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Indium trichloride promoted stereoselective synthesis of O-glycosides from trialkyl orthoformates

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ABSTRACT

A novel, highly stereoselective method for O-glycosylation of glycals and glycosylbromides is developed using orthoformates as acceptors in the presence of $InCl_3$ to afford the corresponding *O*-glycopyranosides in 66–94% yield. Both perbenzyl and peracetyl glycals afford the corresponding 2,3-unsaturated-O-glycosides with high α-selectivity. Stoichiometric amounts of orthoformates are sufficient to bring about this transformation instead of large excesses of alcohols.

The development of methods leading to the efficient and stereoselective synthesis of glycosides has attracted considerable attention in carbohydrate and biological chemistry.[1] Since the development by Koenigs and Knorr of a glycosylation method[2] using glycosyl halides and a silver salt, much attention has been paid to improve O-glycosylation reactions. One of the important O-glycosylation methods for producing 2,3-unsaturated-O-glycosides, which are useful chiral building blocks in the synthesis of biologically active compounds such as glycopeptides,[3] oligosaccharides,[4] and modified carbohydrate derivatives,[5] is allylic rearrangement (the Ferrier rearrangement) of the corresponding glycals upon treatment with various alcohols,[6] in presence of either acid catalysts or redox reagents. However, most of these systems require large excess of alcohol leading to extensive work up. Hence, there is a pressing need for a practical synthetic strategy that will provide access to these important sugar building blocks with good anomeric selectivity using stoichiometric amounts of reagents.

Orthoesters have been used as alkylating agents to convert several carboxylic, sulfonic, and phosphinic acids to their corresponding esters,[7] and primary alcohols to their corresponding ethers.[8] Neutral substrates such as aldehydes and ketones were readily converted into acetals/ketals, while dialkyl aryl amines were converted into formyl derivatives using orthoesters in the presence of a Lewis acid catalyst.[9] Orthoesters also act as mono-C-alkylating agent for arylacetonitriles.[10] Recently, etherification of homoallylic alcohols using trimethylorthoformate has been reported.[11] In carbohydrate chemistry, orthoesters are employed generally only for temporary protection of vicinal hydroxy groups.[12] Very recently, cycloaddition of glucal triacetate with alkyl azides has been carried out in trialkyl orthoformate at elevated temperature to afford triazoline intermediates.[13] Orthoesters can be viewed as the ketals of esters which can release two molecules of alcohols and one molecule of ester upon acid hydrolysis. Thus, we envisaged that they can be used as acceptors, and stoichiometric amount of an

Table 1
A comparative study of the effect of different Lewis acids on the O-glycosylation of glycal **1** to product **1a**

Entry	Acid catalyst[a]	Time (h)	Yield[b] (%) (α:β)[c]
1	$BF_3{\cdot}Et_2O$	3	75 (6:1)
2	$ZnCl_2$	3	60 (5:1)
3	$FeCl_3$	3.2	60 (34:1)
4	$In(OTf)_3$	2	65 (6:1)
5	CAN	4	70 (3:1)
6	$HClO_4$·silica	3	Degraded product
7	I_2	5	Mixture of products
8	TMSOTf	4	35
9	IR120 H^+ resin	6	10
10	BBr_3	4	65 (3:1)
11	PPh_3	8	55 (4:1)
12	$Fe_2(SO_4)_3{\cdot}nH_2O$	4	60 (4:1)
13	$InCl_3$	1.2	92 (8:1)

[a] 10 mol % catalyst loading.
[b] Isolated yield.
[c] Determined by ^1H NMR.

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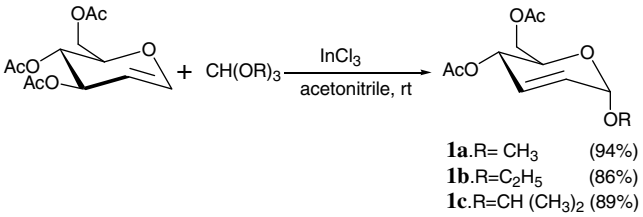
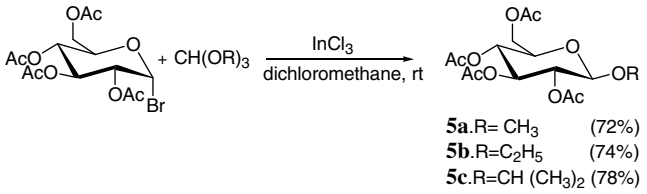


Scheme 1.

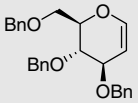
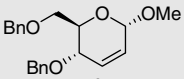
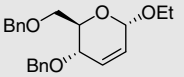
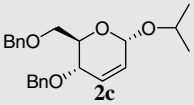
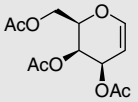
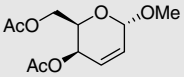
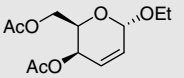
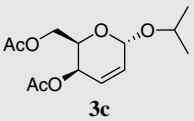
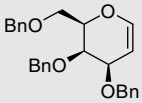
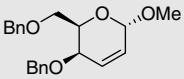
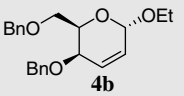
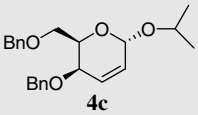


Scheme 2.

orthoester (in the presence of a Lewis acid) in place of an alcohol should be sufficient to bring about the Ferrier transformation.

$InCl_3$ has emerged as a mild Lewis acid[14] for a variety of organic transformations due to its water solubility and simplicity in operation, but to date, its application in glycosylation reactions[6g,15a] does not appear to have been studied in detail. As a part of our ongoing interest[15] in the study of indium chloride as a promoter for glycosylations, we investigated its use as a promoter in O-glycosylation reactions using orthoformates.

Table 2
O-Glycosylation of various glycals with orthoesters in the presence of indium chloride

Entry	Glycal	Acceptor[a]	Product[b]	Time (h)	Yield[c] (%) (α:β)[d]
1	**1**	$CH(OMe)_3$	**1a**	1.2	94 (15:1)
2	**1**	$CH(OEt)_3$	**1b**	1.2	86 (10:1)
3	**1**	$CH(OiPr)_3$	**1c**	1.4	89 (7:1)
4	 **2**	$CH(OMe)_3$	 **2a**	1.2	92 (5:1)
5	**2**	$CH(OEt)_3$	 **2b**	1.2	94 (7:1)
6	**2**	$CH(OiPr)_3$	 **2c**	1	93 (6:1)
7	 **3**	$CH(OMe)_3$	 **3a**	1.5	78 (6:1)
8	**3**	$CH(OEt)_3$	 **3b**	1.6	74 (20:1)
9	**3**	$CH(OiPr)_3$	 **3c**	1.5	76 (8:1)
10	 **4**	$CH(OMe)_3$	 **4a**	1.2	85 (7:1)
11	**4**	$CH(OEt)_3$	 **4b**	1.2	89 (6:1)
12	**4**	$CH(OiPr)_3$	 **4c**	1.2	88 (5:1)

[a] Reaction with 1.2 equiv of orthoformate.
[b] All the products were characterized by ^1H, ^{13}C NMR and mass spectra.
[c] Isolated and unoptimized yields.
[d] Anomeric ratios were determined by ^1H NMR spectroscopy.

Table 3
O-Glycosylation of various glycosyl bromides in the presence of $InCl_3$

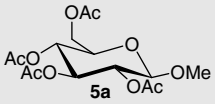
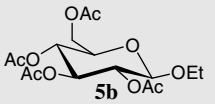
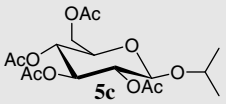
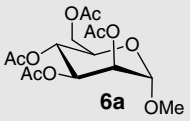
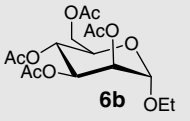
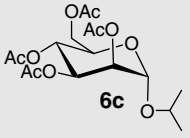
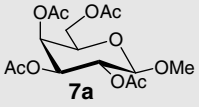
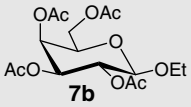
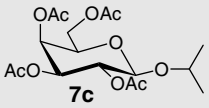
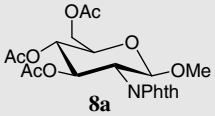
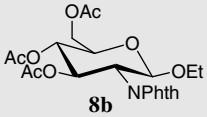
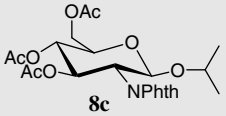
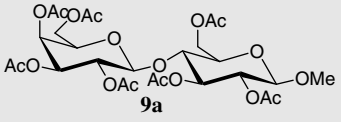
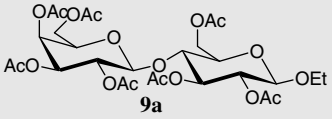
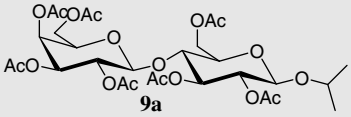
Entry	Donor	Acceptor[a]	Product[b]	Time (h)	Yield[c] (%) (β:α)[d]
1	**5**	$CH(OMe)_3$	 **5a**	4.2	72 (>9:1)
2	**5**	$CH(OEt)_3$	 **5b**	4.5	74 (>9:1)
3	**5**	$CH(OiPr)_3$	 **5c**	3.5	78 (>9:1)
4	Acetobromomannose (**6**)	$CH(OMe)_3$	 **6a**	6	71 (>1:9)
5	**6**	$CH(OEt)_3$	 **6b**	5.2	69 (>1:9)
6	**6**	$CH(OiPr)_3$	 **6c**	4.5	79 (>1:9)
7	Acetobromogalactose (**7**)	$CH(OMe)_3$	 **7a**	4	69 (>9:1)
8	**7**	$CH(OEt)_3$	 **7b**	4.5	74 (>9:1)
9.	**7**	$CH(OiPr)_3$	 **7c**	4.2	71 (>9:1)
10	2-Deoxy-2-phthalimido-acetobromoglucose (**8**)	$CH(OMe)_3$	 **8a**	4	67 (>9:1)
11	**8**	$CH(OEt)_3$	 **8b**	4	69 (>9:1)
12	**8**	$CH(OiPr)_3$	 **8c**	4	69 (>9:1)
13	Acetobromolactose (**9**)	$CH(OMe)_3$	 **9a**	5	66 (>9:1)

Table 3 (*continued*)

Entry	Donor	Acceptor[a]	Product[b]	Time (h)	Yield[c] (%) (β:α)[d]
14	**9**	$CH(OEt)_3$	 **9a**	5.2	69 (>9:1)
15	**9**	$CH(OiPr)_3$	 **9a**	5	71 (>9:1)

[a] Reaction with 1.5 equiv of orthoformate.
[b] All the products were characterized by ^1H, ^{13}C NMR and mass spectra.
[c] Isolated and unoptimized yields.
[d] Ratios >9:1 are conservative minima; no other anomers were detected.

In order to generate preliminary information on this method, initial experiments were performed with peracetyl glucal as the donor and orthoformates as the acceptor in various solvent systems in the presence of a catalyst. Further, to study the effect of the catalyst, various Lewis acids and redox agents were used as promoters. A comparative study, summarized in Table 1, proved that $InCl_3$ (5 mol %) in acetonitrile was superior to other catalysts in terms of yield, reaction time, and stereoselectivity (Scheme 1).

After obtaining acceptable results, other glycals were subjected to the same reaction under the optimized conditions.[16] From the literature,[17] it has been reported that perbenzyl glucal and peracetyl galactal undergo addition reactions to afford 2-deoxy-O-glycosides upon treatment with alcohols in the presence of Lewis acid catalysts. It is noteworthy that under the present conditions, the reaction of 3,4,6-tri-*O*-benzyl glucal and 3,4,6-tri-*O*-acetyl galactal proceeded smoothly leading to the complete conversion of 2,3-unsaturated O-glycosides in high yield with almost exclusive α-selectivity (Table 2).

Encouraged by the results obtained with glycals and orthoformates, we studied the coupling of various glycosyl bromides with orthoformates in the presence of a catalytic amount of indium chloride (20 mol %) at ambient temperature using dichloromethane as solvent[18] (Scheme 2).

Under these conditions glycosides were obtained in all the cases with pronounced β-stereoselectivity (except with acetobromomannose which gave predominantly the α-product) in moderate yield. The results using this reagent system for glycosylations are summarized in Table 3.

A plausible mechanism for the formation of glycosides from orthoformates may occur in the following way: Indium chloride coordinates with the leaving group X^- (X = Br, OAc, OBn) to generate a carbonium ion (stabilized by the ring oxygen) which abstracts an alkoxy group from the orthoester (perhaps with the help of another $InCl_3$) to form the glycoside. The $InCl_3X^-$ species then attacks the $HC(OR)_2^+$ species with the formation of RX and HCOOR, and regeneration of $InCl_3$.

In conclusion, we have demonstrated a new $InCl_3$-catalyzed orthoformate-mediated O-glycosylation method to produce 2,3-unsaturated-O-glycosides from glycals (via Ferrier rearrangement) and alkoxy glycosides from glycosyl bromides. Both peracetyl glucal and perbenzyl glucal gave satisfactory results with good α-selectivity and without the formation of 2-deoxy hexopyranosides as side products.

Acknowledgment

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References and notes

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16. Typical experimental procedure for the preparation of 2,3-unsaturated glycosides from glucals: indium chloride (5 mol %) at ambient temperature was added to a stirred solution of 3,4,6-tri-*O*-acetyl-D-glucal (1 mmol) and triethyl orthoformate (1.2 mmol) in acetonitrile (2 mL). On completion of the reaction (specified time in Table 2), the reaction mixture was concentrated, diluted with ethyl acetate (15 mL), and washed with a saturated solution of aqueous sodium hydrogen carbonate (10 mL). The organic layer was separated,

dried over anhydrous sodium sulfate, and concentrated in vacuo. The product was purified by silica gel column chromatography (ethyl acetate–petroleum ether 1:10). Spectral data of compound **1b**:[6w] Oily liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.8 (m, 2 H), 5.30 (d, J = 9.4 Hz, 1H), 5.0 (s, 1H), 4.07–4.20 (m, 3H), 3.77–3.86 (m, 1H), 3.61–3.68 (m, 1H), 2.08 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.8, 170.3, 129.0, 127.9, 94.2, 64.2, 63.7, 63.4, 63.0, 20.9, 20.7, 15.0.

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18. *Typical procedure for the O-glycosylation of glycosyl bromide:* Indium chloride (20 mol %) was added to a stirred solution of acetobromoglucose (1 mmol) and trimethyl orthoformate (1.5 mmol) in dry dichloromethane (3 mL). On completion of the reaction (Table 3), the reaction mixture was diluted with dichloromethane (10 mL), and washed successively with sodium bicarbonate (10 mL) and water (10 mL). The organic portion was dried over anhydrous sodium sulfate and concentrated on rotary evaporator. The product was obtained by column purification over silica gel (ethyl acetate–petroleum ether 1:5). Spectral data of compound **7a**: Oily liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.33 (d, J = 2.3 Hz, 1H), 5.14 (dd, J = 10.4, 7.8 Hz, 1H), 4.95 (dd, J = 10.4, 3.3 Hz, 1H), 4.34 (d, J = 7.8 Hz, 1H), 4.02–4.13 (m, 2H), 3.82–3.88 (m, 1H), 3.45 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 2.0 (s, 3H); 1.91 (s, 3H).