MAPPING *EXO*-GLYCALS REACTIVITY AND BIOLOGICAL APPLICATION

Julien Janssens[a], Jenny Ha[c], Lucie Pedussaut[b], Stéphane Vincent[c], Guillaume Berionni[b], Raphaël Robiette[a]

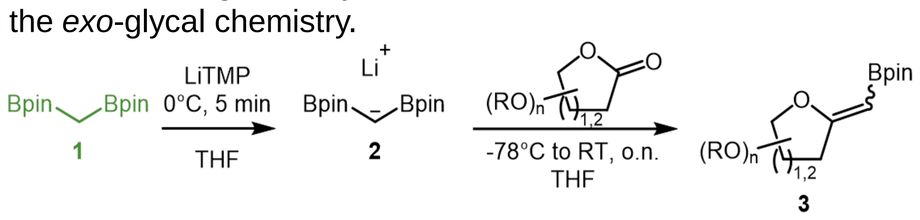
[a] Division of Molecular Chemistry, Materials and Catalysis, Institute of Condensed Matter and Nanosciences, Université catholique de Louvain
[b] Laboratory of Reactivity, catalysis and organic chemistry, Department of Chemistry, University of Namur
[c] Laboratory of Bio-organic chemistry, Department of Chemistry, University of Namur

Glycals are unsaturated sugar derivatives constituting a large family of polyhydroxylated chiral synthons. The *endo*-glycals are widely exploited in the synthesis of natural products and for biochemical applications. In contrast, the chemistry and biology of *exo*-glycals remained unexplored until recently. Their synthetic chemistry suffers from some limitations in terms of substitution of the double bond, and the control of their stereochemistry is challenging.[1] Since the release of Boromycin and Bortezomib drugs, borylated compounds have also stimulated the pharmaceutical industry's interest for various applications, and we became interested in the chemistry of borylated *exo*-glycals.[2]

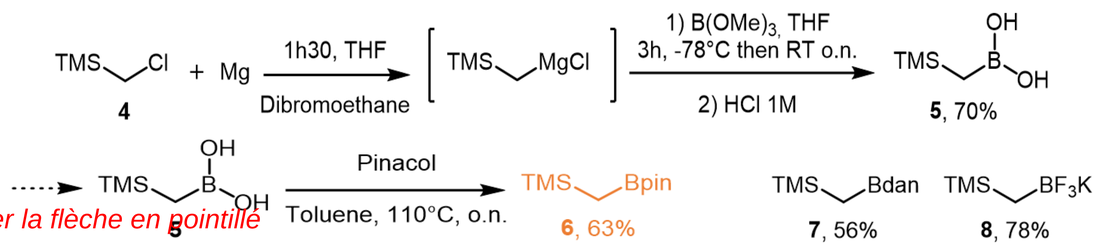
BORYLATED *EXO*-GLYCALS

Olefination strategies

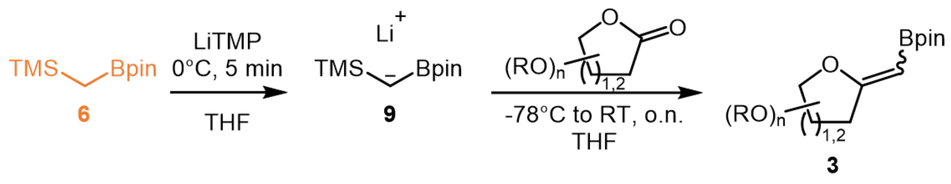
Grygorenko showed the usefulness of *gem*-diborylalkane in Boron-Wittig reaction, a B-O elimination leading to borylated alkenes.[3] We endeavour to adapt this strategy to the *exo*-glycal chemistry.



Despite our efforts, we couldn't obtain more than traces of the desired borylated *exo*-glycal. Consequently, we turned our attention to the silica-based Peterson olefination and synthesized a library of new *gem*-borylsilylalkanes.

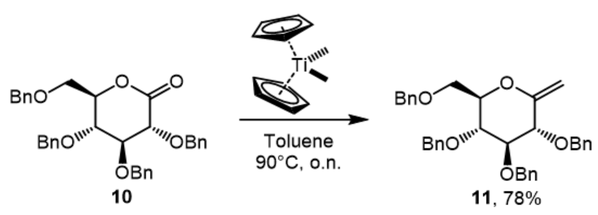


These compounds and their reactions with model lactones (e.g. butyrolactone) are being explored through experimental and computational works. The information gathered will be used to obtain *exo*-glycals via a Peterson olefination.

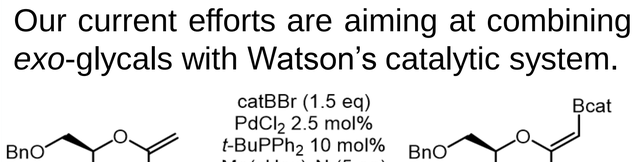


Coupling strategies

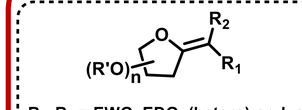
We envisioned that a boryl-Heck-like coupling could enable us to substitute the existing double bond of an *exo*-glycal synthesized by Petasis olefination.



Our current efforts are aiming at combining those methylene *exo*-glycals with Watson's catalytic system.

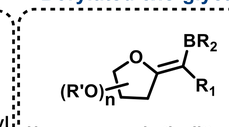


Tetrasubstituted *exo*-glycals



R_1, R_2 = EWG, EDG, (hetero)-aryl, alkyl
R' = protective groups

Borylated *exo*-glycals

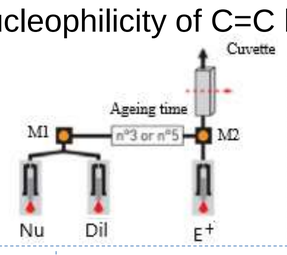


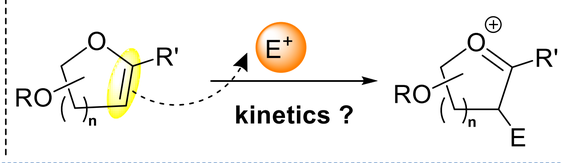
No-occurence in the litterature

Reactivity maps and mechanisms
New synthetic methods ?
New biochemical probes ?

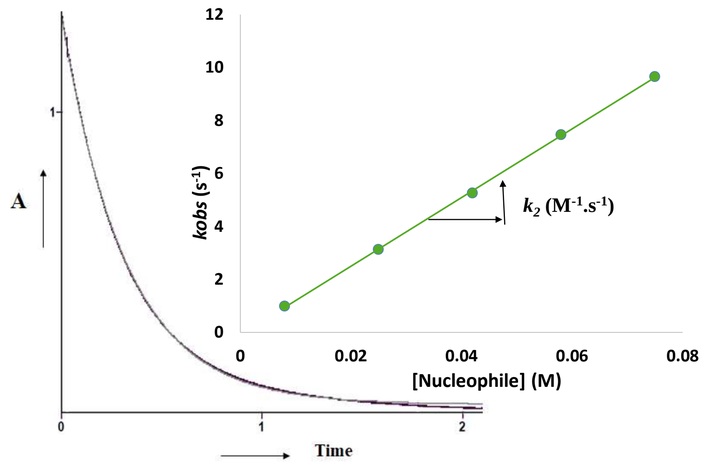
REACTIVITY STUDIES

Kinetics studies are through a stopped-flow UV/Vis spectrometer in absorbance mode run to determine the nucleophilicity of C=C bond.





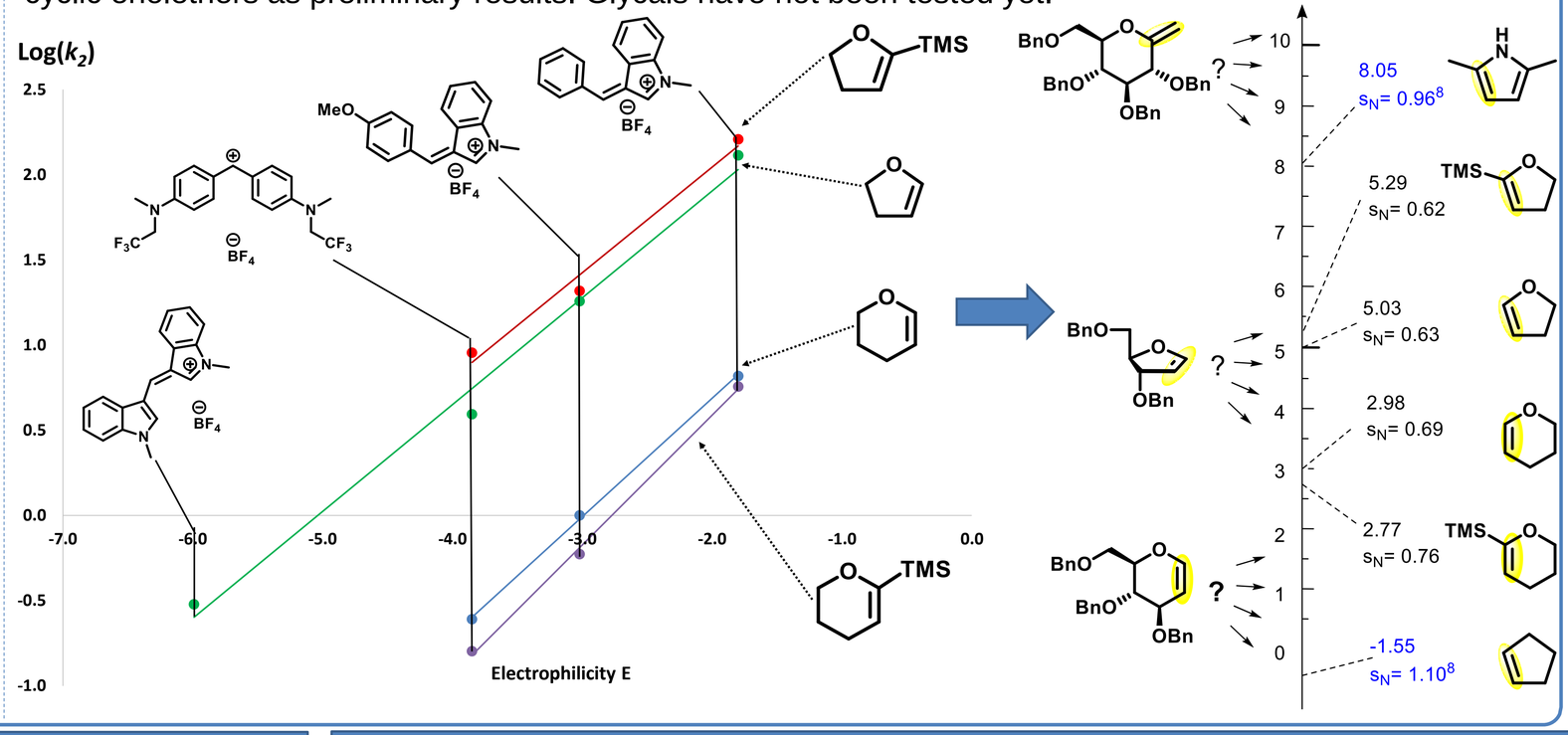
The exponential decays are observed, from which the pseudo-first-order rate constants k_{obs} are obtained. Then, the second order rate constants k_2 can be derived from the slopes of these plots.



The Mayr and Patz equation will be employed for determining the nucleophilicity of a representative set of glycals (Eq. 1).[7]

$$\log(k_2) = s_N(N+E) \qquad (1)$$

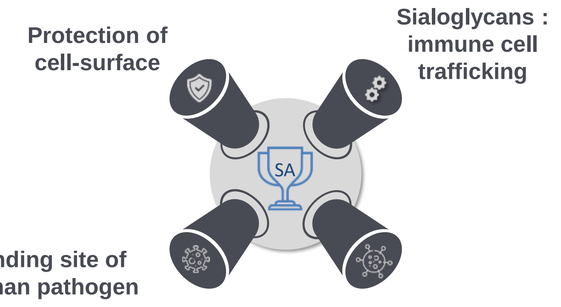
Using equation 1, the *N* parameter can be determined giving us the nucleophilicity scale below of *endo*-cyclic enolethers as preliminary results. Glycals have not been tested yet.



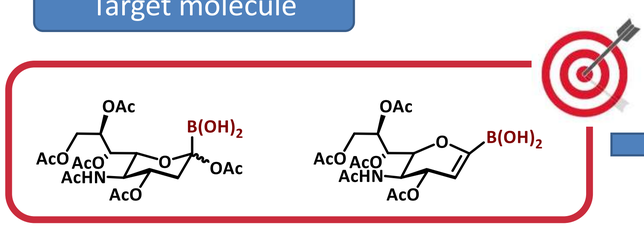
DECARBOXYLATIVE BORYLATION

Model: Sialic acid

- ✓ Family of nine-carbon atoms sugars: *N*-acetylneuraminic acid (**Neu5Ac**)
- ✓ Terminal residues of glycoproteins, glycolipids and oligosaccharides

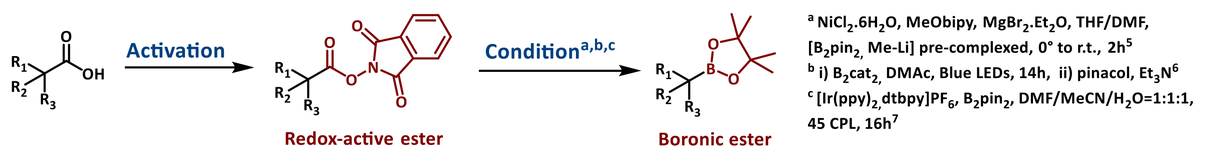


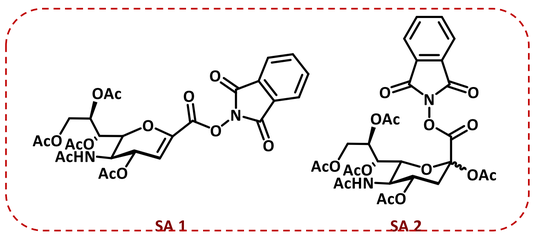
Target molecule



Decarboxylative borylation

Substrates involved in decarboxylative reaction mostly present *N*-hydroxyphtalimide ester to activate carboxylic acid.





CONCLUSIONS AND PERSPECTIVES

- Synthesis of analogues of sialic acid to target viral proteins.
- Conversion of the boronate group to reach unprecedented substitution pattern of the double bond.
- Expansion of our reactivity map of the glycal family using those new tri-/tetrasubstituted *exo*-glycals.

ACKNOWLEDGEMENT

We acknowledge ARC (Actions de recherche concertée, UNamur/UCLouvain) for funding 3 PhD theses (J. Janssens, J. Ha, L. Pedussaut). We also would like to thank the NISM institute and the technological plateform PC².

REFERENCES

[1] Taillefumier, C.; Chapleur, Y. *Chem. Rev.,* **2004**, 104, 263.
[2] W. Moreira, D. B. Aziz, T. Dick, *Frontiers in Microbiology,* **2016**, 7, 1.
[3] Grygorenko, O. O. *Eur. J. Org. Chem.* **2019**, 33, 5624.
[4] C. Li, J. Wang, L. M. Barton, S. Yu, M. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. A. Johnson, A. K. Chatterjee, M. Yan, P. S. Baran, *Science,* **2017**, 356.
[5] A. Fawcett, J. Pradeilles, Y. Wang, T. Mutsuga, E. L. Myers, V. K. Aggarwal, *Science,* **2017**, 357, 283.
[6] D. Hu, L. Wang, P. Li, *Org Lett,* **2017**, 19, 2770.
[7] R. Lucius, R. Loos, H. Mayr, *Angew. Chem. Int. Ed.* **2002**, 41, 91.
[8] https://www.cup.lmu.de/oc/mayr/reaktionsdatenbank/