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## Glycosylation intermediates studied using low temperature $^1\text{H}$ - and $^{19}\text{F}$ -DOSY NMR: new insight into the activation of trichloroacetimidates†

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**Low temperature  $^1\text{H}$ - and  $^{19}\text{F}$ -DOSY have been used for analyzing reactive intermediates in glycosylation reactions, where a glycosyl trichloroacetimidate donor has been activated using different catalysts. The DOSY protocols have been optimized for low temperature experiments and provided new insight into acid catalyzed glycosylation chemistry. From the study a new glycosylation intermediate was characterized.**

The mechanism of the glycosylation reaction is central to carbohydrate chemistry.<sup>1</sup> As the reactions often are complex mixtures containing excess amounts of promoters and additives, such as acid scavengers, drying agents and acceptors, intermediates are notoriously difficult to analyze and impossible to isolate.<sup>2</sup> Half a century ago NMR spectroscopy became available and was immediately applied to study carbohydrates and soon also reactive intermediates at low temperature.<sup>3</sup> The study of glycosylation reactions with low temperature NMR has recently experienced a renaissance, where especially the Crich group has used it extensively to study reactive intermediates, such as glycosyl triflates, and on this basis suggested mechanisms *e.g.* for  $\beta$ -mannosylation.<sup>4</sup> The work by Crich and others<sup>3</sup> in combination with better hardware and software has made this technology accessible and doable for most research groups. The culmination of this development has recently led to the first observation of a carbohydrate oxocarbenium ion by NMR.<sup>5</sup> Despite the advances in NMR resolution one major obstacle remains, *i.e.* the highly complex spectra contain several carbohydrate derived compounds and it is therefore tedious if not impossible to analyze the data fully. To get more information

about the intermediates formed and to separate them in order to analyze and to get information about both the relative amount and the number of intermediates we have studied the use of  $^1\text{H}$ - and  $^{19}\text{F}$  diffusion ordered NMR spectroscopy (DOSY) at low temperature.

Measurements of molecular diffusion by NMR have been carried out since the eighties, but only in recent years has it been part of the routine experiments provided by NMR-manufacturers. The diffusion is dependent on the molecular size, shape and whether the molecule is non-covalently interacting with other species.<sup>6</sup> The relationship between molecular size and diffusion coefficient has been used by several groups to estimate the molecular weights of intermediates<sup>7</sup> and complexes<sup>8</sup> by the use of internal reference compounds. This approach has been applied mainly to  $^1\text{H}$ -DOSY, but also  $^{19}\text{F}$ -DOSY studying Brønsted acid-base complexes.<sup>9</sup> We envisaged that a combination of  $^1\text{H}$ - and  $^{19}\text{F}$ -DOSY could provide information about the intermediates formed under the catalytic activation of trichloroacetimidate (TCA) donors. The most used catalysts, *i.e.* trimethylsilyl trifluoro-sulfonate (TMSOTf) or  $\text{BF}_3\cdot\text{OEt}_2$ , contain fluorine, whereas the TCA donors do normally not. By using this double determination, *i.e.*  $^1\text{H}$ - and  $^{19}\text{F}$ -DOSY, it should be possible to distinguish between intermediates having the catalyst bound or not.

Trichloroacetimidates (TCAs) are one of the most commonly used glycosyl donor types due to its simplicity and catalytic activation.<sup>10</sup> It has therefore been studied using VT-NMR to elaborate the influence of additive,<sup>11</sup> intermolecular participation<sup>12</sup> and it has been used as a source of glycosyl triflates (as **B** in Fig. 1)<sup>13</sup> by using TMSOTf or similar reagents in equivalent amounts. Despite its excessive use, the mechanism of the activation of TCA has only been sparsely investigated and only little is known about the reaction mechanism. It has commonly been illustrated that the Lewis (or Bronsted) acid reacts with the nitrogen atom in the trichloroacetimidate (like **A** in Fig. 1). This activates the TCA group and results in the formation of an oxocarbenium ion intermediate (**C** in Fig. 1) followed by the attack by the nucleophile (acceptor); commonly a hydroxyl group, *i.e.* an  $\text{S}_{\text{N}}1$  type of reaction. (Fig. 1, **C**).<sup>14</sup> Recent studies by Peng and Schmidt have

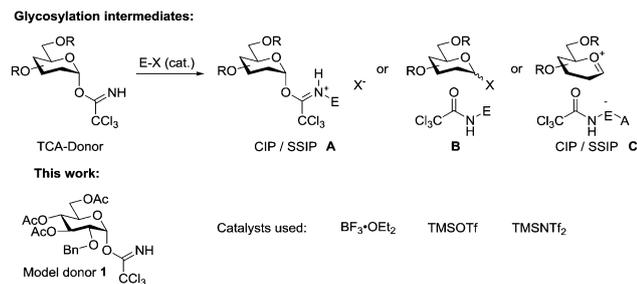
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**Fig. 1** Activation of the TCA donor with an electrophilic catalyst. Three different modes of activation. **(A)** Direct activation forming an activated donor, without departure of the acetimidate (not observed). **(B)** Exchange of the activated TCA by the counter ion (observed by NMR). **(C)** Formation of an oxocarbenium ion (not observed).

shown that such deduction might not always be the scenario, and that the catalyst in some cases could be activated by forming a nucleophile–catalyst complex (similar to **A** in Fig. 1).<sup>15</sup>

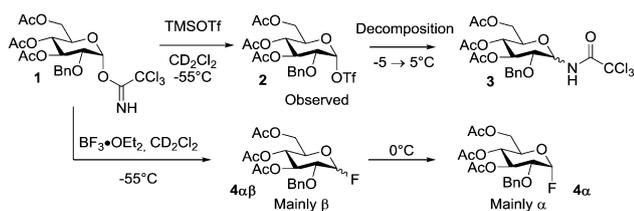
As a model donor for our NMR study, 2-*O*-benzyl-3,4,6-tri-*O*-acetyl  $\alpha$ -D-glucopyranosyl trichloroacetimidate **1**<sup>16</sup> was chosen. It has a commonly used protective group pattern consisting of benzyl and acetyl groups. The 2-*O*-benzyl group was required in order to avoid neighboring group participation, which would give a dioxolonium ion, which is well known and has been thoroughly studied for 2-*O*-acetyl groups.<sup>17</sup> The remaining hydroxyl groups are acetylated, which reduces the donor reactivity and could thereby increase the lifetime of the glycosylation intermediate (not an oxocarbenium ion).<sup>18</sup> Glycosylation reactions with trichloroacetimidates are most often catalyzed by TMSOTf or  $\text{BF}_3\cdot\text{OEt}_2$  and these catalysts were therefore the starting point for the study.<sup>19</sup>

As a standardized condition the donor was dissolved in  $\text{CD}_2\text{Cl}_2$  (conc.: 0.04 M<sup>20</sup>) together with Tris-(trifluoromethyl)-benzene as the internal <sup>19</sup>F-reference compound. In the initial studies the decomposition temperature, *i.e.* when the reactive intermediates disappeared to give a stable product, was determined using the different catalysts. On this basis it was decided to initiate the reactions at  $-55^\circ\text{C}$  using different amounts of the catalyst first in sub-stoichiometric amounts, then in equivalent and finally in excess. The different conditions were analyzed using low temperature NMR. The catalysts were additionally analyzed under the same conditions but independently, *i.e.* without donor presence, to give reference spectra and to check whether they aggregated at low temperature.

The first activation of the TCA-donor using TMSOTf was carried out, and  $\alpha$ -triflate **2** was found to be the main product

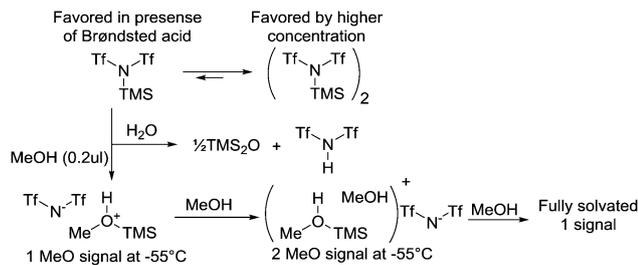
formed as expected from the examples in the literature (Scheme 1).<sup>13</sup> The stereochemistry was confirmed by the small  $^3J_{1-2}$  (3 Hz) coupling constant, which is unambiguous for  $\alpha$ -D-glucosides in the  $^4C_1$  conformation. When using 0.3 equiv. TMSOTf it was found that the donor reacted in a 1:1 ratio and hence did not undergo a catalytic transformation in the absence of an acceptor (see the ESI<sup>†</sup>). Due to the equal size of the donor and the product, these could not be clearly separated by DOSY, but from the comparison of <sup>1</sup>H- and <sup>19</sup>F-DOSY it was clear that the triflate group indeed was attached to the sugar moiety (<sup>19</sup>F-DOSY), whereas the TMS group was not (<sup>1</sup>H-DOSY). This confirms the formation of glucosyl triflate **2**. Upon addition of equivalent amounts or excess of the catalyst full transformation to the  $\alpha$ -triflate was observed. In time an additional product was formed under the reaction conditions at  $-55^\circ\text{C}$ . This product was assigned to be the corresponding trichloroacetamide **3**. The ratio between triflate **2** and amide **3** remained stable until  $-5^\circ\text{C}$ . Between  $-5^\circ\text{C}$  and  $5^\circ\text{C}$  the signals corresponding to the  $\alpha$ -triflate disappeared completely. When a sub-stoichiometric amount ( $\sim 50\%$ ) of  $\text{BF}_3\cdot\text{OEt}_2$  was added to model donor **1** in  $\text{CD}_2\text{Cl}_2$ , the TCA was only consumed according to the amount of catalyst added (approx. 40%) and hence there was no catalytic transformation. Two new products appeared with anomeric signals between 5 and 6 ppm. From the unusual coupling pattern it could be confirmed that the  $\alpha$ - and  $\beta$ -glucosyl fluorides **4 $\alpha\beta$**  had been formed.<sup>21</sup> <sup>19</sup>F-NMR gave rise to three new major peaks, where <sup>19</sup>F-DOSY confirmed that two of them had similar diffusion coefficients and were connected to the sugar moiety (similar diffusion coefficients based on <sup>1</sup>H-DOSY and hence similar size). The <sup>1</sup>H-DOSY confirms the existence of two new sugar species with very similar diffusion coefficients and that the signals of diethyl ether (from  $\text{BF}_3\cdot\text{OEt}_2$ ) are not associated with the sugar. Adding additionally 0.7 equiv. of  $\text{BF}_3\cdot\text{OEt}_2$  resulted in approx. 65% conversion of the TCA, which remained a stable ratio – the donor is not fully consumed even after adding more than 1 equiv. catalyst. The resulting mixture of glucosyl fluorides **4 $\alpha\beta$**  and donor **1** remained stable for  $> 7$  h at  $-55^\circ\text{C}$ . Increasing the temperature stepwise (10  $^\circ\text{C}$  steps) resulted in a slow disappearance of the  $\beta$ -fluoride and at  $-15^\circ\text{C}$  mainly the  $\alpha$ -anomer could be observed. Re-cooling did not change the composition of the sample.

From the results using TMSOTf or  $\text{BF}_3\cdot\text{OEt}_2$ , it was clear that the activation mode of the trichloroacetimidate depends on the catalyst and in particular its counter ion. When this is a triflate ion a clean conversion to the  $\alpha$ -glucosyl triflate **2** was observed; but what if the counter ion is less nucleophilic? Would it then be possible to avoid substitution of the activated trichloroacetimidate and instead observe an activated complex? To study this hypothesis TMSNTf<sub>2</sub><sup>22,23</sup> as a catalyst was investigated, since it has been found to be more Lewis acidic than TMSOTf,<sup>24</sup> but with a less nucleophilic counter ion.<sup>25</sup> To our surprise the NMR, of the catalyst alone at  $-55^\circ\text{C}$  revealed 2 peaks in <sup>1</sup>H- and <sup>19</sup>F-NMR and therefore the existence of 2 compounds (Scheme 2). Upon increasing the temperature to  $20^\circ\text{C}$  one broad signal was observed and hence the compounds are in a slow equilibrium; presumable as the mono- and dimer. This was further supported



**Scheme 1** Activation of the TCA donor using TMSOTf or  $\text{BF}_3\cdot\text{OEt}_2$ .

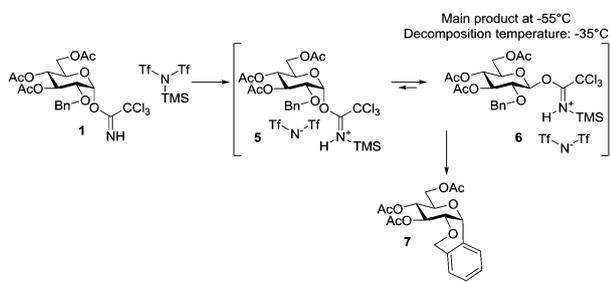




Scheme 2 Reaction of  $\text{Tf}_2\text{NTMS}$  with a model acceptor – MeOH. When present in sub-stoichiometric amounts different complexes are formed.

by increasing the concentration of the catalyst by a factor 5, which increases the amount of the proposed dimer in the sample (Scheme 2). Adding a sub-stoichiometric amount of MeOH (model acceptor) to the catalyst at  $-55\text{ }^\circ\text{C}$  immediately resulted in the disappearance of the peak from the dimer (in  $^1\text{H}$ - and  $^{19}\text{F}$ -NMR) and the formation of a new peak assigned to  $[\text{MeOH-TMS}]^+$  appeared. The addition of more MeOH resulted in full conversion (Scheme 2). MeOH seems to catalyze the monomerization.

When  $\text{TMSNTf}_2$  was added (0.3 equiv.) to model donor **1** at  $-55\text{ }^\circ\text{C}$  no dimer was detected and the signal from trichloroacetimidate **1** disappeared rapidly (Scheme 3), which is in contrast to the same conditions using  $\text{TMSOTf}$  as the catalyst, where a one to one reaction took place.  $^1\text{H}$ -NMR showed a mixture of at least two compounds and  $^{19}\text{F}$ -NMR showed three peaks.  $^1\text{H}$ -DOSY of the mixture confirmed the presence of two sugar based compounds with a small difference in diffusion coefficient and hence size. From  $^1\text{H}$ -DOSY it is, however, clear that the TMS group from the catalyst is covalently attached to the sugar in contrast to when using  $\text{TMSOTf}$ .  $^{19}\text{F}$ -DOSY does not indicate that the sugar and  $\text{NTf}_2^-$  are closely associated and a covalent bond between them can therefore be excluded. Upon the addition of equivalent amounts or excess of the catalyst the donor was immediately transformed and 4 broad peaks, between 5.5 and 6.5 ppm, appeared in  $^1\text{H}$ -NMR (presumable N-H). After 10 min, the mixture equilibrated into mainly one compound with no visible N-H signals. This compound was analyzed by  $^1\text{H}$ ,  $^{19}\text{F}$ , COSY, HSQC Ed,  $^1\text{H}$ -DOSY,  $^{19}\text{F}$ -DOSY, NOESY and N-H-HSQC. The signals from the sugar-part could all be assigned and a chair conformation with an equatorial C1-substituent confirmed



Scheme 3 Activation of TCA donor **1** with  $\text{Tf}_2\text{NTMS}$ . The counter ion  $\text{Tf}_2\text{N}^-$  is not nucleophilic enough to substitute the activated TCA, which instead anomerizes in time and eventually decompose to **7**.

( $^3J$  are large ( $\sim 9\text{ Hz}$ ), COSY, HSQC, NOESY). Two different TMS signals were observed – one attached to the sugar (DOSY) and one from  $\text{TMS}_2\text{O}$  (from the side reaction with trace amounts of water).  $^{19}\text{F}$ -NMR showed 3 peaks, which were significantly different from the ones observed for the catalyst alone and its reaction with methanol, *i.e.* suggesting some interaction with the sugar, however not tightly associated (DOSY), but rather as an ion pair. TMS-activated TCA donor **6** was found to be more labile than the corresponding triflate **2** and even at  $-55\text{ }^\circ\text{C}$  a slow degradation took place. Upon increasing the temperature to  $-20\text{ }^\circ\text{C}$  resulted in full conversion into the Friedel-Crafts product **7** (determined from the crude NMR and confirmed by HRMS), but not trichloroacetamide **3**, which is in contrast to when using  $\text{TMSOTf}$ . As far as it comes to our knowledge this is the first example of observing the activated complex of a trichloroacetimidate donor.<sup>26</sup> The formation of this intermediate, when having a less nucleophile catalyst counter ion support that the triflate ion can act as a nucleophilic catalyst, whereas the triflylimide cannot to the same extent.<sup>28</sup>

The diffusion coefficients obtained are related to the size and shape of the molecules<sup>6</sup> and as all compounds share the sugar moiety it was assumed that the main difference would be related to the molecular weight ( $M_w$ ) of the glycosyl donor and the intermediates. An estimation of  $M_w$  by DOSY<sup>27</sup> could shine light on the composition of the intermediates and other active species in the reaction mixture. Several methods have been developed for the determination of  $M_w$  by DOSY. Normally these involve the use of a set of internal reference compounds. Due to the complexity and number of signals a recent published procedure involving external calibration curves and only one internal reference caught our interest.<sup>29</sup> As the compounds in our study are larger and the solvent is  $\text{CD}_2\text{Cl}_2$  a new calibration curve was prepared. A number of reference compounds with a similar three-dimensional structure were chosen and their diffusion coefficients determined in the presence of one internal reference – 1,3,5-tris(trifluoromethyl)benzene, which can be used as a reference in both  $^1\text{H}$ - and  $^{19}\text{F}$ -DOSY. For the  $^1\text{H}$ -DOSY calibration curve, carbohydrate based structures were preferred, and masses in the range from 74 to 1226 were included (6 compounds, see the ESI† for details). For  $^{19}\text{F}$ -DOSY the available carbohydrate based compounds were limited and only one, *i.e.* 2,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl fluoride, was part of the calibration curve (see the ESI† for details). With the calibration curves in hand the DOSY experiments were repeated to estimate the  $M_w$  of the formed intermediates. Excess of the catalysts were used in order to ensure the formation of mainly one compound and the temperature was kept at  $-55\text{ }^\circ\text{C}$ .

From the initial NMR studies and DOSY experiments good evidence for the structures of the intermediates formed had been obtained and hence their molecular weights ( $M_w$ ) could be predicted and compared with calculated values based on the calibration curve and the internal reference compound (Table 1). Estimation of  $M_w$ s from the calibration curves gave a good estimation for the intermediates formed when using  $\text{BF}_3\cdot\text{OEt}_2$  and  $\text{Tf}_2\text{NTMS}$  as the catalysts. The deviation is within 10% and the predicted  $M_w$  is in-between the results from the two



Table 1  $M_w$  determination by  $^1\text{H}$ - and  $^{19}\text{F}$ -DOSY measurements

Catalysts	$M_{w, \text{pre}}^a$ [g mol $^{-1}$ ]	$M_{w, \text{cat}}^b$ [g mol $^{-1}$ ]		$\Delta M_w$ [%]	
		$^1\text{H}$ -DOSY	$^{19}\text{F}$ -DOSY	$^1\text{H}$ -DOSY	$^{19}\text{F}$ -DOSY
$\text{BF}_3\cdot\text{OEt}_2$	609	627	561	-3	8
TMSOTf	528	565	658	-7	-25
TMSNTf $_2$	894	911	868	-2	3

<sup>a</sup> Predicted  $M_w$  of the intermediates. <sup>b</sup>  $M_w$  calculated by the  $M_w$  calibration curves. See the ESI for details.

calibration curves. Both methods do however estimate larger  $M_w$ s for the activation with TMSOTf and the  $^{19}\text{F}$ -DOSY deviates by 25%. One reason for the less precise  $M_w$  prediction of this compound could be that the calibration curve is based on mainly non-carbohydrate based compounds, which have different three dimensional structures and hence a slightly different relation between diffusion constants and  $M_w$ s. Generally the  $^1\text{H}$ -DOSY calibration curve, which is based on carbohydrate derivatives, gives the best correlation and hence the most accurate estimate. Most importantly the double determination of  $M_w$ s of the new donor system using Tf $_2$ NTMS agrees with the predicted  $M_w$ s and thereby strongly support that intermediate **6** containing the silylated trichloroacetimidate has been formed, which is a new activation pathway and could be a new way to improve the yield and selectivity in catalytic glycosylations.

In conclusion, we have used DOSY NMR for the first time to investigate a glycosylation reaction at low temperature. The interaction between three different catalysts with a glucosyl trichloroacetimidate was studied, and it was found that the reaction pathways and intermediates are different. The two common catalysts,  $\text{BF}_3\cdot\text{OEt}_2$  and TMSOTf, give glucosyl-fluorides and triflates, respectively, as intermediates. The donor is not transformed catalytically under these conditions, where an acceptor is not present. From this insight a new catalyst, Tf $_2$ NTMS was suggested and found to activate the trichloroacetimidate catalytically, but without cleavage of the glycosidic bond. The counter ion is not nucleophilic enough to substitute the leaving group and this is a novel promising concept for catalytic stereospecific glycosylations.

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## Notes and references

- (a) B. Capon, *Chem. Rev.*, 1969, **69**, 407; (b) L. K. Mydock and A. V. Demchenko, *Org. Biomol. Chem.*, 2010, **8**, 497; (c) S. C. Ranade and A. V. Demchenko, *J. Carbohydr. Chem.*, 2013, **32**, 1; (d) L. Bohé and D. Crich, *C. R. Chim.*, 2011, **14**, 3.
- Examples of preactivation and intermediates see: (a) L. Yang, Q. Qin and X.-S. Ye, *Asian J. Org. Chem.*, 2013, **2**, 30; (b) M. T. C. Walvoort, G. A. van der Marel, H. S. Overkleeft and J. D. C. Codée, *Chem. Sci.*, 2013, **4**, 897.
- T. G. Frihed, M. Bols and C. M. Pedersen, *Chem. Rev.*, 2015, **115**, 4963.
- (a) D. Crich and S. Sun, *J. Am. Chem. Soc.*, 1997, **119**, 11217; (b) D. Crich, *Acc. Chem. Res.*, 2010, **43**, 1144.
- A. Martin, A. Arda, J. Désiré, A. Martin-Mingot, N. Probst, P. Sinay, J. Jiménez-Barbero, S. Thibaudeau and Y. Blériot, *Nat. Chem.*, 2016, **8**, 186.
- (a) L. Avram and Y. Cohen, *Chem. Soc. Rev.*, 2015, **44**, 586; (b) Y. Cohen, L. Avram and L. Frish, *Angew. Chem., Int. Ed.*, 2005, **44**, 520.
- D. Li, I. Keresztes, R. Hopson and P. G. Williard, *Acc. Chem. Res.*, 2009, **42**, 270.
- Studies of the complexation of sugars by diffusion-ordered NMR spectroscopy: M. D. Diaz and S. Berger, *Carbohydr. Res.*, 2000, **329**, 1.
- H. Subramanian, C. P. Jasperse and M. P. Sibi, *Org. Lett.*, 2015, **17**, 1429.
- (a) R. R. Schmidt and J. Michel, *Angew. Chem., Int. Ed.*, 1980, **19**, 731–733; (b) Reviewed in: X. Zhu and R. R. Schmidt, in *Handbook of Chemical Glycosylation*, ed. A. V. Demchenko, Wiley-VCH, Weinheim, 2008, pp. 143–185.
- (a) S. R. Lu, Y. H. Lai, J. H. Chen, C. Y. Liu and K. K. T. Mong, *Angew. Chem., Int. Ed.*, 2011, **50**, 7315; (b) Y. H. Lin, B. Ghosh and K. K. T. Mong, *Chem. Commun.*, 2012, **48**, 10910; (c) A. B. Ingle, C. S. Chao, W. C. Hung and K. K. T. Mong, *Org. Lett.*, 2013, **15**, 5290.
- (a) J. H. Kim, H. Yang, J. Park and G. J. Boons, *J. Am. Chem. Soc.*, 2005, **127**, 12090; (b) T. J. Boltje, J. H. Kim, J. Park and G. J. Boons, *Org. Lett.*, 2011, **13**, 284; (c) T. Fang, K. F. Mo and G. J. Boons, *J. Am. Chem. Soc.*, 2012, **134**, 7545; (d) D. J. Cox, G. P. Singh, A. J. A. Watson and A. J. Fairbanks, *Eur. J. Org. Chem.*, 2014, 4624.
- (a) J. Y. Baek, B. Y. Lee, M. G. Jo and K. S. Kim, *J. Am. Chem. Soc.*, 2009, **131**, 17705; (b) A. Rencurosi, L. Lay, G. Russo, E. Caneva and L. Poletti, *Carbohydr. Res.*, 2006, **341**, 903; (c) J. Park, S. Kawatkar, J. H. Kim and G. J. Boons, *Org. Lett.*, 2007, **9**, 1959.
- See for an example: G.-J. Boons and K. J. Hale, *Organic Synthesis with Carbohydrates*, Sheffield Academic Press Ltd, 2000, p. 108.
- P. Peng and R. R. Schmidt, *J. Am. Chem. Soc.*, 2015, **137**, 12653.
- (a) N. J. Davis and S. L. Flitsch, *J. Chem. Soc., Perkin Trans. 1*, 1994, 359–368; (b) N. C. R. van Straten, G. A. van der Marel and J. H. van Boom, *Tetrahedron*, 1997, **53**, 6523.
- (a) Generally: S. Winstein and R. E. Buckles, *J. Am. Chem. Soc.*, 1942, **64**, 2780; (b) Early examples in carbohydrate chemistry have been summarized in: R. U. Lemieux, *Adv. Carbohydr. Chem.*, 1954, **9**, 1.
- (a) M. N. Kamat and A. V. Demchenko, *Org. Lett.*, 2005, **7**, 3215; A 2-O-acetyl can, besides controlling the selectivity also increase the reactivity, when anchimeric assistance is possible: (b) D. Crich and M. Li, *Org. Lett.*, 2007, **9**, 4115; (c) M. Heuckendorff, C. M. Pedersen and M. Bols, *Org. Lett.*, 2011, **13**, 5956.
- (a) R. R. Schmidt and K.-H. Jung, in *Preparative Carbohydrate Chemistry*, ed. S. Hanessian, Marcel Dekker, New York, 1997, pp. 283–312; (b) X. Zhu and R. R. Schmidt, in *Handbook of Chemical Glycosylation*, ed. A. V. Demchenko, Wiley VCH, Weinheim, 2008, p. 143.
- The concentration was optimized for the DOSY experiments.
- Glycosyl fluorides have earlier been observed in glycosylations using trichloroacetimidate donors in combination with  $\text{BF}_3\cdot\text{OEt}_2$ . See: H. M. Christensen, S. Oscarson and H. H. Jensen, *Carbohydr. Res.*, 2015, **408**, 51.
- TMSNTf $_2$  has been used to catalyze the glycosylation using per-methacrylated O-glycosyl trichloroacetimidates with simple acceptors. The yields were however low (up to 40%) and the selectivity controlled by neighboring group participation. See: C. Zandanel, L. Dehuyser, A. Wagner and R. Baati, *Tetrahedron*, 2010, **66**, 3365.
- (a) Tf $_2$ NTMS has previously been used for: Friedel-Craft alkylations e.g. A. Isgii, O. Kotera, T. Saeki and K. Mikami, *Synlett*, 1997, 1145; (b)  $\beta$ -allylation of enones: N. Kuhnert, J. Pevery and J. Robertson, *Tetrahedron Lett.*, 1998, **39**, 3215; (c) Mukayama aldol reaction: K. Ishihara, Y. Hiraiwa and H. Yamamoto, *Synlett*, 2001, 1851; (d) Silylations: G. Simchen and S. Jonas, *J. Prakt. Chem.*, 1998, **340**, 506; (e) See also M. B. Boxer in e-EROS Encyclopedia of Reagents for Organic Synthesis, 2008 (1,1,1-trifluoro-N-[(trifluoromethyl)sulfonyl]-N-(trimethylsilyl)methanesulfonamide).
- B. Mathieu and L. Ghosez, *Tetrahedron Lett.*, 1997, **38**, 5497.
- TfOH has been found to be more Bronsted acidic and its conjugated base more nucleophilic compared to Tf $_2$ NH: J. Foropoulos and D. D. DesMarteau, *Inorg. Chem.*, 1984, **23**, 3720; B. Mathieu, *L. Ghosez Tetrahedron*, 2002, **58**, 8219.
- The structurally related imidinium ion has been observed by VT-NMR: (a) V. Dourtoglou, J.-C. Ziegler and B. Gross, *Tetrahedron Lett.*, 1979, **20**, 4371; (b) Y. Shingu, A. Miyachi, Y. Miura, K. Kobayashi and Y. Nishida, *Carbohydr. Res.*, 2005, **340**, 2236; (c) Y. Nishida, Y. Shingu, H. Dohi and K. Kobayashi, *Org. Lett.*, 2003, **5**, 2377. See also ref. 11.
- Molecular weight determination of oligo- and poly-saccharides by DOSY: (a) O. Assemat, M.-A. Coutouly, R. Hajjar and M.-A. Delsuc, *C. R. Chim.*, 2010, **13**, 412–415; (b) S. Viel, D. Capitani, L. Mannina and A. Segre, *Biomacromolecules*, 2003, **4**, 1843.
- Influence of the counter ion in glycosylation has recently been studied by VT-NMR: Y. Zhu and B. Yu, *Chem. – Eur. J.*, 2015, **21**, 8771.
- R. Neufeld and D. Stalke, *Chem. Sci.*, 2015, **6**, 3354.

