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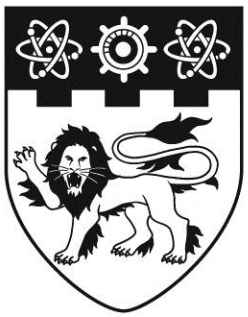

NANYANG TECHNOLOGICAL UNIVERSITY

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XIANG SHAOHUA

SCHOOL OF PHYSICAL & MATHEMATICAL SCIENCES

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A thesis submitted to the Nanyang Technological University
in fulfilment of the requirement for the degree of
Doctor of Philosophy

2014

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ABSTRACT

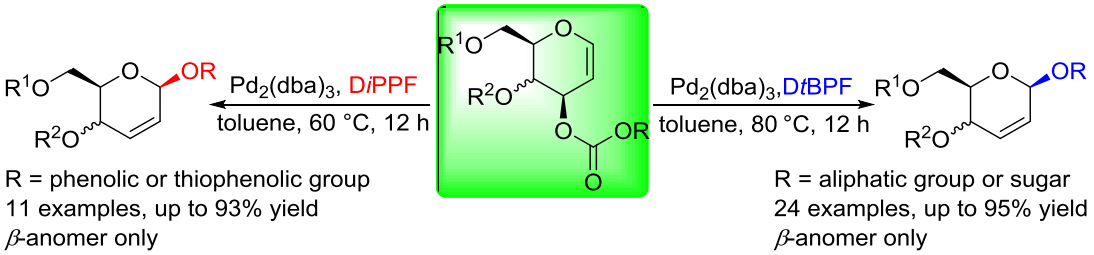
Part 1

Carbohydrates play essential roles in many complex biological processes and are readily available from a wide range of natural sources. The development of glycobiology science has stimulated the growth in demand for oligosaccharides and glycoconjugates in the last few decades. As such, the construction of glycosidic bonds has increased in significance. In this section, a brief introduction to glycosylation and some main factors that affect the stereoselectivity such as anomeric effect, solvent effect and neighbouring group participation are discussed. Besides that, selected well-designed strategies to achieve stereocontrolled glycosylation are also presented. Thereafter, the recent development of transition metal catalyzed glycosylation with glycosyl-type donor is summarized to provide a basic foundation for the extension of our work.

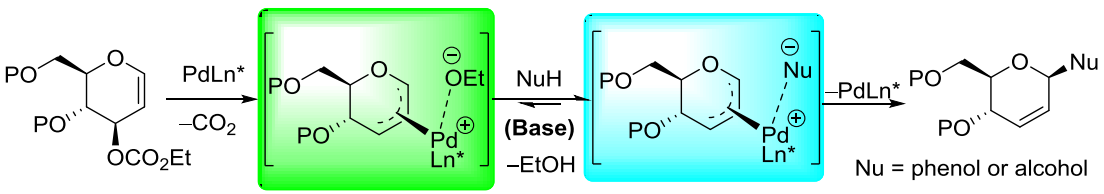
Part 2

In the first chapter of this part, we gave an introduction of transition metal catalyzed glycosylation with glycal-type donor. It was found that the development of palladium catalyzed glycosylation with glycal type donor is limited by the poor reactivity of the Pd-π-allyl intermediate. While the addition of zinc reagent and the employment of pyranone donor were able to solve the problem, the high efficiency and selectivity brought by the palladium source inspired us to further explore this type of reaction. In the second chapter of this part, we presented an *O*-glycosylation

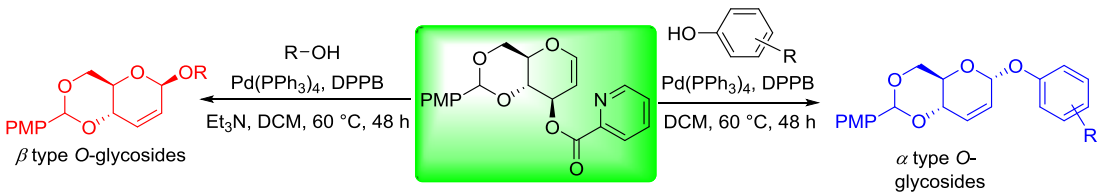
strategy based on a palladium catalyzed decarboxylative allylation. Starting from glycal derived carbonates, both phenolic *O*-glycosides and aliphatic *O*-glycosides, including some examples of disaccharides, were obtained in good to excellent yields with exclusive β-selectivity by employing different ligands.



To circumvent the issue of preparing the carbonate and to broaden the scope of the reaction, an intermolecular version is subsequently developed and presented in Chapter 3. In this section, readily available glucal ethyl carbonate was used as the starting material to generate the Pd-π-allyl intermediate through decarboxylation. With the addition of another nucleophile, the intermolecular glycosylation dominates the reaction to provide the desired product with good yield and excellent β-selectivity. Further studies showed that the outcome of this reaction was greatly affected by the nature and loading of base with phenol-type acceptor. Besides that, this reaction could also give *C*-3 adducts with election-withdrawing group containing phenols. The versatility of this approach is further demonstrated by the synthesis of trisaccharide.

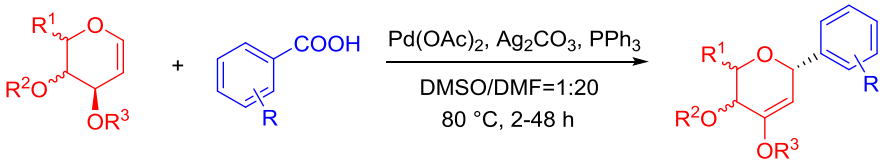


In order to facilitate the coordination between palladium and *C*-3 substituent, a glucal donor with strongly coordinating *O*-picoloyl group in the *C*-3 position was investigated in the fourth chapter of this part. Interestingly, the selectivity of this reaction could be controlled by the nucleophilicity of the glycosyl acceptor. Weak nucleophiles, such as phenols gave α-type *O*-glycoside as the major product while stronger nucleophiles, like alcohols, preferred to yield β-type *O*-glycoside. Excellent chemoselectivity was also obtained when substrate containing both phenolic alcohol and aliphatic alcohol was used generate the desired aliphatic product selectively.

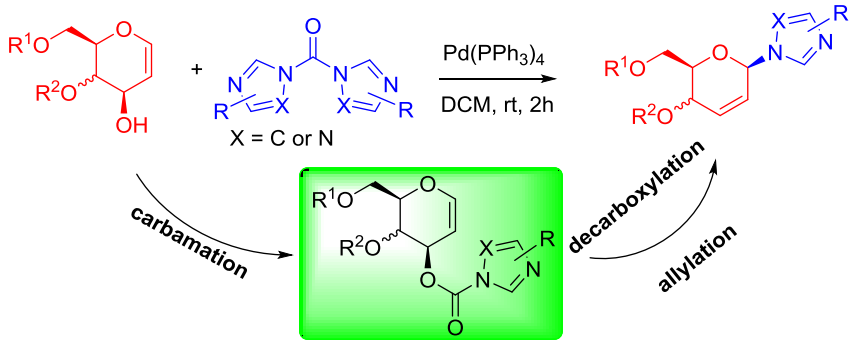


Part 3

The formation of *O*-glycosidic linkage is arguably one of the most important topics in carbohydrate chemistry due to its prevalence in nature. However, the investigation of *C*- and *N*-glycosylation has also attracted considerable research attention due to their unique characters and possible roles as structural analogues. Hence, an efficient approach for construction of 2-deoxy-*C*-aryl glycoside was developed and reported in the first chapter of this part. This method was based on a palladium catalyzed Heck-type coupling reaction and the selectivity of the anomeric center could be controlled by the chirality of C-3 substituent. It is noteworthy that, the aryl group was derived from benzoic acid by a decarboxylative reaction.



In the second chapter of this part, we developed a one-pot reaction to synthesize *N*-glycosyl imidazole analogues from *C*-3 free hydroxyl glycal and CDI analogues. There are three steps involved in this reaction, namely: carbamation, decarboxylation and allylation. Due to the coordination of nitrogen to the palladium catalyst, excellent *β*-selectivity could be obtained from glycal substrates. It should also be mentioned that this reaction also could proceed without palladium catalyst in some cases. However, the *α*-product was observed as the major product.



INDEX OF ABBREVIATIONS

δ	chemical shift	*de*	diastereomeric excess
Δ	reflux or heat	DMAP	4-(*N*,*N*-dimethylamino) pyridine
^{o}C	degree centigrade	D*i*PPF	1,1'-Bis(di-*i*-propylphosphino) ferrocene
Ac	acetyl	D*t*BPF	1,1'-Bis(di-*tert*-butyl phosphino)ferrocene
AcCl	acetyl chloride	DME	dichloroethane
AcOH	acetic acid	DMF	*N*,*N*-dimethylformamide
ACN	acetonitrile	DMSO	dimethyl sulfoxide
Aq	aqueous	DPPB	1,4-bis(diphenylphosphino) butane
Bn	benzyl	*ee*	enantiomeric excess
Boc	*tert*-butoxycarbonyl	EI	electron ionization
brs	broad singlet	equiv	equivalent
Bz	Benzoic	Et	ethyl
calcd.	calculated	ether	diethyl ether
cat.	catalytic	Et_3N	triethylamine
$CDCl_3$	deuterated chloroform	EtOAc	ethylacetate
CH_2Cl_2	dichloromethane	EtOH	ethanol
$CHCl_3$	chloroform	Fmoc	fluorenylmethoxycarbonyl
cm^{-1}	inverse centimeter	FTIR	fourier transfer infrared spectroscopy
d	doublet	g	gram
dd	doublet of doublets	h	hour (time)
dba	Dibenzylideneacetone	Hex	hexane
DBU	1,8-diazabicycloundec-7-ene	HRMS	high resolution mass spectroscopy
DCC	*N*,*N*'-dicyclohexylcarbodiimide	Hz	hertz

Imid	imidazole	*i*Pr	isopropyl
IR	infrared	Pd/C	palladium on carbon
J	coupling constants	Piv	pivaloyl; trimethylacetyl
M	concentration (mol/L)	Ph	phenyl
m	multiplet	PMB	*p*-methoxybenzyl
M^+	parent ion peak(mass spectrum)	PMP	*p*-methoxyphenyl
Me	methyl	ppm	parts per million
MeOH	methanol	Py	pyridine
mg	milligram	q	quartet
MHz	megahertz	RBF	round bottom flask
min	minute	s	singlet
mL	milliliter	sat	saturated
mm	millimeter	t	triplet
mmol	millimoles	TBAF	Tetrabutylammonium fluoride
mol	moles	TBDPS	*tert*-butyldiphenylsilyl
MS	mass spectrum	TBS	*tert*-butyldimethylsilyl
Ms	methane sulfonyl	TFA	trifluoroacetic acid
*n*Bu	*n*-butyl	THF	tetrahydrofuran
N	concentration (normality)	THP	tetrahydropyran
NMR	nuclear magnetic Resonance	TLC	thin layer chromatography
NMO	4-methylmorpholine *N*-oxide	TMS	trimethylsilyl
Nu	nucleophile	Ts	p-toluenesulfonyl
OTf	trifluromethanesulfonate	*t*Bu	*tert*-butyl
p	*para*	v	volume

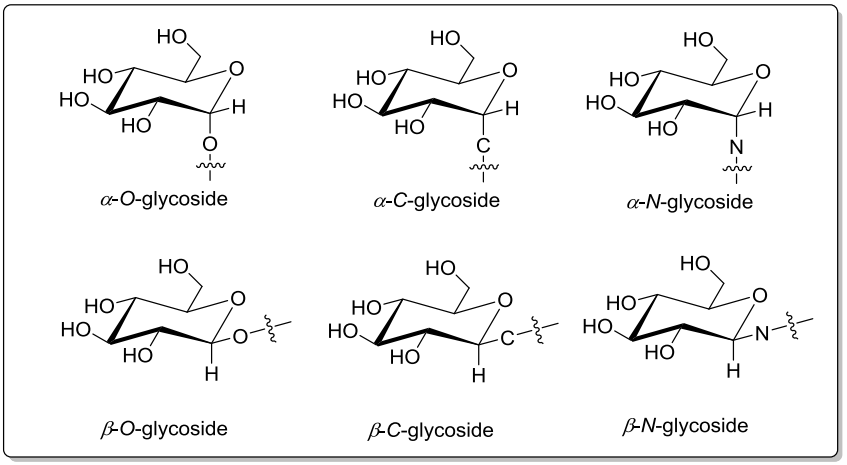
PART 1

An introduction to the stereocontrolled glycosylation strategies

1. Introduction

Sugars, also known as carbohydrate, are ubiquitous in nature and play vital roles in numerous biological functions. In biological processes, carbohydrates serve as energy sources, starting materials in biosynthesis and biological targets in natural products syntheses.[1] Compared to the other three major kinds of important biomolecules, namely protein, nucleic acid and lipids, sugars have not been well studied due to the complexity and diversity of their structures. The isolation, purification and configuration determination constitute a major impediment to the development of carbohydrate chemistry in the earlier years. It was until the 1920s, when the absolute configurations of some simple sugars were first confirmed by Emil Fischer that increasing attention was paid to the research of carbohydrates.[2] Since then, enormous progress has been made in isolation, synthesis and analysis of both natural and unnatural carbohydrates containing bioactive structures. These compounds can be obtained through the following three approaches: isolation from natural products, biosynthesis and chemical synthesis. With the recent development of glycobiology, it has however became impractical to access carbohydrate targets only through isolation from natural products since it was found that the bioactivity of the natural products can be significantly increased through chemical modifications of their structures. On the other hand, biosynthesis has provided an effective way to synthesize some crucial compounds. However, this method is only applicable to selected classes of compounds. Meanwhile, expansive attention and growing interest of bioactive compounds for biological, medicinal and pharmacological studies have led to a demand for large amount of high quality carbohydrates materials. Till now, chemical

synthesis remains the major tool towards the syntheses of complex carbohydrates. To meet these requirements of glycobiology, it is essential to develop efficient methodologies to synthesize a diverse range of useful carbohydrate structures.



Scheme 1.1 Different types of glycosides with D-glucose as the example

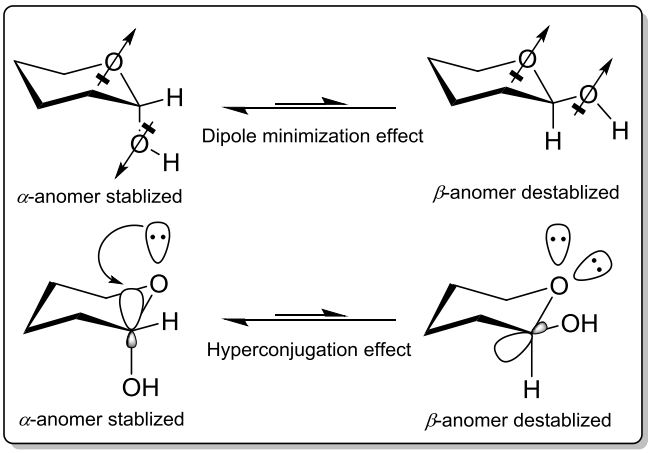
Natural products containing carbohydrates exist as polysaccharides, glycoconjugates, or glycosides. The monosaccharides are connected to one another or aglycone by glycosidic bonds. Compared to other linkages, the structures possessing *O*-, *C*-, or *N*- glycosidic bonds (known as *O*-, *C*-, or *N*-glycosides) are much more important due to their high prevalence in bioactive compounds. As such, the formation of these glycosidic bonds, known as glycosylation, is undoubtedly the most important in the field of glycochemistry. For each kind of linkage, there are two major types of glycosides defined as α- and β- glycosides (**Scheme 1.1**). With the efforts of many carbohydrate chemists, many elegant approaches and protocols have been developed. However, the construction of glycosides with high α- or β-selectivity remains a challenge in this field.

2. Stereocontrolled glycosylation

2.1 Anomeric effect

In order to achieve high efficiency and selectivity for the glycosylation reaction, various types of glycosyl donors, glycosyl acceptors, promoters can be utilized. A good leaving group containing glycosyl donor at *C*-1 position can readily form an oxocarbenium intermediate in the presence of a promoter, which can be coupled with a glycosyl acceptor. Although the detailed mechanism has yet not been demonstrated clearly, different pathways have been proposed and accepted.[3] The S_N2 pathway generally provides good stereocontrol while a mixture is often associated with the S_N1 pathway. It is a challenge to control the selectivity as the glycosylation reaction is unable to participate only in the S_N2 pathway. The considerable S_N1 component contributes to the lack of stereocontrol, which makes the orientation of the leaving group at the anomeric center less important. In this situation, due to the anomeric effect,[4] glycosyl acceptors such as -OR or -SR will attach to the most active anomeric center of the sugar ring in a preferred axial orientation, forming the α-isomer as the major product.

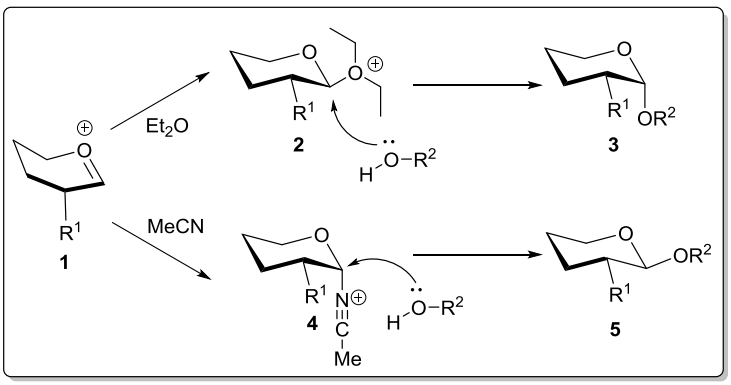
The anomeric effect is mainly due to the repulsive interactions between the lone-pair electrons of the *C*-1 substituent and the ring oxygen known as the dipole minimization effect. Moreover, the electron-withdrawing axial substituent can be stabilized *via* hyperconjugation owing to the periplanar orientation of both nonbonding ring oxygen and antibonding orbital of *C*-1. However, in most situations, the selectivity of *C*-glycosylation cannot be completely controlled through this effect (**Scheme 1.2**).



Scheme 1.2 Anomeric effect for glycosylation

2.2 Solvent effect

Besides the anomeric effect, the involvement of reaction solvent is another important factor which can significantly influence the stereoselectivity of the glycosylation. Generally, polar reaction solvents prefer to give β-isomer product due to the charge separation while non-polar solvents such as CH_2Cl_2, $ClCH_2CH_2Cl$ or toluene, tend to form α-isomer product. In addition, it has been observed that reactions with acetonitrile as the solvent prefer to give β-type glycoside while diethyl ether is an ideal solvent when α-type glycosides are desired.

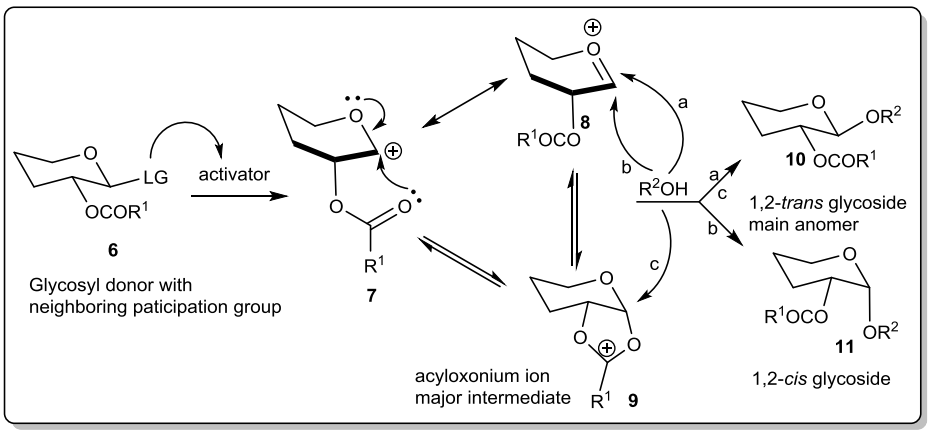


Scheme 1.3 Solvent participation effect

However, in some case when acetonitrile or diethyl ether was employed as the solvent, the stereoselectivity was altered. These observations were attributed to the solvent participation effect. As detailed in the **Scheme 1.3**, starting from oxocarbenium ion **1**, intermediate **2** can be provided by the reaction with ether type solvent. In this condition, the glycosyl acceptor can only attach from the axial face to provide axial glycoside **3**. Alternatively, nitrile-type solvents give nitrilium ion **4** as the intermediate with the axial position occupied by the nitrile at low temperature, forming the equatorial glycoside **5**.[5]

2.3 Neighboring group participation

Though the selectivity can be controlled through the anomeric effect or solvent effect to give the desired anomer, absolute stereocontrol to satisfy the requirements of complex glycosides syntheses and biotesting is usually elusive. Hence, other strategies to improve the selectivity are necessary. Among them, the notable neighboring group participation remains one of the most powerful tools of directing stereoselectivity towards the formation of 1,2-*trans* glycosides till now.[6] It is now well established that the nature of the protecting group has a major effect on the reactivity of glycosyl building blocks and the resultant stereoselectivity and yield of a glycosylation reaction. In general, the substituent on C-2 position of the glycosyl donor is an acyl moiety such as *O*-acetyl, *O*-benzoyl, 2-phthalimido. The detailed glycosylation mechanism with neighboring group participation to 1,2-*trans* glycoside is illustrated as follows (**Scheme 1.4**).

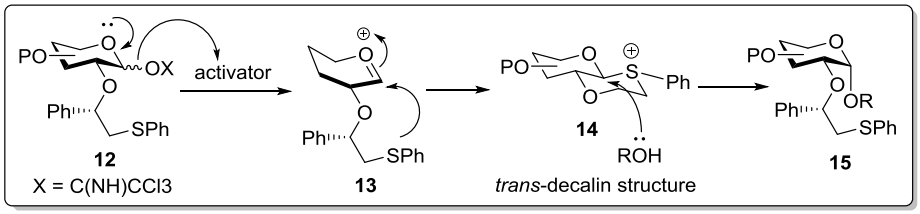


Scheme 1.4 Neighboring group participation with acyl moiety

In the presence of an activator, the glycosyl donor **6** can be readily converted to carbocation **7** by the removal of the leaving group. Oxocarbenium ion **8** is then generated through the electron transfer from sugar ring oxygen to the carbocation. Thereafter, the glycosyl accepter can approach the anomeric center from either face to give 1,2-*trans* product **10** and 1,2-*cis* product **11**. However, when an acyl moiety which can serve as neighboring participation group is present in the adjacent carbon, the major intermediate is acyloxonium ion **9**. In this situation, the glycosyl accepter can attach the anomeric center only from top face, producing 1,2-*trans* product **10** as the major isomer. It should be noted that pure 1,2-*trans C*-glycosides are difficult to achieve through neighboring group participation protocol. A reasonable explanation for this outcome is that the key intermediate acyloxonium ion **9** can also be attacked from the bottom face directly to give 1,2-*cis* product. Hnece, a mixture is most commonly obtained under this condition.

In particular, the 1,2-*trans* glycosidic linkages can usually be synthesized with high levels of stereocontrol by anchimeric assistance of acyl moiety. While the construction of 1,2-*cis* glycosidic bonds has been a long standing problem in

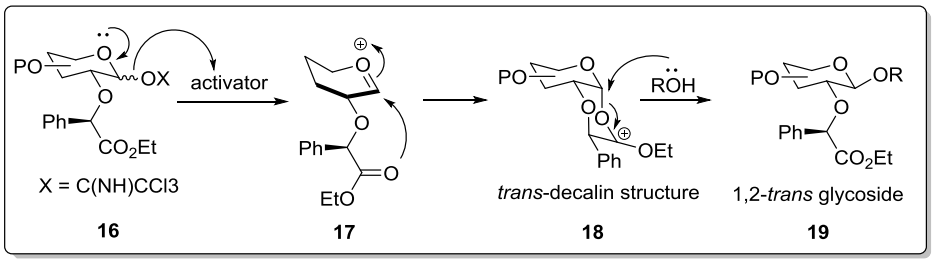
carbohydrate chemistry. Normally non-neighboring protecting groups such as benzyl ethers and substituted benzyl ethers are the most frequently used. However, this is insufficient to guarantee the selectivity without other assistance. Boons's auxiliary (1*S*)-phenyl-2-(phenylsulfanyl)ethyl group which was developed in 2005 offers a good choice to change this situation.[7] As depicted in **Scheme 1.5**, in the presence of activator, the starting material **12** with an auxiliary at *C*-2 position can be readily converted to oxocarbenium **13**. The sulfur atom on the auxiliary then attacks the anomeric center from the bottom face to form meta-stable sulfonium ion **14** with a bicyclic system. The rigid configuration of the structure blocks the possibility of nucleophilic attack from the top face leading to 1,2-*cis* glycoside **15**. In this strategy, the chiral center of the auxiliary plays an important role in determining the selectivity. The *trans*-decalin structure sulfonium ion **14** with a phenyl substituent of the *C*-2 chiral auxiliary occupies an equatorial position that is more favored than the alternative *cis*-decalin system with the phenyl group in axial orientation. Control experiments with no chirality and an opposite chirality further confirmed the importance of the chiral substituent group.



Scheme 1.5 Boons' auxiliary for 1,2-*cis* glycosidic bond formation

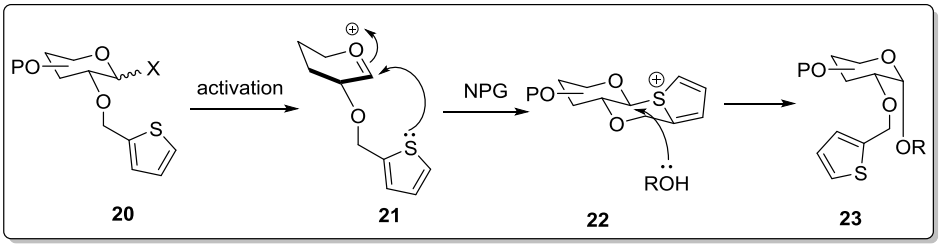
Thereafter, a modification of the chiral auxiliary by the same group was found to be capable of generating 1,2-*trans* glycosidic bonds.[8] In contrast to the former method, the key intermediate of the glycosylation reaction with ethoxycarbonylbenzyl ether as

the neighboring participation group was a *cis*-decalin structure sulfonium ion **18**. In this pathway, the phenyl substituent of the *C*-2 chiral auxiliary also favors the equatorial position to form *cis*-decalin bicyclic system intermediate. As similar to traditional neighboring protecting groups with acyl moiety substrate, 1,2-*trans* glycoside was formed as the major product (**Scheme 1.6**).



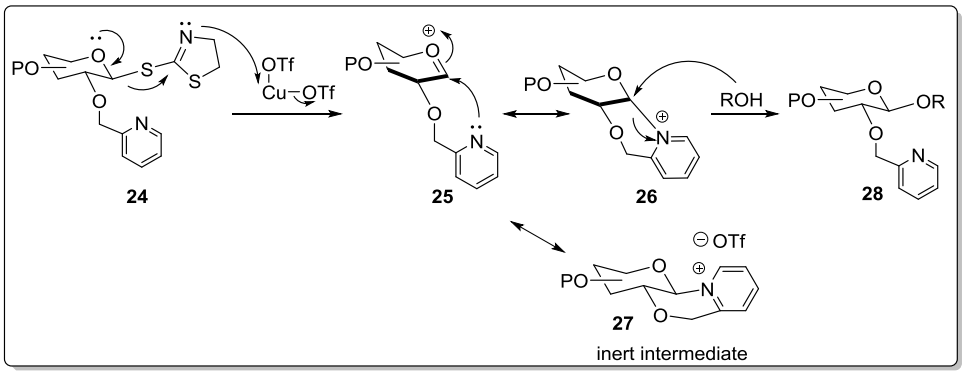
Scheme 1.6 Boons' auxiliary for 1,2-*trans* glycosidic bond formation

Based on same anchimeric sulfur assistance strategy, the donor **20** with 2-*O*-(thiophen-2-yl)methyl group which was introduced by Fairbanks was tested for its efficiency in stereoselective glycosylation.[9] The plausible mechanism is as shown. Similar to Boons's proposed mechanism, the key intermediate sulfonium ion **22** is provided through removal of the leaving group and neighboring group participation (**Scheme 1.7**). However, this strategy is on applicable to a few substrates and its stereocontrol is comparatively less than that of Boons's auxiliary. Meanwhile, another significant drawback of this method is the cleavage of the protecting group.



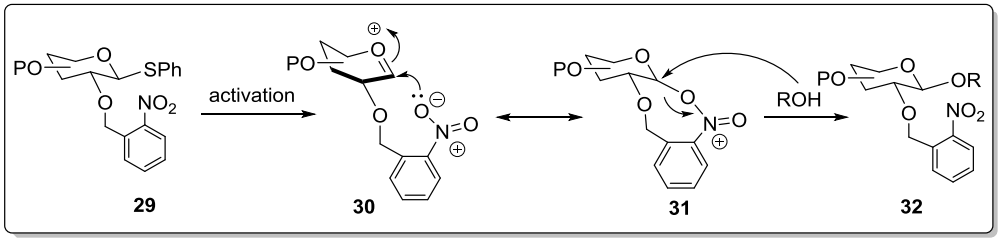
Scheme 1.7 Fairbanks' strategy for 1,2-*cis* glycosidic bond formation

Other than the sulfur atom, nitrogen-based strategies are also widely used in the arming group participation to construct glycosidic bond with high stereocontrol. In 2005, Demchenko first reported the effect of 2-picoloyl ether as directing group.[10] Starting from *S*-thiazolinyl glycosides **24**, oxocarbenium **25** which was generated by the treatment of $Cu(OTf)_2$ and TfOH gave 1,2-*trans* product **28** efficiently *via* the formation of α-oriented pyridinium ion **26** as the major intermediate. Meanwhile, the minor bicyclic intermediate **27** (less than 5%) which may lead to the formation of 1,2-*trans* glycosidic linkage was proved to be completely inert and could be isolated from the reaction mixture (**Scheme 1.8**). The advantage of this strategy is that the 2-*O*-picolyl group acts like a disarming neighboring group to give 1,2-*trans* product but the armed active state is retained. Similar to benzyl group, the 2-*O*-picolyl group could be removed by Pd/C and H_2 efficiently.



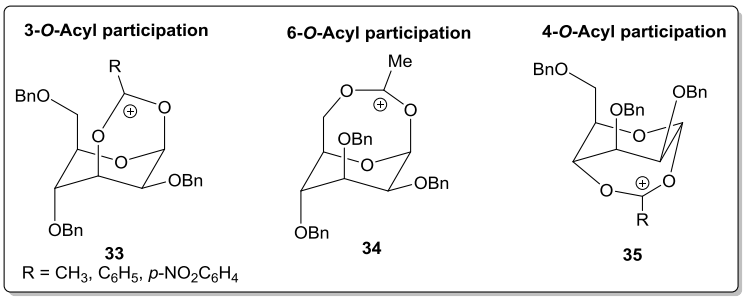
Scheme 1.8 Demchenko's strategy for 1,2-*trans* glycosidic bond formation

In 2013, Mlynarski described a glycosylation method employing *o*-nitrobeznyl as the directing group.[11] Compared to Demchenko's strategy, the selectivity provided by this method is relatively lower and the substrate scope is much narrower. They proposed a seven-membered acetoxonium ion **31** as the key intermediate to control the glycosyl acceptor approach the anomeric carbon from the top face (**Scheme 1.9**).



Scheme 1.9 Mlynarski's strategy for 1,2-*trans* glycosidic bond formation

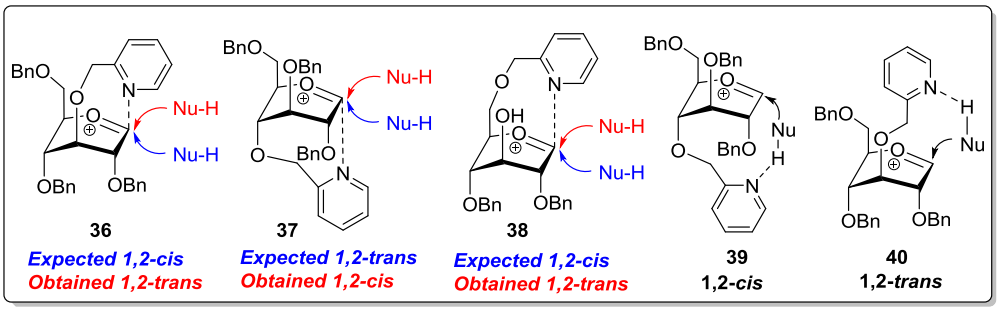
As mentioned above, the protecting groups on the sugar can influence the selectivity dramatically. In most cases, the stereochemistry is controlled by the key bicyclic intermediate generated by a special substituent in the *C*-2 position through the neighboring group participation. However, the impact of other position was hardly studied till 2009.[12] After investigating various electron-withdrawing groups at *O*-3, *O*-4 and *O*-6 positions, Kim demonstrated some evidence for the participation of *O*-3 and *O*-6 acetyl group in mannosylations. Excellent α-selectivity was obtained through the formation of bicyclic oxocarbenium intermediates **33** and **34**. However the poor β-selectivity with *O*-4 acetyl group involvement as shown in the formation of the oxocarbenium intermediate **35** may not be involved in the mannosylations pathway (**Scheme 1.10**).



Scheme 1.10 Remote participation of *O*-3 and *O*-6 acetyl groups in mannosylations

The protecting groups can affect the selectivity not only through the participation to form a bicyclic ring, but also through the hydrogen bonding effect. In 2012,

Demchenko's group reported a stereocontrolled chemical glycosylation by the remote picolinyl and picoloyl substituents.[13] From the results depicted in **Scheme 1.11**, the stereoselectivity results with compounds **36**, **37** or **38** as the starting material are always opposite to that expected, which can be explained by the direct participation at the anomeric center. Hence, an intermolecular H-bond effect was considered as a possible explanation for the obtained selectivities. They proposed the possible rationalization as following: the glycosyl acceptor approaches the donor through the H-bond between the hydrogen and nitrogen, and then the nucleophile is introduced and attacks the oxocarbenium **39** from the bottom face to give 1,2-*cis* glycoside. For oxocarbenium **40**, the picolinyl moiety oriented in the top face, hence, the 1,2-*trans* glycosidic linkage should be formed.

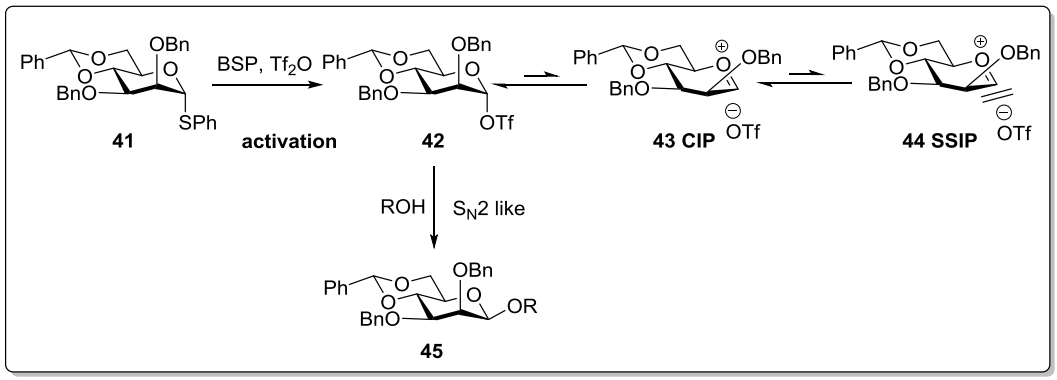


Scheme 1.11 Hydrogen bond mediate aglycone delivery

From the previous results, it was found that the structure of intermediate is crucial for the stereocontrol of glycosylation reaction. Using the same idea, a new strategy was reported to control the selectivity through the glycosyl donors with a bicyclic structure in the starting material. In this strategy, the benzylidene group and cyclic silyl group are normally used.

In 1997, Crich presented an efficient strategy for the formation of *β*-type mannosides with benzylidene protecting group.[14] The importance of benzylidene

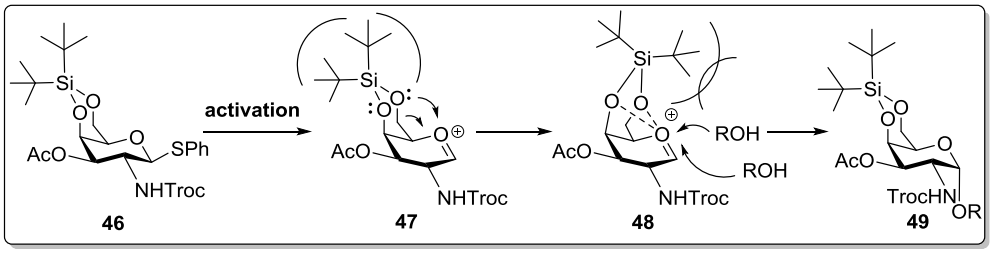
group is demonstrated in the following mechanism (**Scheme 1.12**). Starting from bicyclic compound **41**, three intermediates **42**, **43** and **44** can be generated *in situ*. Among these intermediates, compound **42** with α-triflate glycoside structure is the most favored due to the torsional strain in the other two intermediates. The occupation of axial position shields the α-face and then S_N2-like nucleophilic substitution occurrs to give β-type mannosyl linkage **45**. Low temperature experiments suggested the quick formation of covalent α-triflate **42**. So in this reaction, the benzylidene group serves to shift the equilibrium to covalent α-triflate and prevents the formation of intermediate **44** which may lead to the α-mannoside.



Scheme 1.12 4,6-*O*-benzeylidene directed β-mannosyl glycosidic linkage formation

Cyclic silyl group have also been employed to control the selectivity of glycosylation. In 2003, an α-galactosylation strategy was reported by Kiso with di-*tert*-butylsilylene group even when there is neighboring participation group in the glycosyl donor.[15] The author attributed the α-selectivity to the steric effect of the bulky protecting group and the X-ray crystallographic analysis further confirmed this suggestion. In the X-ray structure of glycosyl donor **46**, the 4,6-*O*-DTBS(di-*tert*-butylsilyl) group was found to be positioned in close proximity to the anomeric

carbon. After activation, oxocarbenium ion **47** was generated. Then intermediate **48** was formed with influence of the "through-space electron donation" effect. Since the top face of the sugar ring was blocked by the 4,6-*O*-DTBS group, the nucleophile can only approach the anomeric center from bottom side to give 1,2-*cis* galactoside **49** (**Scheme 1.13**). Interestingly, this strategy can also be applied to synthesize β-type arabinofuranosides.



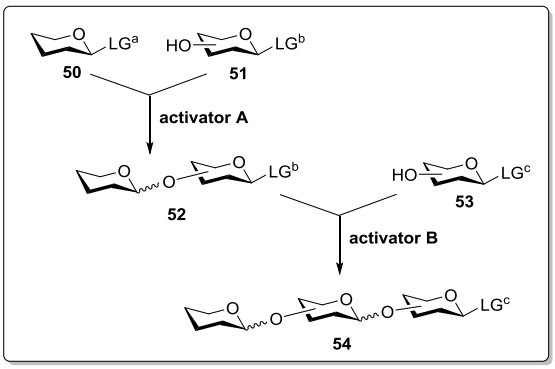
Scheme 1.13 4,6-*O*-DTBS directed α-galactosyl glycosidic linkage formation

2.4 Leaving group, promoter and other effects

The selectivity of glycosylation can be affected not only by the protecting groups but also the leaving groups. Compared to other factors, the leaving group at anomeric center seems to be less important since most of the glycosylation reactions proceed *via* unimolecular S_N1 mechanism. However, the reactivity of the glycosyl donor can be strongly affected by the leaving group. Till now, a large number of leaving groups has been exploited such as halides, acetate, thioglycoside, silyl ether, sulfoxide, hydroxide, *n*-pentenyl glycoside, phosphite, phosphate, carbonate, MOP, trichloroacetimidate and so on. Among the above leaving groups, trichloroacetimidate[16] has been one of the most popular choices for glycosylation since the first report in 1980. Both α-type and β-type of imidate donors can be prepared readily from glycosyl hemiacetals with Cl_3CCN and different bases.

Conventionally, strong bases such as NaH give thermodynamically favored α-product while mild bases like K_2CO_3 often provide β-type trichloroacetimidate. Besides that, the advantage of high stability, high reactivity and general applicability make this donor widely used in glycosylation reactions. More importantly, high chemical yields and high stereoselectivity are usually provided. At the same time, various promoters have been reported to activate the trichloroacetimidate donor. TMSOTf and BF_3•OEt_2 have exhibited their potential in promoting this kind of glycosylation reaction. Various Lewis acids such as TBSOTf, Tf_2O, $Sm(OTf)_3$, $Yb(OTf)_3$, AgOTf, $ZnBr_2$ and protonic acids such as $HClO_4$, $HB(C_6F_5)_4$ were also found to be very effective in this glycosylation protocol. With the development of the metal-catalyzed chemistry, it was found that some metal catalysts like palladium, nickel are able to catalyze this reaction, which will be discussed in greater detail subsequently. It should be noted that, while the development of carbohydrate chemistry has been rapid in the last few decades, glycosylations with imidate type donor is still playing a vital role in this field, and is expected to continue motivating the advancement of carbohydrate chemistry.

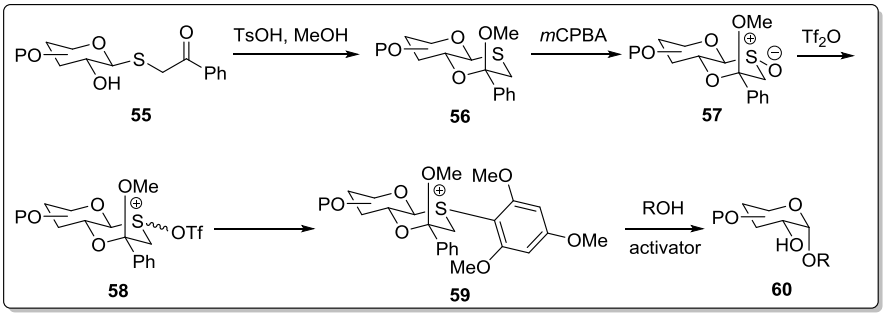
Though the choice of leaving group cannot give sufficient control on the selectivity of glycosylation, the combination of other factors such as solvent, temperature, promoter and protecting group can augment the selectivity. Particularly, contrasting donor reactivity from the difference of protecting group offers a possibility to synthesize oligosaccharides in a convergent approach. The major requirement for the control is the choice of activator or promoter (**Scheme 1.14**).



Scheme 1.14 Leaving group-based strategy for stepwise selective glycosylation

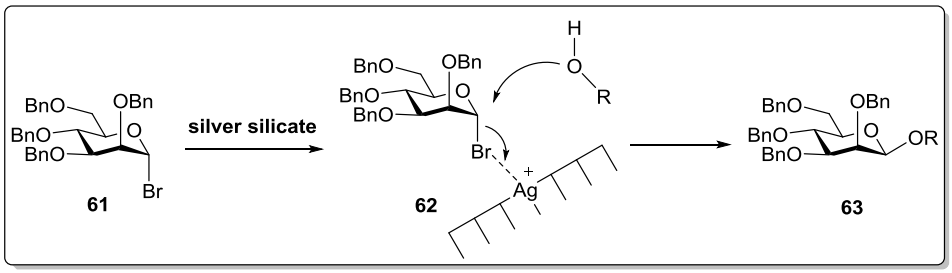
2.5 Special cases for glycosylation

It is very difficult to achieve impressive selectivity by the control of only one of the above factors, but certain notable exceptions exist. As noted above, the Boons auxiliaries provide excellent ways to synthesize 1,2-*cis* and 1,2-*trans* glycosides. However, the tedious synthetic procedures involved to introduce these auxiliaries are major limitations to the application of these strategies. To circumvent this problem, a new type of glycosyl donor **55** with a special leaving group was introduced in 2009 by Turnbell (**Scheme 1.15**).[17] Cyclization, followed by oxidation, occurred to give bicyclic sulfoxide intermediate **57**. Compound **57** was activated with triflic anhydride as before, and allowed to react with trimethoxybenzene to generate an active sulfonium ion **59**. This donor can react with alcohol acceptor to give 1,2-*cis* glycosides **60**, of which primary alcohol gives the best results.



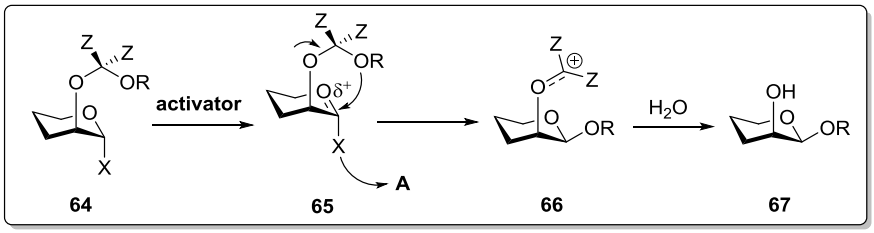
Scheme 1.15 Turnbull's protocol for 1,2-*cis* glycosidic bond formation

A heterogeneous silver silicate catalyst was also found to be efficient in controlling the stereoselectivity in glycosylations.[18] Glycosyl halide **61** is utilized as the glycosyl donor and 1,2-*cis* glycoside **63** is obtained through S_N2 like reaction (**Scheme 1.16**).



Scheme 1.16 1,2-*cis* mannosylation with glycosyl halide and heterogeneous catalyst

Besides the abovementioned synthetic strategies, new methodologies toward the syntheses of the glycosides which are typically hard to achieve should also be given credit. Among these, intramolecular aglycon delivery (IAD), a well-developed method of forming 1,2-*cis* glycosidic linkages is possibility the most popular. Tethering of the 2'-substituent serves as a linkage to connect the glycosyl donor and acceptor, a critical aspect of this reaction. The general mechanism for the IAD reaction is depicted as follows (**Scheme 1.17**).



Scheme 1.17 General mechanism for the IAD reaction

Starting from compound **64**, intermediate **65** was obtained in the presence of activator. The expected pure *cis*-structure **66** was obtained through an intramolecular delivery. Upon hydrolysis, the desired *cis*-glycoside **67** was eventually formed. The

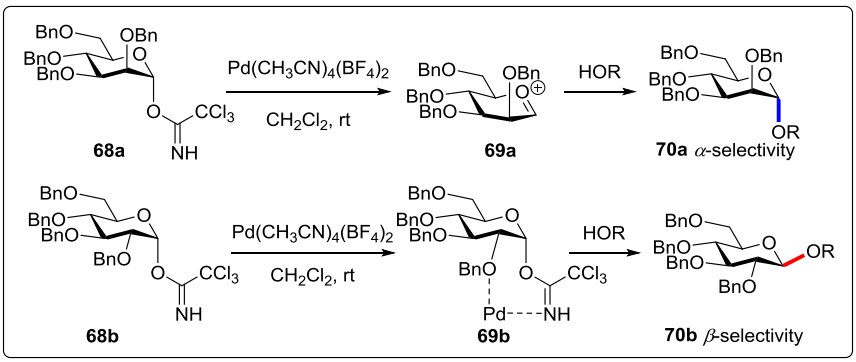
first example utilizing this method was reported by Hindsgaul in 1991 with isopropenyl ketal type tethering.[19] As an extension of this concept, a large amount of other useful acetal linkers were introduced, such as 2-iodoalkylidene type (2-iodopropylidene, 2-iodoethylidene and 2-iodopropenylidene), [20] benzylidene type *(p*-methoxybenzylidene, dimethoxybenzylidene and naphthylidene) [21] and silylene type tethering. [22] With the efforts of many carbohydrate chemists, the construction of 1,2-*cis* glycosides, especially, β-mannosyl linkages has become more facile and efficient.

2.6 Transition metal catalyzed glycosylation

After a few decades of investigation, the potential of transition metal chemistry in catalyzing the formation of C-C and C-heteroatom bond has been discovered, resulting in its increased application. Compared to normal Lewis acid-catalyzed glycosylation, milder reaction conditions and only catalytic amount of metal source are needed for the reaction and remarkable results are often observed. Herein, we will present some cases involving transition metal catalyzed glycosylation.

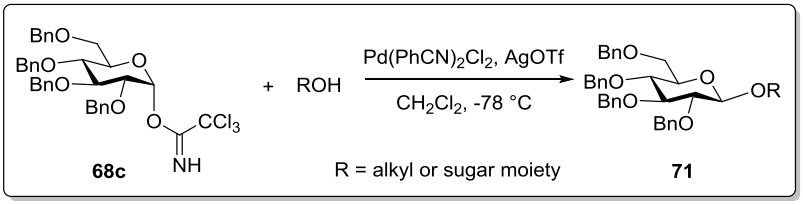
Palladium has to be mentioned first when discussing the transition metal chemistry due to its wide usage and well-studied characteristics. Though palladium catalysts have been recognized as one of the most useful reagents in the syntheses of natural products and the development of typically challenging methodologies, only a few examples have been reported for the construction of glycosidic bonds in the past few years. Since our projects focus on glycal, a detailed discussion on palladium catalyzed glycosylation with this type donors will be elaborated in the next few sections of the thesis, while the reactions with glycosyl type donors will be discussed first.

In 2008, Nguyen's group contributed an efficient glycosylation method to synthesize α-type glycosides with α-mannosyl trichloroacetimidate donor **68a**.[23] The reaction with cationic Pd catalyst $Pd(CH_3CN)_4(BF_4)_2$ was found to be effective for the formation of desired product **70a** *via* intermediate **69a**, while neutral Pd source $Pd(PhCN)_2Cl_2$ showed no activation of the trichloroacetiacetimidate leaving group. The possible reason for this selectivity was the steric effect and anomeric effect. When glucosyl-type donor **68b** was employed, β-type glycoside **69b** was obtained as the major product. The stereoselectivity was controlled through the formation of Intermediate **70b** by double coordination of palladium and donor (**Scheme 1.18**).



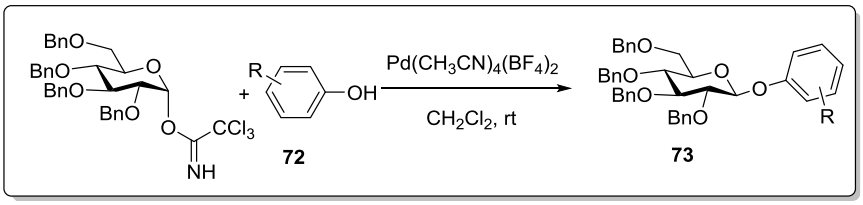
Scheme 1.18 Palladium catalyzed glycosylation with aliphatic alcohol-type acceptors

Interestingly, the β-selectivity was achieved through the alteration of palladium source by Nguyen's group in **2009**.[24] Reactions of AgOTf and $Pd(PhCN)_2Cl_2$ produced another cationic catalyst $Pd(PhCN)_2(OTf)_2$, and good to exclusive β-selectivity was provided with compound **68c** as the glycosyl donor at low temperature *via* an S_N2 reaction (**Scheme 1.19**). However, only a 1:1 mixture was observed when the reaction was performed in 0 °C or room temperature. Under this condition, the reaction may undergo a S_N1 mechanism with the formation of oxocarbenium intermediate first.



Scheme 1.19 Palladium catalyzed glycosylation with $Pd(PhCN)_2(OTf)_2$

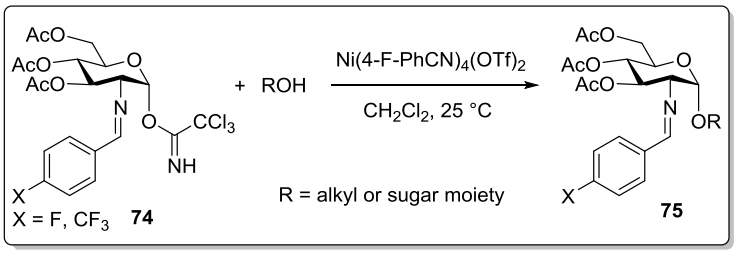
With the same strategy, the phenolic *O*-glycosides were synthesized. It is interesting to note that more active $Pd(PhCN)_2(OTf)_2$ which has the potential to give β-selectivity failed to provide satisfactory α- or β-selectivity with phenol type glycosyl acceptor **72**. On the other hand, the reaction with less active $Pd(CH_3CN)_4(BF_4)_2$ afforded the desired *O*-phenolic glycoside **73** with excellent β-selectivity (**Scheme 1.20**). [25]



Scheme 1.20 Palladium catalyzed glycosylation with phenol-type acceptors

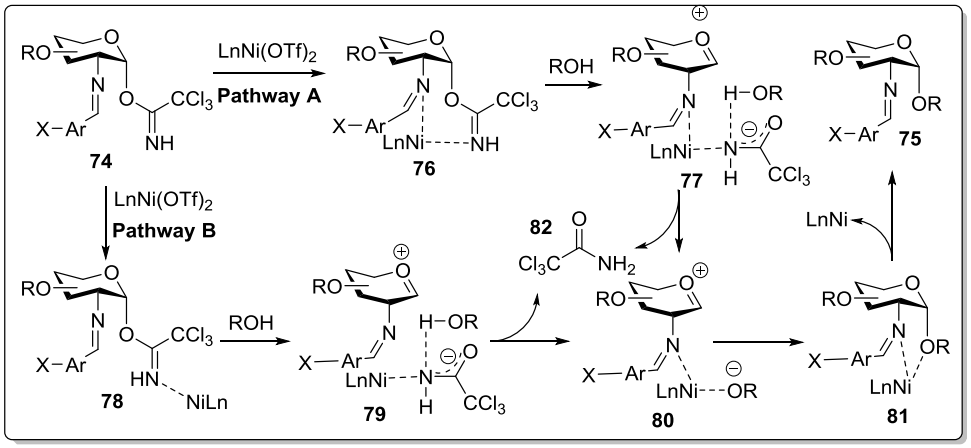
After the investigation of the palladium catalysts, nickel(II) catalysts were then next examined for their effectiveness in catalyzing glycosylation reactions by Nguyen's group in 2009.[26] The optimization of reaction conditions suggests that trichloroacetimidate donors with an electron withdrawing-group such as F, CF_3 on the benzylidene group are more effective. With compound **74** as the glycosyl donor, the $Ni(4\text{-F-PhCN})_4(OTf)_2$ was found to be more superior than other catalysts. 1,2-*cis*-2-Amino glycosides **75**, which are difficult to achieve through traditional protocols, can be readily synthesized with excellent α-selectivity (**Scheme 1.21**). Palladium catalysts

were also investigated, but poor yield and selectivity were obtained. The *N*-benzylidene group can be readily removed with 2N HCl in a mixture of acetone and CH_2Cl_2. This strategy was found to be applicable to a wide range of substrates and a few biologically important carbohydrates molecules were synthesized.



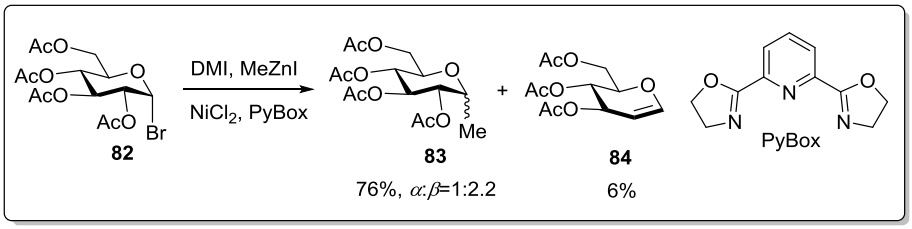
Scheme 1.21 $Ni(4\text{-F-PhCN})_4(OTf)_2$ catalyzed *O*-glycosylation

Based on their studies, they gave the proposed mechanism as below (**Scheme 1.22**). Starting from donor **74**, there are two possible pathways to get the desired product **75**. In the presence of cationic catalyst, the double coordination of both nitrogen atoms to nickel atom gave intermediate **76** from pathway A. After that, the nucleophile will approach the intermediate from bottom face to give ion pair **77** through H-bonding effect. Intermediate **80** was obtained by the elimination of amide **82**. From pathway B, the coordination of the nitrogen on the leaving group to nickel catalyst provided complex **78**. Similarly, ion pair **80** was generated by the approach of nucleophile from bottom face and elimination of **82**. The intramolecular nucleophilic addition gave five-membered ring intermediate **81**. Finally, the 1,2-*cis* glycosidic product **75** was formed with the dissociation of catalyst. After the examination of several well-designed substrates studies, the bouble coordination mechanism (**pathway A**) was found to be consistent with the results.



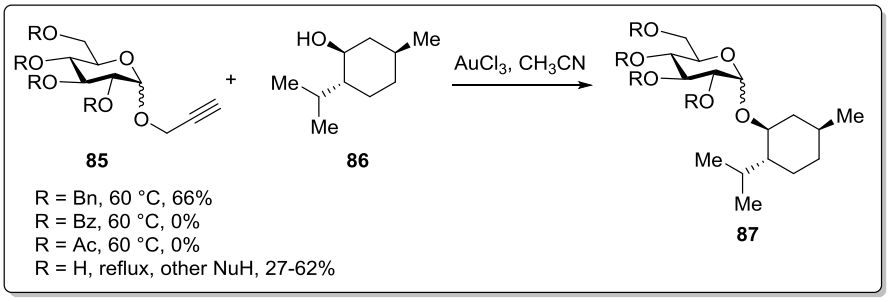
Scheme 1.22 Proposed mechanism for nickel catalyzed glycosylation

The nickel catalyst was also found effective in the synthesis of *C*-glycoside through a Negishi cross-coupling by Gagné in **2007**.[27] Usually, the glycosyl halide is used as the donor with zinc reagent as the other coupling partner. Under the optimized reaction condition, the reaction of α-glycosyl bromide **82** with MeZnI afforded the desired *C*-glycoside **83** in 76% yield and a small amount of glycal **84** (**Scheme 1.23**). However, poor β-selectivity was obtained when glucosyl and galactosyl donor were used. Interestingly, the mannosyl donor was found to be suitable for this condition and high yield accompanied with good α-selectivity was obtained. Thereafter, other types of acceptors were screened by the same group for the nickel catalyzed *C*-glycosylation under the modified reaction conditions to provide various *C*-glycosides.



Scheme 1.23 Nickel catalyzed *C*-glycosylation

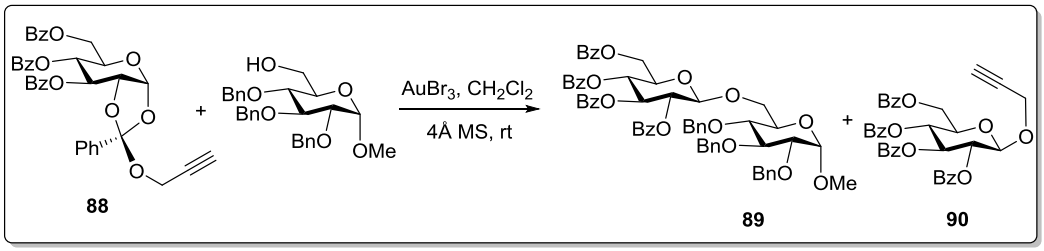
Glycosylation methods with gold as the catalysts have also been developed. In these strategies with alkynophilic gold as catalyst, an alkyne group is always involved in the glycosyl donor. In 2005, Hotha reported a glycosylation method with propargyl glycosides as donors using $AuCl_3$ as the catalyst.[28] Through the investigation of this method, they found that only armed benzyl group can be used in protecting the glycosyl donor. Reactions involving disarmed protecting groups like -Ac, -Bz did not proceed (**Scheme 1.24**). The selectivities with glucosyl and galactosyl donor are very poor, while the reaction with mannosyl donor can provide the 1,2-*trans* product very efficiently. The author attributed this result to the steric hindrance and the anomeric effect. In the proposed mechanism, the leaving group propargylic ether was changed to cyclopropanone as the byproduct in the presence of gold catalyst. Subsequently, glycosylation with unprotected sugars was tested. Though the results obtained are not satisfied, it provides an alternative for the syntheses of unprotected glycosides under mild conditions. Further studies showed that methyl glycoside was also a good glycosyl donor for gold catalyzed glycosylation. Meanwhile, the stereoselectivity of the reaction has no relationship to the orientation of methoxy group.



Scheme 1.24 Gold catalyzed glycosylation with propargyl glycoside as donor

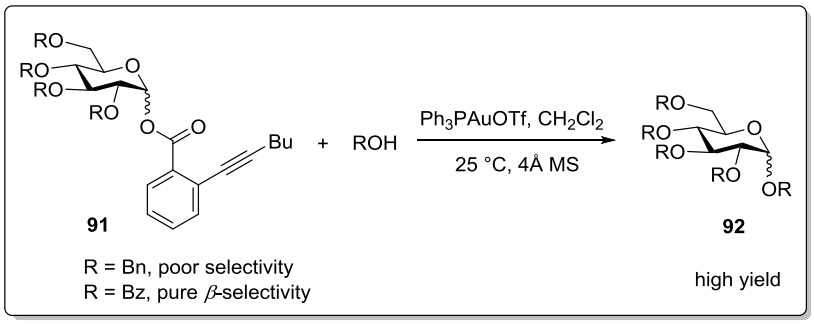
In 2007, propargyl 1,2-orthoesters were introduced as the glycosyl donors by Hotha's group.[29] As similar to the glycosylation with neighboring participation group,

this type of propargyl donor **88** gave the desired glycoside **89** with very good 1,2-*trans* selectivity. However, the β-type propargyl glycoside **90** was always obtained as the byproduct (**Scheme 1.25**). It is noteworthy that this method is applicable to the synthesis of amino acid glycoconjugates.



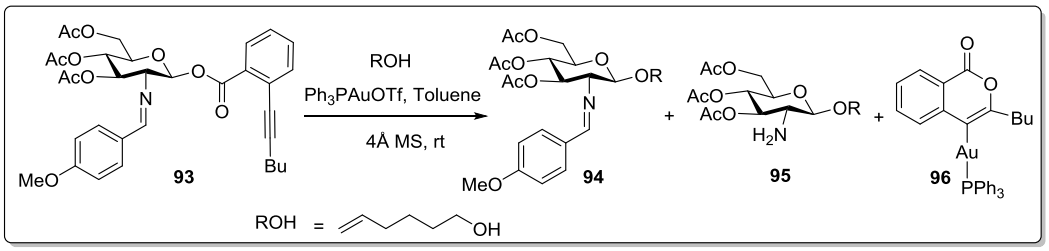
Scheme 1.25 Gold catalyzed glycosylation with propargyl 1,2-orthoesters as donor

Yu's group reported their glycosylation method with *o*-hexynylbenzoate type glycosyl donor (**Scheme 1.26**).[30] $Ph_3PAuOTf$ was used as the catalyst to activate the alkyne donor. Both armed (Bn) and disarmed (Bz) protection group were utilized for this reaction and excellent yield was obtained for each reaction. However, the anomeric control with armed donor was low. Exclusive β-selectivity was furnished with the glycosyl donor equipped with neighboring participation -Bz group at *C*-2 position. Thereafter, the author conducted extensive studies to control the anomeric selectivity through other factors such as anomeric effect and solvent effect with some glycosyl donors, without neighboring participation group.



Scheme 1.26 Yu's gold catalyzed glycosylation method

Combination of the *o*-hexynylbenzoate leaving group and the installation of *para*-methoxybenzylidene amine group at *C*-2 position provided a new glycosyl donor **93**. This donor was then subjected to similar reaction conditions with *n*-pentenol as the glycosyl acceptor by Yu's group in 2010.[31] Besides the promised glycosylation products **94** and **95**, an unprecedented gold complex **96** was isolated (**Scheme 1.27**).[32] This occurrence suggested that an additional strong acid (TfOH) is necessary to regenerate the gold catalyst and maintain the catalytic cycle. Lower loading of the catalyst and shorter reaction time were needed to complete the reaction.



Scheme 1.27 The glycosylation reaction provided evidence of key intermediate **96**

From the above results, it is apparent that transition metal catalyzed glycosylation strategies provide an efficient approach for the syntheses of various oligosaccharides and glycoconjugates with reasonable to good selectivities. The reactions generally involve metal catalyst and can be conducted in mild conditions and short time with broad substrates scope on both glycosyl donor and acceptor. Even in some special condition, the unprotected sugar was discovered to be a flexible donor for direct glycosylation. In addition, it offers a possibility to achieve high anomeric selectivity with the involvement of metal but not dependent on the traditional strategies such as anomeric effect, solvent effect and participation group in some cases. Despite some other metals for instance, ruthenium,[33] titanium[34] and rhenium[35] also showed their

ability to promote certain glycosylation reaction, the investigations are still not conclusive until now. The pace of development of the transition metal catalyzed glycosylation has been dramatic in the last few years, but the exploration of a more universal approach to construct glycosidic bonds with excellent stereocontrol is still a challenge and an unmet need.

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PART 2

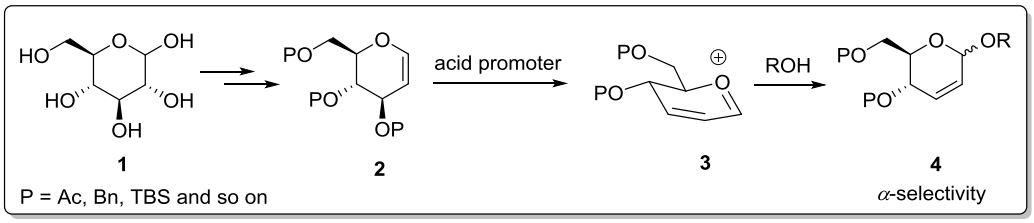
Palladium catalyzed O-glycosylation with glycal derived donor

Chapter 1: Introduction to transition-metal catalyzed glycosylation with glycal donor

Introduction

The construction of glycosidic bonds with extraordinary efficiency and stereoselectivity is of vital importance in carbohydrate chemistry due to their ubiquity in biologically active natural products, oligosaccharides and glycoconjugates.[1] Although great strides have been made to control the stereoselectivity of glycosylation in the past few decades, the synthesis of complex carbohydrate units remains a challenge and continues to be of interest in the carbohydrate research field.[2] We have discussed many excellent methods and approaches to synthesize the glycosidic linkage with good stereocontrol. However, in most of the cases, the selectivities were dependent on by neighboring group participation. Apart from that, the anomeric effect and solvent effect also contributes to the selectivity control. To circumvent the issue of poor selectivities obtained from the glycosyl donor with very weak or negligible effect of the above factors, transition metal catalysts were considered in the catalysis of glycosylation. Though many protocols have been reported in the past decade with glycosyl donor, glycal donors have the potential to be explored as reactants in glycosylation as the olefin group is a very useful group in the reaction with metal catalysts. The obtained desired products 2,3-unsaturated glycosides, in particular, draw synthetic interests in organic synthesis as the double bond can be functionalized readily to various type of glycosides.[3]

Among all the strategies developed with glycal donors, acid catalyzed Ferrier rearrangement, which was first reported by Ferrier, is one of the most powerful methods to approach 2,3-unsaturated α-*O*-glycosides from readily available glycals (**Scheme 2.1.1**).[4] Generally, the pseudoaxial glycoside is the dominant form in the product mixture.[5] Due to vinylogous anomeric effect, the selectivity of *O*- and *N*-glycosylation is much better than *C*-glycosylation. So far, a variety of Lewis acids and Brønsted acids have been found to be effective as promoters to catalyze this type of reactions. Commonly used Lewis acids include $BF_3{\cdot}Et_2O$, $SnCl_4$, $TiCl_3$, $InCl_3$, $AuCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, $Fe(OTf)_3$, $Bi(NO_3)_3$, and $Mg(ClO_4)_2$. Brønsted acids such as PTSA, TFA, CSA and H_3PO_4 can also be employed.

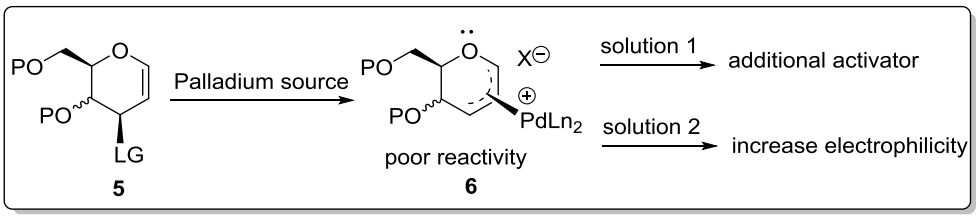


Scheme 2.1.1 Acid catalyzed *O*-glycosylation

In the continuous exploration of transition metal catalyzed reactions, it was found that some metal catalysts such as Pd and Au were also capable of catalyzing Ferrier-type glycosylation. Since there is no substituent on the *C*-2 position for glycal donors, it is impossible to control the selectivity through the neighboring group participation strategy. Gratifyingly, in some conditions the selectivity could be controlled by the coordination effect or the steric hindrance effect of metal complexes. Up to now, a wide range of reagents and conditions have been developed to form glycosides with glycal type donors in the presence of metal catalyst. Since the most ubiquitous group of glycosides in nature is the glycoproteins, in which a protein linked to carbohydrates

unit by *O*-glycosidic bond, we will give a detailed introduction on transition metal catalyzed *O*-glycosylation.

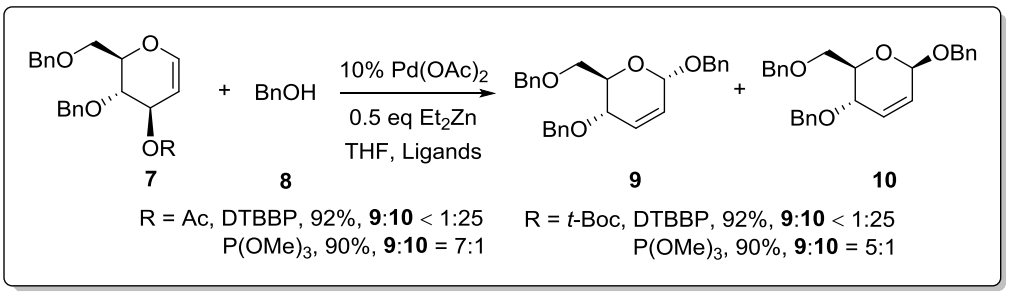
First, palladium catalyst, which is the most popular transition metal used in the formation of C-X bond,[6] was examined for its ability to activate the glycal type donor. Starting from the glycal donor **5** equipped with a good leaving group on *C*-3 position, the Pd-π-allyl intermediates **6** were generated through the removal of *C*-3 substituent. However, in this glycal system, the reactivity of the palladium complex was low due to the electron donation from the anchimeric oxygen of sugar ring.[7] In this situation, there are two possible solutions to this problem. First is the addition of activator and the other alternative is the introduction of electron withdrawing groups on the sugar ring to increase the electrophilicity (**Scheme 2.1.2**).



Scheme 2.1.2 Methods of increasing the reactivity of Pd-π-allyl in glycal donor

Lee reported a solution to the problem with the addition of zinc(II) alkoxides as the activator in 2004.[8a] From their previous results, they found that the main factor is the reactivity mismatch between the glycosyl donor and acceptor. As we know, the alkoxide anion is a hard nucleophile while the Pd-π-allyl cation is a soft electrophile. The zinc reagent, which can be used to soften the hard alkoxides anion nucleophile by increasing the acidity of the alcohol, was utilized in his glycosylation method.

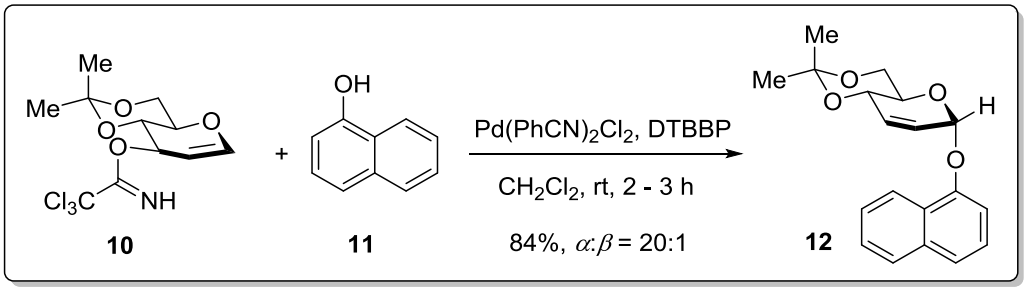
Interestingly, the introduction of zinc reagent is very successful and the reaction went smoothly to give the desired product in almost quantitative yield. It should be noted that starting from glucal donor **7**, the anomeric selectivity was controlled by the alteration of ligand with benzyl alcohol as acceptor **8** in the presence of the same palladium catalyst. Good α-selectivity of **9** was obtained when the reaction was conducted with $P(OMe)_3$ as the ligand while bulky ligand DTBBP (di-*tert*-butyl-2-biphenylphosphine) gave the glycoside **10** with excellent β-selectivity (**Scheme 2.1.3**). In contrast to the considerable influence from the ligand, the nature of protecting group, the leaving group and the glycosyl acceptor were found to contribute very weakly to the outcome of the reaction.



Scheme 2.1.3 Palladium catalyzed glycosylation with zinc reagent

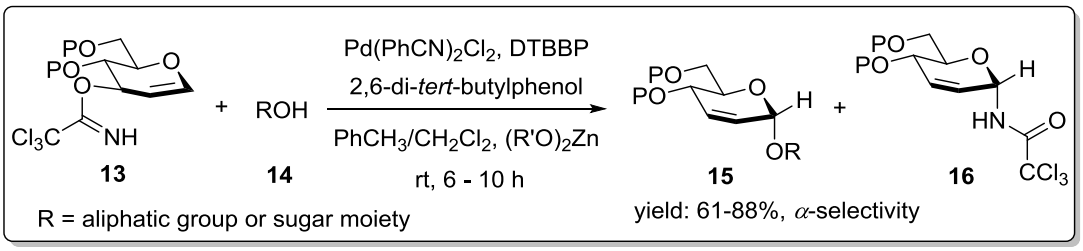
Following Lee's work, Nguyen's group developed a glycosylation method with a different glycal donor **10**.[8b] As mentioned above, the reaction is facile when the acceptor and donor are matched. Thus, they preceded the reaction with a softer nucleophile phenol **11** as the acceptor to match the reactivity of soft Pd-π-allyl cation to provide the desired phenolic *O*-glycosides **12** efficiently without the addition of activator (**Scheme 2.1.4**). In their optimized reaction conditions, trichloroacetimidate was introduced in the *C*-3 position as the leaving group, $Pd(PhCN)_2Cl_2$ was used as

the catalyst and DTBBP as the ligand. Unlike Lee's results, this reaction gave good to excellent α-selectivity for all the examined ligands. It should be noted that the phenol type acceptor also worked as a proton source to affect deoxypalladation.



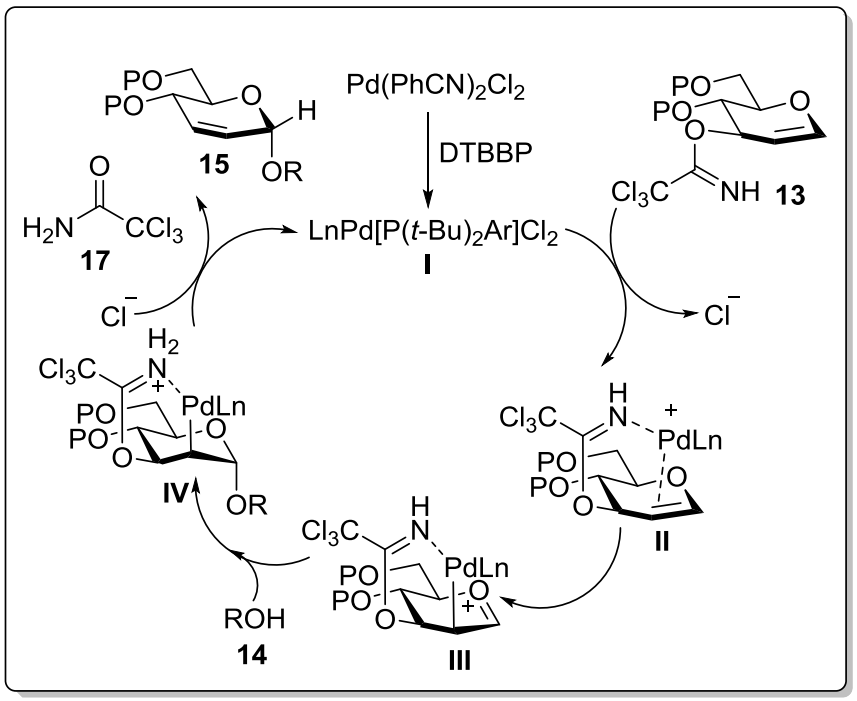
Scheme 2.1.4 Palladium catalyzed glycosylation with phenol acceptor

Nevertheless, the aliphatic alcohol and sugar alcohol were found to be unsuitable for the same reaction condition optimized before. Hence, the addition of zinc reagent is necessary to activate the glycosyl acceptor. As in the previous mechanism, a proton source is required to enable the catalyst turnover and 2,6-di-*tert*-butylphenol with low nucleophility was introduced as the additive. Accordingly, subjecting glycosyl donor **13** and acceptor **14** under the modified conditions resulted in the desired *O*-glycoside **15** being furnished as the major product with exclusive α-selectivity. Meanwhile, *N*-glycoside **16** was always obtained as the byproduct from the [3,3]-sigmatropic rearrangement of starting material (**Scheme 2.1.5**).



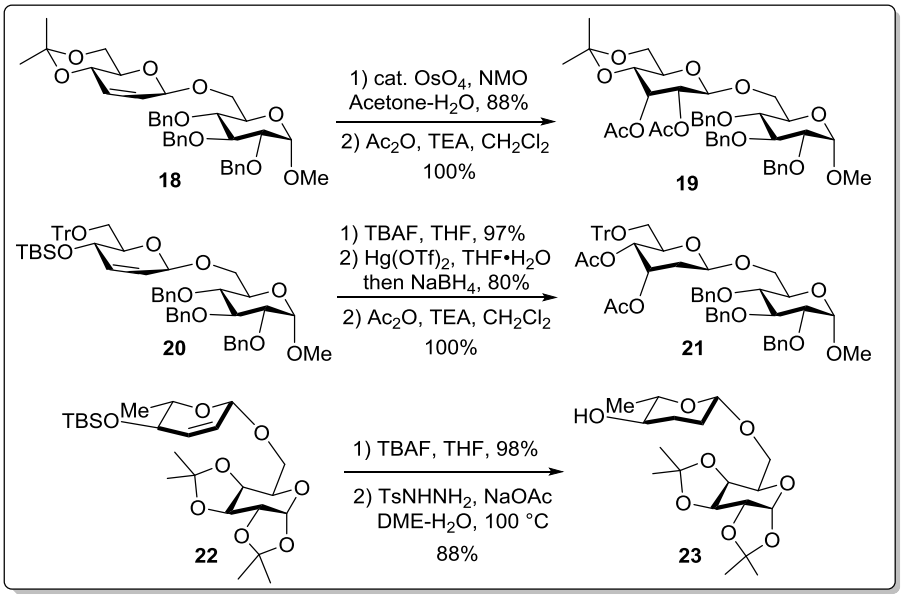
Scheme 2.1.5 Palladium catalyzed glycosylation with aliphatic alcohol acceptor

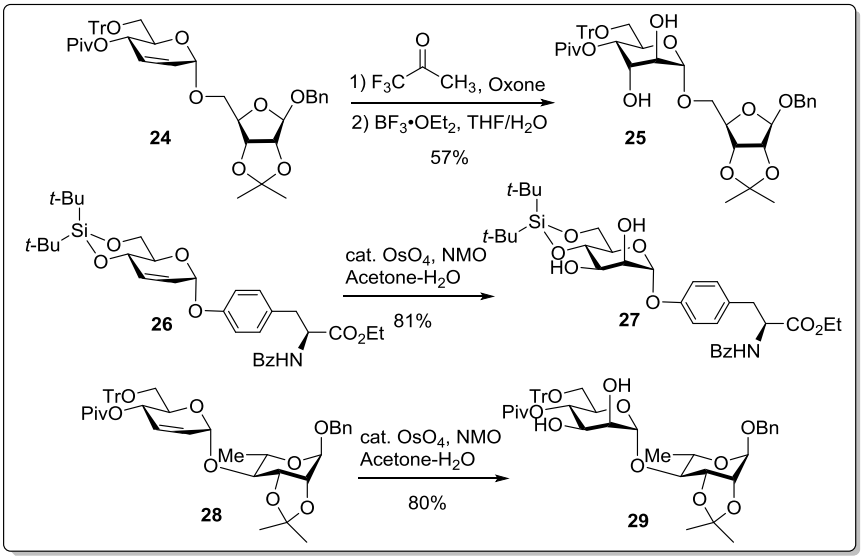
According to the results, the proposed mechanism is given as detailed below (**Scheme 2.1.6**). The first step of the cycle is the association of palladium catalyst and ligand to give the palladium complex **I**. Next, the palladium complex **I** approaches glycal donor **13** from the upper face by the coordination effect between palladium and the nitrogen atom on the leaving group to form the palladium source **II**. Then an oxocarbenium ion intermediate **III** is generated by the electron transformation. In this structure, the palladium and bulky ligand shield the upper face, then the glycosyl donor **14** (for aliphatic or sugar alcohol, zinc reagent is needed as the additive) can only approach the donor from bottom face to give α-type *O*-glycoside **15** and amide **17**. At the same time, the regeneration of the palladium complex **I** completes the catalytic cycle.



Scheme 2.1.6 Proposed mechanism for the palladium catalyzed glycosylation

With the desired 2,3-unsaturated *O*-glycoside product in hand, both Lee's and Nugyen's group demonstrated the utility of their methods by the application in the synthesis of various natural or unnatural carbohydrate structures. We summarized the initial results they obtained as following. Starting from β-type glycoside **18**, β-alloside **19** was synthesized with excellent yield and selectivity through dihydroxylation with OsO_4 and subsequent protection with Ac_2O. Thereafter, β-type glycoside **20** was converted to 2-deoxy sugar **21** successfully through deprotection of TBS group and then Hg(II)-mediated hydration. Finally, 2,3-dideoxy sugar **23** was prepared by deprotection and reduction of α-type glycoside **22**. It should be noted that, 2,3-*trans*-diol structure **25** could also furnished in high selectivity *via* epoxidation and ring open with acid. Similarly, Nugyen's group synthesized compounds **27** and **29** through dihydroxylation with OsO_4 catalyst from α-type glycosides **26** and **28** correspondingly (**Scheme 2.1.7**).

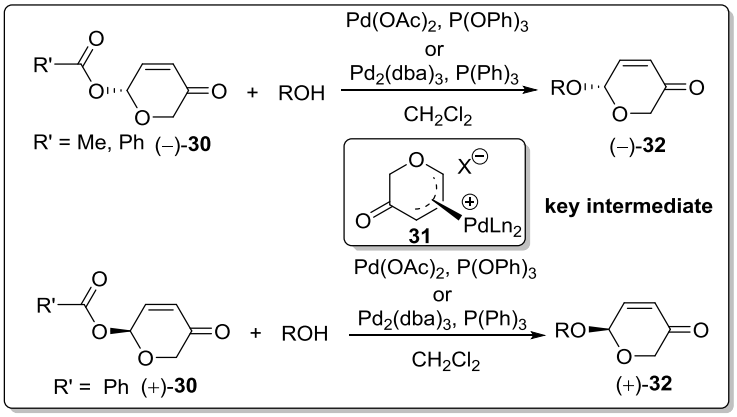




Scheme 2.1.7 Functionalization of olefin

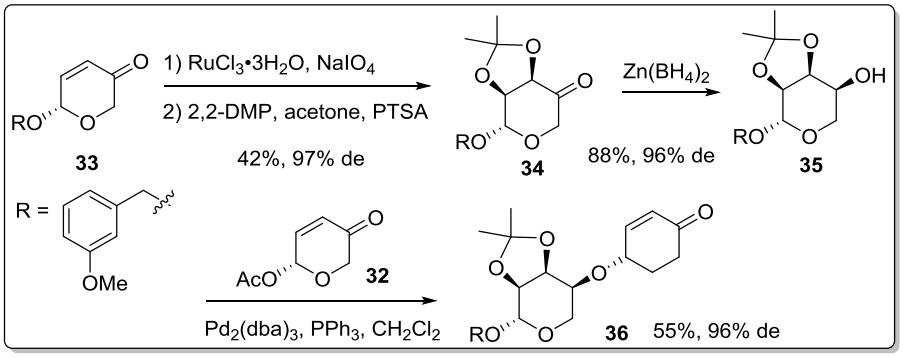
Just before Lee's reports,[8] Feringa and O'Doherty presented their non-Ferrier-type glycosylation strategy with palladium catalyst almost concurrently in 2003.[9] Considering the low reactivity of Pd-π-allyl donor, it is indeed a challenge to form *O*-glycosidic bonds from glycal derivatives. Both of them attempted to solve this problem with pyranone derivatives as the starting material.

Enantiomerically pure cyclic enone compound **30** with chiral allylic acetal, which can be readily achieved from Lipase catalyzed isolation, was applied as the glycosyl donor by Feringa.[9a] The combination of $Pd(OAc)_2$ and $P(OPh)_3$ was found to be a good catalytic system for most of the glycosyl acceptors. In some cases, the combination of $Pd_2(dba)_3$ and PPh_3 was the best choice for this reaction. Interestingly, the stereochemistry of the anomeric center was retained under the reaction condition. In this first report on this *de novo* synthesis of *O*-glycosides **32**, the installation of conjugated ketone is required to decrease the electron density and increase the reactivity of the Pd-π-allyl intermediate **31** generated (**Scheme 2.1.8**).



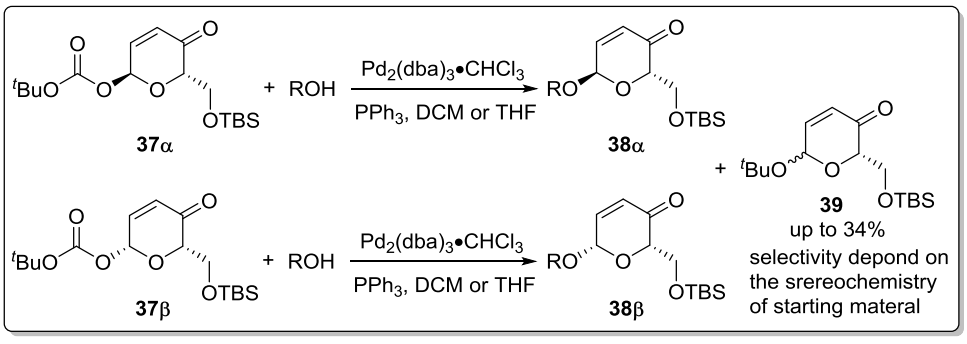
Scheme 2.1.8 Feringa's strategy of palladium catalyzed *O*-glycosylation

The synthetic utility of this approach was demonstrated by the application in iterative oligosaccharide synthesis. Starting from the first glycosylation product **33**, compound **34** was obtained by a dihydroxylation, followed by protection with 2,2-dimethoxypropane. It should be noted that the *cis*-diol was obtained in excellent selectivity. The reduction of ketone with $Zn(BH_4)_2$ gave ribose product **35** in excellent yield and selectivity. Then the second glycosylation with glycosyl donor **32** under the optimized reaction conditions gave compound **36** with excellent selectivity, albeit in moderate yield (**Scheme 2.1.9**).



Scheme 2.1.9 Feringa's palladium catalyzed iterative oligosaccharide synthesis

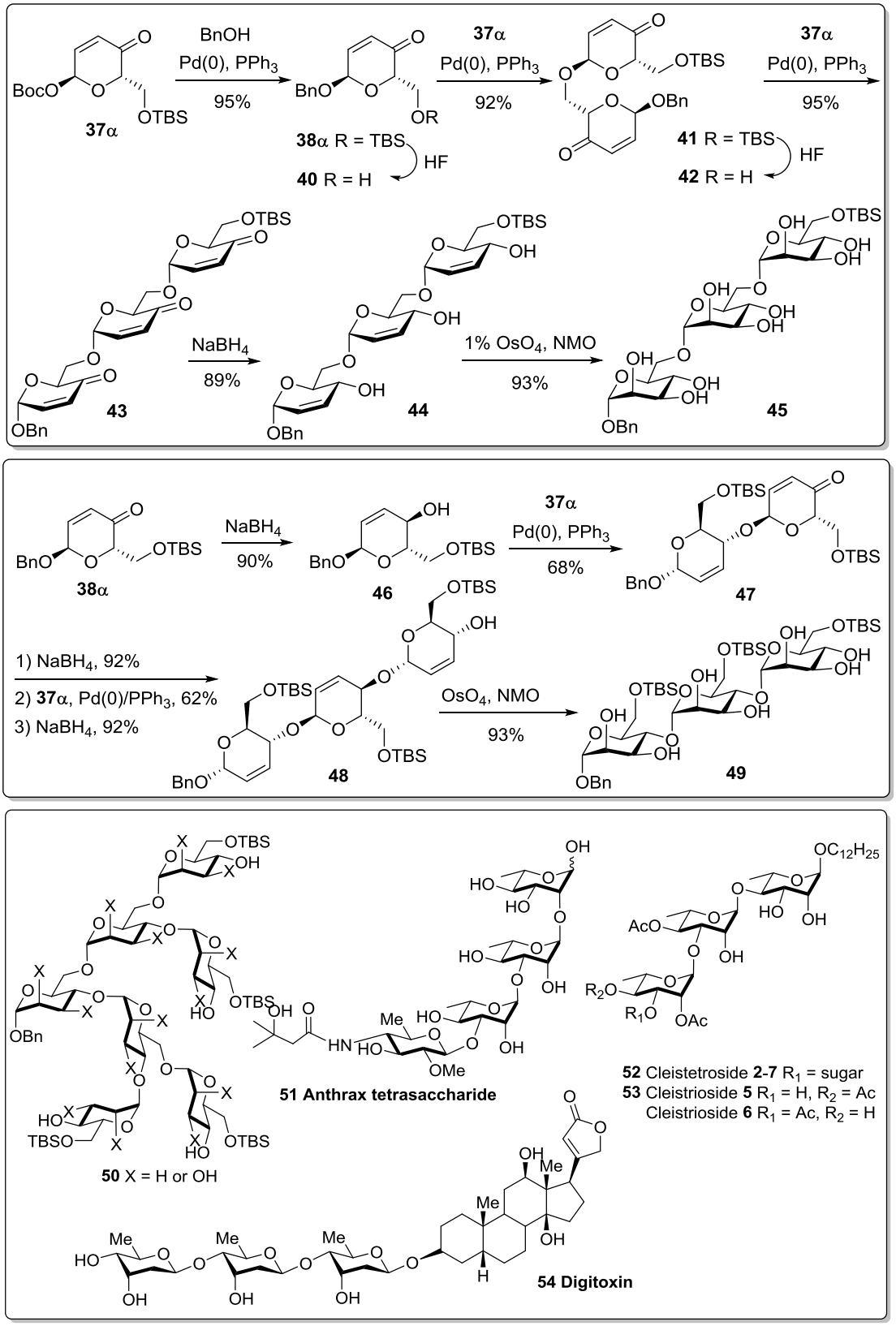
Through the same idea, O'Doherty conducted his glycosylation method with a similar starting material **37**.[9b] Compared to the glycosyl donor **30** used by Feringa, compound **37** containing a chiral substituent on *C*-5 position can be synthesized from furfuryl alcohol *via* an Achmatowicz reaction. Fortunately, the desired product **38** was obtained successfully with palladium catalyst. Interestingly, the chiral substituent was found to be of no influence to the outcome. Generally speaking, *cis*-pyran ring starting material will give β-type product while α-type glycoside can be achieved from *trans*-pyran ring starting material. During the investigation, they found that Boc-group was superior to other protecting group such as -Bz and -Piv. A possible explanation of this result is the Boc-group in the starting material forms an allylic carbonate system which may lead to a decarboxylative allylation pathway in the presence of palladium catalyst instead of serving as a traditional leaving group. However, *tert*-butyl oxide anion, which was generated from the decarboxylation, also offers a possibility to the formation of glycoside **39** as the byproduct (**Scheme 2.1.10**).



Scheme 2.1.10 O'Doherty's strategy of palladium catalyzed *O*-glycosylation

After the successful construction of monosaccharide **38** through the palladium catalyzed glycosylation, the author then set out to the extension and application of this

strategy. First, they examined the applicability in the synthesis of oligosaccharides. With compound **37α** as the donor, the glycosylation with benzyl alcohol gave *α*-glycoside **38α** as the desired product. Subjecting compound **38α** to treatment with HF affords compound **40** with a free -OH group in *C*-6 position. After that, compound **40** was used as the glycosyl acceptor for the second glycosylation with donor **37α** to give compound **41**. Repeating the procedure of deprotection and glycosylation yielded compound **43**. Then 1,6-linked trisaccharide **46** was provided by diastereoselective reduction of ketone and a subsequent dihydroxylation of double bond with common used OsO_4 in NMO (**Scheme 2.1.11**).[10]



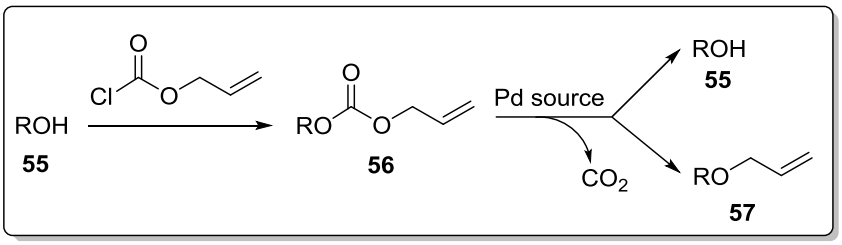
Scheme 2.1.11 Application to the construction of diverse oligosaccharides

Starting from easily prepared *O*-glycoside **38α**, compound **46** was obtained in high diastereoselectivity by the reduction of ketone. With a hydroxyl group on *C*-4 position, compound **46** was able to serve as a glycosyl acceptor to synthesize 1,4-linked glycoside bond through the same strategy. Iteration of the reduction and glycosylation was then conducted to provide a concise way to the formation of 1,4-linked oligosaccharides.[9] Moreover, this palladium catalyzed glycosylation strategy was also applied in the syntheses of many natural or unnatural products. Some selected structures such as compound **50**,[11] Anthrax tetrasaccharide (**51**),[12] Cleistetroside (**52**),[13] Cleistriside (**53**),[13] and Digitoxin (**54**)[14] are listed in **Scheme 2.1.11**.

With the great efforts of related groups, huge achievements have been made with the *de novo* asymmetric synthesis strategy. However, it is still costly to prepare the pyranone structure from aglycone starting material with commonly used methods. Besides that, very few reports about other metals, except palladium catalysts, have provided positive results for the glycosylation with glycal type donor. For instance, gold catalyst which was found to an efficient activator for the glycosylation with glycosyl donor in the presence of neighboring participation group gives poor selectivity in glycal system.[15] Moreover, an additive or a modification to the donor is required to increase the reactivity in the above strategies, so the development of new strategies to construct the *O*-glycosidic linkage with high efficiency and selectivity directly from glycal synthons, especially without any activator, remains a challenge.

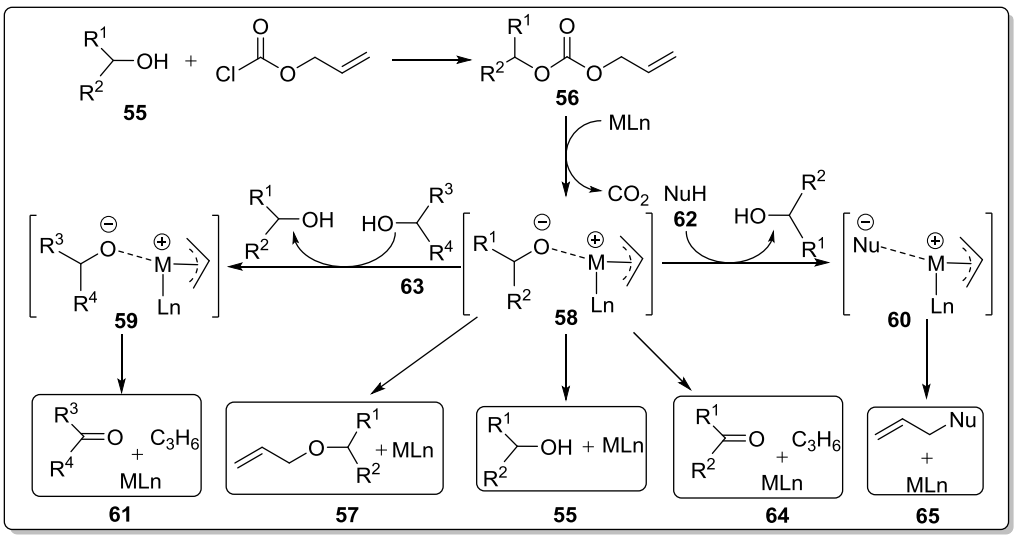
On the other hand, metal catalyzed decarboxylative allylation (DCA), pioneered by Tunge,[16] Trost[17] and Stoltz,[18] has proven its synthetic utility in the formation of C-X

bond with high efficient and selectivity in the earlier investigations. In early 1981, Guibe and M'Leux reported the first example of decarboxylative allylation with the allyl alkyl carbonate **56** as the starting material.[19] Subjecting compound **56**, which can be prepared from alcohol **55** and allyl chloroformate, in the presence of palladium catalyst, the desired alcohol **55** was regenerated and a coupling product **57** was also observed (**Scheme 2.1.12**).



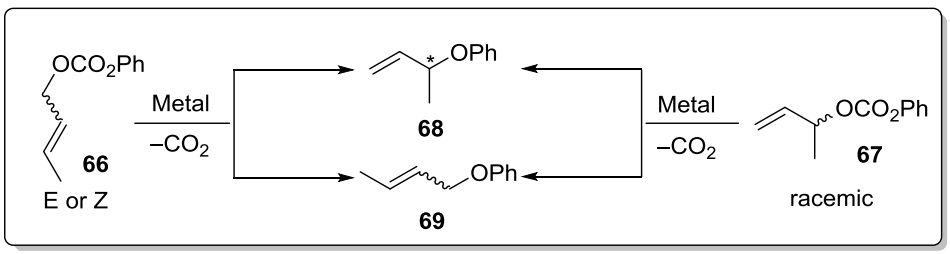
Scheme 2.1.12 First report on decarboxylative coupling with allylic carbonate

Though the decarboxylative coupling reaction was observed as a side reaction, it initiated the investigation into this type of reaction. Then in **1985**, Tsuji gave a detailed study on the Pd-π-allyl complex as the intermediate.[20] They commenced the investigation with allylic carbonate **56** which was able to furnish the π-allyl alkoxides complex **58** in the presence of metal catalyst. From the results of Guibe and M'Leux, both the *O*-allylation product **55** and protonation product alcohol **57** can be obtained in different conditions. Moreover, the ketone or aldehyde **64** could also be formed by the *β*-elimination under some special conditions. When another nucleophile **62** was introduced in the reaction, proton transfer will give complex **60** while subsequent coupling reaction occurred to give allylic product **65**. If the other reagent is a secondary alcohol, the oxidant product **61** was always obtained as the major product (**Scheme 2.1.13**).



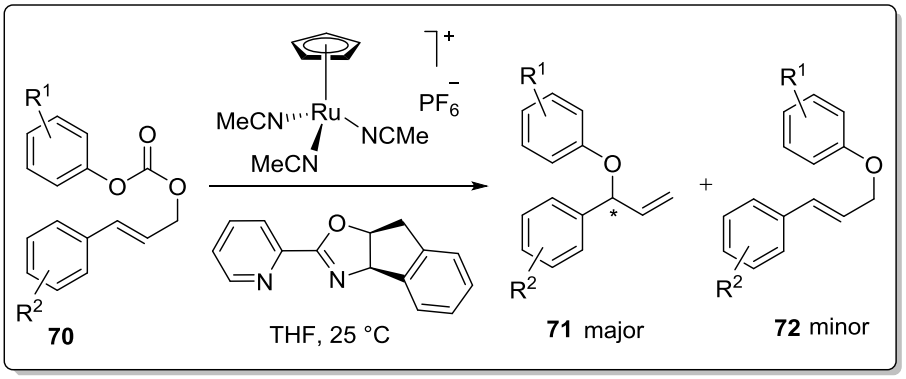
Scheme 2.1.13 Possible products obtained with M-π-allyl intermediate

The substrate scope was then extended to phenyl allylic carbonates in **1989** by Rama.[21] In their report, regardless of the metal used (Ni, Pd or Rh) and with starting material carbonate **66** or **67**, the decarboxylative reaction gave branched product **68** as the major product (**Scheme 2.1.14**). They also found that the reaction was able to produce products with enantiomeric excess in the presence of chiral ligands. Though the selectivity is not as idea under their reaction conditions, it is the first reported enantioselective decarboxylative etherification. Two years later, a further report from Larock presented a more extensive substrate scope and demonstrated the advantage of this approach for the synthesis of ether with bulky aryl or allylic substituent.[22]



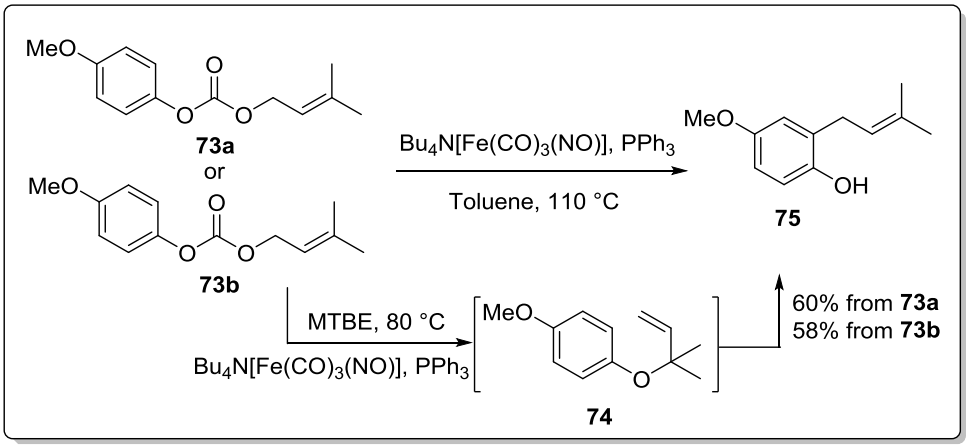
Scheme 2.1.14 Decarboxylation with phenyl allylic carbonates

For better regio- and stereo- selectivity control, a ruthenium catalytic system was employed by Lacour's group.[23] Gratifyingly, the reaction with carbonate **70** as the starting material in the presence of ruthenium catalyst gave the branched product **71** with moderate to good branched selectivity except for substrates with a conjugate system. Meanwhile, reasonable to excellent enantioselectivity was provided for the branched product of each reaction involving the chiral catalyst and ligand (**Scheme 2.1.15**).



Scheme 2.1.15 Enantioselective decarboxylative allylation with ruthenium catalyst

Recently, a cheaper iron catalyzed decarboxylative allylation was reported by Tunge.[24] They conducted the reaction with compound **73** as the starting material and an anionic iron catalyst $Bu_4N[Fe(CO)_3(NO)]$ was utilized in MTBE (methyl *tert*-butyl ether) at 80 °C to give the desired allylation product **74** in high yield and similar selectivity as the previous method. Interestingly, changing the solvent to toluene and increasing the temperature to 110 °C, resulted in the formation of Claisen rearrangement product **75** in moderate yield. It is noteworthy that both carbonates **73a** and **73b** gave the branched product as the major product and similar outcome was obtained for the Claisen rearrangement product.



Scheme 2.1.16 Decarboxylative allylation with iron catalyst

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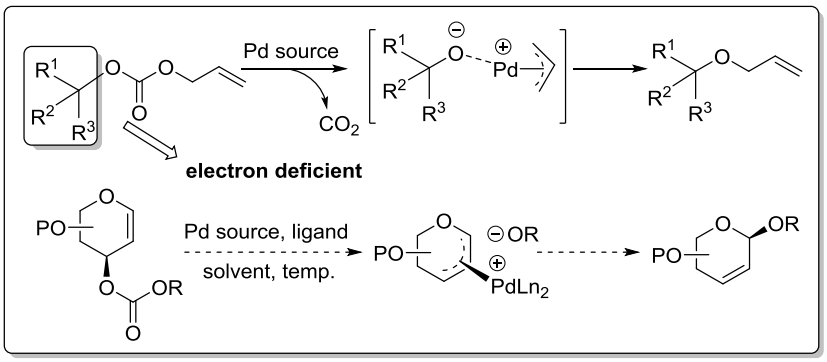
Chapter 2: β-Type glycosidic bond formation *via* palladium catalyzed decarboxylative allylation[1]

Introduction

The reaction through a decarboxylative pathway was found to be more efficient in the previous studies on glycosylation with Boc as the leaving group.[2] Furthermore, an allylic system is contained in the glycal structure, which can be further functionalized to provide more complex carbohydrate structures. We hypothesized that this may provide an additional pathway to solve the problem of formation and low reactivity of the Pd-π-allyl type donor (**Scheme 2.2.1**). The allylic carbonates have been widely used as the starting material to give the allylation ether products.



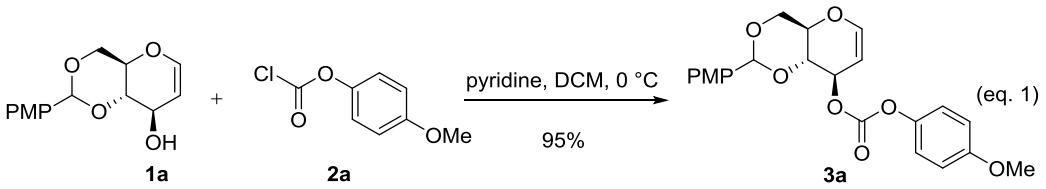
Scheme 2.2.1 Our proposed *O*-glycosylation method *via* a decarboxylative reaction

From the previous results, we can also see the metal catalysts are competent and widely used in both the DcA reaction and glycosylation. Hence, we postulate that it is possible to combine the two concepts and apply it in our own methodology to form

the *O*-glycosidic bonds. It should be noted that the DcA reaction is much easier to occur in electron deficient allylic system, thus it is still a challenge to develop this type of reactions in glycal structure for the glycosylation with glycal donor. As a continuation of our efforts in discovering new glycosylation methods,[3] herein, we report the results of our exploration of palladium catalyzed decarboxylative allylation approach from glycal carbonates.

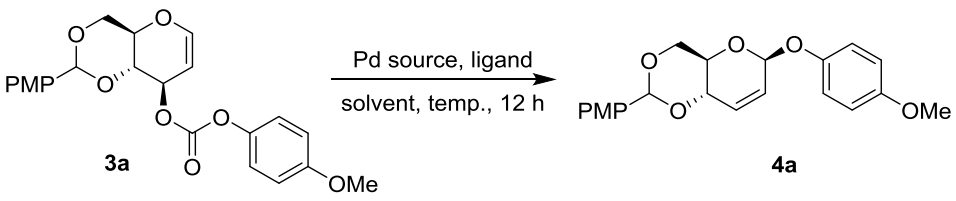
Result and discussion

We commenced the studies with carbonate **3a** as the model substrate. It could be easily prepared by an esterification reaction of 4-methoxyphenyl chloroformate **1a** and 4,6-*para*-methoxybenzylidine-glucal **2a** in 95% yield (**eq**. **1**). We chose this substrate as the starting material because the phenol generated from decarboxylation with an electron-donating *para*-methoxy group has stronger nucleophilicity. Hence, the next step of nucleophilic addition after formation of the Pd-π-allyl species should be easier to proceed.



After the preparation of **3a**, we turned to optimize the reaction conditions. Firstly, different catalytic systems including palladium source and ligand were tested. As the result in **table 2.2.1** shows, with the exception of $Pd(allyl)_2Cl_2$ and D*i*PPF can give a trace amount of desired product **4a** (entry **4**), other catalytic systems were incapable to promote this reaction (entries **1**-**3** and **5**-**6**) with Pd(II) catalysts ($PdCl_2$, $Pd(OAc)_2$ and $Pd(allyl)_2Cl_2$, for instance) and different ligand (such as PPh_3, DPPF and D*i*PPF) by using toluene as solvent in 60 °C. We then proceeded to apply Pd(0) catalyst $Pd(PPh_3)_4$ to this reaction but no desired product was observed (entry **7**). Interestingly, the yield increased to 93% when $Pd_2(dba)_3$ was employed as the catalyst with D*i*PPF as the ligand (entry **8**). Next, other ligands were screened to improve the outcome of the reaction. However, no better results were obtained (entries **9**-**15**). Different solvents were then checked and from the results, we could see toluene was superior as

Table 2.2.1 Optimization of reaction conditions with phenol type substrate

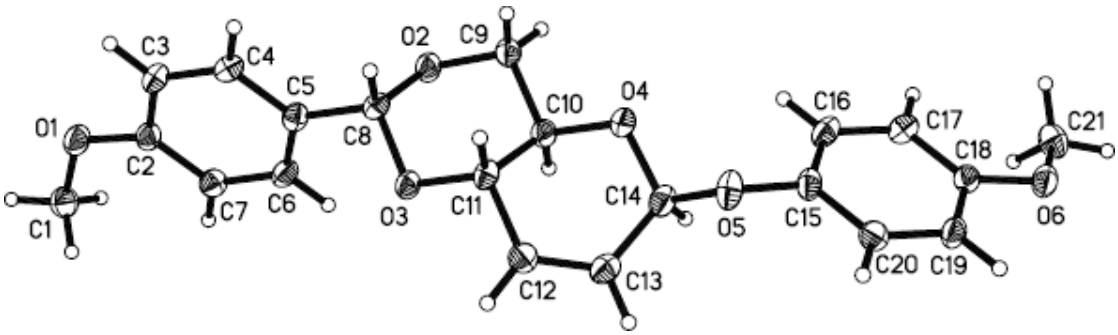


Entry[a]	Pd Source	Ligand	Solvent	Temp. (ºC)	Yield[b] (%)
1	$PdCl_2$	PPh_3	toluene	60	-
2	$Pd(OAc)_2$	PPh_3	toluene	60	-
3	$Pd(OAc)_2$	DPPF	toluene	60	-
4	$Pd(allyl)_2Cl_2$	D*i*PPF	toluene	60	trace
5	$PdCl_2$	D*i*PPF	toluene	60	-
6	$Pd(OAc)_2$	D*i*PPF	toluene	60	-
7	$Pd(PPh_3)_4$	D*i*PPF	toluene	60	-
8	**$Pd_2(dba)_3$**	**D*i*PPF**	**toluene**	**60**	**93**
9	$Pd_2(dba)_3$	DPPE	toluene	60	trace
10	$Pd_2(dba)_3$	DPPP	toluene	60	trace
11	$Pd_2(dba)_3$	DPPB	toluene	60	32
12	$Pd_2(dba)_3$	DPPPent	toluene	60	-
13	$Pd_2(dba)_3$	DPEPhos	toluene	60	79
14	$Pd_2(dba)_3$	Xantphos	toluene	60	74
15	$Pd_2(dba)_3$	DPPF	toluene	60	trace
16	$Pd_2(dba)_3$	D*i*PPF	THF	60	40
17	$Pd_2(dba)_3$	D*i*PPF	CH_2Cl_2	60	11
18	$Pd_2(dba)_3$	D*i*PPF	MeCN	60	trace
19	$Pd_2(dba)_3$	D*i*PPF	toluene	rt	trace
20	$Pd_2(dba)_3$	D*i*PPF	toluene	80	90

[a] Unless otherwise specified, all reactions were carried out with compound **3a** (0.1 mmol), $Pd_2(dba)_3$ (0.01 mmol) and D*i*PPF (0.2 mmol) in 2 mL solvent for 12 hours. [b] Isolated yield

compared to other solvents in yielding the desired *O*-glycoside with much higher yield (entries **16**-**18**). The outcome of the reaction was significantly affected by the reaction temperature and best result was provided when the reaction was conducted at 60 °C (entries **19, 20**). Then optimized reaction conditions were concluded as follows: $Pd_2(dba)_3$ as catalyst, 1,1'-bis(diisopropylphosphino) ferrocene (D*i*PPF) as ligand and toluene as solvent at 60 °C for 12 h. It should be noted that exclusive *β*-selectivity were obtained and the X-ray diffraction crystallographic analysis further confirmed the stereochemistry of product.[4]

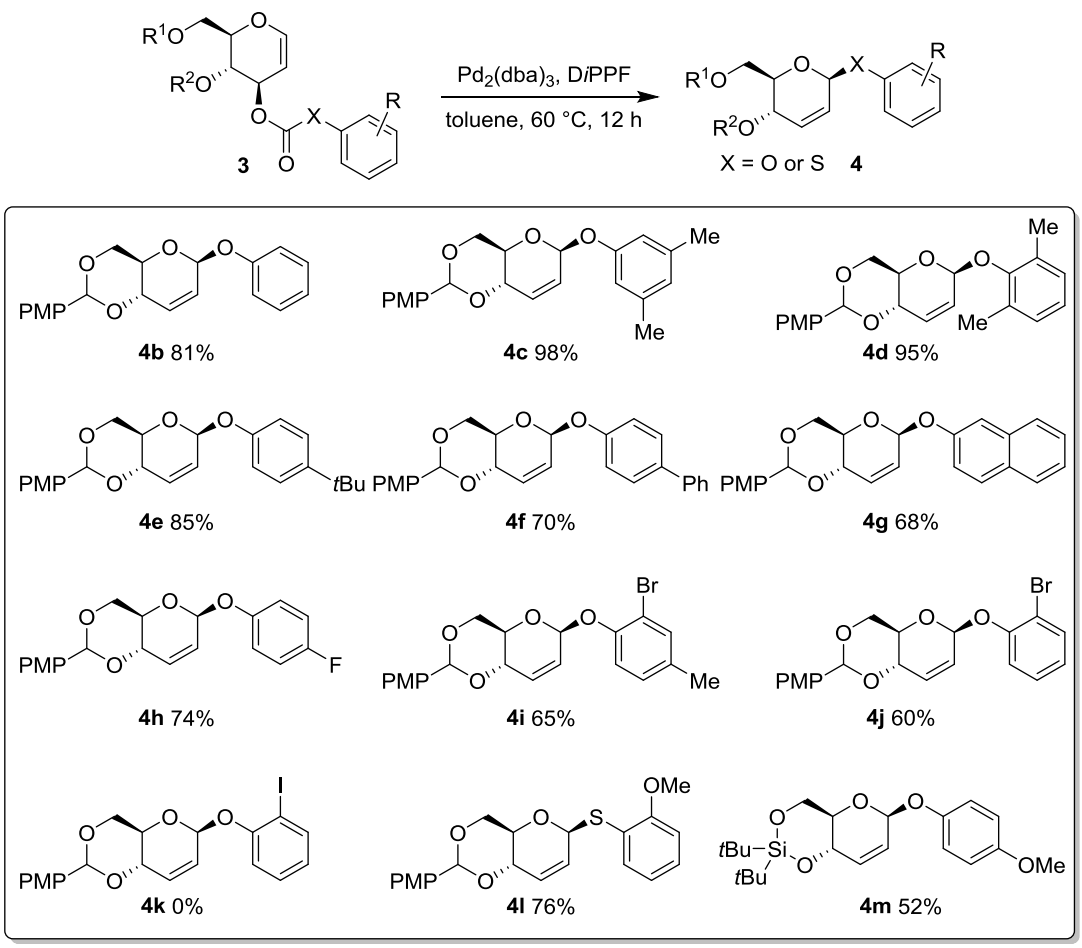
Figure 2.2.1 The X-ray structure of compound **4a (CCDC: 836929)**



After obtaining the optimized conditions, the scope and generality of this method were tested. A plenty of phenolic carbonate substrates **3** was prepared in 90-98% yields by the reaction of **1a** and phenolic acyl chlorides **2**. Compounds **3** were then subjected to optimized conditions and the results are given in **Scheme 2.2.2**. As shown below, substrate **3b** without any substituents on phenol group provided **4b** with 81% yield. Particularly, alkyl-substituted phenol carbonates gave the products with slightly higher yields (**4c**-**4e**). On the other hand, biphenol and 2-naphthalenol derived substrates only gave moderate yields (**4f**-**4g**) because of steric hindrance effect.

Halide moieties substituted substrates were also employed, albeit lower yields (**4h**-**4j**). No desired product **4k** was observed when 2-iodo phenol substrate **3k** was used.[5] Thiophenolic substrate was next studied and, to our delight, the desired thiophenolic *S*-glycoside (**4l**) was generated successfully in 76%. Apart from **1a**, a sterically bulky 4,6-di-*tert*-butylsilyl protected glucal derivative **3m** was also tested. However, the treatment of **3m** under optimized conditions provided a low yield of 52%.

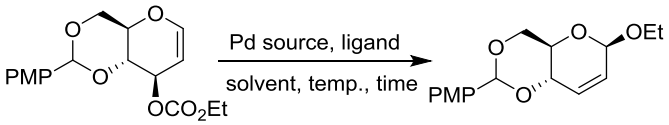
Scheme 2.2.2 Substrate scope of phenolic *O*-glycosides



Reaction conditions: compound **3** (1.0 equiv), $Pd_2(dba)_3$ (0.1 equiv) and D*i*PPF (0.2 equiv) in 20 mL/ mmol toluene were stirred at 60 °C for 12 h.

Phenols are commonly adopted as nucleophiles in palladium catalyzed allylation. On the contrary, the research into the use of aliphatic alcohols as nucleophiles is not as comprehensive to date. In order to further expand the generality of this method, we next focused on investigation of the syntheses of aliphatic *O*-glycosides. Carbonate compound **5a** was then synthesized and selected as the model to examine the flexibility of the reaction with the above conditions. However, this condition gave product **6a** with only 30% yield for the first trial. The study of crude ^{1}H NMR shown 70% of starting material was not reacted after 2h (entry **1**). Then we tried to modify the reaction conditions to pursue better result. As mentioned in **Table 2.2.2**, extension of reaction duration to 12 h increased the reaction yield to 70%, but longer time cannot get significantly improvement (entry **2**). Different ligands were tried to further enhance the yield. From the results we can see the ligands had a dramatic influence to the outcome of reaction and to our delight, the employment of 1,1′-bis(di-*tert*-butylphosphino) ferrocene (D*t*BPF) as the ligand gave 96% conversion of starting material (entry **10**). Other ligands exhibited little or no efficiency for this reaction (entries **3-9**). Other modification such as change the solvent to $CHCl_3$ gave a trace mount of product (entry **11**). Furthermore, increasing the reaction temperature to 80 °C gave a better 99% conversion ratio and the desired product **6a** was isolated in 95% yield (entry **12**).

Table 2.2.2 Optimization of reaction condition with aliphatic alcohol [a]



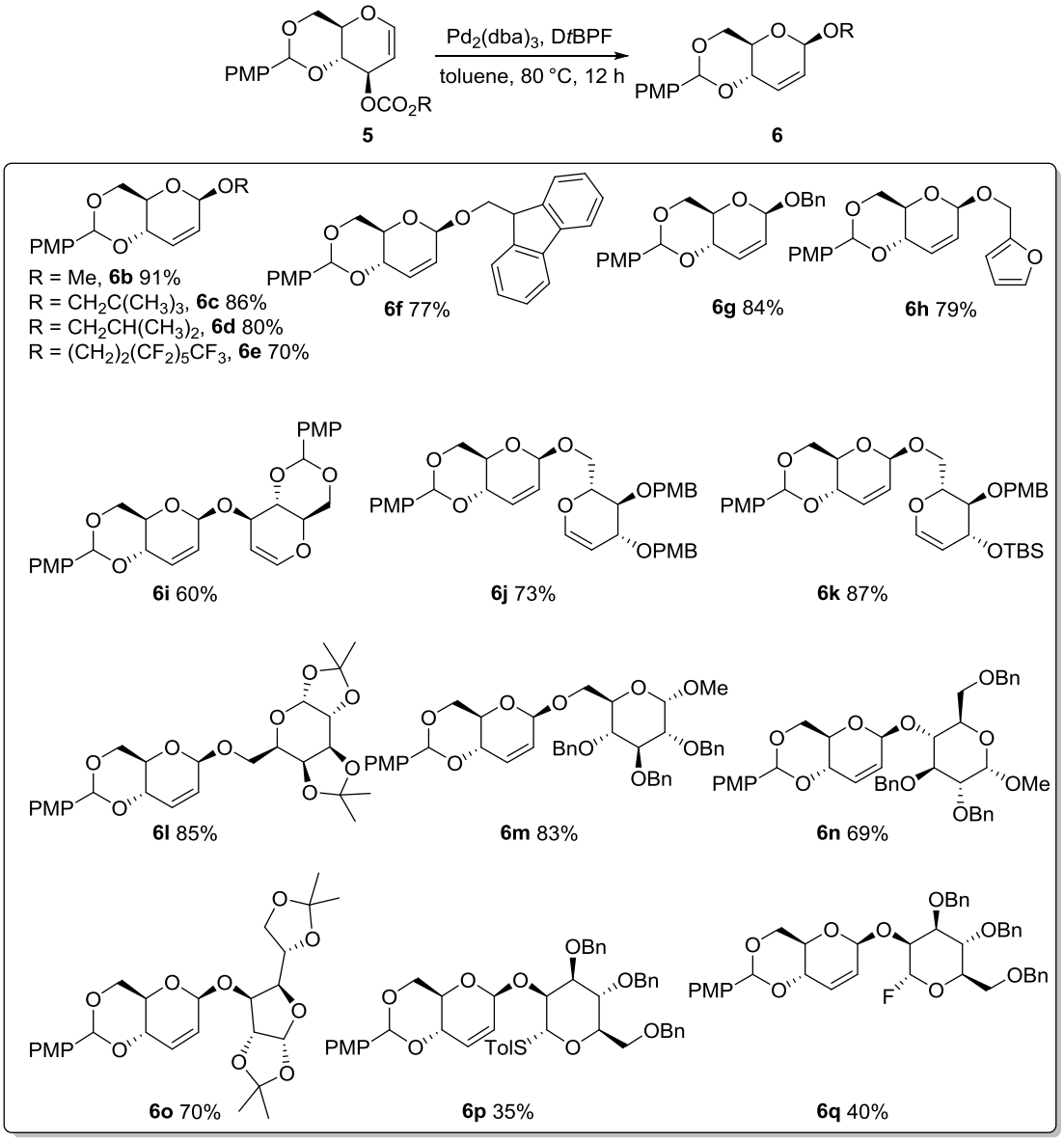
5a **6a**

Entry	Pd Source (10 mol%)	Ligand (20 mol%)	Solvent	Temp. (ºC)	Time(h)	Conversion (%)[b]
1	$Pd_2(dba)_3$	D*i*PPF	toluene	60	2	30
2	$Pd_2(dba)_3$	D*i*PPF	toluene	60	12	70
3	$Pd_2(dba)_3$	Sphos	toluene	60	12	75
4	$Pd_2(dba)_3$	Xantphos	toluene	60	12	80
5	$Pd_2(dba)_3$	DPEPhos	toluene	60	12	31
6	$Pd_2(dba)_3$	Xphos	toluene	60	12	46
7	$Pd_2(dba)_3$	DPPE	toluene	60	12	trace
8	$Pd_2(dba)_3$	DPPP	toluene	60	12	trace
9	$Pd_2(dba)_3$	DPPB	toluene	60	12	trace
10	$Pd_2(dba)_3$	D*t*BPF	toluene	60	12	96
11	$Pd_2(dba)_3$	D*t*BPF	$CHCl_3$	60	12	trace
12	$Pd_2(dba)_3$	D*t*BPF	toluene	80	12	100

[a] Unless otherwise specified, all reactions were carried out with freshly distilled dry solvent for 12 hours. [b] Conversion was determined by ^{1}H NMR of crude product.

Before the application of modified conditions, numerous aliphatic carbonates **5** were prepared by three different conditions in 50-93% yields which have been detailed in the experiment section. As illustrated in **Scheme 2.2.3**, most of examined substrates were able to give the corresponding *O*-glycosides **6** in reasonable to excellent yields. Obviously, substrates provided from primary alcohols could afford high yields (**6b**-**6d**). The treatment of strong electron-withdrawing fluoride atom containing long chain substrates under the optimized conditions yielded **6e** with a yield of 70%. With the same conditions, *O*-glycosides **6f** could be obtained in 77%. Benzyl alcohol and furfuryl alcohol derived substrates were also employed to check the generality of this method and both of the reactions proceeded efficiently to provide the corresponding *O*-glycosidic linkages in 84% and 79% yields respectively (**6g**-**6h**). Due to the importance of disaccharides in carbohydrate chemistry, a variety of carbonates provided by the reactions of glucal **1** and different sugar alcohols were tested. The subjection of carbonate **5i** under standard reaction conditions gave desired disaccharide **6i** in 60% yield. Less steric hindrance 6-OH glucals derived substrates could be used to provide the products in higher yields (**6j**-**6k**). Similarly, the reaction with substrates from 6-OH galactose and glucose derived carbonates yielded satisfactory results (**6l**-**6m**). Similar to the reaction with phenolic substrate, this reaction was also greatly affected by the steric effect and then a bit lower yields were obtained when bulkier substrates, such as **5n** and 5**o** were treated under the same conditions. For further extending the versatility of this decarboxylative glycosylation strategy, 2-OH mannose substrates were also prepared for examination and the desired disaccharide **6p** and **6q** were achieved successfully, albeit lower yield.

Scheme 2.2.3 Substrate scope of aliphatic *O*-glycosides and disaccharides

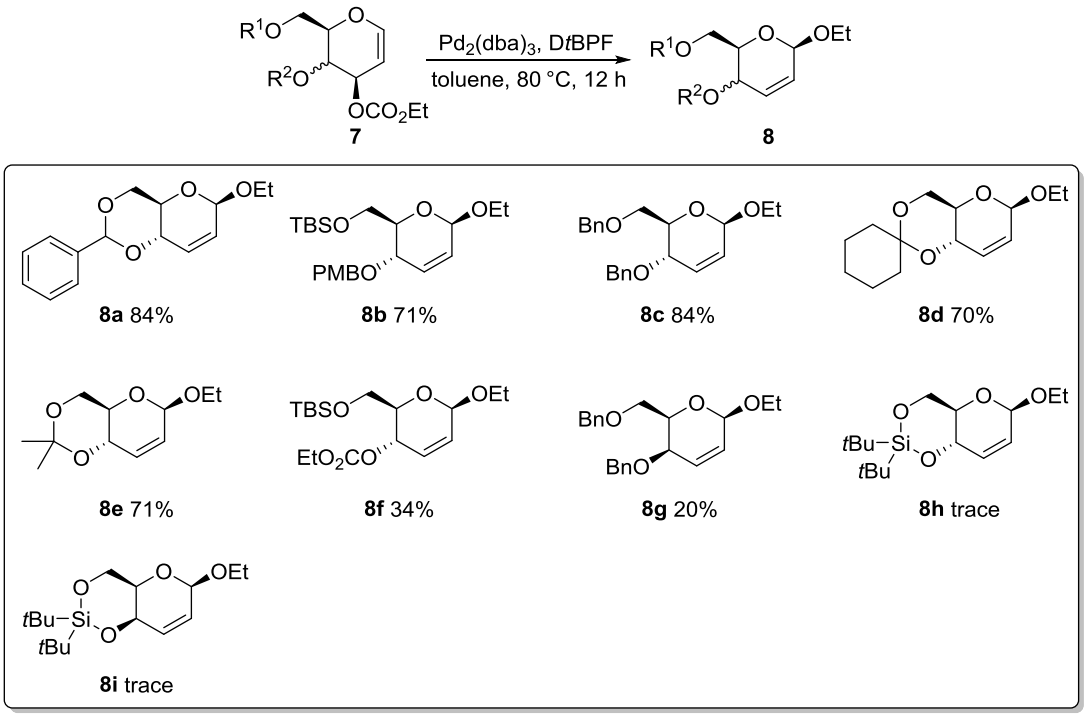


Reaction conditions: compound **5** (1.0 equiv), $Pd_2(dba)_3$ (0.1 equiv) and D*t*BPF (0.2 equiv) in 20 mL/ mmol toluene were stirred at 80 °C for 12 h.

As the protecting group and the structure of the glycal also played important role in controlling the outcome of reaction, then further exploration was focused on these two parts. Different protecting groups containing carbonates **7** were then prepared readily from glucals and ethyl chloroformate in good yields. Next subjection of **7** with

optimized conditions provided the desired *O*-glycosides **8** in moderate to good yields (**8a**-**8f**). Benzyl group protected galactal substrate **7g** was also applied but the reaction gave desired product with only an isolated yield of 20%. However, the selection of 4,6-di-*tert*-butylsilyl as the protecting group for both glucal and galactal substrates (**7h**-**7i**) was failed to provide satisfied results.

Scheme 2.2.4 Substrate scope of glycals with various protecting groups

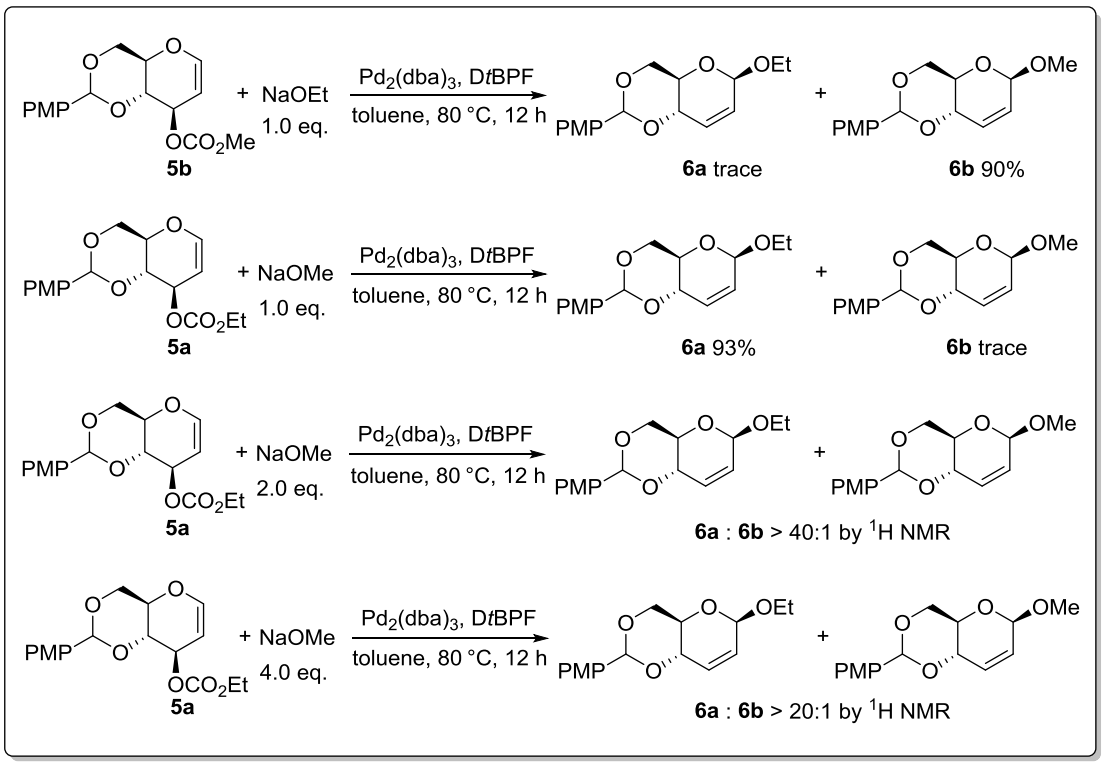


Reaction conditions: compound **7** (1.0 equiv), $Pd_2(dba)_3$ (0.1 equiv) and D*t*BPF (0.2 equiv) in 20 mL/ mmol toluene were stirred at 80 °C for 12 h.

To investigate the mechanism of this reaction, competitive experiments were designed and performed with standard conditions as below (**Scheme 2.2.5**). It could be seen that the addition of nucleophile contributed insignificant influence on the outcome. When **5b** was used with addition of 1.0 eq NaOEt, competing **6b** was

isolated in 90% yield. On the other hand, **6a** was observed as the dominant product when **5a** was utilized as the starting material in the presence of 1.0 eq NaOMe. Similar results were obtained when increasing the amount of NaOMe from 1.0 eq to 2.0 eq and 4.0 eq as confirmed by ^{1}H NMR.

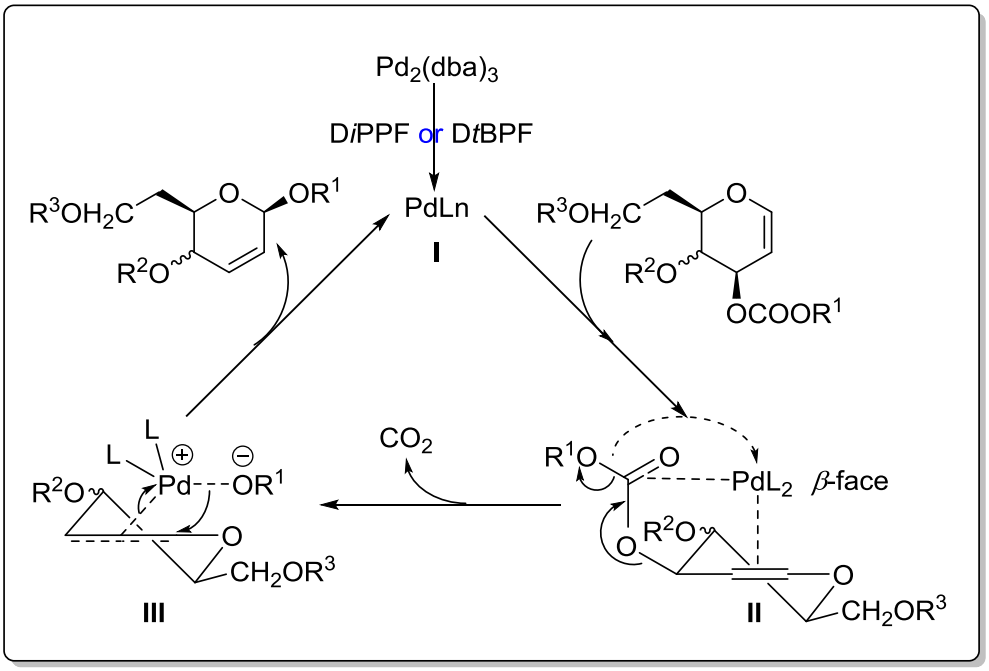
Scheme 2.2.5 Competition experiments



Based on the previous investigation on palladium catalyzed decarboxylation[6] and the results from our studies, we gave the proposed mechanism as following (**Scheme 2.2.6**): the first step of catalytic cycle is the formation of the palladium-D*i*PPF or -D*t*BPF species **I**. Then key intermediate **II** is formed by the followed binary coordination of complex **I** to both the double bond and the carbonyl group of glycals with the palladium complex orientated in β-face. As β-face of the intermediate was

occupied by the palladium species, it is easy to explain that why lower yields were obtained with galactal substrate in comparison with glucal substrates. As stated in the previous literature, an ion pair intermediate **III** normally generates by a subsequent decarboxylation of the intermediate **II** with nonpolar toluene as the solvents.[9c] Finally, *β*-type *O*-glycoside was obtained by an intramolecular nucleophilic addition along with an elimination of the palladium complex **I**, completing the catalytic cycle.

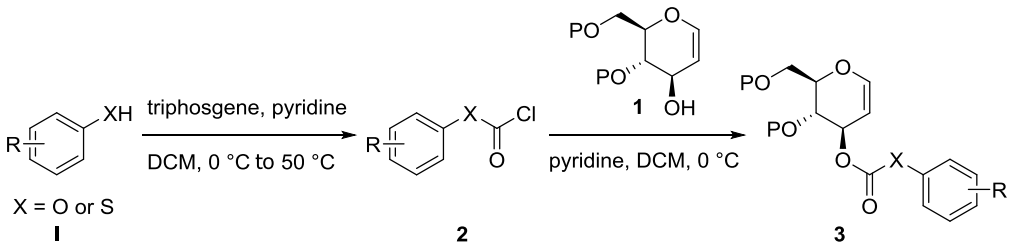
Scheme 2.2.6 Plausible mechanism



Conclusion

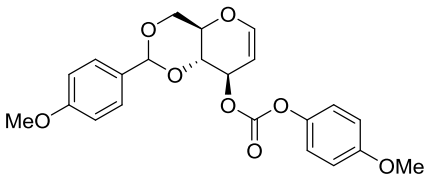
In summary, we have provided a new strategy towards the formation of *O*-glycosidic linkage. This method is based on a palladium catalyzed decarboxylative allylation and various glycosides including phenolic *O*-glycosides, thiophenolic *S*-glycoside, aliphatic *O*-glycosides and disaccharides were afforded from readily available carbonates substrates in moderate to excellent yields. A range of glycals with different protecting groups were also tested and reasonable to excellent yields were provided for most of the situations. Compared to previous methods, this strategy is advantageous as it starts from sugar derived glycal synthons and there is no requirement for an activator. Besides that, all 2,3-unsaturated *O*-glycosides were achieved with exclusive β-selectivity and they were able to serve as versatile synthetic intermediates to synthesize natural and unnatural carbohydrates structures by the functionalization of olefin group.

General procedure for preparing phenolic carbonates (3)



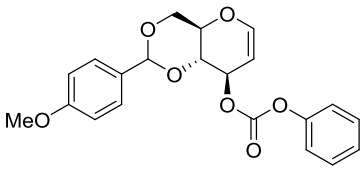
To a solution of phenol (**I**) (1 eq.) in dry DCM (1 mLmmol^{-1}) was added triphosgene (0.33 eq.) at 0 °C. Then Pyridine (1 eq.) was added slowly. The reaction mixture was heated to 50 °C and refluxed for 1 hour. After cooling to room temperature, the mixture was poured into Et_2O and filtered over Celite. The filtrate was concentrated under reduced pressure to afford the crude phenyl carbonochloridate (**2**) which was used directly for the next step. To a solution of glucal (**1**)[7] (1 eq.) in dry DCM (10 mLmmol^{-1}) was added pyridine (8 eq.) at 0 °C and then the mixture was stirred for 10 mins at 0 °C. Next, a solution of phenyl chloroformate (**2**) (2 equiv) in dry DCM (4 mLmmol^{-1}) was added. The mixture was allowed to warm to room temperature and stirred overnight. After that, the mixture was poured into EA and then filtered. The filtrate was washed sequentially with H_2O, brine, and then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with *n*-hexane/EA=20:1) to provide the desired product **3** with 90-98% yields.

4-Methoxyphenyl(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano [3,2-d][1,3]dioxin-8-yl carbonate (3a)



Compound **3a** (98.0 mg, 95%) was obtained as a white solid. m.p. 105-107 °C; $[\alpha]_D^{23}$ = –48.9 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 3.81 (s, 3H), 3.86 (t, *J* = 10.4 Hz, 1H), 4.02 (td, J_1 = 10.2 Hz, J_2 = 4.8 Hz, 1H), 4.13 (dd, J_1 = 10.4 Hz, J_2 = 7.6 Hz, 1H), 4.40 (dd, J_1 = 10.4 Hz, J_2 = 5.2 Hz, 1H), 4.96 (dd, J_1 = 6.0 Hz, J_2 = 2.0 Hz, 1H), 5.47 (dt, J_1 = 6.0 Hz, J_2 = 1.6 Hz, 1H), 5.59 (s, 1H), 6.45 (dd, J_1 = 6.0 Hz, J_2 = 1.2 Hz, 1H), 6.86-6.92 (m, 4H), 7.07-7.10 (m, 2H), 7.43-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 55.6, 68.1, 68.7, 73.1, 76.6, 99.8, 101.7, 113.7, 114.4, 121.8, 127.6, 129.2, 144.6, 146.1, 153.6, 157.4, 160.3 ppm; IR (neat) ν: 1034, 1125, 1215, 1420, 1506, 1757, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{22}O_8Na$ $[M+Na]^+$: 437.1212, found: 437.1216.

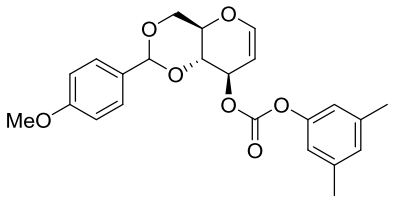
(4a*R*,8*R*,8a*S*)-2-(4-Methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2d][1,3]dioxin-8-yl phenyl carbonate (3b)



Compound **3b** (94.0 mg, 98%) was obtained as a white solid. m.p. 135-137 °C; $[\alpha]_D^{23}$ = –59.2 (*c* = 0.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.86 (t, *J* = 10.2 Hz, 1H), 4.02 (td, J_1 = 10.1 Hz, J_2 = 5.0 Hz, 1H), 4.13 (dd, J_1 = 10.2 Hz, J_2 = 7.8 Hz, 1H), 4.39 (dd, J_1 = 10.4 Hz, J_2 = 5.2 Hz, 1H), 4.96 (dd, J_1 = 6.1 Hz, J_2 = 2.0 Hz, 1H), 5.46-5.52 (m, 1H), 5.59 (s, 1H), 6.45 (d, J_1 = 6.1 Hz, 1H), 6.87-6.94 (m, 2H), 7.16-7.25 (m, 3H), 7.34-7.45 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 68.2,

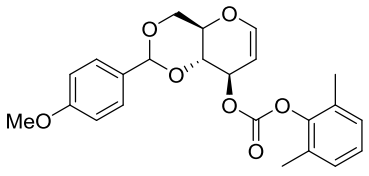
68.8, 73.2, 76.7, 99.8, 101.7, 113.7, 121.0, 126.1, 127.6, 129.3, 129.5, 146.2, 151.0, 153.2, 160.3, ppm; IR (neat) ν: 1022, 1125, 1215, 1420, 1520, 1647, 1761, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{20}O_7Na$ $[M+Na]^+$: 407.1107, found: 407.1117.

3,5-Dimethylphenyl(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl carbonate (3c)



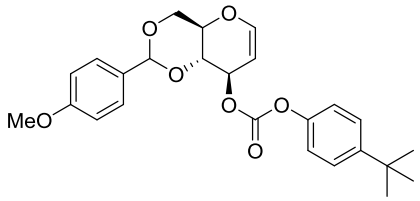
Compound **3c** (99.0 mg, 96%) was obtained as a white solid. m.p. 148-150 °C; $[\alpha]_D^{23}$ = –48.0 (c = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 6H), 3.80 (s, 3H), 3.86 (t, J = 10.4 Hz, 1H), 4.02 (td, J_1 = 10.2 Hz, J_2 = 5.0 Hz, 1H), 4.13 (dd, J_1 = 10.2 Hz, J_2 = 7.8 Hz, 1H), 4.39 (dd, J_1 = 10.2 Hz, J_2 = 5.0 Hz, 1H), 4.96 (dd, J_1 = 6.0 Hz, J_2 = 2.0 Hz, 1H), 5.47 (dt, J_1 = 6.0 Hz, J_2 = 2.0 Hz, 1H), 5.59 (s, 1H), 6.45 (dd, J_1 = 6.0 Hz, J_2 = 1.2 Hz, 1H), 6.78 (s, 2H), 6.85-6.94 (m, 3H), 7.40-7.47 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 55.3, 68.2, 68.7, 73.1, 99.8, 101.7, 113.7, 118.5, 127.6, 127.8, 129.3, 139.3, 146.1, 150.9, 153.4, 160.3 ppm; IR (neat) ν: 1034, 1076, 1096, 1124, 1215, 1420, 1518, 1616, 1645, 1755, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{24}O_7Na$ $[M+Na]^+$: 435.1420, found: 435.1429.

2,6-Dimethylphenyl(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl carbonate (3d)



Compound **3d** (97.0 mg, 94%) was obtained as a yellow solid. m.p. 114-116 °C; $[\alpha]_D^{23}$ = –45.7 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 6H), 3.81 (s, 3H), 3.86 (t, *J* = 10.4 Hz, 1H), 4.02 (td, J_1 = 10.2 Hz, J_2 = 5.2 Hz, 1H), 4.13 (dd, J_1 = 10.4 Hz, J_2 = 7.7 Hz, 1H), 4.39 (dd, J_1 = 10.4 Hz, J_2 = 5.1 Hz, 1H), 4.92 (dd, J_1 = 6.1 Hz, J_2 = 2.0 Hz, 1H), 5.52-5.57 (m, 1H), 5.59 (s, 1H), 6.45 (dd, J_1 = 6.0 Hz, J_2 = 1.2 Hz, 1H), 6.88-6.93 (m, 2H), 7.04 (s, 3H), 7.40-7.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 55.3, 68.1, 68.7, 73.0, 76.8, 99.8, 101.5, 113.6, 126.1, 127.4, 128.7, 129.3, 130.1,146.1, 148.3, 152.6, 160.2 ppm; IR (neat) ν: 1033, 1077, 1096, 1125, 1215, 1254, 1271, 1474, 1520, 1645, 1757, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{24}0_7Na$ $[M+Na]^+$: : 435.1420, found: 435.1423.

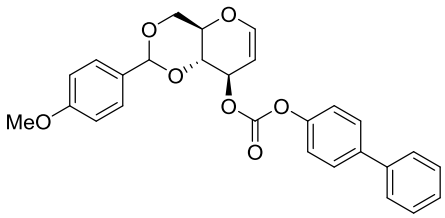
4-Tert-butylphenyl(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl carbonate (3e)



Compound **3e** (104.0 mg, 95%) was obtained as a white solid. m.p. 123-124 °C; $[\alpha]_D^{23}$ = –50.1 (*c* = 0.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 9H), 3.80 (s, 3H), 3.86 (t, *J* = 10.4 Hz, 1H), 4.02 (td, J_1 = 10.0 Hz, J_2 = 5.2 Hz, 1H), 4.13 (dd, J_1 = 10.3 Hz, J_2 = 7.8 Hz, 1H), 4.39 (dd, J_1 = 10.4 Hz, J_2 = 5.1 Hz, 1H), 4.96 (dd, J_1 = 6.2 Hz, J_2 = 1.2 Hz, 1H), 5.48 (dt, J_1 = 6.0 Hz, J_2 = 1.2 Hz, 1H), 5.59 (s, 1H), 6.45 (dd, J_1 = 6.0 Hz, J_2 = 1.2 Hz, 1H), 6.89-6.93 (m, 2H), 7.07-7.12 (m, 2H), 7.35-7.40 (m, 2H), 7.42-7.48 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.4, 34.4, 55.3, 68.1, 68.7, 73.1, 76.6, 99.8, 101.7, 113.7, 120.3, 126.3, 127.6, 129.3, 146.1, 148.6, 148.9, 153.4,

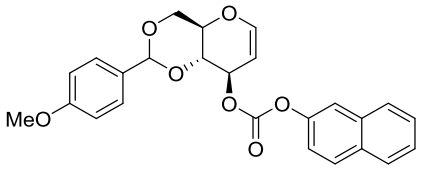
160.3 ppm; IR (neat) *ν*: 1015, 1215, 1420, 1474, 1520, 1616, 1653, 1749, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{28}O_7Na$ $[M+Na]^+$: 463.1733, found: 463.1736.

Biphenyl-4-yl(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl carbonate (3f)



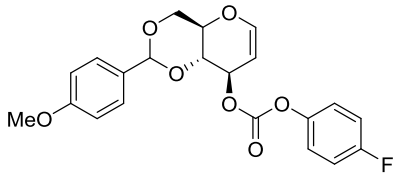
Compound **3f** (106.0 mg, 92%) was obtained as a white solid. m.p. 129-131 °C; $[\alpha]_D^{23}$ = –46.1 (*c* = 0.3 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.88 (t, J = 10.4 Hz, 1H), 4.04 (td, J_1 = 10.2 Hz, J_2 = 5.2 Hz, 1H), 4.15 (dd, J_1 = 10.4 Hz, J_2 = 7.6 Hz, 1H), 4.41 (dd, J_1 = 10.4 Hz, J_2 = 5.0 Hz, 1H), 4.98 (dd, J_1 = 6.4 Hz, J_2 = 2.0 Hz, 1H), 5.51 (dt, J_1 = 6.0 Hz, J_2 = 2.0 Hz, 1H), 5.61 (s, 1H), 6.47 (dd, J_1 = 6.0 Hz, J_2 = 1.2 Hz, 1H), 6.88-6.93 (m, 2H), 7.21-7.60 (m, 11H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5, 68.1, 68.8, 73.3, 76.7, 99.7, 101.7, 113.7, 121.2, 127.1, 127.4, 127.6, 128.2, 128.8, 129.3, 139.3, 140.2, 146.2, 150.4, 153.2, 160.3 ppm; IR (neat) *ν*: 1020, 1125, 1215, 1420, 1474, 1506, 1506, 1520, 1601, 1750, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{27}H_{24}O_7Na$ $[M+Na]^+$: 483.1420, found: 483.1418.

(4a*R*,8*R*,8a*S*)-2-(4-Methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl naphthalen-2-yl carbonate (3g)



Compound **3g** (103.0 mg, 95%) was obtained as a white solid. m.p. 129-131 °C; $[\alpha]_D^{23}$ = –62.5 (*c* = 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ, 3.81 (s, 3H), 3.88 (t, *J* = 10.4 Hz, 1H), 4.04 (td, J_1 = 10.0 Hz, J_2 = 5.2 Hz, 1H), 4.16 (dd, J_1 = 10.4 Hz, J_2 = 7.8 Hz, 1H), 4.41 (dd, J_1 = 10.5 Hz, J_2 = 5.1 Hz, 1H), 5.00 (dd, J_1 = 6.1 Hz, J_2 = 2.0 Hz, 1H), 5.48 (dt, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 5.61 (s, 1H), 6.47 (dd, J_1 = 6.0 Hz, J_2 = 1.2 Hz, 1H), 6.90-6.94 (m, 2H), 7.31 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.44-7.52 (m, 4H), 7.65 (d, *J* = 2.4 Hz, 1H), 7.78-7.87 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 68.2, 68.8, 73.3, 99.8, 101.7, 113.7, 118.0, 120.4, 125.9, 126.7, 127.6, 127.7, 129.3, 129.5, 131.5, 133.6, 146.2, 148.6, 153.3, 160.3 ppm; IR (neat) ν: 1020, 1096, 1125, 1215, 1420, 1474, 1508, 1520, 1603, 1761, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{22}O_7Na$ $[M+Na]^+$: 457.1263, found: 457.1253.

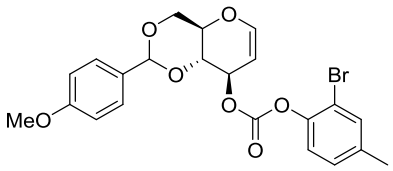
4-Fluorophenyl(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano [3, 2-d][1,3]dioxin-8-yl carbonate (3h)



Compound **3h** (93.0 mg, 93%) was obtained as a white solid. m.p. 163-164 °C; $[\alpha]_D^{23}$ = –53.8 (*c* = 0.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.86 (t, *J* = 10.4 Hz, 1H), 4.02 (td, J_1 = 10.2 Hz, J_2 = 4.8 Hz, 1H), 4.13 (dd, J_1 = 10.2 Hz, J_2 = 7.5 Hz, 1H), 4.40 (dd, J_1 = 10.5 Hz, J_2 = 5.1 Hz, 1H), 4.95 (dd, J_1 = 6.0 Hz, J_2 = 1.8 Hz, 1H), 5.45-5.51 (m, 1H), 5.59 (s, 1H), 6.45 (dd, J_1 = 6.2 Hz, J_2 = 0.8 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.01-7.10 (m, 2H), 7.11-7.18 (m, 2H), 7.43 (d, *J* = 8.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 68.1, 68.7, 73.4, 76.6, 99.6, 101.7, 113.7, 116.0, 116.2, 122.4, 122.5, 127.6, 129.2, 146.3, 146.8(2C), 153.2, 159.1, 160.3, 161.5 ppm;

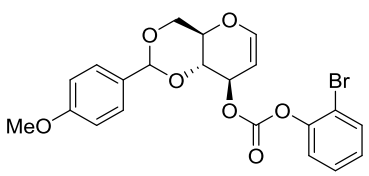
IR (neat) ν: 1034, 1096, 1125, 1215, 1420, 1474, 1506, 1520, 1601, 1645, 1757, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{19}O_7NaF$ $[M+Na]^+$: 425.1013, found: 425.1017.

2-Bromo-4-methylphenyl(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydro pyrano[3,2-d][1,3]dioxin-8-yl carbonate (3i)



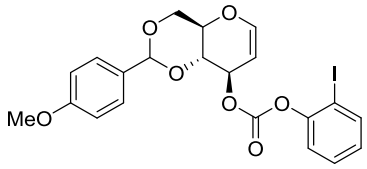
Compound **3i** (113.0 mg, 95%) was obtained as a yellow solid. m.p. 112-113 °C; $[\alpha]_D^{23}$ = –31.3 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.80 (s, 3H), 3.86 (t, J = 10.4 Hz, 1H), 4.02 (td, J_1 = 10.2 Hz, J_2 = 5.1 Hz, 1H), 4.15 (dd, J_1 = 10.4 Hz, J_2 = 7.8 Hz, 1H), 4.39 (dd, J_1 = 10.5 Hz, J_2 = 5.1 Hz, 1H), 4.96 (dd, J_1 = 6.2 Hz, J_2 = 2.0 Hz, 1H), 5.52 (dt, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H), 5.59 (s, 1H), 6.45 (dd, J_1 = 6.0 Hz, J_2 = 1.2 Hz, 1H), 6.88-6.94 (m, 2H), 7.07-7.13 (m, 2H), 7.40-7.46 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 55.3, 68.1, 68.7, 73.5, 76.5, 99.6, 101.5, 113.6, 115.4, 122.7, 127.5, 129.2(2C), 133.7, 137.9, 146.0, 146.2, 152.4, 160.2 ppm; IR (neat) ν: 1020, 1034, 1076, 1096, 1124, 1215, 1418, 1472, 1489, 1518, 1620, 1643, 1767, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{21}O_7NaBr$ $[M+Na]^+$: 499.0368, found: 499.0378.

2-Bromophenyl(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano [3,2-d][1,3]dioxin-8-yl carbonate (3j)



Compound **3j** (109.0 mg, 94%) was obtained as a white solid. m.p. 115-117 °C; $[\alpha]_D^{23}$ = –32.4 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.87 (t, *J* = 10.4 Hz, 1H), 4.02 (td, J_1 = 10.2 Hz, J_2 = 5.0 Hz, 1H), 4.13-4.18 (m, 1H), 4.39 (dd, J_1 = 10.4 Hz, J_2 = 5.1 Hz, 1H), 4.98 (dd, J_1 = 6.4 Hz, J_2 = 1.8 Hz, 1H), 5.53 (dt, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 5.59 (s, 1H), 6.45-6.47 (m, 1H), 6.91 (d, *J* = 9.2 Hz, 2H), 7.12-7.16 (m, 1H), 7.22 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.31-7.35 (m, 1H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.60 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 68.1, 68.7, 73.7, 76.6, 99.6, 101.6, 113.7, 116.0, 123.3, 127.5, 127.7, 128.6, 129.0, 133.5, 146.3, 148.3, 152.3, 160.2 ppm; IR (neat) *ν*: 1022, 1076, 1125, 1215, 1418, 1520, 1653, 1761, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{19}O_7BrNa$ $[M+Na]^+$: 485.0211, found: 485.0220.

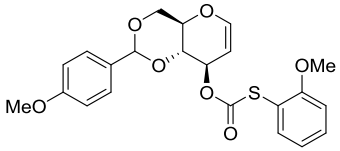
2-Iodophenyl(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl carbonate (3k)



Compound **3k** (115.0 mg, 90%) was obtained as a white solid. m.p. 121-123 °C; $[\alpha]_D^{23}$ = –12.4 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.87 (t, *J* = 10.5 Hz, 1H), 4.02 (td, J_1 = 10.0 Hz, J_2 = 5.0 Hz, 1H), 4.18 (dd, J_1 = 10.5 Hz, J_2 = 7.8 Hz, 1H), 4.40 (dd, J_1 = 10.4 Hz, J_2 = 5.1 Hz, 1H), 4.98-5.02 (m, 1H), 5.55 (d, *J* = 7.8 Hz, 1H), 5.60 (s, 1H), 6.45-6.48 (m, 1H), 6.88-6.93 (m, 2H), 6.96-7.03 (m, 1H), 7.19 (dd, J_1 = 8.2 Hz, J_2 = 0.9 Hz, 1H), 7.36 (td, J_1 = 7.8 Hz, J_2 = 0.9 Hz, 1H), 7.43-7.48 (m, 2H), 7.81-7.84 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 68.1, 68.7, 73.6, 76.5, 89.9, 99.6, 101.5, 113.6, 122.5, 127.5, 127.9, 129.2, 129.6, 139.5,

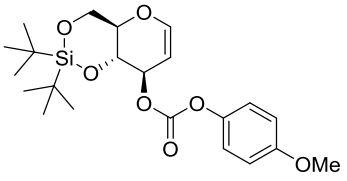
146.2, 151.1, 152.3, 160.2 ppm; IR (neat) ν: 1096, 1472, 1520, 1653, 1769, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{19}O_7NaI$ $[M+Na]^+$: 533.0073, found: 533.0078.

S-2-Methoxyphenyl-*O*-(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl carbonothioate (3l)



Compound **3l** (98.0 mg, 91%) was obtained as a white solid. m.p. 105-107 °C; $[\alpha]_D^{23}$ = –93.8 (c = 0.3 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.79-3.84 (m, 7H), 3.95 (td, J_1 = 9.6 Hz, J_2 = 4.8 Hz, 1H), 4.03 (dd, J_1 = 10.0 Hz, J_2 = 7.2 Hz, 1H), 4.35 (dd, J_1 = 10.4 Hz, J_2 = 5.1 Hz, 1H), 4.87 (dd, J_1 = 6.0 Hz, J_2 = 2.0 Hz, 1H), 5.54 (s, 1H), 5.59 (dt, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 1H), 6.39 (dd, J_1 = 6.0 Hz, J_2 = 1.2 Hz, 1H), 6.88-6.98 (m, 4H), 7.37-7.46 (m, 3H), 7.47-7.52 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 55.9, 68.1, 68.8, 72.1, 76.7, 100.2, 101.5, 111.5, 113.6, 115.6, 120.9, 127.5,129.3, 131.8, 136.9, 145.8, 159.5, 160.2, 168.7 ppm; IR (neat) ν: 1024, 1069, 1215, 1420, 1473, 1520, 1616, 1645, 1750, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{22}O_7NaS$ $[M+Na]^+$: 453.0984, found: 453.0990.

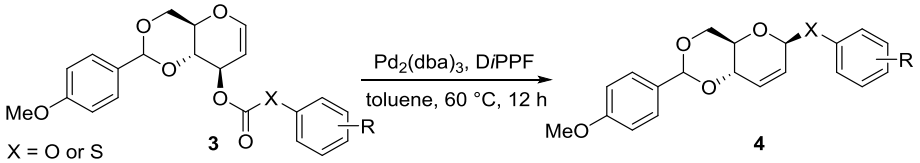
(4a*R*,8*R*,8a*S*)-2,2-Di-tert-butyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasilin-8-yl 4-methoxyphenyl carbonate (3m)



Compound **3m** (98.0 mg, 90%) was obtained as colorless oil.[8] $[\alpha]_D^{23}$ = –34.4 (c = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.00 (s, 9H), 1.08 (s, 9H), 3.80 (s, 3H),

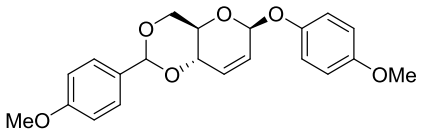
3.90-4.04 (m, 2H), 4.18-4.27 (m, 2H), 4.87 (dd, J_1 = 6.0 Hz, J_2 = 2.0 Hz, 1H), 5.35 (dt, J_1 = 7.6 Hz, J_2 = 1.8 Hz, 1H), 6.37 (dd, J_1 = 6.0 Hz, J_2 = 1.2 Hz, 1H), 6.86-6.91 (m, 2H), 7.09-7.15 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8, 22.7, 26.8, 27.3, 55.6, 72.8, 65.6, 73.6, 76.7, 99.6, 114.4, 121.8, 144.8, 145.6, 153.9, 157.3 ppm; IR (neat) ν: 1009, 1125, 1215, 1418, 1472, 1506, 1601, 1651, 1755, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{32}O_7NaSi$ $[M+Na]^+$: 459.1815, found: 459.1800.

General procedure for preparing phenolic *O*,*S*-glycosides (2)



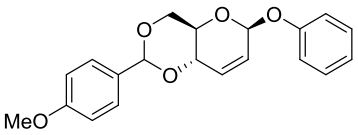
To a mixture of D*i*PPF (0.02 mmol), $Pd_2(dba)_3$ (0.01 mmol) and phenolic carbonate **3** (0.1 mmol) was added toluene (2 mL) under an atmosphere of Argon. After stirring at 60 °C for 12 hours, the solvent was removed under reduce pressure to give crude product which was further purified by column chromatography (eluted with n-hexane / EA = 20:1) to afford the desired glycosides **3** with 52-98% yields.

(4a*R*,8a*S*)-6-(4-Methoxyphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (4a)



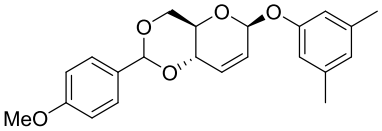
Glycoside **4a** (34.4 mg, 93%) was obtained as a white solid. m.p. 140-142 °C; $[\alpha]_D^{23}$ **= +**31.2 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 3H), 3.80 (s, 3H), 3.83-3.94 (m, 2H), 4.28-4.34 (m, 1H), 4.37-4.42 (m, 1H), 5.58 (s, 1H), 5.80-5.86 (m, 2H), 6.23 (d, *J* = 10.5 Hz, 1H), 6.80-6.86 (m, 2H), 6.87-6.93 (m, 2H), 7.01-7.07 (m, 2H), 7.43 (d, *J* = 8.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 55.6, 69.0, 70.9, 74.7, 97.8, 102.1, 113.7, 114.5, 118.4, 127.3, 127.5, 129.7, 132.0, 150.7, 155.3, 160.2 ppm; IR (neat) ν: 1032, 1215, 1423, 1474, 1520, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{22}O_6Na$ $[M+Na]^+$: 393.1350, found: 393.1350.

(4a*R*,8a*S*)-2-(4-Methoxyphenyl)-6-phenoxy-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (4b)



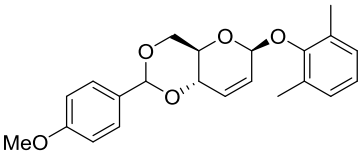
Glycoside **4b** (27.6 mg, 81%) was obtained as a white solid. m.p. 150-151 °C; $[\alpha]_D^{23}$ = +66.6 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.84-3.94 (m, 2H), 4.28-4.36 (m, 1H), 4.39-4.43 (m, 1H), 5.58 (s, 1H), 5.81-5.87 (m, 1H), 5.96 (d, *J* = 1.2 Hz, 1H), 6.25 (d, *J* = 10.4 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.01-7.12 (m, 3H), 7.27-7.34 (m, 2H), 7.43 (d, *J* = 8.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 69.0, 70.9, 74.7, 96.7, 102.1, 113.7, 116.8, 122.7, 127.1, 127.5, 129.5, 129.7, 132.1, 156.8, 160.2 ppm; IR (neat) *v*: 1022, 1215, 1474, 1522, 1618, 1695, 2305, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{20}O_5Na$ $[M+Na]^+$: 363.1208, found: 363.1208.

(4a*R*,8a*S*)-6-(3,5-Dimethylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (4c)



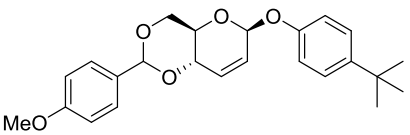
Glycoside **4c** (36.1 mg, 98%) was obtained as a white solid. m.p. 153-155 °C; $[\alpha]_D^{23}$ = +27.6 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 6H), 3.81 (s, 3H), 3.87-3.94 (m, 2H), 4.32-4.36 (m, 1H), 4.40-4.46 (m, 1H), 5.59 (s, 1H), 5.80-5.86 (m, 1H), 5.92-5.95 (m, 1H), 6.24 (d, *J* = 10.1 Hz, 1H), 6.68-6.74 (m, 3H), 6.90 (d, *J* = 9.2 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 55.3, 69.0, 70.9, 74.7, 96.7, 102.1, 113.7, 114.4, 124.4, 127.3, 127.5, 129.7, 131.9, 139.3, 156.8, 160.2 ppm; IR (neat) *v*: 1032, 1080, 1215, 1379, 1423, 1466, 1518, 1593, 1614, 2305, 3017 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{24}O_5Na$ $[M+Na]^+$: 391.1521, found: 391.1517.

(4a*R*,8a*S*)-6-(2,6-Dimethylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydro pyrano[3,2-d][1,3]dioxine (4d)



Glycoside **4d** (35.0 mg, 95%) was obtained as a white solid. m.p. 152-154 °C; $[\alpha]_D^{23}$ = +69.6 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 6H), 6.95-6.99 (m, 1H), 3.67-3.74 (m, 1H), 3.80 (s, 3H), 3.84 (t, J_1 = 10.3 Hz, 1H), 4.20-4.23 (dd, J_1 = 10.2 Hz, J_2 = 4.6 Hz, 1H), 4.41-4.46 (m, 1H), 5.57-5.61 (m, 2H), 5.98 (ddd, J_1 = 10.2 Hz, J_2 = 2.5 Hz, J_3 = 1.5 Hz, 1H), 6.25 (d, *J* = 10.4 Hz, 1H), 6.87-6.92 (m, 2H), 7.01-7.06 (m, 2H), 7.40-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 55.3, 69.0, 70.9, 74.9, 100.5, 102.1, 113.7, 124.6, 127.5(2C), 128.9, 129.8, 131.5, 131.9, 154.0, 160.2 ppm; IR (neat) ν: 1022, 1128, 1215, 1423, 1474, 1518, 1616, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{24}O_5Na$ $[M+Na]^+$: 391.1521, found: 391.1517.

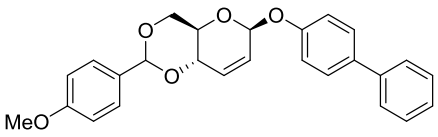
(4a*R*,8a*S*)-6-(4-Tert-butylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropy rano[3,2-d][1,3]dioxine (4e)



Glycoside **4e** (33.5 mg, 85%) was obtained as a white solid. m.p. 154-156 °C; $[\alpha]_D^{23}$ = +64.6 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H), 3.80 (s, 3H), 3.85-3.92 (m, 2H), 4.26-4.34 (m, 1H), 4.39-4.43 (m, 1H), 5.58 (s, 1H), 5.81-5.85 (m, 1H), 5.92-5.96 (m, 1H), 6.24 (d, *J* = 10.1 Hz, 1H), 6.87-6.92 (m, 2H), 7.00-7.04 (m, 2H), 7.29-7.34 (m, 2H), 7.41-7.45 (m, 2H) ppm; ^{13}C NMR (100 M Hz, $CDCl_3$): δ 31.5, 34.2, 55.3, 69.0, 70.9, 74.8, 96.9, 102.1, 113.7, 116.2, 126.3, 127.3, 127.5, 129.7,

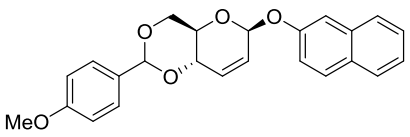
132.0, 145.4, 154.5, 160.2 ppm; IR (neat) ν: 1090, 1128, 1215, 1418, 1508, 1607, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{28}O_5Na$ $[M+Na]^+$: 419.1834, found: 419.1845.

(4a*R*,8a*S*)-6-(Biphenyl-4-yloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano [3,2-d][1,3]dioxine (4f)



Glycoside **4f** (29.1 mg, 70%) was obtained as a white solid. m.p. 167-169 °C; $[\alpha]_D^{23}$ = +18.2 (*c* = 0.5 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.89-3.95 (m, 2H), 4.30-4.37 (m, 1H), 4.41-4.46 (m, 1H), 5.59 (s, 1H), 5.84-5.89 (m, 1H), 5.98-6.02 (m, 1H), 6.28 (d, *J* = 10.5 Hz, 1H), 6.87-6.93 (m, 2H), 7.15-7.19 (m, 2H), 7.30-7.35 (m, 1H), 7.40-7.48 (m, 4H), 7.51-7.57 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 69.0, 71.0, 74.7, 96.7, 102.1, 113.7, 117.0, 126.8, 126.9, 127.0, 127.5, 128.2, 128.7, 129.7, 132.2, 135.7, 140.6, 156.2, 160.2 ppm; IR (neat) ν: 1215, 1423, 1518, 1603, 1653, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{24}O_5Na$ $[M+Na]^+$: 439.1521, found: 439.1516.

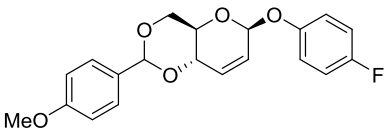
(4a*R*,8a*S*)-2-(4-Methoxyphenyl)-6-(naphthalen-2-yloxy)-4,4a,6,8a-tetrahydropyr ano[3,2-d][1,3]dioxine (4g)



Glycoside **4g** (26.5 mg, 68%) was obtained as a white solid. m.p. 127-128 °C; $[\alpha]_D^{23}$ = +25.0 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.89-3.99 (m, 2H), 4.33-4.41 (m, 1H), 4.43-4.47 (m, 1H), 5.60 (s, 1H), 5.90 (ddd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.7 Hz, 1H), 6.08-6.12 (m, 1H), 6.29 (d, *J* = 10.4 Hz, 1H), 6.87-6.93 (m,

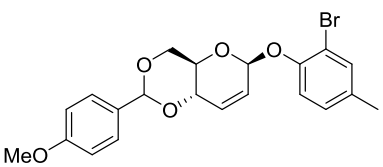
2H), 7.23-7.28 (m, 1H), 7.35-7.40 (m, 1H), 7.42-7.48 (m, 4H), 7.74-7.81 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 69.0, 71.1, 74.7, 96.8, 102.1, 110.9, 113.7, 119.0, 124.4, 126.4, 127.0, 127.1, 127.5, 127.6, 129.5, 129.7, 129.8, 132.3, 134.2, 154.5, 160.2 ppm; IR (neat) ν: 1030, 1090, 1128, 1175, 1215, 1420, 1474, 1518, 1601, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{22}O_5Na$ $[M+Na]^+$: 413.1365, found: 413.1372.

(4a*R*,8a*S*)-6-(4-Fluorophenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (4h)



Glycoside **4h** (26.5 mg, 74%) was obtained as a white solid. m.p. 128-130 °C; $[\alpha]_D^{23}$ = +62.0 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.86-3.94 (m, 2H), 4.29-4.36 (m, 1H), 4.38-4.43 (m, 1H), 5.58 (s, 1H), 5.80-5.90 (m, 2H), 6.25 (d, *J* = 10.4 Hz, 1H), 6.87-6.93 (m, 2H), 6.95-7.11 (m, 4H), 7.41-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 68.9, 71.0, 74.6, 97.4, 102.1, 113.7, 115.8, 116.0, 118.4, 118.5, 126.9, 127.5, 129.6, 132.3, 152.8(2C), 160.2 ppm; IR (neat) ν: 1030, 1215, 1420, 1506, 1614, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{19}O_5NaF$ $[M+Na]^+$: 381.1114, found: 381.1108.

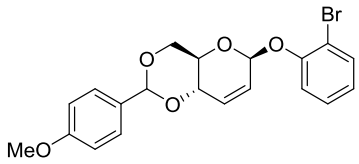
(4a*R*,8a*S*)-6-(2-Bromo-4-methylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (4i)



Glycoside **4i** (28.2 mg, 65%) was obtained as a white solid. m.p. 182-184 °C; $[\alpha]_D^{23}$ = +41.7 (*c* = 0.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 3.77-3.93 (m,

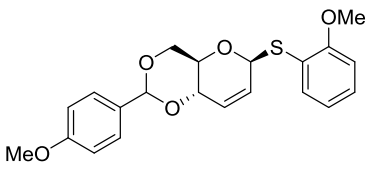
5H), 4.27-4.33 (m, 1H), 4.41-4.46 (m, 1H), 5.90-5.96 (m, 1H), 5.59 (s, 1H), 5.82-5.85 (m, 1H), 6.26 (d, *J* = 10.5 Hz, 1H), 6.87-6.92 (m, 2H), 7.02-7.07 (m, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.40-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 55.4, 69.1, 71.2, 74.7, 98.4, 102.2, 113.7, 113.8, 118.7, 127.0, 127.6, 129.0, 129.8, 132.5, 133.8, 134.4, 151.5, 160.3 ppm; IR (neat) *v*: 1032, 1092, 1215, 1423, 1520, 1615, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{21}O_5NaBr$ $[M+Na]^+$: 455.0470, found: 455.0468.

(4a*R*,8a*S*)-6-(2-Bromophenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (4j)



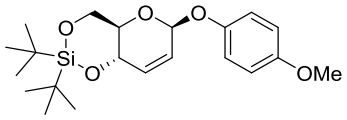
Glycoside **4j** (25.2 mg, 60%) was obtained as a white solid. m.p. 163-164 °C; $[\alpha]_D^{23}$ = +42.5 (*c* = 0.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.82-3.94 (m, 2H), 4.28-4.34 (m, 1H), 4.42-4.48 (m, 1H), 5.59 (s, 1H), 5.88-5.96 (m, 2H), 6.28 (d, *J* = 10.1 Hz, 1H), 6.87-6.97 (m, 3H), 7.25-7.31 (m, 2H), 7.41-7.46 (m, 2H), 7.54-7.58 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 68.9, 71.1, 74.6, 97.9, 102.1, 113.7, 118.2, 124.2, 126.7, 127.5, 128.4, 129.6, 132.5, 133.4, 153.6, 160.2 ppm; IR (neat) *v*: 1032, 1217, 1420, 1476, 1520, 1614, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{19}O_5NaBr$ $[M+Na]^+$: 441.0314, found: 441.0310.

(4a*R*,8a*S*)-2-(4-Methoxyphenyl)-6-(2-methoxyphenylthio)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (4l)



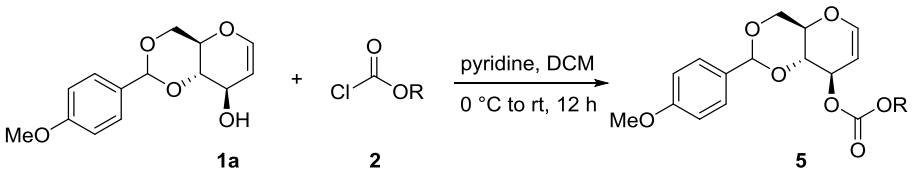
Glycoside **4l** (29.4 mg, 76%) was obtained as a white solid. m.p. 63-64 °C; $[\alpha]_D^{23}$ = +82.5 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.62-3.69 (m, 1H), 3.78-3.85 (m, 4H), 3.89 (s, 3H), 4.08-4.13 (m, 1H), 4.30 (dd, J_1 = 10.3 Hz, J_2 = 4.6 Hz, 1H), 5.50 (s, 1H), 5.76-5.80 (m, 1H), 5.86 (dt, J_1 = 10.2 Hz, J_2 = 2.3 Hz, 1H), 6.03 (d, *J* = 10.0 Hz, 1H), 6.86-6.92 (m, 3H), 6.95 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1H), 7.27-7.33 (m, 1H), 7.38-7.42 (m, 2H), 7.57 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 55.8, 69.2, 71.7, 74.3, 81.6, 101.9, 110.8, 113.7, 120.8, 121.0, 127.5, 127.7, 129.4, 129.6, 129.8, 133.9, 158.3, 160.1 ppm; IR (neat) ν: 1026, 1088, 1125, 1173, 1219, 1362, 1418, 1475, 1520, 1616, 1651, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{22}O_5NaS$ $[M+Na]^+$: 409.1086, found: 409.1084.

(4a*R*,6*S*,8a*S*)-2,2-Di-tert-butyl-6-(4-methoxyphenoxy)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasiline (4m)

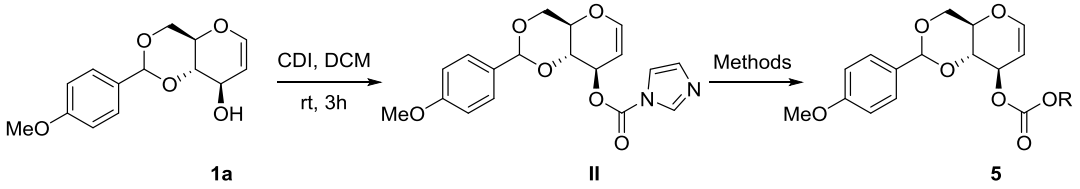


Glycoside **4m** (20.4 mg, 52%) was obtained as a white solid. m.p. 93-94 °C; $[\alpha]_D^{23}$ = –10.7 (*c* = 0.5 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.00 (s, 9H), 1.06 (s, 9H), 3.72-3.79 (m, 4H), 4.00 (t, *J* = 10.4 Hz, 1H), 4.19 (dd, J_1 = 10.0 Hz, J_2 = 5.1 Hz, 1H), 4.58-4.64 (m, 1H), 5.73-5.79 (m, 2H), 6.10-6.15 (m, 1H), 6.79-6.84 (m, 2H), 6.98-7.04 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0, 22.7, 27.0, 27.4, 55.6, 66.7, 69.8, 74.4, 97.6, 114.4, 118.4, 125.9, 135.2, 150.8, 155.2 ppm; IR (neat) ν: 1015, 1126, 1215, 1483, 1520, 1615, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{32}O_5NaSi$ $[M+Na]^+$: 415.1917, found: 415.1924.

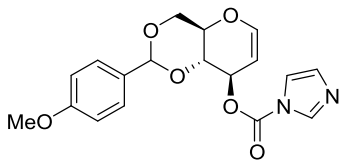
General procedure for preparing carbonates 5a-5q



Method **A**: To a solution of 4,6-*para*-methoxybenzylidene glucal (**1a**) (1 equiv) in DCM was added Pyridine (5 equiv) at 0 °C. Then compound **2** (4 equiv) was added slowly at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. After the reaction was completed, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to provide the desired carbonate **5**.



To a solution of CDI (1.5 equiv) in DCM was added a solution of 4,6-*para*-methoxybenzylidene glucal (**1a**) (1.0 equiv) in DCM dropwisely at 0 °C. Then the mixture was allowed to warm to room temperature and stirred for 3 h. After that, the mixture was washed wish with H_2O, brine, and then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with n-hexane/EA=1:1) to provide the desired intermediate **II**.

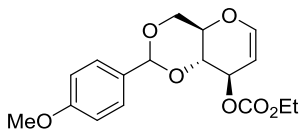


Intermediate **II** was obtained in 94% yield as a white solid. m.p. 127-129 °C; $[\alpha]_D^{23}$ = –150 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 3.89 (t, *J* = 10.4 Hz, 1H), 4.06 (td, J_1 = 10.2 Hz, J_2 = 5.1 Hz, 1H), 4.18 (dd, J_1 = 10.4 Hz, J_2 = 7.7 Hz, 1H), 4.41 (dd, J_1 = 10.6 Hz, J_2 = 5.1 Hz, 1H), 4.92 (dd, J_1 = 6.1 Hz, J_2 = 2.1 Hz, 1H), 5.59 (s, 1H), 5.76 (dt, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H), 6.49 (dd, J_1 = 6.1 Hz, J_2 = 1.2 Hz, 1H), 6.86-6.92 (m, 2H), 7.06 (s, 1H), 7.37-7.45 (m, 3H), 8.14 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 68.0, 68.8, 73.0, 76.4, 99.1, 101.7, 113.7, 117.1, 127.5, 128.9, 130.6, 137.1, 146.7, 148.3, 160.3 ppm; IR (neat) ν: 1094, 1236, 1392, 1518, 1614, 1641, 1759, 3016 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{21}O_7$ $[M+H]^+$: 359.1243, found: 359.1238.

Method **B**: To the solution of intermediate **II** (1.0 equiv) in DCM was added alcohol (1.1 equiv), NaOMe (0.1 equiv). The mixture was stirred for 12 h at room temperature. Then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to provide the desired product **5**.

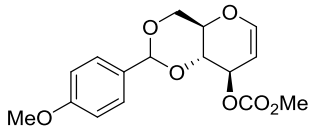
Method **C**: To the solution of intermediate **II** (1.0 equiv) in DMF was added alcohol (1.1 equiv), NaOMe (0.1 equiv). The mixture was stirred for 12 h at 60 °C. Then the mixture was allowed to cool to room temperature and then water was added. The mixture was diluted with Et_2O and extracted with Et_2O (3 times). The collected organic layer was then washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to provide the desired product **5**.

Ethyl-(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3] dioxin-8-yl carbonate (5a)



Carbonate **5a** was prepared according to the general procedure of method **A** (151.2 mg, 90%) as a white solid. m.p. 98-100 °C; $[\alpha]_D^{23}$ = –75.8 (*c* = 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.1 Hz, 3H), 3.75-3.85 (m, 4H), 3.92-4.06 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.35 (dd, J_1 = 10.6 Hz, J_2 = 4.8 Hz, 1H), 4.87 (dd, J_1 = 6.1 Hz, J_2 = 2.0 Hz, 1H), 5.36-5.41 (m, 1H), 5.52 (s, 1H), 6.39 (dd, J_1 = 6.1 Hz, J_2 = 1.3 Hz, 1H), 6.86-6.89 (m, 2H), 7.39-7.42 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 55.1, 64.1, 68.0, 68.6, 72.0, 76.6, 100.1, 101.5, 113.5, 127.5, 129.3, 145.6, 154.5, 160.1 ppm; IR (neat) ν: 1215, 1518, 1615, 1649, 1745, 3018 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{21}O_7$ $[M+H]^+$: 337.1287, found: 337.1285.

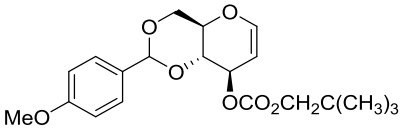
Methyl-(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1, c3] dioxin-8-yl carbonate (5b)



Carbonate **5b** was prepared according to the general procedure of method **A** (132.0 mg, 82%) as a white solid. m.p. 141-143 °C; $[\alpha]_D^{23}$ = –73.4 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.76-3.86 (m, 7H), 3.94-4.08 (m, 2H), 4.37 (dd, J_1 = 10.7 Hz, J_2 = 5.0 Hz, 1H), 4.87 (dd, J_1 = 6.1 Hz, J_2 = 2.0 Hz, 1H), 5.39-5.41 (m, 1H), 5.54 (s, 1H), 6.41 (dd, J_1 = 6.1 Hz, J_2 = 1.2 Hz, 1H), 6.86-6.91 (m, 2H), 7.40-7.42 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 54.9, 68.1, 68.7, 72.4, 76.7, 100.1, 101.6,

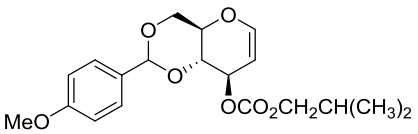
113.6, 127.5, 129.3, 145.8, 155.3, 160.2 ppm; IR (neat) *v*: 1215, 1616, 1641, 1751, 3018 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{19}O_7$ $[M+H]^+$: 323.1131, found: 323.1118.

Neopentyl-(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d] [1,3]dioxin-8-yl carbonate (5c)



Carbonate **5c** was prepared according to the general procedure of method **A** (132.0 mg, 82%) as a white solid. m.p. 85-87 °C; $[\alpha]_D^{23}$ = –73.2 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 9H), 3.77-3.90 (m, 6H), 3.94-4.02 (m, 1H), 4.07 (dd, J_1 = 10.5 Hz, J_2 = 7.7 Hz, 1H), 4.36 (dd, J_1 = 10.5 Hz, J_2 = 5.1 Hz, 1H), 4.87 (dd, J_1 = 6.2 Hz, J_2 = 2.0 Hz, 1H), 5.37-5.42 (m, 1H), 5.55 (s, 1H), 6.40 (dd, J_1 = 6.1 Hz, J_2 = 1.2 Hz, 1H), 6.87-6.92 (m, 2H), 7.40-7.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2, 31.4, 55.2, 68.1, 68.7, 72.1, 76.6, 77.5, 100.2, 101.5, 113.6, 127.5, 129.3, 145.7, 155.0, 160.2 ppm; IR (neat) *v*: 1215, 1616, 1641, 1736, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{27}O_7$ $[M+H]^+$: 379.1757, found: 379.1755.

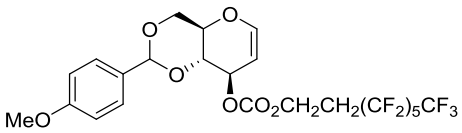
Isobutyl-(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d] [1,3]dioxin-8-yl carbonate (5d)



Carbonate **5d** was prepared according to the general procedure of method **A** (160.2 mg, 88%) as amorphous liquid. $[\alpha]_D^{23}$ = –64.9 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, *J* = 1.4 Hz, 3H), 0.95 (d, *J* = 1.4 Hz, 3H), 1.97 (hepta, *J* = 6.7 Hz, 1H), 3.77-3.86 (m, 4H), 3.87-4.02 (m, 3H), 4.05 (dd, J_1 = 10.4 Hz, J_2 = 7.6 Hz, 1H),

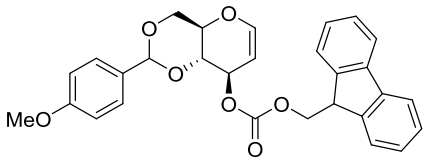
4.37 (dd, J_1 = 10.6 Hz, J_2 = 5.0 Hz, 1H), 4.88 (dd, J_1 = 6.2 Hz, J_2 = 2.0 Hz, 1H), 5.36-5.41 (m, 1H), 5.54 (s, 1H), 6.40 (dd, J_1 = 6.2 Hz, J_2 = 1.3 Hz, 1H), 6.86-6.91 (m, 2H), 7.39-7.43 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9(2C), 27.7, 55.2, 68.1, 68.7, 72.1, 74.3, 76.7, 100.2, 101.5, 113.6, 127.5, 129.3, 145.7, 154.8, 160.2 ppm; IR (neat) ν: 1215, 1616, 1641, 1744, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{25}O_7$ $[M+H]^+$: 365.1600, found: 365.1600.

(4a*R*,8*R*,8a*S*)-2-(4-Methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl carbonate (5e)



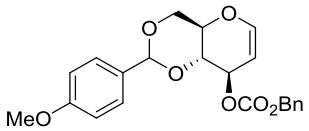
Carbonate **5e** was prepared according to the general procedure of method **B** (245.3 mg, 75 %) as a white solid. m.p. 75-77 °C; $[\alpha]_D^{23}$ = –41.8 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44-2.59 (m, 2H), 3.80 (s, 3H), 3.83 (t, J = 10.3 Hz, 1H), 3.94-4.02 (m, 1H), 4.05 (dd, J_1 = 10.3 Hz, J_2 = 7.5 Hz, 1H), 4.35-4.50 (m, 3H), 4.86 (dd, J_1 = 6.2 Hz, J_2 = 2.0 Hz, 1H), 5.39-5.44 (m, 1H), 5.54 (s, 1H), 6.42 (dd, J_1 = 6.1 Hz, J_2 = 1.2 Hz, 1H), 6.86-6.91 (m, 2H), 7.38-7.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.3, 30.5, 30.7, 55.2, 59.8, 68.1, 68.7, 72.9, 76.6, 99.8, 101.6, 113.6, 127.5, 129.2, 146.1, 154.2, 160.3 ppm; IR (neat) ν: 1215, 1613, 1643, 1751, 3018 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{20}O_7F_{13}$ $[M+H]^+$: 655.1001, found: 655.0991.

(9*H*-fluoren-9-yl)methyl-(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl carbonate (5f)



Carbonate **5f** was prepared according to the general procedure of method **A** (226.0 mg, 93 %) as a white solid. m.p. 116-118 °C; $[\alpha]_D^{23}$ = –59.2 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 3.83 (t, *J* = 10.3 Hz, 1H), 3.98 (td, J_1 = 10.2 Hz, J_2 = 5.0 Hz, 1H), 4.05-4.13 (m, 1H), 4.25 (t, *J* = 7.4 Hz, 1H), 4.34-4.43 (m, 3H), 4.85 (dd, J_1 = 6.1 Hz, J_2 = 2.0 Hz, 1H), 5.41-5.46 (m, 1H), 5.57 (s, 1H), 6.41 (dd, J_1 = 6.1 Hz, J_2 = 1.1 Hz, 1H), 6.86-6.91 (m, 2H), 7.22-7.32 (m, 2H), 7.35-7.45 (m, 4H), 7.56-7.63 (m, 2H), 7.72-7.77 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.7, 55.3, 68.1, 68.7, 69.9, 72.5, 76.6, 100.1, 101.6, 113.6, 120.0, 125.1, 125.2, 127.1, 127.5, 127.8, 129.3, 141.2, 143.1, 143.4, 145.9, 154.7, 160.2 ppm; IR (neat) *ν*: 1254, 1614, 1641, 1746, 3017 cm^{-1}; HRMS (ESI) calcd. for $C_{29}H_{26}O_7$ $[M+H]^+$: 487.1757, found: 487.1750.

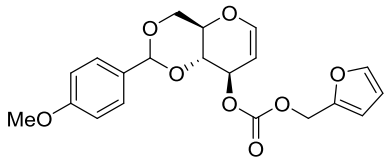
Benzyl-(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3] dioxin-8-yl carbonate (5g)



Carbonate **5g** was prepared according to the general procedure of method **A** (183.1 mg, 92 %) as a white solid. m.p. 111-113 °C; $[\alpha]_D^{23}$ = –99.6 (*c* = 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$):δ 3.74-3.86 (m, 4H), 3.91-4.07 (m, 2H), 4.35 (dd, J_1 = 10.7 Hz, J_2 = 4.8 Hz, 1H), 4.87 (dd, J_1 = 6.2 Hz, J_2 = 2.0 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 5.37-5.45 (m, 1H), 5.51 (s, 1H), 6.38 (dd, J_1 = 6.1 Hz, J_2 = 1.2 Hz, 1H), 6.84-6.91 (m, 2H), 7.30-7.40 (m, 7H) ppm; ^{13}C NMR (75 MHz,

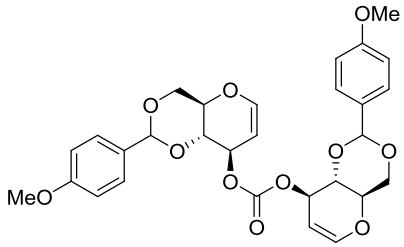
$CDCl_3$): δ 55.2, 68.1, 68.7, 69.8, 72.4, 76.7, 100.1, 101.5, 113.6, 127.5, 128.3, 128.5(2C), 129.3, 135.0, 145.8, 154.8, 160.2 ppm; IR (neat) ν: 1253, 1614, 1641, 1745 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{23}O_7$ $[M+H]^+$: 399.1444, found: 399.1449.

Furan-2-ylmethyl-(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl carbonate (5h)



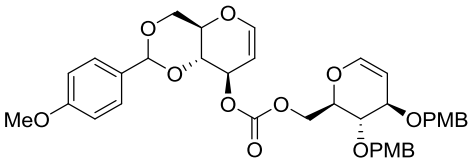
Carbonate **5h** was prepared according to the general procedure of method **B** (131.9 mg, 68 %) as colorless oil. $[\alpha]_D^{23}$ = –84.7 (c = 0.38 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76-3.85 (m, 4H), 3.93-4.06 (m, 2H), 6.44 (d, J = 3.2 Hz, 1H), 4.36 (dd, J_1 = 10.8 Hz, J_2 = 4.9 Hz, 1H), 4.87 (dd, J_1 = 6.2 Hz, J_2 = 2.0 Hz, 1H), 5.08 (d, J = 13.0 Hz, 1H), 5.12 (d, J = 13.0 Hz, 1H), 5.38-5.44 (m, 1H), 5.51 (s, 1H), 6.34 (dd, J_1 = 3.1 Hz, J_2 = 1.8 Hz, 1H), 6.41 (dd, J_1 = 6.1 Hz, J_2 = 1.2 Hz, 1H), 6.85-6.91 (m, 2H), 7.37-7.43 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 61.4, 68.1, 68.7, 72.5, 76.6, 100.0, 101.5, 110.5, 111.3, 113.6, 127.5, 129.3, 143.5, 145.8, 148.4, 154.3, 160.2 ppm; IR (neat) ν: 1252, 1618, 1638, 1741, 1744 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{21}O_8$ $[M+H]^+$: 389.1236, found: 389.1238.

Bis((4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl) carbonate (5i)



Carbonate **3i** was prepared according to the general procedure of method **B** (205.0 mg, 74 %) as a white solid. m.p. 85-87 °C; $[\alpha]_D^{23}$ = –143.0 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75-3.84 (m, 8H), 3.92-4.06 (m, 4H), 4.35 (dd, J_1 = 10.7 Hz, J_2 = 5.0 Hz, 2H), 4.86 (dd, J_1 = 6.1 Hz, J_2 = 1.9 Hz, 2H), 5.35-5.41 (m, 2H), 5.51 (s, 2H), 6.34-6.39 (m, 2H), 6.85-6.93 (m, 4H), 7.36-7.44 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 68.1, 68.6, 72.5, 76.6, 99.9, 101.5, 113.6, 127.5, 129.2, 145.8, 154.2, 160.2 ppm; IR (neat) ν: 1253, 1517, 1615, 1641, 1715, 1750, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{29}H_{31}O_{11}$ $[M+H]^+$: 555.1866, found: 555.1855.

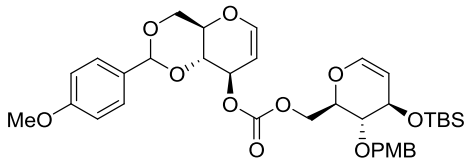
((2*R*,3*S*,4*R*)-3,4-Bis(4-methoxybenzyloxy)-3,4-dihydro-2H-pyran-2-yl)methyl (4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin -8-yl carbonate (5j)



Carbonate **5j** was prepared according to the general procedure of method **B** from the corresponding alcohol[9] (270.4 mg, 80 %) as a white solid. m.p. 117-119 °C; $[\alpha]_D^{23}$ = –48.0 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71-3.87 (m, 11H), 3.94-4.11 (m, 3H), 4.12-4.17 (m, 1H), 4.34-4.45 (m, 3H), 4.47 (d, *J* = 11.3 Hz, 1H), 4.52 (d, *J* = 10.8 Hz, 1H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.73 (d, *J* = 10.8 Hz, 1H), 4.85 (dd, J_1 = 6.1 Hz, J_2 = 2.0 Hz, 1H), 4.87 (dd, J_1 = 6.2 Hz, J_2 = 2.8 Hz, 1H), 5.40-5.45 (m, 1H), 5.53 (s, 1H), 6.35 (dd, J_1 = 6.1 Hz, J_2 = 0.9 Hz, 1H), 6.40 (dd, J_1 = 6.1 Hz, J_2 = 1.2 Hz, 1H), 6.79-6.90 (m, 6H), 7.15-7.21 (m, 2H), 7.23-7.28 (m, 2H), 7.35-7.40 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2(3C), 66.2, 68.1, 68.7, 70.1, 72.5, 73.4, 73.6, 74.8(2C), 76.6, 100.1, 100.2, 101.5, 113.6, 113.8, 127.4, 127.5, 129.2, 129.3, 129.7,

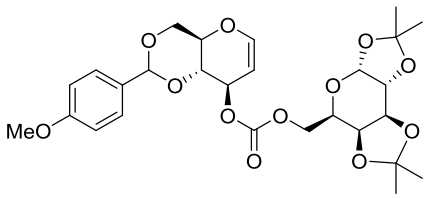
129.9, 130.2, 144.2, 145.8, 154.5, 159.2, 159.3, 160.1 ppm; IR (neat) *ν*: 1253, 1518, 1614, 1635, 1714, 1751, 3018 cm^{-1}; HRMS (ESI) calcd. for $C_{37}H_{41}O_{12}$ $[M+H]^+$: 677.2598, found: 677.2573.

((2*R*,3*R*,4*R*)-4-(Tert-butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-3,4-dihydro-2H-pyran-2-yl)methyl(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydro pyrano[3,2-d][1,3]dioxin-8-yl carbonate (5k)



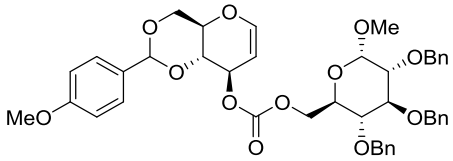
Carbonate **5k** was prepared according to the general procedure of method **B** from the corresponding alcohol[10] (247.9 mg, 74 %) as colorless oil. $[\alpha]_D^{23}$ = –27.8 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.91 (s, 9H), 3.57-3.64 (m, 1H), 3.73-3.87 (m, 7H), 3.93-4.13 (m, 3H), 4.27-4.32 (m, 1H), 4.34-4.42 (m, 3H), 4.53 (d, *J* = 10.9 Hz, 1H), 4.69 (dd, J_1 = 6.1 Hz, J_2 = 2.9 Hz, 1H), 4.74 (d, *J* = 10.9 Hz, 1H), 4.87 (dd, J_1 = 6.1 Hz, J_2 = 1.7 Hz, 1H), 5.40-5.46 (m, 1H), 5.54 (s, 1H), 6.29 (d, *J* = 6.0 Hz, 1H), 6.41 (d, *J* = 6.0 Hz, 1H), 6.78-6.88 (m, 4H), 7.19-7.26 (m, 2H), 7.34-7.43 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.7, -4.4, 17.9, 25.8, 55.2(2C), 66.3, 68.1(2C), 68.7, 72.4, 73.5, 74.6, 75.8, 76.6, 100.1, 101.5, 103.5, 113.6, 113.9, 127.4, 129.3, 129.6, 129.8, 142.9, 145.8, 154.5, 159.3, 160.1 ppm; IR (neat) *ν*: 1251, 1516, 1611, 1642, 1715, 1748, 3016 cm^{-1}; HRMS (ESI) calcd. for $C_{35}H_{47}O_{11}Si$ $[M+H]^+$: 671.2888, found: 671.2873.

(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl((3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo [4,5 -b:4',5'-d]pyran-5-yl)methyl carbonate (5l)



Carbonate **5l** was prepared according to the general procedure of method **B** from the corresponding alcohol[11] (225.5 mg, 82 %) as a white solid. m.p. 69-71 °C; $[\alpha]_D^{23}$ = – 90.9 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.33 (s, 3H), 1.44 (s, 3H), 1.50 (s, 3H), 3.78-3.86 (m, 4H), 3.93-4.10 (m, 3H), 4.22-4.33 (m, 4H), 4.36 (dd, J_1 = 10.8 Hz, J_2 = 5.0 Hz, 1H), 4.61 (dd, J_1 = 7.9 Hz, J_2 = 2.5 Hz, 1H), 4.86 (dd, J_1 = 6.1 Hz, J_2 = 2.0 Hz, 1H), 5.36-5.42 (m, 1H), 5.50-5.55 (m, 2H), 6.40 (dd, J_1 = 6.1 Hz, J_2 = 1.2 Hz, 1H), 6.86-6.91 (m, 2H), 7.38-7.43 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 24.9, 25.9, 26.0, 55.2, 65.4, 66.5, 68.1, 68.7, 70.4, 70.6, 70.7, 72.4, 76.6, 96.2, 100.1, 101.5, 108.7, 109.6, 113.6, 127.5, 129.3, 145.8, 154.5, 160.2 ppm; IR (neat) ν: 1248, 1521, 1614, 1643, 1718, 1752, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{27}H_{35}O_{12}$ $[M+H]^+$: 551.2129, found:551.2126.

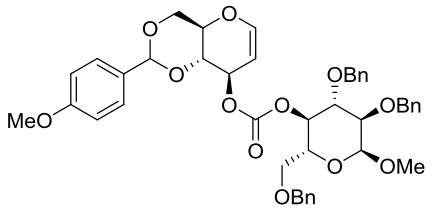
(4a*R*,8*R*,8a*S*)-2-(4-Methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin -8-yl((2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2H-pyran-2-yl)methyl carbonate (5m)



Carbonate **5m** was prepared according to the general procedure of method **B** from the corresponding alcohol[12] (294.1 mg, 78 %) as a white solid. m.p. 143-145 °C; $[\alpha]_D^{23}$ = –18.7 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.32 (s, 3H), 3.46-3.54 (m, 2H), 3.72 (s, 3H), 3.75-3.84 (m, 2H), 3.92-4.05 (m, 3H), 4.24-4.32 (m, 2H), 4.35 (dd,

J_1 = 10.6 Hz, J_2 = 5.0 Hz, 1H), 4.50 (d, J = 10.8 Hz, 1H), 4.55 (d, J = 3.5 Hz, 1H), 4.63 (d, J = 12.1 Hz, 1H), 4.76 (d, J = 12.1 Hz, 1H), 4.79-4.84 (m, 3H), 4.99 (d, J = 10.9 Hz, 1H), 5.38-5.43 (m, 1H), 5.51 (s, 1H), 6.34-6.40 (m, 1H), 6.75-6.80 (m, 2H), 7.17-7.38 (m, 17H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.1, 55.2, 66.4, 68.1, 68.5, 68.7, 72.4, 75.1, 73.3, 75.6, 76.6, 77.0, 79.6, 81.9, 97.9, 100.0, 101.5, 113.5, 127.4, 127.6, 127.8(2C), 127.9, 128.0, 128.1, 128.3, 128.4, 129.2, 137.6, 137.9, 138.6, 145.7, 154.5, 160.1ppm; IR (neat) ν: 1253, 1517, 1615, 1642, 1715, 1744, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{43}H_{47}O_{12}$ $[M+H]^+$: 755.3068, found:755.3076.

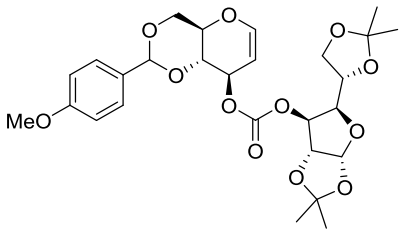
(2*R*,3*R*,4*S*,5*R*,6*S*)-4,5-Bis(benzyloxy)-2-(benzyloxymethyl)-6-methoxytetrahydro-2H-pyran-3-yl(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano [3,2-d][1,3]dioxin-8-yl carbonate (5n)



Carbonate **5n** was prepared according to the general procedure of method **C** from the corresponding alcohol[12] (188.5 mg, 50 %) as colorless oil. $[\alpha]_D^{23}$ = –29.7 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.36 (s, 3H), 3.45 (dd, J_1 = 10.7 Hz, J_2 = 4.6 Hz, 1H), 3.52 (dd, J_1 = 10.7 Hz, J_2 = 2.6 Hz, 1H), 3.58 (dd, J_1 = 9.6 Hz, J_2 = 3.5 Hz, 1H), 3.72 (s, 3H), 3.77-3.86 (m, 2H), 3.92-4.04 (m, 3H), 4.31-4.38 (m, 3H), 4.58-4.72 (m, 4H), 4.77 (d, J = 12.1 Hz, 1H), 4.88-4.96 (m, 2H), 5.36-5.43 (m, 1H), 5.49 (s, 1H), 6.29 (dd, J_1 = 6.1 Hz, J_2 = 1.0 Hz, 1H), 6.76-6.82 (m, 2H), 7.12-7.40 (m, 17H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 55.3, 68.1, 68.3, 68.5, 68.6, 72.6, 73.4, 73.5, 74.8, 75.3, 79.2, 79.3, 98.0, 99.9, 101.6, 113.5, 127.4, 127.5(2C), 127.6, 127.7, 127.9,

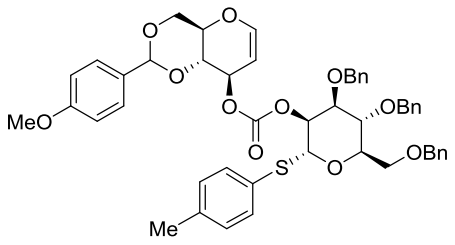
128.1, 128.2(2C), 128.3, 128.4, 129.2, 137.7, 137.8, 138.5, 145.7, 154.0, 160.1 ppm; IR (neat) ν: 1215, 1520, 1613, 1645, 1714, 1741, 3016 cm^{-1}; HRMS (ESI) calcd. for $C_{43}H_{47}O_{12}$ $[M+H]^+$: 755.3068, found:755.3077.

(3a*R*,5*R*,6*S*,6a*R*)-5-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro furo[2,3-d][1,3]dioxol-6-yl(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetra hydropyrano[3,2-d][1,3]dioxin-8-yl carbonate (5o)



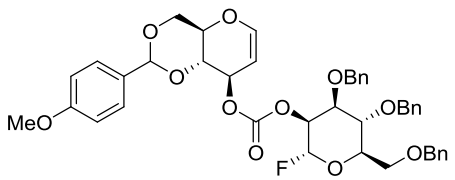
Carbonate **5o** was prepared according to the general procedure of method **B** from the corresponding commercially available alcohol (165.0 mg, 60 %) as colorless oil. $[\alpha]_D^{23}$ = –79.8 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 3H), 1.32 (s, 3H), 1.42 (s, 3H), 1.50 (s, 3H), 3.78-3.87 (m, 4H), 3.95-4.12 (m, 4H), 4.16-4.27 (m, 2H), 4.37 (dd, J_1 = 10.7 Hz, J_2 = 5.0 Hz, 1H), 4.56 (d, J = 3.7 Hz, 1H), 4.88 (dd, J_1 = 6.2 Hz, J_2 = 1.9 Hz, 1H), 5.16 (d, J = 2.8 Hz, 1H), 5.39-5.43 (m, 1H), 5.54 (s, 1H), 5.86 (d, J = 3.6 Hz, 1H), 6.40 (dd, J_1 = 6.1 Hz, J_2 = 1.1 Hz, 1H), 6.86-6.94 (m, 2H), 7.37-7.46 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 26.1, 26.6, 26.8, 55.2, 67.2, 68.1, 68.6, 72.3, 72.9, 76.5, 79.5, 79.8, 83.0, 99.8, 101.6, 104.9, 109.3, 112.2, 113.6, 127.5, 129.2, 145.9, 153.6, 160.2 ppm; IR (neat) ν: 1250, 1525, 1611, 1645, 1714, 1745, 3016 cm^{-1}; HRMS (ESI) calcd. for $C_{27}H_{35}O_{12}$ $[M+H]^+$: 551.2129, found:551.2132.

(2*S*,3*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(p-tolylthio)tetra hydro-2H-pyran-3-yl(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydro pyrano[3,2-d][1,3]dioxin-8-yl carbonate (5p)



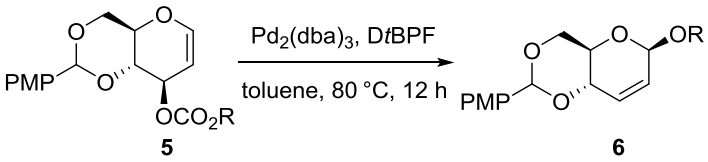
Carbonate **5p** was prepared according to the general procedure of method **B** from the corresponding alcohol[13] (275.0 mg, 65 %) as colorless oil. $[\alpha]_D^{23}$ = +16.9 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.75-3.90 (m, 6H), 3.94-4.05 (m, 3H), 4.06-4.13 (m, 1H), 4.38 -4.46 (m, 2H), 4.51 (d, *J* = 11.9 Hz, 1H), 4.59 (d, *J* = 10.8 Hz, 1H), 4.65-4.71 (m, 2H), 4.73 (dd, J_1 = 6.2 Hz, J_2 = 1.7 Hz, 1H), 4.83 (d, *J* = 11.1 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 5.39-5.45 (m, 1H), 5.50-5.60 (m, 3H), 6.36 (d, *J* = 6.2 Hz, 1H), 6.87-6.92 (m, 2H), 7.06-7.12 (m, 2H), 7.24-7.46 (m, 19H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 55.2, 68.1, 68.7, 68.9, 71.9, 72.5, 72.7, 73.3, 74.1, 74.6, 75.3, 76.4, 78.5, 86.1, 100.0, 101.4, 113.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3(2C), 129.2, 129.4, 129.8, 132.5, 137.7, 138.0, 138.2, 145.7, 154.3, 160.1 ppm; IR (neat) ν: 1215, 1524, 1616, 1650, 1713, 1747, 3015 cm^{-1}; HRMS (ESI) calcd. for $C_{49}H_{51}O_{11}S$ $[M+H]^+$: 847.3152, found:847.3160.

(2*S*,3*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-fluorotetrahydro-2H-pyran-3-yl(4a*R*,8*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano [3,2-d] [1,3]dioxin-8-yl carbonate (5q)



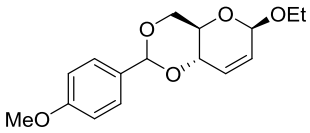
Carbonate **5q** was prepared according to the method **B** from the corresponding alcohol[14] (237.4 mg, 64 %) as colorless oil. $[\alpha]_D^{23}$ = –81.8 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.69 (d, *J* = 10.9 Hz, 1H), 3.74-3.85 (m, 5H), 3.90-3.99 (m, 4H), 4.05 (dd, J_1 = 10.3 Hz, J_2 = 7.7 Hz, 1H), 4.36 (dd, J_1 = 10.6 Hz, J_2 = 5.1 Hz, 1H), 4.48 -4.54 (m, 2H), 4.59-4.67 (m, 3H), 4.75 (d, *J* = 11.0 Hz, 1H), 4.87 (d, *J* = 10.8 Hz, 1H), 5.30-5.33 (m, 1H), 5.34-5.39 (m, 1H), 5.51 (s, 1H), 5.61 (d, *J* = 1.3 Hz, 0.5 H), 5.73 (d, *J* = 1.3 Hz, 0.5 H), 6.30 (dd, J_1 = 6.1 Hz, J_2 = 1.0 Hz, 1H), 6.85-6.91 (m, 2H), 7.13-7.18 (m, 2H), 7.24-7.43 (m, 15H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 68.1, 68.2, 68.7, 70.4, 70.8, 72.1, 73.1, 73.3, 73.5, 73.8(2C), 75.3, 76.4, 99.8, 101.6, 104.1, 106.3, 113.6, 127.5, 127.7(2C), 127.8(2C), 127.9, 128.0, 128.3, 129.2, 137.6, 137.9, 138.0, 145.8, 154.2, 160.2 ppm; IR (neat) *v*: 1251, 1521, 1613, 1644, 1715, 1751, 3018 cm^{-1}; HRMS (ESI) calcd. for $C_{42}H_{44}O_{11}F$ $[M+H]^+$: 743.2868, found:743.2857.

General procedure for aliphatic *O*-glycosides and disaccharides (6a-6q)



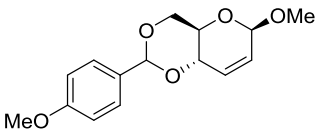
To a mixture of D*t*BPF (0.02 mmol), $Pd_2(dba)_3$ (0.01 mmol) and aliphatic carbonate **5** (0.1 mmol) was added toluene (2 mL) under an atmosphere of Argon. After stirring at 80 °C for 12 hours, the solvent was removed under reduced pressure to give crude product which was further purified by column chromatography to afford the desired glycosides **6** with 35-93% yields.

(4a*R*,6*R*,8a*S*)-6-Ethoxy-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d] [1,3]dioxine (6a)



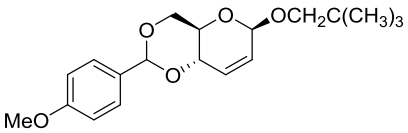
Glycoside **6a** (27.2 mg, 93%) was obtained as a white solid. m.p. 80-82 °C; $[\alpha]_D^{23}$ = +46.1 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.1 Hz, 3H), 3.56-3.65 (m, 1H), 3.71-3.78 (m, 1H), 3.80 (s, 3H), 3.83-3.94 (m, 2H), 4.28 (dd, J_1 = 10.2 Hz, J_2 = 4.5 Hz, 1H), 4.30-4.35 (m, 1H), 5.33-5.36 (m, 1H), 5.56 (s, 1H), 5.69 (ddd, J_1 = 10.3 Hz, J_2 = 2.5 Hz, J_3 = 1.5 Hz, 1H), 6.10-6.15 (m, 1H), 6.87-6.92 (m, 2H), 7.39-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 55.3, 63.8, 69.1, 70.4, 75.0, 98.5, 102.0, 113.7, 127.5, 128.5, 129.8, 131.2, 160.2 ppm; IR (neat) ν: 1215, 1518, 1616, 3017 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{21}O_5$ $[M+H]^+$: 293.1389, found: 293.1390.

(4a*R*,6*R*,8a*S*)-6-Methoxy-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (6b)



Glycoside **6b** (25.3 mg, 91%) was obtained as a white solid. m.p. 123-125 °C; $[\alpha]_D^{23}$ = +39.3 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.48 (s, 3H), 3.72-3.77 (m, 1H), 3.80 (s, 3H), 3.87 (t, *J* = 10.3 Hz, 1H), 4.26-4.34 (m, 2H), 5.27-5.31 (m, 1H), 5.57 (s, 1H), 5.65-5.71 (m, 1H), 6.15 (d, *J* = 10.3 Hz, 1H), 6.86-6.92 (m, 2H), 7.39-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.0, 55.3, 69.0, 70.4, 74.9, 99.3, 102.0, 113.7, 127.5, 128.0, 129.8, 131.6, 160.1 ppm; IR (neat) ν: 1251, 1518, 1614, 3018 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{19}O_5$ $[M+H]^+$: 279.1232, found: 279.1227.

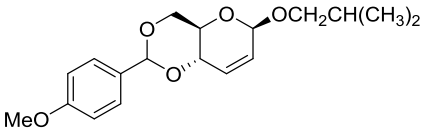
(4a*R*,6*R*,8a*S*)-2-(4-Methoxyphenyl)-6-(neopentyloxy)-4,4a,6,8a-tetrahydropyrano [3,2-d][1,3]dioxine (6c)



Glycoside **6c** (28.8 mg, 86%) was obtained as a white solid. m.p. 86-88 °C; $[\alpha]_D^{23}$ = +46.3 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 9H), 3.16 (d, *J* = 9.2 Hz, 1H), 3.50 (d, *J* = 9.2 Hz, 1H), 3.70-3.77 (m, 1H), 3.80 (s, 3H), 3.86 (t, *J* = 10.3 Hz, 1H), 4.27 (dd, J_1 = 10.2 Hz, J_2 = 4.6 Hz, 1H), 4.30-4.35 (m, 1H), 5.31-5.34 (m, 1H), 5.56 (s, 1H), 5.70 (ddd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.4 Hz, 1H), 6.12 (d, *J* = 10.3 Hz, 1H), 6.86-6.91 (m, 2H), 7.39-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.6, 31.8, 55.3, 69.1, 70.4, 75.1, 78.4, 99.3, 102.0, 113.7, 127.5, 128.7, 129.9, 131.0,

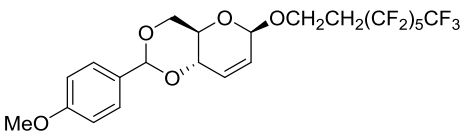
160.1 ppm; IR (neat) *v*: 1248, 1516, 1616, 3016 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{27}O_5$ $[M+H]^+$: 335.1858, found: 335.1864.

(4a*R*,6R,8aS)-6-isobutoxy-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (6d)



Glycoside **6d** (25.6 mg, 80%) was obtained as a white solid. m.p. 88-90 °C; $[\alpha]_D^{23}$ = +51.9 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.90-0.95 (m, 6H), 1.88 (hepta, J = 6.7 Hz, 1H), 3.27 (dd, J_1 = 9.1 Hz, J_2 = 7.2 Hz, 1H), 3.60 (dd, J_1 = 9.1 Hz, J_2 = 6.5 Hz, 1H), 3.71-3.77 (m, 1H), 3.79 (s, 3H), 3.86 (t, J = 10.3 Hz, 1H), 4.24-4.35 (m, 2H), 5.31-5.36 (m, 1H), 5.56 (s, 1H), 5.67-5.73 (m, 1H), 6.12 (d, J = 10.2 Hz, 1H), 6.86-6.92 (m, 2H), 7.39-7.46 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 19.3, 28.5, 55.3, 69.1, 70.4, 74.9, 75.0, 98.8, 102.0, 113.7, 127.5, 128.5, 129.8, 131.0, 160.1 ppm; IR (neat) *v*: 1215, 1520, 1614, 3017 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{25}O_5$ $[M+H]^+$: 321.1702, found: 321.1707.

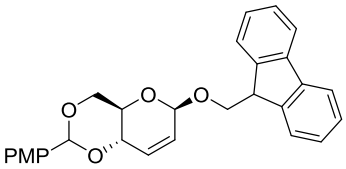
(4a*R*,6*R*,8a*S*)-2-(4-Methoxyphenyl)-6-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl oxy)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (6e)



Glycoside **6** (42.8 mg, 70%) was obtained as a yellow solid. m.p. 102-104 °C; $[\alpha]_D^{23}$ = +30.2 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 2.38-2.54 (m, 2H), 3.71-3.89 (m, 6H), 4.07 (dt, J_1 = 10.1 Hz, J_2 = 6.9 Hz, 1H), 4.25-4.33 (m, 2H), 5.37-5.40 (m, 1H), 5.57 (s, 1H), 5.64-5.70 (m, 1H), 6.18 (d, J = 10.4 Hz, 1H), 6.87-6.92 (m, 2H),

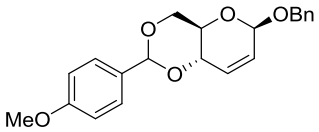
7.39-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.5, 31.7, 31.9, 55.3, 59.7, 68.9, 70.6, 74.8, 98.6, 102.1, 113.7, 127.5(2C), 129.7, 132.0, 160.2 ppm; IR (neat) ν: 1253, 1521, 1614, 1642, 3016 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{20}O_5F_{13}$ $[M+H]^+$: 611.1103, found: 611.1098.

(4a*R*,6*R*,8a*S*)-6-((9H-fluoren-9-yl)methoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetra hydropyrano[3,2-d][1,3]dioxine (6f)



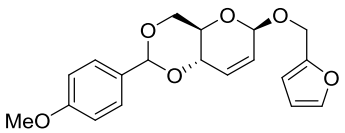
Glycoside **6f** (34.1 mg, 77%) was obtained as a white solid. m.p. 140-142 °C; $[\alpha]_D^{23}$ = +67.9 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66 (t, J = 11.0 Hz, 1H), 3.70-3.78 (m, 1H), 3.78 (s, 3H), 3.85 (t, J = 10.2 Hz, 1H), 4.18-4.24 (m, 2H), 4.26 (dd, J_1 = 10.2 Hz, J_2 = 4.5 Hz, 1H), 4.30-4.35 (m, 1H), 5.39-5.43 (m, 1H), 5.56 (s, 1H), 5.74 (ddd, J_1 = 10.3 Hz, J_2 = 2.2 Hz, J_3 = 1.4 Hz, 1H), 6.16 (d, J = 10.3 Hz, 1H), 6.86-6.91 (m, 2H), 7.27-7.33 (m, 2H), 7.36-7.44 (m, 4H), 7.61 (d, J = 7.5 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 7.5 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.8, 55.3, 69.0, 70.5(2C), 74.9, 98.9, 102.0, 113.7, 119.8, 119.9, 125.1, 125.5, 126.9(2C), 127.5(2C), 128.1, 129.8, 131.6, 141.1, 141.2, 144.1, 145.0, 160.1 ppm; IR (neat) ν: 1215, 1514, 1616, 1646, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{28}H_{26}O_5Na$ $[M+Na]^+$: 465.1678, found: 465.1678.

(4a*R*,6R,8aS)-6-(Benzyloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano [3,2-d][1,3]dioxine (6g)



Glycoside **6g** (29.8 mg, 84%) was obtained as a white solid. m.p. 133-135 °C; $[\alpha]_D^{23}$ = +36.6 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72-3.79 (m, 1H), 3.79 (s, 3H), 3.89 (t, *J* = 10.3 Hz, 1H), 4.28-4.37 (m, 2H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.85 (d, *J* = 11.7 Hz, 1H), 5.42-5.45 (m, 1H), 5.57 (s, 1H), 5.72 (ddd, J_1 = 10.3 Hz, J_2 = 2.5 Hz, J_3 = 1.5 Hz, 1H), 6.15 (d, *J* = 10.2 Hz, 1H), 6.86-6.92 (m, 2H), 7.27-7.38 (m, 5H), 7.40-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 69.0, 69.4, 70.5, 75.0, 97.7, 102.0, 113.7, 127.5, 127.8, 127.9, 128.2, 128.4, 129.8, 131.5, 137.4, 160.1 ppm; IR (neat) ν: 1253, 1521, 1616, 1644, 3017 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{23}O_5$ $[M+H]^+$: 355.1545, found: 355.1537.

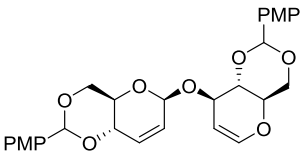
(4a*R*,6*R*,8a*S*)-6-(Furan-2-ylmethoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydro pyrano[3,2-d][1,3]dioxine (6h)



Glycoside **6h** (27.2 mg, 79%) was obtained as yellow oil. $[\alpha]_D^{23}$ = +26.3 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72-3.79 (m, 1H), 3.80 (s, 3H), 3.87 (t, *J* = 10.3 Hz, 1H), 4.27-4.36 (m, 2H), 4.61 (d, *J* = 12.6 Hz, 1H), 4.75 (d, *J* = 12.6 Hz, 1H), 5.42-5.45 (m, 1H), 5.57 (s, 1H), 5.69 (ddd, J_1 = 10.3 Hz, J_2 = 2.5 Hz, J_3 = 1.6 Hz, 1H), 6.15 (d, *J* = 10.3 Hz, 1H), 6.34-6.38 (m, 2H), 6.87-6.92 (m, 2H), 7.40-7.44 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 61.2, 69.0, 70.5, 74.9, 97.3, 102.0, 109.9, 110.3, 113.7, 127.5, 128.0, 129.8, 131.6, 143.1, 150.8, 160.1 ppm; IR (neat) ν: 1216

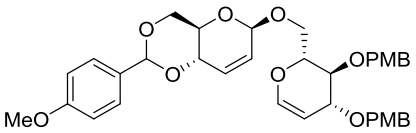
1523, 1612, 1651, 3018 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}O_6$ $[M+H]^+$: 345.1338, found: 345.1353.

(4a*R*,8*R*,8a*S*)-2-(4-Methoxyphenyl)-8-((4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yloxy)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxine (6i)



Glycosides **6i** (30.6 mg, 60%) was obtained as a white solid. m.p. 177-179 °C; $[\alpha]_D^{23}$ = +54.1 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.70-3.98 (m, 11H), 4.22 (dd, J_1 = 10.0 Hz, J_2 = 4.3 Hz, 1H), 4.29-4.37 (m, 2H), 4.54-4.59 (m, 1H), 4.85 (dd, J_1 = 6.1 Hz, J_2 = 1.7 Hz, 1H), 5.53 (s, 1H), 5.56 (s, 1H), 5.57-5.61 (m, 1H), 5.66-5.73 (m, 1H), 6.16 (d, *J* = 10.3 Hz, 1H), 6.36 (d, *J* = 6.0 Hz, 1H), 6.86-6.92 (m, 4H), 7.38-7.45 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 55.3, 68.2, 69.0(2C), 70.8, 71.1, 74.8, 78.2, 97.6, 101.2, 102.0, 102.7, 113.5, 113.7, 127.3, 127.5, 128.5, 129.7, 131.9, 144.5, 160.0, 160.1 ppm; IR (neat) *v*: 1251, 1521, 1615, 1645, 3016 cm^{-1}; HRMS (ESI) calcd. for $C_{28}H_{31}O_9$ $[M+H]^+$: 511.1968, found: 511.1958.

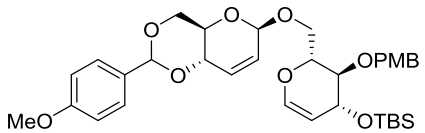
(4a*R*,6*R*,8a*S*)-6-(((2*R*,3*S*,4*R*)-3,4-Bis(4-methoxybenzyloxy)-3,4-dihydro-2H-pyran-2-yl)methoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (6j)



Glycoside **6j** (46.2 mg, 73%) was obtained as a yellow solid. m.p. 116-118 °C; $[\alpha]_D^{23}$ = +31.6 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.68-3.87 (m, 13H), 4.02-

4.09 (m, 2H), 4.18 (m, 1H), 4.14-6.85-6.92 (m, 6H), 4.22-4.29 (m, 2H), 4.49 (d, J = 11.3 Hz, 1H), 4.57 (d, J = 11.3 Hz, 1H), 4.62 (d, J = 11.0 Hz, 1H), 4.77 (d, J = 11.0 Hz, 1H), 4.86 (dd, J_1 = 6.2 Hz, J_2 = 2.7 Hz, 1H), 5.36-5.39 (m, 1H), 5.54 (s, 1H), 5.67 (ddd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.5 Hz, 1H), 6.13 (d, J = 10.3 Hz, 1H), 6.40 (dd, J_1 = 6.2 Hz, J_2 = 0.8 Hz, 1H), 7.22-7.29 (m, 4H), 7.39-7.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 55.3, 65.8, 68.9, 70.1, 70.5, 73.1, 73.6, 74.8, 75.0, 76.3, 98.7, 100.0, 102.0, 113.7, 113.8, 127.5, 127.9, 129.3, 129.5, 129.7, 130.2, 130.3, 131.7, 144.5, 159.2, 159.3, 160.1 ppm; IR (neat) ν: 1219, 1525, 1618, 1653, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{36}H_{41}O_{10}$ $[M+H]^+$: 633.2700, found: 633.2703.

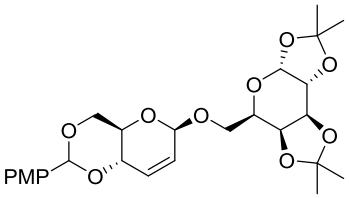
(4a*R*,6*R*,8a*S*)-6-(((2*R*,3*R*,4*R*)-4-(Tert-butyldimethylsilyloxy)-3-(4-methoxybenzyl oxy)-3,4-dihydro-2H-pyran-2-yl)methoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetra hydropyrano[3,2-d][1,3]dioxine (6k)



Glycoside **6k** (54.5 mg, 87%) was obtained as colorless oil. $[\alpha]_D^{23}$ = +42.0 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.11 (s, 3H), 0.12 (s, 3H), 0.93 (s, 9H), 3.60 (dd, J_1 = 8.0 Hz, J_2 = 5.8 Hz, 1H), 3.69-3.76 (m, 1H), 3.79-3.88 (m, 8H), 3.95-4.00 (m, 1H), 4.06-4.12 (m, 1H), 4.22-4.34 (m, 3H), 4.62 (d, J = 11.1 Hz, 1H), 4.68 (dd, J_1 = 6.2 Hz, J_2 = 2.9 Hz, 1H), 4.78 (d, J = 11.1 Hz, 1H), 5.36-5.39 (m, 1H), 5.55 (s, 1H), 5.70 (ddd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.5 Hz, 1H), 6.14 (d, J = 10.3 Hz, 1H), 6.34 (dd, J_1 = 6.2 Hz, J_2 = 1.1 Hz, 1H), 6.87-6.92 (m, 4H), 7.26-7.30 (m, 2H), 7.40-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.7, -4.4, 17.9, 25.8, 55.2, 65.9, 68.5, 68.9, 70.5, 73.3, 74.9, 76.1, 76.2, 98.6, 102.0, 103.4, 113.6, 113.8, 127.5, 128.0, 129.4,

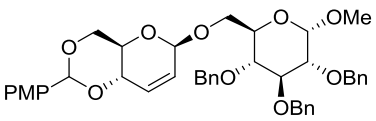
129.8, 130.2, 131.7, 143.2, 159.3, 160.1 ppm; IR (neat) *v*: 1255, 1521, 1611, 1649, 3016 cm^{-1}; HRMS (ESI) calcd. for $C_{34}H_{47}O_9Si$ $[M+H]^+$: 627.2989, found: 627.2985.

(3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-5-(((4a*R*,6*R*,8a*S*)-2-(4-Methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yloxy)methyl)-2,2,7,7-tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran (6l)



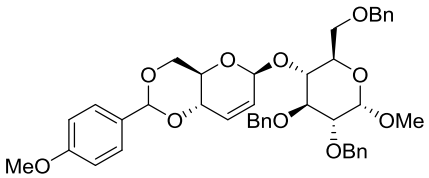
Glycoside **6l** (43.1 mg, 85%) was obtained as colorless oil. $[\alpha]_D^{23}$ = –13.8 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 6H), 1.45 (s, 3H), 1.55 (s, 3H), 3.70-3.78 (m, 2H), 3.79 (s, 3H), 3.84 (t, *J* = 10.2 Hz, 1H), 3.91-4.02 (m, 2H), 4.22-4.34 (m, 4H), 4.60 (dd, J_1 = 7.9 Hz, J_2 = 2.4 Hz, 1H), 5.43-5.46 (m, 1H), 5.53-5.57 (m, 2H), 5.76 (ddd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.4 Hz, 1H), 6.12 (d, *J* = 10.3 Hz, 1H), 6.86-6.92 (m, 2H), 7.39-7.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 24.9, 25.9, 26.0, 55.2, 67.0, 67.5, 69.0, 70.4(2C), 70.6, 71.2, 74.9, 96.2, 99.1, 102.0, 108.6, 109.3, 113.6, 127.5, 128.3, 129.8, 131.2, 160.1 ppm; IR (neat) *v*: 1215, 1518, 1615, 1648, 3018 cm^{-1};HRMS (ESI) calcd. for $C_{26}H_{35}O_{10}$ $[M+H]^+$: 507.2230, found: 507.2234.

(4a*R*,6*R*,8a*S*)-2-(4-Methoxyphenyl)-6-(((2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2H-pyran-2-yl)methoxy)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (6m)



Glycoside **6m** (59.0 mg, 83%) was obtained as a white solid. m.p. 146-148 °C; $[\alpha]_D^{23}$ = +50.5 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$):δ 3.37 (s, 3H), 3.52-3.62 (m, 2H), 3.67-3.80 (m, 7H), 3.92-4.03 (m, 2H), 4.17-4.26 (m, 2H), 4.59-4.68 (m, 3H), 4.77-4.85 (m, 2H), 4.90 (d, *J* = 11.1 Hz, 1H), 4.99 (d, *J* = 10.9 Hz, 1H), 5.26-5.29 (m, 1H), 5.49 (s, 1H), 5.61 (ddd, J_1 = 10.4 Hz, J_2 = 2.4 Hz, J_3 = 1.4 Hz, 1H), 6.11 (d, *J* = 10.4 Hz, 1H), 6.85-6.91 (m, 2H), 7.26-7.42 (m, 17H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2(2C), 65.4, 68.8, 69.6, 70.4, 73.3, 74.8(2C), 75.7, 79.7, 82.1, 98.1, 98.5, 102.0, 113.7, 127.4, 127.6, 127.7(2C), 127.9(3C), 128.1, 128.4(2C), 129.7, 131.7, 138.1, 138.4, 138.7, 160.1 ppm; IR (neat) ν: 1253, 1521, 1611, 1645, 3015 cm^{-1}; HRMS (ESI) calcd. for $C_{42}H_{47}O_{10}$ $[M+H]^+$: 711.3169, found: 711.3168.

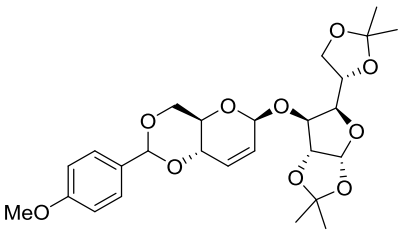
(4a*R*,6*S*,8a*S*)-6-((2*R*,3*R*,4*S*,5*R*,6*S*)-4,5-Bis(benzyloxy)-2-(benzyloxymethyl)-6-methoxytetrahydro-2H-pyran-3-yloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (6n)



Glycoside **6n** (49.0 mg, 69%) was obtained as colorless oil. $[\alpha]_D^{23}$ = +39.0 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.38 (s, 3H), 3.46-3.59 (m, 3H), 3.60-3.74 (m, 3H), 3.79 (s, 3H), 3.86-3.92 (m, 2H), 4.00 (dd, J_1 = 9.4 Hz, J_2 = 3.7 Hz, 1H), 4.13-4.19 (m, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.59-4.70 (m, 3H), 4.78 (d, *J* = 12.2 Hz, 1H), 4.87 (d, *J* = 10.9 Hz, 1H), 4.95 (d, *J* = 10.9 Hz, 1H), 5.32-5.35 (m, 1H), 5.36-5.42 (m, 2H), 5.98 (d, *J* = 10.3 Hz, 1H), 6.86-6.91 (m, 2H), 7.25-7.42 (m, 17H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 55.3, 68.2, 68.8, 69.8, 70.8, 73.5, 73.6, 74.7, 75.4, 77.1, 79.3, 80.6, 98.3, 99.5, 101.9, 113.7, 127.3, 127.4, 127.5, 127.8, 127.9, 128.0, 128.1,

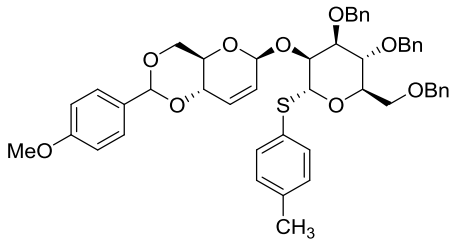
128.2, 128.4, 128.5,129.8, 130.9, 137.6, 138.2, 139.3, 160.1 ppm; IR (neat) *v*: 1248, 1515, 1616, 1649, 3017 cm^{-1}; HRMS (ESI) calcd. for $C_{42}H_{47}O_{10}$ $[M+H]^+$: 771.3169, found: 711.3169.

(4a*R*,6*S*,8a*S*)-6-((3a*R*,5*R*,6*S*,6a*R*)-5-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (6o)



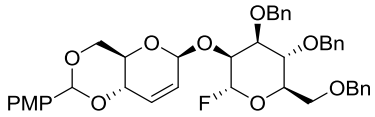
Glycoside **6o** (35.5 mg, 70%) was obtained as colorless oil. $[\alpha]_D^{23}$ = +36.6 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.37 (s, 3H), 1.43 (s, 3H), 1.50 (s, 3H), 3.71-3.78 (m, 1H), 3.80 (s, 3H), 3.87 (t, *J* = 10.4 Hz, 1H), 4.00 (dd, J_1 = 8.6 Hz, J_2 = 6.0 Hz, 1H), 4.07 (dd, J_1 = 8.6 Hz, J_2 = 6.3 Hz, 1H), 4.18-4.22 (m, 1H), 4.25-4.35 (m, 4H), 4.63 (d, *J* = 3.6 Hz, 1H), 5.54-5.57 (m, 1H), 5.59 (s, 1H), 5.67-5.73 (m, 1H), 5.90 (d, *J* = 3.6 Hz, 1H), 6.21 (d, *J* = 10.4 Hz, 1H), 6.87-6.91 (m, 2H), 7.39-7.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5, 26.3, 26.7, 26.8, 55.3, 66.9, 68.9, 70.9, 72.7, 74.8, 77.4, 80.5, 84.0, 97.5, 102.0, 105.1, 108.8, 111.8, 113.7, 127.5(2C), 129.7, 132.9, 160.2 ppm; IR (neat) *v*: 1251, 1521, 1613, 1651, 3015 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{35}O_{10}$ $[M+H]^+$: 507.2230, found: 507.2217.

(4a*R*,6*S*,8a*S*)-6-((2*R*,3*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(p-tolylthio)tetrahydro-2H-pyran-3-yloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (6p)



Glycoside **6p** (28.1 mg, 35%) was obtained as yellow oil. $[\alpha]_D^{23}$ = +59.4 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.58-3.77 (m, 3H), 3.80 (s, 3H), 3.81-3.85 (m, 1H), 3.89-3.98 (m, 2H), 4.10-4.15 (m, 1H), 4.19 (dd, J_1 = 9.7 Hz, J_2 = 4.0 Hz, 1H), 4.21-4.27 (m, 1H), 4.36-4.40 (m, 1H), 4.45-4.54 (m, 2H), 4.61-4.69 (m, 2H), 4.77 (d, *J* = 11.4 Hz, 1H), 4.91 (d, *J* = 10.8 Hz, 1H), 5.47 (s, 1H), 5.54-5.58 (m, 1H), 5.61 (d, *J* = 1.4 Hz, 1H), 5.64-5.70 (m, 1H), 6.13 (d, *J* = 10.3 Hz, 1H), 6.87-6.92 (m, 2H), 7.05-7.10 (m, 2H), 7.18-7.22 (m, 2H), 7.24-7.44 (m, 17H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 55.3, 68.9, 69.2, 70.6, 72.0, 72.9, 73.1, 73.3, 74.8, 74.9, 75.2, 78.8, 87.3, 97.3, 102.0, 113.7, 127.4, 127.5, 127.6, 127.8, 127.9, 128.0, 128.2(2C), 128.3, 128.4, 129.7, 129.8, 130.5, 132.2, 132.5, 137.7, 138.0, 138.3, 138.4, 160.2 ppm; IR (neat) *ν*: 1219, 1523, 1616, 1647, 3018 cm^{-1}; HRMS (ESI) calcd. for $C_{48}H_{51}O_9S$ $[M+H]^+$: 803.3254, found: 803.3252.

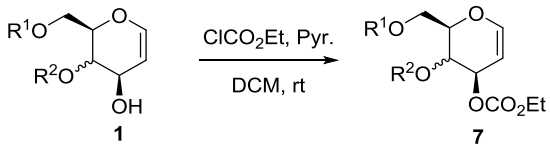
(4a*R*,6*S*,8a*S*)-6-((2*S*,3*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-fluo rotetrahydro-2H-pyran-3-yloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydro pyrano[3,2-d][1,3]dioxine (6q)



Glycoside **6q** (27.9 mg, 40%) was obtained as colorless oil. $[\alpha]_D^{23}$ = +57.7 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.68-3.78 (m, 4H), 3.80 (s, 3H), 3.84-4.00 (m, 3H), 4.16-4.21 (m, 1H), 4.22-4.29 (m, 2H), 4.48-4.55 (m, 2H), 4.63-4.70 (m, 2H),

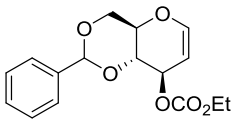
4.73 (d, J = 11.4 Hz, 1H), 4.87 (d, J = 10.8 Hz, 1H), 5.55 (s, 1H), 5.61 (s, 1H), 5.65-5.71 (m, 1.5H), 5.77-5.82 (m, 0.5H), 6.19 (d, J = 10.3 Hz, 1H), 6.87-6.92 (m, 2H), 7.16-7.19 (m, 2H), 7.25-7.44 (m, 15H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 68.5, 68.8, 69.8, 70.1, 70.9, 72.5, 73.4, 73.9(2C), 74.8, 75.1, 77.7, 97.9, 102.1, 106.2, 108.4, 113.7, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.3(2C), 128.4, 129.6, 132.8, 137.9, 138.1(2C), 160.2 ppm; IR (neat) ν: 1253, 1515, 1621, 1650, 3016 cm^{-1}; HRMS (ESI) calcd. for $C_{41}H_{44}O_9F$ $[M+H]^+$: 699.2969, found: 699.2966.

General procedure for preparing carbonates 7a-7g



To a solution of 4,6-protected glycal (1 equiv) in DCM was added Pyridine (5 equiv) at 0 °C. Then ethyl chloroformate (4 equiv) was added slowly at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. After the reaction was completed, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (eluted with *n*-hexane / EA = 10:1) to provide the desired carbonate **7**.

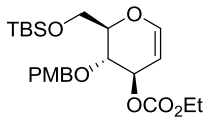
Ethyl-(4a*R*,8*R*,8a*S*)-2-phenyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl carbonate (7a)



Carbonate **7a** was prepared according to the general procedure from the corresponding alcohol[15] (130.1 mg, 85%) as a white solid. m.p. 67-69 °C; $[\alpha]_D^{23}$ = –

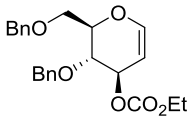
80.0 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, J = 7.1 Hz, 3H), 3.83 (t, J = 10.3 Hz, 1H), 3.95-4.05 (m, 2H), 4.20 (q, J = 7.1 Hz, 2H), 4.38 (dd, J_1 = 10.4 Hz, J_2 = 5.0 Hz, 1H), 4.88 (dd, J_1 = 6.2 Hz, J_2 = 2.0 Hz, 1H), 5.37-5.43 (m, 1H), 5.57 (s, 1H), 6.40 (dd, J_1 = 6.2 Hz, J_2 = 1.3 Hz, 1H), 7.32-7.40 (m, 3H), 7.46-7.51 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 64.2, 68.1, 68.7, 72.0, 76.8, 100.2, 101.6, 126.2, 128.2, 129.2, 136.8, 145.7, 154.6 ppm; IR (neat) ν: 1215, 1521, 1611, 1645, 1747, 3016 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{19}O_6$ $[M+H]^+$: 307.1182, found: 307.1181.

(2*R*,3*S*,4*R*)-2-((Tert-butyldimethylsilyloxy)methyl)-3-(4-methoxybenzyloxy)-3,4-dihydro-2H-pyran-4-yl ethyl carbonate (7b)



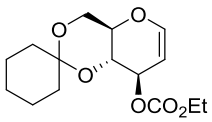
Carbonate **7b** was prepared according to the general procedure from the corresponding alcohol (180.8 mg, 80%) as colorless oil. $[\alpha]_D^{23}$ = +0.7 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.15 (s, 6H), 0.98 (s, 9H), 1.39 (t, J = 7.1 Hz, 3H), 3.83 (s, 3H), 3.92-4.06 (m, 4H), 4.23-4.32 (m, 2H), 4.73 (d, J = 11.0 Hz, 1H), 4.79 (d, J = 11.0 Hz, 1H), 4.86 (dd, J_1 = 6.1 Hz, J_2 = 2.9 Hz, 1H), 5.34-5.38 (m, 1H), 6.49 (dd, J_1 = 6.1 Hz, J_2 = 1.1 Hz, 1H), 6.92-6.97 (m, 2H), 7.32-7.37 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.5, -5.3, 14.2, 18.2, 25.8, 55.2, 61.1, 63.9, 72.4, 73.4, 74.3, 77.9, 98.3, 113.7, 129.5, 130.2, 146.1, 154.7, 159.2 ppm; IR (neat) ν: 1221, 1518, 1615, 1650, 1746, 3017 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{36}O_7SiNa$ $[M+Na]^+$: 475.2128, found: 475.2134.

(2*R*,3*S*,4*R*)-3-(Benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-4-yl ethyl carbonate (7c)



Carbonate **7c** was prepared according to the general procedure from the corresponding alcohol[16] (171.1 mg, 86%) as colorless oil. $[\alpha]_D^{23}$ = +7.9 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 3.75 (dd, J_1 = 10.7 Hz, J_2 = 3.2 Hz, 1H), 3.81 (dd, J_1 = 10.7 Hz, J_2 = 4.7 Hz, 1H), 3.96 (dd, J_1 = 8.6 Hz, J_2 = 6.1 Hz, 1H), 4.08-4.22 (m, 3H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.75 (d, *J* = 11.4 Hz, 1H), 4.83 (dd, J_1 = 6.1 Hz, J_2 = 2.9 Hz, 1H), 5.27-5.32 (m, 1H), 6.45 (dd, J_1 = 6.1 Hz, J_2 = 0.9 Hz, 1H), 7.27-7.35 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 64.0, 67.9, 73.2, 73.4, 73.6, 74.2, 76.6, 98.5, 127.7(2C), 127.8, 128.3(2C), 137.8, 146.1, 154.6 ppm; IR (neat) ν: 1252, 1523, 1616, 1644, 1753, 3015 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{26}O_6Na$ $[M+Na]^+$: 421.1627, found: 421.1627.

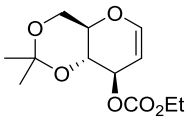
Ethyl-(4a'*R*,8'*R*,8a'*S*)-4',4a',8',8a'-tetrahydrospiro[cyclohexane-1,2'-pyrano[3,2-d][1,3]dioxine]-8'-yl carbonate (7d)



Carbonate **7d** was prepared according to the general procedure from the corresponding alcohol[17] (123.7 mg, 83%) as colorless oil. $[\alpha]_D^{23}$ = –30.4 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.1 Hz, 3H), 1.37-1.69 (m, 8H), 1.86-2.03 (m, 2H), 3.78-3.90 (m, 2H), 3.91-3.98 (m, 1H), 4.07 (dd, J_1 = 10.0 Hz, J_2 = 7.9 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.81 (dd, J_1 = 6.1 Hz, J_2 = 2.0 Hz, 1H), 5.24-

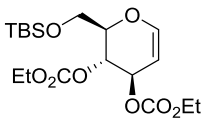
5.29 (m, 1H), 6.36 (dd, J_1 = 6.1 Hz, J_2 = 1.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.4, 22.6, 25.5, 27.5, 37.6, 60.7, 64.0, 68.9, 69.8, 72.7, 99.9, 100.3, 145.6, 154.7 ppm; IR (neat) ν: 1218, 1516, 1611, 1642, 1751, 3019 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{22}O_6Na$ $[M+Na]^+$: 321.1314, found: 321.1315.

(4a*R*,8*R*,8a*S*)-2,2-Dimethyl-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxin-8-yl ethyl carbonate (7e)



Carbonate **7e** was prepared according to the general procedure from the corresponding alcohol[18] (116.1 mg, 90%) as colorless oil. $[\alpha]_D^{23}$ = –76.2 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, J = 7.1 Hz, 3H), 1.42 (s, 3H), 1.53 (s, 3H), 3.76-3.89 (m, 2H), 3.94-4.00 (m, 1H), 4.03-4.10 (m, 1H), 4.17-4.26 (m, 2H), 4.83 (dd, J_1 = 6.1 Hz, J_2 = 2.0 Hz, 1H), 5.20-5.25 (m, 1H), 6.37 (dd, J_1 = 6.1 Hz, J_2 = 1.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 18.9, 28.8, 61.4, 64.1, 69.6(2C), 72.8, 99.8, 100.3, 145.6, 154.6 ppm; IR (neat) ν: 1221, 1511, 1613, 1645, 1745 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{18}O_6Na$ $[M+Na]^+$: 281.1001, found: 281.1002.

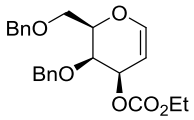
(2*R*,3*S*,4*R*)-2-((Tert-butyldimethylsilyloxy)methyl)-3,4-dihydro-2H-pyran-3,4-diyl diethyl dicarbonate (7f)



Carbonate **7f** was prepared according to the general procedure from the corresponding alcohol[19] (153.5 mg, 76%) as colorless oil. $[\alpha]_D^{23}$ = –6.1 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.061 (s, 3H), 0.064 (s, 3H), 0.89 (s, 9H), 1.32 (t, J = 7.1 Hz,

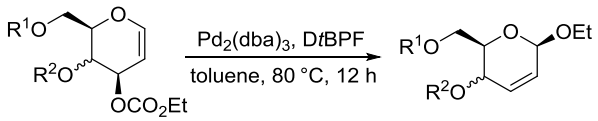
3H), 1.30 (t, J = 7.1 Hz, 3H), 3.84-3.87 (m, 2H), 4.13-4.25 (m, 5H), 4.86 (dd, J_1 = 6.2 Hz, J_2 = 3.5 Hz, 1H), 5.17-5.26 (m, 2H), 6.48 (dd, J_1 = 6.2 Hz, J_2 = 1.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.6(2C), 14.1, 14.2, 18.2, 25.8, 60.8, 64.1, 64.5, 70.6, 70.8, 76.3, 97.5, 146.3, 153.9, 154.5 ppm; IR (neat) ν: 1252, 1521, 1613, 1648, 1744, 3016 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{32}O_8SiNa$ $[M+Na]^+$: 427.1764, found: 427.1764.

(2*R*,3*R*,4*R*)-3-(Benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-4-yl ethyl carbonate (7g)



Carbonate **7g** was prepared according to the general procedure from the corresponding alcohol[20] (143.3 mg, 72%) as colorless oil. $[\alpha]_D^{23}$ = –25.8 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J = 7.1 Hz, 3H), 3.66 (dd, J_1 = 10.4 Hz, J_2 = 4.4 Hz, 1H), 3.79 (dd, J_1 = 10.4 Hz, J_2 = 7.7 Hz, 1H), 4.01-4.06 (m, 1H), 4.12-4.21 (m, 2H), 4.24-4.30 (m, 1H), 4.45 (d, J = 11.9 Hz, 1H), 4.50-4.56 (m, 2H), 4.77 (d, J = 11.8 Hz, 1H), 4.81 (dd, J_1 = 5.9 Hz, J_2 = 3.5 Hz, 1H), 5.31-5.35 (m, 1H), 6.45 (dd, J_1 = 6.1 Hz, J_2 = 1.0 Hz, 1H), 7.23-7.36 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 64.0, 67.7, 68.5, 70.5, 73.3(2C), 75.3, 98.0, 127.6, 127.7, 127.8, 128.0, 128.3, 137.7, 137.9, 145.8, 154.8 ppm; IR (neat) ν: 1215, 1514, 1613, 1641, 1751, 3021 cm^{-1}; HRMS (ESI) calcd. for $C_{23}H_{26}O_6Na$ $[M+Na]^+$: 421.1627, found: 421.1624.

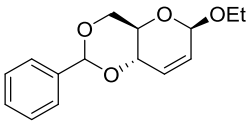
General procedure for preparing *O*-glycosides 8a-8g



7 **8**

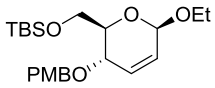
To a mixture of D*t*BPF (0.04 mmol), $Pd_2(dba)_3$ (0.02 mmol) and carbonate **7** (0.2 mmol) was added toluene (4 mL) under an atmosphere of Argon. After stirring at 80 °C for 12 hours, the solvent was removed under reduced pressure to give crude product which was further purified by column chromatography to afford the desired glycosides **8** with 20-84% yields.

(4a*R*,6*R*,8a*S*)-6-Ethoxy-2-phenyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (8a)



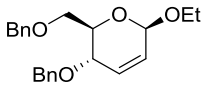
Glycoside **8a** (44.1 mg, 84%) as was obtained a white solid. m.p. 88-90 °C; $[\alpha]_D^{23}$ = +36.5 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J = 7.1 Hz, 3H), 3.64 (dq, J_1 = 9.4 Hz, J_2 = 7.1 Hz, 1H), 3.75-3.82 (m, 1H), 3.87-3.96 (m, 2H), 4.32 (dd, J_1 = 10.3 Hz, J_2 = 4.6 Hz, 1H), 4.35-4.39 (m, 1H), 5.36-5.39 (m, 1H), 5.63 (s, 1H), 5.73 (ddd, J_1 = 10.3 Hz, J_2 = 2.5 Hz, J_3 = 1.5 Hz, 1H), 6.16 (d, J = 10.3 Hz, 1H), 7.35-7.43 (m, 3H), 7.50-7.55 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 63.8, 69.1, 70.4, 75.0, 98.5, 102.1, 126.2, 128.3, 128.5, 129.1, 131.1, 137.3 ppm; IR (neat) ν: 1251, 1516, 1611, 1643, 3015 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{18}O_4Na$ $[M+Na]^+$: 285.1103, found: 285.1101.

Tert-butyl(((2*R*,3*S*,6*R*)-6-ethoxy-3-(4-methoxybenzyloxy)-3,6-dihydro-2H-pyran-2-yl)methoxy)dimethylsilane (8b)



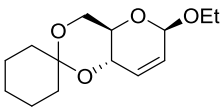
Glycoside **8b** (58.0 mg, 71%) was obtained as yellow oil. $[\alpha]_D^{23}$ = +54.7 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.05 (S, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H), 3.54 (dq, J_1 = 9.4 Hz, J_2 = 7.1 Hz, 1H), 3.72-3.84 (m, 6H), 3.84-3.92 (m, 1H), 3.92-3.97 (m, 1H), 4.53 (s, 2H), 5.06-5.09 (m, 1H), 5.77-5.84 (m, 1H), 6.00 (ddd, J_1 = 10.3 Hz, J_2 = 3.3 Hz, J_3 = 1.6 Hz, 1H), 6.84-6.89 (m, 2H), 7.24-7.29 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.3(2C), 15.2, 18.3, 25.9, 55.2, 63.0, 63.2, 68.7, 70.7, 95.2, 113.8, 128.4, 128.8, 129.5, 130.3, 159.2 ppm; IR (neat) ν: 3019, 1645, 1616, 1520, 1248 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{36}O_5NaSi$ $[M+Na]^+$: 431.2230, found: 431.2227.

(2*R*,3*S*,6*R*)-3-(Benzyloxy)-2-(benzyloxymethyl)-6-ethoxy-3,6-dihydro-2H-pyran (8c)



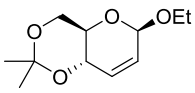
Glycoside **8c** (59.5 mg, 84%) was obtained as colorless oil. $[\alpha]_D^{23}$ = +60.1 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, *J* = 7.1 Hz, 3H), 3.56 (dq, J_1 = 9.4 Hz, J_2 = 7.1 Hz, 1H), 3.67 (dd, J_1 = 10.4 Hz, J_2 = 5.0 Hz, 1H), 3.71 (dd, J_1 = 10.4 Hz, J_2 = 4.4 Hz, 1H), 3.87-4.01 (m, 3H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.56-4.61 (m, 3H), 5.10-5.14 (m, 1H), 5.80-5.86 (m, 1H), 6.03 (ddd, J_1 = 10.3 Hz, J_2 = 2.6 Hz, J_3 = 1.7 Hz, 1H), 7.23-7.35 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 63.6, 69.7, 69.9, 71.0, 73.3, 75.3, 95.9, 127.5, 127.6, 127.7, 127.9, 128.3, 128.4, 128.5, 129.1, 137.9, 138.3 ppm; IR (neat) ν: 1251, 1523, 1618, 1641, 3015 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{26}O_4Na$ $[M+Na]^+$: 377.1729, found: 377.1732.

(4a'*R*,6'*R*,8a'*S*)-6'-Ethoxy-4',4a',6',8a'-tetrahydrospiro[cyclohexane-1,2'-pyrano [3,2-d][1,3]dioxine] (8d)



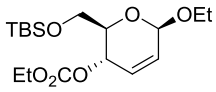
Glycoside **8d** (35.6 mg, 70%) was obtained as colorless oil. $[\alpha]_D^{23}$ = +16.6 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.1 Hz, 3H), 1.38-1.65 (m, 8H), 1.85-2.04 (m, 2H), 3.53-3.62 (m, 2H), 3.82-3.91 (m, 3H), 4.38-4.44 (m, 1H), 5.29-5.32 (m, 1H), 5.65 (ddd, J_1 = 10.3 Hz, J_2 = 2.5 Hz, J_3 = 1.5 Hz, 1H), 5.98-6.04 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 22.5, 22.7, 25.6, 27.7, 38.1, 62.0, 63.6, 66.5, 71.6, 98.5, 100.0, 128.1, 132.1 ppm; IR (neat) ν: 1215, 1517, 1611, 1645 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{23}O_4$ $[M+H]^+$: 255.1596, found: 255.1600.

(4a*R*,6*R*,8a*S*)-6-Ethoxy-2,2-dimethyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3] dioxine (8e)



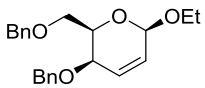
Glycoside **8e** (30.4 mg, 71%) was obtained as colorless oil. $[\alpha]_D^{23}$ = +8.9 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.1 Hz, 3H), 1.43 (s, 3H), 1.52 (s, 3H), 3.52-3.63 (m, 2H), 3.82-3.92 (m, 3H), 4.36-4.42 (m, 1H), 5.29-5.32 (m, 1H), 5.65 (ddd, J_1 = 10.3 Hz, J_2 = 2.5 Hz, J_3 = 1.5 Hz, 1H), 5.99 (d, *J* = 10.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 19.1, 29.2, 62.7, 63.8, 67.4, 71.4, 98.5, 99.9, 128.2, 131.8 ppm; IR (neat) ν: 1247, 1521, 1615, 1643 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{19}O_4$ $[M+H]^+$: 215.1283, found: 215.1283.

(2*R*,3*S*,6*R*)-2-((Tert-butyldimethylsilyloxy)methyl)-6-ethoxy-3,6-dihydro-2H-pyran-3-yl ethyl carbonate (8f)



Glycosides **8f** (24.5 mg, 34%) was obtained as colorless oil. $[\alpha]_D^{23}$ = +54.8 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.65 (s, 6H), 0.89 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 3.56 (dq, J_1 = 9.4 Hz, J_2 = 7.1 Hz, 1H), 3.74-3.84 (m, 2H), 3.85-3.95 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 5.07-5.14 (m, 2H), 5.89-5.94 (m, 1H), 6.03 (ddd, J_1 = 10.2 Hz, J_2 = 3.5 Hz, J_3 = 1.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.4(2C), 14.2, 15.2, 18.3, 25.8, 62.9, 63.5, 64.2, 68.0, 75.6, 95.0, 126.2, 130.9, 154.5 ppm; IR (neat) ν: 1251, 1516, 1621, 1646, 1751 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{32}O_6NaSi$ $[M+Na]^+$: 383.1866, found: 383.1859.

(2*R*,3*R*,6*R*)-3-(Benzyloxy)-2-(benzyloxymethyl)-6-ethoxy-3,6-dihydro-2H-pyran (8g)



Glycoside **8g** (14.2 mg, 20%) was obtained as yellow oil. $[\alpha]_D^{23}$ = –140.2 (*c* = 0.65 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.1 Hz, 3H), 3.56-3.66 (m, 1H), 3.77-3.82 (m, 2H), 3.84-3.89 (m, 1H), 3.90-4.00 (m, 2H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 5.06-5.10 (m, 1H), 5.87-5.92 (m, 1H), 6.05 (dd, J_1 = 10.2 Hz, J_2 = 4.4 Hz, 1H), 7.24-7.36 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 63.8, 68.4, 69.6, 70.8, 73.5, 74.1, 97.1, 127.6(2C), 127.7, 127.8, 128.1, 128.3, 128.4, 131.6, 138.3, 138.5 ppm; IR (neat) ν: 1215, 1518, 1612, 1646, 3015 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{26}O_4Na$ $[M+Na]^+$: 377.1729, found: 377.1726.

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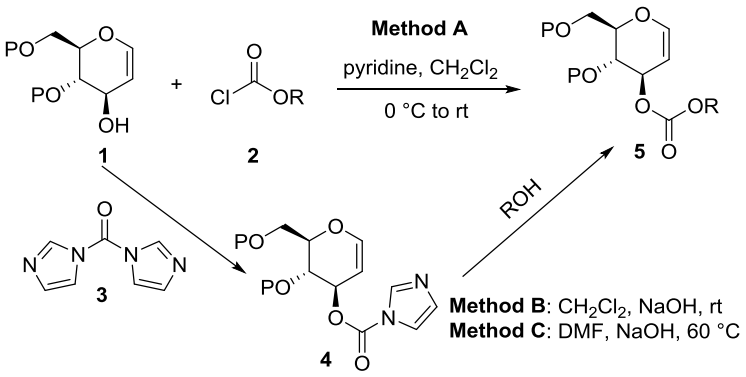
Chapter 3: Highly stereoselective *O*-glycosylation *via* decarboxylative allylation with Pd-π-allyl intermediate as glycosyl donor

Introduction

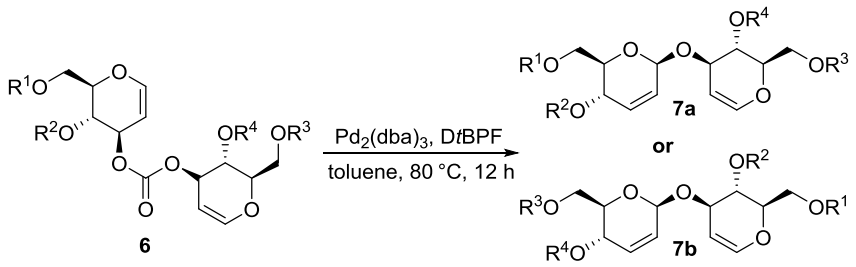
In the previous chapter, we have demonstrated an intramolecular glycosylation strategy based on a decarboxylative allylation. Various glycosyl acceptors have been proved to be suitable for the reaction. However, the extensions and applications were restricted by the following two reasons. One of them is the laborious work for preparing the carbonate starting material.



Scheme 2.3.1 Methods to prepare glycal derived carbonates

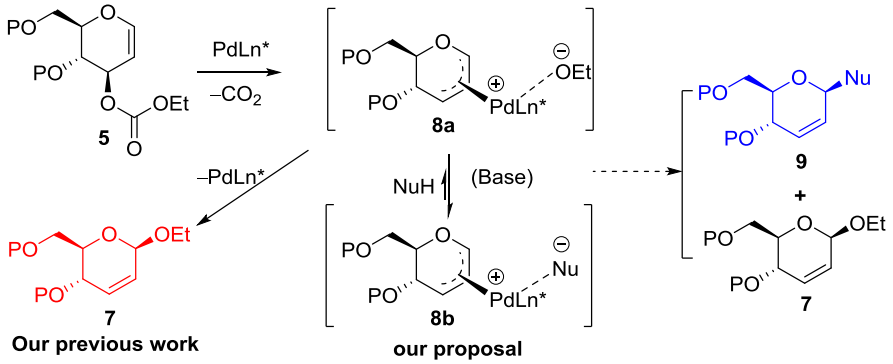
Three methods have been mentioned for the synthesis and the most efficient method is the coupling reaction of 3-OH glycal **1** and chloroformate **2** in the presence of base (**Method A**). But most of chloroformates are hardly to achieve from the

market. The other two methods were associated with carbamate intermediate **4** provided by the reaction of 3-OH glycal and CDI (1,1'-dicarbonylimidazole) **3** (**Methods B and C**). The yields of product **5** from these two methods are usually unsatisfactory. Besides that, some of the carbamate intermediates with other protecting groups are unstable and a decarboxylative allylation will take place to give the *N*-glycosyl imidazole product.[1] Another problem was the regioselectivity of the reaction with substrate **6**. Under the conditions, both products **7a** and **7b** are possible to form (**Scheme 2.3.2**).



Scheme 2.3.2 Glycosylation with substrate **6**

In order to solve the problems mentioned above, we then proposed a decarboxylative glycosylation method *via* intermolecular manner with the carbonate **5** which can be easily prepared by the reaction of 3-OH glycal and ethyl chloroformate as the starting material. It not only complements the previous method but also serves as an extension for the decarboxylative strategy.



Scheme 2.3.3 Our proposal of intermolecular glycosylation

It has been demonstrated that the formation of Pd-π-allyl species **8a** in glycal system is very difficult. We hope the release of CO_2 was able to serve as a driving force to accelerate the formation. In the presence of an external nucleophile, Pd-π-allyl species **8a** is in rapid protic equilibrium with another Pd-π-allyl species **8b**. Moreover, the problem from low reactivity without electron-withdrawing groups such as ketone on the adjacent position could be solved by the intramolecular nucleophilic addition under neutral conditions.[2] Furthermore, the flexibility of the rapid protic equilibrium to give another metal species has been illustrated by Tsuji[3] and O'Doherty.[4] Herein, we describe our studies on this palladium catalyzed intermolecular glycosylation from glucal derived allylic carbonates.

Result and discussion

Compound **1**, which could be readily synthesized, was chosen to be the model glycosyl donor in our initial studies. We hope that ethanol as the product of proton transfer after the decarboxylation with this substrate can be removed from the reaction system under the high temperature, thus eliminating the possibility to form ethyloxy addition product. On the other hand, 3,4,5-trimethoxyphenol **2a** was selected as glycosyl acceptor since these three methoxy groups on the phenol can significantly increase its nucleophilicity and then the next nucleophilic addition to the generated Pd-π-allyl intermediate should be easier. Then our idea was kicked out by the treatment of glucal carbonate **1** with **2a** under the reaction conditions optimized for intramolecular *O*-glycosylation in the last part. However, byproduct **4** was obtained as the major product and the desired product **3a** was provided in 20% yield (entry **1**). As we attributed this result to low nucleophilicity of the protonated phenol, an additional base, sodium ethoxide was then added to enhance it. To our delight, significant improvement of the outcome was observed and only 21% yield of byproduct was isolated even the base had a potential to increase the yield of **4** (entry **2**). This result encouraged us to screen different bases for obtaining better result. Before that, a bulky tertiary butyl group was introduced to the substrate to decrease the yield of byproduct. However, the result obtained was worse than before (entry **3**). Next, the influence of different bases was tested. Form the results, we could see Cs_2CO_3 exhibited best performance in promoting this reaction and other examined bases, such as K_2CO_3, DBU and NaH provided lower chemical yields or poor anomeric selectivities (entries

4-**7**). Noteworthy, the loading of base could also great influence the outcome of reaction. The reaction gave *α*–selectivity with less than 0.5 eq. of base while exclusive *β*–selectivity was achieved with the addition of more than 0.5 eq. of Cs_2CO_3 (entries **8**-**11**). Moreover, best result was obtained when 2.0 eq. of base was used (entry **11**). Both poor yield and selectivity were obtained when an *OAc* group was equipped on the C-3 position indicated the importance of decarboxylative pathway for this reaction (entry **12**). ^{1}H NMR spectra specified the ratios of *α*– and *β*–isomers very clearly and selected results are summarized in **Figure 2.3.1**.

Figure 2.3.1 Selectivities confirmed by ^{1}H NMR under different conditions

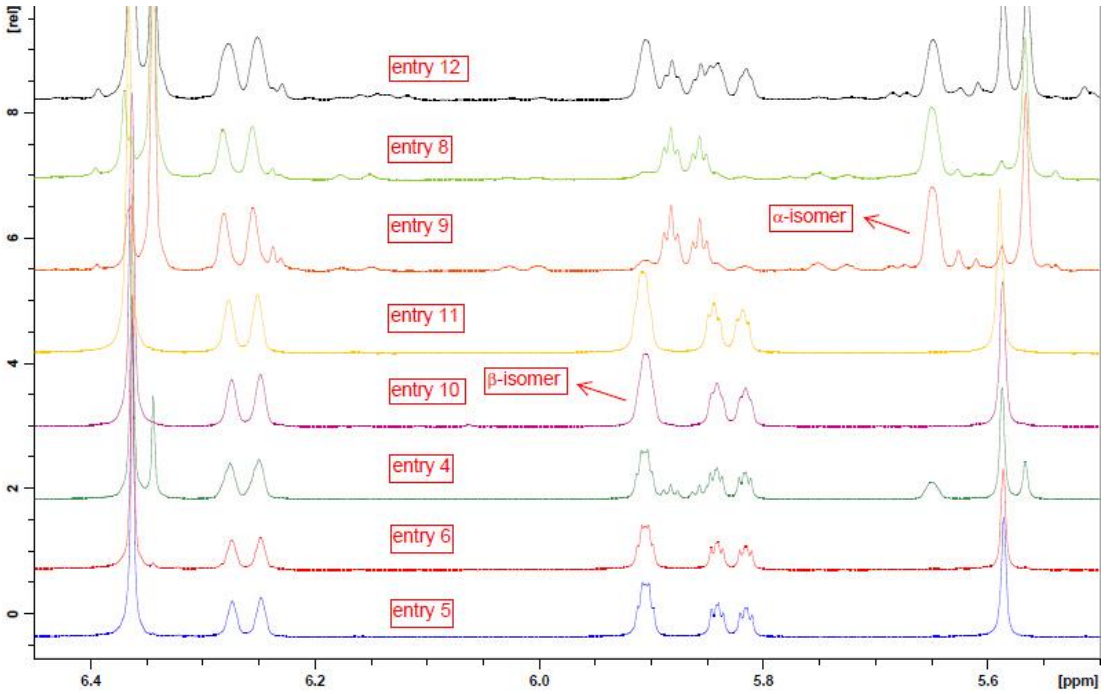
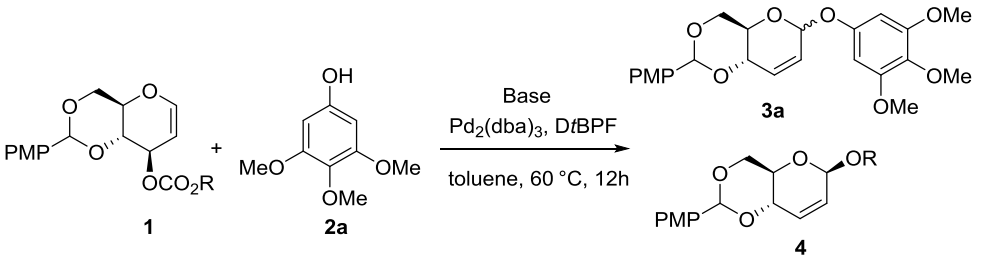


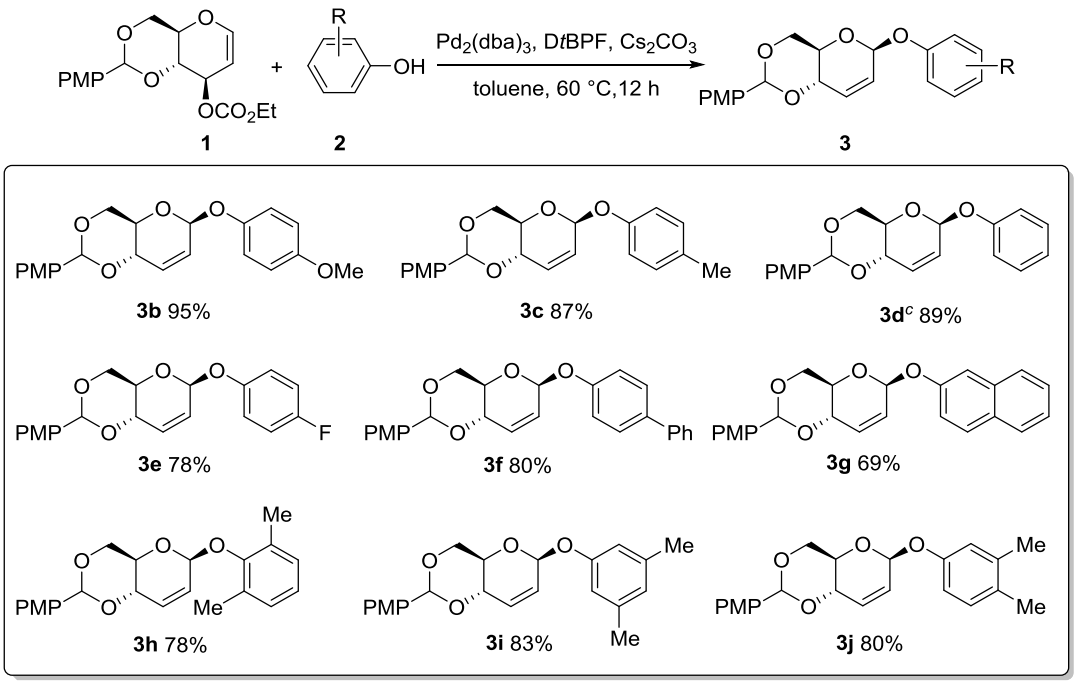
Table 2.3.1 Optimization of reaction conditions [a,b,c]



Entry	R	Base	Base loading	Yield of **3a**	Ratio(α:β)	Yield of **4**
1	Et	-	-	20%	ND	68%
2	Et	NaOEt	1.2	69%	0:1	21%
3	*t*Bu	NaOEt	1.2	55%	ND	25%
4	Et	K_2CO_3	1.2	79%	1:3	-
5	Et	Cs_2CO_3	1.2	92%	0:1	-
6	Et	DBU	1.2	80%	0:1	-
7	Et	NaH	1.2	23%	2:3	-
8	Et	Cs_2CO_3	0.1	45%	6:1	-
9	Et	Cs_2CO_3	0.2	62%	5:1	-
10	Et	Cs_2CO_3	0.5	90%	0:1	-
11	Et	Cs_2CO_3	2.0	93%	0:1	-
12[d]	-	Cs_2CO_3	2.0	45%	1:1	-

[a] Unless otherwise specified, all reactions were carried out with 0.1 mmol **1**, 0.2 mmol **2a**, 0.2 mmol base, 10% catalyst and 20% ligand in toluene at 60 ºC for 12 h. [b] The ratios were determined by ^{1}H NMR. [c] Isolated yield. [d] At the C-3 position, *OCO_2Et* group was replaced by *OAc*.

Scheme 2.3.4 Substrate scope of phenolic *O*-glycosylation [a,b]



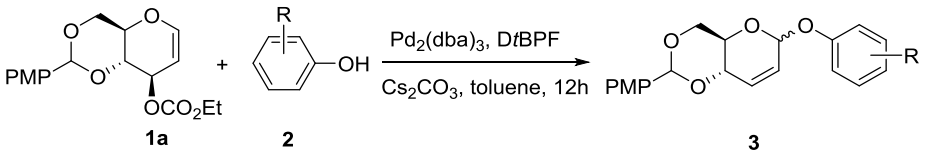
[a] Unless otherwise specified, all reactions were carried out with 0.1 mmol **1**, 0.2 mmol **2**, 0.2 mmol Cs_2CO_3, 10% $Pd_2(dba)_3$ catalyst and 20% D*t*BPF ligand in toluene at 60 °C for 12 h. [b] Isolated yield. [c] Reaction temperature was 50 ºC.

After achieving the optimized conditions, the scope of this reaction was then explored by examining phenol substrates with different substituents. As presented in **Scheme 2.3.4**, 95% yield was obtained when a strong electron-donating methoxy group was installed on phenol (**3b**) while a slightly lower yield was observed for glycosyl acceptor with a weaker electron-donating methyl group (**3c**). With the same reaction conditions, **3d** was obtained in good yield, albeit with a stereoselectivity ratio of α:β = 1:10. By decreasing the temperature to 50 °C, pure β–product was obtained in 89% yield, illustrating that the selectivity was sensitive to the reaction temperature. A fluoro group substituted phenol was then screened and compound **3e** was generated in 78% yield. The reaction with 4-Phenyl phenol and 2-naphthol could also carried

out smoothly to give the desired products **3f** and **3g** in 80% and 69% yields correspondingly. Disubstituted phenols were employed next and similar results were obtained (**3h-3j**). Interestingly, a bulky 2,6-dimethyl phenol was able to give the desired *O*-glycosides in 78% yields (**3h**). Notably, except **3d** mentioned above, only the β–products were observed for all other reactions.

With the exploration of this reaction, it was found that not only the base loading could affect the selectivity of the reaction dramatically as mentioned above, but also the electronic nature of the substituents on the phenol and the reaction temperature. As the results summarized in **Table 2.3.2**, higher selectivity was obtained when the reaction conducted in lower temperature generally. With electron rich phenol as the glycosyl acceptor, good selectivity can be persisted at higher temperatures (entry **1-4**). However, in order to provide good selectivity the reaction temperature should not beyond 60 °C when electron deficient phenol substrate was used. Little difference in yield was observed when the reaction temperature was increased to above 60 °C.

Table 2.3.2 Effects of substituents on the phenol and temperature [a]

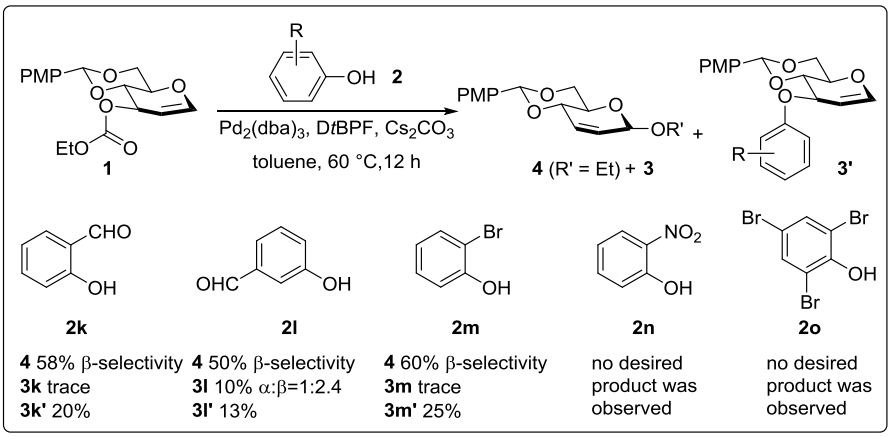


Entry	R	temperature	Ratio (α:β)[b]	Yield of **3**[c]
1	3,4,5-trimethoxy	80	0:1	90%
2	3,4,5-trimethoxy	60	0:1	93%
3	4-methoxy	70	0:1	95%
4	4-methoxy	60	0:1	95%
5	4-fluolo	80	1:1	80%
6	4-fluolo	60	0:1	78%
7	4-phenyl	80	1:1	76%
8	4-phenyl	60	0:1	80%
9	H	60	1:10	92%
10	H	50	0:1	89%
11	4-methyl	80	1:1	89%
12	4-methyl	70	1:11	90%
13	4-methyl	60	0:1	87%
14	3,4-dimethyl	80	1:3	75%
15	3,4-dimethyl	60	0:1	80%
16	3,5-dimethyl	80	1:3	77%
17	3,5-dimethyl	60	0:1	83%

[a] Unless otherwise specified, all reactions were carried out with 0.1 mmol compound **1a**, 0.2 mmol compound **2**, 0.2 mmol Cs_2CO_3, 10% catalyst and 20% ligand in toluene 60 °C for 12 h. [b] The ratios were determined by ^{1}H NMR. [c] Isolated yield.

As further studies about this reaction, it was found that the electronic nature of the substituents can not only affect the stereoselectivity but also the regioselectivity. When electron deficient phenols were utilized in the reaction, nucleophilic addition occurred at C-3 position as well as C-1 position. Meanwhile, byproduct (**4**) generated from the addition of ethoxide to Pd-π-allyl intermediate was obtained as the major product. So the treatment of examined substrate **2k**, **2l** or **2m** with an electron-withdrawing group under optimized reaction conditions to provide *O*-glycoside **4** as the major product (**Scheme 2.3.5**). Although each of the desired product in the reaction mixture was observed by crude NMR, it existed as inseparable α- and β-mixture. Moreover, C-3 position addition products (**3'**) can be isolated in 18%, 13% and 20% yields respectively with excellent β-selectivity.[5] Further investigations revealed that the reactions with highly electron deficient phenols, such as 2-nitro phenol, and 2,4,6-tribromo phenol, gave complex mixture but neither C-3 nor C-1 addition product were detected in the reaction mixture.

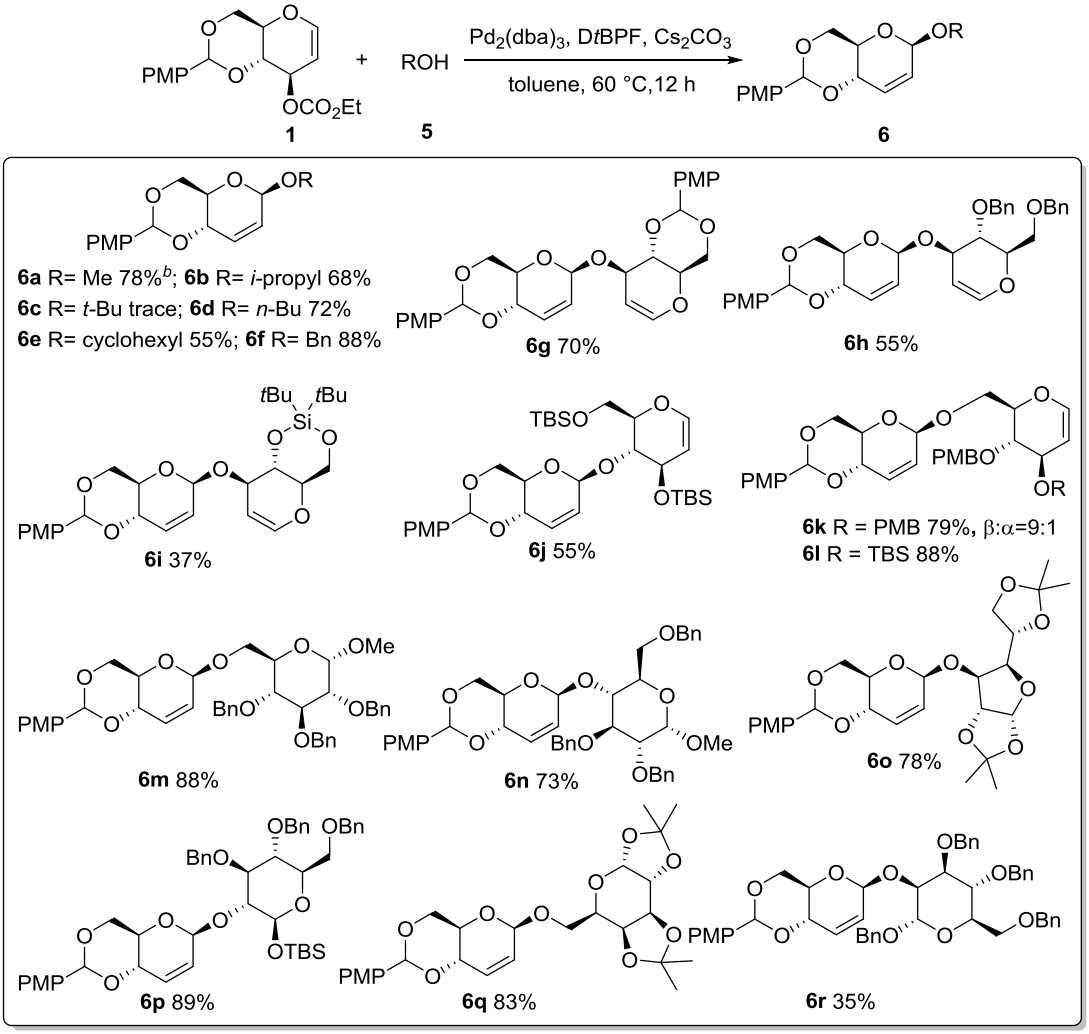
Scheme 2.3.5 Effect of the electronic nature of substituents on the phenol



[a] Unless otherwise specified, all of the reactions were carried out with 0.1 mmol **1**, 0.2 mmol **2**, 0.2 mmol Cs_2CO_3, 10% $Pd_2(dba)_3$ catalyst and 20% D*t*BPF ligand in toluene 60 °C for 12 h. [b] The ratios were determined by ^1H NMR. [c] Isolated yield.

After obtaining satisfactory results with phenol-type substrates, we then set out to investigate the flexibility of this method with aliphatic-type alcohol and attempt to synthesize disaccharides and oligosaccharides. A variety of alcohols were investigated and the results detailed in **Scheme 2.3.6** illustrated that most of the alcohol could be used in this the reaction to give the desired product efficiently with the optimized conditions (**6a**-**6f**) except sterically hindered tertiary butanol (**6c**). Generally, up to 10 equivalents of alcohol was added in each reaction to increase the yield. Next, we focused our attention on the glucals with free hydroxyl group at different positions. To our delight, compounds **6g**-**6i**, which could not be prepared by the intramolecular *O*-glycosylation, were successfully achieved with 3-OH glucals as glycosyl acceptor. The substrate with a free hydroxyl group in C-4 position could also give the desired product excellent β-selectivity, albeit with a lower yield due to the steric effect (**6j**). When more active 6-OH glucal substrates were employed, higher chemical yields (**6k**-**6l**) were obtained. However, a ratio of α:β = 1:10 mixture was observed when PMB was selected as the protecting group of glucal. Glucose derived substrates bearing a free hydroxyl group in different position were then screened and gratifyingly, all the reaction underwent smoothly to give the desire product in good to excellent yields with excellent β–selectivity (**6m**-**6p**). The generality of this method was further proved by the syntheses of galactose and mannose type *O*-glycosides with yields of 83% and 35% respectively (**6q**-**6r**).

Scheme 2.3.6 Substrate scope of aliphatic *O*-glycosides and disaccharides [a,b]

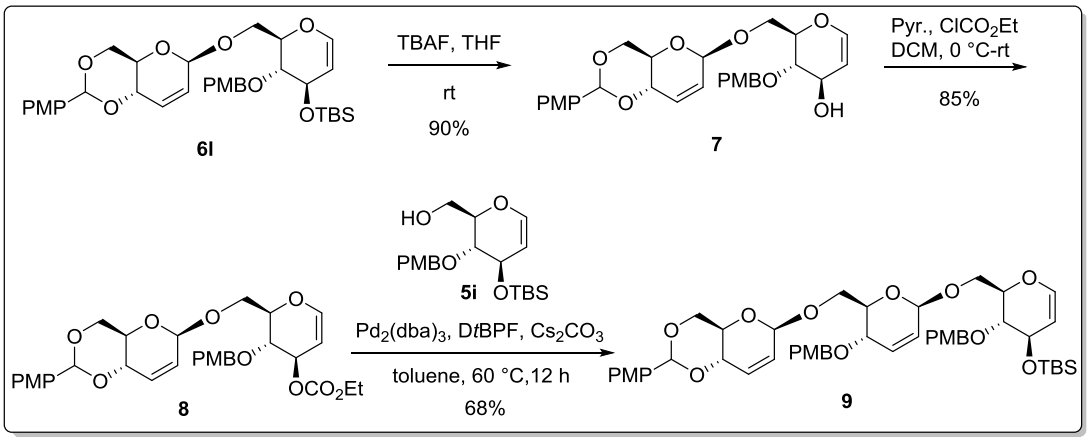


[a] Unless otherwise specified, all reactions were carried out with 0.1 mmol compound **1**, compound **5** (**5a-5f** 1.0 mmol; **5g-5r** 0.2 mmol), 0.2 mmol Cs_2CO_3, 10% $Pd_2(dba)_3$ catalyst and 20% D*t*BPF ligand in toluene at 60 °C for 12 h. [b] Isolated yield.

To illustrate the synthetic utility of this approach, trisaccharide **9** was then designed to synthesize by a second palladium catalyzed glycosylation. The detailed procedures were shown in **Scheme 2.3.7**. Compound **6l** was employed as the starting material to commence the synthesis and intermediate **7** was provided by a deprotection of TBS group with TBAF solution. The starting material for the second glycosylation,

disaccharide carbonate **8**, was prepared by a coupling reaction. After that, compound **8** was treated under optimized condition with compound **5i** as glycosyl acceptor and fortunately, desired product **9** was isolated in 68% yield with exclusive β-selectivity. The successful access to trisaccharide **9** demonstrates the potential of this methodology in the synthesis of more complex oligosaccharide.

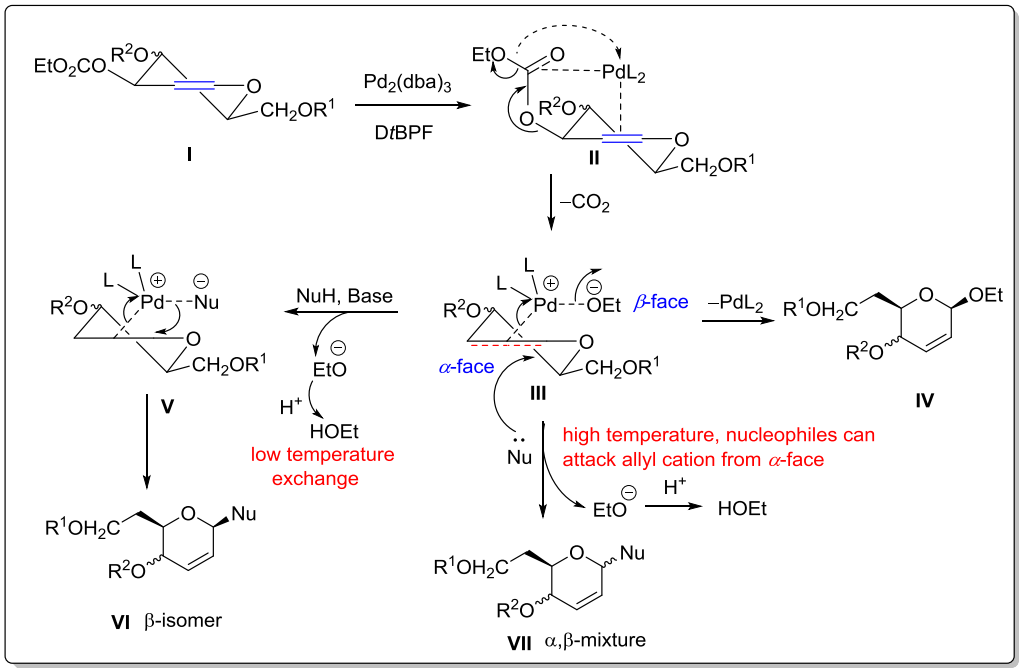
Scheme 2.3.7 Preparation of the trisaccharide **9**



Based on the results presented above and knowledge of related palladium catalyzed reactions,[6] we therefore propose the following plausible mechanism. Similar to traditional palladium catalyzed decarboxylative allylation, we suggested this reaction began at the coordination of palladium complex to compound **I** from the β-face to generate palladium intermediate **II**. Then, intermediate **III** with an ion pair structure was generated by a subsequent decarboxylative reaction. Without the presence of other nucleophiles, intramolecular glycosylation product **IV** is obtained through elimination of Pd-species. With the addition of an external nucleophile, Pd-intermediate **V** was yielded by a proton transfer. Thereafter, β-product **VI** was obtained by the elimination of Pd species. Besides that, nucleophile addition to the

allyl cation from less hinder α-face can furnish the α-product simultaneously at high temperature. Therefore, a mixture of α– and β–isomer **VII** was detected in harsh conditions.

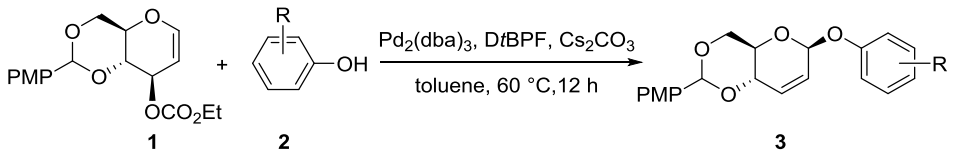
Scheme 2.3.8 Plausible mechanism



Conclusion

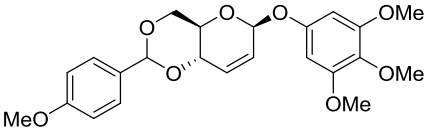
In conclusion, a palladium catalyzed *O*-glycosylation based on a decarboxylative allylation have been developed in our group. Starting from readily available glycal derived carbonate, a board range of glycosyl acceptors were examined and the desired *O*-glycosides, including disaccharides, were generated in moderate to good yields with excellent selectivity. The results from our experiments also demonstrated this reaction was very sensitive to the nature and loading of base, reaction temperature and electronic nature of substrates. In addition, this method not only provides a practical and concise approach to some glycosides which could not be prepared using the method described in the previous chapter but also presented C-3 addition product using electron deficient phenols. The utility of this method was further illustrated by the synthesis of a trisaccharide *via* iterative glycosylation. Further application for the synthesis of complex oligosaccharides is currently progress.

General procedure for preparing phenolic *O*-glycosides



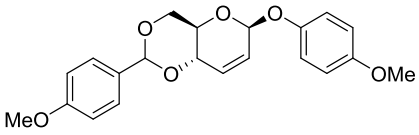
To a mixture of D*t*BPF (0.02 mmol), $Pd_2(dba)_3$ (0.01 mmol), carbonate **1** (0.1 mmol), phenol **2** (0.2 mmol) and Cs_2CO_3 (0.2 mmol) was added toluene (2 mL) under an atmosphere of argon. After stirring at 60 °C for 12 hours, the solvent was removed under reduced pressure to give crude product which was further purified by column chromatography to afford the desired phenolic *O*-glycosides **3** with 69-95% yields.

(4aR,6S,8aS)-2-(4-methoxyphenyl)-6-(3,4,5-trimethoxyphenoxy)-4,4a,6,8a-tetra hydropyrano[3,2-d][1,3]dioxine (3a)



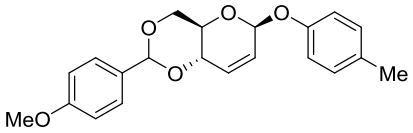
Following the general procedure, phenolic *O*-glycoside **3a** (40.0 mg, 93%) was obtained as a white solid. m.p. 153-155 °C; $[\alpha]_D^{23}$ = +15.0 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 1088, 1215, 1415, 1477, 1616, 1695, 2303, 3016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.79-3.94 (m, 14H), 4.26-4.34 (m, 1H), 4.39-4.44 (m, 1H), 5.59 (s, 1H), 5.83 (ddd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.8 Hz, 1H), 5.89-5.92 (m, 1H), 6.26 (d, *J* = 10.3 Hz, 1H), 6.36 (s, 2H), 6.86-6.93 (m, 2H), 7.41-7.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 56.1, 60.9, 68.9, 71.0, 74.6, 95.1, 97.2, 102.1, 113.7, 126.9, 127.5, 129.6, 132.3, 133.9, 153.1, 153.6, 160.2 ppm; HRMS (ESI) calcd. for $C_{23}H_{26}O_8Na$ [M+Na]: 453.1525, found: 453.1522.

(4a*R*,6S,8a*S*)-6-(4-Methoxyphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyra no[3,2-d][1,3]dioxine (3b)



Following the general procedure, phenolic *O*-glycoside **3b** (35.1 mg, 95%) was obtained as a white solid. m.p. 140-142 °C; $[\alpha]_D^{23}$ = +31.2 (*c* = 1.0 in $CHCl_3$); IR (neat) *ν*: 1023, 1085, 1411, 1479, 1523, 1620, 1694, 2308, 3018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 3.77 (s, 3H), 3.80 (s, 3H), 3.83-3.94 (m, 2H), 4.28-4.34 (m, 1H), 4.37-4.42 (m, 1H), 5.58 (s, 1H), 5.80-5.86 (m, 2H), 6.23 (d, *J* = 10.5 Hz, 1H), 6.80-6.86 (m, 2H), 6.87-6.93 (m, 2H), 7.01-7.07 (m, 2H), 7.43 (d, *J* = 8.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 55.3, 55.6, 69.0, 70.9, 74.7, 97.8, 102.1, 113.7, 114.5, 118.4, 127.3, 127.5, 129.7, 132.0, 150.7, 155.3, 160.2 ppm; HRMS (ESI) calcd. for $C_{21}H_{22}O_6Na$ [M+Na]: 393.1350, found: 393.1350.

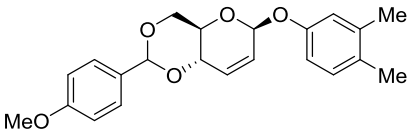
(4aR,6S,8aS)-2-(4-methoxyphenyl)-6-(p-tolyloxy)-4,4a,6,8a-tetrahydropyrano [3,2-d][1,3]dioxine (3c)



Following the general procedure, phenolic *O*-glycoside **3c** (30.8 mg, 87%) was obtained as a white solid. m.p. 154-156 °C; $[\alpha]_D^{23}$ = +26.6 (*c* = 1.0 in $CHCl_3$); IR (neat) *ν*: 1032, 1215, 1423, 1474, 1520, 3019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 2.30 (s, 3H), 3.79 (s, 3H), 3.82-3.92 (m, 2H), 4.25-4.35 (m, 1H), 4.38-4.42 (m, 1H), 5.57 (s, 1H), 5.82 (ddd, J_1 = 10.3 Hz, J_2 = 2.5 Hz, J_3 = 1.7 Hz, 1H), 5.88-5.91 (m, 1H), 6.23 (d, *J* = 10.3 Hz, 1H), 6.87-6.92 (m, 2H), 6.96-7.01 (m, 2H), 7.07-7.11 (m, 2H), 7.40-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 20.6, 55.3, 69.0, 70.9, 74.7,

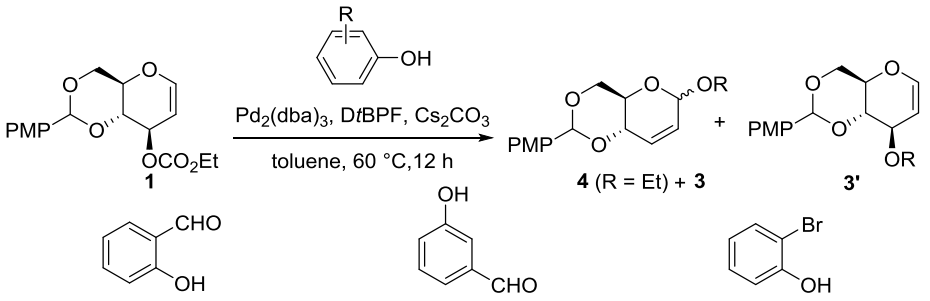
97.0, 102.0, 113.7, 116.8 127.3, 127.5, 129.7, 129.9, 132.0, 132.1, 154.6, 160.2 ppm; HRMS (ESI) calcd. for $C_{21}H_{22}O_5Na$ [M+Na]: 377.1365, found: 377.1359.

(4aR,6S,8aS)-6-(3,4-dimethylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (3j)



Following the general procedure, phenolic *O*-glycoside **3j** (29.4 mg, 80%) was obtained as a white solid. m.p. 107-109 °C; $[\alpha]_D^{23}$ = +29.9 (*c* = 1.0 in $CHCl_3$); IR (neat) *ν*: 1088, 1126, 1217, 1382, 1423, 1476, 1517, 1614, 3022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.24 (s, 3H), 3.80 (s, 3H), 3.83-3.93 (m, 2H), 4.26-4.35 (m, 1H), 4.38-4.43 (m, 1H), 5.58 (s, 1H), 5.79-5.86 (m, 1H), 5.88-5.93 (m, 1H), 6.23 (d, *J* = 10.3 Hz, 1H), 6.81-6.93 (m, 4H), 7.01-7.06 (m, 1H), 7.40-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 20.0, 55.3, 69.0, 71.0, 74.8, 97.1, 102.1, 113.7, 114.1, 118.4, 127.4, 127.5, 129.8, 130.3, 130.8, 131.9, 137.8, 154.9, 160.2 ppm; HRMS (ESI) calcd. for $C_{22}H_{24}O_5Na$ [M+Na]: 391.1521, found: 391.1517.

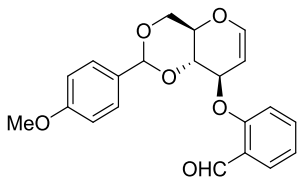
General procedure for preparing compounds 3k', 3l' and 3m'



To a mixture of D*t*BPF (0.02 mmol), $Pd_2(dba)_3$ (0.01 mmol), carbonate **1** (0.1 mmol), phenol **2** (0.2 mmol) and Cs_2CO_3 (0.2 mmol) was added toluene (2 mL) under an

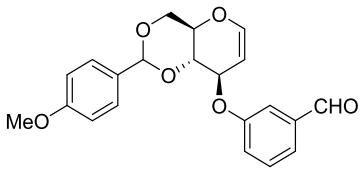
atmosphere of argon. After stirring at 60 °C for 12 hours, the solvent was removed under reduced pressure to give crude product which was further purified by column chromatography to afford compound **3'** with 13-25% yields. For these three substrates, compound **4** was obtained as the major product and compound **3** was observed as a mixture.

2-((4aR,8R,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3] dioxin-8-yloxy)phenol (3k')



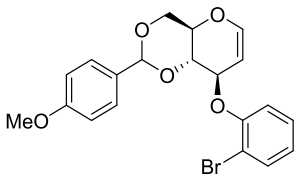
Following the general procedure, compound **3k'** (7.4 mg, 20%) was obtained as a white solid. m.p. 122-124 °C; $[\alpha]_D^{23}$ **= -**123.5 (*c* = 0.35 in $CHCl_3$); IR (neat) *ν*: 1029, 1212, 1415, 1474, 1519, 1603, 3018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 3.90 (t, J = 10.4 Hz, 1H), 4.06 (dt, J_1 = 10.2 Hz, J_2 = 5.1 Hz, 1H), 4.23 (dd, J_1 = 10.3 Hz, J_2 = 7.5 Hz, 1H), 4.43 (dd, J_1 = 10.6 Hz, J_2 = 5.1 Hz, 1H), 4.92 (dd, J_1 = 6.2 Hz, J_2 = 1.8 Hz, 1H), 5.16-5.22 (m, 1H), 5.62 (s, 1H), 6.46 (dd, J_1 = 6.2 Hz, J_2 = 1.2 Hz, 1H), 6.87 (dd, J_1 = 9.6 Hz, J_2 = 2.8 Hz, 2H), 7.05 (t, J = 7.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.33-7.40 (m, 2H), 7.47-7.55 (m, 1H), 7.83 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 68.2, 68.9, 73.6, 78.1, 99.8, 101.5, 113.6, 115.1, 121.5, 126.0, 127.3, 128.4, 129.3, 135.7, 145.8, 160.2, 160.5, 189.8 ppm; HRMS (ESI) calcd. for $C_{21}H_{21}O_6$ [M+H]: 369.1338, found: 369.1337.

3-((4aR,8R,8aS)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3] dioxin-8-yloxy)phenol (3l')



Following the general procedure, compound **3l'** (4.8 mg, 13%) was obtained as a white solid. m.p. 129-131 °C; $[\alpha]_D^{23}$ **=** -33.2 (c = 0.30 in $CHCl_3$); IR (neat) ν: 1125, 1214, 1416, 1477, 1517, 1602, 3020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 3.89 (t, J = 10.4 Hz, 1H), 4.06 (dt, J_1 = 10.2 Hz, J_2 = 5.1 Hz, 1H), 4.17 (dd, J_1 = 10.3 Hz, J_2 = 7.5 Hz, 1H), 4.41 (dd, J_1 = 10.6 Hz, J_2 = 5.1 Hz, 1H), 4.89 (dd, J_1 = 6.2 Hz, J_2 = 1.6 Hz, 1H), 5.13-5.19 (m, 1H), 5.61 (s, 1H), 6.42-6.47 (m, 1H), 6.83-6.89 (m, 2H), 7.22-7.26 (m, 1H), 7.35-7.50 (m, 4H), 7.50-7.54 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 68.2, 68.9, 72.7, 78.2, 100.0, 101.5, 115.2, 123.2, 123.6, 127.4, 129.4, 113.6, 130.1, 137.8, 145.5, 158.4, 160.2, 191.9 ppm; HRMS (ESI) calcd. for $C_{21}H_{21}O_6$ [M+H]: 369.1338, found: 369.1342.

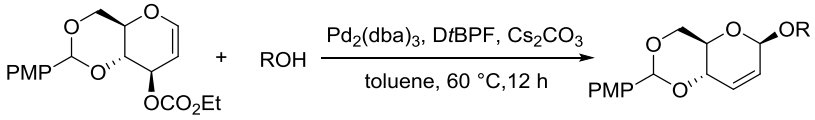
(4aR,8R,8aS)-8-(2-bromophenoxy)-2-(4-methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3]dioxine (3m')



Following the general procedure, compound **3m'** (10.5 mg, 25%) as a white solid. m.p. 92-94 °C; $[\alpha]_D^{23}$ **=** -60.8 (c = 0.75 in $CHCl_3$); IR (neat) ν: 1027, 1133, 1179, 1216, 1514, 1603, 3023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 3.88 (t, J = 10.4 Hz, 1H), 4.00 (dt, J_1 = 10.2 Hz, J_2 = 5.1 Hz, 1H), 4.27 (dd, J_1 = 10.2 Hz, J_2 = 7.5 Hz, 1H), 4.40 (dd, J_1 = 10.4 Hz, J_2 = 5.0 Hz, 1H), 4.95 (dd, J_1 = 6.2 Hz, J_2 = 1.8 Hz, 1H), 5.02-5.09 (m, 1H), 5.62 (s, 1H), 6.40-6.46 (m, 1H), 6.82-6.91 (m, 3H), 7.09-7.15

(m, 1H), 7.18-7.25 (m, 1H), 7.31-7.39 (m, 2H), 7.53 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 68.2, 68.9, 75.0, 78.5, 100.7, 101.2, 113.5, 114.0, 117.4, 123.0, 127.3, 128.3, 129.5, 133.4, 145.3, 155.0, 160.0 ppm; HRMS (ESI) calcd. for $C_{20}H_{20}O_5Br$ [M+H]: 419.0494, found: 419.0493.

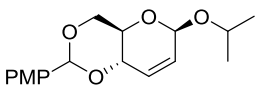
General procedure for preparing aliphatic *O*-glycosides



1 **5** **6**

To a mixture of D*t*BPF (0.02 mmol), $Pd_2(dba)_3$ (0.01 mmol), carbonate **1** (0.1 mmol), alcohol **5** (**5a-5f**, 1.0 mmol) and Cs_2CO_3 (0.2 mmol) was added toluene (2 mL) under an atmosphere of argon. After stirring at 60 °C for 12 hours, the solvent was removed under reduced pressure to give crude product which was further purified by column chromatography to afford the desired aliphatic *O*-glycosides **6a-6f** with 55-88% yields.

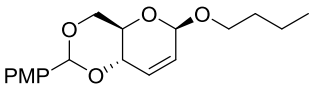
(4aR,6R,8aS)-6-isopropoxy-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano [3,2-d][1,3]dioxine (6b)



Following the general procedure, aliphatic *O*-glycoside **6b** (20.8 mg, 68%) was obtained as a white solid. m.p. 83-85 °C; $[\alpha]_D^{23}$ = +36.6 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 1032, 1219, 1462, 1518, 1595, 1614, 3016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 3.70-3.77 (m, 1H), 3.80 (s, 3H), 3.86 (t, *J* = 10.3 Hz, 1H), 4.03 (septet, *J* = 6.2 Hz, 1H), 4.26 (dd, J_1 = 10.2 Hz, J_2 = 4.5 Hz, 1H), 4.30-4.36 (m, 1H), 5.37-5.41 (m, 1H), 5.60 (s, 1H), 5.62-5.69 (m, 1H), 6.09 (d, *J* = 10.3 Hz, 1H), 6.86-6.91 (m, 2H), 7.39-7.45 (m, 2H) ppm; ^{13}C NMR (100

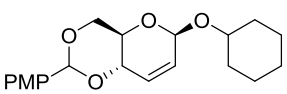
MHz, $CDCl_3$): δ 22.1, 23.6, 55.3, 69.1, 70.5, 71.0, 75.0, 97.3, 102.0, 113.7, 127.5, 129.1, 129.9, 130.8, 160.1 ppm; HRMS (ESI) calcd. for $C_{17}H_{22}O_5Na$ [M+Na]: 329.1365, found: 329.1368.

(4aR,6R,8aS)-6-butoxy-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (6d)



Following the general procedure, aliphatic *O*-glycoside **6d** (23.0 mg, 72%) was obtained as a white solid. m.p. 76-78 °C; $[\alpha]_D^{23}$ = +43.4 (c = 1.0 in $CHCl_3$); IR (neat) ν: 1248, 1422, 1517, 1614, 3017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, J = 7.4 Hz, 6H), 1.33-1.45 (m, 2H), 1.57-1.65 (m, 2H), 3.48-3.57 (m, 1H), 3.70-3.89 (m, 6H), 4.24-4.34 (m, 2H), 5.31-5.35 (m, 1H), 5.59 (s, 1H), 5.65-5.72 (m, 1H), 6.12 (d, J = 10.3 Hz, 1H), 6.86-6.92 (m, 2H), 7.39-7.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 19.2, 31.7, 55.2, 68.0, 69.0, 70.4, 75.0, 98.6, 102.0, 113.7, 127.5, 128.5, 129.8, 131.1, 160.1 ppm; HRMS (ESI) calcd. for $C_{18}H_{25}O_5$ [M+H]: 321.1702, found: 321.1689.

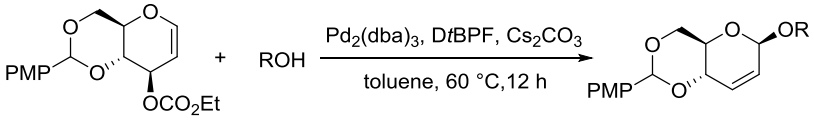
(4aR,6R,8aS)-6-(cyclohexyloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (6e)



Following the general procedure, aliphatic *O*-glycoside **6e** (19.0 mg, 55%) was obtained as a white solid. m.p. 108-110 °C; $[\alpha]_D^{23}$ = +33.7 (c = 1.0 in $CHCl_3$); IR (neat) ν: 1029, 1085, 1252, 1616, 3016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13-1.46 (m, 6H), 1.69-1.80 (m, 2H), 1.87-2.01 (m, 2H), 3.64-3.90 (m, 6H), 4.26 (dd, J_1 =

10.2 Hz, J_2 = 4.5 Hz, 1H), 4.31-4.37 (m, 1H), 5.41-5.46 (m, 1H), 5.56 (s, 1H), 5.63-5.70 (m, 1H), 6.09 (d, J = 10.3 Hz, 1H), 6.86-6.91 (m, 2H), 7.39-7.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 24.3, 25.5, 32.2, 33.7, 55.3, 69.1, 70.5, 75.1, 76.7, 97.1, 102.0, 113.7, 127.5, 129.3, 129.9, 130.7, 160.1 ppm; HRMS (ESI) calcd. for $C_{20}H_{27}O_5$ [M+H]: 347.1858, found: 347.1865.

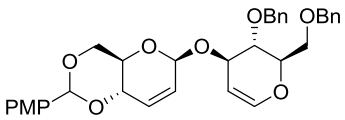
General procedure for preparing disaccharides



1 **5** **6**

To a mixture of D*t*BPF (0.02 mmol), $Pd_2(dba)_3$ (0.01 mmol), carbonate **1** (0.1 mmol), alcohol **5** (**5g**-**5r**, 0.2 mmol) and Cs_2CO_3 (0.2 mmol) was added toluene (2 mL) under an atmosphere of argon. After stirring at 60 °C for 12 hours, the solvent was removed under reduced pressure to give the crude product which was further purified by column chromatography to afford the desired disaccharides **6g-6r** with 35-89% yields.

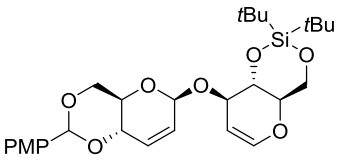
(4aR,6R,8aS)-6-((2R,3S,4R)-3-(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-4-yloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3] dioxide (6h)



Following the general procedure, disaccharide **6h** (31.5 mg, 55%) was obtained as a white solid. m.p. 94-96 °C; $[\alpha]_D^{23}$ = +54.6 (c = 0.7 in $CHCl_3$); IR (neat) ν: 1218, 1466, 1523, 1596, 1614, 2303, 3016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69-3.82 (m, 7H), 3.85 (dd, J_1 = 7.9 Hz, J_2 = 5.8 Hz, 1H), 4.08-4.15 (m, 1H), 4.18-4.26 (m, 2H), 4.45-4.51 (m, 1H), 4.55-4.66 (m, 3H), 4.83-4.91 (m, 2H), 5.48-5.53 (m, 2H), 5.60 (ddd, J_1

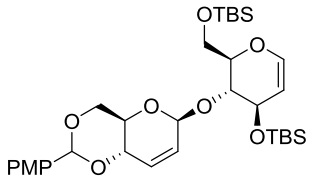
= 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.5 Hz, 1H), 6.12 (d, J = 10.3 Hz, 1H), 6.41-6.46 (m, 2H), 6.86-6.92 (m, 2H), 7.26-7.43 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.5, 69.0, 70.6, 72.8, 73.4, 74.2, 75.0, 96.9, 99.8, 102.0, 113.7, 127.5, 127.6, 127.7, 127.9, 128.3, 128.4(2C), 129.8, 131.5, 138.0, 138.3, 144.9, 160.2 ppm; HRMS (ESI) calcd. for $C_{34}H_{36}O_8Na$ [M+Na]: 595.2308, found: 595.2331.

(4aR,8R,8aS)-2,2-di-tert-butyl-8-((4aR,6R,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yloxy)-4,4a,8,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasiline (6i)



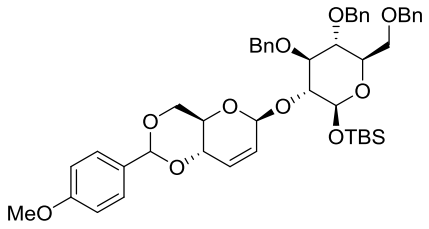
Following the general procedure, disaccharide **6i** (19.7 mg, 37%) was obtained as colorless oil. $[\alpha]_D^{23}$ = +57.4 (c = 0.44 in $CHCl_3$); IR (neat) ν: 1258, 1523, 1608, 1655, 3016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (s, 9H), 1.08 (s, 9H), 3.72-3.88 (m, 6H), 3.97 (t, J = 10.3 Hz, 1H), 4.09 (dd, J_1 = 10.3 Hz, J_2 = 7.3 Hz, 1H), 4.16 (dd, J_1 = 10.3 Hz, J_2 = 4.9 Hz, 1H), 4.25-4.36 (m, 3H), 4.78 (dd, J_1 = 6.0 Hz, J_2 = 2.0 Hz, 1H), 5.58 (s, 1H), 5.65-5.70 (m, 1H), 5.71-5.78 (m, 1H), 6.16 (d, J = 10.3 Hz, 1H), 6.27 (dd, J_1 = 6.0 Hz, J_2 = 1.4 Hz, 1H), 6.86-6.92 (m, 2H), 7.39-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9, 22.7, 26.9, 27.4, 55.3, 65.8, 69.1, 71.0, 73.1, 74.0, 74.9, 75.0, 97.9, 102.0, 103.4, 113.7, 127.5, 129.3, 129.8, 131.4, 144.0, 160.2 ppm; HRMS (ESI) calcd. for $C_{28}H_{40}O_8NaSi$ [M+Na]: 555.2390, found: 555.2380.

tert-butyl(((2R,3R,4S)-4-(tert-butyldimethylsilyloxy)-3-((4aR,6S,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yloxy)-3,4-dihydro-2H-pyran-2-yl)methoxy)dimethylsilane (6j)



Following the general procedure, disaccharide **6j** (34.1 mg, 55%) was obtained as colorless oil. $[\alpha]_D^{23}$ = +20.0 (*c* = 1.0 in $CHCl_3$); IR (neat) *ν*: 1082, 1254, 1522, 1614, 1650, 3015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.05-0.09 (m, 6H), 0.09-0.13 (m, 6H), 0.87-0.94 (m, 18H), 3.72 (ddd, J_1 = 10.3 Hz, J_2 = 8.4 Hz, J_3 = 4.6 Hz, 1H), 3.78-3.88 (m, 5H), 3.91-4.04 (m, 3H), 4.19-4.28 (m, 2H), 4.28-4.34 (m, 1H), 4.70 (dd, J_1 = 6.1 Hz, J_2 = 3.5 Hz, 1H), 5.54-5.58 (m, 2H), 5.73 (ddd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.3 Hz, 1H), 6.10 (d, *J* = 10.3 Hz, 1H), 6.32 (dd, J_1 = 6.2 Hz, J_2 = 0.7 Hz, 1H), 6.86-6.91 (m, 2H), 7.39-7.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.3, -5.2, -4.6(2C), 18.1, 18.3, 25.8, 25.9, 55.3, 61.5, 66.5, 69.0, 70.7, 74.8, 75.0, 78.0, 98.4, 102.0, 102.5, 113.7, 127.5, 128.4, 129.8, 131.1, 143.3, 160.1 ppm; HRMS (ESI) calcd. for $C_{32}H_{52}O_8NaSi_2$ [M+Na]: 643.3098, found: 643.3106.

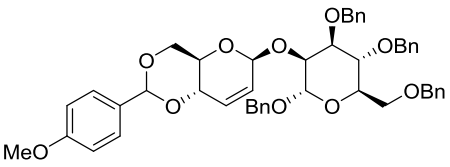
((2S,3R,4S,5R,6R)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-3-((4aR,6S,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yloxy)tetrahydro-2H-pyran-2-yloxy)(tert-butyl)dimethylsilane (6p)



Following the general procedure, disaccharide **6p** (72.1 mg, 89%) was obtained as colorless oil. $[\alpha]_D^{23}$ = +28.7 (*c* = 1.0 in $CHCl_3$); IR (neat) *ν*: 1214, 1252, 1520, 1614, 1650, 3016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.15 (s, 3H), 0.17 (s, 3H), 0.95 (s,

9H), 3.40-3.49 (m, 1H), 3.53-3.73 (m, 6H), 3.75-3.85 (m, 4H), 4.21 (dd, J_1 = 10.2 Hz, J_2 = 4.5 Hz, 1H), 4.25-4.32 (m, 1H), 4.51-4.65 (m, 4H), 4.77-4.88 (m, 3H), 5.53 (s, 1H), 5.60-5.66 (m, 1H), 5.68-5.75 (m, 1H), 6.03 (d, J = 10.3 Hz, 1H), 6.85-6.91 (m, 2H), 7.17-7.43 (m, 17H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.3, -4.1, 18.1, 25.7, 55.2, 68.9(2C), 70.8, 73.4, 74.9, 75.7, 78.2, 81.2, 84.6, 97.0, 99.6, 101.9, 113.6, 127.4(2C), 127.5, 127.7(2C), 127.8, 127.9, 128.3, 128.4(2C), 129.8, 130.4, 138.0, 138.2, 138.3, 160.1 ppm; HRMS (ESI) calcd. for $C_{47}H_{58}O_{10}NaSi$ [M+Na]: 833.3697, found: 833.3661.

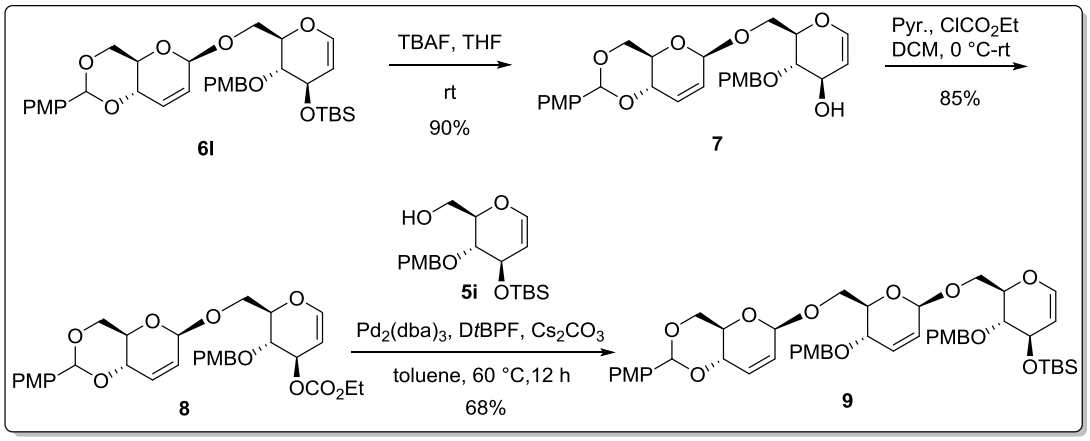
(4aR,6S,8aS)-2-(4-methoxyphenyl)-6-((2S,3S,4S,5R,6R)-2,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-3-yloxy)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (6r)



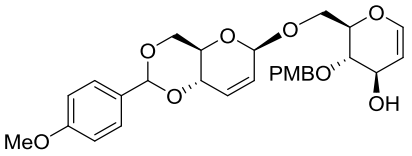
Following the general procedure, disaccharide **6r** (27.5 mg, 35%) was obtained as colorless oil. $[\alpha]_D^{23}$ = +77.3 (c = 1.0 in $CHCl_3$); IR (neat) ν: 1079, 1251, 1523, 1612, 1649, 3014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.47 (t, J = 10.3 Hz, 1H), 3.60-3.69 (m, 1H), 3.70-3.87 (m, 6H), 3.87-3.93 (m, 1H), 3.93-3.99 (m, 1H), 4.05-4.16 (m, 3H), 4.46-4.58 (m, 3H), 4.61-4.69 (m, 2H), 4.69-4.76 (m, 2H), 4.88 (d, J = 10.8 Hz, 1H), 5.01-5.06 (m, 1H), 5.45 (s, 1H), 5.52-5.57 (m, 1H), 5.63-5.69 (m, 1H), 6.13 (d, J = 10.3 Hz, 1H), 6.86-6.92 (m, 2H), 7.14-7.19 (m, 2H), 7.23-7.43 (m, 20H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 68.7(2C), 69.2, 70.6, 71.6, 71.8, 72.1, 73.4, 74.8, 75.1, 78.7, 97.7(2C), 101.9, 113.7, 127.5, 127.6(2C), 127.8, 127.9, 128.1, 128.3(3C),

128.4, 129.8, 132.2, 137.4, 138.3, 138.4(2C), 160.2 ppm; HRMS (ESI) calcd. for $C_{48}H_{50}O_{10}Na$ [M+Na]: 809.3302, found: 809.3300.

Preparation of trisaccharide 9



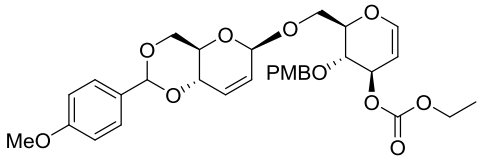
(2R,3S,4R)-3-(4-methoxybenzyloxy)-2-(((4aR,6R,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yloxy)methyl)-3,4-dihydro-2H-pyran-4-ol (7)



Compound **6l** (0.5 mmol) was dissolved in THF (10 ml) under an atmosphere of N_2 and the solution was cooled to 0 °C. After stirring at 0 °C for 10 min, TBAF (1.0 M solution in THF, 0.7 ml) was added over duration of 5 min. The mixture was then allowed to warm to room temperature. After stirring for overnight, the solvent was removed under reduce pressure to give a crude product which was further purified by column chromatography to afford compound **7** (230.6 mg, 90%) as a colorless oil. $[\alpha]_D^{23}$ = +57.5 (*c* = 1.0 in $CHCl_3$); IR (neat) *ν*: 1215, 1244, 1521, 1616, 1652, 3020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.76-1.84 (m, 1H), 3.61 (dd, J_1 = 9.4 Hz, J_2 =

6.6 Hz, 1H), 3.70-3.78 (m, 1H), 3.78-3.90 (m, 8H), 3.97 (ddd, J_1 = 9.3 Hz, J_2 = 4.5 Hz, J_3 = 2.3 Hz, 1H), 4.09 (dd, J_1 = 10.8 Hz, J_2 = 2.3 Hz, 1H), 4.22-4.39 (m, 3H), 4.68-4.79 (m, 3H), 5.40-5.46 (m, 1H), 5.55 (s, 1H), 5.70 (ddd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.5 Hz, 1H), 6.13-6.21 (m, 1H), 6.37 (dd, J_1 = 6.0 Hz, J_2 = 1.4 Hz, 1H), 6.86-6.94 (m, 4H), 7.27-7.33 (m, 2H), 7.39-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 65.5, 68.9, 69.5, 70.6, 73.4, 74.8, 76.4, 76.5, 98.6, 102.0, 102.9, 113.7, 114.0, 127.5, 127.8, 129.6, 129.7, 130.3, 132.0, 144.4, 159.4, 160.2 ppm; HRMS (ESI) calcd. for $C_{28}H_{32}O_9Na$ [M+Na]: 535.1944, found: 535.1943.

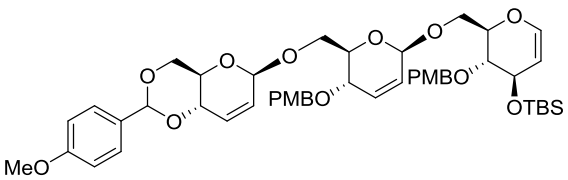
ethyl(2R,3S,4R)-3-(4-methoxybenzyloxy)-2-(((4aR,6R,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yloxy)methyl)-3,4-dihydro-2H-pyran-4-yl carbonate (8)



To a solution of compound **7** (0.2 mmol) in DCM (5 ml) was added pyridine (1.0 mmol) at 0 °C. Then ethyl chloroformate (0.8 mmol) was added slowly. The mixture was allowed to warm to room temperature and stir overnight. After the reaction was completed, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to provide compound **8** (99.4 mg, 85%) as a colorless oil. $[\alpha]_D^{23}$ = +43.3 (c = 1.0 in $CHCl_3$); IR (neat) ν: 1128, 1243, 1417, 1522, 1616, 1649, 3022 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (t, J = 7.1 Hz, 3H), 3.71-3.79 (m, 1H), 3.79-3.94 (m, 9H), 4.04 (dd, J_1 = 10.9 Hz, J_2 = 2.7 Hz, 1H), 4.10-4.15 (m, 1H), 4.20-4.34 (m, 4H), 4.60-4.68 (m, 1H), 4.70-4.78 (m, 1H), 4.87 (dd, J_1 = 6.1 Hz, J_2 = 3.0 Hz, 1H), 5.27-5.35 (m, 1H), 5.38-5.44 (m, 1H), 5.57 (s, 1H), 5.66-5.74

(m, 1H), 6.15-6.22 (m, 1H), 6.47 (dd, J_1 = 6.1 Hz, J_2 = 0.8 Hz, 1H), 6.87-6.95 (m, 4H), 7.26-7.34 (m, 2H), 7.40-7.48 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 55.2, 64.0, 65.0, 68.9, 70.5, 72.6, 73.0, 74.2, 74.8, 76.3, 98.5, 98.6, 101.9, 113.6, 113.8, 127.4, 127.7, 129.4, 129.7, 129.8, 131.9, 145.9, 154.6, 159.3, 160.1 ppm; HRMS (ESI) calcd. for $C_{31}H_{36}O_{11}Na$ [M+Na]: 607.2155, found: 607.2148.

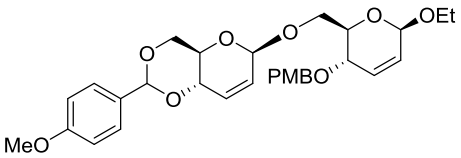
tert-butyl((2R,3R,4R)-3-(4-methoxybenzyloxy)-2-(((2R,5S,6R)-5-(4-methoxybenzyloxy)-6-(((4aR,6R,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yloxy)methyl)-5,6-dihydro-2H-pyran-2-yloxy)methyl)-3,4-dihydro-2H-pyran-4-yloxy)dimethylsilane (9)



To a mixture of D*t*BPF (0.02 mmol), $Pd_2(dba)_3$ (0.01 mmol), carbonate **8** (0.1 mmol), compound **5i** (0.2 mmol) and Cs_2CO_3 (0.2 mmol) was added toluene (2 mL) under an atmosphere of argon. After stirring at 60 °C for 12 hours, the solvent was removed under reduced pressure to give a crude product which was further purified by column chromatography to afford the desired trisaccharide **9** (59.5 mg, 68%) as a colorless oil. $[\alpha]_D^{23}$ = +49.3 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 1130, 1517, 1616, 1652, 3025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.91 (s, 9H), 3.55-3.61 (m, 1H), 3.64-3.82 (m, 13H), 3.88-4.00 (m, 3H), 4.01-4.09 (m, 2H), 4.19-4.26 (m, 2H), 4.29-4.35 (m, 1H), 4.47-4.62 (m, 3H), 4.64 (dd, J_1 = 6.1 Hz, J_2 = 2.7 Hz, 1H), 4.72-4.80 (m, 1H), 5.07-5.15 (m, 1H), 5.29-5.34 (m, 1H), 5.52 (s, 1H), 5.59-5.67 (m, 1H), 5.80-5.89 (m, 1H), 5.96-6.06 (m, 1H), 6.06-6.13 (m, 1H), 6.30 (dd, J_1 = 6.2 Hz, J_2 = 0.8 Hz, 1H), 6.83-6.92 (m, 6H), 7.21-7.29 (m, 4H), 7.38-7.45 (m, 2H) ppm; ^{13}C NMR (100 MHz,

$CDCl_3$): δ -4.6, -4.4, 17.9, 25.8, 55.2, 55.3, 66.5, 67.4, 68.8, 68.9, 69.0, 70.4, 70.5, 73.5, 74.9, 75.0, 76.3, 76.4, 96.0, 98.7, 102.0, 103.5, 113.7, 113.8, 113.9, 127.5, 128.2, 128.4, 128.7, 129.5(2C), 129.8, 130.1, 130.2, 131.4, 143.2, 159.3(2C), 160.1 ppm; HRMS (ESI) calcd. for $C_{48}H_{62}O_{13}Si$ [M+Na]: 897.3857, found: 897.3862.

(4aR,6R,8aS)-6-(((2R,3S,6R)-6-ethoxy-3-(4-methoxybenzyloxy)-3,6-dihydro-2H-pyran-2-yl)methoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (byproduct 10)



From the synthesis of trisaccharide **9**, byproduct compound **10** (13.5 mg, 25%) was obtained as a colorless oil. $[\alpha]_D^{23}$ = +66.4 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 1132, 1220, 1416, 1517, 1615, 1650, 3023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.1 Hz, 3H), 3.51-3.62 (m, 1H), 3.67-3.86 (m, 9H), 3.87-4.00 (m, 4H), 4.21-4.30 (m, 2H), 4.46-4.53 (m, 1H), 4.53-4.59 (m, 1H), 5.07-5.15 (m, 1H), 5.35-5.41 (m, 1H), 5.54 (s, 1H), 5.67 (ddd, J_1 = 10.3 Hz, J_2 = 2.4 Hz, J_3 = 1.5 Hz, 1H), 5.79-5.87 (m, 1H), 5.92-6.05 (m, 1H), 6.09-6.16 (m, 1H), 6.83-6.94 (m, 4H), 7.21-7.29 (m, 2H), 7.38-7.46 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1, 55.3, 63.7, 67.4, 69.0, 69.1, 70.5, 70.6, 75.0, 75.1, 95.9, 98.8, 102.0, 113.7, 113.8, 127.5, 128.2, 128.4, 129.1, 129.5, 129.8, 130.0, 131.5, 159.4, 160.2 ppm; HRMS (ESI) calcd. for $C_{30}H_{36}O_9Na$ [M+Na]: 563.2257, found: 563.2257.

Compounds **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **6a**, **6f**, **6g**, **6k**, **6l**, **6m**, **6n**, **6n**, **6o**, **6q** are reported in the last part and all data of these compounds are checked to be consistent with literature reports.[7]

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2. For selected examples of palladium-catalyzed reactions under neutral conditions, see: a) Guibe, F. *Tetrahedron lett.* **1981**, *22*, 3591-3594. b) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7550-7559. c) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron lett.* **1982**, *23*, 4809-4812. d) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523-1529. e) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776-5788.
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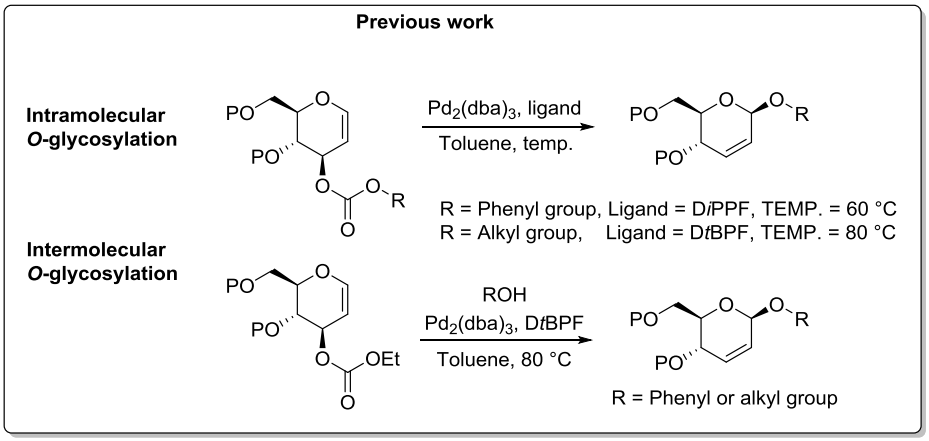
7. Xiang, S.; Lu, Z.; He, J.; Hoang, K. L. M.; Zeng, J.; Liu, X. W. *Chem.-Eur. J.* **2013**, *19*, 14047-14051.

Chapter 4: Palladium catalyzed glycosyl acceptor controlled *O*-glycosylation: a novel strategy to the syntheses of diverse *O*-glycosides

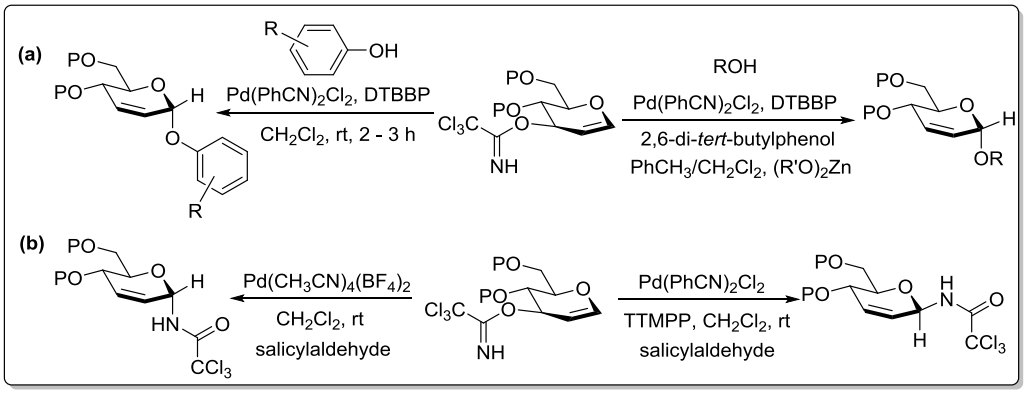
Introduction

With the developments of carbohydrate chemistry in the past decades, 'efficient' glycosylation methods are building up their identities in terms of their association with little or no activator requirement, large scale applicapability and, especially, high yield and selectivity.[1] Traditional glycosylation approaches are hence increasingly deemed unsatisfactory in practice and palladium catalyzed glycosylation strategies which can fulfill these demands are then becoming increasingly attractive.[2] In order to address the problem of low activity of Pd-π-allyl intermediates in glycal system, common used strategies such as introducing zinc reagent as additive[3] or employing pyranone as the starting material[4] were reported. Our group have also presented a glycosylation strategy based on a decarboxylative allylation reaction to solve this problem.[5] Both the intramolecular and intermolecular versions have been demonstrated their flexibility and versatility for the syntheses of glycosidic bonds (**Scheme 2.4.1**).



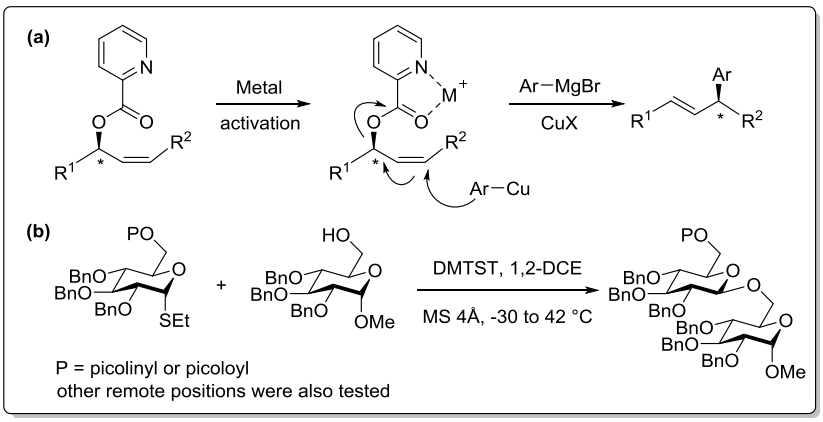
Scheme 2.4.1 Our previous work on decarboxylative glycosylation

Although we have obtained a few successful results *via* the decarboxylative reaction, it is still very hard to deal with different kind of conditions. We attempted to develop more methodologies for the glycosidic bonds formation *via* other strategy. The importance of *O*-glycosides could not be emphasized enough and our lab has chosen glycals as the donors because of their versatility. We next proceeded to focus our attention on the selection of the leaving group for the glycosylation reaction. Unlike the Boc-type protecting group, which could undergo a decarboxylative pathway, the group we designed to install to the C-3 position of glycal should be an efficient leaving group and could coordinate to the palladium catalyst to stabilize the palladium complex. Till now, nitrogen containing trichloroacetimidate[6] is the most suitable choice and has been widely used in transition metal catalyzed glycosylation since its easy removal and strong coordination to metal (**Scheme 2.4.2 a**).[3b] However, its unstability and the side reaction, namely Overman rearrangement,[7] are restrictions to its application occasionally (**Scheme 2.4.2 b**).[8]



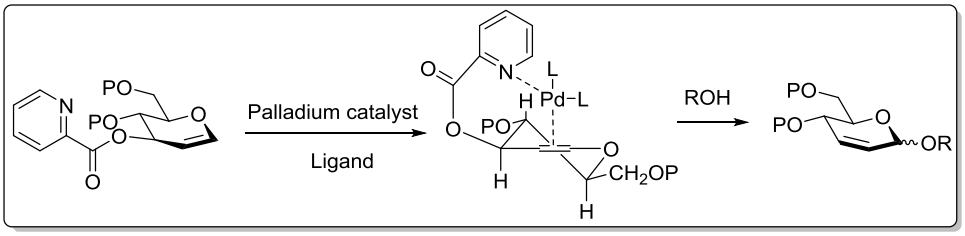
Scheme 2.4.2 Selected glycosylation methods with trichloroacetimidate group

Compared to trichloroacetimidate group, the *O*-picoloyl group which also containing a coordination nitrogen atom and could survive in harsher conditions had attracted respectable attention. Moreover, *O*-picoloyl group provided by Kobayashi in **2008** (**Scheme 2.4.3 a**) has been confirmed to be a good leaving group for allylic substitution with aryl Grignard reagents during several years' investigation.[9] In addition, *O*-picoloyl group was employed as a directing group for stereocontrolled glycosylation with glycosyl donor by Demchenko in **2012**.[10] After testing the influence of picoloyl group in different position, they found that selectivities were controlled by the H-bond effect but not bicyclic intermediates.



Scheme 2.4.3 Selected examples for reaction with *O*-picoloyl group

However, to the best of our knowledge, this group has not been adopted in glycal structure. Inspired by the special features of this group, herein, we proposed our glycosylation method with a glycal donor equipped with *O*-picoloyl group at C3 position.



Scheme 2.4.4 Our proposed glycosylation strategy with *O*-picoloyl group

Result and discussion

We embarked on our studies with the reaction of glycal derivative picolinate ester **1** and 3,4,5-trimethoxyphenol **2a**. Compound **1** can be readily achieved from the coupling of commonly used 4,6-*para*-methoxybenzylideneglucal and 2-picolinic acid. For the selection of **2a** as the acceptor, we hoped that its relatively high nucleophilicity would allow the nucleophilic addition to take place.

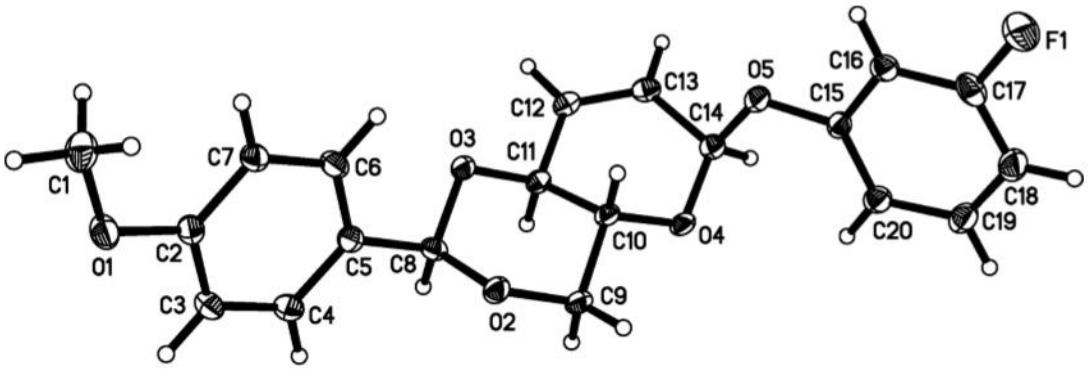
We conducted the reaction with different Pd(0) sources as the catalyst in a schlenk tube with toluene as the solvent at 60 ^{o}C for 48 hours. The initial results were summarized in **Table 1** and $Pd(PPh_3)_4$ exhibited the highest efficiency among all these three examined catalysts (entries **1-3**). Although low yields were obtained, the observation of desired product **3** suggested the flexibility of this reaction. After that, a variety of ligands were screened to improve the outcome of the reaction and to our delight, all the examined ligands showed good performance on accelerating the formation of glycosidic bond to give compound **3** in higher yields (entries **4-10**). It should be noted that the reaction with Xantphos, BIPHEP or DPPB as the ligand gave better control of the anomeric selectivity and α-isomer was obtained as the major product in all cases. Interestingly, the glycosylation product was provided in 80% yield with a ratio of α:β=12:1 when DPPB was employed as the ligand (entry **8**) while the reaction with DPPPentane or DPPPropane resulted in dramatic decrease on the outcome of this reaction (entries **9**-**10**). Next, we proceeded with investigation into the effect of solvents. THF, DCM and DCE were then used as the reaction solvent (entries **11**-**13**). The results illustrated that DCM was superior to other solvents and

could give 88% yield of the desired product. Meanwhile, excellent stereocontrol was obtained (entry **12**). A further attempt to improve the reaction outcome was conducted by altering the temperature, but no significant improvement was observed (entries **14**-**15**). To demonstrate the important role of the pilcoloyl group, a substrate with benzoic group was examined. However, much lower yield and poorer selectivity were detected in comparison with the previous result (entry **16**). Hence, we gave the optimized condition as following: the reaction was performed with $Pd(PPh_3)_4$ as catalyst, DPPB as ligand and in DCM at 60 ^{o}C for 48 h.

To assess the generality of this optimized condition, various phenol were examined. As listed in **Scheme 2.4.5**, a lower yield was obtained when phenol was utilized (**3b**). The reaction with ortho-substituted phenols such as 2-ethyl phenol and 2-Bn phenol gave a slightly lower yield due to the steric effect (**3c-3d**). Remarkable tolerance to halogen substituent was observed for this method and all the halide containing substrates were able to produce the desired *O*-phenolic glycosides in good yields (**3e**-**3j**). Moreover, phenols with a bulky *tert*-butyl or phenyl group on *para*-position were explored but no significant change was observed (**3k**-**3l**). As compared to other tested disubstituented phenols (**3m**-**3p**), 2,6-dimethyl phenol (**3q**) gave a lower yield due to the steric effect. The glycosylation reaction with a withdrawing group substituent phenol proceeded smoothly in generating its desired product **3r** in 86% yield with a ratio of α:β = 20:1. However, strongly electron deficient phenols such as cyano or nitro substituted phenol gave only a trace amount of the desired product. After that, Boc-L-tyrosine methyl ester was efficiently attached to the anomeric center to form the *O*-glycosidic bond, affording the desired product in 74% yield with a ratio of

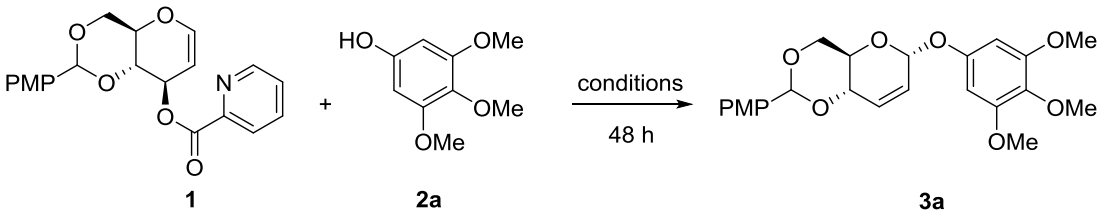
α:β = 16:1 (**3s**). Noteworthy, unless otherwise specified each reaction gave α-isomer as the major product and the stereochemistry of anomeric center could be determined by the X-ray crystallographic analysis of compound **3e** (**Figure 2.4.1**).[11]

Figure 2.4.1 X-ray crystal structure for compound **3e (CCDC number: 989047)**



Subsequently, the scope of this method was further explored by employing various alcohols as glycosyl acceptor. Then 1-butanol **4a** was chosen to coupling with compound **1a** under the optimized conditions. Interestingly, the reaction proceeded successfully to give the desired *O*-glycoside. However, β-isomer was obtained as the major product as opposed to the previous results with α-selectivity. The big difference in selectivity indicated that a different pathway was involved in the reaction withalcohol as glycosyl acceptor. By comparing these two types of nucleophiles, we postulated that the main factor affecting the selectivity was the electron density on the oxygen of the nucleophile. Before we tested this hypothesis, an initial trial to increase the β-selectivity was conducted by screening other ligands such as Xantphos or BIPHEP. The results in **Table 2.4.2** showed that the reaction with Xantphos gave a higher stereoselectivity but with a much lower yield while BIPHEP gave a lower yield with a slight increase of selectivity. So it is impracticable to get satisfied results by

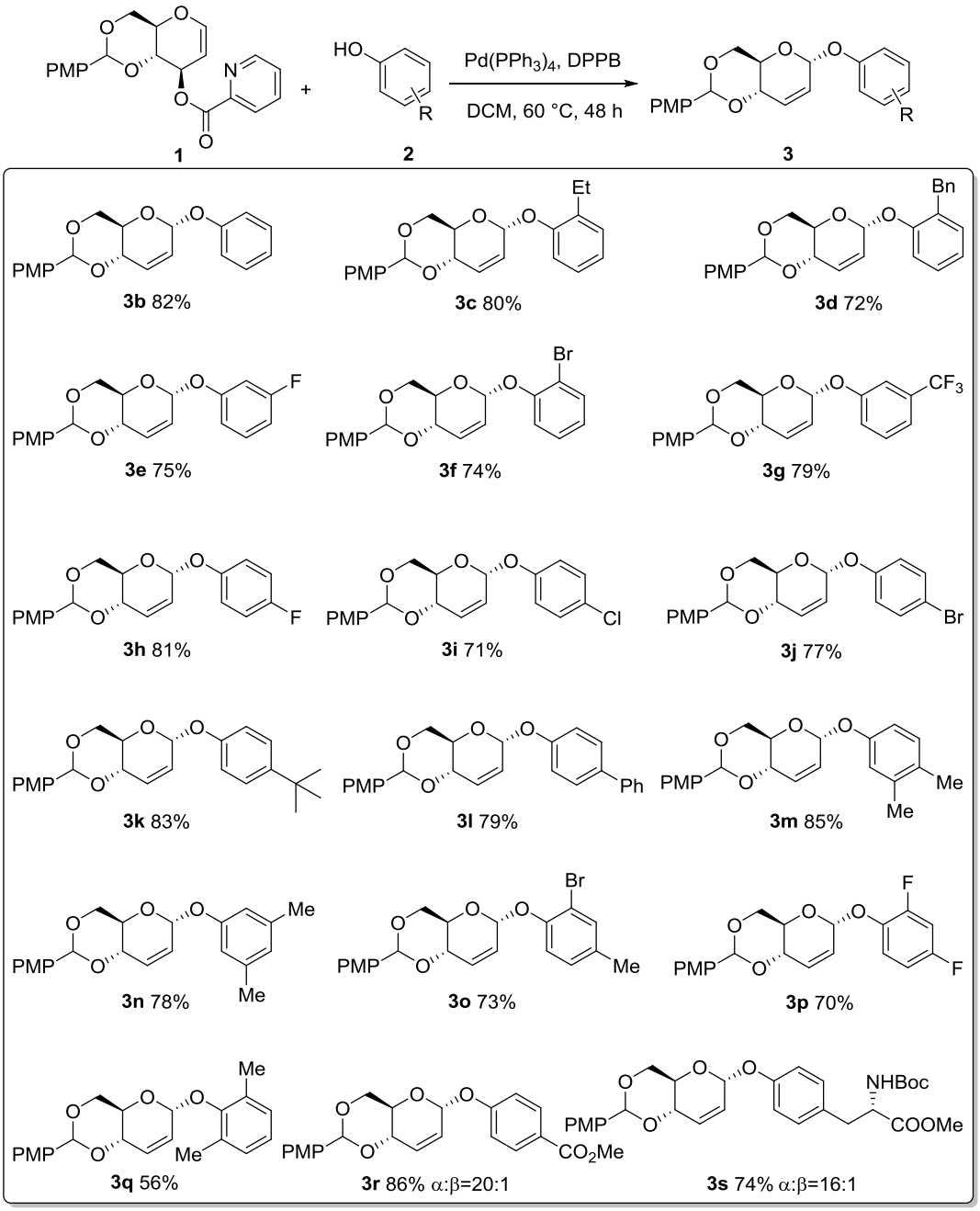
Table 2.4.1 Optimization of the reaction conditions with phenol acceptors [a]



Entry	Catalyst	Ligand	Solvent	Temp.	Yield[b]	α:β[c]
1	$Pd(dba)_2$	-	Toluene	60°C	10%	-
2	$Pd_2(dba)_3$	-	Toluene	60°C	16%	-
3	$Pd(PPh_3)_4$	-	Toluene	60°C	36%	-
4	$Pd(PPh_3)_4$	DPEphos	Toluene	60°C	62%	2:1
5	$Pd(PPh_3)_4$	PPh_3	Toluene	60°C	56%	3:1
6	$Pd(PPh_3)_4$	Xantphos	Toluene	60°C	54%	10:1
7	$Pd(PPh_3)_4$	BIPHEP	Toluene	60°C	68%	8:1
8	$Pd(PPh_3)_4$	DPPB	Toluene	60°C	80%	12:1
9	$Pd(PPh_3)_4$	DPPPe	Toluene	60°C	20%	-
10	$Pd(PPh_3)_4$	DPPPr	Toluene	60°C	48%	6:1
11	$Pd(PPh_3)_4$	DPPB	THF	60°C	40%	-
12	**$Pd(PPh_3)_4$**	**DPPB**	**DCM**	**60°C**	**88%**	**20:1**
13	$Pd(PPh_3)_4$	DPPB	DCE	60°C	75%	10:1
14	$Pd(PPh_3)_4$	DPPB	DCM	50°C	84%	20:1
15	$Pd(PPh_3)_4$	DPPB	DCM	70°C	89%	18:1
16[d]	$Pd(PPh_3)_4$	DPPB	DCM	70°C	39%	8:1

Unless otherwise specified, all reactions were carried out in a schlenk tube with 0.1 mmol **1**, 0.2 mmol **2a**, 10% Pd catalyst, 20% ligand in 2 mL solvent for 48 hours. [b] Isolated yield. [c] All the ratios were determined by ^{1}H NMR. DPPPr = DPPPropane; DPPB = DPPButane; DPPPe = DPPPentane. [d] In compound **1**, the pilcoloyl group was replaced by benzoic group.

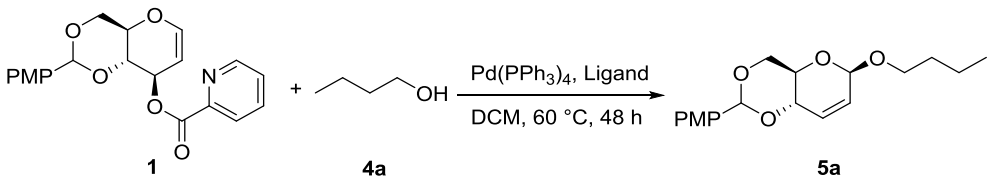
Scheme 2.4.5 Substrate scope of *O*-glycosylation with phenol acceptors [a,b,c]



[a] Unless otherwise specified, all reactions were carried out in a schlenk tube with 0.1 mmol **1**, 0.2 mmol **2**, 10% $Pd(PPh_3)_4$, 20% DPPB in 2 mL DCM at 60 °C for 48 hours. [b] Isolated yield. [c] All the ratios were determined by ^1H NMR.

changing the ligand. We then added base to increase the nucleophilicity of the alcohol for better results. To our delight, the selectivity was improved to α:β=1:40 when Et_3N was used. Weaker base such as DMAP, pyridine brought considerably improvement of the outcome while starting material compound **1** cannot survive under stronger bases such as Cs_2CO_3, K_2CO_3 and NaOH. So Et_3N was introduced as the additive to the reaction for the later glycosylation reaction with alcohol as glycosyl acceptor.

Table 2.4.2 Optimization of the reaction conditions with phenol acceptors [a]



Entry	Ligand	Additive (2.2 eq.)	Yield (%)[b]	α:β[c]
1	DPPB	-	88	1:12
2	XantPhos	-	45	<1:20
3	BIPHEP	-	64	1:15
4	DPPB	DMAP	84	1:3
5	DPPB	Pyridine	85	1:10
6	**DPPB**	**Et_3N**	**90**	**1:40**

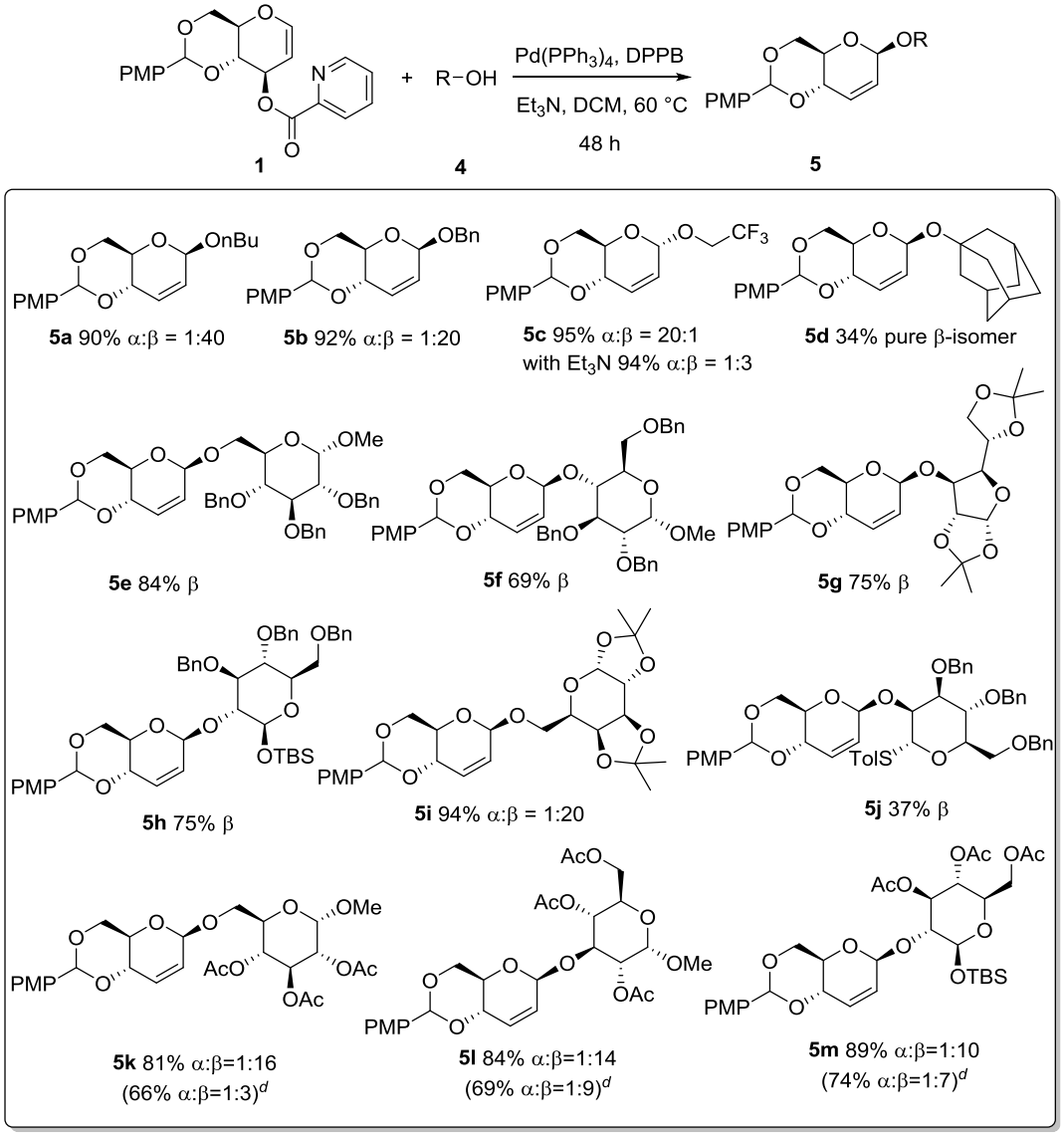
[a] Unless otherwise specified, all reactions were carried out in a schlenk tube with 0.1 mmol **1**, 0.2 mmol **2**, 10% $Pd(PPh_3)_4$, 20% ligand in 2 mL DCM for 48 hours. [b] Isolated yield. [c] All the ratios were determined by ^1H NMR.

After establishing modified reaction conditions suitable for alcohol substrate, we next set out to examine the substrate scope of this method. Active benzyl alcohol was then adopted as the acceptor to give the desire product **5b** with excellent yield and selectivity. Interestingly, the treatment of 2,2,2-trifluoroethanol with optimized condition gave a mixture with a ratio of α:β=1:3 in 94%. Considering that this alcohol

has a similar pKa value as phenol, a reaction without base was conducted to afford the product with excellent α-selectivity (**5c**). These results further proved our hypothesis that the selectivity was controlled by the nucleophilicity of the glycosyl acceptor. Later, a sterically hindered tertiary 1-adamentol was employed and significantly lower yield was obtained, indicating the outcome of this reaction was affected by steric effect. Only β-isomer was isolated from the reaction mixture (**5d**). In addition, the generality of this protocol was demonstrated by screening a number of carbohydrate acceptors. Glycosyl acceptor with a primary alcohol was firstly tested to give the desired product **5e** in 84% yield with β-selectivity. Secondary hydroxyl containing glycosyl acceptors were then utilized to the reaction, providing the β-type disaccharides in lower yields (**5f**-**5h**). Galactosyl acceptor was also found to be suitable for the reaction conditions to give β-selective product in excellent yield (**5i**). When sterically hindered mannosyl type acceptor was taken to the reaction, desired disaccharide **5j** was obtained in a reasonable yield. Next, glycosyl acceptors with electron-withdrawing protecting groups were subjected to the optimized conditions (with or without Et_3N). Results indicated that all substrates gave the desired products in lower chemical yield and unsatisfactory β-selectivity without Et_3N (**5k**-**5m**). The addition of Et_3N resulted in significant improvement on stereo-outcomes of the reactions. Notably, the selectivity for acceptors with electron-withdrawing groups was poorer than that of electron-donating groups.

Encouraged by the above result, we then started to do more investigation about this palladium catalyzed *O*-glycosylation reaction. As we known, the β-selectivity of *O*-glycosylation with alcohol acceptors could be improved by the addition of base. We

Scheme 2.4.6 Substrate scope of O-glycosylation with alcohol acceptors [a,b,c]



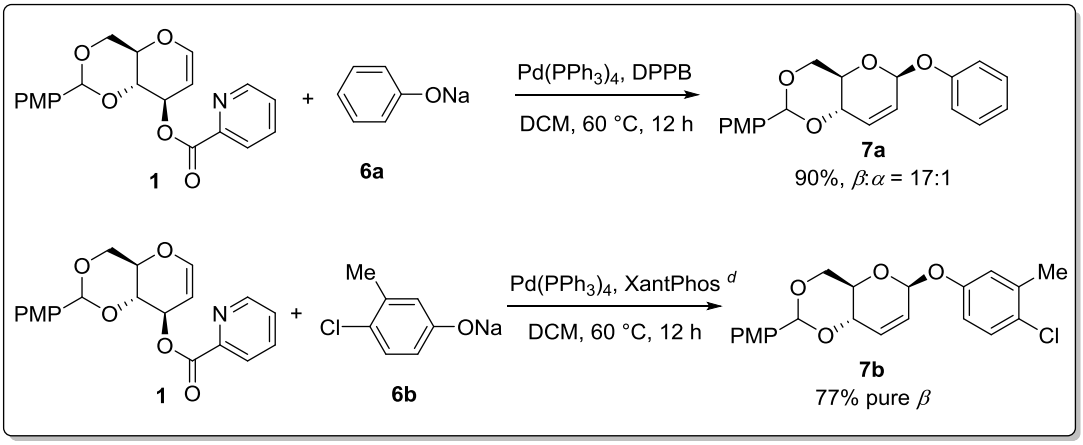
[a] Unless otherwise specified, all reactions were carried out with 0.1 mmol **1**, 0.2 mmol **2**, 2.2 equiv. Et_3N, 10% $Pd(PPh_3)_4$, 20% DPPB in 2 mL DCM at 60 °C for 48 hours. [b] Isolated yield. [c] All the ratios were determined by ^1H NMR. [d] Reaction was conducted without Et3N.

attempted to get phenolic glycosides with *β*-selectivity by addition of various bases such as DMAP, pyridine, Et_3N, DBU, Na_2CO_3, K_2CO_3. Similar results were observed when selected 3,4,5-trimethoxyphenol **2a** as the model glycosyl acceptor and the ratio of *β*-isomer was improved as the increasing of the basicity of base. However, it was

proved impractical to generate satisfactory β-selectivity only by the addition of basedue to the instability of starting material in strong base as mentioned above. For instance, a large amount of compound **1** was decomposed under the reaction condition when K_2CO_3 was selected as base. However, only a ratio of α:β = 1:1 was obtained.

Considering this situation, sodium phenoxides **6a** and **6b** were then used to take place of phenols and to our delight, β-isomer was obtained as major product (**Scheme 2.4.7**). Moreover, the reaction was finished in 12 hours. These results indicated that it was possible to control the selectivity of anomeric center by altering the nucleophilicity of glycosyl acceptor for this strategy.

Scheme 2.4.7 *O*-glycosylation with sodium phenoxides as nucleophiles [a,b,c]

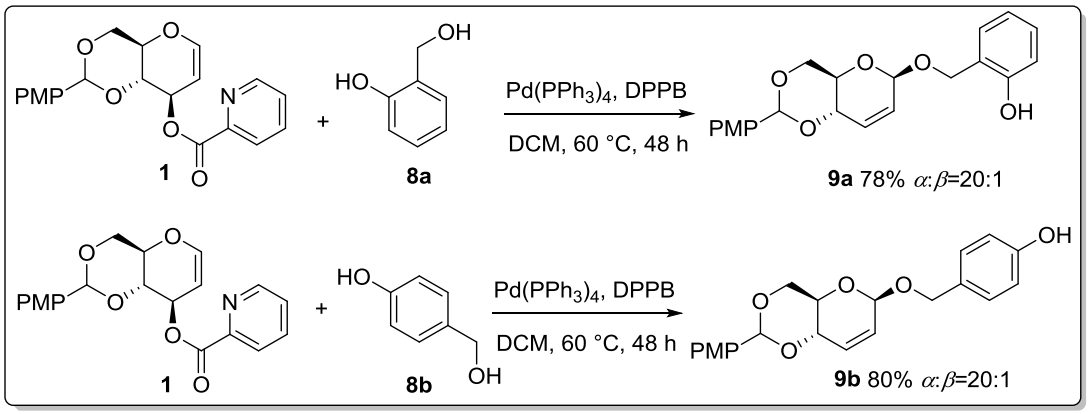


[a] Unless otherwise specified, two reactions were carried out in a schlenk tube with 0.1 mmol **1**, 0.2 mmol **6**, 10% $Pd(PPh_3)_4$, 20% DPPB in 2 mL DCM at 60 °C for 12 hours. [b] Isolated yield. [c] All the ratios were determined by ^{1}H NMR. [d] Xantphos was used.

In order to fully understand the mechanism of this palladium catalyzed glycosylation, we then choose 2-hydroxybenzyl alcohol **8a** as the glycosyl acceptor for this substrate contained both phenolic-type and aliphatic-type alcohols. Then the reaction may give both of glycosidic desired products. Interestingly, aliphatic *O*-

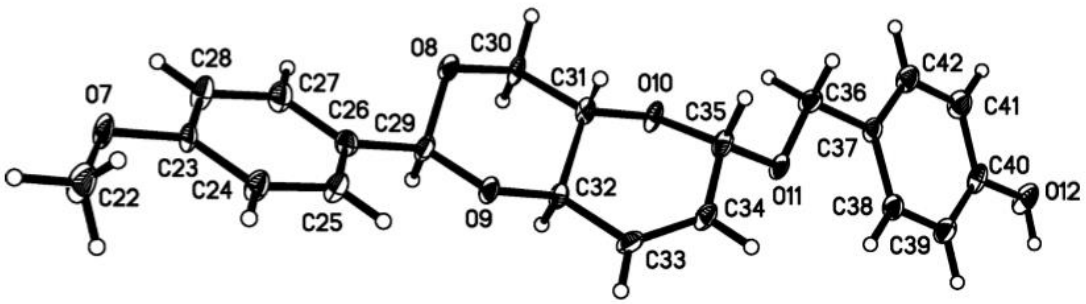
glycoside **9a** was the only product isolated in 78% yield with β-selectivity which can be confirmed by the X-ray crystallographic analysis (**Figure 2.4.2**).[12] Besides that, the other possible product phenolic *O*-glycoside existed as a trace mount in the reaction mixture. The excellent regioselectivity indicated that electron density on the oxygen of the nucleophile is the controller of the reaction rate and the reaction with aliphatic hydroxyl group, which has higher electron density, was much faster than phenolic hydroxyl group due to absence of the conjugate effect between oxygen and aromatic ring (**Scheme 2.4.8**). Similar glycosyl acceptor **8b** was then examined, resulting in the same outcome as **8a**.

Scheme 2.4.8 Competitive reactions [a,b]



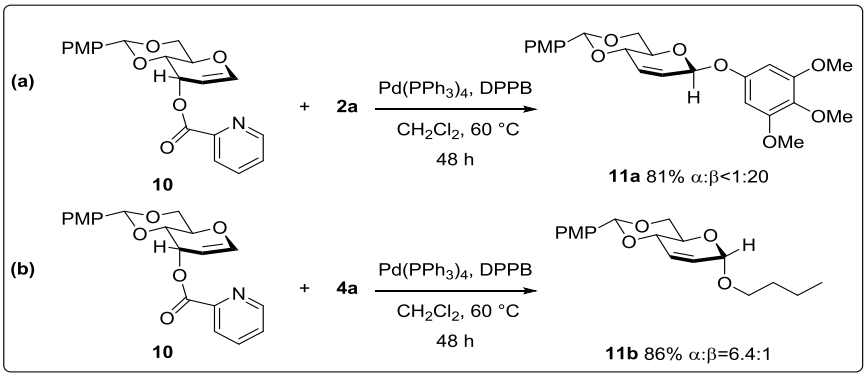
[a] Two reactions were carried out in a schlenk tube with 0.1 mmol **1**, 0.2 mmol **8**, 10% $Pd(PPh_3)_4$, 20% DPPB in 2 mL DCM at 60 ^oC for 48 hours. [b] Isolated yield.

Figure 2.4.2 X-ray crystal structure for compound **9b (CCDC number: 979358)**



To confirm the correlation between palladium complexation and stereoselectivity, C-3 epimer of donor **1** was employed to reverse the stereo-outcome of the reaction. With an axial substituent at C-3, the palladium catalyst should coordinate to allal **10** from α-face. According to our proposed mechanism, phenol **2a** should give more β-product whereas *n*-butanol **4a** should provide more α-isomer. Gratifyingly, β-glycoside **11a** was obtained with ratio of α:β<1:20 (**Scheme 2.4.9a**) and α-glycoside **11b** was obtained with α:β=6.4:1 in high yields (**Scheme 2.4.9b**). This result could serve as a proof of concept to the mechanism.

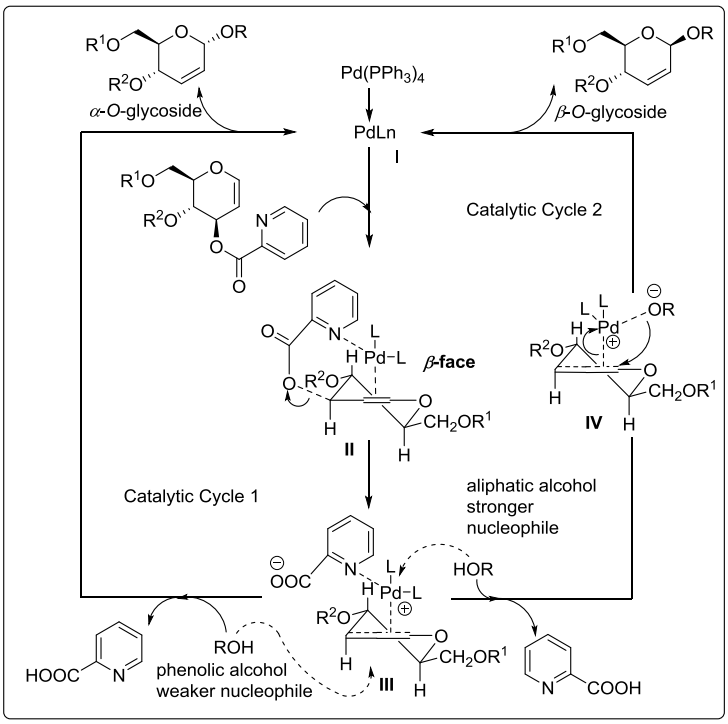
Scheme 2.4.9. Reversing the stereoselectivity with allal donor **10**



After a series of investigation on this palladium catalyzed *O*-glycosylation, a plausible mechanism accounting for the difference in selectivity with two types of nucleophiles was proposed as follows (**Scheme 2.4.10**). The catalytic cycle is beginning with the formation of palladium and ligand complex **I**. Then the coordination of Palladium with both the double bond of compound **1** and the nitrogen of pyridine ring to furnish intermediate **II** with the palladium complex oriented at upper face of the plane.[3b,12] Subsequently, the cleavage of the C-O bond on C-3 position to give key intermediate **III** with Pd-π-allyl structure. Thereafter, a nucleophilic addition occurred with the generated intermediate **III** by the attack of

alcohol nucleophiles. There are two electrophilic reaction sites in this structure but since Pd site was considered as a harder Lewis acid compared to allyl cation site,[13] soft nucleophile such as phenol preferred to approach allyl cation. The approach was from bottom face due to the shielding effect of palladium-ligands complex in β-face, yielding α-isomer as the major product. Concurrently, the catalytic cycle **1** was completed by the release of complex **I**. On the other hand, when stronger nucleophilic aliphatic alcohol or phenoxide was employed, the nucleophile would attach palladium from β-face to afford intermediate **IV** accordingly. Then, a subsequent intramolecular delivery would give β-type *O*-glycosides as well as regenerate palladium complex **I** to finish catalytic cycle **2**. Since the reaction through intramolecular pathway was easier and faster than intermolecular version, so this mechanism also presented a rational explanation for the outcome of competitive reactions.

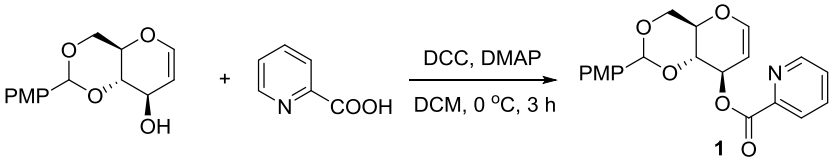
Scheme 2.4.10 Proposed mechanism of stereoselective *O*-glycosylation



Conclusion

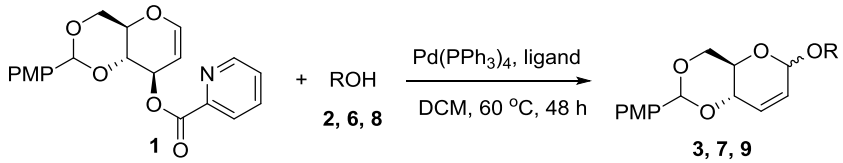
In summary, a high efficient glycosyl acceptor controlled *O*-glycosylation strategy was developed with readily available glucal derivative. The introduction of picoloyl group in glycosyl donor was demonstrated to be important to enhance the selectivity by directing the orientation of palladium catalyst. The versatility and generality of this strategy was illustrated by application to a wide variety of substrate scope. Unlike the previous results, the stereoselectivity of the anomeric center could be effectively controlled by glycosyl acceptor. Generally speaking, weaker nucleophiles like phenol preferred to give α-type phenolic *O*-glycosides as the major product while β-type products were normally obtained with stronger nucleophiles such as aliphatic alcohol or sodium phenoxide. Competitive reaction investigations demonstrated that this reaction also possessed excellent regioselectivity for the substrates containing both phenolic alcohol and aliphatic alcohol. The outcome of dominated aliphatic type product could be clearly explained by mechanism as following: an intramolecular pathway was involved when the reaction was carried out with a strong nucleophile while intermolecular pathway dominated for reaction with a weak nucleophile.

Experimental for preparation of compound 1



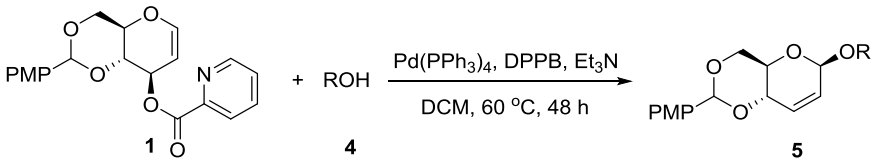
DMAP (0.5 equiv.) and DCC (1.3 equiv.) were added to a suspension of picolinic acid (1.1 equiv.) in DCM (2.0 M) in an ice-water bath. After stirring at 0 °C for 30 min, a solution of 4,6-*para*-methoxybenzylideneglucal (1.0 equiv.) in DCM (2.0 M) was added to the mixture. The reaction mixture was stirred at 0 °C for 2 h before dilution with Et_2O and filtration with Celite. After removal of solvent, the residue was purified by flash column chromatography on silica gel with EtOAc/hexane to give picolinate **1** in 96% yield as a white solid. m.p. 129-130 °C; $[\alpha]_D^{22}$ = -150.3 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 3H), 3.86 (t, J = 10.5 Hz, 1H), 4.05 (dt, J_d = 5.2 Hz, J_t = 10.3 Hz, 1H), 4.31 (dd, J_1 = 7.9 Hz, J_2 = 10.3 Hz, 1H), 4.38 (dd, J_1 = 5.2 Hz, J_2 = 10.5 Hz, 1H), 4.91 (dd, J_1 = 2.1 Hz, J_2 = 6.1 Hz, 1H), 5.58 (s, 1H), 5.89 (dt, J_d = 7.8 Hz, J_t = 1.8 Hz, 1H), 6.44 (dd, J_1 = 1.4 Hz, J_2 = 6.1 Hz, 1H), 6.86-6.82 (m, 2H), 7.40-7.36 (m, 2H), 7.44 (ddd, J_1 = 1.1 Hz, J_2 = 4.8 Hz, J_3 = 7.7 Hz, 1H), 7.80 (dt, J_d = 1.7 Hz, J_t =7.7 Hz, 1H), 8.13-8.09 (m, 1H), 8.77-8.73 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2, 68.2, 68.9, 70.2, 76.6, 100.4, 101.5, 113.5, 125.3, 126.9, 127.5, 129.3, 136.9, 145.9, 147.8, 149.8, 160.1, 164.9 ppm. HRMS (ESI) calcd. for $C_{20}H_{19}NO_6Na$ [M+Na]: 405.1998, found: 405.1995.

General procedure for syntheses of *O*-glycosides 3a-3r, 7a-7b, 9a-9b



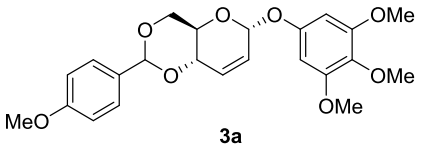
Picolinate **1** (0.1 mmol), nucleophiles **2, 6** or **8** (0.2 mmol), $Pd(PPh_3)_4$ (0.01 mmol) and DPPB (0.02 mmol) were dissolved in DCM (2 mL) in a schlenck tube under nitrogen atmosphere. The solution was heated at 60 ^{o}C for 48 h. Then DCM was removed under reduced pressure and the residue was purified by flash column chromatography to give *O*-glycosides **3**, **7** or **9** in 56% to 90% yields.

General procedure for syntheses of *O*-glycosides 5a-5j



Picolinate **1** (0.1 mmol), nucleophiles **4** (0.2 mmol), $Pd(PPh_3)_4$ (0.01 mmol), DPPB (0.02 mmol) and Et_3N (0.22 mmol) were dissolved in DCM (2 mL) in a schlenck tube under nitrogen atmosphere. The solution was heated at 50 ^{o}C for 48 h. Then DCM was removed under reduced pressure and the residue was purified by flash column chromatography to give *O*-glycosides **5** in 34% to 95% yields.

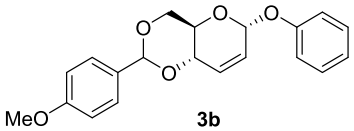
(4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-6-(3,4,5-trimethoxyphenoxy)-4,4a,6,8a-tetra hydropyrano[3,2-*d*][1,3]dioxine



3a

According to the general procedure, **3a** (37.8 mg, 88%) was obtained as a white solid. m.p. 132-134 °C; $[\alpha]_D^{22}$ = +132.8 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.96-3.76 (m, 13H), 4.04 (dt, J_d = 4.7 Hz, J_t = 9.8 Hz, 1H), 4.25-4.19 (m, 1H), 4.31 (dd, J_1 = 4.7 Hz, J_2 = 10.2 Hz, 1H), 5.59 (s, 1H), 5.71-5.64 (m, 1H), 5.89 (dt, J_d = 10.2 Hz, J_t = 2.3 Hz, 1H), 6.32-6.26 (m, 1H), 6.40-6.35 (m, 2H), 6.96-6.89 (m, 2H), 7.49-7.42 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.3, 56.1, 61.0, 64.8, 69.2, 74.8, 93.9, 94.7, 102.2, 113.7, 125.8, 127.6, 129.7, 131.8, 133.5, 153.6, 153.7, 160.3 ppm. HRMS (ESI) calcd. for $C_{23}H_{27}O_8$ [M+H]: 431.1706, found: 431.1703.

(4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-6-phenoxy-4,4a,6,8a-tetrahydropyrano[3,2-*d*] [1,3]dioxine

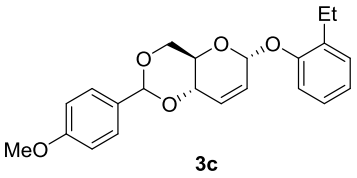


3b

According to the general procedure, **3b** (27.9 mg, 82%) was obtained as a white solid. m.p. 200-202 °C; $[\alpha]_D^{22}$ = +172.6 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83-3.76 (m, 4H), 4.02 (ddd, J_1 = 4.7 Hz, J_2 = 9.0 Hz, J_3 = 10.2 Hz, 1H), 4.23-4.16 (m, 1H), 4.26 (dd, J_1 =4.7 Hz, J_2 = 10.3 Hz, 1H), 5.56 (s, 1H), 5.72-5.68 (m, 1H), 5.88 (dt, J_d = 10.3 Hz, J_t = 2.5 Hz, 1H), 6.30-6.23 (m, 1H), 6.93-6.86 (m, 2H), 7.11-7.00 (m, 3H), 7.34-7.27 (m, 2H), 7.45-7.39 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.3, 64.8, 69.3, 74.9, 93.3, 102.2, 113.7, 116.8, 122.3, 126.0, 127.6, 129.5, 129.8,

131.7, 157.2, 160.2 ppm. HRMS (ESI) calcd. for $C_{20}H_{21}O_5$ [M+H]: 341.1389, found: 341.1391.

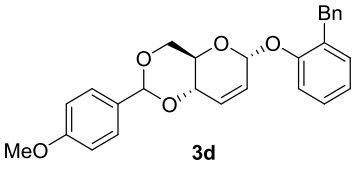
(4a*R*,6*R*,8a*S*)-6-(2-ethylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3]dioxine



3c

According to the general procedure, **3c** (29.5 mg, 80%) was obtained as a white solid. m.p. 95-96 °C; $[\alpha]_D^{22}$ = +146.4 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21 (t, *J* = 7.5 Hz, 3H), 2.66 (q, *J* = 7.4 Hz, 2H), 3.84-3.75 (m, 4H), 4.02 (ddd, J_1 = 4.7 Hz, J_2 = 9.0 Hz, J_3 = 10.2 Hz, 1H), 4.23-4.16 (m, 1H), 4.27 (dd, J_1 = 4.7 Hz, J_2 = 10.2 Hz, 1H), 5.57 (s, 1H), 5.71-5.65 (m, 1H), 5.89 (dt, J_d = 10.2 Hz, J_t = 2.5 Hz, 1H), 6.30-6.22 (m, 1H), 6.93-6.86 (m, 2H), 6.98 (dd, J_1 = 1.5 Hz, J_2 = 7.2 Hz, 1H), 7.21-7.09 (m, 3H), 7.47-7.40 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.4, 23.4, 55.3, 64.9, 69.3, 74.9, 93.6, 102.1, 113.7, 114.9, 122.3, 126.2, 126.8, 127.6, 129.2, 129.8, 131.5, 133.8, 155.1, 160.2 ppm. HRMS (ESI) calcd. for $C_{22}H_{25}O_5$ [M+H]: 369.1702, found: 369.1701.

(4a*R*,6*R*,8a*S*)-6-(2-benzylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3]dioxine

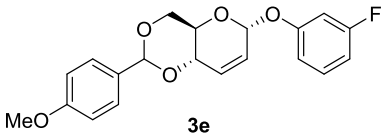


3d

According to the general procedure, **3d** (31.0 mg, 72%) was obtained as a white solid. m.p. 94-95 °C; $[\alpha]_D^{22}$ = +89.7 (*c* = 0.57 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.76 (t, *J* = 10.2 Hz, 1H), 3.81 (s, 3H), 3.87 (ddd, J_1 = 4.6 Hz, J_2 = 8.9 Hz, J_3 = 10.3

Hz, 1H), 3.98-3.92 (m, 1H), 4.05-3.99 (m, 1H), 4.23-4.13 (m, 2H), 5.54 (s, 1H), 5.63-5.58 (m, 1H), 5.67 (dt, J_d = 10.2 Hz, J_t = 2.5 Hz, 1H), 6.25-6.18 (m, 1H), 6.93-6.86 (m, 2H), 6.97 (dt, J_d = 1.1 Hz, J_t = 7.4 Hz, 1H), 7.22-7.12 (m, 6H), 7.30-7.23 (m, 2H), 7.47-7.40 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 36.4, 55.3, 64.8, 69.3, 74.9, 93.5, 102.2, 113.7, 114.9, 122.2, 125.9, 126.0, 127.5, 127.6, 128.2, 128.9, 129.8, 130.7, 130.8, 131.5, 140.9, 155.2, 160.2 ppm. HRMS (ESI) calcd. for $C_{27}H_{25}O_5$ [M+H]: 431.1858, found: 431.1859.

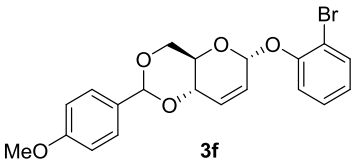
(4a*R*,6*R*,8a*S*)-6-(3-fluorophenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3]dioxine



3e

According to the general procedure, **3e** (26.9 mg, 75%) was obtained as a white solid. m.p. 189-190 °C; $[\alpha]_D^{22}$ = +165.1 (*c* = 0.76 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.84-3.76 (m, 4H), 3.98 (ddd, J_1 = 4.7 Hz, J_2 = 9.0 Hz, J_3 = 10.3 Hz, 1H), 4.23-4.17 (m, 1H), 4.26 (dd, J_1 = 4.6 Hz, J_2 = 10.3 Hz, 1H), 5.56 (s, 1H), 5.70-5.64 (m, 1H), 5.87 (dt, J_d = 10.2 Hz, J_t = 2.5 Hz, 1H), 6.31-6.25 (m, 1H), 6.74 (ddt, J_{d1} = 0.7 Hz, J_{d2} = 2.4 Hz, J_t = 8.3 Hz, 1H), 6.94-6.78 (m, 4H), 7.28-7.20 (m, 1H), 7.46-7.39 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.3, 64.9, 69.2, 74.6, 77.2, 93.3, 102.2, 104.3, 104.6, 108.9, 109.1, 112.4(2C), 113.7, 125.5, 127.6, 129.7, 130.2, 130.3, 132.1, 158.3, 158.4, 160.3, 162.2, 164.7 ppm. HRMS (ESI) calcd. for $C_{20}H_{20}O_5F$ [M+H]: 359.1295, found: 359.1294.

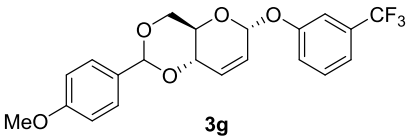
(4a*R*,6*R*,8a*S*)-6-(3-bromophenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3]dioxine



3f

According to the general procedure, **3f** (30.9 mg, 74%) was obtained as a white solid. m.p. 178-179 °C; $[\alpha]_D^{22}$ = +117.1 (*c* = 0.65 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83-3.76 (m, 4H), 4.13 (dt, J_d = 4.6 Hz, J_t = 9.8 Hz, 1H), 4.24-4.19 (m, 1H), 4.29 (dd, J_1 = 4.6 Hz, J_2 = 10.2 Hz, 1H), 5.56 (s, 1H), 5.68-5.62 (m, 1H), 6.02-5.94 (m, 1H), 6.34-6.27 (m, 1H), 6.98-6.87 (m, 3H), 7.22-7.16 (m, 1H), 7.47-7.40 (m, 2H), 7.59-7.53 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.3, 65.0, 69.2, 74.8, 95.1, 102.2, 113.7, 114.4, 118.7, 124.1, 125.6, 127.6, 128.5, 129.7, 132.2, 133.4, 154.0, 160.3 ppm. HRMS (ESI) calcd. for $C_{20}H_{20}O_5Br$ [M+H]: 419.0494, found: 419.0495.

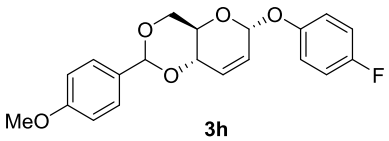
(4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-6-(3-(trifluoromethyl)phenoxy)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3]dioxine



3g

According to the general procedure, **3g** (32.2 mg, 79%) was obtained as a white solid. m.p. 180-182 °C; $[\alpha]_D^{22}$ = +161.8 (*c* = 0.58 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.78-3.68 (m, 4H), 3.92 (ddd, J_1 = 4.7 Hz, J_2 = 9.0 Hz, J_3 = 10.3 Hz, 1H), 4.22-4.11 (m, 2H), 5.50 (s, 1H), 5.68-5.62 (m, 1H), 5.81 (dt, J_d = 10.3 Hz, J_t = 2.5 Hz, 1H), 6.27-6.19 (m, 1H), 6.86-6.79 (m, 2H), 7.27-7.15 (m, 3H), 7.39-7.31 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.3, 65.0, 69.1, 74.7, 93.3, 102.2, 113.7, 118.9, 120.0, 125.4, 127.6, 129.7, 130.0, 132.2, 157.2, 160.3 ppm. HRMS (ESI) calcd. for $C_{21}H_{20}O_5F3$[M+H]: 409.1263, found: 409.1264.

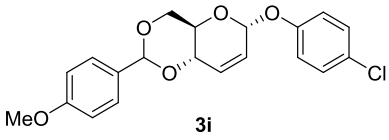
(4a*R*,6*R*,8a*S*)-6-(4-fluorophenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3]dioxine



3h

According to the general procedure, **3h** (29.0 mg, 81%) was obtained as a white solid. m.p. 192-194 °C; $[\alpha]_D^{22}$ = +154.2 (*c* = 0.83 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.85-3.75 (m, 4H), 4.05-3.96 (m, 1H), 4.22-4.16 (m, 1H), 4.26 (dd, J_1 = 4.6 Hz, J_2 = 10.3 Hz, 1H), 5.56 (s, 1H), 5.63-5.58 (m, 1H), 5.87 (dt, J_d = 10.2 Hz, J_t = 2.5 Hz, 1H), 6.31-6.23 (m, 1H), 6.93-6.86 (m, 2H), 7.07-6.94 (m, 4H), 7.47-7.41 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.3, 64.8, 69.2, 74.8, 94.1, 102.2, 113.7, 115.8, 116.0, 118.2, 118.3, 125.8, 127.6, 129.7, 131.9, 153.2(2C), 157.1, 159.4, 160.3 ppm. HRMS (ESI) calcd. for $C_{20}H_{20}O_5F$ [M+H]: 359.1295, found: 359.1298.

(4a*R*,6*R*,8a*S*)-6-(4-chlorophenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3]dioxine

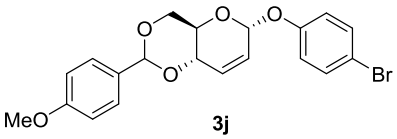


3i

According to the general procedure, **3i** (26.6 mg, 71%) was obtained as a white solid. m.p. 213-215 °C; $[\alpha]_D^{22}$ = +197.8 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83-3.76 (m, 4H), 3.98 (ddd, J_1 = 4.7 Hz, J_2 = 9.0 Hz, J_3 = 10.2 Hz, 1H), 4.21-4.16 (m, 1H), 4.24 (dd, J_1 = 4.6 Hz, J_2 = 10.2 Hz, 1H), 5.56 (s, 1H), 5.67-5.61 (m, 1H), 5.86 (dd, J_1 = 10.3 Hz, J_2 = 2.5 Hz, 1H), 6.31-6.23 (m, 2H), 6.93-6.86 (m, 2H), 7.04-6.96 (m, 2H), 7.29-7.21 (m, 2H), 7.46-7.38 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.3, 64.9, 69.2, 74.8, 93.5, 102.2, 113.7, 118.1, 125.6, 127.3, 127.6, 129.4,

129.7, 132.0, 155.7, 160.2 ppm. HRMS (ESI) calcd. for $C_{20}H_{20}O_5Cl$ [M+H]: 375.0999, found: 375.0998.

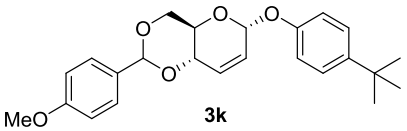
(4a*R*,6*R*,8a*S*)-6-(4-bromophenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3]dioxine



3j

According to the general procedure, **3j** (32.2 mg, 77%) was obtained as a white solid. m.p. 222-224 °C; $[\alpha]_D^{22}$ = +174.1 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83-3.75 (m, 4H), 3.98 (ddd, J_1 = 4.7 Hz, J_2 = 8.9 Hz, J_3 = 10.3 Hz, 1H), 4.21-4.17 (m, 1H), 4.24 (dd, J_1 = 4.6 Hz, J_2 = 10.2 Hz, 1H), 5.56 (s, 1H), 5.67-5.62 (m, 1H), 5.86 (dt, J_d = 10.2 Hz, J_t = 2.5 Hz, 1H), 6.31-6.24 (m, 1H), 6.92-6.87 (m, 2H), 6.99-6.93 (m, 2H), 7.45-7.37 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.3, 64.9, 69.2, 74.8, 93.4, 102.2, 113.7, 114.7, 118.6, 125.6, 127.6, 129.7, 132.0, 132.4, 156.2, 160.3 ppm. HRMS (ESI) calcd. for $C_{20}H_{20}O_5Br$ [M+H]: 419.0494, found: 419.0491.

(4a*R*,6*R*,8a*S*)-6-(4-*tert*-butylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3]dioxine

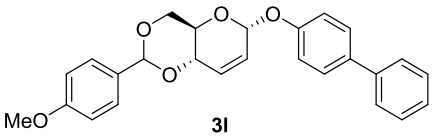


3k

According to the general procedure, **3k** (32.9 mg, 83%) was obtained as a white solid. m.p. 236-238 °C; $[\alpha]_D^{22}$ = +169.6 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.31 (s, 9H), 3.85-3.74 (m, 4H), 4.06-3.96 (m, 1H), 4.22-4.15 (m, 1H), 4.26 (dd, J_1 = 4.6 Hz, J_2 = 10.2 Hz, 1H), 5.55 (s, 1H), 5.70-5.63 (m, 1H), 5.87 (dt, J_d = 10.2 Hz, J_t = 2.2 Hz, 1H), 6.29-6.21 (m, 1H), 6.92-6.86 (m, 2H), 7.05-6.97 (m, 2H), 7.35-7.28 (m, 2H), 7.46-7.39 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 31.5, 34.2, 55.3, 64.7,

69.3, 74.9, 93.5, 102.2, 113.7, 116.3, 126.1, 126.3, 127.6, 129.8, 131.6, 145.1, 154.9, 160.2 ppm. HRMS (ESI) calcd. for $C_{24}H_{28}O_5Na$ [M+Na]: 419.1834, found: 419.1832.

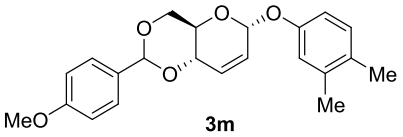
(4a*R*,6*R*,8a*S*)-6-(biphenyl-4-yloxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydro pyrano[3,2-*d*][1,3]dioxine



3l

According to the general procedure, **3l** (32.9 mg, 79%) was obtained as a white soild. m.p. 256-257 °C; $[\alpha]_D^{22}$ = +219.6 (*c* = 0.49 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.85-3.77 (m, 4H), 4.04 (ddd, J_1 = 4.6 Hz, J_2 = 9.0 Hz, J_3 = 10.1 Hz, 1H), 4.24-4.19 (m, 1H), 4.28 (dd, J_1 = 4.6 Hz, J_2 = 10.2 Hz, 1H), 5.57 (s, 1H), 5.76-5.73 (m, 1H), 5.91 (dt, J_d = 10.3 Hz, J_t = 2.4 Hz, 1H), 6.31-6.26 (m, 1H), 6.93-6.87 (m, 2H), 7.18-7.12 (m, 2H), 7.34-7.29 (m, 1H), 7.46-7.39 (m, 4H), 7.58-7.51 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.3, 64.9, 69.3, 74.9, 93.4, 102.2, 113.8, 117.1, 125.9, 126.8, 127.6, 128.2, 128.7, 129.8, 131.9, 135.4, 140.7, 156.7, 160.3 ppm. HRMS (ESI) calcd. for $C_{26}H_{25}O_5Na$ [M+Na]: 439.1521, found: 439.1520.

(4a*R*,6*R*,8a*S*)-6-(3,4-dimethylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahy dropyrano[3,2-*d*][1,3]dioxine

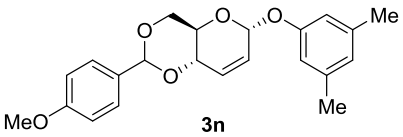


3m

According to the general procedure, **3m** (31.3 mg, 85%) was obtained as a white solid. m.p. 186-188 °C; $[\alpha]_D^{22}$ = +170.1 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.20 (s, 3H), 2.24 (s, 3H), 3.84-3.74 (m, 4H), 4.02 (ddd, J_1 = 4.7 Hz, J_2 = 9.0 Hz, J_3 = 10.2 Hz, 1H), 4.21-4.15 (m, 1H), 4.26 (dd, J_1 = 4.6 Hz, J_2 = 10.2 Hz, 1H), 5.55 (s, 1H), 5.67-5.62 (m, 1H), 5.87 (dt, J_d = 10.3 Hz, J_t = 2.5 Hz, 1H), 6.28-6.21 (m, 1H),

6.84-6.79 (m, 1H), 6.93-6.85 (m, 3H), 7.07-7.02 (m, 1H), 7.46-7.39 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.9, 20.0, 55.3, 64.7, 69.3, 74.9, 93.6, 102.2, 113.7, 114.0, 118.4, 126.2, 127.6, 129.8, 130.3, 130.5, 131.6, 137.8, 155.2, 160.2 ppm. HRMS (ESI) calcd. for $C_{22}H_{25}O_5$ [M+H]: 369.1702, found: 369.1701.

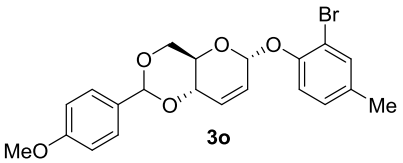
(4a*R*,6*R*,8a*S*)-6-(3,5-dimethylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3]dioxine



3n

According to the general procedure, **3n** (28.7 mg, 78%) was obtained as a white solid. m.p. 185-187 °C; $[\alpha]_D^{22}$ = +134.1 (c = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.30 (s, 6H), 3.84-3.75 (m, 4H), 4.01 (ddd, J_1 = 4.7 Hz, J_2 = 9.0 Hz, J_3 = 10.2 Hz, 1H), 4.21-4.15 (m, 1H), 4.27 (dd, J_1 = 4.7 Hz, J_2 = 10.2 Hz, 1H), 5.56 (s, 1H), 5.70-5.65 (m, 1H), 5.86 (dt, J_d = 10.2 Hz, J_t = 2.5 Hz, 1H), 6.28-6.21 (m, 1H), 6.73-6.66 (m, 3H), 6.92-6.86 (m, 2H), 7.46-7.39 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.4, 55.3, 64.8, 69.3, 74.9, 93.2, 102.2, 113.7, 114.5, 124.1, 126.1, 127.6, 129.8, 131.6, 139.3, 157.2, 160.2 ppm. HRMS (ESI) calcd. for $C_{22}H_{25}O_5$ [M+H]: 369.1702, found: 369.1703.

(4a*R*,6*R*,8a*S*)-6-(2-bromo-4-methylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3]dioxine

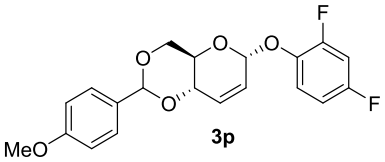


3o

According to the general procedure, **3o** (31.5 mg, 73%) was obtained as a white solid. m.p. 142-144 °C; $[\alpha]_D^{22}$ = +117.0 (c = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.29 (s, 3H), 3.82-3.74 (m, 4H), 4.23-4.10 (m, 2H), 4.29 (dd, J_1 = 4.6 Hz, J_2 = 10.3

Hz, 1H), 5.56 (s, 1H), 5.60-5.57 (m, 1H), 5.97 (dt, J_d = 10.3 Hz, J_t = 2.4 Hz, 1H), 6.31-6.25 (m, 1H), 6.92-6.87 (m, 2H), 7.07-7.04 (m, 2H), 7.39-7.35 (m, 1H), 7.46-7.40 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.3, 55.3, 64.9, 69.2, 74.8, 95.5, 102.2, 113.7, 114.3, 119.1, 125.7, 127.6, 129.0, 129.8, 132.0, 133.7, 134.2, 151.8, 160.2 ppm. HRMS (ESI) calcd. for $C_{21}H_{22}O_5Br$ [M+H]: 433.0651, found: 433.0643.

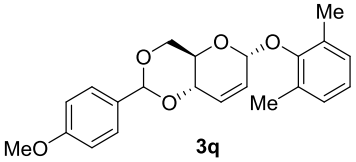
(4a*R*,6*R*,8a*S*)-6-(2,4-difluorophenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydro pyrano[3,2-*d*][1,3]dioxine



3p

According to the general procedure, **3p** (26.3 mg, 70%) was obtained as a white solid. m.p. 188-200 °C; $[\alpha]_D^{22}$ = +76.9 (*c* = 0.59 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83-3.75 (m, 4H), 4.14-4.06 (m, 1H), 4.23-4.16 (m, 1H), 4.27 (dd, J_1 = 4.6 Hz, J_2 = 10.2 Hz, 1H), 5.54-5.49 (m, 1H), 5.56 (s, 1H), 5.94 (dt, J_d = 10.3 Hz, J_t = 2.5 Hz, 1H), 6.32-6.26 (m, 1H), 6.93-6.77 (m, 4H), 7.19-7.11 (m, 1H), 7.46-7.40 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.3, 64.8, 69.1, 74.8, 95.9, 102.2, 104.7, 104.9, 105.0, 105.2, 110.7, 110.8, 111.0(2C), 113.8, 121.3, 121.4(2C), 121.5, 125.4, 127.6, 129.7, 132.3, 160.3 ppm. HRMS (ESI) calcd. for $C_{20}H_{19}O_5F_2$ [M+H]: 377.1201, found: 377.1200.

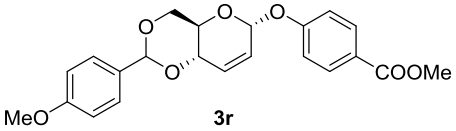
(4a*R*,6*R*,8a*S*)-6-(2,6-dimethylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetra hydropyrano[3,2-*d*][1,3]dioxine



3q

According to the general procedure, **3q** (20.6 mg, 56%) was obtained as a white solid. m.p. 183-185 °C; $[\alpha]_D^{22}$ = +138.4 (*c* = 1.0 in $CHCl_3$);^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.24 (s, 6H), 3.79-3.68 (m, 4H), 4.15-4.04 (m, 2H), 4.27 (dd, J_1 = 3.5 Hz, J_2 = 10.7 Hz, 1H), 5.26-5.19 (m, 1H), 5.50 (s, 1H), 6.02-5.93 (m, 1H), 6.25-6.18 (m, 1H), 6.92-6.80 (m, 3H), 6.99-6.93 (m, 2H), 7.42-7.34 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.0, 55.3, 64.8, 69.3, 74.9, 97.4, 102.1, 113.7, 124.4, 126.1, 127.6, 129.0, 129.8, 130.9, 131.8, 154.8, 160.2 ppm. HRMS (ESI) calcd. for $C_{22}H_{25}O_5$ [M+H]: 369.1702, found: 369.1699.

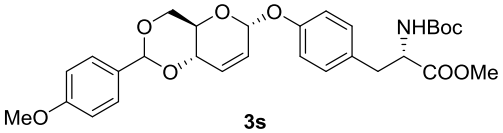
Methyl 4-(((4aR,6R,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)oxy)benzoate



3r

According to the general procedure, **3r** (34.2 mg, 86%, : =20:1) was obtained as a white solid. m.p. 213-214 °C; $[\alpha]_D^{22}$ = +196.6 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.83-3.76 (m, 4H), 3.89 (s, 3H), 4.02-3.93 (m, 1H), 4.26-4.18 (m, 2H), 5.56 (s, 1H), 5.80-5.75 (m, 1H), 5.88 (dt, J_d = 10.2 Hz, J_t = 2.5 Hz, 1H), 6.33-6.27 (m, 1H), 6.92-6.87 (m, 2H), 7.11-7.06 (m, 2H), 7.45-7.39 (m, 2H), 8.02-7.79 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 51.9, 55.3, 65.1, 69.1, 74.7, 92.8, 102.2, 113.7, 116.0, 124.0, 125.4, 127.6, 129.7, 131.5, 132.2, 160.3, 160.8, 166.7 ppm. HRMS (ESI) calcd. for $C_{22}H_{23}O_7$[M+H]: 399.1444, found: 399.1443.

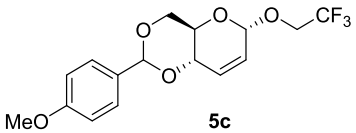
(2*S*)-methyl2-(*tert*-butoxycarbonylamino)-3-(4-((4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3]dioxin-6-yloxy)phenyl)propanoate



3s

According to the general procedure, **3s** (40.0 mg, 74%, : =17:1) was obtained as a white solid. m.p. 167-169 °C; $[\alpha]_D^{23}$ = +132.5 (*c* = 1.0 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.42 (s, 9H), 3.12-2.94 (m, 2H), 3.72 (s, 3H), 3.84-3.75 (m, 4H), 3.99 (dt, J_d = 4.7 Hz, J_t = 10.1 Hz, 1H), 4.22-4.15 (m, 1H), 4.26 (dd, J_1 = 4.6 Hz, J_2 = 10.1 Hz, 1H), 4.68-4.37 (m, 1H), 5.05-4.89 (m, 1H), 5.56 (s, 1H), 5.69-5.63 (m, 1H), 5.86 (dt, J_d = 10.2 Hz, J_t = 2.4 Hz, 1H), 6.29-6.22 (m, 1H), 6.93-6.86 (m, 2H), 7.08-6.97 (m, 4H), 7.46-7.38 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.3, 37.5, 52.2, 54.4, 55.3, 64.8, 69.2, 74.8, 79.9, 93.3, 102.2, 113.7, 116.8, 125.9, 127.6, 129.7, 129.8, 130.3, 131.8, 155.1, 156.3, 160.2, 172.3 ppm. HRMS (ESI) calcd. for $C_{29}H_{36}O_9N$ [M+H]: 542.2390, found: 542.2393.

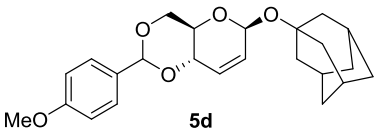
(4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-6-(2,2,2-trifluoroethoxy)-4,4a,6,8a-tetrahydro pyrano[3,2-*d*][1,3]dioxine



5c

According to the general procedure, **5c** (32.9 mg, 95%) was obtained as a white solidl. m.p. 111-113 °C; $[\alpha]_D^{22}$ = +90.6 (*c* = 1.0 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 3.83-3.75 (m, 4H), 4.11-3.85 (m, 3H), 4.18-4.12 (m, 1H), 4.27 (dd, J_1 = 4.5 Hz, J_2 = 10.0 Hz, 1H), 5.11-5.05 (m, 1H), 5.54 (s, 1H), 5.76 (dt, J_d = 10.3 Hz, J_t = 2.4 Hz, 1H), 6.22-6.16 (m, 1H), 6.93-6.86 (m, 2H), 7.45-7.38 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.3, 64.2, 64.9, 65.2, 69.1, 74.9, 95.2, 102.2, 113.7, 122.4, 125.2, 125.3, 127.6, 129.7, 131.9, 160.3 ppm. HRMS (ESI) calcd. for $C_{16}H_{18}O_5F_3$ [M+H]: 347.1106, found: 347.1108.

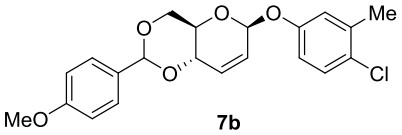
(4a*R*,6*S*,8a*S*)-2-(4-methoxyphenyl)-6-(tricyclo(3.3.1.1(sup3,7))decan-1-oxy)-4,4a, 6,8a-tetrahydropyrano[3,2-*d*][1,3]dioxine



5d

According to the general procedure, **5d** (13.5 mg, 34%) was obtained as a white solid. m.p. 133-135 °C; $[\alpha]_D^{22}$ = +43.9 (*c* = 1.0 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.70-1.59 (m, 6H), 1.90-1.78 (m, 6H), 2.22-2.12 (m, 3H), 3.75 (ddd, J_1 = 4.6 Hz, J_2 = 8.4 Hz, J_3 = 10.3 Hz, 1H), 3.80 (s, 3H), 3.86 (t, *J* = 10.3 Hz, 1H), 4.22 (dd, J_1 = 4.5 Hz, J_2 = 10.2 Hz, 1H), 4.39-4.32 (m, 1H), 5.59-5.53 (m, 2H), 5.65-5.60 (m, 1H), 6.09-6.03 (m, 1H), 6.92-6.85 (m, 2H), 7.45-7.39 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.7, 36.2, 42.5, 55.3, 69.2, 70.7, 75.0, 75.3, 91.9, 102.0, 113.7, 127.5, 130.0, 130.3, 130.5, 160.1 ppm. HRMS (ESI) calcd. for $C_{24}H_{30}O_5Na$ [M+Na]: 421.1991, found: 421.1994.

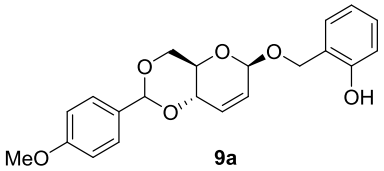
(4a*R*,6*S*,8a*S*)-6-(4-chloro-3-methylphenoxy)-2-(4-methoxyphenyl)-4,4a,6,8a-tetra hydropyrano[3,2-*d*][1,3]dioxine



7b

According to the general procedure, **7b** (29.9 mg, 77%) was obtained as a white solid with XantPhos as the ligand. m.p. 135-137 °C; $[\alpha]_D^{22}$ = +30.6 (*c* = 1.0 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 2.38 (s, 3H), 3.83 (s, 3H), 3.94-3.88 (m, 2H), 4.38-4.31 (m, 1H), 4.46-4.41 (m, 1H), 5.61 (s, 1H), 5.84 (ddd, J_1 = 1.7 Hz, J_2 = 2.5 Hz, J_3 = 10.2 Hz, 1H), 5.95-5.91 (m, 1H), 6.32-6.26 (m, 1H), 6.96-6.89 (m, 3H), 7.02-6.98 (m, 1H), 7.30-7.25 (m, 1H), 7.49-7.43 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.3, 55.3, 68.9, 71.0, 74.6, 96.9, 102.1, 113.7, 115.5, 119.4, 126.8, 127.5, 127.9, 129.6, 132.3, 137.2, 155.2, 160.2 ppm. HRMS (ESI) calcd. for $C_{21}H_{22}O_5Cl$ [M+H]: 389.1156, found: 389.1161.

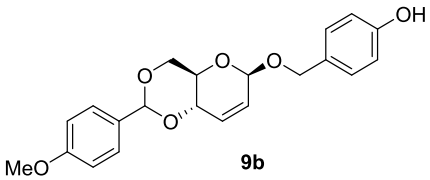
2-(((4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3] dioxin-6-yloxy)methyl)phenol



9a

According to the general procedure, **9a** (28.9 mg, 78%) was obtained as a colorless oil. m.p. 147-149 °C; $[\alpha]_D^{22}$ = +53.8 (*c* = 1.0 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 3.86-3.76 (m, 4H), 3.90 (t, *J* = 10.2 Hz), 4.40-4.29 (m, 2H), 4.78-4.70 (m, 1H), 4.95-4.87 (m, 1H), 5.57-5.52 (m, 1H), 5.59 (s, 1H), 5.76-5.68 (m, 1H), 6.25-6.17 (m, 1H), 6.94-6.83 (m, 4H), 6.97 (s, 1H), 7.14-7.07 (m, 1H), 7.29-7.20 (m, 1H), 7.45-7.38 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.3, 67.4, 68.7, 70.8, 74.7, 97.7, 102.1, 113.7, 116.7, 120.1, 122.1, 126.9, 127.5, 129.4, 129.6, 130.2, 132.4, 155.8, 160.2 ppm. HRMS (ESI) calcd. for $C_{21}H_{23}O_6$ [M+H]: 371.1495, found: 371.1497.

4-(((4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3]di oxin-6-yloxy)methyl)phenol

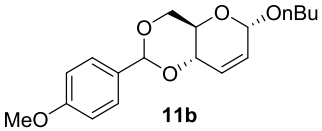


9b

According to the general procedure, **9b** (29.6 mg, 80%) was obtained as a colorless oil. m.p. 149-151 °C; $[\alpha]_D^{22}$ = +33.5 (*c* = 1.0 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 3.82-3.72 (m, 4H), 3.89 (t, *J* = 10.3 Hz, 1H), 4.38-4.26 (m, 2H), 4.59-4.52 (m, 1H), 4.80-4.73 (m, 1H), 5.07 (brs, 1H), 5.45-5.38 (m, 1H), 5.58 (s, 1H), 5.74-5.66 (m, 1H), 6.17-6.10 (m, 1H), 6.83-6.75 (m, 2H), 6.92-6.86 (m, 2H), 7.27-7.20 (m, 2H), 7.46-7.39 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.3, 69.0, 69.2, 70.5, 75.0, 97.5,

102.0, 113.7, 115.3, 127.5, 128.3, 129.1, 129.7, 129.9, 131.4, 155.6, 160.1 ppm. HRMS (ESI) calcd. for $C_{21}H_{23}O_6$ [M+H]: 371.1495, found: 371.1496.

Benzyl 4,6-*O*-(*para*-methoxy)benzylidene-α-D-pseudoglycal 11b



11b

According to the general procedure, the solution of picolinate **10** (9.3 mg, 0.025 mmol), butan-1-ol **4a** (3.7 mg, 0.05 mmol), $Pd(PPh_3)_4$ (2.9 mg, 0.0025 mmol) and DPPB (2.1 mg, 0.005 mmol) in DCM (1 mL) was stirred at 60 ^oC for 48 h and then purified by flash column chromatography to give desired product **11a** (6.9 mg, α:β=6.4:1, 86%) as colorless oil; ^1H NMR of the α–product ($CDCl_3$, 500 MHz): δ 7.44-7.40 (m, 2H), 6.91-6.87 (m, 2H), 6.13-6.08 (m, 1H), 5.72 (td, J_t = 2.5 Hz, J_d = 10.3 Hz, 1H), 5.54 (s, 1H), 5.01-4.97 (m, 1H), 4.27 (dd, J_1 = 4.5 Hz, J_2 = 10.1 Hz, 1H), 4.15-4.10 (m, 1H), 3.92-3.85 (m, 1H), 3.81-3.76 (m, 5H), 3.54-3.48 (m, 1H), 1.66-1.56 (m, 2H), 1.45-1.35 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.2, 130.6, 130.0, 127.6, 126.9, 113.7, 102.1, 95.1, 75.3, 69.5, 68.5, 63.9, 55.3, 31.9, 19.3, 13.8 ppm. HRMS (ESI) calcd. for $C_{18}H_{25}O_5$ [M+H]: 321.1702, found: 321.1701.

Compounds **5a**, **5b**, **5e**, **5f**, **5g**, **5h**, **5i**, **5j**, **7a** are reported in above parts and all data of these compounds are checked to be consistent with literature reports.[5b]

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3. For recent examples about glycosylation by employing zinc(II) alkoxides as an activator, see: (a) Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336-1337. (b) Schuff, B. P.; Mercer, G. J.; Nguyen, H. M. *Org. Lett.* **2007**, *9*, 3173-3176; it should be noted that when phenol type nucleophile was used as the glycosyl acceptor, the reaction can go without zinc(II) reagent.
4. For recent examples about *de novo* catalytic asymmetric synthesis, see: (a) A. C. Comely, R. Eelkema, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2003**, *125*, 8714-8715. (b) R. S. Babu, G. A. O'Doherty, *J. Am. Chem. Soc.* **2003**, *125*, 12406-12407. (c) H.-Y. L. Wang, Y. Rojanasakul, G. A. O'Doherty, *ACS Med. Chem. Lett.* **2011**, *2*, 264-269.
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Kirsch, S. F.; Overman, L. E.; White, N. S. *Org. Lett.* **2007**, *9*, 911-913.

9. (a) Kiyotsuka, Y.; Acharya, H. P.; Katamaya, Y.; Hyodo, T.; Kabayashi, Y. *Org. Lett.* **2008**, *10*, 1719-1722. (b) Kiyotsuka, Y.; Katamaya, Y.; Acharya, H. P.; Hyodo, T.; Kabayashi, Y. *J. Org. Chem.* **2009**, *74*, 1939-1951. (c) Kaneko, Y.; Kiyotsuka, Y.; Acharya, H. P.; Kabayashi, Y. *Chem. Commun.* **2010**, *46*, 5482-5484. (d) Feng, C.; Kobayashi, Y. *J. Org. Chem.* **2013**, *78*, 3755-3766. (e) Feng, C.; Kobayashi, Y. *Eur. J. Org. Chem.* **2013**, 6666-6676.
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12. For more details of the crystal structure, see: CCDC number: 979358.
13. Tusji, J. Palladium Reagents and Catalysts-New Perspectives for the 21st century, John Wiley & Sons, Ltd, **2004**, pp. 438-443, and the references cited therein.

PART 3

Palladium catalyzed *C*- and *N*-glycosylation *via* a decarboxylative strategy

Chapter 1: Regio- and stereo-selective synthesis of 2-deoxy-*C*-aryl glycosides *via* Palladium catalyzed decarboxylative reactions[1]

Introduction

C-Glycosylation has attracted great interests due to the relative structures *C*-glycosides are playing critical role in chemistry and biology in the form of natural products, mimics of glycolipids, oligosaccharides and glycoprotein.[2] When compared to the *O*-glycosides, their *C*-glycoside analogues always exhibited stronger stability to enzymatic or chemical hydrolysis and higher activity.[3] These high potential features stimulated the scientists to gain sufficient *C*-glycosides either from nature or synthesis. With the development of *C*-glycosylation, more and more new compounds were found to be useful for chemotherapeutic application. Among which, *C*-aryl glycoside containing structures occupied most of them (**Figure 3.1.1**).[4]

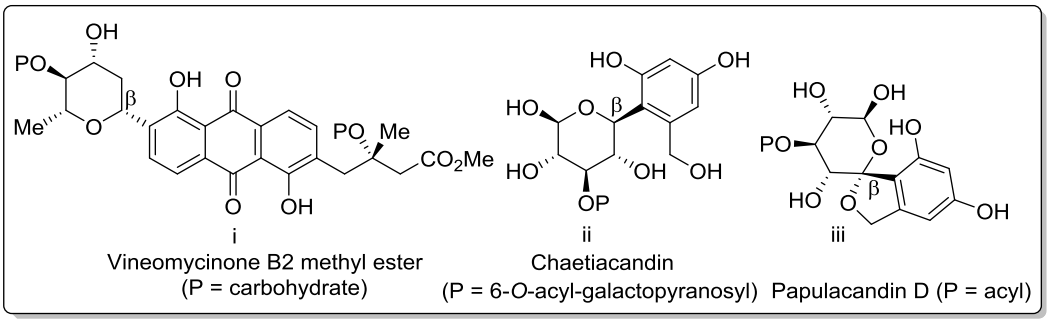
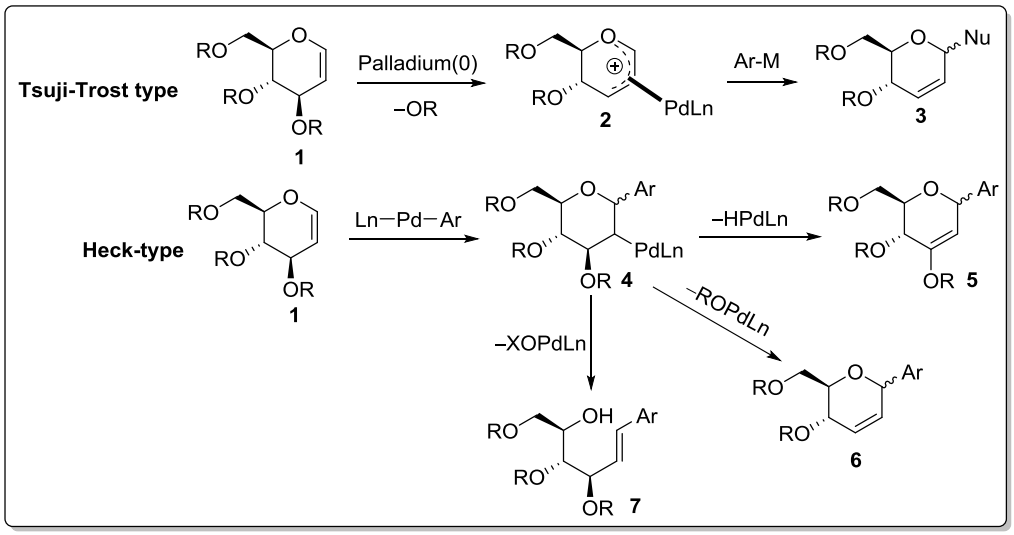


Figure 3.1.1 Biologically active natural products containing *C*-aryl glycosides

Significant efforts have been devoted to develop efficient and practical glycosylation methods for the syntheses of these structures. A plenty of methods and

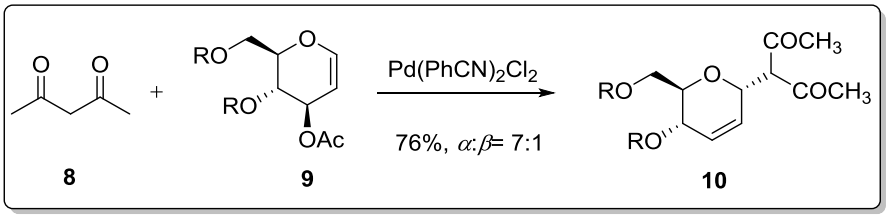
strategies have been developed till now, however, the outcome of these reaction are always very poor due to the lack of the anomeric effect and neighboring group participation. As our continuous interest is to develop glycosylation methods with glycal as the starting material, we herein give a brief introduction about the *C*-glycosylation specifically on palladium-catalyzed reactions.

When a metal catalyst is involved in the reaction, the syntheses of *C*-glycosides from glycal **1** normally have two pathways. The first pathway is called Tsuji-Trost type pathway and its key intermediate is the Pd-π-allyl species **2**, which was then attacked by a nucleophile to give desired product **3**. The second pathway is known as Heck-type reaction. Generally, the oxidative addition product **4** is the intermediate for this type of reaction. Unlike to the prior pathway, three possible reductive elimination products **5**, **6** and **7** could be obtained *via* *syn*-hydride elimination, *anti*-OR elimination and *anti*-OX elimination correspondingly (**Scheme 3.1.1**).



Scheme 3.1.1 Palladium catalyzed *C*-glycosylation

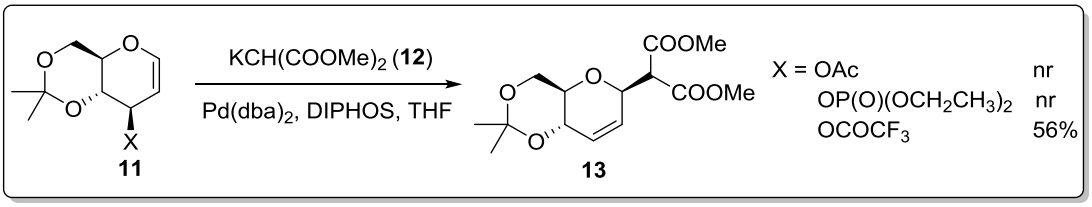
In the last few decades, the Tsuji-Trost reaction has been fully explored. A plenty of glycosylation strategies have been provided based on the classic intermediate **2**, starting from glycal derived starting materials. The allylic features of glycal stimulated their development in carbohydrate chemistry. However, its application was hindered due to the formation and low activity of the Pd π-allyl species in the electron-rich glycal system. In addition, since the low nucleophilicity of *C*-nucleophile, strong Lewis acid and *β*-dicarbonyl compound **8** were commonly used to promote the Ferrier reaction with glycal donor. As such, *O*-, *N*- and *S*- nucleophiles were the most widely used glycosyl acceptors for this type of reaction. It was until 1983, Miwa reported a *C*-glycosylation method with $Pd(PhCN)_2Cl_2$ catalyst to activate acetylated glycals donors **9** and that palladium catalyst displayed a similar effect as a Lewis acid to provide *α*-type *C*-glycoside **10** as the major product.[5]



Scheme 3.1.2 Palladium catalyzed *C*-glycosylation with acetylated glycal

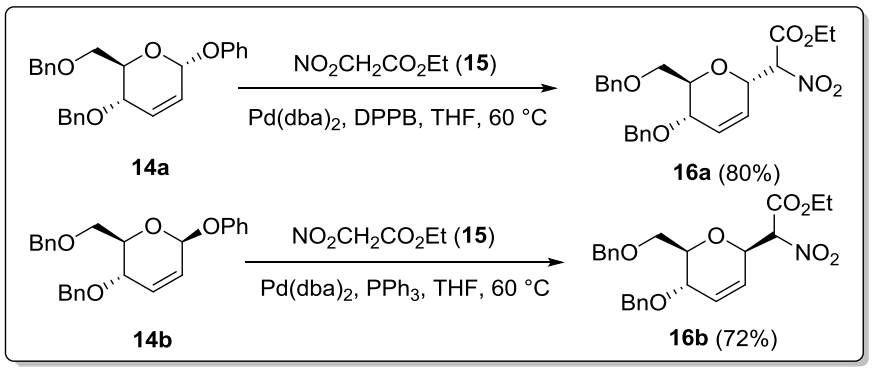
It was found that the installation of a good leaving group at *C*-3 position with strong electron-withdrawing effect was also effective to promote *C*-glycosylation reaction. In 1985, a glycal donor **11** with a trifluoroacetate group was employed by RajanBabu. With active malonate-type *C*-nucleophile **12** as the glycosyl acceptor, the reaction gave the desired *C*-glycoside **13** in a reasonable yield with exclusive *β*-

selectivity (**Scheme 3.1.3**).[6] However, benzylidene protected donor was unstable and failed to give any desired product.



Scheme 3.1.3 Palladium catalyzed *C*-glycosylation with active *C*-nucleophile

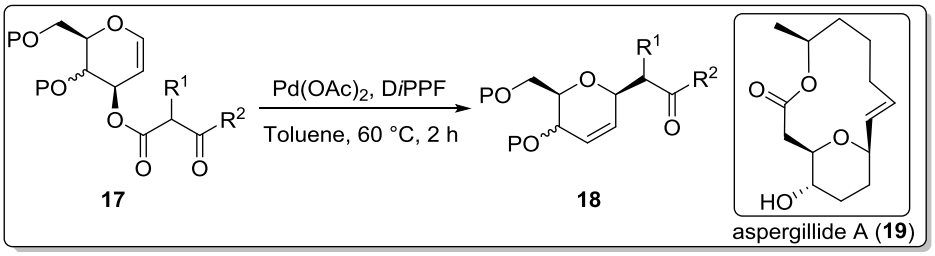
In 1989, more active phenolic glycoside **14** with 2,3-unsaturated structure was also examined for the formation of *C*-glycosidic linkage by Sinou.[7] Similar to the previous results, only malonate-type *C*-nucleophile **15** was able to react. It should be noted that this reaction was preceded with good stereocontrol, and the chirality of the anomeric center was retained in product **16** which indicated that the reaction proceed through double S_N2-like nucleophilic substitutions (**Scheme 3.1.4**).



Scheme 3.1.4 Palladium catalyzed *C*-glycosylation with pyranosyl system

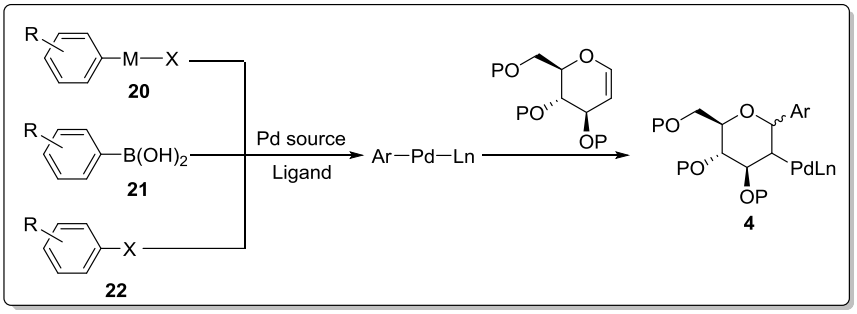
Though great efforts had been paid to develop this type of glycosylation method, no huge improvement was obtained until 2013.[8] Inspired by the features of glycal, Liu's group presented an efficient strategy to synthesize *C*-glycosides **18** with high yield

and excellent selectivity from glycal derivative **17** *via* a decarboxylative allylation reaction (**Scheme 3.1.5**). Moreover, a wide range of substrate scope was examined and the utility of this method was demonstrated by the synthesis of aspergillide A (**19**).



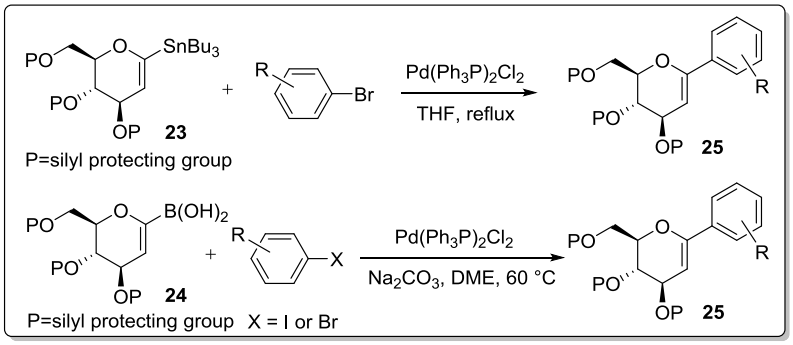
Scheme 3.1.5 Palladium catalyzed decarboxylative *C*-glycosylation

In contrast to Tsuji-Trost type reactions, coupling reaction is more widely used in *C*-glycosylation reactions, especially in the synthesis of *C*-aryl glycoside. As mentioned above, formation of key intermediate **4** is the crucial step for this type of reaction. Besides glycal, another coupling partner Ln-Pd-Ar is usually generated in *situ* under specific reaction conditions. As the Ln-Pd-Ar species can be obtained by many approaches and the reductive elimination could be occurred through three possible pathways, then the scope of substrates and types of *C*-glycosides obtained are much broader. At the beginning, Ln-Pd-Ar species was prepared by cross-coupling of organometallic reagents **20** (Hg compounds) and glycal in the presence of palladium catalyst.[9] However, its application was hindered by the usage of toxicity reagents. Later, the organometallic reagent was replaced by arylboronic acid **21** (Suzuki-type) or aryl halides **22** (Heck-type) and the reaction underwent smoothly to form the desired product.[10] Due to their high stability, availability, and low toxicity, these reagents were more commonly used. However, only TBS protected glycals were able to give good yield and selectivity in the most of cases (**Scheme 3.1.6**).



Scheme 3.1.6 Approaches to form key intermediate **4**

Besides the above methods, another approach to synthesize *C*-aryl glycoside **25** is by coupling glycal derivatives with aryl halides (**Scheme 3.1.7**). Pioneered by Beau and Friesen, the reaction was first tested with stannylated glycals **23** (Stille-type).[11] Similarly, a moderate outcome was provided and the toxicity of stannylated reagent made this approach less popular. It was until recently, Kotora reported another Suzuki-type coupling reaction to construct *C*-glycosidic linkage with glycosyl donor **24** and a much better outcome were obtained.[12] However, the protecting group of glycal was limited to silyl group.

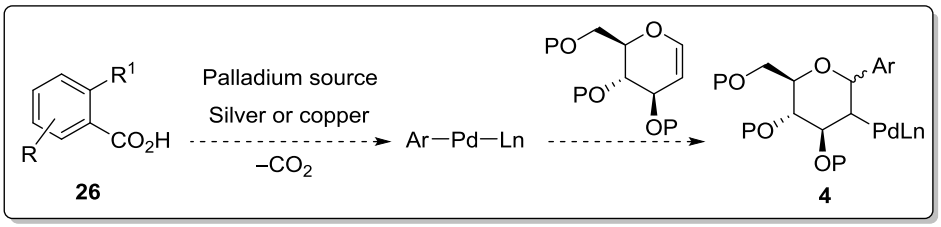


Scheme 3.1.7 Coupling reaction with glycal derivatives

From the above literature survey, we could see that a plenty of synthetic methods have been provided for the construction of *C*-glycosidic bonds. However, limitations are still carried for each of those reactions. Hence, it is still necessary to develop more

flexible and efficient strategies for the construction of *C*-glycosidic bonds. Our group has been investigating palladium-catalyzed decarboxylative reaction for a very long time and our attention has always been focusing on the decarboxylation of glycal derivatives. Hence, we decided to extend our strategy in this area and develop a method on decarboxylation of glycosyl acceptor.

For the glycosyl acceptor, we found that ubiquitous carboxylic acids **26** might be a good choice to give the key intermediate **4** *via* a decarboxylative reaction. Meanwhile, it has been demonstrated by Myers[13] and Goossen[14] that *ortho*-substituted arene carboxylic acids were able to serve as synthetic equivalents of aryl halides. Normally, these Heck-type reactions have always been conducted in the presence of palladium catalysts and stoichiometric amounts of silver or copper additives at high temperatures. Moreover, they exhibited very good tolerance to water and oxygen. Given the successful examples of decarboxylative coupling with benzoic acids and our continuous efforts on developing new synthetic methodologies for synthesis of glycosidic bonds, we envisioned that this strategy could possibly work effectively to provide a good access to synthesize *C*-glycosides. Herein, we explore the possibility for the preparation of 2-deoxy-*C*-aryl glycosides *via* this protocol (**Scheme 3.1.8**).

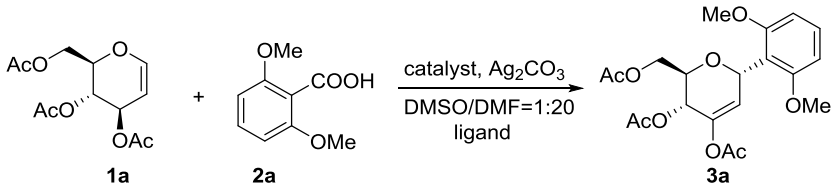


Scheme 3.1.8 Proposed *C*-aryl glycosylation with benzoic acids

Result and discussion

As the claim of pioneer scientists, at least one substituent was necessary for the benzoic acid analogues to occur the decarboxylative reaction. Then 2,6-dimethoxybenzoic acid (**2a**) was selected as one of the coupling partner. As for the glycosyl donor, 3,4,6-tri-*O*-acetyl-D-glucal (**1a**) was employed due to its commercial availability. To commence our idea, we conducted the reaction by subjecting of **1a** and **2a** in the presence of $Pd(OAc)_2$ and Ag_2CO_3 in DMSO/DMF (1:20) at 80 °C for 12 h. To our delight, this set of condition gave the desired product **3a** in 50% yield as a single diastereomer (entry **1**). Considering the stability of sugar scaffold at high temperature, we reduced the duration of the reaction to 4 h, a yield of 59% was obtained while 29% of compound **1a** was recovered (entry **2**). When the reaction temperature was decreased to 60 °C or 70 °C, trace to poor yields of product were obtained (entries **3**-**4**). Next, different palladium source such as $PdCl_2$, $Pd(TFA)_2$ and $Pd(PPh_3)_2Cl_2$ was screened and $Pd(OAc)_2$ was found to be the best catalyst suitable to promote this coupling reaction (entries **5**-**7**). Subsequently, different ligands were used to optimize this reaction. As shown in **Table 3.1.1**, it was found that the ligand can affect the outcome of reaction significantly (entries **8-13**). Some of the ligands examined were able to improve the outcome such as PPh_3 and R-monophos (entries **8-10**) while others failed to provide good results (entries **11-13**). Based on the optimizing results, PPh_3 exhibited the best ability to accelerate the coupling of the two reagents (entry **8**). Thus, we concluded our optimization as follows: the reaction of **1a** (1.0 equiv) and **2a** (2.0 equiv) in the presence of $Pd(OAc)_2$ (0.1 equiv), Ag_2CO_3 (3.0 equiv), PPh_3 (0.4 equiv) in DMSO/DMF (1:20) at 80 °C for 4 h.

Table 3.1.1 Optimization of the decarboxylative coupling reaction [a]

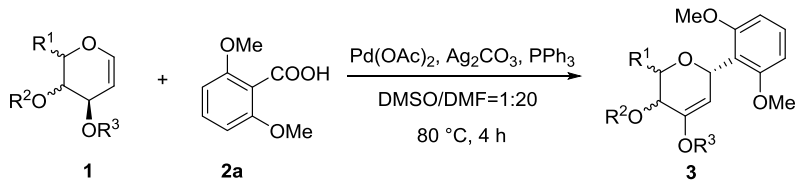


Entry	Catalyst	Ligand	Temp (°C)	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$	none	80	12	50
2	$Pd(OAc)_2$	none	80	4	59
3	$Pd(OAc)_2$	none	60	4	trace
4	$Pd(OAc)_2$	none	70	4	<5
5	$PdCl_2$	none	80	4	54
6	$Pd(TFA)_2$	none	80	4	<5
7	$Pd(PPh_3)_2Cl_2$	none	80	4	<10
8	$Pd(OAc)_2$	PPh_3	80	4	79
9	$Pd(OAc)_2$	R-monophos	80	4	77
10	$Pd(OAc)_2$	X-phos	80	4	63
11	$Pd(OAc)_2$	S-phos	80	4	46
12	$Pd(OAc)_2$	Xantphos	80	4	28
13	$Pd(OAc)_2$	$(2\text{-MeOPh})_3P$	80	4	10

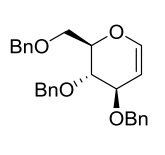
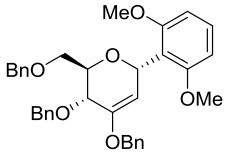
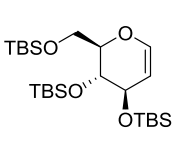
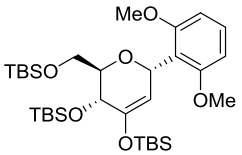
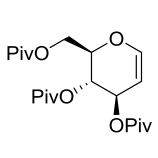
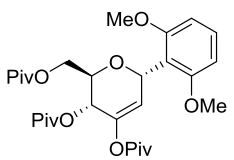
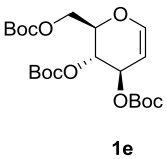
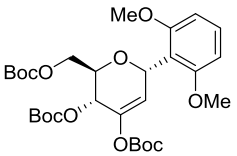
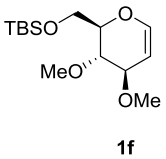
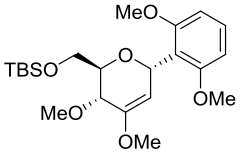
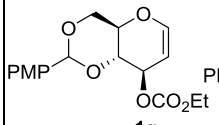
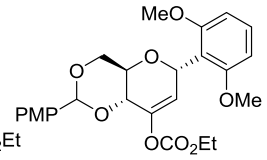
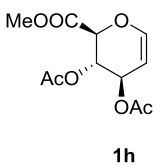
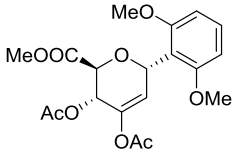
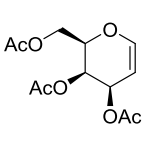
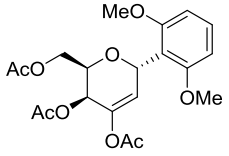
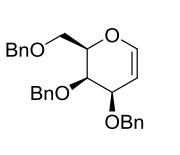
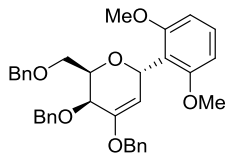
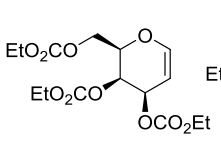
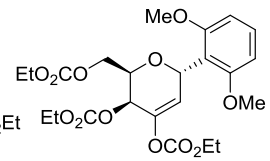
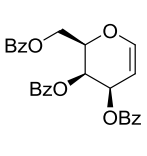
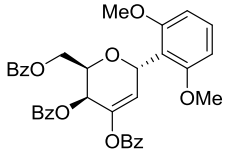
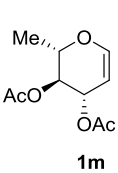
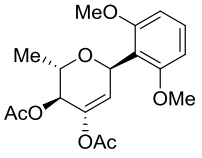
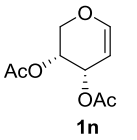
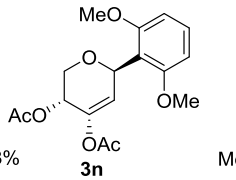
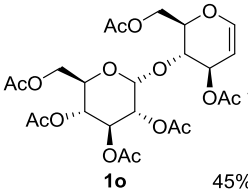
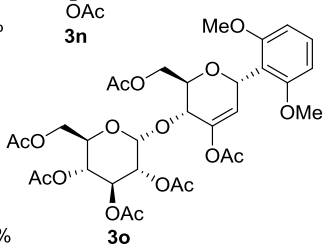
[a] Reaction conditions: 3,4,6-tri-*O*-acetyl-D-glucal 0.2 mmol, 2,6-dimethoxybenzoic acid 0.4 mmol (2.0 equiv), Ag_2CO_3 0.6 mmol (3.0 equiv), catalyst 0.02 mmol (0.1 equiv), ligand 0.08 mmol (0.4 equiv), DMF/DMSO = 2 mL/0.1 mL. [b] Isolated yields.

Following the establishment of optimized reaction conditions, a variety of glycals with different protecting group were proceeded to extend the substrate scope. The results were summarized in **Table 3.1.2** and all the examined glycals were able to give the desired *C*-glycosides in moderate to good yields with excellent α-selectivity. Glucal-type substrates were first used for the optimized condition. Both electron-donating (**3b**, **3c, 3f**) and electron-withdrawing protecting groups (**3d**, **3e**) containing donors can be involved in the reaction to afford the desired products in 55-73% yields. Moreover, the reaction with substrates bearing bulky protecting group could also proceed smoothly to generate the C-aryl glycosidic bonds (**3c**-**3e**). These results indicated that the protecting group is independent to the reaction. After that, compound **1g** with conformationally rigid structure was utilized, to furnish the desired **3g** with a yield of 73%. Subsequently, 63% yield of compound **3h** was obtained by the treatment of glucal derivatives with an ester group at *C*-5 position with **2a**. To test the generality of this method, various galactal-type substrates were then examined. Gratifyingly, all the tested donors were converted to the corresponding products with good outcome (**3i**-**3l**). In addition, rhamnose-type *C*-aryl glycosides **3m** and ribose-type *C*-aryl glycosides **3n** were also achieved successfully to give 72% and 58% yields respectively when **1m** and **1n** were used as the glycosyl donors. Notably, the coupling of 2,6-dimethoxybenzoic acid (**2a**) with disaccharide substrate **1o** also conducted efficiently to provide **3o** in 45% yield. Remarkably, only one isomer was isolated from the reaction system for each reaction. The stereochemistry of the anomeric center can be clearly confirmed by the X-ray crystallographic analysis attached later.

Table 3.1.2 Decarboxylative coupling of **2a** with different kinds of glycals [a,b,c]



1 2a 3

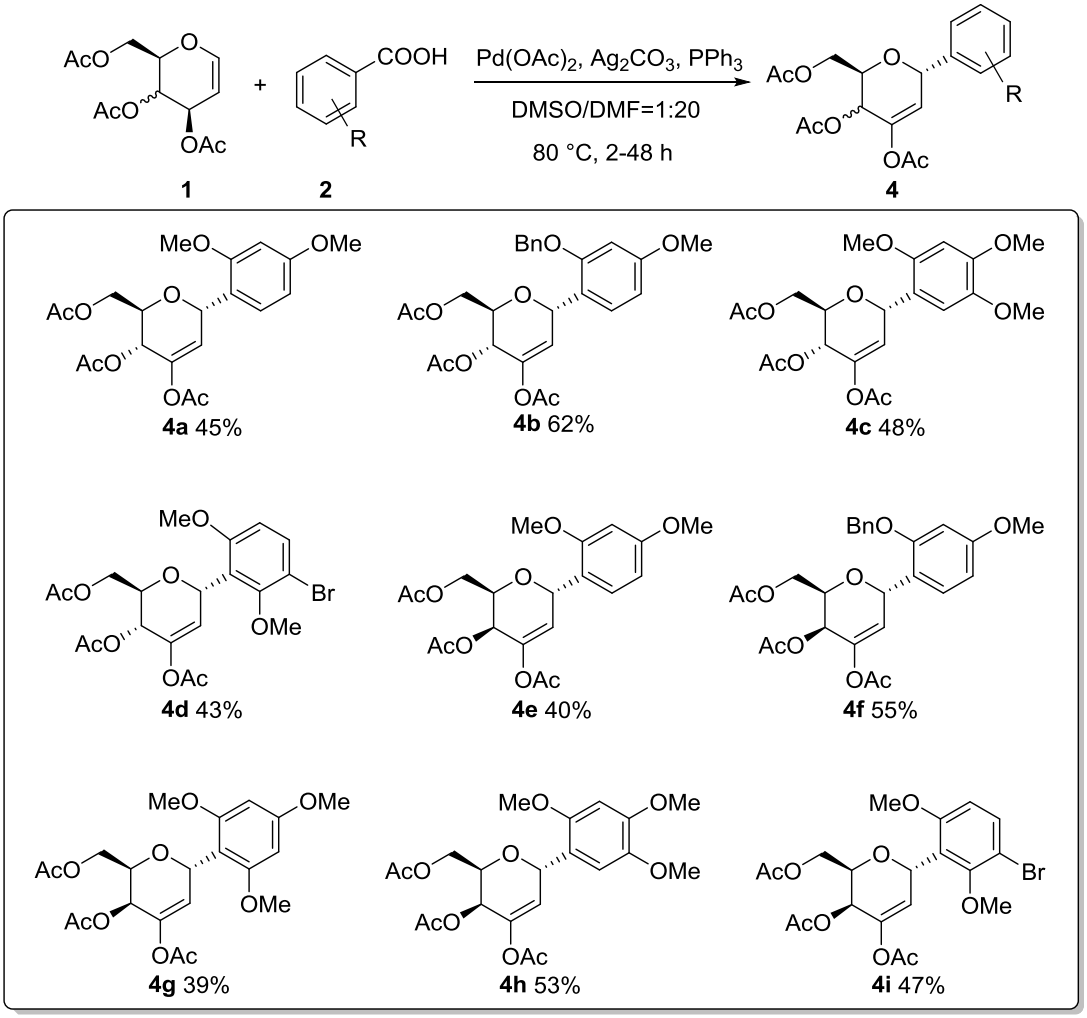
	1b	70%		3b	
	1c	73%		3c	
	1d			3d	
	1e	55%		3e	
	1f	75%		3f	
	1g	73%		3g	
	1h	63%		3h	
	1i	80%		3i	
	1j	60%		3j	
	1k	69%		3k	
	1l	71%		3l	
	1m	72%		3m	
	1n	58%		3n	
	1o	45%		3o	

[a] Isolated yields. [b] Only one single anomer was obtained for each reaction. [c] Compound **3f** is unstable in $CDCl_3$.

To further extend the scope of this decarboxylative coupling reaction, numerous of benzoic acid derivatives were examined. From the results presented in **Scheme 3.1.9**, we can see that all the reactions could proceed smoothly to give the desired *C*-aryl glycosides **4** in moderate yields. Interestingly, it was found that the duration of this reaction was very sensitive to the electron density of the aromatic ring. This observation was first noticed when 2,4-disubstituted benzoic acids such as **2a** and **2b** were subjected to the optimized conditions with glucal **1a**, and a slightly longer durations were needed to give compound **4a** and **4b** in 45% and 62% respectively. On the other hand, the reaction with 2,4,5-trimethoxybenzoic acid **2c** could be completed in 2 h, albeit with 48% yield of **4c**. To supply more evidence for the effect of electron density, an electron-withdrawing bromine containing substrate was then examined. As predicted, this reaction was only found to complete in 48 h to obtain **4d** with 43% yield. Similar results were obtained by coupling these benzoic acids with compound **1l**. With appropriate reaction duration, galactal type *C*-aryl glycosidic linkages were produced in 39% to 55% yields (**4e-4i**). Despite efforts were paid to present boarder substrate scope, the trials were failed to give good results with following benzoic acid derivatives such as 6-methylpicolinic acid, 2-naphthoic acid, 2,3-dimethoxybenzoic acid, 2-bromo-4-methoxybenzoic acid, 2-bromo-4,5-dimethoxybenzoic acid and so on.

As mentioned above, excellent stereocontrol of the desired *C*-aryl glycoside was detected for this method. Fortunately, crystal structures of both glucal-type product **4d** and galactal-type product **4i** were obtained. The stereochemistry of anomeric center was demonstrated to be α-selectivity by X-ray crystallographic analysis. The related structures were shown in **Figure 3.1.2** (**4d**)[15] and **Figure 3.1.3** (**4i**) respectively.[16]

Scheme 3.1.9 Decarboxylative coupling of glycals with different benzoic acid derivatives [a,b]



[a] Isolated yields. [b] Only one anomer was obtained for each reaction.

Figure 3.1.2 The X-ray structure of compound **4d** (CCDC: **836929**)

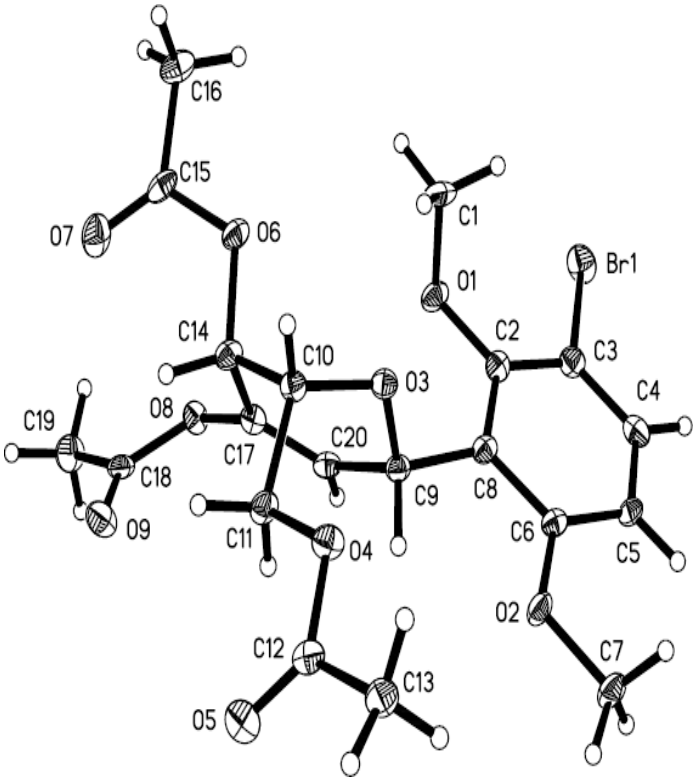
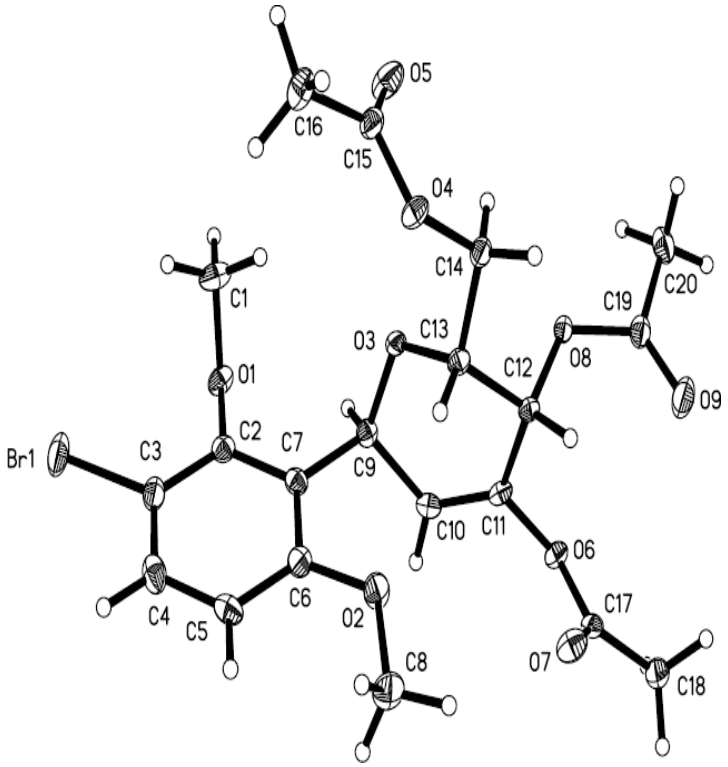
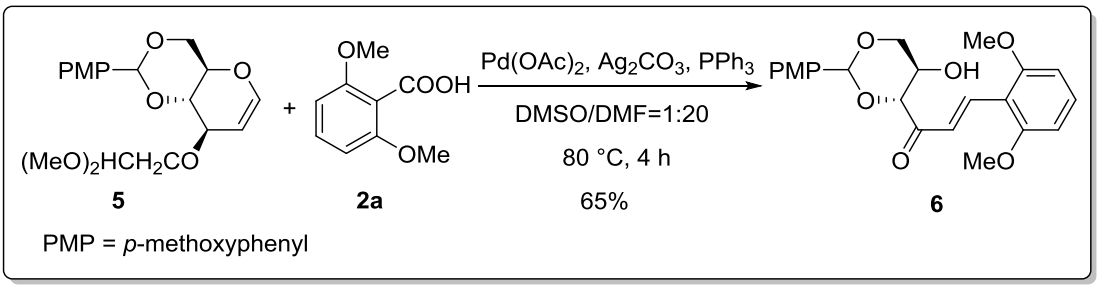


Figure 3.1.3 The X-ray structure of compound **4i** (CCDC: **836928**)

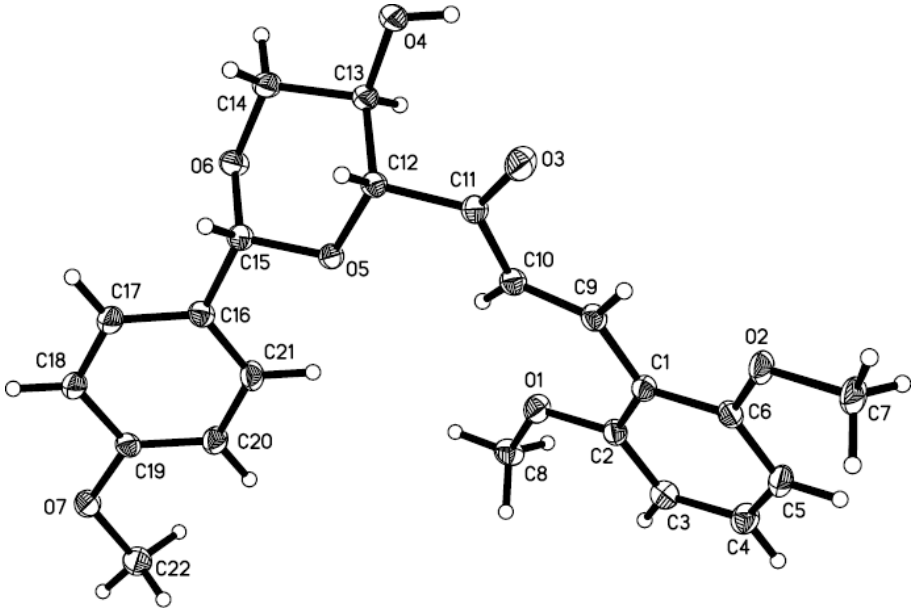


Scheme 3.1.10 Decarboxylative coupling of 2,6-dimethoxybenzoic acid with **5**



Interestingly, treatment of compound **5** with 2,6-dimethoxybenzoic acid (**2**) under the optimized conditions resulted in ring opening of the sugar scaffold to give an α,β-unsaturated ketone (**5**) as the major product[9a, 10c, 10e] (**Scheme 3.1.10**). The structure of the product was confirmed by X-ray diffraction crystallographic analysis.[17]

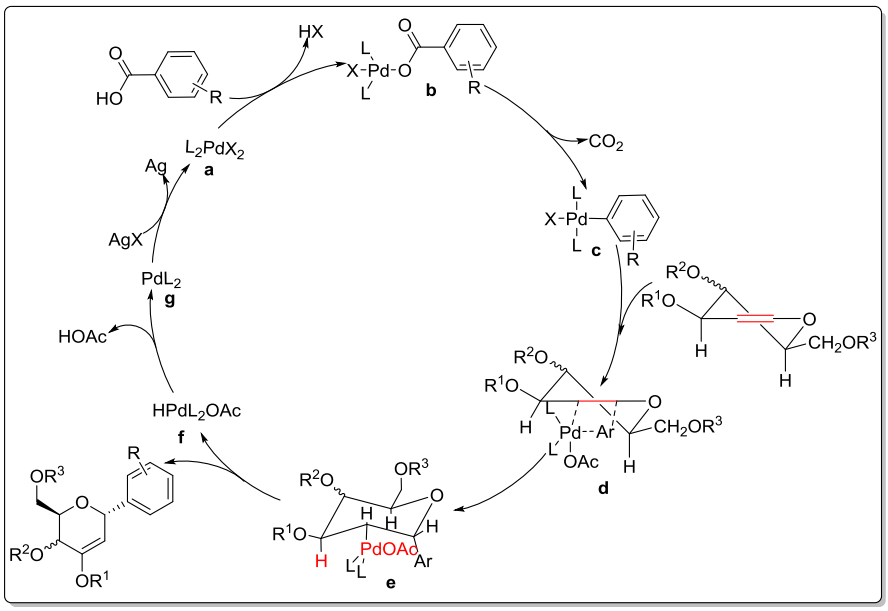
Figure 3.1.4 The X-ray structure of compound **6** (CCDC: **995073**)



The proposed mechanism for this palladium-catalyzed Heck-type decarboxylative reaction to give excellent α-selectivity is detailed in **Scheme 3.1.11**. In the presence of a palladium source and ligand, Pd (II) species **a** was formed under the reaction

condition. Next, Pd species **b** is obtained by salt change with benzoic acid **2**. Subsequently, classic palladium intermediate **c** was then yielded by a decarboxylative reaction. With this palladium complex **c**, key intermediate **d** was generated by a carbopalladation of the glycal substrates. Generally, intermediate **c** would approach the glycals from the bottom face as *C*-3 substituent oriented at top face of sugar ring and then hindered the attack from this side. Thereafter, chair conformational intermediate **e** with low energy was furnished by the electron transfer. In this structure, H_3 and palladium complex were in a *syn*-configuration while the *C*-3 substituent and aryl group were in an *anti*-configuration. Then *syn*-*β*-hydrogen elimination provided the desired 2-deoxy-*C*-aryl glycoside with aryl group opposed to the substituent on *C*-3 position as well as a Pd(0) species **f**. Finally, the catalytic cycle was completed by regeneration of Pd species **a** through subsequent elimination of HOAc and oxidation with silver carbonate.

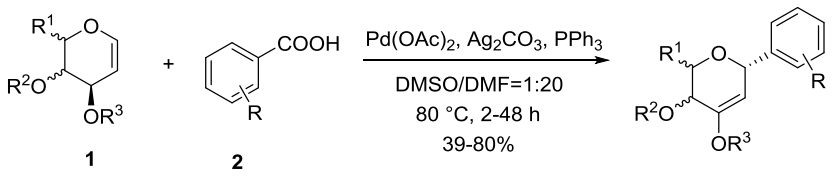
Scheme 3.1.11 Plausible reaction mechanism



Conclusion

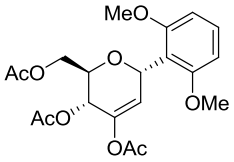
In summary, we have developed a new strategy for the syntheses *C*-aryl glycosides *via* a palladium-catalyzed Heck-type decarboxylative coupling of benzoic acids and glycals. The flexibility and generality of this method is demonstrated by a board range of substrates and most of the reactions could give the desired products in good yields with excellent stereocontrol by the *C*-3 substituent. The obtained 2-deoxy-*C*-aryl glycosides were versatile intermediates and could be utilized to the syntheses of *C*-aryl glycosides occurring natural products by stereoselective functionalization of the olefin moiety.

General procedure



Glycal **1** (1.0 equiv), benzoic acid derivative **2** (2.0 equiv), $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.4 equiv) and Ag_2CO_3 (3.0 equiv) were suspended in DMF/DMSO (20/1) under nitrogen. The reaction mixture was stirred at 80 °C for 2-48 h. After cooling to room temperature, the mixture was poured into Et_2O and then filtered. The filtrate was washed sequentially with H_2O and brine, then dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel to afford the desired product.

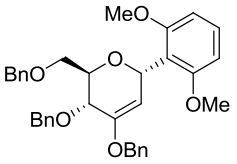
(1*S*)-1,5-anhydro-2-deoxy-1-C-(2,6-dimethoxyphenyl)-3,4,6-tris-O-acetyl-D-erythro-Hex-2-enitol (3a)



Following the general procedure, product **3a** (64.5 mg, 79%) was obtained as light yellow oil. $[\alpha]_D^{23}$ +33.0 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1109, 1250, 1476, 1595, 1744, 2839, 2939 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.25 (t, J = 8.4 Hz, 1H), 6.55 (d, J = 8.4 Hz, 2H), 5.99 (t, J = 2.0 Hz, 1H), 5.77 (d, J = 2.3 Hz, 1H), 5.37 (t, J = 2.2 Hz, 1H), 4.51 (dd, J = 11.4, 6.8 Hz, 1H), 4.39 (ddd, J = 6.8, 5.5, 2.6Hz, 1H), 4.28 (dd, J = 11.4, 5.5 Hz, 1H), 3.82 (s, 6H), 2.15 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 170.7, 169.2, 159.4, 139.8, 130.3, 122.4, 114.4, 104.6,

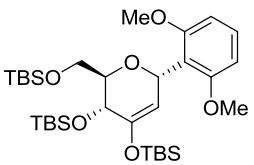
74.2, 65.2, 63.7, 61.8, 55.9, 21.1, 20.8(2C) ppm; MS (ESI): 409 *m/z* (M+H); HRMS (ESI) calcd. for $C_{20}H_{24}O_9Na$ [M+Na]: 431.1318; found: 431.1319.

(1*S*)-1,5-anhydro-2-deoxy-1-C-(2,6-dimethoxyphenyl)-3,4,6-tris-O-(phenylmethyl) -D-erythro-Hex-2-enitol (3b)



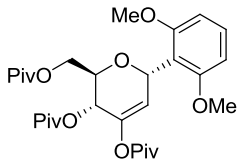
Following the general procedure, **3b** (77.3 mg, 70%) was obtained as light yellow oil. $[\alpha]_D^{23}$ +30.1 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1109, 1250, 1474, 1593, 1670, 2934, 3030 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.19-7.25 (m, 16H), 6.52 (d, *J* = 8.4 Hz, 2H), 5.97 (t, *J* = 1.9 Hz, 1H), 5.00 (d, *J* = 2.3 Hz, 1H), 4.86 (d, *J* =11.9 Hz, 1H), 4.83 (d, *J* = 1.6 Hz, 2H), 4.76 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 2.5 Hz, 2H), 4.49 (dt, *J* = 3.0, 5.9 Hz, 1H), 4.09 (dd, *J* = 2.9, 1.7 Hz, 1H), 3.79 (dd, *J* = 10.2, 6.1 Hz, 1H), 3.71 (s, 6H), 3.66 (dd, *J* = 10.2, 5.8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.5, 149.3, 139.3, 138.4, 137.4, 129.6, 128.3, 128.2(2C), 128.1, 127.9, 127.7, 127.6, 127.5, 127.4, 127.2(2C), 116.5, 104.5, 102.2, 75.7, 73.1, 71.2, 70.8, 68.9, 68.7, 64.0, 55.8 ppm; MS (ESI): 553 *m/z* (M+H); HRMS (ESI) calcd. for $C_{35}H_{37}O_6$ [M+H]: 553.2590; found: 553.2571.

(1*S*)-1,5-anhydro-2-deoxy-1-C-(2,6-dimethoxyphenyl)-3,4,6-tris-O-(*tert*-butyldi methylsilyl)-D-erythro-Hex-2-enitol (3c)



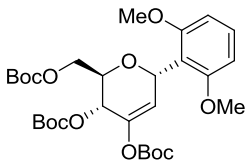
Following the general procedure, **3c** (91.1 mg, 73%) was obtained as colorless oil. $[\alpha]_D^{23}$ +26.7 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 1111, 1252, 1474, 1595, 1672, 2857, 2929, 2953 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.19 (t, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 8.3 Hz, 2H), 5.75 (t, *J* = 1.5 Hz, 1H), 4.83 (d, *J* = 2.0 Hz, 1H), 3.98-4.02 (m, 2H), 3.81-3.88 (m, 2H), 3.78 (s, 6H), 0.94 (s, 9H), 0.93 (s, 9H), 0.90 (s, 9H), 0.16 (s, 6H), 0.14 (s, 3H), 0.12 (s, 3H), 0.07 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.7, 146.1, 129.4, 117.4, 106.6, 105.1, 80.5, 66.9, 63.6, 62.3, 56.3, 26.0(2C), 25.9, 18.3, 18.2, 18.1, -3.9, -4.3, -4.4(2C), -5.4, -5.5 ppm; MS (ESI): 625 *m/z* (M+H); HRMS (ESI) calcd. for $C_{32}H_{61}O_6Si_3$ [M+H]: 625.3776; found: 625.3774.

(1*S*)-1,5-anhydro-2-deoxy-1-C-(2,6-dimethoxyphenyl)-3,4,6-tris-O-pivaloyl-D-erythro-Hex-2-enitol (3d)



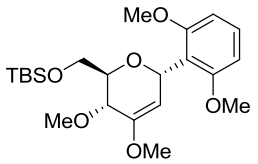
Following the general procedure, **3d** (69.4 mg, 65%) was obtained as light yellow oil. $[\alpha]_D^{23}$ +41.2 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 1113, 1252, 1477, 1595, 1732, 2936, 2972 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.24 (t, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 2H), 6.01 (t, *J* = 2.1 Hz, 1H), 5.78 (d, *J* = 2.2 Hz, 1H), 5.32 (t, *J* = 2.2 Hz, 1H), 4.43 (dd, *J* = 10.8, 7.9 Hz, 1H), 4.34-4.38 (m, 1H), 4.30 (dd, *J* = 10.8, 4.1 Hz, 1H), 3.81 (s, 6H), 1.25 (s, 9H), 1.22 (s, 9H), 1.18 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.0, 177.9, 176.6, 159.5, 140.2, 130.2, 122.0, 114.5, 104.5, 74.5, 64.8, 63.4, 61.5, 55.9, 38.8(2C), 38.7, 27.1, 27.0 ppm; MS (ESI): 535 *m/z* (M+H); HRMS (ESI) calcd. for $C_{29}H_{42}O_9Na$ [M+Na]: 557.2727; found: 557.2725.

(1*S*)-1,5-anhydro-2-deoxy-1-C-(2,6-dimethoxyphenyl)-3,4,6-tris-O-(*tert*-butoxy carbonyl)-D-erythro-Hex-2-enitol (3e)



Following the general procedure, **3e** (64.0 mg, 55%) was obtained as colorless oil. $[\alpha]_D^{23}$ +4.1 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1109, 1252, 1476, 1595, 1746, 2936, 2980 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.22 (t, *J* = 8.3 Hz, 1H), 6.52 (d, *J* = 8.3 Hz, 2H), 6.03 (t, *J* = 2.2 Hz, 1H), 5.80 (d, *J* = 2.6 Hz, 1H), 5.27 (dd, *J* = 3.8, 2.0 Hz, 1H), 4.38-4.50 (m, 2H), 4.25 (dd, *J* = 11.4, 4.6 Hz, 1H), 3.79 (s, 6H), 1.51 (s, 9H), 1.49 (s, 9H), 1.46 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.5, 153.4, 153.3, 151.2, 140.3, 130.2, 121.4, 114.5, 104.4, 83.2, 82.2, 82.1, 73.4, 67.3, 64.7, 64.1, 55.8, 27.8, 27.7(2C) ppm; MS (ESI): 605 *m/z* (M+Na); HRMS (ESI) calcd. for $C_{29}H_{42}O_{12}Na$ [M+Na]: 605.2574; found: 605.2574.

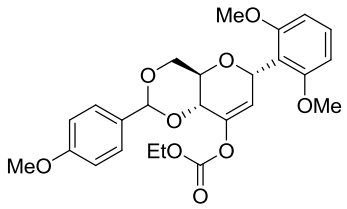
(1*S*)-1,5-anhydro-2-deoxy-1-C-(2,6-dimethoxyphenyl)-3,4-di-O-methyl-6-O-(*tert*-butyldimethylsilyl)-D-erythro-Hex-2-enitol (3f)



Following the general procedure, **3f** (63.6 mg, 75%) was obtained as colorless oil. $[\alpha]_D^{23}$ +4.2 (*c* 1.0, CH_2Cl_2); IR (neat) *ν*: 1109, 1250, 1474, 1593, 1672, 2856, 2934, 2949 cm^{-1}; ^1H NMR (CD_3COCD_3, 400 MHz): δ 7.22 (t, *J* = 8.4 Hz, 1H), 6.61 (d, *J* = 8.4 Hz, 2H), 5.88 (t, *J* = 2.1 Hz, 1H), 4.84 (d, *J* = 2.5 Hz, 1H), 4.01 (dt, *J* = 3.4, 5.5 Hz, 1H), 3.84 (dd, *J* = 10.6, 5.3 Hz, 1H), 3.80 (dd, *J* = 10.6, 5.6 Hz, 1H), 3.73-3.78

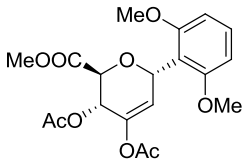
(m, 7H), 3.55 (s, 3H), 3.43 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (CD_3COCD_3, 100 MHz): δ 161.1, 152.0, 130.9, 119.1, 106.3, 101.9, 78.1, 73.7, 65.6, 64.3, 57.4, 56.8, 54.9, 26.9, 19.4, -4.6 ppm; MS (ESI): 425 *m*/*z* (M+H); HRMS (ESI) calcd. for $C_{22}H_{36}O_6SiNa$ [M+Na]: 447.2179; found: 447.2180.

(4a*R*,6*S*,8a*R*)-6-(2,6-dimethoxyphenyl)-2-(4-methoxyphenyl)-4,4a,6,8a-tetra hydropyrano[3,2-d][1,3]dioxin-8-yl ethyl carbonate (3g)



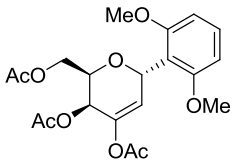
Following the general procedure, **3g** (68.9 mg, 73%) was obtained as a white solid. M.p. 98-100 °C (Hexane/CH_2Cl_2); $[\alpha]_D^{23}$ +15.8 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 1105, 1248, 1476, 1593, 1759, 2839, 2938 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.44 (m, 2H), 7.26 (t, *J* = 8.4 Hz, 1H), 6.85-6.90 (m, 2H), 6.56 (d, *J* = 8.4 Hz, 2H), 6.09 (t, *J* = 2.8 Hz, 1H), 5.64 (t, *J* = 2.5 Hz, 1H), 5.55 (s, 1H), 4.50 (dt, *J* = 8.3, 2.5 Hz, 1H), 4.21-4.29 (m, 3H), 4.13 (ddd, *J* = 10.2, 8.3, 4.6 Hz, 1H), 3.74-3.82 (m, 10H), 1.31 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.9, 159.1, 152.8, 142.2, 130.2, 130.1, 127.5, 116.1, 115.8, 113.4, 104.2, 101.3, 74.1, 69.9, 67.3, 66.2, 64.6, 55.8, 55.3, 14.2 ppm; MS (ESI): 495 *m*/*z* (M+Na); HRMS (ESI) calcd. for $C_{25}H_{28}O_9Na$ [M+Na]: 495.1631; found: 495.1630.

(2*S*,3*R*,6*S*)-6-(2,6-dimethoxyphenyl)-2-(methoxycarbonyl)-3,6-dihydro-2*H*-pyran -3,4-diyl diacetate (3h)



Following the general procedure, **3h** (49.6 mg, 63%) was obtained as colorless oil. $[\alpha]_D^{23}$ +42.4 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 1111, 1251, 1477, 1595, 1746, 2839, 2953 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.26 (t, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 6.48 (t, *J* = 1.6 Hz, 1H), 5.77-5.79 (m, 2H), 4.81 (d, *J* = 1.4 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 6H), 2.17 (s, 3H), 2.14 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 169.0, 159.6, 138.9, 130.5, 123.2, 114.0, 104.4, 76.2, 66.2, 64.7, 56.0, 52.4, 21.1, 20.8 ppm; MS (ESI): 395 *m/z* (M+H); HRMS (ESI) calcd. for $C_{19}H_{22}O_9Na$ [M+Na]: 417.1162; found: 417.1163.

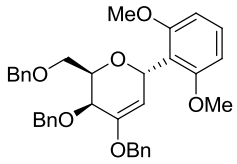
(2*R*,3*S*,6*S*)-2-(acetoxymethyl)-6-(2,6-dimethoxyphenyl)-3,6-dihydro-2*H*-pyran-3,4-diyl diacetate (3i)



Following the general procedure, **3i** (65.3 mg, 80%) was obtained as colorless oil. $[\alpha]_D^{23}$ –187.1 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 1109, 1248, 1476, 1593, 1744, 2839, 2937 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.26 (t, *J* = 8.3 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 2H), 6.10 (d, *J* = 3.5 Hz, 1H), 5.84 (d, *J* = 3.5 Hz, 1H), 5.58 (d, *J* = 2.1 Hz, 1H), 4.59 (dt, *J* = 2.1, 6.8 Hz, 1H), 4.20 (dd, *J* = 11.1, 7.4 Hz, 1H), 4.09 (dd, *J* = 11.1, 6.5 Hz, 1H), 3.81 (s, 6H), 2.15 (s, 3H), 2.11 (s, 3H), 1.96 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 170.5, 169.5, 159.4, 141.6, 130.3, 122.1, 114.5, 104.2, 70.6, 66.2,

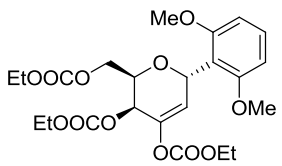
65.2, 62.1, 55.7, 20.8(2C), 20.7 ppm; MS (ESI): 409 *m/z* (M+H); HRMS (ESI) calcd. for $C_{20}H_{24}O_9Na$ [M+Na]: 431.1318; found: 431.1317.

(2*R*,3*S*,6*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-6-(2,6-dimethoxyphenyl)-3,6-dihydro-2*H*-pyran (3j)



Following the general procedure, **3j** (66.2 mg, 60%) was obtained as colorless oil. $[\alpha]_D^{23}$ –34.5 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1109, 1254, 1475, 1593, 1670, 2864, 2930 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.18-7.38 (m, 16H), 6.53 (d, *J* = 8.3 Hz, 2H), 6.19 (d, *J* = 2.9 Hz, 1H), 4.98 (d, *J* = 2.9 Hz, 1H), 4.70-4.89 (m, 4H), 4.41-4.52 (m, 3H), 4.10 (d, *J* = 2.2 Hz, 1H), 3.82 (dd, *J* = 9,6, 7.1 Hz, 1H), 3.73 (s, 6H), 3.68 (dd, *J* = 9.6, 5.9 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 159.3, 151.1, 139.1, 138.5, 137.3, 129.4, 128.4, 128.2, 128.1, 127.9, 127.8, 127.6, 127.4, 127.3, 127.2, 117.7, 104.5, 101.2, 73.6, 73.3, 72.1, 72.0, 69.4, 68.8, 66.0, 55.8 ppm; MS (ESI): 575 *m/z* (M+Na); HRMS (ESI) calcd. for $C_{35}H_{36}O_6Na$ [M+Na]: 575.2410; found: 575.2402.

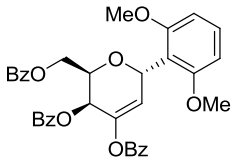
(1*S*)-D-Glucitol-1,5-anhydro-1-C-(2,6-dimethoxyphenyl)-3,4,6-tri(ethylcarbonate) (3k)



Following the general procedure, **3k** (68.7 mg, 69%) was obtained as colorless oil. $[\alpha]_D^{23}$ –150.6 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1107, 1250, 1476, 1593, 1748, 2841, 2940, 2981 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.25 (t, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 8.4

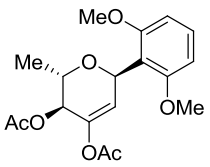
Hz, 2H), 6.12 (d, *J* = 3.5 Hz, 1H), 5.93 (d, *J* = 3.5 Hz, 1H), 5.52 (d, *J* = 2.1 Hz, 1H), 4.66 (dt, *J* = 2.4, 6.5 Hz, 1H), 4.17-4.31 (m, 6H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 6H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3, 155.1, 154.7, 153.1, 141.2, 130.3, 122.4, 114.5, 104.3, 70.9, 68.7, 65.9, 65.5, 64.6, 64.3, 64.0, 55.7, 14.1 ppm; MS (ESI): 521 *m*/*z* (M+Na); HRMS (ESI) calcd. for $C_{23}H_{30}O_{12}Na$ [M+Na]: 521.1635; found: 521.1632.

(2*R*,3*S*,6*S*)-2-(benzoyloxymethyl)-6-(2,6-dimethoxyphenyl)-3,6-dihydro-2*H*-pyran-3,4-diyl dibenzoate (3l)



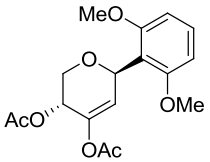
Following the general procedure, **3l** (84.3 mg, 71%) was obtained as colorless oil. $[\alpha]_D^{23}$ –137.2 (*c* 1.0, $CHCl_3$); IR (neat) ν: 1109, 1250, 1265, 1474, 1593, 1722, 2936 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03-8.09 (m, 4H), 7.84-7.88 (m, 2H), 7.26-7.68 (m, 10H), 6.58 (d, *J* = 8.4 Hz, 2H), 6.25 (d, *J* = 3.5 Hz, 1H), 6.15 (d, *J* = 3.5 Hz, 2H), 4.87 (dt, *J* = 2.5, 6.9 Hz, 1H), 4.65 (dd, *J* = 11.2, 7.1 Hz, 1H), 4.37 (dd, *J* = 11.2, 6.7 Hz, 1H), 3.85 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.1, 166.0, 165.0, 159.5, 141.7, 133.3, 133.1, 132.8, 130.3, 130.1, 130.0, 129.9, 129.8, 129.7, 129.6, 128.4, 128.3, 128.2, 122.5, 114.5, 104.3, 71.2, 66.4, 66.1, 62.7, 55.9 ppm; MS (ESI): 595 *m*/*z* (M+H); HRMS (ESI) calcd. for $C_{35}H_{30}O_9Na$ [M+Na]: 617.1788; found: 617.1793.

(2*S*,3*S*,6*R*)-6-(2,6-dimethoxyphenyl)-2-methyl-3,6-dihydro-2*H*-pyran-3,4-diyl diacetate (3m)



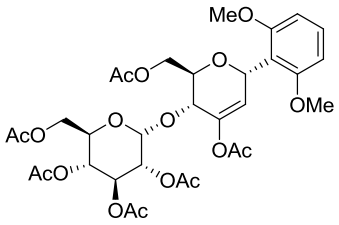
Following the general procedure, **3m** (50.4 mg, 72%) was obtained as colorless oil. $[\alpha]_D^{23}$ –47.8 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1109, 1250, 1476, 1593, 1732, 1755, 2839, 2938 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.24 (t, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 5.97 (t, *J* = 1.8 Hz, 1H), 5.76 (d, *J* = 2.0 Hz, 1H), 5.15 (t, *J* = 1.7 Hz, 1H), 4.33 (dq, *J* = 1.7, 6.9 Hz, 1H), 3.82 (s, 6H), 2.15 (s, 3H), 2.14 (s, 3H), 1.48 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.1, 169.4, 159.4, 139.7, 130.1, 122.7, 114.8, 104.5, 72.9, 69.4, 61.8, 56.0, 21.2, 20.9, 15.7 ppm; MS (ESI): 351 *m/z* (M+H); HRMS (ESI) calcd. for $C_{18}H_{22}O_7Na$ [M+Na]: 373.1263; found: 373.1273.

(3*R*,6*R*)-6-(2,6-dimethoxyphenyl)-3,6-dihydro-2*H*-pyran-3,4-diyl diacetate (3n)



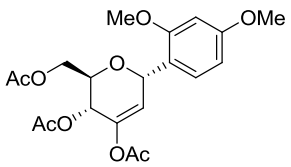
Following the general procedure, **3n** (39.0 mg, 58%) was obtained as colorless oil. $[\alpha]_D^{23}$ +144.9 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1109, 1246, 1476, 1593, 1736, 1757, 2839, 2938 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.25 (t, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 5.99 (dd, *J* = 2.8, 1.5 Hz, 1H), 5.82 (d, *J* = 3.0 Hz, 1H), 5.56 (dt, *J* = 1.4, 3.9 Hz, 1H), 4.31 (dd, *J* = 12.0, 3.8 Hz, 1H), 3.83 (dd, *J* = 12.0, 4.1 Hz, 1H), 3.81 (s, 6H), 2.15 (s, 3H), 2.11 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 169.0, 159.3, 141.2, 130.3, 122.3, 114.6, 104.2, 66.4, 66.3, 65.9, 55.7, 21.0, 20.8 ppm; MS (ESI): 337 *m/z* (M+H); HRMS (ESI) calcd. for $C_{17}H_{20}O_7Na$ [M+Na]: 359.1107; found: 359.1109.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-((2*R*,3*R*,6*S*)-4-acetoxy-2-(acetoxymethyl)-6-(2,6-dimethoxy phenyl)-3,6-dihydro-2*H*-pyran-3-yloxy)-6-(acetoxymethyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (3o)



Following the general procedure, **3o** (62.6 mg, 45%) was obtained as colorless oil. $[\alpha]_D^{23}$ +91.3 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1037, 1224, 1477, 1595, 1748, 2841, 2957 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.26 (t, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 5.94 (t, *J* = 1.8 Hz, 1H), 5.74 (d, *J* = 2.0 Hz, 1H), 5.52-5.59 (m, 2H), 5.09 (t, *J* = 9.7 Hz, 1H), 4.87 (dd, *J* = 10.3, 3.8 Hz, 1H), 4.53 (dd, *J* = 11.3, 7.6 Hz, 1H), 4.42-4.47 (m, 1H), 4.21-4.29 (m, 3H), 4.05-4.11 (m, 2H), 3.83 (s, 6H), 2.16 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.02 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6(2C), 170.1, 170.0, 169.6, 169.4, 159.5, 140.7, 130.4, 122.3, 114.1, 104.4, 95.9, 75.7, 71.5, 70.9, 70.0, 68.4, 67.6, 63.0, 61.8(2C), 55.9, 20.8(2C), 20.7, 20.6(3C) ppm; MS (ESI): 719 *m/z* (M+Na); HRMS (ESI) calcd. for $C_{32}H_{40}O_{17}Na$ [M+Na]: 719.2163; found: 719.2158.

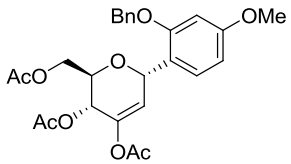
(1*S*)-1,5-anhydro-2-deoxy-1-C-(2,4-dimethoxyphenyl)-3,4,6-tris-O-acetyl-D-erythro-Hex-2-enitol (4a)



Following the general procedure, **4a** (36.7 mg, 45%) was obtained as colorless oil. $[\alpha]_D^{22}$ +61.6 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1159, 1209, 1229, 1587, 1612, 1746, 2837,

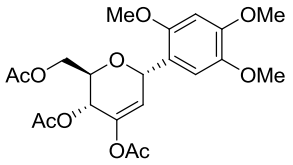
2963 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40 (d, J = 8.4 Hz, 1H), 6.51 (dd, J = 8.4, 2.3 Hz, 1H), 6.48 (d, J = 2.3 Hz, 1H), 5.78-5.80 (m, 2H), 5.44 (dd, J = 4.6, 1.3 Hz, 1H), 4.35-4.41 (m, 1H), 4.12-4.19 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 170.5, 168.9, 161.2, 158.3, 142.0, 129.6, 120.8, 118.9, 104.1, 98.8, 71.9, 67.0, 64.9, 62.2, 55.6, 55.4, 20.9, 20.8, 20.7 ppm; MS (ESI): 409 *m/z* (M+H); HRMS (ESI) calcd. for $C_{20}H_{24}O_9Na$ [M+Na]: 431.1318; found: 431.1317.

(2*R*,3*R*,6*S*)-2-(acetoxymethyl)-6-(2-(benzyloxy)-4-methoxyphenyl)-3,6-dihydro-2*H*-pyran-3,4-diyl diacetate (4b)



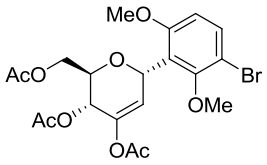
Following the general procedure, **4b** (60.0 mg, 62%) was obtained as light yellow oil. $[\alpha]_D^{22}$ +46.6 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 1163, 1229, 1504, 1612, 1746, 2876, 2947 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.43 (m, 6H), 6.50-6.54 (m, 2H), 5.87-5.89 (m, 1H), 5.82 (d, J = 2.9 Hz, 1H), 5.45 (dd, J = 4.5, 1.6 Hz, 1H), 5.11 (s, 2H), 4.33-4.40 (m, 1H), 4.13-4.21 (m, 2H), 3.78 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 2.02 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 170.5, 168.9, 161.1, 157.4, 142.1, 136.8, 129.9, 128.6, 127.9, 127.1, 120.8, 119.4, 104.7, 100.3, 72.0, 70.3, 67.1, 65.0, 62.2, 55.4, 20.9, 20.8, 20.7 ppm; MS (ESI): 485 *m/z* (M+H); HRMS (ESI) calcd. for $C_{26}H_{28}O_9Na$ [M+Na]: 507.1631; found: 507.1632.

(1*S*)-1,5-anhydro-2-deoxy-1-C-(2,4,5-trimethoxyphenyl)-3,4,6-tris-O-acetyl-D-erythro-Hex-2-enitol (4c)



Following the general procedure, **4c** (42.0 mg, 48%) was obtained as yellow oil. $[\alpha]_D^{23}$ +39.6 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1034, 1209, 1227, 1371, 1514, 1746, 2833, 2941 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.14 (s, 1H), 6.55 (s, 1H), 5.81 (dd, *J* = 2.8, 1.7 Hz, 1H), 5.79 (d, *J* = 2.8 Hz, 1H), 5.42 (dd, *J* = 4.0, 1.7 Hz, 1H), 4.37-4.44 (m, 1H), 4.17-4.23 (m, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 2.15 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 170.6, 170.4, 169.0, 151.6, 149.8, 143.0, 141.7, 121.1, 117.8, 112.6, 97.7, 72.4, 66.8, 65.0, 62.1, 56.7, 56.5, 56.1, 20.9, 20.7(2C) ppm; MS (ESI): 439 *m/z* (M+H); HRMS (ESI) calcd. for $C_{21}H_{26}O_{10}Na$ [M+Na]: 461.1424; found: 461.1425.

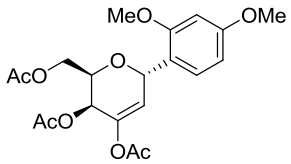
(1*S*)-1,5-anhydro-2-deoxy-1-C-(3-bromo-2,6-dimethoxyphenyl)-3,4,6-tris-O-acetyl-D-erythro-Hex-2-enitol (4d)



Following the general procedure, **4d** (41.9 mg, 43%) was obtained as a white solid. M.p. 97-99 °C (Hexane/CH_2Cl_2); $[\alpha]_D^{22}$ +52.0 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1092, 1231, 1468, 1581, 1746, 2841, 2941 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.49 (d, *J* = 8.9 Hz, 1H), 6.61 (d, *J* = 8.9 Hz, 1H), 5.91 (t, *J* = 1.9 Hz, 1H), 5.81 (d, *J* = 2.0 Hz, 1H), 5.33 (t, *J* = 1.7 Hz, 1H), 4.57 (dd, *J* = 11.6, 7.8 Hz, 1H), 4.38-4.42 (m, 1H), 4.31 (dd, *J* = 11.6, 5.4 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 2.14 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 170.6, 170.5, 169.3, 158.6, 157.4, 140.0,

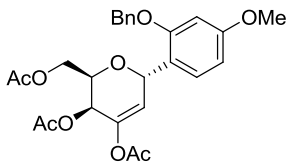
134.0, 121.9(2C), 108.9, 108.8, 74.9, 65.0, 64.0, 62.4, 61.1, 56.1, 21.1, 20.8(2C) ppm; MS (ESI): 487 *m/z* (M+H); HRMS (ESI) calcd. for $C_{20}H_{23}O_9BrNa$ [M+Na]: 509.0423; found: 509.0425.

(2*R*,3*S*,6*S*)-2-(acetoxymethyl)-6-(2,4-dimethoxyphenyl)-3,6-dihydro-2*H*-pyran-3,4-diyl diacetate (4e)



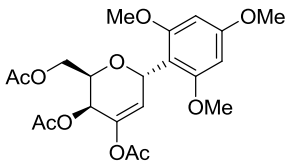
Following the general procedure, **4e** (32.6 mg, 40%) was obtained as a white solid. M.p. 86-88 °C (Hexane/CH_2Cl_2); $[\alpha]_D^{23}$ −121.6 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1157, 1209, 1229, 1585, 1609, 1746, 2839, 2940 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29 (d, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 6.46 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.89 (d, *J* = 3.9 Hz, 1H), 5.85 (d, *J* = 3.9 Hz, 1H), 5.45 (d, *J* = 2.1 Hz, 1H), 4.11-4.21 (m, 2H), 4.04 (dd, *J* = 9.4, 5.1 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H), 1.95 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.4, 169.7, 161.5, 159.1, 143.9, 130.3, 120.9, 117.3, 103.3, 99.3, 68.6, 67.9, 64.3, 61.7, 55.8, 55.4, 20.8, 20.7, 20.6 ppm; MS (ESI): 409 *m/z* (M+H); HRMS (ESI) calcd. for $C_{20}H_{24}O_9Na$ [M+Na]:431.1318; found: 431.1317.

(2*R*,3*S*,6*S*)-2-(acetoxymethyl)-6-(2-(benzyloxy)-4-methoxyphenyl)-3,6-dihydro-2H-pyran-3,4-diyl diacetate (4f)



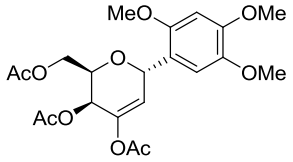
Following the general procedure, **4f** (53.2 mg, 55%) was obtained as a white solid. M.p. 116-118 °C (Hexane/CH_2Cl_2); $[\alpha]_D^{23}$ –102.4 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1163, 1229, 1585, 1609, 1744, 2938 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.45 (m, 6H), 6.55 (d, *J* = 2.3 Hz, 1H), 6.47 (dd, *J* = 8.4, 2.3 Hz, 1H), 5.97 (d, *J* = 3.9 Hz, 1H), 5.88 (d, *J* = 3.9 Hz, 1H), 5.46 (d, *J* = 2.2 Hz, 1H), 5.14 (d, *J* = 12.0 Hz, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 4.13-4.23 (m, 2H), 4.06 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.78 (s, 3H), 2.18 (s, 3H), 2.13 (s, 3H), 1.94 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.4, 169.7, 161.3, 158.2, 143.9, 136.7, 130.4, 128.5, 127.9, 127.1, 121.0, 117.8, 103.8, 100.8, 70.4, 68.7, 67.8, 64.3, 61.7, 55.3, 20.8(2C), 20.6 ppm; MS (ESI): 507 *m/z* (M+Na); HRMS (ESI) calcd. for $C_{26}H_{28}O_9Na$ [M+Na]: 507.1631; found: 507.1632.

(2*R*,3*S*,6*S*)-2-(acetoxymethyl)-6-(2,4,6-trimethoxyphenyl)-3,6-dihydro-2*H*-pyran-3,4-diyl diacetate (4g)



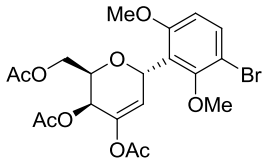
Following the general procedure, **4g** (34.2 mg, 39%) was obtained as a white solid. M.p. 131-133 °C (Hexane/CH_2Cl_2); $[\alpha]_D^{23}$ –154.1 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1121, 1227, 1371, 1591, 1607, 1741, 2841, 2940 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.11 (s, 2H), 6.00 (d, *J* = 3.6 Hz, 1H), 5.82 (d, *J* = 3.6 Hz, 1H), 5.56 (d, *J* = 2.1 Hz, 1H), 4.54 (dt, *J* = 2.3, 6.9 Hz, 1H), 4.18 (dd, *J* = 11.1, 7.4 Hz, 1H), 4.08 (dd, *J* = 11.1, 6.5 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 6H), 2.15 (s, 3H), 2.11 (s, 3H), 1.97 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.9, 170.5, 169.5, 161.7, 160.3, 141.6, 122.4, 107.3, 90.8, 70.3, 66.1, 65.2, 62.1, 55.7, 55.3, 20.8(2C), 20.7 ppm; MS (ESI): 439 *m/z* (M+H); HRMS (ESI) calcd. for $C_{21}H_{26}O_{10}Na$ [M+Na]: 461.1424; found: 461.1427.

(2*R*,3*S*,6*S*)-2-(acetoxymethyl)-6-(2,4,5-trimethoxyphenyl)-3,6-dihydro-2*H*-pyran-3,4-diyl diacetate (4h)



Following the general procedure, **4h** (46.4 mg, 53%) was obtained as yellow oil. $[\alpha]_D^{23}$ –112.6 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1031, 1209, 1227, 1371, 1514, 1609, 1746, 2853, 2955 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.07 (s, 1H), 6.59 (s, 1H), 5.92 (d, *J* = 3.9 Hz, 1H), 5.87 (d, *J* = 3.9 Hz, 1H), 5.44 (d, *J* = 2.1 Hz, 1H), 4.15-4.21 (m, 2H), 4.06 (dd, *J* = 13.7, 9.2 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 6H), 2.19 (s, 3H), 2.13 (s, 3H), 1.96 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 170.3, 169.7, 152.5, 150.0, 143.7, 142.5, 121.2, 116.3, 113.3, 98.3, 68.6, 68.0, 64.2, 61.8, 57.0, 56.5, 56.1, 20.7(2C), 20.60 ppm; MS (ESI): 439 *m*/*z* ($M+H^+$); HRMS (ESI) calcd. for $C_{21}H_{26}O_{10}Na$ $[M+Na]^+$: 461.1424; found: 461.1433.

(2*R*,3*S*,6*S*)-2-(acetoxymethyl)-6-(3-bromo-2,6-dimethoxyphenyl)-3,6-dihydro-2*H*-pyran-3,4-diyl diacetate (4i)



Following the general procedure, **4i** (45.8 mg, 47%) was obtained as a white solid. M.p. 112-114 °C (Hexane/CH_2Cl_2); $[\alpha]_D^{23}$ –154.8 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 1087, 1229, 1468, 1578, 1746, 2839, 2941 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, *J* = 8.9 Hz, 1H), 6.61 (d, *J* = 8.9 Hz, 1H), 6.04 (d, *J* = 3.5 Hz, 1H), 5.84 (d, *J* = 3.5 Hz, 1H), 5.61 (d, *J* = 2.5 Hz, 1H), 4.57 (dt, *J* = 2.5, 6.8 Hz, 1H), 4.18 (dd, *J* = 11.2, 6.8 Hz, 1H), 4.12 (dd, *J* = 11.2, 6.8 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 2.15 (s, 3H), 2.13

(s, 3H), 1.97 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 170.5, 169.4, 158.9, 157.3, 142.1, 134.0, 122.1, 121.2, 108.9, 108.5, 70.7, 67.2, 64.9, 62.5, 62.0, 55.8, 20.8(2C), 20.7 ppm; MS (ESI): 487 *m/z* (M+H); HRMS (ESI) calcd. for $C_{20}H_{23}O_9BrNa$ [M+Na]: 509.0423; found: 509.0423.

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15. For more details of the crystal structure, see: CCDC number: 836929.

16. For more details of the crystal structure, see: CCDC number: 836928.

17. For more details of the crystal structure, see: CCDC number: 995073.

Chapter 2: One-pot synthesis of β-*N*-glycosyl imidazole analogues *via* a palladium-catalyzed decarboxylative allylation[1]

Introduction

N-Glycosidic linkage is embedded in a large number of important carbohydrate structures and natural products. They are existed as *N*-linked glycopeptides and glycoproteins and many of which hold play important roles in an organism.[2] As such, *N*-glycoside containing structures are often the essential components of pharmacological agents (**Figure 2.2.1**). Due to their great potential in the field of medicinal chemistry,[3] tremendous efforts have been made to access these structures during the past decades.[4] The syntheses of *O*-glycosides arguably contributed to the majority of chemical glycosylation for their high occurrence in the bioactive structures. Subsequently, over the years, more syntheses on *C*-glycosides are emerging as they are famous for mimics of *O*-glycosides which are greatly known for increasing the bioactivity. Nevertheless, reports pertaining to *N*-glycosyl amino-containing compounds were very rare and the most classic strategy normally involved reducing azide group. However, the employment of toxic and explosive reagent limited its application. Though the demand of the *N*-glycosides has obtained significant growth in the last decade, the formation of *N*-glycosidic linkage especially with high efficiency and stereoselectivity has remained and continue to be a challenge.

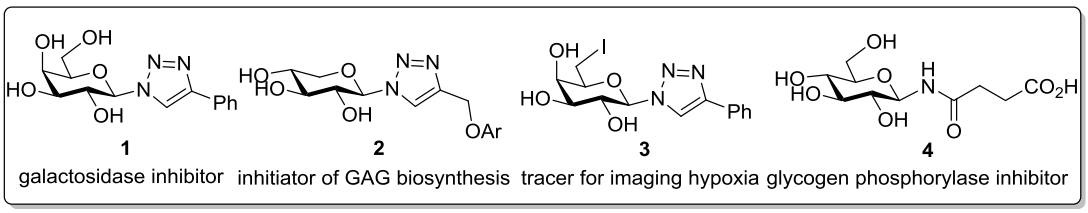
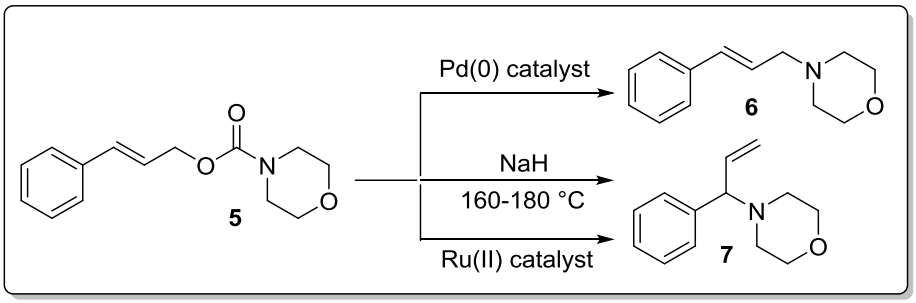


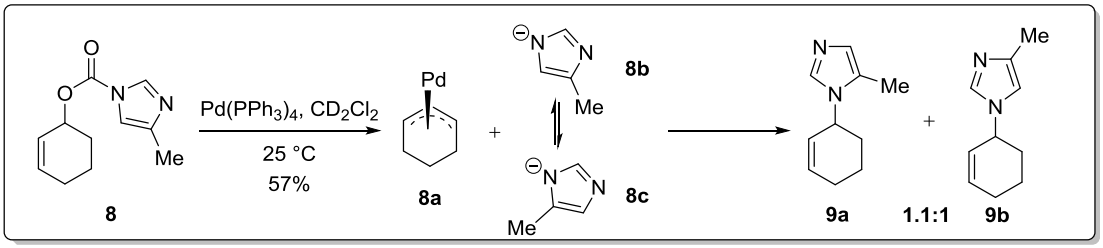
Figure 3.2.1 Important *N*-glycosides containing carbohydrate structures

From the results in the last chapter, we can see that the decarboxylative allylation offer an effective approach to the formation of *O*-glycosidic bonds with glycal donor. Meanwhile, the decarboxylative allylation of allyl alcohol derivatives have provided a convenient tool for the formation of C-N bond with transition metal catalyst. In 2005, Tunge demonstrated the advantage of transition metal in catalysing the decarboxylative coupling to give a large diverse of allylic amine.[5] In that reaction, allylic carbamate **5** was employed as the starting material. Up to 180 °C was needed to make the reaction proceed in the presence of NaH, while the reaction can proceed smoothly in very mild conditions in the presence of metal catalyst. They also illustrated that the palladium catalyst was in favour to provide the linear product **6** while branched amine product **7** was normally obtained with ruthenium catalyst (**Scheme 3.2.1**).



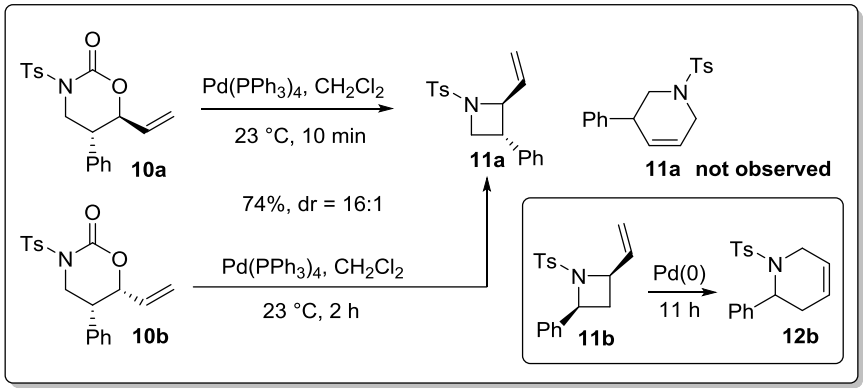
Scheme 3.2.1 Decarboxylative allylation with carbamate

The substrates scope included aliphatic amines and some heteroaromatic amines. Notably, for the substrates with imidazole analogues, low temperature was required and both of the nitrogen can be served as the nucleophile to give two regioselective product. This was proved by the reaction with compound **8** as the starting material. Under his reaction conditions, an electrophile **8a** and two possible nucleophiles **8b** and **8c** (resonance structures) were then generated by a decarboxylative reaction. Then both **9a** and **9b** were obtained with a ratio of 1.1:1. In addition, they also demonstrated the outcome of the reaction was strongly affected by the pKa of the amine.



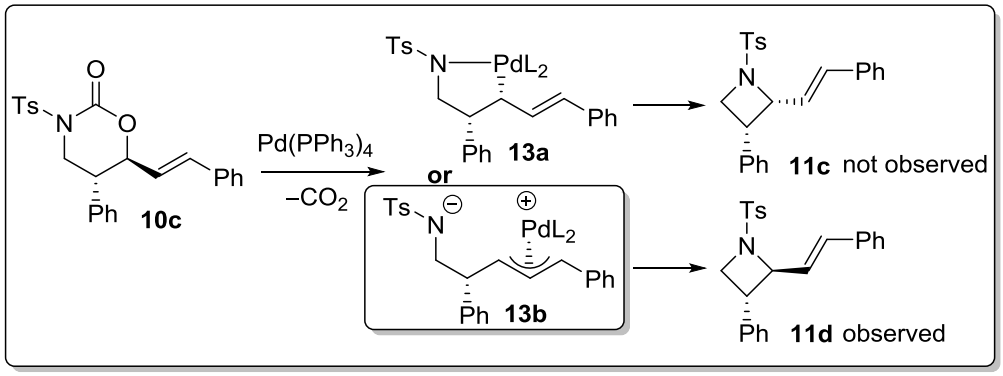
Scheme 3.2.2 Decarboxylation with imidazole analogues substrate

One year later, Tunge's group reported an intramolecular decarboxylative cyclization with cyclic carbamates.[6] During their investigation, they found that a *trans*-vinyl azetidine **11a** was obtained from both *cis*- or *trans*-carbamate **10**. Meanwhile, exact same stereoselectivity was observed for two reactions and no tetrahydropyridine **12a** was provided. Further study showed that the kinetical product **11b** was able to convert to tetrahydropyridine **10b** with the same palladium catalyst if sufficient reaction time is allowed (**Scheme 3.2.3**).



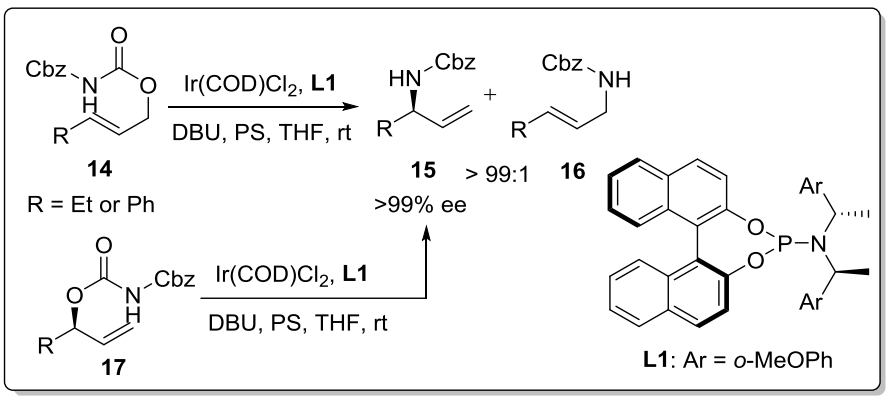
Scheme 3.2.3 Intramolecular decarboxylative cyclization with cyclic carbamates

With the above results in hand, they gave the plausible mechanism as follows. Subjection of compound **10c** under the standard reaction conditions, two possible intermediates **13a** and **13b** could be generated. Five-member ring complex **13a** which was generated by the coordination of palladium and nitrogen from bottom face would provide *cis*-product **11c** *via* a one-time inversion of the stereochemistry by reductive elimination. While Pd-π-allyl complex **13b** was formed when palladium was coordinated to the double bond from bottom side and hence give the *trans*-product **11d** by the nucleophilic addition with double inversion of the stereochemistry. However, only *trans*-product **11d** was observed in this reaction. Thus, they proposed that this reaction proceeded through zwitterionic π-allyl palladium sulfonamide **13b** intermediate (**Scheme 3.2.4**). Based on their mechanism, an extension to the synthesis of highly substituted dihydroquinoline was then developed in 2008.[7]



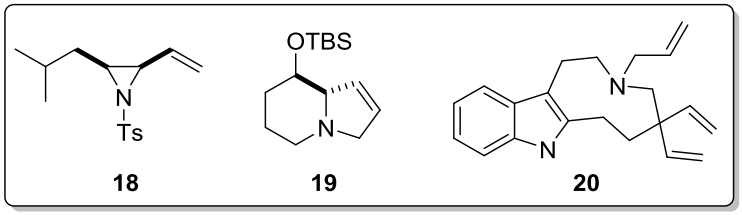
Scheme 3.2.4 Plausible mechanism for the formation of *trans*-vinyl azetidine

Iridium catalyst was also introduced to catalyze the decarboxylative amidation of allylic carbamate by Han's group.[8] Cbz group was selected as the protecting group for amide and $Ir(COD)Cl_2$ which was commonly used for regio- and enantioselective amination was selected as the catalyst. The reaction was performed with linear carbamate **14** in the presence of DBU, proton sponge and chiral ligand **L1** to give the branched product **15** with excellent enantio- and regio- selectivity. Later, they employed the optically enriched branched carbamate **17** to extend the scope of the allylic amide **15**.



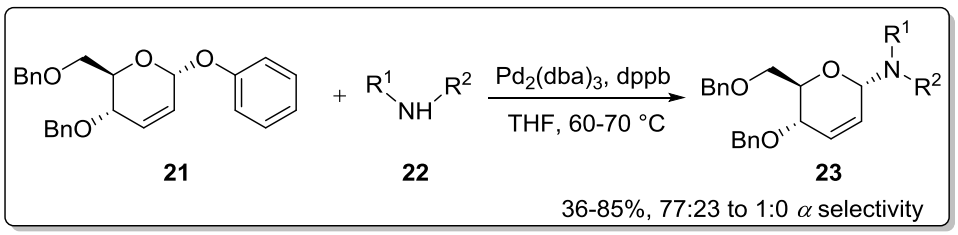
Scheme 3.2.5 Iridium catalyzed decarboxylative allylic amidation

In addition, Yamamoto's group employed this strategy to synthesize vinyl aziridines **18** from vinyl oxozalidinones.[9] Later, the DcA reaction was utilized as a key step to form Pyne's intermediate **19** by Bate's group to complete the formal total synthesis of swainsonine.[10] In 2009, a well-designed DcA reaction, which was used by Hoveyda to replace the standard Calverley protocol, provided a more concise synthesis of quebranchamine **20** (**Scheme 3.2.6**).[11]



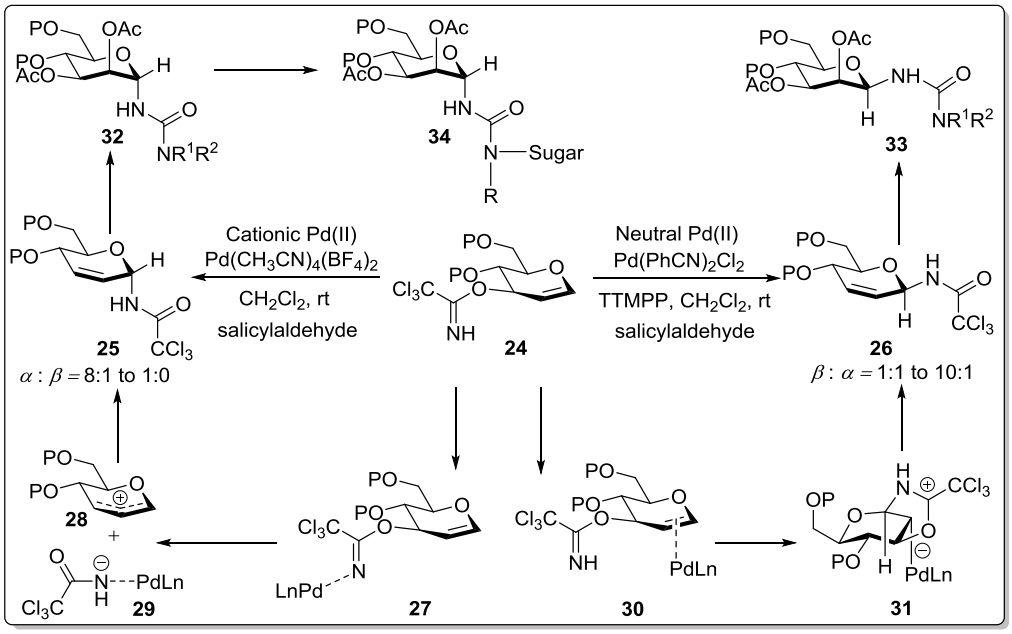
Scheme 3.2.6 Selected applications of decarboxylative allylic amidation

Compared to the investigations of metal catalyzed *O*-glycosylation, the studies about highly efficient *N*-glycosylation with metal catalyzed seems to be very rare. Till now, there are only two good examples. In 1992, Sinou reported the first reaction with 2,3-unstaturated phenolic α-*O*-glycoside **21** as the glycosyl donor, $Pd_2(dba)_3$ as the catalyst, DPPB as the ligand, THF as the solvent. When the *N*-nucleophile **22** was used as the glycosyl acceptor, the desired *N*-glycoside **23** was obtained in 36-85% with good to pure α-selectivity (**Scheme 3.2.7**).[12]



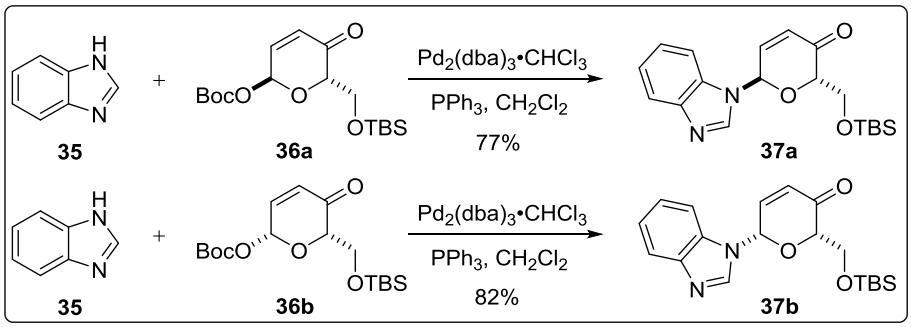
Scheme 3.2.7 Palladium catalyzed *N*-glycosylation

A few years later, Nguyen's group developed a palladium catalyzed glycosylation method to synthesize *N*-glycosyl trichloroacetamides based on a side reaction of the *O*-glycosylation with trichloroacetimidate glycal donor **24**.[13] They demonstrated that the stereoselectivity of anomeric centre can be controlled by the selection of different type of palladium source. The cationic $Pd(CH_3CN)_4(BF_4)_2$ would coordinate to the nitrogen to form complex **27** as the intermediate. Then allylic cation **28** and nucleophile **29** were generated by the ionization. This was followed by nucleophilic addition from the less steric α-face to give the product **25** with excellent α-selectivity. With neutral $Pd(PhCN)_2Cl_2$ as the catalyst, palladium would coordinate to the double bond to give compound **30** as the key intermediate. Next, β-type *N*-glycoside was obtained through an Overman rearrangement from palladium complex **31**. Notably, the outcome of the reaction was significant improved when salicylaldehyde was used as the additive (**Scheme 3.2.8**). After establishing the methodology, they continued to explore the applications specifically on functionalization of double bond and trichloroacetamide group.[14] Next, various types of glycosyl ureas and unsymmetrical urea-linked disaccharides **32**-**34** were synthesized to demonstrate the utility of this methodology.



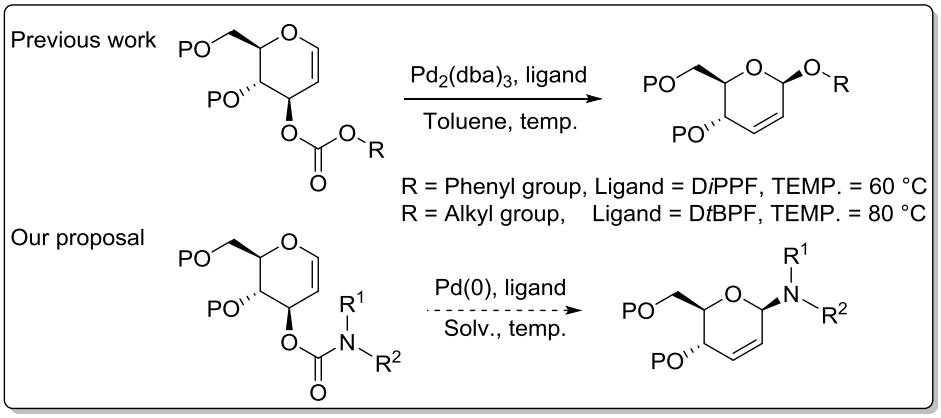
Scheme 3.2.8 Palladium catalyst controlled *N*-glycosylation

A palladium-catalyzed *N*-glycosylation was disclosed by O'Doherty in 2006.[15] In their strategy, the 2-substituted 6-*tert*-butoxycarboxy-2H-pyran-3(6H)-ones **36a** and **36b** which can be prepared from furfural alcohol *via* an asymmetric *de novo* synthesis were selected as the glycal donors while benzimidazole **35** was chosen as the glycosyl acceptor. When the reaction was conducted in the presence of palladium catalyst, desired *N*-glycoside **37a** or **37b** were generated in high yield and exclusive selectivity. Later, the method was extended to synthesize hexopyranose adenosine analogues.



Scheme 3.2.9 Palladium-catalyzed *N*-glycosylation

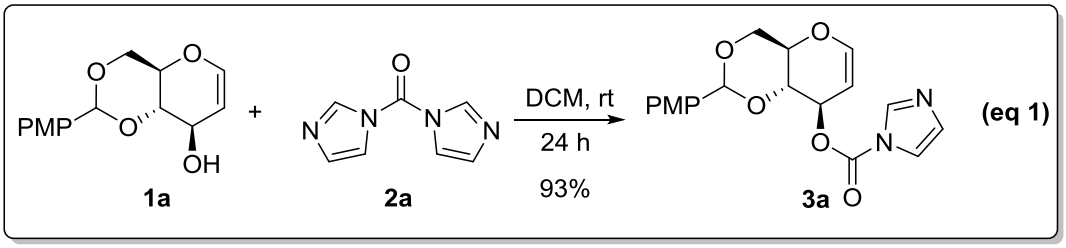
From the literature survey we conclude that transition metal is competent to catalyze the decarboxylative allylation with carbamate. However, related reports for the syntheses of *N*-glycosides are not sufficient till now and hence, it is still in need to develop more protocols to satisfy the demand. As such, an extension and complement of our methodology of decarboxylative glycosylation with glycal donor was made to synthesize *N*-glycosidic linkage in our lab (**Scheme 3.2.10**). Meanwhile, it was mentioned before that the Ferrier rearrangement product was a useful synthetic unit to synthesize diverse range of carbohydrate structures. Herein, we demonstrate its application to the synthesis of *N*-glycosyl imidazole analogues.



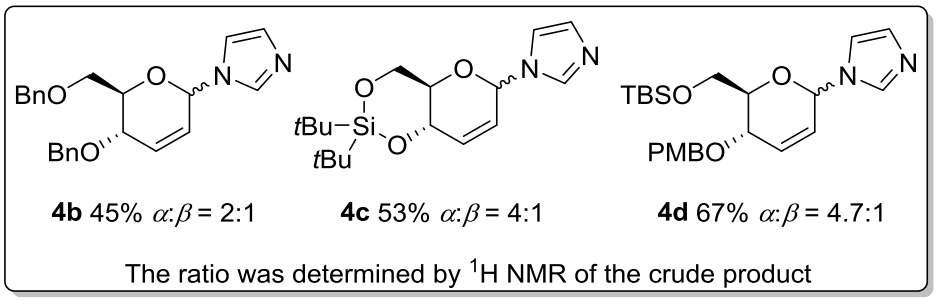
Scheme 3.2.10 Proposed idea on palladium catalyzed *N*-glycosylation

Result and discussion

To commence our proposal, carbamates **3a** which can be prepared by 4,6-*para*-methoxybenzylidene-glucal **1a** and CDI (1,1'-Carbonyldiimidazole) **2a** was selected as the model for the further study. To our delight, the reaction underwent smoothly in CH_2Cl_2 to give the desired product **3a** in 93% yield (**eq 1**).



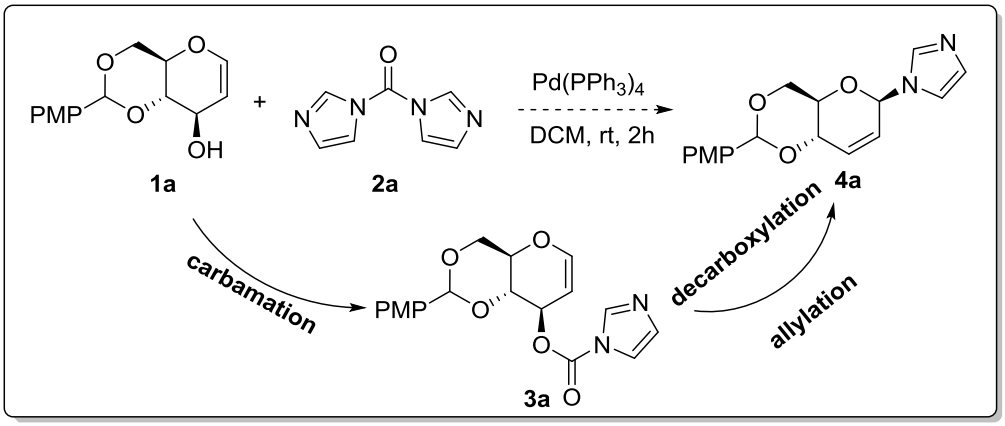
Next, we set out to prepare carbamate substrates using the same method for the latter substrate scope examination. However, it was found that carbamates **3b**-**3d** were very difficult to obtain and instead the glycosylation product **4b**-**4d** were obtained. This was because the decarboxylation occurred fast during the reaction or the purification step, even the silica was pre-treatment with Et_3N. Upon decarboxylation, the imidazole anion and the allylic cation undergoes nucleophilic addition to yield the *N*-glycosyl imidazole compound. However, only moderate yield and poor selectivity were obtained for each of these tested reactions. Notably, as detailed in **Scheme 3.2.11**, the products were provided with α-selectivity.



Scheme 3.2.11 Decarboxylation of the carbamates without palladium catalyst

With the desired product far away from our requirement, we propose solutions to improve the yield and selectivity. Since the introduction of palladium source produces the dominating β-selectivity in this type of reaction,[16,17] we proposed a one-pot reaction to form unstable carbamate intermediates **3a** *in situ* and then the generated **3a** could be converted to the desired *N*-glycosides *via* a palladium catalyzed decarboxylative allylation reaction (**Scheme 3.2.12**).

Considering the dominated β-selectivity with the introduction of palladium source in this type of reaction,[16,17] we then proposed the following one-pot reaction (**Scheme 3.2.12**). With this design, we hope that the *in situ* generated unstable carbamate intermediates **3a** could be converted the desired *N*-glycosides through a palladium involved mechanism.



Scheme 3.2.12 Our modified proposal on palladium catalyzed *N*-glycosylation

To test our idea, the reaction of **1a** with **2a** was proceeded in THF with commonly used $Pd(PPh_3)_4$ at room temperature. After two hours, it was found that *N*-glycoside **4a** was isolated in 45% yield with a single isomer. However, more than 40% of **1a** was recovered from the reaction mixture. Inspired by this result, we started to screen different solvents to increase the yield. As detailed in **Table 3.2.1**, CH_3CN was found

to be unsuitable for this reaction and only a trace amount of **4a** was observed (entry **2**). Similar result was obtained when the reaction carried out in DMF or toluene (entries **3**-**4**). We found that the bad solubility of CDI in these solvent was the main factor to account for the poor results. Gratifyingly, when DCM was utilized as the reaction solvent (entry **5**), the chemical yield was significantly improved to 93%. Next, optimization was focused on examining the catalytic system. A few sets of Pd (II) catalyst and ligand combinations were tested but there is no better result was detected when compared to the usage of $Pd(PPh_3)_4$ (entry **6**-**10**). From the information shown in the ^1H NMR spectra, we found that only one isomer was detected in each reaction and the stereochemistry of anomeric center was confirmed to be β-selectivity based on the X-ray diffraction crystallographic analysis of compound **4a** (**Figure 3.2.1**).[18]

Figure 3.2.1 X-ray structure of compound **4a** (CCDC number: **957218**)

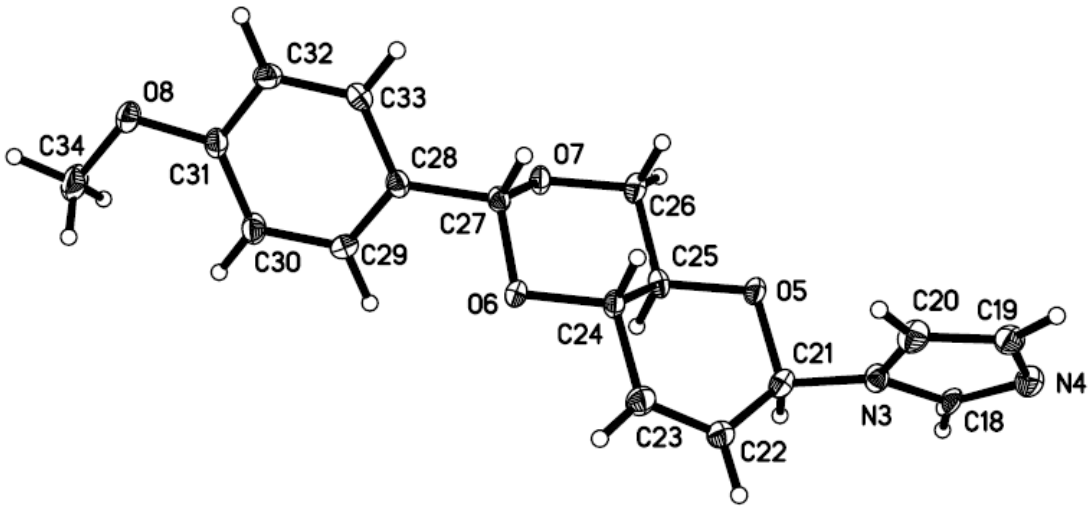
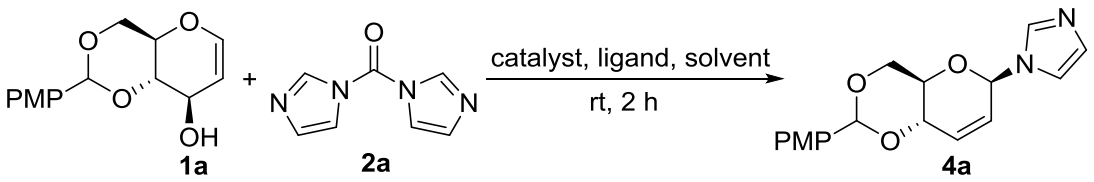


Table 3.2.1 Optimization of the reaction conditions [a]



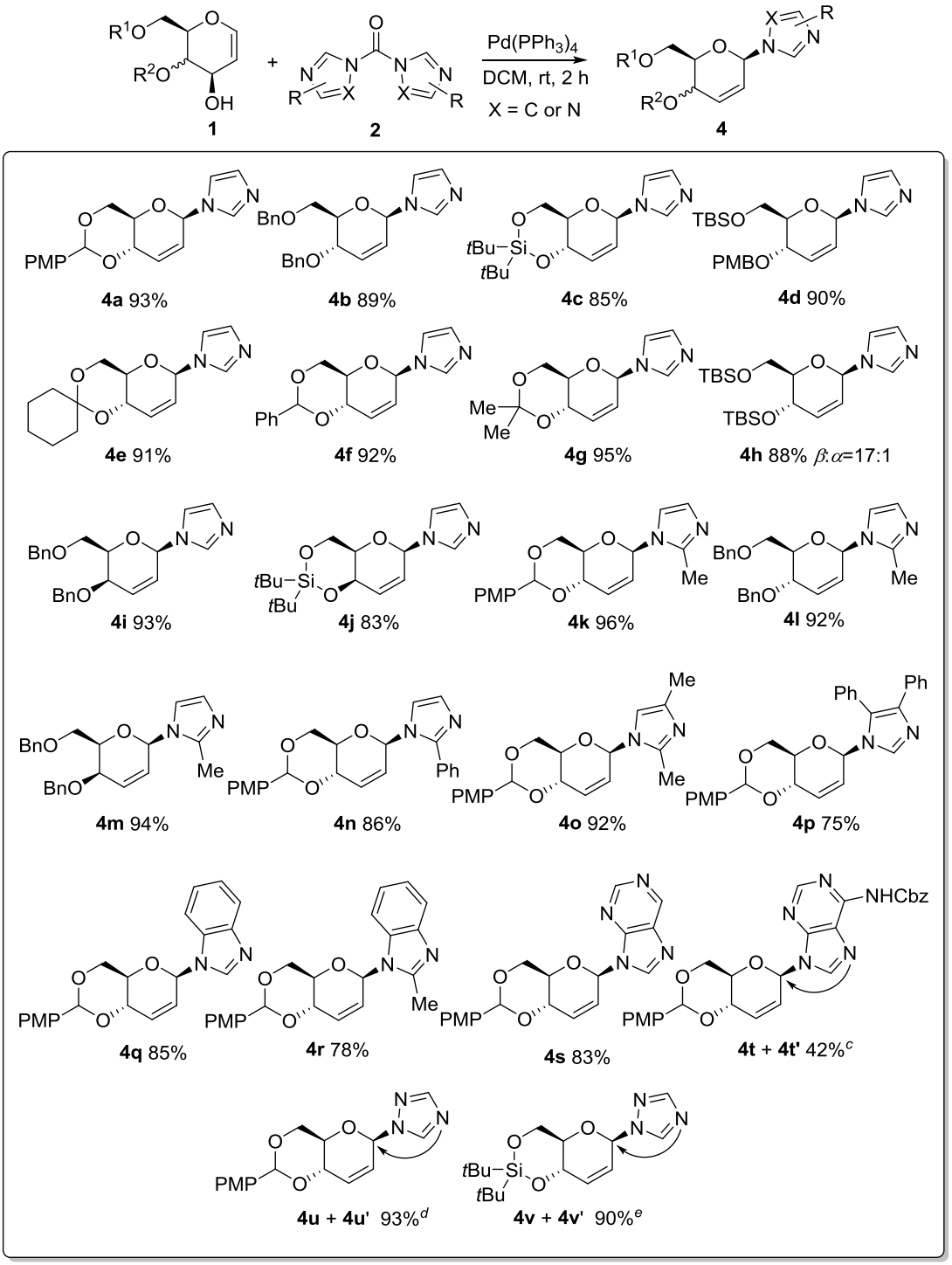
entry	catalyst	ligand	solvent	yield (%)[b]
1	$Pd(PPh_3)_4$	No	THF	45
2	$Pd(PPh_3)_4$	No	CH_3CN	trace
3	$Pd(PPh_3)_4$	No	toluene	NR[c]
4	$Pd(PPh_3)_4$	No	DMF	NR
5	$Pd(PPh_3)_4$	No	DCM	93
6	$Pd(OAc)_2$	PPh_3	DCM	30
7	$Pd_2(dba)_3$	PPh_3	DCM	41
8	$PdCl_2$	PPh_3	DCM	NR
9	$Pd(TFA)_2$	PPh_3	DCM	NR
10	$Pd(PPh_3)_2Cl_2$	PPh_3	DCM	NR

[a]Reaction conditions: 0.2 mmol of glycal **1a**, 0.3 mmol of CDI **2a**, 0.01 mmol of Pd source, in 4 mL solvent at rt for 2 h; [b]Isolated yield; [c]NR = No reaction.

This palladium catalyzed one-pot reaction was then expanded to a series of glycals and imidazole analogues. As shown in **Scheme 3.2.13**, all the examined substrates could give the desired products in good to excellent yields. As we encountered some problem on the preparations of carbamates **3b**-**3d** previously. Hence, compounds **1b**-**1d** were first screened under the optimized reaction condition and to our delight, these three substrates were able to provide the desired *N*-glycosides (**4b**-**4d**) with excellent yields. Moreover, all the formed *N*-glycosides showed excellent *β*-selectivity. The improvement of selectivity displayed the importance of palladium catalyst in controlling the stereochemistry of this reaction. To extend the generality of this

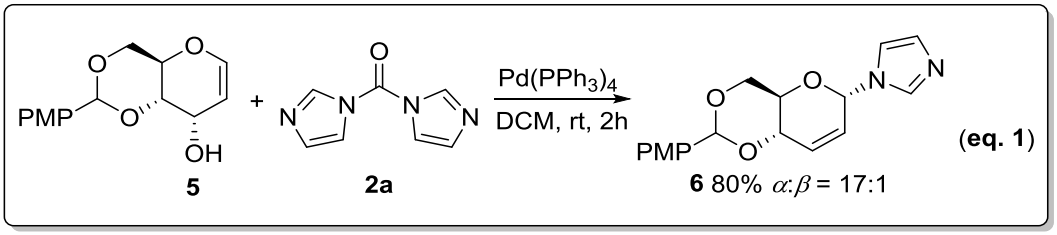
methodology, commonly used protecting groups were then installed on the glucal to give **1e**-**1h** as the glycosyl donors. Notably, this reaction exhibited good tolerance to different protecting groups of glucal and the construction of *N*-glycosidic bonds were successfully achieved with excellent yields (**4e**-**4h**). Howeer, unlike exclusive β-selectivity provided by other substrates, di-*tert*-butylsilyl protected glucal gave **4h** with a ratio of β:α = 17:1. After that, different glycals were tested. Treatments of **1i** and **4j** with the optimized condition gave the corresponding products in 93% and 83% yields respectively with pure β-selectivity. After the examination of glycals, numerous CDI analogues were screened to assay the versatility of this method. Readily accessible substituted CDI analogues such as **2b** and **2c** were found to be effective to react with different glycals, affording coumpounds **4k**-**4n** in excellent yields and exclusive β-selectivity. Later, disubstitued CDI analogues were employed and the reactions proceeded smoothly to give exclusive β-type products **4o** and **4p** in 92% and 75% yields respectively. Benzimidazole glycosylated products **4q** and **4r** were also achieved by the same strategy with 85% and 78% yields respectively. To broaden the usability of this methodology, In addition, the syntheses of *N*-glycosidic hexopyranosyl nucleosides were attempted due to their natural occurance. Fortunately, the reactions with purine and adenine type imidazole analogues generated **4s** and **4t** in 83% and 42% yields respectively. Although both of the nitrogen can serve as a nucleophile to form the glycosidic bond, compound **4s** was obtained with good regioselectivity while **4t** was provided as a mixture of 1:9.[6] When 1,1'-carbonylbis(1,2,4-triazole) was used as reactant to generate an asymmetric acceptor, *N*-glycosides **4u** and **4v** were obtained as inseparable mixtures with excellent yields.

Scheme 3.2.13 Substrate scope of *N*-glycosyl imidazole analogues [a,b]

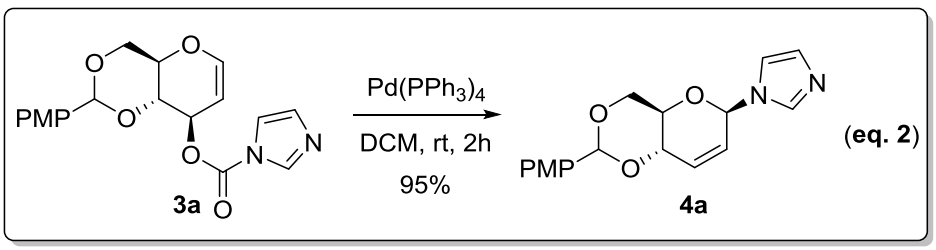


[a] Reaction conditions: 0.2 mmol of glycal **1**, 0.3 mmol of **2**, 0.01 mmol of $Pd(PPh_3)_4$, in 4 mL DCM at room temperature for 2 h; [b] Isolated yields; [c] Inseparable mixture with a ratio of 1:9; [d] Inseparable mixture with a ratio of 1:10; [e] Inseparable mixture with a ratio of 1:5.

To demonstrate the coordination effect between nitrogen and palladium, compound **5** was then synthesized by the chirality conversion of hydroxyl group on C-3 position. Subjection of compound **5** with CDI **2a** under the same condition afforded compound **6** with a yield of 80%. As predicted, α-isomer was the dominating product (**eq. 1**).[19]



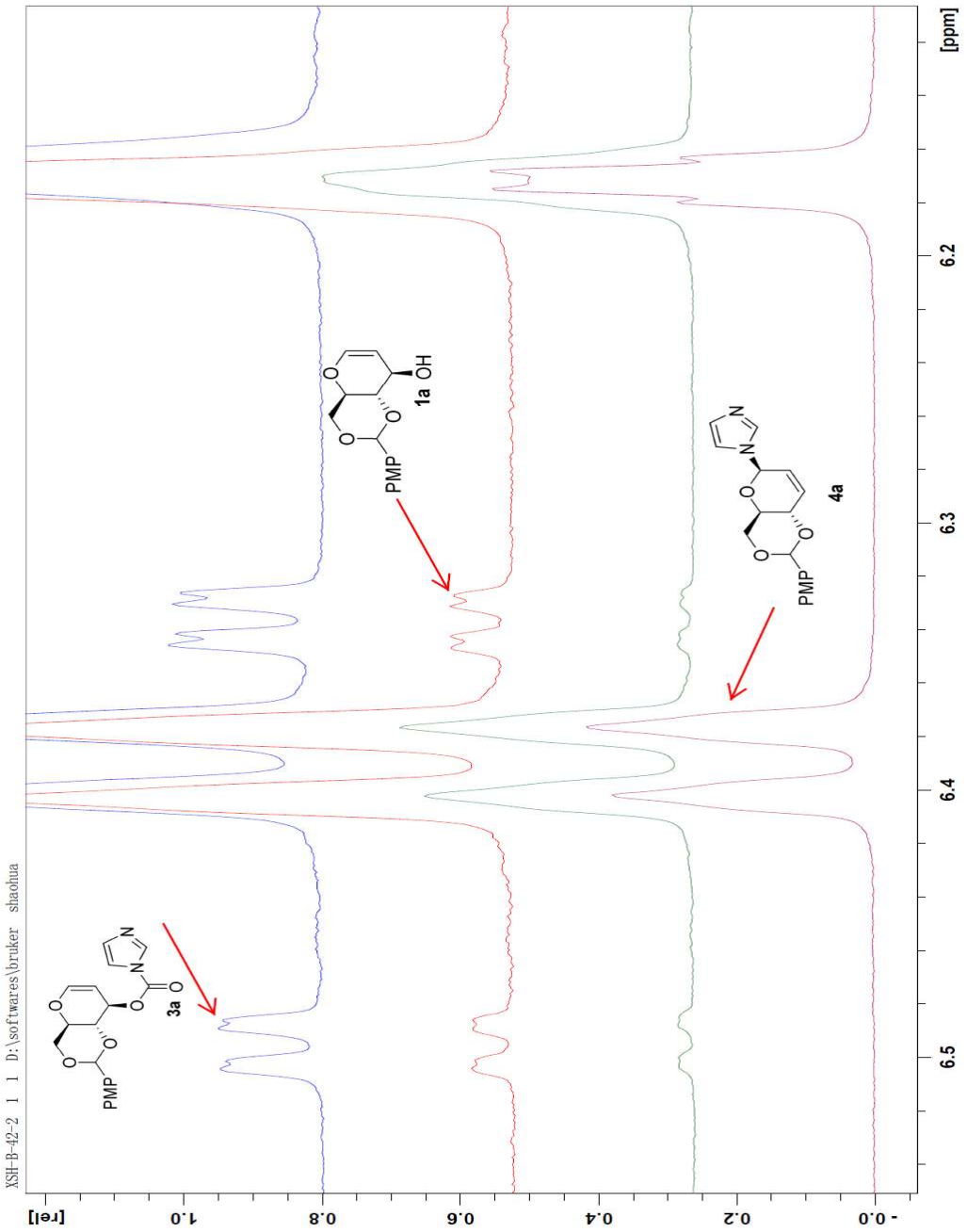
Further investigation was conducted by reacting carbamate **3a** with our optimal conditions and exclusive β-type product **4a** was formed in 95% yield (**eq 2**). Hence, this proved that our reaction proceeded with carbamate **3** as the intermediate. In addition, the reaction of **1a** and CDI with $Pd(PPh_3)_4$ was monitored *in situ* in $CDCl_3$ by proton NMR (**Figure 3.2.2**). From the results summarized in **Figure 3.2.2** we can see that carbamate intermediate **3a** could be formed in this reaction and the amount of intermediate **3a** decreased as the reaction progressed. Finally, all the starting material **1a** converted to desired product **4a**.



Since most of the important *N*-glycosides known as nucleosides are found in furanosyl structure, we then attempted to apply this strategy in the syntheses of furanosyl *N*-glycosides. Because of the big difference in conformation and reactivity,

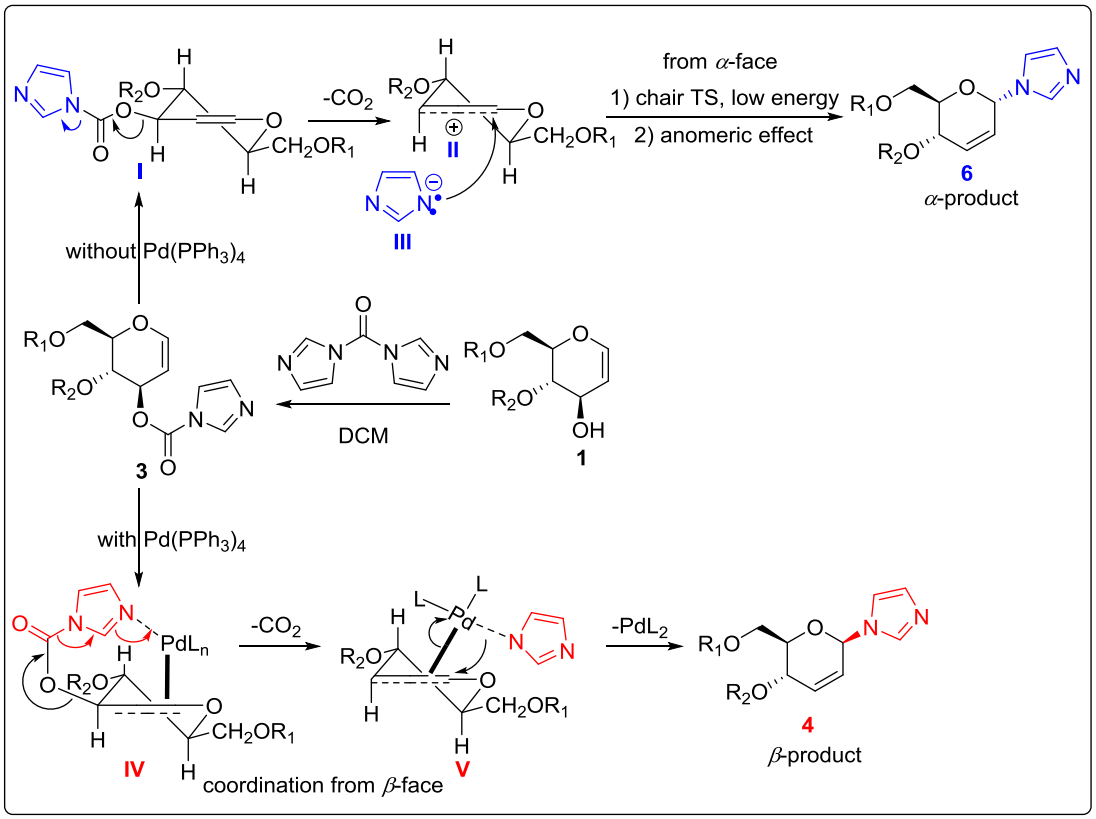
the desired product was obtained in low yield and meanwhile, poor stereoselectivity was observed. Though the result didn't reach our requirement, this methodology may offer an approach to this kind of *N*-furanosyl linkage.

Figure 3.2.2 Monitoring of reaction progress by ^{1}H NMR



In the previous reports about palladium catalyzed glycosylation, steric effect of *C*-3 substituent have always been taken into considerate for the clarification of α-selectivity.[20] Further experiments have also been done in our lab on this type of reaction. However, the control experiments indicated that this factor was not suitable to explain the results.[21] With the starting material containing imidazole, the coordination between nitrogen and palladium should be mentioned for explaining the stereoselectivity.[18] Hence, we proposed our mechanism with a more reasonable double coordination effect as stated below. Given that glycal **1** and CDI analogues **2** were the reactants, intermediate **3** could be readily formed by a carbamation reaction. However, due to the instability of compound **3**, a decarboxylation may occur to generate an allylic cation **II** electrophile and imidazole anion **III** nucleophile *in situ*. In the absence of palladium source, the reaction preferred to give α-type product **6**. One factor to account for this predominant was the anomeric effect and that the nucleophilic addition provided a new C-N bond oriented in axial position. In addition, the imidazole anion approached glycal from the bottom face *via* a chair-form transition state with lower energy. Hence, α-selectivity was observed under this set of reaction. On the other hand, when palladium catalyst was used, the palladium coordinate to glycal and nitrogen from the upper face to give intermediate **IV** as the preferred structure. Then the decarboxylation took place readily to form intermediate **V** with imidazole anion at β-face. Therefore, compound **4** was yielded with excellent β-selectivity by the subsequent nucleophilic addition and elimination of palladium catalyst. Notably, since both of two nitrogen may be involved in the reaction and hence a mixture could be observed for some of the reactions (**Scheme 3.2.14**).

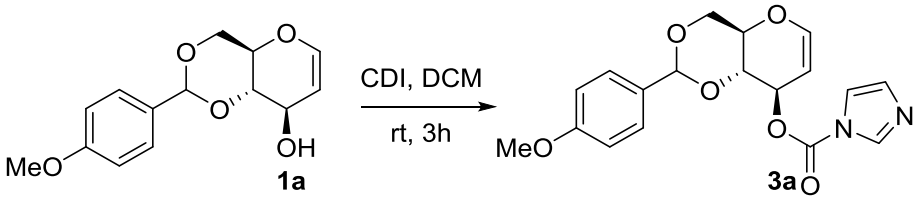
Scheme 3.2.14 Proposed mechanism



Conclusion

In summary, a concise method to synthesize *N*-glycosyl imidazole analogues was developed. Starting from *C*-3 free OH glycal and CDI analogue, useful *N*-glycosides could be achieved efficiently with excellent selectivity by a one-pot three steps reaction (carbamation, decarboxylation and allylation). Various types of glycals, protecting groups and CDI analogues were screened to demonstrate the generality of this methodology. The stereochemistry of the anomeric center was controlled by the orientation of *C*-3 OH group in the presence of palladium catalyst and both α- and β-isomers were able to furnish with high stereoselectivites by the selection of appropriate glycals.

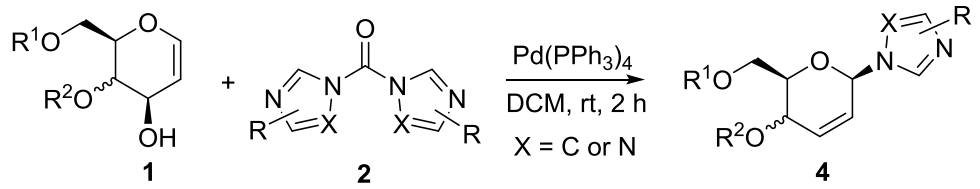
Procedure for the preparing compound 3a



To a solution of CDI (1.5 equiv) in DCM (0.1 M) was added a solution of 4,6-*para*-methoxybenzylidene glucal **1a** (1.0 equiv) in DCM dropwisely at 0 °C. Then the mixture was allowed to warm to room temperature and stirred for 3 h. After that, the mixture was washed wish with H_2O, brine, and then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluted with n-hexane/EA=1:1) to provide the desired carbamate compound **3a**.

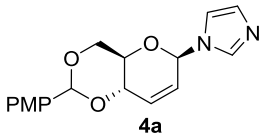
Compound **3a** was obtained in 94% yield as a white solid. M.p. 127-129 °C; $[\alpha]_D^{23}$ – 150 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 1094, 1236, 1392, 1518, 1614, 1641, 1759, 3016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 3.89 (t, J = 10.4 Hz, 1H), 4.06 (td, J_1 = 10.2 Hz, J_2 = 5.1 Hz, 1H), 4.18 (dd, J_1 = 10.4 Hz, J_2 = 7.7 Hz, 1H), 4.41 (dd, J_1 = 10.6 Hz, J_2 = 5.1 Hz, 1H), 4.92 (dd, J_1 = 6.1 Hz, J_2 = 2.1 Hz, 1H), 5.59 (s, 1H), 5.76 (dt, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H), 6.49 (dd, J_1 = 6.1 Hz, J_2 = 1.2 Hz, 1H), 6.86-6.92 (m, 2H), 7.06 (s, 1H), 7.37-7.45 (m, 3H), 8.14 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 68.0, 68.8, 73.0, 76.4, 99.1, 101.7, 113.7, 117.1, 127.5, 128.9, 130.6, 137.1, 146.7, 148.3, 160.3 ppm; HRMS (ESI) calcd. for $C_{17}H_{21}O_7$ [M+H]: 359.1243, found: 359.1238.

General procedure for the preparing *N*-glycosyl imidazole analogues from the glycals 1



To a solution of CDI analogues (0.3 mmol) and $Pd(PPh_3)_4$ (0.01 mmol) in DCM (2 mL) was added a solution of glucal compound **1** (0.2 mmol) in DCM (2 mL) slowly at 0 °C under nitrogen atmosphere. Then the mixture was allowed to warm to room temperature and stirred for 2 h. After that, the solvent DCM was removed under reduced pressure. The residue was purified by column chromatography on silica gel to provide the desired *N*-glycosyl imidazole analogues compound **4** in 83-96% yields.

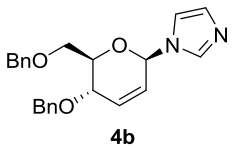
1-((4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3] dioxin-6-yl)-1*H*-imidazole (4a)



4a

Following the general procedure, the desired product **4a** was obtained by column chromatography on silica gel (eluted with *n*-hexane/EA=1:2) in 93% yield as a white solid. M.p. 160-162 °C; $[\alpha]_D^{22}$ +85.8 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 2941, 2881, 1614, 1517, 1249, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.67 (s, 1H), 7.41-7.46 (m, 2H), 7.10 (s, 1H), 7.04 (s, 1H), 6.88-6.94 (m, 2H), 6.38 (d, J = 10.2 Hz, 1H), 6.14-6.18 (m, 1H), 5.88 (ddd, J_1 = 10.2, J_2 = 2.4, J_3 = 1.9 Hz, 1H), 5.60 (s, 1H), 4.38-4.44 (m, 1H), 4.29 (dd, J_1 = 10.0, J_2 = 4.2 Hz, 1H), 3.87-3.94 (m, 1H), 3.79-3.86 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.3, 136.5, 132.8, 130.0, 129.4, 127.5, 125.6, 117.3, 113.7, 102.2, 81.1, 74.1, 71.6, 68.7, 55.3 ppm; HRMS (ESI) calcd. for $C_{17}H_{19}O_4N_2$ [M+H]: 315.1345; found: 315.1345.

1-((2*R*,5*S*,6*R*)-5-(benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-2*H*-pyran-2-yl)-1*H*-imidazole (4b)

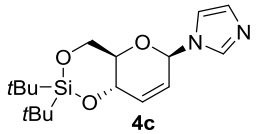


4b

Following the general procedure, the desired product **4b** was obtained by column chromatography on silica gel (eluted with MeOH/DCM=1:60) in 89% yield as a white solid. M.p. 82-84 °C; $[\alpha]_D^{22}$ +121.5 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 2941, 2866, 1616, 1495, 1452, 1265, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.63 (s, 1H), 7.24-7.36 (m, 10H), 7.06 (s, 1H), 7.01 (s, 1H), 6.24 (dt, J_1 = 10.2, J_2 = 1.8 Hz, 1H), 5.96-5.99

(m, 1H), 5.82 (dt, J_1 = 10.2, J_2 = 1.5 Hz, 1H), 4.64 (d, J = 11.4 Hz, 1H), 4.48-4.58 (m, 3H), 4.13-4.18 (m, 1H), 3.86-3.91 (m, 1H), 3.73 (dd, J_1 = 11.0, J_2 = 2.1 Hz, 1H), 3.66 (dd, J_1 = 11.0, J_2 = 5.3 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.9, 137.4, 136.4, 131.9, 129.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.6, 126.1, 117.4, 80.4, 77.7, 73.4, 71.7, 69.4, 68.9 ppm; HRMS (ESI) calcd. for $C_{23}H_{25}O_3N_2$ [M+H]: 377.1865; found: 377.1862.

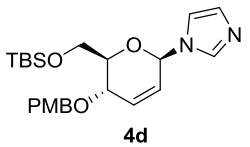
1-((4a*R*,6*R*,8a*S*)-2,2-di-*tert*-butyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3,2] dioxasilin-6-yl)-1*H*-imidazole (4c)



4c

Following the general procedure, the desired product **4c** was obtained by column chromatography on silica gel (eluted with MeOH/DCM=1:60) in 85% yield as a white solid. M.p. 139-141 °C; $[\alpha]_D^{22}$ +45.5 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 2931, 2858, 1613, 1472, 1129, 1094 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (s, 1H), 7.07 (s, 1H), 7.00 (s, 1H), 6.27 (dt, J_1 = 10.2, J_2 = 2.6 Hz, 1H), 6.06-6.09 (m, 1H), 5.72-5.77 (m, 1H), 4.57-4.63 (m, 1H), 4.17 (dd, J_1 = 10.0, J_2 = 4.9 Hz, 1H), 3.91 (t, J = 10.2 Hz, 1H), 3.80 (ddd, J_1 = 10.4, J_2 = 8.6, J_3 = 5.0 Hz, 1H), 1.07 (s, 9H), 1.01 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.4, 135.9, 129.8, 124.1, 117.3, 80.8, 75.1, 69.3, 66.4, 27.4, 26.9, 22.7, 20.0 ppm; HRMS (ESI) calcd. for $C_{17}H_{29}O_3N_2Si$ [M+H]: 337.1947; found: 337.1945.

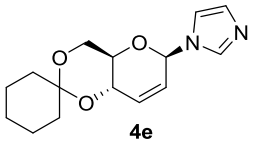
1-((2*R*,5*S*,6*R*)-6-((*tert*-butyldimethylsilyloxy)methyl)-5-(4-methoxybenzyloxy)-5,6-dihydro-2*H*-pyran-2-yl)-1*H*-imidazole (4d)



4d

Following the general procedure, the desired product **4d** was obtained by column chromatography on silica gel (eluted with *n*-hexane/EA=1:2) in 90% yield as colorless oil. $[\alpha]_D^{22}$ +110.2 (*c* 1.0, $CHCl_3$); IR (neat) ν: 2926, 2853, 1607, 1514, 1458, 1254, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.61 (s, 1H), 7.26-7.30 (m, 2H), 7.04 (s, 1H), 6.98 (s, 1H), 6.87-6.91 (m, 2H), 6.22 (dt, J_1 = 10.3, J_2 = 1.9 Hz, 1H), 5.94-5.97 (m, 1H), 5.81 (dt, J_1 = 10.3, J_2 = 1.7 Hz, 1H), 4.62 (d, J = 11.2 Hz, 1H), 4.55 (d, J = 11.2 Hz, 1H), 4.18 (ddd, J_1 = 8.5, J_2 = 4.3, J_3 = 2.0 Hz, 1H), 3.77-3.86 (m, 5H), 3.70 (ddd, J_1 = 8.5, J_2 = 4.0, J_3 = 2.6 Hz, 1H), 0.84 (s, 9H), -0.01 (s, 3H), -0.06 (s, 3H)ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.4, 136.3, 132.5, 129.8, 129.6, 129.4, 125.8, 117.4, 113.9, 80.4, 78.9, 71.6, 68.6, 62.3, 55.2, 25.8, 18.3, -5.26, -5.31 ppm; HRMS (ESI) calcd. for $C_{23}H_{35}O_4N_2Si$ [M+H]: 431.2366; found: 431.2380.

1-((4a'*R*,6'*R*,8a'*S*)-4',4a',6',8a'-tetrahydrospiro[cyclohexane-1,2'-pyrano[3,2-d][1,3]dioxine]-6'-yl)-1*H*-imidazole (4e)

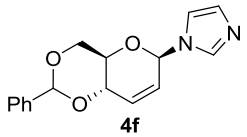


4e

Following the general procedure, the desired product **4e** was obtained by column chromatography on silica gel (eluted with MeOH/DCM=1:60) in 91% yield as yellow oil. $[\alpha]_D^{22}$ +67.0 (*c* 1.0, $CHCl_3$); IR (neat) ν: 2934, 2860, 2939, 1637, 1495, 1267, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64 (s, 1H), 7.07 (s, 1H), 7.02 (s, 1H), 6.26 (d, J = 10.2 Hz, 1H), 6.10-6.14 (m, 1H), 5.76 (dt, J_1 = 10.3, J_2 = 2.2 Hz, 1H), 4.45-4.51 (m, 1H), 3.88 (dd, J_1 = 10.5, J_2 = 5.2 Hz, 1H), 3.81 (t, J = 10.2 Hz, 1H),

3.68-3.76 (m, 1H), 1.88-2.05 (m, 2H), 1.39-1.69 (m, 8H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.5, 133.7, 129.8, 125.3, 117.4, 100.3, 81.2, 72.9, 65.9, 61.7, 38.0, 27.6, 25.5, 22.7, 22.5 ppm; HRMS (ESI) calcd. for $C_{15}H_{21}O_3N_2$ [M+H]: 277.1552; found: 277.1552.

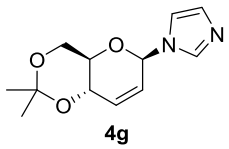
1-((4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)-1*H*-imidazole (4f)



4f

Following the general procedure, the desired product **4f** was obtained by column chromatography on silica gel (eluted with *n*-hexane/EA=1:2) in 93% yield as a white solid. M.p. 142-144 °C; $[\alpha]_D^{22}$ +85.1 (*c* 1.0, $CHCl_3$); IR (neat) ν: 2976, 2878, 1614, 1495, 1402, 1223, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (s, 1H), 7.47-7.54 (m, 2H), 7.36-7.42 (m, 3H), 7.10 (s, 1H), 7.04 (s, 1H), 6.39 (d, J = 10.3 Hz, 1H), 6.14-6.18 (m, 1H), 5.82 (dt, J_1 = 10.3, J_2 = 1.9 Hz, 1H), 5.64 (s, 1H), 4.40-4.45 (m, 1H), 4.31 (dd, J_1 = 9.8, J_2 = 4.1 Hz, 1H), 3.81-3.95 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.9, 136.5, 132.7, 130.0, 129.3, 128.4, 126.1, 125.6, 117.3, 102.1, 81.1, 74.1, 71.6, 68.7 ppm; HRMS (ESI) calcd. for $C_{16}H_{17}O_3N_2$ [M+H]: 285.1239; found: 285.1238.

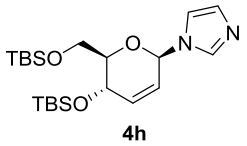
1-((4a'*R*,6'*R*,8a'*S*)-4',4a',6',8a'-tetrahydrospiro[cyclohexane-1,2'-pyrano[3,2-d][1,3]dioxine]-6'-yl)-1*H*-imidazole (4g)



4g

Following the general procedure, the desired product **4g** was obtained by column chromatography on silica gel (eluted with *n*-hexane/EA=1:3) in 95% yield as yellow oil. $[\alpha]_D^{22}$ +70.5 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 2993, 2885, 1614, 1494, 1375, 1267, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.62 (s, 1H), 7.06 (s, 1H), 7.00 (s, 1H), 6.24 (d, J = 10.2 Hz, 1H), 6.10-6.14 (m, 1H), 5.75-5.80 (m, 1H), 4.43-4.49 (m,1 H), 3.90 (dd, J_1 = 10.5, J_2 = 5.0 Hz, 1H), 3.81 (t, J = 10.4 Hz, 1H), 3.68-3.76 (m, 1H), 1.45 (s, 3H), 1.45 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.4, 133.5, 129.8, 125.2, 117.3, 100.1, 81.1, 72.6, 66.7, 62.3, 29.0, 18.9 ppm; HRMS (ESI) calcd. for $C_{12}H_{17}O_3N_2$ [M+H]: 237.1239; found: 237.1239.

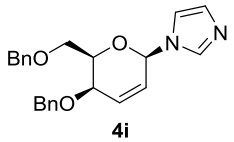
1-((2*R*,5*S*,6*R*)-5-(*tert*-butyldimethylsilyloxy)-6-((*tert*-butyldimethylsilyloxy)methyl) -5,6-dihydro-2*H*-pyran-2-yl)-1*H*-imidazole (4h)



4h

Following the general procedure, the desired product **4h** was obtained by column chromatography on silica gel (eluted with *n*-hexane/EA=1:1) in 88% yield as a white solid. IR (neat) *ν*: 2954, 2929, 2857, 1613, 1494, 1471, 1256, 1096 cm^{-1}; ^1H NMR of the major product (-isomer) ($CDCl_3$, 400 MHz): δ 7.61 (s, 1H), 7.03 (s, 1H), 6.98 (s, 1H), 6.05 (dt, J_1 = 10.2, J_2 = 1.7 Hz, 1H), 5.94-5.97 (m, 1H), 5.75 (dt, J_1 = 10.2, J_2 = 1.5 Hz, 1H), 4.38-4.43 (m, 1H), 3.79-3.82 (m, 2H), 3.53-3.58 (m, 1H), 0.90 (s, 9H), 0.83 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), -0.04 (s, 3H), -0.08 (s, 3H) ppm; ^{13}C NMR of the major product (-isomer) ($CDCl_3$, 100 MHz): δ 159.4, 136.3, 132.5, 129.8, 129.6, 129.4, 125.8, 117.4, 113.9, 80.4, 78.9, 71.6, 68.6, 62.3, 55.2, 25.8, 18.3, -5.26, -5.31 ppm; HRMS (ESI) calcd. for $C_{21}H_{41}O_3N_2Si_2$ [M+H]: 425.2656; found: 425.2657.

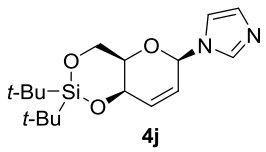
1-((2*R*,5*R*,6*R*)-5-(benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-2*H*-pyran-2-yl)-1*H*-imidazole (4i)



4i

Following the general procedure, the desired product **4i** was obtained by column chromatography on silica gel (eluted with MeOH/DCM=1:60) in 89% yield as colorless oil. $[\alpha]_D^{23}$ –81.2 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 3030, 2918, 2868, 1614, 1495, 1454, 1269, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.66 (s, 1H), 7.26-7.37 (m, 10H), 7.04-7.10 (m, 2H), 6.30 (ddd, J_1 = 10.0, J_2 = 5.2, J_3 = 1.4 Hz, 1H), 5.91-5.98 (m, 2H), 4.68 (d, J = 11.9 Hz, 1H), 4.61 (d, J = 11.9 Hz, 1H), 4.58 (d, J = 11.9 Hz, 1H), 4.50 (d, J = 11.9 Hz, 1H), 4.03 (td, J_1 = 6.4, J_2 = 2.3 Hz, 1H), 3.86-3.92 (m, 1H), 3.75 (dd, J_1 = 10.0, J_2 = 5.6 Hz, 1H), 3.71 (dd, J_1 = 10.0, J_2 = 6.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.1, 137.8, 136.5, 129.6, 129.4, 129.3, 128.4, 128.3, 127.8, 127.7(2C), 127.6, 117.5, 80.5, 76.1, 73.6, 71.0, 69.3, 67.1 ppm; HRMS (ESI) calcd. for $C_{23}H_{25}O_3N_2$ [M+H]: 377.1865; found: 377.1866.

1-((4a*R*,6*R*,8a*R*)-2,2-di-*tert*-butyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3,2]dioxasilin-6-yl)-1*H*-imidazole (4j)

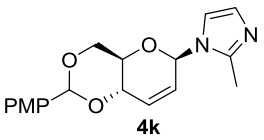


4j

Following the general procedure, the desired product **4j** was obtained by column chromatography on silica gel (eluted with MeOH/DCM=1:60) in 83% yield as a white solid. M.p. 118-120 °C; $[\alpha]_D^{23}$ –39.5 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 2933, 2859, 1614, 1497, 1474, 1263, 1146, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.66 (s, 1H), 7.06

(s, 2H), 6.30-6.37 (m, 1H), 5.92-5.97 (m, 2H), 4.50-4.55 (m, 1H), 4.36 (dd, J_1 = 12.8, J_2 = 2.3 Hz, 1H), 4.17 (dd, J_1 = 12.8, J_2 = 1.6 Hz, 1H), 3.67-3.72 (m, 1H), 1.06 (s, 9H), 0.97 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.8, 132.2, 129.5, 127.0, 117.9, 81.0, 73.2, 66.2, 64.8, 27.4, 27.1, 23.1, 20.3 ppm; HRMS (ESI) calcd. for $C_{17}H_{29}O_3N_2Si$ [M+H]: 337.1947; found: 337.1947.

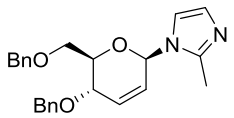
1-((4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)-2-methyl-1*H*-imidazole (4k)



4k

Following the general procedure, the desired product **4k** was obtained by column chromatography on silica gel (eluted with MeOH/DCM=1:40) in 96% yield as a white solid. M.p. 136-138 °C; $[\alpha]_D^{23}$ +66.9 (*c* 1.0, $CHCl_3$); IR (neat) ν: 2970, 2933, 2879, 1614, 1517, 1417, 1249, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.46 (m, 2H), 6.88-6.93 (m, 4H), 6.35 (d, J = 10.3 Hz, 1H), 6.08-6.12 (m, 1H), 5.77 (ddd, J_1 = 10.3, J_2 = 2.4, J_3 = 2.0 Hz, 1H), 5.59 (s, 1H), 4.36-4.42 (m, 1H), 4.28 (dd, J_1 = 10.0, J_2 = 4.2 Hz, 1H), 3.90 (ddd, J_1 = 10.3, J_2 = 8.4, J_3 = 4.4 Hz, 1H), 3.78-3.86 (m, 4H), 2,46 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.2, 145.1, 132.2, 129.4, 127.5, 127.4, 125.8, 116.7, 113.6, 102.0, 80.1, 74.1, 71.5, 68.6, 55.2, 13.1 ppm; HRMS (ESI) calcd. for $C_{18}H_{21}O_4N_2$ [M+H]: 329.1501; found: 329.1501.

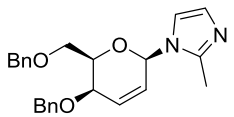
1-((2*R*,5*S*,6*R*)-5-(benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-2*H*-pyran-2-yl)-2-methyl-1*H*-imidazole (4l)



4l

Following the general procedure, the desired product **4l** was obtained by column chromatography on silica gel (eluted with MeOH/DCM=1:40) in 92% yield as yellow oil. $[\alpha]_D^{23}$ +83.9 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 3030, 2920, 2866, 1614, 1531, 1454, 1417, 1273, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.24-7.37 (m, 10H), 6.88 (s, 1H), 6.87 (s, 1H), 6.21-6.27 (m, 1H), 5.91-5.95 (m, 1H), 5.78-5.83 (m, 1H), 4.64 (d, J = 11.4 Hz, 1H), 4.47-4.58 (m, 3H), 4.14-4.20 (m, 1H), 3.86-3.92 (m, 1H), 3.74 (dd, J_1 = 11.0, J_2 = 2.0 Hz, 1H), 3.68 (dd, J_1 = 11.0, J_2 = 5.1 Hz, 1H), 2.44 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.1, 137.9, 137.5, 131.6, 128.4, 128.3, 127.9(2C), 127.7, 127.6, 127.2, 126.2, 117.0, 79.6, 77.7, 73.4, 71.7, 69.5, 69.0, 13.2 ppm; HRMS (ESI) calcd. for $C_{24}H_{27}O_3N_2$ [M+H]: 391.2022; found: 391.2021.

1-((2*R*,5*R*,6*R*)-5-(benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-2*H*-pyran-2-yl)-2-methyl-1*H*-imidazole (4m)

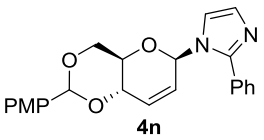


4m

Following the general procedure, the desired product **4m** was obtained by column chromatography on silica gel (eluted with MeOH/DCM=1:40) in 94% yield as yellow oil. $[\alpha]_D^{23}$ −82.6 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 2920, 2868, 1614, 1537, 1497, 1545, 1417, 1273, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.40 (m, 10H), 6.98 (d, J = 1.2 Hz, 1H), 6.93 (d, J = 1.2 Hz, 1H), 6.33 (ddd, J_1 = 10.1, J_1 = 5.3, J_2 = 1.8 Hz, 1H), 5.98 (dd, J_1 = 10.2, J_2 = 1.2 Hz, 1H), 5.88-5.92 (m, 1H), 4.70 (d, J = 11.9 Hz, 1H), 4.63 (d, J = 11.9 Hz, 1H), 4.61 (d, J = 11.8 Hz, 1H), 4.53 (d, J = 11.8 Hz, 1H),

4.06 (td, J_1 = 6.2, J_2 = 2.3 Hz, 1H), 3.89-3.94 (m, 1H), 3.82 (dd, J_1 = 10.0, J_2 = 5.7 Hz, 1H), 3.74 (dd, J_1 = 10.0, J_2 = 6.5 Hz, 1H), 2.46 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.1, 138.2, 137.9, 129.6, 129.1, 128.4, 127.7(2C), 127.6, 127.3, 117.3, 79.8, 76.2, 73.6, 71.1, 69.3, 67.1, 13.3 ppm; HRMS (ESI) calcd. for $C_{24}H_{27}O_3N_2$ [M+H]: 391.2022; found: 391.2022.

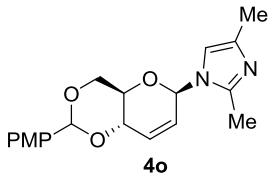
1-((4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)-2-phenyl-1*H*-imidazole (4n)



4n

Following the general procedure, the desired product **4n** was obtained by column chromatography on silica gel (eluted with *n*-hexane/EA=1:1) in 86% yield as a white solid. M.p. 186-188 °C; $[\alpha]_D^{23}$ –38.5 (*c* 1.0, $CHCl_3$); IR (neat) ν: 2933, 2868, 1614, 1517, 1467, 1250, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68-7.74 (m, 2H), 7.40-7.51 (m, 5H), 7.16 (d, J = 1.2 Hz, 1H), 7.13 (d, J = 1.2 Hz, 1H), 6.88-6.93 (m, 2H), 6.32 (d, J = 10.2 Hz, 1H), 6.16-6.21 (m, 1H), 5.73 (dt, J_1 = 10.3, J_2 = 2.1 Hz, 1H), 5.61 (s, 1H), 4.40-4.48 (m, 1H), 4.29-4.39 (m, 1H), 3.84-3.94 (m, 2H), 3.80 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.2, 148.3, 132.0, 129.9, 129.4, 129.2, 129.1, 129.0, 128.6, 127.5, 126.3, 117.7, 113.7, 102.1, 80.4, 74.2, 71.6, 68.7, 55.3 ppm; HRMS (ESI) calcd. for $C_{23}H_{23}O_4N_2$ [M+H]: 391.1658; found: 391.1658.

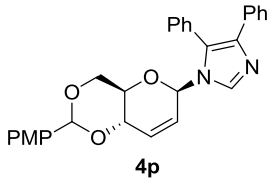
1-((4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)-2,4-dimethyl-1*H*-imidazole (4o)



4o

Following the general procedure, the desired product **4o** was obtained by column chromatography on silica gel (eluted with DCM/MeOH=50:1) in 92% yield as a yellow oil. $[\alpha]_D^{21}$ +78.9 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 2969, 2935, 2870, 1616, 1521, 1469, 1249, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.46 (m, 2H), 6.87-6.93 (m, 2H), 6.62 (s, 1H), 6.32 (d, J = 10.2 Hz, 1H), 6.00-6.05 (m, 1H), 5.74 (dt, J_1 = 10.2, J_2 = 2.0 Hz, 1H), 5.58 (s, 1H), 4.34-4.40 (m, 1H), 4.27 (dd, J_1 = 9.6 Hz, J_2 = 3.8 Hz, 1H), 3.77-3.91 (m, 5H), 2.42 (s, 3H), 2.16 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.2, 144.4, 136.5, 132.0, 129.5, 127.4, 126.1, 113.7, 112.8, 102.1, 80.1, 74.2, 71.4, 68.7, 55.2, 13.4, 12.9 ppm; HRMS (ESI) calcd. for $C_{19}H_{23}O_4N_2$ [M+H]: 343.1658; found: 343.1655.

1-((4a*R*,6*R*,8a*S*)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxi n-6-yl)-4,5-diphenyl-1*H*-imidazole (4p)

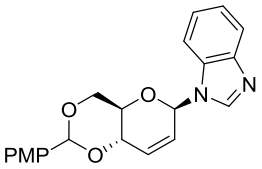


4p

Following the general procedure, the desired product **4p** was obtained by column chromatography on silica gel (eluted with *n*-hexane/EA=1:1) in 75% yield as a yellow solid. M.p. 189-191 °C; $[\alpha]_D^{21}$ +5.8 (*c* 1.0, $CHCl_3$); IR (neat) *v*: 2983, 2940, 2874, 1620, 1523, 1467, 1253, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.76 (s, 1H), 7.38-7.49 (m, 9H), 7.12-7.23 (m, 3H), 6.86-6.91 (m, 2H), 6.27 (d, J = 10.2 Hz, 1H), 5.84-5.88 (m, 1H), 5.76 (dt, J_1 = 10.2, J_2 = 2.2 Hz, 1H), 5.56 (s, 1H), 4.28-4.33 (m,

1H), 4.26 (dd, J_1 = 9.6 Hz, J_2 = 3.8 Hz, 1H), 3.73-3.86 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.2, 138.6, 135.3, 134.1, 132.4, 131.2, 129.8, 129.5, 128.9(2C), 128.1(2C), 127.5, 126.8, 126.6, 125.8, 113.7, 102.1, 79.5, 74.1, 71.6, 68.7, 55.3 ppm; HRMS (ESI) calcd. for $C_{29}H_{27}O_4N_2$ [M+H]: 467.1971; found: 467.1975.

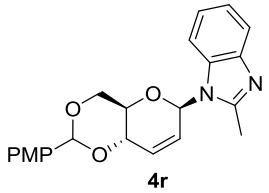
1-((4aR,6R,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]diox in-6-yl)-1H-benzo[d]imidazole (4q)



4q

Following the general procedure, the desired product **4q** was obtained by column chromatography on silica gel (eluted with *n*-hexane/EA=1:1) in 85% yield as a white solid. a light yellow oil. $[\alpha]_D^{23}$ = +63.2 (*c* = 1.0 in $CHCl_3$); IR (neat) ν: 2968, 2937, 2871, 1615, 1520, 1466, 1254, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-8.40 (m, 1H), 7.76-7.89 (m, 1H), 7.48-7.58 (m, 1H), 7.40-7.48 (m, 2H), 7.27-7.36 (m, 2H), 6.88-6.95 (m, 2H), 6.41-6.50 (m, 2H), 5.86-5.95 (m, 1H), 5.63 (s, 1H), 4.47-4.54 (m, 1H), 4.30 (dd, J_1 = 10.4 Hz, J_2 = 4.6 Hz, 1H), 4.00 (ddd, J_1 = 10.2 Hz, J_2 = 8.6 Hz, J_3 = 4.7 Hz, 1H), 3.77-3.87 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 133.2, 129.5, 127.5, 125.6, 123.5, 122.9, 120.7, 113.7, 110.7, 102.2, 80.5, 74.3, 71.7, 68.7, 55.3 ppm; HRMS (ESI) calcd. for $C_{21}H_{21}N_2O_4$ [M+H]: 365.1501, found: 365.1497.

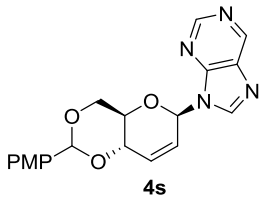
1-((4aR,6R,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3] dioxin-6-yl)-2-methyl-1H-benzo[d]imidazole (4r)



4r

Following the general procedure, the desired product **4r** was obtained by column chromatography on silica gel (eluted with *n*-hexane/EA=1:1) in 78% yield as light yellow oil. $[\alpha]_D^{23}$ = +132.3 (*c* = 1.0 in $CHCl_3$); IR (neat) *ν*: 2935, 2870, 1614, 1518, 1467, 1253, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64-7.73 (m, 1H), 7.39-7.49 (m, 3H), 7.18-7.28 (m, 2H), 6.88-6.96 (m, 2H), 6.37-6.46 (m, 2H), 5.81-5.88 (m, 1H), 5.66 (s, 1H), 4.51-4.59 (m, 1H), 4.31 (dd, J_1 = 10.3 Hz, J_2 = 4.6 Hz, 1H), 4.02 (ddd, J_1 = 10.2 Hz, J_2 = 8.5 Hz, J_3 = 4.6 Hz, 1H), 3.86 (t, *J* = 10.3 Hz, 1H), 3.81 (s, 3H), 2.68 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 151.5, 142.8, 133.8, 132.1, 129.5, 127.5, 126.5, 122.5(2C), 119.4, 113.8, 110.7, 102.3, 80.4, 74.5, 71.9, 68.7, 55.3, 14.5 ppm; HRMS (ESI) calcd. for $C_{22}H_{23}N_2O_4$ [M+H]: 379.1658, found: 379.1669.

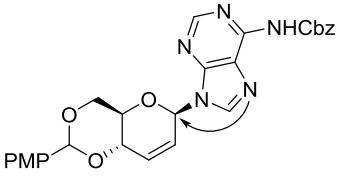
9-((4aR,6R,8aS)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3] dioxin-6-yl)-9H-purine (4s)



4s

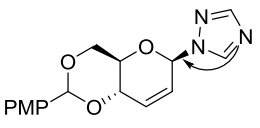
Following the general procedure, the desired product **4s** was obtained by column chromatography on silica gel (eluted with DCM/MeOH = 50:1) in 83% yield as a colorless oil. $[\alpha]_D^{21}$ +34.0 (*c* 1.0, $CHCl_3$); IR (neat) *ν*: 2944, 2875, 1618, 1521, 1475, 1250, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 9.04 (s, 1H), 8.22 (s, 1H), 7.42-7.47 (m, 2H), 6.88-6.94 (m, 2H), 6.81-6.84 (m, 1H), 6.51 (d, *J* = 10.2 Hz,

1H), 5.90 (dt, J_1 = 10.2, J_2 = 2.2 Hz, 1H), 5.63 (s, 1H), 4.47-4.53 (m, 1H), 4.33 (dd, J_1 = 10.4, J_2 = 4.6 Hz, 1H), 4.02 (ddd, J_1 = 10.2, J_2 = 8.5, J_3 = 4.7 Hz, 1H), 3.78-3.86 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 153.0, 150.9, 148.9, 143.1, 134.1, 133.9, 129.3, 127.4, 124.5, 113.7, 102.2, 77.9, 74.0, 71.8, 68.5, 55.2 ppm; HRMS (ESI) calcd. for $C_{19}H_{19}N_4O_4$ [M+H]: 367.1406, found: 367.1401.



4t + 4t'

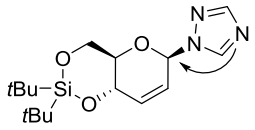
Following the general procedure, the desired product **4t** was obtained by column chromatography on silica gel (eluted with DCM/MeOH = 50:1) in 42% yield as yellow oil. ^{1}H NMR of the major product (400 MHz, $CDCl_3$): δ 8.97 (s, 1H), 8.80 (s, 1H), 8.05 (s, 1H), 7.33-7.46 (m, 7H), 6.88-6.94 (m, 2H), 6.71-6.75 (m, 1H), 6.47 (d, J = 10.2 Hz, 1H), 5.80 (dt, J_1 = 10.3, J_2 = 2.3 Hz, 1H), 5.61 (s, 1H), 5.30 (s, 2H), 4.42-4.48 (m, 1H), 4.32 (dd, J_1 = 10.3, J_2 = 4.6 Hz, 1H), 3.99 (ddd, J_1 = 10.2, J_2 = 8.6, J_3 = 4.7 Hz, 1H), 3.76-3.87 (m, 4H) ppm; ^{13}C NMR of the major product (100 MHz, $CDCl_3$): δ 160.3, 153.3, 151.1, 151.0, 149.6, 140.8, 135.4, 133.9, 129.3, 128.6, 128.5(2C), 127.5, 124.5, 121.9, 113.7, 102.2, 78.2, 74.0, 71.8, 68.6, 67.8, 55.3 ppm; HRMS (ESI) calcd. for $C_{27}H_{26}N_5O_6$[M+H]: 516.1883, found: 516.1891.



4u + 4u'

Following the general procedure, the desired products **4u** and **4u'** (an inseparable mixture with a ratio of 10:1) were obtained by column chromatography on silica gel

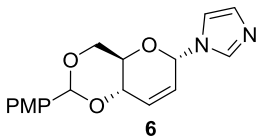
(eluted with *n*-hexane/EA=1:2) in 93% yield as a white solid. IR (neat) ν: 2933, 2887, 1614, 1516, 1375, 1252, 1103 cm^{-1}; ^1H NMR of the major product ($CDCl_3$, 400 MHz): δ 8.27 (s, 1H), 8.01 (s, 1H), 7.39-7.50 (m, 2H), 6.87-6.97 (m, 2H), 6.38-6.48 (m, 2H), 5.87-5.94 (m, 1H), 5.61 (s, 1H), 4.42-4.49 (m, 1H), 4.32 (dd, J_1 = 10.1, J_2 = 4.3 Hz, 1H), 3.91-4.00 (m, 1H), 3.75-3.90 (m, 4H) ppm; ^{13}C NMR of the major product ($CDCl_3$, 100 MHz): δ 160.3, 152.4, 142.7, 133.3, 129.4, 127.5, 124.2, 113.7, 102.2, 83.0, 74.0, 71.7, 68.6, 55.3 ppm; HRMS (ESI) calcd. for $C_{16}H_{18}O_4N_3$ [M+H]: 316.1297; found: 316.1297.



4v + 4v'

Following the general procedure, the desired products **4v** and **4v'** (an inseparable mixture with a ratio of 5:1) were obtained by column chromatography on silica gel (eluted with *n*-hexane/EA=1:1) in 90% yield as a white solid. IR (neat) ν: 2964, 2932, 2884, 2859, 1635, 1504, 1473, 1277, 1130, 1094 cm^{-1}; ^1H NMR of the major product ($CDCl_3$, 400 MHz): δ 8.24 (s, 1H), 7.98 (s, 1H), 6.31-6.36 (m, 2H), 5.81-5.87 (m, 1H), 4.63-4.68 (m, 1H), 4.21 (dd, J_1 = 9.8, J_2 = 4.8 Hz, 1H), 3.94 (t, J = 10.3 Hz, 1H), 3.81-3.89 (m, 1H), 1.07 (s, 9H), 1.01 (s, 9H) ppm; ^{13}C NMR of the major product ($CDCl_3$, 100 MHz): δ 152.2, 142.6, 136.5, 122.7, 82.8, 75.2, 69.1, 66.3, 27.3, 26.9, 22.6, 20.0 ppm; HRMS (ESI) calcd. for $C_{16}H_{28}O_3N_3Si$ [M+H]: 338.1900; found: 338.1897.

1-((4a*R*,6*S*,8a*S*)-2-(4-methoxyphenyl)-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxin-6-yl)-1*H*-imidazole (6)



6

Following the general procedure, the desired product **6** (α:β=17:1) was obtained by column chromatography on silica gel (eluted with *n*-hexane/EA = 1:2) in 80% yield as a white solid. IR (neat) ν: 2967, 2934, 2882, 1614, 1518, 1302, 1250, 1096 cm^{-1}; ^1H NMR of compound **6** (α-isomer) ($CDCl_3$, 400 MHz): δ 7.73 (s, 1H), 7.39-7.44 (m, 2H), 7.14 (s, 2H), 6.87-6.93 (m, 2H), 6.46 (d, J = 10.2 Hz, 1H), 5.98-6.02 (m, 1H), 5.94 (dt, J_1 = 10.2, J_2 = 2.6 Hz, 1H), 5.57 (s, 1H), 4.23-4.29 (m, 1H), 4.17 (dd, J_1 = 10.2, J_2 = 4.6 Hz, 1H), 3.80 (s, 3H), 3.76 (t, J = 10.2 Hz, 1H), 3.61-3.68 (m, 1H) ppm; ^{13}C NMR of compound **6** (α-isomer) ($CDCl_3$, 100 MHz): δ 160.3, 136.9, 133.5, 129.6, 129.4, 127.5, 123.4, 118.5, 113.7, 102.2, 78.1, 74.3, 69.0, 64.9, 55.3 ppm; HRMS (ESI) calcd. for $C_{17}H_{19}O_4N_2$ [M+H]: 315.1345; found: 315.1346.

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1. **Xiang, S.**; He, J.; Ma, J.; Liu, X.-W. *Chem. Commun.* **2014**, *50*, 4222.
2. **Xiang, S.**; He, J.; Tan, Y.; Liu, X.-W. *J. Org. Chem.* **2014**, *79*, 11473.
3. **Xiang, S.**; Hoang, K. L. M.; He, J.; Tan, Y.; Liu, X.-W. Reserving the Stereoselectivity of a Palladium-Catalyzed *O*-Glycosylation through an Inner-Sphere or Outer-Sphere Pathway. *Angew. Chem. Int. Ed.* **2014**, *53*, DOI: 10.1002/anie.201408739.
4. **Xiang, S.**; Lu, Z.; He, J.; Hoang, K. L. M.; Zeng, J.; Liu, X.-W. *Chem. Eur. J.* **2013**, *19*, 14047.
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Conference

"Regio- and stereo-selective synthesis of 2-deoxy-c-aryl glycosides *via* palladium catalyzed decarboxylative reactions." Xiang, Shaohua and Liu, Xue-Wei. "14th Tetrahedron Symposium", Vienna, Austria. Jun 25-28, **2013** (poster presentation).