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Switchable reactivity of 2-benzoyl glycals towards stereoselective access of 1-3 and 1-1 *S*/*O* linked disaccharides†

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We have developed a synthesis of 1-3 and 1-1 disaccharides from 2-benzoyl glycal and anomeric thiol and/or hydroxy sugar acceptors under mild conditions at room temperature. The regio and stereoselectivity of the newly formed inter-glycosidic linkages are dependent on the nature of the glycal donor (D or L) and anomeric acceptor.

Oligosaccharides are biologically important carbohydrates embedded in various natural products and are essential components of many bioactive molecules.[1] Oligosaccharides in the form of glycoconjugates play a pivotal role in many biological processes including the regulation of gene expression, immune response, cell recognition, and signaling.[2] Among all the disaccharides 1-1 and 1-3 *O*/*S*-linked disaccharides have great importance in the field of glycobiology. In particular, 1-3 *S*-linked disaccharides have been extensively explored as mimetics of biologically active *O*-glycosides and act as a powerful tool to probe various biological processes (Fig. 1).[3] Besides 1-3 linked thiodisaccharides, 1-1 linked *O*-disaccharides were also found to have great potential in various biologically active compounds including anti-bacterial, anti-microbial active components and various natural products such as maradolipids, trehalosamine, everninomicins, tunicamycin V, and avilamycin A (Fig. 1).[4] Chemical synthesis of 1-1 *O*-linked disaccharide-like trehalose derivatives is more challenging as the stereochemistry of both the anomeric centers needs to be controlled out of four possible diastereomers. It is always desirable if we can have a common donor and mild metal-free conditions to access the above mentioned glycosidic linkages stereo-selectively. Synthesis of C3-thio glycosylation is always difficult. A classical approach is to use an orthogonally protected glycosyl donor with a good leaving group like axial triflate at the C-3 position with anomeric thiol as reported by Maria *et al.*, which requires multiple steps, cryogenic/harsh conditions, and formation of multiple side products (Scheme 1A).[5] On the other hand, a handful of stereo-controlled 1-1 *O* disaccharides has been reported so far due to the possibility of the formation of α/β mixtures of each anomeric center of the glycosyl donor and acceptor. Nicolaou and his group reported a stereoselective synthesis of 1-1 disaccharides by coupling cyclic stannanes as a glycosyl acceptor and trichloroacetaimidates as the donor, but the substrate scope was limited to mannose (Scheme 1B).[6] Moreover, Takemoto has developed a stereocontrolled 1-1 disaccharide synthesis from glycosyl 1,2-diol and glycosyl donors in the presence of a boronic acid catalyst.[7] Recently, Galan *et al.* described gold catalyzed dehydrative glycosylation using a hemiacetal glycosyl donor to get 1,1-α,α-linked 2-deoxy trehalose derivatives.[8] Glycosylation reactions using sugar-enol-ether-like glycals as a glycosyl donor have been well explored with different glycosyl acceptors for the synthesis of glycosides due to the predictability of new glycosidic linkages. While the external nucleophiles in unsubstituted glycals usually happen from the C-1 position, popularly known as Ferrier glycosylation, the presence of an electron-withdrawing substituent at the C-2 position often switches the reactivity to the C-3 position resulting in C-3 substituted glycosides.[9] These 2-*C*-substituted glycals have

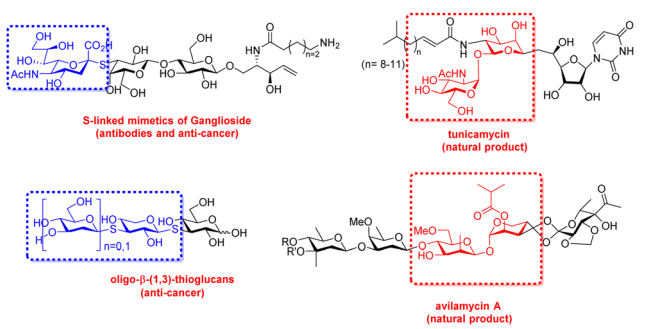

Fig. 1 Naturally occurring 1-3 linked *S*-disaccharides and 1-1 linked *O*-disaccharides.

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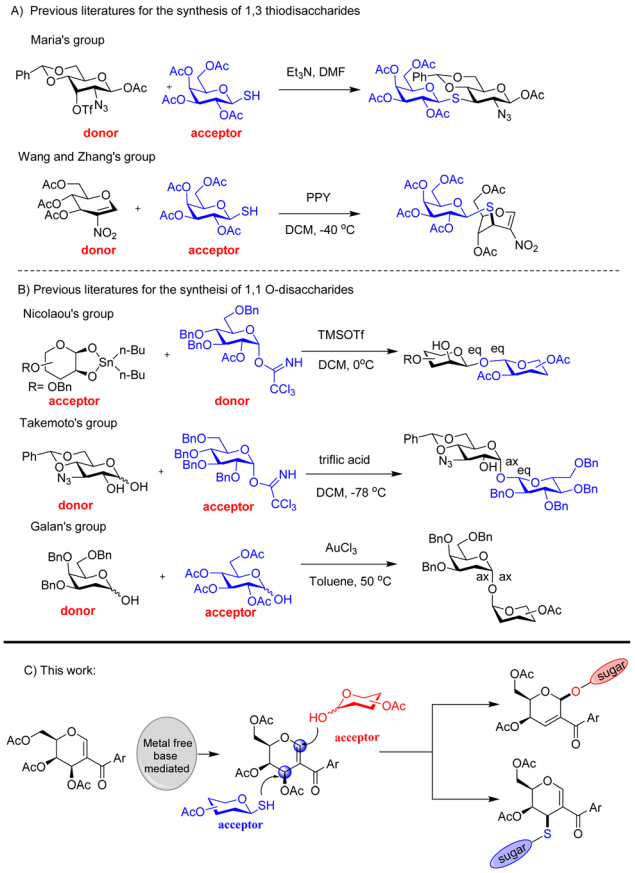


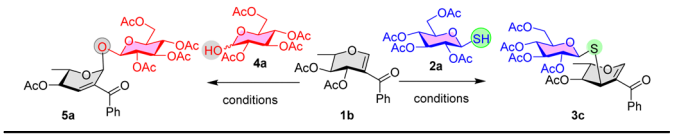
Scheme 1 (A) Previous literature on the synthesis of 1,3 thiodisaccharides. (B) Previous literature on the synthesis of 1,1 *O*-disaccharides. (C) This work.

recently emerged as versatile intermediates for the synthesis of bioactive molecules. Recently, our group[10] and others[11] have demonstrated the importance of 2-*C*-substituted glycals bearing α, β-unsaturated carbonyl systems such as 2-*C*-formyl glycals and 2-benzoyl glycals. We have transformed 2-*C*-benzoyl of a new single product with a complete consumption of **1b** glycals into 3, 5-disubstituted furans which have immense biological importance and are extensively used in the field of pharmaceuticals, agrochemicals, and cosmetics.[12] From our previous work, we realized that the installation of the benzoyl group at the 2-position of glycals allows softer nucleophiles like thiol to attack at C-3 with an inversion of the configuration whereas a harder nucleophile preferred C-1 attack under Lewis acid conditions. However, we were unable to introduce anomeric hydroxy or thiol sugar acceptors under such conditions.

In the present work, we have taken up the stereoselective synthesis of more challenging ax–eq 1-3 and eq–eq 1-1 *S* and *O* linked disaccharides, respectively, under metal-free mild basic conditions at room temperature. While we were completing our experimental work, Zhang's group reported the synthesis of 2-amino-2-deoxy dithioglycosides *via* the 4-pyrrolidinopyridine-mediated relay glycosylation of 2-nitroglycals, but this approach requires cryogenic conditions with a mixture of isomers and is only restricted to thiol acceptors.[13]

Considering the importance of 1-3 linked disaccharides, we commenced our study by taking 2-benzoyl-L-rhamnal **1b** with

Table 1 Representative results for the optimization of 1-3 *S* and 1-1 *O* linked disaccharides[ab]

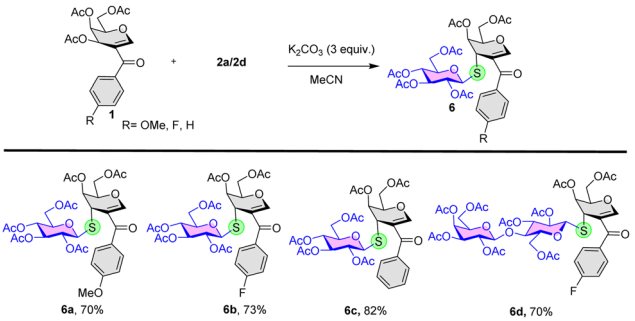


Entry	Base (3.0 equiv.)	Temp. (°C)	Solvent	Yield [b] (%) 3c	5a
1	NaH	30	MeCN	40	—
2	**K_2CO_3**	**30**	**MeCN**	**82**	**64**
3	$AgCO_3$	30	MeCN	Trace	NR
4	Cs_2CO_3	30	MeCN	60	40
5	Et_3N	30	MeCN	Trace	NR
6	K_2CO_3	0	MeCN	40	Trace
7	K_2CO_3	60	MeCN	30	30
8	K_2CO_3	30	DCM	55	60
9	K_2CO_3	30	DCE	NR	NR

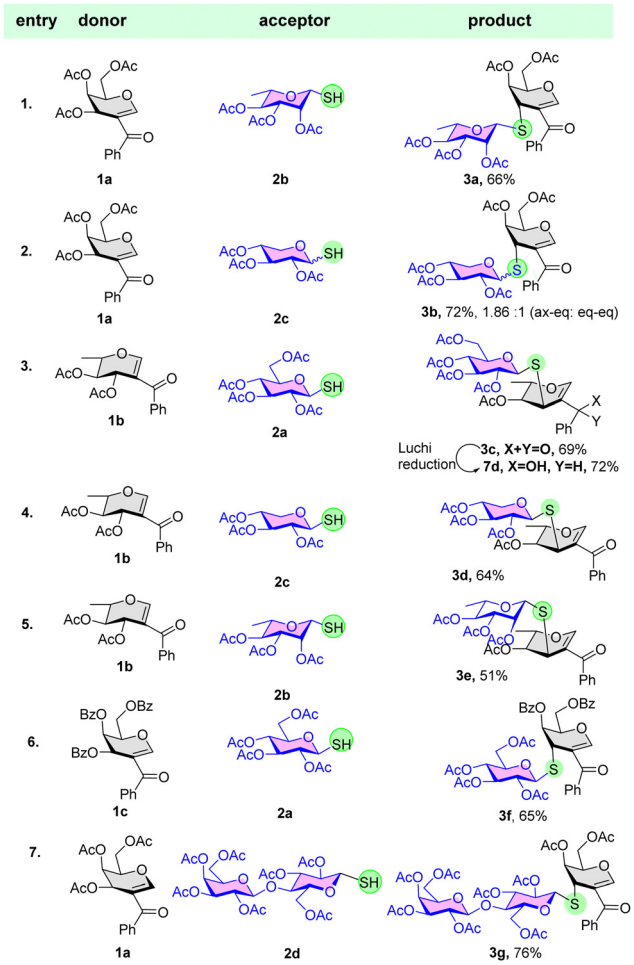
[a] Reaction was carried out by using **1b** (1 equiv.), **2a**/**4a** (1 equiv.), and K_2CO_3 (3 equiv.) as a base in 3 mL of MeCN at room temperature (30 °C) for 24 h. [b] Yield was calculated after column chromatography.

per-*O*-acetylated glycosyl thiols as an acceptor **2a** in the presence of a suitable base and solvent at different temperatures (Table 1). Compounds **1b** and **2a** were allowed to react with NaH as a base in acetonitrile at room temperature. After the completion of the reaction according to TLC, we observed the formation (Table 1, entry 1). On characterization, we were delighted to obtain the desired product 1-3 disaccharide **3c** with complete eq–eq selectivity in 40% isolated yield (entry 1). The stereochemistry was determined by extensive 1D and 2D NMR analysis (see ESI†). Gratifyingly, when we switched the base from NaH to K_2CO_3, the yield of the desired product enhanced up to 82% (entry 2). Subsequently, we tested different bases like $AgCO_3$ and Cs_2CO_3, with the former giving only a trace of the desired product and the latter yielding 60% of the desired product (entries 3 and 4). Use of triethylamine as an organic base in acetonitrile gives a low amount of yield of the desired product (entry 5). These findings prompted us to keep K_2CO_3 as a standard base for the reaction. Treating the reaction with different temperatures lowers the yield of the desired product (entries 6 and 7). Further screening with different solvents like DCE and DCM found that MeCN gives the best result. After continuous optimization, we concluded that K_2CO_3 (3 equiv.) in acetonitrile at room temperature for 24 h are the optimal reaction conditions for further studies.

After the successful launch of anomeric glycosyl thiol, next to verify the DG controlled regiodivergent approach, an anomeric OH glycosyl acceptor was used to switch the regioselectivity. The initial reaction was carried out with the same reaction conditions; K_2CO_3 in acetonitrile at room temperature generated successfully the desired 1-1 *O*-disaccharide **5a** selectively with the translocation of the double bond from the C1-C2 to C2-C3 position where the C3 δ value shifted to 134.6. The stereochemistry was determined by extensive 1D and 2D NMR analysis (see SI). Furthermore, different bases (entries 3–5), temperatures (entries 6 and 7) and solvents (8 and 9) were examined and give a yield up to 60%. After meticulous optimization, we concluded that K_2CO_3 (3 equiv.) in



Scheme 2 Substrate scope of thiodisaccharides: variation in glycosyl donor. [b]Yield was calculated after column chromatography.

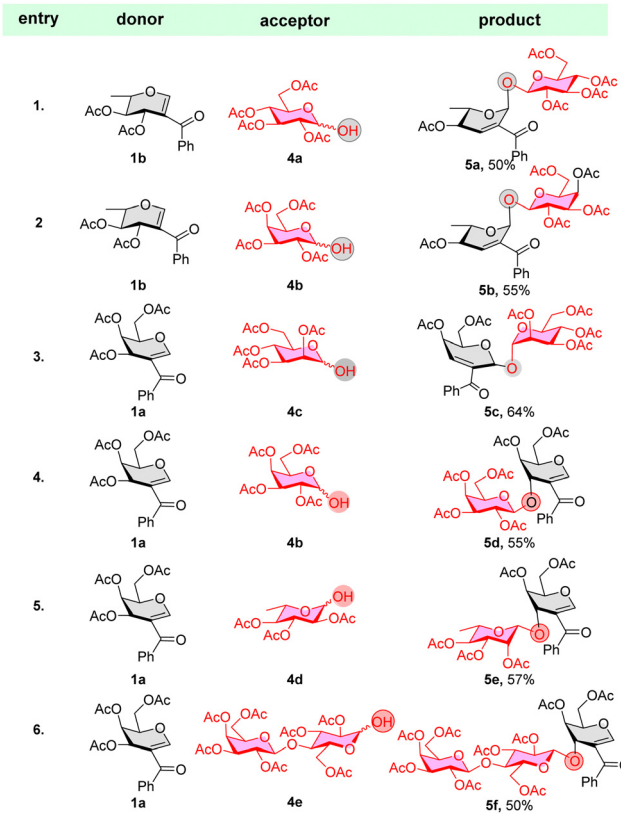


Scheme 3 Substrate scope of 1-3 linked thiodisaccharides.[a,b,c]. [a]Reaction conditions: acceptor (1 equiv.), donor (1 equiv.) and K_2CO_3 (3 equiv.) in 2 mL of acetonitrile at room temperature for 24 h. [b]Yield was calculated after column chromatography. [c]The ratio was determined by ^{1}H NMR analysis. [d]Reactions were performed using **3c** (1 equiv.), $NaBH_4$ (1.2 equiv.) and $CeCl_3.7H_2O$ (1.5 equiv.) in MeOH:THF (1 : 1) at 0 °C for 1 h.

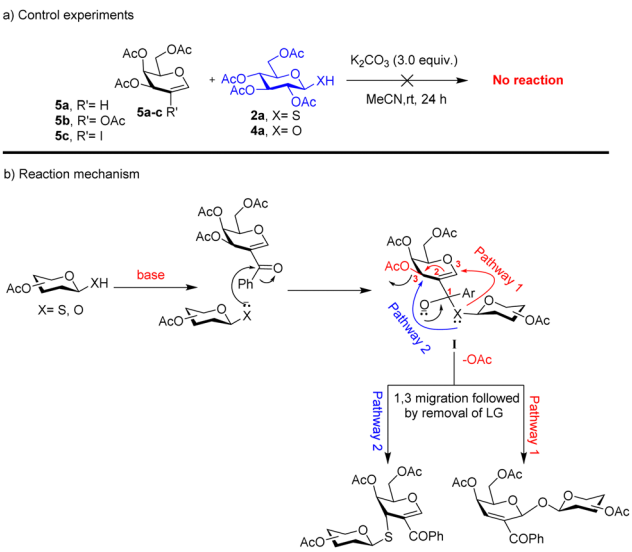
MeCN at rt for 24 h gives the best result for further studies. With the best reaction conditions in hand, we became curious to find out the effect of substituents on the aromatic moiety of the benzoyl group at the C-2 position of the donor (Scheme 2). It was apparent that substituents have little effect on glycosylation, so we used an unsubstituted benzoyl group in the rest of the study. However, we failed with 2-benzoyl glucal to get an inseparable mixture of disaccharides. This is probably due to the orientation of C4 OAc adjacent to the leaving group at C3 (trans diequitorial in the case of D-glucal) for selectivity loss.

With the optimized conditions in hand, we next varied the glycosyl thiol acceptors. Thus, using **1a** with 1-thio-L-rhamnose tetraacetate **2b** as an acceptor, 1,3-thiodisaccharide **3a** was obtained in a good yield with complete axial–equatorial selectivity (Scheme 3, entry 1). However, the selectivity was to some extent lost for 1-thio-β-D-xylose tetraacetate **2c** with donor **1a** (Scheme 3, entry 2). Changing donors from D to L-sugar, the selectivity was excellent (entries 3–5). The method worked well with other ester-protecting groups like benzoate (entry 6, **3f**). To our satisfaction, disaccharide acceptor **2d** was coupled with **1a** to produce trisaccharide **3g** in good yield and selectivity (entry 7). Furthermore, in order to demonstrate the importance of the synthesized disaccharides we have selectively reduced the keto group under Luchi conditions to obtain a hydroxyl group flanked between the pyran and aryl moiety in a good yield, which may be used for oxadecaline core synthesis.[14] Subsequently, we checked the reactivity of our synthetic method for 1-1 *O*-disaccharides with different acceptors having an anomeric oxygen heteroatom. We first examined glycosyl donor 2-benzoyl glycal **1b** with acceptor **4a** under the optimized conditions, and a new product 1-1 disaccharide **5a** was obtained with eq–eq selectivity in a moderate yield (Scheme 4, entry 1). Using galactosyl acceptor **4b** afforded 1-1 *O*-disaccharide **5b** with complete selectivity in a good yield (entry 2). Unexpectedly, when we shifted to a D-glycosyl donor **1a** and reacted with different glycosyl acceptors **4b** and **4d** derived from D-galactose and L-rhamnose, respectively, it afforded the 1-3 *O*-linked disaccharides **5d** and **5e** with complete axial–equatorial selectivity in a good yield (Scheme 4, entries 4 and 5). Lactose-derived glycosyl acceptor **4e** afforded the 1-3 linked *O*-disaccharide **5f** with good yield, whereas except in the case with mannose-derived acceptor **4c**, 1-1 *O*-linked disaccharide **5c** was obtained with eq–ax selectivity in a moderate yield.

To verify the role of the directing group, we have conducted a few control experiments, as shown in Scheme 5a. On reaction of tri-*O*-acetyl-D-glucal **5a** with 1-thio glycosyl acceptor **2a**, the expected 1-3 linked disaccharide product was not obtained and the unreacted compound **5a** and **2a** was recovered. Again, with the same reaction conditions, tetra-*O*-acetyl-D-glucal **5b** and 2-iodo glucal **5c** on reaction with **2a**, the 1-3 linked disaccharide product was not obtained. Similar control experiments were conducted with 1-*O*-glucose tetra-acetate **4a** acceptor under the same reaction conditions and the expected 1-1 *O*-disaccharide was not observed and unreactive substrates were recovered. Based on these control experiments we have established a reaction mechanism, as shown in Scheme 5b. The anomeric glycosyl acceptor after deprotonation by base attacks the C2 carbonyl to form an intermediate **I**. Now depending upon the nature of the nucleophile, regioselective 1,3-migration takes place. As anticipated, the anomeric thiol acceptor prefers to attack from the opposite side of C-3 acetate whereas the anomeric hydroxyl undergoes Ferrier-type α attack at C-1 for



Scheme 4 Substrate scope of 1-1 linked *O*-disaccharides.[a,b] Yield was calculated after column chromatography. [a] Reaction conditions: acceptor (1 equiv.), donor (1 equiv.) and K_2CO_3 (3 equiv.) in 2 mL of acetonitrile at room temperature for 24 h. [b] Yield was calculated after column chromatography.



Scheme 5 (a) Control experiment and (b) reaction mechanism.

D-glycals except in the case of benzoyl containing D-galactal, which prefers C-3 attack probably due to comparatively easy accessibility from the opposite side of the adjacent axially oriented β C-4-OAc.

In conclusion we have developed a metal free mild base regio- and stereo-selective strategy for the synthesis of 1-1 *O*-disaccharides and 1-3 thiodisaccharides from 2-benzoyl glycals with different acceptors at room temperature. This mild and broadly applicable mechanistically intriguing reaction can be used with a variety of glycal donors and nucleophile acceptors. The stereochemistry of both the 1-3 thiodisaccharides and 1-1 *O* disaccharides is completely controlled with the ax–eq and eq–eq—configuration in a good-excellent yield.

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Conflicts of interest

There are no conflicts to declare.

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