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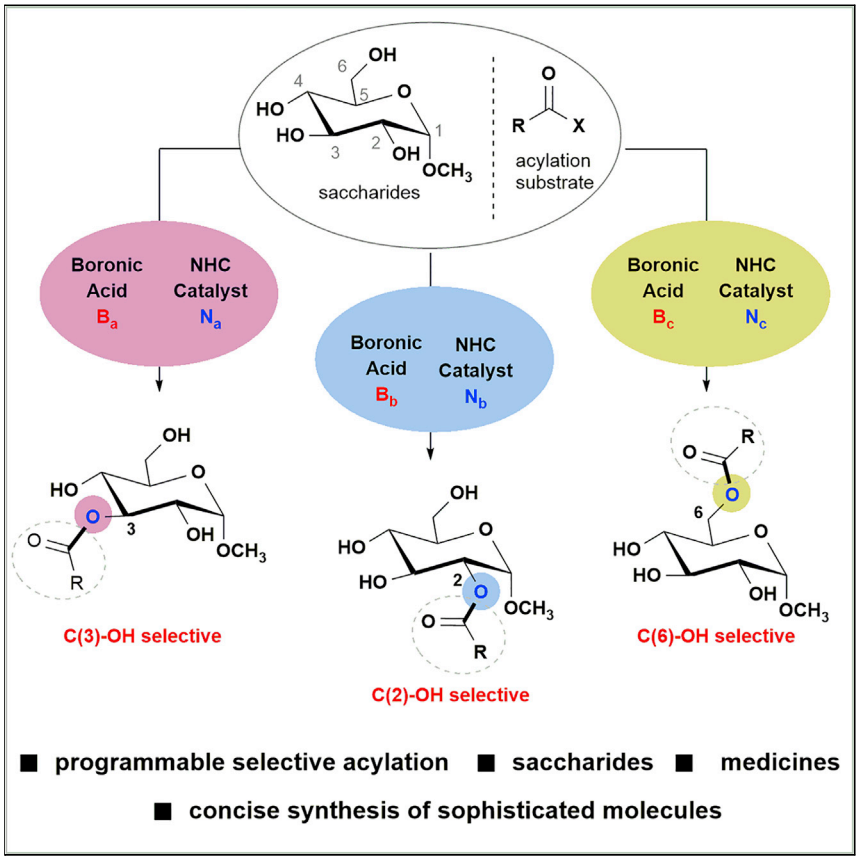
Programmable selective acylation of saccharides mediated by carbene and boronic acid



A readily programmable strategy for site-selective acylation of unprotected monoglycosides is developed. Excellent site selectivity was achieved by proper combinations of commercially available N-heterocyclic carbene (NHC) catalysts and boronic acids for the acylation of C(2)-, C(3)-, and (C6)-OH groups of various monosaccharides and their analogs. This strategy features extraordinary substrate scope and excellent functional-group tolerance. It leads to unprecedented opportunities for glycobiology research, as demonstrated by its applications in the straightforward and concise synthesis of sophisticated saccharide derivatives.

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Highlights

Programmable selective acylation of unprotected monoglycosides

Excellent site selectivity enabled by NHC catalysts and boronic acids

Extraordinary substrate scope for both monosaccharides and acylation partners

Concise construction of sophisticated saccharide derivatives

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Programmable selective acylation of saccharides mediated by carbene and boronic acid

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SUMMARY

Chemical synthesis or modification of saccharides remains a major challenge largely because site-selective reactions on their many similar hydroxyl groups are difficult. The lack of efficient chemical synthetic tools has therefore become a main obstacle to understanding saccharide-related biological processes and developing saccharide-based pharmaceuticals. Here, we disclose a programmable multilayered selectivity-amplification strategy enabled by boronic acids and N-heterocyclic carbene (NHC) catalysts for site-specific acylation of unprotected monoglycosides. The boronic acids provide transient shielding on certain hydroxyl groups (while simultaneously promoting reactions of other hydroxyl units) via dynamic covalent bonds to offer the first sets of selectivity controls. The NHC catalysts provide further layers of control by mediating selective acylation of the unshielded hydroxyl moieties. Multiple activating and deactivating forces can be easily modulated to yield programmable selectivity patterns. Structurally diverse monosaccharides and their analogs can be precisely reacted with different acylating reagents, leading to quick construction of sophisticated saccharide-derived products.

INTRODUCTION

Saccharides are a major class of biomolecules involved in numerous biological activities. Saccharide derivatives and multi-hydroxyl group (polyol)-containing structures are also widely found in natural products and synthetic molecules with important functions[1–7] (Figure 1A). It has been proved that modulation of saccharides or saccharide segments can lead to therapeutic agents, such as vaccines and antibiotics, with billion-dollar commercial success.[8–10] For example, bacterial-capsule polysaccharides attached to proteins have been a main choice for conjugated vaccines.[11] Multiple saccharide-derived small molecules, such as Empagliflozin, are among the best-selling drugs.[12] However, despite the enormous applications and potential, our understanding of saccharide-related biological processes and the development of saccharide-based pharmaceuticals remain challenging. A major obstacle lies in the lack of efficient chemical synthetic tools for access to saccharides and their derivatives. It is difficult to selectively functionalize the many hydroxyl (OH) groups present in saccharides because the reactivity differences of the various OH groups are very small.

Numerous approaches from the best chemists of many generations have been designed to achieve site-selective reactions on the different OH groups of saccharides and polyol molecules. The dominant approach involves elegantly designed

The bigger picture

Chemical synthesis or modification of saccharides remains a difficult challenge in modern science, posing a major hurdle to the study of saccharide-related biological processes and development of new therapeutics. The synthetic challenge is largely due to the difficulty of site-selective reactions on the many similar hydroxyl groups of saccharides. Here, we disclose a programable multilayered selectivity amplification strategy for site-selective acylation of unprotected monoglycosides and their derivatives. Through proper combinations of N-heterocyclic carbene (NHC) organic catalysts and boronic acids to introduce multiple tunable driving forces, the reactivity difference of the similar hydroxyl groups can be amplified or inverted. With our strategy, it becomes feasible to identify suitable conditions for site-selective acylation of essentially most (mono)saccharides and polyol molecules. Our study will have both fundamental and practical impacts in the broad fields ranging from chemistry to medicine.

orthogonal protection-deprotection chemistry through typically long-step operations, as demonstrated by many pioneers, such as Wong and Danishefsky.[13–19] Although improvements are being made in this protection-deprotection approach, new strategies with shorter steps that avoid (or minimize) conventional protection-deprotection operations have attracted intense attention for obvious reasons. For instance, the Hanessian and Taylor groups have studied organoboron[20,21] and metal reagents (such as organotin)[22] to amplify the intrinsic selectivity of *cis*-1,2-diols based on the inherent reactivity differences between equatorial and axial OH groups. Blaszczyk and Tang developed a selective acylation protocol for *trans*-1,2-diols in S-glycosides via nicely designed chiral catalysts and an adamantyl directing group.[23] Miller and co-workers designed small-molecule enzyme mimics for chemo- and/or stereoselective reactions of saccharides and polyols.[24,25] Kawabata and colleagues developed chiral pyridine-based organic catalysts that can selectively acylate OH groups at the C4-carbon of glucose.[26,27] Studer and co-workers found selective reactions of partially protected monosaccharides with NHC catalysts.[28] The use of other organic or metal catalysts and reagents for site-selective reactions of saccharides with minimized protections has also been reported.[29–35] Each of these methods has its own merits and limitations. For example, in these previous approaches, pre-protection of the C6- and/or C4-OH groups (of monosaccharides) is still necessary before selective reaction can be performed on the remaining OH units. The generality of monosaccharide partners is typically limited to those with certain structural requirements (such as the presence of *cis*-diols). Individual access to different sites (such as to C2-, C3-, and C6-sites individually) via each of these approaches is still difficult. Further breakthroughs in this arena of saccharide-selective reactions remain to emerge. Given the complexity of saccharides and the corresponding reacting partners, it appears that introducing more controlling parameters that can be modularly tuned could offer attractive solutions.

Here, we disclose a programmable strategy mediated by multiple driving forces for site-selective acylation of unprotected monoglycosides, their analogs, and their derivatives (Figure 1B). We break down the challenging selectivity problem into a few smaller issues, each of which can be addressed by different cooperative catalysts and additives. With D-glucoside (primary alcohol group unprotected) as a model example, the use of boronic acid additive can selectively shield the two OH groups at the C4- and C6-carbons by forming a six-membered boronic ester with labile boron-oxygen bonds. This dynamic boronic ester formation temporarily protects these two OH groups from further reactions, providing the first layer of selectivity control. The introduction of boronic acid additives can also simultaneously accelerate reactions of certain OH groups,[36] offering a second layer of selectivity control. In the same reaction solution, an N-heterocyclic carbene (NHC) organic catalyst is introduced to provide a further layer of site-selectivity control. Multiple parameters involving stereo-electronic effects and covalent and/or non-covalent interactions (NCIs) brought by the boronic acids and NHC catalysts can be readily modulated. With our approach, through appropriate combined choices of boronic acids and/or NHCs, the acyl group can be site-selectively installed on the C(2)-OH, C(3)-OH, or C(6)-OH of D-glucoside. Our strategy can be easily tuned for site-specific acylation of various monosaccharides and their analogs by varying the structures of boronic acids and/or NHC catalysts (as illustrated in the left graph of Figure 1B). Sophisticated molecules (such as natural products) containing saccharide fragments can also undergo selective acylation reactions with different carboxylic acids and derivatives, including those with commercial applications as medicines (such as artesunate and dehydrocholic acid). Applications of our selective acylation strategy can allow for concise synthesis of saccharide-derived products, such as

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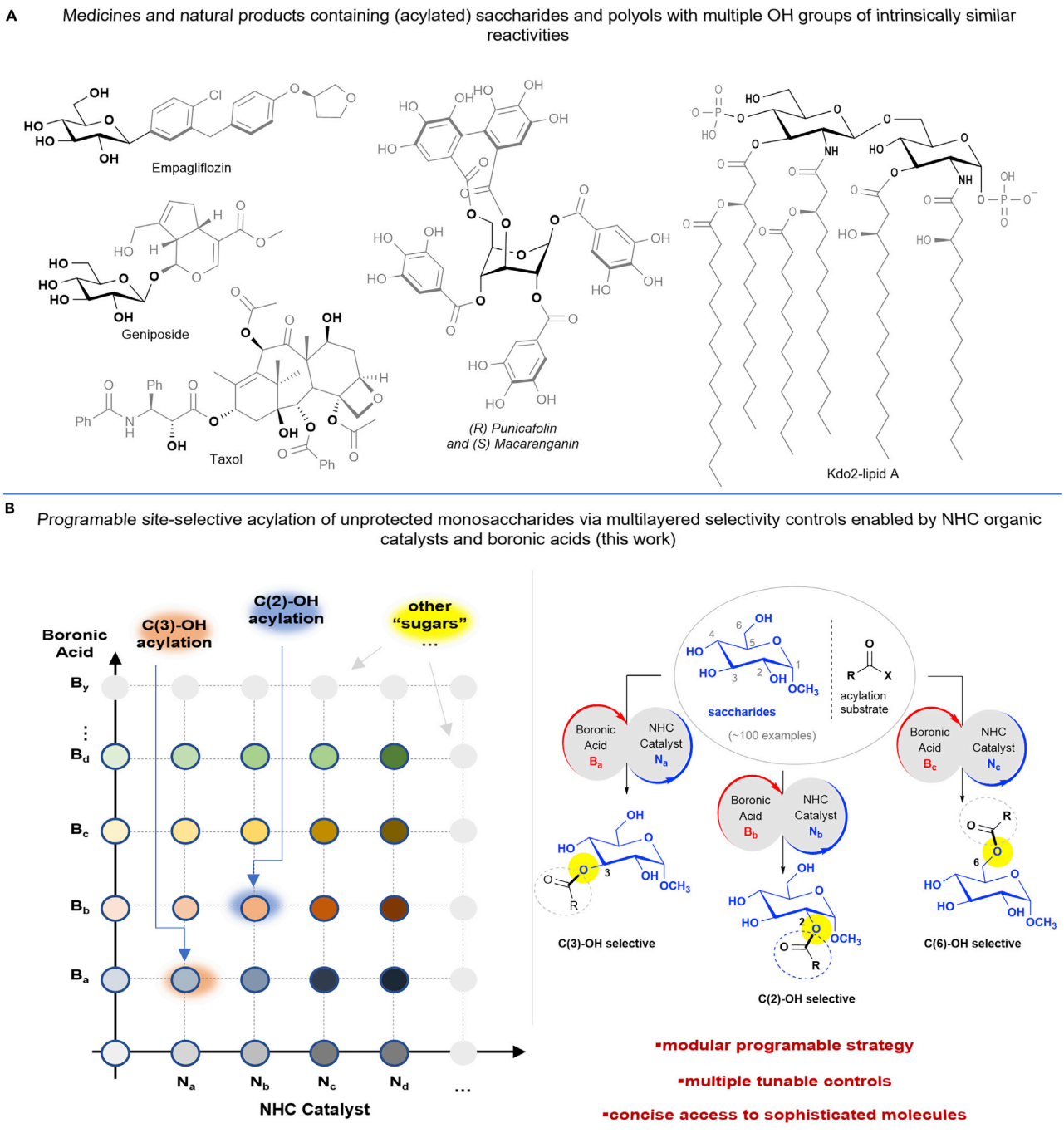
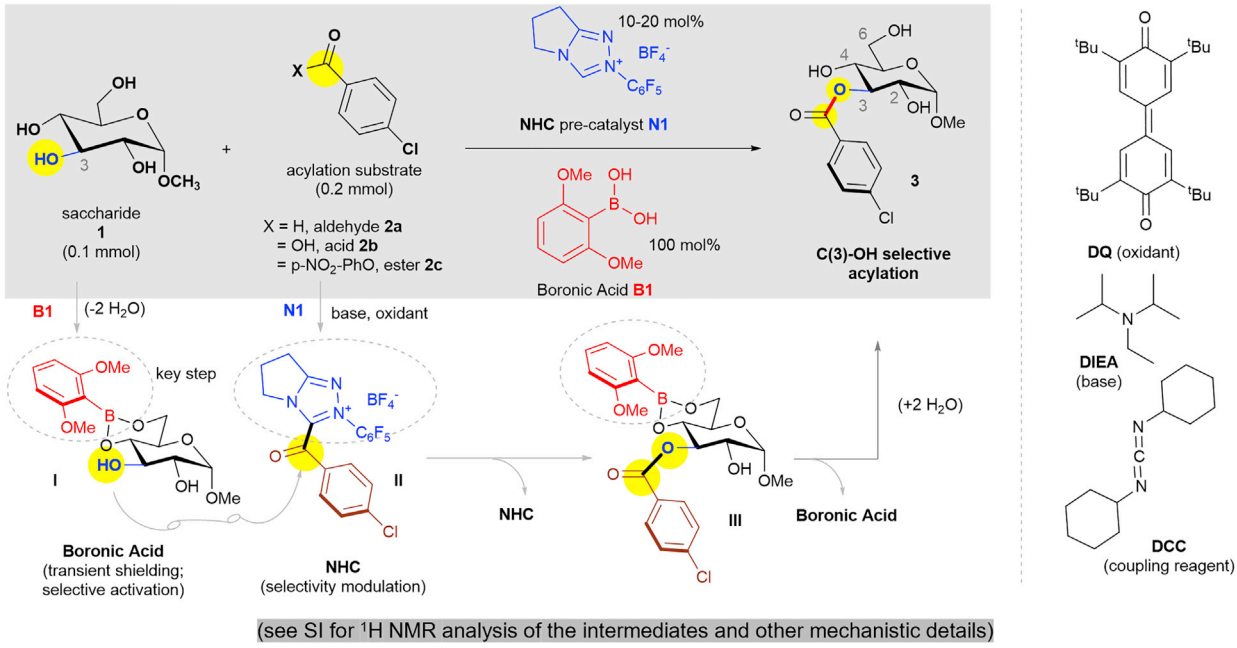


Figure 1. New strategy for selective acylation of saccharides and polyols

(R)-punicafolin, (S)-macaranganin,[37,38] and disaccharide laminaribiose,[39] with important bioactivities.

RESULTS AND DISCUSSION

Summarized in Figure 2 are key results of a model reaction (with D-glucoside [1] as the monosaccharide) from extensive studies on the effects of boronic acids, NHC



(see SI for ^{1}H NMR analysis of the intermediates and other mechanistic details)

	optimal conditions	regio-selectivity (C2:C3:C4:C6)	isolated yield% of **3** (C3)
#1A	**2a**, **DQ**, K_2CO_3, EtOAc	1:**16**:0:0	**80**
#1B	**2a**, **DQ**, K_2CO_3, CH_3CN	2:12:1:1	**78***
#2A	**2b**, **DCC**, Li_2CO_3	1:**14**:0:0	**71**
#3A	**2c**, DIEA	1:**6**:0:0	**70**

Figure 2. Typical conditions and a mechanistic pathway for selective C(3)-OH acylation of α-glucoside as a model saccharide

catalysts, and other parameters such as bases and solvents. Further details of condition optimizations are provided in the supplemental information. The reaction and its simplified mechanistic pathway are briefly illustrated in Figure 2. A glucoside (**1**), acylation substrate (**2a**, **2b**, or **2c**), NHC pre-catalyst (**N1**, 10–20 mol %), boronic acid (**B1**, 100 mol %), and base (20–200 mol %) were dissolved in an organic solvent (e.g., CH_3CN or EtOAc). The reaction involves reversible reactions between two OH groups (C4- and C6-OH groups) of glucoside with boronic acid to form boronic ester **I** as an intermediate (detectable via ^{1}H NMR of the crude reaction mixture or isolable depending on the specific substrates; see supplemental information part 2.6).[40–43] This dynamic boronic ester formation not only provides a transient protection of the two OH groups from subsequent acylation reactions but also assists in regulating the acylation tendency of other OH groups by variating the substituents of boronic acids. In the same reaction solution, the NHC catalyst reacts with the acylation substrate to form acyl azolium intermediate **II**.[44,45] The acylation substrates in our studies (as precursors of acyl azolium intermediates) can be aldehydes (**2a**; in the presence of an oxidant, such as DQ), carboxylic acids (**2b**; in the presence of a coupling reagent, such as dicyclohexyl carbodiimide [DCC]), or carboxylic esters (**2c**) (Figure 2; for details, see supplemental information parts 2.3–2.5). The acylation reaction between intermediates **I** and **II** first forms an acylated boronic ester of the glucoside as adduct **III** (as observed via ^{1}H NMR analysis of the crude reaction

mixture). In this step (from intermediates I and II to adduct III), regioselectivity between the C(2)-OH and C(3)-OH moieties is controlled by the structures of both the NHC catalyst and the boronic acid. The boronic ester moiety of this adduct (III) then undergoes hydrolysis in the same reaction mixture or upon silica-gel column chromatography to eventually form the site-selective acylated saccharide product **3**. It is worth noting that the boronic ester formation (thermodynamically favorable under the reaction condition) and hydrolysis are a facile and reversible process for both intermediates I and III (for details, see supplemental information parts 2.6 and 3.3). It is technically necessary to use a stoichiometric amount of the boronic acid to achieve optimal regioselectivity and avoid over-acylation on more than one OH group. Four sets of conditions (1A, 1B, 2A, and 3A; Figure 2) were identified to give acceptable results. We chose condition 1B to study the effects of NHC catalysts and boronic acids given that four possible mono-acylated saccharide adducts could be observable under this type of condition (CH_3CN as solvent; 1 equiv of DQ and boronic acid).

The loadings of boronic acid (**B1**) had a clear influence on the reaction yields and selectivity (Figure 3A). Increasing the loadings of boronic acid significantly increased the yield of C3-*O*-acylate while decreasing those of C6-*O*-acylate and C4-*O*-acylate. The yield of C2-*O*-acylate remained largely unchanged as the boronic acid loadings were varied. The structures of the boronic acids (as exemplified by selected examples **B1**–**B7**) also dramatically affected the yields and selectivity of the reactions (Figure 3B). For example, removing the methoxy substituents on the phenyl ring of **B1** (to give boronic acid **B3**) led to a big drop in yields of C3-*O*-acylate and the ratios (selectivity) between C3-*O*-acylate and C2-*O*-acylate. The presence of boronic acid generally increased the overall acylation yields (e.g., 68% overall acylation yield with the presence of 1 equiv of **B1** versus 38% overall yield without **B1**; Figures 3A and 3B). These results suggest that the formation of boronic ester intermediate (I; Figure 2) also simultaneously activates C(3)-OH toward acylation reactions. Such activation effects can be designed to occur on other OH groups, such as the C(2)-OH moiety, as observed in other examples of this study. The structures of NHC catalysts also showed profound effects on both reaction yields and selectivity values (Figure 3C; for details, see supplemental information part 2.7).

Our results (Figures 3A–3C) clearly show that both NHCs and boronic acids have distinct effects on each of the different OH groups present in saccharides and their analogs. These effects can be deactivation (temporary shielding) or activation on different OH groups, providing amplified reactivity differentiations of these moieties. It is therefore feasible to engineer these effects in a combinatorial and programmable manner (Figures 1B, 5, and 7) to achieve site-selective acylation on different OH groups of various types of saccharides (and polyols) with diverse acylation partners. For example, selective C(2)-OH acylation of glucoside (**1**) could be achieved by the combined use of chiral NHC pre-catalyst **N6** and boronic acid **B8** under a slightly modified condition to give C2(OH)-acylated product in 63% yield and 7:1 regioselectivity (Figures 3D and 4). Acylation of C(6)-OH of glucoside (**1**) selectively was achieved with the NHC pre-catalyst (**N4**) alone (Figures 3E and 4). In other examples of this study, selective C(6)-OH acylation was obtained via the combined use of an NHC pre-catalyst and a boronic acid.

We next evaluated the scope and applications of our strategy. Our condition screening in this study ended up with the use of five NHC catalysts and eight boronic acids (with 5 × 8 possible combinations) for optimal outcomes of the different types of saccharides and acylation partners. Although a definite relation between

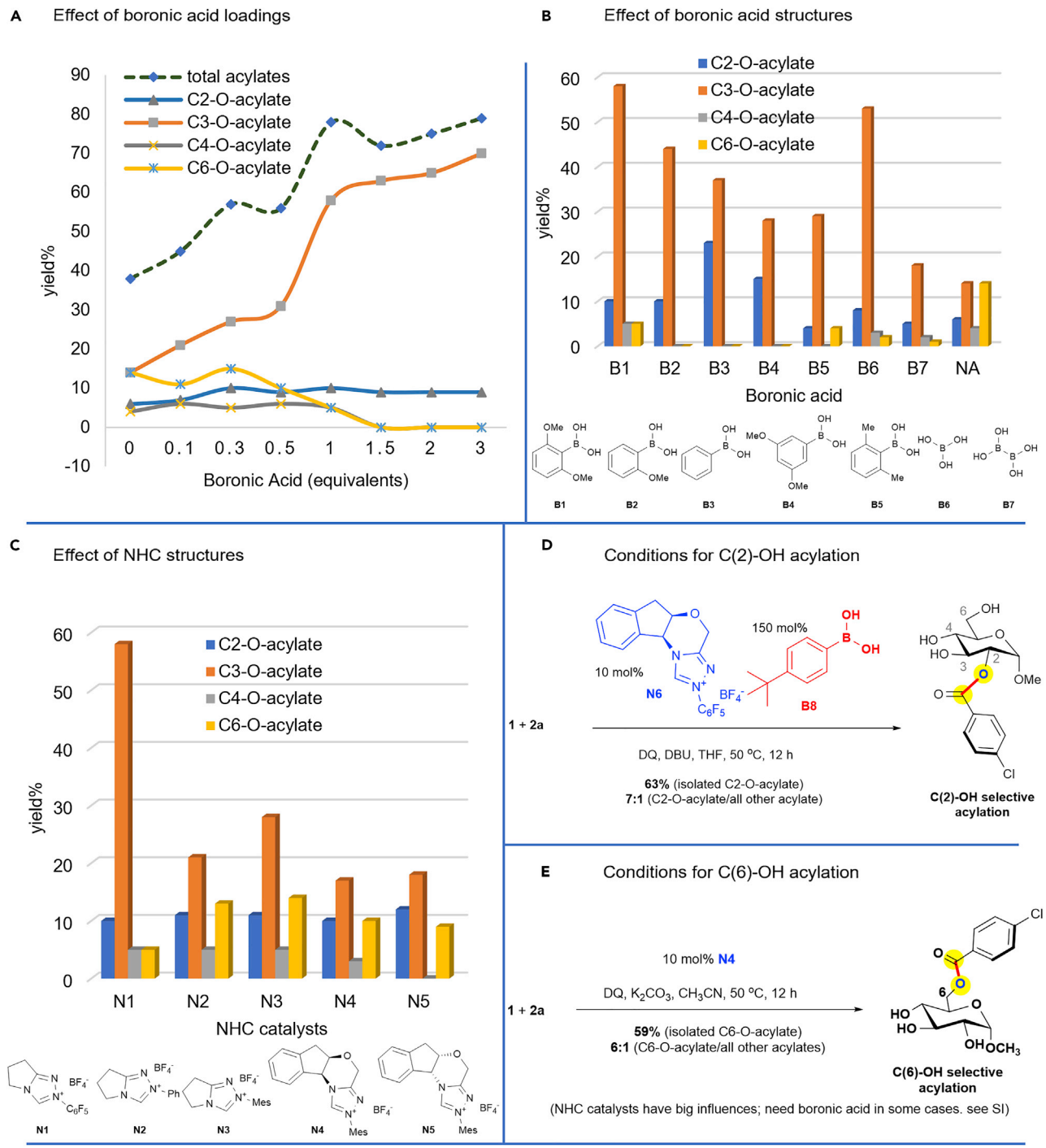
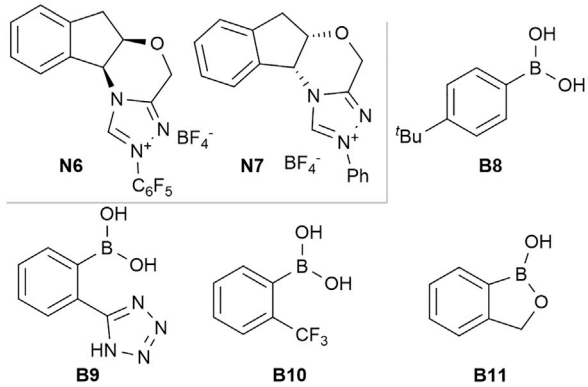


Figure 3. Conditions for site-selective acylation of a model saccharide as mediated by NHC catalysts and boronic acids

structures and reaction outcomes cannot be drawn at this point, a number of guiding trends were observed, as illustrated in Figure 4. For instance, the combination of **N1** and **B1** worked well for C(3)-OH acylation of α- and β-glucoside (combination 2 in Figure 4). This combination (**N1** + **B1**) also worked effectively for similar selectivity patterns when we used carboxylic acids or esters as the acylation agents (Figure 7). We eventually identified 12 combinations of NHCs and boronic acids (combinations

	NA	B1	B2	B3	B7	B8	B9	B10	B11
N1	#1	#2		#3	#4		#5	#6	
N4	#7		#8						#9
N5	#10								
N6						#11			
N7									#12



combination	selectivities/saccharides
#1	C(3)-OH/rhamnopyranoside; C(6)-OH/aminoglycoside, etc
#2	C(3)-OH of α-/β-glucosides
#3	C(3)-OH of aminoglycoside
#4	C(3)-OH of α-/β-xylopyranosides
#5	C(3)-OH of α-/β-galactosides
#6	C(2)-OH of β-galactosides

combination	selectivities/saccharides
#7	C(6)-OH of α- and β-glucosides
#8	C(3)-OH of glucal
#9	C(3)-OH of mannoside C(6)-OH of β-galactosides
#10	C(6)-OH of mannoside
#11	C(2)-OH of α-glucosides
#12	C(6)-OH of glucal

Figure 4. Modular combinations of NHCs and boronic acids

1–12 in Figure 4) for various selective reactions on a large set of saccharides and acylation partners (Figures 5 and 7; for details, see supplemental information parts 2.8 and 2.9).

The substrate tolerances and limitations using aldehydes as the acylation reagents were studied (Figure 5). With glucoside (**1**) as a model saccharide, C(3)-OH selective acylation could be achieved with various aryl aldehydes (**3**–**17**) and α,β-unsaturated aldehydes (**18** and **19**). The use of alkyl aldehyde gave little saccharide acylation adducts. Multiple different types of monosaccharides and their analogs could undergo selective C(3)-OH acylation as well (**20**–**38**). For example, β-glucosides and their derivatives, including a natural product (geniposide),[46] could be selectively acylated (**20**–**23**) with 66%–75% yields and around 10:1 regioselectivity. Diabetes drugs containing analogs of monosaccharides, dapagliflozin and empagliflozin,[19] could be acylated with good yields and excellent regioselectivity (**24** and **25**). The C(3)-OH acylation of α- and β-galactosides was achievable with NHC **N1** and boronic acid **B9** (combination 5) (**26**–**32**). Examples of other monosaccharides evaluated under current conditions for C(3)-OH acylations include aminoglycoside (**33**), α- and β-xylopyranosides (**34** and **35**), mannoside (**36**), rhamnopyranoside (**37**), and glucal (**38**).

Site-selective acylations on C(2)-OH moieties were obtained by a combination of **N6** + **B8** (combination 11) or **N1** + **B10** (combination 6) (Figure 5). Examples of saccharides that gave satisfactory yields and selectivity values for C(2)-OH acylation under current conditions include glucoside and galactosides (**39**–**46**). The C(6)-OH of various saccharides and analogs (**47**–**60**) could be selectively acylated through the sole use of an NHC catalyst ("combinations" 1, 7, and 10) or in the presence of both NHCs and boronic acids (combinations 9 and 12). For example, the C(6)-OH of α- and β-glucosides was selectively acylated by NHC pre-catalyst **N4** alone (**47**–**50**). Acylation on the C(6)-OH of β-galactosides (**51**–**55**) was realized by **N4** and **B11** (combination 9).

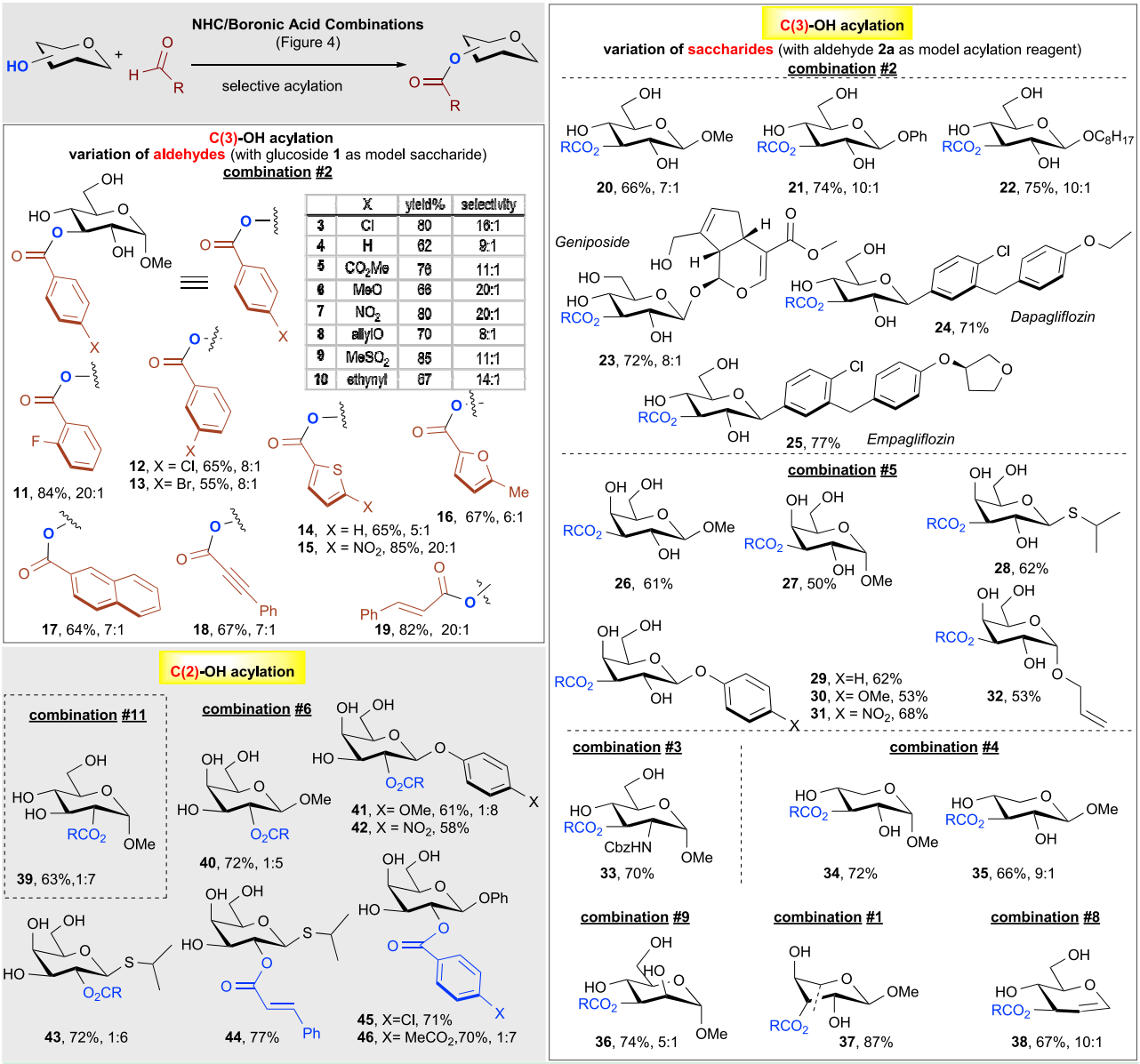

NHC/Boronic Acid Combinations
(Figure 4)
selective acylation
C(3)-OH acylation
variation of aldehydes (with glucoside 1 as model saccharide)
combination #2
X yield% selectivity
3 Cl 80 16:1
4 H 62 9:1
5 CO2Me 76 11:1
6 MeO 66 20:1
7 NO2 80 20:1
8 allylO 70 8:1
9 MeSO2 85 11:1
10 ethynyl 67 14:1
11, 84%, 20:1
12, X = Cl, 65%, 8:1
13, X= Br, 55%, 8:1
14, X = H, 65%, 5:1
15, X = NO2, 85%, 20:1
16, 67%, 6:1
17, 64%, 7:1
18, 67%, 7:1
19, 82%, 20:1
C(3)-OH acylation
variation of saccharides (with aldehyde 2a as model acylation reagent)
combination #2
20, 66%, 7:1
21, 74%, 10:1
22, 75%, 10:1
Geniposide
23, 72%, 8:1
24, 71%
Dapagliflozin
25, 77%
Empagliflozin
combination #5
26, 61%
27, 50%
28, 62%
29, X=H, 62%
30, X= OMe, 53%
31, X = NO2, 68%
32, 53%
combination #3
33, 70%
combination #4
34, 72%
35, 66%, 9:1
combination #9
36, 74%, 5:1
combination #1
37, 87%
combination #8
38, 67%, 10:1
C(2)-OH acylation
combination #11
39, 63%,1:7
combination #6
40, 72%, 1:5
41, X= OMe, 61%, 1:8
42, X = NO2, 58%
43, 72%, 1:6
44, 77%
45, X=Cl, 71%
46, X= MeCO2,70%, 1:7
C(6)-OH acylation
combination #7
47, 59%, 10:1
48, X = OMe, 60%,12:1
49, X = OPh,70%, 10:1
50, X = OC8H17, 62%, 10:1
51, X= OMe, 63%
52, X = OPh,75%
combination #9
53, X = MeO, 68%
54, X = NO2, 69%
55, 68%
combination #1
56, 56%, 5:1
57, 60%
58, 68%
combination #10
59, 97%
combination #12
60, 71%, 7:1

Figure 5. Scope of selective saccharide acylation using aldehydes as the acylation reagent

Yields are isolated yields of the major product; regioselectivity refers to C3/C2-O-acylate for **3**–**37** and **39**–**46**, C3/C6-O-acylate for **38**, and C6/C3-O-acylate for **47**–**60**. Yields are isolated yields of two combined monoacylates for **36** and **40**. R = p-Cl-Ph. Other possible acylation products were unobservable or minimal (less than 5%) via thin-layer chromatography and NMR analysis of the crude reaction mixture.

It is worth keeping in mind that for the same set of saccharide and acylation reagent, the use of different conditions offers dramatically different selectivity outcomes. For example, for the same aminoglycoside, the use of an NHC catalyst (**N1**) alone gave C(6)-OH acylation product **56**, whereas a combined use of **N1** and boronic acid **B3** gave C(3)-OH acylation product **33**. Similar comparisons can be made for other examples, such as products **3**, **39**, and **47** from α-glucoside (acylation on C3, C2, and C6, respectively). As a technical note, changes to both NHC catalysts and boronic acids are often needed for achieving optimal yields and selectivity values for each of the different OH groups on the same saccharides.

To understand how the various interactions between the components of the reaction affect regioselective acylation, we chose five model reactions to study (Figures 6 and S36) by focusing on the key regio-determining step via density functional theory (DFT) calculations (see supplemental information part 3.2 for details). We aimed to discern how boronic acids (by comparing reactions 1 and 2), monosaccharide identity and chirality (by comparing reactions 3 and 4), and NHC chirality (by comparing reactions 4 and 5) affect the site-selectivity outcomes. Given that the carbonyl carbon of the acyl azolium intermediate under attack by the monosaccharide is prochiral, allowing attack from either the (*Re*)-face or the (*Si*)-face by OH group (Figure S37; see supplemental information part 3.4 for details), we considered the regio-divergent intermediates arising from both possibilities. Within each reaction, independent conformational sampling converges to the lowest energy structures such that the same backbone orientation demonstrates similar interactions (Figure S38).

When boronic acid forms boronic ester by condensing with 4,6-diol of the monosaccharides, only the C(2)-OH and C(3)-OH groups are amenable to acylation (Table S5). This happens in reactions 1 and 2. In reaction 1, the NH group of the tetrazole ring of the boronic acid can form a hydrogen bond with the oxyanion oxygen atom. This formation of hydrogen bonding strategically places the C(3)-OH group close to the carbonyl C=O group for productive C–O bond formation (Figure 6). For the formation of the O(C2)–C(carbonyl) bond, however, this approach is hindered by the geometric restraints. In reaction 2, replacing the tetrazole in **B9** with a trifluoromethyl group in **B10** prevents the possibility of hydrogen bonding from the boronic acid moiety; instead, the CF_3 group interacts with the acyl azolium differently to favor C(2)–OH over C(3)–OH acylation.

In reactions 3–5, the monosaccharides are not protected by the formation of 4,6-boronato-monosaccharides because the boronic acids do not have two OH groups. The acyl azolium intermediates in these reactions each adopt a particular conformation stabilized by NCIs (Figure S38), thus creating a specific site pocket, much akin to an enzyme's active site, for biased interaction with one particular OH group of the monosaccharide substrate over all other OH groups. In reaction 3, C(6)–OH acylation would benefit from favorable interactions including additional CH···O(anomeric) and CH···π interactions that are not present in the other three intermediates. In reaction 4, as compared with reaction 3, a change in the sugar stereochemistry (mannoside versus galactoside with different chirality at C(2)-OH and C(4)-OH) leads the most stable intermediates to come from the (*Si*)-face attack rather than the (*Re*)-face attack in reaction 3. Now, the intermediate formed at C(3)-OH is the most stable

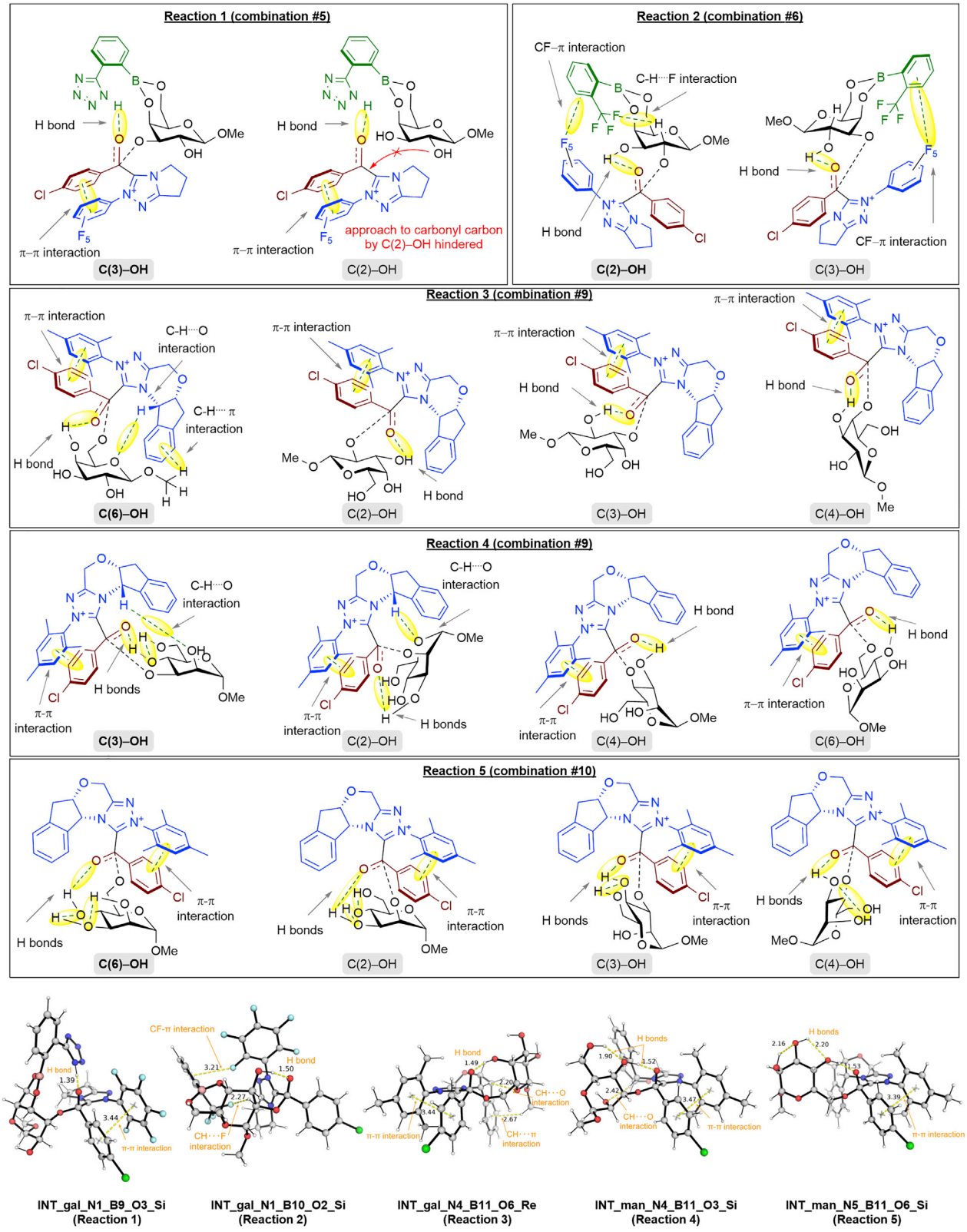


Figure 6. Schematic representation of the NCIs involved in the key regioselective step for model reactions considered by DFT calculations

because it forms two hydrogen bonds and an additional CH···O interaction compared with the *O*-acylation at other sites. In reaction 5, both the mannoside and the NHC have different stereochemistry from the galactoside and NHC used in reaction 3. The most stable intermediates result from the (*Re*)-face attacks in reaction 3 and from the (*Si*)-face attacks in reaction 5. The double inversion of the stereochemistry in both the sugar and the NHC could explain why both reactions 3 and 5 favor the same OH-functionalization (both at C(6)-OH). For example, when we compare the most stable intermediates in reactions 3 and 5 (INT_gal_N4_B11_O6_Re and INT_man_N5_B11_O6_Si, respectively; Figure 6), the dihydroindene groups of the NHC in both cases have orientations (pointing "downward") similar to those of the sugar OH groups form various interactions. These two structures are almost mirror images, except where the stereochemistry of the sugar substrate differs. Both structures have the more favorable interactions than intermediates from other *O*-site functionalizations within each of reactions 3 and 5. In reactions 4 and 5, both the intermediates resulting from the (*Si*)-face attack of the acyl azolium have lower energy than the corresponding intermediates from the (*Re*)-face attack. When we compare the intermediates from the (*Si*)-face attack in reactions 4 and 5 (INT_man_N4_B11_O3_Si and INT_man_N5_B11_O6_Si, respectively; Figure 6), we see that only the orientation of the dihydroindene group of the NHCs differs across these two reactions. This is consistent with our expectation given that the NHCs used are enantiomers (**N4** versus **N5**). This difference in the NHC side-group orientation favors different *O*-functionalization (C(6)-OH in reaction 5 versus C(3)-OH in reaction 4) as a result of the differing electronic and steric interactions (see more details of the individual interactions in supplemental information part 3.4).

Although this preliminary analysis of molecular interactions of various reaction components (NHC, boronic acid, and sugar) was performed on the regio-divergent intermediates, a similar analysis on the transition states (TSs) using reaction 4 lends validity to our current analysis, as we see that the same favorable interactions feature in both the intermediates and their corresponding TSs (compare Figure S40 and reaction 4 in Figure S38; for details, see supplemental information part 3.5).

An emerging theme from these DFT studies is that the regioselective outcome of sugar *O*-functionalization results from a combination of steric interactions (due to side groups of the NHCs and/or boronic acids used) and electronic interactions between the sugar OH and/or CH groups and the NHC and/or boronic acid side chains. The acyl azolium intermediate is stereogenic because the carbonyl carbon can be attacked by the sugar OH group from either the (*Re*)- or (*Si*)-face. This provides opportunities for unique interactions that favor the functionalization of one OH group over all others given that the OH group attacks the carbonyl carbon of acyl azolium, thus giving unique regioselective outcomes.

Carboxylic acids and esters have a much bigger presence than aldehyde moities in natural and synthetic bioactive molecules, such as pharmaceuticals; we therefore moved to employ acids and esters as the acylation reagents (Figure 7). To our delight, the same set of NHC-boronic acid combinations offers nearly the same selectivity preference when carboxylic acids and esters are used. Only minor changes to conditions such as solvents and bases are required. When carboxylic acids were used, a coupling agent (DCC) was used to convert the carboxylic acid to its reactive ester form for subsequent reaction with the NHC catalyst to form the NHC-bound acyl azolium intermediate (**II**; Figure 2). A typical reaction condition using carboxylic acid is illustrated in Figure 2 (optimal condition 2A). With a similar

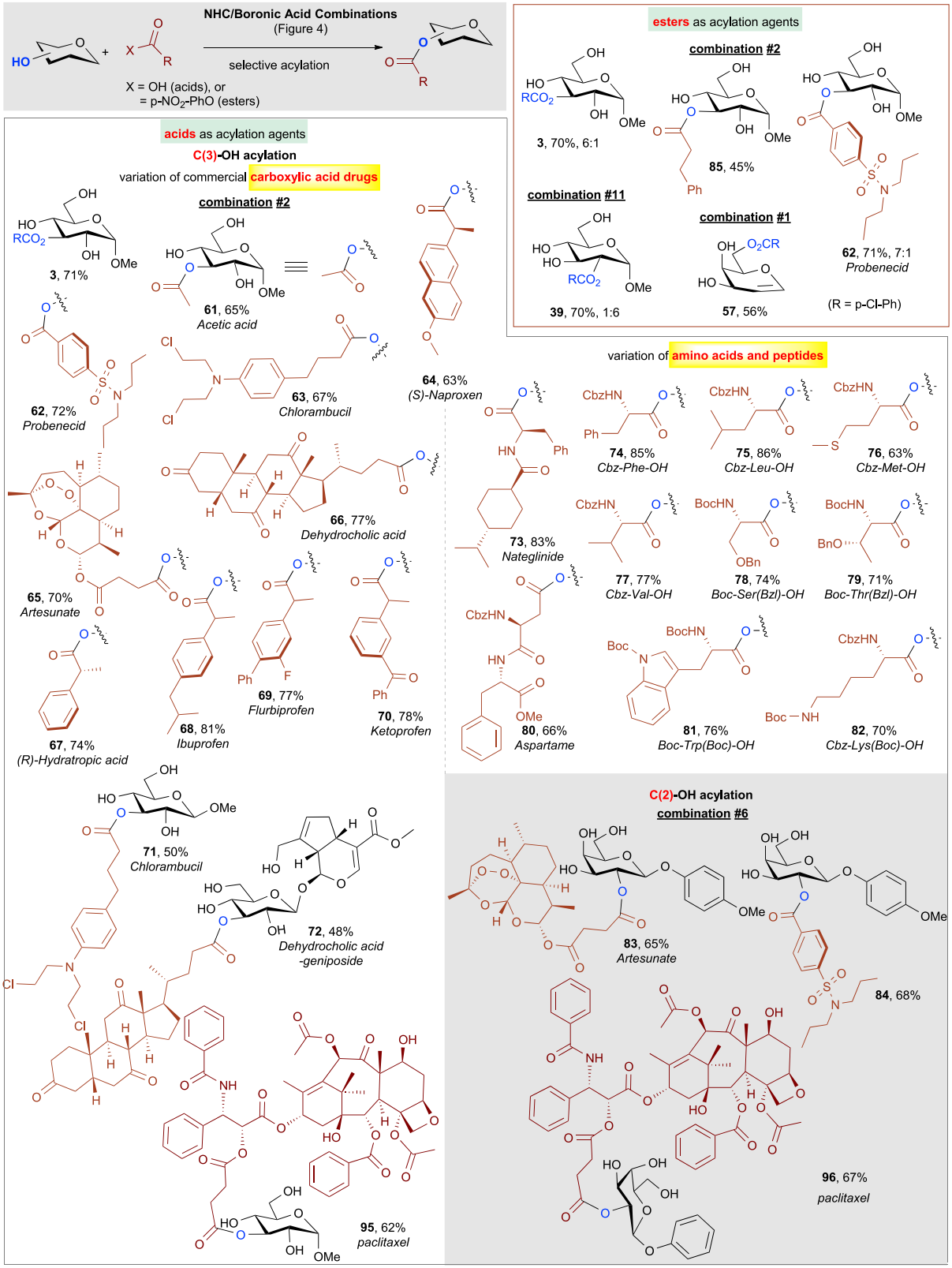

NHC/Boronic Acid Combinations
(Figure 4)
selective acylation
X = OH (acids), or
= p-NO2-PhO (esters)
esters as acylation agents
combination #2
3, 70%, 6:1
85, 45%
combination #11
combination #1
39, 70%, 1:6
57, 56%
62, 71%, 7:1
Probenecid
(R = p-Cl-Ph)
acids as acylation agents
C(3)-OH acylation
variation of commercial carboxylic acid drugs
combination #2
3, 71%
61, 65%
Acetic acid
64, 63%
(S)-Naproxen
62, 72%
Probenecid
63, 67%
Chlorambucil
66, 77%
Dehydrocholic acid
65, 70%
Artesunate
69, 77%
Flurbiprofen
70, 78%
Ketoprofen
68, 81%
Ibuprofen
67, 74%
(R)-Hydratropic acid
variation of amino acids and peptides
74, 85%
Cbz-Phe-OH
75, 86%
Cbz-Leu-OH
76, 63%
Cbz-Met-OH
73, 83%
Nateglinide
77, 77%
Cbz-Val-OH
78, 74%
Boc-Ser(Bzl)-OH
79, 71%
Boc-Thr(Bzl)-OH
80, 66%
Aspartame
81, 76%
Boc-Trp(Boc)-OH
82, 70%
Cbz-Lys(Boc)-OH
71, 50%
Chlorambucil
72, 48%
Dehydrocholic acid
-geniposide
95, 62%
paclitaxel
C(2)-OH acylation
combination #6
83, 65%
Artesunate
84, 68%
96, 67%
paclitaxel

Figure 7. Scope of selective saccharide acylation using carboxylic acids and esters as the acylation reagent

Yields are isolated yields of the major product; regioselectivity refers to C3/C2-O-acylate for **3**, **62**, and **39** (acylations on other OH groups are minimal). Yields are isolated yields of two combined acylates for **39** and **62**. The regioselectivity value is not given when acylation on all other OH groups is trace. R = p-Cl-Ph for products **3**, **39**, and **57**.

effort, conditions for using carboxylic esters (4-nitrophenol esters of carboxylic acids) could be readily realized, as exemplified by optimal condition 3A (Figure 2).

The reaction generality is exceptional with aryl or alkyl carboxylic acids and esters bearing various functional groups. For example, carboxylic-acid-containing commercial pharmaceuticals reacted with monosaccharides in a highly regioselective manner to give the corresponding drug-saccharide conjugates (**62–72**, **83–84**, and **95–96**) with good isolated yields. Our reaction conditions are mild and tolerate sensitive functional groups, such as the endoperoxide 1,2,4-trioxane ring in artesunate[47] (**65** and **83**). Carboxylic-acid-containing amino acids, peptides, and their derivatives (**73–82**) were also excellent acylation partners under our approach. These results (**73–82**) suggest that our method could be further developed for the preparation of conjugates of saccharides and peptides or proteins. Our strategy could also be used to link two molecules with synergistic medicinal effects for possible combinatory therapeutics. Here, we show that two sophisticated bioactive molecules (dehydrocholic acid and geniposide) can be linked via saccharide selective acylation (**72**). Conjugation of paclitaxel with sugars has shown improved pharmaceutical properties (such as solubility and stability) and better target cancer cell specificity.[48,49] These reported studies used the conventional protection-deprotection approach to link sugars to paclitaxel. Our method allows for concise access to glycoside-conjugated paclitaxel (**95** and **96**) in one step by using succinic acid as the linker. A number of carboxylic esters (**3**, **85**, **39**, **57**, and **62**; Figure 7) were also examined as acylation reagents. Similarly, there are no apparent limitations with respect to the core scaffolds and substituents of the carboxylic esters.

Our site-selective acylation of monosaccharides enables the concise synthesis of complex molecules such as oligosaccharides and functional molecules containing saccharide fragments and their derivatives (Figure 8; see supplemental information parts 2.11 and 2.12 for details). For example, starting from C(3)-OH acylated glucoside adduct (**61**) prepared by our strategy, antiseptic disaccharide laminaribiose could be prepared via a few straightforward operations in 38% overall yield from commercially available glucoside **1**, as illustrated in Figure 8A. It is reasonable to expect that by varying the reactive site (such as C(3)-OH of **1**) and the monosaccharide coupling units (such as **87**), our method should allow for rapid access to a diverse set of useful disaccharides and their analogs,[50] including those that are expensive and difficult to obtain. Our method can also allow for efficient synthesis of saccharide-derived complex molecules (Figure 8B). Here, we demonstrate a formal total synthesis of puncafolin and macaranganin,[37,38] natural products of the ellagitannin family,[51] containing a monosaccharide core with important bioactivities. The first total synthesis of these two natural products was recently reported by Ueda, Kawabata, and colleagues.[26] In their approach, sequential selective acylations at the C(4)- and C(2)-OH groups (of **90**) as mediated by Kawabata's elegant pyrrolidinopyridine-based catalysts are key steps in preparing intermediate **94** (Kawabata's intermediate in Figure 8B) for further conversion to the final natural products. We used a different reaction sequence enabled by our new strategy for access to the same intermediate **94**. Key steps in our approach are sequential NHC- and boronic-acid-mediated selective acylations at the C(3)- and C(6)-OH moieties. The (un-optimized) overall yield from **90** to **94** is 49%, comparable to that of Kawabata's

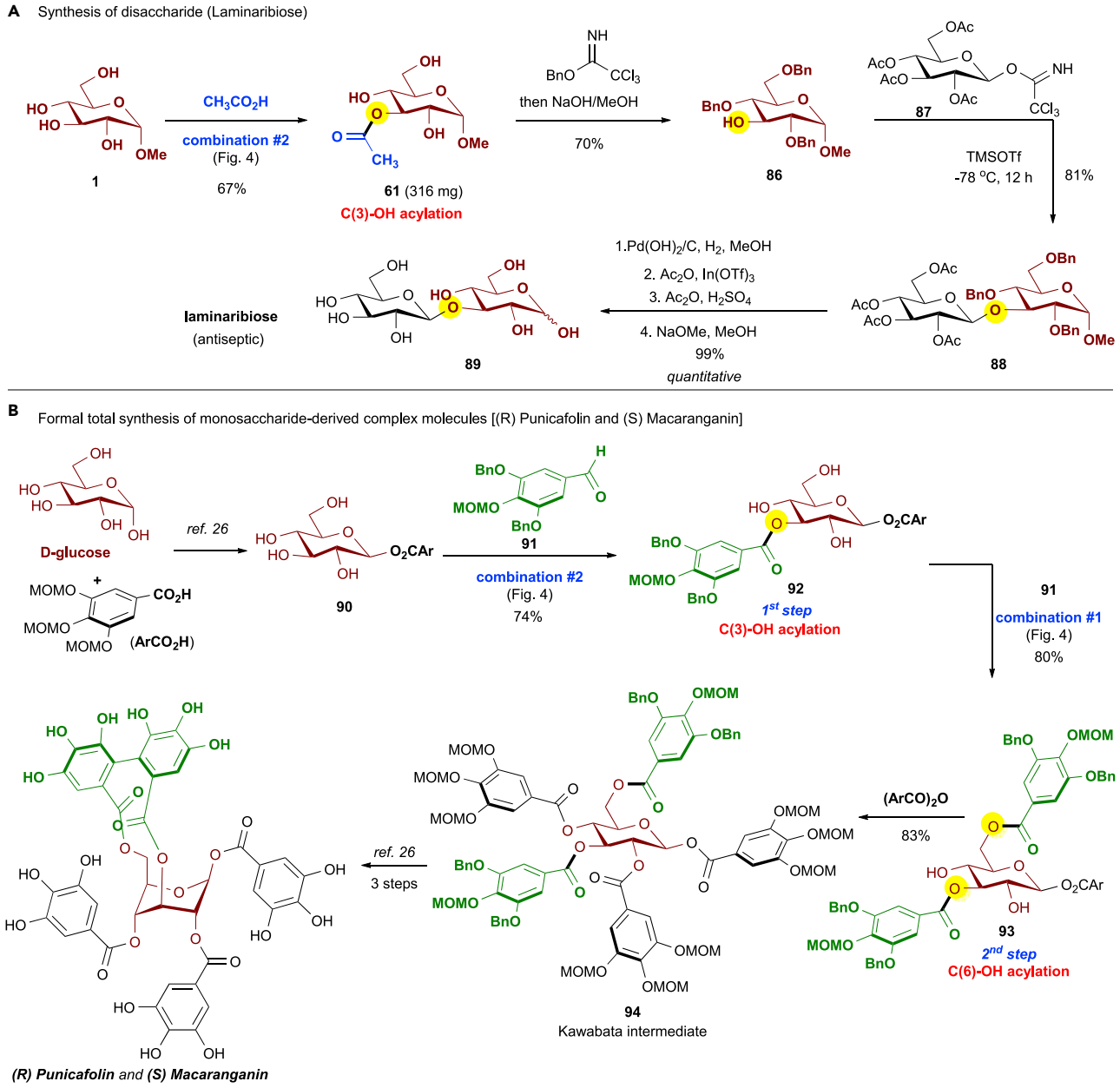


Figure 8. Concise synthesis of sophisticated functional molecules as enabled by our site-selective acylation strategy

method (35% overall yield from **90** to **94**). As a technical note, because many NHC catalysts and boronic acids are commercially available or easily accessible, further improvements in reaction efficiency and alternative site selectivity are readily achievable by our strategy. Molecular libraries of these natural products and their analogs can most likely be prepared in scalable quantities for bioactivity evaluations.

In summary, we have developed a readily programmable strategy for site-selective acylation of unprotected monoglycosides. The selectivity was achieved by proper combinations of commercially available NHC organic catalysts and boronic acids. The synergistic activation and deactivation effects brought by the NHC and boronic

acid dramatically amplify the reactivity difference of the multiple otherwise similar OH groups on saccharides. Such synergistic effects can also invert the initial reactivity preference of these OH moieties, offering selectivity patterns that are not available with previous strategies. Our approach can selectively acylate the C(2)-, C(3)-, and (C6)-OH groups of various monosaccharides and their analogs. Aldehydes, carboxylic acids, and carboxylic esters can all be used as the acylation reagents. We have also demonstrated that carboxylic-acid- or saccharide-containing pharmaceuticals, peptides, natural products, and other functional molecules can be site-selectively modified by our strategy. Application of our site-selective reaction can allow for concise and scalable access to such complex molecules as disaccharides and bioactive natural products. Given the unarguable significance and challenges associated with saccharides, we expect our approach to offer both fundamental and practical impacts in broad fields ranging from chemistry to medicine. Ongoing studies in our laboratories include site-selective reactions of complicated oligosaccharides, concise synthesis of sophisticated molecules bearing saccharide fragments, and bioactivity evaluation of saccharide-containing bioactive molecules for medicinal and agricultural applications.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Yonggui Robin Chi (robinchi@ntu.edu.sg).

Materials availability

All materials generated in this study are available from the lead contact without restriction.

Data and code availability

Details about methods, experimental procedures, mechanistic and DFT studies, characterization data, and NMR spectra are available in the supplemental information.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2022.04.019.

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AUTHOR CONTRIBUTIONS

Y.R.C. conceptualized and directed this research; W.-X.L. performed the main methodology development, scope evaluation, and synthetic application; Y.L., S.W., and Z.J. contributed to earlier studies; H.C., C.C.H., S.W., and H.W. contributed to scope evaluation and synthetic application; X.Z. performed DFT studies; and all authors contributed to discussions and manuscript preparation.

DECLARATION OF INTERESTS

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