

Site-Selective, Stereocontrolled Glycosylation Catalyzed by Bis-Thioureas

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Abstract

The identification of general and efficient methods for the construction of oligosaccharides stands as one of the great challenges for the field of synthetic chemistry. Selective glycosylation of unprotected sugars and other polyhydroxylated nucleophiles is a particularly significant goal, requiring not only control over the stereochemistry of the forming bond but also differentiation between similarly reactive nucleophilic sites in stereochemically complex contexts. Chemists have generally relied on multi-step protecting-group strategies to achieve site control in glycosylations, but practical inefficiencies arise directly from the application of such approaches. We describe here a new strategy for small-molecule-catalyst-controlled, highly stereo- and site-selective glycosylations of unprotected or minimally protected mono- and disaccharides using precisely designed bis-thiourea small-molecule catalysts. Stereo- and site-selective galactosylations and mannosylations of a wide assortment of polyfunctional nucleophiles is thereby achieved. Kinetic and computational studies provide evidence that site selectivity arises from stabilizing C–H/ π interactions between the catalyst and the nucleophile, analogous to those documented in sugar-binding proteins. This work demonstrates that highly selective glycosylation reactions can be achieved through control of stabilizing noncovalent interactions, a potentially general strategy for selective functionalization of carbohydrates.

Full Text

The challenge of distinguishing similarly reactive sites in molecules lies at the heart of organic synthesis and is illustrated particularly dramatically by the coupling of polyhydroxylated partners underlying the construction of oligosaccharides^{8,9}. While enzymes have evolved precise complex machineries to achieve site-selectivity in many molecular contexts including glycosylation^{10,11}, laboratory chemists have traditionally relied on the use of “protecting groups” to effectively circumvent the problem (Fig. 1a). Protecting-group strategies have been advanced to a sophisticated level and have long stood as a pillar of laboratory carbohydrate synthesis, enabling site-control and often influencing stereocontrol in a wide range of chemical glycosylations^{5,6,12}. However, the installation and removal of specific protecting groups requires multi-step synthetic sequences, and often results in steric and electronic deactivation of the unprotected hydroxyl groups that are the targets of reaction^{13,14}. Because of these intrinsic inefficiencies, protecting-group-free carbohydrate synthesis that is both highly site- and stereo-selective and broad in scope remains an important goal for the field of carbohydrate chemistry¹⁵.

There have been several important efforts to achieve non-enzymatic catalyst-controlled approaches to site selectivity in glycosylation reactions. One successful approach relies on the ability of certain Lewis acids to form cyclic covalent adducts with vicinal diols while selectively activating one of the transiently protected oxygens toward reaction^{16–20}. In this manner, *cis*-1,2-diols can be converted to cyclic adducts and induced to undergo selective glycosylations at the equatorial oxygen. α -Selective glycosylation of *trans*-diols was also demonstrated recently with a diboron catalyst, with site selectivity controlled by the

size of protecting groups on the nucleophiles rather than the catalyst²¹. Despite these successes, a general method for catalyst-controlled glycosylation of *trans*-diols to generate β -glycosides is still lacking.

We considered a different catalyst-controlled approach, one that is not dictated by the inherent stereochemical properties of the substrates but would instead take advantage of noncovalent interactions to activate a specific hydroxyl group (Fig. 1a). Carbohydrates are known to engage in various types of attractive noncovalent interactions, with extensive evidence for C–H/ π interactions between carbohydrates and electron-rich aromatic side chains in carbohydrate-protein complexes^{22–24}. Such interactions are pivotal to saccharide recognition and have been exploited to design synthetic receptors for carbohydrate binding^{25,26}. Precisely tailored catalysts capable of harnessing such interactions could enable site-selective glycosylation at hydroxyl groups previously inaccessible by strategies that rely on the catalytic formation of cyclic adducts. Although attractive noncovalent interactions have been utilized in site-selective protection of carbohydrates^{3,27–30}, examples of catalyst-controlled glycosylation where both stereo- and site selectivity are controlled by noncovalent interactions remain scarce and are generally only moderately selective^{31,32}.

With the goal of developing a catalyst-controlled stereo- and site-selective glycosylation reaction, we hypothesized that the recently reported stereospecific β -glycosylation approach catalyzed by precisely designed bis-thiourea derivatives could be applied to site-selectively functionalize minimally protected nucleophiles containing *trans*-diols (Fig. 1b).^{33–36} Bis-thiourea derivatives **ent-cat-1** and **cat-1** have been shown to catalyze highly β -selective glycosylation reactions with pyranosyl phosphates through a proposed dual general-base/general-acid activation mode, which allows for stereospecific couplings with a variety of protic nucleophiles.^{34,36} In initial studies, **ent-cat-1** was found to catalyze the galactosylation of unprotected monosaccharide **b-3a** with poor site selectivity (1:1.3 (1,2):(1,3)), slightly favoring the (1,3)-product; however, a switch in site preference and a dramatic increase in site selectivity (8.8:1 (1,2):(1,3)) were observed when **cat-1** was employed (Fig. 1b). The preference for (1,2)-glycosylation achieved with **cat-1** is complementary to the (1,3)-selectivity obtained with current cyclic-adduct activation methods^{16–20}. The dependence of site selectivity on catalyst absolute stereochemistry provided early evidence that selectivity originated from specific catalyst-substrate interactions, implying that further catalyst modifications might lead to enhanced selectivity.

The amide groups of catalysts such as **1** have been proposed to act as the general base responsible for nucleophile activation in glycosylation reactions, and variation of the arylpyrrolidino groups has been shown to affect the degree of stereospecificity in reactions of protected sugar nucleophiles.^{33–36} We hypothesized that altering the arylpyrrolidino amide components of the catalyst might also influence the

site-selectivity of glycosylation, so we systematically evaluated the effect of the aryl substituents on (1,2)-selectivity. The selectivity of galactosylation with **b-3a** was indeed found to be highly responsive to changes in the "northern" aryl pyrrolidine amides (Fig. 1b). While an unsubstituted pyrrolidine catalyst lacking the "northern" arene (**cat-2**) promoted unselective galactosylation, catalysts bearing different "northern" arenes (**cat-1, 3-6**) induced site selectivity that correlated with the electron density of the arene. The 5-*N*-methyl indole catalyst (**cat-6**) was thus identified as the optimal catalyst for site-selective galactosylation ((1,2):(1,3) = 17:1). In contrast, variation of the "southern" arene (**cat-1, 7-8**) had little influence on site selectivity, suggesting that only the "northern" arylpyrrolidino amide is involved in nucleophile recognition. As discussed in greater detail below, the positive correlation between site selectivity and the electron density of the "northern" arene suggests that attractive noncovalent interactions influenced by the electronic properties of the catalyst substituents may play a critical role in controlling site selectivity.

We adopted an analogous approach toward the development of catalysts for site-selective mannosylations (Fig. 1b). In contrast to the trend observed in galactosylation, site selectivity was observed to be most responsive to alterations of the "southern" arene (**cat-1, 7-8**) rather than the "northern" arene (**cat-1, 5-6**). The catalyst framework thus appears to promote glycosylation by engaging either of the two amido arylpyrrolidines as general bases depending on the identity of the electrophilic coupling partner. As observed in galactosylation, (1,2)-selectivity was sensitive to the electronic properties of the arene, with more electron-rich arenes affording higher selectivity. Incorporation of an electron-rich arene (2-naphthyl) on both "northern" and "southern" aryl pyrrolidines in an attempt to develop a universal catalyst for both galactosylation and mannosylation resulted in similar site selectivity but lower reactivity compared to **cat-7** (30% vs 60% conversion, see Supplementary Fig. S6). Thus, catalysts bearing specifically tuned "northern" and "southern" arylpyrrolidines afforded the best combination of site selectivity and reactivity, and **cat-6** and **cat-8** were selected for further studies of galactosylation and mannosylation, respectively.

With precisely tailored bis-thiourea catalysts thus identified, the scope of β -selective and site-selective galactosylation and mannosylation was explored (Fig. 2). β -Monosaccharides such as **b-3a-c** and minimally protected disaccharides containing a β -galactose or β -glucose motif (**3d-g, 3l-m**) underwent both reactions with high selectivity for the C-2 hydroxyl, with no observable over-glycosylation. β -Glucoside-containing pharmaceuticals and natural products (**3h-i, 3n**) also underwent glycosylation with synthetically useful levels of (1,2)-selectivity. The insensitivity of site selectivity to the identity of the β -anomeric group suggests that the anomeric substituent projects away from the key interactions with the catalyst that are responsible for imparting selectivity. However, the anomeric configuration of nucleophiles was found to have a profound impact on site selectivity, as α -monosaccharides (**a-3a** and **a-3b**) displayed significantly lower site selectivity (2.1:1 and 1:1.7 (1,2):(1,3) respectively).

We studied the divergent behavior of **a-** and **b-3a** with the hope of gleaning insight into the origins of catalyst-controlled site selectivity. Site selectivity for galactosylation of **a-** and **b-3a** were found to respond very differently to electronic perturbation of catalyst arenes (Fig. 3a). The site selectivity in galactosylation of **b-3a** increased as catalyst arenes became more electron-rich, while little variation in site selectivity was observed in galactosylation of **a-3a**. We hypothesized that the contrasting behaviors observed with **a-** and **b-3a** could result from their differing ability to effectively engage in CH/ π interactions with catalyst arenes in the glycosylation event. The strength and facial preference of such interactions is known to depend strongly on the sugar configuration: experimental and theoretical studies have shown that stacking preferentially occurs on the face presenting multiple axially oriented C–H bonds^{22,23,37,38}. We compared the experimental DDG[‡] derived from the (1,2):(1,3) ratio with computed interaction energies between β -galactose and different arenes. A good correlation was observed in the case of **b-3a**, while no statistically significant correlation was seen with **a-3a**. These observations support the hypothesis that, when not precluded due to steric effects, attractive CH/ π interactions can play a critical role in controlling site selectivity.

We explored the possibility of exploiting other catalyst features to enforce site control in the galactosylation of **a-3a**. Expansion of the catalyst “northern” aryl group to 1-naphthyl and replacement of the *tert*-leucine residue with alanine (**cat-9**) enabled the highly (1,2)-selective galactosylation of **a-3a** (16:1 (1,2):(1,3), Fig. 3b). Although the mechanisms of catalyst control are clearly distinct for the reactions of **a-3a** and **b-3a**, these intriguing results demonstrate the potential generality of a catalyst-controlled approach for achieving site selectivity and suggest that noncovalent interactions other than CH/ π interactions can be harnessed to impart site selectivity in glycosylation.

We sought to understand the mechanism by which CH/ π interactions in the selectivity-determining step lead to enhanced site selectivities. In theory, site selectivity could arise either from increased binding of a pre-reactive *pro*-(1,2) complex or from stabilization of the transition state leading to (1,2)-product. Prior kinetic analyses of glycosylation reactions promoted by **cat-1** demonstrated that a ternary phosphate•catalyst•nucleophile complex is accessible under catalytically relevant conditions³⁴. Michaelis–Menten kinetic analyses of reactions promoted by bis-thiourea **cat-6** bearing a 5-*N*-methyl indole substituent and the relatively unselective bis-thiourea **cat-2** bearing an unsubstituted pyrrolidine revealed that both catalyzed glycosylation with a similar Michaelis constant (K_M) (Fig. 4a). Therefore, the enhanced site selectivity cannot be attributed to the ability of **cat-6** to form more stable ternary complexes: instead, the faster maximum rate (k_{cat}) observed for **cat-6** indicates that the site selectivity induced by **cat-6** can be attributed to acceleration of the glycosylation step. The higher $k_{cat_{(1,2)}}$ and lower $k_{cat_{(1,3)}}$ for **cat-6** relative to **cat-2** indicates that higher site selectivity is achieved by accelerating the major (1,2)-pathway and decelerating the minor (1,3)-pathway. In separate studies, it was found that the analog of **b-3b** bearing benzyl protecting groups at all but the C-2 hydroxyl position was ca. 10 times less reactive than **b-3b** itself under otherwise identical catalytic conditions (Supplementary Table S6). Taken together, these observations highlight key advantages of non-covalent catalyst control relative to traditional protecting-group approaches: while neighboring protecting groups typically result in reduced

reaction rates due to steric congestion and electronic deactivation, non-covalent activation of the targeted site on unprotected nucleophiles relies on rate acceleration relative to the uncatalyzed pathway.

Density-functional theory calculations on the galactosylation of β -galactose were carried out to further investigate the origins of site selectivity. Both (1,2)- and (1,3)-transition states were located and found to feature an asynchronous S_N2 -like mechanism involving 4H-activation of the diphenylphosphate group and amide-mediated nucleophile activation (Fig. 4b). The computed general-base activation mechanism was consistent both with prior proposals and the experimental observation that replacing the “northern” amide with a thioamide, a weaker general base, resulted in diminished site selectivity (Supplementary Fig. S11). However, the predicted sense of site selectivity was opposite from that observed experimentally. We hypothesized that the disagreement with experimental results might be caused by poor modelling of solvation: while unprotected sugars are likely to engage in explicit hydrogen-bonding interactions with the ethereal solvent, these interactions will be poorly described by implicit solvent models.^{39,40} Indeed, QM/MM molecular dynamics simulations in explicit solvent suggest that the C-4 hydroxyl on the nucleophile engages in strong hydrogen-bonding interactions with the solvent. Replacing the poorly modelled C-4 hydroxyl with a methoxy resulted in a computed preference for reaction at the C2 hydroxyl, in line with experiment. Further explicit solvent calculations were used to construct a 2D free-energy surface for nucleophile binding to the “northern” amide-phosphate complex (Supplementary Fig. S18), and revealed the existence of three roughly isoenergetic minima corresponding to binding of the C2 hydroxyl, the C3 hydroxyl, or both to the amide group. This supports the conclusion drawn from kinetic studies that the observed (1,2)-selectivity arises from transition-state stabilization and not from preferential binding of one hydroxyl group in the nucleophile-bound ternary complex.

Analysis of the computed transition-state structures reveals that the (1,2)-transition state features markedly closer CH/ π contacts than the (1,3)-transition state, consistent with the increase in (1,2)-selectivity induced by electron-rich aryl groups (Fig. 4b). The differences can be understood intuitively by considering how general-base activation of the nucleophile affects the CH/ π interaction between the arene and the axial C–H bonds at C1, C3, and C5. Activation of the C3 hydroxyl group by the aryl pyrrolidine amide results in pulling the nucleophile away from the arene and weakening the interaction with the C3 methine. In contrast, amide-mediated activation of the C2 hydroxyl better preserves the CH/ π interactions between the nucleophile and the arene.

We have developed highly (1,2)-selective galactosylations and mannosylations of b-carbohydrates using bis-thioureas bearing electron-rich arenes. Structure–selectivity-relationship studies demonstrate the importance of CH/ π interactions between nucleophiles and catalyst arenes in controlling the site selectivity of glycosylation. Kinetic and computational analyses point to selective stabilization of the major (1,2)-pathway via attractive carbohydrate C–H-aromatic interactions. This work supports the notion

that carbohydrate-aromatic interactions can be leveraged productively in glycosylation reactions, and more broadly showcases the feasibility of exploiting attractive noncovalent interactions to achieve high stereo- and site control in small-molecule-catalyzed glycosylations.

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Declarations

Data availability

The data that support the findings in this work are available within the paper and Supplementary Information.

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Author contributions Q.L., S.M.L., A.E.W. and E.N.J. conceived the work, S.M.L., Q.L., A.E.W. and C.C.W. conducted the experiments, E.N.J. directed the research, and Q.L., S.M.L., C.C.W., and E.N.J. wrote the manuscript.

Competing interests The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at.

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Figures

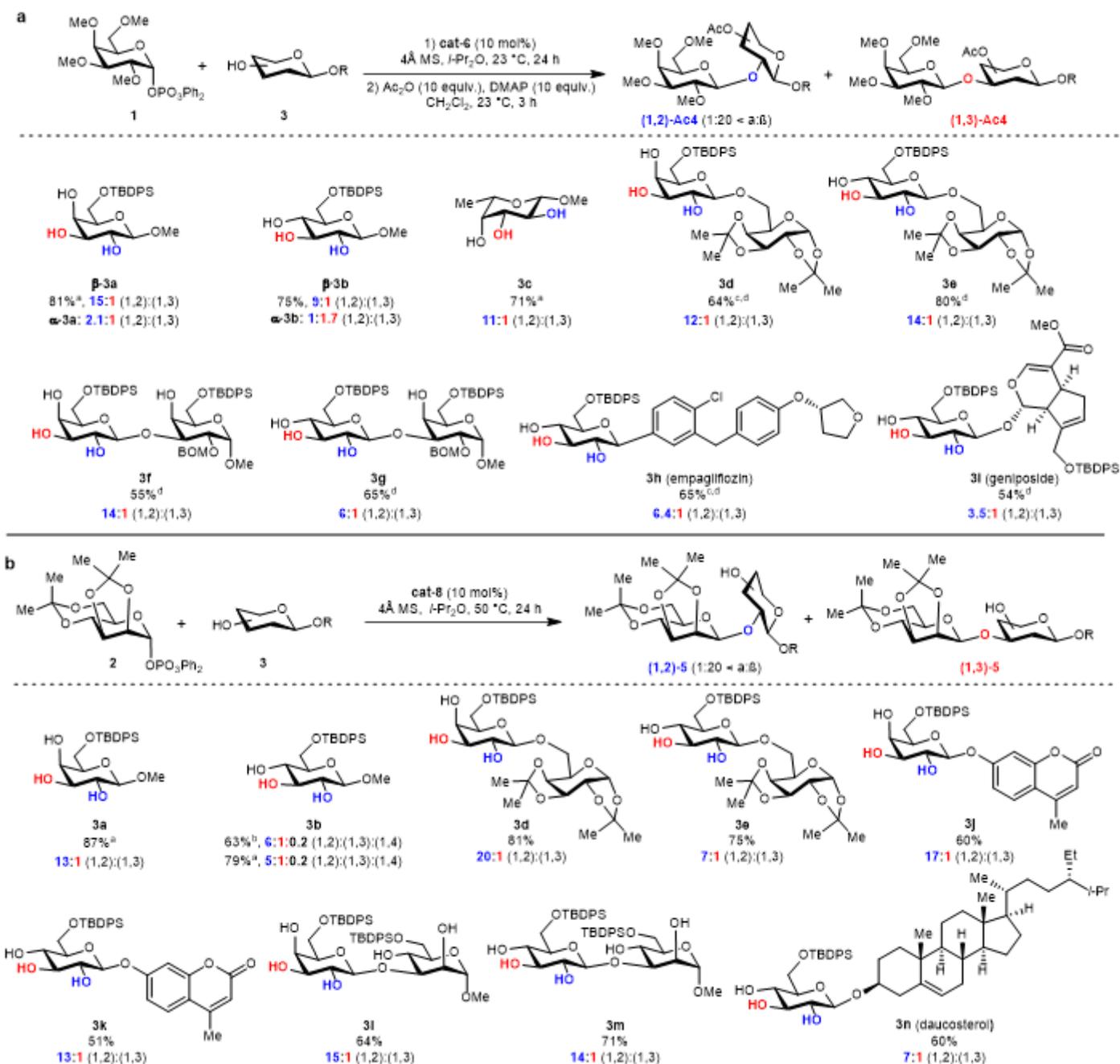


Figure 2

Scope studies. **a**, Nucleophile scope of site-selective galactosylations. **b**, Nucleophile scope of site-selective mannosylations. . High stereoselectivities (>20:1 β:α) were observed in every case. Selectivities were determined by ¹H NMR analysis of crude unacylated product mixtures. Yields of site-selective galactosylations reflect isolated yields of acylated (1,2)-product after the two-step galactosylation/acylation sequence. Yields of site-selective mannosylations reflect isolated yields of a mixture of unacylated (1,2)- and (1,3)-products. ^aReaction performed at 40 °C. ^bReaction performed at 23 °C. ^cReaction performed at 4 °C. ^d48 h reaction time. Additional substrates are provided in Supplementary Fig. S10.

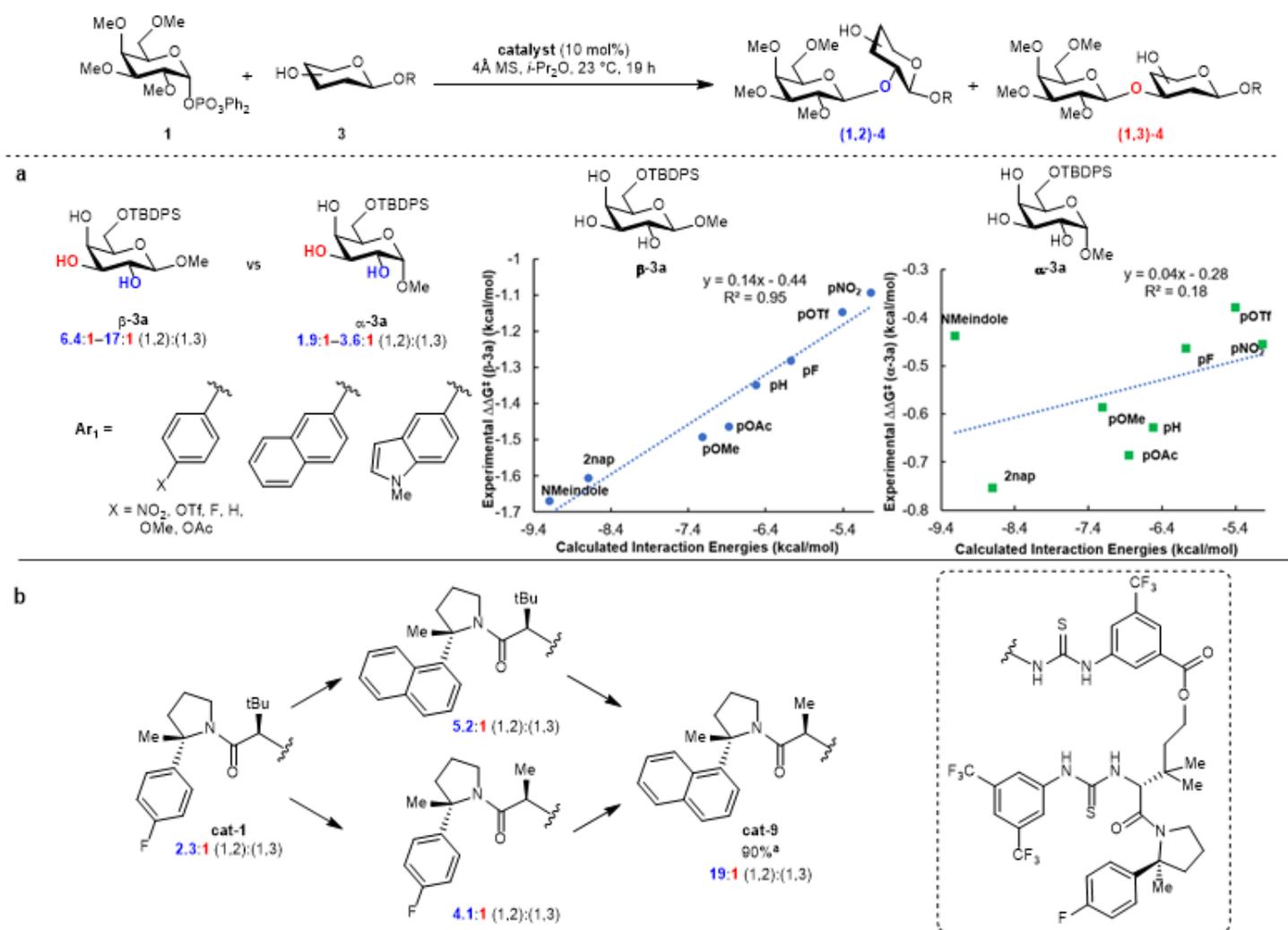


Figure 3

Linear-free-energy relationship study and catalyst optimization for galactosylation of **a-3a.** **a**, Correlation of experimental site selectivity ($\Delta\Delta G^\ddagger = -RT\ln(r.r.)$) with computed interaction energies between substituted catalyst arenes and galactose. **b**, Catalyst optimization for galactosylation of **a-3a**. Selectivities were determined by ^1H NMR analysis of crude unacylated product mixtures. ^a MTBE instead of isopropyl ether. Yields reflect isolated yields of acylated (1,2)-product after the two-step galactosylation/acylation sequence. Counterpoise corrections were performed to correct for basis set superposition error (BSSE) and obtain corrected electronic energies.

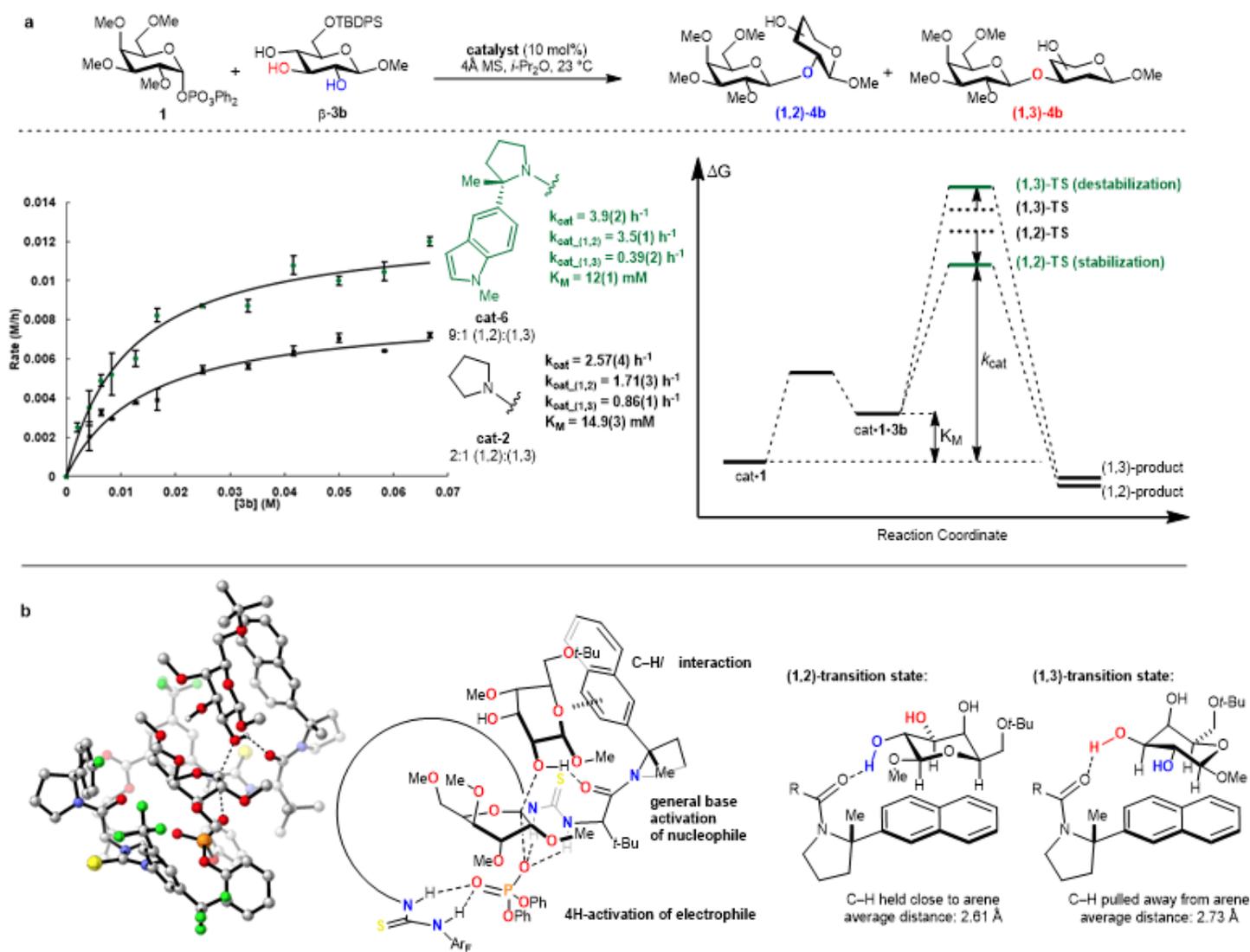


Figure 4

Kinetic and computational studies. **a**, Michaelis-Menten kinetic analyses of reactions catalyzed by (1,2)-selective **cat-6** and unselective **cat-2**. **b**, Computed (1,2)-transition state structure for galactosylation of β -galactose and differences in CH/ π contacts between (1,2)- and (1,3)-transition states. Selectivities were determined by 1H NMR analysis of crude unacylated product mixtures.

Supplementary Files

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