*TSA (413 mg, 2.41 mmol, 0.50 eq) and THF (24 mL, 0.2 M) was added to the reaction mixture. The reaction was stirred at 40 ^oC for overnight, and the reaction was quenched with $NaHCO_3$. The crude mixture was extracted with DCM three times and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Crude material was purified by a flash column chromatography on SiO_2 (5 : 1 to 3 : 1 / Hex : EtOAc) to afford **1-33e** (1.1 g, 85 %) as a white solid.

IR (thin film, cm^{-1}): 3455, 2938, 2858, 1739, 1669, 1640, 1447, 1141, 1047, 984, 959, 856, 635 **HRMS (ESI+)** (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{24}O_3$ 289.1804, found 289.1802.

Major diastereomer: **^{1}H NMR** (700 MHz, Chloroform-*d*) δ 5.85 (s, 1H), 4.46 (s, 1H), 2.56 – 2.46 (m, 2H), 2.41 – 2.35 (m, 2H), 2.25 (ddd, *J* = 12.1, 5.6, 2.5 Hz, 1H), 2.22 – 2.16 (m, 2H), 2.14 – 2.07 (m, 2H), 1.98 – 1.94 (m, 1H), 1.93 – 1.86 (m, 2H), 1.70 – 1.62 (m, 1H), 1.51 – 1.30 (m, 6H), 1.09 (s, 3H), 1.04 (qd, *J* = 12.9, 3.5 Hz, 1H). **^{13}C NMR** (175 MHz, Chloroform-*d*) δ 220.39, 201.98, 167.50, 125.14, 80.2, 53.19, 52.22, 43.64, 41.94, 35.61, 32.94, 32.11, 31.23, 27.91, 26.38, 25.41, 25.38, 12.84. **$[\alpha]_D$** = -38.4 (*c* 0.34, MeOH).

Minor diastereomer: **^{1}H NMR** (700 MHz, Chloroform-*d*) δ 5.85 (s, 1H), 4.55 (s, 1H), 2.52 (dt, *J* = 19.6, 9.9 Hz, 1H), 2.46 – 2.42 (m, 1H), 2.41 – 2.37 (m, 2H), 2.32 – 2.28 (m, 1H), 2.24 – 2.15 (m, 2H), 2.13 (dd, *J* = 9.7, 2.4 Hz, 2H), 2.10 – 2.03 (m, 2H), 1.97 – 1.92 (m, 1H), 1.65 – 1.60 (m, 1H), 1.51 – 1.47 (m, 2H), 1.45 – 1.40 (m, 2H), 1.39 – 1.37 (m, 2H), 1.09 (s, 3H). **^{13}C NMR** (175 MHz, Chloroform-*d*) δ 220.40, 202.30, 171.80, 122.85, 47.87, 43.79, 38.03, 37.66, 33.00, 31.21, 30.59, 29.01, 27.92, 26.33, 24.29, 13.00. **$[\alpha]_D$** = -55.5 (*c* 0.16, MeOH) Enantiopurity was determined to be 93% ee by chiral HPLC (DAICEL CHIRALPAK IA, 4.6 X 250 mm, hexanes/2-proponal = 80/20, flow rate = 1 mL/min, λ = 242.0 nm, RT(major) = 10.3 min, RT(minor) = 35.2 min).

Structure Determination of 1-33e by X-ray crystallography.

Colorless needles of **1-33e** were grown from a diethyl ether solution of the compound at -10 deg. C. A crystal of dimensions 0.24 x 0.06 x 0.03 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 3 sec. for high angle.

Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 22575 reflections to a maximum 2θ value of 138.70° of which 2743 were independent and 2706 were greater than 2σ(I). The final cell constants (Table 1) were based on the xyz centroids of 15492 reflections above 10σ(I). Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2016/6) software package, using the space group P2(1)2(1)2(1) with Z = 4 for the formula $C_{18}H_{24}O_3$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in a combination of idealized and refined positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0327 and wR2 = 0.0833 [based on I > 2sigma(I)], R1 = 0.0333 and wR2 = 0.0847 for all data. Additional details are presented in Table 1 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

Table 1.10.1. Crystal data and structure refinement for **1-33e**.

Identification code	**1-33e**
Empirical formula	C18 H24 O3
Formula weight	288.37
Temperature	85(2) K
Wavelength	1.54184 A
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 6.18680(10) A alpha = 90 deg.
	b = 12.45830(10) A beta = 90 deg.
	c = 19.1309(3) A gamma = 90 deg.

Volume	1474.55(4) A^3
Z, Calculated density	4, 1.299 Mg/m^3
Absorption coefficient	0.691 mm^-1
F(000)	624
Crystal size	0.240 x 0.060 x 0.030 mm
Theta range for data collection	4.235 to 69.349 deg.
Limiting indices	-7<=h<=7, -14<=k<=15, -23<=l<=22
Reflections collected / unique	22575 / 2743 [R(int) = 0.0668]
Completeness to theta = 67.684	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.85056
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2743 / 0 / 196
Goodness-of-fit on F^2	1.068
Final R indices [I>2sigma(I)]	R1 = 0.0327, wR2 = 0.0833
R indices (all data)	R1 = 0.0333, wR2 = 0.0847
Absolute structure parameter	0.22(11)
Extinction coefficient	0.0051(8)
Largest diff. peak and hole	0.175 and -0.199 e.A^-3

Table 1.10.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **1-33e**.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

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	x	y	z	U(eq)
O(1)	1401(2)	8491(1)	8424(1)	30(1)
O(2)	6363(2)	8256(1)	7292(1)	30(1)
O(3)	7681(2)	8059(1)	5926(1)	32(1)
C(1)	2063(3)	8326(2)	7836(1)	23(1)
C(2)	1938(3)	9101(2)	7228(1)	25(1)
C(3)	3118(3)	8544(1)	6619(1)	23(1)
C(4)	4563(3)	7703(2)	6982(1)	20(1)
C(5)	5394(3)	6784(1)	6521(1)	19(1)
C(6)	6862(3)	7156(2)	5932(1)	22(1)
C(7)	7391(3)	6360(2)	5401(1)	23(1)
C(8)	6436(3)	5389(2)	5377(1)	20(1)
C(9)	7245(3)	4513(2)	4902(1)	24(1)
C(10)	5425(3)	3970(2)	4487(1)	26(1)
C(11)	3676(3)	3585(2)	4986(1)	25(1)
C(12)	2788(3)	4518(2)	5414(1)	24(1)
C(13)	4555(3)	5094(1)	5841(1)	19(1)
C(14)	3599(3)	6049(1)	6244(1)	19(1)
C(15)	2176(3)	5662(1)	6851(1)	24(1)
C(16)	1333(3)	6582(1)	7304(1)	23(1)
C(17)	3169(3)	7295(2)	7594(1)	22(1)

C(18)	4407(4)	6745(2)	8181(1)	33(1)

Table 1.10.3. Bond lengths [A] and angles [deg] for **1-33e**.

O(1)-C(1)	1.215(2)
O(2)-C(4)	1.438(2)
O(2)-H(2)	0.93(4)
O(3)-C(6)	1.234(2)
C(1)-C(2)	1.513(3)
C(1)-C(17)	1.527(2)
C(2)-C(3)	1.540(3)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.543(3)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.534(2)
C(4)-C(17)	1.540(3)
C(5)-C(6)	1.520(3)
C(5)-C(14)	1.534(2)
C(5)-H(5)	1.0000
C(6)-C(7)	1.456(3)

C(7)-C(8)	1.347(3)
C(7)-H(7)	0.9500
C(8)-C(9)	1.506(2)
C(8)-C(13)	1.509(2)
C(9)-C(10)	1.534(3)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.520(3)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-C(12)	1.524(3)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.542(2)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-C(14)	1.536(2)
C(13)-H(13)	1.0000
C(14)-C(15)	1.534(2)
C(14)-H(14)	1.0000
C(15)-C(16)	1.527(3)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900

C(16)-C(17)	1.546(3)
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900
C(17)-C(18)	1.522(3)
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800

C(4)-O(2)-H(2)	104(2)
O(1)-C(1)-C(2)	125.97(17)
O(1)-C(1)-C(17)	124.96(18)
C(2)-C(1)-C(17)	109.07(15)
C(1)-C(2)-C(3)	105.67(15)
C(1)-C(2)-H(2A)	110.6
C(3)-C(2)-H(2A)	110.6
C(1)-C(2)-H(2B)	110.6
C(3)-C(2)-H(2B)	110.6
H(2A)-C(2)-H(2B)	108.7
C(2)-C(3)-C(4)	103.86(14)
C(2)-C(3)-H(3A)	111.0
C(4)-C(3)-H(3A)	111.0
C(2)-C(3)-H(3B)	111.0
C(4)-C(3)-H(3B)	111.0

H(3A)-C(3)-H(3B)	109.0
O(2)-C(4)-C(5)	109.61(15)
O(2)-C(4)-C(17)	106.19(15)
C(5)-C(4)-C(17)	112.25(15)
O(2)-C(4)-C(3)	108.02(15)
C(5)-C(4)-C(3)	116.19(15)
C(17)-C(4)-C(3)	103.99(14)
C(6)-C(5)-C(14)	111.03(14)
C(6)-C(5)-C(4)	113.58(15)
C(14)-C(5)-C(4)	113.69(15)
C(6)-C(5)-H(5)	105.9
C(14)-C(5)-H(5)	105.9
C(4)-C(5)-H(5)	105.9
O(3)-C(6)-C(7)	121.50(17)
O(3)-C(6)-C(5)	121.96(17)
C(7)-C(6)-C(5)	116.36(16)
C(8)-C(7)-C(6)	122.46(17)
C(8)-C(7)-H(7)	118.8
C(6)-C(7)-H(7)	118.8
C(7)-C(8)-C(9)	121.71(16)
C(7)-C(8)-C(13)	122.46(16)
C(9)-C(8)-C(13)	115.79(16)
C(8)-C(9)-C(10)	112.82(16)

C(8)-C(9)-H(9A)	109.0
C(10)-C(9)-H(9A)	109.0
C(8)-C(9)-H(9B)	109.0
C(10)-C(9)-H(9B)	109.0
H(9A)-C(9)-H(9B)	107.8
C(11)-C(10)-C(9)	109.66(15)
C(11)-C(10)-H(10A)	109.7
C(9)-C(10)-H(10A)	109.7
C(11)-C(10)-H(10B)	109.7
C(9)-C(10)-H(10B)	109.7
H(10A)-C(10)-H(10B)	108.2
C(10)-C(11)-C(12)	110.69(15)
C(10)-C(11)-H(11A)	109.5
C(12)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11B)	109.5
C(12)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	108.1
C(11)-C(12)-C(13)	112.60(16)
C(11)-C(12)-H(12A)	109.1
C(13)-C(12)-H(12A)	109.1
C(11)-C(12)-H(12B)	109.1
C(13)-C(12)-H(12B)	109.1
H(12A)-C(12)-H(12B)	107.8

C(8)-C(13)-C(14)	113.79(15)
C(8)-C(13)-C(12)	110.37(15)
C(14)-C(13)-C(12)	110.70(15)
C(8)-C(13)-H(13)	107.2
C(14)-C(13)-H(13)	107.2
C(12)-C(13)-H(13)	107.2
C(5)-C(14)-C(15)	110.03(15)
C(5)-C(14)-C(13)	110.93(15)
C(15)-C(14)-C(13)	110.94(14)
C(5)-C(14)-H(14)	108.3
C(15)-C(14)-H(14)	108.3
C(13)-C(14)-H(14)	108.3
C(16)-C(15)-C(14)	112.91(14)
C(16)-C(15)-H(15A)	109.0
C(14)-C(15)-H(15A)	109.0
C(16)-C(15)-H(15B)	109.0
C(14)-C(15)-H(15B)	109.0
H(15A)-C(15)-H(15B)	107.8
C(15)-C(16)-C(17)	112.60(16)
C(15)-C(16)-H(16A)	109.1
C(17)-C(16)-H(16A)	109.1
C(15)-C(16)-H(16B)	109.1
C(17)-C(16)-H(16B)	109.1

H(16A)-C(16)-H(16B)	107.8
C(18)-C(17)-C(1)	112.37(15)
C(18)-C(17)-C(4)	115.28(16)
C(1)-C(17)-C(4)	101.73(15)
C(18)-C(17)-C(16)	112.11(17)
C(1)-C(17)-C(16)	105.28(15)
C(4)-C(17)-C(16)	109.16(14)
C(17)-C(18)-H(18A)	109.5
C(17)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(17)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 1.10.4. Anisotropic displacement parameters (A^2 x 10^3) for **1-33e**.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	31(1)	32(1)	26(1)	-10(1)	2(1)	6(1)
O(2)	21(1)	32(1)	38(1)	-16(1)	-3(1)	-3(1)
O(3)	32(1)	23(1)	41(1)	-4(1)	10(1)	-9(1)
C(1)	20(1)	22(1)	27(1)	-7(1)	-4(1)	0(1)
C(2)	24(1)	16(1)	35(1)	-3(1)	1(1)	0(1)
C(3)	27(1)	16(1)	27(1)	2(1)	1(1)	0(1)
C(4)	19(1)	18(1)	23(1)	-3(1)	-2(1)	-2(1)
C(5)	21(1)	17(1)	19(1)	-1(1)	-1(1)	-1(1)
C(6)	21(1)	21(1)	23(1)	1(1)	-1(1)	-1(1)
C(7)	24(1)	26(1)	18(1)	2(1)	1(1)	-2(1)
C(8)	21(1)	23(1)	16(1)	1(1)	-2(1)	1(1)
C(9)	25(1)	26(1)	20(1)	-3(1)	2(1)	0(1)
C(10)	32(1)	27(1)	19(1)	-5(1)	-1(1)	0(1)
C(11)	30(1)	21(1)	24(1)	-5(1)	-2(1)	-4(1)

C(12)	25(1)	22(1)	24(1)	-4(1)	-1(1)	-4(1)
C(13)	21(1)	16(1)	19(1)	-1(1)	0(1)	-2(1)
C(14)	22(1)	16(1)	18(1)	0(1)	0(1)	-2(1)
C(15)	30(1)	17(1)	25(1)	-1(1)	7(1)	-3(1)
C(16)	28(1)	17(1)	24(1)	1(1)	6(1)	-3(1)
C(17)	25(1)	21(1)	19(1)	-2(1)	0(1)	4(1)
C(18)	40(1)	40(1)	19(1)	1(1)	-1(1)	17(1)

Table 1.10.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **1-33e**.

	x	y	z	U(eq)
H(2)	7170(60)	8480(30)	6909(17)	67(10)
H(2A)	2653	9788	7347	30
H(2B)	414	9248	7103	30
H(3A)	4000	9064	6351	28
H(3B)	2076	8195	6298	28
H(5)	6311	6326	6831	23
H(7)	8448	6532	5059	27
H(9A)	8001	3964	5185	29

H(9B)	8305	4821	4570	29
H(10A)	4801	4486	4149	31
H(10B)	6012	3353	4222	31
H(11A)	4283	3035	5304	30
H(11B)	2488	3251	4716	30
H(12A)	1665	4245	5737	29
H(12B)	2096	5041	5096	29
H(13)	5103	4570	6196	22
H(14)	2677	6473	5916	23
H(15A)	931	5259	6659	29
H(15B)	3023	5165	7147	29
H(16A)	498	6280	7699	27
H(16B)	340	7030	7022	27
H(18A)	5650	7188	8314	50
H(18B)	4915	6042	8021	50
H(18C)	3454	6652	8586	50

Table 1.10.6. Torsion angles [deg] for **1-33e**.

O(1)-C(1)-C(2)-C(3)	176.52(18)
C(17)-C(1)-C(2)-C(3)	-3.3(2)

C(1)-C(2)-C(3)-C(4)	-20.85(19)
C(2)-C(3)-C(4)-O(2)	-75.25(18)
C(2)-C(3)-C(4)-C(5)	161.16(15)
C(2)-C(3)-C(4)-C(17)	37.28(17)
O(2)-C(4)-C(5)-C(6)	-59.6(2)
C(17)-C(4)-C(5)-C(6)	-177.32(15)
C(3)-C(4)-C(5)-C(6)	63.2(2)
O(2)-C(4)-C(5)-C(14)	172.17(15)
C(17)-C(4)-C(5)-C(14)	54.4(2)
C(3)-C(4)-C(5)-C(14)	-65.1(2)
C(14)-C(5)-C(6)-O(3)	145.09(18)
C(4)-C(5)-C(6)-O(3)	15.5(2)
C(14)-C(5)-C(6)-C(7)	-39.7(2)
C(4)-C(5)-C(6)-C(7)	-169.26(15)
O(3)-C(6)-C(7)-C(8)	-176.66(18)
C(5)-C(6)-C(7)-C(8)	8.1(3)
C(6)-C(7)-C(8)-C(9)	-169.99(17)
C(6)-C(7)-C(8)-C(13)	7.6(3)
C(7)-C(8)-C(9)-C(10)	-132.61(19)
C(13)-C(8)-C(9)-C(10)	49.6(2)
C(8)-C(9)-C(10)-C(11)	-53.4(2)
C(9)-C(10)-C(11)-C(12)	57.9(2)
C(10)-C(11)-C(12)-C(13)	-58.3(2)

C(7)-C(8)-C(13)-C(14)	9.9(2)
C(9)-C(8)-C(13)-C(14)	-172.38(15)
C(7)-C(8)-C(13)-C(12)	135.03(18)
C(9)-C(8)-C(13)-C(12)	-47.2(2)
C(11)-C(12)-C(13)-C(8)	51.2(2)
C(11)-C(12)-C(13)-C(14)	178.09(15)
C(6)-C(5)-C(14)-C(15)	178.57(14)
C(4)-C(5)-C(14)-C(15)	-51.9(2)
C(6)-C(5)-C(14)-C(13)	55.42(19)
C(4)-C(5)-C(14)-C(13)	-175.03(14)
C(8)-C(13)-C(14)-C(5)	-41.0(2)
C(12)-C(13)-C(14)-C(5)	-165.97(14)
C(8)-C(13)-C(14)-C(15)	-163.60(16)
C(12)-C(13)-C(14)-C(15)	71.42(19)
C(5)-C(14)-C(15)-C(16)	52.3(2)
C(13)-C(14)-C(15)-C(16)	175.40(16)
C(14)-C(15)-C(16)-C(17)	-55.6(2)
O(1)-C(1)-C(17)-C(18)	-30.0(3)
C(2)-C(1)-C(17)-C(18)	149.78(17)
O(1)-C(1)-C(17)-C(4)	-153.88(18)
C(2)-C(1)-C(17)-C(4)	25.92(19)
O(1)-C(1)-C(17)-C(16)	92.3(2)
C(2)-C(1)-C(17)-C(16)	-87.92(17)

O(2)-C(4)-C(17)-C(18)	-46.5(2)
C(5)-C(4)-C(17)-C(18)	73.2(2)
C(3)-C(4)-C(17)-C(18)	-160.36(16)
O(2)-C(4)-C(17)-C(1)	75.35(17)
C(5)-C(4)-C(17)-C(1)	-164.90(15)
C(3)-C(4)-C(17)-C(1)	-38.49(17)
O(2)-C(4)-C(17)-C(16)	-173.73(14)
C(5)-C(4)-C(17)-C(16)	-53.97(19)
C(3)-C(4)-C(17)-C(16)	72.43(17)
C(15)-C(16)-C(17)-C(18)	-74.0(2)
C(15)-C(16)-C(17)-C(1)	163.52(15)
C(15)-C(16)-C(17)-C(4)	55.0(2)

Symmetry transformations used to generate equivalent atoms:

Table 1.10.7. Hydrogen bonds for **1-33e** [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...O(3)	0.93(4)	1.98(3)	2.749(2)	139(3)

Symmetry transformations used to generate equivalent atoms:

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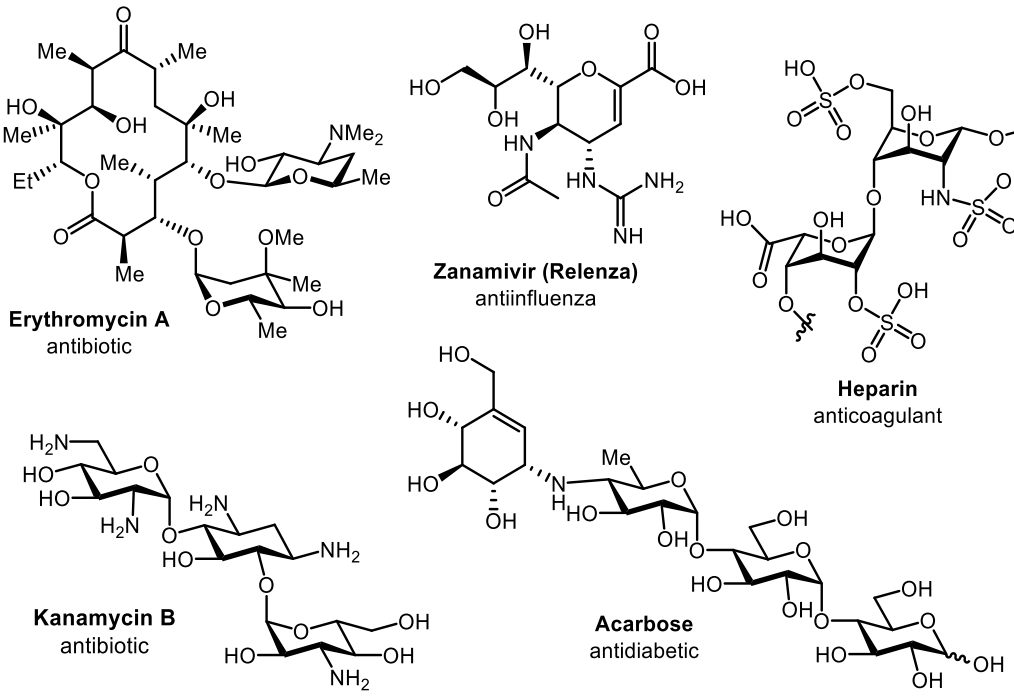
Chapter 2

Regioselective Derivatization of Polyols by Chiral Brønsted Acids

2.1 Introduction

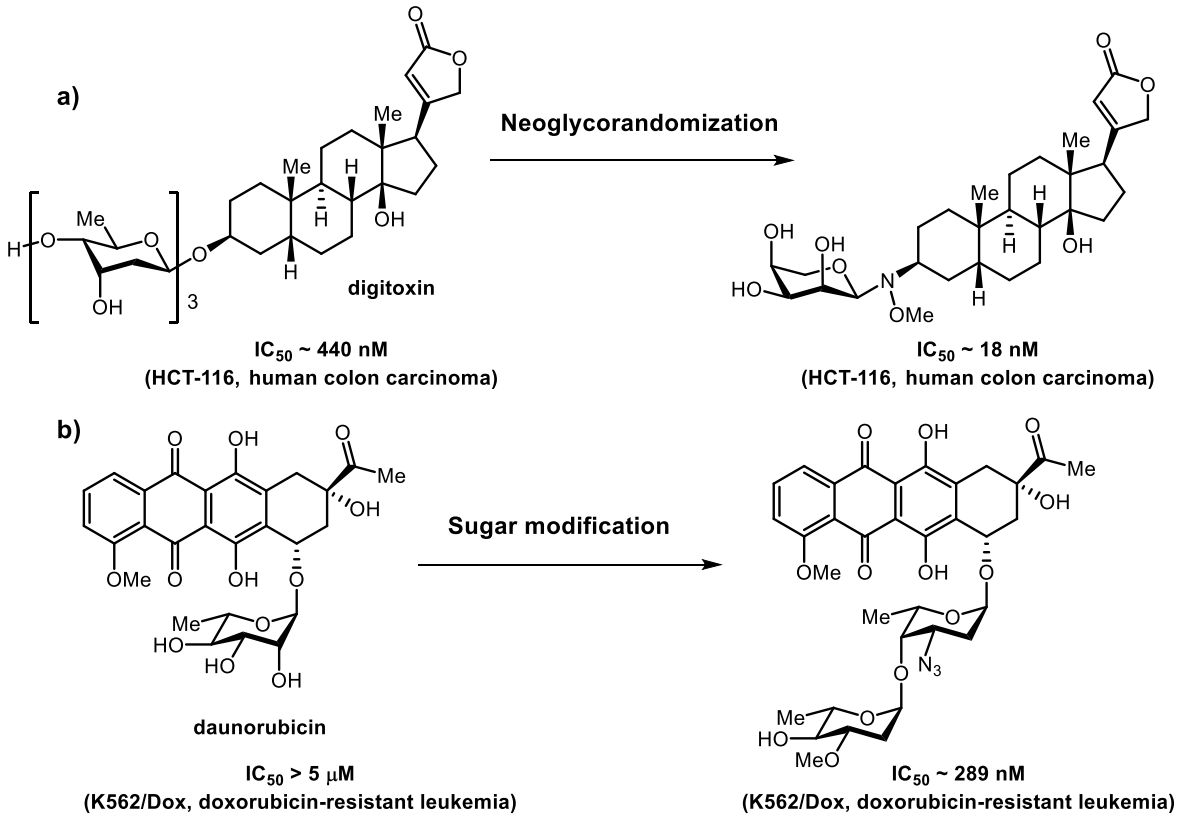
Polyols, such as carbohydrates and other compounds containing multiple hydroxyl groups, represent an important class of organic molecules. The selective functionalization of polyol-containing compounds is of great importance as a number of easily accessible polyol building blocks can be transformed into more synthetically useful compounds, which may be used as pharmaceuticals, cosmetics, or in polymer industry.[1] Among various selective organic transformations, selective glycosylation of polyols has attracted a lot of attention over the past decades. This is partly due to the fact that simple carbohydrates like mono- and oligosaccharides

Figure 2. 1. Examples of polyol-containing drugs.



are common structural motifs in drug discovery.[2] Due to their drug-like characteristics, numerous carbohydrate scaffolds are found in many prescribed drugs such as erythromycin (antibiotic), zanamivir (antiviral), heparin (anticoagulant), kanamycin (antibiotic) acarbose (antidiabetic) (Figure 2.1). The importance of selective glycosylation of polyol-containing molecule is emphasized again by observing the improvement of therapeutic properties by sugar modifications[3] (Scheme 2.1). For instance, Thorsen group has demonstrated that *in vitro* cytotoxicity of cardiac glycoside digitoxin was enhanced by neoglycorandomization (Scheme 2.1a).[3d] In one of their examples, the IC_{50} value of digitoxin against human cancer cell line, HCT-116 was improved from 440 nM to 18 nM after modifications in the sugar structure. Similarly, Zhang group has investigated the development of new analogues of daunorubicin to improve its properties against drug-resistant leukemia (Scheme 2.1b) [3a] By modifying L-rhamnose portion of doxorubicin into more complex 3-azidosugar, Zhang and coworkers achieved ~17 fold improvement in the IC50 value against K563/Dox, which is doxorubicin-resistant leukemia cell line. These examples suggest that the modification in the sugar structure may significantly enhance the biological activity of natural products. However, these medicinal chemistry explorations are often hindered by inability to selectively introduce sugar into natural products in a regioselective fashion.

Scheme 2. 1. Improving the therapeutic properties of natural polyols s by sugar modification: a) Thorsen group's neoglycorandomization work. b) Zhang group's sugar modification work.

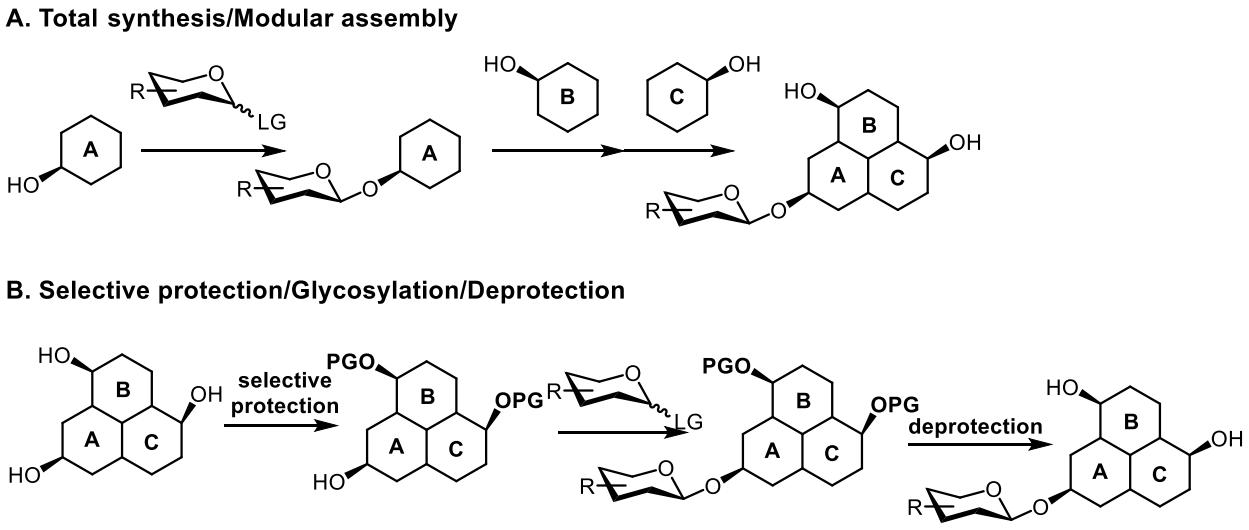


2.2 Regioselective glycosylation of poylols

The selective functionalization of polyols is challenging due to the intrinsic complexity of these molecules. In addition to their intricate structures, unpredictable inherent reactivity of primary and secondary alcohols introduces the synthetic hurdles for their selective functionalization. Accomplishing selective glycosylation of polyols is even more difficult because it requires optimization and control of many factors, such as protecting groups, leaving groups, promoters, solvents, concentrations, and reaction temperature.[4] In carbohydrate synthesis, not only the control of regioselectivity, but also the stereoselectivity is crucial. To avoid the inherent complex outcome of glycosylation reactions, three general methods for regioselective glycosylations are described (Scheme 2.2).

One of the approaches relies on using a glycosylated fragment, and then synthetically modifying it to produce the desired glycosylated natural product (Scheme 2.2A). This approach avoids dealing with regioselectivity issues as carbohydrate is pre-installed. However, there are certain limitations with this approach because it essentially requires accomplishing total synthesis of a complex structure.

Scheme 2. 2. Three approaches of regioselective glycosylation reaction.

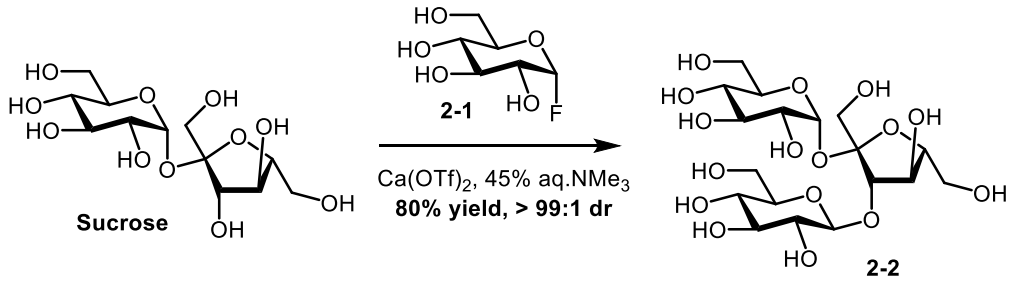


Another approach is based on site-selective derivatization of the existing natural products. This may be done through selective protecting group manipulations (Scheme 2.2B) or by a direct glycosylation (Scheme 2.2C). The former approach typically requires selective protection, glycosylation of the remaining site and subsequent deprotection. This approach is achievable only when the selective protection of the other alcohols is possible, with the desired alcohol being

unprotected. While it is frequently being used to generate semisynthetic derivatives, this approach might require laborious protecting-group manipulations.

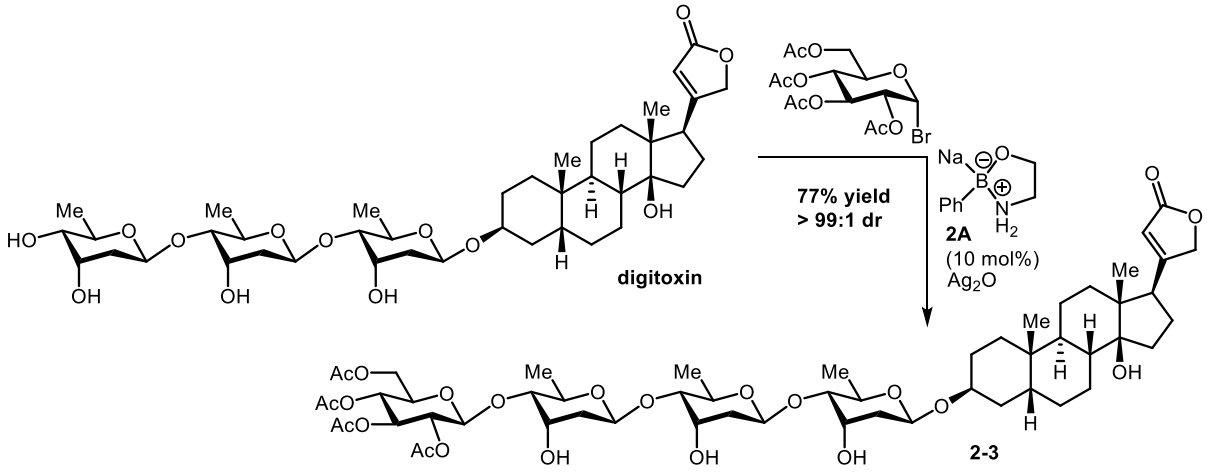
The last approach to regioselective glycosylation reaction relies on the direct glycosylation of polyols without pre-protection (Scheme 2.2C). This approach is the most direct and straightforward way of introducing carbohydrate to the polyol system. Often, the desired selectivity may be imposed through the substrate control. For instance, Miller group explored nonenzymatic site-selective glycosylation of sucrose under aqueous conditions (Scheme 2.4).[8] For this glycosylation, unprotected sucrosyl acceptors and unprotected glycosyl fluoride donors were used to construct trisaccharides in a regioselective manner. Given that the enzyme glycosyltransferases also use unprotected sugar in buffered water for regioselective glycosylation reaction,[9] this method perfectly mimics the enzymatic processes with a chemical control. The reaction was performed under very mild conditions, and the combination of a calcium salt with triethylamine as a base were essential for achieving both the reactivity and the selectivity in this transformation. From this condition, the glycosylation was promoted with complete stereoinversion at the anomeric position of the glycosyl donor as well as high regioselectivity for either 1'-position or 3'-position (mainly) of the fructofuranoside unit of sucrose acceptor.

Scheme 2. 3. Millers' example of regioselective glycosylation in aqueous condition.



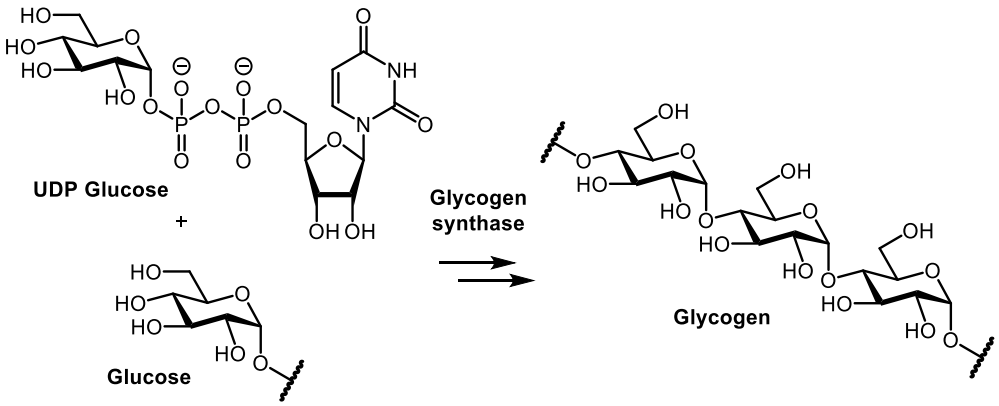
Another noticeable substrate controlled-site-selective glycosylation method was reported by the Taylor group in their regioselective glycosylation of digitoxin (Scheme 2.4).[10] Digitoxin contains 5 free hydroxyl groups in the structure, and only the hydroxyl group at 4'-position of terminal sugar was regioselectively glycosylated by using a borinic acid-based catalyst. In the presence of organoboron catalyst **2A**, different kinds of glycosyl donors were selectively connected to the digitoxin in a single step. As a result, the organoboron-catalyzed late-stage regioselective glycosylation method allowed them to access novel cardiac glycoside analogs.

Scheme 2. 4. Regioselective glycosylation of digitoxin by Taylor and coworkers.



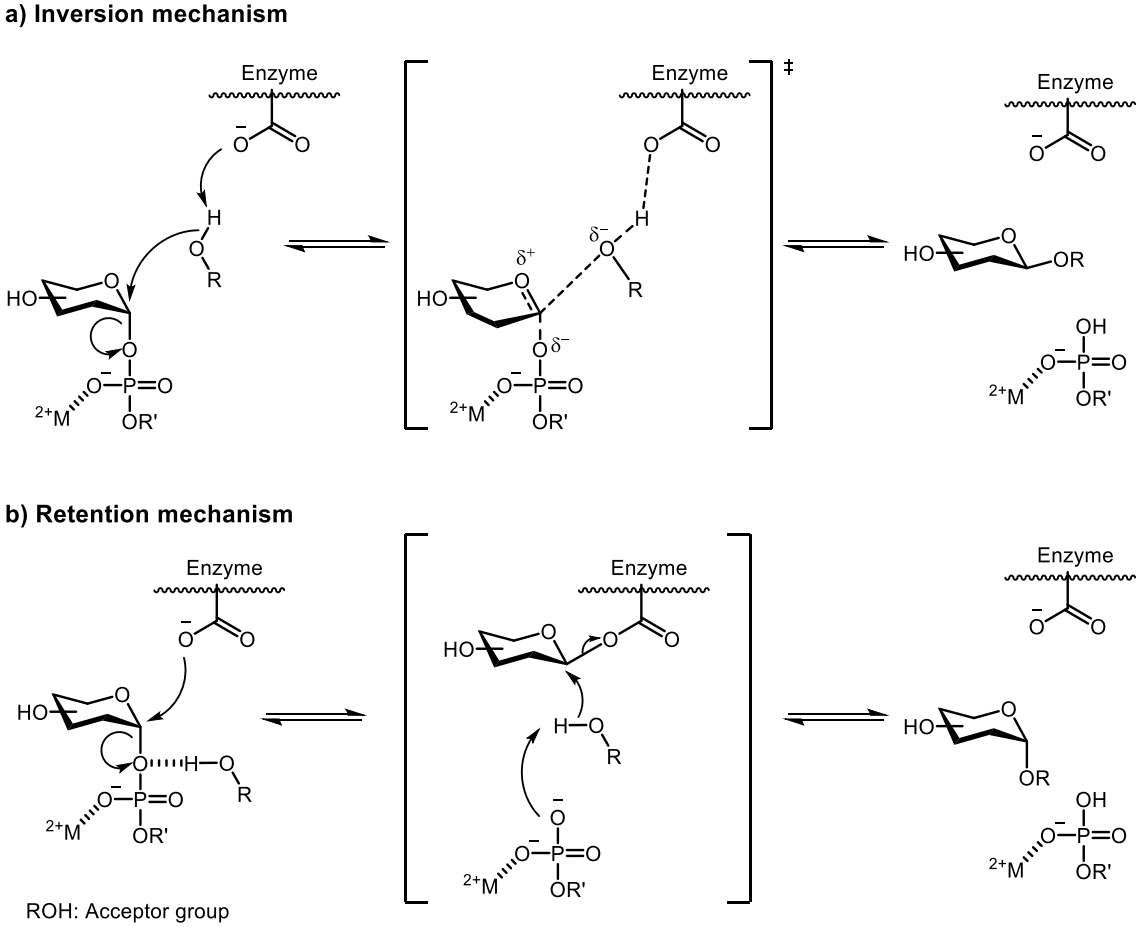
However, very often the direct substrate-controlled functionalization is not possible. To overcome this problem, nature uses enzymes to introduce carbohydrate moiety with high selectivities. For instance, glycogen synthase, the enzyme belonging to glycosyltransferase family, catalyzes the conversion of glucose to glycogen by promoting the formation of α(1→4) glycosidic linkage (Scheme 2.5). The glycogen synthase employs unprotected uridine diphosphate glucose (UDP-Glucose) and unprotected glucose as building blocks, and oligosaccharide primer, called glycogenin is required to initiate the glycosylation reactions.[6] It is truly amazing to see the

Scheme 2. 5. Example of enzyme controlled regioselective glycosylation reaction (glycogen synthase).



enzyme's precise control of the site-selectivity in such a complex polyol system. In addition to controlling the regioselectivity of glycosylation reactions, enzyme-catalyzed glycosylations feature remarkable levels of stereocontrol. In order to access both α- and β-stereoisomers, nature employs two different glycosyltransferase enzymes, an inverting glycosyltransferase, and a retaining glycosyltransferase (Scheme 2.6).[7] The inverting glycosyl-transferases catalyze the glycosylation reaction through a direct displacement S_N2-like reaction via single oxocarbenium ion-transition state, which results in inverted stereogenic center at the anomeric position. On the other hand, the retaining glycotransferases catalyze the glycosylation reactions with retention of the stereogenic center at the anomeric positions through double-displacement mechanism, which involves the formation of a covalent linkage between the enzyme and the sugar donor. Inspired by these spectacular examples of enzyme-controlled selective glycosylations, a great number of researches have searched for small-molecule-based catalysts capable of achieving similar levels of control.

Scheme 2. 6. Example of enzyme controlled stereoselective glycosylation reaction (inverting glycosyltransferase and retaining glycosyltransferase).



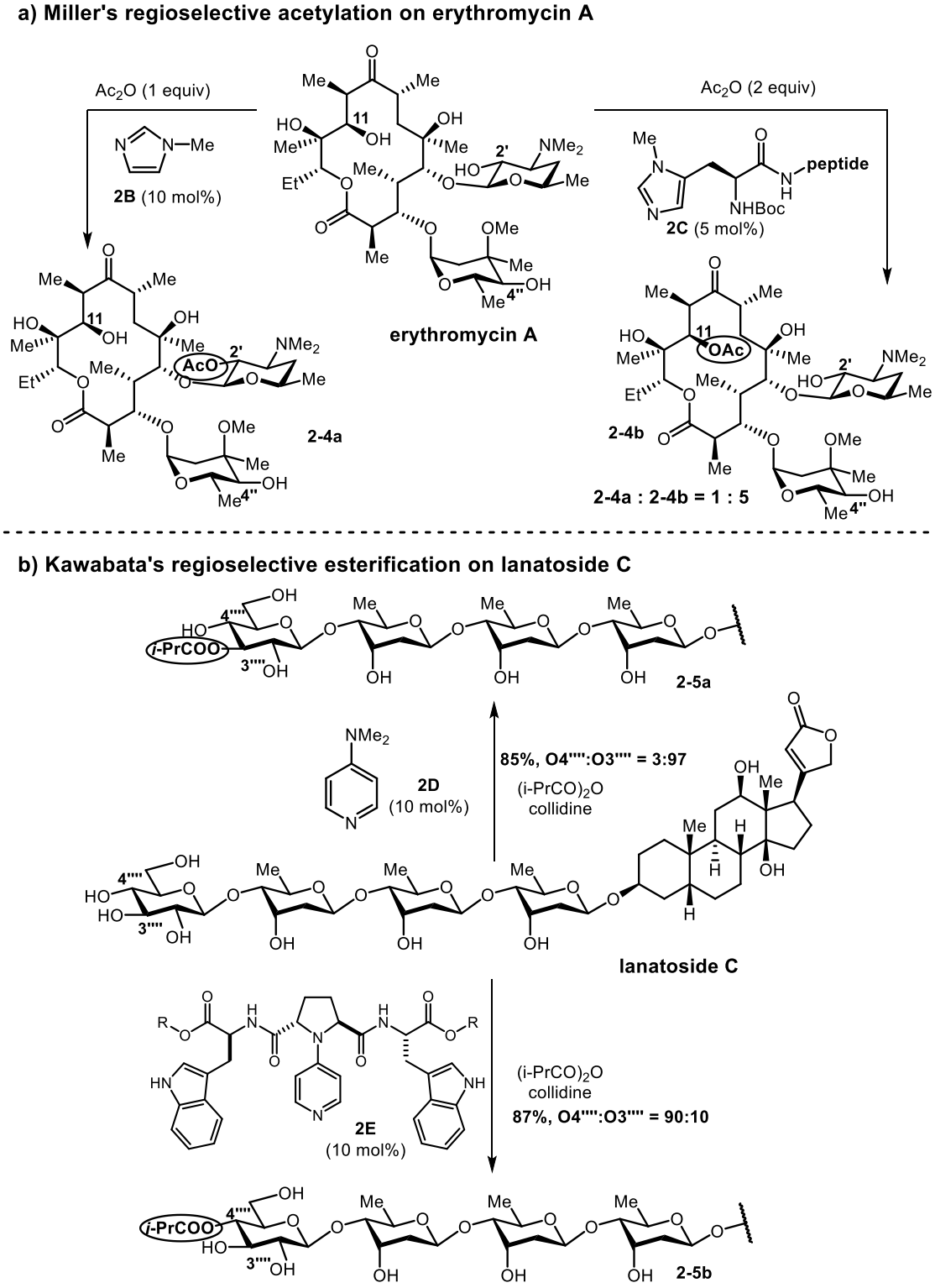
2.3 Chiral catalyst-controlled regioselective functionalization of polyols.

As already discussed above, direct functionalization of poylols represents the most direct and straightforward way to access polyol derivatives. Inspired by the work of the Miller group, a number of studies have investigated the use of chiral catalysts to control regioselective functionalization of polyols (Scheme 2.7a). In their pioneering study, the Miller group achieved catalyst-controlled site-selective acylation of polyol erythromycin A by using simple peptides as the chiral catalysts.[11] While achiral catalyst *N*-methylimidazole (**2B**)-catalyzed acetylation of the C2'-alcohols present in the sugar moiety, the peptide-based chiral catalyst **2C** promoted the

acetylation reaction of the C11-alcohols of the macrolactone ring in erythromycin A. The selectivity that was produced by the catalyst **2B** is dictated by the substrates; however, the catalysts **2C** clearly overturned this selectivity. Following the Miller's study, the Kawabata group also demonstrated the possibility of catalyst-controlled regioselective acylation of lanatoside C by employing a chiral organocatalyst **2E** (Scheme 2.7b).[12] The chiral catalyst **2E** promoted acylation reaction with regioselectivity on C4''''-position of the terminal sugar of lanatoside C with 90:10 = C4'''':C3'''' selectivity. On the other hand, the achiral DMAP-based catalyst **2D** introduced the acyl group to the C3''''-position of the terminal sugar of latanoside C with 3:97 = C4'''':C3'''' selectivity, which is essentially the substrate-controlled selectivity. Using these catalysts, a diverse set of the acyl groups was introduced in both C3''''-and C4''''-position in latanoside C selectively. These results highlight the utility of the chiral catalysts for controlling site-selective modification of natural polyols.

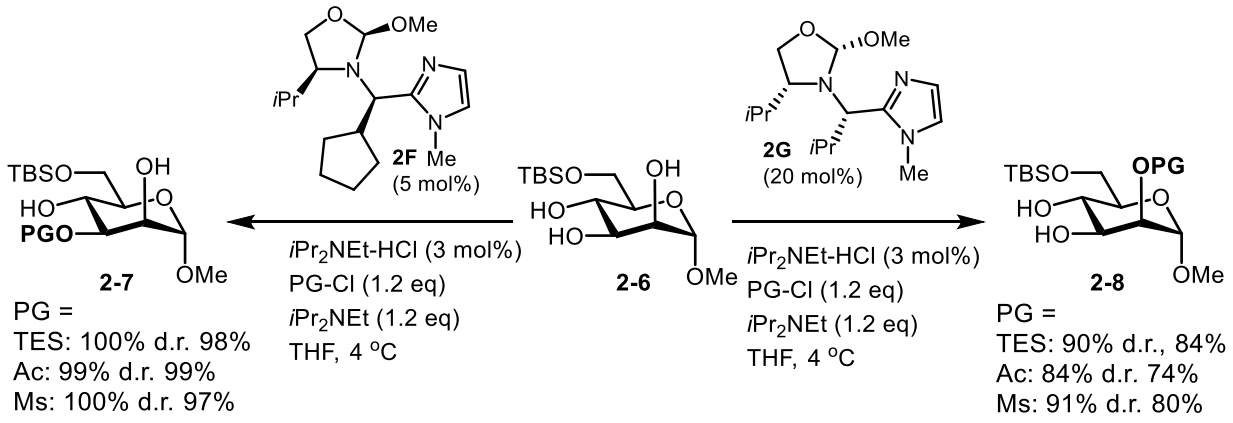
In addition to the polyol natural products, simple monosaccharides have also been targeted for regioselective functionalization. In 2013, Tan group reported chiral catalyst-controlled regioselective functionalization of 1,2-*cis*-diol- and 1,2,3-triol-containing monosaccharides (Scheme 2.8).[13] Tan and coworkers were able to employ two different chiral organocatalysts **2F** and **2G**, which are pseudoenantiomers of each other, to achieve a regiodivergent protection of 1,2-cis diol moiety in D-(+)-mannose derivative **2-6** and other monosaccharides to afford **2-7** and **2-8** respectively. The regioselectivity was imposed by the chiral catalysts **2F** and **2G** that form a reversible covalent bond with one of the alcohols in the diol or triol moieties based on the recognition of the substrate chirality within the chiral binding pocket. This regioselective protection method was also successfully applied to different monosaccharides like L-rhamnose, D-arabinose, D-galactose. Once the method for the regioselective functionalization of 1,2-diols was

Scheme 2. 7. Chiral-catalysts driven regioselective protection of polyols. a) Miller's regioselective acetylation on erythromycin A. b) Kawabata's regioselective esterification on lanatoside C.



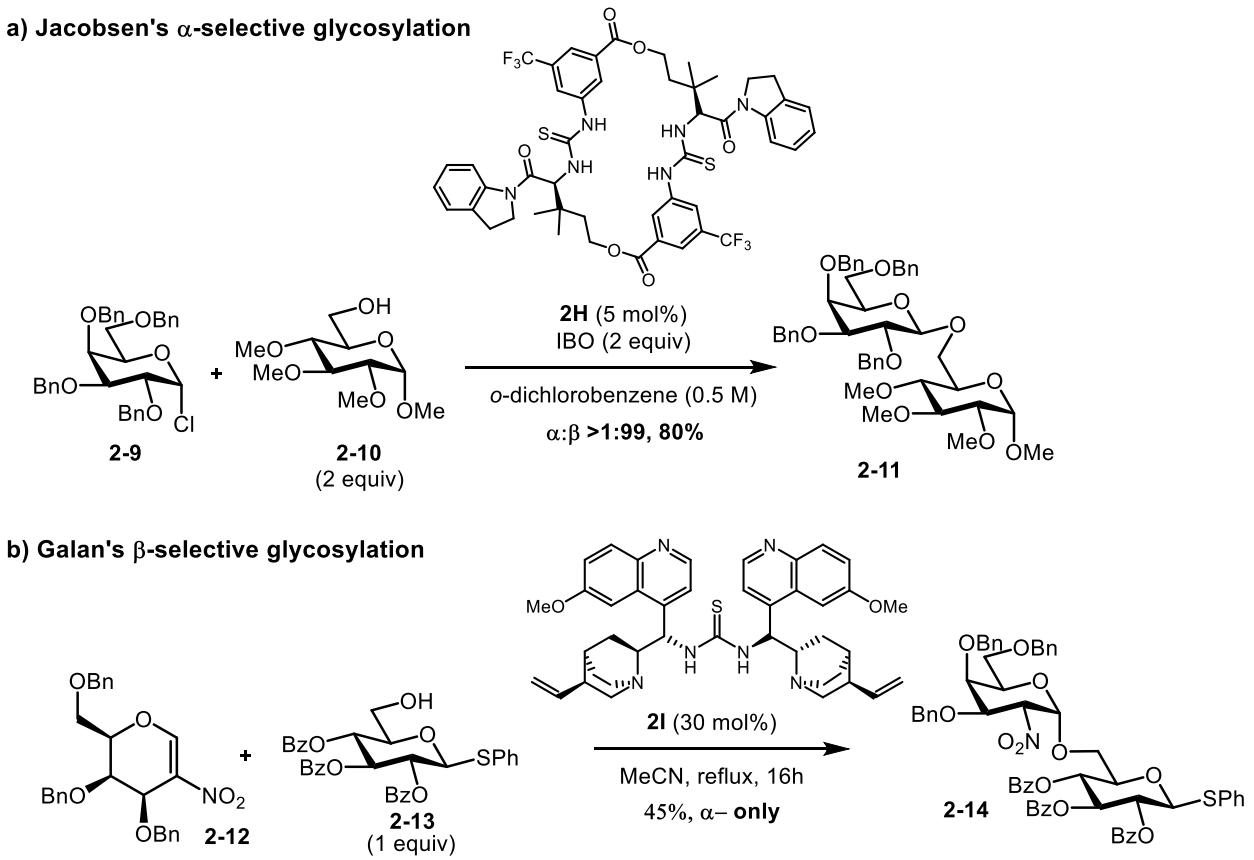
developed for the monosaccharide-based substrates, Tan group successfully expanded this method to other diols, such as uridine, mupirocin methyl ester, and digitoxin. This method was very selective in that even the less kinetically reactive sites within 1,2-diol moieties were protected with high regioselectivities.

Scheme 2. 8. Tan's chiral catalyst-controlled regioselective functionalization of *cis*-1,2-diols.



Chiral catalysts can be employed not only for the selective protection of polyols, but also for the selective glycosylation reactions of carbohydrates. The Jacobsen group in 2012 introduced a catalyst-controlled stereoselective glycosylation reaction using glycosyl chloride donors **2-9** and acceptor **2-10** with a macrocyclic *bis*-thiourea chiral (*R,R*)-catalyst **2H** and isobutylene oxide (IBO) as a base (Scheme 2.9a).[14] This method provided β-selective glycosides of various monosaccharide, such as D-glucose, D-galactose, D-mannose, 2-deoxy-D-glucose, L-fucose, D-xylose. Following the Jacobsen's study, Galan promoted α-stereoselective glycosylation using a different thiourea-based chiral (*S,S*)-catalyst **2I** (Scheme 2.9b).[15] Galan used 2-nitroglycal donor **2-12** and acceptor **2-13** to access α-selective glycoside **2-14**. In addition to the aforementioned studies, several studies including ours have demonstrated the use of chiral phosphoric acid to achieve functionalization and glycosylation of chiral polyols. The following sub-chapter provides an overview of this work.

Scheme 2. 9. Chiral thiourea-catalyzed stereoselective glycosylation reaction. a) Jacobsen's β-selective glycosylation. b) Galan's α-selective glycosylation.



2.4 BINOL-based chiral phosphoric acid

Among the various chiral catalysts explored to date, chiral phosphoric acids demonstrated a lot of promise as the catalysts for the site-selective and stereoselective functionalization of polyols. The following chapters overview the use of chiral phosphoric acid to achieve control over the selectivity in functionalization of carbohydrates. As a guide for understanding the mechanistic intricacies of chiral phosphoric acid catalysis, a brief history of chiral phosphoric acid, and their utility is provided. (*vide infra*)

Organocatalysis is a term that describes the use substoichiometric quantities of organic compounds to accelerate chemical transformations. Considering the usefulness and importance of

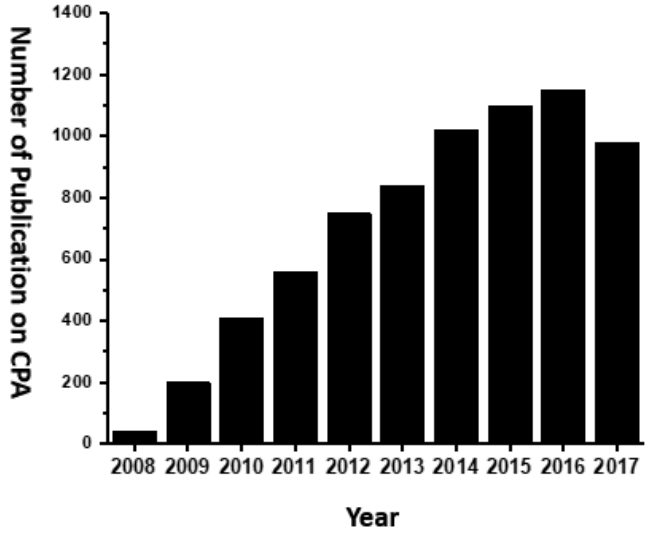
organocatalysis nowdays, the history of organocatalysis is surprisingly short. One of the most famous early example of organocatalysis is proline-catalyzed aldol reaction for the synthesis of optically active steroid partial structures, independently reported by Eder, Sauer and Wiechert in 1971.[16] and Hajos and Parrish in 1974.[17] Even with few successful examples of organocatalyzed transformation, organocatalysis was not still considered as a mainstream in the field of catalysis until 1990s. In 1990, Dieter Seebach even excluded the organocatalysis from future of organic synthesis[18] by emphasizing only the importance the fields of biological and organometallic chemistry in his review of organic synthesis.[19] In the late 1990s, however, the field of organocatalysis became more and more popular as organocatalysis was conceptualized. Since early 2000s, the usage of organocatalysis has been exploded in many fields, such as assymetric catalysis and organic synthesis, owing to considerable contribution from Shi,[20] Denmark,[21] Yang,[22] Jacobsen,[23] Corey,[24] Miller,[25] Barbas, Lerner and List,[26] and MacMillan[27] groups.

One of the major factors that were responsible for the huge success of organocatalysts was identifying generic modes of catalyst activation. Understanding the generic modes of catalyst induction is useful as we can use them as a platform to devise enantioselective transformation.[18] Since late 1990s, various types of generic modes of organocatalyst activation, such as imminium, enamine, ammonium, ylide, phase transfer, carbene, and hydrogen bonding, have been found. By utilizing these concepts of organocatalyst activation, numerous enantioselective reactions have been designed and carried out successfully.

As an outcome of hydrogen bonding activation mode in organocatalyst, chiral Brønsted acid catalysts were devised for asymmetric reactions. Among the chiral Brønsted acids reported, chiral phosphoric acids derived from axially chiral biaryls were widely applied in variety of organic transformations.[28] In 2004, Akiyama[29] and Terada[30] group independently introduced 1,1'-Bi-2-

naphthol (BINOL)-based chiral phosphoric acid (CPA) as a chiral organocatalyst in the asymmetric Mannich reaction. Both studies suggested that the enantioselectivity is controlled by chiral environment of the BINOL backbone, which is connected via hydrogen bonding network with the amine and alcohol substrate. Interestingly, BINOL-CPA was present even 30 years before Akiyama and Terada's report in 2004. This shows the power of the concept of organocatalysis, which turned on the potential of already existing molecule to a powerful tool in an asymmetric catalysis. After Terada and Akiyama's report on BINOL-CPA in asymmetric transformation, the number of studies on CPA catalysis have been grown dramatically (Figure 2.2).[31] These numerous studies on CPA established the new routes of asymmetric synthesis and enantioselective catalysis, which were not accessible before. Now, CPAs are considered as the major subclass of organocatalysts.[31]

Figure 2. 2. Number of papers on CPA-catalyzed reactions between 2008 and 2017.[31]

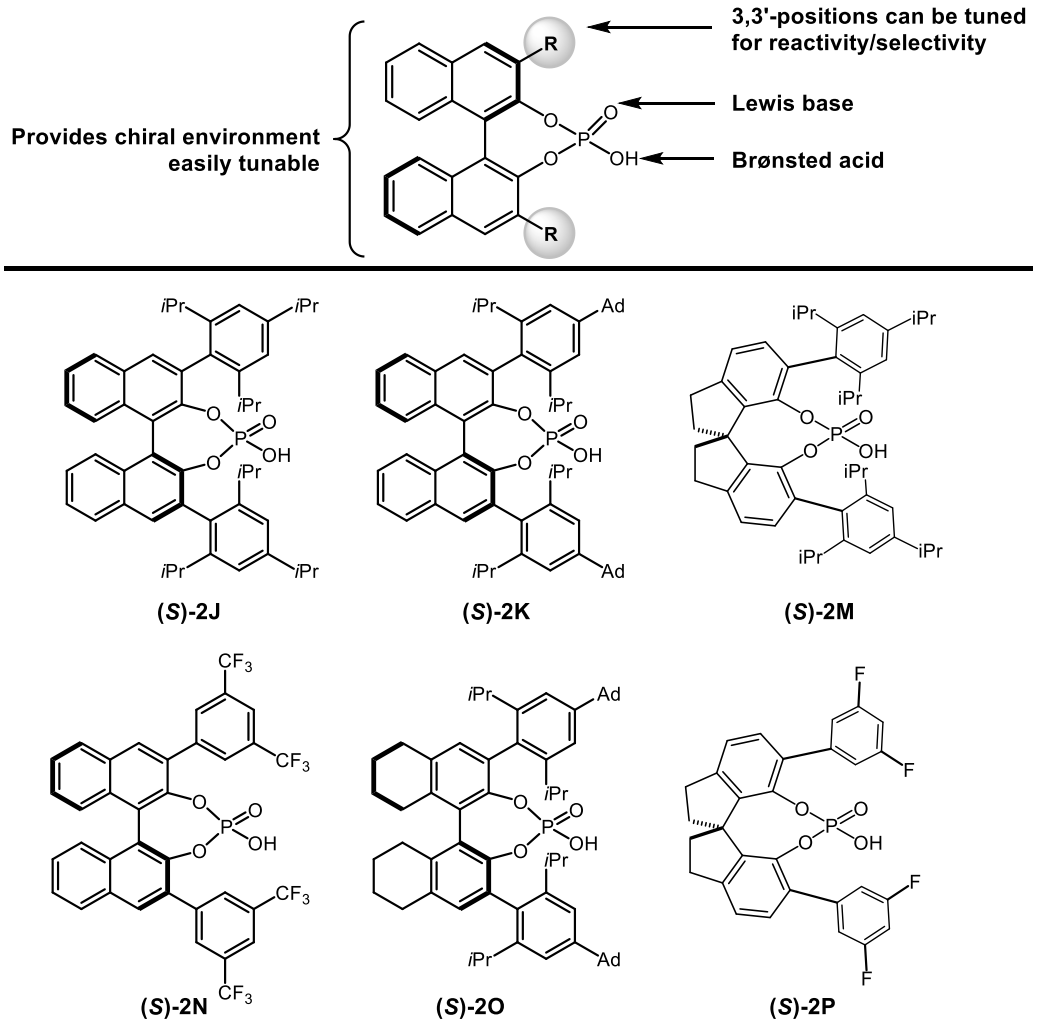


The important factor of huge success on BINOL-CPA is in part due to three features of its structure (Figure 2.3). First, the axially chiral biaryl skeleton of BINOL backbone provides chiral environment for the asymmetric reactions. Due to its axially chiral characteristics, BINOL

backbone has been actively ued as a ligand for metal-mediated asymmetric catalysis since Noyori's discovery in 1979.[32] Second, BINOL-CPA contains both Brønsted acidic proton and Lewis basic lone pair, which is beneficial in activating the substrate in the reaction. While the acidic proton can activate the electrophile through either hydrogen bond or protonation, the Lewis basic lone pair can be involved in a hydrogen bond with an acidic proton in the substrate. These interactions would enhance the reactivity by either increasing the nucleophilicity or electrophilicity of the corresponding substrate. The final feature is that the reactivity and acidity of the catalyst can be tuned by altering the substitution on 3,3'-position of the BINOL backbone. Considering that the reaction rate can be greatly dependent on the acidity of the catalysts, the ability to tune CPA acidity is a very important feature of the BINOL-CPA catalysis. The acidity of phosphoric acid could be enhanced by installing an electron withdrawing group and be decreased by installing a donating group at the 3,3'-position of the BINOL backbone. In addition to the reactivity and the acidity of the catalyst, the substitution at the 3,3'-position of the BINOL backbone can also affect the selectivity of the reactions. Terada reported that bulky substituents enabled both high enantioselectivity with high yield.[30] Not only 3,3'-position, but other positions of the BINOL backbone can also be substituted with functional groups to tune the catalyst. In addition to altering the substitution patterns, BINOL can be directly hydrogenated to H-8 BINOL using single step redox manipulations developed by the Nagorny group.[33] Catalyst's highly tunable structure and its ability to engage in various modes of activation made BINOL-CPA be of great utility in a wide range of organic transformations.

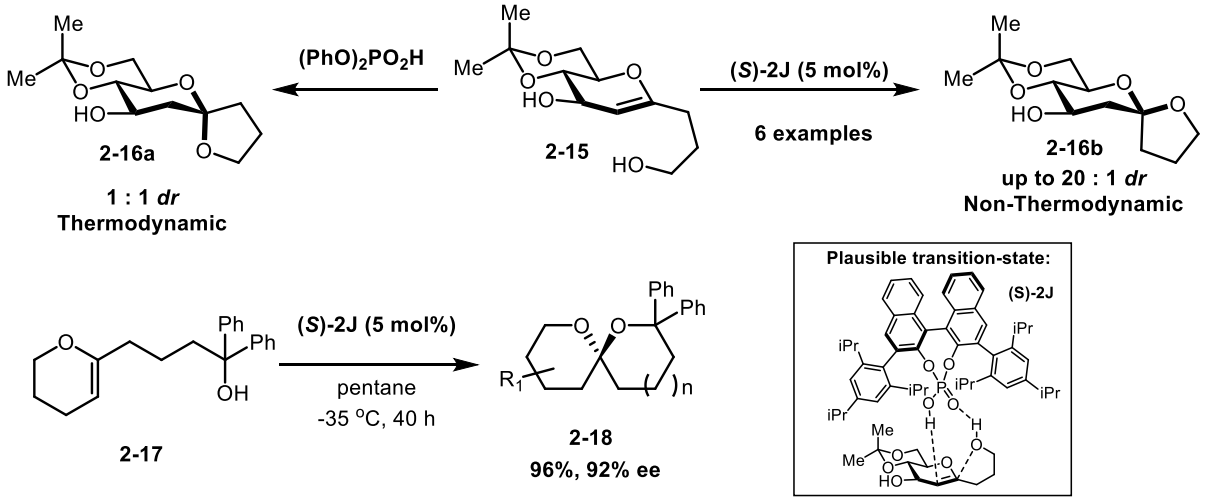
As a result, BINOL-based CPAs have emerged as powerful Brønsted acid catalysts and have been extensively used in asymmetric catalysis. [28] In 2012, our group disclosed the CPA-catalyzed enantioselective and diastereoselective spiro-ketalizations (Scheme 2.10).[34] The chiral

Figure 2. 3. Structure of a BINOL-based CPA and examples of CPAs.



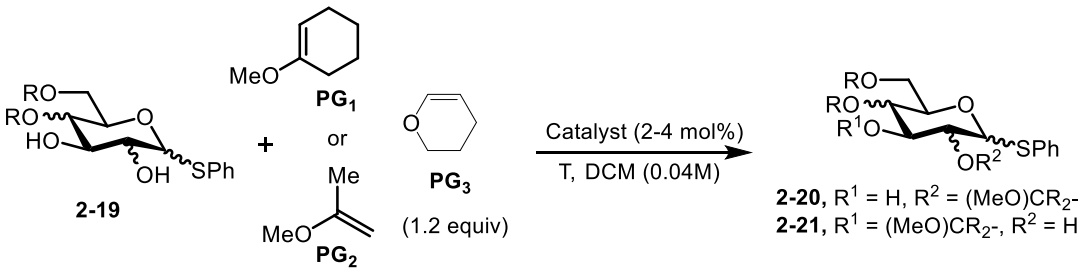
catalyst **(*S*)-2J** was able to override the intrinsic preference for the thermodynamic α-spiroketal **2-16a** formation, and promoted highly selective spiroketalization leading to nonthermodyamic β-product **2-16b**. The reaction mechanism and rationale for the high selectivity were subsequently elucidated by the mechanistic and computational studies, which suggested that the reaction happened through an asynchronous concerted mechanism proceeding through a short-lived oxocarbenium-like transition state. This result suggested that BINOL-CPA **(*S*)-2J** can promote highly selective addition to cyclic enol ethers.

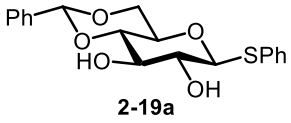
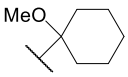
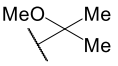
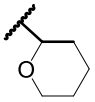
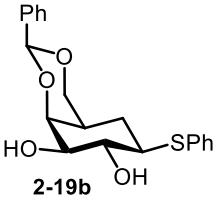
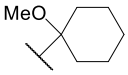
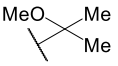
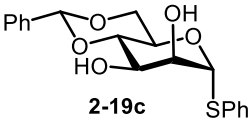
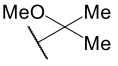
Scheme 2. 10. Nagorny's CPA-catalyzed stereoselective spiroketalization.



Along with the highly selective CPA-catalyzed diastereoselective and enantioselective spiroketalization method, our group has also developed a method for the CPA-catalyzed regioselective acetailization of carbohydrate-derived 2,3-diols (cf. Table 2.1).[35] This approach featured high regioselectivity, which was directly controlled by the catalyst **(*R*)-2K**. Catalyst **(*R*)-2K** promoted C2-selective protection of D-glucose and D-galactose-based substrates **2-20a** and **2-20b**, which is the opposite to the inherent C3-regioselectivity exhibited by the diol substrate **2-19a** and **2-19b** respectively (entry 1-2). D-Mannose based-substrate **5-3c**, in contrast, exhibited preference for the formation of the C3-product for the **(*R*)-2K** catalyzed acetalization reaction (entry 3). When compared to D-glucose and D-galactose substrates **2-20a** and **2-20b**, the relative value of regioselectivity was lower for the D-mannose-based substrate **2-21c**. In this study, three enol ethers, 4-dihydro-2H-pyran, 2-methoxypropene and 1-methoxycyclohexene, were used for acetalization, and the highest regioselectivities were afforded with 2-methoxypropene as an electrophile. These conditions tolerated various protecting groups at the 4,6-positions of substrates (benzylidine acetal, dimethyl acetal, *tert*-Butyldimethylsilyl, benzyl, etc) as well as the anomeric position (thioglycoside, *O*-glycosides).

Table 2. 1. Nagorny's CPA-catalyzed regioselective acetalization on sugar-derived 2,3-diols.



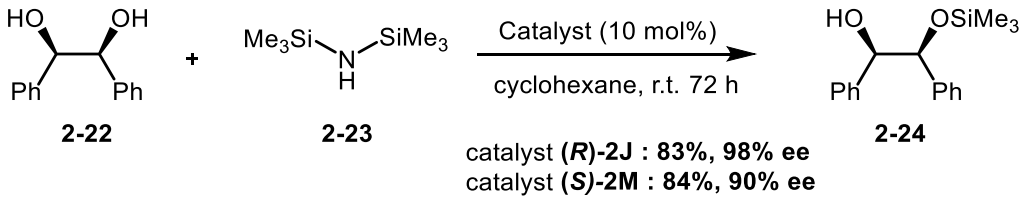
Entry	diol	PG	Catalyst	Yield [%][b] (Conv)	**2-20**/**2-21**[c]
1	 **2-19a**		(***R***)-**2K**	95 (97)	> 25 : 1
			(***S***)-**2K**	n.d. (79)	1 : 1.7
			$(PhO)_2PO_2H$	62 (67)	1 : 1.3
			(***R***)-**2K**	72 (95)	> 25 : 1
			(***S***)-**2K**	n.d. (69)	1 : 2.7
			$(PhO)_2PO_2H$	39 (79)	1 : 1.7
			(***R***)-**2K**	86 (87)	11 : 1
			(***S***)-**2K**	n.d. (15)	1 : 2
			$(PhO)_2PO_2H$	43 (48)	1 : 2.2
2	 **2-19b**		(***R***)-**2K**	76 (83)	10 : 1
			(***S***)-**2K**	n.d. (30)	2.3 : 1
			$(PhO)_2PO_2H$	40 (45)	1 : 2.3
			(***R***)-**2K**	93 (95)	20 : 1
			(***S***)-**2K**	n.d. (95)	12 : 1
			$(PhO)_2PO_2H$	79 (88)	1 : 2.3
3	 **2-19c**		(***R***)-**2K**	60 (84)	1 : 12.6
			(***S***)-**2K**	n.d. (81)	1 : 7.2
			$(PhO)_2PO_2H$	18 (39)	1 : 2.6

[a] Reactions were performed on 0.05 mmol scale (0.04m solution, 18-24 h) at -55°C (1-methoxycyclohexene) or -78 °C (2-methoxypropene). [b] Yield of isolated product; conversion values are given in parentheses. [c] Determined by 1 H NMR analysis of the crude reaction mixtures.

In 2015, List group demonstrated that axially chiral biaryl phosphoric acids could promote desymmetrizative silylation of *meso*-1,2-diols (Scheme 2.13).[36] Generally, the enantioselective desymmetrization of *meso*-alcohols is one of the most popular methods to access the corresponding mono-protected derivatives in their enantiopure form.[36] The nonenzymatic desymmetrization of *meso*-alcohols has been achieved through asymmetric monoacylation[37], hydrolysis of acetals[38], hydrolysis of *meso*-diesteres and oxidation of diols[39]. While those approaches commonly include

the use of chiral amines or chiral Lewis acids as the catalysts, the List group reported the methods for desymmetrization of *meso*-alcohols catalyzed by axially chiral biaryl phosphoric acid catalysts. In this study, the catalyst **(*R*)-2J** and **2M** promoted enantioselective desymmetrizative silyation of *meso*-compound **2-22** using the silylating reagent **2-23** to afford **2-24**.

Scheme 2. 11. List's CPA-catalyzed desymmetrizative silylation of *meso*-1,2-diol.



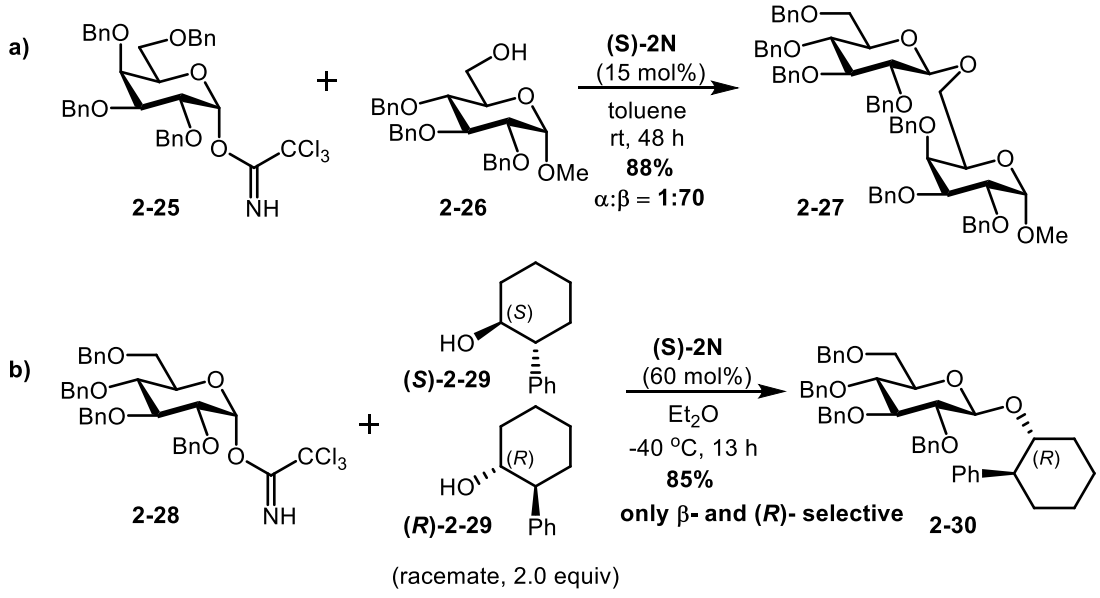
2.5 CPA-catalyzed steroselective and regioselective glycosylations

The chiral backbone of CPA has been used to achieve stereodifferentiation in a variety of chemical transformation. Considering the possible complicated outcomes of glycosylation arising from the formation of mixtures of stereoiosmers, regioisomers, and diastereomers, the use of CPAs can potentially reduce the number of isomeric entities and render glycosylation reactions selective.

The first example of CPA-catalyzed glycosylation reaction was reported by the Fairbanks group, who demonstrated stereoselective glycosylation with BINOL-CPA **(*S*)-2N** (Scheme 2.12a).[40] As a result, β-selective glycoside **2-27** was obtained from the D-glucose-derived donor **2-25** and acceptor **2-26**. Interestingly, both **(*R*)-2N** and **(*S*)-2N** catalyst could promote β-selective glycosylation, but the **(*S*)-2N** produced higher β-selectivity than **(*R*)-2N**, which indicated that the catalyst chirality can affect the stereochemical outcome of the reaction. This result suggested that the choice of chirality of CPA catalyst is important for the selectivity control. Later, the Toshima

group developed a glycosylation-based resolution of racemic alcohols using CPAs (Scheme 2.12b).[41] Based on Fairbanks' work, Toshima group employed the same CPA **(*S*)-2N** to promote glycosylative resolution of racemic alcohol **2-29** that resulted in selective glycosylation of one of the stereoisomers only to afford **2-30**.

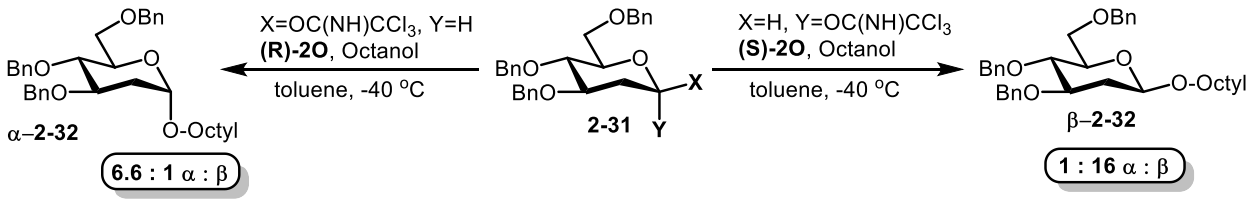
Scheme 2. 12. a) Fairbanks' CPA-catalyzed stereoselective glycosylation. b) Toshima's CPA-catalyzed glycosylation-based resolution of racemic alcohols.



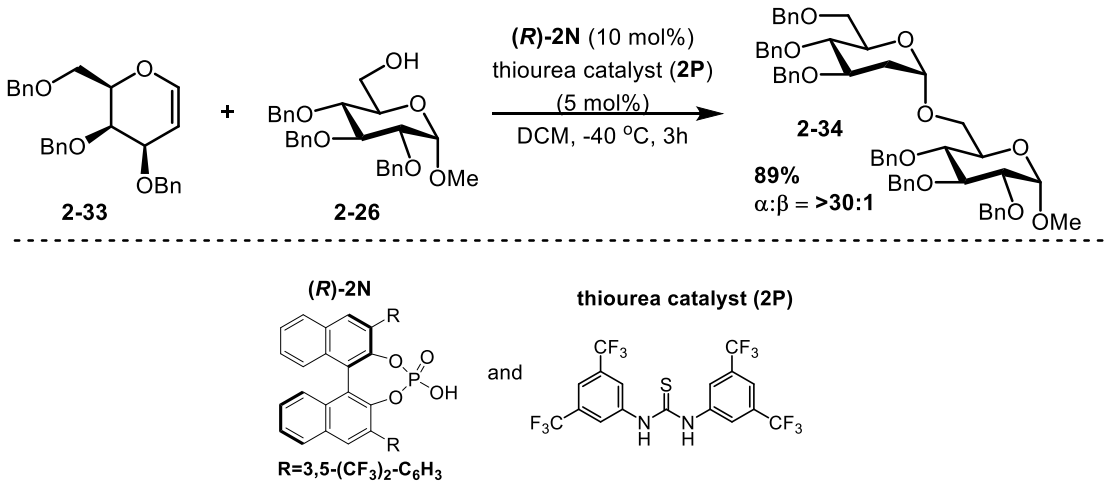
Similarly, Bennett group reported stereoselective glycosylation of 2-deoxy-D-glucose derivative **2-31** using a hydrogenated CPA **2O** (Scheme 2.13).[42] In this study, the authors observed matched and mismatched relationships between the CPA and the stereochemistry of trichloroacetimidate (TCA) donor **2-31**. For the α-donor, (*S*)-CPA matched better and catalyzed the glycosylation reaction to afford the β-product **β-2-32**. On the other hand, β-donor **β-2-31** matched with (*R*)-CPA, and α-glycoside **α-2-32** was obtained as a main product in this reaction. The authors hypothesized that different combinations of the donor and catalyst configurations could take different reaction pathways, which resulted in different outcomes of the reactions.

Following these interesting observations of stereoselectivity control by CPAs, the Galan group introduced another interesting use of CPA in glycosylations. The Galan group suggested that a combination of the CPA **(*R*)-2N** and thiourea catalyst **2P** can produce a synergistic effect in α-stereoselective glycosylatation of glycal substrate **2-33** (Scheme 2.14). [43] The authors suggested that the stereoselectivity was soley controlled by the chirality of CPA, while H-bonding between **(*R*)-2N** and **2P** can enhance the glycosylation reaction rate.

Scheme 2. 13. Bennett's H8-BINOL-CPA catalyzed matched and mismatched glycosylations.

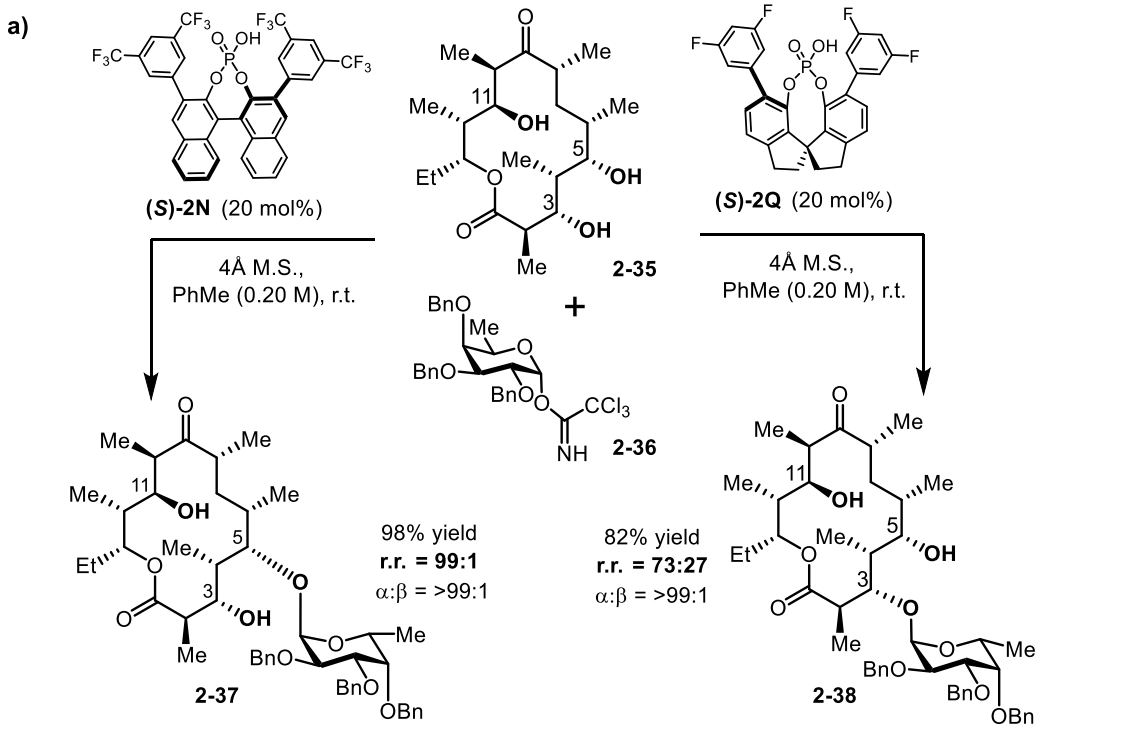


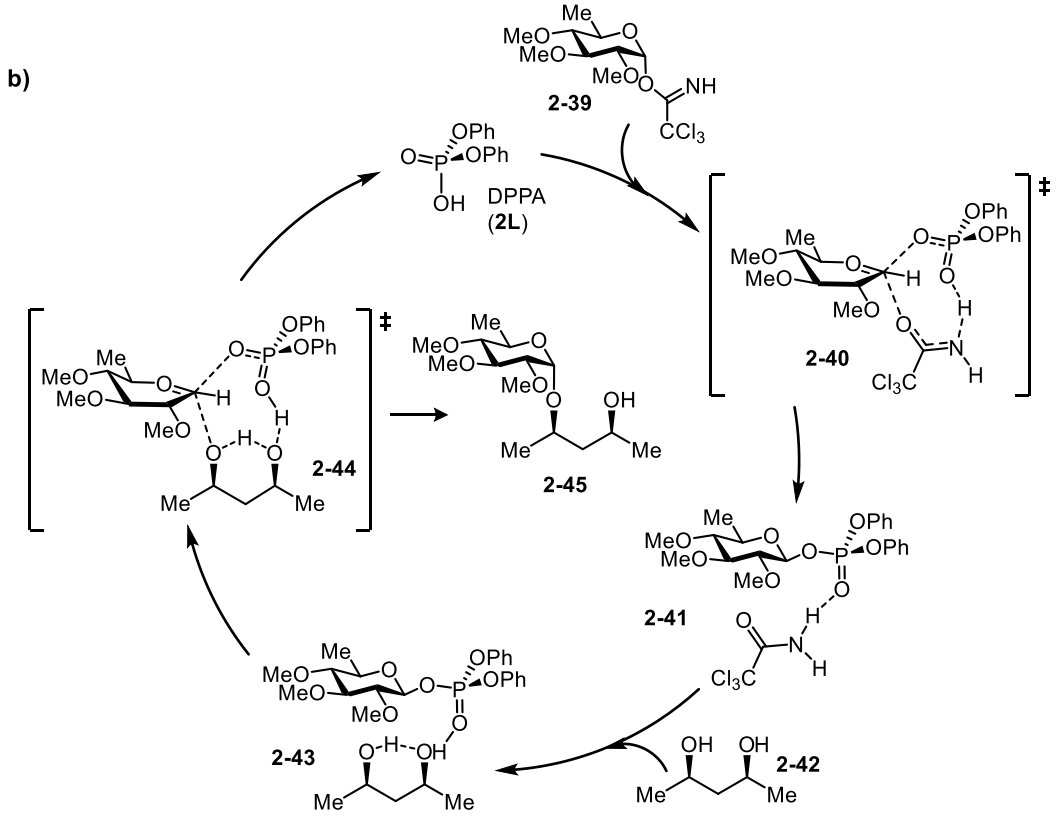
Scheme 2. 14. Galan's CPA and thiourea cooperative catalyzed stereoselective glycosylation.



While previous examples were mainly focused on stereoselectivity control, the Nagorny and Sherman groups reported CPA catalyzed regioselective glycosylation reactions on 6-deoxy-Erythronolide B (6-dEB) (Scheme 2.15a).[44] Nature transforms 6-dEB to erythromycin A by enzyme-catalyzed regioselective glycosylations and subsequent oxidations. Our group accessed the glycosylated 6-dEB analogs by mimicking the enzymes glycosyltransferases with chiral acids. In this study, various phosphoric acids with different axially chiral biaryls backbones were used to control the regioselectivity for the glycosylation of macrolide. While (*S*)-SPINOL-based CPA **(*S*)-2Q** catalyzed regioslective glycosylation of the C3-OH of 6-dEB **2-35**, (*S*)-BINOL-based CPA **(*S*)-2N** catalyzed regioselective glycosylation of the C5-OH of 6-dEB **2-35** with high regioselectivity (r.r. = 73:27 and r.r. = 99:1 respectively) and excellent stereoseletivity (α:β = 99:1). Regioselective glycosylation of C11-OH of macrolactone was also accomplished using transient protection of the C3, C5-hydroxyl groups with phenylboronic acid. This followed by the *in situ* glycosylation and deprotection to provide the desired C11-glycoside. In this study, the authors proposed that mechanism for the CPA-catalyzed glycosylation involved in a covalently linked anomeric phosphates rather than oxocarbenium-phosphate ion pairs as a reaction intermediate (Scheme 2.15b). Using ^{31}P NMR, the formation of β-anomeric phosphate **2-41** was observed arising from the α-donor **2-39** and diphenyl phosphoric acid **2L** in a S_N2-type of mechanism through transition state of **2-40**. The anomeric phosphate intermediate **2-41** was then exchanged with 2,4-pentadiol **2-42** to generate an intermediate **2-43**, followed by another S_N2-like reaction to afford α-glycoside **2-45**. The authors revealed that *syn*-1,3 diol moiety is geometrically suited for the inversion at the anomeric center during the glycosylation reaction. The proposed mechanism was supported by a combined experimental and computational studies.

Scheme 2. 15. a) Nagorny's chiral Brønsted acid catalyzed regiodivergent glycosylation on 6-dEB and b) the proposed reaction mechanism of the glycosylation reactions.





2.6 Conclusions

The importance of selective transformation of polyol-containing compounds and various methods for the selective functionalization of polyols were discussed. Organocatalysis, involving CPAs in particular, have been widely employed to functionalize polyols and several examples demonstrated that CPA could serve as a powerful tool in controlling the selectivity for polyol functionalization. The following chapters of this dissertation discuss new applications of CPA catalysts in 1) desymmetrizative glycosylation, which provides a direct access to new types of aminoglycosides, 2) regioselective and stereoselective glycosylations in carbohydrate-derived 2,3-diols, 3) regioselective single-pot functionalization of monosaccharides. These studies provide new and effective methods for the selective modification of carbohydrates and expand the frontiers of the CPA catalysis.

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Chapter 3

Chiral Phosphoric Acid-Catalyzed Desymmetrizative Glycosylation of 2-Deoxystreptamine and its Application to Aminoglycoside Synthesis

(This chapter was partially published in: Lee, J.; Borovika, A.; Khomutnyk, Y.; Nagorny, P., *Chem. Commun.* **2017**, 53 (64), 8976-8979.)

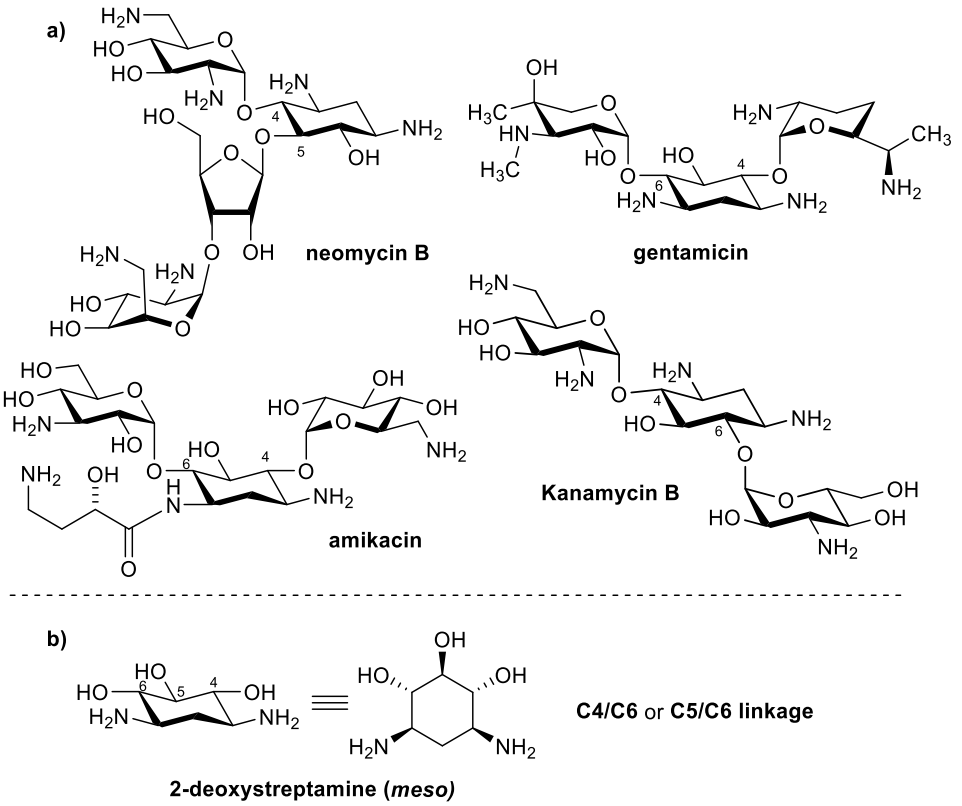
3.1 Introduction of aminoglycosides

Aminoglycosides are a group of carbohydrate-based antibiotics used broadly in clinical application against microbial infections in humans. Under physiological conditions, the protonated amine functionalities of aminoglycosides would provide good affinity for negatively charged nucleotides,[1] particularly the acceptor (A) site of 16S rRNA. Aminoglycosides interfere with the recognition of tRNA by rRNA during the translation and perturb translocation of tRNA from A site to the P (peptidyl-tRNA) site, which leads to the inhibition of protein synthesis and cell death. Crystallographic analysis supports these ideas as the 30S ribosomal particle or an A-site oligonucleotide sequence was revealed to bind in 2-DOS with similar binding pattern throughout different AGAs leading to the same damage of translational fidelity.[2] In addition to their antibacterial properties, aminoglycosides are potent antiviral (HIV) agents that could be employed to suppress genetic diseases.[3] While certain aminoglycosides, such as paromomycin or gentamycin, are FDA-approved drugs for the treatment of bacterial infections, their extensive clinical use has been curtailed by both their toxicity and the rapid increase of aminoglycoside resistant strains of bacteria.[4] Even though their usage has not completely died out, their importance decreased due to

the appearance of other classes of broad-spectrum antibiotics with fewer side effects, such as fluoroquinoloes, carbapenems, cephalosporins, and β-lactam/β-lactamase inhibitor combinations.[5]

Recently the focus has returned to development of new aminoglycosides in the face of prevalent antibiotic resistant to the other classes of antibiotics. These issues represent an important challenge in the design of new modified aminoglycosides with improved pharmacological properties. Despite the extensive interest in this class of natural products, specific challenges of current synthetic approaches to aminoglycosides include the time, which often prohibitively long, and limitations in the structural modifications that can be introduced.[6] In terms of structure of aminoglycoside, aminoglycosides are mainly built up by diverse aminosugars, which often consist of 6-amino or 2,6-diamino functional groups as the name aminoglycoside suggests. The key

Figure 3. 1. a) Examples of aminoglycoside. b) structure of 2-deoxystreptamine.



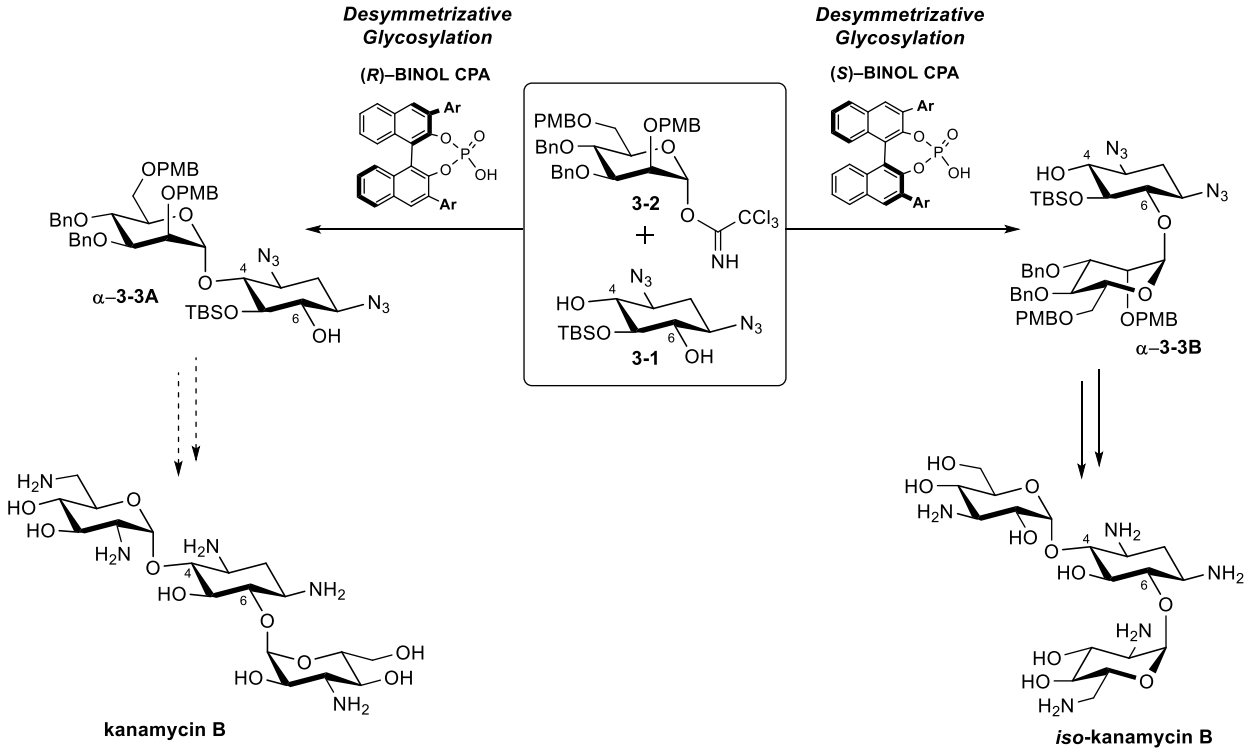
significant feature in each aminoglycoside structure would be a cyclohexitol ring termed 2-deoxystreptamine (1,3-diamino-4,5,6-trihydroxycyclohexane, 2-DOS) (Figure 3.1b). The importance of 2-DOS present in almost all aminoglycosides could be explained by its crucial role for the biological activity, particularly against Gram-negative bacteria. The majority of aminoglycosides contain an achiral (*meso*) 2-DOS subunit that carries glycosylation at either the C4/C5 (i.e. neomycin B) or C4/C6 (i.e. amikacin) hydroxyl groups (Figure 3.1a). The possibility of desymmetrizing 2-DOS has attracted significant attention as the obtained desymmetrized derivatives can be used to provide a direct access to a wide range of functionalized aminoglycosides.[7, 6b, 8, 9] While the most concise way to desymmetrize 2-DOS is through the direct glycosylation, only enzymatically controlled glycosylations of the C4 position of 2-DOS are known.[10] These enzymatic transformations provide powerful means for the assembly of aminoglycosides, but at the same time suffer from the limited substrate scope, indicating that the desirability of complementary non-enzymatic methods for the desymmetrizative glycosylation of 2-DOS.

3.2 Chiral phosphoric acid catalyzed regioselective functionalization of carbohydrates

Our group has long-standing interests in developing and exploring chiral phosphoric acid (CPA)-catalyzed reactions of acetals.[11,12] Recently, our group[13] along with Toshima and co-workers[14] demonstrated that CPA-catalyzed acetal/glycoside formation might proceed with the recognition of alcohol chirality in racemic alcohols and carbohydrate-derived diols. Based on these observations, we surmised that CPA-catalyzed glycosylation of 2-DOS derivative **3-1** (Scheme 3.1) with protected D-mannose donor **3-2** (Scheme 3.2) might proceed selectively and lead to desymmetrization of 2-DOS, thus providing key disaccharides **α -3-3A** and **α -3-3B** (Table 3.1). These compounds can be further used for the assembly of various aminoglycoside antibiotics and

their isomeric forms with the inversed C4/C6 connectivity (Figure 3.2). This work presents our studies on selective synthesis of **α -3-3A** and **α -3-3B** through CPA-controlled desymmetrizative

Figure 3. 2. Application of desymmetrizative glycosylation to synthesis of aminoglycosides.



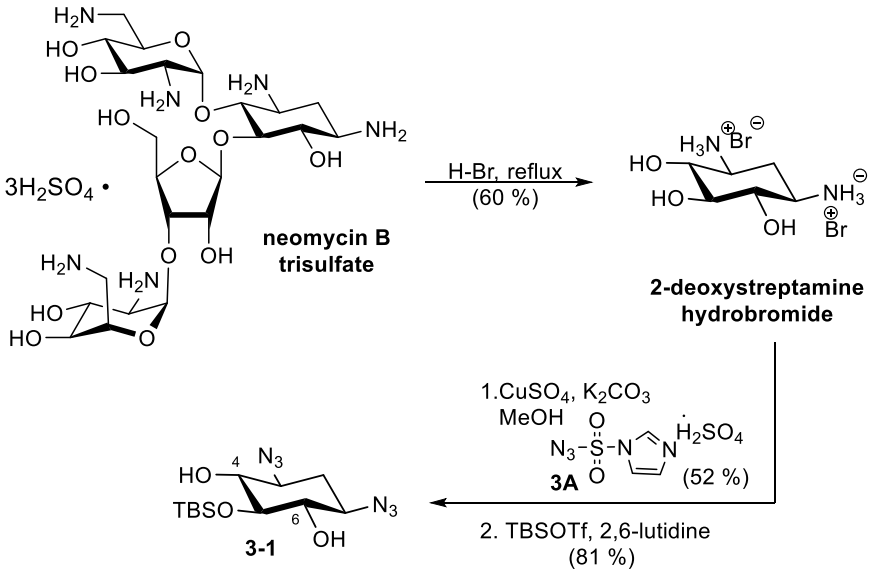
glycosylation of *meso*-diol **3-1**, and further functionalization of **α -3-3B** to provide isomeric neamine **3-5** and kanmycin B derivative **3-18** that are not readily accessible by the traditional semisynthetic methods.[6]

3.3 Preparataion of 2-DOS acceptor 3-1 and D-mannose-derived trichloroacetimidate donor 3-2

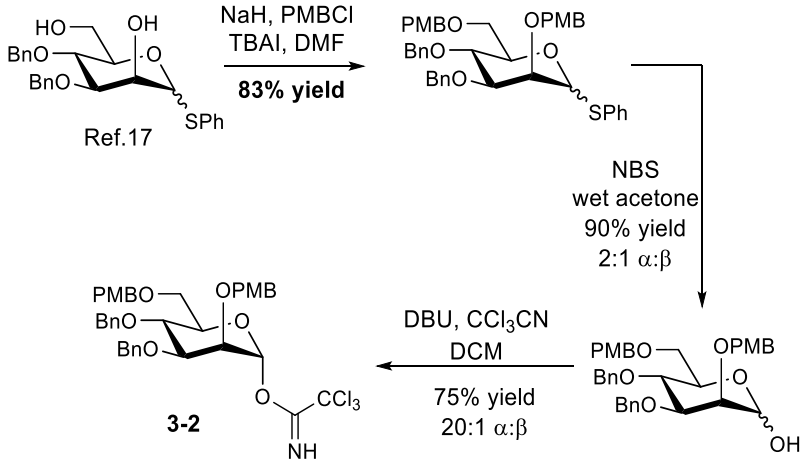
These studies were done by Dr. Alina Borovika (Part of her dissertation thesis: Borovika, A. (**2015**) *Advances in Bronsted Acid Catalysis: Reactions of Oxocarbenium Ions*. Ph.D dissertation, University of Michigan, Ann Arbor, MI)

Our studies commenced with the synthesis of 2-DOS *meso*-derivative **3-1** (Scheme 3.1). This substrate can be obtained by direct derivatization of 2-deoxystreptamine hydrobromide salt, which is readily available by degradation of neomycin B trisulfate.[15] This salt was subjected to a two-step protocol that involves protection of amines as azides (52% yield),[16] and the selective TBS-protection of more reactive C5 hydroxyl group (81% yield) to provide *meso*-derivative **3-1**. The azide-based protection of C1 and C3 amines of **3-1** was selected due to the relatively small steric size and polarity of the azido group, which is beneficial for the reactivity of **3-1** in glycosylation reactions. As the introduction of two azides into six carbon-containing 2-DOS resulted in a shock-sensitive triol, the stability of azide was evaluated. There are several tests available to evaluate the stability of organic azides. The impact sensitivity of energetic compounds is tested with the fall hammer equipment. Samples are exposed to the impact of a falling weight from variable heights and the measured sensitivity parameter is the height at which the samples explode or decompose. The drop test was performed on diazo-2-deoxystreptamine **3-1**, and it showed some mild shock sensitivity. Thus, 10 mg of **3-1** went off in 30 % of tests when 1 lbs weight was dropped from 145 cm height; however, it did not explode or decompose when the same weight was dropped from 125 cm height. While this test gave us only preliminary data, it became clear that diazo-2-deoxystreptamine **3-1** has to be treated with caution. Hence, this compound has always been stored in small, up to 200 mg, quantities. Diazo-2-deoxystreptamine **3-1** was not found to be heat-sensitive based on the Differential Scanning Calorimetry (DSC) analysis, and its melting point is was determined to be 110.6 ^{o}C.

Scheme 3. 1. Preparation of 2-deoxystreptamine derivative **3-1**.



Scheme 3. 2. Synthesis of D-mannose trichloroacetimidate **3-2**.



Along with preparation of the 2-deoxystreptamine-based acceptor **3-1**, the D-mannose-based trichloroacetimidate donor was also prepared from the reported intermediate.[17] The diol was protected by *para*-methoxy benzyl group, and then, the anomeric sulfide was hydrolyzed by NBS, acetone and water. Finally, trichloroacetonitrle was introduced to afford α-selective D-mannose trichloroacetimidate donor **3-2**.

3.4 CPA-catalyzed desymmetrizative glycosylation reactions

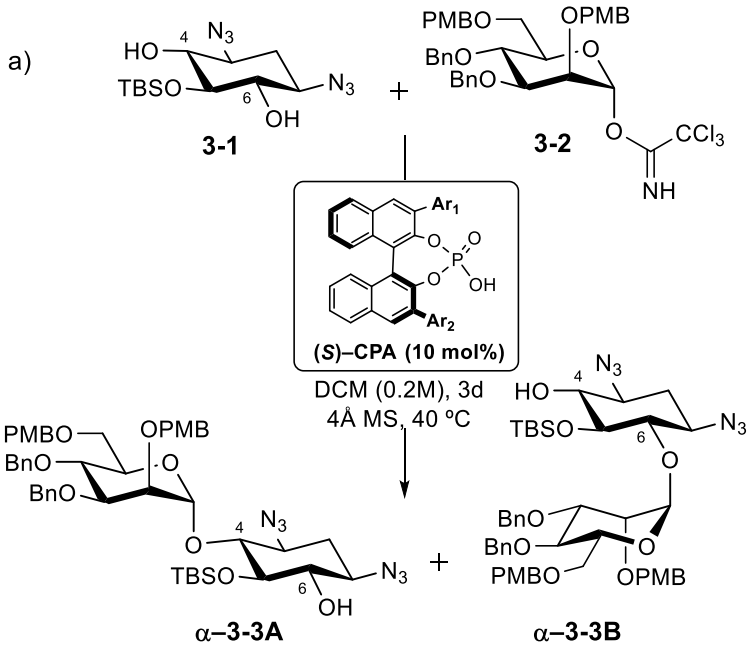
These studies were done by Dr. Alina Borovika (Part of her dissertation thesis: Borovika, A. (**2015**) *Advances in Bronsted Acid Catalysis: Reactions of Oxocarbenium Ions*. Ph.D dissertation, University of Michigan, Ann Arbor, MI)

With the *meso*-derivative **3-1** and **3-2** in hand, the catalyst-controlled glycosylation of **3-1** with trichloroacetimidate **3-2** was investigated next (Table 3.1). The D-mannose-derived trichloroacetimidates undergo α -selective glycosylations, which is required for the synthesis of natural aminoglycosides, such as kanamycin B.[18] To test the inherent selectivity of the glycosylation reaction, the mixture of **3-1** and **3-2** was subjected to catalytic quantities of TMSOTf. While the formation of ~1 : 1 mixture of disaccharides **α-3-3A** and **α-3-3B** was indeed observed, the substantial quantities of other isomeric disaccharides inseparable from **α-3-3A** and **α-3-3B** complicated further analysis.

Similarly, the attempts to promote the reaction by using diphenylphosphoric acid (**2L**) as the catalyst (entry 1), did not result in clean formation of **α-3-3A** or **α-3-3B**, but rather led to decomposition of the starting materials. To our delight, BINOL backbone-containing CPAs[19] were found to be significantly better catalysts of this glycosylation.[13,14,20,21] One limitation, however, was the observed strong dependence of the catalytic activity on the nature of the 3,3'-aryl substituents, which affects glycosylation reaction. CPAs without electron withdrawing group on their backbones (entry 2) failed to promote the reaction at all. However, more acidic catalysts with electron withdrawing 3,3' -aryl groups did promote the formation of inseparable mixtures of **α-3-3A** and **α-3-3B** with variable selectivities (entries 3–15). Remarkably, the use of **(*S*)-3I** resulted in **α-3-3B** as the main product (86:14 d.r., 74% yield, entry 14). Finally, the use of enantiomeric **(*R*)-3I** overturned the selectivity and favored **α-3-3A**. (67:33 d.r., 51% yield, entry 15).

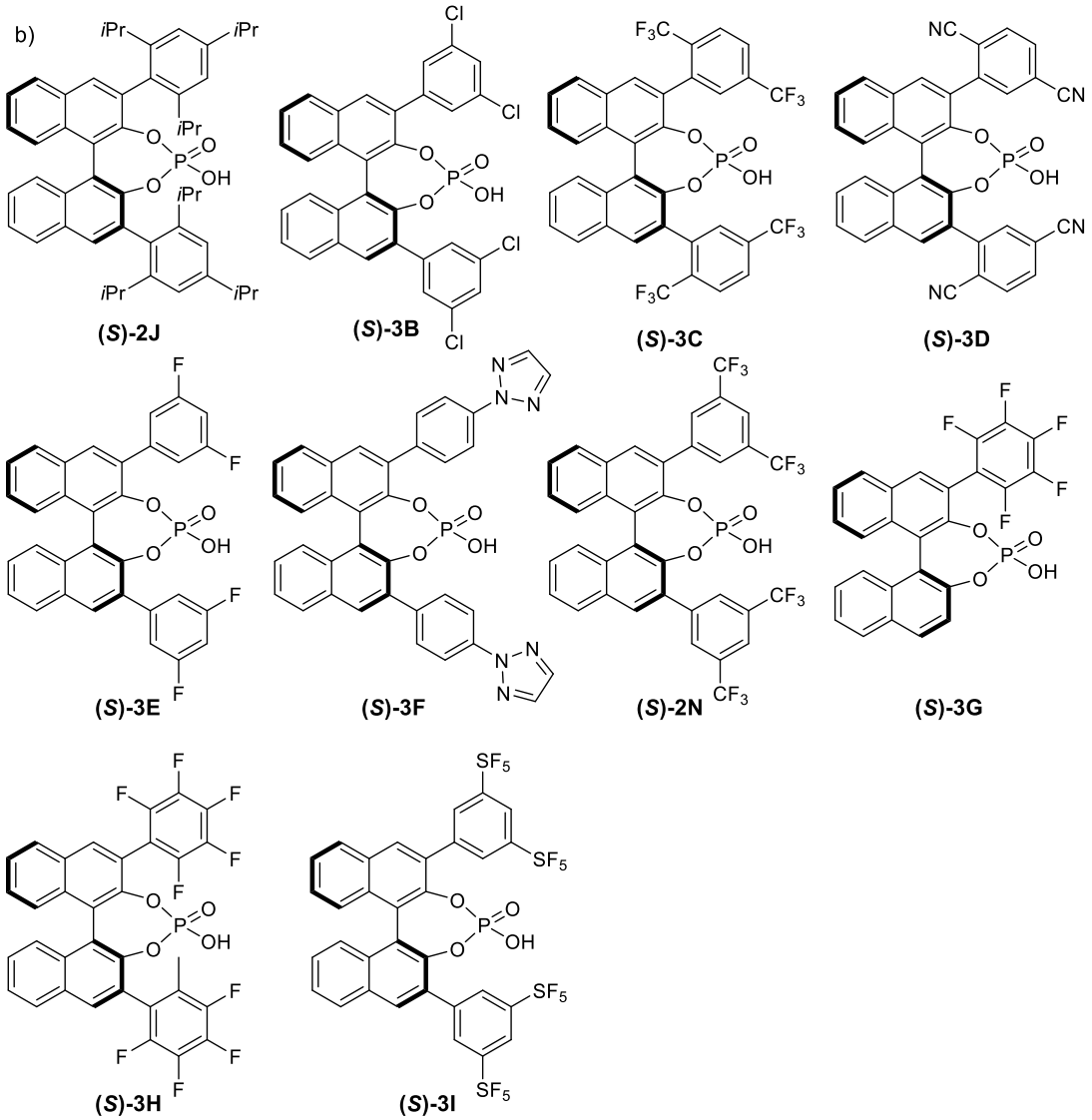
Table 3. 1. a) Optimization of desymmetrizative glycosylation of protected 2-deoxystreptamine **3-1** and functionalized D-mannose **3-2.**[a] b) List of CPAs used in the desymmetrizative glycosylation.

a)



entry	Catalyst	conversion, % (yield, %)	diastereoselectivity (α–3-3A : α–3-3B)
1	$(PhO)_2PO_2H$ (**2L**)	Decomposition	N/A
2	(***S***)-**2J**	no rxn	N/A
3	(***S***)-**3B**	<25	50 : 50
4	(***S***)-**3C**	<25	26 : 74
5	(***S***)-**3D**	<25	50 : 50
6	(***S***)-**3E**	37	33 : 67
7	(***S***)-**3F**	<25	42 : 58
8	(***R***)-**2N**	52	60 : 40
9	(***S***)-**2N**	25	30 : 70
10	(***R***)-**3G**	<25	50 : 50
11	(***S***)-**3G**	34	26 : 74
12	(***R***)-**3H**	30	58 : 42
13	(***S***)-**3H**	61	25 : 75
14[b]	(***S***)-**3I**	88 (74)	**14 : 86**
15	(***R***)-**3I**	62 (51)	**67 : 33**

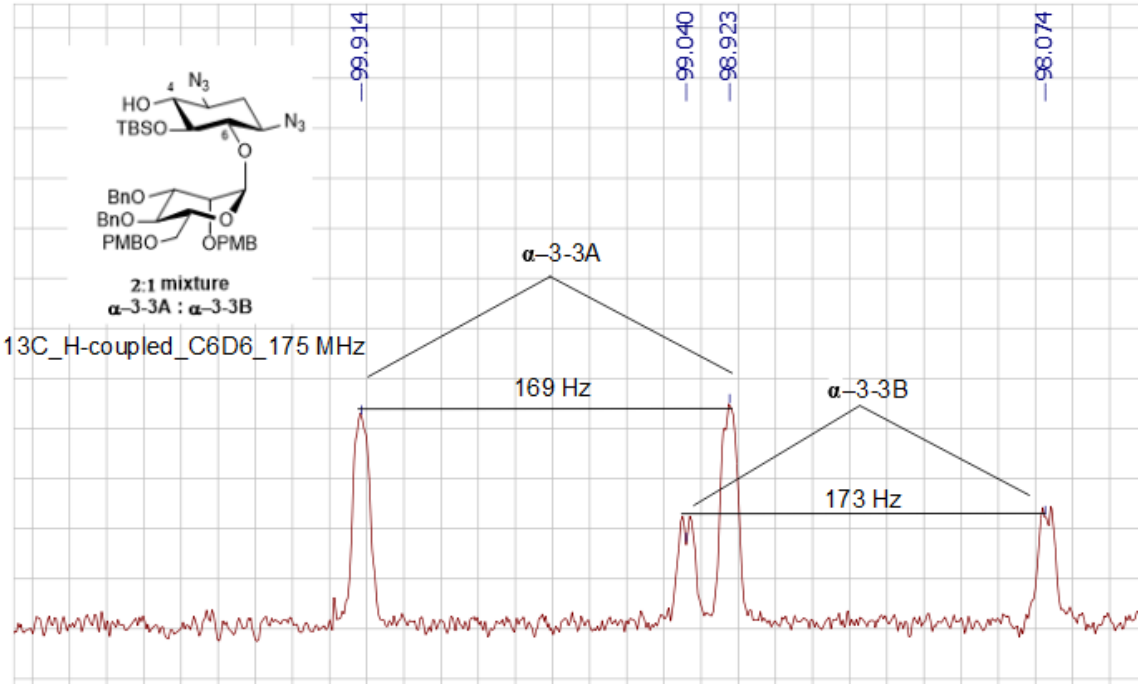
[a]Conditions: donor **3-2** (1.5 equiv.), acceptor **3-1** (1 equiv.), catalyst (10 mol%), DCM (0.2 M) 4 Å MS, 40 °C for 3 days; *d.r.* was determined by NMR analysis of the crude mixture.



3.5 Confirmation of structure

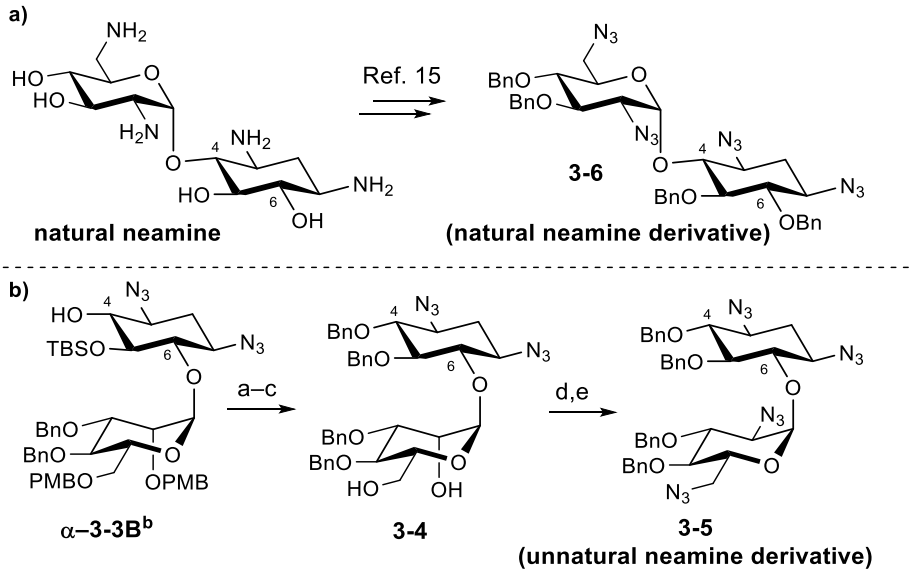
The α -C1 configuration of **3-3A** and **3-3B** could be conveniently confirmed by observing the J(C1–H) to be 173 and 169 Hz (Figure 3.3), which is consistent with the values typically observed for the α -mannosides (~170 Hz) and inconsistent with the J(C1–H) for the β-mannosides (~160 Hz). However, the proposed connectivity (i.e. C4-vs. C6) required further validation (Scheme 3.3). This was achieved by converting the 86 : 14 mixture of **α-3-3B** and **α-3-3A** into molecule **3-5** and comparing it with the known neamine derivative **3-6**. The synthesis of **3-5**

Figure 3. 3. Confirmation of α-stereoselectivity from J(C1–H) coupling (~170 Hz).



(Scheme 3.3b) from **α-3-3B** commenced with subjecting **α-3-3B** to TBAF to remove C5-TBS group (82% yield), reprotecting the resultant diol as a benzyl ether (84% yield), and removing of the PMB protecting groups on D-mannose subunit by DDQ (67% yield) to provide disaccharide **3-4**. Diol **3-4** was subjected to a two-step protocol that included converting the D-mannose subunit to 2,6-*bis*-triflate, which was subjected to nucleophilic substitution with sodium azide in DMF to provide desired derivative **3-5** in 30% yield (2 steps). The ^{1}H and ^{13}C NMR spectra for the synthetic derivative **3-5** were distinctly different from the corresponding spectra of known natural neamine derivative **3-6** (Scheme 3.3a)[15] supporting the glycosylation at the C6 position of 2-DOS in **α-3-3B**. (The synthesis of neamine derivatives and structure confirmation were done by Dr. Yaroslav Khomutnyk).

Scheme 3. 3. Stereochemical assignment of products **3-3**. a) synthesis of protected natural-neamine **3-6**. b) synthesis of protected unnatural-neamine **3-5** from **α-3-3B**.[a]



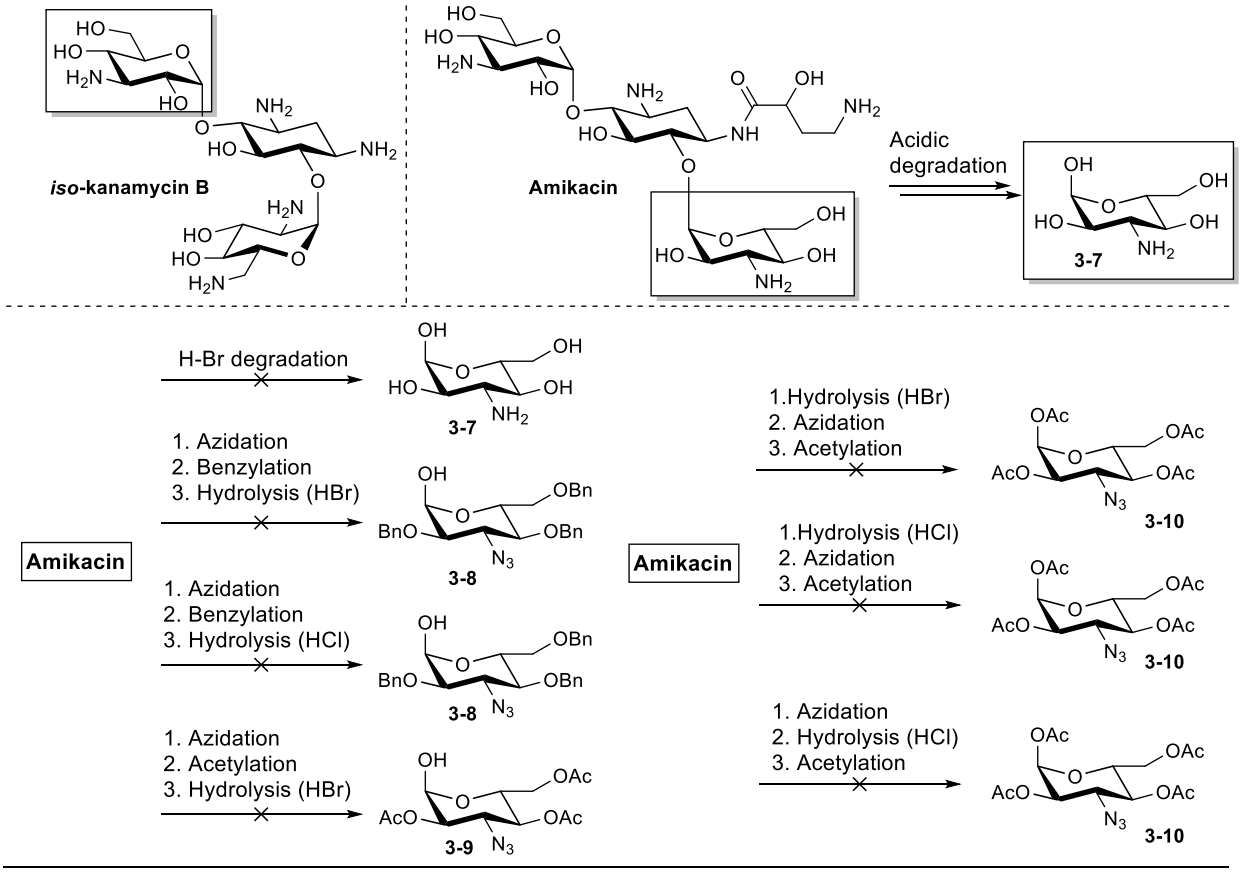
[a]Conditions: (a) TBAF, THF, 4 Å MS, 82% yield; (b) NaH, BnBr, DMF, 40 °C, 84% yield; (c) DDQ, DCM/H_2O, (10 : 1), 0 °C to r.t. overnight, 67% yield; (d) Tf_2O, pyridine, DCM, -15 °C; (e) NaN_3, DMF, 40 °C, 30% yield (2 steps). [b]Transformations a–e were carried on 86 : 14 mixture of α**-3-3B** : α**-3-3A** the mixture was separated after the first step (a) and only deprotected α**-3-3B** was advanced to **3-5**

3.6 Synthesis of the donor 3-13

The synthesis of the isomeric kanamycin B from **α-3-3B** required access to amino-sugar derivative **3-7**. The first attempt to obtain this amino-sugar was based on the acidic degradation of aminoglycoside amikacin (Scheme 3.4). This idea originated from our prior studies where we produced 2-DOS, using the degradation of neomycin B (Scheme 3.1). However, this simple hydrolysis-based approach did not provide us the desired amino-sugar **3-7**, but rather produced a complex, and inseparable mixture of unprotected saccharides. To avoid these problems, protection/hydrolysis strategy was attempted instead. We hoped that pre-protection would simplify the separation of the hydrolysis product **3-8** or **3-9**. Amine groups of amikacin were substituted with azides, and all of the hydroxyl groups were protected as benzyl ethers. The resulting protected amikacin was then, hydrolyzed by HBr and HCl under reflux condition. Unfortunately, these

conditions were too harsh and the cleavage of the benzyl ethers was observed. Rather than protection/hydrolysis, a hydrolysis/protection sequence was also attempted, but this was not successful and the desired amino-sugar **3-10** was not isolated.

Scheme 3. 4. Failed attempt of hydrolysis of amikacin to generate desired sugar moiety **3-7**.

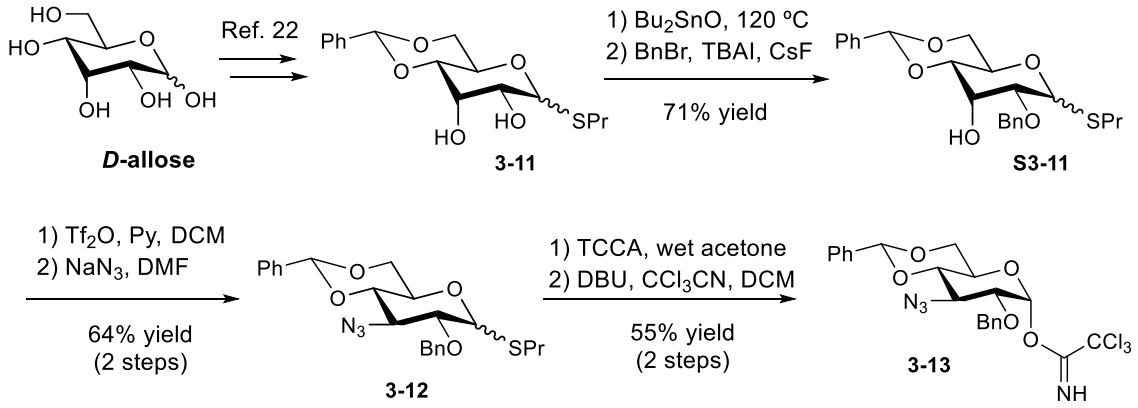


Conditions: azidation: **3A** (4.4 equiv) Na_2CO_3 (8 equiv), $CuSO_4$ (0.2 equiv), H_2O/MeOH (3/7), Benzylation: NaH (20 equiv), BnBr (20 equiv), DMF, Hydrolysis: acid (neat), 150 ^oC

While the hydrolysis strategy was inefficient and unpredictable, chemical synthesis seemed to be a more realistic method to access the amino-sugar **3-13** (Scheme 3.5). In our synthetic approach, D-allose was chosen as a starting material since it contains the desired stereochemistry for the installation of the C3-amino group. The synthesis of the desired donor **3-13** commenced with the preparation of thioglycoside **3-11** by using a known procedure.[22] The equatorial alcohol

of **3-11** was then selectively protected as the benzyl ether using Sn(IV)-alkoxide chemistry to provide the inverted derivative S**3-11**. The remaining C3-hydroxyl group was triflated and then reacted with NaN_3. The anomeric sulfide moiety of **3-12** was hydrolyzed by trichloro-cyanuric acid (TCAA) in acetone and water, and then trichloroacetimidate functionality was introduced to afford **3-13**.

Scheme 3. 5. Synthesis of the trichloroacetimidate donor **3-13**.



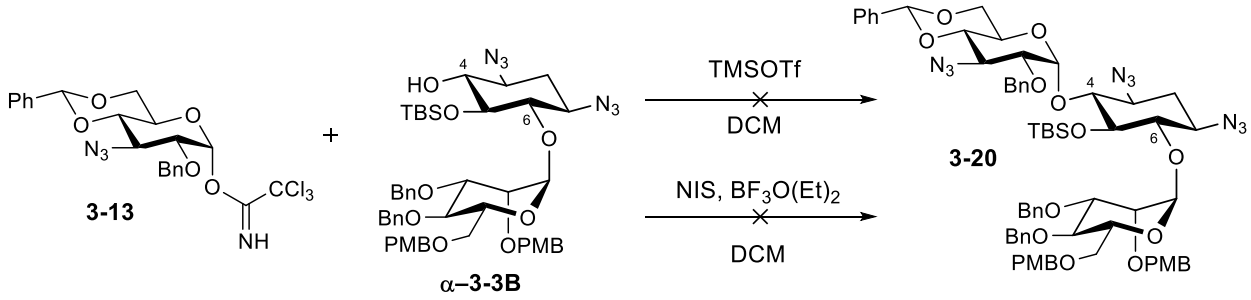
3.7 Synthesis of isomeric kanamycin B derivative

The stereoselective synthesis of disaccharide **α-3-3B** offered an intriguing possibility of converting this substrate to isomeric kanamycin B with reverse connectivity of the sugars at the C4 and C6 position (Scheme 3.5). The direct functionalization of kanamycin B to form this derivative represents a significant challenge, while the desymmetrizative functionalization of 2-DOS would provide a more straightforward access to aminoglycosides of this type.[6]

In order to install all of the functionalities required for the *iso*-kanamycin B, direct glycosylation of donor **3-13** to the disaccharide **α-3-3B** was attempted to generate the desired saccharide **3-20**. However, the common glycosylation promoter did not promote the desired glycosylation reactions, and only the just the starting material was recovered after the reaction

(Scheme 3.6). Later we realized that the C5-TBS group of **α-3-3B** was too sterically hindered and blocked the access of donor **3-13** to C4-alcohol of **α-3-3B**.

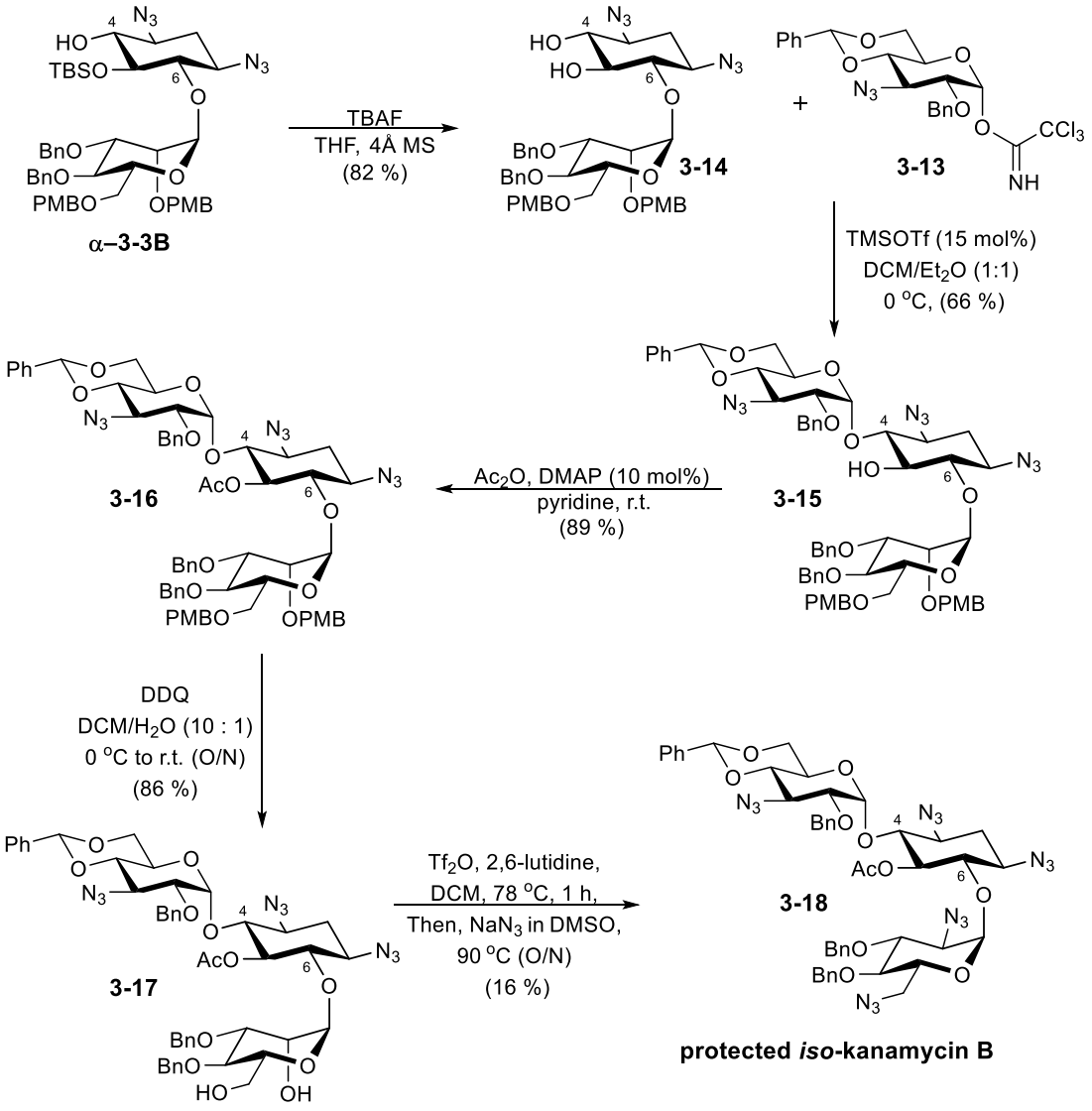
Scheme 3. 6. Failed attempts to carry a direct glycosylation of **3-13** to **α-3-3B**.



Thus, the synthesis of iso-kanamycin B commenced with the cleavage of the C5 TBS group of **α-3-3B** that resulted in diol **3-14** (70% yield) along with the regioisomeric product arising from the deprotection of **α-3-3A** (12% yield). This deprotection was necessary as the TBS group obstructed the glycosylation of the C4 position. The product **3-14** was subjected to glycosylation with trichloroacetimidate **3-13** to provide trisaccharide **3-15** as a single diastereomer and regioisomer in 66% yield, and the observed J(H1–H2) = 3 Hz for the new anomeric stereocenter of **3-15** was consistent with the α-configuration.

The formation of protected *iso*-kanamycin B (**3-18**) was completed by oxidizing the trisaccharide with DDQ to remove the PMB groups in the D-mannose subunit (86% yield). The resultant diol was subjected to *bis*-triflation and azide substitution to yield compound **3-18**. While the *bis*-triflation proceeded smoothly, the displacement of the C2-triflate of the D-mannose subunit with sodium azide[23] was found to be sluggish and provided the desired protected *iso*-kanamycin B in only 16% yield (2 steps).

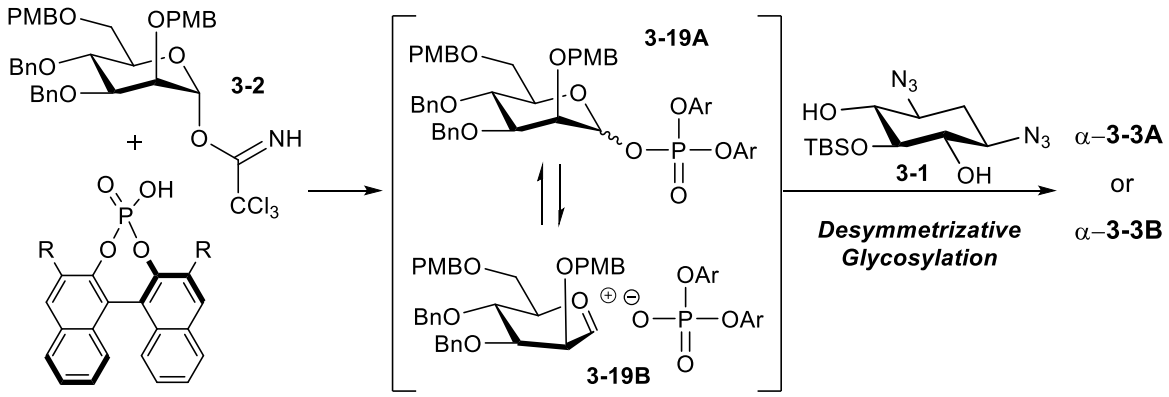
Scheme 3. 7. Application to the synthesis of isomeric kanamycin B derivative **3-18**.



3.8 Plausible mechanism

The plausible reaction intermediates for the formation of **α-3-3A** and **α-3-3B** are proposed in figure 3.4. Our prior mechanistic and theoretical studies of CPA-catalyzed regioselective glycosylation of 6-dEB- and oleandomycin-derived macrolactones[24] identified covalently linked anomeric phosphates such as **3-19A** as viable reaction intermediates. However, considering that the exclusive formation of **α-3-3A** and **α-3-3B** from **α-3-2** is observed in these studies, the formation of an oxocarbenium-based ion pair **3-19B** cannot be ruled out.

Figure 3. 4. Plausible mechanism of glycosylation.



3.9 Conclusions

In summary, we were able to demonstrate that chiral phosphoric acids could catalyze desymmetrizative glycosylation of 2-deoxystreptamine-derived *meso*-diol **3-1** with D-mannose-derived trichloroacetimidate donor **3-2**. While the evaluated achiral acids could not promote this glycosylation selectively, the (*S*)-enantiomer of CPA (Ar = 3,5-$(SF5)_2$-C_6H_3) catalyzed diastereoselective formation of the C6 glycosylated product **α-3-3B** in 86 : 14 *d.r.* This transformation was accomplished on significant scale (0.3 g of **α-3-3B**), and is of utility for the preparation of functionalized aminoglycosides. Thus, intermediate **α-3-3B** was converted into the isomeric protected aminoglycosides neamine and kanamycin B with reversed connectivity at the C4 and C6 positions of 2-DOS.

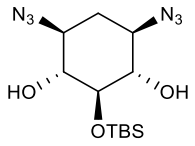
3.10 Experimental Information

Methods and Reagents:

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Toluene (PhMe), dichloromethane (DCM) and diethyl ether (Et_2O) were filtered through a column (Innovative Technology PS-MD-5) of activated alumina under nitrogen atmosphere. All reactions were carried out under an atmosphere of nitrogen in flame-or oven-dried glassware with magnetic stirring. Reactions were cooled via external cooling baths: ice water (0 °C), Neslab Cryotrol CB-80 immersion cooler (0 to -60 °C) or Neslab Cryocool immersion cooler CC-100 II. Purification of the reactions mixtures was performed by flash column chromatography on SiO_2 using SiliCycleSiliaFlash P60 (230-400 mesh) silica gel.

Instrumentation :

All spectra were recorded on Varian vnmrs 700 (700 MHz), Varian vnmrs 500 (500 MHz), Varian MR400 (400 MHz), Varian Inova 500 (500 MHz) spectrometers and chemical shifts (δ) are reported in parts per million (ppm) and referenced to the ^1H signal of the internal tetramethylsilane according to IUPAC recommendations. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, m = multiplet; coupling constant(*S*) in Hz; integration). High resolution mass spectra (HRMS) were recorded on MicromassAutoSpecUltima or VG (Micromass) 70-250-S Magnetic sector mass spectrometers in the University of Michigan mass spectrometry laboratory. Infrared (IR) spectra were recorded as thin films on NaCl plates on a Perkin Elmer Spectrum BX FT-IR spectrometer. Absorption peaks were reported in wavenumbers (cm^{-1}).

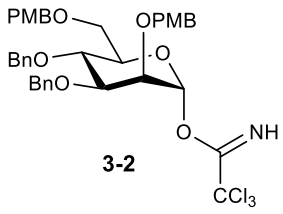


3-1

(*1R,2R,3S,4R,6S*)-4,6-diazido-2-((tert-butyldimethylsilyl)oxy)-cyclohexane-1,3-diol (3-1).

(1R,2r,3S,4R,6S)-4,6-diazidocyclohexane-1,2,3-triol[8b] (770 mg, 3.60 mmol) was dissolved in 33 mL of dry THF under nitrogen, and cooled down to 0 °C. To the solution 2,6-lutidine (1.51 mL, 13.1 mmol) and *tert*-butyldimehylsilyl trifluoromethanesulfonate (1.66 mL, 7.2 mmol) were added dropwise. The reaction mixture was warmed up to room temperature and quenched with methanol after 3 h. Column chromatography on SiO_2 (10 : 1 to 8 : 1 hexanes/ethyl acetate) resulted in of white crystalline material **1** (964 mg, 81%). NMR spectra of **3-1** matched to the NMR spectra of the same compound from the previous report.[25]

^{1}H NMR (400 MHz, Chloroform-d) δ 3.43 – 3.31 (m, 5H), 2.43 (s, 2H), 2.22 – 2.16 (m, 1H), 1.44 – 1.31 (m, 1H), 0.92 (s, 9H), 0.16 (s, 6H). **^{13}C NMR** (100 MHz, Chloroform-*d*) δ 77.3, 76.7, 60.3, 32.1, 26.1, 18.4, -4.2. **IR (thin film, cm^{-1}):** 3489, 2926, 2170, 2103, 1472, 1357, 1249, 1137, 1071, 1029, 982, 874, 834, 778, 691.



3-2

(*2R,3S,4S,5R,6R*)-4,5-*bis*(benzyloxy)-3-((4-methoxybenzyl)oxy)-6-(((4methoxy benzyl)oxy)methyl) tetrahydro-2H-pyran-2-yl 2,2,2-trichloroacetimidate (3-2).

A 250 mL round bottom flask was charged with **S1** (2.17g, 3.119 mmol) and dissolved in a 9 : 1 mixture of acetone (18 mL) and water (2 mL). The reaction mixture was cooled down to 0 °C and

N-bromosuccinimide (NBS, 1.16 g, 6.55 mmol) was added. The reaction mixture was monitored by TLC and was quenched with solid $NaHCO_3$ upon reaction completion. Acetone was removed *in vacuo* and organics were extracted with ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate and brine, dried with magnesium sulfate, and concentrated *in vacuo*. The crude product **S2** was purified by flash column chromatography on SiO_2 (3:1 to 1:1 hexanes/ ethyl acetate) resulting in 1.69 g (90 %) of colorless oil (α/β = 2 : 1). An oven dried and nitrogen flushed 250 mL round bottom flask was charged with the D-mannose derivative **S2** (1.69 g, 2.81 mmol) from the previous step and dry DCM (20 mL). The reaction mixture was cooled down to 0 °C and trichloroacetonitrile (0.847 mL, 8.40 mmol) was added, followed by 1,8-diaza bicyclo(5,4,0)undec-7ene (0.21 mL, 1.40 mmol). The resulting reaction mixture was warmed up to room temperature and stirred for 6 h. The crude product was purified by column chromatography on SiO_2 (5 : 1 to 3 : 1 hexanes/ethyl acetate) resulting in the pure product **3-2** as pale-yellow oil (1.57 g, 75%, α/β = 20 : 1).

^{1}H NMR δ_H (700 MHz, Benzene-d_6, α only) δ 8.47 (s, 1H), 7.30 (t, *J* = 7.8 Hz, 4H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.14 (dt, *J* = 7.5, 3.6 Hz, 3H), 7.10 – 7.04 (m, 2H), 6.77 – 6.72 (m, 5H), 5.00 (d, *J* = 11.0 Hz, 1H), 4.65 (d, *J* = 11.0 Hz, 1H), 4.61 – 4.56 (m, 3H), 4.56 – 4.49 (m, 3H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.28 – 4.25 (m, 1H), 4.16 (dd, *J* = 9.6, 3.1 Hz, 1H), 4.03 (t, *J* = 2.6 Hz, 1H), 3.89 (dd, *J*= 11.3, 4.1 Hz, 1H), 3.73 (dd, *J* = 11.3, 1.7 Hz, 1H), 3.30 (s, 3H), 3.29 (s, 3H). **^{13}C NMR** δ_C (175 MHz, C_6D_6, α only) 160.7, 159.9, 159.7, 139.4, 139.0, 131.2, 130.7, 129.9, 129.7, 128.6, 128.5, 128.3, 127.8, 127.6, 114.1, 114.1, 97.0, 91.7 79.8, 76.1, 75.5, 74.9, 74.0, 73.4, 73.4, 72.8, 72.3, 68.9, 54.8, 54.8. **IR** (thin film, cm^{-1}): 3473, 2928, 1723, 1612, 1514, 1454, 1363, 1249, 1108, 1035, 836, 698. **HRMS (ESI+) (*m*/*z*):** $[M+NH_4]^+$ calcd for $C_{38}H_{44}Cl_3N_2O_8$ 761.2158, found 761.2152.

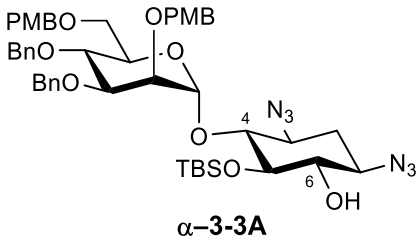
Chiral phosphoric acid-catalyzed glycosylation studies

General protocol for the CPA-catalyzed glycosylation reactions:

A flame-dried 4 mL vial was charged with D-mannose trichloroacetimidate **3-2** (0.024 mmol), 2-deoxystreptamine **3-1** (0.012 mmol), 4 Å MS (~20 mg), and CPA catalyst (0.0024 mmol). The resulting mixture was refluxed in dry dichloromethane (0.1 mL) for 3 days, then quenched with triethylamine and analyzed by crude ^{1}H NMR.

(*1R,2S,3S,4R,6S*)-4,6-diazido-3-(((*2S,3S,4S,5R,6R*)-4,5-*bis*(benzyloxy)-3-((4-methoxybenzyl)oxy)-6-(((4-methoxybenzyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-2-((tert-butyldimethylsilyl)oxy)cyclohexan-1-ol (α-3-A and α-3-3B).

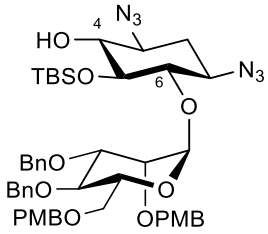
A flame-dried 4 mL vial was charged with the D-mannose trichloroacetimidate donor **3-2** (544 mg, 0.73 mmol), 2-deoxystreptamine acceptor **3-1** (150 mg, 0.457 mmol), flame dried 4 Å MS (150 mg), and (*S*)-SF_5-chiral phosphoric acid (CPA) catalyst[26] (45.9 mg, 0.0457 mmol). The resulting mixture was flushed with nitrogen, then dry DCM (2.4 mL) was added. The resulting mixture was refluxed for 3 days, then quenched with triethylamine. Crude ^{1}H NMR showed 88% conversion with 1:6 selectivity. The mixture was purified by column chromatography on SiO_2 (9:1 hexanes/ethyl acetate). Purification resulted in some mixed fractions of glycal with glycosylated product and fractions of pure glycosylation products (5.7:1 diastereoselectivity). All fractions containing glycosylation products were combined as a colorless oil (**α-3-3A/B mix,** 307mg, 74% yield) The J^1(C-H) coupling constant for the anomeric C-H groups is consistent with the **α-3-3A** and **α-3-3B** configuration (169.05 and 173.425 Hz respectively). An aliquot of this mixture was purified by preparative HPLC to obtain the characterization data for **α-3-3A** and **α-3-3B** provided below:



α–3-3A

α-3-3A (C4-glycosylated isomer):

^{1}H NMR 700 MHz, C_6D_6) δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.39 (2 H, d, *J* = 8.5 Hz), 7.30 (2 H, d, *J* = 7.5 Hz), 7.25 (2 H, d, *J* = 8.5 Hz), 7.21-7.17 (m, 3H), 7.14-7.05 (m, 3H), 6.82 (2 H, d, *J* = 8.5 Hz), 6.76 (2 H, d, *J* = 8.5 Hz), 5.70 (1 H, d, *J* = 1.6 Hz), 5.16 (1 H, d, *J* = 11.0 Hz), 5.01 (2 H, d, *J* = 11.7 Hz), 4.85 (1 H, d, *J* = 11.9 Hz), 4.79 (1 H, d, *J* = 11.0 Hz), 4.76 (1 H, d, *J* = 11.9 Hz), 4.67 (1 H, d, *J* = 11.4 Hz), 4.62 (1 H, d, *J* = 11.4 Hz), 4.55 (1 H, dd, *J* = 9.5, 5.0 Hz), 4.45 (1 H, d, *J* = 11.7 Hz), 4.34 (1 H, dd, *J* = 9.5, 2.4 Hz), 4.22 (1 H, t, *J* = 2.4 Hz), 3.96 (1 H, dd, *J* = 11.0, 4.8 Hz), 3.89 (1 H, dd, *J* = 11.0, 1.4 Hz), 3.50 (1 H, t, *J* = 9.5 Hz), 3.32 (s, 3H), 3.315 (s, 3H), 3.23 (1 H, t, *J* = 8.9 Hz), 2.68 (1 H, dd, *J* = 9.5, 4.0 Hz), 2.47 (1 H, ddd, *J* = 12.3, 9.7, 4.6 Hz), 1.81(1 H, d, *J* = 3.9 Hz), 1.49 (1 H, dt, *J* = 12.3, 4.6 Hz), 1.0 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H). **IR** (thin film, cm^{-1}):3478, 3031, 2933, 2857, 1612, 1514, 1248, 1095, 1037, 837. **HRMS (ESI+) (*m*/*z*):** $[M+NH_4]^+$ calcd for $C_{48}H_{62}N_6O_{10}SiNH_4$ 928.4635, found 928.4635.

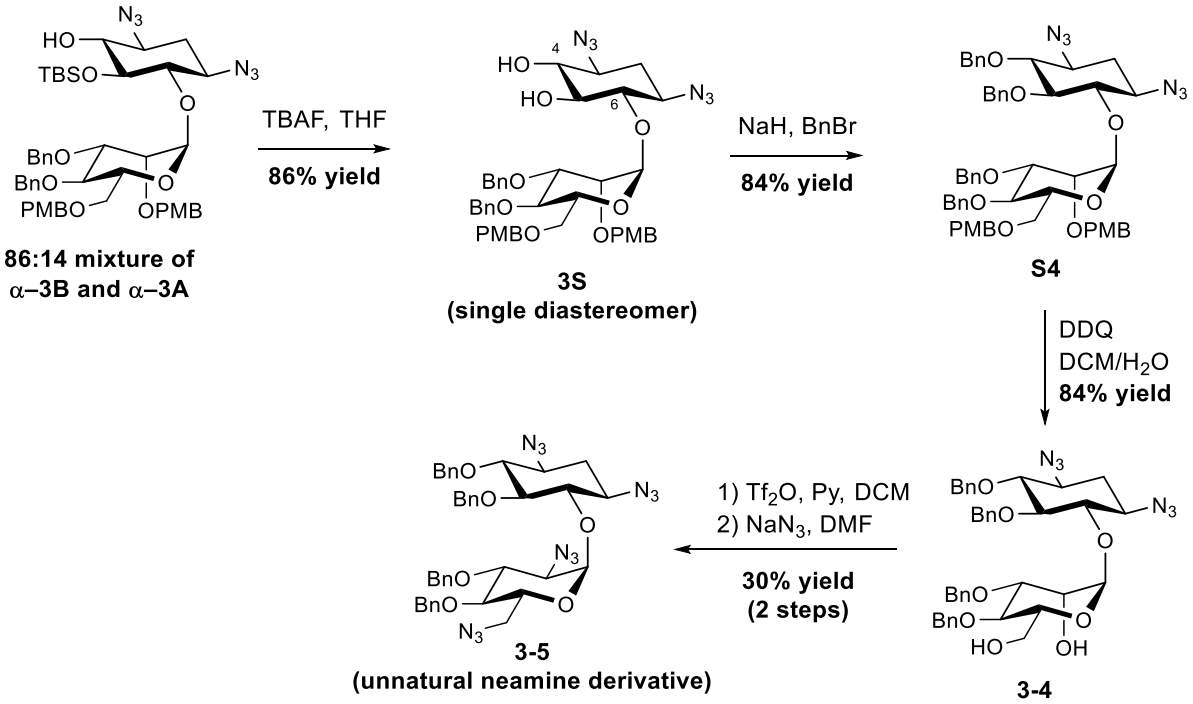


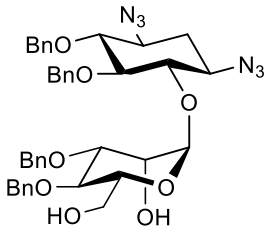
α–3-3B

α-3-3B (<u>C6</u>-glycosylated isomer):

^{1}H NMR 700 MHz, C_6D_6) δ 7.40 (4 H, t, *J* = 8.0 Hz), 7.34 (2 H, d, *J* = 7.3 Hz), 7.30-7.25 (m, 3H), 7.25-7.18 (m, 2H), 7.12-7.07 (m, 3H), 6.82 (2 H, d, *J* = 8.3 Hz), 6.78 (2 H, d, *J* = 8.3 Hz), 5.64 (1

H, d, *J* = 1.7 Hz), 5.02 (1 H, d, *J* = 10.9 Hz), 4.85 (1 H, d, *J* = 12.5 Hz), 4.78 (1 H, d, *J* = 10.9 Hz), 4.75 (1 H, d, *J* = 5.5 Hz), 4.68 (1 H, d, *J* = 11.7 Hz), 4.62 (1 H, d, *J* = 10.9 Hz), 4.60 (1 H, d, *J* = 10.9 Hz), 4.46-4.38 (m, 3H), 4.29-4.26 (m, 2H), 3.92 (1 H, dd, *J* = 10.1, 4.7 Hz), 3.84 (1 H, d, *J* = 10.9 Hz), 3.33 (s, 3H), 3.31 (s, 3H), 3.17 (2 H, dd, *J* = 12.5, 8.1 Hz), 2.79 (1 H, dt, *J* = 12.2, 9.5, 4.2 Hz), 2.49 (1 H, ddd, *J* = 12.5, 9.8, 4.8 Hz), 1.90 (1 H, d, *J* = 3.6 Hz), 1.45 (1 H, dt, *J* = 12.5, 4.5 Hz), 1.02 (s, 9H), 0.88 (1 H, q, *J* = 12.7 Hz), 0.33 (s, 3H), 0.21 (s, 3H). **^{13}C NMR** (only major isomer (α-3B) reported, 175 MHz, C_6D_6) δ 159.8, 159.6, 139.6, 139.4, 131.4, 131.3, 129.7, 128.7, 128.5, 128.3, 128.1, 128.0, 128.0, 127.8, 114.1, 114.0, 99.8, 99.0, 81.6, 80.1, 77.8, 76.6, 75.9, 75.1, 74.0, 73.3, 73.2, 72.5, 69.9, 60.7, 60.0, 54.8, 54.7, 32.2, 26.4, 18.6, -3.2. **IR** (thin film, cm^{-1}):3478, 3031, 2933, 2857, 1612, 1514, 1248, 1095, 1037, 837. **HRMS (ESI+) (*m*/*z*):** $[M+NH_4]^+$ calcd for $C_{48}H_{62}N_6O_{10}SiNH_4$ 928.4635, found 928.4631.



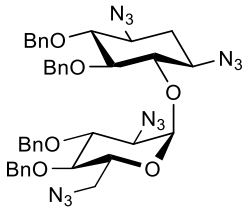


3-4

(*2S,3S,4R,5R,6R*)-4,5-*bis*(benzyloxy)-2-(((*1S,2S,3R,4S,6R*)-4,6-diazido-2,3-*bis*(benzyl oxy)cyclohexyl)oxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-3-ol (3-4)

The benzylated product **S4** from above (45.8 mg, 0.0469 mmol) was mixed together with DDQ (21.3 mg, 0.0937 mmol), then 0.32 mL of DCM was added along with 1 drop of water. The mixture was stirred at room temperature for 1.5 h. Then the reaction was quenched with saturated sodium bicarbonate, and extracted with DCM. Organics were washed with saturated sodium bicarbonate, brine, dried with magnesium sulfate. Column chromatography on SiO_2 (4:1 to 3:2 hexanes/ethyl acetate resulted in 23.1 mg (67%) of **3-4** as a colorless oil.

^{1}H NMR (400 MHz, Benzene-d_6) δ 7.37 – 7.31 (m, 4H), 7.26 – 7.21 (m, 4H), 7.18 (d, *J* = 7.3 Hz, 3H), 7.14 – 7.02 (m, 9H), 5.65 (d, *J* = 1.7 Hz, 1H), 4.86 (dd, *J* = 18.6, 11.1 Hz, 2H), 4.75 – 4.62 (m, 4H), 4.53 (s, 2H), 4.29 (t, *J* = 2.4 Hz, 1H), 4.15 – 4.04 (m, 2H), 3.97 (dd, *J* = 8.5, 3.2 Hz, 1H), 3.73 (dd, *J* = 12.2, 2.1 Hz, 1H), 3.61 (d, *J* = 12.1 Hz, 1H), 3.28 (t, *J* = 9.5 Hz, 1H), 2.96 (dt, *J* = 26.3, 9.3 Hz, 2H), 2.65 (dddd, *J* = 19.0, 16.2, 11.6, 5.5 Hz, 3H), 1.44 (dt, *J* = 13.1, 4.5 Hz, 1H), 0.85 (q, *J* = 12.7 Hz, 1H).



3-5

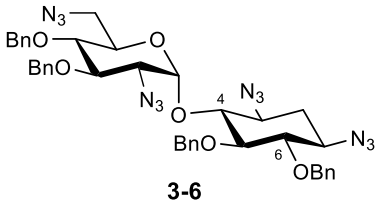
(unnatural neamine derivative) **(*2R,3R,4R,5R,6R*)-3-azido-6-(azidomethyl)-4,5-*bis*(benzyloxy) -2-(((*1S,2S,3R, 4S,6R*)-4,6-diazido-2,3-*bis*(benzyloxy)cyclohexyl)oxy) tetrahydro-2H-pyran (3-5).**

Diol **3-4** (23.1 mg, 0.0314 mmol) was dissolved in 0.17 mL of dry DCM and cooled down to -15 °C under nitrogen. To this mixture pyridine (12.6 μL, 0.157 mmol) was added, followed by trifluoromethanesulfonic anhydride (21.1 μL, 0.125 mmol). The resulting solution was stirred at the same temperature for 10 mins before being diluted with DCM and water. Organics were extracted with DCM, and the extracts were washed with saturated sodium bicarbonate and water and then dried with magnesium sulfate, filtered and concentrated *in vacuo*.

The resulting crude triflate from above was dissolved in dry DMF under nitrogen. To that solution sodium azide (7.8 mg, 0.120 mmol) was added, the mixture was stirred at 40 °C for 4 h, and then was diluted with DCM and water. The organics were extracted with DCM, then washed with brine/water (1:1) and brine, dried over magnesium sulfate and concentrated *in vacuo*. The product was purified by column chromatography on SiO_2 (4:1 hexanes/ethyl acetate). The procedure yielded 3 mg (30 %, 2 steps) of the desired product **3-5**.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.39 – 7.31 (m, 7H), 7.28 (d, *J* = 9.6 Hz, 7H), 7.24 – 7.10 (m, 6H), 5.56 (d, *J* = 3.8 Hz, 1H), 5.30 (d, *J* = 0.8 Hz, 1H), 5.02 (d, *J* = 11.0 Hz, 1H), 4.90 – 4.86 (m, 3H), 4.84 (d, *J* = 10.5 Hz, 1H), 4.79 (d, *J* = 11.1 Hz, 1H), 4.68 (d, *J* = 11.1 Hz, 1H), 4.47 (d, *J* = 11.1 Hz, 1H), 4.01 – 3.97 (m, 1H), 3.87 (t, *J* = 9.6 Hz, 1H), 3.61 – 3.56 (m, 1H), 3.54 – 3.47 (m,

4H), 3.45 – 3.43 (m, 2H), 3.40 (dd, *J* = 10.3, 3.7 Hz, 1H), 3.04 (dd, *J* = 13.6, 2.4 Hz, 1H), 2.68 (dd, *J* = 13.5, 3.5 Hz, 1H), 2.31 (dt, *J* = 13.4, 4.5 Hz, 1H), 1.51 – 1.47 (m, 1H). **^{13}C NMR** (175 MHz, Chloroform-*d*) δ 138.1, 137.8, 137.6, 137.3, 128.6, 128.5, 128.5, 128.4, 128.2, 128.2, 128.1, 127.9, 127.9, 127.8, 127.7, 127.4, 97.6, 84.8, 81.9, 80.1, 78.6, 76.2, 76.0, 75.6, 75.1, 70.5, 63.6, 61.6, 60.5, 50.4, 32.8, 29.9. **IR** (thin film, cm^{-1}): 2924, 2103, 1722, 1454, 1361, 1260, 1124, 739, 697. **HRMS (ESI+) (*m*/*z*)**: $[M+Na]^+$ calcd for $C_{40}H_{42}N_{12}O_6Na$ 809.3242, found 809.3232.

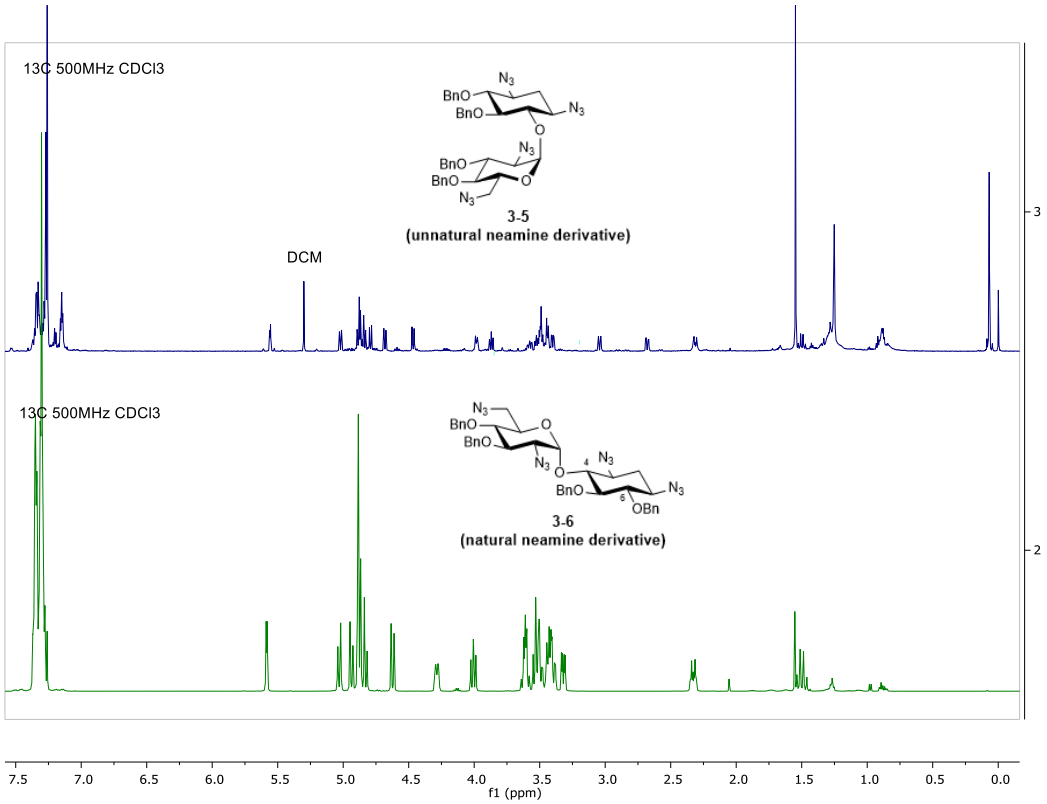


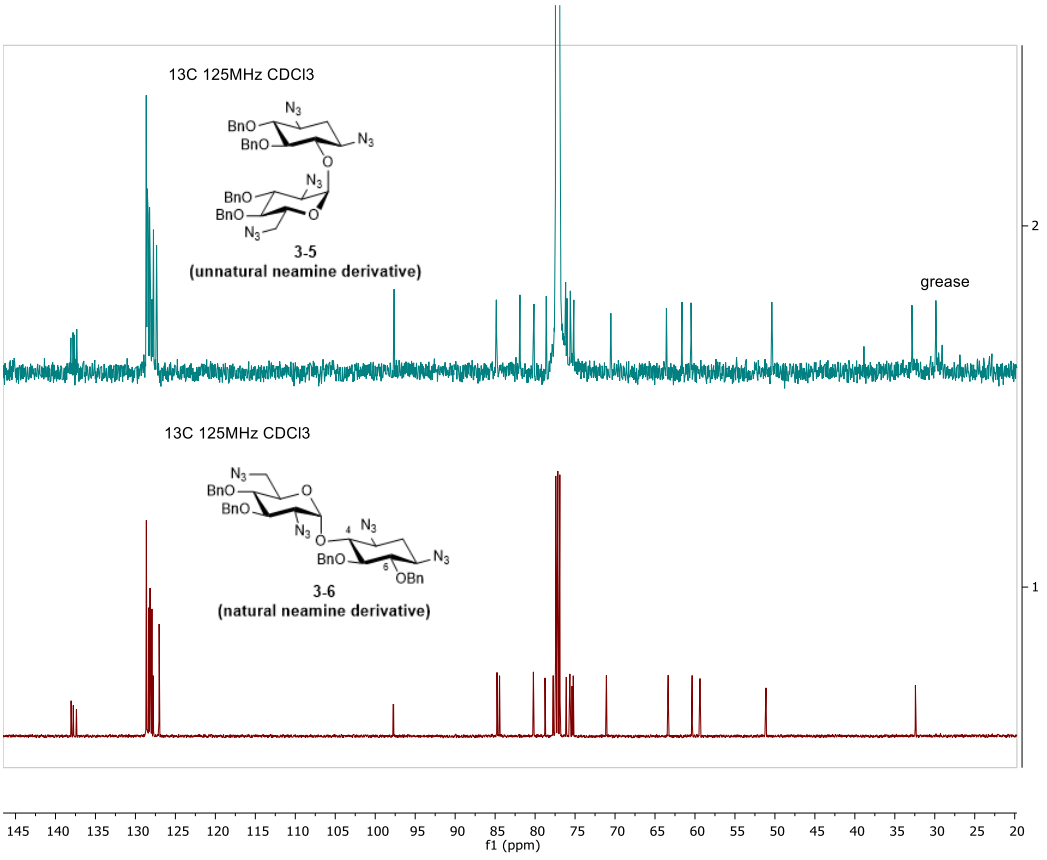
3-6
(natural neamine derivative)

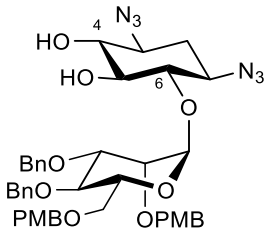
(*2R,3R,4R,5R,6R*)-3-azido-6-(azidomethyl)-4,5-*bis*(benzyloxy)-2-(((*1R,2R, 3S,4R,6S*)-4,6-diazido-2,3-*bis*(benzyloxy)cyclo hexyl)oxy)tetrahydro-2H-pyran (3-6).

Protected neamine **3-6** was prepared from kanamycin B by following the literature prep.[27] The spectra of **3-5** and **3-6** were compared to each other in the spectra section below.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.26 (m, 19H), 5.58 (d, *J* = 3.9 Hz, 1H), 5.03 (d, *J* = 10.8 Hz, 1H), 4.94 (d, *J* = 10.9 Hz, 1H), 4.88 (d, *J* = 8.8 Hz, 4H), 4.83 (d, *J* = 10.5 Hz, 2H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.28 (ddd, *J* = 10.0, 4.3, 2.4 Hz, 1H), 4.01 (dd, *J* = 10.3, 8.9 Hz, 1H), 3.66 – 3.57 (m, 2H), 3.56 – 3.47 (m, 3H), 3.47 – 3.37 (m, 3H), 3.32 (dd, *J* = 10.4, 3.9 Hz, 1H), 2.38 – 2.29 (m, 1H), 1.50 (d, *J* = 12.7 Hz, 1H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 138.1, 137.8, 137.8, 137.4, 128.7, 128.6, 128.6, 128.6, 128.3, 128.2, 128.2, 128.1, 128.1, 127.9, 127.8, 127.0, 97.7, 84.8, 84.5, 80.2, 78.8, 77.7, 76.1, 75.7, 75.4, 75.2, 71.1, 63.4, 60.4, 59.4, 51.1, 32.4.


13C 500MHz CDCl3
3-5
(unnatural neamine derivative)
DCM
13C 500MHz CDCl3
3-6
(natural neamine derivative)
f1 (ppm)


13C 125MHz CDCl3
3-5
(unnatural neamine derivative)
grease
13C 125MHz CDCl3
3-6
(natural neamine derivative)
f1 (ppm)



3-14

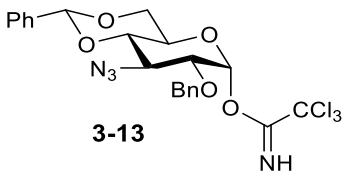
(*1R,2S,3S,4R,6S*)-4,6-diazido-3-(((*2S,3S,4S,5R,6R*)-4,5-*bis*(benzyloxy)-3-((4-methoxybenzyl)oxy)-6-(((4-methoxybenzyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)cyclohexane-1,2-diol (3-14).

The 86:14 mixture of disaccharide **a-3-3B : a-3-3A** (30 mg, 0.0329 mmol) was mixed with 25 mg of 4Å MS, flushed with nitrogen, and then dissolved in 1.5 mL dry THF. The reaction was cooled down to 0 °C, and tetra-n-butylammonium fluoride (TBAF, 1.0 M in THF, 0.066 mL, 0.066 mmol) was added. The reaction mixture was warmed up to room temperature and was stirred for overnight. Then the reaction mixture was quenched with saturated sodium bicarbonate and extracted with ethyl acetate. Organics were washed with brine/water (1:1) two times, then brine. Extracts were dried with magnesium sulfate, and solvent was evaporated. The mixture was purified by column chromatography on SiO_2 (3:1 to 2:1 hexanes/ethyl acetate) to afford compound **3-14** (18.3 mg, 70%).

C6-glycosylated diastereomer (3-14).

^{1}H NMR δ_H (500 MHz, Benzene-d_6) δ 7.45 – 7.39 (m, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.26 – 7.18 (m, 6H), 7.15 – 7.07 (m, 4H), 6.86 – 6.78 (m, 4H), 5.06 – 4.92 (m, 3H), 4.74 – 4.58 (m, 4H), 4.45 (d, *J* = 11.4 Hz, 1H), 4.27 – 4.20 (m, 3H), 4.15 (t, *J* = 2.5 Hz, 1H), 4.09 (dd, *J* = 9.1, 2.9 Hz, 1H), 4.01 (t, *J* = 9.5 Hz, 1H), 3.81 (dd, *J* = 9.6, 1.9 Hz, 1H), 3.53 (t, *J* = 9.1 Hz, 1H), 3.35 (s, 3H), 3.30 (s, 3H), 3.18 (t, *J* = 9.4 Hz, 1H), 3.06 (td, *J* = 8.8, 3.0 Hz, 1H), 2.96 – 2.83 (m, 3H), 2.56 (ddd, *J* = 12.7, 9.5, 4.7 Hz, 1H), 1.50 (dt, *J* = 13.2, 4.6 Hz, 1H). **^{13}C NMR** δ_C (125 MHz, C_6D_6) 160.1, 160.1,

139.1, 139.1, 130.6, 130.1, 130.0, 129.9, 128.7, 128.6, 128.5, 128.3, 128.0, 127.9, 114.2, 114.2, 100.4, 88.1, 80.5, 76.4, 75.6, 75.2, 75.1, 75.1, 73.4, 73.3, 73.0, 72.0, 70.1, 59.6, 59.6, 54.9, 54.8, 32.3. **IR** (thin film, cm^{-1}): 3469, 2654, 1702, 1613, 1586, 1369, 1256, 1109, 1033, 816, 689, 658. **HRMS (ESI+) (*m*/*z*):** $[M+NH_4]^+$ calcd for $C_{42}H_{52}N_7O_{10}$ 814.3770, found 814.3767.



3-13

(*2R,4aR,6R,7R,8S,8aS*)-8-azido-7-(benzyloxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-6-yl 2,2,2-trichloroacetimidate (3-13).

(Check scheme 3.5 for the whole reaction scheme of synthesis of **3-13**)

Thioglycoside **3-12** (784 mg, 1.77 mmol) was dissolved in 25% (v/v) solution of water in acetone and cooled to 0 ºC. To this solution trichloroisocyanuric acid (825 mg, 3.55 mmol) was added. The resultant mixture was allowed to warm up to room temperature while being monitored by TLC. Upon the full conversion to hemiacetal, the mixture was concentrated *in vacuo* and diluted with methylene chloride. The resultant mixture was washed with saturated solution of sodium bicarbonate and water, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residual oil was purified by flash column chromatography on SiO_2 (3:1 hexanes/ethyl acetate) to provide the corresponding product (400 mg, 59%) as a colorless oil.

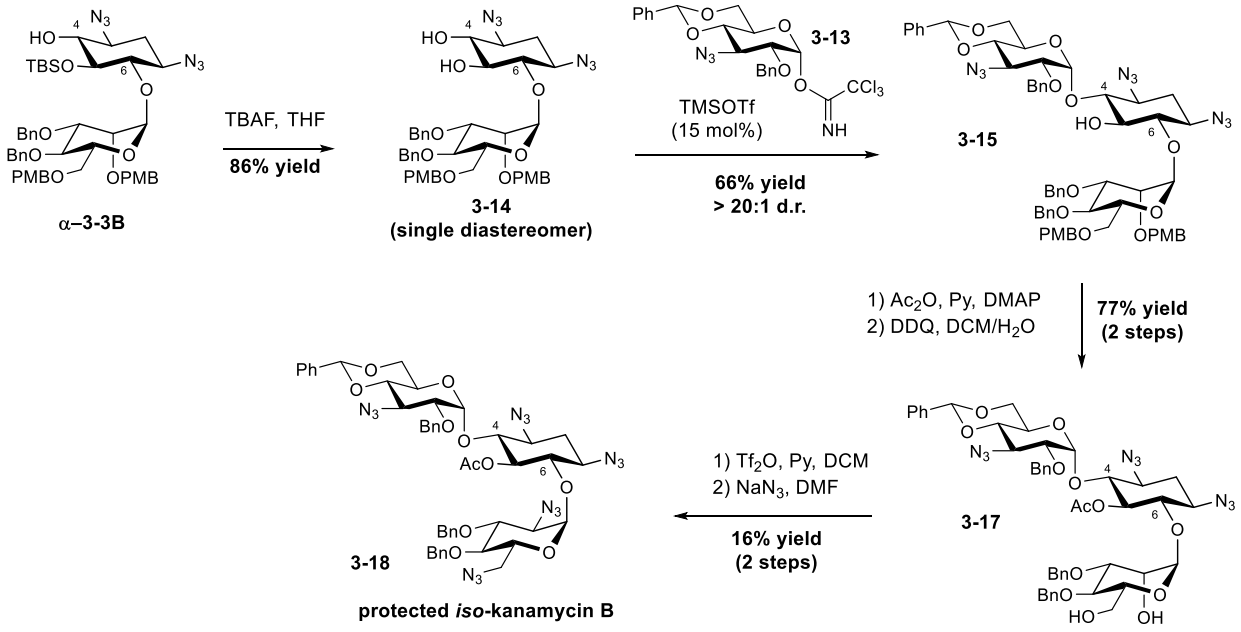
The product from above (355 mg, 0.928 mmol) was dissolved in DCM (17 mL) in the atmosphere of N_2. The reaction mixture was cooled down to 0 ºC, and trichloroacetonitrile (0.28 mL, 2.783 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU, 0.069 mL, 0.464 mmol) were added sequentially. The reaction mixture was allowed to stir until reaction mixture was warmed up to room temperature. The reaction mixture was diluted with toluene and the solvent was evaporated

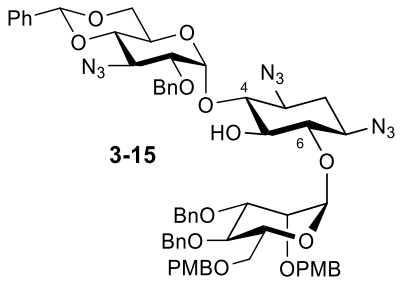
in vacuo. The mixture was purified by flash column chromatography on SiO_2 (5:1 to 3:1 hexanes/ethyl acetate) to afford the title compound **3-13** (1.20 g, 91%).

^{1}H NMR δ_H (500 MHz, Chloroform-*d*) 8.65 (1 H, s), 7.50 (2 H, dd, *J* = 7.6, 1.9 Hz), 7.41 – 7.28 (8 H, m), 6.40 (1 H, d, *J* = 3.6 Hz), 5.57 (1 H, s), 4.73 (2 H, s), 4.33 (1 H, dd, *J* = 10.5, 4.9 Hz), 4.12 (1 H, t, *J* = 10.0 Hz), 4.04 (1 H, td, *J* = 9.9, 4.9 Hz), 3.71 (1 H, t, *J* = 10.3 Hz), 3.61 (1 H, dd, *J* = 9.8, 3.6 Hz), 3.54 (1 H, t, *J* = 9.9 Hz).**^{13}C NMR** δ_C (125 MHz, Chloroform-*d*) 161.4, 137.1, 136.7, 129.3, 128.7, 128.5, 128.3, 128.1, 126.1, 101.8, 93.6, 91.0, 79.5, 77.4, 73.3, 68.8, 65.3, 61.7.

IR (thin film, cm^{-1}): 3329, 2923, 2867, 2108, 1908,1672, 1454, 1370, 1278, 1088, 986, 905.

Preparation of *iso*-kanamycin B derivative 3-18





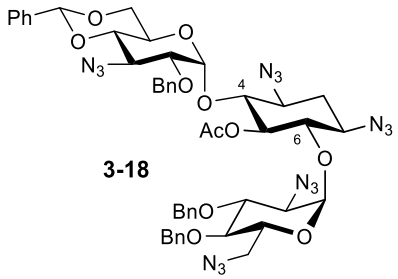
3-15

(1*S*,2*R*,3*S*,5*R*,6*S*)-3,5-diazido-2-(((2*R*,4a*R*,6*S*,7*R*,8*S*,8a*S*)-8-azido-7-(benzyloxy)-2-phenylhexahydro pyrano[3,2-*d*][1,3]dioxin-6-yl)oxy)-6-(((2*R*,3*R*, 4*R*,5*S*,6*S*)-4,5-*bis*(benzyloxy)-3-((4-methoxybenzyl)oxy) -6-(((4-methoxybenzyl)oxy)methyl) tetra-hydro-2*H*-pyran-2-yl)oxy)cyclohexan-1-ol (3-15).

The disaccharide acceptor **3-14** obtained above (119 mg 0.150 mmol) and donor **3-13** (119 mg, 0.224 mmol) were azeotropped with toluene three times, and further dried under high vacuum for 3 h. To the flask containing the resultant residue under the atmosphere of N_2, dried 4 Å molecular sieves and dried DCM (0.6 mL) and Et_2O (0.6 mL) were added. The reaction was cooled down to -78 °C, and TMSOTf (4 μL, 0.022 mmol) was injected. The reaction was stirred at -78 ^oC for 1 h, and quenched by the addition of triethyl amine at -78 ^oC and warmed up. The reaction mixture was diluted with DCM and the mixture was concentrated *in vacuo*. The mixture was purified by flash column chromatography on SiO_2 (5:1 to 2:1 hexanes/ethyl acetate) to afford the trisaccharide **3-15** (single diastereomer, 115 mg, 66 %).

^{1}H NMR δ_H (700 MHz, Benzene-d_6) 7.71 (2 H, d), 7.52 (2 H, d), 7.41 (2 H, d), 7.38 (2 H, d, *J* = 8.5 Hz), 7.30 (2 H, d), 7.28 – 7.17 (12 H, m), 7.13 – 7.04 (5 H, m), 6.84 – 6.80 (4 H, m), 5.66 (1 H, d, *J* = 3.8 Hz), 5.36 (1 H, s), 5.15 (1 H, d, *J* = 1.9 Hz), 5.08 (1 H, d, *J* = 11.1 Hz), 4.77 (1 H, d, *J* = 11.8 Hz), 4.72 (1 H, d, *J* = 11.8 Hz), 4.68 (1 H, d, *J* = 11.9 Hz), 4.63 (1 H, d, *J* = 11.9 Hz), 4.56 (2 H, dd, *J* = 11.2, 6.3 Hz), 4.50 – 4.46 (2 H, m), 4.44 – 4.36 (5 H, m), 4.26 – 4.21 (3 H, m), 4.13 (1 H, dd, *J* = 9.3, 3.0 Hz), 3.87 (1 H, dd, *J* = 10.3, 1.8 Hz), 3.73 (1 H, dd, *J* = 10.2, 7.0 Hz), 3.56 (1 H, t, *J* = 10.2 Hz), 3.38 (3 H, s), 3.34 (1 H, t, *J* = 1.9 Hz), 3.33 – 3.32 (1 H, m), 3.31 (3 H,

s), 3.29 (1 H, dd, *J* = 8.9, 2.1 Hz), 3.22 (1 H, dd, *J* = 10.0, 8.7 Hz), 2.91 (1 H, t, *J* = 9.3 Hz), 2.54 (1 H, ddd, *J* = 12.6, 9.9, 4.5 Hz), 2.47 (1 H, ddd, *J* = 12.6, 9.8, 4.4 Hz).**^{13}C NMR** δ_C (125 MHz, C_6D_6) 160.1, 159.8, 139.3, 139.1, 139.0, 138.2, 138.0, 130.7, 130.6, 130.1, 129.8, 129.1, 128.9, 128.7, 128.6, 128.5, 128.4, 128.4, 128.2, 128.0, 127.8, 126.7, 114.2, 114.1, 102.0, 101.2, 97.7, 86.3, 80.6, 80.3, 80.2, 78.5, 75.7, 75.6, 75.4, 74.8, 73.6, 73.6, 73.2, 72.8, 72.0, 70.2, 69.4, 63.8, 62.7, 60.0, 59.1, 54.9, 54.8, 31.7. **IR (thin film, cm^{-1}):** 3498, 2922, 2855, 2339, 2102, 1512, 1456, 1254, 1092, 972. **HRMS (ESI+)** (*m*/*z*): $[M+NH_4]^+$ calcd for $C_{62}H_{71}N_{10}O_{14}$ 1179.5146 found 1179.5141.



3-18

protected *iso*-kanamycin B **(1*R*,2*S*,3*R*,5*S*,6*R*)-3,5-diazido-2-(((2*S*,3*S*,4*S*,5*S*,6*S*)-3-azido-6-(azido methyl)-4,5-*bis*(benzyloxy)tetrahydro-2*H*-pyran-2-yl)oxy)-6-(((2*R*, 4*R*,6*S*,7*R*,8*S*,8a*S*)-8-azido-7-(benzyloxy)-2-phenylhexahydropyrano [3,2-*d*][1,3]dioxin-6-yl)oxy)cyclohexyl acetate (3-18).**

To a solution of diol **3-17** (12.2 mg, 0.0126 mmol) in DCM (0.3 mL) at -78 ^oC, dried 2,6-lutidine (14 µl, 0.126 mmol) and triflic anhydride (8 µL, 0.0504 mmol) were added sequentially. The reaction mixture was stirred at -78 ^oC for 1h and then quenched with water / THF solution before being warmed up to room temperature. The resulting mixture was extracted with DCM three times, and the combined organic layers were washed with water (x 3), dried over anhydrous sodium

sulfate, filtered and concentrated to obtain *bis*-triflate (14.5 mg, 0.0118 mmol). To the solution of resulting crude triflate (14.5 mg, 0.0118 mmol) in dimethyl sulfoxide (2 mL), sodium azide (15 mg, 0.236 mmol) was added in one portion. The reaction mixture was allowed to stir at 90 ºC overnight. The mixture was diluted with brine, and then organic layers were extracted with DCM (x 3) and dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting crude oil was purified by flash column chromatography on SiO_2 (7:1 to 3:1 hexanes / ethyl acetate) to afford the protected *iso*-kanamycin **3-18** (3.6 mg, 16% yield, 2 steps).

^{1}H NMR δ_H (700 MHz, Benzene-d_6) 7.70 – 7.65 (2 H, m), 7.38 (2 H, d, *J* = 7.6 Hz), 7.33 (2 H, d, *J* = 7.5 Hz), 7.27 (3 H, s), 7.21 (5 H, s), 7.13 – 7.07 (5 H, m), 7.05 (2 H, s), 5.34 (1 H, s), 4.99 (1 H, d, *J* = 3.4 Hz), 4.95 (1 H, t, *J* = 9.5 Hz), 4.92 (1 H, d, *J* = 10.9 Hz), 4.86 (1 H, d, *J* = 3.2 Hz), 4.78 (2 H, d, *J* = 11.3 Hz), 4.52 – 4.50 (1 H, m), 4.50 – 4.46 (2 H, m), 4.35 (1 H, d, *J* = 11.8 Hz), 4.25 – 4.17 (2 H, m), 4.03 (1 H, t, *J* = 9.6 Hz), 3.97 (1 H, dt, *J* = 9.8, 3.4 Hz), 3.53 (1 H, t, *J* = 10.4 Hz), 3.47 (1 H, t, *J* = 9.4 Hz), 3.39 (1 H, dd, *J* = 13.5, 2.5 Hz), 3.23 – 3.19 (2 H, m), 3.16 (1 H, t, *J* = 9.7 Hz), 3.09 – 3.04 (2 H, m), 2.87 (2 H, qd, *J* = 9.6, 5.5 Hz), 2.39 (1 H, ddd, *J* = 12.3, 9.4, 4.7 Hz), 1.97 (3 H, s), 1.05 (1 H, dd, *J* = 11.8, 6.7 Hz).**^{13}C NMR** δ_C (175 MHz, C_6D_6) 169.9, 138.5, 138.4, 137.8, 137.8, 129.2, 128.9, 128.7, 128.7, 128.7, 128.7, 128.4, 128.4, 128.3, 128.3, 127.8, 126.7, 102.1, 99.2, 98.5, 82.3, 80.2, 79.8, 78.6, 75.6, 75.2, 74.0, 72.1, 69.3, 64.6, 64.3, 62.3, 61.4, 60.4, 60.1, 51.0, 30.2, 21.6. **IR (thin film, cm^{-1}):** 2920, 2845, 2101, 1755, 1457, 1201, 1116. **HRMS (ESI+) (*m*/*z*):** $[M+Na]^+$ calcd for $C_{48}H_{51}N_{15}O_{11}Na$ 1036.3790, found 1036.37.

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Chapter 4

Chiral Phosphoric Acid-Catalyzed Stereoselective and Regioselective Glycosylation

4.1 Introduction to selective glycosylation

Glycosylation is referred to as a reaction of glycosyl donors, generally, carbohydrates with a leaving group, coupled to a glycosyl acceptor, generally, compounds that contain free hydroxyl groups, to form a glycoside. Carbohydrates, products of glycosylation reactions, play pivotal roles in biological systems, such as intracellular and extracellular targeting,[1] protein folding, [2] peptide transportation,[3] immunomodulation,[4] and so on.[5] Beyond in-flask carbohydrate synthesis, the glycosylation reaction itself is important in that most post-translational modifications of proteins occur through glycosylation across more than half of the eukaryotic proteome.[6] Due to the important roles of carbohydrates in biological processes, even simple carbohydrates like mono- and oligosaccharides are commonly found as structural motifs in drug discovery.[7] With this background, numerous studies of the glycosylation of bioactive compounds have been carried out to enhance their therapeutic properties. Indeed, glycosylation of biologics improved a wide range of drug properties including *in vivo* circulatory half-life[8], immunogenicity,[9] and enhancement of efficacy and safety. [5,10]

In order to produce these positive effects through glycosylation, specific carbohydrates must be placed in a specific position of a bioactive compound, which implies that regioselective glycosylation is necessary. Nature employs enzymes called glycosyltransferases to carry out regioselective glycosylation. [11] The selective chemical glycosylation, however, is challenging due to the intrinsic complexity of carbohydrates. In carbohydrate synthesis, especially, not only the

control of regioselectivity, but also the control of stereoselectivity is crucial, which otherwise complicates the outcome of glycosylation.

Despite the difficulties in selectivity control for chemical glycosylation, a considerable number of regioselective glycosylation methods are available. These regioselective glycosylation approaches could be divided into two main categories: substrate- (i.e. donor/acceptor-) controlled glycosylations and reagent/catalyst-controlled glycosylations.[12]

First, the regioselectivity outcome can vary depending on the kind of glycosyl donors and glycosyl acceptors. For instance, compounds that contains multiple hydroxyl groups can have their own intrinsic selectivity, which could result in moderate to high regioselectivities for some glycosylation reactions.[13] Different types of sugars possess different intrinsic reactivity of their hydroxyl groups, therefore, regioselectivity is affected by the types of sugar in glycosyl acceptors. In addition to that, the protecting groups of glycosyl acceptor and glycosyl donor can affect the regioselectivity outcome. For instance, the intrinsic reactivity of the hydroxyl groups on the glycosyl acceptor can be manipulated by changing the protecting groups. [14] The reactivity of the glycosyl donor is also known to be affected by the protecting groups. The concept of armed and disarmed donor is the representative example of the effect of different protecting groups enhancing or attenuating the reactivity of a glycosyl donor. Besides the type of sugars and protecting group, match/mismatch of glycosyl donor and acceptors also affects the regioselectivity of glycosylation. Both the type of the leaving group and the configuration of the glycosyl donor will impact the regioselectivity of glycosylation reactions.

Second, the regioselectivity of the glycosylation reaction can be controlled either by a reagent or a catalyst. The reagents, such as organotin, silver-based activators, triphenylmethyl ethers, or boronic esters have been used to accomplish the regioselective glycosylations. A more

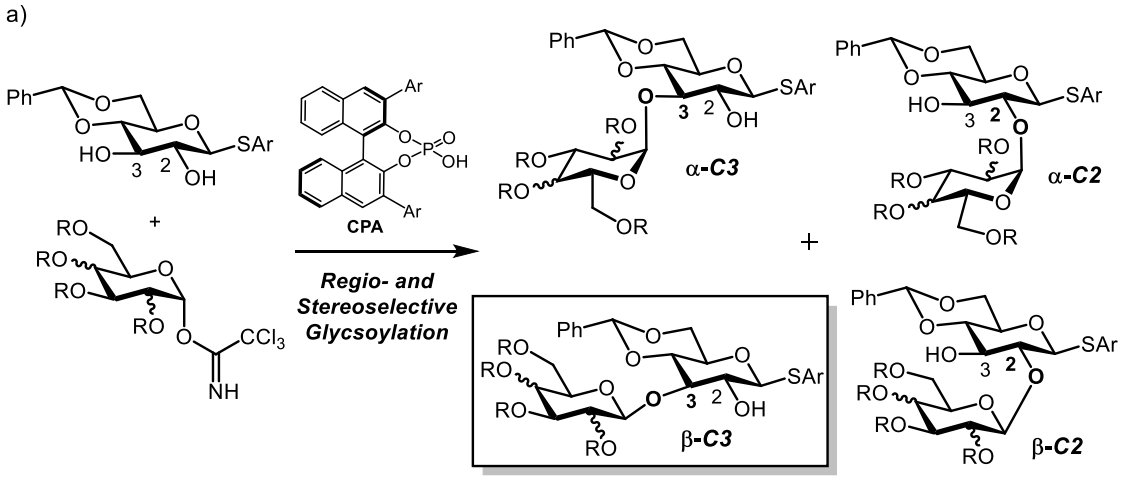
indirect way to control the regioselectivity of glycosylation is by using catalysts. Many examples of regioselective and stereoselective glycosylation methods are available (Refer to chapter 2). [15] This chapter focuses on the chiral catalyst-controlled regioselective glycosylation reactions.

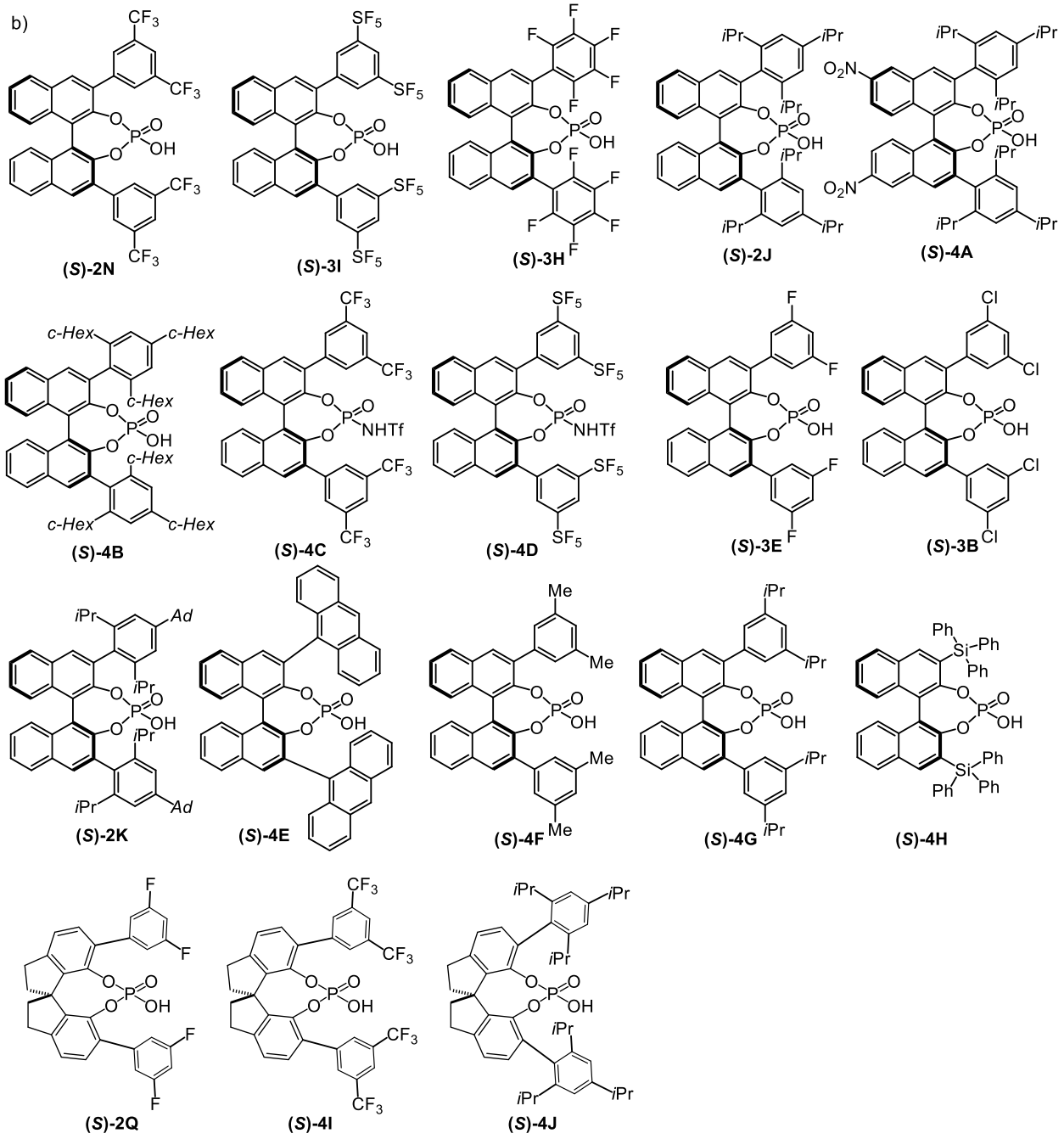
4.2 CPA catalysis in carbohydrate system

In organic synthesis, chiral phosphoric acids (CPAs) have received substantial attention as the catalysts for promoting asymmetric transformations (*vide supra*). The application of the CPA to achieve control of stereoselectivity is particularly beneficial in glycosylation reactions because it may help to avoid handling mixtures of isomeric glycosides by biasing the formation of only one glyco-form. By taking the advantage of CPA catalysts, the Fairbanks group was the first group to apply BINOL-based CPAs to enhance the stereoselectivity of β-selective galactoside formations.[16] Subsequently, Toshima group achieved racemic secondary alcohol resolution using diastereoselective glycosylation with CPA catalysis.[17] The Bennett group also reported stereoselective glycosylation of 2-deoxyglucose using a hydrogenated BINOL-CPA.[18] Finally, Galan group suggested that a combination of the CPA and thiourea catalysts can produce a synergistic effect in α-stereoselective glycosylatation of glycal substrates.[19] Our group also has long-term interests in using CPA to perform regioselective glycosylation of polyol system. The desymmetrizative glycosylation studies summarized in Chapter 3 represent an example of some of our efforts in this area.[20] In addition, our group has also demonstrated that chiral phosphoric acids could control regioselective glycosylation of 6-deoxyerythronolide B (6-dEB), and the site of glycosylation was dependent on the structure and chirality of the chiral Bronsted acid.[21] Given the successful application of CPA in the preceding studies, CPA catalysis is a very powerful tool for controlling the stereo- and regioselectivity of glycosylation reactions.

In addition to developing CPA-catalyzed methods for glycosylation, our group has discovered that chiral phosphoric acids are excellent catalysts for site-selective acetalization of carbohydrate-derived 2,3-diols.[22] The reactions of carbohydrate-derived 2,3-diols are not inherently selective, therefore achiral catalysts promote the formation of both C2- and C3-acetals with C3-acetalization products slightly prevailing in the mixture. However, some BINOL-derived CPAs were found to provide very high regioselectivity, which was opposite to the achiral catalyst-controlled selectivity. Considering that the CPA was able to distinguish the C2-and C3-position in the D-glucose-based system for acetalization reaction, we hypothesized that CPA-catalyzed regioselective glycosylation would also be possible using the same 2,3-diol as an acceptor. Various prior studies have already demonstrated the ability of CPA to control stereoselectivity; however, the potential of CPAs in controlling both stereo- and regioselectivity is yet to be revealed. Based on our prior experiences (vide supra), we believe that CPAs could control both the site-selective and stereoselective glycosylation of 2,3-diols (Figure 4.1a).

Figure 4. 1. a) CPA-catalyzed regioselective and stereoselective glycosylation of D-glucose derived 2,3-diol. b) List of CPAs for the glycosylation study.





This chapter is focused on summarizing our work on exploring CPAs as the catalysts that control both regioselective and stereoselective glycosylation of carbohydrate-derived diols.

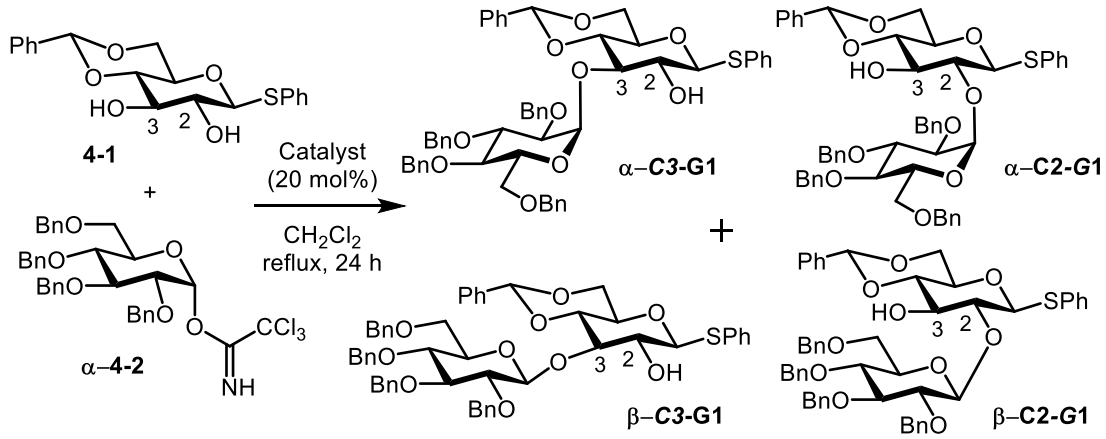
4.3 CPA-catalyzed glycosylation reaction of D-glucose-derived 2,3-diols

Our studies commenced with establishing the optimal glycosylation conditions. A benzylated D-glucose-derived trichloroacetimidate (TCA) donor **4-2** and the D-glucose-derived 2,3-diol acceptor **4-1** were selected for our initial studies. **(*R*)-2N** was selected as the initial catalyst for the glycosylation reaction. The reaction was performed with 1.5 equivalent of donor **4-2** and 20 mol% of CPA in anhydrous DCM at room temperature for 24 h. Unlike the acetalization reaction, the glycosylation reaction was found to be significantly slower. The observed low reactivity is likely due to the low solubility of the acceptor diol in DCM. After the reaction was warmed up to 40 ^{o}C, higher conversion was obtained (71%). This glycosylation reaction generated 4 different isomers, which were α-C2, α-C3, β-C2, and β-C3 isomers as expected (Figure 4.1a). **(*R*)-2N** favored the formation of the C3 isomer (C3:C2 = 75:25) and β-anomer (α:β = 12:88).

With the promising initial results observed for the **(*R*)-2N**-catalyzed glycosylation, various CPAs were evaluated as the catalysts for the glycosylation of **4-1** and **4-2** (Table 4.1). First, the control experiment was carried out with diphenyl phosphoric acid (DPPA) as the catalyst (entry 1), and the intrinsic β-selectivity (α:β = 36:64) and C3-selectivity (C3:C2 = 70:30) were observed. Compared to the control experiments, CPAs containing electron withdrawing group substituents at the 3,3'-aryl rings provided favored β-C3 diastereomer (entries 3-8). Compared to (*R*)-CPA catalysts, (*S*)-CPA catalysts afforded better C3-selectivity in general. In particular, **(*S*)-2N** and **(*S*)-3H** were found to induce high C3-selectivities (C3:C2 = 81:19 and 85:15 correspondingly). While electron-withdrawing groups on 3,3'-aryl rings of CPAs promoted glycosylation reaction effectively, the CPAs with 3,3' aryl groups containing electron donating substituents could not promote the glycosylation reaction at all (entries 9-13). This result has already been observed before in glycosylation of 2-deoxysterptamine, which was described in Chapter 3 of this thesis. In

order to see if further enhancing the acidity of catalyst is beneficial, the *N*-triflamide-based catalysts **4C** and **4D** were employed for the glycosylation reactions, which resulted in α-and C3-selective formation of the products (entry 14-16).

Table 4. 1. CPA-catalyzed glycosylation of benzyl protected α-trichloroacetimidate donor **4-2**.

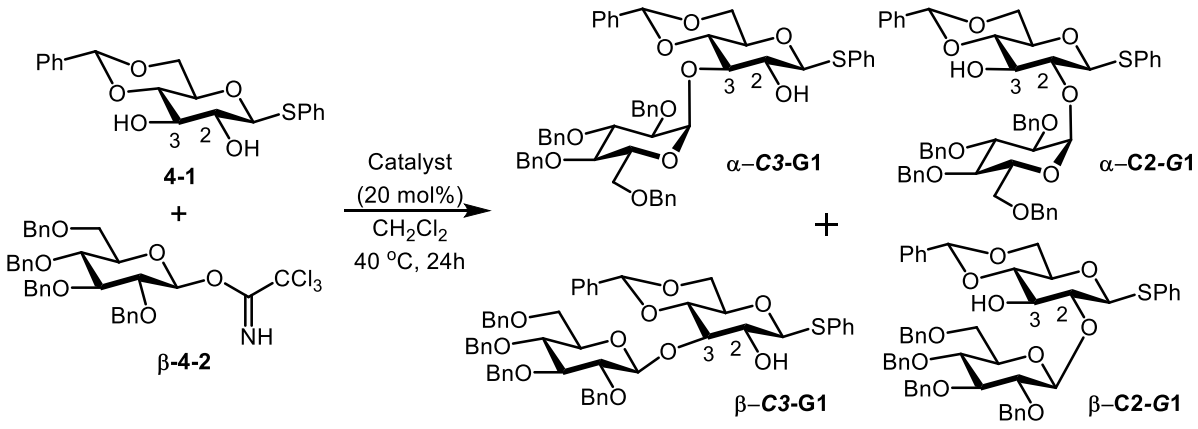


Entry	Catalyst	Conv (%)	α-C_3 : α-C_2 : β-C_3 : β-C_2	α : β	C3 : C2
1	$(PhO)_2PO_2H$	41	22.6 : 13.8 : 47.1 : 16.5	36 : 64	70 : 30
2	$(PhO)_2PO_2H$ (1 eq)	62	46.3 : 31.7 : 10.4 : 11.6	78 : 22	57 : 43
3	(*S*)-2N	65	17.3 : 9.1 : 63.6 : 10.0	26 : 74	81 : 19
4	(*R*)-2N	71	7.1 : 4.7 : 67.8 : 20.4	12 : 88	75 : 25
5	(*S*)-3I	60	19.0 : 4.7 : 71.1 : 5.2	24 : 76	90 : 10
6	(*R*)-4I	40	4.6 : 3.1 : 75.4 : 16.9	8 : 92	80 : 20
7	(*S*)-3H	55	6.2 : 3.0 : 70.0 : 20.7	9 : 91	85 : 15
8	(*R*)-3H	35	15.1 : 5.0 : 69.5 : 10.4	20 : 80	76 : 24
9	(*S*)-2J	no rxn			
10	(*R*)-2J	no rxn			
11	(*S*)-4A	no rxn			
12	(*S*)-4B	no rxn			
13	(*R*)-4B	no rxn			
14	(*S*)-4C	40	33.6 : 22.1 : 33.2 : 11.1	67 : 33	67 : 33
15	(*R*)-4C	40	32.9 : 27.4 : 35.6 : 4.1	68 : 32	68 : 32
16	(*S*)-4D	<10	34.8 : 19.5 : 38.9 : 6.8	74 : 26	74 : 26

condition : **4-1** (1 equiv), α–**4-2** (1.4 equiv), catalyst (20 mol%), DCM (0.04M)
regio- and stereoselectivity was measured by NMR and HPLC assay

Based on the observed stereochemistry switched from β- to α- with more acidic catalyst, we investigated the possibility of increasing the amount of acid catalyst with the hope to further enhance the a-stereochemistry of glycosylation. One equivalent of diphenyl phosphoric acid was used for glycosylation reaction, and α-glycoside was obtained as the major product (entry 2). Considering that 20 mol% of diphenyl phosphoric acid provided β-selectivity, this result confirmed that more acidic medium favors α-selective glycosylation. In order to understand and rationalize the selectivity, glycosylation reactions with different conditions were performed.

Table 4. 2. CPA-catalyzed glycosylation reaction with β-trichloroacetimidate donor **4-2**.



Entry	Catalyst	Conv (%)	α-C_3 : α-C_2 : β-C_3 : β-C_2	α : β	C3 : C2
1	(*S*)-3I	45	27.7 : 23.1 : 28.9 : 20.3	**51**:49	57:43
2	(*R*)-3I	40	45.6 : 21.7 : 21.9 : 10.8	**67**:33	67:33
3	(*R*)-2N	35	43.2 : 21.7 : 27.7 : 7.5	**71**:29	65:35
4	$(PhO)_2PO_2H$	55	40.7 : 41.1 : 10.2 : 8.1	**82**:18	51:49

condition : **4-1** (1 equiv), β-**4-2** (1.4 equiv), catalyst (20 mol%), DCM (0.04M)
Regio- and stereoselectivity was measured by NMR and HPLC assay

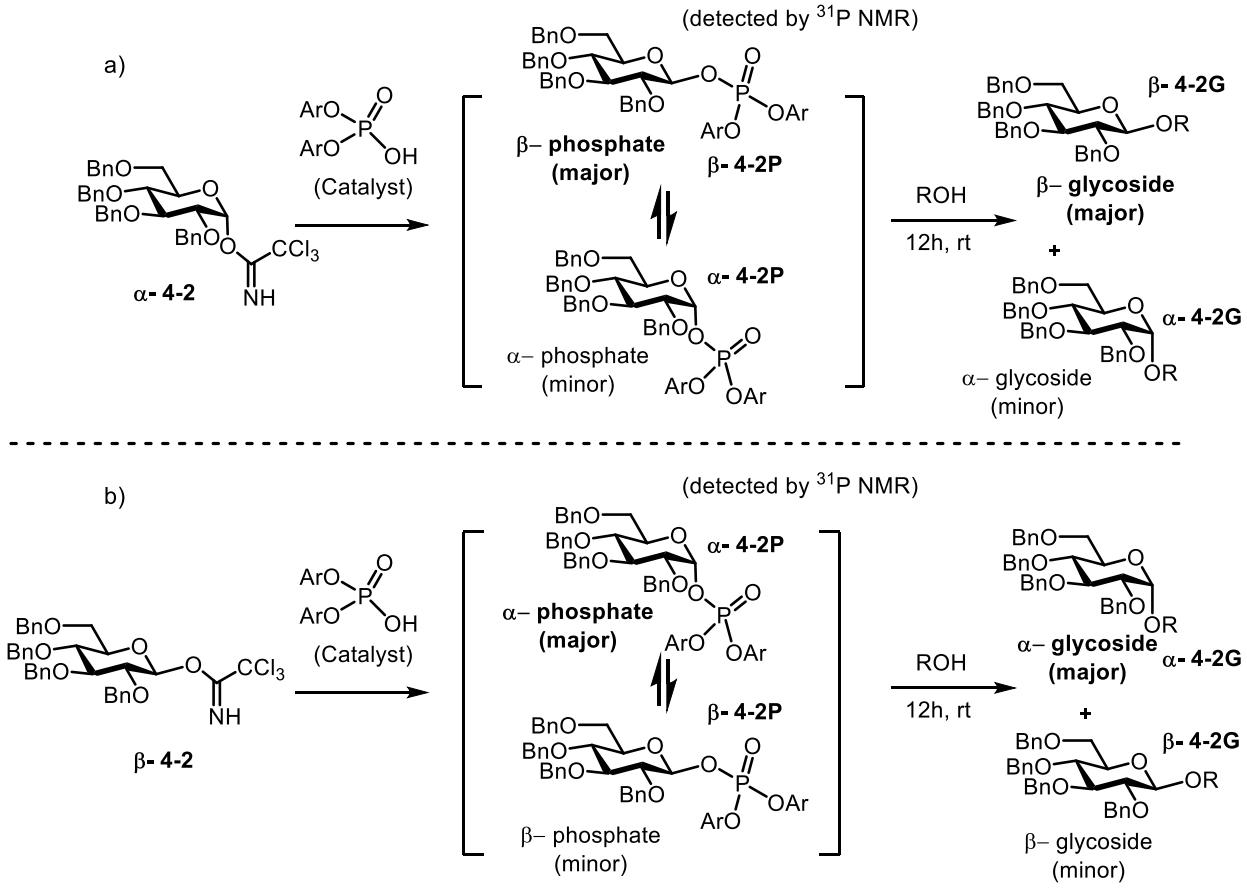
Next, to see if the selectivity is affected by the stereochemistry of trichloroacetimidate's anomeric position, **β-4-2** donor was employed for the glycosylation reaction instead of **α-4-2** donor (Table 4.2). Interestingly, α-configured product prevailed in the glycosylation with β-

trichloroacetimidate **β-4-2**, and the opposite stereochemical outcome was observed if **α-4-2** is used. This result suggests that the stereochemistry of the donor influences the stereoselectivity of the glycosylation reaction. The catalyst still favored the reaction at the C3-position; however, the regioselectivity diminished in comparison to glycosylation with α-donor **α-4-2**. These results suggest that α-donors favor β-glycoside formation and β-donors favor α-glycoside formation.

4.4 Mechanism of CPA-catalyzed glycosylation reactions

With interesting preliminary data in hand, we investigated the glycosylation reaction mechanism. Initially, ^{31}P NMR study was carried out with glycosyl donor **α-4-2** and CPA **(*R*)-2N**. Our prior mechanistic and computational studies of CPA-catalyzed glycosylations with glycosyl trichloroacetimidates suggested that these reactions proceed through sugar-phosphate covalent intermediates.[21] To validate that it is also the case in our system, **α-4-2** and CPA **(*R*)-2N** were mixed together in *d*-Chloroform at room temperature, and ^{31}P NMR was recorded right away (5 min).We indeed observed that a-trichloroacetimidate donor **α-4-2** reacted with CPA to form anomeric β-phosphate intermediate **β-4-2P**. Over the time, β-phosphate **β-4-2P** slowly epimerized to the corresponding α-phosphate **α-4-2P** (Scheme 4.1a). Within 12 h, which is the operation time frame for the glycosylation reaction, β-sugar phosphate **β-4-2P** was still the major observed intermediate for the glycosylation reaction. From our observations, β-glycoside was obtained as the major product from a α-trichloroacetimidate donor unless higher catalyst loading was used (entry 1, 3-8, Table 4.1). This result excludes the possibility of a S_N2 mechanism since the product of a S_N2 mechanism should contain the inverted stereochemistry, but α-glycoside was not the major product. To confirm this result, the same NMR study was carried out with β-trichloroacetimidate donor **β-4-2** (Scheme 4.1b). After mixing with **β-4-2** and CPA, the exclusive formation of α-phosphate **α-4-2P** was

Scheme 4. 1. NMR study of CPA catalyzed glycosylation reactions: a) α-donor **4-2** forming β-glycoside. b) β-donor **4-2** forming α-glycoside.

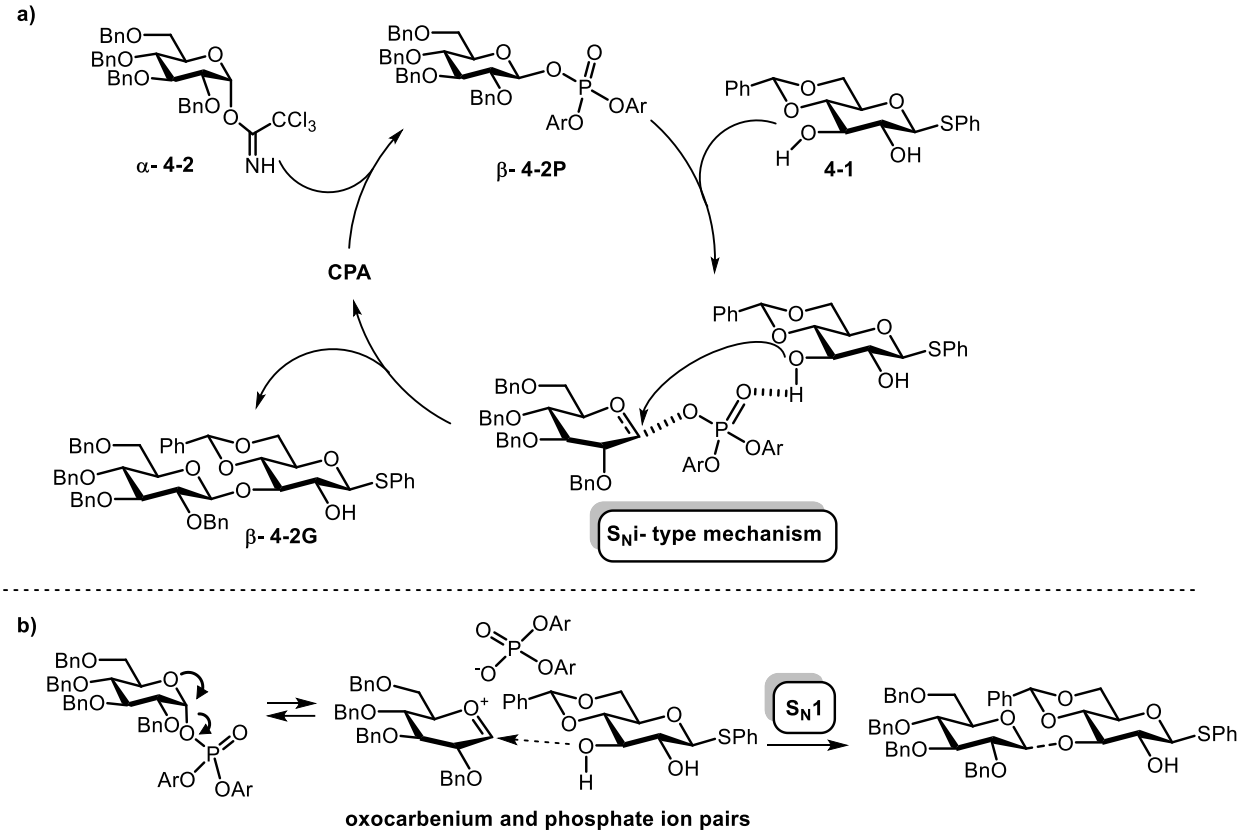


observed, and α-phosphate **α-4-2P** slowly epimerized to β-phosphate **β-4-2P** over time. Within 12 h, the α-phosphate **α-4-2P** was still the major species in solution, and the α-glycoside was formed as the major product. Altogether, α-donor **α-4-2** produced β-phosphate **β-4-2P** as an intermediate, which eventually provided β-glycoside **β-4-2G**. Similarly, β -donor **β-4-2** formed α -phosphate **α-4-2P** as an intermediate, which then reacted to provide α-glycoside **α-4-2G**. Simple S_N1/S_N2 mechanism does not explain these results, but S_Ni mechanism[23] perfectly rationalizes the observed stereoselectivity of these glycosylation reactions. The S_Ni mechanism explains the stereoselectivity of the glycosylation reaction when the departure of the leaving group of the activated glycosyl donor and the front-side nucleophilic attack of the glycosyl acceptor are synchronized. Using this

S_Ni model, the mechanism of the CPA-catalyzed glycosylation reaction was defined as following (Figure 4.2a). Once the CPA and α-donor **α-4-2** (as an example) formed β-phosphate **β-4-2P**, the glycosyl acceptor **4-1** came in participation. Here, we proposed that phosphoryl oxygen of the sugar phosphate and hydroxyl group of the acceptor form a hydrogen bond. Due to the H-bond interaction, nucleophilic attack of the acceptor's oxygen of the C3-position happens from the same face as the β-phosphate, therefore, β-glycoside is obtained as the main product. However, we cannot completely rule out a S_N1 mechanism as there is still possibility for the formation of oxocarbenium/phosphate ion pairs from the covalent phosphate intermediate **4-2P** (Figure 4.2b). To rationalize the results for the α-selective glycosylation starting with the α-donor under highly acidic conditions, we have carried out ^{31}P NMR study of the reaction of donor **α-4-2** and acceptor **4-1** with both 0.2 and 1.0 equivalent of diphenyl phosphoric acid. ^{31}P NMR reaction monitoring showed that both reactions initially produced β-phosphate, but the reaction containing 1.0 equivalent of diphenyl phosphoric acid promoted rapid β-phosphate epimerization to form α-phosphate. This observation provided an answer to the puzzling α-selectivity from the glycosylation reaction with α-donor **α-4-2** with stoichiometric acid as the catalyst. Thus, when stronger acids are employed, α-donor **α-4-2** initially forms β-phosphate **β-4-2P**, which subsequently epimerized to form α-phosphate **α-4-2P**. The subsequent glycosylation reaction of the α-phosphate intermediate **α-4-2P** and acceptor **4-1** through S_Ni type mechanism results in α-glycoside **α-4-2G** as the major product.

(These and subsequent studies were carried in collaboration with Alonso Arguelles.)

Figure 4. 2. Plausible mechanism of CPA-catalyzed glycosylation reaction. a) S_Ni mechanism. b) S_N1 mechanism.



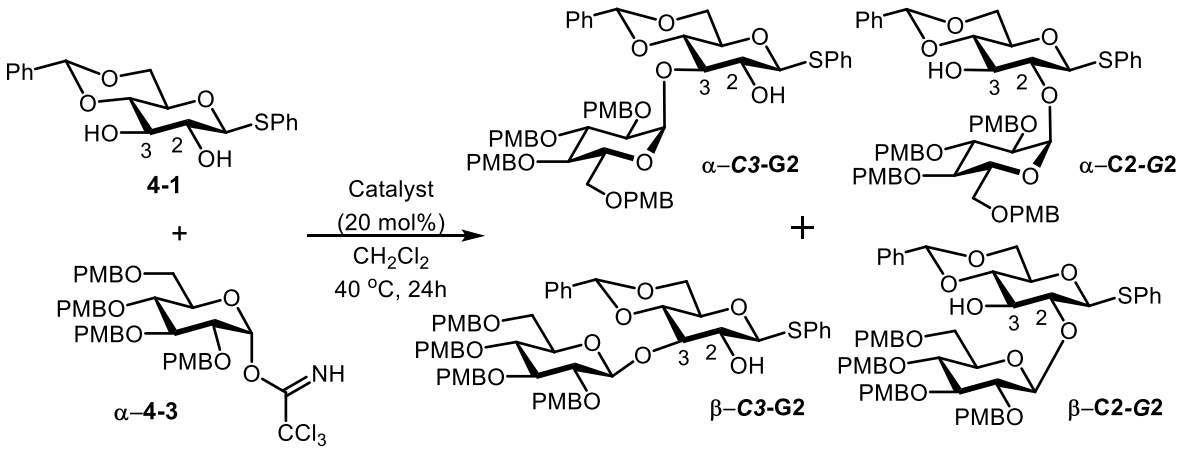
4.5 Further optimization of the glycosylation conditions

Given that glycosylation reactions were not sufficiently fast at room temperature, the further optimization of the reaction conditions was investigated. Due to the low reactivity under previously investigated condition, elevated reaction temperatures were required. However, higher temperatures can diminish the selectivity emposed by CPAs. In order to increase the reactivity and the stereoselectivity/regioselectivity, the reaction conditions were optimized by modifying several parameters of glycosylation reaction.

Initially, the effect of the protecting groups of glycosyl donors in glycosylation reactions was investigated. Consequently, the glycosylation reactions were performed with *para*-methoxy

benzyl (PMB) protected donor **4-3** (Table 4.3) instead of benzylated donor **4-2**. This switch in the donor protecting groups resulted in reduced reactivity and selectivity when compared to the correspondingly benzyl-protected donor (Table 4.1 entry 3-4). The glycosylation product arising from **α-4-3** was so polar that the separation of the isomeric products could not be achieved. As PMB protection did not improve the reaction rate, other parameters were investigated instead.

Table 4. 3. CPA-catalyzed glycosylation reaction with PMB protected **D**-glucose donor **4-3**.



Entry	Catalyst	Conv (%)	α-C_3 : α-C_2 : β-C_3 : β-C_2	α : β	C3 : C2
1	(*S*)-2N	60	8.9 : 4.2 : 72.2 : 14.8	13:87	81:19
2	(*R*)-2N	65	14.0 : 6.4 : 65.0 : 14.6	20:80	79:21

conditions : **4-1** (1 equiv), α–**4-3** (1.4 equiv), catalyst (20 mol%), DCM (0.04M)
Regio- and stereoselectivity was measured by 1H NMR.

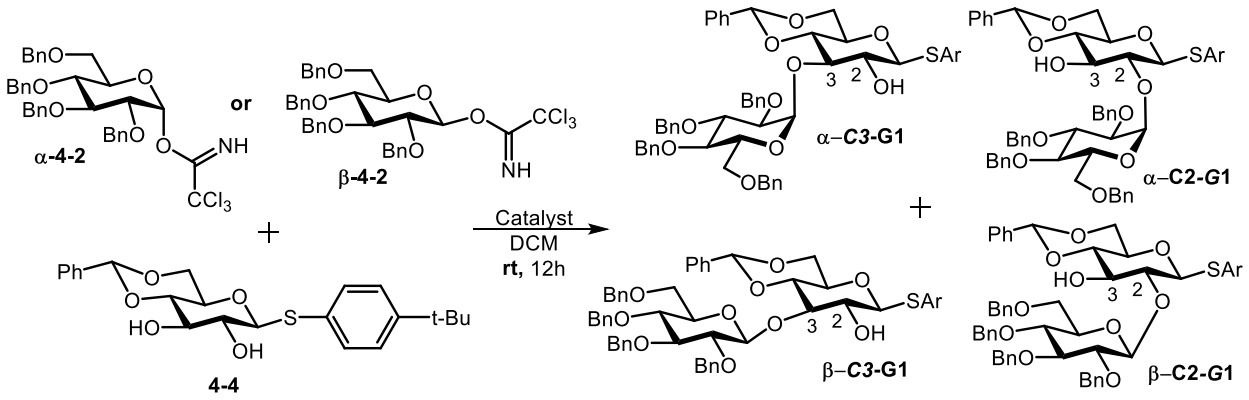
Next, in order to enhance the reactivity and selectivity of the glycosylation with **4-1** and **4-2** were performed using Lewis acids such as BBr_3, $SiCl_4$, $AlCl_3$, $SnCl_4$, LiCl, $ZnCl_2$ as the co-catalysts. Since these reactions at room temperature mostly resulted in the decomposition of the sugar donors, the glycosylations were carried out at -60 °C instead. The glycosylation reaction with Lewis acid co-catalysts, unfortunately, did not increase the regioselectivity, but provided α-stereoselectivity. This result matched to our previous NMR investigation, which was that acidic

conditions facilitate the β-sugar-phosphate to epimerize to form α-position. Following after S_Ni type mechanism, more α-glycoside is obtained as a major stereoselectivity.

The huge limitation of diol acceptor **4-1** is that **4-1** is too polar to be dissolved in many organic solvents including DCM. Large amount of DCM was needed to fully dissolve the diol before the glycosylation reaction, and that was a part of reason for low conversion and necessity of introducing heat to promote the reaction. With a careful optimization, 4-*tert*-butyl thiophenol-containing diol **4-4** found to be a suitable acceptor for our glycosylation reactions. Most importantly, this substrate was well-soluble in organic solvents. In addition to solubility, the substrate introduces the additional steric bulk arising from the *t*-butyl substituent, which could induce the regioselectivity in glycosylation reactions.

While the glycosylation reaction with diol acceptor **4-1** did not work at room temperature at all, the glycosylation reaction with diol **4-4** provided at least with 20% conversion (Table 4.4). This result implied that the reactivity was increased with the diol **4-4** compared to **4-1**. In this study, both α-donor **α-4-2** and β-donor **β-4-2** were used for the glycosylation reaction with acceptor **4-4** and **(*R*)-2N** as the catalyst. In general, C3-selectivity was favored in all cases, and α-donor favored the β-glycoside and β-donor favored the α-glycoside. In terms of regioselectivity and stereoselectivity, the glycosylation reaction with **4-4** resulted in an incremental improvement when compared to **4-1**. With **α-4-2,** acceptor **4-4** provided C3:C2 = 79:21 regioselectivity, and acceptor **4-1** provided C3:C2 = 75:25 (Table 4.1, entry 4). With **β-4-2,** acceptor **4-4** reacted to produce C3:C2 = 89:31, and acceptor **4-1** produced C3:C2 = 65:35 (Table 4.2, entry 3). Slight increase in C3-selectivity could be reasoned by the steric hinderance from *t*-Bu in acceptor **4-4**, which can block of nucleophilic attack on C2-OH. However, the difference is so subtle that it could possibly be generated from experimental error.

Table 4. 4. CPA-catalyzed glycosylation reaction with donor **4-2** and acceptor **4-4**.



Entry	Donor	Catalyst	Conv (%)	α-C_3 : β-C_3 : α-C_2 : β–C_2	α : β	C3 : C2
1	α-	Ph_2PO_2H	25	14.0 : 49.1 : 11.7 : 25.2	26:74	63:37
2	α-	(*R*)-2N	20	7.4 : 71.6 : 5.5 : 15.4	13:87	79:21
3	β-	(*R*)-2N	20	43.1 : 19.6 : 25.5 : 11.8	63:37	69:31

conditions : **4-4** (1 equiv), **4-2** (1.4 equiv), catalyst (20 mol%), DCM (0.04M)
Regio- and stereoselectivity was measured by 1H NMR.

Even though diol **4-4** improved the solubility in organic solvents, and the reactivity of glycosylation reactions, there was still a lot of room for further optimization, especially in glycosylation reactivity.

4.6 CPA-catalyzed glycosylation reaction with 6-deoxy-D-glucose donor α-4-10

From our previous CPA-catalyzed glycosylation study,[21] we found that deoxy-sugar donors were more reactive than more oxygenated sugar moieties. In order to enhance the rate of glycosylation reaction, use of deoxy-sugar was investigated next. The synthesis of 6-deoxyl-D-glucose derivative **α-4-10** is depicted in Scheme 4.2. The synthesis commenced with the tosylation of the 6-hydroxyl group of methyl α-D-glucopyranoside **4-5**, and the resultant derivative **4-6** was reduced by lithium aluminum hydride to generate **4-7**. The resulting alcohols of **4-7** were then benzylated and the methoxy group in anomeric position was hydrolyzed by acid. After introducing

trichloroacetimidate moiety by the reaction of **4-9** with trichloroacetonitrile and DBU, the benzylated 6-deoxy D-glucose-derived trichloroacetimidate donor **α-4-10** was obtained in 52% yield after 5 steps (based on recovered starting material).

Scheme 4. 2. Preparation of benzylated trichloroacetimidate 6-deoxy glucose **α-4-10**.

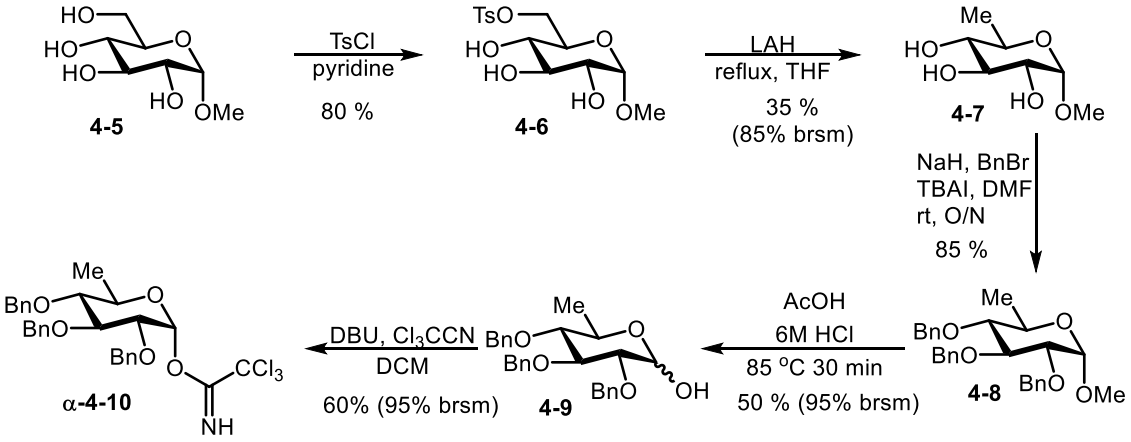
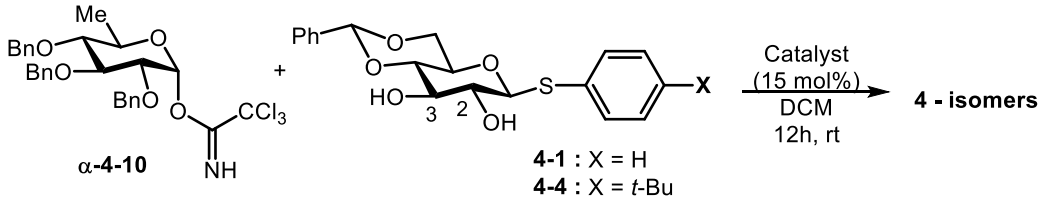


Table 4. 5. Glycosylation reactivity comparison between acceptor **4-1** and **4-4**.



Entry	Acceptor	Catalyst	Conv (%)	α-C_3 : β-C_3 : α-C_2 : β-C_2	α : β	C3 : C2
1	**4-1**	(***R***)-**2N**	65	6.12 : 58.59 : 5.56 : 29.71	12:88	65:35
2	**4-4**	(***R***)-**2N**	**70**	10.40 : 64.4 : 6.01 : 19.21	**17:83**	**75:25**

conditions : **4-1** or **4-4** (1 equiv), **4-5** (1.4 equiv), catalyst (15 mol%), DCM (0.04M)
Regio- and stereoselectivity was measured by 1H NMR + HPLC assay.

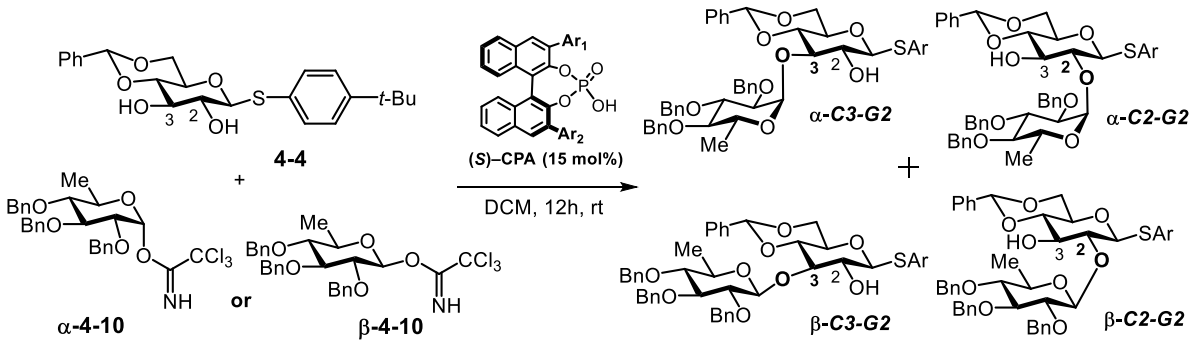
To examine the reactivity of new donor **α-4-10**, glycosylation reactions were performed with diol acceptor **4-1** and **4-4** (Table 4.5). Delightfully, the glycosylation reaction with 6-deoxy glucose donor **α-4-10** was efficient and high conversion was observed. With **(*R*)-2N** as the catalyst,

65% of desired glycoside was obtained from **4-1** and 70% of the desired glycoside was afforded from **4-4**. This result confirmed that diol **4-4** is a more suitable substrate for these studies. In addition to the higher conversion, **4-4** provided better regioselectivity (C3:C2 = 75:25) than **4-1** (C3:C2 = 65:35), which could be rationalized by *tert*-butyl substituent being involved in steric interactions in the transition state leading to C3-selective glycosylation.

With this successful preliminary results in hand, the effect of the CPA catalysts on the reactions of glycosyl donor **4-10** and acceptor **4-4** were further evaluated (Table 4.6). In a control reaction with diphenyl phosphoric acid (entries 1 and 2), low levels of regiocontrol favoring the C3-glycoside were observed. As before (Table 4.1), 1.0 equivalent of diphenyl phosphoric acid provided α-glycoside as the major product (entry 1), presumably due to the fast epimerization of the β-phosphate to the α-phosphate when higher amounts of the catalysts were used. Next, CPAs with various electron withdrawing groups at the aryl rings of 3,3'-BINOL positions were evaluated with **α-4-10** (Entry 3-14). In general, the glycosylation reaction was carried out efficiently at room temperature with stirring for 12 h. The general trend was that (*S*)-catalyst promoted better C3-regioselectivity and β-stereoselectivity than the corresponding (*R*)-catalyst.

Like in the case of CPA-catalyzed glycosylation of 2-deoxystreptamine (Chapter 3), **(*S*)-3I** provided greater stereo- and regio-selectivity (entry 6), but the best C3-selectivity was obtained with C_6F_5-containing catalyst **(*S*)-3H**, which provided 79:21 = C3:C2 ratio, and high stereoselectivity of α:β = 87:13 (entry 8). **(*R*)-4I** also provided high C3-selectivity result (C3:C2 = 75:25) and excellent β-stereoselectivity (α:β = 6:94) with 70% conversion (Entry 13). Next, the glycosylation reaction with anomeric β-glycosyl donor **β-4-10** were performed (entry 15-17). As expected from the prior studies (Section 4.4), α-selectivity was favored with the β-donor **β-4-10**. Compared to the α donor **α-4-10**, **β-4-10** provided diminished C3-selectivity, which was consistent

Table 4. 6. CPA-catalyzed glycosylations of 6-deoxyglucose donor **4-10** and acceptor **4-4**.



Entry	Donor	Catalyst	Conv (%)	α-C_3 : β-C_3 : α-C_2 : β-C_2	α : β	C_3 : C_2
1	α	$(PhO)_2PO_2H$ (1 equiv)	90	**50.19** : 6.70 : **30.48** : 12.61	**81:19**	**57:43**
2	α	$(PhO)_2PO_2H$	60	10.73 : **52.66** : 10.61 : **25.99**	**21:79**	**63:37**
3	α	(***R***)-**2N**	70	10.40 : **64.4** : 6.01 : **19.21**	**17:83**	**75:25**
4	α	(***S***)-**2N**	70	5.27 : **68.06** : 3.46 : **23.21**	**9:91**	**72:28**
5	α	(***R***)-**3I**	70	7.50 : **64.66** : 5.45 : **22.38**	**13:87**	**72:28**
6	α	(***S***)-**3I**	70	6.49 : **58.51** : 3.74 : **31.24**	**10:90**	**65:35**
7	α	(***R***)-**3H**	55	19.36 : 55.40 : 6.81 : 18.44	**26:74**	**75:25**
8	α	(***S***)-**3H**	60	9.67 : **69.66** : 3.41 : **17.26**	**13:87**	**79:21**
9	α	(***R***)-**3E**	45	11.52 : **43.61** : 11.97 : **32.90**	**24:76**	**55:45**
10	α	(***S***)-**3E**	40	7.42 : **58.70** : 7.80 : **26.09**	**15:85**	**66:34**
11	α	(***R***)-**3B**	45	12.80 : **42.59** : 8.95 : **35.67**	**22:78**	**55:45**
12	α	(***S***)-**3E**	35	8.03 : **55.77** : 5.11 : **31.09**	**13:87**	**63:77**
13	α	(***R***)-**4I**	70	4.64 : **70.49** : 1.53 : **23.34**	**6:94**	**75:25**
14	α	(***S***)-**2Q**	60	10.72 : **55.47** : 5.49 : **28.31**	**16:84**	**66:34**
15	β	$(PhO)_2PO_2H$	55	**40.82** : 10.20 : **41.22** : 8.16	**82:18**	**51:49**
16	β	(***R***)-**3I**	40	**45.55** : 21.9 : **21.69** : 10.85	**67:33**	**67:33**
17	β	(***R***)-**2N**	35	**43.14** : 25.49 : **19.61** : 11.76	**63:37**	**69:31**
18	α	(***R***)-**2K**	40	3.49 : **37.75** : 2.66 : **56.09**	**6:94**	**41:59**
19	α	(***R***)-**4B**	20	2.63 : **35.95** : 2.85 : **58.57**	**5:95**	**39:61**
20	α	(***R***)-**2J**	40	2.05 : **23.18** : 2.35 : **72.43**	**4:96**	**25:75**
21	α	(***S***)-**4B**	<5	3.55 : **53.69** : 5.18 : **37.57**	**9:91**	**57:43**
22	α	(***S***)-**2J**	20	2.46 : **55.11** : 3.68 : **38.74**	**6:94**	**58:42**
23	α	(***R***)-**4E**	10	16.71: **27.43** : 13.71 : **42.15**	**30:70**	**44:56**
24	α	(***R***)-**4F**	45	15.93 : **35.09** : 20.85 : **28.12**	**37:63**	**51:49**
25	α	(***R***)-**4G**	40	19.09 : **39.96** : 17.98 : **22.97**	**37:63**	**59:41**

Conditions : **4-4** (1 equiv), **4-10** (1.4 equiv), catalyst (15 mol%), DCM (0.04M)
Regio- and stereoselectivity was measured by 1H NMR + HPLC assay.

with what was typically observed for the reactions with other β-donors (Section 4.3 and 4.6).

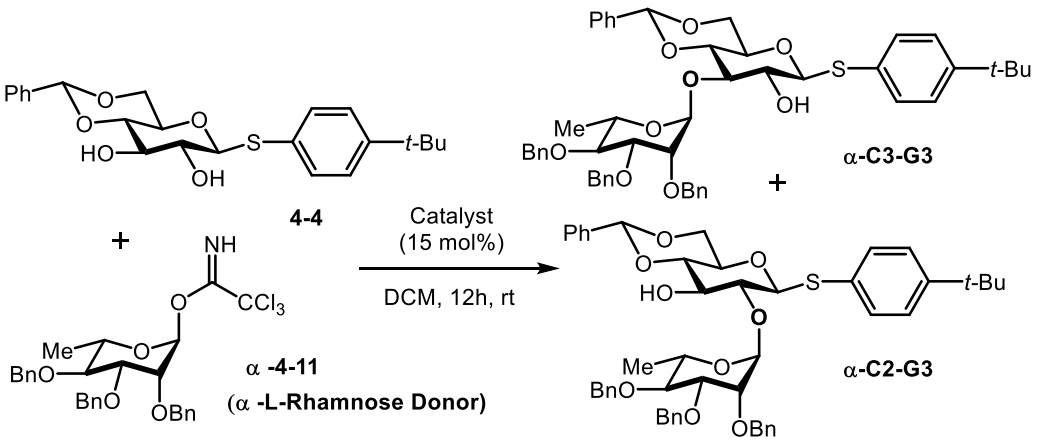
At this point, we identified catalysts that helped to achieve control over α- or β-selectivities and enhance the C3-regioselectivity. However, there was still one missing piece that we were very interested in, which was developing conditions for controlling the C2-regioselectivity. Unfortunately, using enantiomeric catalysts did not result in regioselectivity switch (entry 3-14). As a result, CPAs with electron donating substituents on the aryl groups at the 3,3'-positions of BINOL were evaluated. While such catalysts were not effective in promoting glycosylation reactions with donor **α-4-2**, the glycosylation reaction with more reactive donor **α-4-10** was now successfully promoted (entry 18-25). (*R*)-CPA catalysts could now favor reversed selectivity resulting in C2-selective glycoside formation (entry 18-20, 23). Among them, **(*R*)-2J** provided the best C2-selectivity (C3:C2 = 25:75) with excellent β-selective stereochemistry (α:β = 4:96) (entry 20). In general, (*R*)-CPA was found to favor C2-selectivity and (*S*)-CPA was found to favor C3-selectivity, and both catalysts promoted glycosylation to generate β-selective glycosides.

4.7 CPA-catalyzed glycosylation reactions with other deoxy-sugar donors

The prior studies with acceptor **4-4** and donor **4-10** helped to identify **(*S*)-3H** as the catalyst that favors C3-selectivity, and catalyst **(*R*)-2J** that provided highest C2-selectivity for the formation of the corresponding disaccharide. Our subsequent studies were focused on identifying other glycosyl donors that follow these trends. To do so, the same acceptor **4-4** was reacted with different deoxy-sugars (**α-4-11, α-4-12, α-4-13**).

Our studies commenced with L-rhamnose derivative **α-4-11**. The glycosylation with acceptor **4-4** and donor **α-4-11** was evaluated with 11 different catalysts, which provided various levels of regiocontrol (Table 4.7). Unlike the prior studies, the reaction with L-rhamnose donor **α-4-11** resulted in the formation of α-glycosides **α-C2-G3** and **α-C3-G3** as products. The reaction

Table 4. 7. Glycosylation reaction with acceptor **4-4** and α-L-rhamnose donor **4-11**.



Entry	Catalyst (15 mol%)	Yield (%)	α-C_2 : α-C_3
1	$(PhO)_2PO_2H$	20	50 : 50
2	**(*R*)-2N**	80	58 : 42
3	**(*S*)-2N**	70	64 : 36
4	**(*R*)-4I**	50	52: 48
5	**(*S*)-3H**	65	**29 : 71**
6	**(*S*)-3I**	55	48 : 52
7	**(*R*)-2J**	65	**88 : 12**
8	**(*R*)-2K**	20 (80)	**84 : 16**
9	**(*R*)-4H**	<1 (<1)	-
10	**(*R*)-4E**	5 (~10)	71 : 29
11	**(*R*)-4B**	5 (~10)	79 : 21

Conditions : **4-4** (1 equiv), **4-11** (1.4 equiv), catalyst (15 mol%), DCM (0.04M) Regio- and stereo-selectivity was measured by 1H NMR. ( ) : reaction at 36 ^{o}C for 12 h,

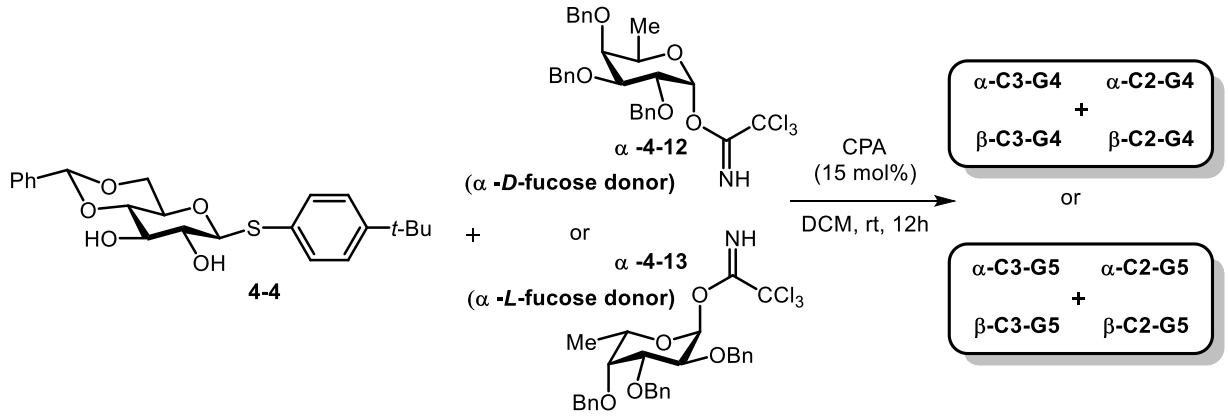
was very efficient in most of cases, and no inherent regioselectivity trends were observed as the achiral diphenyl phosphoric acid provided C3:C2 = 50:50 selectivity (entry 1). The results of screening different CPAs provided the same general trend as before. Thus, (*S*)-CPAs favored **α-C3-G3** and (*R*)-CPAs favored **α-C2-G3** as the product. As before, more acidic catalysts containing electron withdrawing substituents were more effective in promoting higher conversions. Compared to the glycosylation with donor **α-4-10** (Section 4.6), the same trends were observed for

the glycosylation with α-L-rhamnose donor **4-11** as the catalyst **(*S*)-3H** provided the highest C3-selectivity (C3:C2 = 71:29, entry 5), and **(*R*)-2J** provided the highest C2-selectivity (C3:C2 = 12:88, entry 7). These results suggest that generality in donor scope may be achieved, and that regiodivergent catalyst-controlled glycosylations are possible with two different catalysts. In addition to **(*R*)-2J**, **(*R*)-2K** also promoted C2-selective glycosylation reaction, but the conversion in this case was significantly lower, and elevated temperature was required to enhance the reaction rate.

Next, D-fucose donor **α-4-12** was selected for the glycosylation study. The benzylated fucose trichloroacetimidate **α-4-12** and the acceptor **4-4** were reacted with different CPAs as the catalysts (Table 4.8 entry 1-5). It was gratifying to see that **(*S*)-3H** promoted the glycosylation reaction very efficiently (95% conversion) with high C3 regioselectivity (C3:C2 = 91:9) and with high β stereoselectivity (α:β = 15:85) (entry 4). Unlike the previously observed for **α-4-10** and **α-4-11** trends, the reaction catalyzed with CPA **(*R*)-2J** favored C3- products as ~1:1 mixture of α- and β- isomers (entry 5).

The fact that glycosylation reaction with L-rhamnose donor **α-4-11** favored the C2- product **α-C2-G3**, and D-fucose donor **α-4-12** favored C3-glycosylated product promoted us to consider the effect of switching the donor enantiomeric configuration (D- or **L**-). For that reason, benzylated L-fucose trichloroacetimidate donor **α-4-13** was prepared and subjected to the glycosylation reaction with accept **4-4** and CPA catalysts **(*S*)-3H** and **(*R*)-2J** (Table 4.8, entries 6-7). Interestingly, both regioselectivity and stereoselectivity of glycosylation reaction with D-and L-fucose donors **α-4-12** and **α-4-13** were different. The glycosylation reaction with D-fucose **α-4-12** provided very high C3-regioselectivity, whereas for the glycosylation reaction with L-fucose **α-4-13**, the regioselectivity favored C2-glycosides. While **(*S*)-3H** provided C3:C2 = 91:9 with D-fucose

Table 4. 8. Glycosylation reaction with acceptor **4-4** and α-D-fucose donor **4-12** and α-L-fucose donor **4-13**.



Entry	donor	CPA	Conv (%)	α-C_3 : α-C_2 : β-C_3 : β-C_2	α : β	C_3 : C_2
1	α **-4-12**	**(*S*)-3I**	45	45.1 : 9.8 : 37.6 : 7.5	55:45	83:17
2	α **-4-12**	**(*S*)-2N**	60	33.3 : 11.9 : 45.7 : 9.1	45:55	79:21
3	α **-4-12**	**(*S*)-4J**	50	18.1 : 2.0 : 69.1 : 10.8	20:80	87:13
4	α **-4-12**	**(*S*)-3H**	95	13.3 : 1.33 : 77.5 : 7.9	**15:85**	**91:9**
5	α **-4-12**	**(*R*)-2J**	20 (70[a])	25.6 : 20.5 : 42.2 : 11.8	45:55	68:32
6	α **-4-13**	**(*S*)-3H**	95	63.7 : 8.3 : 10.2 : 17.8	72:28	**74:26**
7	α **-4-13**	**(*R*)-2J**	20 (40[a])	17.8 : 3.7 : 4.4 : 74.1	21:79	**22:78**

Condition : **4-4** (1 equiv), **4-12** or **4-13** (1.4 equiv), CPA (15 mol%) DCM (0.04M) Regio- and stereoselectivity was measured by 1H NMR, [a]reaction at 36 °C for 24h

donor **α-4-12** (Table 4.8, entry 4), the regioselectivity of C3:C2 = 74:26 was obtained with L-fucose donor **α-4-13** (Table 4.8, entry 6). Similarly, with D-fucose donor case, **(*R*)-2J** did not favor the formation of the C2-product (C3:C2 = 68:32, Table 4.8, entry 5), whereas C2-regioselectivity (C3:C2 = 22:78) was obtained with L-fucose donor from **(*R*)-2J** (Table 4.8, entry 7). These observations suggest that the chirality of sugar donor can affect the stereoselectivity and regioselectivity of the glycosylation reactions with chiral catalysts.

4.8 Conclusions

In this chapter, we summarized our studies on the regioselective and stereoselective glycosylation reactions catalyzed by CPAs. Initial studies were focused on identifying the suitable donors and acceptors, and then, different CPA catalysts were employed to pose control over the regioselectivity and stereoselectivity in their glycosylation reactions. In general, the stereochemistry of the donor impacted the observed stereoselectivity result. Thus, α-donors favored β-selective glycosylations and β-donors favored α-selective glycosylations. These observations were rationalized by a S_Ni mechanism, which suggested that the sugar donor reacts with CPA to form covalent glycosyl phosphate, and the nucleophilic attack happens from the face of phosphate departure due to the hydrogen bonding interaction between the phosphate and the hydroxyl groups of acceptor. Increasing loadings of CPA facilitated the epimerization of β-phosphate to the α-phosphate, therefore the α-glycoside was obtained as the major product. Regioselectivity was not only catalyst-dependent, but also donor chirality-dependent. Depending on the specific enantiomer of the sugar donor (D- and L-), the trends were reversed. From the observation of D- and L-fucose-based donors, D-sugar donors favored C3-selective glycosylation, whereas L-sugar donors favored C2-selective glycosylation reactions. Even though these factors affected the regioselectivity of glycosylation, **(*S*)-3H** promoted C3-selective glycosylation and **(*R*)-2J** promoted C2-selective glycosylations of acceptor **4-4**. We expect that the described results will be further optimized and generalized, and this would provide comprehensive insights on the role of CPAs in control of selective glycosylation reactions.

4.9 Experimental information

Methods and Reagents :

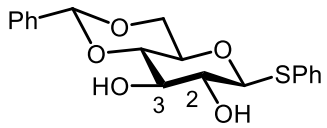
Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Tetrahyrofuran (THF), dichloromethane (DCM) and diethyl ether (Et_2O) were filtered through a column (Innovative Technology PS-MD-5) of activated alumina under nitrogen atmosphere. All reactions were carried out under an atmosphere of nitrogen in flame- or oven-dried glassware with magnetic Fstirring. Reactions were cooled using Neslab Cryocool CB-80 immersion cooler (0 to -60 °C) and Neslab Cryocool immersion cooler CC-100 II, or via external cooling baths: ice water (0 °C), sodium chloride/ ice water (-10 °C), or dry ice/acetone (-78°C). Heating was achieved by use of a silicone bath with heating controlled by electronic contact thermometer. Deionized water was used in the preparation of all aqueous solutions and for all aqueous extractions. Solvents used for extraction and chromatography were ACS or HPLC grade. Purification of reactions mixtures was performed by flash column chromatography on SiO_2 using SiliCycle SiliaFlash P60 (230-400 mesh). Diastereomeric ratios were determined by 1 H NMR analysis. Enantiomeric excess was determined by HPLC analysis using a Waters e2695 Separations Module with a Waters 2998 photodiode array detector.

Instrumentation :

All spectra were recorded on Varian vnmrs 700 (700 MHz), Varian vnmrs 500 (500 MHz), Varian MR400 (400 MHz), Varian Inova 500 (500 MHz) spectrometers and chemical shifts (δ) are reported in parts per million (ppm) and referenced to the ^1H signal of the internal tetramethylsilane according to IUPAC recommendations. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, m = multiplet; coupling constant(*S*) in Hz; integration). High resolution mass spectra (HRMS) were recorded on MicromassAutoSpecUltima

or VG (Micromass) 70-250-S Magnetic sector mass spectrometers in the University of Michigan mass spectrometry laboratory. Infrared (IR) spectra were recorded as thin films on NaCl plates on a Perkin Elmer Spectrum BX FT-IR spectrometer. Absorption peaks were reported in wavenumbers (cm^{-1}).

CPA-catalyzed Glycosylation of 4-1 and 4-2 (Table 4.1)



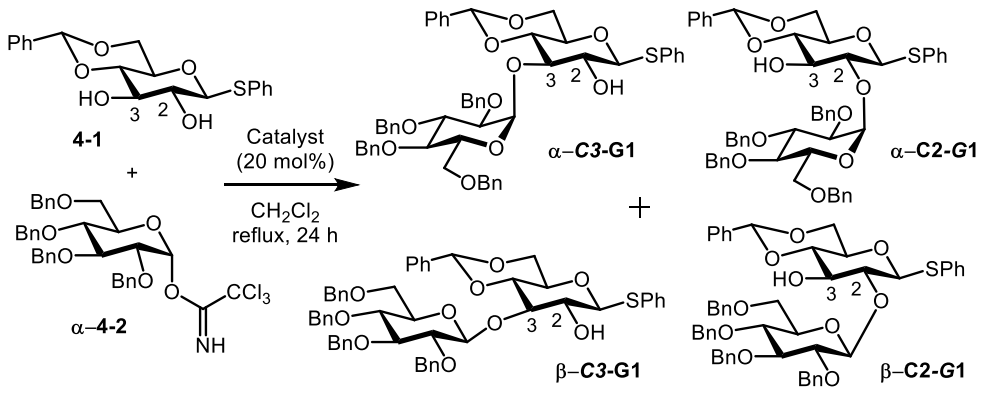
4-1

(*2R,4aR,6S,7R,8R,8aS*)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-d][1,3]dioxine-7,8-diol (4-1).

To a solution of (*2R,3S,4S,5R,6S*)-2-(hydroxymethyl)-6-(phenylthio)tetrahydro-2H-pyran-3,4,5-triol (2.3 g, 8.45 mmol) and $PhCH(OMe)_2$ (1.66 mL, 11.0 mmol) in dry CH_3CN (45 mL) was added p-TsOH (78 mg 0.42 mmol). The reaction mixture was stirred at 60 °C overnight. The resulting mixture was neutralized by Et_3N (3.0 mL), diluted with EtOAc (50 mL), then washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on a silica gel (10:1, Hexanes-EtOAc). Compound **4-1** as a white solid, yield 2.22 g (75%).

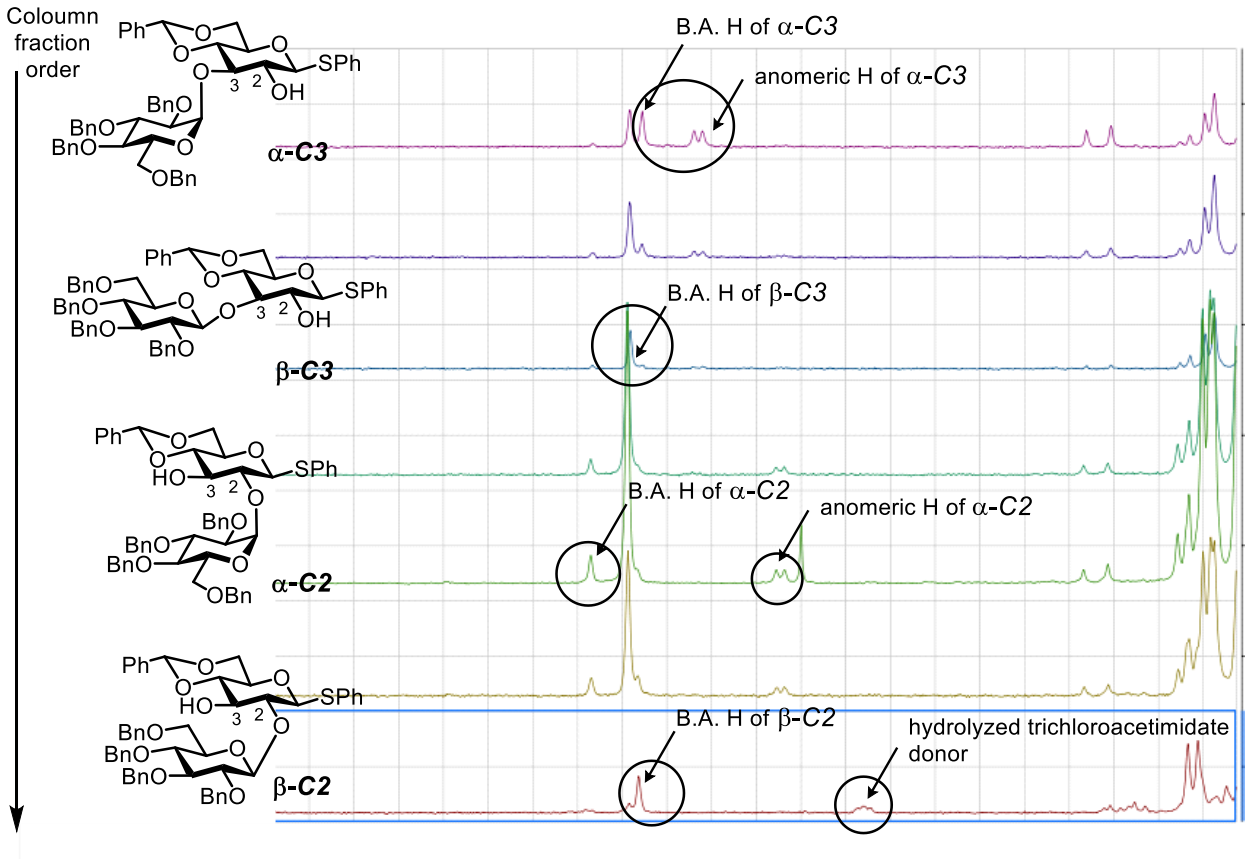
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.60 – 7.51 (m, 2H), 7.50 – 7.44 (m, 2H), 7.39 – 7.29 (m, 6H), 5.53 (s, 1H), 4.63 (dd, *J* = 9.7, 1.2 Hz, 1H), 4.40 – 4.36 (m, 1H), 3.84 (t, *J* = 8.2 Hz, 1H), 3.81 – 3.75 (m, 1H), 3.57 – 3.50 (m, 2H), 3.47 (t, *J* = 9.1 Hz, 1H), 2.88 (s, 1H), 2.73 (s, 1H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 136.98, 133.22 (2C), 131.40, 129.48, 129.28 (2C), 128.64, 128.51

(2C), 126.42 (2C), 102.09, 88.76, 80.34, , 74.72, 72.73, 70.69, 68.72. **HRMS (ESI+) (*m/z*):** $[M+Na]^+$ calcd for $C_{19}H_{20}NaO_5S$ 383.0929, found 383.0923.



General Procedure:

A flame-dried 2 dram vial was charged with the D-glucose-derived 2,3-diol **4-1** (1.0 equiv), D-glucose trichloroacetimidate donor **4-2** (1.4 equiv) and chiral phosphoric acid (CPA) catalyst (0.02 equiv). The resulting mixture was flushed with nitrogen, then dry DCM (0.04M) was added. The resulting mixture was refluxed for 1day, then quenched with triethylamine. The mixture was purified by a flash column chromatography on SiO_2 (10:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate). Purification resulted in some mixed fractions of hydrolyzed donor with glycosylated product **G1** and fractions of pure isomeric mixture of glycosylation products **G1**. All fractions containing glycosylation products were combined and concentrated to afford a colorless oil.



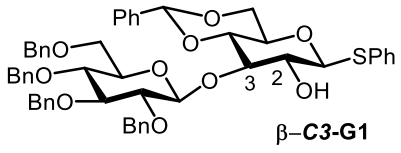
In order to measure the selectivity, an NMR study and reverse phase HPLC (RP HPLC) assay were carried out. For the NMR assay, the crude mixture of glycosylation product was purified by flash column chromatography on SiO_2 and distinct proton peaks, such as the proton adjacent to the benzylidine acetal and anomeric proton, of each isomer were assigned. Using that information, each isomer's distinct proton peak in the NMR of a crude product mixture was integrated and then the selectivity was measured. However, there was a limitation to this approach due to the overlap of the proton peak of one isomer with the proton peak of another to isomer as well as the the proton peaks of the side products. For these reasons, a reverse phase HPLC assay was developed. In order to measure the desired selectivity more accurately, relatively clean samples of the four different isomers were injected to the reverse phase HPLC. Once the retention

time of each isomer was found, the crude product mixture was injected to the reverse phase HPLC and then the peaks corresponding to each isomer were integrated to determine the selectivity between isomers. The conditions and retention time results are following:

Reverse phase HPLC (Shimadzu Prominence SPD M20A, 3.9*150mm C18 column, 77% acetonitrile in water with isocratic flow):

Retention time: **α-C3** : 14.647 min, **β-C3**: 15. 277 min, **α-C2** : 16.973 min, **β-C2**: 17. 115 min.

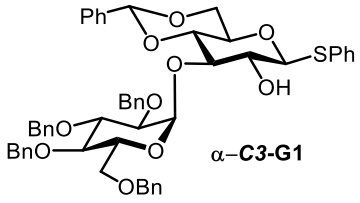
Under these conditions, the retention times of two isomers (α-C2 and β-C2) were close enough to complicate the integration, and these ratios were determined by NMR. Fortunately, combination of selectivity information from the NMR and RP HPLC provided complementary results. The glycosylation reactions of diol **4-1** and α-trichloroacetimidate **4-2** were carried out with various chiral phosphoric acids with different substitution at the 3- and 3'- position of the BINOL backbone. The selectivity between 4 isomers was determined from the crude mixture by using the aformentioned NMR and HPLC analysis.



β–***C3*-G1**

(*2R,4aR,6S,7R,8aR*)-2-phenyl-6-(phenylthio)-8-(((*2S,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)hexahydropyrano[3,2-d][1,3]dioxin-7-ol (**β-C3-G1**).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.55 – 7.50 (m, 2H), 7.48 – 7.42 (m, 2H), 7.38 – 7.26 (m, 19H), 7.26 – 7.22 (m, 6H), 7.13 (dd, *J* = 6.9, 2.6 Hz, 2H), 5.49 (s, 1H), 4.88 – 4.79 (m, 4H), 4.76 (d, *J* = 10.8 Hz, 1H), 4.69 (d, *J* = 7.8 Hz, 1H), 4.64 (d, *J* = 9.8 Hz, 1H), 4.52 (dd, *J* = 11.5, 4.7 Hz, 2H), 4.40 (d, *J* = 12.1 Hz, 1H), 4.33 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.89 (t, *J* = 8.9 Hz, 1H), 3.76 (t, *J* = 10.3 Hz, 1H), 3.67 – 3.57 (m, 6H), 3.53 (t, *J* = 8.3 Hz, 1H), 3.45 (dtd, *J* = 25.7, 9.1, 8.7, 3.7 Hz, 2H), 3.34 (q, *J* = 4.1 Hz, 1H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 138.48, 138.33, 138.13, 137.79, 137.32, 133.27, 131.95, 129.09, 128.69, 128.56, 128.54, 128.51, 128.45, 128.43, 128.33, 128.23, 128.17, 128.07, 128.01, 127.93, 127.92, 127.83, 127.71, 126.38, 103.33, 101.50, 88.04, 85.30, 84.16, 81.98, 78.52, 78.05, 75.73, 75.40, 75.20, 75.11, 73.78, 72.80, 71.22, 68.92, 68.70. **HRMS (ESI+) (*m/z*):** $[M+Na]^+$ calcd for $C_{53}H_{54}NaO_{10}S$ 905.3335, found 905.3351.



α–***C3*-G1**

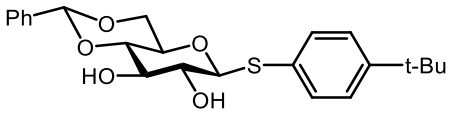
(*2R,4aR,6S,7R,8R,8aR*)-2-phenyl-6-(phenylthio)-8-(((*2R,3R,4S,5R,6R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)hexahydropyrano[3,2-d][1,3]dioxin-7-ol (α-C3-G1).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.52 (d, *J* = 7.0 Hz, 2H), 7.39 (d, *J* = 7.4 Hz, 2H), 7.37 – 7.26 (m, 17H), 7.23 (d, *J* = 7.0 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.11 – 7.04 (m, 4H), 6.87 (d, *J* = 7.5 Hz, 2H), 5.48 (s, 1H), 5.42 (d, *J* = 3.6 Hz, 1H), 4.97 (d, *J* = 10.9 Hz, 1H), 4.76 (dd, *J* = 10.8, 4.0 Hz, 2H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.54 (dd, *J* = 19.4, 11.0 Hz, 2H), 4.42 (t, *J* = 11.1 Hz, 2H), 4.37 (dd, *J* = 10.7, 5.1 Hz, 1H), 4.32 – 4.25 (m, 2H), 4.02 (t, *J* = 9.1 Hz, 1H), 3.92 (t, *J* = 9.3 Hz, 1H), 3.74 (ddd, *J* = 29.5, 15.6, 6.8 Hz, 3H), 3.64 (d, *J* = 10.5 Hz, 1H), 3.61 – 3.53 (m, 2H), 3.52 –

3.44 (m, 2H), 2.75 (s, 1H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 163.38, 138.85, 138.13, 137.82, 137.53, 136.92, 133.69, 130.41, 129.44, 129.15, 128.64, 128.44, 128.36, 128.32, 128.14, 128.08, 128.06, 127.83, 127.73, 127.48, 127.41, 126.36, 102.07, 96.48, 88.73, 81.59, 81.05, 78.49, 78.01, 77.44, 75.63, 75.15, 73.51, 71.19, 70.63, 70.59, 69.98, 68.72, 68.32. **HRMS (ESI+) (*m*/*z*):** $[M+Na]^+$ calcd for $C_{53}H_{54}NaO_{10}S$ 905.3335, found 905.3351.

α-C2-G1 and **β-C2-G1** were inseparable.

CPA-catalyzed Glycosylation of 4-4 and 6-deoxy glucose donor 4-10 (Table 4.6).



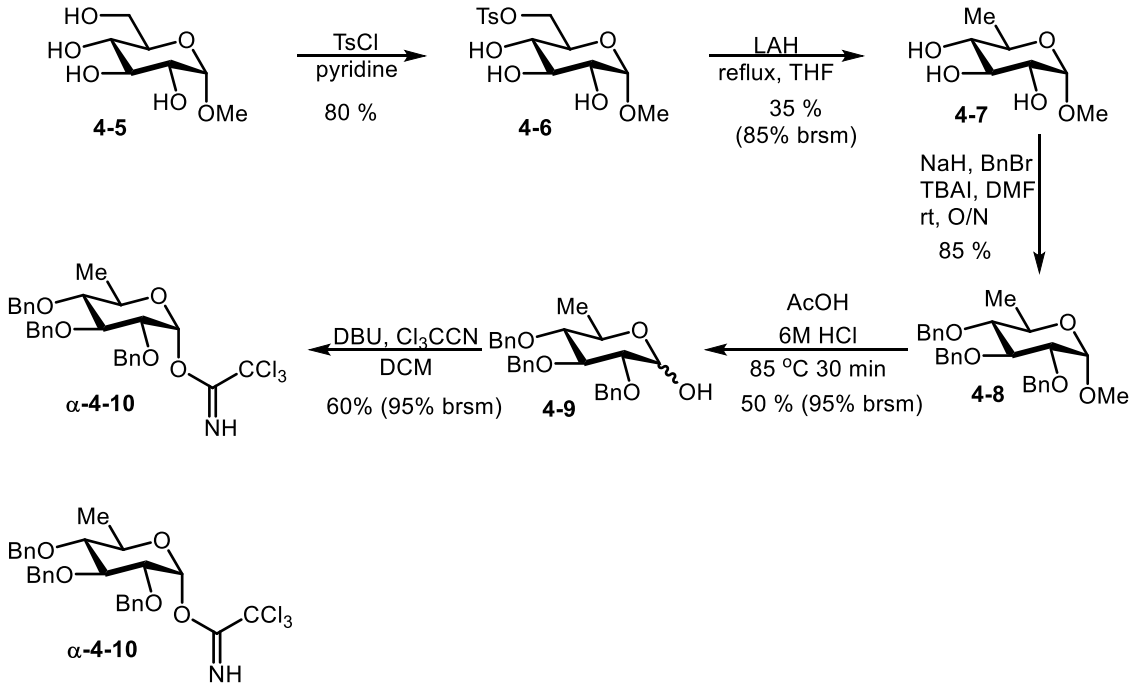
4-4

(2R,4aR,6S,7R,8R,8aS)-6-((4-(tert-butyl)phenyl)thio)-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diol (**4-4**).

To a solution of glucose tetraol phenyl thioglycoside (2.5 g, 7.61 mmol) and $PhCH(OMe)_2$ (1.49 mL, 9.90 mmol) in dry CH_3CN (50 mL) was added p-TsOH (65.5 mg 0.38 mmol). The reaction mixture was stirred at 60°C overnight. The resulting mixture was neutralized by Et_3N (3.0 mL), diluted with EtOAc (50 mL), then washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography on a silica gel (10:1, Hexanes-EtOAc). Compound **4-4** as a white solid, yield 1.85g (68%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.53 – 7.44 (m, 4H), 7.39 – 7.32 (m, 5H), 5.53 (s, 1H), 4.59 (d, *J* = 9.7 Hz, 1H), 4.39 (dd, *J* = 10.6, 3.5 Hz, 1H), 3.89 – 3.75 (m, 2H), 3.56 – 3.49 (m, 2H), 3.45 (t, *J* = 9.2 Hz, 1H), 2.79 (s, 1H), 2.65 (s, 1H), 1.33 (s, 9H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 152.12, 137.01, 133.40 (2C), 132.47, 129.47, 128.50 (2C), 127.48, 126.41 (2C), 126.38 (2C),

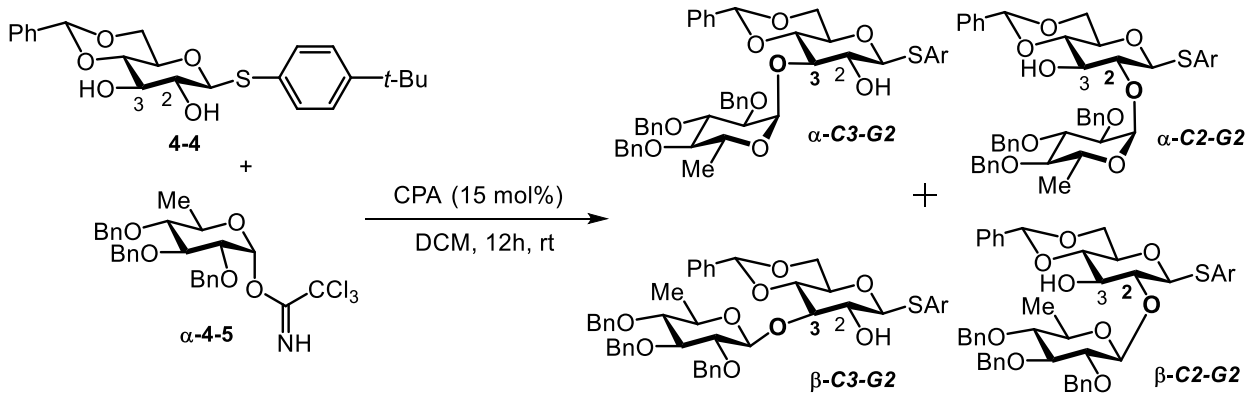
102.08, 88.90, 80.37, 74.71, 72.64, 70.71, 68.75, 34.83, 31.37 (3C). **HRMS (ESI+) (*m*/*z*):** $[M+Na]^+$ calcd for $C_{23}H_{28}NaO_5S$ 439.1555, found 439.1447.



(2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-*tris*(benzyloxy)-6-methyltetrahydro-2H-pyran-2-yl 2,2,2-trichloroacetimidate (**α-4-10**).

An oven dried and nitrogen flushed 250 mL round bottom flask was charged with **4-9** (440 mg, 1.01 mmol) and dry DCM (10 mL). The reaction mixture was cooled down to 0 °C and trichloroacetonitrile (0.31 mL, 3.04 mmol) was added, followed by 1,8-diaza bicyclo(5,4,0)undec-7ene (45 µL, 0.30 mmol). The resulting reaction mixture was warmed up to room temperature and stirred for 3 h. The crude product was purified by a flash column chromatography on SiO_2 (1% Et_3N and 10 : 1 to 5 : 1 hexanes/ethyl acetate) resulting in the pure product **4-10** as a clear oil (α: 250 mg, 43%, β: 180 mg, 31%).

α-product: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.55 (s, 1H), 7.38 – 7.28 (m, 15H), 6.40 (d, *J* = 3.5 Hz, 1H), 5.00 – 4.88 (m, 2H), 4.83 (d, *J* = 10.9 Hz, 1H), 4.77 – 4.62 (m, 3H), 4.08 – 3.89 (m, 2H), 3.72 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.22 (t, *J* = 9.4 Hz, 1H), 1.27 (d, *J* = 6.2 Hz, 3H). **HRMS (ESI+) (*m*/*z*):** $[M+Na]^+$ calcd for $C_{29}H_{30}NaNO_5Cl_3$ 600.1087, found 600.1079.



General Procedure:

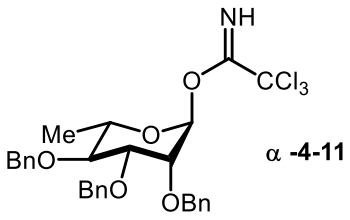
A flame-dried 1 dram vial was charged with the 2,3-diol **4-4** (1.0 equiv), donor **α-4-10** (1.4 equiv) and chiral phosphoric acid (CPA) catalyst (0.015 equiv). The resulting mixture was flushed with nitrogen, then dry DCM (0.04M) was added. The resulting mixture was stirred at room temperature for 12 h, then quenched with triethylamine. The mixture was purified by a flash column chromatography on SiO_2 (10:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate). Purification resulted in some mixed fractions of hydrolyzed donor with glycosylated product **G2** and fractions of pure isomeric mixture of glycosylation products **G2**. All fractions containing glycosylation products were combined and concentrated to afford a white solid.

- The regioselectivity and stereoselectivity was measured by a reverse phase HPLC assay.

Retention time (Reverse phase HPLC assay (isocratic 87% acetonitrile in water)

α-C3-G2: 12.837 min, **β-C3-G2:** 13.928 min**, α-C2-G2:** 16.583 min, **β-C2-G2:** 17.980 min.

CPA-catalyzed glycosylation of 4-4 and L-rhamnose donor 4-11 (Table 4.7)



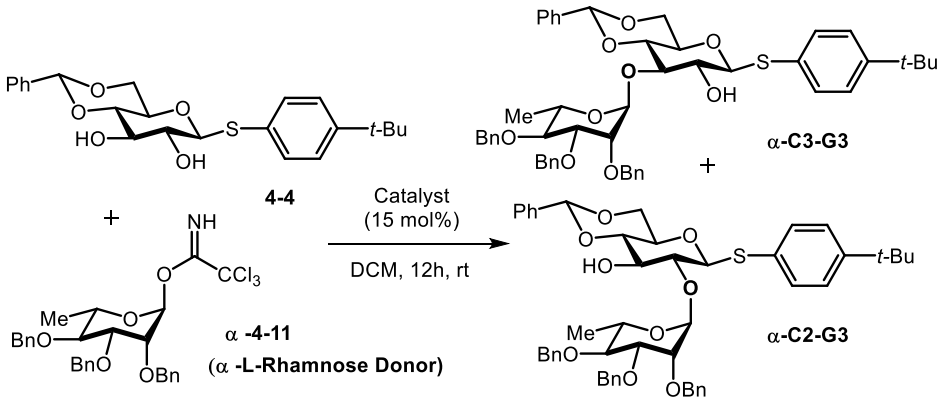
α **-4-11**

(*2S,3R,4R,5S,6S*)-3,4,5-*tris*(benzyloxy)-6-methyltetrahydro-2H-pyran-2-yl 2,2,2-trichloroacetimidate (**α-4-11**).

An oven dried and nitrogen flushed 250 mL round bottom flask was charged with the *tri-O*-benzyl-L-rhamnose with free alcohol at anomeric position (2.1 g, 4.83 mmol) and dry DCM (40 mL). The reaction mixture was cooled down to 0 °C and trichloroacetonitrile (0.97 mL, 9.67 mmol) was added, followed by 1,8-diaza bicyclo(5,4,0)undec-7ene (0.22 mL, 1.45 mmol). The resulting reaction mixture was warmed up to room temperature and stirred for 3 h. The crude product was purified by a flash column chromatography on SiO_2 (1% Et_3N and 10 : 1 to 5 : 1 hexanes/ethyl acetate) resulting in the pure product **α-4-11** as clear oil (α only 78 %).

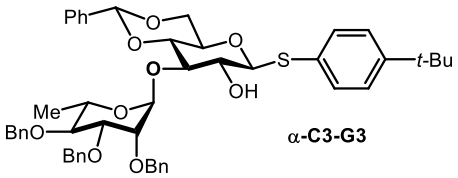
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 7.45 – 7.29 (m, 15H), 6.26 (s, 1H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.78 (s, 2H), 4.64 (dt, *J* = 23.4, 11.2 Hz, 3H), 3.97 – 3.85 (m, 3H), 3.72 (t, *J* = 9.5 Hz, 1H), 1.36 (d, *J* = 6.0 Hz, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 160.67, 138.45, 138.27, 138.04, 128.56 (2C), 128.53 (2C), 128.52 (2C), 128.33 (2C), 128.09 (4C), 127.94, 127.92, 127.86,

96.15, 91.19, 79.92, 79.03, 75.72, 73.98, 72.94, 72.47, 71.22, 18.19. **HRMS (ESI+) (*m*/*z*):** $[M+Na]^+$ calcd for $C_{29}H_{30}NaNO_5Cl_3$ 600.1087, found 600.1100.



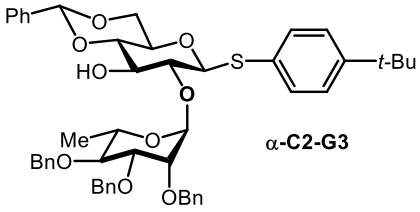
General Procedure:

A flame-dried 1 dram vial was charged with the 2,3-diol **4-4** (1.0 equiv), trichloroacetimidate donor **α-4-11** (1.4 equiv) and chiral phosphoric acid (CPA) catalyst (0.015 equiv). The resulting mixture was flushed with nitrogen, then dry DCM (0.04M) was added. The resulting mixture was stirred at room temperature for 12 h, then quenched with triethylamine. The mixture was purified by column chromatography on SiO_2 (10:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate). Purification resulted in some mixed fractions of hydrolyzed donor with glycosylated product **G3** and fractions of pure isomeric mixture of glycosylation products **G3** that were concentrated to provide a clear oil.



(*2R,4aR,6S,7R,8R,8aR*)-6-((4-(tert-butyl)phenyl)thio)-2-phenyl-8-(((*2S,3R,4R,5S,6S*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)hexahydropyrano[3,2-d][1,3]dioxin-7-ol (**α-C3-G3**).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.46 – 7.43 (m, 4H), 7.38 – 7.36 (m, 4H), 7.32 – 7.27 (m, 12H), 7.25 – 7.21 (m, 4H), 5.49 (s, 1H), 5.28 (s, 1H), 4.88 (d, *J* = 11.0 Hz, 1H), 4.71 (q, *J* = 12.6 Hz, 2H), 4.60 – 4.52 (m, 5H), 4.36 (dd, *J* = 10.6, 4.3 Hz, 1H), 4.00 (dt, *J* = 12.4, 6.2 Hz, 1H), 3.88 – 3.82 (m, 3H), 3.75 (t, *J* = 9.8 Hz, 1H), 3.54 (t, *J* = 9.2 Hz, 1H), 3.50 – 3.41 (m, 3H), 2.34 (d, *J* = 2.4 Hz, 1H), 1.33 (s, 9H), 1.00 (d, *J* = 6.2 Hz, 3H). **HRMS (ESI+) (*m/z*):** $[M+Na]^+$ calcd for $C_{50}H_{56}NaO_9S$ 855.3543, found 855.3529.

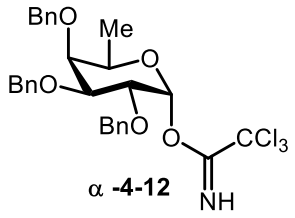


α-C2-G3

(*2R,4aR,6S,7R,8S,8aS*)-6-((4-(tert-butyl)phenyl)thio)-2-phenyl-7-(((*2S,3R,4R,5S,6S*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)hexahydropyrano[3,2-d][1,3]dioxin-8-ol (**α-C2-G3**).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 – 7.44 (m, 4H), 7.38 – 7.35 (m, 6H), 7.33 – 7.30 (m, 14H), 5.50 (s, 1H), 5.33 (d, *J* = 1.7 Hz, 1H), 4.96 – 4.93 (m, 1H), 4.80 – 4.75 (m, 1H), 4.69 – 4.63 (m, 3H), 4.57 – 4.52 (m, 2H), 4.35 (dd, *J* = 10.6, 4.3 Hz, 1H), 4.27 – 4.20 (m, 1H), 3.95 – 3.89 (m, 2H), 3.83 – 3.79 (m, 1H), 3.78 – 3.71 (m, 2H), 3.69 – 3.56 (m, 3H), 2.46 (d, *J* = 2.4 Hz, 1H), 1.37 (d, *J* = 6.2 Hz, 3H), 1.31 (s, 9H). **HRMS (ESI+) (*m/z*):** $[M+Na]^+$ calcd for $C_{50}H_{56}NaO_9S$ 855.3543, found 855.3529.

CPA-catalyzed glycosylation of 4-4 and fucose donor 4-12 and 4-13 (Table 4.8)



α **-4-12**

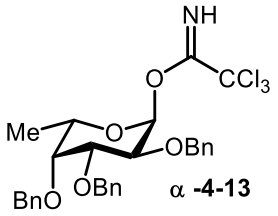
(*2R,3R,4S,5S,6R*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2H-pyran-2-yl 2,2,2-trichloroacetimidate (**α-4-12**).

An oven dried and nitrogen flushed 250 mL round bottom flask was charged with the *tri-O*-benzyl-D-fucose with free alcohol at anomeric position (295 mg, 0.68 mmol) and dry DCM (6 mL). The reaction mixture was cooled down to 0 °C and trichloroacetonitrile (0.14ml, 1.36 mmol) was added, followed by 1,8-diaza bicyclo(5,4,0)undec-7ene (30 µL, 0.203 mmol). The resulting reaction mixture was warmed up to room temperature and stirred for 3 h. The crude product was purified by a flash column chromatography on SiO_2 (1% Et_3N and 10 : 1 to 5 : 1 hexanes/ethyl acetate) resulting in the pure product **α-4-12** as white solid (α: 160 mg, 41%, β: 120 mg, 31%).

NMR spectra matched the previously reported data (*Org. Biomol. Chem*. **2014**, 12 (17), 2729-2736).

IR (film) 3343, 3064, 3030, 2935, 2904, 2874,1731, 1669, 1603, 1497, 1454, 1356, 1293, 1216, 1103, 1066, 1027, 968, 943, 838, 794, 735, 697, 644 cm-1 **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.53 (s, 1H, NH), 7.41–7.29 (m, 15H, aromatic), 6.55 (d, $J_{1,2}$ = 3.4 Hz, 1H, H-1), 5.04 (d, J = 11.5 Hz, 1H, CH-a, 4-O-Bn), 4.89 (d, J = 11.7 Hz, 1H, CH-a, 3-O-Bn), 4.80 – 4.78 (m, 3H, CH-b, 3-O-Bn, CH-a, CH-b, 2-O-Bn), 4.71 (d, J = 11.5 Hz, 1H, CH-b, 4-O-Bn), 4.27 (dd, $J_{2,3}$ = 10.0 Hz, $J_{1,2}$ = 3.4 Hz, 1H, H-2), 4.12 (q, $J_{5,6}$ = 6.4 Hz, 1H, H-5), 4.06 (dd, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 2.6 Hz, 1H, H-3), 3.74 (s, 1H, H-4), 1.19 (d, J5,6 = 6.4 Hz, 1H, H-6). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ

161.3, 138.6, 138.5, 138.4, 128.5 (2C), 128.42 (2C), 128.37 (2C), 128.29 (2C), 128.26, 127.74 (2C), 127.70, 127.6, 127.5 (2C), 95.3, 91.6, 78.3, 77.3, 75.8, 75.0, 73.2, 72.8, 69.6, 16.7;. **HRMS (ESI+) (*m*/*z*):** $[M+Na]^+$ calcd for $C_{29}H_{30}NaNO_5Cl_3$ 600.1087, found 600.1095.



α **-4-13**

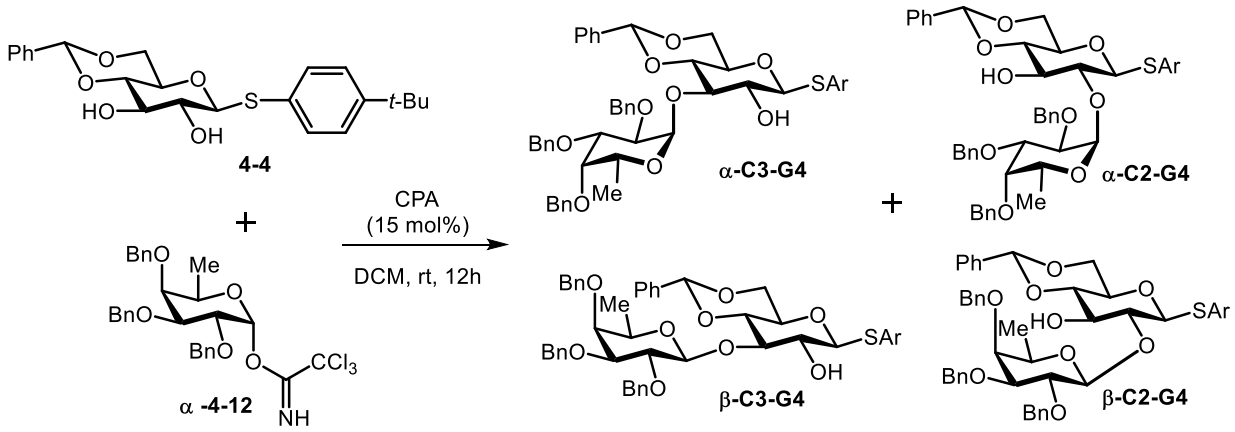
(*2S,3S,4R,5R,6S*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2H-pyran-2-yl 2,2,2-trichloroacetimidate (**α-4-13**).

An oven dried and nitrogen flushed 250 mL round bottom flask was charged with the (*3S,4R,5R,6S*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2H-pyran-2-ol (680 mg, 1.56 mmol) and dry DCM (13 mL). The reaction mixture was cooled down to 0 °C and trichloroacetonitrile (0.32 mL, 3.13 mmol) was added, followed by 1,8-diaza bicyclo(5,4,0)undec-7ene (70 µL, 0.47 mmol). The resulting reaction mixture was warmed up to room temperature and stirred for 3 h. The crude product was purified by a flash column chromatography on SiO_2 (1% Et_3N and 10 : 1 to 5 : 1 hexanes/ethyl acetate) resulting in the pure product **α-4-13** as white solid (α: 450 mg, 50%, β: 300 mg, 33%).

NMR spectra matched the previously reported data (*Chem.: Eur. J.* **2012**, 18 (46), 14671-14679).

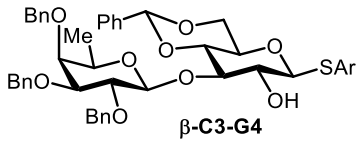
IR (film) 3343, 3064, 3030, 2935, 2904, 2874,1731, 1669, 1603, 1497, 1454, 1356, 1293, 1216, 1103, 1066, 1027, 968, 943, 838, 794, 735, 697, 644 cm^{-1}, **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.53 (s, 1H, NH), 7.41–7.29 (m, 15H, aromatic), 6.55 (d, $J_{1,2}$ = 3.4 Hz, 1H, H-1), 5.04 (d, J = 11.5 Hz, 1H, CH-a, 4-O-Bn), 4.89 (d, J = 11.7 Hz, 1H, CH-a, 3-O-Bn), 4.80 – 4.78 (m, 3H, CH-b, 3-O-Bn, CH-a, CH-b, 2-O-Bn), 4.71 (d, J = 11.5 Hz, 1H, CH-b, 4-O-Bn), 4.27 (dd, $J_{2,3}$ = 10.0 Hz,

$J_{1,2}$ = 3.4 Hz, 1H, H-2), 4.12 (q, $J_{5,6}$ = 6.4 Hz, 1H, H-5), 4.06 (dd, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 2.6 Hz, 1H, H-3), 3.74 (s, 1H, H-4), 1.19 (d, J5,6 = 6.4 Hz, 1H, H-6)**^{13}C NMR** (126 MHz, Chloroform-*d*) δ 161.3, 138.6, 138.5, 138.4, 128.5 (2C), 128.42 (2C), 128.37 (2C), 128.29 (2C), 128.26, 127.74 (2C), 127.70, 127.6, 127.5 (2C), 95.3, 91.6, 78.3, 77.3, 75.8, 75.0, 73.2, 72.8, 69.6, 16.7;. **HRMS (ESI+) (*m*/*z*):** $[M+Na]^+$ calcd for $C_{29}H_{30}NaNO_5Cl_3$ 600.1087, found 600.1097.



General Procedure:

A flame-dried 1 dram vial was charged with the 2,3-diol **4-4** (1.0 equiv), trichloroacetimidate donor **α-4-12** (1.4 equiv) and chiral phosphoric acid (CPA) catalyst (0.015 equiv). The resulting mixture was flushed with nitrogen, then dry DCM (0.04M) was added. The resulting mixture was stirred at room temperature for 12 h, then quenched with triethylamine. The mixture was purified by a flash column chromatography on SiO_2 (10:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate). Purification resulted in some mixed fractions of hydrolyzed donor with glycosylated product **G4** and fractions of pure isomeric mixture of glycosylation products **G4** as a clear oil.



β-C3-G4

(*2R,4aR,6S,7R,8R,8aR*)-6-((4-(tert-butyl)phenyl)thio)-2-phenyl-8-(((*2S,3R,4S,5S,6R*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)hexahydropyrano[3,2-d][1,3]dioxin-7-ol (β-C3-G4).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.54 – 7.42 (m, 4H), 7.38 – 7.27 (m, 20H), 5.51 (s, 1H), 4.93 (d, *J* = 11.6 Hz, 1H), 4.85 (s, 2H), 4.73 – 4.64 (m, 3H), 4.56 (dd, *J* = 19.9, 8.8 Hz, 2H), 4.34 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.98 (d, *J* = 2.1 Hz, 1H), 3.93 (dd, *J* = 9.6, 7.8 Hz, 1H), 3.82 – 3.71 (m, 2H), 3.63 – 3.49 (m, 3H), 3.47 – 3.29 (m, 3H), 1.32 (s, 9H), 1.16 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 151.63, 138.65, 138.25, 137.91, 137.36, 133.57, 128.87, 128.66, 128.61, 128.59, 128.43, 128.28, 128.10, 128.05, 127.88, 127.71, 126.26, 126.10, 104.24, 100.94, 87.83, 85.31, 83.65, 78.85, 78.52, 77.34, 77.16, 76.98, 76.04, 75.44, 74.77, 72.68, 72.47, 71.23, 70.86, 68.68, 63.11, 34.78, 31.40, 17.04. **HRMS (ESI+) (*m*/*z*):** $[M+Na]^+$ calcd for $C_{50}H_{56}NaO_9S$ 855.3543, found 855.3554.

β-C3-G4 was the major product and the only separable isomer.

4.10 References

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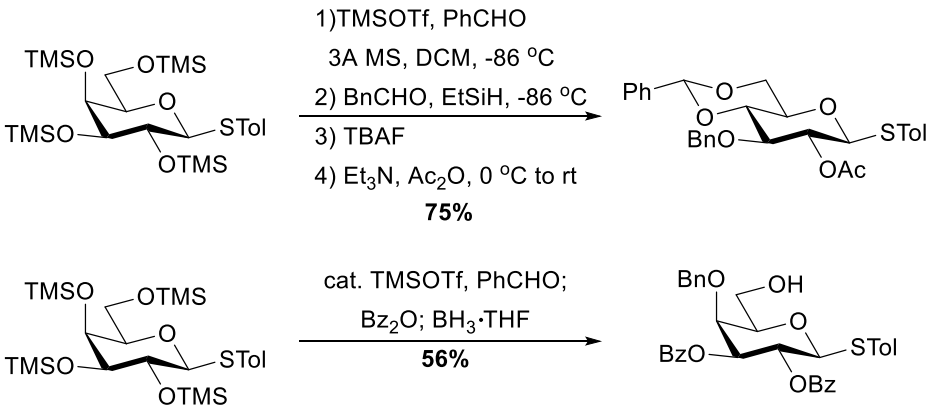
Chapter 5

Regioselective Single-Pot Functionalization of Carbohydrates Based on Chiral Phosphoric Acid Directed Regioselective Acetalization

5.1 Introduction

Carbohydrates are essential molecules that not only serve as immediate energy sources, but also are also associated with numerous biological activities.[1] Accordingly, the studies of carbohydrates have been the focus of many ongoing investigation in the fields of organic chemistry, biochemistry, and drug discovery.[2] More complex oligosaccharides are comprised of the simpler building blocks- monosaccharides. Common monosaccharides such as D-glucose, D-galactose, and D-mannose are abundant in nature, but they need to be functionalized to be useful as unique building blocks in modern carbohydrate synthesis. Functionalization of monosaccharides, however, represents a synthetic challenge as they contain many stereocenters with multiple hydroxyl groups, which have similar selectivity.[3] To address the challenges associated with selective functionalization of monosaccharides, numerous efficient methods have been previously developed.[4] Among these methods is a highly efficient single-pot procedure for regioselective protection of D-glucose through silylated intermediate by the Hung group.[5] This method allowed to achieve rapid synthesis of hundreds of monosaccharide building blocks starting with D-glucose.

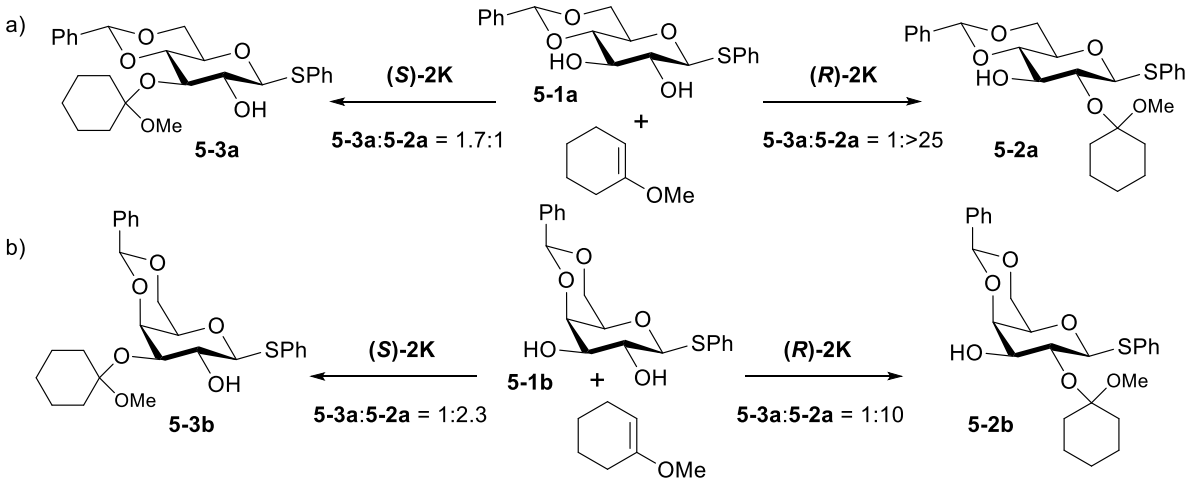
Scheme 5. 1. Hung group's single-pot regioselective protection of D-glucose.



5.2 CPA-catalyzed regioselective acetalization of carbohydrate derived 2,3-diols

Previously, our group disclosed selective functionalization of monosaccharides using 1,1'-bi-2-naphthol (BINOL)-derived chiral phosphoric acids (CPAs) as the catalysts to direct regioselective acetalization of carbohydrate-derived 2,3-diols (discussed in section 2.4).[6] Even though this study introduced a powerful method for highly regioselective installation of acetal protection in carbohydrates in an exclusively regioselective manner, there is a limitation as the regioselectivity was controlled in only one direction. In D-glucose or D-galactose substrates, exclusive C2-selectivity was obtained with the catalyst **(*R*)-2K**, but low C3-selectivity was observed with **(*S*)-2K** as the catalyst (Scheme 5.2). Based on the observations made for CPA-catalyzed glycosylations, we surmised that increased steric size for the anomeric thiophenol will result in higher selectivities for the C3-control. Therefore, we investigated acetalization of substrates **5-1d - 5-1f** (Table 5.1). Similar to the previous examples, the **(*R*)-2K** catalyzed the acetalization reaction to form C2-products selectively. Delightfully, **5-1f** could also undergo a regioselective acetalization at the C3-position when **(*S*)-2K** was employed as the catalyst (entry 3). The diol **5-1f** contains dimethyl groups in the *ortho*-positions of the anomeric thiophenol, and the *ortho*-positions

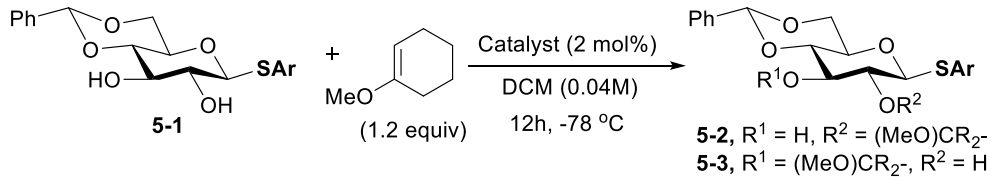
Scheme 5. 2. CPA-catalyzed C2-selective acetalization of 2,3-diol. a) D-glucose moiety. b) D-galactose moiety.

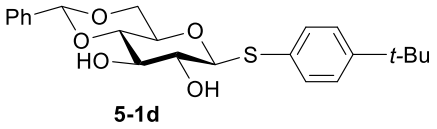
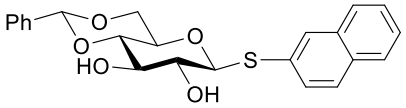
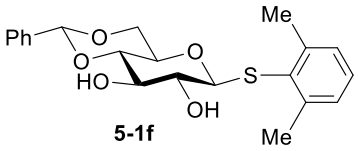


are adjacent to the C2-hydroxyl group of the diol. It is likely that the steric control comes in play to induce the **(*S*)-2K** to preferably coordinate to the C3-hydroxyl group of the diol **5-1f**. Considering that an achiral catalyst, biphenyl phosphoric acid, promoted acetalization with barely any regioselectivity, there is no inherent C3-regioselectivity exhibited by the diol substrate. This result indicates the C3-regioselectivity originates from the catalyst **(*S*)-2K** control. Interestingly, not only **(*S*)-2K**, but the commercially available (*S*)-TRIP CPA catalyst **(*S*)-2J** also catalyzed the acetalization reaction of the diol **5-1f** to provide the same C3-regioselectivity as in the **(*S*)-2K** case. Considering that prior screening experiments[6] indicated that **(*R*)-2K** induced higher C2-selectivity than **(*R*)-2J** in substrate **5-1a**, the presence of adamantyl group in the catalyst has less effect on the C3-regioselective acetalization of **5-1f**.

Table 5. 1. a) CPA-catalyzed regioselective acetalization of substituted thioglycosides **5-1d** – **5-1f**.[a] b) Structures of catalysts used for this study.

a)

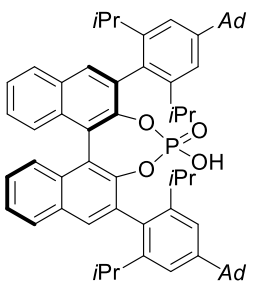


Entry	Diol starting material	Catalyst	Conv (%)	**5-2**/**5-3**[b]
1	 **5-1d**	(***R***)-**2K**	92	> 25 : 1
		(***S***)-**2K**	88	1 : 1.5
		BPPA	89	1 : 1.1
2	 **5-1e**	(***R***)-**2K**	99	> 25 : 1
		(***S***)-**2K**	45	1 : 1.6
		BPPA	94	1 : 1.2
3	 **5-1f**	(***R***)-**2K**	90	22 : 1
		(***S***)-**2K**	71	**1 : 5.6**
		BPPA	93	1 : 1.1
		(***S***)-**2J**	**90**	**1 : 5.5**

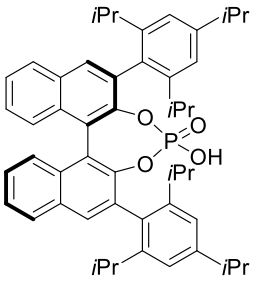
[a] Reactions were performed on 0.04 mmol scale

[b] Determined by ^{1}H NMR analysis of the crude reaction mixtures.

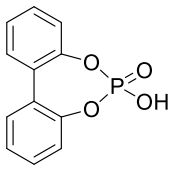
b)



(***R***)-**2K**



(***R***)-**2J**

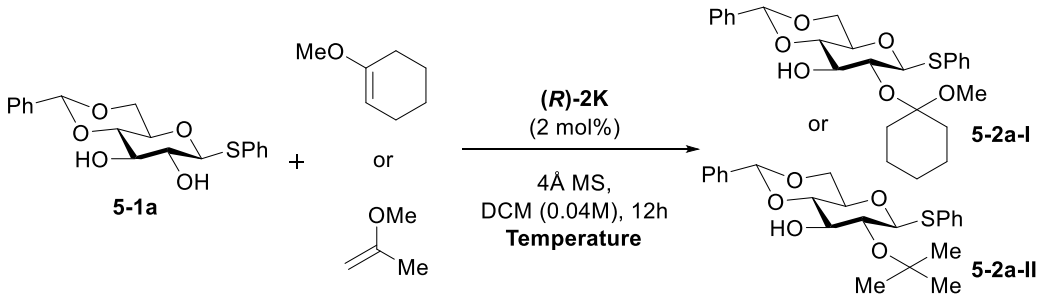


Biphenyl phosphoric acid (BPPA)

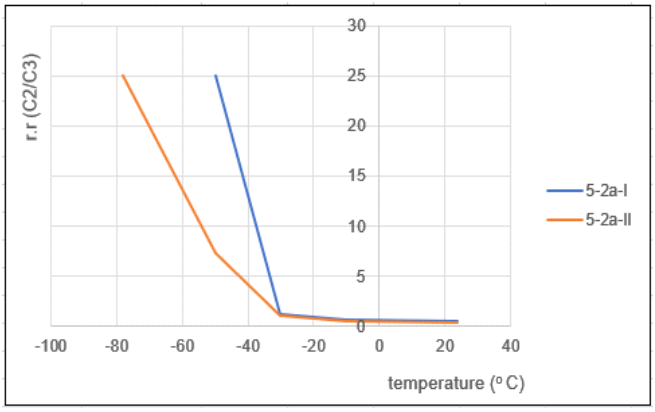
Along with the studies of anomeric substituent effect on the regioselectivity in CPA-catalyzed acetalization reactions, the role of the temperature was also examined (Figure 5.1). Both 2-methoxypropene and 1-methoxycyclohexene were subjected to the **(*R*)-2K**-catalyzed acetalization reaction of diol **5-1a** at different temperatures. Generally, the acetalization of 1-methoxycyclohexene was prone to induce higher C2-selectivity than the

reaction with 2-methoxypropene at the same temperature. The role of the reaction medium temperature was found to be very significant. At the relatively higher temperature (-10 ºC – 0 ºC), low selectivities with the slight preference for the C3-acetal were observed. Similarly, little-to-no regioselectivity was observed at -30 ºC. However, a sudden increase in the C2-regioselectivity was observed for both enol ethers at -50 ºC. At -78 ºC, the exclusive formation of C2-acetals was observed in both cases. These observations imply that there is a switch of mechanism happening at ~ -40 ºC.

Figure 5. 1. Dependence of selectivity on reaction temperature for the **(*R*)-2K**-catalyzed acetalization of **5-1a**.



Temp (°C)	C2/C3 (5-2a-I)	C2/C3 (5-2a-II)
24	0.54	0.37
-10	0.71	0.53
-30	1.20 (avg)	1.15 (avg)
-50	> 25	7.30
-78	> 25	> 25



With these results in hands, the application of this method to the synthesis of functionalized carbohydrates was investigated. The regioselective acetalization reaction resulted in derivatized monosaccharides containing strategically positioned free hydroxyl groups (C3-OH for D-glucose and D-galactose, and C2-OH for D-mannose). By utilizing

this free hydroxyl group, regioselective functionalization can be achieved, and the acetal moiety may serve as an easily removable mask for the hydroxyl group. Removal of the acetal can be accomplished under very mild, slightly acidic conditions, and it would provide another free hydroxyl group that could be further functionalized. Inspired by the studies of the Hung's group, we investigated the possibility of performing further functionalization of acetal products in a single-pot.

This chapter describes efficient and selective single-pot monosaccharides functionalization based on the following operations: selective C2-acetalization, protection of free C3-OH, selective C-2 acetal cleavage, and protection/glycosylation of resulting free C2-OH. This single-pot regioselective protection/glycosylation protocol was generally applied to generate valuable derivatives of different sugars such as D-glucose, D-galactose, and D-mannose.

5.3 Initial optimization of regioselective single-pot functionalization of monosaccharides

Our study was commenced with a selective C2-acetalization reaction. To ensure the full conversion which is essential for the subsequent studies, the acetalization reaction was stirred until completion at -50 ^{o}C with 1-methoxycyclohexene, and at -78 ^{o}C with 2-methoxypropene. Reaction monitoring revealed that the acetalization is completed in 24 h. In addition to the reaction time, the quenching temperature was also important for maintaining high conversions. From our observations, we noted that reaction should be quenched at the same temperature as the temperature at which the reaction was running. When the reaction was quenched at the room temperature, a higher amount of the starting diol **5-1a** was regenerated, and the lower overall conversions were observed. With the 24 h reaction time and low-temperature quenching step, the conversions of regioselective

acetalization of D-glucose, D-galactose, and D-mannose were consistently 99%, 99%, and 95% respectively.

To accomplish full functionalization of monosaccharide-based substrates in a single-pot, a method for the *in situ* selective acetal cleavage was also necessary. As acetals are generally acid labile, 0.05M HCl solution in DCM was prepared. This solution corresponded to the acidity range, which was required for selective cleavage of C2-acetals without deprotecting the 4,6-benzylidine acetal. In addition, high volatility of 0.05 M HCl solution in DCM was also suitable for the overall single-pot functionalization process as it could be removed without reaction work up.

5.4 Regioselective single-pot protection of carbohydrate derived 2,3-diols

After establishing a reliable method for introducing and removing C2-acetals in hand, we explored the selective functionalization of these derivatives. The following discussions are based on single-pot functionalization of D-glucose substrate **5-1a**.

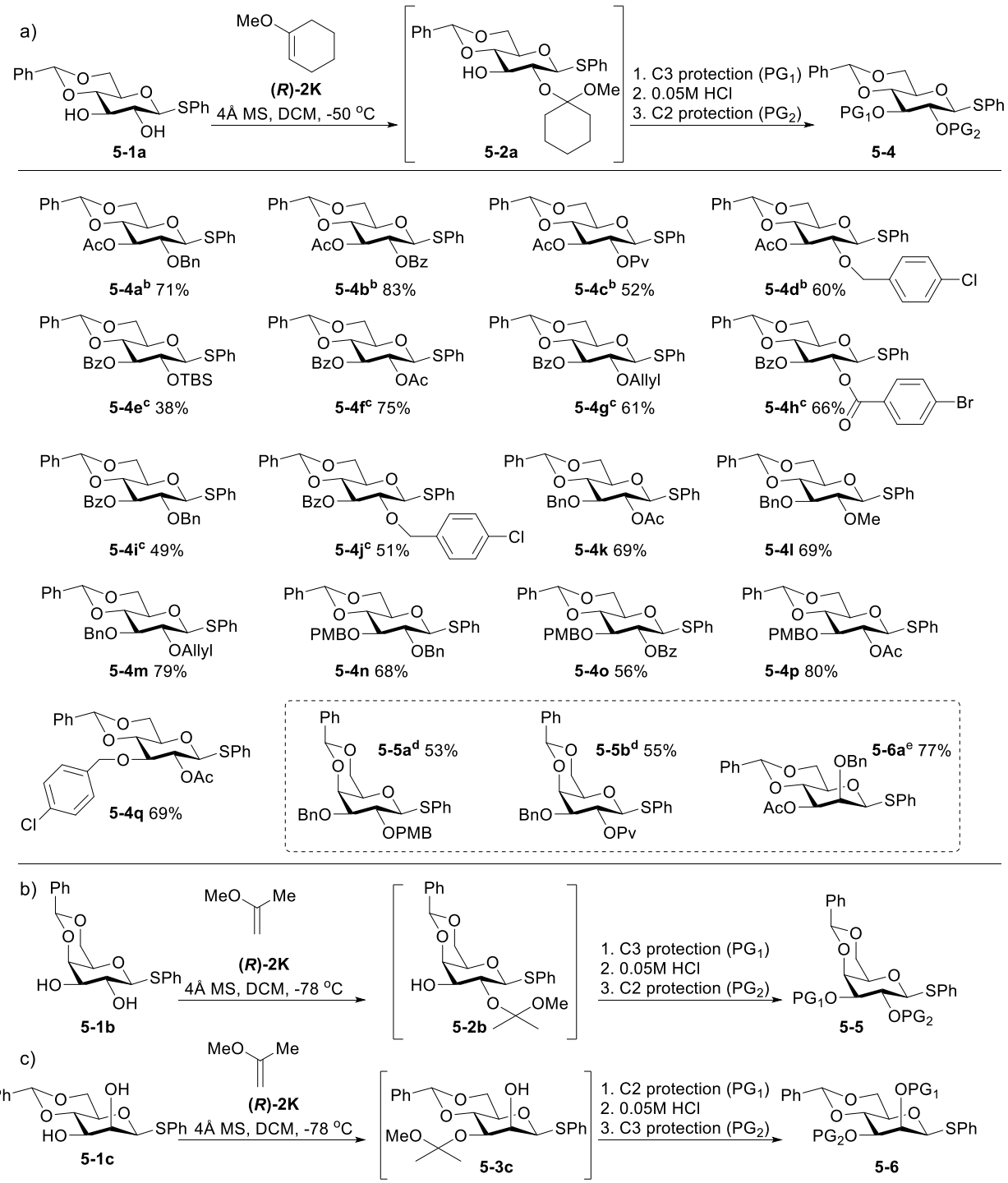
CPA-direct regioselective acetalization was performed, and the resultant C2-acetal **5-2a** was successfully obtained in full conversion. At this point, the mixture was dried with a gentle N_2 flow and high vacuum before the next step. Initially compound **5-2a** was subjected to free C3-hydroxyl group protection without affecting the C2-acetal. Since mixed acetals are acid- and heat-labile, acidic conditions and high reaction temperatures were avoided. The regioselective protection of the C3-OH with an acetyl group was successful using pyridine as a base and acetic anhydride as an acetylating agent. However, both the benzoyl protection by benzoyl chloride and pivaloyl protection by pivaloyl chloride in the presence of pyridine were leading to unselective functionalization due to the competitive C2-acetal cleavage.

To explain this puzzling result, we hypothesized that acyl chloride and pyridine eventually provides pyridinium hydrochloride, which is acidic enough to cleave the acetal. This possibility was investigated by mixing C2-acetal **5-2a** with pyridinium hydrochloride, which did indeed lead to the cleavage of acetal. Considering that the combination of acyl chloride with pyridine could generate pyridinium hydrochloride, these conditions were avoided for C2-functionalization. In contrast, other bases were well-tolerated and a selective protection of the C3-hydroxyl group with various protecting groups, such as acetyl, benzoyl, benzyl, para-methoxy benzyl, was achieved without inducing the C2-acetal cleavage.

After the C3-OH protection, 0.05M HCl solution was added to the N_2 stream/vacuum dried crude product obtained in the previous step. The HCl solution promoted selective cleavage of the C2-acetal, and the solution was cleanly removed in the subsequent drying step. The resulting free C2-OH was, then, protected in the same pot without isolation. At this point, a wide range of protecting conditions were employed as acids- and heat- labile mixed acetal was already removed. Diverse protecting groups were selectively installed with decent- to good yields in single-pot (Scheme 5.3a). Different combinations of selective protection of the C3- and C2-positions successfully provided various D-glucose-derived building blocks **5-4a**-**5-4q**.

In addition to the D-glucose-based substrate **5-1a**, this method was also successfully applied to D-galactose-based substrate **5-1b** and D-mannose-derived substrate **5-1c**. Even though the D-galactose and D-mannose derivatives were generated with somewhat lower regioselectivity (C2:C3 = 18:1 and 1:12), the resulting carbohydrates were still selectively functionalized following the single-pot protocols (Scheme 5.3b and 5.3c). In particular, since D-mannose derivative **5-1c** had reversed C3-selectivity for the acetalization, the functionalization was also performed in a reverse way (C2-protection, C3-acetal cleavage, and C3-protection) to afford compound **5-6a**

Scheme 5. 3. Regioselective single-pot protection of a) D-glucose-based substrate **5-1a**. b) D-galactose-based substrate **5-1b**. c) D-mannose-based substrate **5**-1c.[a]

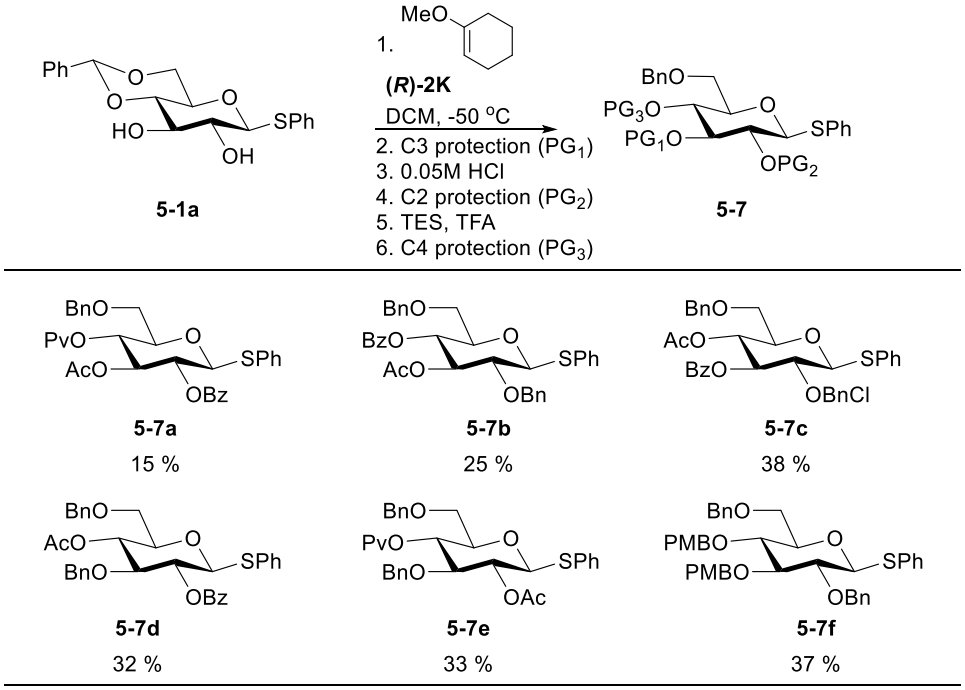


[a] isolated yield after one-pot reaction. 1-2 mol % catalyst was used. [b]For acetylation, Ac_2O (1.1 eq), DMAP (10 mol%), Et_3N (5 eq) was used. [c]For benzoylation, BzCl (1.1 eq), DMAP (10 mol%), Et_3N (5eq) was used [b,c]Combination of acyl chloride and pyridine was avoided. [d]**5-5a** and **5-5b** were functionalized from galactose-derived 2,3-diol. [e]**5-6a** was functionalized from from mannose-derived 2,3-diol. The selectivity was reversed in the mannose substrate.

5.5 Single-pot synthesis of fully functionalized D-glucose

After developing a strategy for the regioselective protection of C3- and C2-hydroxyls in derivatives **5-1a**, **5-1b**, and **5-1c**, we investigated the possibility of further functionalization of the C4 and C6 hydroxyl groups. In our carbohydrate systems, the C4 and C6 hydroxyl groups were initially protected as a 4,6-benzylidene acetal. The regioselective cleavage of such acetals has been widely investigated.[7] Among the variety of available methods, we selected the reagent based on the combination of triethyl silane and trifluoroacetic acid. These reagents are known to open the 4,6-benzylidene acetals to provide C6-benzyl protected product with the C4-free hydroxyl group. This condition was applied to unpurified compounds **5-4**, and the corresponding crude products were successfully obtained (Scheme 5.4).

Scheme 5. 4. Single-pot regioselective synthesis of fully functionalized D-glucose.



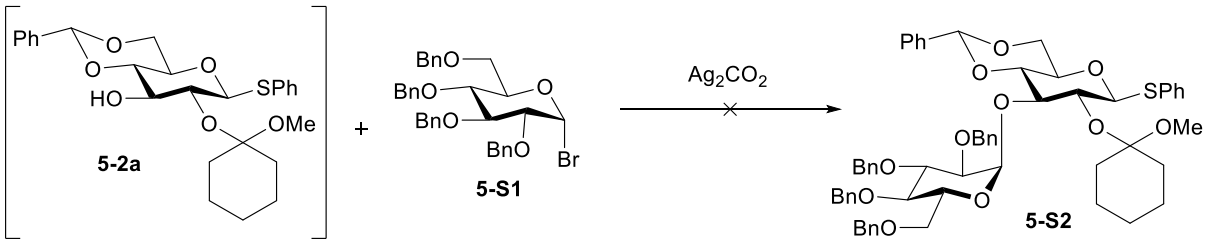
isolated yield after one-pot reaction. 1-2 mol % catalyst was used.

The resultant C4-free hydroxyl containing intermediates were dried and subjected to the final protection to afford fully elaborated D-glucose derivatives. Various combinations of protecting groups were selectively introduced in different positions of D-glucose, leading to a series of fully protected derivatives **5-7a** to **5-7f** in single-pot (Scheme 5.4).

5.6 Regioselective single-pot protection/glycosylation of monosaccahride

With the regioselective single-pot protection protocol leading to functionalized monosaccharides developed, regioselective single-pot protection/glycosylation was also explored. Our initial attempts to accomplish the direct glycosylation of the free C3-OH after the C2-acetalization was not successful, as commonly used glycosylation promoters were not compatible with the acid-sensitive acetal. Even trace amounts of triflic acid (TfOH) or trimethylsilyl trifluoromethanesulfonate (TMSOTf), which likely generates TfOH, were enough to cleave the C2-acetal. As the C2-acetal was removed, glycosylation reaction took place in an unselective way leading to the mixture of the C2-and C3-glycosides. Instead of the acidic promoters, basic catalyst, silver (II) carbonate, was introduced along with glucosyl bromide donor **5-S1** for the glycosylation of the C3-free hydroxyl group (Scheme 5.5). Unfortunately, even these conditions failed to provide the desired disaccharide **5-S2**.

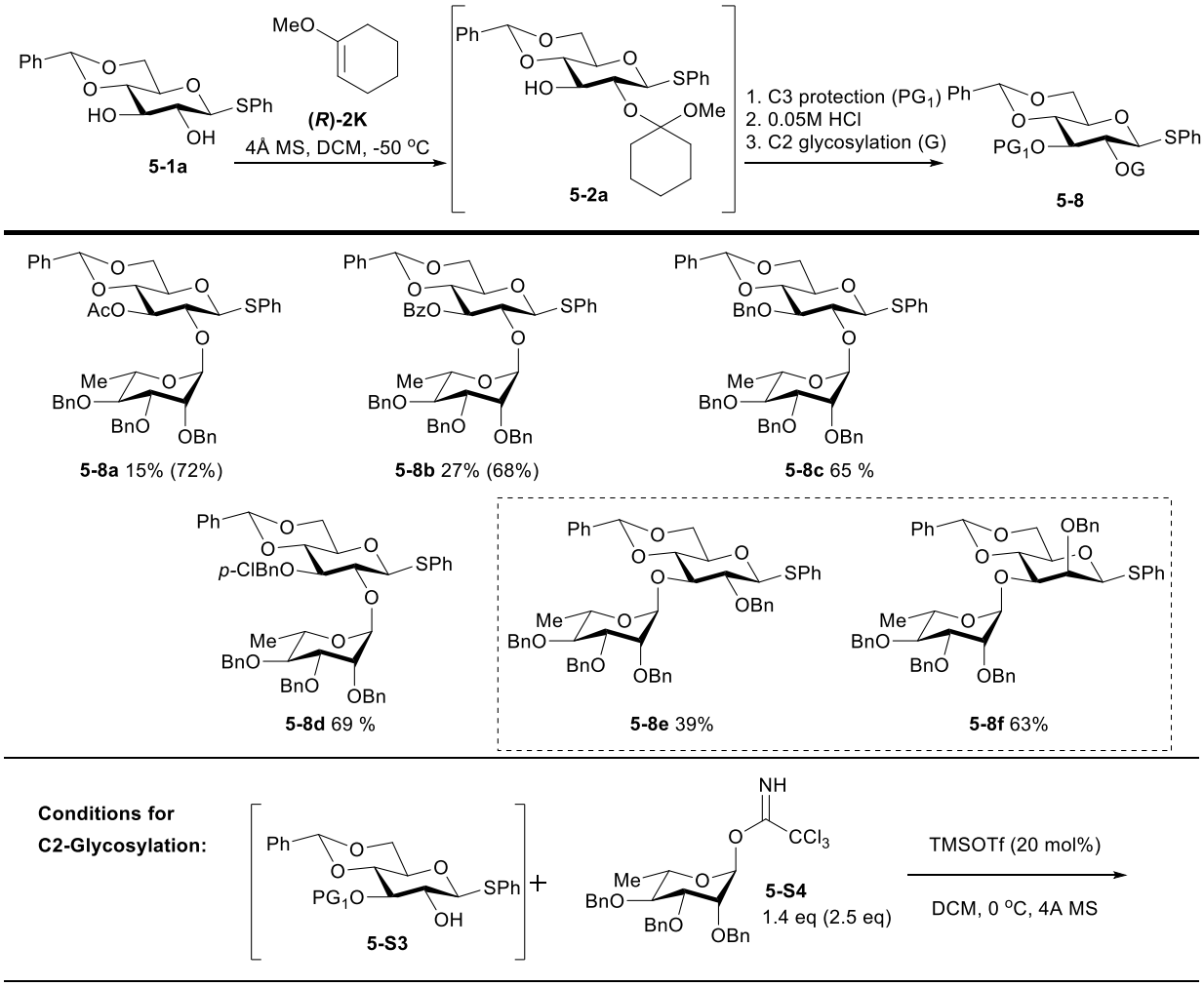
Scheme 5. 5. Failed attempt of the direct C3-selective glycosylation of C2-acetal **5-2a** with glucosyl bromide **5-S1**.



Compared to the direct C3-selective glycosylation, a C2-selective glycosylation followed by C3-selective protection was expected to be more feasible as common glycosylation promoters can be utilized in the absence of the acid-labile acetal. In order to perform C2-selective glycosylation, the strategically positioned free C2-hydroxyl group was prepared by modifying **5-1a** via sequential CPA **(*R*)-2K** directed regioselective C2-acetalization, C3-OH protection, and C2-acetal cleavage as described above.

The free C2-OH with different protecting groups at the C3-position was then subjected to glycosylation reaction with a per-benzylated L-rhamnosyl trichloroacetimidate (TCA) donor **5-S4** (1.4 equiv) in single-pot (Scheme 5.6). With acetyl protection at the C2-position, the yield of the C3-glycoside **5-8a** was only 15 % after 4 steps in single-pot. The lower yield was explained by lower amount of the TCA donor participating in glycosylation reaction as it was acetylated with previous reagent before glycosylation. The yield was increased to 72% after increasing the amount of donor (2.5 equiv). A substrate with benzoyl protection at the C3-position also had a similar problem in single-pot C2-glycosylation as the TCA donor **5-S4** gets benzoylated before the glycosylation. However, after increasing the amount of donor, the single-pot glycosylation protocol provided C3-OBz-containing C2-glycoside **5-8b** in 68% isolated yield. In contrast, glycosylation reaction of the free C2-OH of the intermediate with C3-benzyl protection was efficiently carried out as 65% of the desired C2-glycoside **5-8c** was afforded in a single-pot with only 1.4 equivalents of the L-rhamnose-based donor **5-S4**. The side reactions between the donor **5-S4** and prior reagents were not observed in this case. Similarly, C3-4-chloro-benzyl ether containing intermediate was also cleanly glycosylated with L-rhamnose donor **5-S4** to afford the C2-glycoside **5-8d** in 69% (one-pot). At the same time,

Scheme 5. 6. Single-pot C3-selective protection/C2-selective glycosylation of monosaccharide derivative **5-1a** and **5-1c**.



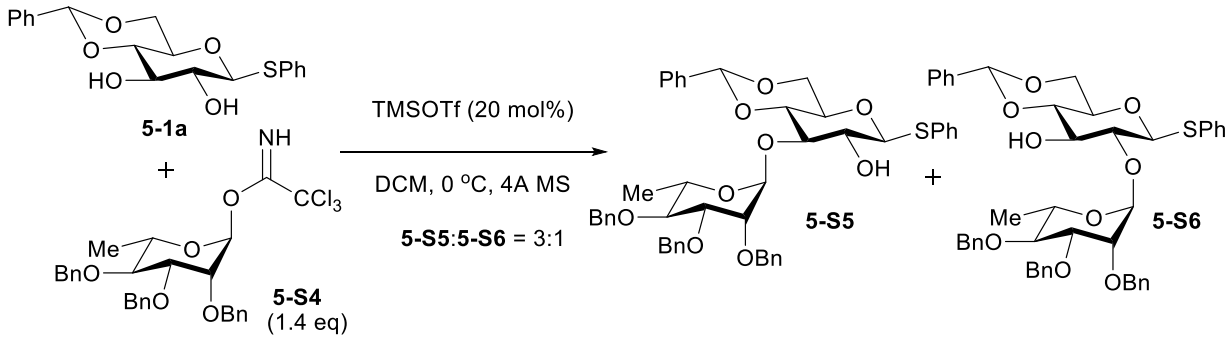
C2- glycosylation reaction conditions: C3-protected glucose (1.0 equiv), benzylated rhamnose trichloroacetimidate donor (1.4 equiv), TMSOTf (20mol %), 4A molecular sieves, DCM (0.2 M). 1 h at 0 °C. isolated yield after one-pot.
Yields with 2.5 equiv TCA donor were given in parenthesis.

t-butyldimethylsilyl (TBS) protection at the C3-position was not compatible with glycosylation condition as the TBS group was cleaved faster than the glycosylation reaction happened. In addition to the C2-selective glycosylation, C3-selective glycosylation was also performed. Following the sequence comprised of C2-acetalization, C3-acetylation, C2-acetal cleavage, C2-benzylation, and C3-deacetylation, the C3-free hydroxyl group was obtained. The single-pot glycosylation was initially attempted with the L-rhamnose-based

TCA donor **5-S4**, but the desired product was not obtained. After running a short column with the reaction mixture containing the free C3-OH-containing substrate, the glycosylation reaction was successfully performed and the desired disaccharide **5-8e** was obtained in 39% overall yield. Lastly, the single-pot protection/glycosylation method was applied to the D-mannose-based substrate **5-1c**, and the desired C2-benzyl protected product, containing C3-glycoside **5-8f** was obtained in 63% yield in a single-pot.

In order to observe the inherent regioselectivity exhibited by the diol **5-1a**, the control glyocosylation reaction was performed by a direct glycosylation to the diol with TMSOTf promoter (Scheme 5.7). The direct glycosylation of benzylated L-rhamnose TCA donor **5-S4** to the diol **5-1a** provided the regioselectivity favored in C3-glycoside **5-S5** over C2 glycoside **5-S6** (**5-S5**/**5-S6** = 3:1). Perhaps, this is due to the higher nucleophilicity of the C3-hydroxyl groups in comparison to the C2-OH.[8]

Scheme 5. 7. Control experiment for glycosylation of **5-1a** and **5-S4**.

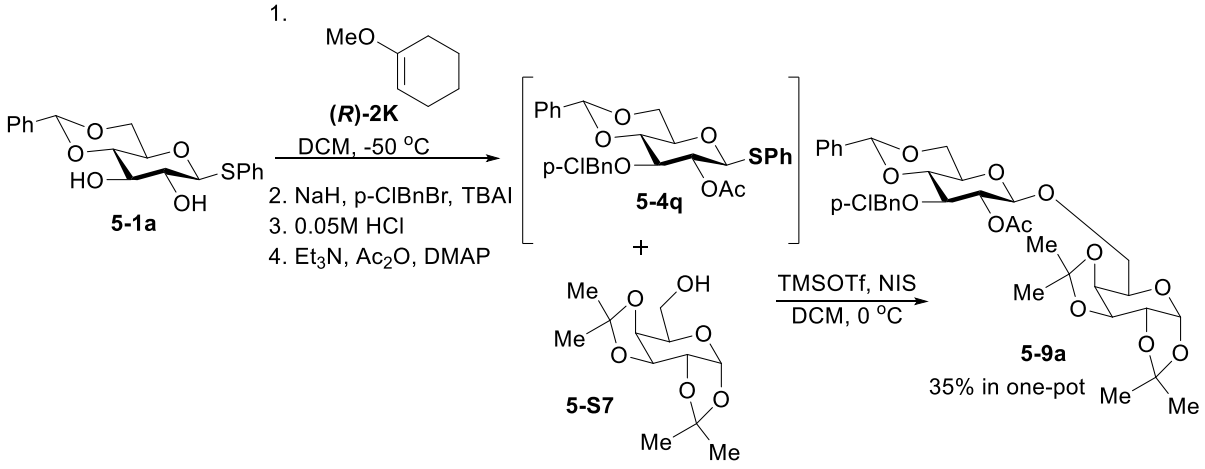


5.7 Single-pot glycosylation of regioselectively functionalized thioglycoside

All of the carbohydrate substrates selectively functionalized using this protocol, were thioglycosides that contain an anomeric thioether moiety. Such thioglycosides are common glycosyl donors in various glycosylation reactions.[8] The single-pot glycosylation of

thioglycoside **5-4q** pre-generated *in situ* via the protocols described above and D-galactose derivative **5-S7** was investigated (Scheme 5.8). After the thioglycoside **5-4q** was activated by NIS and TMSOTf, the glycosylation was successfully carried out and the desired disaccharide **5-9a** was afforded with 35% overall yield (single-pot).

Scheme 5. 8. Single-pot glycosylation of regioselectively functionalized thioglycoside.



5.8 Conclusions

In summary, we have described the versatile single-pot methods for the regioselective functionalization of carbohydrates. Using the CPA-catalyzed regioselective acetalization approach on carbohydrate-derived 2,3-diols, a strategically positioned free hydroxyl group was installed. The C2-OH and C3-OH of various D-glucose, D-galactose, and D-mannose derivatives, were then, selectively functionalized in a single-pot through subsequent protection, acetal cleavage, and re-protection protocol. The D-glucose-based substrate **5-1a** was further functionalized to afford the derivatives with different protecting groups in all four positions in a single-pot. The regioselectivity was achieved by leaving one free hydroxyl group in a different position until the final protection was achieved. In addition

to the single-pot protection, the single-pot glycosylation was also performed on the C3-protected/C2-OH in D-glucose derivatives. Various protecting groups and different sugar donors were well-tolerated in this single-pot glycosylation reaction. The functionalized carbohydrates from this single-pot protocol are even more valuable as they could be utilized as a thioglycoside donor in glycosylation reactions.

5.9 Experimental information

Methods and Reagents :

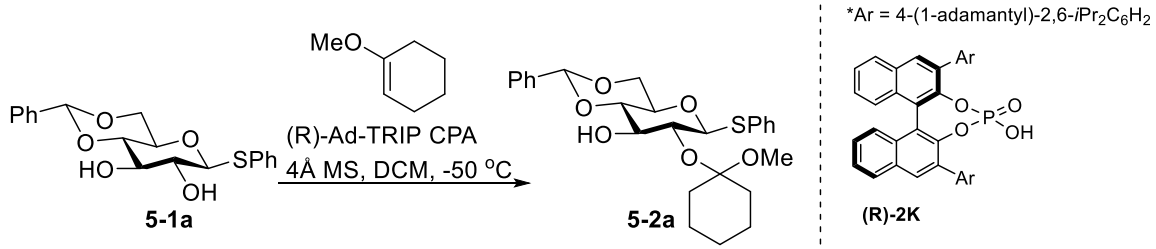
Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Tetrahyrofuran (THF), dichloromethane (DCM) and diethyl ether (Et_2O) were filtered through a column (Innovative Technology PS-MD-5) of activated alumina under nitrogen atmosphere. All reactions were carried out under an atmosphere of nitrogen in flame- or oven-dried glassware with magnetic Fstirring. Reactions were cooled using Neslab Cryocool CB-80 immersion cooler (0 to -60 °C) and Neslab Cryocool immersion cooler CC-100 II, or via external cooling baths: ice water (0 °C), sodium chloride/ ice water (-10 °C), or dry ice/acetone (- 78°C). Heating was achieved by use of a silicone bath with heating controlled by electronic contact thermometer. Deionized water was used in the preparation of all aqueous solutions and for all aqueous extractions. Solvents used for extraction and chromatography were ACS or HPLC grade. Purification of reactions mixtures was performed by flash column chromatography on SiO_2 using SiliCycle SiliaFlash P60 (230-400 mesh). Diastereomeric ratios were determined by 1 H NMR analysis. Enantiomeric excess was determined by HPLC analysis using a Waters e2695 Separations Module with a Waters 2998 photodiode array detector.

Instrumentation :

All spectra were recorded on Varian vnmrs 700 (700 MHz), Varian vnmrs 500 (500 MHz), Varian MR400 (400 MHz), Varian Inova 500 (500 MHz) spectrometers and chemical shifts (δ) are reported in parts per million (ppm) and referenced to the ^{1}H signal of the internal tetramethylsilane according to IUPAC recommendations. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, m = multiplet; coupling constant(*S*) in Hz; integration). High resolution mass spectra (HRMS) were recorded on MicromassAutoSpecUltima or VG (Micromass) 70-250-S Magnetic sector mass spectrometers in the University of Michigan mass spectrometry laboratory. Infrared (IR) spectra were recorded as thin films on NaCl plates on a Perkin Elmer Spectrum BX FT-IR spectrometer. Absorption peaks were reported in wavenumbers (cm^{-1}).

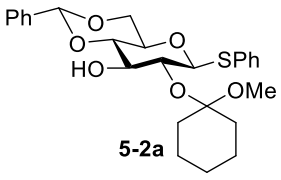
5.9.1 General procedure for the single-pot reaction

All the reactions were performed in the same vial in single-pot. Nitrogen blow and high vacuum were used to dry the reaction mixture in between every reaction. DCM was used as a solvent throughout whole single-pot protocol because it is easily dried and also is compatible with most of conditions of protection/glycosylation reactions. Functionalization of D-glucose and D-galactose cases can be carried out as the same way (selective C2-acetalization, C3-functionalization, C2-acetal cleavage, C2 functionalization), but functionalization of D-mannose is performed in a reversed way (selective C3-acetalization, C2-functionalization, C3-acetal cleavage, C3 functionalization).



Procedure for D-galactose and D-mannose substrate:

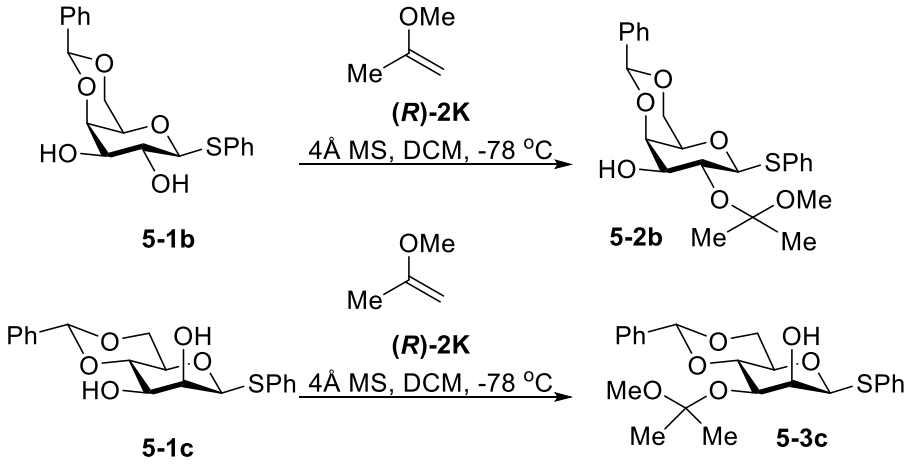
A round bottom flask was flame dried and purged with nitrogen. Then 4,6-benzylidine acetal protected thioglycoside diol **5-1b** (D-galactose) or **5-1c** (D-mannose) (1.0 equivalent), (which was previously dried by azeotropic removal of moisture with toluene) and activated 4A molecular sieves (powder) were charged in the flask. Anhydrous dichloromethane (0.04M) was added to the flask and the reaction mixture was sonicated for 5 mins to dissolve the diol completely in DCM. Then the reaction mixture was submerged in dry ice-acetone (-78 °C) bath, and 2-methoxypropene (1.2 equivalent) was added, followed by **(*R*)-2K** (2 mol%). The reaction mixture was transferred to Neslab CB 80 immersion cooler and stirred at -78 °C for 24 h. After the reaction completion, the reaction mixture was quenched with triethyl amine at -78 °C. **(IMPORTANT!) THE REACTION MIXTURE WAS COMPLETELY DRIED BY PASSING A STREAM OF NITROGEN FOLLOWED BY APPLYING HIGH VACUUM AND SUBJECTED TO THE FOLLOWING STEP WITHOUT WORK UP OR PURIFICATION.**

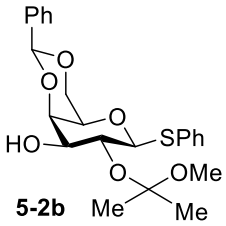


(*2R,4aR,6S,7R,8S,8aS*)-7-((1-methoxycyclohexyl)oxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-d][1,3]dioxin-8-ol (5-2a).

Using diol **5-1a** (20 mg, 0.056 mmol, 1.0 equiv.) as the starting material, preparation of **5-2a** was accomplished by following general procedure. This product was purified by flash column chromatography on SiO_2 (7/1 Hexanes/Ethyl acetate + 2% triethylamine) to afford **5-2a** as a pale yellow oil (18.6 mg, 69%, C2:C3 = 25:1).

^{1}H NMR (500 MHz, CD_3OD) δ 7.76 (s, 0.02H), 7.56 – 7.52 (m, 0.1H), 7.51 – 7.43 (m, 5H), 7.41 – 7.30 (m, 6H), 7.29 – 7.23 (m, 1H), 5.59 (s, 1H), 5.54 (s, 0.02H), 4.85 (d, J = 8.5 Hz, 1H), 4.26 (dd, J = 10.0, 5.0 Hz, 1H), 3.83 – 3.71 (m, 3H), 3.59 (at, J = 9.2 Hz, 1H), 3.56 – 3.48 (m, 1H), 3.34 (s, 3H), 3.18 (s, 0.1H), 2.88 – 2.80 (m, 0.2H), 1.98 – 1.79 (m, 2H), 1.74 – 1.70 (m, 1H), 1.67 – 1.60 (m, 2H), 1.55 – 1.45 (m, 2H), 1.43 – 1.35 (m, 2H), 1.29 – 1.25 (m, 1H), 1.14 (t, J = 7.3 Hz, 1H). **^{13}C NMR** (125 MHz, CD_3OD) δ 147.3, 146.5, 137.6, 134.0, 132.2, 131.3, 130.9, 128.6, 128.5, 127.6, 127.6, 127.0, 126.1, 125.9, 101.6, 101.6, 101.5, 101.4, 87.9, 87.0, 79.7, 79.6, 74.9, 74.3, 72.5, 70.2, 69.7, 68.2, 48.1, 47.9, 47.7, 47.6, 47.4, 47.2, 47.1, 45.9, 43.2, 36.6, 36.1, 33.8, 33.0, 32.9, 31.0, 30.8, 29.2, 25.0, 24.9, 22.3, 22.2. **IR** (thin film, cm^{-1}): 3380, 2931, 2857, 1581, 1557, 1541, 1463, 1367, 1272, 1250, 1149, 1090, 1014, 917. **HRMS (ESI+)** Calcd. $C_{26}H_{32}O_6SNa$ $[M + Na]^+$: 495.1812, found : 495.1826; **$[\alpha]^{26}_D$** = = –27.5° (c 0.35, DCM).

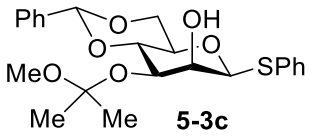




5-2b **(*2S,4aR,6S,7R,8S,8aR*)-7-((2-methoxypropan-2-yl)oxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-d][1,3]dioxin-8-ol (5-2b).**

Using D-galactose diol **5-2a** (20 mg, 0.056 mmol, 1.0 equiv.) as the starting material, preparation of **5-2b** was accomplished by following general procedure B. This product was purified by flash column chromatography on SiO_2 (1/1 Hexanes/Ethyl acetate + 1% triethylamine) to afford **5-2b** as a pale yellow oil (22.2 mg, 93%, C2:C3 = 20:1).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.70 – 7.62 (m, 2H), 7.54 (dd, J = 7.5, 1.6 Hz, 2H), 7.42 – 7.33 (m, 3H), 7.25 – 7.18 (m, 3H), 5.58 (s, 1H), 5.16 (s, 1H), 4.60 (d, J = 9.3 Hz, 1H), 4.37 (dd, J = 12.3, 1.1 Hz, 1H), 4.31 (d, J = 3.2 Hz, 1H), 4.17 – 4.02 (m, 2H), 3.65 (dd, J = 8.6, 3.0 Hz, 1H), 3.50 (s, 1H), 3.31 (s, 3H), 1.43 (s, 3H), 1.14 (d, J = 18.0 Hz, 3H). **^{13}C NMR** (125 MHz, Chloroform-*d*) δ 138.0, 133.4, 131.7, 129.0, 128.8, 128.1, 127.1, 126.6, 101.9, 101.4, 86.0, 77.3, 77.0, 76.8, 75.4, 73.8, 70.9, 70.1, 69.3, 49.7, 25.0, 23.6. **IR** (thin film, cm^{-1}): 3382, 2989, 2923, 2857, 1471, 1456, 1439, 1375, 1156, 1099, 1044. **HRMS (ESI+)** Calcd. for $C_{23}H_{28}O_6SNa$ $[M + Na]^+$ 455.1499, found 455.1509; **$[\alpha]^{26}_D$** = – 5.4° (c 0.02, DCM).

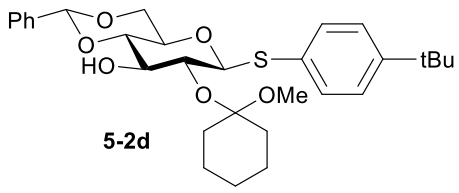


5-3c **(*2R,4aR,6S,7S,8R,8aR*)-8-((2-methoxypropan-2-yl)oxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-d][1,3]dioxin-7-ol (5-3c).**

Using diol **5-3a** (20 mg, 0.04 mmol, 1.0 equiv.) as the starting material, synthesis of **5-3c** was accomplished by following general procedure B. This product was purified by flash column

chromatography on SiO_2 (3/1 Hexanes/Ethyl acetate + 1% triethylamine) to afford **5-3c** as a pale yellow oil (16.2 mg, 78%, C2:C3 = 1:12.6).

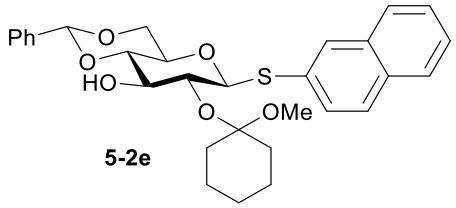
^{1}H NMR (500 MHz, CD_3OD) δ 7.54 – 7.43 (m, 4H), 7.39 – 7.25 (m, 6H), 5.58 (s, 1H), 5.48 (s, 1H), 4.29 (td, J = 9.8, 4.8 Hz, 1H), 4.22 (d, J = 3.0 Hz, 1H), 4.19 (dd, J = 10.0, 3.1 Hz, 1H), 4.11 (dd, J = 10.2, 4.8 Hz, 1H), 4.05 (at, J = 9.7 Hz, 1H), 3.82 (at, J = 10.3 Hz, 1H), 3.21 (s, 3H), 1.40 (d, J = 12.0 Hz, 3H), 1.37 (s, 3H). **^{13}C NMR** (125 MHz, CD_3OD) δ 137.9, 133.7, 131.6, 128.8, 128.5, 127.6, 127.3, 126.0, 102.0, 101.5, 89.5, 77.3, 72.5, 68.1, 65.7, 48.6, 48.1, 47.1, 24.5, 24.2. **IR** (thin film, cm^{-1}): 3433, 2985, 2923, 2853, 1456, 1373, 1211, 1169, 1095, 1031, 970. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{23}H_{28}O_6SNa$ 455.1499, found 455.1513; **$[\alpha]^{26}_D$** = +48.9° (c 0.51, DCM).



5-2d

(*2R,4aR,6S,7R,8S,8aS*)-6-((4-(tert-butyl)phenyl)thio)-7-((1-methoxycyclohexyl)oxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-ol (5-2d).

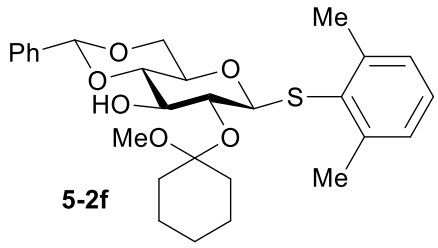
^{1}H NMR (500 MHz, CD_3OD) δ 7.54 – 7.32 (m, 9H), 5.60 (s, 1H), 4.82 – 4.78 (m, 1H), 4.29 (dd, *J* = 10.4, 4.9 Hz, 1H), 3.82 – 3.72 (m, 3H), 3.65 – 3.57 (m, 1H), 3.52 (td, *J* = 9.7, 5.0 Hz, 1H), 3.34 (s, 3H), 1.91 – 1.42 (m, 10H), 1.32 (s, 9H). **^{13}C NMR** (126 MHz, CD_3OD) δ 152.05, 139.03, 132.76 (2C), 131.63 (2C), 129.95, 129.02 (2C), 127.53 (2C), 127.07 (2C), 103.01, 102.92, 88.71, 81.20, 75.78, 75.63, 71.13, 69.63, 48.62, 47.02, 35.43, 34.40, 34.25, 31.68 (3C), 26.29, 23.75, 23.72.



5-2e

(*2R,4aR,6S,7R,8S,8aS*)-7-((1-methoxycyclohexyl)oxy)-6-(naphthalen-2-ylthio)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-ol (5-2e).

^{1}H NMR (500 MHz, CD_3OD) δ 7.99 – 7.95 (m, 1H), 7.87 – 7.78 (m, 3H), 7.58 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.49 (pt, *J* = 6.8, 3.4 Hz, 4H), 7.34 (dtd, *J* = 6.1, 4.8, 3.8, 1.5 Hz, 3H), 5.61 (s, 1H), 4.99 (d, *J* = 9.0 Hz, 1H), 4.30 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.86 – 3.75 (m, 3H), 3.65 – 3.54 (m, 2H), 3.36 (s, 3H), 1.92 – 1.68 (m, 5H), 1.62 – 1.39 (m, 5H). **^{13}C NMR** (126 MHz, CD_3OD) δ 139.02, 135.08, 133.86, 132.67, 131.05, 129.96, 129.85, 129.56, 129.03 (2C), 128.74, 128.46 (2C), 127.74, 127.53, 127.36, 103.07, 102.94, 88.28, 81.19, 75.88, 75.78, 71.14, 69.64, 49.29, 34.49, 34.37, 26.31, 23.73 (2C).



5-2f

(*2R,4aR,6S,7R,8S,8aS*)-6-((2,6-dimethylphenyl)thio)-7-((1-methoxycyclohexyl)oxy)-2-phenylhexahydropyrano[3,2-d][1,3]dioxin-8-ol (5-2f).

^{1}H NMR (700 MHz, CD_3OD) δ 7.52 – 6.96 (m, 8H), 5.57 (s, 1H), 4.55 (d, *J* = 9.3 Hz, 1H), 4.11 (dd, *J* = 10.4, 5.1 Hz, 1H), 3.82 (dd, *J* = 9.3, 7.5 Hz, 1H), 3.73 – 3.67 (m, 2H), 3.59 (t, *J* = 9.4 Hz, 1H), 3.37 (s, 3H), 3.28 (td, *J* = 9.8, 5.1 Hz, 1H), 2.55 (s, 6H), 1.97 – 1.76 (m, 5H), 1.61 – 1.28 (m, 5H). **^{13}C NMR** (176 MHz, CD_3OD) δ 145.28 (2C), 139.02, 132.47, 130.18, 129.91, 129.19 (2C),

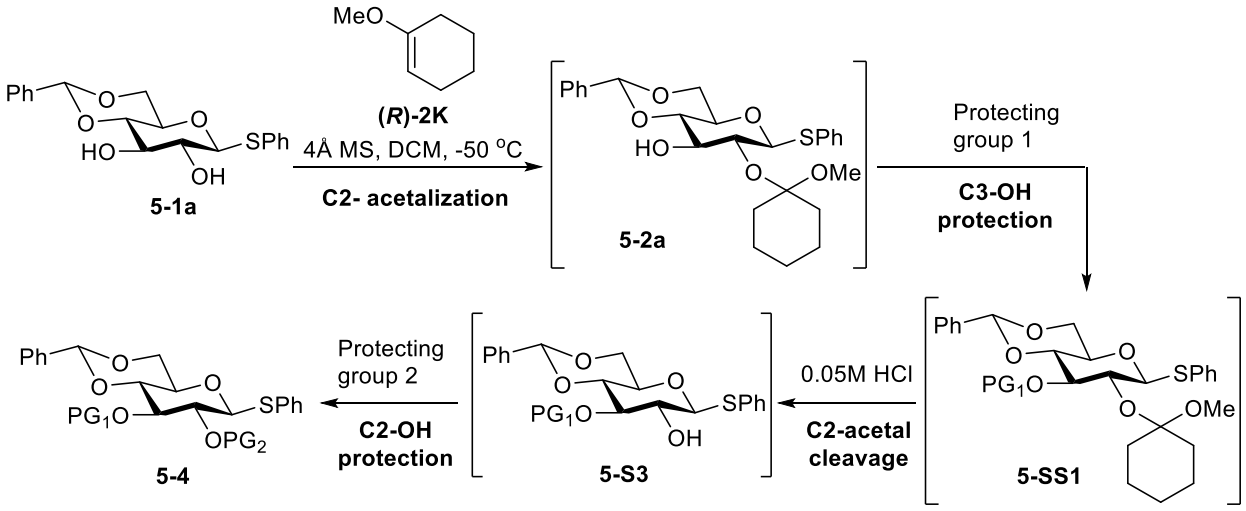
128.99 (2C), 127.49 (2C), 103.08, 102.88, 90.12, 81.24, 76.66, 75.74, 70.66, 69.54, 48.67, 34.60, 26.38 (2C), 23.86, 23.77 (2C), 22.80 (2C).

5.9.2 Regioselective single-pot protection of carbohydrate-derived 2,3-diols (Chapter 5.4)

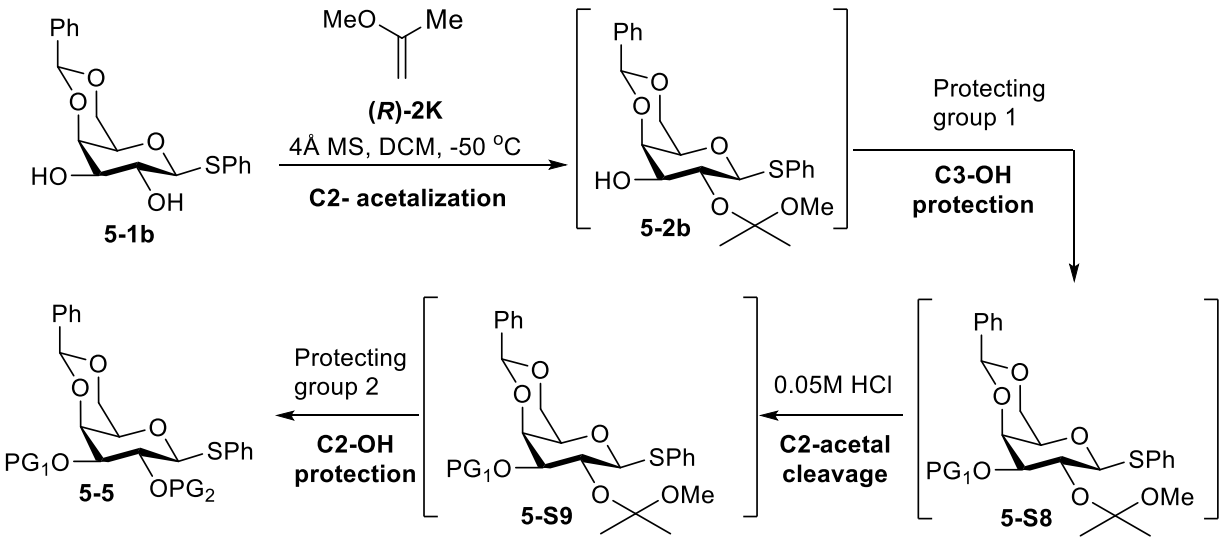
General procedure (D-glucose and D-galactose substrate):

C2 acetalization → C3-OH protection → C2-acetal cleavage → C2-OH protection

General scheme of regioselective protection of **D-glucose**



General scheme of regioselective protection of **D-galactose**



1) CPA directed regioselective C2-acetalization

- The procedure was described above (Section 5.9.1).

2) C3-OH protection

Instruction:

Most of reaction conditions are tolerated to protect C3-OH selectively except the conditions that could cleave C2-acetal such as high temperature, acidic conditions, or a combination of acyl halide and pyridine. Acyl halide and pyridine forms a pyridinium halide salt, which is acidic enough remove the C2-acetal. The following procedure was written based on the functionalization of the D-glucose-derived substrate.

Procedure:

* The resulting dried C2-acetal protected substrate **5-2a** was subjected to one of the following conditions below.

Acetyl protection: Triethyl amine (5.0 equiv) and anhydrous dichloromethane (0.3M) were added to the reaction mixture. Then anhydrous acetic anhydride (1.1 equiv), and 4-dimethyaminopyridine (DMAP) (0.1 equiv) were added to the mixture. The reaction was stirred at room temperature until the reaction completion, which was monitored by TLC. After the reaction was completed, the mixture was completely dried through N_2 gas flow and high vacuum.

Benzoyl protection: Triethyl amine (5.0 equiv) and anhydrous dichloromethane (0.3M) were added to the reaction mixture. Then benzoyl chloride (1.2 equiv), and 4-dimethyaminopyridine (DMAP) (0.10 equiv) were added to the mixture. The reaction was stirred at room temperature until the reaction completion, which was monitored by TLC. After the reaction was completed, the mixture was completely dried by passing a stream of N_2 followed by applying high vacuum.
(Typically, benzoyl chlorides were found to be more reactive than benzoic acid anhydrides.)

Benzyl protection: Anhydrous dichloromethane (0.2M) was added to the reaction mixture. Then sodium hydride (60% dispersion in mineral oil) (1.2 equiv), and benzyl bromide (1.1 equiv), tetrabutylammonium iodide (TBAI) (0.10 equiv) were subsequently added to the mixture. Then 3-5 drops of anhydrous dimethylformamide (DMF) was added to the solution to dissolve the NaH efficiently. The reaction mixture was stirred at room temperature until the reaction completion, as judged by TLC. After completion, the reaction was carefully quenched with methanol. The solution was then, filtered through a HPLC

filter to remove the slurry containing mineral oil from sodium hydride. The resulting filtered solution was completely dried by passing a stream of N_2 followed by applying high vacuum.

***para*-methoxy benzyl (PMB)** protection: same as benzyl protection, except using PMB chloride instead of benzyl bromide.

4-chlorobenzyl protection: same as benzyl protection, except using 4-chlorobenzyl bromide instead of benzyl bromide.

* The crude reaction mixture was subjected to the next reaction step without purification.

(*Common procedure)

3) C2-acetal cleavage

Instruction:

When a clean C2-acetal product **5-2a** was dissolved in $CDCl_3$ for NMR, the acetal cleavage was observed. We hypothesized that even the trace amount of hydrochloric acid in the $CDCl_3$ could cleave the mixed acetal. To test this idea, 0.05M HCl solution was prepared in chloroform, and this solution was indeed acidic enough to remove the C2-acetal. Therefore, $CDCl_3$ should be avoided as the NMR solvent.

0.05M HCl solution did not cleave 4,6-benzylidine acetal moiety, which was excellent for our system. Furthermore, the HCl solution can be used to neutralize the previous basic conditions.

Procedure:

0.05 M HCl solution in dichloromethane was added to the resulting reaction mixture firstly to neutralize the basic reaction condition. While the HCl solution is added, the pH of solution was monitored by pH paper. The 0.05M HCl solution was added until the reaction medium became slightly acidic (around pH 5-6). This acidic solution was stirred until the reaction completion (C2-acetal cleavage), and the reaction can be monitored by TLC. Once the reaction is completed, the resulting reaction mixture was completely dried by passing a stream of N_2 followed by applying high vacuum.

4) C2-OH protection

Instruction:

The scope of the protecting groups for the C2-OH protection was significantly wider due to the absence of acid-labile mixed acetal (Combination of acyl chloride and pyridine was also available). In addition, more equivalents of reagents can be used to achieve higher reaction conversions since this is the last step of the single-pot protocol.

Procedure:

* The resulting dried compound with free C2-OH was subjected to one of the following conditions below.

Acetyl protection: Triethyl amine (5.0 equiv) and anhydrous dichloromethane (0.3M) were added to the reaction mixture. Then anhydrous acetic anhydride (1.2 equiv), and 4-dimethyaminopyridine (DMAP) (0.2 equiv) were added to the mixture. The reaction was stirred at room temperature until TLC analysis indicated reaction completion. After

completion, the reaction was slowly quenched with methanol. The solvent was then removed under vacuum and the residue was dissolved in DCM and washed with NH_4Cl (x3). The resultant aqueous layers were extracted with DCM (x2), and the organic layers were combined and dried over $MgSO_4$ solution. The dried crude solution was concentrated *in vacuo* and purified by a flash column chromatography on SiO_2 (hexanes : ethyl acetate, 15:1 → 10:1 → 4:1).

Benzoyl protection: Pyridine (10.0 equiv) and anhydrous dichloromethane (0.3M) were added to the reaction mixture. Then benzoyl chloride (1.2 equiv), and 4-dimethyaminopyridine (DMAP) (0.2 equiv) were added to the mixture. The reaction was stirred at room temperature until TLC analysis indicated reaction completion. After completion, the reaction was slowly quenched with methanol. The solvent was then removed under vacuum and the residue was dissolved in DCM and washed with NH_4Cl (x3). The resultant aqueous layers were extracted with DCM (x2), and the organic layers were combined and dried over $MgSO_4$ solution. The dried crude solution was concentrated *in vacuo* and purified by a flash column chromatography on SiO_2 (hexanes : ethyl acetate, 15:1 → 10:1 → 4:1).
(Benzoyl chloride was found to be more reactive than benzoic anhydrides.)

4-bromobenzoyl protection: same as benzoyl protection, except using 4-bromobenzoyl chloride instead of benzoyl chloride.

Pivaloyl protection: Pyridine (10.0 equiv) and anhydrous dichloromethane (0.5M) were added to the reaction mixture. Then pivaloyl chloride (1.2 equiv), and 4-dimethyaminopyridine (DMAP) (0.2 equiv) were added to the mixture. The reaction was stirred at room temperature until TLC analysis indicated reaction completion After completion, the reaction was slowly quenched with methanol. The solvent was then removed under vacuum and the residue was dissolved in DCM and washed with NH_4Cl (x3). The resultant aqueous layers were extracted with DCM (x2), and the organic layers were combined and dried over $MgSO_4$ solution. The dried crude solution was concentrated *in vacuo* and purified by a flash column chromatography on SiO_2 (hexanes : ethyl acetate, 15:1 → 10:1 → 4:1).

Benzyl protection: Anhydrous dichloromethane (0.2M) was added to the reaction mixture. Then, sodium hydride (60% dispersion in mineral oil) (1.5 equiv), and benzyl bromide (1.2 equiv), tetrabutylammonium iodide (TBAI) (0.2 equiv) were sequentially added to the mixture. This followed by the addition of 3-5 drops of anhydrous DMF to dissolve the NaH more efficiently. The reaction was stirred at room temperature until TLC analysis indicated reaction completion. After completion, the reaction was slowly quenched with methanol. The solvent was then removed under vacuum and the residue was dissolved in DCM and washed with NH_4Cl (x3). The resultant aqueous layers were extracted with DCM (x2), and the organic layers were combined and dried over $MgSO_4$ solution. The dried crude solution was concentrated *in vacuo* and purified by a flash column chromatography on SiO_2 (hexanes : ethyl acetate, 15:1 → 10:1 → 4:1).

***para*-methoxy benzyl (PMB) protection**: same as benzyl protection, except using PMB chloride instead of benzyl bromide.

4-chlorobenzyl protection: same as benzyl protection, except using 4-chlorobenzyl bromide instead of benzyl bromide.

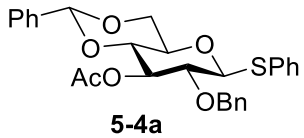
2-Naphthyl protection: same as benzyl protection, except using 2-naphthylmethyl bromide instead of benzyl bromide.

Allyl protection: Anhydrous dimethylformamide (DMF) (0.2M) was added to the reaction mixture. Then sodium hydride (60% dispersion in mineral oil) (1.5 equiv) was added slowly and the solution was stirred for 30 min under the atmosphere of N_2. Then allyl bromide (1.2 equiv) was added slowly, and the resultant mixture was stirred at 50 ^oC until TLC analysis indicated reaction completion. The reaction was quenched with methanol carefully. The solvent was then removed under vacuum and the residue was dissolved in DCM and washed with water (x3). After drying over $MgSO_4$, the resulting crude product was purified by a flash column chromatography on SiO_2 (hexanes : ethyl acetate, 15:1 → 10:1 → 4:1).

Methyl protection: Anhydrous dimethylformamide (DMF) (0.2M) was added to the reaction mixture. Then sodium hydride (60% dispersion in mineral oil) (1.5 equiv) was added slowly and the solution was stirred at room temperature for 30 min under the atmosphere of N_2. Then methyl iodide (1.5 equiv) was added slowly, and the reaction mixture was stirred at room temperature overnight. After reaction completion, the mixture

was poured into ice water and extracted with Et_2O (x3). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting crude product was purified by a flash column chromatography on SiO_2 (hexanes : ethyl acetate, 15:1 → 10:1 → 4:1).

tert-Butyldimethylsilyl (TBS) protection: Anhydrous dimethylformamide (DMF) was added to the reaction mixture. Then imidazole, (5.0 equiv), and tert-butyldimethylsilyl chloride (TBS-Cl) (1.5 equiv) were sequentially added to the mixture. The reaction was stirred at room temperature until TLC analysis indicated reaction completion. After reaction completion, the mixture was poured into ice water and extracted with Et_2O (x3). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting crude product was purified by a flash column chromatography on SiO_2 (hexanes : ethyl acetate, 15:1 → 10:1 → 4:1).



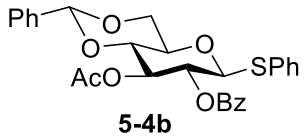
5-4a

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-7-(benzyloxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yl acetate (5-4a).

(Followed by a general single-pot procedure 1, 2, 3, 4):

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.57 – 7.51 (m, 2H), 7.44 – 7.39 (m, 2H), 7.37 – 7.28 (m, 11H), 5.48 (s, 1H), 5.39 (dd, *J* = 9.7, 8.8 Hz, 1H), 4.91 (d, *J* = 10.9 Hz, 1H), 4.83 (d, *J* = 9.7 Hz, 1H), 4.63 (d, *J* = 10.9 Hz, 1H), 4.37 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.78 (t, *J* = 10.2 Hz, 1H), 3.60 (t,

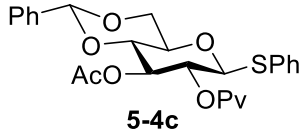
J = 9.5 Hz, 1H), 3.58 – 3.52 (m, 2H), 1.96 (s, 3H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 169.85, 137.70, 137.00, 133.03, 132.45 (2C), 129.26 (2C), 129.19, 128.60 (2C), 128.36 (2C), 128.28 (2C), 128.17, 128.09, 126.26 (2C), 101.48, 88.58, 79.30, 78.68, 75.37, 74.42, 70.50, 68.74, 21.05. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{28}H_{28}O_6S$ 515.1504, found 515. 1496.



5-4b

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-8-acetoxy-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-*d*][1,3]dioxin-7-yl benzoate (5-4b).

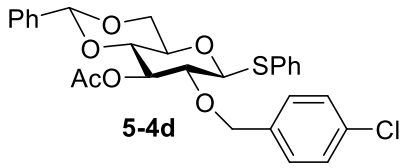
^{1}H NMR ^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.06 – 8.03 (m, 2H), 7.62 – 7.58 (m, 1H), 7.49 – 7.46 (m, 2H), 7.45 – 7.42 (m, 4H), 7.37 – 7.34 (m, 3H), 7.33 – 7.28 (m, 3H), 5.55 – 5.51 (m, 2H), 5.28 (dd, *J* = 10.0, 9.1 Hz, 1H), 4.95 (d, *J* = 10.0 Hz, 1H), 4.43 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.85 (t, *J* = 10.3 Hz, 1H), 3.76 (t, *J* = 9.6 Hz, 1H), 3.67 (td, *J* = 9.7, 4.9 Hz, 1H), 1.94 (s, 3H). **^{13}C NMR** ^{13}C NMR (176 MHz, Chloroform-*d*) δ 170.11, 165.36, 136.87, 133.65, 133.22 (2C), 131.92, 130.09 (2C), 129.33, 129.30, 129.16 (2C), 128.70 (2C), 128.56, 128.41 (2C), 126.31 (2C), 101.71, 87.10, 78.36, 72.86, 71.29, 71.02, 68.65, 20.87. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{28}H_{26}O_7S$ 539.1900, found 539.1908.



5-4c

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-8-acetoxy-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-*d*][1,3]dioxin-7-yl pivalate (5-4c).

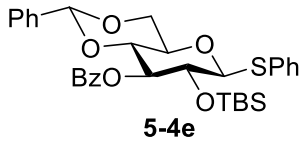
^{1}H NMR(700 MHz, Chloroform-*d*) δ 7.49 – 7.45 (m, 2H), 7.43 – 7.41 (m, 2H), 7.37 – 7.31 (m, 6H), 5.50 (s, 1H), 5.40 (t, *J* = 9.4 Hz, 1H), 5.02 (dd, *J* = 10.1, 9.1 Hz, 1H), 4.82 (d, *J* = 10.1 Hz, 1H), 4.39 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.81 (t, *J* = 10.3 Hz, 1H), 3.68 (t, *J* = 9.6 Hz, 1H), 3.59 (td, *J* = 9.7, 5.0 Hz, 1H), 2.01 (s, 3H), 1.23 (s, 9H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 176.92, 169.93, 136.94, 133.06 (2C), 132.25, 129.30, 129.20 (2C), 128.54, 128.39 (2C), 126.34 (2C), 101.73, 87.27, 78.37, 72.75, 70.91, 70.26, 68.66, 38.95, 27.19 (3C), 20.87.**HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{30}O_7S$ 509.1610, found 509.1599.



5-4d

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-7-((4-chlorobenzyl)oxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yl acetate (5-4d).

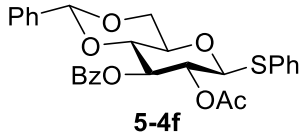
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.56 – 7.51 (m, 2H), 7.45 – 7.40 (m, 2H), 7.37 – 7.28 (m, 8H), 7.26 – 7.23 (m, 2H), 5.48 (s, 1H), 5.38 (dd, *J* = 9.7, 8.8 Hz, 1H), 4.86 (d, *J* = 11.1 Hz, 1H), 4.81 (d, *J* = 9.7 Hz, 1H), 4.59 (d, *J* = 11.1 Hz, 1H), 4.37 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.78 (t, *J* = 10.2 Hz, 1H), 3.60 (t, *J* = 9.6 Hz, 1H), 3.56 – 3.51 (m, 2H), 1.98 (s, 3H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 169.83, 136.96, 136.21, 133.86, 132.89, 132.42 (2C), 129.46 (2C), 129.31 (2C), 129.23, 128.74 (2C), 128.38 (2C), 128.25, 126.26 (2C), 101.51, 88.46, 79.41, 78.63, 74.43, 74.40, 70.52, 68.72, 21.07. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{28}H_{27}ClO_6S$ 549.1115, found 549.1106.



5-4e

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-7-((*tert*-butyldimethylsilyl)oxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yl benzoate (5-4e).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.06 (dt, *J* = 8.2, 1.4 Hz, 2H), 7.58 – 7.54 (m, 1H), 7.51 (dt, *J* = 6.9, 1.4 Hz, 2H), 7.44 (td, *J* = 7.8, 1.3 Hz, 2H), 7.34 (ddtd, *J* = 6.9, 3.9, 2.7, 1.5 Hz, 4H), 7.32 – 7.26 (m, 4H), 5.55 (dd, *J* = 9.8, 8.3 Hz, 1H), 5.47 (s, 1H), 4.83 (dd, *J* = 9.5, 1.2 Hz, 1H), 4.38 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.95 (ddd, *J* = 9.3, 8.2, 1.2 Hz, 1H), 3.80 (t, *J* = 10.3 Hz, 1H), 3.74 (t, *J* = 9.5 Hz, 1H), 3.63 (td, *J* = 9.7, 5.0 Hz, 1H), 0.82 (s, 9H), 0.20 (s, 3H), -0.11 (s, 3H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 165.61, 137.03, 134.07, 133.16, 131.61 (2C), 130.31, 129.95 (2C), 129.22 (2C), 128.99, 128.49 (2C), 128.28 (2C), 127.80, 126.15 (2C), 101.34, 90.62, 79.05, 76.50, 72.96, 70.22, 68.81, 26.04 (3C), 18.31, -3.71 (2C). **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{32}H_{38}O_6SSi$ 601.2056, found 601.2044.

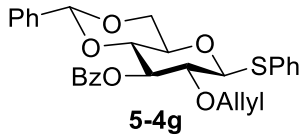


5-4f

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-7-acetoxy-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yl benzoate (5-4f).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.03 – 7.98 (m, 2H), 7.57 – 7.52 (m, 1H), 7.51 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.38 (dt, *J* = 6.5, 4.0 Hz, 2H), 7.35 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.30 (p, *J* = 3.6 Hz, 3H), 5.62 (t, *J* = 9.4 Hz, 1H), 5.51 (s, 1H), 5.22 (t, *J* = 9.6 Hz, 1H), 4.90 (d, *J* = 10.0 Hz, 1H), 4.43 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.83 (dt, *J* = 13.5, 9.9 Hz, 2H), 3.68 (td, *J* = 9.7,

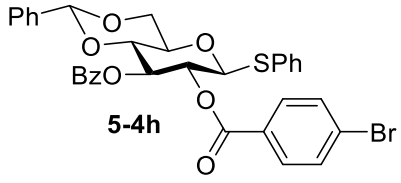
5.0 Hz, 1H), 2.01 (s, 3H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 169.56, 165.76, 136.79, 133.43, 133.03 (2C), 132.04, 130.00 (2C), 129.47, 129.23 (2C), 129.20, 128.58 (2C), 128.54, 128.34 (2C), 126.24 (2C), 101.60, 86.94, 78.58, 73.48, 70.94, 70.69, 68.64, 20.90. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{28}H_{26}O_7S$ 529.1297, found 529.1286.



5-4g

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-7-(allyloxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yl benzoate (5-4g).

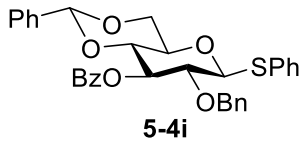
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.10 – 8.04 (m, 2H), 7.59 – 7.53 (m, 3H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.40 – 7.27 (m, 9H), 5.79 – 5.68 (m, 1H), 5.61 (dd, *J* = 9.8, 8.7 Hz, 1H), 5.49 (s, 1H), 5.11 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.01 (dq, *J* = 10.3, 1.3 Hz, 1H), 4.84 (d, *J* = 9.7 Hz, 1H), 4.40 (dd, *J* = 10.6, 5.0 Hz, 1H), 4.32 (ddt, *J* = 12.1, 5.5, 1.3 Hz, 1H), 4.10 (ddt, *J* = 12.2, 6.4, 1.3 Hz, 1H), 3.79 (dt, *J* = 24.9, 9.9 Hz, 2H), 3.65 – 3.56 (m, 2H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 165.48, 136.96, 134.28, 133.26, 133.17, 132.40 (2C), 130.02, 129.93 (2C), 129.24 (2C), 129.11, 128.53 (2C), 128.30 (2C), 128.12, 126.26 (2C), 118.01, 101.48, 88.65, 79.04, 78.76, 75.15, 74.37, 70.61, 68.80. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{29}H_{28}O_6S$ 527.1504, found 527.1493.



5-4h

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-8-(benzoyloxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-*d*][1,3]dioxin-7-yl 4-bromobenzoate (5-4h).

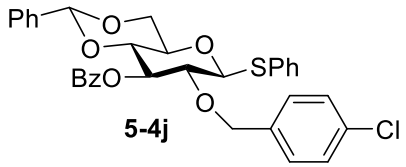
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.96 – 7.89 (m, 2H), 7.82 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.56 – 7.29 (m, 16H), 5.83 – 5.73 (m, 1H), 5.54 (s, 1H), 5.49 – 5.40 (m, 1H), 5.03 (ddd, *J* = 11.2, 10.0, 1.0 Hz, 1H), 4.47 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.90 (dt, *J* = 14.5, 10.1 Hz, 2H), 3.79 – 3.71 (m, 1H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 165.71, 164.64, 136.76, 133.35, 133.19 (2C), 131.95 (2C), 131.52 (2C), 130.03, 129.93 (2C), 129.22 (2C), 129.17, 128.79, 128.63, 128.56, 128.47 (2C), 128.35 (2C), 128.13, 126.25 (2C), 101.65, 87.12, 78.59, 73.33, 71.45, 71.14, 68.66.**HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{33}H_{27}BrO_7S$ 669.0559, found 669.0545.



5-4i

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-7-(benzyloxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yl benzoate (5-4i).

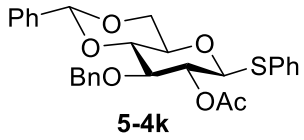
^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.02 (dt, *J* = 8.4, 1.1 Hz, 2H), 7.60 – 7.54 (m, 3H), 7.43 (ddd, *J* = 8.4, 7.4, 0.9 Hz, 2H), 7.40 – 7.33 (m, 5H), 7.30 – 7.27 (m, 3H), 7.20 – 7.12 (m, 5H), 5.67 (ddd, *J* = 9.8, 8.7, 0.9 Hz, 1H), 5.50 (s, 1H), 4.90 (dd, *J* = 9.7, 0.9 Hz, 1H), 4.85 (d, *J* = 10.5 Hz, 1H), 4.61 (d, *J* = 10.5 Hz, 1H), 4.41 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.82 (t, *J* = 10.3 Hz, 1H), 3.80 – 3.76 (m, 1H), 3.72 (ddd, *J* = 9.6, 8.6, 0.9 Hz, 1H), 3.62 (td, *J* = 9.6, 4.9 Hz, 1H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 165.49, 137.32, 136.96, 133.23, 133.16, 132.45 (2C), 129.99, 129.94 (2C), 129.28 (2C), 129.10, 128.51 (2C), 128.45 (2C), 128.41 (2C), 128.30 (2C), 128.16, 128.00, 126.25 (2C), 101.49, 88.71, 79.40, 78.83, 77.34, 75.18, 70.60, 68.80. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{33}H_{30}O_6S$ 577.1649, found 577.1661.



5-4j

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-7-((4-chlorobenzyl)oxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yl benzoate (5-4j).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.99 – 7.95 (m, 2H), 7.60 – 7.53 (m, 3H), 7.45 – 7.42 (m, 2H), 7.39 – 7.33 (m, 5H), 7.31 – 7.27 (m, 3H), 7.08 (s, 4H), 5.64 (dd, *J* = 9.8, 8.7 Hz, 1H), 5.49 (s, 1H), 4.89 (d, *J* = 9.6 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.56 (d, *J* = 11.0 Hz, 1H), 4.41 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.82 (t, *J* = 10.3 Hz, 1H), 3.77 (t, *J* = 9.6 Hz, 1H), 3.68 (dd, *J* = 9.7, 8.7 Hz, 1H), 3.62 (td, *J* = 9.7, 5.0 Hz, 1H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 165.47, 136.91, 135.86, 133.79, 133.36, 133.05, 132.37 (2C), 129.84 (2C), 129.82, 129.71 (2C), 129.33 (2C), 129.13, 128.58 (2C), 128.55 (2C), 128.31 (2C), 128.23, 126.24 (2C), 101.51, 88.65, 79.47, 78.75, 75.01, 74.55, 70.65, 68.78. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{33}H_{29}ClO_6S$ 661.1271, found 661.1263.

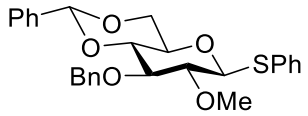


5-4k

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-8-(benzyloxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-*d*][1,3]dioxin-7-yl acetate (5-4k).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.51 – 7.44 (m, 4H), 7.42 – 7.27 (m, 11H), 5.58 (s, 1H), 5.06 – 5.00 (m, 1H), 4.86 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 10.1 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.39 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.81 (t, *J* = 10.3 Hz, 1H), 3.77 – 3.73 (m, 2H), 3.51 (td, *J* = 9.5, 4.8 Hz, 1H), 2.03 (d, *J* = 1.6 Hz, 3H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 169.47,

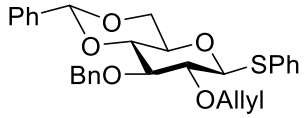
138.18, 137.23, 132.80 (2C), 132.40, 129.21, 129.10 (2C), 128.48 (2C), 128.44 (2C), 128.29, 128.06 (2C), 127.88, 126.13 (2C), 101.38, 86.96, 81.45, 79.84, 74.52, 71.45, 70.65, 68.70, 21.12.



5-4l

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-8-(benzyloxy)-7-methoxy-2-phenyl-6 (phenylthio)hexahydropyrano-[3,2-*d*][1,3]dioxine (5-4l).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.55 – 7.52 (m, 2H), 7.49 – 7.46 (m, 2H), 7.40 – 7.35 (m, 5H), 7.33 – 7.27 (m, 6H), 5.57 (s, 1H), 4.92 (d, *J* = 11.2 Hz, 1H), 4.79 (d, *J* = 11.3 Hz, 1H), 4.64 (d, *J* = 9.8 Hz, 1H), 4.37 (dd, *J* = 10.6, 5.1 Hz, 1H), 3.78 (t, *J* = 10.3 Hz, 1H), 3.73 (dd, *J* = 9.4, 8.3 Hz, 1H), 3.65 (m, 1H, s, 3H), 3.45 (td, *J* = 9.8, 5.1 Hz, 1H), 3.21 (dd, *J* = 9.8, 8.3 Hz, 1H). **^{13}C** (176 MHz, Chloroform-*d*) δ 138.49, 137.41, 133.14, 132.50 (2C), 129.12 (2C), 128.55 (2C), 128.50 (2C), 128.40 (2C), 128.19, 127.99, 127.89, 126.15 (2C), 101.29, 88.20, 83.06, 82.39, 81.38, 75.30, 70.40, 68.85, 61.63.**HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{27}H_{28}O_5S$ 487.1555, found 487.1567.

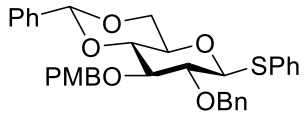


5-4m

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-7-(allyloxy)-8-(benzyloxy)-2-phenyl-6-(phenylthio)hexahydro-pyrano[3,2-*d*][1,3]dioxine (5-4m).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.56 – 7.45 (m, 4H), 7.41 – 7.28 (m, 11H), 5.98 (ddt, *J* = 16.4, 10.9, 5.8 Hz, 1H), 5.57 (s, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.19 (d, *J* = 10.4 Hz, 1H), 4.91 (d, *J* = 11.2 Hz, 1H), 4.78 (d, *J* = 11.1 Hz, 1H), 4.69 (d, *J* = 9.8 Hz, 1H), 4.40 – 4.28 (m, 3H), 3.78 (q,

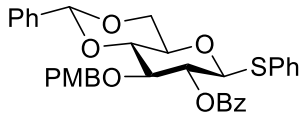
J = 9.5, 8.5 Hz, 2H), 3.66 (t, *J* = 9.4 Hz, 1H), 3.46 (td, *J* = 9.6, 4.9 Hz, 1H), 3.38 (dd, *J* = 9.7, 8.3 Hz, 1H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 138.41, 137.39, 134.81, 133.26, 132.42 (2C), 129.12 (2C), 128.56, 128.51 (2C), 128.40 (2C), 128.27 (2C), 127.96, 127.91, 126.13 (2C), 117.48, 101.27, 88.40, 83.01, 81.43, 80.37, 75.45, 74.84, 70.43, 68.84. (*m*/*z*): $[M+Na]^+$ calcd for $C_{29}H_{30}O_5S$ 513.1712, found 513.1698.



5-4n

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-7-(benzyloxy)-8-((4-methoxybenzyl)oxy)-2-phenyl-6-(phenylthio)-hexahydropyr-ano[3,2-*d*][1,3]dioxine (5-4n).

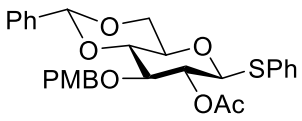
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.56 – 7.46 (m, 4H), 7.42 – 7.29 (m, 11H), 7.26 – 7.23 (m, 2H), 6.85 – 6.78 (m, 2H), 5.59 (s, 1H), 4.88 – 4.78 (m, 3H), 4.73 (dd, *J* = 17.1, 10.3 Hz, 2H), 4.39 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.85 – 3.79 (m, 2H), 3.78 (s, 3H), 3.68 (t, *J* = 9.3 Hz, 1H), 3.52 – 3.44 (m, 2H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 159.45, 138.20, 137.41, 133.20, 132.51 (2C), 130.55, 129.97 (2C), 129.15 (2C), 129.13, 128.55 (2C), 128.41 (2C), 128.33 (2C), 128.01 (2C), 126.13 (2C), 113.94 (2C), 101.27, 88.39, 82.78, 81.61, 80.54, 76.01, 75.14, 70.41, 68.86, 55.41. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{34}H_{34}O_6S$ 593.1974, found 593.1963.



5-4o

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-8-((4-methoxybenzyl)oxy)-2-phenyl-6-(phenylthio)hexahydro-pyrano[3,2-*d*][1,3]dioxin-7-yl benzoate (5-4o).

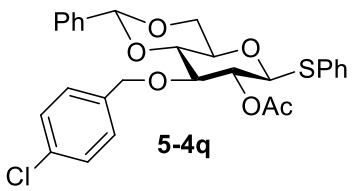
^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.04 – 7.98 (m, 2H), 7.61 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.53 – 7.35 (m, 10H), 7.30 – 7.27 (m, 3H), 7.04 – 7.00 (m, 2H), 6.60 – 6.55 (m, 2H), 5.61 (s, 1H), 5.25 (ddd, *J* = 10.3, 8.8, 1.6 Hz, 1H), 4.84 (d, *J* = 10.0 Hz, 1H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.42 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.89 – 3.78 (m, 3H), 3.69 (s, 3H), 3.56 (td, *J* = 9.7, 5.0 Hz, 1H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 165.12, 159.25, 137.34, 133.32, 133.10 (2C), 132.36, 130.08 (2C), 129.96, 129.93 (2C), 129.20, 129.04 (2C), 128.50 (2C), 128.44 (2C), 128.31, 126.16 (2C), 113.81, 113.69 (2C), 101.43, 87.16, 81.61, 78.89, 74.01, 72.15, 70.78, 68.77, 55.24. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{34}H_{32}O_7S$ 607.1766, found 607.1759.



5-4p

(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-8-((4-methoxybenzyl)oxy)-2-phenyl-6-(phenylthio)hexahydro-pyrano[3,2-*d*][1,3]dioxin-7-yl acetate (5-4p).

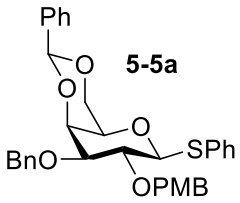
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.52 – 7.43 (m, 4H), 7.41 – 7.36 (m, 3H), 7.31 (dd, *J* = 5.1, 2.0 Hz, 4H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.85 – 6.82 (m, 2H), 5.57 (s, 1H), 5.00 (t, *J* = 9.4 Hz, 1H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.69 (d, *J* = 10.1 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.39 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.83 – 3.80 (m, 1H), 3.79 (s, 3H), 3.74 – 3.71 (m, 2H), 3.50 (dq, *J* = 9.6, 5.0 Hz, 1H), 2.05 (s, 3H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 169.44, 159.39, 137.26, 132.80 (2C), 132.41, 130.26, 129.76 (2C), 129.20, 129.09 (2C), 128.43 (2C), 128.27, 126.13 (2C), 113.85 (2C), 101.37, 86.95, 81.44, 79.30, 74.09, 71.51, 70.67, 68.70, 55.42, 21.16.



5-4q

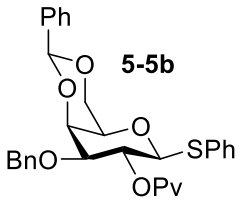
(2*R*,4a*R*,6*S*,7*R*,8*S*,8a*R*)-8-((4-chlorobenzyl)oxy)-2-phenyl-6-(phenylthio)hexahydropyrano-[3,2-*d*][1,3]dioxin-7-yl acetate (5-4q).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.46 (dtd, *J* = 9.0, 5.0, 4.2, 2.5 Hz, 4H), 7.41 – 7.36 (m, 3H), 7.33 – 7.30 (m, 3H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.25 (s, 1H), 7.21 – 7.16 (m, 2H), 5.56 (s, 1H), 5.05 – 4.99 (m, 1H), 4.81 (d, *J* = 12.2 Hz, 1H), 4.70 (d, *J* = 10.1 Hz, 1H), 4.63 (d, *J* = 12.2 Hz, 1H), 4.39 (dd, *J* = 10.6, 5.0 Hz, 1H), 3.80 (t, *J* = 10.3 Hz, 1H), 3.75 – 3.69 (m, 2H), 3.50 (dq, *J* = 9.5, 4.7 Hz, 1H), 2.06 (s, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 169.41, 137.16, 136.72, 133.60, 132.84, 132.34, 129.27, 129.26, 129.12, 128.61, 128.46, 128.34, 126.12, 101.46, 86.97, 81.32, 80.07, 73.62, 71.46, 70.64, 68.68, 21.13.



(2*S*,4a*R*,6*S*,7*R*,8*S*,8a*S*)-8-(benzyloxy)-7-((4-methoxybenzyl)oxy)-2-phenyl-6-(phenylthio)-hexahydropyr-ano[3,2-*d*][1,3]dioxine (5-5a).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.78 – 7.67 (m, 2H), 7.56 – 7.51 (m, 2H), 7.42 – 7.27 (m, 10H), 7.24 – 7.14 (m, 3H), 6.91 – 6.84 (m, 2H), 5.50 (s, 1H), 4.73 (d, *J* = 4.7 Hz, 2H), 4.65 – 4.58 (m, 3H), 4.37 (dd, *J* = 12.3, 1.6 Hz, 1H), 4.15 (d, *J* = 4.1 Hz, 1H), 3.99 (dd, *J* = 12.3, 1.7 Hz, 1H), 3.90 (t, *J* = 9.4 Hz, 1H), 3.81 (s, 3H), 3.62 (dd, *J* = 9.2, 3.4 Hz, 1H), 3.42 (s, 1H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 159.42, 138.32, 138.03, 132.96, 132.83 (2C), 130.84, 130.01 (2C), 129.19, 129.00 (2C), 128.55 (2C), 128.31 (2C), 127.94 (2C), 127.55, 126.77, 126.76 (2C), 113.91 (2C), 101.49, 86.72, 81.51, 75.29, 75.26, 73.91, 72.04, 69.99, 69.58, 55.46.

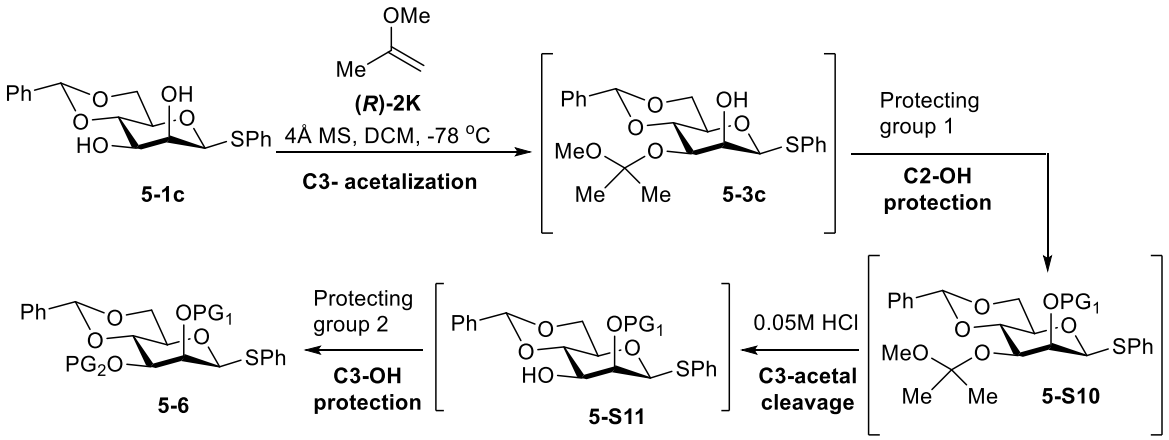


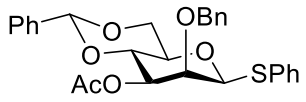
(2*S*,4a*R*,6*S*,7*R*,8*S*,8a*S*)-8-(benzyloxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-*d*][1,3]dioxin-7-yl pivalate (5-5b).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.62 – 7.55 (m, 2H), 7.43 (dd, *J* = 6.7, 3.1 Hz, 2H), 7.38 – 7.33 (m, 3H), 7.31 – 7.26 (m, 6H), 7.25 – 7.20 (m, 2H), 5.44 (s, 1H), 5.34 (t, *J* = 9.7 Hz, 1H), 4.70 (d, *J* = 9.9 Hz, 1H), 4.67 – 4.59 (m, 2H), 4.35 (dd, *J* = 12.4, 1.6 Hz, 1H), 4.15 (dd, *J* = 3.4, 1.0 Hz, 1H), 3.98 (dd, *J* = 12.4, 1.7 Hz, 1H), 3.69 (dd, *J* = 9.7, 3.4 Hz, 1H), 3.44 (s, 1H), 1.25 (s, 9H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 176.59, 138.06, 137.76, 133.45 (2C), 132.22, 129.12, 128.85 (2C), 128.47 (2C), 128.22 (2C), 127.98, 127.88, 127.68 (2C), 126.67 (2C), 101.26, 85.87, 78.86, 73.51, 71.46, 70.10, 69.45, 68.08, 38.90, 27.37 (3C).

General procedure (D-mannose-based substrates):

C3 acetalization → C2-OH protection → C3-acetal cleavage → C3-OH protection





5-6a

(2*R*,4a*R*,6*S*,7*S*,8*S*,8a*R*)-7-(benzyloxy)-2-phenyl-6-(phenylthio)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yl acetate (5-6a).

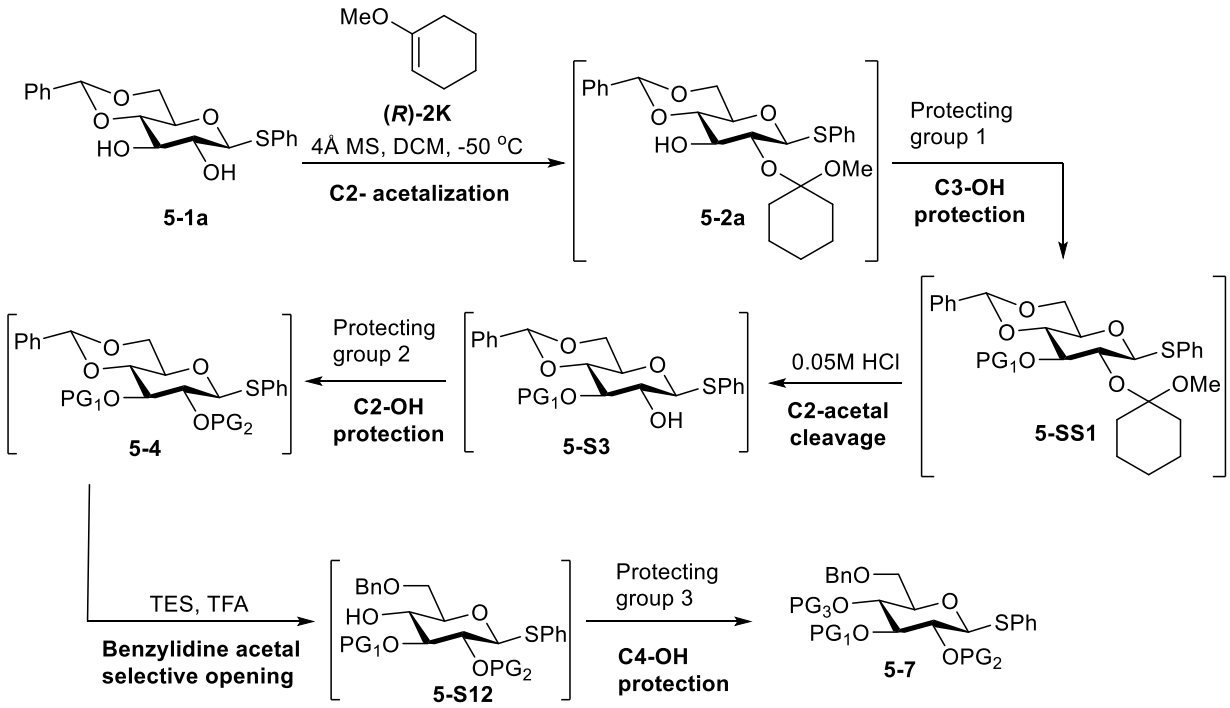
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.54 – 7.42 (m, 4H), 7.39 – 7.27 (m, 11H), 5.58 (s, 1H), 5.54 (s, 1H), 5.28 (dd, *J* = 10.5, 3.4 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.40 (td, *J* = 9.8, 4.8 Hz, 1H), 4.27 – 4.20 (m, 3H), 3.88 (t, *J* = 10.3 Hz, 1H), 2.03 (s, 3H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 170.31, 137.41, 137.39, 133.74, 131.96 (2C), 129.32 (2C), 129.22, 128.69 (2C), 128.40 (2C), 128.27, 128.21 (2C), 127.90, 126.38 (2C), 101.99, 86.52, 77.75, 76.37, 73.21, 70.66, 68.65, 65.44, 21.13.

5.9.3 Single-pot synthesis of fully functionalized D-glucose-derivatives (Chapter 5.5)

General procedure:

C2 acetalization → C3-OH protection → C2-acetal cleavage → C2-OH protection

→ Benzylidine acetal selective opening → C4-OH protection



1**) C2 acetalization**

- The procedure was described above (Section 5.9.1).

2) C3-OH protection

- The procedure was described above (Section 5.9.2).

3) C2-acetal cleavage

- The procedure was described above (Section 5.9.2).

4) C2-OH protection

- The procedure was described above (Section 5.9.2).

- Instead of performing purification on compound **5-4**, the crude mixture **5-4** was dried completely dried by passing a stream of N_2 followed by applying high vacuum, and was directly advanced to the next step.

5) 4-6-benzylidine acetal selective opening

Instruction:

The condition for this step may cleave some protecting groups like acetyl (Ac), *tert*-butyldimethyl silyl (TBS), *para*-methoxybenzyl (PMB) groups. We observed a side-reactions with substrates containing such protecting groups, and undesired C2-and C3-deprotection was observed under the condition. In particular, this happened when the reaction was stirred for more than 2 h at room temperature. To address the problem, the reaction was stirred at 0 ^{o}C for 2 h and was quenched with base after 2 h. Even though reaction might not be completed, the conversion was mostly higher than 70%. In addition, the unreacted benzylidine acetal containing compound **5-4** could be successfully recovered along with the final product **5-7** using the column purification after the final protection step (Compound **5-4** does not react with the reagents in the last step).

Procedure:

The crude C2, C3-protected glucose derivative **5-4** (1.0 equiv) was dissolved in DCM (0.2 M) and the mixture was cooled to 0 ^{o}C. Then triethyl-silane (5 equiv) was added to the mixture followed by the slow addition of trifluoroacetic acid (5 equiv) at 0 ^{o}C. The reaction mixture was stirred for 2 h at 0 ^{o}C, before being quenched with triethyl-amine after 2 h period. The resulting crude compound **5-S5** was completely dried by passing a stream of N_2 followed by applying high vacuum.

6) C4-OH protection

Instruction:

At this point, various reagents still remained in the reaction pot from previous steps. However, the desired crude product is supposed to have only one free C4-OH. To avoid undesired side-reactions with previous reagents, a large excess of the protection step reagents was used. This would also ensure protecting reagents to be sufficiently reactive with the C4-OH.

Procedure:

* The resulting dried crude compound **5-4** was subjected to one of the following conditions below.

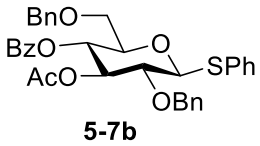
Acetylation: Pyridine (20.0 equiv) and anhydrous dichloromethane (0.5M) were added to the reaction mixture. Then acetic anhydride (2.0 equiv), and 4-dimethyaminopyridine (DMAP) (0.3 equiv) were added to the mixture. The reaction mixture was stirred at room temperature until TLC analysis indicated reaction completion. After completion, the reaction was slowly quenched with methanol. The solvent was then removed under vacuum and the residue was dissolved in DCM and washed with NH_4Cl (x3). The resultant aqueous layers were extracted with DCM (x2), and the organic layers were combined and dried over $MgSO_4$. The dried crude solution was concentrated *in vacuo* and purified by a flash column chromatography on SiO_2 (hexanes : ethyl acetate, 15:1 → 10:1 → 4:1).

Benzoylation: Pyridine (20.0 equiv) and anhydrous dichloromethane (0.5M) were added to the reaction mixture. Then, benzoyl chloride (2.0 equiv), and 4-dimethyaminopyridine (DMAP) (0.3 equiv) were added to the mixture. The reaction mixture was stirred at room temperature until TLC analysis indicated reaction completion. After completion, the reaction was slowly quenched with methanol. The solvent was then removed under vacuum and the residue was dissolved in DCM and washed with NH_4Cl (x3). The resultant aqueous layers were extracted with DCM (x2), and

the organic layers were combined and dried over $MgSO_4$. The dried crude solution was concentrated *in vacuo* and purified by a flash column chromatography on SiO_2 (hexanes : ethyl acetate, 15:1 → 10:1 → 4:1).

Pivaloylation: Pyridine (20.0 equiv) and anhydrous dichloromethane (0.5M) were added to the reaction mixture. Then pivaloyl chloride (2.0 equiv), and 4-dimethyaminopyridine (DMAP) (0.3 equiv) were added to the mixture. The reaction was stirred at room temperature until TLC analysis indicated reaction completion. After completion, the reaction mixture was slowly quenched with methanol. The solvent was then removed under vacuum and the residue was dissolved in DCM and washed with NH_4Cl (x3). The resultant aqueous layers were extracted with DCM (x2), and the organic layers were combined and dried over $MgSO_4$. The dried crude solution was concentrated *in vacuo* and purified by a flash column chromatography on SiO_2 (hexanes : ethyl acetate, 15:1 → 10:1 → 4:1).

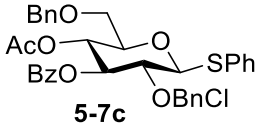
***Para*-methoxybenzylation:** Anhydrous DMF (0.2M) was added to the reaction mixture. Then sodium hydride (60% dispersion in mineral oil) (2.5 equiv), and benzyl bromide (2.0 equiv), tetrabutylammonium iodide (TBAI) (0.3 equiv) were sequentially added. The resultant reaction was stirred at room temperature until TLC analysis indicated reaction completion. After completion, the reaction was slowly quenched with methanol. The solvent was then removed under vacuum and the residue was dissolved in DCM and washed with NH_4Cl (x3). The resultant aqueous layers were extracted with DCM (x2), and the organic layers were combined and dried over $MgSO_4$. The dried crude solution was concentrated *in vacuo* and purified by a flash column chromatography on SiO_2 (hexanes : ethyl acetate, 15:1 → 10:1 → 4:1).



5-7b

(2R,3R,4S,5R,6S)-4-acetoxy-5-(benzyloxy)-2-((benzyloxy)methyl)-6-(phenylthio)tetrahydro-2H-pyran-3-yl benzoate (5-7b).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 8.3 Hz, 2H), 7.63 – 7.58 (m, 2H), 7.58 – 7.54 (m, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.26 (m, 8H), 7.25 – 7.19 (m, 5H), 5.43 (t, *J* = 9.4 Hz, 1H), 5.24 (t, *J* = 9.8 Hz, 1H), 4.88 (d, *J* = 11.2 Hz, 1H), 4.81 (d, *J* = 9.7 Hz, 1H), 4.59 (d, *J* = 11.2 Hz, 1H), 4.53 – 4.45 (m, 2H), 3.86 – 3.79 (m, 1H), 3.69 – 3.59 (m, 3H), 1.78 (s, 3H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 170.06, 165.62, 137.97, 137.79, 133.57, 133.40, 132.20 (2C), 129.98 (2C), 129.22, 129.18 (2C), 128.64 (2C), 128.58 (2C), 128.40 (2C), 128.20 (2C), 128.04, 127.91, 127.79 (2C), 127.69, 87.76, 78.61, 77.81, 75.58, 75.18, 73.70, 69.97, 69.46, 20.80. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{35}H_{34}O_7S$ 621.1923, found 621.1912.

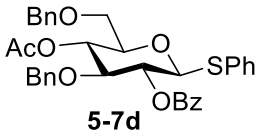


5-7c

(2R,3R,4S,5R,6S)-3-acetoxy-2-((benzyloxy)methyl)-5-((4-chlorobenzyl)oxy)-6-(phenylthio)tetrahydro-2H-pyran-4-yl benzoate (5-7c).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 – 7.83 (m, 2H), 7.63 – 7.54 (m, 3H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.37 – 7.27 (m, 8H), 7.06 – 6.97 (m, 4H), 5.47 (t, *J* = 9.4 Hz, 1H), 5.19 (t, *J* = 9.8 Hz, 1H), 4.83 – 4.72 (m, 2H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.49 (dd, *J* = 17.0, 11.5 Hz, 2H), 3.74 (ddd, *J* = 9.9, 5.3, 2.9 Hz, 1H), 3.66 – 3.57 (m, 3H), 1.81 (s, 3H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 169.81, 165.76, 137.96, 135.79, 133.76, 133.53, 133.28, 132.18, 129.82, 129.74, 129.40, 129.25,

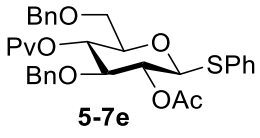
128.64, 128.55, 128.51, 127.98, 127.85, 87.68, 78.40, 77.50, 76.16, 74.25, 73.71, 69.10, 69.07, 20.73.



5-7d

(2S,3R,4S,5R,6R)-5-acetoxy-4-(benzyloxy)-6-((benzyloxy)methyl)-2-(phenylthio)tetrahydro-2H-pyran-3-yl benzoate (5-7d).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 5.85 (s, 1H), 2.16 (s, 2H), 2.14 (s, 2H), 1.91 (s, 3H), 1.00 (s, 6H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 169.69, 165.12, 138.08, 137.67, 133.43, 133.03, 132.50 (2C), 130.03(2C), 129.88, 129.01(2C), 128.60 (2C), 128.51 (2C), 128.42 (2C), 128.00 (2C), 127.95 (2C), 127.87, 127.85, 127.84, 86.46, 81.59, 78.10, 74.29, 73.82, 72.26, 70.88, 70.01, 20.96.**HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{35}H_{34}O_7S$ 621.1923, found 621.1911.

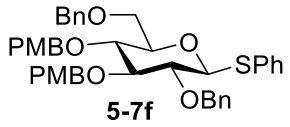


5-7e

(2R,3R,4S,5R,6S)-5-acetoxy-4-(benzyloxy)-2-((benzyloxy)methyl)-6-(phenylthio)tetrahydro-2H-pyran-3-yl pivalate (5-7e).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 7.7 Hz, 2H), 7.35 – 7.28 (m, 7H), 7.26 – 7.16 (m, 6H), 5.14 – 5.05 (m, 2H), 4.71 (d, *J* = 10.0 Hz, 1H), 4.62 (d, *J* = 11.1 Hz, 1H), 4.59 – 4.54 (m, 2H), 4.49 (d, *J* = 11.8 Hz, 1H), 3.78 (t, *J* = 9.2 Hz, 1H), 3.71 (t, *J* = 8.5 Hz, 1H), 3.60 – 3.55 (m, 1H), 3.50 (d, *J* = 11.0 Hz, 1H), 1.99 (s, 3H), 1.12 (s, 9H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 176.97, 169.49, 138.02, 137.82, 133.45, 132.49, 131.90 (2C), 129.05 (2C), 128.53 (2C), 128.52

(2C), 127.93 (2C), 127.85, 127.82, 127.61 (2C), 86.45, 82.04, 78.45, 73.86, 73.77, 71.27, 69.89, 69.61, 38.90, 27.18 (3C), 21.08.



5-7f

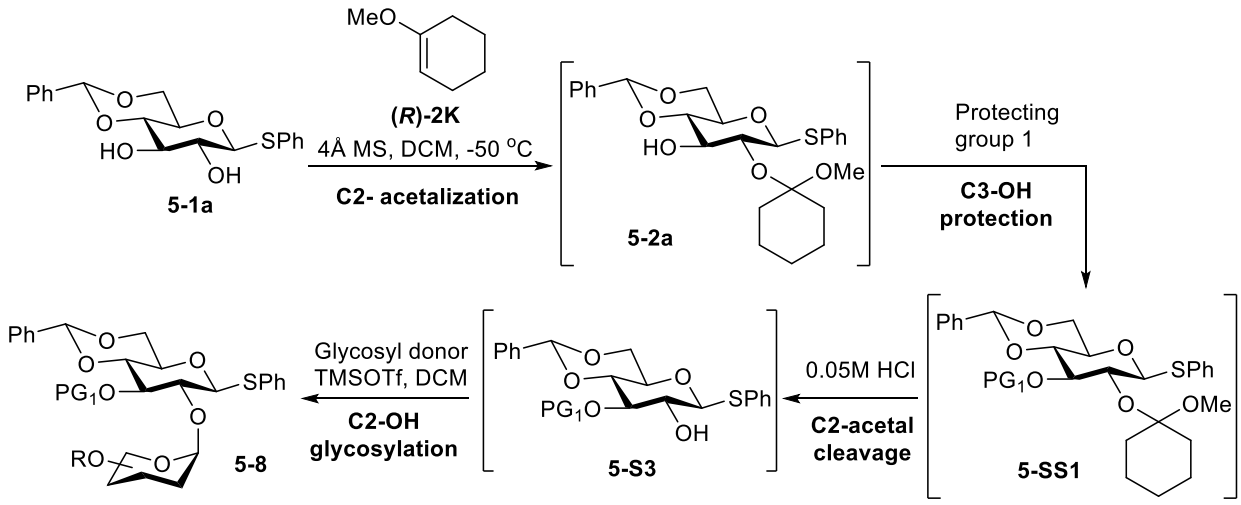
(2S,3R,4S,5R,6R)-3-(benzyloxy)-6-((benzyloxy)methyl)-4,5-*bis*((4-methoxybenzyl)oxy)-2-(phenylthio)tetrahydro-2H-pyran (5-7f).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.58 (dt, *J* = 7.0, 3.3 Hz, 2H), 7.47 – 7.27 (m, 11H), 7.24 – 7.20 (m, 4H), 7.15 – 7.05 (m, 2H), 6.88 – 6.79 (m, 4H), 4.88 (d, *J* = 10.4 Hz, 1H), 4.84 – 4.70 (m, 4H), 4.68 – 4.64 (m, 1H), 4.62 – 4.58 (m, 1H), 4.56 – 4.49 (m, 2H), 3.82 – 3.75 (m, 7H), 3.73 – 3.65 (m, 2H), 3.60 (dd, *J* = 11.3, 8.1 Hz, 1H), 3.51 – 3.45 (m, 2H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 159.46, 159.39, 138.48, 138.26, 133.97, 132.07 (2C), 130.77, 130.40, 129.75 (2C), 129.61 (2C), 129.02 (2C), 128.56 (2C), 128.48 (2C), 128.31 (2C), 127.98, 127.78 (2C), 127.67, 127.54, 114.02 (2C), 113.99 (2C), 87.56, 86.65, 80.99, 79.27, 77.70, 75.66, 75.54, 74.84, 73.55, 69.20, 55.43 (2C). **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{42}H_{44}O_7S$ 715.2705, found 715.2692.

5.9.4 Regioselective single-pot protection/glycosylation of monosaccharide (Chapter 5.6).

General procedure:

C2 acetalization → C3-OH protection → C2-acetal cleavage → C2-OH glycosylation



1) C2 acetalization

- The procedure was described above (Section 5.9.1).

2) C3-OH protection

- The procedure was described above (Section 5.9.2).

3. C2-acetal cleavage

- The procedure was described above (Section 5.9.2).

4. C2-OH glycosylation

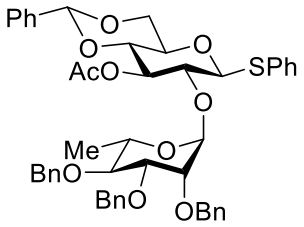
Instruction:

Some of the residual reagents used in prior steps could affect the yield of this step (especially acetyl, benzoyl protection in C3-position) We observed that trichloroacetimidate glycosyl donors may react with acetyl anhydride, benzoyl chloride, etc. As a result, acetylated and benzoylated glycosyl donor was obtained and the glycosylation yields were diminished. To address this problem, 2.5 equiv of donor (instead of 1.4 equiv) were used for the glycosylation reactions, and, indeed the yield increased substantially. Filtering on compound **5-S3** after 3 steps could also

improve final glycosylation yield. Besides acetyl and benzoyl glycosylation, we did not observe any side-reactions of trichloroacetimidate donors, and relatively high yields were achieved.

Procedure:

The resulting C3-OH protected substrate **5-S2** (1.0 equiv) was dried by azeotropic removal of moisture with toluene (x3). Then, trichloroacetimidate donor (1.4 equiv) and activated 4Å MS were added to the mixture. The reaction mixture was then dissolved in DCM (0.2M) and cooled down to 0 ^{o}C. Then trimethylsilyl trifluoromethanesulfonate (20 mol%) was added to the resultant mixture, and the solution was stirred for 1 h at 0 ^{o}C. After the reaction completion, the mixture was quenched with triethyl amine and the crude product was purified by a flash column chromatography on SiO_2 (hexanes : ethyl acetate, 13:1 → 8:1 → 3:1).

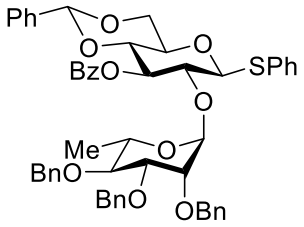


5-8a

(*2R,4aR,6S,7R,8S,8aR*)-2-phenyl-6-(phenylthio)-7-(((*2S,3R,4R,5S,6S*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)hexahydropyrano[3,2-d][1,3]dioxin-8-yl acetate (5-8a).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.56 – 7.51 (m, 2H), 7.47 – 7.27 (m, 23H), 5.45 (s, 1H), 5.35 (t, *J* = 8.7 Hz, 1H), 5.07 (d, *J* = 2.3 Hz, 1H), 4.87 (d, *J* = 11.0 Hz, 1H), 4.74 – 4.69 (m, 2H), 4.67 – 4.60 (m, 4H), 4.34 (dd, *J* = 10.6, 4.5 Hz, 1H), 4.23 (dt, *J* = 12.3, 6.3 Hz, 1H), 3.84 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.80 (t, *J* = 8.9 Hz, 1H), 3.78 – 3.76 (m, 1H), 3.73 (t, *J* = 9.8 Hz, 1H), 3.64 (t, *J* = 9.1 Hz, 1H), 3.57 – 3.50 (m, 2H), 1.95 (s, 3H), 1.36 (d, *J* = 6.0 Hz, 3H). **^{13}C NMR** (176 MHz,

Chloroform-*d*) δ 169.88, 138.76, 138.71, 138.52, 137.01, 132.86 (2C), 132.67, 129.21, 129.15 (2C), 128.50 (2C), 128.49 (2C), 128.45 (2C), 128.38 (2C), 128.17, 128.07 (2C), 127.75, 127.73 (2C), 127.70 (2C), 127.64, 126.23 (2C), 101.49, 100.12, 87.13, 80.59, 79.78, 78.34, 76.47, 75.75, 75.02, 73.28, 72.41 (2C), 70.15, 69.45, 68.69, 21.04, 18.03. (**HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{48}H_{50}O_{10}S$ 841.3022, found 841.3011.

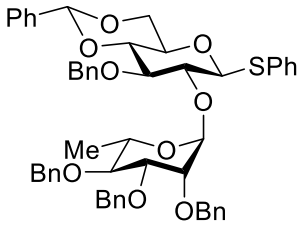


5-8b

(*2R,4aR,6S,7R,8S,8aR*)-2-phenyl-6-(phenylthio)-7-(((*2S,3R,4R,5S,6S*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)hexahydropyrano[3,2-d][1,3]dioxin-8-yl benzoate (5-8b).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.14 – 8.05 (m, 2H), 7.58 – 7.53 (m, 3H), 7.44 – 7.28 (m, 20H), 7.20 – 7.12 (m, 3H), 7.01 – 6.89 (m, 2H), 5.72 – 5.64 (m, 1H), 5.47 (s, 1H), 5.10 (d, *J* = 2.0 Hz, 1H), 4.87 (d, *J* = 11.1 Hz, 1H), 4.80 (d, *J* = 9.5 Hz, 1H), 4.63 – 4.52 (m, 3H), 4.38 (dd, *J* = 10.6, 4.9 Hz, 1H), 4.29 (dq, *J* = 9.6, 6.2 Hz, 1H), 4.14 (d, *J* = 11.6 Hz, 1H), 3.96 (t, *J* = 9.0 Hz, 1H), 3.85 (d, *J* = 11.7 Hz, 1H), 3.82 – 3.76 (m, 2H), 3.72 (t, *J* = 9.6 Hz, 1H), 3.66 – 3.61 (m, 2H), 3.58 (t, *J* = 9.4 Hz, 1H), 1.33 (d, *J* = 6.3 Hz, 3H) **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 165.38, 138.81, 138.76, 138.36, 136.91, 133.77, 132.93, 132.60, 130.10, 130.05, 129.50, 129.17, 129.14, 128.85, 128.52, 128.46, 128.41, 128.35, 128.32, 128.20, 128.11, 127.67, 127.58, 127.51, 127.39, 127.34, 126.23, 101.50, 100.34, 87.10, 80.18, 79.77, 78.41, 77.84, 77.41, 77.16, 76.91, 76.69,

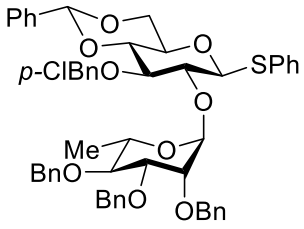
76.25, 75.16, 72.98, 71.94, 70.32, 69.44, 68.71, 17.84. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{53}H_{52}O_{10}S$ 903.3179, found 903.3170.



5-8c

(*2R,4aR,6S,7R,8S,8aR*)-8-(benzyloxy)-2-phenyl-6-(phenylthio)-7-(((*2S,3R,4R,5S,6S*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)hexahydropyrano[3,2-d][1,3]dioxine (5-8c).

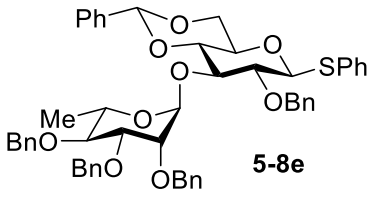
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.59 – 7.52 (m, 2H), 7.47 – 7.26 (m, 20H), 7.26 – 7.17 (m, 8H), 5.54 (s, 1H), 5.30 (s, 1H), 4.99 (d, *J* = 11.4 Hz, 1H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.70 – 4.56 (m, 5H), 4.40 – 4.34 (m, 2H), 4.33 – 4.25 (m, 2H), 3.86 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.79 – 3.63 (m, 6H), 3.48 (td, *J* = 9.6, 5.0 Hz, 1H), 1.36 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 138.94, 138.90, 138.80, 138.30, 137.27, 132.91, 132.84 (2C), 129.15, 129.05 (2C), 128.56 (2C), 128.46 (2C), 128.43 (2C), 128.41 (2C), 128.22 (2C), 128.10 (2C), 127.98, 127.85, 127.73 (2C), 127.67, 127.63, 127.60 (2C), 127.45 (2C), 127.38, 126.08 (2C), 101.27, 100.36, 87.01, 83.56, 81.67, 80.66, 79.98, 78.41, 76.81, 75.21, 74.76, 72.60, 72.40, 70.04, 69.19, 68.79, 17.92. δ **HRMS (ESI+)** (*m*/*z*): $[M+NH_4]^+$ calcd for $C_{53}H_{54}O_9S$ 884.3832, found 884.3835.



5-8d

(*2R,4aR,6S,7R,8S,8aR*)-8-((4-chlorobenzyl)oxy)-2-phenyl-6-(phenylthio)-7-(((*2S,3R,4R,5S,6S*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)hexahydropyrano[3,2-d][1,3]dioxine (5-8d).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.56 – 7.49 (m, 2H), 7.39 – 7.28 (m, 18H), 7.25 – 7.12 (m, 9H), 5.50 (s, 1H), 5.28 (d, *J* = 2.1 Hz, 1H), 4.88 (dd, *J* = 19.0, 11.3 Hz, 2H), 4.70 (d, *J* = 11.8 Hz, 1H), 4.66 – 4.61 (m, 3H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 12.1 Hz, 1H), 4.35 (dd, *J* = 10.7, 5.1 Hz, 1H), 4.32 – 4.26 (m, 2H), 3.85 (dd, *J* = 9.0, 2.9 Hz, 1H), 3.76 – 3.64 (m, 6H), 3.46 (td, *J* = 9.6, 5.0 Hz, 1H), 1.36 (d, *J* = 6.2 Hz, 3H).. **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 138.89, 138.83, 138.62, 137.19, 136.79, 133.55, 132.91, 132.81 (2C), 129.23, 129.07 (2C), 128.84 (2C), 128.66 (2C), 128.50 (2C), 128.46 (2C), 128.43 (2C), 128.35 (2C), 128.11 (2C), 128.01, 127.75 (2C), 127.71, 127.68, 127.51, 127.39 (2C), 126.07 (2C), 101.36, 100.30, 87.04, 83.66, 81.55, 80.74, 79.91, 78.12, 76.88, 75.16, 73.86, 72.70, 72.58, 70.02, 69.25, 68.77, 17.96.. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{53}H_{53}ClO_9S$ 923.2997, found 923.2993.

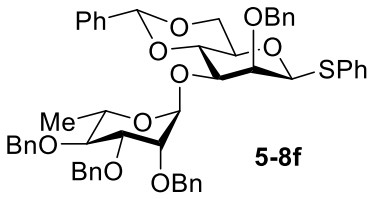


5-8e

(*2R,4aR,6S,7R,8S,8aR*)-7-(benzyloxy)-2-phenyl-6-(phenylthio)-8-(((*2S,3R,4R,5S,6S*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)hexahydropyrano[3,2-d][1,3]dioxine (5-8e).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.51 – 7.48 (m, 2H), 7.48 – 7.45 (m, 2H), 7.35 – 7.27 (m, 20H), 7.25 – 7.22 (m, 3H), 7.18 – 7.17 (m, 2H), 7.14 – 7.13 (m, 1H), 5.50 (s, 1H), 5.21 (d, *J* = 1.8 Hz, 1H), 5.02 (d, *J* = 11.0 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.76 (d, *J* = 9.8 Hz, 1H), 4.65 (d, *J*

= 11.8 Hz, 1H), 4.59 – 4.56 (m, 2H), 4.53 (d, *J* = 11.0 Hz, 1H), 4.38 – 4.34 (m, 2H), 4.30 (d, *J* = 12.2 Hz, 1H), 4.03 – 3.96 (m, 2H), 3.85 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.77 (t, *J* = 10.1 Hz, 1H), 3.70 – 3.68 (m, 1H), 3.55 – 3.44 (m, 4H), 0.85 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 139.04, 138.98, 138.60, 137.93, 137.12, 133.46, 132.14 (2C), 129.23 (2C), 129.14, 128.61 (2C), 128.42 (2C), 128.37 (2C), 128.28 (2C), 128.23 (2C), 128.01, 127.94 (2C), 127.92, 127.68 (2C), 127.60, 127.57, 127.47 (2C), 127.40, 127.18 (2C), 126.54 (2C), 101.98, 98.98, 88.63, 81.97, 80.77, 80.13, 79.47, 79.21, 76.39, 75.18 (2C), 72.61, 72.44, 70.86, 68.82, 68.27, 17.54 **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{53}H_{54}O_9S$ 889.3386, found 889.3381.



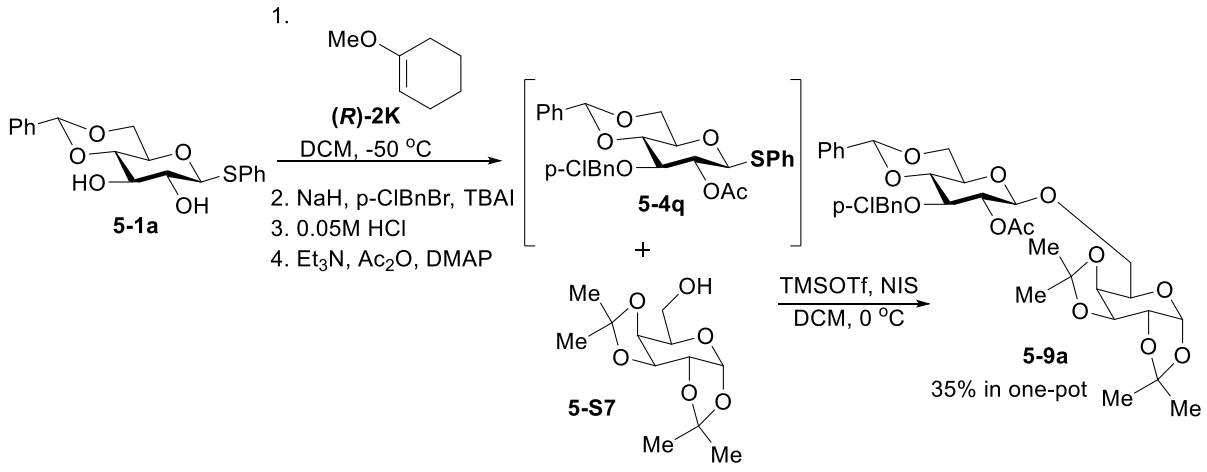
5-8f

(*2R,4aR,6S,7S,8S,8aR*)-7-(benzyloxy)-2-phenyl-6-(phenylthio)-8-(((*2S,3R,4R,5S,6S*)-3,4,5-tris(benzyloxy)-6-methyltetrahydro-2H-pyran-2-yl)oxy)hexahydropyrano[3,2-d][1,3]dioxine (5-8f).

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.47 (d, *J* = 7.7 Hz, 2H), 7.44 – 7.39 (m, 2H), 7.36 – 7.26 (m, 20H), 7.26 – 7.23 (m, 4H), 7.20 (t, *J* = 7.6 Hz, 2H), 5.58 (s, 1H), 5.52 (s, 1H), 4.89 (d, *J* = 11.0 Hz, 1H), 4.81 – 4.75 (m, 2H), 4.67 (d, *J* = 11.7 Hz, 1H), 4.61 (dd, *J* = 11.5, 4.5 Hz, 3H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 4.29 (td, *J* = 9.7, 4.8 Hz, 1H), 4.20 (dd, *J* = 10.3, 4.8 Hz, 1H), 4.14 (dd, *J* = 10.2, 3.1 Hz, 1H), 4.12 – 4.04 (m, 2H), 3.94 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.90 (dd, *J* = 3.1, 1.4 Hz, 1H), 3.84 (t, *J* = 10.3 Hz, 1H), 3.75 – 3.71 (m, 1H), 3.59 (t, *J* = 9.5 Hz, 1H), 1.13 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (176 MHz, Chloroform-*d*) δ 139.16, 138.88, 138.48, 137.67, 137.50, 133.89, 131.78 (2C), 129.31 (2C), 128.82, 128.63 (2C), 128.56 (2C), 128.48 (2C), 128.34

(2C), 128.24 (2C), 128.17 (3C), 127.98 (2C), 127.91, 127.83, 127.80 (2C), 127.65 (2C), 127.62, 127.51, 126.20 (2C), 101.59, 95.77, 87.07, 80.84, 80.27, 77.25, 77.10, 75.09, 75.01, 73.62, 73.21, 72.65, 72.38, 68.60, 68.25, 65.68, 17.83. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{53}H_{54}O_9S$ 889.3386, found 889.3369.

5.9.5 Single-pot glycosylation of regioselectively functionalized thioglycoside (Chapter 5.7)



(*2R,4aR,6R,7R,8S,8aR*)-8-((4-chlorobenzyl)oxy)-2-phenyl-6-(((*3aR,5R,5aS,8aS,8bR*)-2,2,7,7-tetramethyltetrahydro-5H-*bis*([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methoxy) hexahydropyrano[3,2-d][1,3]dioxin-7-yl acetate (5-9a).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 – 7.44 (m, 2H), 7.43 – 7.36 (m, 3H), 7.26 – 7.24 (m, 2H), 7.22 – 7.18 (m, 2H), 5.56 (s, 1H), 5.50 (d, *J* = 4.9 Hz, 1H), 5.02 (t, *J* = 8.3 Hz, 1H), 4.81 (d, *J* = 12.3 Hz, 1H), 4.64 (d, *J* = 12.3 Hz, 1H), 4.61 – 4.53 (m, 2H), 4.35 (dd, *J* = 10.5, 5.0 Hz, 1H), 4.29 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.17 (dd, *J* = 7.9, 1.9 Hz, 1H), 4.00 (dd, *J* = 11.3, 3.5 Hz, 1H), 3.91 (ddd, *J* = 7.5, 3.5, 1.8 Hz, 1H), 3.83 – 3.61 (m, 4H), 3.43 (td, *J* = 9.6, 5.0 Hz, 1H), 2.06 (s, 3H),

1.51 (s, 3H), 1.44 (s, 3H), 1.32 (s, 6H). **^{13}C NMR** (126 MHz, Chloroform-*d*) δ 169.72, 137.27, 136.92, 133.49, 129.22 (3C), 128.56 (2C), 128.44 (2C), 126.14 (2C), 109.53, 108.82, 102.53, 101.46, 96.35, 81.60, 78.68, 73.39, 72.80, 71.38, 70.77, 70.62, 69.74, 68.84, 67.88, 66.33, 26.22, 26.11, 25.22, 24.48, 21.06. **HRMS (ESI+)** (*m*/*z*): $[M+Na]^+$ calcd for $C_{34}H_{41}ClO_{12}$ 699.2184, found 699.2176.

5.10 References

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