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Recent Advances in Transition Metal-Catalyzed Glycosylation

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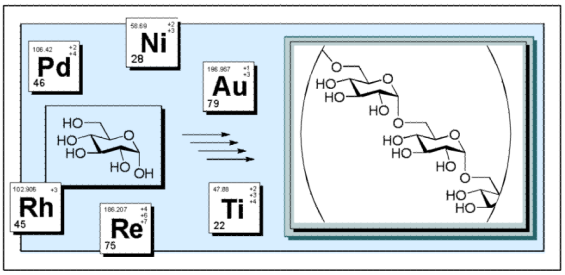
Abstract



Having access to mild and operationally simple techniques for attaining carbohydrate targets will be necessary to facilitate advancement in biological, medicinal, and pharmacological research. Even with the abundance of elegant reports for generating glycosidic linkages, stereoselective construction of α- and β-oligosaccharides and glycoconjugates is by no means trivial. In an era where expanded awareness of the impact we are having on the environment drives the state-of-the-art, synthetic chemists are tasked with developing cleaner and more efficient reactions for achieving their transformations. This movement imparts the value that prevention of waste is always superior to its treatment or cleanup. This review will highlight recent advancement in this regard by examining strategies that employ transition metal catalysis in the synthesis of oligosaccharides and glycoconjugates. These methods are mild and effective for constructing glycosidic bonds with reduced levels of waste through utilization of sub-stoichiometric amounts of transition metals to promote the glycosylation.

Keywords

transition metals; carbohydrates; glycosylation; anomeric selectivity

1. INTRODUCTION

The field of glycobiology has exploded in the last few decades, identifying oligosaccharides and glycoconjugates to serve critical roles in a wide range of biological processes. The rapid expansion of knowledge surrounding the function of carbohydrates has led to increasing attention from biological, medicinal, and pharmacological study. To meet their demands, investigators require access to significant quantities of well-defined bioactive carbohydrates. This necessity has prompted resurgence in synthetic interest, with a predominant focus on new approaches to the glycosidic bond. Despite the numerous elegant strategies and methods developed for the efficient formation of glycosidic linkages,[1-7] stereoselective construction of α- and β-glycosides remains challenging. Most of the current methodology

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relies on the nature of the substrate's protecting groups to control selectivity during formation of glycosidic bonds. In addition, most coupling scenarios require stoichiometric amounts of activating agents to sufficiently activate glycosyl donors, resulting in the excessive waste of materials. Furthermore, some of these activating agents can be air- and moisture-sensitive and must be used under strictly anhydrous and low temperature conditions, especially if the glycosyl donors or acceptors incorporate acid-labile protecting groups. In some glycosylation methods, water must be removed azeotropically from glycosyl donors and acceptors prior to the coupling reaction.

With the recent development of automated solid phase carbohydrate synthesis by Seeberger[8,9] and fluorous-based carbohydrate microarrays by Pohl,[10,11] mild, room-temperature, and less anhydrous reaction conditions, in conjunction with sub-stoichiometric amounts of activating agents, could further advance the field of carbohydrate chemistry. In this review article, we highlight recent advances in transition metal-catalyzed glycosylation. The use of these transition metal catalysts is conducive to achieving "greener" chemistry, where air- and moisture-tolerance, performance at room temperature, and enhanced synthetic efficiency through reduction of unnecessary waste is attained. In some methods, the ligand-transition metal complex system provides stereocontrol during the glycosylation, rather than the nature of protecting groups on the substrate. As stated by Schmidt in a recent review on glycosylation,[12] "there are three main requirements for an efficient glycosylation method: 1) small amounts of the reagents must be used; that is, the glycosyl donor must be generated in a simple process and the donor activated by a catalytic amount of reagent; 2) the glycosylation step must be stereoselective and high-yielding; and 3) the method must be applicable on a large scale." The methods presented in this review largely satisfy these tenets, providing mild and operationally simple conditions that could potentially allow for the full utilization of solid phase and fluorous chemistry to overcome the long standing problems in the field, in contrast to peptide and DNA synthesis where automated techniques have been employed for decades.

The following review will be divided into four sections based on the type of donor used in the reaction. The first will be the transition metal-catalyzed activation of glycosyl donors with trichloroacetimidate, *O*-alkynyl-benzoate, and halide leaving groups, the second will cover donors with methyl and propargyl leaving groups, the third will cover glycal-derived donors, and the final will cover 1-hydroxy sugar donors. This review will only discuss the transition metal-catalyzed glycosylation of carbon and oxygen nucleophiles.

2. GLYCOSYL TRICHLOROACETIMIDATE, ORTHO-ALKYNYL-BENZOATE, AND HALIDE DONORS

Significant advancement has been made to the elaboration of carbohydrates in recent years. Transition metal catalysis is helping enable chemists to install anomeric functionality without being confined to neighboring participation or anomeric effect to direct orientation at the newly formed glycosidic bond. Remarkable anomeric selectivities and yield can be achieved through careful selection of ligand-catalyst complex systems to activate glycosyl donors. The increased reaction efficiency is a natural consequence of the mild activation strategies, where undesired lateral reactivity can be kept to a minimum. The following section details recent advances to glycosylation strategies involving the mild activation of trichloroacetimidate, *ortho*-alkynyl benzoate, and halide donors.

2.1 Trichloroacetimidate Donors

Since Schmidt first developed his glycosylation protocol in the 1980s,[13-15] the trichloroacetimidate leaving group has been one of the most widely used glycosyl donors;[16]

its popularity stemming from ease of preparation via base-catalyzed addition of trichloroacetonitrile to the anomeric hydroxyl group.[17-19] The glycosyl trichloroacetimidate is usually activated with strong and moisture-sensitive Lewis acids such as $BF_3{\cdot}OEt_2$,[13,20,21] TMSOTf,[17,22-25] TBSOTf,[26] Tf_2O,[27] and $ZnBr_2$.[28] However, there are drawbacks to their use in glycosylation, such as low reaction temperature requirements for avoiding decomposition of acid-sensitive substrates and anhydrous reaction conditions. More recently, $LiClO_4$[29] and LiOTf[30] have been demonstrated to effectively activate glycosyl trichloroacetimidates, though a significant excess of the potentially explosive $LiClO_4$ is required with the former, and a mixture of α- and β-glycosides is achieved with the latter. Therefore, methodology using transition metal catalysts to activate trichloroacetimidates for selective construction of glycosidic linkages is highly desirable. The following section details recent advances in this regard from the Nguyen group.

A. Palladium Catalysis

I) Pd(II)-Catalyzed *Trans*-Selective Glycosylation: Due to its relative moisture and air-stability, ease in handling, and commercial availability, the cationic $Pd(CH_3CN)_4(BF_4)_2$ catalyst[31] was the first explored for activation of glycosyl trichloroacetimidates.[16] Accordingly, α-D-mannopyranosyl donor **1** (Table 1) was reacted with benzyl alcohol in the presence of 5 mol% $Pd(CH_3CN)_4(BF_4)_2$, affording 85% (entry 1) of glycoside product **2** as the α-isomer, exclusively. Prompting further investigation, 20 mol% of an acid scavenger di-*tert*-butylpyridine was added (entry 2) to determine if HBF_4, (possibly formed in the reaction), was responsible for activation of the glycosyl trichloroacetimidate. This addition resulted in no change to the yield or selectivity observed in the reaction. Another control experiment was conducted with a neutral Pd(II) species (entry 3), $Pd(PhCN)_2Cl_2$. Here, only trace formation of **2** was observed, illustrating the importance of the cationic palladium catalyst for activation of the trichloroacetimidate.

With optimized conditions in hand, a variety of alcohol acceptors (Table 2) were screened in the glycosylation protocol. Reaction of donor **1** with secondary carbohydrate acceptor **3** resulted in formation of the desired disaccharide **4** (entry 1) in excellent yield (94%) and exclusively as the 1,2-*trans*-configured products. Similar results were attained during reactions with L-rhamnose donor **5** (entry 2), providing the α-linked disaccharide **7** upon treatment with carbohydrate acceptor **6**. Installation of a C(2)-participating group on glucose donors **8** and **11** (entries 3 and 4) provided **10** and **13** in 70 – 92% with exclusive β-selectivity. Similar glycosylation of dihydrocholesterol acceptor **15** (entry 5) with per-*O*-benzylated galactose trichloroacetimidate donor **14** provided the corresponding β-glycoconjugate **16** in 80% yield.

II) 2nd Generation Pd(II)-Catalyst: To further demonstrate the efficacy of the commercially available palladium catalyst, $Pd(CH_3CN)_4(BF_4)_2$, in activating the anomeric trichloroacetimidate leaving group, per-*O*-benzylated glucose trichloroacetimidate donor **17** (Scheme 1) was screened in the condition as well. To this end, reaction of donor **17** with carbohydrate acceptor **18** (entry 1) resulted in formation of disaccharide **19** in 72% yield as a 1:7 α/β-mixture. This result demonstrates the ability of the cationic palladium catalyst to direct formation of β-disaccharides in the absence of a neighbor participating group.

While attempting to improve the β-selectivity in the reaction, the activity of the $Pd(CH_3CN_4)(BF_4)_2$ catalyst was discovered to be highly temperature dependant. The reactions became sluggish at 0°C and little conversion was observed at −78°C. This observation, in consideration with the relatively high expense of the commercial catalyst, prompted the authors to pursue alternative cationic palladium(II) species for the transformation. Knowing that weakly-coordinated counterions can increase transition metal

catalyst activity,[32] a second generation catalyst was developed to enhance the β-selective nature of this reaction.[33] Accordingly, cationic $Pd(PhCN)_2(OTf)_2$ (Table 3), generated *in situ* from neutral $Pd(PhCN)_2Cl_2$ and AgOTf, was explored. AgOTf was chosen in this study for its relative ease of handling in comparison with other silver salts. Upon treatment of donor **17** with the carbohydrate acceptor **18** in the presence of 2 mol% $Pd(PhCN)_2(OTf)_2$ at 25°C (entry 1), 98% yield of disaccharide **19** was obtained as a 1:1 α/β-mixture. Lowering the reaction temperature to 0°C (entry 2) offered no improvement to this selectivity, though further reduction to −78°C (entry 3) significantly improved β-selectivity (1:10 α/β-mixture). Overall, there is an increase in yield and β-selectivity of **19** over higher loading with the first generation cationic palladium catalyst, $Pd(CH_3CN)_4(BF_4)_2$. An explanation for this elevated selectivity is that the coupling reaction may proceed through an oxocarbenium intermediate at 0°C, resulting in a 1:1 α/β-mixture of products, as opposed to −78°C, where the reaction likely proceeds through an S_N2-type reaction.

The substrate scope of the $Pd(PhCN)_2(OTf)_2$ catalyzed β-selective glycosylation was explored with a number of donors and acceptors (Table 4). Reaction of **17** with dihydrocholesterol **15** (entry 1) provided glycoconjugate **20** in 85% yield as a 15:1 β/α-mixture. Coupling of hindered tertiary alcohol **22** (entry 2) with glycosyl donor **17** provided disaccharide **22** as the β-isomer, exclusively. Donor **23** (entries 3 and 4), bearing a C(2)-allyl ether group, was able to facilitate formation of disaccharides **24** and **26** in 82 – 99% with excellent β-selectivity. This result was encouraging because it suggests the ability of the Pd(II) catalyst to coordinate trichloroacetimidate nitrogen in the presence of the allyl group. screened next under the palladium condition was the benzylated D-xylose donor **27** (entries 5 and 6) and the D-quinnovose donor **30** (entries 7 and 8), substrates which lack the C(6)-hydroxyl group and are found in a variety bioactive oligosaccharides.[34-36] These donors were able to provide the corresponding disaccharides (**28**-**27**, Table 4).

A limitation common to many glycosylation protocols is that while they may be effective for constructing disaccharides, they often break down during oligosaccharide formation. To test the current method for its utility in oligosaccharide synthesis (Scheme 2), glycosyl donor **17** was reacted with the disaccharide acceptor **33** to provide trisaccharide **34** in 71% yield and with β/α = 12:1.

III) β-*O*-Aryl Glycoside Formation in the Absence of C(2)-Ester Participating Group:
The palladium-catalyzed glycosylation methodology was extended to construction of β-*O*-aryl glycosides[37] due to recent discovery of the anti-tumor, anti-HIV, and antibiotic activities that these compounds exhibit.[38] It is worth mentioning that attaining these structures can be quite problematic for a variety of reasons. First, the electron-withdrawing nature of the aryl ring attenuates nucleophilicity of phenol acceptors. Second is the competing rearrangement of *O*-aryl glycosides to their corresponding *C*-aryl counterparts. Finally, difficulties associated with steric interference from aryl ring substituents make certain substrates unreactive in many glycosylation protocols.[39-42] Also, these reactions can be highly sensitive to electronic properties of substituted aryl alcohols, limiting scope to specific phenol nucleophiles.[43]

The Nguyen group explored the optimal conditions for formation of β-*O*-aryl glycosides (Table 5). Based on prior success with the catalyst,[16] per-*O*-benzylated donor **17** was treated with 2-naphthol **35** in the presence of 2 mol % of $Pd(PhCN)_2(OTf)_2$ (entry 1) at −78°C,[16,33] providing the desired *O*-aryl glycoside **36** in 60% yield with 2:1 β/α selectivity. A further increase in temperature to 25°C accelerated the rate of the reaction, but did not affect anomeric selectivity. Switching to the commercially available $Pd(CH_3CN)_4(BF_4)_2$ (entry 3) proved optimal for the transformation, affording **36** in 80% yield with excellent β-selectivity (β/α= 11:1). A further attempt to enhance β-selectivity was examined by reducing the

temperature to 0°C, but once again the condition would fail to result in appreciable catalytic turnover. Compared to AgOTf and BF_3-OEt_2 (entries 4 and 5), both shorter reaction times and higher yields and β-selectivities are observed with this system.[34-36] The scope of the reaction was established by screening different phenols and glycosyl donors (Table 6). Sterically hindered 2-methylphenol **37** (entry 1) and 2,6-dimethylphenol **39** (entry 2) successfully coupled with **17** to provide **38** and **40**, respectively, in 75% yield and with excellent anomeric selectivity (10:1–11:1 β/α). Attempts to showcase the generality of this methodology prompted reactions with D-galactose donor **41** (entries 3 and 4) and D-xylose donor **27** (entries 5-8). The desired glycoconjugates were obtained in good yield and with exclusive β-selectivity.

B. Nickel Catalysis in the Stereoselective Synthesis of 1,2-Cis-2-Amino Glycosides—Glycoproteins are one of the most important classes of naturally occurring molecules.[22] C(2)-aminosugars are a key component of glycoproteins which are found on cellular surfaces and serve as receptor ligands for enzymes and other macromolecules.[51-54] Glycosides of C(2)-aminosugars are linked to other carbohydrates or amino acids via either a 1,2-*cis*- or a 1,2-*trans*-linkage. Direct synthesis of 1,2-*trans*-2-aminoglycosides can be accomplished by incorporating participating groups at the C(2)-position of glycosyl donors. However, selective formation of the 1,2-*cis*-2-amino glycosides remains problematic because of the necessity for non-participating groups at C(2) of the donor. Even though there have been a variety of methods reported for stereoselective construction of 1,2-*cis*-2-aminosugars,[17-25,28,29,31,32] each have their own set of disadvantages or limitations. The Nguyen group has made recent advances to overcome these limitations using cationic nickel(II) catalysis.[66,67]

Initial studies commenced by treatment of the C(2)-*p*-methoxy benzylidene glucosamine donor **51** (Table 7, entry 1) with galactose acceptor **18** in the presence of 5 mol % of $Pd(PhCN)_2)(OTf)_2$. After 10 h at room temperature, disaccharide **55** (entry 1) was isolated in 60% yield and with 4:1 α-selectivity. Investigation continued by changing the nature of the catalyst. Switching from a palladium species to $Ni(PhCN)_4)(OTf)_2$ (entry 2) reduced the reaction time to 4 h, providing 95% yield of **55** with a significant increase in anomeric selectivity (4:1 → 8:1 α/β). Optimization of this catalyst system continued by investigating the effect that the electronic nature of ligands had on selectivity (entries 3 and 4). It was found that the best combination of yield (93%) and selectivity (10:1 α/β) was obtained with the more electron withdrawing benzonitrile ligands of the $Ni(4\text{-F-PhCN})_4)(OTf)_2$ catalyst system (entry 3). For comparison, less than 1% of **55** was isolated after reacting for 10 h in the presence of 10 mol% AgOTf alone (entry 6), and 10 mol% triflic acid (entry 7) provided only 10% yield of **55** as a 3:1 α/β-mixture. Several other donors **52**-**54** (entries 8-10) were screened, and it was found that the electron deficient benzylidene-containing donors **53** and **54** were the most reactive, reducing reaction time to 1 h (entries 9 and 10).

With optimized conditions in hand, the authors set out to establish the generality of their method with a variety of acceptors and glucosamine acceptors **51** - **54** (Table 8). The cationic nickel(II) catalyst was found to provide the desired α-glycosides **60**-**72** in high yield and with excellent anomeric selectivity, notably in the reaction with sterically the hindered tertiary adamantol **21** (entry 6) which provided the desired glycoconjugate **72** in 96% yield and with a 17:1 α-selectivity. Additionally, examination of the secondary hydroxyl carbohydrate acceptor **69** (entry 5) with the different iterations of glucosamine donors clearly illustrates the importance of the nature of the benzylidene group in the coupling process; showing increased yield and α-selectivity with the *p*-CF_3-benzylidene over the *p*-OMe derivative. After completing the reactions involving glucosamine donors, the group proceeded to investigate the potential of galactosamine trichloroacetimidate **73** to serve as a

viable donor (Table 9). Once again, these reactions were found to be highly α-selective and provide 1,2-*cis*-2-amino glycosides in high yield.

To illustrate the utility of the nickel-catalyzed glycosylation method for oligosaccharide synthesis (Scheme 3a), coupling of the disaccharide acceptor **77** with the C(2)-*N*-*para*-trifluoromethyl benzylidene glucosamine donor **54** was performed to provide trisaccharide **78** in 76% yield and with high α-selectivity (α:β= 11:1). Furthermore, in a [2+2] strategy (Scheme 3b), glycosylation of disaccharide acceptor **79** with disaccharide donor **80** provided tetrasaccharide **81** in 72% yield as an 11:1 α/β-mixture.

To demonstrate the synthetic merits of their nickel-catalyzed glycosylation protocol, the authors illustrate model reactions for the synthesis of biologically relevant carbohydrates (Scheme 4), first with the highly selective construction of the glucosamine-α-(1→4)-linked glucuronic acid disaccharide **84** (Scheme 4a) found in heparin sequence. To this end, electron-withdrawing *p*-CF_3-*N*-benzylidene glucosamine trichloroacetimidate **54** was found to be the most effective donor. Glycosylation of the methyl ester of D-glucuronic acid **82** with **54** afforded the desired disaccharide **83** in 87% yield with exclusive α-selectivity. This approach to construction of the glucosamine-α-(1→4)-linked glucuronic acid unit of well-defined heparin oligosaccharides is more selective and higher yielding than other available methods.[68-73] The second model reaction the authors report is the selective synthesis of α-GalNAc-threonine (or tumor associated T_N-antigen) derivative **86** (Scheme 4b), which has received considerable attention in cancer vaccine therapies.[74] Accordingly, galactosamine donor **84** was reacted with protected threonine residue **85** to provide the corresponding glycopeptide (**86**) in good yield and excellent α-selectivity (α:β= 15:1). In continuation of their goal of synthesizing α-GalNAc-glycopeptide, the authors screened a number of acidic conditions for removal of the *N*-benzylidene group. It was found that the use of 1.1 eq. of 2N HCl in a mixture of acetone and CH_2Cl_2 was optimal for the deprotection. Subsequent acylation of the amine salt provided the fully protected α-GalNAc in 81% yield over two steps.

The authors suggest a possible mechanism for the selectivities observed during formation of 1,2-cis-2-amino glycosides under cationic nickel(II) catalysis (Figure 1). In pathway A, the nickel catalyst reversibly coordinates the C(2)-benzylidene nitrogen and the nitrogen of the C(1)-trichloroacetimidate of donor **87** to form the seven-member ring intermediate **88**. The authors speculate that hydrogen bonding with the nucleophile promotes ionization to the oxocarbenium intermediate **89**. Ligand exchange between the external oxygen nucleophile and trichloroacetamide, followed by dissociation of trichloroacetamide provides ion pair **92**. The intermediate **92** (Figure 1) recombines in a stereoselective manner to form the five-member ring intermediate **93**. Subsequent dissociation of the nickel catalyst affords the 1,2-*cis*-2-amino glycoside **94**. Alternatively, the cationic nickel catalyst could act as a mild Lewis acid, (pathway B), and coordinate the C(1)-trichloroacetimidate nitrogen of **87**. Hydrogen bonding with the nucleophile promotes ionization to the oxocarbenium intermediate **91**. Ligand exchange with the nucleophile would result in expulsion of the trichloroacetamide, forming the ion pair **92** which then recombines to form a five-member intermediate **93**. Finally, dissociation of the nickel catalyst provides α-isomer **94** (Figure 1).

2.2 *Ortho*-Alkynylbenzoate Donors

Development of novel glycosylation protocols that operate under unique activation strategies is vital to the advancement of carbohydrate synthesis. Recently, there has been an explosion in the number of reports involving the gold-catalyzed activation of alkynes. In order to capitalize on this movement, several research groups have applied the concept to the activation of carbohydrate donors with latent leaving groups containing alkynyl

functionality. Such research, including the work of Hotha (see section 3) and Yu (see this section, 2.2), has exploited the low oxophillic character of gold catalysts and the extensive functional group compatibility they exhibit in developing unique activation strategies for glycosylation.[75-78] An example is seen below in Yu's proposed mechanism for the activation of glycosyl ortho-alkynylbenzoates (Figure 2).[80] In this cycle, the benzylic triple bond in *o*-hexynylbenzoate donor **94** is activated by the Au(I) catalyst to form complex **95**. Attack of the proximal carbonyl oxygen followed by cleavage of the glycosidic bond provides the oxocarbenium **96** with expulsion of gold-isocoumarin complex **97** (Figure 2). Nucleophilic addition of a glycosyl acceptor to **96** provides the corresponding glycoside product **98**. The Au(I) catalyst is regenerated by protonolysis of the Au-*C* bond of **97**.

B. Reactivity and Scope of Gold-Catalyzed Glycosylation with Ortho-Alkynylbenzoate Donors—Representative examples of *o*-hexynylbenzoate donors, **100** and **101** (Table 10), were explored with a number of glycosyl acceptors. For instance, coupling 2,6-dimethylphenol **39** (entry 1) with disarmed donor **100**, in presence of 10 mol% $Ph_3PAuOTf$, provided the expected β-glycoconjugate (**102**) in a remarkable, nearly-quantitative yield (97%). In addition to phenol, other acceptors were screened under the condition as well (entries 2 and 3). Good to excellent yields were obtained in each reaction. The synthetic utility of this protocol was demonstrated with tetra-benzylated glucose donor **101**. Although the desired products were obtained in high yields, poor anomeric selectivities were observed in the reactions. To summarize, the authors have reported a novel glycosylation protocol using catalytic amounts of $Ph_3PAuOTf$ for activation of *o*-hexynylbenzoate donors. The reaction provides exclusive formation of β-glycosides when employing participating groups at the C(2)-position of the glycosyl donor. The reaction is fast and highly efficient, and conditions are compatible with thioglycosides and 4-pentenyl glycosides. Lastly, the anomeric orientation of the leaving group on the donor does not affect the transformation.

Yu and coworkers have made further attempts to increase their selectivity with glycosyl donors that do not contain participating groups at the C(2)-position by changing the solvent in the reaction.[81] It is known that ether as a solvent leads to α-selective glycosylations.[40,41] Therefore, C(2)-*O*-benzyl donor **101**, C(2)-azido donor **106**, and C(2)-deoxy donor **108** (Table 11) were screened with a variety of acceptors in both CH_2Cl_2 and Et_2O (Scheme 5). In each experiment, the reaction was found to be more α-selective in Et_2O than in CH_2Cl_2. For example, switching to the Et_2O solvent (Scheme 5a vs. Table 10) significantly increased the α-selectivity (1:2 → 4.4:1) when coupling galactoside acceptor **18** with donor **101**. A similar result was obtained with C(2)-azido donor **106** (Scheme 5b). When glycosylating **18** with **106**, even though disaccharide **107** was obtained in excellent yield in both the CH_2Cl_2 and Et_2O solvent, reactions were found to be more α-selective in Et_2O than in CH_2Cl_2 (2.7:1 → 10.2:1). Interestingly, switching to the Et_2O solvent was detrimental to α-selectivity when C(2)-deoxy donor **108** was employed in the coupling process. The lack of selectivity with donor **108** is of little concern, however, because it was found that substitution of the catalyst for 20 mol % Ph_3AuNTf_2 (Scheme 5c) at −72°C provided disaccharide **109** as the α-anomer exclusively. This α-selectivity is unprecedented for 2-deoxy substrates.[86-89] The result obtained in Scheme 5c clearly illustrates the anomeric effect to be the sole factor governing selectivity in that the oxocarbenium intermediate is not coordinated with other species such as solvent or Ph_3AuNTf_2 catalyst.

Additional mechanistic insights were gained after isolating isochromen-4-yl-gold(I) intermediate **114** (91% by catalyst loading) from the reaction of *n*-pentenol (**111**) with the 2-deoxy *o*-hexynylbenzoate donor **110** (Scheme 6).[90] In this reaction, the desired product **112** was produced in poor yield (37%) and a majority of the newly formed glycoconjugate ended

up as the hydrolysis product **113** (47%), where decomposition of the benzylidene consumed an equivalent of H_3O^+ in the reaction. This occurrence was sufficient for preventing the protodeauration of **114** needed to regenerate the catalyst in this cycle (see Figure 2).

The catalytic cycle was found to resume upon the addition of strong protic acids, TfOH or CF_3COOH in the reaction, though common alcohols like MeOH and EtOH would not facilitate regeneration of the catalyst. This finding prompted a series of reactions to elucidate the role of the protic acid in the reaction (Table 11), where It was found that the isochromen-4-yl-gold(I) intermediate **114** was not able to catalyze the glycosylation, even at 10% catalyst loading. However, upon addition of 10% TfOH to the reaction, the intermediate **114** behaved exactly the same as $Ph_3PAuOTf$, providing 92% and 82% isolated yield of the desired disaccharide **115** with only 1% and 0.1% loading, respectively. This astonishing discovery illustrates that in the presence of catalytic amounts of TfOH, not only can the Ph_3AuOTf catalyst be substituted with the more stable isochromen-4-yl-gold complex (**114**), but a 100-fold reduction in catalyst loading can be implemented using either and still maintain an efficient reaction.

C. Synthetic Applications—The Au(I)-catalyzed glycosylation with *ortho*-hexynylbenzoate donors has been applied in the preparation of a number of bioactive carbohydrate molecules, including anti-tumor lobatoside E,[91] cardiac-glycoside digitoxin,[92] and TMG-chitotriomycin.[93] Additionally, it has been applied in the synthesis of kaempferol glycoconjugates,[94,95] ginsenosides,[96] and the chemoselective glycosylation of carboxylic acids.[97] The method is amenable to *N*-glycosylation strategies, which was demonstrated with the synthesis of purine and pyrimidine nucleobases.[98] In this review, we will showcase the utility of Au(I)-catalyzed glycosylation with *ortho*-hexynylbenzoate donors in the synthesis of TMG-chitotriomycin, lupane-type saponins, and glycopolymers.

I) Synthesis of TMG-Chitotriomycin: Exhibiting potent and selective inhibition of β-*N*-acetylglucosaminidase activity in insects and fungi,[99] TMG-chitotriomycin **117** (Figure 3) was identified by Yu as a desirable target for the Au(I)-catalyzed glycosylation protocol due to its potential as an antifungal or insecticidal agent.[100,101] Originally, when first isolated and characterized from the culture filtrate of *Streptomyces anulatus* NBR13369 by Kanzaki and coworkers,[261] the structure of the molecule was proposed to be **116** (Figure 3). However, upon synthesis and characterization of the compound by the Yu group,[93] it was determined that the anomeric configuration of the terminal sugar at the non-reducing end of **116** had been assigned incorrectly.

The synthesis of TMG- Chitotriomycin **117** (Scheme 6) began with the β-selective formation of disaccharide **122** in 72% yield by the coupling of C(2)-azido glucopyranosyl α-imidate **118** with the C(4)-hydroxyl group of glucosamine acceptor **120** under BF_3-Et_2O activation. Conversion of the *p*-methoxybenzyl disaccharide **122** to the corresponding *o*-hexynylbenzoate **125** was carried out in a two step procedure involving the CAN-mediated deprotection of the *p*-methoxybenzyl group followed by condensation of the resulting lactol with carboxylic acid **124** to provide *o*-hexynylbenzoate **125** in 69% yield over the two steps. With disaccharide donor in hand, the authors commenced with the synthesis of the disaccharide acceptor **126**. Accordingly, the coupling of 2-*N*-Phth-glucopyranosyl *o*-hexynylbenzoate donor **121** with acceptor **119** was carried out in the presence of 20 mol% Ph_3AuOTf in DCM to provide disaccharide **123** (Scheme 6), quantitatively. A selective opening of the benzylidene acetal (Et_3SiH, BF_3-Et_2O, CH_2Cl_2) provided the C(4)-hydroxyl disaccharide acceptor **126** in 78% yield. The key step in this convergent synthesis was carried out next; Au(I)-catalyzed coupling of acceptor **1126** with donor **125** to afford tetrasaccharide **127** in 76% yield. Removal of the *N*-phthalimide groups; acylation of the

resulting amines; conversion of the azide functionality to the *N,N,N*-trimethyl amine at the non-reducing end of the tetrasaccharide; removal of the *O*-acetates and hydrogenolysis of the benzyl ethers, and removal of the *p*-methoxyl benzyl group provided TMG-chitotriomycin **117** (Scheme 7) in 7 steps and 28% yield overall.

II) Synthesis of Lupane-Type Saponins: The lupane-type saponins are plant derived[102] glycoconjugates exhibiting anticancer[103,104], anti-inflammatory,[105] and pancreatory lipase inhibiting character.[106] Further research into the unique biological properties of these compound is limited by their existence in micro-heterogeneous form. Synthetic approaches[107-116] to the saponins have been reported; identifying glycosylation of the 28-COOH of betulinic acid to be problematic in acidic media from a competing Wagner-Meerwein rearrangement (Figure 4). To overcome this problem, Yu applied his gold(I)-catalyzed activation of glycosyl *o*-hexynylbenzoates to the synthesis of betulin and betulinic acid glycoconjugates[117]

In the synthesis of lupane-type saponin **135** (Scheme 8), Yu was able to successfully glycosylate the 3-OH of the derivatized betulinic acid (**130**) with donor (**131**) in presence of 10 mol % $Ph_3PauNTf_2$. The reaction proceeded smoothly, affording the desired 1,2-*trans*-glycosides **132** in 93% yield. After deprotection of **132** under basic conditions, simultaneous glycosylation of the 2′-OH and troublesome 28-OH of betulinic acid (**133**) was carried out to arrive at the trisaccharide glycoconjugate **134** (92% yield) without competition from the Wagner-Meerwein rearrangement. The synthetic target **135** was completed with a series of deprotection steps and an oxidation.

III) Preparation of Neo-Glycopolymers: The Yu group has reported a unique application of the O-hexynylbenzoate donor involving the glycosylation initiated polymerization of tetrahydrofuran.[118] It was observed that 3,4,6-tri-O-acetyl-2-azido-2-deoxy-D-glucopyranosyl ortho-hexynylbenzoate and PPh_3AuOTf (.3 equiv) in deuterated tetrahydrofuran in the absence of an acceptor would quickly turn the clear solution turbid upon stirring and become viscous if left overnight. ^1H NMR of the resultant gel-like solid in $CDCl_3$ revealed a glycosyl polytetrahydrofuran, or G-PTHF (e.g. **138**, Scheme 9). The formation of this glycopolymer can be rationalized through a cationic ring-opening polymerization (CROP), such as the one seen below (Scheme 9). Even though this type of reaction has been employed for nearly a century[119,120] and can be accomplished using oxonium ions, carbenium ions, strong protic acids and Lewis acids,[121-126] this is the first example of an oxocarbenium initiating such a polymerization.

2.3 Glycosyl Halide Donors

C-glycosides are an important class of biologically active compounds.[127-139] They are of particular interest because of their resistance to metabolic processing, making them viable drug candidates and competitive inhibitors of processing enzymes.[127-132] While catalytic approaches to *C*-glycosides are somewhat rare, there are numerous methods available for constructing the anomeric carbon-carbon bond, where generation of electrophilic, nucleophilic, or radical character is observed at C(1). However, most of these approaches rely on substrate control to provide selectivity in the reaction. Cross-coupling reactions are an obvious approach to *C*-glycosides, however fully-oxygenated and saturated structures are usually not attainable through such methods because of the susceptibility of C(1)-substituted metal complex to undergo β-hydride or alkoxy-elimination.

A. Negishi Cross-Coupling Reactions—The use of pincer-ligated organometallic complexes has been reported to inhibit β-hydride elimination.[140-147] Additionally, Fu has reported an effective coupling of 2° alkyl halides with alkyl zinc reagents using *i*Pr-PyBox/

Ni(II) complexes.[148,149] Therefore, use of these ligands seemed logical for Gagné to commence his investigation of a Negishi cross-coupling approach to *C*-alkyl glycosides.[150] A screening of solvents was first conducted, where it was determined that DMI, THF, and DMF were acceptable for the transformation. The model substrate used in the screening of ligands was *O*-acetyl-bromo-D-glucose **139**, which was coupled to MeZnI in the presence of 10 mol% $NiCl_2$ and 15 mol% ligand (Table 12). Use of unsubstituted PyBox ligand (entry 4) provided the coupling product **140** in 76% yield with α:β = 1:2.2 along with 6% yield of undesired glucal **141**. In contrast, using the terpy ligand (entry 5) afforded **140** as the β-isomer, exclusively, albeit at the expense of yield (30%).

The reaction was screened with a variety of α-bromo glycoside donors (**139**,**148**,**150**,**154**,**156**, Table 13) where the glucosyl and galactosyl halides **140**, **148**, and **154** were found to couple with an alkyl zinc reagent to provide the desired products **147** (entry 1), **149** (entry 2), and **157** (entry 6) in moderate yield with slight preference for β-isomer formation. On the other hand, the α-mannosyl halides afforded the coupling products **151**, **153**, and **155** (entries 3-5) in high yield and α-selectivity. Benzyl protecting groups were also examined in the reaction, but the α-bromides were too reactive and underwent rapid decomposition. As a result, the more stable α-chlorides would have to be employed (entries 4-6).

The reaction was further extended to the construction of *C*-aryl glycosides.[151] Using optimized nickel-catalyzed *C*-alkylation conditions in the reaction of **139** with PhZnI-LiCl (Table 14, entry 1) resulted only in the glucal elimination product. A trace amount of *C*-aryl product **158** (entry 1) was obtained using the $Ni(COD)_2$/PyBox system. Switching from the DMI solvent to the DMA solvent improved the yield of **158** to 20%. Ultimately, it was found that $Ni(COD)_2$/tBu-Terpy in DMF was optimal for the reaction of glucosyl bromide **139** with PhZnI-LiCl; where the desired product **158** was obtained in 72% yield with excellent β-selectivity and minimal losses to glucal elimination. With optimal conditions in hand, the next step was to determine the scope of the transformation with a variety of organozinc reagents (Table 13). The reaction was found to be compatible to both electron-rich and electron-poor aryl zinc reagents (entries 1 and 2). The coupling products **158** – **163** were formed in moderate to good yield (30 – 77%) and with excellent β-selectivity (1:10–1:14). While both *meta*- and *para*-substituents on the phenyl ring were tolerated in these reactions, aryl compounds bearing *ortho*-substituents were not. Additionally, conditions worked well for heteroaromatic compounds (entries 3–5), providing glycosides **164** – **167** in good yield and β-selectivity. In most cases, only trace amounts of undesired glucal were observed.

B. Sn-Free Ni-Catalyzed Cross-Coupling Reactions of Glycosyl Bromides & Activated Alkenes—Gagné has also reported a novel entry into *C*-alkyl-α-glycosides through the reductive coupling of glycosyl bromides to electron deficient alkenes.[152] By carefully selecting a Ni catalyst in conjunction with stoichiometric reductant and a proton source, it was envisioned that the limitations associated with reductive trapping of glycosyl radicals with Bu_3SnH, (requiring excess alkene (6-20 equiv) and stoichiometric amounts of the toxic heavy metal), could be overcome. Investigation commenced with the reaction of tetraacetyl α-glucosyl bromide **139** and methyl acrylate **168** (Scheme 10) in the presence of $Ni(COD)_2$ and (R)-Ph-Pybox ligand **145** with Zn as the terminal reductant and NH_4Br as the proton source. The α-*C*-glucoside **169** was obtained in 70% yield with trace amounts of the elimination product (**141**). The scope of the nickel-catalyzed reductive coupling was then investigated with a variety of glycosyl bromides and acrylate derivatives. Coupling products were isolated in moderate to good yield with excellent levels of α-selectivity.

C. Intermolecular Addition of Glycosyl Halides to Alkenes Mediated by Visible Light—Gagné has reported another radical coupling of glycosyl halides to electron deficient alkenes, this time using photoredox catalysis (Scheme 11) to generate fully saturated α-C-alkyl glycosides.[153] The reaction uses $[Ru^{II}(bpy)_3](BF_4)_2$, excited to the MLCT state by visible light, which generates a reducing equivalent from stoichiometric addition of Hunig's base. This reducing equivalent, $[Ru^{II}(bpy)_2(bpy\cdot-)]^{2+}$ reacts with glycosyl bromide to generate a C(1) radical. At this stage, the electron deficient radical can undergo reduction to the glycosyl alkane or be trapped by a second equivalent of alkene to generate the oligomerization product. To suppress oligomerization, Hantzsch's ester (**170**) was employed as a terminal reducing agent in the reaction. Using DCM as a solvent and running at high concentration was found to improve the reaction of glycosyl bromide **139** with methyl acrylate to 92% yield of *C*-glycoside **169**.

2.4 Summary

Having access to mild and broadly applicable glycosylation strategies is highly desirable in the synthesis of carbohydrates. Such approaches reduce the level of waste from undesired reactivity, extend the scope of the reaction to partners which incorporate a broader range of protecting groups, and allow for the chemoselective activation of donors in solution. The use of transition metal catalysis could be a potential solution to achieving high selectivity at the newly-formed glycosidic bond; being no longer confined to C(2)- neighboring group participation or reliance on the nature of protecting groups on substrates to direct selectivity. The transition metal catalyzed activation of glycosyl trichloroacetimidate donors has been widely explored by Nguyen, providing access to 1,2-*trans*-glycosides with cationic Pd(II) species and 1,2-*cis*-2-amino glycosides from cationic Ni(II)-catalysis. Yu has identified *ortho*-alkynyl benzoates as glycosyl donors upon activation with Au(I)-catalysts, whereas β-glycosides are achieved in remarkably high yield with neighboring participating groups at C(2) and excellent yield and α-selectivities are observed with C(2)-ether protecting groups. The strategy is applied in the synthesis of TMG-chitotriomycin, lupane-type saponin trisaccharides, and glycopolymers with tetrahydrofuran. Finally, Gagné has reported new methods for accessing *C*-alkyl and aryl glycosides via nickel-catalyzed Negishi cross-coupling and reductive coupling reactions as well as visible light mediated addition of glycosyl halides to alkenes.

3. DONORS WITH STABLE METHYL AND PROPARGYL LATENT LEAVING GROUPS

An inherent obstacle in the synthesis of complex oligosaccharide is selective activation of anomeric leaving groups within the functionally-dense carbohydrate environment. Often carried out by the use of a Lewis acid promoter or transition metal catalyst, the construction of a new glycosidic bond involves the addition of a suitable nucleophilic acceptor to the anomeric center of an activated donor. To circumvent undesired reactivity, selective protection/deprotection steps are generally required for donors and acceptors prior to glycosylation. The guiding principle for functionalizing these donor/acceptor pairs is one of orthogonal reactivity, where one anomeric latent leaving group is activated with a given reagent under a specific set of conditions while others are not, even though both are present in the same reaction vessel. Therefore, having access to robust anomeric latent leaving groups that are tolerant of functionalizing glycosyl donors prior to the coupling process, yet maintain their ability to be selectively activated under catalytic control, is an enticing prospect in carbohydrate synthesis. The following section details recent advancement in Au-catalyzed glycosylation utilizing glycosyl donors which incorporate 'stable' leaving groups, namely the alkyne functionality and methyl glycosides.

3.1 Glycosyl Alkynes

A. Pyranoside Donors—Due to the stability of *n*-pentenyl glycosides and their ability to be activated as donors in the presence of a suitable promoter,[154-160] Hotha envisioned propargyl glycosides to serve as novel, stable glycosyl donors when selectively activated with a transition metal catalyst.[75] The salient alkynophilicity exhibited by gold catalysts[176] encouraged investigation of their ability to activate propargyl glycoside donors. Initial studies were performed with propargyl 2,4,3,6-tetra-*O*-benzyl-glycoside **171** (Scheme 12) as the glycosyl donor and menthol **174** as the glycosyl acceptor in presence of 3 mol% $AuCl_3$ in CH_3CN at 60 °C for 6 h to afford glycoconjugate **175** in 68% yield and with α:β = 1:1. Interestingly, changing protecting groups from benzyl ethers to ester derivatives (donors **172** and **173**, Scheme 12) resulted in no reaction. This result demonstrates the Au(III) protocol to be highly sensitive to the electronic nature of protecting groups on the donor and only extendable to activation of those with electron-donating protecting groups.

While establishing the scope of the reaction, it was found that a variety of acceptors (Figure 5) could be efficiently glycosylated.[75] For instance, reaction of tetra-benzylated glucose donor **171** with acceptor **59** resulted in disaccharide **178** in 74% yield and with α/β= 1:1.5. When substituting the acceptor for cholesterol **15**, glycoconjugate **20** was isolated in 39% yield.[161] The reaction was further examined with per-*O*-benzylated galactoside and mannoside donors (Figure 5). Coupling of menthol with a galactoside donor afforded glycoconjugate **180** in 73% yield with an α/β–ratio of 1:2. Likewise, reaction of a mannoside donor with glucose acceptor afforded the 1,2-trans-disaccharide **181** in 68% yield.

To establish the synthetic utility of the protocol for use in sequential glycosylation, Hotha probed the disparity in activation rate between armed/disarmed propargyl glycosides.[63, 176] Initially, Au(III)Cl_3-catalyzed glycosylation of “disarmed” propargyl mannoside acceptor **183** with “armed” propargyl mannoside donor **182** (Figure 6) was carried out in CH_3CN to afford 68% of α-linked disaccharide **184**. This was followed by a protecting group exchange to provide the “armed” propargyl disaccharide donor **185**.[176] Anticipating formation of trisaccharide **186**, donor **185** was allowed to react with a second equivalent of the disarmed acceptor **183** in presence of $AuCl_3$ (Figure 6). Unexpectedly, disaccharide **184** (53%) and 1,6-anhydro sugar **187** (16%) were formed in lieu of the trisaccharide.

The unusual reactivity can be rationalized through a double activation of donor **185** (Figure 7) by gold catalyst, although the exact sequence of events has not been determined.[177] As such, the $AuBr_3$ catalyst activates the interglycosidic oxygen of **185**, resulting in formation of oxocarbenium **188** and simultaneous expulsion of propargyl intermediate **189**. Nucleophilic addition of the disarmed acceptor **183** to oxocarbenium **188** results in transglycoside **184**. Secondary activation of intermediate **189** by $AuBr_3$ provides oxocarbenium **190**, which is intramolecularly trapped to provide the corresponding 1,6-anhydrosugar **187** (Figure 7). This Au(III)-mediated activation strategy has been applied to propargyl furanoside donors as well.[177]

B. Furanoside Donors—The identification of bioactive natural products containing oligofuranoside moieties, (such as glycosyl phosphatidyl inositol,[178,179] arabinogalactan,[180] lipoarabinomannan,[180] and helminothosporium toxins),[181] has prompted chemists to pursue novel and catalytic methods for their selective construction.[182-192] Hotha is among them, having recently extended his novel Au(III)-catalyzed activation of propargyl glycosides to furanosyl donors (Table 15).[200]

Toward this end, a variety of propargyl furanosides **188–191** (Table 15) were investigated as glycosyl donors in coupling to the primary alcohol of glucopyranoside acceptor **59**. Initial studies commenced with glycosylation of **59** using propargyl ribofuranoside **188** in presence of 8 mol % $AuCl_3$ in CH_3CN at room temperature. After 3 days, disaccharide **191** (entry 1) was isolated in 40% yield as the β-isomer exclusively. It was found that the yield of **191** could be improved to 72% using cationic $Au(OTf)_3$, generated *in situ* from $AuBr_3$ and AgOTf. Prompting further experimentation, furanoside donors **189**–**191** (entries 2 - 4) were screened in the reaction as well. Employing propargyl xylofuranoside **189** (entry 2) as the donor provided 67% of disaccharide **193** as a 5:1 α:β–mixture. Substituting donors for those with opposing geometry at C2, D-ara*f* **190** and D-lyx*f* **191** (entries 3 and 4), resulted in an inversion of the observed anomeric selectivity. These results illustrate that activation of propargyl furanosides with a gold catalyst is selective for the formation of 1,2-*trans*-furanosides.

To reiterate, the Hotha group has developed a novel protocol for the construction of glycosidic linkages utilizing Au(III)salt activation of propargyl glycosides. This procedure is highly dependent on the electronic nature of the protecting groups, and can only be accomplished when the donor is armed. Interglycosidic cleavage is problematic when both the non-reducing and reducing ends of the propargyl disaccharide contain arming protecting groups, limiting utility for oligosaccharide synthesis. The method is amenable to both pyranoside[161,176] and furanoside[177] donors and facilitates glycosylation of many different types of glycosyl acceptors.

3.2. Propargyl 1,2-Orthoesters

In efforts to overcome the aforementioned limitations involving use of the “disarmed” propargyl glycoside donors for oligosaccharide synthesis, Hotha investigated the activation of propargyl 1,2-orthoesters for service as glycosyl donors.[194] It was found that the coupling of methyl glucopyranoside acceptor **59** with disarmed glucose 1,2-orthoester **195** (Scheme 13a) in presence of 10 mol% $AuCl_3$ provided disaccharide **197** in 65% yield with exclusive β-selectivity. To further test the limitations of this protocol, the reaction of disarmed 1,2-orthester donor **195** and propargyl glycoside acceptor **196** was investigated under the standard gold conditions (Scheme 13b), where disaccharide **198** was obtained in 72% yield as a single isomer. This result suggests that the gold catalyst preferentially activates the propargyl 1,2-orthoester to generate the 1,2-*trans*-glycoside product without disruption of propargyl ether.

The generality of the propargyl 1,2-orthoester activation strategy was further explored in the coupling of serine/threonine residues (Scheme 14).[194] To this end, propargyl 1,2-orthoester donor **199** was reacted with Cbz-protected serine benzyl ester **200** (Scheme 14a) in presence of 7 mol% of $AuBr_3$to afford glycopeptide **201** in 63% yield. The versatility of the methodology was further defined by extending the scope to lactosyl propargyl 1,2-orthoester **202** (Scheme 14b), furnishing the desired glycopeptide **204** in 64% yield.

3.3. Unprotected Propargyl Glycosides

Due to the vast complexity of oligosaccharides in nature, the development of a widely applicable method for their construction remains daunting, even with significant advances being made in the field. An unfortunate limitation in the multi-step poly-functionalization of carbohydrates is the necessity for protection/deprotection sequences to limit undesired reactivity. Such manipulations require large amounts of additional resources (solvent, reagents, and time) and can effectively remove a target from the realm of economic feasibility. As a consequence, development of catalytic glycosylation protocols involving stable and unprotected donors is an enticing prospect in the field. Mamidyala and Finn were

intrigued by Hotha's success using Au(III)salts to activate propargyl glycosides,[161,176,177,194] and envisioned similar activation could be achieved with unprotected variants of such donors due to the characteristics of Au(III) catalysts; functioning well in protic solvents and possessing inherently low oxophilicity.[195]

To this end, coupling of the primary alcohol of galactoside acceptor **18** with unprotected propargyl galactoside **205** was carried out under a range of temperatures and solvents. The iterations performed in refluxing CH_3CN (Table 16) were found to be significantly higher yielding (51% yield, entry 1) than those run at 60 °C, or reactions in CH_3NO_2, DMF, or THF, indicating coordination of the metal to be significant in the reaction. In addition, a large excess (10 eq.) of the glycosyl acceptor **18** is required to facilitate an acceptable yield due to secondary function of the unprotected donors to behave as nucleophiles. Once optimized, these reaction conditions were applied to propargyl glucoside donor **206** (entry 2) and mannoside donor **207** (entry 3) to generate the corresponding disaccharides (**209** and **210**, respectively) in moderate yields. Overall, these results imply the feasibility of gold catalyzed oligosaccharide synthesis with minimal protection/deprotection of coupling partners.

3.4. Methyl Glycosides

While investigating the propargyl glycosides for use as donors in glycosylation, the Hotha group noticed an unusual reactivity in one of their experiments.[161] It was during construction of disaccharide **181** (Scheme 15) via the coupling of glucopyranoside **211** with propargyl mannoside donor **182** that formation of an unexpected 1,6-anhydrosugar **187** was observed in the reaction as well.[196-198] This unusual reactivity prompted further studies where it was discovered that appearance of the 1,6-anhydrosugar is highly dependant on temperature,[151,193,199,200] (running at 25 °C will effectively inhibit its formation.) In addition, it was found that substitution of the arming benzyl groups with disarming benzoates on the acceptor is sufficient for preventing its appearance in the reaction as well. Formation of the 1,6-anhydrosugar **187** can be rationalized through gold-activation of methyl pyrannoside **211**, generating an oxocarbenium that gets trapped by the alcohol at C(6).

Encouraged by these observations, Hotha set out to establish conditions that could exploit methyl glycosides as the donors.[201] Accordingly, methyl per-*O*-benzylated-α-D-mannopyranoside **214α** (Scheme 16a) was allowed to react in the presence of 10 mol% $AuBr_3$ with "disarmed" acceptor **12** in acetonitrile at 70°C. After 18 h, the corresponding disaccharide **212** was obtained in 65% yield. It is interesting to note that the orientation of the methyl glycoside on the donor has little effect on the outcome of the reaction; both anomers providing the desired disaccharide in nearly identical yield and similar α/β selectivity (Scheme 16a vs. 16b). The protocol has also been extended to the construction of oligosaccharide synthesis in moderate to good yield employing "partially armed" saccharide donors. A complex mixture of products was formed when "fully armed" saccharide donors were used in the reaction, indicating interglycosidic bond activation to be problematic.[201]

3.5. Summary

Having access to robust anomeric leaving groups that are tolerant to diverse chemical reactions, yet still retain the ability for selective activation under catalytic control, is enticing in the field of carbohydrate synthesis. This section has detailed recent advances in this regard using Au(III)-catalyzed glycosylation of donors bearing stable anomeric leaving groups. Propargyl glycosides, propargyl 1,2-orthoesters, and methyl glycosides have been identified as donors in the presence of Au(III) salts.[176,177,199,200] This reactivity has been further exploited with unprotected propargyl glycosides.[69] In addition, propargyl

oligosaccharide donors may only be armed at the reducing end, otherwise interglycosidic bond cleavage becomes problematic in the reaction.[176] Interestingly, the Au(III)-catalyzed coupling reaction also works well with propargyl furanoside donors to provide exclusively the 1,2-*trans*-glycoside product formation. Selective activation of propargyl 1,2-orthoester donors in the presence of glycosyl acceptors bearing additional *O*-propargyl groups has been demonstrated.[193] In addition, methyl glycosides were identified as donors in the presence of Au(III) salts, where orientation of the anomeric leaving group was found to have little or no effect on selectivity in yield of the reaction.[193,201]

4. GLYCAL DONORS

Glycosylation strategies involving glycal donors present several distinct advantages. These include: 1) construction of the anomeric linkage can be carried out with excellent selectivity, 2) commonly-employed olefin manipulations can be used to functionalize products and provide access to a variety of pyranosides, and 3) many of the donors are commercially available. The following section will examine recent advancement to the activation of glycal donors with transition metal catalysts.

4.1. Glycosylations via π-Allyl Intermediates

This section will be divided into two categories: Ferrier-type and non-Ferrier-type glycosylation. The Ferrier reaction is the coupling of a nucleophile to a 1,2-unsaturated glycal with a leaving group at the C(3)-position. Traditionally, a Lewis acid is usually required to facilitate the allylic rearrangement. When Pd catalysts are used to ionize the leaving group of glycal donor, a Pd-π-allyl metal intermediate is generated and excellent stereocontrol at the newly-formed glycosidic linkage is observed during subsequent nucleophilic addition. An alternate approach to accessing Pd-π-allyl metal complexes is the ionization of a C(1)-leaving group on a 2,3-unsaturated pyranone donor. The synthetic utility of such reactions has been established by the O'Doherty group and is referred to as non-Ferrier-type glycosylation.[203]

A. Ferrier-Type Glycosylation—In efforts to supersede the Lewis acid-mediated Ferrier paradigm, a number of investigators have focused their attention on transition metal catalysis for activating C(3)-leaving groups of glycal donors for glycosylation. These methods, referred to as Ferrier-type processes, are generally mild, require low catalyst loading, and rely on the nature of the ligand-catalyst system to control α- and β-selectivity. In this regard, the transition metal catalyzed Ferrier-type glycosylation is able to distance itself from traditional Lewis acid-mediated process. The following section details recent advancement to palladium- and gold-mediated glycosylation strategies using glycal-derived donors with leaving groups at the C(3)-position.

I) Pd-Catalyzed *O*-oGlycosylation: In carbohydrate synthesis, having the ability to direct the selective formation of glycosidic linkage with specific reagents, rather than relying on substrate control (i.e. the neighboring participating group, nature of the protecting groups on substrates, and anomeric effect), is highly desirable. A pivotal contribution in this regard was Lee's recent Pd-catalyzed *O*-glycosylation strategy using glycal donors.[201] Lee envisioned the use of activated zinc(II)-alkoxides to overcome the poor reactivity of alcohol acceptors and glycal donors in η^3-metal mediated reactions.[202-205] Accordingly, investigations commenced with the palladium-catalyzed reaction of glycal **215a** (bearing acetyl group at the C(3)-position) and benzyl alcohol in the presence of Et_2Zn (0.5 equiv) with different ligands (Table 17). The desired *O*-glycoside **216** was obtained in excellent yield. In this strategy, using the bulky ligand di(*tert*-butyl)phosphine (DTBBP), provided exclusive β-anomer formation (**216,** entries 1 and 3). On the other hand, using trimethyl

phosphite (entry 2) afforded the opposite anomer with good selectivity (7:1 α/β). These reactions were found to work equally well with a *t*-butyl carbonate installed at C(3) (entries 3 and 4). Overall, these results clearly illustrate that the nature of the Pd-ligand complex can be employed to control anomeric selectivity; a task not achievable in the Lewis acid-mediated reaction.

After achieving such high β-selectivity with the DTBBP ligand, the scope of the Pd-catalyzed glycosylation reaction was then investigated with a variety of glycal donors and acceptors (Table 18). Interestingly, altering the nature of protecting groups and reactive sites on acceptors, along with the addition of torsional strain to the donors (entries 1 and 2), was found to have little impact in the reaction (α/β >1:25 in each case.) The desired disaccharides (**220**-**223**) were isolated in moderate to good yield (69 – 77%).

The synthetic utility of this strategy was demonstrated by functionalizing the 2,3-unsaturated *O*-glycoside products (Scheme 17). Both natural and unnatural disaccharides **224** and **225** can be achieved by olefin manipulations on the glycal products.

An extension to the palladium-catalyzed Ferrier-type glycosylation has been reported by Nguyen using glycal donors with a trichloroacetimidate leaving group.[207] In his approach, glycosylation of phenol acceptors can be achieved without prior activation by Et_2Zn(II). However, during reactions involving aliphatic alcohols, an initial conversion to the more reactive zinc alkoxide is necessary. Nguyen's studies commenced with the coupling of glycal donor **226** and 1-naphthol (Table 19) in presence of 2.5 mol% $Pd(CH_3CN)_2Cl_2$. Within 2 h, 55% of the desired glycoside **227** was attained as a 3:1 α/β-mixture of anomers. Anticipating that a change in ligands could improve the selectivity, a number of Buchwald's biaryl phosphine ligands were screened (Table 19).[208] Using DTTBP (entry 5) made a substantial improvement to the yield and α-selectivity of **227**.

The authors propose a mechanistic rationale to account for the α-selective nature of the reaction (Figure 8). First, the palladium-phosphine catalyst undergoes reversible coordination to the imidate nitrogen and olefin of glucal donor **226** to create palladium-alkene complex **227** (Figure 8). Subsequent migratory insertion generates oxocarbenium **228**, where nucleophilic approach from the β-face is impeded by the biaryl phosphine ligand. Thus, complex **229** arises from α-addition of 1-naphthol and undergoes deoxypalladation (catalyst dissociates to arrive at α-glycoside **230**). In this catalytic cycle, 1-naphthol serves as both the acceptor and as the proton source for the deoxypalladation.

To establish the reaction as a versatile entry into α-*O*-aryl-glycosides, donors with a variety of protecting groups were screened against an array of phenols (Table 20). Within 2-6 h, α-glycoconjugates **231**-**236** were obtained in good yield (76-98%) with excellent to exclusive α-selectivity, further implicating the bulky ligand's role in determining orientation at the newly formed glycosidic bond.

The generality of this protocol was explored through screening of aliphatic alcohol acceptors as well (Table 21). Due to the poor reactivity exhibited by this type of nucleophile with glycal donors, conversion to the more reactive Zn(II) alkoxide was necessary to facilitate a reaction. The procedure was determined to be compatible with a variety of alcohols, providing exclusively α-linked glycosides (**237**-**241**) in good yield. The major byproduct in the reaction was the C(1)-trichloroacetamide derived from [3,3]-sigmatropic rearrangement of the starting material, though losses in this regard were minimal.

II) Pd-catalyzed *C*-Glycosylation: The transition-metal-catalyzed Ferrier-type reaction is not exclusive to *O*-glycosylation. In fact, RajanBabu's approach to carbon-carbon bond construction[202] predates the work of Lee and Nguyen by two decades.

A lack of glycosylation strategies that involve mild conditions for the addition of malonate-type carbanion nucleophiles to glycal donors (Figure 9) prompted RajanBabu to explore Pd(0)-catalysis. In recognizing that electron-rich allylic acetate **141** required strong Lewis acids[209] or high temperatures to be activated for service as a glycosyl donor,[210,211] RajanBabu determined that an appropriate matching of leaving group and catalyst would be necessary to facilitate such a reaction under milder conditions. It was found that the coupling of dimethyl malonate with glucal **242c** could be achieved in presence of 2%-5 mol% $Pd(dba)_2$ and bis(diphenylphosphino)ethane, producing **244** in 56% yield with exclusive β-selectivity (Scheme 18).

III) Au-Catalyzed Glycosylation: Transition-metal catalyzed activation of glycals with leaving groups at the C(3)-position is not limited to the use of Pd catalysis. A gold-catalyzed Ferrier-type *O*-glycosylation strategy has been reported as well.[212]

In an attempt to access β-2,3-unsaturated glycosides, Balamurugan investigated gold catalysis in the Ferrier reaction. His prediction was that the larger size of the gold catalyst (previously reported by Hotha to activate propargyl glycosides) would selectively promote β-glycoside formation, similar to the use of $Pd(OAc)_2$ catalyst in complex with bulky biaryl phosphine ligands.[76] Accordingly, his investigation commenced with the treatment of 3,4,6-tri-*O*-acetyl-D-glucal to an array of glycosyl acceptors in presence of 0.5-2.0 mol% $AuCl_3$ catalyst (Table 22). In each case, the glycosylation reaction proceeded smoothly in generating the corresponding 2,3-unsaturated *O*-glycoside product (**245-248**) with good yield (74-85%) and moderate α-selectivity (α:β = 3:1 – 6:1). This method was also investigated with 3,4,6-tri-*O*-acetyl-D-galactal donor. In comparison to reactions involving glucal donor, these were found to be quite sluggish at 0.5 mol% Au catalyst loading. Rates were improved by increasing catalyst loading to 2 mol%, and the desired glycoside products were isolated with high α-selectivity.

B. Non-Ferrier-Type Glycosylation—Another type of transition metal catalyzed glycosylation has been reported where pyranone-derived donors are used to overcome the low reactivity observed during reactions with aliphatic alcohols. These strategies will be referred to as non-Ferrier-type. Remarkable selectivity is observed in this type of reaction and is attributed to retention of stereochemical integrity at the anomeric carbon during generation of the π-ally-Pd intermediate and subsequent addition of nucleophile. This section will detail the discovery of the non-Ferrier-type reaction and include several synthetic applications which utilize the transformation.

I) Reactivity and Limitations: The cyclic enone has been widely recognized as a viable platform for accessing functionalized carbohydrates.[213-223] The allylic acetal embedded in **249** (Scheme 19) is particularly useful because retention of stereochemistry is observed at the newly-formed glycosidic bond after ionization. The first to report on this observation was Feringa, who developed an iterative carbohydrate synthesis using a pyranone donor (Scheme 19).[204]

During his investigation, it was observed that substitution of the enantiomerically pure cyclic pyranone donor **249** with benzyl alcohol in the presence of 10 mol% $Pd(OAc)_2$ and triphenyl phosphite as catalyst provided the desired 2,3-unsaturated glycosides **250A** (Table 23) in 83% yield with nearly complete retention of stereochemical integrity.[209] However, during attempted couplings with amino acid **H** and carbohydrate acceptor **D** to glycosyl

donor **249**, the catalyst system would fail in the reaction. Exchanging the $Pd(OAc)_2/P(OPh)_3$ catalyst for $Pd_2(dba)_3/PPh_3$ was required for the transformation. This new catalyst system provided the desired products (**250D** and **250H**, respectively) in good yield (77 – 78%) and excellent selectivity.

Subsequently, Feringa explored an iterative approach to the synthesis of oligosaccharide **256** (Scheme 20). Diastereoselective dihydroxylation of 2,3-unsaturated glycosides **250C** with $RuCl_3$ and $NaIO_4$ afforded a *cis*-diol, which was then protected as the dioxolane **254**. Subsequent direct reduction of the ketone functionality with $Zn(BH_4)_2$ provided the β-L-ribose product **255** in 88% yield with 96% *de.* Palladium catalyzed glycosylation of glycosyl acceptor **255** with pyranone donor **249** was then explored. Gratifyingly, oligosaccharide **250C** was formed in 55% yield with excellent selectivity.

Shortly after the submission from Feringa, a similar transformation was reported by O'Doherty. During an investigation of π-allyl palladium complexes as glycosylation intermediates,[203] O'Doherty attempted to ionize the C(3)-acetoxy group of glycal donor **141** (Scheme 21a) using a Pd(0) catalyst. After proving unsuccessful, the leaving group was moved to C(1) (e.g. **258a** and **258b,** Scheme 5b) in an attempt to generate the π-allyl palladium complex. This modification was sufficient to provide the desired intermediate (**260,** Scheme 21b) in the presence of $Pd(0)/PPh_3$; though it was discovered that even the simplest of alcohols would fail to react with it. With this in mind, O'Doherty set out to construct a presumably more electrophilic π-allyl Pd intermediate **272** (Scheme 21c) from pyranone-derived donors **261a-c** using C(1)-leaving groups. The coupling could be achieved with pyranone donors **261a** and **261b** which incorporate C(1)-benzoate and pivaloate leaving groups, respectively. When Boc-protected donor **259c** was employed, a significantly faster and cleaner reaction was observed.

After the authors had established the optimal palladium conditions for coupling alcohol acceptors with pyranone donors **261a–c**, the scope of the reaction was explored with an array of alcohol nucleophiles (Table 24). Using either donor α-**261c** or β-**261c** provided the glycosides **264a-g** in moderate to excellent yield (52–85%) with retention of stereochemical integrity at the anomeric center. When sterically hindered adamantol acceptor was employed in the glycosylation (entry 7), a significant amount (34% yield) of the *tert*-butyl acetal byproduct **264f** was observed. This undesired reactivity could be avoided by using an excess of the donor or by switching to the less reactive pyranone **261b** with the pivaloate leaving group; effectively raising the yield from 54% to 74%. The 2,3-unsaturated glycoside products **264a-g** obtained from these coupling reactions were successfully converted to the corresponding saturated pyranosides containing the 2,3-*cis* diol functionality via Luche reduction of the ketone group and subsequent dihydroxylation.

C. Synthetic Applications

I) Oligosaccharide Synthesis: The palladium strategy developed by the O'Doherty group has been applied to constructing 1,6-linked oligosaccharides (Scheme 22).[225] Accordingly, the coupling of benzyl alcohol with donor **263α** and subsequent unmasking of the C(6)-hydroxyl group was carried out to provide the corresponding 2,3-unsaturated glycoside **266** (Scheme 12) in 86% yield over two steps. A second coupling was carried out using **266** as the glycosyl acceptor with $Pd(0)/PPh_3$ catalyst, providing **267** in 92% yield as a single diastereomer. A second iteration of the deprotection/glycosylation sequence was then employed to generate **269** in 86%. The product **269** was converted to its corresponding trisaccharide **271** (Scheme 22) through diastereoselective ketone reduction and subsequent olefin dihydroxylation.

The synthesis of 1,4-linked oligosaccharides (Scheme 23)[225] is also attainable from **263a**. Instead of unmasking the C(6)-hydroxyl functionality, diastereoselective ketone reduction of **263a** was performed with $NaBH_4$ (Scheme 23) to generate **272** with equatorial hydroxyl group at C(4). Compound **272** was subsequently coupled to donor **263a** under palladium conditions. An iterative glycosylation sequence then led to the 1,4-linked trisaccharide **275**.

II) Cleistrioside and Cleistetroside Natural Products: Further demonstrating the utility of his glycosylation strategy, O'Doherty reported a total synthesis of several biologically active cleistrioside and cleistetroside natural products (Scheme 24).[210,211] Using a non-Ferrier glycosylation approach with Pd(0) catalysis and pyranone donors during key transformations, the repeating rhamnosyl cores of the trisaccharide and tetrasaccharide variants were synthesized in 9 steps from the common precursor **278** (Scheme 24). In turn, the Boc-protected pyranone intermediate **277** was derived from commercially available acetylfuran **276**.

III) Anthrax Tetrasaccharide: *Bacillus anthracis* is a Gram-positive bacteria, and infections caused by this pathogen are severely detrimental as it constitutes a potent agent for biological warfare.[259] *Bacillus anthracis* penetrates the lungs of people and will kill the infected patient within 24-48 h if treatment is not available.[260] The release of anthrax spores through contaminated letters killed five people in the US in 2001.[260] O'Doherty has recently reported the synthesis of anthrax tetrasaccharide **281** (Scheme 25) utilizing his method of palladium-catalyzed *O*-glycosylation with both enantiomers of pyranone **277**.[227] In turn, donors **277** were prepared from acetylfuran **276** in three steps via the Noyori reduction and Achmatowicz rearrangement. Subsequent iterative glycosylation with *ent*-**277** followed by functional group exchange led to the formation of L-rhamnosyl trisaccharide acceptor **279** (Scheme 25). Furthermore, glycosyl phosphate **280** could be obtained from Pd-catalyzed glycosylation with pyranone **277**, a significantly cheaper route than using D-fucose as the starting material. Finally, glycosylation of the trisaccharide acceptor **279** with the donor **280** in presence of a sub-stoichiometric amount of TMSOTf, followed by introduction of the amide side chain and removal of protecting groups, afforded the desired anthrax tetrasaccharide **281** (Scheme 25). The natural product target was achieved in 39 steps from the common precursor, acetylfuran (**276**, 13% yield).

IV) Digitoxin: A novel assembly of the cardiac glycoside digitoxin (**282**) has been recently achieved through the Pd-catalyzed iterative β-glycosylation strategy (Scheme 26).[228] In this approach, the aglycon acceptor digitoxigenin **282** was coupled with the pyranone donor **283** under standard $Pd(0)/PPh_3$ conditions to generate the corresponding glycoconjugate **284** in 98% yield. A five-step sequence of manipulations (Luche reduction, Meyer's reductive rearrangement, dihydroxylation, selective acylation) provided the desired acceptor **285** in 67% yield (Scheme 26). Two additional iterations of the palladium-catalyzed glycosylation with pyranone donor **283** were then applied, followed by functional group manipulations, to generate the fully protected digitoxin precursor (9 steps from **285**, 40% yield). Finally, deacetylation at C(3) and C(3′) with LiOH provided the desired digitoxin **285** (Scheme 26, 15 steps, 19% overall).

V) Trisaccharide Subunit of Landomycin A: Demonstrating antitumor activity across 60 cancer cell lines,[229,230] Landomycin A (Scheme 27) is known to interact with DNA and inhibit its synthesis and cell cycle progress.[231] However, the specific mechanism of action of how Landomycin A (**289**) inhibits cancer cell growth is not fully understood. Being the most complex member of its class, Landomycin A is comprised of the landomycinone core, which is connected to a hexasaccharide unit consisting of 2 repeating trisaccharide subunits. There have been several groups to report syntheses of the oligosaccharide component of the

natural product.[232-235] In one approach, O'Doherty uses his palladium-catalyzed glycosylation strategy to stereoselectively install 22 stereocenters within the trisaccharide unit of Landomycin (**289**, Scheme 27) starting from the achiral acetylfuran (**274**).[238] As proof of concept, this chemistry would not applied to completion of the natural product, which has been reported by Yu recently in the first total synthesis of Landomycin A.[237]

In addition to these synthetic applications, O'Doherty's glycosylation protocol has been applied in the enantioselective synthesis of the kaempferol glycoside SL0101, its analogues, and their enantiomers from acetylfuran.[239] This activation strategy is also amenable to cyclitolization with carbasugars,[240] (derivatives of carbohydrates which lack the ring oxygen.)

4.2. Additional Reaction Types

The final section detailing transition metal activation of glycal donors will examine additional reaction types that do not proceed through π-allyl intermediates. It will be divided into two sections, anomeric carbon-carbon bond and anomeric carbon-oxygen bond construction.

A. C-Glycoside Construction

I) Rhodium(I)-Catalyzed 1,4-Addition of Arylboronic Acids to Pyranone: While examining a general cross-coupling method for generating *C*-aryl glycosides,[241] Maddaford became interested in the rhodium(I)-catalyzed addition of arylboronic acids to cyclic and linear enones.[242-244] This approach appeared to be a viable method for accessing the carbon-carbon anomeric bond (Scheme 28). Studies[245] began with the coupling of phenylboronic acid to pyranone **290** in the presence of $Rh(acac)(C_2H_4)_2$ and phosphine ligand. Undiscouraged when the 1,4-addition product was not observed in the reaction, the authors proceeded to screen additional Rh(I) catalysts, though the efforts would prove fruitless as well. Lewis acids such as $BF_3{\cdot}OEt_2$, TMSOTf, and $SnCl_4$ would also fail in the reaction. When the Rh(I)-complex $Rh(COD)_2BF_4$ was examined, the coupling of phenylboronic acid was achieved 4 h, providing 76% yield of *C*-aryl-glycoside **291** (Scheme 28). The authors proceeded to define the scope of the reaction with a variety of arylboronic acids. The electron-rich boronic acids provided *C*-aryl-glycosides (e.g. **292**, 81%) in higher yield than the electron-deficient ones (e.g. **293**, 50%). In each case, only the α-product was observed.

II) Oxidant-Controlled Heck-Type Coupling of Arylboronic Acids to Glycals: Arylboronic acids are among the most popular organometallic reagents due to their availability, stability to moisture and air, and the low toxicity that they exhibit.[246] A Heck-type coupling of arylboronic acid to 1,2-unsaturated glycals has been reported[247] in which access to three structural motifs can be attained by changing oxidants in the reaction (Table 25). As such, the coupling of phenylboronic acid to glucals **295a-c** was investigated in presence of 10 mol% $Pd(OAc)_2$ and benzoquinone (BQ) as the oxidant (entries 1-3). The product **296a** (entry 1) was not observed in the reaction with the use of glucal **295a**. Donor **296b** (entry 2) provided the 1,4-addition product **296b** in poor yield (32%). Glucal **295c** (entry 3) was the most effective donor in the Heck-type cross coupling reaction, providing pyranone glycoside **296c** in 84% yield. Changing the oxidant to a combination of $Cu(OAc)_2$ and O_2 provided the enol ether **297c** (entry 4) in 94% yield and exclusive α-product formation. Finally, the use of DDQ as oxidant provided Heck-type product **268c** (entry 5) in 69% yield. The three conditions were found to be compatible with a variety of electron-withdrawing and electron-donating arylboronic acids. However, acceptable yields of the products were limited to glycals containing TBS-ethers at the C(3)-position.

III) Decarboxylative Heck Coupling of Benzoic Acids and Glycals with Palladium: The palladium catalyzed formation of anomeric carbon-carbon bonds has been achieved using benzoic acid derivatives (Table 26).[248] Treatment of 3,4,6-tri-O-acetyl-D-glucal **295a** (entry 1) and 6-dimethylbenzoic acid **299** in presence of $Pd(OAc)_2/PPh_3$ and Ag_2CO_3 afforded a 79% yield of *C*-aryl glycoside **300a**. The electronic nature of the protecting groups (electron-donating groups **295b-c** vs. electron-withdrawing groups **295d-e**) on glucal donors was found to have little effect on the reaction. In addition, glucals bearing sterically hindered protecting groups (**300c-d**, Table 26, entry 1) did not impede the reactivity of the coupling process. Furthermore, the Pd-catalyzed decarboxylative coupling of disaccharide glucal **295f** (Table 26, entry 2) with benzoic acid **299** proceeded smoothly to provide glycoconjugate **300f** in 45% yield.

B. Rhenium(V)-Catalyzed Glycosylation—A mild method for generating anomeric carbon-oxygen bonds on C(2)-deoxy sugars has been reported by Toste using rhenium(V)-catalysis.[249] During optimization studies, it was found that a Re(V)-oxo-complex, $ReOCl_3(Sme_2)(Ph_3PO)$, was suitable for the glycosylation of a variety of carbohydrate nucleophiles with glycal donors (Table 27); providing the desired disaccharides and trisaccharides in good yield and excellent α-selectivity. Notably, disaccharide acceptor **305** (entry 3) was able to couple with glucal **304** to give the corresponding trisaccharide in 78% yield as the α-isomer, exclusively. These results illustrate the potential for α-2-deoxy-oligosaccharide construction.

The process is compatible with thiol acceptors (Scheme 29) and glycal nucleophiles containing electron withdrawing groups at the C(3)-position. This enables iterative α-2-deoxy oligosaccharide synthesis in overall good yield and high α-selectivity.

4.3. Summary

Significant advances have been made to the field of carbohydrate chemistry involving the activation of glycal donors with transition metal catalysts. These reactions have been demonstrated to proceed with excellent selectivity, providing a scaffold for accessing a variety of natural and unnatural pyranosides. Lee and Nguyen have extended the Ferrier reaction to provide selective access to α- and β-*O*-glycosides by relying on reagent- rather than substrate-control.[201,207] RajanBabu has also utilized this reaction type to generate anomeric carbon-carbon linkage under palladium catalysis.[202] The activation of glycal donors with leaving groups at C(3) has been demonstrated to work with gold catalysts as well by Balmurugan. Balmurugan's method is compatible with a variety of nucleophiles including thiols, which generally poison transition metal catalysts. Feringa and O'Doherty have reported the activation of pyranone donors with leaving groups at the C(1)-position.[224,225] These reactions are highly selective; generating glycosides that retain stereochemical integrity at the anomeric center. O'Doherty has applied the utility of this method in key transformations of several natural product and oligosaccharide syntheses.[225-228,238] Maddaford has reported that phenylboronic acids undergo 1,4-addition to enones derived from glycals under rhodium(I)-catalysis.[245] Several other cross coupling reactions have been reported for generating *C*-aryl glycosides as well.[247,248] Toste has reported high oxidation state rhenium to activate glycals for anomeric *C-O* and *C-S* bond construction.[249] This method is tolerant to moisture and air and provides an iterative strategy for the construction of α-2,3-dideoxy oligosaccharides.

5. 1- HYDROXY SUGAR DONORS

The final section of this review will detail the use of two additional donor types employed in transition metal catalyzed glycosylation; 1-hydroxy sugar donors and unprotected

carbohydrates. These glycosylation strategies are unique in that they lack a necessity for pre-installation of latent anomeric leaving groups at the C(1)-position and involve activation of donors with catalytic amounts of titanium. This method would first be applied to construction of glycosidic linkage by Mukaiyama in his 1991 synthesis of 1,2-*trans*-ribofuranosides.[250]

5.1. Glycosyl Hemiacetal Donors

During efforts to develop new synthetic methods involving titanium oxide catalysis, Mukaiyama established a convenient entry into stereoselective glycosidic bond construction by activating 1-hydroxy sugars with titanium oxide and triflic anhydride to couple with alcohol- and trimethylsilated-nucleophiles.[250] After screening several titanium oxides, amine bases, and solvents in the reaction, the combination of [1,2-benzenediolato(2-)-O,O']-oxotitanium (**312**), diisopropylethylamine, and CsF was determined optimal for providing the highest yield and β-selectivity in constructing the 1,2-*trans*-ribofuranosides (Table 28). This is in contrast to the use of triflic anhydride alone, which provided very little glycoside formation under the same condition.

Although the process required an excess of the titanium oxide promoter, Kobayashi and Mukaiyama were able to improve the procedure in the synthesis of 1,2-*cis*-Arabino-furanosides by accomplishing the transformation with a catalytic amount of titanium.[251] The stereoselective synthesis of these β-arabinofuranosides can problematic because they are readily isomerized to the more thermodynamically stable α- (or 1,2-*trans*-) counterpart under many conventional Lewis acid- mediated procedures. During this investigation, a dynamic ^{1}H-NMR experiment was conducted that indicated the conversion of the 1-hydroxy sugar to the trimethylsilyl sugar to be the initial step in the transformation. This trimethylsilyl sugar would then react with the trimethylsilyl ether to generate the corresponding *O*-glycoside. To simplify the reaction system, the authors decided to prepare the trimethysilyl sugar to directly serve as the donor in the glycosylation. Also, It was found that CsF generated trimethylsilyl fluoride upon exposure to TMSOTf, which had the unexpected effect of accelerating the isomerization, so it was excluded from the reaction. Better selectivities were also observed at reduced temperature.

These conditions were found to be compatible with a variety of trimethylsilylated nucleophiles (Table **29**); notably in the reaction of 1-*O*-trimethylsilyl sugar **314** and trimethylsilyl benzyl ether **315b**, where 91% of the desired glycoside **316d** was obtained as a 1:9 α/β-mixture with only 20 mol% catalyst loading at −23°C. A mechanism has been proposed to account for the β-selectivity observed in the reaction (Scheme 30). Initially, the α- and β- anomers of the 1-*O*-trimethylsilylated sugar are in equilibrium when the activated titanium complex **317** preferentially interacts with the α-arabinofuranoside. The trimethylsilyl ether nucleophile then approaches from the β- face to displace the activated leaving group and invert the anomeric center. Finally, the TMSOTf and titanium oxide are regenerated to complete the catalytic cycle.

5.2 Unprotected Carbohydrate Donors

Significant advancement to the construction of glycosidic linkage under titanium catalysis has been made with Mahrwald's recent report of a direct glycosylation using unprotected carbohydrate donors.[252] Bypassing many of the previously examined challenges in carbohydrate chemistry, including multistep protection sequences and selective activation requirements, this glycosylation protocol presents a unique approach to the activation of the anomeric center using titanium(IV) alkoxides and α-hydroxy acids (Scheme 31).

During investigation of *C-C* bond forming reactions mediated by ligand-exchange processes, Mahrwald was finding substantial amounts of acetalization byproducts in the reactions. After optimizing conditions for this observation, tetrahydrofuran- and tetrahydropyran-hemiacetals were successfully converted to their corresponding acetals in nearly quantitative yields upon exposure to 10% $Ti(OtBu)_4$ with 4% mandelic acid (**322**) in isopropanol. This finding encouraged further experimentation, where it was discovered that the reaction could be applied to glycosylation with unprotected sugars. Interestingly, when D-ribose was treated to this condition in isopropanol (Scheme 32), only the ribofuranoside product was observed, indicating kinetic control in the reaction (the pyranoside is the thermodynamic product). Little pyranoside was detected after prolonged reaction times (12 days) as well, which is contrary to results obtained under Fischer glycosylation conditions.[253] Additionally, the β-selectivities observed with the ribose substrate are higher than those attained with the Fischer glycosylation of MeOH.[254,255]

The reactions were slow under the current condition and showed only partial conversion after several days. Efforts were therefore applied to accelerating the process, where it was discovered that addition of lithium bromide significantly affects the rate and selectivity of the reaction. This effect can be seen in Scheme 33, where the glycosylation strategy was applied to a number of alcohol nucleophiles, both with and without the addition of the lithium salt. The yields in the reactions were substantially better in the presence of LiBr, though the selectivity was diminished in most cases. After the 2nd day of the reaction, furanoside products were predominantly observed with the LiBr additive, though appearance of pyranosides became evident with longer reaction times.

It is interesting to note that solvent optimization was attempted to determine the minimum requirements of acceptor needed for an efficient glycosylation. In the absence of the LiBr additive, 5 equivalents of the acceptor isopropanol were employed to furnish 58% (1:4 α/β) of the ribofuranoside in two days using propylene carbonate as a solvent. However, when addition of the lithium salt was employed in the reaction, the observed product after 2 days consisted of the more thermodynamically stable pyranoside only (71% yield). This observation is quite fortuitous because it demonstrates a convenient procedure for accessing both furanoside and pyranoside donors by a simple change to solvent in the reaction.

5.3. Summary

An efficient method for direct dehydrative glycosylation, which employs the titanium catalyst to induce a controlled condensation between 1-hydroxy glycosyl donors and nucleophilic acceptors, has been developed for the synthesis of a variety of glycoconjugates and disaccharides. This approach eliminates the need for extensive anomeric derivatization prior to anomeric activation and glycosidic bond formation. The dehydrative glycosylation procedure has been recently extended to unprotected glycosyl donors.

6. CONCLUSION AND FUTURE OUTLOOK

Mild and broadly applicable glycosylation strategies are highly desirable in the synthesis of oligosaccharides and glycoconjugates. Such approaches reduce the amount of waste resulting from undesired reactivity, extend the scope of the reaction to partners with a wider range of protecting groups, and allow for the chemoselective activation of donors in solution. The use of transition metal catalysis enables chemists to achieve remarkable selectivity in the construction of glycosidic bonds; being no longer confined to neighboring group participation or anomeric effect for directing orientation at the newly-formed anomeric linkage. The Nguyen group's use of cationic palladium with trichloroacetimidate donors provides access to both *cis*- and *trans*-selective products. In addition, their cationic nickel activation of 2-deoxy glycosyl trichloroacetimidates has provided an efficient means

for accessing the troublesome 1,2-*cis*-2-amino glycosidic linkage. Recently, the Yu group has illustrated the gold activation of *O*-glycosyl alkynylbenzoates to be a highly efficient method of glycosylation and the utility of their method is demonstrated in the synthesis of bioactive carbohydrate targets. Finally, The Gagné group has reported several elegant glycosylation reactions for stereoselectively accessing *C*-alkyl and *C*-aryl glycosides from glycosyl halides via Negishi-coupling and photoredox reactions.

Having access to robust anomeric leaving groups that are tolerant to diverse chemical reactions, yet retain the ability for selective activation under catalytic control, is enticing for synthetic carbohydrate chemists. Hotha has developed an Au-catalyzed propargyloxy- and methoxy-glycoside activation strategy to facilitate glycosylation, though such reactions are highly dependent on the electronic properties of substrates. Similar use of the alkynophilic gold catalyst has been demonstrated to activate unprotected *O*-hexynyl-glycosides by Mamidyala and Finn, thereby implying the potential for oligosaccharide and glycoconjugate synthesis with minimal protection steps.

Reactions involving the transition metal catalyzed activation of glycals have greatly advanced the field of carbohydrate chemistry. These reactions have been demonstrated to proceed with excellent selectivity, providing a scaffold for accessing a variety of natural and unnatural pyranosides. Such reactions are generally high in anomeric selectivity and provide access to a variety of free sugars through subsequent functionalization of the coupling products. Lee and Nguyen have demonstrated reagent-controlled selectivity in Ferrier reactions, though use of poorly reactive aliphatic alcohol acceptors requires preactivation with zinc. RajanBabu has employed the palladium catalyzed Ferrier reaction to the synthesis of *C*-glycosides as well. Proceeding through Pd-π-allyl intermediates as well are the glycal activation strategies of Feringa and O'Doherty, demonstrating the cyclic enone platform to be highly selective for donation of the anomeric center. The O'Doherty group has applied this strategy to key transformations in several natural product syntheses. Maddaford has reported the cyclic enone platform to be viable for anomeric *C*-*C* bond construction as well through cationic rhodium catalyzed 1,4-additions using widely available arylboronic acids. These aglycons have been employed in Heck-type couplings with other allylic alcohol derivatives. However, acceptable yields of coupling products in these reactions are limited to reactions with donors containing TBS-ethers at C(3). Toste has developed an elegant strategy that is both tolerant to moisture and air for constructing C(2)-deoxyglycosides with high-oxidation state rhenium. The reactivity of the donors in this approach is highly dependant on the nature of the protecting group at C(3), which has been exploited by Toste in his iterative 2-deoxy-oligosaccharide synthesis.

Many of the challenges involved in synthesizing carbohydrates are derived from a necessity for selective activation of a latent anomeric leaving group in the presence of dense carbohydrate functionality. Such syntheses can be streamlined by incorporating strategies that reduce the total number of steps required to accomplish this; namely, having access to glycosyl donors that do not require pre-installation of a leaving group. Kobayashi and Mukaiyama have addressed this challenge with their report of titanium-catalyzed glycosylation with 1-hydroxy sugars. The method has been applied to the stereoselective synthesis of 1,2-*cis*-arabinofuranosides, known to be challenging due to the unfavorable interactions of acceptors with functional groups at C2. The use of titanium catalyzed strategies for glycosylation has been extended recently with Mahrwald's reported direct glycosylation with unprotected carbohydrate donors. This process allows for construction of either furanosides and pyranosides by changing solvent in the reaction.

Although significant achievement has been made recently in the use of transition metal-catalyzed construction of glycosidic linkages, there are several hurdles that remain in the

field. For example, the synthesis of 2-deoxy-β-glycosides and α-sialosides are two problems that have yet to be resolved, even with state of the art technology. Although remarkable advancement has been made in the synthesis of β-mannosides by Crich,[256-258] the construction of β-mannosides can only be accomplished with the 4,6-*O*-benzylidene mannosyl donors, limiting the scope of this transformation. Such challenges present a unique opportunity for exploring transition metals as potential catalysts to overcome these problems.

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REFERENCES

(1). Schmidt RR, Kinzy W. Adv. Carbohydr. Chem. Biochem. 1994; 50:21. [PubMed: 7942254]
(2). Davis BG. J. Chem. Soc. Perkin Trans. 1. 2000:2137.
(3). Jensen KJ. J. Chem. Soc. Perkin Trans. 1. 2002:2219.
(4). Demchenko AV. Synlett. 2003:1225.
(5). Toshima K. Carbohydr. Res. 2006; 341:1282. [PubMed: 16630601]
(6). Galonic DP, Gin DY. Nature. 2007; 446:1000. [PubMed: 17460660]
(7). Demchenko, AV. Handbook of Chemical Glycosylation. Wiley-VCH; Weinheim: 2008.
(8). Plante OJ, Palmacci ER, Seeberger PH. Science. 2001; 291:1523. [PubMed: 11222853]
(9). Marcaurelle LA, Seeberger PH. Curr. Chem. Bio. 2002; 6:289.
(10). Ko K-S, Jaipuri FA, Pohl NL. J. Am. Chem. Soc. 2005; 127:13162. [PubMed: 16173741]
(11). Mamidyala SK, Ko K-S, Jaipuri G, Park NL, Pohl NL. J. Fluorine Chem. 2006; 127:571.
(12). Zhu X, Schmidt RR. Angew. Chem. Int. Ed. 2009; 48:1900.
(13). Schmidt RR, Michel J. Angew. Chem. Int. Ed. 1980; 19:731.
(14). For a comprehensive review, see: Schmidt RR, Kinzy W. Adv. Carbohydr. Chem. Biochem. 1994; 50:21. [PubMed: 7942254]
(15). Schmidt RR, Jung K-H. Adv. Carbohydr. Chem. Biochem. 2000:5.
(16). Yang J, Cooper-Vanosdell C, Mensah EA, Nguyen HM. J. Org. Chem. 2008; 73:794. [PubMed: 18184010]
(17). Schmidt RR. Angew. Chem., Int. Ed. 1986; 25:212.
(18). Hoos R, Huixin, Vasella J,A, Weiss P. Helv. Chim. Acta. 1996; 79:1757.
(19). Patil VJ. Tetrahedron Lett. 1996; 37:1481.
(20). Schmidt RR, Michel JJ. Carbohydr. Chem. 1985; 4:141.
(21). Zimmermann P, Bommer R, Bär T, Schmidt RR. J. Carbohydr. Chem. 1988; 7:435.
(22). Schmidt RR, Behrendt M, Toepfer A. Synlett. 1990:694.
(23). Schaubach R, Hemberger J, Kinzy W. Liebigs. Ann. Chem. 1991:607.
(24). Paulsen H, Wilkens R, Reck F, Brockhausen I. Liebigs. Ann. Chem. 1992:1303.
(25). Kulkarni SS, Hung S-C. Lett. Org. Chem. 2005; 2:670.
(26). Haase WC, Seeberger PH. Curr. Org. Chem. 2000; 4:481.
(27). Dobarro-Rodriguez A, Trumtel M, Wessel HP. J. Carbohydr. Chem. 1992; 11:255.
(28). Ubran FJ, Moore BS, Breitenbach R. Tetrahedron Lett. 1990; 31:4421.
(29). Waldmann H, Böhm G, Schmid U, Röttele H. Angew. Chem., Int. Ed. 1994; 33:1944.
(30). Lubineau A, Drouillat B. J. Carbohydr. Chem. 1997; 16:1179.
(31). Reed CA. Acc. Chem. Res. 1998; 31:133.
(32). Mecking S. Coord. Chem. Rev. 2000; 203:325.
(33). Mensah EA, Azzarelli JM, Nguyen HM. J. Org. Chem. 2009; 74:1650. [PubMed: 19161277]
(34). Pereda-Miranda R, Kaatz GW, Gibbons J. J. Nat. Prod. 2006; 69:406. [PubMed: 16562846]

(35). Lee K-H, Morris-Natschke SL. Pure. Appl. Chem. 1999; 71:1045.
(36). Sun IC, Kashiwada Y, Morris-Natschke SL, Lee KH. Curr. Med. Chem. 2003; 3:155.
(37). McKay MM, Naab BD, Mercer G, Nguyen H. J. Org. Chem. 2009; 74:4705. [PubMed: 19485363]
(38). Bililign T, Griffith BR, Thorson JS. Nat. Prod.Prep. 2005; 22:475.
(39). Ogawa T, Matsui M. Carbohydr. Res. 1976; 51:C13.
(40). Clerici F, Gelmi ML, Mottadelli S. J. Chem. Soc., Perkin Trans.1. 1994:985.
(41). Mukaiyama T, Katsurada M, Iida Y. Chem. Lett. 1992:2105.
(42). Kroger L, Thiem J. J. Carbohydr. Chem. 2003; 22:9.
(43). Jacobsson M, Malmberg J, Ellervik U. Carbohydr. Res. 2006; 341:1266. [PubMed: 16650391]
(44). Petitou M, van Boeckel CAA. Angew. Chem., Int. Ed. 2004; 43:3118.
(45). Echardt K. J. Nat. Prod. 1983; 46:544. [PubMed: 6631437]
(46). Magnet S, Blanchard JS. Chem. Rev. 2005; 105:477. [PubMed: 15700953]
(47). Danishefsky SJ, Allen JR. Angew. Chem., Int. Ed. 2000; 39:836.
(48). Marcaurelle LA, Bertozzi CR. Glycobiology. 2002; 12:69R.
(49). Ferguson MAJ, Williams AF. Annu. Rev. Biochem. 1988; 57:285. [PubMed: 3052274]
(50). Bongat AFG, Demchenko AV. Carbohydr. Res. 2007; 342:374. [PubMed: 17125757]
(51). Lemieux RU. Chem. Soc. Rev. 1989; 18:347.
(52). Herzner H, Reipen T, Schultz M, Kunz H. Chem. Rev. 2000; 100:4495. [PubMed: 11749356]
(53). Davis BG. Chem. Rev. 2002; 102:579. [PubMed: 11841255]
(54). Lehle L, Strahl S, Tanner W. Angew. Chem., Int. Ed. 2006; 45:6802.
(55). Paulsen H, Kalar C, Stenzel W. Chem. Ber. 1978; 111:2358.
(56). Lemieux RU, Ratclife RM. Can. J. Chem. 1979; 57:1244.
(57). Paulsen H, Lorentzen JP, Kutschker W. Carbohydr. Res. 1985; 136:153.
(58). Seeberger PH, Roehrig S, Schell P, Wang Y, Christ WJ. Carbohydr. Res. 2000; 328:61. [PubMed: 11005576]
(59). Marcaurelle LA, Bertozzi CR. Glycobiology. 2002; 12:69R.
(60). Benakli K, Zha C, Kerns RJ. J. Am. Chem. Soc. 2001; 123:9461. [PubMed: 11562237]
(61). Manabe S, Ishii K, Ito Y. J. Am. Chem. Soc. 2006; 128:10666. [PubMed: 16910646]
(62). Winterfeld GA, Schmidt RR. Angew. Chem., Int. Ed. 2001; 40:2654.
(63). Ryan DA, Gin DY. J. Am. Chem. Soc. 2008; 130:15228. [PubMed: 18950157]
(64). Watanabe I, Tsuchiya T, Takase T, Umezawa S, Umezawa H. Bull. Chem. Soc. Jpn. 1977; 50:2369.
(65). Mootoo DR, Konradsson P, Fraser-Reid B. J. Am. Chem. Soc. 1989; 111:8540.
(66). Mensah EA, Nguyen HM. J. Am. Chem. Soc. 2009; 131:8778. [PubMed: 19496537]
(67). Mensah EA, Yu F, Nguyen HM. J. Am. Chem. Soc. 2010; 132:14288. [PubMed: 20860359]
(68). Petitou M, van Boeckel CAA. Prog. Chem. Org. Nat. Prod. 1992; 60:143.
(69). van Boeckel CAA, Petitou M. Angew. Chem., Int. Ed. 1993; 32:1671.
(70). Arungundram S, Al-Mafraji K, Asong J, Leach FE III, Amster IJ, Venot A, Turnbull JE, Boons GJ. J. Am. Chem. Soc. 2009; 131:17394. [PubMed: 19904943]
(71). Petitou M, van Boeckel CAA. Prog. Chem. Org. Nat. Prod. 1992; 60:143.
(72). van Boeckel CAA, Petitou M. Angew. Chem., Int. Ed. 1993; 32:1671.
(73). Arungundram S, Al-Mafraji K, Asong J, Leach FE III, Amster IJ, Venot A, Turnbull JE, Boons GJ. J. Am. Chem. Soc. 2009; 131:17394. [PubMed: 19904943]
(74). Danishefsky SJ, Allen JR. Angew. Chem., Int. Ed. 2000; 39:836.
(75). Hotha S, Kashyap S. J. Am. Chem. Soc. 2006; 128:9620. [PubMed: 16866502]
(76). Sureshkumar G, Hotha S. Tetrahedron Lett. 2007; 48:6564.
(77). A glycosylation method involving the intermediacy of a propynyl cation has been reported, see: Mukai C, Itoh T, Hanaoka M. Tetrahedron Lett. 1997; 38:4595.

(78). For a recent review on gold catalyzed reactions, see: Hashmi ASK. Chem. Rev. 2007; 107:3180. [PubMed: 17580975]

(79). Asao N, Aikawa H, Tago S, Umetsu K. Org. Lett. 2007; 9:4299. [PubMed: 17880231]

(80). Li Y, Yang Y, Yu B. Tetrahedron Lett. 2007; 49:3604.

(81). Li Y, Yang Y, Liu Y, Zhu C, Yang Y, Yu B. Chem. Eur. J. 2010; 16:1871–1882. [PubMed: 20039348]

(82). Wulff G, Röhle G. Angew. Chem.Int. Ed. 1974; 86:173–187.

(83). Demchenko A, Stauch T, Boons GJ. Synlett. 1997:818.

(84). Adinolfi M, Iadonisi A, Ravida A, Schiattarella M. Tetrahedron Lett. 2004; 45:4485.

(85). Oberli MA, Bindschadler P, Werz DB, Seeberger PH. Org. Lett. 2008; 10:905. [PubMed: 18232704]

(86). Marzabadi CH, Frank RW. Tetrahedron. 2000; 56:8385.

(87). Hou D, Lowary TL. Carbohydr. Res. 2009; 344:1911. [PubMed: 19716123]

(88). For recent examples, see: Park J, Boltje TJ, Boons G. J. Org. Lett. 2008; 10:4367.

(89). Lu YS, Li Q, Zhang LH, Ye XS. Org. Lett. 2008; 10:3445. [PubMed: 18630923]

(90). Yugen Z, Yu B. Angew. Chem. Int. Ed. 2011; 50:8329.

(91). Zhu C, Tang P, Yu B. J. Am. Chem. Soc. 2008; 130:5872. [PubMed: 18407637]

(92). Ma Y, Li Z, Shi H, Zhang J, Yu B. J. Org. Chem. 2011; 76:9748. [PubMed: 22054226]

(93). Yang Y, Li Y, Yu B. J. Am. Chem. Soc. 2009; 131:12076. [PubMed: 19663423]

(94). Yang W, Sun J, Lu W, Li Y, Shan L, Han W, Zhang W, Yu B. J. Org. Chem. 2010; 75:6879. [PubMed: 20839821]

(95). Yang W, Ma Y, Sun J, Shan L, Zhang W, Yu B. Synlett. 2011; 7:915.

(96). Liao J, Sun J, Niu Y, Yu B. Tetrahedron Lett. 2011; 52:3075.

(97). Yang Y, Li Y, Yu B. Tetrahedron Lett. 2010; 51:1504.

(98). Zhang Q, Sun J, Zhu Y, Zhang F, Yu B. Angew. Chem. Int. Ed. 2011; 50:4933.

(99). Usuki H, Nitoda T, Ichikawa M, Yamaji N, Iwashita T, Komura H, Kanzaki H. J. Am. Chem. Soc. 2008; 130:4146. [PubMed: 18307344]

(100). Merzendorfer H, Zimoch L. J. Exp. Biol. 2003; 206:4393. [PubMed: 14610026]

(101). Horsch M, Mayer C, Sennhauser U, Rast DM. Pharmacol. Ther. 1997; 76:187. [PubMed: 9535180]

(102). Gauthier C, Legault J, Pichette A. Mini-Rev. Org. Chem. 2009; 6:321.

(103). Cioffi G, Braca A, Autore G, Morelli I, Pinto A, Venturella F, De Tommasi N. Planta Med. 2003; 69:750. [PubMed: 14531027]

(104). Braca A, Autore G, De Simone F, Marzocco S, Morelli I, Venturella F, De Tommasi N. Planta Med. 2004; 70:960. [PubMed: 15490325]

(105). Just MJ, Recio MC, Giner RM, Cuellar MJ, Manez S, Bilia AR, Rios J-L. Planta Med. 1998; 64:404. [PubMed: 9690340]

(106). Yoshizumi K, Hirano K, Ando H, Hirai Y, Ida Y, Tsuji T, Tanaka T, Satouchi K, Terao J. J. Agric. Food Chem. 2006; 54:335. [PubMed: 16417288]

(107). Odinokova LE, Oshitok GI, Denisenko VA, Afufriev VF, Tolkach AM, Uvarova NI. Khim. Prir. Soedin. 1984:182.Chem. Abstr. 1985; 102:24940.

(108). Odinokova LE, Denisenko MV, Denisenko VA, Uvarova NI. Khim. Prir. Soedin. 1988:212.Chem. Abstr. 1988; 109:231406.

(109). Klinotova E, Krecek V, Klinot J, Endova M, Eisenreichova J, Budesinsky M, Sticha M. Collect. Czech. Chem. Commun. 1997; 62:1776.

(110). Samoshina NF, Denisenko MV, Denisenko VA, Uvarova NI. Chem. Nat. Compd. 2003; 39:575.

(111). Ohara S, Ohira TJ. Wood Sci. 2003; 49:59.

(112). Gauthier C, Legault J, Lebrun M, Dufour P, Pichette A. Bioorg. Med. Chem. 2006; 14:6713. [PubMed: 16787747]

(113). Thibeault D, Gauthier C, Legault J, Bouchard J, Dufour P, Pichette A. Bioorg. Med. Chem. 2007; 15:6144. [PubMed: 17614290]

(114). Gauthier C, Legault J, Lavoie S, Rondeau S, Tremblay S, Pichette A. Tetrahedron. 2008; 64:7386.

(115). Gauthier C, Legault J, Lavoie S, Rondeau S, Tremblay S, Pichette A. J. Nat. Prod. 2009; 72:72. [PubMed: 19115839]

(116). Cmoch P, Pakulski Z, Swaczynova J, Strnad M. Carbohydr. Res. 2008; 343:995. [PubMed: 18328468]

(117). Li Y, Sun J, Yu B. Org. Lett. 2011; 13:5508. [PubMed: 21923107]

(118). Li Y, Yu B. Chem. Commun. 2010; 46:6060.

(119). Meerwein H, Hinz G, Hoffman E, Kroning E, Pfeil E. J. Prakt. Chem. 1937; 147:257.

(120). Meerwein H, Delfs D, Morschel H. Angew. Chem. Int. Ed. 1960; 72:927.

(121). McCarthy BJ, Hogen-Esch TE. Macromolecules. 1996; 29:3035.

(122). Yoshida E, Sugita A. Macromolecules. 1996; 29:6422.

(123). Dubreuil MF, Farcy NG, Goethals EJ. Macromol. Rapid Commun. 1999; 20:383.

(124). Oike H, Yoshioka Y, Kobayashi S, Nakashima M, Tezuka Y, Goethals EJ. Macromol. Rapid Commun. 2000; 21:1185.

(125). van Renterghem LM, Goethals EJ, du Prez FE. Macromolecules. 2006; 39:528.

(126). Theiler S, Hovetborn T, Keul H, Moller M. Macromol. Chem. Phys. 2009; 210:614.

(127). For recent a review in C-glycoside biology, see: Hultin PG. Curr. Top. Med. Chem. 2005; 5:1299. [PubMed: 16305533]

(128). Zou W. Curr. Top. Med. Chem. 2005; 5:1363. [PubMed: 16305536]

(129). Compain P, Martin OR. Bioorg. Med. Chem. 2001; 9:3077. [PubMed: 11711283]

(130). Nicotra F. Top. Curr. Chem. 1997; 187:55.

(131). Levy, DE.; Tang, C. The Chemistry of C-Glycosides. Pergamon; Tarrytown, NY: 1995.

(132). Lin CH, Lin HC, Yang WB. Curr. Top. Med. Chem. 2005; 5:1431–1457. [PubMed: 16305538]

(133). For reviews in C-glycoside synthesis, see: Postema MHD. C-Glycoside Synthesis. 1995CRC Press, Inc.Boca Raton, FL

(134). Somsak L. Chem. Rev. 2001; 101:81. [PubMed: 11712195]

(135). Meo, P.; Osborn, HMI. Best Synthetic Methods. Carbohydrates; Elsevier Science Ltd.; New York: 2003. p. 337

(136). Du Y, Linhardt RJ, Vlahov IR. Tetrahedron. 1998; 54:9913.

(137). For reviews in *C*-aryl glycoside biology and synthesis, see: Bililign T, Griffith BR, Thorson JS. Nat. Prod. Rep. 2005; 22:742. [PubMed: 16311633]

(138). Lee DYW, He M. Curr. Top. Med. Chem. 2005; 5:1333. [PubMed: 16305534]

(139). Wellington KW, Benner SA. Nucleosides Nucleotides Nucleic Acids. 2006; 25:1309. [PubMed: 17067955]

(140). For inhibition of β-H elimination in nonpincer Pd systems, see: Oestereich M, Dennison PR, Kodanko JJ, Overman LE. Angew. Chem., Int. Ed. 2001; 40:1439.

(141). Zhang L, Zetterberg K. Organometallics. 1991; 10:3806.

(142). Arnek R, Zetterberg K. Organometallics. 1987; 6:1230.

(143). Arai I, Daves GD Jr. J. Am. Chem. Soc. 1981; 103:7683.

(144). Hahn C, Cucciolito ME, Vitagliano A. J. Am. Chem. Soc. 2002; 124:9038. [PubMed: 12148993]

(145). Cucciolito ME, D'Amora A, Vitagliano A. Organometallics. 2005; 24:3359.

(146). Kerber WD, Koh JH, Gagné MR. Org. Lett. 2004; 6:3013. [PubMed: 15330671]

(147). Feducia J, Campbell AN, Doherty MQ. J. Am. Chem. Soc. 2006; 128:13290. [PubMed: 17017811]

(148). Arp FO, Fu GC. J. Am. Chem. Soc. 2005; 127:10482. and references therein. [PubMed: 16045323]

(149). Cárdenas DJ. Angew. Chem., Int. Ed. 2003; 42:384.

(150). Gong H, Sinisi R, Gagné MR. J. Am. Chem. Soc. 2007; 129:1908. [PubMed: 17261000]

(151). Gong H, Gagné MR. J. Am. Chem. Soc. 2008; 130:12177. [PubMed: 18698769]

(152). Gong H, Andrews S, Zuccarello JL, Lee SJ, Gagné MR. Org. Lett. 2009; 11:879. [PubMed: 19170565]
(153). Andrews RS, Becker JJ, Gagné MR. Angew. Chem. Int. Ed. 2010; 49:7274.
(154). Fraser-Reid BO, Konradsson P, Mootoo DR, Udodong UE. J. Chem. Soc, Chem. Commun. 1988:823.
(155). Zufan W, Ottosson H, Merritt R, Rao S, Roberts C, Madsen R. Synlett. 1992:927.
(156). Udodong UE, Madsen R, Roberts C, Fraser-Reid BO. J. Am. Chem. Soc. 1993; 115:7886.
(157). Merritt JR, Fraser-Reid BO. J. Am. Chem. Soc. 1994; 116:8334.
(158). Fraser-Reid B, Wu Z, Udodong UE, Ottosson H. J. Org. Chem. 1990; 55:6068.
(159). Mootoo DR, Date V, Fraser-Reid BO. J. Am. Chem. Soc. 1988; 110:2662.
(160). Mootoo DR, Konradsson P, Fraser-Reid BO. J. Am. Chem. Soc. 1989; 111:8540.
(161). The diminished conversion in the reaction is attributed to the poor solubility of the cholesterol acceptor in acetonitrile, see reference 75.
(162). Hashmi ASK, Frost TM, Bats JW. J. Am. Chem. Soc. 2000; 122:11553.
(163). Hashmi ASK, Ding L, Bats JW, Fischer P, Frey W. Chem.sEur. J. 2003; 9:4339.
(164). Asao N, Aikawa H, Yamamoto Y. J. Am. Chem. Soc. 2004; 126:7458. [PubMed: 15198590]
(165). Arcadi A, Bianchi G, Marinelli F. Synthesis. 2004:610.
(166). Yao T, Zhang X, Larock RC. J. Am. Chem. Soc. 2004; 126:11164. [PubMed: 15355093]
(167). Hashmi ASK, Sinha P. AdV. Synth. Catal. 2004; 346:432.
(168). Staben ST, Kennedy-Smith JJ, Toste FD. Angew. Chem., Int. Ed. 2004; 43:5350.
(169). Nieto- Oberhuber C, Munoz MP, Bunuel E, Nevado C, Cardenas DJ, Echavarren AM. Angew. Chem., Int. Ed. 2004; 43:2402.
(170). Zhang L, Kozmin SA. J. Am. Chem. Soc. 2005; 127:6962. [PubMed: 15884934]
(171). Yao X, Li CJ. J. Am. Chem. Soc. 2004; 126:6884. [PubMed: 15174855]
(172). Shi Z, He C. J. Am. Chem. Soc. 2004; 126:5964. [PubMed: 15137751]
(173). Shi Z, He C. J. Org. Chem. 2004; 69:3669. [PubMed: 15152995]
(174). Shi X, Gorin DJ, Toste FD. J. Am. Chem. Soc. 2005; 127:5802. [PubMed: 15839674]
(175). Genin E, Toullec PY, Antoniotti S, Brancour C, Genet JP, Michelet V. J. Am. Chem. Soc. 2006; 128:3112. [PubMed: 16522069]
(176). Kayastha AK, Hotha S. Tetrahedron Lett. 2010; 52:5269.
(177). Vidadala SR, Gayatri G, Sastry GN, Hotha S. Chem. Commun. 2011:9906.
(178). Previato JO, Gorin PA, Mazurek M, Xavier MT, Fournet B, Wieruszesk JM, Mendoca-Previato L. J. Biol. Chem. 1990; 265:2518. [PubMed: 2406236]
(179). Schofield L, Hewitt MC, Evans K, Siomos MIA, Seeberger PH. Nature. 2002; 418:785. [PubMed: 12181569]
(180). Schaeffer ML, Khoo KH, Besra GS, Chatterjee D, Brennan PJ. J. Biol. Chem. 1999; 274:31625. [PubMed: 10531370]
(181). Macho V, Acklin W, Hildenbrand C, Weiber F, Arigoni D. Experientia. 1983; 39:343.
(182). Mukaiyama T, Yamada M, Suda S, Yokomizo Y, Kobayashi S. Chem. Lett. 1992:1401.
(183). Mukaiyama T, Hashimoto Y, Shoda S. Chem. Lett. 1983:935.
(184). Kawabata Y, Kaneko S, Kusakabe I, Gama Y. Carbohydr. Res. 1995; 267:39. [PubMed: 7697668]
(185). Ding X, Kong F. Carbohydr. Res. 1996; 286:161.
(186). D'Souza FW, Lowary TL. Org. Lett. 2000; 2:1493. [PubMed: 10814481]
(187). D'Souza FW, Ayers JD, McCarren PR, Lowary TL. J. Am. Chem. Soc. 2000; 122:1251.
(188). Banhaoud T, Sanchez S, Prandi J. Chem. Commun. 2000:659.
(189). Sanchez S, Banhaoud T, Prandi J. Tetrahedron Lett. 2000; 41:7447.
(190). Mereyala HB, Hotha S, Gurjar MK. Chem. Commun. 1998:685.
(191). Arasappan A, Fraser-Reid B. Tetrahedron Lett. 1995; 36:7967.
(192). Lu J, Fraser-Reid B. Org. Lett. 2004; 6:3051. [PubMed: 15330585]

(193). Sureshkumar G, Hotha S. Chem. Commun. 2008:4282.
(194). Shaikh AY, Sureshkumar G, Pati D, Gupta SS, Hotha S. Org. Biomol. Chem. 2011; 9:5951. [PubMed: 21483986]
(195). Mamidyala SK, Finn MG. J. Org. Chem. 2009; 74:8417. [PubMed: 19827757]
(196). Shafizadeh F, Furneaux RH, Stevenson TT, Cochran TG. Carbohydr. Res. 1978; 67:433.
(197). Černý M, Staněk J. Adv. Carbohydr. Chem. Biochem. 1977; 34:23.
(198). Hann RM, Hudson CS. J. Am. Chem. Soc. 1942; 64:2435.
(199). Sureshkumar G, Hotha S. Tetrahedron Lett. 2007; 48:6564.
(200). Vidadala SR, Hotha S. Chem. Commun. 2009:2505.
(201). Kim H, Men H, Lee C. J. Am. Chem. Soc. 2004; 126:1336. [PubMed: 14759180]
(202). The difficulty of forming a π-allyl palladium species from a glycal system has been noted, see: RajanBabu TV. J. Org. C zhem. 1985; 50:3642.
(203). Babu RS, O'Doherty GA. J. Am. Chem. Soc. 2003; 125:12406. [PubMed: 14531673]
(204). Comely AC, Eelkema R, Minnaard AJ, Feringa BL. J. Am. Chem. Soc. 2003; 125:8714. [PubMed: 12862452]
(205). Wang H-YL, Rojanasakul Y, O'Doherty GA. ACS Med. Chem. Lett. 2011; 2:264. [PubMed: 21660118]
(206). Fraser-Reid B, Wu Z, Andrews CW, Skowronski E, Bowen JP. J. Am. Chem. Soc. 1991; 113:1434.
(207). Schuff BP, Mercer GJ, Nguyen HM. Org. Lett. 2007; 9:3173. [PubMed: 17616145]
(208). Barder TE, Buchwald SL. J. Am. Chem. Soc. 2007; 129:5096. [PubMed: 17388595]
(209). Yougai S, Miwa T. J. Chem. Soc., Chem. Commun. 1983:68.
(210). Dunkerton LV, Serino AJ. J. Org. Chem. 1982; 47:2812.
(211). Trost BM, Gowland FW. J. Org. Chem. 1979; 44:3448.
(212). Balamurugan R, Koppolu SR. Tetrahedron. 2009; 65:8139.
(213). For a review, see: Holder NL. Chem. Rev. 1982; 82:287.
(214). For selected examples, see: Plaumann DE, Fitzsimmons BJ, Ritchie BM, Fraser-Reid B. J. Org. Chem. 1982; 47:941.
(215). Achmatowicz O Jr. Burzyńska MH. Tetrahedron. 1982; 38:3507.
(216). Panfil I, Chmielewski M. Tetrahedron. 1985; 41:4713.
(217). Georgiadis MP, Couladouros EA. J. Heterocycl. Chem. 1991; 28:1325.
(218). López Tudanca PL, Jones K, Brownbridge P. J. Chem. Soc., Perkin Trans. 1. 1992:533.
(219). Taniguchi T, Nakamura K, Ogasawara K. Synlett. 1996:971.
(220). Taniguchi T, Ohnishi H, Ogasawara K. Chem. Commun. 1996:1477.
(221). Caddick S, Khan S, Frost LM, Smith NJ, Cheung S, Pairaudeau G. Tetrahedron. 2000; 56:8953.
(222). Hoffmann HMR, Krumwiede D, Mucha B, Oehlerking HH, Prahst GW. Tetrahedron. 1993; 49:8999.
(223). Harris JM, Keränen MD, Nguyen H, Young VG, O'Doherty GA. Carbohydr. Res. 2000; 328:17. [PubMed: 11005573]
(224). Van der Deen H, Van Oeveren A, Kellogg RM, Feringa BL. Tetrahedron Lett. 1999; 40:1755.
(225). Babu RS, Zhou M, O'Doherty GA. J. Am. Chem. Soc. 2004; 126:3428. [PubMed: 15025462]
(226). Wu B, Li W, O'Doherty GA. Org. Lett. 2010; 12:5466. [PubMed: 21038879]
(227). Guo H, O'Doherty GA. J. Org. Chem. 2008; 73:5211. [PubMed: 18563936]
(228). Zhou M, O'Doherty GA. Org. Lett. 2006; 8:4339. [PubMed: 16956221]
(229). Depenbrock H, Bornschlegl S, Peter R, Rohr J, Schmid P, Schweighart P, Block T, Rastetter J, Hanauske AR. Ann. Hematol. 1996; 73:A80.
(230). Rohr J, Wohlert SE, Oelkers C, Kirschning A, Ries M. Chem. Commun. 1997:973.
(231). Crow RT, Rosenbaum B, Smith R III, Guo Y, Ramos KS, Sulikowski GA. Bioorg. Med. Chem. Lett. 1999; 9:1663. [PubMed: 10397496]
(232). For chemical synthesis of the trisaccharide, see: Kirschning A. Eur. J. Org. Chem. 1998:2267.

(233). For chemical synthesis of hexasaccharide, see: Guo Y, Sulikowski GA. J. Am. Chem. Soc. 1998; 120:1392.

(234). Yu B, Wang P. Org. Lett. 2002; 4:1919. [PubMed: 12027647]

(235). Roush WR, Bennett CE. J. Am. Chem. Soc. 2000; 122:6124.

(236). Tanaka H, Yamaguchi S, Yoshizawa A, Takagi M, Shin-ya K, Takahashi T. Chem.—Asian J. 2010; 5:1407. [PubMed: 20480491]

(237). For total synthesis of Landomycin A, see: Yang X, Fu B, Yu B. J. Am. Chem. Soc. 2011; 133:12433. [PubMed: 21780843]

(238). Zhou M, O'Doherty GA. Org. Lett. 2008; 10:2283. [PubMed: 18461951]

(239). Shan M, O'Doherty GA. Org. Lett. 2006; 8:5149. [PubMed: 17048865]

(240). Shan M, O'Doherty GA. Org. Lett. 2010; 12:2986. [PubMed: 20518547]

(241). Benhaddou R, Czernecki S, Ville G. J. Org. Chem. 1992; 57:4612.

(242). Sakai M, Hayashi H, Miyaura N. Organometallics. 1997; 16:4229.

(243). Takaya Y, Ogasawara M, Hayashi T. J. Am. Chem. Soc. 1998; 120:5579.

(244). Sakuma S, Sakai M, Itooka R, Miyaura N. J. Org. Chem. 2000; 65:5951. [PubMed: 10987927]

(245). Ramnauth J, Poulin O, Bratovanov SS, Rakhit S, Maddaford SP. Org. Lett. 2001; 3:2571. [PubMed: 11483063]

(246). Kotha S, Lahiri K, Kashinath D. Tetrahedron. 2002; 58:9633.

(247). Xiong DC, Zhang LH, Ye XS. Org. Lett. 2009; 11:1709. [PubMed: 19301870]

(248). Xiang S, Cai S, Zeng J, Liu XW. Org. Lett. 2011; 13(17):4608. [PubMed: 21815638]

(249). Sherry BD, Loy RN, Toste FD. J. Am. Chem. Soc. 2004; 126:4510. [PubMed: 15070356]

(250). Suda S, Mukaiyama T. Chem. Lett. 1991:431.

(251). Mukaiyama T, Yamada M, Suda S, Yokomizo Y, Kobayashi S. Chem. Lett. 1992:1401.

(252). Pfaffe M, Mahrwald R. Org. Lett. 2012; 14:792. [PubMed: 22263888]

(253). Sanki AK, Boucau J, Srivastava P, Adams SS, Ronning DR, Sucheck SJ. Bioorg. Med. Chem. 2008; 16:5672. [PubMed: 18450455]

(254). Wu J, Serianni AS. Carbohydr. Res. 1991; 210:51. [PubMed: 1652354]

(255). Schulze O, Voss J, Adiwidjaja G. Synlett. 2001:229.

(256). Crich D, Sun S. J. Am. Chem. Soc. 1998; 120:435.

(257). Crich D, Chandrasekera NS. Angew. Chem. Int. Ed. 2004; 43:5386.

(258). Crich DJ. Carbohydr. Chem. 2002; 21:667.

(259). Mock M, Fouet A. Annu. Rev. Microbiol. 2001; 55:647. [PubMed: 11544370]

(260). Brossier F, Mock M. Toxicon. 2001; 39:1747. [PubMed: 11595637]

(261). Usuki H, Nitoda T, Ichikawa M, Yamaji N, Iwashita T, Komura H, Kanzaki H. J. Am. Chem. Soc. 2008; 130:4146. [PubMed: 18307344]

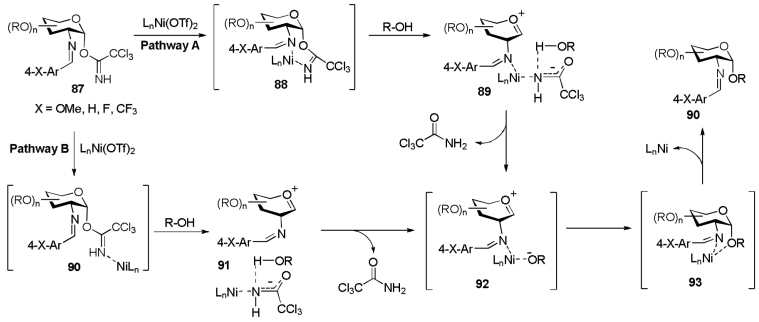


Figure 1.
Proposed Mechanism for Nickel-Catalyzed 1,2-*Cis*-2-Amino Glycosylation

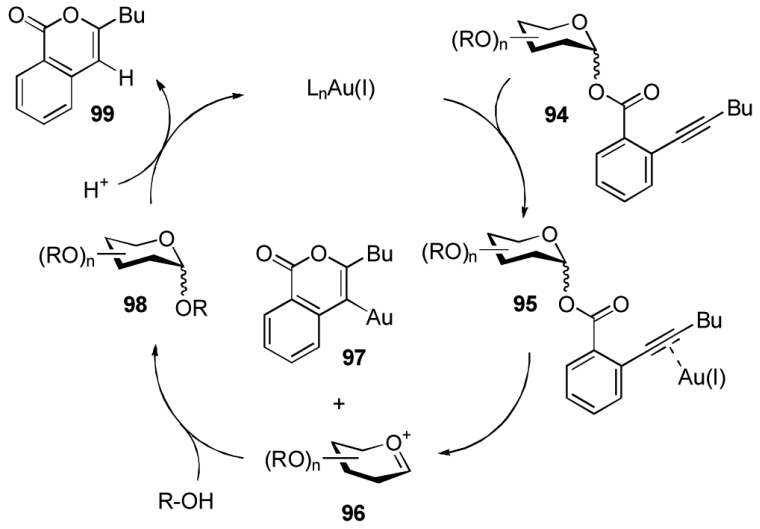


Figure 2.
Proposed Catalytic Cycle of Gold-Catalyzed Glycosylation

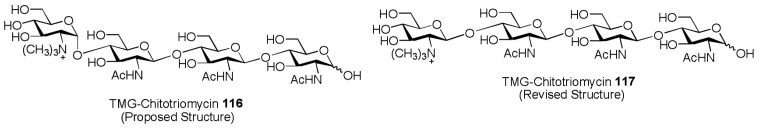


Figure 3.
Proposed and Revised Structure of TMG Chitotriomycin

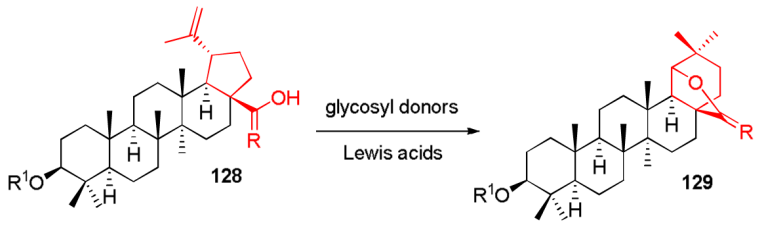


Figure 4.
Wagner-Meerwein Rearrangement in Presence of Lewis Acid

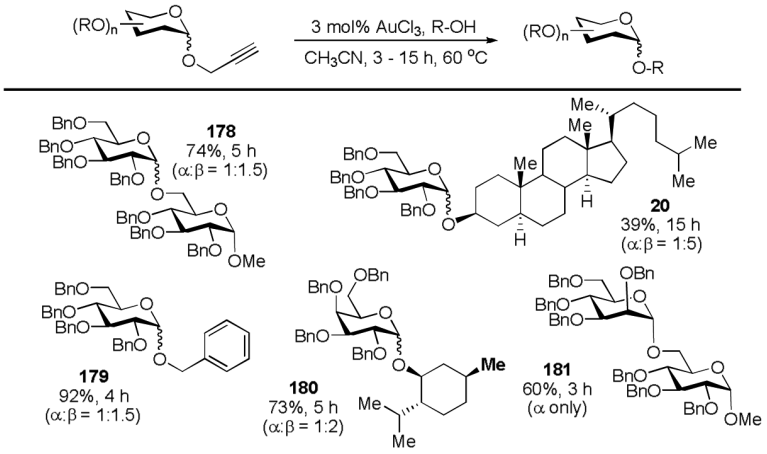


Figure 5.
Synthesis of Glycosides from Propargyl Glycosides

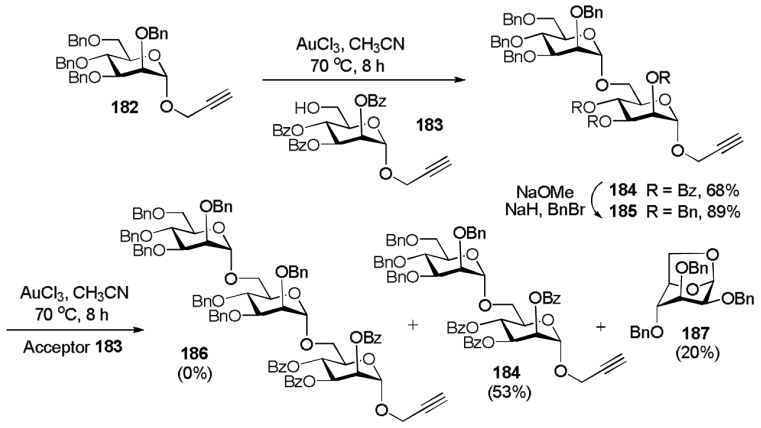


Figure 6.
Attempted Synthesis of Trisaccharide

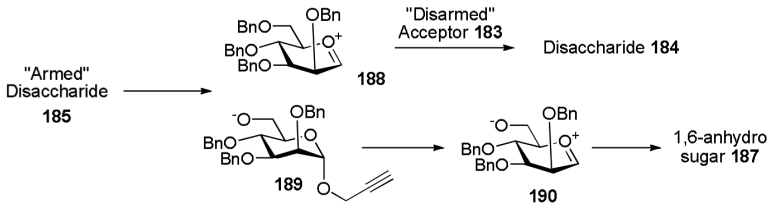


Figure 7.
Mechanistic Rationale

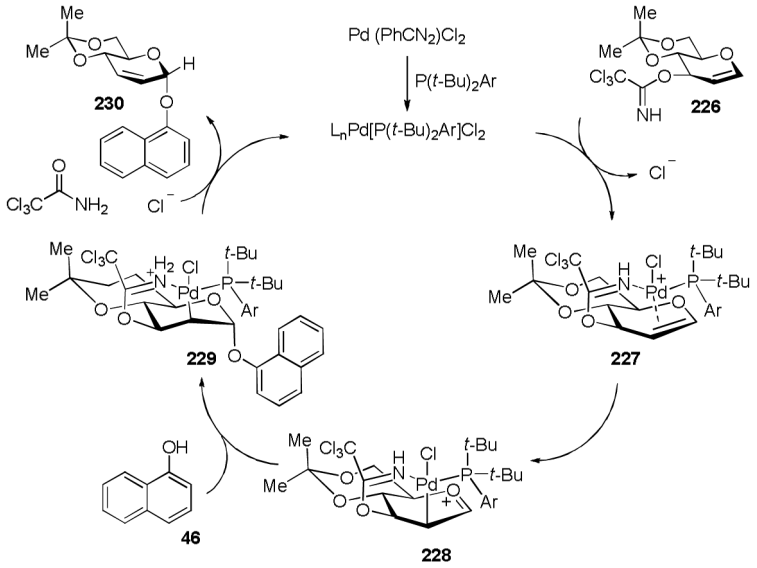


Figure 8.
Proposed Catalytic Cycle of Pd(II)-Catalyzed Glycosylation

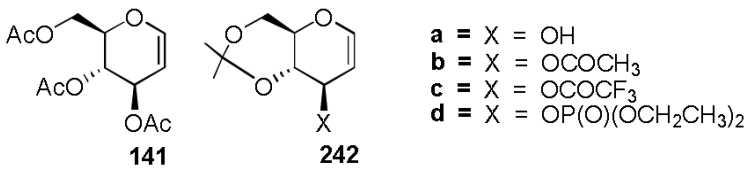
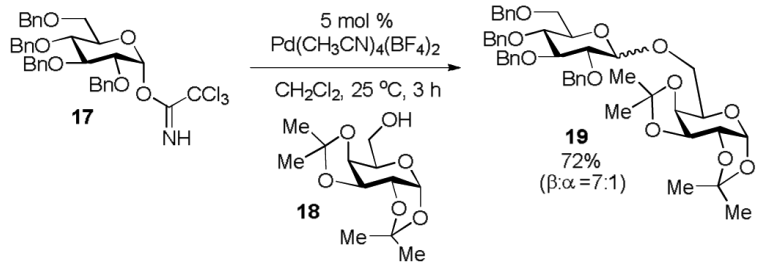
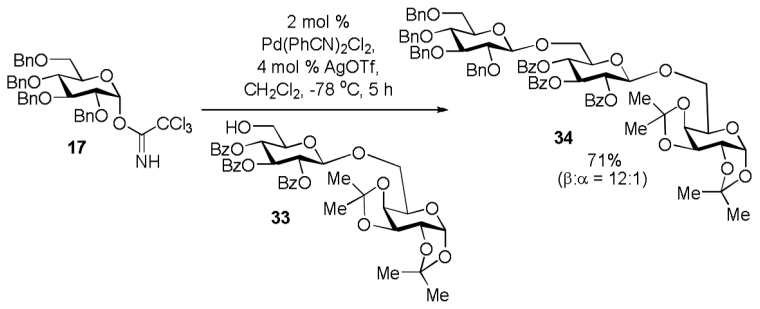


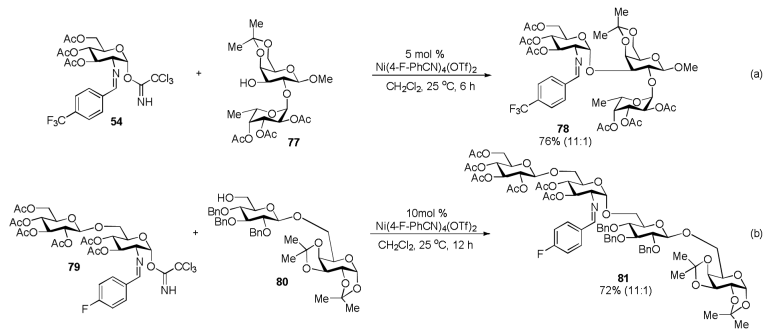
Figure 9.
Screening Glycosyl Donors



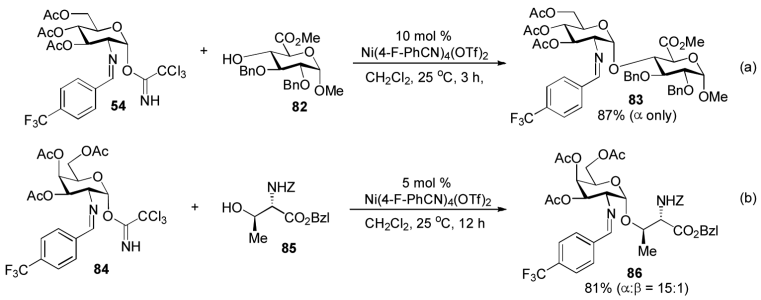
Scheme 1.
Cationic Palladium-Catalyzed β-Selective Coupling



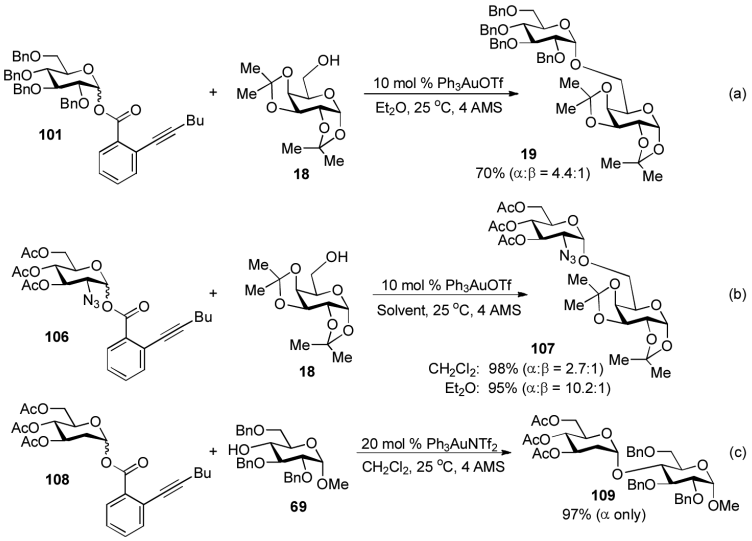
Scheme 2.
$Pd(PhCN)_2(OTf)_2$ Catalyzed Formation of Trisaccharide



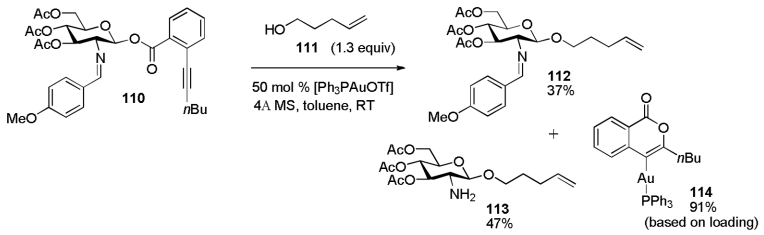
Scheme 3.
Nickel-Catalyzed α-Oligosaccharide Formation



Scheme 4.
Synthesis of Biologically Important Carbohydrate Molecules

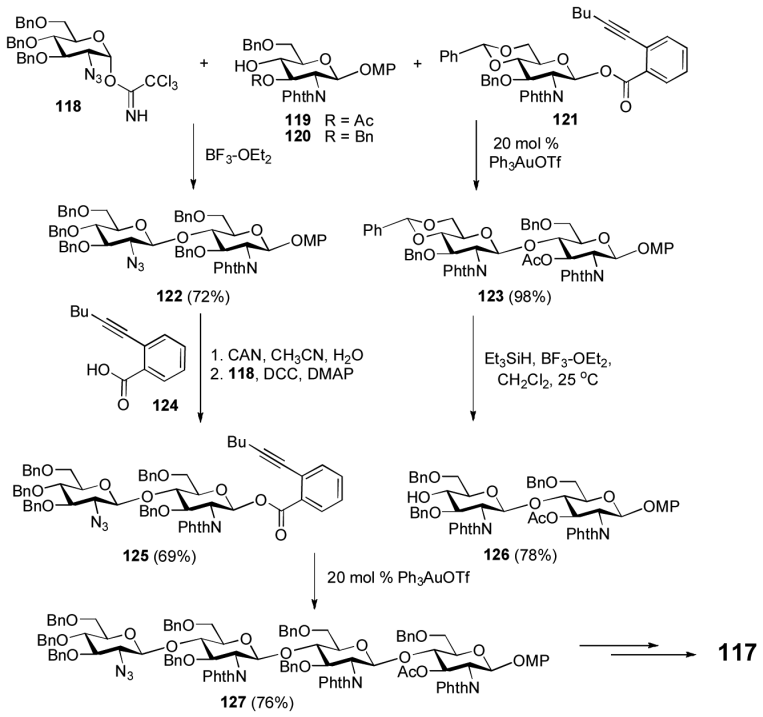


Scheme 5.
Au(I)-Catalyzed Coupling with C(2)-Non-Neighboring Participation Donors

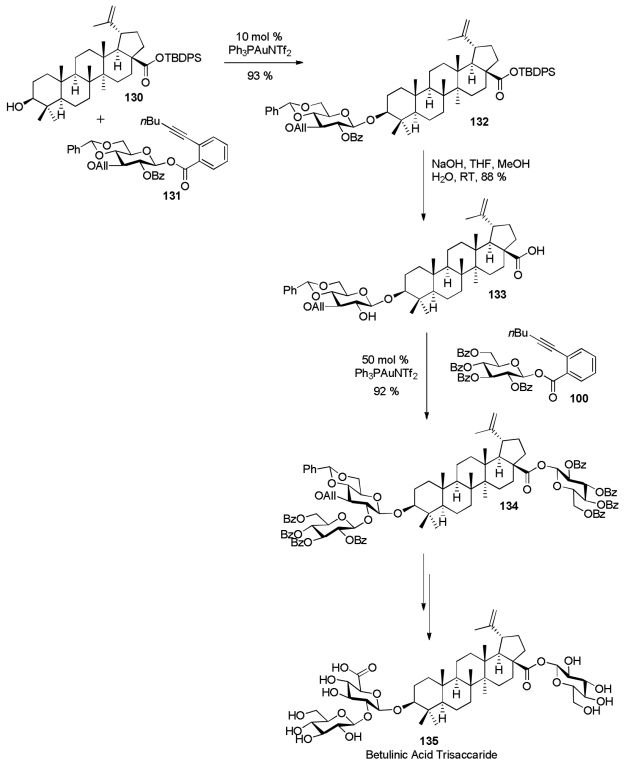


Scheme 6.

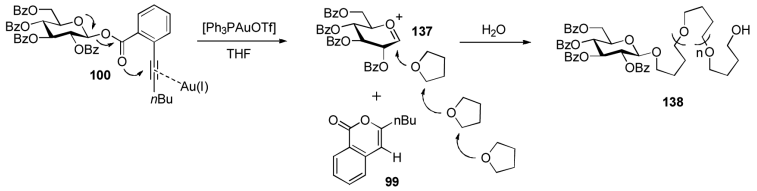
Glycosylation with 2-*p*-methoxybenzilideneamino-β-D-glucopyranosyl *o*-hexynylbenzoate **110**



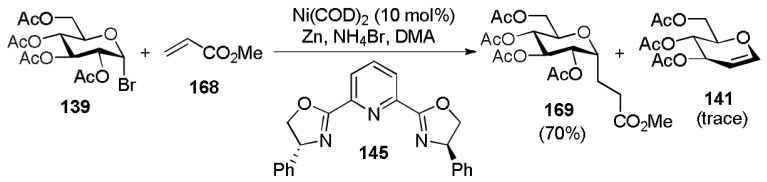
Scheme 7.
Synthesis of TMG-Chitotriomycin



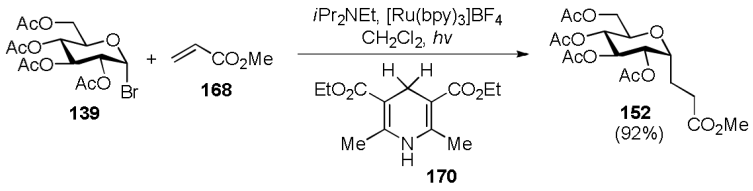
Scheme 8.
Synthesis of Lupane-Type Saponin Betulinic Acid Trisaccharide



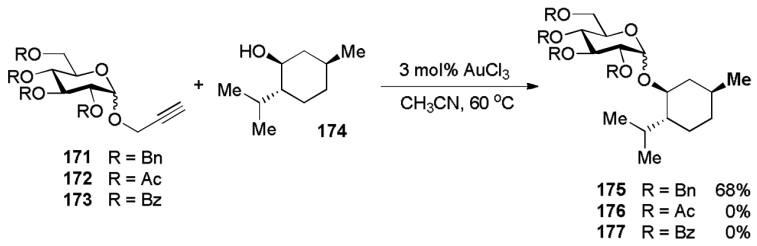
Scheme 9.
Glycosylation-Initiated Polymerization of tetrahydrofuran



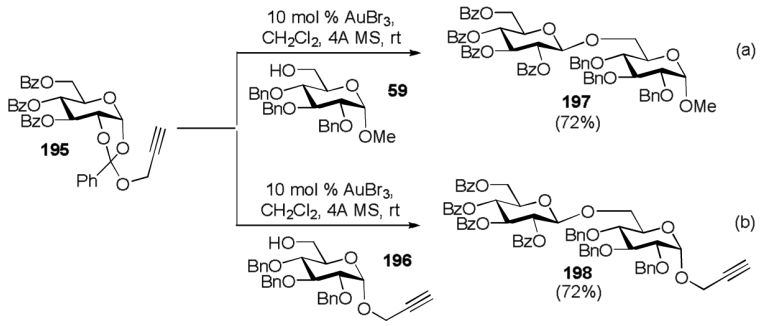
Scheme 10.
Optimization Studies



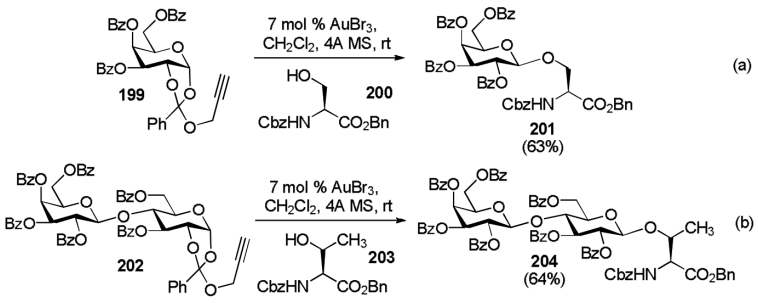
Scheme 11.
Visible Light Mediated Addition of Glycosyl Bromide to Alkene



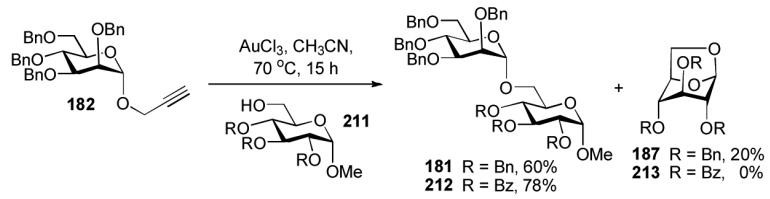
Scheme 12.
Propargyl Glycosides as Glycosyl Donors



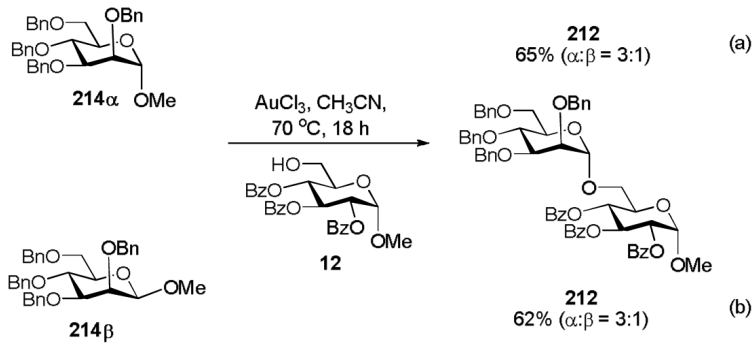
Scheme 13.
Propargyl 1,2-Orthoester as Glycosyl Donor



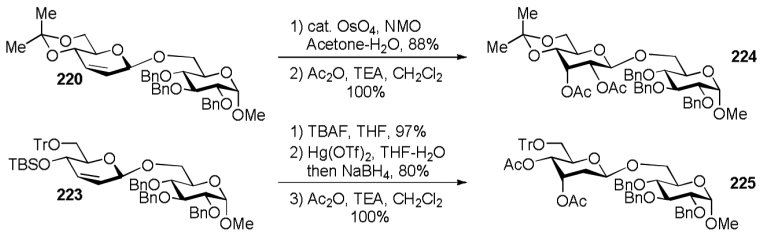
Scheme 14.
Synthesis of Amino Acid *O*-Glycosides



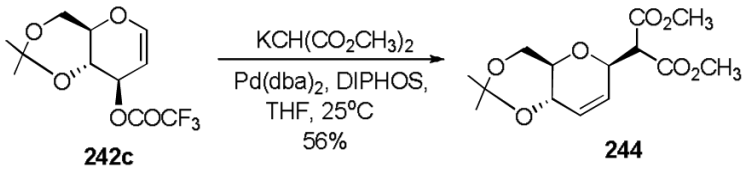
Scheme 15.
Synthesis of Disaccharides



Scheme 16.
Synthesis of Disaccharide from α/β-Methyl Glycoside Donors

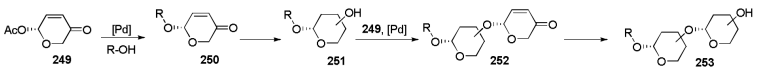


Scheme 17.
Functionalization of 2,3-Unsaturated *O*-Glycosides

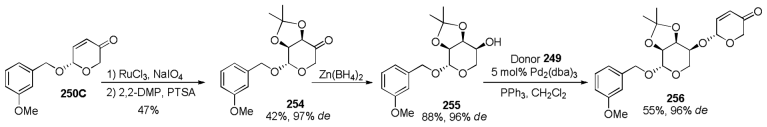


242c 244

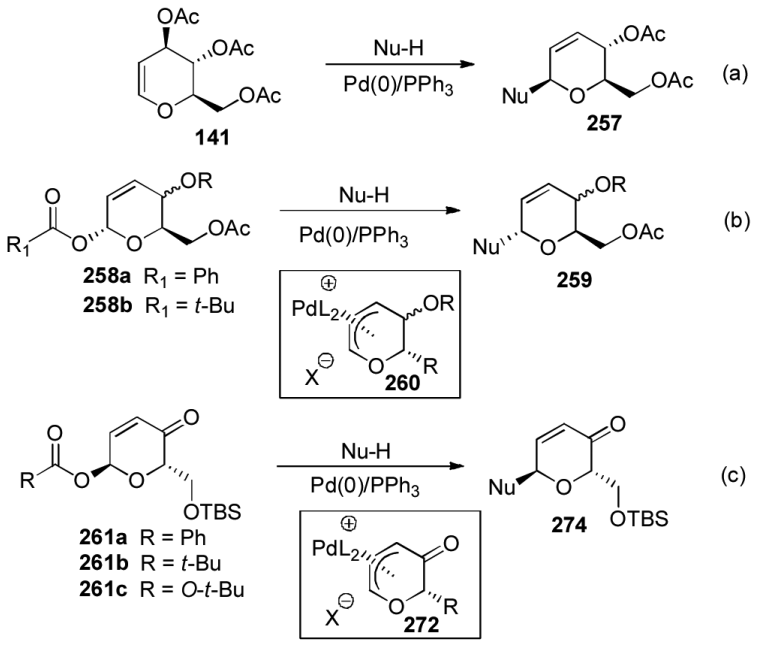
Scheme 18.
Pd-Catalyzed *C*-Glycosylation



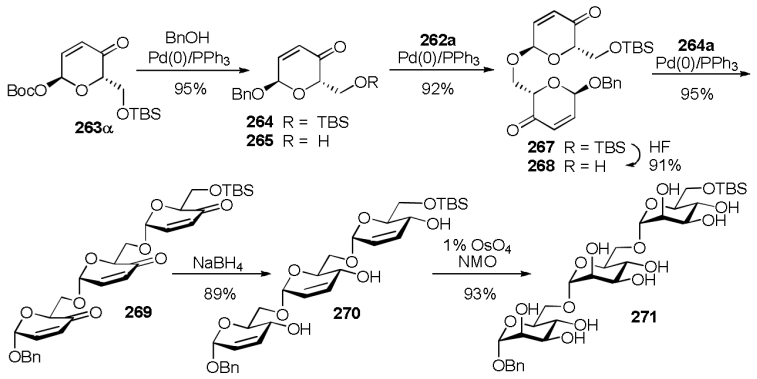
Scheme 19.
Iterative Oligosaccharide Synthesis via Palladium Catalysis



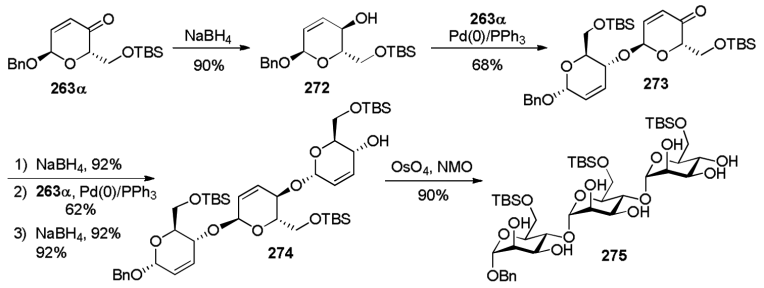
Scheme 20.
Iterative Oligosaccharide Synthesis



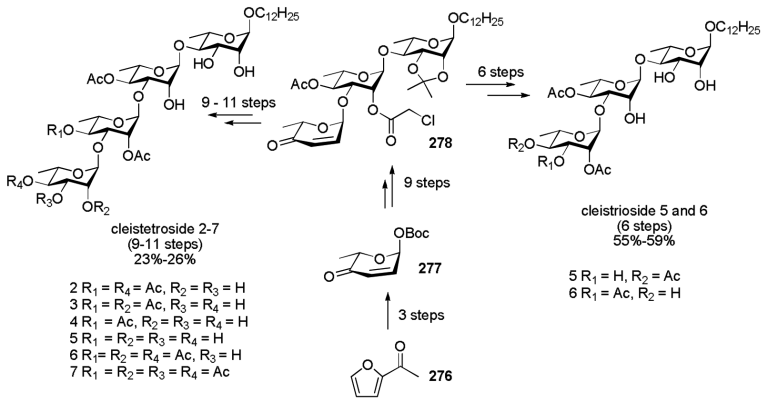
Scheme 21.
Pd-Catalyzed Glycosylation with Pyranone Donors



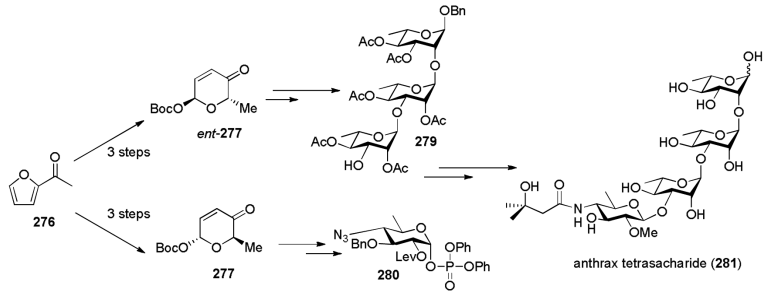
Scheme 22.
Synthesis of α-1,6-Linked Trisaccharide



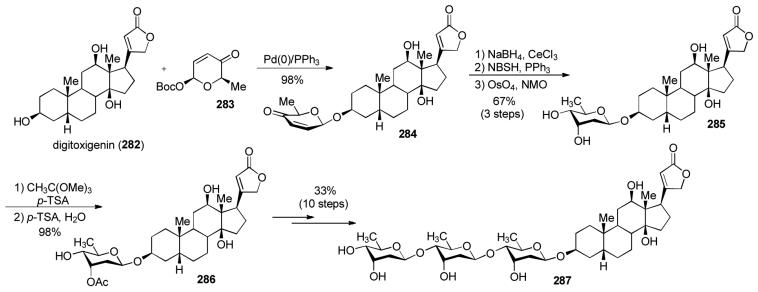
Scheme 23.
Synthesis of 1,4-Linked Trisaccharide



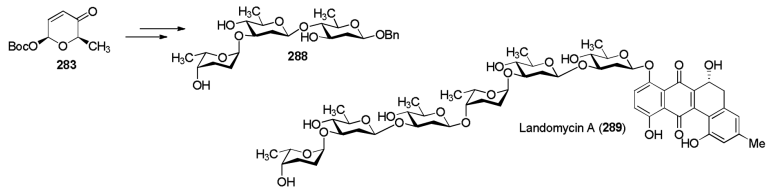
Scheme 24.
Synthesis of Cleistriosides and Ceistetrosides via Palladium Catalysis



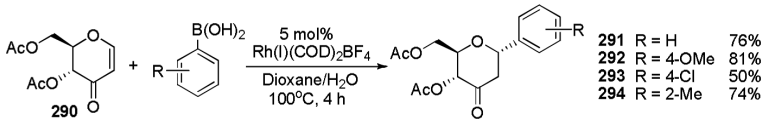
Scheme 25.
Synthesis of Anthrax Tetrasaccharide via Palladium Catalysis



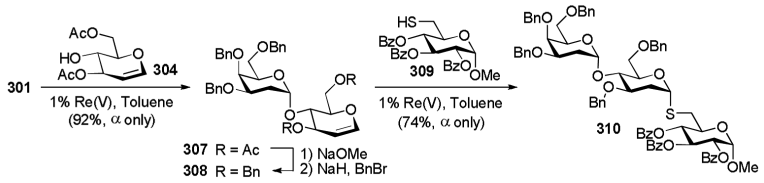
Scheme 26.
Synthesis of Digitoxin via Palladium Catalysis



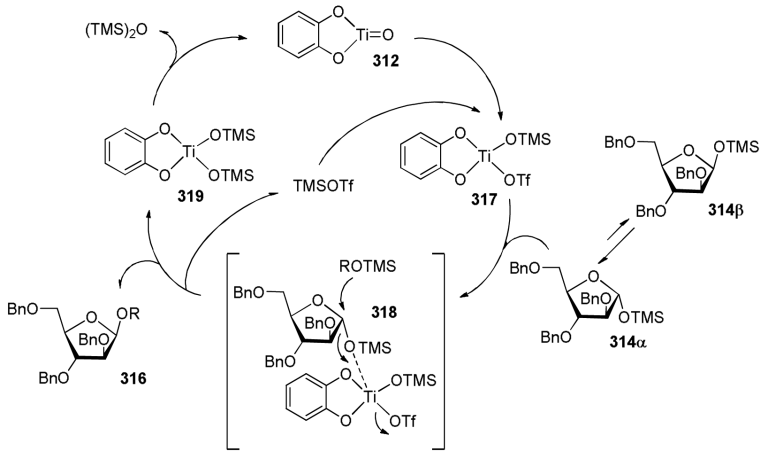
Scheme 27.
Synthesis of Landomycin Trisaccharide via Palladium Catalysis



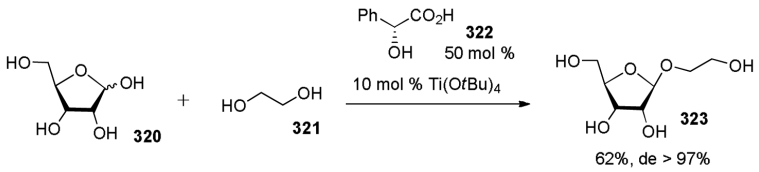
Scheme 28.
Rh(I)-Catalyzed 1,4-Addition of Boronic Acids to Enone



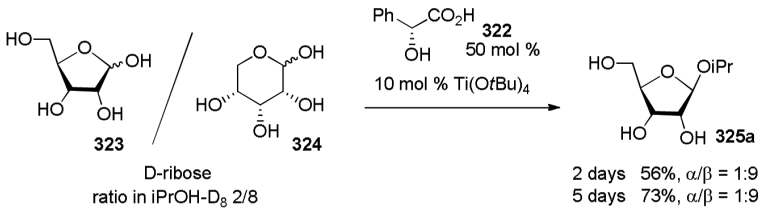
Scheme 29.
Synthesis of Trisaccharides



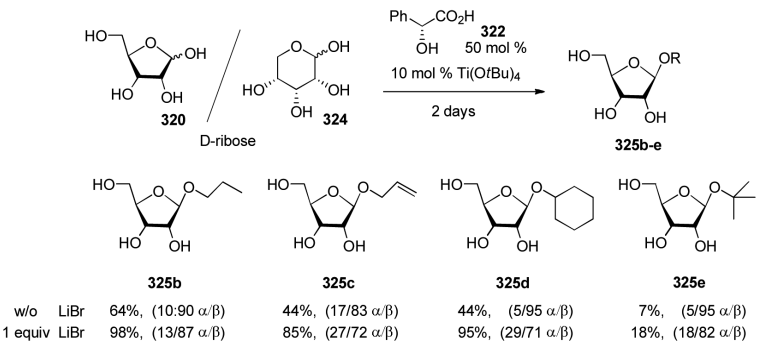
Scheme 30.
Catalytic Cycle of Titanium Glycosylation



Scheme 31.
Direct Glycosylation with Unprotected Carbohydrates



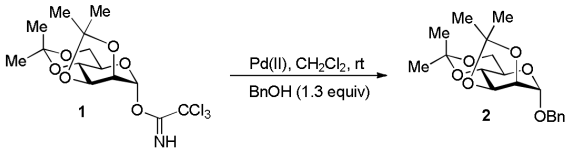
Scheme 32.
Direct Glycosylation of D-Ribose



Scheme 33.
Effect of LiBr Additive

Table 1

Initial Studies with Cationic Palladium Catalyst



Entry	Pd(II) sources	mol % Pd(II)	Additive	Time	Yield	α:β
1	$Pd(CH_3CN)_4(BF_4)_2$	5 mol %	None	3 h	85%	a only
2	$Pd(CH_3CN)_4(BF_4)_2$	5 mol %	DTBP	4 h	83%	a only
3	Pd(PhCN)2Cl2	5 mol %	None	8 h	<5%	-

Table 2

Glycosylation with Various Trichloroacetimidate Donors

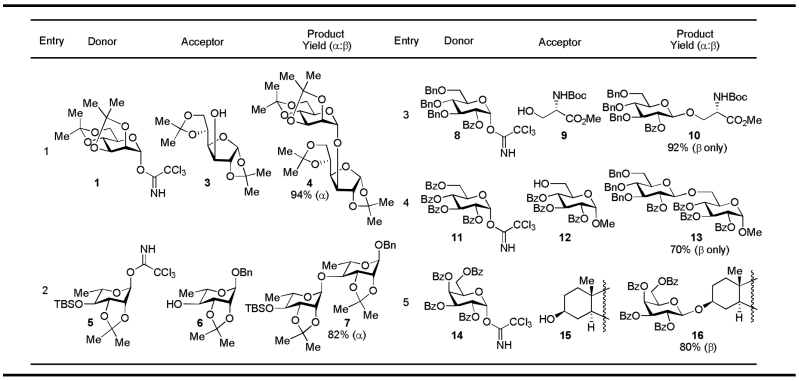
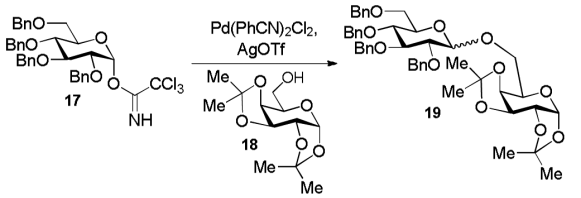


Table 3

Initial Studies with $Pd(PhCN)_2(OTf)_2$ Controlled β-Selective Glycosylation



Entry	Palladium	AgOTf	Temp	Time	Yield	β:α
1	1 mo1 %	2 mol%	25 °C	15 min	96%	1:1
2	1 mo1 %	2 mol%	0°C	30 min	83%	1:1
3	1 mol %	2 mol%	−78 °C	1 h	87%	10:1

Table 4

Substrate Scope of $Pd(PhCN)_2(OTf)_2$ Controlled β-Selective Glycosylation

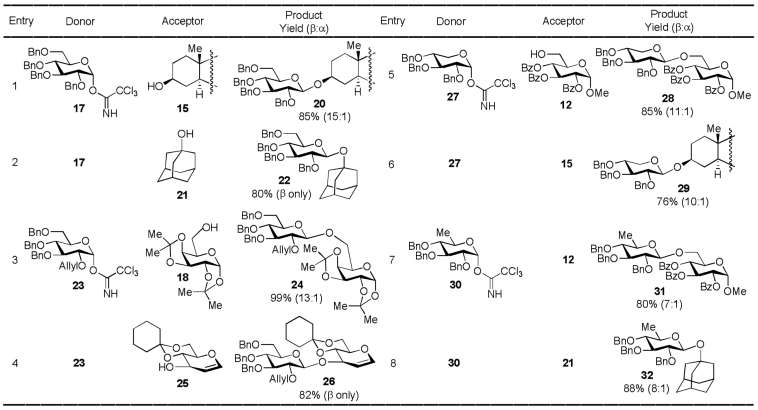
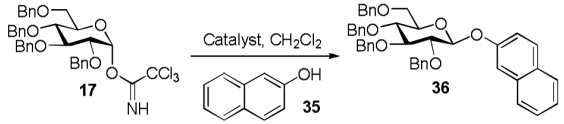


Table 5

Initial Studies with Palladium-Catalyzed β-Selective *O*-Aryl Glycosylation



Entry	Pd(II) sources	Loading	Temp	Time	Yield	β:α
1	$Pd(PhCN)_2(OTf)_2$	2 mol %	−78 °C	6 h	60%	2:1
2	$Pd(PhCN)_2(OTf)_2$	2 mol %	25 °C	1 h	75%	1:1
3	$Pd(CH_3CN)_4(BF_4)_2$	2 mol %	25 °C	2 h	80%	11:1
4	AgOTf	4 mol %	25 °C	12 h	68%	1:1
5	$BF_3.OEt_2$	4 mol %	25 °C	6 h	66%	3:1

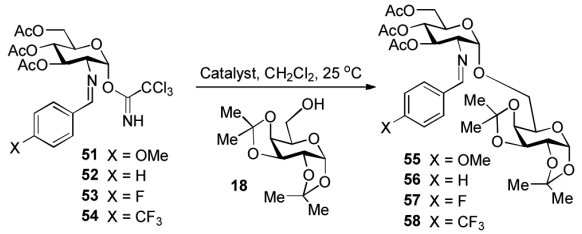
Table 6

Coupling of Phenol Nucleophiles with a Variety of Glycosyl Donors

Entry	Donor	Acceptor	Product Yield (β:α)
1	**17**	**37**	**38** 75% (11:1)
2	**17**	**39**	**40** 75% (10:1)
3	**41**	**37**	**42** 73% (β only)
4	**41**	**35**	**43** 78% (β only)
5	**27**	**44**	**45** 84% (β only)
6	**27**	**46**	**47** 74% (β only)
7	**27**	**39**	**48** 72% (β only)
8	**27**	**49**	**50** 74% (β only)

Table 7

Optimized Conditions for Selective Formation of 1,2-*Cis*-2-Amino Glycosides



Entry	Donor	Catalyst	Loading	Time	Yield	α:β
1	**51**	$Pd(PhCN)_2(OTf)_2$	5 mol%	10 h	60%	4:1
2	**51**	$Ni(PhCN)_4(OTf)_2$	5 mol%	4h	95%	8:1
3	**51**	$Ni(4\text{-F-PhCN})_4(OTf)_2$	5 mol%	3h	93%	10:1
4	**51**	$Ni(4\text{-MeO-PhCN})_4(OTf)_2$	5 mol%	6h	76%	10:1
5	**51**	$Ni(4\text{-F-PhCN})_4Cl_2$	5 mol%	10 h	-	-
6	**51**	AgOTf	10 mol%	10 h	-	-
7	**51**	TfOH	10 mol%	5h	10%	3:1
8	**52**	$Ni(4\text{-F-PhCN})_4(OTf)_2$	5 mol%	3h	92%	10:1
9	**53**	$Ni(4\text{-F-PhCN})_4(OTf)_2$	5 mol%	1h	96%	9:1
10	**54**	$Ni\ (4\text{-F-PhCN})_4\ (OTf)_2$	5 mol%	1 h	87%	9:1

Table 8

Substrate Scope of Nickel-Catalyzed 1,2-*Cis*-2-Amino Glycosylation

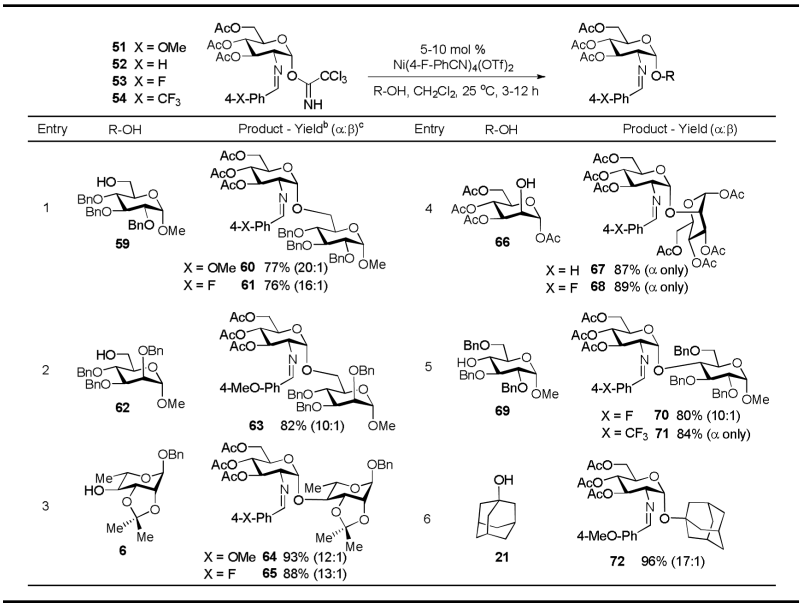
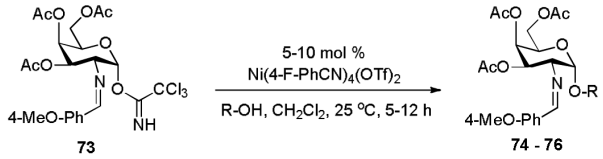


Table 9

α-Selective Coupling with D-Galactosamine Trichloroacetimidate



73 **74 - 76**

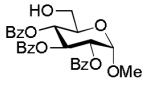
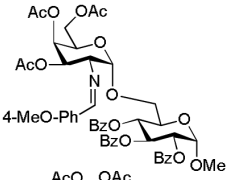
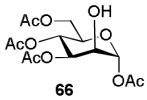
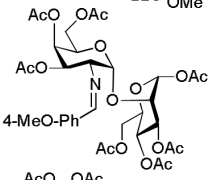
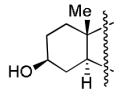
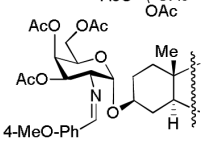
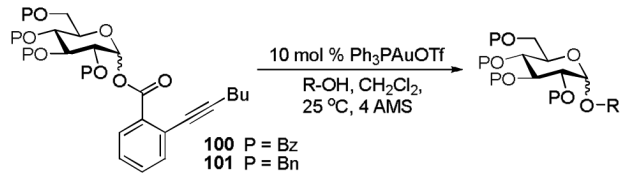
Entry	R-OH	Product		Yield (α:β)
1	 **12**		**74**	74% (14:1)
2	 **66**		**75**	93% (α only)
3	 **15**		**76**	80% (10:1)

Table 10

Au(I)-Catalyzed Coupling with *Ortho*-Hexynylbenzoates



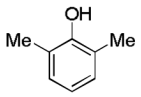
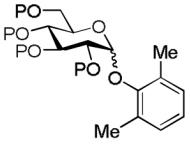
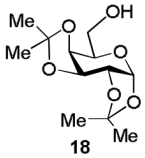
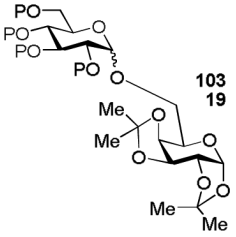
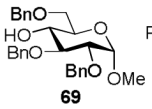
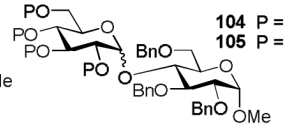
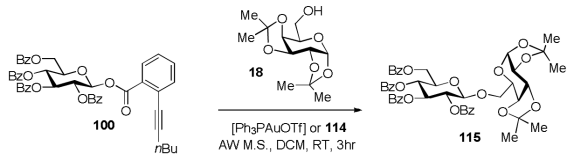
Entry	R-OH	Products - Yield (α:β)
1	 **39**	 **102** P = Bz, 97% (β only) **40** P = Bn, 92% (1:1.2)
2	 **18**	 **103** P = Bz, 99% (β only) **19** P = Bn, 99% (1:1.4)
3	 **69**	 **104** P = Bz, 81% (β only) **105** P = Bn, 71% (1:2)

Table 11

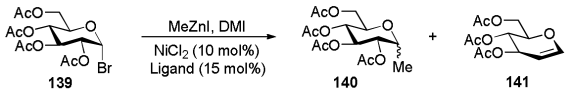
Au(I)-Catalyzed Glycosylation With or Without TfOH Co-Catalyst



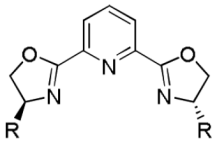
Entry	Gold (i) catalyst	loading [eq.]	TfOH [eq.]	Yield
1	[Ph_3PAuOTf]	0.1	–	95%
2	[Ph_3PAuOTf]	0.01	–	23%
3	[Ph_3PAuOTf]	0.01	0.1	92%
4	[Ph_3PAuOTf]	0.005	0.1	86%
5	[Ph_3PAuOTf]	0.001	0.1	82%
6	[Ph_3PAuOTf]	0.0001	0.1	trace
7	**114**	0.1	–	0
8	**114**	0.01	0.1	92%
9	**114**	0.001	0.1	82%
10	**114**	0.0001	0.1	trace

Table 12

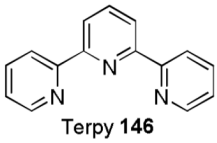
Ligand Screening



Entry	Ligand	Yield (a:p)	Glucal 141
1	S-*i*Pr-PyBox	50% (1:1.5)	10%
2	S-*s*Bu-PyBox	20% (1:1.5)	trace
3	S-Ph-PyBox	trace	N/A
4	PyBox	76% (1:2.2)	6%
5	Terpy	30% (β only)	trace



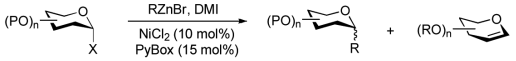
142 R = H, PyBox
143 R = *i*Pr, *i*PrPyBox
144 R = *s*Bu, *s*BuPyBox
145 R = Ph, PhPyBox



Terpy **146**

Table 13

C-Alkylation with Functionalized Alkyl Zinc Reagents



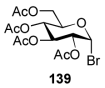
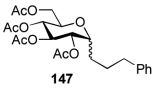
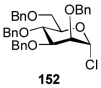
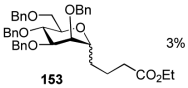
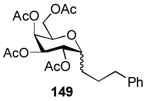
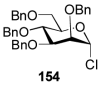
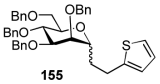
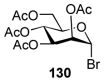
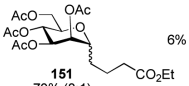
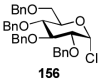
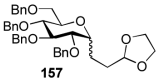
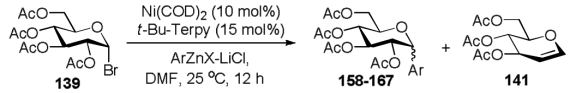
Entry	Glycosyl Halides	Products Yield (α:β)	Glycal	Entry	Glycosyl Halides	Products Yield (α:β)	Glycal
1	 **139**	 **147** 53% (1:2.5)	9%	4	 **152**	 **153** 76% (α only)	3%
2	 **148**	 **149** 43% (1:2)	trace	5	 **154**	 **155** 43% (α only)	20%
3	 **130**	 **151** 70% (8:1)	6%	6	 **156**	 **157** 65% (1:1.1)	9%

Table 14

C-Arylation with Functionalized Aryl Zinc Reagents



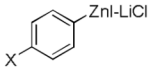
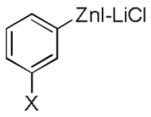
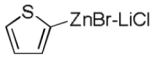
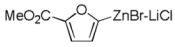
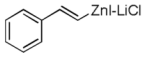
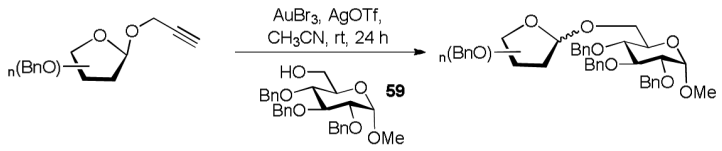
Entry	Zinc Reagents	products 158-167	Yield (α:β)	Glycal 141
1		**158** X = H	71% (1:12)	7%
		159 X= OMe	64% (1:13)	11%
		160 X= CO_2Me	66% (1:10)	trace
		161 X= I	30% (1:10)	trace
2		**162** X= CO_2Me	72% (1:14)	8%
		163 X = CI	75% (1:13)	trace
		164 X = I	77% (1:14)	trace
3		**165**	78% (1:16)	14%
4		**166**	65% (1:14)	trace
5		**167**	65% (1:11)	trace

Table 15

Propargyl Furanosides as Glycosyl Donors



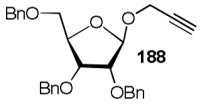
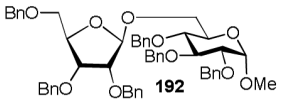
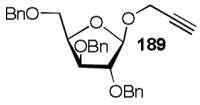
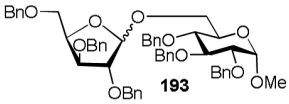
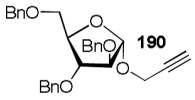
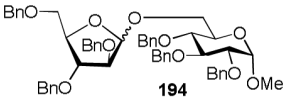
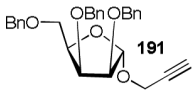
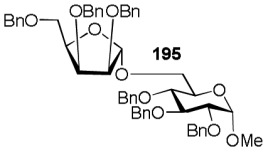
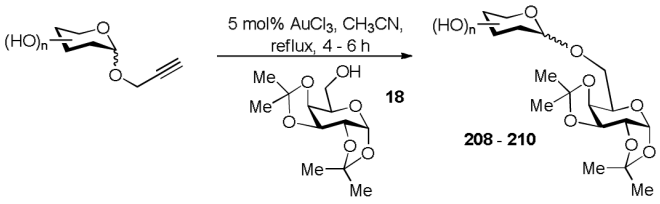
Entry	Donor	Disaccharide	Yield (%)	α/β Ratio
1	 **188**	 **192**	72	β only
2	 **189**	 **193**	67	1:5
3	 **190**	 **194**	66	10:1
4	 **191**	 **195**	69	α only

Table 16

Glycosylation with Unprotected Propargyl Donors



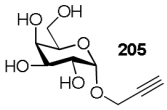
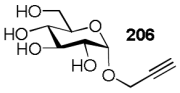
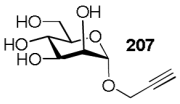
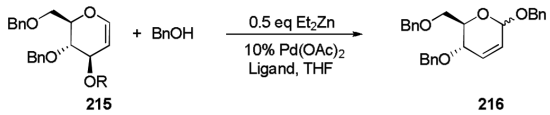
Entry	Donors	Disaccharides	Yield (%)	α/β Ratio
1	 **205**	**208**	51	1:3
2	 **206**	**209**	45	1:1
3	 **207**	**210**	45	1.6:1

Table 17

Pd-Catalyzed Glycosylation of Benzyl Alcohol with Glycal



215 216

entry	glycal	ligand	yield	α:β
1	215a R = Ac	15% DTBBP	92%	<1:25
2		30% $P(OMe)_3$	90%	7:1
3	215b R = *t*-Boc	15% DTBBP	92%	<1:25
4		30% $P(OMe)_3$	90%	5:1

Table 18

Pd-Catalyzed Synthesis of Disaccharides

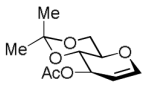
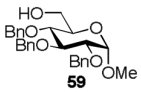
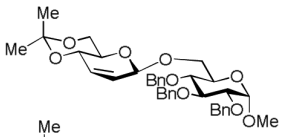
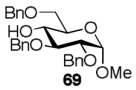
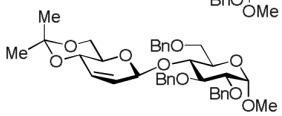
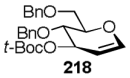
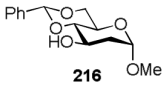
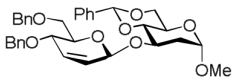
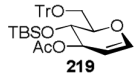
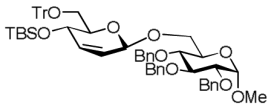
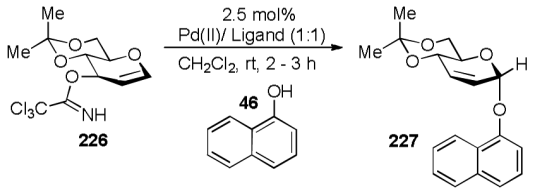
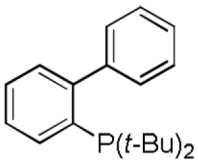
Entry	Glycal	Acceptor	Product	Yield
1	 **217**	 **59**		**220** 77%
2	**217**	 **69**		**221** 70%
3	 **218**	 **216**		**222** 69%
4	 **219**	**59**		**223** 77%

Table 19

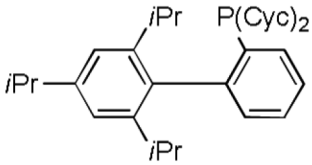
Pd(II)-Catalyzed Glycosylation of 1-Napthol With Glucal Imidate



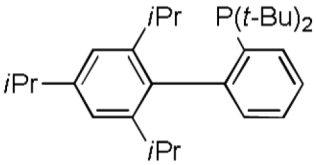
entry	Pd (II) sources	phosphine ligands	yield	α:β
1	$Pd(CH_3CN)_2Cl_2$	None	55%	3:1
2	$Pd(CH_3CN)_2Cl_2$	JohnPhos	53%	3:1
3	$Pd(PhCN)_2CI_2$	JohnPhos	91%	4:1
4	$Pd(PhCN)_2CI_2$	X-Phos	70%	8:1
5	**$Pd(PhCN)_2Cl_2$**	***t*-BuX-Phos**	**84%**	**20:1**



JohnPhos



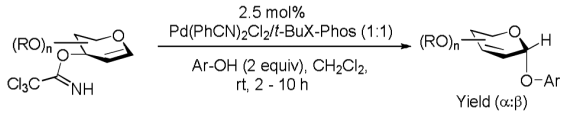
X-Phos



t-BuX-Phos

Table 20

Pd(II)-Catalyzed Stereoselective Formation of α-*O*-Aryl Glycosides



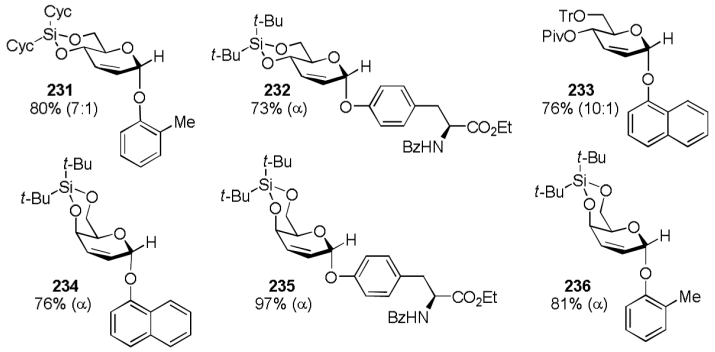
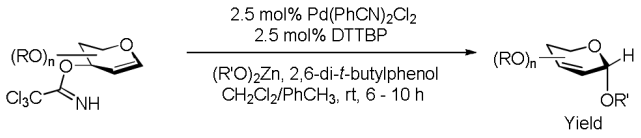


Table 21

Pd(II)-Catalyzed Stereoselective Formation of α-*O* Glycosides



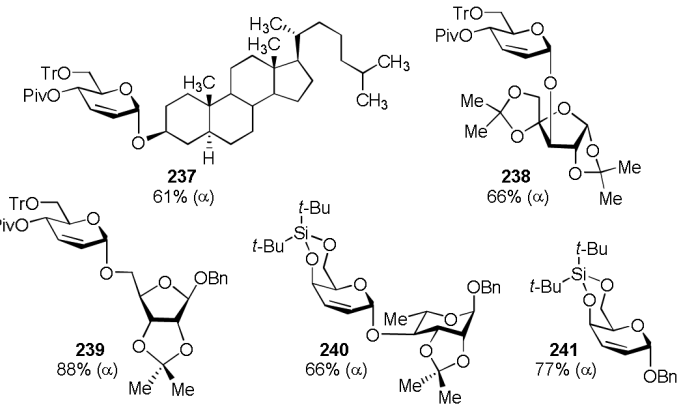
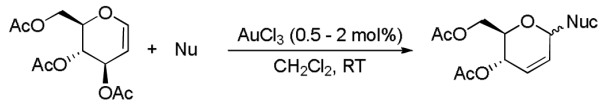


Table 22

Gold-Catalyzed Formation of *O*- and *C*-Glycosides



141 **245-248**

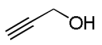
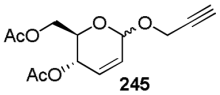
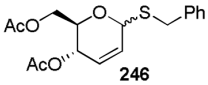
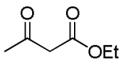
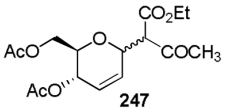
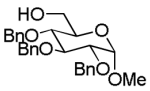
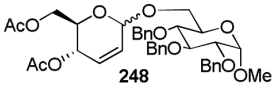
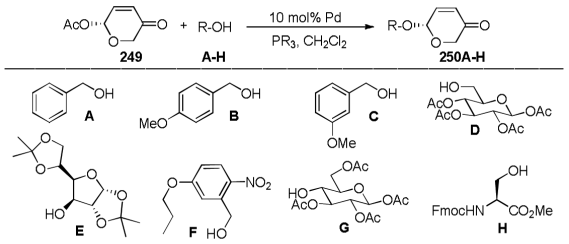
entry	nucleophile	product	yield	(α/β)
1		 **245**	85%	(6.5:1)
2		 **246**	82%	(3:1)
3		 **247**	80%	(4.4:1)
4		 **248**	74%	(4.2:1)

Table 23

Pd-Catalyzed Stereoselective Acetal Bond Formation



product	% yield	% *de*	product	% yield	% *de*
250A	83	94	**250E**	70	97
250B	87	98	**250F**	84	98
250C	98	99	**250G**	65	91
250D	77	94	**250H**	78	97

product	**% yield**	**% *de***	**product**	**% yield**	**% *de***
250A	83	94	**250E**	70	97
250B	87	98	**250F**	84	98
250C	98	99	**250G**	65	91
250D	77	94	**250H**	78	97

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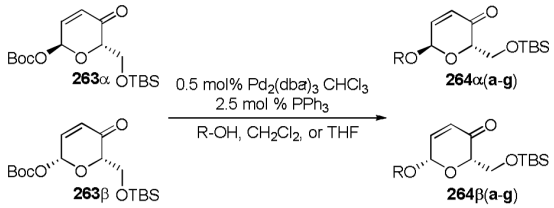
Table 24

Substrate Scope

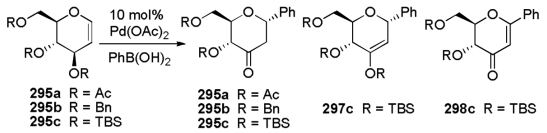


Entry	R-OH	Product (264a-g)	Yield 264α	Yield 264β	Yield 264β
1	CH_3OH	**264a**	87%	85%	0%
2	BnOH	**264b**	89%	85%	0%
3	PhOH	**264c**	85%	76%	2%
4	CyOH	**264d**	88%	80%	2%
5	menthol	**264e**	82%	72%	12%
6	*t*-BuOH	**264f**	78%	75%	—
7	adamantol	**264g**	54%	52%	34%

ACS Catal. Author manuscript; available in PMC 2013 August 03.

Table 25

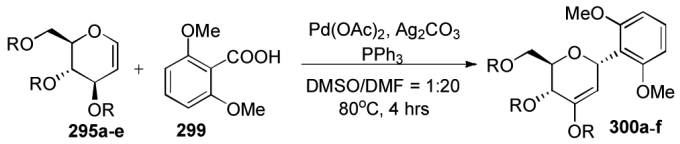
Heck-Type *C*-Glycosylation of Glycal Donors



Entry	Substrate	Oxidant	Product	Yield
1	**295a**	BQ (2 equiv)	**296a**	0%
2	**295b**	BQ (2 equiv)	**296b**	32%
3	**295c**	BQ (2 equiv)	**296c**	84%
4	**295c**	$Cu(OAc)_2$ (2 equiv)/O_2	**296c**	94%
5	**295c**	DDQ (2 equiv)	**296c**	59%

Table 26

Palladium-Catalyzed Decarboxylative Coupling



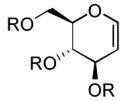
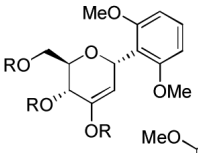
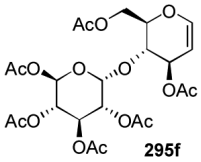
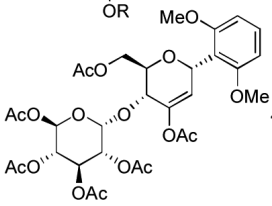
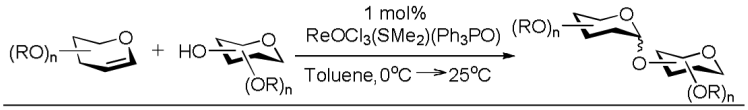
Entry	Glycal Donors	Products	Yield
1	 **295a** = R = Ac **295b** = R = Bn **295c** = R = TBS **295d** = R = Piv **295e** = R = Boc		79% (**300a**) 70% (**300b**) 73% (**300c**) 65% (**300d**) 55% (**300e**)
2	 **295f**		45% (**300f**)

Table 27

Re(V)-Catalyzed *O*-Glycosylation



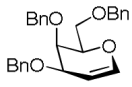
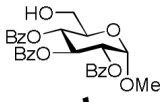
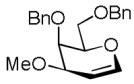
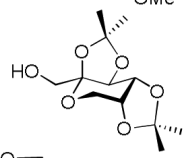
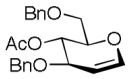
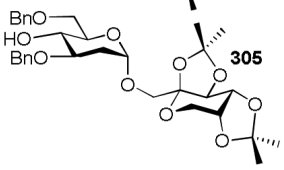
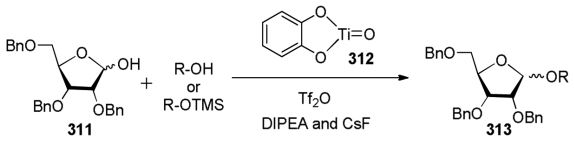
Entry	Glycal		Acceptor		Product Yield (α/β)
1		**301**		**12**	79% (α)
2		**302**		**303**	86% (α)
3		**304**		**305**	78% (α)

Table 28

Synthesis of β-Ribofuranosides



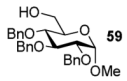
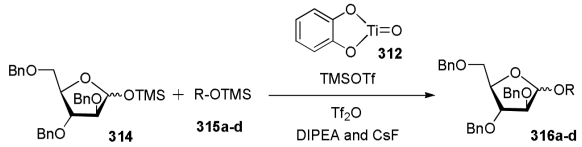
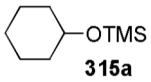
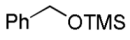
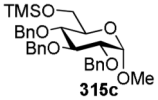
R-OH / R-OTMS	yield	(α/β)
cyclohexanol	95%	5/95
MeOTMS	92%	4/96
3B-cholestanyl-OTMS	88%	1/99
 59	94%	11/89

Table 29

Synthesis of 1,2-*cis*-Arabinofuranosides



entry	R-OTMS	TMSOTf (equiv)	X (equiv)	temp °C	yield	(α/β)
1	 **315a**	2.0	**1**.0	0	76	**1**8/82
2		2.0	**1**.0	−23	90	9/91
3		0.8	0.4	−15	77	**1**0/90
4		0.4	0.2	0	62	**1**4/86
5	 **315b**	0.8	0.2	−23	96	**1**3/87
6		0.4	0.**1**	−23	91	**1**0/90
7	 **315c**	0.8	0.4	−23	84	8/92
8	3B-cholestanyl-OTMS **315d**	5 0.8	0.4	0	96	**1**3/87