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FULL PAPER

Synthesis of Diverse C2-Glyco-Acyl Azides and -Ureas via Palladium-Catalyzed Carbonylation Coupling of 2-Iodoglycals

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Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

Abstract: Herein, we describe the synthesis of acyl azides and acyl urea glycals, a new class of C-2 branched glycoconjugates, employing Pd-catalyzed carbonylative coupling. A new strategy was developed to obtain acyl azides via carbonylative coupling between 2-iodo-glycals and NaN_3 catalyzed by $Pd(dba)_2$/Xantphos and carbon monoxide as a carbonyl source. Acyl azide glycals were used as synthetic intermediates in obtaining new acyl urea glycals via carbonylative coupling catalyzed by $Pd(OAc)_2$ and 1,10-Phen. Different glycal substrates including disaccharide-type were studied, and various acyl azides and acyl ureas were prepared. Reaction yields were moderate to high (31–99%) and reaction time varying from short to long (0.5 – 20 h).

Introduction

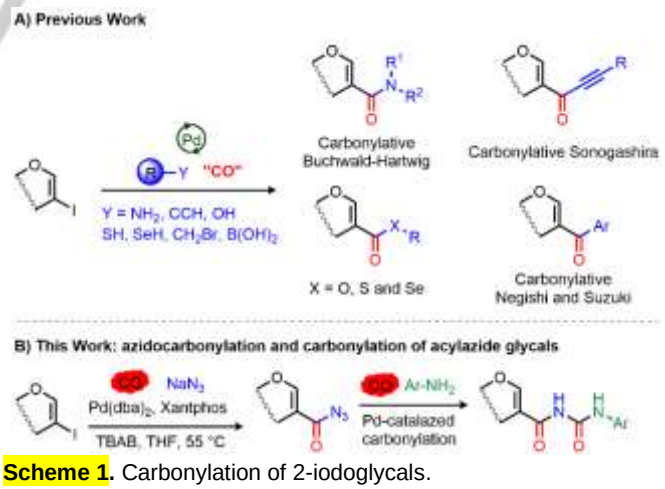
Carbohydrates are an important class of compounds that participate in several biological processes in living organisms.[1] In the field of organic chemistry, this class of molecules is widely used as a building block in the synthesis of natural products and biologically active molecules.[2] Several of these molecules, which have therapeutic properties, are from glycoconjugates type formed through C-C bonds between the saccharide moiety and an aglycone.[3,4] This type of link increases the stability of the molecule in face of enzymatic processes and chemical hydrolysis when compared to its C-O and C-N analogues.[5]

New synthetic methodologies for the formation of glycoconjugates, specially C-2 branched ones, have been constantly developed.[6,7] Among the many existing strategies, the C-2 functionalization of unsaturated sugars, known as glycals, has been widely explored in recent years. Many of these synthetic methods involve classical Suzuki-Miyaura,[8] Heck,[9] Sonogashira[10] and Stille[11] cross-coupling reactions. Recently, some research groups, including ours, have been expanding these synthetic methods by adding carbonylative conditions to obtain new C2-glycoconjugates (scheme 1A).[12–19]

Acyl azides are valuable synthetic intermediates once, from them, it is possible to obtain a huge variety of compounds like isocyanates (the Curtius rearrangement), oxazoles,[20] amides, thiazolidinone,[21] iminophosphoranes,[22] peptides[23], several heterocycles[24] and ureas[25]. Also, it is possible to design important mimics of N-acetylglycoconjugates from C2-branched analogues of carbohydrates functionalized with acyl azides. Unfortunately, the number of methodologies to reach acyl azides is still very limited. They are commonly obtained through the reaction between sodium azide and acid chlorides,[26] anhydrides[27] and N-acyl benzotriazoles[28]. Typically, these synthetic methods use highly reactive substrates, which may be a problem when they are employed in the carbohydrate chemistry.

The synthesis of *N*-acyl urea derivatives includes the activation of the corresponding acid and coupling it to a urea, or the reaction between an amide and phenyl carbamate,[29] isocyanates and acyl isocyanates with amines and phosgene.[30] Alternatively, the *N*-acyl urea motif could be obtained applying transition-metal catalyzed carbonylation chemistry.[31] After the reports of the Pd-catalyzed carbonylation of haloarenes reactions,[32–34] the interest of organic chemists has increased due to its application in the synthesis of *N*-acyl urea.

With these considerations in mind, and based on our experience in synthetic studies of D-glycals,[12–15] we would like to know whether it was feasible to obtain glyco acyl azide from glycal substrates and use it as a synthetic intermediary. Therefore, here we describe the easy access to several C2-glycoconjugates via palladium-catalyzed azidocarbonylation reaction of 2-iodoglycals (scheme 1B).



Scheme 1. Carbonylation of 2-iodoglycals.

Results and Discussion

Our study was initiated by the synthesis of several different 2-iodo-glycals (for details, see SI). For this, it was used the methodology developed by Vankar et al[9], where iodination

occurs via electrophilic iodine catalyzed by $AgNO_3$. The iodides derived from D-glycal, D-galactal and D-maltal with the hydroxyl groups functionalized with benzyl, acetyl and methyl were obtained with yields from 48% to 64%.

With the 2-iodo-glycals in hand, the optimization of the Pd-catalyzed azidocarbonylation was initiated. The reaction between compound **1a** and an inorganic azide (NaN_3) source was selected as a model reaction to investigate the formation of acyl azide (Table 1).

In order to determine the ideal conditions to obtain acyl azides, several parameters such as catalysts, solvents, ligands, temperatures, and additives were investigated. Initially, a catalytic system formed by $Pd(OAc)_2$ and Xantphos in THF was used, leading to the formation of acyl azide **2a** at only a 12% yield (Table 1, entry 1). Other solvents such as MeCN, DMF, and PhMe showed lower efficiency in the formation of the compound **2a**, with DMF and PhMe causing a complete shutdown of the reaction (Table 1, entry 2-4). The presence of water in the reaction was evaluated as a way to increase the solubility of NaN_3 in the medium; however, the THF/H_2O mixture led to a lower yield compared to anhydrous conditions (Table 1, entry 5).

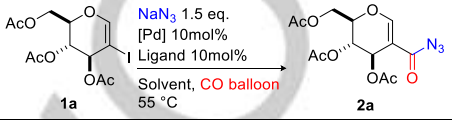
$Mo(CO)_6$ is a classic carbon monoxide source in carbonylative coupling reactions, being also used in the synthesis of some C2-glyconjugates. [13–15] The use of $Mo(CO)_6$ to obtain the acyl azide **2a** was evaluated, but it was not observed the formation of the product **2a** (Table 1, entry 6).

Then, it was investigated how different palladium catalysts influence the formation of the acyl azide **2a**. Initially, based on the conditions published by Grushin et al for azidocarbonylation,[35] the catalyst was changed to $Pd(dba)_2$ favoring the formation of acyl azide at 20% (Table 1, entry 7). Other catalysts such as $Pd_2(dba)_3$, $Pd(acac)_2$, $PdCl_2(PPh_3)_2$, $PdCl_2$ and $PdBr_2$ were tested presenting inferior efficiency. The use of PEPPSI-IPr, a general Pd-NHC catalyst for Buchwald-Hartwig reactions of esters and amides,[36] also led to inferior results (Table 1, entries 8–13). Reports in the literature indicate that ligands with electron donating groups are more efficient in carbonylation reactions because they decrease the formation of Pd-black.[37] In addition, in order to prevent the poisoning of the palladium by multiple bonds with CO, bidentate ligands were used because they usually present better results in this type of reaction in relation to monodentate ligands.[38] With this in mind, different ligands based on phosphine were tested. Mono and bi-dentate ligands such as PPh_3, RuPhos, DPEPhos, SPhos, DavePhos and dppf were inefficient in the formation of acyl azide, leading to yields ranging from 0 to 12% (Table 1, entries 14–19), being Xantphos still the best choice.

Even varying the sources of palladium, ligand and solvent, the formation of acyl azide proved to be inefficient. The low yields and long reaction time were attributed to the low solubility of sodium azide in THF. So, in order to increase the efficiency of this carbonylation coupling reaction (that uses an inorganic salt in organic solvent), it was used a phase transfer agent (Table 1, entries 20–22).[39]

Tetrabutylammonium salts with different anions (chloride-TBACl, bromide-TBAB and iodine-TBAI) were evaluated as phase transfer agents, being TBAB the only one to lead to obtaining acyl azide with 53% yield in 50 min (Table 1, entry 20). Interestingly, TBACl and TBAI led to complete reaction shutdown (Table 1, entry 21-22). Different temperatures were evaluated to obtain acyl azide, where the ideal reaction condition was established at 55 °C (Table S2, entries 1–3). Finally, the progress of the reaction in different amounts and ratios of Pd-Ligand were investigated, and it was determined that the best catalytic system was with a ratio of 1:1 10 mol% $Pd(dba)_2$ and Xantphos, which result was in accordance with a previous report by Buchwald (Table S2, entries 4–7).[40] Unfortunately, in all tests a complex mixture was obtained as a by-product. Therefore, the best condition found to obtain acyl azide glycosides from 2-iodo-glucal is CO balloon (1 atm), NaN_3 (1.5 equivalent), TBAB (0.5 equiv.), $Pd(dba)_2$ (10 mol%), Xantphos (10 mol%), in THF at 55 °C.

Table 1. Optimization of the reaction conditions.



Entry	[Pd]	Ligand	Additive	Solvent	Time	Yield
Effect of Solvent						
1	$Pd(OAc)_2$	Xantphos	-	THF	17 h	12%
2	$Pd(OAc)_2$	Xantphos	-	PhMe	17 h	5%
3	$Pd(OAc)_2$	Xantphos	-	MeCN	17 h	NR
4	$Pd(OAc)_2$	Xantphos	-	DMF	18 h	NR
5[a]	$Pd(OAc)_2$	Xantphos	-	THF/H_2O	18 h	10%
6[b]	$Pd(OAc)_2$	Xantphos	-	THF	17 h	NR
Effect of Catalyst						
7	$Pd(dba)_2$	Xantphos	-	THF	20 h	20%
8	$Pd_2(dba)_3$	Xantphos	-	THF	20 h	16%
9	$Pd(acac)_2$	Xantphos	-	THF	21 h	12%
10	$PdCl_2(PPh_3)_2$	Xantphos	-	THF	21 h	NR
11	PEPPSI-IPr	Xantphos	-	THF	20 h	NR
12	$PdBr_2$	Xantphos	-	THF	20 h	NR
13	$PdCl_2$	Xantphos	-	THF	21 h	NR
Effect of Ligand						
14	$Pd(dba)_2$	PPh_3	-	THF	22 h	5%
15	$Pd(dba)_2$	RuPhos	-	THF	22 h	7%
16	$Pd(dba)_2$	DPEphos	-	THF	15 h	5%
17	$Pd(dba)_2$	Sphos	-	THF	15 h	12%
18	$Pd(dba)_2$	Davephos	-	THF	15 h	12%
19	$Pd(dba)_2$	dppf	-	THF	15 h	NR
Effect of Additive						
20	$Pd(dba)_2$	Xantphos	TBAB	THF	50 min	53%
21	$Pd(dba)_2$	Xantphos	TBACl	THF	21 h	NR
22	$Pd(dba)_2$	Xantphos	TBAI	THF	21 h	NR

[a]THF/H_2O in the ratio of 5/3 (v/v). [b] Use of $Mo(CO)_6$ as a source of CO.

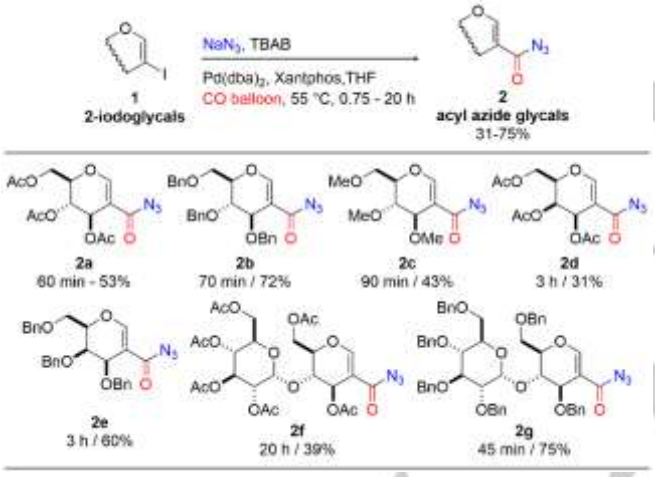
NR: no product **2a** was found.

With the reaction conditions in hand, different glycal substrates including disaccharide-type were then converted to the corresponding acyl azides using the 2-iodo-glycals to investigate the scope of the reaction (Table 2).

In addition to the 2-iodo-D-glucal protected with the acetyl group **1a** which provided the respective acyl azide in 53%, we also tested our approach with benzyl **1b** and methyl groups **1c**. The respective acyl azides were obtained in 72% and 43%, respectively (Table 2). The reaction time for D-glucal-derived acyl azides was similar, ranging from 70–90 min. Acetyl- and benzyl-protected D-galactose and D-maltose were also evaluated. Acyl azides derived from galactose were obtained with moderate to good yields, with acetyl-acyl azide **2d** being obtained at 31% and benzyl-acyl azide **2e** at 60%. Glycal disaccharide (2-iodo-D-maltal) with acetyl **1f** and benzyl **1g**-protected hydroxyls were also subjected to an azidocarbonylation reaction, affording the respective acyl azide **2f** and **2g** with 39% and 75% yields, respectively.

Additionally, acylazides **2a-g** showed relatively high stability when stored in a fridge (ca. 5 °C), showing no signs of degradation for a period of two months.

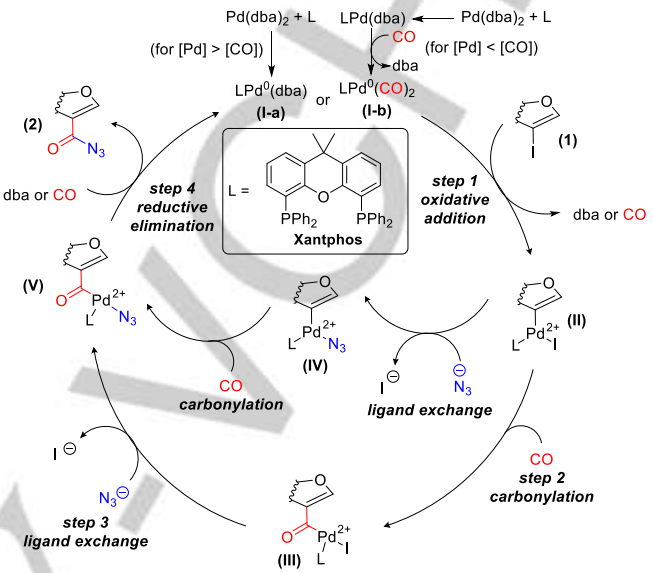
Table 2. Synthesis of D-glycal Acyl azides.[a]



[a]Reaction conditions: 2-iodoglycal (0.1 mmol), sodium azide (1.5 equiv.); TBAB (0.5 equiv.); CO balloon; $Pd(dba)_2$ (10 mol%), Xantphos (10 mol%) in THF (1 mL) at 55 °C with time ranging from 0.75 to 20 h.

A proposal for the reaction mechanism of the formation of acyl azide **2a** is described in Scheme 2. Based on the previous results reported by Grushin et al,[41] the active Pd^0 species **I** is dependent on the concentration of CO, where it can be $LPd^0(dba)$ **I-a** (for [Pd] > [CO]) or $LPd^0(CO)_2$ **I-b** (for [Pd] < [CO]). Inspired by a classical Pd^0/Pd^{2+}-catalytic cycle, the step 1 of the reaction involves an oxidative addition of Pd^0 at the C-I bond of glycal **1** to generate complex **II**. The next steps of carbonylation (step 2) and ligand exchange (step 3) can occur simultaneously, causing complexes **III** and **IV** to co-exist in the reaction medium. Then, complexes **III** and **IV** are converted into acylpalladium complex **V**. Finally, a reductive elimination occurs (step 4), to originate acyl azide **2** and regenerate active Pd^0 species.

Knowing the importance that urea-based compounds represent for life sciences, we decided to use the compounds obtained in the synthesis of novel glycoureas. For that, we used the methodology developed by Jiao et al[25] that uses a catalytic system formed by $Pd(OAc)_2$ as a source of palladium, 1,10-phenanthroline as ligand, THF as solvent and CO as the carbonyl source. Under the Jiao conditions, the scope of the reaction was investigated. We built a small urea library, using different amines as shown in Table 3.



Scheme 2. Proposed catalytic cycle for the carbonylative coupling of 2-iodoglycals with sodium azide.

Initially, it was investigated how the the acetyl, benzyl and methyl groups present in glycals interfered with the reaction. Acyl azides **2a**, **2b** and **2c** were subjected to a carbonylation reaction with *p*-methoxyaniline, and the respective acylureas were obtained at 89% (**3a**, acetyl), 99% (**3b**, benzyl), and 86% (**3c**, methyl). As in obtaining acyl azides, acyl azideglycals bearing benzyl groups provided the desired product in better yields when compared to acetyl and methyl groups. Knowing that, several ureas were prepared from the compound **2b**. The results described in Table 3, with different substituted aromatic substrates showed us that all D-glucal urea derivatives were synthesized in moderate to very high yields, ranging from 37% to 99%.

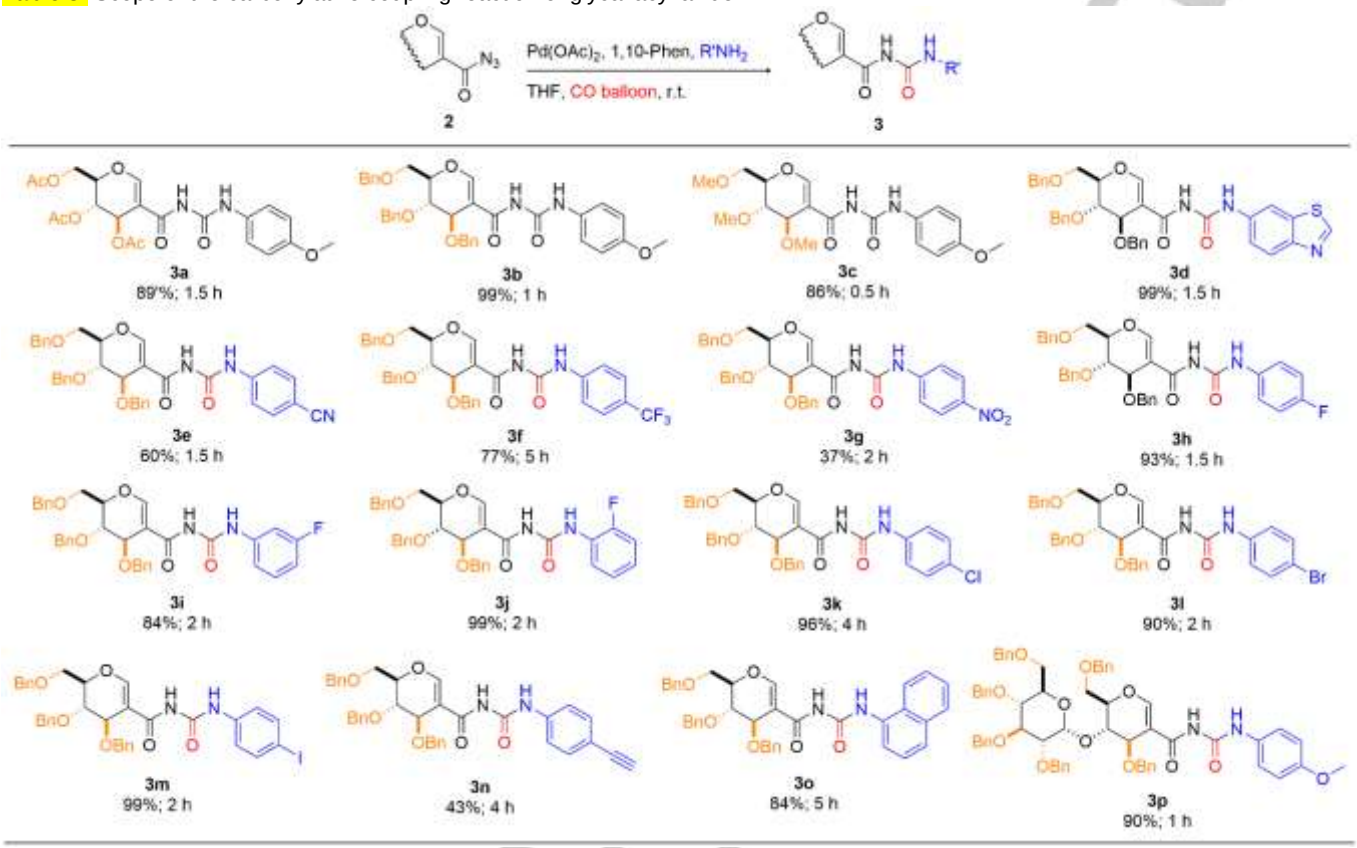
The reaction yields were affected by the presence of electron donating and withdrawing groups in different positions of the phenyl ring. For electron-withdrawing groups in *para* positions, like CN (**3e**), CF_3 (**3f**), NO_2 (**3g**) and ethynyl (**3n**) the products were achieved at yields of 60%, 77%, 37% and 43%, respectively. In the case of the fluorite group, regardless if it is located in the *ortho* (99%) (**3j**) or *para* (93%) (**3h**) positions, the products were obtained in very high yields, but for the *meta* position (**3i**), the product was formed at a slightly lower yield (84%). All reactions were carried out with time varying from 1.5 to 2 hours. In addition, the chlorine (**3k**), bromine (**3l**) and iodine (**3m**) atoms at *para* position did not seem to affect the reaction yields, leading to yields of 96%, 90% and 99% respectively, with reaction time varying from 2 to 4 hours.

Anilines functionalized with strongly donating groups such as methoxy and benzothiazole led to obtaining urea in quantitative yields of 99% (**3a** and **3d**, respectively). Additionally, naphthylamine led to the formation of acyl urea **3o** in 99% quantitative yield. Finally, besides the derivatives of D-glucal (a

monosaccharide), a disaccharide (D-maltal) also provided the urea **3p** in high yield (90%) in only 1h of reaction. Unfortunately, no products were obtained in the cases of alkyl, benzyl and vinyl amines despite our efforts, and this is a limitation of the reaction.

In order to make the synthesis of these compounds more attractive, a urea derivative with free hydroxy groups was synthesized. For this, urea **3a** was subjected to basic hydrolysis conditions to allow urea **4** to be obtained in good yield (74%) (Scheme 3).

Table 3- Scope of the carbonylative coupling reaction of glycal acyl azide.[a]



[a]Reaction conditions: Acyl azide **2** (0.1 mmol); $ArNH_2$ (1.2 equivalent); CO balloon; $Pd(OAc)_2$ (5 mol %), 1,10-Phenanthroline (5 mol %) in THF at room temperature with time ranging from 0.5 to 5 h.

Scheme 3. Deprotected D-acylglucal urea.

Conclusion

In summary, we have synthesized a new class of C2-glyco-acylazides and –ureas from different 2-iodoglycals through palladium-catalyzed carbonylation coupling. Seven acyl azides were obtained from derivatives of D-glucal, D-galactal and D-maltal in moderate and good yields. In addition, the new acyl azide glycals obtained were used in the synthesis of a library containing 16 new ureas in moderate to excellent yields ranging from 37 to 99%. In both approaches, subtracts with different substituents and different glycals were tolerated, showing the versatility of the syntheses performed. A limitation of the reaction is the non-formation of ureas when alkyl, benzyl, and vinyl amines were employed, despite our efforts.

Experimental Section

General

THF was dried over sodium wire using benzophenone as indicator and was freshly distilled before use. HPLC-grade acetonitrile was dried over CaH_2 and distilled before use. THF was degassed by the freeze-pump-thaw method. All reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics, Oakwood or Fluorochem. Flash column chromatography was performed using silica gel with a pore size of 60 Å, 230-400 Mesh (Sigma-Aldrich, cat.# 22,719-6). Reactions were monitored by thin-layer chromatography on silica gel plates (60 F^{254} aluminum sheets) which were rendered visible by ultraviolet 254 nm and/or spraying with vanillin/sulfuric acid in EtOH followed by heating. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ using a Bruker DPX 300 instrument (^1H at 300 MHz, ^{13}C at 75 MHz). Chemical shifts, δ, are reported in parts per million (ppm) and are referenced to the TMS signal. ^1H peaks are quoted to the nearest 0.01 Hz and ^{13}C peaks are quoted to the nearest 0.1 Hz. High-resolution mass spectra (HRMS) were recorded on a micrOTOF-QII Bruker (with electrospray ionization by flight time (ESI-TOF)), nebulization gas pressure 0.4 Bar, drying gas 4l/h, drying temperature 180 °C, capillary voltage 4 kV, collision energy 8 eV, flow to the mass 180 µl/h. FTIR data were obtained using an Agilent Technologies Cary 630. Optical rotations were obtained in a 200 mm cell on an Anton

Paar MCP 200 polarimeter at 589 nm. $[\alpha]_D$ is reported in deg.cm^3.g^{-1}.dm^{-1} and c is expressed in g/100 cm^3. CAUTION! All compounds (intermediates, reagents and final products) were manipulated in a fume hood and avoiding contact with skin.

General Synthesis Procedures

General Procedure A: Synthesis of 2-iodo-glycals

See Supporting Information.

General Procedure B: Azidocarbonylation of 2-Iodo-Glycals

Preparation of the catalyst

To a flame-dried 4-mL reaction tube under N_2 atmosphere were added $Pd(dba)_2$ (6 mg; 0.01 mmol Pd), Xantphos (6 mg; 0.01 mmol) and dry and degassed THF (0.5 mL) was stirred for 30 min. The complex Pd-L was transferred to the reaction flask via cannula.

General Procedure

To a flame-dried 10-mL schlenk tube containing a magnetic stir bar were added 2-iodoglycal (0.1 mmol), NaN_3 (10 mg; 0.15 mmol) and TBAB (0.05 mmol). The flask was sealed and evacuated to a vacuum of 10 mbar and fitted with a CO balloon in 3 cycles. Dry and degassed THF (0.5 mL) was added to the system. The reaction mixture was vigorous stirring at 55 °C and then the catalyst was added. A CO-filled balloon was connected to the schlenk tube. The reaction was kept under stirring until total consumption of the starting material (TLC monitoring). The reaction mixture was filtered through a plug of Celite®, which was thoroughly washed with EtOAc in sequence and evaporated. The reaction mixture was purified by flash column chromatography with an eluent mixture of hexane/EtOAc.

Notes for this procedure

1- THF was degassed via freeze-thaw technique in 3 cycles. Vacuum broken with CO in the last freeze-thaw cycle.

2- The progress of the reaction is accompanied by a color change of the reaction mixture to dark red.

(2R,3S,4R)-2-(acetoxymethyl)-5-(azidocarbonyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (2a). Product **2a** was synthesized according to General Procedure B (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a dark red solid. Yield = 53%. m.p. 53 – 55 °C. $[\alpha]_D^{20}$ = +96.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 2073, 1685, 1628, 1568, 1324, 1264, 1143, 991, 875, 797, 715. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 5.65 – 5.51 (m, 1H), 5.22 – 5.02 (m, 1H), 4.64 – 4.48 (m, 1H), 4.37 (dd, *J* = 12.1, 7.9 Hz, 1H), 4.11 (dd, *J* = 12.2, 4.5 Hz, 1H), 2.02 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 170.1, 169.2, 169.0, 158.2, 105.8, 75.3, 65.4, 61.5, 60.7, 20.6, 20.5, 20.5. ESI-qTOF-HRMS (m/z): $[M + Na]^+$ calcd for $C_{13}H_{15}N_3NaO_8$, 364.0751; found, 364.0756.

(2R,3S,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-5-carbonyl azide (2b). Product **2b** was synthesized according to General Procedure B (chromatography eluent: 5% EtOAc in hexanes) and was obtained as a yellow viscous oil. Yield = 72%. $[\alpha]_D^{20}$ = +13.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 2820, 2769, 2065, 1622, 1566, 1406, 1253, 1214, 1153, 1052, 1033, 994, 881, 711, 674. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.30 – 7.11 (m, 15H), 4.66 – 4.51 (m, *J* = 11.2 Hz, 2H), 4.48 – 4.30 (m, 5H), 4.30 – 4.20 (m, *J* = 1.9 Hz, 1H), 3.80 – 3.72 (m, *J* = 1.6 Hz, 1H), 3.66 (dd, *J* = 10.5, 7.7 Hz, 1H), 3.52 (dd, *J* = 10.6, 5.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 157.8, 138.0, 137.7, 137.3, 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 127.7, 107.8, 77.8, 73.4, 72.6, 71.6, 71.1, 68.2, 67.4. ESI-qTOF-HRMS (m/z): $[M – N_2 + Na]^+$ calcd for $C_{28}H_{27}NNaO_5$, 480.1787; found, 480.1797.

(2R,3S,4R)-3,4-dimethoxy-2-(methoxymethyl)-3,4-dihydro-2H-pyran-5-carbonyl azide (2c). Product **2c** was synthesized according to General Procedure B (chromatography eluent: 20% EtOAc in hexanes) and was obtained as a dark red oil. Yield = 43%. $[\alpha]_D^{20}$ = +33.0° (c = 0.2, $CHCl_3$). IR: ν_{max} (thin film) 2887, 2834, 2732, 2175, 20631624, 1564, 1411, 1361, 1253, 1223, 1199, 1147, 1048, 916, 877, 719, 823. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 4.66 – 4.47 (m, 1H), 4.02 (s, 1H), 3.63 – 3.54 (m, 3H), 3.39 (s, 3H), 3.37 (s, 3H), 3.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 157.5, 107.5, 77.1, 73.0, 70.4, 68.5, 59.1, 57.4, 57.4. HRMS-TOF-ESI (m/z): $[M - N_2 + Na + MeOH]^+$ calcd for $C_{11}H_{19}NNaO_6$, 284.1105; found, 284.1101.

(2R,3R,4R)-2-(acetoxymethyl)-5-(azidocarbonyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (2d). Product **2d** was synthesized according to General Procedure B (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a dark red solid. Yield = 31%. m.p. 78 – 80 °C. $[\alpha]_D^{20}$ = +14.0° (c = 0.2, $CHCl_3$). IR: ν_{max} (thin film) 2186, 2073, 1689, 1572, 1689, 1631, 1326, 1160, 1011, 881. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 5.97 (d, *J* = 4.3 Hz, 1H), 5.40 (t, *J* = 4.1 Hz, 1H), 4.54 – 4.48 (m, 1H), 4.43 (dd, *J* = 11.8, 8.6 Hz, 1H), 4.29 (dd, *J* = 11.9, 3.0 Hz, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 169.9, 169.8, 169.5, 158.2, 107.3, 74.6, 64.6, 61.4, 60.8, 20.8, 20.7, 20.6. ESI-qTOF-HRMS (m/z): $[M - N_2 + Na + MeOH]^+$ calcd for $C_{14}H_{19}NNaO_9$, 368.0958; found, 368.0948.

(2R,3R,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-5-carbonyl azide (2e). Product **2e** was synthesized according to General Procedure B (chromatography eluent: 5% EtOAc in hexanes) and was obtained as a dark red oil. Yield = 60%. $[\alpha]_D^{20}$ = -5.5° (c = 0.2, $CHCl_3$). IR: ν_{max} (thin film) 2823, 2775, 2067, 1665, 1622, 1449, 1408, 1153, 1058, 1026, 994, 713, 676. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.38 – 6.87 (m, 15H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.66 (d, *J* = 11.1 Hz, 1H), 4.63 – 4.54 (m, 2H), 4.54 – 4.45 (m, 3H), 4.38 (d, *J* = 11.9 Hz, 1H), 4.00 – 3.83 (m, 2H), 3.76 (dd, *J* = 5.5, 3.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 157.8, 138.8, 138.1, 137.5, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 109.4, 77.6, 74.5, 73.9, 73.6, 71.9, 68.4, 67.2. ESI-qTOF-HRMS (m/z): $[M – N_2 + Na]^+$ calcd for $C_{28}H_{27}NNaO_5$, 480.1787; found, 480.1791.

(2R,3S,4R,5S,6S)-2-(((2R,3S,4R)-4-acetoxy-2-(acetoxymethyl)-5-(azidocarbonyl)-3,4-dihydro-2H-pyran-3-yl)oxy)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (2f). Product **2f** was synthesized according to General Procedure B (chromatography eluent: 50% EtOAc in hexanes) and was obtained as a yellow oil. Yield = 39%. $[\alpha]_D^{20}$ = +36.0° (c = 0.2, $CHCl_3$). IR: ν_{max} (thin film) 2075, 1685, 1631, 1574, 1324, 1173, 1104, 1000, 910, 869. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (s, 1H), 5.38 – 5.24 (m, 3H), 4.94 (t, *J* = 9.8 Hz, 1H), 4.78 (dd, *J* = 10.3, 3.8 Hz, 1H), 4.74 – 4.67 (m, 1H), 4.29 (dd, *J* = 11.9, 8.8 Hz, 1H), 4.12 – 4.06 (m, 2H), 4.05 – 4.01 (m, 1H), 3.98 – 3.89 (m, 2H), 2.04 – 2.01 (m, 9H), 1.98 – 1.93 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 170.5, 170.3, 170.1, 170.0, 169.7, 169.5, 157.9, 105.2, 97.3, 76.0, 72.6, 70.2, 69.8, 68.4, 68.3, 61.9, 61.6, 60.8, 20.6, 20.6, 20.5, 20.4. HRMS-TOF-ESI (m/z): $[M – N_2 + Na]^+$ calcd for $C_{25}H_{31}N_3NaO_{16}$, 624.1535; found, 624.1552.

(2R,3S,4R)-4-(benzyloxy)-2-((benzyloxy)methyl)-3-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-3,4-dihydro-2H-pyran-5-carbonyl azide (2g). Product **2g** was synthesized according to General Procedure B (chromatography eluent: 10% EtOAc in hexanes) and was obtained as a dark red oil. Yield = 75%. $[\alpha]_D^{20}$ = +21.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 2820, 27656, 2067, 1676, 1624, 1572, 1408, 1320, 1220, 1158, 1037, 996, 676. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.31 – 7.13 (m, 30H), 7.08 – 7.01 (m, 2H), 4.84 (d, *J* = 10.8 Hz, 1H), 4.77 – 4.69 (m, 3H), 4.70 – 4.63 (m, 1H), 4.60 (d, *J* = 3.0 Hz, 1H), 4.56 (d, *J* = 2.3 Hz, 1H), 4.53 (d, *J* = 3.8 Hz, 1H), 4.50 – 4.44 (m, 1H), 4.43 – 4.35

(m, 3H), 4.33 (s, 1H), 4.31 – 4.21 (m, 1H), 3.98 (s, 1H), 3.78 (t, *J* = 9.3 Hz, 1H), 3.72 – 3.59 (m, 3H), 3.58 – 3.48 (m, 3H), 3.43 (dd, *J* = 9.6, 3.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 158.0, 138.9, 138.3, 138.2, 138.0, 137.9, 128.6, 128.5, 128.5, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7, 127.7, 107.6, 97.2, 81.7, 79.8, 78.6, 75.7, 75.3, 73.6, 73.4, 73.2, 72.5, 71.2, 70.4, 68.5, 68.1, 67.1. HRMS-TOF-ESI (m/z): [M - N_2 + Na]$^+$ calcd for $C_{55}H_{55}NNaO_{10}$, 912,3718; found, 912.3745.

General Procedure C: Carbonylation of Acyl Azides

To a flame-dried 10-mL schlenk tube containing a magnetic stir bar were added acylazide (0.2 mmol), $ArNH_2$ (0.24 mmol, 1.2 equiv.), $Pd(OAc)_2$ (0.01 mmol, 5 mol%) and 1,10-Phen (0.01 mmol, 5 mol%). The flask was sealed and evacuated to a vacuum of 10 mbar and fitted with a CO balloon in 3 cycles. Dry and degassed THF (3.0 mL) was added to the system. The reaction mixture was vigorous stirring at room temperature. The reaction was kept under stirring until total consumption of the starting material (TLC monitoring). The reaction mixture was filtered through a plug of Celite®, which was thoroughly washed with EtOAc in sequence and evaporated. The reaction mixture was purified by flash column chromatography with an eluent mixture of hexane/EtOAc.

Notes for this procedure

1- THF was degassed via freeze-thaw technique in 3 cycles. Vacuum broken with CO in the last freeze-thaw cycle.

2- The progress of the reaction is accompanied by a color change of the reaction mixture to black.

3- In some cases, it was necessary to perform an acid-base extraction of the reaction mixture to eliminate residues of the aromatic amine.

(2R,3S,4R)-2-(acetoxymethyl)-5-(((4-methoxyphenyl)carbamoyl)carbamoyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (3a). Product **3a** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a beige solid. Yield = 89%. m.p. 84 – 87 °C. $[\alpha]_D^{20}$ = +56.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 3129, 3034, 1685, 1635, 1601, 1546, 1501, 1324, 1149, 992, 871, 801, 735. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.57 (s, 1H), 9.99 (d, *J* = 13.3 Hz, 1H), 7.99 (d, *J* = 13.9 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 2H), 6.79 (d, *J* = 7.8 Hz, 2H), 5.75 (s, 1H), 5.14 (d, *J* = 14.4 Hz, 1H), 4.51 (d, *J* = 20.7 Hz, 1H), 4.44 – 4.26 (m, 2H), 4.15 (dd, *J* = 18.5, 10.7 Hz, 1H), 3.71 (s, 3H), 2.19 – 1.91 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.3, 169.8, 169.3, 169.0, 166.6, 166.1, 157.2, 156.5, 155.8, 152.5, 152.5, 130.1, 122.0, 114.2, 107.1, 106.2, 74.7, 71.6, 65.8, 65.2, 61.8, 61.2, 60.9, 60.8, 55.4, 20.8, 20.8, 20.7, 20.6, 20.5. ESI-qTOF-HRMS (m/z): [M + Na]$^+$ calcd for $C_{21}H_{24}N_2NaO_{10}$: 487.1323, found 487.1329.

(2R,3S,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-((4-methoxyphenyl)carbamoyl)-3,4-dihydro-2H-pyran-5-carboxamide (3b). Product **3b** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a yellow oil. Yield = 99%. $[\alpha]_D^{20}$ = +11.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 3129, 2824, 2769, 1633, 1601, 1544, 1497, 1460, 1443, 1257, 1205, 1182, 1154, 1054, 1033, 996, 802. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.23 (s, 1H), 7.66 (s, 1H), 7.49 – 7.27 (m, 17H), 6.86 (d, *J* = 9.0 Hz, 2H), 4.64 (d, *J* = 3.3 Hz, 2H), 4.62 – 4.52 (m, 3H), 4.50 (s, 2H), 4.29 (s, 1H), 3.79 (s, 3H), 3.76 – 3.62 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 156.4, 155.8, 151.2, 137.6, 137.2, 136.4, 130.5, 128.8, 128.7, 128.5, 128.5, 128.4, 128.2, 127.9, 127.9, 127.7, 122.0, 114.2, 106.5, 76.7, 73.5, 72.0, 71.1, 69.9, 69.8, 67.2, 55.5. ESI-qTOF-HRMS (m/z): [M + Na]$^+$ calcd for $C_{36}H_{36}N_2NaO_7$: 631.2420, found 631.2421.

(2R,3S,4R)-3,4-dimethoxy-2-(methoxymethyl)-N-((4-methoxyphenyl)carbamoyl)-3,4-dihydro-2H-pyran-5-carboxamide (3c). Product **3c** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a beige solid. Yield = 86%. m.p. 51 – 54 °C. $[\alpha]_D^{20}$ = +76.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 3132, 3037, 2834, 2738, 1637, 1603, 1544, 1501, 1436, 1371, 1257, 1205, 1164, 1059, 1004, 804, 741. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.60 (s, 1H), 9.01 (s, 1H), 7.73 (s, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.46 (d, *J* = 4.2 Hz, 1H), 4.22 (s, 1H), 3.83 – 3.75 (m, 4H), 3.72 – 3.60 (m, 2H), 3.53 (s, 3H), 3.50 (s, 3H), 3.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 156.4, 156.0, 151.7, 130.6, 122.0, 114.3, 106.8, 76.7, 72.4, 71.7, 69.7, 59.2, 58.1, 56.1, 55.5. ESI-qTOF-HRMS (m/z): [M + Na]$^+$ calcd for $C_{21}H_{24}N_2NaO_{10}$: 403.1476, found 403.1486.

(2R,3S,4R)-N-(benzo[d]thiazol-6-ylcarbamoyl)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyran-5-carboxamide (3d). Product **3d** was synthesized according to General Procedure C (chromatography eluent: 40% EtOAc in hexanes) and was obtained as a yellow solid. Yield = 99%. m.p. 134 – 136 °C. $[\alpha]_D^{20}$ = +25.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 2961, 2929, 2767, 1601, 1637, 1520, 1492, 1359, 1229, 1154, 1052, 1033, 806, 709, 674. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.99 (s, 1H), 8.92 (s, 1H), 8.85 (s, 1H), 8.46 (d, J = 2.0 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.82 (s, 1H), 7.47 – 7.23 (m, 16H), 4.63 (s, 3H), 4.59 (s, 2H), 4.47 (s, 2H), 4.42 – 4.37 (m, 1H), 4.14 – 4.07 (m, 1H), 3.80 – 3.66 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.0, 153.2, 151.5, 149.9, 137.6, 137.2, 136.6, 135.3, 134.8, 128.8, 128.6, 128.5, 128.4, 128.4, 128.2, 127.9, 127.9, 127.7, 123.6, 119.6, 112.6, 106.6, 76.8, 73.5, 72.0, 71.3, 70.1, 69.4, 67.3. ESI-qTOF-HRMS (m/z): [M + Na]$^+$ calcd for $C_{36}H_{33}N_3NaO_6S$: 636.2163, found 636.2171.

(2R,3S,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-((4-cyanophenyl)carbamoyl)-3,4-dihydro-2H-pyran-5-carboxamide (3e). Product **3e** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a white solid. Yield = 60%. m.p. 65 – 68 °C. $[\alpha]_D^{20}$ = +17.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 2963, 2929, 2769, 2151, 1642, 1533, 1486, 1443, 1367, 1257, 1156, 1035, 812, 715. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.04 (s, 1H), 8.75 (s, 1H), 7.74 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.43 – 7.20 (m, 15H), 4.74 – 4.60 (m, 3H), 4.58 (d, *J* = 4.8 Hz, 1H), 4.54 (d, *J* = 4.9 Hz, 1H), 4.49 (s, 2H), 4.41 – 4.30 (m, 1H), 4.22 – 4.05 (m, 1H), 3.82 – 3.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 156.5, 151.2, 141.8, 137.6, 137.2, 136.4, 133.3, 128.9, 128.8, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 120.1, 119.0, 107.1, 106.4, 77.0, 73.6, 72.2, 71.3, 70.1, 69.7, 67.3. ESI-qTOF-HRMS (m/z): [M + Na]$^+$ calcd for $C_{36}H_{33}N_3NaO_6$: 626.2262, found 626.2278.

(2R,3S,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-((4-(trifluoromethyl)phenyl)carbamoyl)-3,4-dihydro-2H-pyran-5-carboxamide (3f). Product **3f** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a colorless oil. Yield = 77%. $[\alpha]_D^{20}$ = +15.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 2929, 3127, 2771, 1642, 1609, 1544, 1493, 1443, 1408, 1279, 1156, 1078, 1032, 814, 711. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.98 (s, 1H), 8.88 (s, 1H), 7.77 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.47 – 7.18 (m, 15H), 4.62 (s, 3H), 4.57 (s, 2H), 4.55 – 4.42 (m, 2H), 4.37 (d, *J* = 2.8 Hz, 1H), 4.08 (t, *J* = 3.3 Hz, 1H), 3.81 – 3.60 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 156.2, 151.5, 140.8, 137.6, 137.3, 136.7, 128.9, 128.8, 128.6, 128.5, 128.3, 128.0, 127.8, 126.4, 126.3, 126.1, 125.7, 122.5, 119.9, 106.7, 76.9, 73.6, 72.1, 71.4, 70.2, 69.6, 67.4. ESI-qTOF-HRMS (m/z): [M + Na]$^+$ calcd for $C_{36}H_{33}F_3N_2NaO_6$: 669.2183, found 669.2210.

(2R,3S,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-((4-nitrophenyl)carbamoyl)-3,4-dihydro-2H-pyran-5-carboxamide (3g). Product **3g** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a yellow oil. Yield = 37%. $[\alpha]_D^{20}$ = +15.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 3229, 2929, 2769, 1601, 1611, 1585, 1566, 1527, 1449, 1406, 1320, 1249, 1153, 1030, 894, 711, 676. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.12 (s, 1H), 8.51 (s, 1H), 8.20 (d, *J* = 9.1 Hz, 2H), 7.71 (d, *J* = 5.8 Hz, 2H), 7.67 (s, 1H), 7.41 – 7.22 (m, 15H), 4.67 – 4.57 (m, 4H), 4.56 – 4.49 (m, 3H), 4.30 (s,

1H), 4.14 (t, *J* = 3.2 Hz, 1H), 3.72 (ddd, *J* = 16.0, 10.4, 6.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 156.9, 150.9, 143.7, 143.7, 137.6, 137.2, 136.2, 129.1, 128.9, 128.8, 128.7, 128.5, 128.1, 127.9, 125.2, 119.6, 106.1, 77.0, 73.7, 72.3, 71.2, 70.1, 69.9, 67.2. ESI-qTOF-HRMS (m/z): $[M + Na]^+$ calcd for $C_{35}H_{33}N_3NaO_8$: 646.2160, found 646.2153.

(2R,3S,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-((4-fluorophenyl)carbamoyl)-3,4-dihydro-2H-pyran-5-carboxamide (3h). Product **3h** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a beige oil. Yield = 93%. $[\alpha]_D^{20}$ = +12.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 3129, 2931, 2767, 1637, 1555, 1501, 1460, 1443, 1408, 1257, 1154, 1052, 1033, 806, 711, 674. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.81 (s, 1H), 7.74 (s, 1H), 7.55 – 7.42 (m, 2H), 7.41 – 7.18 (m, 15H), 7.05 – 6.94 (m, 2H), 4.62 (s, 3H), 4.56 (s, 2H), 4.48 (d, *J* = 1.8 Hz, 2H), 4.41 – 4.30 (m, 1H), 4.07 (t, *J* = 3.2 Hz, 1H), 3.80 – 3.62 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 159.35 (d, *J* = 243.1 Hz), 155.8, 151.5, 137.6, 137.2, 136.6, 133.5, 133.4, 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 127.9, 127.9, 127.8, 127.7, 121.99 (d, *J* = 7.9 Hz), 115.6 (d, *J* = 22.5 Hz), 106.6, 76.8, 73.5, 72.0, 71.3, 70.1, 69.5, 67.3. ESI-qTOF-HRMS (m/z): $[M + Na]^+$ calcd for $C_{35}H_{33}FN_2NaO_6$: 619.2215, found 619.2227.

(2R,3S,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-((3-fluorophenyl)carbamoyl)-3,4-dihydro-2H-pyran-5-carboxamide (3i). Product **3i** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a white solid. Yield = 84%. m.p. 86 – 88 °C. $[\alpha]_D^{20}$ = +14.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 2963, 2987, 2769, 1642, 1601, 1546, 1493, 1402, 1391, 1257, 1231, 1156, 1054, 994, 849, 709, 674. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.83 (s, 1H), 8.77 (s, 1H), 7.74 (s, 1H), 7.46 (d, *J* = 10.9 Hz, 1H), 7.40 – 7.12 (m, 17H), 6.76 (t, *J* = 8.3 Hz, 1H), 4.69 – 4.54 (m, 5H), 4.48 (s, *J* = 12.9 Hz, 2H), 4.36 (s, 1H), 4.14 – 4.04 (m, 1H), 3.88 – 3.62 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 163.16 (d, *J* = 244.5 Hz), 156.1, 151.4, 139.19 (d, *J* = 11.0 Hz), 137.7, 137.3, 136.7, 130.14 (d, *J* = 9.4 Hz), 128.9, 128.8, 128.6, 128.5, 128.3, 128.0, 128.0, 127.8, 115.65 (d, *J* = 2.7 Hz), 110.82 (d, *J* = 21.3 Hz), 107.73 (d, *J* = 26.3 Hz), 106.6, 76.9, 73.6, 72.1, 71.4, 70.1, 69.6, 67.4. ESI-qTOF-HRMS (m/z): $[M + Na]^+$ calcd for $C_{35}H_{33}FN_2NaO_6$: 619.2215, found 619.2227.

(2R,3S,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-((2-fluorophenyl)carbamoyl)-3,4-dihydro-2H-pyran-5-carboxamide (3j). Product **3j** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a yellow oil. Yield = 99%. $[\alpha]_D^{20}$ = +20.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 2963, 2931, 2771, 1641, 1601, 1566, 1542, 1497, 1408, 1257, 1225, 1201, 1154, 1052, 1033, 709, 674. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.99 (s, 1H), 8.87 (s, 1H), 8.19 (t, *J* = 8.0 Hz, 1H), 7.77 (s, 1H), 7.44 – 7.21 (m, 15H), 7.14 – 7.04 (m, *J* = 8.2 Hz, 2H), 7.04 – 6.94 (m, 1H), 4.66 – 4.53 (m, 5H), 4.48 (s, 2H), 4.40 (s, 1H), 4.11 – 4.05 (m, 1H), 3.80 – 3.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 156.1, 153.1 (d, *J* = 245.2 Hz), 151.4, 137.7, 137.3, 136.8, 128.9, 128.8, 128.6, 128.5, 128.4, 128.3, 128.0, 128.0, 127.8, 126.2 (d, *J* = 10.4 Hz), 124.5 (d, J = 3.6 Hz), 124.3 (d, *J* = 7.5 Hz), 122.0, 115.2, 115.0, 106.7, 77.0, 73.6, 72.1, 71.4, 70.3, 69.6, 67.5. ESI-qTOF-HRMS (m/z): $[M + Na]^+$ calcd for $C_{35}H_{33}FN_2NaO_6$: 619.2215, found 619.2233.

(2R,3S,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-((4-chlorophenyl)carbamoyl)-3,4-dihydro-2H-pyran-5-carboxamide (3k). Product **3k** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a yellow solid. Yield = 96%. m.p. 108 – 110 °C. $[\alpha]_D^{20}$ = +18.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 3119, 2985, 2769, 1641, 1601, 1536, 1441, 1408, 1354, 1261, 1158, 1056, 1039, 713, 676. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.79 (s, 1H), 7.67 (s, 1H), 7.33 (s, 4H), 7.30 – 7.14 (m, 15H), 4.51 (d, *J* = 16.7 Hz, 5H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.38 (d, *J* = 12.4 Hz, 1H), 4.29 (s, 1H), 4.02 – 3.96 (m, 1H), 3.72 – 3.54 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 156.0, 151.5, 137.7, 137.3, 136.7, 136.7, 132.1, 128.8, 128.8, 128.6, 128.4, 128.3, 128.0, 127.8, 121.9, 116.8, 106.7, 76.9, 73.6, 72.1, 71.4, 70.2, 69.5, 67.4. ESI-qTOF-HRMS (m/z): $[M + Na]^+$ calcd for $C_{35}H_{33}ClN_2NaO_6$: 635.1919, found 635.1947.

(2R,3S,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-((4-bromophenyl)carbamoyl)-3,4-dihydro-2H-pyran-5-carboxamide (3l). Product **3l** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a beige solid. Yield = 90%. m.p. 97– 99 °C $[\alpha]_D^{20}$ = +15.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 3123, 2929, 2767, 1639, 1601, 1538, 1443, 1408, 1357, 1259, 1229, 1186, 1156, 1058, 1037, 802, 713, 676. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.76 (s, 1H), 8.80 (s, 1H), 7.74 (s, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.40 – 7.22 (m, 17H), 4.64 – 4.55 (m, 5H), 4.54 – 4.43 (m, 2H), 4.36 (s, 1H), 4.07 (s, 1H), 3.78 – 3.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 155.9, 151.4, 137.6, 137.2, 136.6, 136.1, 129.1, 129.0, 128.8, 128.7, 128.5, 128.4, 128.2, 127.9, 127.7, 121.5, 106.6, 76.8, 73.5, 72.0, 71.3, 70.1, 69.5, 67.3. ESI-qTOF-HRMS (m/z): $[M + Na]^+$ calcd for $C_{35}H_{33}BrN_2NaO_6$: 679.1414, found 679.1410.

(2R,3S,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-((4-iodophenyl)carbamoyl)-3,4-dihydro-2H-pyran-5-carboxamide (3m). Product **3m** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a beige solid. Yield = 99%. m.p. 64 – 66 °C. $[\alpha]_D^{20}$ = +17.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 2961, 2929, 2769, 1641, 1601, 1533, 1492, 1350, 1262, 1158, 1056, 1037, 795, 713, 676. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.77 (s, 1H), 8.85 (s, 1H), 7.74 (s, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.46 – 7.22 (m, 17H), 4.59 (d, *J* = 17.4 Hz, 5H), 4.54 – 4.43 (m, 2H), 4.36 (s, 1H), 4.10 – 4.03 (m, 1H), 3.79 – 3.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 156.0, 151.4, 138.0, 137.7, 137.4, 137.3, 136.7, 128.8, 128.8, 128.6, 128.4, 128.3, 128.0, 127.8, 122.2, 106.7, 87.3, 76.9, 73.6, 72.1, 71.4, 70.2, 69.6, 67.4. ESI-qTOF-HRMS (m/z): $[M + Na]^+$ calcd for $C_{35}H_{33}IN_2NaO_6$: 725.1276, found 727.1275.

(2R,3S,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-((4-ethynylphenyl)carbamoyl)-3,4-dihydro-2H-pyran-5-carboxamide (3n). Product **3n** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a yellow solid. Yield = 43%. m.p. 58 – 61 °C. $[\alpha]_D^{20}$ = +14.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 3166, 2961, 2931, 1641, 1601, 1531, 1486, 1443, 1266, 1156, 1054, 1035, 713, 676. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.77 (s, 1H), 8.52 (s, 1H), 7.70 (s, 1H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.39 – 7.24 (m, 15H), 4.70 – 4.62 (m, *J* = 7.2 Hz, 2H), 4.62 – 4.58 (m, *J* = 1.8 Hz, 1H), 4.55 (d, *J* = 4.7 Hz, 2H), 4.52 – 4.44 (m, *J* = 4.5 Hz, 2H), 4.37 – 4.29 (m, 1H), 4.14 – 4.08 (m, *J* = 3.2 Hz, 1H), 3.80 – 3.63 (m, *J* = 16.0, 10.4, 6.1 Hz, 2H), 3.03 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 156.3, 151.0, 138.2, 137.7, 137.3, 136.5, 133.1, 129.0, 128.8, 128.6, 128.6, 128.4, 128.1, 128.1, 127.9, 119.9, 117.6, 106.5, 83.7, 76.9, 73.6, 72.2, 71.3, 70.0, 69.9, 67.3. ESI-qTOF-HRMS (m/z): $[M + Na]^+$ calcd for $C_{37}H_{34}N_2NaO_6$: 625.2309, found 625.2323.

(2R,3S,4R)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)-N-(naphthalen-1-ylcarbamoyl)-3,4-dihydro-2H-pyran-5-carboxamide (3o). Product **3o** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a beige solid. Yield = 84%. m.p. 134 – 136 °C. $[\alpha]_D^{20}$ = +23.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 2987, 27,90 1644, 1594, 1510, 1443, 1255, 1190, 1149, 1043, 829, 715. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.97 (s, 1H), 9.01 (s, 1H), 8.17 (s, 1H), 7.85 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.75 (t, *J* = 8.5 Hz, 2H), 7.52 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.45 – 7.04 (m, 17H), 4.67 – 4.53 (m, 5H), 4.49 – 4.36 (m, 3H), 4.14 – 3.99 (m, 1H), 3.83 – 3.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 155.8, 151.7, 137.6, 137.3, 136.8, 135.0, 134.0, 130.6, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 126.4, 124.9, 120.4, 116.9, 106.8, 76.9, 73.5, 72.0, 71.4, 70.2, 69.4, 67.4. ESI-qTOF-HRMS (m/z): $[M + Na]^+$ calcd for $C_{39}H_{36}N_2NaO_6$: 651.2466, found 651.2462

(2R,3S,4R)-4-(benzyloxy)-2-((benzyloxy)methyl)-N-((4-methoxyphenyl)carbamoyl)-3-(((2R,3R,4S,5R,6R)-3,4,5-

tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-3,4-dihydro-2H-pyran-5-carboxamide (3p). Product **3p** was synthesized according to General Procedure C (chromatography eluent: 30% EtOAc in hexanes) and was obtained as a yellow viscous oil. Yield = 90%. $[\alpha]_D^{20}$ = +17.0° (c = 0.1, $CHCl_3$). IR: ν_{max} (thin film) 2821, 2769, 1633, 1601, 1462, 1449, 1408, 1257, 1207, 1158, 1054, 1035, 1005, 996, 802, 713, 676. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.54 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.49 (d, *J* = 8.9 Hz, 2H), 7.38 – 7.28 (m, 30H), 7.23 – 7.17 (m, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.02 – 4.96 (m, 2H), 4.91 – 4.79 (m, 3H), 4.77 (s, 1H), 4.67 – 4.58 (m, 3H), 4.57 – 4.44 (m, 5H), 4.35 (s, 1H), 4.29 (s, 1H), 3.99 – 3.85 (m, 2H), 3.82 (s, 3H), 3.79 – 3.67 (m, 5H), 3.61 (dd, *J* = 9.8, 3.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 156.5, 155.8, 151.4, 138.9, 138.3, 138.2, 138.0, 137.7, 136.5, 130.6, 128.9, 128.7, 128.6, 128.5, 128.5, 128.2, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 122.2, 114.4, 106.2, 97.4, 81.8, 80.2, 77.7, 77.4, 75.8, 75.3, 73.7, 73.6, 73.5, 71.2, 70.8, 68.7, 68.7, 68.6, 67.1, 55.6. ESI-qTOF-HRMS (m/z): $[M + Na]^+$ calcd for $C_{63}H_{64}N_2NaO_{12}$: 1063.4351, found 1063.4393.

General Procedure D: Deprotection

Urea **3a** (0.1 mmol, 1.0 equiv.) were dissolved in methanol (1.1 mL) at room temperature. K_2CO_3 (20 mol%) was added and the resulting mixture was stirred for 4 h. The mixture was concentrated under reduced pressure and the crude products were purified by flash column chromatography with an eluent mixture of CH_2Cl_2/MeOH (9:1).

(2R,3S,4R)-3,4-dihydroxy-2-(hydroxymethyl)-N-((4-methoxyphenyl)carbamoyl)-3,4-dihydro-2H-pyran-5-carboxamide (4). Product **4** was synthesized according to General Procedure D (chromatography eluent: 10% MeOH in CH_2Cl_2) and was obtained as a white solid. Yield = 75%. m.p. 95 – 95 °C. $[\alpha]_D^{20}$ = +116.0° (c = 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 10.64 (s, 1H), 9.90 (sl, 1H), 7.66 (s, 1H), 7.44 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.41 (s, 1H), 4.85 (s, 1H), 4.32 (d, *J* = 5.0 Hz, 1H), 4.02 (d, *J* = 5.2 Hz, 1H), 3.75 (s, 4H), 3.70 (s, 3H). ^{13}C NMR (75 MHz, DMSO-*d6*) δ 168.1, 155.6, 155.0, 150.9, 130.6, 121.3, 114.1, 108.7, 81.4, 67.4, 65.1, 59.7, 55.2. ESI-qTOF-HRMS (m/z): $[M + Na]^+$ calcd for $C_{15}H_{18}N_2NaO_7$: 361.1006, found 361.1001.

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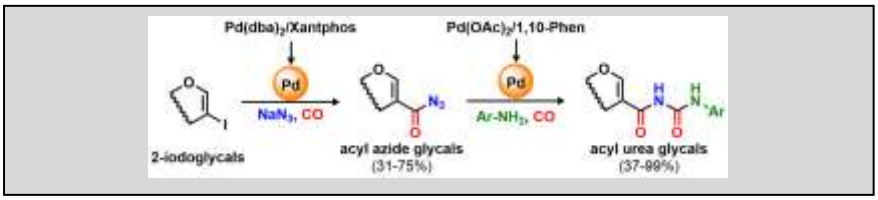

Various C-2 branched glycoconjugates were obtained from 2-iodoglycals via Pd-catalyzed azidocarbonylative coupling reaction. Several O-protected glycal substrates including disaccharides were tolerated. The glyco-acyl azides obtained were employed as a synthetic intermediary in the synthesis of new glycoureas with different functional groups.

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