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Review

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Recent Advances in Transition Metal-Catalyzed Glycosylation

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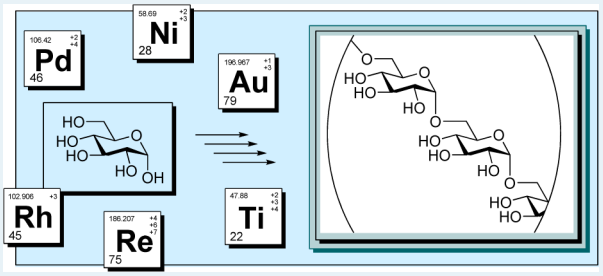
ABSTRACT: Having access to mild and operationally simple techniques for attaining carbohydrate targets will be necessary to facilitate advancement in biological, medicinal, and pharmacological research. Even with the abundance of elegant reports for generating glycosidic linkages, stereoselective construction of α- and β-oligosaccharides and glycoconjugates is by no means trivial. In an era when 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 substoichiometric 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 the interest of synthesis, 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 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 substoichiometric amounts of activating agents, could further advance the field of carbohydrate chemistry. In this Review, 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 in which automated techniques have been employed for decades.

This Review is divided into four sections on the basis of the type of donor used in the reaction: The first is the transition metal-catalyzed activation of glycosyl donors with trichloroacetimidate, *O*-alkynyl benzoate, and halide leaving groups. The second covers donors with methyl and propargyl leaving groups. The third covers glycal-derived donors, and the final covers 1-hydroxy sugar donors. This review discusses only the

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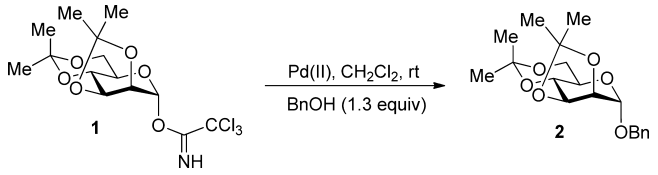
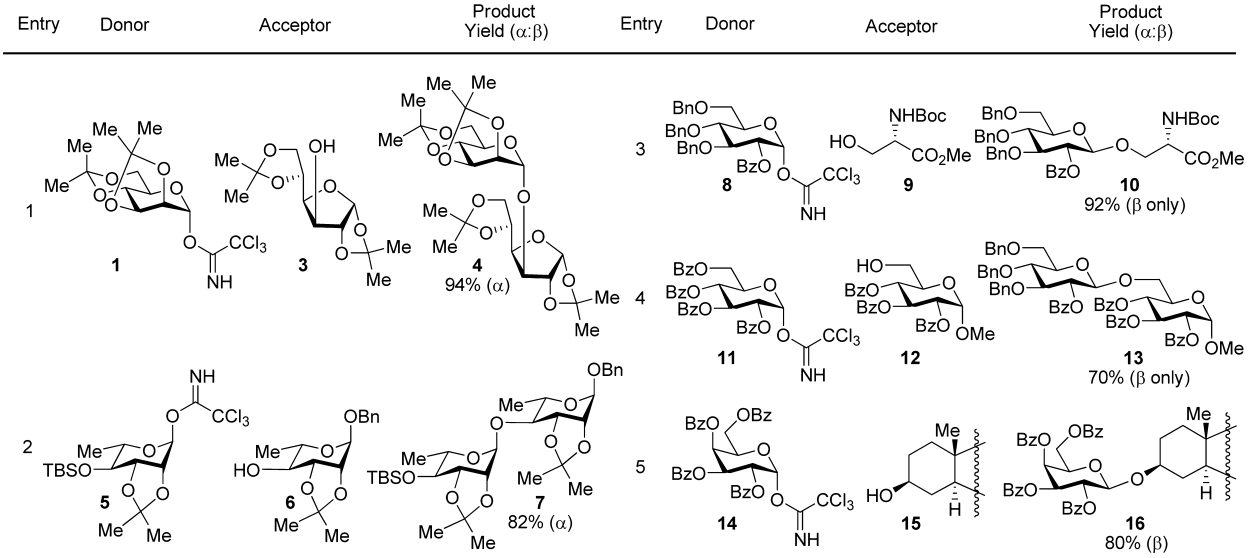
Table 1. Initial Studies with Cationic Palladium Catalyst



entry	Pd(II) sources	mol % Pd(II)	additive	time, h	yield, %	α/β
1	$Pd(CH_3CN)_4(BF_4)_2$	5	none	3	85	α only
2	$Pd(CH_3CN)_4(BF_4)_2$	5	DTBP	4	83	α only
3	$Pd(PhCN)_2Cl_2$	5	none	8	<5	

Table 2. Glycosylation with Various Trichloroacetimidate Donors



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, in which 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, although 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 of 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

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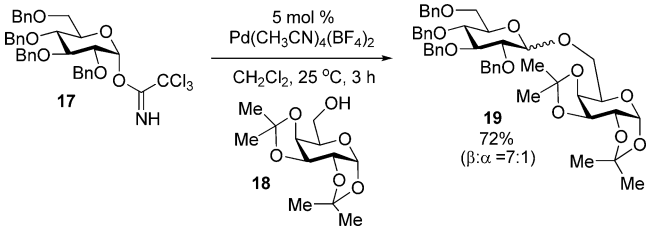
cationic palladium catalyst for activation of the trichloroacetimidate.

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, $Pd(CH_3CN)_4(BF_4)_2$, for activating the anomeric trichloroacetimidate leaving group, per-*O*-benzylated glucose trichloroacetimidate donor **17** (Scheme 1) was screened under the

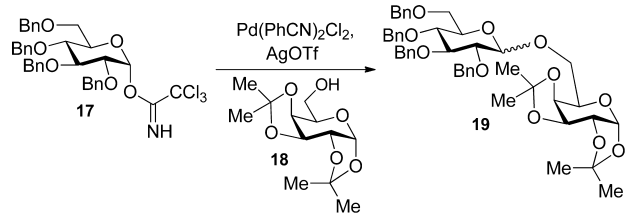
Scheme 1. Cationic Palladium-Catalyzed β-Selective Coupling



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-dependent: 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, although further reduction to −78 °C (entry 3) significantly improved the 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

Table 3. Initial Studies with $Pd(PhCN)_2(OTf)_2$ Controlled β-Selective Glycosylation



entry	palladium, mol %	AgOTf, mol %	temp, °C	time	yield, %	β/α
1	1	2	25	15 min	96	1:1
2	1	2	0	30 min	83	1:1
3	1	2	−78	1 h	87	10:1

cationic palladium catalyst, $Pd(CH_3CN)_4(BF_4)_2$. An explanation for the 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 of 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] because of the recent discovery of the antitumor, 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 the 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] In addition, these reactions can be highly sensitive to electronic properties of substituted aryl alcohols, limiting the scope to specific phenol nucleophiles.[43]

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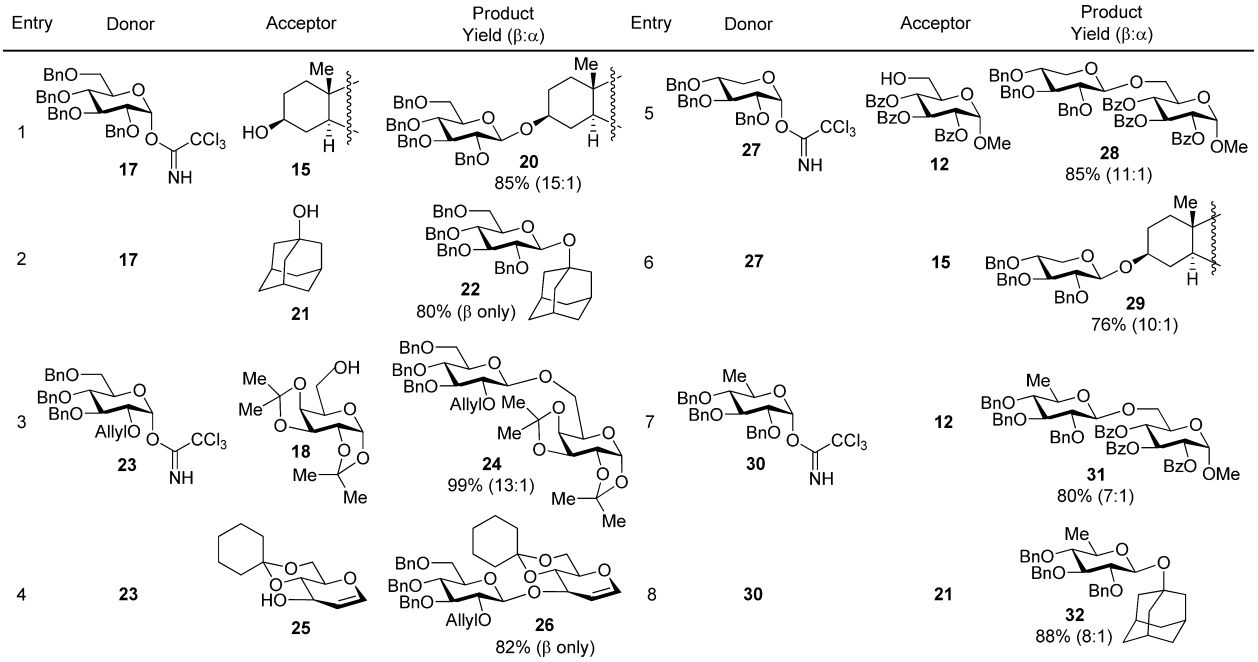
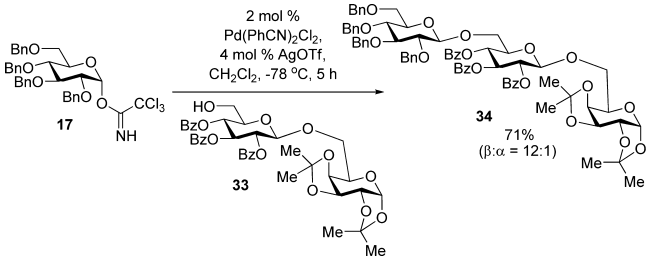
Table 4. Substrate Scope of $Pd(PhCN)_2(OTf)_2$-Controlled β-Selective Glycosylation



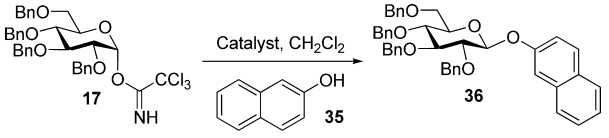
Scheme 2. $Pd(PhCN)_2(OTf)_2$-Catalyzed Formation of Trisaccharide



The Nguyen group explored the optimal conditions for formation of β-*O*-aryl glycosides (Table 5). On the basis of 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 with 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)-Amino sugars are a key component of glycoproteins that are found on cellular surfaces and serve as receptor ligands for enzymes and other macromolecules.[44−54] Glycosides of C(2)-amino sugars are linked to other carbohydrates or amino acids

Table 5. Initial Studies with Palladium-Catalyzed β-Selective *O*-Aryl Glycosylation



entry	Pd(II) sources	loading, mol %	temp, °C	time, h	yield, %	β/α
1	$Pd(PhCN)_2(OTf)_2$	2	−78	6	60	2:1
2	$Pd(PhCN)_2(OTf)_2$	2	25	1	75	1:1
3	$Pd(CH_3CN)_4(BF_4)_2$	2	25	2	80	11:1
4	AgOTf	4	25	12	68	1:1
5	$BF_3{\cdot}OEt_2$	4	25	6	66	3:1

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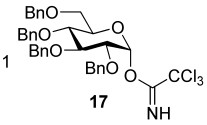
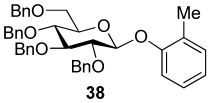
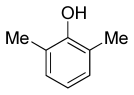
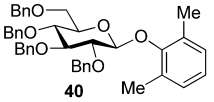
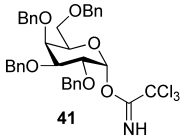
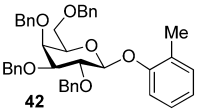
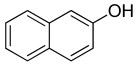
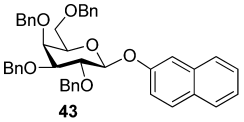
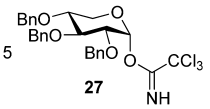
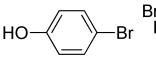
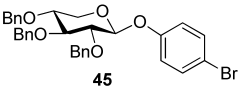
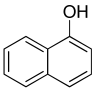
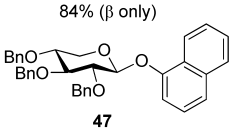
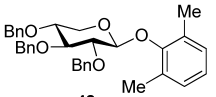
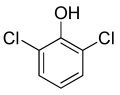
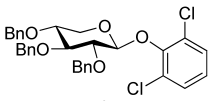
Table 6. Coupling of Phenol Nucleophiles with a Variety of Glycosyl Donors

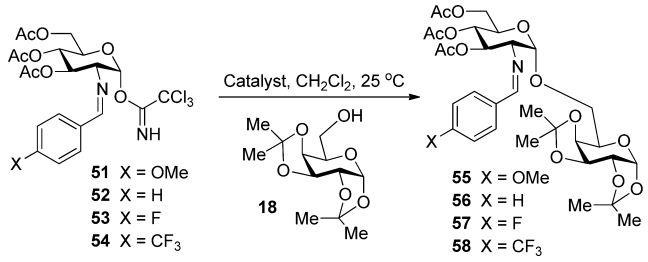
Entry	Donor	Acceptor	Product Yield (β:α)
1	 **17**	 **37**	 **38** 75% (11:1)
2	**17**	 **39**	 **40** 75% (10:1)
3	 **41**	**37**	 **42** 73% (β only)
4	**41**	 **35**	 **43** 78% (β only)
5	 **27**	 **44**	 **45** 84% (β only)
6	**27**	 **46**	 **47** 74% (β only)
7	**27**	**39**	 **48** 72% (β only)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

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 nonparticipating groups at C(2) of the donor.[55−59] Even though there have been a variety of methods reported for stereoselective construction of 1,2-*cis*-2-amino sugars,[17−25,28,29,31,32,60−65] 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*-methoxybenzylidene 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 the 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, <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

Table 7. Optimized Conditions for Selective Formation of 1,2-*Cis*-2-Amino Glycosides



entry	donor	catalyst	loading, mol %	time, h	yield, %	α/β
1	**51**	$Pd(PhCN)_2(OTf)_2$	5	10	60	4:1
2	**51**	$Ni(PhCN)_4(OTf)_2$	5	4	95	8:1
3	**51**	$Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$	5	3	93	10:1
4	**51**	$Ni(4\text{-Meo-}PhCN)_4(OTf)_2$	5	6	76	10:1
5	**51**	$Ni(4\text{-}F\text{-}PhCN)_4Cl_2$	5	10		
6	**51**	AgOTf	10	10		
7	**51**	TfOH	10	5	10	3:1
8	**52**	$Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$	5	3	92	10:1
9	**53**	$Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$	5	1	96	9:1
10	**54**	$Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$	5	1	87	9:1

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. In addition, 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 trichloroacetimi-

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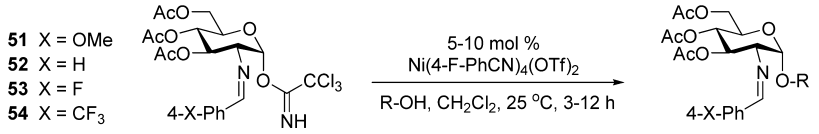
Table 8. Substrate Scope of Nickel-Catalyzed 1,2-*cis*-2-Amino Glycosylation



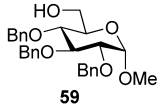
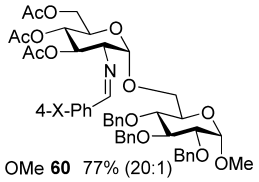
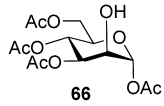
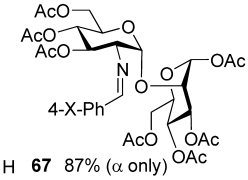
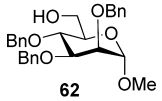
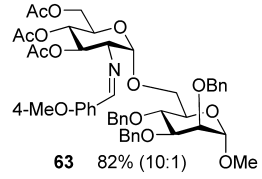
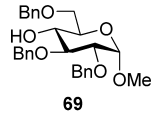
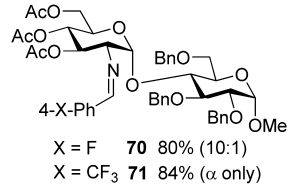
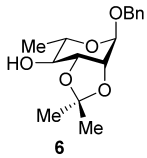
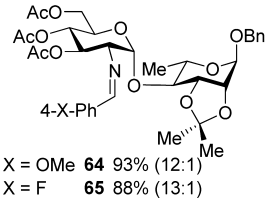
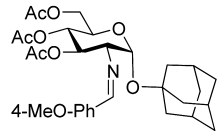
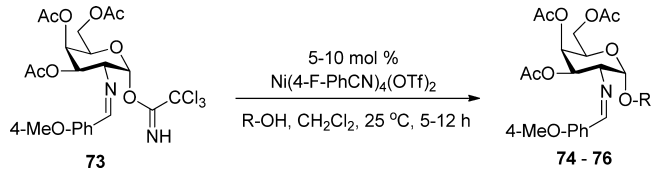
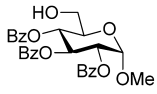
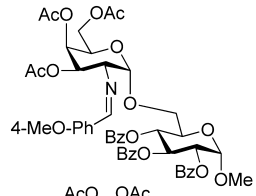
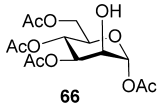
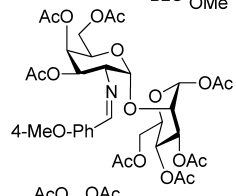
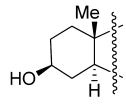
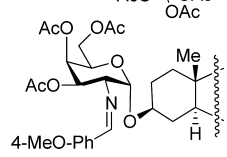
Entry	R-OH	Product - Yield[b] (α:β)[c]	Entry	R-OH	Product - Yield (α:β)
1	 **59**	 X = OMe **60** 77% (20:1) X = F **61** 76% (16:1)	4	 **66**	 X = H **67** 87% (α only) X = F **68** 89% (α only)
2	 **62**	 **63** 82% (10:1)	5	 **69**	 X = F **70** 80% (10:1) X = CF_3 **71** 84% (α only)
3	 **6**	 X = OMe **64** 93% (12:1) X = F **65** 88% (13:1)	6	 **21**	 **72** 96% (17:1)

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)

date **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*-*p*-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

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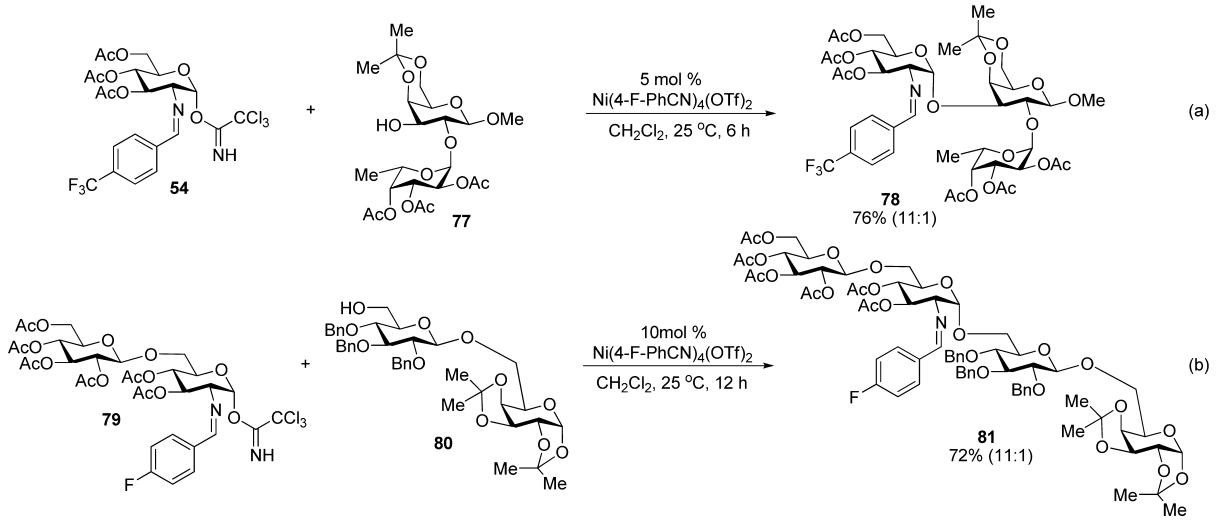
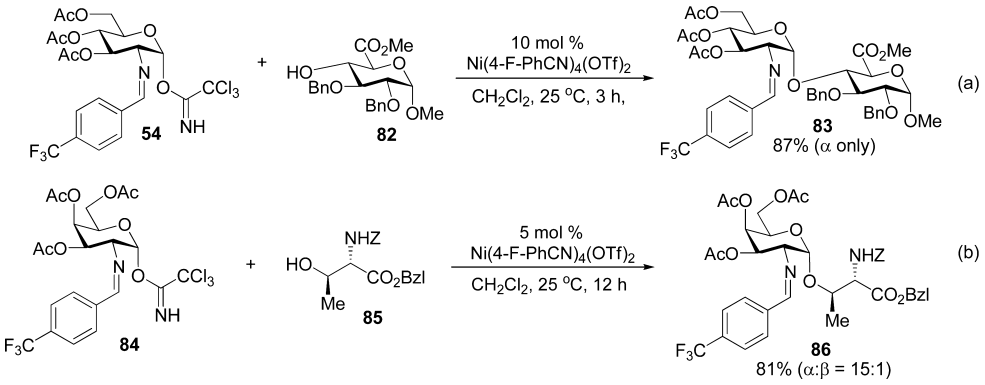
Scheme 3. Nickel-Catalyzed α-Oligosaccharide Formation



Scheme 4. Synthesis of Biologically Important Carbohydrate Molecules



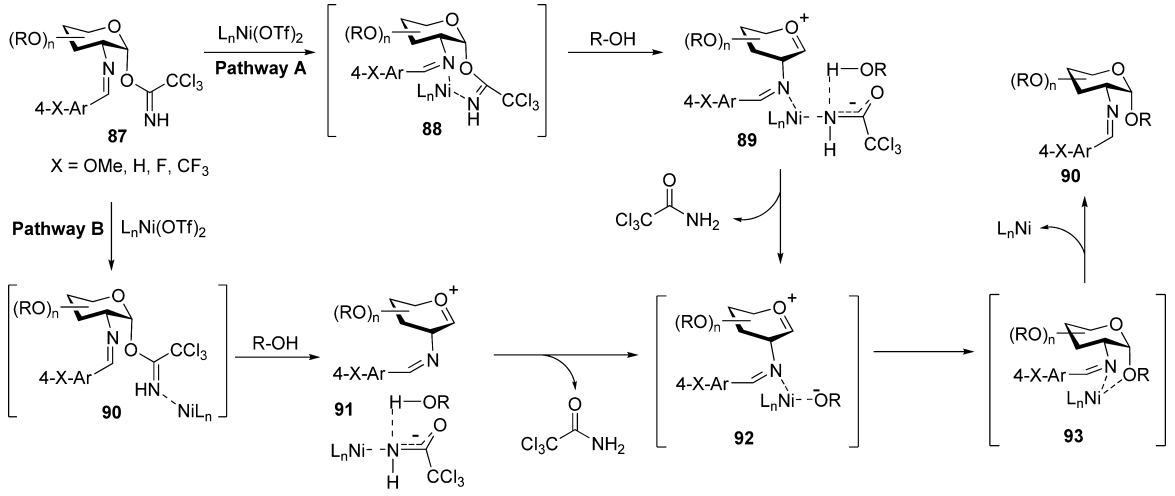


Figure 1. Proposed mechanism for nickel-catalyzed 1,2-*cis*-2-amino glycosylation.

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] Accord-

dx.doi.org/10.1021/cs3002513 | ACS Catal. 2012, 2, 1563−1595

ingly, 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 equiv 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. 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 (this section), has exploited the low oxophilic 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).[79,80] 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 the 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

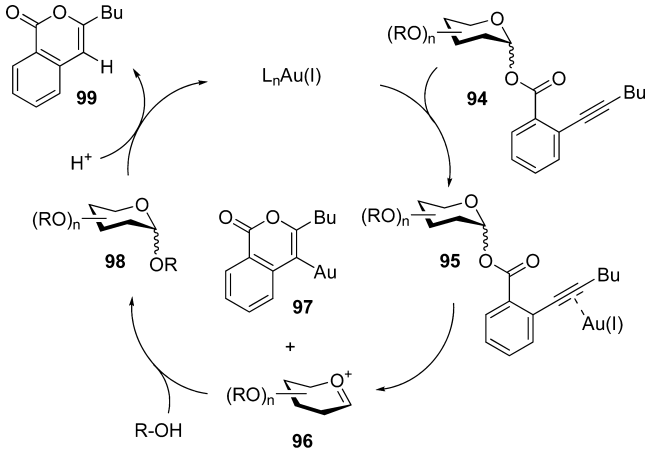
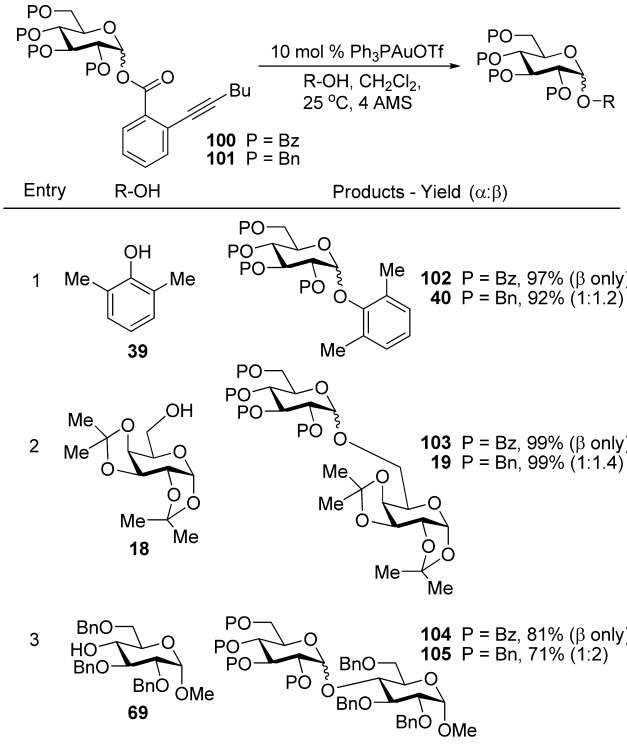


Figure 2. Proposed catalytic cycle of gold-catalyzed glycosylation.

Table 10. Au(I)-Catalyzed Coupling with *ortho*-Hexynylbenzoates



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 tetrabenzylated 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. Last, the anomeric orientation of the leaving group on the donor does not affect the transformation.

Yu and co-workers have made further attempts to increase their selectivity with glycosyl donors that do not contain

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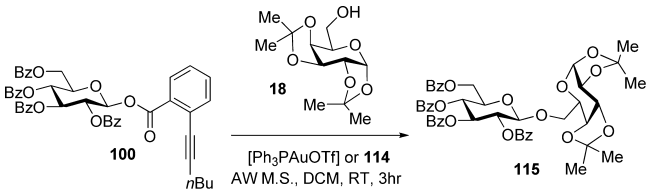
participating groups at the C(2) position by changing the solvent in the reaction.[81] It is known that ether as a solvent leads to α-selective glycosylations.[82−85] Therefore, C(2)-*O*-benzyl donor **101**, C(2)-azido donor **106**, and C(2)-deoxy donor **108** (Table 11) were screened with a variety of acceptors

Table 11. Au(I)-Catalyzed Glycosylation with or without TfOH Cocatalyst



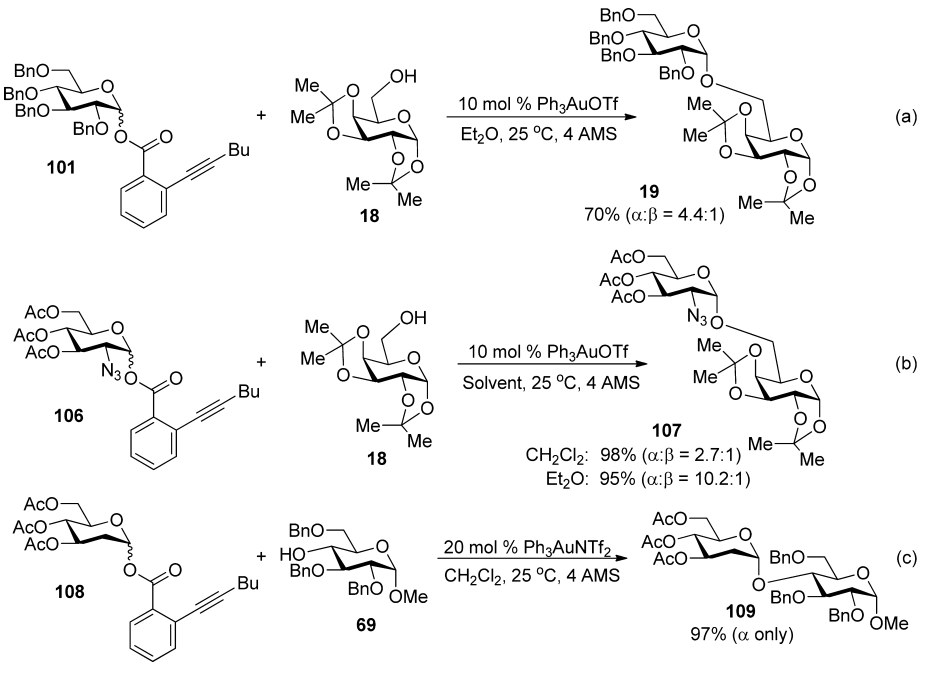
entry	gold(i) catalyst	loading (equiv)	TfOH (equiv)	yield, %
1	[$Ph_3PAuOTf$]	0.1		95
2	[$Ph_3PAuOTf$]	0.01		23
3	[$Ph_3PAuOTf$]	0.01	0.1	92
4	[$Ph_3PAuOTf$]	0.005	0.1	86
5	[$Ph_3PAuOTf$]	0.001	0.1	82
6	[$Ph_3PAuOTf$]	0.0001	0.1	trace
7	**114**	0.1		0
8	**114**	0.01	0.1	92
9	**114**	0.001	0.1	82
10	**114**	0.0001	0.1	trace

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**, disaccharide **107** was obtained in excellent yield in both the CH_2Cl_2 and Et_2O solvent, though 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%), in which 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).

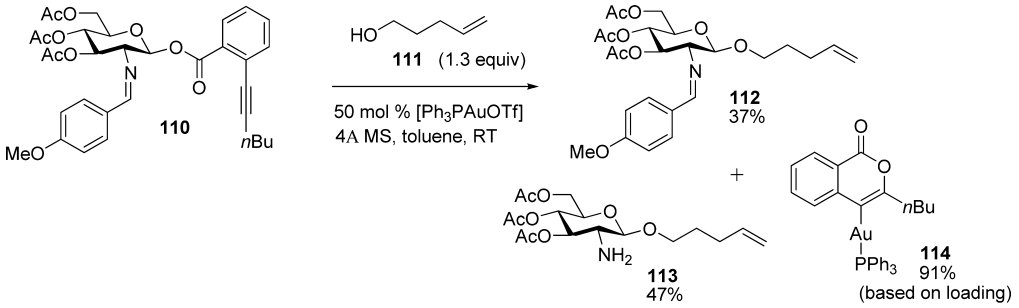
The catalytic cycle was found to resume upon the addition of strong protic acids, TfOH or CF_3COOH, to the reaction, although common alcohols such as MeOH and EtOH would not facilitate regeneration of the catalyst. This finding prompted a series of reactions to elucidate the role of the protic acid in 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

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



dx.doi.org/10.1021/cs3002513 | *ACS Catal.* 2012, 2, 1563−1595

Scheme 6. Glycosylation with 2-*p*-Methoxybenzilideneamino-*β*-D-glucopyranosyl *o*-Hexynylbenzoate 110



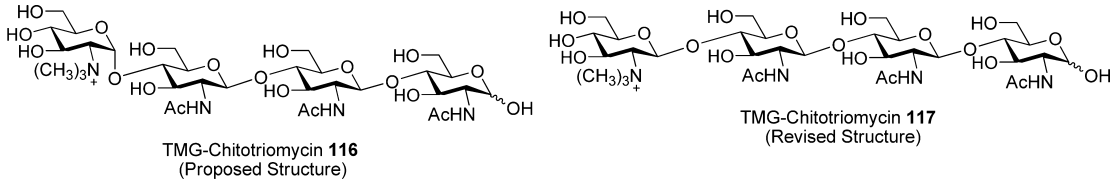
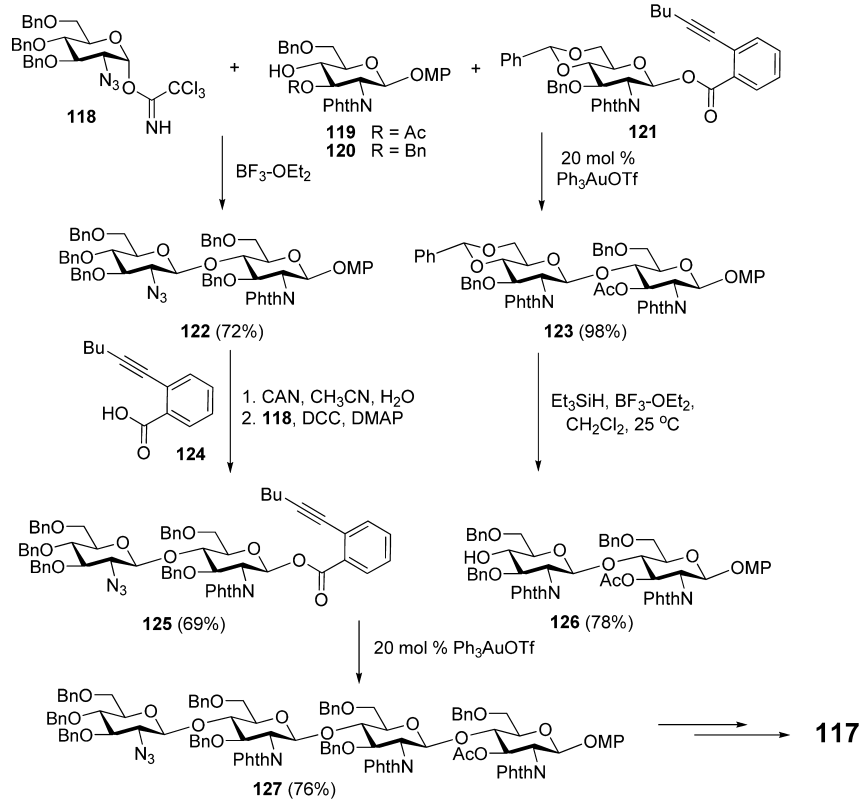


Figure 3. Proposed and revised structure of TMG chitotriomycin.

Scheme 7. Synthesis of TMG−Chitotriomycin



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 when 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 antitumor lobatoside E,[91] cardiac-glycoside digitoxin,[92] and TMG−chitotriomycin.[93] In addition, 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*-acetyl glucosaminidase activity in insects and fungi,[99] TMG−chitotriomycin **117** (Figure 3) was identified by Yu as a desirable target for the Au(I)-catalyzed

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glycosylation protocol because of 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 co-workers,[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 nonreducing 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 **126** 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 nonreducing 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 compounds is limited by their existence in microheterogeneous 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 a donor (**131**) in the 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.

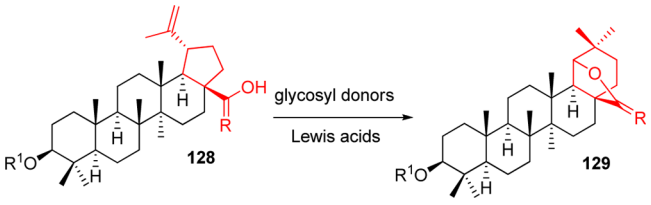

Figure 4. Wagner−Meerwein rearrangement in the presence of Lewis acid.

III. Preparation of Neo-Glycopolymers. The Yu group has reported a unique application of the *O*-hexynyl benzoate 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 (0.3 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. ^{1}H 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, such as the one seen in 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] Although catalytic approaches to *C*-glycosides are somewhat rare, there are numerous methods available for constructing the anomeric carbon−carbon bond, in which 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] In addition, 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, in which 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) in which the glucosyl and galactosyl halides **140**, **148**, and **154** were

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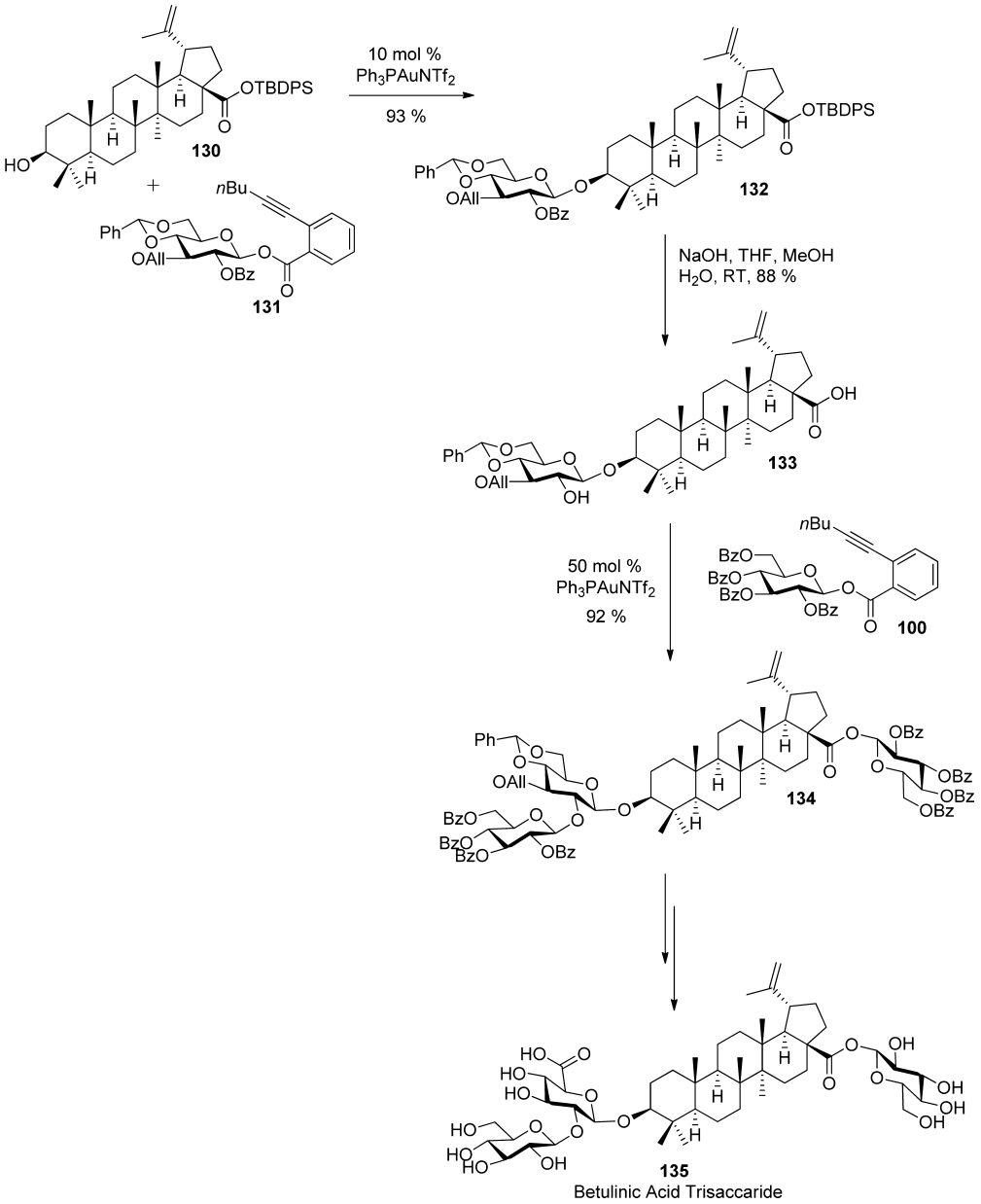
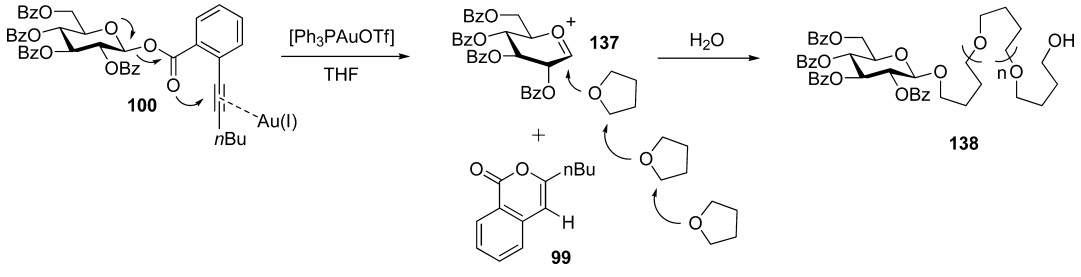
Scheme 8. Synthesis of Lupane-Type Saponin Betulinic Acid Trisaccharide



Scheme 9. Glycosylation-Initiated Polymerization of Tetrahydrofuran



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 had 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

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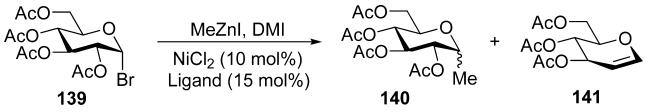
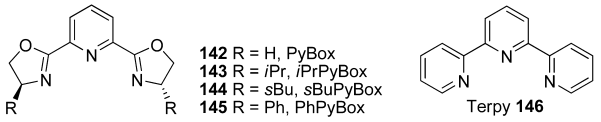
Table 12. Ligand Screening

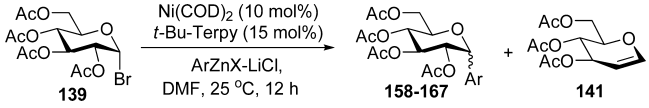


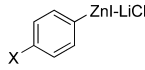
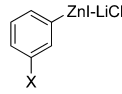
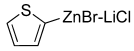
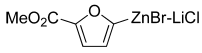
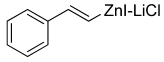
Entry	Ligand	Yield (α:β)	Glucal **141**
1	*S*-*i*Pr-PyBox	50% (1:1.5)	10%
2	*S*-*s*Bu-PyBox	20% (1:1.5)	trace
3	*S*-Ph-PyBox	trace	N/A
4	PyBox	76% (1:2.2)	6%
5	Terpy	30% (β only)	trace



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 loss 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). Although both meta and para substituents on the phenyl ring were tolerated in these reactions, aryl compounds bearing ortho substituents were not. In addition, 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.

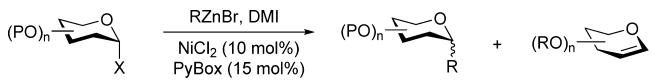
Table 14. C-Arylation with Functionalized Aryl Zinc Reagents

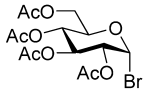
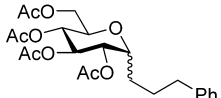
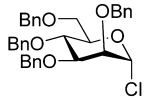
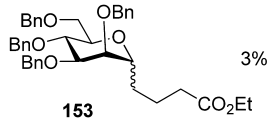
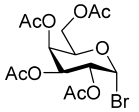
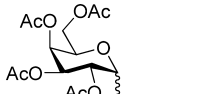
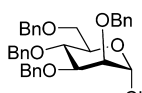
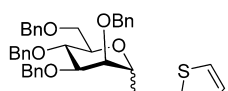
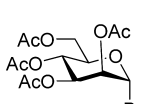
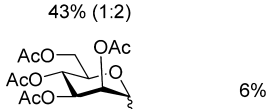
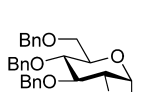


Entry	Zinc Reagents	products **158-167**	Yield (α:β)	Glycal **141**
1		**158** X = H **159** X = OMe **160** X = CO_2Me **161** X = I	71% (1:12) 64% (1:13) 66% (1:10) 30% (1:10)	7% 11% trace trace
2		**162** X = CO_2Me **163** X = Cl **164** X = I	72% (1:14) 75% (1:13) 77% (1:14)	8% trace trace
3		**165**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

B. Sn-Free, Ni-Catalyzed, Cross-Coupling Reactions of Glycosyl Bromides and 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

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%

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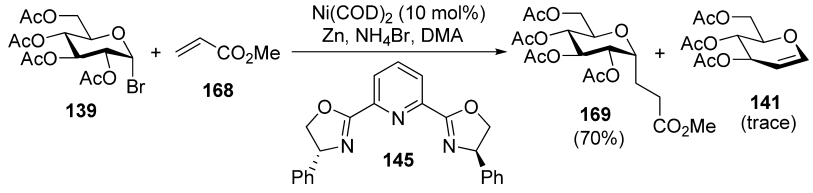
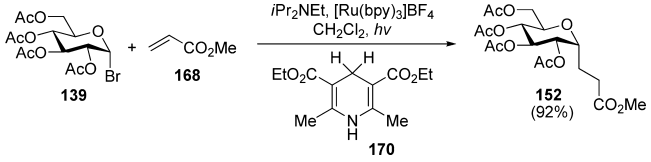
Scheme 10. Optimization Studies



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

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



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, $[Ru^{II}(bpy)_2(bpy^{\bullet-})]^{2+}$ 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 **168** 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 that 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.

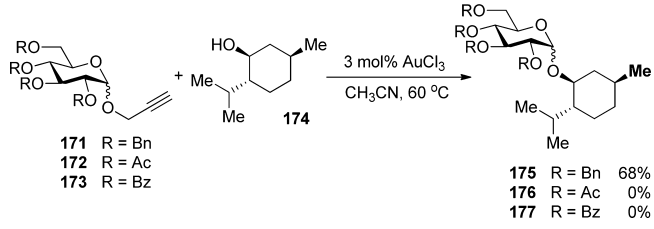
The transition-metal-catalyzed activation of glycosyl trichloroacetimidate donors has been widely explored by Nguyen, providing access to 1,2-*trans*-glycosides with cationic Pd(II) species and 1,2-*cis*-2-amino glycosides from cationic Ni(II)-catalysis. Yu has identified *ortho*-alkynyl benzoates as 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, in which 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.* Because of 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[162−175] 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 the 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

Scheme 12. Propargyl Glycosides as Glycosyl Donors



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result demonstrates the Au(III) protocol to be highly sensitive to the electronic nature of protecting groups on the donor and only extendable to the 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

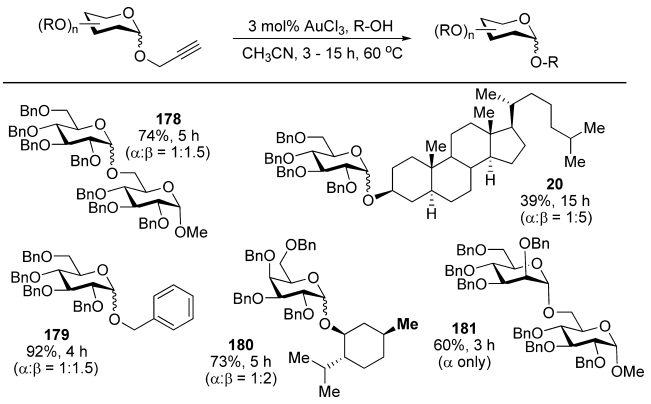

Figure 5. Synthesis of glycosides from propargyl glycosides.

glycosylated.[75] For instance, reaction of tetrabenzylated 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.[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 the 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 helminthosporium 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 the 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. This prompted further experimentation, where 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.

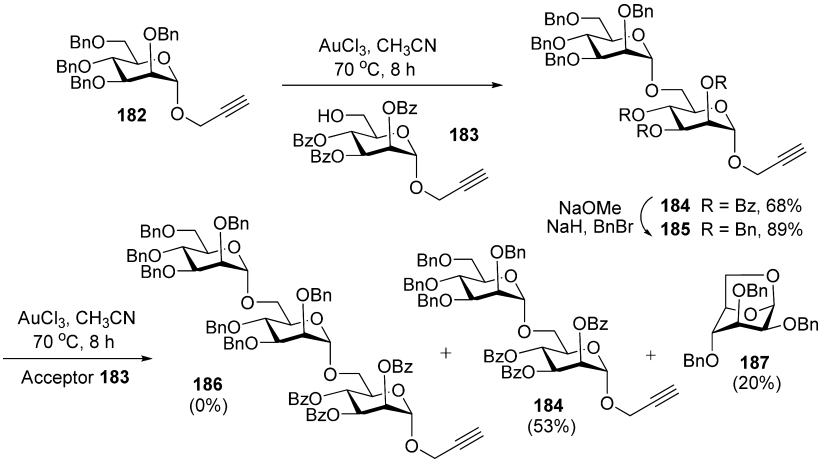

Figure 6. Attempted synthesis of trisaccharide.

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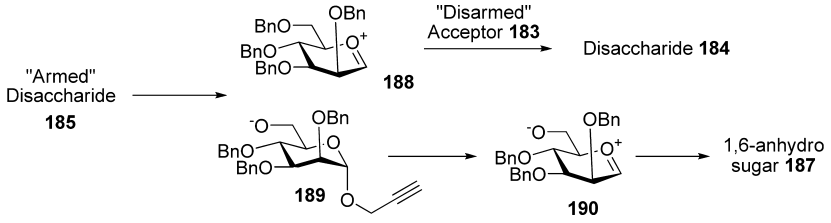
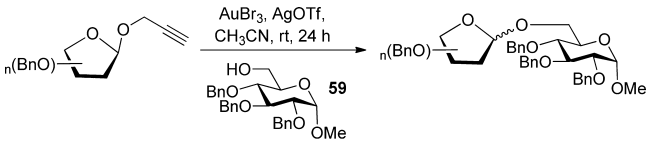
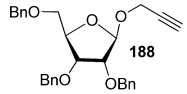
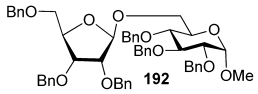
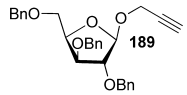
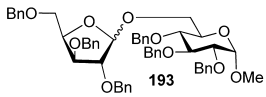
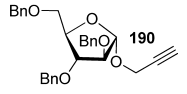
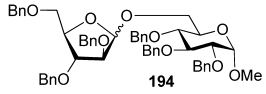
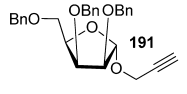
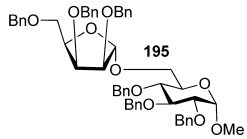


Figure 7. Mechanistic rationale.

Table 15. Propargyl Furanosides as Glycosyl Donors



Entry	Donor	Disaccharide	Yield (%)	α/β Ratio
1			72	β only
2			67	1:5
3			66	10:1
4			69	α only

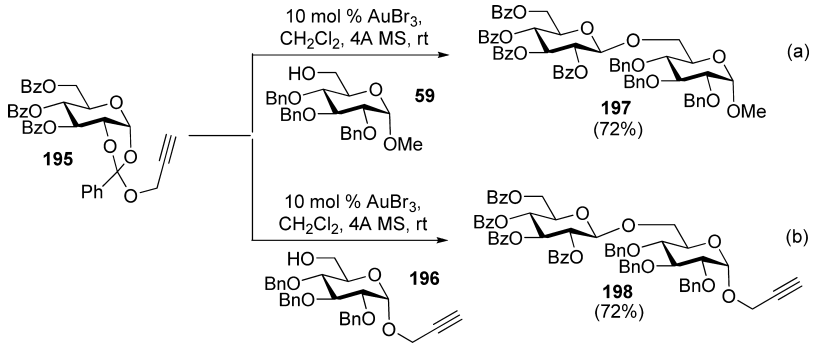
To reiterate, the Hotha group has developed a novel protocol for the construction of glycosidic linkages utilizing Au(III)salt activation of propargyl glycosides. This procedure is highly dependent on the electronic nature of the protecting groups and can be accomplished only when the donor is armed. Interglycosidic cleavage is problematic when both the nonreducing and reducing ends of the propargyl disaccharides 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 the 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), in which 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 the 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. Because of 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 multistep polyfunctionalization 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

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



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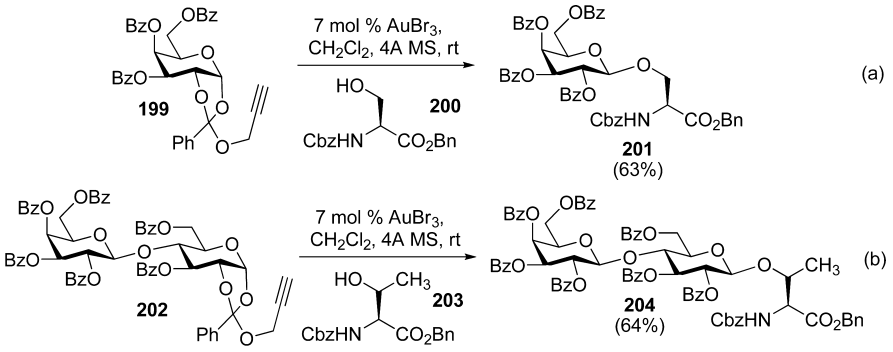
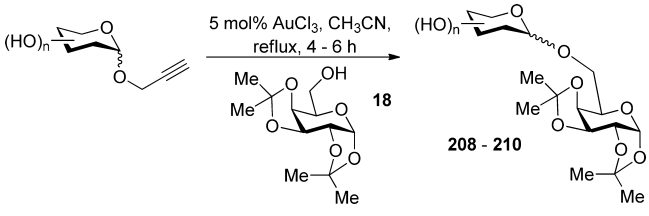
Scheme 14. Synthesis of Amino Acid *O*-Glycosides

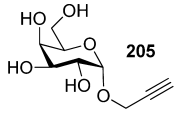
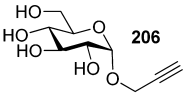
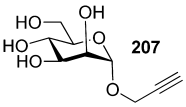


using Au(III)salts to activate propargyl glycosides[161,176,177,194] and envisioned that similar activation could be achieved with unprotected variants of such donors because of the characteristics of Au(III) catalysts: functioning well in protic solvents and possessing inherently low oxophilicity.[195]

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 equiv) of the glycosyl acceptor **18** is required to facilitate an acceptable yield because of 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.

Table 16. Glycosylation with Unprotected Propargyl Donors

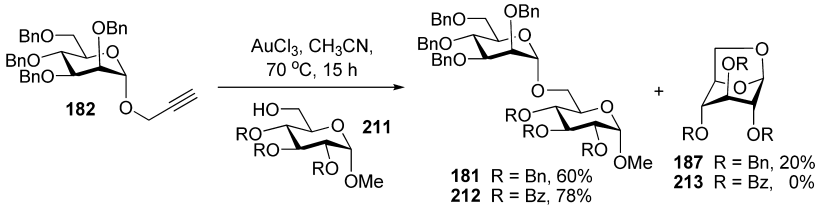


Entry	Donors	Disaccharides	Yield (%)	α/β Ratio
1	 **205**	**208**	51	1:3
2	 **206**	**209**	45	1:1
3	 **207**	**210**	45	1.6:1

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 dependent 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 **214*α*** (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

Scheme 15. Synthesis of Disaccharides



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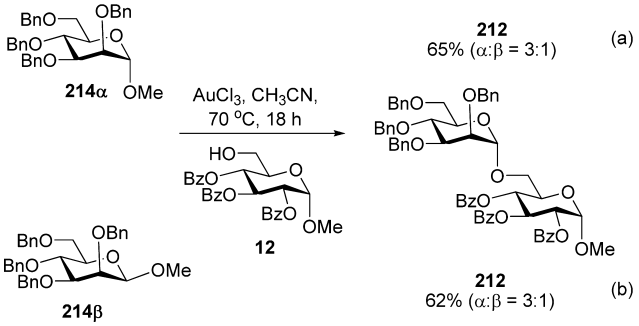
Scheme 16. Synthesis of Disaccharide from α/β-Methyl Glycoside Donors



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 be armed only 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 or yield of the reaction.[193,201]

4. GLYCAL DONORS

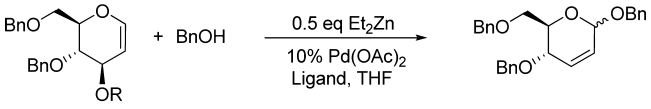
Glycosylation strategies involving glycal donors present several distinct advantages. These include: (1) construction of the anomeric linkage can be carried out with excellent selectivity, (2) commonly employed olefin manipulations can be used to functionalize products and provide access to a variety 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-Glycosylation. 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 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

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

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).[206]

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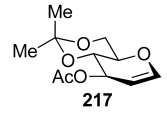
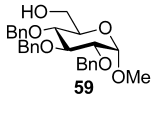
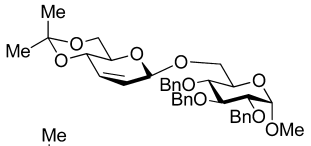
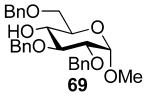
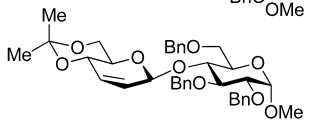
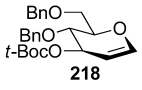
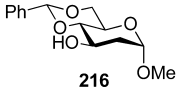
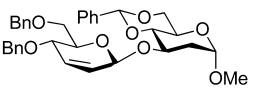
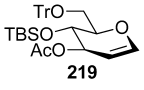
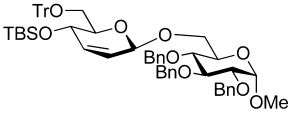
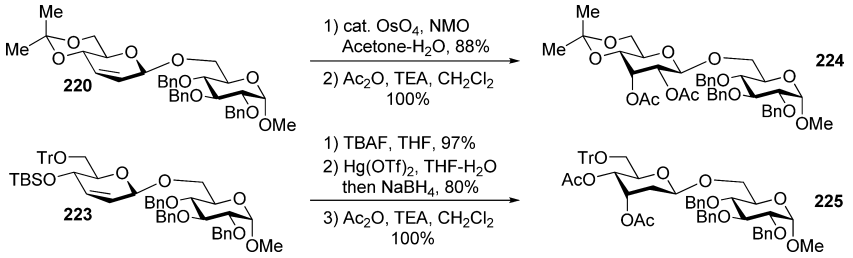
Table 18. Pd-Catalyzed Synthesis of Disaccharides

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%

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



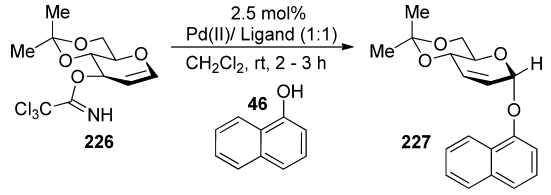
The desired disaccharides (**220**−**223**) were isolated in moderate to good yield (69−77%).

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.

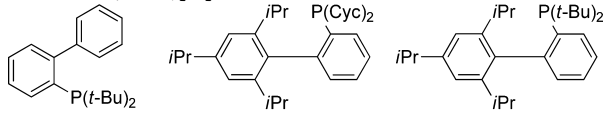
An extension to the palladium-catalyzed Ferrier-type glycosylation has been reported by Nguyen using glycal donors with the trichloroacetimidate leaving group.[207] In his approach, glycosylation of phenol acceptors can be achieved without prior activation by $Et_2Zn(II)$; however, during reactions involving 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 the 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**, in which 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 the proton source for the deoxypalladation.

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	$Pd(PhCN)_2Cl_2$	JohnPhos	91	4:1
4	$Pd(PhCN)_2Cl_2$	X-Phos	70	8:1
5	$Pd(PhCN)_2Cl_2$	*t*-BuX-Phos	84	20:1



JohnPhos X-Phos *t*-BuX-Phos

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.

dx.doi.org/10.1021/cs3002513 | *ACS Catal.* 2012, 2, 1563−1595

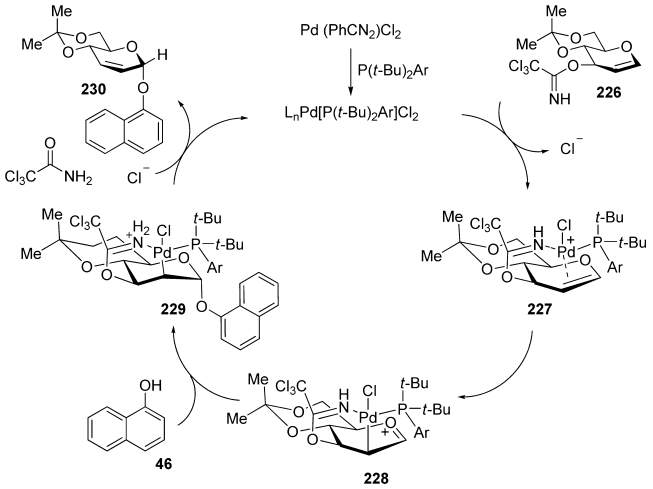


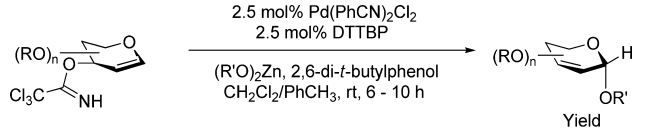
Figure 8. Proposed catalytic cycle of Pd(II)-Catalyzed Glycosylation.

The generality of this protocol was explored through the screening of aliphatic alcohol acceptors as well (Table 21). Because of 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, although 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 use as a glycosyl donor,[210,211] RajanBabu

Table 21. Pd(II)-Catalyzed Stereoselective Formation of α-*O*-Glycosides



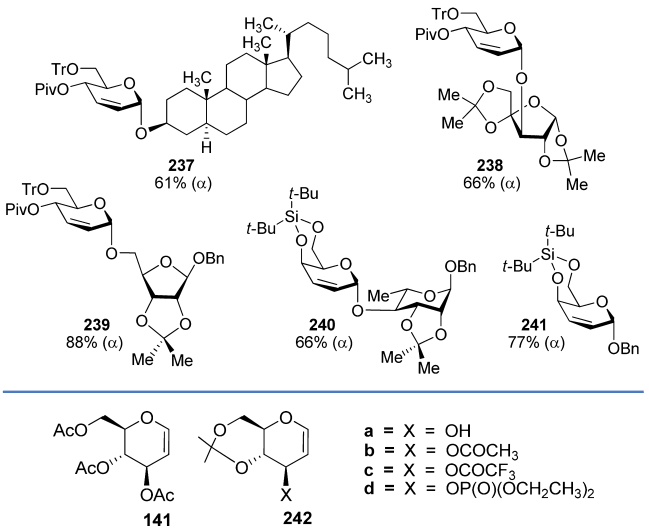


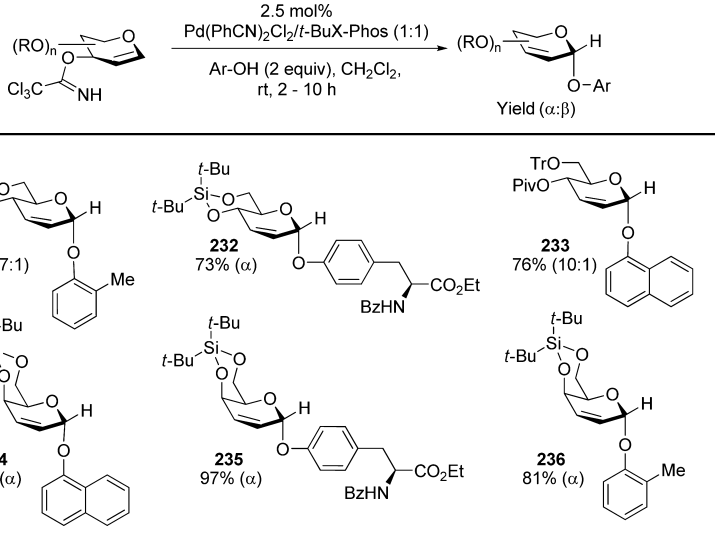
Figure 9. Screening glycosyl donors.

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 the 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]

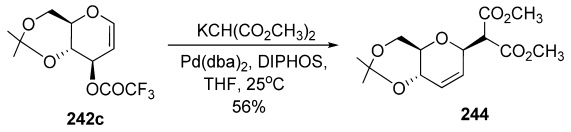
In an attempt to access β-2,3-unsaturated glycosides, Balamurugan investigated gold catalysis in the Ferrier reaction.

Table 20. Pd(II)-Catalyzed Stereoselective Formation of α-*O*-Aryl Glycosides



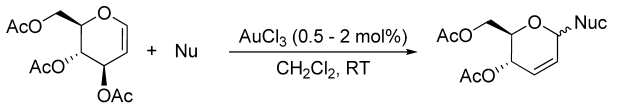
dx.doi.org/10.1021/cs3002513 | ACS Catal. 2012, 2, 1563−1595

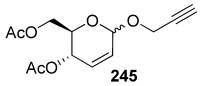
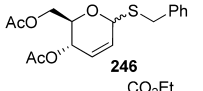
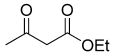
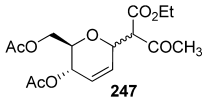
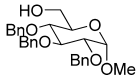
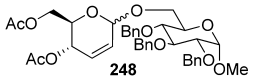
Scheme 18. Pd-Catalyzed C-Glycosylation



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 the presence of 0.5−2.0 mol % $AuCl_3$ catalyst (Table 22). In each case, the glycosylation reaction

Table 22. Gold-Catalyzed Formation of *O*- and *C*-Glycosides



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)

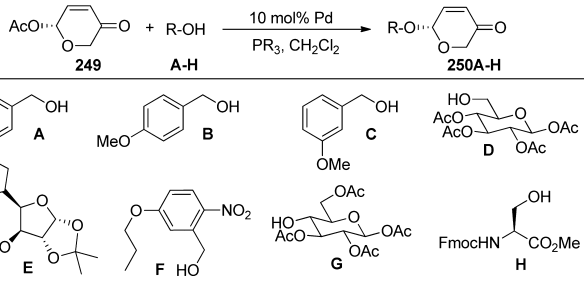
proceeded smoothly in generating the corresponding 2,3-unsaturated *O*-glycoside product (**245**−**248**) with good yield (74−85%) and moderate α-selectivity (α/β = 3:1−6:1). This method was also investigated with 3,4,6-tri-*O*-acetyl-D-galactal donor. In comparison with reactions involving glucal donor, these were found to be quite sluggish at 0.5 mol % Au catalyst loading. Rates were improved by increasing the 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 where pyranone-derived donors are used to overcome the low reactivity observed during reactions with aliphatic alcohols has been reported. 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 that 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

Table 23. Pd-Catalyzed Stereoselective Acetal Bond Formation



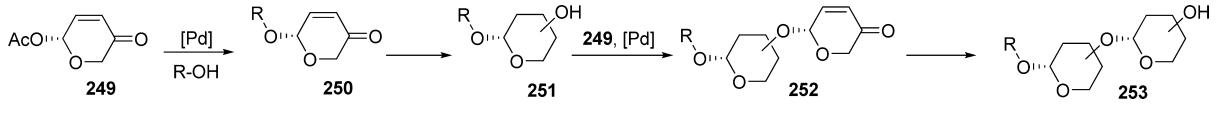
product	yield, %	de, %	product	yield, %	de, %
250A	83	94	**250E**	70	97
250B	87	98	**250F**	84	98
250C	98	99	**250G**	65	91
250D	77	94	**250H**	78	97

nearly complete retention of stereochemical integrity.[209] However, during the attempted couplings of amino acid **H** and carbohydrate acceptor **D** with 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.

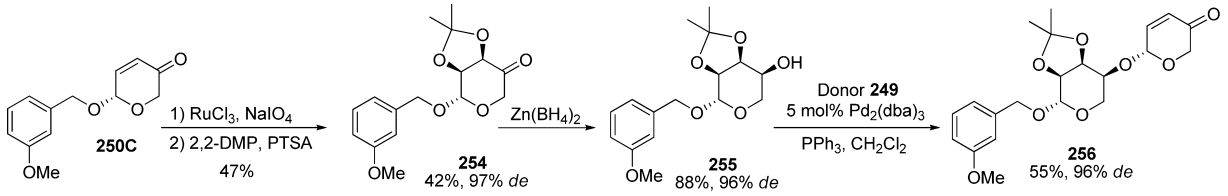
Shortly after the submission from Feringa, a similar transformation was reported by O'Doherty. During an investigation of π-allyl palladium complexes as glycosylation

Scheme 19. Iterative Oligosaccharide Synthesis via Palladium Catalysis



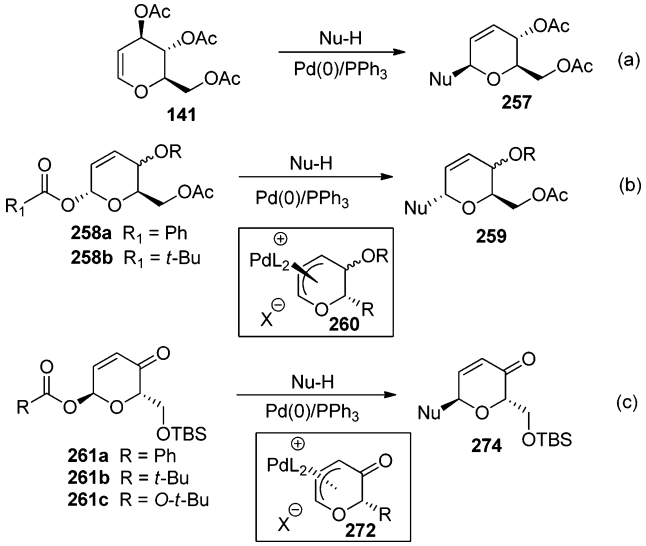
dx.doi.org/10.1021/cs3002513 | ACS Catal. 2012, 2, 1563−1595

Scheme 20. Iterative Oligosaccharide Synthesis



intermediates,[203] O'Doherty attempted to ionize the C(3)-acetoxy group of glycal donor **141** (Scheme 21a) using a Pd(0)

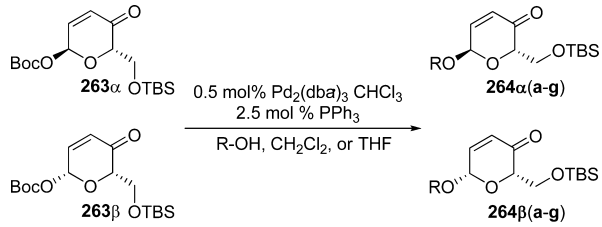
Scheme 21. Pd-Catalyzed Glycosylation with Pyranone Donors



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, although 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

Table 24. Substrate Scope



			yield, %		
entry	R–OH	product (**264a–g**)	**264**α	**264**β	**264**β
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

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.

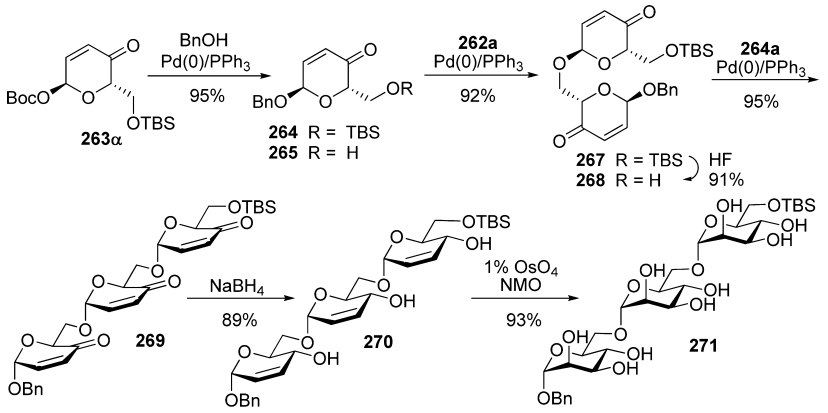
C. Synthetic Applications. I. Oligosaccharide Synthesis. The palladium strategy developed by the O'Doherty group has been applied to constructing 1,6-linked oligosaccharides (Scheme 22).[225] Accordingly, the coupling of benzyl alcohol with donor **263**α and subsequent unmasking of the C(6)-hydroxyl 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% yield. 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**.

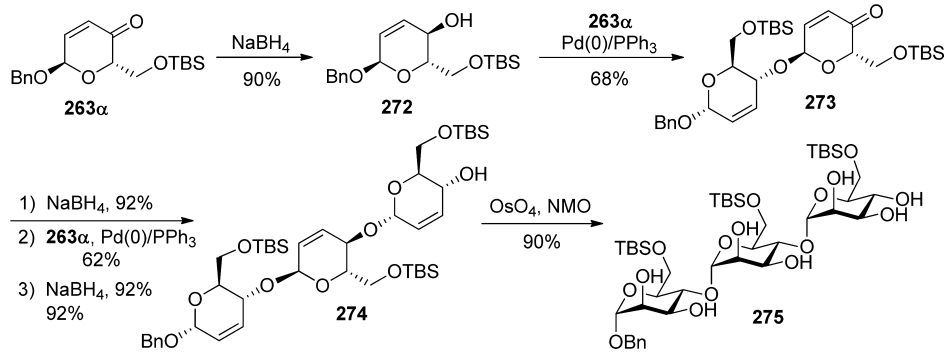
II. Cleistrioside and Cleistetroside Natural Products. Further demonstrating the utility of his glycosylation strategy, O'Doherty reported a total synthesis of several biologically active cleistrioside and cleistetroside natural products (Scheme 24).[210,211] Using a non-Ferrier glycosylation approach with Pd(0) catalysis and pyranone donors during key transformations, the repeating rhamnosyl cores of the trisaccharide

dx.doi.org/10.1021/cs3002513 | *ACS Catal.* 2012, 2, 1563–1595

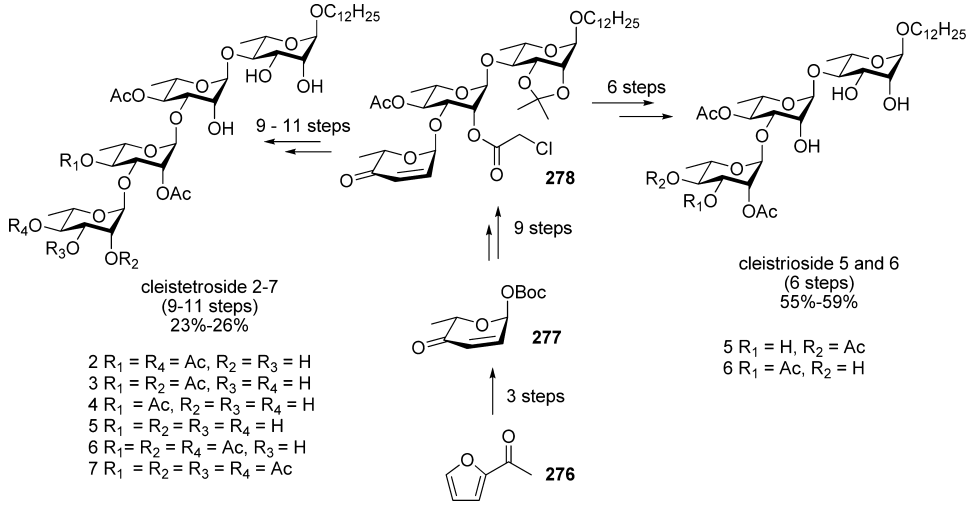
Scheme 22. Synthesis of α-1,6-Linked Trisaccharide



Scheme 23. Synthesis of 1,4-Linked Trisaccharide



Scheme 24. Synthesis of Cleistriosides and Ceistetrosides via Palladium Catalysis



and tetrasaccharide variants were synthesized in nine 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] *B. 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 United States 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 the presence of a substoichiometric

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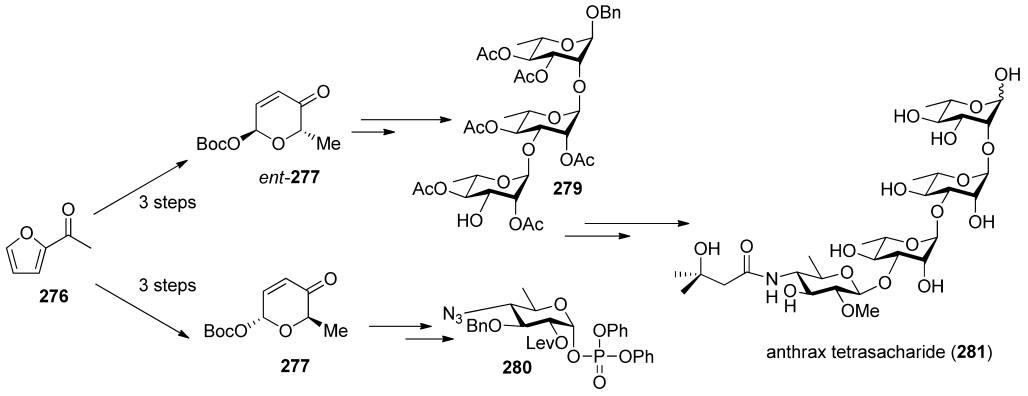
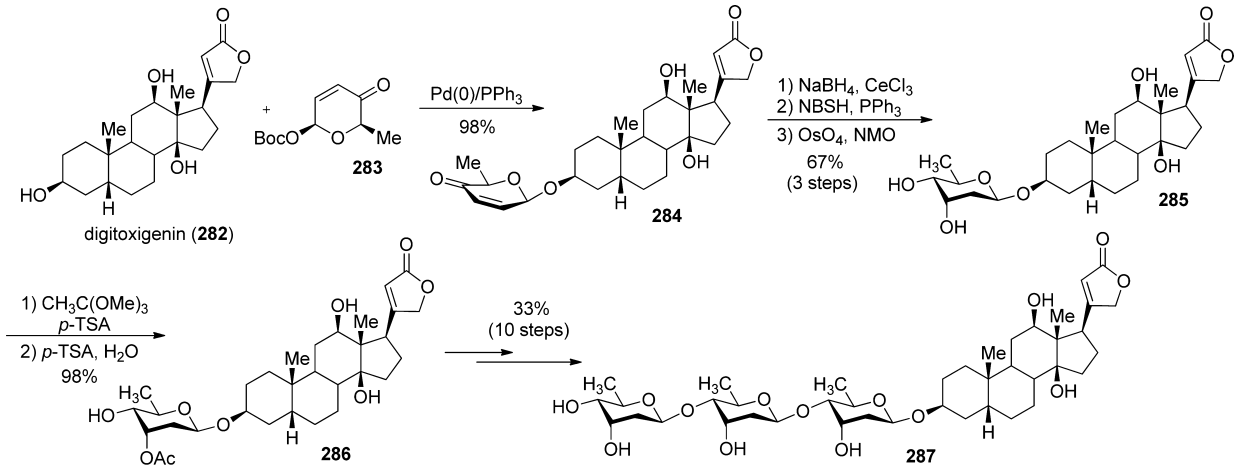
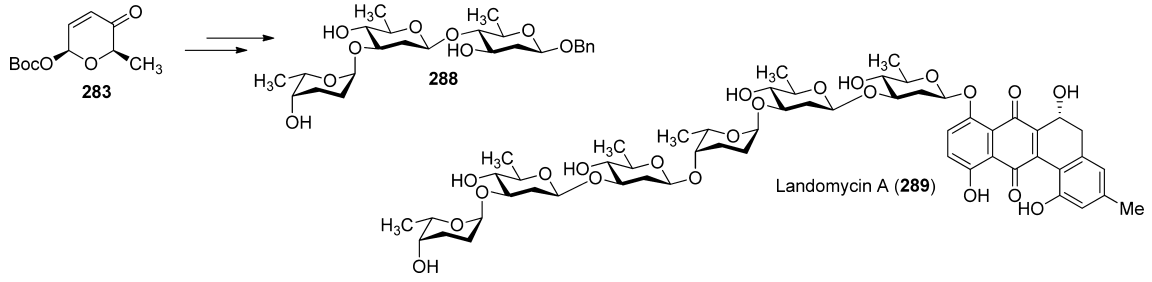
Scheme 25. Synthesis of Anthrax Tetrasaccharide via Palladium Catalysis



Scheme 26. Synthesis of Digitoxin via Palladium Catalysis



Scheme 27. Synthesis of Landomycin Trisaccharide via Palladium Catalysis



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 (nine 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 yield).

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 consists of the landomycinone core, which is connected to a hexasaccharide unit consisting of two repeating trisaccharide subunits. There have been several groups to report syntheses of the oligosaccharide component of the natural product.[232−236] In

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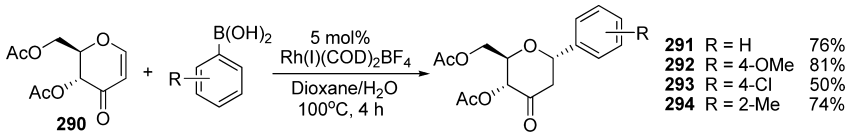
Scheme 28. Rh(I)-Catalyzed 1,4-Addition of Boronic Acids to Enone



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 apply to completion of the natural product, which has been reported by Yu recently in the first total synthesis of Landomycin A.[237]

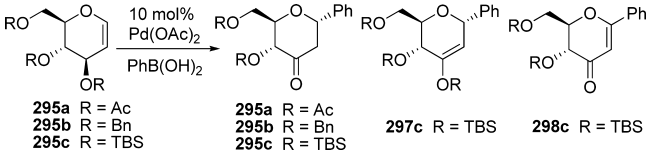
In addition to these synthetic applications, O'Doherty's glycosylation protocol has been applied in the enantioselective synthesis of the kaempferol glycoside SL0101, its analogues, and their enantiomers from acetylfuran.[239] This activation strategy is also amenable to cyclitolization with carbasugars,[240] (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 is 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, although those 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 in 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 because of their availability, their 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 in which access to three structural motifs can be attained by changing oxidants in the reaction (Table 25) has been reported[247]. As such, the coupling of phenylboronic acid to glucals **295a−c** was investigated in the 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 with 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.

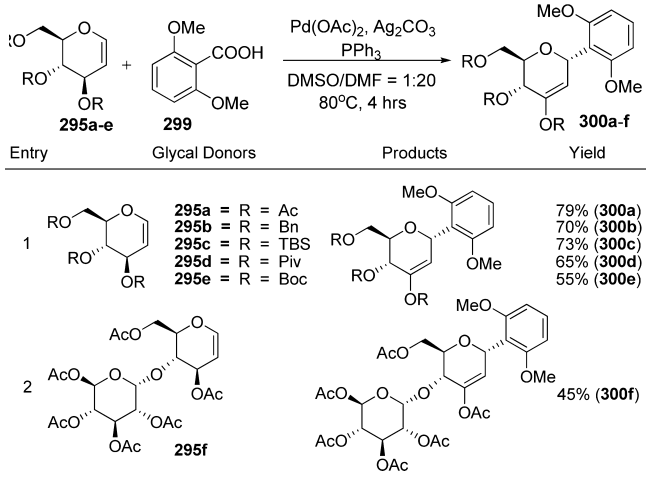
Table 25. Heck-Type C-Glycosylation of Glycal Donors



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

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 the 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 cou-

Table 26. Palladium-Catalyzed Decarboxylative Coupling



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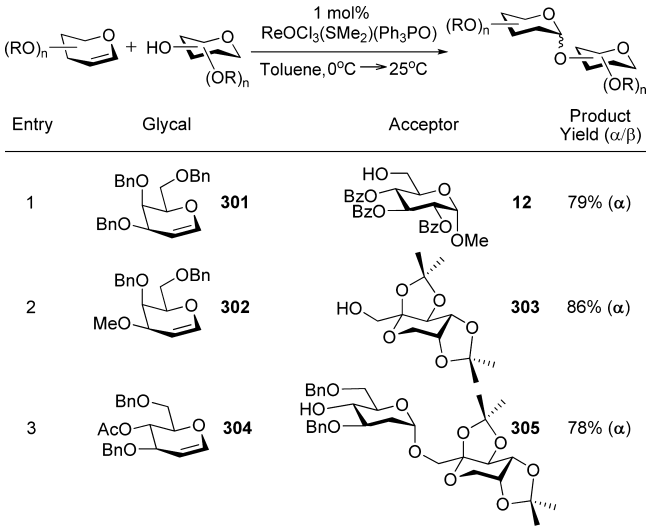
pling of disaccharide glucal **295f** (Table 26, entry 2) with benzoic acid **299** proceeded smoothly to provide glycoconjugate **300f** in 45% yield.

B. Rhenium(V)-Catalyzed Glycosylation. A mild method for generating anomeric carbon−oxygen bonds on C(2)-deoxy sugars using rhenium(V) catalysis has been reported by Toste.[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

Table 27. Re(V)-Catalyzed *O*-Glycosylation



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-deoxyoligosaccharide 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 involving the activation of glycal donors with transition metal catalysts have been made to 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. 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

This final section of this review details 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 preinstallation 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 conditions.

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*-arabinofuranosides by accomplishing the transformation with a catalytic amount of titanium.[251] The stereoselective synthesis of these β-arabinofuranosides can be problematic because they are readily isomerized to the more thermodynamically stable α- (or 1,2-*trans*-) counterpart under many conventional Lewis acid-

Scheme 29. Synthesis of Trisaccharides

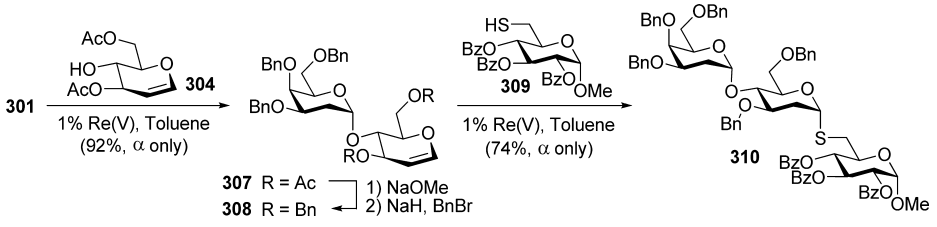


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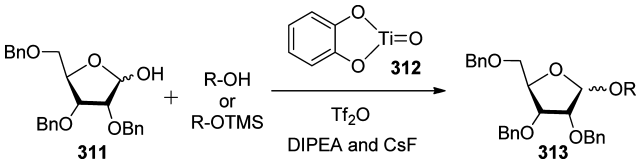
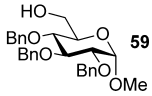
Table 28. Synthesis of β-Ribofuranosides



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

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. In addition, 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.

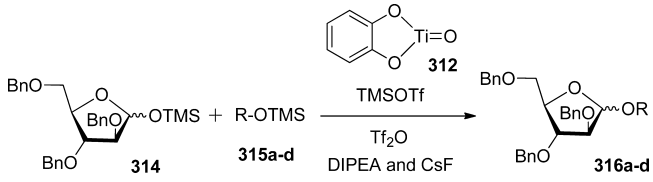
These conditions were found to be compatible with a variety of trimethylsilylated nucleophiles (Table 29), notably in the reaction of 1-*O*-trimethylsilyl sugar **314** and trimethylsilyl benzyl ether **315b**, where 91% of the desired glycoside **316d** was obtained as a 1:9 α/β-mixture with only 20 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.

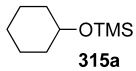
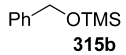
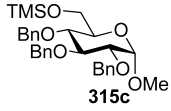
5.2. Unprotected Carbohydrate Donors. Significant advancement to the construction of glycosidic linkage under titanium catalysis has been made with Mahrwald's recent report of a direct glycosylation using unprotected carbohydrate donors.[252] Bypassing many of the previously examined challenges in carbohydrate synthesis, 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 found 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(O*t*Bu)$_4$ with 4% mandelic acid (**322**) in isopropyl alcohol. This finding encouraged further experimentation, during which it was discovered that the reaction could be applied to glycosylation with unprotected sugars. Interestingly, when D-ribose was treated to this condition in isopropyl alcohol (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] In addition, 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 conditions and showed only partial conversion after several days. Efforts were therefore applied to accelerating the process, and 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

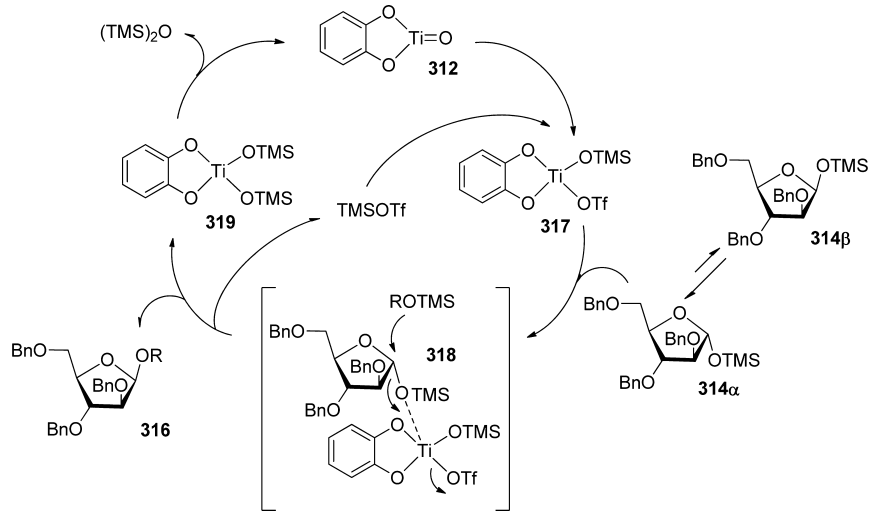
Table 29. Synthesis of 1,2-*cis*-Arabinofuranosides



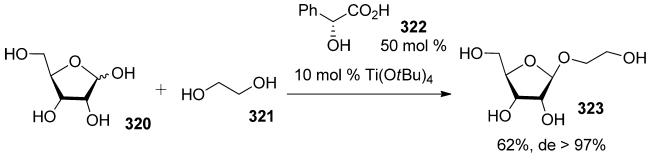
entry	R-OTMS	TMSOTf (equiv)	**X** (equiv)	temp °C	yield	(α/β)
1	 **315a**	2.0	1.0	0	76	18/82
2		2.0	1.0	-23	90	9/91
3		0.8	0.4	-15	77	10/90
4		0.4	0.2	0	62	14/86
5	 **315b**	0.8	0.2	-23	96	13/87
6		0.4	0.1	-23	91	10/90
7	 **315c**	0.8	0.4	-23	84	8/92
8	3B-cholestanyl-OTMS **315d**	0.8	0.4	0	96	13/87

dx.doi.org/10.1021/cs3002513 | *ACS Catal.* 2012, 2, 1563−1595

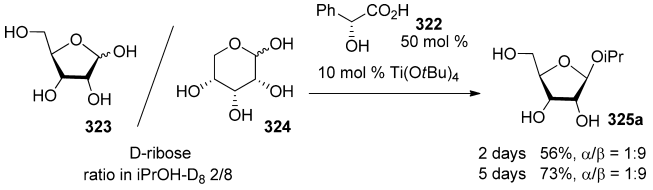
Scheme 30. Catalytic Cycle of Titanium Glycosylation



Scheme 31. Direct Glycosylation with Unprotected Carbohydrates



Scheme 32. Direct Glycosylation of D-Ribose

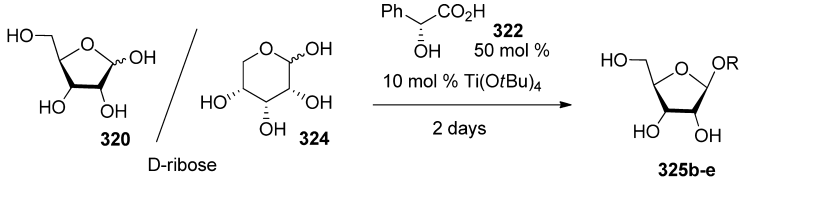


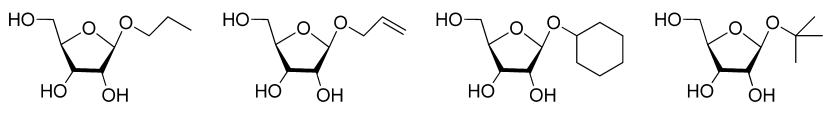
addition of the lithium salt. The yields in the reactions were substantially better in the presence of LiBr, although the selectivity was diminished in most cases. After the second day of the reaction, furanoside products were predominantly observed with the LiBr additive, although appearance of pyranosides 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 equiv of the acceptor isopropyl alcohol was employed to furnish 58% (1:4 α/β) of the ribofuranoside in 2 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 of 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.

Scheme 33. Effect of LiBr Additive





	325b	325c	325d	325e
w/o LiBr	64%, (10:90 α/β)	44%, (17/83 α/β)	44%, (5/95 α/β)	7%, (5/95 α/β)
1 equiv LiBr	98%, (13/87 α/β)	85%, (27/72 α/β)	95%, (29/71 α/β)	18%, (18/82 α/β)

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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-deoxyglycosyl 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 of diverse chemical reactions yet retain the ability for selective activation under catalytic control is enticing for synthetic carbohydrate chemists. Hotha has developed a Au-catalyzed propargyloxy- and methoxyglycoside activation strategy to facilitate glycosylation, although 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, although 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 tolerant of both moisture and air for constructing C(2)-deoxyglycosides with high-oxidation-state rhenium. The reactivity of the donors in this approach is highly dependent on the nature of the protecting group at C(3), which has been exploited in an iterative 2-deoxyoligosaccharide 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 preinstallation 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 the construction of either furanosides or 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 syntheses 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 be accomplished only 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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Notes

The authors declare no competing financial interest.

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