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Pd-catalyzed stereoselective synthesis of chromone *C*-glycosides†

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Herein, we present an efficient Pd-catalysed method for stereoselective synthesis of chromone *C*-glycosides from various glycals. We successfully applied this method to various glycals with different protecting groups, yielding the corresponding glycosides in 41–78% yields. Additionally, we investigated the potential of this approach for the late-stage modification of natural products and pharmaceutical compounds linked to glycals, leading to the synthesis of their respective glycosides. Furthermore, we extended our research to gram-scale synthesis and demonstrated its applicability in producing various valuable products, including 2-deoxy-chromone *C*-glycosides. In summary, our work introduces a novel library of chromone glycosides, which holds promise for advancing drug discovery efforts.

C-Glycosides constitute an important class of organic compounds having a direct C–C linkage between glycan and aglycon moieties.[1,2] Recently, there has been significant attention directed toward developing novel techniques for synthesizing *C*-glycosides.[3] This heightened interest is primarily driven by the widespread occurrence of these glycosides in various natural products and pharmaceuticals.[4] The enhanced chemical and enzymatic stability exhibited by *C*-glycosides in comparison to *O*-glycosides has captured the interest of synthetic organic chemists, leading to the discovery of numerous synthetic *C*-glycosides in recent years. In light of the diverse biological applications of *C*-glycosides, multiple synthetic strategies have been devised for various types of *C*-glycosides, including *C*-aryl,[5] alkyl,[6] acyl,[7] alkenyl,[8] alkynyl,[9] and more. These glycosides have been successfully synthesized with the assistance of various transition metals and photo-redox catalysis (Fig. 1B).[10] Of particular focus and exploration within the realm of *C*-glycosides are *C*-aryl glycosides. This emphasis arises from their presence in numerous natural products and synthetic drugs. Notably, the recent success story in drug discovery revolves around a series of *C*-aryl glycoside analogues, exemplified by dapagliflozin, canagliflozin, and empagliflozin (Fig. 1A).[11] These compounds function as SGLT-2 inhibitors and are employed in the treatment of type-2 diabetes, underscoring the significant strides made in harnessing *C*-aryl glycosides for pharmaceutical purposes.[12]

C-Glycosides derived from polyphenols predominantly consist of flavonoid glycosides, including well-known compounds like vitexin, isovitexin, orientin, and isoorientin (Fig. 1A).[13] These flavonoid glycosides exhibit a wide array of biological activities. The chromone structure is the core backbone of flavonoids and is also a common structure in many naturally occurring *C*-glycosides.[14] Chromone *C*-glycosides, belonging to the class of secondary metabolites found in numerous plant species, have been extensively studied for their biological effects.[13e,15] The assessment of chromone *C*-glycosides has unveiled their involvement in various biological processes. For instance, aloesin and its analogues (Fig. 1A), isolated from aloe, are employed to regulate hyperpigmentation by inhibiting tyrosinase enzymes. Another example is macrolobin (Fig. 1A),[16] a natural compound derived from *Macrolobium latifolium*, which acts as an acetylcholinesterase inhibitor. Similarly, two natural products, uncinosides A and B, sourced from the Chinese herbal medicine *Selaginella uncinate*, have demonstrated potent activity against respiratory syncytial virus, with IC_{50} values of 6.9 and 1.3 μg mL^{-1}, respectively.[17] Due to the natural occurrence of these glycosides and promising biological activities, there is a keen interest in developing new synthetic pathways for *C*-chromone glycosides. The method for synthesizing chromone *C*-glycosides remains elusive, although a successful synthesis of *C*-glycosides of chromanones has been achieved. This synthesis involves utilizing glycals with 4-chromanone through a one-pot Mukaiyama-type reaction, facilitating the formation of *C*-glycosides.[18] These synthetic targets could be valuable for conducting various biological evaluations. In our ongoing efforts[19] to explore glycals as a platform for synthesizing biologically important compounds, we hypothesize that combining glycals with readily available or easily synthesized 3-halo chromone derivatives could serve as potential substrates for the synthesis of

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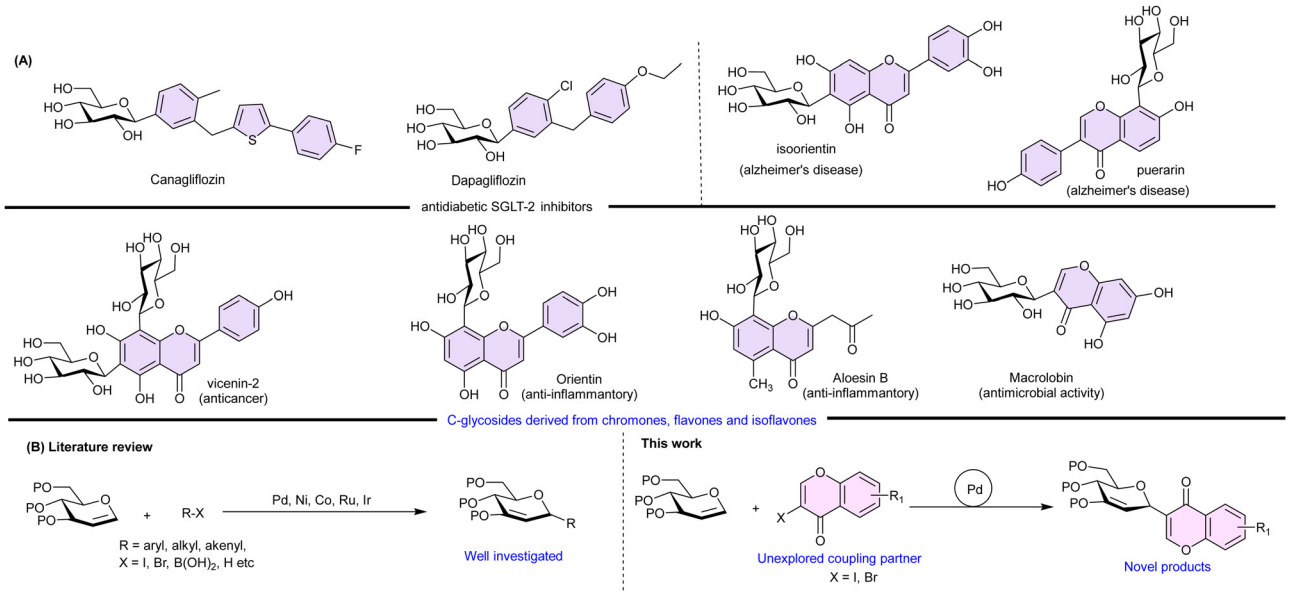
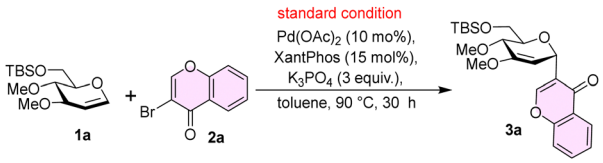


Fig. 1 (A) Biologically active *C*-aryl and polyphenolic *C*-glycosides. (B) Literature review and our work.

C-glycosides of chromones. This approach holds promise for advancing our understanding of these compounds and their potential applications in diverse biological contexts. The optimization study commenced with the reaction between di-*O*-methyl-*tert*-butyldimethyl silyl-D-glucal **1a** and 3-bromo chromone **2a**. The optimal reaction conditions were determined after extensive experimentation involving the screening of various reaction parameters, catalysts, and ligands (please refer to the ESI† for detailed information). When the standard substrates were combined with $Pd(OAc)_2$ (10 mol%), xantphos (15 mol%), and K_3PO_4 (3 equiv.) as the base in toluene (0.1 M) at 90 °C for 30 hours, the desired product **3a** was obtained with a yield of 78% (Table 1, entry 1). Substituting $Pd(OAc)_2$ with $Pd(dba)_2$ and $Pd(dba)_3$ resulted in a lower yield, and $Pd(CH_3CN)_2Cl_2$ was found to be largely inactive in this cross-coupling process, yielding only 20% of the desired product (Table 1, entries 2–4). Further investigation into ligand screening, including XPhos, 1,10-phenanthroline, and R/S BINAP, revealed that xantphos is the most effective choice of ligand for yielding the desired product. In terms of solvent optimization (please refer to the ESI† for details), it was observed that the reaction proceeded only in non-polar or slightly polar solvents such as toluene, DCE (1,2-dichloroethane), and xylene. Among these solvents, toluene and DCE proved to be the most suitable, providing final product yields of 73–78%. The screening of different bases reveals that both K_2CO_3 and K_3PO_4 are the most effective in comparison to others like Cs_2CO_3 and Na_2CO_3. Deviating from the reaction temperature of 90 °C, either higher or lower, resulted in reduced yields. It is noteworthy that the reaction required a 0.1 M concentration of the solvent to give the optimal results. Sometimes, it did not show initiation until 12–20 hours had passed if the solvent was in excess quantity. For substrates **1a** and **2a**, the reaction yield was only 53% after 48 hours when the concentration of toluene was 0.05 M.

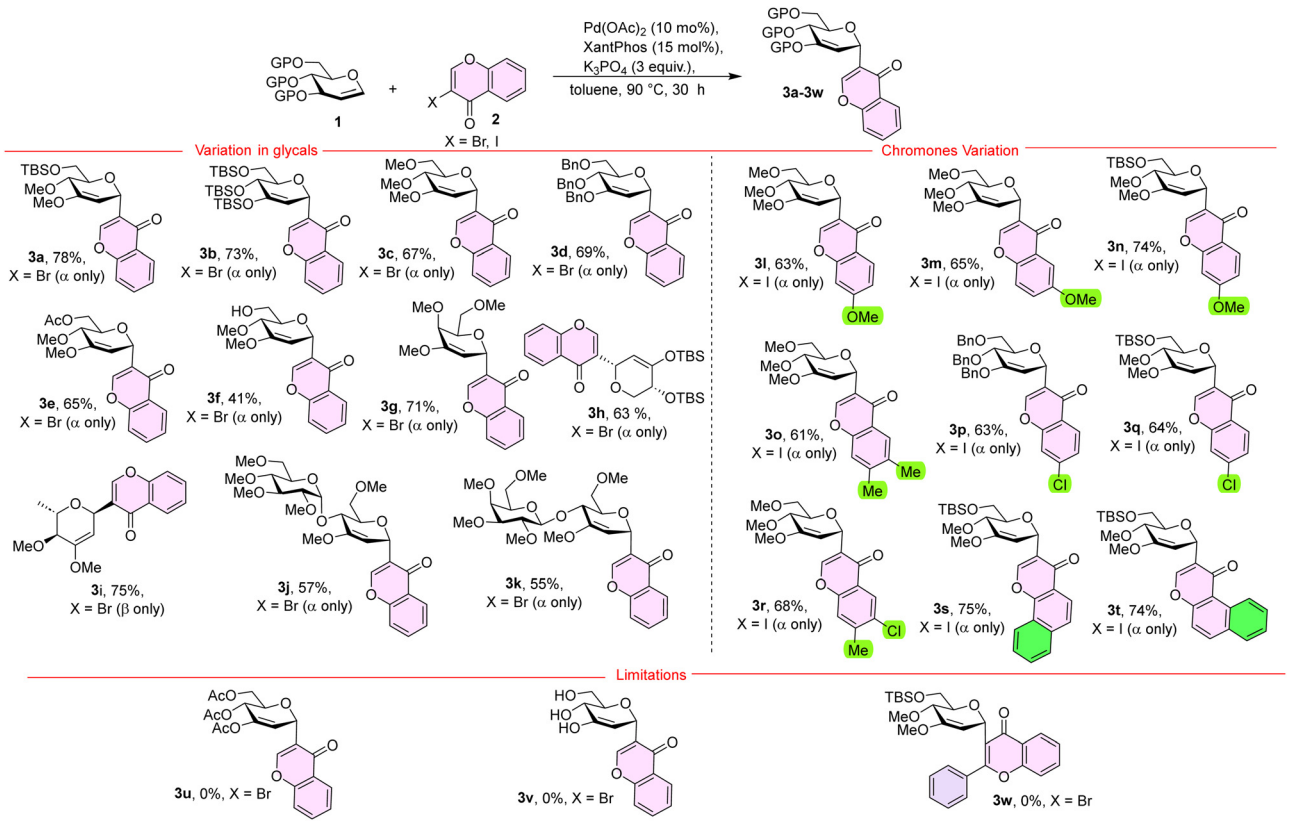
Following the optimized reaction conditions, we explored the substrate scope for chromone *C*-glycosides as shown in Scheme 1, encompassing compounds **3a–3w**. Initial investigations involved glycals with various protective groups, including ether, ester, and silyl groups. A 3,4-dimethylated glucal featuring a *tert*-butyl-silyl group at the primary hydroxyl group effectively underwent the reaction under standard conditions, yielding the desired product **3a** in a 78% yield. Similarly, tri-*O*-silyl-protected D-glucal smoothly coupled to provide the expected product **3b** in good yields. Subsequently, we examined ether-protected glycals such as benzylated and methylated glucals, successfully transforming them into the corresponding

Table 1 Optimization of reaction conditions[a]



Entry	Variation from standard reaction conditions	Yield[b] (%)
1	None	78
2	$Pd(dba)_2$ instead of $Pd(OAc)_2$	52
3	$Pd(dba)_3$ instead of $Pd(OAc)_2$	67
4	$Pd(CH_3CN)_2Cl_2$ instead of $Pd(OAc)_2$	20
5	XPhos instead of xantphos	15
6	1,10-Phenanthroline instead of xantphos	24
7	BINAP instead of xantphos	63
8	DCE instead of toluene	73
9	Xylene instead of toluene	47
10	Na_2CO_3 instead of K_3PO_4	67
11	K_2CO_3 instead of K_3PO_4	77
12	Cs_2CO_3 instead of K_3PO_4	43
13	110 °C instead of 90 °C	62
14	Toluene 0.05 M	53

[a] Reaction conditions, unless otherwise stated: **1a** (1 equiv.), **2a** (1.2 equiv.), Pd-source (10 mol%), ligand (15 mol%), base (3 equiv.), in solvent (0.1 M), for 30 h. [b] Yields are of the purified products after column chromatography.

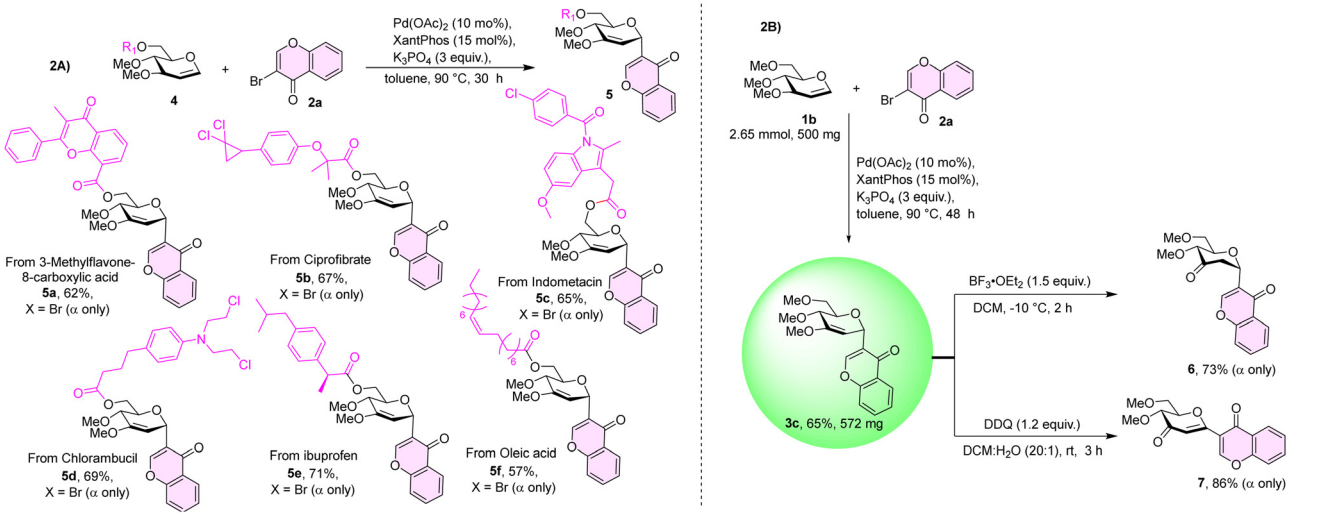


Scheme 1 Substrate scope: variation in glycals and chromones. [a] Reaction conditions: **1** (1 equiv.), **2** (1.2 equiv.), $Pd(OAc)_2$ (10 mol%), xantphos (15 mol%), K_3PO_4 (3 equiv.), in toluene 0.1 M for 30 h. [b] Yields are of the purified products after column chromatography.

chromone *C*-glycosides **3c and 3d** in 67% to 69% yields. A dimethylated glucal with ester protection at the primary hydroxyl group also yielded the respective product **3e** in a 65% yield. Our exploration extended to glycals other than glucals, including those derived from D-galactose, D-xylose, and L-rhamnose, which, under similar reaction conditions, produced glycosylated products with 71–75% yields (**3g–3i**). We broadened the substrate scope further by using disaccharide glycals like methylated D-maltal and D-lactal. When subjected to the standard conditions, these yielded chromone *C*-glycosides **3j and 3k** in 57–63% yields. We also tested a wide range of substituted 3-iodo-chromone derivatives with different substituents on the aromatic ring. 3-Iodo-chromones featuring electron-releasing groups such as methoxy and methyl at various positions on the aromatic ring proved to be effective substrates, yielding the desired *C*-glycosides in 63–61% yields under standard conditions (**3l–3o**). Similarly, some halo-substituted chromone derivatives, including 7-chloro and 6-chloro-7-methyl, were well-tolerated under the reaction conditions, resulting in 63 and 64% of the product (**3p–3r**) yields. To further showcase the versatility of the substrate scope, we utilized 3-iodo-benzochromone derivatives in the study, and, as expected, these yielded the respective products (**3s and 3t**) in yields ranging from 68% to 75%. It is worth noting that glycals with ester protections on all three hydroxyl groups, such as tri-*O*-acetyl-glycals, were not found to be compatible substrates, yielding only trace amounts of product **3u** on TLC. Similarly, unprotected glucal and flavones (**3v and 3w**) were also not found as ideal substrates under the optimized reaction conditions.

To further highlight the applicability of this protocol, we sought to prepare some complex natural products and pharmaceuticals linked with the glycals. Towards this direction, the derivatives of 3-methyl flavone-8-carboxylic acid, linked with glycals, were seamlessly incorporated with chromone, yielding its *C*-glycosides in 62% yield (**5a**; Scheme 2). Moreover, several pharmaceuticals, including modified derivatives of ciprofibrate, indomethacin, chlorambucil, and ibuprofen, linked with D-glucal, were successfully converted into the desired chromone *C*-glycosides (**5b–5e**). This demonstrates the tolerance for various functional groups, resulting in high yields of the target compounds. Lastly, we applied an oleic acid-protected glucal derivative, which provided the product **5f** with a yield of 64%. This showcases the adaptability of the methodology to more complex substrates, including fatty acid derivatives.

Finally, the gram-scale synthesis and synthetic utility were conducted as illustrated in Scheme 2B. Product **3c** was synthesized by utilizing 2.65 mmol of the starting material and the desired product **3c** was obtained with 65% yield. 2-Deoxy-*C*-glycosides represent an important class of compounds and are found in many natural products and bioactive molecules. To our surprise, when compound **3c** was treated with 1.5 equiv. $BF_3{\cdot}OEt_2$ in DCM at −10 °C, the 2-deoxy product **6** was formed



Scheme 2 (A) Substrate scope with biologically active molecules and (B) gram-scale synthesis and synthetic utility.

with concomitant keto–enol tautomerization and methyl group removal. Further, on reacting **3c** with DDQ (2,3-dichloro-5, 6-dicyano-1,4-benzoquinone), the enone **7** formation takes place with excellent yields *via* oxidative transposition of the double bond and elimination of the methyl group.

In conclusion, we have developed a Pd-catalysed synthetic strategy for chromone *C*-glycoside synthesis. To our knowledge, this is the first report on chromone *C*-glycoside synthesis. The reactions proceed under mild reaction conditions in which various protecting groups on carbohydrates survived and delivered the respective products. The scope and limitations of the methodology were well studied by employing different sugars and 3-halo chromone derivatives. The late-stage modifications of various pharmaceutical and natural products were also carried out to strengthen the applicability of this methodology further. Finally, the scale-up experiment and synthetic utility were shown for synthesizing valuable products such as 2-deoxy-chromone *C*-glycosides.

N. H. initially designed the project. M. K. S. and B. T. performed the experiments and characterized the compounds. Finally, N. H. M. K. S. wrote and edited the manuscript.

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Conflicts of interest

There are no conflicts to declare.

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