Coordination chemistry approach to the long-standing challenge of stereocontrolled chemical glycosylation†

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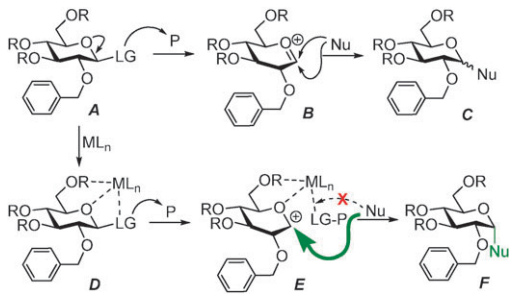
This study clearly demonstrates that a multi-dentate metal coordination to the leaving group, along with O-5 and/or a protecting group at O-6, has a strong effect on the stereoselectivity of chemical glycosylation.

Although complete information about the functions of natural complex carbohydrates is yet to emerge, some aspects of their involvement in many biological phenomena are already known.[1,2] Further improvement in this field would be significantly facilitated if we could rely on detailed knowledge of the structure, conformation and properties of the carbohydrate molecules involved. Therefore, the development of effective methods for assembling simple carbohydrates into more elaborate networks (oligosaccharides and conjugates thereof) has become critical for the field of glycosciences.[3–5]

Since the *O*-glycosylation reaction leads to the formation of a new chirality (anomeric) center, particular care has to be taken with regards to stereocontrol, which is particularly important when the synthesis of challenging 1,2-*cis*-glycosides is undertaken.[6,7] A generic reaction pathway for glycosyl donors with a non-participating 2-*O*-benzyl substituent (**A**) is depicted in Scheme 1. Promoter (P) mediated departure of the anomeric leaving group (LG) results in formation of the oxocarbenium ion **B**. In uncontrolled glycosylation, nucleophilic attack of the glycosyl acceptor (Nu) can then take place from either the top or the bottom face of the flattened ring, often leading to anomeric mixtures **C** (Scheme 1).[8]

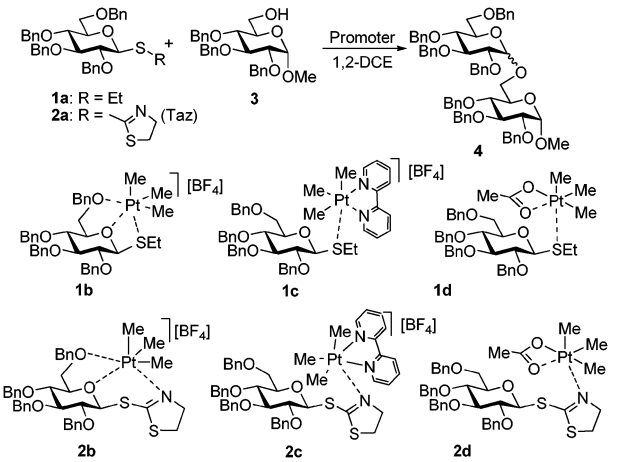
The central hypothesis at the base of this study is whether metal coordination (ML_n), in particular multi-dentate coordination to the leaving group along with the O-5 and/or remote position(s) (intermediate **D**), has an effect on the stereoselectivity of glycosylation. We assumed that even upon promoter-assisted LG "departure", such a complex would sterically hinder the top face of the key intermediate **E**



Scheme 1 Direct *vs.* coordination-mediated glycosylations.

(for sugars of the D-series). As a result, the nucleophilic attack of the glycosyl acceptor would be primarily directed from the opposite side, resulting in an α-D-linked (1,2-*cis* for D-gluco) product **F**. We began investigating this concept by using conventional thioglycoside **1a**[9] and trimethylplatinum(IV) complexes thereof.[10,11] Typical MeOTf-promoted glycosidation[12] of **1a** with glycosyl acceptor **3** provided no stereoselectivity for the formation of disaccharide **4** (entry 1.1, Table 1). Although

Table 1 Investigation of per-benzylated *S*-ethyl and *S*-thiazolinyl glycosides as glycosyl donors and ligands



Entry	Donor	Promoter	Time	Yield (%)	α/β
1.1	**1a**	MeOTf	10 min	92	1.0/1
1.2	**1b–d**	MeOTf, NIS/TfOH, or DMTST	48 h	0	—
1.3	**2a**	$Cu(OTf)_2$	1 h	95	1.5/1
1.4	**2b**	$Cu(OTf)_2$	20 h	62	2.4/1
1.5	**2c**	$Cu(OTf)_2$	15 h	88	2.5/1
1.6	**2d**	$Cu(OTf)_2$	16 h	79	2.3/1

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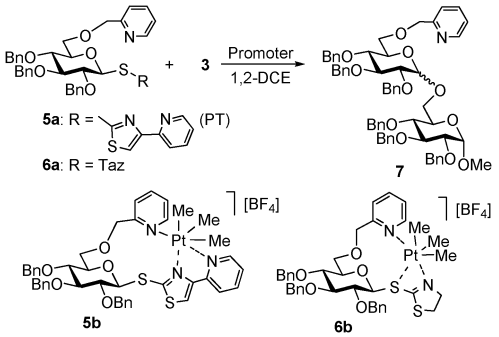
a variety of factors, such as the effect of the reaction solvent, can dramatically increase the stereoselectivity,[13–15] herein, we chose 1,2-dichloroethane (1,2-DCE), which has a minimal solvation effect on the reactants and intermediates. The synthesis of various platinum(IV) complexes **1b–d**, all of which are coordinated to the platinum atom *via* the anomeric sulfur, was successfully achieved (see the ESI†). Unfortunately, all of our attempts to glycosidate such complexes under conventional conditions for thioglycoside activation[16] have failed (entry 1.2). No glycosylation took place and only partial hydrolysis of glycosyl donor and methylation of glycosyl acceptor **3** (with MeOTf) were observed as major side reactions.

It is possible that coordination of platinum to the anomeric sulfur prevents its subsequent interaction with electrophilic promoters. In this context, glycosyl donors with multiple reactive centers on the leaving group, such as glycosyl thioimidates,[17] would help to address this concern. Arguably, even upon complexation, these compounds would allow for activation *via* the non-engaged center. Theoretically, either direct coordination of a metal to the anomeric sulfur or remote coordination to the nitrogen should improve the thioimidoyl leaving group ability.[18,19] The discovery of the temporary deactivation concept, however, implies that some complexes of non-ionizing nature may have an opposite, deactivating, effect on the thioimidoyl leaving group ability.[20,21] It has been demonstrated that trimethylplatinum complexes coordinate to carbohydrates and to *N*,*S*-heterocycles like thiazoline-2-thione without being reduced.[10,11,22] Therefore, investigation of *S*-thiazolinyl (STaz) derivative **2a**[23,24] was of particular interest. Encouragingly, glycosidation of complexes **2b–d** in the presence of $Cu(OTf)_2$ provided a notable improvement in stereoselectivity (entries 1.4–1.6) in comparison to that achieved in the glycosidation of the uncomplexed glycosyl donor **2a** (entry 1.3). In compounds **2b–d** the carbohydrate ligands were found to coordinate to the platinum atom *via* the nitrogen atom of the STaz group and additionally for compound **2b** through the oxygen atoms of glucopyranose (see the ESI†).

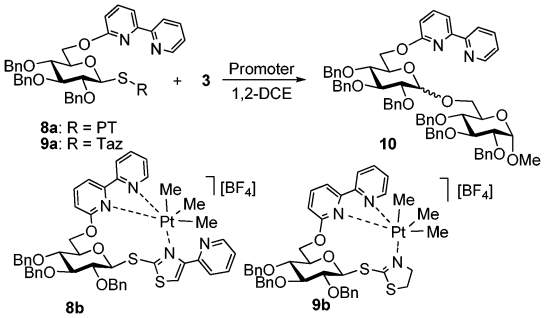
Weakly coordinating donor sites in neutral carbohydrates afford complexes that are often unstable in the presence of stronger donor sites. Therefore, these results could not serve as a reliable proof of the concept of coordination-assisted improvement in stereoselectivity. These glycosylations could partially proceed *via* the complex destruction that would result in the complete leaving group departure as occurs in direct glycosylations. Hence, we assumed that targeted enhanced coordination of the carbohydrate ligands can be achieved by introducing stronger *N*-Lewis-basic substituents. To execute this approach, we obtained 6-*O*-picolyl derivatives of 4-(pyridin-2-yl)thiazol-2-yl thioglycosides (SPT)[21] and STaz glycosides, **5a** and **6a**, respectively. Direct glycosidation of these glycosyl donors proceeded with poor stereoselectivity (entries 2.1 and 2.2, Table 2), whereas glycosidation of the corresponding complexes **5b** and **6b** under essentially the same activation conditions gave improved (2–2.5 fold) stereoselectivity (entries 2.3 and 2.4). This result is a clear indication that improved stereoselectivity can be achieved by applying specifically designed ligands capable of stronger coordination.

Table 2 Investigation of 6-*O*-picolylated *S*-pyridylthiazolyl and *S*-thiazolinyl glycosides as glycosyl donors and ligands



Entry	Donor	Promoter	Time/h	Yield (%)	α/β
2.1	**5a**	AgOTf	22	66	1.1/1
2.2	**6a**	$Cu(OTf)_2$	16	83	2.0/1
2.3	**5b**	AgOTf	20	58	2.1/1
2.4	**6b**	$Cu(OTf)_2$	24	62	5.2/1

Table 3 Investigation of 6-*O*-bipyridine-substituted *S*-ethyl and *S*-thiazolinyl glycosides as glycosyl donors and ligands

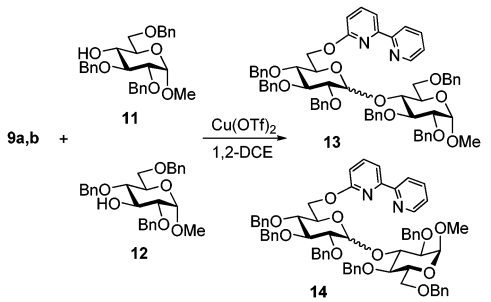


Entry	Donor	Promoter	Time/h	Yield (%)	α/β
3.1	**8a**	AgOTf	14	82	1.5/1
3.2	**9a**	$Cu(OTf)_2$	48	73	1.7/1
3.3	**8b**	AgOTf	16	67	2.2/1
3.4	**9b**	$Cu(OTf)_2$	24	65	9.4/1

In order to pursue this concept further, we obtained glycosyl donors **8a** and **9a** bearing a bipyridine protecting group at C-6. The results of this study are highlighted in Table 3. While the improvement in the case of the SPT glycosyl donor was unremarkable, a 5-fold improvement with the complexed glycosyl donor **9b** is significant. Thus, while glycosidation of **9a** showed only a slight preference for the α-anomer (1.7/1, entry 3.2), the glycosidation of its complexed counterpart **9b** allowed a 9.4/1 α/β-anomeric ratio of disaccharide **10** (entry 3.4). The coordination sites in the complex **9b** (three nitrogen atoms as shown in Table 3) were unambiguously proven (see the ESI†).

Similarly, a 3–3.5 fold improvement was achieved in the glycosylation of common secondary glycosyl acceptors **11** and **12** with the complexed STaz glycosyl donor **9b**. The results of this study are highlighted in Table 4, and are available in more detail as a part of the ESI.†

Table 4 Investigation of secondary glycosyl acceptors **11** and **12**



Entry	Donor	Acceptor	Product	Yield (%)	α/β
4.1	**9a**	**11**	**13**	53	2.2/1
4.2	**9a**	**12**	**14**	61	2.0/1
4.3	**9b**	**11**	**13**	50	7.2/1
4.4	**9b**	**12**	**14**	48	6.0/1

It should be noted that although significant improvements of the chemical glycosylation have already emerged,[8] examples of highly stereocontrolled glycosylations are still rare. To date, very little is known about the effect of metal coordination on the reactivity and stereoselectivity of carbohydrates in glycosylations. We expect that the studies presented herein will ultimately evolve into a well-rounded and versatile metal-assisted methodology for the synthesis of a broad range of complex glycostructures.

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