CATALYTIC GLYCOSYLATIONS USING GLYCOSYL FLUORIDE BY BORATE COMPLEX

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Glycosyl fluorides offer effective approaches for glycan synthesis because they are easy to handle and provide access to diverse glycosidic linkages. Various methods for the activation of glycosyl fluorides have been developed. However, catalytic activation of glycosyl fluorides remains a challenging, as highly fluorophilic reagents that activate stable C-F bonds are generally deactivated upon fluoride attachment. In particular, low-reactive disarmed glycosyl fluorides, protected with electron-withdrawing groups (e.g., acyl), have not been catalytically activated without trapping in-situ-generated HF.

Herein, we present $BF_3{\cdot}Et_2O$-catalyzed glycosylation of glycosyl fluorides with alcohol acceptors (unsilylated nucleophiles) using 1 mol% $BF_3{\cdot}Et_2O$ under nitrogen-filled glovebox conditions, without any HF-trapping agents.[1] The present conditions smoothly activate both armed and disarmed glycosyl fluorides, thereby affording the desired glycoside products in high yields. Notably, this reaction exhibits reaction vessel dependency, proceeding catalytically only in a glass flask. The formation of SiF_4 has been confirmed, suggesting that a mixed Lewis acid species of BF_3 and SiF_4 serves as the active catalytic species.

However, glycosylation exhibits significant variations in reactivity depending on the structure of substrates, making it difficult to develop a universal glycosylation method applicable to a wide range of substrates. To address this issue, we harnessed the tunable Lewis acidity of cage-shaped borates to develop practical glycosylation methods tailored to the reactivities of individual substrates. After optimizing the reaction conditions for the efficient catalytic (1–10 mol%) activation of glycosyl fluorides using cage-shaped borates, we systematically explored a range of glycosylation reactions employing various borates. As anticipated, each borate exhibited distinctive reactivity; thus, systematic screening of borate catalysts enabled the efficient activation of glycosyl fluorides under mild conditions. Glycosylation was successfully achieved by fine-tuning the Lewis acidity to match the substrate reactivity. This glycosylation methodology addresses the fundamental challenges of glycosylation and the highly structure-dependent nature of reactivity, thereby paving the way for efficient glycan synthesis.

References:

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