# Base catalyzed acylation of sterically crowded conformationally locked galactosides

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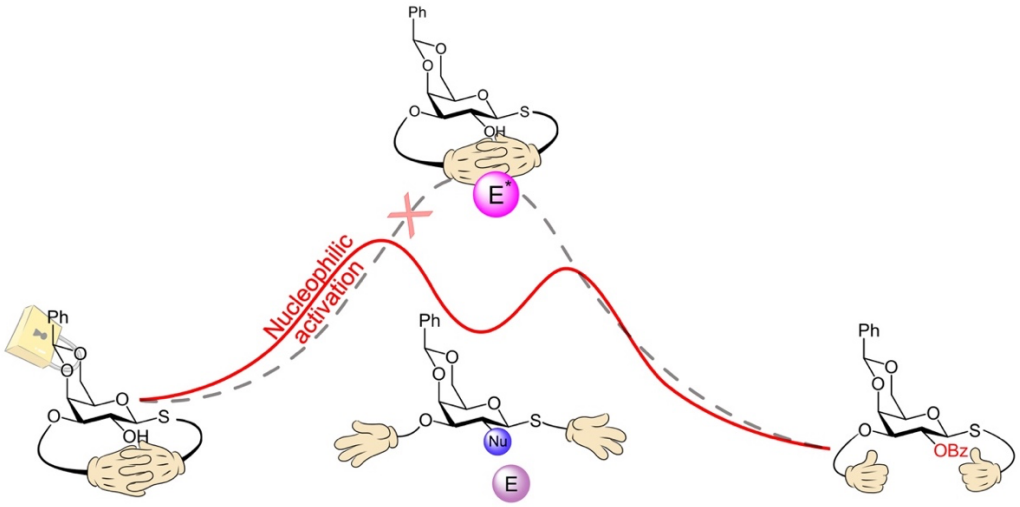
Access to fully protected glycoside monomeric building blocks is essential for the bottom-up synthesis of well-defined oligosaccharides. Alongside introduction of novel glycosylation strategies, development of reliable and efficient protocols for regioselective installation of protecting groups is equally crucial and challenging. The control of protecting group installation on partially protected monosaccharides is often unpredictable and depends on the electronic, the steric and the conformational effects of other substituents. We uncovered an O-2 masking effect in Lewis base catalyzed acylation of the valuable conformationally locked 4,6-O-benzylidene thiogalactoside intermediate that is highly dependent on the 3-O-ether substituent. A combination of crystallographic data, investigation of analogous O-3 ether protected systems and computational efforts revealed previously overlooked steric effects on the accessibility of the nucleophilic species. Characterization of the O-2 masking effect allowed for development of an alternative protecting group installation strategy *via* nucleophilic activation. This insight facilitated access to the target galactoside building block whilst preserving the envisioned stepwise strategy and protecting group hierarchy. Adapting this strategy for obtaining a diverse set of orthogonally protected galactoside monomeric building blocks will be valuable in the synthesis of complex oligosaccharides.




Nucleophilic activation of sterically crowded O-2 in a conformationally locked system allows for an alternative facile acylation strategy