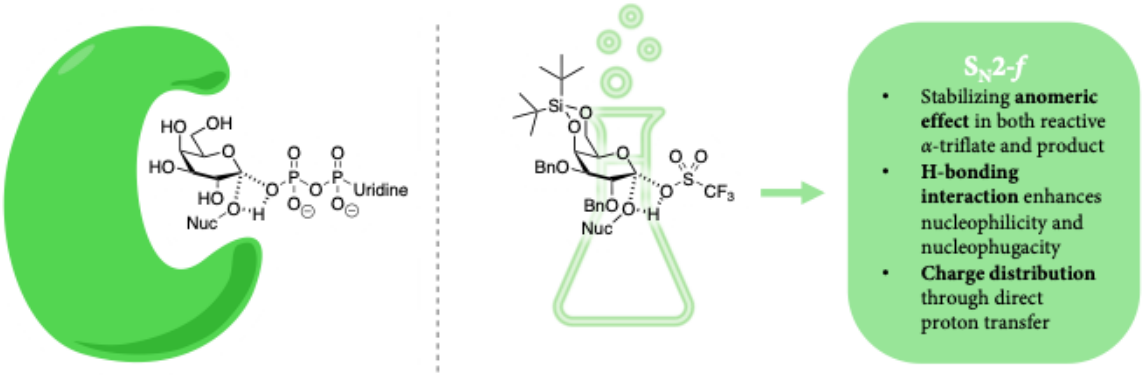
FRONTSIDE S_N2 GLYCOSYLATION REACTIONS

Daan Hoogers[a], Koen N.A. van de Vrande[a], Frank F. J. de Kleijne[b], Jacob M. A. van Hengst[a], Wouter A. Remmerswaal[a], Paul B. White[b], Thomas J. Boltje[b], Thomas Hansen[c], Jeroen D. C. Codée[a]

[a] Leiden Institute of Chemistry, Einsteinweg 55, 2333 CC Leiden, The Netherlands
d.hoogers@lic.leidenuniv.nl
[b] Institute for Molecules and Materials (IMM), Synthetic Organic Chemistry, Radboud University, 6525 AJ Nijmegen, The Netherlands
[c] Department of Theoretical Chemistry, Amsterdam Institute of Molecular and Life Sciences (AIMMS), Amsterdam Center for Multiscale Modeling (ACMM), Vrije Universiteit Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands

Controlling the stereochemical outcome of glycosylation reactions remains one of the fundamental challenges in carbohydrate chemistry. Mechanistic models generally describe chemical glycosylation reactions as proceeding via S_N1 or backside S_N2 (S_N2-*b*) pathways [1]. Notably, retaining glycosyl transferases operate via a different mechanism, and substitution reactions on nucleotide diphosphate sugar donors can take place through a front face substitution mechanism (termed S_Ni) [2]. This mechanism has been largely ignored to play a role in chemical glycosylation reactions, but we here provide evidence for a concerted frontside S_N2-like (S_N2-*f*) displacement mechanism in glycosylations of 4,6-*O*-di-*tert*-butylsilylene (DTBS)-protected galactosyl donors.
Through ^{19}F EXSY and ^{1}H CEST NMR spectroscopy, we demonstrate that steric hindrance introduced by the DTBS group suppresses triflate exchange, restricting glycosylation reactions to the α-triflate and α-face of the donor. Acceptor concentration-dependent kinetics and primary ^{13}C KIE values support an associative mechanism featuring an “exploded” transition state with retention of stereochemistry. Density functional theory (DFT) calculations further reveal that strong hydrogen bonding between the nucleophile and the triflate leaving group stabilizes the transition state, making this frontside displacement pathway favour more acidic nucleophiles. This was substantiated by acceptor competition experiments, in which the more electron poor *O*-nucleophiles provided faster glycosylation reactions.
Our findings establish a new paradigm in chemical glycosylation chemistry, demonstrating that triflates can be substituted in a stereoretentive manner by exploiting the S_N2-*f* reaction pathway. This work provides new insights to understand the outcome of glycosylation reactions and offers new perspectives for future mechanistic exploration.



References:
1. P.O. Adero, *et al*. *Chem Rev* **2018,** *118,* 8242-8284.
2. S. Lee, *et al*. *Nat Chem Biol* **2011**, *7*, 631-638.