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Advances in *C*-alkynylation of sugars and its application in organic synthesis

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***C*-Glycosidation plays a significant role in the synthesis of optically active scaffolds. Among *C*-glycosylations, *C*-alkynylation have emerged as a synthetic tool in organic or natural product synthesis since it make use of carbohydrates as chiral pool and source of carbon as well. In this present review several modes of *C*-alkynyl-glycosylations have been summarized based on different glycosyl donors such as glycals, anomeric acetates, anomeric halosugars, 1,2-anhydrosugars, 1,6-anhydrosugars, lactones, lactols and activated/unactivated terminal alkynes as a glycan partner under various Lewis acids like $TiCl_4$, I_2, BF_3•OEt_2, $Cu(OTf)_2$, TMSOTf and/or metals like In, Zn. Further, total/fragment stereoselective synthesis of some important natural products have been elaborated.**

1.0. Introduction

C-glycosides are stable analogs of *O*-glycosides[1] and are unlikely to be hydrolysed by biological catalysts (enzymes). The study of *C*-glycosides is of utmost importance in the fields of carbohydrate and biological chemistry[2] as they constitute the sub-structures of many biologically important scaffolds[3a-c] which are potential inhibitors of carbohydrate processing enzymes, and are also useful as chiral building blocks in the synthesis of natural products like palytoxin, spongistatin, halichondrin etc.[3d-f] Because of their significance in organic, medicinal or biological chemistry, synthesis of these *C*-glycosides (called *C*-glycosidation) has attracted considerable attention in the recent decades. *C*-Glycosidation is very important in the synthesis of optically active skeletons because of two reasons: (1) it is useful in the introduction of C-chains into carbohydrate moiety and (2) it allows the use of carbohydrate unit as chiral pool and carbon sources as well.[4]

In the last several decades, there are huge advancements in the development of methods towards efficient and stereoselective *C*-glycosidations. Among several approaches towards *C*-glycosidations, *C*-alkynyl glycosidation is particularly important as it generates the products containing a C-C triple bond which could be easily transformed into other chiral molecules and sugar derivatives.[5] These alkynylated sugars derivatives (also sugar acetylenes or *C*-glycosides) have also been exploited in the syntheses of natural products like ciguatoxin and tautomycin.[6] Among the several approaches for *C*-alkynyl glycosidations available in literature, the Ferrier rearrangement has been found to be the most common approach. Over the years several technical advances in Ferrier glycosylation have been made to circumvent problems in reaction yields and stereo selectivity. This review is intended to focus on the *C*-alkynyl glycosidation methods that have been reported till 2015.

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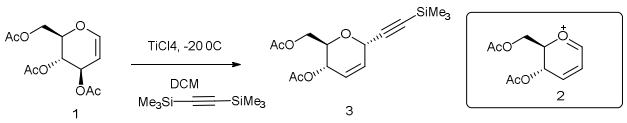
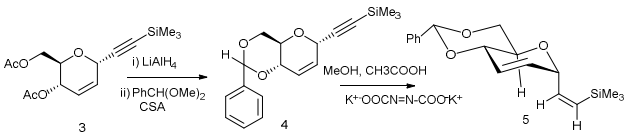
2.0. Methods of *C*-alkynyl glycosidations

2.1. Ti (IV)-mediated *C*-alkynylation

Minoru isobe[6] and colleagues reported that sillylacetylenes have been found to be the most prominent nucleophiles for the preparation of C-alkynyl glycosides. In this reaction, bis(trimethylsilyl)acetylene reacted with glycal **1** in presence of Ti(IV) producing C-alkynyl glycoside **3** with α-stereoselectivity as depicted in scheme 1. Mechanistically, the reaction involves the Ti(IV)-mediated generation of oxonium ion 2 followed by the nucleophilic attack of TMS-acetylene on the anomeric centre from the α-face selectively. Isobe explained the α-selectivity by electronic effects on the oxocarbenium intermediates involved in the transformation. The desired product was obtained when the glycal 1 was introduced into the mixture of Ti(IV) and TMS-acetylene at temperatures less than 0o C. Use of another Lewis acid, boron trifluoride etherate, produced a small amount of 3 as the polymerization of glycal 1 was prominent in this case. Compound 3 was later converted to alkenyl glycoside 5 (an important scaffold in organic synthesis) as shown in scheme 2. Other nucleophiles like trimethylphenylsilane, trimethylvinylsilane, ethynyltrimethylsilane were unable to produce *C*-glycosides when subjected to similar conditions due to the rapid polymerization of glycal triacetate 1.



Scheme 1. Ti(IV)-mediated *C*-alkynylation.



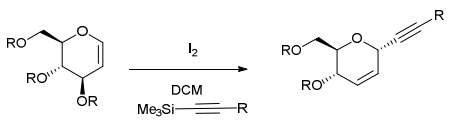
Scheme 2. Conversion of *C*-alkynyl glycoside**3** to alkenyl glycoside **5**.

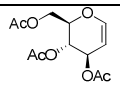
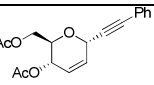
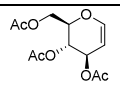
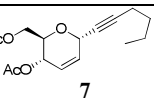
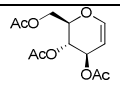
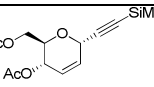
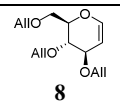
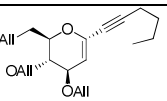
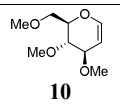
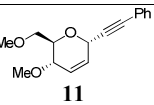
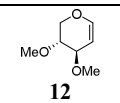
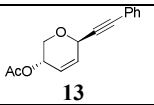
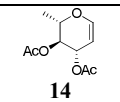
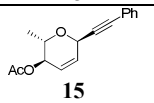
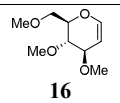
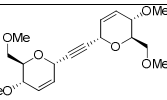
The configuration of alkynyl glycosides **3** and **4** was proved by ^{1}H NMR spectrometry. Compound **4** having a fixed configuration was partially reduced to the corresponding dihydro derivative **5**. A clear NOE effect was observed with 3.5% enhancement between the H signal appearing at 6.47 (dd, *J* 14.2, 9.1 Hz) and the H-5' signal at 3.70 (ddd, *J* 10.4, 8.2, 4.4 Hz). This result indicated that the vinyl substituent in **5** is located in α-axial orientation and that the initial reaction with bis(trimethylsilyl)acetylene had produced the α-anomer in the Ti(IV)-mediated *C*-alkynyl glycosidation.

2.2. Iodine-mediated *C*-alkynylation

Ti(IV)-mediated *C*-alkynylation produced *C*-alkynyl glycosides in low to good yields, however, this reagent is corrosive in nature, moisture sensitive and is required in stoichiometric amounts. Later on the groups of J.S.Yadav[7] (in 2002) and M. Isobe[8] (in 2003) independently solved this problem by demonstrating iodine-mediated simple, inexpensive, catalytic protocol for the synthesis of *C*-alkynyl glycosides in a stereoselective manner with improved yields. Differentially protected glycals were subjected to these conditions using different TMS-acetylene nucleophiles and the results are summarized in table 1.

Table 1. Iodine-mediated *C*-alkynylation using different nucleophiles and glycals.



Entry	Substrate	Product	Time (h)	Yields (%)
1	 **1**	 **6**	3	90
2	 **1**	 **7**	3.5	87
3	 **1**	 **3**	3	85
4	 **8**	 **9**	2.5	83
5	 **10**	 **11**	2.5	87
6	 **12**	 **13**	3	90
7	 **14**	 **15**	4	92
8	 **16**	 **17**	3	87

In all cases glycal (5 mmol), trimethylsilylacetylene (5 mmol) and iodine (5 mol%) in CH_2Cl_2 (10 mL) were used at rt.

2.3. Indium(0)-mediated Ferrier-type *C*-alkynylation of glycals

N. L. Germain et al[9] reported an efficient Indium(0)-mediated Ferrier-type *C*-alkynylation reaction between glycals and iodoalkynes (table 2) with good stereoselectivity and further they synthesised *C*-disaccharide.

The iodoalkynes required in this reaction, were generated by the action of iodine and morpholine on desired alkynes.[10] The Indium(0)-mediated reaction of tri-*O*-acetyl-D-glucal with these iodoalkynes provided the *C*-alkynyl glycosides (scheme 3) with excellent α-selectivity which was confirmed from signals of H5 and C-5.

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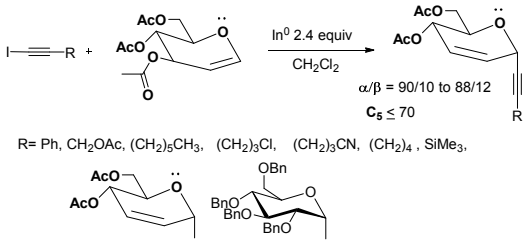
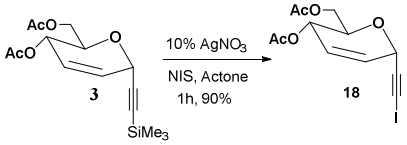


Scheme 3. Indium mediated Ferrier-type *C*-alkynylation of glycals.

The reactions were carried under reflux conditions for 3-24 hours. Isobe established that in the case of α-anomer the NMR signal for H-5 appears at 4.07-4.09 ppm while in the case of β-anomer it appears at 3.74-3.77 ppm.[11] Further, the ^{13}C-NMR signal for C-5 appears lower than 75 ppm in the case of α-anomer.[12]

The authors exploited the current Barbier conditions for the synthesis of *C*-disaccharides via the In^0-mediated-Ferrier-type *C*-alkynylation as demonstrated in scheme 4. The trimethylsilylethynyl-*C*-glycoside **3** generated above, was converted to iodoethynyl-*C*-glycoside **18** on reaction with $AgNO_3$-NIS reagent combination (scheme 4). The desired *C*-disaccharide **19-21** was produced when **18** was subjected to current reaction conditions with appropriate sugar donar like tri-*O*-acetyl-D-glucal.



Scheme 4. Preparation of iodoethynyl-*C*-glycoside (**28**).

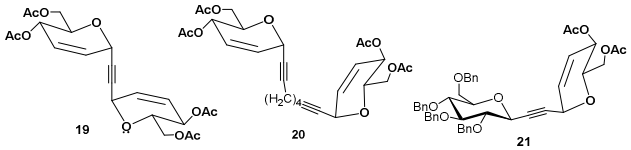
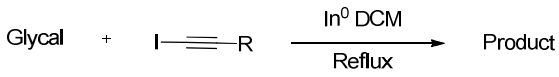
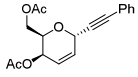
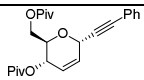
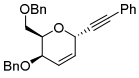
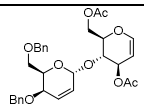
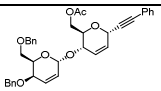


Figure 1. *C*-disaccharides **19**, **20** and **21** synthesized using present method.

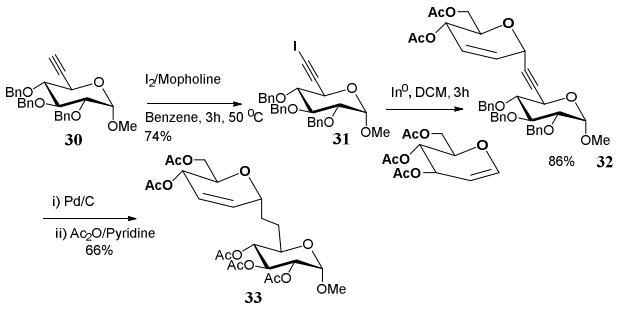
The Indium(0)-mediated Ferrier-type *C*-alkynylation was also applied to other glycosidic electrophiles thus, producing the *C*-alkynyl glycosides in good to excellent yields as summarized in table 3.[6b] It has been proposed that the mechanism is similar to that given by Minehan's group under Grignard conditions, as the selectivity does not depend on sugar protecting groups.[12,13] This reaction found application in the synthesis of α-(1-6)-*C*-disaccharide **33** via the following reaction sequence (scheme 5).

Table 2. The Indium(0)-mediated Ferrier-type *C*-alkynylation of glycosidic electrophiles.[a]



S. No.	Glycal	Time	Product[a,b]	α/β-Ratio
1	 **22**	16h	 **23**	83/17
2	 **24**	24h	 **25**	85/15
3	 **26**	48h	 **27**	>95/5
4	 **28**	16h	 **29**	78/22

[a]All reactions were carried out at reflux of dichloromethane (0.166 M solution) with 2 equiv of In(0) and 2.4 equiv of iodophenylacetylene. [b]product Yields varied from 65-95%.



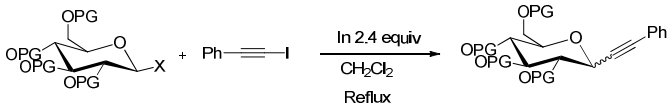
Scheme 5. Synthesis of α-(1-6)-*C*-disaccharide.

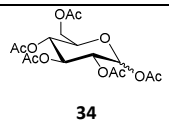
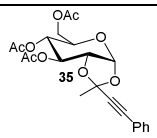
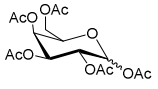
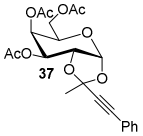
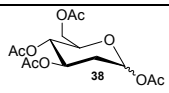
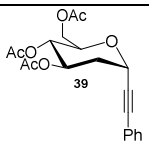
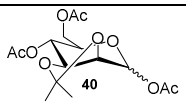
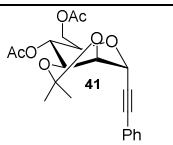
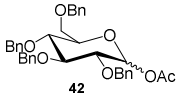
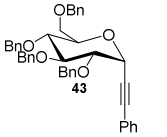
2.4. Indium(0)-mediated *C*-alkynylation of peracetylated sugars.

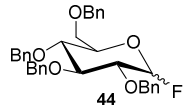
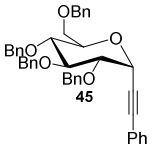
The previous methods for *C*-alkynylation suffer from the formation of byproducts[14] and toxicity of reagents,[15] the organometallic reagents have been successfully exploited for the preparation of *C*-alkynyl glycosides when these were reacted with sugarlactone and glycal epoxides.[16-18] Taking inspiration from the success of organometallic reagents and from their own work on indium(0)-mediated Ferrier-type *C*-alkynylation of glycals, N. L. Germain applied the similar reaction conditions for the *C*-alkynylation of peracetylated sugars (pyranose as well as furanose sugars) and the results are summarized in tables 3 and 4.

The acetylated sugars with C-2 participating group (compounds **34** and **36** table 3) gave cyclic acetal **35** and **37** (entry 1 and 2, table 5) which results from the action of indium acetylenide to the acetoxonium intermediate generated by the participation of C-2 acetate group.[19] While the acetylated sugars with no C-2 participating group (compounds **40, 42, 44, 51**) on reaction with iodoalkynes produced *C*-alkynyl glycosides under In^0 conditions with excellent α-selectivity (entries 3-6, table 3).

Table 3. *C*-Alkynylation of pyranosyl sugars.

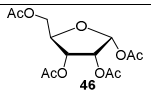
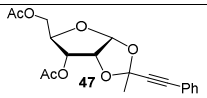
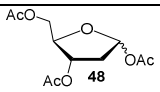
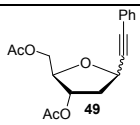
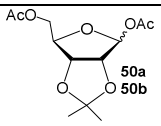
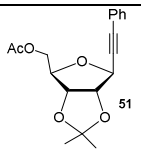
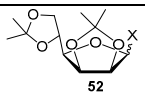
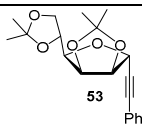
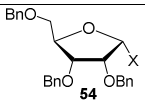
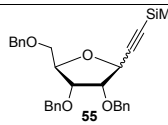


Entry	Substrate	Selectivity	Time (h)	Yield (%)	Product	C1 Configuration
1	 **34**	α/β=20/80 α/β=95/5	24 24	86	 **35**	α/β=98/2 dr=98/2
2	 **36**	α/β=2/98	26	92	 **37**	α/β=98/2 dr=89/11
3	 **38**	α/β=25/75 α/β=88/12	16 48	70 71	 **39**	α/β=98/2
4	 **40**	α/β=98/2	24	66	 **41**	α/β=98/2
5	 **42**	α/β=25/75	48	60	 **43**	α/β=75/25

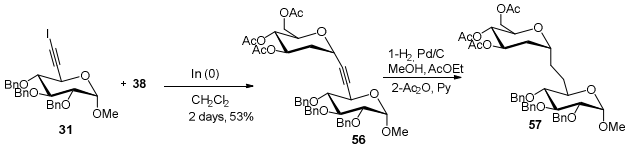
6	 44	α/β=10/90	16	52	 45	α/β=80/20

When the furanosyl sugars were subjected to indium(0)-mediated C-alkynylation, similar results were obtained and the results are summarized in table 5 h the stereochemistry of the *C*-alkynyl glycosides depends on both the C-3 configuration [20] and the nature of the protecting group.[21-22]

Table 4. *C*-Alkynylation of furanosyl sugars.

S. No.	Substrate	Selectivity	R	Time (h)	Yield (%)	Product	C-1 selectivity
1	 46	α/β=30/70	Ph	27h	68	 47	α/β=98/2 dr=98/2
2	 48	α/β=40/60	Ph	3h	96	 49	dr=32/68
3	 50a 50b	α/β=14/86 α/β=90/10	Ph	24h 24h	60 53	 51	α/β= 3/97 α/β= 10/90
4	 52	α/β=10/90	Ph	48h	44	 53	α/β =94/6
5	 54	α/β<5/95	Ph	16h	67	 55	α/β =50/50

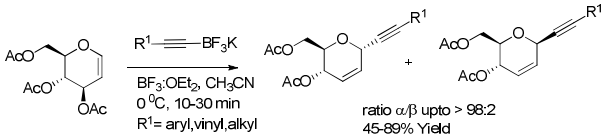
This method found application in the synthesis of an α-(1-6)-*C*-disaccharide analogue of methyl isomaltoside. 2-Deoxyglucopyranose **57**, on reaction with benzylated iodoglucopyranoside **31**[9] produced the **56** which after reduction and acetylation produced α-(1-6)-*C* disaccharide **57** as described in scheme 6.[17a,23]



Scheme 6. Synthesis of methyl-2-deoxy-α-(1-6)-*C*-isomaltoside.

2.5. $BF_3{\cdot}OEt_2$-mediated *C*-alkynylation of glycals

H.A. Stefani et al reported a highly stereoselective method for *C*-alkynylation of D-glucal using potassium alkynyltrifluoroborates as nucleophiles under $BF_3{\cdot}OEt_2$ conditions.[24] The reaction involves oxonium ion intermediates which produces α-*C*-alkynyl glycosides preferentially (scheme 7).



Scheme 7. $BF_3{\cdot}OEt_2$-mediated *C*-alkynylation of glycals.

It has been shown that $BF_3{\cdot}OEt_2$ is best for reactions involving potassium organotrifluoroborates as the reaction did not occur in its absence.[25] The detailed results are depicted in table 5. Effect of solvent was found to be noteworthy in this reaction. When the reaction was carried out in CH_3CN or toluene, better yields (84% and 78%) and diastereoselectivity (95:05 α/β-selectivity) were observed. No product could be observed when DMF was used as solvent. Furthermore, CH_2ClCH_2Cl (1,2-dichloroethane) and CH_2Cl_2 produced similar results.

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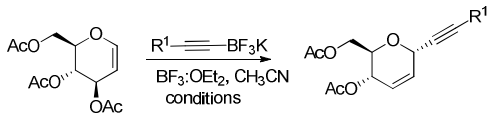
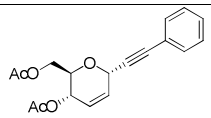
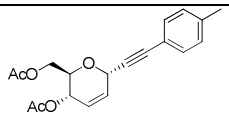
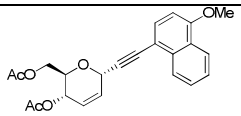
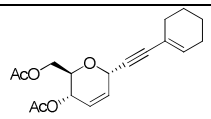
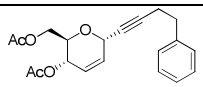
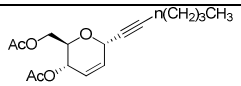
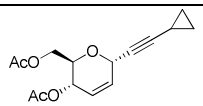
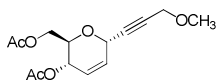
Table 5. $BF_3{\cdot}OEt_2$-Mediated *C*-alkynylation using potassium alkynyltrifluoroborates.[c]



Entry	Conditions	Product	Yield (%)[a]	α/β ratio[b]
1	**a** **b**	 **6**	85 89	96:04 94:06
2	**a** **b**	 **58**	78 45	95:05 93:07
3	**a** **b**	 **59**	64 31	>98:02 >98:02
4	**a** **b**	 **60**	49 26	95:05 93:07
5	**a** **b**	 **61**	78 93	>98:02 >98:02
6	**a** **b**	 **7**	45 66	94:06 93:07
7	**a** **b**	 **62**	23 47	94:06 92:08
8	**a** **b**	 **63**	79 82	>98:02 >98:02

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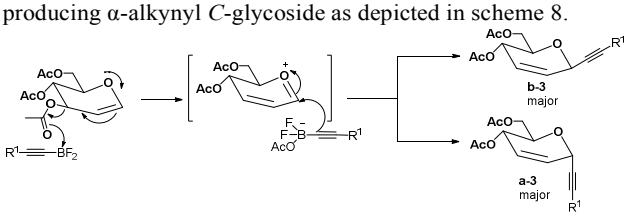
[a] Isolated yield of the pure products. [b] The ratio of α and β anomers was determined by GC analysis of the crude mixture. **Condition a**: 4.0 equiv $BF_3{\cdot}OEt_2$, 20 min, -45 °C. **Condition b**: 2.0 equiv $BF_3{\cdot}OEt_2$, 10 min, 0 °C.

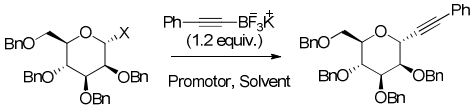
^1H and ^{13}C NMR observations of H-5 and C-5 confirmed the stereochemistry of *C*-glycosides (α-selective) on comparison with literature data.[26-28] Mechanistically, the reaction involves the generation of organoboron difluoride [R-B(OAc)F_2] by the reaction of BF_3 with the alkynyltrifluoroborate.[29,30] [R-B(OAc)F_2], a Lewis acid, activates the per acetylated glucal to generate oxonium ion and nucleophile which attacks the oxonium ion at anomeric centre selectively from α-side producing α-alkynyl *C*-glycoside as depicted in scheme 8.



Scheme 8. Mechanism of $BF_3.OEt_2$- mediated *C*-alkynylation of glycal.

2.6. $BF_3{\cdot}OEt_2$-mediated *C*-alkynylation of glycosyl Fluorides

After the successful *C*-alkynylation of D-glucal via $BF_3{\cdot}OEt_2$-mediated reaction using potassium alkynyltrifluoroborates by Stafani and colleagues, X. W. Liu et al. in 2011 extended similar strategy for *C*-alkynylation of glycosyl fluorides (scheme 9).[31]



Scheme 9. $BF_3.OEt_2$- mediated *C*-alkynylation of glycosyl fluorides.

In their initial studies, benzylated mannose derivatives (glycosyl donors) were chosen because of two reasons; (1) mannosylation exhibits excellent α-selectivity and (2) mannosylation plays an important role in medicinal and biological chemistry.[32] Preliminary attempts to exploit potassium alkyl- or aryl-trifluoroborates did not work due to intramolecular arylation of anomeric position by 2-OBn group. The authors standardized the reaction by using methyl mannoside, mannosyl acetate and mannosyl fluoride in presence of different Lewis acids (as promoter) such as $TiCl_4$, $SnCl_4$, $SiCl_4$, TMSOTf and $BF_3{\cdot}Et_2O$. It was found that the reaction proceeded best with $BF_3{\cdot}Et_2O$ producing *C*-alkynyl glycosides in α-selective manner (scheme 9 and figure 2 & 3). Alkenyl trifluoroborates has also been subjected to these conditions, thereby, producing alkenyl *C*-glycosides in lower yields due to lesser reactivity of the *sp*2-carbons (**68**, **69**, figure 2). Both pyranosyl fluorides and furanosyl fluorides were successfully alkynylated under these conditions. It has been found that the stereoselectivity for both furanose and pyranose derivatives does not depend on anomeric fluoride configuration but depends on the conformation of the oxonium intermediates.[33]

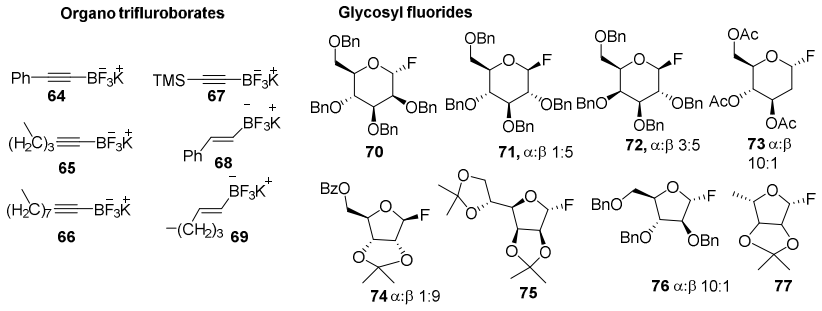


Figure 2. Different organo-trifluoroborates and glycosyl fluorides.

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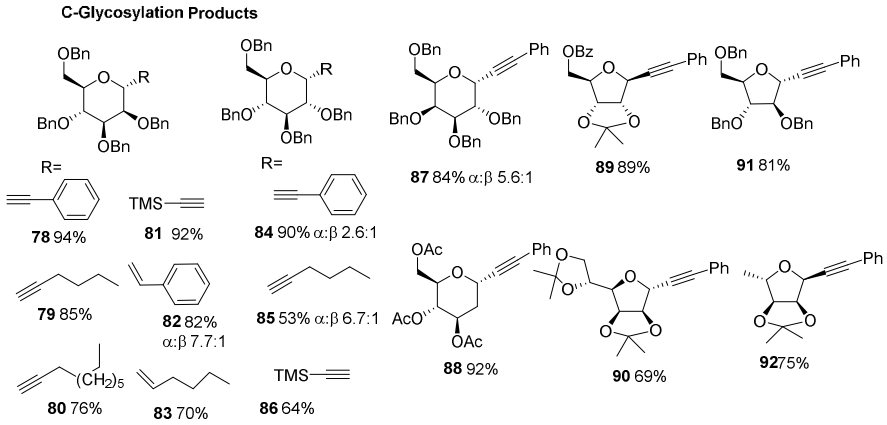
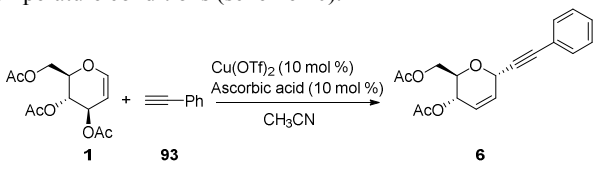


Figure 3. Different C-alkynyl glycosides generated via $BF_3.OEt_2$- mediated C-alkynylation of organo-trifluoroborates and glycosyl fluoride

2.7. $Cu(OTf)_2$-Ascorbic acid-mediated *C*-alkynylation

In 2013 our group (D. Mukherjee and colleagues) developed an excellent protocol for the *C*-alkynylation of glycals using glycals and unactivated alkynes in presence of $Cu(OTf)_2$-ascorbic acid combination under low catalyst loading at room temperature conditions (scheme 10).[34]



Scheme 10. $Cu(OTf)_2$-ascorbic acid-mediated *C*-Alkynylation.

The idea of using Cu-ascorbic acid couple struck our minds from the success story of ascorbic acid in combination with transition metals[38] and its ability to reduce Cu(II) to Cu(I) under neutral condition[24] (pH 7.2). The stereochemistry of *C*-alkynyl glycoside was determined through spectroscopic studies and comparison with literature reports. The cross peaks between H-1 and H-4 as well as H-6 in the NOE spectrum of *C*-alkynyl glycoside proved α-selectivity.

The present conditions were applied to 3,4,6-tri-*O*-acetyl-D-glucal **1** with various phenylacetylenes carrying either electron donating or electron withdrawing groups (figure 4) to produce the *C*-alkynyl glycosides in good to excellent yield with >99% α-selectivity and the results are summarized in figure 4.

It was found that acetylenes with electron donating groups react faster than those having electron withdrawing ones. Encouraged by the results, other glycals with both ether and ester protecting groups like tri-*O*-benzyl-D-glucal and tri-*O*-benzoyl-D-glucal were also subjected to the same reaction to obtain the corresponding products (figure 4, entries **98-111**). Similarly, tri-*O*-acetyl-D-galactal was also subjected to reaction with phenyl acetylene under standardised reaction conditions. The reaction proceeded to completion within a minute leading to acetylene galactoside **112** in high yield with excellent stereoselectivity. Other acetylenes were also allowed to react with tri-*O*-acetyl-D-galactal to afford the galactosides **112-115**. Tri-*O*-benzoyl-D-galactal also undergoes the same reaction under optimised reaction conditions to afforddesired alkynyl glycoside in 68% yield. It has been observed that in general the glucal series reacted faster than galactal (figure 4). Again tri-*O*-acetyl glycal reacted faster than the tri-*O*-benzyl glycal.

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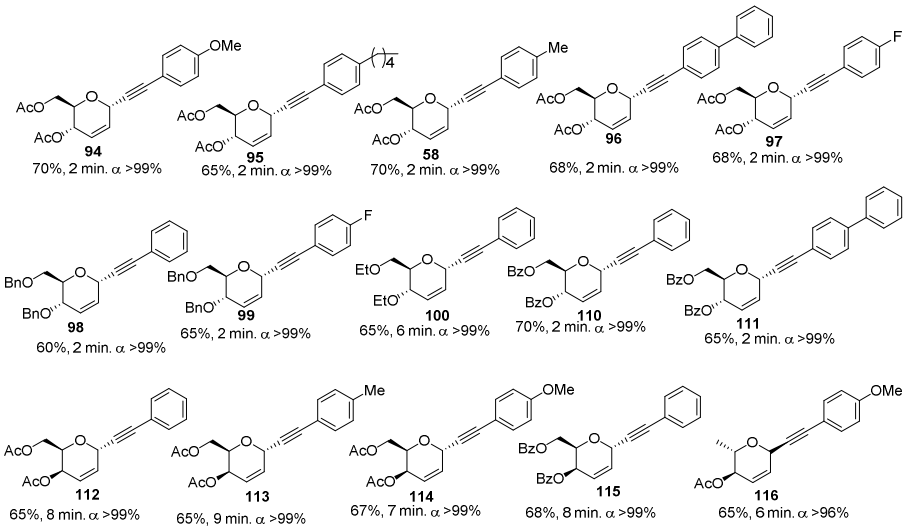
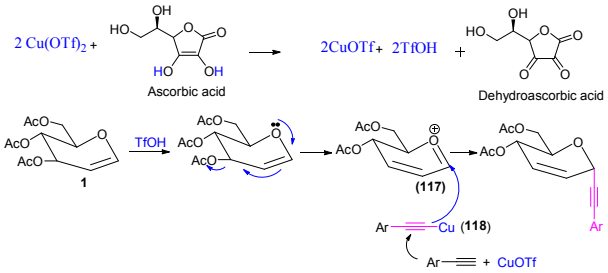


Figure 4. C-alkynyl glycosides synthesized via Cu(II)-ascorbic acid-mediated reaction.

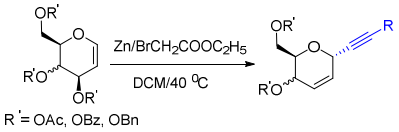
Based on these results and copper triflate chemistry,[39] we proposed a plausible mechanism as shown in scheme 11. In literature it has been suggest that the metal triflatescan act as a source of TfOH in presence of reductants. [36] The active catalyst in the eliminative formation of oxocarbonium ion (**117**) is the TfOH generated during the reduction of $Cu(OTf)_2$) by ascorbic acid. Cu(I)OTf plays a key role in the formation of copper acetylide (**118**). The stereochemistry should largely be determined by the coordination between two π-electron orbitals of the oxocarbonium ion and acetylene groups, while the stereoelectronic control allows the α-pseudo-axial orbital to make the bond.[37]



Scheme 11. Plausible mechanism of $Cu(OTf)_2$ mediated reaction of acetylene and glucal.

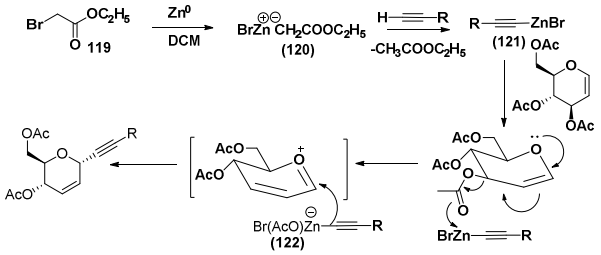
2.8. Zn-mediated *C*-Alkynylation

The $Cu(OTf)_2$/Ascorbic acid system was not successful in the case of aliphatic alkynes. Therefore, continued efforts from our group led to the development of another stereoselective method for *C*-alkynylation of glycal using unactivated alkynes via a Zn-mediated reaction (scheme 12).[35] This protocol overcomes the main demerit of inefficient system to activate aliphatic alkynes and glycosyl donors other than glycals.



Scheme 12. Zn-mediated C-alkynylation of glycals.

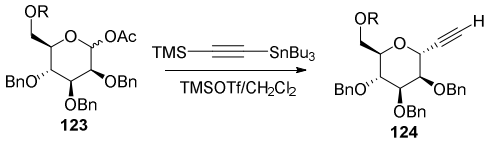
Mechanistically, the reaction involves the formation of organo-zinc compound (**110**) from α-haloester (**119**) and zinc metal.[36,37] Exchange of sp-hybridized proton from alkynes to organo-zinc species (**120**) gives zinc acetylide (**121**) which attacks the glycal through an allylic oxocarbonium ion and a zin-complex (**122**) at anomeric centre from the α-side, therefore, producing *C*-alkynyl glycosides α-selective manner as described in scheme 13.



Scheme 13. Plausible mechanism for Zn-mediated *C*-alkynylation of glycals.

2.9. TMSOTf-mediated *C*-Alkynylation using activated alkynes

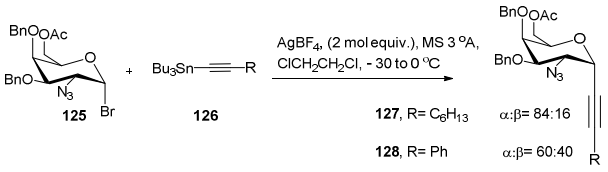
Minoru Isobe[40] and his coworkers reported the activation of glycosylacetate in presence of TMSOTf (scheme 14). The authors choosen mannosyl acetate as a starting material for C-glycosylation in which steric hindrance of β-benzyloxy group at C2-position and also the stereoelectronic effect would facilitate highly α-selective C–C bond formation *via* the axial attack of silylacetylene at an oxonium ion. Unfortunately they were unable to find any conditions that would give the desired product **124**. Even reaction with the relatively reactive 1-phenyl-2-(trimethylsilyl)acetylene gave only a 20% yield of the corresponding product. Finally combination of much more reactive *n*-butylstannyl(trimethylsilyl)acetylene and TMSOTf in CH_2Cl_2 provides **124** as a single product in high yield. Interestingly, the acetyl group at the C6- hydroxyl group of **123** increases the yield of **124** presumably by an arming/disarming effect.



Scheme 14. C-Alkynylation of glycals using TMSOTf developed by Minoru Isobe .

2.10. Silver trifluoroborate- mediated *C*-alkynylation

A. Veyrieres et al[41] showed glycosyl bromide allowed coupling of various alkynyltributylstannanes in the presence of silver tetrafluoroboranuide (silver tetrafluoroborate), thus affording the corresponding *C*-glycoside (scheme 15). The poorer α-selectivity encountered with the metallated phenylacetylene comes from its greater nucleophilicity, an observation which has often been made in *O*-glycosylation of reactive alcohols.



Scheme 15. Silver trifluoroborate- mediated *C*-alkynylation.

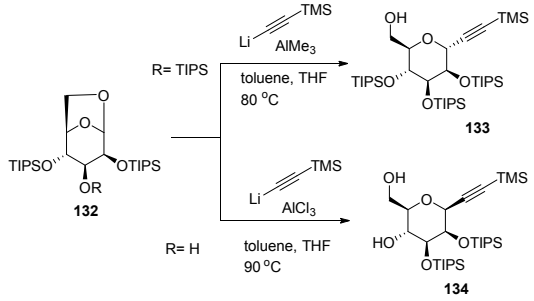
2.11. *n*-BuLi mediated *C*-alkynylation

J. H. Van Boom & his coworkers [42] showed stereoselective synthesis of α-*C*-glycoside via ring opening of α-1,2-anhydrosugars using lithium alkyl derivatives in the presence of zinc chloride proceeds with retention of configuration to afford α -*C*-alkynyl-glycosides in reasonable yields (scheme 16).

Scheme 16. Silver *n*-BuLi mediated *C*-alkynylation.

2.12. Trihalo/trialkyl aluminium mediated *C*-alkynylation

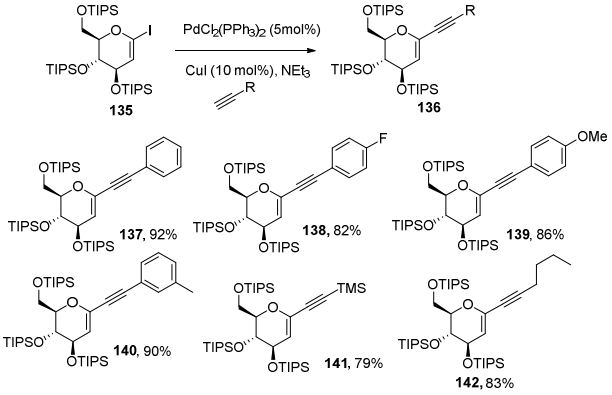
A. Vasella and his co-workers established new strategy for both α- and β-alkynylation using 1,6-anhydromannopyranose and lithium acetylide in the presence of Me_3Al to afford α-*C*-glycoside[43] On the other hand, when a similar substrate was treated with lithium acetylide in the presence $AlCl_3$, α-*C*-glycoside[44] was exclusively obtained (scheme 17).



Scheme 17. Trihalo/trialkyl aluminium-mediated *C*-alkynylation.

2.13. Pd-catalysed *C*-alkynylation

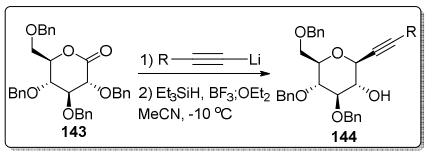
D.B. Werz et al[45] reported a sonogashira-hagihara reaction with 1-iodonated glycals using several aromatic and aliphatic alkynes using Pd-catalyst thus producing alkynyl *C*-glycosides (scheme 18). Chemoselective reduction of the triple bond in the resulting enyne system by the action of the Raney-Ni furnished enol ethers which could be readily refunctionalised.



Scheme 18. Pd-catalysed *C*-alkynylation

2.14. Lactone as a glycan in the synthesis of β-*C*-alkynylation

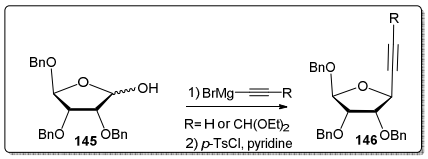
Sinay and co-workers [46] also used sugar lactone 143 towards the preparation of β-*C*-alkynyl glycosides via the addition of lithium acetylide to the protected gluconolactone which provides the mixture of epimers. Stereoselective reduction with triethylsilane and boron trifluoride etherate provides β-anomer as the exclusive product (scheme 19).



Scheme 19. *C*-alkynylation using sugar lactone.

2.15. Hemi acetals in *C*-alkynylation

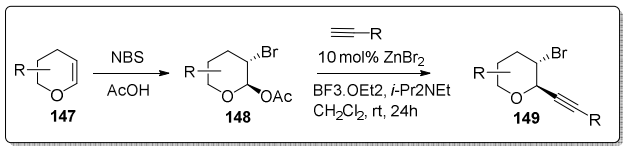
Buchnan and his group synthesized several C-nucleoside starts from the key ethynyl C-glycoside, which is prepared by the condensation of an appropriate acetylene with the hemiacetal of D-ribo sugar. In this reaction, they observed mixture of isomers which are cyclized via the O_3 sulfonate to give the desired β-isomer (Scheme 20).[47]



Scheme 20. *C*-alkynylation using sugar lactol.

2.16. Bromonium assisted *C*-alkynylation

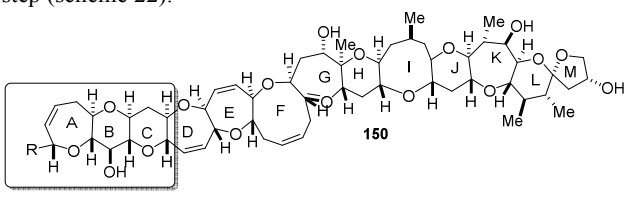
M. P. Watson[48] developed a bromination/alkynylation sequence that enables highly diastereselective, zinc-catalyzed addition of terminal alkynes to α-bromo oxocarbenium ions, formed in situ via ionization of acetal precursors. mild reaction conditions for the addition of unfunctionalized, terminal alkynes to α-halo oxocarbenium ions, formed in situ from acetal precursors makes the process convenient. this method enables the preparation of difunctionalized oxygen heterocycles from simple enol ether precursors in excellent diastereoselectivities (Scheme 21).

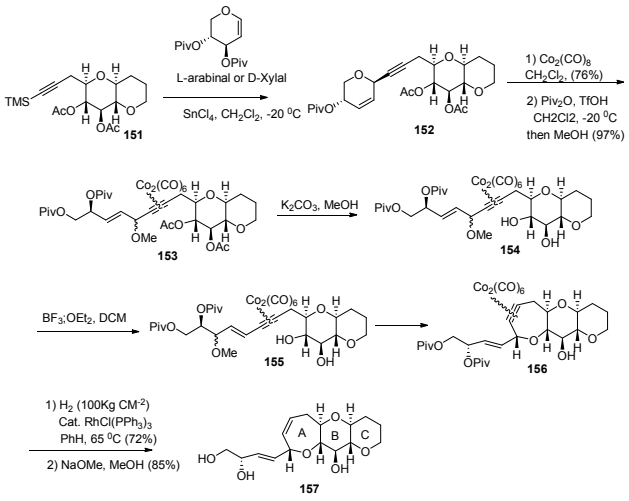


Scheme 21. Bromonim assisted *C*-alkynylation

3.0 Other important application of C-akynyl glycosides

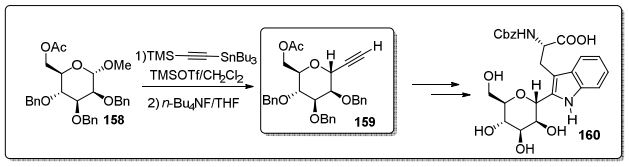
Application of C-alkynylation to the synthesis of ABC-ring system of ciguatoxin : Minoru Isobe and colleagues showed the importance of *C*-alkynylation by synthesising ABC-ring system of natural product ciguatoxin in which they used $SnCl_4$ instead of $TiCl_4$ for the *C*-alkynylation of a deoxy glycal in the initial step (scheme 22).[6]





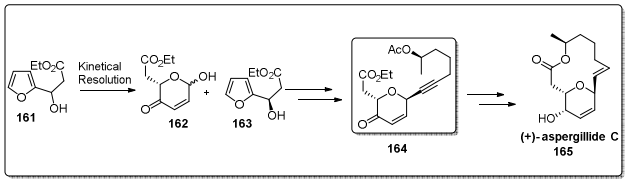
Scheme 22. Application of C-alkynylation to the synthesis ABC-ring system of ciguatoxin.

Application of C-alkynylation to the synthesis of C-mannosyltryptophan: In 2004 Minoru Isobe[49] group demonstrate the interesting total synthesis of α-*C*-mannosyltryptophan (C-Man-Trp) **160**, a naturally occurring *C*-glycosylamino acid (Scheme 23), was accomplished from a commercially available α-methyl-D-mannoside in 10 steps including the *C*-glycosidation of a mannose derivative with a stannylacetylene as a key step. In addition *C*-Mannosyltryptophan (*C*-Man-Trp) is the first example of a molecule with a *C*-glycosidic linkage between amino acid and carbohydrate found in proteins (Scheme 23).



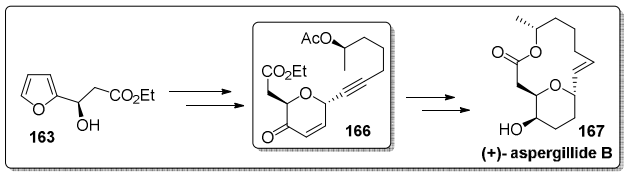
Scheme 23. Synthesis of *C*-alkynyl glycoside for α-*C*-mannosyltryptophan preparation

***Application of C-alkynylation towards the synthesis of aspergillide synthesis*:** Srihari *et al*.[50] reported the synthesis of aspergillide C from furfuryl alcohol derivative (**163**). Racemate **161** was kinetically resolved under sharpless conditions into two heteromers, i.e., pyranone lactal **162** and an enantio-pure furfuryl alcohol **163.** Acetylation of **162,** followed by alkynalation in the presence of $SnCl_4$ provides **164**. This key alkynyl glycoside was converted to aspergillide C through a sequence of steps (scheme 24).



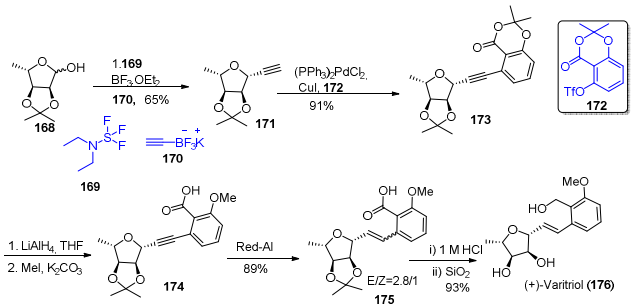
Scheme 24. Synthesis of *C*-alkynyl glycoside for aspergillide C preparation

Later the same group [51] reported the stereoselective total syntheses of (+)-aspergillide B starting from chiral furfuryl alcohol derivative **163**, this undergoes Achmatowicz rearrangement followed by acetylation produces mixture of the corresponding anomeric acetates fallowed by $SnCl_4$ mediated alkynylation generates the key intermediate **166** which is later converted into desired aspergillide **B** in sequence of steps (Scheme 25).



Scheme 25. Synthesis of *C*-alkynyl glycoside for aspergillide B preparation

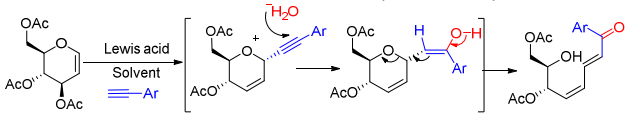
***Application of C-alkynylation to the synthesis of varitriol*:** This method of *C*-alkynylation has been employed for the synthesis of natural product (+)-varitriol (**176**), isolated from marine-derived strain of the fungus *Emericella*V*ariecolor* which exhibits significant anticancer activity.[52] Based on this methodology, a total syntheses of (+)-varitriol have been reported it has been proposed that the reaction of glycosyl fluoride with organotrifluoroborate **170** would be the key step in the synthesis of (+)-varitriol (**176**) as depicted in scheme 26.[53, 54]



Scheme 26. Application of $BF_3.OEt_2$- mediated *C*-alkynylation of glycosyl fluorides towards the synthesis of (+)-varitriol.

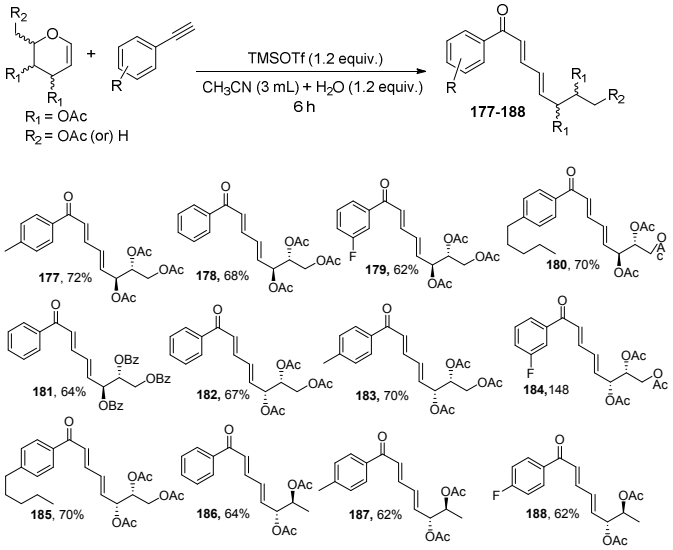
Mukherjee and his group[52] reported a one pot formation of *C*-alkynyl glycoside followed by ring opening using TMSOTf paving the way for direct transformation of glycals to α,β,γ,δ-conjugated chirons under metal free condition as depicted in scheme 27 and 28. Generation of a conjugated (*E*,*E*)-diene that is in conjugation with a carbonyl group and possible stereodiversity of two predefined chiral centers make this protocol a potential candidate for target-oriented synthesis.

The direct conversion of glycals to α,β,γ,δ-conjugated scaffolds via *C*-alkynylation, was conceptualized on the basis of our previously reported works on Cu-mediated synthesis of C-alkynyl glycosides and preparation of halogenated vinyl *C*-glycosides from aryl acetylenes. [37a-b,53] In the former case, there is *in situ* formation of TfOH, and in the latter case, the vinylic position is attacked by a halide ion. Further, Lewis acids such as like TMSOTf can open pyran rings in the presence of nucleophiles like silyl enol ethers and thiols.[54] Thus, we conceptualized that the benzylic position might be attacked by HO^- (nucleophile from water) instead of halogens affording vinyl glycosides containing an enol unit which may tautomerize to the keto form with ring opening through 5-β-O-elimination, thus, lead to the formation of alcohals (Scheme 27).



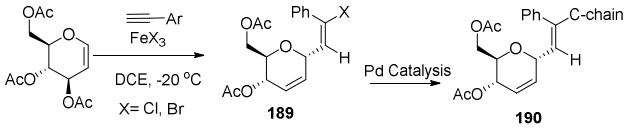
Scheme 27. Proposed *C*-alkynylation and *in situ* transformation to α,β,γ,δ-conjugated chirons.

This inspired us to revisit the reaction of glycals and acetylenes in presence of nonhalogenated Lewis acids and to standardize the reaction conditions for the *in situ* transformation of *C*-alkynyl glycosides into open-chain systems as depicted in scheme 27. Various synthetically important α,β,γ,δ-conjugated scaffolds were synthesized using this method and are listed in (scheme 28).



Scheme 28. TMSOTf-mediated *C*-alkynylation and *in situ* transformation to α,β,γ,δ-conjugated scaffolds.

Mukherjee et al [55] reported a one pot functionalisation of C-alkynyl glycosides to halo vinyl glycosides using halogenated Lewis acids and this tandem atom economic process provides an alternative approach for the synthesis of extended carbon chain attached to sugar pyranoside unit (scheme 29).



Scheme 29. One pot functionalisation of c-alkynyl glycosides for the synthesis of halovinyl glycosides.

Conclusions

From the above discussions, it can be concluded that *C*-alkynylation of sugars is an emerging modern synthetic interest which have found applications in synthetic organic chemistry for the generation of chiral scaffolds as well as natural product syntheses. Over the years, several elegant protocols have emerged in literature for *C*-alkynylation of sugars. Most of these methods involve the generation of oxonium ion intermediate in presence of Lewis acids such as $TiCl_4$, $BF_3{\cdot}OEt_2$, I_2, $Cu(OTf)_2$, TMSOTf etc. An Indium(0)-promoted Ferrier-type *C*-alkynylation provided an excellent methodology. In almost all the cases discussed in this review the *C*-alkynylation reactions are α-selective. A wide range of alkynes and many catalysts have been studied to bring about *C*-alkynylation leading to α-*C*-glycosides. *C*-alkynylations have been exploited for the synthesis of natural products like ciguatoxins, (+)-varitriol, disaccharide of isomaltoside etc. Although a much progress in terms of improvements in efficiency, yield, selectivity, substrate scope etc. has been reported, there is still scope for further development of novel and better protocols. It is also useful in the generation of unusual chiral scaffolds like α,β,γ,δ-conjugated chirons, disaccharides etc. This chemistry will further open up new avenues towards chiral natural product syntheses.

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Advances in C-alkynylation of sugars and its application in organic synthesis

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