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Self-Promoted Glycosylation for the Synthesis of β-*N*-Glycosyl Sulfonyl Amides

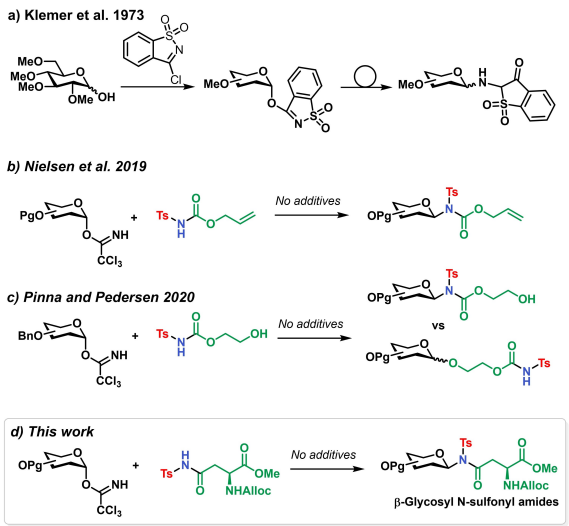
Patrycja Mała[b] and Christian Marcus Pedersen*[a]

N-Glycosyl *N*-sulfonyl amides have been synthesized by a self-promoted glycosylation, i.e. without any catalysts, promotors or additives. When the reactions were carried out at lower temperatures a mixture of *N*- and *O*-glycosides were observed, where the latter rearranged to give the β-*N*-glycosides at elevated temperatures. By this method sulfonylated asparagine derivatives can be selectively β-glycosylated in high yields by trichloroacetimidate glycosyl donors of different reactivity including protected glucosamine derivatives. The chemoselectivity in the glycosylations as well as the rearrangements from *O*-glycosides to β-*N*-glycosides gives information of the glycosylation mechanism. This method gives access to glycosyl sulfonyl amides under mild conditions.

Introduction

Glycosyl amides are ubiquitous in nature and hence an important target in organic synthesis. The β-linkage between asparagine and carbohydrates is the most common, e.g. in various membrane proteins, and have been found to be crucial for biological processes on the cell surface.[1] To understand the role of posttranslational modifications of proteins and peptides with carbohydrates, their chemical synthesis is important.[2] Glycosyl amides are generally synthesized from the glycosyl amines via glycosyl azides, which after reduction is used as the coupling partner to the activated carboxylic acid derivative.[3] There are however two major problems with this approach. Firstly the undesired anomerization of the glycosyl amine to give the α-anomer[4] and secondly the activated aspartic acid in the peptide chain, which is the precursor for the *N*-glycosylated asparagine, can cyclize to give the undesired aspartimide.[5,6] Hence, it is desired to develop methods avoiding both the unstable glycosyl amine and the need for activating an aspartic acid residue, in the peptide chain. Alternatively, but less established, is the direct glycosylation of the amide.[7] This approach suffers from the low nucleophilicity of an amide, resulting in side reaction using the normally highly reactive activated glycosyl donors and therefore only a few methods for direct catalytic glycosylation of amides have been developed over the years. For an example Takemoto successfully used organocatalysis for the *N*-glycosylation using trichloroacetimidate donors.[8,9] *N*-Phenyltrifluoroacetimidates have also been used as glycosyl donors for direct *N*-glycosylation of amides.[10–12] *O*-glycosylation of the amide is though a common side reaction,[13] which has limited the general use of the direct *N*-glycosylation of amides. In order to circumvent this chemoselectivity problem Kahne introduced *N*-silylated amides as glycosyl acceptors.[14] As the *N*-silyl bond is weak the *N*-silylated reagents are unstable and often not easily available, which has limited their general use.

The *N*-glycosylation of sulfonyl amides, has been less studied. An early example is the synthesis of D-glucosesaccharin derivatives by Klemer et al. via a thermic rearrangement (see Scheme 1a).[15] Glycosylated sulfonamides have also been observed as a by-product in glycosylations.[16] Interestingly, glycosyl sulfonyl amides have been found to be an interesting group of compounds, e.g. as carbonic anhydrase inhibitors and antitumor agents, which has resulted in renewed interest in their synthesis.[17–21] In a glycosylation method



Scheme 1. First example of the synthesis of an *N*-glycosyl sulfonamide and self-promoted *N*-glycosylations developed in by us.

[a] *Prof. C. M. Pedersen*
Department of Chemistry
University of Copenhagen
Universitetsparken 5, 2100 Copenhagen O, Denmark
E-mail: cmp@chem.ku.dk
[b] *P. Mała*
Faculty of Chemistry
Adam Mickiewicz University
Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland

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development, Miller has shown that sulfonamides can be used as catalyst for the activation of TCA donors, which conclude that their acidity is sufficient for activation this group of glycosyl donors.[22] When the acceptor is acidic, glycosylation can take place without the need of catalysts. This kind of acceptor promoted glycosylation, we termed self-promoted glycosylations. Stereoselective self-promoted *O*-glycosylation with TCA donors has been known for decades[23–28] and recently, we demonstrated that *N*-sulfonyl carbamates are acceptors in self-promoted *N*-glycosylations (Scheme 1b).[29] As the glycosylations are highly stereospecific, and the TCA donors can be synthesized in a stereoselective manner,[30] one can influence the stereochemical outcome in the glycosylation already in the donor synthesis. Besides access to interesting *N*-glycosides the self-promoted glycosylations are also interesting when studying the glycosylation mechanism. As an example, it was observed in competition experiments, that stereoselective *N*-glycosylation was favored in apolar solvents, whereas the competing *O*-glycosylation became favored in polar solvents and proceeded unselectively, hence suggesting a more dissociated mechanism (Scheme 1c).[31] In this communication, we study the direct self-promoted *N*-glycosylation of electron poor amides (Scheme 1d).

Results and Discussion

To study the *N*-glycosylation of sulfonyl amides we decided to use a plethora of glycosyl donors (Figure 1; **1**–**7**) with different reactivity and anomeric configurations. The anomeric set of glucosyl donors **1** and **2** were used for studying the stereospecificity and **1** was used to optimize the reaction conditions. The per benzylated cellobiosyl trichloroacetimidate **3** was used as a more complex donor for the synthesis of *N*-glycosyl sulfonyl amides. As the β-glycosyl amides are by far the most common in nature we decided to study the less reactive acetylated glycosyl donors (**4** and **5**) as well, as these provide a different protective group pattern and neighboring group participation ensuring β-selectivity. Lastly, two glucosamine derivatives **6** and **7** were studied in order to synthesize the synthetically challenging β-GlcNAc amides commonly found in nature. As glycosyl acceptors simple acetamides with either a *N*-tosyl (Ts) or *N*-nosyl (Ns) group were used. Ns is more EWD than Ts and hence expected to be more reactive in the self-promoted glycosylation as they are more acidic. Asparagine is the amino acid used for *N*-linking of carbohydrates to peptides and proteins, hence protected derivatives thereof are essential for the scope of the reaction and therefore central substrates in this study.

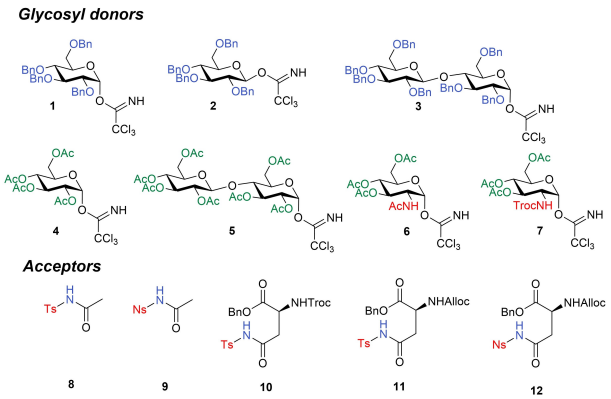
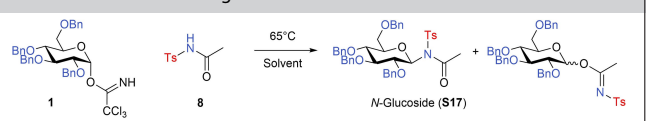


Figure 1. Glycosyl donors and acceptors used in this study. Ts = p-toluene-sulfonyl; Ns = nosyl (4-nitrobenzene-1-sulfonyl).

In the preliminary screening it was found that the *N*-glycosylation, between donor **1** and acceptor **8** was slow at room temperature and a solvent screening was therefore performed at 65 °C and the reaction followed by TLC to determine completion times (see Table 1 for details). In all solvents, except THF, mixtures of *O*- and *N*-glycosides were observed. The isomeric products could be distinguished by IR, with the *O*-glycosides given a peak at ~1627 cm^{-1} (O–C=N) and the *N*-glycoside one at ~1715 cm^{-1} (N–C=O). NMR was used for the full assignment, which was somewhat challenging due to rotamers (see SI for further information). Interestingly, only the β-*N*-glycosides were observed, whereas the anomeric ratio of the *O*-glycosides depended on the solvent. The least polar solvents, i.e. DCE (1,2-dicloroethane), DCB (o-dichlorobenzene) and toluene, gave high β-selectivity (of the *O*-glycosides) in line with the reaction mechanism being more associated and hence more stereospecific. Polar solvents like DMF and $MeNO_2$ gave α- or no selectivity in the *O*-glycosylation (See Table 1). The reactions were slightly slower in the least polar solvent, with up to 8 h reaction time for full conversion of starting material, whereas polar solvent gave slightly faster reactions.

As the *N*-glycosides were the targets of this study, a temperature screening was performed and DMF was chosen as a solvent spanning a broad temperature range (details in SI). At rt the reaction was slow and 6 days were required for full conversion of the glycosyl donor **1** and the *O/N* selectivity was 1:1. Increasing the temperature gradually improved the chemoselectivity towards the *N*-glycosides and reduced the reaction time. At 105 °C only the *N*-glycoside was observed, and the reaction was complete within an hour. The initially formed *O*-glycosides can clearly be effectively transformed into the desired *N*-glycosides by rearrangement similar to the Chapman-like rearrangement.[32,33] This was further demonstrated by

Table 1. Solvent Screening.[a]

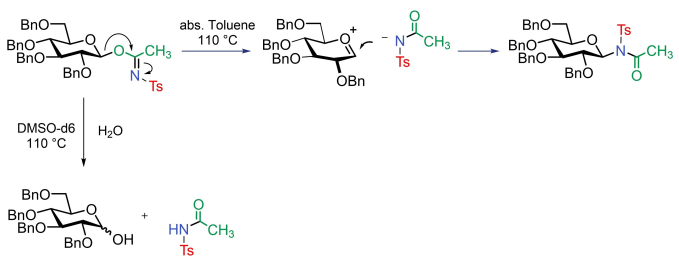


Solvent	t [h][b]	*O/N*-Glc[c]	α/β O-Glc[c]	α/β N-Glc[c]
DCE	8 h	2.2:1	0.03:1	0:1
THF	3 h	–	–	0:1
DMF	3 h	0.3:1	2.7:1	0:1
MeCN	4 h	2.8:1	0.2:1	0:1
Toluene	7 h	2.4:1	0.05:1	0:1
$MeNO_2$	8 h	3.6:1	1:1	0:1
DCB	4 h	1:1	n.a.	5:95

[a] Glycosylation conditions: Donor **1** was mixed with **8** (0.05 M) and heated to 65 °C in the given solvent. [b] Completion time estimated from TLC. [c] Chemo- and diastereoselectivity determined from crude ^{1}H-NMR.

heating a sample of the *N*- and *O*-glycosides in DMSO-d6, where the transformation into the *N*-glycosides could be monitored. Residual water in the solvent did however also result in the formation of the hemiacetal, which suggest a more dissociative mechanism, and not a concerted rearrangement, in a polar solvent like DMSO. In order to study the potential rearrangement further, the same mixture of *N*- and *O*-glycosides, was heated in anhydrous toluene. The rearrangement was found to proceed faster in more polar solvents, and therefore the sample in toluene was allowed to heat for a longer time (24 h at 110 °C). As expected, the ratio of *O*- and *N*-glycosides, as determined from NMR, changed significantly from 64:36 to 21:79 (See SI). Noticeably, the altered ratio did not originate from the decomposition of the glycosyl acetimidate, as neither the hemiacetal nor additional signals were detected. The observed β-selectivity in the *N*-glycosylation is therefore not only due to a stereospecific substitution of a α-trichloroacetimidate, but also a stereoselective rearrangement of the *O*-glycosides initially formed (Scheme 2).

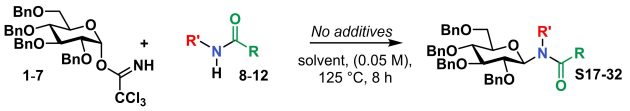
Next, the influence of concentration was studied by keeping the ratio between the reactants and all other conditions unchanged (see SI for details). The concentration was varied in the range from 0.01 M to 0.2 M. The *O/N* selectivity only changed marginally with the concentration, and the anomeric β-selectivity in the *N*-glycosylation remained, but the undesired *O*-glycosylation became more α-selective at lower concentrations. This could suggest a reaction pathway at high concentration where one acceptor works as the catalyst activating the trichloroacetimidate, while another acceptors acts as the nucleophile. A concentration of 0.1 M was found to be optimal. The molecularity was also studied by using 50% excess of either the glycosyl donor or acceptor. Increasing the amount of glycosyl donor increased the yields slightly to 67% compared to 60% with 50% excess of the acceptor. As hydrolysis of the glycosyl donor became a major side-reaction at the higher temperatures, a less hydroscopic solvent with a high boiling point was preferred over DMF. o-Dichlorobenzene was found to have the desired properties and the yield could readily be improved to 83% in the model reaction between **1** and **8**, when performing the reaction at 125 °C, which was used as the conditions for the remaining glycosylations. The slightly increased temperature was compensating for the slower rearrangement in less polar solvents.



Scheme 2. Rearrangement of *O*-glucoside to *N*-glucoside in toluene. Competing hydrolysis in dimethyl sulfoxide-d_6 by residual water led to partly hydrolysis.

The scope of the glycosylations was then studied under the optimized conditions using glycosyl donor **1**–**7** and acceptors **8**–**12** (Table 1). *N*-Glycosylations using **1** all gave high β-selectivity and isolated yields ranging from 69–83% based on the glycosyl donor, which is very satisfying as this is the more reactive reactant (Table 2, entry 1–5). The direct glycosylation of the asparagine derivatives **10**–**12** (entry 3–5) all gave yields and selectivities similar to the glycosylation on the simpler acceptors **8**–**9** (entry 1–2). Changing to the β-TCA glycosyl donor **2** (entry 6) gave significantly more of the α-product albeit still being β-selective and hence the selectivity is only modestly dependent of the stereochemistry of the glycosyl donor, in contrast to the earlier work on sulfonyl carbamates. This is in line with a more dissociative mechanism, when using the less reactive sulfonyl amides. When cellobiosyl donor **3** was used the yields and selectivities were essentially as with the simpler glucosyl donor **1**, although glycosylation of the nosylated asparagine acceptor **12** was slightly lower yielding (entry 10). Encouraged by the promising results with the more reactive armed TCA donors (**1**–**3**), which were all β-selective, we decided to challenge our self-promoted reactions with disarmed glucosyl donors of various kinds. Glycosylation, using disarmed glycosyl donor **4**, of the simple sulfonyl amides **8** and **9** resulted in yields and selectivities similar to the ones observed for the armed donors (entry 11–12), but the reaction time for the less acidic tosyl amide **8** was now increased to 12 h (entry 11). Moving to the asparagine acceptor **10** the yield took a hit (entry 13), but could easily be improved by using 1.5 equiv. of

Table 2. Self-promoted *N*-glycosylation of sulfonyl amides.[a]



Entry	Donor	Acceptor	Donor [equiv.]	Acceptor [equiv.]	t [h]	α/β[b]	Yield [%][c]
1	**1**	**8**	1.0	1.5	4	5:95	83
2	**1**	**9**	1.0	1.5	2	4:96	81
3	**1**	**10**	1.0	1.5	4	2:98	69
4	**1**	**11**	1.0	1.5	4	>9:91	76
5	**1**	**12**	1.0	1.5	2	>9:91	71
6	**2**	**9**	1.0	1.5	2	21:79	n.d.
7	**3**	**8**	1.0	1.5	4	6:94	72
8	**3**	**9**	1.0	1.5	2	7:93	74
9	**3**	**11**	1.0	1.5	4	8:92	76
10	**3**	**12**	1.0	1.5	2	>9:91	56
11	**4**	**8**	1.0	1.5	12	2:98	73
12	**4**	**9**	1.0	1.5	2	2:98	84
13	**4**	**11**	1.0	1.5	4	>9:91[d]	56
14	**4**	**11**	1.5	1.0	8	>9:91[d]	89
15	**5**	**8**	1.0	1.5	10	2:98	65
16	**5**	**9**	1.0	1.5	2	3:97	76
17	**5**	**11**	1.5	1.0	8	>9:91[d]	66
18	**5**	**12**	1.0	1.5	2	>9:91[d]	72
19	**7**	**9**	1.0	1.5	2	>9:91[d]	49
20	**7**	**9**	1.5	1.0	2	>9:91[d]	70
21	**7**	**11**	1.5	1.0	6	>9:91[d]	77
22	**7**	**12**	1.5	1.0	2	>9:91[d]	64

[a] Glycosylation conditions: Donor conc. 0.1 M in $C_6H_4Cl_2$ at 125 °C. [b] Determined from crude ^{1}H-NMR. [c] Isolated yield. [d] Ratio difficult to determine from crude NMR, but the reactions were highly β-selective due to NGP.

the donor instead of excess acceptor (entry 14). The prolonged reaction time is clearly resulting in a competing degradation of the glycosyl donor. The same trend was seen with the peracetylated cellubiosyl donor **5** (entry 15–18), where the tosylated acceptors (**8** and **11**) gave prolonged reaction times and lower yields (entry 15 and 16), which could be partly improved by using excess of **5** (entry 17). The β-selectivities for both **4** and **5** were maintained when having neighboring group participation and no signs of the formation of *N*-acylorthoamide were observed. As the ultimate test of our self-promoted glycosylation the peracetylated GlcNAc glycosyl donor **6** was attempted glycosylated using the same conditions, but no product could be isolated. The low reactivity of the donor combined with a favourable oxazoline formation of the donor is making the *N*-glycosylation unachievable (not shown). This observation is in line with Grundler and Schmidt's synthesis and attempted glycosylation with donor **6**.[34] The donor has due to this only sporadically been used since the work by Schmidt and only to glycosylate reactive alcohols,[35,36] i.e. no carbohydrate alcohols, amino acid alcohols[37] or weak nucleophiles like amides. The inherent problem with glycosylation using a GlcNAc donor could be overcome by using the *N*-Troc protected donor **7**, which gave good yields and high selectivity, when using excess of the donor (entry 19 vs 20). The asparagine acceptors were also effectively glycosylated by **7** and the nosylated acceptor **12** was again found to give shorter reaction times (entry 22).

With access to the glycosyl sulfonyl amides selective desulfonylation became relevant. From our experience with the orthogonal deprotection of the glycosyl sulfonyl carbamates, where nosyl was found to be the most promising protective group, as this could be deprotected under milder conditions using thiolates. Exposing the glycosyl sulfonyl amides, under these conditions did however result in cleavage of the amide bond rather than the sulfonyl amide bond. Changing the base used, solvents or the thiolate, did unfortunately not yield the desired glycosyl amides and the nosyl group therefore should be sought exchanged with a sulfonyl group, which can be deprotected under less nucleophilic conditions. Returning to the tosylated products, removal with Mg in MeOH was attempted, but only traces of product could be observed. Effective and selective deprotection of the sulfonyl groups will have to be investigated further.

Conclusion

In conclusion, we have developed a self-promoted glycosylation of sulfonyl amides, which is performed at elevated temperatures without any additives. Various solvents can be used, but dichlorobenzene was found to be superior at higher temperatures. The synthesized glycosyl sulfonyl amides were found to be more labile than the corresponding sulfonyl carbamates and milder desulfonylation methods, or other sulfonyl groups, have therefore to be developed to access the glycosyl amides in practical yields. Our method gives easy access to β-N-glycosides at mild conditions with a minimal use of chemicals.

Experimental Section

All the chemicals and solvents were provided from commercial suppliers and used without further purification. Dry DCM, acetonitrile, toluene, DMF and THF were obtained from an Innovative Technology PSMD-05 solvent drying system. Other solvents were dried with 4 Å molecular sieves. Thin layer chromatography (TLC) was carried out using aluminum sheets coated with silica gel (60F). TLC plates were visualized with UV-light or with a 10% solution of H_2SO_4 in ethanol and heat. Column chromatography was performed using Kieselgel 230–400 mesh silica gel. Optical rotations were measured on an Anton Paar polarimeter. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 500 MHz Ultra Shield Plus spectrograph equipped with a cryo-probe. Chemical shifts were reported relative to TMS (δ 0.00) or solvent residual signals. High resolution mass spectra (HRMS) were obtained from a Bruker SolariX XR 7T ESI/MALDI-FT-ICRMS instrument using matrix-assisted laser desorption ionization (MALDI).

***N*$^{\alpha}$-(2,2,2-trichloroethoxycarbonyl)-*N*-(tosyl)-L-asparagine benzyl ester (10)** A solution of $TsNH_2$ (0.41 g, 2.38 mmol) and DIPEA (0.8 ml, 4.77 mmol) in abs. CH_2Cl_2 (20 ml) was cooled down to −20 °C. Then a solution of the acyl chloride **S14** (0.99 g, 2.38 mmol) in abs. CH_2Cl_2 (20 ml) was added dropwise. The reaction mixture was slowly allowed to warm up and stirred at r.t. overnight. After this time the resulting solution was diluted with CH_2Cl_2 (100 ml) and washed with 1 M HCl (2×100 ml). The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was pourified by column chromatography (1:5→1:2 Acetone/Cyclohexane) to yield the compound **10** (0.64 g, 1.17 mmol, 49%) as a white solid. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.43 (s, 1H, *N*H), 7.90 (d, *J* = 8.6 Hz, 2H, Ar^{Ts}), 7.40–7.29 (m, 5H, Ar^{Bn}), 7.26–7.21 (m, 2H, Ar^{Ts}), 6.00 (d, *J* = 8.3 Hz, *N*H), 5.12 (d, *J* = 12.2 Hz, CH_2^{Bn}), 5.06 (d, *J* = 12.2 Hz, CH_2^{Bn}), 4.68 (s, 2H, CH_2^{Troc}), 4.59 (dt, *J* = 8.6, 4.5 Hz, 1H, CH^{Asn}), 3.04 (dd, *J* = 17.1, 4.5 Hz, 1H, CH_2^{Asn}), 2.88 (dd, *J* = 17.1, 4.5 Hz, 1H, CH_2^{Asn}), 2.44 (s, 3H, CH_3^{Ts}) ppm. **^{13}C NMR** (500 MHz, Chloroform-*d*) δ 169.78 ($C{=}O^{Amide/Ester}$), 168.21 ($C{=}O^{Amide/Ester}$), 154.53 ($C{=}O^{Carbamate}$), 145.62 ($iAr^{Ts/Bn}$), 135.46 ($iAr^{Ts/Bn}$), 134.89 ($iAr^{Ts/Bn}$), 129.93 (2×Ar^{Bn}), 128.80 (2×Ar^{Bn}), 128.74 (Ar^{Bn}), 128.44 (2×Ar^{Ts}), 128.39 (2×Ar^{Ts}), 95.23 (CCl_3), 74.90 (CH_2^{Troc}), 68.14 (CH_2^{Bn}), 50.48 (CH^{Asn}), 38.03 (CH_2^{Asn}), 21.87 (CH_3^{Ts}) ppm. **HRMS** (MALDI+): Calculated for $C_{21}H_{21}Cl_3N_2O_7SNa^+$ m/z 573.0033; found m/z 573.0033. $[\alpha]_D^{589} = 37.0°$ (c = 0.7, $CHCl_3$).

***N*$^{\alpha}$-(alloxycarbonyl)-*N*-(tosyl)-L-asparagine benzyl ester (11)** A solution of $TsNH_2$ (0.47 g, 2.75 mmol) and DIPEA (0.9 ml, 5.01 mmol) in abs. CH_2Cl_2 (18 ml) was cooled down to 0 °C. Then a solution of the acyl chloride **S16** (0.82 g, 2.50 mmol) in abs. CH_2Cl_2 (15 ml) was added dropwise. The reaction mixture was slowly allowed to warm up and stirred at r.t. for 1 h. After this time the resulting solution was diluted with CH_2Cl_2 and washed with 1 M HCl (2×100 ml). The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was pourified by column chromatography (1:5→1:2 Acetone/Cyclohexane) to yield the compound **11** (0.90 g, 1.95 mmol, 78%) as a pale-yellow solid. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 8.82 (s, 1H, *N*H), 7.90 (d, *J* = 8.6 Hz, 2H, Ar^{Ts}), 7.39-7.28 (m, 5H, Ar^{Bn}), 7.25 (d, *J* = 8.6 Hz, 2H, Ar^{Ts}), 5.92-5.79 (m, 1H, $=CH^{Alloc}$), 6.79 (d, *J* = 8.0 Hz, *N*H), 5.27 (broad d, *J* = 17.1 Hz, $=CH_2^{Alloc}$), 5.19 (broad d, *J* = 10.2 Hz, $=CH_2^{Alloc}$), 5.12 (d, *J* = 12.1 Hz, CH_2^{Bn}), 5.05 (d, *J* = 12.1 Hz, CH_2^{Bn}), 4.60–4.48 (m, 3H, CH^{Asn}, CH_2^{Alloc}), 2.97 (broad d, *J* = 16.6 Hz, 1H, CH_2^{Asn}), 2.86 (broad d, *J* = 16.6 Hz, 1H, CH_2^{Asn}), 2.42 (s, 3H, CH_3^{Ts}) ppm. **^{13}C NMR** (500 MHz, Chloroform-*d*) δ 170.4 (C=O), 168.6 (C=O), 156.2 (C=O), 145.3 (Ar), 135.7 (Ar, 135.1 (All), 132.4 (Ar), 129.8 (Ar), 128.7 (Ar), 128.6 (Ar), 128.3 (Ar), 118.1 ($=CH_2^{Alloc}$), 67.9 (CH_2^{Bn}), 66.3 (CH_2^{Alloc}), 50.4 (CH_2^{Asn}), 38.4 (CH_2^{Asn}), 21.8 (Me) ppm. **HRMS** (MALDI+): Calculated for $C_{22}H_{24}N_2O_7SNa^+$ m/z 483.1202; found m/z 483.1197. $[\alpha]_D^{589} = 39.4°$ (c = 0.6, $CHCl_3$).

***N*$^{\alpha}$-(alloxycarbonyl)-*N*-(nosyl)-L-asparagine benzyl ester (12)** PyBroP (1.54 g, 3.30 mmol) was added to a stirred solution of **S15** (0.80 g, 2.59 mmol), $NsNH_2$ (0.48 g, 2.36 mmol), DIPEA (1.0 ml, 5.90 mmol) and DMAP (14.4 mg, 0.12 mmol) in abs. CH_2Cl_2 (24 ml). The reaction mixture was stirred at r.t. for 1 h. After this time the resulting solution was diluted with CH_2Cl_2 (100 ml) and washed with 1 M HCl (2×100 ml). The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was pourified by column chromatography (1:3→2:1 EtOAc/Heptane) to yield the compound **12** (1.07 g, 1.65 mmol, 70%) as a pale-yellow solid. **^{1}H NMR** (500 MHz, DMSO-*d*) δ 12.60 (broad s, 1H, *N*H), 8.40 (d, *J*= 8.0 Hz, 2H, Ar^{Ns}), 8.15 (d, *J*=8.0 Hz, 2H, Ar^{Ns}), 7.74 (d, *J*=8.1 Hz, *N*H), 7.40-7.21 (m, 5H, Ar^{Bn}), 5.91–5.77 (m, 1H, $=CH^{Alloc}$),5.23 (broad d, *J*= 17.4 Hz, $=CH_2^{Alloc}$), 5.14 (broad d, *J*=10.7 Hz, $=CH_2^{Alloc}$), 5.09-4.99 (m, 2H, CH_2^{Bn}), 4.51-4.33 (3H, CH^{Asn}, CH_2^{Alloc}), 2.87 (dd, *J*=16.9, 5.8 Hz, 1H, CH_2^{Asn}), 2.66 (dd, *J*=16.9, 7.9 Hz, 1H, CH_2^{Asn}) ppm. **^{13}C NMR** (500 MHz, Chloroform-*d*) δ 170.7 (C=O), 169.0 (C=O), 150.2 (C=O), 144.6 (Ar), 135.7 (Ar, 133.3 (All), 129.2 (Ar), 128.4 (Ar), 128.0 (Ar), 127.5 (Ar), 124.4 (Ar), 117.1 ($=CH_2^{Alloc}$), 66.2 (CH_2^{Bn}), 64.6 (CH_2^{Alloc}), 49.7 (CH_2^{Asn}), 37.3 (CH_2^{Asn}) ppm. **HRMS** (MALDI+): Calculated for $C_{21}H_{21}N_3O_9SNa^+$ m/z 514.0896; found m/z 514.0888.

General procedure A for glycosylations: Amide acceptor (1.5 equiv.) was added to a stirred solution of trichloroacetimidate glycosyl donor (1.0 equiv., 0.2 mmol) in dry $C_6H_4Cl_2$ (2.0 mL) under a nitrogen atmosphere in flame-dried glassware. Depending on the glycosyl donor used, the reaction was stirred at 125 °C for h. After completion the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 ml), washed with 1 M NaOH solution (50 ml) to remove trichloroacetamide and brine (50 ml). The products were purified by flash column chromatography and evaporated to dryness. **General procedure B for glycosylations**: Amide acceptor (1.0 equiv.) was added to a stirred solution of trichloroacetimidate glycosyl donor (1.5 equiv., 0.2 mmol) in dry $C_6H_4Cl_2$ (2.0 mL) under a nitrogen atmosphere in flame-dried glassware. Depending on the glycosyl donor used, the reaction was stirred at 125 °C for h. After completion the solvent was removed *in vacuo*. The obtained residue was dissolved in CH_2Cl_2 (100 ml), washed with 1 M NaOH solution (50 ml) to remove trichloroacetamide and brine (50 ml). The products were purified by flash column chromatography and evaporated to dryness.

Full experimental details for the glycosylation reactions can be found in the supporting material together with assigned spectral data as well as copies of spectra.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Asparagine · Chemoselectivity · Diastereoselectivity · *N*-Glycosylation · Sulfonyl amides

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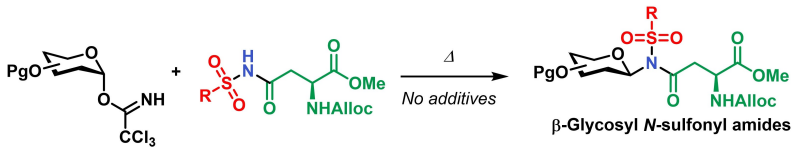

Glycosyl sulfonyl amides are synthesized in a self-promoted *N*-glycosylation with high β-selectivity and in high yields. Armed and disarmed glycosyl donors of different size and with different protective groups react smoothly with sulfonyl amides, such as protected asparagine derivatives. Influence of solvents, concentration, temperature and stoichiometry is studied.

*P. Mała, Prof. C. M. Pedersen**