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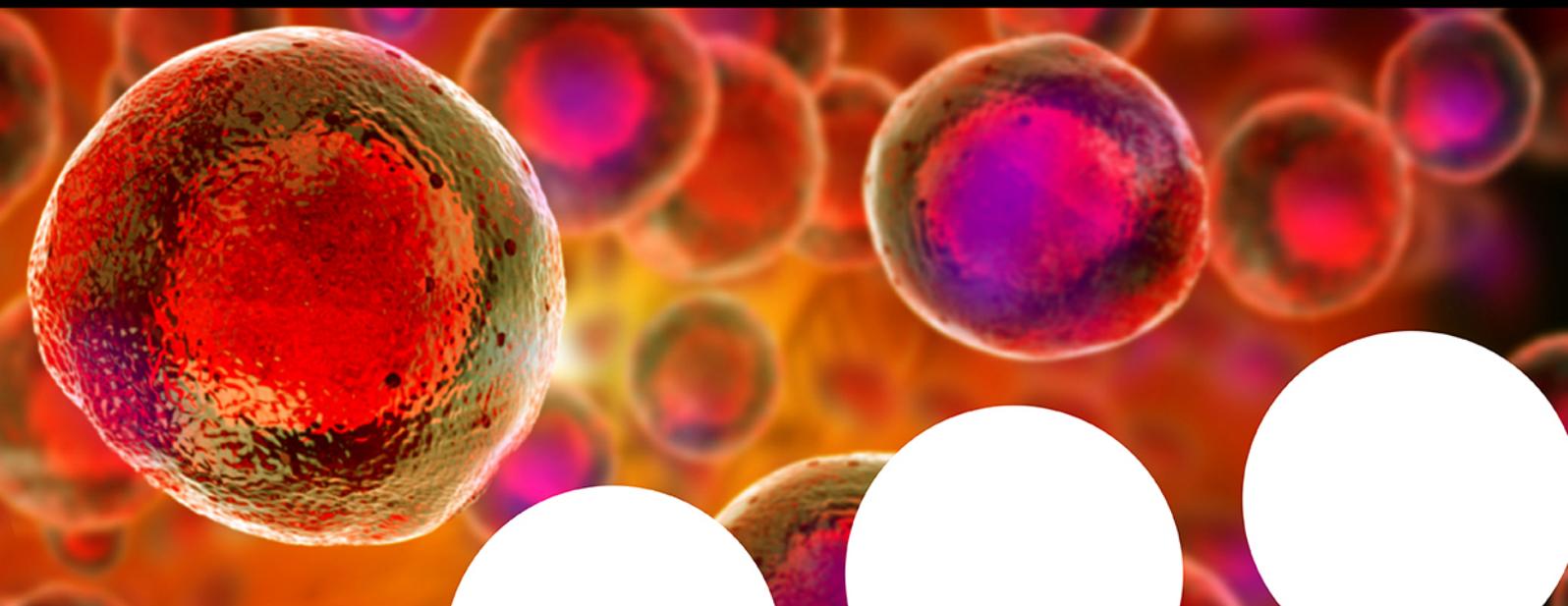
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# Azoliums and Ag(I)-N-Heterocyclic Carbene Thioglycosides: Synthesis, Reactivity and Bioactivity

Dmytro Ryzhakov,<sup>[a]</sup> Audrey Beillard,<sup>[b]</sup> Franck Le Bideau,<sup>[a]</sup> Riyadh Ahmed Atto Al-Shuaeeb,<sup>[a]</sup> Mouad Alami,<sup>[a]</sup> Xavier Bantreil,<sup>[b, c]</sup> Aurore Bonnemoy,<sup>[d]</sup> Arnaud Gautier,<sup>\*,[d]</sup> Frédéric Lamaty,<sup>\*,[b]</sup> and Samir Messaoudi<sup>\*,[a]</sup>

A versatile protocol for the synthesis of azolium thioglycosides is reported. This protocol is based on a PdG3-catalyzed Migita cross-coupling between *p*-di-iodo azoliums and protected or unprotected β-1-thioglucose partners. Moreover, a solvent-free mechanochemistry approach was developed as a unique access

to the corresponding Ag(I)-N-heterocyclic carbene thioglycosides. Finally, chemical reactivity and antiproliferative bioactivity were examined with azoliums and Ag(I)-NHC thioglycosides. This study demonstrates a promising potential of these newly synthesized carbohydrate-based N-heterocyclic derivatives.

## Introduction

In 1968, Wanzlick and Öfele concomitantly reported the preparation of respectively a bis-carbenic complex of mercury(II)<sup>[1]</sup> and a carbenic complex of chromium(0),<sup>[2]</sup> based on the deprotonation of imidazolium salts, as the first isolated metal-N-heterocyclic carbene (metal-NHCs) complexes. But it was not until the late 80's, that Bertrand and Arduengo isolated the first persistent triplet and singlet carbenes.<sup>[3]</sup> Therefore, huge progress was made in the synthesis of metal-NHCs,<sup>[4]</sup> leading to various applications in the fields of catalysis,<sup>[5]</sup> material<sup>[6]</sup> and medicinal<sup>[7]</sup> chemistry.

For such applications, carbohydrates, which are naturally abundant, inexpensive, water soluble, biocompatible and non-toxic chiral compounds that play an important role in many biological processes, quickly emerged as ligands of choice in the construction of metal complexes.<sup>[8]</sup> Nevertheless, the first occurrences of organometallic species incorporating a carbohydrate substituent on the NHC ligand<sup>[9]</sup> have not been reported before 2007 with the syntheses of iridium<sup>[10]</sup> and palladium<sup>[11]</sup>

derivatives, obtained by transmetalation of the corresponding silver complexes with the appropriate metallic sources, and a rhodium complex prepared by deprotonation of an imidazolium salt in the presence of [RhCl(COD)]<sub>2</sub>.<sup>[12]</sup> Three years later, their use as catalysts was validated with the involvement of two sugar-incorporated NHC ruthenium(II) complexes in metathesis reactions.<sup>[13]</sup> Since then there have been a few other reports dealing with Suzuki coupling,<sup>[14]</sup> asymmetric hydrosilylation of ketones,<sup>[15]</sup> base-free alcohol and amine oxidations<sup>[16]</sup> and transfer hydrogenation of ketones under basic conditions.<sup>[17]</sup>

Surprisingly, their use as molecules of therapeutic interest has not yet been reported, although two platinum complexes bearing carbohydrate-substituted-NHCs have been described in a study<sup>[18]</sup> on the development of potentially anti-cancer substances. Such a substitution could indeed favor the water solubility of the corresponding compounds<sup>[19]</sup> and hence their efficiency in biological media.

While a great variety of NHC complexes are known, to date NHC-carbohydrate complexes appear only to have been reported for complexes in which the sugar moiety is attached to the 5-membered nitrogen imidazolium or 1,2,3-triazolium heterocycles such as Glorious' imidazolium **1**,<sup>[20]</sup> Grubbs' carbohydrate-based-NHC **2**<sup>[21]</sup> and the asymmetric C2-NHC-glycosides **3** developed by Galan<sup>[22]</sup> (Figure 1). Hybrid cyclodextrin-NHC ligands have been also explored by the group of Sollougoub to introduce a metal center (Au, Ag or Cu) in the cavity of cyclodextrins. This confinement induced unprecedented reactivity, stereoselectivity and regioselectivity.<sup>[23]</sup> One of the rare examples of carbohydrate-based-NHCs in which the sugar is attached to the aromatic nucleus of the azolium was reported by some of us (compound **5**). A CuAAC-auto-click reaction was used during this study between *p*-azido-Cu(I)-NHCs and unprotected alkynyl-α-glucose to generate the triazole linker.<sup>[24]</sup> Besides, various research groups including us focused their studies on the synthesis of NHC-Au(I)-thioglucose complexes as analogues of the well-known anti-arthritis and antitumor Au(I) drug Auranofin.<sup>[25]</sup> These studies revealed that Auranofin analogues such as **4** which retained the thioglucopyranose moiety linked to the Au(I)-metal but incorporated an

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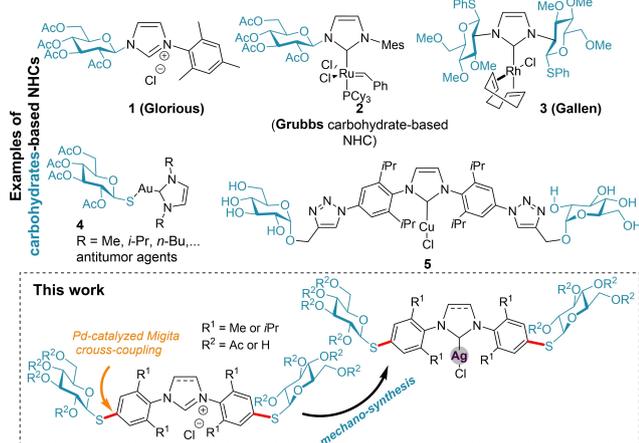


Figure 1. Selected examples of carbohydrate–NHCs.

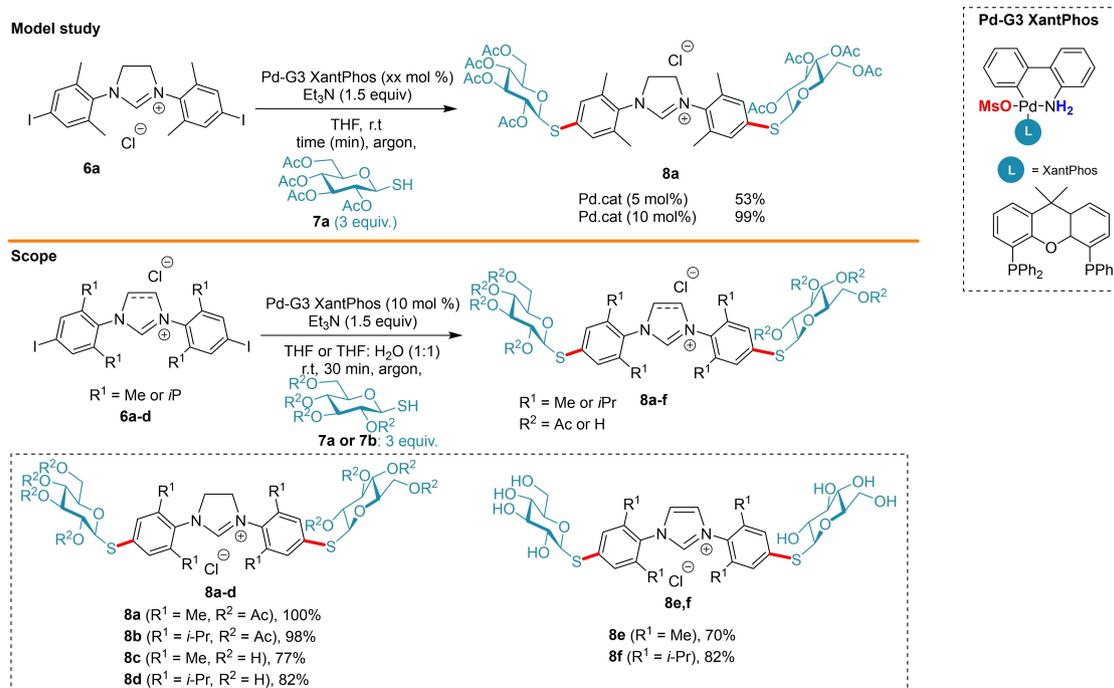
NHC ligand in place of the  $\text{PEt}_3$  group showed very promising anticancer activities against various cancer cell lines.

While all these carbohydrates NHC-derivatives hold great interests, strikingly, to the best of our knowledge there is no report concerning NHC–thioglycosides complexes in which the sugar moiety is attached onto the aromatic nucleus, despite the relevance of such compounds for organometallic catalysis as well as biological investigations. Herein, we describe a simple Pd-catalyzed method to synthesize imidazoli(ni)um-thioglycosides and their organometallic Ag(I)-NHC thioglycosides through a mechanochemistry approach (Figure 1). Furthermore, the potential catalytic reactivity of the synthesized

imidazoli(ni)um-thioglycosides in the context of performing reactions in water such as oxidation of benzaldehyde was examined. Finally, the biological activity of the new Ag(I)-NHC thioglycosides was evaluated by measuring their antiproliferative activity against colon cancer cell line.

## Results and Discussion

First, the synthesis of the di-iodinated imidazolium and imidazolium salts **6a,b** and **6c,d** (Scheme 1) has been achieved over three steps following a reproducible and robust previously described method.<sup>[26]</sup> We recently reported an efficient method allowing the introduction of glycosyl thiols to various iodo(hetero)aryles,<sup>[27]</sup> nucleic acids<sup>[28]</sup> and peptides,<sup>[29]</sup> under simple and mild conditions. The C–S bond-forming reaction was realized at room temperature by using the G3–Xantphos palladacycle pre-catalyst (1 mol%), in the presence of  $\text{Et}_3\text{N}$  (1.0 equiv) in THF. We envisioned in the present study whether bis-iodo aryl imidazolium and imidazolium salts could be utilized as building blocks in the synthesis of a range of imidazolium/imidazolium  $\beta$ -thioglycosides (Scheme 1). To establish the appropriate conditions for this coupling, *tetra-O*-acetylated 1-thio- $\beta$ -D-glucopyranose **7a** and imidazolium salt **6a** were initially selected as the coupling model substrates. Thus, reaction of **7a** with **6a** in the presence of Pd–G3–Xantphos (5 mol%) and  $\text{Et}_3\text{N}$  (1.5 equiv) in THF for 2 h at room temperature led to only 53% yield of **8a**. This result clearly indicated that di-iodo-imidazolium salt **6a** is less reactive compared to a classical iodoarene. To enhance the reactivity of **6a**, the model reaction was conducted with 10 mol% of the



Scheme 1. Coupling of various imidazolium and imidazolium **6a–d** with thiosugars **7a–b**.

Pd–G3 catalyst instead of 5 mol% under otherwise identical conditions. To our delight, under these conditions, full conversion of **6a** was achieved in only 30 min and the desired product **8a** was isolated in 99% yield. It should be noted that the palladium catalyst is necessary to achieve this transformation since no reaction occurs when the coupling is conducted in the absence of Pd–G3-precatalyst. Hence, with a catalytic amount of Pd–G3–Xantphos in THF (see the experimental section for details), protected imidazolium thioglycoside **8b** was formed in excellent 98% yield when imidazolium **6b** was used. These reactions were conducted at room temperature, solvents were not dried prior to use, and reactions could be performed on the gram scale (1 g) with the same efficiency and with maintaining the  $\beta$ -anomeric configurations of the sugar moieties. The reaction was also successful with fully unprotected-thiogluco-**7b** to generate thioglycosylated imidazolium **8c–d** and imidazolium **8e–f** in good yields ranging from 70% to 82% (Scheme 1). A mixture of THF and water was utilized in this case to enhance the solubility of thiogluco-**7b** in the reaction medium. Owing to the strong polarity of products **8c–f** generated in that case, reverse phase column chromatography C18 was used for their purification.

### Preparation of Ag(I) carbenes

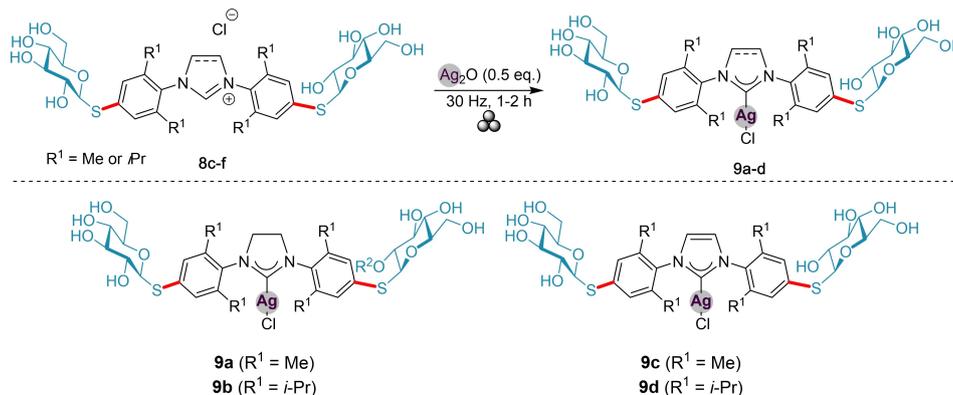
With substantial amounts of **8c–f** in hand (Scheme 1), we focused our attention on demonstrating whether these substrates could be employed as a platform for the preparation of the corresponding metallated hydrosoluble carbenes. However, all our attempts to achieve the reaction with various metals such as Ag, Cu and Au using the classically reported methods of NHCs-metalation failed, probably due to the presence of the thiosugar. Indeed, the low solubility of the compounds in dichloromethane did not allow the silver oxide<sup>[30]</sup> route which left the starting material unchanged. We also tested methanol at room temperature and 30 °C without success. We then turned our attention to the aqueous media using the ammonia protocol to introduce either copper or silver.<sup>[31]</sup> Here once again,

no reaction was observed after exposition of azolium salts to silver or copper oxides even after a prolonged reaction time.

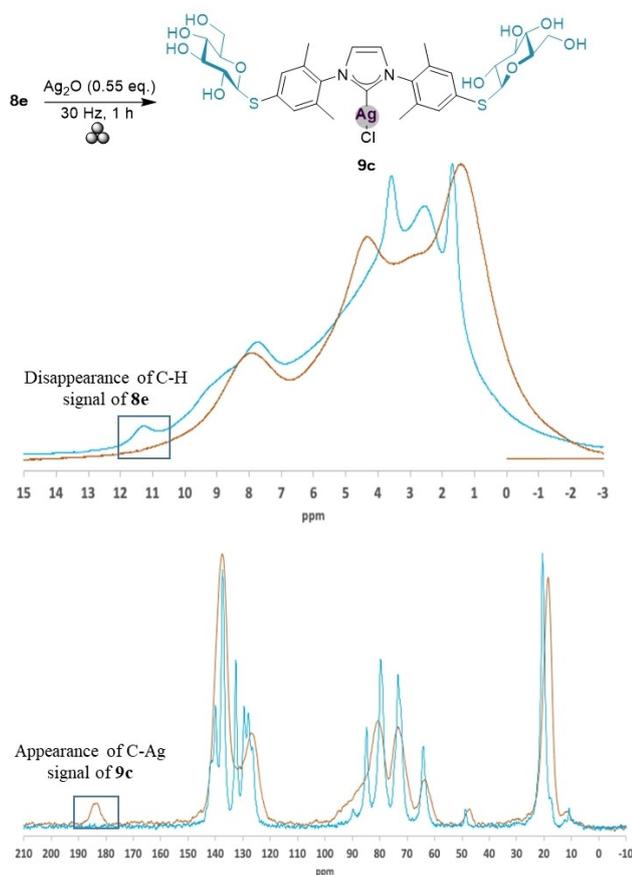
Seeing the low solubility of **8c–f** in organic media, which could be the cause for a lack of reactivity, we considered a solvent-free mechanochemical approach.<sup>[32]</sup> Indeed, some of us recently reported the solvent-free/solvent-less mechanosynthesis of metal–NHCs-complexes using ball-mills.<sup>[33]</sup> Such approaches allowed to not only drastically reduce reaction times but also access unprecedented structures that could not be obtained through classical solution synthesis.<sup>[34]</sup> Imidazolium salt **8e** was thus grinded with a slight excess of silver(I) oxide (0.55 eq.) in a stainless-steel jar agitated at 30 Hz in a vibratory ball-mill (Scheme 2). After 1 h of milling, the reaction mixture was analyzed without further treatment using solid-state HR-MAS (high resolution magic angle spinning) <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy on a 600 MHz spectrometer. Comparison with the spectra obtained for **8e** showed the disappearance of the C–H proton of **8e** at 11.3 ppm in <sup>1</sup>H NMR (Figure 2, top) and the concomitant appearance of the characteristic carbenic carbon signal of **9c** at 182.8 ppm in <sup>13</sup>C NMR (Figure 2, bottom). These observations confirmed the formation of the desired complex **9c**. Quick optimization of the reaction conditions showed that the same result was obtained when 0.5 equivalent of silver(I) oxide was used, thus allowing to recover the pure product directly by scratching the wall of the milling jar. The milling technique was thus applied to salts **8c–f** (Scheme 2). In all cases, full conversion was obtained as witnessed by HR-MAS <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. However, no reaction was observed with acylated imidazolium salt **8a**, probably because of an increased steric hindrance compared to **8e**. It should be noted that solution NMR analysis of complexes **9a–d** was not possible as they were found to be poorly soluble in most organic solvents and slightly unstable in D<sub>2</sub>O.

### Chemical reactivity of azolium thioglycoside salts

In 2011, Bode and co-workers<sup>[35]</sup> reported an example of NHC-catalyzed oxidation of aldehydes under air. This catalytic system has a good tolerance for cinnamaldehydes but is less efficient

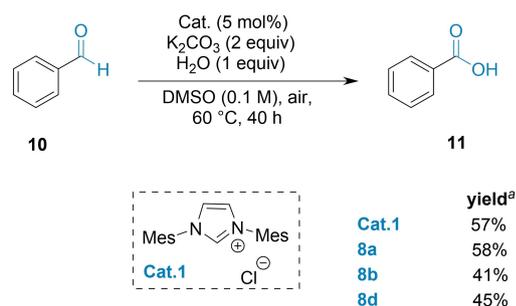


**Scheme 2.** Preparation of NHC–Ag(I)-thioglycosides **9a–d** using vibratory ball mill approach. Reaction conditions: **8c–f**,  $Ag_2O$  (0.5 equiv.), 10 mL stainless steel jar, 1 cm diameter stainless steel ball, vibratory ball-mill, 30 Hz, 1–2 h.



**Figure 2.** HRMAS  $^1\text{H}$  (top) and  $^{13}\text{C}$  (bottom) NMR spectra of **8e** (Light blue) and **9c** (Orange).

with benzaldehydes and aliphatic aldehydes. Inspired by this study, we evaluated our catalysts **8a–b** (OAc sugar) and **8d** (OH sugar) in the aerobic oxidation of benzaldehyde **10** as a model system and yields, displayed in Scheme 3, were compared with the previously reported organocatalyst **cat.1** (57% yield, Scheme 3). In general, all the synthesized thiosugar–NHC displayed a reactivity similar to the one of **cat.1**. Thus, catalysts **8a** and **8b**, featuring OAc–sugar protected groups, gave



**Scheme 3.** Evaluation of azolium **8a–b**, **8d** in the oxidation of benzaldehyde **10**: Reaction conditions: A flask was charged with **10** (1 equiv, 0.9 mmol),  $\text{K}_2\text{CO}_3$  (2 equiv) and catalyst (5 mol%),  $\text{H}_2\text{O}$  (1 equiv) in DMSO. <sup>a</sup> Yield of isolated product.

benzoic acid **11** in 58% and 41% yields, respectively. Moreover, unprotected NHC–thioglycoside **8d** resulted in the isolation of **11** in a moderate yield of 45%. These results demonstrate clearly that the introduction of a thiosugar moiety on the aromatic ring is compatible with the reactivity of the carbene function.

## Biological assays

Upon completion of their syntheses, the *in vitro* activity of imidazoli(ni)um **8a–f** and corresponding silver complexes **9a–d** was evaluated by their growth-inhibitory potency against human colon carcinoma HCT-116 cells at the concentrations of  $10^{-5}$  M.<sup>[36]</sup> The quantification of cell survival in this cell line was established by using MTT assays after 72 h exposure (Table 1). The results of this study, summarized in Table 1, demonstrated that all tested imidazoli(ni)um compounds **8a–f** were not active at  $10^{-5}$  M since 100% survival of cells was measured. In contrast, thioglycosylated Ag(I)-NHC complexes **9a–d** were able to decrease the cell viability in HCT-116 cells until 41–64% survival. Interestingly, compound **9a** induced a significant decrease of the cell viability in HCT-116 cells (41% survival), indicating that the growth inhibition constant  $\text{GI}_{50}$  would be less than  $10\ \mu\text{M}$ . These results clearly validate the biological potential of thioglycosylated NHC pharmacophore in this series. Since complexes **9a–d** were found to be slightly unstable in  $\text{D}_2\text{O}$ , focus will be put in the development of more stable thioglycosylated–NHC-based complexes. Structure-activity relationship study (SAR) is currently ongoing in our laboratory to enhance the biological activity of this series of analogues.

## Conclusion

In summary, we described here a flexible route for the synthesis of a family of novel thioglycoside-based NHCs. Protected and unprotected 1-thio- $\beta$ -glucose unit is readily linked to the azolium core through a Pd-catalyzed Migita cross-coupling and this provides tunable access to a diverse range of azolium thioglycosides. The corresponding Ag(I)-NHC complexes are accessed easily and uniquely through a solvent free mechano-

**Table 1.** Growth inhibitory potency against HCT116 cell line.<sup>[a]</sup>

Compound	Viability [%]
<b>8a</b>	110 ± 3
<b>8b</b>	113 ± 0.7
<b>8c</b>	109 ± 7
<b>8d</b>	107 ± 6
<b>8e</b>	104 ± 8
<b>8f</b>	99 ± 1
<b>9a</b>	41 ± 4
<b>9b</b>	63 ± 2
<b>9c</b>	63 ± 0.84
<b>9d</b>	64 ± 0.64

[a] The growth-inhibitory potency against human colon carcinoma HCT-116 cells at the concentrations of  $10^{-5}$  M.

chemical approach. Overall, this study reported here highlights the potential of this new family of carbohydrate derived NHCs as catalysts as well as potential bioactive compounds.

## Experimental Section

### General methods

All operations involving air or moisture sensitive materials were performed under a dry argon atmosphere using syringes, oven-dried glassware, and freshly dried solvents (THF, toluene and CH<sub>2</sub>Cl<sub>2</sub> were purified by passage through a solvent drying column and stored under argon over 3 Å molecular sieves). Air and moisture-sensitive liquids, reagents and solvents were transferred via syringe using standard techniques. All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Organic solutions were concentrated by rotary evaporation (house vacuum, ca. 40 Torr) at 30 °C, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel 60 F254 (0.25 mm thickness) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), and/or vanillin, followed by brief (ca. 30 s) heating on a stream of hot air (ca. 300 °C). Flash column chromatography was performed as described by Still et al.,<sup>[37]</sup> employing silica gel (60 Å pore size, 40–63 mm). IR spectra were recorded as thin films for oils and for solids by the reflexion method on a FT IR spectrometer. NMR spectra were run in CDCl<sub>3</sub> or CD<sub>3</sub>OD at 300 or 400 MHz for <sup>1</sup>H and at 75 or 100 MHz for <sup>13</sup>C using as internal standards the residual CHCl<sub>3</sub> or MeOH signals for <sup>1</sup>H NMR (δ = 7.26 or 3.31) and <sup>13</sup>C NMR (δ = 77.0 or 49.0). A combination of COSY, HSQC, HMBC and nOe experiments was used to aid assignment when necessary. The milling reactions were carried out in a vibratory Retsch Mixer Mill 400 (vbm) operated at up to 30 Hz. Solid-State NMR spectra were recorded on a Varian VNMRS600 spectrometer (Larmor frequencies: ν<sup>1</sup>H = 599.818 MHz and ν<sup>13</sup>C = 150.839 MHz) using a 3.2 mm magic angle spinning (MAS) probe (T3 Wide Bore HX). Values of the isotropic chemical shifts of <sup>1</sup>H and <sup>13</sup>C are given using a secondary reference: Adamantane (1.8 ppm for <sup>1</sup>H and 38.5 ppm for <sup>13</sup>C). For the imidazolium salts, the studies were carried out with a π/2 pulse length of 4 μs, and a recycle delay of 10 s for <sup>1</sup>H and 5 s for <sup>13</sup>C. The used contact time is 2 ms. For the silver complexes, the studies were carried out with a π/2 pulse length of 7 μs, and a recycle delay of 1 s for <sup>1</sup>H and 2 s for <sup>13</sup>C. The used contact time is 1 ms. Low resolution mass spectra were obtained with an ion trap (ESI source) by the FAB method. Mass spectra were realized by electrospray impact (ESI) and atmospheric pressure chemical ionisation (APCI). Melting points were measured on a digital melting point capillary apparatus and were uncorrected. Specific optical rotations were measured in solution using sodium light (D line 589 nm).

The XantPhos Palladium precatalyst Pd–G3 was synthesized according to literature protocol.<sup>[38]</sup>

### Synthetic procedures

#### General procedure for the synthesis of 8a–f

A flame dried tube was charged with XantPhos Pd–G<sub>3</sub> (10 mol%), diiodinated imidazolium (1 equiv) or imidazolium salts (1 equiv), a THF/H<sub>2</sub>O mixture (1/1, 0.03 M) and Et<sub>3</sub>N (1.5 equiv). The mixture was stirred at room temperature for 5 min and a solution of 1-thio-β-glucopyranose (**7a** or **7b**) in THF or H<sub>2</sub>O (3 equiv. in 1 mL) was added dropwise over a period of 20 min. The tube was then capped

with a rubber septum, evacuated, backfilled with argon, sealed and the mixture was stirred at room temperature for 30 min. The residue was purified by flash chromatography over silica gel (DCM/MeOH = 99:1) or by inverse column chromatography (Column used: Biotage SNAP Ultra C18, 12 g, HP-Sphere C18 25 μm; Flow rate: 20 ml/min; 100% of H<sub>2</sub>O during 3 min then linear gradient during 25 min until 100% of CAN; The crude is solubilized in 10 mL of (10% ACN in H<sub>2</sub>O) and filtered on nylon 2 μm filter; Injected volume: 2 mL) to afford the desired products.

**3-(2,6-dimethyl-4-(((2R,3S,4R,5S,6S)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)thio)phenyl)-1-(2,6-dimethyl-4-(((2S,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)thio)phenyl)-4,5-dihydro-1H-imidazol-3-ium chloride (8a):** Following the general procedure, the reaction was carried out starting from Pd–G3 (8.5 mg, 0.009 mmol), 1,3-bis(4-iodo-2,6-dimethylphenyl)-4,5-dihydro-1H-imidazol-3-ium chloride **6a** (50 mg, 0.088 mmol), THF (3.0 mL), Et<sub>3</sub>N (18 μL, 0.13 mmol) and *tetra-O*-acetylated 1-thio-β-D-glucopyranose **7a** (96 mg, 0.264 mmol) dissolved in THF (1 mL). The residue was purified by flash chromatography over silica gel (DCM/MeOH = 99:1) to afford the desired pure product **8a** (91.5 mg, 0.088 mmol, 100%) as a dark brown solid; mp (132–133 °C); TLC: R<sub>f</sub> = 0.7 (DCM/MeOH = 85:15); IR (thin film, neat) ν<sub>max</sub>/cm<sup>-1</sup>: 2954, 2880, 2185, 1755, 1737, 1629, 1478, 1433, 1377, 1365, 1247, 1206, 1089, 1062, 1031, 979, 957, 914, 826, 726, 645; [α]<sub>D</sub><sup>19</sup>: -36 (c 0.25, DCM); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 9.17 (s, 1H), 7.23 (s, 4H), 5.21 (t, J = 9.3 Hz, 2H), 5.02 (t, J = 9.7 Hz, 2H), 4.93 (t, J = 9.6 Hz, 2H), 4.76 (d, J = 10.2 Hz, 2H), 4.63 (s, 4H), 4.22 (dd, J = 12.4, 4.8 Hz, 2H), 4.13 (bd, J = 12.1 Hz, 2H), 3.84–3.75 (m, 2H), 2.42 (s, 12H), 2.06 (s, 12H), 1.99 (s, 6H), 1.95 (s, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 170.5, 170.0, 169.5, 169.4, 136.2, 135.4, 132.7, 132.2, 85.2, 75.9, 73.8, 69.8, 68.1, 62.2, 52.3, 21.0, 20.8, 20.6, 18.8; HR-MS(ESI): for C<sub>47</sub>H<sub>59</sub>N<sub>2</sub>O<sub>18</sub>S<sub>2</sub> (M)<sup>+</sup>: m/z calcd 1003.3204 found 1003.3198.

**3-(2,6-diisopropyl-4-(((2R,3S,4R,5S,6S)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)thio)phenyl)-1-(2,6-diisopropyl-4-(((2S,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)thio)phenyl)-4,5-dihydro-1H-imidazol-3-ium chloride (8b):** Following the general procedure, the reaction was carried out starting from Pd–G3 (7 mg, 0.007 mmol), 1,3-bis(4-iodo-2,6-diisopropylphenyl)-4,5-dihydro-1H-imidazol-3-ium chloride **6b** (50 mg, 0.074 mmol), THF/H<sub>2</sub>O (1:1, 3.0 mL), Et<sub>3</sub>N (15 μL, 0.11 mmol) and *tetra-O*-acetylated 1-thio-β-D-glucopyranose **7a** (80 mg, 0.22 mmol) dissolved in THF (1 mL). The residue was purified by flash chromatography over silica gel (DCM/MeOH = 99:1) to afford the desired pure product **8b** (84 mg, 0.073 mmol, 98%) as a dark brown solid; mp (142–143 °C); TLC: R<sub>f</sub> = 0.7 (DCM/MeOH = 85:15); IR (thin film, neat) ν<sub>max</sub>/cm<sup>-1</sup>: 2966, 2929, 2870, 2185, 1756, 1737, 1628, 1466, 1442, 1366, 1327, 1249, 1211, 1090, 1066, 1034, 981, 916, 829, 726, 645; [α]<sub>D</sub><sup>19</sup>: -28 (c 0.25, DCM); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 8.70 (s, 1H), 7.36 (d, J = 11.1 Hz, 4H), 5.20 (t, J = 9.3 Hz, 2H), 5.01 (t, J = 9.8 Hz, 2H), 4.88 (t, J = 9.6 Hz, 2H), 4.82 (s, 4H), 4.72 (d, J = 10.0 Hz, 2H), 4.30 (dd, J = 12.5, 4.5 Hz, 2H), 4.11 (d, J = 12.1 Hz, 2H), 3.79 (dd, J = 9.8, 2.2 Hz, 2H), 3.15 (dd, J = 14.7, 7.3 Hz, 1H), 3.04 (dd, J = 12.4, 5.9 Hz, 3H), 2.06 (d, J = 3.2 Hz, 12H), 1.98 (s, 6H), 1.94 (s, 6H), 1.43–1.34 (m, 12H), 1.26 (d, J = 6.6 Hz, 12H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 170.6, 170.0, 169.5, 169.2, 158.1; 147.0, 135.5, 129.8, 129.3, 84.8, 76.2, 74.0, 69.5, 67.9, 62.2, 55.1, 46.5, 29.3, 25.4, 25.3, 24.0, 20.9, 20.8, 20.6; HR-MS(ESI): for C<sub>55</sub>H<sub>75</sub>N<sub>2</sub>O<sub>18</sub>S<sub>2</sub> (M)<sup>+</sup>: m/z calcd 1115.4456 found 1115.4465.

**3-(2,6-dimethyl-4-(((2R,3S,4R,5R,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)thio)phenyl)-1-(2,6-dimethyl-4-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)**

**tetrahydro-2H-pyran-2-yl)thio)phenyl)-4,5-dihydro-1H-imidazol-3-ium chloride (8c):** Following the general procedure, the reaction was carried out starting from Pd-G3 (33.5 mg, 0.03 mmol), 1,3-bis(4-iodo-2,6-dimethylphenyl)-4,5-dihydro-1H-imidazol-3-ium chloride **6a** (200 mg, 0.35 mmol), THF/H<sub>2</sub>O (1:1, 12.0 mL), Et<sub>3</sub>N (74  $\mu$ L, 0.52 mmol) and 1-thio- $\beta$ -D-glucopyranose **7b** (207 mg, 1.06 mmol) dissolved in distilled water (1 mL). When the reaction was finished, a mixture of MeOH and H<sub>2</sub>O (10:10 mL) was added to the resulting residue followed by filtration and evaporation of the resulting filtrate. The residue thus obtained was dissolved in 10% ACN in H<sub>2</sub>O (10 mL) and purified by reverse phase column (see general procedure) to afford the desired pure product **8c** (190.6 mg, 0.27 mmol, 77%) as a beige solid; mp (173–174 °C); TLC:  $R_f$ =0.0 (DCM/MeOH=80:20); IR (thin film, neat)  $\nu_{\max}/\text{cm}^{-1}$ : 2926, 1611, 1476, 1454, 1361, 1295, 1257, 1212, 1103, 1066, 1034, 989, 878, 831, 670, 618;  $[\alpha]_D^{20}$ : -44 (c 0.25, MeOH); <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  (ppm): 7.50 (s, 4H), 4.72 (d,  $J$ =9.7 Hz, 2H), 4.61 (s, 4H), 4.10–4.00 (m, 1H), 4.95–3.50 (m, 7H), 3.45–3.15 (m, 11H), 2.47 (s, 12H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  (ppm): 139.3, 137.6, 133.0, 131.4, 88.5, 82.1, 79.5, 73.8, 71.4, 62.8, 52.7, 18.2; <sup>1</sup>H solid state NMR (600 MHz)  $\delta$  (ppm): 9.6, 7.8, 5.7, 3.7, 3.0, 1.7; <sup>13</sup>C solid state NMR (151 MHz)  $\delta$  (ppm): 161.6, 159.9, 140.7, 140.2, 138.8, 138.2, 137.7, 163.5, 135.9, 135.2, 133.3, 131.0, 128.5, 127.4, 127.0, 88.6, 84.0, 80.2, 79.6, 76.9, 76.2, 74.0, 72.8, 72.0, 70.4, 63.2, 61.6, 54.5, 22.9, 21.1, 20.2, 19.3. HR-MS(ESI): for C<sub>31</sub>H<sub>43</sub>N<sub>2</sub>O<sub>10</sub>S<sub>2</sub> (M)<sup>+</sup>:  $m/z$  calcd 667.2359 found 667.2354.

**3-(2,6-diisopropyl-4-(((2R,3S,4R,5R,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)thio)phenyl)-1-(2,6-diisopropyl-4-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)**

**tetrahydro-2H-pyran-2-yl)thio)phenyl)-4,5-dihydro-1H-imidazol-3-ium chloride (8d):** Following the general procedure, the reaction was carried out starting from Pd-G<sub>3</sub> (28 mg, 0.03 mmol), 1,3-bis(4-iodo-2,6-diisopropylphenyl)-4,5-dihydro-1H-imidazol-3-ium chloride **6b** (200 mg, 0.29 mmol), THF/H<sub>2</sub>O (1:1, 10 mL), Et<sub>3</sub>N (62  $\mu$ L, 0.44 mmol) and 1-thio- $\beta$ -D-glucopyranose **7b** (174 mg, 0.88 mmol) dissolved in distilled water (1 mL). When the reaction was finished, a mixture of MeOH and H<sub>2</sub>O (10:10 mL) was added to the resulting residue followed by filtration and evaporation of the resulting filtrate. The residue thus obtained was dissolved in 10% ACN in H<sub>2</sub>O (10 mL) and purified by reverse phase column (see general procedure) to afford the desired pure product **8d** (196 mg, 0.24 mmol, 82%) as an orange solid; mp (190–191 °C); TLC:  $R_f$ =0.0 (DCM/MeOH=80:20); IR (thin film, neat)  $\nu_{\max}/\text{cm}^{-1}$ : 2964, 2930, 2871, 1610, 1577, 1467, 1444, 1389, 1368, 1327, 1291, 1266, 1199, 1104, 1070, 1037, 988, 943, 875, 828, 621;  $[\alpha]_D^{20}$ : -20 (c 0.5, MeOH); <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  (ppm): 7.62 (s, 4H), 4.72 (d,  $J$ =9.6 Hz, 2H), 4.65 (s, 4H), 3.97 (d,  $J$ =11.1 Hz, 2H), 3.74 (dd,  $J$ =12.0, 5.6 Hz, 2H), 3.46 (dd,  $J$ =16.8, 8.1 Hz, 4H), 3.35–3.23 (m, 4H), 3.16 (sept,  $J$ =6.5 Hz, 4H), 2.21 (bs, 3H), 1.48 (d,  $J$ =6.6 Hz, 12H), 1.37 (d,  $J$ =6.1 Hz, 12H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  (ppm): 148.3, 140.4, 129.6, 128.0, 88.8, 82.3, 79.6, 73.6, 71.4, 62.9, 55.1, 30.4, 25.4, 24.1, 24.0; <sup>1</sup>H solid state NMR (600 MHz, none)  $\delta$  (ppm): 10.8, 7.9, 4.0, 1.6, 1.55, 1.4; <sup>13</sup>C solid state NMR (151 MHz, none)  $\delta$  (ppm): 160.4, 148.0, 141.7, 139.6, 131.0, 128.7, 123.8, 90.8, 86.2, 80.8, 73.1, 63.0, 55.5, 48.2, 30.0, 26.0. HR-MS(ESI): for C<sub>39</sub>H<sub>59</sub>ClN<sub>2</sub>O<sub>10</sub>S<sub>2</sub> (M)<sup>+</sup>:  $m/z$  calcd 779.3611 found 779.3601.

**3-(2,6-diisopropyl-4-(((2R,3S,4R,5R,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)thio)phenyl)-1-(2,6-diisopropyl-4-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)**

**tetrahydro-2H-pyran-2-yl)thio)phenyl)-1H-imidazol-3-ium chloride (8e):** Following the general procedure, the reaction was carried out starting from Pd-G<sub>3</sub> (30 mg, 0.03 mmol), 1,3-bis(4-iodo-2,6-diisopropylphenyl)-4,5-dihydro-1H-imidazol-3-ium chloride **6c** (200 mg, 0.29 mmol), THF/H<sub>2</sub>O (1:1, 10 mL), Et<sub>3</sub>N (62  $\mu$ L, 0.44 mmol)

and 1-thio- $\beta$ -D-glucopyranose **7b** (174 mg, 0.88 mmol) dissolved in distilled water (1 mL). When the reaction was finished, a mixture of MeOH and H<sub>2</sub>O (10:10 mL) was added to the resulting residue followed by filtration and evaporation of the resulting filtrate. The residue thus obtained was dissolved in 10% ACN in H<sub>2</sub>O (10 mL) and purified by reverse phase column (see general procedure) to afford the desired pure product **8e** (192 mg, 0.24 mmol, 82%) as a pale yellow solid; mp (249–250 °C); TLC:  $R_f$ =0.0 (DCM/MeOH=80:20); IR (thin film, neat)  $\nu_{\max}/\text{cm}^{-1}$ : 2965, 2874, 1609, 1581, 1540, 1513, 1469, 1443, 1415, 1389, 1368, 1330, 1285, 1221, 1076, 1035, 987, 952, 872, 834, 688, 616;  $[\alpha]_D^{20}$ : -2 (c 0.5, MeOH); <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  (ppm): 8.30 (s, 2H), 7.68 (s, 4H), 4.76 (d,  $J$ =9.7 Hz, 2H), 3.96 (bd,  $J$ =12.2 Hz, 2H), 3.73 (bdd,  $J$ =12.0, 5.8 Hz, 2H), 3.50–3.22 (m, 14H), 2.48 (sept,  $J$ =6.7 Hz, 4H), 1.37 (d,  $J$ =6.6 Hz, 12H), 1.29 (d,  $J$ =6.6 Hz, 12H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  (ppm): 147.0, 141.6, 129.9, 127.5, 88.7, 82.4, 79.6, 73.7, 71.4, 62.9, 30.5, 24.6, 23.7; <sup>1</sup>H solid state NMR (600 MHz, none)  $\delta$  (ppm): 11.3, 9.0, 8.7, 7.7, 3.6, 2.6, 1.7; <sup>13</sup>C solid state NMR (151 MHz, none)  $\delta$  (ppm): 141.0, 140.6, 136.6, 131.8, 128.8, 127.2, 125.9, 89.1, 84.3, 79.2, 72.8, 63.7, 20.4. HR-MS(ESI): for C<sub>39</sub>H<sub>57</sub>N<sub>2</sub>O<sub>10</sub>S<sub>2</sub> (M)<sup>+</sup>:  $m/z$  calcd 777.3455 found 777.3452.

**3-(2,6-dimethyl-4-(((2R,3S,4R,5R,6S)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)thio)phenyl)-1-(2,6-dimethyl-4-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)**

**tetrahydro-2H-pyran-2-yl)thio)phenyl)-1H-imidazol-3-ium chloride (8f):** Following the general procedure, the reaction was carried out starting from Pd-G<sub>3</sub> (28 mg, 0.03 mmol), 1,3-bis(4-iodo-2,6-dimethylphenyl)-4,5-dihydro-1H-imidazol-3-ium chloride **6d** (166 mg, 0.29 mmol), THF/H<sub>2</sub>O (1:1, 10 mL), Et<sub>3</sub>N (62  $\mu$ L, 0.44 mmol) and 1-thio- $\beta$ -D-glucopyranose **7b** (174 mg, 0.88 mmol) dissolved in distilled water (1 mL). When the reaction was finished, a mixture of MeOH and H<sub>2</sub>O (10:10 mL) was added to the resulting residue followed by filtration and evaporation of the resulting filtrate. The residue thus obtained was dissolved in 10% ACN in H<sub>2</sub>O (10 mL) and purified by reverse phase column (see general procedure) to afford the desired pure product **8f** (145 mg, 0.21 mmol, 71%) as a white milky to light yellow solid; mp (231–232 °C); TLC:  $R_f$ =0.0 (DCM/MeOH=80:20); IR (thin film, neat)  $\nu_{\max}/\text{cm}^{-1}$ : 3076, 2984, 1582, 1543, 1477, 1456, 1366, 1301, 1225, 1130, 1088, 1067, 1030, 987, 950, 881, 837, 671, 618;  $[\alpha]_D^{20}$ : -16 (c 0.5, MeOH); <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD)  $\delta$  (ppm): 8.13 (s, 2H), 7.58 (s, 4H), 4.79 (d,  $J$ =9.7 Hz, 2H), 3.95 (bd,  $J$ =12.1 Hz, 2H), 3.70 (dd,  $J$ =11.9, 6.3 Hz, 2H), 3.47–3.20 (m, 16H), 2.24 (s, 12H); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>OD)  $\delta$  (ppm): 140.6, 136.5, 133.1, 131.3, 88.5, 82.3, 79.7, 73.9, 71.5, 62.9, 17.5; <sup>1</sup>H solid state NMR (600 MHz, none)  $\delta$  (ppm): 12.0, 8.1, 4.1, 3.5, 1.6; <sup>13</sup>C solid state NMR (151 MHz, none)  $\delta$  (ppm): 148.1, 146.4, 142.0, 130.4, 128.7, 126.2, 125.9, 125.5, 121.6, 89.8, 87.5, 81.4, 79.8, 78.0, 73.6, 72.7, 72.3, 69.8, 64.3, 62.0, 30.1, 27.0, 26.1, 24.6, 22.2, 21.0. HR-MS(ESI): for C<sub>31</sub>H<sub>41</sub>N<sub>2</sub>O<sub>10</sub>S<sub>2</sub> (M)<sup>+</sup>:  $m/z$  calcd 665.2203 found 665.2198.

### General procedure for the mechanochemical reactions

Imidazolium salt and silver oxide were introduced in a 10 mL stainless steel grinding bowl with one stainless steel ball (10 mm diameter). The bowl was closed and subjected to grinding at 30 Hz. The powder was recovered with a spatula.

**Compound 9a:** General procedure was followed with **8c** (80.0 mg, 0.114 mmol, 1.0 eq) and silver oxide (13.2 mg, 57.0  $\mu$ mol, 0.5 eq.). Reaction mixture was grinded for 1 hour at 30 Hz to afford **9a** as a grey solid. <sup>1</sup>H solid state NMR (600 MHz)  $\delta$  7.8, 5.3, 5.1, 2.8, 1.6, 1.56, 1.3; <sup>13</sup>C solid state NMR (151 MHz)  $\delta$  207.4, 137.8, 132.0, 127.8, 90.7, 86.2, 80.4, 73.5, 63.0, 52.7, 46.9, 18.6.

**Compound 9b:** General procedure A was followed with **8d** (80.0 mg, 0.123 mmol, 1.00 eq) and silver oxide (14.2 mg, 61.3  $\mu$ mol,

0.50 eq). Reaction mixture was grinded for 1 hour at 30 Hz to afford **9b** as a grey solid. <sup>1</sup>H solid state NMR (600 MHz) δ 7.8, 5.1, 3.9, 2.2, 1.3; <sup>13</sup>C solid state NMR (151 MHz) δ 207.4, 137.8, 132.0, 127.8, 90.7, 86.2, 80.4, 73.5, 63.0, 52.7, 46.9, 18.6.

**Compound 9c:** General procedure was followed with **8e** (80.0 mg, 0.114 mmol, 1.0 eq) and silver oxide (13.2 mg, 57.0 μmol, 0.5 eq). Reaction mixture was grinded for 1 hour at 30 Hz to afford **9c** as a grey solid. <sup>1</sup>H solid state NMR (600 MHz) δ 7.8, 4.7, 2.2; <sup>13</sup>C solid state NMR (151 MHz) δ 182.8, 136.7, 126.2, 80.0, 72.8, 63.4, 18.3.

**Compound 9d:** General procedure was followed with **8f** (100.0 mg, 0.123 mmol, 1.0 eq) and silver oxide (14.2 mg, 61.5 μmol, 0.5 eq). Reaction mixture was grinded for 2 hours at 30 Hz to afford **9d** as a grey solid. <sup>1</sup>H solid state NMR (600 MHz) δ 7.9, 4.3, 2.9, 1.4; <sup>13</sup>C solid state NMR (151 MHz) δ 183.7, 146.8, 140.8, 136.2, 133.1, 127.6, 85.9, 79.8, 72.5, 63.2, 29.7, 25.3.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Keywords:** Glycosides · Mechanochemistry · Migita cross-coupling · N-Heterocyclic carbenes · Palladium

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