Organocatalysis

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α-Selective Organocatalytic Synthesis of 2-Deoxygalactosides**

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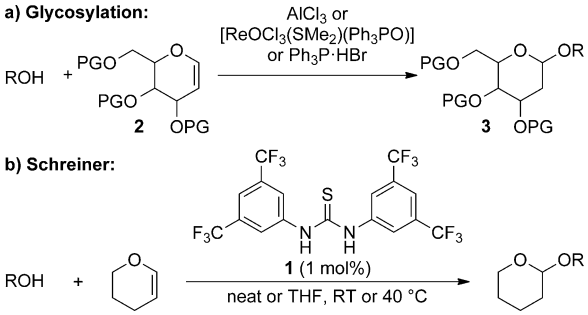
The stereoselective synthesis of acetals is of great interest, especially because of the abundance of cyclic acetals in nature.[1,2] Recently, there have been several reports of organocatalytic approaches to stereoselective acetal formation.[2b–d] Organocatalysis has become a powerful synthetic tool[3] and is attractive because the reactions are often tolerant of water and air, and tend to be relatively simple to perform. Arguably, the most important acetals are carbohydrates, of which 2-deoxysugars form an important and synthetically challenging subclass. They occur widely in natural products[1] and are frequently present in antibiotics, anti-cancer, and cardiotonic agents[1,4] where the deoxysugar component is often crucial for the bioactivity of the drug.[5] Herein, we describe our efforts to develop an organocatalytic method for the synthesis of 2-deoxygalactosides.

Considerable efforts have been made to develop stereoselective chemical methods for the assembly of oligosaccharides containing 2-deoxysugars.[4,6] However, the absence of groups at C-2 that can act to direct the coupling reaction often leads to syntheses of 2-deoxyglycosides as mixtures of anomers. Another concern is that 2-deoxyglycosides tend to be more difficult to manipulate compared to the C-2 hydroxylated analogues because of their greater susceptibility to hydrolysis.[7] Using directing groups at C-2 that are later removed is inherently inefficient.[6,8] Many direct methods rely on stoichiometric promoters and/or precursors that require several steps to synthesize.[9] Catalyzing the direct addition of an alcohol to a glycal (**2**) is the most atom-efficient route to 2-deoxyglycosides.[10] Existing methods (Scheme 1 a) tend to be mostly confined to primary alcohol acceptors and give either moderate yields or variable selectivities.[10] Herein, we describe a highly atom-efficient method for the direct reaction of readily available galactals with alcohols to give α-linkages with high stereoselectivity using an organocatalyst.



Scheme 1. Catalytic acetal formation from enol ethers.[10,13] PG = protecting group; THF = tetrahydrofuran.

Glycosylation reactions involving glycals tend to give better stereoselectivities under mild conditions.[10] Organocatalysts often work under such conditions and tend to be more tolerant of sensitive functional groups.[11,12] Recently, Kotke and Schreiner reported the use of thiourea **1** to catalyze the protection of alcohols with dihydropyran (DHP) under mild conditions (Scheme 1 b).[13,14] We reasoned that if glycals could be used in place of DHP, it could provide a more efficient glycosylation method than is currently available. Modification of Schreiner's reaction for use in stereoselective glycosylations was not a trivial task, as the physical properties and solubilities of our substrates were not amenable to the methods described.[13] We optimized the reaction of protected galactal **2a**[15] (1.2 equiv.) with model acceptor **3a** and found that 1 mol % of catalyst **1,** in a solution of CH_2Cl_2 heated to reflux, gave excellent results. Disaccharide **4a** was produced in 90 % yield in under six hours, exclusively as the α-glycoside (Table 1, entry 1).[16] The high selectivity is not the result of a postglycosylational anomerization (see below).

Having shown that thiourea **1** could be used as an efficient and mild catalyst in our test reaction, we studied its use with galactals bearing a range of different protecting groups. Thus galactals **2b–f** bearing ethyl, allyl, benzyl, methoxymethyl ether (MOM), and silyl ether protecting groups were prepared[17] and subjected to the optimized reaction conditions with **3a** as acceptor (Table 1). In all cases, high yields and excellent selectivities for α-linked glycosides were obtained, albeit with longer reaction times being required for substrates with bulkier protecting groups. In the case of acetate-protected galactal **2g**,[18] no reaction was detected after two days. Substrates **2h** and **2j** show that acetates can be tolerated by the reaction but not in close proximity to the reacting alkene, as is the case for **2h** with an acetate at C-3 (Table 1, entry 8). We attribute the lack of reactivity of **2g** to the deactivation of the double bond.[19] Entries 8 and 9 in Table 1 also show that the reaction is not sensitive to the conformational restrictions imposed by the *cis*-decalin system.

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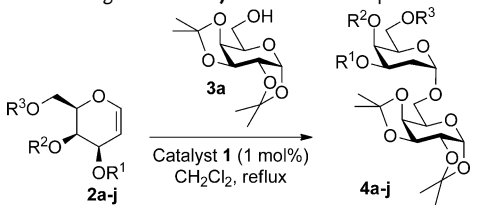
Table 1: Reaction of galactals **2a–j** with model acceptor **3a**.[a]



Entry		R^1	R^2	R^3	t [h]	Yield [%][b]	α:β[c]
1	**2a**	Me	Me	Me	6	90	α
2	**2b**	Et	Et	Et	18	92	α
3	**2c**	Allyl	Allyl	Allyl	18	96	α
4	**2d**	Bn	Bn	Bn	24	96	α
5	**2e**	TBS	TBS	TBS	48	72	α
6	**2f**	MOM	MOM	MOM	18	96	α
7	**2g**	Ac	Ac	Ac	48	0	-
8	**2h**	Ac	$Si(tBu)_2$	$Si(tBu)_2$	48	14	α
9	**2i**	MOM	$Si(tBu)_2$	$Si(tBu)_2$	24	92	α
10	**2j**	Bn	Bn	Ac	24	89	α

[a] 1.2 equiv. of **2a–j** were used. [b] Yield of isolated product. No Ferrier rearranged product was observed. [c] Determined by ^{1}H NMR spectroscopy.

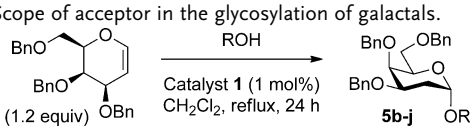
Encouraged by these results, the scope of other common glycosyl acceptors was investigated (Table 2). To that end, perbenzylated galactal **2d** was used as a model donor and reacted with a range of differentially protected glycosyl acceptors **3b–3j** under the optimized reaction conditions. Glycosyl acceptors with a primary alcohol[20] and either benzyl or benzoyl protecting groups, as well as either methoxy or thiophenyl as the anomeric substituents gave yields of the isolated product of 87–98% and α-selectivity (Table 2, entries 1, 2, 8, 9).

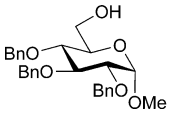
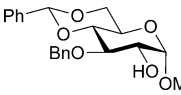
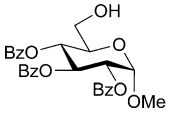
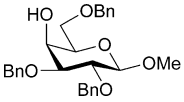
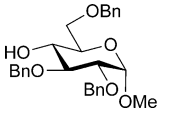
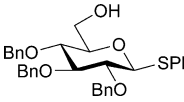
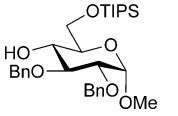
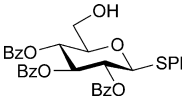
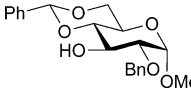
This high selectivity was maintained regardless of the position of the free hydroxy group on the acceptor. Couplings to secondary hydroxy groups[21] at C-2, C-3, or C-4 proceeded extremely well with yields of the isolated product of 83–96% and complete α-stereocontrol (Table 2, entries 3–7). These reactions were also independent of the configuration of the OH group (axial vs. equatorial). For instance, galactoside **3h** with an axial secondary hydroxy group (Table 2, entry 7) gave an excellent yield of 85%, which is comparable to the result obtained for glycosyl acceptor **3d** (89%). Individual optimization of the reaction conditions was not required except in the case of **3g**. Because of its lower solubility in CH_2Cl_2 this reaction was run at a higher dilution of **3g** with 2 equiv. of galactal **2d** and 2 mol% catalyst **1**.

These results highlight that the organocatalyzed reaction is tolerant of most commonly used alcohol protecting groups, that is, benzyl and silyl ethers, benzoyl esters, and acetals. Furthermore, the reaction works well across a range of reactivity profiles[22] and the overall mild nature of the reaction conditions makes this procedure remarkably general.

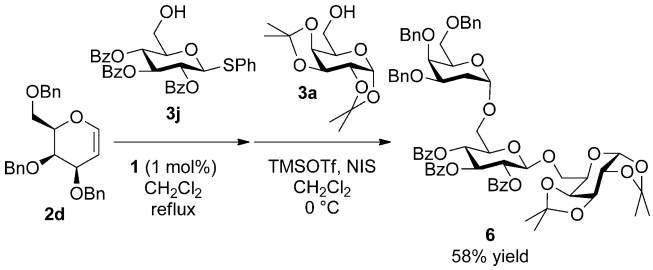
Having found that thioacetals were inert under the organocatalytic glycosylation conditions (Table 2, entries 8,9), we evaluated the new method in a three-component, one-pot synthesis of trisaccharide **6** (Scheme 2). Thus, galactal **2d** was reacted with thioglycoside **3j** under our standard conditions. Following disaccharide formation,

Table 2: Scope of acceptor in the glycosylation of galactals.



	ROH		Yield [%][a]		ROH		Yield [%][a]
1		**3b**	98	6		**3g**	83[b]
2		**3c**	98	7		**3h**	85
3		**3d**	89[c]	8		**3i**	92
4		**3e**	94[d]	9		**3j**	87
5		**3f**	96				

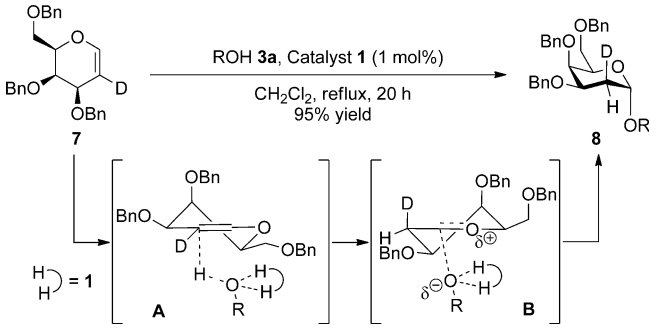
[a] Yield of isolated product. [b] 30 h; 2 equiv. of **2d** and 2 mol% catalyst **1** with respect to **3g** was used; 0.4 M ROH (all other reactions were approximately 0.8 M). [c] 18 h. [d] Product was isolated as the desilylated disaccharide for purification purposes.



Scheme 2. One-pot trisaccharide synthesis.

acceptor **3a** was added to the same pot along with *N*-iodosuccinimide (NIS) and catalytic trimethylsilyl trifluoromethanesulfonate (TMSOTf).[23] This stepwise, one-pot addition reaction afforded trisaccharide **6** in 58% yield with complete stereoselectivity.

To probe the mechanism of this reaction,[24] an α/β-mixture of disaccharide **5b** was subjected to the reaction conditions and showed no change in the anomeric ratio, indicating that the high α-selectivity is not the result of anomerization. Moreover, the reaction with deuterated galactal **7** yielded disaccharide **8** with the newly formed bonds *cis* to each other (Scheme 3), thus the C–O *and* the C–H bond formation steps are both diastereoselective. We hypothesize that an alcohol–thiourea complex delivers the proton selectively to the less hindered face of the enol ether (**A**) followed by rapid collapse of the ion pair (**B**) to give **8**. The selective C–H bond formation may be dictated by steric forces. The α C–O bond-forming step, as shown in **B**, should



Scheme 3. Mechanistic investigation and hypothesis.

be favored by sterics, the anomeric effect, and a chair-like transition state, thus a low energy barrier is expected compared to competing pathways that would lead to the β-product.[24b] A similar face selectivity was observed by others in the addition of azido radicals to the C2 position of galactals.[25]

In conclusion, we have described the first example, to our knowledge, of an efficient direct glycosylation of galactals with a wide range of glycosyl acceptors using a readily available thiourea organocatalyst **1**. This mechanistically interesting reaction proceeds with excellent yields and high selectivity for the α-anomer with only 1.2 equiv. of the galactal donor. Furthermore, we have exemplified the versatility of this reaction by the one-pot, chemo- and stereoselective synthesis of a trisaccharide. Work is currently underway to extend this method to the stereoselective synthesis of other deoxyglycosides. The simplicity of the method, mild conditions, high yields, and stereoselectivity should make this diastereoselective acetal formation a valuable addition to synthetic chemistry with applications in, and beyond, the field of carbohydrates.

Experimental Section

The monosaccharide acceptor (0.50 mmol) was weighed into a round-bottom flask and placed under vacuum for 1 h. Then the flask was filled with N_2, followed by the addition of the galactal (1.2 equiv.) and a stock solution of thiourea **1** (0.6 mL, 1 mol%) in anhydrous dichloromethane. The solutions were then heated at reflux under N_2 until the reaction was determined to be complete by either TLC or NMR spectroscopy analysis of the crude material. The solution was then concentrated under vacuum and purified by column chromatography.

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[1] a) X. M. He, H. W. Liu, *Curr. Opin. Chem. Biol.* **2002**, *6*, 590–597; b) A. Kirschning, A. F. W. Bechthold, J. Rohr, *Top. Curr. Chem.* **1997**, *188*, 1–84.

[2] a) E. Carreira, L. Kvaerno in *Classics in Stereoselective Synthesis*, Wiley-VCH, Weinheim, **2009**, pp. 187–214. Recent examples of stereoselective organocatalytic acetal formation: b) I. Čorić, B. List, *Nature* **2012**, *483*, 315–319; c) Z. Sun, G. A. Winschel, A. Borovika, P. Nagorny, *J. Am. Chem. Soc.* **2012**, *134*, 8074–8077; d) I. Čorić, S. Vellalath, B. List, *J. Am. Chem. Soc.* **2010**, *132*, 8536–8537.

[3] a) F. Giacalone, M. Gruttadauria, P. Agrigento, R. Noto, *Chem. Soc. Rev.* **2012**, *41*, 2406–2447; b) *Enantioselective Organocatalysis: Reactions and Experimental Procedures* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**.

[4] T. K. Lindhorst in *Glycoscience: Chemistry and Chemical Biology*, 2nd ed. (Eds.: B. O. Fraser-Reid, K. Tatsuta, J. Thiem, G. L. Coté, S. Flitsch, Y. Ito, H. Kondo, S.-i. Nishimura, B. Yu), Springer, Berlin, **2008**, chap. 12.6.

[5] a) M. Sastry, D. J. Patel, *Biochemistry* **1993**, *32*, 6588–6604; b) P. T. Daniel, U. Koert, J. Schuppan, *Angew. Chem.* **2006**, *118*, 886–908; *Angew. Chem. Int. Ed.* **2006**, *45*, 872–893.

[6] a) C. H. Marzabadi, R. W. Franck, *Tetrahedron* **2000**, *56*, 8385–8417; b) D. Hou, T. L. Lowary, *Carbohydr. Res.* **2009**, *344*, 1911–1940.

[7] W. G. Overend, J. S. Sequeira, C. W. Rees, *J. Chem. Soc.* **1962**, 3429–3440.

[8] a) T. B. Durham, W. R. Roush, *Org. Lett.* **2003**, *5*, 1871–1874; b) R. M. De Lederkremer, C. Marino, *Adv. Carbohydr. Chem. Biochem.* **2007**, *61*, 143–216; c) W. R. Roush, D. P. Sebesta, R. A. James, *Tetrahedron* **1997**, *53*, 8837–8852; d) D. Hou, T. L. Lowary, *J. Org. Chem.* **2009**, *74*, 2278–2289; e) J. Thiem, W. Klaffke, *J. Org. Chem.* **1989**, *54*, 2006–2009.

[9] a) J. Park, T. J. Boltje, G. J. Boons, *Org. Lett.* **2008**, *10*, 4367–4370; b) Y. S. Lu, Q. Li, Y. Wang, X.-S. Ye, *Synlett* **2010**, 1519–1524; c) J. M. Nogueira, S. H. Nguyen, C. S. Bennett, *Org. Lett.* **2011**, *13*, 2814–2817; d) Y. Li, X. Yang, Y. Liu, C. Zhu, Y. Yang, B. Yu, *Chem. Eur. J.* **2010**, *16*, 1871–1882; e) C. Kolar, G. Kneissl, *Angew. Chem.* **1990**, *102*, 827–828; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 809–811.

[10] a) B. D. Sherry, R. N. Loy, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4510–4511; b) V. Bolitt, C. Mioskowski, S.-G. Lee, J. R. Falck, *J. Org. Chem.* **1990**, *55*, 5812–5813; c) H.-C. Lin, J.-F. Pan, Y.-B. Chen, Z.-P. Lin, C.-H. Lin, *Tetrahedron* **2011**, *67*, 6362–6368.

[11] For regioselective protection of glycosides using organocatalysts see: a) T. Kawabata, W. Muramatsu, T. Nishio, T. Shibata, H. Schedel, *J. Am. Chem. Soc.* **2007**, *129*, 12890–12895; b) W. Muramatsu, K. Mishiro, Y. Ueda, T. Furuta, T. Kawabata, *Eur. J. Org. Chem.* **2010**, 827–931; c) D. Lee, M. S. Taylor, *J. Am. Chem. Soc.* **2011**, *133*, 3724–3727.

[12] For organocatalytic glycosylations: a) D. J. Cox, M. D. Smith, A. J. Fairbanks, *Org. Lett.* **2010**, *12*, 1452–1455; b) S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 7198–7199; c) C. Gouliaras, D. Lee, L. Chan, M. S. Taylor, *J. Am. Chem. Soc.* **2011**, *133*, 13926–13929.

[13] M. Kotke, P. R. Schreiner, *Synthesis* **2007**, 779–790.

[14] For reviews of thiourea/H-bond/Brønsted acid organocatalysis see: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296; b) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427; c) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743.

[15] a) T. Linker, D. Schanzenbach, E. Elamparuthi, T. Sommermann, W. Fudickar, V. Gyollai, L. Somsak, W. Demuth, M. Schmittel, *J. Am. Chem. Soc.* **2008**, *130*, 16003–16010; b) S. Fischer, C. H. Hamann, *J. Carbohydr. Chem.* **1995**, *14*, 327–339.

[16] In the absence of the catalyst no reaction was detected under these conditions. The purity of the precursors was crucial to obtaining reproducible results: in particular we note that small amounts of salts in the precursors caused the reaction to fail.

[17] a) D. C. Xiong, L. H. Zhang, X. S. Ye, *Org. Lett.* **2009**, *11*, 1709–1712; b) D. Lafont, G. Descotes, *Carbohydr. Res.* **1987**, *166*, 195–209.

[18] P. Levecque, D. W. Gammon, H. H. Kinfe, P. Jacobs, D. De Vos, B. Sels, *Adv. Synth. Catal.* **2008**, *350*, 1557–1568.

[19] This effect has been noted with regards to olefin glycal activation with rhenium(V) catalysts (ref. [10a]).
[20] a) S. Boonyarattanakalin, X. Y. Liu, M. Michieletti, B. Lepenies, P. H. Seeberger, *J. Am. Chem. Soc.* **2008**, *130*, 16791 – 16799; b) R. Verduyn, M. Douwes, P. A. M. van der Klein, E. M. Mosinger, G. A. van der Marel, J. H. van Boom, *Tetrahedron* **1993**, *49*, 7301 – 7316; c) M. S. Motawia, J. Marcussen, B. L. Moller, *J. Carbohydr. Chem.* **1995**, *14*, 1279 – 1294; d) A. T. Tran, R. Burden, D. T. Racys, M. C. Galan, *Chem. Commun.* **2011**, *47*, 4526 – 4528.
[21] a) M. P. Deninno, J. B. Etienne, K. C. Duplantier, *Tetrahedron Lett.* **1995**, *36*, 669 – 672; b) M. Matwiejuk, J. Thiem, *Eur. J. Org. Chem.* **2011**, 5860 – 5878; c) M. Matwiejuk, J. Thiem, *Chem. Commun.* **2011**, *47*, 8379 – 8381; d) C. C. Wang, J. C. Lee, S. Y. Luo, H. F. Fan, C. L. Pai, W. C. Yang, L. D. Lu, S. C. Hung, *Angew. Chem.* **2002**, *114*, 2466 – 2468; *Angew. Chem. Int. Ed.* **2002**, *41*, 2360 – 2362; e) E. Attolino, G. Catelani, F. D'Andrea, *Eur. J. Org. Chem.* **2006**, 5279 – 5292; f) A. T. Tran, R. A. Jones, J. Pastor, J. Boisson, N. Smith, M. C. Galan, *Adv. Synth. Catal.* **2011**, *353*, 2593 – 2598.
[22] Z. Y. Zhang, I. R. Ollmann, X. S. Ye, R. Wischnat, T. Baasov, C. H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 734 – 753.
[23] R. Konradsson, U. E. Udodong, B. Fraser-Reid, *Tetrahedron Lett.* **1990**, *31*, 4313 – 4316.
[24] a) Control experiments using acids of a similar pK_a in place of **1** showed no change to the starting materials (see Supporting Information for details). Thus, the role of the catalyst is not simply as a proton source; b) Schreiner proposed that the THP-protection proceeds by an asynchronous concerted addition of alcohol to DHP (ref. [13]).
[25] a) R. U. Lemieux, R. M. Ratcliffe, *Can. J. Chem.* **1979**, *57*, 1244 – 1251; b) S. Czernecki, E. Ayadi, D. Randriamandimby, *J. Org. Chem.* **1994**, *59*, 8256 – 8260; c) F. Santoyo-González, F. G. Calvo-Flores, P. García-Mendoza, F. Hernández-Mako, J. Isac-García, R. Robles-Díaz, *J. Org. Chem.* **1993**, *58*, 6122 – 6125.

