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One-pot construction of carbohydrate scaffolds mediated by metal catalysts

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Owing to the environmental concern worldwide and also due to cost, time and labour issues, use of one-pot reactions [domino/cascade/tandem/multi-component (MC) or sequential] has gained much attention among the scientific and industrial communities for the generation of compound libraries having different scaffolds. Inclusion of sugars in such compounds is expected to increase the pharmacological efficacy because of the possibility of better interactions with the receptors of such unnatural glycoconjugates. In many of the one-pot transformations, the presence of a metal salt/complex can improve the reaction/change the course of reaction with remarkable increase in chemo-/regio-/stereo-selectivity. On the other hand because of the importance of natural polymeric glycoconjugates in life processes, the development and efficient synthesis of related oligosaccharides, particularly utilising one-pot MC-glycosylation techniques are necessary. The present review is an endeavour to discuss one-pot transformations involving carbohydrates catalysed by a metal salt/complex.

1. Introduction

At each and every moment, Nature is creating and/or regenerating chemical and biochemicals from its own feedstock with the help of metal catalysts and/or enzymes and coenzymes. In many of the corresponding biogenetic processes, cascade/

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domino one-pot reactions are involved to generate several new bonds in a process, and the reactions occur with exclusive specificity in terms of regio- and stereo-structures and sometimes even generating complex structures from simple starting renewable substrates. Nature takes care of its own necessary energy demanding cycles. The synthesis of organic compounds mostly uses multi-step reactions which involve extraction, purification (chromatographic or others) and characterisation of the product/s of each step. The demand for design and synthesis of such organic molecules in one-pot towards the generation of a library of compounds having different scaffolds, is gradually increasing in order to make the syntheses environmentally, economically and in terms of time, more viable. In several cases conversion of some of the multistep syntheses to the corresponding one-pot version is feasible, provided the reagents, solvents and conditions used in multistep processes are compatible with one-another and also with the products formed at subsequent steps. Learning from Nature's classroom, translating Nature's laboratory procedure into *in vitro* experiments and sometimes utilising Mother Nature's chiral feedstock, it has now been possible to create biologically potent chiral compound-libraries in one-pot, minimising cost, energy, labour and waste and thus addressing some of the green aspects relating to the environment.

One-pot domino/cascade/tandem/multicomponent (MC) reactions are considered to be the most important synthetic tools for construction of structurally and regio- or stereochemically diverse molecules for generation of compound libraries. All these are greener approaches compared to their corresponding multistep versions, as all of these occur with high atom economy saving time, labour, money, energy and environment with minimisation of waste production. Several reviews have been published in the literature covering such one-pot reactions.[1] In many of these one-pot reactions, metal salts or metal complexes play immense importance in formation of typical bond and help to carry out the transformations in highly chemo-, regio- and stereo-selective manner. Generally domino/cascade and tandem processes occur in one-pot maintaining same condition throughout the reaction. Such reactions involve usually mild reaction condition and proceed with formation of new other bonds between C–C or C–heteroatom with multiple consequential transformations on new functionalities, formed during the successive reactions, and sometimes is associated with rearrangement where the intermediates are not isolable. MC reactions are convergent chemical processes where more than two components react, the components along with the reagents are usually taken in the same pot at the beginning, but one/two component/s may also be added with some additional reagents with change in reaction condition sequentially during the reaction in the same pot. In MC reactions intermediates may be isolated.

Application of tandem/domino/cascade/sequential-/MC-one-pot reactions in carbohydrate field started its journey much later compared to those applied in other organic syntheses. Because of possibility of better interaction with the receptor biomolecules, tailor-made unnatural small glycoconjugates and sugar mimics are regarded as important targets with improved biological and pharmacological properties, and syntheses involving carbohydrates are gradually gaining the attention of researchers.[2] Sugars like monosaccharides are important chiral inexpensive feedstock toward their utilisation in native form or in the form of their suitable derivative in the synthesis of medicinally and industrially potential chiral organic molecules.[3] On the other hand, carbohydrates, particularly natural glycoconjugates involving biopolymers play immense importance in several life processes like cell–cell interaction, cell proliferation, transport mechanism, bacterial and viral infection and even in cancer metastasis.[4] Instead of increasing the number of unplanned synthetic molecules toward drug development, nowadays there has now been creation of new combinatorial libraries which are designed based on natural product scaffolds.[5]

In the present comprehensive review we have concentrated our dissertation on one-pot reactions (tandem/domino/cascade/sequential/MC, even including those which involve 2/3/4 separate reactions occurring sequentially in one-pot) which are in some-way or other, metal catalysed and applied to carbohydrate field. Although L. F. Tietze suggested in a review on domino reactions[1a] not to use the term tandem, as according to his logic "*Tandem means two at the same time and does not describe a time-resolved transformation*", but in this manuscript, in a few particular one-pot reactions we have used the terminology as were termed in the original papers. Our discussion will be focused mainly on the one-pot regio-/stereo-selective protection–deprotection of monosaccharides or on their suitable derivatives, on one-pot synthesis of sugar derived compounds and unnatural glycoconjugates, and also on the synthesis of oligosaccharides related to natural glycoconjugates utilising

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sequential one-pot glycosylations. Development of unnatural glycoconjugates has gained special interest of academic as well as industrial communities, as many of such compounds reveal themselves to be glycosidase or glycosyltransferase inhibitors. Use of inhibitors is now considered as one of the important avenues for disease management; several of such glycoconjugates already are or supposed to be considered as established drugs to treat diseases like bacterial and viral infections, metabolic diseases and even cancer.[4b]

A review on 'One-pot construction of carbohydrate scaffolds mediated by metal catalysts' is supposed to remain incomplete without inclusion of researches on metal catalysed one-pot conversion of carbohydrate biomass to other simple industrially important chemicals or bio-fuels. That the latter topic has gained tremendous attention during the past several years is reflected in the plethora of research publications in this direction. During the last few years a good number of reviews[6] including several reviews in 2019,[6h–s] and one in 2020 (ref. 6*t*) have also been published on the above field. For this obvious reason we have excluded this topic from our discussion. We have also excluded the domino/tandem one-pot syntheses involving click reaction leading to macrocycles or oligosaccharide mimics,[7] as those can be considered for a separate review. Although, for literature search we have depended on different online search engines with relevant keywords, but still in spite of our sincere effort a few publications may be missed particularly where this review-related one-pot reaction may have been employed as part of a total synthesis and published under different keywords.

2. One-pot protection–deprotection of sugars

Being polyhydroxylated compounds, synthetic advancement of carbohydrate molecules demands extensive functional group transformation/modification by means of suitable protection–deprotection of hydroxy groups. In a one-pot version, appropriate conditions are to be chosen and maintained throughout the reaction as much as possible. For management of protecting groups and anomeric leaving groups toward preparation of glycosyl donor and acceptor building blocks necessary for oligosaccharide synthesis, use of one-pot reactions are gradually increasing in place of some of their corresponding multistep approaches, and in the recent years with increase of sophistication also. One-pot synthesis of different glycosyl donor and acceptor building units in terms of regioselectivity and protecting groups, may however, need to be considered separately in some instances on case to case basis.

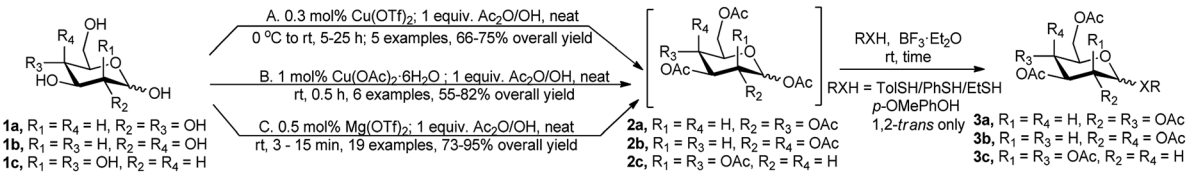
2.1. Sequential protection of free sugar for synthesis of acetylated *O*-/*S*-glycosides

Per-*O*-acetylation of the free sugars is considered as the most commonly utilised protection profile adopted for further functional group manipulation, as these per-*O*-acetylated sugars can be easily transformed toward their corresponding *S*-/*O*-glycosides mediated by suitable Lewis acids. In the evolution of catalysts for per-*O*-acetylation reaction, there comes some Lewis acids that can *in situ* activate the anomeric acetate group toward further *S*-/*O*-glycosylation reaction, or that can be used in combination with traditionally employed acetate activation reagent $BF_3 \cdot Et_2O$ for the same purpose.

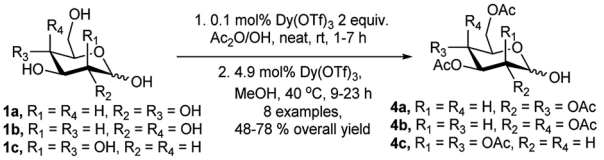
The first example of simple one-pot approaches in the two-step preparation of per-*O*-acetylated 1,2-*trans* thioglycosides (*e.g.*, **3a**/**3b** or **3c**) from native monosaccharides (*e.g.*, **1a**/**1b** or **1c**) *via* intermediate formation of the corresponding per *O*-acetylated sugars (**2a**/**2b** or **2c**), was reported in 2003 ((A) in Scheme 1) by Hung's research group.[8] In the seminal report, per-*O*-acetylation was carried out under neat condition using stoichiometric amount of Ac_2O, and catalytic amount of Lewis acid, such as $Cu(OTf)_2$, followed by treatment with $BF_3 \cdot Et_2O$, and the *p*-thiocresol as glycosyl acceptor, which resulted in the formation of the 1,2-*trans* thioglycosides in 66–75% overall yield. This was followed by a similar report by Dasgupta *et al.* in 2007 based on $La(OTf)_3$ catalyst.[9] The latter group achieved $La(OTf)_3$ catalysed efficient one-pot conversion of free sugars under neat condition by sequential one-pot per-*O*-acetylation based on Ac_2O followed by tandem *O*-/*S*-glycosylation in the presence of $BF_3 \cdot Et_2O$ and 2-bromoethanol/*p*-methoxyphenol or *p*-cresol as the nucleophile.

Another Cu(II) salt, *viz* $Cu(OAc)_2 \cdot 6H_2O$ was used by Chatterjee *et al.* for the same purpose in 2015.[10] The principle for the reaction sequences is the same as the previous one; here they used 1 mol% $Cu(OAc)_2 \cdot 6H_2O$ as catalyst for per-*O*-acetylation step followed by thioglycosidation with *p*-thiocresol using 2 equivalents of $BF_3 \cdot Et_2O$ ((B) in Scheme 1).

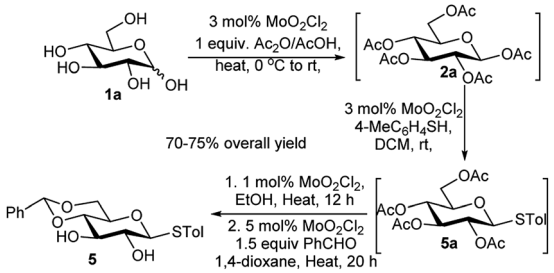
In a broader case study for this tandem sequence Mukherjee *et al.* used 0.5 mol% of $Mg(OTf)_2$ as recyclable and robust catalyst for per-*O*-acetylation of unprotected mono and disaccharides, and subsequent one-pot transformation to the corresponding *O*-/*S*-glycosides, in reaction with various thiols and *p*-methoxyphenol, in the presence of 1.2 equivalents of $BF_3 \cdot Et_2O$ ((C) in Scheme 1).[11] The corresponding *S*-/*O*-glycosides were isolated in excellent yields and exclusive 1,2-*trans* selectivity



Scheme 1 One-pot per-*O*-acetylation–thioglycosidation reaction.



Scheme 2 $Dy(OTf)_3$-catalysed conversion of free sugars to per-*O*-acetylated hemiacetals.



Scheme 3 MoO_2Cl_2-catalysed one-pot multistep reaction.

without any sign of anomerisation. They also reported the recyclability of the catalyst used for further reactions. After work-up, the catalyst was recovered from the aqueous phase by evaporation, followed by drying overnight over P_2O_5. The recycle protocol was repeated five times, the percentage of the catalyst recovered was always more than 90% while the yields of phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside and phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside were always more than 93% and 90%, respectively.

Recently in a different approach Yan *et al.* have reported $Dy(OTf)_3$ as recyclable catalyst for per-*O*-acetylation of free sugars followed by a semi-one-pot sequential conversion into their corresponding glycosyl hemiacetals (Scheme 2).[12] They utilised 0.1 mol% of the catalyst under neat condition for per-*O*-acetylation step followed by additional use of 4.9 mol% of the same catalyst in methanol at 40 °C generating the glycosyl hemiacetals (**4a**/**4b** or **4c**) within several hours in moderate to good yields.

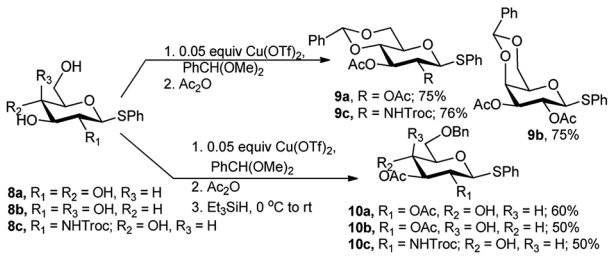
In 2006, Weng *et al.* published a very interesting report where MoO_2Cl_2 was employed as the sole catalyst for a one-pot four-step reaction. D-Glucose (**1a**) was acetylated using 3 mol% of the afore-mentioned catalyst, to form the per-*O*-acetylated glucose (**2a**) under neat condition, followed by one-pot thioglycosidation with *p*-thiocresol in dichloromethane (DCM) using 3 mol% of the foresaid catalyst generating the thioglycoside **5a**, then subsequent deacetylation again after addition of 1 mol% of the catalyst in hot EtOH, and at last 4,6-*O*-benzylidenation reaction using 5 mol% of the catalyst afforded the final product **5** in 70–75% yield without isolation of any intermediate (Scheme 3).[13]

2.2. Sequential arylidenation–acetylation of *S*-/*O*-glycosides

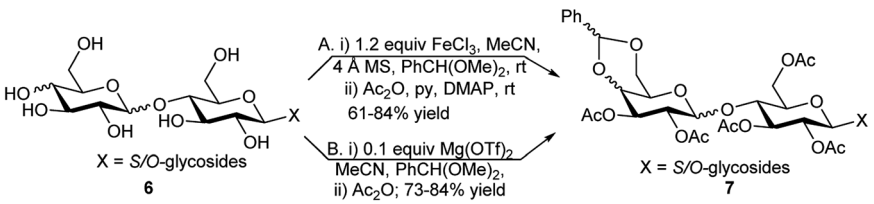
Protection of 4,6-diols as 4,6-*O*-benzylidene is of immense importance in the synthesis of complex carbohydrates[14a,b] as these can be selectively transformed into the corresponding 6-deoxy sugars under oxidative condition.[14c–f] These benzylidene acetals can either be selectively transformed, under reductive conditions[14g–i] to their corresponding 4-*O*-benzylated or 6-*O*-benzylated analogue leaving the alternate hydroxy group free to be utilised further as glycosyl acceptor during oligosaccharide synthesis or to produce the corresponding 4,6-diol.[14j–l]

Ghosh *et al.* observed that although catalytic $FeCl_3$ (20 mol%) could benzylidinate monosaccharide-based glycosides but 1.2 equivalents of $FeCl_3$ was necessary along with 1.5 equivalents of benzaldehyde dimethylacetal and 4 Å MS in dry MeCN for 4′,6′-*O*-benzylidene formation of the corresponding disaccharide glycosides of lactose, maltose or cellobiose (*e.g.*, **6**); this followed by acetylation of the remaining hydroxy groups in the same pot using excess pyridine and Ac_2O, furnished completely acetylated-4′,6′-*O*-acetalated glycosides (*e.g.*, **7**) in 61–84% overall yield ((A) in Scheme 4).[15] Later the same group used 0.1 equivalent of $Mg(OTf)_2$ as a single catalyst for 4,6- or 4′,6′-*O*-benzylidene formation of mono and disaccharide glycosides followed by acetylation of the remaining free hydroxy groups in the same pot ((B) in Scheme 4) in comparable overall yield, 73–84%.[11]

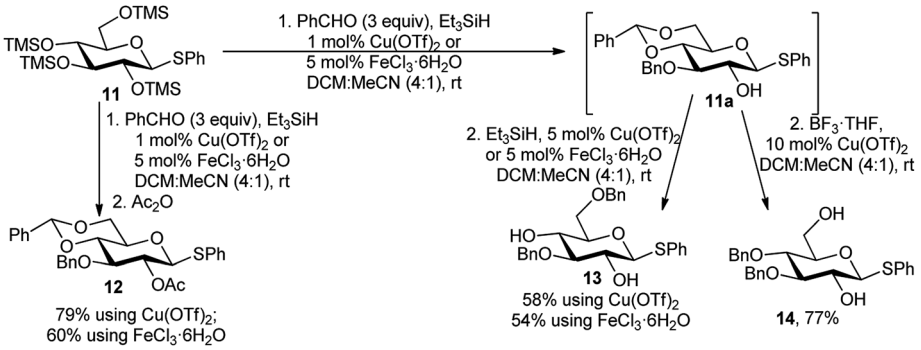
Galan and co-workers employed $Cu(OTf)_2$ as catalyst for one-pot synthesis of diverse sugar derivatives. The one-pot procedure involving 4,6-*O*-benzylidene ring formation was extended



Scheme 5 $Cu(OTf)_2$-catalysed tandem acetalation/acetylation/reductive opening of acetal ring.



Scheme 4 One-pot acetalation–acetylation reaction of disaccharide glycosides.



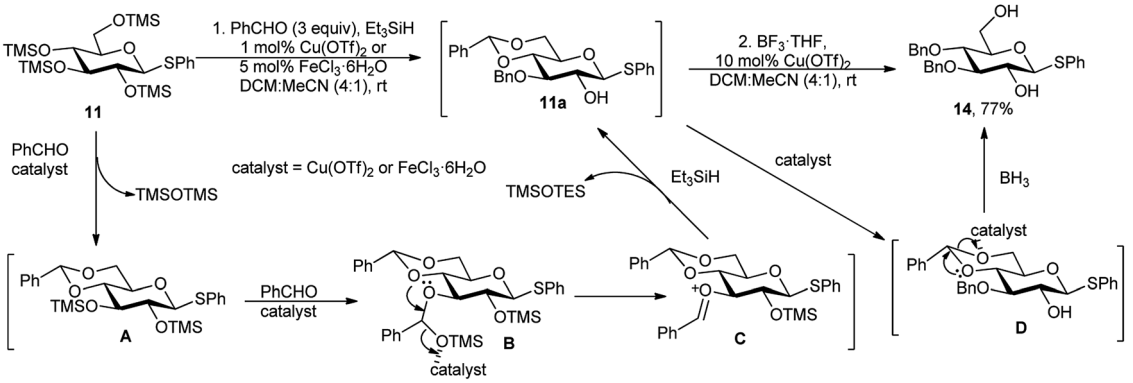
Scheme 6 One-pot regioselective protection of TMS-derived glucose towards glycosyl donor (**12**) and acceptors (**13** and **14**).

to traditional acetylation and finally *in situ* reductive benzylidene ring opening. When phenyl 1-thio glucoside (**8a**), or galactoside (**8b**) and NHTroc protected glucosamine substrate (**8c**) was subjected to one-pot 4,6-*O*-benzylidenation–acetylation reaction, the corresponding fully protected products **9a** and **9b** were obtained in 75%, and **9c** in 76% yields (Scheme 5). Further regioselective reductive opening of the 4,6-*O*-benzylidene ring using Et_3SiH as one-pot three-step reaction sequence resulted in their corresponding 4-hydroxy, 6-*O*-benzyl derivatives **10a** in 60% yield and **10c** and **10b** in 50% yield (Scheme 5).[16]

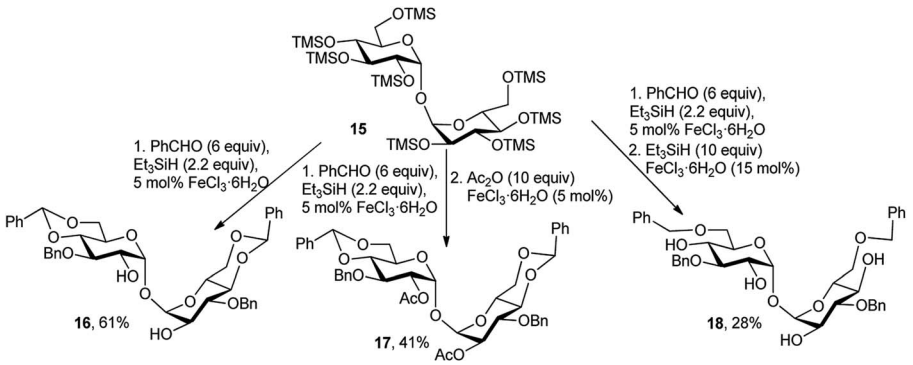
2.3. Regioselective sequential protection of TMS-derived sugars involving acetalation

Regioselective sequential protection of TMS-derived sugars was first utilised by Hung and co-workers.[17] TMS-protected sugars were chosen over normal free sugars to overcome the solubility barrier of native sugars. They used NEt_3 and TMSCl for silylation of free sugar and then used catalytic amount of TMSOTf for large number of versatile one-pot transformation of carbohydrates involving acetalation reaction as the backbone reaction followed by several other one-pot reactions toward multiple directions. After this first report of such TMSOTf catalysed regioselective transformations, a plethora of reports were published thereafter.[18] We are not going into the details of these type of reactions as "Si" is a metalloid. Inspired by these encouraging reports on TMSOTf-catalysed reactions, Beau and co-workers investigated metal catalysis for similar purposes. They reported a tandem process of benzylidenation – regioselective reductive etherification–acylation, catalysed initially by $Cu(OTf)_2$,[19a] and in another case by $FeCl_3 \cdot 6H_2O$,[19b] as a key step of orthogonally protected sugar derivatives. Scheme 6 illustrates the approach, with per-*O*-trimethylsilylated thioglucoside **11**. In the presence of $Cu(OTf)_2$ or $FeCl_3 \cdot 6H_2O$, the per-*O*-silylated glucosides (**11**) underwent a sequential reaction with benzaldehyde and Et_3SiH, providing 4,6-*O*-benzylidene-3-*O*-benzyl derivatives *in situ*, and subsequent reaction with Ac_2O finally provided the 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-benzyl glucopyranosides **12** in moderate to good yield. Moreover, after *in situ* generation of 4,6-*O*-benzylidene-3-*O*-benzyl free C-2-hydroxy intermediate **11a**, followed by reductive opening of the corresponding 4,6-*O*-benzylidene acetal at *O*-4 or *O*-6 produced the respective 2,4-diol **13** or 2,6-diol **14** in good yields as well. Whereas, the *O*-6 ring opening using $BH_3 \cdot THF$ was not compatible with $FeCl_3 \cdot 6H_2O$ but well-suited with $Cu(OTf)_2$.

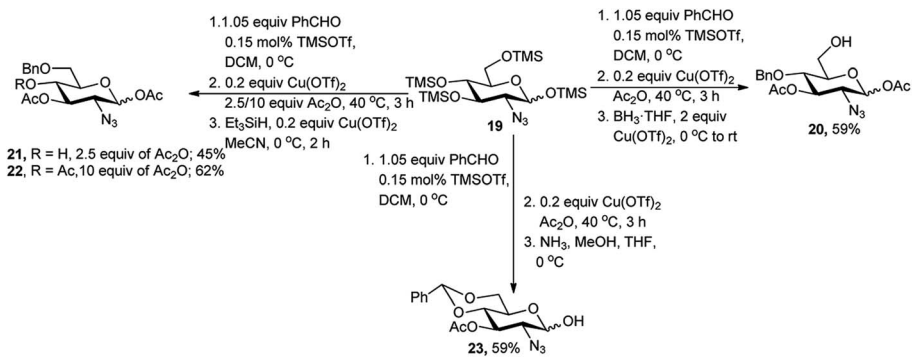
The proposed reaction mechanism for the regioselectivity of *O*-3 benzylation is that at room temperature, a 4,6-*O*- and 2,3-*O*-dibenzylidene intermediate could be generated, and then after regioselective reductive ring opening of the less stable 2,3-*O*-dibenzylidene acetal, the *O*-3 benzylated compound **11a** was formed exclusively, non-upsetting the more stable 4,6-*O*-benzylidene ring (Scheme 7). While anhydrous $FeCl_3$ is as effective as the aforesaid catalysts, and other iron salts such as $Fe(acac)_3$, $(FeCl_3)_2(TMEDA)_3$, $Fe(NO_3)_3 \cdot 9H_2O$, or $FeCl_2 \cdot 4H_2O$ were either inefficient or furnish lower yields.[19b]



Scheme 7 Probable mechanism for one-pot protection sequence of TMS derived sugar.



Scheme 8 Tandem $FeCl_3 \cdot 6H_2O$-catalysed reaction of TMS protected α,α-D-trehalose.

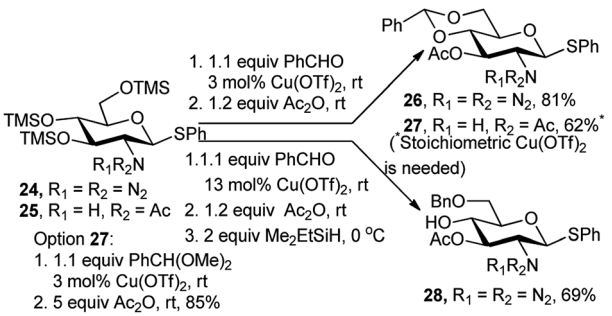


Scheme 9 Regioselective sequential one-pot protection protocols of TMS derived 2-azido-2-deoxy-D-glucose.

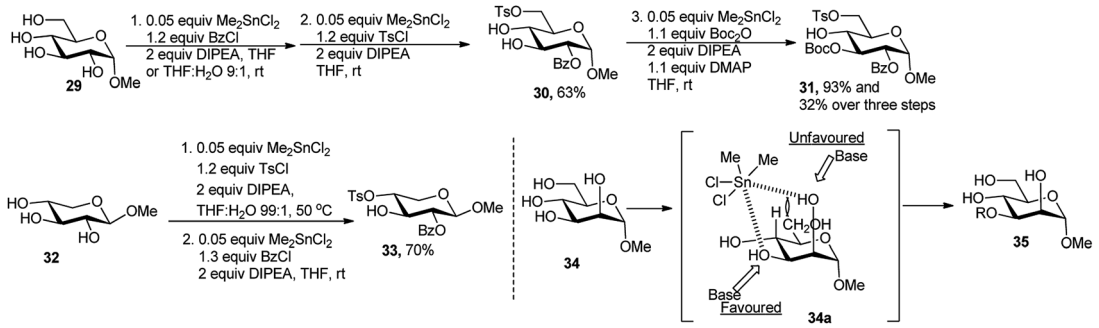
Later, J.-M. Beau's group also demonstrated the catalytic efficacy of $FeCl_3 \cdot 6H_2O$ in one-pot synthesis of several disaccharide derivatives.[19b,c] Thus, one-pot reaction of C-2-symmetric per-*O*-silylated-α,α-D-trehalose **15** with 6 equivalents of benzaldehyde, 2.2 equivalents of Et_3SiH, and 5 mol% of $FeCl_3 \cdot 6H_2O$ provided the symmetric benzylated compound **16**, in 61% isolable yield (Scheme 8). This procedure could also be prolonged to a three-step process to obtain totally protected disaccharide **17** (Scheme 8). Thus, adding an excess of Ac_2O (10 equivalents) and 5 mol% of $FeCl_3 \cdot 6H_2O$ furnished the expected 2,2′-di-*O*-acetylated-α,α-D-trehalose **17** in 41% yield. The shortcoming of this method was perceived with the one-pot bis-reductive benzylidene ring opening using 10 equivalents of Et_3SiH and 15 mol% of the catalyst, which afforded the expected compound **18** in only a moderate overall yield of 28%.

The one-pot protocol with TMS derived sugar was also used for regioselective one-pot protection of 2-azido-2-deoxy-D-glucose derivative by Chang *et al.* in 2010.[20] TMS protected 2-azido-2-deoxy-D-glucose substrate **19** was subjected to 4,6-*O*-benzylidene protection reaction followed by $Cu(OTf)_2$ catalysed acetylation with excess Ac_2O, and then reductive opening of the benzylidene ring with $BH_3 \cdot THF$, afforded free 6-hydroxy-2-azido-2-deoxy-D-glucose derivative **20** in 59% overall yield. To alter the ring opening pattern, they replaced the reducing agent $BH_3 \cdot THF$ by Me_2EtSiH and observed that the acetylation condition plays critical role in the outcome of the one-pot process. When 2.5 equivalents of Ac_2O were used then 4-hydroxy group free product **21** was isolated in 45% yield, whereas use of 10 equivalents of Ac_2O produced its corresponding acetylated analogue **22** in 62% overall yield (Scheme 9). They extended this one-pot reaction sequence toward generation of the hemiacetal **23**, starting from the same tetra-*O*-TMS derivative **19**.[20] In this case, after formation of the 4,6-*O*-benzylidene ring, the 1,3-di-*O*-acetylation was accomplished under $Cu(OTf)_2$-catalysis and further treatment with NH_3 resulted in anomeric deacetylation with 59% overall yield (Scheme 9).

Instead of changing the promoter in the course of the one-pot protocol, a tandem catalysis with $Cu(OTf)_2$ worked well



Scheme 10 $Cu(OTf)_2$-catalysed one-pot regioselective protection of D-glucosamine.



Scheme 11 Me_2SnCl_2-catalysed one-pot regioselective protection of polyols.

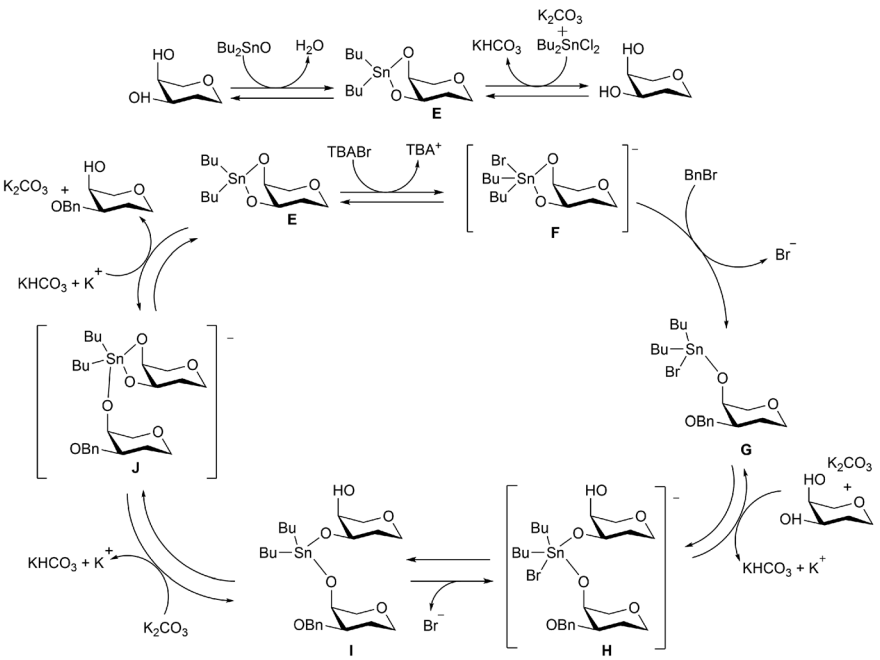
during the entire process. Starting from the phenyl 1-thio-β-D-glucosamine derivatives **24** and **25**, catalysis of the acetalation/acetylation steps proceeded properly with the azido substrate providing 81% of **26**, using only 3 mol% of $Cu(OTf)_2$ (Scheme 10).[21] With benzaldehyde for the acetalation step, a stoichiometric amount of the copper salt was required for completion of the reaction with the acetamido substrate **27**. Notwithstanding, use of benzaldehyde dimethyl acetal enabled a clean formation of **27** in 85% yield under catalytic conditions (Scheme 10). In the azido series, extension of the copper catalysis to a three-step sequence ending with a selective reductive opening of the benzylidene ring provided the 4-OH derivative **28** in 69% overall yield.

2.4. Regioselective one-pot protection involving tin coordination

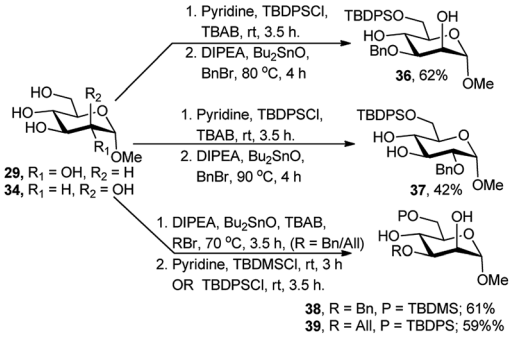
Use of stoichiometric amount of tin salt in regioselective protection of vicinal diols or spatially accessible diols (*e.g.* 4- and 6-hydroxy) has a long history in the carbohydrate field.[22] Later, Demizu *et al.* reported catalytic use of tin salt for the first time, toward regioselective protection of polyols.[23a]

Thus, methyl glucoside (**29**) was selectively mono-benzoylated using 0.05 equivalent of Me_2SnCl_2 as catalyst along with 1.2 equivalents of benzoyl chloride and 2 equivalents of *N*,*N*-diisopropylethylamine (DIPEA) in tetrahydrofuran (THF).

One-pot tosylation under similar condition using 1.1 equivalents of tosyl chloride produced the corresponding methyl 2-*O*-benzoyl-6-*O*-tosyl-α-D-glucopyranoside **30** in 63% overall yield. Interestingly, differentiation of the remaining 3,4-*trans*-diequatorial dihydroxy groups in **30** using Boc_2O as the reagent under similar Me_2SnCl_2-catalysed conditions was successfully achieved to yield the 3-*O*-Boc protected product **31** in excellent yield (93% for this step and 32% for overall three steps) and regioselectivity (Scheme 11). Regioselective mono-benzoylation of 2-position followed by one-pot tosylation at 4-position of β-methyl xylopyranoside **32** resulted in compound **33** in 70% yield over two steps (Scheme 11). The excellent selectivity can be attributed to (a) the reversible interaction between Me_2SnCl_2



Scheme 12 Catalytic cycle of organo-tin-catalysed reaction as proposed by Xu *et al.* (2014)[25] (reproduced from ref. 25 with permission from John Wiley and sons, copyright 2020).



Scheme 13 Bu_2SnO-catalysed regioselective one-pot protection of 2,3,4,6-tetraols.

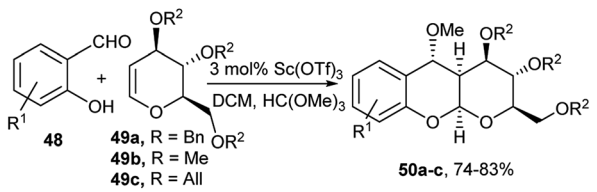
with the 1,2-*cis*-dioxygen atoms of the α-glucoside **29**; (b) the increase of the proton acidity in the tin-coordinated intermediate which can be deprotonated easily by a weak base, such as DIPEA or 1,2,2,6,6-pentamethylpiperidine (PEMP);[23b] and (c) the nucleophilic addition on benzoyl chloride from the less hindered alkoxide to provide the corresponding 2-*O*-benzoyl derivatives for glucose and xylose in high yield. A similar phenomenon was observed in the case of the α-mannoside **34** (Scheme 11). The 3-*O*-functionalised product **35** was isolated *via* the proposed 2,3-*cis*-oriented five-membered ring intermediate **34a**, presumably formed *via* elimination of 2 equivalents of HCl and further activation of the C-3 hydroxy group.[23b]

The use of a catalytic amount of Bu_2SnO under solvent-free conditions was first developed by Iadonisi and co-workers for organotin-catalysed benzylation and allylation of sugar polyols.[24] Dong and Pei further demonstrated that regioselective benzylation could also be executed in toluene in the presence of organotin reagents, such as Bu_2SnO, Bu_2SnCl_2, or Me_2SnCl_2, and also proposed a catalytic cycle as shown in Scheme 12.[25] After the formation of dibutylstannylene acetal intermediate **E** between substrates and 0.1 equivalent of organotin, the intermediate **E** would further react with BnBr in the presence of 0.1 equivalent of tetrabutyl ammonium bromide (TBAB), leading to intermediate **G** where one position is benzylated and the other occupied by the tin species coordinated by a bromide. Deprotonated by a base, such as potassium carbonate, the unbenzylated substrate would also coordinate to the tetracoordinate tin atom to form pentacoordinate tin intermediate **H**. After tin species exchange through intermediates **I** and **J**, the final benzylated product would be generated from intermediate **J**, leading to the regeneration of dibutylstannylene acetal **E** from the un-benzylated substrate and further starting the next cycle.

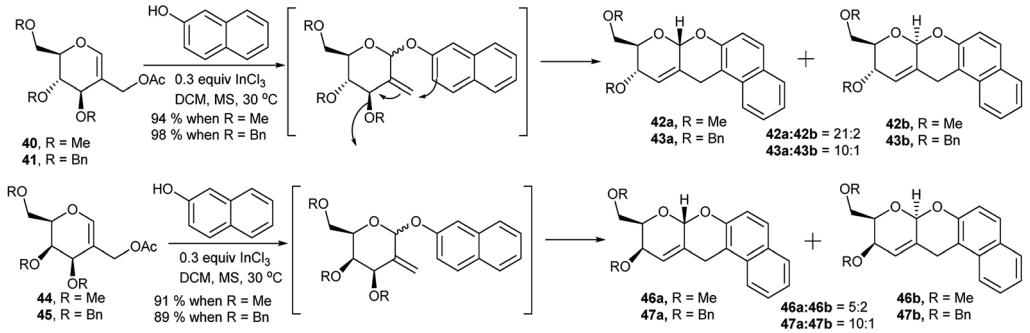
Recently, orthogonal protection of saccharide polyols, under solvent-free condition and regioselective one-pot sequence employing TBDPS- or TBDMS-silylation at *O*-6 followed by Bu_2SnO-catalysed benzylation or allylation, was reported by Iadonisi and co-workers (Scheme 13).[26] This one-pot two-step protocol worked for the 2,3,4,6-tetraols **29** and **34**, affording the 6-*O*-silylated and 3-*O*-benzylated/allylated diols **36**, **38** and **39** and 6-*O*-silylated and 2-*O*-benzylated diol **37** in moderate to good yields (42–62%). The lower yields could be the results of the competitive reaction in the second silylation reaction due to residual etherification reagents from the first step for compounds **36** and **39** or the cleavage of the TBDPS group in the second benzylation step under high temperature for compound **37**. They also showed that Bu_2SnO-catalysed alkylation/silylation reaction combination is independent of their operational sequence.

3. Metal-catalysed tandem/domino/cascade/sequential one-pot reactions on glycal-based substrates

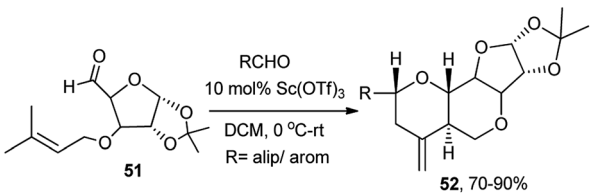
Glycals have been used as potential substrates for generation of sugar-based scaffolds.[27] Lewis acid catalysed synthesis of sugar-fused chiral pyrano-pyran motifs was first reported by Balasubramanian *et al.* in 1993 and then after a decade in 2003.[28] Role



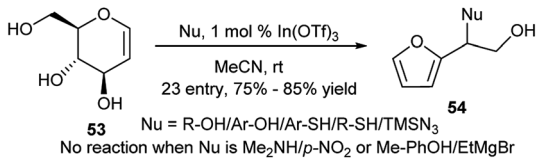
Scheme 15 $Sc(OTf)_3$-catalysed synthesis of pyrano[3,2-*b*]-1-benzopyrans.



Scheme 14 $InCl_3$-catalysed Ferrier rearrangement-tandem cyclisation of 2-*C*-acetoxy glycal.



Scheme 16 $Sc(OTf)_3$-catalysed ene-Prins reaction for generation of hexahydro-2*H*-furo[3,2-*b*]pyranopyrans.



Scheme 17 $In(OTf)_3$-catalysed synthesis of α-substituted furan derivatives.

of $InCl_3$ as metal catalyst toward such transformation of 2-*C*-acetoxymethyl glycals in more efficient fashion was observed by Ghosh *et al.* in 2005.[29a] Later on they prepared a number of such derivatives by coupling between 2-*C*-acetoxymethyl glycals and 2-napthol (Scheme 14) and studied the gelation property of one of these pyrano-pyran ring systems in detail.[29b,c] In the presence of catalytic amount of $InCl_3$ methylated 2-*C*-acetoxy glucal (**40**) underwent Ferrier rearrangement with 2-napthol, followed by tandem cyclisation producing the corresponding products (**42a** and **42b**) in excellent yield and stereoselectivity (94%, **42a : 42b** = 21 : 2, Scheme 14) whereas the same for galactal analogue **44** resulted in good yield but poor stereoselectivity (91%, **46a : 46b** = 5 : 2, Scheme 14). For both benzylated glucal **41** and galactal (**45**) derivative, the reactions were almost equally good yielding and stereoselective (98% of **43** with **43a : 43b** = 10 : 1 and 89% of **47** with **47a : 47b** = 10 : 1, Scheme 14).

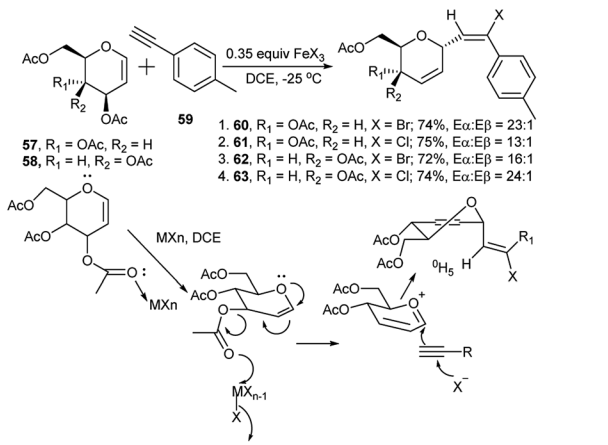
An easy efficient access to highly diastereoselective pyrano [3,2-*b*]-1-benzopyrans following a different one-pot route was developed by Yadav *et al.* (Scheme 15) where pyranopyrans (**50**) were generated from $Sc(OTf)_3$ catalysed three-component one-pot reaction of glycals (**49**), trimethylorthoformate and substituted salicylaldehyde (**48**).[30]

In continuation to the prior work on iodine catalysed Prins cyclisation on sugar based homoallylic alcohols in reaction with aldehydes toward generation of sugar annulated tetrahydropyrans,[31a–d] Yadav *et al.* further utilised $Sc(OTf)_3$ for a similar application in other related sugar systems (**51**), which afforded high yields of highly stereoselective hexahydro-2*H*-furo[3,2-*b*] pyranopyrans (**52**),[31e] formed *via* tandem ene-Prins cyclisation routes (Scheme 16).

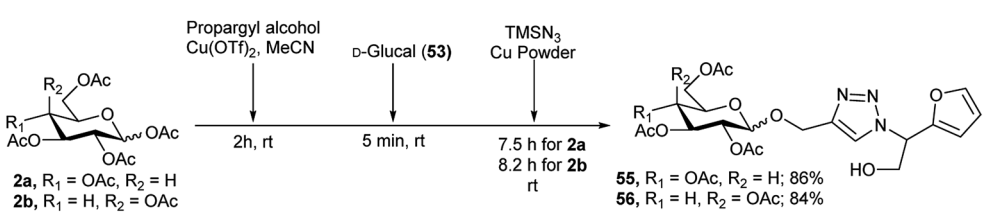
Another indium(III) salt, $In(OTf)_3$ has been used by Mukherjee *et al.* for the one-pot transformation of the D-glucal toward racemic α-substituted α-hydroxymethylfurfuryl derivatives in the presence of nucleophiles.[32] Thus, reactions of free D-glucal (**53**) with most of the *O*-, *S*-, *C*- and *N*-nucleophiles resulted in their corresponding furan-based products (**54**) in good yields (Scheme 17). However the reaction protocol is not valid for few nuleophiles like free amine, Grignard reagent, *p*-NO_2/Me-phenols, but reason behind this is not known.

Extending this idea to another aspect where α-azido-α-hydroxymethyl furan was formed by the reaction of D-glucal with $TMSN_3$ in combination with a click reaction of this azide with propargyl group, the same group then reported Cu-catalysed construction of various triazole fused furan-based glycoconjugates.[33] Thus, they first converted per-*O*-acetylated glucose (**2a**)/galactose (**2b**) to its corresponding propargyl glycosides by reaction with propargyl alcohol in the presence of 10 mol% $Cu(OTf)_2$ catalyst, then subsequent reaction with D-glucal (**53**) and $TMSN_3$ resulted in their corresponding triazole-furan-based gluco (**55**)/galacto (**56**) derivatives in good yields (Scheme 18).

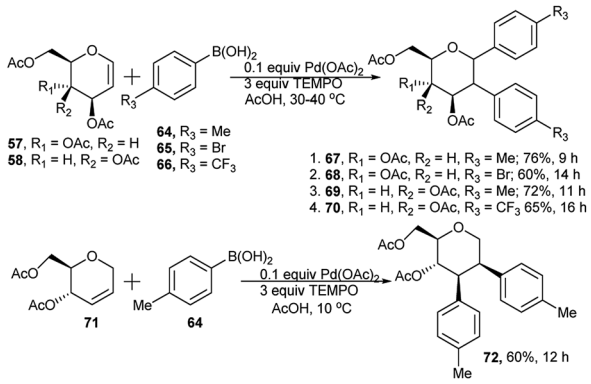
In 2013, Mukherjee's group reported halogenated Lewis acid promoted tandem glycosylation–halogenation of aryl acetylenes with glycals to form stereo defined α,*E*-trisubstituted halo vinyl glycosides and their subsequent application in Pd-catalysed cross-coupling reactions.[34]



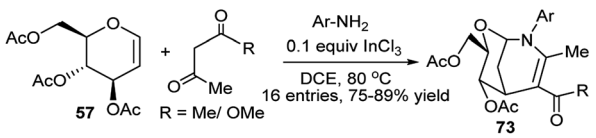
Scheme 19 $FeCl_3$ or $FeBr_3$-catalysed tandem halogenated *C*-vinyl glycoside synthesis using inactivated aryl acetylene.



Scheme 18 $Cu(OTf)_2$-catalysed one-pot MC-synthesis of triazole-furan-based glycoconjugates.

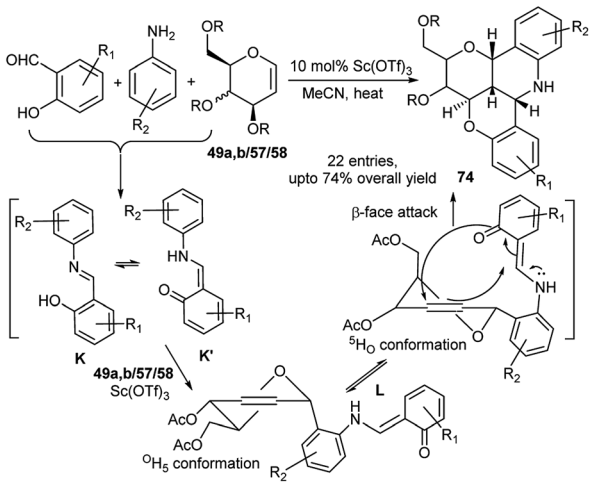


Scheme 20 Pd(II)-catalysed domino Heck–Suzuki arylation of glycals.

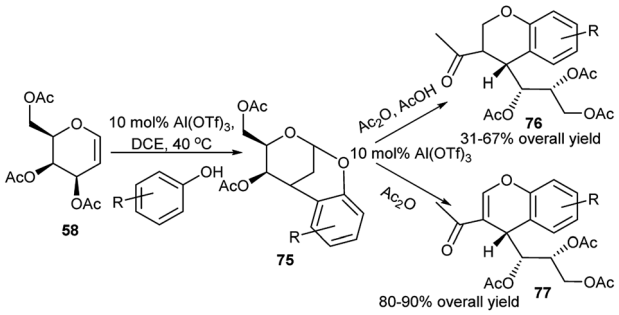


Scheme 21 $InCl_3$-catalysed three component preparation of oxaaza bicyclononene scaffolds.

Reaction of tri-*O*-acetyl-D-glucal (**57**) with *p*-methyl phenyl acetylene (**59**) using 0.35 equivalent of $FeBr_3$ at −25 °C produced the corresponding brominated *C*-vinyl glycoside **60** in 74% yield ($E\alpha : E\beta = 23 : 1$, entry 1, Scheme 19), whereas the same reaction with its galactal analogue (**58**) also resulted in the corresponding product **62** in almost similar yield albeit with relatively lower stereoselectivity (72%, $E\alpha : E\beta = 16 : 1$, entry 3, Scheme 19). Reaction of the same acetylene **59** with glucal **57** under $FeCl_3$ catalysed reaction condition produced the corresponding chlorinated *C*-vinyl glycoside **61** in good yield and moderate stereoselectivity (75%, $E\alpha : E\beta = 13 : 1$, entry 2, Scheme 19) and that with galactal **58** resulted in the corresponding chlorinated product **63** in excellent yield and stereoselectivity (74%, $E\alpha : E\beta = 24 : 1$, entry 4, Scheme 19). As a plausible mechanism they presumed the possibility of the Lewis acid to play two major roles when phenyl acetylene and glucal triacetates were reacted. At first, the metal salt coordinates with the allylic acetoxy group of the glycal, making it more labile, and then the ring oxygen participates to generate a glycosyl oxocarbenium ion intermediate, that is subsequently attacked from the α-face by the alkyne which is concomitantly attacked by a halide ion, ultimately resulting in the formation of the corresponding product.

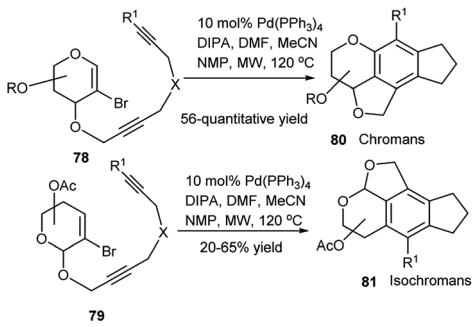


Scheme 22 $Sc(OTf)_3$-catalysed one-pot domino synthesis of pentacyclic benzopyran fused pyranoquinolines.

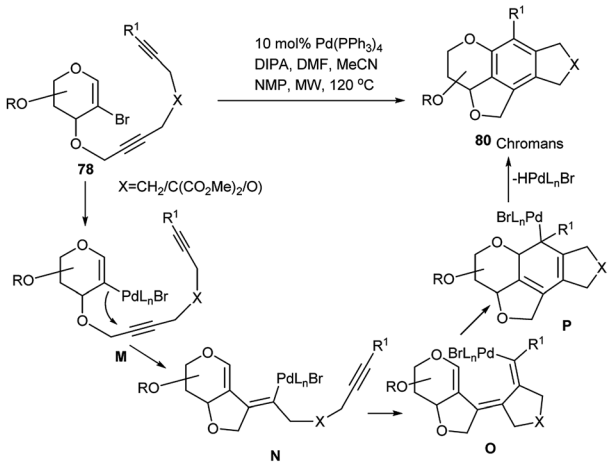


Scheme 23 $Al(OTf)_3$-catalysed tandem synthesis of chiral bridged benzopyrans, and sugar-appended chromans and chromenes.

Palladium-catalysed, TEMPO mediated regio- and diastereo-selective domino Heck–Suzuki arylation of glycal (**57**/**58**) and pseudo glycals (**71**) was reported by Kusunuru *et al.*[35] When glycals were allowed to react with a wide range of arylboronic acids using 10 mol% of $Pd(OAc)_2$ as catalyst and 3 equivalents of TEMPO as radical initiator in acetic acid, the corresponding diaryl glycosides were obtained in excellent yield and diastereoselectivity. The resulting diaryls are C1–C2 (α,α) in the case of glycals and C1–C2 (β,β) for pseudoglycals and both were confirmed by NOSEY spectrum. Thus, reaction of D-glucal derivative **57** separately with arylboronic acids **64** and **65** at 30–40 °C produced the corresponding *cis*(α,α) 1,2-diarylated glucosides **67** and **68** in 76% and 60% respective yields (entries 1 and 2, Scheme 20). Similar reaction between D-galactal derivative **58** and arylboronic acids **64** and **66** separately resulted in the corresponding 1,2-diarylated galactosides **69** and **70** in 72% and 65% respective yields (entries 3 and 4, Scheme 20). Apart from the reaction of glycals, pseudoglycal **71**, when subjected to react with *p*-



Scheme 24 Pd(0)-catalysed domino synthesis of chromans and isochromans.



Scheme 25 Proposed mechanistic pathway for one-pot conversation of **78** to **80**.

methylphenylboronic acid **64** under the similar reaction conditions but at relatively lower temperature, produced its corresponding *cis*(β,β) 2,3-diarylated glycoside **72** in moderate yield (60%, Scheme 20). They also provided a possible reaction mechanism and a catalytic cycle of Pd(II)/Pd(0), showing involvement of TEMPO playing a key role in blocking *syn*-and *anti*-elimination of C2-PdOAc and C3-α/β-OAc from an anomeric aryl, 2-PdOAc intermediate (thus minimising the possibility of a side reaction generating *C*-aryl pseudoglycal); this was also corroborated by the corresponding quantum chemical analysis.

Yadav *et al.* has used glucal (**57**) as the sugar substrate for $InCl_3$-catalysed three-component (3C) one-pot reactions with aryl amines and 1,3-dicarbonyl compounds (β-diketone/β-ketoester) in refluxing 1,2-dichloroethane (DCE) to generate the corresponding oxaaza bicyclononene scaffolds (**73**) in excellent yields and high diastereoselectivity. *In situ* generated β-enaminoketone or β-enaminoester is supposed to react further with the glycal to afford the bicycloheterocycles (Scheme 21).[36a]

Yadav's group also reported a one-pot 3C condensation using 2-deoxyribose, acetyl acetone and aromatic amines to give similar 2-deoxyribose-based bicyclic aminols in good yields albeit moderate or no stereoselectivity.[36b]

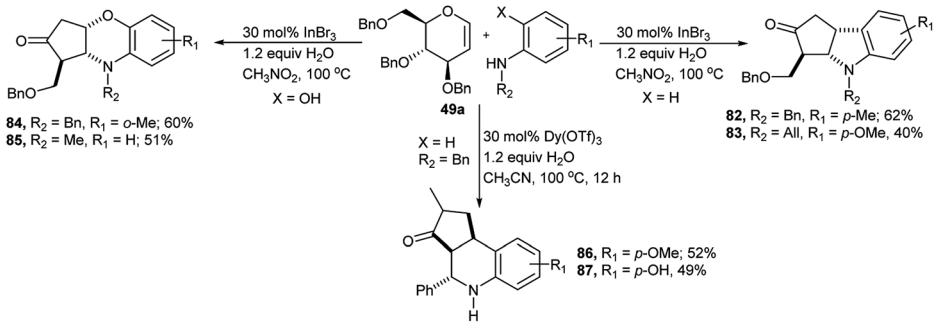
A library of pentacyclic benzopyran fused pyranoquinolines (**74**) were prepared by another research group in low to high yields by $Sc(OTf)_3$-catalysed one-pot 3C reactions of glycals (**49a,b**/**57**/**58**) with salicylaldehyde or its derivatives and aryl amines in acetonitrile at elevated temperature (Scheme 22).[37a]

This proceeded by domino Ferrier rearrangement and Povarov like reactions with polycyclisation, as also observed by this group earlier in another case.[37b] As proposed by the authors, the reaction proceeds initially by the formation of imino phenol **K** that remains in equilibrium with the corresponding enaminone **K′**, the latter then reacts with $Sc(OTf)_3$ activated glycal generating intermediate **L**; **L** in its ^5H_O conformation undergoes intramolecular polycyclisation from the β-face of the pseudoglycal ring (Scheme 22). The reactions based on aniline or salicylaldehyde rings bearing electron withdrawing substituent proceeded smoothly giving the corresponding pentacyclic product in good yield, but aromatic rings bearing electron donor substituent generated the expected products in low yield. Further CAN mediated oxidative ring opening of one such pentacyclic product afforded an enantiopure chromenoquinoline, holding at C6, a trioxypropyl pendant.[37a]

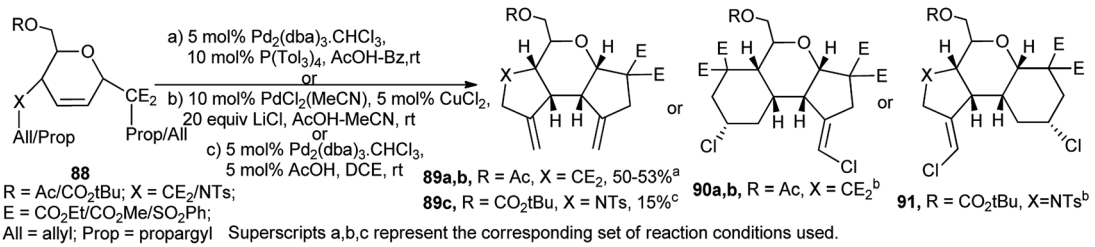
$Al(OTf)_3$ has been exploited as Lewis acid catalyst by Williams and co-workers for tandem reaction on D-galactal triacetate (**58**). This in reaction with phenol or its ring derivatives underwent tandem process as proposed by the authors: initial Ferrier rearrangement followed by tandem Friedel–Crafts C–C bond formation, assisted anchimerically by C4-OAc group, ultimately generating chiral bridged benzopyrans (**75**), as shown in Scheme 23.[38a] It is to be noted that D-glucal triacetate (**57**) when treated under the above condition underwent 1-*C*-arylation.[38b] Interestingly, further $Al(OTf)_3$ catalysed reaction of **75** with Ac_2O in the presence or absence of acetic acid afforded respectively sugar appended optically pure chromans (**76**) or chromenes (**77**).[38a]

A synthetic protocol for highly substituted structurally diverse tetracyclic chromans **80** and isochromans **81** having sugar-aromatic hybrid structures, was developed by Werz's research group using diyne derived 2-bromoglycal system **78** or diyne-based 2-bromo-2,3-unsaturated sugar glycosides **79** by Pd(0) catalysed domino reaction involving oxidative addition, two successive carbopalladation and cyclisation steps (Scheme 24).[39a,b]

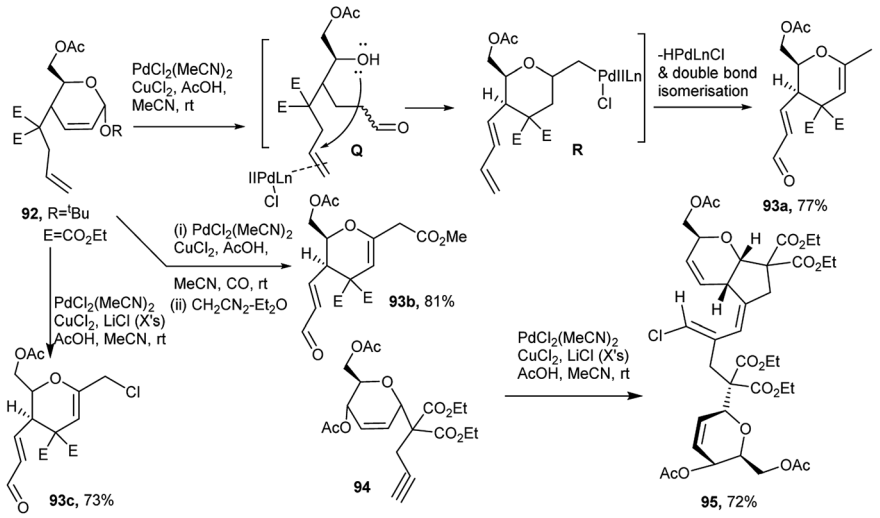
Inspired by the initial success of this domino protocol, this group further elaborated the method toward synthesis of chiral



Scheme 26 One-pot cascade transformation of D-glucal into drug like scaffolds.



Scheme 27 $Pd_2(dba)_3$-catalysed cascade reactions on sugar-based 1,6-enynes.

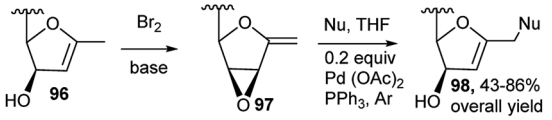


Scheme 28 Pd^{II}–$CuCl_2$-mediated domino reactions of sugar-based 1,6-diene and -enyne.

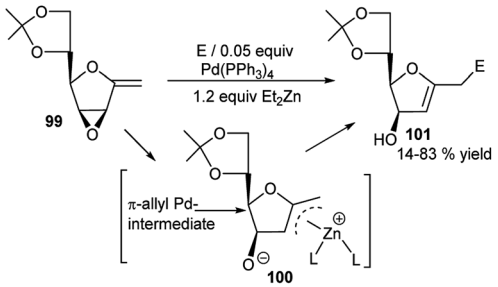
substituted biaryl systems from sugar-disubstituted tetra-alkynes[39c] and also synthesis of anthracycline aglycone mimics by domino carbopalladation of glycal-based bisalkynes.[39d] The mechanistic pathway as proposed[39b] by the authors is shown in detail in Scheme 25. Oxidative addition of Pd(0) into C–Br of the 2-bromoglycal substrate (**78**) generates an intermediate **M**, then after two successive steps involving cyclisation reactions *via* attack at alkyne carbon of carbapalladium intermediates (**M** and **N**) a new intermediate **O** is formed. Final Pd(II)-mediated intramolecular cyclisation of **O** followed by aromatisation of the resulting intermediate **P** affords the tetracyclic chroman **80**.

Yao *et al.* reported diversely-oriented synthesis of three different types of structurally drug like N-heterocyclic fused ring from one-pot cascade reaction between 2,3,6-tri-*O*-benzyl-D-glucal **49a** and aromatic amines (Scheme 26).[40] Reaction of D-glucal **49a** with substituted aromatic amines produced their corresponding indolines in moderate yields. Reaction of **49a** with *N*-benzyl-*p*-methylaniline in the presence of 30 mol% $InBr_3$ and 1.2 equivalent water in nitromethane at 100 °C produced the corresponding indoline derivative **82** in 62% yield; whereas similar reaction between the same D-glucal **49a** and aniline carrying electron withdrawing group at phenyl ring and allyl substitution at nitrogen produced their corresponding indoline derivative **83** in lower yield (40%, Scheme 26). On the other hand, similar reaction of D-glucal **49a** with secondary aniline bearing an *o*-hydroxyl group produced the corresponding benzoxazine-fused heterocycles **84** or **85** in relatively higher yields (Scheme 26). The comparative higher yield for this second kind of products was attributed to a more energetically favoured formation of the six-membered fused ring system compared to the five-membered ring and the superior nucleophilicity of the hydroxy moiety present in the aniline substrate. $Dy(OTf)_3$-catalysed reaction of the D-glucal **49a** and *N*-benzyl-aniline produced in moderate yields tetrahydroquinoline-fused *cyclo*-pentanones in acetonitrile at 100 °C in the presence of 1.2 equivalent of water for 12 hours *via* Ferrier reaction followed by cascade interrupted Nazarov rearrangement. Under this condition *N*-benzyl-*p*-methoxy aniline and *N*-benzyl-*p*-hydroxyl aniline generated the corresponding fused rings **86** and **87** in 52% and 49% respective yields (Scheme 26).

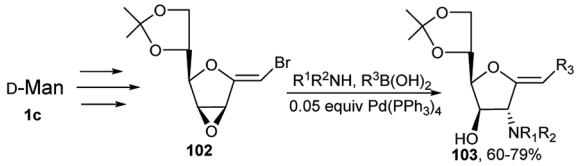
Holzapfel *et al.* employed pseudoglycal derived 1,6-enyne **88** for palladium-catalysed cascade carbocyclisation toward



Scheme 29 Pd-catalysed domino synthesis of functionalised *C*-glycals.



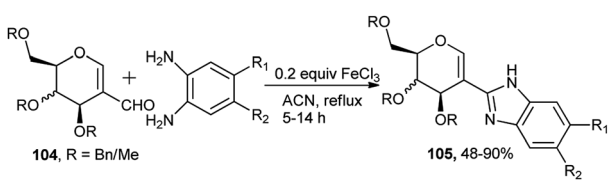
Scheme 30 Pd(0)-catalysed electrophilic reactions of *exo*-glycal-based vinyl oxiranes.



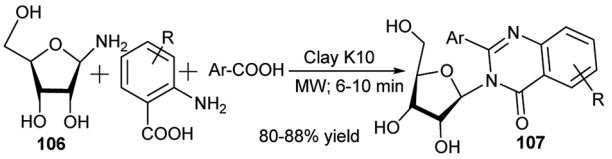
Scheme 31 One-pot synthesis of furanose-based carbohydrate templates.

synthesis of enantiomerically pure tricyclic compounds (**89–91**). Under Wacker conditions in the presence of LiCl, the reactions proceeded with highly stereoselective ring expansion where two new C–Cl bonds were formed in the products (**90a**, **90b** and **91**). The products were thus dependent on the substrates and also on the corresponding reaction conditions (Scheme 27).[41] This research group also reported interesting palladium-catalysed domino reactions in sugar 1,6-dienes and -enynes.[42a,b]

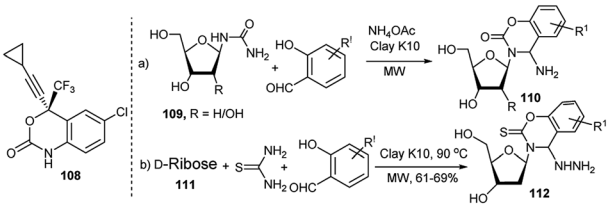
Thus, the 1,6-diene, *viz*. 4-homoallyl substituted pseudoglycals **92** in the presence of $PdCl_2(MeCN)_2$ and $CuCl_2$ in acetic acid-methanol at room temperature, underwent domino ring opening (to **Q**) – ring closure process forming an intermediate (**R**) which after elimination of HPdLnCl followed by double bond isomerisation finally afforded the corresponding functionalised *C*-glycals (dihydropyrans) **93a.** In the presence of CO and the above set of reagents, alkoxycarbonylation of the terminal alkene and domino ring opening-ring closure finally produced functionalised chiral tetrahydropyrans **93b** after methylation by diazomethane. But, under a Wacker condition in the presence of excess LiCl, **92** produced the chlorinated product **93c** (Scheme 28).[42a] Under the Wacker condition, the reaction course was a bit different based on the sugar derived 1,6-enyne substrate, **94**, where the substituted homopropargyl



Scheme 32 $FeCl_3$-catalysed tandem synthesis of sugar-based benzimidazoles.



Scheme 33 4-(3*H*)-Quinazolinone *N*-nucleoside synthesis.



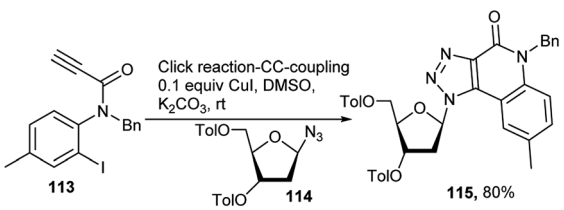
Scheme 34 Clay K10-catalysed 3C-one-pot synthesis of 4-amino-benzoxazinone *N*-nucleosides (**110**) and 1,3-benzoxazine-2-thione *N*-nucleosides (**112**).

group was at C1 of the pseudoglycal, and a dimeric chlorovinyl appended product **95** was formed (Scheme 28).[42b]

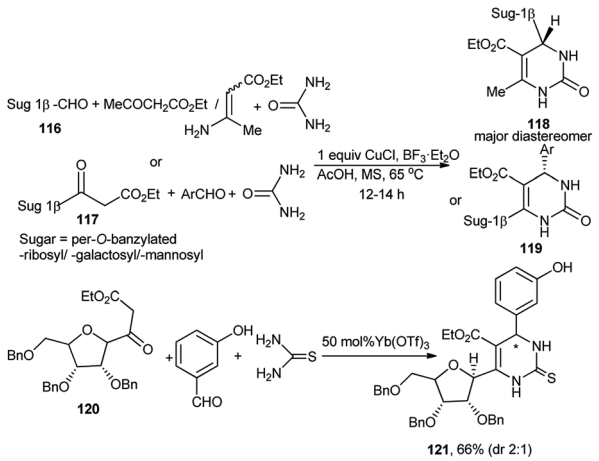
Sugar derived *exo*-glycals having 2,3-oxirane were used by several researchers for one-pot generation of functionalised *C*-glycals under nucleophilic and electrophilic conditions. Thus, Gómez and co-workers utilised 1-*exo*-methylene-2,3-anhydro furanoses **97**, and obtained new functionalised *C*-glycals **98** in two-step one-pot reaction by Br_2 and base from *C*-glycals **96**, for Pd(0)-catalysed nucleophilic addition *vis-à-vis* epoxide opening (Scheme 29).[43]

They further employed vinyl oxiranes having *exo*-glycal skeleton **99** in the presence of Pd(0)-Et_2Zn for reaction with carbonyl electrophiles. This proceeded by domino epoxide opening *via* formation of an allyl-Zn intermediate (**100**) from an initially formed π-allyl-Pd intermediate, followed by subsequent attack by the electrophile, and ultimately generated the corresponding new functionalised *C*-glycal derivatives **101** (Scheme 30).[44] Although the protocol was compatible with highly oxygenated substrates and was highly regioselective in reaction with aldehyde electrophile generating always 1,5-diol, but the stereoselectivity varied from moderate to excellent depending upon the reaction partners.

This group also developed a complete regio- and stereo-controlled one-pot 3C synthesis of 2-aminoglycosylidene type compounds **103** from Pd(0) catalysed reaction of mannose derived halo-alkenyl allylic-oxirane system **102**,



Scheme 35 One-pot tandem synthesis of triazolyl 2-quinolinone.



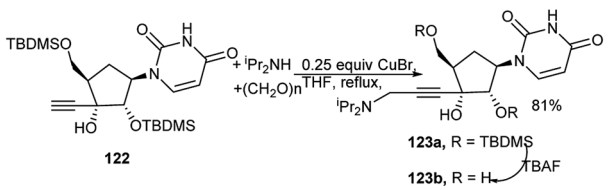
Scheme 36 One-pot synthesis of sugar derived DHP ones.

boronic acids or alkyl boronates and a variety of amines (Scheme 31).[45]

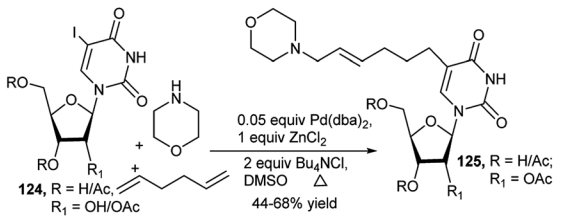
Very recently Mishra *et al.* reported $FeCl_3$-catalysed tandem synthesis of optically pure sugar-based benzimidazoles.[46a] Efficient reaction of benzylated or methylated glycal aldehydes (**104**) with varieties of substituted *ortho*-phenylenediamines in the presence of 20 mol% of $FeCl_3$ catalyst in refluxing acetonitrile produced their corresponding sugar attached benzimidazoles (**105**) in moderate to excellent yield (Scheme 32). $FeCl_3$ catalysed both cyclisation and aromatisation steps. It is to be noted that the efficacy of the tandem reaction is not hampered by carrying out the reaction under nitrogen. It is also to be mentioned that synthesis of similar sugar derived benzimidazoles was effected earlier based on $VO(acac)_2$–$CeCl_3$ combo catalyst in the presence of molecular oxygen.[46b]

4. Metal-catalysed domino/tandem/sequential one-pot (a) syntheses of unnatural nucleosides and (b) reactions on nucleosides

Chemical modification, either in the sugar part or in the base part gives rise to unnatural nucleosides or nucleoside analogues. Many of such compounds are already in use worldwide for treatment of virally infected or cancer patients; several other new nucleosides are under pre-clinical or clinical trial.[47] More efforts are being made for development of new tailor-made nucleosides by synthesis or reactions on other nucleosides, utilising one-pot MC reactions.[48]



Scheme 37 CuBr-catalysed 3C one-pot synthesis of uridine analogues.



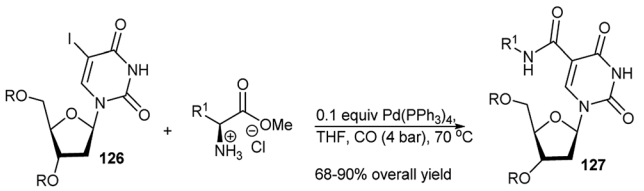
Scheme 38 Palladium-catalysed one-pot synthesis of C-5 aminoalkyl substituted nucleosides.

4.1. One-pot syntheses of novel nucleosides catalysed by metal salt/complex

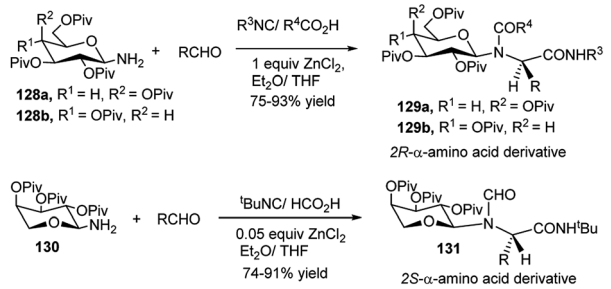
In 2008, Siddique *et al.* reported clay K10 [49a,b]-catalysed one-pot synthesis of 4-(3*H*)-quinazolinone *N*-nucleosides (**107**) from 3C reaction of unsubstituted anthranilic acid, ribosyl amine (**106**) and benzoic acid or its derivatives under solvent-free microwave conditions (Scheme 33).[49c]

In addition to other established nucleoside analogous drugs, a new FDA approved drug called Efavirenz (Sustiva, **108**) having benzoxazinone scaffold is also being used for treatment of AIDS. In order to have nucleoside and benoxazinone in one compound, Yadav and Rai in 2006 synthesised a library of new 4-aminobenzoxazinone *N*-nucleosides (**110**) in 68–80% yields by clay K10-catalysed microwave mediated 3C-coupling reactions under solvent free condition of ribosyl/deoxyribosyl urea (**109**), substituted salicylaldehydes and ammonium acetate (Scheme 34a).[50a] The authors proposed that the reaction proceeds through cycloisomerisation of an aldimine intermediate. In 2013 Rai and Singh reported the 3C one-pot synthesis of several 1,3-benzoxazine-2-thione *N*-nucleosides (**112**). They noted that D-ribose (**111**) in reaction with thiosemicarbazide and salicylaldehyde or its derivatives under microwave condition in the presence of clay K10 afforded the corresponding unnatural nucleosides in 61–69%; interestingly, the corresponding microwave mediated 2C-reactions of the pre-generated sugar anomeric thiosemicarbazides, obtained from combination of ribose and thiosemicarbazides catalysed by $CeCl_3 \cdot 7H_2O$–NaI furnished the corresponding products in better (83–93%) yields (Scheme 34b).[50b] The resulting hydrazinated unnatural nucleosides were finally dehydrazinated.

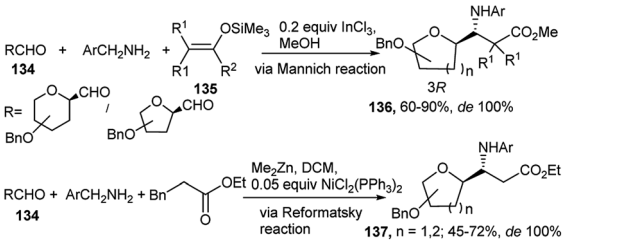
For the synthesis of a group of unnatural fused triazolyl 2-quinolinone (FQuon) nucleosides **115**, Bag *et al.* used *N*-benzyl-*N*(2-iodo-4-methylphenyl)propiolamide **113** for a CuI-catalysed one-pot click reaction with sugar anomeric azide **114** followed by tandem Ullmann type C–C coupling reaction for generation



Scheme 39 Pd(0)-catalysed domino synthesis of amino acid anchored uracil nucleosides.



Scheme 40 Diastereoselective synthesis of sugar appended *R*- or *S*-amino acid derivatives.



Scheme 42 $InCl_3$ and $NiCl_2(PPh_3)_2$-catalysed diastereoselective synthesis of *C*-glycosyl β-amino acid derivatives.

of **115** in its protected form (Scheme 35).[51] Compound **115** is having both donor and acceptor H-bonding site and a conically projected benzene ring. The researchers further studied the photophysical properties of **115**, which exhibited good interaction with BSA, good DNA duplex stabilisation property, as also supported by theoretical studies.

The Biginelli reaction has been widely used for preparation of dihydropyrimidinone scaffolds.[52] A 3C promoter (CuCl/AcOH/BF_3) system using stoichiometric Cu(I) was at first employed by Dondoni *et al.* for 3C one-pot diastereoselective synthesis of a series of N1/C4/C6-monoglycosylated and C4, C6 bisglycosylated dihydropyrimidinone (DHPone) glycoconjugates (**118** and **119**) from Biginelli reaction of sugar (pyranose/furanose) derived anomeric-carboxaldehyde **116**, ethyl acetoacetate or sugar derived β-ketoester **117**, benzaldehyde, respectively and urea[53a–c] in THF at 65 °C (Scheme 36). They also observed that when β-aminoacrylate was used instead of ethyl acetoacetate for the one-pot reaction based on sugar anomeric carboxadehyde; $Yb(OTf)_3$ was established to be the best Lewis acid catalyst. Utilising the 3C promoter based protocol, this group also synthesised bis-*C*-glycosylated dihydropyrimidinones.[53a] They further noticed that whereas the above 3C promoter system was not compatible for the Biginelli reaction for preparation of the thiourea-based products, but use of 50 mol% $Yb(OTf)_3$ could serve the purpose. Thus, $Yb(OTf)_3$ catalysed the one-pot Biginelli reaction of ribofuranosyl-based ketoester **120** with 3-hydroxybenzaldehyde and thiourea generating the corresponding C6-glycosylated DHPone **121** in fair yield albeit lower diastereoselectivity (dr 2 : 1) (Scheme 36).[53b,c]

4.2. Synthesis of novel nucleosides by reactions on other nucleoside derivatives

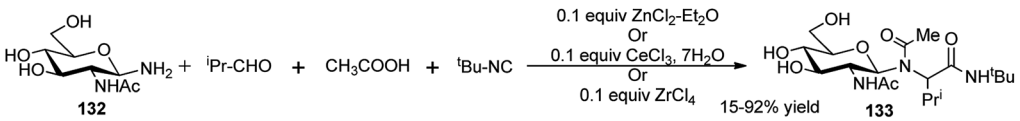
An ethynyl nucleoside (**122**) was utilised to prepare the corresponding C-3′-propargyl amine nucleoside (**123a**) by a CuBr-catalysed one-pot three-component reaction of **122** with diisopropyl amine and paraformaldehyde in refluxing THF (Scheme 37). Eventually further deprotected novel uridine analogue (**123b**) exhibited antitumor activity.[54]

Larock *et al.* used commercially available 5-iodo-2′-deoxyuridine (**124**) for generation of tailor-made nucleosides (**125**) by one-pot MCR. Thus, Pd(0)-catalysed 3C-couplings of (**124**) with 1,2-, 1,3- or 1,ω-diene and different primary/secondary amines in the presence of $ZnCl_2$ afforded a wide variety of C-5 amino-alkyl substituted nucleosides **125** (Scheme 38). It was observed that secondary amines are the most effective amines toward this end. Both acyclic and cyclic dienes can be used, and simple non-conjugated dienes provide good yields. But with increase in chain length/branching, yields get reduced. In the later case, pre-derivatisation of the sugar hydroxy groups was beneficial.[55]

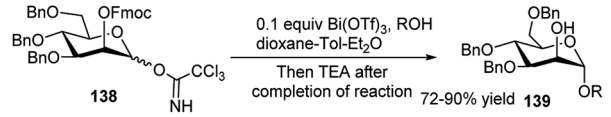
Synthesis of amino acid functionalised uracil nucleosides (**127**) was reported by Gheerardijn *et al.* by a Pd(0)-catalysed domino carboxamidation reaction of uracil nucleosides (**126**) using amino acid esters and carbon monoxide under pressure at 70 °C (Scheme 39).[56] $Pd_2(dba)_3$ was utilised by Grigg *et al.* to catalyse 3C reactions of purine/thymidine/uridine-based allene, aryl/heteroaryl iodide and adamantyl amine or other amines for generation of trisubstituted *Z*-alkenes bearing the corresponding nucleoside skeleton. They further developed a Pd(0)-mediated MC-reaction protocol based on a 1,3,5,7-tetrakis(4-iodophenyl)adamantane, purine derived allene and different amines for generation of a tetrakis adamantane skeleton.[57]

5. Metal-catalysed one-pot synthesis of sugar-based amino acids

Owing to be considered as building blocks for peptidomimetic research and also due to important biological properties of non-proteinogenic amino acids, their design and synthesis have gained much attention among the researchers worldwide toward their future potent application in the fields related to life science.[58] 4C Ugi reaction is the mostly applied isocyanide-based MC reaction for the synthesis of a wide variety of such compounds.[59] Kunz and co-workers extensively studied 4C-Ugi reaction on sugar amines as chiral auxiliaries toward



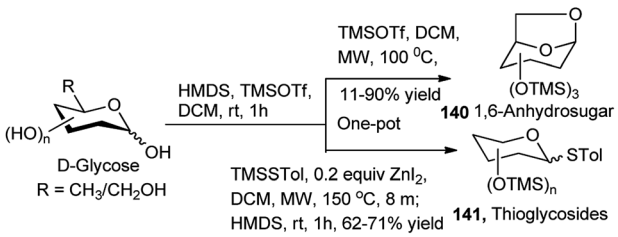
Scheme 41 Sugar-based α-amino acid derivative.



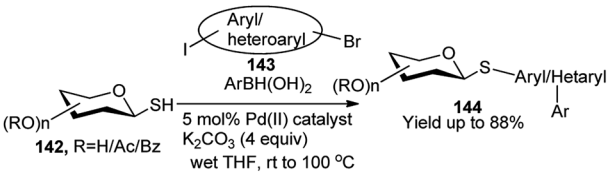
Scheme 43 $Bi(OTf)_3$-catalysed one-pot glycosylation–deprotection.

generation of chiral α-amino acid derivatives by asymmetric induction.[60a–e] For synthesis of chiral *R*-α-amino acid derivatives **129a**, Kunz *et al.* first used 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl amine **128a** as chiral auxiliary for asymmetric synthesis of amino acids; later other sugars were also used. Thus, **128a**[60a,b] or 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosyl amine **128b**[60c] was initially utilised as the chiral amine for $ZnCl_2$-mediated highly diastereoselective 4C-Ugi reaction employing a variety of aldehydes (aliphatic and aromatic), *tert*-butyl or phenyl isocyanide and different carboxylic acids (aliphatic and aromatic); in both of these reports the corresponding *R*-α-amino acid derivatives were obtained (**129a** or **129b**) as shown in Scheme 40.[60a–c] Interestingly, when they made use of 2,3,4-tri-*O*-pivaloyl-β-L-arabinosyl amine **130** as the chiral amine, and reacted it in the presence of catalytic amount of $ZnCl_2$ with a variety of aldehydes (aliphatic, aromatic and heteroaromatic), formic acid and *tert*-butylisocyanide in THF, in each case the corresponding *S*-α-amino acid derivative **131** was obtained in excellent yield (>95%) and high diastereoselectivity (Scheme 40).[60c]

Thus, by proper choice of the sugar as chiral auxiliary, it is possible to generate ultimately both 2*R*- and 2*S*-α-amino acids after removal of the carbohydrate surrogate. Later on, Kunz and co-workers also undertook $ZnCl_2$-mediated stereoselective combinatorial 4C-Ugi reactions on solid support based on polymer bound sugar amine derivatives for synthesis of α-amino acid derivatives;[60d,e] this time equivalent amount of the Lewis acid gave better results, and the performance in the solution phase reactions were better in terms of yields and stereoselectivities than those obtained in the solid phase reactions. Toward synthesis of optically pure α-amino acids, Ugi also studied in detail the effect of substituents and Lewis acids (type and load) on the yield and diastereoselectivity of 4C-sequential one-pot Ugi reactions on unprotected glycosyl amines (glucose, xylose and *N*-acetylglucosamine) as the chiral amine, aldehydes (aliphatic/aromatic), different acids including also *N*-protected amino acids and varied isocyanates. Best results in terms of yield (99%) and diastereoselectivity (de 95–99%) of the resulting α-amino acid derivative **133** were obtained based on GlcNAc-1-



Scheme 44 One-pot synthesis of 1,6-anhydrosugars and thioglycosides.



Scheme 45 Palladium-catalysed tandem synthesis of unsymmetrical biaryl thioglycosides.

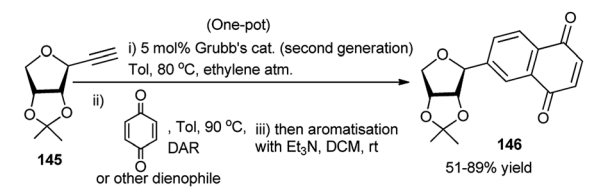
NH_2 (**132**), *iso*-propylcarboxaldehyde, acetic acid and *tert*-butyl isocyanide in the presence of 10 mol% of $ZnCl_2 \cdot Et_2O$ or $CeCl_3 \cdot 7H_2O$ in methanol using 4 Å molecular sieves (Scheme 41). A $ZrCl_4$ catalysed similar reaction also could furnish almost quantitative yield of the corresponding α-amino acids albeit in lower de (80%).[61]

Metal mediated one-pot reactions have also been used for generation of β-amino acids. Toward this end, an $InCl_3$-catalysed asymmetric Mannich type 3C condensation reaction protocol in methanol was developed by Dondoni *et al.* based on formyl *C*-glycoside (**134**), benzyl amine and ketene silyl acetal (**135**) to afford a highly diastereoselective *C*-glucosyl/galactosyl/ribosyl/mannosyl-β-amino acid derivatives **136** (Scheme 42).[62a,b] For the mannose derived amino acid DCM was proved to be the best solvent (due to poor solubility of the corresponding imine intermediate).[62b] Dondoni's group further synthesised *C*-glycosylated β-amino acids (**137**) from one-pot Reformatsky reaction of sugar (glucosyl/mannosyl/ribosyl) aldehyde, *p*-methoxybenzyl amine and bromozinc enolate as the d^2 synthon (Scheme 42).[62b] For the Reformatsky reaction, use of 5 mol% $NiCl_2(PPh_3)_2$ in DCM was established as the best catalyst. Both of these reactions proceeded with complete asymmetric induction and with generation of the 3*R*-configured amino acid.

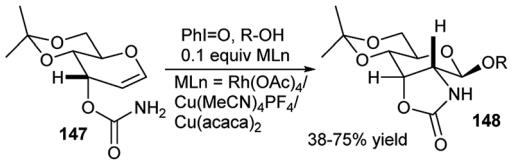
6. Metal-catalysed other miscellaneous domino/tandem/sequential/MC-one-pot reactions based on monomeric sugar substrates

Apart from the different types of product categories already discussed, a wide variety of scattered sugar scaffolds of different kinds have also been synthesised by metal-catalysed one-pot transformations, and those will be illustrated as miscellaneous examples in this section.

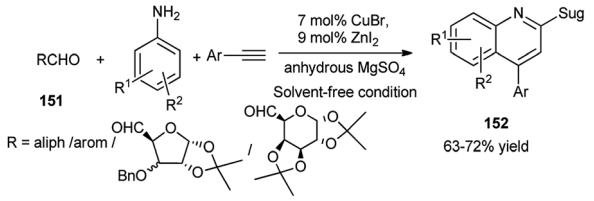
A $Bi(OTf)_3$-catalysed one-pot α-glycosylation–deprotection protocol was examined by Pastore *et al.* in dioxane–toluene–



Scheme 46 One-pot synthesis of *C*-aryl glycosides.



Scheme 47 Meta-catalysed one-pot amidoglycosylation.



Scheme 49 CuBr–ZnI_2-catalysed one-pot synthesis of quinoline glycoconjugates.

Et_2O mixed solvent, based on mannosyl trichloroacetimidate glycosyl donor **138**, bearing Fmoc protection on the C2–O (Scheme 43). After completion of the glycosylation reaction simple addition of triethylamine to the reaction mixture caused one-pot Fmoc deprotection; thus, this reaction sequence led to direct access to a glycosyl acceptor **139**. This protocol has then been extended for iterative synthesis of linear and branched oligomannoses related to HIV gp120.[63] Along with other transformations Hung's group has described a microwave assisted one-pot conversion of native sugars to 1,6-anhydrosugars **140** or thioglycosides **141** (Scheme 44). It proceeds with initial reaction of the free sugar with HMDS and TMSOTf generating the corresponding per-*O*-trimethylsilylated monosaccharide, which further reacts *in situ* with TMSOTf under microwave condition giving the corresponding anhydrosugar (**140**). Inspired by the success of this one-pot reaction they have further extended it for one-pot synthesis of fully protected thioglycosides from native sugars as shown in Scheme 44; here the initially formed per-*O*-silylated intermediate sequentially reacted with trimethyl(4-methylphenylthio)silane in the presence of ZnI_2 under microwave condition affording the corresponding thioglycoside (**141**). They then applied the one-pot generated thioglycoside for *in situ* glycosylation with glycosyl acceptor in the presence of AgOTf, thus getting the corresponding disaccharide in one-pot from its glycosyl donor-based native sugar.[64]

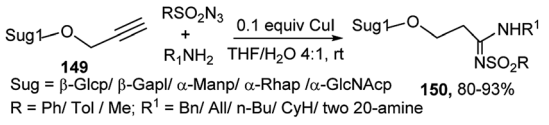
Recently, Messaoudi and co-workers have employed one Pd(II) complex for catalytic one-pot 3C reactions of thiosugars **142**, bromo-iodo arenes/heteroarenes (**143**) and aryl boronic acid to prepare a variety of the corresponding unsymmetrical biaryl thioglycosides **144** as shown in Scheme 45.[65] It is to be noted that a variety of biologically important natural products contain unique aryl *S*-glycosidic[66] and aryl *C*-glycosidic scaffolds (Scheme 45).[67] During their stepwise diversity-oriented synthesis of a variety of *C*-arylglycosides and spiro-*C*-aryl glycosides, Kaliappan's group prepared an intermediate compound (**145**) for its onward transformation to the corresponding *C*-aryl glycoside (**146**) by a sequential tandem Ru-catalysed enyne metathesis/Diels–Alder cycloaddition/aromatisation in one-pot (Scheme 46). The one-pot yields were however lower (30–35%) than the combined yields (>50%) of the respective stepwise conversion of **145** to the corresponding *C*-aryl glycosides.[68]

A highly diastereoselective tandem amidoglycosylation reaction was explored from reaction of allal 3-carbamates **147** with alcohol either under photochemical condition or using combined I(III)–MLn [M = Ru/Cu] reagent (Scheme 47). The researchers proposed that the reaction proceeds *via* formation of a Ru/Cu-acyl nitrenoid intermediate that undergoes tandem amidation–glycosylation with sequential C2–N bond formation-β-glycosylation furnishing the corresponding C2–N anchored glycosides **148**.[69]

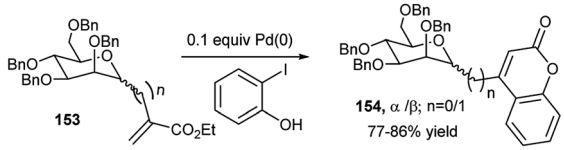
Mukhopadhyay's group used propargyl glycosides for 3C coupling reactions with aromatic aldehydes and aromatic amines in the presence of CuBr–$RuCl_3$ combined catalyst under microwave condition for generation of the corresponding glycosylated propargyl amine derived glycoconjugates in high to excellent yields.[70] A series of glycosylated *N*-sulfonylamidines **150** were prepared in high yields by this research group employing Cu(I) catalyst by 3C reactions of propargyl glycosides **149**, different amines and sulfonyl azides in THF at room temperature (Scheme 48).[71]

A variety of quinolines including sugar **152** were synthesised by Maity's research group by CuBr–ZnI_2 dual catalysed one-pot oxidative 3C-coupling reactions of aldehydes including sugar derived aldehydes (**151**), aryl amines and aryl acetylenes in the presence of anhydrous $MgSO_4$ under solvent free condition (Scheme 49). They further proved involvement of a Cu(I)–Cu(III) switching process, as evidenced from the peak at 529 nm in the UV-Vis spectrum of the corresponding reaction mixture. This was also corroborated by appearance of respective peaks of Cu(I) and Cu(III) from the XPS experiment. Based on these observations, they also proposed the mechanistic pathway including a catalytic cycle.[72]

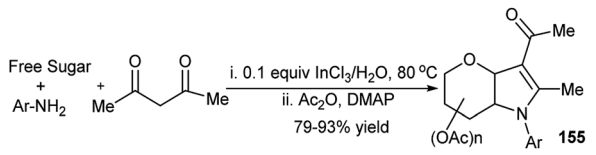
For the synthesis of C2 and C4-substituted quinoline-derived glycoconjugates, Mohan Das's group employed earlier per-acetylated propargyl glycoside (glucose and galactose-based), aryl amine and substituted benzaldehyde in THF at 65 °C using CuBr–ZnI_2 dual catalyst.[73] A series of coumarin appended



Scheme 48 Cu(I)-catalysed one-pot synthesis of glycosylated *N*-sulfonylamidines.



Scheme 50 Domino synthesis of *C*-mannopyranocoumarins.



Scheme 51 Synthesis of sugar annulated pyrroles.

mannopyranosides (**154**) were prepared by Pd(0)-catalysed one-pot domino Heck reaction followed by lactonisation of methyl per-*O*-benzylated *C*-mannopyranosyl acrylates (**153**) and 2-iodophenols (Scheme 50).[74]

Previously, J. S. Yadav *et al.* developed an aqueous-mediated synthesis of sugar annulated pyrroles from 3C one-pot reactions of free aldoses, aryl amines and acetylacetone at 80 °C and isolated the acetylated products (**155**, Scheme 51) after *in situ* acetylation with Ac_2O and dimethylaminopyridine.[75]

Further reports were made by this group on the microwave-mediated clay K10-catalysed highly *cis* diastereoselective synthesis of thiosugar annulated bicyclic dihydropyrimidines (**157**, **158**) (or thiones)[76] or bicyclic tetrahydropyrimidinones,[76] (**159**, **160**) in high yields under solvent-free condition from 3C one-pot reactions of aldoses and 2-methyl-2-phenyl-1,3-oxathiolan-5-one (**156**) separately with urea/thiourea[76] or amidines[77] (Scheme 52). The mechanistic pathway of one reaction, as proposed by the researchers, is shown hereunder; the reaction proceeded *via* intramolecular domino cyclocondensation of the intermediate **S**, formed from reaction of xylose and **156** (Scheme 52).

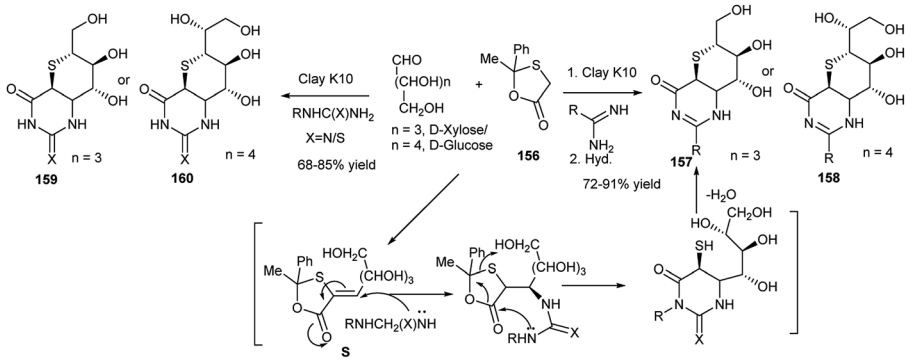
This group also explored the one-pot synthesis of a series of iminosugar-annulated perhydropyrimidines (**161a** and **161b**, Scheme 53) using a Ce(III)-catalysed microwave mediated Biginelli reaction.[78] They further synthesised 1,3-oxazin-2-ones **162** (or thiones, **163**, Scheme 53) in high yields by clay K10-catalysed microwave enhanced reactions of D-glucose/D-xylose and semi(thiosemi)carbazide under solvent-free condition. They proposed that the reaction proceeds *via* one-pot domino cycloisomerisation, dehydrazination and dehydration of the initially formed sugar-semi(thiosemi)carbazones.[79] They further utilised the tailor-made 1,3-oxazin-2-ones **162** (or thiones, **163**) toward diversity-oriented synthesis of other 1,3-oxazin-2-one(thione) fused N-/O-heterocyclic compounds.

Cao *et al.* described the synthesis of optically pure epimeric aminocyclopentitols (**168** and **169**) from the corresponding *R*-/*S*-*tert*-butyl sulphonamides (**166** and **167**), which were prepared by $Fe(CO)_5$-catalysed intramolecular tandem isomerisation-Mannich reaction from sugar derived corresponding anomeric *R*-/*S*-*tert*-butyl sulphonamides (**164** and **165**) under photochemical condition in THF (Scheme 54).[80]

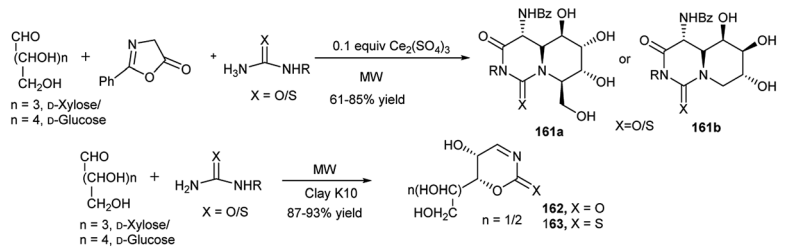
An earlier report[81] revealed that *N*-benzyl-β-aminocyclopentitol (**168**) has a much greater inhibitory activity of α-L-fucosidases from different sources than the corresponding α-amino epimer (**169**).

7. Metal-catalysed one-pot synthesis of oligosaccharides

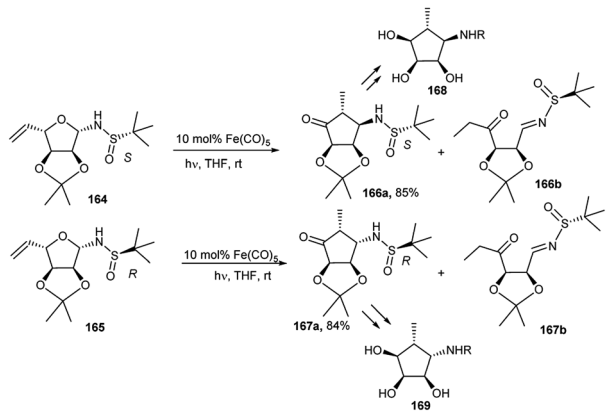
During the past two decades, one-pot glycosylation strategies have been successfully utilised for the construction of various



Scheme 52 Microwave-mediated clay K10-catalysed one-pot synthesis of thiosugar annulated bicyclic dihydropyrimidines (**157** and **158**) and bicyclic tetrahydropyrimidinones (or thiones) (**159** and **160**).



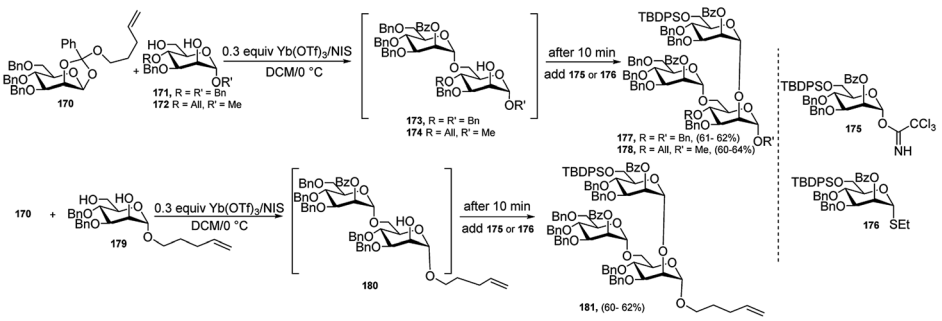
Scheme 53 Iminosugar annulated perhydropyrimidines (**161**) and 1,3-oxazin-2-one/thione (**162**, **163**) synthesis.



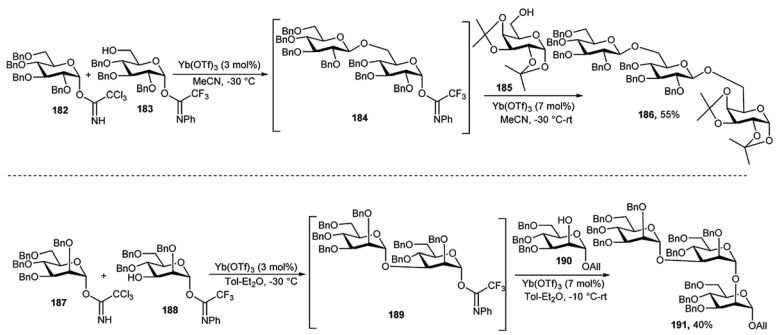
Scheme 54 $Fe(CO)_5$-catalysed intramolecular tandem isomerisation-Mannich reaction of sugar derived anomeric sulphonamides toward preparation of epimeric chiral aminocyclopentitols.

oligosaccharides. In general, one-pot glycosylation strategies mainly include orthogonal one-pot glycosylation, reactivity-based one-pot glycosylation, and preactivation-based iterative one-pot glycosylation, among which orthogonal one-pot is particularly more significant. Different combination of glycosyl donors and acceptors, for example, glycosyl trichloroacetimidate (TCAI) and thioglycoside,[82] glycosyl *N*-phenyltrifluoroacetimidate (PTFAI) and thioglycoside,[83] *S*-benzoxazolyl (SBox) glycoside and thioglycoside,[84] glycosyl bromide and thioglycoside,[85] glycosyl phosphites and thioglycoside, and glycosyl phosphates and thioglycoside[86] have been exploited for the two-step, orthogonal one-pot synthesis of several oligosaccharides. Generally, common activator systems like TMSOTf and NIS/TMSOTf, or $Cu(OTf)_2$ and NIS/TMSOTf, or Ag-salt and NIS/TMSOTf were used to accomplish the one-pot oligosaccharide construction. Different metal triflates and transition metals like Pd, Au, Ni, and Fe have been employed extensively as catalyst or promoter system for the activation of TCAI or PTFAI in glycosylation reaction. Interestingly, although these metal catalysts were used in chemoselective glycosylation, but hardly had been exploited to the one-pot synthesis of oligosaccharides. Only a few examples were found in literature. These metal catalysts were used exclusively or in combination with other promoter system in two-step, three-step, or four step orthogonal one-pot syntheses of oligosaccharides.

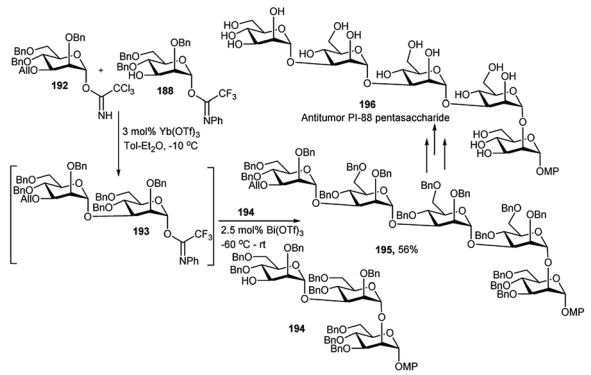
In 2004, Fraser-Reid's research group[87] developed a one-pot, double-differential glycosylation strategy based on an *n*-pentenyl *ortho* ester activation with NIS and catalytic amount of $Yb(OTf)_3$. In this glycosidation protocol, an acceptor diol was chemo- and regioselectively glycosylated by using an *n*-pentenyl *ortho* ester which was activated by NIS/catalytic $Yb(OTf)_3$ followed by subsequent addition of second glycosyl donor, which was either glycosyl trichloroacetimidate or thioglycoside and led to generate several branched oligosaccharides by one-pot under the action of the same activator system. For example, diol **171** or **172** was treated with *n*-pentenyl *ortho* ester **170** in the presence of NIS (2.5 equivalents) and $Yb(OTf)_3$ (30 mol%), and after 10 minutes, when the initial glycosylation reaction was supposed to be completed by generation of the intermediate disaccharide **173** or **174,** the second donor **175** or **176** was added to the reaction vessel to produce ultimately trisaccharide **177** or



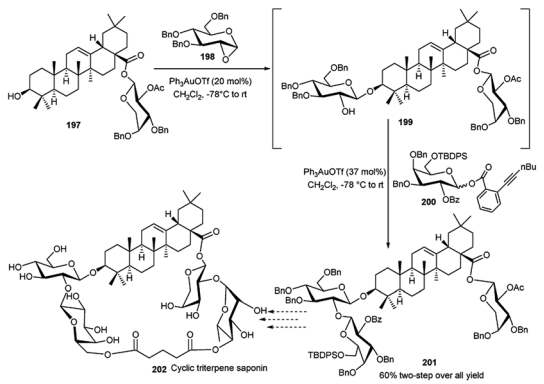
Scheme 55 $Yb(OTf)_3$-catalysed one-pot, double-differential glycosidation strategy.



Scheme 56 $Yb(OTf)_3$-catalysed one-pot glycosylations toward trisaccharide derivatives.



Scheme 57 Synthesis of a pentasaccharide derivative by sequential metal-catalysed one-pot glycosylations.



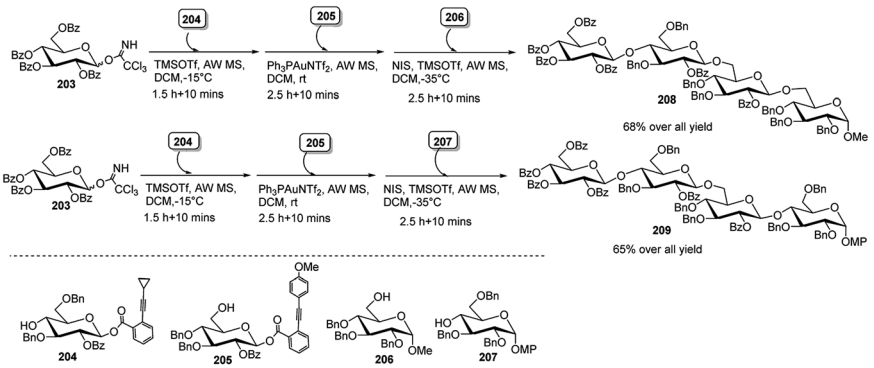
Scheme 58 Synthesis toward cyclic triterpene saponin utilising Au(I)-catalysed sequential one-pot glycosylation reactions.

178. Using the same protocol with same donor **170** and acceptor **179** resulted in the intermediate disaccharide **180**, followed by addition of the second donor **175** or **176** finally generated the corresponding trisaccharide **181** in good yield (Scheme 55).

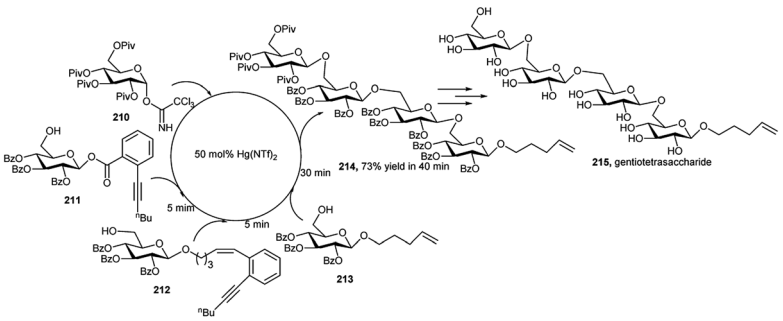
In 2006, M. Adinolfi *et al.*[88] described the catalytic activity of $Yb(OTf)_3$ in the selective activation of glycosyl trichloroacetimidate over glycosyl *N*-phenyltrifluoroacetimidate with similar protecting groups. In the same paper, they have extended the efficacy of this methodology for the multistep-glycosylation in one-pot. Two model oligosaccharides **186** and **191** were synthesised exploiting this method. Glycosyl donor **182** and acceptor **183** in acetonitrile at −30 °C in the presence of a catalytic amount of $Yb(OTf)_3$ (0.03 equivalent) led to the consumption of the more reactive donor **182** and provided a disaccharide intermediate **184** with anomeric *N*-phenyltrifluoroacetimidate. On addition of acceptor **185** together with an additional amount of $Yb(OTf)_3$ (0.07 equivalent) in the reaction mixture generated trisaccharide **186**. Likewise, catalytic amount of $Yb(OTf)_3$ (0.03 equivalent) was added to a mixture of mannosyl trichloroacetimidate **187** and mannosyl *N*-phenyltrifluoroacetimidate **188**, at −30 °C offering *in situ* disaccharide intermediate **189**, which was then coupled to mannose-based acceptor **190**, in the presence of added catalytic amount of $Yb(OTf)_3$ (0.07 equivalent), providing trisaccharide **191** in 40% overall yield (Scheme 56).

S. Valerio *et al.*[89] demonstrated a one-pot synthesis of pentasaccharide intermediate **195** during the synthesis of an antitumor PI-88 pentasaccharide **196** using the above-mentioned glycosylation protocol in 2008, except instead of using $Yb(OTf)_3$ only, $Bi(OTf)_3$ was employed for the activation of PFTA. Thus, compound **192** and **188** were treated with a catalytic amount of $Yb(OTf)_3$ (0.03 equivalent), and after the consumption of relatively more reactive mannosyl TCAI **193**, a catalytic amount of $Bi(OTf)_3$ (0.025 equivalent) and a trisaccharide acceptor **194** which was also prepared by one-pot manner following above-mentioned technique, were sequentially added, finally providing pentasaccharide **195** in excellent overall one-pot yield (Scheme 57).

Yu and coworkers[90] have recently demonstrated that 1,2-anhydrosugar could be activated by $Ph_3PAuOTf$ to undergo glycosylation in the presence of a suitable acceptor, and the resulting 2-OH, generated by *in situ* epoxide ring opening, can further be glycosylated in a one-pot fashion with a glycosyl *ortho*-hexynylbenzoate and additional portion of $Ph_3PAuOTf$. During the assembly of cyclic triterpene saponin **202**,[91] Yu's group applied this technique to synthesise the intermediate **201**. Compound **197** was allowed to react with 1,2-anhydroglucose **198** in the presence of PPh_3AuOTf (0.2 equivalent) to provide intermediate **199** which then underwent a smooth reaction with *ortho*-hexynylbenzoate **200** in the presence of an additional portion of PPh_3AuOTf (0.37 equivalent) leading



Scheme 59 Synthesis of tetrasaccharide derivatives by Au(I)-catalysed sequential one-pot glycosylation reactions.



Scheme 60 Single catalyst-based one-pot synthesis of tetrasaccharide **214**.

finally to desired trisaccharide derivative **201** in a good 60% yield (Scheme 58).

Very recently, Sun's group[92] has developed a chemoselective alkyne-activation-based glycosylation strategy employing *o*-alkynylbenzoate (ABz) and *O*-(*p*-methoxyphenylethynyl)phenyl (MPEP) glycosyl donor. Selective activation of ABz donor over MPEP with $Ph_3PAuNTf_2$ allowed them to construct complex oligosaccharides *via* one-pot orthogonal strategy, involving glycosyl trichloroacetimidate (TCAI), *o*-alkynylbenzoate (ABz) glycosyl donor and *o*-(*p*-methoxyphenylethynyl)phenyl (MPEP) glycoside. Two tetrasaccharide, for example, **208** and **209** were thus successfully synthesised. First, TCAI donor **203** and ABz glycosyl acceptor **204** were treated with TMSOTf, providing a disaccharide intermediate, which was then treated with $Ph_3PAuNTf_2$ and MPEP glycosyl acceptor **205**, giving a trisaccharide intermediate having MPEP as a leaving group, which was further activated with NIS/TMSOTf in the presence of monosaccharide **206** that led to tetrasaccharide **208**.

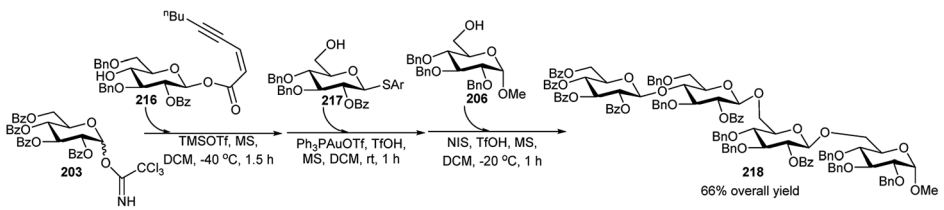
Likewise, synthetically more challenging tetrasaccharide **209** having a 1,4-linked at the non-reducing end was synthesised following the same strategy of consecutive reactions among **203** with **204** followed by **205** and finally **207** (Scheme 59).

Zu *et al.*[93a] used 5 mol% of $Hg(NTf)_2$ as single catalyst for one-pot synthesis of gentiotetrasaccharide **215,** found in lichens and can be employed as a bifidus factor to promote animal growth.[93b] Per-*O*-pivaloyl glycosyl trichloroacetimidate donor **210** and bifunctional glucosyl alkynylbenzoate acceptor **211** were treated with 5 mol% of $Hg(NTf)_2$ for 5 minutes. Then, bifunctional enynyl glycosyl acceptor **212** was added to couple with the newly formed disaccharide intermediate, affording the trisaccharide in 5 minutes under the same $Hg(NTf)_2$ catalyst. After that, pentenyl acceptor **213** was injected in the reaction mixture to react with the trisaccharide intermediate. After 30 minutes, the protected tetrasaccharide **214** was formed in 73% overall yield by use of a single catalyst in the reaction system (Scheme 60).

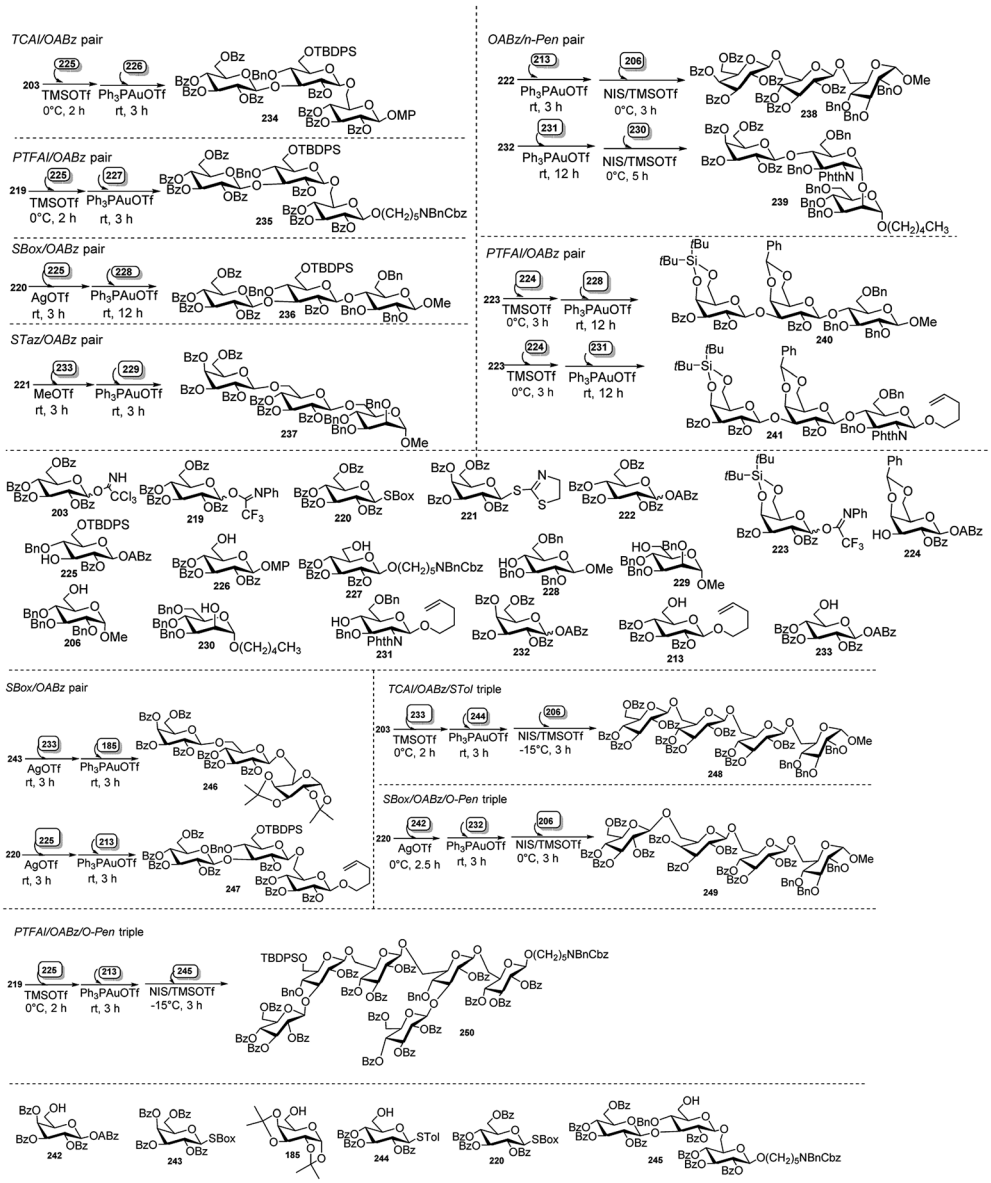
Very recently Yang's group[94] reported multistep orthogonal one-pot synthesis of the tetrasaccharide **218.** Orthogonal glycosylation of trichloroacetimidate donor **203** with ynenoate acceptor **216** under catalysis of TMSOTf (0.2 equivalent) at −40 °C for 1.5 hours afforded the disaccharide intermediate donor, which was coupled with thioglycoside acceptor **217** under the catalytic activation by $Ph_3PAuOTf$ (0.2 equivalent) and TfOH (0.1 equivalent) at room temperature for another 1 hour to provide the intermediate trisaccharide. Coupling of the above intermediate trisaccharide with acceptor **206**, promoted by NIS/TfOH at −20 °C for another 1 hour furnished the tetrasaccharide **218**, in 66% overall yield (Scheme 61).

Xiao's research group[95] effectively employed glycosyl *o*-alkynylbenzoate (ABz), which can be activated under mild and neutral glycosylation condition, *viz* only needing Au(I) catalyst, for synthesis of oligosaccharides. They demonstrated a new and highly efficient orthogonal one-pot method for synthesis of oligosaccharides on the basis of glycosyl *o*-alkynylbenzoate (ABz). Different type of glycosyl donors including glycosyl TCAI,[96] glycosyl PTFAI,[97] *p*-toluene thioglycoside (STol),[98] SBox glycoside,[99] STaz glycoside,[100] and glycosyl isoquinoline-1-carboxylate (IQC)[101] were utilised in pairing with ABz to develop the corresponding orthogonal one-pot strategy (Scheme 62).

Recently, Ghosh *et al.*[102] applied orthogonal one-pot glycosylation strategies for the synthesis of pentasaccharide **254**, involving glycosyl trichloroacetimidate (TCAI) and thioglycoside. $FeCl_3$ was successfully employed as a catalyst for the activation of glycosyl trichloroacetimidate in the sequential reaction. Pentasaccharide **254** was constructed by two different one-pot glycosylation approaches, one involving [1 + 2 + 2], and the other one [1 + 2 + 1 + 1]. In the [1 + 2 + 2] approach, 0.1

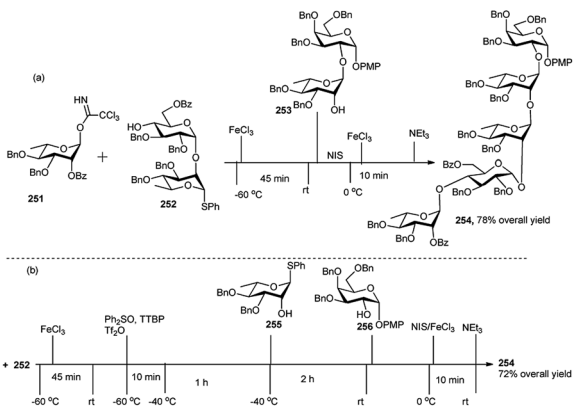


Scheme 61 One-pot synthesis of tetrasaccharide-based on glycosyl ynenoate.



Scheme 62 Different orthogonal one-pot strategies toward oligosaccharides.

equivalent of $FeCl_3$ was used as a catalyst for activation of rhamnopyranosyl trichloroacetimidate **251** in the presence of disaccharide acceptor **252** in the first step of the one-pot synthesis, providing a thioglycoside trisaccharide intermediate, which was further activated with NIS/$FeCl_3$ with addition of the acceptor **253** leading to fully protected pentasaccharide **254** (Scheme 63). While in the second approach *i.e.*, [1 + 2 + 1 + 1], rhamnopyranosyl trichloroacetimidate **251** was activated similarly with 0.1 equivalent $FeCl_3$ in the presence of disaccharide **252**, yielding a trisaccharide intermediate having a thio glycoside terminal. This was then activated *in situ* by Ph_2SO/Tf_2O at −60 °C followed by addition of monosaccharide **255** at −40 °C, generating a tetrasaccharide intermediate. This intermediate tetrasaccharide was finally subjected to another round of NIS/$FeCl_3$-mediated glycosylation with acceptor **256** and



Scheme 63 Synthesis of pentasaccharide derivative by (a) sequential 3C one-pot glycosylation reactions; (b) sequential 4C one-pot glycosylation reactions.

ultimately providing pentasaccharide **254** in good yield (Scheme 63).

8. Conclusion and perspectives

This review is an endeavour to illustrate the metal based one-pot (domino/cascade/tandem/sequential MC) reactions on native sugar feedstock or their suitable derivatives for generation of chiral intermediates for further synthetic application, or of medicinally potent glycoconjugates, or of oligosaccharides of biological relevance. Such metal catalysed single-pot reactions allow construction of library compounds having diverse structures with high regio-, chemo- and stereo-selectivity, sometimes generating high complexity in a simple manner. Because of operational simplicity, avoidance of isolation, purification and characterisation of intermediates, and involvement of much less solvents, time, labour and money unlike those in multistep syntheses, application of such one-pot reactions is increasing gradually.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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