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Unleashing the Power of Domino Reactions on Carbohydrates: State of the Art

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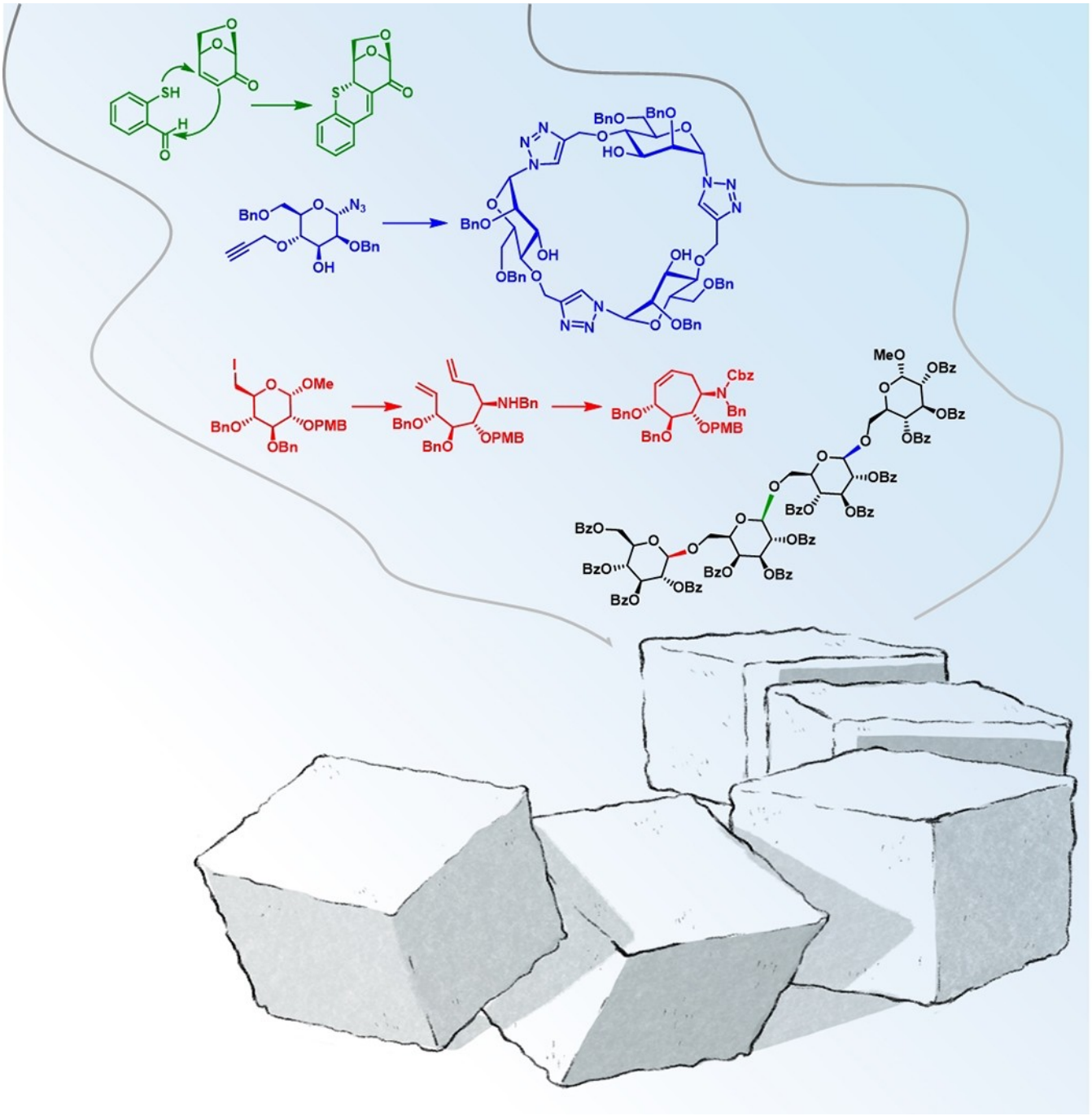

Review
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The intricate nature of carbohydrate structures has prompted the scientific community to seek efficient protocols for their manipulation. Lengthy synthetic pathways, often necessary to achieve complex sugar structures, pose challenges not only in terms of time and cost but also regarding environmental sustainability. Consequently, domino transformations serve as valuable tools in streamlining drug discovery processes. Sequential procedures involving fewer steps and minimal isolation/purification steps are particularly appealing to organic chemists in the field of carbohydrate chemistry. This review highlights several examples of domino transformations applied to carbohydrates, aiming to summarize their chemical potential in delivering sugar-based compounds with significant applications in the generation of new chemical scaffolds for drug discovery and chemical biology.

1. Introduction

Glycans and glycoconjugates fulfill a myriad of physiological functions. They serve as energy sources, facilitate intercellular communications and cell adhesion,[1–4] and contribute to structural integrity.[5] Owing to their relevance, natural carbohydrates and their synthetic derivatives gain significant interest in drug discovery, playing a crucial role in advancing our comprehension regarding the biological mechanisms of glycoconjugates.[6–10] Sugar derivatives are present in several commercially available drugs and vaccines; they are important platforms employed in the design and development of pharmaceuticals.[7,11] In this context, the investigation of innovative methodologies for the synthesis, modification and functionalization of carbohydrates is of great importance.[12,13]

As chiral, complex molecules featuring multiple and similar hydroxyl groups, the manipulation of sugars often requires long synthetic pathways, involving protection and deprotection strategies with a decrease of the overall synthetic efficiency.[12,13] Therefore, the feasibility in modifying carbohydrates remains a twisted task in terms of number of steps, regio- and stereoselectivity, yields and time-consuming synthetic routes. Hence, an important challenge of modern glycoscience is to reach facile and convenient methods that give access to complex chiral structures like sugar-based compounds.[14] Nowadays, in the field of carbohydrate chemistry, the development of sequential processes with reduced steps, minimizing isolation and purification procedures of intermediates is of primary interest for organic and medicinal chemists.[15–17]

A domino reaction, as originally defined by Tietze, encompasses a series of chemical transformations involving at least two bond formations, occurring under the initial reaction conditions and without the addition of supplementary reagents.[18–21] In this strict concept, each transformation must be the consequence of the chemical functionality formed by the preceding step. Over the time, tandem (or cascade) reactions, which entail the successive incorporation of a reagent or catalyst, including changes in reaction conditions, have been included in domino classification.[22–24] Today, the terms domino, tandem and cascade have not a clear differentiation in literature and are often considered interchangeable.[25,26] Among the domino one-pot processes, multicomponent reactions are powerful tools for the straightforward preparation of natural product derivatives and biologically active molecules. Typically, these reactions involve the coupling or condensation of at least three elements in the same vessel and without the need of further addition of reagents.[27–29] Domino reactions have proven to be effective strategies to facilitates the synthesis of complex molecules like carbohydrates bypassing the need of isolating intermediates. This approach offers several advantages, both in an economic and environmental perspectives, in academia and industry, such as the reduction of steps and reagents required for the synthesis. Domino reaction procedures are typically associated with high yields and stereoselectivity. Moreover, the minimization of purification steps, coupled with the reduction of chemicals used and waste generation, result in lower production times and costs.[18,20,21,24–29] Over the years, several reviews have discussed the usefulness of domino processes in organic synthesis and described various types of substrate transformations.[19,21–26,30] Notably, there is a paucity of comprehensive review articles specifically focused on carbohydrate-related domino reactions, with the exception of a book,[16] a book chapter[17] and a review article by Mukherjee published in 2020 that explored one-pot reactions on carbohydrates mediated by metal catalysts.[31]

In the context of domino reactions on carbohydrates, the use of enzymatic and chemoenzymatic one-pot protocols is certainly noteworthy, as evidenced by a wealth of literature showcasing the application of these methods. The advancements of one-pot multienzyme (OPME) systems in carbohydrate synthesis is extensively covered in several recent review articles.[32–34]

This review presents a state of the art regarding the domino processes applied on sugar substrates reported in the past two decades, showcasing their importance in carbohydrate chemistry. Specifically, research studies in carbohydrate chemistry mentioning "domino," "tandem," or "cascade" processes have been included in the text based on the provided definition(s) of domino reactions. A specific emphasis has been consistently maintained throughout the manuscript on the scopes of the presented domino transformations and their

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reaction mechanisms or pathways. The inclusion of several synthetic schemes aims to illustrate the potential of this reaction family.

The manuscript is organized according to the different substrates involved in the domino process. Section 2 is focused on the domino ring-opening reactions since they occur frequently in carbohydrate chemistry. The classification then includes the three most common sugar precursors of domino processes: glycosides (Section 3), glycals (Section 4) and halosugars (Section 5). Within the glycoside category, the discussion is further organized in *O*/*S*- and *N*-glycosides.

2. Domino Ring-Opening Reactions

Various domino reactions that involve carbohydrates typically include a ring-opening step, in which cyclic sugars are converted into open-chain intermediates typically through a

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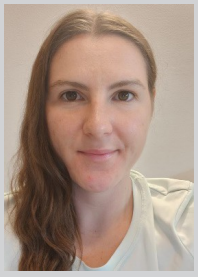

Laura Petrosilli received her master's degree in chemical sciences in 2019 at University of Milan. She is specialized in organic chemistry and biochemistry, especially in the field of carbohydrates. In 2020 she started her Ph.D. working on the synthesis of the capsular polysaccharide repeating unit of Streptococcus pneumoniae 6 A and 6 C, under the supervision of Prof. Luigi Lay. She also spent six months as an exchange student in the group of Prof. Demchenko at Saint Louis University, working on automated solution phase HPLC synthesis.

Ilaria Giussani graduated with a bachelor's degree in chemistry in 2022 at the University of Milan and she received her master's degree at the same university in 2024. She is currently pursuing her Ph.D. at the Ludwig-Maximilians University of Munich, under the supervision of prof. Ivan Huc, on the synthesis of tailored foldamers for the supramolecular sensing of carbohydrates.

M. Gessica Ciulla obtained her Ph.D (2017) from the University of Urbino (Italy) in Chemical and Pharmaceutical Sciences for her work on carbohydrate chemistry and for the design and synthesis of novel cannabinoid receptor ligands. As a guest researcher in Prof. Waldmann's and Dr. Kumar's group in Max Planck Institute of Molecular Physiology (Germany), she was involved in the development of asymmetric synthesis of polycyclic and biologically active compounds. In 2021 she moved to Dr. Gelain lab (Niguarda Hospital, Milan, Italy) as a postdoc working on the synthesis and characterization of peptides for nanomedicine applications. In 2023, she joined as a postdoc researcher at the University of Milan (Italy) in Prof. Sara Sattin's group working on the design and synthesis of small molecules with the aim to eradicate chronic infections. Then, she moved to University of Modena and Reggio Emilia (Italy) as assistant professor.

Sarah Mazzotta received her Master's degree from the University of Calabria in 2016 and she obtained her PhD at University of Seville (2020). Her PhD research activity was focused on the design and synthesis of novel antimicrobial small molecules, especially against adenovirus infections. She was also involved in the preparation of new bioactive compounds from natural sources. In 2020, she started her postdoctoral fellowship at the University of Milan working on the generation of novel glycomimetics as bacterial lectin ligands useful in antimicrobial anti-adhesion therapy. Since 2023 she is a organic chemistry researcher at the same university.

Giuseppe D'Orazio completed his Ph.D. and postdoctoral research at the University of Milano Bicocca, under the supervision of Prof. Barbara La Ferla and Prof. Francesco Nicotra. His primary research focus has been on the synthesis of glycomimetics and glycoderivatives as potential bioactive compounds. After gaining experience as chemistry researcher in an agrochemical company and later at the Polytechnic University of Bari, he joined University of Milan in 2022, where he works as an organic chemistry researcher, specifically focusing on the synthesis of biologically important oligosaccharides for carbohydrate-based vaccine development.

metal-promoted reductive elimination. The obtained intermediates can undergo various *in situ* modifications, leading to a wide range of products. Consequently, domino processes initiated by ring-opening reactions find numerous applications in synthetic carbohydrate chemistry.

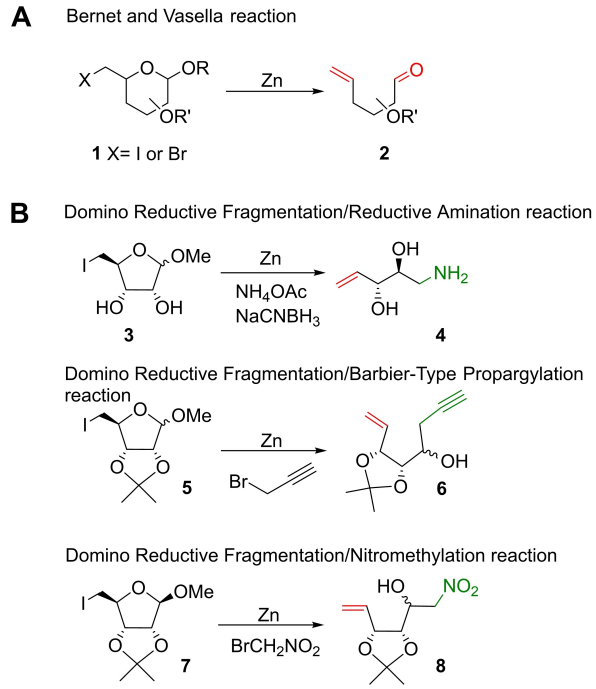

Figure 1. (A) Schematic representation of Bernet-Vasella reaction of a 6-bromo or 6-iodopyranoside. In the presence of zinc powder, the corresponding 5-hexenal is obtained. The reaction can be performed in same condition also starting from 5-halofuranosides affording a 4-pentenal. (B) Examples of domino processes involving the trapping of Bernet-Vasella aldehyde.

2.1. The Bernet-Vasella Approach

In 1979, Bernet and Vasella first reported the conversion of haloglycosides into non-cyclic aldehyde with a terminal double bond promoted by zinc powder[35] (Figure 1A). Since its initial publication, this reaction found applications in several synthetic procedures. However, the aldehyde obtained from this reaction often proved unstable, leading to side reactions. In order to prevent this issue, various synthetic processes have been developed that involve the *in situ* trapping of the aldehyde group with different nucleophiles, giving rise to domino processes. For instance, aldehyde can be trapped by a primary amine to afford alkenylamine,[36] by propargyl bromide to afford enyne,[37] or by bromonitromethane to afford nitroalkenes[38] (Figure 1B). These varied trapping facilitate the creation of a diverse array of products, broadening the scope of the initial ring-opening process in synthetic carbohydrate chemistry. The dienes formation through the trapping of aldehydes obtained by the Bernet-Vasella reaction with allyl halides (domino reductive fragmentation/Barbier-type allylation) is of particular interest. These functionalized dienes serve as key intermediates in various synthetic pathways. Indeed, the diene can subsequently participate in a ring-closing metathesis (RCM) reaction, leading to the creation of various carbocycles. This versatile methodology finds extensive applications both in the synthesis of natural-derived compounds and in the design of biologically relevant synthetic products.

Based on this methodology, in 2009 Madsen and coworkers reported the synthesis of (+)-calystegine A3, a natural alkaloid with glycosidase inhibitory activity, originally isolated from *Calystegia sepium* (Figure 2A). In the proposed synthesis[39] an iodine derivative accessible from D-glucose is treated with zinc to perform the Bernet-Vasella fragmentation. This step generates an intermediate aldehyde, which is directly converted into the corresponding imine using benzylamine. Then, in the

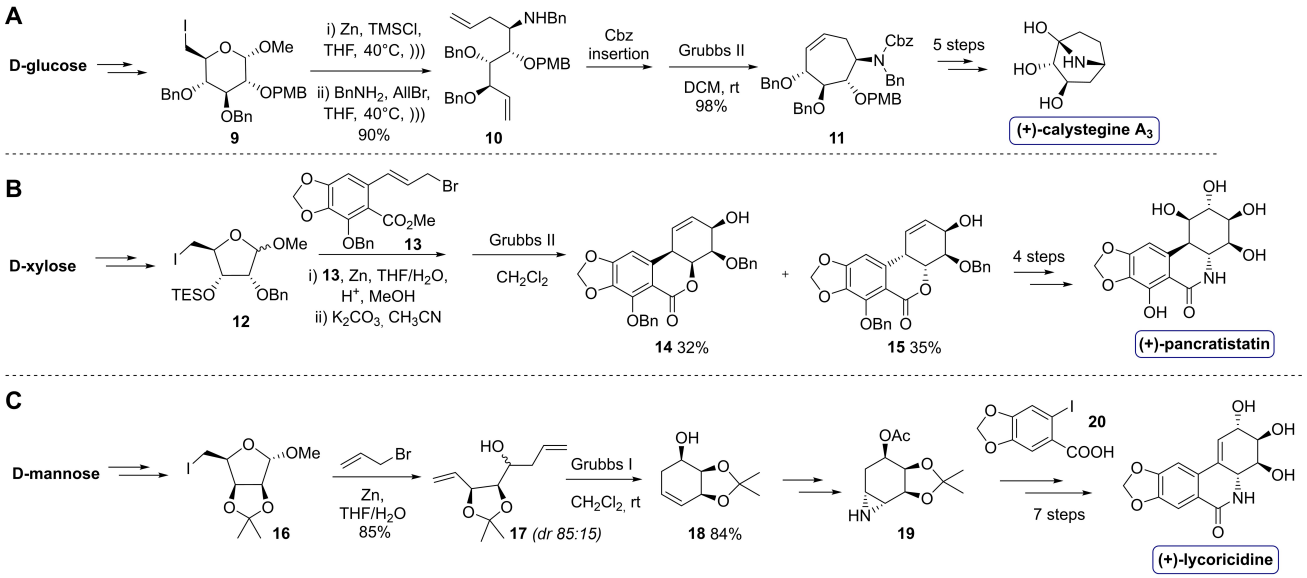

Figure 2. Synthetic approaches for the synthesis of alkaloids involving a domino reductive fragmentation/Barbier-type allylation, starting from (A) D-glucose; (B) D-xylose; and (C) D-mannose.

concurrent step, the so formed imine is allylated by allyl bromide giving the intermediate **10** in good yield. Subsequently, this diene undergoes an olefin metathesis reaction using the Grubbs' 2nd generation catalyst, performed after the protection of amine functionality with benzyloxycarbonyl (Cbz) group. The resulting seven-membered carbocycle **11** is a key intermediate, leading to (+)-calystegine A3 in five steps. In the same year, Madsen and colleagues also reported the synthesis of a natural compound with anti-cancer activities, (+)-pancratistatin, initially isolated from *Pancratium littorale* (Figure 2B).[40] In this synthesis, the iodine derivative **12** from D-xylose is treated with the classical Bernet-Vasella conditions in the presence of the allylating agent **13** prepared from commercially available piperonal. The reaction generates a 1.1:1 mixture of two inseparable diastereomers.

These allylation products are both converted into the corresponding lactones, and then subjected to a metathesis reaction, performed using the Hoveyda-Grubbs 2nd generation catalyst. Two separable cyclohexenes **14** and **15** are obtained, and (+)-pancratistatin is synthesized over the course of four subsequent steps.

In 2010 Yadav and colleagues reported the synthesis of the antitumor alkaloid (+)-lycoricidine, related to (+)-pancratistatin, which was originally isolated from *Calystegia sepium* (Figure 2C).[41] In the proposed procedure, the ω-iodo glycoside **16** derived from d-mannose is treated under the reductive fragmentation/Barbier-type allylation conditions, yielding the diene **17** in good yield as an in inseparable diastereomeric mixture (dr 85:15 erythro/threo). Then, a ring closing metathesis step takes place, giving the cyclohexenol derivative **18** as main product. From this intermediate, the desired (+)-lycoricidine is obtained in few steps, including the conversion into the aziridine **19** and the following coupling with the 6-iodopiperonylic acid **20**. In 2010, the synthesis of Tamiflu® (oseltamivir phosphate) from D-ribose was published. Tamiflu® is a neuraminidase inhibitor used for the treatment of infections caused by both influenza A and B viruses. The industrial production of this antiviral drug is mainly based on the use of (−)-shikimic acid as starting material, but its natural availability is limited. Thus, different alternative approaches have been proposed in the last decade,[42] including the one proposed by Kongkathip and coworkers (Figure 3A).[43] Similarly to the synthesis of Tamiflu® reported by Osato et al. in the same year,[44] the authors proposed a synthetic procedure that begins with the easily accessible and cost-effective starting material D-ribose. The key step involves a zinc-mediated reductive elimination of an iodo-riboside **21**, followed by *in situ* alkylation of the aldehyde intermediate using ethyl 2-(bromomethyl)acrylate as allylation reagent, affording the intermediate **22** (Figure 3A). The authors also investigated the use of indium to promote this ring-fragmentation/allylation domino step. The reaction is found to be feasible using indium together with a catalytic amount of acetic acid, furnishing the same desired diene with a comparable yield (71% with Zn, 70% with In). Diene **22** is then involved in a ring-closing metathesis reaction by utilizing the 2nd-generation Grubbs' catalyst, providing the

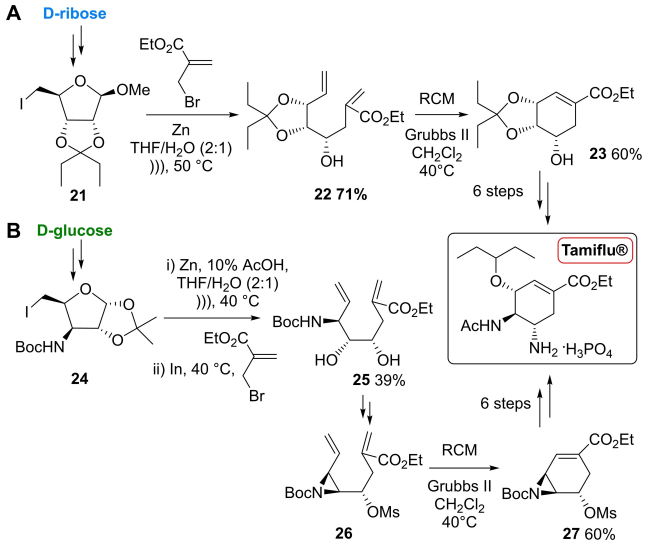

Figure 3. (A) Synthesis of Tamiflu from D-ribose and (B) from D-glucose

5-*epi*-shikimic acid derivative **23**, which was the key intermediate to obtain Tamiflu®.

Five years later, in 2015, the authors presented a novel asymmetric synthesis of Tamiflu®, replacing the starting reagent with D-glucose (Figure 3B).[45] The procedure mirrors the previous one: the 5-iodo-α-D-xylofuranose derivative **24**, accessible from D-glucose, reacts with ethyl 2-(bromomethyl)acrylate in the presence of zinc powder to promote the reductive fragmentation reaction/allylation. The obtained diene **25** is subsequently converted into the aziridine **26**, which is subjected to a ring closing metathesis step to afford the cyclohexene aziridine **27**. The desired final product is achieved from this cyclic aziridine within six steps.

2.2. Synthesis of Carbocyclic and Heterocyclic Compounds

The direct conversion of carbohydrates into novel carbocycles through ring-opening reactions became of great significance in organic synthetic chemistry. These reactions facilitate the construction of cyclic compounds with varying complexities. Examples include highly strained fused rings, and densely functionalized carbocycles with congested stereocenters. This peculiar conversion of carbohydrates into carbocycles can be achieved under several conditions, depending on the specific reaction and desired product.

In 2008 Rao and coworkers reported the synthesis of cyclopentitols using 5-enofuranosides as starting reagents (Figure 4A).[46] In the presented synthesis, the isopropyl glycoside **28**, derived from D-ribose, is treated with Tebbe reagent, a Ti- and Al- containing organometallic compound characterized by Lewis acidity, usually employed for the conversion of carbonyl groups into the corresponding olefins. The reaction consists of an initial methylenation followed by the cleavage of isopropyl group, which is necessary to promote a carbocyclization *via* intramolecular aldol reaction. A subsequent further methylation

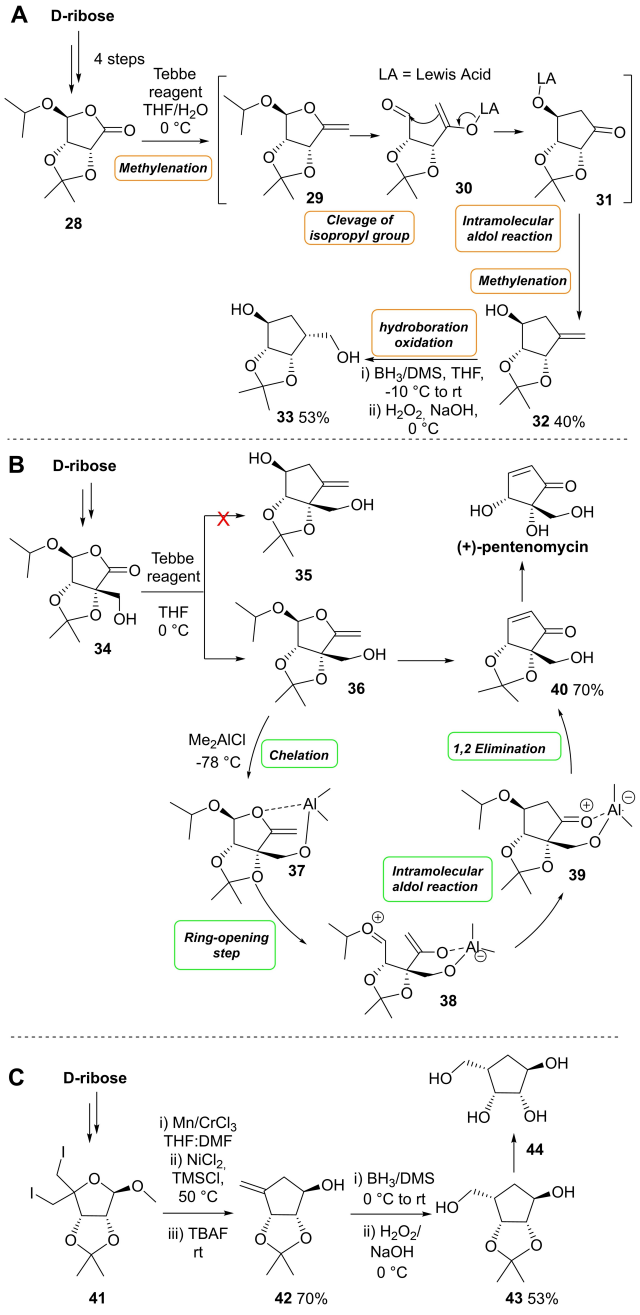

Figure 4. (A) Synthesis of cyclopentitols promoted by Tebbe reagent. (B) Synthesis of (+) pentenomycin through a Tebbe reagent–Me_2AlCl mediated domino process. (C) Synthesis of cyclopentitol via reductive elimination/ intramolecular Nozaki–Hiyama–Kishi reaction.

reaction occurs, triggered by the Tebbe reagent. The olefinic cyclopentane derivative **32** is gained as product. Surprisingly, the cyclization resulted from a 5-(enol-*endo*)-*exo-trig* pathway, considered as disfavoured according to Baldwin rules.[47] The last step of the synthesis involves the functionalization of the exocyclic double bond through a hydroboration-oxidation step, furnishing the diol **33** as major product.

Few years later, Rao and colleagues tried to apply the same Tebbe-mediated domino process to synthesize (+)-pentenomycin, compound with antibacterial activity against both Gram-positive and Gram-negative pathogens, starting from D-ribose (Scheme 4B).[48] Thus, the authors treat compound **34**, derived from D-ribose, with the Tebbe reagent expecting the formation of the compound **35**. However, olefin derivative **36** is isolated instead of the desired carbocyclic product, suggesting that the domino process discovered few years before did not take place, probably due to steric hindrance of the quaternary center in position 2. The conversion of intermediate **36** into carbocycle intermediate **40** is then performed using Me_2AlCl. This reaction occurs through a first step of chelation of the alkoxyaluminum to the ring oxygen, favoured by the 1,3-chelating ability of Me_2AlCl. Then, the ring opening step ensues, followed by an intramolecular aldol reaction *via* 5-(enol-*endo*)-*exo-trig* cyclization. An 1,2 elimination takes place in the same pot furnishing the enone **40**, affording the desired (+)-pentenomycin after the removal of isopropylidene group. The same synthetic process was applied by the authors to furnish the other enantiomer (−)-pentonomycin by replacing the starting sugar with D-mannose.

In 2017, the same research group reported a different procedure for synthesizing five-membered cyclopentitol. Their suggested strategy involved of a domino reductive elimination of a diiodo derivate of a natural sugar, followed by intramolecular C–C bond formation under the Nozaki–Hiyama–Kishi (NHK) conditions.[49] With this approach, the authors successfully obtained five-membered cyclitols avoiding the unfavoured 5-(enol-*endo*)-*exo-trig* cyclisation. According to the proposed strategy (Scheme 4C), the diiodo derivate **41**, prepared from D-ribose, participates in a domino process activated by $Mn/CrCl_3$, together with trimethylsilyl chloride (TMSCl) and a catalytic amount of $NiCl_2$.

This conversion includes a reductive elimination and an intramolecular Nozaki–Hiyama–Kishi reaction, giving the *exo*-olefin **42** *via* a 5/6-*exo-trig* cyclisation. The desired final cyclitol **44** is obtained from the intermediate **42** after hydroboration-oxidation and deprotection steps. The described strategy showed to be versatile, as the authors applied it also for the synthesis of both six-membered systems (starting from D-glucose) and tetrasubstituted cyclobutanes (starting from D-glucose).

Recently, Oka *et al.* reported the synthesis of functionalized cyclopentenes discovered in a serendipitous way. They were trying to perform the Julia – Kocienski reaction to synthesize 5′-alkylidene-5′-deoxynucleoside starting from ribose-derived sulfone (Figure 5A).[50] However, the treatment of sulfone **45** with p-anisaldehyde and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), did not generate the desired 5′- alkylidene-5′-deoxythymidine derivative **46** *via* Julia – Kocienski olefination, but unexpectedly the cyclopentene nucleoside derivative **47** was identified after isolation. The same unintentional product was formed by performing the reaction without *p*-anisaldehyde. This resulted to be the first DBU-promoted domino process consisting of a ring opening reaction and followed by successive carbocyclization, to produce a carbocyclic nucleoside. In the mechanism suggested by the authors (Figure 5B) an elimination firstly occurs, which is triggered by the α-deprotonation of the starting sulfone derivative. This generates an α,β-unsaturated sulfone bearing a formyl group and thymine anion

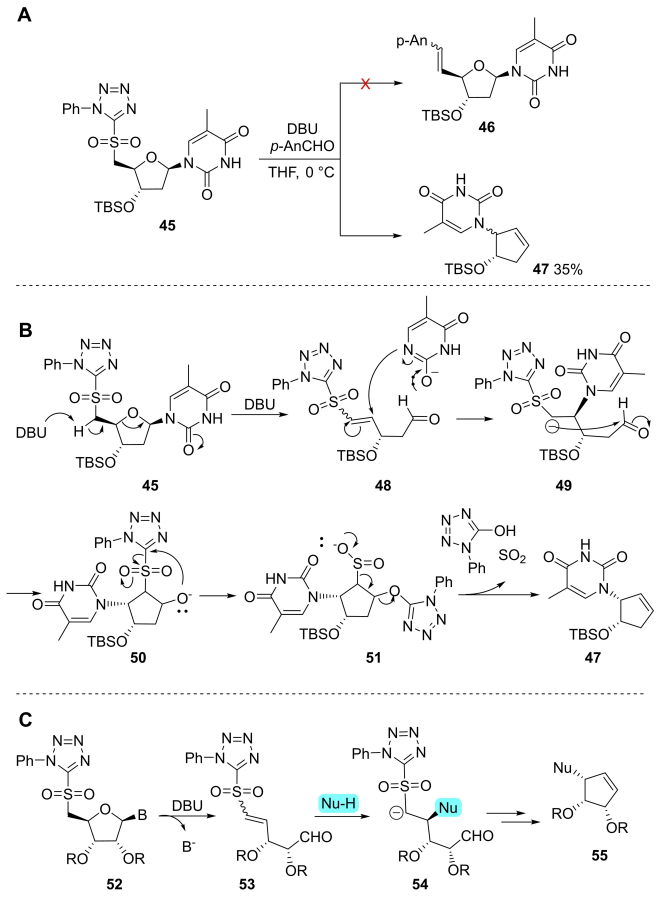

Figure 5. Synthesis of functionalized cyclopentenes *via* DBU-promoted domino reaction.
(A) Synthesis of cyclopentene nucleosides and (B) proposed reaction mechanism. (C) Synthesis of trisubstiuted cyclopentenes using alternative Michael nucleophiles.

as products. Then, they participate in a Michael addition reaction, forming a carbanion at the α-position of the sulfone. The following steps consist in an intramolecular attack to the formyl group, followed by a Julia – Kocienski olefination, that produced the final product **47**.

The authors successfully validated this serendipitous synthetic procedure with other substrates, such as the uridine-derived and adenosine-derived sulfones. Moreover, they proposed the possibility of performing the domino process using various nucleophilic reagents as alternative Michael donors (Figure 5C). These reagents could replace the nucleobase in the process, thereby generating other classes of trisubstituted cyclopentenes.

In 2018, Hedberg *et al.* reported a new approach for the synthesis of six-membered carbasugars, starting from lactones.[51] In the proposed synthesis, the lactone acetal **56** is treated with an excess of vinylmagnesium bromide together with tetramethylethylenediamine (TMEDA) affording the carbocyclic product **57** (Figure 6A). For this conversion, the authors suggested a double possible mechanism: a S_N2' reaction or a 1,4-addition. Following an initial reaction with a Grignard reagent to generate intermediate **58**, it could subsequently react with vinylmagnesium bromide through a S_N2' step, yielding an open-chain intermediate. Alternatively, the Grignard reagent could react *via* a 1,4-addition with the α,β-unsaturated intermediate **58-I** derived from **58**, forming the same open-chain intermediate. The reaction proceeds through an elimination of MeOMgBr, an intramolecular aldol reaction and a final reaction with a third equivalent of Grignard reagent to give the final product **57**. This approach resulted to be applicable to different starting substrates, such as D-mannose- or D-galactose-derived lactones.

Carbocycles are not the only compounds that can be derived from carbohydrates; iminosugars are another class of carbohydrate-derived compounds. These can be obtained through a conversion process that includes a ring-opening step.

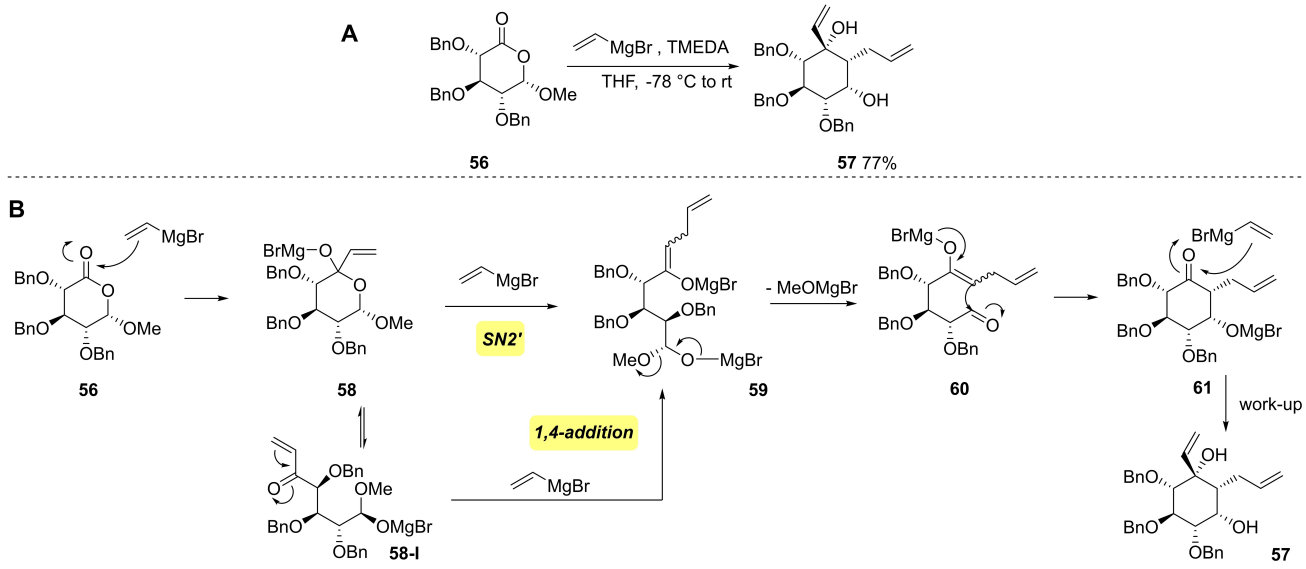

Figure 6. (A) Synthesis of six-membered carbasugars promoted by Grignard reagent and (B) the proposed mechanism for the reaction

Iminosugars serve as sugar analogues, where the endocyclic oxygen is replaced by a nitrogen atom. An example of ring-opening mediated synthesis of iminosugars was reported by Rao and colleagues in 2017.[52] Starting from a sugar lactol derivative, the conversion to iminosugar analogue consists of an *in situ* formation of *N,O*-acetal, followed by the treatment with $Pd(OAc)_2$, Et_2Zn and allyl alcohol (Figure 7A). This procedure results to be a Pd-catalyzed double allylation with allyl alcohol that generated substituted pyrrolidines, as well as piperidines (if hexose lactol derivatives are used as starting reagents).

2.3. Synthesis of Multicyclic Compounds

Over the past decade, few articles have been published describing the direct synthesis of bi- or multicyclic compounds from monocyclic sugar derivatives, using domino processes that include a ring-opening step. An early example of this type of process is the synthesis of bicyclic *C*-glycoside–fused tetrahydrofurans proposed by Voigt and Mahrwald in 2014 (Figure 7B).[53] The bicyclic product **69** was obtained fortuitously. The authors investigated the amine-catalysed chain-elongation reaction with unprotected sugar in the presence of β-keto esters as nucleophiles. By performing the reaction with DBU and proline as catalysts, the carbon-chain elongation of unprotected D-ribose did not occur. Instead, the functionalized fused-tetrahydrofuran compound **69** was isolated as a single stereoisomer, discovering a new organocatalyzed domino reaction able to convert unprotected sugars directly into bicyclic tetrahydrofuran derivatives. The authors suggested that this unexpected conversion could occur through a Knoevenagel–ketalization–oxa-Michael reaction. The Knoevenagel reaction involves the sugar, the β-keto esters and the L-proline, forming an unsaturated intermediate with the double bond in the *E*-configuration selectively. Then a stereoselective ketalization occurs, followed by an oxa-Michael step. The reaction worked successfully with various substituted β-keto esters, as well as different unprotected pentoses and hexoses. In all cases, the resulting products were consistently in their furanoid forms.

The preparation of pharmaceutical active molecules primarily focuses on generating complex and stereodefined products. Most of these molecules consist of substituted cyclic structures. The most straightforward method to obtain them is by starting with substrates that already contain stereocenters, known as the "chiron approach".

Ideally, these substrates should also be easy to functionalize and sugars represent ideal structures for this purpose. Ring-opening domino reactions on sugars enable these transformations; by starting with a suitable cyclic monosaccharide, it is possible to obtain a noncyclic sugar structure, often bearing a reactive group (such as an olefin or an aldehyde) that promotes the domino reaction *in situ*. These structures can then undergo various transformations, such as ring-closing metathesis (RCM) reactions, leading to the creation of different complex carbocycles. Several important active ingredients, such as Tamiflu, are obtained using these strategies from both D-ribose and D-glucose. However, a significant drawback of these transformations is the use of catalysts often composed of heavy metals, such as zinc, palladium, or metals used in Grubbs catalysts. Although these methods are extensively used in the pharmaceutical industry for drug synthesis, research into greener and more environmentally sustainable methods to address ring-opening reactions is advisable.

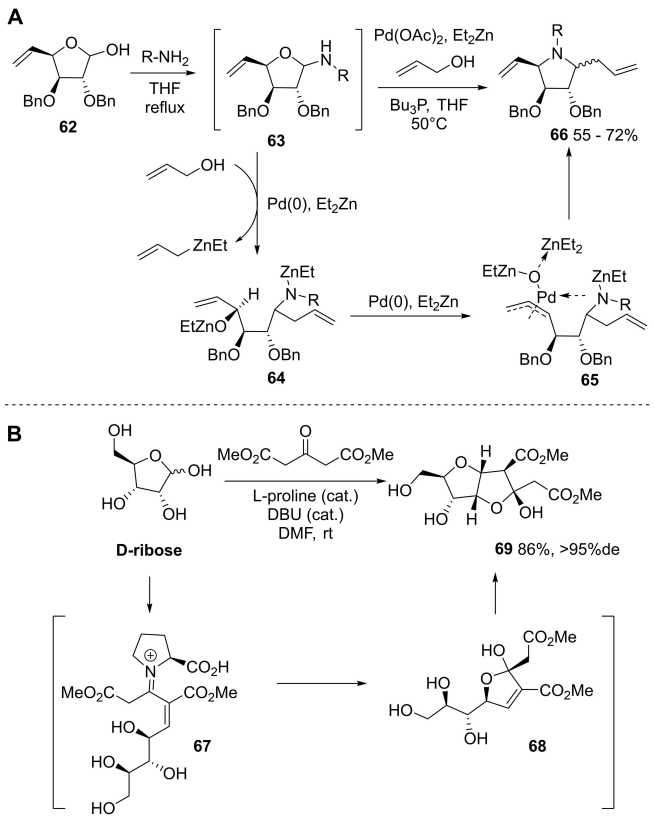

Figure 7. (A) Conversion of carbohydrate into iminosugar through a domino ring-opening reaction. (B) Domino synthesis of bicyclic *C*-glycoside–fused tetrahydrofurans.

3. Domino Reactions on *O*/*S* Glycosides

The synthesis of natural oligosaccharides or their analogs is a major challenge for the study of biological processes. Domino reactions play a key role in this field, especially in achieving good regioselectivity and stereoselectivity of the glycosidic bond. They are therefore very attractive for the design and synthesis of complex oligosaccharides. Efficient regio- and stereoselective glycosylations have been developed using organoboronic reagents, which allow the specific positioning of a hydroxyl group reversibly bound to *cis*- 1,2- or 1,3-diol under mild conditions.[54,55] An increase in the nucleophilicity of boron-bonded oxygen atoms was achieved by forming a tetra-coordinated boronate ester from a tri-coordinated boronic ester. In particular, the less hindered B–O group of the boronic ester underwent stereospecific glycosylation from the same side as the 2-O functional group of the glycosyl donor, resulting in the formation of the corresponding 1,2-*cis*-α-glycoside with

excellent regio- and stereoselectivity. The unprotected sugar acceptor **70** in presence of catalytic amount of boronic acid catalyst and 10 eq. of water were refluxed to prepare glycosyl-acceptor-derived boronic ester **71**; the glycosylation with 1,2-anhydroglucose **72** in acetonitrile at low temperatures resulted in the successful formation of α-(1,4) glycoside **74** (Figure 8A). However, most methods were not applicable to the regio- and stereoselective glycosylation of 1,2-*cis*-glycosides, which was only achieved by using a novel concept where a tri-coordinated Lewis acid boronic ester activates a 1,2-anhydro donor and simultaneously regio- and stereoselectively activates a hydroxyl group *via* a tetra-coordinated boronate ester. This glycosylation method was employed for the stereoselective formation of a β-mannosidic bond, which is considered one of the most challenging tasks in carbohydrate synthesis.[56] Additionally, it drove the regio- and stereoselective glycosylation of unprotected sugar acceptors (Figure 8B).[55]

A method for regio- and 1,2-*trans*-stereoselective glycosylation with glycosylmethanesulfonate using a borinic acid catalyst was developed by Taylor *et al.*.[57] The glycosylation of mannoside **80** with glycosylmethanesulphonate **82** in the absence of a borinic acid catalyst resulted in the formation of the α-glycoside. In contrast, β-glycoside **83** was obtained with high regio- and stereoselectivity when glycosylation is carried out with borinic acid catalyst in dichloromethane at room temperature (Figure 8C). Domino reactions involving ester, ether, thiol glycosides are mostly related to the 1,2-*cis* glycosylation. While stereoselective 1,2-*trans* isomers are obtained exploiting neighboring group participation effect of *C*-2 substituent, as for example carbonyl-bearing groups, the stereoselective synthesis of 1,2-*cis* glycosides is much more challenging.[56,58] Among several strategies to achieve this bond, intramolecular aglycon delivery is part of domino reactions in glycans, particularly for acetal moieties. Hindsgaul and Barresi introduced the concept of intramolecular aglycon delivery (IAD) and demonstrated it for the synthesis of β-mannosides using a mixed acetal tether.[59,60] The tethering was achieved by acid catalysed–using camphorsulfonic acid (CSA) or *p*-toluensulfonic acid (TsOH) - addition of the aglycon alcohol to an enol ether formed by the Tebbe reagent on a mannose-2-*O*-acetate.

Fairbanks *et al.*[61,62] reported the challenging formation of mixed acetal moiety from the reaction of isopropenyl ether and primary alcohols, which mainly led to the hydrolysis of the isopropenyl ether. To address this issue, they explored the use of *N*-iodosuccinimide (NIS) as an alternative electrophile for the formation of mixed acetals (ketals) **91**–**93** by iodoetherification of exomethylene compounds **87**–**89** which were in turn prepared from **84**, **85** and **86**, respectively (Figure 9A).[60]

p-Methoxybenzyl (PMB) is as a commonly used hydroxy-protecting group; it can be selectively removed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[63,64]

In 1994, Ito and Ogawa anticipated the mixed acetal formation by the reaction between 2-OPMB-protected mannosyl donor and alcohol acceptors under anhydrous conditions in presence of DDQ. The subsequent activation of the anomeric position (e.g., *via* thioglycoside) facilitated the transfer of an aglycon from the *p*-methoxybenzylidene acetal to the anomeric position, resulting in the desired stereoselective preparation of β-mannopyranosides.[60,65]

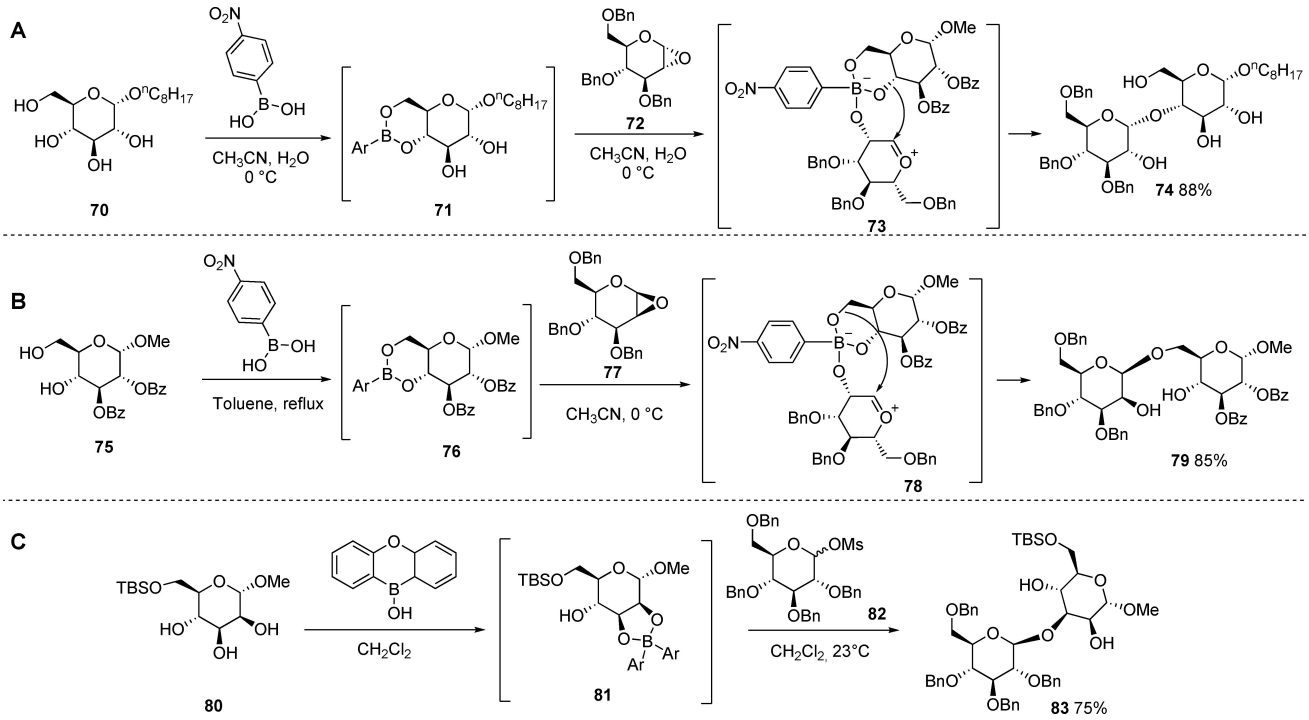

Figure 8. (A) Regio- and stereoselective glycosylation of unprotected α-glucoside acceptor with *p*-nitrophenylboronic acid catalyst in the presence of water. (B) Regio- and -stereoselective β-glycosylation between a C4-C6 diol glucosidic acceptor and a 1,2-anhydromannose. (C) Regio- and 1,2-*trans*- stereoselective glycosylation with glycosyl mesylate using a borinic acid catalyst.

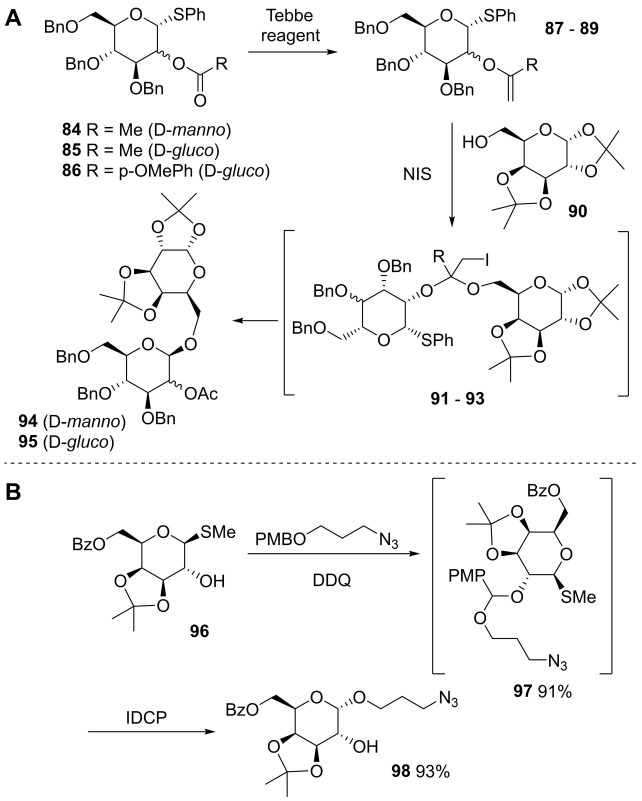

Figure 9. (A) Intramolecular aglycon delivery through 2-iodomethyl-1-methyl and 2-iodomethyl-1-(4-methoxyphenyl)-ketal tethered intermediates. (B) PMB-mediated domino glycosylation for α-galactopyranosides synthesis.

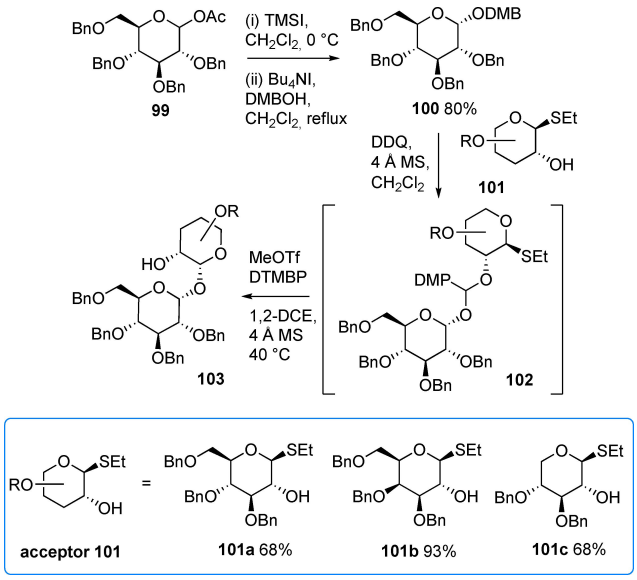

Figure 10. DMB-mediated domino glycosylation.

Field *et al.* applied PMB-assisted intramolecular aglycon delivery to the construction of the 1,2-*cis*-α linkage of galactopyranosides (Figure 9B).[66] Subsequent IAD was carried out using iodonium dicollidine perchlorate (IDCP), which was more effective than dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) or NIS in terms of stereoselectivity affording to the 1,2-*cis*-α-galactopyranoside **98** after acidic work-up, following the formation of the mixed acetal **97** by reaction between thiogalactoside donor **96** and PMB-protected 3-azido-1-propanol.

A cleverly designed synthesis of trehalose derivatives *via* IAD (Figure 10) was reported by Bertozzi *et al.*[67,68] The use of a dimethoxybenzyl (DMB) group proved advantageous over PMB in this case. Under *in situ* anomerization type conditions, the required α-glycoside **100** was obtained from the anomeric acetate **99** *via* glycosyl iodide. The mixed acetal **102** was obtained by coupling with 2-OH-released thioglycoside **101**. The 1,1-α glycosidic linkage of **103** was constructed by subsequent activation with MeOTf/DTBMP (2,6-di-*tert*-butyl-4-methylpyridine). The DMB-assisted domino glycosylation was effectively applied to the stereospecific synthesis of the glucosyl-, galactosyl- and xylosyl-trehalosides of **101 a**, **101 b** and **101 c**, as well as *Mycobacterium tuberculosis* sulfolipid-1.[69]

Meanwhile, the use of the 2-naphthylmethyl (NAP) group as a tether was found to be and extension of DMB and PMB based strategy.[70–73] To explore the application of this strategy to α-Glc formation, the 2-*O*-NAP-linked thioglucoside **104** was used. The mixed acetal was readily formed both from the 2-*O*-NAP-linked glucose donor **104** and glucose acceptor **105**, and from the 2-*O*-non-linked donor **106** and 2-*O*-NAP-linked acceptor **107** (Figure 11A). Afterward, the intramolecular glycosylation of mixed acetal **108** resulted in the formation of the desired 1,2-*cis* glycoside. Following acid treatment and acetylation, the product was isolated as pentaacetate **109**.[60,74–77] The same approach was employed by Ito and colleagues for the obtainment of 1,2-*cis*-glycosidic linkages on mannosides substrates. Upon DDQ-mediated activation of NAP-protected thiomannoside donor (**110**), the mixed acetal **112** was obtained and in turn converted into the final products using different acceptors (**111 a-c**, Figure 11B). In the same work, the stereoselective synthesis of the tetrasaccharide β-D-mannopyranosyl-(1–4)-β-D-xylopyranosyl-(1–4)-β-D-mannopyranosyl-(1–4)-β-D-xylopyranoside, proposed as the structural component of the novel natural antifreeze xylomannan, was reported.[78,79] Until now, we have explained the use of specific ether and thiol leaving groups to obtain the desired stereoselectivity of the glycosidic bond, how the orthogonality of the donor leaving group could allow the carbohydrate research to be more attractive and efficient thank to the domino reaction on oligosaccharide synthesis, very common substrates in automated synthesis.[80]

In 2019, it was reported that the orthogonal one-pot glycosylation strategy using glycosyl *ortho*-alkynylbenzoates (ABz) can be effectively applied to synthesize various glycans.[81] This approach addresses several issues such as aglycon transfer, presence of interfering species, and unpleasant smell associated with the orthogonal one-pot glycosylation with thioglycosides.[82,83] Subsequent investigations explored whether glycosyl polyvinyl butyral (PVB) could be selectively coupled with other bifunctional acceptors during the activation of NIS and trimethylsilyl trifluoromethanesulfonate (TMSOTf). Notably, due to the significantly higher reactivity of glycosyl PVB compared to thioglycosides,[84] the desired disaccharide was

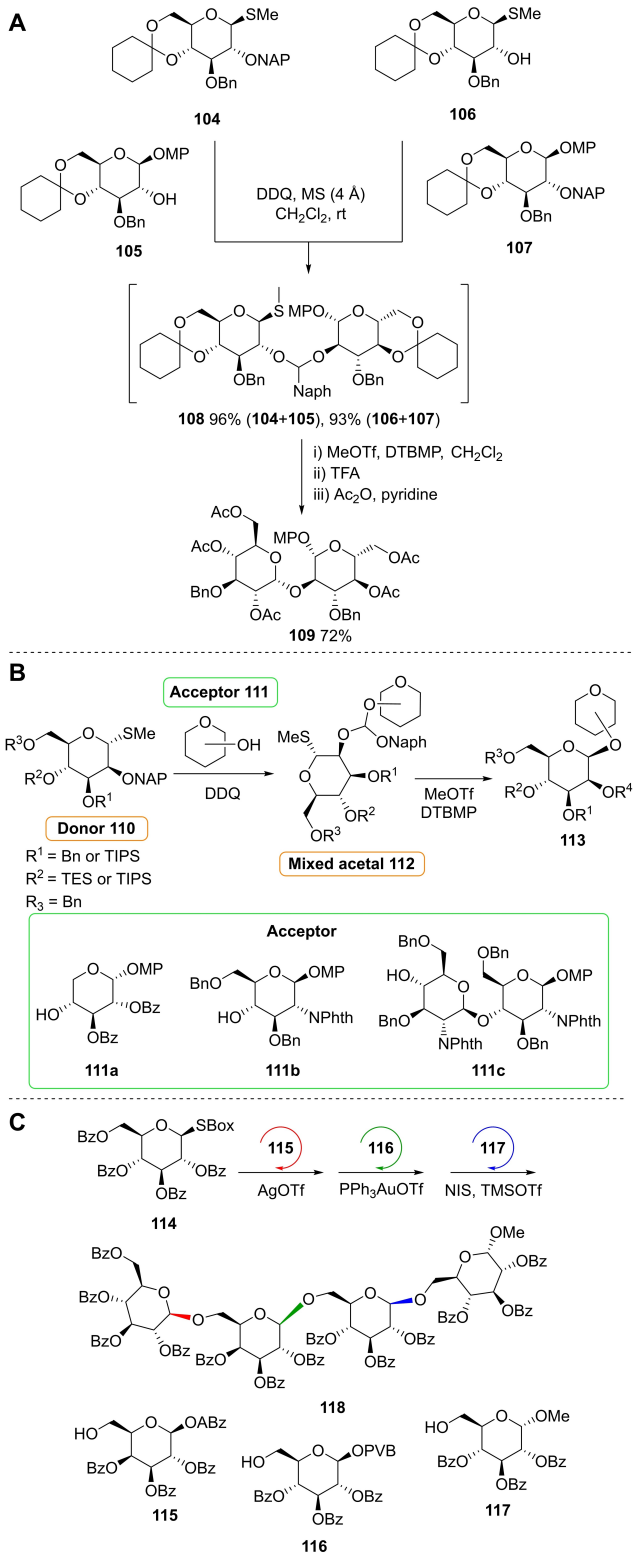

Figure 11. (A) NAP mediated domino glycosylation for α-glucopyranoside synthesis. MP: *p*-methoxyphenyl. (B) NAP-ether mediated domino 1,2-*cis* glycosylation. (C) SBox, OABz, OPVB group domino glycosylation reactions.

indeed obtained in an excellent yield.[85] Similarly, for a group of SBox- (**114**), ABz- (**115**) and PVB-glycosydes (**116**), orthogonal one-pot glycosylation efficiently provided the PVB trisaccharide, which was then joined with the and α-OMe glucosyl acceptor **117** in the presence of NIS and TMSOTf at 15 °C, producing the tetrasaccharide **118** in 65 % yield (Figure 11C).

Numerous examples of orthogonal one-pot reactions for synthesizing long oligosaccharide chains have been reported by Kulkarni and colleagues.[86] Specifically, domino reactions involving α-OMe or thioglucosides, which are properly manipulated to have the appropriate acceptor or donor, are essential for performing domino glycosylations in long oligosaccharide synthesis. Among these, stannylene chemistry is particularly interesting for domino reactions, as it allows the manipulation of simple building blocks to regioselectively protect a specific hydroxyl group with benzyl or allyl ether. The resulting oligosaccharides are biologically-relevant molecules, and the domino approach for their synthesis is an inspiring method for solid or solution phase automated synthesis.[87,88]

A very recent technique called cut-insert stitch-editing reaction (CISteR) is a final example of glycoside domino reactions.[89] Post-synthetic surgical editing enables the synthesis of diverse molecules from a shared scaffold. However, the insertion of a foreign glycan into carbohydrates remains a distant objective for synthetic chemists. In this study, a domino chemical approach was used to edit glycoconjugates. It consists of three steps: the first step cleaves one of the inner glycosidic bonds where the corresponding oxacarbenium ion is treated to react in turn (second step) with an aglycon containing an orthogonally activatable ethynylcycloxyl carbonate group; the third step involves the joining of the chains through the activation of the carbonate donor. The CISteR protocol allowed for the incorporation of both branched and linear arabinofuranose glycan from *M. tuberculosis* cell wall in a trimannoside chain.

The importance of carbohydrate chemistry is now recognized worldwide. However, making oligosaccharide synthesis attractive remains challenging due to lengthy synthetic routes and complex coupling reactions. Automation aims to make these reactions more reproducible on different scales, with the choice of protective groups being crucial. For example, Fmoc is highly effective in terms of orthogonality with the glycosylation reaction and is commonly used for solid-phase oligosaccharide synthesis. The ability to use orthogonal protective groups that can participate in glycosylation reactions will promote regioselective glycosylation, leading to the one-pot formation of long oligosaccharide chains. The introduction of the intramolecular aglycon delivery strategy, utilizing suitable mixed acetal-tethers, has significantly improved the preparation of complex glycosidic bonds, including the challenging synthesis of β-mannosides. Domino approaches for generating complex and long oligosaccharide chains are gaining attention for creating synthetically relevant carbohydrates, particularly for developing semisynthetic anticancer agents[90–92] and carbohydrate-based vaccines.[93–95] Research into faster and cleaner chemical strategies is essential to address this crucial task.

4. Domino Reactions on *N*-Glycosides

N-glycosides serve as suitable substrates for a wide range of domino sequences, typically leading to the synthesis of biologically relevant molecules. Glycosyl azides are extensively employed in the synthesis of glycomimetics, which exhibit diverse biological properties. Additionally, they represent valuable tools for exploring biochemical events associated with natural glycoconjugates. In 2014 and 2015, Bellucci and coworkers reported an efficient multicomponent domino reaction for the synthesis of glycopeptide mimics starting from azido or amino sugars, aiming to bypass existing multi-step synthetic routes (Figure 12A). This methodology enables the easy introduction of structural diversity and the generation of diverse compound libraries at reduced costs, thereby facilitating the discovery of new bioactive compounds. Firstly, the author focused on the regioselective synthesis of *N*-glycosyl conjugates (Figure 12A) using amino sugars as precursors, together with fumaric acid monoester and carbodiimides. The beginning of the domino sequence corresponds to the reaction between fumaric acid and the carbodiimide to obtain **121**. An intramolecular aza-Michael cyclization leads to the formation of cyclic *O*-acylisourea **124**.

This intermediate demonstrates to be reactive towards nucleophilic attack of glycosyl amines, with subsequent ring opening and generation of glycoconjugate **127**. A set of variously protected *N*-glycosylamines and *N*-glycosyl azides (previously reduced *in situ* by a Staudinger reaction) were used to investigate and optimize the reaction conditions, together with different substituted carbodiimides.[96] With the aim to generate fluorinated versions of glycopeptide mimics, which modulate the biophysical and pharmacological properties of the target compounds, the authors explored a similar methodology starting from glycosyl azides and substituted isocyanates. 4,4,4-trifluoro-3-trifluoromethyl-crotonic acid and nucleophilic amines were used to generate hexafluorovaline glycomimetics (Figure 12B). The domino reaction proceeds similarly to the already described procedure from amino sugars and involves the first formation of the sugar carbodiimide **132** that reacts with the carboxylic acid with subsequent cyclization, affording compound **134**. The last step depends on the presence of the nucleophilic amine that furnishes the product **136**. In its absence, compound **134** undergoes an *O*/*N*-acyl migration rearrangement, leading to the formation of the hydantoin derivative **135** (Figure 12B). As a natural consequence in this field, multivalent presentations of these types of glycomimetics were synthesized by adding a second amino sugar moiety as the nucleophilic partner for the ring opening reaction, affording aminoglycoside derivative **137**. This methodology could be applied for the preparation of new functionalized aminoglycosides.[97,98] Glycosyl ureas and glycosyl amides could be synthetized by alternative convenient one pot processes. For glycosyl ureas, the reported common methodologies furnish α/β mixture and require multiple steps. The stereoselective one pot domino method developed by Bernardi *et al.* allows to easily obtain α-glycosyl ureas starting from α-azido sugars in good yields (Figure 13). The reaction implies the reduction of

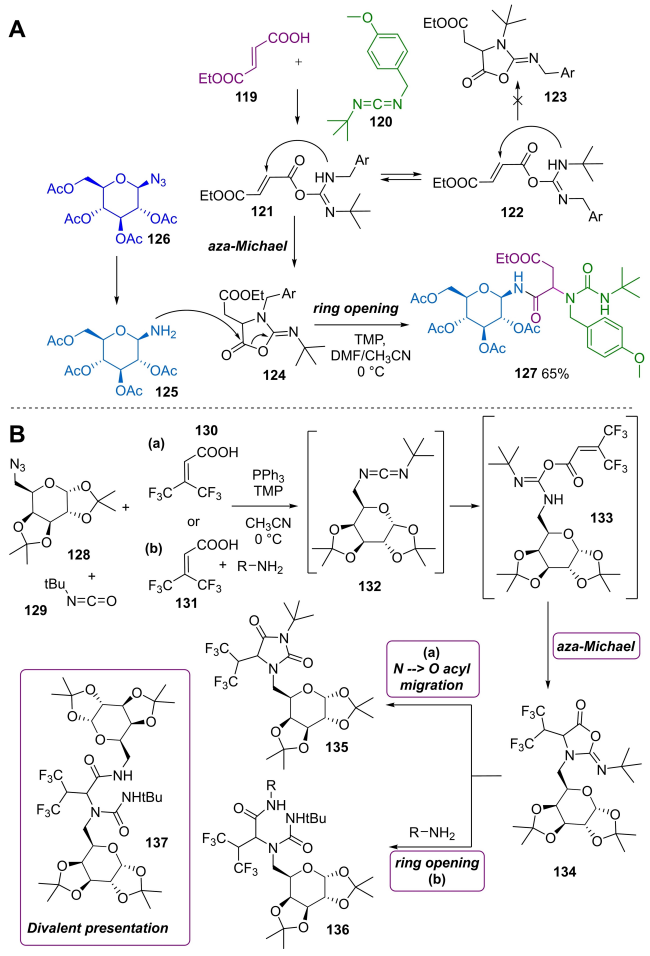

Figure 12. (A) Multicomponent domino reaction on glycosyl amines for the synthesis of glycopeptide mimics. TMP: (2,4,6-trimethylpyridine). (B) Multicomponent domino reaction on glycosyl azides for the synthesis of glycopeptide mimics and their multivalent presentations.

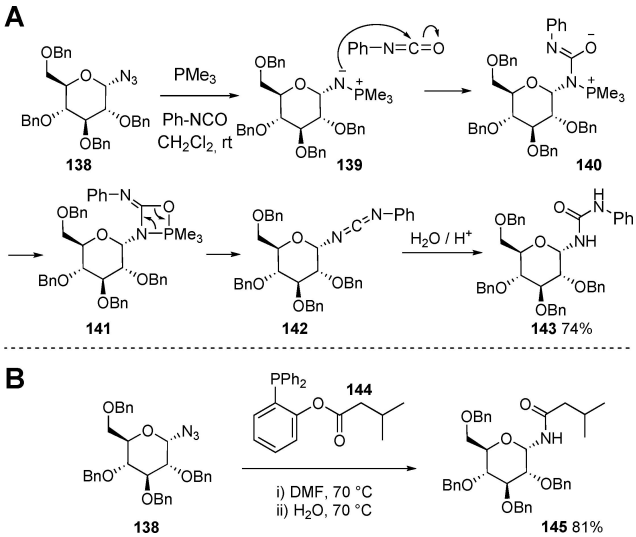

Figure 13. Synthesis of glycosyl ureas (A) and glycosyl amide (B) by one pot domino reaction.

glycosyl azide **138** by trimethylphosphine to form the corresponding iminophosphorane **139**, which reacts with the substituted isocyanate and furnishes the intermediate **140**. It evolves with the formation of the carbodiimide **142** and the release of the phosphine oxide. The desired urea derivative **143** is obtained by a final hydrolysis in acidic conditions (Figure 13A). The reaction was optimized for benzylated glucosyl- and galactosyl- azides using a set of substituted isocyanates.[99]

Glycosyl amide are useful tool for sugar mimic design. Their synthesis is easily accessible by traceless Staudinger ligation, which implicates the *in situ* reduction of azide function and subsequent acylation with activated carboxylic acids.[100–106] This methodology prevents anomeric equilibration problems observed for isolated glycosyl amine intermediates, due to the rapid formation of the amide linker. Optimization of the procedure could be achieved by using functionalized triaryl phosphines, that lead to a faster intramolecular trapping of the reduced azide with sequent acyl transfer and retention of configuration at the anomeric carbon (Figure 13B). The employed phosphines could be synthesized from (2-hydroxyphenyl)diphenylphosphine by an acylation step (compound **144**). This reaction is efficiently applied to azide derived from *O*-benzyl α-glucose, galactose and fucose, with good yields and stereoselectivity when in combination with polar aprotic solvents.[104] Despite the advantages of this method, the steric hindrance of the acyl group could slow down the acyl transfer step, limiting its use in some instances.

Over time, domino sequences were used to synthesize key intermediates for bioactive molecules involving *N*-glycosides. 1,2-Dihydropyridin-3-ones (Figure 14A) represent important precursors of imino sugar-based glycosidase antagonists, and their derivatives have been developed as nicotinic acetylcholine receptor ligands involved in Alzheimer's disease. The optimization of the synthesis of these building blocks through a domino approach allows to simply obtain a set of substituted 1,2-dihydropyridin-3-one analogues (Figure 14A). The employed azido furanose precursor **146** is firstly deprotected from the isopropylidene group by TFA (**147**) and then undergoes hydrogenation affording the corresponding amine **148**. This intermediate evolves into a six-membered hemiaminal **150**, an unstable intermediate due to the presence of the anomeric hydroxyl group that promotes the loss a water molecule and the formation of the imine species **151**. Isomerization to enol intermediate and tautomerization establishes the keto form (**153**), followed by the Boc protection (**154**) and the final acetylation with concurrent elimination of acetic acid and generation of the α,β-unsaturated ketone **155** (Figure 14A).[107]

The azido furanose substrate **146** can be also employed to generate δ-lactam-fused furanose derivative **156** (Figure14B), useful for the development of biologically relevant alkaloids. Staudinger reaction initiates the domino sequence, and the obtained amine intermediate (**145-I**) promotes an intramolecular cyclization through the nucleophilic attack at the carbonyl group and subsequent elimination of the ethoxy group. The *N*-acetyl derivative **156** can be obtained by the final addition of acetic anhydride to the reaction mixture (Figure 14B).[107]

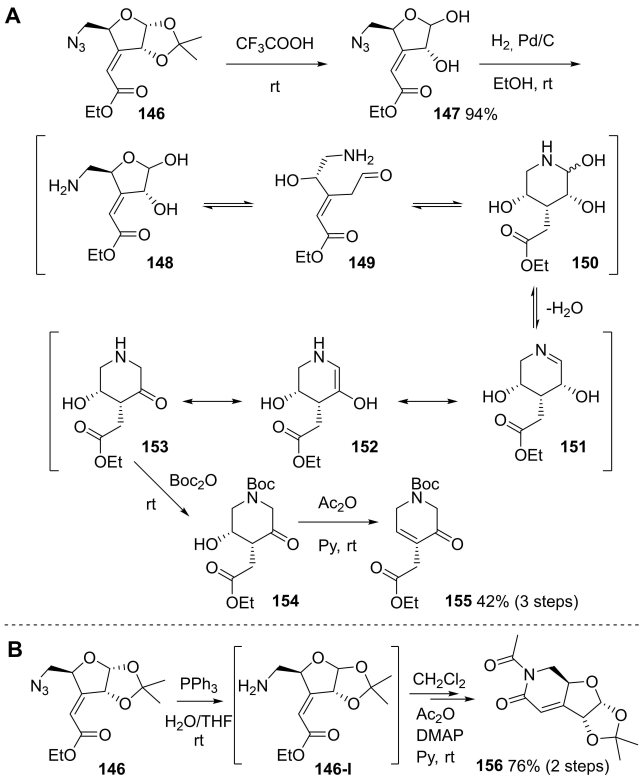

Figure 14. Tandem reactions from azido furanose of bioactive scaffolds (A) 1,2-dihydropyridin-3-ones and (B) α,β-unsaturated δ-lactam-fused furanoses.

Deoxy sugars also gain attention in the field of drug discovery, as important scaffolds for the development of macrolides and tetracycline analogues. Therefore, optimizing their synthesis is an important aspect from a medicinal chemistry perspective. Hwu and co-workers reported a new convenient method for the preparation of deoxy sugars from amino sugars through a reductive deamination domino reaction.[108] The reaction was tested on different amino mono- and di-saccharides, that were converted in thiazolidine-2-thione that reacted with benzyne furnishing the corresponding enol acetates. These intermediates were subsequently deprotected and subjected to a cyclization affording the desired deoxy sugar (Figure 15A). The domino reaction consists of three subsequent seps: 1,2-elimination, [3 + 2]-cycloaddition and a retro [3 + 2]-ring-opening reaction. The mechanism of the reductive amination showed in the Figure 15A implicates the first reaction between the benzyl amino group of **158**, previously prepared from the amino sugar **157** by the formation and reduction of the Schiff base, and the carbon disulfide. The formed thiazolidine-2-thione **160** undergoes a [3 + 2]-cycloaddition reaction with benzyne, synthesized *in situ* through a 1,2-elimination starting from 2-silylphenyl triflate, providing the intermediate **161**. The benzyne acts as reducing agent towards the carbon in position C2 of the sugar. The subsequent step involves a retro [3 + 2] ring-opening reaction, that leads to a cleavage of the C–O bond and formation of enol acetate **162**, with the contemporary loss of 2-imino-1,3-benzodithiole. At this point, sodium methoxide promotes the cleavage of the acetyl

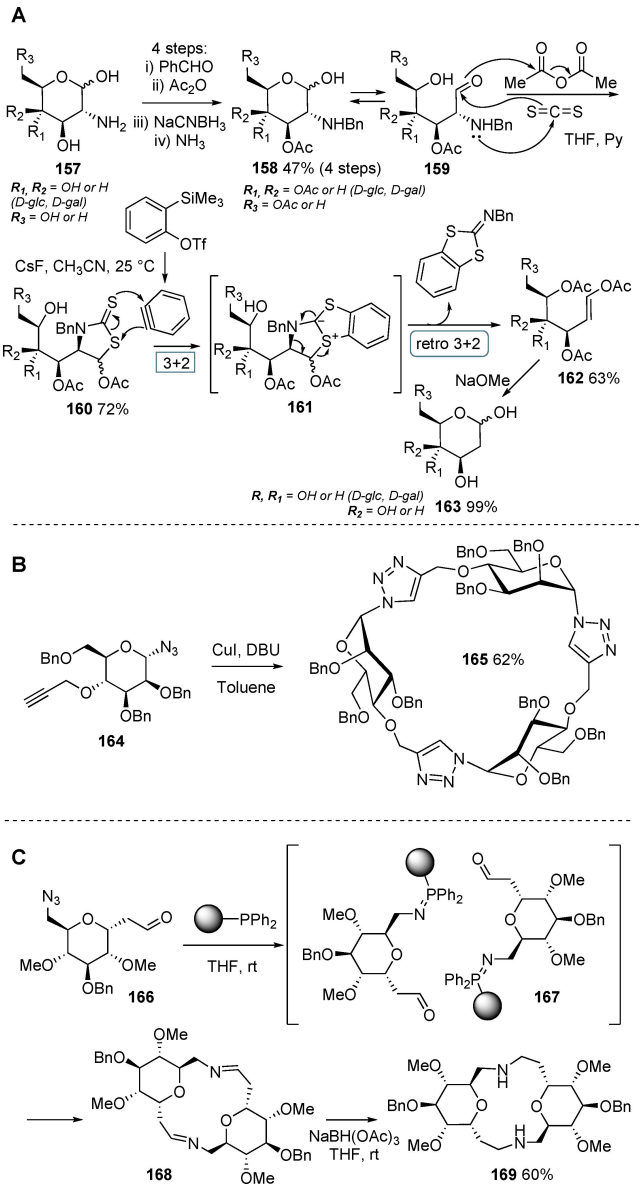

Figure 15. (A) Synthesis of deoxy sugars from amino sugars through a reductive deamination domino reaction. (B) Domino Huisgen cycloaddition on glycosyl azide for the synthesis of symmetrical cyclotrimer macrocycles; (C) Synthesis of sugar-aza-crowns *via* reductive amination or Staudinger/aza-Wittig reaction.

protecting groups and the cyclization to regenerate the endocyclic C–O bond (Figure 15A).[108]

Finally, glycosyl azide showed to be important tools for the generation of sugar-based macrocycles *via* domino approaches, which serve as scaffolds for supramolecular architectures. Gin *et al.* developed a convergent approach for the obtention of symmetrical cyclotrimer macrocycles (Figure 15B) by using a Huisgen reaction.[109] The monosaccharide precursor **164** features an anomeric azide and 4-propagyl ether function, which undergoes a domino cycloaddition reaction in CuI and DBU conditions, furnishing the cyclotrimer **165** in good yield (Figure 15B). The same reaction performed on the disaccharide led to the formation of the corresponding cyclodimer. In addition, further studies on the use of trisaccharides highlight the possibility to introduce selective functionalizations on the scaffold and diversify the nature of the synthetic macrocycles.[109]

Sugar-based macrocycles was also described in 2006 by Ménand *et al.* they reported the synthesis of sugar-aza-crowns (SACs) using an azido aldehydes derivative as starting reagent and exploiting a reductive amination or Staudinger/aza-Wittig domino reaction.[110] The proposed process (Figure 15C) results to be the first macrocyclization of *C*-glycosyl azido aldehyde **166** which combines a Staudinger reaction, performed using polymer-bound diphenylphosphine, together with an aza-Wittig step of the intermediate iminophosphoranes **167**. Final reduction leads to the desired SAC **169**, that could find application as complexing agent, building blocks in the synthesis of more complex structures, or as catalysts for asymmetric synthesis.

Given the synthetic potential of many glycomimetics through domino reactions on sugar-bearing azides, the interest in sugar-based macrocycles within the glycochemistry community is growing. It is important to emphasize the optimization process undertaken to achieve selective, regio- and stereodefined *N*-glycosyl conjugates, particularly α-glycosyl ureas, via domino reactions. The use of triaryl or trialkyl phosphine has improved the one-pot process to obtain glycosyl amides, which have significant biological applications. Similar and efficient approaches have been used to generate structurally diverse molecules, such as *N*-based heterocycles or more complex macrocycles, by exploiting the targeted reactivity of azido groups.

5. Domino Reactions on Glycals

Glycals are stable unsaturated sugar derivatives and play a versatile role in synthetic organic chemistry. Despite their stability and ease of manipulation as donor derivatives, these chiral building blocks exhibit remarkable reactivity, which enables both regio- and stereoselective transformations, for the synthesis of various natural products and their analogues, including oligosaccharides and complex natural products of biological significance.[111–114] The enol ether double bond in glycals makes these compounds challenging substrates for domino or tandem reactions. In this section, we present recent examples of domino transformations involving *endo*-glycals, primarily focusing on developments over the last decade. Specifically, this section covers the following aspects: new glycal-derived *O*-, *N*-, and *C*-glycosides, including the synthesis of vinyl, alkynyl-glycal derivatives and aryl/heteroaryl glycosides, the generation of novel sugar-derived scaffolds, as annulated and glycofused polycyclic structures and chiral furan derivatives, and the synthesis of glycal-derived structures which serve as chemical tools for chemical biology applications.

5.1. Transformations Delivering *C*- and *O*-Glycosides

The presence of a double bond in endoglycals makes them ideal substrates for electrophilic reactions, leading to the generation of *C*- and *O*-glycosides.

In 2013, Xue-Wei Liu *et al.* described a new strategy to achieve β-*C*-glycosides with a precise stereochemical control on 4,6-protected glycals, bearing a β-ketone ester group on C3 position (compound **170**, Figure 16A). This method involves a palladium-catalyzed decarboxylation of the C-3 ester of glycal, with a simultaneous cascade intramolecular *C*-glycosylation, by means of a formation of a Pd-π-allyl intermediate which accomplishes the desired *C*-glycoside with the desired stereoselectivity.[115] Diverse Pd catalysts and ligands were screened, and the best results in terms of yield and stereoselectivity were obtained with $Pd(OAc)_2$ and bis(diisopropylphosphino)ferrocene (DiPPF, Figure 16A). The substrate scope was achieved by varying the protecting groups on the C4 and C6 position of the glycal, as well as installing different β-ketoesters on the C-3 position. The practical applicability of this transformation was further showcased through the formal total synthesis of aspergillide A.

In 2014, the same researchers employed a similar strategy for the synthesis of *O*-glycosides using palladium-catalyzed decarboxylative allylation (DcA) (Figure 16A).[116] Starting from carbonate-derived glucal (compound **172**, Figure 16A), various *O*-glycosides (including phenolic, aliphatic, and di/trisaccharide derivatives) were formed via a palladium-catalyzed tandem reaction involving decarboxylation, proton abstraction, and nucleophilic addition. These reactions yielded moderate to good yields with excellent selectivity. In a previous work by the same authors, they investigated a regio- and stereoselective intramolecular β-*O*-glycosylation reaction using palladium-catalyzed decarboxylative *O*-glycosylation on 3-*O*-carbonate-derived glycals. In this case, the nucleophilic acceptor was located on the carbonate group at the C3 oxygen of the glycal donor, accomplishing the intramolecular *O*-glycosylation.[117] In their article of 2014, the optimized reaction conditions facilitated the generation of new *O*-glycosides using an external nucleophilic acceptor that participated in the domino reaction mechanism (as depicted in Figure 16B). The release of CO_2 during the reaction represents the driving force allowed for the formation of fast and efficient Pd-π-allyl species from carbonate substrates, as mentioned in.[117] The efficacy of the method was further demonstrated through the iterative synthesis of a trisaccharide.

In 2014 Xia *et al.* introduced a domino strategy for synthesizing 2-amino-2-deoxyglycosides,[118] which are common glycosides in biological systems, where are linked to lipids, amino acids, or glycans through 1,2-*cis* or 1,2-*trans* glycosidic bonds. Synthetic methods delivering 2-amino-2-deoxysugars and the respective 2-acetamido derivatives are of particular interest in organic and medicinal chemistry; in fact, these sugars play a crucial role in drug development and chemical biology, due to their ability to interact and interfere with many biological processes associated with particular pathological states, such as cell adhesion and proliferation, inflammation, and tumor metastasis.[119,120] While established methods often rely on activated species of protected or masked 2-amino-2-deoxysugar donors, researchers have also explored glycals as building blocks for 2-amino-2-deoxyglycoside synthesis over the years. These glycals participate in cycloaddition reactions with nitrogen donor active compounds. However, achieving stereoselectivity and addressing further derivatization challenges remain ongoing pursuits. In this context, the work of Xia *et al.* aimed to the preparation of this glycosides *via* C2-amidoglycosylation reaction, exploiting a regio- and stereoselective cascade mechanism initiated by the sterically hindered, *N*-centered benzenesulfonimide radical generated by the reaction between NFSI reagent (*N*-fluorobenzenesulfonimide) and TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) (Figure 17). The generated *N*-centered radical **178** can attack regioselectively and in an electrophilically mode the glycal double bond, to give a radical intermediate **180** on the anomeric carbon. The latter undergoes a transformation into the respective oxocarbenium ion intermediate **181** by reacting with the oxidized form of $TEMPO^+$. Finally, the oxocarbenium intermediate reacts with nucleophilic acceptor to give the 1,2-*trans* directed glycosylated product **182**; the stereoselectivity is ensured by the hindrance of the benzenesulfonimide and/or the neighbouring effects of the sulfonyl group. Various glycal donors and acceptor monosaccharides have been tested to demonstrate the wide scope of the approach. Furthermore, the disulfonyl group can be converted to an acetyl group in a one-pot process, through the

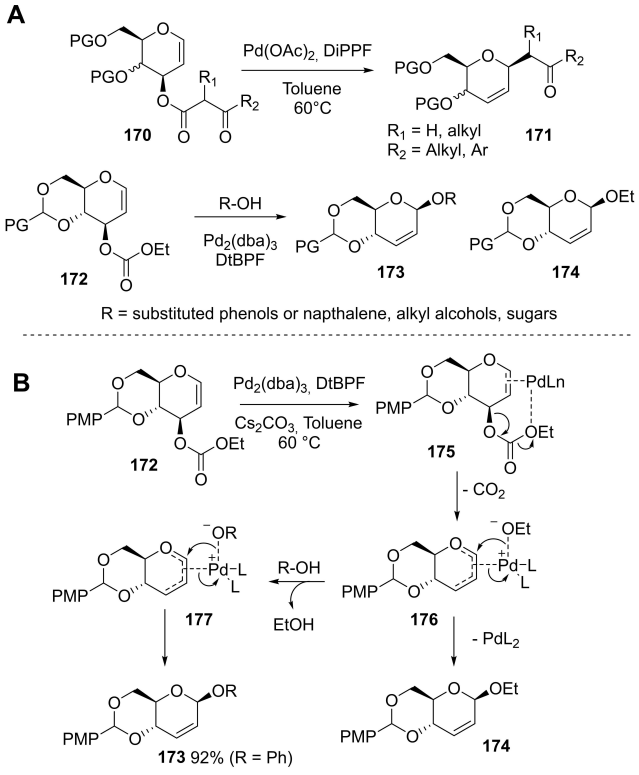

Figure 16. (A) Synthesis of β-*C*-glycosides and β-*O*-glycosides through palladium-catalyzed domino decarboxylation (DcA), as reported by Xue-Wei Liu in 2013 and 2014. (B) Proposed mechanism of the domino reaction for the synthesis of *O*-glycosides.

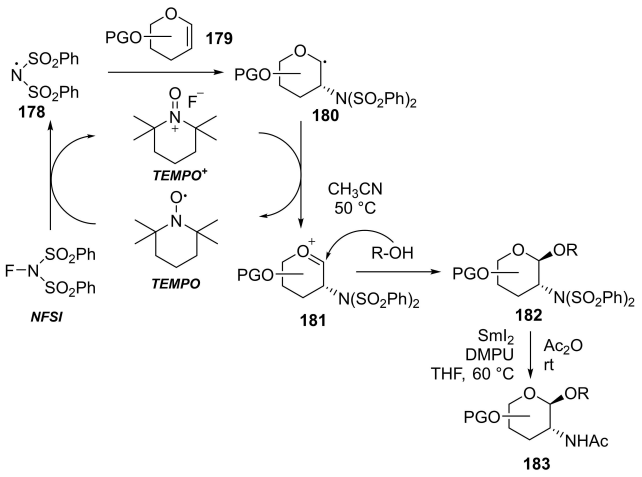

Figure 17. Synthesis of 2-amino-2-deoxyglycosides by domino reaction mediated by nitrogen-centered radical species and conversion of disulfonyl group into acetyl group in a one-pot process for the preparation of 2-deoxy-2-amidoglycosides.

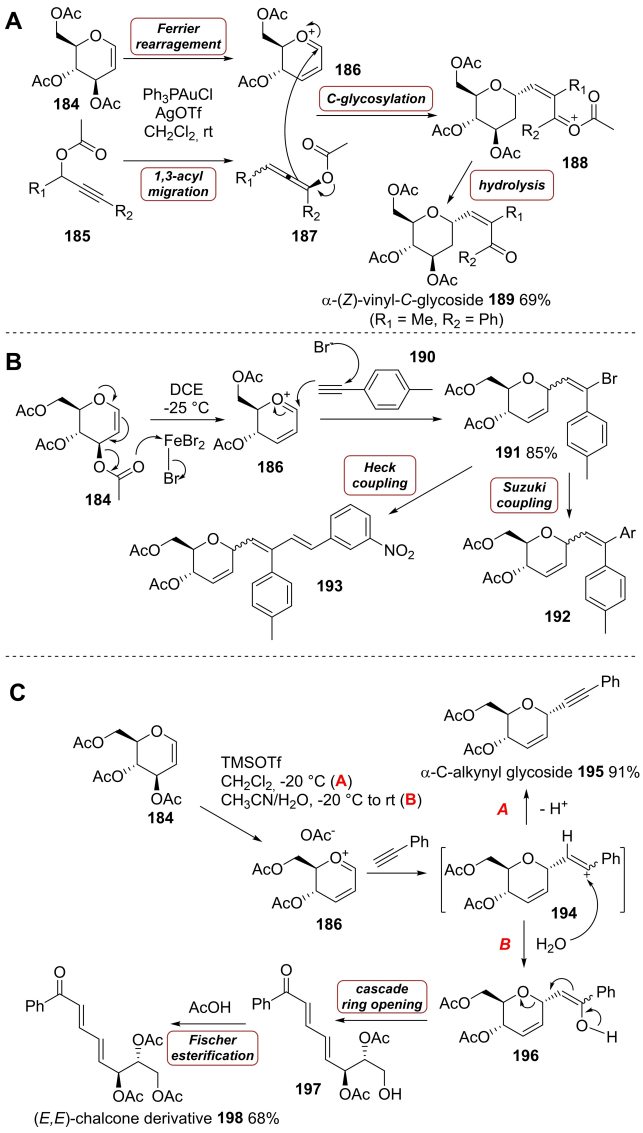

Figure 18. (A) Synthesis of *C*-vinyl glycosides *via* gold(I)-catalyzed tandem 1,3-acyloxy migration/Ferrier rearrangement reported by Xue-Wei Liu *et al.* in 2018. (B) Synthesis of halo-*C*-vinyl glycosides by domino pathway from glycals and unactivated arylacetylenes and plausible mechanism as reported by Mukherjee's group in 2013. (C) Domino transformation of glycals, with arylacetylenes into α-*C*-alkynyl glycosides **195** and optical pure α,β,γ,δ-conjugated chalcone derivatives **198**.

action of SmI_2 and a following treatment with acetic anhydride, delivering 2-deoxy-2-amidoglycosides (**183**) (Figure 17).

Recent research has explored the synthesis of anomeric vinyl and alkynyl *C*-glycosides using a domino pathway initiated from glycal sources. Notably, in 2018 Xue-Wei Liu and colleagues reported a gold(I)-catalysed diastereoselective synthesis of α-*C*-vinyl glycosides - essential motifs found in pharmaceuticals and natural products.[121] The reaction involves a reaction between an allenic ester intermediate species **187**, which serves as the activated form of propargylic ester glycosyl acceptor **185** and glycal **184**. Of the two proposed pathways for the reaction, the one that yields to vinyl-*C*-glycoside product **189** involves a Ferrier-type rearrangement. This results in an allylic carbocation intermediate on the glycal donor, followed by an electrophilic attack on the allenic intermediate formed through an intramolecular 1,3-acyloxy migration occuring on the propargylic ester acceptor. Experimental results led to obtain vinyl-*C*-glycosides with high α-selectivity and *Z*-selectivity. It is suggested that the gold catalyst (PPh_3AuOTf, generated *in situ* from PPh_3AuCl/AgOTf) serves as promoter both promoting the Ferrier rearrangement to form an allylic oxocarbenium ion on the glycal and facilitating the transformation of propargylic carboxylate into a nucleophilic allenic intermediate (Figure 18A).

In 2013, Mukherjee's group conducted a study focused on the synthesis of *C*-vinyl-glycosides, involving the halogenated Lewis acid-promoted tandem glycosylation–halogenation of inactivated aryl acetylenes with glycals.[122] The team hypothesized the use of metal halogen reagents that act as both Lewis acids and nucleophilic halide sources. Their proposed cascade reaction involves the formation of a glycosyl oxocarbenium ion intermediate and an *anti*-addition of the glycosyl cation and a halide ion across the alkyne, leading to the creation of a new path to trisubstituted halo-vinyl glycosides. Reactions between tri-*O*-acetyl-D-glucal **184** and *p*-methylphenyl acetylene **190** in the presence of $FeBr_3$ at low temperatures yielded the desired brominated *C*-vinyl glycoside **191** in 85% yield and good stereoselectivity ($E\alpha{:}E\beta = 11{:}1$). The use of $FeCl_3$ instead of $FeBr_3$ led to the corresponding vinyl chloride *C*-glycosides. The substrate scope was then extended to include various phenylacetylenes and different glycals. The proposed mechanism involves the elimination of the allylic acetoxy group and the subsequent attack on the glycosyl oxocarbenium ion by aryl acetylenes. The first step is represented by the coordination between the metal salt of the Lewis acid and the allylic acetoxy group of the glycal, making it more labile; next, the ring oxygen in the glycal participates in the mechanism, generating the glycosyl oxocarbenium ion intermediate **186**. Finally, the alkyne **190** attacks the intermediate from the α-face, while concur-

rently, a halide ion attacks the triple bond, generating the brominated *C*-vinyl glycoside **191** (Figure 18B).[122] The obtained stereo-defined α,*E*-trisubstituted halo vinyl glycosides were then applied as substrates in Pd-catalyzed cross-coupling chain elongation steps, as Suzuki and Heck reactions.

The synthesis of alkynyl *C*-glycosides, as intermediate for the synthesis of α,β,γ,δ-conjugated structures was the subject of a work by the same group in 2014.[123] The authors developed a new metal-free domino process for the conversion of glycals into α-*C*-alkynyl glycosides and diastereoselectively pure α,β,γ,δ-conjugated (*E,E*)-chalcone derivatives. The synthetic strategy was based on their previous works involving copper-mediated synthesis of *C*-alkynyl glycosides[124] and the above-mentioned work on preparation of halogenated vinyl *C*-glycosides.[122] They proposed that water might function as a nucleophile instead of halogens, targeting the benzylic position to create vinyl glycosides containing an enol unit. These glycosides could subsequently undergo tautomerization to a keto form, ultimately resulting in ring-opening and the production of alcohols. To validate this hypothesis, they re-examined the reaction between glycals and acetylenes using a non-halogenated Lewis acid (TMSOTf) and water in acetonitrile at −20 °C, which led to the obtainment of a alkynyl glycosides **195** (path A, Figure 18C) as well as (*E,E*)-chalcone derivatives **198** through a successful ring-opening process (path B, Figure 18C). A proposed mechanism for the formation of the open-chain product involves the creation of an oxocarbenium ion from the glycal substrate through TMSOTf-mediated elimination, followed by nucleophilic attack by water molecule and subsequent ring-opening cascade reactions leading to final chalcone derivatives.

The synthetic domino approach using glycals is the goal of several works aimed at the preparation of aryl and heteroaryl glycosides. One example is the work of Tang and coworker in 2018, in which a stereocontrolled, two-step tandem synthesis of α- and β-2-deoxy-*C*-aryl glycosides starting from glycals and aromatic amines was reported.[125] *C*-glycopyranosyl arenes are important building blocks in the development of biologically active compounds and drugs due to their intrinsic stability. The authors reported a new protocol based on the use of palladium-catalyzed Heck-type cross-coupling reactions. Initial experiments with various palladium catalysts identified $Pd(dba)_2$ as the most effective one, yielding α-*C*-glycosides **200** in satisfactory yields. The mechanism of the two-step domino transformation involved the formation of α-*C*-glycosides through C–C bond formation and their subsequent anomerization to β-*C*-glycosides **203**, through activation of the oxocarbenium ion by HBF_4 (Figure 19A).

In addition to the classical aryl glycosidations, domino reactions involving glycals are also harnessed for creating more complex and different structures, including biaryl glycosides and heteroaryl glycosides. A notable instance of this approach emerged from a 2015 study conducted by Mukherjee's research group.[126] They introduced a novel method for synthesizing vicinal diaryl glycosides using C1-C2 glycals **204** and C2-C3 glycals **205** as starting materials. The domino reaction is catalysed by palladium diacetate and mediated by TEMPO as a radical initiator and oxidizing agent (Figure 19B). The process

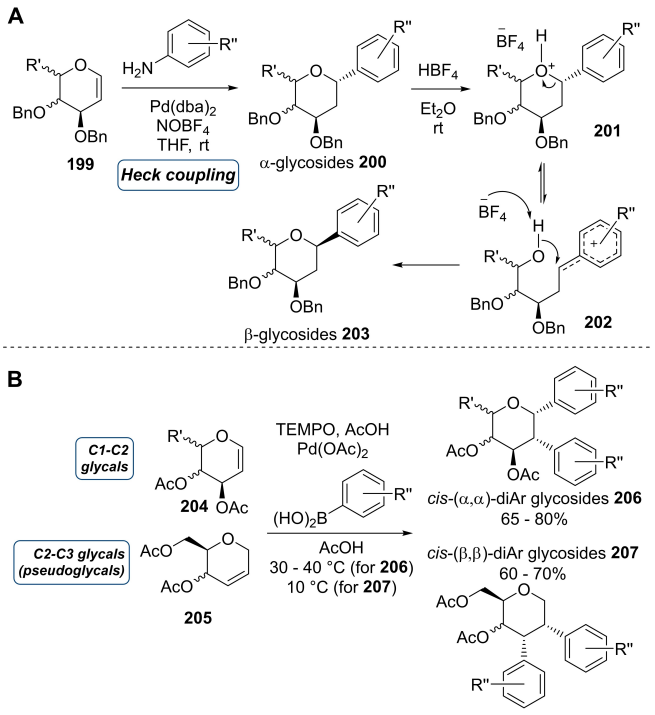

Figure 19. (A) Stereocontrolled/two-step tandem synthesis of 2-deoxy-*C*-Aryl glycosides using glycals and aryl amines reported by Tang *et al.* in 2018. (B) Vicinal diarylation of glycals and pseudoglycals through domino Heck – Suzuki arylation described by Mukherjee group in 2015.

involves a Heck-Suzuki arylation with aryl boronic acids. When tri-*O*-acetyl-D-glucal or galactal derivatives reacted with substituted phenylboronic acids, the corresponding *cis*-(α,α)-1,2-diaryl glycosides **206** were obtained in satisfactory yields. The same reaction was extended to pseudoglycals **205** (glycals with unsaturation on C2-C3 position); in this case the *cis*-(β,β)-2,3-diarylated glycoside **207**, with an opposite stereochemistry on C2-C3 positions was obtained.

Very recently, J. Liu and coworkers reported an interesting example of structurally diverse indolyl-*C*-glycosides synthesis *via* a domino reaction route.[127] Indolyl-*C*-glycosides represent a significant subclass of *C*-glycosides due to their biological relevance and stability. While traditional methods exist for synthesizing this class of compounds, recent advancements have turned to palladium-catalyzed C–H glycosylation. However, these methods often involve directing groups, leading to additional synthetic steps, as extensively discussed in a very recent review article.[128] In their study, Liu and colleagues achieved the desired indolyl-*C*-glycosides **210** and **211** through a palladium-catalyzed aminopalladation and subsequent Heck glycosylation, on readily available 2-alkynylanilines and D- or L-glycals. The proposed plausible catalytic cycle involves the formation of an active Pd(II) catalyst, its coordination by the triple bond of 2-alkynylaniline (intermediate **213**), a next intramolecular *trans*-nucleopalladation to create an indolyl-palladium intermediate **214**, and the key regioselective step of insertion across the double bond of the glycal (Figure 20).

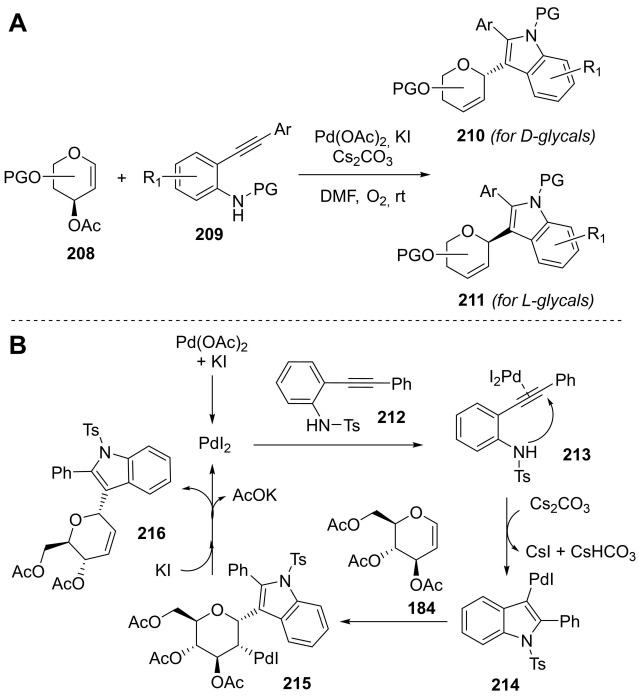

Figure 20. (A) Synthesis of indolyl-*C*-glycosides by domino aminopalladation and Heck glycosylation of 2-alkynylanilines with glycals, reported by Xiao *et al.* in 2023, and (B) scheme of the reaction mechanism as proposed by the authors.

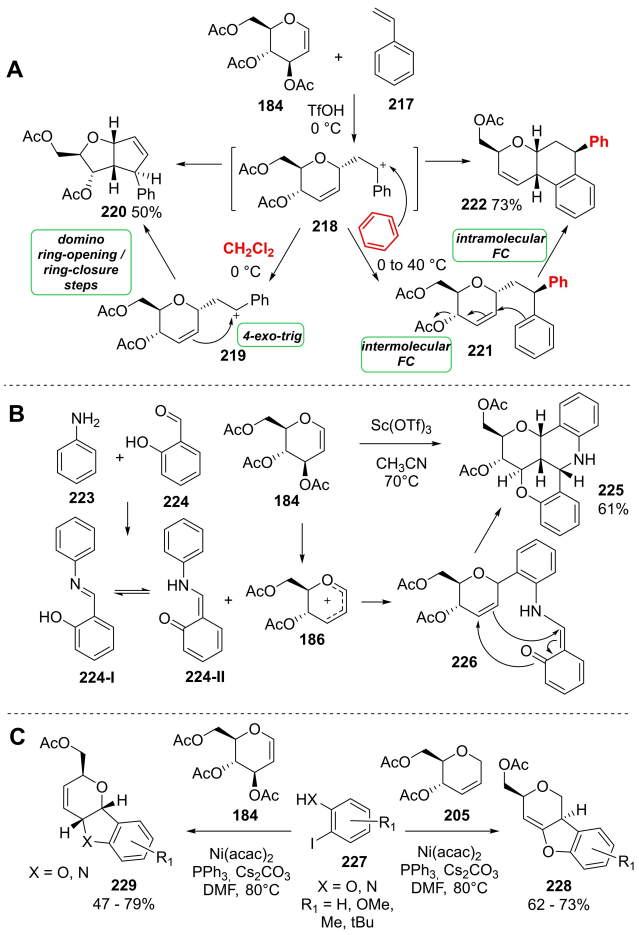

Figure 21. (A) Chiral *cis*-cyclopentanofuran **220** and *cis*-oxadecalin **222** scaffolds prepared by Bhardwaj in 2019 (B) Synthesis of benzopyran-fused pyranoquinolines and proposed reaction mechanism. (C) Ni-catalyzed synthesis of pyrano-fused heterocycles from C1-2 or C2-3 glycals.

5.2. Generation of Novel Glycal-Derived Scaffolds

Another noteworthy aspect of applying domino reactions to glycals lies in their capacity to create novel chemical scaffolds. These reactions paved the way for structurally diverse and complex compounds. Specifically, the endocyclic double bond within glycals lends itself to domino cyclization reactions, resulting in polycyclic and fused sugar derivatives. Remarkably, this process preserves the stereochemical integrity of the original glycal.

5.2.1 Polycyclic Structures

In a work of 2019 by Bhardwaj et al, the authors highlighted a novel domino reaction that combine glycals with styrenes to create chiral oxabicyclic scaffolds, specifically chiral cyclopenta[*b*]furans and oxadecalins (compounds **220** and **222**, respectively, Figure 21A).[129] Authors explored the possibility of using styrene, a weak nucleophile, to react with glycals in the presence of Lewis acids. Aside from the use of halogenated acids like $FeCl_3$ and $FeBr_3$, which yielded diastereomeric mixtures, non-halogenated acids as TfOH at low temperatures led the formation of a novel polycyclic sugar derivative. A different isomeric outcome of the reaction was observed in dependence to the solvent used: cyclopenta[*b*]furan derivatives were obtained using dichloromethane, whereas aromatic solvents led to the formation of oxadecalins. The reaction mechanism starts with the Lewis acid-mediated activation of glucal **184**, resulting in the formation of an oxocarbenium ion. Subsequently, styrene **217** preferentially attacks from the α-side, leading to the creation of a Ferrier *C*-glycosylation product **218**, bearing a stable benzyl carbocation. In the presence of contributing solvents like benzene or toluene (which serve as external nucleophiles), this intermediate can undergo a double cascade Friedel-Crafts (FC) reaction, resulting in the formation of densely chiral benzofused oxadecalins. Conversely, when dichloromethane is employed, unprecedented intramolecular cyclization steps occur, through a first 4-*exo*-*trig* intramolecular cyclization followed by a ring-opening/ring-closing sequence, which generates *cis*-cyclopentanofurans (Figure 21A).

The 2016 study by Moshapo et al. aimed to achieve the synthesis of polycyclic sugar-based frameworks using a domino reaction sequence starting from glycals. Specifically, the authors focused on creating a library of pentacyclic benzopyran-fused pyranoquinolines through a one-pot reaction catalyzed by $Sc(OTf)_3$,[130] using *in situ* generated dienophile-hydroxybenzaldimine tether **226** (Figure 21B). In their initial endeavor, the researchers aimed to synthesize a tricyclic pyranobenzopyran adduct by employing tri-*O*-acetyl-D-glucal **184**, aniline, and salicylaldehyde in acetonitrile with Lewis acid catalysts. How-

ever, the reaction did not proceed as expected. Subsequently, they modified the reaction conditions, and upon heating to 70 °C with a $Sc(OTf)_3$ catalyst, an unexpected pentacyclic adduct formed. According to the authors' hypothesis, the process involves a domino Ferrier rearrangement and a stepwise intramolecular cyclization. In particular, one of the steps is based on a modified version of the Povarov reaction, a synthetic method commonly used to create tetrahydroquinolines. This process was previously exploited by the same research group in a previous work.[131] Initially, an imino phenol **224-I** is formed by the condensation between aniline **223** and salicylaldehyde **224** (Figure 21B). This compound exists in equilibrium with the corresponding enaminone **224-II**, that reacts with $Sc(OTf)_3$-activated glucal **184-I**, leading to the formation of the α-tethered intermediate **226**. The final pentacyclic scaffold **225** is then formed through an intramolecular ring formation between the sugar alkene and the aromatic tethered moiety.

In a recent study conducted by the Mukherjee lab, a novel one-pot method for the preparation of pyrano-fused heterocycles has been reported (Figure 21C).[132] These heterocycles include both *cis*-fused dihydrobenzofurans and indoles, which hold significant value in the production of pharmacologically active compounds and complex natural products, such as Chafuroside A (an anti-inflammatory natural product), Medicarpin, a natural antifungal, or the drug Edotolac. The synthesis involves a domino pathway catalyzed by a nickel catalyst. This efficient process allows for the delivery of pyrano-fused heterocycles **228** and **229** from unsaturated enopyranoses (both C1-C2 and C2-C3 glycals, **184** and **205**) and *o*-iodo phenols/anilines **227**, with excellent chemo-selectivity (Figure 21C). The use of nickel catalyst in this context offers several advantages over the traditionally employed palladium catalyst. Specifically, nickel is a more sustainable metal, making it an environmentally friendly choice, and is cost-effective compared to the traditionally used palladium; further, it allows an easier olefin insertion, due to the shorter ligand bond lengths and multiple oxidation states of this metal. The $Ni(acac)_2$-catalyzed reaction between tri-*O*-acetyl-D-glucal and 2-iodophenol, in presence of Cs_2CO_3 and PPh_3 as ligand, successfully produced a pyrano *cis*-fused C-2 oxygenated dihydrobenzofuran **229** with a translocated double bond.

Additionally, the synthesis of pyrano C3-C2 fused dihydrobenzofuran **228**, achieving a novel product by reacting specific enopyranosides with 2-iodophenols was investigated. According to authors' findings, reaction mechanism is based on an initial Heck-type C–C bond formation followed by cyclization *via* an S_N2' type reaction under basic conditions.

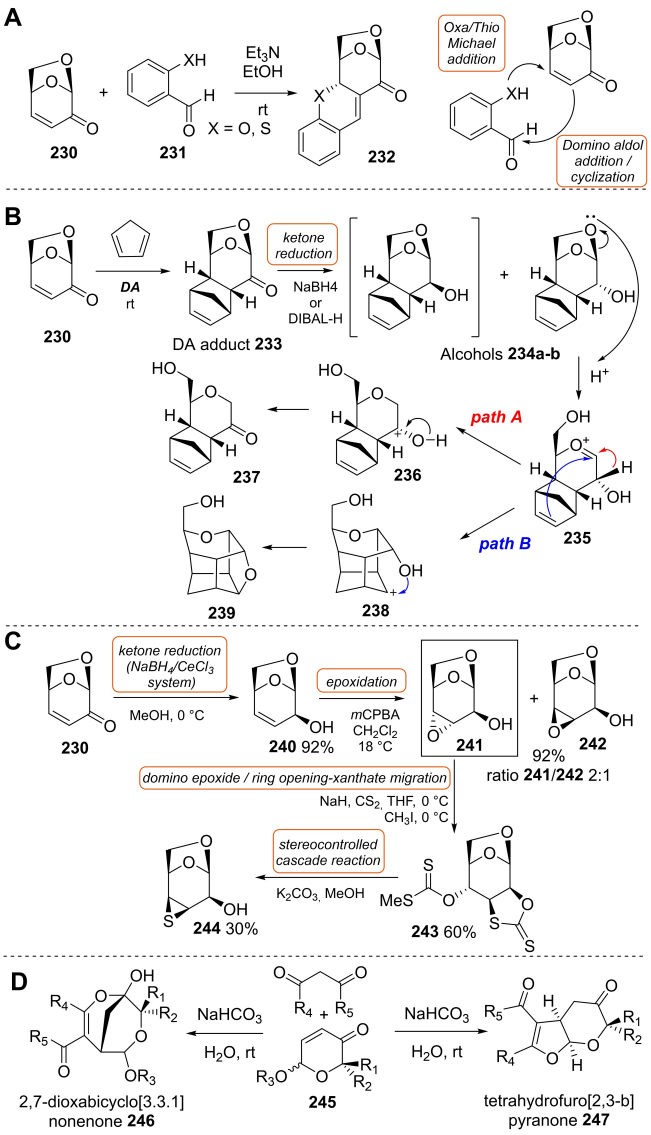

Figure 22. (A) Stereoselective domino reaction of levoglucosenone with o-(thio)hydroxybenzaldehyde. (B) Domino reaction pathway for the Montmorillonite - K10 clay-catalyzed synthesis of chiral dioxa-caged compounds. (C) Stereocontrolled preparation of 1,3-oxathiolane-2-thiones and 2,3-episulfide alcohols starting from levoglucosenone. (D) Polycyclic furopyranones obtained by Ramasastry and coworkers, using pyranone glycals by means of cascade Michael addition–cycloacetalization reaction.

5.2.2 Domino Reaction with Levoglucosenone Glycal

An interesting pseudo-glycal builing block, extensively studied and used for the synthesis of more elaborated frameworks is levoglucosenone glycal (compound **230**, Figure 22A), a bicyclic chiral α,β-unsaturated ketone derived from the pyrolysis of cellulose.[133] This bicyclic chiral α,β-unsaturated ketone possesses a 1,6-anhydro group and a 2-keto-3,4-unsaturated function; the latter moiety has been harnessed over years for domino transformations, primarily involving oxa-Michael addition reactions. An early instance of domino reactions involving levoglucosenone glycal is reported in 1998, when Isobe and coworkers described the stereoselective domino reaction between this pseudoglycal and furfural.[134] In another study of 2011, Samet and coworkers explored the reaction between hydroxybenzaldehydes and levoglucosenone via a stereoselective domino oxa-Michael-aldol reaction.[135] More recently, Witczak and Bielski introduced an analogous approach for synthesizing thiochromenes **232**. This method relies on the domino thio-Michael aldol condensation of 2-(thio)salicylic aldehyde **231** with levoglucosenone **230**.[136,137] The base-

catalyzed reaction proceeds via a thio-Michael addition of the thiol group on the beta position of the unsaturated ketone of levoglucosenone glycal, coupled with a simultaneous domino aldol condensation of the C3 carbon of the glycal with the aldehyde group of thiobenzaldehyde, as depicted in Figure 22A.

In a 2015 paper, Zurita and colleagues detailed the synthesis of chiral dioxa-caged compounds from levoglucosenone. These highly strained organic molecules have potential applications as chelating agents and in medicinal chemistry. Levoglucosenone served as the starting material for creating cyclofused alcohol derivatives **234a-b** via a Diels-Alder adduct **233**. The next transformation involved a cascade 3-step cationic cyclization and produced either the ketone derivative **237** or a new pentacyclic caged compound **239**. The authors explored various reaction conditions to optimize yield and selectivity to afford the caged compound, achieving the best results using Montmorillonite K-10 clay as a heterogeneous catalyst (88% yield, ketone **237**: caged compound **239** in a ratio 3 : 97). The reaction mechanism was proposed to involve oxocarbenium ion formation and could either follow a semi-pinacol rearrangement or an electrophilic cyclization (Figure 22B).[138] Montmorillonite K-10 clay was also the protagonist of a previous work, where its role as catalyst in a domino transformation of some 2-*C*-hydroxymethyl-D-glycals with substituted phenols, to produce new chiral α-pyrano[*2,3-b*]benzopyrans was established.[139]

Another example of a domino process involving levoglucosenone as substrate material was reported in the work of Comba and coworkers in 2018. The authors detailed the sterereospecific synthesis of certain thiosugars, which serve as valuable building blocks for creating thiooligosaccharides with potential biological properties. They achieved this synthesis starting from the levoglucosenone epoxide derivative **241**, employing a domino epoxide ring opening alongside a simultaneous xanthate migration, ultimately yielding the 1,3-oxathiolane-2-thione derivative **243**. The latters were subjected to a further stereocontrolled cascade reaction, achieving the corresponding 2,3-episulfide alcohol **244** (Figure 22C).[140]

In 2014, Ramasastry and colleagues employed a domino reaction on similar substrates, using pyran-4-one-2,3-glycals to synthesize polycyclic furopyranones **246** and **247**. The acetoxy and benzoyloxy pyranone building blocks (**245**) react with 1,3-dicarbonyl compounds (such as acetylacetone) through a cascade Michael addition followed by a successive cycloacetalization step. This transformation occurs under mild aqueous conditions, catalyzed by bases, triggering a tandem Michael addition – cycloacetalization cascade. Depending on the specific pyranone used, it is possible to obtain tetrahydrofuro[2,3-*b*]pyranones **246** and dioxabicyclo[3.3.1]nonenones **247** (Figure 22D). These compounds serve as interesting scaffolds for various bioactive natural products and pharmacologically active compounds.[141]

5.2.3 Synthesis of 1,2-Annulated Sugars

Among carbohydrate derivatives, glycofused and 1,2-annulated sugars in particular represents important glycomimetics exhibiting remarkable structural diversity and biological activities. These sugars fuse a sugar backbone with another unit at the C-1 and C-2 positions. The resulting scaffold is commonly found in natural products with diverse biological activities. For example, they as could act as mimic of transition states of diverse sugar-processing enzymes, such as glycosidases and glycosyltransferases[142]; they serve as valuable building blocks for the synthesis of medicinal chemistry-interesting compounds, such as ligands for Aβ amyloid peptides[143,144] and as synthons in the synthesis of complex molecules like ansamycins.[145] Traditionally, the synthesis of 1,2-annulated sugars involves multiple synthetic steps. However, recent efforts focus on one-pot reactions using glycals, thus simplifying the process. The research group led by Vankar has contributed to this field by developing a one-pot domino protocol, based on a domino double-Michael addition reaction, for creating 1,2-annulated sugars, in particular oxa-oxa and oxa-carbasugar fused skeletons, starting from 2-nitroglycals (**248**) or glycal-derived enone (**252**) (Figure 23A).[146] The synthesis of 1,2-annulated oxa-oxasugars was achieved through the reaction between 2-nitrogalactal and aryl substituted Baylis-Hillman alcohols **249**, mediated by KOtBu. A proposed mechanism for the stereoselective formation of the annulated sugars involves an initial intermolecular Michael addition by the OH group of the Baylis-Hillman alcohol on the anomeric carbon the nitroglycal, followed by an intramolecular further Michael addition on the α,β-unsaturated ester **250**, with the steric hindrance from β-side directing the formation preferentially from the α-face. The reaction between a sugar-derived dienone **252**, prepared from 2-formylgalactal, and soft α-dianions bearing active methylene pronucleophiles as Michael donors (**253**) results in the formation of oxa-carba 1,2-annulated sugars **255** (Figure 23B). The reaction proceeds through an initial intermolecular Michael addition of the active pronucleophile dicarbonyl group, mediated by CH_3ONa, followed by a second intramolecular Michael addition at the β-position of the dienone group by a second active pronucleophile intermediate.

Previously, Vankar reported the synthesis of bicyclic hybrid sugar structures, which included oxa-aza, oxa-oxa, and oxa-carbasugar fused frameworks.[147] These synthesized compounds were evaluated for their inhibitory effects on commercially available glycosidases; sugar-piperidine and sugar-pyran hybrids emerged as effective and selective inhibitors of this enzyme class. Among the synthesized compounds, azasugar hybrid molecules were crafted starting from C-2 acetoxyglucal, through the pivotal Ferrier rearrangement step, using *N*-allyl-4-methylbenzenesulfonamide and $BF_3{\cdot}Et_2O$, according to a method previously reported by Ding, William, and Liu in 2013.[148] This reaction yielded enone sugars *N*-glycosides, with a preferential α-anomer selectivity.

A few years earlier, the same authors developed an efficient approach to obtain 3-arylsulphonamino-2,3-dideoxysugars. This method involves a selective tandem hydroamination/glycosyla-

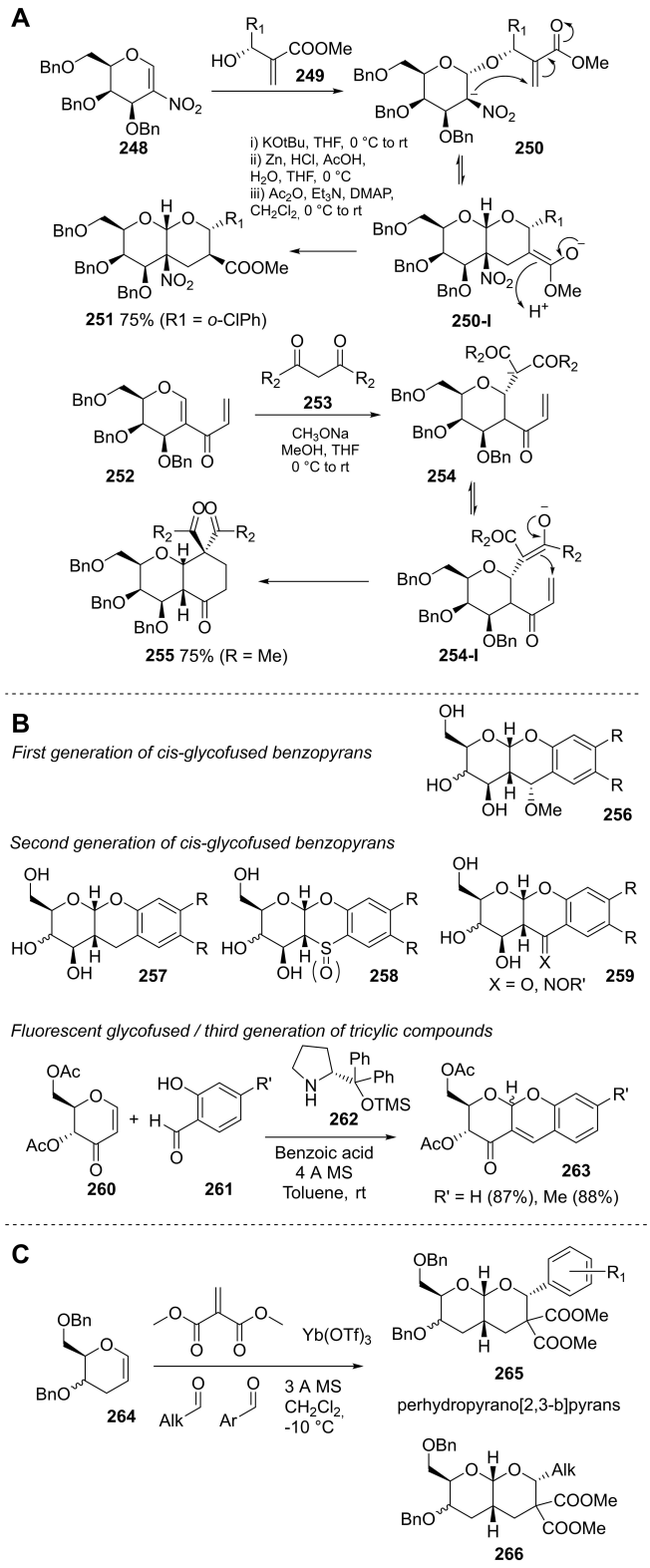

Figure 23. (A) Domino double-Michael addition reaction on 2-nitroglycal **248** and glycal-derived enone **252** for the synthesis of oxa-oxa and oxa-carba 1,2 annulated sugars. (B) Glycofused tricyclic compounds developed by La Ferla and coworkers through domino reactions on glycals and 3-oxoglycals **260**. (C) Synthesis of perhydropyranopyran compounds from 3-deoxyglycals.

tion process on peracetylated D-glucal and D-galactal substrates.[149] These last two works are further and later mentioned in the text for the synthesis of certain glycoderivatives, used for the preparation of mono- and polyvalent neoglycoconjugates.

Other examples of 1,2-annulated sugars derive from a work of La Ferla and co-workers, where they explored the synthesis of glycofused tricyclic compounds (**263**) by reacting enone glycals with salicylaldehydes **261** (Figure 23B).[150] They employed a suitably protected 3-oxoglycal **260**, a derivative of hexenuloses, which are the subject of a recent published review,[151] as glycal precursor. The reactivity of 3-oxoglycals, arising from an α,β-unsaturated ketone system with an electron-donating oxygen on the β-carbon, facilitated Michael/hetero Michael additions. Specifically, the 1,2-annulation transformation involved a chiral silylprolinol **262** organocatalyzed domino conjugate oxa-Michael aldol condensation.

The obtained compounds effectively interacted with amyloid β 1–42 peptide aggregates and bound to amyloid plaques in brain tissue samples from transgenic mice models of Alzheimer's disease. The electronic conjugate system with the annulated aromatic portion provides intrinsic fluorescent properties on these compounds, akin to those of Thioflavin T, allowing direct staining of amyloid plaques.[150] The aforementioned work is part of a series of research studies conducted by the same group, with a focus on developing novel tricyclic compounds capable of interacting with Aβ peptides and preventing their aggregation into amyloid plaques associated with Alzheimer's disease (Figure 23B, compounds **256**–**259**).[144,152–154] The first generation of *cis*-glyco-fused benzopyrans was synthesized by Cardona and coworkers exploiting an annulation process between glucals and galactals and *o*-hydroxybenzaldehydes, catalyzed by $Sc(OTf)_3$,[155] inspired by the work on the access to diastereoselective pyrano[3,2-*b*]-1-benzopyrans by Yadav in 2002.[156] In the second generation of glycofused tricyclic scaffold based-compounds, whose preparation relied on the same synthetic approach, several modifications on the central pyran ring as well as on the aromatic ring were included, with the aim to study the influence on such modifications on binding ability toward the amyloid β 1–42 peptide.

In 2018, Shao and colleagues described a $Yb(OTf)_3$-promoted synthesis of 1,2-annulated glycofused compounds based on a perhydropyranopyran skeleton, starting from 3-deoxyglycals.[157] In this domino transformation, 3-deoxy glycals **264**, alkylidene malonate, and aromatic or alkyl aldehydes were employed to yield the desired bispyran compounds **265** and **266** (Figure 23C). The reaction exhibited diastereoselectivity, high yields, and operated under mild conditions. Evaluation of the reaction scope included various aromatic and aliphatic aldehydes, with electron-donating groups on aromatic aldehydes and smaller aliphatic aldehydes favoring higher yields and stereoselectivity.

5.2.4 Synthesis of N*-Heterocyclic Derivatives*

In the last years, domino protocol applied to glycal was adopted by other research groups for the generation of other different frameworks, as for example glycofused *N*-heterocyclic rings. In 2019, Yao and coworkers reported the synthesis of diverse tricyclic *N*-heterocyclic glycofused compound of high molecular complexity, such as indoline-fused cyclopentanones or benzoxazines, through a versatile and environmentally friendly domino process involving the reaction of glucals (as 3,4,6-tri-*O*-benzyl-D-glucal **267**) and secondary anilines (**268**), mediated by Lewis Acid such as $InBr_3$ or $Dy(OTf)_3$.[158]

Most FDA-approved small molecule drugs contain nitrogen heterocycles, emphasizing the importance of synthetic methods that can incorporate nitrogen into carbohydrate-derived scaffolds. Although similar reactions were already reported in the literature,[159,160] this represented the first example of cascade reaction promoted by a Lewis acid in which the ring-opening of the glucal occurred, followed by an imino-Nazarov reaction to generate an indoline-fused cyclopentanone derivative. The reaction with *N*-benzyl- or *N*-allyl anilines in the presence of $InBr_3$ led to the corresponding indoline derivatives (compound **271**, Figure 24A), in different yields depending on the presence of electron-donating or withdrawing groups on the phenyl ring of aniline. When *ortho*-hydroxyl-substituted secondary aniline is used, a different reaction pathway occurs, leading to the different 1,4-benzoxazine scaffold (compound **269**, Figure 24A), in higher yields compared to the first reaction group using anilines, maybe due to the higher nucleophilicity that the hydroxy group confers to the aniline. The authors tested also different Lewis acids, discovering a further peculiarity. When lanthanide Lewis acid catalyst $Dy(OTf)_3$ was used, the same D-glucal reacted with *N*-benzyl-anilines affording the tetrahydroquinoline-fused cyclopentenones (compound **270**, Figure 24A), expanding the scope of the methodology.

Upon complete mechanistic investigation, the authors elucidated how diverse products can arise from the identical initial glucal substrate (Figure 24B). The mechanism comprised an initial Ferrier reaction triggered by Lewis acid, and the following ring opening step to furnish an open-chained α,β-unsaturated aldehyde. The latter reacted with the aniline generating a pentadienyl cation (**267-V**), from which a cyclic oxyallyl cation was generate through a 4π symmetry-allowed conrotatory ring closure. This was identified as a key intermediate, that could be trapped by *ortho*-hydroxyl group affording derivative **269**, or an intramolecular arene trapping could occur leading to derivative **271**. When the reaction was carried out using lanthanide Lewis acid catalyst, first derivative **271** was

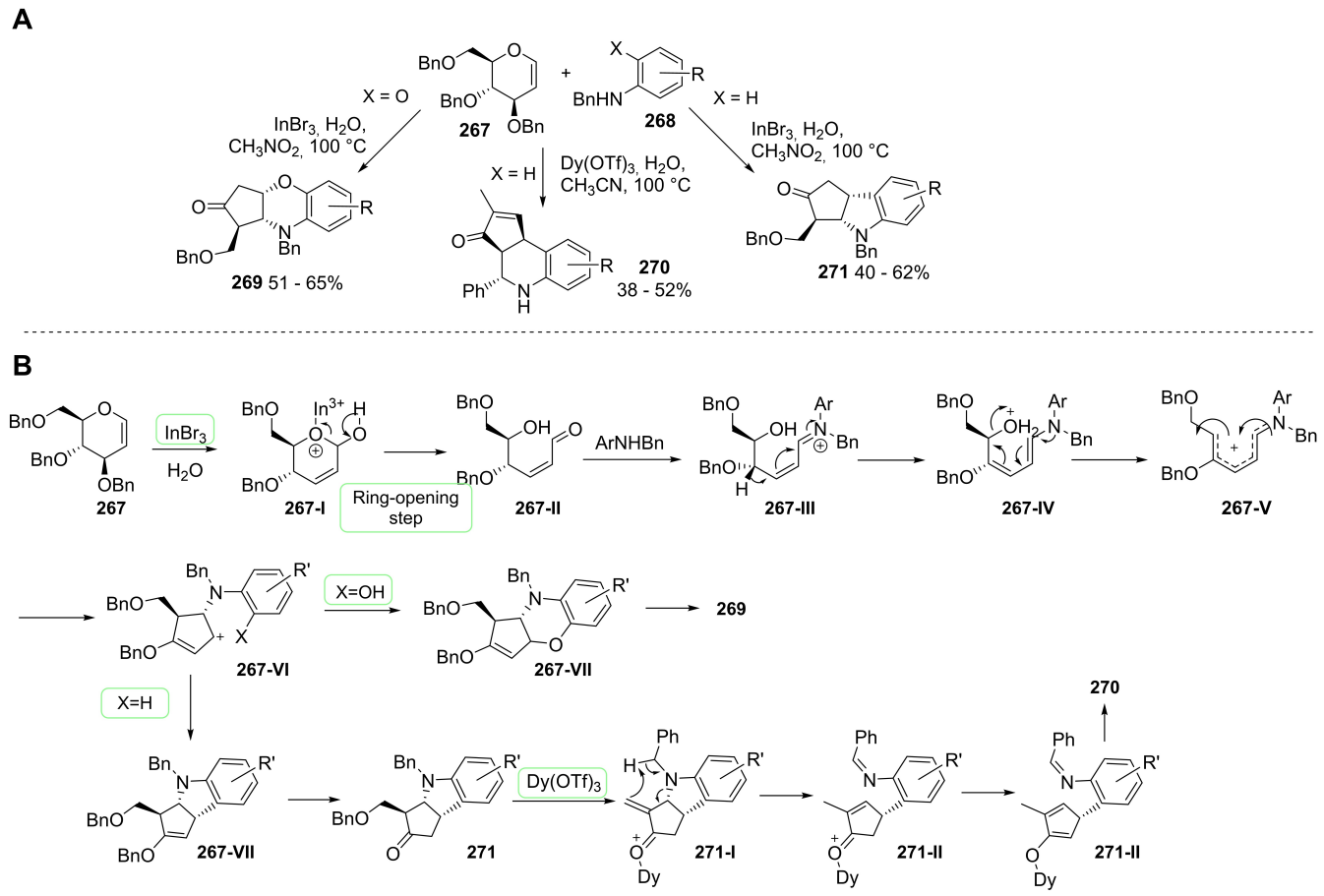

Figure 24. (A) Domino synthesis of tricyclic-fused compounds (benzoxazines **269**, tetrahydroquinoline-fused cyclopentenones **270** and indoline-fused cyclopentanones **271**) from tri-*O*-benzyl glucal **267** and secondary anilines or *ortho*-hydroxyl-substituted secondary anilines. (B) Mechanism for the conversion of glucal **267** into the three different tricyclic-fused compounds.

obtained, then it further reacted through an elimination, followed by a retro-ene-type reaction and an intramolecular Mannich reaction, furnishing the alternative product **269**. The described approach resulted to be a step-economical, environment-friendly and highly versatile domino transformation. Starting from the abundant and cost-effective reagent glucal, that can easily be derived from biomass, this process efficiently produced three distinct types of fused *N*-heterocycles with varying substituents. Notably, this domino process showcased remarkable versatility, particularly within the context of total synthesis.

A work of 2020 by Mishra et al. reported the generation of another nitrogen-based scaffold obtained by a domino process with glycals. The authors described the chemo-selective synthesis of chiral benzimidazoles through a $FeCl_3$-catalyzed tandem process.[161] Benzimidazole derivatives are especially noteworthy for their wide range of pharmacological properties, such as antiviral, antibacterial, antifungal, antitumor, and anthelminthic effects; noteworthy, benzimidazole sulfoxide framework is present in many approved and experimental drugs, as for example in proton pump inhibitors (PPIs).

The domino process that led to this nitrogen-containing heterocyclic derivatives involved the formation of an imine intermediate between *o*-phenylenediamine and glycal-derived aldehydes, followed by chelation and oxidation steps. Some of the synthesized benzimidazoles were active against *Candida* species, exhibiting also mild antibacterial activities.

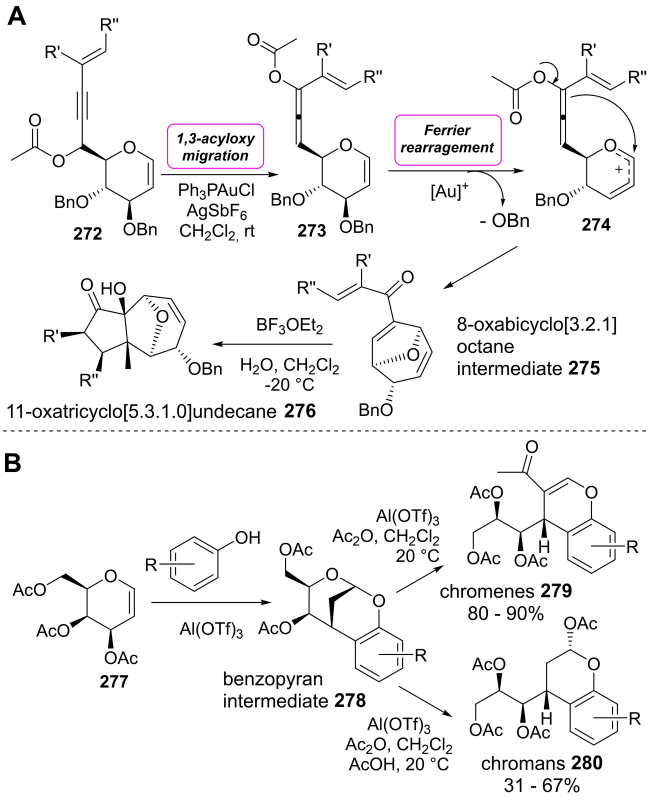

Figure 25. (A) Gold-catalyzed tandem process on glycal-derived 1,6-enyne substrates for the generation of oxabicyclic and oxatricyclic structures. (B) Synthesis of benzopyran, chromenes and chromans by $Al(OTf_3)$-catalyzed domino process.

5.2.5 Generation of Chiral Chroman and Furan Derivatives and Other Polycyclic Compounds

The synthesis of chiral 8-oxabicyclo[3.2.1]octane and 11-oxatricyclo[5.3.1.0]undecane structures - important motifs found in various bioactive natural products - mediated by a tandem process starting from glycal-derived propargylic esters was the subject of a published work of Liu *et al.* in 2017.[162] The transformation involved a gold-catalyzed tandem process involving glycal-derived 1,6-enyne substrates (**272**, Figure 25A) with propargylic carboxylates, which represent an intramolecular version of the same reaction exploited for the synthesis of *C*-vinyl-glycosides, already mentioned previously.[121] Also in this case, the process includes a gold-catalyzed 1,3-acyloxy migration on the propargylic carboxylate moiety, affording the allene intermediate **273**, which react in a domino fashion with the Ferrier-rearranged oxonium glycal portion, affording the intermediate 8-oxabicyclo[3.2.1]octane **275**. Subsequently, this intermediate undergoes a $BF_3{\cdot}OEt_2$-catalyzed Nazarov cyclization in water, leading to the formation of diastereomerically pure 11-oxatricyclo[5.3.1.0]undecanes **276** (Figure 25A). The cyclization step involves the generation of a cyclopentenyl cation intermediate, which is subsequently trapped by water to yield the final polycyclic product. The synthesis of benzopyran, chromenes and chromans through a domino process starting from glycals was the subject of a paper published by Williams and coworkers in 2014. They described the preparation of benzopyrans starting from the formation of a C–C bond, by means of a coupling reaction between 3,4,6-tri-*O*-acetyl-D-galactal **277** and different substituted phenols, catalyzed by aluminum triflate. The obtained benzopyran **278** can undergo a successive transformation into chromenes **279**, if additionally treated with acetic anhydride, whereas the use of the same reagent alongside with acetic acid provides sugar-derived chromans **280**. The mechanism of the transformation involves an initial Ferrier rearrangement and a successive domino Friedel–Crafts reaction, with the generation of a new C–C bond leading to the chiral benzopyran scaffold (Figure 25B).[163]

Domino reaction pathways applied to glycals allows to obtain a significant structural variety of furan and imidazole derivatives, as reported in several published works over the last years. These structures play a crucial role in heterocyclic chemistry and natural product synthesis due to their presence in biologically active compounds and their utility as synthetic intermediates. One notable study by Mal and Das of 2016 focused on a catalyst/ligand-free domino process involving 2-haloenone glycals and 1,3-dicarbonyl compounds or amidines (Figure 26A).[164] The authors explored a novel cascade annulation process using haloenones and bidentate nucleophiles or active methylene compounds. This approach led to the successful synthesis of optically active substituted furans and imidazoles through a sequence of Michael-type addition, substitution, and rearrangement.

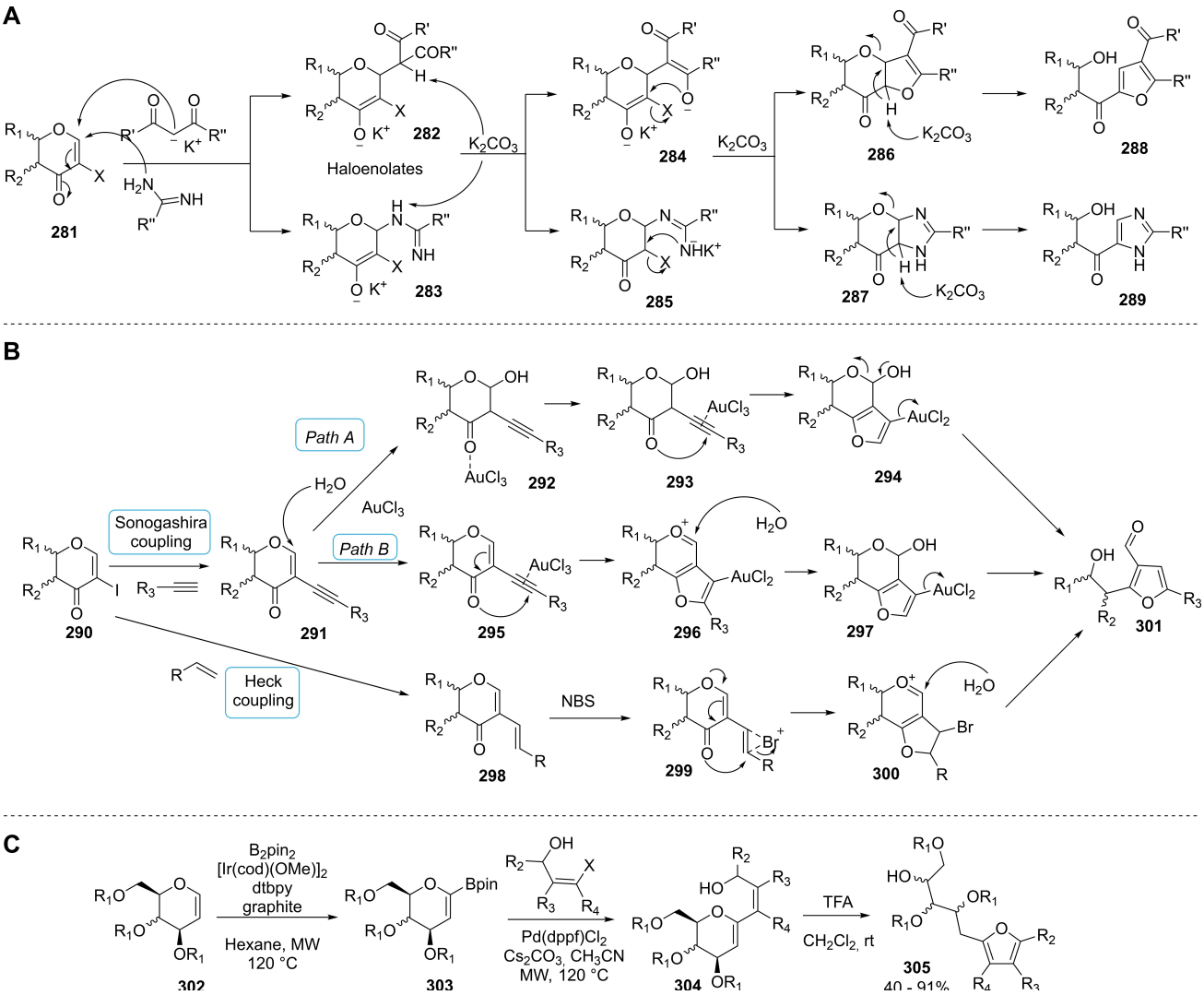

Figure 26. (A) Synthesis of substituted furans and imidazoles from 2-haloenoneglycals based on domino Michael-type addition, cyclization and rearrangement steps. B) and C) Domino strategies for furan synthesis from glycals. (B) Synthesis of 3-formyl furan derivatives 136 from 2-iodoglycals: gold(III)-catalyzed route and NBS-based route. (C) Polysubstituted furan derivatives obtained from glycals through the formation of glycal boronates.

It is suggested that the reaction mechanism proceeds through a first base-induced Michael-type addition amidines or 1,3-dicarbonyl compounds to haloenone **281**, forming haloenolates **282–283**; then, successive tautomerizations and cascade enolates formation leads to intermediates that finally collapse to give the final sugar-ring opened products **288–289** (Figure 26A).

A domino cyclization process was at the basis of the synthesis of 3-formylfurans from glycals, as reported by the same researcher in 2014.[165] These molecules play a crucial role in natural products and serve as key chiral building blocks for complex bioactive compounds. The authors introduced a novel gold(III)-catalyzed route to chiral 3-formyl furans, using water as a nucleophile. Starting from protected 5-(1-alkynyl)-2,3-dihydropyran-4-ones **291**, derived from 2-iodoglycals **290** *via* Sonogashira coupling with aromatic, aliphatic, and TMS-protected terminal alkynes, chiral furan derivatives **301** were obtained through a domino cyclization route (Figure 26B). Among the gold-containing catalysts tested, $AuCl_3$ achieved rapid completion of the reaction with excellent yields. The reaction tolerated various substitutions and protections on both the alkyne and hexopyranose ring, with yield variations based on substituent nature on the alkyne moiety. The proposed mechanism(s) involve an initial formation of an alkyne-gold intermediate, followed by a nucleophilic attack by water on the activated enone glycal and a domino anti-*endo-dig*-cyclization (path A) or the Au-promoted cyclic oxonium ion formation, that upon the next attack by H_2O leads to the final furan derivative (path B) (Figure 26B).

In 2015, the same authors introduced a new, cost-effective method for synthesizing chiral, substituted 3-formylfurans from readily available glycal-derived 2-iodoenones.[166] The protocol of 2014, relying on expensive and air-sensitive gold(III)-chloride catalysts, had limitations in its broad applicability. The novel approach exploited electrophilic heteroatom cyclization of substituted alkenes. The synthesis involved two key steps: at

first, the haloglycal derivative underwent a Heck coupling with terminal alkenes using the $Pd(OAc)_2/PPh_3/Ag_2CO_3$ system, generating the glycal derivative **298**, followed by the NBS-mediated domino cyclization step. The proposed mechanism begins with the formation of a halonium ion intermediate (**299**) from the olefinic bond of the 2-haloenone glycal. Electrophilic cyclization induced by the halonium species leads to the creation of an oxonium ion (**300**). A cascade intramolecular nucleophilic attack by oxygen then yields the desired chiral, substituted 3-formylfurans upon the addition of water (Figure 26B).

Glycal boronates were included as substrates in a tandem protocol developed by Butkevich *et al.* in 2013,[167] aimed to the synthesis of polysubstituted furans with 2-(ω-hydroxyalkyl) side chains (**305**), which are valuable intermediates for creating complex molecules. The domino reaction sequence involved a one-pot Suzuki-Miyaura coupling followed by an acid-catalyzed cyclization sequence, starting from vinyl ether boronates and vinyl halides. Among the tested substrates, glycal boronates (**303**) showed moderate to satisfactory yields during the domino borylation/cross-coupling/cyclization process. The borylation step was accomplished by means of a Ir-catalyzed C–H borylation Suzuki-Miyaura coupling. The crude boronates underwent to the next Pd-catalyzed cross coupling and tandem acid cyclization sequence (Figure 26C).

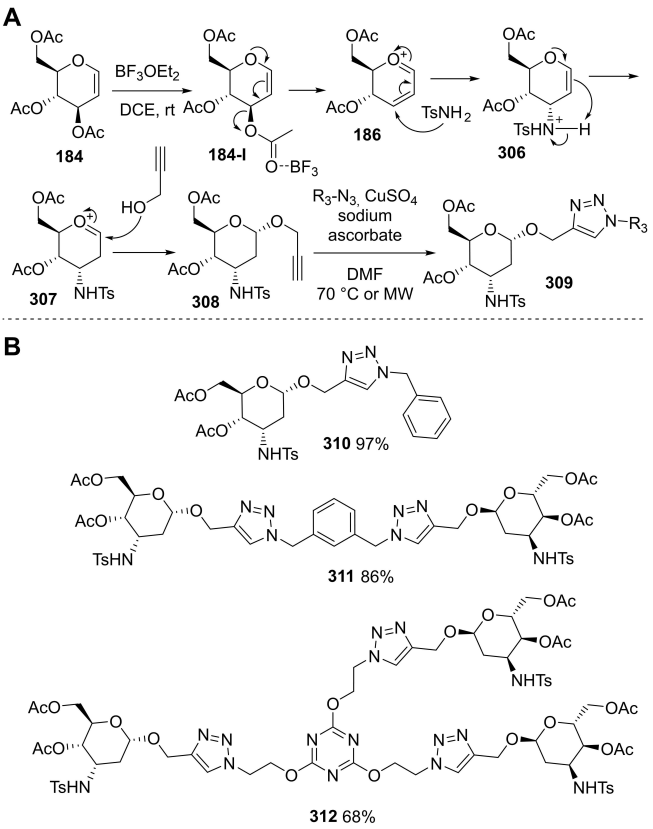

Figure 27. Monomeric and multivalent neoglycoconjugates reported by Xue-Wei Liu in 2014.
(A) Scheme and reaction mechanism of the domino synthesis of α-propargyl-3-tosylamino-2,3-dideoxyglycosides and the following CuAAC-based preparation of triazolyl neoglyconjugates. (B) Structures of some monomeric and multivalent neoglycoconjugates.

5.2.6 Tools for Chemical Biology

Domino reactions involving glycals are remarkably versatile and have paved the way for new mild, rapid, and efficient protocols. These reactions are not only valuable for generating organic frameworks of pharmacological interest but also for creating chemical tools applicable in chemical biology. Such tools enable fast, orthogonal, and precise transformations, including those performed in aqueous media and even on living cells. A more recent example comes from a 2014 study by Xue-Wei Liu and colleagues.[168] They devised a domino-based method to address glycal-derived monosaccharide scaffolds. These scaffolds were then used to generate multivalent neoglycoconjugates through click reactions. The significance lies in the role of multivalent interactions in carbohydrate recognition, making these neoglycoconjugates valuable for chemical biology applications. The process involves a domino reaction on various acetylated glycals, adopting a prior tandem hydroamination/glycosylation protocol developed by the same authors,[169–172] and allows for the stereochemically defined synthesis of α-propargyl 3-tosylamino-2,3-dideoxyglycosides (**308**). Subsequently, these glycoderivatives undergo a copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC), resulting in a series of 3-tosylamino-2,3-dideoxyneoglycoconjugates (**309**), using different nonsugar azides (Figure 27A).[168] The resulting mono-, di-, and trivalent triazole-linked glycoconjugates **310**–**312** (Figure 27B) can find significant applications in glycoscience, including the generation of oligosaccharides, glycopeptide mimics, and multivalent carbohydrate systems. Remarkably, Mukherjee *et al.* described the synthesis of similar glycoconjugate structures in 2010, adopting a domino transformation of glucal into furan-bearing hydroxy triazole glycoconjugates.[173]

The same domino hydroamination/glycosylation protocol was also used in 2015 by Liu *et al.* to address the synthesis of the natural product penaresidin B.[174]

In summary, domino reactions involving glycals play a pivotal role in both organic framework synthesis for pharmacological purposes and the creation of useful chemical tools in the field of chemical biology. These versatile reactions enable rapid and precise transformations, even within aqueous environments and living cells, making them indispensable for advancing glycoscience and multivalent carbohydrate systems.

The low cost, easy commercial availability, and straightforward synthetic methods make glycals powerful substrates for domino-based transformations.[114,175] Glycals serve as the starting point for creating very complex structures involving sugars, heterocycles, and large natural molecules. Endoglycals are ideal substrates for generating a wide variety of *C*-, *O*-, and *N*-glycosides. Most domino reactions carried out on glycals rely on Lewis acid activation of the double bond, generating intermediates based on Ferrier-type rearrangement. This paves the way for a myriad of cascade-based reactions, such as cyclizations or rearrangements. However, this also presents a critical and improvable point, as most reported examples of domino *O*-

glycosylation with glycals lead to 2-deoxy sugars. An exception is the synthesis of 2-amino-2-deoxy-glycosides (Section 5.1), where the domino route allows the insertion of an amino group through the creation of nitrogen-centered radical species, useful for delivering 2-acetamido sugars. The approach reported by Xiang in 2014, based on a domino stereoselective intramolecular glycosylation, represents an interesting method to obtain *O*-glycosides from glycals. In most cases, the activation of glycals and the subsequent domino steps require the use of Lewis acids and metal catalysts, such as Pd, Au, or lanthanides. An interesting alternative is the transformation of glycals into their respective enones, which can undergo straightforward and selective domino reactions by converting into reactive Michael acceptors towards many nucleophiles, as reported for levoglucosenone or 3-oxo-glycals, substrates for annulation reactions. A significant challenge is to continue developing increasingly attractive and regio- and stereoselective domino reactions to build complex scaffolds through intramolecular coupling reactions, while maintaining the chirality of the sugar moiety.

6. Domino Reactions on Halo-Sugars

Halosugars, compounds that combine a sugar moiety with a halogen atom, represent versatile and easily accessible substrates for various synthetic processes, making them useful building blocks for creating complex molecules. They can participate in diverse chemical reactions, including domino processes.

In 2010, Leibeling *et al.* introduced a domino reaction for synthesizing highly substituted chromans and isochromans from carbohydrates.[176,177] Chromans and isochromans represent a class of heterocycles with significant biological and pharmaceutical properties; they are of particular interest in medicinal chemistry as they exhibit many potential biological activities, as antitumor, antiviral, or antimicrobial agents.[17] Over the past decades, various synthetic approaches have emerged for their construction, and these strategies typically involve an aromatic ring as the starting reagent and incorporate the introduction of a pyran system. In contrast to these common synthetic approaches, the one developed by Leibeling *et al.* started from the pyran unit, which consists in a 2-bromoglycal easily synthetized from monosaccharides. This starting compound is then functionalized with a dialkyne chain in position 3 for chromans synthesis, or in position 1 for isochromans synthesis. The benzene moiety is generated through a domino step, performed after the appropriate deprotection of the substrates. The domino process hinges on the oxidative addition of Pd(0) catalyst into the C–Br bond of the 2-bromoglycal. This generates an intermediate that undergoes two successive carbopalladation steps, leading to the occurrence of cyclization reactions. Ultimately, this process results in the aromatization of the polycyclic (iso)chroman system (Figure 28A).

The peracetylated bromoglycal **313** is prepared through a bromination-elimination sequence. Then, a Lewis acid promotes Ferrier reaction with propargylic alcohols (**315**) installing the chain in anomeric position with subsequent double bond shift and affording the intermediate **316**. The 2-bromoglycal derivative **314** is easily accessible from intermediate **313**. This isopropylidene-containing 2-bromoglycal is then functionalized in position 3 with propargylic halides (**317**) affording compound **318**. After the installation of the dialkyne chains, compounds **318** and **316** could take part in the domino step triggered by Pd catalyst. After the oxidative addition of Pd^0 into the C–Br bond of the substrate (intermediate **322**, Figure 28B), two intramolecular carbopalladiation occur, generating a diene intermediate (**324**). The latter compound is then involved in an electrocyclic 6π electron ring closure step, from which the final isochromans or chromans skeleton is obtained together with the regeneration of the catalytic species.

An intermolecular version of this methodology for chromans and isochromans synthesis was reported in 2011 from the same research group. The new approach, using an external alkyne to address a twofold domino intermolecular carbopalladation/cyclization sequence, results to be more versatile than the previous one, leading to the synthesis of highly substituted products.[178] The components and the steps of this intramolecular version of the reaction are analogue to that described above (Figure 28C); the alkyne chains could be attached to the 2-bromoglycal either through a nucleophilic substitution or Ferrier reaction, depending on the desired final product. Then the domino step occurs, consisting of a first intramolecular carbopalladation, followed by a second intermolecular one, and a last cyclization to afford the final products. A further extension of this approach was reported in a paper of 2012, where Leibeling and Werz described the adoption of the tandem process for the synthesis of glycal-derived biphenyl structures with a chiral axis, as new more complex scaffolds. An analogue domino pathway is the key transformation applied to both sides of a linear C2-symmetric precursor, that led to the creation of a chiral axis in the final cyclization step of the pathway.[179]

In 2013, Leibeling and Werz successfully employed the synthetic methodology described for chromans and isochromans to synthesize mimic of another class of compounds known for their chemotherapeutic properties: anthracyclines.[180] These polyketides are characterized by a linear, fourfold annulated ring system comprising two benzene rings, a benzoquinone moiety, and a six-membered ring bearing carbohydrate functionalities, critical for the biological activity. The anthracycline mimics proposed by the authors presented a pyranose ring instead of the terminal six-membered ring (Figure 29A). The synthesis of the anthracycline skeleton starts from 2-bromoglycal **314** derived from D-glucose. This reagent was coupled with compound **329** through silyl ether formation promoted by Br_2. The halogen forms the highly reactive silyl bromide intermediate, which is then trapped by the hydroxy group at C3 of the sugar derivative. The intermediate **330** obtained takes part in the domino reaction as previously described; the domino carbopalladiation-cyclization proves to work well also with this different substrate, affording fourfold annulated ring intermediate **331**. The latter could be easily converted into derivative **332**, which is the substrate for the

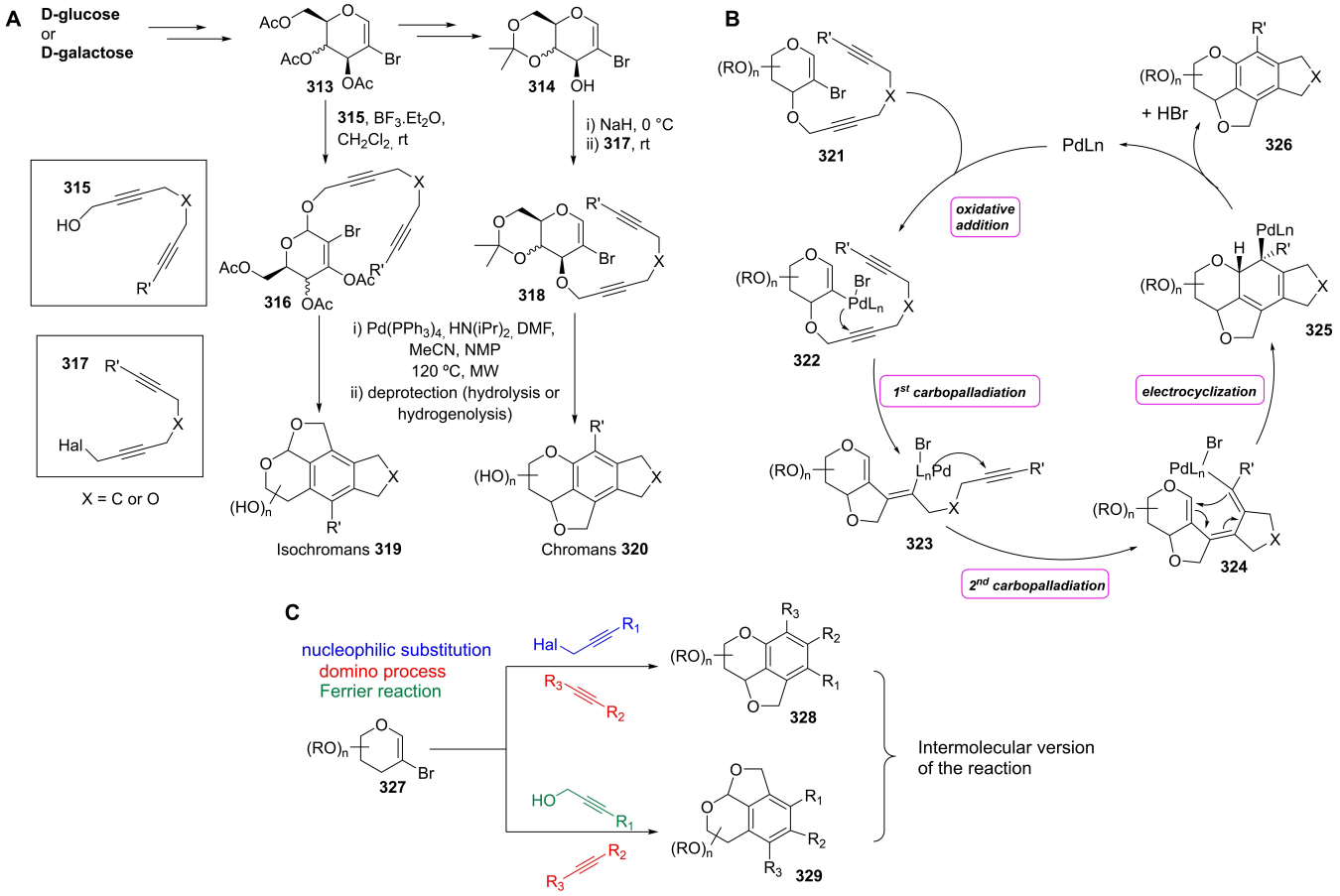

Figure 28. Synthesis of chromans and isochromans from 2-bromoglycal *via* intramolecular (A and B) or intermolecular (C) domino reaction.

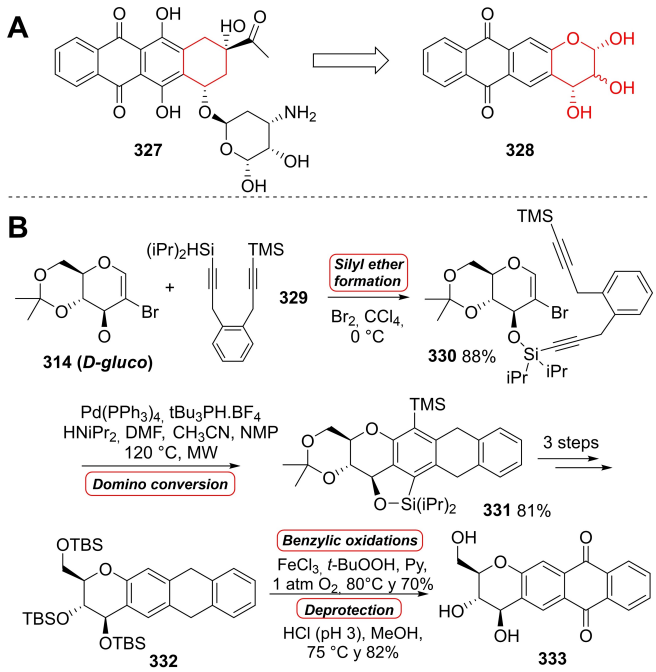

Figure 29. Synthesis of anthracycline mimic from bromoglycal derivative.

next step of benzylic oxidation to afford the benzoquinone moiety. The final hydrolysis leads to the desired anthracycline scaffold bearing a terminal pyranose ring (**333**) (Figure 29B).

Beside brominated derivatives, other haloglycosides could take part in domino processes. Recently, Traboni and colleagues reported the solvent free and under air synthesis of α-glycosides starting from glycosyl chlorides, which proceeded with high yield and stereoselectivity.[181] In the methodology described, the glycosyl chloride, easier to handle with respect to bromine and iodine analogue, is activated as glycosyl acceptor with a combination of $P(OEt)_3$ and TBAB, in the presence of a slight excess of DIPEA, at 90 °C. Curiously, the reaction is performed under air and without adding additional organic solvent, as it is performed in the neat liquid amine. In the mechanism proposed (Figure 30A), the glycosyl chloride **334** reacts with the nucleophile $P(OEt)_3$ to form a reactive β-adduct **335** that undergoes S_N2-like glycosylation to afford the α-glycosylated product **336** with good yields and good stereoselectivity. The authors developed also a one-pot version of this conversion, which included a *in situ* chlorination and a α-glycosylation of 1-hydroxy sugars without isolation of the glycosyl chloride. This one-pot version leads successfully to the synthesis of α-fucosides oligosaccharides, relevant and of interest but usually difficult to obtain (Figure 30B). In this synthesis, the fucosyl-hemiacetal **337** is converted to intermediate **338** thanks to a

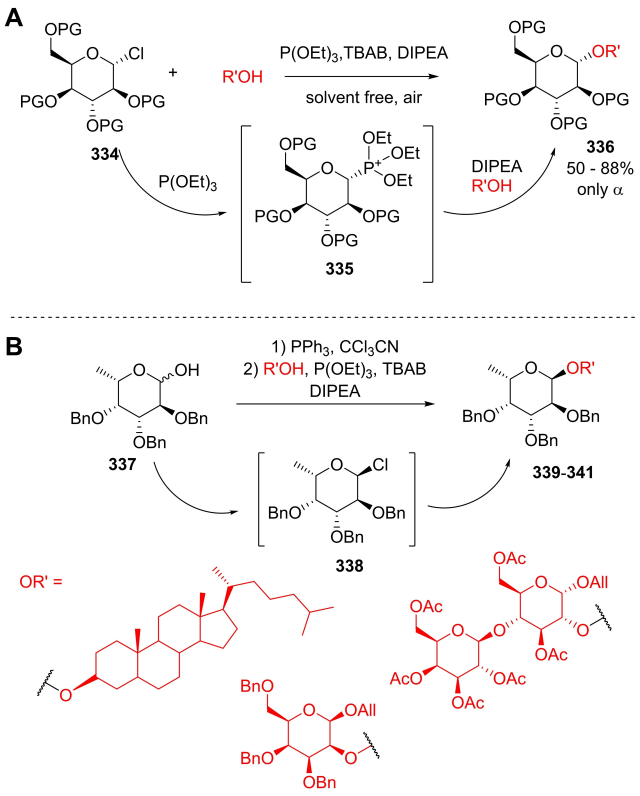

Figure 30. α-glycosylation from glycosyl chloride (A), and one-pot glycosylation without isolation of chlorinated intermediate (B).

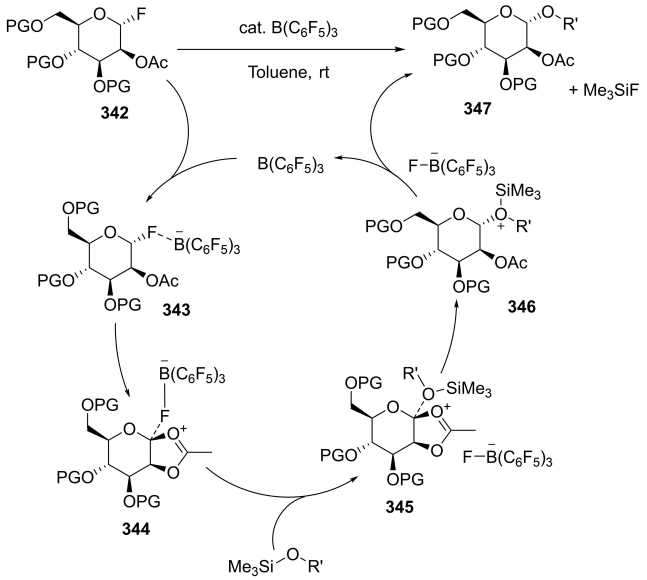

Figure 31. Proposed mechanism for the boron-catalyzed coupling between glycosyl fluoride and silyl ethers.

solvent-free chlorination with a combination of PPh_3 and CCl_3CN as chlorinating agents. The chlorinated intermediate is directly converted to final α-glycosylated products (**339–341**) adding $P(OEt)_3$, DIPEA, TBAB, and the desired glycosyl acceptors.

In the same year, a boron-catalyzed glycosylation method was developed by Montgomery and colleagues.[182] In the proposed reaction, glycosyl fluorides act as donors while silyl ethers as acceptors in a room temperature, fast glycosylation. Glycosyl fluorides have been extensively used as building block for glycosylation, due to their stability and accessibility. They usually react with silyl ethers as acceptors, but in this type of reaction a Lewis acid is required to activate the fluoride, while a nucleophilic Lewis base is needed to cleave the stable Si–O bond of the acceptor.[183] An organoboron catalyst such as tris(pentafluorophenyl)borane ($B(C_6F_5)_3$), which exhibits Frustrated Lewis Pairs characteristic (FLP) could be used as sole catalyst for coupling between glycosyl fluorides and silyl ethers. Thus, the authors studied the reaction between donor and acceptor using $B(C_6F_5)_3$ as catalyst, preferred over other catalysts as it is commercially available, easy to handle, water tolerant and it has a high catalytic activity and tuneable structure. Computational studies were performed to elucidate the mechanistic pathway of this reaction, and the proposed mechanism is depicted below in Figure 31. The boron catalyst coordinates and abstracts the fluorine ion from the starting fluoride, obtaining the charged glycosyl donor intermediate **344**, which is stabilized by the neighbouring acetate at C2 and by ion pairing with $[FB(C_6F_5)_3]^-$. Then, coordination of the cation by the silyl ether occurs, followed by its addition generating the intermediate **346**. After this, the anion $[FB(C_6F_5)_3]^-$ re-transports fluoride to obtain final product and the stable silicon fluoride byproduct. The presence of an acetate group at position C2 directs the formation of *trans* C1-C2 linkages due to the neighbouring group participation effect. As a result, high stereoselectivity is achieved. This methodology is applied to perform domino glycosylations using multiple monosaccharides as building blocks.

Three component glycosylation were performed and examined; representative examples are reported below in Figure 32. By coupling donor **348** with acceptor **350** and, after 30 minutes, adding donor **349**, branched product **351** is obtained (Figure 32A). The first glycosidic linkage occurs between donor **348** and the least hindered silyl ether at C4 of the acceptor. After this first glycosylation, the later added donor **349** could only react with the most hindered group at C6, thus performing regioselective domino reaction. Complementary, by varying the order of addition of the donor (first **349** and after 30 minutes **348**), product **352** is obtained. As illustrated in Figure 32A, branched glycosylation patterns are achieved if the employed acceptor presents two or more silyl ethers. However, a linear pattern could also be obtained if a silicon unit is installed in the donor glycosyl fluoride, as depicted in Figure 32B. In this case, compound **353** first reacts with acceptor **354** as donor, then reacts as acceptor when compound **348** is added to the reaction mixture, obtaining linear trisaccharide **355**.

Halogen sugars have historically been widely used in carbohydrate chemistry, particularly as donor substrates in glycosylations. Their use for forming complex structures to obtain biologically and pharmacologically active molecules is more recent and has been made possible by domino reactions on halogen-bearing glycals. In particular, several works by D.

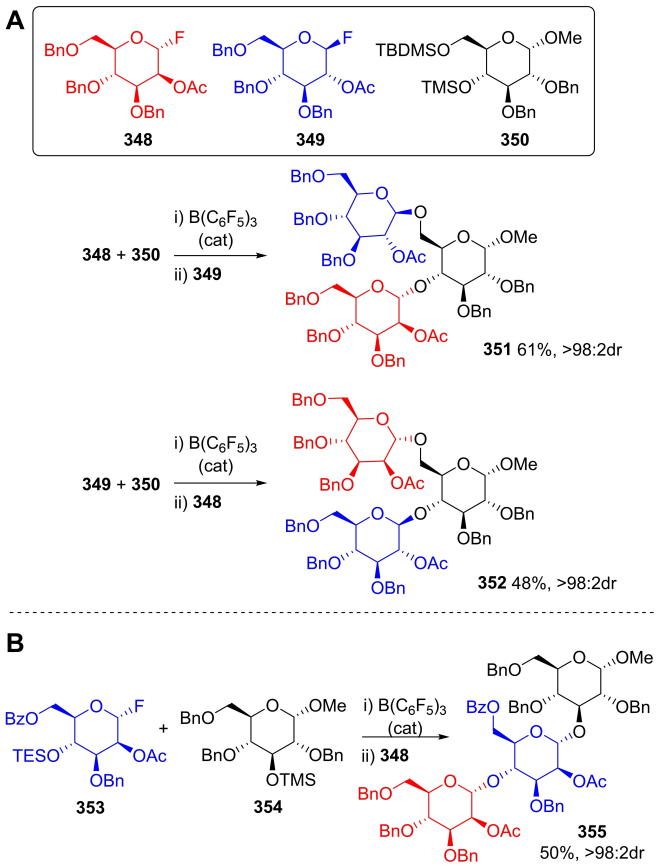

Figure 32. Examples of a domino three components branched (A) or linear (B) glycosylation.

Werz report the use of bromoglycals as starting materials for generating complex polycyclic chromans and isochromans, exploiting the marked reactivity of the bromoenolether functionality. The C–C coupling reactions with alkyne groups installed on the 3-OH position of the glycal, followed by successive domino cyclization steps, represent an elegant strategy to deliver multicyclic structures. However, the use of Pd catalysts could be a limiting factor in this strategy, despite the chemical setup and approach leading to novel and intriguing structures in high yields. The higher reactivity of glycosyl chlorides and fluorides allows for the generation of both simple and longer *O*-glycosides under milder reaction conditions, using organophosphorous or organoboron-based reagents and catalysts.

7. Summary and Outlook

To sum up, this comprehensive review emphasizes the potential and versatility of domino reactions in carbohydrate chemistry. The complex nature of carbohydrate structures implies long synthetic routes that move organic chemists to find novel and efficient protocols for their manipulation. Domino reactions, as tandem and/or one pot processes, emerged as a powerful strategy for the drug development requirements. They can provide complex biologically relevant compounds, like carbohydrate derivatives, in a faster and more efficient way compared to traditional methodologies. In particular, the reduction of intermediate steps results in less waste formation and isolation procedures which entails a decrease in production costs, improving the sustainability and efficiency of the process. For these reasons, domino reactions have found applications in both industry and academia fields, especially for drug and material development. Despite the versatility of domino reactions in carbohydrates and their facing a fast-growing field, not all the structures may enable domino transformations, and sugars remain a tough cookie of the chemistry. Glycosidic bond, stereoselectivity, and overall yield are limitations that require further advancements.[184] Moreover, collateral byproducts can affect the scalability of the synthetic schemes. Salient challenges in the use of domino reactions include the metal-free and greener approach, which are desirable features for the pharmaceutical industry and sustainable research. We provide an overview about the reported domino reactions on carbohydrate scaffolds, discussing their mechanisms and highlighting the usefulness in organic synthesis. In this work, we provided insightful and illustrative examples of domino ring-opening reactions, which are valuable for synthesizing novel and more intricate compounds. Additionally, we highlighted the role of *O*/*S* and *N*-glycosides in the construction of glycomimetics and other biologically relevant frameworks. We focused on substrates that enable the formation of *O*, *N*, and *C*-glycosides through domino processes, as well as glycal-derived structures with useful applications in chemical biology. Herein, the authors described enlightening and representative examples regarding domino ring opening reactions useful to obtain novel and more complex compounds. Furthermore, *O*/*S* and *N* glycosides are showed to serve for the synthesis of glycomimetics and other biological relevant scaffolds. A deep analysis emphasized substrates which give access to *O*, *N*, and *C* glycosides through domino processes, as well as glycal derived structures as tools for biological applications. In conclusion, with the aim to investigate the most intriguing domino reactions and related processes in the jungle of sugars, this non-exhaustive review offers an insight to expand and invite researchers to enrich even more this area of synthetic carbohydrate chemistry. As domino and related reactions are efficient and powerful tools in synthetic chemistry, they can find significant applications in the Synthesis of natural products, their pharmacologically active derivatives, and in chemical biology. The former will benefit from increasingly selective domino transformations on sugars, resulting in shorter synthetic routes, fewer reagents, fewer purification steps, and higher degrees of chemo-, regio-, and, most importantly, stereoselectivity. The recent literature presented in this review offers many suggestions to address this challenging task; the efficiencies and selectivities achieved by domino reactions are improving and will undoubtedly lead to many successes in this field. In chemical biology, the creation of site-selective, stereodefined, and precise domino routes will positively impact processes such as the *in vitro* and *in vivo* bioorthogonal functionalization of biomacromolecules. In this context, the search for metal-free and biocompatible methods

(*i.e.*, reactions conducted in aqueous media) is crucial to expanding the potential of carbohydrate chemistry in life sciences.

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Conflict of Interests

The authors declare no conflict of interest.

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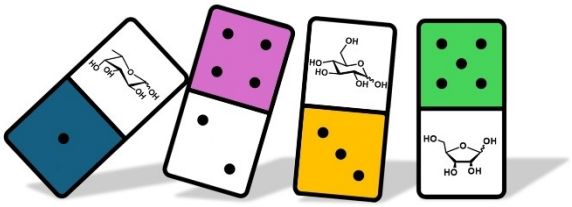

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Unleashing the Power of Domino Reactions on Carbohydrates: State of the Art

Domino transformations play a crucial role as chemical tools in drug discovery processes. This review showcases various instances of domino transformations applied to carbohydrates, with the goal of summarizing their chemical potential in producing sugar-derived compounds. These compounds have significant applications in generating new chemical scaffolds for drug discovery and chemical biology.