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Synergistic catalysis: Unlocking site-selective functionalization of carbohydrate hydroxyl groups for advanced glycoscience

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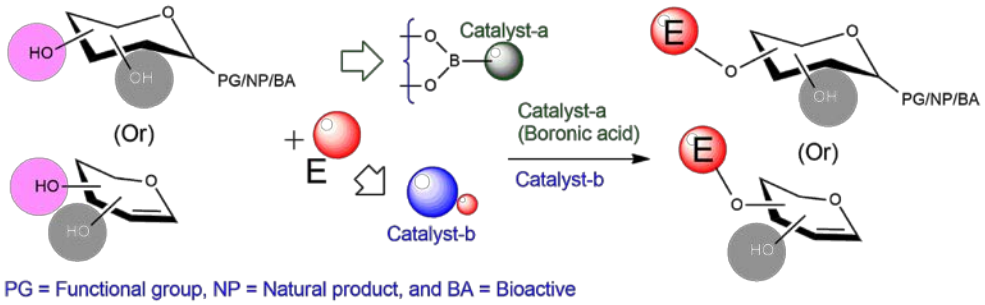
Review

ABSTRACT



PG = Functional group, NP = Natural product, and BA = Bioactive

Selective functionalization of carbohydrate hydroxyl groups is challenging due to their abundance and similar reactivity. Synergistic catalysis—using multiple catalysts to activate different substrates—offers a promising solution, outperforming traditional single-catalyst approaches. This review presents recent advances in synergistic systems employing transition metals, chiral ligands, and organoboron compounds to achieve regio-, stereo-, and enantioselective transformations. These methods enable the construction of glycosidic linkages and carbohydrate mimics with potential biological activity. The role of non-covalent interactions, dynamic kinetic resolution, and computational tools in guiding selectivity is also discussed. Emphasis is placed on reaction efficiency, sustainability, and scalability, alongside persistent challenges such as hydroxyl differentiation, catalyst compatibility, and system optimization. Future directions include developing novel catalytic platforms, integrating computational design, and adopting greener methodologies to expand access to carbohydrate-based molecules with valuable functional properties.

Keywords: Synergistic catalysis, Carbohydrates, Site-selective, Bioactive, Artificial Intelligence (AI) and Machine Learning

INTRODUCTION

Carbohydrates are essential biomolecules involved in biological processes like cellular recognition, signal transduction, and immune response.[1] Their structural complexity, with multiple chiral centers and hydroxyl groups, makes them challenging yet intriguing targets for chemical modification.[2] The selective functionalization of carbohydrates - particularly at specific hydroxyl positions - is crucial for their use in medicinal chemistry, glycobiology, and materials science.[3] Modified carbohydrates play key roles in the development of vaccines, diagnostics, and therapeutics, but the similar reactivity of hydroxyl groups has historically required protecting groups and lengthy synthetic sequences to achieve selectivity.[4]

To address these challenges, synergistic catalysis has emerged as a powerful strategy.[5] By employing multiple catalysts that work together, synergistic catalysis enables site- and stereoselective reactions under milder conditions, eliminating the need for protecting groups and enhancing step- and atom-economy.[6] This approach has proven invaluable in differentiating hydroxyl groups in carbohydrate molecules, facilitating the development of complex, bioactive sugar derivatives.

As key contributors to biological complexity, carbohydrates are involved in essential processes including energy metabolism, cellular communication, and the modulation of immune responses.[7] Their structural intricacy presents significant challenges in synthetic chemistry, particularly for regio- and stereocontrol in oligosaccharide and glycoconjugate construction. Traditional synthetic methods often fall short of the selectivity and efficiency required by modern glycoscience.

Advances in metal catalysis,[8] organocatalysis,[9] and photoredox chemistry[10] have ushered in a new era of catalytic innovation, with synergistic catalysis[11] at the forefront. This strategy enables precise control over transformations in carbohydrates, even in their densely functionalized hydroxyl landscapes. Furthermore, the ability to selectively functionalize carbohydrates has led to the creation of glycohybrids—molecular architectures combining sugar scaffolds with bioactive motifs.[12] These hybrids are valuable tools for studying protein-carbohydrate interactions and advancing therapeutic and diagnostic applications.[13]

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Photoredox catalysis, which uses visible light to drive sustainable transformations, has shown promise in overcoming longstanding challenges in glycosylation and hydroxyl group differentiation.[10, 14] Despite significant progress, challenges remain in developing fully catalytic, site-selective transformations compatible with minimally protected carbohydrates. Innovations in chiral catalysis,[8-11] organoboron chemistry,[15] and biomimetic approaches[16] are paving the way for more atom-economical methods, by passing the labor-intensive protection-deprotection cycles typical in carbohydrate synthesis. This review discusses recent breakthroughs in synergistic catalysis for carbohydrate functionalization, with a focus on selective hydroxyl group modification in minimally protected sugars (Figure 1). We examine the design principles, mechanistic insights, and applications of these strategies, highlighting their transformative impact on glycoscience and exploring future directions, including the integration of sustainable catalysis and AI-assisted design.

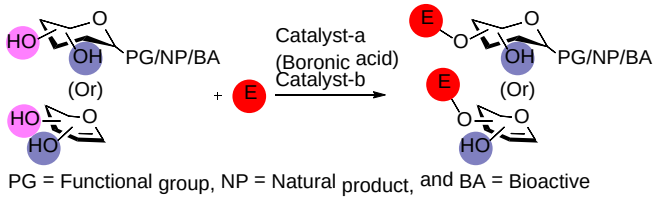


Figure 1. Site-selective functionalization of carbohydrate hydroxyl groups enabled by synergistic catalysis.

2. The Dawn of Synergistic Catalysis in Carbohydrate Functionalization

The synthesis of complex carbohydrates is a significant challenge in organic chemistry due to their intricate stereochemistry and multiple reactive sites. Traditional methods, relying on protecting group strategies, often introduce inefficiencies, excessive steps, and waste. Synergistic catalysis offers a transformative solution, overcoming these bottlenecks and opening new possibilities in carbohydrate functionalization.[11, 17]

At the core of synergistic catalysis is cooperative activation, where two distinct catalysts work together to enhance selectivity and efficiency.[5] This dual activation mechanism enables regio-, stereo-, and chemo-selective transformations with greater precision than single-catalyst systems. For example, a Lewis acid can selectively activate a hydroxyl group, while a transition metal catalyst concurrently activates an electrophilic partner, improving reaction efficiency and selectivity.

Carbohydrate functionalization, especially for polyol-rich sugars, traditionally requires labor-intensive protection-deprotection strategies.[4] Synergistic catalysis simplifies this by directly activating target functionalities, reducing steps, byproducts, and aligning with green chemistry principles. This approach also expands synthetic capabilities, allowing for enantioselective transformations and providing control essential for biologically active oligosaccharides and glycoconjugates, where small stereochemical changes can significantly impact biological activity.

These advances are not limited to academia but have practical applications in pharmaceuticals, biotechnology, and materials science. The ability to generate diverse, selectively modified sugars supports drug discovery, glycomimetic design, and vaccine development. Glycoengineered therapeutics and carbohydrate-based biomaterials benefit from the increased precision and diversity enabled by synergistic catalysis.

As the field progresses, continued advancements in catalyst design and mechanistic understanding promise to redefine carbohydrate functionalization, enabling entirely new modes of reactivity and shaping the future of glycoscience.

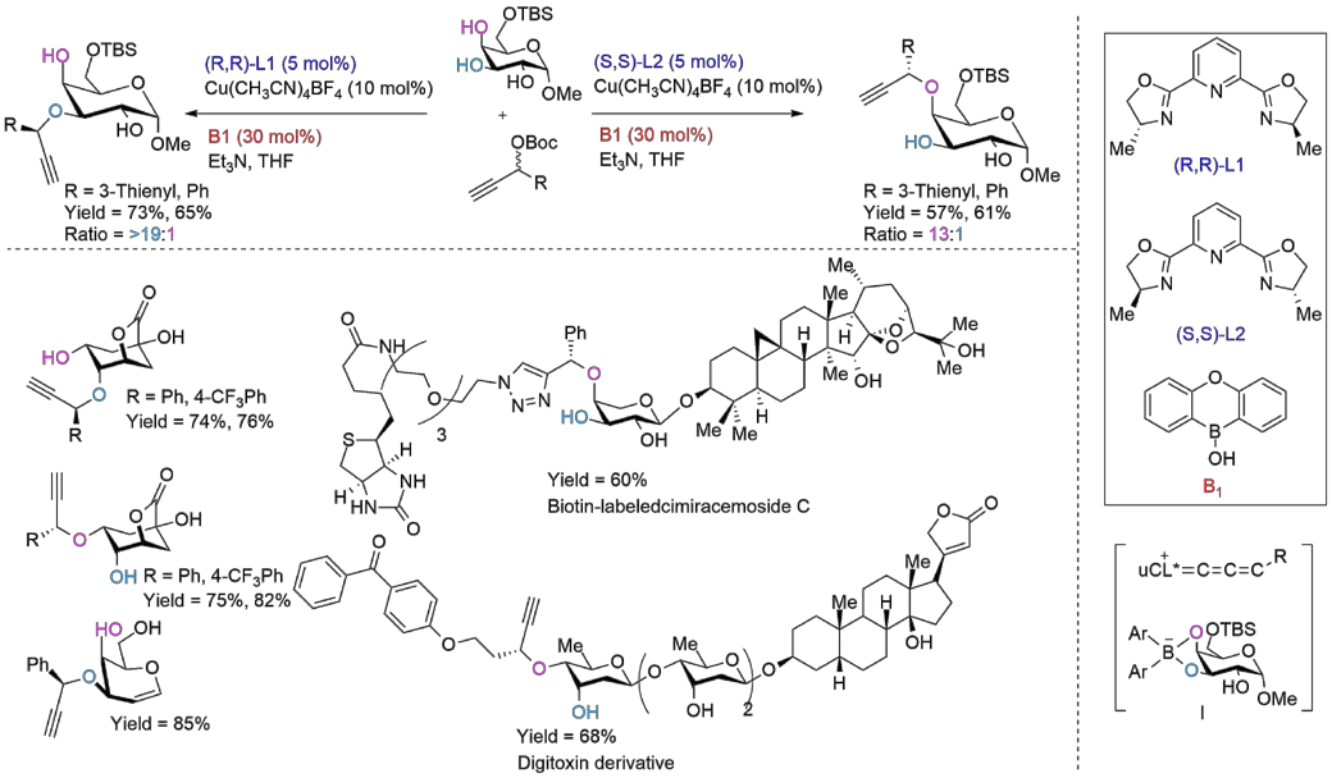
3. Synergistic Catalytic Site-Selective Carbohydrate Hydroxyl Groups Functionalizations

In the realm of organic chemistry, carbohydrates have long presented a formidable challenge to researchers striving for precision in molecular modification. These complex molecules, adorned with multiple hydroxyl (-OH) groups, resist selective transformation, making targeted modifications daunting. Yet, the ability to functionalize carbohydrates at specific hydroxyl positions is crucial, particularly for synthesizing biologically relevant molecules such as glycosides, therapeutic agents, and oligosaccharides.[18]

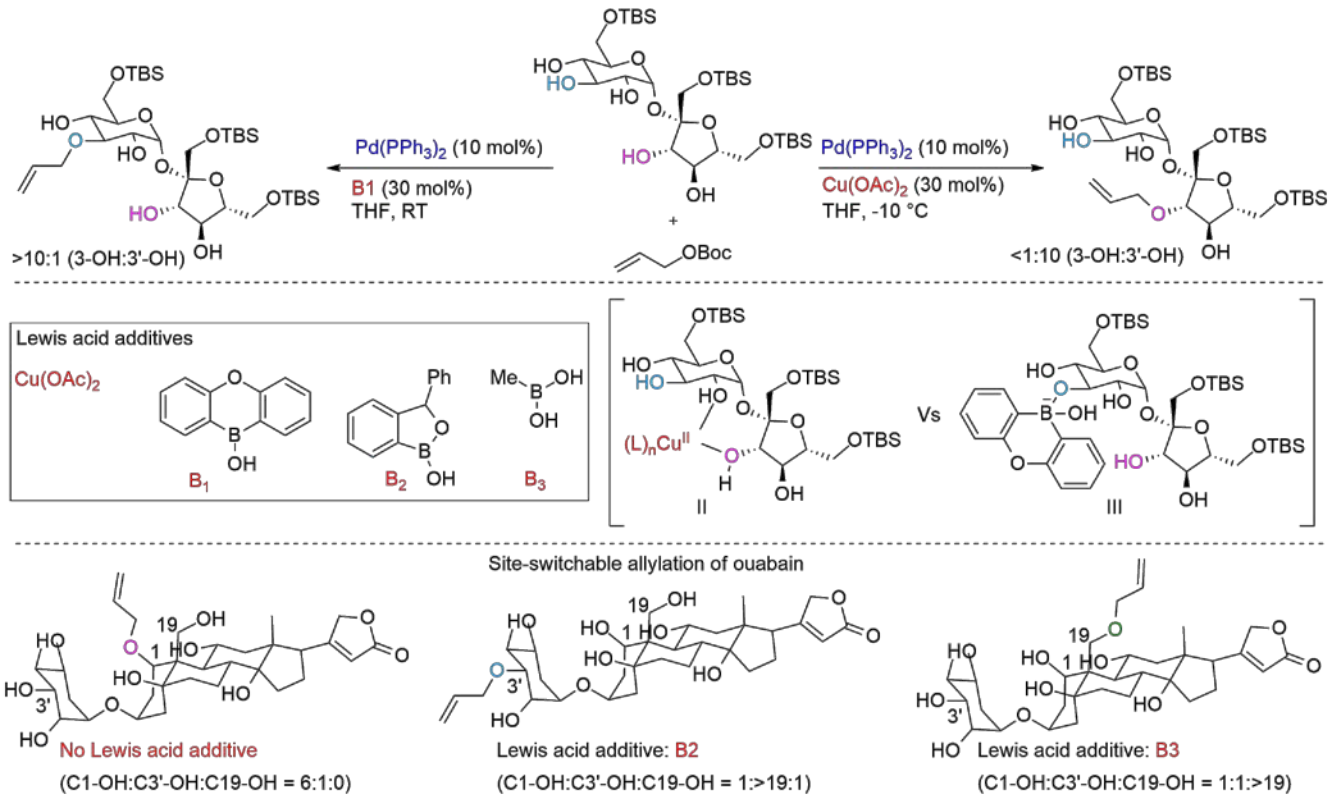
A groundbreaking approach has emerged through synergistic catalytic strategies, in which multiple catalysts work in concert to achieve site-selective functionalization. This innovative method leverages the complementary strengths of different catalysts to precisely target and modify specific hydroxyl groups while leaving others unaltered. By employing a dual-catalyst system, scientists can now achieve unprecedented selectivity in carbohydrate functionalization, enabling the synthesis of complex derivatives with enhanced biological and chemical utility.

3.1 Synergistic Chiral Copper/Boronic Acid Catalyzed Site-Selective and Site-Divergent Delivery of Terminal Propargyls to various monosaccharides

Niu and colleagues have addressed the long-standing challenge of site-selective modifications of carbohydrates with an innovative synergistic catalytic strategy, first introduced by the group in 2017.[19] This method enables the precise differentiation of hydroxyl groups on monosaccharides, facilitating the installation of terminal propargyl groups. By employing a chiral copper complex derived from the bis-oxazolidine (BOX) ligand and Taylor's borinic acid, the team demonstrated that site selectivity can be effectively controlled by altering the enantiomeric identity of the chiral ligand (Scheme 1). This versatile protocol has been successfully applied to a wide range of common sugars and extended to complex glycosidic natural product frameworks, such as Cimiracemoside C and the oligosaccharide digitoxin. Additionally, the method allows for the straightforward incorporation of biologically relevant labels, such as biotin or photoaffinity tags, broadening its applications in biological research.



Scheme 1: Site-selective installation of terminal propargyl groups on monosaccharides using a synergistic catalytic strategy.



Scheme 2. Site-Switchable Mono-O-Allylation of Polyols Using Pd/Lewis Acid Co-Catalysis.

Mono-O-Allylation of Polyols

Selective functionalization of one hydroxyl group in a carbohydrate substrate, while leaving others unaffected, is a significant challenge due to the similar reactivity of these functional groups.[18] Differentiation between these groups usually arises from subtle steric and electronic differences, with reaction site selectivity often determined by altering conditions. Even more difficult is the ability to switch the reaction site, which requires precise control over the reaction conditions. In 2020, Niu and colleagues addressed this challenge by developing a site-switchable mono-O-allylation strategy for polyols using a Pd/Lewis acid co-catalytic system.[20] Their approach capitalized on varying Lewis acid additives, which selectively interact with specific hydroxyl groups within the polyol framework, enabling the installation of an allyl group at different hydroxyl sites (Scheme 2). The Lewis acid additive played a pivotal role in directing the regioselectivity of the reaction, allowing for controlled site-switching simply by altering the identity of the Lewis acid—a concept not previously explored systematically.

This method demonstrated a broad substrate scope, enabling selective derivatization of complex, bioactive natural products. Notably, Niu's team successfully applied this strategy to the site-switchable allylation of polyhydroxylated natural products such as ouabain, achieving selective modification at the C1-OH, C3'-OH, or C19-OH positions using the same Pd catalyst but different Lewis acid additives.

3.3. Synergistic N-Heterocyclic Carbene and Boronic Acid-Mediated Programmable Site-Selective Acylation of Unprotected Saccharides

The selective acylation of unprotected saccharides remains one of the foremost challenges in carbohydrate chemistry, primarily due to the densely functionalized and stereochemically similar hydroxyl groups across sugar molecules.[21] In a landmark 2022 study, Chi and co-workers introduced a powerful synergistic catalytic strategy that enables programmable, site-selective acylation of saccharides through a dual catalytic system comprising N-heterocyclic carbenes (NHCs) and boronic acids (Scheme 3).[22]

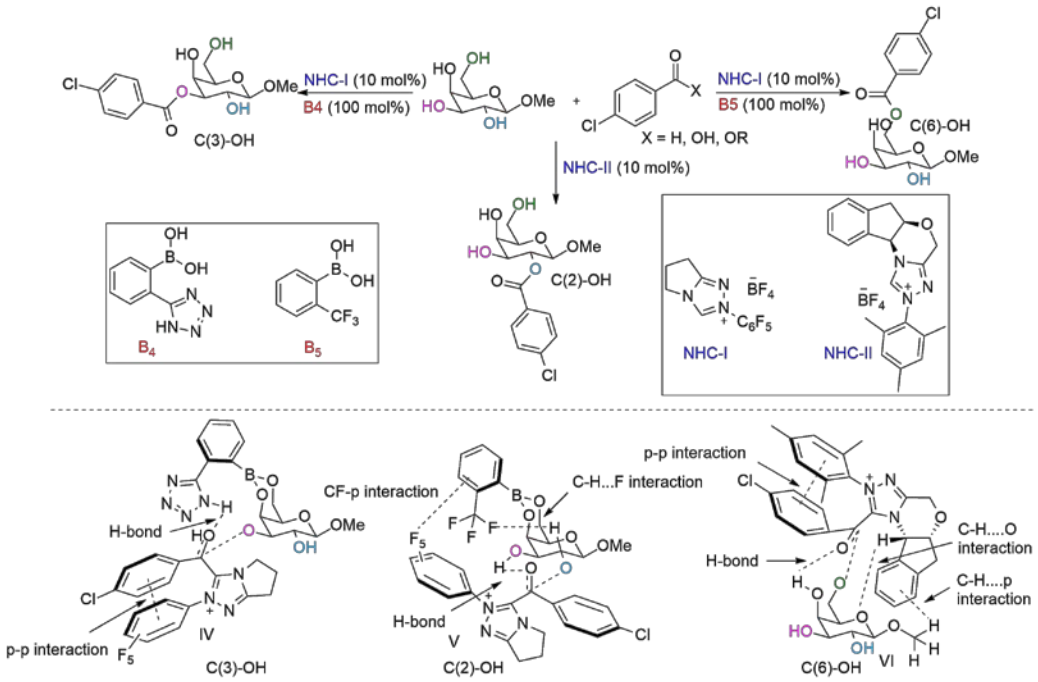
This innovative method operates via a multilayered selectivity-amplification mechanism. Boronic acids engage in reversible covalent interactions with specific hydroxyl groups, effectively shielding them and directing the acylation to unbound positions. Simultaneously, NHCs catalyze the acyl transfer to these unprotected hydroxyl groups with remarkable precision. This cooperative interplay offers finely tunable regioselectivity, as variations in the structures of both the boronic acids and NHCs modulate the activation and deactivation pathways—allowing for modular, programmable control over site-selectivity.

Chi and colleagues demonstrated the broad utility of this approach across a diverse array of monosaccharides and analogs, enabling efficient and regioselective synthesis of complex saccharide-derived architectures. Notably, the strategy supports rapid diversification of carbohydrate scaffolds using a consistent reagent set, where subtle changes in catalyst combinations yield dramatically different selectivity profiles.

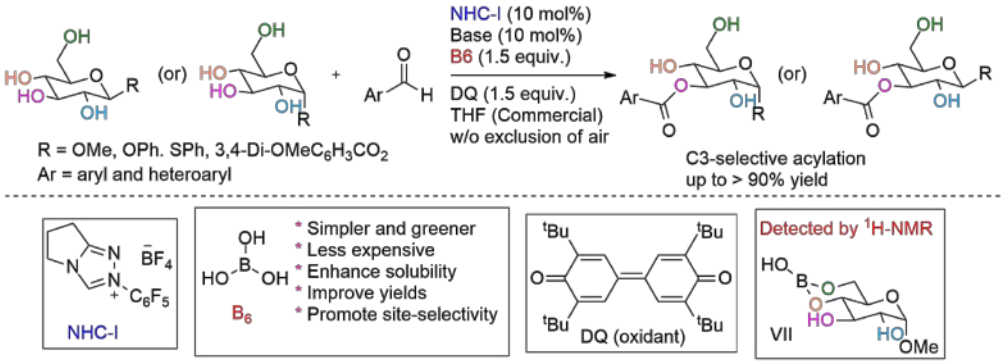
Mechanistic insights supported by density functional theory (DFT) calculations revealed that the observed regioselectivities arise from a network of non-covalent interactions (NCIs), as well as steric and electronic effects between catalyst side chains and sugar hydroxyl or C–H groups. These findings highlight the critical role of molecular design in optimizing catalyst performance and reinforce the concept that site-selectivity in carbohydrate functionalization is an emergent property shaped by multiple, synergistic interactions.

3.4. NHC and Boric Acid Co-Catalysis for Site-Selective C3–OH Acylation of Unprotected Monosaccharides

While the aforementioned strategy offers remarkable control over selectivity, it also underscores the intrinsic complexity of saccharide systems. These findings highlight the continuing challenge of developing universal protocols, as carbohydrate functionalization often demands bespoke catalytic systems tailored to each sugar and specific hydroxyl group.



Scheme 3. Synergistic NHC and boronic acid-mediated site-selective acylation of unprotected saccharides.



Scheme 4. Mild and selective C3–OH acylation of unprotected monosaccharides using N-heterocyclic carbene (NHC) catalysis in conjunction with boric acid ($B(OH)_3$) as a promoter.

Among the enduring challenges in carbohydrate chemistry, the selective acylation of hydroxyl groups in unprotected saccharides remains particularly formidable. In this context, a recent contribution by Chi and co-workers represents a significant breakthrough. They developed a mild, operationally simple, and environmentally benign method for the selective acylation of the C3–OH group in unprotected monosaccharides. This approach employs N-heterocyclic carbene (NHC) catalysis in synergy with boric acid [$B(OH)_3$] as a promoter (Scheme 4).[23]

A key strength of this protocol lies in its emphasis on simplicity and sustainability. The reaction is performed in commercially available tetrahydrofuran (THF), without the need for rigorous exclusion of moisture or air—marking a departure from conventional moisture- or air-sensitive conditions often required in carbohydrate acylation. Despite this operational simplicity, the methodology consistently affords good to excellent yields, including on gram scales, thus demonstrating strong practical applicability.

Central to the success of this method is boric acid—an inexpensive, readily accessible, and environmentally friendly boron reagent. Rather than serving as a passive additive, $B(OH)_3$ fulfills several critical mechanistic roles: it enhances substrate solubility via transient borate ester formation, selectively shields the C6–OH group, and directs regioselectivity toward the C3–OH position. These regioselectivity-determining effects, corroborated by ^{1}H NMR studies, effectively mimic the behavior of more complex aryl boronic acids, while avoiding their associated drawbacks such as toxicity, cost, and handling difficulty.

From a green chemistry perspective, this protocol is especially noteworthy. It eliminates the need for protecting groups, reduces the number of synthetic steps, proceeds under ambient conditions, and enables the recycling of both the NHC catalyst and boric acid. Notably, boric acid can be readily recovered through simple extraction and reused over multiple cycles with minimal loss in activity.

3.5. Synergistic Chiral Rh(I)/Organoboron Catalyzed Site-Selective Carbohydrate Functionalization

Bhaskara Rao et al. reported a highly efficient method for the stereocontrolled synthesis of arylhydronaphthalene glycosides using cooperative Rh(I) and boronic acid catalysis (Scheme 5).[24] This strategy achieves four levels of stereocontrol: (1) site-selective functionalization of carbohydrate polyols, (2) enantiocontrol in Rh(I)-mediated oxidative addition, (3) dynamic kinetic resolution in anomeric oxygen functionalization, and (4) trans-diastereocontrol on the hydronaphthalene scaffold. The method demonstrated excellent regio- and diastereoselectivity, highlighting the compatibility of chiral Rh(I) catalysis with boronic acid as a co-catalyst.

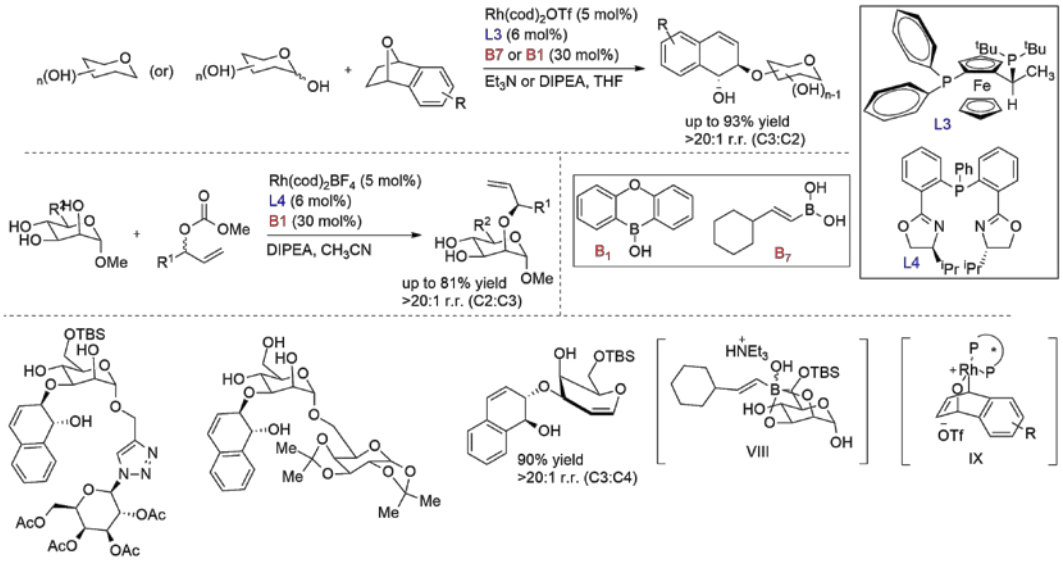
Cyclohexylvinylboronic acid was identified as the optimal boronic acid catalyst, with ligand selection being key to reaction stereoselectivity. Kinetic and computational studies confirmed the active participation of both Rh and boronic acid catalysts in the rate-limiting step. This synergistic approach provides access to biologically relevant arylnaphthalene glycosides, enabling precise control over enantio-, diastereo-, regio-, and anomeric configurations.

The method was applied to a broad range of carbohydrate polyols and meso-oxanorbornadienes. Carbohydrate polyols—including mannose, galactose, fucose, and unprotected anomeric saccharides—yielded predominantly trans-hydronaphthalene glycosides with excellent stereocontrol. Both α- and β-anomers were tolerated in several cases. The stereoselectivity and yields were influenced by the chirality of the ligand, the structure of the carbohydrate polyol, and the electronic properties of the organoboron reagent. The absolute and regiomeric configurations of the products were confirmed by X-ray crystallography and vibrational circular dichroism (VCD) analysis.

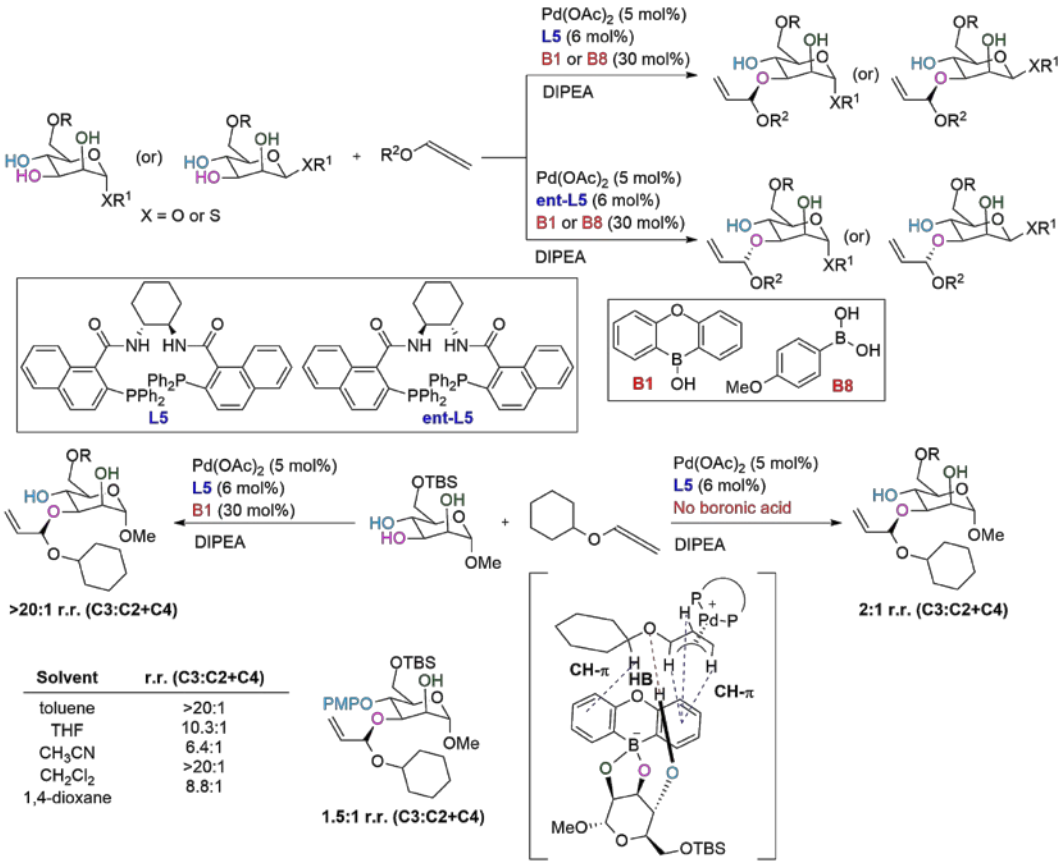
Additionally, the method was extended to meso-oxanorbornadienes and allylic carbonate substrates, showing efficient reactions and high regio- and diastereoselectivity, despite adjustments to ligand and solvent conditions.

3.6. Synergistic Chiral Palladium/Organoboron Site-Selectivity Carbohydrate Functionalization with Alkoxyallenes

Until recently, the mechanistic basis for the enhanced site-selectivity observed in the synergistic functionalization of carbohydrate hydroxyl groups—enabled by organoboron catalysts in combination with transition metal/chiral ligand systems or N-heterocyclic carbenes (NHCs)—remained poorly understood. Although the superior regioselectivity of organoboron catalysis is well-documented, its origin remains a topic of debate. Both experimental observations and density functional theory (DFT) studies suggest that electronic factors play a predominant role.



Scheme 5. Site-selective functionalization of carbohydrate polyols in the synthesis of arylhydronaphthalene glycosides via synergistic Rh(I) and boronic acid catalysis.



Scheme 6. Synergistic site-selective hydroalkoxylation of carbohydrate polyols using a chiral Pd/organoboron catalytic system. Non-covalent interactions (e.g., hydrogen bonding, CH–π interactions), substrate hydroxyl patterning, and solvent effects collectively influence the selectivity outcome.

Emerging data indicate that chiral ligands in transition metal catalysis can override electronic preferences, steering the reaction toward alternative regioisomers. This underscores the nuanced interplay between substrate electronics and catalyst control, and highlights that the mechanisms governing regioselectivity are still not fully elucidated.[11] A central challenge persists: can the stereochemical information embedded within chiral metal complexes be harnessed to achieve precise site-selectivity and stereocontrol in densely functionalized carbohydrate polyols?

In 2024, Loh and co-workers reported a breakthrough in this area with the development of a site-selective functionalization method using alkoxyallenes. Their approach leveraged a synergistic system combining a chiral palladium catalyst with an organoboron reagent, successfully addressing the challenges of site-, enantio-, and diastereoselectivity.[25] The method demonstrated broad applicability across diverse saccharide scaffolds and alkoxyallene partners. Structural assignments—including the regioselectivity on carbohydrate polyols, allene selectivity, and the absolute configuration of the new chiral center—were confirmed via X-ray crystallography, attesting to the robustness and precision of this strategy.

Mechanistic investigations—including in situ NMR shift analyses, kinetic profiling, and DFT calculations—revealed that a network of non-covalent interactions (NCIs), particularly hydrogen bonding and CH–π interactions, governs the observed selectivities. While the chiral palladium complex directed stereocontrol, substrate-driven site-selectivity remained dominant. This was confirmed through control experiments: omission of the organoboron reagent led to significantly reduced site-selectivity (r.r. = 2:1, C3:C2+C4), reinforcing its critical role. Optimal selectivity required a fine balance between catalyst influence and intrinsic substrate bias.

Solvent effects further highlighted the role of hydrogen bonding in site-selectivity. Protic or polar aprotic solvents capable of engaging in hydrogen bonding with the saccharide (e.g., THF, acetonitrile, 1,4-dioxane) negatively impacted regioselectivity. In contrast, non-coordinating solvents such as toluene and dichloromethane preserved high selectivity. Additionally, selective protection of the O4-hydroxyl group on a mannosyl substrate led to a marked decrease in site-selectivity (r.r. = 1.5:1, C3:C2+C4), underscoring the importance of specific hydroxyl groups in guiding regioselectivity (Scheme 6).

Advantages, Challenges in Synergistic Catalysis in Carbohydrate Transformation

4.1. Advantages

Synergistic catalysis offers a powerful approach to accessing complex carbohydrate structures with exceptional site-selectivity. This methodology is particularly advantageous for creating unusual glycosidic linkages, leading to the synthesis of novel carbohydrate mimics with potential biological activity. Unlike single-catalyst systems, synergistic catalysis employs two or more separate catalysts to activate distinct reactants, facilitating transformations that would otherwise be difficult or impossible to achieve. This collaborative activation enhances reaction efficiency and selectivity, making challenging glycan targets more accessible.[11, 19-25]

Furthermore, researchers are exploring new catalytic strategies to generate a wider range of carbohydrate structures with unique biological properties.[26] The integration of sustainable approaches, such as using renewable feedstocks and environmentally benign catalysts, is gaining traction to ensure greener carbohydrate synthesis.

4.2. Challenges

Despite its advantages, synergistic catalysis remains a relatively new and evolving area of research. Significant challenges include:

- Differentiating Hydroxyl Groups: Carbohydrates contain numerous hydroxyl groups, presenting a challenge when attempting to selectively modify one without impacting the others. Due to their comparable reactivities, chemists must develop more efficient synergistic catalytic strategies to distinguish between them effectively.
- Stereocontrol: The synthesis of carbohydrates typically involves numerous stereocenters, requiring meticulous management of stereochemistry during glycosidic bond formation. Effective synergistic catalysis must ensure both regioselectivity and stereoselectivity.
- Enantioselectivity: Developing catalytic systems that offer greater control over enantioselectivity remains a major hurdle.
- Compatibility of Multiple Catalytic Systems: Optimizing synergistic catalysis, which involves the use of multiple catalysts, can be difficult since the catalysts need to function together efficiently without hindering one another's actions.
- Limited Versatility of Catalysts: The absence of effective catalytic strategies beyond the aforementioned examples for simultaneous stereocontrol presents a significant barrier to the broader use of chiral catalysis in the precise construction of a wide range of complex, biologically relevant glycosides with stereochemical accuracy.

Opportunities and Future Perspectives

To overcome these challenges, future research should focus on expanding the utility of synergistic catalysis for selective functionalization of saccharide cores. This will enable the synthesis of more complex and biologically relevant glycosides. Additionally, integrating computational tools, machine learning algorithms, and automated reaction optimization will likely accelerate the discovery and refinement of catalytic systems.[27] By addressing these challenges and emphasizing sustainability through the use of renewable resources and eco-friendly catalysts, researchers can unlock new possibilities in carbohydrate chemistry, leading to advancements in pharmaceuticals, biomaterials, and glycoscience applications.

Future efforts should also explore innovative catalytic strategies to further expand the range of accessible carbohydrate structures with unique biological properties. Integrating sustainable approaches, including the utilization of renewable feedstocks and environmentally benign catalysts, will be crucial in making carbohydrate synthesis both efficient and eco-friendly.

- Sustainability: Expanding the application of sustainable and bio-inspired catalysts is essential for environmentally friendly processes.
- Scalability: Efficient catalytic processes suitable for large-scale carbohydrate production are still underdeveloped.
- Optimization: Implementing AI-driven reaction optimization strategies can enhance reaction efficiency, reproducibility, and predictive capabilities.[28]

Future directions in synergistic catalysis for carbohydrate functionalizations involve leveraging the power of multiple catalysts, especially chiral transition metal and organoboron catalysis, and photoredox strategies, to achieve site-selective and stereocontrolled transformations, ultimately enabling access to complex and biologically relevant glycosides. Developing new catalytic systems and reaction protocols is essential for addressing the challenges in carbohydrate synthesis. Further research into the mechanisms of synergistic catalysis is needed to fully understand and optimize these strategies.

CONCLUSIONS

Synergistic catalysis represents a transformative strategy in the selective functionalization of carbohydrate hydroxyl groups. The reviewed methodologies exemplify how combining catalytic modalities—metal/organoboron, Pd/Lewis acid, NHC/boronic acid—enables unprecedented control over site- and stereoselectivity. These approaches provide practical, sustainable, and scalable routes to complex glycosides and sugar derivatives, paving the way for innovations in glycoscience, medicinal chemistry, and chemical biology.

The road ahead involves expanding catalyst diversity, refining mechanistic insights, and developing generalizable, scalable solutions. With continued exploration and interdisciplinary collaboration, synergistic catalysis holds immense potential to unlock new frontiers in carbohydrate chemistry.

CONFLICTS OF INTEREST

There are no conflicts to declare.

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