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Glycosylation Catalyzed by a Chiral Brønsted Acid

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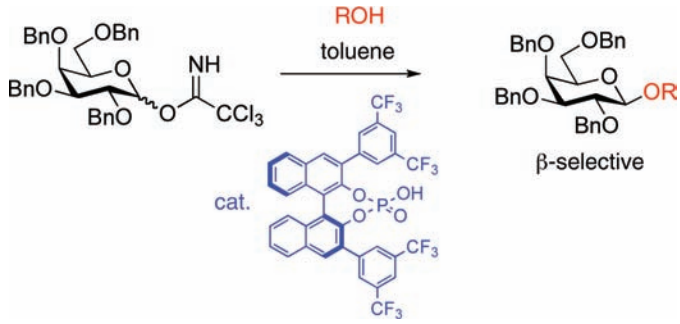
ABSTRACT



The use of a chiral Brønsted acid catalyst for the activation of trichloroacetimidate glycosyl donors has been demonstrated for the first time. In toluene the chirality of the acid catalyst is seen to influence the stereochemical outcome of the glycosylation processes, hinting that perhaps diastereocontrol of glycosylation processes may become achievable through the judicious use of chiral organic catalysts.

The conceptually simple process of linking carbohydrate units by glycosylation has proven to be one of the most difficult synthetic processes to control from a stereochemical perspective.[1] Although significant advances have been made, ranging from neighboring group participation of 2-O-acyl protected glycosyl donors[2] and recent refinements,[3] to intramolecular strategies,[4] stereochemical control of glycosylation is one of the last areas of diastereoselective synthesis to be entirely resolved.

The techniques of asymmetric synthesis have frequently been applied to control a variety of processes, hinting that reagent control could perhaps be applied to influence the diastereochemical outcome of glycosylation processes. However it is difficult to see how, for example, the use of asymmetric transition metal complexes could be applied in glycosylation chemistry, and correspondingly there are only very scant reports in the literature of previous efforts that have been made to control the stereochemical outcome of such reactions using chiral catalysts. Recent developments in the field of organocatalysis[5] may represent a paradigm shift since these principles could be applied to control the stereochemistry of glycosylation processes.[6] Among the many emerging applications of organocatalysis, the use of asymmetric Brønsted acid catalysis has been noteworthy. In particular the levels of stereochemical control obtained using

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(3) (a) Kim, J. H.; Yang, H.; Boons, G. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 947–949. (b) Kim, J. H.; Yang, H.; Park, J.; Boons, G. J. *J. Am. Chem. Soc.* **2005**, *127*, 12090–12097. (c) Park, J.; Kawatkar, S.; Kim, J. H.; Boons, G. J. *Org. Lett.* **2007**, *9*, 1959–1962. (d) Cox, D. J.; Fairbanks, A. J. *Tetrahedron: Asymmetry* **2009**, *20*, 773–780.
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BINOL-derived phosphoric acid catalysts, such as **1**, have in many cases exceeded expectations in a quite spectacular fashion.[7]

We therefore initiated an investigation to see if asymmetric Brønsted acid catalysis could be used to control the stereochemical outcome of glycosylation reactions. Considering the wide variety of glycosyl donors that are available, acid-catalyzed activation should be a straightforward process to achieve. In particular, glycosyl trichloroacetimidates,[8] one of the most reliable and generally applicable classes of glycosyl donors, should be amenable to activation by catalytic quantities of a Brønsted acid. Toste recently reported the activation of trichloroacetimidate leaving groups in a noncarbohydrate context using a chiral Brønsted acid.[9] We therefore sought to investigate the feasibility of effecting glycosylation of glycosyl trichloroacetimidate donors using both enantiomers of the chiral BINOL-derived phosphoric acid **1**[10] as chiral catalytic activators.

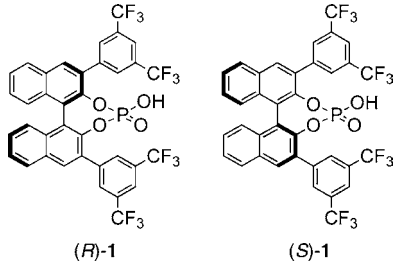
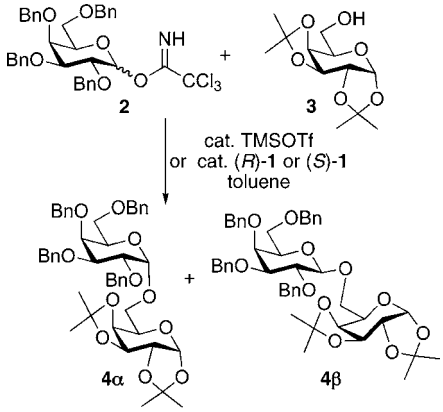


Figure 1. Chiral BINOL-derived Brønsted acids **1**.

To investigate any dependence of the stereochemical outcome of glycosylation upon the stereochemistry of the catalytic activator, protection of the hydroxyl groups of the glycosyl donor with nonparticipating protecting groups, such as benzyl ethers, would be required so that neighboring group participation did not predominate. Thus the tetrabenzyl-protected galactose donor **2** was synthesized and used as a donor in a variety of glycosylation processes.

Scheme 1. Glycosylation of a Trichloroacetimidate Donor Catalyzed by Chiral Brønsted Acid



First the actual feasibility of activation of donor **2** by a Brønsted acid was investigated using diacetone galactose **3** as the acceptor (Scheme 1, Table 1). Trichloroacetimidates are most commonly activated using catalytic quantities of Lewis acids, such as boron trifluoride etherate ($BF_3{\cdot}OEt_2$) or trimethylsilyl triflate (TMSOTf). Therefore to provide a benchmark control process for investigation of any stereochemical effects of using a chiral acid activator, activation of donor **2** was first performed in the presence of **3** using catalytic TMSOTf. The desired disaccharide **4** was rapidly formed in excellent yield as an almost equimolar anomeric mixture of compounds in which the α-anomer predominated slightly (**4α**:**4*β***, 1.2:1, Table 1, entry 1).

Table 1. Yield and Stereoselectivity of Glycosylation of Acceptor **3** by Donor **2**[a]

entry	activator (15 mol %)	yield of **4** (%)	ratio of **4α**:**4*β***
1	TMSOTf	98[b]	1.2:1
2	(*R*)-**1**	88[c]	1:2
3	(*S*)-**1**	80[c]	1:7
4	$(PhO)_2P(O)OH$	19[d]	1:1.9

[a] Anomeric ratio of donor **2α**:**2*β***, 7.9:1. [b] Reaction complete after 15 min at rt. [c] Reactions required 48 h at rt to reach completion. [d] Isolated yield of product after 48 h at rt.

Glycosylation was then performed using a catalytic quantity of (*R*)-**1** (15 mol %). Although the reaction was considerably slower than when TMSOTf was used as activator, requiring 48 h to reach completion at rt, efficient glycosylation did occur, and disaccharide **4** was isolated in 88% yield. Interestingly the anomeric ratio of the products was altered, and the *β*-anomer now predominated (**4α**:**4*β***, 1:2, Table 1, entry 2). To investigate whether the chirality of the acid catalyst affected the stereochemical outcome of the glycosylation reaction, activation of donor **2** in the presence of **3** was then undertaken in the presence of a catalytic quantity of the (*S*)-enantiomer of **1**. The disaccharide product **4** was isolated in similar yield to when (*R*)-**1** had been used, but significantly, the anomeric ratio of product was altered considerably—the *β*-anomer was now markedly favored over the α-anomer (**4α**:**4*β***, 1:7, Table 1, entry 3). A second control experiment was then undertaken, namely glycosylation of donor **2** with acceptor **3** catalyzed by an achiral phosphoric acid, diphenylphosphoric acid being selected as a suitable activator (Table 1, entry 4). Glycosylation catalyzed by $(PhO)_2P(O)OH$ was considerably slower than by either enantiomer of **1**, and the product was formed in only 19% yield after 48 h. Although the stereochemical outcome of the reaction was similar to that obtained using

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(*R*)-**1** (**4α**:**4*β***, 1:1.9), it was significantly different to that obtained using (*S*)-**1** as catalyst. These results demonstrate that the stereochemical outcome of the glycosylation reaction is dependent on the chirality of the acid catalyst used, and indicate that the acid, or most likely its counterion, is involved in the glycosylation step. On the basis of previous explanations for the stereodirecting effects of chiral BINOL-derived acids in other stereoselective processes, this is presumably by way of ion-pair formation. Such tight ion pair formation would be expected to be a solvent-dependent process. Solvent effects are well-known in glycosylation chemistry,[11] and frequently solvent participation can be used to increase the formation of one desired anomer over the other. Therefore the effect of reaction solvent on the stereochemical outcome of glycosylation of **2** with acceptor **3** was next investigated using the less selective (*R*)-enantiomer of **1** (Table 2).

Table 2. Effects of Solvent and Donor/Acceptor Concentrations on Stereoselectivity of Glycosylation of **2**[a] Using Acceptor **3**

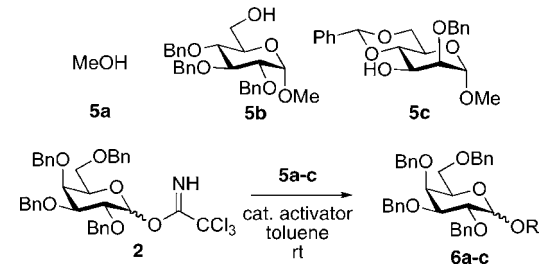
entry	solvent/concn	activator (15 mol %)	yield of **4** (%)	ratio of **4α**:**4*β***
1	toluene/73 mM	(*R*)-**1**	88	1:2
2	DCM	(*R*)-**1**	67	1:1.1
3	DCE	(*R*)-**1**	63	1:1
4	toluene/24 mM	(*R*)-**1**	80	1:1.7
5	toluene/12 mM	(*R*)-**1**	77	1:1.8

[a] Anomeric ratio of donor **2α**:**2*β***, 7.9:1.

Changing the solvent from toluene to either dichloromethane (DCM) or dichloroethane (DCE) led to an erosion of stereoselectivity as compared to the equivalent reaction in toluene. A plausible explanation for this observation is that ion pair separation is more pronounced in the two more polar chlorinated solvents, leading to a diminution of the stereochemical influence of the chiral catalyst. Following on from a recent report[12] on the observation of interesting concentration effects on the stereochemical outcome of glycosylation processes led us to perform the glycosylation of **2** with acceptor **3** as catalyzed by (*R*)-**1** at three different substrate concentrations in toluene. No effective changes were seen in the stereochemical outcome of these reactions, indicating no participation of the solvent in the glycosylation process.

Attention then turned to the variation of the nature of the glycosyl acceptor (Table 3). It is well-established that the stereochemical outcome of glycosylation can be highly dependent on the acceptor used in the glycosylation step; in particular matching and mis-matching of donor and acceptor may occur.[13] Donor **2** was therefore glycosylated with

Table 3. Glycosylation of Donor **2**[a] with a Variety of Glycosyl Acceptors **5a**−**c**



entry	acceptor	activator (15 mol %)	product/% yield	time (h)	α:*β* ratio
1	**5a**	TMSOTf	**6a**/97	0.25	1:10
2	**5a**	(*R*)-**1**	**6a**/87	16	1:47
3	**5a**	(*S*)-**1**	**6a**/88	16	*β* only
4	**5b**	TMSOTf	**6b**/99	0.25	1:1.2
5	**5b**	(*R*)-**1**	**6b**/84	48	1:5.7
6	**5b**	(*S*)-**1**	**6b**/88	48	1:70
7	**5c**	TMSOTf	**6c**/97	0.25	1:3.9
8	**5c**	(*R*)-**1**	**6c**/71	72	1:6
9	**5c**	(*S*)-**1**	**6c**/73	72	1:4.9

[a] Anomeric ratio of donor **2α**:**2*β***, 7.9:1.

acceptors **5a**−**c**, giving rise to products **6a**−**c**, respectively. In each case glycosylation was undertaken using TMSOTf as a control achiral catalytic activator, and both the (*R*) and (*S*) enantiomers of **1**. Perhaps surprisingly the most stereoselective reactions were obtained using MeOH **5a** as the acceptor (Table 3 entries 1−3). With TMSOTf activation these reactions were complete within 15 min, and the methyl glycosides **6a** were isolated in 97% yield as an anomeric mixture in which the *β*-anomer predominated (**5bα**:**5b*β***, 1:10). Use of the chiral acid **1** as catalytic activator again led to a slower glycosylation reaction, though notably this reaction was complete in 16 h, and was thus considerably faster than when diacetone galactose **3** had been used as the acceptor. Thus, use of (*R*)-**1** led to the isolation of glycoside **5b** in 87% yield as almost entirely the *β*-anomer (**5bα**:**5b*β***, 1:47). Subsequently the use of (*S*)-**1** as the activator led to the formation of methyl glycoside **5b** in 88% yield as pure *β*-anomer. The variation in stereochemical outcome of these reactions, although the *β*-anomer predominated in each case, does again indicate an influence of the chirality of the catalyst on the stereoselectivity of the glycosylation process.

Attention then moved to other carbohydrate acceptors, which themselves may have more of an inherent stereochemical preference (*i.e.*, match/mis-match with the donor). The use of the *gluco* configured primary alcohol acceptor **5b** with TMOSTf as the activator led to the formation of disaccharide **6b** in excellent yield as an almost equimolar anomeric mixture (**6bα**:**6b*β***, 1:1.2). Glycosylation catalyzed by (*R*)-**1**, though slower (48 h to reach completion), produced disaccharide **6b** in good yield and with significantly increased *β*-stereoselectivity (**6bα**:**6b*β***, 1:7). The trend was continued when (*S*)-**1** was used as the catalytic activator, and disaccharide **6b** was produced as almost exclusively the *β*-anomer

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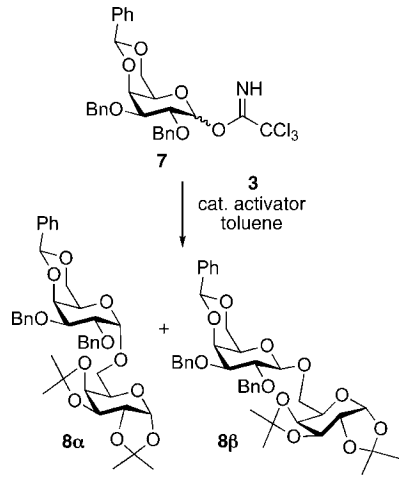
Table 4. Glycosylation of 4,6-Benzylidene Protected Donor **7**[a] with Acceptor **3**



entry	activator (15 mol %)	yield of **8** (%)	ratio of **8α**:**8*β***
1	TMSOTf	94[b]	1:1.1
2	(*R*)-**1**	76[c]	1:1.2
3	(*S*)-**1**	87[c]	1:3.4

[a] Anomeric ratio of donor **7α**:**7*β***, 10:1. [b] Reaction complete after 15 min at −40 °C. [c] Reactions required 16 h at rt to reach completion.

(**6bα**:**6b*β***, 1:70, Table 3, entry 6). However when the *manno* secondary alcohol acceptor **5c** was used two things became apparent. First the glycosylation catalyzed by TMSOTf was itself β-selective (**6cα**:**6c*β***, 1:3.9). Second glycosylation catalyzed by the chiral acids **1** was both considerably slower, and, in this instance, no significant difference between the stereochemical outcomes of the two reactions was observed. In this one instance the (*R*)-enantiomer was the slightly more β-selective of the two (**6cα**:**6c*β***, 1:6).

To conclude this initial study, the influence of the protecting group pattern of the glycosyl donor on the stereochemical outcome of the reaction was investigated briefly. Thus the 4,6-benzylidene protected donor **7** was accessed and subjected to glycosylation again using diacetone galactose **3** as the glycosyl acceptor (Table 4). In this instance the use of TMSOTf as activator produced disaccharide **8** as an almost equimolar mixture of the α- and β-anomers (ratio of **8α**:**8*β***, 1:1.1, Table 4 entry 1). This ratio remained essentially unchanged when the (*R*)-enantiomer of **1** was used as activating catalyst (Table 4, entry 2). However when (*S*)-**1** was used the reaction was again found to favor formation of the β-anomer (ratio of **8α**:**8*β***, 1:3.4).

Overall the results contained herein demonstrate that the stereochemical outcome of a glycosylation reaction can be affected by the chirality of a catalytic acid that is used as an activator. As compared to activation with an achiral Lewis acid (TMSOTf) the reactions are generally seen to be more β-selective. While the (*R*)-enantiomer of **1** induces quite low levels of β-selectivity, the use of the (*S*)-enantiomer of **1** generally caused highly selective β-glycosylation, and in certain cases the β-product was formed exclusively. A corollary to these findings is that this β-selectivity is to some extent still dependent on the identity of the glycosyl acceptor employed. The ultimate objective of a research program such as this would be to develop a chiral catalytic activating system that was β-selective for one enantiomer of the catalyst, and α-selective for the other, independently of the identities of glycosyl donor and acceptor. Although such a "Holy-Grail" of glycosylation chemistry remains very distant, this first report on the feasibility of achieving effective chemical glycosylation using a chiral catalytic activator, together with the observation that the stereochemical outcome of glycosylation *is* dependent on the chirality of the activating catalyst, does indicate that this is certainly an avenue worthy of further investigation.

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Note Added in Proof. For a recent example of Pd catalyzed activation of glycosyl trichloroacetimidate donors which resulted in β-selective glycosylation in the absence of neighboring group participation, see: Mensah, E. A.; Azzarelli, J. M.; Nguyen, H. M. *J. Org. Chem.* **2009**, *74*, 1650. This paper was published ASAP March 3, 2010 and reposted on March 11, 2010 with this Note.

Supporting Information Available: Synthetic procedures, together with characterization and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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