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Pd-Catalyzed Stereospecific Glycosyl Cross-Coupling of Reversed Anomeric Stannanes for Modular Synthesis of Nonclassical *C*-Glycosides

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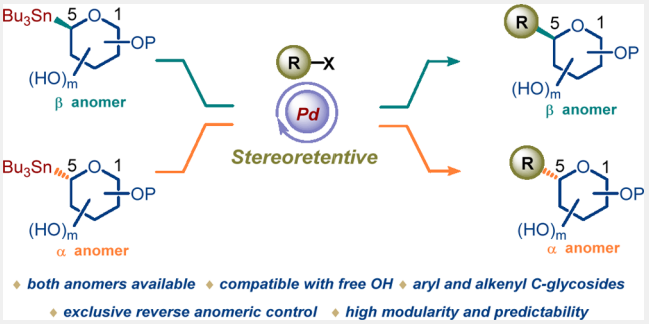
ABSTRACT: Nonclassical *C*-glycosides, distinguished by their unique glycosidic bond connection mode, represent a promising avenue for the development of carbohydrate-based drugs. However, the accessibility of nonclassical *C*-glycosides hinders broader investigations into their structural features and modes of action. Herein, we present the first example of Pd-catalyzed stereospecific glycosylation of nonclassical anomeric stannanes with aryl or vinyl halides. This method furnishes desired nonclassical aryl and vinyl *C*-glycosides in good to excellent yields, while allowing for exclusive control of nonclassical anomeric configuration. Of significant note is the demonstration of the generality and practicality of this nonclassical *C*-glycosylation approach across more than 50 examples, encompassing various protected and unprotected saccharides, deoxy sugars, oligopeptides, and complex molecules. Furthermore, biological evaluation indicates that nonclassical *C*-glycosylation modifications of drug molecules can positively impact their biological activity. Additionally, extensive computational studies are conducted to elucidate the rationale behind differences in reaction reactivity, unveiling a transmetalation transition state containing silver (Ag) within a six-membered ring. Given its remarkable controllability, predictability, and consistently high chemical selectivity and stereospecificity regarding nonclassical anomeric carbon and *Z*/*E* configuration, the method outlined in this study offers a unique solution to the longstanding challenge of accessing nonclassical *C*-glycosides with exclusive stereocontrol.



KEYWORDS: *Glycosylation, Cross-coupling, Nonclassical C-glycosides, Reversed anomeric stannanes, Stereospecificity*

INTRODUCTION

Aryl *C*-glycosides **1** are commonly encountered in a range of bioactive natural products and pharmaceutical compounds, and they are highly favored due to their more stable C−C bond, which enhances in vivo metabolic stability as compared to their *O*-glycoside counterparts that possess hydrolytically labile C−O bonds.[1,2] Nonclassical (Nc) aryl *C*-glycosides **3** represent a specific subclass characterized by aryl substituents on the C-5 position in pyranoses or C-4 position in furanoses, while classical *C*-glycosides bear aryl substituents on the anomeric C-1 position. Owing to their unique glycosidic bond connection mode, nonclassical aryl *C*-glycosides have been demonstrated to be promising anticancer agents,[3] antibiotics,[4] or inhibitors for diabetes.[5] In some cases, their therapeutic effects are even more remarkable than those of classical aryl *C*-glycosides. For example, the classical aryl *C*-glucoside **2**, dapagliflozin, is a US FDA approved market inhibitor of SGLT2 (sodium-dependent glucose transporter 2). In contrast, the nonclassical aryl *C*-glucoside **4**, sotagliflozin, not only functions as a dual inhibitor of SGLT1 and SGLT2, but also exhibits therapeutic effects on cardiovascular disease complications in diabetes (Figure 1A).[6] Despite the attractive biological properties of nonclassical aryl *C*-glycosides, their synthesis has received limited attention. Compared to the rapid and well-studied synthesis of classical *C*-glycosides,[1,2,7−31] the synthesis of nonclassical *C*-glycosides lags behind and poses several challenges,[32−37] impeding the development of more biomedically valuable sugar-based drugs. Traditional methods for synthesizing nonclassical aryl *C*-glycosides include the $ZnBr_2$-mediated syn-selective addition reaction of aryl-zinc reagents to 4α-epoxypyranosides,[38] and the selective [4 + 2] cycloaddition between aromatic aldehydes **7** and Danishefsky's dienes **8**, yielding glycal derivatives **9**[39−41] (Figure 1B). However, these strategies encounter obstacles such

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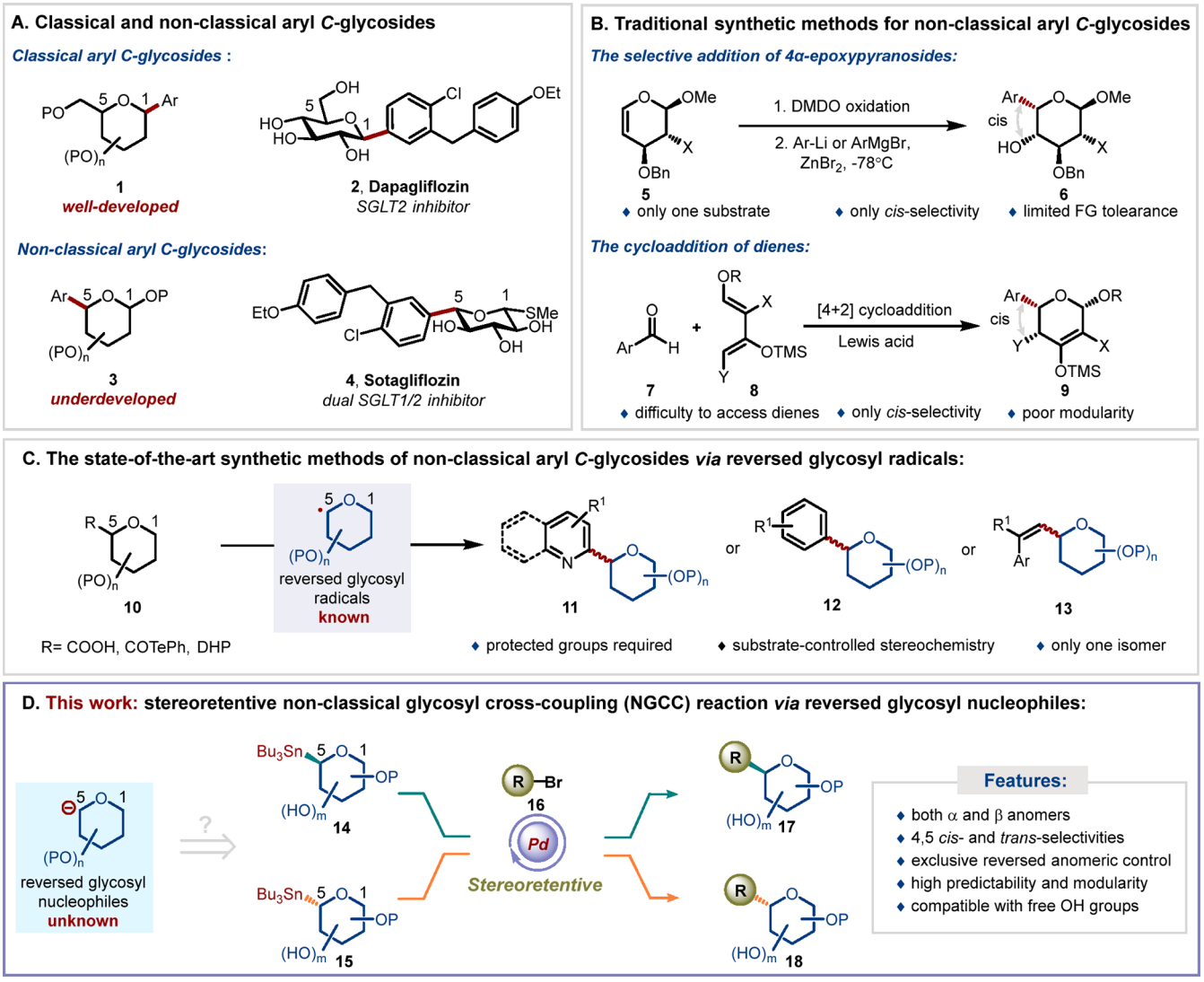

Figure 1. Nonclassical aryl or vinyl *C*-glycosylation: general overview and our work. (A) Classical and nonclassical aryl *C*-glycosides. (B) Traditional synthetic methods of nonclassical aryl *C*-glycosides. (C) State-of-the-art synthetic methods of nonclassical aryl *C*-glycosides via reversed glycosyl radicals. (D) Stereoretentive nonclassical glycosyl cross-coupling (NGCC) reaction via reversed glycosyl nucleophiles (our work).

as difficulties in obtaining starting materials, poor modularity, limited substrate scope, and poor functional group tolerance.

Recently, the glycosylation reactions involving glycosyl radicals generated in situ from various radical precursors have garnered significant attention within the glycochemistry community emerging as highly efficient routes for the synthesis of classical *C*-glycosides.[42,43] Such processes feature several advantages, including broad substrate scope, mild reaction conditions, simple operation, and good functional group tolerance, which has fueled the exploration of nonclassical glycosyl radical-involved glycosylation reactions to prepare nonclassical *C*-glycosides. For example, considerable efforts have been directed toward the synthesis of nonclassical heteroaryl *C*-glycosides **11** through Minisci type C−H glycosylation reactions of *N*-heteroarenes with nonclassical glycosyl radicals generated from uronic acids or α-alkoxyacyl tellurides, with key contributions from Vismara,[44] Inoue,[45] Li,[46] and Liu.[47] These elegant approaches offer a streamlined pathway to the desired structures and signify significant advances. However, they necessitate stoichiometric amounts of oxidants and radical initiators to ensure the smooth progression of reactions. Consequently, the pursuit of alternative strategies that allow for efficient, sustainable, and scalable synthesis of nonclassical *C*-glycosides remains a pivotal goal in the field.

In recent years, 4-Nc-glycosyl-1,4-dihydropyridine (4-Nc-glycosyl DHP) reagents have emerged as exciting nonclassical glycosyl radical precursors, garnering attention for their potential in synthesizing nonclassical aryl *C*-glycosides (Figure 1C). In 2018, Molander and co-workers reported an elegant Ni/photoredox dual-catalyzed nonclassical glycosylation of 4-Nc-glycosyl DHPs with (hetero)aryl bromides, leading to nonclassical aryl *C*-glycosides **12** with d.r. values ranging from 1:1.5 to >20:1.[48] Notably, both saccharide and aromatic backbones were intimately tied to the stereochemical course, leading in certain cases to substrate-controlled products. Although the authors demonstrated that diastereoselectivity could be improved by modifying the ligand backbone on a case-by-case basis, the relationship between diastereoselectivity and substrate structure remains elusive. Subsequently, Chen and He reported a novel radical method for the diasteroselective synthesis of nonclassical aryl *C*-glycosides through Minisci-type glycosylation of *N*-heteroarenes with 4-Nc-glycosyl DHPs under visible

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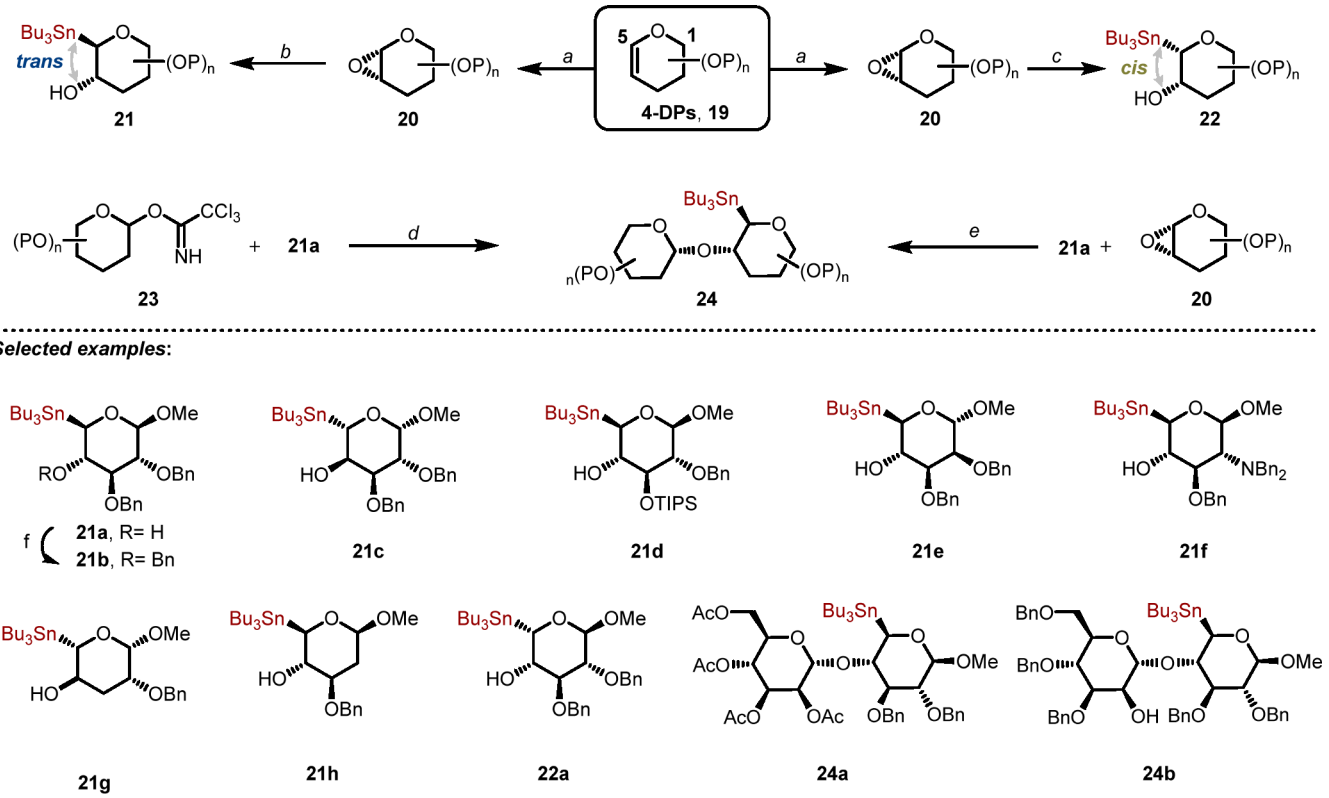
Scheme 1. Synthesis of Nonclassical Anomeric Stannanes[a]



[a]Reagents and conditions: (a) Oxone (4.0 equiv), acetone, $NaHCO_3$, CH_2Cl_2/H_2O, 0 °C to rt, 99%; (b) *n*-$Bu_3SnMgMe$ (3.00 equiv), THF, −20 °C, 12%−41%; (c) (i) *n*-Bu_3SnLi (6.00 equiv), $ZnBr_2$ (7.00 equiv), THF, −78 °C to −30 °C, 16 h, 10%; (d) TMSOTf (0.25 equiv), 5 Å MS, THF, −20 °C, 30%; (e) Ph_3PAuCl (0.30 equiv), AgOTf (0.30 equiv), 4 Å MS, −78 °C to rt, 3 d, 33%; (f) BnBr (2.0 equiv), KHMDS (1.5 equiv), THF, 0 °C to rt, 2.5 h, 93%.

light irradiation.[49] Remarkably, the stereochemical outcomes in glycosidic bond formation are solely governed by the saccharide skeleton rather than the heteroaryl skeleton, leading to excellent stereoselectivity. More recently, Olofsson and co-workers disclosed an intriguing radical-mediated C−C bond formation strategy through photoredox- catalyzed reactions of 4-Nc-glycosyl DHPs and vinylbenziodoxol(on)es to afford non-classical vinyl *C*-glycosides **13**.[50] This method efficiently synthesizes nonclassical vinyl *C*-glycosides with excellent diastereoselectivity, filling a research gap in the synthesis of nonclassical vinyl *C*- glycosylation. It is widely recognized that simultaneous access to both α and β anomers via radical glycosylation methods has been challenging due to the stereoelectronic and steric effects of sugar rings, which significantly influence the stereoconfiguration preference of glycosyl radicals. Therefore, a concise, highly controllable, and predictable nonclassical *C*-glycosylation strategy is urgently needed to effic iently produce a diverse range of structurally complex nonclassical *C*-glycosides.

Transition metal-catalyzed glycosylation cross-coupling (GCC) reactions involving glycosyl nucleophiles representing a novel design strategy for glycosylation reactions.[51] In this context, we have successfully developed highly stereospecific cross-coupling reactions of both anomers of C1-stannanes with aryl halides catalyzed by Pd, enabling the precise synthesis of classical aryl *C*-glycosides. The method exhibits broad substrate scope, excellent functional group compatibility, and consistently high stereospecificity.[52−54] The key stereocontrol step in this glycosylation is the stereoretentive transmetalation, which enables exclusive anomeric control, independent of the steric and electronic environment of the saccharide. Such a criterion is crucial for assessing the potential scalability of any glycosylation approach. Encouraged by the excellent controllability, predictability, and stereoselectivity of demonstrated in our preliminary work, we aimed to develop a stereospecific nonclassical glycosyl cross-coupling (NGCC) process. This process aims to achieve a stereoretentive transmetalation of reverse glycosylstannes, thereby efficiently and precisely constructing nonclassical *C*-glycosidic bonds. In order to provide a meaningful solution to these fundamental issues, several key obstacles must be overcome: 1) accessing a wide range of nonclassical glycosyl stannanes; 2) addressing the structural disparities between nonclassical and classical glycosyl stannanes that may influence reaction activity, requiring the screening of stereospecific C−C bond formation conditions; 3) surpassing the limitations of sp^2-hybridized electrophiles in classical C−C glycosylation reactions to achieve alkenyl *C*-glycosides.

Herein, we present the first example of Pd-catalyzed stereospecific cross-coupling reaction of nonclassical glycosyl stannanes with aryl and vinyl electrophiles for the synthesis of nonclassical *C*-glycosides. This innovative method enables exclusive stereocontrol over the anomeric configuration of both nonclassical anomers derived from various saccharides (Figure 1D). This novel nonclassical glycosylation method has been fully demonstrated in over 50 examples, featuring by high predictability and modularity, and chemical selectivity. It is compatible with various protected or deprotected nonclassical sugars and electrophiles, including peptides, bioactive com-

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pounds and drugs. Furthermore, computational studies were conducted to elucidate the underlying factors contributing to the differences in reactivity observed among nonclassical stannanes and additives, and to reveal new reaction processes.

RESULTS AND DISCUSSION

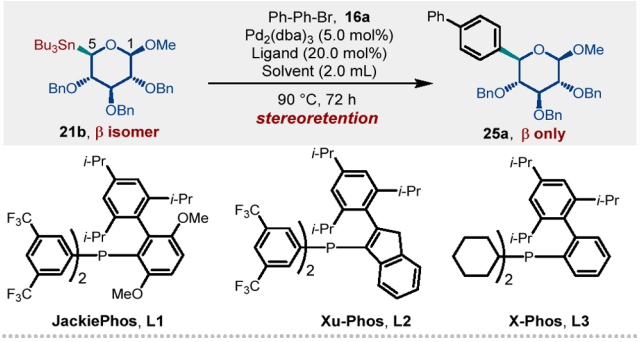
Synthesis of Nonclassical Anomeric Stannanes

Structurally diverse and optically pure nonclassical anomeric stannanes serve as the foundation for developing a general highly modular, and stereoselective, nonclassical glycosylation reaction. Therefore, our investigation commenced with the synthesis of nonclassical anomeric stannanes. As illustrated in Scheme 1, a series of synthetic transformations of 4-deoxypentenosides (4-DPs) **19** were carried out to access both anomers of saccharides. During the preparation of the 4,5-*trans* nonclassical anomeric stannanes **21**, we observed that subtle differences in the structure of 4-DPs, such as the stereoconfiguration of C1-OMe, led to stannanes with distinct stereochemical configurations. For instance, highly facioselective epoxidation of β-glc-4-DPs, followed by a trans ring-opening reaction with $Bu_3SnMgMe$, can smoothly afford reversed β-anomeric stannanes **21a**. However, due to the moderately facioselective epoxidation of α-glc-4-DPs (β:α = 5:1), a separable mixture of α- and β- nonclassical anomeric stannanes with completely opposite stereoconfiguration at the C4 and C5 positions were obtained upon ring opening, resulting in obtaining the major product **21c**. By modifying the preparation conditions, we successfully obtained various saccharides on a gram scale (**21a**-**21h**). Inspired by $ZnBr_2$ mediated *syn* addition of 4-epoxypyranoside,[38] we also successfully obtained 4,5-*cis*-α-stannanes **22a** through a *cis* ring-opening reaction with $Bu_3SnZnBr$. The diversity and complexity of nonclassical anomeric nucleophiles were successfully broadened through the transformation of monosaccharide stannanes into oligosaccharides. To achieve this, we employed the commonly used conditions involving TMSOTf (25 mol %) for the activation of Schmidt donors, leading to the formation of disaccharide stannanes **24a** in a yield of 33%. Additionally, we broadened the scope of nonclassical anomeric stannanes by employing the classical gold catalyic syntem (Ph_3PAuCl/AgOTf) developed by Yu group[55] in reactions between acceptor **21a** and glycal epoxide **20**, resulting in the formation of disaccharide stannanes **24b**.

Reaction Development

Having obtained a series of nonclassical anomeric stannanes, the subsequent objective was to identify optimal catalytic conditions for achieving stereospecific nonclassical glycosyl coupling (NGCC) reactions of the nonclassical anomeric nucleophiles (Table 1). Initially, we utilized the standard $Pd_2(dba)_3$/Jackiephos **L1** catalysis system, known for its success in synthesizing classical aryl *C*-glycosides, to investigate the model reaction of nonclassical anomeric stannanes **21b** and 4-bromobiphenyl **16a**. This resulted in the formation of the desired nonclassical aryl *C*-glycosides **25a** in 68% NMR yield, accompanied by 98% of the byproduct 4-deoxypentenosides (for more detail, see SI). To mitigate the issue of competitive β-elimination of the oxygen-based groups at C4, we reduced the reaction temperature and omitted the use of KF. Gratifyingly, the yield of **25a** was inproved to 77%, and the β-elimination was completely suppressed when Ag_2CO_3 was used as an additive, along with 1 equiv of CuCl (entry 1). Toluene or DMF was used as an alternative solvent, the NMR yields were decreased to 59%

Table 1. Optimization of the Reaction Conditions[a]



Entry	Ligand	Additives	Solvent	NMR Yield
1	L1	Ag_2CO_3	1,4-Dioxane	77%
2	L1	Ag_2CO_3	Toluene	59%
3	L1	Ag_2CO_3	DMF	54%
4	L1	Ag_2CO_3	*t*BuOH	79%
5	L1	Ag_2CO_3	1,4-Dioxane/*t*BuOH 1:1	81%
6[b]	L1	Ag_2CO_3	1,4-Dioxane/*t*BuOH 1:1	82%
7[b]	L2	Ag_2CO_3	1,4-Dioxane/*t*BuOH 1:1	54%
8[b]	L3	Ag_2CO_3	1,4-Dioxane/*t*BuOH 1:1	17%
9[bc]	L1	Ag_2CO_3	1,4-Dioxane/*t*BuOH 1:1	50%
10[bd]	L1	Ag_2CO_3	1,4-Dioxane/*t*BuOH 1:1	11%
11[b]	L1	Ag_2O	1,4-Dioxane/*t*BuOH 1:1	83%
12[b]	L1	AgF	1,4-Dioxane/*t*BuOH 1:1	86%
13[be]	L1	AgF	1,4-Dioxane/*t*BuOH 1:1	72%
14[bf]	L1	AgF	1,4-Dioxane/*t*BuOH 1:1	91%
15[bfg]	**L1**	**AgF**	**1,4-Dioxane/*t*BuOH1:1**	**97% (93%)**
16[bh]	L1	AgF	1,4-Dioxane/*t*BuOH 1:1	N.R.
17[bfgi]	L1	AgF	1,4-Dioxane/*t*BuOH 1:1	8%, 93%,16%
18	**L1**	**AgF**	**1,4-Dioxane/H_2O1:1**	**74%**

[a]Standard reaction conditions: **16a** (0.10 mmol), **21b** (0.20 mmol), $Pd_2(dba)_3$ (5 mol %), ligand (20 mol %), CuCl (1.0 equiv), Ag salts (1.0−2.0 equiv), 1,4-dioxane (2.00 mL), 90 °C, 72 h, N_2, isolated yields. [b]48 h was used. [c]CuBr was used. [d]CuI was used. [e]110 °C was used. [f]70 °C was used. [g]$Pd_2(dba)_3$ (2.5 mol %) and ligand (10 mol %) were used. [h]Without $Pd_2(dba)_3$ or Cu salts. [i]4-Chlorobiphenyl, 4-Iodobiphenyl, or trifluoromethanesulfonic acid 4-biphenylyl ester was used. The stereochemical outcome was determined by ^{1}H NMR analysis of crude reaction mixtures.

and 54%, respectively (entries 2−3). However, the use of *t*BuOH or a cosolvent of *t*BuOH and 1,4-dioxane resulted in slightly increased yields (entries 4−5). Shortening the reaction time did not adversely affect the yield (entry 6). It is noteworthy that the choice of ligand significantly influences efficiency, as observed in classical glycosyl cross-coupling reactions, although it does not impact stereoselectivity. As demonstrated, JackiePhos **L1** outperformed other ligands tested, with ligand **L2** and **L3** exhibiting lower yields (entries 7 and 8). Be noted that copper salts and their counteranion significantly influenced the reaction outcome. Using CuBr as the copper source resulted in a 50% yield of the coupling product, while CuI only yielded the desired product in 11% NMR yield. The speculated reasons include the solubility of copper salts and the favorable formation of electrophilic palladium species facilitated by chloride ions, which are advantageous for the transmetalation step. Cuprous salts are commonly used as an additive in Stille cross-coupling reactions. It is generally accepted that its function is to enhance the transmetalation process between the stannane reagent and the palladium catalyst.[52−54] Variation of the reaction conditions with different sliver salts revealed that Ag_2O and AgF also

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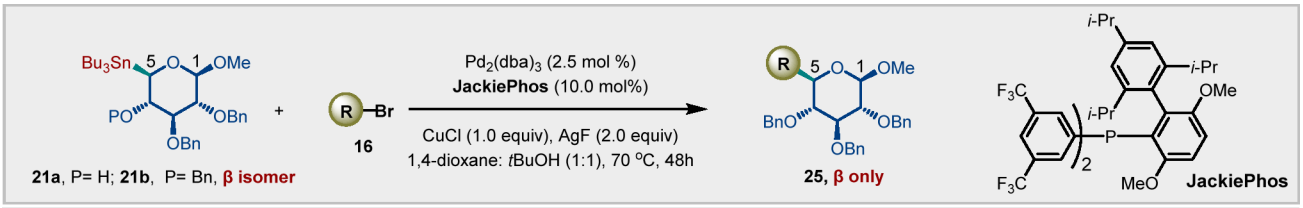
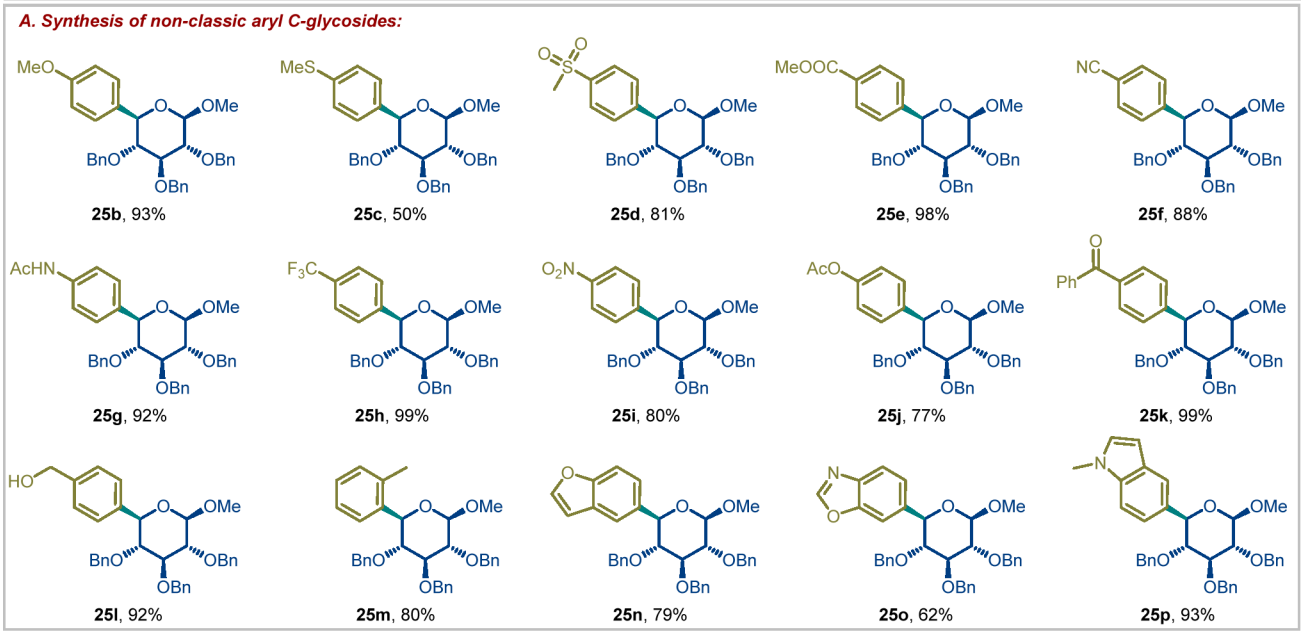
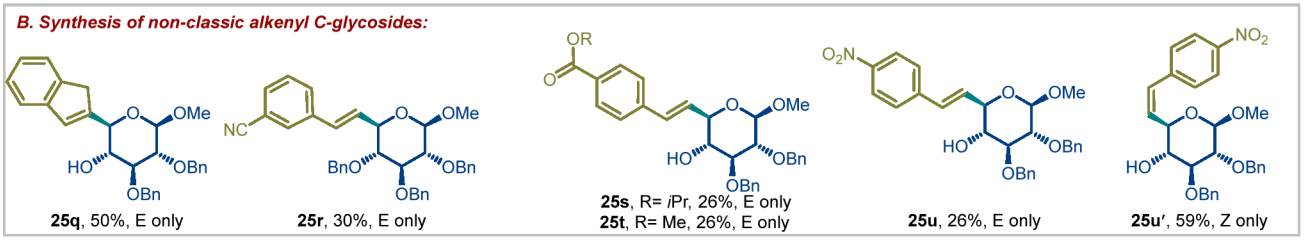
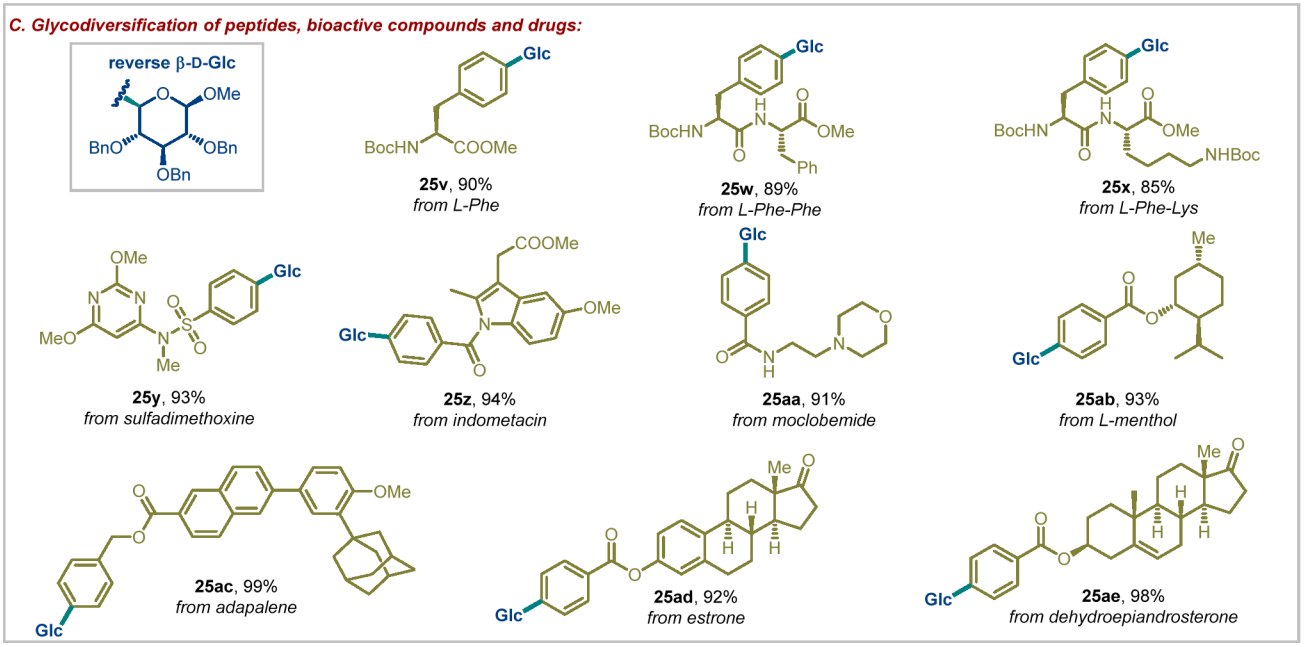
Scheme 2. Scope of Electrophilic Coupling Partners[a]









[a]Standard reaction conditions: **16** (0.10 mmol), **21a** or **21b** (0.20 mmol), $Pd_2(dba)_3$ (2.5 mol %), JackiePhos (10 mol %), CuCl (1.0 equiv), AgF (2.0 equiv), 1,4-dioxane/*t*BuOH (1:1, 2.0 mL), 70 °C, 48 h, N_2, isolated yields.

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provided successful conversion (entries 11 and 12). Elevated temperatures decreased the yield of **25a** (entry13), but lowering the temperature to 70 °C improved yields to 91% (entry 14). Pleasingly, reducing the amount of palladium catalyst to 5% resulted in a97% NMR yield and a 93% isolated yield(entry 15). Control experiments confirmed the necessity of both Pd catalysts and Cu salts in the nonclassical arylation *C*-glycosylation reaction (entry 16). Exploring other common aryl electrophiles, such as aryl chloride, aryl iodide, and aryl triflate, resulted in coupling products with yields of 8%, 93%, and 16%, respectively. Surprisingly, this Pd-catalyzed cross-coupling reaction of nonclassical anomeric stannane can be successfully carried out in a 1:1 mixture of 1,4-dioxane and H_2O, yielding **25a** in a 74% yield. This approach holds promise for late-stage glycodiversification of water-soluble biomacromolecules. It should be noted that only β isomers were determined under all the conditions evaluated.

Scope and Application

Scope of Electrophilic Coupling Partners. With the optimal reaction conditions established, we proceeded to investigate the scope of electrophilic coupling partners. As depicted in Scheme 2, a diverse arrary of (hetero)aryl bromides demonstrated excellent compatibility with the reaction, resulting in good to excellent yields with exclusive nonclassical anomeric control. Electronic modifications of the aromatic ring exhibited minimal impact on the reaction yields, as observed with both electron-rich (**25b**, **25c**, **25g**, and **25j**) and electron-poor (**25d**-**25f**, **25h**, **25i**, and **25k**) substituents. However, it is noteworthy that the coordination of sulfur atoms could potentially lead to palladium catalyst poisoning and deactivation, resulting in lower yields (**25c**). Notably, **25l**, containing unprotected hydroxyl groups, underwent an efficient reaction, producing the desired product without any detectable byproducts arising from C−O coupling. It is crucial to underscore that the hindered 2-methylbromobenzene readily underwent the NGCC reaction to furnish **25m** in an impressive 80% isolated yield. Moreover, a wide array of functional groups, such as methoxy, thiomethyl, methylsulfonyl, ester, cyano, acetylamino, trifluoromethyl, nitro, and benzoyl, were well tolerated. Notably, the NGCC reaction extended beyond aryl electrophiles to encompass heteroaromatic entities such as benzofuran, benzoxazole, and indole, which readily engaged in nonclassical *C*-glycosylation, providing the desired products **25n**−**25p** in isolated yields ranging from 62% to 93%.

Nonclassical vinyl *C*-glycosides constitute a valuable class of compounds with considerable synthetic potential. However, their synthesis poses substantial challenges, and presently, only a few efficient methods are available for their production.[50] To our delight, we found that the Pd-catalyzed cross-coupling reaction of nonclassical anomeric stannanes and vinyl bromides was effecitive in constructing vinyl C−C bonds with excellent anomeric control and Z/E- configuration stereoretention. While the yields obtained in this reaction may not be high (**25q**-**25u'**), they serves as a promising starting point for further optimization and the development of new synthetic routes for nonclassical vinyl *C*-glycosides. The yields of the synthesis for alkenyl *C*-glycosides are relatively low compared to those of the *C*-arylations, due to the challenging nature of oxidative addition of alkenyl electrophiles. Optimizing ligands may effectively address this challenge. It is worth emphasizing that the Pd-catalyzed glycosyl cross coupling of classical anomeric stannanes and vinyl bromides is not effective, thereby underscoring the impact of structural differences between anomeric and nonclassical anomeric stannanes on reaction activities. The presented method represents the first stereoselective synthesis approach capable of concurrently achieving nonclassical aryl and alkenyl *C*-glycosides.

To further explore the scope and versatility of the nonclassical glycosyl cross-coupling method, we investigated the late-stage glycodiversification of various commercially available pharmaceuticals and biologically active molecules using **21b** as the glycosyl donors under the standard reaction conditions. For example, amino acids, and dipeptides reacted smoothly under the standardized conditions to furnish corresponding products **25v**-**25x** in 85−90% yields. Along similar lines, several commercially available drugs and small natural products that were prefunctionalized with aryl electrophiles, such as sulfadimethoxine(**25y**), moclobemide (**25aa**), *L*-menthol (**25ab**), adapalene (**25ac**), estrone (**25ad**), and dehydroepiandrosterone (**25ae**), readily underwent coupling with nonclassical anomeric stannanes **21b** under standard conditions, achieving yields greater than 91%. These outcomes demonstrate the versatility and wide applicability of the method in synthesizing a diverse range of glycoconjugates that could potentially possess biological activity.

Scope of Nonclassical Anomeric Stannanes. Encouraged by the aforementioned results, we further evaluate the scope of nonclassical anomeric stannanes, using methyl 4-bromobenzoate as a model stubstrate. As shown in Scheme 3, a diverse array of nonclassical anomeric stannanes with different sugar types efficiently reacted to produce the desired coupling products in good to excellent yields with exclusive β- or α-selectivity. We demonstrated that the 4,5-*trans* anomers of nonclassical anomeric stannanes obtained from fully substituted β-glc-4-DPs (**27a**), α-glc-4-DPs (**27b** and 27**c**), and α-man-4-DPs (**27d**) smoothly converted into the desired aryl *C*-glycosides, retaining the anomeric configuration with yields ranging from 64% to 99%. Our method also successfully converted deoxysugar stannanes into nonclassical aryl *C*-glycosides with excellent stereoselectivity, even in cases where deoxysugars posed challenges in controlling the anomeric configuration during glycosylation (**27e** and **27f**). Similarly, impeccable stereoretentivity was observed for 4,5-*cis* isomers of stannanes (**27g**). To our delight, nonclassical aryl *C*-glucosamine **27h** can also be obtained in excellent yield. Nonclassical anomeric stannanes protected with common protecting groups such as OTIPS, ONap, and OAc demonstrated compatibility with standard conditions, exemplified by the successful synthesis of **27i**, **27j** and **27m** with isolated yields of 75%−90%. The stereoselective glycosylation of unprotected sugars represents an attractive and highly challenging research area. We were delighted to observe that nonclassical anomeric stannanes containing free protected hydroxyl groups exhibited excellent reactivity under the standard reaction conditions (**27a**−**27i**, **27k**−**27m**). These substrates displayed remarkable stereoselectivity and chemical selectivity, yielding products with commendable yields. Significantly, oligosaccharide stannanes **24a** and **24b**, derived from glycosylation reactions involving monosaccharide stannanes (as depicted in Scheme 1), were successfully employed in nonclassical glycosyl cross-coupling

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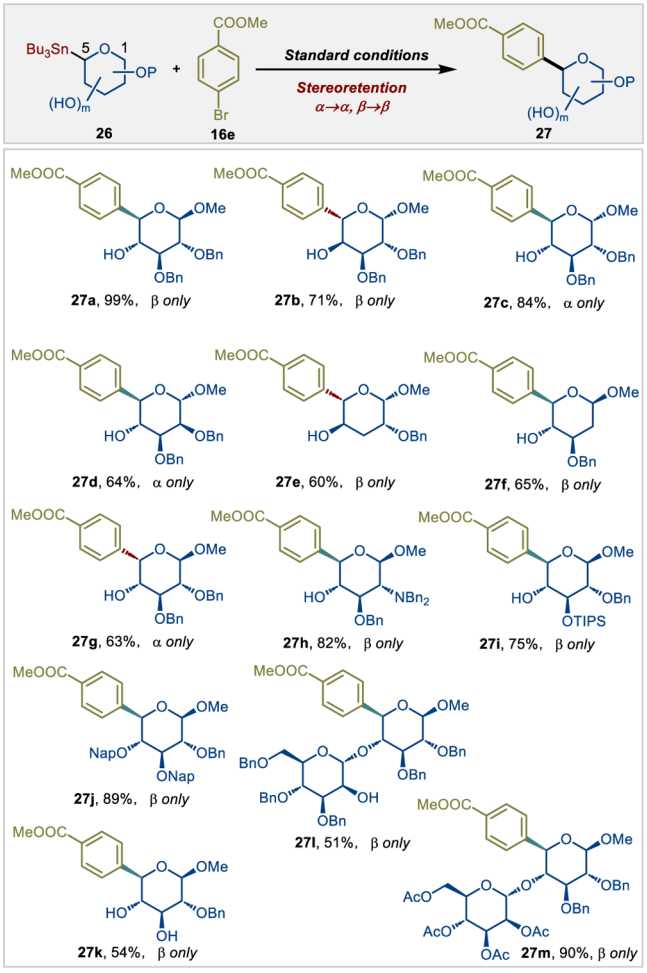
Scheme 3. Scope of Nonclassical Anomeric Stannanes[a]



[a]Standard reaction conditions: **16e** (0.10 mmol), **26** (0.20 mmol), $Pd_2(dba)_3$ (2.5 mol %), JackiePhos (10 mol %), CuCl (1.0 equiv), AgF (2.0 equiv), 1,4-dioxane/*t*BuOH (1:1, 2.00 mL), 70 °C, 48 h, N_2, isolated yields.

reactions without any modifications of the standard conditions. This enabled the formation of nonclassical *C*-disaccharides containing a (1 → 4) glycosidic bond in 51% and 90% isolated yields.

Application

To demonstrate the practicality of the reaction, various applications and downstream transformations were conducted. In Scheme 4A, 1,4-dibromobenzen readily work with **21b** to yield the diglycosylated product **29** in 73% isolated yield with exclusive β-selectivity. Next, through optimization, we found that adjusting the equivalency of the halide electrophile allowed for the facile synthesis of the monoglycosylated product **30** from 1,4-dibromobenzene (5.0 equiv). This intermediate was obtained in a synthetically acceptable yield (42%), with a bromine atom remaining on the aromatic ring as a reaction handle for further transformations. Several classic cross-coupling transformations such as Suzuki reaction, Sonogashira reaction, C−N coupling, and Stille coupling could be conducted by Pd-catalyzed cross-coupling reactions of **30** (Scheme 4B). All reactions performed well without any decrease in nonclassical anomeric selectivity (only β anomer). In this study, the coupling products were exclusively observed as either α or β anomers, as determined by ^{1}H NMR analysis of crude reaction mixtures. The configuration of the nonclassical anomeric carbon in compounds **25** and **27** was assigned based on the analysis of $^3J_{(HH)}$ coupling constants of the H5 proton signal. The stereochemistry of **25i** were unambiguously confirmed by X-ray crystallographic analysis (Scheme 4C).

The late-stage C-glycosylation reaction of fully deprotected glycosyl donors with various aryl halides is an ideal approach for rapidly building a library of *C*-glycoside candidate drugs. However, it poses challenges in achieving stereoselective control of anomeric configuration and chemical selectivity of hydroxyl groups, constituting a longstanding challenge in glycosylation reactions of free deprotected glycosyl donors.[48] Given the aforementioned challenges, our aim was to showcase the potential applications of the current method. In order to steer clear of employing relatively harsh Birch reduction conditions, our initial efforts were directed toward the exploration of a straightforward and efficient synthesis for nonclassical anomeric stannanes with fully deprotected hydroxyl groups. Drawing inspiration from the innovative and efficient deprotection of benzyl-derived groups through the photochemically mesolytic cleavage of C−O bonds, as reported by the Xia group,[56] we subsequently utilized benzyl-protected nonclassical anomeric stannanes under standard conditions. Encouragingly, this approach yielded the desired nonclassical anomeric stannanes **33** with free hydroxyl groups in satisfactory yields (62−68%). Subsequently, we coupled the aforementioned free hydroxyl-protected anomeric stannanes **33** with a series of aryl electrophiles of SGLT2 inhibitors, obtaining corresponding reverse gliflozin analogues in yields ranging from 62% to 87%. These analogues hold the potential to serve as potent new gliflozin drugs.[57] Furthermore, ongoing biological studies related to type 2 diabetes are currently underway.

Biological Evaluations

Returning to the original intention of our research project, nonclassical *C*-glycosylation offers a novel direction for glycosylation of drug molecules, which may result in more remarkable biological activities. In order to validate this hypothesis, nonclasscical mannosyl indomethacin **35** was designed and synthesized (Scheme 5A): subjecting indomethacin derivatives **16z** to our standard reaction conditions with nonclassical mannose stannanes **21e**, followed by deprotection of the OBn, OAc, and COOMe groups provided the nonclassical *C*-mannosyl indomethacin derivatives (**35**).

Previous studies have indicated that glycosylated drug molecules may exhibit different absorption, distribution, metabolism, and excretion (ADME) profiles compared to their parent molecules.[58,59] In our study, compound **35**, which features a C-5-glycoside motif, demonstrated enhanced metabolic stability in mouse liver microsomes and higher kinetic solubility compared to the parent compound indomethacin **36**. Furthermore, compound **35** displayed potent antimycobacterial activity against wild type M. smegmatis MC^2 155, with a Minimum Inhibitory Concentration (MIC) of 16 μg/mL, a level comparable to that of the prototype molecule indomethacin **36** (16 μg/mL). These results indicate that nonclassical *C*-glycosylation modifications might offer medicinal chemists new avenues to explore novel chemical space and optimize lead compounds and drug candidates.

Mechanistic and Computational Studies. *Mechanistic Studies.* Upon evaluating the scope of nonclassical anomeric stannanes, we observed that the stereochemistry of the OMe

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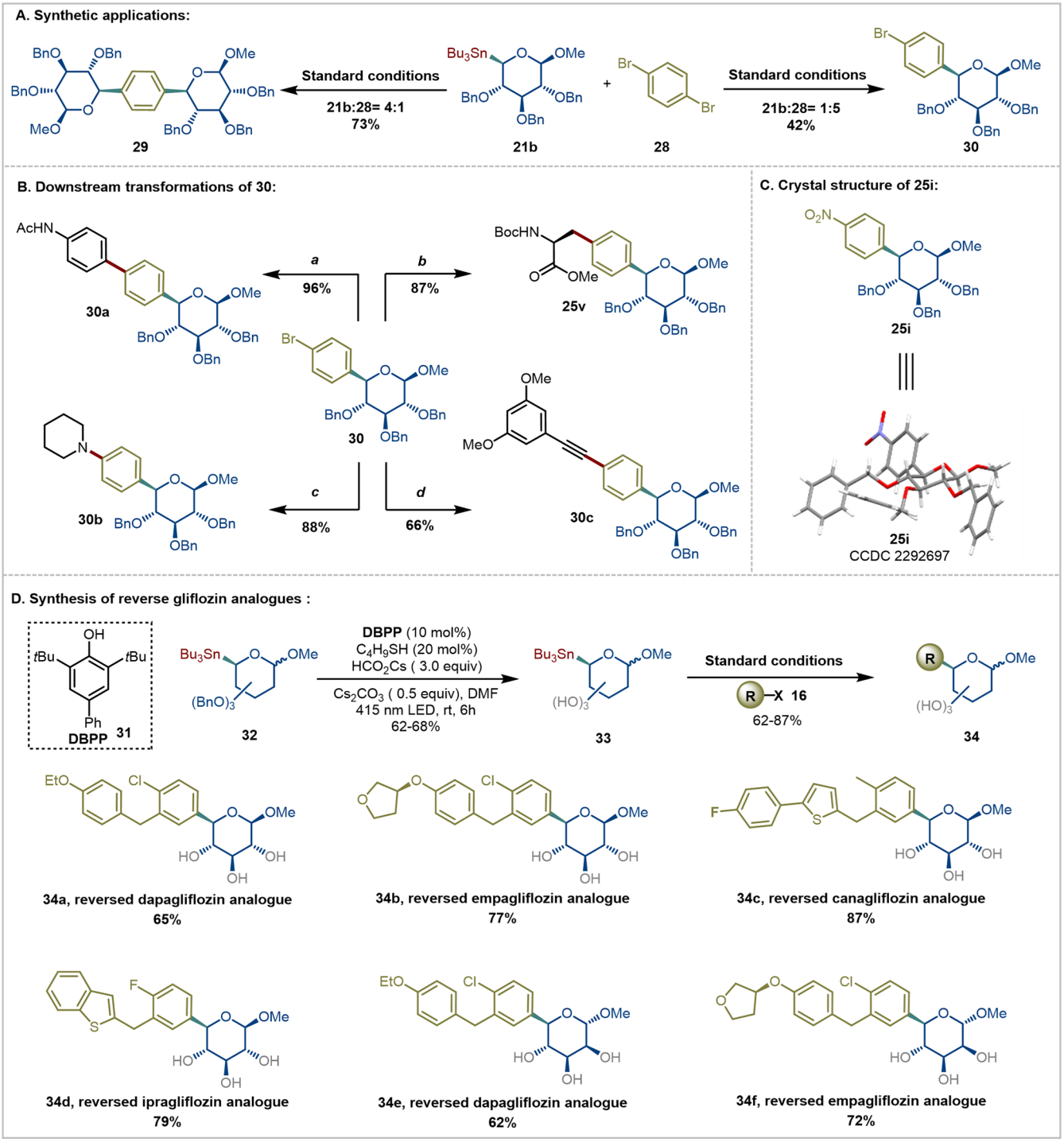
Scheme 4. Synthetic Applications and Downstream Transformations[e]



[a]Reaction conditions: **30** (0.05 mmol), **4**-Acetamidophenylboronic acid (0.10 mmol), K_3PO_4 (0.15 mmol), PCy_3 (10 mol %), $Pd_2(dba)_3$ (5.0 mol %), 1,4-dioxane (0.7 mL), H_2O (0.3 mL), 110 °C, 27 h, N_2. [b]**30** (0.05 mmol), Boc-Ala^{Sn}-OMe(0.10 mmol), $Pd_2(dba)_3$ (2.5 mol %), JackiePhos (10 mol %), CuCl (50 mol %), 1,4-dioxane (1.0 mL), 100 °C, 24 h, N_2. [c]**30** (0.05 mmol), piperidine (0.10 mmol), $Pd(OAc)_2$ (10 mol %), Cs_2CO_3 (0.075 mmol), Xphos (20 mol %), toluene (1.0 mL), 100 °C, 24 h, N_2. [d]**30** (0.05 mmol),1-ethynyl-3,5-dimethoxybenzene (0.100 mmol), $Pd(PPh_3)_4$ (5.0 mol %), CuI (10 mol %), Et_2NH (1.0 mL), 60 °C, 24 h, N_2. [e]Standard reaction conditions: Stannane reagents (0.10 or 0.20 mmol), electrophilic reagent (0.10 mmol), $Pd_2(dba)_3$ (2.5 mol %), JackiePhos (10 mol %), CuCl (1.0 equiv), AgF (2.0 equiv), 1,4-dioxane/*t*BuOH (1:1, 2.0 mL), 70 °C, 48 h, N_2, isolated yields.

group at the C1 position does not affect the stereospecificity of the reaction. However, it does affect the overall reaction efficiency. To gain deeper understanding into the relationship between steric hindrance and reaction reactivity of nonclassical anomeric stannanes, control experiments were conducted as outlined in Scheme 6. Interestingly, despite **21b** having larger steric hindrance than **21k**, it exhibited higher coupling yields. This observation suggests that while the stereoconfiguration of

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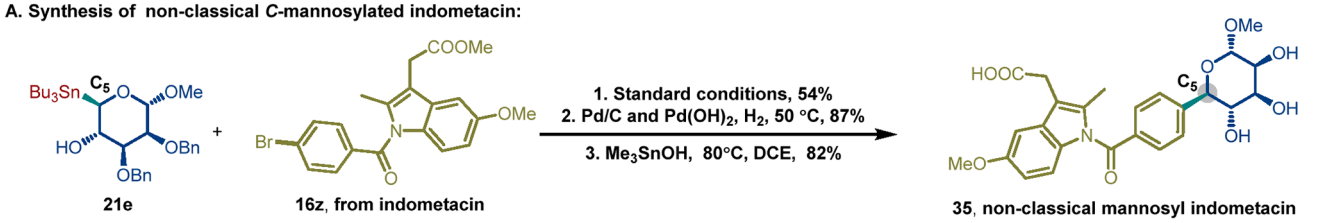
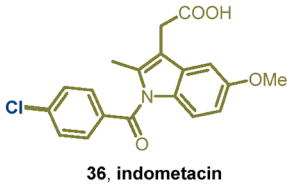
Scheme 5. Biological Evaluations



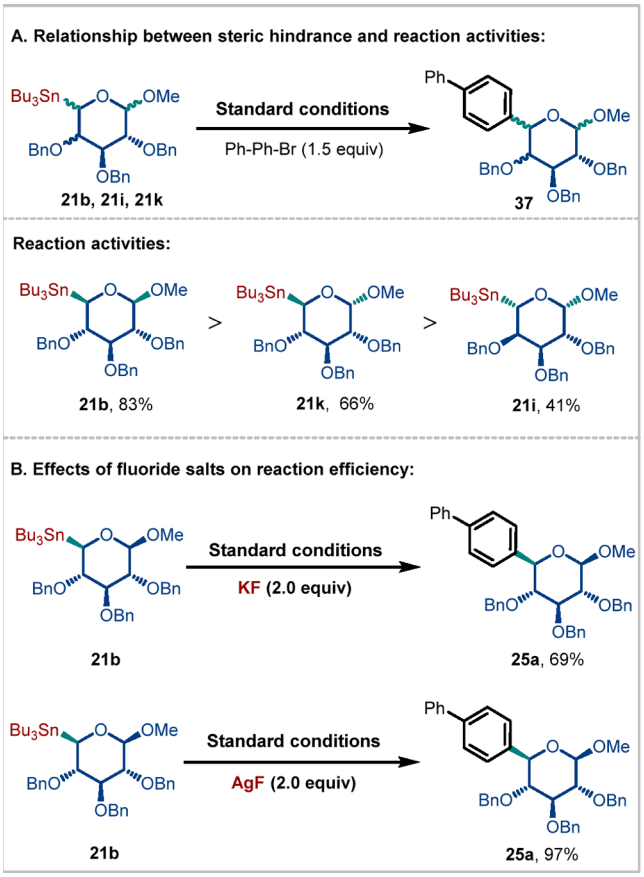
B. Biological evaluation of 35 and 36:

Antimycobacterial activitiy, metabolic stability in mouse liver microsomes and kinetic solubility of 35 *vs* 36

Compound	MIC (μg/ml)	$T_{1/2}$ (min)	Kinetic solubility (μg/ml)
35	16	>145	92.5
36	16	138.5	64.1



Scheme 6. Control Experiments



the OMe group in **21k** appears to introduce favorable steric hindrance, it actually has unfavorable effects on accelerating the transmetalation step. On the other hand, the lower activity of **21i** compared to **21b** and **21k** implies that the type of sugar has a more pronounced impact on the reaction efficiency than the C1-OMe stereoconfiguration. Furthermore, model reactions were conducted in the presence of additives KF or AgF, affording the desired product **25a** in 69% and 97%, respectively. This observation raises important questions about the role of AgF and KF in the reaction mechanism.

Computational Studies. In order to investigate the root cause of the variations in reactivity between nonclassical anomeric stannanes and anomeric stannanes, we conducted density functional theory (DFT) calculations, as depicted in the top of Figure 2. Based on our previous mechanistic studies,[52] the stereospecific nonclassical glycosyl cross-coupling reaction primarily involves oxidative addition, transmetalation, and reductive elimination steps. To optimize computational efficiency, the OBn group was replaced with OMe, and Bu_3Sn was replaced with Me_3Sn in the nonclassical anomeric stannanes.

The cross-coupling reaction initiates with the oxidative addition of the Pd(0) species to bromobenzene, leading to the formation of a phenyl palladium(II) bromide complex **int2** with a barrier of 6.7 kcal/mol (**ts1**). Subsequently, the stereoretentive transmetalation with the nonclassical anomeric stannanes **21b'** occurs via a four-membered cyclic transition state (**ts5**), requiring a high activation energy of 39.0 kcal/mol. Interestingly, the presence of AgF was found to promote this transmetalation process. The coordination of AgF facilitates the transmetalation step through a six-membered cyclic transition state (**ts4**) to form **int4**, significantly lowering the energy barrier to 21.5 kcal/mol. **Int4** then proceeds through a barrierless rapid reductive elimination to yield the desired product **25a'** and regenerate the **PdL** catalyst. Additionally, an alternative pathway involving AgF-assisted halide exchange in **int2** to generate a more stable palladium(II) fluoride species **int3** was considered, followed by transmetalation (**ts2**). However, this process exhibits an activation energy of 34.5 kcal/mol, rendering it unfavorable. The flipping of the aryl group in **int3** to form **int3'** was investigated, as it was expected to significantly reduce the energy of transmetalation (**ts2'**, $\Delta G^{\ddagger}$ = 21.8 kcal/mol). However, we found that **int3** would be difficult to isomerize to **int3'** around the P−Ar bond rotation ($\Delta E^{\ddagger}$ = 28.9 kcal/mol, see Supporting Information for details). Therefore, this pathway was ruled out.

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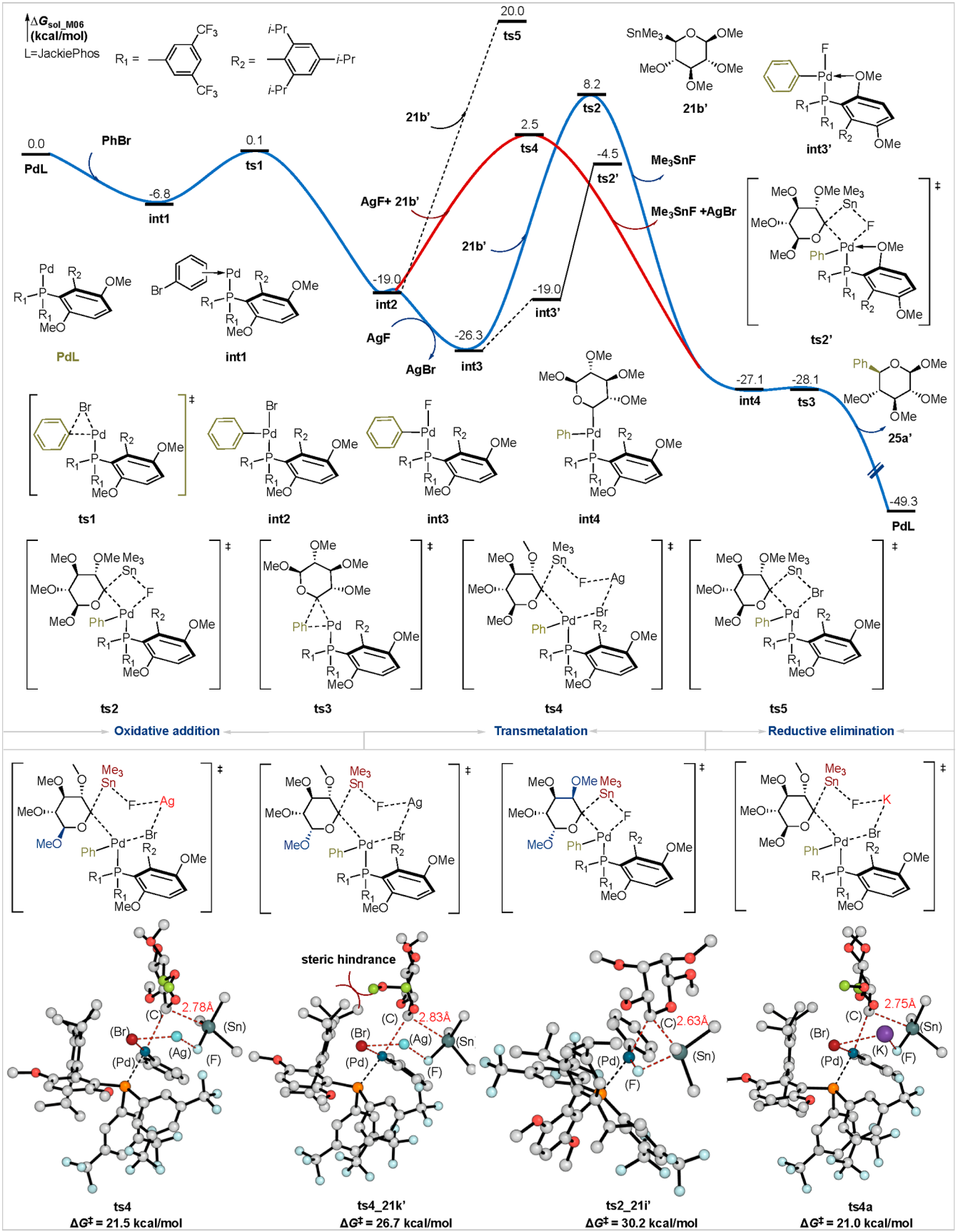

Figure 2. Reaction energy profile of the Pd-catalyzed stereospecific nonclassical glycosyl cross-coupling of nonclassical anomeric stannanes with bromobenzene using JackiePhos ligand. DFT calculations were performed at the M06/SDD-6-311+G(d,p)/SMD(DCE)//B3LYP/SDD-6-31G(d) level of theory.

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We then performed computational analysis to gain insights into the reactivity differences among different configurations of nonclassical anomeric stannanes, as illustrated in the bottom of Figure 2. The transmetalation process, which is crucial for the overall reaction rate, was identified as the rate-determining step. Upon replacing substrate **21b'** with **21k'**, the activation energy of the transition state (**ts4_21k'**) increases to 26.7 kcal/mol due to steric hindrance between the downward-oriented OMe group and the aryl functional group of the ligand in **ts4_21k'**. In contrast, substrate **21i'** does not allow for a favorable six-membered transmetalation transition state with the ligand, leading to the identification of a four-membered transition state (**ts2_21i'**) with an activation energy of 30.2 kcal/mol. The calculations clearly indicate that substrate **21i'** has lower activity than **21b'** and **21k'**. Finally, we investigated the impact of AgF and KF on the reaction. Initial comparison revealed no significant difference in reaction energy between the transition states. Further analysis led us to investigate the stability of dimeric forms of AgF and KF in our reaction. The energy barriers for the transition states with dimer AgF were determined to be 22.4 kcal/mol, whereas those associated with dimer KF were notably higher at 34.2 kcal/mol (detail in SI). This substantial difference in energy barriers implies a significant contrast in the reactivity of these dimers. Our findings indicate that the dimer AgF and KF exhibit enhanced stability, with the conversion of dimer to monomers requiring 23.8 and 28.2 kcal/mol, respectively. This observation leads us to speculate that the superior performance of AgF might be attributed to its ability to achieve a more favorable reaction pathway compared to KF.

CONCLUSION

In conclusion, we have successfully developed a concise and versatile method for synthesizing nonclassical *C*-glycosides through Pd-catalyzed highly stereospecific glycosyl cross-coupling of nonclassical anomeric stannanes. This innovative approach incorporates a stereoretentive transmetalation step, enabling precise control over the nonclassical anomeric configuration irrespective of the stereoelectronic environment of the saccharides, which distinguishes it from known nonclassical *C*-glycosylation methods. The method is highly controllable, predictable, and modular, showcasing a broad substrate scope, excellent functional group tolerance, and consistently high levels of chemoselectivity and stereospecificity. The discovery of stereospecific nonclassical *C*-glycosylation is both timely and significant, addressing a notable gap in the highly stereoselective synthesis of nonclassical *C*-glycosides and catalyzing broader biological research on these compounds as potential sugar-based drugs. Therefore, the delineated strategy not only provides an attractive tool for the exclusive control of nonclassical anomeric configuration to access medicinally relevant nonclassical *C*-glycosides but also advances the development of glycosyl cross-coupling (GCC) of anomeric nucleophiles.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/prechem.4c00042.

Detailed experimental procedures, copies of NMR spectra for all new compounds (PDF)

X-ray crystallographic data for **25i** (CIF)

Accession Codes

CCDC 2292697 (**25i**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 441223 336033.

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Notes

The authors declare the following competing financial interest(s): F. Zhu and G. Cheng are inventors on a Chinese

patent application (Application No. CN 202311347581.1). The other authors declare no competing interests.

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