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Acid-base catalysis in glycosidations: A nature derived alternative to the generally employed methodology

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Inverting glycosyltransferases enforce in the active site an intramolecular, acid-base catalyzed glycosidation that, due to proximity of the donor anomeric carbon and the acceptor hydroxyl group, follows an SN₂-type reaction. Spacer, tethering donor and acceptor via nonreacting functional groups, led in intramolecular glycosidations to excellent yields and independent of the donor anomeric configuration, to either the α - or the β -anomer. The requirement of a demanding protecting group pattern confines the application of this efficient method. The most elegant method, tethering donor and acceptor covalently to the spacer via the leaving group and the reacting functional group, was so far not as efficient as hoped. This method is very efficient when donor and acceptor are temporarily assembled through a hydrogen-bond facilitating a stretched hexagon-like transition state. This follows from the stereoselective O-glucopyranosyl trichloroacetimidate transformation into O-glucopyranosyl phosphate with dibenzyl phosphoric acid as acceptor that can be regarded as A=B-C-H acceptor type. Generalizing this concept to the use of alcohols as acceptors requires reversible generation of an A-B-C-H adduct where A-H represents the acceptor (RO-H) and B=C a catalyst that has to fulfill several criteria. Among these criteria are low affinity to nitrogen, avoiding glycosyl donor activation in the absence of acceptor, and high affinity to oxygen in order to generate the A-B-C-H adduct with increased proton acidity. Thus, hydrogen-bond mediated self-assembly of donor and acceptor and concomitant donor activation via a transition state is available, which enforces an acid-base catalyzed SN₂-type reaction.

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