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O-Glycosidation reactions promoted by in situ generated silver N-heterocyclic carbenes in ionic liquids

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ABSTRACT

We herein report O-glycosidation reactions promoted via silver N-heterocyclic carbene complexes formed in situ in ionic liquids. Seven different room temperature ionic liquids were screened for the glycosidation reaction of 4-nitrophenol with tetra-*O*-acetyl-α-D-galactopyranosyl bromide. Good to excellent yields were obtained using Ag–NHC complexes derived from imidazolium halide salts to promote the glycosidation reaction, whereas yields considered moderate to low were obtained without use of the silver carbene complex. Anion metathesis of the ionic liquids with inexpensive alkylammonium halides also resulted in silver *N*-heterocyclic carbene formation and subsequent O-glycosidation in the presence of silver carbonate. Effective utility of this methodology has been demonstrated with biologically relevant acceptors (including flavones and steroids) where O-β-glycoside products were obtained selectively in moderate to good yields. We have also demonstrated that the Ag–NHC complex is a superior promoter to traditionally used silver carbonate for the glycosidation of polyphenolic acceptors. The ionic liquids used in the study could be recycled three times without apparent loss in activity.

1. Introduction

The investigations of stereoselective glycosidation reactions, driven by the need to synthesize therapeutically active carbohydrates,[1–3] have led to numerous advances in donor, acceptor, promoter, and solvent technology.[4–6] There have been a number of reports in this context describing the use of ionic liquids (ILs) as both solvents and promoters for glycosidation reactions.[7–9] A few examples of IL-facilitated glycosidation reactions include acid-promoted O- and C-glycosidation of glycosyl fluorides with aliphatic or aromatic alcohols in imidazolium-based ILs,[10,11] IL-mediated stereoselective addition of aliphatic alcohols to trichloroacetimidate donors in the presence of a Lewis acid,[12,13] and IL-promoted reaction of thioglycosides and trichloroacetimidates with aliphatic alcohols.[14,15] The benefits of employing ILs over traditional organic solvents and promoters often include higher product yields, control over reaction stereoselectivity, and recyclability of the IL solvent.

In our ongoing effort to produce therapeutically relevant carbohydrates for the treatment of cancer, we recently reported on halide molten salts as novel glycosidation media for Koenigs–Knorr type reactions.[16] This method produced O-glycosides in high yields under ambient atmosphere without using molecular sieves, although it required high reaction temperatures that might be unsuitable for sensitive substrates. As a result of this study, we subsequently identified silver N-heterocyclic carbene (Ag–NHC) complexes of imidazolium salts as promoters for O-glycosidation reactions of various steroid, coumarin, and flavone acceptors with glycosyl halide donors (Fig. 1).

This method produced O-glycoside derivatives in yields considered to be good to excellent in traditional organic solvents, and the reaction mechanism involved the dual role of Ag–NHC complexes as heavy metal ion sources and as bases. We herein describe an in-depth study of room temperature IL (RTIL) mediated O-glycosidation reactions promoted by Ag–NHC complexes generated in situ from imidazolium halides, which are present either as additives or generated by anion metathesis.

2. Results and discussion

Glycosidation reactions of tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**1a**) and 4-nitrophenol were performed with silver carbonate in various imidazolium RTILs both in the absence or presence of the corresponding imidazolium chloride. In general, glycosidation yields without imidazolium chloride were low regardless of the nature of the RTIL anion or cation (Table 1, entries 1–10). Previously, we demonstrated that treatment of imidazolium halide salts with silver carbonate generated Ag–NHC complexes that subsequently promoted O-glycosidation reactions.[16] Therefore, to see the effect of the added salt, we next doped the RTILs with the corresponding imidazolium halide. As expected,

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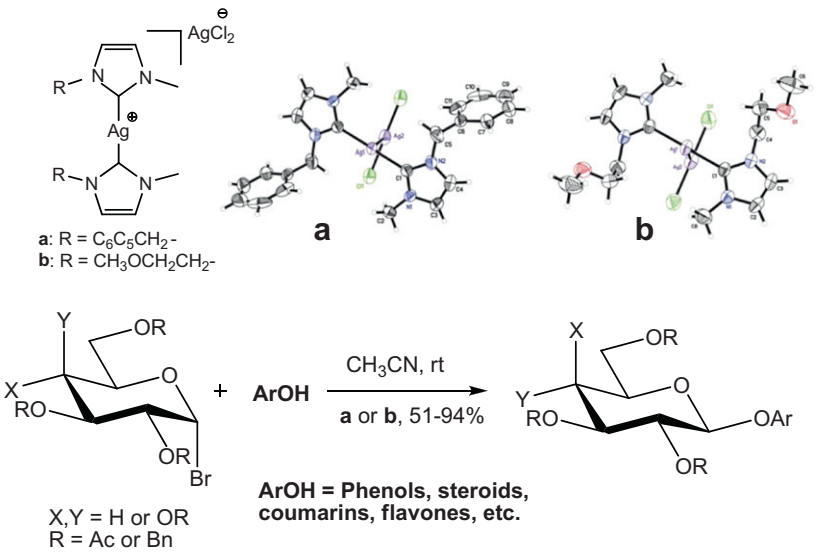
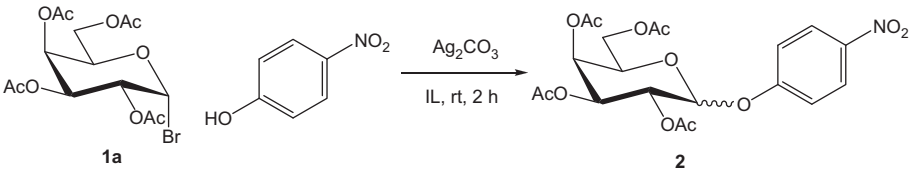


Figure 1. Glycosidation reactions promoted by isolated Ag–NHC complexes **a** and **b** in acetonitrile.

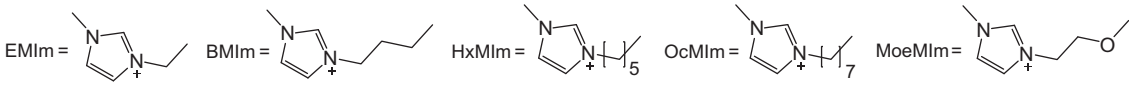
Table 1
Effect of chloride salts on glycosidation of tetra-*O*-acetyl-α-D-galactopyranosyl bromide and *p*-nitrophenol in RTILs[a]



Entry	IL[b]	Isolated yield (%)	α:β ratio	Entry	IL[b]/Cl⁻ additive[c]	Isolated yield (%)	α:β ratio
1	BMIm·OTf	16	nd[d]	11	BMIm·OTf/BMIm·Cl	83	β only
2	BMIm·Tf_2N	33	nd[d]	12	BMIm·Tf_2N/BMIm·Cl	80	β only
3	BMIm·PF_6	18	nd[d]	13	BMIm·PF_6/BMIm·Cl	80	β only
4	EMIm·BF_4	41	β only	14	EMIm·BF_4/EMIm·Cl	69	β only
5	BMIm·BF_4	21	β only	15	BMIm·BF_4/BMIm·Cl	82	β only
6	HxMIm·BF_4	46	β only	16	HxMIm·BF_4/HxMIm·Cl	81	β only
7	OcMIm·BF_4	24	β only	17	OcMIm·BF_4/OcMIm·Cl	82	β only
8	BMIm·$N(CN)_2$	33	nd[d]	18	BMIm·$N(CN)_2$/BMIm·Cl	59	β only
9	MoeMIm·Ms	14	β only	19	MoeMIm·Ms/MoeMIm·Cl	67	nd[d]
10	MoeMIm·Tf_2N	37	nd[d]	20	MoeMIm·Tf_2N/MoeMIm·Cl	79	β only

[a] Reactions were pre-stirred in the RTILs (1.5 g) with Ag_2CO_3 (2 equiv) and *p*-nitrophenol (3 equiv) at room temperature (rt) for 5–15 min; tetra-*O*-acetyl-α-D-galactopyranosyl bromide (1 equiv) was then added and the mixture was stirred at rt for 2 h.

[b] Structures of IL cations:



[c] The mixture of Cl^- additive (2 equiv) and the IL (1.5 g) was pre-stirred with phenol and base for 1 h and the reaction was performed as in (a).

[d] nd = not determined.

formation of Ag–NHC complexes (vide infra) by pre-stirring silver carbonate and imidazolium chloride in the RTIL for one hour had a dramatic effect on the reaction. Yields improved by 50–60% utilizing in situ Ag–NHC complexes instead of silver carbonate (Table 1, entries 11–20). The yield in 1-butyl-3-methylimidazolium dicyanamide [BMIm·$N(CN)_2$] was slightly lower than the yields resulting from the use of other anions (Table 1, compare 11–13, 15, and 18). 1-Ethyl-4-methylimidazolium tetrafluoroborate (EMIm·BF_4) did not perform as efficiently as RTILs with longer alkyl cations having the same anion (Table 1, compare 14–17). Further optimization studies revealed that increasing the reaction temperature had no effect on the overall yield, while bases, such as NaH, Cs_2CO_3, K_2CO_3, and LiOH were ineffective for the transformation. Interestingly, the ability of NHC carbenes to act as strong bases has been previously reported. For example, Alder et al. demonstrated that the conjugate acid of 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene, an imidazolium carbene structurally similar to our N-heterocylic carbene, had a pK_a of 24 in DMSO, which made it significantly more basic than 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicycloundec-7-ene (DBU).[17] Given our previous report describing the merits of Ag–NHCs in similar reactions, the higher yields that were obtained with in situ complexes suggested that they act as sources of carbene bases and heavy metal ions that were more effective in promoting the glycosidation reaction than silver carbonate. We speculate that this may be due, in part, to more efficient deprotonation of the phenol by the carbene.

Table 2
Effect of different halide salts as metathesis promoters on glycosidation of tetra-*O*-acetyl-α-D-galactopyranosyl bromide and *p*-nitrophenol in BMIM·BF_4[a]

Entry	Halide salts	Isolated yield (%)	α:β ratio
1	Tetrabutylammonium chloride (TBACl)	84	β only
2	Tetrabutylammonium bromide (TBABr)	82	β only
3	Tetrabutylammonium iodide (TBAI)	79	β only
4	Benzyltriethyltetraammonium chloride (BTEACl)	87	β only
5	Benzyltriethyltetraammonium bromide (BTEABr)	79	β only

[a] BmIM·BF_4 (1.5 g), halide source (2 equiv), Ag_2CO_3 (2 equiv) and 4-nitrophenol (3 equiv) were premixed at rt for 1 h followed by addition of tetra-*O*-acetyl-α-D-galactopyranosyl bromide (1 equiv), and the mixture was stirred at rt for 2 h.

Although the ionic liquid was easily recycled (vide infra) using current protocol, the expensive imidazolium halides were consumed during the course of the reaction. Toward developing a method amenable to process applications, we decided to test inexpensive and readily available ammonium halide salts in metathesis reactions with imidazolium RTILs. The ability of imidazolium salts to undergo halide exchange reactions is well known in the literature. For example, the exchange of iodide with chloride was reported by Lin and co-workers when imidazolium iodide salts were reacted with silver in dichloromethane.[18] We examined a series of ammonium salts as halide sources for the model reaction of tetra-*O*-acetyl-α-D-galactopyranosyl bromide with 4-nitrophenol in the presence of silver carbonate and BMIm·BF_4. The results are summarized in Table 2. In all cases, the yields were significantly improved via the addition of ammonium salts (compare Table 2, entries 1–5 with Table 1, entry 1). In some cases, the yields were higher with alkylammonium chlorides than with imidazolium chlorides (compare Table 2, entries 1 and 4 with Table 1, entries 11–20). Tetrabutylammonium chloride (TBACl) performed slightly better than its bromide and iodide analogs (Table 2, compare entries 1–3) as did benzyltriethylammonium chloride (BTEACl) compared with its bromide analog. Although the difference in yields may be within the range of experimental error, this trend correlated with the order of stability of halogeno Ag–NHC complexes, which increases from chloride to iodide.[19]

In situ formation of Ag–NHC complexes via metathesis with alkylammonium halides was supported by ^1H and ^{13}C NMR spectroscopy. The mixture of silver carbonate (1 equiv), BTEACl (1 equiv), and BMIm·BF_4 (1 equiv) was stirred for 3 h at room temperature and analyzed by ^1H NMR spectroscopy using $CDCl_3$ as solvent. For comparison, the ^1H NMR of BMIm·BF_4 and BMIm·Cl were taken under identical conditions. As the mechanism of Ag–NHC carbene formation involves abstraction of the H2 imidazolium proton, H2 signals of imidazolium halides disappear when they are converted to Ag–NHC complexes. The ^1H NMR spectra of BMIm·BF_4, BMIm·Cl, and the above mixture illustrated the loss of the H2 imidazolium proton which suggested in situ carbene formation under our reaction protocol (Fig. 2). While NMR solvents, such as D_2O and DMSO-d_6, have been known to undergo deuterium exchange with the labile H2 proton of imidazolium salts, we did not observe this phenomenon with $CDCl_3$ under our experimental conditions for BMIm·Cl and BMIm·BF_4. A ^{13}C NMR spectrum in

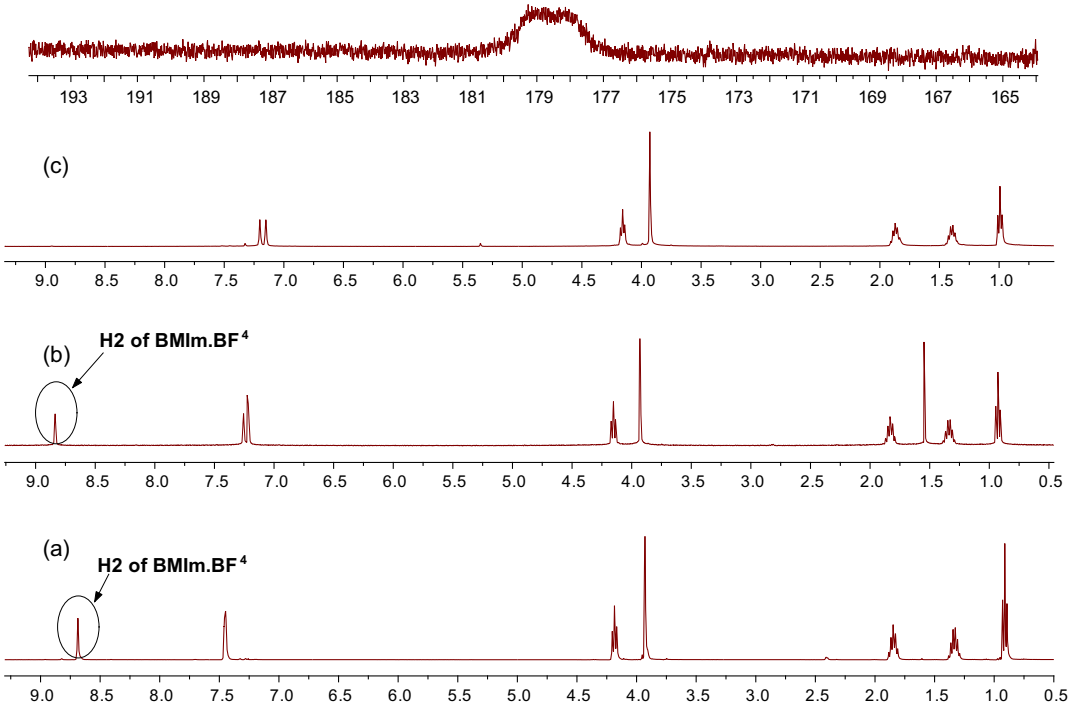


Figure 2. (a) ^1H NMR spectra of BMIm·BF_4; (b) ^1H NMR spectra of BMIm·BF_4 (1 equiv) + Ag_2CO_3 (1 equiv) after stirring for 3 h; (c) ^1H NMR spectra of BMIm·BF_4 (1 equiv) + BTEACl (1 equiv) + Ag_2CO_3 (1 equiv) after stirring for 3 h; (d) ^{13}C NMR spectra of a mixture of BMIm·BF_4 (1.5 g), BTEACl (1.5 mmol), and Ag_2CO_3 (1.5 mmol) showing the appearance of the carbene resonance.

CD_2Cl_2 was also obtained of a mixture of BMIm·BF_4 (1.5 g), BTEACl (1.5 mmol), and Ag_2CO_3 (1.5 mmol). A weak, broad resonance was observed at 179.8 ppm which was characteristic of an Ag–NHC complex (Fig. 2d). The low intensity of the signal was most likely due to the high dilution of the species in BMIm·BF_4 and the large number of species present in the sample mixture (e.g., BMIm·BF_4, BTEABF_4, and Ag–NHC). A mixture of silver carbonate and BMIm·BF_4 that lacked a halide ion source did not produce the Ag–NHC complex as observed by ^{1}H and ^{13}C NMR spectroscopy. Thus, halide exchange with the RTIL anion appears to be a prerequisite for carbene formation.

We next examined the glycosidation of various simple and complex phenol acceptors with the goal of developing efficient methodology to synthesize therapeutically relevant aromatic O-glycosides. The biological activity of these types of compounds is well known in the literature. For example, chimeric hybrids of novobiocin and derrubone were recently reported by Blagg and co-workers to have antiproliferative activity against SkBr3 and MCF-7 breast cancer cell lines.[20] Steroid glycosides such as estradiol-β-3-glucoside have been evaluated in hormone replacement therapies,[21] and glycosylated coumarin derivatives have been evaluated as prodrugs for antifungal therapy;[22] in the latter case, glycosidation was employed as a means to increase coumarin solubility. To screen the arylation of **1a** using these types of substrates, we chose BTEACl as our halide additive. The results are summarized in Tables 3 and 4. Simple phenols with electron-withdrawing groups gave higher yields compared to those with neutral or electron-donating substituents (Table 3, compare entries 1–11) with the exception of trifluoromethyl substituted acceptors. Galactosyl bromide **1a** produced higher yields than the corresponding glucosyl bromide **1b** due to the increased tendency of **1b** to undergo β-elimination (Table 3: compare entries 2, 4, and 10 with Table 4, entries 1–3). For example, when 4-nitrophenol was coupled with **1b**, 47% of glycoside **3a** and 36% of the elimination product were isolated after column chromatography. All reactions with flavones (Table 3, entries 13, 14, and 18), isoflavone (Table 3, entry 15), chromanone (Table 3, entry 16), and coumarin (Table 3, entry 17) afforded corresponding glycoside derivatives in good to excellent yields. This is in contrast to reactions performed with silver carbonate in organic solvents. For example, reaction of 7-hydroxyflavone with **1a** in acetonitrile using silver carbonate gave only 32% of the glycoside product after 24 h, whereas silver carbene-promoted glycosidation afforded 59% of the product in 3 h (Table 3, entry 13). Thus, Ag–NHC complexes may be superior promoters to silver carbonate for O-glycosidation of polyphenolic acceptors. In the case of 3,7-dihydroxyflavone (Table 3, entry 14), a 1:7 separable mixture of monoglycoside **2n** and diglycoside **2o** was produced. Interestingly, monoglycosidation was observed only in the vinylic hydroxyl group suggesting that it may be more reactive toward O-glycosidation under our reaction conditions. A similar observation was made for the reaction of 3,3′-dihydroxyflavone, where glycosidation occurred exclusively in the vinylic hydroxyl group (Table 3, entry 18). All of the products were isolated exclusively as the β anomer with the exception of compound **2c**, which was isolated as a 10:90 α:β mixture. The reactions were complete within 3 h upon addition of glycosyl bromide, and little decomposition to anomeric hydroxide was observed in the absence of molecular sieves or inert conditions. In contrast, reaction with carbohydrate acceptors such as tetra-*O*-acetyl-D-glucopyranose, tetra-*O*-acetyl-D-galactopyranose, and tetra-*O*-benzyl-D-glucopyranose resulted primarily in decomposition of the halide donor to the anomeric hydroxide. For the reaction of tetra-*O*-acetyl-D-galactopyranose with **1a**, the acceptor was recovered by column chromatography in addition to a small quantity of peracetylated galactose as determined by LC–MS and ^{1}H NMR spectroscopy of the pure fractions. No disaccharide was isolated from the reaction mixture. This suggested that an acidic hydroxyl group was necessary for glycosidation reactions using in situ Ag–NHC complexes.

To examine the recyclability of RTILs with this methodology, we repeated multiple coupling cycles of 4-nitrophenol with **1a** in BMIm·BF_4. In this case, an aqueous workup was used to separate the water-soluble BMIm·BF_4 from the product, which was extracted into dichloromethane. Drying and concentrating the organics in vacuo afforded a syrup, which was purified by flash chromatography to give the product; the IL was recovered from the aqueous layer. In this manner, BMIm·BF_4 was used for three cycles with no loss of product yield (Table 5). Trace metal analysis of the recovered IL showed only 246 ppm of silver, and CHNCl analysis showed 0.28% of chlorine. The results suggested that the majority of Ag_2CO_3 and BTEACl are consumed during the course of the reaction and workup.

3. Conclusion

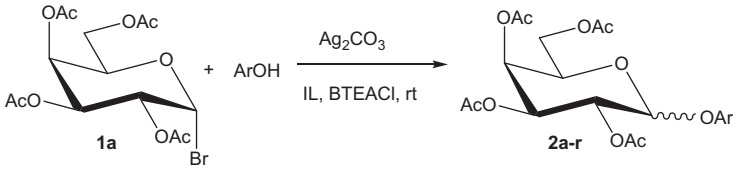
In conclusion, we have shown the application of in situ generated Ag–NHC complexes in RTILs for efficient and selective O-glycosidation reactions. The results suggest that Ag–NHC complexes are superior promoters to traditional heavy-metal bases for glycosidation reactions of glycosyl halides with polyphenolic acceptors, which are therapeutically valuable substrates. The method is particularly amenable to process development because inexpensive alkylammonium halides can be used to promote Ag–NHC formation via anion metathesis with imidazolium RTILs. Formation of the Ag–NHC complex in situ has the advantage of circumventing its preparation and storage, and the RTIL reaction medium can be easily recovered and reused in subsequent glycosidations. High yields were obtained using commercially available donors with a variety of simple and biologically relevant phenolic acceptors under ambient conditions.

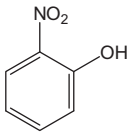
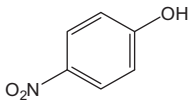
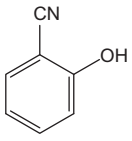
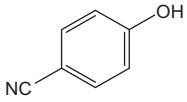
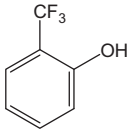
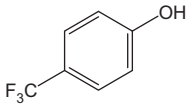
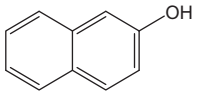
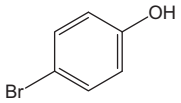
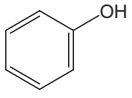
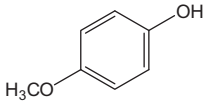
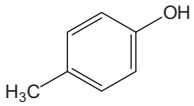
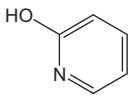
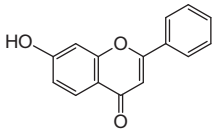
4. Experimental

4.1. General methods

TLCs were run on pre-coated E. Merck Silica Gel 60 F254 plates and observed by charring with 3.5% H_2SO_4–1% AcOH–2.5% *p*-anisaldehyde–EtOH and with UV light. The products were isolated and purified using a Teledyne ISCO Rf flash chromatography system with hexanes and EtOAc as eluents. For verification of the product and purity analysis, the LC–MS was taken on an Agilent 1200 series system with an Agilent 6210 Time-Of-Flight (TOF) mass detector. The ^{1}H (400 MHz), ^{13}C (101 MHz), gCOSY and gHSQC NMR spectra were taken on a Varian 400MR spectrometer. Chemical shifts (δ) are expressed in ppm, coupling constants (J) are expressed in hertz (Hz), and splitting patterns are described as follows: s = singlet; d = doublet; t = triplet; q = quartet; q_{AB} = AB quartet; quintet; sextet; septet; br = broad; m = multiplet; dd = doublet of doublets; dt = doublet of triplets; td = triplet of doublets; ddd = doublet of doublet of doublets. Trace metal (ICP–OES) and elemental analyses were performed by Robertson Microlit Laboratories, Ledgewood, NJ, USA. All the imidazolium ionic liquids used in this study were purchased from E. Merck KgaA (EMD Chemicals), Darmstadt, Germany. 1-Butyl-3-methyl imidazolium chloride (BMIm·Cl) and all other chemicals were purchased from Sigma–Aldrich Chemical Co. and used without any further purification. The spectral characteristics of previously reported compounds **2a–g**, **2i**, **2j**, **2m**, **2p–r**, and **3a–c** were analyzed and determined to be consistent with literature values.

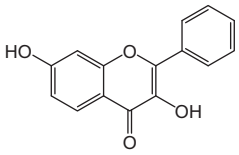
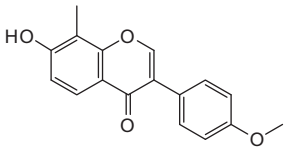
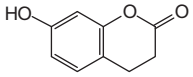
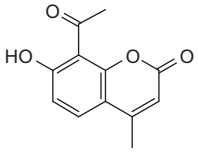
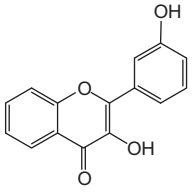
Table 3
Glycosidation of **1a** and different acceptors in RTILs using TBEAC and silver carbonate[a]



Entry	Acceptor (ArOH)	Product	Isolated yield (%)	
			$BMIm{\cdot}BF_4$/α:β ratio	$BMIm{\cdot}PF_6$/α:β ratio
1		**2a**	94/β only	90/β only
2		**2b**	88/β only	82/nd[b]
3		**2c**	91/10:90	92/9:91
4		**2d**	72/β only	76/β only
5		**2e**	60/β only	61/β only
6		**2f**	59/β only	61/β only
7		**2g**	70/β only	57/β only
8		**2h**	82/β only	–
9		**2i**	63/β only	–
10		**2j**	63/β only	–
11		**2k**	62/β only	–
12		**2l**	51/β only	–
13		**2m**	59/β only	–

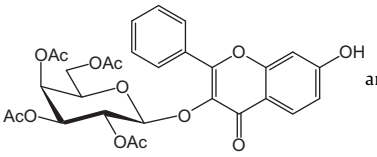
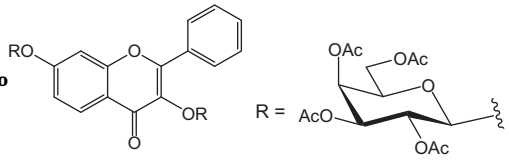
(*continued on next page*)

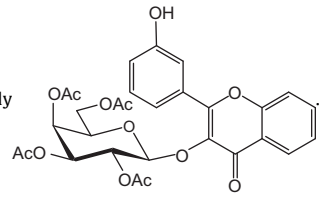
Table 3 (*continued*)

Entry	Acceptor (ArOH)	Product	Isolated yield (%)	
			$BMIm{\cdot}BF_4$/α:β ratio	$BMIm{\cdot}PF_6$/α:β ratio
14		**2n/2o**	74(11[c])/both β only	–
15		**2p**	76/β only	–
16		**2q**	79/β only	–
17		**2r**	82/β only	–
18		**2s**	69[d]/β only	–

[a] BmIM·BF_4 (1.5 g), BTEACl (2 equiv) and Ag_2CO_3 (2 equiv) were premixed at rt for 1 h followed by addition of ArOH (1.5 equiv) and tetra-*O*-acetyl-α-D-galactopyranosyl bromide (1 equiv); the mixture was stirred at rt for 3 h.

[b] nd = not determined.

[c] Isolated monoglycoside **2n**  and diglycoside **2o** 

[d] Isolated monoglycoside **2s** only 

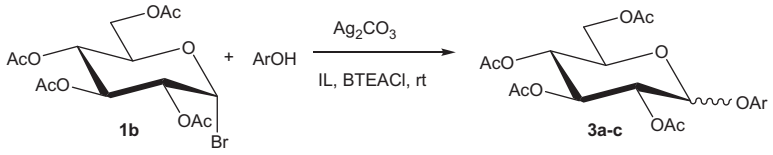
4.2. General procedure for glycosidation of 1a and 4-nitrophenol in RTILs

The ionic liquid (1.5 g), Ag_2CO_3 (2 equiv) and 4-nitrophenol (3 equiv) were mixed together in a 14-mL borosilicate glass vial. The mixture was stirred at 25 °C for 15 min followed by addition of **1a** (0.7 mmol). To check the progress of the reaction, a small aliquot of the reaction mixture was taken out and diluted with dichloromethane, and this solution was used for TLC spotting. The TLC was performed using an 40:60 EtOAc–hexanes solvent system as the mobile phase. After completion of the reaction in approximately 3 h, the reaction mixture was diluted with 1–2 mL of dichloromethane and loaded onto a silica gel cartridge for product isolation by flash chromatography using a gradient of EtOAc–hexanes (0–40% EtOAc). The desired product was obtained as white foam; the yields with corresponding RTILs are given in Table 1.

4.3. General procedure for glycosidation of 1a and 4-nitrophenol in RTILs with halide additive

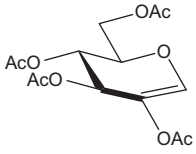
Ag_2CO_3 (2 equiv) and the halide salt (2 equiv) were stirred in the RTIL (1.5 g) at room temperature for 1 h followed by addition of 4-nitrophenol (3 equiv). After 20 min at 25 °C, **1a** (0.7 mmol) was added to the reaction mixture. To check the progress of the reaction, a small aliquot of the reaction mixture was taken out and diluted with dichloromethane, and this solution was used for TLC spotting. The TLC was performed using an 40:60 EtOAc–hexanes solvent system as the mobile phase. After completion of the reaction in approximately 3 h, the reaction mixture was diluted with 1–2 mL of CH_2Cl_2 and loaded onto a silica gel cartridge for product isolation by flash chromatography using a gradient of EtOAc–hexanes (0–40% EtOAc). The desired product was obtained as white foam, and the yields with corresponding RTILs are given in Tables 1 and 2.

Table 4
Glycosidation of **1a** using in situ generated Ag–NHC complexes[a]



Entry	Acceptor	Product	Isolated yield (%)	α:β ratio
1	4-Nitrophenol	**3a**	47/36[b]	nd[c]
2	4-Cyanophenol	**3b**	35	β only
3	4-Methoxyphenol	**3c**	37	β only

[a] BmIM·BF_4 (1.0 g), BTEACl (2 equiv), and Ag_2CO_3 (2 equiv) were premixed at rt for 1 h followed by addition of ArOH (3 equiv) and **1a** (0.24 mmol); the mixture was stirred at rt for 3 h.
[b] Isolated elimination product.



[c] Not determined.

Table 5
Recycling of BMIm·BF_4 from glycosidation of **1a** with *p*-nitrophenol[a]

No. of cycle	Isolated yield (%)	α:β ratio
0	82	β only
1	80	β only
2	78	β only

[a] BmIM·BF_4 (1.0 g), BTEACl (2 equiv), and Ag_2CO_3 (2 equiv) were premixed at rt for 1 h followed by addition of 4-nitrophenol (3 equiv) and **1a** (0.24 mmol); the mixture was stirred at rt for 3 h.

4.4. General procedure for glycosidation of 1a with various phenols in BMIm·BF_4 or BMIM·PF_6

Ag_2CO_3 (2 equiv) and BTEACl (2 equiv) were stirred in the RTIL (1.5 g) at room temperature for 1 h followed by addition of phenol (1.5 equiv). After 20 min at 25 °C, **1a** (0.7 mmol) was added to the reaction mixture. To check the progress of the reaction, a small aliquot of reaction mixture was taken out and diluted with CH_2Cl_2, and this solution was used for TLC spotting. The TLC was performed using an 40:60 EtOAc–hexanes solvent system as the mobile phase. After completion of the reaction in approximately 3 h, the reaction mixture was diluted with 1–2 mL of CH_2Cl_2 and loaded onto a silica gel cartridge for product isolation by flash chromatography using a gradient of EtOAc–hexanes (0–40% EtOAc). The desired product was obtained as white foam, and the yields with corresponding RTILs are given in Table 3.

4.4.1. *p*-Bromophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (2h)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 5.47 (dd, J = 8.6, 6.1 Hz, 1H), 5.45 (d, J = 3.5 Hz, 1H), 5.11 (dd, J = 10.4, 3.4 Hz, 1H), 5.00 (d, J = 7.9 Hz, 1H), 4.19 (ddd, J = 17.5, 11.3, 6.6 Hz, 2H), 4.05 (t, J = 6.7 Hz, 1H), 2.18 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.43, 170.31, 170.20, 169.44, 156.05, 132.60 (2C's), 118.90 (2C's), 115.97, 99.76, 71.24, 70.86, 68.67, 66.93, 61.46, 20.84, 20.77, 20.69. LC–MS (ESI-TOF): $[M+Na]^+$ calcd for $C_{20}H_{23}BrO_{10}$+Na, m/z 525.0367; found, m/z 525.0315.

4.4.2. *p*-Tolyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (2k)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (dd, J = 8.7, 0.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.47 (dd, J = 9.8, 7.3 Hz, 1H), 5.45 (dd, J = 3.3, 1.1 Hz, 1H), 5.10 (dd, J = 10.5, 3.4 Hz, 1H), 4.99 (d, J = 8.0 Hz, 1H), 4.20 (ddd, J = 27.9, 11.3, 6.7 Hz, 2H), 4.04 (td, J = 6.9, 1.1 Hz, 1H), 2.30 (s, 3H), 2.18 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.48, 170.39, 170.26, 169.52, 155.07, 132.97, 130.12 (2C's), 117.09 (2C's), 100.24, 71.07, 71.01, 68.85, 67.04, 61.48, 20.87, 20.80, 20.79, 20.73. LC–MS (ESI-TOF): $[M+Na]^+$ calcd for $C_{21}H_{26}O_{10}$+Na, m/z 461.1418; found, m/z 461.1405.

4.4.3. Pyridin-2-yl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (2l)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 3.8 Hz, 1H), 7.68–7.59 (m, 1H), 6.99 (dd, J = 6.6, 5.5 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.20 (d, J = 8.3 Hz, 1H), 5.51 (dd, J = 10.2, 8.5 Hz, 1H), 5.48 (d, J = 3.1 Hz, 1H), 5.18 (dd, J = 10.4, 3.4 Hz, 1H), 4.20–4.12 (m, 3H), 2.18 (s, 3H), 2.02–2.01 (m, 6H), 1.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.46, 170.40, 170.22, 169.65, 161.46, 146.87, 139.48, 118.97, 111.90, 94.00, 71.27, 71.23, 68.56, 67.13, 61.14, 20.83, 20.81, 20.78, 20.73. LC–MS (ESI-TOF): $[M+Na]^+$ calcd for $C_{19}H_{23}NO_{10}$+Na, m/z 448.1214; found, m/z 448.1254.

4.4.4. 7-Hydroxy-4-oxo-2-phenyl-4*H*-chromen-3-yl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (2n)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10–8.04 (m, 3H), 7.98 (s, 1H), 7.46 (dd, J = 5.3, 1.9 Hz, 3H), 6.99–6.93 (m, 2H), 5.60 (d, J = 7.9 Hz, 1H), 5.39 (dd, J = 10.4, 7.9 Hz, 1H), 5.35 (d, J = 3.4 Hz, 1H), 5.07 (dd, J = 10.4, 3.4 Hz, 1H), 4.11 (ddd, J = 16.0, 13.9, 6.9 Hz, 1H), 3.84 (s, 3H), 2.12 (s, 6H), 1.99 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.06, 170.56, 170.44, 170.32, 170.23, 162.01, 157.43, 157.28, 136.10, 130.87, 130.82, 129.20 (2C's), 128.18 (2C's), 127.44, 117.60, 115.33, 102.97, 99.71, 71.01, 70.76, 69.42, 66.99, 60.91, 21.12, 20.74, 20.72, 20.68. LC–MS (ESI-TOF): m/z $[M+H]^+$ calcd for $C_{29}H_{28}O_{13}$+H: 585.1603; found 585.1517. LC–MS (ESI-TOF): $[M+Na]^+$ calcd for $C_{29}H_{28}O_{13}$+Na, m/z 607.1422; found, m/z 607.1424.

4.4.5. 3-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyloxy)-4-oxo-2-phenyl-4*H*-chromen-7-yl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (2o)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8.9 Hz, 1H), 8.09–8.03 (m, 2H), 7.54–7.45 (m, 3H), 7.12 (d, J = 2.2 Hz, 1H), 7.06 (dd, J = 8.9, 2.3 Hz, 1H), 5.66 (d, J = 7.9 Hz, 1H), 5.55 (dd, J = 10.5,

7.9 Hz, 1H), 5.50 (d, J = 3.0 Hz, 1H), 5.41–5.34 (m, 2H), 5.19 (d, J = 7.9 Hz, 1H), 5.15 (dd, J = 10.4, 3.4 Hz, 1H), 5.08 (dd, J = 10.4, 3.4 Hz, 1H), 4.25–4.06 (m, 3H), 3.89–3.80 (m, 3H), 2.20 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 2.09 (s, 3H), 2.05 (d, J = 3.2 Hz, 3H), 2.03 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.50, 170.44, 170.31, 170.26, 170.21, 170.17, 170.13, 169.41, 160.92, 157.39, 156.61, 136.38, 130.91, 130.73, 129.18, 128.19, 127.52, 119.87, 115.54, 104.26, 99.51, 99.12, 71.70, 70.97, 70.83, 70.76, 69.31, 68.46, 66.95, 66.92, 61.68, 60.81, 21.09, 20.85, 20.77, 20.74, 20.70, 20.67. LC–MS (ESI-TOF): $[M+Na]^+$ calcd for $C_{43}H_{46}O_{22}$+Na, m/z 937.2373; found, m/z 937.2374.

4.5. Recycling ionic liquids from the reaction mixture

The ability to recycle ionic liquids was demonstrated via the reaction of **1a** and 4-nitrophenol in BMIm·BF_4. Once the reaction was complete, water (5 mL) and CH_2Cl_2 (5 mL) were added to the reaction mixture. The organic and aqueous layers were separated, and the residual product in the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was loaded onto a silica gel cartridge to isolate the product. The aqueous layer was concentrated in vacuo to recover the ionic liquid, which was dried under vacuum at 80 °C overnight and used for the next cycle without further purification. The results are given in Table 5.

4.6. NMR experiments

A mixture of Ag_2CO_3 (1 equiv), BTEACl (1 equiv), and BMIm·BF_4 (1 equiv) was stirred for 3 h at room temperature. An aliquot (50 mg) was diluted with $CDCl_3$ (0.75 mL), filtered through a 0.22 μm PFTE filter and analyzed by ^{1}H NMR spectroscopy. For comparison, the ^{1}H NMR spectrum of BMIm·BF_4 and BMIm·Cl was taken under identical conditions. Using a similar protocol, an aliquot (250 mg) of the BMIm·BF_4 (1.5 g), BTEACl (1.5 mmol), and Ag_2CO_3 (1.5 mmol) mixture was analyzed by ^{13}C NMR spectroscopy (20,000 scans) in CD_2Cl_2.

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Supplementary data

Supplementary data (^{1}H, ^{13}C NMR, GCOSY, and GHSQC relating to compounds **2h**, **k**, **l**, **n** and **o** and the full ^{13}C NMR in Figure 2d) associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.03.007.

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