# Ionic liquid promoted atom economic glycosylation under Lewis acid catalysis†

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Straightforward glycosylation of various alcohols with unprotected and non-activated monosaccharides were performed under scandium triflate catalysis. Rate and yield of glycosylation were highly improved when using 1-butyl-3-methylimidazolium trifluoromethanesulfonate as a green solvent. This ionic liquid was allowed to be recycled at least three times without loss of activity. The possibility of drastically reducing the amounts of catalyst (down to 1 mol%) and aglycone (down to 1 equiv) when performing the reaction in ionic liquid opens new perspectives in *O*-glycosylation, as a direct coupling between an aglycone and free sugars.



## Introduction

Carbohydrates play a fundamental role in many aspects of chemistry and biology, and subsequently the chemistry of glycosides and glycoconjugates has gained much attention for many years. In spite of continuous progress of *O*-glycosylation methodologies since the historical Koenigs Knorr reaction, the chemical methods suffer from tedious protection/deprotection steps. Besides, an appropriate activating group must be introduced at the anomeric position which induces supplementary waste. Such a reaction sequence for *O*-glycosylation leads to a low global atom economy and to a high E-factor; these reaction metrics can now be easily calculated for a complete sequence[1] and such a calculation is extremely instructive to figure out the greenness of a process.[2] Even enzymatic methods using glycosyltransferases require the introduction of an auxiliary, such as an expensive sugar nucleotide; besides, the nucleoside diphosphates generated during the reaction are potent glycosyltransferase inhibitors.[3] New enzymatic methods using glycosidases are emerging, such as the glycosynthase[4] or the transglycosidase[5] approach, but these methods are very specific and require activated sugars, such as fluoro or nitrophenyl glycosides, respectively.

When starting from unprotected carbohydrates, enzymatic reactions using glycosidases are driven more easily towards the hydrolysis than towards the formation of glycosides, since the natural medium of enzymes is water.[6] The thermodynamic enzyme-catalyzed equilibrium could be driven towards the formation of glycosides if a strong excess of aglycone is used.[7] Such an equilibrium is also a limiting factor in aqueous protic acid-catalyzed Fischer glycosylation. High temperatures are required which leads to by-products. Using non-aqueous solvents such as THF or dioxane, Plusquellec and coworkers have shown that the direct *O*-glycosylation of reducing sugars in the presence of ferric chloride (3 equiv. are however required) afforded furanosides in good to excellent yields.[8] In the presence of $BF_3.Et_2O$ (4 equiv.), alkyl α-pyranosides were obtained with a moderate yield.

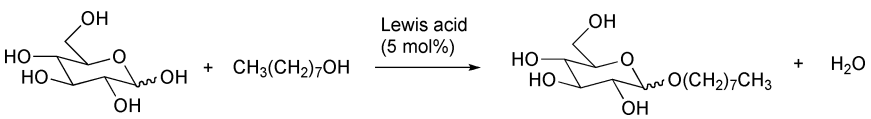
We have shown than it was possible to use only a catalytic amount of Lewis acid in the *O*-glycosylation in order to produce alkylpyranosides in good yields. Since such a reaction goes through an oxocarbenium ion, we have investigated the possibility of improving both the rate and the yield of the reaction in the presence of an ionic liquid.[9] Besides their low vapour pressure and their good thermal stability, an important advantage is the possibility of tuning their solubility and coordination properties by varying the nature of the anions and cations.[10]

At this stage we must keep in mind that the main challenge in using ionic liquids in organic synthesis is the strong necessity to recycle it after use, and subsequently the choice of the ionic liquid will be dictated by the facility to recycle it after use in order to reuse it. This is a crucial condition to keep green a process in which ionic liquids are involved.[11]

## Results and discussion

### Choice of the Lewis acid catalyst

As a reaction model (Scheme 1), we have chosen to test the direct glucosylation of octanol in the presence of various Lewis acid catalysts. In this reaction model no solvent was added. A first comparison was realized between indium chloride and indium




**Scheme 1**

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**Table 1** Lewis acid screening

| Lewis acid | 50 °C | 80 °C | 110 °C |
|---|---|---|---|
| $InCl_3$ | 0% | 0% | traces |
| $In(OTf)_3$ | 3% (71/29) | 21% (67/33) | 40% (65/35) |
| $Sc(OTf)_3$ | 11% (70/30) | 44% (64/36) | 40% (75/25) |
| $Yb(OTf)_3$ | 12% (100/0) | 45% (62/38) | 35% (65/35) |

triflate which are known as efficient catalysts in many reactions.[12] We then anticipated that lanthanide, scandium and indium triflates could be good candidates as catalysts owing to the oxophilicity of the metal and the absence of nucleophilicity and basicity of the triflate. As a matter of fact, all these Lewis acids give encouraging results in the following conditions: glucose (0.5 mmol), Lewis acid (0.05 equiv), octanol (2.5 mmol, 5 equiv), 16 h. Table 1 displays both isolated yields and α/β selectivity of octylglucopyranosides, as evidenced by $^1$H NMR spectroscopy.

A more precise investigation has proved that some degradation occurs at 110 °C; reducing reaction time at that temperature allows us to improve the yields. For example after 3 hours at 110 °C, we obtained 51% of octylglucopyranoside (α/β ratio = 75/25) under $Sc(OTf)_3$ catalysis. On the other hand at 80 °C, reaction yields could be enhanced by lengthening the reaction time. $Sc(OTf)_3$ turned out to be the best compromise.

## Neat glycosylation

Glycosylation of octanol with various carbohydrate moieties (D-glucose, D-galactose, D-mannose, D-xylose, L-fucose, 2-deoxyglucose and *N*-acetylglucosamine) was then carried out in the presence of scandium triflate affording fair to good isolated yields of octylglycopyranosides as α/β-anomeric mixtures, with the exception of mannose which gave only α anomer (Table 2). D-Xylose and 2-deoxyglucose reacted quite quickly (3 h) and extending the reaction time up to 24 h resulted in lower yield probably due to decomposition. Traces of octylglycofuranosides were detected by TLC with D-glucose and D-galactose.

Our efforts next turned toward the synthesis of glucopyranosides from various alcohols using the same strategy (Table 3). The selectivity was still in favour of the α-anomer. The results obtained with cyclohexanol and 1-chloro-3-hydroxypropane are encouraging for the preparation of more elaborated glucosides.

These results show that it is possible to use only a catalytic amount of Lewis acid in the O-glycosylation in order to produce alkylpyranosides in moderate to good yields. Since such a reaction goes through an oxocarbenium ion, we anticipate that both the rate and the yield of the reaction could be improved in the presence of ionic liquid.

**Table 2** Neat glycosylation of octanol under $Sc(OTf)_3$ catalysis

| Carbohydrate | Temperature/°C | Heating time/h | Isolated yield(%) | α/β |
|---|---|---|---|---|
| D-Glucose | 80 | 24 | 44 | 79/21 |
| D-Galactose | 80 | 24 | 14 | 65/35 |
| D-Mannose | 80 | 24 | 14 | 100/0 |
| D-Xylose | 80 | 3 | 72 | 59/41 |
| L-Fucose | 80 | 24 | 42 | 71/29 |
| 2-Deoxyglucose | 80 | 3 | 59 | 85/15 |
| *N*-Acetylglucosamine | 110 | 24 | 49 | 82/18 |

**Table 3** Neat glucosylation of alcohols under $Sc(OTf)_3$ catalysis

| Alcohol | Temperature/°C | Heating time/h | Isolated yield(%) | α/β |
|---|---|---|---|---|
| n-Octanol | 80 | 24 | 44 | 79/21 |
| n-Butanol | 80 | 24 | 44 | 67/33 |
| Cyclohexanol | 80 | 3 | 21 | 55/45 |
| 1-Chloro-3-hydroxypropane | 80 | 24 | 75 | 75/25 |
| Allyl alcohol | 80 | 24 | 64 | 77/23 |
| Propargyl alcohol | 80 | 24 | 53 | 66/34 |

## Scope of the available ionic liquids

A rapid screening of commercially available ionic liquids was realized using similar reaction conditions, with $Sc(OTf)_3$ as the catalyst for glucosylation of octanol. The only modification was the addition of 1 mL of the ionic liquid per mmol of sugar.

Ionic liquid literature is dominated by 1-alkyl-3-methylimidazolium salts, of which 1-butyl-3-methylimidazolium [BMIM] salts are the most recurrent.[13] They are easily prepared from 1-methylimidazole and many of them are commercially available. Their properties are strongly dependent on the coordination properties of their anion. It was demonstrated that the ability of ionic liquids to dissolve free sugars mainly depends on the hydrogen bond accepting properties of the anion.[14] Thus 1-butyl-3-methylimidazolium chloride ([BMIM][Cl]) dissolves massive amounts of cellulose;[15] 1-butyl-3-methylimidazolium dicyanamide ([BMIM][$N(CN)_2$]) is also known to dissolve free sugars.[16] These ionic liquids are miscible in water. This is also the case for 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][$BF_4$]) and 1-butyl-3-methylimidazolium trifluoromethanesulfonate ([BMIM][OTf]), although these hydrophilic ionic liquids do not dissolve simple sugars to an appreciable degree. By contrast 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][$PF_6$]) and 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide ([BMIM][$NTf_2$]) are not water-miscible, owing to the poor coordinating properties of the anion. Obviously they don't dissolve free sugars.

Our starting point was to test a range of 1-alkyl-3-methylimidazolium salts, which have shown promising results in organic synthesis. Since the properties of ionic liquids are highly dependent on the anions, particularly due to the possibility of hydrogen bonding with the sugar,[17] we have investigated nine ionic liquids which fundamentally differ from their anions, namely 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][$PF_6$]), tetrafluoroborate ([BMIM][$BF_4$]), dicyanamide ([BMIM][$N(CN)_2$]), bis(trifluoromethanesulfonyl)imide ([BMIM][$NTf_2$]), trifluoromethanesulfonate ([BMIM][OTf]), methanesulfonate ([BMIM][$MeSO_3$]), acetate ([BMIM][OAc]), 1,3-dimethylimidazolium methyl-phosphonate ([DMIM][(MeO)(H)$PO_2$]) and 1,2,3-trimethylimidazolium methylsulfate ([TMIM][$MeSO_4$]) (Fig. 1).

Among them some are hydrophobic ([BMIM][$PF_6$], [BMIM][$NTf_2$]), two are solid at room temperature but liquid in the condition reaction used ([BMIM][$MeSO_3$], [TMIM][$MeSO_4$]), and two are room-temperature ionic liquids that dissolve carbohydrates ([BMIM][$N(CN)_2$], [DMIM][(MeO)(H)$PO_2$]).

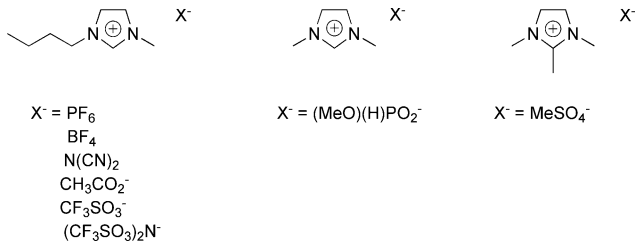



**Fig. 1** Ionic liquids tested.

The properties of the two hydrophobic ionic liquids strongly differ from their viscosity coefficient, [BMIM][$PF_6$] being much more viscous than [BMIM][$NTf_2$]. The high viscosity of [BMIM][$PF_6$] is probably the reason for the failure of the glycosylation reaction in our conditions. By contrast, when using [BMIM][$NTf_2$], the reaction mixture at the beginning is a heterogeneous mixture of glucose, $Sc(OTf)_3$, octanol and ionic liquid, but once the reaction is complete there is no solid phase left, the octylglucopyranoside formed being soluble in the reaction mixture. Unfortunately the separation of the ionic liquid from the octylglucoside was difficult and the ionic liquid could not be completely removed which is a major drawback in such a process. In hydrophilic ionic liquids such as [BMIM][$N(CN)_2$], [BMIM][$MeSO_3$], [BMIM][OAc], [TMIM][$MeSO_4$] the glycosylation reaction did not occur, owing to a strong hydrogen bond with the anion, preventing the anomeric hydroxyl group to be activated by the Lewis acid. With intermediate ionic liquids, such as [BMIM][$BF_4$] and more particularly [BMIM][OTf] the results were encouraging. We anticipated that this latter ionic liquid which allows an immobilisation of the scandium triflate catalyst could be an ionic liquid of choice as it was in the benzylation of aromatics under $Sc(OTf)_3$ or $Yb(OTf)_3$ catalysis.[18] At the outset of our investigation we have considered that there could be some advantage to using the same anion in the catalyst and in the ionic liquid. Moreover triflate as an anion has no nucleophilicity.

At this stage, we must pay attention to using ionic liquids of high purity, as is frequently recommended.[19,20] In one assay we have used [BMIM][OTf] prepared using a metathesis method from [BMIM][Br]; the glycosylation reaction failed and no octylglucopyranoside has been isolated. As halide impurities are difficult to remove from [OTf] salts,[21] we first thought that traces of $[Br]^-$ could inhibit the reaction. We then carried out various experiments in order to find accurately which impurity was involved in the failure of the glycosylation reaction. We tested the reaction in [BMIM][Br] and the desired compound was obtained even if the yield was slightly lower than in [BMIM][OTf] (52%). In [BMIM][OTf] in which some [BMIM][Br] has been added the result is similar as the one without [BMIM][Br] traces. We also run assays in [BMIM][OTf] with traces of bromobutane or N-methylimidazole or KOTf and only the one with N-methylimidazole showed no formation of octylglucopyranoside. So the presence of N-methylimidazole in our prepared [BMIM][OTf] seems to be responsible for the reaction failure. Indeed, a further examination of the $^1H$ NMR spectrum of the prepared [BMIM][OTf] tested revealed that it was contaminated with N-methylimidazole and another reaction carried out in prepared [BMIM][OTf] showing no traces of N-methylimidazole was successful.

### Glycosylation in [BMIM][OTf]

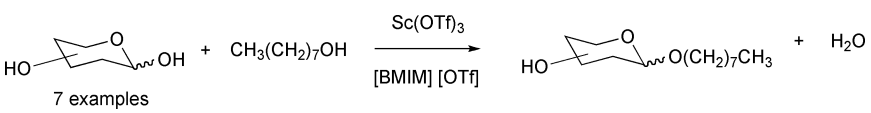
Glycosylation of octanol (Scheme 2) and glucosylation of various alcohols (Scheme 3) under $Sc(OTf)_3$ catalysis were run in [BMIM][OTf]. The results are summarized in Tables 4 and 5. Compared to the reaction performed without ionic liquid, glycosylation reaction yields are higher. However α-selectivity, as the outcome of the stability of the product, is unchanged. The glycosylation reaction goes through an oxocarbenium ion which could then be stabilised by the ionic liquid. Note that

**Table 4** Glycosylation of octanol under $Sc(OTf)_3$ catalysis in [BMIM][OTf]

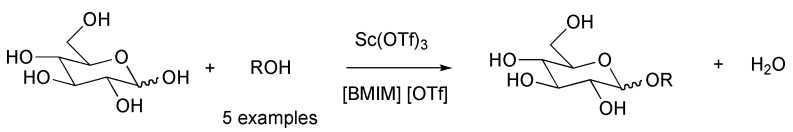
| Carbohydrate | Temperature/°C | Heating time/h | Isolated yield(%) | α/β |
|---|---|---|---|---|
| D-Glucose | 80 | 24 | 74 | 75/25 |
| D-Galactose | 80 | 24 | 70 | 61/39 |
| D-Mannose | 80 | 24 | 88 | 100/0 |
| D-Xylose | 80 | 3 | 78 | 66/34 |
| L-Fucose | 80 | 24 | 51 | 67/33 |
| 2-Deoxyglucose | 80 | 3 | 72 | 85/15 |
| *N*-Acetylglucosamine | 110 | 24 | 60 | 79/21 |

**Table 5** Glucosylation of alcohols under $Sc(OTf)_3$ catalysis in ionic liquid

| Alcohol | Temperature/°C | Heating time/h | Isolated yield(%) | α/β |
|---|---|---|---|---|
| n-Octanol | 80 | 24 | 74 | 75/25 |
| n-Butanol | 80 | 24 | 76 | 80/20 |
| Cyclohexanol | 80 | 3 | 80 | 64/36 |
| 1-Chloro-3-hydroxypropane | 80 | 24 | 100 | 71/29 |
| Allyl alcohol | 80 | 24 | 65 | 73/27 |




**Scheme 2**




**Scheme 3**

**Table 6** Catalyst and aglycone amount optimisation: dramatic effect of ionic liquid

| Ionic liquid | $Sc(OTf)_3$ amount | Octanol (eq) | Isolated yield | α/β |
|---|---|---|---|---|
| [BMIM][OTf] | 5 mol% | 5 | 74 | 75/25 |
| | 1 mol% | 5 | 74 | 70/30 |
| | 1 mol% | 1.5 | 63 | 70/30 |
| | 1 mol% | 1 | 58 | 71/29 |
| — | 5 mol% | 5 | 44 | 79/21 |
| | 1 mol% | 5 | Traces | |

the polarity of [BMIM][OTf] ($E_T^N = 0.656$) is similar to that of ethanol.[22] As suggested by the hydrogen bond basicity (β-value) of [BMIM][OTf] (β = 0.464), we presume that OTf anion might stabilise the oxocarbenium ion as a specific solvent–solute interaction.[23] As a matter of fact, the interaction of ionic liquid triflate with the oxonium cation was clearly evidenced in the glycosylation using trichloroacetamidates as activating anomeric groups.[24] Other activating groups were recently used with [BMIM][OTf] as versatile glycosylation promoter. In each case the reaction goes through the oxocarbenium ion.[25]

Another aspect we wanted to explore was the recyclability of the ionic liquid. Reactions were carried out using D-glucose with octanol. The crude reaction was then filtered through a silica gel pad and eluted with MeOH/AcOEt mixture to afford the mixture of α and β glycosides, free from octanol and ionic liquid. The ionic liquid is recovered by elution with more MeOH. It could be used at least three times without loss of yield and selectivity. The process still needs chromatography; we are aware of this inconvenience, but we must highlight that it allows a total retrieval of the ionic liquid.

Finally, we also tried to reduce the quantity of catalyst and glycoside acceptor used for our model reaction. In a one gram scale reaction we have shown that catalyst amount could be reduced down to 1 mol% in [BMIM][OTf] (Table 6). It is interesting to note that a further decrease of the amount of the catalyst down to 0.1 mol% brings about the formation of non-negligible amounts of glycofuranosides.

Noteworthy, the model reaction performed with only one equivalent of octanol and 1 mol% of $Sc(OTf)_3$ gave the desired product with a still satisfactory 58% yield. Without liquid ionic a huge decrease of yield occurs when decreasing the quantity of alcohol or catalyst.

## Experimental

### General methods

Room temperature ionic liquids were purchased from Solvionic and all other chemicals from Acros or Aldrich. Purities of ionic liquids used: [BMIM][$PF_6$] 99.5%, Cl, Br, I < 5 ppm, $H_2O$ < 0.05%; [BMIM][$BF_4$] 99.5%, Cl, Br, I < 25 ppm, $H_2O$ < 0.05%; [BMIM][$N(CN)_2$] 99%, Cl, Br, I < 100 ppm, $H_2O$ < 0.8%; [BMIM][$NTf_2$] 99.5%, Cl, Br, I < 5 ppm, $H_2O$ < 0.05%; [BMIM][OTf] 99.5%, Cl, Br, I < 25 ppm, $H_2O$ < 0.05%; [BMIM][$MeSO_3$] 99.5%, Cl, Br, I < 25 ppm, $H_2O$ < 0.05%; [BMIM][OAc] >98%, Cl, Br, I < 250 ppm, $H_2O$ < 1%; [DMIM][(MeO)(H)$PO_2$] > 98%, $H_2O$ < 1%. Column chromatography was performed on silica gel 60 (0.063–0.2 mm, Macherey-Nagel). Reactions were monitored by TLC on silica gel 60 $UV_{254}$ (Macherey-Nagel) with detection by charring with 10% sulfuric acid in ethanol. Solvents were removed under reduced pressure at < 50 °C.

### Instrumentation

$^1H$ NMR spectra and $^{13}C$ NMR spectra were recorded at 25 °C with a Jeol ECX 400 MHz spectrometer.

### General procedure for glycosylation reaction

A suspension of carbohydrate (0.5 mmol) and Lewis acid (0.05 eq) in alcohol (5 eq) with or without ionic liquid (0.5 mL) was heated at 80 °C for 24 h. The crude reaction was then filtered through a silica gel pad eluting with 0 to 15% MeOH in AcOEt to afford the desired glycoside as an anomeric mixture and then to recover the ionic liquid.

### NMR characterisation

Identification of the glycopyranosides obtained was done by NMR. Spectroscopic data were identical with those previously reported in the literature. α/β selectivity was determined from $^1H$-NMR spectra after addition of $D_2O$ in NMR sample.

## Conclusion

A new method has been established for the synthesis of *O*-glycopyranosides from unprotected and unactivated carbohydrates and alcohols using a metal triflate as a catalyst. When glycosylation was conducted in 1-butyl-3-methylimidazolium trifluoromethanesulfonate better yields were obtained. The notable feature of this procedure is the reusability of the ionic liquid which makes it an eco-friendly chemical process for the synthesis of glycopyranosides of synthetic importance. The possibility of drastically reducing the amount of aglycone is promising for the synthesis of more elaborate *O*-glycosides with α-selectivity. Pure α-anomer could then be obtained after enzymatic hydrolysis using β-glycosidase.

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