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Glycosylation *mediated*—BAIL in aqueous solution

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ABSTRACT

The use of Brønsted acid ionic liquid (BAIL) as a catalyst for the activation of unreactive and unprotected glycosyl donors has been demonstrated for the first time in aqueous solution.

1. Introduction

Carbohydrates are abundant natural resources and renewable feedstock that can be used particularly in chemistry in various application fields. Linking carbohydrate units by glycosylation has proven to be one of the most difficult synthetic processes to control stereoselectivity. Among all the existing strategies for the glycosylation of sugars, Fischer's glycosylation is the earliest and the simplest. Despite many innovative glycosylation strategies[1] developed to improve the overall yield, chemoselectivity, regioselectivity, and stereoselectivity (from neighboring group participation of 2-*O*-acyl protected glycosyl donors to intramolecular strategies, use of asymmetric transition metal complexes and more recently asymmetric Brønsted acid catalysis), most of them require temporary protection of both acceptor and donor.

The development of a useful and environmentally friendly glycosylation, which is one of the most important and fundamental transformation reactions of carbohydrates, is now becoming more and more important, and urgently needed both in laboratory and in industry. With the approach to minimize the use of hazardous materials or volatile solvents, Ionic Liquids (ILs) have attracted much attention because of their advantageous properties as a reaction media, which include negligible vapor pressure and high thermal stability.

Brønsted acid ionic liquids (BAILs)[2] are a class of ionic liquids that can be used as solvent and/or as acid catalysts. Among all the good reasons to study ionic liquids as alternative Brønsted acids[3] in acid catalyzed reactions, one of them is the possibility to adjust solubility properties by different cation/anion combinations to allow a systematic optimization of the biphasic reaction. For example, BAILs have been studied in Mannich reaction,[4] Friedel–Crafts alkylation,[5] Fischer indole synthesis,[6] and esterification.[7–9]

Glycosylation using unprotected and unactivated donors[10] is often preferable as it can reduce the number of steps, allow for a different stereochemistry, and increase prospects for further process modifications. However, their use involves a number of challenges, including poor solubility in most conventional organic solvents.

Glycosylation reactions performed in Ionic Liquids (ILs) are now emerging. Linhardt[11,12] and Augé[13] have recently reported a convenient method to catalyze O-glycosylation with free carbohydrates. Whereas Linhardt was studying the sole 1-ethyl-3-methylimidazolium benzoate [emIm][ba] in the presence of Amberlite IR-120 (H^+) or *p*-toluenesulfonic acid (TsOH) to promote the glycosylation in the presence of a large excess of alcohol acceptor, Augé screened various commercially available ILs demonstrating that the best combination was obtained for 1-butyl-3-methylimidazolium triflate [BMIM][OTf] and the robust lewis acid scandium triflate $Sc(OTf)_3$ with 5 equiv of alcohol. In both cases, α-anomer was the major product.

The combination of ILs and Lewis acid has also been achieved to perform the β-selectivity by using protected and activated glycosyl

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donors such as glycosyl trichloroacetamidate,[14,15] glycosyl phosphite,[16] glycosyl fluoride,[17] and thioglycoside.[18] A wide range of acid reagents such as montmorillonite K10,[19] amberlite resin,[20] H_2SO_4–silica,[21] $AuCl_3$,[22] $FeCl_3$, $ZnCl_2$, BF_3.OEt, TMSOTf, $Cu(OTf)_2$[23] also provided the *O*-glycosyl derivatives on unreactive and unprotected sugars. Moreover, many of the Lewis acids are moisture sensitive and metal triflates or gold catalysts are highly expensive. Therefore, the search for newer and efficient synthetic methodologies with greater efficiency and convenient procedures continues to be a challenge.

Besides the use of ILs as a new tool for green processes, the use of water as a solvent has also received considerable attention in synthetic organic chemistry for several reasons. Water will reduce the use of harmful organic solvents and it is also unnecessary to dry co-solvents, substrates and reagents leading to time and energy savings.

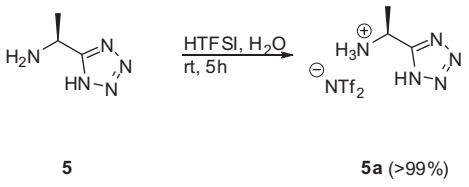
However, the use of water as a reaction medium can also limit the efficiency of the reaction especially if equilibrium is disadvantaged as in the case of steps involving dehydration. A representative example is the Fischer acid-catalyzed O-glycosylation. This drawback could be easily circumvented. Kobayashi and co-workers[24] reported the use of dodecylbenzenesulfonic acid (DBSA) as a surfactant-type to catalyze etherification. Some examples of esterification catalyzed by BAILs have also been described.[7–9]

We therefore initiated an investigation to see if Brønsted acid ionic liquid could be used to catalyze the simple glycosylation using water as co-solvent.

2. Results and discussion

Considering the wide variety of ionic liquids, we choose $TFSI^-$ as anion for its hydrophobic properties and its high stability and the tetrazole ring as anion since they represent good bio-isosteres of carboxylic acid. Moreover, they are planar and aromatic and generally have proven better reactivity and/or selectivity due to a greater charge-stabilization compared to their corresponding carboxylic acid isoster.

As a preliminary study, we synthesized BAIL **2**. Tetrazole-proline **1** was readily prepared from natural L-proline (Scheme 1). Because of its high efficiency in a number of reactions,[25] compound **1** is lately commercially available. The multistep synthesis will be described for similar amino acids a little later. The metathesis exchange was then accomplished with an aqueous solution of HTFSI. After elimination of water under vacuo, compound **2** was obtained.



5 **5a** (>99%)

Scheme 3.

The chemical yield is essentially quantitative. Moreover, since neither reaction produces byproducts (except water), the ILs synthesis is 100% atom efficient.

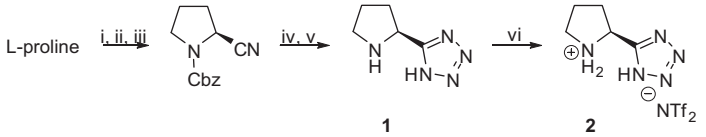
The ILs derivatives **3a** and **4a** were obtained in a similar way (Scheme 2). After a classical Z-protection of the amino group of D- or L-phenylalanine, the carboxylic group was transformed into amide by using Boc_2O, NH_4HCO_3 in pyridine–acetonitrile. After dehydration by $POCl_3$, the nitrile derivatives were obtained. Addition of sodium azide in DMF afforded the cyclic tetrazoles **3** in 14% and tetrazole **4** in 23% overall yield (over 5 steps). Those modest yields are attributed to the last step of Cbz deprotection. In the case of L-Pro (Scheme 1), a slight hydrogen pressure was exerted during the hydrogenation step. These conditions would probably increase this last step (performed under atmospheric pressure) as well as the addition of a catalytic amount of acetic acid. Metathesis exchange with HTFSI led quantitatively to ILs **3a** and **4a**. Similarly, the known alanine tetrazole **5**[26] was exchanged with HTFSI to afford IL **5a** (Scheme 3).

Thermal stability (Fig. 1).

2.1. Thermogravimetric analysis (TGA)

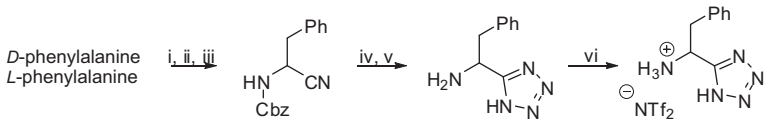
The stability of the synthesized BAILs was determined by TGA measurements to prove their compatibility with the thermal glycosylation reactions conditions ($T = 80$ °C). It appears that BAILs **3a** and **4a** are stable until 150 °C whereas **2** and **5a** start to decompose around 178 °C and 190 °C respectively which correspond to the degradation of the cation moiety, mostly into CO_2 and N_2. The beginning of the degradation of the anion $TFSI^-$ which is more stable than organic cations, starts around 320 °C for every IL.

The newly synthesized ILs were screened as solvent/catalysts for the catalytic evaluation of direct glycosylation (Table 1). We initiated our study with D-mannose which is known to give preferentially α-pyranoside and thus easy purification. In this reaction



1 **2**

Scheme 1. Reagents and conditions: (i) NaOH 2 M, Cbz-Cl (1.5 equiv), 5 °C, 2 h (95%), (ii) Boc_2O (1.5 equiv), NH_4HCO_3 (1.5 equiv), pyridine (0.7 equiv), CH_3CN, rt, 68 h (90%), (iii) cyanuric chloride, DMF, Argon, 1 h at 0 °C then rt for 3 h (>99%), (iv) NaN_3 (1.1 equiv), NH_4Cl (1.1 equiv), DMF, 90 °C, 8 h (>99%), (v) Pd/C (10%), H_2, EtOH, 24 h, rt (90%), (vi) $(CF_3SO_2)_2NH$ (1 equiv), H_2O, rt, 5 h (>99%).



(*D*)-**3** 14% (over 5 steps) **3a** (>99%)
(*L*)-**4** 23% (over 5 steps) **4a** (>99%)

Scheme 2. Reagents and conditions: (i) NaOH 2 M, Cbz-Cl (1.1 equiv), 5 °C, 2 h, (ii) Boc_2O (1.3 equiv), NH_4HCO_3 (1.2 equiv), pyridine (3 equiv), CH_3CN, rt, 68 h, (iii) $POCl_3$ (1.2 equiv) in DCM, pyridine, −10 °C, 3 h, (iv) NaN_3 (1.1 equiv), NH_4Cl (1.1 equiv), DMF, 90 °C, 8 h, (v) Pd/C (10%), H_2, EtOH, 24 h, rt, (vi) $(CF_3SO_2)_2NH$ (1 equiv), H_2O, rt, 5 h.

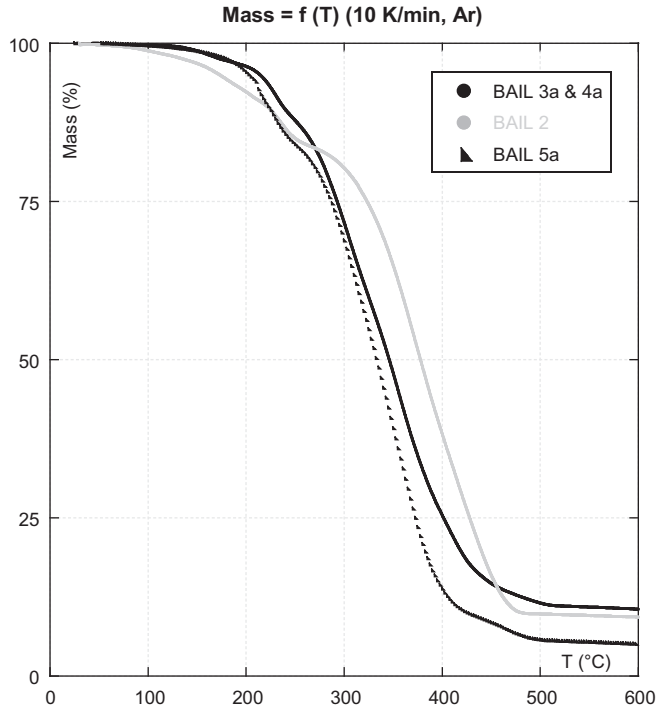
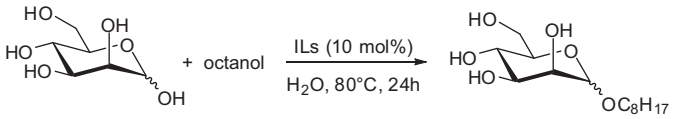


Figure 1. TGA curves of compounds **2**, **3a**, **4a,** and **5a**.

Table 1
Optimization of the reaction conditions[a]



Entry	IL	Yield[b] (%)	α/β[c]
1	**2**	62	91/9
2	**3a**	69[d]	94/6
3	**4a**	64	90/10
4	**5a**	46	80/20

[a] Typical procedure: D-mannose, octanol (5 equiv), H_2O (2 equiv), and IL (10 mol %) were stirred at 80 °C. After 24 h, water was eliminated by evaporation and the reaction mixture purified by flash chromatography.
[b] Isolated yield.
[c] Determined by NMR.
[d] No reactivity when the reaction was performed at room temperature.

model, water was added to dissolve the unprotected sugar otherwise no reactivity was observed. Glycosylation of octanol with D-mannose was carried out in the presence of the synthesized ILs. After 24 h of reaction at 80 °C, water was eliminated under vacuum. Due to the small amount of water used in the following reactions, water has not been recycled. Nonetheless, the reaction was also controlled by mass spectrometry and the only detected compounds were the alcohol, the sugar, the *O*-glycoside, the tetrazole moiety and the presence of its anion $TFSI^-$ detected by ESI^- (negative electrospray). No by-products were detected by MS and TLC. As a matter of fact, these ILs gave encouraging results especially with BAILs **2** and **3a** (62% and 69% yield respectively) with α-selectivity higher than 90%. The catalyst **1** precursor of BAIL **2** was already known to be an efficient catalyst in many reactions.[27] For example, Saito and Yamamoto[28] have demonstrated that the acidity of the protonic acids of catalyst **1** plays a critical role in enhancing reactivity, catalyst efficiency, and enantioselectivity. Adding that, increasing the water ratio leads to an enhancement of the reactivity.

Table 2
Glycosylation of alcohols using BAIL **3a** as catalyst[a]

Alcohol	Yield[b]	α/β[c]
n-Butan-1-ol	61[d]	89/11
n-Heptan-1-ol	50	91/9
n-Octan-1-ol	69[e]	94/6
n-Decan-1-ol	38	93/7
n-Dodecan-1-ol	47	91/9
Cyclohexanol	45[f]	90/10
Allyl alcohol	Traces	n.d.[g]
Propargyl alcohol	25	99/1
Benzyl alcohol	Traces	n.d.

[a] Typical procedure: D-mannose, octanol (5 equiv), H_2O (2 equiv), and BAIL (10 mol %) were stirred at 80 °C. After 72 h, water was eliminated by evaporation and the reaction mixture was purified by flash chromatography.
[b] Isolated yield.
[c] Determined by NMR.
[d] 48 h reaction time.
[e] 24 h reaction times.
[f] 47% yield obtained after 24 h.
[g] Not determined.

Nonetheless when more water was added in our glycosylation reaction (5 equiv instead of 2 equiv, entry **1**), the conversion rate was lower than 30%. A large excess of water probably shifts disadvantageously the equilibrium involved to the classical oxocarbenium formation under thermodynamic control. Moreover, the chirality brought by ILs **3a** and **4a** (L-series vs D-series) showed no difference either on the α/β ratio (94/6 vs 90/10) or on the yield (69% vs 64%).

After screening the different ILs as catalyst, we focused our attention toward the potential versatility of these BAILs and particularly **3a** (Table 2) which offered the best yield in the model reaction (Table 1) in the glycosylation of D-mannose with various alcohols. Interestingly, with lipophilic alcohols such as heptan-1-ol to dodecan-1-ol or cyclohexanol, the yields were obtained between 45% and 69% yield with a high α-selectivity (>85%). In contrast, with benzyl alcohol (more liphophilic alcohol), so as with water-soluble allylic alcohol, no glycosylation products were obtained. We supposed that these results could be attributed to the fact that those alcohols were firstly dehydrated by the BAIL and that, unlike propargyl alcohol, they could be stabilized by resonance effects, thus preventing the O-glycosylation.

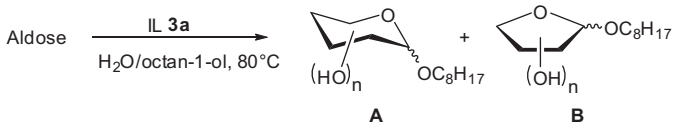
Finally, various sugars were tested to expand the scope and limitation of this reaction and the results were summarized in Table 3.

Starting from D-glucose and after 24 h at room temperature, an anomeric mixture of pyranoside **A** was obtained in a low 14% yield (entry 1) accompanied by the formation of the kinetic furanoside **B**. This moderate yield was ascribed to the weak reactivity of the starting D-glucose. To overcome the formation of the furanosides, the reaction was performed by using 30 mol % of BAIL **3a** (entry 2). Surprisingly, the pyranoside **A** was only formed in a 1.5/1 anomeric ratio with a better 35% yield. In a similar fashion, D-galactose (entry 5) also led to a mixture of furanoside and pyranoside. Nevertheless, when D-mannose was treated with catalyst **3a**, only the more stable pyranoside was obtained in a good yield of 69% (entry 8). In view of these results, we performed the other reactions involving the pentoses D-fucose, D-xylose, D-arabinose, D-ribose and L-arabinose. Similarly, the glycoside derivatives were obtained as a mixture of furanosides and pyranosides with yields ranging from 52% to 79%. In all cases, the more stable pyranoside derivative was obtained except for D-ribose where the furanoside was mostly formed (entry 9).

2.2. Determination of pK_a

Many chemical transformations are sensitive to the acidity. Therefore, knowledge of the pK_a value is important in order to

Table 3
Glycosylation of octanol using BAIL **3a** as catalyst[a]



Entry	Carbohydrate	Yield[b]	**A**:**B**	**A**α/**A**β[c]	**B**α/**B**β[c]
1	D-Glucose	14[d,e]	75:25	1/1.1	1/1.5
2	D-Glucose	35[f]	100:0	1.5/1	/
3	D-Galactose	20[g]	60:40	2.2/1	1/2.5
4	D-Mannose	69	100:0	15.6/1	/
5	D-Fucose	79	80:20	2/1	1/2
6	D-Xylose	52	80:20	1/1	1.3/1
7	D-Arabinose	68	70:30	2/1	1/3
8	L-arabinose	62	75:25	2.2/1	1/3.5
9	D-Ribose	62	15:85	1.8/2	6.1/1

[a] Typical procedure: Sugar, octanol (5 equiv), H_2O (2 equiv), and BAIL (10 mol %) were stirred at 80 °C. After 24 h, water was eliminated by evaporation and the reaction mixture was purified by flash chromatography.
[b] Isolated yield.
[c] Determined by NMR.
[d] 13% yield with 5 equiv of water.
[e] 14% yield using BAIL **4a**.
[f] Yield was obtained when BAIL was used in 30 mol %.
[g] 18% yield with 4 equiv of water.

decide about their possible application as reaction media, especially for the Fischer's glycosylation. The pK_a values of the BAILs **2**, **3a**, **4a,** and **5a** (Table 4) have been determined by titration with NaOH in water. As one might expect, all the ILs showed 2 pK_a values. pK_{a1} were ranging from 2.25 to 2.58. The strongest acid in the series is the IL **2** (pK_{a1} = 2.25). Meanwhile, the second deprotonation step (pK_{a2}) for all the BAILs were ranging from 8.29 to 9.69.

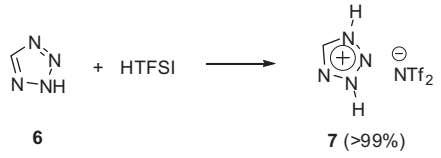
A direct correlation between the acidity of the synthesized ILs **2**–**5a** and the yield of octyl mannoside (Table 1) showed that the acidity of the alanine derivative **5a** (pK_{a1}: 2.58) led to a lower yield (46%) than for the more acidic IL **2**, **3a,** and **4a** which led to 62–69% yield (pK_{a1}: 2.25–2.46). Because no direct correlation can be established between the experimental results obtained so far and the different pK_a values, we nonetheless believe that a stronger pK_a value could increase the hydrogen-bonding interaction between the cation of IL and the sugar starting material. In addition, the chirality of the synthesized **2**–**5a** seems to have a small impact both on the stereoselectivity (α/β) and the furanose/pyranose proportion. We then decided to undertake the synthesis of a more acidic derivative and unsubstituted tetrazolic BAIL **7** (Scheme 4). Starting from commercially available tetrazole **6**, a metathesis exchange between **6** with HTFSI led to the new BAIL **7** in a quantitative yield with an acidity (pK_{a1} = 1.83, Table 4) being comparable with HTFSI (pK_a = 1.90, Table 4). The pK_{a2} value (4.80) corresponds approximately to the pK_a of the corresponding tetrazole without considering any counter-anion effects of $TFSI^-$. TGA curve revealed that ILs **7** is stable until 180° (degradation of the tetrazolium part mainly into N_2).

BAIL **7** was then studied in the direct O-glycosylation reaction. Compared to the others BAILs, **7** led to the octyl mannoside derivative (Table 5, entry 1) in a similar yield. A slight modification has been observed for D-glucose (entry 2) where the glycoside was obtained in 40% yield in the lone pyranoside form whereas in Table 3, the glycoside has been obtained in 14% yield as a mixture of pyranose and furanose.

Similar results were expected with D-galactose, D-fucose, D- and L-arabinose and D-ribose, but the yield could not be improved compared to the result obtained in Table 3 (entries 3, 5, 7, 8, and 9).

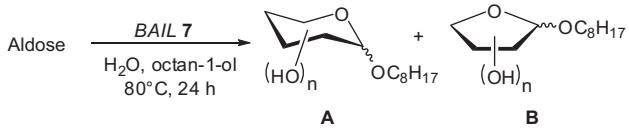
Table 4
pK_a values of BAILs

BAILs	pK_{a1}	pK_{a2}
2	2.25	9.69
3a	2.37	8.34
4a	2.46	8.29
5a	2.58	8.78
HTFSI	1.70	
7	1.83	4.80



Scheme 4.

Table 5
Glycosylation of octan-1-ol using BAIL 7 (10 mol %) as catalyst[a]



Entry	Aldose	Yield[b]	**A**:**B**[c]	**A**α/**A**β[c]	**B**α/**B**β[c]
1	D-Mannose	54	100:0	92/8	/
2	D-Glucose	40	100:0	70/30	/
3	D-Galactose	19	73:27	70/30	31/69
4	D-Xylose	68	94:6	64/36	44/56
5	D-Arabinose	64	72:28	66/34	22/78
6	D-Ribose	72	17:83	64/36	86/14

[a] Typical procedure: sugar, octanol (5 equiv), H_2O (2 equiv), and BAIL (10 mol %) were stirred at 80 °C. After 24 h, water was eliminated by evaporation and the reaction mixture was purified by flash chromatography.
[b] Isolated yield.
[c] Determined by NMR.

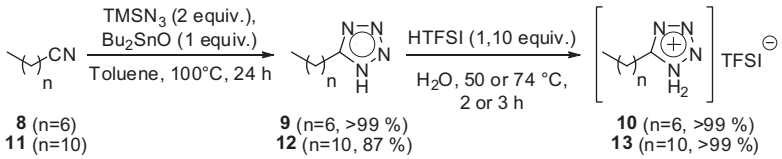
Yield of the reaction involving D-xylose was slightly enhanced with BAIL **7** (68%) in comparison with BAIL **3a** (52%, Table 3, entry 6).

Keeping in mind that pK_{a1} value of **7** (1.83) seems to favourably affect the formation of *O*-glycoside, we decided to undertake the synthesis of two new analogs of **7** with a longest alkyl chain in order to study the influence of their lipophily and their impact on the O-glycosylation reactions. Alkyl chains ranging from 7 to 11 carbons were installed at the position 5 of BAIL **7**. Syntheses of BAILs **10** and **13** are depicted in Scheme 5.

BAILs **10** and **13** were prepared in three steps starting from commercially available alkylnitrile derivatives **8** and **11**. Firstly, they were converted into the corresponding tetrazoles **9** and **12** in 99% and 87% yields, respectively, by reaction with a mixture of trimethylsilyl azide and dibutyltin oxide in toluene. Protonation of **9** and **12** by HTFSI led quantitatively to BAILs **10** and **13**. TGA curves showed that ILs **10** and **13** are stable until 200 and 210 °C, respectively.

2.3. Determination of pK_a

The pK_a values of the BAILs **7**, **10,** and **13** (Table 6) have been determined by titration with NaOH in EtOH. As expected and observed for BAILs **2**, **3a**, **4a,** and **5a**, all the ILs showed 2 pK_a values.

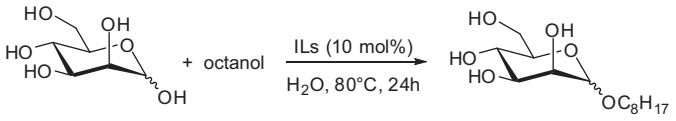


Scheme 5.

Table 6
pK_a values of BAILs

BAILs	pK_{a1}	pK_{a2}
7	0.20	5.45
10	0.34	6.14
13	0.53	5.11

Table 7
Screening of tetrazole-derived BAILs[a]



Entry	BAIL	Yeild[b] (%)	α/β[c]
1	**7**	54	92/8
2	**10**	64	92/8
3	**13**	62	91/9

[a] Typical procedure: D-mannose, octanol (5 equiv), H_2O (2 equiv), and IL (10 mol %) were stirred at 80 °C. After 24 h, water was eliminated by evaporation and the reaction mixture was purified by flash chromatography.
[b] Isolated yield.
[c] Determined by NMR.

pK_{a1} were ranging from 0.20 to 0.53. The strongest acid in the series is IL **7** (pK_{a1} = 0.20). Meanwhile, the second deprotonation step (pK_{a2}) for all the BAILs were ranging from 5.11-6.14.

Compounds **10** and **13** were studied in the reaction model involving D-mannose and octan-1-ol (Table 7). Following our hypothesis, **10** which is structurally similar to octan-1-ol affords the *O*-glycoside derivative with 10% yield higher than tetrazole **7**. BAIL **13** with the longest alkyl chain slightly decreases the yield by 62% suggesting that the reaction can be improved if the alcohols and the BAILs are structurally close in terms of the alkyl chain length. Moreover the results are opposed to pK_{a1} values suggesting that strong pK_{a1} is necessary to optimize the reaction but cannot rule the O-glycosylation by itself. Interactions between the nature of the alcohol and the BAIL must be considered. In Table 1, with close pK_{a1}, BAIL **5a** which is probably less lipophilic clearly shows a yield drop of about 10% compared to the more lipophilic **2** and **3a**/**4a**. In this series, at similar pK_a, the more lipohilic BAIL (**3a**/**4a** > **2** > **5a**) gave better results.

Next, BAIL **13** with the longest alkyl chain was screened in the reaction between D-mannose and different alcohols (Table 8). To our delight, the fatty alcohols heptan-, decan-, and dodecan-1-ol gave better results (58–67% yield) with a classical α-selectivity ruled under thermodynamic control. Interestingly, the yield dropped down to 19% for the reaction with butan-1-ol, highlighting the importance of interactions between the alkyl chain of BAIL **13** and alcohols.

Surprisingly, allylic alcohol, miscible in water, which showed no reactivity with BAIL **3a** (Table 2) allowed the formation of 36% of the corresponding glycosyl derivative with BAIL **13** (See Table 8).

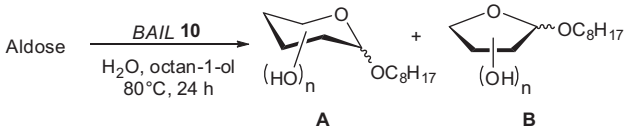
Finally, the O-glycosylation of octan-1-ol with different sugars was re-examined but in this case hexyltetrazole **10** was used

Table 8
Glycosylation of alcohols using BAIL **13** as catalyst[a]

Alcohol	Yield[b]	α/β[c]
n-Butan-1-ol	19	90/10
n-Heptan-1-ol	67	93/7
n-Decan-1-ol	66	92/8
n-Dodecan-1-ol	58	90/10
Cyclohexanol	42	96/4
Allyl alcohol	36	88/22
Propargyl alcohol	31	95/5
Benzyl acohol	Traces	n.d.[d]

[a] Typical procedure: sugar, octanol (5 equiv), H_2O (2 equiv), and BAIL (10 mol %) were stirred at 80 °C. After 24 h, water was eliminated by evaporation and the reaction mixture purified by flash chromatography.
[b] Isolated yield.
[c] Determined by NMR.
[d] Not determined.

Table 9
Glycosylation of octan-1-ol using BAIL **10** (10 mol %) as catalyst[a]



Entry	Aldose	Yield[b]	**A**:**B**[c]	**A**α/**A**β[c]	**B**α/**B**β[c]
1	D-Mannose	64	100:0	92/8	/
2	D-Glucose	53	100:0	72/28	/
3	D-Galactose	22	80:20	74/26	21/79
4	D-Xylose	72	94:6	66/34	50/50
5	D-Arabinose	76	76:24	67/33	25/75
6	D-Ribose	72	15:85	67/33	84/16

[a] Typical procedure: sugar, octanol (5 equiv), H_2O (2 equiv), and BAIL (10 mol %) were stirred at 80 °C. After 24 h, water was eliminated by evaporation and the reaction mixture was purified by flash chromatography.
[b] Isolated yield.
[c] Determined by NMR.

(Table 9). Interestingly, compared with BAIL **3a** (Table 3), BAIL **10** allowed to increase yields in every glycosylation reaction. No differences were observed concerning the α/β anomer ratios and the pyranose/furanose form with this catalyst. In addition, BAIL **10** permitted to improve yields in every case compared with the results obtained with BAIL **7** (Table 5).

3. Conclusions

A series of aminotetrazoles and alkyltetrazoles have been synthesized and used in catalytic quantity as BAIL in water for the direct O-glycosylation of unreactive and unprotected sugars (pentoses and hexoses). The chirality brought about by **3a** and **4a** affected the reactivity less in terms of yield and selectivity (α/β or pyranose/furanose). The second series of alkyltetrazoles showed that the reactivity can be enhanced when the alkyl chain length of the IL and the alcohol alkyl chain are similar. Attempts to recycle the catalyst were unsuccessful. In fact, after flash chromatography, tetrazoles were

the only recovered compounds. Modification of the anion could probably modify the reactivity of the alkyltetrazole. Others reactions such as esterification catalyzed by BAIL would also be tested. This work is in progress and will be reported in due course.

4. Experimental part

4.1. Materials and methods

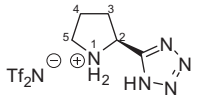
Optical rotations were recorded in CH_3OH or CH_2Cl_2 solution on a digital micropolarimeter Perkin Elmer 343™. ^1H NMR (300.13 MHz) and ^{13}C NMR (75.47 MHz) spectra were recorded in CD_3OD, D_2O, or $CDCl_3$ (internal Me_4Si) respectively, on a Bruker™ Avance-300 spectrometer. TLC was performed on Silica F254 and detection by UV light at 254 nm or by charring with *p*-anisaldehyde–H_2SO_4–AcOH–EtOH reagent. FTIR spectra were obtained on a AVATAR™ 320 neat using ATR and are reported in cm^{-1}. Mass spectral data were acquired on a WATERS Micromass™ Q-TOFF spectrometer. Viscosities were recorded on a Brookfield™ viscosimeter DVII + Pro. TGA experiments were carried out on a Netzsch® STA 449 C *Jupiter*® coupled with a quadrupole mass spectrometer QMS 403 C *Aëlos*®. Samples were placed in a Pt−Rh + Al_2O_3 crucible and then heated up to 1200 °C under air or under an atmosphere of Ar, at 10 K min^{-1}. To determine T_g, T_c, and T_m, DSC experiments were carried out on a Netzsch® DSC 204F1 heat flux differential calorimeter at a heating rate of 10 K min^{-1}, from −100 to 100 °C (cycle done two times), under a constant argon flow of 200 mL min^{-1}. Calibration was performed with indium. Data processing was performed with Proteus software®. When T_g were detected, they were measured at the intersection of the two tangents of the second heating curve at the start of the endothermic phenomenon. Column chromatography was effected on Silica Gel 60 (230 mesh) or using Combiflash companion®/TS with cyclohexane, ethyl acetate and methanol, distilled before use.

4.2. General procedure

4.2.1. Method A: Synthesis of Brønsted acidic ionic liquids (*BAILs*) by protonation of tetrazole derivatives with HTFSI

1.10 Equiv of HTFSI (90% wt. in water) was added to an aqueous solution of tetrazole-substituted α-amino acid, 1*H*-tetrazole-1-ium or 1*H*-5-alkyled tetrazole-1-ium (1.00 equiv). After stirring at least 30 min at rt, water was eliminated by freeze drying to afford pure ionic liquid.

4.2.2. [(*S*)-2-(1*H*-Tetrazol-5-yl)pyrrolidinium][NTf_2] (2)



Following the general method **A**, (*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole **1**[29] (1.00 g, 7.19 mmol, 1.00 equiv) and HTFSI (2.53 g, 7.91 mmol, 1.10 equiv) were dissolved in 25 mL of water to afford compound **2** (3.00 g, >99%) as a slightly orange transparent liquid. $[\alpha]_D^{20}$ +17° (*c* = 0.13, CH_3OH); IR (ATR): *ν* (cm^{-1}) 3178, 2362, 2337, 1653, 1344, 1181, 1128, 1053, 791, 742, 653; $T°_g$: −38.3 °C; $T°_c$: −; $T°_m$: −; $\eta^{25\ °C}$ = 9099 cP; ^1H NMR (D_2O, 300 MHz): *δ* (ppm) 9.56 s, 1H, NH), 9.15 (s, 1H, NH), 5.96 (s, 1H, NH), 5.11 (t, 1H, $J^3_{2,CH2}$ = 7.6 Hz, H-2), 3.42-3.67 (m, 2H, H-5a, H-5b), 2.53–2.75 (m, 1 H, H-3a), 2.12–2.43 (m, 3 H, H-3b, H-4a, H-4b); ^{13}C NMR (D_2O, 75 MHz): *δ* (ppm) 158.2 (NC═N), 120.9 (q, $J^1_{C,F}$ = 320 Hz, 2 × CF_3), 54.8 (C-2), 47.1 (C-5), 30.5 (C-3), 24.2 (C-4); MS (ESI): $[M^+]$ = 140 *m*/*z*, $[M^-]$ = 279.6 *m*/*z*; HRMS calcd for $C_5H_{10}N_5^+$: 140.0936, found: 140.0949. Contains 0.90% of water.

4.2.2. [(*S*)-2-Phenyl-1-(1*H*-tetrazol-5-yl)ethanaminium][NTf_2] (3a)

Following the general method **A**, (*S*)-2-phenyl-1-(1*H*-tetrazol-5-yl)ethanamine **3** (1.01 g, 5.33 mmol, 1.00 equiv) and HTFSI (1.87 g, 5.86 mmol, 1.10 equiv) were dissolved in 25 mL of water to afford compound **3a** (2.48 g, >99%) as a slightly yellow solid. $[\alpha]_D^{20}$ +17° (*c* = 0.13, CH_3OH); IR (ATR): *ν* (cm^{-1}) 3136, 1653, 1628, 1603, 1515, 1495, 1369, 1325, 1181, 1125, 1053, 795, 743, 701; $T°_g$: −7.3 °C; $T°_c$: −; $T°_m$: 90 °C; $\eta^{95\ °C}$ = 2740 cP; ^1H NMR (CD_3OD, 300 MHz): *δ* (ppm) 7.03–7.37 (m, 5H, Ph), 5.10 (s, NH_2), 5.02 (t, 1H, $J^3_{CH,CH2}$ = 7.6 Hz, CH), 3.40 (d, 2H, $J^3_{CH2,CH}$ = 7.6 Hz, CH_2); ^{13}C NMR (CD_3OD, 75 MHz): *δ* (ppm) 159.4 (NC═N), 136.3, 130.5, 130.2, 129, 127.6 (Ph), 121.3 (q, $J^1_{C,F}$ = 320 Hz, 2 × CF_3), 49.3 (CH), 40.0 (CH_2); MS (ESI): $[M^+]$ = 189.7 *m*/*z*, $[M^-]$ = 279.8 *m*/*z*; HRMS calcd For $C_9H_{12}N_5^+$: 190.1093, found: 190.1102. Contains 1.30% of water.

4.2.3. [(*R*)-2-Phenyl-1-(1*H*-tetrazol-5-yl)ethanaminium][NTf_2] (4a)

Following the general method **A**, (*R*)-2-phenyl-1-(1*H*-tetrazol-5-yl)ethanamine **4** (0.41 g, 2.15 mmol, 1.00 equiv) and HTFSI (1.87 g, 2.43 mmol, 1.13 equiv) were dissolved in 15 mL of water to afford compound **4a** (2.48 g, >99%) as a slightly yellow solid. $[\alpha]_D^{20}$ −15° (*c* = 0.13, CH_3OH); IR (ATR): *ν* (cm^{-1}) 3125, 1652, 1629, 1603, 1515, 1495, 1370, 1325, 1181, 1125, 1053, 796, 743, 701; $T°_g$: 3.4 °C; $T°_c$: −; $T°_m$: 85 °C; $\eta^{95\ °C}$ = 2740 cP; ^1H NMR (CD_3OD, 300 MHz): *δ* (ppm) 7.09–7.43 (m, 5H, Ph), 5.13 (s, NH_2), 5.02 (t, 1H, $J^3_{CH,CH2}$ = 7.6 Hz, CH), 3.40 (d, 2H, $J^3_{CH2,CH}$ = 7.6 Hz, CH_2); ^{13}C NMR (CD_3OD, 75 MHz): *δ* (ppm) 159.3 (NC═N), 135.2, 130.4, 130.2, 129.0 (Ph), 121.2 (q, $J^1_{C,F}$ = 320 Hz, 2 × CF_3), 49.3 (CH), 40 (CH_2); MS (ESI): $[M^+]$ = 189.7 *m*/*z*, $[M^-]$ = 279.8 m/z; HRMS calcd. For $C_9H_{12}N_5^+$: 190.1093, found: 190.1101. Contains 0.58% of water.

4.2.4. [(*S*)-1-Methyl-1-(1*H*-tetrazol-5-yl)ethanaminium][NTf_2] (5a)

Following the general method **A**, (*S*)-1-(1*H*-tetrazol-5-yl)ethanamine **5** (0.17 g, 1.50 mmol, 1.00 equiv) and HTFSI (0.49 g, 1.58 mmol, 1.05 equiv) were dissolved in 7 mL of water to afford **5a** (0.59 g,>99%) as a slightly yellow solid. $[\alpha]_D^{20}$ −4° (*c* = 0.15, CH_3OH); IR (ATR): *ν* (cm^{-1}) 3561, 3163, 1652, 1520, 1343, 1184, 1128, 1052, 792, 743, 654; $T°_g$: −44.3 °C; $T°_c$: −; $T°_m$: −; $\eta^{25\ °C}$ = n.d.; ^1H NMR (CD_3OD, 300 MHz): *δ* (ppm) 5.10 (s, NH_2), 4.90 (q, 1H, CH, $J^3_{CH,CH3}$ = 6.9 Hz), 1.75 (d, 3H, CH_3, $J^3_{CH3,CH}$ = 7.0 Hz); ^{13}C NMR (D_2O, 75 MHz): *δ* (ppm) 156.2 (NC═N), 118.9 (q, $J^1_{C,F}$ = 320 Hz, 2 × CF_3), 42.2 (CH), 16.8 (CH_3); MS (ESI): $[M^+]$ = 114.1 m/z, $[M^-]$ = 280 *m*/*z*; HRMS calcd. for $C_3H_8N_5^+$: 114.0780, found 114.0786. Contains 1.05% of water.

4.2.5. [1*H*-Tetrazol-1-ium][NTf_2] (7)

Following the general method **A**, 1*H*-tetrazole **6** (CAS number: 288-94-8) (0.50 g, 7.00 mmol, 1.00 equiv) and HTFSI (2.40 g, 7.70 mmol, 1.10 equiv) were dissolved in 10 mL of water to afford BAIL **7** (2.45 g, >99%) as a yellow transparent liquid. IR (ATR): *ν* (cm^{-1}) 3114, 2893, 1539, 1340, 1317, 1186, 1119, 1052, 792, 743, 653, 640; $T°_g$: −49.6 °C; $T°_c$: −; $T°_m$: −; $\eta^{25\ °C}$ = 1500 cP; ^1H NMR (CD_3OD, 300 MHz): *δ* (ppm) 9.48 (s, 1H, H-5), 7.90 (s, NH); ^{13}C NMR (CD_3OD, 75 MHz): *δ* (ppm) 143.4 (C-5), 120.8 (q, $J^1_{C,F}$ = 320.1 - Hz, 2 × CF_3); MS (ESI): $[M^+]$ = 71.1 *m*/*z*, $[M^-]$ = 279.8 m/z; HRMS calcd for $CH_3N_4^+$: 71.0358, found 71.0343. Contains 1.75% of water.

4.2.6. [5-Heptyl-1*H*-tetrazol-1-ium][NTf_2] (10)

Following the general method **A**, 5-heptyl-1*H*-tetrazole **9**[30] (0.50 g, 2.97 mmol, 1.00 equiv) and HTFSI (1.02 g, 3.03 mmol,

1.10 equiv) were dissolved in 10 mL of water to afford BAIL **10** (1.33 g, >99%) as a slightly yellow syrup. IR (ATR): ν (cm^{-1}) 3521, 3124, 2934, 2861, 1608, 1347, 1198, 1136, 1059, 794, 743, 656; $T°_g$: −62.7 °C; $T°_c$: −; $T°_m$: −; $\eta^{25\,°C}$ = 689 cP; ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm) 5.30 (s, NH), 3.03 (t, 2H, $J^3_{CH2,CH2}$ = 7.8 Hz, =CCH_2), 1.70–1.89 (m, 2 H, CH_2), 1.20–1.47 (m, 6 H, 3 x CH_2), 0.88 (t, 3H, $J^3_{CH3,CH2}$ = 6.8 Hz, CH_3); ^{13}C NMR (CD_3OD, 75 MHz): δ (ppm) 157.7 (C_5), 121.2 (q, $J^1_{C,F}$ = 320.5 Hz, 2 × CF_3), 32.8, 30.0, 29.8, 28.0, 23.9, 23.6 (6 × CH_2), 14.4 (CH_3); MS (ESI): [M^+] = 169.0 m/z, [M^-] = 279.7 m/z; HRMS calcd. for $C_8H_{17}N_4^+$: 169.14477, found 169.14487. Contains 1.18% of water.

4.2.7. [5-undecyl-1*H*-tetrazol-1-ium][NTf_2] (13)

Following the general method **A**, 5-undecyl-1*H*-tetrazole **12**[30] (0.20 g, 0.89 mmol, 1.00 equiv) was heated at 80 °C, then HTFSI (0.28 g, 0.89 mmol, 1.00 equiv) was added and the reaction mixture was stirred for 30 min to afford BAIL **13** (0.45 g, >99%) as a slightly yellow syrup. IR (ATR): ν (cm^{-1}) 3522, 3111, 2928, 2857, 1607, 1468, 1347, 1200, 1135, 1060, 793, 743, 654; $T°_g$: −; $T°_c$: −30.7 °C; $T°_m$: 11.4 °C; $\eta^{25\,°C}$ = 729 cP; ^{1}H NMR (CD_3OD, 300 MHz): δ (ppm) 5.44 (s, NH), 3.01 (t, 2 H, $J^3_{CH2,CH2}$ = 7.8 Hz, =CCH_2), 1.70–1.90 (m, 2H, CH_2), 1.17–1.47 (m, 16 H, 8 × CH_2), 0.88 (t, 3H, $J^3_{CH3,CH2}$ = 6.8 Hz, CH_3); ^{13}C NMR (CD_3OD, 75 MHz): δ (ppm) 157.7 (C_5), 121.3 (q, $J^1_{C,F}$ = 320.0 Hz, 2 × CF_3), 33.1, 30.7, 30.6, 30.5, 30.2, 30.0, 28.1, 23.9, 23.8 (10 × CH_2), 14.5 (CH_3); MS (ESI): [M^+] = 225.1 *m*/*z*, [M^-] = 279.7 *m*/*z*; HRMS calcd. for $C_{12}H_{25}N_4^+$: 225.2079, found 225.2088; Contains 0.83% of water.

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