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Highly stereoselective synthesis of α-glycosylated carboxylic acids by phenanthroline catalysis†

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Carbohydrate molecules with an α-glycosylated carboxylic acid motif provide access to biologically relevant chemical space but are difficult to synthesize with high selectivity. To address this challenge, we report a mild and operationally simple protocol to synthesize a wide range of functionally and structurally diverse α-glycosylated carboxylic acids in good yields with high diastereoselectivity. Although there is no apparent correlation between reaction conversion and pK_a of carboxylic acids, we found that carboxylic acids with a pK_a of 4–5 provide high selectivity while those of a pK_a of 2.5 or lower do not. Our strategy utilizes readily available 2,9-dibutyl-1,10-phenanthroline as an effective nucleophilic catalyst to displace a bromide leaving group from an activated sugar electrophile in a nucleophilic substitution reaction, forming phenanthrolinium intermediates. The attack of the carboxylic acid takes place from the α-face of the more reactive intermediate, resulting in the formation of α-glycosylated carboxylic acid. Previous calculations suggested that the hydroxyl group participates in the hydrogen bond interaction with the basic C2-oxygen of a sugar moiety and serves as a nucleophile to attack the C1-anomeric center. In contrast, our computational studies reveal that the carbonyl oxygen of the carboxylic acid serves as a nucleophile, with the carboxylic acid-OH forming a hydrogen bond with the basic C2-oxygen of the sugar moiety. This strong hydrogen bond (1.65 Å) interaction increases the nucleophilicity of the carbonyl oxygen of carboxylic acid and plays a critical role in the selectivity-determining step. In contrast, when alcohol acts as a nucleophile, this scenario is not possible since the –OH group of the alcohol interacts with the C2-oxygen and attacks the C1-anomeric carbon of the sugar moiety. This is also reflected in alcohol-OH's weak hydrogen bond (1.95 Å) interaction with the C2-oxygen. The O(C2)–HO (carboxylic acid) angle was measured to be 171° while the O(C2)–HO (alcohol) angle at 122° deviates from linearity, resulting in weak hydrogen bonding.

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Introduction

Carboxylic acids are widely used in various applications for human health.[1] They are found in amino acids[2] and fatty acids,[3] contributing to the development of cell membranes, controlling nutrient utilization, and regulating metabolism within the human body. Additionally, they are used in the production of polymers,[4] biopolymers,[5] and pharmaceutical drugs.[6] In addition, α- and β-glycosylated carboxylic acids (also referred to as glycosyl esters), whose monosaccharide and oligosaccharide are incorporated with carboxylic acid moieties at the C1-anomeric carbon, are found in natural products[7] and pharmaceutical drugs (Fig. 1a).[8] Glycosyl esters have also been reported as effective electrophilic donors due to their operational stability and ease of activation by transition metals (Fig. 1b).[9–14] Therefore, robust and stereoselective protocols for the synthesis of α- or β-glycosyl esters are crucial, especially α-glycosyl esters that are attractive biomolecules and privileged donors in stereoselective glycosylations.[9,10,14] However, access to their synthesis remains challenging,[9,11,12,15] as a mixture of α- and β-glycosyl esters is often produced. In some cases, the newly-formed α-glycosyl esters need to be separated from their β-counterparts before their use as glycosyl electrophilic donors in the stereospecific glycosylation reactions (Fig. 1b).[9,10]

Glycosylated carboxylic acid is typically formed through a nucleophilic substitution reaction, in which a carboxylic acid or carboxylate anion displaces a leaving group from an activated carbohydrate electrophile (Fig. 2a).[16] This C–O bond-forming reaction creates a new stereocenter at the C1-carbon, wherein the α-1,2-*cis*- and/or β-1,2-*trans*-glycosyl ester (viewed in respect to C2 of carbohydrate moiety) could be formed.[16] However, achieving highly stereoselective formation of glycosyl esters can be challenging and unpredictable due to the variable nature of sugar electrophilic partners.[17] Various factors, such as protecting groups, specific reagents, temperature, and

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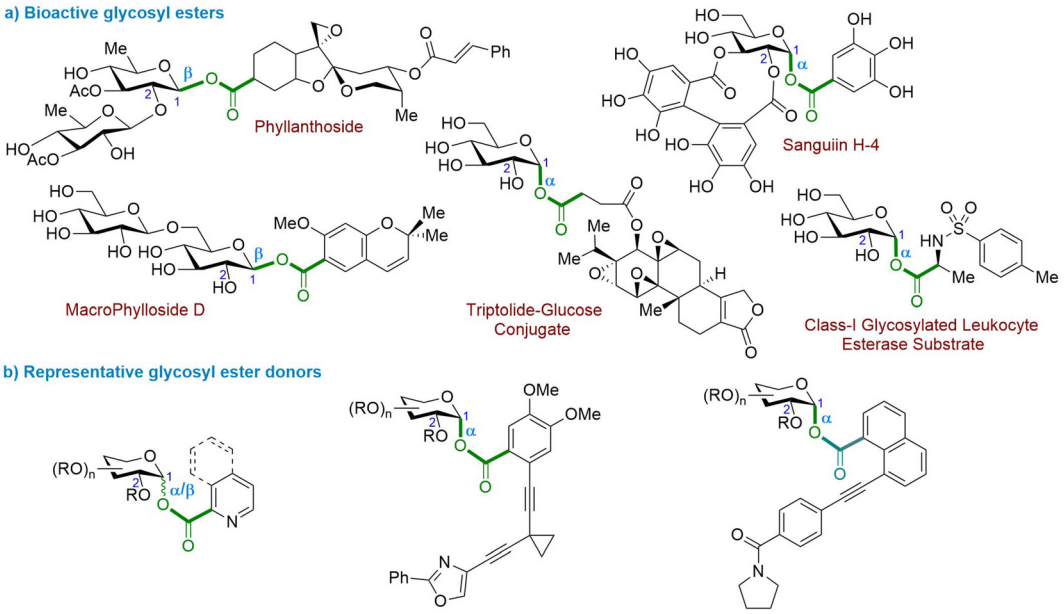


Fig. 1 (a) Representative biologically relevant glycosyl ester molecules. (b) Glycosyl esters as electrophilic donors.

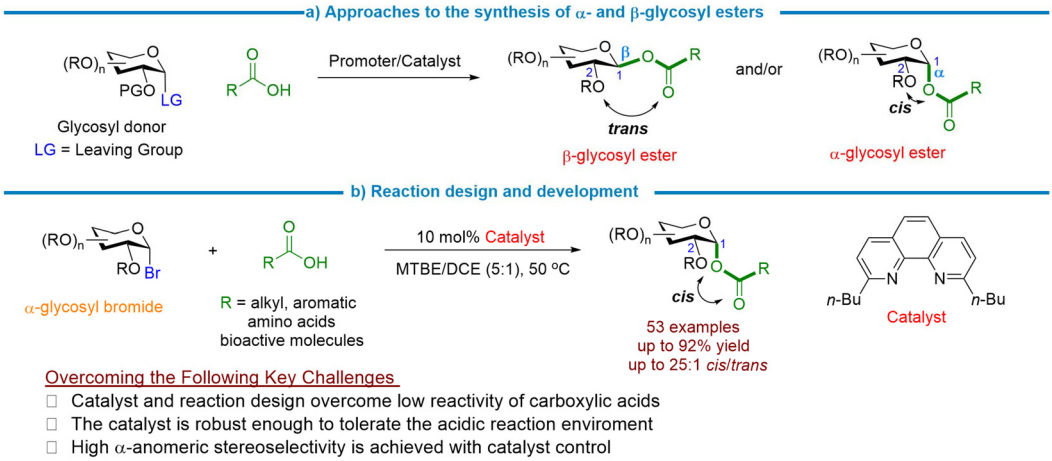


Fig. 2 (a) General glycosylation methodologies for synthesizing α- and β-glycosyl esters. (b) Reaction design and development.

solvents, significantly influence the stereochemical outcome of the glycosylation products.[18] Glycosylation strategies that utilize a Lewis basic protecting group at the C2 position of glycosyl donors afford β-1,2-*trans*-glycosyl esters (also referred to as β-glycosyl esters).[19–21] However, this approach cannot be used for the diastereoselective construction of α-1,2-*cis*-glycosyl esters (also referred to as α-glycosyl esters) because of the absence of the C2-Lewis basic protecting groups. Given the importance of α- and β-glycosyl esters, several alternative strategies have been developed to construct these motifs.[22–28]

Despite recent advancements, the stereoselective synthesis of α-glycosyl esters bearing aliphatic and aromatic carboxylic acids remains limited.[23–25] Aiming to expand the availability of glycosylation methods for creating biomedically relevant sugar libraries for tool development and research applications, small-molecule catalysts have emerged as a promising strategy to broaden the chemical space of glycosylation reactions. Our group[29–33] and others[34] discovered that small molecule catalysts can promote the selective addition of alcohols to glycosyl donors, producing α-*O*-glycosides. While there are reports on the selective coupling of aliphatic carboxylic acids,[22] reactions with aromatic carboxylic acids remained underdeveloped, likely due to the lower reactivity of aromatic carboxylic acids compared to aliphatic carboxylic acids.[26]

Our group recently discovered that readily available phenanthrolines can effectively catalyze the stereoselective addition of alcohol nucleophiles to glycosyl bromide donors.[29–33] The extension of this strategy to carboxylic acids remains unknown

due to the reactivity and acidity difference between alcohol and carboxylic acid. To achieve the stereoselective synthesis of α-glycosylated carboxylic acids, the catalyst and reaction design must overcome the low reactivity of carboxylic acids to ensure efficient reaction and high α-selectivity. Small-molecule catalysts used for glycosylation must withstand acidic conditions without being too basic to deprotonate carboxylic acid. Herein, we describe a new glycosylation methodology for the diastereoselective construction of α-glycosylated carboxylic acids based on the readily available 2,9-dibutyl-1,10-phenanthroline catalyst to facilitate the coupling of aliphatic and aromatic carboxylic acids with glycosyl bromide donors (Fig. 2b). DFT computations have revealed that hydrogen bond interactions between the carboxylic acid-OH and the C2-oxygen of a sugar moiety enable α-selectivity and enhance the nucleophilicity of the carbonyl oxygen to attack the C1-anomeric carbon. We have demonstrated the utility of this new protocol by efficiently constructing a variety of α-glycosyl esters containing biologically relevant carboxylic acids in good yields with excellent selectivity.

Results and discussion

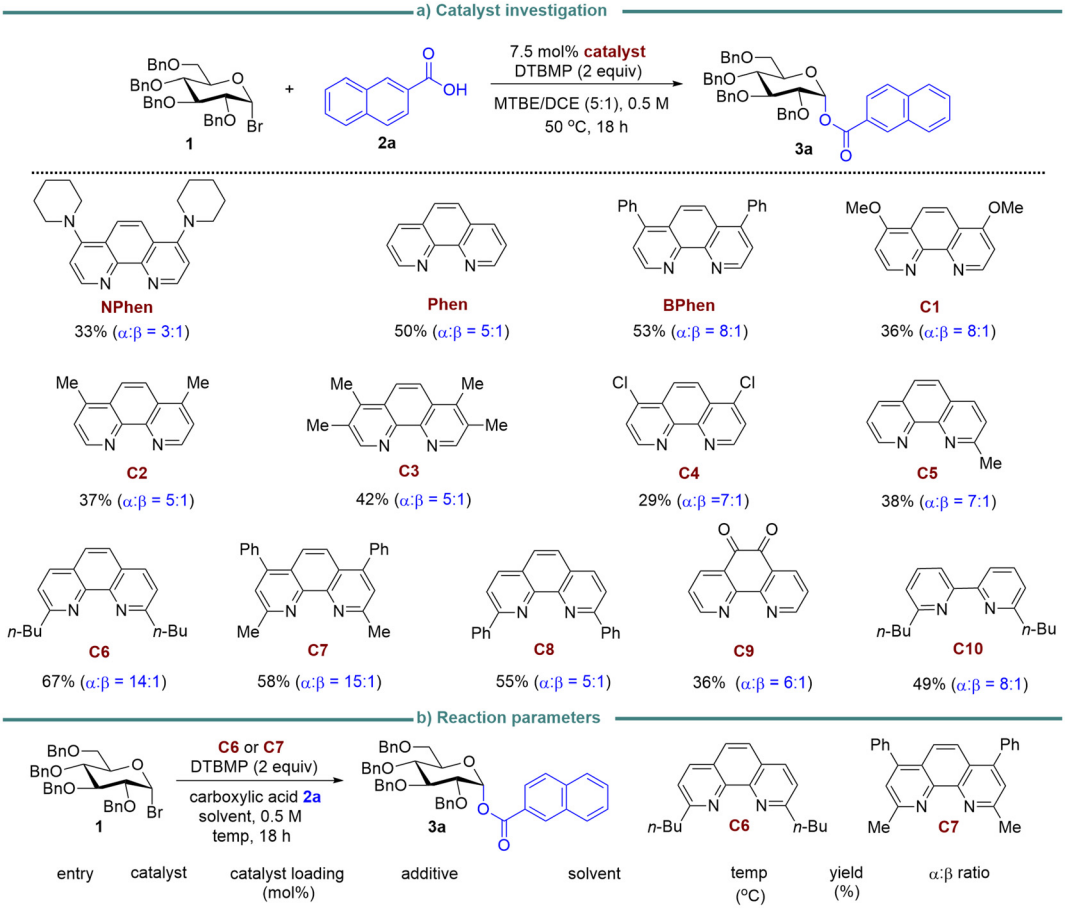
The use of readily available phenanthroline catalysts provides a range of options for finding the optimal catalyst. In a model reaction, the coupling of 2-naphthoic acid **2a** with glycosyl bromide **1** was investigated (Table 1a). Initially, our previously reported 4,7-piperidine-1,10-phenanthroline (NPhen) was used as the catalyst,[29–31] which resulted in poor yield (33%) and low α-selectivity ($\alpha:\beta$ = 3 : 1) of glycosyl ester **3a**. It was speculated that the 4,7-piperidine substituents might be basic enough to deprotonate carboxylic acid, inhibiting catalyst activity. This led us to consider unsubstituted 1,10-phenanthroline (Phen), which provided an improvement in both yield (33% → 50%) and selectivity ($\alpha:\beta$ = 3 : 1 → 5 : 1). A further enhancement ($\alpha:\beta$ = 5 : 1 → 8 : 1) was observed with the 4,7-diphenyl-1,10-phennathroline (BPhen) catalyst.[32] Other 4,7-substituted phenanthroline catalysts (**C1–C4**) resulted in reduced yield and/or selectivity. Evaluating 2,9 substituents on the phenanthroline framework confirmed their ability to modulate reaction reactivity and selectivity. For instance, 2,9-disubstituted alkyl catalysts (**C6** and **C7**) significantly increased the α-selectivity of **3a** ($\alpha:\beta$ = 14 : 1–15 : 1). However, increasing the steric bulk of the 2,9-disubstituted substituent (**C8**) diminished both the yield and selectivity of product **3a**. The 9-monosubstituted (**C5**) and the 5,6-di-ketone (**C9**) catalysts decreased both yield and α-selectively. The 6,6′-dibutyl-2,2′-bipyridine (**C10**) catalyst exhibited lower α-selectivity and conversion than the phenanthroline **C6** catalyst (Table 1a).

Given that **C6** and **C7** are the most effective phenanthroline catalysts, we assessed the impact of reaction parameters (Table 1b). The increase in catalyst loading to 10 mol% further improved the yield and α-selectivity of **3a** (entries 3 and 4). Notably, **C6** outperformed **C7** (85% *vs.* 65%). As a result, we employed **C6** to optimize reaction conditions. It was observed that reaction rate and selectivity are influenced by temperature. At 25 °C, the reaction proceeded slowly, drastically reducing yield and α-selectivity (entry 5). This outcome is likely due to the low reactivity of carboxylic acid **2a** and the slow equilibration of the less reactive phenanthroline intermediate to the more reactive isomer at 25 °C.[29,33] Solvent evaluations indicated that a 5 : 1 mixture of MTBE and DCE solvent (entry 4) gave rise to higher α-anomeric selectivity. Conversely, using MTBE (entry 6) or DCE (entry 7) individually led to decreased α-selectivity. It was found that the presence of **C6** and acid scavenger 2,6-di-*tert*-butylmethyl pyridine (DTBMP) is essential to achieve both high product yield and α-selectivity (entries 8–10). For comparison, we conducted the reaction with silver triflate known to activate glycosyl bromide,[35] and product **3a** did not form (entry 11). Collectively, the optimal reaction conditions, employing 10 mol% of 2,9-dibutyl-1,10-phenanthroline **C6** in MTBE/DCE (5 : 1) at 50 °C for 18 h, yielded **3a** in 85% NMR yield with $\alpha:\beta$ = 19 : 1 (Table 1b, entry 4).

Next, a series of benzoic acids were examined to assess their relative reactivity and selectivity. It was observed that the pK_a of carboxylic acids has a significant impact on both product yield and α-selectivity based on a subset of benzoic acids listed in Table 2. Specifically, electron-donating benzoic acids with pK_a values of 3.84–4.22 resulted in high α-selectivity ($\alpha:\beta$ = 11 : 1–20 : 1) and good yield (59–88%) for products **3a–3g** (Table 2). Conversely, electron-withdrawing benzoic acids with pK_a values of 1.48–3.65 produced **3h–3m** in lower α-selectivity (Table 2). Benzoic acids with pK_a values of 2.9–3.7 produced **3h–3j** in moderate to good diastereocontrol ($\alpha:\beta$ = 5 : 1–9 : 1), while carboxylic acids with pK_a values of 2.5 or lower showed unsatisfactory selectivity (**3k–3m**). The decrease in reactivity of catalyst **C6** as the pK_a of the benzoic acid decreases can be attributed to the likely protonation of its pyridine nitrogen atoms (see Fig. S4†), leading to a shift in the reaction closer to the S_N1 end. Notably, reactions with nitro-substituted benzoic acids **2i** and **2k** were sluggish, and the α-glycosylated products **3i** and **3k** were obtained in lower yields (~32%) relative to other benzoic acids (47–88%).

Next, we investigated a series of aromatic, heteroaromatic, and unsaturated carboxylic acids with a pK_a ~4 (Table 3) to establish the scope and limitation. The coupling of three benzoic acids with both electron-donating and electron-withdrawing groups yielded α-glycosyl esters **4–6** in good yield (58–89%) and selectivity ($\alpha:\beta$ = 15 : 1–18 : 1). Heterocyclic-2-carboxylic acids, commonly found in various pharmaceuticals,[36] also produced **7–10** in 66–79% yield with $\alpha:\beta$ = 15 : 1–21 : 1. Indole-2-carboxylic acid **11** exhibited slightly lower selectivity ($\alpha:\beta$ = 9 : 1). Cinnamic acid proved to be an excellent nucleophile, producing **12** in 73% yield with excellent selectivity ($\alpha:\beta$ = 20 : 1). A number of aliphatic carboxylic acids, such as levulinic acid and palmitic acid, reacted to produce **13–15** with $\alpha:\beta$ = 10 : 1–20 : 1.[37] Glycosylated ibuprofen **16** was readily synthesized in 60% yield with $\alpha:\beta$ = 20 : 1. Reaction with hindered cyclohexane-, pyran- and piperidine-4-, and 1-adamantane-carboxylic acid resulted in **17–20** in 74–92% yield with $\alpha:\beta$ = 17 : 1–20 : 1. Glycosyl esters **21–23** were synthesized from indomethacin,

Table 1 Reaction optimization studies



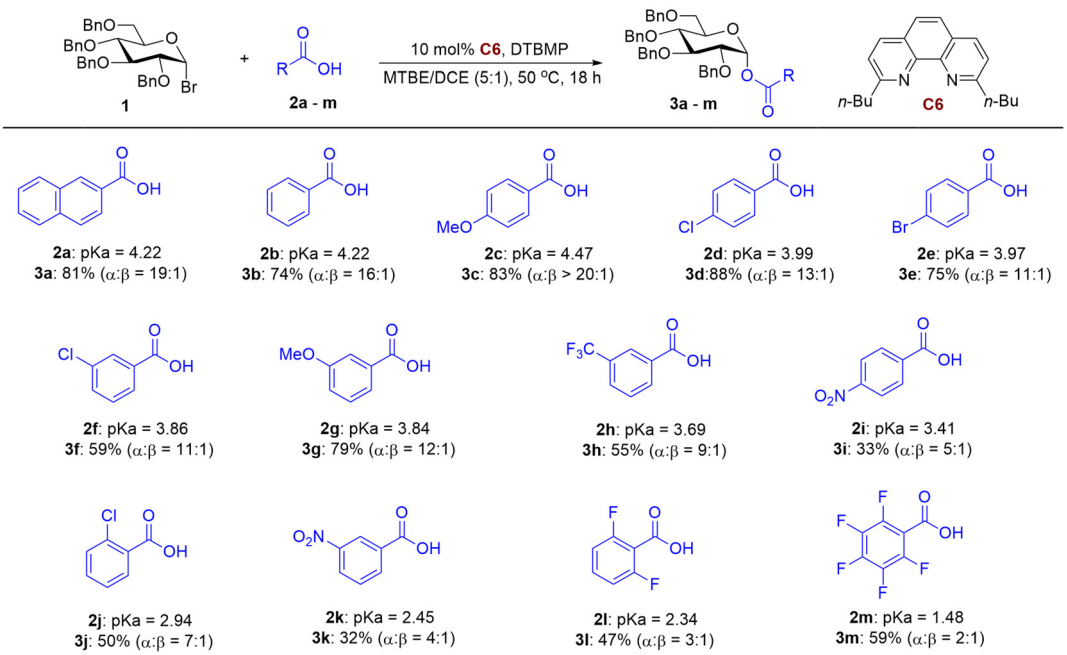
Entry	Catalyst	Catalyst loading (mol%)	Additive	Solvent	Temp. (°C)	Yield (%)	$\alpha:\beta$ ratio
1	**C6**	7.5	DTBMP	MTBE/DCE (5 : 1)	50	67	14 : 1
2	**C7**	7.5	DTBMP	MTBE/DCE (5 : 1)	50	58	15 : 1
3	**C7**	10	DTBMP	MTBE/DCE (5 : 1)	50	65	19 : 1
4	**C6**	10	DTBMP	MTBE/DCE (5 : 1)	50	85	19 : 1
5	**C6**	10	DTBMP	MTBE/DCE (5 : 1)	25	14	10 : 1
6	**C6**	10	DTBMP	MTBE	50	54	13 : 1
7	**C6**	10	DTBMP	DCE	50	57	5 : 1
8	**C6**	10	None	MTBE/DCE (5 : 1)	50	12	8 : 1
9	None	None	DTBMP	MTBE/DCE (5 : 1)	50	28	5 : 1
10	None	None	None	MTBE/DCE (5 : 1)	50	Trace	ND
11	AgOTf	200	None	MTBE/DCE (5 : 1)	50	Trace	ND

[a] The reaction was carried out with glycosyl bromide **1** (0.2 mmol), **2a** (0.1 mmol), and catalyst (7.5 mol%) with respect to donor **1**. [b] The reaction was carried out using donor **1** (0.2 mmol), **2a** (0.1 mmol), **C6** or **C7** (7.5–10 mol%) with respect to donor **1**. The crude product's yield and α/β or ratio were determined by ^{1}H NMR using 1,3-dinitrobenzene as an internal standard.

deoxycholic acid, and oleanolic acid, respectively, in 63–87% yield with high diastereocontrol ($\alpha:\beta$ = 17 : 1–20 : 1). We also attempted glycosylation of amino acids. Products **24–27** were formed with varying selectivity ($\alpha:\beta$ = 8 : 1–20 : 1). We observed that Fmoc-protected proline, with a pK_a value similar to that of a typical carboxylic acid (pK_a ~4–5),[38] exhibited more α-selectivity compared to other Fmoc-protected cysteine and tryptophan amino acids with a pK_a value of around 3.3.

Altering sugar structures with distinct stereochemistry or protecting groups located away from the C1-coupling site can significantly affect the reactivity and selectivity of the reaction.[39] We investigated whether the developed protocol could override substrate effects. Initially, we examined the coupling of four aliphatic and aromatic carboxylic acids with benzyl-protected L-fucose electrophile (see Table 4a). We successfully obtained coupling products **28–31** in 62–69% yield with excellent selectivity ($\alpha:\beta$ = 16 : 1–20 : 1). Encouraged by these results, we further assessed whether **C6** catalyst could selectively promote the formation of α-glycosyl ester resulting from the coupling of the heterocyclic carboxylic acid with

Table 2 Effect of pK_a of carboxylic acids on reaction reactivity and selectivity[a]



[a] The reaction was carried out with glycosyl electrophilic bromide **1** (0.2 mmol), **2a–2m** (0.1 mmol), **C6** catalyst (10 mol%) with respect to glycosyl bromide **1**, DTBMP (2 equiv.) at 50 °C in 5 : 1 MTBE/DCE for 18 h. Isolated yield of the purified product was calculated. The α/β ratio was determined by ^{1}H NMR of the crude product.

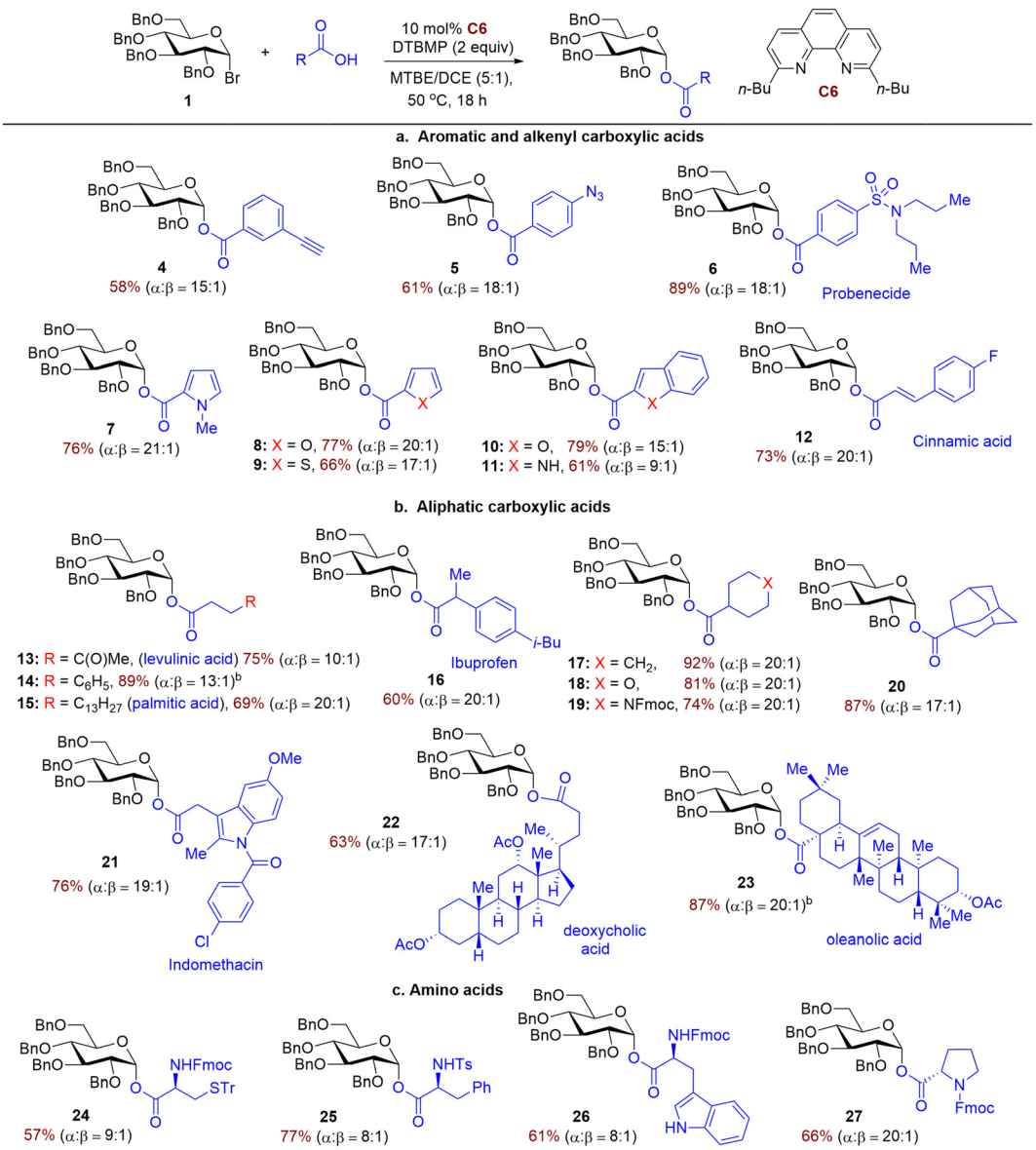
D-galactosyl bromide bearing an axial C(4) group.[40] Galactosylated carboxylic acids **32** and **33** were obtained with good α-selectivity ($\alpha:\beta$ = 8 : 1), indicating that this catalysis protocol is partially α-selective of D-galactose substrate. In contrast, using phase-transfer glycosylation conditions (K_2CO_3 and TBABr)[41] afforded **32** in 69% yield with poor selectivity ($\alpha:\beta$ = 1 : 2), favoring the expected β-isomer. The absence of the C6-methylhydroxyl renders D-xylose and L-arabinose substrates more likely to proceed *via* S_N1 pathways.[42] Nevertheless, the use of a **C6** catalyst partially overrides the inherent bias of the substrate, resulting in arabinosyl esters **34** and **35** in 78% and 67% yield, respectively, with synthetically useful β-selectivity ($\alpha:\beta \sim 8:1$). A similar selectivity trend was also observed with D-xylose, affording **36** with moderate stereocontrol ($\alpha:\beta$ = 6 : 1).

Next, we evaluated the scope and limitations of the established protocol with the more electron-withdrawing 2-azido-D-glucosyl bromide (Table 4a).[43] As expected, the reaction with the less reactive 2-azido-D-glucose substrate was slow, resulting in **37** in 33% yield albeit with high selectivity ($\alpha:\beta$ = 15 : 1). The *cis*-1,2-*O*-glycosylation of D-mannosyl bromide is strongly disfavored, both sterically and electronically.[44] Consequently, the glycosylation of D-mannosyl bromide with carboxylic acids predominantly yielded **38** and **39** as the 1,2-*trans*-α-products (Table 4a). In our study of phenanthroline-catalyzed glycosylation of alcohol nucleophiles, we observed that the type of furanosyl bromide donors significantly affect the selectivity of the furanosyl product.[32] This has prompted us to explore whether this trend also applies to carboxylic acid nucleophiles. Our findings with products **40–42** (Table 4a) indicate that regardless of their stereochemical nature, we consistently obtained moderate α-selectivity for furanosyl substrates. We also evaluated the potential extension of the developed protocol to the unprotected amide. Our findings revealed that no reaction was observed. Additionally, it was noted that this protocol is not well-suited for a regioselective reaction when the acceptor bears two unprotected carboxylic acids.

The question remains whether the phenanthroline catalysis system could be used for the highly α-selective synthesis of glycosyl ester donors. To demonstrate this potential, we examined the coupling of several carboxylic acids with glucosyl bromide **1** (Table 4b). Both glycosyl ester products **43** and **44** were previously synthesized as a mixture of α- and β-isomers.[11,15] In our approach, the **C6** catalyst proved effective in providing highly α-selective products **43** ($\alpha:\beta$ > 20 : 1) and **44** ($\alpha:\beta$ = 15 : 1). It is challenging to obtain α-glycosyl ester **45** in high yield and selectivity as it can undergo 6-*endo-dig* cyclization to form six-membered ring lactone.[12] Nevertheless, product **45** was formed with excellent diastereocontrol ($\alpha:\beta$ = 20 : 1) despite a low yield (33%). Finally, glycosylated carboxylic acid **46**, the key intermediate of α-glycosyl ester donor bearing an amide-directing group (see Fig. 1b), was obtained in 75% yield with $\alpha:\beta$ > 20 : 1.[9]

Next, we initiated our mechanistic studies by examining the reaction of glucosyl bromide **1** with phenanthroline **C6** (Fig. 3a). Although the pyranosyl phenanthrolinium ion intermediate **1a** could not be detected by ^{1}H NMR, it was confirmed

Table 3 Scope of aromatic and aliphatic carboxylic acids[a]

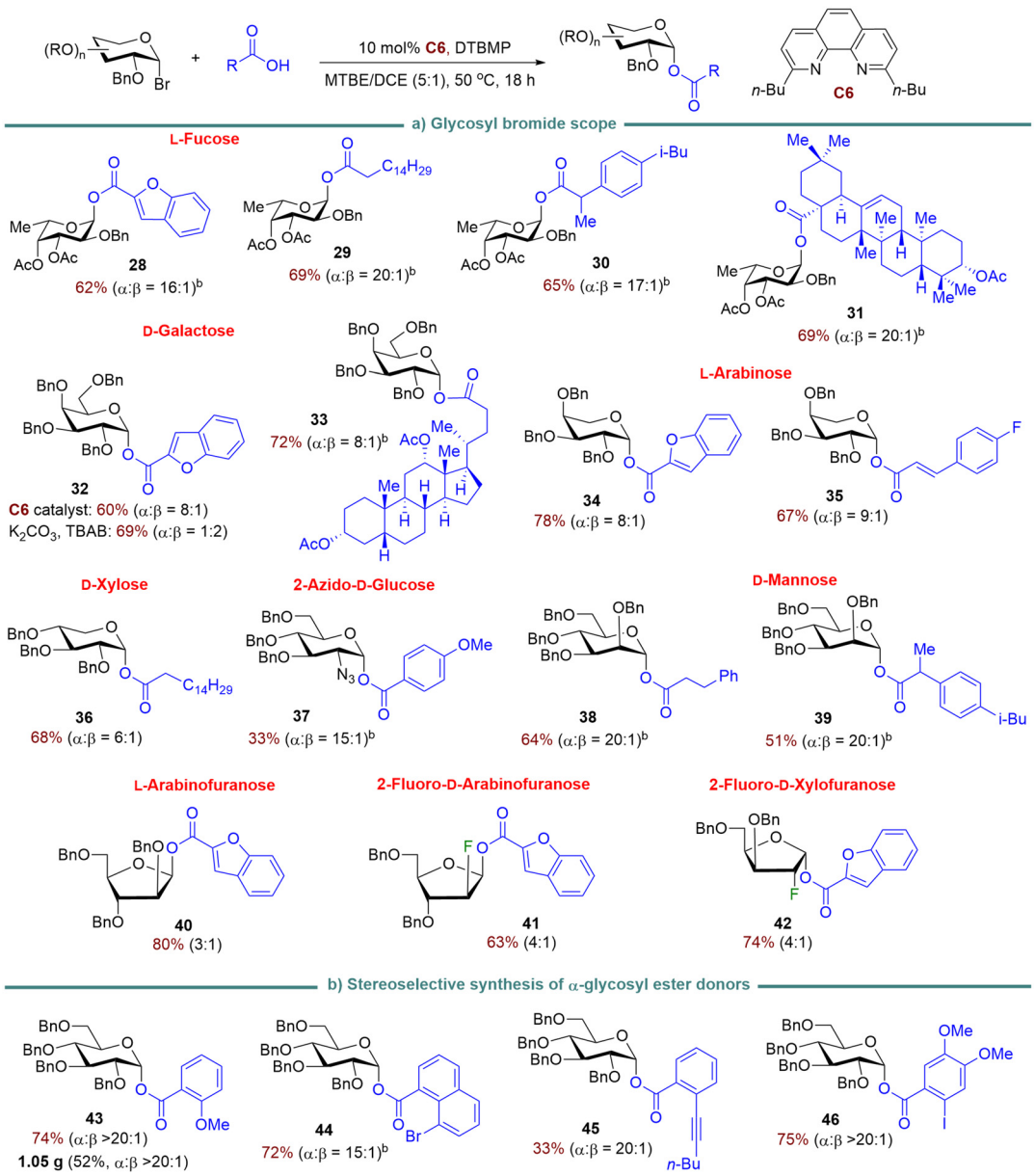


[a] The reaction was carried out with glycosyl bromide **1** (0.2 mmol), carboxylic acid (0.1 mmol), **C6** (10 mol%). Isolated yield was calculated, and α/β or ratio was determined by ^{1}H NMR of the crude product [b] Donor **1** (0.3 mmol), carboxylic acid (0.1 mmol), and **C6** (7 mol%)

by ESI mass spectrometry (Fig. 3b). This finding implies that the glycosyl phenanthrolinium ion intermediate **1a** is likely to revert to the initial bromide donor **1**.[29,30] However, when carboxylic acid **2a** was added, product **3a** formed in similar yield and α-selectivity to that obtained under optimized conditions (see Table 1b, entry 4). We also subjected α- and β-glycosyl ester **3a** to the optimized conditions and found no change in the anomeric ratio (Fig. S3†), indicating that the high α-selectivity is not the result of anomerization.

In our NMR experiment, we observed that 2,6-di-*tert*-butylmethyl pyridine (DTBMP) is not a sufficiently strong base to deprotonate 2-naptholic acid **2a** in deuterated chloroform forming carboxylate (Fig. S4†). To further confirm if carboxylate could directly attack the reacting β-phenanthrolinium ion intermediate,[31] sodium carboxylate **47** was subjected to the reaction with glucosyl bromide **1** in the presence and the absence of **C6** catalyst (Fig. 3b1). We found poor yield and α-selectivity for product **3a** in both cases, likely due to the solubility of sodium carboxylate **47**. Control experiments were carried out to address this solubility issue in the presence of a strong base, penta-methylpiperidine (PMP). It is hypothesized that PMP, with pK_a value of 11.5, could effectively deprotonate carboxylic acid *in situ*. Accordingly, **3a** was obtained with excellent yield (88–93%) despite low selectivity ($\alpha:\beta$ = 3 : 1) in the presence or absence of **C6** (Fig. 3b2). These results suggest that the reaction of carboxylic acid with glycosyl bromide does not occur *via* a direct S_N2 pathway.

Table 4 Scope of glycosyl bromides and stereoselective synthesis of α-glycosyl ester donors[a]



[a] The reaction was carried out using glycosyl bromide (0.2 mmol), carboxylic acid (0.1 mmol), **C6** (10 mol%) with respect to glycosyl bromide, DTBMP (2 equiv.) at 50 °C in 5 : 1 MTBE/DCE for 18 h. Isolated yield was calculated. ^{1}H NMR of the crude product determined the *α*/*β* ratio. (a) Coupling of donors with carboxylic acids. (b) Stereoselective synthesis of α-glycosyl ester donors. [b] Glycosyl bromide (0.3 mmol), carboxylic acid (0.1 mmol), and **C6** (7 mol%) with respect to glycosyl bromide.

Next, we conducted a comparison experiment involving the reaction of aromatic carboxylic acid **2a** with glycosyl bromide **1** using benzo[h]quinoline (**C11**, Fig. 3b3). It was observed that the **C11** catalyst, in contrast to the phenanthroline **C6** catalyst, exhibited lower reactivity and α-selectivity, resulting in **3a** in a yield of only 36% and moderate selectivity ($\alpha:\beta = 5:1$). This finding confirms the significance of the second nitrogen atom of phenanthroline in influencing the reactivity and selectivity of the reaction. Previous NMR evidence has indicated the existence of a hydrogen bonding interaction between the second nitrogen of phenanthroline and the C1-anomeric proton. This hydrogen bond interaction stabilizes the reacting β-phenanthrolinium ion complex, thereby enhancing the attack of carboxylic acid on its α-face.

It has been reported that the hydrogen bonding interaction between the alcohol-OH and C2-oxygen of a carbohydrate unit plays a crucial role in modulating reaction selectivity.[45] To elucidate this interaction, a control experiment was performed using 2-deoxy-glucosyl bromide **45** (Fig. 3c) to probe the nature of the interaction of carboxylic acid-OH with the Lewis basic

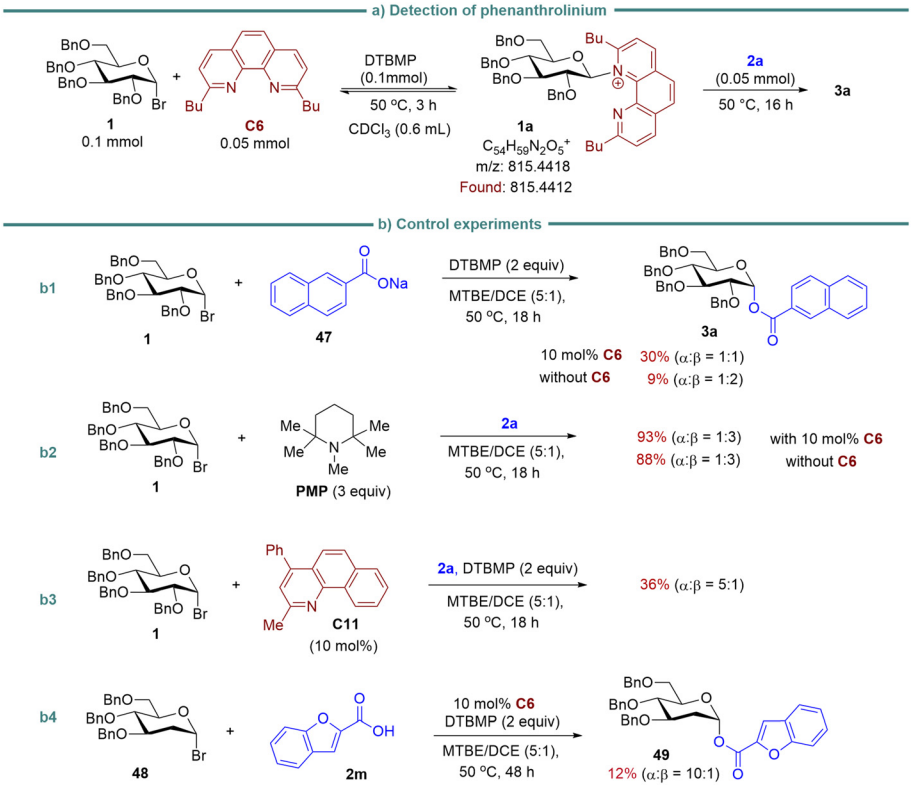


Fig. 3 (a) Detection of phenanthrolinium ion intermediate. (b) Control experiments.

C2-oxygen of a carbohydrate moiety. The 2-deoxy substrate was unstable under our reaction conditions, leading to significant decomposition. Consequently, the desired α-2-deoxy glycosyl ester **46** was obtained in only 12% yield (Fig. 3d), albeit with good selectivity ($\alpha:\beta = 10:1$). As a result, drawing a conclusive inference from the study with 2-deoxy donor substrate **45** is impeded due to the potential decomposition of the β-product at a faster rate than the α-product.

To determine the hydrogen bonding interaction between the carboxylic acid-OH and the C2-ether oxygen of the sugar substrate, we need to evaluate the chemical shift of the sugar C2-carbon. This will help us determine if it has a more pronounced shift than the adjacent carbons of other ether linkages. However, we cannot specifically measure the chemical shift of the sugar C2-carbon using ^{13}C NMR because the hydrogen bonding interaction takes place in the transition state. Therefore, we examined the correlation between the ^{13}C NMR chemical shift for the carbonyl carbon of carboxylic acid **2b** to determine potential hydrogen bond interactions between benzoic acid-OH and the basic oxygen atoms of glucoside **50**. We selected benzoic acid **2b** as a model nucleophile. We carried out ^{1}H NMR titrations in $CDCl_3$ at 25 °C to determine the complexation-induced changes in the chemical shift of the carbonyl carbon **C7** of **2b**.[46,47] The ^{13}C NMR chemical shifts of carbon **C7** were significantly shifted upfield ($\Delta\delta$ = 0.044–0.7717 ppm) with increased sugar **50** concentration, indicating increased hydrogen bond interactions between benzoic acid **2b** and glucoside **50**. This suggests that shielding effects are likely due to the redistribution of electron density upon the formation of new intermolecular hydrogen bonds of benzoic acid-OH with the basic oxygens of glucoside **50**.[46]

Carboxylic acids form dimers in concentrated solution (>1 mM) in alkanes, held together by two cooperative hydrogen bonding interactions.[48,49] In its dimeric form, the carboxylic acid's hydrogen-bond donor site cannot be involved in a hydrogen bond with the hydrogen-bond acceptor molecule. Since our glycosylation reaction was conducted at 0.5 M concentration (see Table 1), competition between the dimerization process of benzoic acid and hydrogen bond interactions of benzoic acid with the basic oxygen acceptors of sugar may play a critical role in determining reactivity and selectivity. As a result, the association constant, K_A, for hydrogen-bonded complexes of benzoic acid **2b** and perfluorobenzoic acid **2m** with glucoside **50** was measured using UV-vis absorption titrations (Fig. 4b). The K_A value was calculated based on the absorbance of the benzoic acid·glucoside complex at 228, 230, and 232 nm and the absorbance of perfluorobenzoic acid·glucoside complex at 226, 228, and 230 nm. The titration data were then fitted to a 1 : 1 binding isotherm with a linear correction to account for the absorbance of carboxylic acid at higher glucoside concentrations. The K_A value for the interaction of benzoic acid **2a** with **50** was 263 M^{-1}, while the KA value for perfluorobenzoic acid **2m** was 387 M^{-1}. The data suggest that **2a** and **2m** are sufficiently exposed to form hydrogen bonds

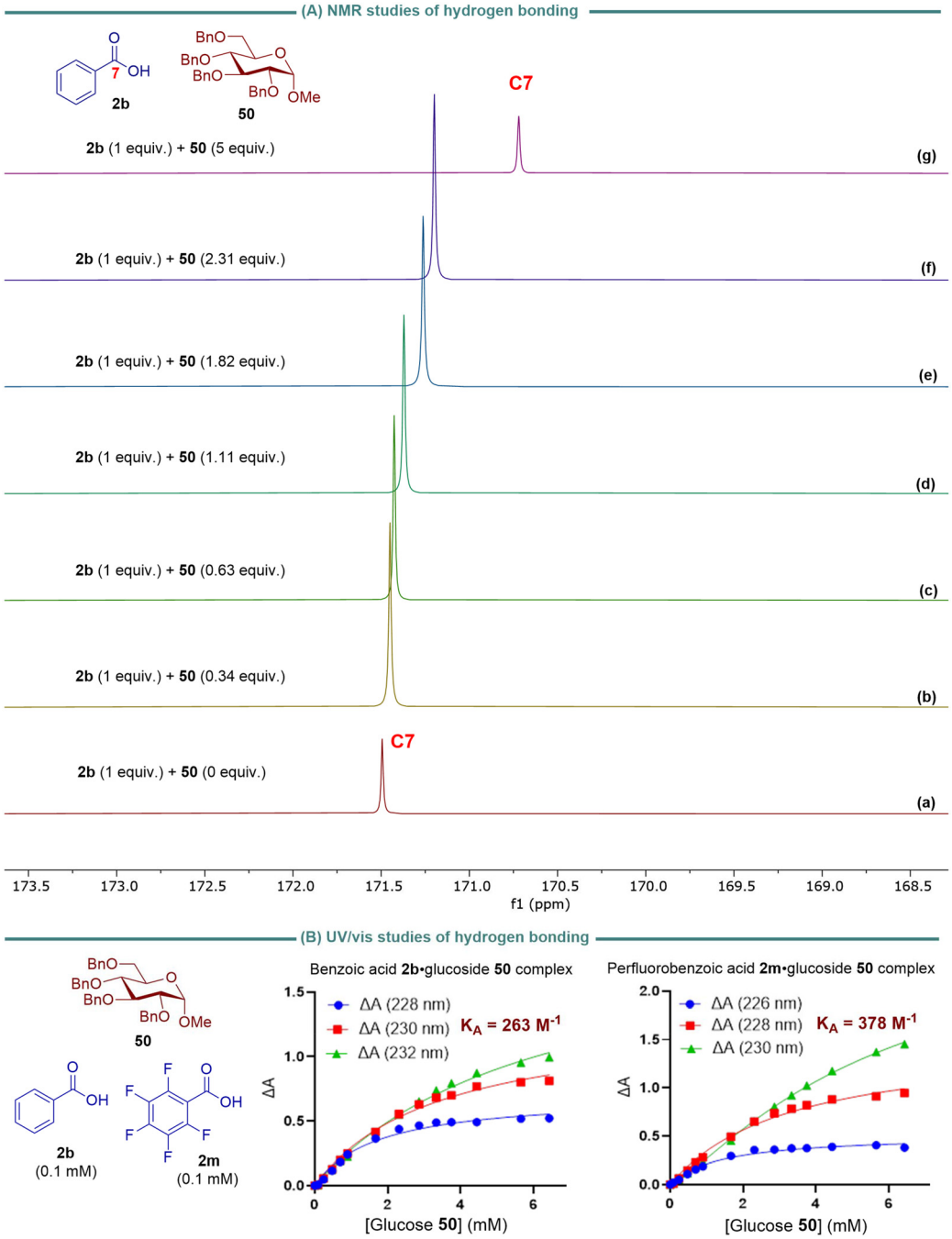


Fig. 4 (A) NMR studies of interactions between benzoic acid OH and oxygen atoms of **50** in $CDCl_3$ at 20 mM. (B) Binding isotherms for the formation of complexes of carboxylic acids **2b** and **2m** with glucoside **50** – fit of the experimental shifts of the UV-vis signals of **2a** and **2m** upon titration with **50** in dichloromethane.

with **50**, and **2m** forms a stronger hydrogen bond with **50** than **2b**. The K_A value was determined based on the absorbance of the benzoic acid·glucoside complex at 228, 230, and 232 nm, as well as the absorbance of perfluorobenzoic acid·glucoside complex at 226, 228, and 230 nm. The titration data were then fitted to a 1 : 1 binding isotherm with a linear correction to account for the absorbance of carboxylic acid at higher glucoside concentrations. The K_A value for the interaction of benzoic acid **2a** with **50** was found to be 263 M^{-1}, while the K_A value for perfluorobenzoic acid **2m** was 387 M^{-1}. These results indicate that **2a** and **2m** have sufficient exposure to form hydrogen bonds with **50**, with **2m** showing a stronger hydrogen bond formation with **50** compared to **2b**.

Next, we conducted density functional theory (DFT) calculations to examine the hydrogen bond interaction between carboxylic acid-OH and the glycosyl C2-oxygen. We focus on ana-

lyzing the rate-limiting transition states for the formation of both α- and β-glycosyl ester products (Fig. 5). To simplify the calculations, we used tetramethyl-protected glucosyl bromide and acetic acid as the model coupling partners, with phenanthroline (Phen) as the catalyst. The computed free energy profile and the optimized structures of key intermediates and transition states are shown in Fig. 5. The Phen catalyst displaces the bromide leaving group of the glycosyl donor, forming the β-phenanthrolinium ion intermediate **Int1**, where phenanthroline is bound to the C1-carbon of a sugar moiety. The subsequent attack of acetic acid on the intermediate **Int1**, *via* transition state **TS-alpha**, leads to the formation of the major product, α-glycosyl ester, with a barrier of 16.90 kcal mol^{-1} (Fig. 5). On the other hand, if phenanthroline is bound to the C1-carbon on the α-face, the phenanthrolinium ion intermediate **Int1′** is 3.02 kcal mol^{-1} higher in energy than **Int1**. When carboxylic acid attacks from the β-face of the higher energy **Int1′**, the minor product, β-glycosyl ester, is formed *via* transition state **TS-beta** with a barrier of 19.79 kcal mol^{-1}. Overall, **TS-alpha** is 2.88 kcal mol^{-1} lower in energy than **TS-beta**, thus strongly favoring the formation of α-glycosyl ester over β-glycosyl ester. This computational result is consistent with our experimental findings. Inspection of **TS-beta** and **TS-alpha** transition states revealed the CH_3 group of carboxylic acid had an unfavorable interaction with the catalyst's phenyl ring in **TS2-beta**, leading to the minor β-product, while this CH_3 group pointed away from the phenyl rings in **TS-alpha** leading to the major α-product.

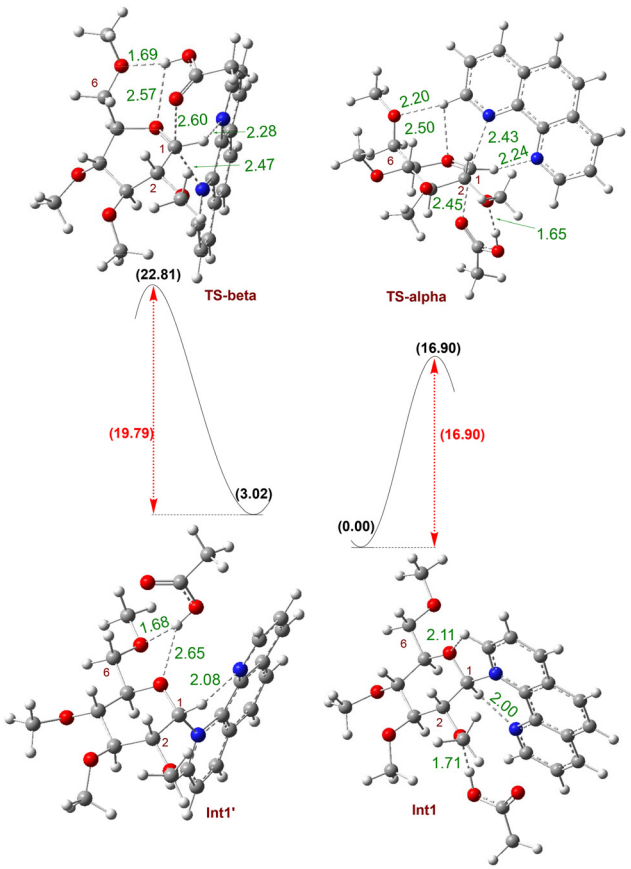


Fig. 5 Kinetic barriers for the α- and β-glycosyl ester products from glucosyl bromide. The free energy changes (Δ*G* at 50 °C) are in kcal mol^{-1} and are computed with the Gaussian 16 program[50] and at M06-2X/def2-TZVPP //M06-2X/def2-SVP level of theory[51] using diethyl ether with SMD implicit solvation.[52] Hydrogen bonding interactions are reported in Å.

In examining the impact of hydrogen bonding on enhancing the nucleophilicity of carboxylic acid, conducted a comparative analysis of the optimized geometries of transition states for the formation of α-glycosyl ester and α-*O*-glycosides products from glucosyl bromide with carboxylic acid and alcohol as nucleophiles, respectively (Fig. 6a). Previous DFT calculations have focused on the hydrogen bonding interaction between the C2-oxygen of sugar electrophile and the hydroxyl group (–OH) nucleophile.[45a] Our DFT calculations primarily centered on the disparity between alcohol and carboxylic acid. An α-glycosyl ester is produced upon nucleophilic attack from the α-face of the reacting β-phenanthrolinium ion intermediate. The calculations underscored the pivotal role of hydrogen bond interaction between the hydroxyl group (–OH) of carboxylic acid and the C2-oxygen of a carbohydrate moiety, influencing the nucleophilicity of the incoming carboxylic acid. The strong hydrogen bond (1.65 Å) between carboxylic acid-OH and the basic O atom at the C2-carbon of sugar increases the nucleophilicity of the carbonyl oxygen (C═O) of carboxylic acid. In contrast, when alcohol acts as a nucleophile, this scenario is not possible since the –OH group of the alcohol interacts with the C2-oxygen and attacks the C1-anomeric carbon of the sugar moiety. This is further evident in alcohol-OH's weak hydrogen bond (1.95 Å) interaction with the C2-oxygen. The weak hydrogen bond interaction is further supported by the fact that hydrogen bonds between two electronegative atoms and hydrogen prefer a linear arrangement, maximizing orbital overlap for a stronger hydrogen bond interaction. As illustrated in Fig. 6a, the O(C2)–HO (carboxylic acid) angle was calculated to be 171°. Conversely, the O(C2)–HO (alcohol) angle at 122° deviates from linearity, resulting in weak hydrogen bonding when alcohol approaches the C2 carbon of the sugar moiety.

Based on both experimental and computational results, we propose a plausible mechanism for the phenanthroline **C6**-catalyzed stereoselective formation of α-glycosyl ester (Fig. 6b). Upon displacement of a bromide leaving group from glycosyl bromide donor with the **C6** catalyst, the major reacting $^4C_1$ chair-liked β-phenanthrolinium ion intermediate is likely to be formed in the reaction.[31] To achieve high conversion and selectivity, we propose the formation of hydrogen bonding interaction between carboxylic acid OH and the basic C2-oxygen of the carbohydrate moiety (O–H···O),[45] forming the hydrogen-bond phenanthrolinium complex. This consequently increases the nucleophilicity of carboxylic acid and directs its attack from the α-face of the β-phenanthrolinium ion intermediate. As previously observed in related phenanthroline-catalyzed glycosylation of alcohol acceptors with glycosyl bromide donors,[31] there was a hydrogen bonding interaction between the C1-anomeric proton and the second nitrogen of

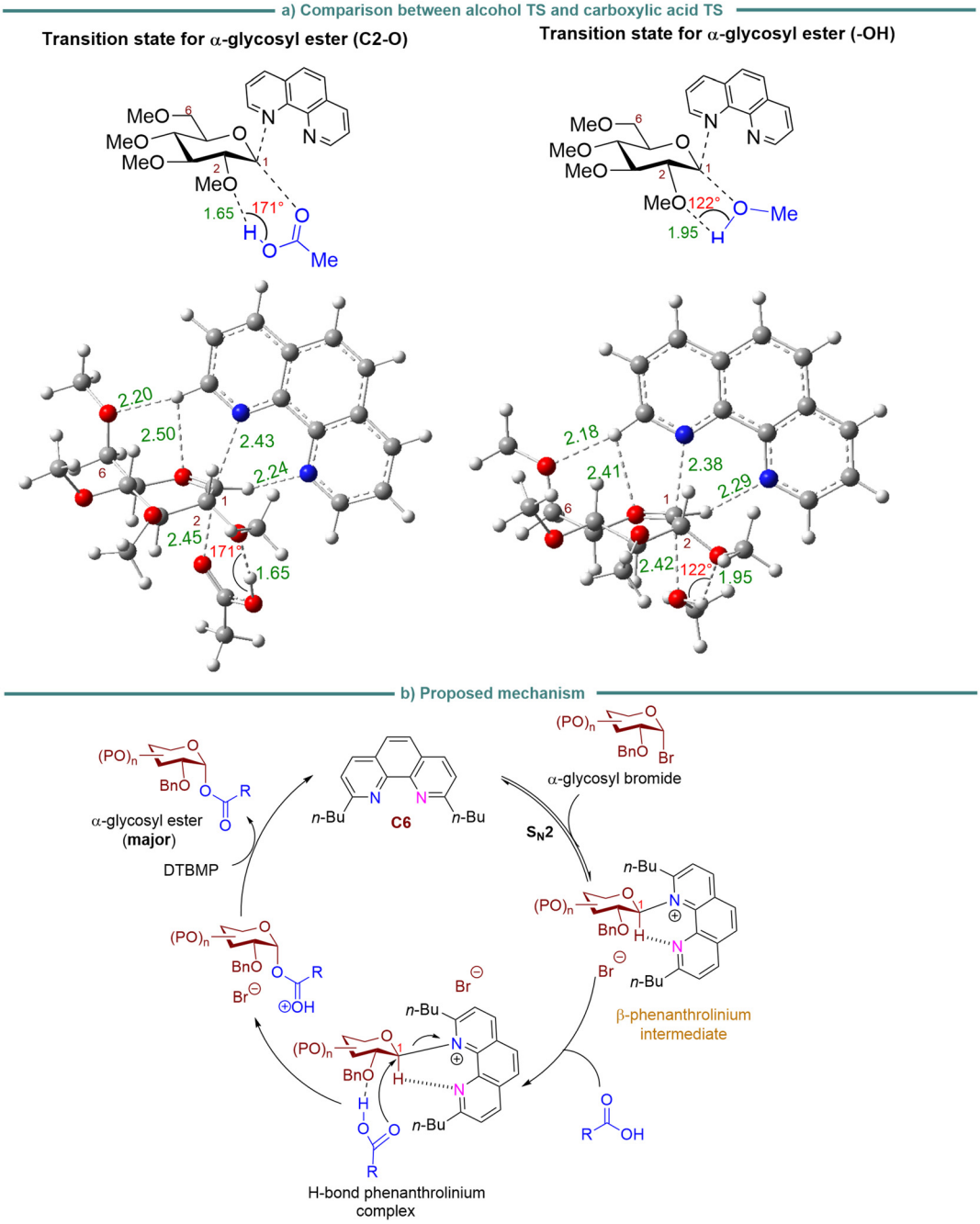


Fig. 6 (a) Comparison between the optimized transition states leading α-glycosyl ester products using carboxylic acid and alcohol nucleophiles. Hydrogen bonding interactions are reported in Å. (b) Proposed reaction mechanism.

phenanthroline. This could rule out the possibility that the carboxylic acid-OH forms a hydrogen bond with the secondary nitrogen of phenanthroline before attacking the C1-site. Subsequent attack of carboxylic acid from the axial face of the reacting $^4C_1$ chair-like equatorial complex affords α-glycosyl ester as the major product. The minor β-glycosyl ester product will likely be derived from a minor $B_{2,5}$ boat-liked α-phenanthrolinium ion.[31] The two phenanthrolinium ion conformers, a $^4C_1$ chair-liked β-conformer and a $B_{2,5}$ boat-like α-conformer, have been detected previously in a ratio of 2 : 1 ($\beta : \alpha$) using variable temperature NMR experiments.[31]

Conclusions

A newly developed glycosylation methodology utilizes a precisely tailored phenanthroline catalyst to produce challenging α-glycosylated carboxylic acids selectively. This readily available

catalyst facilitates the displacement of the bromide leaving group from glycosyl bromide donors, forming the reactive β-phenanthrolinium ion intermediate. Various alkyl and aromatic carboxylic acids and amino acid residues selectively attack the α-face of this intermediate, resulting in the formation of α-glycosyl esters with high selectivity and good yields. Both theoretical calculations and experimental data demonstrate the crucial role of hydrogen bonding between the carboxylic acid-OH and the basic C2-oxygen of the sugar moiety of the phenanthrolinium ion intermediate in the stereoselectivity-determining step of glycosylation. In addition, this hydrogen bond interaction enhances the nucleophilicity of the carboxylic acid, allowing it to attack the C1-anomeric carbon of the sugar moiety of the reactive intermediate. It has been observed that carboxylic acids with pK_a values between 4 and 5 produce α-glycosyl esters with high selectivity, whereas those with pK_a values of 2.5 or lower do not yield satisfactory results. This developed glycosylation protocol is mild, operationally simple, tolerant of various functional groups, and broadly applicable for the synthesis of a range of α-glycosylated carboxylic acids.

Author contributions

H.M.N. conceived the idea. N.E.A. designed the experiments and performed all of the experiments. N.R. performed the DFT calculations. H.B.S. helped with the analysis of computational data. H.M.N. supervised the research and co-wrote the manuscript.

Data availability

All relevant experimental and computational data and characterization details are provided in the ESI.†

The data supporting this article have been included in the ESI,† including experimental procedures, spectral characterization of all the new products, detection of the phenanthrolinium intermediate, experiment for isomerization of α- and β-glycosyl ester, effect of carboxylic acid's pK_a, NMR titration experiment for hydrogen bonding, UV-vis for hydrogen bonding constant, computational data, and the ^{1}H, ^{13}C, and ^{19}F NMR spectra of all the new products (PDF).

Conflicts of interest

There are no conflicts to declare.

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