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Pd-catalyzed stereoretentive synthesis of reversed C-acyl glycosides: access to rare L-sugars and higher-carbon sugars

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Reversed C-acyl glycosides represent a versatile class of nonclassical glycosides with potential in complex carbohydrate synthesis, including L-sugars, higher-carbon sugars, and medicinal chemistry. Conventional strategies for L- and higher-carbon sugars are limited by multi-step protection–deprotection sequences and poor stereocontrol. Herein, we report a general Pd-catalyzed reversed acyl C-glycosylation that efficiently couples configurationally stable reversed glycosyl stannanes with C(sp²)- and C(sp³)-derived thioesters under mild conditions. The reaction proceeds with complete stereoretentive transfer, enabling precise access to both D- and L-type glycosides, including higher-carbon sugar derivatives and C-ferrocenecarbonyl glycosides. The broad substrate scope, excellent functional group tolerance, and predictable stereochemical outcome highlight the robustness and synthetic versatility of this approach. Applications of the resulting reversed C-acyl glycosides as chiral synthons enable D-to-L interconversion, construction of L-sugar analogues, and derivatization toward designer carbohydrate frameworks. Importantly, this transformation enables a distinct D-to-L conversion featuring simultaneous C4 and C5 inversion, unlike conventional methods that modify only C5 configuration. Overall, this protocol establishes a general platform for stereocontrolled construction and diversification of structurally defined nonclassical glycosides, providing a foundation for glycodiversification, complex sugar synthesis, and exploration of biologically relevant C-glycosyl scaffolds.

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Introduction

Carbohydrates are among the most abundant and structurally diverse biomolecules in nature, serving as essential components in energy storage, cellular architecture, and molecular recognition.^{1–4} Among them, higher-carbon sugars, defined as carbohydrates containing more than six carbon atoms, are broadly distributed in nature and fulfill diverse biological roles. For instance, L-glycero-D-manno-heptose (L,D-Hep), D-glycero-D-manno-heptose (D,D-Hep), and 3-deoxy-D-manno-oct-2-ulosonic acid (Kdo) are key constituents of Gram-negative bacterial lipopolysaccharides (LPS), predominantly located in the inner core region but also present in the outer core or O-antigen domains (Fig. 1A).^{5–7} Unlike the more common D-hexoses, their enantiomeric counterparts, L-sugars are less prevalent in nature yet frequently embedded in structurally and functionally

significant biomolecules.⁸ Despite the commercial availability of certain L-sugars and higher-carbon sugars, their high cost and limited supply significantly hinder broader biological and synthetic investigations. To fully explore their bioactivities and potential as functional molecules, the development of efficient synthetic strategies is essential. The synthesis of L-sugars and higher-carbon sugars from readily available carbohydrate feedstocks has long been a central focus in carbohydrate chemistry, and a variety of strategies for accessing L-sugars from their D-counterparts have been developed.^{9,10} However, due to the inherent structural complexity and diversity of carbohydrates, tedious protecting-group manipulations and consequently lengthy synthetic routes are often inevitable. From the perspective of green synthesis and atom economy, therefore, the development of efficient catalytic methods represents an especially appealing strategy.^{11,12}

Non-anomeric C-acyl glycosides **1**, also referred to as reversed C-acyl glycosides,^{13,14} are characterized by the presence of an acyl substituent at the C-5 position of pyranoses or the C-4 position of furanoses, representing a distinct subclass of C-glycosides. In contrast to classical C-acyl glycosides,^{15–17} which have been extensively studied, the synthesis of these nonclassical motifs has remained relatively underexplored. Nevertheless, they hold significant potential as versatile building blocks for accessing diverse C-glycomimetics through various

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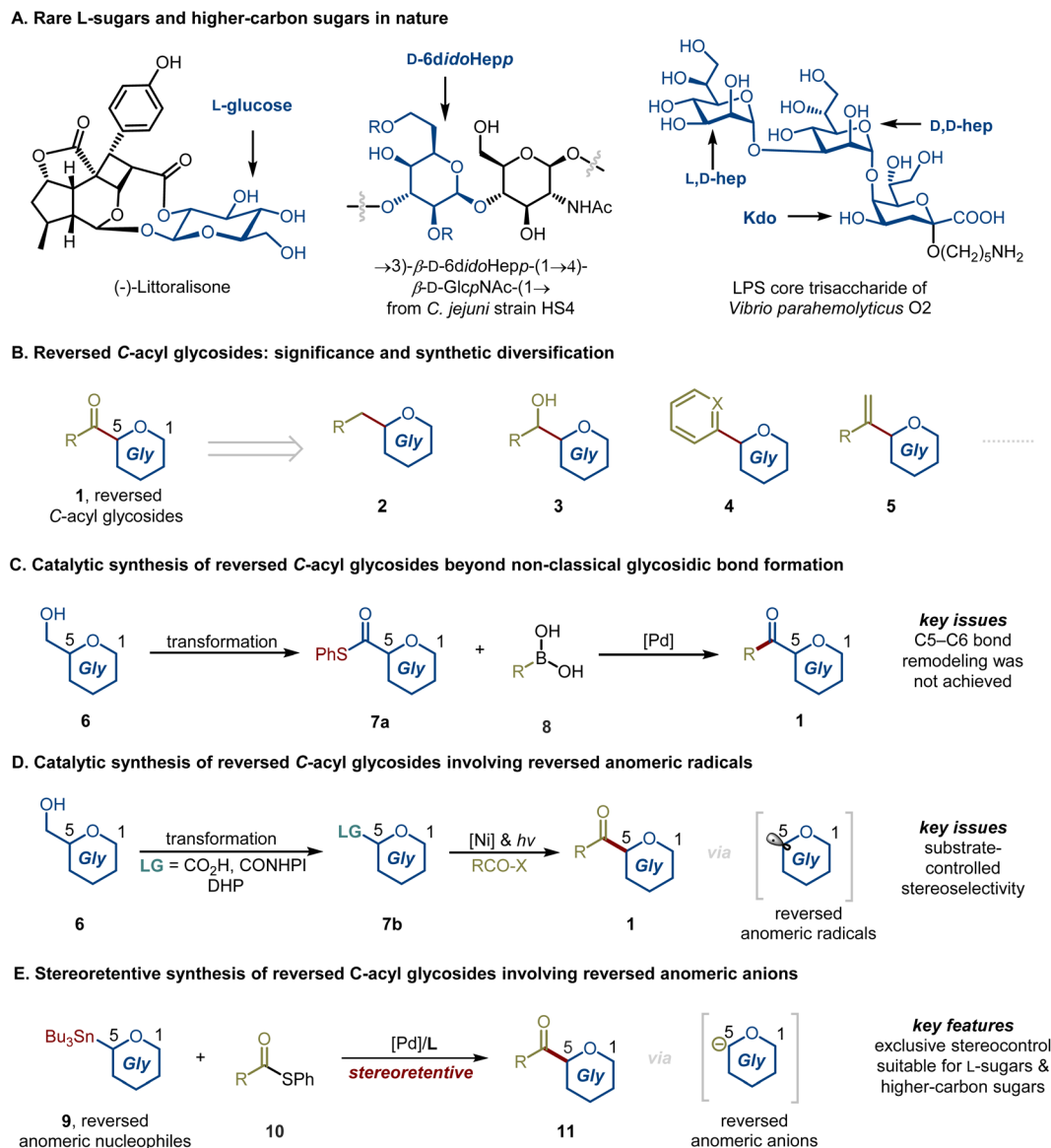


Fig. 1 Overview and background of reversed C-acyl glycosides. (A) Representative examples of rare L-sugars and higher-carbon sugars found in nature. (B) Significance and synthetic diversification of reversed C-acyl glycosides. (C) Catalytic synthesis of reversed C-acyl glycosides beyond non-classical glycosidic bond formation. (D) Catalytic synthesis of reversed C-acyl glycosides involving reversed anomeric radicals. (E) Stereoretentive synthesis of reversed C-acyl glycosides involving reversed anomeric anions (this work).

downstream transformations (Fig. 1B), including reversed CH_2 -linked glycosides (L-sugars) 2, glycosyl alcohols 3, reversed C-aryl glycosides 4, and reversed C-vinyl glycosides 5, many of which occur in bioactive compounds or challenging molecular architectures. According to whether the construction of a glycosidic bond is involved, the synthesis of reversed C-acyl glycosides can be divided into two categories. Traditionally, reversed C-acyl glycosides have been prepared through multi-step oxidation-coupling sequences that require harsh conditions and highly reactive reagents, often leading to poor chemoselectivity, limited functional group tolerance, and tedious protecting-group manipulations.^{18–22} Notably, catalytic methods have also been reported. For instance, in independent studies, Ye,¹⁶ Hu,²³ and Li²⁴ disclosed catalytic variants based on Liebeskind–Srogl cross-coupling reactions of thioesters derived

from glycosyl acids with arylboronic acids, thereby enabling the synthesis of reversed C-acyl glycosides. However, the incompatibility of alkylboronic acids limits the structural diversity of accessible reversed C-acyl glycosides. Although such methods bypass the stereochemical challenges associated with reversed glycosidic bond formation, they also restrict access to more diverse sugar scaffolds, such as the conversion of D-sugars to L-forms *via* C5 stereoinversion during acylation (Fig. 1C). An alternative and elegant approach involves Ni(II)/photoredox-catalyzed radical couplings of sugar-derived carboxylic acids,¹⁴ active esters (NHPI),²⁵ and 1,4-dihydropyridines (DHPs).¹³ Despite these advances, the diastereoselectivity of these radical-mediated reactions is strongly substrate-dependent, and predictable stereocontrol across different sugar scaffolds remains elusive (Fig. 1D).^{26–28} Consequently, a general, mild,



and stereoretentive catalytic platform for constructing reversed *C*-acyl glycosides, particularly one capable of delivering both *D*- and *L*-type configurations with excellent stereoselectivity, has not yet been realized.

In response to the aforementioned synthetic challenges and potential applications of reversed *C*-acyl glycosides, we herein report the first example of a Pd-catalyzed stereospecific cross-coupling of reversed glycosyl stannanes with aryl, alkenyl, and alkyl carboxylic acid-derived thioesters under mild conditions, affording reversed *C*-acyl glycosides in good to excellent yields with retention of C5 stereochemistry (Fig. 1E). This new glycosylation strategy has been demonstrated in over 45 examples, showcasing high predictability, modularity, and chemoselectivity. This robust and modular catalytic platform demonstrates remarkable substrate generality and functional group tolerance, accommodating protected and unprotected sugars, diverse aromatic and aliphatic thioesters, and complex drug-derived electrophiles. Importantly, thioesters derived from alkyl carboxylic acids bearing multiple stereocenters participate robustly, delivering higher-carbon sugar precursors in a fully stereoretentive manner, independent of substrate stereochemistry. A further advantage of this method is its applicability to both α - and β -anomers, while uniquely enabling a stereoretentive *D*-to-*L* transformation to *L*-sugar precursors through a revised acylation pathway that achieves formal C5 epimerization.

Results and discussion

Reaction development

Building on our previous studies on the modular synthesis of reversed *C*-aryl glycosides,²⁹ we conveniently obtained a series of reversed glycosyl stannanes **9a** for further exploration. Our next objective was to identify optimal conditions for their stereoretentive non-classical acylation (Table 1). As a model, we examined the coupling between reversed glycosyl stannane **9a** and benzoyl *S*-phenyl thioester **10a** under the catalytic system of Pd₂(dba)₃/P(OMe)₃ (**L1**).¹⁵ Although the desired reversed *C*-acyl glycoside **12a** was obtained, the NMR yield was modest (32%, entry 1). To enhance the reaction efficiency, a series of phosphine ligands were evaluated. Employing a bulky, electron-deficient ligand **L2** significantly improved the yield (entry 2). Subsequent fine-tuning of the ligand structure (entries 3–5) revealed that JackiePhos (**L5**), featuring greater steric bulk, afforded the best result (entry 5). Further structural modification of JackiePhos led to the development of ligand **L6**, which provided an even higher yield (86%, entry 8). The ligand primarily affects reaction efficiency rather than stereochemical outcome. Consistent with prior studies on Pd-catalyzed Stille couplings using electron-deficient phosphine ligands,^{29,30} the ligand likely facilitates catalyst activation and promotes transmetalation by maintaining an electron-deficient palladium center. In contrast, lowering the reaction temperature or shortening the reaction time both resulted in decreased efficiency (entries 6 and 7). Notably, reducing the Pd loading to 5 mol% or decreasing the amount of copper salt to 3.0 equiv did not compromise the yield (entries 9 and 10). Solvent screening

indicated that MeCN or DMF completely suppressed the reaction (entries 11 and 12), while toluene and THF afforded slightly diminished yields (entries 13 and 14). Ultimately, employing 1.0 equiv of CuCl delivered the desired reversed *C*-acyl glycoside in 85% NMR yield and 80% isolated yield. Replacement of CuCl with CuBr reduced the NMR yield to 60%, whereas Cu₁ led to a further decrease to 9%. No cross-coupling occurred in the absence of CuCl (see SI for details). These observations are consistent with prior reports that copper salts facilitate transmetalation from organostannanes to palladium by activating the otherwise inert Sn–C bond.³¹ In addition to thioesters, other commonly used acyl sources were evaluated, including acyl chlorides and acid anhydrides. In these cases, the coupling efficiency decreased significantly, affording the corresponding products in NMR yields of 42% and 67%, respectively (see SI for details). Importantly, no evidence of configurational inversion at the C5 of the nonclassical glycosyl stannane was observed (see SI for details). Across all conditions examined, exclusive formation of the *L*- and β -configured sugar was observed.

Scope and application

Scope of thioesters derived from both C(sp²)- and C(sp³)-carboxylic acids. With the optimized reaction conditions in hand, we set out to explore the substrate scope of thioesters derived from both C(sp²)- and C(sp³)-carboxylic acids, employing reversed glycosyl stannane **9a** as the coupling partner (Scheme 1). Under the optimized conditions, a wide range of aromatic thioesters bearing either electron-donating or electron-withdrawing substituents were smoothly transformed into the corresponding reversed *C*-acyl glycosides (**12b–12l**) in moderate to excellent yields. The protocol exhibited remarkable functional group tolerance, accommodating substituents such as methoxy, trifluoromethyl, phenyl, naphthyl, benzoyl, fluoro, chloro, phenoxy, ester, cyano, and methyl groups without compromising efficiency. Notably, pharmaceutically relevant heteroaromatic scaffolds, including indole **12m**, benzoxazole **12n**, and furan **12o** moieties, were well tolerated, affording the desired products in good yields. Moreover, for diacid-derived substrates such as terephthalic thioesters, a simple increase in the loading of glycosyl stannane enabled efficient double acylation to furnish the bis-glycosylated product **12p** in 84% yield. Vinyl thioesters were also competent coupling partners, as demonstrated by the smooth formation of cinnamyl-derived glycoside **12q** in 69% yield. Beyond the scope of C(sp²)-derived thioesters, C(sp³)-carboxylic acid-derived thioesters also underwent the transformation efficiently to provide the desired reversed glycosides (**12r–12u**), further underscoring the broad substrate generality of this catalytic system. To further illustrate the versatility and synthetic potential of this nonclassical glycosyl cross-coupling platform, we applied the optimized acylation conditions to the late-stage glycodiversification of a series of commercially available pharmaceuticals and bioactive molecules using stannane **9a**, offering a valuable strategy for rapid molecular diversification through the direct installation of glycan motifs. A variety of reversed glycosyl ketones were successfully prepared from drug-derived thioesters, including



Table 1 Optimization of the reaction conditions^a

9a, L type, β only + **10a** $\xrightarrow[\text{CuCl (4.0 equiv), solvent (2.0 mL), 90 °C, 72 h}]{\text{Pd}_2\text{dba}_3 (7.5 \text{ mol}\%), \text{Ligand (30.0 mol}\%)}$ **12a, L type, β only**

stereoretention

Entry	Ligand	Solvent	CuCl (equiv)	NMR yield (%)
1	L1	1,4-Dioxane	4.0	32%
2	L2	1,4-Dioxane	4.0	63%
3	L3	1,4-Dioxane	4.0	71%
4	L4	1,4-Dioxane	4.0	72%
5	L5	1,4-Dioxane	4.0	82%
6 ^b	L5	1,4-Dioxane	4.0	63%
7 ^{b,c}	L5	1,4-Dioxane	4.0	53%
8	L6	1,4-Dioxane	4.0	86%
9 ^d	L6	1,4-Dioxane	4.0	86%
10 ^d	L6	1,4-Dioxane	3.0	86%
11 ^d	L6	MeCN	3.0	2%
12 ^d	L6	DMF	3.0	2%
13 ^d	L6	Toluene	3.0	81%
14 ^d	L6	THF	3.0	81%
15 ^d	L6	1,4-Dioxane	1.0	85% (80%)

L1

L2

L3

L4

L5

L6

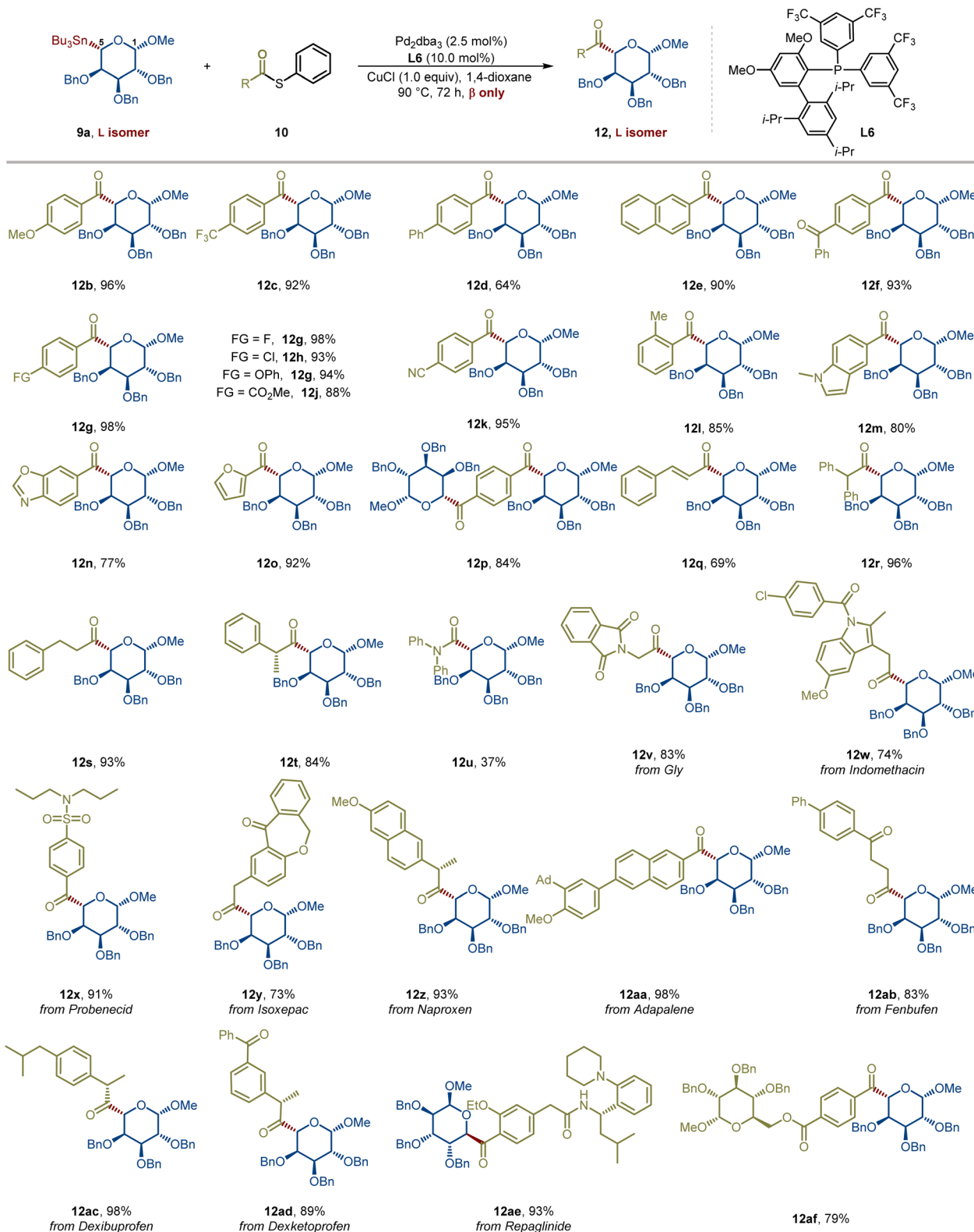
^a General reaction conditions: thioester **10a** (0.10 mmol), reversed anomeric stannane **9a** (2.0 equiv), Pd₂(dba)₃ (7.5 mol%), ligand (30.0 mol%), CuCl (4.0 equiv), and anhydrous 1,4-dioxane (2.0 mL) under Ar, 90 °C, 72 h; NMR yields are reported, and values in parentheses refer to isolated yields. ^b 70 °C was used. ^c 24 h was used. ^d Pd₂(dba)₃ (2.5 mol%) and ligand (10.0 mol%) were used. The stereochemical outcome was determined by ¹H NMR analysis of crude reaction mixture.

those derived from glycine (**12v**), indomethacin (**12w**), probenecid (**12x**), isoxepac (**12y**), naproxen (**12z**), adapalene (**12aa**), fenbufen (**12ab**), dexibuprofen (**12ac**), dexketoprofen (**12ad**), and repaglinide (**12ae**). In addition, a glycoside-containing thioester was also compatible with the reaction conditions, delivering the desired product (**12af**) in 79% isolated yield.

Scope of reversed glycosyl stannanes. The scope of the reversed acylative glycosylation was next examined using a diverse set of reversed glycosyl stannanes, with *p*-methoxybenzoyl *S*-phenyl thioester **10b** serving as the representative acyl coupling partner. As shown in Scheme 2, a broad array of both

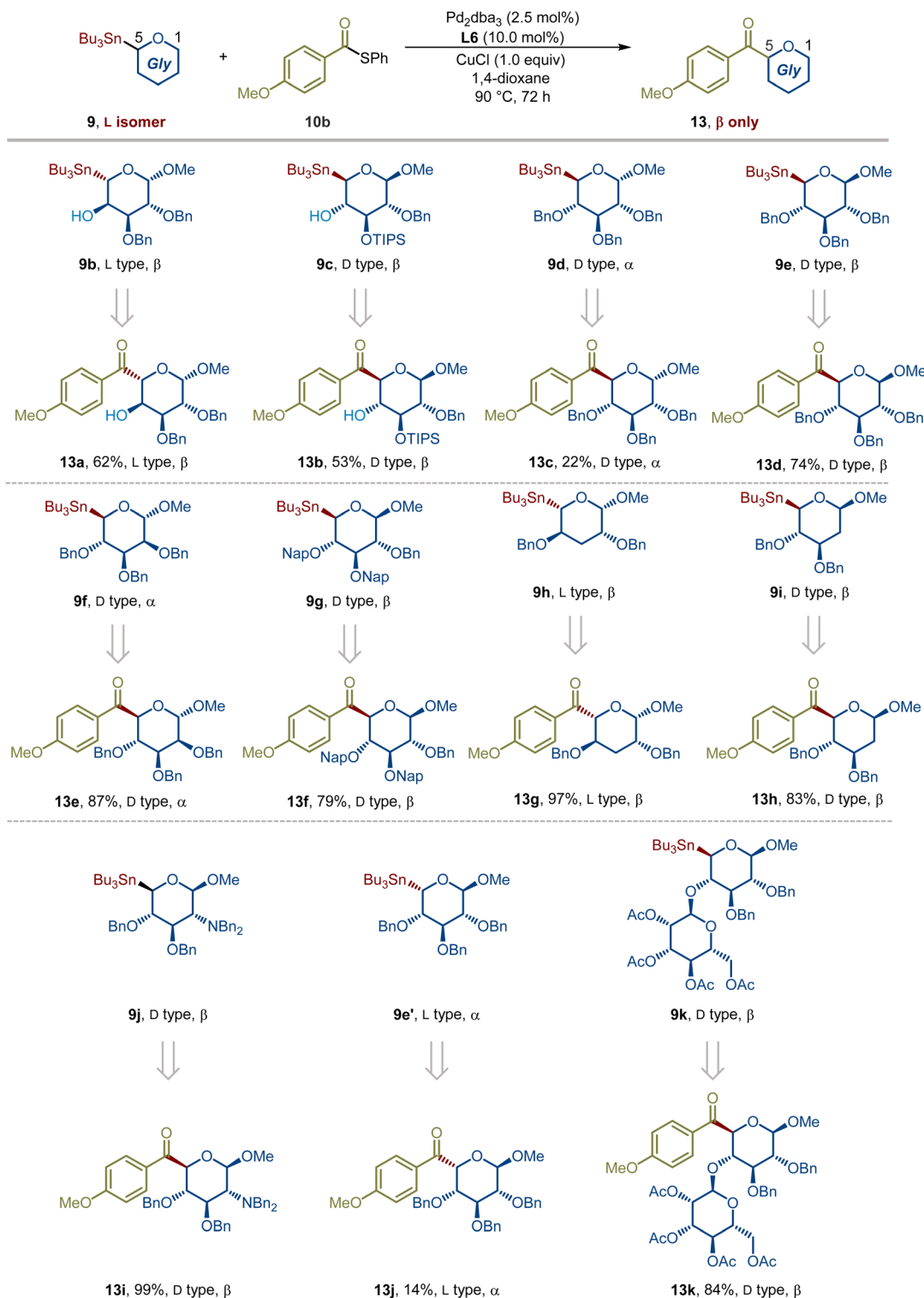
protected and unprotected glycosyl stannanes underwent smooth cross-coupling to furnish the corresponding reversed *C*-acyl glycosides in moderate to excellent yields. The reactions proceeded with complete and predictable stereochemical control, delivering either the β- or α-anomer exclusively. Stereoselective glycosylation of unprotected sugars has long been recognized as both a fascinating and challenging area in carbohydrate chemistry. Delightfully, both β- and α-configured reversed glycosyl stannanes bearing a C4-hydroxyl group reacted efficiently to give the corresponding products **13a** and **13b** in isolated yields of 62% and 53%, respectively. The moderate





Scheme 1 Scope of thioesters derived from both C(sp²)- and C(sp³)-carboxylic acids.^aStandard reaction conditions: thioesters **14** (0.10 mmol), reversed anomeric stannane **9a** (2.0 equiv), Pd₂(dba)₃ (2.5 mol%), ligand **L6** (10.0 mol%), CuCl (1.0 equiv), anhydrous 1,4-dioxane (2.0 mL), 90 °C, 72 h, Ar, isolated yields.





Scheme 2 Scope of reversed glycosyl stannanes^a. ^aStandard reaction conditions: thioesters **10b** (0.10 mmol), reversed anomeric stannane **9** (2.0 equiv), Pd₂(dba)₃ (2.5 mol%), ligand **L6** (10.0 mol%), CuCl (1.0 equiv), and anhydrous 1,4-dioxane (2.0 mL), 90 °C, 72 h, Ar, isolated yields.

yields observed for certain substrates primarily arise from a competing β-O elimination of the glycosyl stannane, leading to the corresponding alkenes as the major byproduct. Common protecting groups, including OBn, ONap, and OTIPS, were fully compatible under the standard reaction conditions. Moreover,

stannanes derived from C3-deoxy, C2-deoxy, and C2-amino sugars also participated smoothly, affording the desired reversed acyl glycosides **13g–13i** in high yields. Compared to the 4,5-*trans* glycosyl stannane **9e**, the 4,5-*cis* analogue **9e'** afforded exclusively the 4,5-*cis* product **13j** in 14% yield, with no

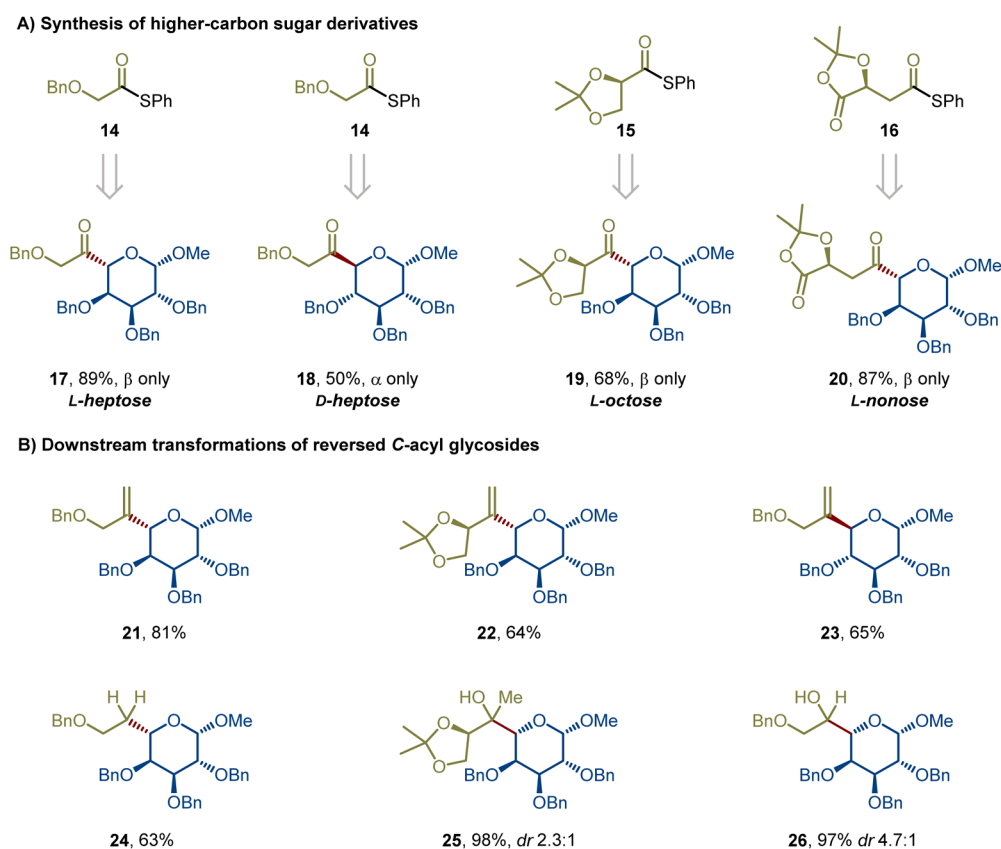


detectable *trans* isomer; extensive β -elimination to the corresponding glycal was observed (88% NMR yield), along with 51% recovered starting material. Notably, a disaccharide-derived glycosyl stannane **9k**, bearing both ether and ester protecting groups, smoothly underwent the reaction to afford the desired product **13k** in 84% isolated yield. The present system exhibited excellent stereochemical fidelity. *L*-type reversed glycosyl stannanes were converted with complete stereospecificity into *L*-type reversed *C*-acyl glycosides, representing a formal inversion at C5, while *D*-type analogues gave *D*-type products with equal precision. This one-to-one stereochemical correspondence highlights the inherent configurational control of the Pd-catalyzed reversed acylative glycosylation.

Synthesis of higher-carbon sugar derivatives and down-transformation of reversed acyl *C*-glycosides. The synthesis of sugars bearing carbon chains longer than six atoms remains a compelling synthetic challenge. Conventional strategies for accessing higher-carbon sugar typically involve homologation of shorter sugars, necessitating the controlled installation of additional stereogenic centers. Although elegant methods for the preparation of such building blocks have been reported,^{32–34} the efficient synthesis of higher-carbon sugars, particularly those of the *L*-configuration, remains highly demanding. Encouraged by the excellent compatibility of thioesters derived from $C(sp^3)$ -carboxylic acids and to further demonstrate the versatility of the reversed acyl *C*-glycosylation, we applied the optimized

conditions to the synthesis of higher-carbon sugar derivatives using a series of protected hydroxy acid-derived thioesters and reversed anomeric stannanes. As shown in Scheme 3A, this strategy enabled the efficient synthesis of heptose, octose, and nonose derivatives. *L*-type reversed glycosyl stannanes were transformed with complete stereospecificity into the corresponding *L*-type reversed *C*-acyl glycosides (**17**, **19**, **20**), while *D*-type analogues afforded the *D*-type counterparts with equal precision **18**. Notably, variations in the stereochemical environment of the hydroxy acid moiety exerted negligible influence on bond-forming efficiency or stereoselectivity, highlighting the high robustness of this system. Subsequently, as illustrated in Scheme 3B, the acylated higher-carbon sugars could be further transformed into both $C(sp^2)$ - and $C(sp^3)$ -linked higher-carbon sugars through a series of downstream reactions. Under Peterson olefination conditions (TMSCH₂MgCl followed by KHMDS), the corresponding olefinic higher-carbon sugars (**21–23**) were readily obtained. Reduction of the carbonyl group with NaBH₄ or MeMgBr furnished the corresponding sugar alcohols (**25** and **26**). Further transformation of sugar alcohol **26** *via* a Barton–McCombie deoxygenation smoothly delivered the CH₂-linker higher-carbon sugars **24**.³⁵

Synthesis of *L*-sugars *via* a *D* to *L* strategy and access to *C*-ferrocenecarbonyl glycosides. As illustrated in Scheme 4A, starting from *D*-glucose, 3-deoxy-*D*-glucose (3-deoxy-*D*-allose), and a *D*-idose derivative, the corresponding *L*-type reversed



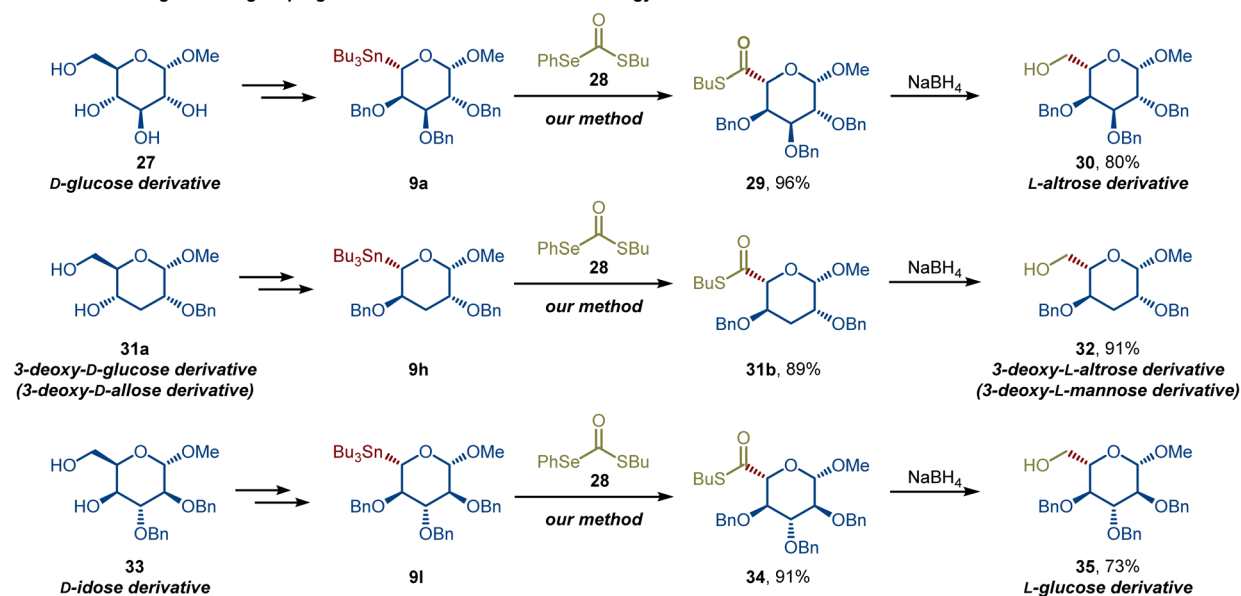
Scheme 3 Synthesis of higher-carbon sugar derivatives and downstream transformation of reversed *C*-acyl glycosides.^a Standard reaction conditions: thioesters (0.10 mmol), reversed anomeric stannane (2.0 equiv), Pd₂(dba)₃ (2.5 mol%), ligand **L6** (10.0 mol%), CuCl (1.0 equiv), and anhydrous 1,4-dioxane (2.0 mL), 90 °C, 72 h, Ar, isolated yields.



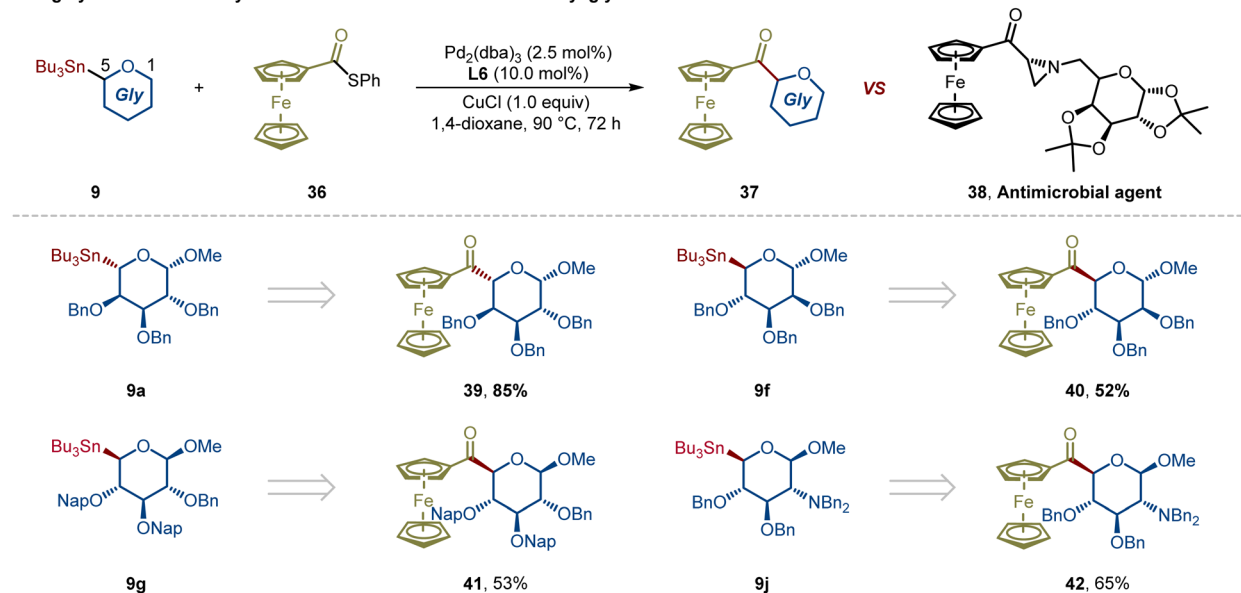
anomeric stannanes (**9a**, **9h**, and **9i**) were readily prepared. Subsequent acylation with *S*-butyl *Se*-phenyl carbonoselenothioate **28** afforded the key glycosyl carbonoselenothioates, which, upon NaBH₄ reduction, delivered the respective *L*-altrose derivative **30**, 3-deoxy-*L*-altrose (3-deoxy-*L*-mannose) derivative **32**, and *L*-glucose derivative **35** in good yields. Notably, for *L*-sugars **30** and **32**, both the C4 and C5 configurations are inverted relative to their *D*-sugar precursors, representing a distinct transformation mode from conventional *D*-to-*L* conversion strategies that typically involve only C5 inversion. This *D*-to-*L* interconversion platform thus establishes a broadly applicable and stereochemically precise approach for accessing *L*-sugars, opening new opportunities for the synthesis of rare and unnatural carbohydrate frameworks.

C-Ferrocenyl glycosides are known to display a broad spectrum of biological activities, including anticancer, anti-fucosidase, and antimicrobial effects, as exemplified by compound **38**.³⁶ However, *C*-ferrocenecarbonyl glycosides have not yet been explored, despite their potential as versatile precursors for the synthesis of other *C*-linked *C*-ferrocenyl glycosides. To address this gap, we envisioned that the reversed acyl *C*-glycosylation platform could be employed to construct these novel ferrocenyl glycosides in a stereocontrolled manner. As illustrated in Scheme 4B, *L*- and *D*-type reversed anomeric stannanes were reacted with ferrocenecarbonyl thioester **36** under the optimized conditions, efficiently delivering the corresponding *C*-ferrocenecarbonyl glycosides **39–42** in good yields and with complete stereochemical fidelity. This strategy not

A. Access to *L*-sugars through a programmable “*D*-to-*L*” conversion strategy.



B. Highly stereoselective synthesis of reversed *C*-ferrocenecarbonyl glycosides



Scheme 4 Synthesis of *L*-Sugars via a *D* to *L* strategy and access to *C*-ferrocenecarbonyl glycosides.



only provides direct access to previously unexplored *C*-ferrocenecarbonyl glycosides but also establishes a general route for the preparation of diverse *C*-linked ferrocenyl sugar derivatives.

Conclusions

In summary, we have developed a general and stereoretentive reversed acyl *C*-glycosylation of nonclassical anomeric nucleophiles with thioesters. This method enables a stereoretentive transfer of configuration from configurationally stable reversed glycosyl stannanes, allowing efficient access to both *D*- and *L*-type reversed *C*-acyl glycosides with complete stereochemical fidelity. The broad substrate scope encompasses C(sp²)- and C(sp³)-derived thioesters as well as a variety of protected and unprotected glycosyl stannanes, highlighting the robustness and functional group tolerance of the transformation. Furthermore, the resulting reversed *C*-acyl glycosides serve as versatile chiral synthons for the synthesis of higher-carbon sugars, *L*-sugar analogues *via* *D*-to-*L* interconversion, and *C*-ferrocenecarbonyl glycosides, providing a practical route to both natural and designer sugar frameworks. Taken together, the reversed acyl *C*-glycosylation offers an unprecedented combination of stereocontrol, efficiency, and synthetic flexibility, establishing a general platform for the preparation and diversification of structurally defined nonclassical glycosides. Applications in glycodiversification, medicinal chemistry, and the synthesis of complex architectures are currently underway.

Author contributions

F. Z. conceived and directed the project. G. C. performed the experiments and analyzed the data. F. Z. and B. Y. wrote the manuscript with input from all the authors. All authors have read and approved the final version of the manuscript.

Conflicts of interest

The authors declare no competing financial interest.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d5sc08224b>.

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