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Microreview

Catalyzed Stereoselective Glycosylation

Glycosylation via Transition-Metal Catalysis: Challenges and Opportunities

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Abstract: Development of efficient, mild, and easily operable stereoselective glycosylations is of critical importance to access sufficient amounts of pure and structurally well-defined carbohydrates for studies of their biological functions. Such studies will facilitate our understanding of the role of complex oligosaccharides and glycoconjugates in biological processes as well as the development of carbohydrate-based effective therapeutic agents. This review highlights recent advances in the transition metal catalyzed stereoselective glycosylations for the synthesis of a variety of structurally complex and biologically significant *O*-, *N*-, *C*-, and *S*-glycosides.

Contents

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1. Introduction

During the past a few decades, tremendous efforts in glycobiological studies have proved that oligosaccharides and glycoconjugates, such as glycoproteins, glycopeptides, peptidoglycans, glycolipids, and lipopolysaccharides, play essential roles in numerous biological processes.[1] In addition, deoxy sugars[2] are an important class of carbohydrates existing in a wide range of bioactive natural products and clinical agents and are known to influence their physical, chemical, and biological properties.[3] The quality understanding of the function of complex oligosaccharides and glycans demands the availability of sufficient amounts of pure and structurally well-defined carbohy-

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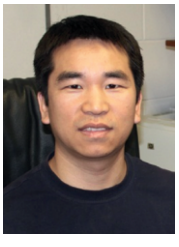

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drate molecules. Unlike the other two classes of biopolymers, i.e. polypeptides and polynucleotides, which can be synthesized via modular assembly following well-established protocols, the highly intrinsic complexity of carbohydrate structures renders their stereocontrolled synthesis extremely challenging. Such a challenge, indeed, has inspired the development of numerous chemical glycosylation methods and strategies[4] for the synthesis of complex oligosaccharides and glycoconjugates for biological studies. Despite such great success, efficient stereoselective synthesis of complex carbohydrates remains a non-trivial process. In traditional glycosylations, stoichiometric amounts of promoters are often utilized for the activation of glycosyl donors, which generates substantial amounts of chemical wastes. In addition, in order to achieve high stereo-, chemo- and regio-selectivity and yields in glycosylation, extensive studies of anomeric leaving groups, promoters, and solvents as well as careful protecting group manipulations are required. Therefore, it is of constant interest to develop mild, "green", efficient, and "easy-operable" stereoselective glycosylation methodologies for the synthesis of complex carbohydrates.

Recently, the power of transition-metal catalysis has been successfully harnessed for efficient and stereoselective synthesis of oligosaccharides/glycoconjugates and has demonstrated advantages over traditional glycosylations. First, the use of catalytic amounts of transition metal complexes as promoters minimizes the production of chemical waste which is usually a problem in traditional glycosylation reactions as stoichiometric amounts of Lewis acid promoter or electrophilic activator is involved. In addition, stereoselective glycosylations can be achieved by tuning the stereoelectronic nature of the ligands to the transition metals or through the coordination of transition metals to the hetero-atoms (e.g., oxygen and nitrogen) of glycosyl donors and acceptors, in contrast to most of the current methods relying on the nature of the substrates or protecting groups. Furthermore, the development of various transition metal complexes-promoted chemoselective activation of anomeric leaving groups has enriched the "toolbox" for orthogonal glycosylation strategies.

In early 2012, the authors wrote a review article[5] on "transition-metal catalyzed *O*-glycosylations" which specifically summarized the efforts involving the use of transition metal complexes in catalytic glycosylation reactions for the synthesis of *O*-linked glycosides.[6] Besides the *O*-glycosides, transition metal catalysis has also been widely used for the synthesis of *C*-, *N*-, and *S*-linked glycosides during the past years. In this Review, recent advances in stereoselective synthesis of *O*-, *N*-, *C*-, and *S*-linked glycosides via transition metal catalysis has been systematically discussed in the order of group numbers of the transition metals according to the Periodic Table of the Elements, from Group 3 to Group 11. In each section, glycosylation reactions and their associated mechanisms are generally surveyed chronologically, from earliest discovery to the most recent accomplishments. This Review briefly comments on those efforts mentioned in our previous article[5] and highlights the most recent development in this field, with a special emphasis on homogeneous transition metal complexes catalyzed glycosylations.

2. Synthesis of *O*-, *N*-, *C*-, and *S*-Glycosides by Group 3 Metal (Sc, Lanthanides) Catalysis

Group 3 transition metals, e.g., scandium and lanthanides, have been used as environmentally friendly Lewis acid catalysts or promoters for a varierty of chemical transformations, including glycosylations.[7] Scandium(III) salts, especially scandium(III) triflate [$Sc(OTf)_3$], were extensively studied over the past two decades as catalysts for activation of various glycosyl donors. For instance, Kobayashi and Hachiya first reported the use of scandium(III) perchlorate [$Sc(ClO_4)_3$] as catalyst for activation of 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-β-D-ribofuranose which then reacted with trimethylsilylated nucleophiles to afford the corresponding α-*N*- and *C*-ribofuranosides in high yields with good selectivities.[8] The catalyst could be recovered and reused. Later, scandium(III) triflate was investigated by a number of groups as catalyst for various type of glycosylations: 1) activation of glycosyl acetates for the synthesis of *O*- and *C*-glycosides;[9] 2) activation of glycals for the synthesis of 2,3-unsaturated *O*-alkyl and aryl glycosides, glycosyl cyanides, glycosyl azides, and thioglycopyranosides via Ferrier rearrangement reported by Yadav and co-workers;[10] 3) activation of unprotected carbohydrates in aqueous media for the synthesis of *C*-glycosides;[11] 4) activation of glycosyl orthoesters for the synthesis of *O*-glycosides.[12] In addition, Sato and co-workers described scandium cation-exchanged montmorillonite catalyzed direct *C*-glycosylation of a 1,3-diketone, dimedone, with unprotected sugars in aqueous solution.[13] Recently, Li and co-workers reported an efficient *C*-glycosylation reaction between D-glucose and dimedone using a novel nanospherically ordered mesoporous Lewis acid polymer $Sc(OTf)_2$-NSMP as catalyst, prepared by functionalizing the mesoporous phenol–formaldehyde polymer framework with scandium triflate groups. It was shown that other xanthone glycosides can also be obtained from various sugars with moderate to good yields. Furthermore, the catalyst can be easily recovered and reused at least seven times without loss of catalytic activity.[14]

In 1994, Kiessling and Sanders reported that $Yb(OTf)_3$ and $Ho(OTf)_3$ were effective catalysts for activation of α-D-glucopyranose-1,2-cyclic sulfites for the stereoselective synthesis of β-*O*-glycosides.[15] Later, various lanthanide triflates, such as $Yb(OTf)_3$, $Sm(OTf)_3$, $La(OTf)_3$, $Dy(OTf)_3$, and $Nd(OTf)_3$, were also studied for promoting glycosylations; however, it was found that $Sc(OTf)_3$ was superior in terms of reaction rate.[9g] Ytterbium(III) triflate, $Yb(OTf)_3$, was used by Yamanoi and Yamazaki as efficient catalyst for activation of glycosyl acetates which reacted with triaryloxyborane acceptors to afford aryl *O*-glycosides in excellent yields.[16] Ytterbium(III) triflate was also reported to activate orthoesters for glycosylations,[12a,12b] In the presence of catalytic amount of Lewis acid $Yb(OTf)_3$ and *N*-iodosuccinimide (NIS) as oxidant, exquisitely regioselective glycosylations of diol acceptors can be carried out with *N*-pentenyl orthoesters (NPOEs), while the use of stronger Lewis acid $Sc(OTf)_3$ gave double glycosylation as the major reaction.[12a] In addition, it was found that glycosylation of disarmed and armed *N*-pentenyl glycoside donors (NPGs) can only be triggered by the stronger Lewis acid salt $Sc(OTf)_3$, not by $Yb(OTf)_3$.[12a] Recently, Rauter and co-workers demonstrated that praseodymium tri-

flate [$Pr(OTf)_3$] was an effective catalyst for direct glycosylation of an unprotected flavanone with unprotected and reducing sugars to access *C*-glycosylflavanones. It was also discovered that the efficiency of this method was significantly improved when the reactions were assisted by ultrasound irradiation.

In summary, scandium(III) and lanthanide(III) complexes serve as general environmentally friendly oxophilic Lewis acids for activation of a number of glycosyl donors. In particular, they are water tolerable and can be applied to the activation of unprotected carbohydrates in aqueous media. Experimental evidences indicated that scandium(III) triflates are more acidic than those lanthanide triflates and can activate less reactive glycosyl donors, while milder lanthanide salts can be more selective. To the best of our knowledge, there has no report on using actinides as catalysts for glycosylations.

3. Synthesis of *O*-, *N*-, *C*-, and *S*-Glycosides by Group 4 Metal (Ti, Zr, Hf) Catalysis

In our previous review,[5] we discussed the synthesis of 1,2-*cis*-β-arabinofuranosides catalyzed by titanium complex reported by Kobayashi and co-workers.[17] As shown in Scheme 1, in the presence of an oxophilic titanium catalyst, generated from [1,2-benzenediolato(2⁻)-*O*,*O*′]oxotitanium (**3**) (0.2 equiv.) and trimethylsilyl triflate (TMSOTf, 0.1 equiv.), benzyl 2,3,5-tri-*O*-benzyl-β-D-arabinofuranoside (**4**) was obtained in 91 % yield (α/β = 1:9) from 1-*O*-trimethylsilyl-2,3,5-tri-*O*-benzyl-D-arabinofuranose (**1**) and benzyl trimethylsilyl ether (**2**). The mechanism of this titanium catalyzed *O*-glycosylation was reviewed previously.[5]

Another example of *O*-glycosylation involving titanium catalysis was reported in 2002 by Mahrwald and co-workers.[18] In the presence of catalytic amounts of titanium *tert*-butoxide and mandelic acid, furanoid glycosides were exclusively produced from unprotected and unactivated carbohydrates and simple alcohols in moderate to excellent β/α selectivity.

Besides titanium, zirconium and hafnium complexes have also been utilized as catalysts for glycosylations. For instance, zirconium(IV)-chloride-catalyzed synthesis of 2,3-unsaturated *O*-, *N*-, *C*-, and *S*-glycosides via Ferrier rearrangement was reported independently by Reddy[19] and Venkateswarlu.[20] In addition, hafnium(IV) triflate was also used by Zhao and co-workers as a highly efficient catalyst in Ferrier rearrangement for the synthesis of *O*- and *S*-glycosides.[21] Furthermore, Ikegami and co-workers described a hafnium(IV)-triflate-catalyzed decarboxylative glycosylation for the β-selective synthesis of glycosides from acyl-protected sugar donors.[22]

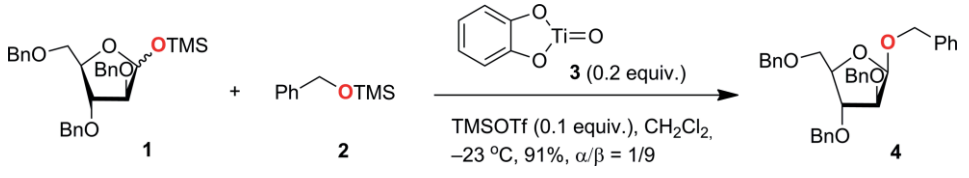
In summary, similar to group 3 metal complexes, group 4 metal (Ti^{IV}, Zr^{IV}, and Hf^{IV}) complexes are also generally regarded as oxophilic Lewis acids for activation of glycosyl donors including unprotected carbohydrates.

4. Synthesis of 2-Deoxy *O*-, *N*-, and *S*-Glycosides by Group 7 Metal (Re) Catalysis

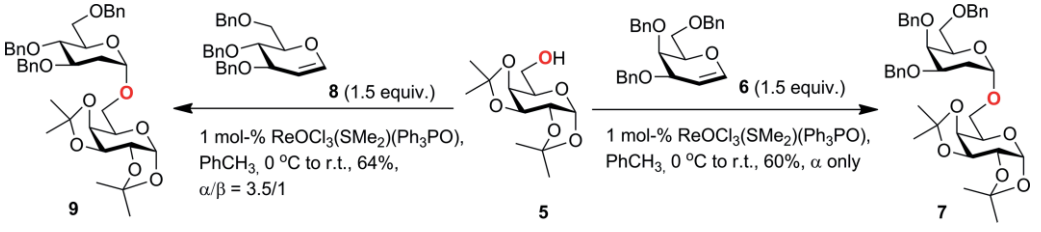
4.1 Synthesis of *O*-Glycosides by Re Catalysis

Previously, we reviewed[5] the stereoselective synthesis of 2-deoxy-α-glycosides from glycals bearing *equatorial* C3 substituents using a high-oxidation-state rhenium–oxo complex, [$ReOCl_3(SMe_2)(Ph_3PO)$], reported by Toste and co-workers.[23] As shown in Scheme 2, in the presence of 1 mol-% [$ReOCl_3(SMe_2)(Ph_3PO)$], 3,4,6-tri-*O*-benzyl-D-galactal (**6**) and 3,4,6-tri-*O*-benzyl-D-glucal (**8**) reacted with acceptor diacetone-D-galactose (**5**) to afford 2-deoxy-α-disaccharides **7** and **9** in 60 % yield (α only) and 64 % yield (α/β = 3.5:1), respectively. This method tolerates a range of sugar-derived alcohol acceptors and commonly employed protecting groups; however, glycals bearing *O*-3 ester protecting group are unreactive in this rhenium catalysis. In general, high α-selectivity can be obtained with glycals bearing C4-*axial* substituents, while moderate α-selectivity was obtained with glycals bearing C4-*equatorial* substituents. The mechanism of this rhenium(V)-catalyzed glycosylation has previously reviewed.[5]

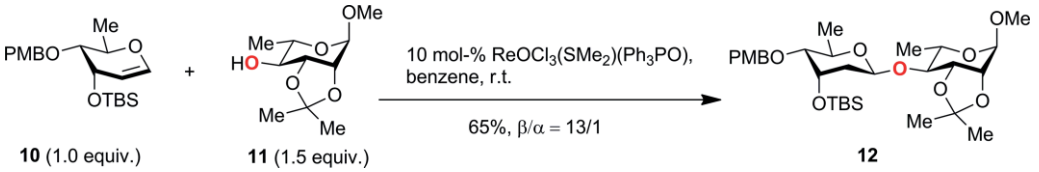
Based on Toste's work, Zhu and co-workers disclosed a rhenium(V)-catalyzed stereoselective synthesis of β-digitoxosides from 6-deoxy-D-allals bearing *axial* C3-substituents later in 2013.[24] For instance, in the presence of 10 mol-% [$ReOCl_3$-



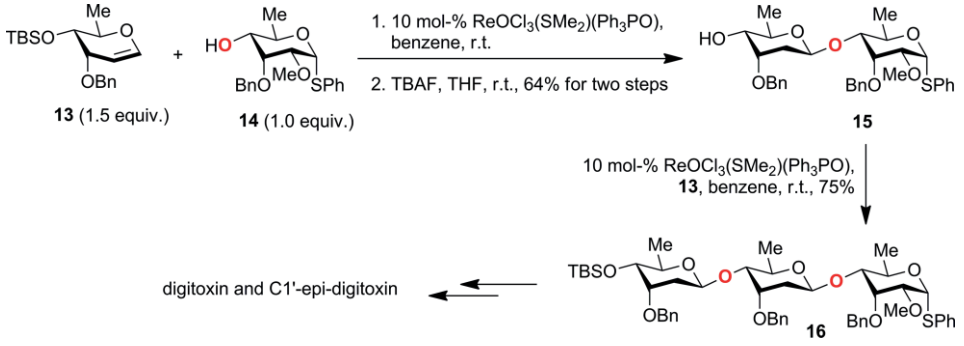
Scheme 1. Titanium-catalyzed stereoselective synthesis of 1,2-*cis*-β-arabinofuranosides.



Scheme 2. Rhenium-catalyzed stereoselective synthesis of 2-deoxy-α-glycosides from glycals.



Scheme 3. Rhenium-catalyzed stereoselective synthesis of β-digitoxosides.



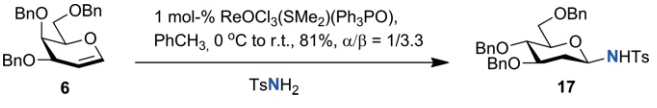
Scheme 4. Application of Re^{V} catalysis for the synthesis of the digitoxin trisaccharide.

$(SMe_2)(Ph_3PO)$], 6-deoxy-D-allal **10** reacted with L-rhamnose-derived secondary alcohol **11** to afford desired β-digitoxosides **12** in 65 % yield (β/α = 13:1) (Scheme 3). The stereoselective formation of the β-anomers was probably because the production of corresponding α-anomers is disfavored due to 1,3-diaxial interactions.

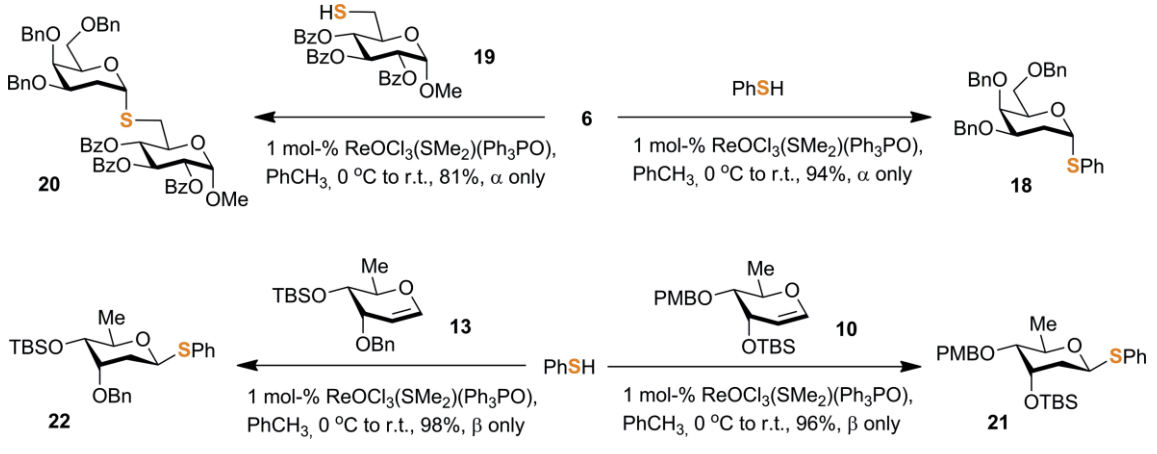
This method was successfully applied to the synthesis of the trisaccharide subunit of digitoxin.[24] As shown in Scheme 4, Re^{V}-catalyzed glycosylation between 6-deoxy-D-allal **13** and acceptor **14** followed by tetra-*n*-butylammonium fluoride (TBAF)-mediated desilylation afforded disaccharide **15** in 64 % yield over two steps. A second Re^{V}-catalyzed glycosylation between 6-deoxy-D-allal **13** and disaccharide acceptor **15** gave rise to β-linked trisaccharide **16** in 75 % yield which was subsequently used in the synthesis of digitoxin (β-isomer) and C1′-*epi*-digitoxin.[24]

4.2 Synthesis of 2-Deoxy-*N*-glycosides by Re Catalysis

In addition, Toste demonstrated the synthesis of 2-deoxy-*N*-glycoside by rhenium catalysis. As shown in Scheme 5, 2-deoxy-β-*N*-glycoside **22** in 81 % yield (α/β = 1:3.3)was obtained from 3,4,6-tri-*O*-benzyl-D-galactal (**6**) and *p*-toluenesulfonamide in the presence of 1 mol-% Re^{V} catalyst.[23]



Scheme 5. Rhenium-catalyzed stereoselective synthesis of 2-deoxy-*N*-linked glycosides.



Scheme 6. Rhenium-catalyzed stereoselective synthesis of 2-deoxy-*S*-linked glycosides.

4.3 Synthesis of 2-Deoxy-*S*-glycosides by Re Catalysis

Not only was the Re^V catalysis employed for the stereoselective synthesis of 2-deoxy-*O*- and -*N*-glycosides, it was also applied to the synthesis of 2-deoxy-*S*-glycosides (thioglycosides). As shown in Scheme 6, in the presence of 1 mol-% Re^V catalyst, 3,4,6-tri-*O*-benzyl-D-galactal (**6**) reacted with thiophenol and methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-6-mercapto-α-D-glucopyranoside (**19**) to afford α-thioglycosides **18** and **20** in 94 % and 81 % yield (α only), respectively.[23] In addition, Zhu and co-workers also reported that 6-deoxy-D-allals **10** and **13** reacted with thiophenol under Re^V catalysis to afford β-thioglycosides **21** and **22** in 96 % and 98 % yield (β only), respectively.[24]

4.4 Summary

Among group 7 transition metals, rhenium(V) complex, $[ReOCl_3(SMe_2)(Ph_3PO)]$, has been the only one reported for activation of glycals for the stereoselective synthesis of 2-deoxy-*O*-, *N*-, and *S*-glycosides. The glycosylations involving Re^V as catalyst are atom-economic and have been demonstrated in the preparation of complex biologically significant oligosaccharides.

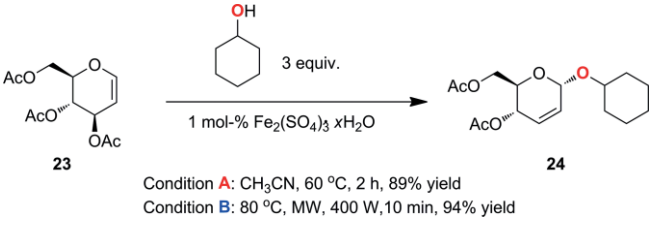
5. Synthesis of *O*-, *N*-, and *C*-Glycosides and Glycosyl Bromides by Group 8 Metal (Fe, Ru) Catalysis

5.1 Synthesis of *O*- and *N*-Glycosides by Fe Catalysis

The use of iron salts as promoters for glycosylations can be traced back to late 1970s when Kiso and Anderson reported anhydrous ferric chloride ($FeCl_3$)-promoted glycosylation of 2-acylamido-2-deoxy-β-D-glucopyranose 1-acetates with simple alcohols.[25] Later, they extended this method to the synthesis of β-linked disaccharides by coupling of 2-acylamido-2-deoxy-β-D-glucopyranose 1-acetates with protect sugar acceptors using ferric chloride as the promoter.[26] A year after that, Kiso and co-workers described the synthesis of glycolipids using ferric chloride as the promoter.[27] In all the above-mentioned research, stoichiometric amounts of anhydrous ferric chloride were used. In 1990, Lerner reported the use of a combination of ferric chloride-molecular sieves for the synthesis of β-D-ribofuranosy β-D-ribofuranoside hexabenzoate from L-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose or 1,2,3,5-tetra-*O*-benzoyl-β-D-ribofuranose.[28] In the presence of either catalytic or stoichiometric amounts of ferric chloride, β-D-ribofuranosy β-D-ribofuranoside hexabenzoate was obtained in moderate yields. Later in 1998, Nuhn and Chatterjee described the stereoselective synthesis of peracetylated α-glucosides, α-galactosides, and α-mannosides from their corresponding peracetylated sugar precursors using stoichiometric amounts of ferric chloride as the promoter.[29] Recently, Du and co-workers disclosed a $FeCl_3$-promoted α-glycosidation of glycosamine pentaacetates for the synthesis of α-*N*-acetylglycosaminides, such as fluorogenic Tn-antigen probes and an α-GalNAc-Ser derivative.[30]

5.1.1 Synthesis of *O*-Glycosides by Fe Catalysis

The first practical *O*-glycosylation using catalytic amount of iron salts was reported by Zhang and co-workers.[31] As shown in Scheme 7, in the presence of 1 mol-% ferric sulfate hydrate $[Fe_2(SO_4)_3{\cdot}xH_2O]$, tri-*O*-acetyl-D-glucal **23** reacted with cyclohexanol (3 equiv.), via Ferrier rearrangement, to give desired 2,3-unsaturated D-*O*-glucoside **24** in excellent yields with exclusive α-selectivity. Although the reactions can be carried out with or without microwave irradiation, it was found that microwave irradiation really speeded up this type of Ferrier rearrangement. This method tolerates per-benzylated glucal and a variety of alcohol acceptors. In addition, $Fe(OTf)_3$ was also reported as an effective Lewis acid catalyst for direct glycosylation of GalNAc 1- pivalate donors with alcohols to afford corresponding *O*-glycosides.[32]

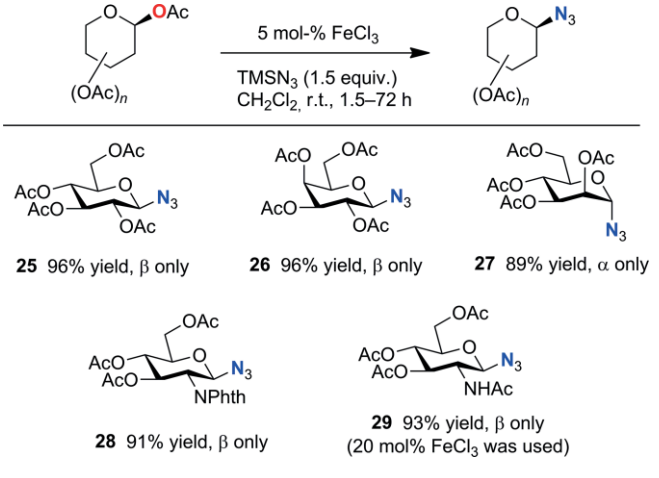


Scheme 7. Ferric sulfate hydrate-catalyzed Ferrier *O*-glycosylation of glucals.

5.1.2 Synthesis of *N*-Glycosides by Fe Catalysis

Most recently, Chen and co-workers described a highly efficient and mild method for the synthesis of 1,2-*trans* glycosyl azides via $FeCl_3$-catalyzed azido glycosylation of glycosyl β-peracetates.[33] As described in Table 1, in the presence catalytic amounts of $FeCl_3$, peracetylated D-glucose, D-galactose, D-mannose, and protected D-glucosamine reacted with $TMSN_3$ in dichloromethane at room temperature to afford desired 1,2-*trans* glycosyl azides **25**–**29** in excellent yields. In addition, the authors demonstrated that, for the first time, $FeCl_3$ in combination with copper powder can promote 1,3-dipolar cycloaddition of azido glycosides with terminal alkynes to provide corresponding 1,2,3-triazoles as exclusively a single regioisomer in good to excellent yields.

Table 1. $FeCl_3$-catalyzed synthesis of 1,2-*trans* glycosyl azides.



5.2 Synthesis of *O*- and *C*-Glycosides and Glycosyl Bromides by Ru Catalysis

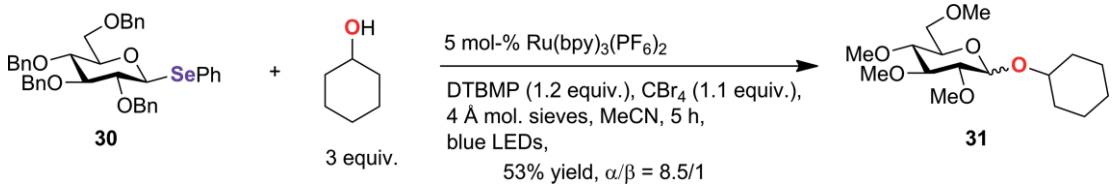
5.2.1 Synthesis of O-Glycosides by Ru Catalysis

Due to the fact that visible light photoredox catalysis enables efficient single electron transfer (SET) redox transformation, its application in organic synthesis has increasingly attracted the attention of synthetic community.[34] In 2013, Ragains and co-workers reported a mild visible light photocatalytic activation of selenoglycoside donors for the selective synthesis of 1,2-*cis*-α-pyranosides.[35] For instance, blue LED irradiation of a mixture of 1-phenylselenyl-2,3,4,6-tetra-*O*-benzyl glucoside **30** and cyclohexanol (3.0 equiv.) in the presence of 5 mol-% $Ru(bpy)_3(PF_6)_2$, 1.1 equiv. of the electron acceptor tetrabromomethane, and 1.2 equiv. of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in CH_3CN for 5 hours resulted in complete consumption of **30** and a 53 % yield of glycosylation product **31** (α/β = 8.5:1) (Scheme 8).

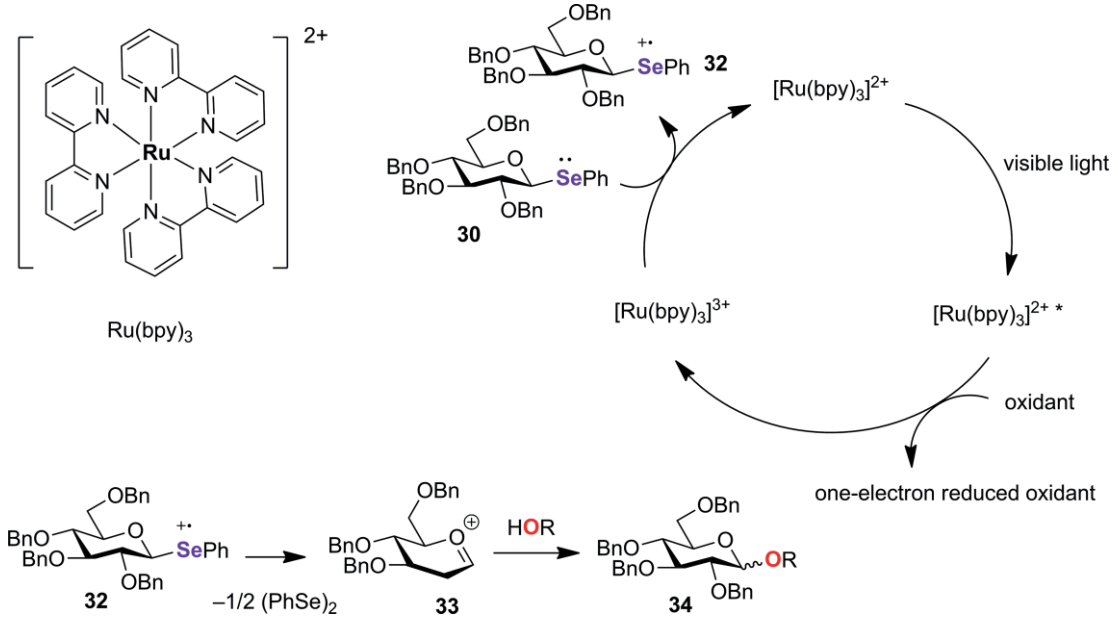
Presumably, visible light irradiation of tris(2,2′-bipyridyl)ruthenium(II) $[Ru(bpy)_3]^{2+}$ should lead to a photoexcited Ru^{II} species $[Ru(bpy)_3^{2+*}]$ which may then be oxidized by oxidant, e.g., tetrabromomethane, to form $[Ru(bpy)_3^{3+}]$. Subsequent one-electron oxidation of selenoglycoside (**30**) by $[Ru(bpy)_3^{3+}]$ should lead to the formation of resulting selenoglycoside radical cation **32** and regeneration of $[Ru(bpy)_3]^{2+}$. Selenoglycoside radical cation **32** may be unstable and disproportionate to the requisite glycosyl cation **33** which then reacts with glycosyl acceptors to afford desired glycosylated products **34** (Scheme 9). Notably, this type of *O*-glycosylation is also effected by an organocatalyst, diphenyldiselenide.

Besides the use of ruthenium complexes for photoredox synthesis of *O*-glycosides, in 2014 Kashyap and co-workers reported ruthenium(III) chloride catalyzed synthesis of 2,3-unsaturated α-glycosides and disaccharides via Ferrier glycosylation.[36] As shown in Scheme 10, treatment of a mixture of 3,4,6-tri-*O*-acetyl-D-glucal **23** and diacetone-D-galactose **5** with catalytic amounts of ruthenium(III) chloride in acetonitrile at room temperature for 16 hours selectively afforded 2,3-unsaturated α-glycosides **35** in 86 % yield (α/β = 86:14). This method tolerates various acceptors as well as several sensitive groups, such as isopropylidene, olefins, acetylene, Fmoc, ether, and esters.

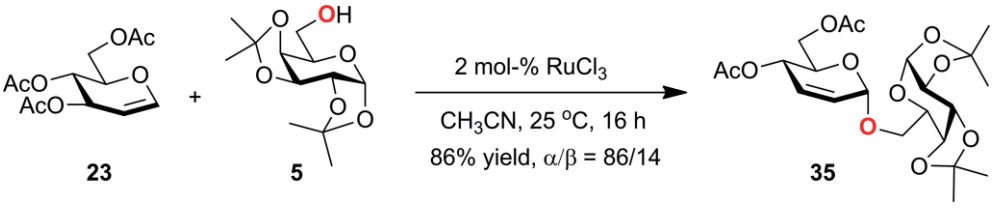
In addition, Kashyap and co-workers disclosed "one-pot" access to a-D-mannopyranosides from glycals employing ruthenium catalysis followed by dihydroxylation later.[37] As shown in Scheme 11, in the presence of 5 mol-% $RuCl_3$, glycosylation reaction of 3,4,6-tri-*O*-acetyl-D-glucal **23** and D-mannose-derived acceptor **36** proceeded smoothly to give the corresponding 2,3-unsaturated glycosides which upon in situ dihydroxylation of resultant C(2)–C(3) olefin in pyran ring by introducing aqueous solution of $NaIO_4$ as secondary oxidant in the presence of catalytic amount of $CeCl_3 \cdot 7H_2O$ at 0 °C and subsequent per-



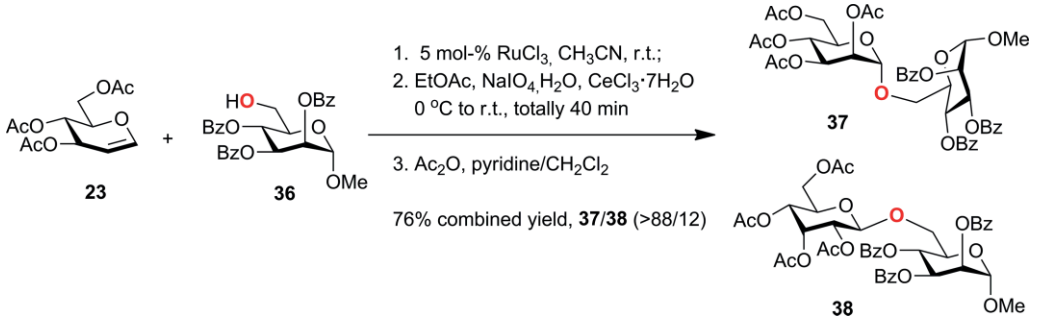
Scheme 8. $Ru(bpy)_3(PF_6)_2$-catalyzed photoredox synthesis of *O*-glycosides.



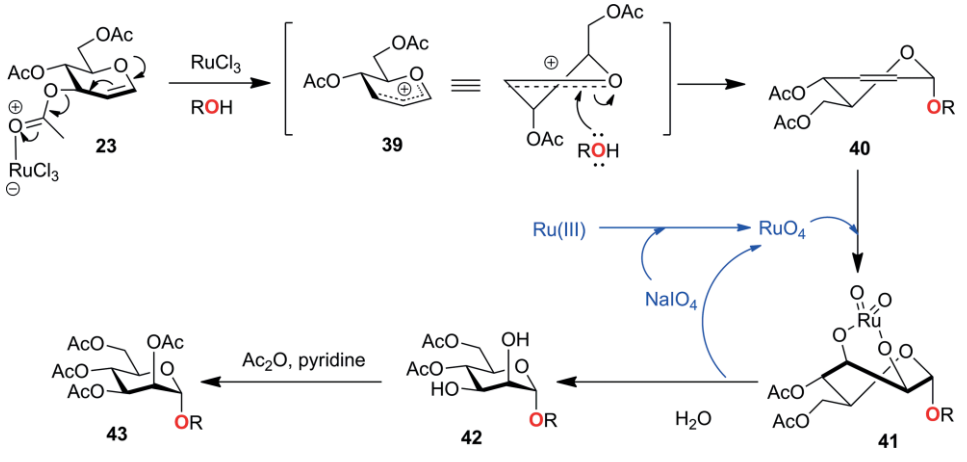
Scheme 9. Proposed mechanism of $Ru(bpy)_3(PF_6)_2$-catalyzed photoredox synthesis of *O*-glycosides.



Scheme 10. $RuCl_3$-catalyzed Ferrier glycosylation.



Scheme 11. $RuCl_3$-catalyzed one-pot glycosylation-dihydroxylation.



Scheme 12. Proposed mechanism for ruthenium(III)-catalyzed glycosylation-dihydroxylation.

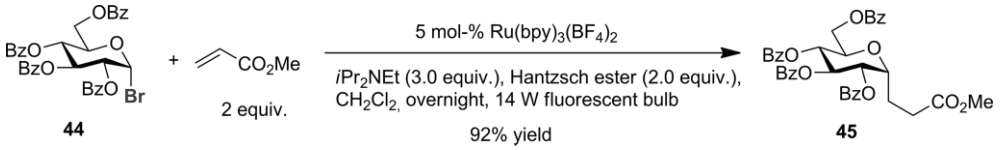
acetylation afforded α-D-mannopyranoside **37** as major product and β-allopyranoside **38** as minor product in combined 76 % yield (**37**/**38** > 88:12). This Ru-catalyzed synthesis of α-D-mannopyranosides from glucal is found to be amenable to a variety of acceptors, including carbohydrate-derived and amino-acid containing alcohols.

The mechanism for this $RuCl_3$-catalyzed one-pot glycosylation-dihydroxylation is described in Scheme 12. Thus, activation of the C3-acetate in **23** by Ru(III) would lead to the formation of allyloxycarbenium ion **39** which may exist as half chair conformation. Preferentially attack of the alcohol nucleophile from the α-face to this carbenium ion would lead to the selective formation of 2,3-unsaturated α-glycosides **40**, probably due to anomeric effect and steric effect. Next, oxidation of Ru(III) to Ru^{VIII} by IO_4^- followed by [3+2]-*syn*-cycloaddition of RuO_4 to the C(2)–C(3) olefin from the less sterically hindered face should furnish cycloadduct **41**. This cycloadduct upon oxidation followed hydrolytic cleavage of Ru-complex should provide desired α-D-mannosides **42** as major product which can be further converted to the per-acetylated glycosides **43**.

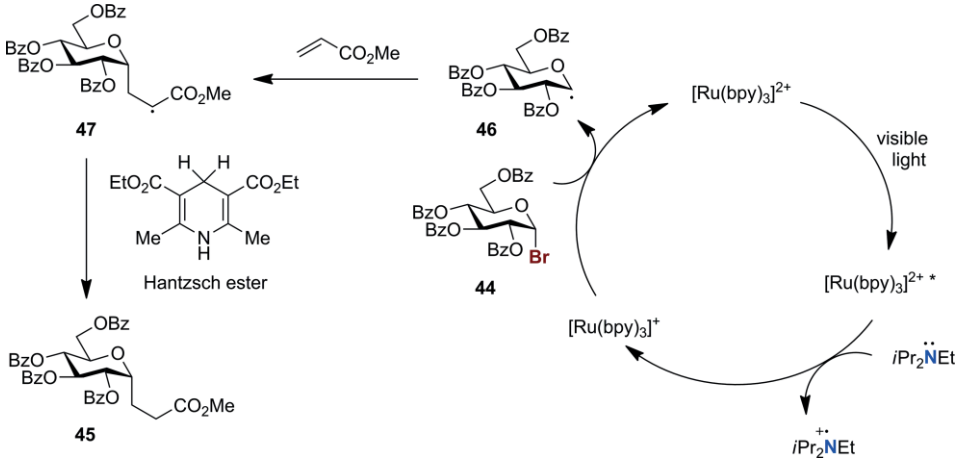
5.2.2 Synthesis of C-Glycosides by Ru Catalysis

In 2010, Gagné and co-workers reported an interesting $Ru(bpy)_3(BF_4)_2$-catalyzed photoredox synthesis of *C*-linked glycosides.[38] As shown in Scheme 13, photo-irradiation of a mixture of 5 mol-% $[Ru(bpy)_3](BF_4)_2$, α-glucosyl bromide **44**, methyl acrylate (2.0 equiv.), *N*,*N*-diisopropylethylamine (3.0 equiv.), and Hantzsch ester (2.0 equiv.) in dichloromethane at room temperature overnight with a 14 W fluorescent bulb provided α-*C*-glycoside (**45**) in 92 % yield. It was found that use of Hantzsch ester as hydrogen radical donor successfully suppressed the oligomerization.

A plausible mechanism for this ruthenium-catalyzed photoredox synthesis of *C*-glycosides is described in Scheme 14. Electron transfer from $[Ru(bpy)_3]^+$, obtained via photo-activation of $[Ru(bpy)_3]^{2+}$ and subsequent reduction by *N*,*N*-diisopropylethyl-



Scheme 13. $Ru(bpy)_3(BF_4)_2$-catalyzed photoredox synthesis of α-*C*-linked glycosides.

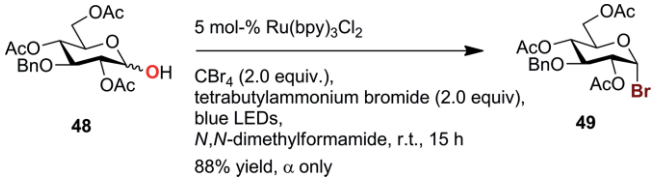


Scheme 14. Proposed mechanism.

amine, to glycosyl bromide **44** selectively generates the more stable α-anomeric radical **46**,[39] which can be added to the alkene of methyl acrylate to afford radical **47**. Subsequent termination of the carbon radical **47** by Hantzsch ester gave the desired *C*-glycoside **45**. Further studies[40] by the same group indicated that $Ru(dmb)_3^{2+}$ (dmb = 4,4′-dimethyl-2,2′-bipyridine) was more effective than $[Ru(bpy)_3]^{2+}$. This method was also applied to the continuous photoredox synthesis of *C*-glycoamino acids and *C*-glycolipids in a photoflow reactor.[41]

5.2.3 Synthesis of Glycosyl Bromides by Ru Catalysis

In 2014, Xue and co-workers reported the synthesis of α-glycosyl bromides using visible light photocatalysis.[42] For instance, in the presence of 5 mol-% $Ru(bpy)_3Cl_2$, 2.0 equiv. of tetrabromomethane and 2.0 equiv. of tetrabutylammonium bromide, Blue LEDs irradiation of 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-D-glucopyranose **48** in *N*,*N*-dimethylformamide for 15 hours afforded desired α-glycosyl bromide **50** in 88 % isolated yield (Scheme 15). This method was found to tolerate various commonly used protecting groups, such as acetals, silyl ethers, acetates, benzyl ethers, and benzoates. Mechanistically, a Vilsmeier–Haack reagent or its variant may be generated in situ from carbon tetrabromide and *N*,*N*-dimethylformamide by irradiation in the presence of a photocatalyst, $Ru(bpy)_3Cl_2$.[43] This



Scheme 15. $Ru(bpy)_3Cl_2$-catalyzed photoredox synthesis of glycosyl bromides.

Vilsmeier–Haack reagent or its variant then reacts with sugar-derived lactols to afford corresponding α-glycosyl bromides.

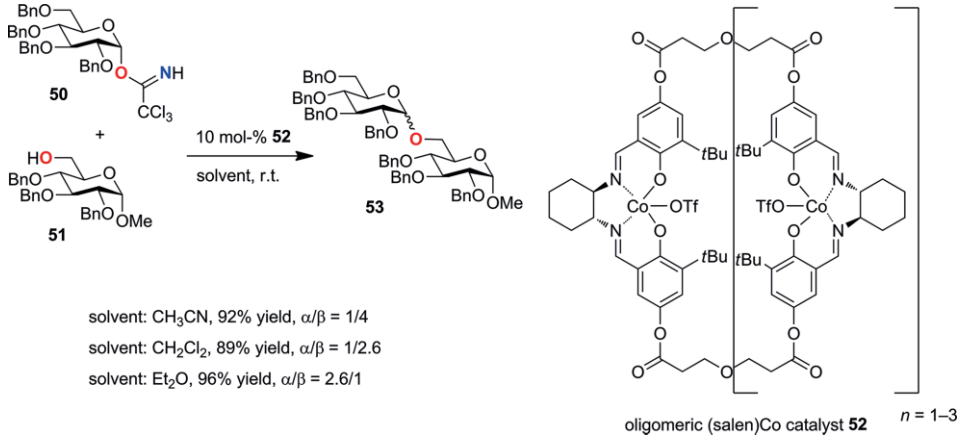
5.3 Summary

Of the group 8 transition metals, iron(III) and ruthenium(III) salts have been used as Lewis acid catalysts for activation of glycosyl acetates or glycals for glycosylation. In particular, iron is one of the earth abundant metals and the development of iron-catalyzed glycosylations is appealing due to its cost effectiveness. In addition, new visible light photoredox chemistry developed based on Ru^{II} complexes has been applied to the glycosylations for the stereoselective synthesis of *O*- and *C*-glycosides as well as glycosyl bromides. Although the Ru^{II}-catalyzed visible light photoredox *O*-glycosylation has been limited to the use of electron rich selenoglycoside donors, use of this Ru^{II}-based chemistry have been well demonstrated in the continuous photoredox synthesis of *C*-glycosides.

6. Synthesis of *O*- and *C*-Glycosides by Group 9 Metal (Co, Rh, Ir) Catalysis

6.1 Synthesis of *O*-Glycosides by Co Catalysis

In 2015, Galan and co-workers reported the first time using (salen)Co complexes as a new class of bench-stable catalysts for stereoselective glycosylation involving trichloroacetimidate glycosyl donors at room temperature.[44] As shown in Scheme 16, in the presence of 10 mol-% oligomeric (salen)Co catalyst **52** bearing triflate as counter ion, perbenzylated glucosyl trichloroacetimidate **50** reacted with glycoside acceptor **51** in acetonitrile at room temperature to selectively give desired



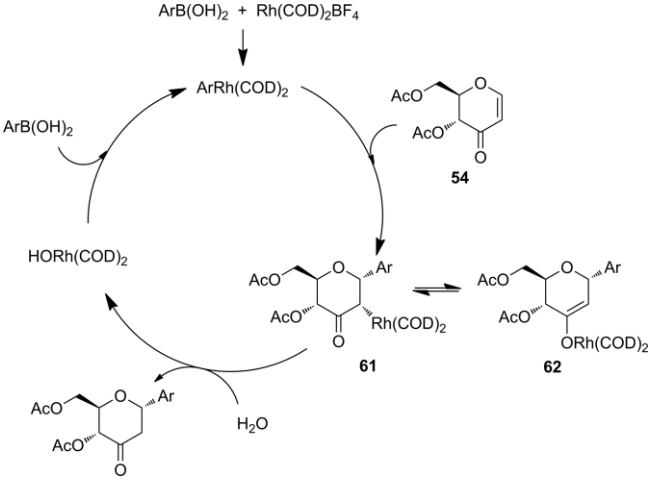
Scheme 16. (salen)Co catalyst-promoted glycosylations using glycosyl trichloroacetimidate donors.

β-disaccharide **53** in 92 % yield (α/β = 1:4). User of dichloromethane as solvent led to the inferior yield and anomeric selectivity. Notably, when diethyl ether was employed as solvent, α-disaccharide **53** was found to be the major anomer (α/β = 2.6:1), albeit the yield of **53** was slightly better. The authors also discovered that monomeric (salen)Co complexes were not as effective as oligomeric (salen)Co catalyst, such as **52**. It is noteworthy that molecular sieves, which are typically used in glycosylation reactions to remove traces of water, were not needed. This glycosylation method is amenable to different types of glycosyl donors and acceptors and tolerates various common hydroxyl protecting groups, such as acetates, benzoates, alkyl and benzyl ethers and acetals, as well as thioglycoside functionality.

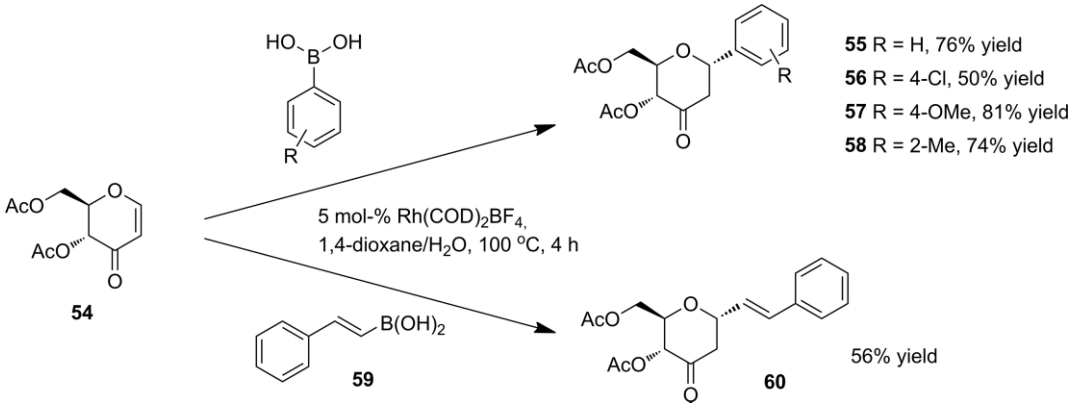
6.2 Synthesis of *C*-Glycosides by Rh Catalysis

In 2001, Maddaford and co-workers described stereoselective synthesis of *C*-glycosides by a rhodium(I)-catalyzed 1,4-addition of arylboronic acids to glycal-derived enones.[45] As shown in Scheme 17, in the presence of 5 mol-% rhodium complex $Rh(COD)_2BF_4$, the addition of phenylboronic acid to D-glucal-derived pyranone **54** occurred in a mixture of 1,4-dioxane and water at 100 °C to afford *C*-aryl glycoside **55** in 76 % yield. Among various arylboronic acids, it was found that electron-poor boronic acid furnished *C*-aryl glycoside (cf. **56**, 50 %) in lower yield than the electron-rich one (cf. **57**, 81 %). Interesting, addition of alkenyl boronic acid **59** to pyranone **54** also successfully provided *C*-alkenyl glycoside **60** in 56 % yield. Notably, only the α-*C*-glycosides were observed in all cases.

The plausible mechanism for this rhodium(I)-catalyzed 1,4-addition of arylboronic acid derivatives to enone is shown in Scheme 18. First, transmetalation of the aryl group from boron



Scheme 18. Proposed mechanism for Rh^I complex-catalyzed *C*-glycosylation.



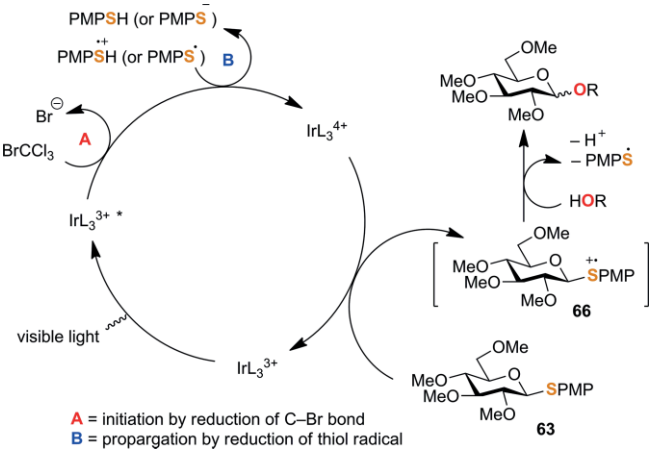
Scheme 17. Stereoselective synthesis of *C*-glycosides by Rh^I-catalyzed 1,4-addition of aryl boronic acids to glycal-derived enone.

to rhodium occurs to form rhodium complex $ArRh(COD)_2$. This rhodium complex $ArRh(COD)_2$ then adds stereoselectively to the α-face of the olefin of enone **54** to afford intermediate **61** which probably is in equilibration with its isomer **62**. Subsequent hydrolysis of intermediates **61** or its isomer **62** provides the desired α-*C*-glycosides and rhodium complex $HORh(COD)_2$ which reacts with arylboronic acid to regenerate rhodium complex $ArRh(COD)_2$.[45]

6.3 Synthesis of *O*-Glycosides by Ir Catalysis

Use of visible light photoredox catalysis for the synthesis of *O*-glycosides involving iridium catalyst was first reported by Bowers and co-workers.[46] This chemistry was inspired by recent increasing application of visible light photoredox catalysis in organic synthesis[19] and electronic activation of thioglycosides.[47] For example, visible light irradiation of a mixture of *S*-(*p*-methoxy)phenyl-tetra-*O*-methyl-thioglycosides **63**, 1-adamantanol (2 equiv.), 5 mol-% $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ catalyst **64**, 2 equiv. of bromotrichloromethane, and 10 equiv. of hexafluoroisopropanol (HFIP) in anhydrous acetonitrile using blue LEDs at room temperature for 9 hours afforded desired 1-adamantyl glycoside (**65**) in 96 % (α/β = 1.6:1) (Scheme 19). In addition, the symmetric bis(p-methoxyphenyl) disulfide could be isolated in near-quantitative yield. Notably, it was found that **63** can not be activated by $Ru(bpy)_3Cl_2$, probably due to the known oxidation potentials. It is also worth noting that when the hydroxyl groups were protected as acetates (disarmed donor), the corresponding glycosyl donors can not be activated under the aforementioned conditions. This type of reactions afforded the *O*-glycosides as a mixture of α- and β-anomers with poor selectivity, probably due to the non-participating group at C2. Although α-*O*-glycosides were usually formed as the major anomer, β-anomers were selectively produced in some cases.

The authors found that this iridium complex-catalyzed synthesis of *O*-glycosides is light-dependent and decomposition of an oxidatively generated sulfur radical cation and propagation via reduction of the thiol side product is involved. As illustrated in Scheme 20, the excited iridium complex IrL_3^{3+*}, generated via photoactivation of IrL_3^{3+}, is oxidized to IrL_3^{4+} by bromotrichloromethane (initially, A) or by *S*-(*p*-methoxy)phenylthiol radical or radical cation (during propargation, B). The IrL_3^{4+} complex then oxidizes the thioglycoside **63** to the corresponding thioglycoside radical cation **66**. Decomposition of thioglycoside radical cation **66** leads to the formation of corresponding oxocarbenium ion which reacts with alcohol acceptors to afford desired *O*-glycosides.

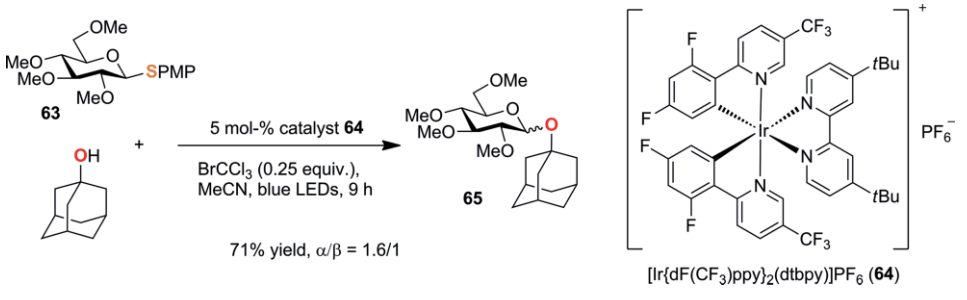


Scheme 20. Proposed mechanism for iridium complex-catalyzed photoredox *O*-glycosylation.

Recently, Tang, Guo and co-workers disclosed an interesting iridium-catalyzed dynamic kinetic isomerization of dihydropyranone hemiacetal to 3,4-dihydro-2-pyrone for the expedient synthesis of carbohydrates via Achmatowicz rearrangement.[48] This was an excellent addition of using iridium complex for De novo carbohydrate synthesis.

6.4 Summary

The group 9 transition metal complexes have not been well explored for catalytic glycosylations. Thus far, (salen)Co complexes were reported to catalyze the activation of glycosyl trichloroacetimidate donors. In addition, the rhodium(I)-catalyzed 1,4-addition of arylboronic acids to enones has been extended to the synthesis of *C*-glycosides through the use of glycal-derived enones as substrates. By engaging visible light photoredox chemistry, the use of iridium complex and aforementioned ruthenium complex has gained some success for catalytic activation of reactive thioglycosides and selenoglycosides under mild conditions, respectively; however, the scope of this method is rather limited.



Scheme 19. $[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$-catalyzed photoredox synthesis of *O*-glycosides.

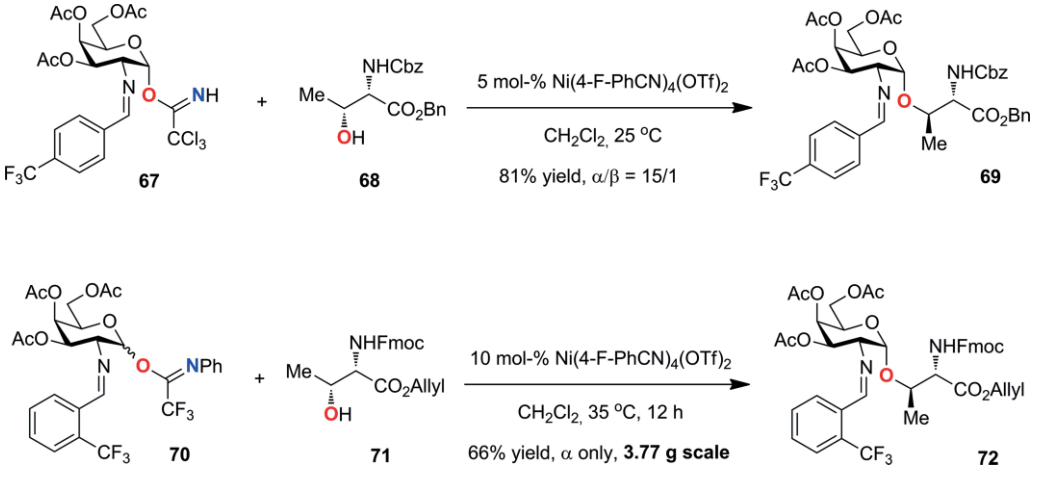
7. Synthesis of *O*-, *N*-, *C*-, and *S*-Glycosides by Group 10 Metal (Ni, Pd, Pt) Catalysis

7.1 Synthesis of *O*-, *N*-, and *C*-Glycosides by Ni Catalysis

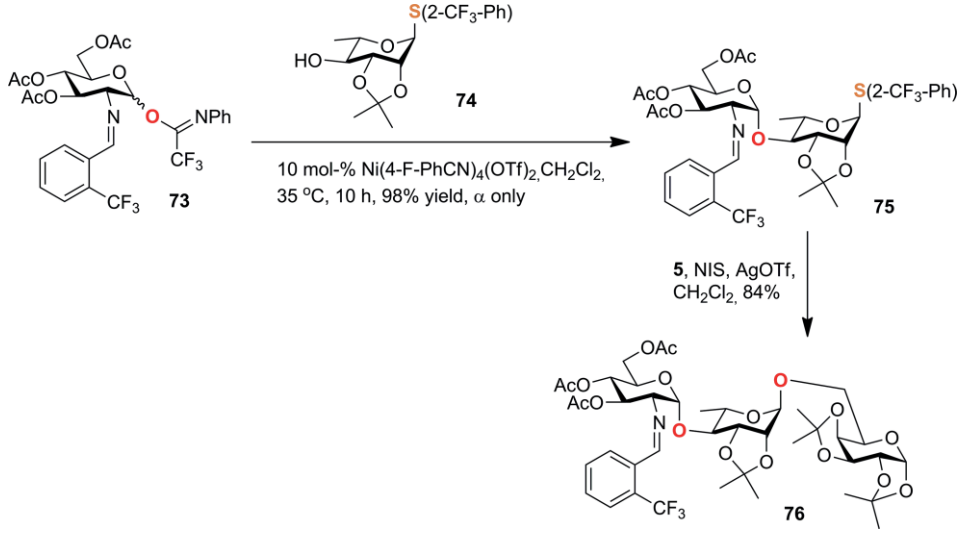
7.1.1 Synthesis of O-Glycosides by Ni Catalysis

Previously in our review,[5] we discussed cationic nickel(II) complexes catalyzed *O*-glycosylation of C2-benzylideneamino trichloroacetimidates to furnish α-2-deoxy-2-amino glycosides with excellent α/β selectivity, reported by Nguyen and co-workers.[49] This method was applied to D-glucosamine and D-galactosamine trichloroacetimidate donors as well as a range of primary, secondary, and tertiary alcohol nucleophiles to provide the desired *O*-linked 1,2-*cis*-α-pyranosides in good yields with excellent α-selectivity. Experimental results indicated that the presence of benzylidene functionality at the C2-amino position of glycosyl donors is critical for the high α-selectivity observed in the coupling products. In addition, α-orientation of the C1-trichloroacetimidate group as well as the presence of the external alcohol nucleophile is necessary for the facile ionization of glycosyl trichloroacetimidate donors.[50] The Nguyen group also demonstrated that α-2-deoxy-2-amino glycosides bearing C2-benzylideneamino substituent can be converted to the naturally occurring 1,2-*cis* glycosides and glycoconjugates containing C2-acetamide and C2-sulfonamide functionality, such as Tn-tumor associated antigen and structural analogue of heparin derivatives.

For instance, $Ni(4\text{-F-PhCN})_4(OTf)_2$ effectively catalyzed a glycosylation of α-C(2)-*para*-(trifluoromethyl)benzylidenamino trichloroacetimidate donor **67** with Cbz-protected threonine residue **68** to afford glycosyl amino acid **69** in 81 % yield with (α/β = 15:1) (Scheme 21). However, employing 5 mol-% of $Ni(4\text{-F-PhCN})_4(OTf)_2$ to promote the coupling of donor **67** with Fmoc-protected amino acid **71** only afforded desire α-glycosyl amino acid in poor yield and anomeric selectivity.[51] Later, it was found that this problem can be solved by the use of *N*-phenyl trifluoroacetimidate **70** as the glycosyl donor. As shown in Scheme 21, in the presence of 10 mol-% $Ni(4\text{-F-PhCN})_4(OTf)_2$, *N*-phenyl trifluoroacetimidate **70** reacted with Fmoc-protected amino acid **71** in dichloromethane at 35 °C for 12 hours to give desired α-glycosyl amino acid **72** in 66 % yield (α only, 3.77



Scheme 21. Cationic Ni^{II}-catalyzed synthesis of α-glycosyl amino acids.



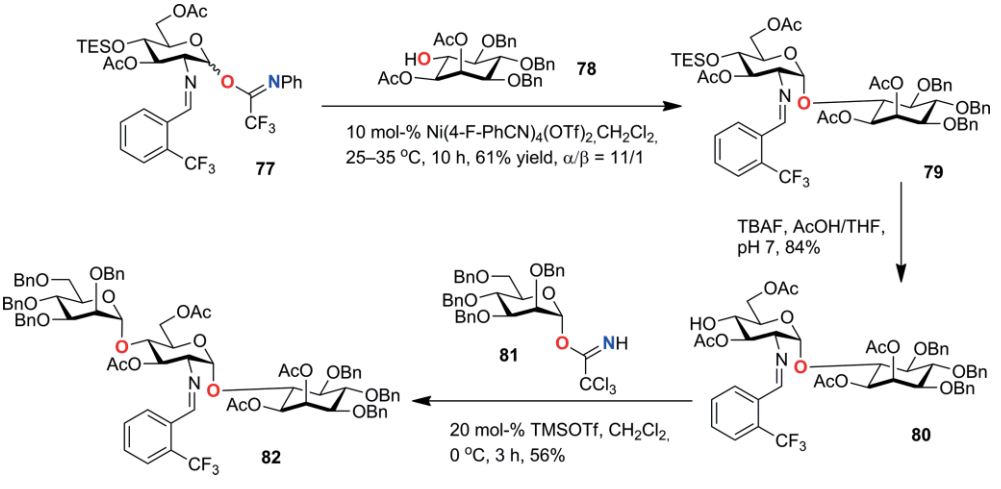
Scheme 22. Cationic Ni^{II}-catalyzed synthesis of 1,2-*cis*-2-amino glycosides bearing anomeric sulfide group.

gram scale).[51] This method tolerates a number of Fmoc-protected threonine amino acids to afford the desired 1,2-*cis*-2-amino glycosides in good yields with excellent α-selectivity. The desired 1,2-*cis*-2-amino glycoside **72** can be readily converted into the Fmoc-protected GalNAc-threonine and Tn antigen in a few steps.

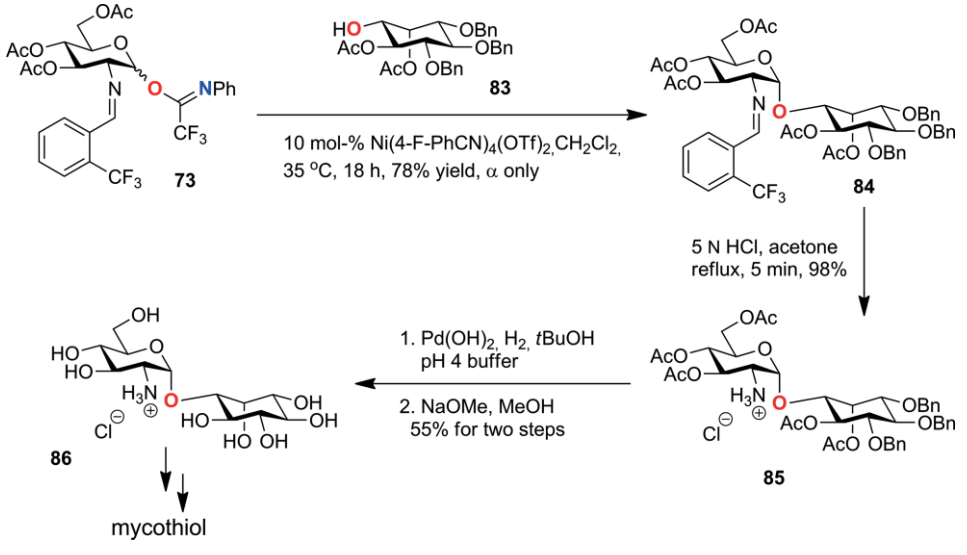
In addition, Nguyen and co-workers investigated this cationic Ni^{II}-catalyzed synthesis of 1,2-*cis*-2-amino glycosides bearing anomeric sulfide group which can serve as donor for another glycosylation reaction.[52] As shown in Scheme 22, employing 5 mol-% of $Ni(4\text{-F-PhCN})_4(OTf)_2$ as catalyst, glycosylation of D-glucosamine-derived electron deficient 2-trifluoromethylphenyl thioglycoside **73** with acceptor **74** bearing 2-trifluoromethylphenyl sulfide gave the desired disaccharide **75** in 98 % yield (α only). The sulfide transfer from acceptor **74** to donor **73**, a common problem observed during traditional glyosylation, was found to be completely blocked in this case. Next, disaccharide **75** can be employed as glycosyl donor which reacted under traditional glycosylation condition with diacetone-D-galactose **5** to furnish desired trisaccharide **76** in 84 % yield.

This cationic Ni^{II}-catalyzed *O*-glycosylation chemistry was also employed in the synthesis of GPI anchor pseudo-oligosaccharides bearing 1,2-*cis*-2-amino glycoside moiety.[53] As shown in Scheme 23, Ni^{II}-catalyzed glycosylation of *N*-phenyl trifluoroacetimidate **77** bearing TES protecting group at the C4 position with C6-hydroxyl of myo-inositol **78** proceeded smoothly to afford pseudodisaccharide **79** in 61 % yield and with 11:1 α/β ratio. After removing the TES ether of **79**, the resulting disaccharide acceptor **80** was then employed in a glycosylation with tetrabenzylated D-mannose trichloroacetimidate **81** catalyzed by TMSOTf to provide α-pseudotrisaccharide **82** exclusively in 56 % yield.

This cationic Ni^{II} catalysis was further utilized in the formal synthesis of mycothiol.[54] As shown in Scheme 24, Ni^{II}-catalyzed glycosylation of *N*-phenyl trifluoroacetimidate **73** with C1-hydroxyl of myo-inositol **83** furnished pseudo-disaccharide **84**



Scheme 23. Cationic Ni^{II}-catalyzed synthesis of GPI anchor pseudo-oligosaccharides.



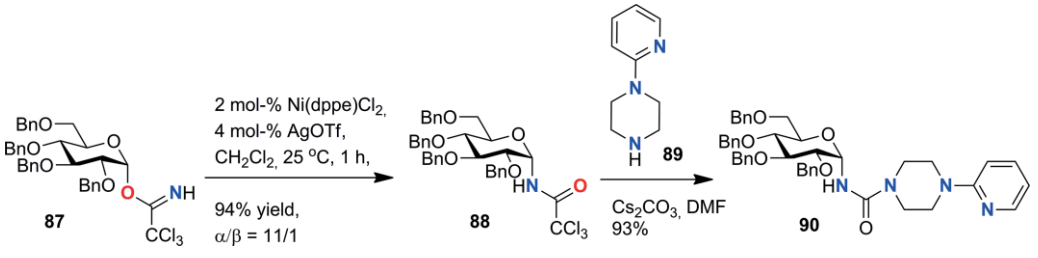
Scheme 24. Utilization of cationic Ni^{II} catalysis for the formal synthesis of mycothiol.

in 78 % yield (α only). The 2-trifluoromethyl-benzylidene group in **84** was removed with 5 N HCl and the resulting salt **85** underwent sequential hydrogenolysis and de-acetylation to give pseudo-disaccharide **86** in 55 % yield over two steps, which can be converted to mycothiol following the known literature precedents.

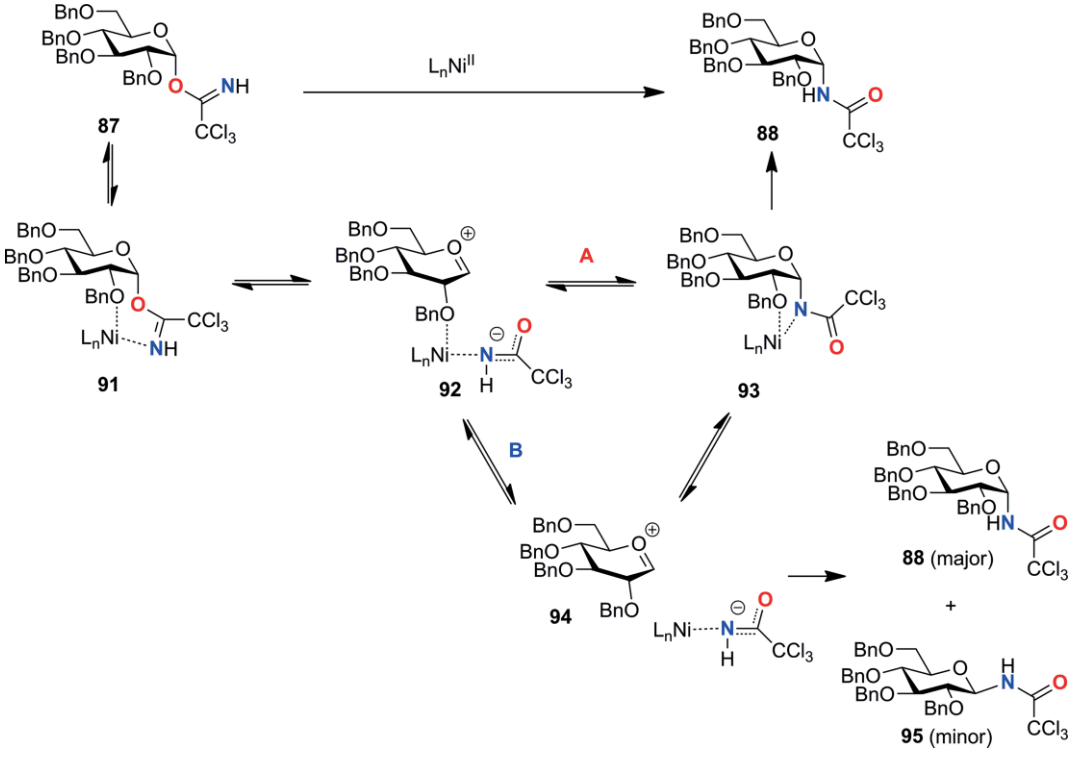
7.1.2 Synthesis of N-Glycosides by Ni Catalysis

In 2009, Nguyen and co-workers reported a new method for the stereoselective synthesis of α-glycosyl ureas via nickel-catalyzed [1,3]-rearrangement of glycosyl trichloroacetimidates.[55] For example, in the presence of 2 mol-% Ni(dppe)OTf, generated in situ from 2 mol-% Ni(dppe)Cl_2 and 4 mol-% AgOTf, perbenzylated D-glucopyranosyl trichloroacetimidate **87** underwent smooth [1,3]-rearrangement to provide α-trichloroacetamide **88** in 94 % yield with excellent α-selectivity (α/β = 11:1) (Scheme 25). During the studies, a variety of palladium and nickel catalysts were screened and Ni(dppe)OTf was proven to be the most efficient catalyst for this type of transformation. This method is amenable to a number of trichloroacetimidate substrates. In addition, the α-glycosyl trichloroacetamides can be directly converted into α-glycosyl ureas in the presence of amines. As shown in Scheme 25, α-trichloroacetamide **88** reacted with piperazine derivative **89** in DMF in the presence of cesium carbonate as base to afford α-glycosyl urea **90** in 93 % yield.

Later in 2104, Nguyen and co-workers investigated the scope and mechanism of this nickel-catalyzed transformation of glycosyl trichloroacetimidates to glycosyl trichloroacetamides.[56] As shown in Scheme 26, the nickel catalyst may first coordinate the imidate nitrogen and the C2-ether oxygen of substrate **87** to form complex **91**. Subsequent ionization of complex **91** via departure of the trichloroacetimidate may lead to the formation of oxocarbenium intermediate **92**. Selective delivery of the trichloroacetamide group to the anomeric center from the α-face of **92** provides the corresponding complex **93** (Pathway A). Subsequent dissociation of the cationic nickel(II) catalyst will provide the desired α-glycosyl trichloroacetamide **88**. Alternatively, **92** can dissociate to generate tight ion pair **94** (Pathway B), which then recombines in a stereoelectronically favored mode



Scheme 25. Cationic Ni^{II}-catalyzed [1,3]-rearrangement of glycosyl trichloroacetimidates and synthesis of glycosyl ureas.



Scheme 26. Proposed mechanism of cationic Ni^{II}-catalyzed [1,3]-rearrangement of glycosyl trichloroacetimidates.

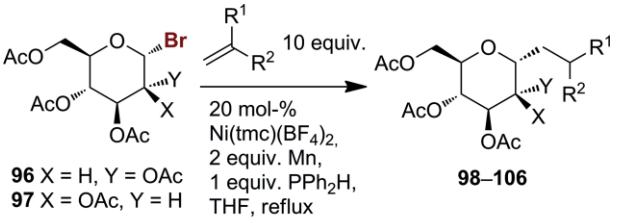
to form α-trichloroacetamide **88** as the major product and β-trichloroacetamide **95** as minor product. Experimental evidences suggested that this transformation does not proceed in an exclusively intramolecular fashion, and that there is competition between the redelivery of the trichloroacetamide group by nickel catalyst (Pathway A) and an intermolecular ion pair (Pathway B).

7.1.3 Synthesis of C-Glycosides by Ni Catalysis

In 2000, Marsden and co-workers reported a nickel-catalyzed synthesis of *C*-glycosides from glycosyl bromides.[57] As shown in Table 2, α-bromotetraacetyl-D-glucose **96** and α-bromotetraacetyl-D-mannose **97** reacted with ten-fold excess of radical acceptors in the presence of catalytic amounts of nickel(II) (tetramethylcyclam) tetrafluoroborate salt, diphenylphosphine (1 equiv.) as hydride source, and co-reductant powdered manganese (2 equiv.) in THF to provide desired α-*C*-glucosides and α-*C*-mannosides **98**–**106** in moderate to excellent yields, respectively. The participation of the nickel salts as catalyst was indispensable, since no reaction was observed in the absence of Ni(tmc)$(BF_4)_2$. The yields of **89** were moderate to excellent in both the glucose and mannose series with the electron deficient radical acceptors methyl/butyl acrylate, methyl methacrylate and acrylonitrile. In most cases, the yields in the glucose series were slightly higher than those for the mannose series, which may reflect the increased instability of the α-glycosyl radical in the latter case. This reaction was also applied to the synthesis of C1-deoxysugars in the absence of radical acceptors.

Later in 2007, Gagné and co-workers described the synthesis of *C*-alkyl glycosides via room temperature Negishi cross-coupling reactions of glycosyl halides and functionalized alkyl zinc reagents.[58] As shown in Table 3, in the presence of 10 mol-% catalyst (PyBox)$NiCl_2$, in situ generated from 10 mol-% $NiCl_2$ and 15 mol-% PyBox, α-glucosyl bromide **96**, α-mannosyl bromide **97**, and α-galactosyl bromide **107** reacted with $Ph(CH_2)_3ZnBr$ (3 equiv.) in DMI (*N*,*N*′-dimethylimidazolidinone) at room temperature for 12 h to afford corresponding *C*-alkyl glycosides **108**–**110** in moderate to good yields, respectively. A small amount of corresponding glycals were also detected. The anomeric selectivity was found to be high for mannosyl bromide, but modest for glucosyl and galactosyl bromides. This reaction tolerates various functional groups on the zinc reagent, such as acetal, ester, alkene, thiophene, and phthalimide, as well as both armed (benzyl) and disarmed (ester) protecting groups

Table 2. Nickel-catalyzed synthesis of *C*-glycosides from glycosyl bromides.

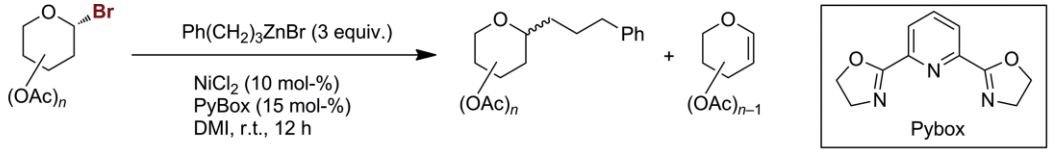


96 X = H, Y = OAc
97 X = OAc, Y = H

98–**106**

98, 69% yield, X = H, Y = OAc, $R^1 = CO_2Me$, R^2 = H
99, 62% yield, X = OAc, Y = H, $R^1 = CO_2Me$, R^2 = H
100, 98% yield, X = H, Y = OAc, $R^1 = CO_2Me$, R^2 = Me
101, 48% yield, X = OAc, Y = H, $R^1 = CO_2Me$, R^2 = Me
102, 46% yield, X = H, Y = OAc, $R^1 = CO_2Bu$, R^2 = H
103, 53% yield, X = OAc, Y = H, $R^1 = CO_2Bu$, R^2 = H
104, 76% yield, X = H, Y = OAc, R^1 = CN, R^2 = H
105, 49% yield, X = OAc, Y = H, R^1 = CN, R^2 = H
106, 51% yield, X = H, Y = OAc, $R^1 = CO_2Me$, R^2 = NHZ

Table 3. Nickel-catalyzed synthesis of *C*-alkyl glycosides via room temperature Negishi cross-coupling reactions of glycosyl halides and functionalized alkyl zinc reagents.



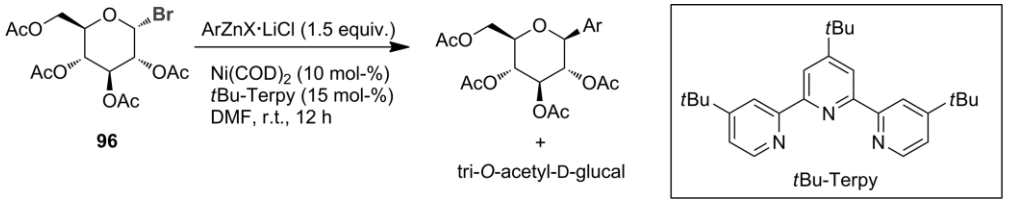
Entry	Glycosyl bromides	Products	Yields, α/β ratio	Glycal
1	**96**	**108**	53% (1:2.5)	9%
2	**97**	**109**	75% (8:1)	9%
3	**107**	**110**	43% (1:2)	trace

on the carbohydrate. In addition, glycosyl chlorides were also suitable substrates for this type of reaction.

Next, Gagné and co-workers attempted to extend the aforementioned Ni-catalyzed Negishi cross-coupling approach for the synthesis of *C*-aryl glycosides.[59] As shown in Table 4, by employing $Ni(COD)_2$/*t*Bu-Terpy as the optimal catalyst, peracetylated α-glucosyl bromide **96** reacted with PhZnI·LiCl in *N*,*N*-dimethylformamide (DMF) to provide desired *C*-aryl glycoside **111** in 71 % yield with excellent β-selectivity together with a small amount of tri-*O*-acetyl-D-glucal as the side product (entry 1, Table 4). In contrast, the use of (PyBox)$NiCl_2$ as catalyst for this reaction in DMI or DMA (*N*,*N*-dimethylacetamide) as solvent afforded only trace amount or 20 % yield of *C*-aryl glycoside **111**, respectively, while formation of tri-*O*-acetyl-D-glucal via elimination was found to be the main problem. This type of reaction was compatible to both electron-rich and electron-poor aryl zinc species and desired *C*-aryl glycosides **111**–**118** were isolated in moderate to good yields with excellent β-selectivity (entries 1 and 2). While *meta*- and *para*-substituted arylzinc species were tolerated, *ortho*-substituted arylzinc reagents were not effective in this type of reaction. In addition, heteroaromatic zinc reagents, such as thiophene or furan-derived arylzinc reagents reacted with α-glucosyl bromide **96** to give corresponding *C*-heteroaryl glycoside **119**–**122** in good yields with excellent β selectivity (entries 3–6). However, 2-pyridylzinc iodide/lithium chloride reagent did not work in this type of reaction. Furthermore, although alkenylzinc reagent reacted with α-glucosyl bromide **96** to afford desired *C*-alkenyl glycoside **123** in 60 % yield, no anomeric selectivity was observed (entry 7).

During their continuous studies in the preparation of *C*-glycosides, in 2009 Gagné and co-workers reported a mild tin-free Ni-catalyzed reductive coupling of glycosyl bromides with activated alkenes for the stereoselective synthesis of α-*C*-alkylglycosides.[60] As shown in Table 5, in the presence of 10 mol-% $Ni(COD)_2$, 15 mol-% (*R*)-Ph-Pybox ligand, Zn as the reductant, and NH_4Br as the proton source, α-glucosyl bromide **96** reacted with methyl acrylate to afford desired α-*C*-glucoside **124** in 70 % yield. A trace amount of tri-*O*-acetyl-D-glucal was isolated through the elimination of **96**. In addition, α-mannosyl bromide **97** and α-galactosyl bromide **107** also reacted with methyl acrylate under the same conditions to give corresponding α-*C*-glycoside **125** and **126** in good yields, respectively. The scope of the nickel-catalyzed reductive coupling was investigated

Table 4. Nickel-catalyzed synthesis of *C*-aryl glycosides.



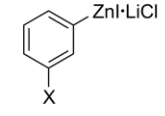
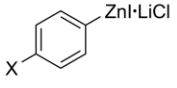
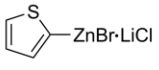
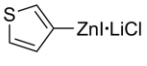
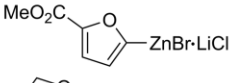
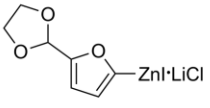
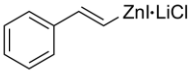
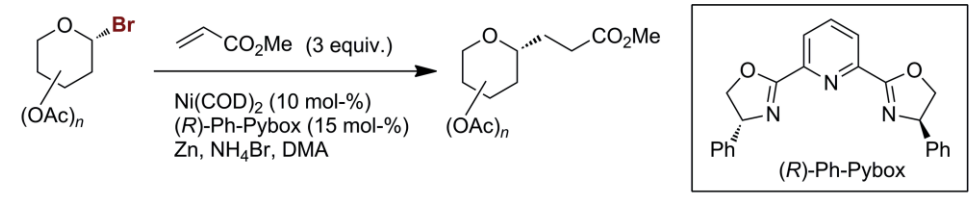
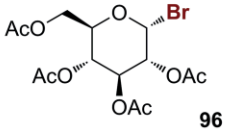
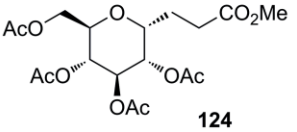
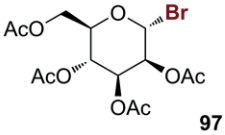
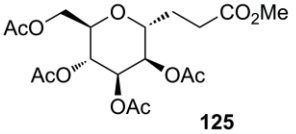
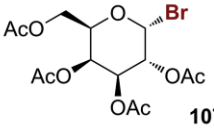
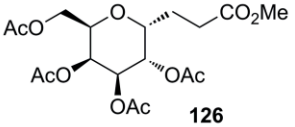
Entry	Arylzinc reagents	Products	Yields (α/β ratio)	Tri-*O*-acetyl-D-glucal
1		**111** X = H, **112** X = Cl, **113** X = Br, **114** X = CO_2Me	71% (1/12) 75% (1/13) 77% (1/14) 72% (1/14)	7% 5% trace 8%
2		**115** X = I, **116** X = CO_2Me **117** X = OMe **118** X = CN	30% (1/10) 66% (1/10) 64% (1/13) 79% (1/>12)	trace trace 11% trace
3		**119**	78% (1/16)	14%
4		**120**	83% (1/16)	5%
5		**121**	65% (1/14)	n.d.
6		**122**	80% (1/>10)	n.d.
7		**123**	60% (1/1)	n.d.

Table 5. Tin-free Ni-catalyzed reductive coupling of glycosyl bromides with activated alkenes for the stereoselective synthesis of α-*C*-alkylglycosides.



Entry	Glycosyl bromides	Products	Yields, α/β ratio
1	 **96**	 **124**	70% (α only)
2	 **97**	 **125**	76% (α only)
3	 **107**	 **126**	60% (α only)

with various glycosyl bromides and acrylate derivatives, and in general coupling products were isolated in moderate to good yield with excellent levels of α-selectivity. Notably, diastereoselective coupling with 2-substituted acrylate derivatives was made possible through the use of 2,4-dimethyl-3-pentanol as a proton source.

In 2014, Ye and co-workers disclosed an indirect approach for the synthesis of aryl-*C*-glycosides involving nickel-catalyzed "ring-opening–ring closure" strategy.[61] This strategy exploited the nickel-catalyzed regioselective β-*O*-elimination of glycals through reactions with various aryl boronic acids or potassium aryltrifluoroborates to yield the ring-opened products, which underwent the Lewis acid, protonic acid, PhSeCl, or NBS mediated ring closure reactions to afford diverse aryl-*C*-glycosides.

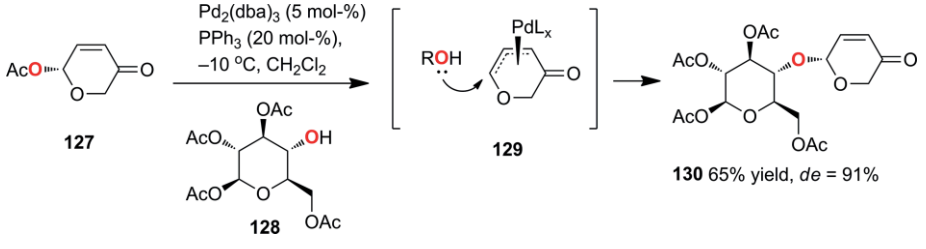
7.2 Synthesis of *O*-, *N*-, *C*-, and *S*-Glycosides by Pd Catalysis

Heterogeneous and homogeneous palladium catalysts have been widely used for organic transformations,[62] including hydrogenation, cross-coupling reactions, and C–H activations. Recently, the use of palladium complexes in catalytic stereoselective glycosylations has been developed and applied in the synthesis of complex oligosaccharides and glycoconjugates.

7.2.1 Synthesis of O-Glycosides by Pd Catalysis

7.2.1.1 Palladium-Catalyzed Stereoselective O-Glycosylation of 6-Acetoxy-2H-pyran-3(6H)-ones

In 1999, Feringa and co-workers reported a palladium-catalyzed stereoselective synthesis of optically active 5-alkoxy-2(*5H*)-furanones and 6-alkoxy-*2H*-pyran-3(*6H*)-ones using corresponding glycosyl ester donors and simple alcohol acceptors,[63] which we previously reviewed.[5] This type of glycosylation was catalyzed by 5 mol-% $Pd(OAc)_2$ and 20 mol-% PPh_3 and believed to proceed through allylpalladium intermediates with nearly complete retention of stereochemistry. Later in 2003, they found that by use $[Pd_2(dba)_3/PPh_3]$ as catalyst, 6-acetoxy-*2H*-pyran-3(*6H*)-one **127** can react with sugar-derived acceptor **128** to afford disaccharide **130** (65 % yield, *de* = 91 %) probably via allylpalladium intermediate **129** (Scheme 27).[64]



Scheme 27. Palladium-catalyzed stereoselective *O*-glycosylation of 6-acetoxy-*2H*-pyran-3(*6H*)-ones.

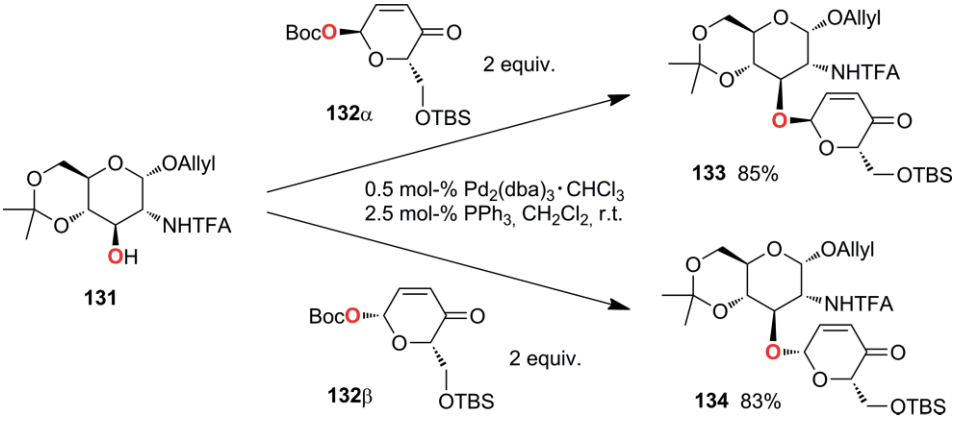
7.2.1.2 Palladium-Catalyzed Stereoselective O-Glycosylation Using Glycosyl Donors Bearing tert-Butyl Carbonate as Leaving Group

Previously, we also discussed palladium-catalyzed stereoselective *O*-glycosylation using glycosyl *tert*-butylcarbonate (Boc) donors developed by O'Doherty and co-workers.[65,66] It was found that use of glycosyl donor bearing *tert*-butyl carbonate as leaving group led to significantly faster and cleaner reactions than those bearing ester as leaving group and with complete stereochemical retention. As shown in Scheme 28, sugar-derived alcohol acceptor **131** reacted with **132**α and **132**β in the presence of 0.5 mol-% $[Pd_2(dba)_3]$·$CHCl_3$ and 2.5 mol-% PPh_3 in CH_2Cl_2 at room temperature to afford glycosides **133** and **134** in 85 % and 83 % yields, respectively. The versatile ketone and alkene functionality in **133** and **134** can be further functionalized to enable the de novo synthesis of complex oligosaccharides.[67] This palladium-catalyzed *O*-glycosylation reaction was later successfully applied to the de novo synthesis of a number of complex oligosaccharides and bioactive natural molecules bearing complex oligosaccharides, including trehalose analogues,[68] daumone,[69] homoadenosine,[70] *manno*-disaccharide fragments of mannopeptimycin-E,[71] aza-analogues of the glycosylated tyrosine portion of mannopeptimycin-E,[72] D- and L-Swainsonine,[73] digitoxin and digitoxigenin analogs,[74] kaempferol glycoside SL0101 and its analogs,[75] anthrax tetrasaccharide,[76] trisaccharide portion of landomycin A,[77] trisaccharide portion of PI-080 and vineomycin B_2,[78] deoxyaltropyranoside,[79] cleistrioside and cleistetroside natural products,[80] disaccharide portion of SCH-47554,[81] cleistriosides,[82] complex oligosaccharides,[83] and merremoside D.[84]

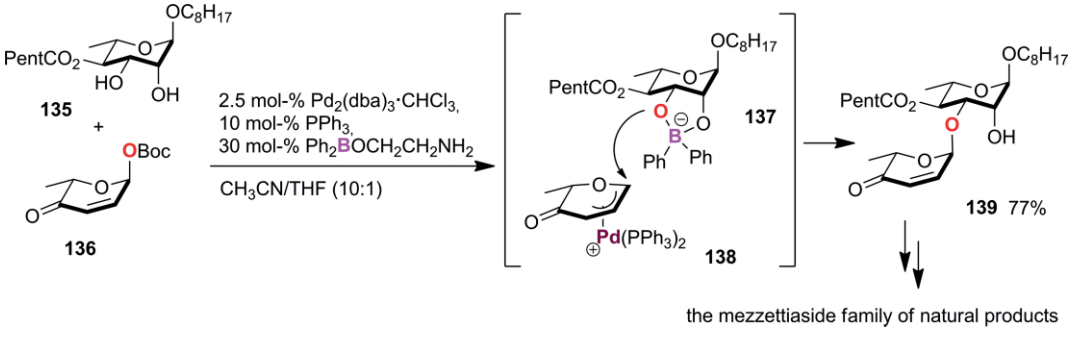
Recently, O'Doherty and co-workers achieved the synthesis of mezzettiaside family of natural products via nucleophilic boron/electrophilic palladium catalyzed regio- and stereo-selective glycosylations.[85] As shown in Scheme 29, under the optimal condition {2.5 mol-% $[Pd_2(dba)_3]$·$CHCl_3$, 10 mol-% PPh_3, 30 mol-% $Ph_2BOCH_2CH_2NH_2$ in CH_3CN/THF(10:1)}, a mixture of acceptor **135** and donor **136** (**135**/**136** = 1:1.1) was coupled to provide desired disaccharide **139** in 77 % yield as the major regioisomer (regioselectivity is 7.5:1). This reaction is proposed to proceed via boron-activation[86] of the *cis*-diol of **135** to generate intermediate **137** which attacks the electrophilic allylpalladium intermediate **138** in regio- and stereo-selective manner. Disaccharide **139** was further utilized for the synthesis of mezzettiaside family of natural products.

7.2.1.3 Palladium-Catalyzed Stereoselective O-Glycosylation Using Glycal Donors

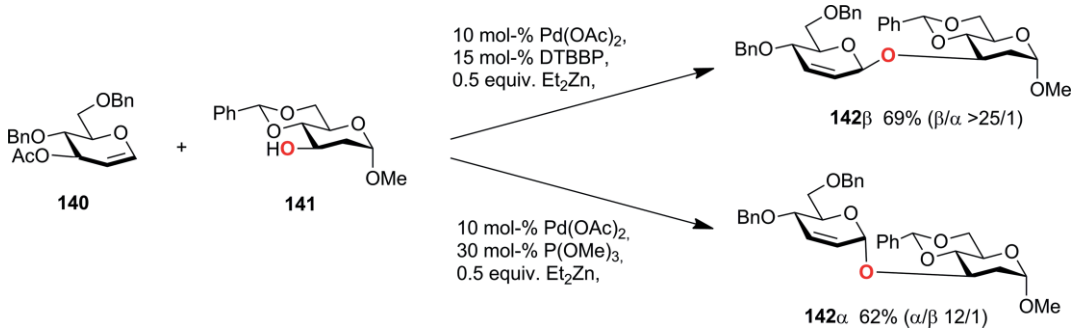
We also previously reviewed[5] palladium-catalyzed stereoselective *O*-glycosylation using glycal donors, an interesting work disclosed by Lee and co-workers.[87] In this type of highly efficient stereoselective *O*-glycosylation, 2,3-unsaturated-*O*-glycosides were obtained via Ferrier rearrangement employing glycal 3-acetate or carbonate and zinc(II) alkoxide acceptors. In these glycosylation reactions, the anomeric stereochemical outcome was influenced by ligand coordinating to the palladium. Specifi-



Scheme 28. Palladium-catalyzed stereoselective *O*-glycosylation using glycosyl donors bearing *tert*-butyl carbonate as leaving group.



Scheme 29. Synthesis of mezzettiaside family of natural products via nucleophilic boron/electrophilic palladium catalyzed regio- and stereo-selective glycosylations.



Scheme 30. Palladium-catalyzed stereoselective *O*-glycosylation using glycal donors.

cally, a complex of palladium acetate and 2-di(*tert*-butyl)phosphinobiphenyl (DTBBP) catalyzed the formation of exclusive β-glycosides, while the same reaction using trimethyl phosphite ligand furnished the α-anomer as the major product. As shown in Scheme 30, glycal **140** bearing C3-acetate reacted with acceptor **141** in the presence of 10 mol-% $Pd(OAc)_2$, 15 mol-% DTBBP, and 0.5 equiv. Et_2Zn to provide major anomeric β-glycoside **142**β in 69 % yield (β/α > 25:1), while change the ligand to $P(OMe)_3$ resulted in the selective production of α-glycoside **142**α in 62 % yield (α/β = 12:1). Similarly, the glycosides containing versatile alkene moiety, e.g., **142**, can be further functionalized to complex oligosaccharides which are otherwise difficult to prepare.

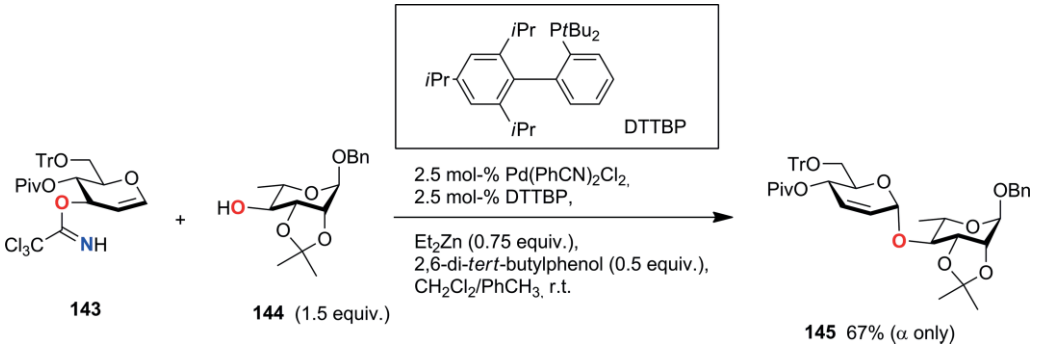
Recently, inspired by work from the Lee group, Zawisza and co-workers reported synthesis of 2,3- and 3,4-unsaturated β-*O*-arylglycosides via arylation of 6-*O*-*tert*-butyldiphenylsilyl-3,4-di-*O*-isobutyloxycarbonyl-D-glucal with various phenols in the presence of a catalytic amount of palladium(0).[88] The reactions were found to be highly stereoselective, and only the β-anomers were formed in all cases.

7.2.1.4 Palladium-Catalyzed Stereoselective O-Glycosylation Using Glycal Imidate Donors

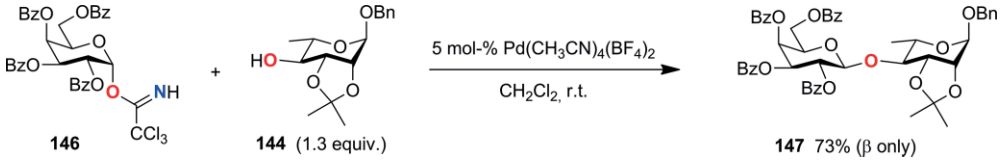
We also discussed[5] Palladium-catalyzed stereoselective α-*O*-glycosylation using glycal imidate donors developed by Nguyen and co-workers.[89] This type of reaction was found to be independent of the nature of protecting groups on the glycal donors and anomeric selectivity was controlled by palladium-biaryl phosphine catalyst-glycal donor complexation. As depicted in Scheme 31, under optimal condition {2.5 mol-% $[Pd(PhCN)_2Cl_2]$, 2.5 mol-% DTTBP, acceptor (1.5 equiv.), Et_2Zn (0.75 equiv.), 2,6-di-*tert*-butylphenol (0.5 equiv.), $CH_2Cl_2/PhCH_3$, room temp.}, glycal imidate donor **143** reacted with acceptor **144** (1.5 equiv.) to furnish α-glycoside **145** bearing 2,3-unsaturation in 67 % yield and excellent α-selectivity. Notably, when aliphatic alcohols or sugar-derived alcohol acceptors were used it was necessary to add 2,6-di-*tert*-butylphenol as the proton donor to facilitate the catalyst turnover. When phenols were used as acceptors, desired *O*-aryl glycosides were obtained in good yield with excellent α-selectivity without the use of 2,6-di-*tert*-butylphenol. This reaction tolerates a variety of protecting groups and α-glycoside products bearing 2,3-unsaturation can be functionalized to access α-mannosides and α-altrosides, depending on the reaction conditions.

7.2.1.5 Cationic Palladium(II)-Catalyzed Stereoselective Glycosylation with Glycosyl Trichloroacetimidates

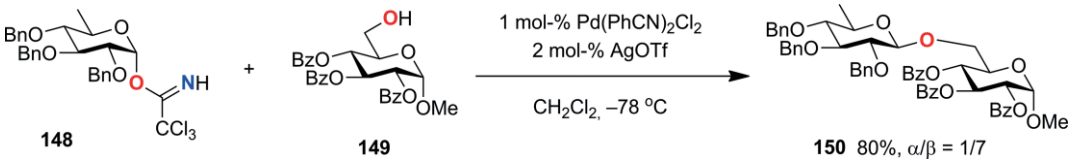
Cationic palladium(II)-catalyzed stereoselective glycosylation with glycosyl trichloroacetimidates was developed by Nguyen and co-workers.[90] This reaction employed a catalytic amount of cationic palladium(II) as activator which enabled synthesis of a variety of disaccharides and glycoconjugates. As shown in Scheme 32, in the presence of 5 mol-% $[Pd(CH_3CN)_4(BF_4)_2]$ glycosyl trichloroacetimidate **146** reacted with acceptor **144** (1.3 equiv.) to afford β-disacchairde **147** in 73 % yield and excellent β-selectivity. It was proposed that cationic palladium(II) may reversibly coordinate to the imidate nitrogen to facilitate ionization to generate oxocarbenium intermediate which may be attacked by nucleophiles to provide corresponding *O*-glycoside products, in most cases anomeric stereochemistry is con-



Scheme 31. Palladium-catalyzed stereoselective *O*-glycosylation using glycal imidate donors.



Scheme 32. Palladium-catalyzed stereoselective *O*-glycosylation using glycosyl trichloroacetimidates.



Scheme 33. Palladium-catalyzed β-selective *O*-glycosylation using glycosyl trichloroacetimidates without C2-ester group.

trolled by steric and anomeric effect as well as neighbouring group participation (NGP). This reaction tolerates a variety of donors and acceptors bearing various protecting groups.

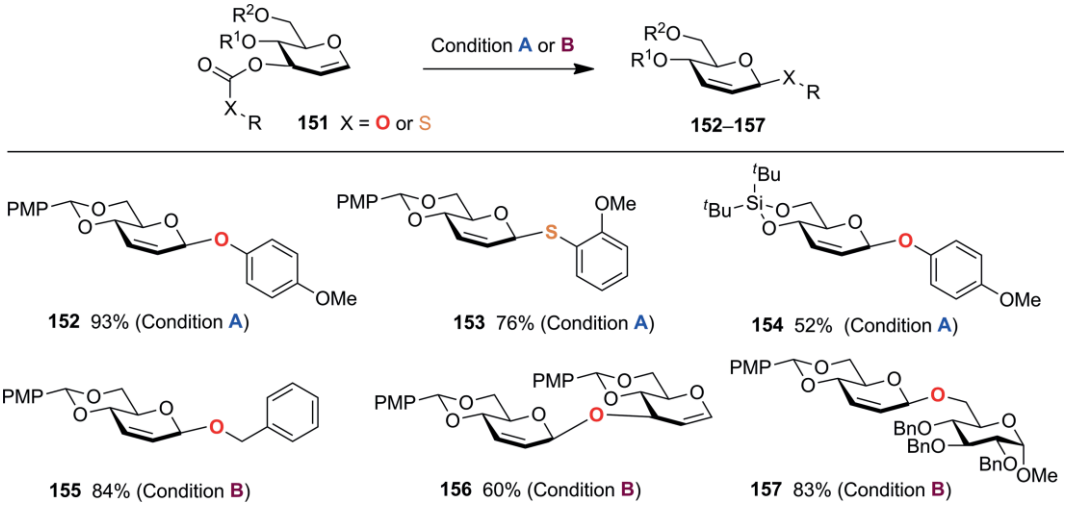
Nguyen and co-workers also found that, in the presence of cationic palladium catalyst, glycosyl trichloroacetimidates without traditional C2-ester group can react with acceptors to directly form β-glycosides. To improve this reaction, they discovered that by using cationic palladium catalyst, $[Pd(PhCN)_2(OTf)_2]$, generated in situ from $[Pd(PhCN)_2Cl_2]$ and AgOTf, glycosyl trichloroacetimidate **148** reacted with acceptor **149** to provide β-linked disaccharide **150** in 80 % yield (α/β = 1:7) (Scheme 33).[91] This glycosylation reaction proceeded under mild conditions with low catalyst loading and was applied to a number of glucose donors with benzyl, allyl, and *p*-methoxybenzyl groups incorporated at the C2-position as well as tribenzylated xylose and quinovose donors to prepare various disaccharides and trisaccharides with good to excellent β-selectivity.

In addition, Nguyen and co-workers later successfully applied this cationic palladium(II)-catalyzed direct β-glycosylation for stereoselective synthesis of β-*O*-aryl glycosides.[92] This β-glycosylation reaction was highly diastereoselective and typically employed 2–3 mol-% of $[Pd(CH_3CN)_4](BF_4)_2$ to activate glycosyl trichloroacetimidate donors at room temperature. It was found that electron-donating, electron-withdrawing, and hindered phenols were also suitable to this methodology. In all cases, the facile rearrangement of the resulting β-*O*-aryl glycosides to the corresponding *C*-aryl glycosides was not observed in the coupling.

7.2.1.6 Synthesis of β-Glycosides by Palladium-Catalyzed Decarboxylative Allylation

In 2013, Liu and co-workers reported synthesis of β-glycosides by palladium-catalyzed decarboxylative allylation of glycals bearing C3-arylcarbonates.[93] As shown in Table 6, treatment of glycal bearing C3-arylcarbonate or C3-thioarylcarbonate **151** with 10 mol-% $[Pd_2(dba)_3]$, 20 mol-% 1,1′-bis(diisopropylphosphino)ferrocene (DiPPF), $PhCH_3$, 60 °C 12 h to provide desired β-*O*-aryl glycosides (**152** and **154**) and β-*S*-arylglycoside **153** (thioglycoside) in good yields, respectively. For glycal bearing

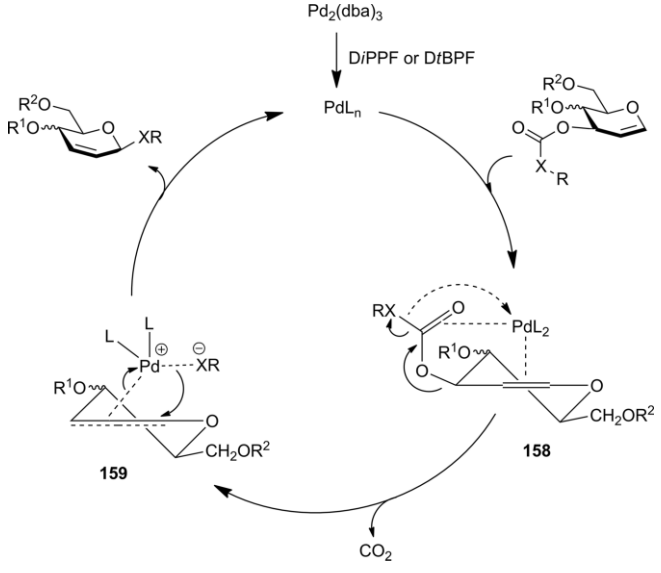
Table 6. Synthesis of β-*O*- and *S*-glycosides by palladium-catalyzed decarboxylative allylation.



Condition **A**: 10 mol-% $Pd_2(dba)_3$, 20 mol-% D*i*PPF, $PhCH_3$, 60 °C 12 h
Condition **B**: 10 mol-% $Pd_2(dba)_3$, 20 mol-% D*t*BPF, $PhCH_3$, 80 °C 12 h

C3-alkyl or sugar-derived alkyl carbonate, changing the ligand from DiPPF to DtBPF[1,1′-bis(di-*tert*-butylphosphino)ferrocene] and elevating the reaction temperature to 80 °C were required to afford the desired β-*O*-glycoside **155**–**157** in good yields. In all these cases, the aryloxy, arylthio, or alkoxy group from the C3-carbonate were intramolecularly transferred to the anomeric carbon in highly stereoselective manner (only β-anomers were observed). This reaction tolerates various protecting group on the glycals.

Based on previous mechanistic studies of palladium-catalyzed decarboxylation[94] and the results from competition experiments, the authors proposed the mechanism as shown in Scheme 34. It is believed that the catalytic cycle begins with the formation of the palladium–D*i*PPF or palladium–D*t*BPF complex PdL_n. After the binary coordination of PdL_n complex to both the olefin double bond and the carbonyl group of the glycal carbonate from the β-face, intermediate **158** is produced. In nonpolar solvents such as toluene, a subsequent decarboxylation of the intermediate **158** generates an ion-pair intermediate **159**. Subsequent intramolecular nucleophilic addition and the elimination of the palladium complex PdL_n result in the desired β-glycosides, completing the catalytic cycle.

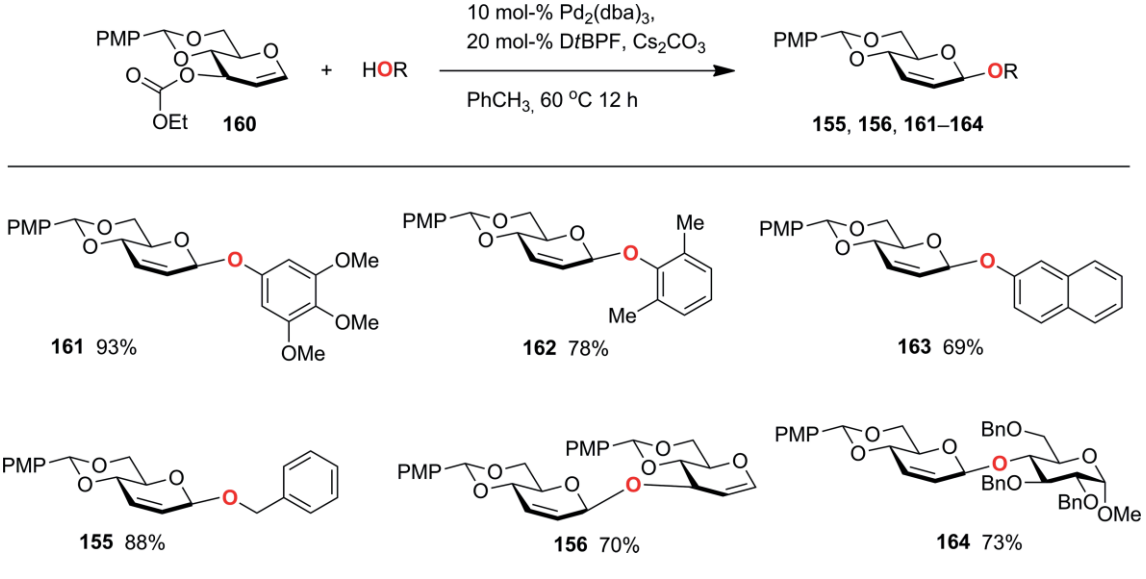


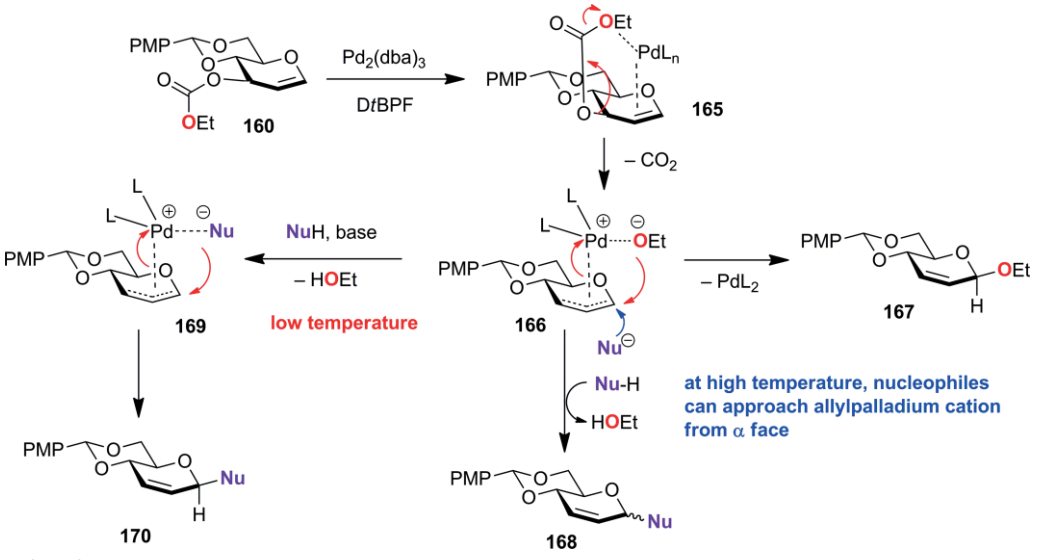
Scheme 34. Proposed mechanism.

As described above, the aforementioned synthesis of β-glycosides by palladium-catalyzed decarboxylative allylation involves the intramolecular transfer of the aryloxy, arylthio, or alkoxy group from the C3-carbonate to the anomeric carbon, which requires the pre-installation of those groups to the C3-carbonate and limits the reaction scope. A year later, Liu and co-workers developed a new protocol for the synthesis of β-glycosides by palladium-catalyzed decarboxylative allylation involves the use of external nucleophiles.[95] As shown in Table 7, in the presence of 10 mol-% [$Pd_2(dba)_3$], 20 mol-% D*t*BPF[1,1′-bis(di-*tert*-butylphosphino)ferrocene], and cesium carbonate (2 equiv.), glycal-derived ethyl carbonate **160** reacted with various phenols, alcohols, and sugar-derived alcohol acceptors in $PhCH_3$ at 60 °C for 12 hours to afford desired β-*O*-glycosides (**155**, **156**, **161**–**164**) in good yields, respectively. It was found that the phenols bearing electron-donating groups afford the desired β-*O*-aryl glycosides in higher yields than those with electron-withdrawing groups, while substitution pattern has little influence on this reaction. In some cases, the side products β-*O*-ethyl glycosides (cf. **167**, Scheme 35), obtained via ethoxide addition, were observed as the major products when phenols with electron-withdrawing groups were used.

On the basis of the experimental results and precedent work on palladium-catalyzed reactions, a plausible mechanism for this intermolecular glycosylation is proposed as shown in Scheme 35. Initially, D-glucal-derived ethyl carbonate **160** reacts with palladium complex to generate the palladium intermediate **166** via **165** through coordination from the β-face and a subsequent decarboxylative reaction. In the absence of other nucleophiles, the intramolecular product **167** is then obtained

Table 7. Synthesis of β-glycosides by palladium-catalyzed decarboxylative allylation using external nucleophiles.





Scheme 35. Proposed mechanism.

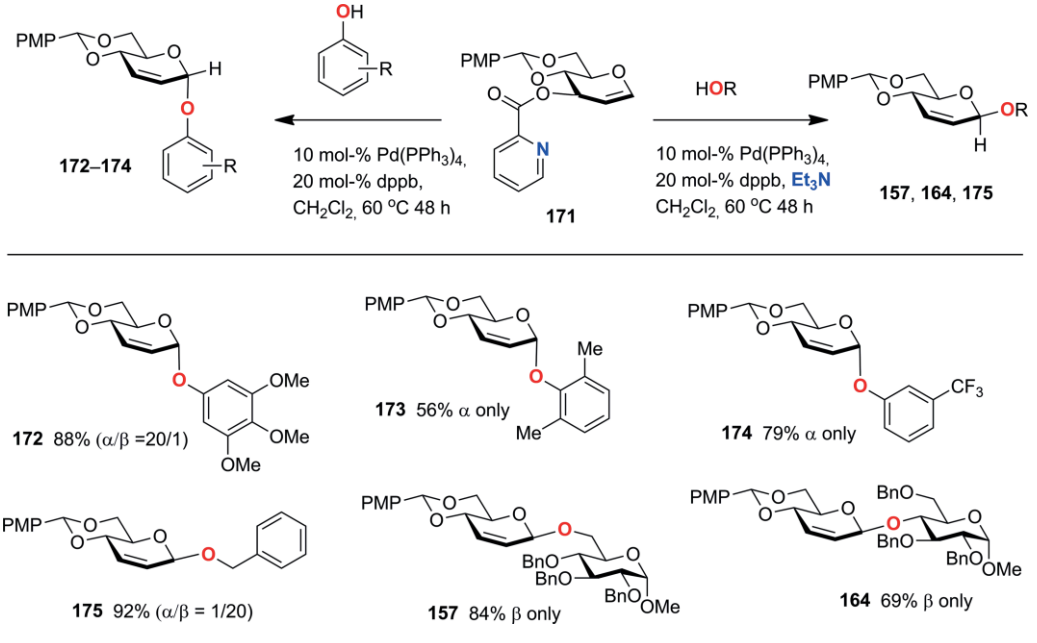
through an elimination of the palladium species. In the presence of an external nucleophile, the reaction is intercepted by a proton transfer between the ethoxide anion and the external nucleophile, yielding Pd intermediate **169**. Thereafter, the desired β-product **170** is obtained with the elimination of the palladium species. In addition, besides the proton transfer, a nucleophile addition to the allylpalladium cation from the α-face, which can furnish the α-product, can take place simultaneously at high temperature. Under such conditions, a mixture of α- and β-product **168** is thus observed.

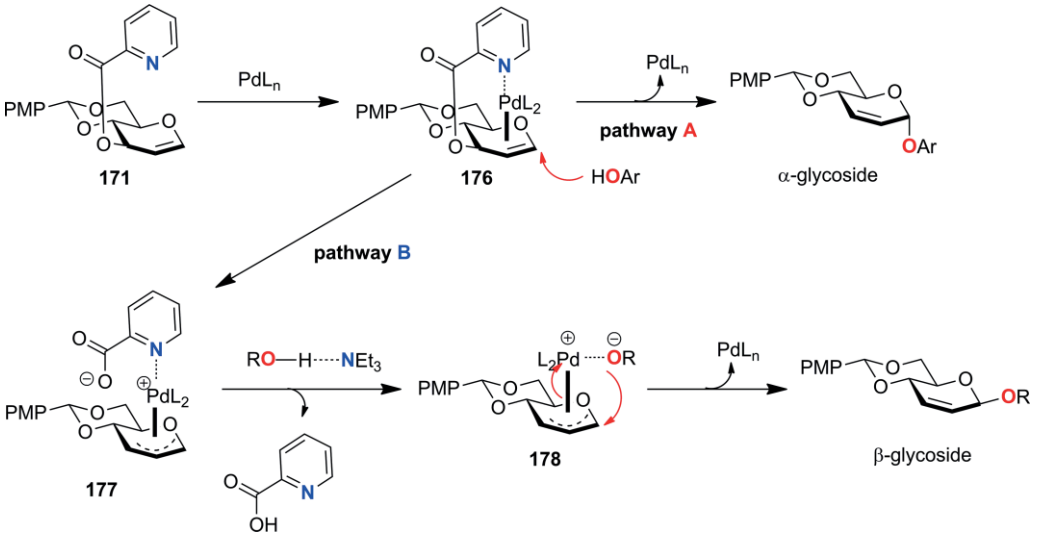
7.2.1.7 Palladium-Catalyzed O-Glycosylation Using 3-O-Picoloyl Glycal Donors

Recently, Liu group described an efficient palladium catalyzed *O*-glycosylation using 3-*O*-picoloyl D-glucal donors.[96] As shown in Table 8, in the presence of 10 mol-% [$Pd(PPh_3)_4$] as a catalyst and 20 mol-% 1,4-bis(diphenylphosphino)butane (dppb) as a ligand, 3-*O*-picoloyl D-glucal donor **171** reacted with various phenols (regarded as soft nucleophiles) in CH_2Cl_2 at 60 °C for 48 h to afford α-*O*-aryl glycosides **172**–**174** in good to excellent yield and excellent anomeric selectivity. Notably, attempts to replace the 4,6-*O*-*p*-methoxybenzylidene on donor **171** with other protecting groups, including benzyl and di-*tert*-butylsilyl, resulted in poorer yields and selectivity.

Interestingly, when aliphatic or sugar-derived alcohols (regarded as hard nucleophiles) were used as acceptors, this reaction required triethylamine (Et_3N) as base and afforded β-*O*-glycosides, such as **157**, **164**, and **175** in good to excellent yield and excellent anomeric selectivity. All substrates gave the desired products in lower chemical yield and unsatisfactory β-selectivity in the absence of triethylamine. The addition of trieth-

Table 8. Palladium-catalyzed synthesis of *O*-glycosides using 3-*O*-picoloyl glycal donors.





Scheme 36. Proposed mechanism.

ylamine 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. Use of phenoxides as nucleophiles also gave β-*O*-arylglycosides in excellent yields and anomeric selectivity.

It is believed that coordination of PdL$_n$ complex with both of the olefin and the nitrogen atom of the picoloyl group of **171** generates the intermediate **176** in which the β-face is blocked by palladium complex. In pathway **A**, nucleophilic addition of soft nucleophiles, such as phenols, occurs at the allylic carbocation and the α-glycoside is afforded. Regeneration of PdL$_n$ complex completes the catalytic cycle. In pathway **B**, ionization of the picoloyl group generates the intermediate **177** as a palladium π-allyl complex. In this structure, the palladium ion is considered to be a harder Lewis acid, while the allylic carbocation site is considered a softer Lewis acid. Aliphatic alcohols or phenoxide, having stronger nucleophilicity, prefer to coordinate to the palladium(II) center to generate the intermediate **178** with the elimination of picolinic acid. The presence of triethylamine likely enhances the nucleophilicity of the acceptor and facilitates its addition to the palladium(II) center. Following intramolecular nucleophilic addition, the β-glycoside is formed and PdL$_n$ complex is regenerated (Scheme 36).

7.2.2 Synthesis of N-Glycosides by Pd Catalysis

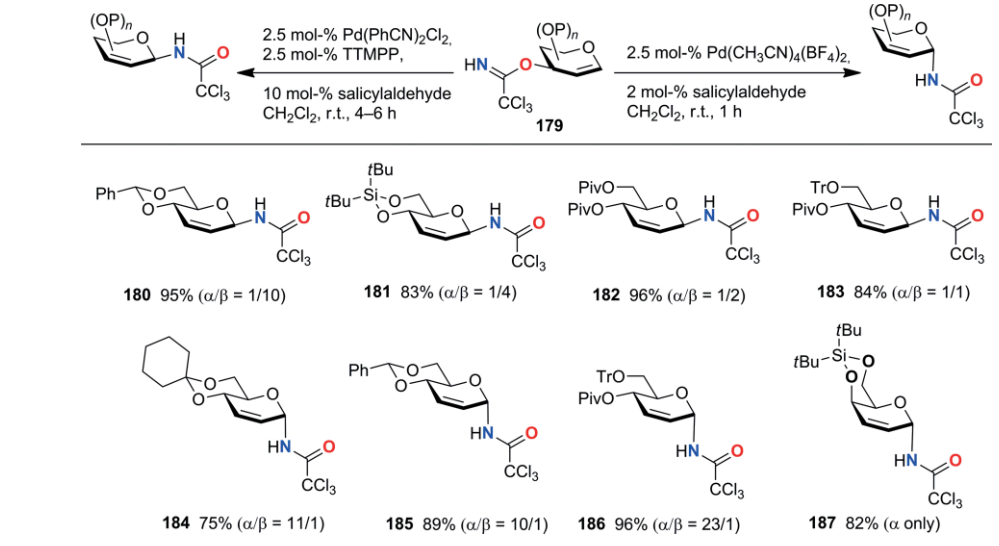
In 2007, Nguyen and co-workers first reported a novel palladium(II)-catalyzed stereoselective synthesis of α- and β-*N*-glycosyl trichloroacetamides using glycal C3-imidates in the absence of acceptors.[97] As shown in Table 9, in the presence of 2.5 mol-% of [Pd(PhCN)$_2$Cl$_2$], 2.5 mol-% tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP), and 10 mol-% salicylaldehyde, D-glucal C3-imidates **179** can undergo rearrangement in CH_2Cl_2 at room temperature to afford corresponding β-*N*-glycosyl trichloroacetamides **180**–**183** bearing 2,3-unsaturation in good to excellent yields with poor to good β-selectivity. When 2.5 mol-% of [Pd(CH$_3$CN)$_4$](BF$_4$)$_2$ was used as the catalyst, rearrangement of glycal C3-imidates in the presence of 2 mol-% salicylaldehyde provided α-*N*-glycosyl trichloroacetamides **184**–**187** bearing 2,3-unsaturation in good to excellent yields with excellent α-selectivity. Thus, the α- and β-selectivity at the anomeric carbon depends on the nature of the palladium–ligand catalyst. While the cationic palladium(II) promotes the α-selectivity, the neutral palladium(II) favors the β-selectivity.

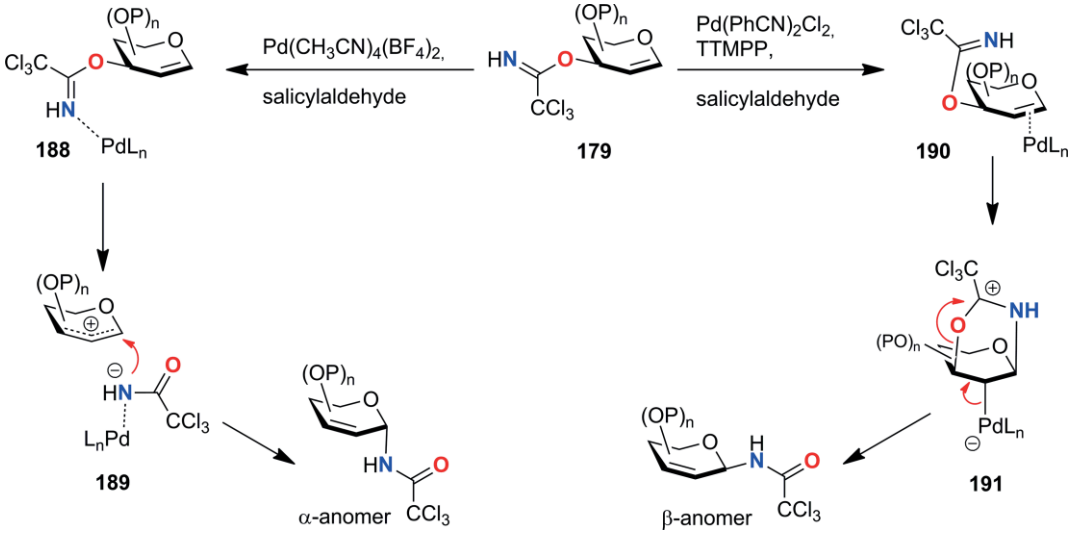
The observed anomeric selectivity may be explained in the Scheme 37. In the presence of the cationic palladium, the [Pd(CH$_3$CN)$_4$](BF$_4$)$_2$–salicylaldehyde complex coordinates to the imidate nitrogen of **179** to form **188** which subsequently undergoes ionization to generate allylic cation and palladium trichloroacetamide complex **189**. Regioselective addition of trichloroaacetamide from the α-face to the allylic cation provides α-anomer. In contrast, use of the [Pd(PhCN)$_2$]Cl$_2$–TTMPP–salicylaldehyde complex promotes a cyclization-induced rearrangement.[98] In this pathway, the palladium catalyst coordinates to the double bond of **179** to form π-complex **190**, which is activated toward nucleophilic attack by the imidate nitrogen. Subsequent cyclization of **190** provides complex **191** which upon Grob-like fragmentation followed by dissociation furnishes the β-anomer.

As glycosyl urea was found in nature as a structural unit of glycocinnamoylspermidine antibiotics,[99] the authors demonstrated the utilization of α- and β-*N*-glycosyl trichloroacetamides bearing 2,3-unsaturation for the synthesis of glycosyl ureas (Scheme 38). Diastereoselective dihydroxylation of the olefin moiety of **181** and **186** followed by urea formation and per-acetylation afforded D-mannose-type ureas **192** and **193** in good yields over three steps, respectively. This method was later applied to the synthesis of disaccharides and trisaccharide-derived unsymmetrical glycosyl ureas.[100]

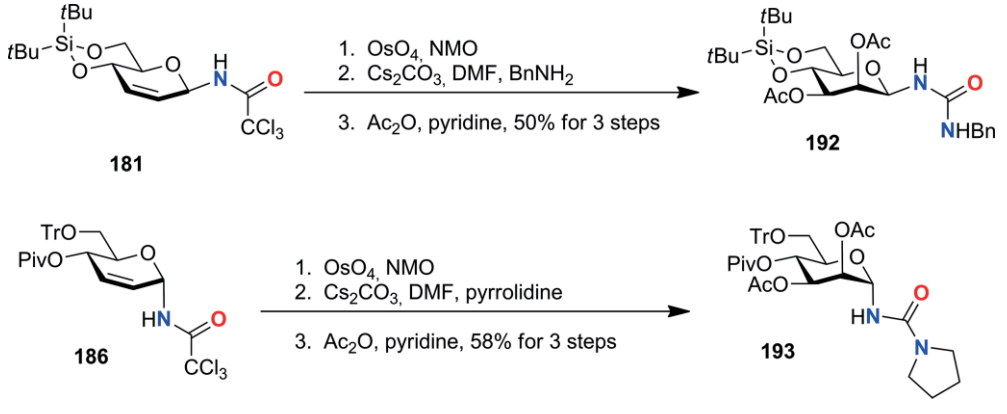
In addition, use of palladium catalysis for the synthesis of *N*-aryl glycosides was reported by Chida.[101] In his studies, [Pd$_2$dba$_3$] (10 to 200 mol-%) and large excess of ligand (2.5 equiv. to Pd) were used to catalyze the coupling of per-*O*-benzylated D-glucopyranosylamine with activated bromoarenes

Table 9. Palladium-catalyzed stereoselective synthesis of α- and β-*N*-glycosyl trichloroacetamides.





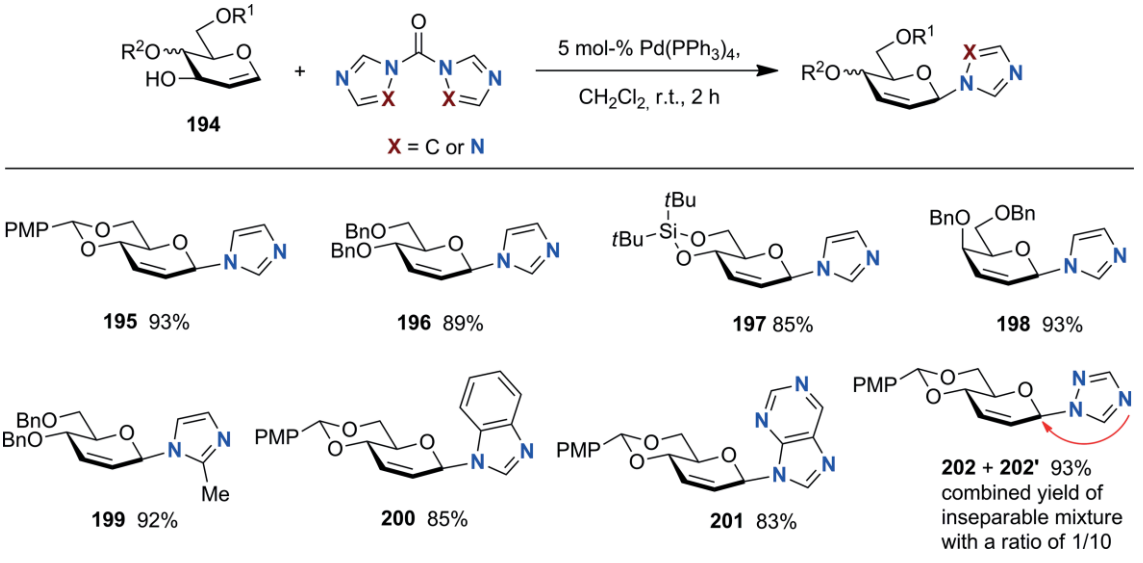
Scheme 37. Proposed mechanism.



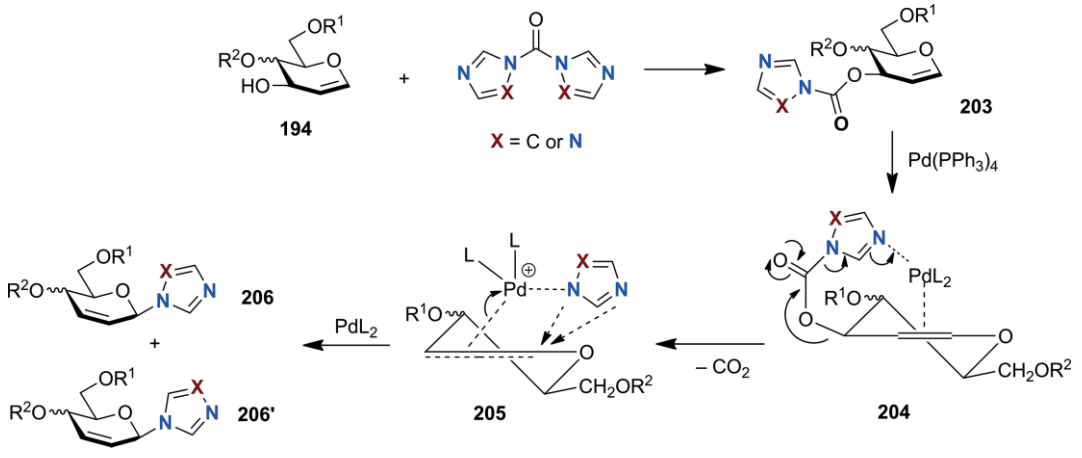
Scheme 38. Synthesis of glycosyl ureas.

(2 to 15 equiv.) to afford *N*-aryl glycosides as a mixture of anomers (α/β = 2.4:1 to 1:9.3), albeit in satisfactory yields. Although this method demonstrated the possibility of using of glycosylamines as nucleophiles for transition metal catalysis, but it was

Table 10. Synthesis of β-*N*-glycosyl imidazole analogues.



Scheme 39. Proposed mechanism.



not practical due to the high loading of catalyst and excess bromoarenes.

Recently, Liu and co-workers reported a one-pot synthesis of β-*N*-glycosyl imidazole analogues via a palladium-catalysed decarboxylative allylation.[102] As shown in Table 10, β-*N*-glycosyl imidazole analogues 195–201 were produced in excellent yields and anomeric selectivity under the optimal reaction condition: glycal 194 (1.0 equiv.), CDI (carbonyldiimidazole, 1.5 equiv.), [Pd(PPh$_3$)$_4$] (0.05 equiv.) in dichloromethane at room temperature for 2 h. β-*N*-glycosyl 1,2,4-triazole analogues **202** and **202′** were isolated as an inseparable mixture of regioisomers.

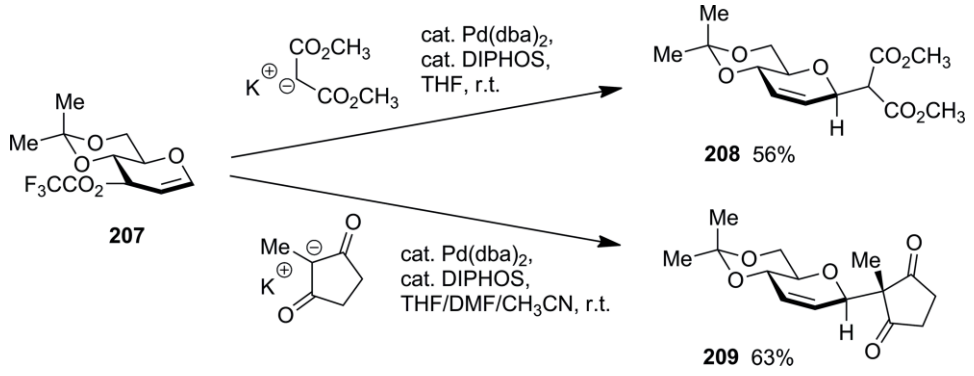
To explain the β-selectivity of palladium catalyzed *N*-glycosylation, it is believed that initially glycal **194** reacts with CDI to form the carbamate intermediate **203**. In the presence of [Pd(PPh$_3$)$_4$], double coordination of the palladium catalyst to **203** resulted in the formation of key intermediate **204** with the palladium species on the β-face. Subsequently, intermediate **205** was generated through a palladium catalyst-promoted decarboxylative reaction. Next, nucleophilic addition gave compound **206** and **206′** with β-selectivity and the elimination of the palladium catalyst. For asymmetric CDI analogues, since both of the nitrogen can serve as a nucleophile in the next step, two regioisomeric products (cf. **202** and **202′**) can be obtained (Scheme 39).

7.2.3 Synthesis of C-Glycosides by Pd Catalysis

Use of palladium catalysis for the synthesis of *C*-glycosides has been extensively studied over the past a few decades.[103] In general, palladium-catalyzed synthesis of *C*-glycosides can be classified into the following two categories: 1) use of glycals in palladium catalysis for the synthesis of *C*-glycosides; and 2) use of 1-substituted glycals in palladium catalysis for the synthesis of *C*-glycosides.

7.2.3.1 Palladium-Catalyzed Synthesis of C-Glycosides Using Glycals as Coupling Partners

Use of unfunctionalized glycals in palladium catalysis for the synthesis of *C*-glycosides has been widely investigated. In 1985,



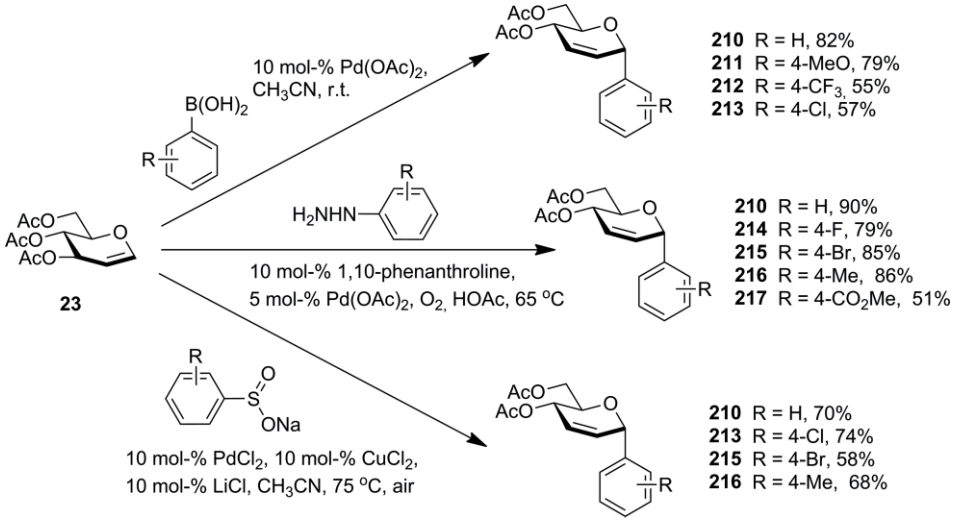
Scheme 40. Palladium-catalyzed *C*-glycosylation of D-glucal bearing C3-trifluoroacetate leaving group.

RajanBabu reported the first palladium-catalyzed *C*-glycosylation.[104] Due to the difficulty of ionization of glycals bearing C3-acetate or phosphate, D-glucal bearing C3-trifluoroacetate **207** was employed to facilitate the ionization for the formation of π-allyl palladium species. As shown in Scheme 40, in the presence of catalytic amount of [Pd(dba)$_2$] and ligand 1,2-bis(diphenylphosphino)ethane (DIPHOS), D-glucal **207** reacted with the potassium salts of dimethyl malonate and 2-methylcyclopentane-1,3-dione to afford desired β-*C*-glycoside **208** and **209** in 56 % and 63 % yield, respectively.

Besides enolates as nucleophiles, arylboronic acids, aryl hydrazines, and arylsulfinates were also employed as coupling partners for glycals for the synthesis of *C*-aryl glycosides via palladium catalyzed Ferrier-type coupling reaction (Scheme 41). In 2001, Maddaford and co-workers reported the palladium catalyzed synthesis of α-*C*-aryl glycosides, such as **210**–**213** in good yields from 3,4,6-tri-*O*-acetyl-D-glucal **23** and various arylboronic acids.[105] It was found that arylboronic acids bearing electron-withdrawing groups afforded the desired α-*C*-aryl glycosides in inferior yields. In 2013, Liu and co-workers described the synthesis of α-*C*-aryl glycosides, such as **210** and **214**–**217** in good to excellent yields from **23** and various aryl hydrazines.[106] Recently, Liu and co-workers also disclosed the synthesis of α-*C*-aryl glycosides, such as **210**, **213**, and **215**–**216** in good yields from **23** and various arylsulfinates.[107] Notably, under this condition the *C*-aryl glycoside **213** bearing chlorine at *para*-position was obtained in higher yield than the Maddaford's method.

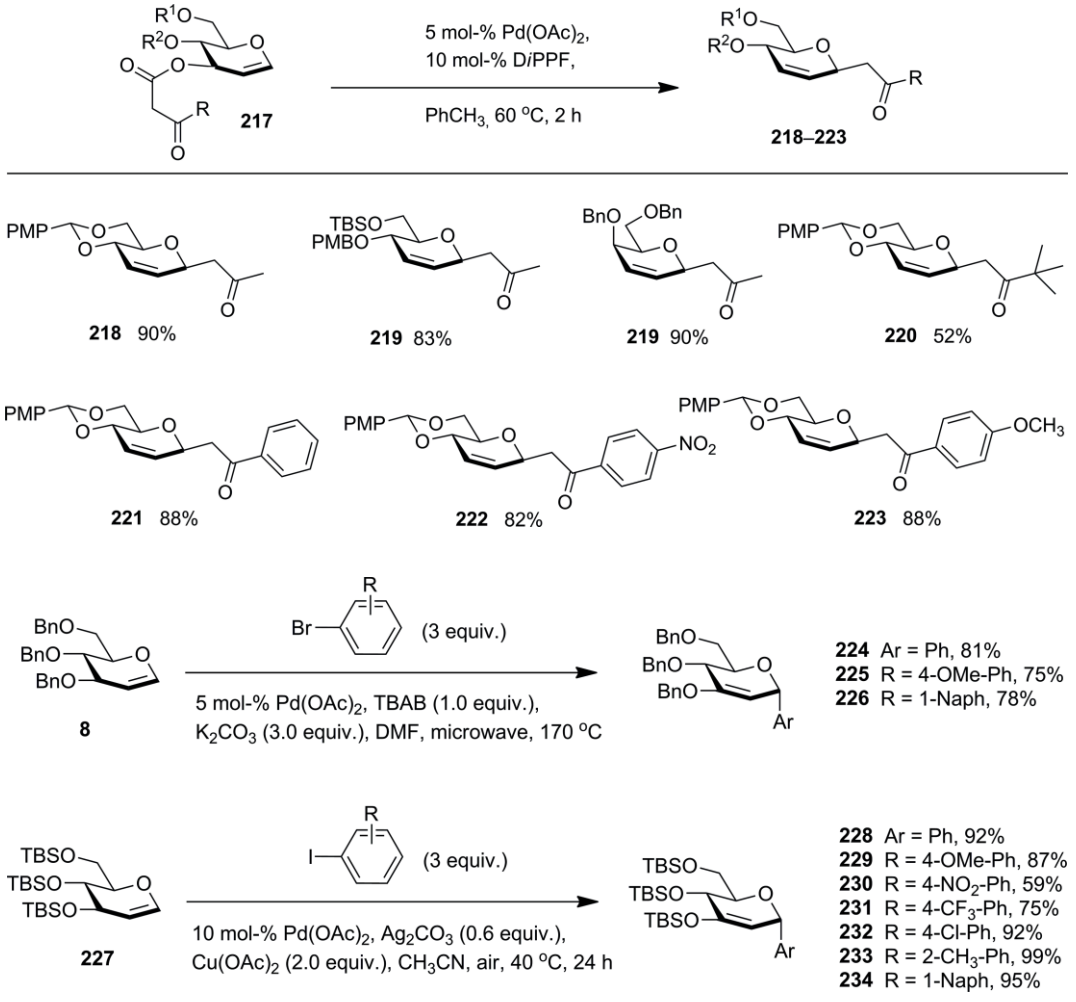
In addition, Liu and co-workers developed a palladium-catalyzed decarboxylative allylation using glycals bearing C3-β-keto esters for the stereoselective synthesis of β-*C*-glycosides.[108] As shown in Table 11, in the presence of 5 mol-% Pd(OAc)$_2$ and 10 mol-% 1,1′-bis(diisopropylphosphino)ferrocene (D*i*PPF), heating glycals bearing C3-β-keto esters **217** in toluene at 60 °C for 2 h afforded desired β-*C*-glycosides 218–223 in good to excellent yields and excellent anomeric selectivity. This method tolerates both electron-donating and electron-withdrawing group on the aromatic ring (cf. 222 and 223) and was also applied to the formal synthesis of aspergillide A. In addition, Liu and co-workers also reported the synthesis of *C*-glycosides via palladium and *N*-heterocyclic carbene-catalyzed decarboxylative allylation through addition of (*o*-azaaryl)carbaldehyde to glycals bearing C3-ethylcarbonate.[109]

Synthesis of α-*C*-aryl glycosides via palladium-catalyzed Heck-type coupling of glycals with aryl halides were also reported. As shown in Scheme 42, Yang and co-workers disclosed



Scheme 41. Palladium-catalyzed *C*-glycosylation of glycals with various coupling partners.

Table 11. Synthesis of β-*C*-glycosides by palladium-catalyzed decarboxylative allylation.

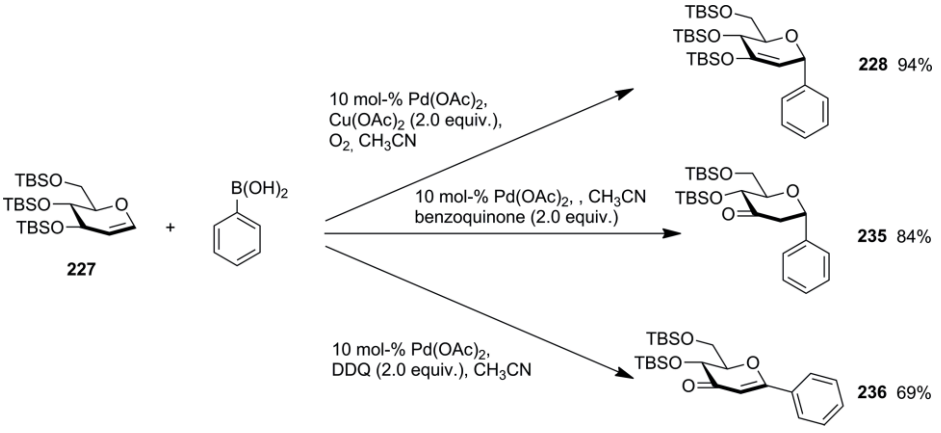


Scheme 42. Palladium-catalyzed Heck-type *C*-glycosylation of glycals with aryl halides.

palladium-catalyzed Heck-type coupling of 3,4,6-tri-*O*-benzyl-D-glucal **8** with various aryl bromides in the presence of 5 mol-% $Pd(OAc)_2$, TBAB (tetra-*n*-butylammonium bromide) (1.0 equiv.), and K_2CO_3 (3.0 equiv.) in DMF under microwave irradiation at 170 °C afforded α-*C*-aryl glycosides **224**–**226** in good yields and excellent anomeric selectivity.[110] In the same year, Ye and co-workers described palladium-catalyzed Heck-type coupling of 3,4,6-tri-*O*-*tert*-butyldimethylsilyl-D-glucal **227** with various aryl iodides in the presence of 10 mol-% $Pd(OAc)_2$, Ag_2CO_3 (0.6 equiv.), and $Cu(OAc)_2$ (2.0 equiv.) in CH_3CN under air at 40 °C for 24 h provided α-*C*-aryl glycosides **228**–**234** in good to excellent yields and excellent anomeric selectivity.[111] Notably, under Ye's condition, neither 3,4,6-tri-*O*-benzyl-D-glucal **8** nor 3,4,6-tri-*O*-acetyl-D-glucal **23** was an effective substrate.

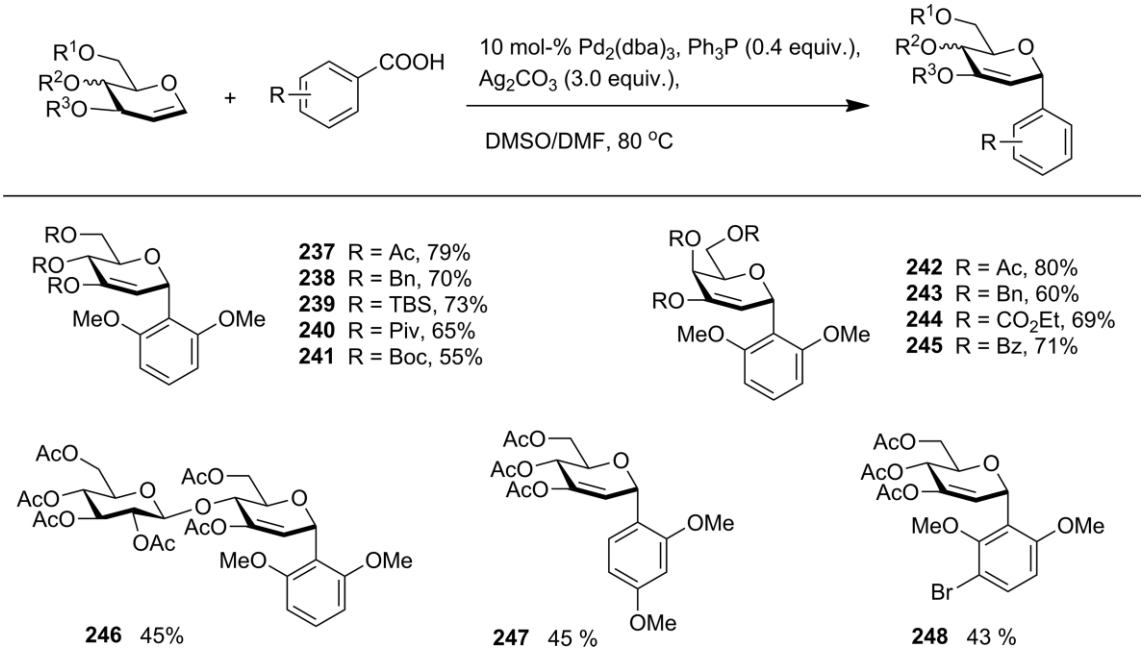
Synthesis of α-*C*-aryl glycosides via palladium-catalyzed Heck-type coupling of glycals can also be carried out using aryl boronic acids as coupling partners.[112] The structures of the α-*C*-aryl glycosides obtained in this type of reaction depends on the condition or choice of oxidants. As shown in Scheme 43, Coupling of 3,4,6-tri-*O*-*tert*-butyldimethylsilyl-D-glucal **227** with phenylboronic acid in the presence of 10 mol-% $Pd(OAc)_2$ and $Cu(OAc)_2/O_2$ afforded α-*C*-aryl glycosides **228** in 94 % yield. In addition, changing the oxidant from $Cu(OAc)_2/O_2$ to benzoquinone provided C3-oxo α-*C*-aryl glycosides **235** in 84 % yield. Notably, while 3,4,6-tri-*O*-benzyl-D-glucal **8** was found to be less effective than 3,4,6-tri-*O*-*tert*-butyldimethylsilyl-D-glucal **227** and gave the corresponding C3-oxo α-*C*-aryl glycosides in 32 % yield, use of 3,4,6-tri-*O*-acetyl-D-glucal **23** did not afford any product. Furthermore, changing the oxidants to DDQ led to the formation of enone-type *C*-glycosides **236** in 69 % yield.

In adiditon, Liu and co-workers developed a palladium-catalyzed Heck-type decarboxylative *C*-glycosylation of glycals with benzoic acids for the synthesis of α-*C*-aryl glycosides.[113] Although 3,4,6-tri-*O*-acetyl-D-glucal **23** was not a suitable substrate in both Yang[110] and Ye's method,[111,112] it was found that **23** was an effective substrate under Liu's condition. As shown in Table 12, in the presence of 10 mol-% $Pd(OAc)_2$, 0.4 equiv. Ph_3P, and Ag_2CO_3 (3.0 equiv.), heating a mixture of glycals and various benzoic acids in a DMSO/DMF (1:20) solvent 80 °C afforded α-*C*-aryl glycosides **237**–**248** in moderate to



Scheme 43. Palladium-catalyzed Heck-type *C*-glycosylation of glycals with aryl boronic acids.

Table 12. Palladium-catalyzed Heck-type decarboxylative *C*-glycosylation of glycals.



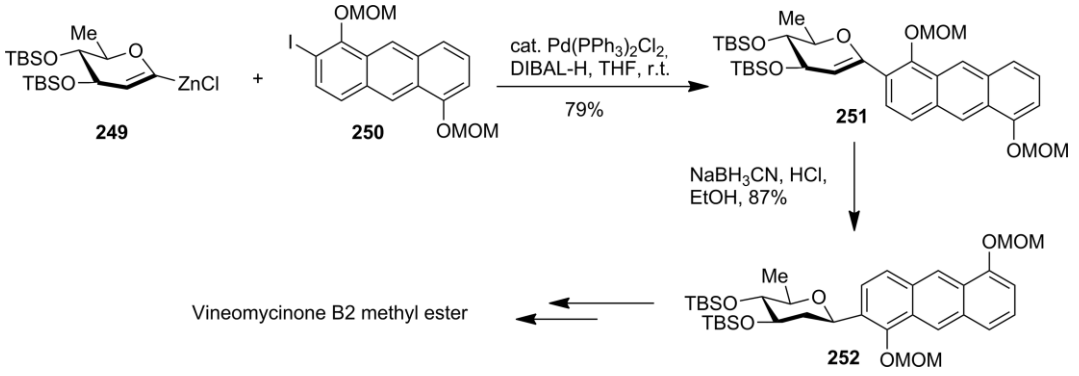
good yields. This reaction tolerates various protecting group on glycals and electron-rich benzoic acids with different substitution patterns.

7.2.3.2 Palladium-Catalyzed Synthesis of C-Glycosides Using 1-Substituted Glycals as Coupling Partners

Use of 1-substituted glycals in palladium catalysis for the synthesis of *C*-glycosides has also been extensively studied. Typically, the synthesis involves the standard cross coupling of glycal-derived metal species with sp^2-halide (aryl or alkenyl) or halo-glycal with alkyl or aryl metal species.

Tius and co-workers utilized palladium-catalyzed Negishi-type coupling for the synthesis of *C*-aryl glycosides.[114] As shown in Scheme 44, Negishi coupling of D-glucal-derived zinc species **249** with aryl iodide **250** afforded desired product **251** in 79 % yield. Stereoselective reduction of enol ether of **251** was achieved by exposing **251** to $NaBH_3CN$ and HCl in EtOH and 2-deoxy-β-*C*-aryl glycoside **252** was isolated in 87 % yield. This 2-deoxy-β-*C*-aryl glycoside **252** was further functionalized to complete the synthesis of antitumor antibiotic Vineomycinone B2 Methyl Ester.

Beau and co-workers described palladium-catalyzed Stille coupling glycal-derived stannanes with organic halides to form corresponding *C*-glycosides.[115] Friesen and co-workers also disclosed the synthesis of C-aryl glucals via Stille coupling of glucal-derived stannanes with aryl bromides.[116] In addition, Werz and co-workers reported the synthesis of (1→2)-, (1→3)-, and (1→4)-*C*-disaccharides employing Stille-type reaction of stannylglycals and exocyclic bromoolefins.[117] Recently, Zhu and co-workers used a similar strategy for the synthesis of antitumor antibiotic derhodinosylurdamycin A which involves a Stille coupling of D-glucal-derived stannane and aryl ioide followed by stereoselective reduction.[118]



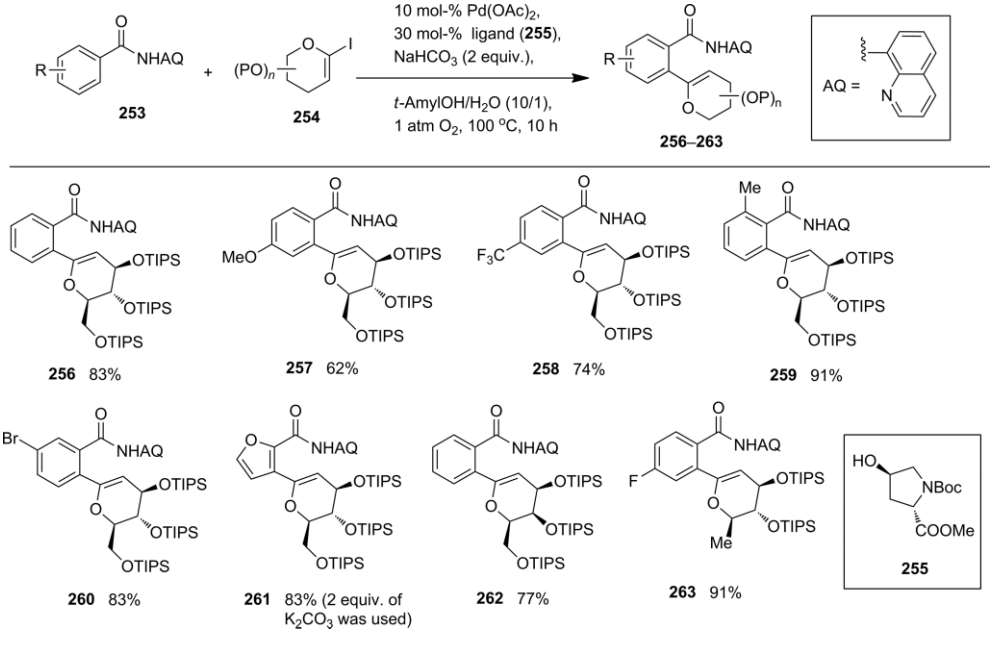
Scheme 44. Synthesis of 2-deoxy-β-*C*-aryl glycosides by palladium-catalyzed Negishi coupling followed by stereoselective reduction.

In 2008, Miyaura and co-workers reported the synthesis of *C*-glycosides by palladium-catalyzed cross coupling of haloarenes, benzyl bromide, and allyl bromide with glucal-derived organoborons (or borylglucals).[119] The glucal-derived organoborons were obtained via iridium complexes-catalyzed vinylic C–H borylation of cyclic vinyl ethers by bis(pinacolato)diboron or pinacolborane. In 2003, Minehan and co-workers reported the synthesis of *C*-aryl glycals by palladium-catalyzed cross coupling of glucal-derived indium reagents with aryl halides.[120]

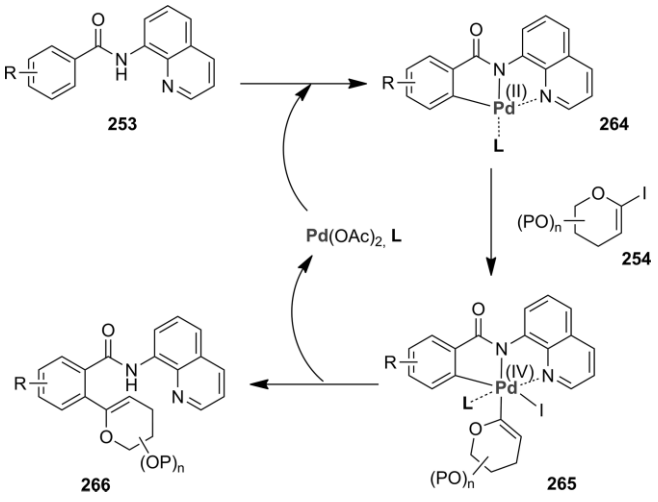
Friesen and co-workers also disclosed the synthesis of *C*-aryl glucals via Stille coupling of 1-iodoglucal aryl zinc, boron, and stannanes.[101] In addition, Tan and co-workers reported synthesis of C1-alkyl- and acyl-glycals by palladium-catalyzed Suzuki–Miyaura cross coupling of 1-iodoglycals with alkylboranes.[121] In 1997, Nicolaou and co-workers described the synthesis C1-vinyl glycals using palladium-catalyzed cross coupling of glycal-derived cyclic ketene acetal phosphates with vinylstannane.[122] Most recently, Wu, Ye and co-workers discovered a new approach for the synthesis of diverse *C*-aryl glycals (aryl-*C*-$\Delta^{1,2}$-glycosides, cf. **256**–**263**, Table 13) from various 1-iodoglycals **254** and *N*-quinolyl benzamides **253** via palladium-catalyzed *ortho*-C–H activation.[123] As shown in Table 13, various *C*-aryl glycals **256**–**263** were obtained in good to excellent yields under optimal condition {10 mol-% $Pd(OAc)_2$, 30 mol-% ligand (**255**), 2 equiv. of $NaHCO_3$, *tert*-amyl alcohol/H_2O (10:1), 1 atm oxygen, 100 °C, 10 h}. This method tolerates both electron rich and electron poor substituents on various substitutions on the aromatic substrates. It was found that use of an amino acid-derived ligand (**255**) was crucial in order to improve the yield and suppress the formation of bis-*C*-glycosylated products. This approach bypasses the pre-functionalization of aromatic coupling partners and leads to improved synthetic efficiency. Ye also demonstrated that the *C*-aryl glycals, e.g., **256**–**263**, were utilized for the concise synthesis of the skeletons of several bioactive natural products or molecules.

The proposed mechanism for the abovementioned couping reaction is shown in Scheme 45. Coordination of palladium(II) acetate to *N*-quinolyl benzamides **253** followed by C–H activation leads the palladacycle intermediate **264** which undergoes oxidative addition to 1-iodoglycals **254** to afford palladium(IV)

Table 13. Synthesis of *C*-aryl glycals via palladium-catalyzed C–H functionalization.



intermediate **265**. The amino acid ligand **255** may coordinate to the palladium and decrease the reaction rate of the oxidative addition to the 1-iodoglycals. Reductive elimination of palladium(IV) intermediate **265** gives desired *C*-aryl glycals **266** and regenerates the catalyst.



Scheme 45. Proposed mechanism.

Hayashi and co-workers reported the synthesis of carbohydrate-containing carbocyclic coumpounds by palladium catalyzed cross coupling of 2-bromoglucal Br with alkene or vinylstannane followed by Diels–Alder reaction.[124] Werz and co-workers reported the synthesis of (1→6)-*C*-glycosides employing Sonogashira coupling of 1-iodoglucal with sugar-derived C5-alkyne followed by hydrogenation.[125] They also described the synthesis of alkynyl *C*-glycosides using Sonogashira coupling of 1-iodinated and 2-brominated glycals using several aromatic and aliphatic alkynes.[126]

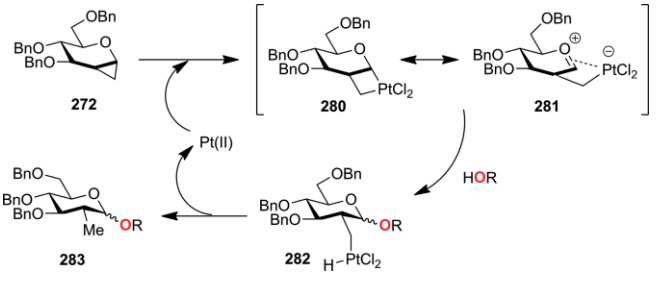
7.2.4 Synthesis of S-Glycosides by Pd Catalysis

In 2013, Liu and co-workers reported synthesis of β-*S*-arylglycoside **153** (thioglycoside) by palladium-catalyzed decarboxylative allylation (Table 6).[93] In addition, use of palladium catalyst for the synthesis of *S*-glycosides has also been achieved via coupling of aryl halide and glycosyl thiols. As shown in Scheme 46, *N*-glycosyl phenylthioglycosides **269** bearing both C–N and C–S β-glycosidic bonds could easily be prepared in 70 % yield via a Pd-catalyzed coupling reaction of *N*-4-iodoaryl glycosides **267** with glycosyl thiol **268**.[127]

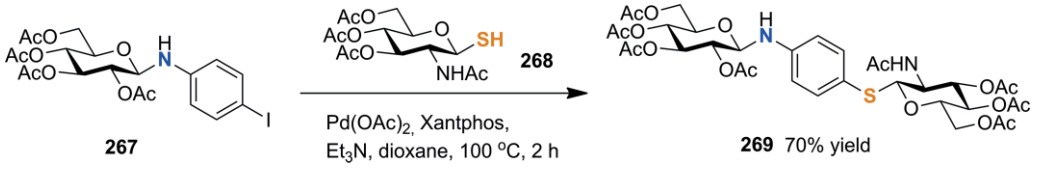
7.3 Synthesis of 2-*C*-Branched *O*-Glycosides by Pt Catalysis

The use of platinum complexes for catalytic glycosylations was rare. To the best of our knowledge, there was only one report by Madsen and co-workers which described platinum-catalyzed synthesis of α-2-*C*-branched carbohydrates via ring opening of 1,2-cyclopropanated sugars.[128] As shown in Table 14, in the presence of 3.7 mol-% of Zeise's dimer $[Pt(C_2H_4)Cl_2]_2$, various 1,2-cyclopropanated sugars **270**–**274** were able to react with simple alcohols to selectively afford 2-*C*-branched α-glycosides **275**–**279** in good to excellent yields and good anomeric selectivity. This method also tolerates other type of oxygen nucleophiles, such as water, monosaccharides, and phenol acceptors, to afford corresponding lactols, disaccharides, and *O*-arylglycosides, respectively. In addition, it was found that 1,2-cyclopropanated sugars bearing carboalkoxy and alkoxy groups are less reactive towards platinum catalysis as compared to those containing unsubstituted cyclopropanes.

When 1,2-cyclopropanated sugar **270** was subjected to deuterium labeling experiment involving monodeuterated benzyl alcohol (BnOD), the corresponding 2-*C*-branched glycoside was found to be completely monodeuterated at the 2-*C*-methyl group. Based on this observation, the authors proposed the mechanism for this platinum-catalyzed glycosylation as shown in Scheme 47. Initially, an intermediate platinacyclobutane **280** is formed by oxidative addition of the cyclopropane to platinum(II). Platinacyclobutane **280** is believed to have substantial oxocarbonium ion character (cf. **281**) as previously observed for certain palladium species. Nucleophilic attack of the *O*-nucleophile, e.g., alcohols and water, gives the glycoside/hemiacetal **282** with the α-anomer dominating according to the anomeric effect. Reductive elimination from **282** completes the catalytic cycle to give the *C*-branched sugar **283** and regenerating platinum(II).

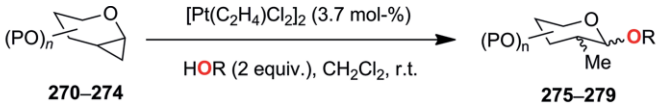


Scheme 47. Proposed mechanism.

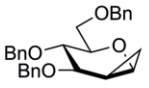
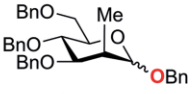
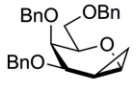
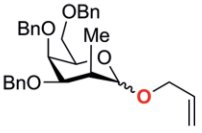
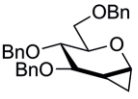
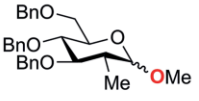
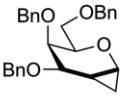
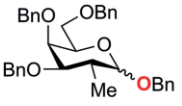
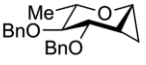
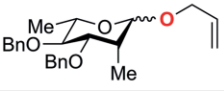


Scheme 46. Synthesis of *S*-glycosides by Pd catalysis.

Table 14. Platinum-catalyzed synthesis of α-2-*C*-branched carbohydrates.



270–274 275–279

Entry	1,2-Cyclopropanated sugars		Products		Yields, α/β ratio
1		**270**		**275**	95% (α/β = 12/1)
2		**271**		**276**	84% (α/β = 24/1)
3		**272**		**277**	80% (α/β = 7/1)
4		**273**		**278**	87% (α/β = 7/1)
5		**274**		**279**	96% (α/β = 12/1)

7.4 Summary

The group 10 transition metal complexes, especially those derived from nickel and palladium, have been widely employed for catalytic stereoselective glycosylations. By taking advantage of azaphilic nature of cationic nickel(II) complexes, synthesis of 1,2-*cis*-α-2-deoxy-2-aminoglycosides has been realized via activation the corresponding trichloroacetimidate donors. In addition, cationic nickel(II) complexes were also used for [1,3]-rearrangement of glycosyl trichloroacetimidates to provide corresponding α-trichloroacetamides which can be utilized for preparation of glycosyl ureas. Furthermore, nickel complexes were also employed for stereoselective synthesis of *C*-glycosides from glycosyl halides, presumably via Negishi type cross-coupling or radical type mechanism. Palladium complexes, especially palladium(0) catalysts, have been extensively investigated for catalytic stereoselective synthesis of a variety of *O*-, *N*-, *C*-, and *S*-glycosides under mild conditions owning to its power in the formation of allylpalladium intermediates as well as cross coupling reactions. Besides, cationic palladium(II) catalysts were also utilized for activation of glycosyl trichloroacetimidates for the synthesis of *O*- and *C*-glycosides. In contrast, the use of platinum complexes for glycosylations is rather under explored.

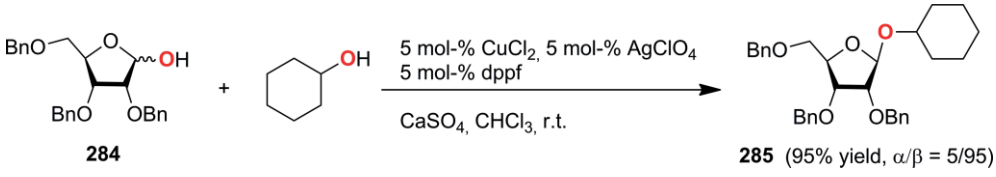
8. Synthesis of *O*-, *N*-, *C*-, and *S*-Glycosides by Group 11 Metal (Cu, Ag, Au) Catalysis

8.1 Synthesis of *O*- and *N*-Glycosides by Cu Catalysis

8.1.1 Synthesis of O-Glycosides by Cu Catalysis

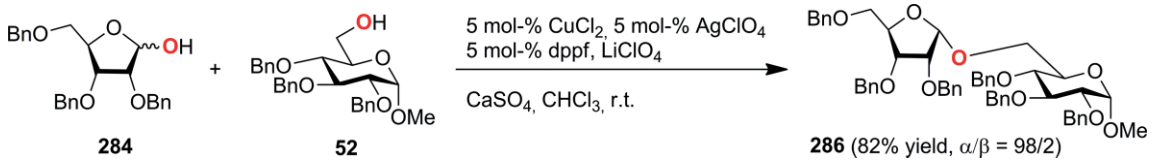
Although copper complexes-promoted glycosylations have been known,[129] reports on copper-catalyzed glycosylations are rare. In our previous review,[5] we discussed the synthesis of 1,2-*trans*-β-ribofuranosides via Cu^{II}-catalyzed dehydrative glycosylation reported by Hiroi and co-workers.[130] As described in Scheme 48, under the catalysis of Cu^{II} complex prepared from $CuCl_2$, bis(diphenylphosphino)ferrocene, and $AgClO_4$, a mixture of 2,3,5-tri-*O*-benzyl-D-ribofuranose **284** and cyclohexanol in chloroform afforded preferentially more stable β-ribofuranoside **285** in 95 % yield in the presence of $CaSO_4$ as a dehydrating agent. Experimental results suggested that $Cu(ClO_4)_2$ is the active catalyst in this glycosylation.

In addition, it was found that, in the presence of $LiClO_4$ as additive, the synthesis of 1,2-*cis*-α-ribofuranosides via Cu^{II}-catalyzed dehydrative glycosylation can be achieved.[112] As shown in Scheme 49, a mixture of **284** and acceptor **52** in chloroform



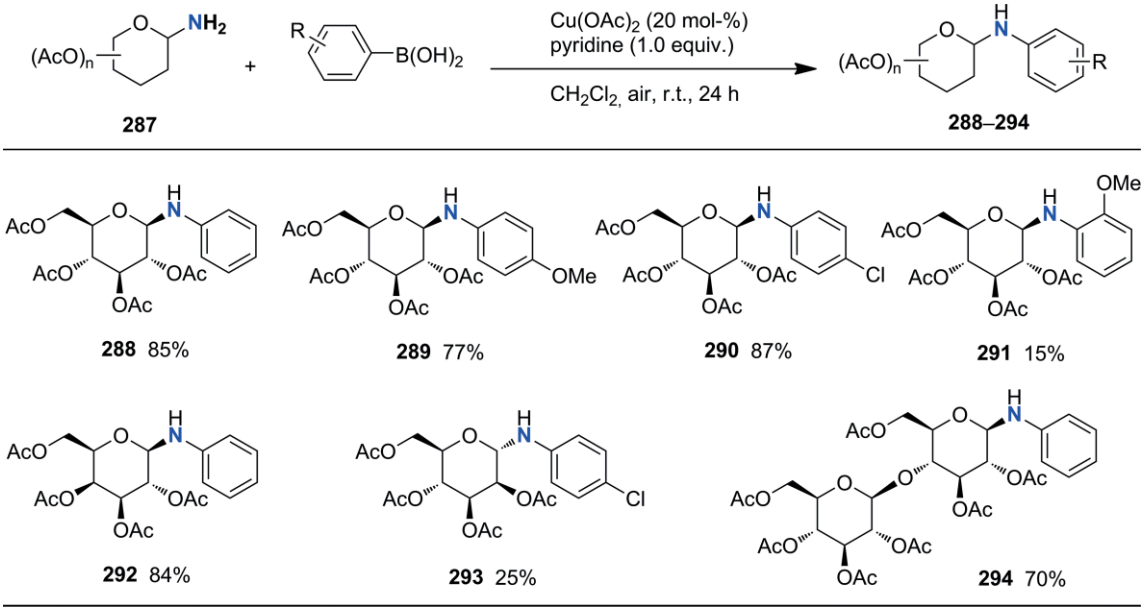
284 **285** (95% yield, α/β = 5/95)

Scheme 48. Copper-catalyzed synthesis of β-ribofuranosides.



Scheme 49. Copper-catalyzed synthesis of α-ribofuranosides in the presence of $LiClO_4$.

Table 15. Copper-catalyzed synthesis of β-*N*-aryl glycosides.



under the catalysis of Cu^{II} complex prepared from $CuCl_2$, bis(diphenylphosphino)ferrocene, and $AgClO_4$ in the presence of $LiClO_4$ afforded α-ribofuranoside **286** in 82 % yield (α/β = 98:2). Addition of $LiClO_4$ led to the reversed stereoselectivity, probably because $LiClO_4$ was able to suppress the isomerization of initially formed α-ribofuranoside to the more stable β-ribofuranoside.

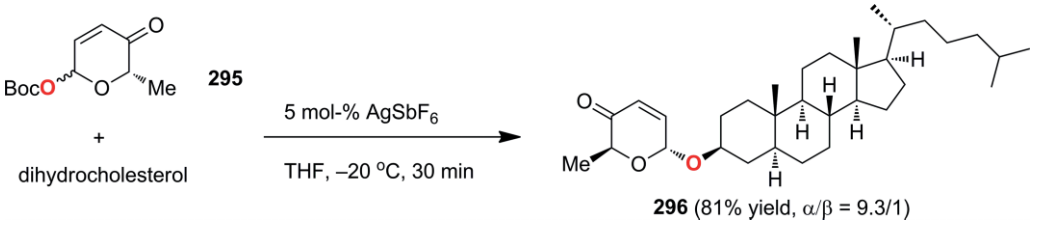
8.1.2 Synthesis of N-Glycosides by Cu Catalysis

In 2013, Alami and Messaoudi reported stereoselective synthesis of β-*N*-aryl glycosides via copper-catalyzed Chan–Lam–Evans coupling[131] of various glucosamines **287** and arylboronic acids at room temperature.[127] As shown in Table 15, using 20 mol-% $Cu(OAc)_2$, a variety of aryl *N*-glucosides **288**–**290**, galactoside **292**, as well as *N*-aryl disaccharide **294** were obtained in good to excellent yields with exclusive β-selectivity. This method seemed not to tolerate *ortho*-substituents on the aromatic boronic acids as aryl β-*N*-glucoside **291** was formed in 15 % yield. In addition, α-*N*-aryl mannoside **293** was obtained in poor yield.

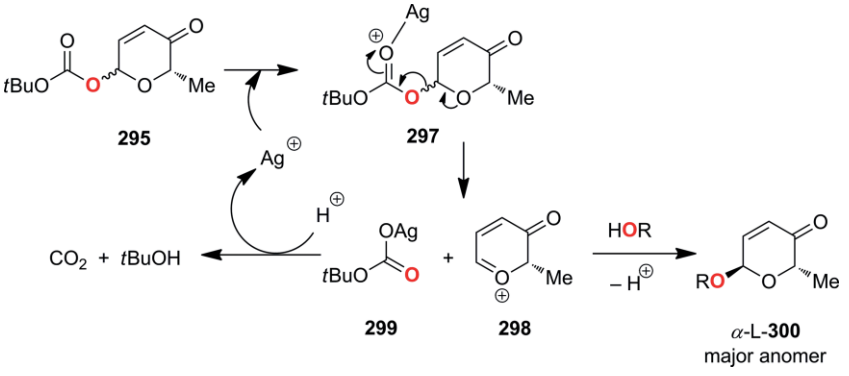
8.2 Synthesis of *O*-Glycosides by Ag Catalysis

Silver(I) salts, such as silver triflate (AgOTf) and silver perchlorate ($AgClO_4$), are usually employed with other metal (e.g., Ni, Cu, Pd, and Au) chlorides for the generation of more reactive cationic metal complexes for activation of corresponding glycosyl donors. Recently, silver salts were also reported as Lewis acid catalysts for activation of glycosyl donors. For instance, Du and co-workers reported that silver triflate (AgOTf) can be efficient and mild alternative catalyst for activation of glycosyl trichloroacetimidate donors.[132] In those glycosylations sensitive to trimethylsilyl triflate (TMSOTf), use of AgOTf as catalyst was found to suppress the migration and decomposition significantly. In addition, O'Doherty and co-workers described that cationic silver(I) salt was able to catalyze an efficient synthesis of L-pyranone derived α-glycosides.[133] As shown in Scheme 50, in the presence of 5 mol-% silver hexafluoroantimonate ($AgSbF_6$), *tert*-butyl L-pyranone glycosyl carbonate **295** (used as a mixture of α/β isomers) reacted with dihydrocholesterol in THF at –20 °C for 30 min to afford the corresponding α-glycoside **296** in 81 % yield (α/β = 9.3:1). This glycosylation protocol tolerates various primary, secondary, and tertiary alchol acceptors and provides the desired α-glycosides in good yields and anomeric selectivities.

In contrast to the previous Pd^0-catalyzed glycosylations developed by the same group which involve allylpalladium intermediates,[65,66] this cationic silver(I)-catalyzed glycosylation is believed to undergo different mechanism. As depicted in Scheme 51, activation of glycosyl donor **295** through coordination of cationic silver(I) to the carbonyl oxygen may lead to the formation of onium **298** and *tert*-butyl silver carbonate **299** (via intermediate **297**). Reaction of onium **298** with alcohol accept-



Scheme 50. Silver-catalyzed synthesis of L-pyranone derived α-glycosides.



Scheme 51. Proposed mechanism.

ors affords desired α-L-**300** as the major anomer and releases a proton, while cationic silver(I) catalyst is regenerated by decomposition of *tert*-butyl silver carbonate **299** in the presence of acid.

8.3 Synthesis of *O*-, *N*-, *C*-, and *S*-Glycosides by Au Catalysis

Due to the particular affinity of gold to alkynes, gold catalysts have been widely used in organic synthesis through the activation of alkynes.[134] The capability of gold complexes in chemoselective activation of alkynes under mild conditions renders it appealing to of synthetic carbohydrate chemists. As a result, development of new glycosylation modes based on the gold catalysts has been realized by several groups.

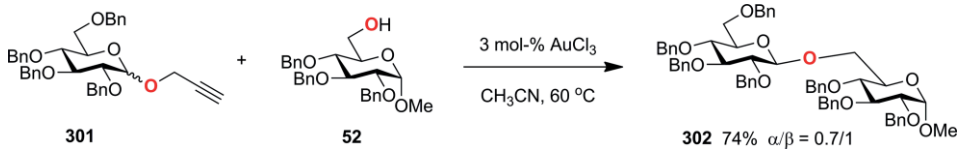
8.3.1 Synthesis of O-Glycosides by Au Catalysis

8.3.1.1 Gold(III)-Catalyzed O-Glycosylation with Propargyl Glycoside Donors

Previously in our review,[5] we discussed several gold-catalyzed stereoselective synthesis of *O*-glycosides. For instance, use of gold catalyst for *O*-glycosylation was first reported by Hotha and co-workers in 2006.[135] As shown in Scheme 52, under gold(III)-chloride catalysis, propargyl glycosides **301** reacted with acceptor **52** in acetonitrile at 60 °C to form a α,β-mixture of disaccharides **302** in good yield. This reaction took advantage of the high alkynophilicity of Au(III) for anomeric activation of propargyl glycosides to furnish corresponding oxonium ion which then reacted with various aglycones. However, this type of gold-catalyzed glycosylation does not tolerate acyl protected propargyl glycoside donors. Later in 2009, Finn and Mamidyala successfully applied this gold(III) chloride-catalyzed glycosylation to the synthesis of glycosides using unprotected propargyl glycosyl donors.[136] Later in 2012, Hotha discovered a more effective propargyl glycoside donor, 1-ethynylcyclohexanyl glycoside, which can be activated by 5 mol-% $AuCl_3$ and 5 mol-% $AgSbF_6$ at room temperature.[137]

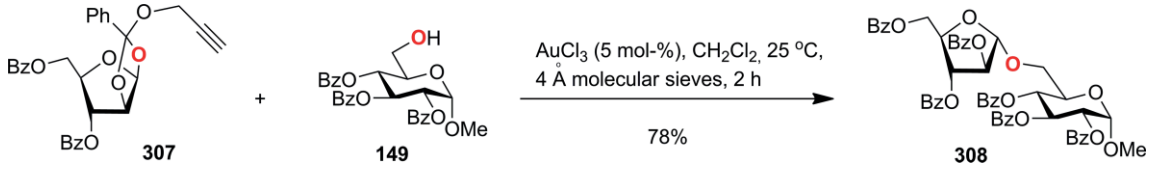
8.3.1.2 Gold(III)-Catalyzed O-Glycosidation with Propargyl 1,2-Orthoesters

Due to aforementioned limitation of Au(III)-catalyzed *O*-glycosylation using propargyl glycoside donors, Hotha and co-workers later developed $AuBr_3$-catalyzed *O*-glycosylation using propargyl 1,2-orthoesters (cf. **303** and **304**) as useful glycosyl donors for the synthesis of 1,2-*trans* glycosides and glycoconjugates **305** and **306**, respectively (Scheme 53).[138] This method tolerates a variety of aglycones comprising aliphatic, alicyclic, steroidal and sugar alcohols. Presumably, $AuBr_3$ may activate the alkyne resulting in the formation of a 1,2-dioxolenium ion and also behave as a Lewis acid to facilitate the attack of the glycosyl acceptor.

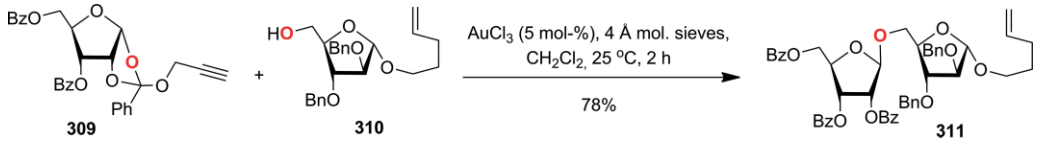


Scheme 52. Gold(III)-catalyzed *O*-glycosylation with propargyl glycosides.

Scheme 53. Gold(III)-catalyzed *O*-glycosylation with propargyl 1,2-orthoesters.



Scheme 54. Gold-catalyzed synthesis of 1,2-*trans*-α-arabinofuranosides.



Scheme 55. Synthesis of 1,2-*trans*-β-ribofuranosides via gold catalysis.

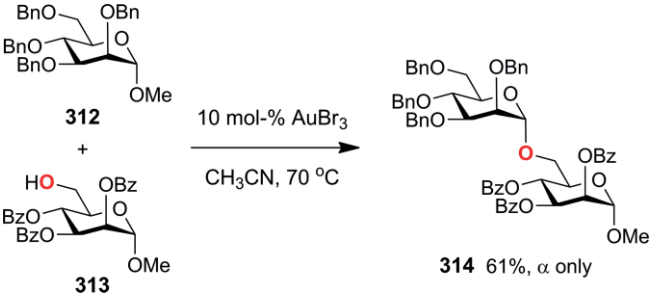
Hotha and co-workers also demonstrated orthogonal activation strategy using propargyl 1,2-orthoesters as glycosyl donors. They discovered that $AuBr_3$-catalyzed selective activation of propargyl 1,2-orthoesters can be achieved in the presence of propargyl glycosides and propargyl ethers 2008.[139] Later, they found that propargyl 1,2-orthoesters can be selectively activated with $AuBr_3$ in the presence of *n*-pentenyl glycosides, while pentenyl 1,2-orthoesters can be selectively activated with NIS/Yb(OTf)$_3$ in the presence of propargyl glycosides.[140] This $AuBr_3$-catalyzed *O*-glycosylation using propargyl 1,2-*O*-orthoesters as donors was later applied to the stereoselective synthesis of 1,2-*trans* protected glycosyl amino acids,[141] glycomonomers,[142] tetrasaccharide motif of the Leishmania donovani lipophosphoglycan,[143] pentaarabinofuranoside of the mycobacterial cell surface,[144] and pyrimidine nucleosides.[145]

Recently, Hotha and co-workers exploited the use of propargyl 1,2-orthoesters of arabinose for the synthesis of 1,2-*trans*-α-arabinofuranosides via gold catalysis. Accordingly, the propargyl 1,2-orthoester of arabinofuranose **307** was subjected to standard gold-catalyzed glycosylation condition ($AuCl_3$/4 Å powdered molecular Sieves. /CH_2Cl_2/25 °C) with acceptor **149** to give 1,2-*trans* furanoside **308** in 78 % yield (Scheme 54).[146]

In addition, 1,2-*trans*-β-ribofuranosides were also readily accessed by the above delineated propargyl 1,2-orthoester strategy. As shown in Scheme 55, ribofuranosyl donor **309** was subjected to the aforementioned gold catalyzed glycosidation with acceptor **310** to obtain corresponding β-ribofuranosides **311** in 78 % yield.[146]

8.3.1.3 Gold(III)-Catalyzed O-Glycosylation Involving Methyl Glycoside Donors

Hotha and co-workers also disclosed that stable methyl glycosides, such as **312**, can also be employed as glycosyl donors in the presence of $AuBr_3$ catalysis.[147] As shown in Scheme 56, "armed" D-mannose-derived methyl glycoside donor **312** reacted with "disarmed" D-mannose-derived methyl glycoside acceptor **313** in the presence of 10 mol-% $AuBr_3$ to afford desired α-disaccharide **314** in 61 % yield. Notably, "disarmed" methyl glycoside donors can not be activated by $AuBr_3$ catalyst. This method tolerates a diverse range of aglycones, such as aliphatic, alicyclic, steroidal and sugar alcohols. In addition, this methodology enabled the synthesis of tri- and tetra-saccharides from respective di- and tri-saccharides.



Scheme 56. Gold(III)-catalyzed *O*-glycosylation involving methyl glycoside donors.

Hotha and co-workers demonstrated that various 1,6-anhydro sugars can be prepared utilizing these gold-catalyzed glycosylations of 6-hydroxy propargyl/methyl monosaccharides, disaccharides, and trisaccharides.[148] In addition, 2-*C*-branched methyl glycosides reacted with various alcohols under gold catalysis to provide α-configured 2-*C*-nitromethyl glycosides.[149] Furthermore, gold(III) bromide was shown as a suitable catalyst for the stereoselective cyclization of 2-*C*-malonyl carbohydrates to the anomeric center under retention of one ester group.[150]

Moreover, Hotha and co-workers reported that gold(III)-catalyzed glycosylation were suitable for the synthesis of furanosides.[151] Interestingly, propargyl/methyl D-ribofuranosides and D-lyxofuranosides gave only 1,2-*trans* glycosides, whereas D-arabinofuranoside and D-xylofuranoside resulted in a mixture of 1,2-*trans* and 1,2-*cis* glycosides.

8.3.1.4 Gold(I)-Catalyzed O-Glycosylation with Glycosyl ortho-Alkynylbenzoate Donors

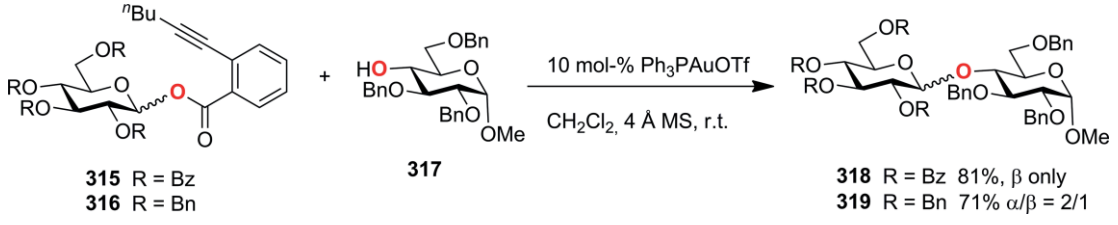
In 2008, Yu and co-workers first reported the use of homogeneous cationic gold(I) catalyst for *O*-glycosylation involving glycosyl *ortho*-alkynylbenzoates as donors (Scheme 57).[152] This glycosylation method was inspired by a report from Asao and co-workers which disclosed gold-catalyzed etherification and Friedel–Crafts alkylation using *ortho*-alkynylbenzoic acid alkyl ester as an efficient alkylating agent.[153] The glycosyl *ortho*-hexynylbenzoate donors (cf. **315** and **316**) can be readily prepared as a mixture of anomers by condensation of the corresponding lactols with *o*-hexynylbenzoic acid. Experiments indicated that α- and β-anomers of glycosyl *ortho*-hexynylbenzoate donors showed comparable reactivity toward the gold catalysis. As shown in Scheme 57, in the presence of 10 mol-% $Ph_3PAuOTf$, glycosyl *ortho*-hexynylbenzoate donors **315** and **316** reacted with acceptor **317** to provide corresponding *O*-glycosides **318** and **319** in good yields, respectively. Mechanistically, activation of the benzylic triple bond with cationic Au^I followed by nucleophilic attack of the proximal carbonyl oxygen should result in the cleavage of the glycosidic bond to give oxocarbenium and gold-isocoumarin complex, which was discussed in our previous review.[5] The mechanism of this glycosylation was later studied by the authors in details.[154] Since the oxocarbenium is formed as the key intermediate for *O*-glycosides, the anomeric stereochemistry was controlled by steric and anomeric effect, neighbouring group participation as well as solvent and temperature.

The Yu group discovered that gold(I)-catalyzed glycosylation of glycosyl *ortho*-hexynylbenzoates with acceptors bearing both carboxylic acid and alcohol functionality was able to chemoselectively provide the corresponding ester glycosides in high yields in the presence of BF_3•Et_2O and DBU.[155] In addition, by employing glycosyl *ortho*-hexynylbenzoates as donors and cationic gold(I) as catalyst, a highly efficient glycosylation initiated cationic ring-opening polymerization (CROP) of tetrahydrofuran occurred to afford novel glycopolymers which could self-assemble into nanostructures.[156]

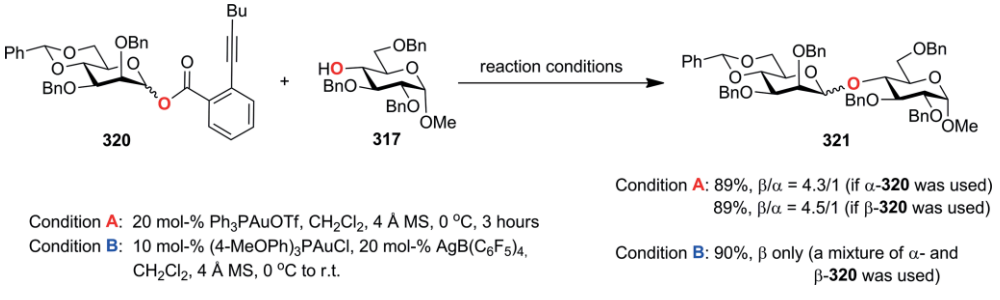
This gold(I)-catalyzed glycosylation using glycosyl *ortho*-alkynylbenzoates as donors was later successfully applied to the synthesis of a number of *O*-linked glycosides and glycoconjugates,[157] such as β-*N*-acetylglucosaminidases inhibitor TMG-chitotriomycin,[158] cyclic triterpene saponin,[159] kaempferol 3-*O*-(3′′,6′′-di-*O*-*E*-*p*-coumaroyl)-β-D-glucopyranoside,[160] nucleoside,[161] ginsenoside Rh2 and chikusetsusaponin-LT8,[162] kaempferol 3-*O*-(3′′,6′′-di-*O*-*E*-*p*-coumaroyl)-α-L-rhamnopyranosides,[163] lupane-type saponins,[164] digitoxin,[165] kaempferol 3,7-*O*-bisglycosides,[166] saponin P57,[167] *N*–*O* linked saccharides,[168] Starfish Saponin Goniopectenoside B,[169] diverse ginsenosides,[170] Nucleoside Antibiotic A201A,[171] Linckosides A and B,[172] astrosterioside A,[173] Tunicamycins,[174] immunosuppressant periploside A.[175]

Besides cationic $Ph_3PAuOTf$, during the course of research Yu and co-workers developed several versions of gold catalysts for the activation of glycosyl *ortho*-hexynylbenzoates, such as $Ph_3PAuNTf_2$, a Au^I π-bis(*tert*-butyldimethylsilyl)acetylene triphenylphosphine complex,[176] a polystyrene-bound triphenylphosphine gold(I) catalyst.[177]

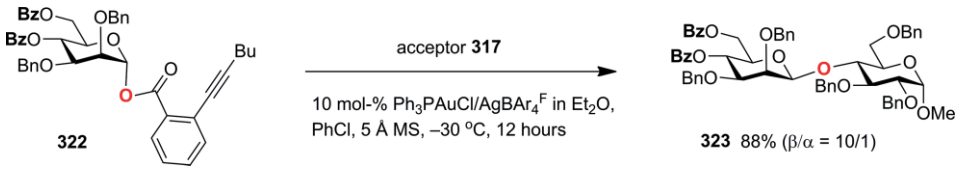
Recently, this homogeneous cationic gold(I) catalyst for *O*-glycosylation involving glycosyl *ortho*-alkynylbenzoates as donors has been employed in the stereoselective synthesis of β-mannopyranosides.[178] As shown in Scheme 58, while Yu and



Scheme 57. Gold(I)-catalyzed *O*-glycosylation with glycosyl *ortho*-alkynylbenzoate donors.



Scheme 58. Synthesis of 4,6-*O*-benzylidene protected β-mannopyranoside by gold catalysis.



Scheme 59. Synthesis of 4,6-di-*O*-benzoyl-protected β-mannopyranoside by gold catalysis.

co-workers found that glycosylation of 4,6-*O*-benzylidene protected (Crich-type) D-mannosyl *ortho*-alkynylbenzoate α- or β-donor **320** with acceptor **317** catalyzed by $Ph_3PAuOTf$ afforded desired β-mannopyranosides **321** in 89 % yield (β/α ratio, ca. 4:1, Condition A),[178a] Li and co-workers discovered the use of $(4\text{-}MeOPh)_3PAuB(C_6F_5)_4$ provided β-mannopyranosides **321** in 90 % yield (β only, Condition B).[178b] In addition, Li and co-workers applied this gold-catalyzed β-mannosylation to the synthesis of acremomannolipin A and its analogue.[178b]

In additin, Yu and co-workers observed that replacement of the triflate in gold(I) complex $Ph_3PAuOTf$ with less nucleophilic counter anions (e.g., $^-NTf_2$, $^-SbF_6$, $^-BF_4$, and $^-BAr_4^F$) led to complete loss of β-selectivity with the D-mannosyl *ortho*-alkynylbenzoate β-donors (cf. **320**-β). If D-mannosyl *ortho*-alkynylbenzoate α-donors (cf. **320**-α) were used, under the catalysis of $Ph_3PAuBAr_4^F$ {BAr_4^F = tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate} these mannosylation reactions were found to be highly β-selective and can tolerate a broad scope of substrates.[178a] For the *ortho*-alkynylbenzoate β-donors, an anomerization and glycosylation strategy can be employed to ensure the highly β-selective mannosylation. NMR experiments indicated that the 1-α-mannosyloxy-isochromenylium-4-gold(I) complex, generated upon activation of the α-mannosyl *ortho*-alkynylbenzoate with $Ph_3PAuBAr_4^F$ at –35 °C, accounts for the high β-selectivity of the mannosylation.

Interestingly, Yu and co-workers also found that 4,6-di-*O*-benzoyl-α-mannosyl *ortho*-hexynylbenzoate donor **322** without 4,6-*O*-benzylidene protecting group can also be employed as efficient glycosyl donor for the preparation of corresponding β-mannopyranoside **323** in excellent yield and anomeric selectivity (Scheme 59).[178a] It was found that the occurrence of 1-α-mannosyloxy-isochromenylium-4-gold(I) complex, generated upon activation of the α-mannosyl *ortho*-alkynylbenzoate (**322**) with $Ph_3PAuBAr_4^F$, accounts for the high β-selectivity in the mannosylation. Based on this observation, Yu and co-workers developed stereoselective synthesis of β-rhamnopyranosides via gold(I)-catalyzed glycosylation with α-rhamnopyranosyl 2-alkynyl-4-nitro-benzoate donors.[179]

Inspired by the work from the Yu group, Balamurugan and co-workers discovered a gold(III)-catalyzed glycosylation using glycosyl ester donors bearing branched bis-alkyne functionality, an readily accessible leaving group.[180] Evaluation of various copper, silver, gold, and platinum complexes indicated the a combination of $AuCl_3$ and $AgSbF_6$ was the optimal catalyst system for this glycosylation.

8.3.1.5 Gold(I)-Catalyzed Glycosylation with Stable Alkynyl Glycosyl Carbonates

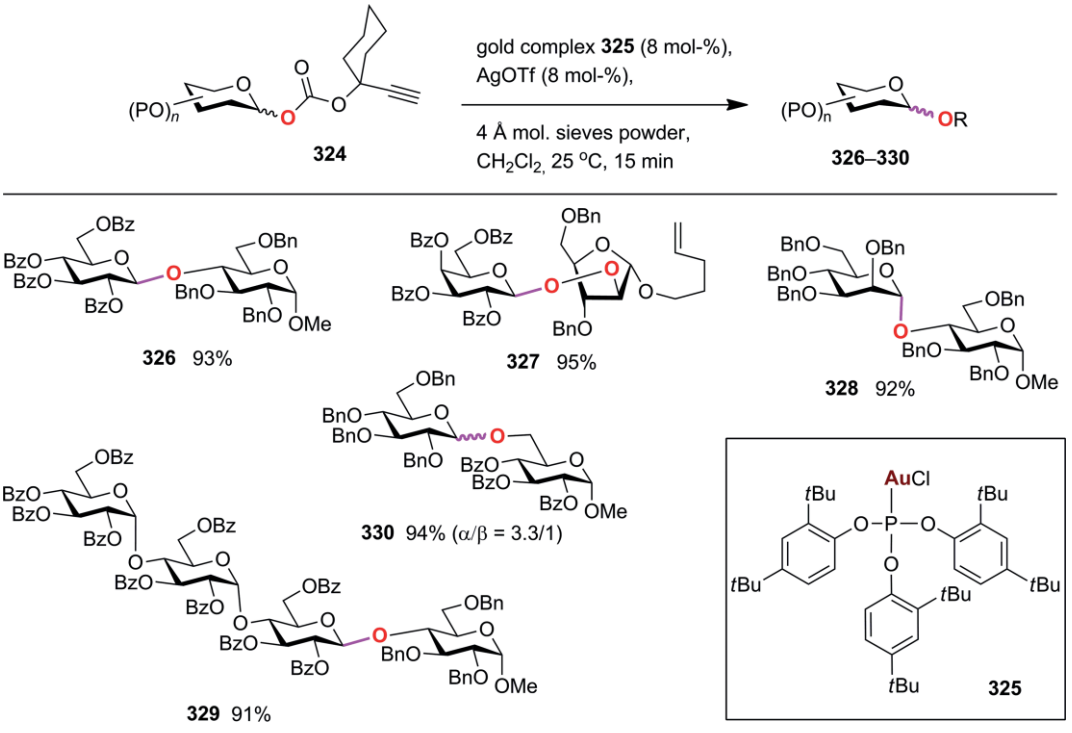
Early this year, Hotha and co-workers developed cationic gold(I)-catalyzed glycosylation using stable alkynyl glycosyl carbonate donors.[181] Previously, Yu and co-workers reported cationic gold can activate *ortho*-alkynyl esters but not 2-butynyl carbonates even at an elevated temperature.[159] Hotha reasoned that the failure to activate 2-butynyl carbonates may be attributed to the possible higher degree of freedom of the leaving group. Based on their observed acceleration of glycosylation by replacing propargyl with ethynylcyclohexyl glycoside donors owing to the well-understood Thorpe–Ingold effect,[137a] Hotha prepared a number of alkynyl glycosyl carbonate donors and found that those bearing 1,1-dialkylpropargyl glycosyl carbonate donors (e.g., **324**, Table 16) showed excellent reactivity towards activation by Au(III) and cationic Au^I. As shown in Table 16, under optimal condition (8 mol-% gold complex **325**, 8 mol-% AgOTf, powdered molecular sieves (4 Å), CH_2Cl_2, 25 °C, 15 min), various glycosyl donors bearing ethynylcyclohexyl carbonate functionality **324** reacted with glycosyl acceptors to afford corresponsing glycosides **326**–**329** in excellent yield and anomeric selectivity. In the absence of neighboring group participation, disaccharide **330** was obtained in 94 % yield as a mixture of α- and β-anomers. This operationally simple glycosylation method was utilized for the efficient synthesis of a variety of nucleosides, amino acids, phenolic and azido glycoconjugates, as well as highly convergent synthesis of tridecaarabinomannan reminiscent of mycobacterium tuberculosis cell wall lipoarabinomannan.[159]

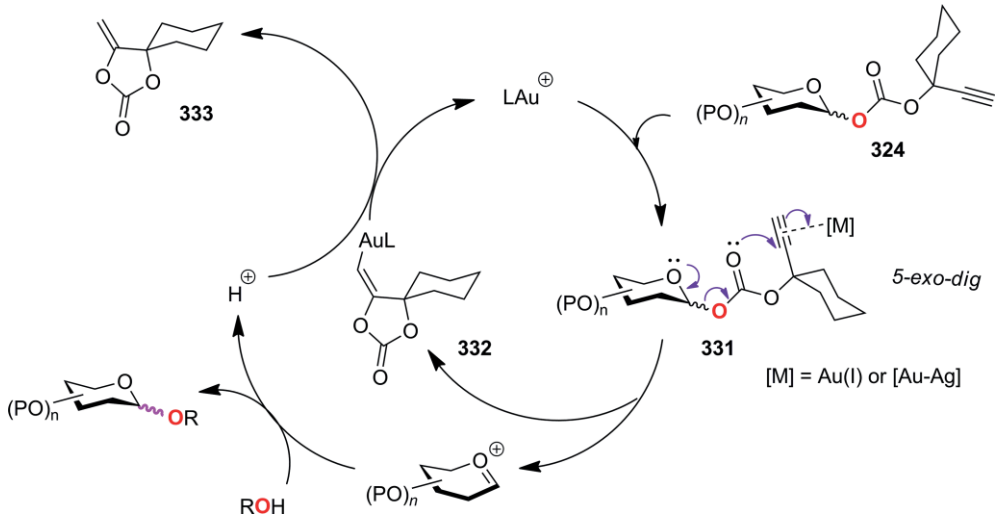
The proposed mechanism for this glycosylation is shown in Scheme 60. Activation of the alkyne group of the donor **324** by either cation gold(I) or Au–Ag complex followed by *5-exo-dig* attack of the anomeric oxygen and subsequent ionization affords the oxocarbenium ion and alkenylgold cyclic carbonate **332** (via intermediate **331**). Reaction of oxocarbenium ion with acceptor provides the *O*-glycosides as well as a proton. Protodeauration of alkenylgold cyclic carbonate **332** regenerates the gold(I) catalyst and cyclic carbonate **333**.

8.3.1.6 Gold(I)-Catalyzed Glycosidation with 1,2-Anhydrosugars

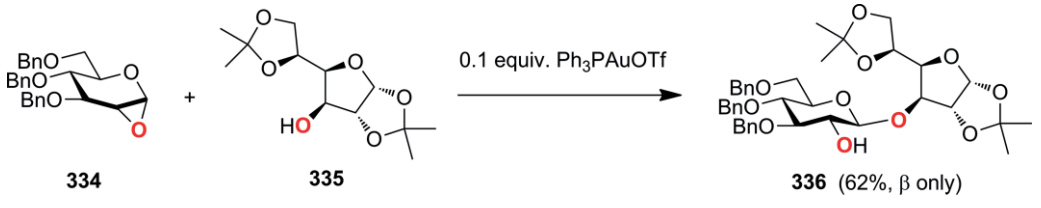
Yu and co-workers also discovered a gold(I)-catalyzed glycosylation of 1,2-anhydrosugars donors. As shown in Scheme 61, 1,2-anhydrosugars donor **334** reacted with acceptor **335** in the presence of 10 mol-% $Ph_3PAuOTf$ to give desired β-glycoside **336** with a free C2-hydroxyl group.[182] 1,2-Anhydrosugars (cf. **334**) can be prepared from corresponding glycals by DMDO epoxidation following known procedure[183] and were previously used in various Lewis acid promoted glycosylation. This glycosylation catalyzed by cationic gold(I) complex, $Ph_3PAuOTf$, was able to provide desired glycosides (cf. **336**) with significantly higher yield compared to the conventional use of anhydrous zinc chloride (> 1 equiv.) as a promoter.

Table 16. Gold(I)-catalyzed glycosidation with stable alkynyl glycosyl carbonates.





Scheme 60. Proposed mechanism.



Scheme 61. Gold(I)-catalyzed glycosylation with 1,2-anhydrosugar donors.

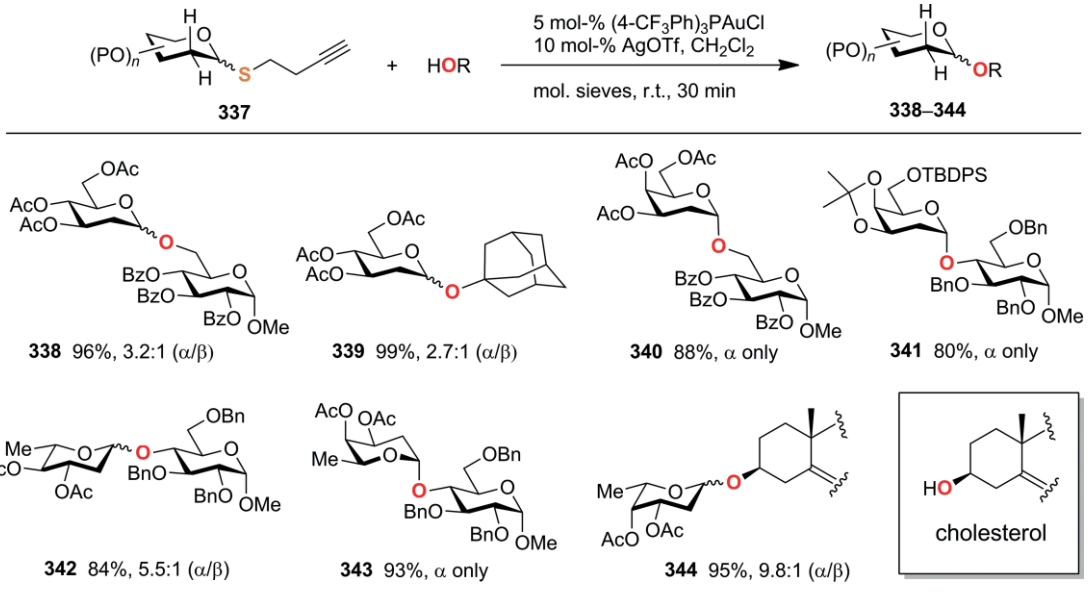
8.3.1.7 Gold-Catalyzed Synthesis of Glycosides Using S-But-3-ynyl Thioglycoside Donors

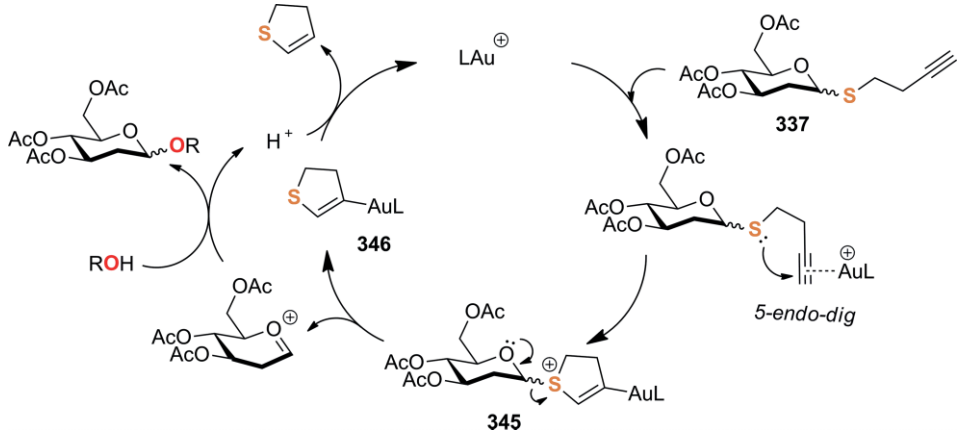
In 2012, Zhu and co-workers reported the use of 2-deoxy-*S*-but-3-ynyl thioglycoside donors (cf. **337**, Table 17) in cationic gold(I) catalysis for the synthesis of 2-deoxy-α-glycosides.[184] As depicted in Table 17, treatment of a mixture of 2-deoxy- or 2,6-dideoxy-*S*-but-3-ynyl thioglycoside donor **337** and alcohol acceptors with 5 mol-% $(4\text{-}CF_3\text{-}Ph)_3PAuCl$ and 10 mol-% AgOTf in the presence of molecular sieves (4 Å) in anhydrous CH_2Cl_2 at room temperature for 30 min afforded corresponding glycosides **338**–**344** in good to excellent yields and α-selectivity.

Based on the identification of 2,3-dihydrothiophene as by-product, Zhu and co-workers proposed a mechanism for this gold-catalyzed glycosylation. As shown in Scheme 62, activation of the alkyne functionality of *S*-but-3-ynyl thioglycoside **337** by cationic gold(I) catalyst followed by attack of *exo*-sulfur atom provides sulfonium ion **345**. Subsequent cleavage of the glycosidic bond of **345** results in the formation of oxocarbenium ion and 2,3-dihydrothiophen-4-yl-gold(I) complex **346**. Nucleophilic addition of alcohol acceptor to the oxocarbenium ion provides selectively desired 2-deoxy-α-glycosides and a molecule of triflic acid. Proto-deauration of 2,3-dihydrothiophen-4-yl-gold(I) complex **346** leads to the formation of 2,3-dihydrothiophene and regeneration of the cationic gold(I) catalyst.

In addition, Zhu and co-workers later reported the use of *gem*-dimethyl *S*-but-3-ynyl thioglycoside donors in gold catalysis for the synthesis of other types of glycosides (2-oxy- and 2-deoxy-2-amino sugars).[185] Experimental results indicate that *gem*-dimethyl *S*-but-3-ynyl thioglycoside donors are more reactive than their *S*-but-3-ynyl thioglycoside counterparts, probably due to the Thorpe–Ingold effect. Furthermore, Yu and co-workers disclosed the use of *ortho*-alkynylphenyl thioglycosides as a new type of glycosylation donors under the catalysis of gold(I) complexes.[186]

Table 17. Gold-catalyzed synthesis of 2-deoxy-α-glycosides using *S*-but-3-ynyl thioglycoside donors.





Scheme 62. Proposed mechanism.

8.3.1.8 Gold-Catalyzed Activation of O-Glycosyl Trichloroacetimidate Donors

In 2009, Kunz and co-workers reported the use of Au^{I} chloride, a soft Lewis acid, for activation of glycosyl halides and glycosyl trichloroacetimidates.[187] In particular, this AuCl-catalyzed *O*-glycosylation using glycosyl trichloroacetimidate donors was found to tolerate acid-sensitive protecting groups.

Recently, Schmidt described the use of gold(III) chloride as catalyst for *O*-glycosyl trichloroacetimidate activation.[188] As shown in Table 18, premixing of $AuCl_3$, molecular sieves, and alcohol acceptors in dichloromethane followed by addition of α-glycosyl trichloroacetimidate donors **347** at –70 °C afforded corresponding β-glycosides (e.g., **348**–**350**) in good to excellent yields and excellent anomeric selectivity. However, use of α-D-mannosyl trichloroacetimidate donors in this type of reaction provided only α-D-mannoside **351** in good yield. This glycosylation also tolerates partially protected glycosyl acceptors to furnish desired β-glycosides (e.g., **352**–**354**) in good to excellent yields and excellent anomeric selectivity.

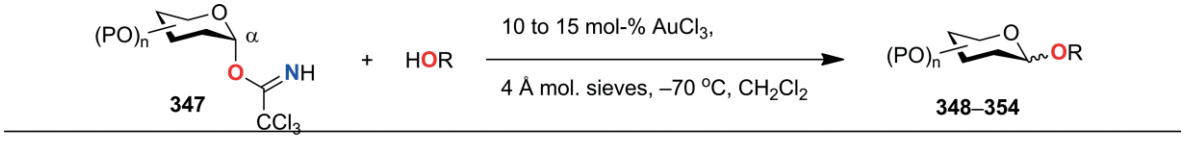
It was discovered that catalyst (AuCl or $AuCl_3$) showed low affinity to the glycosyl donor but high affinity to the hydroxy group of the acceptor alcohol moiety, thus leading to catalyst–acceptor adduct formation (Scheme 63). It is believed that charge separation in this catalyst–acceptor adduct increases the proton acidity and the oxygen nucleophilicity. Interaction of this catalyst–acceptor adduct with glycosyl trichloroacetimidate donors leads to transition state **355** which enables acceptor transfer in a hydrogen-bond mediated S_N2-type reaction to afford the β-glycoside as major anomer.

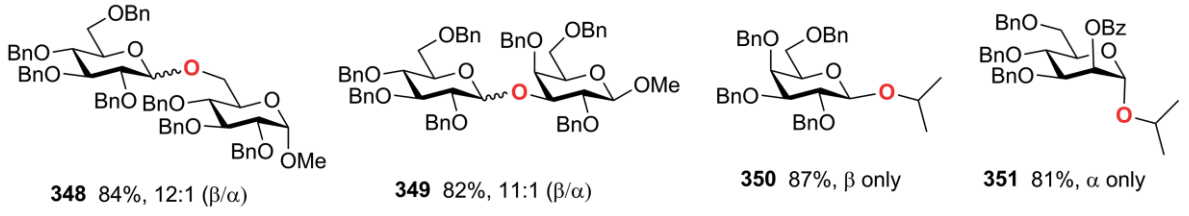
Catalytic activation of glycosyl trichloroacetimidate donors by $AuCl_3$ or $AuCl_3$-phenylacetylene was also reported by Vankar and co-workers.[189] It was found that the $AuCl_3$–phenylacetylene catalyst provided the desired glycosides in higher yields in most cases. In addition, Vankar and co-workers demonstrated that Au(III) halide-phenylacetylene catalyst system was also able to activate 1-*O*-acetylfuranoses and pyranose 1,2-orthoesters for glycosylations.[190] It was proposed by the authors that Au(III) halide forms a relay catalyst entity with phenylacetylene and this AuX_3/phenylacetylene complex activates the anomeric trichloroacetimidate, acetate, or 1,2-orthoester. Furthmore, Balamurugan and Koppolu reported a $AuCl_3$-catalyzed Ferrier-type *O*-glycosylation using per-*O*-acetylated glycal donors.[191]

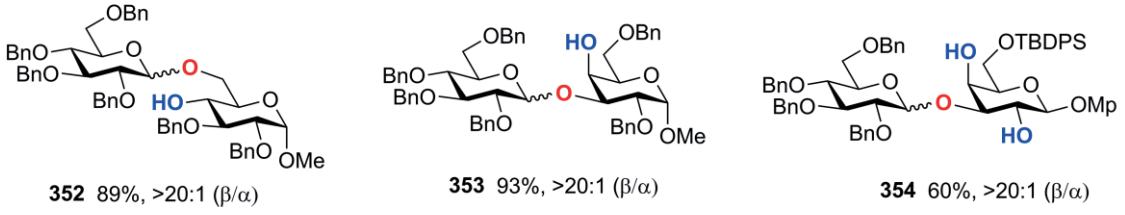
8.3.2 Synthesis of N-Glycosides by Au Catalysis

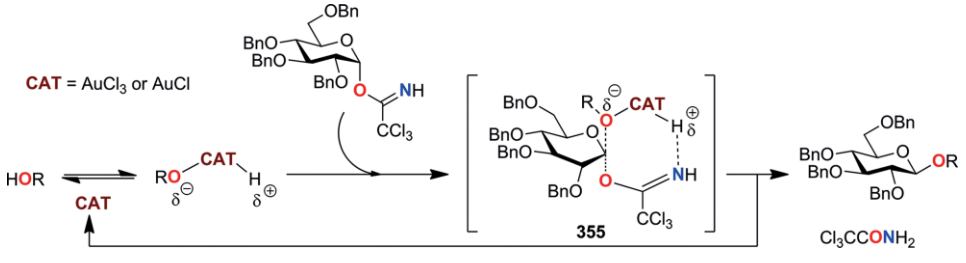
Although there have intense studies on the *O*-glycosylation using gold catalyst, synthesis of *N*-glycosides by Au catalysis has been rare. In 2012, Yu and co-workers reported the synthesis of 2′-deoxy-β-ribonucleosides via gold-catalyzed stereoselective

Table 18. $AuCl_3$-catalyzed synthesis of *O*-glycosides using glycosyl trichloroacetimidate donors.

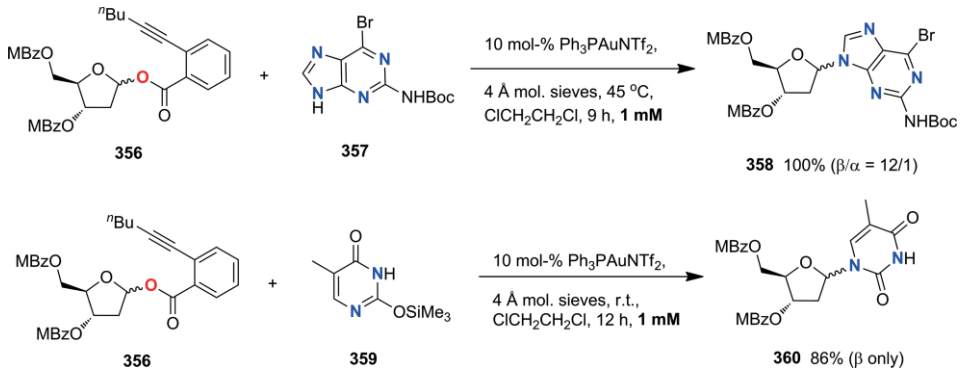




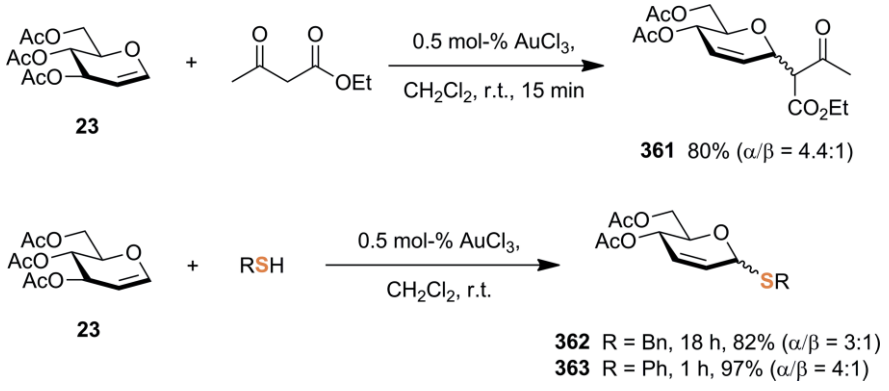




Scheme 63. Proposed mechanism.



Scheme 64. Synthesis of 2′-deoxy-β-ribonucleosides via gold-catalyzed stereoselective *N*-glycosylation.



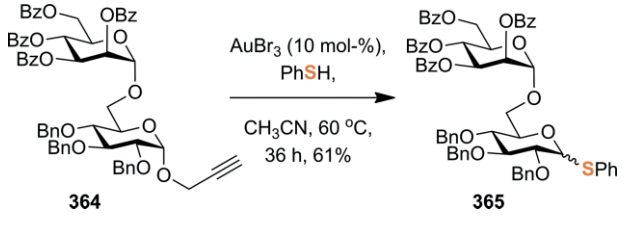
Scheme 65. Synthesis of 2,3-unsaturated *C*- and *S*-glycosides by gold catalysis.

N-glycosylation.[192] As shown in Scheme 64, in the presence of 10 mol-% $Ph_3PAuNTf_2$ as catalyst, 3,5-di-*O*-*p*-methoxybenzoyl-D-ribofuranosyl *ortho*-hexynylbenzoate **356** reacted with purine-derived base 357 and silylated pyrimidine-derived base **359** at low concentration (1 mM) to afford desired 2′-deoxy-β-ribonucleosides **358** and **360** in excellent yield and anomeric selectivity, respectively. It is believed that the high β-selectivity is attributed to the low-concentration facilitated remote-participation of 3-*O*-*p*-methoxybenzoyl group. In fact, it was found that increasing the concentration leads to the dramatic loss of the stereoselectivity.

8.3.3 Synthesis of C- and S-Glycosides by Au Catalysis

$AuCl_3$-catalyzed Ferrier type *C*- and *S*-glycosylation strategy was recently reported by Balamurugan and Koppolu.[191] During their attempts to access 2,3-unsaturated *O*-glycosides, they investigated the use of carbon- and sulfur nucleophiles in the gold-catalyzed Ferrier reaction for the synthesis of 2,3-unsaturated *C*- and *S*-glycosides. As shown in Scheme 65, in the presence of 0.5 mol-% $AuCl_3$ catalyst, tri-*O*-acetyl-D-glucal **23** reacted with ethyl acetoacetate to give 2,3-unsaturated *C*-glycoside **361** in 80 % yield (α/β = 4.4:1). Use of benzyl thiol or thiophenol as nucleophiles afforded 2,3-unsaturated *S*-glycoside **362** and **363** in good to excellent yields with moderate anomeric selectivity. This method also tolerates other types of glycals, such as D-galactal and L-rhamnal.

Synthesis of *S*-linked glycosides (thioglycosides) via gold catalysis using propargyl glycoside donors was also reported by Hotha and co-workers.[193] As shown in Scheme 66, in the presence of 10 mol-% gold(III) bromide, propargyl glycoside **364** reacted with thiophenol to afford corresponding phenyl thioglycosides **365** in 61 % yield as a mixture of α- and β-isomers. Similarly, synthesis of *S*-linked glycosides and 1-thiotrehaloses was also accomplished by Hotha and co-workers using propargyl 1,2-orthoester donors via gold catalysis.[194]



Scheme 66. Synthesis of *S*-linked glycosides using propargyl glycoside donors.

8.4 Summary

The group 11 (Cu, Ag, Au) complexes have been applied as mild oxophilic Lewis acid catalysts for activation of oxygen-containing leaving groups. In addition, based on well-developed Chan–Lam–Evans coupling, copper(II) acetate was used as the efficient catalyst in stereoselective synthesis of β-*N*-aryl glycosides. The utilization of gold catalysts in glycosylation has mainly focused on the activation of glycosyl donors with various carefully de-

signed alkyne-containing leaving groups under mild conditions, which may provide opportunities for orthogonal glycosylations. However, in many cases the relatively high loading of gold catalysts limits their practicality in the scaling up the carbohydrate building blocks.

9. Conclusions and Outlook

Unlike traditional glycosylations involving the use of stoichiometric amounts of promoters, transition metal catalysis has opened a new venue for activation of glycosyl donors for stereoselective synthesis of a variety of complex *O*-, *N*-, *C*-, and *S*-linked oligosaccharides and glycoconjugates. Use of transition metal catalysis has provided efficient, mild, and easily operable approaches for stereoselective glycosylations, minimized the generation of chemical waste, and enriched the "toolbox" for orthogonal glycosylation strategies through chemoselective activation of the anomeric leaving group. In addition, the anomeric selectivity of glycosylations can be controlled by transition metal complexes, rather than depending on the stereochemical nature and protecting groups of the glycosyl donors and acceptors.

Group 3 metal complexes, especially scandium and lanthanide triflates, have been widely used as environmentally friendly and water-tolerant Lewis acid catalysts for various glycosylations via different activation mechanisms. It was found that scandium triflate is a stronger Lewis acid in comparison with lanthanide triflates and is able to accelerate the reaction rate or activate less reactive glycosyl donors. Due to their less Lewis acidity, lanthanide triflates, such as $Yb(OTf)_3$, are more selective and able to achieve regioselective glycoyslations when acceptors bearing more than one unprotected alcohols.

Group 4 transition metal, including titanium, zirconium, and hafnium, complexes have been explored for glycosylations. By taking advantage of its oxophilic nature, Kobayashi used titanium catalyst for the synthesis of 1,2-*cis*-β-*O*-arabinofuranosides and later Mahrwald employed catalytic amounts of titanium *tert*-butoxide and mandelic acid for the synthesis of *O*-furanoid glycosides from uprotected and unactivated carbohydrates and simple alcohols. In addition, Reddy and Venkateswarlu used zirconium(IV) chloride and Zhao employed hafnium(IV) triflate for the synthesis of 2,3-unsaturated *O*-, *N*-, *C*-, and *S*-glycosides via catalytic Ferrier rearrangement. Furthermore, hafnium(IV) triflate-catalyzed decarboxylative glycosylation for the β-selective synthesis of glycosides from acyl-protected sugar donors was also developed by Ikegami and co-workers.

Use of group 7 transition metals for catalytic glycosylation has limited to the element rhenium. The Toste group initially used oxophilic Re^V complex for the synthesis of 2-deoxy-α-*O*- and *S*-glycosides as well as 2-deoxy-β-*N*-glycosides from glycals bearing C3-equatorial substituents. Inspired by Toste's work, the Zhu group was able to prepare β-*O*- and *S*-linked digitoxosides from 6-deoxy-D-allals bearing C3-axial substituents. The anomeric selectivity in Re^V-catalyzed glycosylation relies on the stereochemical nature of the substrates.

Among the group 8 transition metals, limited studies have been reported using iron (Fe) and ruthenium (Ru) catalysts for the synthesis of *O*-, *N*-, and *C*-glycosides. For instance, iron(III) and ruthenium(III) salts were utilized as catalysts for synthesis of 2,3-unsaturated *O*-glycosides via Ferrier rearrangement, as reported by Zhang and Kashyap, respectively. In addition, Chen disclosed the synthesis of glycosyl azides catalyzed by $FeCl_3$. Based on recent development of using ruthenium complexes in visible-light photoredox catalysis, Ragains reported a mild ruthenium-catalyzed activation of selenoglycoside donors for the selective synthesis of 1,2-*cis*-α-pyranosides, while Gagné and Xue used ruthenium catalysts for the synthesis of α-*C*-glycosides as well as α-glycosyl bromides.

Use of group 9 transition metals for glycosylation has also not been well explored. As to cobalt, use of oligomeric cobalt (Co) salen catalyst for activation of glycosyl trichloroacetimidate donors for the synthesis of *O*-glycosides has been the only example as reported by Galan. Another member of this group, rhodium (Rh), has solely been used by Maddaford for synthesis of *C*-glycosides via rhodium(I)-catalyzed 1,4-addition of aryl or alkenyl boronic acids to glycal-derived enones. Recently, Bowers utilized iridium (Ir) complex as visible-light photoredox catalyst for *O*-glycosylation.

Nickel and palladium, two group 10 elements, have been extensively studied for the synthesis of complex *O*-, *N*-, *C*-, and *S*-glycosides during the past a few decades, while there was only one report involving the use of platinum (Pt) complex in the preparation of 2-*C*-branched *O*-glycosides. By taking advantage of the aza-philic nature of cationic nickel complexes, The Nguyen group has applied cationic nickel complexes in the efficient and stereoselective synthesis of 1,2-*cis*-2-deoxy-2-amino-*O*-glycosides and glycosyl ureas. In addition, nickel catalysts have also been employed by Marsden and Gagné to prepare *C*-glycosides through coupling of glycosyl halides with organometallic reagents or activated alkene radical acceptors. Based on the power of palladium complexes in the formation of palladium π-allyl species, palladium catalysts have been widely used for stereoselective *O*-glycosylations. The low reactivity of glycals in the formation of palladium π-allyl species can be tuned by employing more reactive leaving groups at C3, such as trifluoroacetate (RajanBabu), acetate (Lee), trichloroacetimidate (Nguyen), picoloyl (Liu), and carbonate (Liu, via decarboxylative allylation). In addition, due to the low reactivity of Pd–π-allyl complexes formed from glycals, several strategies have been invented to solve such a challenge: 1) use of activated cyclic pyranones for generation of more electrophilic Pd–π-allyl complexes reported by Feringa and O'Doherty; 2) use of zinc(II) alkoxide acceptors as more reactive nucleophiles in glycosylations (Lee); 3) use of decarboxylative allylation strategy to facilitate the glycosidic bond formation (Liu). Besides the utilization of palladium π-allyl species for glycosylation, use of cationic palladium(II) catalysts for activation of glycosyl trichloroacetimidate was also demonstrated by Nguyen for the direct synthesis of β-glycosides in the absence of classical C2-ester–induced neighbouring group participation. Palladium catalysts have also been used for the synthesis of *N*-glycosides, e.g., *N*-glycosyl trichloroacetamides and ureas (Nguyen), and β-*N*-glycosyl imidazole analogues (Liu). Synthesis of *C*-glycosides via palladium-catalyzed decarboxylative allylation,cross coupling of glycals or 1-substi-

tuted glycal derivatives, or C–H functionalization have been extensively investigated by many research groups, such as Liu, RajanBabu, Maddaford, Yang, Ye, Tius, Beau, Friesen, Werz, Miyaura, Minehan, Tan, Nicolaou, and Hayashi. However, there have only few examples involving the use of palladium catalysts for the synthesis of *S*-glycosides.

While there are some reports on the use of catalytic amounts of copper and silver complexes for the synthesis of *O*- and *N*-glycosides, main efforts involving the group 11 transition metal catalysts in the synthesis of *O*-, *N*-, *C*-, and *S*-glycosides has focused on the gold complexes. As to the copper-catalyzed glycosylation, Hiroi reported copper-catalyzed synthesis of 1,2-*trans*-β- and 1,2-*cis*-α-ribofuranosides, and Alami and Messaoudi described stereoselective synthesis of β-*N*-aryl glycosides via copper-catalyzed Chan–Lam–Evans coupling. Due to the well-known high affinity of gold complex to alkynes, gold catalysts have been widely employed for the stereoselective synthesis of *O*-glycosides via chemoselective activation of a number of alkyne-containing glycosyl donors, such as propargyl glycosides, propargyl 1,2-orthoesters, and conformationally restricted alkynyl glycosyl carbonates as reported by Hotha, *ortho*-alkynylbenzoate donors and *ortho*-alkynylphenyl thioglycosides reported by Yu, *S*-but-3-ynyl thioglycoside donors developed by Zhu, glycosyl ester donors bearing branched bis-alkyne functionality described by Balamurugan. A few other types of glycosyl donors, such as stable methyl glycoside donors (Hotha), 1,2-anhydrosugars (Yu), and *O*-glycosyl trichloroacetimidate donors (Kunz and Schmidt), can also be activated by gold catalysis for stereoselective synthesis of *O*-linked glycosides. In addition, some studies on gold-catalyzed synthesis of *N*-, *C*-, and *S*-linked glycosides has also been reported by Yu, Balamurugan, and Hotha.

Despite such remarkable success, there are several challenges and opportunities in the development of transition metal catalysis for glycosylations: 1) As discussed above, a majority of efforts involving transition metal catalysis in glycosylations have focused on the late transition metal complexes, such as nickel, palladium, and gold. In contrast, use of early and middle transition metals has not been extensively explored in glycosylations. How to discover new reactivity of cheap and earth abundant transition metals, such as iron (Fe), titanium (Ti), and manganese (Mn) and utilize them in catalytic stereo-, regio- and chemo-selective glcosylations is of a challenge. 2) To the best of our knowledge, no transition metal catalyzed glycosylation has been utilized in the solid phase synthesis of complex carbohydrate structures thus far. Therefore, development of suitable glycosylation methods involving transition metal catalysis for solid phase carbohydrate synthesis is surely of particular interest and also poses a challenge to the synthetic chemists. 3) Development of solid-supported transition metal complexes, especially those from precious metals, for efficient glycosylation is appealing and challenging, as recycling precious and expensive transition metals would greatly save the cost and improve the practicality of such glycosylation processes. As an excellent example, Yu has developed a polystyrene-bound triphenylphosphine gold(I) catalyst for glycosylation.[177] 4) Despite some success, use of transition metal catalysis for stereoselective construction of challenging glycosidic linkages, such as 2-deoxy-α- and β-glycosides, 1,2-*cis*-glycosidic linkages (e.g., α-glucosides and β-mannosides), and α-sialosides, has been rather limited. Such a challenge also poses a great opportunity for synthetic chemists to develop new transition metal-catalyzed glycosylations for stereoselective construction of those difficult glycosidic linkages.

As looking forward, development of cooperative transition metal catalysis and organocatalysis[195] for synergistic stereo-, regio- and chemoselective glycosylations would also be appealing. An eminent example by O'Doherty has demonstrated the use of palladium catalyst in conjunction with borinic acid catalyst for regio- and stereoselective glycosylations.[85] In addition, strategic combination of efficient catalytic chemical glycosylation and enzymatic syntheses[196] would be a great approach to access complex oligosaccharides and glycoconjugates, such as complex glycoproteins, for biological studies.

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