Title: Programmable Selective Acylation of Saccharides Mediated by Carbene and Boronic Acid

Authors: Wen-Xin Lv[1,2], Hang Chen[2], Chang Chin Ho[2], Yingguo Liu[2], Shuquan Wu[1], Zhichao Jin[1], Yonggui Robin Chi[1,2]*

Affiliations:
[1]Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China.
[2]Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore.

*Corresponding author. Email: robinchi@ntu.edu.sg

Abstract: 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 understand saccharide-related biological processes and develop 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 monosaccharides. The boronic acids provide transient shielding on certain hydroxyl groups (while simultaneously promote reactions of other hydroxyl units) via dynamic covalent bonds to offer the first sets of selectivity controls. The NHC catalysts provide further layers of controls by mediating selective acylation of the unshielded hydroxyl moieties. Multiple activating/deactivating forces can be easily modulated to achieve 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.

Keywords: saccharides, polyols, site-selective acylation, multilayered selectivity amplification, programmable reaction, N-heterocylic carbene catalysis, boronic acid, saccharide-based pharmaceuticals.

Main Text:

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] (Fig. 1A). It has been proven 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 of the enormous applications and potentials, understanding of saccharide-related biological processes and development of saccharide-based pharmaceuticals remain challenging. A major obstacle lies on 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 hydroxyl groups of saccharides and polyol molecules. The dominated approach involves elegantly designed orthogonal protection/deprotection chemistry through typically long-step operations, as demonstrated by many pioneers such as Wong and Danishefsky[13-19]. While improvements are being made in this protection/deprotection approach, new strategies with shorter steps that avoid (or minimize) conventional protection/deprotection operations attract intense attentions for obvious reasons. For instance, Miller designed small molecule enzyme mimics for chemo- and/or stereo-selective reactions of saccharides and polyols[20,21]. Kawabata developed chiral pyridine-based organic catalysts that can selectively acylate hydroxyl groups at the C4-carbon of glucose[22,23]. Taylor has pioneered the use of boronic acids and borinic acids to shield *cis*-diols and modulate selective reactions of saccharides[24,25]. Studer found selective reactions of partially protected monosaccharides with NHC catalysts[26]. The use of other organic or metal catalysts and reagents for site-selective reactions of saccharides with minimized protections have also been reported[27,28]. Each of these methods has its own merits and limitations, and breakthroughs in this arena remain to emerge. Given the complexity of saccharides and the corresponding reacting partners, it appears introducing more controlling parameters that can be modularly tuned may offer attractive solutions.

Here we disclose a programmable multiple driving forces-mediated strategy for site-selective acylation of unprotected saccharides, their analogs and derivatives (Fig. 1B). We break down the challenging selectivity problem into a few smaller issues, each of which can be addressed by different while 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 hydroxyl groups at 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 hydroxyl groups from further reactions, providing the first layer of selectivity control. The introduction of boronic acid additives may also simultaneously accelerate reactions of certain hydroxyl groups[29], offering a second layer of selectivity control. In the same reaction solution, an N-heterocyclic carbene (NHC, or abbreviated as carbene) organic catalyst is introduced to provide a further layer of site

selectivity control. Multiple parameters involving stereo electronic effects and covalent/non-covalent interactions 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, acyl group can be site-specifically installed on C(2)-OH, C(3)-OH, or C(6)-OH of D-glucoside. Our strategy can be easily turned 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 Fig. 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 (R)-Punicafolin, (S) Macaranganin[30,31] and disaccharide laminaribiose[32] with important bioactivities.

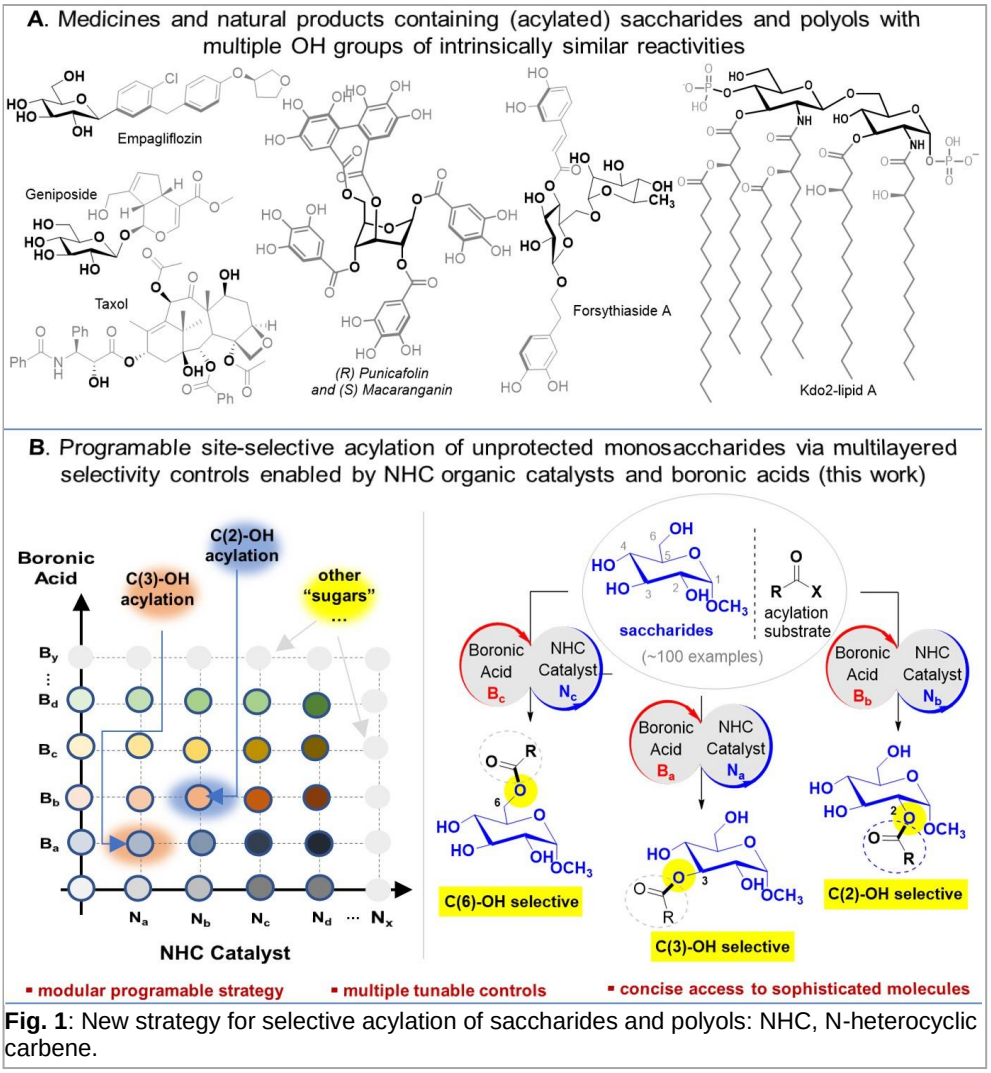


Fig. 1: New strategy for selective acylation of saccharides and polyols: NHC, N-heterocyclic carbene.

Summarized in Fig. 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 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 were briefly illustrated in Fig. 2A. 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, EtOAc). The reaction involves reversible reactions between two hydroxyl groups (C4- and C6-OH groups) of glucoside with boronic acid to form boronic ester **I** as an intermediate (detectable via ^1H NMR of the crude reaction mixture or isolable, depending on the specific substrates, see SI) [25]. This dynamic boronic ester formation provides a transient protection of the two hydroxyl groups from subsequent acylation reactions. In the same reaction solution, NHC catalyst reacts with acylation substrate to form an acyl azolium intermediate **II**[33,34]. 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 DCC), or carboxylic esters (**2c**) (Fig. 2A). The acylation reaction between intermediate **I** and **II** first forms acylated boronic ester of the glucoside as adduct **III** (as observed via ^1H NMR analysis of the crude reaction mixture). In this step (from intermediates **I** and **II** to adduct **III**), chemo-selectivity between C(2)-OH and C(3)-OH moieties is controlled by the structures of both 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 to note that the boronic ester formation (thermodynamically favorable under the reaction condition) and hydrolysis is a facile and reversible process for both intermediates **I** and **III**. Technically it's necessary to use a stoichiometric amount of the boronic acid to achieve optimal chemo-selectivity and avoid over acylation on more than one hydroxyl groups. Four sets of conditions (#1A, #1B, #2A, and #3A, Fig. 2A) were identified to give acceptable results. Condition #1B was chosen to study the effects of NHC catalysts and boronic acids since four possible mono-acylated saccharide adducts could be observable under this type of conditions (CH_3CN as solvent, one equivalent of DQ and boronic acid).

The loadings of boronic acid (**B1**) have clear influence on the reaction yields and selectivity (Fig. 2B). Increasing the loadings of boronic acid significantly increased the yield of C3-O-acylate while decreased those of the C6-O-acylate and C4-O-acylate. The yield of C2-O-acylate remained largely unchanged with variation of boronic acid loadings. The structures of the boronic acids (as exemplified by selected examples **B1** to **B7**) could also dramatically impact the yields and selectivity of the reactions (Fig. 2C). For example, removing the methoxy substituents on the phenyl ring of **B1** (to give boronic acid **B3**) led to a big drop on yields of C3-O-acylate and 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 1.0 equivalent **B1**, vs 38% overall yield without **B1**, Fig. 2B and 2C). These results suggest that the formation of boronic ester intermediate (**I**, Fig. 2A) 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 (Fig. 2D).

Our results (Fig. 2A-D, and SI) clearly showed that both NHCs and boronic acids have distinct effects on each of the different hydroxyl 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 (Fig. 1B, Fig.3, 4) to achieve site-selective acylation on different hydroxyl groups of various types

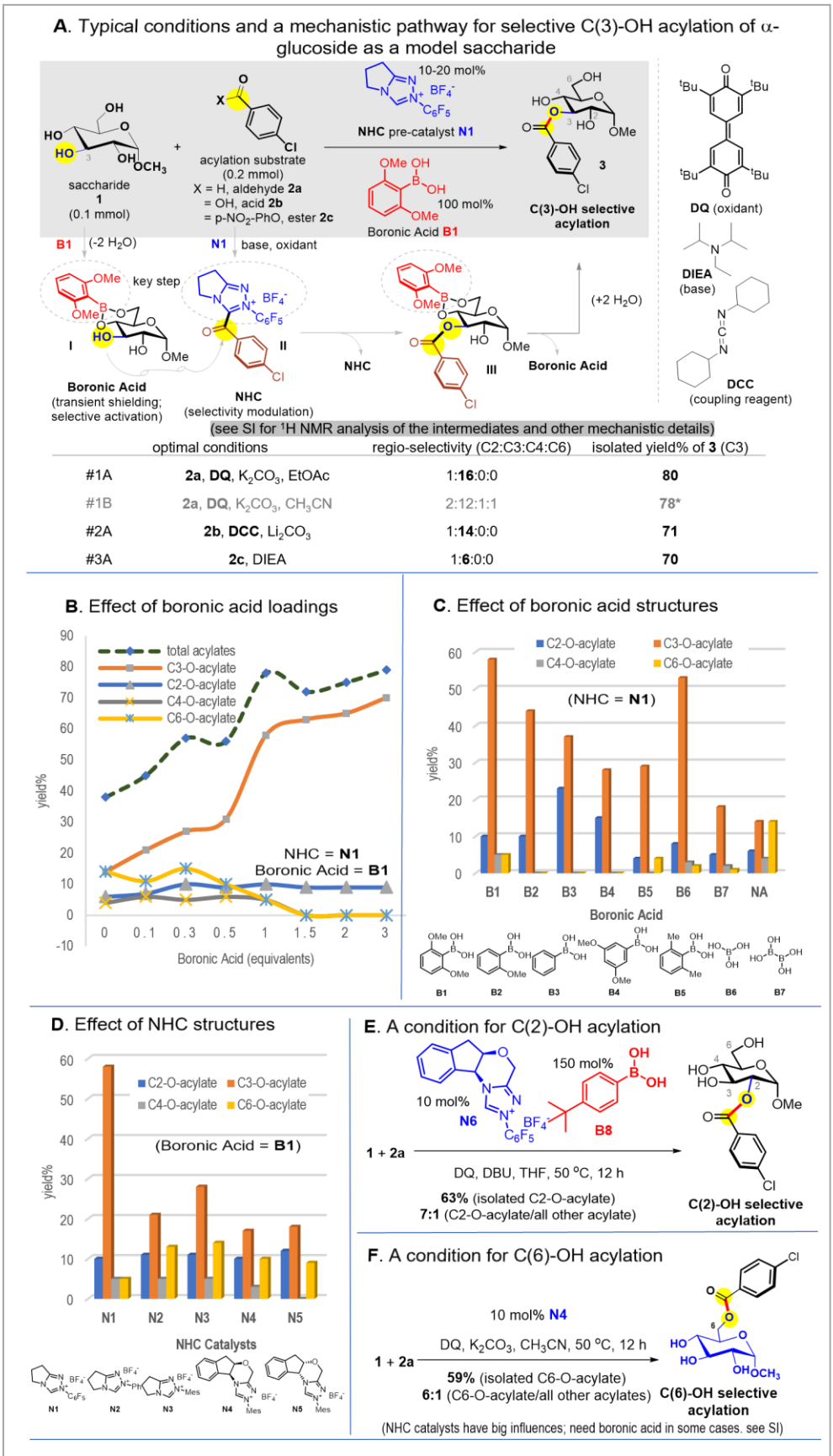


Fig. 2: Conditions for site-selective acylation of a model saccharide mediated by NHC catalysts and boronic acids (see supplemental information for more details).

of saccharides (and polyols) with diverse acylation partners. For example, selective C(2)-OH acylation of glucoside (**1**) could be achieved by combined use of a chiral NHC pre-catalyst **N6** and a boronic acid **B8** under a slightly modified condition to give C2(OH)-acylated product in 63% yield and 7:1 regio-selectivity; Fig. 2E and Fig. 3A) . Acylation of C(6)-OH of glucoside (**1**) selectively was achieved by using NHC pre-catalyst (**N4**) alone (Fig. 2F and Fig. 3A). In other examples of this study, selective C(6)-OH acylation was obtained via combined use of a 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 5x8 possible combinations) for optimal outcomes of different types of saccharides and acylation partners. Although a definite relation between structures and reaction outcomes cannot be drawn at this point, a number of guiding trends were observed, as illustrated in Fig. 3A. For instance, the combination of **N1** and **B1** worked well for C(3)-OH acylation of α- and β-glucoside (combination #2, Fig. 3A). This combination (**N1**, **B1**) also worked effectively for similar selectivity patterns when using carboxylic acids or esters as the acylation agents (Fig.4). We eventually identified twelve combinations of NHCs and boronic acids (combination #1-12, Fig. 3A) for various selective reactions on a large set of saccharides and acylation partners (Fig. 3-4).

The substrate tolerances and limitations using aldehydes as the acylation reagents were studied (Fig. 3B). With glucoside (**1**) as a model saccharide, C(3)-OH selective acylation could be achieved using various aryl aldehydes (**3**-**17**) and α,β-unsaturated aldehyde (**18**,**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)[35], could be selectively acylated (**20**-**23**) with 66-75% yields and around 10:1 regio-selectivity. Diabetes drugs containing analogs of monosaccharides, Dapagliflozin and Empagliflozin[19], could be acylated with good yields

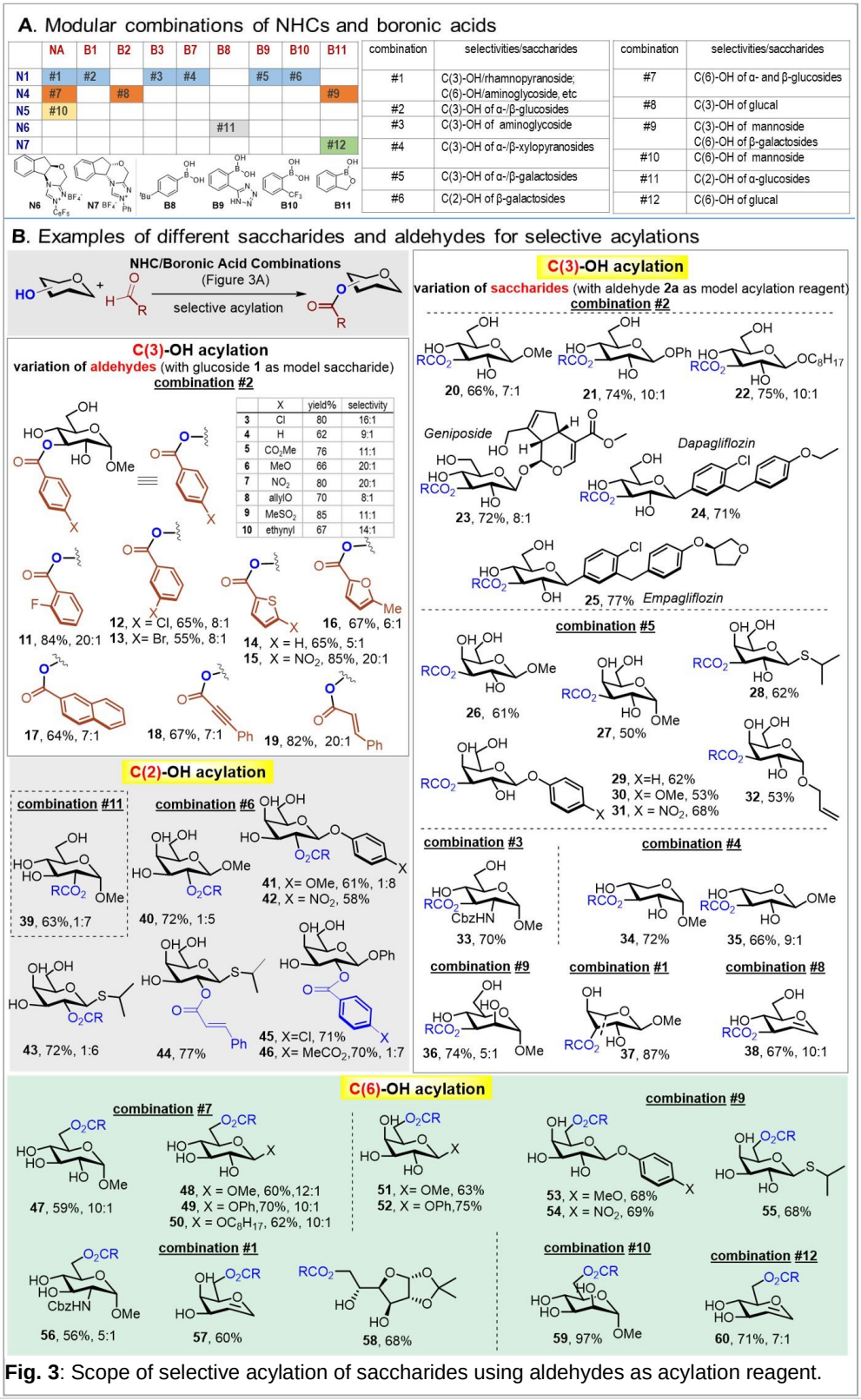


Fig. 3: Scope of selective acylation of saccharides using aldehydes as acylation reagent.

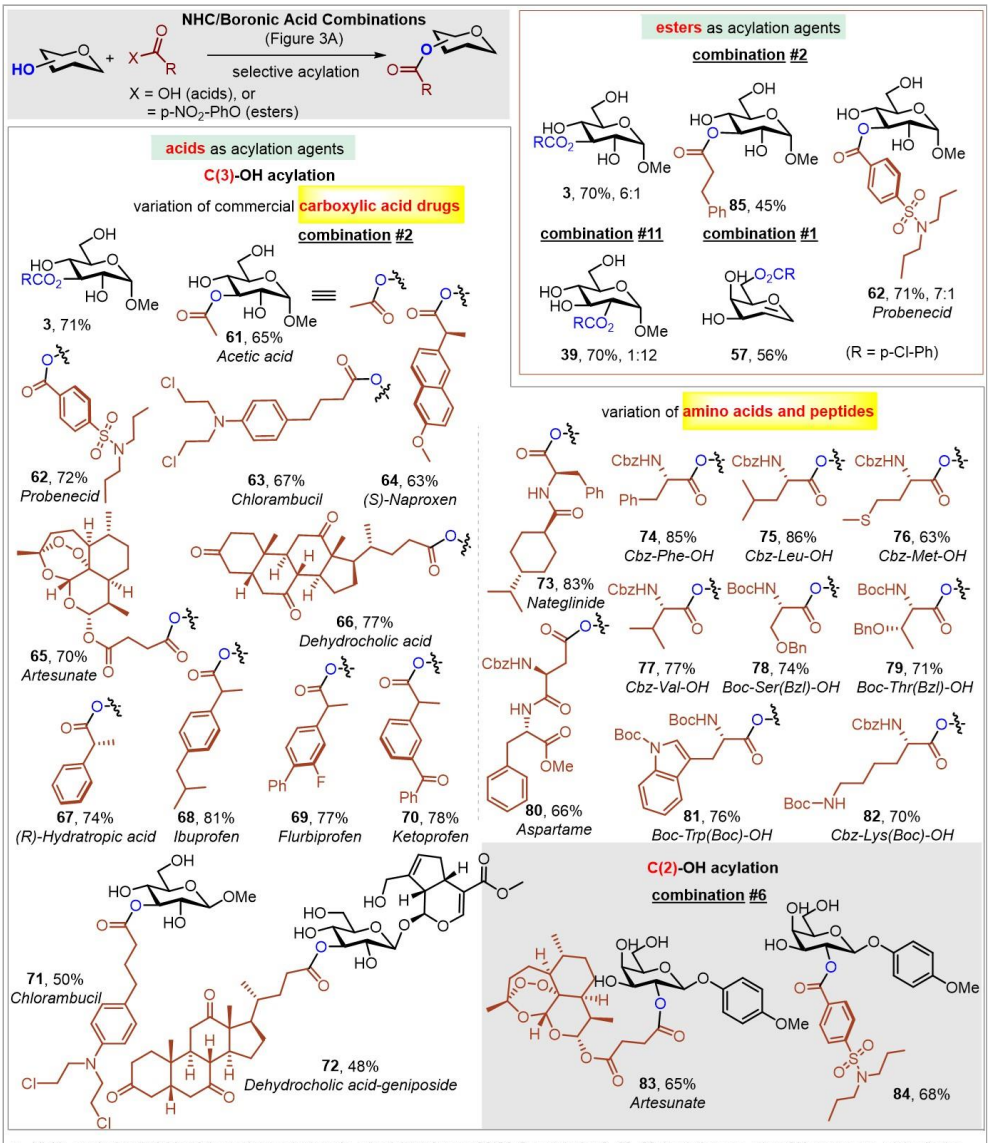
and excellent regio-selectivity (**24**, **25**). The C(3)-OH acylation of α- and β-galactosides were achievable using NHC **N1** and boronic acid **B9** (combination #5) (**26**-**32**). Examples of other monosaccharides evaluated under current conditions for C(3)-OH acylations include aminoglycoside **33**, α- and β-xylopyranosides (**34**, **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) (Fig. 3B). Examples of saccharides that gave satisfactory yields and selectivityvalues 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 by through sole use of NHC catalyst ("combination" #1, 7, 10) or in the presence of both NHCs and boronic acids (combination #9 and 12). For example, the C(6)-OH of α- and β-glucosides were selectively acylated by use of NHC pre-catalyst **N4** alone (**47**-**50**). Acylation on the C(6)-OH of β-galactosides (**51**-**55**) was realized by using **N4** and **B11** (combination #9).

It is worth to remind 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 NHC catalyst (**N1**) alone gave C(6)-OH acylation product (**56**); while a combined use of **N1** and boronic acid **B3** gave C(3)-OH acylation product (**33**). Simplar comparisons can be made to other examples such as products **3**/**39**/**47** from α-glucoside (acylation on C3, C2, and C6 respectivley). As a technical note, changes to both NHC catalysts and boronic acids are often needed in order to achieve optimal yields and selectivity values for each of the different OH groups on the same saccharides.

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 (Fig. 4). To our delights, 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, dicyclohexyl carbodiimide) was used to convert the carboxylic acid to its reactive ester form for subsequent reaction with NHC catalyst to form the NHC-bound acyl azolium intermediate (**II**, Fig. 2A). A typical reaction condition using carboxylic acid is illustrated in Fig 2A (optimal condition #2A). With a similar effort, conditions for using carboxylic esters (4-nitrophenol esters of carboxylic acids) could be readily realized, as examplified by optimal condtion #3A (Fig. 2A).

The reaction generality is exceptional with aryl/alkyl carboxylic acids and esters bearing various functional groups. For example, carboxylic acid-containing commercial phamaceuticals reacted with monosaccharides in a highly regio-selective manner to give the corresponding drug-saccharide conjugates (**62**-**72**, **83**-**84**) with good isolated yields. Our reaction



▪ Yields are isolated yields of the major product; regio-selectivity refers to C3/C2-O-acylate for **3, 62, 39** (acylations on other OH groups are minimal); the regio-selectivity value is not given when acylation on all other OH groups are trace (see SI). R = p-Cl-Ph for product **3, 39, 57**.

Fig. 4: Scope of selective acylation of saccharides using carboxylic acids and esters as acylation reagent.

conditions are mild and tolerate sensitive functional groups, such as the endoperoxide 1,2,4-trioxane ring in Artesunate[36] (**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 may be further developed to prepare conjugates of saccharides and peptides/proteins. Our strategy may 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**). A number of carboxlic esters (**3**, **85**, **39**, **57**, **62**; Fig. 4) as acylation reagents were also examined. Similarly, there are no apparent limitations with respect to the core scalfolds and substituents of the carboxylic esters.

Our site-selective acylation of monosaccharides enables concise synthesis of complex molecules such as oligosaccharides and functional molecules containing saccharide fragments and their derivatives (Fig. 5). For example, starting from C(3)-OH acylated glucoside adduct (**61**) prepared using 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 Fig. 5A. By varying the reactive site (such as C(3)-OH of **1**) and the monosaccharide coupling units (such as **87**), it is reasonable to expect that our methods shall allow for rapid access to a diverse set of useful disaccharides and their analogs[37], including those that are expensive and difficult to obtain. Our method can also allow for efficient synthesis of saccharide-derived complex molecules (Fig. 5B). Here we demonstrate a formal total synthesis of puncafolin and macaranganin[30,31], natural products of the ellagitannin family[38] containing a monosaccharide core with important bioactivities. The first total synthesis of these two natural products were recently reported by Ueda and Kawabata[22]. In their approach, sequential selective acylation at the C(4)- and C(2)-OH groups (of **90**) mediated by Kawabata's elegant pyrrolidinopyridine-based catalysts are key steps to prepare intermediate **94** (Kawabata's intermediate as named in Fig. 5B) 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 selective acylations at the C(3)- and C(6)-OH moieties mediated by NHC and boronic acid. The (un-optimized) overall yield from **90** to **94** is 49%, comparable to that of Kawabata's method (35% overall yield from **90** to **94**). As a technical note, since many NHC catalysts and boronic acids are commercially available or easily accessible, further reaction efficiency improvements and alternative site-selectivity are readily achievable using our strategy. Molecular libraries of these natural products and their analogues can be likely prepared in scalable quantities for bioactivity evaluations.

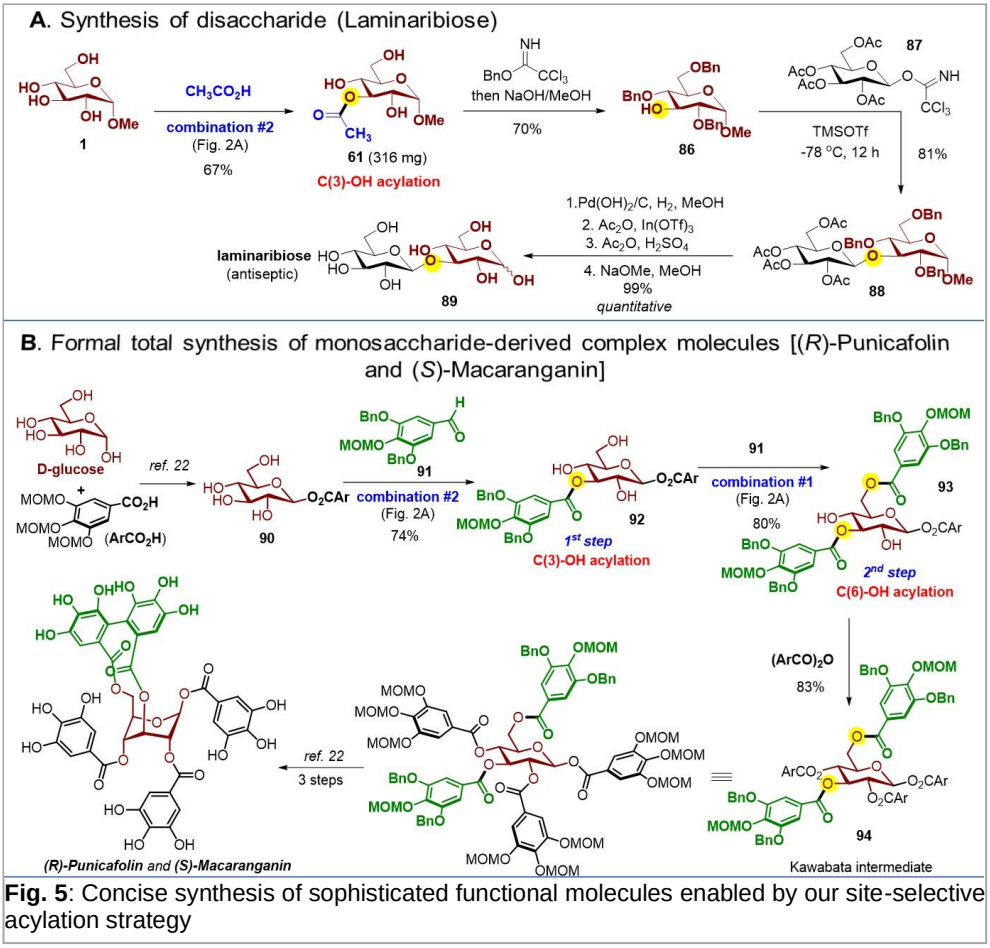


Fig. 5: Concise synthesis of sophisticated functional molecules enabled by our site-selective acylation strategy

In summary, we have developed a readily programmable strategy for site-selective acylation of unprotected monosaccharides. 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 hydroxyl groups on saccharides. Such synergistic effects can also invert the initial reactivity preference of these hydroxyl moieties, offering selectivity patterns that are not available with previous strategies. With our approach, the C(2)-, C(3)-, and (C6)-OH groups of various monosaccharides and their analogues can be selectively acylated. Aldehydes, carboxylic acids, and carboxylic esters can all be used as the acylation reagents. We have also demonstrated that carboxylic acid/saccharide-containing pharmaceuticals, peptides, natural products and other functional molecules can be site-selectively modified using our strategy. Application of our site-

selective reaction can allow for concise and scalable access to complex molecules such 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 from chemistry to medicines. 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 studies, characterization data and NMR spectra are available in the supplemental information.

Supplemental Information

Document SI: Supplemental experimental procedures, Figures S1–S14, and Tables S1–S4, NMR spectra, Supplemental references.

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

Declaration of interests: The authors declare no competing financial interests.

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