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Sonogashira cross-coupling as a key step in the synthesis of new glycoporphyrins†

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Glycoporphyrins are an important subclass of the porphyrin family of compounds. They have been intensively studied because of their biological importance, *i.e.* they exhibit increased solubility in polar solvents and they might provide better selectivity towards biological targets. New methods for the efficient synthesis of these compounds are highly desired. Unfortunately, in most of the described methodologies, carbohydrate-linked porphyrins are obtained through hydrolyzable connections. Herein, the original route to new C–C conjugated glycoporphyrins *via* the Sonogashira cross-coupling is presented. The optimal conditions have been established and the most convenient synthetic strategy has been determined.

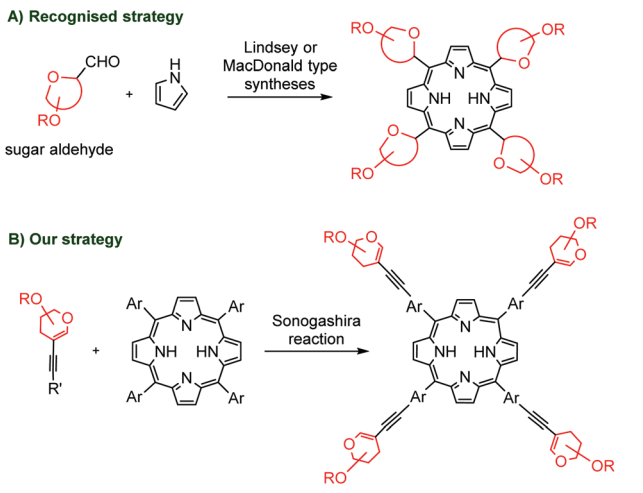
1. Introduction

Over the last decades, porphyrins and porphyrinoids have become well recognised as therapeutic agents in modern anticancer therapies such as photodynamic therapy (PDT).[1] Porphyrins possess an interesting set of features that make them potential photosensitizers (PS) *i.e.* biocompatibility, high affinity towards cancer cells, absorption in the visible range of the electromagnetic spectrum, and efficient phototoxicity towards cancer cells. Despite the indisputable advantages of using porphyrins as PS, there are still challenges that need to be overcome to fully reveal their potential in PDT. The new generation of PS is expected to be more selective, with increased amphiphilicity and preferably with a red-shifted absorption maximum.[2]

Nowadays, new synthetic strategies towards amphiphilic porphyrin systems are of great interest.[3] Especially intriguing are the methods leading to glycoporphyrin hybrids, because these compounds may have a better solubility in polar solvents and they might exhibit an increased potential to aggregate nearby cancer cells.[4,5] However, the synthesis of new porphyrin–sugar hybrids suffers from the absence of general methodologies.

The covalent binding of porphyrins with carbohydrates is mainly achieved *via* C–O,[6] C–S,[7] and C–N bonds,[8] an amide or ester function,[9] or a triazole linker.[10] The C–C conjugated porphyrins with sugars might be considered particularly interesting as non-hydrolyzable hybrids. The well-recognized methodologies to obtain *meso*-glyco-substituted porphyrins are the Lindsey and the MacDonald strategy (Scheme 1A).[11] However, the final products are often complex mixtures of atropoisomers that are difficult to interpret.

To the best of our knowledge, except for a singular example of a 12-step synthesis,[12] the literature does not cover any other



Scheme 1 Strategies towards C–C linked glycoporphyrins.

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examples of methods to introduce carbohydrate units into *meso*-aryl rings *via* C–C bonds. What is more, palladium-catalysis has not yet been explored in the field of C–C linked glycoporphyrins.

On the other hand, in recent years, continuous progress has been made in the recognition of 2-haloglycals as convenient starting materials for metal-catalyzed reactions.[13] New methodologies have been developed, focusing mostly on the creation of new C–C bonds *via* the Heck[14] and Suzuki–Miyaura reactions,[15] cyanation,[16] or other transformations.[17] More recently, carbonylative equivalents have been put in the spotlight,[18] as well as reactions leading to new C-heteroatom bonds.[19]

Since the first report of palladium-catalyzed couplings between aryl halides and acetylenes in the presence of copper(I),[20] the Sonogashira reaction has become one of the most reliable and default strategies to conjugate molecules *via* ethynyl linkers.[21] The potential of this reaction has already been demonstrated for 2-iodoglycals, and conditions for the Sonogashira coupling have been developed for peracetylated sugar starting materials, however only relativily simple alkynes have been applied in these methodologies.[22] On the other hand, the Sonogashira reaction has been widely exploited in the chemistry of porphyrins and other macroheterocycles.[23] Despite this, no porphyrin–glycal hybrids have been developed till date using this strategy. This approach is particularly interesting since the possibility of using metal-catalysis opens a range of new routes towards C–C conjugated glycoporphyrins and therefore towards PS of a new generation.

Taking all of this into account, we focused our attention on the development of new suitable conditions for the Sonogashira cross-coupling to couple two groups of compounds that are quite different in terms of chemical origins: porphyrins and glycals (Scheme 1B). Herein, we present a new, short and efficient synthetic route towards non-hydrolyzable C–C conjugated glycoporphyrin hybrids.

2. Results and discussion

In the literature, there are two general approaches to introduce the carbohydrate moiety into macroheterocycles. The first one involves the prefunctionalization of the starting material by combining a simple scaffold with a sugar, followed by the formation of porphyrinoids. This approach gives the opportunity to easily obtain a diverse library of compounds. However, it is limited to acid-resistant functions and it is possible that porphyrin cyclisation step is a low-yield process. The second strategy is based on the creation of a macroheterocyclic system at first, followed by the introduction of a sugar unit in the second stage. In this approach, attention must be paid to the glycosylation step which should be performed very efficiently to avoid the separation of the complex, statistical mixtures resulting from low-yield reactions.

A. Glycosylation prior to the porphyrin formation

We began our research with the exploration of the first strategy to conjugate perbenzylated 2-iodo-D-glucal (**1**) with the easily accessible 4-ethynylbenzaldehyde (**2**). The crucial transformation leading to the porphyrin was expected to be realized in the next stage *via* the Lindsey or the Adler–Longo method. Thus, the protective groups on the sugar moiety should be resistant to the acidid milieu. We chose the benzyl protecting groups as they were proven to be resistant to Lindsey's reaction conditions.[11]

As the initial conditions for the conjugation of **1** with **2**, we selected reagents inspired by the procedures developed for the Sonogashira cross-couplings of peracetylated glycals (Table 1, entries 1 and 2).[22] However, in both cases, the procedures proved to be unsuitable for the chosen starting materials. We believe that this is due to the differences in the solubility of peracetylated glycals *vs.* perbenzylated ones and/or the stereoelectronic effects that make the oxidative addition step in the catalytic cycle more challenging.

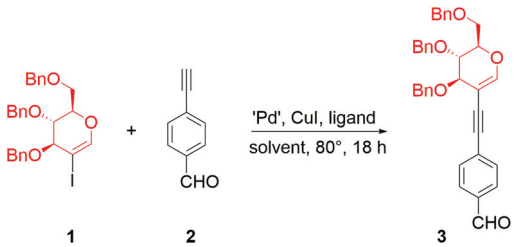
The lack of conversion of **1** and the decomposition of aldehyde **2** were observed when Cs_2CO_3 was used as a base (Table 1, entry 1). Changing the palladium source to Pd$(PPh_3)_2Cl_2$ and the base to triethylamine (used herein as a solvent) slightly improved the conversion; however the product was obtained in a moderate yield (Table 1, entry 2).

Due to the lack of appropriate conditions for the coupling of **1** with **2**, we decided to determine the optimized reaction conditions (for a detailed study, see the ESI†). The use of various solvents with 2 equivalents of triethylamine improved the yield only slightly (Table 1, entries 3 and 4). In Sonogashira cross-couplings, high yields are usually observed when triethylamine is used as a solvent, especially for copper-free variants. However, in our case, a modest yield was observed when triethylamine was used as the only solvent. We anticipated that using a mixture of solvents might limit the solubility issues while, on the other hand, providing quite high concentrations of triethylamine. Indeed, some noticeable improvement was observed when a mixture of toluene and triethylamine (1 : 1) was used as solvent (Table 1, entry 5), especially when the reaction was performed under diluted conditions (Table 1, entry 6).

Changing the catalytic system from Pd$(PPh_3)_2Cl_2$ to palladium(0), *i.e.* Pd$(PPh_3)_4$, improved the yield to an acceptable level (Table 1, entry 7). The influence of copper(I) iodide was tested, proving its beneficial effect on the reaction (Table 1, entry 8); however, the reaction proceeded without the presence of a cocatalyst as well. Palladium(II) chloride with PPh_3 as a ligand also catalysed the reaction, but an improvement in the yield was observed when the more sterically hindered ligand XPhos was used (Table 1, entry 9 *vs.* entry 10). Encouraged by these results, we decided to test Pd-XPhos-G3 as a well-recognized source of active palladium(0) species. The new catalytic system led to a very good yield (86%, Table 1, entry 11). Pd-XPhos-G3 enabled the lowering of the reaction temperature; however, halving the catalyst loading resulted in a slight decrease in the yield (Table 1 entry 12 *vs.* 13).[24]

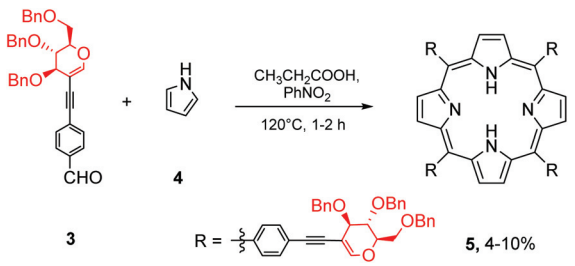
With aldehyde **3** in hand, we next subjected it to porphyrin cyclocondensation conditions (Scheme 2). Despite several attempts, we were not able to detect porphyrin formation

Table 1 Optimization of the Sonogashira reaction on aldehyde **2**[a]



Entry	Solvent	Catalyst (eq.)	CuI (eq.)	Other (eq.)	Yield[b]
1	DMF	$Pd(OAc)_2$ (0.1)	—	Cs_2CO_3 (1.5)	0%[c]
2	Et_3N	$Pd(PPh_3)_2Cl_2$ (0.1)	0.2	—	21%[c]
3	Toluene	$Pd(PPh_3)_2Cl_2$ (0.1)	0.2	NEt_3 (2.0)	29%[c]
4	1,4-Dioxane	$Pd(PPh_3)_2Cl_2$ (0.1)	0.2	NEt_3 (2.0)	28%[c]
5	Toluene/NEt_3 (1 : 1)	$Pd(PPh_3)_2Cl_2$ (0.1)	0.2	—	44%[c]
6	Toluene/NEt_3 (1 : 1)	$Pd(PPh_3)_2Cl_2$ (0.1)	0.2	—	51%
7	Toluene/NEt_3 (1 : 1)	$Pd(PPh_3)_4$ (0.1)	0.2	—	59%
8	Toluene/NEt_3 (1 : 1)	$Pd(PPh_3)_4$ (0.1)	—	—	35%
9	Toluene/NEt_3 (1 : 1)	$PdCl_2$ (0.1)	0.2	PPh_3 (0.20)	53%
10	Toluene/NEt_3 (1 : 1)	$PdCl_2$ (0.1)	0.2	XPhos (0.20)	63%
11	**Toluene/NEt_3 (1 : 1)**	**Pd-XPhos-G3 (0.1)**	**0.2**	**XPhos (0.10)**	**86%**[d]
12	Toluene/NEt_3 (1 : 1)	Pd-XPhos-G3 (0.1)	0.1	XPhos (0.10)	85%[e]
13	Toluene/NEt_3 (1 : 1)	Pd-XPhos-G3 (0.05)	0.05	XPhos (0.05)	75%[e]

[a] General conditions: perbenzylated 2-iodo-D-glucal (0.110 mmol, 1.0 eq.), 4-ethynylbenzaldehyde (0.130 mmol, 1.2 eq.), catalyst (0.011 mmol, 0.1 eq.), copper(I) iodide (0.022 mmol, 0.2 eq.), toluene (0.5 mL), triethylamine (0.5 mL), 80 °C, 18 h, argon atmosphere. [b] Determined from the crude mixture by ^1H NMR with the internal standard. [c] Reaction in 0.5 mL of solvent(s). [d] Corresponds to 85% of the isolated product. [e] Reaction at 60 °C.



Scheme 2 The Adler–Longo method in the synthesis of porphyrin **5**.

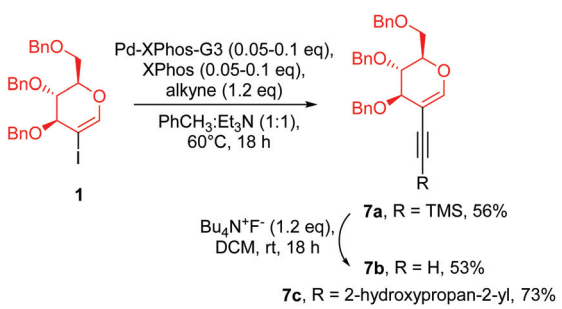
when Lindsey's procedure was applied to **3** (TFA or $BF_3{\cdot}Et_2O$ used as catalysts). Pyrrole polymerisation was mostly observed in reactions with a higher concentration of catalyst whereas lowering the amount of catalyst did not induce the condensation step and no conversion of **3** was observed. However, inspired by published results of porphyrin formation from 4-ethynylbenzaldehyde *via* the Adler–Longo strategy,[25] we synthesized the expected product **5** in 10% yield. Since the reaction itself was hardly reproducible and sometimes led to a mixture of products that were difficult to separate, we decided to change the strategy and obtain the final glycoporphyrins using another approach.

B. Glycosylation of porphyrins – benzyl group protection of the hydroxyl function

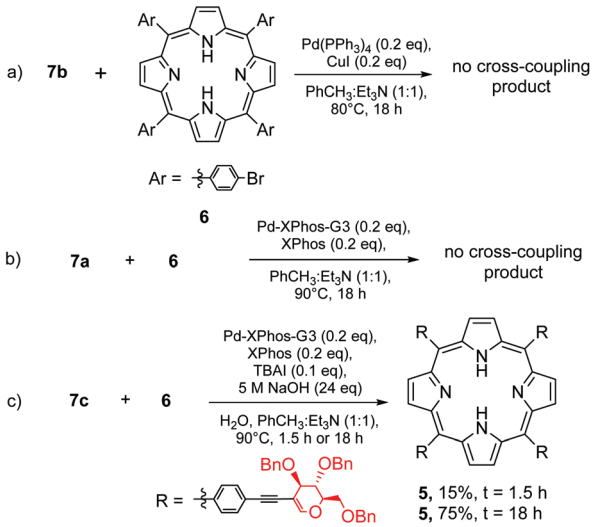
In this strategy we started with the synthesis of a porphyrin core, followed by the introduction of a glycal moiety *via* the Sonogashira reaction. As a model porphyrin we chose (5,10,15,20)-tetrakis(4-bromophenyl)porphyrin (**6**) because it is bench-stable and smoothly obtained from the reaction of 4-bromobenzaldehyde and pyrrole under Lindsey's conditions.[26] The glycal starting materials (Scheme 3, **7a–7c**) were obtained from perbenzylated 2-iodo-D-glucal under the optimised conditions described in Table 1.

The route to synthesize porphyrin **5** from **6** required highly efficient conditions for the cross-coupling step. In the case of an incomplete process, a complicated mixture of products was obtained, making the separation process laborious.

At first, we allowed alkyne **7b** to react with **6** under the standard conditions of Sonogashira cross-coupling (Scheme 4, path a). As a catalyst amount, we decided to use 0.20 equivalents of palladium(0) with regard to porphyrin which corresponded to 0.05 equivalents of palladium with regard to the



Scheme 3 Synthesis of starting materials for the Sonogashira coupling.



Scheme 4 Variation of the Sonogashira cross-coupling reaction performed on porphyrin **6**.

aryl halide in the molecule. However, from the post-reaction mixture, unreacted **6** was isolated and a product resulting from the homocoupling of **7b** was observed. This Glaser-type reactivity is a common side-reaction usually detected in unsuccessful Sonogashira transformations.[21]

To suppress this dimerization process, we decided to utilize **7a** as the starting material and to apply the sila-Sonogashira reaction (Scheme 4, path b) to produce the desired alkyne **7b** *in situ*. Despite that, this reaction also showed a similar result: porphyrin **6** was recovered and a product of homocoupling was observed. We concluded that a high concentration of compound **7b** is undesirable and this was observed in both experiments, thus resulting in glycal homocoupling. To slow down the *in situ* production of **7b**, another strategy to produce ethynyl compounds in a controlled manner was studied *via* β-alkynyl elimination.[27] Indeed, the reaction of **7c** with porphyrin **6** under conditions similar to those given in Table 1 led to the glycosylated product **5** in a very good overall yield of 76% (Scheme 4, path c). It seems that among all the tested variations under the Sonogashira conditions, the β-alkynyl elimination strategy provided the required amount of alkyne at the most optimal pace. Low concentration of alkyne **7b** supressed the catalytic cycle path leading to homocoupling, and enabled a cross-coupling process. The desired product has been observed even after a shortening of reaction time to 90 min (Scheme 4c). Another crucial parameter for the porphyrin glycosylation strategy was using a suitable excess of glycal substrate. The change in the ratio between **6** and **7c** from 1 : 8 to 1 : 6 resulted in a significant decrease in the reaction yield (32%) with the formation of a complex mixture of products.

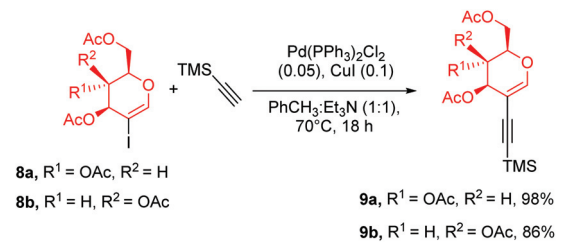
With the discovery of an efficient route to glycoporphyrin **5**, we faced the problem of removal of the benzyl group. Since unsaturated bonds were present in **5**, the hydrogenolysis conditions were excluded. The first strategy involved the application of BCl_3 in dichloromethane. However, the nature of this reagent limited the choice to a non-coordinating reaction solvent. Dichloromethane was an appropriate solvent to solubilize **5**; however, the polarity of intermediates was increased significantly with progressive removal of the benzyl groups and their precipitation was observed in the reaction mixture. All of this resulted in the formation of a complex and inseparable mixture of semi-deprotected products. We tested several different solvents and their mixtures ($CHCl_3$, THF, CH_3CN, $PhCH_3$, 1,4-dioxane, *etc.*) and higher temperatures; however, no change in the reaction outcome was observed. Polar solvents provided good solubility of intermediates and deactivated BCl_3, while non-polar solvents led to the precipitation of intermediates. Acid hydrolysis did not bring about any improvement either (MsOH or 6 N HCl), similar to the strategies involving an exchange of the benzyl group with the acetyl one (AcCl with $SnBr_2$ or TMSOTf in Ac_2O).[28] Since the persistence of the benzyl group terminated this synthetic pathway, we finally applied the glycosylation strategy to glycals with a group more prone to removal, namely the acetyl group.

C. Glycosylation of porphyrins –acetyl group protection of the hydroxyl function

The final approach towards glycoporphyrins was inspired by the experience gained from using perbenzylated glycals. As the most suitable model porphyrin, compound **6** was chosen. Glycal starting materials **9a** and **9b** were synthesized according to the described procedure,[22b] with a modification of solvent and products **9a** and **9b** were furnished in excellent yields (Scheme 5). Once again we observed the beneficial effect of a mixed solvent system on the reaction outcome, since the alkynylation process almost doubled the yield of **9b** in comparison to its previously published yields.

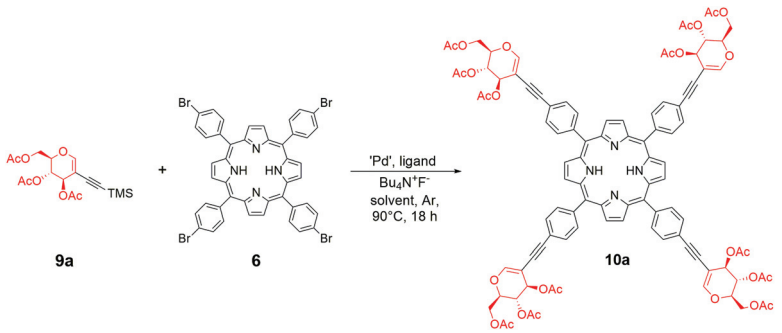
With peracetylated glycal as the starting material in hand, we started the optimization of the sila-Sonogashira cross-coupling with **6** (Table 2, for expanded studies, see the ESI†). Initially, the conditions, catalytic system, and reagent ratios described for **5** were applied (Scheme 4). The copper-free variant allowed the avoidance of the risk of porphyrin metalation that often occurs when copper(I) iodide is used in the reaction.

Similar to the results obtained with the perbenzylated analogue, the direct Sonogashira cross-coupling mainly resulted in the oxidative dimerization of the glycal (Table 2, entry 1). However, the sila-Sonogashira conditions in a mixture of solvents allowed glycoporphyrin **10a** to be obtained in an acceptable yield (Table 2, entry 2). We observed the improvement in



Scheme 5 Synthesis of peracetylated starting materials.

Table 2 Optimisation of the sila-Sonogashira reaction on alkyne **9a**[a]



Entry	Catalyst (eq.)	Ligand (eq.)	Solvent	Yield[b]
1	Pd-XPhos-G3 (0.2)	XPhos (0.2)	Toluene/NEt_3 (1 : 1)	0%[c]
2	Pd-XPhos-G3 (0.2)	XPhos (0.2)	Toluene/NEt_3 (1 : 1)	56%
3	Pd-XPhos-G3 (0.2)	XPhos (0.2)	1,4-dioxane/NEt_3 (1 : 1)	75%
4	Pd-XPhos-G3 (0.2)	XPhos (0.2)	1,4-dioxane/NEt_3 (1 : 1)	71%[d]
5	Pd-XPhos-G3 (0.2)	XPhos (0.2)	1,4-dioxane (+ NEt_3, 8.0 eq.)	42%
6	Pd-XPhos-G3 (0.2)	XPhos (0.2)	NEt_3	13%
7	**Pd-XPhos-G3 (0.15)**	**XPhos (0.15)**	**1,4-dioxane/NEt_3 (1 : 1)**	**85%**
8	Pd-XPhos-G3 (0.2)	—	1,4-dioxane/NEt_3 (1 : 1)	60%
9	Pd-XPhos-G3 (0.2)	XPhos (0.4)	1,4-dioxane/NEt_3 (1 : 1)	48%
10	$PdCl_2$ (0.2)	XPhos (0.2)	1,4-dioxane/NEt_3 (1 : 1)	45%
11	Pd-RuPhos-G3 (0.15)	RuPhos (0.15)	1,4-dioxane/NEt_3 (1 : 1)	56%
12	Pd-XantPhos-G3 (0.15)	XantPhos (0.15)	1,4-dioxane/NEt_3 (1 : 1)	42%

[a] General conditions: porphyrin **6** (0.024 mmol, 1.0 eq.), glycal **8a** (0.190 mmol, 8.0 eq.), $Bu_4N^+F^-$ (0.194 mmol, 8.2 eq.), Pd-XPhos (0.005 mmol, 0.2 eq.), XPhos (0.005 mmol, 0.2 eq.), 1,4-dioxane (2.5 mL), triethylamine (2.5 mL), 18 h, 90 °C, argon atmosphere. [b] Yield of the isolated product. [c] The reaction was performed on peracetylated 2-ethynyl-D-glucal as a glycal substrate. [d] Reaction time was 1.5 h.

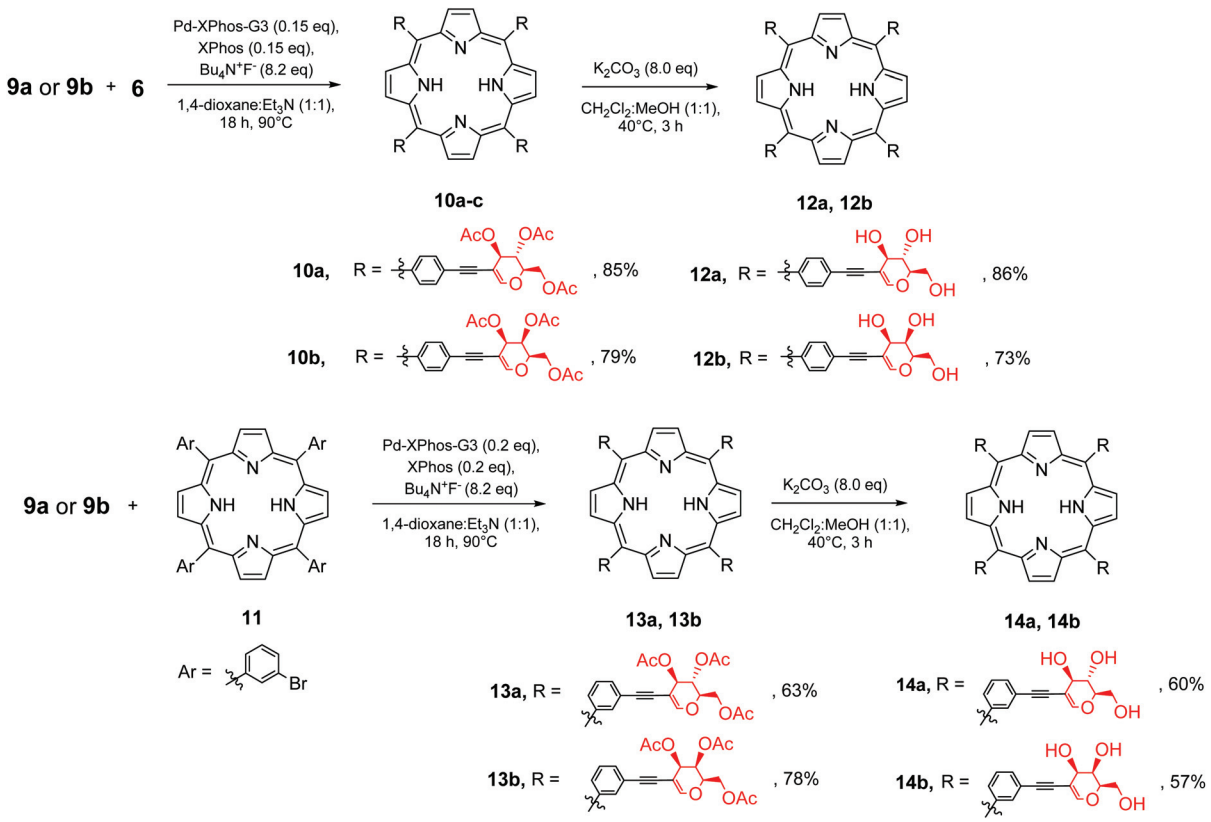
the reaction when 1,4-dioxane was used as a co-solvent (Table 2, entry 3). In contrast to the results obtained with the perbenzylated glycal **7a** (Scheme 4, path a), probably, the catalytic pathway of the Sonogashira reaction was more efficient for compound **9a**, and the reaction was almost complete after 90 min (Table 2, entry 4). It seems plausible that both starting materials differed in the electron density of their alkyne part, which has been proposed to be one of the crucial factors determining the final Sonogashira mechanism and the catalytic cycle rate.[29] Using a mixture of solvents was beneficial for this reaction, providing porphyrin **6** with good solubility and a high concentration of triethylamine (Table 2, entry 3 *vs.* entries 5 and 6) and improving the conversion of the starting material significantly. Decreasing the amount of the catalyst to 0.15 equivalents furnished product **10a** in a very good overall yield of 85% (Table 2, entry 7). The equimolar amount of ligand was optimal, since an increased amount resulted in a lower yield. This can be explained by the high stabilization of palladium(0). On the other hand, the lack of additional XPhos probably makes the catalyst insufficiently stable during the reaction (Table 2, entries 8 and 9). Other catalytic systems proved to be active in the reaction; however, their use resulted in a lower yield (Table 2, entries 10–12) and in the formation of a mixture of semi-glycosylated porphyrins.

To check the utility of the developed methodology towards glycoporphyrins, the optimal conditions used for the synthesis of **10a** were then applied to another porphyrin ((5,10,15,20)-tetrakis(3-bromophenyl)porphyrin, **11**) and tested on peracetylated galactal **9b** as well (Scheme 6). The products of the sila-Sonogashira reaction (for **9a** and **9b**) were obtained in good to very good yields.

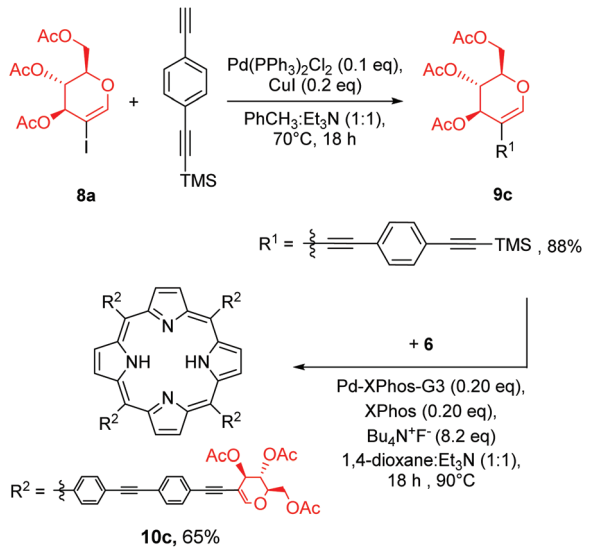
The deprotection step required a small modification in comparison to the typical approach. Since porphyrins **10** and **13** were only slightly soluble in alcohol, in order to ensure efficient methanolysis, dichloromethane was used as the co-solvent, which significantly improved the solubility of the starting material.

The final products showed significantly improved solubility in polar solvents including DMSO and methanol. However, only a negligible solubility in water was observed for the final glycoporphyrins.

To further test our strategy, we decided to check if linker prolongation does not change the outcome of our methodology. In particular we became interested if more complex linkers, such as ethynyl–aryl–ethynyl substituents might be introduced into the *meso*-phenyl rings. As a linker we decided to use 4-ethynyl-(2-trimethylsilylethynyl)benzene. The installation of the linker on glycal **8a** (Scheme 7) proceeded in a manner similar to previously discussed reactions, and product **9c** was obtained in a very good yield. Then glycal **9c** was reacted with porphyrin **6** under our developed conditions, affording product **10c** in a good yield. This proved that this strategy could be used with the ethynyl–aryl–ethynyl linkers as well without any particular modifications.



Scheme 6 Synthesis of the final glycoporphyrin hybrids.



Scheme 7 Developed methodology applied to a more complex linker.

3. Conclusions

A new strategy to access glycoporphyrin hybrids has been developed using a methodology applying Sonogashira cross-coupling. The optimal conditions suitable for the cross-coupling of perbenzylated 2-iodoglycal with alkynes including 4-ethynylbenzaldehyde have been identified and after a slight modification, they were appropriate for coupling with halogenated porphyrins at the *meso*-aryl rings.

The presented strategy is the first example of an organometallic cross-coupling between glycals and porphyrins leading to C–C conjugated products. In the context of the great importance of glycoporphyrins in the area of biomedicine, the reported strategy might be a starting point for diverse alternative strategies to be developed in the future. The biological evaluation of the deprotected hybrids is in progress.

A new, direct route towards glycoporphyrins has been established and will be expanded in future projects with respect to meeting the requirements of photodynamic therapy.

Conflicts of interest

The authors declare no conflict of interest.

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