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# Site-Selective Acylation of Pyranosides with Immobilized Oligopeptide Catalysts in Flow

Alexander Seitz,[a] Raffael C. Wende,[a] and Peter R. Schreiner*[a]

**Abstract:** We report the site-selective acetylation of partially protected monosaccharides using immobilized oligopeptide catalysts, which are readily accessible via solid-phase peptide synthesis. The catalysts are able to invert the intrinsic selectivity, which was determined using *N*-methylimidazole, for a variety of pyranosides. We demonstrate that the catalysts are stable for multiple reaction cycles and can be easily reused after separation from the reaction solution. The catalysts can also be used in flow without loss of reactivity and selectivity.

## Introduction

It is a worthwhile but challenging task for chemists to develop catalysts that mimic the extraordinary reactivities and selectivities of enzymes.[1–2] Synthetic oligopeptides as organocatalysts turned out to be especially useful to provide insights into how enzymes work as already a few amino acids are sufficient to form secondary structures.[3–7] These structures, which typically form due to noncovalent interactions such as H-bonds and London dispersion interactions,[4,8–9] are important for peptide catalysts to perform selective reactions.[10–13] Still, the oligopeptides must retain some flexibility, allowing them to adapt to the substrate and hence perform reactions comparable to enzymes.[7,9,14–17] Over the years, peptides were used to catalyze various reactions like oxidations,[18–21] reductions,[22–23] group transfers,[15,24–26] among others.[3,6,27–28] One important and thoroughly investigated type of reactions are acylations, which were first investigated using peptide catalysts by the Miller group.[25] Several groups used various histidine or pyridine-based catalytic motifs integrated into oligopeptides to perform acylation reactions.[15,29–33]

One general problem is that most of the peptide catalysts are comparatively expensive and difficult to recover from the reaction solution.[34–35] Immobilizing a catalyst meets this challenge, as it is easier to recover and reuse it; this usually allows also easier product purification.[36] Furthermore, immobilized catalysts can be used in continuous flow experiments, which combines all of its benefits in a single operation.[36–37] Therefore, some effort has been put into the development of immobilized oligopeptide catalysts.[38–42] One especially interesting publication concerns the selective acetylation of carbohydrates by Kirsch et al., who were the first to immobilize an acylating peptide catalyst retaining its reactivity.[35] The immobilized hexapeptide catalyst bearing a catalytically active DMAP-unit achieved high selectivities in the acylation of different methyl 4,6-*O*-protected monosaccharides.[33,35] However, an excess of triethylamine as auxiliary base was employed, which by itself may also lead to site selective acylation of carbohydrates in some cases.[43] We recently published a site-selective acylation of different methyl 4,6-*O*-protected monosaccharides using tetrapeptide catalysts bearing π-methyl histidine (Pmh) as the catalytically active moiety. These peptide catalysts were able to overcome the intrinsic preference of the "parent" *N*-methylimidazole (NMI) motif for the 3-*O*-position.[44]

Here we report the immobilization of oligopeptide catalysts bearing Pmh as the catalytic moiety and their ability to perform site-selective acetylation reactions of different 4,6-*O*-protected carbohydrates. Importantly, we demonstrate that the catalysts are stable under the reaction conditions and therefore applicable to flow chemistry.

## Results and Discussion

We commenced our investigation by immobilizing highly active catalyst **1** (Table 1)[15,44] on Wang-resin using solid-phase peptide synthesis (SPPS) without cleaving the catalyst from the resin, and performed the acetylation of methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**5**). Although this catalyst is known to perform with loadings down to 1 mol%,[15] and other peptide catalysts work with even lower loadings,[45–46] previous studies on this system encouraged us to work with 10 mol% **1**.[44] To determine the intrinsic selectivity we used NMI, since without a catalyst there was no reaction for any substrate (Figure 1). Fortunately, the immobilized catalyst still shows high conver-

[a] *A. Seitz, Dr. R. C. Wende, Prof. Dr. P. R. Schreiner*
*Institute of Organic Chemistry*
*Justus Liebig University Giessen*
*Heinrich-Buff-Ring 17*
*35392 Giessen (Germany)*
*E-mail: prs@uni-giessen.de*

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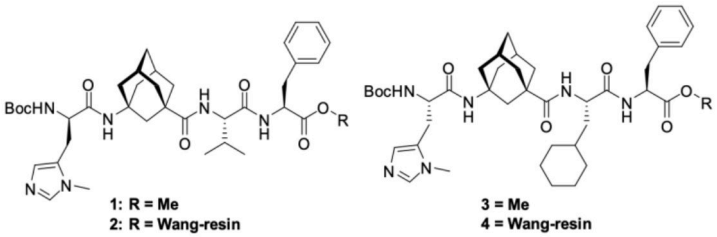
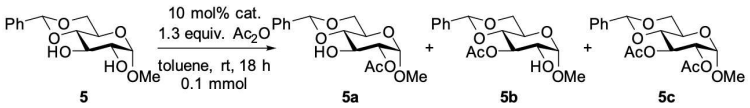
**Table 1.** Acetylation of methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**5**) with NMI and oligopeptide catalysts **1**–**4**.




| Entry | Catalyst | **5a** [%] | **5b** [%] | **5c** [%] | C (%) | Selectivity [%][c] |
|---|---|---|---|---|---|---|
| 1 | NMI | 20 | 62 | 5 | 87 | 23 |
| 2 | 1[a] | 70 | 19 | 3 | 92 | 76 |
| 3 | 2[b] | 58 | 29 | 7 | 94 | 62 |
| 4 | 3 | 55 | 37 | 8 | >95 | 55 |
| 5 | 4[b] | 50 | 27 | 11 | 88 | 56 |

[a] 5 mol% cat.; [b] For determination of catalyst loading, see Supporting Information; [c] x = **5a**/(**5a** + **5b** + 5**c**) × 100; Product ratios and conversions determined via $^1$H NMR spectroscopy.

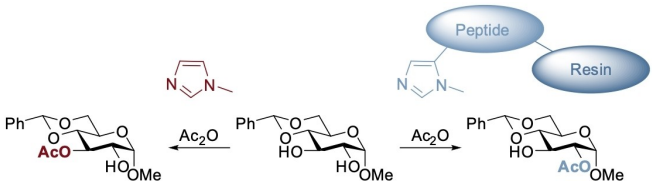



**Figure 1.** Site-selective acetylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside using immobilized peptide catalysts.

sion of 94% (Table 1, Entry 3), which is comparable to the non-immobilized catalyst **1** (92%, Table 1, Entry 2). The selectivity is lower compared to the reaction with unbound **1** (76%, Table 1, Entry 2), but still the intrinsically less favored (Table 1, Entry 1) 2-*O* acetylated product **5a** was obtained with a selectivity of 62%. Moreover, catalyst **2** performs better than other immobilized catalysts, for example, **4**, which showed similar reactivity (88%) but lower selectivity (56%, Table 1, Entry 5). Catalyst **4** showed comparable results to its non-immobilized form **3**, being somewhat less reactive (Table 1, Entry 4). We envisioned that the catalyst, although it is immobilized, is still able to form a "dynamic binding pocket" that is key for high reactivity and selectivity.[9,15] Carbohydrate **5** is suggested to bind to this pocket, which leads to the observed selectivities, with hydrogen bonding and dispersion interactions playing a key role.[9,44]

To investigate the effect of the pre-installed protecting groups we tested further glucopyranoside derivatives and observed high conversions for the α-anomers **6** (90%, Table 2, Entry 1) and **7** (77%, Table 2, Entry 2). Both showed comparable (62% for **6**, Table 2, Entry 1) or even higher (71% for **6**, Table 2, Entry 2) selectivity than for methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**5**). For methyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**8**) we observed low conversion of 20%, which is due to the poor solubility of the starting material in toluene, and low selectivity of 40% (Table 2, Entry 3), in agreement with earlier results.[44] The same is true for thio-β-derivative **9**, which shows high conversion of 89% and 2-*O*-acetylated derivative **8a** as the preferred product (48% selectivity, Table 2, Entry 4).

With a well-performing catalyst in hand, we decided to test catalyst recycling experiments and reusability. The selectivity as well as reactivity are constant over time, with notable changes occuring only after about ten cycles (Figure 2). This implies that the catalyst is reasonably stable under the reaction conditions, and that it is amenable to flow experiments. Note that there are only a few reports on peptide catalysts that perform well in flow.[40,42,47–48] Therefore, we used a 1/8" HPLC tube sealed using a Frit-in-a-Ferrule™ and packed with 50 mg (0.027 mmol) of **2**. The other end of the tube was connected to a syringe pump,

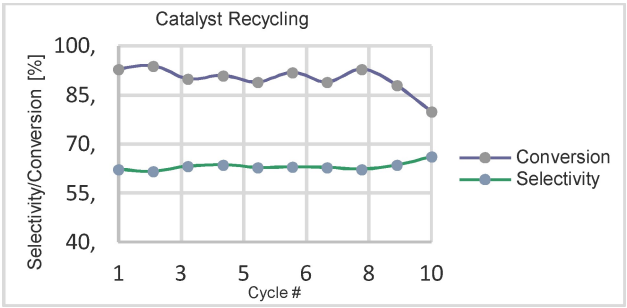
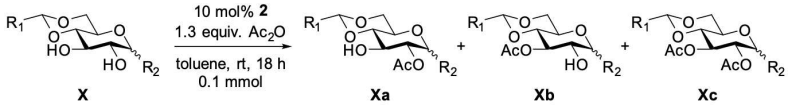
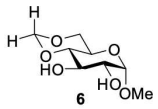
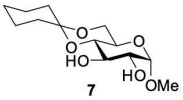
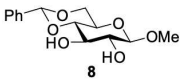
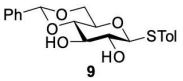



**Figure 2.** Using immobilized catalyst **2** in up to ten reaction cycles.

**Table 2.** Acetylation of glucopyranosides **6**–**9** with immobilized oligopeptide catalyst **2**.




X Xa Xb Xc

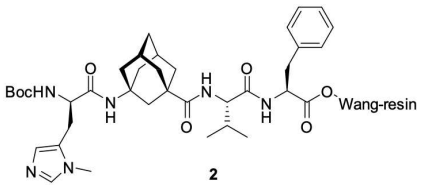
| Entry | Starting Material | Xa [%] | Xb [%] | Xc [%] | C [%] | Selectivity [%][a] |
|---|---|---|---|---|---|---|
| 1 |  6 | 56 | 29 | 5 | 90 | 62 |
| 2 |  7 | 55 | 20 | 2 | 77 | 71 |
| 3 |  8 | 8 | 9 | 3 | 20 | 40 |
| 4 |  9 | 43 | 38 | 8 | 89 | 48 |

[a] x = **Xa**/(**Xa** + **Xb** + **Xc**) × 100; Product ratios and conversions determined via $^1$H NMR spectroscopy.

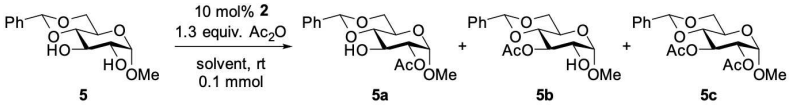
which was equipped with a syringe containing starting material and acetic anhydride dissolved in toluene.

In the first experiment we used the standard conditions (0.1 mmol of starting material, 10 mL toluene, 1.3 equiv. acetic anhydride) and a flow of 2 mL h$^{-1}$. Unfortunately, the starting material did not dissolve completely and some of it had to be filtered off before running the experiment. Still, we were able to isolate a total of 80% deployed material (IM = ratio of total amount of isolated compounds to deployed amount of glucopyranoside), a high conversion > 95%, and the same selectivity, but somewhat more diacetylated product (Table 3, Entry 1), compared to the experiments in a flask (Table 1, Entry 3). Similar results were achieved by conducting the reaction at 3 mL h$^{-1}$ (Table 3, Entry 2) but at 4 mL h$^{-1}$ the amount of isolated material compared to deployed material dropped and less diacetylated product **5c** as well as lower conversion was observed (Table 3, Entry 3). This indicates that at a flow of 4 mL h$^{-1}$ the dwell time is too short for efficient catalysis since the catalyst seems to be saturated. Running the reaction at higher dilution with 4 mL h$^{-1}$ prevents saturation, and we were able to isolate 94% of deployed material and observed only 6% of

**Table 3.** Acetylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**5**) with immobilized oligopeptide catalyst **2** in flow.




2

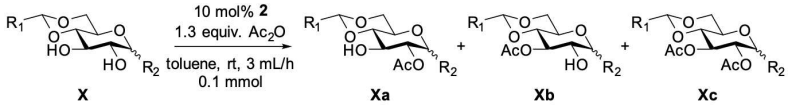



5 5a 5b 5c

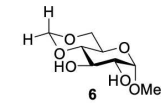
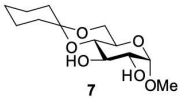
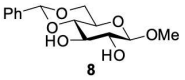
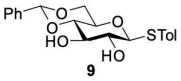
| Entry | Flow/mL h$^{-1}$ | Volume/mL (solvent) | 5a [%] | 5b [%] | 5c [%] | C [%] | IM [%][a] |
|---|---|---|---|---|---|---|---|
| 1 | 2 | 10 (toluene) | 57 | 29 | 12 | 98 | 80 |
| 2 | 3 | 10 (toluene) | 58 | 28 | 13 | 99 | 85 |
| 3 | 4 | 10 (toluene) | 57 | 28 | 11 | 96 | 66 |
| 4 | 4 | 10 (DCM) | 23 | 12 | – | 35 | 97 |
| 5 | 4 | 15 (toluene) | 57 | 27 | 6 | 90 | 94 |
| 6 | 6 | 15 (toluene) | 55 | 25 | 6 | 86 | 77 |

[a] IM = $n$(**5** + **5a** + **5b** + **5c**)$_{isolated}$ · $n^{-1}$(**5**)$_{deployed}$; Product ratios and conversions determined via $^1$H NMR spectroscopy.

**Table 4.** Acetylation of glucopyranoside **6**–**9** with immobilized oligopeptide catalyst **2** in flow.

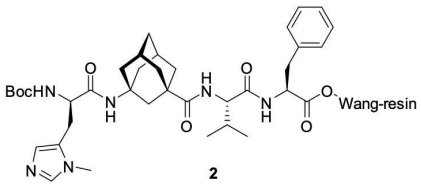



**X** **Xa** **Xb** **Xc**

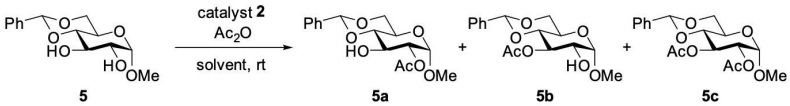
| Entry | Starting Material | **Xa** [%] | **Xb** [%] | **Xc** [%] | C [%] | IM [%][a] |
|---|---|---|---|---|---|---|
| 1 |  **6** | 53 | 26 | 21 | >95 | 55 |
| 2 |  **7** | 62 | 23 | 6 | 91 | 75 |
| 3 |  **8** | 21 | 25 | 44 | 90 | 12 |
| 4 |  **9** | 38 | 34 | 28 | >95 | 42 |

[a] IM = $n(\mathbf{X}+\mathbf{Xa}+\mathbf{Xb}+\mathbf{Xc})_{isolated} \cdot n^{-1}(\mathbf{X})_{deployed}$; Product ratios and conversions determined via $^1$H NMR spectroscopy.

**Table 5.** Large scale acetylation of methyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**5**) with immobilized oligopeptide catalyst **2** in flow.




**2**




**5** **5a** **5b** **5c**

| Entry | Flow/mL h$^{-1}$ | Solvent | Reaction Scale [mmol] | Equiv. $Ac_2O$ | **3a** [%] | **3b** [%] | **3c** [%] | C [%] | IM [%][a] | Selectivity [%][b] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3 | Toluene | 0.1 | 1.3 | 59 | 29 | 10 | >95 | 6 | 60 |
| 2 | 4 | Toluene/DCM (10:1) | 0.1 | 1.3 | 48 | 23 | 3 | 74 | >95 | 65 |
| 3 | 4 | Toluene/DCM (10:1) | 0.1 | 2.0 | 59 | 28 | 5 | 92 | >95 | 64 |
| 4[d] | 4 | Toluene/DCM (10:1) | 2.1 | 2.0 | 50[c] | 20[c] | 7[c] | – | – | 66 |
| 5[e] | 4 | Toluene/DCM (10:1) | 1.7 | 2.0 | 54[c] | 23[c] | 6[c] | – | – | 65 |
| 6[f] | 4 | Toluene/DCM (10:1) | 1.0 | 2.0 | 52 | 21 | 5 | 78 | >95 | 66 |
| 7[f],[g] | 4 | Toluene/DCM (10:1) | 1.0 | 2.0 | 50[c] | 19[c] | 4[c] | – | – | 68 |
| 8[h] | 4 | Toluene/DCM (10:1) | 4.4 | 2.0 | 56[c] | 24[c] | 6[c] | – | – | 65 |

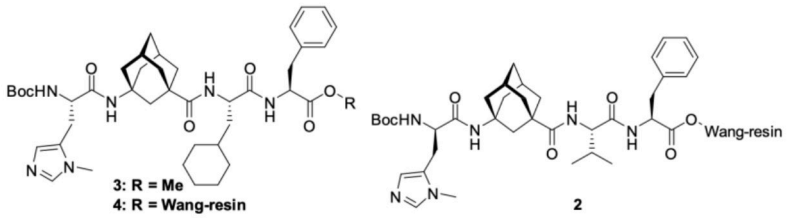
[a] IM = $n(\mathbf{5}+\mathbf{5a}+\mathbf{5b}+\mathbf{5c})_{isolated} \cdot n^{-1}(\mathbf{5})_{deployed}$; [b] x = **5a**/(**5a**+**5b**+**5c**) ×100; [c] Yield of isolated product; [d] 96 h flow time; [e] 72 h flow time; [f] **7** was used as starting material; [g] 24 h flow time; [h] 184 h flow time; Product ratios and conversions determined via $^1$H NMR spectroscopy.

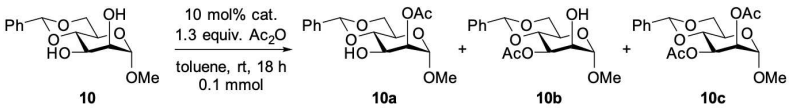
diacetylated product **5c** (Table 3, Entry 5). Further increasing the flow rate to 6 mL h$^{-1}$ led to pressure build up and leaks in the setup (77% IM). At the same time the conversion dropped to 86%, which again indicates saturation of the catalyst, but we achieved the same selectivity as at lower flow rates (Table 3, Entry 6).

Performing the reaction in dichloromethane, in which the solubility of the starting material is higher, the conversion dropped to 35% but the 2-*O*-acetylated **5a** was still the main product (Table 3, Entry 4). We assume the poor conversion being a result from suppression of crucial noncovalent interactions between the catalyst and the substrate, which in batch reactions usually leads to decreased selectivity.[15,49–50]

Testing derivatives **6**–**9** with a flow rate of 3 mL h$^{-1}$ was hampered by the low solubility of the starting materials in toluene, resulting in overall lower amounts of isolated material (Table 4, IMs) and larger amounts of diacetylated products. The large amount of diacetylated product forms due to more equivalents of acetic anhydride present compared to starting material when undissolved starting

**Table 6.** Acetylation of methyl-4,6-*O*-benzylidene-α-D-mannopyranoside (10) with different catalysts and conditions.




| Entry | Catalyst | **10a** [%] | **10b** [%] | **10c** [%] | C [%] | Selectivity [%][e] |
|---|---|---|---|---|---|---|
| 1 | NMI | 4 | 55 | 14 | 73 | 5 |
| 2 | **3**[a] | 57 | 5 | 38 | >95 | 57 |
| 3 | **4** | 38 | 22 | 20 | 80 | 48 |
| 4 | **4**[b] | 41 | 21 | 15 | 77 | 53 |
| 5 | **2** | 17 | 41 | 12 | 70 | 24 |
| 6 | **4**[c] | 38 | 24 | 23 | 85 (IM[d]: >95) | 45 |
| 7 | **2**[c] | 16 | 44 | 16 | 76 (IM[d]: >95) | 21 |

[a] 5 mol% cat.; [b] 1.0 equiv. $Ac_2O$; [c] reaction performed in flow: 4 mL $h^{-1}$; [d] IM = $n$(**10** + **10a** + **10b** + **10c**)$_{isolated}$ · $n^{-1}$(**10**)$_{deployed}$; [e] x = **10a**/(**10a** + **10b** + **10c**) × 100; Product ratios and conversions determined via $^1$H NMR spectroscopy.

material is filtered off. Nevertheless, the converted starting material still showed the expected selectivities. For **6**, twice the amount of 2-*O*-acetylated product **6a** compared to **6b** formed (Table 4, Entry 1), which is comparable to the experiment in the flask (Table 2, Entry 1). Cyclohexyl-derivative **7**, the best soluble of the four, showed a selectivity of 68% (Table 4, Entry 2), which is close to the 71% achieved in the batch experiment (Table 2, Entry 2). Methyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**8**) is poorly soluble, therefore the amount of isolated material was only 12%, of which 44% were diacetylated product **8c** and the two monoacetylated products formed in a nearly 1:1 ratio (Table 4, Entry 3). Thio-β-derivative **9** also yields both monoacetylated products in the same ratio, with high conversion and a little less diacetylated product (Table 4, Entry 4).

As the immobilized catalyst performed well under flow conditions, the reaction was scaled up using an HPLC pump. Using 2.0 equiv. of acetic anhydride, a solvent mixture of toluene/DCM (10:1), and a flow of 4 mL $h^{-1}$, the amount of isolated material is >95%, with a conversion of 92%, a selectivity of 64%, and only 5% of diacetylated product **5c** (Table 5, Entry 3). Thus, the scaled-up reaction gives comparable results to that at smaller scale (Table 3, Entry 5). However, we had to use a mixture of toluene and DCM, since using only toluene led to precipitation of starting material and clogging of the system (Table 5, Entry 1). In addition, the amount of acetic anhydride was increased, as with 1.3 equiv. the amount of isolated material was high (>95%), but the conversion was just 74% with only small amounts of diacetylated product (Table 5, Entry 2). Running the reaction with the optimized setup we were able to deploy a total of 2.1 mmol of starting material in 96 h, being able to isolate 341 mg **5a** (1.05 mmol, 50%), 140 mg **5b** (0.43 mmol, 20%) and 52 mg **5c** (0.14 mmol, 7%) (Table 5, Entry 4). Performing the reaction for further 72 h (1.7 mmol starting material), we got similar results (298 mg **5a** (0.92 mmol, 54%), 134 mg **5b** (0.39 mmol, 23%), 37 mg **5c** (0.10 mmol, 6%)), showing that no loss of reactivity and selectivity occurred (Table 5, Entry 5). Next, we changed the starting material to **7** and were able to isolate 81 mg **7a** (0.25 mmol, 50%), 31 mg **7b** (0.10 mmol, 19%) and 7 mg **7c** (0.02 mmol, 4%) after 24 h (0.51 mmol starting material deployed) (Table 5, Entry 7). Note that under the changed conditions the results for **7** are different than before (Table 5, Entry 6 vs. Table 4, Entry 2). Changing back to starting material **5** and deploying a total of 4.37 mmol (184 h flow time), the catalyst still maintains its reactivity and selectivity, yielding 794 mg **5a** (2.45 mmol, 56%), 345 mg **5b** (1.06 mmol, 24%), and 101 mg **5c** (0.28 mmol, 6%). These results show that for the first time an immobilized peptide catalyst bearing Pmh as the catalytic moiety can perform a selective reaction *in flow*, giving comparable results to the reaction in the flask. Remarkably, the immobilized catalyst is stable under the reaction conditions and did not lose reactivity or selectivity over time; we performed all flow experiments with the same charged flow tube. In total, 50 mg (0.027 mmol) of **1** were used to convert more than a combined amount of 9.0 mmol of different starting materials without any loss of reactivity and selectivity. Among other products, in those reactions we were able to isolate a combined amount of >1.4 g of **5a**.

To determine whether the immobilized catalysts also work for other sugars, we tested methyl 4,6-*O*-benzylidene-α-D-mannopyranoside (**10**). The non-immobilized catalyst **3** is known to be selective for acetylation of the 2-*O*-position (Table 6, Entry 2) also inverting the selectivity of NMI (Table 6, Entry 1).[44] We observed that **10** shows good conversion (80%) with a selectivity of 48% (Table 6, Entry 3), which is approximately 10% lower than with **3**. The difference of 10% selectivity is about the same as observed with **1** and **2** for glucopyranoside **5**. A significant difference between the catalysts is that **3** provides a lot of diacetylated product **10c** (38%, Table 6, Entry 2), whereas **4** yields a lot of the 3-*O*-acetylated product **10b** (22%, Table 6, Entry 3). Reducing the amount of acetic anhydride to 1.0 equiv., we were able to slightly improve the selectivity (53%, Table 6, Entry 4) Still, **4** performs better than the previously used immobilized catalyst **2** (24%, Table 6, Entry 5)), indicating that beneficial H-bonding interactions, which are crucial for the selectivity, are still present using the immobilized catalyst. As the immobilized catalysts still show some selectivity, we used them in flow experiments and observed comparable results, with slightly higher conversions but somewhat more diacetylated product **10c**. For catalyst **4** we isolated 38% of the 2-*O*-acetylated product **10a** with a very good amount of isolated material (Table 6, Entry 6). Using immobilized catalyst **2**, 44% of 3-*O*-acetylated product **10b** formed with 76% conversion and an overall amount of isolated material $>95\%$ (Table 6, Entry 7). These results demonstrate that there is no significant difference between the reaction in flow and with the immobilized catalyst in a flask.

For all tested substrates we were able to overcome the intrinsic selectivity, determined using NMI, using the immobilized catalysts **2** and **4**, and achieved results that just slightly differ from the results with the non-immobilized catalysts.[44] We expect that the catalysts still form a "dynamic binding pocket", although they are immobilized, and are able to beneficially interact with the substrates.[9,15] As shown before, dispersion forces are likely to have a high impact on peptide catalysis, which is also the case for our substrates, since substrates and catalysts have several donor and acceptor groups.[9,51] This is supported by the decreased conversion in dichloromethane, a polar solvent that perturbs noncovalent interactions.[49]

## Conclusion

We demonstrate that peptide catalyst **1** can be immobilized via SPPS and performs selective acylation reactions of pyranosides without loss of reactivity or selectivity. For glucopyranoside derivatives the selectivity towards the *OH*-group in the 2-position is comparable to that of the non-immobilized catalyst **1**,[44] as it also inverts the intrinsic site-selectivity of the parent NMI motif. For methyl-4,6-*O*-benzylidene-α-D-mannopyranoside the immobilized catalyst is still able to preferably target the 2-*OH*-group, however, a large amount of 3-*O*-acetylated product forms as well. The main improvements shown are the stability and reusability of the immobilized catalyst. Even though the activity seems to drop after nine rounds (Figure 2), long term activity of the catalyst during the flow-experiments shows that the stability of the catalyst is remarkably high and even in the last experiments performed, the reactivity was still the same as in the beginning. This indicates that with an optimized recycling procedure, the catalyst should be stable much longer than ten cycles. The use of different starting materials shows that the catalyst is easily reusable as well, as just rinsing the reaction tube with a small amount of solvent allows us to perform the next reaction. Elaborate efforts to improve the selectivity further were unsuccessful.

## Experimental Section

**Synthesis of immobilized catalyst 2**: *Deprotection 1*: Wang polystyrene resin endcapped and preloaded with Fmoc-L-Phe (0.462 g, 0.65 mmol/g, 0.3 mmol) was filled into a 5 mL syringe for peptide synthesis and shaken twice for 20 min with 2 mL piperidine in DMF (25%). The resin was washed with DMF (5×3 mL), DCM (5×3 mL), and DMF (5×3 mL). After drying *in vacuo*, the resin was directly used for the next coupling. *Coupling 1*: The resin was treated twice (1 h shaking per coupling) with Fmoc-L-Val-OH (0.203 g, 0.6 mmol, 2.0 equiv.), HBTU (0.228 g, 0.6 mmol, 2.0 equiv), HOBt (0.092 g, 0.6 mmol, 2.0 equiv), and DIPEA (0.156 g, 209 μL, 1.2 mmol, 4.0 equiv.) in 2.5 mL DMF. After washing with DMF (5×3 mL), DCM (5×3 mL), and DMF (5×3 mL) the resin was directly used for the next deprotection. *Deprotection 2*: The deprotection was performed as described above for deprotection 1. *Coupling 2*: The coupling of the resin bound dipeptide and Fmoc-$^{A}$Gly-OH (2×0.251 g, 0.6 mmol, 2.0 equiv.) was performed on 0.3 mmol scale according to the procedure described for coupling 1 (see above). The obtained resin was directly used for the next deprotection. *Deprotection 3*: The deprotection was performed as described above for deprotection 1. *Coupling 3*: The coupling of the resin bound tripeptide and Boc-D-Pmh-OH (2×0.121 g, 0.45 mmol, 1.5 equiv.) was performed on 0.3 mmol scale according to the procedure described for coupling 1 (see above). After washing with additional DCM (5×3 mL), EtOAc (5×3 mL), and $Et_2O$ (5×3 mL), the resin was dried *in vacuo*, yielding **2** as a yellowish solid (0.552 g, 0.3 mmol, quant., Loading: 0.54 mmol/g). To verify that the couplings were successful the peptide was cleaved from an aliquot of the resin. Therefore, 0.092 g (0.05 mmol) of the resin were shaken twice for 48 h with 5 mL MeOH/$Et_3N$/THF (9:1:1) each and washed several times with a total amount of 20 mL THF. The solvent was removed *in vacuo* and the residue analyzed. The data are in accordance with those reported in literature.[51]

**Calculation of resin and catalyst loading**: Since after the cleavage of the resin no peptides other than the catalyst could be found, we assumed a quantitative yield for the peptide synthesis. Using this assumption, we were able to calculate the loading of the peptide-bound resin using equation (1) (see SI).[35] The calculated loading was then used to calculate the amount of catalyst needed for each reaction.

**General procedure for catalyzed reactions using oligopeptide catalysts**: The catalyzed reactions were carried out on a 0.1 mmol scale in dry toluene. The starting material and the catalyst were dissolved and after 15 min stirring at the desired temperature acetic anhydride was added. The resulting mixture was stirred for the given time at the given temperature. Afterwards some drops of methanol were added to quench the reaction. All volatiles were removed under reduced pressure and the residue was dissolved in deuterated solvent and directly transferred to an NMR tube. The

choice of the solvent was based on solubility and stability of all starting materials and the desired products.

**General procedure for catalyzed reactions using immobilized oligopeptide catalysts**: The catalyzed reactions were carried out on a 0.1 mmol scale. The starting material, the catalyst, and the solvent were first stirred for 15 min at the desired temperature, then acetic anhydride was added. The resulting mixture was stirred for the given time at the given temperature. Afterwards some drops of methanol were added to quench the reaction. The catalyst was filtered off, all volatiles were removed under reduced pressure, and the residue was dissolved in deuterated solvent and directly transferred to an NMR tube.

**General procedure for flow reactions using immobilized oligopeptide catalysts**: The catalyzed reactions were carried out on a 0.1 mmol scale. The starting material and acetic anhydride were stirred in the chosen solvent for 30 min. After filtering off non-dissolved starting material, the resulting solution was poured into a glass syringe which was connected to the prepared reaction chamber via a Luer lock system. The solution was pumped through the chamber using the given flow and the chamber was rinsed with additional 2 mL of the used solvent. All volatiles were removed under reduced pressure and the residue weighted to determine the yield. It was then dissolved in deuterated solvent and transferred to an NMR tube.

**General procedure for upscaled flow reactions using immobilized oligopeptide catalysts**: The starting material and acetic anhydride were stirred in the chosen solvent for 30 min. After filtering off non-dissolved starting material, the resulting solution was poured into a sealed glass bottle. This bottle was connected to the HPLC pump, and the reaction solution was pumped through the reaction chamber with the given flow. Afterwards, the reaction chamber was rinsed with additional 10 mL of solvent. All volatiles were removed under reduced pressure and the resulting residue was used to determine the amount of isolated product, conversion, and selectivity. Afterwards the residue was purified via column chromatography to determine yields for the three possible isolated products.

Selectivity and conversion for all reactions were determined by integration of signals in the $^1$H NMR spectra shown in Figures S2–S7.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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