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General Access to C-Glycosides via Redox-Neutral Radical Cross-Coupling of Glycohydrazides

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Abstract

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Abstract: Carbohydrates are among the most abundant and structurally diverse biomolecules in nature, playing central roles in energy storage, molecular recognition, and cell signaling. Within this domain, C-glycosides, in which the oxygen atom of the glycosidic bond in O-glycosides is replaced by carbon, have emerged as valuable motifs in medicinal chemistry due to their resistance to enzymatic hydrolysis. Of particular importance are C-aryl glycosides, exemplified by the SGLT2 inhibitors dapagliflozin, canagliflozin, and empagliflozin, which are frontline therapies for type 2 diabetes. However, scalable syntheses of C-aryl glycosides have traditionally relied on protected sugar derivatives, lengthy sequences, or conventional cross-couplings that often suffer from poor selectivity, limited scope, and extensive protecting-group manipulation. Herein, we report a practical approach to C-aryl glycosides using glycosyl sulfonyl hydrazides as redox-neutral radical precursors for cross-coupling. Prepared directly from unprotected native sugars, these reagents generate glycosyl radicals under mild conditions and enable efficient access to diverse C-aryl glycosides, including all approved SGLT2 inhibitors, natural products such as salmochelins and neopetrosins, and medicinally relevant probes. Beyond anomeric

functionalization, this platform enables C–C bond formation at multiple positions on carbohydrate scaffolds and supports stereoretentive radical coupling that can override inherent stereochemical biases, expanding practical access to carbohydrate-derived therapeutics and chemical tools.

Main text

Carbohydrates are ubiquitous in biology, where they mediate processes ranging from energy storage to molecular recognition and cell signalling[1, 2]. Among carbohydrate-based motifs, C-glycosides, where the anomeric oxygen of an O-glycoside is replaced by carbon, have attracted sustained interest due to enhanced resistance to hydrolytic and enzymatic degradation[3, 4]. This feature has made them particularly important pharmacophores, most notably in sodium-glucose cotransporter 2 (SGLT2) inhibitors such as dapagliflozin (**1**), canagliflozin (**2**)**,** and empagliflozin (**3**), which are widely used for the treatment of type 2 diabetes (Figure 1A)[4, 5]. Five medicines of this type are currently FDA-approved, with combined annual sales exceeding $20 billion. Their clinical success illustrates how a robust $C(sp^3)$–$C(sp^2)$ linkage can translate into favorable metabolic stability and durable biological activity, underscoring the need for efficient and scalable synthetic strategies to access diverse C-aryl glycoside architectures.

Historically, the synthesis of C-aryl glycosides (**7**) has relied on methods wherein a glycosyl electrophile or nucleophile equivalent is utilized (**9**)[6]. For example, Friedel-Crafts-type glycosylations with electron-rich arenes or nucleophilic additions of organometallic aryl reagents (e.g., aryl lithium or Grignard species) to glycosyl electrophiles. Whereas these approaches have enabled the construction of key C-glycosidic bonds, they are often plagued by significant limitations including extensive protecting group manipulations, poor stereoselectivity at the anomeric center, limited substrate scope, and multi-step preparations of activated donors from native sugars. For instance, the general synthesis of **7** relies on polar bond disconnections through a multistep sequence with only one strategic C–C bond forming step[7-9].

Recent advances since 2007 in the arena of conventional cross-coupling, including Pd- and Ni-catalyzed glycosyl cross-couplings[6, 8-12], have addressed some of these issues but still frequently demand protected sugars, specialized catalysts, or organotin intermediates, hindering late-stage diversification and large-scale synthesis (Figure 1B). In contrast, radical cross-coupling (RCC) can, in principle, offer a more direct and chemoselective approach to such targets via a glycosyl radical (**8**). Yet, practical implementation remains limited, as the preparation of these intermediates

typically still relies on lengthy sequences involving protecting-group manipulations, particularly in the cases of **12**–**16**[13-17]. Against this backdrop, glycosyl donor **17**, introduced by Koh, stands out for its direct preparation from an unprotected native sugar[18]. However, its synthetic utility has so far been confined to radical addition reactions (e.g. Giese addition), and the application into more versatile radical cross-coupling has yet to be realized[19].

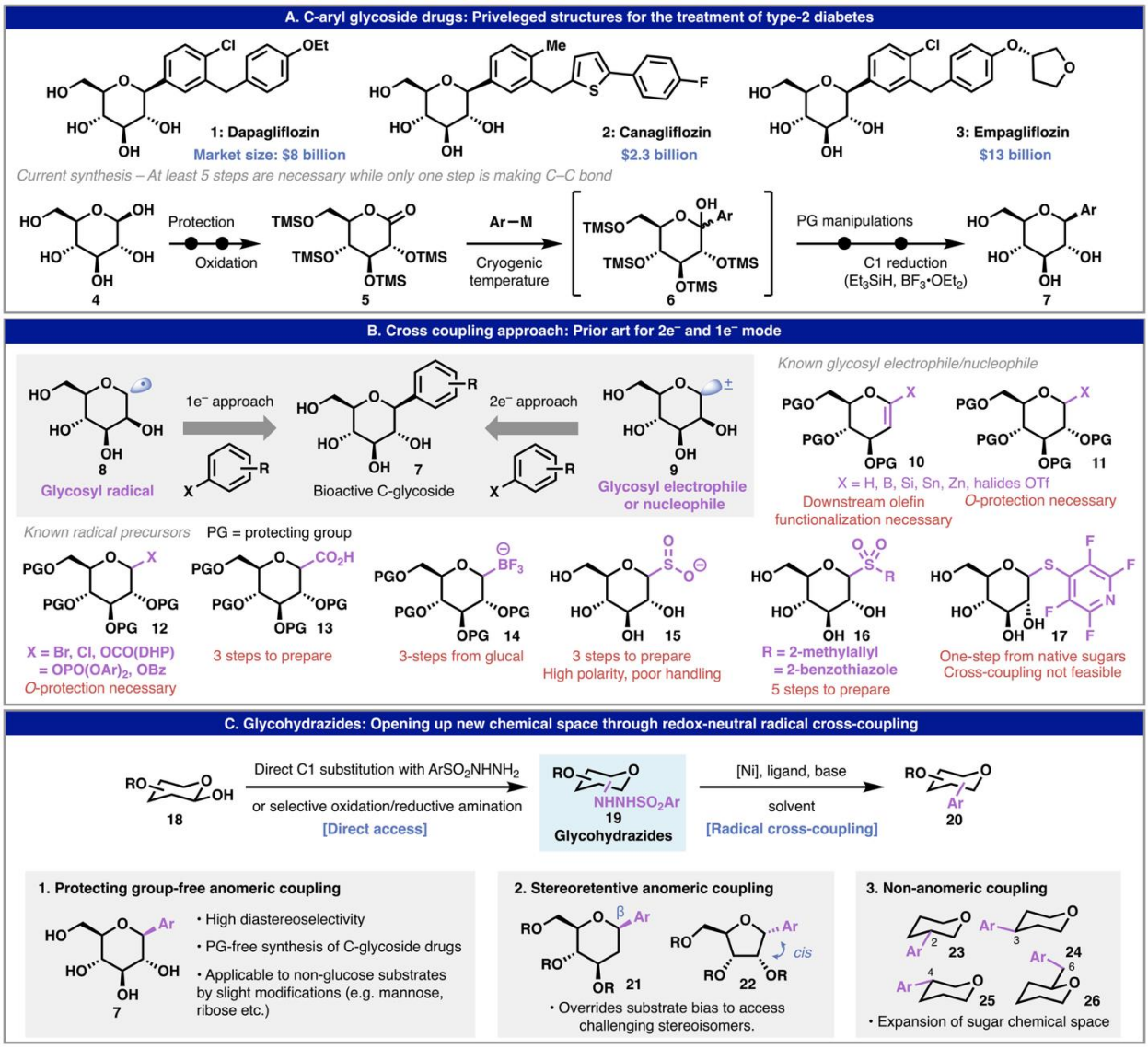

Figure 1. (a) C-aryl glycoside drugs: Privileged structures for the treatment of type 2 diabetes. (b) Cross-coupling approach: Prior art for 2e⁻ and 1e⁻ mode. (c) Glycohydrazides: Opening up new chemical space through redox-neutral radical cross-coupling.

In this work, a transformative approach to C-aryl glycoside synthesis is presented utilizing easily accessible glycosyl sulfonyl hydrazides as redox-neutral radical precursors for RCC (Figure 1C) [20-24]. Derived in a single step from unprotected native sugars without the need for protecting groups, stable, crystalline glycohydrazides (**19**) enable straightforward generation of glycosyl radicals under mild and scalable conditions, facilitating couplings with a variety of aryl partners. This methodology not only streamlines access to bioactive molecules, including all currently approved SGLT2 inhibitor C-aryl glycosides (**7**), but also unlocks new possibilities for radical-mediated sugar modifications, including cross-couplings at non-anomeric sites (across positions C2–C6, **23-26**). Moreover, the unique reactivity of hydrazides can override inherent stereochemical biases that have represented unanswered challenges for radical-based cross-coupling (cf. **21** and **22**) by enabling a stereoretentive RCC approach[22, 24]. Collectively, glycohydrazides address longstanding challenges in efficiency, selectivity, and scalability in C-glycoside synthesis and provide a practical platform for the rapid exploration of carbohydrate-derived therapeutics, natural products, and chemical probes.

The development of suitable conditions for RCC-arylation of unprotected glycohydrazides required extensive optimization, the highlights of which are graphically summarized in Figure 2A (for a more complete summary, see SI). Glucosyl hydrazides such as **27** can be easily prepared on a decagram scale by simply stirring a 1:1 mixture of sugar (glucose **4** in the case of **27**) and sulfonylhydrazine in AcOH followed by simple crystallization[25]. Screening commenced with glucose-derived hydrazide **27** and aryl iodide **28** using the previously reported conditions[20] for redox-neutral RCC with the identity of the sulfonylhydrazide, solvent, base, temperature, and ligand being systematically evaluated. Sulfonylhydrazides are uniquely tunable radical precursors; the electronic nature of the sulfonyl group can dictate the rate of radical formation to reach an optimal level of kinetic matching in the coupling process[23]. Glycohydrazide **27**, when subjected to standard conditions at 70 °C, provided only trace quantities of product with a slight increase in temperature (100 °C) leading to 12% yield of coupled product **1** as a 1:1 mixture of diastereoisomers. Although the use of more electron-deficient hydrazides such as **29**, **30**, and **31** led to a modest increase in yield at 70 °C, glycohydrazide **27** was chosen for further optimization owing to its lower cost, easy accessibility, and suitability for large-scale synthesis of gliflozin-based medicines. Next, a solvent screen was performed (0.1 M), resulting in a higher yield using DMSO (27% yield) but unfortunately still as a 1:1 mixture of isomers. The most striking

breakthrough came from an exploration of base. A variety of organic and inorganic bases were evaluated, differing in basicity, leading to an increase in yield (up to 45% with K_2CO_3) but still with a 1:1 mixture of diastereomers. Surprisingly, tetramethylguanidine (TMG) was singularly successful in boosting both the yield (81%) and selectivity (β:α = 11:1) as well as reducing the temperature to 70 °C. Although this outcome is difficult to rationalize given the lack of a clear correlation between base strength and either yield or diastereomeric ratio (dr) (see SI for exhaustive listing of bases screened), we speculate that hydrogen bonding between TMG and the glucose hydroxyl groups may be important, as β-selectivity drops substantially with the corresponding Bn-protected glucose substrate (44%, β:α = 3.6:1). Consistent with this observation, the Niu group also observed high β-selectivity in RCCs with unprotected glucose in the presence of TMG, whereas the corresponding protected substrate showed much lower β-selectivity[15]. Finally, a number of ligands (**L1**-**L5**) were screened to see if that parameter could be simplified as **L6** (dNH_2bpy) is more expensive. **L1** was chosen considering the balance of yield (88%) and dr (β:α > 19:1) observed, but other inexpensive ligands such as bpy (**L3**) or dtbbpy (**L4**) can also be employed. Ultimately, a simple protocol using these conditions was developed that involves mixing all reaction components and heating to 70 °C for 1 h followed by a standard aqueous workup.

As depicted in Figure 1B, glycohydrazide-based RCC could be employed to access nearly all currently known FDA-approved gliflozin-based medicines (**1**, **2**, **3**, **33**, **34**) as well as several analogs that are currently in clinical trials (**35**, **36**, **37**). In addition, the known ketone-containing intermediate **38**[26] was prepared, which previously necessitated protecting groups due to the harsh conditions of Grignard addition. Accessing these structures via the less expensive aryl bromide was also possible (**32**, **33**, **34**, **35**, **36**, **37**) using **L6**. Remarkably, di- and trisaccharide aryl-linked structures such as **39**, **40**, **41**, and **42** could also be accessed directly from inexpensive lactose, cellobiose, maltose, and maltotriose, respectively.

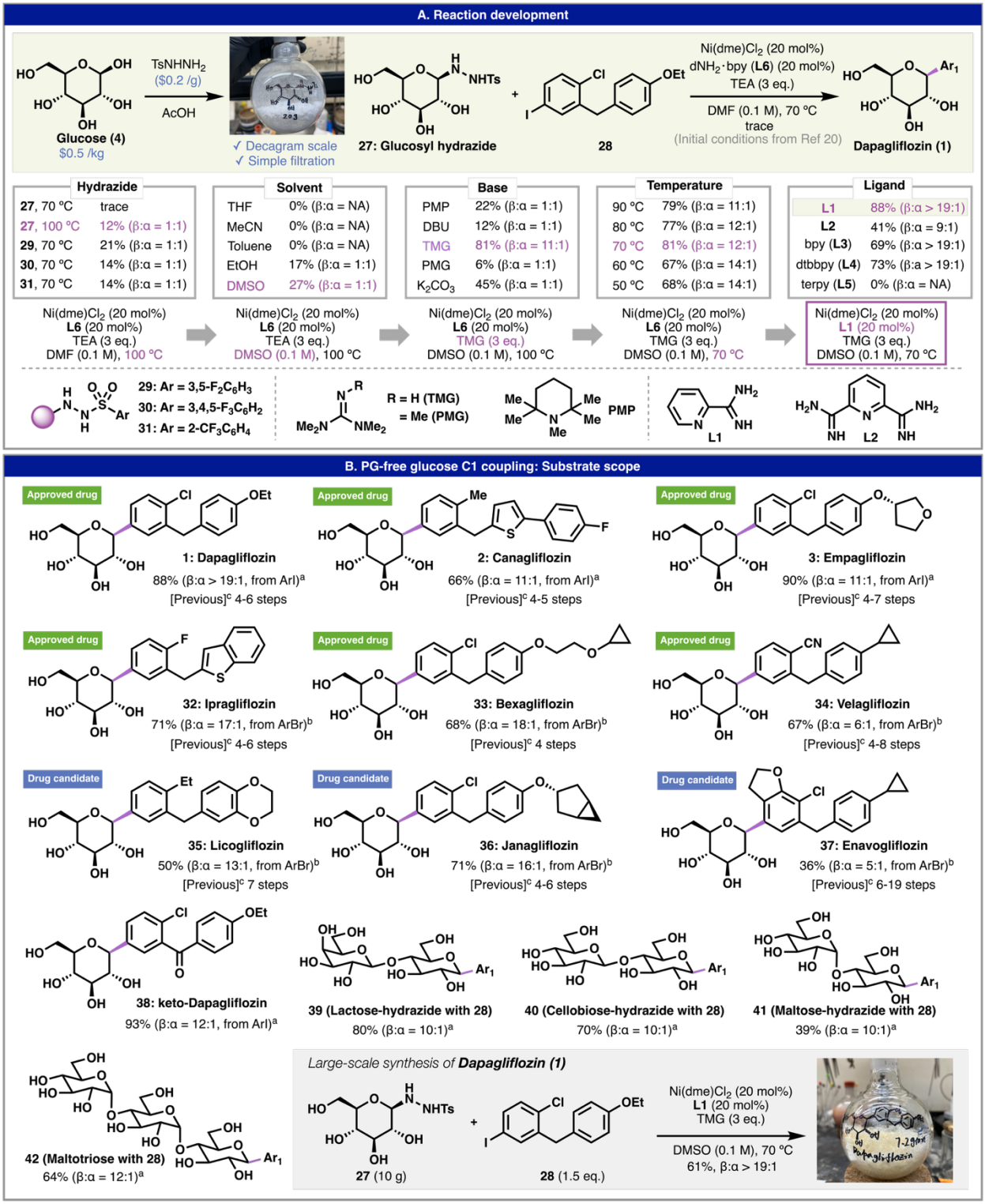

Figure 2. (a) Reaction development. (b) Protecting group (PG)-free glucose C1 coupling: Substrate scope. [a]Reaction Condition A: 20 mol% $NiCl_2$·DME, 20 mol% **L1**, 3.0 equiv. TMG, 0.1 M DMSO, 70 °C. [b]Reaction

Condition B: 20 mol% $NiCl_2$·DME, 20 mol% **L6**, 3.0 equiv. TMG, 0.1 M DMSO, 70 °C. [c]Step counts were calculated from the sugar source rather than from the coupling partner.

Importantly, the general procedure could be applied to a decagram-scale synthesis of **1**. For this scale-up, glycohydrazide **27** was prepared directly from commercially available dextrose powder (purchased at Walmart for $5/pound) by treatment with $TsNHNH_2$ in 70% household vinegar and stirring for 6 h, followed by simple ether precipitation to afford the crystalline intermediate. The key cross-coupling took place smoothly to provide **1** in 61% isolated yield with high dr (β:α > 19:1) after extraction and chromatography. On larger scales, the product should be easily purified through direct recrystallization without the need for column chromatography[27].

The strategic application of redox-neutral glycohydrazide-based radical cross-coupling to a variety of natural products and medicinally relevant structures beyond gliflozins was next explored, as documented in Figure 3. Salmochelin-SX (**44**), a C-aryl glycosidic natural product in the salmochelin family known as siderophores excreted by *Salmonella enterica* and uropathogenic *Escherichia coli* strains under low-iron stress, [28] was previously procured through a nine-step polar approach relying on conventional cross-coupling, pyrophoric reagents, and protecting group interchanges[11]. In contrast, a 4-step approach commencing with crystalline glycohydrazide **27** led to **44** after coupling with aryl iodide **43** followed by a sequence of hydrolysis, amidation, and debenzylation. The critical radical cross-coupling took place in 61% isolated yield, favoring the desired diastereomer (β:α > 10:1). Beyond glucose-derived hydrazide **27**, mannose-derived hydrazide **46** likewise enabled efficient access to C-glycosides. Notably, neopetrosin C (**48**), a rare indole C-glycoside alkaloid whose congeners have been reported to exhibit moderate hepatoprotective activity[29], was prepared directly from **46** in a single step in 52% isolated yield with α:β > 19:1. In this case, the desired cross-coupling product was obtained under modified conditions using a more electron-deficient sulfonyl group (Ar = 2-$CF_3C_6H_4$) and Et_3N (TEA) in place of the more strongly basic TMG. The pronounced α-selectivity likely reflects a matched scenario in which both steric and anomeric effects converge to favor formation of the α-anomer, consistent with prior studies of radical cross-coupling in related systems[15, 30]. Radical cross-coupling has been applied to this natural product but it requires the use of expensive peracetyl mannosyl bromide **50** (1g/$218 commercial compound that needs to be stabilized by 2% $CaCO_3$) via photoinduced electron transfer involving numerous additives and expensive iridium

photocatalysts[31]. A polar-bond-based disconnection strategy utilizing a Larock coupling of alkynyl glycoside **51** traversing through 10 steps is also known[32]. Similarly, the naturally occurring tryptophan-mannose conjugate **53** can be procured from **46** and **52** in 56% isolated yield as a single diastereomer (α-anomer) after alkaline hydrolysis of the Trp-containing TFA motif. Conventional polar strategies required over 20 steps[33] and redox-reliant radical cross-coupling could achieve the same transformation, albeit requiring a cocktail of additives and an expensive Ir-catalyst[34]. Finally, the ribose-derived IMPDH inhibitor **59** could be accessed concisely from ribohydrazide **57** and *m*-iodobenzamide **58** as a single diastereomer (β-anomer) in 43% isolated yield, representing a substantial simplification relative to the previous five-step route involving extensive protecting-group manipulations[35].

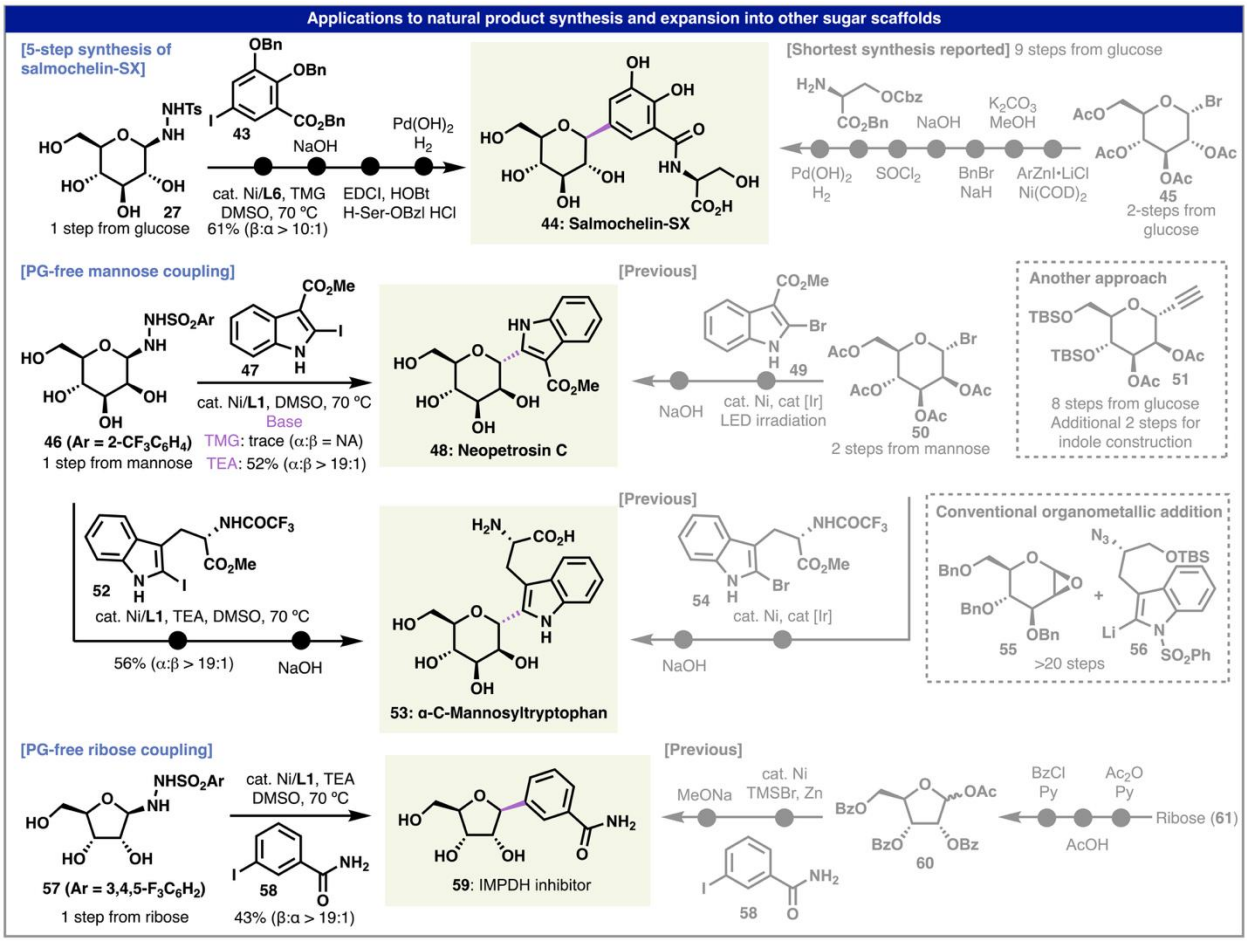

Figure 3. Applications to natural product synthesis and expansion into sugar scaffolds.

Up to this stage, stereochemical control in our redox-neutral platform arises exclusively from *post-radical* control, wherein product configuration is set during bond formation through the interplay of substrate stereoelectronic bias and catalyst steric effects. To our knowledge, all previously reported RCC approaches (Giese[18, 36], Minisci[19], and analogous innate radical additions are not included as they are not considered cross-coupling, which involves catalytic organometallic intermediates) to C-glycosides operate by this same principle[15]. Although high selectivity, and in some cases stereodivergence, can be achieved, these outcomes are typically confined to particular substrates rather than representing a general solution. This limitation is evident across carbohydrate scaffolds: whereas glucose-derived systems have furnished numerous stereoselective examples by leveraging either steric effects (favoring β-anomer[16, 17, 34, 37]) or the anomeric effect (favoring α-anomer[13, 30, 38-43]), several other scaffold classes still lack any stereoselective RCC manifold (Figure 4, grey highlights). Collectively, these observations underscore the inherent substrate dependence of *post-radical* stereocontrol and the need for a more general, programmable approach.

Departing from this paradigm, programmable *pre-radical* stereocontrol was envisioned building on the recent discovery of stereoretentive radical cross-coupling (Figure 4)[22]. For these studies, Bn-protected sugars were utilized to simplify the preparation and purification of either anomeric series (α or β). The divergent preparation of either the β– or α–glycohydrazides could be accomplished commencing with **62** using either a Mitsunobu reaction or through Yu-glycosylation[44] with benzaldehyde *p*-toluenesulfonylhydrazone **63**, respectively. With configurationally enriched anomers in hand, stereoretentive RCC was investigated using a variety of ligands, bases, and solvents (see SI for a more complete listing). In line with previous reports on substrate controlled RCC of protected glucose derivatives, the result is a near 1:1 mixture of products (entry 1) in 32% yield (Figure 2). Reducing the strength of the base to TEA improved the yield albeit with a poor stereoselectivity (entry 2). After an extensive ligand screen (entries 3-8) and in accordance with results from our studies of stereoretentive RCC arylation[22], electron-deficient bipyridine ligand **L12** enabled product formation in good yield (68%) with synthetically useful levels of stereocontrol (1:5) favoring the β-product. Turning attention to α-**64**, the same set of conditions could be applied to deliver 70% of adduct **66** in a 3:1 ratio favoring the α-product, unequivocally demonstrating that the stereochemistry was retained through the process.

Unsurprisingly, the use of **L1** (non-stereoretentive ligand) delivered a 1:1 mixture of isomers once again, highlighting the critical importance of the ligand.

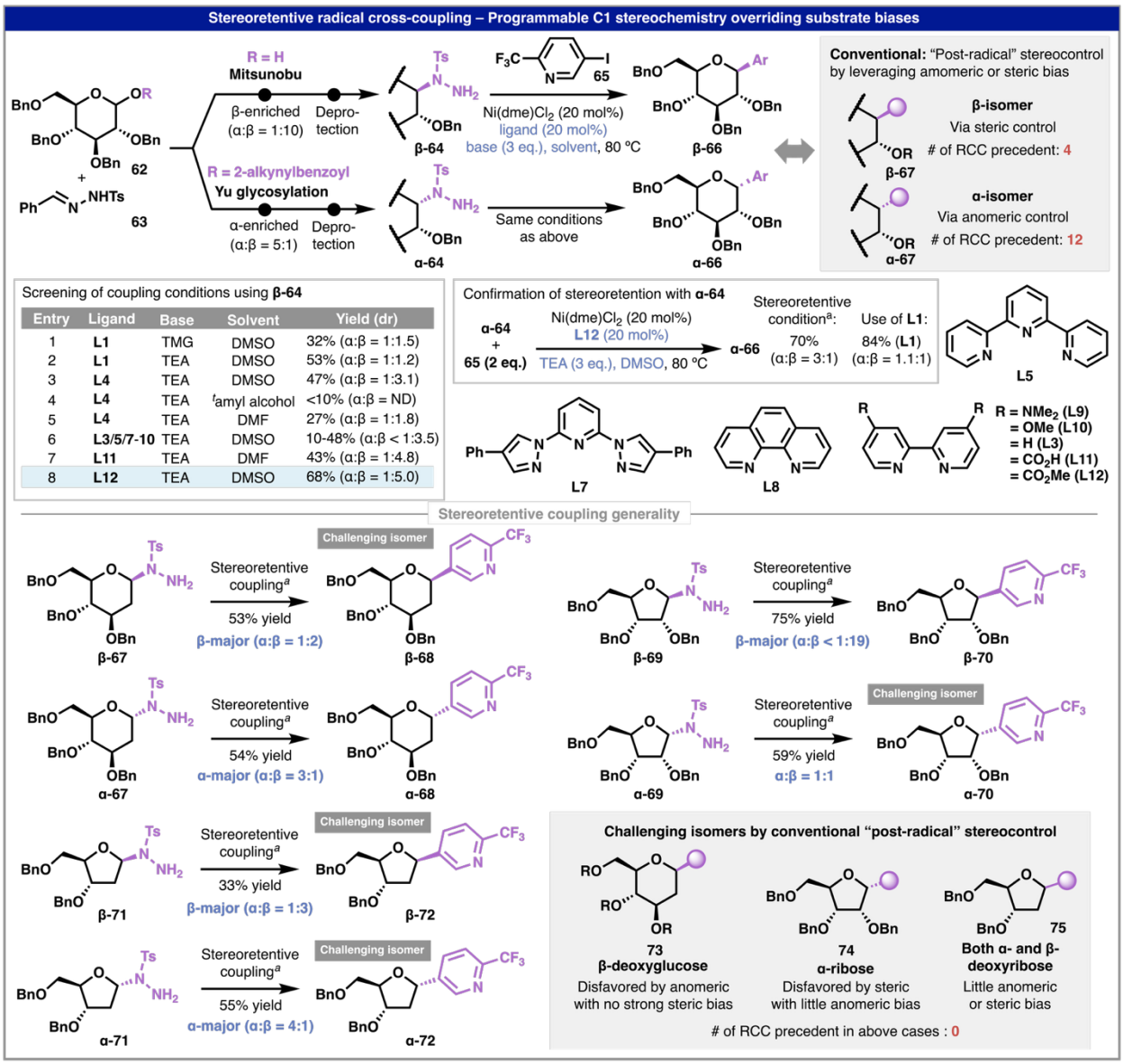

Figure 4. Stereoretentive radical cross-coupling: Programmable C1 stereochemistry overriding substrate biases. [a]Stereoretentive Condition: 20 mol% $Ni(dme)Cl_2$, 20 mol% **L12**, 3.0 equiv. TEA, 0.1 M DMSO, 80 °C.

Stereoretentive couplings of this type were explored on three additional substrates, such as 2-deoxyglycohydrazides β-**67** and α-**67**, ribohydrazides β-**69** and α-**69**, and 2-deoxyribohydrazides β-**71** and α-**71**. In most cases, a modest to good level of stereoretention could be observed, thereby

enabling the practitioner to enrich diastereochemical outcomes independent from inherent substrate biases. The results presented herein represent a significant advance in stereoretentive radical C-glycosylation given past precedent. For instance, ribose systems favor β-products exclusively due to steric considerations; in 2-deoxyglucose and 2-deoxyribose, the stereoelectronic effect dominates to give the α-product[40]. Notably, several anomeric configurations including β-2-deoxyglucose (**73**), α-ribose (**74**), β-2-deoxyribose (**75**) have not previously been accessed through RCC.

At this juncture the scope of glycohydrazide-based RCC was explored to enable peripheral C–C bond formation at positions beyond the anomeric center. To date, a systematic exploration of RCC across all alcohol-containing positions of riboses and glucoses has not been reported. Accessing such chemical space could potentially open many new opportunities for diversification of carbohydrate scaffolds. The results of these investigations are depicted in Figure 5A and commence with the preparation of 2, 3, 4, and 6-substituted glucohydrazides **79**, **85**, **91**, and **97** via reductive amination from the corresponding carbonyl compounds. For these studies, additional optimization was conducted leading to the use of difluorophenyl sulfonyl hydrazide, 1,10-phenanthroline as ligand, and TEA as base (see SI for summary). Using these conditions, a library of 20 RCC products (16 of which are depicted herein, see SI for full listing) was obtained in synthetically useful yields with *post-radical* stereocontrol (stereoretentive RCC was not attempted, nor was optimization of any individual reaction). Notably, the first examples of RCC-based sugar olefinations were also achieved in synthetically useful yields, providing adducts **90**, **96**, **102**. Similarly, ribose and deoxy-ribose derived hydrazides **103**, **105**, **107**, **109**, and **111** were prepared and subjected to RCC to produce a library of 19 RCC-derived adducts, five of which are depicted in Figure 5A.

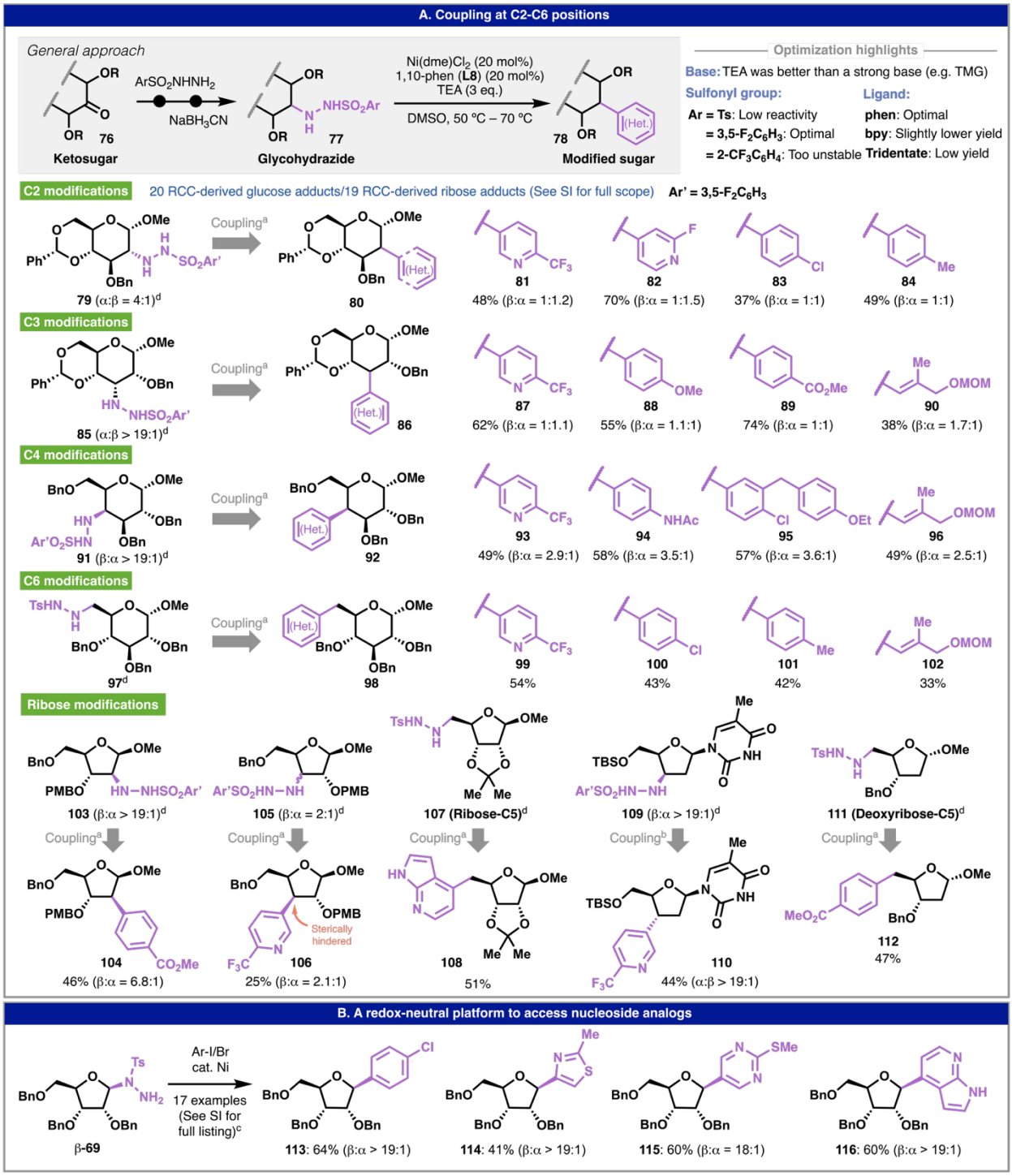

Figure 5. Coupling at C2-C6 positions. [a]Condition: 20 mol% $Ni(dme)Cl_2$, 20 mol% **L8**, 3.0 equiv. TEA, 0.1 M DMSO, 50 – 70 °C. [b]Condition: 20 mol% $Ni(dme)Cl_2$, 20 mol% **L6**, 3.0 equiv. PMP, 0.1 M DMF, 75 °C. [c]Condition: 20 mol% $Ni(dme)Cl_2$, 20 mol% **L4**, 3.0 equiv. TEA, 0.1 M DMF, 100 °C. [d]Step counts for synthesizing the hydrazides: glucose C2 hydrazide **79** (3 steps from commercially available **SF5**); glucose C3 hydrazide **85** (3 steps from **SF5**); glucose C4 hydrazide **91** (4 steps from **SF5**); glucose C6 hydrazide **97** (4 steps

from commercially available **SF9**); ribose C2 hydrazide **103** (5 steps from commercially available **SF12**); ribose C3 hydrazide **105** (5 steps from **SF12**); ribose C5 hydrazide **107** (2 steps from commercially available **SF15**); 2-deoxyribose C3 hydrazide **109** (5 steps from commercially available **SF16**); 2-deoxyribose C5 hydrazide **111** (6 steps from **SF16**). (See SI for detailed procedures)

Finally, given the broad importance of unnatural nucleosides across biology and medicine, we sought to demonstrate concise entry into this chemical space (Figure 5B). Using conditions closely related to those developed for the non-anomeric couplings in Figure 5A, C1-arylated ribose derivatives **113**–**116** were obtained in synthetically useful yields, with 13 additional examples provided in the Supporting Information. The efficiency of this transformation is comparable to that of the recent photochemical approach reported by Britton and co-workers[45], yet the ribohydrazide platform offers a practical advantage by avoiding the engineering constraints associated with photochemical reaction setups. Notably, high β-selectivity is achieved without invoking a stereoretentive manifold, as the intrinsic steric bias of the ribose scaffold is sufficient to enforce conventional *post-radical* stereocontrol.

Conclusion

This work represents another step[15, 18, 46, 47] in dismantling the long-held belief that meaningful synthetic elaboration of carbohydrates demands extensive protecting groups and redox manipulations. By converting unprotected sugars in a single step into stable sulfonyl hydrazides that serve as versatile radical donors, a direct, efficient, highly chemoselective, and scalable route to C1-glycosides has been unlocked. This chemistry provides rapid access to all current FDA-approved SGLT2 inhibitors, challenging natural products, and a host of new glyco-architectures—including modifications at non-anomeric positions and stereoisomers previously considered out of reach. In doing so, it shifts carbohydrates from being among the most cumbersome classes of molecules to synthesize into versatile and readily diversifiable building blocks. We anticipate that this platform, amenable to derivatization of other sites on sugars and to stereoretentive coupling, will catalyze a significant expansion in the exploration of carbohydrate chemical space and help unleash the full therapeutic potential of glycomimetics in the coming years.

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Competing interests

The authors declare no competing financial interest.

Data Availability. The data that support the findings in this work are available within the paper and Supporting Information.

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