The carbon-Ferrier rearrangement: an approach towards the synthesis of *C*-glycosides

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This article is respectfully dedicated to Professor Dr. Richard R. Schmidt on the occasion of his 78th birthday

DOI: http://dx.doi.org/10.3998/ark.5550190.0014.223

Abstract

The carbon-Ferrier rearrangement is the reaction of appropriately functionalised glycals, with a variety of carbon nucleophiles such as allyltrimethylsilanes, alkynyltrimethylsilanes, silyl cyanides etc. involving the corresponding nucleophilic addition at the anomeric carbon with concomitant loss of a substituent at C-3. This leads to double bond migration to give 2,3-unsaturated sugars which act as useful chiral substrates for further manipulations in organic synthesis.

Keywords: Ferrier rearrangement, C-glycosides, unsaturated carbohydrates, allyltrimethylsilanes, alkynylsilanes

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1. Introduction

The well-known Ferrier rearrangement[1] involves the reaction of a suitably protected 1,2-glycal with an alcohol under Lewis acid catalysis to form the corresponding 2,3-unsaturated 1-*O*-glycosides. Such 1-*O*-glycosides have been transformed into a variety of useful intermediates both in organic synthesis as well as specifically in carbohydrate chemistry. Likewise, there have been reports on aza-[1h] and thia-[1i] Ferrier rearrangements. Several papers and reviews on this and allied topics have appeared in the literature.[1]

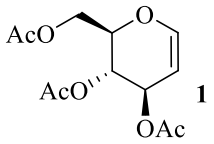
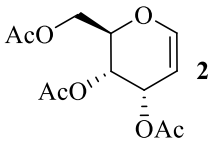
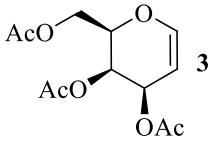
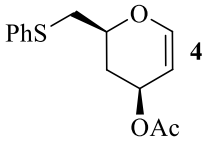
Since *C*-glycosides are stable analogs of *O*-glycosides and less prone to cleavage at the anomeric carbon, they have gained considerable importance in the last few decades. Among several approaches towards *C*-glycosides, the Ferrier rearrangement utilising C-nucleophiles has been found to be quite useful. Several catalysts and nucleophiles have been introduced in the literature addressing α/β-selectivity, mildness of the method, effect of solvent, effect of acid (or Lewis acid) catalyst, and yields of the products. In this review, a brief account of several methods that have been reported in the literature since 1982 is presented.

2. Allylic Silanes as Nucleophiles

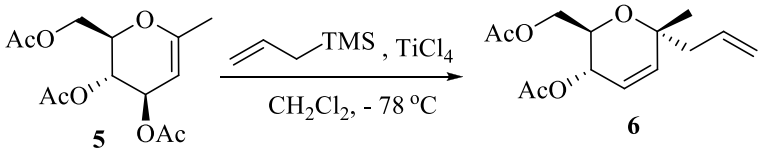
2.1 Allyl silanes

Amongst the carbon nucleophiles used for *C*-Ferrier reactions, allyltrimethylsilanes (ATMS) have been most prominent. The first examples of such reactions were reported by Danishefsky *et al*.[2] where glycal acetates **1-4** (Table 1) were observed to undergo nucleophilic displacement and double bond migration in the presence of equimolar amounts of $TiCl_4$ as a Lewis acid. The reactions were highly regioselective with allyl group addition at C_1 position and shifting of double bond to C_2-C_3. The reaction proceeds with preference towards attack from the α-side but the selectivity varied depending upon the stereochemistry of other groups on the pyranose ring.

Table 1. Reaction of glycals with 1 eq. $TiCl_4$ and 1.5 eq. ATMS at -78 ºC

Glycals	Yield	$\alpha:\beta$
 **1**	85%	16:1
 **2**	95%	6:1
 **3**	93%	30:1
 **4**	95%	1:0

Stereoselective allylation at the C_1 position in 1-alkylglucal **5** was reported by Nicolaou and group using $TiCl_4$ (Scheme 1).[3] The nucleophile attacks from the α-face of the molecule as the oxonium ion intermediate would preferentially convert into the energetically favoured half chair conformer **7** (Figure 1).



Scheme 1

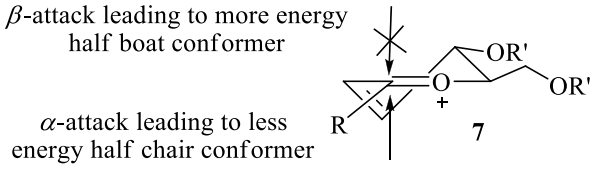
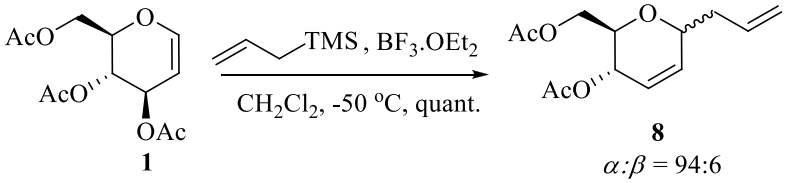


Figure 1. Proposed explanation to α-selectivity of allyl addition.

Isobe *et al.*[4] reported the use of $BF_3.OEt_2$ as a catalyst for the generation of the α– and β–anomers **8** from acetylated glucal **1** in 94:6 ratio, which were separated by column chromatography with great difficulty (Scheme 2).

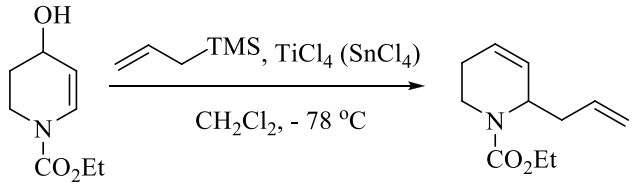


1 **8**

$\alpha:\beta$ = 94:6

Scheme 2

The first aza-Ferrier reaction on *N*-carbethoxytetrahydropyridine derivative **9** with two equivalents of allyltrimethylsilane was reported by Kozikowski *et al.*[5] (Scheme 3). While excellent yields of the product **10** were observed in the presence of $SnCl_4$ (90%) and $TiCl_4$ (89%), $BF_3.OEt_2$ and TMSOTf produced the desired compound in moderate yields of 43% and 51%, respectively.

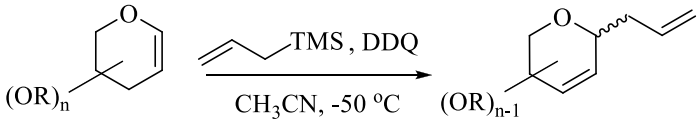


9 **10**

Scheme 3

Toshima and co-workers[6] reported highly stereoselective formation of allyl-α-*C*-glycosides when glycal acetates such as **1, 3, 11-13** were treated with allyltrimethylsilane in the presence of 30-50 mol% of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as a neutral activator (Table 2). Increase or decrease in the amount of activator caused lowering of product yield. Use of allyltributyltin under similar conditions yielded the product in 58% yield.

Table 2. Reactivity and selectivity in various glycals with allyltrimethylsilane and DDQ



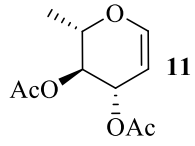
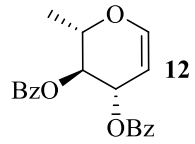
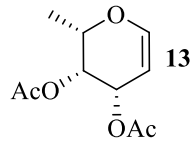
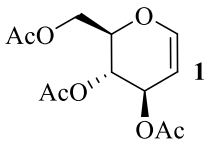
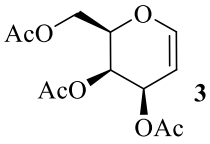
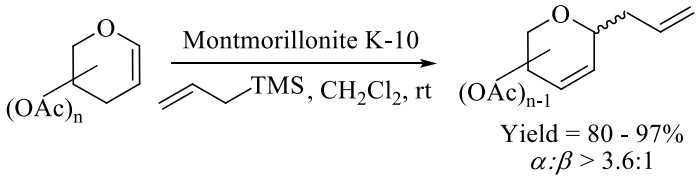
Glycals	T (°C)	Time (h)	Yield (%)	$\alpha:\beta$
 **11**	50	12	90	15:1

Table 2. Continued

Glycals	T (°C)	Time (h)	Yield (%)	*α:β*
 **12**	70	48	77	10:1
 **13**	70	48	74	>99:1
 **1**	50	48	85	16:1
 **3**	70	48	76	>99:1

From the same group, 10 mass % of Montmorillonite K-10 was found to be a suitable catalyst for effecting Ferrier rearrangement in acetylated glycals using allyltrimethylsilane as the source of nucleophile (Scheme 4). The reaction followed good *α*-selectivity irrespective of the stereochemical disposition of the groups on the glycal.[7]



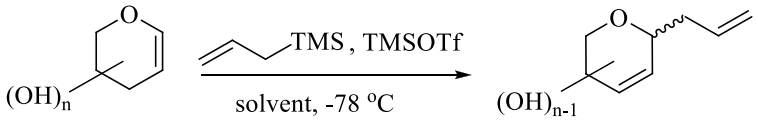
Scheme 4

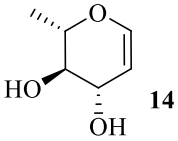
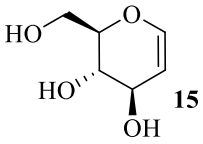
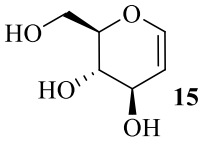
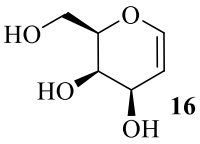
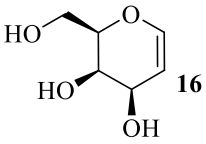
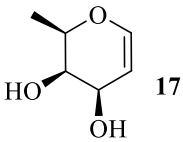
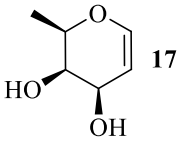
Also, stereoselective allyl α-C-glycosidation using unprotected glycals **14-17** (Table 3) was successfully achieved in the presence of equimolar amounts of TMSOTf at low temperatures by the same group.[8] Selective formation of *C*-glycosides was promoted by low temperature conditions (-78 °C). The yield of the reactions was observed to be dependent on the solvent.

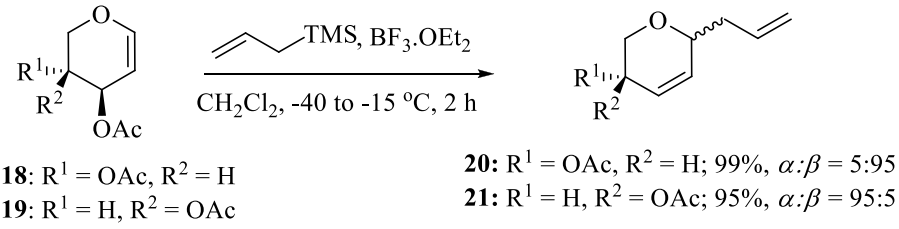
Studies on pentapyranose derivatives **18** and **19** by Isobe and co-workers[9] revealed 1,4-*anti* diastereoselectivity (>95:5) in the addition of allyl nucleophile, giving **20** and **21** in the presence of $BF_3.OEt_2$ (Scheme 5). This observation is in contrast to the reactions of hexapyranoses which

exhibit 1,5-*anti* diastereoselectivity. The authors have rationalised this difference by the conformations of the oxonium ion intermediates. While for the hexapyranoses the stereochemistry is guided by the equatorial orientation of the C-5 substituent, the pentapyranoses favour the transition state having quasi-axial orientation of the C-4 substituent which is 1.5 kcal/mol more stable than the quasi-equatorial conformer.

Table 3. Reaction of unprotected glycals with TMSOTf



Glycals	Solvent	Time (h)	Yield(%)
 **14**	CH_2Cl_2	0.5	91
 **15**	CH_2Cl_2	0.5	14
 **15**	CH_2Cl_2 – CH_3CN	0.5	91
 **16**	CH_2Cl_2	0.5	2
 **16**	CH_2Cl_2 – CH_3CN	1	90
 **17**	CH_2Cl_2	0.5	9
 **17**	CH_2Cl_2 – CH_3CN	2	66



Scheme 5

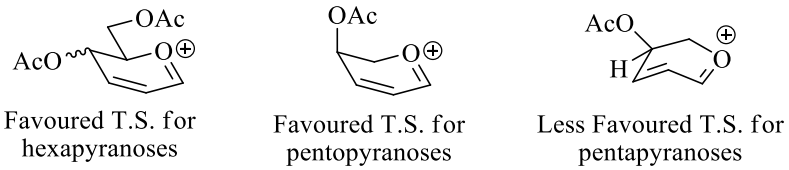
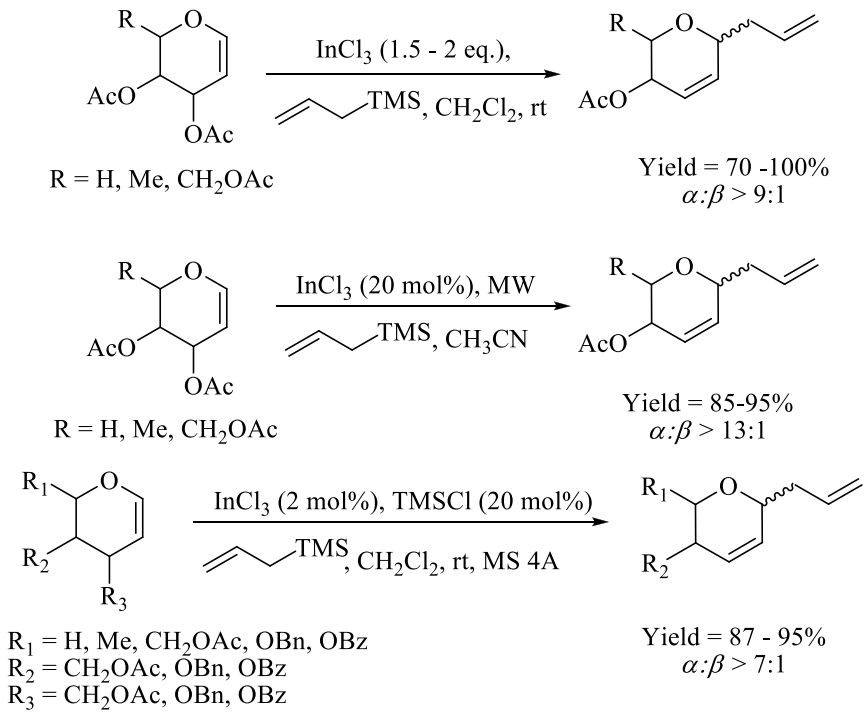


Figure 2. Transition state analysis for pentapyranoses.

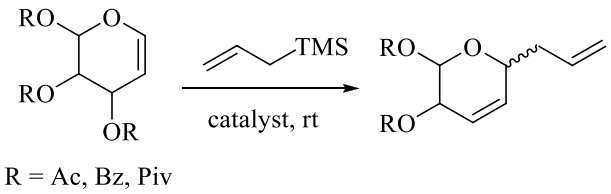
C-glycosylation of acetylated glycals using allyltrimethylsilane in the presence of 1.5–2 equivalents of $InCl_3$ in dichloromethane has been reported by Ghosh *et al.*[10a] The reaction proceeded with 1,5-*anti* diastereoselectivity giving the products in good to excellent yields. Consecutively, Das *et al.*[10b] have modified the reaction condition using 20 mol% of $InCl_3$ to the reaction mixture in acetonitrile under microwave irradiation. The reaction was complete in 30 seconds and the products were obtained in excellent yields with very good diastereoselectivity. Later, Ghosh *et al.*[10c] reported that addition of 2 mol% of $InCl_3$ and 20 mol% of trimethylsilyl chloride was found to be effective in generating the desired pseudoglycals. The catalyst system was observed to be equally effective when used in neat allyltrimethylsilane.[10c] These results are summarised in Scheme 6.

Yadav *et al*. have reported the use of several Lewis acids for *C*-Ferrier reactions on variously protected glycals. with allyltrimethylsilane as the nucleophile. Catalytic amounts of $Sc(OTf)_3$,[11a] molecular iodine,[11b] $InBr_3$,[11c] $Bi(OTf)_3$,[11d] phosphomolybdic acid (PMA) supported on silica gel[11e] have been found to be efficient in producing the *C*-pseudoglycosides in 85–95% yields with very high α-anomeric selectivity (Table 4). Equimolar amount of $LiBF_4$[11f] has also been observed to be competent as a promoter for this reaction giving the desired products in excellent yields and selectivity.



Scheme 6

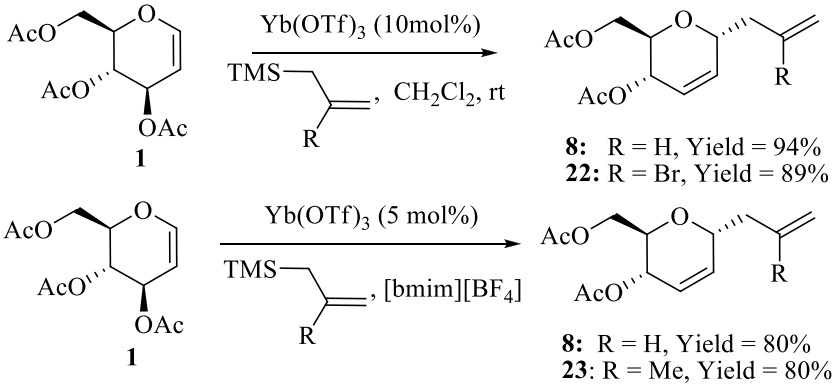
Table 4. Lewis acids used for carbon-Ferrier reactions with ATMS as nucleophile



Catalyst	Solvent	Yield(%)	$\alpha:\beta$	Ref.
$Sc(OTf)_3$	CH_2Cl_2	84 – 93	9:1	11a
I_2	CH_2Cl_2	84 – 95	>8:2	11b
$InBr_3$	CH_2Cl_2	88 – 93	9:1	11c
$Bi(OTf)_3$	CH_3CN	88 – 95	>9:1	11d
PMA-SiO_2	CH_3CN	85 – 90	Only α	11e

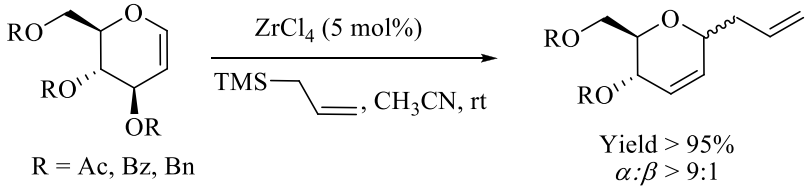
As reported by Schmidt *et al.*,[12a] reaction of per-*O*-acetylated glycals with allyltrimethylsilane and (2-bromoallyl)trimethylsilane in the presence of 10 mol% of $Yb(OTf)_3$ was observed to generate the corresponding α-glycosides **8** and **22** stereospecifically in excellent yields. This method, as shown in Scheme 7, has been utilised later by Sasaki *et al*. for the synthesis of neodysiherbaine.[12b] Subsequently, Grée *et al*. reported that glycals react smoothly with allyltrimethylsilanes under $Yb(OTf)_3$ catalysis when used in [bmim][BF_4] as ionic liquid,

resulting in the corresponding *C*-glycosides **8** or **23** in 80% yield. The reaction was observed to be highly stereoselective with preference towards the α-anomer.[12c]



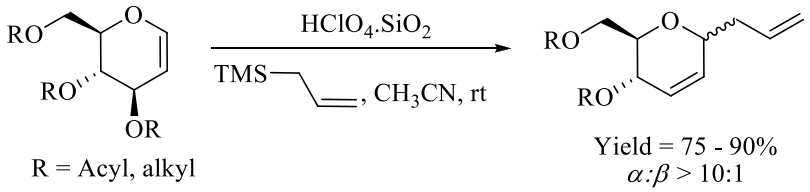
Scheme 7

Venkateswarlu *et al.*[13] have reportedly used 5 mol% of $ZrCl_4$ as catalyst for Ferrier reaction on acetylated glycals with allyltrimethylsilane as nucleophile producing the expected products in excellent yields with very good selectivity (Scheme 8).



Scheme 8

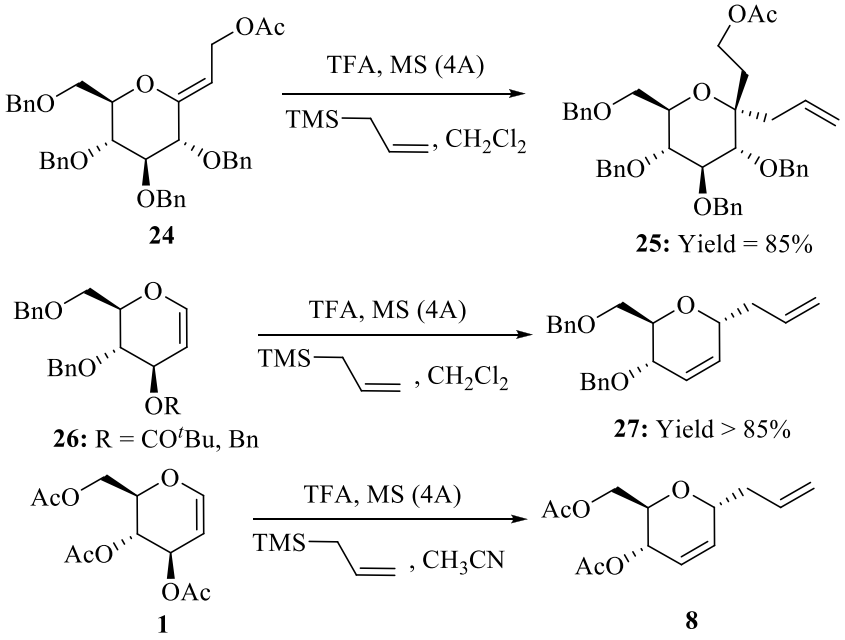
Misra and co-workers[14] have reported $HClO_4$-SiO_2 as an insoluble catalyst promoting the Ferrier rearrangement on glycals. 50 mg of the solid supported catalyst was found to be effective for 1 mmol of the glycal, rapidly generating the desired products in 75–85% yields with excellent selectivity as shown in Scheme 9.



Scheme 9

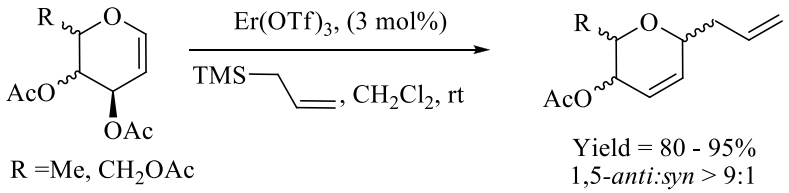
Lin and coworkers[15a] reported the reaction of *exo*- and *endo*-glycals with allyltrimethyl-silane in the presence of 10 equivalents of trifluoroacetic acid (TFA) yielding the desired products in about 85%, with selectivity towards the α-anomer **25** and **27** (Scheme 10). The same

reagent was used by Gallagher *et al.*[15b] in the synthesis of a novel laulimalide analogue via intermediate **8**.



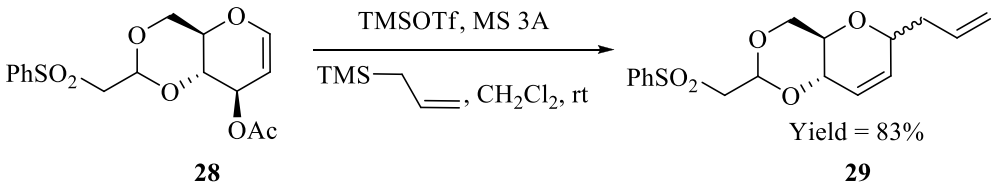
Scheme 10

Erbium(III) triflate when used in 3 mol% with allyltrimethylsilane produced *C*-pseudo-glycosides from acetylated glycals (Scheme 11).[16] The corresponding α-glycosides were obtained in good yields.



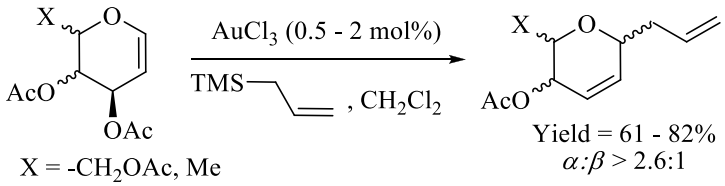
Scheme 11

Phenylsulfonylethylidene (PSE) protected glycals **28** were observed to undergo the Ferrier reaction with allyltrimethylsilane on being activated by TMSOTf to give product **29** as shown in Scheme 12.[17]



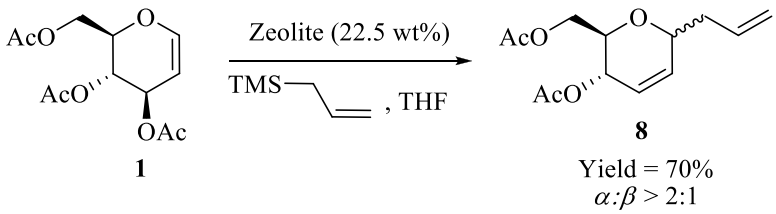
Scheme 12

A catalytic amount of $AuCl_3$ was also found to be efficient in promoting *C*-allyl product formation.[18] The reaction produced the expected compounds in good yields with the α-isomer predominating (Scheme 13).



Scheme 13

Ultrastable Y-zeolites have been reported by Gammon *et al.*[19] to catalyze *C*-allylation on acetylated glycal with formation of the corresponding α-anomer selectively (Scheme 14).

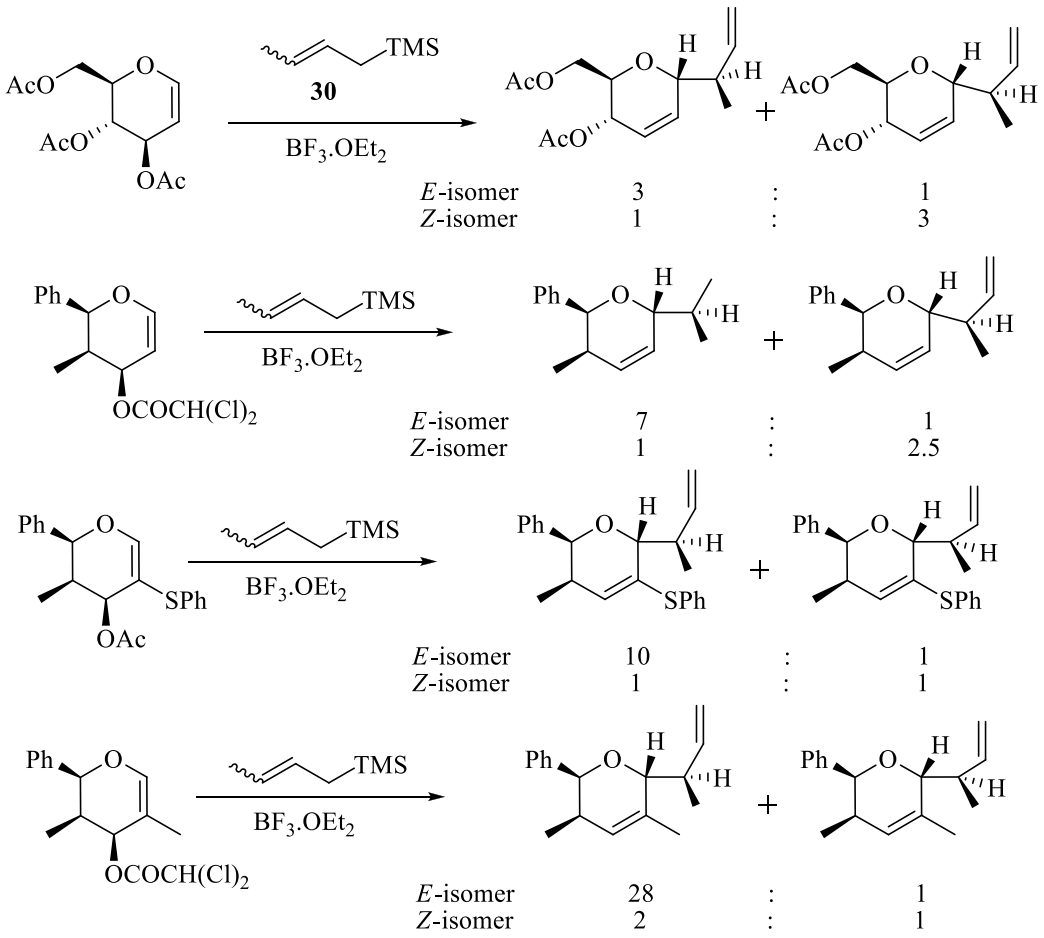


Scheme 14

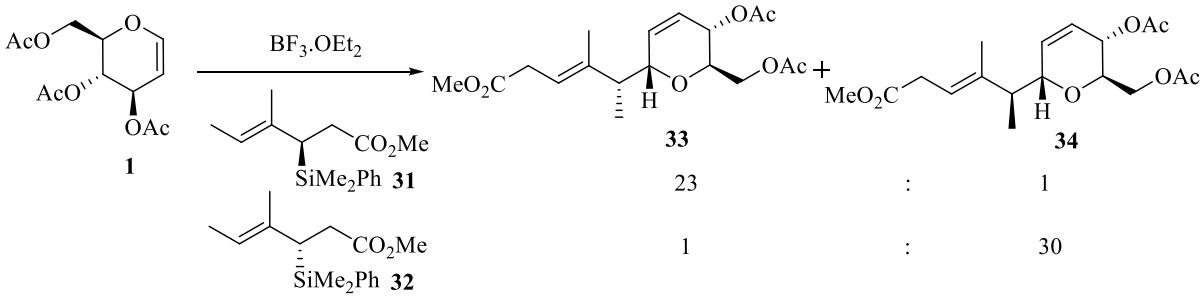
2.2 Substituted allylsilanes as nucleophiles

Danishefsky *et al.*[20] explored the selectivity of nucleophilic attack of (*E*)- and (*Z*)- crotylsilanes **30** on substituted glycals. The rearrangement was promoted by $BF_3.OEt_2$ to give the α-configurated pseudoglycosides. Several glycal-like substrates were treated by the silanes. While the *E*-silane yielded predominantly C_1-*anti* product, the *Z*-silane gave the C_1-*syn* isomer as the major products. On incorporating a substituent at C-2 position or an electron withdrawing group at C-3 position, the *anti:syn* ratio increased considerably. These observations are summarised in Scheme 15.

Subsequently, Panek *et al.*[21] reported the Lewis acid mediated attack of substituted crotylsilanes **31** and **34** on glycal **1** as shown in Scheme 16. In their work, $BF_3.OEt_2$ was found to be most effective as a Lewis acid in contrast to TMSOTf and $TiCl_4$. Upon treatment of triacetylated glucal **1** with (*R*)-silane **31**, the isomer **33** was obtained as the major product while the (*S*)-silane **32** produced **34** as the major isomer.



Scheme 15



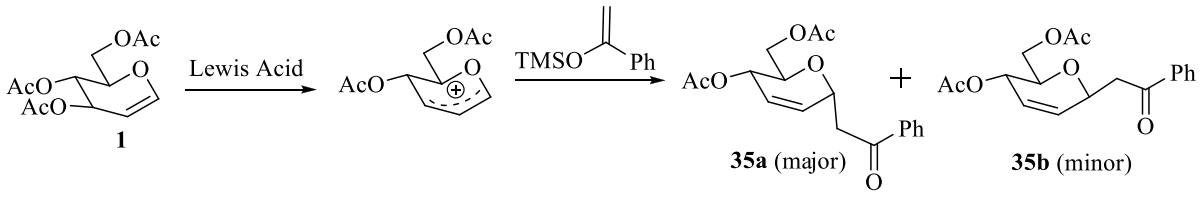
Scheme 16

3. Enol Silyl Ethers as Nucleophiles

Reaction of 1-(trimethylsilyloxy)styrene with tri-*O*-acetyl glucal **1** was first reportedly observed by Dawe and Fraser-Reid.[22] The reaction proceeded in presence of 1.4 equivalents of $BF_3.OEt_2$

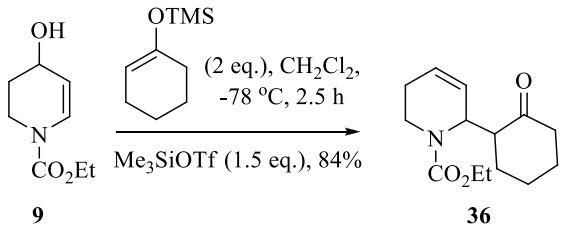
at -40 °C producing the *C*-pseudoglycoside **35** in 99% yield with α-anomeric selectivity (Table 5). Although the authors expected an increment in the ratio of selectivity in acetonitrile as solvent due to formation of nitrilium ion that would adopt a β-orientation, changing the solvent from dichloromethane to acetonitrile failed to provide any improvement.

Table 5. Silyl enol ether as nucleophile on acetylated glucal



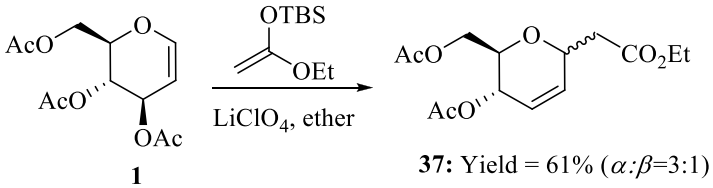
Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)	α:β
$BF_3.OEt_2$	CH_2Cl_2	-40 – 0	0.5	99	4:1
$AlCl_3$	THF	23	36	77	7:3
$AlCl_3$	CH_3CN	-45 – 0	1	97	4:1

An Aza-Ferrier reaction on the *N*-carbethoxytetrahydropyridine derivative **9** with two equivalents of silyl enol ether in presence of 1.5 equivalents of TMSOTf to give the 1-acetyl-2-oxopropyl derivative **36** in 84% yield has been reported by Kozikowski and Park,[5] as shown in Scheme 17.



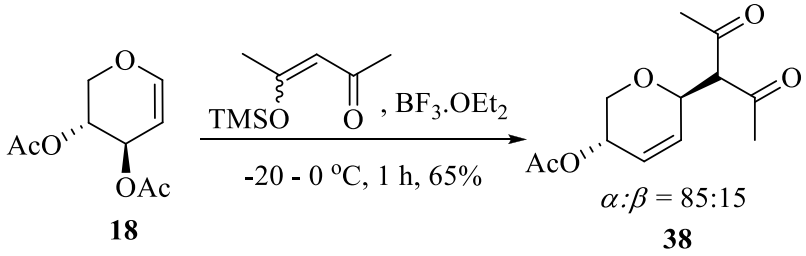
Scheme 17

Lithium perchlorate has been identified as an effective promoter for the Ferrier reaction on acetylated glucal with silyl enol ether (ketene acetal) by Pearson and Schkeryantz.[23] The α-anomer of the ester **37** so formed was observed to be the major product (Scheme 18).



Scheme 18

Isobe *et al*.[9] have reported the reaction of enol silyl ether on acetylated xylal **18** in presence of $BF_3.OEt_2$ to form the C-C coupling product **38** in 65% yield. The reaction was observed to follow 1,4–*anti* selectivity in the ratio of 85:15 as shown in Scheme 19.



Scheme 19

$Yb(OTf)_3$ has been found to be a good catalyst for reaction of several enol silyl ethers on acetylated glucal by Schmidt *et al*.[12a] The reaction proceeded with good selectivity and excellent yields. Subsequently, Grée *et al.*[12c] have reported the utilisation of $Yb(OTf)_3$ in ionic liquid in the reaction of similar silyl enol ethers with glucal forming the desired products in moderate yields and good diastereoselectivity. These observations are summarized in Table 6.

Table 6. Ferrier rearrangement with enol silanes using catalytic $Yb(OTf)_3$

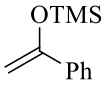
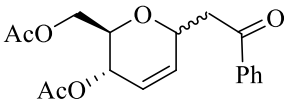
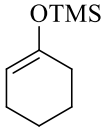
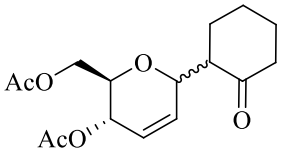
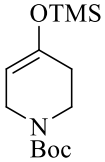
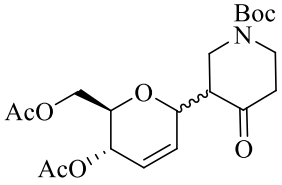
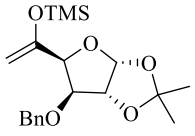
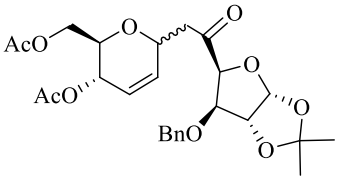
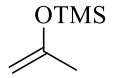
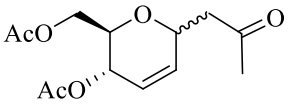
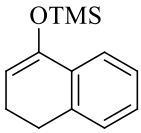
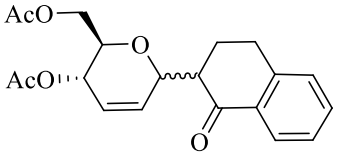
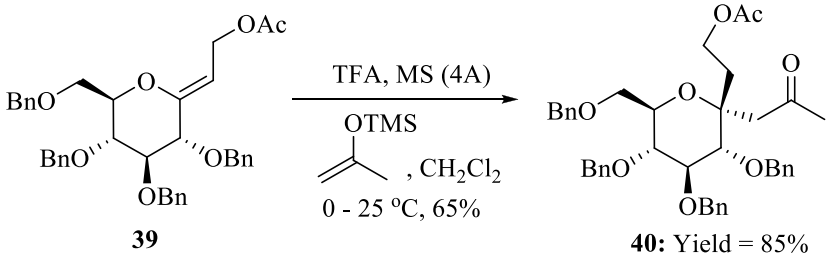
Acceptor	Product	10 mol % $Yb(OTf)_3$			5 mol % $Yb(OTf)_3$ in $[bmim][NTf_2]$		
		Time (h)	Yield (%)	*α:β*	Time (h)	Yield (%)	*α:β*
		10	90	8:1	0.5	65	>95:5
		12	89	11:1	0.5	60	>95:5
		15	84	8:1	-	-	-
		12	88	5:1	-	-	-

Table 6. Continue

Acceptor	Product	10 mol % $Yb(OTf)_3$			5 mol % $Yb(OTf)_3$ in $[bmim][NTf_2]$		
		Time (h)	Yield (%)	$\alpha:\beta$	Time (h)	Yield (%)	$\alpha:\beta$
		-	-	–	0.5	40	>95:5
		-	-	–	1.5	60	>95:5

Exo-Ferrier reaction on **39** with a silyl enol ether in the presence of trifluoroacetic acid, resulting in the formation of compound **40,** containing a quaternary anomeric carbon, in 65% yield, has been reported by Lin and co-workers (Scheme 20).[15a]



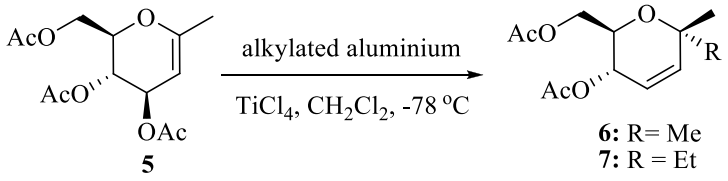
Scheme 20

4. Organometallic Nucleophiles

In 1986, Nicolaou and his group[3] reported trialkylaluminium and alkylaluminium chloride as sources of the carbon nucleophile in Ferrier rearrangements of the triacetylated 1-methyl glucal **5** (Table 7). The reaction was promoted by $TiCl_4$ and successfully yielded 1,1-dialkylated pseudoglycals **6** and **7** stereospecifically. The reaction proceeded via the transition state as described in Figure 1.

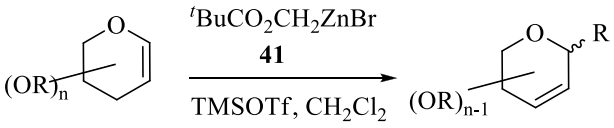
Orsini and Pelizzoni[24] reportedly used the Reformatsky reagent *tert*-butoxy-carbonylmethylzinc bromide **41** on acetylated glycals to bring about formation of pseudoglycosides in the presence of TMSOTf at 0 °C. While the D-glucose derived olefin produced the α-anomer as the major product, the selectivity was reversed in the D-galactose and L-rhamnose derived olefins **11** as shown in Table 8. The reactions produced the desired products in poor to moderate yields only.

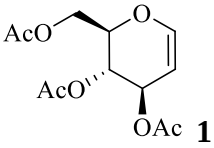
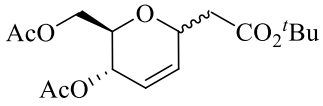
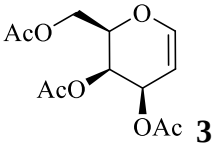
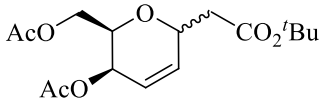
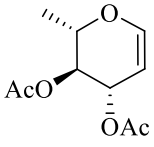
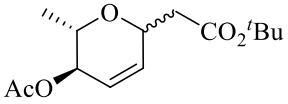
Table 7. Aluminium alkyls as carbon nucleophiles



Reagent	R	Yield (%)
$AlMe_3$	Me	92
$AlEt_3$	Et	82
$AlEt_2Cl$	Et	85
$AlEtCl_2$	Et	81

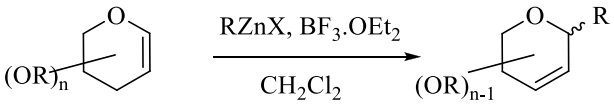
Table 8. TMSOTf-mediated addition of Reformatsky reagent on glycals

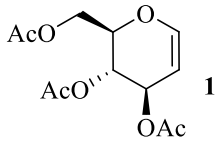
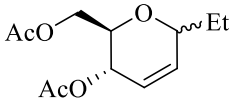
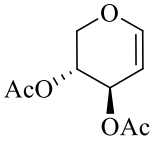
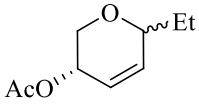
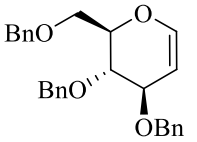
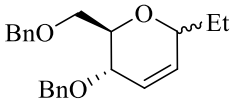
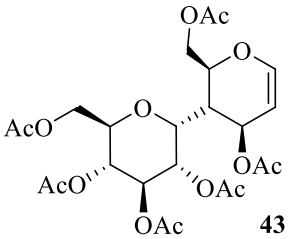
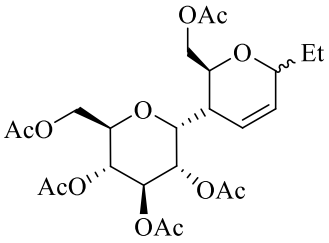
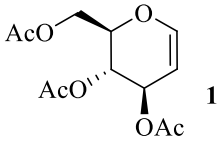
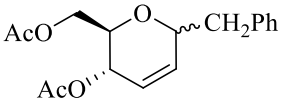
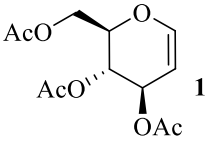
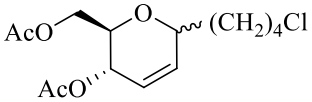
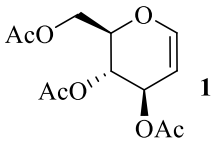
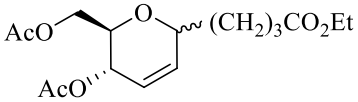
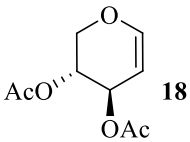
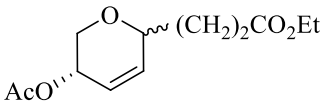


Glycal	Product	Yield (%)	*α:β*
 **1**		48.6	2:1
 **3**		16.1	1:2
 **11**		48.4	1:2

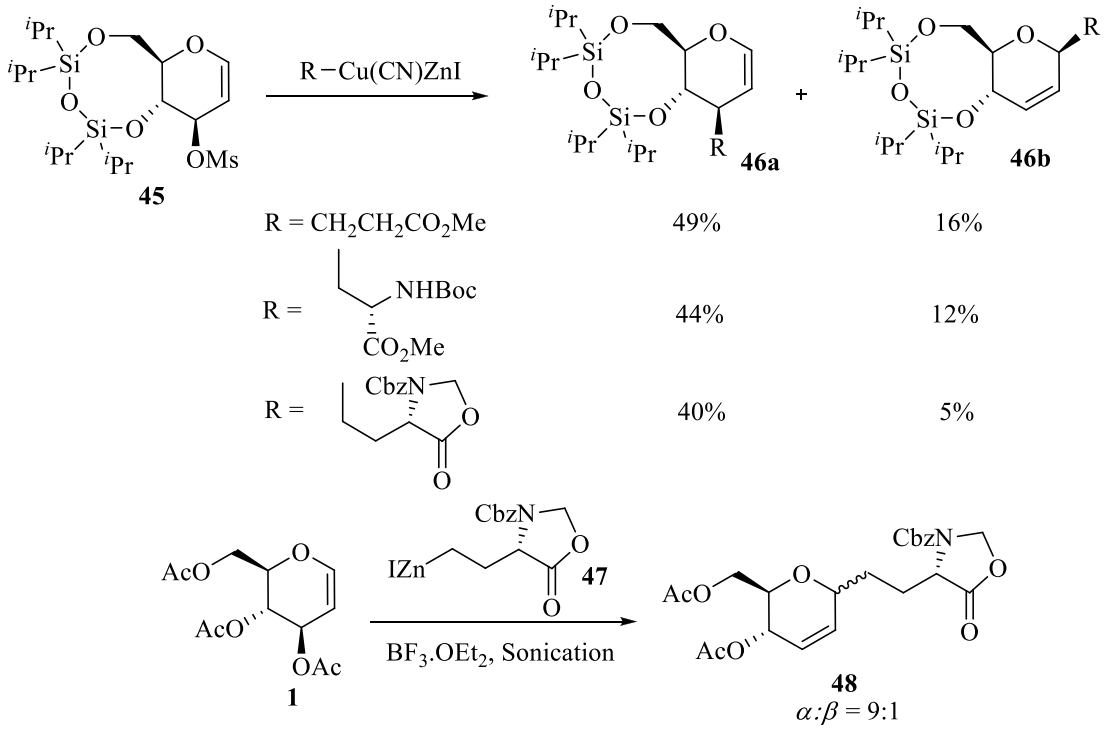
Alkylated zinc reagents have been reported by Gallagher *et al.*[25a] for the Ferrier rearrangements on various protected glycals in the presence of $BF_3.OEt_2$ or TMSOTf as a Lewis acid. The reaction yielded the *α* anomer predominantly (Table 9). Attempts to utilise Zn(Cu) couple with alkyl halides for similar organometallic reaction in presence of Lewis acids resulted in the formation of C-3 substituted glycals. The authors have subsequently reported[25b] that alkylated zinc halides react with a *β*-selectivity similar to that earlier reported by Isobe *et al.* (Scheme 5, Figure 2), forming **44** from di-*O*-acetyl-D-xylal **18**, as shown in Table 9.

Table 9. Alkylated zincs as nucleophiles in the presence of $BF_3.OEt_2$



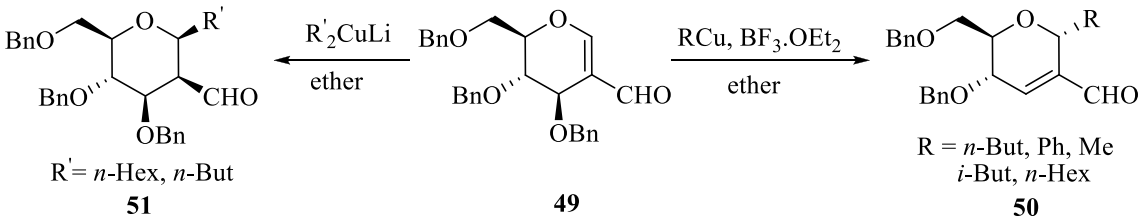
Glycal	Zinc reagent	Product	Yield (%)	α:β
 **1**	Et_2Zn		95	3.2:1
 **18**	Et_2Zn		80	24:1
 **42**	Et_2Zn		87	4.1:1
 **43**	Et_2Zn		81	2:1
 **1**	$PhCH_2ZnBr$		57	1.7:1
 **1**	$Cl(CH_2)_4ZnI$		63	9:1
 **1**	$EtO_2C(CH_2)_3ZnI$		87	5:1
 **18**	$EtO_2C(CH_2)_2ZnI$	 **44**	95	1:22

R.F.W. Jackson and co-workers[26] reported the use of alkylated zinc/copper reagents on the novel tetra(isopropyl)disiloxane glucal derivative **45** bearing a leaving group at C-3 as shown in Scheme 21. *β*-Selectivity for both nucleophilic substitution at C-3 giving **46a**, and Ferrier rearrangement at C-1 resulting in **46b** was observed. Several amino acid derived alkanes have been used as nucleophiles. Also, glutamic acid derived zinc reagent **47** when reacted with tri-*O*-acetyl-D-glucal **1** produced the C-1 adduct only **48** with *α*-selectivity in the presence of $BF_3.OEt_2$.



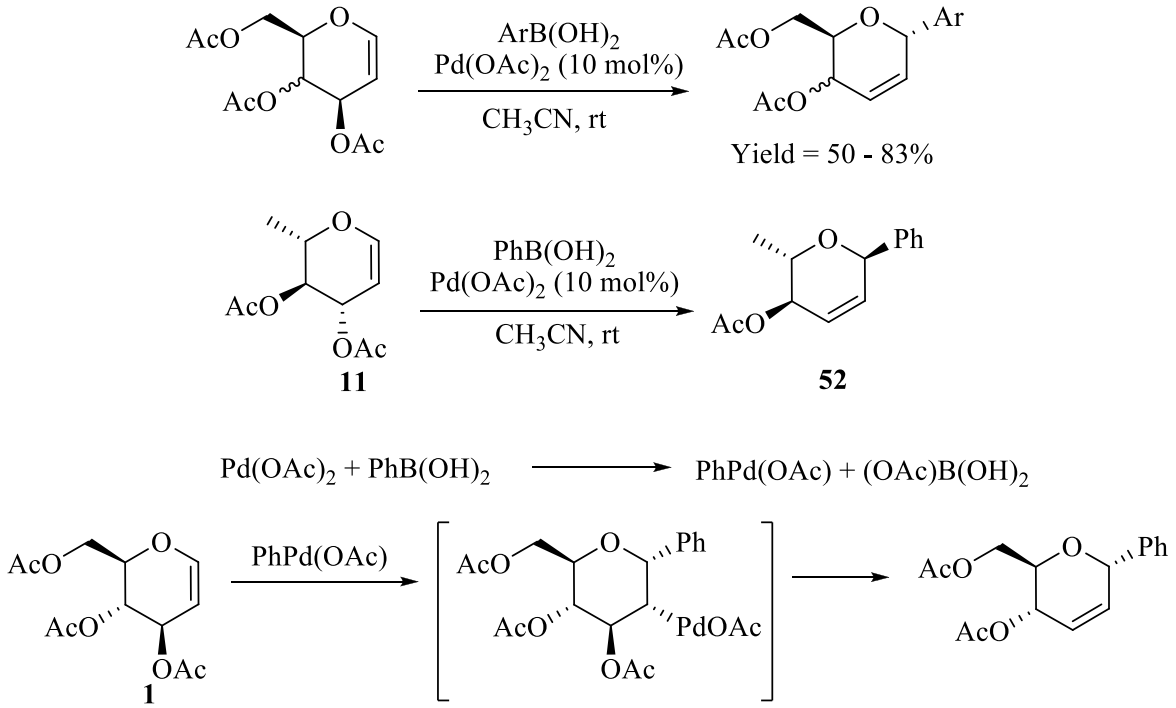
Scheme 21

Cossy and Rakotoarisoa[27] reported efficient nucleophilic attack by alkyl copper reagents on C-2-formylated tri-*O*-benzyl-D-glucal **49** in the presence of $BF_3.OEt_2$. The reactions were observed to be stereospecific, yielding only the *α* anomer of the Ferrier products **50** (Scheme 22). On the contrary, the glycals underwent a 1,4-Michael addition in the presence of lithium dialkyl cuprates with no elimination of the C-3 substituent to form adducts **51** without the activation with a Lewis acid.



Scheme 22

Several σ-aryl-Pd compexes synthesized via transmetalation reaction between boronic acid and palladium (II) salt were observed to be efficient in carrying out Ferrier rearrangements on acetylated glycals. The reagent system, developed by Maddaford *et al.*,[28] produced the desired product with α-selectivity on the D-glycal substrates (Scheme 23).

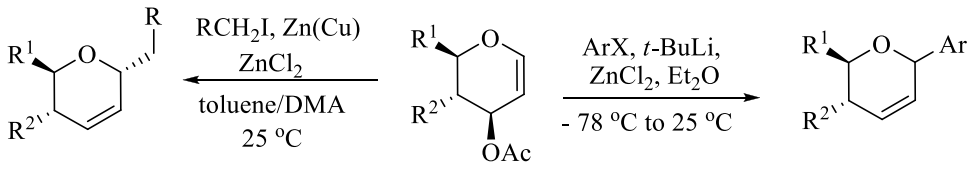


Scheme 23

The proposed mechanism involves *syn* addition of the *in situ* generated PhPdOAc from the α-face of the glycal followed by *anti* elimination which results in the formation of $Pd(OAc)_2$. When L-rhamnal diacetate **11** was subjected to the reagent system, the β-anomer **52** was obtained as the only product, thus supporting the proposed mechanism where the metal complex approaches from the less hindered face of the glycal. The reaction was successful with 10 mol% of $Pd(OAc)_2$ and electron withdrawing groups on the boronic acid reduced the yield of the reactions considerably.

Du Bois and co workers[29] have demonstrated the use of alkyl and aryl zinc reagents as efficient nucleophiles on 1,2-dihydropyranylacetate derivatives. Several phenyl and heteroarylzinc reagents were synthesized smoothly from the *in situ* generated lithiated aryl intermediates via transmetallation with $ZnCl_2$ at -78 ^oC as shown in Table 10. The Ferrier rearrangement proceeded with good stereoselectivity with preference for the α-anomers at 25 ^oC. Both electron donating and withdrawing groups on the phenyl ring furnished the desired products in comparable rates and yield. Correspondingly, the authors have generated alkylated zinc reagents using Zn(Cu) couple, $ZnCl_2$, with DMA as an additive with alkyl iodides. The 1,2-dihydropyranyl acetates reportedly underwent Ferrier rearrangement with these zinc intermediates to furnish *trans*-2,6-dialkyl-substituted pyrans.

Table 10. Alkyl and aryl iodides in the presence of $ZnCl_2$



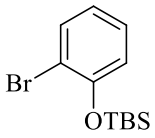
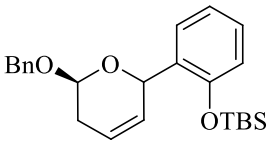
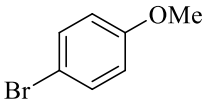
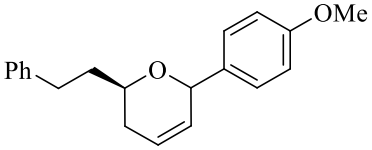
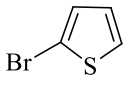
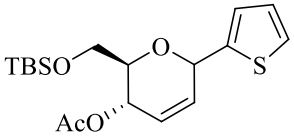
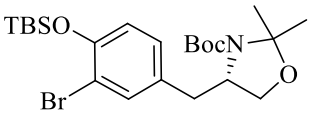
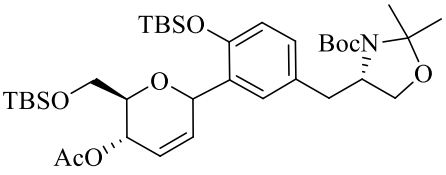
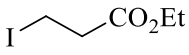
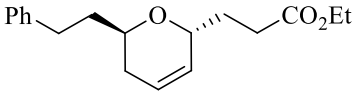
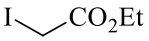
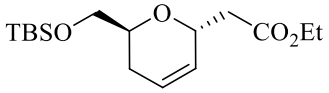
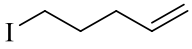
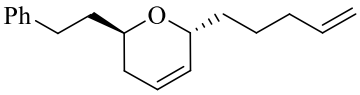
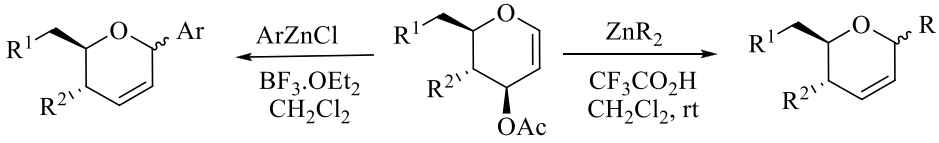
R^1	R^2	Ar/R	Product	Yield (%)
CH_2OBn	H			82
CH_2CH_2Ph	H			88
CH_2OTBS	OAc			69
CH_2OTBS	OAc			75
CH_2CH_2Ph	H			72

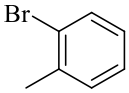
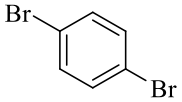
Table 10. Continued

R1	R2	Ar/R	Product	Yield (%)
CH_2OTBS	H			60
CH_2CH_2Ph	H			63

Xue *et al.*[30] have reported the formation of alkyl *C*-pyranosides from dialkylated zincs, and aryl *C*-pyranosides from arylzinc halides, using trifluoroacetic acid and $BF_3.OEt_2$, respectively (Table 11) in good yields with predominant α–selectivity.

Table 11. Organozinc nucleophiles in the presence of $BF_3.OEt_2$

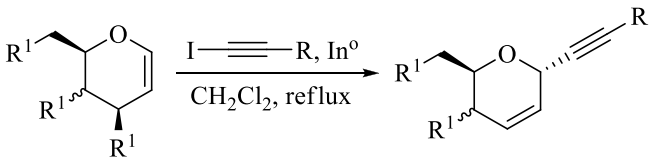


R^1	R^2	R/ArBr	Yield (%)	$\alpha:\beta$
OAc	OAc	Me	97	2.3:1
OTBS	OAc	Ph	88	19:1
CH_2Ph	H	Et	89	10:1
OAc	OAc		97	7:1
OAc	OAc		94	7:1

Lubin-Germain *et al.*[31] reported the synthesis of alkynated pseudoglycosides catalysed by indium metal from the corresponding alkyne iodide in more than 9:1 stereoselectivity favoring the α-anomer as shown in Table 12. The presence of the iodide functionality on the alkynes was found to be essential for the Ferrier reaction to occur. Indium metal was observed to be superior to other metals like zinc, manganese or their salts for product formation with better yields and selectivity. The trimethylsilylethynyl-*C*-glycoside was treated with silver nitrate and *N*-iodosuccinimide to obtain the corresponding iodide which in turn was reacted with substituted

glycals to give *C*-disaccharides. Glycals containing pivaloyl and benzyl protecting groups were also reported to undergo rearrangement under these conditions.

Table 12. Indium metal mediated carbon-Ferrier rearrangement



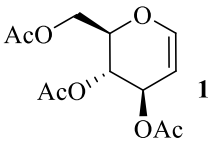
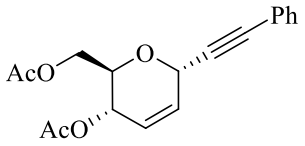
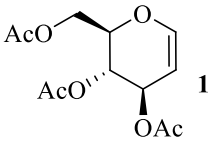
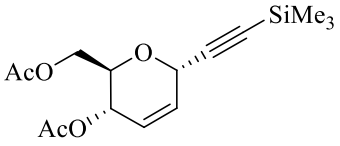
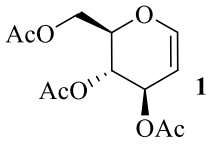
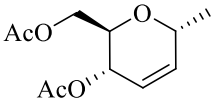
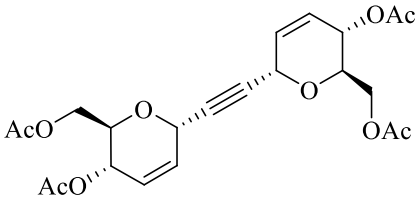
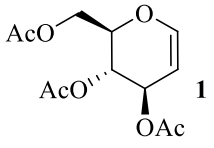
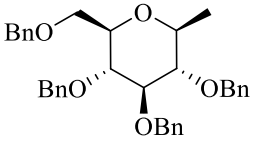
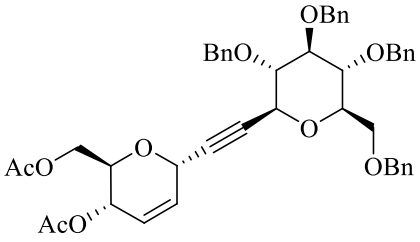
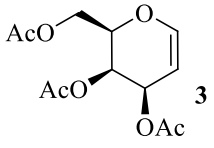
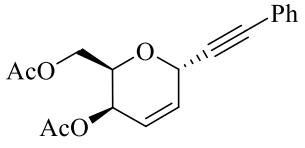
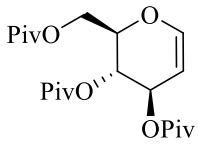
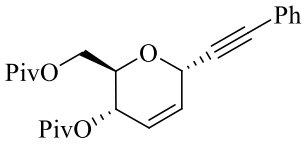
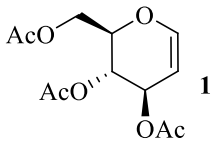
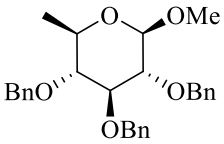
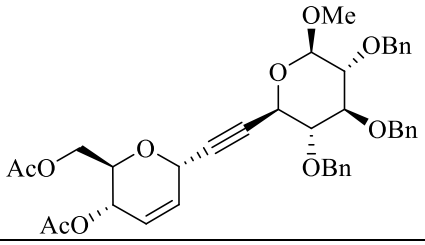
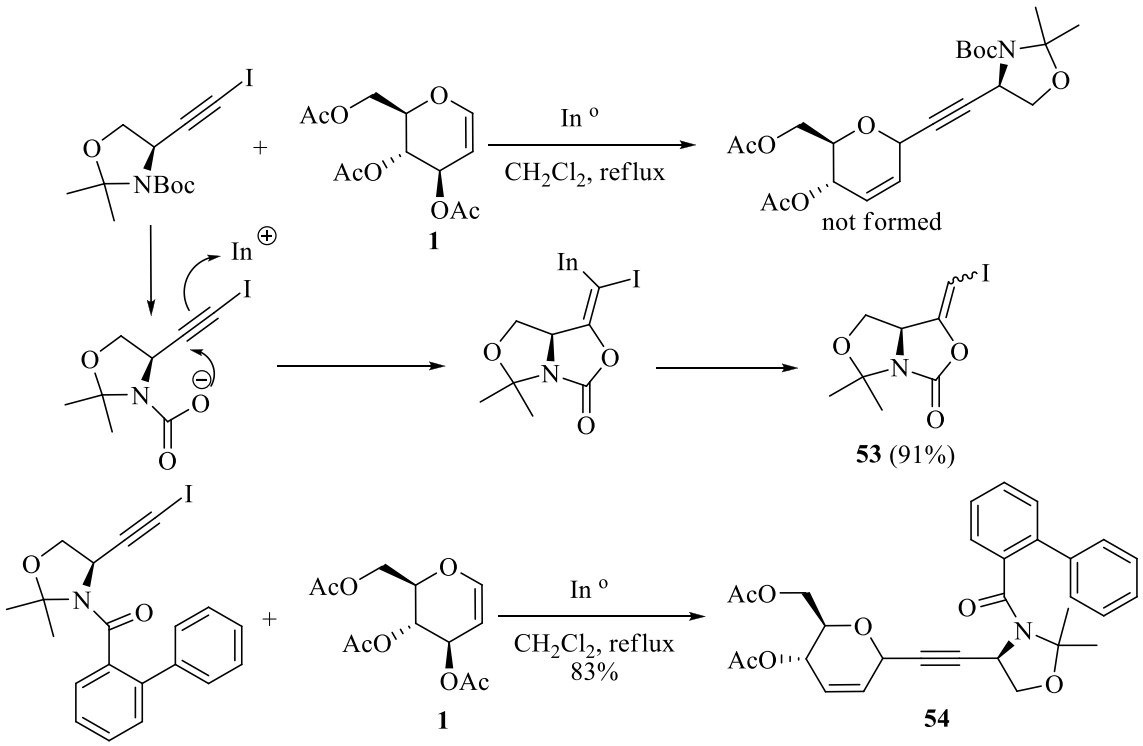
Glycal	R	Major Product	Time (h)	Yield (%)	*α:β*
	Ph		4	79	90:10
	$SiMe_3$		24	82	85:15
			24	75	84:16
			3	94	95:5
	Ph		16	95	83:17
	Ph		24	93	85:15

Table 12. Continued

Glycal	R	Major Product	Time (h)	Yield (%)	*α:β*
 **1**			3	86	*90:10*

The above mentioned protocol has been employed by the same authors with Garner's aldehyde-derived alkynyl iodide but failed to provide the desired pseudoglycal (Scheme 24).[32] A bicyclic alkene **53** was obtained, the formation of which has been suggested to be via indium mediated carbamate reduction followed by cyclization. On changing the amine protection from Boc to *o*-diphenylamide, Ferrier-rearranged products **54** were obtained in good yields.

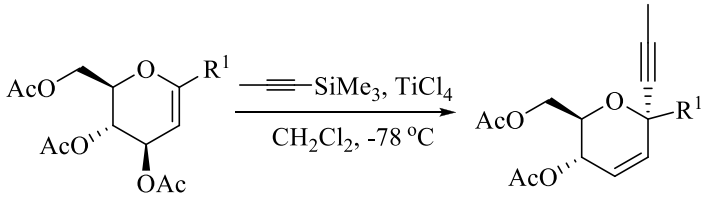


Scheme 24

5. Propargyl or Alkynyl Silanes

In a manner analogous to the allylsilane addition to the anomeric centre of D-hexopyranose rings, silylacetylenes were found to be reactive enough to generate the corresponding 'sugar

acetylenes'. As mentioned earlier, Nicolaou *et al*. have explored the reaction of various nucleophiles on 1-substituted glycals **5** and **56** using 1 equiv. of $TiCl_4$.[3] On reacting methyl trimethylsilyl acetylene with these substrates, they obtained products in good yields in a highly stereospecific manner (Scheme 25). Utilising this protocol, many 1,1-disubstituted glycosides **55** and **57** respectively have been obtained.

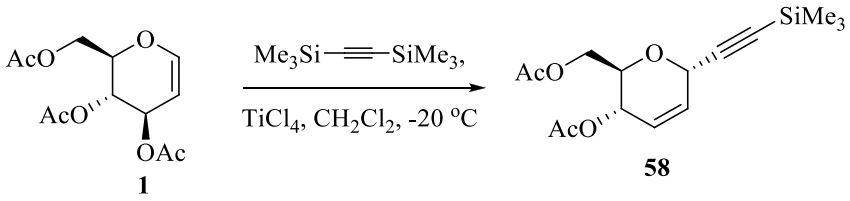


5: R^1 = Me
56: R^1 = allyl

55: R^1= Me
57: R^1= allyl

Scheme 25

During the course of their study towards the synthesis of okadaic acid, Isobe *et al.*[4] explored the *C*-glycosidation on glycals with silyl acetylenes instead of the usual allylsilanes using $TiCl_4$ (Scheme 26). Interestingly, the stereoselectivity of this reaction was observed to be excellent, yielding only the α-anomer **58**, as compared to the 16:1 ratio of isomers in the case of allylsilanes.[2] Other nucleophiles such as trimethylphenylsilane, trimethylvinylsilane, ethynyltrimethylsilane and dihydropyran failed to react owing to the rapid polymerisation of glucal **1**. In their next report, Isobe *et al.*[33a] carried out the glycosylation studies on tri-*O*-acetyl-D-glucal **1** with bistrimethylacetylenes, under the influence of $SnCl_4$, to obtain the product **58** in quantitative yield. The same reaction was performed with tributylstannyl- and trimethylsilyl-acetylene using $TiCl_4$ in high yields. The noteworthy fact is the observation of complete stereoselectivity in all examples.

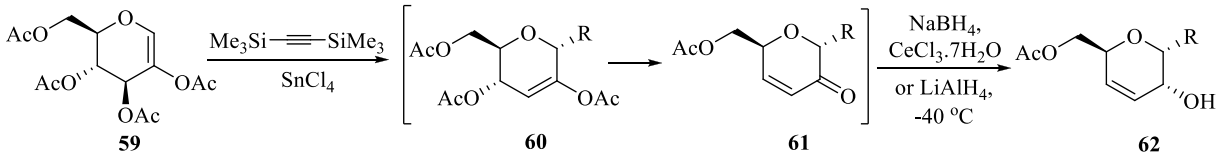


1 **58**

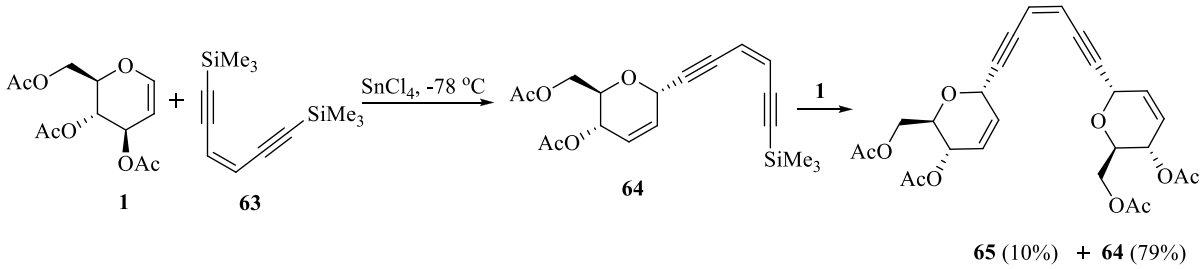
Scheme 26

Similar *C*-glycosidation on 2-acetoxy-D-glucal **59** with $SnCl_4$ proceeded to give products **60** which were unstable (Scheme 27) and were converted into α,β-unsaturated ketones **61** on aqueous workup, and reduced using $NaBH_4$ or $LiAlH_4$ to give allylic alcohols **62** for analysis.

Isobe *et al*. were able to isolate some of the doubly glycosidated product **65** (Scheme 28), from the reaction of the ene diyne nucleophile **63** with glucal **1**, albeit in only 10% yield with 20% conversion of the starting monoglycosylated compound **64**. Moreover, the reaction was unsuccessful in other cases.

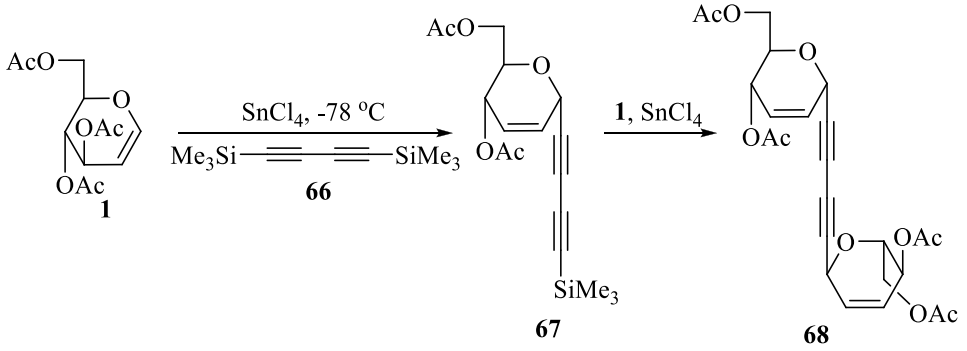


Scheme 27



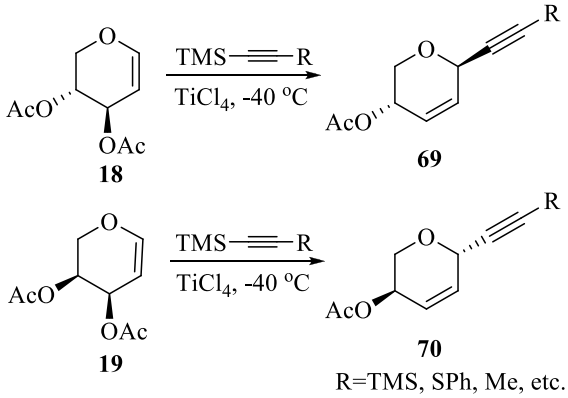
Scheme 28

Later, the same group attempted double glycosidation using bistrimethylsilylacetylene on glucal triacetate **1** in the presence of $SnCl_4$, but failed.[34] However, glucal **1** on reaction with 1,4-bis(trimethylsilyl)-1,3-butadiyne **66** with 1% $SnCl_4$ at 0 °C in 3 hours led to the second glycosidation product **68** in 55% yield along with 19% of the monoglycosylated product **67** (Scheme 29). Bis-glycosylated product **68**, on the other hand, was obtained in one pot without isolating the intermediate in 54% yield by further treatment with **1** in presence of $SnCl_4$. The same reaction was observed with the glucal derivative **59** but the yields were not very encouraging. Furthermore, similar reaction employing 1,6-bis(trimethylsilyl)-hex-3-en-1,5-diyne **63** and glucal acetate **1** gave the monoglycosylated product **64** in just 1.25 h in 79% yield , and the bis-glycosylated product **65** in 68%, without isolating the intermediate. The second glycosidation took place faster in this case. In all the reactions, the acetylenic group entered in α orientation with exclusive regio- and stereoselectivity.



Scheme 29

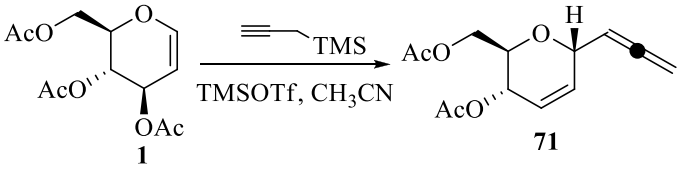
Isobe *et al.*[9] went on to expand the scope of acetylenic glycosylations on pentopyranose derivatives such as di-*O*-acetyl-D-xylal **18** and di-*O*-acetyl-D-arabinal **19** (Scheme 30). The reaction was carried out with bistrimethylsilylacetylene using $TiCl_4$ at -40 °C. In striking contrast to the observations for glucal **1**, the product in these cases bore predominantly 1,4-*anti* stereochemistry. The products **69** and **70** exhibited the same optical rotation with opposite sign proving that they were enantiomers of each other. Several other nucleophiles such as Me_3Si-C≡C-R, where R = Me, SPh, etc. were also used.



Scheme 30

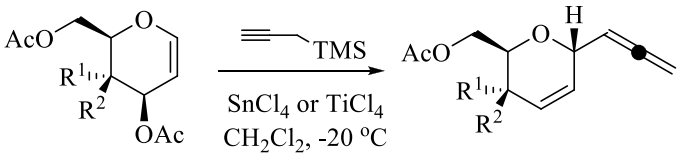
The stereochemical outcome was rationalised as a consequence of the stereoelectronic effect, as discussed earlier, *vide supra* (see Figure 2), while dealing with similar reactions using allyl trimethylsilane.

In the same year, Vogel[35a] and Isobe[35b] reported for the first time the reaction of glucal **1** with propargyltrimethylsilane and obtained α-C-allenyl product **71**. Vogel *et al*. performed the reaction in CH_3CN using TMSOTf as a catalyst, as part of a disaccharide synthesis (Scheme 31).



Scheme 31

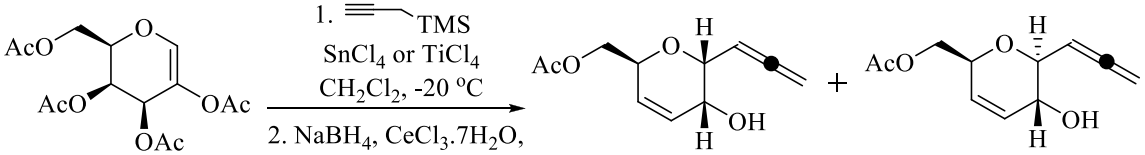
Isobe's group carried out the same reaction with 1.5 equiv. of propargyltrimethylsilane in dichloromethane at -20 °C (Scheme 32). By using $SnCl_4$ as a catalyst, they reported 83.3% yield, whereas by using $TiCl_4$, the yield increased slightly to 88.5%. Reaction of propargyl silane with tri-*O*-acetyl-D-galactal **3** under the influence of $SnCl_4$ or $TiCl_4$, gave the α-C-allenyl product **72** in 81.6 or 75.7% yield respectively. Surprisingly the same reaction with 2,3,4,5-tetra-*O*-acetyl-D-galactal **59**, followed by reduction gave a mixture of α- and β-allenyl products **73** and **74** in 7.3:1 ratio with $SnCl_4$ and 5.2:1 in the case of $TiCl_4$ (Scheme 33).



1: R^1=OAc, R^2=H
3: R^1=H, R^2=OAc

71: R^1=OAc, R^2=H
72: R^1=H, R^2=OAc

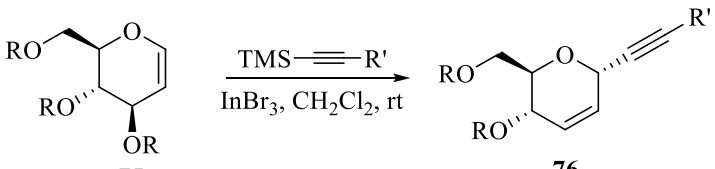
Scheme 32



59 **73** **74**

Scheme 33

Yadav *et al.*[36] reported *C*-alkynylation of glycals **75** with the much milder Lewis acid $InBr_3$ (Scheme 34). Employing only 5 mol% of the catalyst, they obtained very good yields of **76** in shorter reaction time, with high anomeric selectivity, and recoverability of the catalyst. Other Lewis acids were also tried, such as $InCl_3$, $In(OTf)_3$, $Sc(OTf)_3$, $Tb(OTf)_3$, YCl_3 and $YbCl_3$, but $InBr_3$ gave the best results in terms of conversion and selectivity. As earlier, 1,4-*anti* selectivity was observed in the case of pentose sugars.

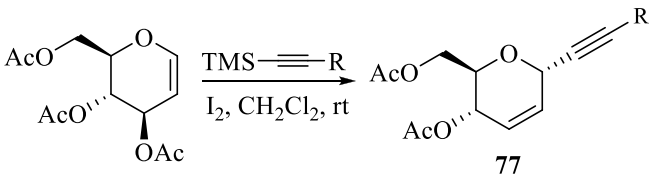


75
R= Ac, Piv, Me, Bn, Allyl
R'= Ph, TMS, propyl, pentyl, etc.

76

Scheme 34

Iodine was found to catalyse the *C*-glycosidation of tri-*O*-acetyl-D-glucal **1** with various silylacetylenes at room temperature, in high yield (Scheme 35).[37] Optimum conditions for this reaction were investigated and it was found that 1 equiv. of I_2 in dry CH_2Cl_2, with 2 equiv. of



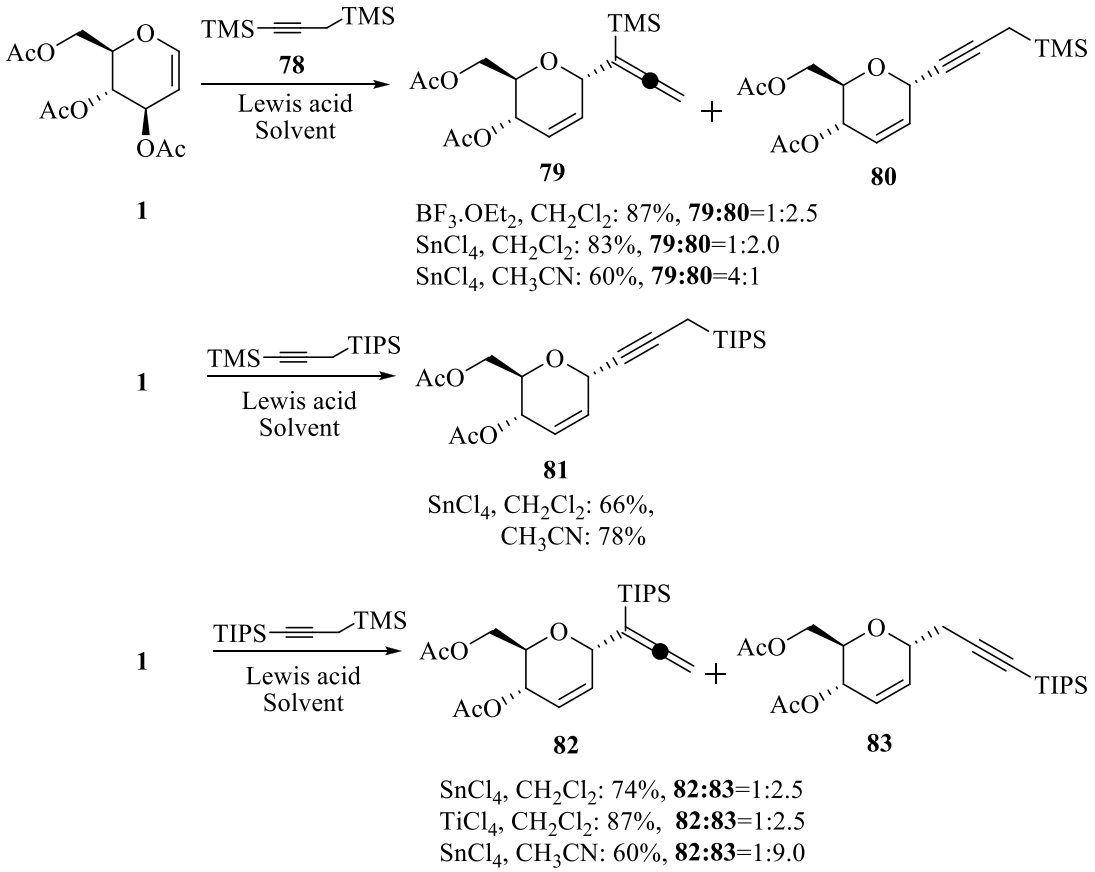
1

77
R=Ph, TMS, Me, CH_2TMS, CH_2TIPS, CH_2TBDPS, etc.

Scheme 35

acetylene nucleophile was effective for this reaction. In agreement with previous observations, the stereochemistry at the C-1 position in the product **77** was exclusively α-orientation.

Isobe *et al.*[38] then carried out a comparative study of the reactivity of alkynyl and propargyl silanes. The nucleophile **78** containing both propargyl and alkynyl moieties was of interest since it is suitable for the evaluation of reactivities of both groups under the same conditions. In the reaction between 1,3-bis(trimethylsilyl)propyne **78** and glucal **1**, a mixture of allene **79** and alkyne **80** was obtained in 1:2.5 ratio (Scheme 36) using $SnCl_4$ as a Lewis acid. The ratio was found inverted to 4:1, on changing the solvent from dichloromethane to acetonitrile. The reason for the reversal of ratio was proposed to be due to the stabilisation of the cationic intermediate by acetonitrile (Figure 3). Different substrates with different silyl groups were investigated. In the silyl nucleophile with 2 triisopropylsilyl groups, no reaction took place. With triisopropylsilyl group in the propargylic position, the alkyne product **81** was obtained exclusively. When the triisopropylsilyl group was in the acetylenic position, the major product was found to be the propargylic compound **83**, along with a small amount of allenic product **82**. On changing the medium of reaction from dichloromethane to acetonitrile, the formation of **83** was favoured.



Scheme 36

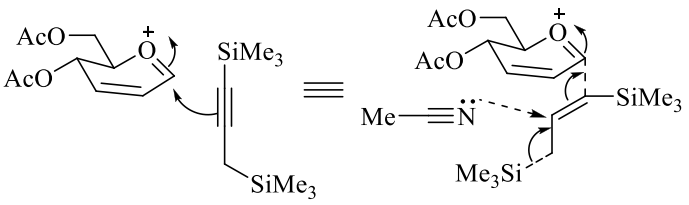
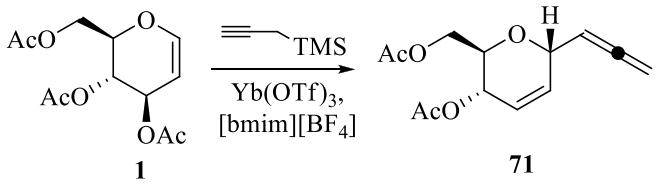


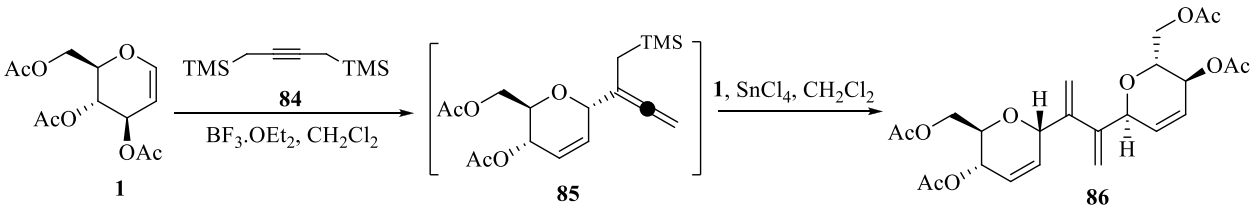
Figure 3

In a study of the carbon-Ferrier rearrangement in an ionic liquid [bmim][BF_4] using Yb(OTf)$_3$ as a catalyst (only 5 mol%),[12c] tri-*O*-acetyl-D-glucal **1** underwent reaction with propargylsilane in 8 hours to give 65% of the α-anomer **71** as the only product (Scheme 37).

A new nucleophile, 1,4-bis(trimethylsilyl)-2-butyne **84** was introduced by Isobe *et al.*[39] that reacted with glucal **1** in the presence of $BF_3.Et_2O$, to give silylallene glycoside **85** with *α*-orientation (Scheme 38). On reacting 2 equiv. of the glucal with 1 equiv. of nucleophile using $BF_3.Et_2O$ provided a new symmetrical diene glycoside **86** along with monoglycosidation product **85**. Changing the Lewis acid to TMSOTf or $SnCl_4$ did not improve yields of the reaction. However, when 3 equiv. of **1** were used under the influence of $SnCl_4$, the diene glycoside **86** was obtained in 92% yield in just 15 minutes. In a similar manner, other symmetrical and unsymmetrical diene glycosides were prepared using this method.

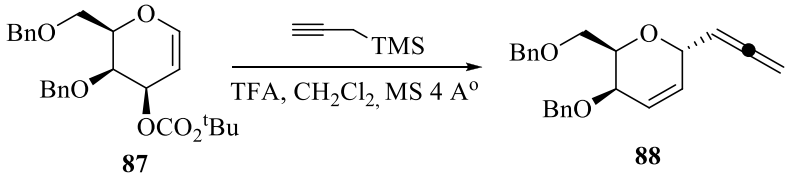


Scheme 37



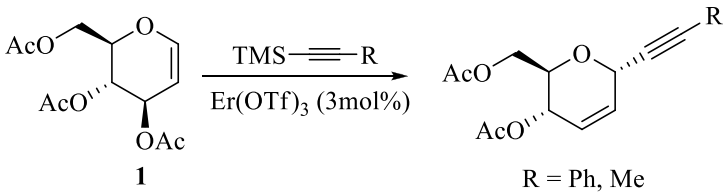
Scheme 38

In a detailed investigation of acid-catalysed glycosidation of *endo*- and *exo*-glycals using TFA,[15a] different nucleophiles were allowed to attack glycal, among which propargylsilane reacted with the galactal **87** to give sugar allene **88** in 79% yield (Scheme 39).



Scheme 39

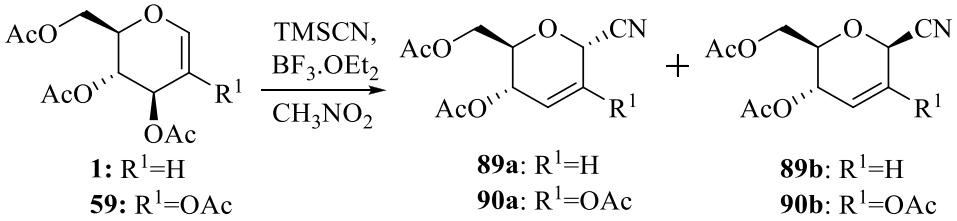
Procopio and co-workers[16] explored the catalytic action of $Er(OTf)_3$ on the *C*-glycosidation of glycals with various nucleophiles. In a typical reaction, 3 mol% of $Er(OTf)_3$ was sufficient to catalyse the *C*-Ferrier rearrangement using the propargyltrimethylsilanes or 1-phenyl-2-(allyltrimethylsilyl)acetylene (Scheme 40). Mostly the reaction yielded exclusively α-oriented products, but in the case of 3,4-di-*O*-acetyl-6-deoxy-L-glucal, β-oriented products were major.



Scheme 40

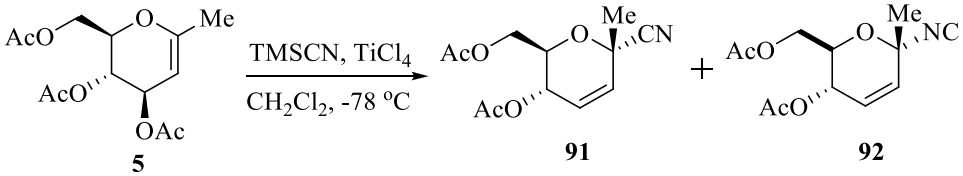
6. Silyl Cyanides

Glycosyl cyanides are important intermediates in the synthesis of C-glycosyl derivatives, since the cyano group can be easily converted into other functional groups. The first Lewis-catalysed addition of trimethylsilyl cyanide (TMSCN) on glycals was reported by De Las Heras *et al.* in 1983.[40] The reaction on **1** was carried out in nitromethane as a solvent in the presence of a catalytic amount of $BF_3.OEt_2$, yielding **89a** and **89b** in 57 and 42% yields respectively (Scheme 41). The same reaction on glucal derivative **59** afforded a mixture of α- and β- anomers **90a** and **90b** in 46 and 34% yields respectively. The reaction was better than that using Lewis acid and sodium cyanide, in terms of yields and reaction conditions.



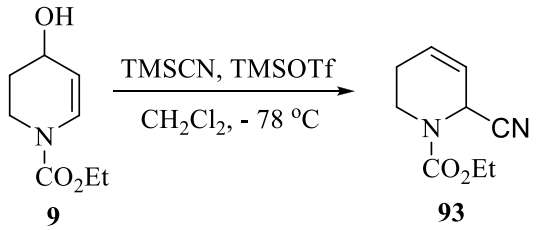
Scheme 41

Nicolaou *et al*., in their earlier report,[3] also carried out the reaction of 1-alkylated glycals **5** with TMSCN using $TiCl_4$, and observed the formation of 82% of exclusively α-anomer **91**, along with 11% of the isocyanide **92** (Scheme 42).



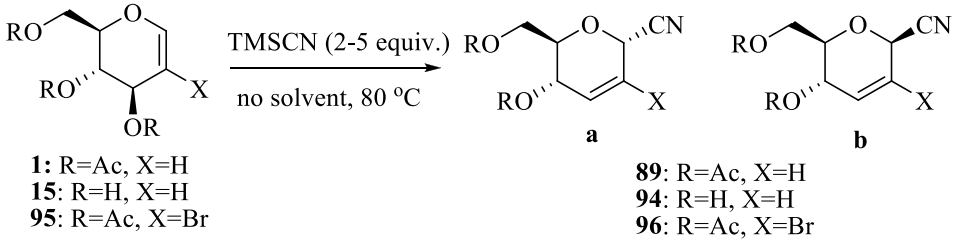
Scheme 42

During the synthesis of streptazolin, Kozikowski and Park[5] investigated a Ferrier-type reaction on piperidinol **9** with various nucleophiles. The reaction of **9** with 6 equiv. of TMSCN, in the presence of TMSOTf (1.5 equiv.) at -78 ºC afforded the product **93** in 3 hours in 70% yield (Scheme 43). As expected, nucleophilic attack on the pyridinium ion occurred at the site α- to the ring nitrogen atom.



Scheme 43

The first example of a *C*-Ferrier rearrangement on acetylated and unprotected glycals without a catalyst, under thermal conditions, was reported by Hayashi's group.[41] The reaction of TMSCN on glucal **1** at 80 ºC, remarkably gave 95% yield of a 58:42 mixture of α– and β–glycosyl cyanides **89a** and **89b** (Scheme 44). Similarly, unprotected glucal **15** in the absence of solvent and catalyst was found to react with TMSCN to give products **94a** and **94b** in 74:26 ratio, in 84% yield. 2-bromo-D-glucal **95** reacted under the same conditions to yield 72% of a 4:1 ratio of **96a** and **96b**.

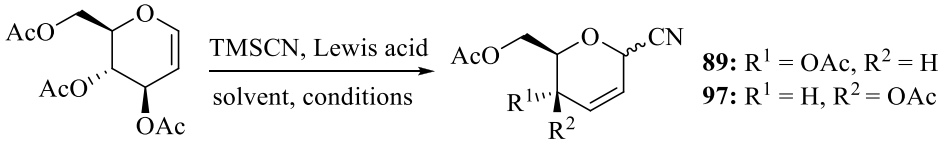


Scheme 44

Yadav *et al.*[11a] reported the treatment of glycals with various silyl nucleophiles in the presence of only 3 mol% of $Sc(OTf)_3$, to afford the corresponding 2,3-unsaturated C-glycosides in excellent yields with α-selectivity. Thus, for example, TMSCN reacted with **1** leading to **89** in 90% yield and the anomers were formed in 6:4 ratio (cf. Table 13, entry 1). Several glycals were successfully employed for this reaction. $Sc(OTf)_3$ proved to be an efficient and reusable catalyst for this reaction, along with milder reaction conditions, lower catalyst usage and simple experimental procedure. Again the same group investigated the catalytic action of iodine on the addition of cyanide to glycals.[11b] Only 8 mol% of iodine was found to be sufficient to catalyse the reaction of glucal **3** with TMSCN in 12 hours, yielding a 6:4 mixture of α- and β-cyanides in 80% yield, while galactal **18** gave 7:3 ratio of α- and β-cyanides in 72% yield (Table 13, entries 2 and 3). The same group[11c] later explored the $InBr_3$-catalysed Ferrier rearrangement of glucal **3**

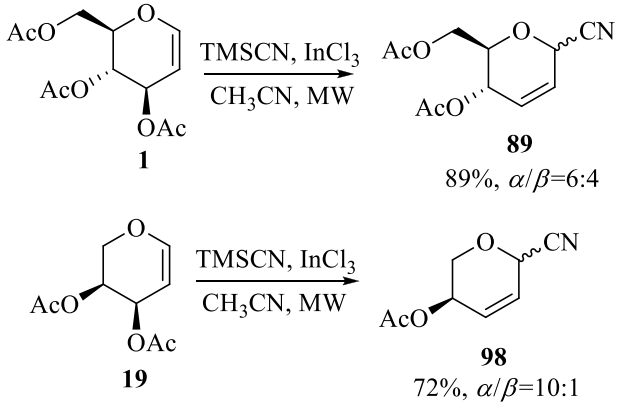
with TMSCN at ambient temperature and obtained high yields and good selectivity (Table 13, entries 4 and 5) of the cyano product. In a similar manner, $Bi(OTf)_3$ was employed in the *C*-Ferrier rearrangement of glycals.[11d] $Bi(OTf)_3$, being inexpensive and easy to prepare on gram-scale in laboratory conditions, provided a convenient alternative to other lanthanide-based Lewis acids used for this reaction. Only 2 mol% of the catalyst with 1.25 equiv. of TMSCN afforded a 7:3 mixture of cyanides in excellent yields (Table 13, Entry 6).

Table13. Lewis acid mediated *C*-glycosyl cyanide formation



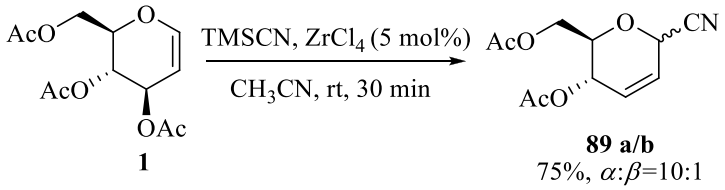
Entry	Glycal	Lewis Acid	Solvent	Yield	α:β	Product	Ref.
1	**1**	$Sc(OTf)_3$, 3 mol%	CH_2Cl_2, rt	90	6:4	89	11a
2	**1**	I_2, 8 mol%	CH_2Cl_2, rt	80	6:4	89	11b
3	**3**	I_2, 8 mol%	CH_2Cl_2, rt	72	7:3	97	11c
4	**1**	$InBr_3$, 5 mol%	CH_2Cl_2, rt	90	6:4	89	11d
5	**3**	$InBr_3$, 5 mol%	CH_2Cl_2, rt	87	7:3	97	11e
6	**1**	$Bi(OTf)_3$, 2 mol%	CH_3CN, rt	92	7:3	89	11f

An eco-friendly and rapid microwave-assisted method, using 6 equiv. of TMSCN and 20 mol% of $InCl_3$ (Scheme 45), was developed by Das *et al*.[10b] The reactants were taken in CH_3CN in an open vessel and irradiated for a few seconds. High yields of glycosyl cyanides **89** and **98** were obtained from acetyl glycals **1** and **19** respectively. The yields and selectivities were comparable to usual reflux methods.



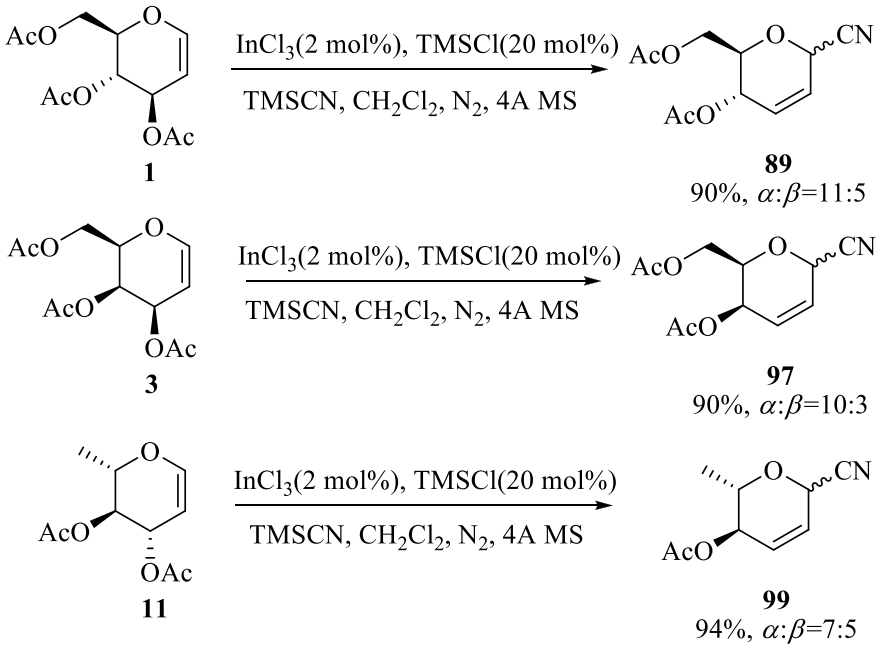
Scheme 45

The inexpensive $ZrCl_4$ was successfully employed in the *C*-Ferrier rearrangement of tri-*O*-acetyl-D-glucal using several nucleophiles.[13] Herein, only 1.1 equiv. of TMSCN was required to react with glucal **1**, in the presence of just 5 mol% of $ZrCl_4$, in acetonitrile, in 30 mins. (Scheme 46), affording 75% of 10:1 mixture of α- and β-glycosyl cyanides **89**.



Scheme 46

In a bid to enhance the catalytic activity and also lower the catalytic loading of $InCl_3$ in C-Ferrier reactions, TMSCl was evaluated for its synergistic effect,[10c] (*vide supra*). Thus, glucal **1** reacted with 1.5 equiv. of TMSCN in 1 hour in dichloromethane over molecular sieves, to give 90% of 11:5 mixture of α- and β-glycosyl cyanides **89** (Scheme 47). Galactal **3** and rhamnal **11** also underwent reaction in good yields of **97** and **99** respectively. The catalytic system was also observed to be effective in solvent-free conditions.



Scheme 47

The proposed reaction mechanism for the regeneration of $InCl_3$ by TMSCl is illustrated in Figure 4.

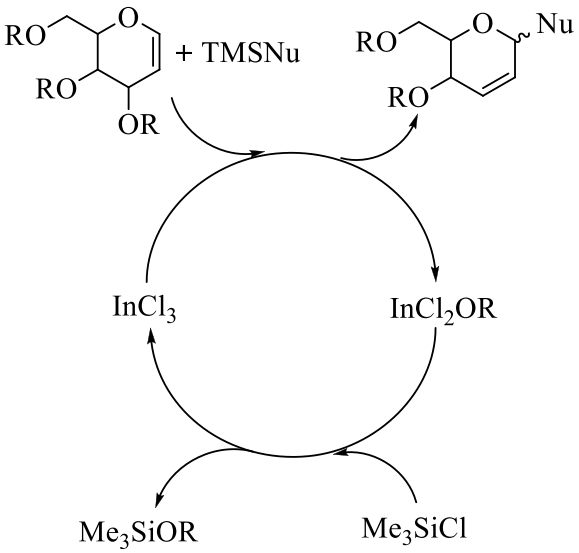


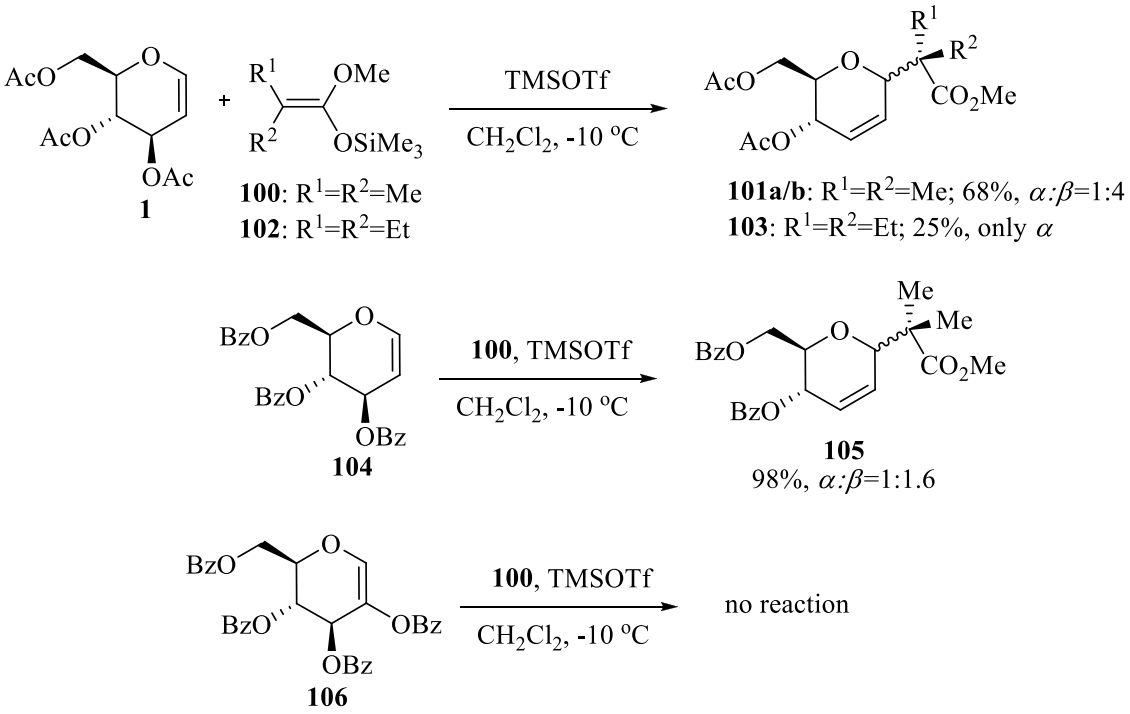
Figure 4. Catalytic cycle and regeneration of $InCl_3$ from TMSCl.

Glucal **1** and galactal **3** also underwent Ferrier rearrangement with TMSCN in the presence of $HClO_4$-SiO_2 catalyst to form the corresponding cyano products **89** and **97** respectively, although the α/β ratio (2:1) was only marginally favoring the α-anomer.[14] Likewise, $Er(OTf)_3$ also catalysed the reaction of glycals with TMSCN affording 95% of glycosyl cyanides (6:4) in the case of glucal **1** and 76% of cyanides (7:3) in the case of galactal **3** favoring α-anomers.[16]

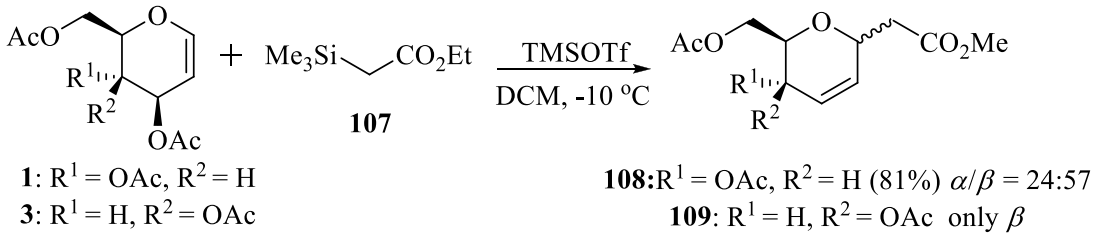
7. Other Nucleophiles

7.1 Silyl ketene acetals

Csuk *et al*.[42] reported reaction of glycals with trimethylsilyl ketene acetals under the influence of TMSOTf. Glucal **1** reacted with ketene acetal **100** and afforded a 1:4 mixture of **101a** and **101b** in a combined yield of 68% (Scheme 48). Interestingly the same reaction with ketene acetal **102** gave exclusively product **103** but surprisingly in a low yield of only 25%. Moreover, benzoylated glucal **104** gave better yields of **105** on reacting with **100**, but 2,3,4,6-tetra-*O*-benzoyl-1,5-anhydro-D-*arabino*-hex-1-enitol **106** gave no reaction at all. Since silyl ketene acetals can be regarded as synthetic equivalents of α-trimethylsilyl substituted esters, the expected reaction of glucal **1** with **107** gave a mixture of β-(57%) and α-(24%) products **108**, while the galactal **3** gave exclusively the product of β-configuration **109** (Scheme 49).

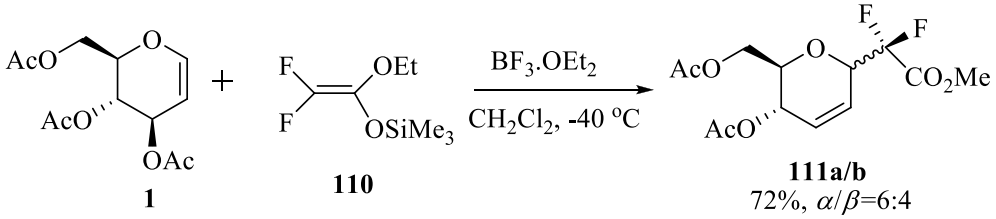


Scheme 48



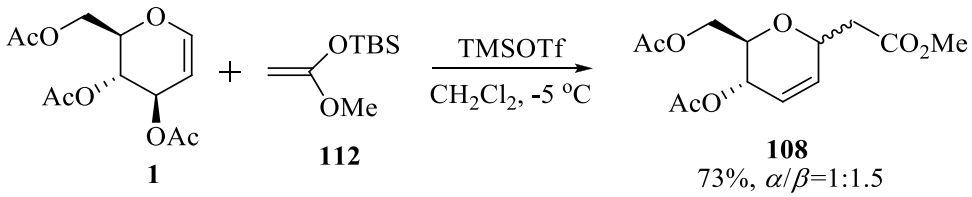
Scheme 49

Recently, a silylated difluoro-ketene acetal **110** was reported to react with glucal **1**,[43a] yielding 72% of a 6:4 mixture of α- and β-substituted products **111a** and **111b** (Scheme 50), and the product was applied to the synthesis of α-CF_2-mannosides and fluorinated analogs of pseudoglycopeptides,[43] and more recently, 2-deoxy-2-aminoglycosides and CF_2-amino-pyranosides.[43b]



Scheme 50

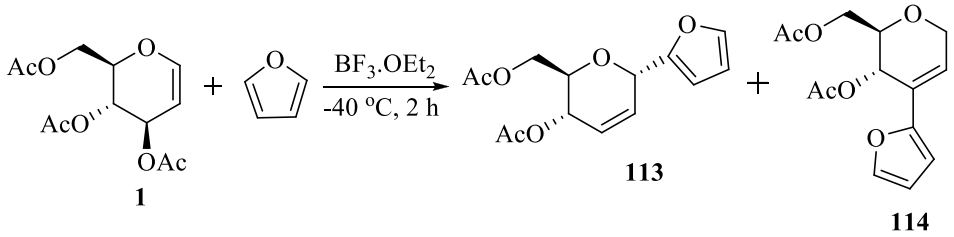
Marcaurelle *et al.*[44] investigated the reaction of glucal **1** with ketene acetal **112** under various conditions, and found the reaction to be best carried out in the presence of TMSOTf in dichloromethane, yielding 73% of a 1:1.5 mixture of **108**, favouring the β-anomer (Scheme 51). However on changing the solvent to CH_3CN, the ratio of isomers reversed (α:β = 1.5:1) but the yield of **108** lowered to 65%. See also ref. 23.



Scheme 51

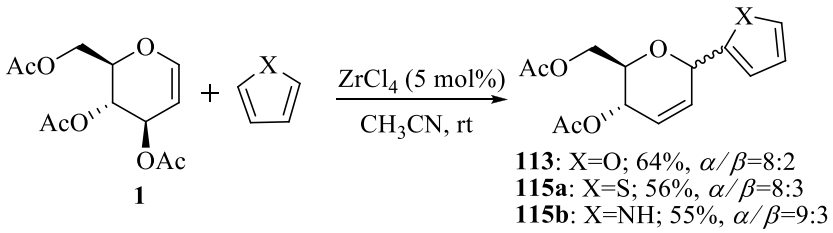
7.2 Aromatic nucleophiles

Synthetic routes towards *C*-aryl glycosides have gained considerable importance over the past few years since they are part of many biologically active molecules. Hence, the task of coupling the aryl moiety into glycosides is now a challenge in organic synthesis. As early as 1987, Isobe and co-workers carried out glycosidation with furan using glucal **1** in the presence of $BF_3.Et_2O$,[4] and obtained a 1:1 mixture of 1- and 3-substituted products **113** and **114** respectively (Scheme 52).



Scheme 52

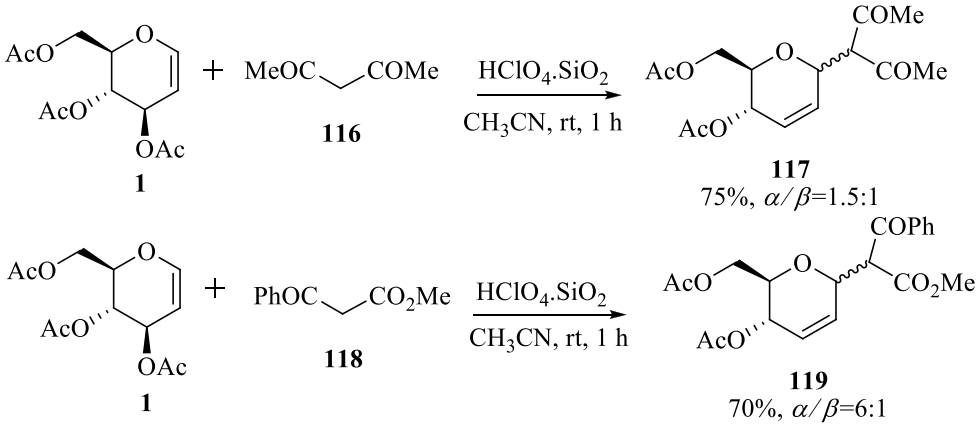
In the $ZrCl_4$-catalysed Ferrier rearrangement, which was mentioned earlier,[13] the reaction was also carried out with aromatic nucleophiles such as furan, pyrrole and thiophene, in good yields (Scheme 53) of the corresponding products **113**, **115a** and **115b** respectively.



Scheme 53

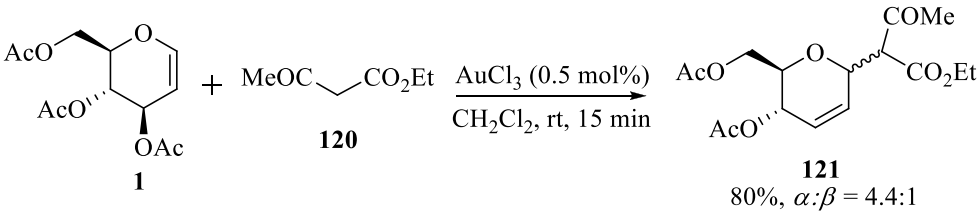
7.3 Electron-rich nucleophiles

The 1,3-dione **116** and β-ketoester **118** have been employed in the preparation of corresponding *C*-glycosides **117** and **118** from **1** using $HClO_4.SiO_2$ (Scheme 54).[14]



Scheme 54

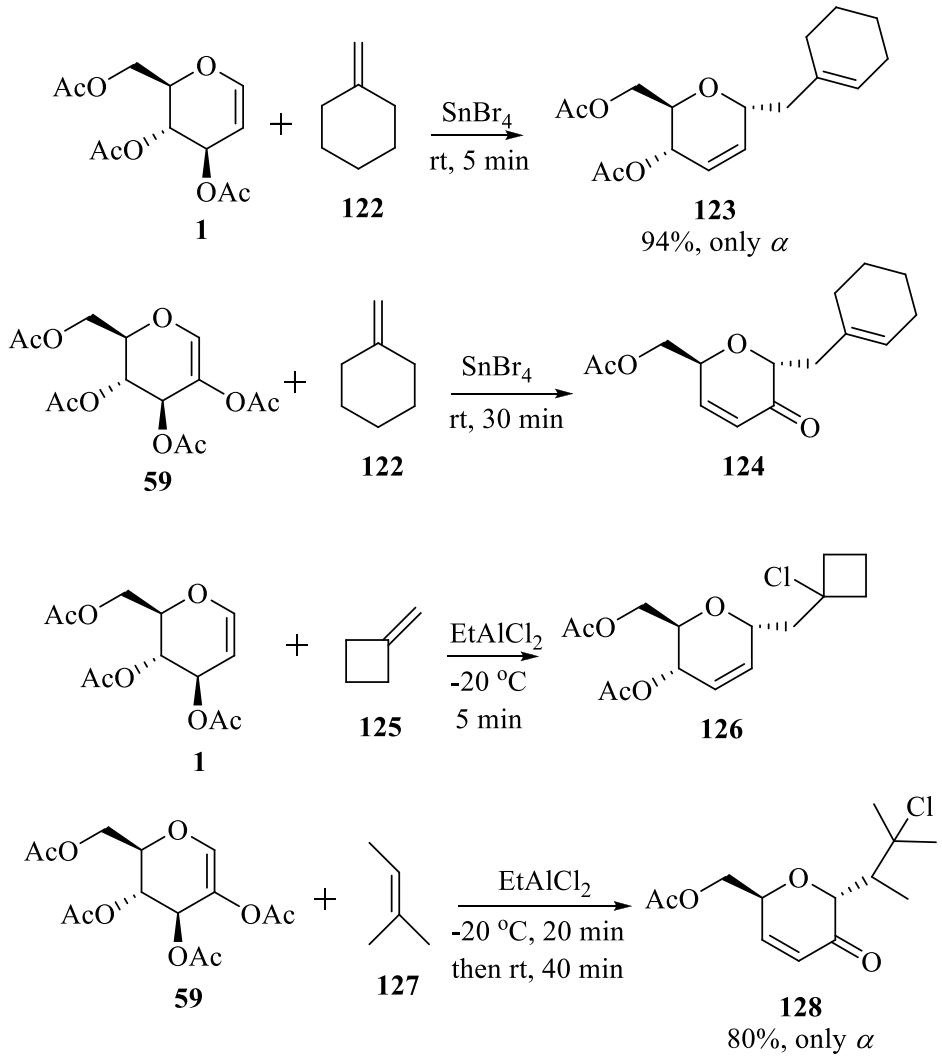
Ethyl acetoacetate (**120**) has also been utilised in the Ferrier rearrangement on **1** using only 0.5 mol% of $AuCl_3$, giving 80% of the product **121** in just 15 minutes (Scheme 55).[18]



Scheme 55

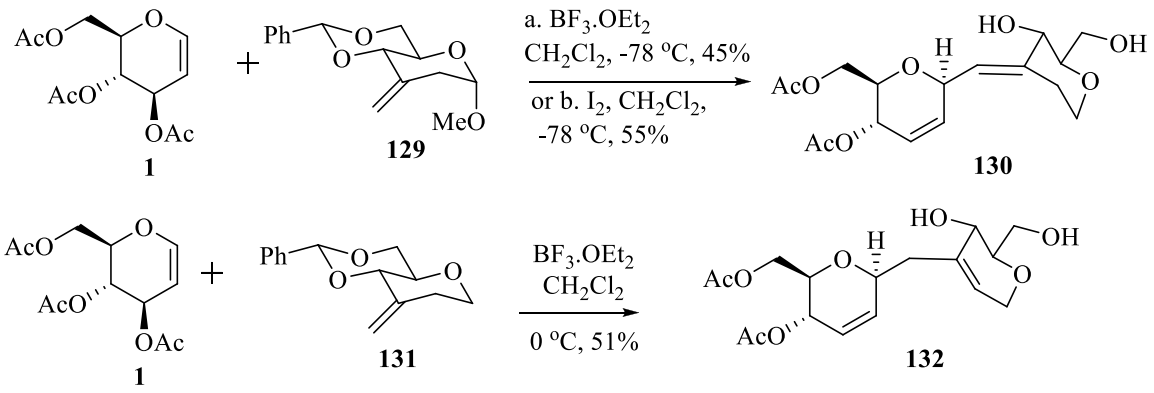
7.4 Olefins

Peracetylated glycals underwent Ferrier rearrangement with olefins in the presence of Lewis acids such as $SnBr_4$ and $BF_3.Et_2O$ with complete regioselectivity and high diastereoselectivity, with the α-anomer being the major product.[28] Thus, glucal **1** reacted with olefin **122** to give exclusively α-anomer the C-glycosylated **123** in 94% in the presence of $SnBr_4$ (Scheme 56). In the same way, glucal **59** gave 70% of only α-anomer **124**. In the case of methylenecyclobutane **125** and open-chain olefins such as **127**, some halogeno derivatives **126** and **128** were obtained when the reaction was carried out in the presence of $EtAlCl_2$.



Scheme 56

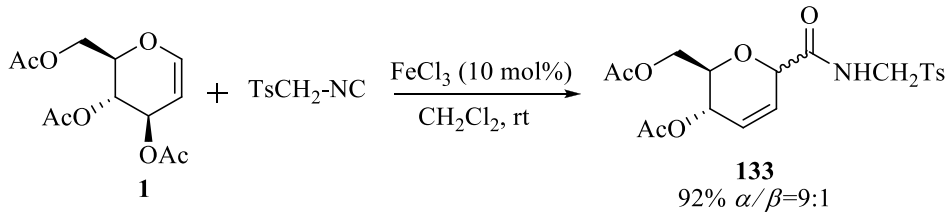
More recently, Osborn *et al.*[46] prepared the olefin **129** to carry out a similar Ferrier reaction on glycals using $BF_3.Et_2O$ or I_2 as a promoter (Scheme 57), leading to the 1-deoxy-*C*-linked disaccharide **130**. The reaction was optimised with 2:1 ratio of glycal and olefin. Anomeric methoxide undergoes cleavage which also reacts with glycal, hence 2 equiv of glucal is required. The oxonium ion formed by cleavage of the acetal at the anomeric carbon of **129** is reduced by the transfer of hydride from the benzylidene acetal, leading to the subsequent removal of the benzylidene group. Reaction of glucal **1** with olefin **131** under the same conditions led to disaccharide **132** in 51% yield. Likewise, some other glucal and galactal derivatives also underwent analogous reactions.



Scheme 57

7.5 Isocyanides

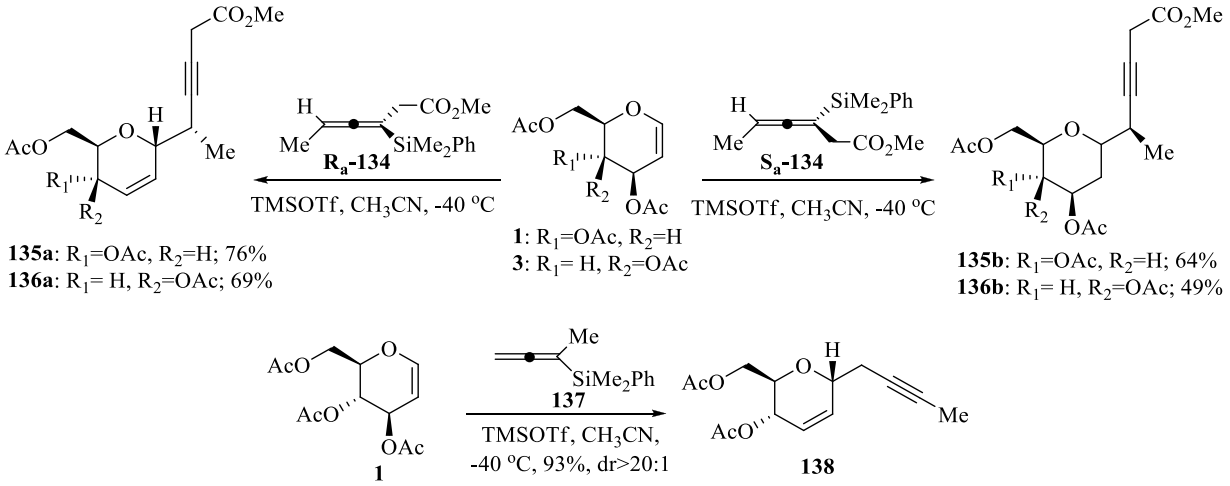
Yadav *et al*.[47] reported Ferrier rearrangements with isocyanides as nucleophiles using a catalytic amount of $FeCl_3$ at room temperature. Under these mild reaction conditions, *C*-glycosyl amides **133** were obtained in good yields with high selectivity (Scheme 58). Several differently protected glucals reacted efficiently with the isonitriles in the presence of only 10 mol% $FeCl_3$ at room temperature.



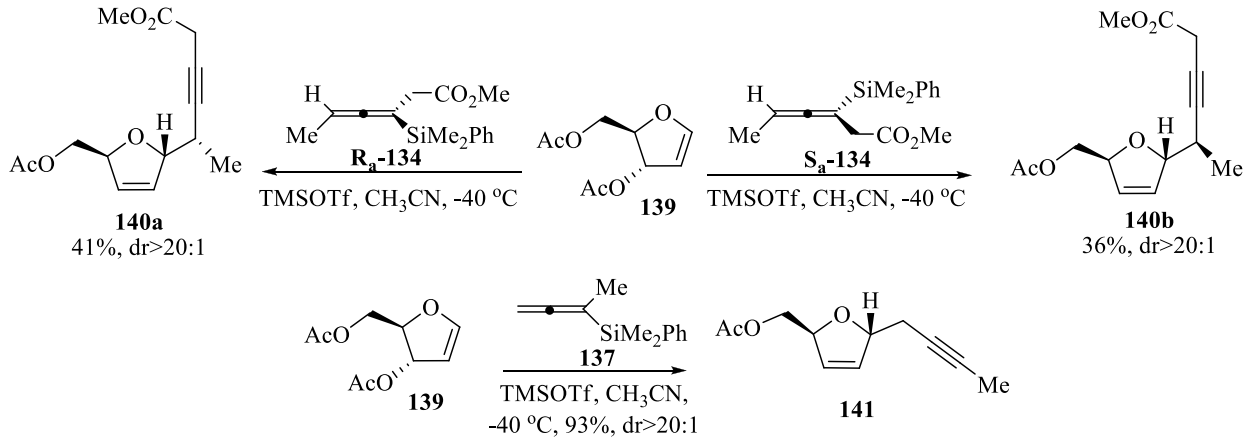
Scheme 58

7.6 Allenyl silanes

Very recently, enantio-enriched allenyl silane **134** has been used for *C*-glycosidation under the influence of TMSOTf.[48] The products **135** and **136** displayed very good diastereoselectivity, favouring the α-isomer (Scheme 59). Additions on glucal were considerably higher yielding than the analogous galactal additions. Even achiral allenyl silane **137** was used for this reaction, giving similar results forming **138**. Moreover, the 2,3-dihydrofuran **139**, prepared from D-ribose, underwent reaction with both enantiomers of **134**, affording *trans* dihydrofuran products **140a** and **140b**, albeit in lower yields (Scheme 60). Again, addition of **137** on dihydrofuran **139** gave moderate to high yield of 2,5-*trans*-dihydrofuran **141**.



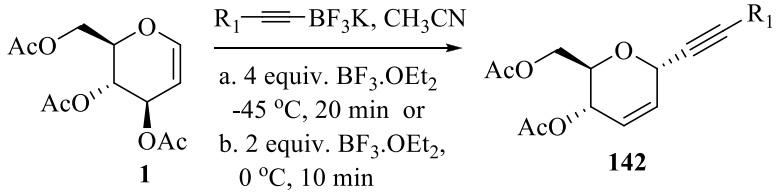
Scheme 59



Scheme 60

7.7 Organoboron compounds

Potassium alkynyltrifluoroborates have been successfully employed in the *C*-glycosidation of D-glucal **1** using $BF_3.OEt_2$.[48] These salts are stable in air and moisture, and more nucleophilic as compared to organoboron compounds. The reaction was performed under 2 sets of conditions- using 4 equiv. of $BF_3.OEt_2$ at -45 °C in acetonitrile gave products **142** in 20 min or using 2 equiv. of $BF_3.OEt_2$ at 0 °C allowed the reaction to complete within 10 minutes (Scheme 61). Both methods gave good yields with high α-selectivity, with the former method giving higher selectivity in some cases.



Scheme 61

$BF_3.Et_2O$ is believed to convert the trifluoroborate into the organoboron difluoride **143**, which is able to activate the acetate of the glucal **1**, generating a $[R\text{-}B(OAc)F_2]^-$ kind of nucleophilic species, which attacks the C-1 oxonium ion, ultimately giving rise to **142** (Figure 5).

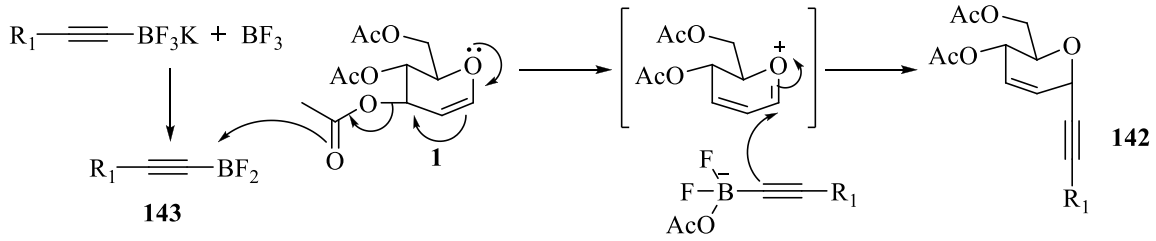


Figure 5. Mechanistic representation of C-Ferrier rearrangment by potassium alkynyltrifluoroborates.

8. Conclusions

From the foregoing discussion, it is clear that a wide range of carbon nucleophiles and a great number of catalysts have been studied to bring about the carbon-Ferrier rearrangement leading to C-glycosides. Although a good amount of progress in terms of improvements in yield, selectivity etc. has been reported, there is still in many reactions room for improvement. It is expected that this review will give sufficient impetus to readers to embark on the development of new catalysts and introduction of new nucleophiles in the carbon-Ferrier rearrangement.

9. Acknowledgements

We thank the Department of Science and Technology, New Delhi and Council of Scientific and Industrial Research (CSIR), New Delhi for financial support. AAA and RL thank the CSIR, New Delhi for Senior Research Fellowships.

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