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Validation of the Copper(I)-Catalyzed Azide−Alkyne Coupling in Ionic Liquids. Synthesis of a Triazole-Linked *C*-Disaccharide as a Case Study

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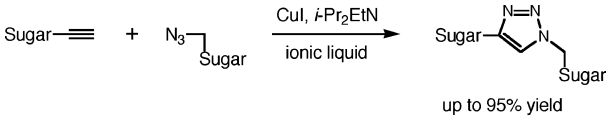

The first study of a copper(I)-catalyzed azide−alkyne click reaction in ionic liquids (ILs) is reported. The cycloaddition of a sugar azide with a sugar acetylene (CuI, *i*-Pr_2EtN, 80 °C) was carried out in 10 ILs as well as in standard molecular solvents (toluene and DMF) to give the 1,4-disubstituted triazole-linked *C*-disaccharide. The highest yields (84 and 95%) were registered in Ammoeng 110 and $[C_8dabco][N(CN)_2]$. The latter solvent was recycled in four subsequent reactions without loss of the reaction efficiency. Reactions carried out in the absence of the Hünig's base afforded mixtures of 1,4- and 1,5-disubstituted triazole regioisomers.

Since Sharpless and co-workers' seminal reports[1] on the so-called click chemistry concept, a huge number of papers have been published[2] on the use of the prototypical click reaction constituted the copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC) to give under mild conditions 1,4-disubstituted 1,2,3-triazoles in very high yields. This metal-catalyzed reaction discovered independently in the Sharpless and Meldal laboratories[3] constitutes a substantial improvement of the classical Huisgen-type thermal 1,3-dipolar cycloaddition[4,5] which instead affords mixtures of 1,4- and 1,5-disubstituted triazoles. It has been amply documented that this highly regioselective triazole annulation served as a powerful ligation tool of the most disparate molecular fragments, thus leading to the metaphoric view of the triazole ring as a robust keystone in complex molecular architectures.[6] The wide scope of CuAAC is firmly demonstrated by the use in different areas of life and material sciences. DNA labeling[7] and oligonucleotide synthesis,[8] assembly of glycoclusters[9] and glycodendrimers,[10] preparation of stationary phases for HPLC column,[11] development of microcontact printing,[12] new polymer synthesis,[13] conjugation of molecular cargos to the headgroup of phospholipids,[14] and construction of bolaamphiphilic structures[15] are just a few examples. While a lot of efforts have been made on the search of improved copper-based catalysts, the issue regarding the green aspect of the method has not so far been addressed. While it is well-known that the CuAAC can be carried out in water as a green solvent, the lack of solubility of the reactants can create a serious obstacle to the use of this reaction medium. The use of ionic liquids (ILs)[16] is another way to meet the principles of green chemistry. In addition to this fundamental aspect which is however occasionally questioned,[17] recent studies have shown substantial effects on reactions carried out in ILs[18] while most reactions proceed as in ordinary organic liquids. Innovations on the use of chiral ILs in asymmetric synthesis have been

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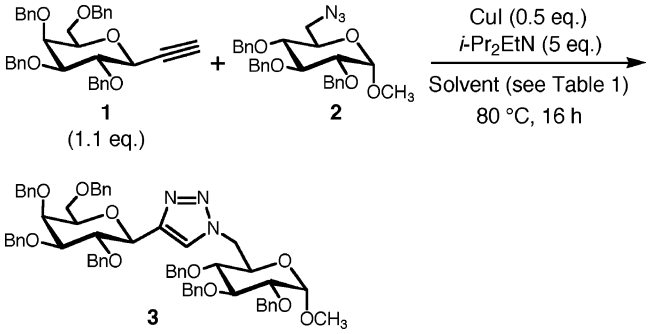
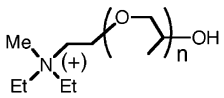
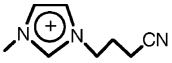
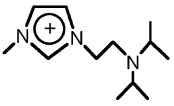
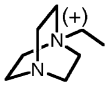
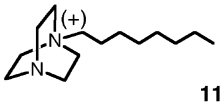
SCHEME 1



reported.[19] ILs can be excellent solvents for metal-catalyzed reactions because they are able to dissolve metal salts and stabilize the formation of metal nanoparticles, nanorods, and so on.[20] The economical aspect regarding the use of these solvents is still a pending problem due to their high cost. This, however, is partly compensated by their potential recycling. New techniques based on IL-supported species[21] may contribute to relieve this serious drawback. Also in respect to this broader outlook, it is quite surprising that studies have not so far been reported on the CuAAC reaction carried out in ILs.[22] Therefore, we were spurred to address this issue and considered a model CuAAC reaction in a field of our direct interest such as the assembly of triazole-linked oligosaccharides[23] and glycoconjugates.[9,24] Toward this end, we have selected the hitherto unreported coupling of perbenzylated ethynyl *C*-galactoside[25] **1** with methyl 6-azidoglucopyranoside[26] **2** to give the triazole-linked disaccharide **3** (Scheme 1). Carbohydrates are densely functionalized compounds and therefore are perfect test vehicles to probe the fidelity of the click reaction in ILs. Moreover, performing a click reaction in ILs appeared to us a non-trivial task, the main inconvenience that might occur being the sequestering of the copper catalyst by complexation with the solvent. Three types of ILs were considered by cation variation (i.e., the ammonium derivative **4**, the bmim-based derivatives **5**−**9**, and the *N*-alkyl dabco-cation-based derivatives **10**−**13**). Structural diversity was also introduced by the anion change. Crucial to the use of the selected ILs was the ability to dissolve CuI and a low viscosity, thus enabling an efficient stirring of the reaction mixture.

The cycloaddition of **1** and **2** was first performed at room temperature overnight on a 0.1 mmol scale in the presence of CuI (0.5 equiv) and freshly distilled *i*-Pr_2EtN (Hünig's base, 5 equiv) using the ionic liquids **4**−**6** as the solvents. Under these conditions, the *C*-disaccharide **3** was obtained in only 25−30% isolated yield, while the reaction mixtures were mainly formed by unreacted alkyne **1** and azide **2**. Raising the reaction temperature to 80 °C, we found that the cycloadduct **3** was recovered in much higher yields (50−84%, entries 3−5). Reactions under these optimized conditions were carried out in other ILs as well as in toluene and DMF as standard molecular solvents (Table 1, entries 1, 2, and 6−12). In all cases, with one exception only (entry 8), the reaction afforded exclusively the cycloadduct **3** in fair to excellent isolated yields. A yield of **3** (91%) comparable to that in toluene (96%) was obtained in the *N*-octyl dabco-cation-based dicyanamide ([C_8dabco][$N(CN)_2$],

TABLE 1. Effect of the Solvent in the Cu-Promoted Cycloaddition of 1 and 2 on a 0.1 mmol Scale to Give the *C*-Disaccharide 3 (see Scheme 1)

entry	solvent: cation	solvent: anion	yield (%)[a]
1	toluene		96
2	DMF		70
3	 **4**[b]	$Cl^{(-)}$	84[c]
4	 **5**	$BF_4^{(-)}$	68
5	" **6**	$N(CN)_2^{(-)}$	50
6	" **7**	$Tf_2N^{(-)}$	71
7	 **8**	$BF_4^{(-)}$	61
8	 **9**	$N(CN)_2^{(-)}$	51[d]
9	 **10**	$Br^{(-)}$	62
10	 **11**	$Br^{(-)}$	76
11	" **12**	$BF_4^{(-)}$	70
12	" **13**	$N(CN)_2^{(-)}$	91 (95)[e]

[a] After extraction of the reaction mixture with AcOEt and column chromatography on silica gel. [b] Washed twice with Et_2O, then dried under vacuum, before the cycloaddition reaction. [c] Reaction mixture extracted with Et_2O instead of AcOEt. [d] Contaminated by 5% of the 1,5-regioisomer **14**. [e] Isolated yield on a 1 mmol scale.

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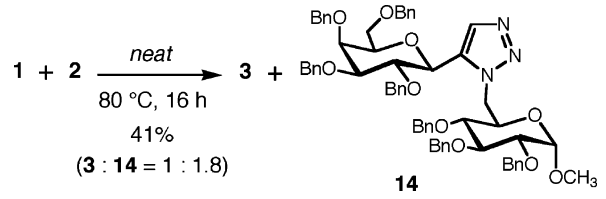
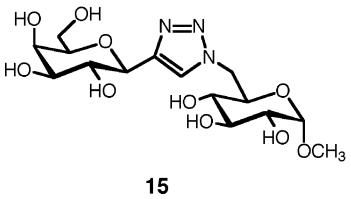
SCHEME 2

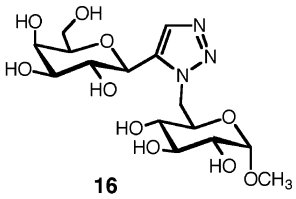


13, entry 12). The yields in this IL decreased by shortening the reaction time (74% in 4 h and 81% in 8 h), which indicated the convenient reaction time employed (16 h).

The 1,4-disubstitution pattern of the triazole linker in **3** was established by ^{13}C NMR spectroscopy according to our recent method.[9] In fact, a large and positive $\Delta(\delta_{C4}-\delta_{C5})$ value (22.0 ppm) was found in the ^{13}C spectrum[27] as observed in other compounds prepared by click reaction, including triazole-linked *C*-glycoside clusters,[9] *C*-oligosaccharides,[23] and *C*-glycosyl amino acids.[24] On the other hand, in agreement with earlier findings,[9,27] the 1,5-disubstituted triazole **14** prepared by thermal coupling of **1** and **2** neat (Scheme 2) displayed a small and negative $\Delta(\delta_{C4}-\delta_{C5})$ value as small as −3.3 ppm.

It is worth noting that the empirical rule[3b,28] establishing that the H-5 proton in 1,4-disubstituted triazoles resonates always downfield compared to the H-4 proton in the corresponding 1,5-isomer is not always reliable, especially in the case of complex molecules such as the disaccharides **3** and **14**. Actually, the triazole proton in **3** was at upper field (δ_{H5} = 7.57 ppm) than that of the proton of the regioisomer **14** (δ_{H4} = 7.68 ppm). Instead, the free hydroxy *C*-disaccharides **15** and **16**, obtained by catalytic hydrogenation of **3** and **14**, respectively, displayed in their NMR spectra chemical shift values in accord with both rules [**15**: (δ_{H5} = 8.02 ppm; $\Delta(\delta_{C4}-\delta_{C5})$ = +21.6 ppm; **16**: (δ_{H4} = 7.79 ppm; $\Delta(\delta_{C4}-\delta_{C5})$ = −5.3 ppm)].





The workup of the reaction mixture was a non-trivial operation for reactions carried out in ILs. Although ethyl acetate appeared to be the solvent of choice[29] for the efficient extraction of the product **3**, small amounts of the IL were extracted by this solvent[30] and then retained by the silica gel column used for the chromatographic purification of **3**. Consequently, the method suffered from the partial loss of these costly IL solvents. Nevertheless, the recycling of **13** was considered. To this end, following the workup of the reaction mixture, to the recovered IL still containing the copper catalyst was added the Hünig's base, and the resulting mixture was employed in a subsequent run. Noteworthy, the registered yields of isolated **3** in four subsequent runs were 91, 77, 80, and 80%. Hence, a single stock of **13** enabled the coupling of 0.4 mmol (ca. 200 mg) of each reaction partner **1** and **2** to give the disaccharide **3** with an average yield of 82%. The preparative value of the CuAAC under study was further demonstrated by a reaction carried out on a 1 mmol scale of each reagent **1** and **2**. In this case, the yield of isolated **3** (0.98 g) was 95%.

TABLE 2. Cycloaddition in the Absence of Hünig's Base (80 °C, 16 h)

entry	solvent	yield (%)[a]	**3**:**14** ratio[b]
1	toluene	96[c]	1:0
2	**4**	60[d]	25:1
3	**9**	61	1.7:1
4	**10**	62	1:1.5
5	**11**	34[e]	1:1.0
6	**12**	71	6.0:1
7	**13**	41[e]	9.0:1

[a] After extraction of the reaction mixture with AcOEt and column chromatography on silica gel. [b] From ^1H NMR analysis. [c] The reaction mixture was concentrated and applied directly to a column of silica gel. [d] Reaction mixture extracted with Et_2O instead of AcOEt. [e] The reaction mixture was diluted with H_2O and extracted with AcOEt.

While all runs reported in Table 1 were carried out in the presence of *i*-Pr_2EtN, we planned on performing reactions in ILs without this base since successful click azide−alkyne reactions were reported in the absence of such an additive.[31] Moreover, we observed that, contrary to literature precedent which encourages use of excess Hünig's base,[3b] the reaction of **1** and **2** in toluene without added *i*-Pr_2EtN afforded exclusively the cycloadduct **3** with the same high yield (96%) as in the presence of the base (Table 1, entry 1; Table 2, entry 1). Quite disappointedly, applying the same conditions to the reaction carried out in the non-basic IL **4**, we found that the 1,4- and 1,5-regioisomers **3** and **14** were formed in low overall yield although with a net predominance of the former (Table 2, entry 2). Hence, the presence of *i*-Pr_2EtN appeared to be crucial for the occurrence of the effective click cycloaddition in the IL **4**. Therefore, we hoped that click chemistry could take place again in a basic IL such as the bmim-based **9** displaying a structural motif around the basic nitrogen atom in the alkyl chain similar to that in Hünig's base. In the event, the IL would serve as promoter and reaction medium. Instead, a modest yield was again registered, and the two regioisomers formed in nearly equal amounts (Table 2, entry 3). Similar results were found in other basic ILs such as the dabco-derived ILs **10**−**13**. We suggest that the event feared at the outset of the research about copper sequestering by the IL[32] and therefore impairing the catalytic cycle[33] did in fact occur. The presence of *i*-Pr_2EtN serving as a copper ligand[32] prevents such a drawback by the

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(29) When using IL **4** as the solvent, the reaction mixture was extracted with diethyl ether because this ionic liquid is quite soluble in AcOEt (ca. 70 mg/mL). The solubility of **4** in AcOEt did not vary significantly in the presence of H_2O.

(30) The solubility of pure IL **13** in AcOEt at rt was ca. 25 mg/mL.

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IL. Considerations on some physicochemical properties of ILs may clarify this point. The interactions between anions and cations in ILs produce ionic organized networks in the solid, liquid, and gas phase, with the charge ordering degree determined mainly by the nature of anion and cation, while the presence of sufficiently long alkyl chains on cation determines the existence of polar and unpolar domains.[34] The ability of the anion and cation to interact with dissolved species, including catalysts, is therefore a property partially determined by the anion−cation interaction inside the network. The addition of uncharged species affects the three-dimensional structure of ILs and changes their physicochemical properties. Hence, the Hünig's base may affect both the ability of the medium to sequester the copper catalyst and the aptitude of the effective catalyst to approach the reagents.

In summary, of the various ILs examined, the most suitable one for performing the model CuAAC reaction examined is the $[C_8dabco][N(CN)_2]$ using CuI as catalyst and *i*-Pr_2EtN as additive. The validation of a synthetically important CuAAC such as that involving carbohydrates in ILs opens new perspectives on the use of this prototypical click reaction in glycochemistry.

Experimental Section

Cycloaddition in Molecular Solvents. A mixture of sugar azide **2** (49 mg, 0.10 mmol), *C*-galactoside **1** (60 mg, 0.11 mmol), freshly distilled *N*,*N*-diisopropylethylamine (87 μL, 0.50 mmol), CuI (9.5 mg, 0.05 mmol), and anhydrous toluene (1 mL) was sonicated in an ultrasound cleaning bath for ca. 1 min, then stirred in the dark at 80 °C for 16 h, cooled to room temperature, and concentrated. The residue was eluted from a column of silica gel with 2:1 cyclohexane/AcOEt to give first unreacted azide **2** (2.5 mg, 5%). Eluted second was the disaccharide **3** (100 mg, 96%) as a colorless foam. When the same cycloaddition was performed without the Hünig's base, the unmodified alkyne **1** (9 mg, 15%) and the disaccharide **3** (100 mg, 96%) were isolated by column chromatography.

Cycloaddition in Ionic Liquids. A mixture of sugar azide **2** (49 mg, 0.10 mmol), *C*-galactoside **1** (60 mg, 0.11 mmol), and ionic liquid (0.50 g; previously dried at 0.1 mbar/50 °C for 4 h) was sonicated or magnetically stirred at room temperature for a few minutes to obtain a solution, then CuI (9.5 mg, 0.05 mmol) was added. The mixture was sonicated for ca. 1 min, then diluted with freshly distilled *N*,*N*-diisopropylethylamine (87 μL, 0.50 mmol), and stirred in the dark at 80 °C. After 16 h, the reaction mixture was cooled to room temperature and extracted with AcOEt (4 × 6 mL), waiting each time 15 min for a clear phase separation (in some cases, 1 mL of H_2O was also added to improve the extraction yield; see Table 2). The combined extracts were concentrated and dried under high vacuum to give crude **3** together with variable amounts of ionic liquid. The residue was eluted from a column of silica gel with 2:1 cyclohexane/AcOEt to give pure disaccharide **3**. An identical procedure was followed for reactions performed without the Hünig's base.

Cycloaddition in the Absence of Solvent. A mixture of syrupy azide **2** (49 mg, 0.10 mmol) and crystalline alkyne **1** (60 mg, 0.11 mmol) was stirred at 80 °C for 16 h under a nitrogen atmosphere (after a few minutes, the mixture became a homogeneous solution), then cooled to room temperature, diluted with toluene (ca. 0.5 mL), and eluted from a column of silica gel with cyclohexane−AcOEt (from 3:1 to 2:1) to give first a mixture of unreacted **1** and **2**, then the disaccharide **3** (15 mg, 14%), and finally the regioisomer **14** (28 mg, 27%).

Disaccharide 3: Mp 110−111 °C (AcOEt/cyclohexane); $[\alpha]_D$ = +25.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H, H-5 Tr.), 7.39−7.20 (m, 30H, Ar), 7.18−7.12 (m, 3H, Ar), 7.05−7.02 (m, 2H, Ar), 5.00 and 4.66 (2d, 2H, J = 11.6 Hz, PhCH_2), 4.93 and 4.78 (2d, 2H, J = 10.9 Hz, PhCH_2), 4.87 and 4.76 (2d, 2H, J = 10.8 Hz, PhCH_2), 4.78 and 4.73 (2d, 2H, J = 11.7 Hz, PhCH_2), 4.66 and 4.26 (2d, 2H, J = 10.6 Hz, PhCH_2), 4.58 and 4.42 (2d, 2H, J = 12.0 Hz, PhCH_2), 4.53 (dd, 1H, $J_{5,6a}$ = 5.6 Hz, $J_{6a,6b}$ = 14.3 Hz, H-6a), 4.52 (d, 1H, $J_{1',2'}$ = 9.7 Hz, H-1′), 4.46 and 4.40 (2d, 2H, J = 11.6 Hz, PhCH_2), 4.44 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.44 (dd, 1H, $J_{5,6b}$ = 2.8 Hz, H-6b), 4.20 (dd, 1H, $J_{2',3'}$ = 9.5 Hz, H-2′), 4.06 (dd, 1H, $J_{3',4'}$ = 3.0 Hz, $J_{4',5'}$ = 0.8 Hz, H-4′), 3.94 (dd, 1H, $J_{2,3}$ = 9.7 Hz, $J_{3,4}$ = 8.8 Hz, H-3), 3.91 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, H-5), 3.73 (dd, 1H, H-3′), 3.72 (ddd, 1H, $J_{5',6'a}$ = 7.0 Hz, $J_{5',6'b}$ = 6.2 Hz, H-5′), 3.60 (dd, 1H, $J_{6a',6'b}$ = 9.0 Hz, H-6′a), 3.57 (dd, 1H, H-6′b), 3.23 (dd, 1H, H-2), 3.12 (dd, 1H, H-4), 3.11 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2 (C-4 Tr.), 138.9, 138.5, 138.4, 138.1, 138.0, 137.89, and 137.82 (C Ar), 128.5−127.5 (CH Ar), 124.2 (C-5 Tr.), 98.0 (C-1), 84.3 (C-3′), 81.8 (C-3), 79.9 (C-2), 78.7 (C-2′), 77.7 (C-4), 77.4 (C-5′), 75.6 (Ph*C*H_2), 74.9 (2 Ph*C*H_2), 74.61 (C-1′), 74.59 (Ph*C*H_2), 74.0 (C-4′), 73.5 (Ph*C*H_2), 73.3 (Ph*C*H_2), 72.5 (Ph*C*H_2), 68.9 (C-5), 68.7 (C-6′), 55.3 (CH_3), 50.3 (C-6). MALDI-TOF MS (1038.23): 1038.9 (M^+ + H), 1060.9 (M^+ + Na), 1076.7 (M^+ + K). Anal. Calcd for $C_{64}H_{67}N_3O_{10}$: C, 74.04; H, 6.50; N, 4.05. Found: C, 73.88; H, 6.41; N, 3.90.

Disaccharide 14: $[\alpha]_D$ = +28.3 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H, H-4 Tr.), 7.42−7.20 (m, 33H, Ar), 7.00−6.96 (m, 2H, Ar), 4.96 and 4.78 (2d, 2H, J = 11.0 Hz, PhCH_2), 4.92 and 4.62 (2d, 2H, J = 11.5 Hz, PhCH_2), 4.90 and 4.70 (2d, 2H, J = 10.9 Hz, PhCH_2), 4.77 and 4.69 (2d, 2H, J = 11.6 Hz, PhCH_2), 4.68 and 4.54 (2d, 2H, J = 12.3 Hz, PhCH_2), 4.68 and 4.15 (2d, 2H, J = 10.6 Hz, PhCH_2), 4.64 (dd, 1H, $J_{5,6a}$ = 2.8 Hz, $J_{6a,6b}$ = 14.3 Hz, H-6a), 4.46 (d, 1H, $J_{1',2'}$ = 9.6 Hz, H-1′), 4.46 and 4.40 (2d, 2H, J = 12.0 Hz, PhCH_2), 4.44 (dd, 1H, $J_{5,6b}$ = 6.5 Hz, H-6b), 4.38 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.10 (dd, 1H, $J_{2',3'}$ = 9.4 Hz, H-2′), 4.04 (dd, 1H, $J_{3',4'}$ = 2.8 Hz, $J_{4',5'}$ = 0.5 Hz, H-4′), 3.94 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, H-5), 3.93 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 3.63−3.54 (m, 4H, H-3′, H-5′, 2 H-6′), 3.46 (dd, 1H, H-4), 3.38 (dd, 1H, H-2), 3.00 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 138.5, 138.2, 138.1, 137.9, 137.6, and 137.5 (C Ar), 136.0 (C-5 Tr.), 132.7 (C-4 Tr.), 129.9−127.4 (CH Ar), 97.6 (C-1), 84.3 (C-3′), 82.0 (C-3), 79.7 (C-2), 78.7 (C-4), 78.1 (C-2′), 75.6, 75.2, 74.8, 74.7, and 73.5 (Ph*C*H_2), 73.4 (C-4′), 73.3 and 72.2 (Ph*C*H_2), 72.1 (C-1′), 69.1 (C-5), 68.4 (C-6′), 55.0 (CH_3), 48.6 (C-6). MALDI-TOF MS (1038.23): 1038.7 (M^+ + H), 1060.7 (M^+ + Na), 1076.7 (M^+ + K). Anal. Calcd for $C_{64}H_{67}N_3O_{10}$: C, 74.04; H, 6.50; N, 4.05. Found: C, 73.81; H, 6.39; N, 3.92.

Supporting Information Available: Experimental procedures and physical data of ILs **9**, **10**, **13**, and disaccharides **15** and **16**. Copies of the ^{1}H and ^{13}C NMR spectra of **3**, **9**, **10**, and **13**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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