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ARTICLE

Iridium-promoted Deoxyglycoside Synthesis: Stereoselectivity and Mechanistic Insight

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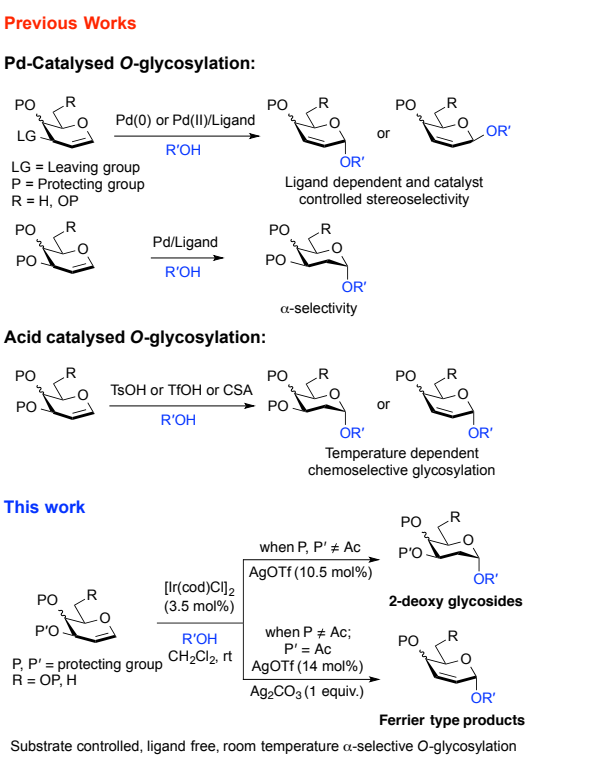
Herein, we devised a method for the stereoselective *O*-glycosylation using Ir(I)-catalyst which enables both hydroalkoxylation and nucleophilic substitution of glycals with varying substituent at C3 position. In this transformation, 2-deoxy- α -*O*-glycosides were acquired when glycals equipped with a notoriously poor leaving group at C3 were used, on the contrary 2,3-unsaturated-α-*O*-glycosides were produced from glycals that bear a good leaving group at C3. Mechanistic studies indicate that both reactions proceed via directing mechanism, through which the acceptor coordinates to the Ir(I) metal in the α-face-coordinated Ir(I)-glycal π-complex and then attacks the glycal that entails *O*-glycosidic bond in a syn-addition manner. This protocol exhibits good functional group tolerance and is exemplified with the preparation of a library of oligosaccharides in moderate to high yields and excellent stereoselectivities.

Introduction

Deoxy sugars, constituting essential structural components in a variety of biologically active natural products, have drawn significant attention from carbohydrate chemists lately.[1] Over the past few years, acid and base promoted synthesis of 2-deoxy sugars became popular in the field of carbohydrate chemistry.[2] However, glycosylation by these approaches are often conducted at either low or high temperatures, with the possibility of getting appreciable amounts of unwanted hemiacetal side products.[2b,2c,2e,3] In comparison, transition metal catalyzed glycosylation with glycals, compatible with acid and base-labile substates and amenable to moderate conditions, promise improved alternatives to the conventional methods. During recent years, transition metal has featured an important role in the chemical synthesis of oligosaccharides, with a flow of intriguing glycosylation methodologies involving a variety of transition metal catalysts reported.[4-16] Conceptually, by installing specific substituents onto the donors[6] and/or control of the oxidation state of the transition metal in the catalysts, face-selective coordination of the catalytic metal complex with the olefinic pyranose ring can be feasibly achieved,[7] enabling stereoselective construction of glycosidic linkages. Additionally, glycal donors can be activated with a catalytic amount of transition metal catalyst, while in conventional acid or base promoted glycosylation reactions, saturated glycosyl donors consume stoichiometric amounts of activating agents.



Scheme 1. (a) Recent development on stereoselective conversion of glycals to 2-deoxy glycosides and 2,3-unsaturated glycosides; (b) Ir(I)-catalyzed substrate controlled α stereoselective-*O*-glycosylation of glycals.

An important class of the transition metal catalyzed glycosylation methodologies are those which exploit Palladium catalysts for stereoselective synthesis of 2,3-unsaturated and 2-deoxy glycosides from glycals, under anhydrous reaction

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conditions to preclude formation of the hydrolyzed products.[7,8] Nevertheless, to access different types of glycoside structures, glycosylation of glycals require different Pd-catalytic systems with various phosphine ligands. And with certain Pd-catalysts, chemo-selectivity is achieved by conducting the reaction at varying temperatures.[7,8] Analogous to the established Palladium catalysts, iridium complexes have been well known to be efficient catalysts for allylic substitution reactions[9] and hydro-functionalisation[10] of olefins, while the aptness of iridium catalysts for glycosylation has scarcely been explored. Though Nishimura *et al*.[17] had reported a pioneering iridium-catalyzed stereoselective *C*-glycosylation of glycals via C-H activation of arenes, no iridium-catalyzed-*O*-glycosylation with direct activation of glycal scaffolds has been reported to date.

Inspired by the success of Pd-catalyzed glycosylation methodologies and advancements in development of Ir(I)-catalyst towards allylic addition, substitution reactions and as a part of our continuing effort on exploring the advanced stereo- and regioselective glycosylation, we envisioned that the Ir-catalyzed chemistry can be applied to the olefinic glycal substrates to achieve stereoselective *O*-glycosylation. In this article, we describe the novel ligand free iridium-catalyzed *O*-glycosylation, that enables substrate-controlled access to both 2-deoxy glycosides and 2,3-unsaturated glycosides from easily accessible protected glycals at room temperature, with exclusive α-stereoselectivity (Scheme 1).

Results and discussion

Our attempt commenced with the screening of catalyst employing 3,4,6-tri-*O*-benzyl-D-galactal (**1a**) as glycosyl donor and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2a**) as model glycosyl acceptor (Table 1). Not a trace amount of the 2-deoxy-*O*-glycoside was detected when 3.5 mol% $[Ir(COD)Cl]_2$ was used as the catalyst. It provided the desired 2-deoxyglycoside (**3a**) with the addition of $[Ir(COD)Cl]_2$/AgOTf and

Table 1. Optimization of the Ir(I)-catalyzed glycosylation for the synthesis of 2-deoxy glycosides with glycal **1a** and model acceptor **2a**.

Entry	Catalyst (mol%)	Ag-Salt (mol%)	Solvent	yield	α:β[a]
1	$[Ir(COD)Cl]_2$ (3.5)	-	DCM	-	NA
2	$[Ir(COD)Cl]_2$ (2.5)	AgOTf (5)	DCM	30%	1:0
3	$[Ir(COD)Cl]_2$ (3.5)	AgOTf (7)	DCM	45%	1:0
4	$[Ir(COD)Cl]_2$ (3.5)	AgOTf (10.5)	DCM	77%	1:0
5[b]	$[Ir(COD)Cl]_2$ (3.5)	AgOTf (10.5)	DCM	-	NA
6	-	AgOTf (10.5)	DCM	29%	1:0
7	$[Ir(COD)Cl]_2$ (3.5)	AgOTf (10.5)	MeCN	27%	15:1
8	$[Ir(COD)Cl]_2$ (3.5)	AgOTf (10.5)	Toluene	41%	1:0
9	$[Ir(COD)Cl]_2$ (3.5)	AgOTf (10.5)	DCE	52%	1:0
10	$[Ir(COD)Cl]_2$ (3.5)	AgOTf (10.5)	$CHCl_3$	66%	1:0
11	$[Ir(COD)Cl]_2$ (3.5)	AgOTf (10.5)	1,4-Dioxane	-	NA
12	$[Ir(COD)Cl]_2$ (3.5)	$AgSbF_6$ (10.5)	DCM	23%	1:0
13	$[Ir(COD)Cl]_2$ (3.5)	$AgBF_4$ (10.5)	DCM	40%	1:0
14	$[Ir(COD)Cl]_2$ (3.5)	$AgPF_6$ (10.5)	DCM	-	NA
15	$[Ir(COE)_2Cl]_2$ (3.5)	AgOTf (10.5)	DCM	33%	1:0

All the reactions were carried out with 0.15 mmol **1a** and 0.1 mmol **2a**. [a]Stereoselectivity was determined by crude ^1H NMR. [b]$P(OPh)_3$ was used as a ligand. Isolated yields.

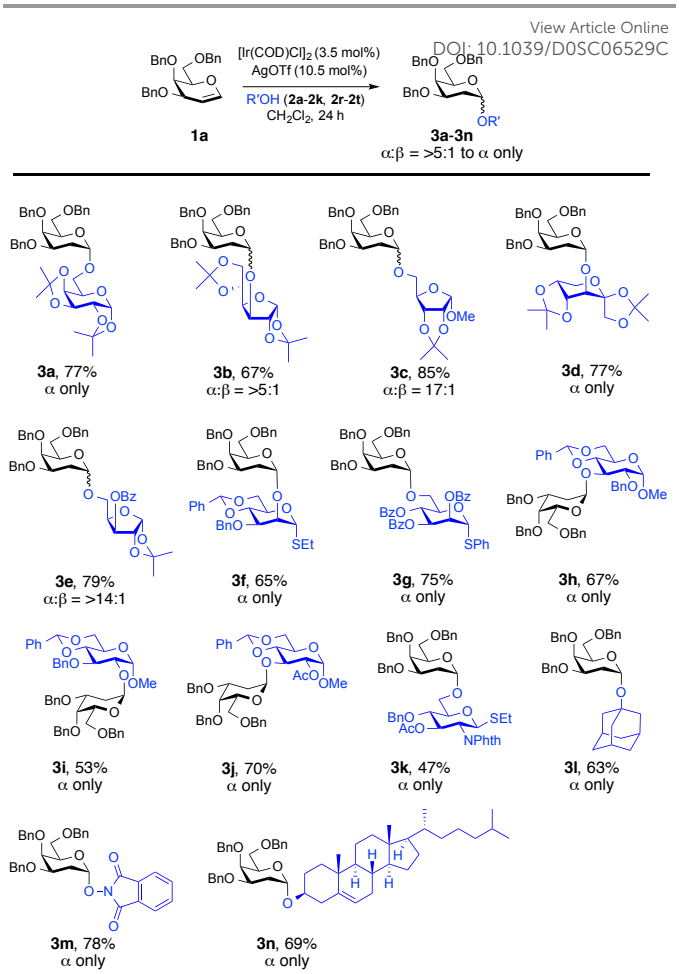
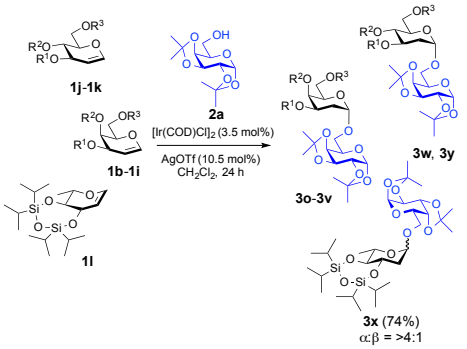


Figure 1. Stereoselective α-*O*-glycosylation of **2a** with a range of glycosyl acceptors (**2a-2n**). Reactions were carried out under N_2 atmosphere using 1.5 equiv. 3,4,6-Tri-*O*-benzyl-D-galactal (**1a**), 1.0 equiv. of acceptor, 3.5 mol% $[Ir(COD)Cl]_2$, and 10.5 mol% AgOTf in dry CH_2Cl_2 for 24 h at rt. Stereoselectivity was determined by crude ^1H NMR. Isolated yields.

to our satisfaction yield of the reaction was improved significantly to 77% with 10.5 mol% loading of AgOTf in CH_2Cl_2 (Table 1, entry 4). Screening of the silver salts implied that the *O*-glycosylation occurred most efficiently in the presence of AgOTf (10.5 mol%). While assessing the solvents, we found that the reaction didn't proceed in 1,4-dioxane, however, the use of MeCN, toluene, DCE and $CHCl_3$ as solvent provided 27%, 41%, 52% and 66% yield of the desired 2-deoxyglycoside respectively, but turned out to be less effective compare to CH_2Cl_2 (Table 1). It is noteworthy that not a trace of desired glycosylated product was observed with the bulky $P(OPh)_3$ ligand, possibly due to the obstruction of the nucleophile acceptor from approaching the glycal considering the sterically hindered Ir[$P(OPh)_3$]-glycal π-complex (Table 1, entry 5). As summarized in Table 1, $[Ir(COE)_2Cl]_2$ afforded the desired glycosylated product **3a**, but lower yield (33%) was attained. With optimized conditions in hand, a range of nucleophilic acceptors was reacted with the 3,4,6-tri-*O*-benzyl-D-galactal (**1a**) to investigate the donor scope of the Ir-catalyzed hydro-alkoxy addition (Figure 1). A large variety of substituents on the glycosyl acceptors were well tolerated, constituting commonly used carbohydrate protecting

Table 2. Reaction of Glycals **1b–1i**, **1j–1k**, and **1l** with model glycoside acceptor **2a**



Entry	Donor	R^1	R^2	R^3	Product	Yield (%)	α:β
1	**1b**	Me	Me	Me	**3o**	83%	1:0
2	**1c**	Et	Et	Et	**3p**	78%	23:1
3	**1d**	Allyl	Allyl	Allyl	**3q**	82%	1:0
4	**1e**	TBDMS	TBDMS	TBDMS	**3r**	80%	1:0
5	**1f**	TBDMS	Ac	TBDMS	**3s**	76%	1:0
6	**1g**	Bn	Bn	TBDPS	**3t**	79%	10:1
7	**1h**	Bn	Bn	Ac	**3u**	86%	>30:1
8	**1i**	Bn	Ac	Bn	**3v**	81%	1:0
9	**1j**	O[Si(iPr)$_2$]$_2$		TBDPS	**3w**	78%	1:0
10[a]	**1k**	TBDMS	TBDMS	TBDMS	**3y**	8%	1:0

All the reactions were carried out under N_2 atmosphere using 1.5 equiv. glycosyl donors (**1b-1k**), 1.0 equiv. acceptor (**2a**) in dry CH_2Cl_2 for 24 h. [a]**4r** obtained as a major product (71%). Stereoselectivity was determined by crude ^{1}H NMR. Isolated yields.

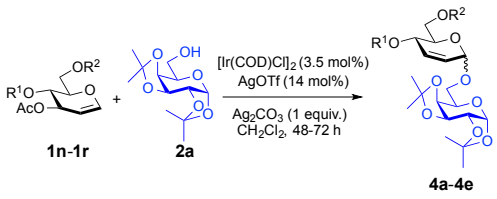
groups, e.g. acetal, ester, ether, and phthalimide, and all the reactions afforded desired 2-deoxy glycosides in a yield range of 47-85% with α-stereoselectivity. It is worth noting that, in the case of **3b** (α:β = >5:1), **3c** (α:β =17:1) and **3e** (α:β = >14:1) β-isomers were identified from ^{1}H NMR but with the favourable α-stereoselectivity and good yield (67%, 85% and 79% respectively, Figure 1). The reaction proceeded equally well with secondary hydroxyl groups positioning at variable positions of pyranose ring of different carbohydrates including glucose (**2h**, **2i** and **2j**, see ESI), glucosamine (**2k**, see ESI), mannose (**2f**, **2g**, see ESI), and fructose (**2d**, see ESI). To our satisfaction, the transformation provided the desired glycosides in moderate to high yield while maintaining excellent α-stereoselectivity. The reported method enabled glycosylations of the sterically hindered alcohols (**2f**, **2r**, see ESI) that gave the corresponding products (**3f** and **3l** respectively, Figure 1) in high yields with α-stereoselectivity upon isolation. We then assessed the reaction with an array of glycal donors embedded with a variety of ether and ester protections and satisfactorily all the tested donors were well compatible, afforded desired α-glycosides in good to excellent yields (summarized in Table 2). It is important to note that when we have carried out the reaction with conformationally unrestricted glucal **1k**, we obtained more Ferrier product (71%, entry 10, table 2) than 2-deoxy glycoside (8%), whereas we acquired only 2-deoxy glycoside with conformationally restricted glucal (**1j**, entry 9, table 2) and rhamnal (**1l**). Thus, the formation of either glycosidic product greatly depends both on the stereochemistry and conformation of the protecting groups in the glycals.[3b, 3c]

Table 3. Optimization of the Ir(I)-catalyzed glycosylation for the synthesis of 2,3-unsaturated glycosides with glycal **1n** and model acceptor **2a**.

Entry	Catalyst (mol%)/Ag-Salt (mol%)	Base	Solvent	yield
1	[Ir(cod)Cl]$_2$ (2.5)/ AgOTf (5)	Ag_2CO_3	DCM	23%
2	[Ir(cod)Cl]$_2$ (3.5)/ AgOTf (7)	Ag_2CO_3	DCM	42%
3	[Ir(cod)Cl]$_2$ (3.5)/ AgOTf (10.5)	Ag_2CO_3	DCM	66%
4	[Ir(cod)Cl]$_2$ (3.5)/ AgOTf (14)	Ag_2CO_3	DCM	73%
5	AgOTf (14)	Ag_2CO_3	DCM	36%
6	[Ir(cod)Cl]$_2$ (3.5)/ AgOTf (14)	Ag_2CO_3	MeCN	39%
7	[Ir(cod)Cl]$_2$ (3.5)/ AgOTf (14)	Ag_2CO_3	Toluene	52%
8	[Ir(cod)Cl]$_2$ (3.5)/ AgOTf (14)	Ag_2CO_3	DCE	34%
9	[Ir(cod)Cl]$_2$ (3.5)/ AgOTf (14)	Ag_2CO_3	$CHCl_3$	57%
10	[Ir(cod)Cl]$_2$ (3.5)/ AgOTf (14)	Cs_2CO_3	DCM	45%

All the reactions were carried out with 0.15 mmol **1n**, 0.1 mmol **2a** and 1 mmol of base for 48 h. For all entry we got exclusively α selectivity. Isolated yields.

Table 4. Ferrier type glycosylation of various glycals **1n**-1r with glycoside acceptor 2a.



Entry	Donor	R^1	R^2	Product	Yield (%)	α:β[a]
1	**1n**	Allyl	Allyl	**4a**	73%	1:0
2	**1o**	Et	Et	**4b**	61%	>8:1
3	**1p**	Bn	Bn	**4c**	79%	9:1
4	**1q**	PMB	PMB	**4d**	75%	>13:2
5	**1r**	PX	PX	**4e**	70%	19:1

All the reactions were carried out under N_2 atmosphere using 1.5 equiv. glycosyl donors (**1n-1r**), 1.0 equiv. acceptor (**2a**) in dry CH_2Cl_2 for 48-72 h. [a]Stereoselectivity was determined by crude ^{1}H NMR. Isolated yields. PX = *p*-Xylyl.

We have shown that glycals bearing poor leaving group at C3 reacted with alcohols to provide 2-deoxy-α-*O*-glycosides, thus we became intrigued about the possible outcome of repeating the same transformation on glycals with good leaving group at C3 position. We initiated our studies by employing 3-*O*-acetyl-4,6-di-*O*-allyl-D-glucal with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2a**) and found that optimal conditions (3.5 mol% [Ir(COD)Cl]$_2$, 14 mol% AgOTf, and 1 equiv. of Ag_2CO_3) worked just as effectively as it did for the 2-deoxy-*O*-glycoside synthesis (entry 4, table 3). We examined the effect of solvation and found that solvents like MeCN (39%, entry 6, table 3), DCE (34%, entry 8) constrained the desired product formation (table 3). Toluene (entry 7, table 3) and $CHCl_3$ (entry 9, table 3) provided the product in 52% and 57% yield respectively, but we attained finest yield (73%) for the allylic substitution reaction when we carried out the reaction in CH_2Cl_2 (entry 4, table 3). After optimizing the parameters, we turned our attention to exploring the feasibility of the donor scope and we found that our reaction condition worked well with the set of commonly used carbohydrate protecting groups with 61-79% yield (table 4). The protecting groups at C4 and C6 positions in the glycosyl donors had a pronounced effect on the yields and outcome of the reactions. Specifically, applying *m*-nitrobenzyl protection (**1s**, see ESI) on the donor didn't afford the desired product as

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providing only a complex mixture. Taking the strong electron-withdrawing nature of *m*-nitro group into account, we suggest that it disrupts the positively charged π-allylic system, thus leading the reaction to fail. We observed a similar outcome in case of peracetylated glucal, perhaps due to the same sort of electron-withdrawing nature of the acetyl group. The reported method also failed to provide the desired glycoside with 4,6-*O*-*p*-methoxybenzylidene-3-*O*-acetyl-D-glucal (**1t**, see ESI) signifying the requirement of conformationally flexible C4 and C6 protecting groups.

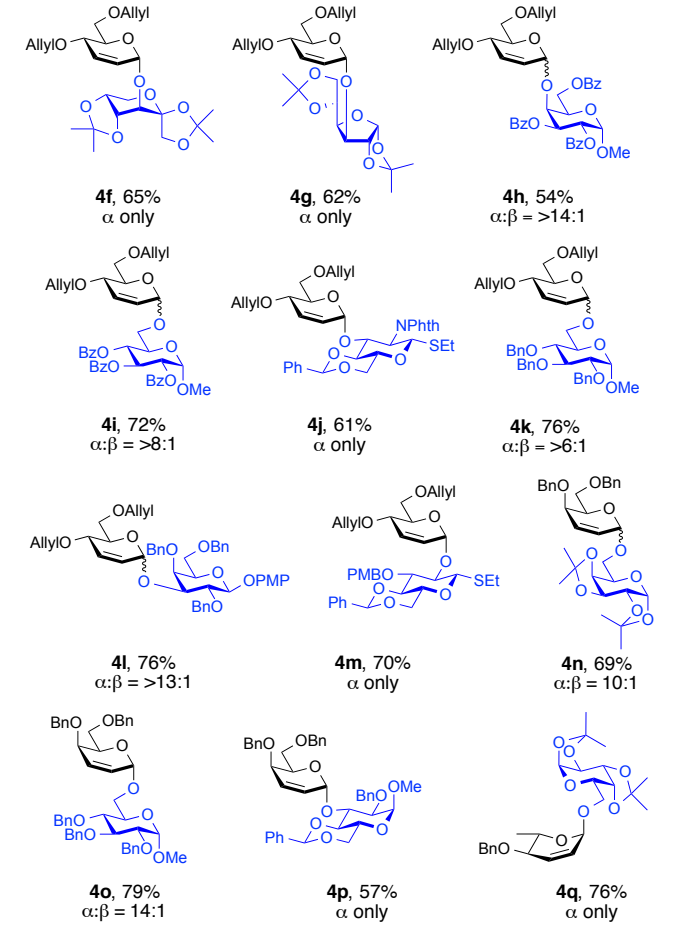

Figure 2. α-Selective Ferrier type *O*-glycosylation of **1n**, **1u** and **1v** with a variety of glycosyl acceptors. Reactions were carried out under N_2 atmosphere using 1.5 equiv. glycosyl donor (**1**), 1.0 equiv. of acceptor (**2**), 3.5 mol% $[Ir(COD)Cl]_2$, 14.0 mol% AgOTf, and 1.0 equiv. of Ag_2CO_3 in dry CH_2Cl_2 for 48-72 h at rt. Stereoselectivity was determined by crude ^1H NMR. Isolated yields.

To evaluate the synthetic applicability of this method, we set out the use of a series of glycosyl acceptors for the Ferrier-type nucleophilic substitution reactions (Figure 2). To our delight, the versatility proved to be highly efficient since glycosylations proceeded smoothly to furnish the desired glycosides in yields of 54-79% and high α-selectivity (>6:1 α:β to α only, Figure 2). Notably, sterically hindered alcohols **2l**, **2p** (see ESI) underwent coupling stereoselectively to give **4h** (α:β, >14:1) and **4l** (α:β, >13:1), in 54% and 76% yield respectively. Glycosyl acceptors containing benzoate and phthalimide protecting groups (**2l**, **2m** and **2n**, see ESI) are also well tolerated by this procedure, with desired disaccharides **4h**, **4i** (α:β, >8:1) and **4j** (α only) generated in moderate to good yields (54%, 72%, and 61% respectively, Figure 2).

Moreover, this method is quite amenable with several primary and secondary alcohols, yielding desired disaccharides in high efficiency and good α-selectivity. To interpret the mechanism of this reaction, we carried out DFT study. We proposed that to start the catalytic cycle, $[Ir(COD)Cl]_2$ first reacts with AgOTf to generate active species $[Ir(COD)OTf]_2$ (Figure 3).[18] The dimer complex then dissociates into two transient monomeric Ir(COD)OTf complexes (see ESI), which in turn coordinate to the

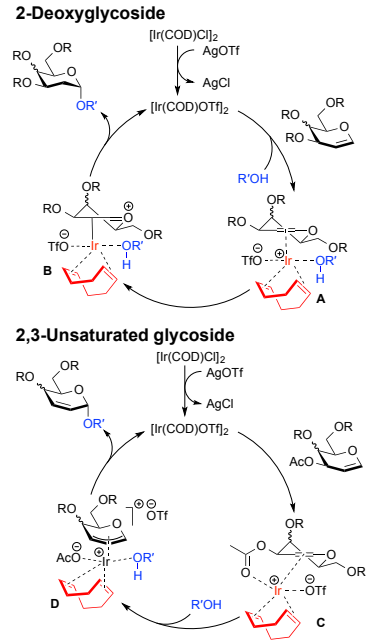

Figure 3. Schematic representation of the proposed mechanism giving rise to 2-deoxy-α-glycoside and 2,3-unsaturated-α-glycoside arising from Ir(I)-catalyzed *O*-glycosylation.

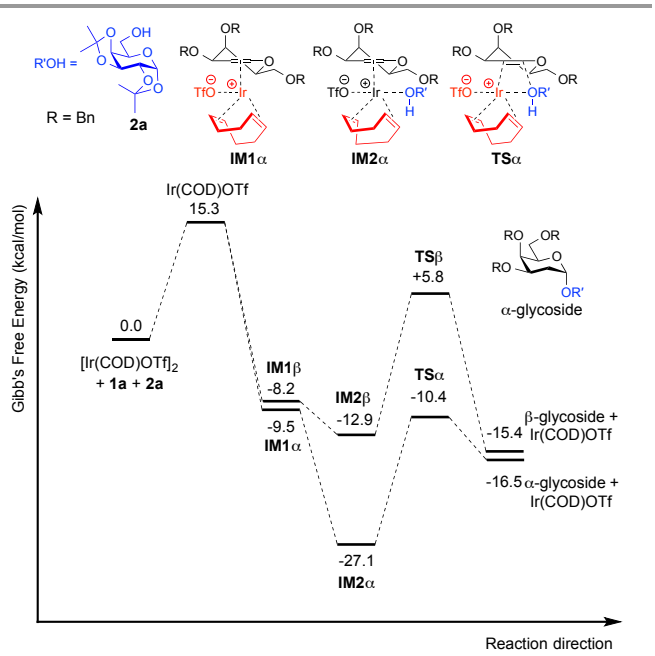

Figure 4. Free energy profile for the catalytic cycle of Ir (I)-catalyzed glycosylation of 3,4,6-tri-*O*-benzyl galactal (**1a**) with model acceptor **2a**.

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glycal. We rationalize that for the 3,4,6-tri-*O*-benzyl glycal donor **1a**, the iridium metal center coordinates to the olefinic C1 and C2 carbon to form stable η^2 π-allyl intermediates; while for the 3-*O*-acetaly-4,6-di-*O*-benzyl-D-galactal donor **1u**, which carries a better leaving group at 3-position, the Ir(COD)OTf species first coordinates to C1 and C2 to form η^2 π-allyl intermediates, then, upon dissociation of the triflate anion from the metal center, the metal center further coordinates with C3 to form a η^3 π-allyl complex, expelling the 3-acetyl substituent as an acetate anion, which may then coordinates to the metal center as a free ligand (Figure 3). Importantly, Ir(COD)OTf can coordinate to the glycal

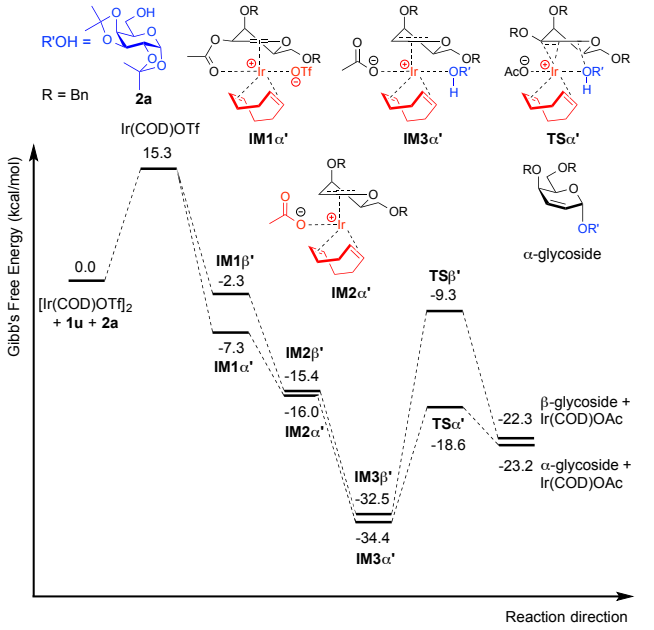

Figure 5. Free energy profile for the catalytic cycle of iridium catalyzed glycosylation of 3-*O*-acetyl-4,6-di-*O*-benzyl galactal (**1u**) with model acceptor **2a**.

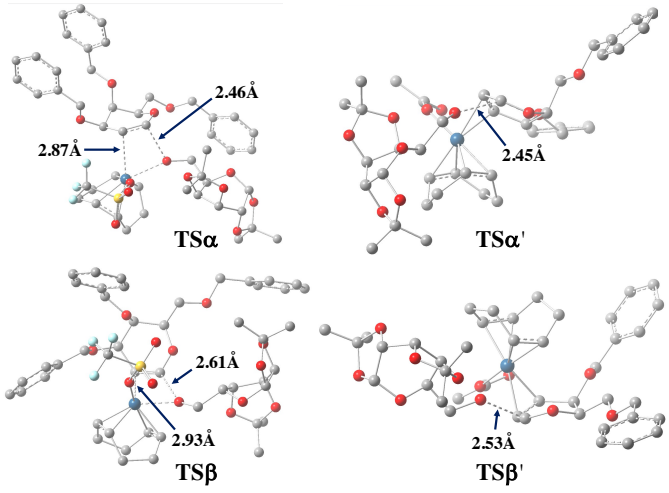

Figure 6. Optimized trasition state structures arising from nucleophilic attack of **2a** on **1a** (left) and **1u** (right).

at either face of the pyranose ring, with one face preferred over another due to steric and electronic factors. The relative stability of possible intermediates species, as well as the activation energy of the following nucleophilic attack on the iridium coordinated glycal intermediate by the acceptor determine the favored reaction routes and have a major influence on the stereochemical outcome of the glycosylation reaction. Upon formation of the major iridium-glycal π-allyl complex intermediates, anomeric carbon on the glycal become activated, and we hypothesized that the acceptor coordinates to the iridium center in the metal-glycal complex first (See ESI for a detailed discussion), then attacks the adjacent anomeric carbon in a *syn*-addition manner, leading to the formation of corresponding 2-deoxy or 2,3-unsaturated glycosides, while regenerating the catalytic complex (Figure 3). DFT computed energetic profile of important intermediates and transition states are shown in Figure 4 and Figure 5.

For galactal **1a**, intermediates arising from η^2 π-allyl coordination of Ir(COD)OTf to the glycal donor from both faces (**IM1α** and **IM1β**) are energetically similar (Figure **4**). The stronger steric repulsion in β-face coordinated **IM1β** might be compensated by the stabilization of hydrophobic interactions between the C3 benzyl group and the cyclohexadiene group in the complex. Contrarily, for galactal **1u**, η^2 π-allyl complex with Ir(COD)OTf from α-face (**IM1α'**) is sizably more stable than the β-face counterpart **IM1β'** (Figure **5**), probably due to the difficulty of covalently linked C3 acetyl to interact with the iridium metal center and stabilize the intermediate complex. The explanation is corroborated by the results that the η^3 π-allyl coordinated complexes **IM2α'** and **IM2β'**, both having the dissociated acetate ligand coordinating to the iridium metal center, are rather similar in energy level.

Although the metal coordinated intermediates without the acceptor coordinating to the metal center show minor facial preference for both **1a** and **1u**, for the acceptor coordinated intermediates arising from **1a**, computation results suggest an appreciable α-face preference. The higher energy level of the β-face coordinated intermediates with acceptor coordinated to the metal center can be mainly attributed to the steric crowding of the β-face intermediate **IM2β** (See ESI). The steric repulsion effect is significantly less pronounced in the **IM3β'** arising from C3 acetyl galactal **1u**, which, without the absence of a bulky C3 benzyl substituent, leaves the β-face coordinated Ir(COD) group, larger space for accommodating the additional coordination to the acceptor (See ESI).

For both **1a** and **1u**, activation energy of the transition state of nucleophilic attack step shows a strong α-face preference. For all TSs (transition states) arising from nucleophilic attack of the acceptor on the glycal donor, the iridium metal center dissociates from C1 yet remain largely coordinated to C2 (Figure **6**). Similar to the scenario of the acceptor coordinated intermediates, the α-face preference of TS arising from nucleophilic attack on iridium-coordinated **1a** mainly results from steric crowding of the β-face TS. While for the TSs arising from nucleophilic attack on iridium-coordinated **1u**, the α-preference possibly due to a combination of steric factors and anomeric effect.

DFT computation results suggest that both the reaction routes leading to α-products are kinetically favored. The reaction proceeds through a directing mechanism, with α-face intermediates generally more stable than the β-counterparts

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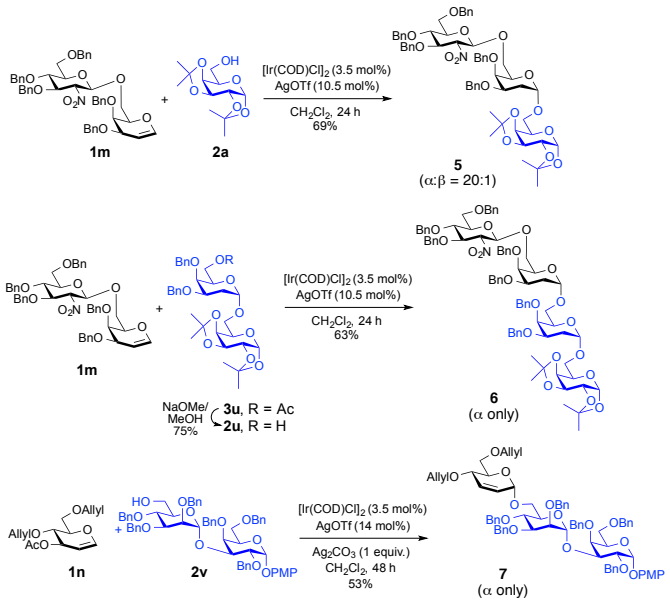
along the reaction routes, and the energy of the transition state for nucleophilic attack from α-face significantly lower than the energy of the TS of the β-face nucleophilic attack, which likely arises from a combination of the unfavorable steric interactions between the 3-substituents and the metal complex in the TSs and anomeric effect. The theoretically inferred coordination of acceptor to the iridium is further corroborated by ^{1}H NMR investigations, in which addition of the iridium catalyst (equimolar w.r.t. **2a**) to the acceptor in CD_2Cl_2 result in a pronounced downfield shifting of the hydroxy proton from 1.714 ppm to 2.231 ppm, indicating probable coordination between the OH group and the Ir(I) center. The theoretically proposed coordination of iridium metal to the glycal substrate in the catalytic cycle is also supported by ^{1}H NMR experiments, in which addition of the iridium catalyst to a solution of **1a** in CD_2Cl_2 resulted in an appreciable downfield shifting of the alkene protons from 6.333 ppm and 4.843 ppm to 6.613 ppm and 5.007 ppm respectively, indicating probable coordination between the glycal π-system and the iridium center. The downfield shifting of alkene protons upon coordination to iridium metal center is rationalized by computation of the partial charges of the C2 atom in both free **1a** substrate and the stable intermediate arising from **1a** complexed to iridium metal center at α face, with alcohol coordinated to the iridium. The computed partial charge of C2 in the coordinated intermediate is more positive (-0.147) with respect to the partial charge of C2 in free **1a** (-0.168), indicating a chemical environment of lower electron density for alkene protons upon coordination. The computed partial charge of C1 in same intermediate is also significantly more positive (0.230) with respect to C1 in free **1a** (0.187), agreeing with our hypothesis that coordination of the glycal to the iridium catalyst enhances the electrophilicity of the donor anomeric center and facilitates the nucleophilic attack by alcohol at mild condition.



Scheme 2. Ir(I)-catalyzed α-stereoselective-*O*-glycosylation for the synthesis of model trisaccharides and tetrasaccharide.

To demonstrate the applicability of this newly developed methodology, synthesis of oligosaccharides has been conducted. As shown in scheme 2, disaccharide donor **1m** was reacted with the model acceptor **2a**, which afforded the corresponding trisaccharide, **5** in 69% yield with desirable high α-selectivity (α:β = 20:1). Then previously synthesized disaccharide **3u** was subjected for selective deacetylation[19] using NaOMe in MeOH which afforded acceptor **2u** in 75% yield. On a similar note, glycosylation of same disaccharide donor **1m** with glycosyl acceptor **2u** proceeded smoothly to give the corresponding tetrasaccharide, **6** in 63% yield with an absolute α-stereoselectivity. Finally, in a separate experiment, we employed Ir(I)-catalyst successfully to synthesize 2,3-unsaturated *O*-glycoside containing trisaccharide, **7** with a complete α-selectivity from monosaccharide donor **1n** and disaccharide acceptor **2v** in a decent yield (53%), which demonstrate the practical utility of this method in the synthesis of higher analogue glycans.

Conclusion

To summarize, we have demonstrated two concurrent Ir(I)-catalyzed glycosylation events, that can be independently adjusted by exploiting a substrate-controlled approach on the glycal donors. The Ir(I)-catalyzed glycosylation reaction of glycal donors with an armed group at C3 affords 2-deoxy-*O*-glycoside, while glycosylation of a C3-acetyl glycal donor affords 2,3-unsaturated-*O*-glycoside. For both types of the Ir(I)-catalyzed glycosylation, we optimized the reaction conditions with α stereoselectivity, then, the generality of the Ir(I)-catalyzed glycosylation has shown in over 40 examples featuring a range of glycal donors and acceptors bedecked with commonly used protecting groups. Our results confirm that the Ir(I)-catalyzed alcohol glycosylation reaction can be feasibly performed at mild conditions, requiring a catalytic amount of Ir(I)-catalyst for activation of glycal donors. The mechanism accounting for the α-stereoselectivity of the Ir(I)-catalyzed-glycosylation by glycal donors was investigated with DFT calculations. We further demonstrated that our Ir(I)-catalyzed glycosylation methods can be implemented for the construction of trisaccharides and tetrasaccharides, and presumably oligosaccharides, enabling facile access to biologically important oligosaccharides comprising 2-deoxy-sugar structures connected by α-glycosidic linkages.

Conflicts of interest

The authors declare no competing financial interests.

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Ir(I)-catalyzed highly α-selective *O*-glycosylation of glycals has been developed, providing an efficient access to both 2-deoxy-*O*-glycosides and 2,3-unsaturated-*O*-glycosides with a comprehensive substrate scope. Underlying rationale of α-selectivity was illustrated by DFT and ^{1}H NMR study, which demonstrated a probable directing mechanism for both conversions.