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Zweifel olefination for C-glycosylation

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C-glycosides are significant in medicinal chemistry due to their resistance to enzymatic hydrolysis, making them more stable and bioavailable compared to O-glycosides. Their unique structure also offers potential for developing drugs with improved therapeutic properties, particularly in treating diseases like diabetes and cancer. The main challenge in synthesizing C-glycosides lies in forming the carbon-carbon bond between the sugar and aglycone efficiently, while controlling the stereochemistry and minimizing side reactions. Starting from glycal derivatives, the Zweifel olefination presents an elegant opportunity to access C-glycosides in a selective manner. α -Lithiation of D-glucal, L-rhamnal, D-xylal and L-arabinal scaffolds was employed as a starting point in the synthesis of corresponding unsaturated aryl-, heteroaryl- and alkenyl-C-glycosides. This provides a straightforward strategy towards pharmacorelevant gliflozins and other unreported rhamnal- and xylal-analogs.

Carbohydrates play a pivotal role in drug discovery and in the pharmaceutical industry, being omnipresent in bioactive compounds and natural derivatives^{1–3}. They constitute the base of genetic material and are essential building blocks in epigenetic studies^{4–6}.

Naturally occurring C-glycosides include Vitexin⁷, an apigenin (flavone) derivative found in different flowers and leaves, Bergenin⁸, isolated from *Bergenia* flowering plants and α -C-Mannosyltryptophan⁹, a product of post-translational modification by C-mannosyltransferases (Fig. 1A). Among synthetic pharmaceuticals of interest, gliflozins – compounds that we later access through our method – are a class of SGLT2 inhibitors used in the treatment of type 2 diabetes, as they exert effects on the sodium glucose cotransporter¹⁰. These C-glycosides are based on the glucose scaffolds, arylated at position 2, and include Empagliflozin, Dapagliflozin and Canagliflozin. More importantly, the FDA has recently approved Empagliflozin in the treatment of cardiovascular dysfunctions and chronic kidney diseases¹¹.

When compared with O- and N-glycosylations, methods for C-glycosylation^{12–14} remain limited and mostly rely on either nucleophilic attack at the anomeric position or radical reactions¹⁵.

We envisioned that C-glycosides could easily be accessed from their parent unsaturated structures, strategically placing a double bond between C1 and C2. Such C=C bond can be regarded as polarized alkoxy-alkenes, prone to deprotonation at the α -position (C1) in the presence of appropriate bases, which provides a regioselective anchor for further functionalization. The carbohydrate integrity can then be restored through classical double bond manipulation such as the hydroboration/oxidation sequence (Fig. 1C)^{16,17}.

Among the various elegant methods available for double bond manipulation, Zweifel olefination is most appealing because of its high efficiency, good versatility and stereocontrol. Pioneered by Zweifel in 1967^{18,19}, it has received increasing attention over the last decade as an

indispensable tool in total synthesis, especially by the group of Aggarwal^{20–22}. In this reaction, a 1,2-metallate rearrangement is triggered upon addition of iodide onto a bis-organoborinate species **1** (Fig. 1B). The creation of an electrophilic site at the position α to the boron atoms via the intermediate iodonium species **2** promotes the key 1,2-rearrangement, transferring the organyl moiety in an intramolecular substitution reaction that leads to an α,β -iodoboronic ester intermediate **3**. An elimination then proceeds in the presence of a base, usually sodium methanolate, providing the formal coupling product between the organyl group and the former double bond.

Our recent interest on Zweifel olefination stems from the ability to perform C(sp²)-C(sp²) bond formation without the use of precious, often toxic transition metals. Aiming at improving its efficiency and applicability, we have established different methods that rely on the in situ formation of bisorganoborinate intermediates²³ or the use of organocerium species, generated through halogen-cerium exchange^{24,25}. Moreover, thorough investigations of reaction mechanism and de novo design of organoborate species led us to develop one-electron electro- and photocoupling processes based on an oxidative pseudo-1,2-metallate rearrangement^{26–30}.

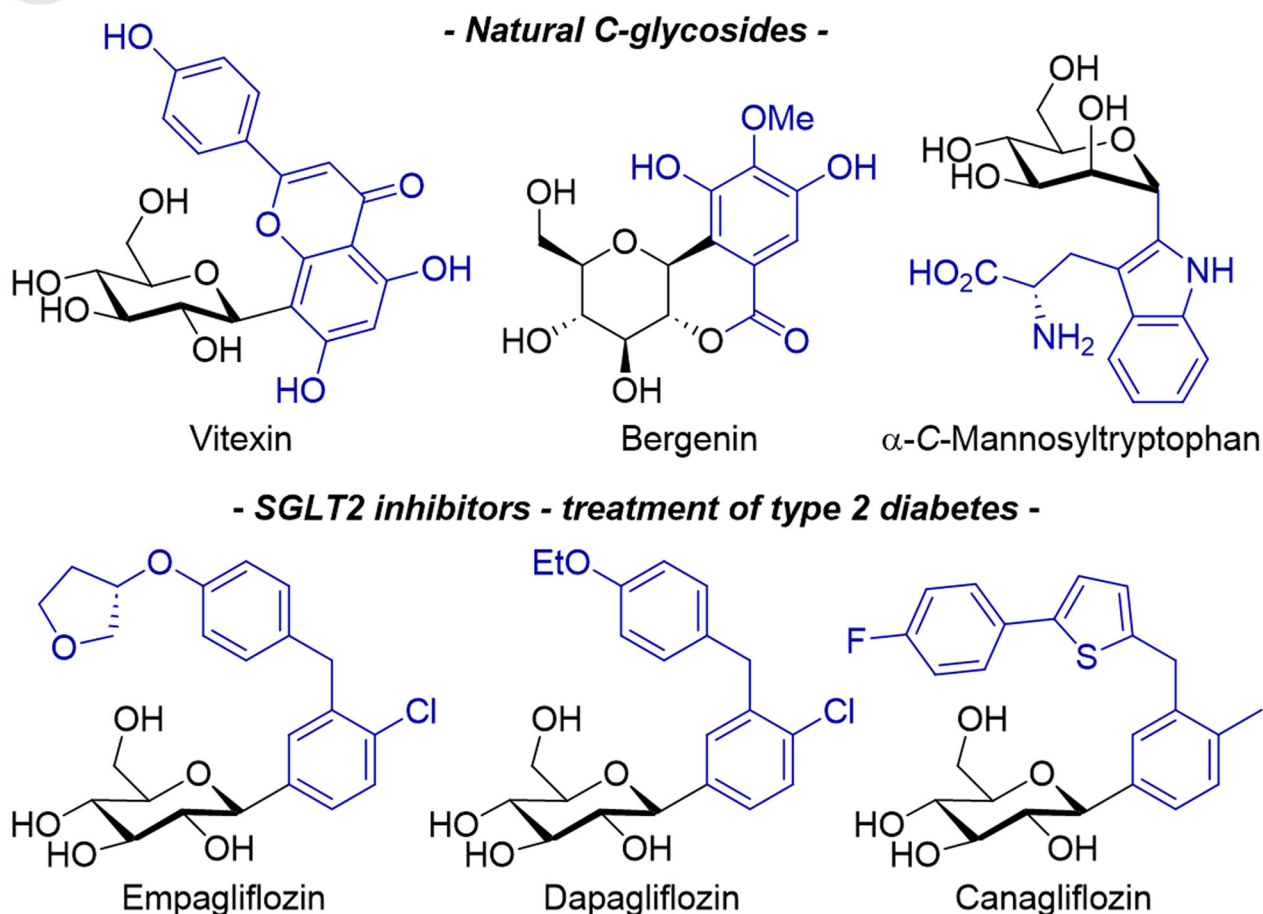
Results and discussion

Optimizations of reaction conditions

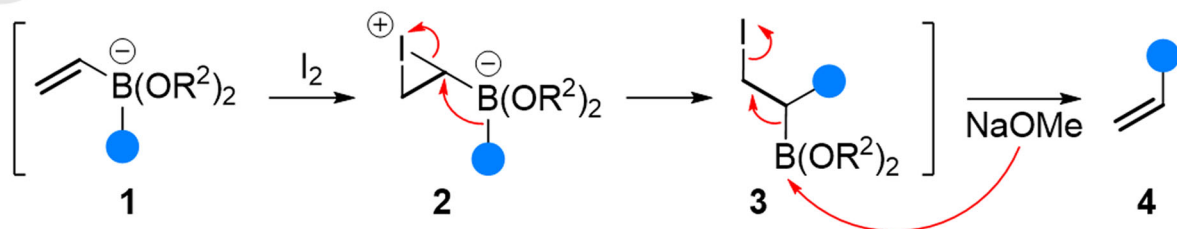
Metallation conditions were optimized first on a benchmark substrate, a protected D-glucal derivative (**5a**, Fig. 2A). In contrast with classical vinyl-ethers that can be easily metallated at the position α to the heteroatom, the metallation of protected glucal **5a** proved more difficult, with no conversion observed between -78°C and -60°C , using either *n*-BuLi, *s*-BuLi or even *t*-BuLi (entries 1 and 2, Fig. 2A). The first iodolysis product **6** was isolated in 51% yield when conducting the reaction for 15 min at -50°C (entry 3). Warming the temperature up to -30°C allowed the metallation to reach its maximum conversion, allowing for the isolation of **6** in 73% after 30 min

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A Selected pharmacologically relevant C-glycosides



B Zweifel olefination - reaction mechanism



C This work - C-glycosylation

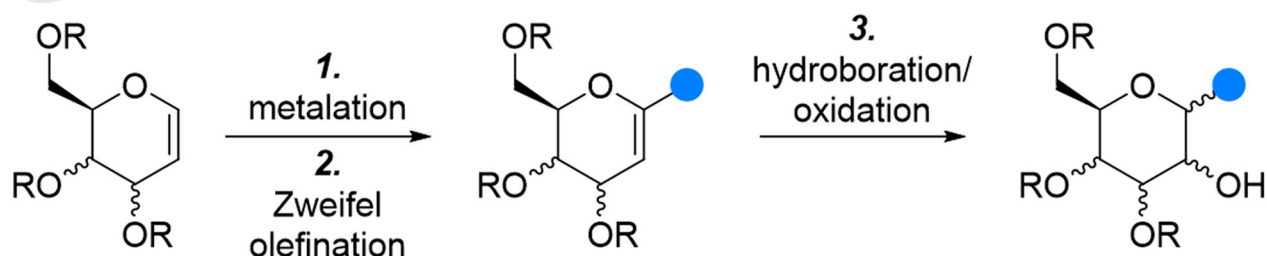
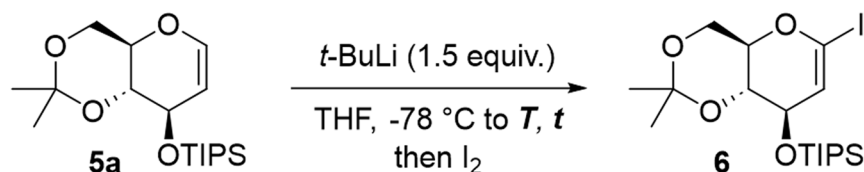
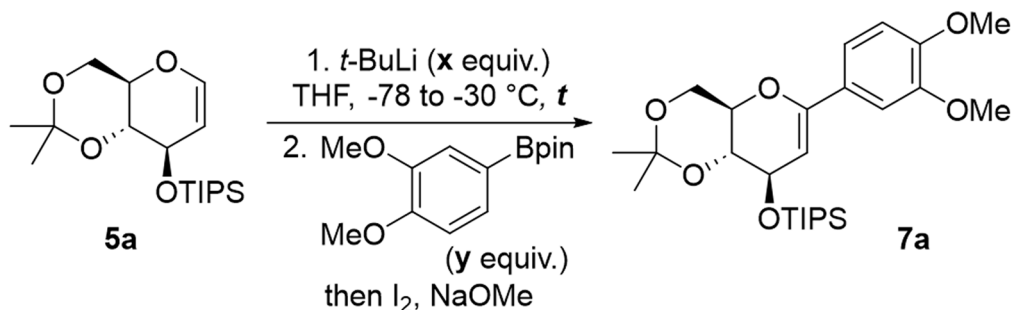


Fig. 1 | Our conceptual approach to C-glycosides in the context of current research interests. A Selected examples of pharmacologically relevant C-glycosides; B General mechanism of the Zweifel olefination; C Our strategic design to

stereoselectively access C-glycosides via a sequence of Zweifel olefination/Brown oxidation.

A Optimization of the α -metalation step

entry	T (°C)	t (min)	yield (%)
1	-78	15	0
2	-60	15	0
3	-50	15	51
4	-40	15	55
5	-40	30	65
6	-30	15	70
7	-30	30	73
8	-20	15	71
9	-10	15	60
10	0	15	40

B Optimization of the one-pot Zweifel olefination

entry	x	t (min)	y	yield (%)
1	1.3	45	0.9	< 50
2	1.3	45	1.15	67
3	1.3	45	1.3	69
4	1.3	60	1.5	54
5	1.1	45	1.15	71
6	1.1	60	1.15	74

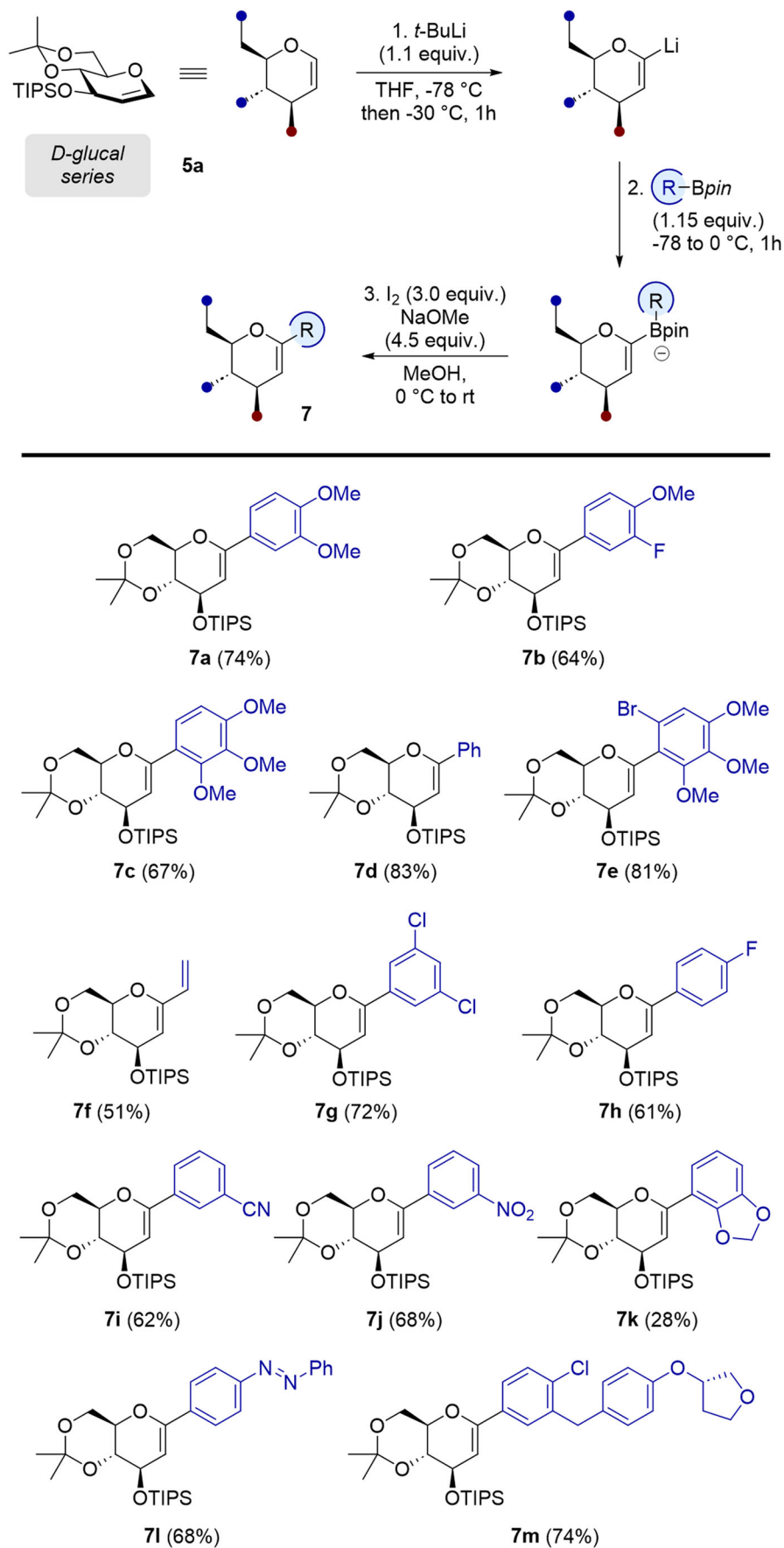
Fig. 2 | Stepwise optimization of reaction conditions. **A** Condition optimizations for the α -O-metalation step, controlled by iodolysis; **B** Optimization of the Zweifel olefination step using a *m,p*-dimethoxyarylboronic ester as benchmark reagent.

(entry 7), while both lower and higher temperatures show any improvements (entries 5,6 and 8–10).

These first optimized conditions were then applied to the Zweifel olefination of compound 5a, adding a boron pinacol ester as the

organoboron partner (Fig. 2B). The reaction conducted in the presence of substoichiometric amount of boron species (0.9 equiv., entry 1, Fig. 2B) only yielded low amounts of desired products. However, employing a slight excess of ArBpin (entry 2) furnished 7a in 67% yield. No significant

Fig. 3 | Zweifel olefination's scope on D-Glucal substrates. The scope of the reaction with D-glucal was evaluated through the introduction of aryl and heteroaryl moieties, displaying both electron-donating and -withdrawing functional groups.



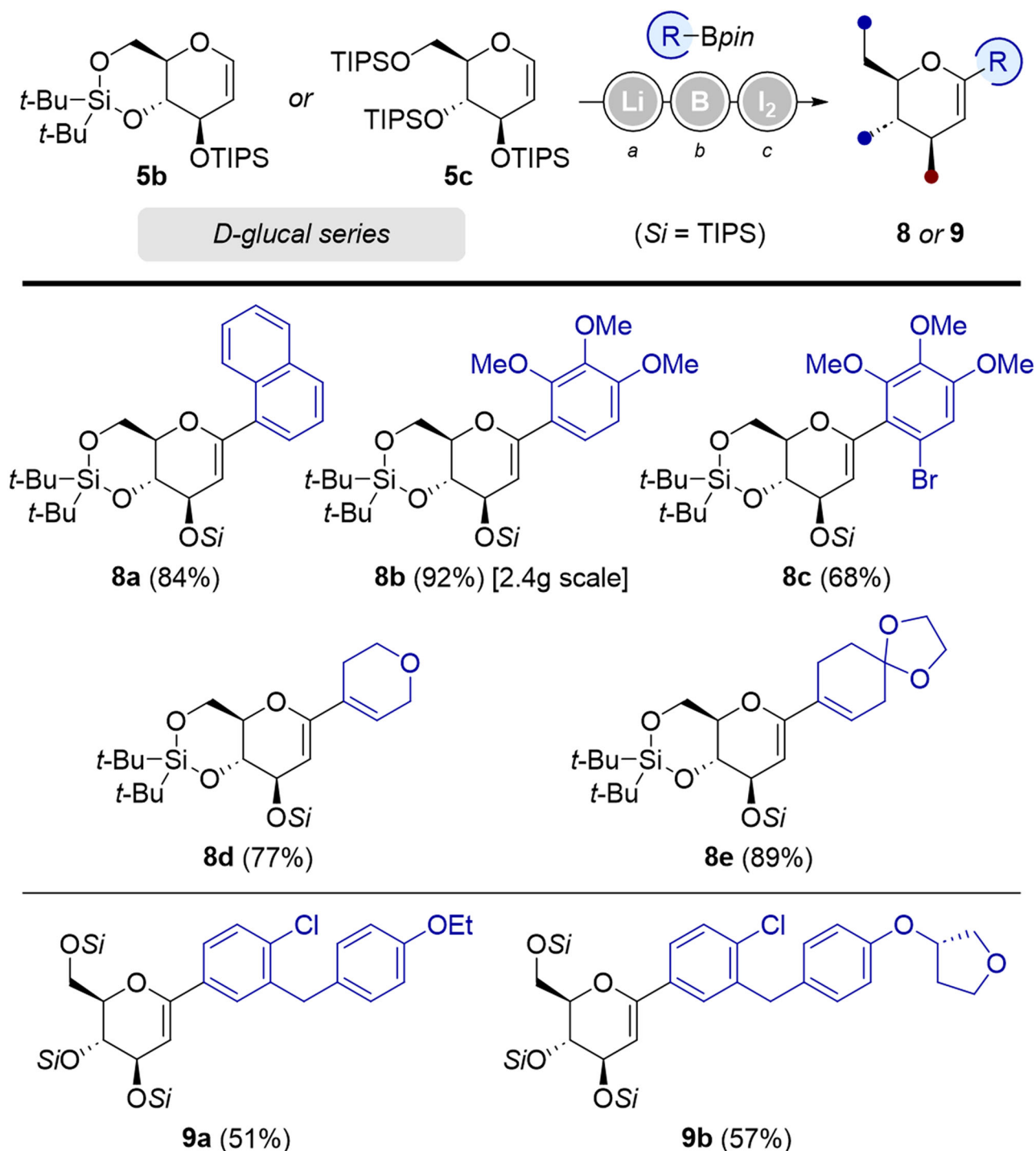


Fig. 4 | Variation of protecting groups on D-Glucal substrates. ^a*t*-BuLi (1.3 equiv.), THF, −78 to −30 °C, 30 min. ^bRBpin (1.15 equiv.), −78 to 0 °C, 1 h. ^cI₂ (3.0 equiv.), NaOMe (4.5 equiv.), MeOH, 0 °C to rt.

improvement was noticed when further increasing the amount of organo-boron species (entries 3 and 4). However, lowering the amount of based used in the initial α -metalation step to 1.15 equiv. provided **7a** in 71% (entry 5), value that was further increased to 74% under prolonged metalation time (60 min, entry 6).

Scope of the reaction on D-Glucal derivatives

With optimized conditions in hands, we further evaluated the scope of the transformation on protected D-glucal **5a** (Fig. 3). Neutral phenylboronic pinacol ester gave **7d** in 83%, and electron-poor aryl boronic esters gave

similarly high yields than electron-rich ones (**7b-c**, **7e** and **7g-j**, 61–81%). Drops in yields were however observed with acetal-protected reagent (**7k**, 28%), which could be attributed to sensitivity issues during the purification process, as we ruled out the question of sterical hindrance with examples **7c** and **7e** (67 and 81%, respectively). Interestingly, the addition of vinylboronic ester enabled the formation of diene **7f** in 51%. The procedure proved quite robust for the introduction of a diazobenzene moiety at glycosidic position (**7l**, 68%). The aryl substituent typically found in Empagliflozin was also introduced via its corresponding boronic ester to provide **7m** - a dehydrated Empagliflozin precursor - in 74%.

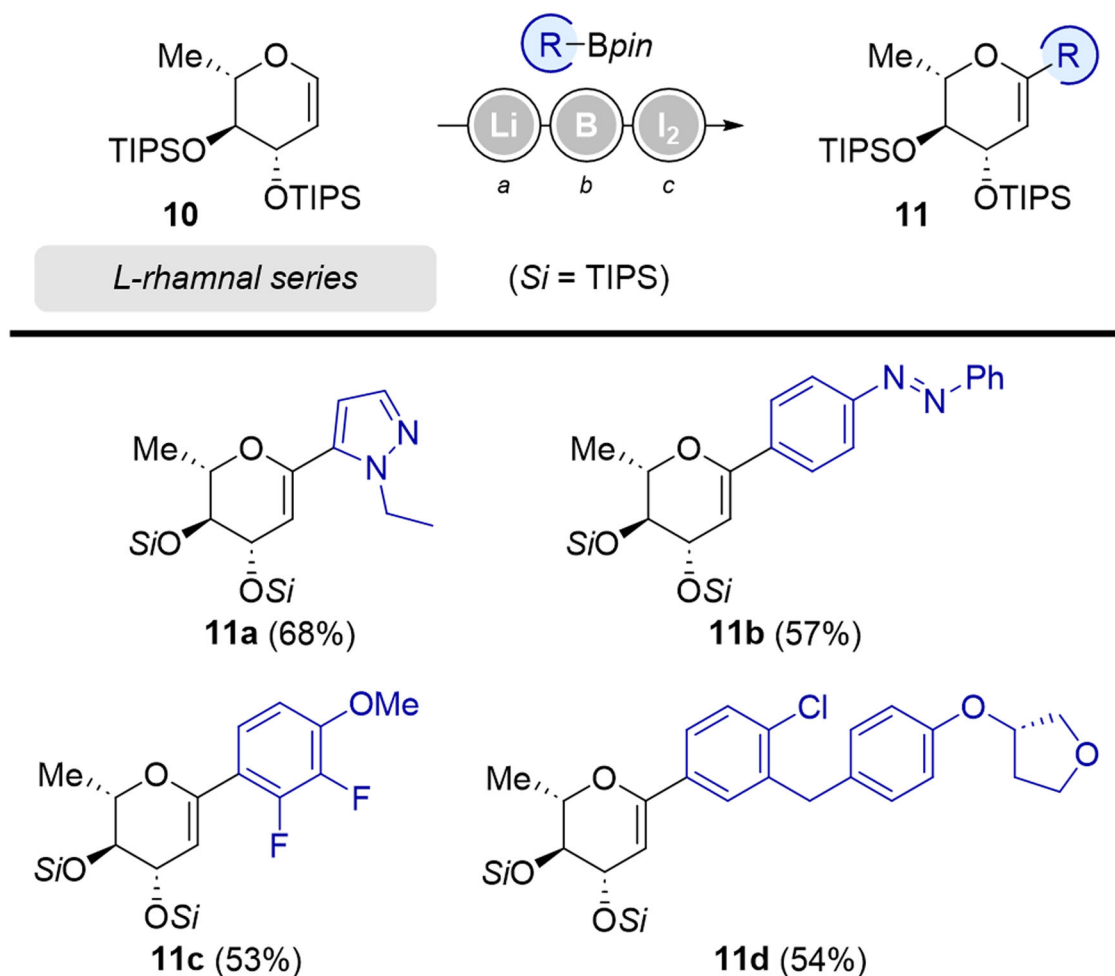


Fig. 5 | Scope of Zweifel's olefination on L-Rhamnal substrates. ^a*t*-BuLi (1.3 equiv.), THF, −78 to −30 °C, 30 min. ^bRBpin (1.15 equiv.), −78 to 0 °C, 1 h. ^cI₂ (3.0 equiv.), NaOMe (4.5 equiv.), MeOH, 0 °C to rt.

Other protecting groups on D-glucal substrates were successfully applied to the Zweifel olefination (Fig. 4). Arylated glucals **8a** and **8b** were obtained in good yields from silylacetal **5b**. The use of alkenylboronic esters as partners in the Zweifel olefination provided embedded diene systems **8d** and **8e** in 77 and 89% yield, respectively. The reaction proved less efficient when employing tris-TIPS protected D-glucal **5c**, furnishing dehydrated precursors of Dapagliflozin and Empagliflozin **9a** and **9b** in up to 57%.

Scope of the reaction on other Glycal derivatives

The L-rhamnal series (6-deoxy-L-glucal) was examined next (Fig. 5), starting from bis-TIPS protected structure **10**. The same reaction sequence than for the D-glucal series was employed, providing a range of dehydrated C-rhamnosides **11**. Electron-rich pyrazol-containing boronic ester gave the heteroaryl derivative **11a** in 68%.

Lower yields were obtained for the introduction of diazobenzene (**11b**) and bisfluorinated anisole (**11c**). The rhamnose-analog precursor of Empagliflozin (**11d**) was isolated in 54% yield.

The variation of the carbohydrate core drove us to challenge unsaturated pentopyranoses **12** and **13** (D-xylal and L-arabinal series, respectively). Applying the optimized conditions described above provided dehydrated C-xylosides **14** and C-arabinosides **15** (Fig. 6). Yields in the D-xylal series (from *trans*-bis-TIPS protected D-xylal **12**) were generally lower than the ones obtained in the D-glucal and L-rhamnal series, independently from the nature of the boronic ester used in the transformation. Both electron-donating and electron-withdrawing partners provided

olefination products **14a-f** with moderate yields (36–53%). The nature of the boronic ester was also evaluated via the introduction of alkyl substituents. Product **14g** was isolated in 53%.

Despite lower yields in the D-xylal series, it is worth noting that two new D-xylal precursors of Empagliflozin (**14c**, 49%) and Canagliflozin (**14d**, 53%) were obtained.

Cis-acetal-protected L-arabinal substrates led to the corresponding arylated L-arabinal series in similarly high yields up to 82% (**15a-b**), whatever the electronic nature of the boronic ester partner. Interestingly, when a bis-boronic ester was engaged in Zweifel olefination, both products of mono- and bis-olefination (**15c** and **15d**) were isolated, in 51 and 36% (overall yield of 87%).

Further applications

To demonstrate the applicability of this procedure, selected examples were engaged in further useful transformations. Given the paramount significance of fluorinated substituents as well as cyclopropyl-rings in drug discovery, gem-difluorocyclopropanes are anticipated to offer sophisticated frameworks for enhancing therapeutic attributes³¹. Therefore, L-rhamnal derivative **11e** was subjected to difluorocyclopropanation conditions recently described, providing stereoselectively the bicyclic compound **16** in 82% (Fig. 7A). The diastereoselectivity of electrophilic additions onto the double bond of glycal derivatives was demonstrated in previous reports and seemed to be dependent on the orientation of the silyl-ether substituent at position 3. Epoxidation of D-glucal **8c** was performed in the presence of DMDO, furnishing stereoselectively D-oxyglucal compound **17** in 62%

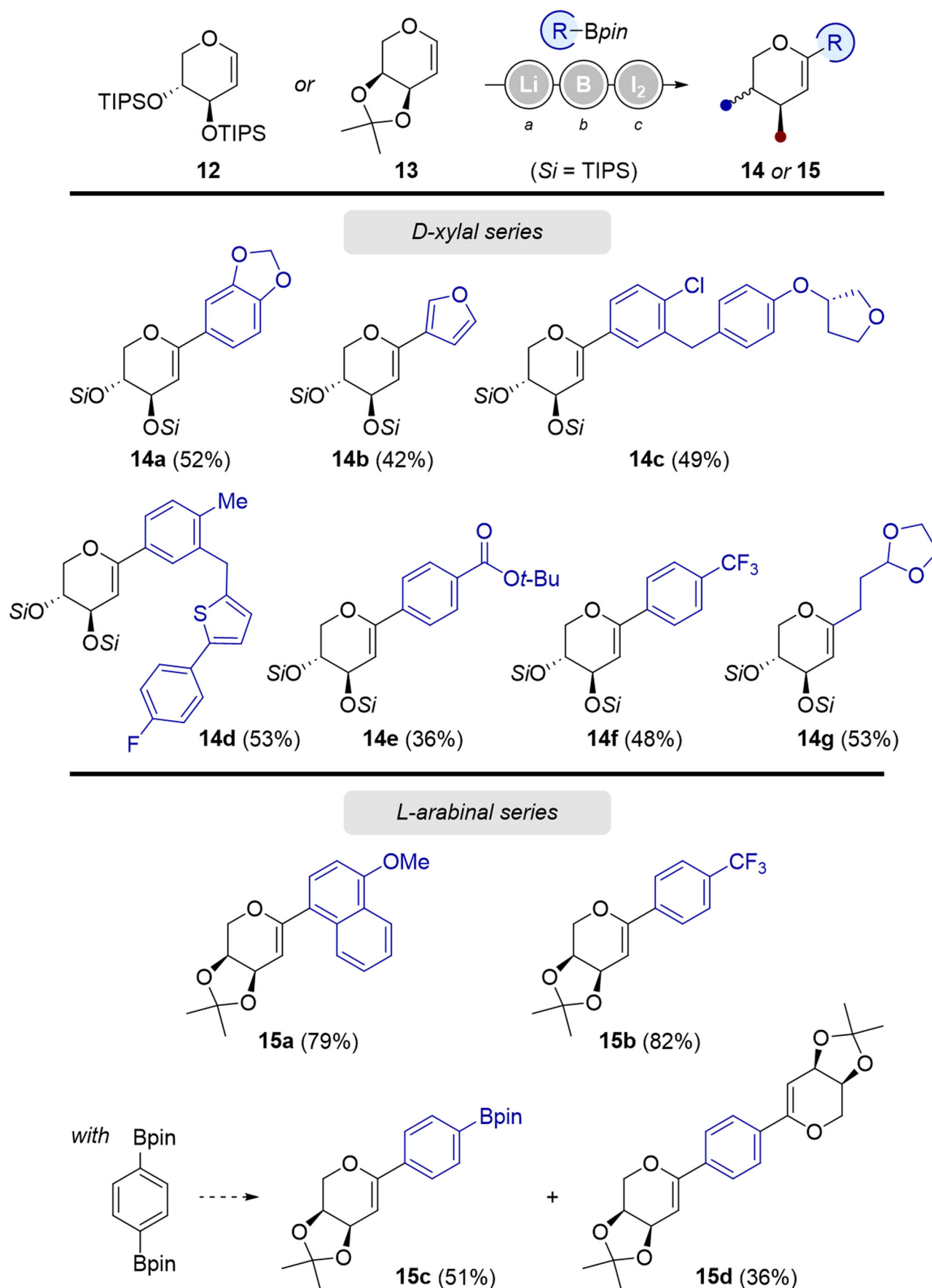


Fig. 6 | Scope of Zweifel's olefination on D-Xylal and L-Arabinal substrates. ^a*t*-BuLi (1.1 equiv.), THF, −78 to −30 °C, 30 min. ^bRBpin (1.15 equiv.), −78 to 0 °C,

1 h for the D-Xylal series, 30 min for the L-Arabinal series. I₂ (3.0 equiv.), NaOMe (4.5 equiv.), MeOH, 0 °C to rt.

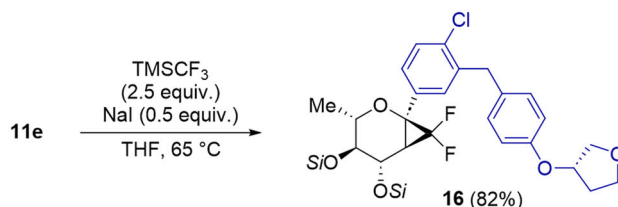
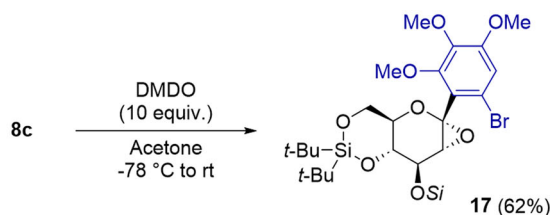
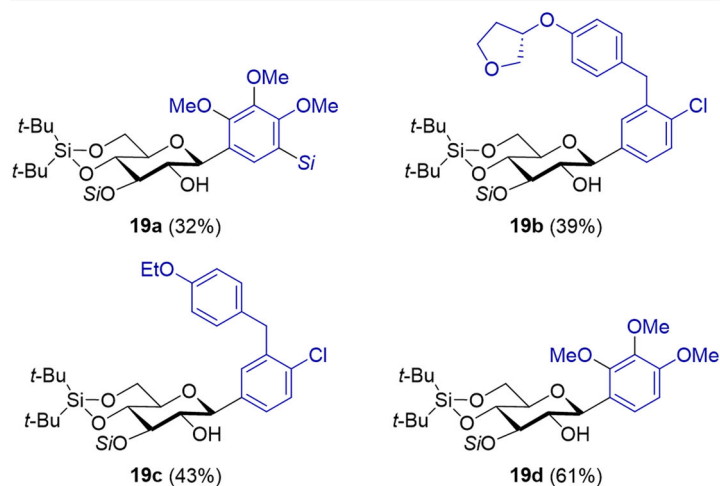
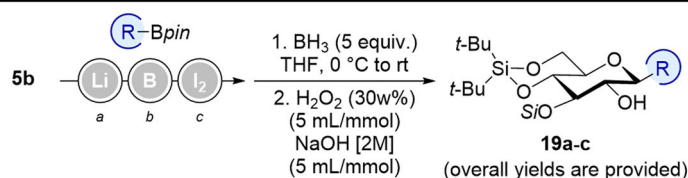
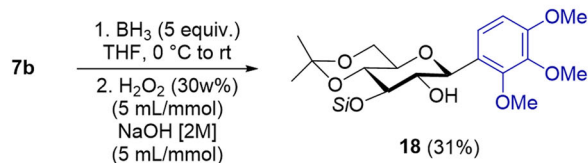
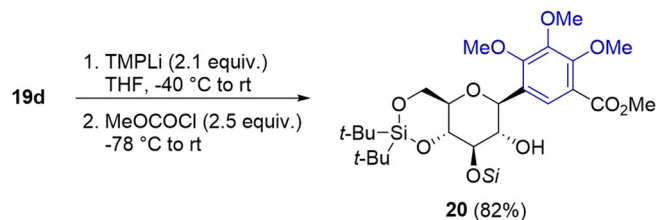
A Difluorocyclopropanation**B** Epoxidation**C** Regeneration of carbohydrates integrity**D** Application in direct metallation

Fig. 7 | Further applications of glycal-based C-glycosides. Glycal derivatives obtained via Zweifel olefinations were engaged in further selective transformations:

A Difluorocyclopropanation; **B** Epoxidation; **C** Regioselective Brown oxidation towards the regeneration of the carbohydrate integrity; **D** Directed metallation.

(Fig. 7B). The regeneration of the carbohydrate entity was demonstrated on D-glucal **7a** through a first step of hydroboration followed by Brown's oxidation (Fig. 7C). Protected C-glucoside **18** was obtained stereoselectively (anti-Markovnikov product) in moderate yield (31% over two steps). With a clean and straightforward Zweifel olefination procedure, we showed that the application of Brown's oxidation did not necessitate purification of intermediates to yield C-glucosides **19a–c** in 32 to 43% (over 3 steps). This method offers a straightforward and highly stereoselective route towards protected Empagliflozin **19b** and Dapagliflozin **19c**. **19d** was also accessed in 61% from **5b** (Fig. 7C) and used in further metalation chemistry using TMPLi (Fig. 7D)³². This strategy proceeds regioselectively ortho to one of the methoxy groups on the aryl scaffold, allowing the introduction of an ester upon addition of methylchloroformate as electrophile. **20** was isolated in 82% as a single regioisomer.

Conclusions

The simplicity of metal olefination was applied to the synthesis of C-glycosides, providing an efficient and selective alternative to oftentimes fastidious carbohydrate chemistry. A single-pot sequence based on a transition-metal free 1,2-boronate rearrangement allowed us to access functionalized D-glucals, L-rhamnals, D-xylals and L-arabinals in moderate to high yields, compounds that were further engaged in the regeneration and sophistication of sugar-based drug-like molecules and natural scaffolds. Given the importance of C-glycosides such as gliflozins in drug discovery, the efficiency and simplicity of this strategy could easily be applied in high-throughput screening methodology.

Methods

Optimization of reaction conditions

See Supplementary Methods, section 2 p.4–8.

Synthetic procedures

See Supplementary Methods, section 4 p.10–14.

Analytical data

See Supplementary Methods, section 4 p.15–84.

NMR spectra

See Supplementary Data 1.

Data availability

Data for this manuscript has been deposited in figshare: <https://doi.org/10.6084/m9.figshare.27233724.v1>. "Supplementary Methods" contains detailed protocols for the preparation of substrates, reaction optimizations, scope evaluation and description of analytical data (¹H and ¹³C NMR, HRMS). "Supplementary Data 1" contains all ¹H and ¹³C NMR spectra.

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Author contributions

Conceptualization and supervision: D.D. Experimental investigation: F.T., B.B., F.P., V.W. Writing: D.D. Supporting information: F.T., B.B., F.P. Proof reading: D.D., F.T., B.B.

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Competing interests

The author declares no competing interests.

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