

Advances in Site-Selective Acylation of Pyranosides

From Oligopeptide Catalysis to Immobilized Catalysts in Flow

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für **Marta** und **Emilio**

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Abstract

In the search for potential new applications for our group's catalysts, we explored the idea of combining two catalytic motifs, that we have extensively studied before, in a multicatalytic reaction. The initial step involves performing a site-selective acetylation of partially protected pyranosides using a π -methyl-histidine (PMH)-containing oligopeptide catalyst. The resulting mono-alcohols could then be utilized in a selective, thiourea-catalyzed glycosylation reaction to generate 2-deoxy disaccharides. This thesis focuses on the first reaction of the proposed sequence.

In the first part, we present the site-selective acylation of various methyl 4,6-O-protected pyranosides. We screened several tetrapeptide catalysts containing PMH and an adamantane moiety as the backbone. We identified catalysts capable of overcoming the intrinsic reactivity, which we determined using *N*-methylimidazole (NMI), for most of the pyranosides studied. To optimize the reaction conditions, we employed design of experiments (DOE) studies. We also investigated the impact of the 4,6-O-protecting group and the acylation reagent. Furthermore, we demonstrated that the selectivity of the reaction increased with the length of the applied peptide catalyst, suggesting that hydrogen-bonding interactions play a crucial role in selectivity. Finally, we showed that the observed reactivity could be maintained in more complex systems, as we successfully combined a benzylidene protection and the site-selective acetylation in a one-pot reaction.

In the second part, we investigated the same pyranosides using peptide catalysts immobilized onto Wang-resin. We developed this approach to enhance the sustainability of our reaction, but also after initial studies concerning multicatalysis with thiourea and oligopeptide catalysts showed interference between the two, indicating that they must be separated locally. During the study, we demonstrated that we could easily synthesize the immobilized catalysts *via* solid-phase peptide synthesis (SPPS) and that they were still able to overcome the intrinsic reactivity of the substrates. We found that the catalysts could be reused for several reaction cycles with consistent results. Additionally, we showed that we could apply the catalyst in a continuous flow reaction without a significant loss in reactivity and selectivity. We used the long-term activity of the catalyst to convert large quantities of substrate and observed that the catalyst's selectivity remained intact even after a temporary change in substrate.

Zusammenfassung

Auf der Suche nach potenziellen neuen Anwendungen für die Katalysatoren unserer Gruppe haben wir die Idee verfolgt, zwei katalytische Motive, die wir zuvor ausgiebig untersucht haben, in einer multikatalytischen Reaktion zu kombinieren. In einem ersten Schritt planten wir eine ortsselektive Acetylierung von teilweise geschützten Pyranosiden mit einem π -Methyl-Histidin (PMH) enthaltenden Oligopeptidkatalysator durchzuführen. Die resultierenden Monoalkohole könnten dann in einer selektiven, Thioharnstoff-katalysierten Glykosylierungsreaktion zur Erzeugung von 2-Desoxy Disacchariden verwendet werden. Diese Arbeit konzentriert sich auf die erste Reaktion der vorgeschlagenen Sequenz.

Im ersten Teil wird die ortsselektive Acylierung verschiedener 4,6-O-geschützter Pyranoside vorgestellt. Wir untersuchten mehrere Tetrapeptid-Katalysatoren, die PMH und eine Adamantan-Einheit als Rückgrat enthalten. Wir identifizierten Katalysatoren, die in der Lage sind, die intrinsische Reaktivität, die wir mit *N*-Methylimidazol (NMI) bestimmten, für die meisten der untersuchten Pyranoside umzukehren. Um die Reaktionsbedingungen zu optimieren, haben wir DOE-Studien (Design of Experiments) durchgeführt. Wir untersuchten auch den Einfluss der 4,6-O-Schutzgruppe und des Acylierungsreagenzes. Darüber hinaus konnten wir zeigen, dass die Selektivität der Reaktion mit der Länge des verwendeten Peptidkatalysators zunahm, was darauf hindeutet, dass Wasserstoffbrückenbindungen eine entscheidende Rolle bei der Selektivität spielen. Außerdem konnten wir zeigen, dass die beobachtete Reaktivität auch in komplexeren Systemen aufrechterhalten werden kann, da wir erfolgreich eine Benzylidene Schützung und die ortselektive Acetylierung in einer Eintopfreaktion kombiniert haben.

Im zweiten Teil untersuchten wir dieselben Pyranoside mit Peptidkatalysatoren, die auf Wang-Harz immobilisiert waren. Wir haben diesen Ansatz entwickelt, um die Nachhaltigkeit unserer Reaktion zu verbessern, aber auch, nachdem erste Studien zur Multikatalyse mit Thioharnstoff- und Oligopeptid-Katalysatoren Interferenzen zwischen den beiden Katalysatoren zeigten, was darauf hindeutet, dass sie lokal getrennt werden müssen. Während der Studie haben wir gezeigt, dass wir die immobilisierten Katalysatoren leicht über Festphasen-Peptidsynthese (SPPS) synthetisieren können und dass sie weiterhin in der Lage sind, die intrinsische Reaktivität der Substrate zu überwinden. Wir fanden heraus, dass die Katalysatoren für mehrere Reaktionszyklen mit konsistenten Ergebnissen wiederverwendet werden konnten. Darüber hinaus haben wir gezeigt, dass wir den Katalysator in einer kontinuierlichen Flussreaktion ohne signifikanten Verlust an Reaktivität und Selektivität einsetzen können. Wir nutzten die Langzeitaktivität des Katalysators, um große Mengen an Substrat umzuwandeln, und stellten fest, dass die Selektivität des Katalysators auch nach einem vorübergehenden Wechsel des Substrats erhalten blieb.

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1 Introduction

1.1 History and General Concepts of Organocatalysis

The importance of organocatalysis as one of the three pillars of asymmetric synthesis¹ was emphasized in 2021, when two of the pioneers, Benjamin List and David W. C. MacMillan, were awarded the Nobel Prize in Chemistry “for the development of asymmetric organocatalysis”.² The interest in organocatalysis, which is the usage of small organic molecules to catalyze reactions,^{3, 4} has seen a big increase since the beginning of this century, even though the first reaction using an organocatalyst was performed already in 1860 by Justus Liebig, who performed an oxamide synthesis catalyzed by acetaldehyde.^{3, 5} The first asymmetric organocatalytic reaction was published in 1912 by Bredig and Fiske, who were using the alkaloids quinine **5** and quinidine **6** to catalyze the hydrocyanation of benzaldehyde **1** (Figure 1, top).⁶⁻⁹ The first organocatalyzed reaction showing significant enantioselectivity was published by Pracejus in 1960.⁸⁻¹⁰ He was using *O*-acetyl protected quinine and quinidine to catalyze the reaction of phenyl methyl ketene **3** and methanol or ethanol to give α -phenyl propionates **4** in high yields (80-90%) and up to 74% enantiomeric excess (ee) (Figure 1, bottom).¹⁰

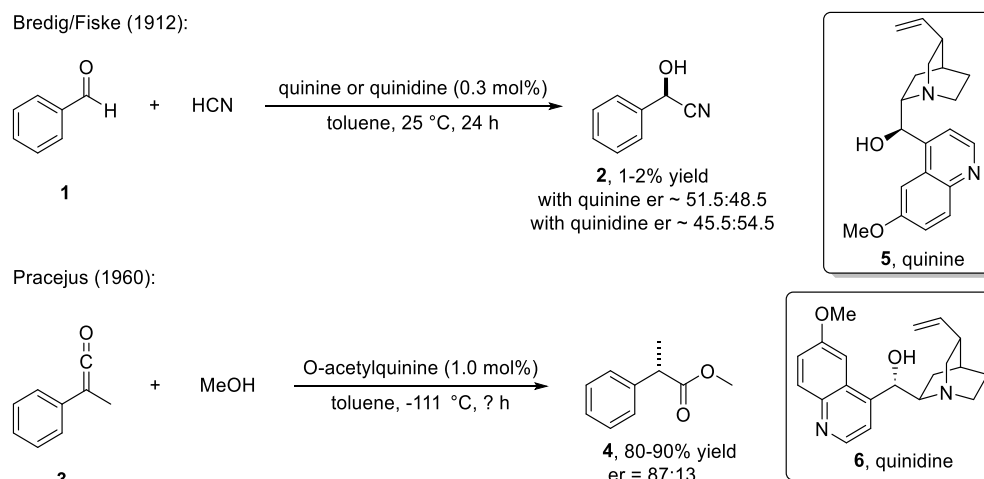


Figure 1 Top: First asymmetric reaction using an organocatalyst by Bredig and Fiske.⁷ Bottom: First organocatalyzed reaction showing significant enantioselectivity by Pracejus.¹⁰

There are more sole publications on the topic, but only the publications of Ahrendt, Borths, and MacMillan as well as List, Lerner, and Barbas in 2000 mark the beginning of the modern age of “organocatalysis” as an own field of research.^{4, 11-13} Since then the field of organocatalysis grew rapidly and the number of publications and newly introduced catalytic motifs reached a remarkably broad variety.^{4, 13, 14} There are different approaches when trying to classify organocatalysts. A first classification was introduced by List in 2007, who described four types of organocatalysts: Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids (Figure 2, A).^{3, 15} “These catalysts initiate their catalytic cycles by either providing or removing electrons or protons from a substrate or a transition state”.^{3, 13} A different approach to classify organocatalysts is by their mode of interaction with the substrate; either as covalent or as non-covalent (Figure 2, A).¹⁶ Some examples of catalytic activation modes assigned to their

corresponding properties are shown in Figure 3.¹³ Of course nowadays there are several further activation modes not mentioned in the given Figure, for example *N*-Heterocyclic carbenes.^{17, 18}

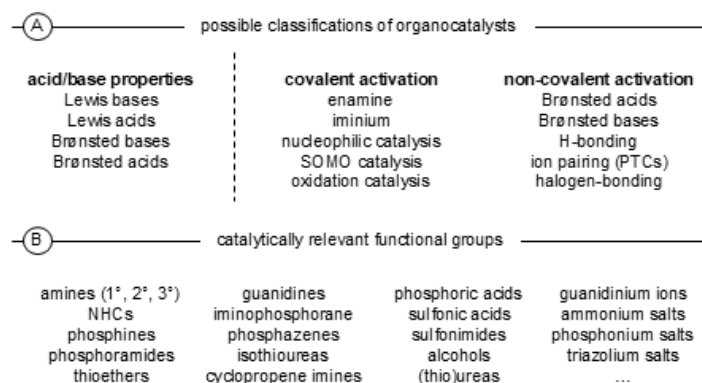


Figure 2 A) Possible Classifications of organocatalysts. B) Some established catalytically relevant functional groups.¹³

The broad variety of catalytic motifs (Figure 2, B) enables a just as huge variety of compound classes to act as organocatalysts.^{13, 16, 19} Amino acid based catalysts are a class of special interest since they demonstrated to be effective catalysts for an increasingly wide array of motifs possibly attached to them.^{20, 21}

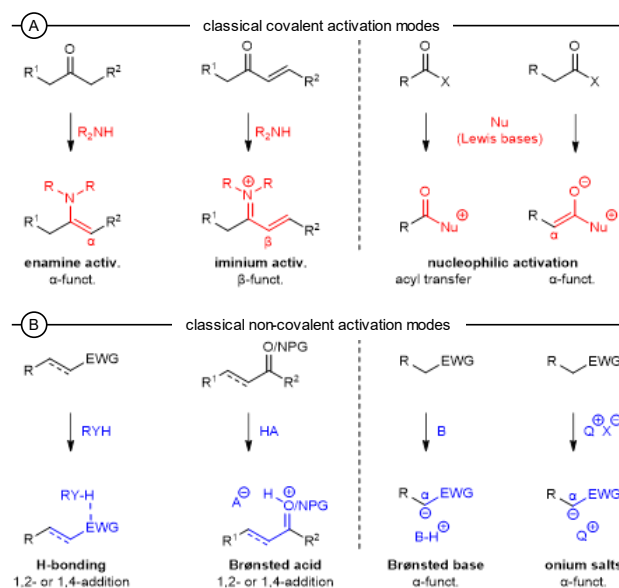


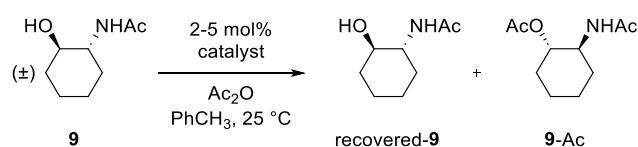
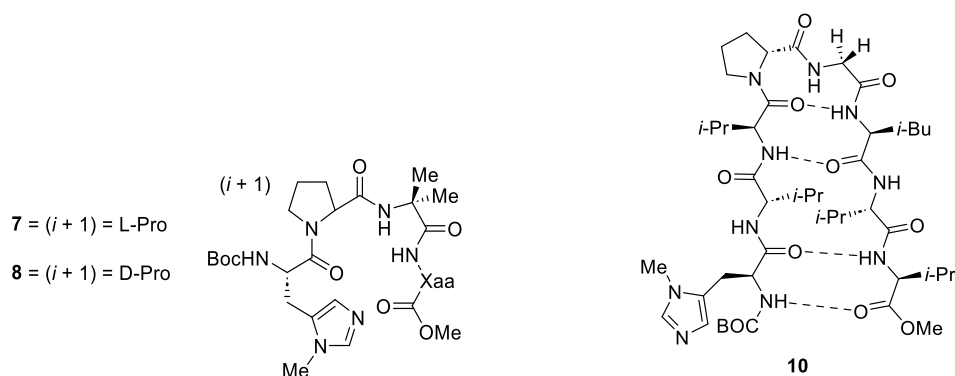
Figure 3 Overview about some of the most classical organocatalytic activation modes.¹³

1.2 Amino Acid based Organocatalysts

In the early 1970s the amino acid proline was used for the first time as organocatalyst to catalyze the now called Hajos-Parrish-Eder-Sauer-Wiechert reaction by two independent industrial groups at Hoffmann La Roche and at Schering.²²⁻²⁴ The two aforementioned publications by List *et al.* and MacMillan *et al.*, which herald the beginning of the modern age of organocatalysis, also used catalysts based on amino acids. List used proline to catalyze a direct asymmetric aldol reaction between acetone

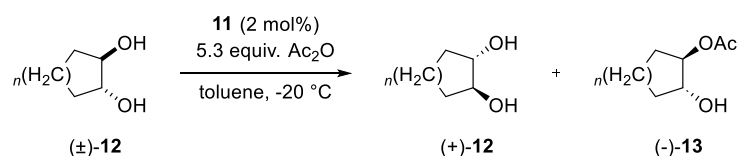
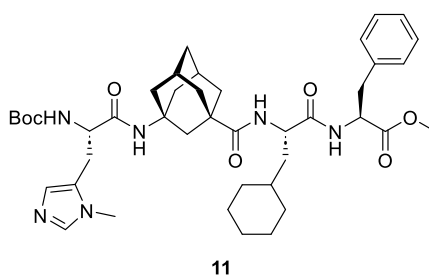
and *p*-nitrobenzaldehyde.¹² MacMillan used an imidazolidinone, which derived from phenylalanine, to catalyze the first stereoselective Diels-Alder reaction between α,β -unsaturated aldehydes and cyclopentadiene.¹¹ Besides catalysts based on only a single amino acid, oligopeptides are of special interest. They can be used to mimic enzymes, which are known to be efficient and selective catalysts since ages.^{20, 25} It was also in the 1970s that Oku, Ito; and Inoue published the use of diketopiperazines (cyclic dipeptides) to catalyze an asymmetric cyanohydrin reaction.²⁶ Another early example is the epoxidation of chalcones with hydrogen peroxide using poly-L-leucine as the catalyst (nowadays known as Juliá-Colonna epoxidation).²⁷ This reaction was introduced by Juliá *et al.* in 1980; and further investigated by Juliá *et al.* and Colonna *et al.* in 1982.^{27, 28}

Since the late 1990s and early 2000s, the number of different oligopeptide catalysts grew as rapidly as the field of organocatalysis itself, and most of the above-mentioned catalytically relevant functional groups (see Figure 2) were at some point also investigated as catalytic motifs in oligopeptide catalysts. Consequently, those catalysts are nowadays investigated for a wide variety of reactions, including oxidations,^{27, 29-31} aldol reactions,³²⁻³⁴ group transfers,³⁵⁻³⁷ and many others.^{20, 21} When it comes to group transfer reactions, one of the earliest catalytic motifs is π -methyl-histidine (PMH), which was first used by Miller *et al.* in a catalyst.³⁷ Investigating the kinetic resolution of different secondary alcohols *via* an acetylation reaction, they applied various tetrapeptides and octapeptides.^{37, 38} Inspired by enzymatic models, they build-up the tetra peptide catalysts in a way that they can form a type II β -turn and strongly favor interactions with one of the two enantiomers of *trans*-1,2-acetamidocyclohexanol, which was designed itself to allow favorable interactions with the catalyst. During initial studies catalysts with the same amino acid sequence, differing only in L-proline **7** or D-proline **8**, not only showed a difference in the favored enantiomer (Table 1, entries 1-5 vs. entries 6-10), but also in the overall reactivity.³⁷ Those results suggested that the rigidity introduced by the type II β -turn has a big impact onto the selectivity of the reaction, which was further proven by subsequent experiments using octapeptide **10**, for which even higher selectivity's were achieved (Table 1, Entry 11), .^{20, 37, 39}

Table 1 Kinetic resolution of *trans*-2-*N*-acetamidocyclohexanol **9** using tetrapeptide catalysts **7** and **8**, and octapeptide catalyst **10**.^{37, 39}


Entry	catalyst	Xaa	% conversion (Based on 9)	(s)	%ee of recovered 9	%ee of 9-Ac
1	7a	Xaa = L-Phe	56	3.0	44 (<i>R,R</i>)	34 (<i>S,S</i>)
2	7b	Xaa = D-Phe	71	5.7	89 (<i>R,R</i>)	36 (<i>S,S</i>)
3	7c	Xaa = L-Val	61	3.4	54 (<i>R,R</i>)	35 (<i>S,S</i>)
4	7d	Xaa = D-Val	63	4.3	65 (<i>R,R</i>)	39 (<i>S,S</i>)
5	7e	Xaa = Gly	57	3.5	50 (<i>R,R</i>)	38 (<i>S,S</i>)
6	8a	Xaa = L-Phe	58	28	98 (<i>S,S</i>)	73 (<i>R,R</i>)
7	8b	Xaa = D-Phe	57	14	89 (<i>S,S</i>)	66 (<i>R,R</i>)
8	8c	Xaa = L-Val	61	21	99 (<i>S,S</i>)	63 (<i>R,R</i>)
9	8d	Xaa = D-Val	62	9.2	88 (<i>S,S</i>)	55 (<i>R,R</i>)
10	8e	Xaa = Gly	63	14	97 (<i>S,S</i>)	57 (<i>R,R</i>)
11	10	Octapeptide	50	51	N/A	N/A

A view years later the Schreiner group investigated oligopeptide catalysts containing the non-natural amino acid γ -adamantyl glycine,⁴⁰ which, also inspired by enzymes, supports the formation of a dynamic binding pocket for the investigated substrates.³⁵ In their initial studies they used tetrapeptide catalyst **11** equipped with PMH as catalytic moiety to perform a kinetic resolution of different *trans*-1,2-diols **12** (see Table 2), achieving high selectivity values $s > 50$ (determined according to Fiaud and Kagan⁴¹).³⁵ The initial assumption, that a pocket is formed based on hydrophobic interactions, in particular London dispersion interactions,⁴² and H-bonding between the catalyst and the substrates was later further investigated and demonstrated using advanced NMR techniques.⁴³⁻⁴⁶

Table 2 Enantioselective kinetic resolution of *trans*-cycloalkane-1,2-diols with oligopeptide catalyst **11**.³⁵

Entry	substrate	t [h]	conversion [%] ^[a]	ee [%] (+)-12	ee [%] (-)-13	s ^[a]
1	 (±)-12a	4	57	>99	75	>50
2	 (±)-12b	9	63	85	49	8 ^[b]
3	 (±)-12c	5	57	>99	77	>50
4	 (±)-12d	6	55	>99	83	>50

^[a] Conversions and s factors determined following the procedure of Kagan and Fiaud.⁴¹ ^[b] Dichloromethane added for solubility.

In later studies, the same group applied catalysts with the same motif for selective Steglich esterification and to perform the first ever enantioselective Dakin-West reaction.^{47, 48} In case of the Dakin-West reaction the applied peptides not only catalyzed the initially performed Steglich rearrangement with noteworthy selectivity's, but also a subsequent stereoselective decarboxylative protonation reaction. In further studies, the catalysts were expanded with a second catalytic motif to show that they are suitable for multicatalytic approaches.⁴⁹⁻⁵² The versatility of the investigated multicatalysts was shown by applying catalyst **17** for two different reaction types: oxidation and acetylation. In the first study, the catalyst was used to initially perform a selective acetylation, leading to the desymmetrization of *cis*-1,2-diols **14**, and subsequently catalyze the oxidation of the remaining hydroxyl group to give product **16** (Figure 4, top).⁴⁹ In the second study on the other hand the catalyst was also able to initially catalyze the oxidative formation of mixed anhydrides **19** starting from aldehydes **18** and carboxylic acids and perform a subsequent selective acylation of *trans*-1,2-diols **12a** (Figure 4, bottom).⁵⁰ Besides the investigations regarding

enantioselective reactions, site-selective catalysis as a research field has seen a raising interest recently.

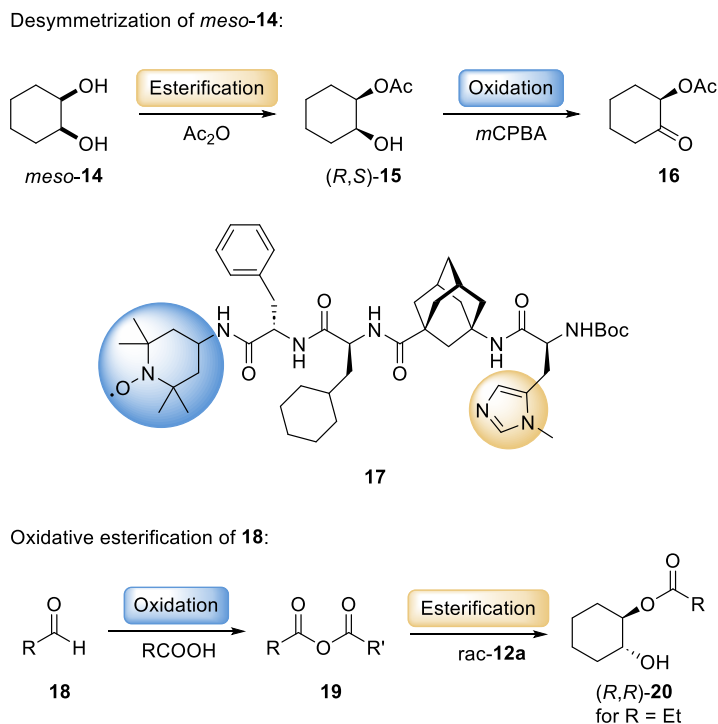
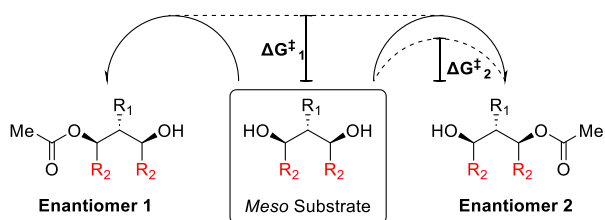


Figure 4 Top: Multicatalytic reaction sequence using catalyst **17** for an initial esterification and a subsequent oxidation.⁴⁹ Bottom: Multicatalytic reaction sequence using catalyst **17** for an initial oxidation and a subsequent esterification.⁵⁰

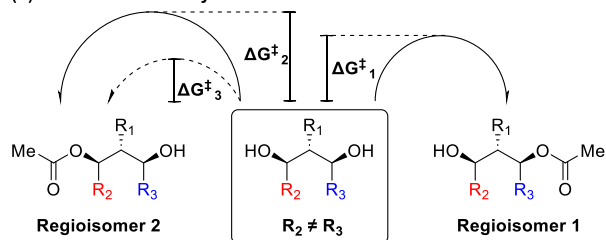
1.3 Organocatalytic Site-Selective Catalysis

(a) Enantioselective Catalysis



ΔG^\ddagger_1 = intrinsic barrier to reactivity, the same for both hydroxyls
 ΔG^\ddagger_2 = barrier to reactivity *in the presence of a chiral catalyst*
 $\Delta\Delta G^\ddagger$ (**achiral** catalyst) = $\Delta G^\ddagger_1 - \Delta G^\ddagger_2 = 0$; racemic product
 $\Delta\Delta G^\ddagger$ (**chiral** catalyst) = $\Delta G^\ddagger_1 - \Delta G^\ddagger_2 \neq 0$; **enantioenriched** product

(b) Site-Selective Catalysis



ΔG^\ddagger_1 = intrinsic barrier to reactivity of the R_3 hydroxyl
 ΔG^\ddagger_2 = intrinsic barrier to reactivity of the R_2 hydroxyl
 $\Delta G^\ddagger_1 \neq \Delta G^\ddagger_2$
 ΔG^\ddagger_3 = R_3 hydroxyl barrier *in the presence of a site-selective catalyst*
 $\Delta\Delta G^\ddagger_{1,2}$ (**non-selective** catalyst) = $\Delta G^\ddagger_2 - \Delta G^\ddagger_1 = (+)$;
 reaction at R_3 hydroxyl favored, intrinsic reactivity dominates
 $\Delta\Delta G^\ddagger_{1,3}$ (**site-selective** catalyst) = $\Delta G^\ddagger_3 - \Delta G^\ddagger_1 = (-)$;
 reaction at R_2 hydroxyl favored, *intrinsic reactivity reverted*

Figure 5 (a) Simplified reaction coordinate diagram for an enantioselective desymmetrization reaction. (b) Simplified reaction coordinate diagram for a site-selective reaction⁵³

Site-Selective functionalization or modification describes the preferred reaction of one particular functional group amongst further similar groups.^{53, 54} Those reaction have been of particular interest because they enable, amongst others, the late stage functionalization of complex natural molecules.⁵³ The challenge hereby is to address

the inherently less favored positions in those molecules, whereas in enantioselective reactions both enantiomers have by definition the same activation barrier. As can be seen in Figure 5 (a), for enantioselective catalysis, both enantiomers have the same intrinsic barrier ΔG^\ddagger . A chiral catalyst is able to lower the reaction barrier for one of the two enantiomers, and yield an enantioenriched product.⁵³ On the other hand, for site-selective catalysis, one of the regioisomers is having an intrinsically lower reaction barrier (Figure 5 (b), regioisomer 1). To perform a selective reaction at the less favored regioisomer, a catalyst must be able to lower the intrinsic barrier below the intrinsic barrier of the initially preferred regioisomer. One way to achieve reactions in inherently less favored positions is to design catalysts that accelerate the reactions for those positions *via* a precise molecular recognition of the desirable site. From the beginning of their studies of the already mentioned PMH motif, Miller *et al.* were also interested in finding site-selective applications for their catalysts. The first compound they were investigating was cyclohexanol compound **23**, which derived from D-myoinositol.³⁶ During this study, they screened a library of 39 different peptide catalysts in the phosphorylation reaction of **23**, achieving yields up to 65% with catalyst **21** for the phosphorylation in 1-position and yields up to 56% with catalyst **22** for the phosphorylation in 3-position.^{36, 55}

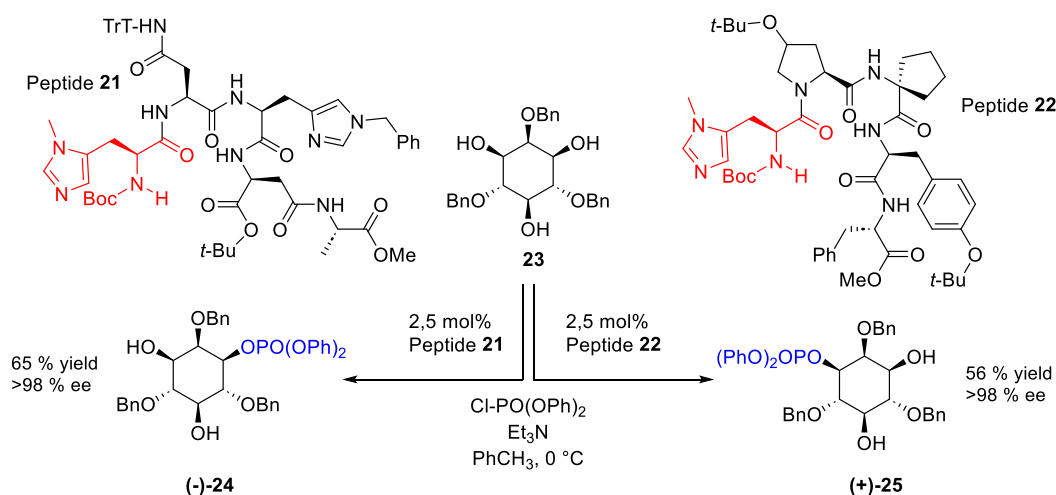
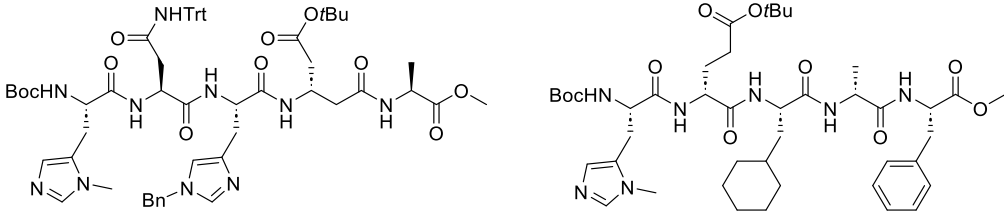
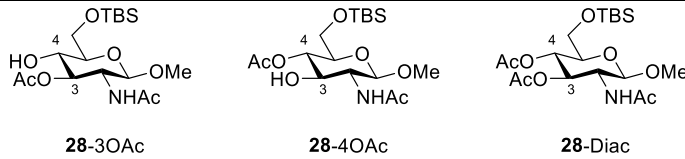


Figure 6 Enantioselective phosphorylation of **23** by peptide catalysts **21** and **22**.⁵³

Later, Miller *et al.* also applied the same catalytic motif in site-selective acetylation of carbohydrates. They again screened a catalyst library, in this case containing 150 different oligopeptide catalysts, and compared the selectivity to the results with NMI, which was used to determine the intrinsic reactivity of substrate **28** during the acetylation with acetic anhydride.⁵⁶ Most of the employed catalysts showed an enhanced selectivity for the acetylation in 3-position, with **26** giving the highest selectivity with a ratio of 97:3, 88% conversion, and no diacetylated product **28-Diac** formed.⁵⁶ However, none of the tested catalysts was able to invert the selectivity, but **27** showed a ratio of almost 1:1 for the two different monoacetylated products with 80% conversion and again no diacetylated product. The shift in selectivity towards product **28-4OAc** compared to the reaction with NMI indicates that this peptide catalyst can overcome the inherent reactivity of the substrate.⁵⁶

Table 3 Site-selective acetylation of diol **28** using peptide catalysts **26** and **27**.⁵⁶

				
				Total conversion [%]
Catalyst	28-3OAc	28-4OAc	28-Diac	
NMI	50	22	28	86
26	97	3	0	88
27	53	47	0	80

In general, carbohydrates are of special interest, since they naturally contain several hydroxyl groups and are present in a lot of different natural compounds.⁵⁷ Furthermore, selective protection of carbohydrates is crucial while building up synthetic polysaccharides and therefore a site-selective manipulation might save several steps in the synthesis of complex polysaccharides.⁵⁴ Today there can be found publications regarding carbohydrate protections for all the four initially by List described types of organocatalysts (see 1.1): Lewis bases,⁵⁸⁻⁶⁰ Lewis acids,⁶¹⁻⁶³ Brønsted bases,^{64, 65} and Brønsted acids.^{66, 67}

Besides the already mentioned oligopeptide catalysts bearing PMH and being inspired by NMI, other well performing Lewis base catalysts are based on 4-dimethylaminopyridine (DMAP). Kawabata *et al.* applied 4-pyrrolidinopyridine (PPY) derivative **29** in the acylation of octyl β -D-glucopyranoside **30** and achieved a remarkable yield of 96% for only the 4-O-acylated product **31** (Figure 7).⁶⁸ Selectivity could also be shown for octyl β -D-thioglucopyranoside **32** (89% yield), octyl β -D-mannopyranoside **33** (52% yield), and more complex molecules like disaccharides (e.g., **34**, 28% yield) or lanatoside C **35** (78% yield).⁶⁸⁻⁷⁰

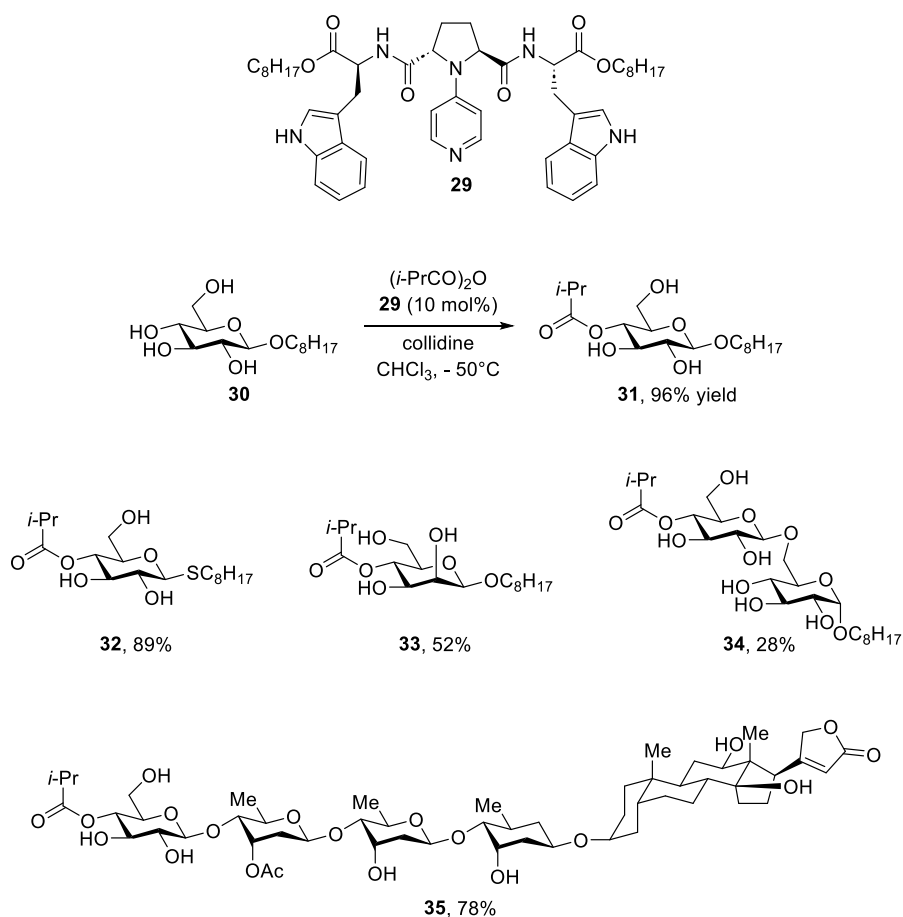


Figure 7 Site-selective acylation of different carbohydrate derivatives using 4-pyrrolidinopyridine (PPY) derivative **29**.⁶⁸⁻⁷⁰

A versatile Lewis acid catalyst is diphenylborinic acid ester **37**, which was introduced by Taylor.⁷¹ This catalyst was found to be selective not only in the acylation of pyranoside **38**, but could also be applied for the selective sulfonylation of **40** and alkylation of **42** and **44** (Figure 8).⁷² Furthermore, **37** was also used to catalyze regioselective glycosylation reactions and the formation of β -2-deoxyglycosides.^{73, 74} For all reactions it is mandatory that *cis*-1,2-diols or *cis*-1,3-diols are present in the substrates, since the diol binds to the borinate to form an activated complex that is part of the catalytic cycle.⁷²

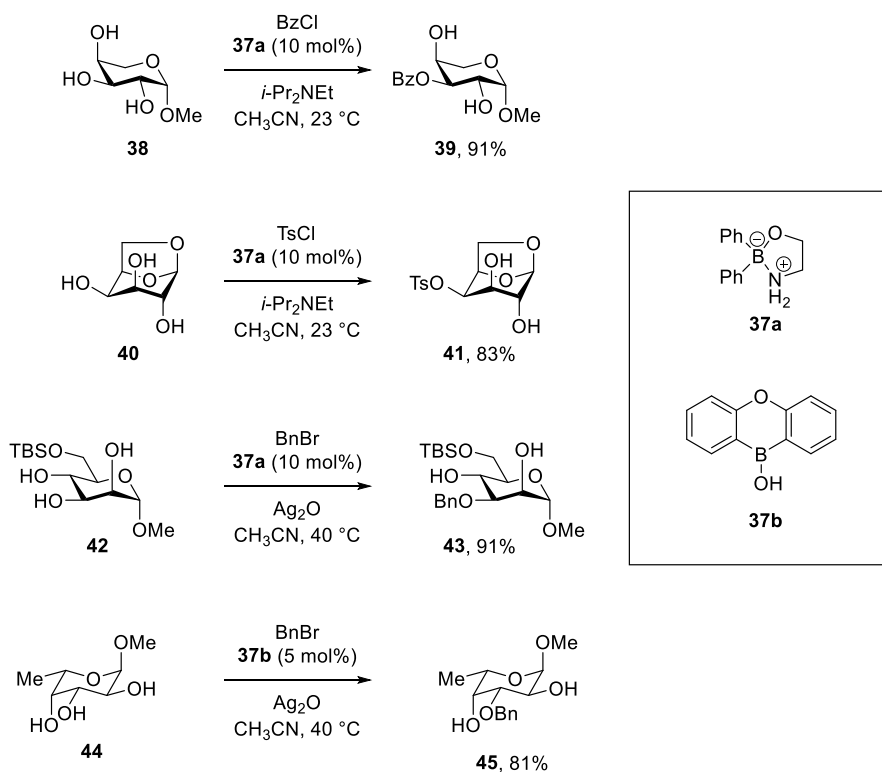


Figure 8 Borinic acid catalyzed monoacylations, sulfonylations and alkylations of cis-1,2-diol groups in pyranoside substrates.⁵⁷

Chiral phosphoric acids, which are used as Brønsted acid catalysts, were applied in the selective acetalization of monosaccharides by Nagorny *et al.*⁶⁷ During their initial studies they investigated different catalysts, monosaccharides, and protecting groups, achieving site-selectivity's up to >25:1 and yields up to 95%.⁶⁷ Similarly high yields up to 93% for a single product could be achieved by Dong *et al.* in the selective acetylation of different carbohydrates using tetrabutylammonium acetate as Brønsted base catalyst.^{65, 75} During the investigation of the reaction mechanism they showed that, similar to the catalysis using peptide catalysts, H-bonding between substrate and catalyst is crucial for the reactions selectivity.⁶⁵ As shown in several of the above given examples, a commonly used and powerful method to selectively protect carbohydrates is by performing selective acylation reactions.⁷⁶

1.4 Selective Acylation of Pyranosides

It is crucial to get an inside of the reactivity of the different hydroxyl groups to obtain an understanding about the reactivity of pyranosides towards acylation reactions. Initial studies were conducted by Richardson and Williams in the 1950s, who used benzoyl chloride in pyridine to rank the reactivity of the secondary hydroxyl groups of the three pyranosides **46**, **47**, and **48** (Figure 9).^{77, 78} Due to easier accessibility, the primary hydroxyl group in 6-position reacts preferentially for all pyranosides.⁷⁸ For the secondary hydroxyl groups the authors determined that for methyl α -D-glucopyranoside **46** the order of reactivity is 2-OH > 3-OH > 4-OH, whereas for methyl α -D-mannopyranoside **47** reactivity is switched for the 2-OH and 3-OH (3-OH > 2-OH

> 4-OH). For methyl α -D-glucopyranoside **46**, due to the low selectivity towards dibenzoylation, it could not be distinguished between the 2-OH and 3-OH, but the 4-OH was found to be the least reactive position again.⁷⁷ The same order of reactivity was later shown for all three corresponding 6-deoxy-pyranosides, indicating that the 6-OH group appears to have little to no effect upon the reactivity of the 4-OH group.^{79, 80} They proposed that amongst many other factors, intramolecular hydrogen bonding is possibly influencing the reactivity of the secondary hydroxyl groups.^{76, 77} The observed reactivity is similar in carbon tetrachloride, a solvent that is promoting intramolecular H-bonding and the basic pyridine, in which intramolecular H-bonds are unlikely due to the strong interactions between alcohol groups and the solvent.⁷⁷

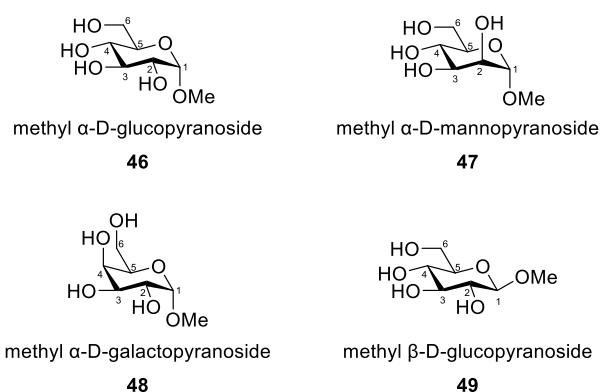


Figure 9 Position numbering of methyl α -D-glucopyranoside **46**, methyl α -D-mannopyranoside **47**, methyl α -D-galactopyranoside **48**, and methyl β -D-glucopyranoside **49**.⁷⁶

A more detailed study on intramolecular H-bonding interactions in pyranosides was later published by Vasella *et al.*⁸¹ During their study they applied (amongst others) 4,6-O-benzylidene protected pyranosides in IR- and ¹H NMR spectroscopy experiments to show the existing H-bond network (Figure 10) and its impact on the acidity of the different hydroxyl groups.⁸¹

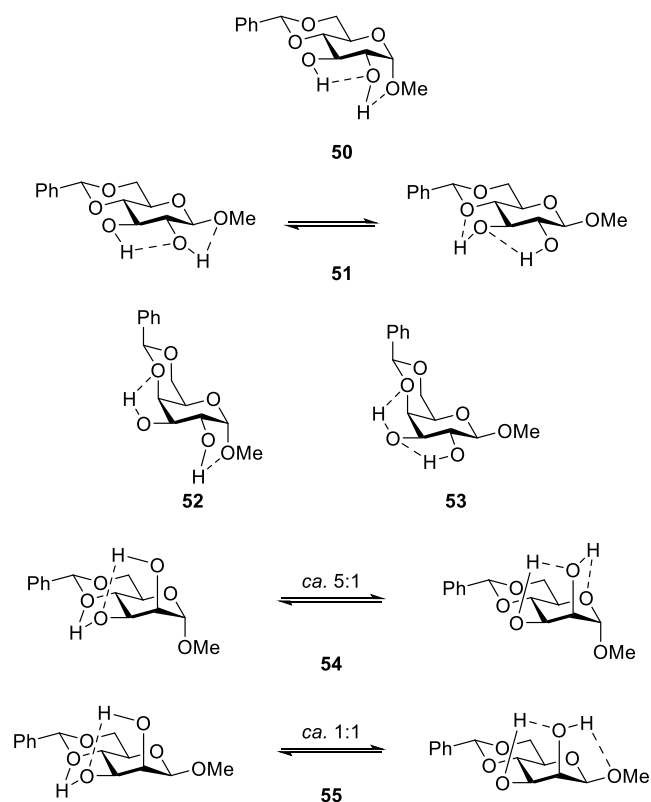


Figure 10 Intramolecular hydrogen bond network of various monosaccharides determined by IR and NMR.^{76, 81}

In 1999, Yoshida *et al.* used DMAP for the acylation of pyranosides and could observe reactivities that were completely different than the ones mentioned above.⁸² For both, α -glucopyranoside (Table 4, Entry 2) and β -glucopyranoside (Table 4, Entry 1), the primary hydroxyl in 6-position was clearly not the most reactive. Additionally, the 2-OH was barely acetylated under the employed reaction conditions, which was shown for all the investigated pyranosides. The 4-OH group, which was found to be the least reactive using benzoyl chloride, is now favored for α -glucopyranoside (Table 4, Entry 2). Deviating results were obtained also for the mannopyranosides, which still showed 4-OH being the most reactive, but notably higher amounts of 6-O-acetylated product formed (Table 4, Entries 3 and 4); and for galactopyranosides, for which the 6-position is the most reactive (Table 4, Entries 5 and 6).⁸² In general, the observed results correlate with earlier mentioned reports by Kawabata *et al.* (see Figure 7), which also investigated octyl protected pyranosides.⁶⁸ Yoshida *et al.* later continued their research and used DMAP analogues with acid moieties in the acylation of the pyranosides, increasing the 6-OH selectivity for all substrates.⁵⁸

Table 4 DMAP-catalyzed acetylation of different monosaccharides.⁸²

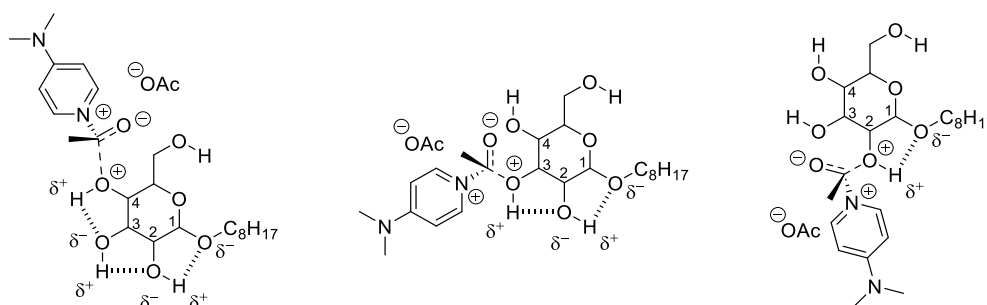
OC[C@H]1O[C@@H](OC8H17)[C@H](O)[C@@H](O)[C@H]1O
 $\xrightarrow[296\text{ K, 1 h}]{0.7\text{ equiv. Ac}_2\text{O, 0.05 equiv. DMAP, K}_2\text{CO}_3, \text{CHCl}_3}$
CC(=O)OC[C@H]1O[C@@H](OC8H17)[C@H](O)[C@@H](O)[C@H]1O

56

Entry	Substrate	2-O-Acetate	3-O-Acetate	4-O-Acetate	6-O-Acetate	Total yield [%]
1	Octyl β-D-gluco.	0.02	0.42	0.37	0.19	quant.
2	Octyl α-D-gluco.	n.d.	0.25	0.61	0.14	98
3	Octyl β-D-manno.	n.d.	0.22	0.46	0.32	72
4	Octyl α-D-manno.	0.07	0.16	0.40	0.37	75
5	Octyl β-D-galacto.	n.d.	0.16 ^[a]	0.14 ^[a]	0.70	81
6	Octyl α-D-galacto.	n.d.	0.14 ^[a]	0.28 ^[a]	0.58	73

n.d. = not detected; ^[a] Product ratio could not be determined accurately due to poor separation of signals.

The initially given results can be explained by the stabilization of the positive charge build up in the transition state of the reaction *via* the earlier mentioned hydrogen bonding network of the pyranosides (Figure 11). When more hydroxyl-groups are part of the network in the transition state, the positive charge is better stabilized, which results in a stabilization of the associated transition state.^{76, 82}


Figure 11 Schematic representation of delocalized positive charge through hydrogen-bonding networks.⁸²

It must be noted that the protecting group at the anomeric center is much bigger than in the investigations by Richardson and Williams. Additionally, the acylation agent being an anhydride instead of an chloride might have an impact on the selectivity of the reaction.⁷⁶ This shows, that there are several factors that influence the selectivity of acylation reactions of pyranosides: the amount of free hydroxyl groups, the used protective groups, the applied catalyst, the used acylating agent, the reaction conditions (e.g., solvent), etc.-

Several studies were conducted using methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **50**, which was introduced earlier in course of the investigations of its intramolecular H-bonding network.⁸¹ In 1956, Jeanloz and Jeanloz studied the selectivity using different acylation reagents in pyridine, showing that the reaction with anhydrides yielded mainly the 3-*O*-acylated products **58** (Table 5, Entries 1, 2), whereas with the corresponding chlorides the 2-*O*-acylated products **57** were preferred. (Table 5, Entries 3,4).⁸³ In

contrast, 2-O-selectivity could be achieved with acetic anhydride when using pyridine in combination with Zinc dichloride, however also notable amounts of 3-O-acylated products **58** and diacylated products **59** formed (Table 5, Entry 5).⁸⁴ Even higher selectivity was achieved when using triethylamine as base/additive; the reaction with acetic anhydride (80% yield, Table 5, Entry 6) and benzoic anhydride (93% yield, Table 5, Entry 7) yielded the 2-O-acylated products **57** in good yields.⁸⁵ Similar results could be achieved when using catalytic amounts of tetrabutylammonium acetate in combination with an organosilicon (65% yield, Table 5, Entry 8)⁸⁶; using only tetrabutylammonium acetate afforded an even higher yield of 88% (Table 5, Entry 9).⁷⁵ A remarkable isolated yield up to 98% of the 2-O-acetylated product **57** was shown when using enzymes (lipases *pseudomonas cepacian* and *pseudomonas fluorescens*, Table 5, Entry 10).^{87, 88} A good yield for the 3-O-acylated product **58** (81%) was achieved by Ye *et al.* using a silver oxide mediated transformation, including catalytic amounts of potassium iodide (Table 5, Entry 11).⁸⁹

Table 5 Acylation of methyl 4,6-O-benzylidene- α -D-glucopyranoside **50** with different catalysts and additives.

Entry	Catalyst	Acyating agent	Conversion/yield [%]		
			57	58	59
1	pyridine ⁸³	Ac ₂ O	3	42	26
2		(C ₆ H ₅ CO) ₂ O	13	25	9
3		AcCl	16	-	21
4		C ₆ H ₅ COCl	24	6	35
5	ZnCl ₂ , pyridine ⁸⁴	Ac ₂ O	53	13	23
6	Et ₃ N ⁸⁵	Ac ₂ O	80	-	-
7		(C ₆ H ₅ CO) ₂ O	93	-	-
8	TBAOAc, Me ₂ Si(OMe) ₂ ⁸⁶	Ac ₂ O	65	-	-
9	TBAOAc ⁷⁵	Ac ₂ O	88	-	-
10	Lipases (PFL, PS) ^{87, 88}	Vinyl acetate	98	-	-
11	Ag ₂ O, KI ⁸⁹	AcCl	15	81	-
12	DMAP (DCM) ⁵⁹	Ac ₂ O	49	51	-
13	DMAP (THF) ⁵⁹	Ac ₂ O	45	55	-
14	CuCl ₂ -(R)-PhBOX (60) ⁹⁰	C ₆ H ₅ COCl	86	6	-
15	CuCl ₂ -(S)-PhBOX (61) ⁹⁰		14	80	-
16	CuCl ₂ -(R)-PhBOX (60) ⁹⁰	AcCl	80	11	-
17	CuCl ₂ -(S)-PhBOX (61) ⁹⁰		14	65	-
18	CuCl ₂ -(R)-PhBOX (60) ⁹⁰	Ac ₂ O	44	25	-
19	CuCl ₂ -(S)-PhBOX (61) ⁹⁰		46	29	-
20	(R)-BTM (62) ⁹¹	Isobutyric anhydride	4	92	-
21	(S)-BTM (63) ⁹¹		94	5	-

22	Peptide 64 , 20 equiv. Et ₃ N ⁹²	(C ₆ H ₅ CO) ₂ O	91	-	-
23	NMI ⁹³	Ac ₂ O	18	61	5
24	Azoepptide 65 ⁹³		42	35	4
25	Azoepptide 65 (365 nm) ⁹³		37	39	4

DMAP was used for the acetylation as well, but did not show any selectivity in two different solvents (DCM, THF) and yielded both mono-acetylated products in an almost 1:1 ratio (Table 5, Entries 12, 13).⁵⁹ An interesting approach was introduced by Allen and Miller in 2013, who used chiral copper(I) complexes **60** and **61** for the acetylation of **50**.⁹⁰ Depending on the used enantiomer of the catalyst, divergent selectivity in the products was observed. For both, benzoyl chloride and acetyl chloride, the (*R*)-enantiomer of the catalyst **60** gave the 2-*O*-acylated products **57** with a ratio of up to 15:1 (Table 5, Entries 14, 16), whereas the (*S*)-enantiomer **61** preferably gave the 3-*O*-acylated products **58** with a ratio of up to 6:1 (Table 5, Entries 15,17).⁹⁰ However, when using acetic anhydride the overall selectivity was much lower and no difference could be observed for the two enantiomers (Table 5, Entries 18,19), which might be due to a complex formed by the electrophile (acetic acid) and the copper, displacing the chiral ligands in the complex.⁹⁰ The same idea was used by Tang *et al.* in 2017.⁹¹ Using the two different enantiomers of benzetetramisole (BTM) **62** and **63**; and isobutyric anhydride as the acylation reagent yielded 92% of the 3-*O*-acylated product **58** using (*R*)-BTM **62** (Table 5, Entry 20) and 94% of the 2-*O*-acylated product **57** using (*S*)-BTM **63** (Table 5, Entry 21).⁹¹

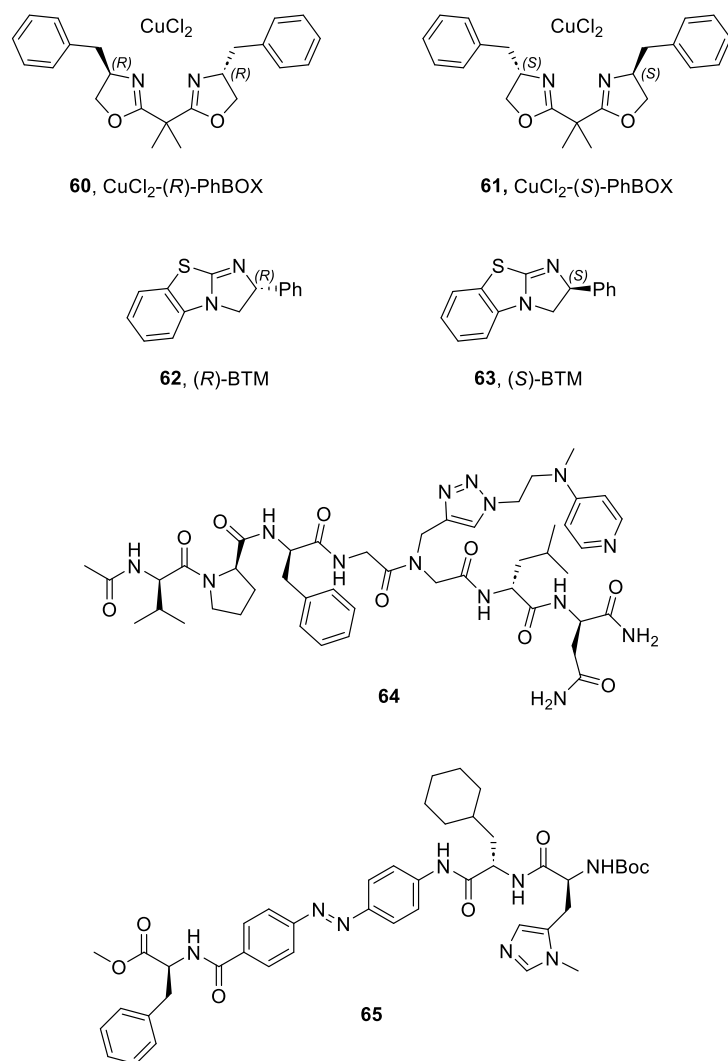


Figure 12 Different catalysts used for the site-selective acylation of **50**.

In 2016, Huber and Kirsch screened a library of 154 oligopeptides containing a catalytic moiety based on DMAP in their ability to selectively acylate different substrates, one being methyl 4,6-*O*-benzylidene- α -D-glycopyranoside **50**.⁹² Using heptapeptide **64**, they were able to achieve up to 91% yield for the 2-*O*-acylated product **57** (Table 5, Entry 22), however, an excess of triethylamine was employed, which by itself also leads to site-selective acylation (Table 5, Entry 7).^{85, 92} A few years later, Schreiner *et al.* introduced azopeptide catalysts using PMH as the catalytic moiety (**65**), which not only were able to switch the selectivity compared to NMI (Table 5, Entry 23), but also showed slightly different selectivity depending on whether the reaction was irradiated at 365 nm (Table 5, Entry 25) or performed in the dark (Table 5, Entry 24).⁹³ This is due to the photoisomerization of the azobenzene moiety in the catalyst backbone, which changes the catalyst shape and therefore the chemical environment around the catalytic motif.⁹³ The impact on the selectivity was even greater when methyl 4,6-*O*-benzylidene- α ,D-mannopyranoside **54** was used as substrate, for which a change in selectivity from 2:1 to 1:5 (2-*O*-Ac:3-*O*-Ac) was achieved.⁹³ This is something that is also true for most of the reactions introduced in Table 5. When methyl 4,6-*O*-benzylidene- α ,D-mannopyranoside **54**, methyl 4,6-*O*-benzylidene- α ,D-

galactopyranoside **53**, or the β -anomers of the pyranosides were used under the same conditions, in most of the cases the selectivity and/or reactivity changed drastically.

1.5 Immobilized Organocatalysts

In our modern world, sustainability is becoming increasingly important as humanity has realized that the world we live in is changing rapidly due to climate change and that resources are finite. In chemistry, sustainability is strongly connected to the term “green chemistry”, which first appeared in the 1980s and is nowadays guided by 12 principles that were introduced by Anastas and Warner in 1998.^{94, 95} Amongst those principles are prevention of waste, better atom economy, and the use of efficient catalysts.⁹⁵ One way to address those principles is by immobilizing catalysts, which reduces waste, reduces the work up of reactions, and ultimately allows to reuse the catalyst for several reaction cycles.⁹⁶ Consequently, the investigation of immobilized organocatalysts is driven forward since the beginning of the “modern age” of organocatalysis, as with the progress in research, catalysts got more complex and expensive, and therefore the immobilization more and more interesting.⁹⁷ As early as in 1998, Sigman and Jacobsen published an asymmetric Strecker reaction using immobilized Schiff base catalysts.⁹⁸ During their investigation, they optimized the catalyst in three steps, building up bigger libraries of immobilized compounds each time, ultimately achieving an enantiomeric excess of 80% for product **68** using catalyst **66** immobilized onto a polystyrene resin. This catalyst was then synthesized in solution and applied in the same reaction, using HCN instead of TBSCN as cyanide source, achieving an even higher ee of 91% and a yield of 78% (Figure 13).⁹⁸

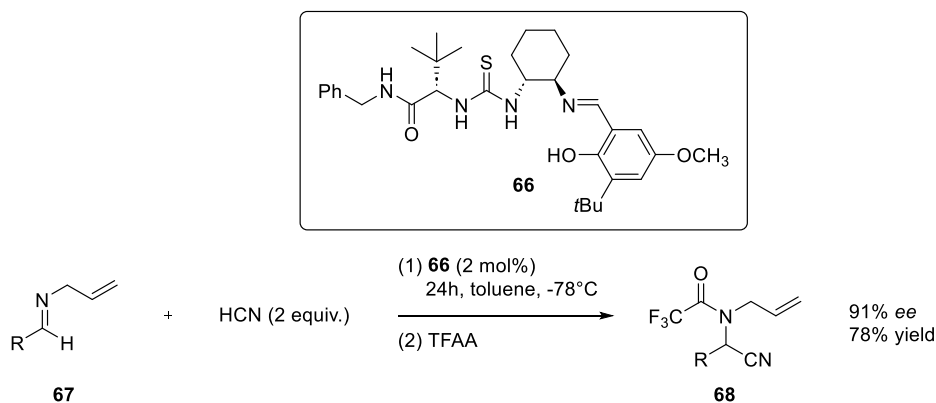
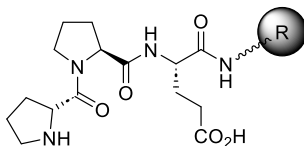


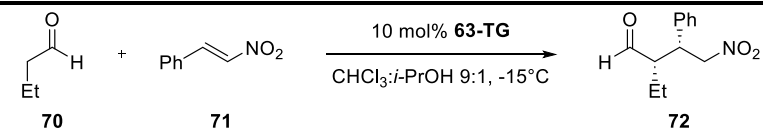
Figure 13 The by Sigman *et al.* identified best catalyst **66** for the asymmetric Strecker reaction.⁹⁸

During the following years, numerous other immobilized organocatalysts were investigated, including immobilized oligopeptide catalysts.^{21, 96, 97, 99} Wennemers and co-workers published several applications for tripeptide catalyst H-D-Pro-L-Pro-L-Asp-NH₂,¹⁰⁰⁻¹⁰² and later also showed that the catalyst is able to catalyze asymmetric aldol reactions when immobilized on a resin, achieving ee's similar to the non-immobilized catalyst (80%) and high yields (up to 93%).¹⁰³ In 2011, the same group published a study with tripeptide catalyst H-D-Pro-L-Pro-L-Glu-NH₂ **69** immobilized on different

resins.¹⁰⁴ They could not only achieve remarkable selectivity's (up to 96% ee and a *syn:anti* ratio of >99:1) with a quantitative conversion for conjugate addition between *n*-butanal **70** and β -nitrosytyrene **71**, but furthermore showed, that the catalyst immobilized on TentaGel-resin **69-TG** (TG-resin) is reusable for at least 30 cycles without loss of reactivity and selectivity (Table 6, Entries 1-7), which clearly demonstrates the major advantages of immobilized catalysts in terms of sustainability.¹⁰⁴

Table 6 Reusability of the solid-supported catalyst **69-TG**.¹⁰⁴

						
		69	R = H			
		69-PS	R = Polystyrene			
		69-PEGA	R = PEGA			
		69-TG	R = TentaGel			


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Entry	Cycle	Time [h]	Conversion [%] ^[a]	Yield [%] ^[b]	<i>syn:anti</i>	ee [%]
1	1	20	quant.	quant.	>99:1	96
2	2-10	20-24	quant.	96-quant.	>99:1	96
3	11-13	20-24	quant.	nd	nd	nd
4	14	23	quant.	quant.	>99:1	96
5	15-25	20-24	quant.	97-quant.	>99:1	96
6	26	24	99	nd	>99:1	96
7	27-30	24 (48)	quant.	quant.	>99:1	96

^[a] Determined by ¹H NMR spectroscopy of the reaction mixture. ^[b] Isolated yield. nd = not determined.

In 2017, Kirsch *et al.* investigated heptapeptide **64**, which was introduced earlier here, immobilized onto a Gly-Merrifield resin, synthesized *via* simple SPPS.¹⁰⁵ Good yields up to 96% for benzoylchlorid as acylating agent (further acylating agents also gave good yields, see Figure 14) were achieved in the selective acylation of methyl 4,6-O-benzylidene- α -D-glucopyranoside **50** using the immobilized catalyst **73** (Figure 14).¹⁰⁵ Additionally, they showed a reusability for at least 11 cycles without loss of selectivity and reactivity for another heptapeptide catalyst, which they found to be the most selective in the benzoylation of an ouabagenin derivative.¹⁰⁵ The general proof that the immobilized catalysts are stable over several cycles without losing reactivity enables their use in continuous flow reactions.

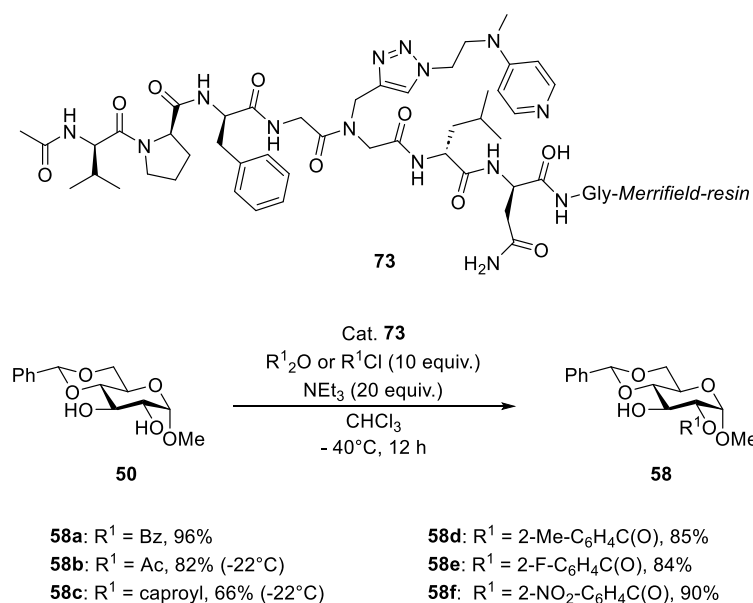
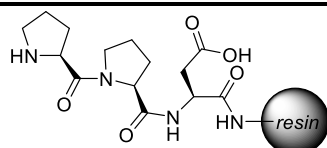


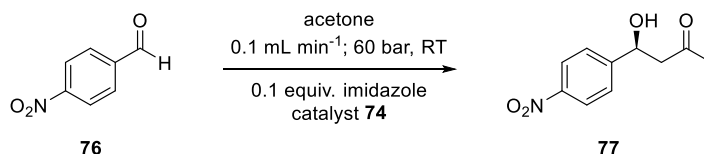
Figure 14 Acylation of glucose-derived diol **50** using immobilized peptide catalyst **73** and different acylating agents.¹⁰⁵

1.6 Oligopeptides as Catalysts in Continuous Flow Reactions

Reactions in continuous flow (CF) are of special interest, since the reactions allow constant formation of product and an easy scale up.¹⁰⁶ Therefore, especially the industry uses CFs not only in the production of chemical commodities and the petroleum field, but also when expensive catalysts are used.¹⁰⁷ Logically, catalysts applied in CF reactions can be found in almost all research fields investigating asymmetric reactions, including only a few reports using organocatalysts based on oligopeptides.^{21, 107} In 2012, Fülöp *et al.* published an asymmetric aldol reaction in CF catalyzed by the well investigated (see chapter 1.5) tripeptide H-L/D-Pro-L-Pro-L-Asp, immobilized on TentaGel **74** or PS resin **75** with a 4-methylbenzhydrylamine linker (PS-MBHA).¹⁰⁸ During their study they optimized the reaction parameters for the addition of *p*-nitrobenzaldehyde **76** and acetone, achieving a yield of 99% and an ee of 80%. The reaction was repeated several times using the same resin (up to 20 cycles), without any loss in reactivity or selectivity (Table 7, Entries 1-4), ultimately resulting in a turnover number of 710.¹⁰⁸ A year later, the Wennemers group showed that the immobilized tripeptide H-D-Pro-L-Pro-L-Glu-NH₂, which achieved good results in the selective addition between *n*-butanal **70** and β -nitrosytyrene **71** (see Table 6), could also be applied in a CF reaction without a significant change in reactivity.^{104, 106} Immobilizing the catalyst on cross-linked polystyrene (PS) because of its higher loading capacity and less swelling compared to TG, the reaction could be carried out for at least 610 turnovers, and no loss in selectivity or reactivity was observed, indicating that the catalyst is even able to achieve a higher TON.¹⁰⁶

Table 7 Testing of reusability of catalyst **74** in CF under optimized conditions.

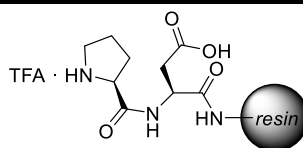
74: resin = TentaGel
75: resin = PS-MBHA



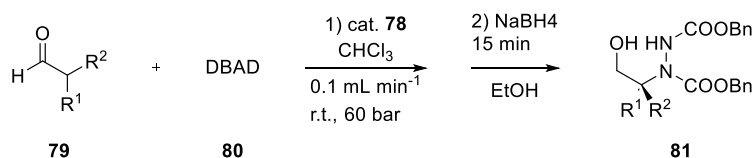
Entry	Cycle	Conversion [%] ^[a]	Yield [%] ^[b]	ee [%]
1	1-5	98-quant.	97-99	79-80
2	6-10	quant.	97-99	78-81
3	11-15	quant.	>99	79-80
4	16-20	99-quant.	98-99	79-80

In 2014, dipeptide L-Pro-Aib-NCy, immobilized onto Luna silica gel *via* an alkyl chain at the nitrogen of proline, was introduced by Paixão *et al.*, catalyzing the Michael addition between different β -nitroolefins and aldehydes with high yields, diastereomeric ratios, and *ee*'s.¹⁰⁹ Screening all reactions in a row using the same CF reactor, they achieved a total TON of 304, without any indication of loss of reactivity. In 2015, Fülöp *et al.* investigated the α -amination of aldehydes in a CF reaction with a subsequent reduction using NaBH₄, as the resulting α -hydrazino aldehydes are prone to racemization.¹¹⁰ Initially they tested immobilized tripeptide catalysts containing two prolines and an acidic amino acid (aspartic or glutamic acid) again.¹¹⁰ During their investigation, however, they found that for this reaction the dipeptide catalyst H-L-Pro-L-Asp-NH immobilized on both, TentaGel (>99% conversion, 75% *ee*) and PS-MBHA (>99% conversion, 76% *ee*), gave better results than the investigated tripeptides.¹¹⁰ After optimizing the reaction conditions, a conversion of 87% and 90% *ee* was achieved for product **81** (Table 8, Entry 1). When screening further aldehydes, the catalyst showed high yields and selectivity's for almost all products (Table 8, Entries 2-7), only if in α -position a second carbon branch was added the reactivity dropped (Table 8, Entry 8).¹¹⁰

Table 8 Investigation of the scope and applicability of the continuous-flow α -amination with catalyst **78**.



78: resin = TentaGel



Entry	R ¹	R ²	Conv. [%] ^[a]	ee [%]	Prod. ^[b]
1	Me	H	86	90	5.38
2	Et	H	93	99	5.81
3	<i>n</i> -Pr	H	96	93	6.00
4	<i>n</i> -Bu	H	100	90	6.25
5	CH ₂ =CH(CH ₂) ₇	H	100	90	6.25
6	Bn	H	100	95	6.25
7	<i>i</i> -Pr	H	92	98	5.75
8	Me	Me	trace	-	-

^[a] Determined by ¹H NMR spectroscopic analysis of the crude material.

^[b] Productivity in mmol product x mmol catalyst⁻¹ x h⁻¹.

The few examples of continuous flow reactions using organocatalysts show that the field, although well investigated in the last two and a half decades, still has a lot of room for improvement, especially when it comes to the optimization of sustainability.

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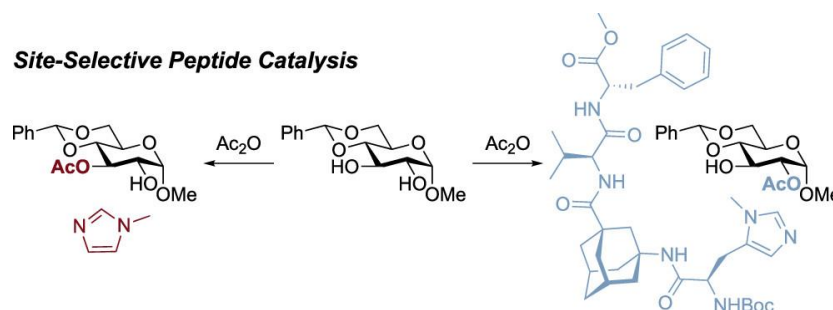
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2 Publications

2.1 Site-Selective Acylation of Pyranosides with Oligopeptide Catalysts



Abstract

“Herein, we report the oligopeptide-catalyzed site-selective acylation of partially protected monosaccharides. We identified catalysts that invert site-selectivity compared to *N*-methylimidazole, which was used to determine the intrinsic reactivity, for 4,6-*O*-protected glucopyranosides (*trans*-diols) as well as 4,6-*O*-protected mannopyranosides (*cis*-diols). The reaction yields up to 81% of the inherently unfavored 2-*O*-acetylated products with selectivities up to 15:1 using mild reaction conditions. We also determined the influence of protecting groups on the reaction and demonstrate that our protocol is suitable for one-pot reactions with multiple consecutive protection steps.”

Reference

A. Seitz, R. C. Wende, E. Roesner, D. Niedek, C. Topp, A. C. Colgan, E. M. McGarrigle, P. R. Schreiner, *J. Org. Chem.* **2021**, 86, 5, 3907–3922. DOI: 10.1021/acs.joc.0c02772

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Site-Selective Acylation of Pyranosides with Oligopeptide Catalysts

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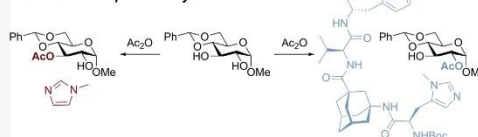
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Supporting Information

ABSTRACT: Herein, we report the oligopeptide-catalyzed site-selective acylation of partially protected monosaccharides. We identified catalysts that invert site-selectivity compared to *N*-methylimidazole, which was used to determine the intrinsic reactivity, for 4,6-*O*-protected glucopyranosides (*trans*-diols) as well as 4,6-*O*-protected mannopyranosides (*cis*-diols). The reaction yields up to 81% of the inherently unfavored 2-*O*-acetylated products with selectivities up to 15:1 using mild reaction conditions. We also determined the influence of protecting groups on the reaction and demonstrate that our protocol is suitable for one-pot reactions with multiple consecutive protection steps.

Site-Selective Peptide Catalysis



INTRODUCTION

Carbohydrates are omnipresent as oligosaccharides and glycoconjugates and are vital to a variety of biological processes.¹ Among other things, nature uses carbohydrates to encode information.² Synthesizing these complex compounds is a challenging task as multiple monosaccharides have to be selectively linked to each other.³ Consequently, much effort has been devoted to the development of selective glycosylation reactions, for which temporary site-selective functionalization (e.g., protection) of the monosaccharide building blocks is often indispensable.⁴ The hydroxy groups in monosaccharides show reactivities that are depending on various influences, some important ones being the intramolecular hydrogen bonding network, steric effects, the protecting groups already installed, and the reaction conditions.⁵ Hence, a lot of different methods were discovered to change the initial reactivity and selectively to address specific hydroxy groups.⁶ One way to accomplish these protections is through the use of catalysts that can site-selectively distinguish between the different hydroxy groups by using metal-based catalysts,⁷ organocatalysts,^{8,9} and enzymes.^{4c,9} Given the importance of carbohydrate recognition in biological systems, oligopeptides are of special interest among the class of organocatalysts.^{8g,10} Pioneering studies in the site-selective acylation of carbohydrates using oligopeptide catalysts have been performed by the Miller group in 2003, screening 150 different oligopeptide catalysts bearing a *p*-methyl histidine (Pmh) moiety for their ability to site-selectively acetylate an amino sugar derivative, and compared the results to *N*-methylimidazole (NMI), the reference catalyst.¹¹ Most catalysts enhanced the selectivity for the acetylation at the intrinsically favored 3-hydroxy group, and the best catalyst afforded up to 97% of the corresponding monoacetylated product. However, some of the catalysts were able to change the selectivity and shifted the distribution of the

products toward the typically highly unfavored 4-*O*-acetylation. The best catalyst "favoring" 4-*O*H was able to give an almost 1:1 ratio of the monoacetylated products.¹¹ Kirsch's group screened a library of oligopeptide catalysts bearing a 4-(dimethylamino)pyridine (DMAP) moiety, achieving site-selective acylation for different methyl 4,6-*O*-protected monosaccharides.¹² An excess of triethylamine was employed, which, however, also leads to site-selective acylation in some cases.¹³ Recently, we reported the application of photoisomerizable azobenzene-based oligopeptides that allowed switching the site selectivity in the acetylation of carbohydrate diols and the natural product quercetin through irradiation.¹⁴

Here, we report the site-selective acylation of carbohydrates using oligopeptide catalysts (Figure 1) bearing Pmh as the catalytically active site and an adamantane moiety in the backbone to improve solubility in organic solvents¹⁵ and to provide a dynamic binding pocket for the substrates.¹⁶ These

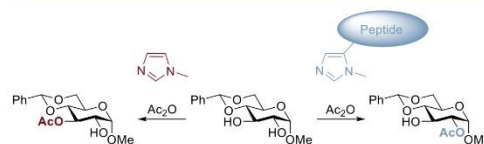


Figure 1. Site-selective acylation of methyl 4,6-*O*-benzylidene- α -D-glucopyranoside using peptide catalysts.

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Table 1. Acetylation of Methyl 4,6-*O*-Benzylidene- α -D-glucopyranoside **3** with NMI and Oligopeptide Catalysts **1** and **2**

Entry	Catalyst	3a [%]	3b [%]	3c [%]	C (%)	Selectivity (%) ^d
1	none	-	-	-	-	-
2	NMI ^[a]	20	62	5	87	23
3	1 ^[b]	55	37	8	>95	55
4	2 ^[b]	70	19	3	92	76
5	2 ^[c]	81	17	2	>95	82

^a10 mol % cat, rt, [3] = 0.01 mol L⁻¹. ^b5 mol % cat, rt, [3] = 0.01 mol L⁻¹. ^cConditions obtained by DoE: 5 mol % cat, 0 °C, [3] = 0.005 mol L⁻¹. ^dx = 3a/(3a + 3b + 3c) × 100; product ratios and conversion determined via ¹H NMR.

catalysts permit enantioselective acylations of cyclic diols with high yield and selectivity.^{15,17} We now developed this class of oligopeptides into site-selective catalysts for the acylation of monosaccharides that are building blocks for subsequent glycosylation reactions. Furthermore, we investigated the substrate–catalyst interactions by changing the 4,6-*O*-acetal protecting groups and by modifying the anomeric center.

RESULTS AND DISCUSSION

We commenced our investigation using methyl 4,6-*O*-benzylidene- α -D-glucopyranoside (**3**), which is commercially available and has already been investigated as a substrate in site-selective acylation reactions.^{8f,g,12a,13,18} First, we synthesized the monoacetylated derivatives **3a** and **3b** as well as the diacetylated product **3c**, using DMAP as the catalyst. We chose ¹H NMR analysis as our analytical method of choice as it allowed the unambiguous differentiation between all products as well as the starting material, and the product ratios and conversions could be readily determined (see the Supporting Information for details).

We tested the peptide catalysts using conditions similar to those of Griswold and Miller¹¹ and used NMI as a reference catalyst to gauge the intrinsic reactivity. Without catalyst, the substrates showed no reactivity under these conditions. NMI favors formation of **3b** with a ratio of 20:62:5 (**3a**:**b**:**c**; Table 1, entry 2). Screening of different peptide catalysts (see the Supporting Information for the complete catalyst library) showed that most of them preferentially led to the formation of

2-*O*-acetylated product **3a**. Catalyst **1**, for example, which has proven excellent for the acylation of 1,2-alkane diols,^{15,17a,b} achieved an overall yield higher than 95% with a selectivity of 55% for **3a** (Table 1, entry 3). Of all tested catalysts, tetrapeptide **2** with a selectivity of 76% performed best (Table 1, entry 4; 66% of **3a** were isolated performing the reaction on a 5.0 mmol scale). To optimize the reaction conditions, a design of experiments (DoE) study was carried out (see the Supporting Information for details).¹⁹ We used a Custom Design approach using JMP and chose five different variables for optimization: Concentration (0.1–0.005 mmol), catalyst loading (0.1–10%), amount of acetic anhydride (1.0–10 equiv), reaction time (1–18 h) and temperature (–20 to +20 °C). These starting conditions for DoE optimization contained a total of 27 experiments in random order for optimization of all variables, which is much less than would be needed in a typical step-by-step optimization. After performing the reactions (plus repeating an additional five reactions for a higher accuracy) we were able to generate a prediction profiler (Figure S13), which was used to determine the best reaction conditions. Using these conditions, we could further increase the selectivity to 82% (Table 1, entry 5). These results are as good as the best currently available in the literature (see Table S3 for comparisons) and use mild reactions conditions, making the reaction interesting for multi-step sequences.

To investigate the influence of the 4,6-*O*-protecting group and the anomeric center on the pyranoside, we performed experiments with other monosaccharides as well. Using methylidene instead of benzylidene as the protecting group,

Table 2. Acetylation of 4,6-*O*-Protected Glucopyranoside Derivatives 4–7 with NMI and Tetrapeptide Catalyst 2

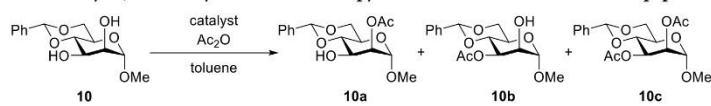
Entry	Starting Material	Catalyst	Xa [%]	Xb [%]	Xc [%]	C (%)	Selectivity (%) ^d
1		NMI ^[a]	23	33	2	58	40
2		2 ^[b]	76	20	4	>95	76
3		2 ^[c]	74	13	3	90	82
4		NMI ^[a]	18	18	-	36	50
5		2 ^[b]	55	9	-	64	86
6		2 ^[c]	59	10	-	69	86
7		NMI ^[a]	6	18	8	32	19
8		2 ^[b]	21	29	25	75	28
9		2 ^[c]	6	8	1	15	40
10		NMI ^[a]	22	36	4	62	35
11		2 ^[b]	53	38	9	>95	53
12		2 ^[c]	58	37	5	>95	58

^a10 mol % cat, rt, [X] = 0.01 mol L⁻¹. ^b5 mol % cat, rt, [X] = 0.01 mol L⁻¹. ^cConditions obtained by DoE: 5 mol % cat, 0 °C, [X] = 0.005 mol L⁻¹. ^dx = Xa/(Xa + Xb + Xc) × 100; product ratios and conversion determined via ¹H NMR.

 Table 3. Acylation of 4,6-*O*-Protected Glucopyranoside Derivatives 3 and 4 Using Isobutyric Anhydride

Entry	Starting Material	Catalyst	Xa [%]	Xb [%]	Xc [%]	C (%)	Selectivity (%) ^d
1		NMI ^[a]	22	47	2	71	31
2		2 ^[b]	76	11	2	89	85
3		2 ^[c]	76	10	6	92	83
4		NMI ^[a]	26	25	3	54	48
5		2 ^[b]	79	8	4	91	87
6		2 ^[c]	68	7	6	81	84

^a10 mol % cat, rt, c = 0.01 mol L⁻¹. ^b5 mol % cat, rt, c = 0.01 mol L⁻¹. ^cConditions obtained by DoE: 5 mol % cat, 0 °C, 0.005 mol L⁻¹. ^dx = Xa/(Xa + Xb + Xc) × 100; product ratios and conversion determined via ¹H NMR.

Table 4. Acetylation of Methyl 4,6-*O*-Benzylidene- α -D-mannopyranoside **10** with NMI and Tetrapeptide Catalysts **1** and **2**

Entry	Catalyst	10a [%]	10b [%]	10c [%]	C (%)	Selectivity (%) ^d
1	none	-	-	-	-	-
2	NMI ^a	4	55	14	73	5
3	2 ^b	25	43	15	83	30
4	1 ^b	57	5	38	>95	57
5	1 ^c	65	5	5	75	87

^a10 mol % cat., 1.3 equiv Ac₂O, 18 h, rt, $c = 0.01 \text{ mol L}^{-1}$. ^b5 mol % cat., 1.3 equiv Ac₂O, 18 h, rt, $c = 0.01 \text{ mol L}^{-1}$. ^cConditions obtained by DoE: 10 mol % cat., 1.0 equiv Ac₂O, 2 h, 20 °C, 0.005 mol L⁻¹. ^d $x = 10a/(10a + 10b + 10c) \times 100$; product ratios and conversion determined via ¹H NMR.

catalyst **2** was still able to overcome the reactivity and selectivity of NMI (Table 2, entry 1), giving 76% selectivity for the desired 2-*O*-acetylated product **4a** (Table 2, entry 2). Applying the reaction conditions given by DoE, the yield slightly decreased but the selectivity improved up to 82% (Table 2, entry 3). Even better selectivity of 86% was observed with cyclohexylidene-protected derivative **5**. No diacetylated product **5c** formed, but the overall conversion was significantly lower (64%; Table 2, entry 5). Note that with **5** as starting material, NMI no longer favored the formation of 3-*O*-acetylated product **5b** but rather gave both monoacetylated products in a 1:1 ratio with only 36% yield (Table 2, entry 4). The outcome of the reaction was just slightly different using DoE conditions (Table 2, entry 6). With β -anomer **6**, NMI showed similar selectivity to the α -anomer, favoring **6b** over **6a**; however, an appreciable amount of diacetylated product **6c** formed and the overall conversion was low (Table 2, entry 7). Catalyst **2** was able to raise the overall conversion to 75% but still a large amount of diacetylated product **6c** ensued. Interestingly, the selectivity collapses (Table 2, entry 8), indicating that the anomeric configuration is important. This must be due to changes in the interactions between the substrate and the catalyst, which might be owing, in part, to changes in the diol intramolecular hydrogen bonding patterns (H-bonding from 2-OH to 1-OMe would be expected to be stronger for the α -anomer). We also tested β -thioglucofuranoside derivative **7**, which may be an interesting precursor in glycosidic bond formation.²⁰ We again observed a lower selectivity of 53% compared to the α -derivatives (Table 2, entry 11). Compared to NMI (Table 2, entry 10), the selectivity was again inverted, and the overall conversion increased. Applying the conditions obtained by DoE, we could slightly increase the selectivity to 58% and decrease the amount of diacetylated product **7c** (Table 2, entry 12).

We also investigated the influence of the acylation reagent employing isobutyric anhydride²¹ [(*i*PrCO)₂O] and carbohydrate derivatives **3** and **4** as starting materials; these starting materials were investigated by Xiao et al. as well.⁸¹ When **3** was used, we achieved good reactivity and a selectivity of 85% for

2-*O*-acetylated product **8a** (Table 3, entry 2). The selectivity further increased up to 87% using **4** as the starting material (Table 3, entry 5). For both derivatives, the selectivity increased compared to acetic anhydride, the intrinsic reactivity of NMI was inverted and the overall conversion was high, although less reactive isobutyric anhydride was used.

To explore whether our peptide-based catalyst would invert NMI selectivity with other sugars, we also employed methyl 4,6-*O*-benzylidene- α -D-mannopyranoside (**10**) as the substrate. NMI again favored the formation of 3-*O*-acetylated product with an even higher selectivity and overall good conversion of 73% but also accompanied by an appreciable amount of diacetylated product **10c** (Table 4, entry 2). Peptide catalyst **2** catalyzed the acetylation of **10** with an overall good conversion of 83%. The intrinsic reactivity was not inverted but slightly altered toward the 2-*O*-acetylated product, yielding a selectivity of 30% (Table 4, entry 3). With catalyst **1**, we observed high reactivity and good selectivity of 57%, but also a lot of diacetylated product **10c** formed (Table 4, entry 4). To decrease the amount of diacetylated product as well as to further increase the selectivity, we employed a DoE strategy.^{19c} As a result, the selectivity increased up to 87% (Table 4, entry 5). The dramatic reduction in the diacetylated product was accompanied by a slight increase in the **10a**:**b** ratio from 11:1 to 13:1. This was the best ratio of mono-acetylated products we had observed at this stage; and, to the best of our knowledge, the best results for a nonenzymatic selective acetylation at the 2-OH-group of methyl 4,6-*O*-benzylidene- α -D-mannopyranoside **10** known (see Table S4 for comparison). One might have expected that **10b** would be acetylated more rapidly than **10a** as it bears the same 2-OH as the starting diol; the large reduction in **10c** might have been expected to have led to an increase in the amount of **10b** versus **10a**. Even allowing for the greater concentration of **10a**, the improved selectivity seems to imply that the diacetylation process exhibits quite a different selectivity for 2-OH versus 3-OH than in the reaction with diol **10**. Performing the reaction on a larger scale (1.0 mmol), we were able to isolate 68% of the

Table 5. Acetylation of 4,6-*O*-Protected Mannopyranoside Derivatives 11 and 12 with NMI and Tetrapeptide Catalyst 1

Entry	Starting Material	Catalyst	Xa [%]	Xb [%]	Xc [%]	C (%)	Selectivity (%) ^d
1		NMI ^[a]	7	33	6	46	15
2		1 ^[b]	68	11	21	>95	68
3		1 ^[c]	40	12	3	55	73
4		NMI ^[a]	3	16	3	22	14
5		1 ^[b]	62	4	22	88	70
6		1 ^[c]	59	4	6	69	86

^a10 mol % cat., 1.3 equiv Ac₂O, 18 h, rt, $c = 0.01 \text{ mol L}^{-1}$. ^b5 mol % cat., 1.3 equiv Ac₂O, 18 h, rt, $c = 0.01 \text{ mol L}^{-1}$. ^cConditions obtained by DoE: 10 mol % cat., 1.0 equiv Ac₂O, 2 h, 20 °C, 0.005 mol L⁻¹. ^d $x = Xa/(Xa + Xb + Xc) \times 100$; product ratios and conversion determined via ¹H NMR. Naph = 2-Naphthyl.

Table 6. Acetylation of Methyl 4,6-*O*-Benzylidene- α -D-galactopyranoside 13 with NMI and Tetrapeptide Catalysts 1 and 2

Entry	Catalyst	13a [%]	13b [%]	13c [%]	C (%)	Selectivity (%) ^d
1	none	-	-	-	-	-
2	NMI ^[a]	25	35	3	63	56
3	2 ^[b]	26	69	6	>95	68
4	1 ^[b]	22	65	3	90	72

^a10 mol % cat., $c = 0.01 \text{ mol L}^{-1}$. ^b5 mol % cat., $c = 0.01 \text{ mol L}^{-1}$. ^c $x = 13b/(13a + 13b + 13c) \times 100$; product ratios and conversion determined via ¹H NMR.

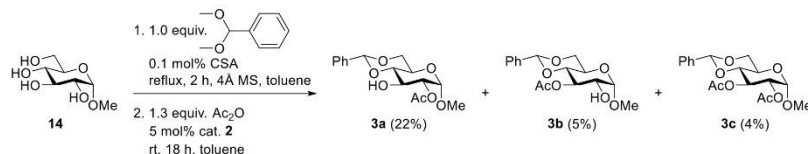
desired methyl 2-*O*-acetyl-4,6-*O*-benzylidene- α -D-mannopyranoside **10a**.

We also investigated the influence of the 4,6-*O*-protecting group, first using again methylidene instead of benzylidene. NMI prefers formation of 3-*O*-acetylated product **11b** with an overall moderate conversion of 46% (Table 5, entry 1). Catalyst **1** showed similar reactivity to **10**; the formation of **11a** was favored with a selectivity of 68% (Table 5, entry 2). Applying the conditions from the DoE reduced the amount of diacetylated product **11c**, but the overall conversion (55%) dropped and the selectivity was just slightly increased to 73% (Table 5, entry 3). Using methyl 4,6-*O*-(2-naphthylidene)- α -D-mannopyranoside (**12**), which was already studied by us previously,¹⁴ NMI gave only 22% conversion but was still favoring **12b** (Table 5, entry 4). Catalyst **1** provided a high selectivity of 70% for **12a**, and the overall conversion increased

to 88% (Table 5, entry 5). The large amount of diacetylated product **12c** decreased employing the DoE conditions, thereby achieving a high selectivity of 86% (Table 5, entry 6). As found for **10**, the overall conversion dropped to 69%, but the ratio of mono-acetylated products **12a:b** remained at approximately 15:1—the highest we observed.

Isobutyric anhydride was also tested as the acylation reagent. NMI favored the formation of 3-*O*-acetylated product **18b** with diacetylated product, and a moderate conversion of 54% was achieved (**18a:b:c** 6:42:6; Table S2, entry 2). Catalyst **1** provided a good selectivity of 75% for the 2-*O*-acetylated product, but also a notable amount of the diacetylated product formed. The overall conversion increased to 94% (**18a:b:c** 70:6:17; Table S2, entry 3).

For 4,6-*O*-benzylidene- α -D-galactopyranoside (**13**), NMI slightly favored **13b** with an overall moderate conversion of

Figure 2. One-pot double protection of methyl α -D-glucopyranoside.Table 7. Acetylation of Methyl 4,6-O-Benzylidene- α -D-mannopyranoside 10 with Catalysts with Increasing Size

Entry	Catalyst	10a [%]	10b [%]	10c [%]	C (%)	Selectivity (%) ^a
1	NMI	4	55	14	73	5
2		8	39	14	61	13
3		27	22	26	75	36
4		63	8	20	91	69
5		69	7	11	87	79

^ax = 10a/(10a + 10b + 10c) × 100; product ratios and conversion determined via ¹H NMR.

63% (Table 6, entry 2). Catalyst 2 did not change the preference for 13b but slightly amplified the formation of it and increased the conversion to >95% (Table 6, entry 3). Catalyst 1 gave the best selectivity of 72% for 13b and an overall conversion of 90% (Table 6, entry 4). These results again indicate that the change from an equatorial to an axial configuration at the C4-position has a significant influence on the interaction between the substrate and catalyst. Here too, this may in part be due to changes in the substrate hydrogen bonding patterns as the 3,4-*cis*-configuration in 13 would be expected to be more favorable for a hydrogen bond between the 3-OH and the 4-O.

Finally, we decided to determine whether it is possible to combine benzylidene protection followed by selective acetylation (Figure 2). Therefore, 14 was first benzylidene-protected using camphor sulfonic acid as the catalyst and toluene as the solvent, as well as 4 Å molecular sieves to remove the formed methanol. Subsequently, catalyst 2 and acetic anhydride were added. This procedure gave 22% 2-O-acetylated product 3a, 5% 3-O-acetylated product 3b, and 4%

diacetylated product 3c. The ratio (3a/3b/3c = ~4:1:1) compares well with the results observed for methyl 4,6-O-benzylidene- α -D-glucopyranoside (3) (Table 1, entry 4), and the overall yield is comparable to just the benzylidene protection of 14 (30% yield) under the given conditions; that is, the protection step limits the yield. This result indicates that the reactivity of the peptide is preserved even in a more complex system; 3 is selectively acetylated and the protection of all but one hydroxy group is achieved in a one-pot reaction sequence.

For almost all investigated pyranoside derivatives, the inherent reactivity, determined using NMI as the catalyst, was at the 3-OH group. Catalyst 2 and most other tested catalysts (Table S1) can switch the selectivity and preferably acylate the tested α -glucopyranosides at the 2-OH group under mild conditions with high yields. To do so, we expect the oligopeptides to form a “dynamic binding pocket,” with which the monosaccharides can interact.^{15,16} A first insight into the substrate recognition process is given by the fact that the selectivity essentially vanishes when using methyl 4,6-O-

benzylidene- β -D-glucopyranoside (**6**) and methyl 4,6-O-benzylidene- α -D-galactopyranoside (**13**), which, like the glucopyranoside derivatives, also bears two *trans* OH-groups. This indicates that an axial α -position (the vicinal methoxy group has a *cis* relationship with the favored OH group) and an equatorial 4-O-position are necessary for a beneficial interaction between monosaccharide and oligopeptide **2**. The interaction seems to be different but even more important for methyl 4,6-O-benzylidene- α -D-mannopyranoside (**10**), which bears two *cis* OH-groups, as only oligopeptide catalyst **1** provides good selectivity. As shown in Table 7, selectivity increased with the size of the oligopeptide catalyst, which indicates that more interactions are beneficial for the reaction. NMI (5% selectivity; Table 7, entry 1) and Boc-L-Pmh-OMe **15** (13% selectivity; Table 7, entry 2), two catalysts which we expect to not interact with the substrates so much, favored the 3-O-position. By increasing the peptide chain length by one amino acid (Boc-L-Pmh^AGly-OMe **16**), the interaction is increased as well, evidenced by the increase in the 2-O-acetylated product formed (36% selectivity; Table 7, entry 3). Adding another amino acid (Boc-L-Pmh^AGly-L-Cha-OMe **17**) enables the formation of a binding pocket and results in enough interaction to selectively acylate in the 2-O-position (69% selectivity, Table 7, entry 4). Finally, catalyst **1** improved the selectivity further up to 79%. At this stage, we can only speculate about the exact nature of the interactions between the catalyst and substrate. We expect that hydrogen bonding interactions will play a key role as both substrates and catalysts have competent hydrogen-bonding donor and acceptor groups. To provide deeper insights into those interactions, we plan on executing detailed NMR studies in due course.¹⁶

CONCLUSIONS

We demonstrate that oligopeptides bearing Pmh as the catalytic moiety enable site-selective acylation reactions of pyranosides with anhydrides as the acylation reagents. For mannopyranoside and glucopyranoside derivatives, we show that tetrapeptides can selectively acylate the OH-group in the 2-position, leaving the monosaccharides with just one free OH group in the 3-position. The peptide catalyst structure overrides the intrinsic preference of the "parent" NMI motif for the 3-OH. A DoE approach was employed to optimize the reaction conditions for methyl 4,6-O-benzylidene-protected α -D-pyranosides; the optimal conditions vary for derivatives with other protecting groups. As our reaction conditions are mild and as we have demonstrated that it is possible to perform benzylidene protection followed by site-selective acylation in a one-pot reaction, our approach may also be amenable to other one-pot syntheses of orthogonally protected carbohydrate derivatives.

EXPERIMENTAL SECTION

General Information. All chemicals were purchased from commercial suppliers and used without further purification. Boc-4-aminoadamantanecarboxylic acid (Boc^AGly-OH),²² Boc-Pmh-OH,²³ and H-Pmh-OMe-2HCl²⁴ were prepared according to literature procedures. Solvents for column chromatography, extractions, and filtrations were distilled prior to use. Dry solvents were purchased from Acros Organics (AcroSeal) and stored under a N₂ atmosphere and over activated molecular sieves (3 or 4 Å). Acetic anhydride was distilled and stored under N₂. Column chromatography was carried out using silica gel 60 M (Macherey-Nagel; 0.040–0.063 mm, 230–400 mesh ASTM). Thin-layer chromatography was performed using precoated plastic sheets Polygram SIL G/UV 254 (Macherey-Nagel;

0.2 mm silica gel layer with fluorescent indicator). For visualization, UV light (254 nm) or staining solutions [KMnO₄: 2.5 g KMnO₄, 8.3 g K₂CO₃, 250 mL H₂O; Hanessian's stain: 12 g (NH₄)₆Mo₇O₂₄·4H₂O, 0.5 g (NH₄)₄Ce(SO₄)₄·4H₂O, 15 mL concn H₂SO₄, 235 mL H₂O] were utilized. NMR spectra were recorded on Bruker AV600, AV400 or AV400HD spectrometers. Chemical shifts (δ) are given in parts per million (ppm) relative to the respective solvent residual peaks (CDCl₃: δ 7.26 and 77.16 ppm; DMSO-*d*₆: δ 2.50 and 39.52 ppm; MeOH-*d*₄: δ 3.31 and 49.00 ppm; acetone-*d*₆: δ 2.05 and 29.84 ppm). ¹H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad, app = apparent, or combinations thereof), coupling constants (Hz), and integration. For ¹³C NMR, the chemical shifts are given. High-resolution mass spectrometry (HRMS) was performed with a Bruker MicrOTof (ESI). IR spectra were measured with a Bruker Alpha spectrometer.

General Procedures. *Procedure 1: Synthesis of Standards.* The pyranoside derivative (1.0 equiv) and 4-dimethylaminopyridine (DMAP) (0.05 equiv) were dissolved in dichloromethane (DCM) (10 mL/mmol), the carboxylic acid anhydride (1.3 equiv) was added, and the solution was stirred at rt for 24 h. The reaction was quenched with MeOH (1 mL/mmol) and stirred for further 30 min. The solvent was removed under reduced pressure, and the crude products were purified via column chromatography to obtain the three desired products.

Procedure 2: Amide Bond Formation (Peptide Coupling). The amino acids (1.0 equiv), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC-HCl; 1.2 equiv), and 1-hydroxybenzotriazole (HOBt; 1.2 equiv) were suspended in CH₂Cl₂ (10 mL/mmol). Triethylamine (Et₃N; 1.2 equiv) was added, and the mixture was stirred at rt for 24 h. It was diluted with EtOAc (50 mL/mmol) and subsequently washed three times (10 mL/mmol) each with 0.5 M citric acid solution, saturated aqueous NaHCO₃ solution, and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude peptide as a solid (if necessary, a column chromatography was performed).

Procedure 3: Boc-Deprotection. The Boc-protected peptide (1.0 equiv) was treated with 2 mL/mmol 4 M HCl in 1,4-dioxane, and the resulting solution was stirred for 60 min. The reaction flask was flushed with nitrogen to remove residual HCl, and the solvent was removed under reduced pressure. After drying in vacuo, the resulting peptide hydrochloride was directly used for the next coupling step.

*Procedure 4: Boc-*n*-methyl Histidine (Boc-Pmh) Coupling.* The amino acids (1.0 equiv), EDC-HCl (2.2 equiv), and HOBt (2.2 equiv) were suspended in 10 mL/mmol CH₂Cl₂. Et₃N (2.2 equiv) was added, and the mixture was stirred at rt for 24 h. It was diluted with EtOAc (50 mL/mmol) and subsequently washed three times (10 mL/mmol) each with saturated aqueous NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The product was obtained after column chromatography as a colorless solid.

General Procedure for the Catalyzed Reactions. 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 desired time at the given temperature. Afterward, some drops of methanol were added to quench the reaction. All volatiles were removed under reduced pressure, and the residue was dissolved in a 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. Selectivity and yields were determined by integration of signals in the ¹H NMR spectra, as shown in Figures S1–S12.

Procedure for Preparative Scale Reactions. The starting material and the catalyst were dissolved in dry toluene, and after 15 min stirring at the desired temperature, acetic anhydride was added. The resulting mixture was stirred for the desired time at the given temperature. Afterward, some drops of methanol were added to quench the reaction. All volatiles were removed under reduced

pressure, and the crude product was purified via column chromatography to give the desired products.

Starting Materials. *Methyl 4,6-O-Methylidene- α -D-glucopyranoside (4)*. The title compound was synthesized according to a literature procedure.²⁵ The crude product was purified via column chromatography (acetone/Et₂O 1:1), and it was obtained in 2.24 g yield (10.9 mmol, 22%) as a colorless solid. $R_f = 0.23$ (acetone/Et₂O 1:1). ¹H NMR (400 MHz, CDCl₃): δ 5.06 (d, $J = 6.3$ Hz, 1H), 4.74 (d, $J = 3.9$ Hz, 1H), 4.61 (d, $J = 6.3$ Hz, 1H), 4.14 (dd, $J = 10.3, 4.9$ Hz, 1H), 3.86 (td, $J = 9.2, 2.1$ Hz, 1H), 3.67 (ddd, $J = 10.6, 9.5, 4.9$ Hz, 1H), 3.57 (td, $J = 9.3, 3.9$ Hz, 1H), 3.43 (m, 4H), 3.28 (d, $J = 2.4$ Hz, 1H), 3.21 (t, $J = 9.4$ Hz, 1H), 2.69 (d, $J = 9.4$ Hz, 1H) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 99.9, 93.9, 80.8, 73.1, 71.7, 68.8, 62.7, 55.7 ppm.

Methyl 4,6-O-Cyclohexylidene- α -D-glucopyranoside (5). The title compound was synthesized according to a literature procedure.²⁷ The crude product was purified via column chromatography (EtOAc), and it was obtained in 0.33 g (1.2 mmol, 12%) yield as a colorless solid. $R_f = 0.28$ (EtOAc). ¹H NMR (400 MHz, MeOH-*d*₄): δ 4.67 (d, $J = 3.8$ Hz, 1H), 3.83–3.71 (m, 2H), 3.64 (t, $J = 9.0$ Hz, 1H), 3.59–3.43 (m, 3H), 3.39 (s, 3H), 2.15–1.84 (m, 2H), 1.71–1.35 (m, 8H) ppm. ¹³C{¹H} NMR (100 MHz, MeOH-*d*₄): δ 102.0, 100.9, 74.5, 74.1, 72.4, 64.9, 62.8, 55.7, 39.1, 28.8, 26.8, 23.8, 23.5 ppm.²⁶

Methyl 4,6-O-Benzylidene- β -D-glucopyranoside (6). The title compound was synthesized according to a literature procedure.²⁷ The crude product was purified via column chromatography (EtOAc), and it was obtained in 5.22 g (18.5 mmol, 88%) yield as a colorless solid. $R_f = 0.39$ (EtOAc). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.49–7.41 (m, 2H), 7.41–7.34 (m, 3H), 5.57 (s, 1H), 5.31 (dd, $J = 16.9, 5.0$ Hz, 2H), 4.26 (d, $J = 7.8$ Hz, 1H), 4.20 (dd, $J = 10.3, 4.1$ Hz, 1H), 3.70 (td, $J = 8.2, 6.9, 3.6$ Hz, 1H), 3.50–3.29 (m, 4H), 3.08 (td, $J = 8.0, 4.7$ Hz, 1H) ppm. ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 137.8, 128.8, 128.0, 126.3, 104.5, 100.6, 80.6, 74.2, 72.8, 67.9, 65.8, 56.3 ppm.²⁸

1,2,3,4,6-Pentaacetate-D-glucopyranose (7d).²⁹ 19.85 g (110 mmol, 1.0 equiv) of D-glucose and 10.75 g (131 mmol, 1.2 equiv) of sodium acetate were dissolved in 100 mL of acetic anhydride. After stirring for 8 h at 80 °C, the solution was poured onto 300 mL of ice and extracted with DCM (3 × 200 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (2 × 150 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Recrystallization from ethanol gave 35.0 g (89.7 mmol, 82%) of 7d (mixture α/β 1:4) as a colorless solid. ¹H NMR (400 MHz, CDCl₃): δ 6.27 (d, $J = 3.7$ Hz, 1H α), 5.65 (d, $J = 8.3$ Hz, 1H β), 5.41 (t, $J = 9.9$ Hz, 1H α), 5.19 (t, $J = 9.4$ Hz, 1H β), 5.11–5.01 (m, 2H α , 2H β), 4.27–4.18 (m, 1H α , 1H β), 4.09–4.00 (m, 2H α , 1H β), 3.77 (ddd, $J = 10.0, 4.5, 2.2$ Hz, 1H β), 2.14–1.92 (m, 15H α , 15H β) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 170.8, 170.7, 170.4, 170.2, 169.8, 169.5, 169.4, 169.1, 168.9, 91.8, 89.2, 72.9, 72.8, 70.3, 70.0, 69.3, 68.0, 67.9, 61.6, 21.0, 21.0, 20.8, 20.8, 20.7, 20.6 ppm.³⁰

(4-Methylphenyl)-1-thio-2,3,4,6-pentaacetate- β -D-glucopyranoside (7e).²⁹ 31.2 g (80.0 mmol, 1.0 equiv) of 7d and 10.8 g (88 mmol, 1.1 equiv) of *p*-toluene thiol were dissolved in 200 mL of dry DCM. The solution was cooled to 0 °C and 48.4 g (36 mL, 340 mmol, 4.25 equiv) of BF₃·Et₂O was slowly added. After stirring for 18 h at rt, the solution was poured onto 200 mL of ice and extracted with DCM (3 × 100 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (2 × 150 mL), dried over Na₂SO₄, and concentrated under reduced pressure. Column chromatography (*n*-hexane/EtOAc 2:1) gave 7e as a colorless solid (yield not determined as only a part of the crude product was purified). $R_f = 0.24$ (*n*-hexane/EtOAc 2:1). ¹H NMR (400 MHz, CDCl₃): δ 7.42–7.35 (m, 2H), 7.16–7.09 (m, 2H), 5.20 (t, $J = 9.4$ Hz, 1H), 5.02 (t, $J = 9.8$ Hz, 1H), 4.93 (dd, $J = 10.1, 9.2$ Hz, 1H), 4.63 (d, $J = 10.0$ Hz, 1H), 4.26–4.13 (m, 2H), 3.69 (ddd, $J = 10.1, 4.8, 2.7$ Hz, 1H), 2.35 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 170.7, 170.3, 169.5, 169.4, 138.9, 134.0, 129.8, 127.7, 86.90, 75.9, 74.2, 70.1, 68.4, 62.3, 21.3, 20.9, 20.9, 20.7, 20.7 ppm.³¹

(4-Methylphenyl)-1-thio- β -D-glucopyranoside (7f).²⁹ 0.124 g (5.4 mmol, 1.2 equiv) of sodium was dissolved in 20 mL of dry methanol, and 2.05 g (4.5 mmol, 1 equiv) of 7e were added. After stirring for 18 h, the solution was neutralized with Amberlyst 15(H), filtered off, and all volatiles were removed under reduced pressure to give 1.30 g of the desired product 7f as a colorless solid, which was used in the next step without any further purification.

(4-Methylphenyl)-4,6-O-benzylidene-1-thio- β -D-glucopyranoside (7). 1.30 g (4.5 mmol, 1.0 equiv) of 7g, 0.90 g (0.89 mmol, 1.3 equiv) of benzaldehyde dimethyl acetal, and 2 mg (0.01 mmol, 0.0025 equiv) of camphor sulfonic acid were suspended in 20 mL of chloroform. The suspension was placed into a preheated oil bath (90 °C), and chloroform was continuously distilled off. After distilling off, another 15 mL of chloroform were added. This procedure was repeated five times, and the mixture was then filtered while hot. After cooling to rt, all volatiles were removed under reduced pressure, and the residue was purified by column chromatography (*n*-hexane/EtOAc 1:1) to obtain 7 in 1.18 g (3.2 mmol, 70%) yield as a colorless solid. $R_f = 0.37$ (*n*-hexane/EtOAc 1:1). ¹H NMR (400 MHz, CDCl₃): δ 7.51–7.40 (m, 4H), 7.44–7.31 (m, 3H), 7.18–7.12 (m, 2H), 5.52 (s, 1H), 4.55 (d, $J = 9.7$ Hz, 1H), 4.41–4.33 (m, 1H), 3.88–3.69 (m, 2H), 3.54–3.43 (m, 2H), 3.42 (dd, $J = 9.7, 8.5$ Hz, 1H), 2.88 (s, 1H), 2.72 (s, 1H), 2.36 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 139.0, 137.0, 133.8, 130.0, 129.5, 128.5, 127.4, 126.4, 102.1, 88.8, 80.4, 74.7, 72.6, 70.7, 68.7, 21.3 ppm.³²

Methyl 4,6-O-Benzylidene- α -D-mannopyranoside (10). The title compound was synthesized according to a literature procedure.³³ The crude product was purified via column chromatography, and it was obtained in 0.97 g (3.4 mmol, 17%) yield as a colorless solid. $R_f = 0.34$ (*n*-hexane/EtOAc 1:2). ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.55–7.46 (m, 2H), 7.38–7.29 (m, 3H), 5.60 (s, 1H), 4.67 (s, 1H), 4.20 (dd, $J = 10.0, 4.7$ Hz, 1H), 3.97–3.86 (m, 3H), 3.81 (t, $J = 10.2$ Hz, 1H), 3.74–3.67 (m, 1H), 3.39 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, MeOH-*d*₄): δ 139.3, 129.9, 129.0, 127.5, 103.7, 103.4, 80.2, 72.6, 69.9, 69.6, 65.1, 55.3 ppm.

Methyl 4,6-O-Methylidene- α -D-mannopyranoside (11). The title compound was synthesized according to a literature procedure.²⁵ The crude product was purified via column chromatography (acetone/Et₂O 2:7), and it was obtained in 0.59 g (2.9 mmol, 29%) yield as a colorless solid. $R_f = 0.47$ (acetone/Et₂O 2:7). ¹H NMR (400 MHz, MeOH-*d*₄): δ 5.00 (d, $J = 6.2$ Hz, 1H), 4.66 (d, $J = 6.2$ Hz, 1H), 4.62 (d, $J = 1.5$ Hz, 1H), 4.05 (dd, $J = 9.5, 3.7$ Hz, 1H), 3.87–3.76 (m, 2H), 3.67–3.48 (m, 3H), 3.36 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, MeOH-*d*₄): δ 103.7, 95.1, 80.1, 72.6, 69.6, 69.5, 65.3, 55.3 ppm.

Methyl 4,6-O-(2-Naphthylidene)- α -D-mannopyranoside (12). The title compound was synthesized according to a literature procedure.¹⁴ The crude product was purified via column chromatography (*n*-hexane/EtOAc 1:2), and it was obtained in 0.85 g (2.6 mmol, 12%) yield as a colorless solid. $R_f = 0.31$ (*n*-hexane/EtOAc 1:2). ¹H NMR (400 MHz, MeOH-*d*₄): δ 8.01–7.98 (m, 1H), 7.91–7.80 (m, 3H), 7.62 (dd, $J = 8.6, 1.7$ Hz), 7.53–7.45 (m, 2H), 5.77 (s, 1H), 4.69 (d, $J = 1.5$ Hz, 1H), 4.25 (dd, $J = 10.0, 4.8$ Hz, 1H), 4.04–3.82 (m, 4H), 3.76 (ddd, $J = 10.3, 8.8, 4.7$ Hz, 1H), 3.41 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, MeOH-*d*₄): δ 136.7, 135.1, 134.3, 129.3, 128.7, 128.7, 127.4, 127.2, 126.8, 125.2, 103.8, 103.4, 80.3, 72.6, 70.0, 69.6, 65.1, 55.4 ppm.

Methyl 4,6-O-Benzylidene- α -D-galactopyranoside (13). The title compound was synthesized according to a literature procedure.²⁷ The product was obtained in 4.56 g (16.2 mmol, 90%) yield as a colorless solid. ¹H NMR (400 MHz, CDCl₃): δ 7.52–7.47 (m, 2H), 7.40–7.34 (m, 3H), 5.54 (s, 1H), 4.92 (d, $J = 3.1$ Hz, 1H), 4.28 (dd, $J = 12.5, 1.6$ Hz, 1H), 4.25–4.24 (m, 1H), 4.07 (dd, $J = 12.6, 1.8$ Hz, 1H), 3.96–3.86 (m, 2H), 3.68 (d, $J = 1.6$ Hz, 1H), 3.45 (s, 3H), 2.37 (s, 2H) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 137.7, 129.3, 1284, 126.4, 101.4, 100.4, 76.0, 70.0, 69.9, 69.5, 62.9, 55.9 ppm.³⁴

Standards. *Methyl 2-O-Acetyl-4,6-O-benzylidene- α -D-glucopyranoside (3a)*. **Procedure 1.** Methyl 4,6-O-benzylidene- α -D-glucopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac₂O (132.7 mg, 122 μ L, 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain 3a after column chromatography (*n*-

hexane/EtOAc 1:1) in 62.1 mg (0.19 mmol, 19%) yield as a colorless solid. $R_f = 0.42$ (*n*-hexane/EtOAc 1:1). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.53–7.48 (m, 2H), 7.43–7.34 (m, 3H), 5.55 (s, 1H), 4.96 (d, $J = 3.7$ Hz, 1H), 4.81 (dd, $J = 9.7, 3.8$ Hz, 1H), 4.30 (dd, $J = 9.9, 4.5$ Hz, 1H), 4.18 (t, $J = 9.5$ Hz, 1H), 3.85 (td, $J = 9.6, 4.5$ Hz, 1H), 3.76 (t, $J = 10.2$ Hz, 1H), 3.56 (t, $J = 9.3$ Hz, 1H), 3.41 (s, 3H), 2.46 (bs, 1H), 2.16 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 170.8, 137.1, 129.5, 128.5, 126.4, 102.2, 97.7, 81.5, 73.7, 69.0, 68.8, 62.1, 55.6, 21.1 ppm.³⁵

Methyl 3-O-Acetyl-4,6-O-benzylidene- α , β -glucopyranoside (3b). *Procedure 1.* Methyl 4,6-O-benzylidene- α , β -glucopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac_2O (132.7 mg, 122 μL , 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain **3b** after column chromatography (*n*-hexane/EtOAc 1:1) in 183.7 mg (0.51 mmol, 51%) yield as a colorless solid. $R_f = 0.26$ (*n*-hexane/EtOAc 1:1). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.48–7.42 (m, 2H), 7.39–7.33 (m, 3H), 5.49 (s, 1H), 5.32 (t, $J = 9.7$ Hz, 1H), 4.81 (d, $J = 3.8$ Hz, 1H), 4.30 (dd, $J = 10.2, 4.7$ Hz, 1H), 3.87 (td, $J = 9.8, 4.7$ Hz, 1H), 3.75 (t, $J = 10.3$ Hz, 1H), 3.66 (dd, $J = 9.5, 3.8$ Hz, 1H), 3.58 (t, $J = 9.6$ Hz, 1H), 3.47 (s, 3H), 2.12 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 171.2, 137.1, 129.2, 128.4, 126.3, 101.7, 100.2, 78.8, 72.4, 72.0, 69.0, 62.9, 55.7, 21.2 ppm.³⁶

Methyl 2,3-O-Diacetyl-4,6-O-benzylidene- α , β -glucopyranoside (3c). *Procedure 1.* Methyl 4,6-O-benzylidene- α , β -glucopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac_2O (132.7 mg, 122 μL , 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain **3c** after column chromatography (*n*-hexane/EtOAc 1:1) in 43.9 mg (0.12 mmol, 12%) yield as a colorless solid. $R_f = 0.63$ (*n*-hexane/EtOAc 1:1). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.49–7.41 (m, 2H), 7.40–7.31 (m, 3H), 5.58 (t, $J = 9.7$ Hz, 1H), 5.51 (s, 1H), 4.96–4.88 (m, 2H), 4.30 (dd, $J = 10.3, 4.8$ Hz, 1H), 3.93 (td, $J = 9.9, 4.8$ Hz, 1H), 3.77 (t, $J = 10.3$ Hz, 1H), 3.65 (t, $J = 9.6$ Hz, 1H), 3.41 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 170.6, 169.9, 137.1, 129.2, 128.4, 126.3, 101.7, 97.8, 79.4, 71.7, 69.1, 69.0, 62.5, 55.5, 21.0, 20.9 ppm.³⁷

Methyl 2-O-Acetyl-4,6-O-methylidene- α , β -glucopyranoside (4a). *Procedure 1.* Methyl 4,6-O-methylidene- α , β -glucopyranoside (206.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac_2O (132.7 mg, 122 μL , 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain **4a** after column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 40:1) in 46.9 mg (0.19 mmol, 19%) yield as a colorless solid. $R_f = 0.17$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 40:1). $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 5.02 (d, $J = 6.3$ Hz, 1H), 4.85 (d, $J = 3.8$ Hz, 1H), 4.67 (dd, $J = 9.7, 3.8$ Hz, 1H), 4.58 (d, $J = 6.3$ Hz, 1H), 4.09 (dd, $J = 10.3, 4.9$ Hz, 1H), 4.05 (t, $J = 9.5$ Hz, 1H), 3.66 (td, $J = 10.0, 4.9$ Hz, 1H), 3.42 (t, $J = 10.4$ Hz, 1H), 3.32 (s, 3H), 3.23 (t, $J = 9.4$ Hz, 1H), 2.09 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 170.9, 97.6, 94.0, 81.2, 77.4, 77.2, 77.0, 73.9, 68.8, 68.8, 62.3, 55.5, 21.1 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_{16}\text{O}_7\text{Na}$, 271.0788; found, 271.0788. IR (ATR) ν/cm^{-1} : 3542, 3432, 2944, 2852, 1717, 1471, 1374, 1341, 1243, 1226, 1199, 1168, 1142, 1114, 1095, 1042, 1023, 987, 969, 921.

Methyl 3-O-Acetyl-4,6-O-methylidene- α , β -glucopyranoside (4b). *Procedure 1.* Methyl 4,6-O-methylidene- α , β -glucopyranoside (206.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac_2O (132.7 mg, 122 μL , 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain **4b** after column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 40:1) in 40.4 mg (0.16 mmol, 16%) yield as a colorless solid. $R_f = 0.26$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 40:1). $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 5.23 (t, $J = 9.7$ Hz, 1H), 5.03 (d, $J = 6.3$ Hz, 1H), 4.76 (d, $J = 3.8$ Hz, 1H), 4.56 (d, $J = 6.3$ Hz, 1H), 4.16 (dd, $J = 10.4, 4.9$ Hz, 1H), 3.74 (td, $J = 9.9, 4.9$ Hz, 1H), 3.61 (dd, $J = 9.6, 3.9$ Hz, 1H), 3.48–3.42 (m, 4H), 3.29 (t, $J = 9.6$ Hz, 1H), 2.13 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3): δ 171.3, 100.1, 93.8, 78.8, 72.4, 71.8, 68.8, 63.0, 55.7, 21.2. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_{16}\text{O}_7\text{Na}$, 271.0788; found, 271.0789. IR (ATR) ν/cm^{-1} : 3541, 3432, 2943, 2873, 1736, 1431, 1364, 1240, 1225, 1167, 1135, 1094, 1073, 1044, 1023, 985, 971, 920, 892.

Methyl 2,3-O-Diacetyl-4,6-O-methylidene- α , β -glucopyranoside (4c). *Procedure 1.* Methyl 4,6-O-methylidene- α , β -glucopyranoside (206.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac_2O (132.7 mg, 122 μL , 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain **4c** after column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 40:1) in 58.5 mg (0.20 mmol, 20%) yield as a colorless solid. $R_f = 0.52$ (*n*-hexane/EtOAc 1:1). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.48 (t, $J = 9.8$ Hz, 1H), 5.04 (d, $J = 6.2$ Hz, 1H), 4.89 (d, $J = 3.8$ Hz, 1H), 4.85 (dd, $J = 9.9, 3.8$ Hz, 1H), 4.57 (d, $J = 6.2$ Hz, 1H), 3.81 (td, $J = 9.9, 4.9$ Hz, 1H), 3.47 (t, $J = 10.3$ Hz, 1H), 3.39 (s, 3H), 3.36 (t, $J = 9.7$ Hz, 1H), 2.07 (s, 3H), 2.06 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 170.5, 170.1, 97.7, 93.9, 79.5, 71.6, 69.1, 68.8, 62.6, 55.5, 20.9, 20.9 ppm.³⁸

Methyl 2-O-Acetyl-4,6-O-cyclohexylidene- α , β -glucopyranoside (5a). *Procedure 1.* Methyl 4,6-O-cyclohexylidene- α , β -glucopyranoside (274.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac_2O (132.7 mg, 122 μL , 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain **5a** after column chromatography (*n*-hexane/EtOAc 1:1) in 64.7 mg (0.20 mmol, 20%) yield as a colorless solid. $R_f = 0.33$ (*n*-hexane/EtOAc 1:1). $^1\text{H NMR}$ (400 MHz, $\text{MeOH}-d_4$): δ 4.86–4.84 (m, 1H; overlap with OH of $\text{MeOH}-d_4$), 4.66 (dd, $J = 9.7, 3.8$ Hz, 1H), 3.87–3.75 (m, 3H), 3.65–3.54 (m, 2H), 3.35 (s, 3H), 2.09 (s, 3H), 2.07–1.97 (m, 1H), 1.97–1.87 (m, 1H), 1.71–1.36 (m, 8H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{MeOH}-d_4$): δ 172.2, 101.0, 99.0, 75.3, 74.5, 69.8, 64.8, 62.6, 55.6, 39.1, 28.8, 26.8, 23.8, 23.5, 20.7 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{24}\text{O}_7\text{Na}$, 339.1414; found, 339.1416. IR (ATR) ν/cm^{-1} : 3446, 2935, 1741, 1446, 1367, 1235, 1194, 1146, 1124, 1097, 1027, 988, 950, 924.

Methyl 3-O-Acetyl-4,6-O-cyclohexylidene- α , β -glucopyranoside (5b). *Procedure 1.* Methyl 4,6-O-cyclohexylidene- α , β -glucopyranoside (274.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac_2O (132.7 mg, 122 μL , 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain **5b** after column chromatography (*n*-hexane/EtOAc 1:1) in 40.4 mg (0.13 mmol, 13%) yield as a colorless solid. $R_f = 0.39$ (*n*-hexane/EtOAc 1:1). $^1\text{H NMR}$ (400 MHz, $\text{MeOH}-d_4$): δ 5.13 (t, $J = 9.5$ Hz, 1H), 4.73 (d, $J = 3.8$ Hz, 1H), 3.86–3.75 (m, 2H), 3.70–3.60 (m, 3H), 3.43 (s, 3H), 2.09 (d, $J = 12.2$ Hz, 2H), 2.07 (s, 3H), 1.79–1.67 (m, 1H), 1.63–1.28 (m, 8H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{MeOH}-d_4$): δ 172.3, 102.0, 100.8, 73.8, 72.6, 72.1, 64.9, 62.8, 55.8, 39.0, 28.7, 26.7, 23.9, 23.7, 21.0 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{24}\text{O}_7\text{Na}$, 339.1414; found, 339.1415. IR (ATR) ν/cm^{-1} : 3469, 2936, 1741, 1446, 1366, 1229, 1175, 1144, 1120, 1099, 1082, 1032, 990, 950, 925.

Methyl 2,3-O-Diacetyl-4,6-O-cyclohexylidene- α , β -glucopyranoside (5c). *Procedure 1.* Methyl 4,6-O-cyclohexylidene- α , β -glucopyranoside (274.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac_2O (132.7 mg, 122 μL , 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain **5c** after column chromatography (*n*-hexane/EtOAc 1:1) in 58.5 mg (0.16 mmol, 16%) yield as a colorless solid. $R_f = 0.66$ (*n*-hexane/EtOAc 1:1). $^1\text{H NMR}$ (400 MHz, $\text{MeOH}-d_4$): δ 5.30 (t, $J = 9.6$ Hz, 1H), 4.91 (d, $J = 3.8$ Hz, 1H), 4.88–4.84 (m, 2H), 3.86–3.81 (m, 2H), 3.78 (t, $J = 9.6$ Hz, 1H), 3.71–3.64 (m, 1H), 3.39 (s, 3H), 2.10 (d, $J = 8.9$ Hz, 1H), 2.03 (s, 3H), 2.03 (s, 3H), 1.84–1.72 (m, 1H), 1.65–1.28 (m, 7H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{MeOH}-d_4$): δ 171.7, 171.7, 101.1, 99.0, 72.8, 72.5, 71.0, 64.8, 62.6, 55.7, 38.9, 28.7, 26.6, 23.9, 23.7, 20.7, 20.5 ppm.³⁹

Methyl 2-O-Acetyl-4,6-O-benzylidene- β , β -glucopyranoside (6a). *Procedure 1.* Methyl 4,6-O-benzylidene- β , β -glucopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac_2O (112.6 mg, 105 μL , 1.1 mmol, 1.1 equiv), and 10 mL of DCM were used to obtain **6a** after column chromatography (*n*-hexane/EtOAc 1:1) in 89.0 mg (0.27 mmol, 27%) yield as a colorless solid. $R_f = 0.42$ (*n*-hexane/EtOAc 1:1). $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$): δ 7.49–7.34 (m, 5H), 5.61 (s, 1H), 5.54 (d, $J = 5.5$ Hz, 1H), 4.64 (dd, $J = 9.2, 8.1$ Hz, 1H), 4.52 (d, $J = 8.1$ Hz, 1H), 4.23 (dd, $J = 10.2, 4.2$ Hz, 1H), 3.80–3.63 (m, 2H), 3.56–3.45 (m, 2H), 3.37 (s, 3H), 2.04 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{DMSO}-d_6$): δ 169.1, 137.6, 128.9, 128.0, 126.3, 101.4, 100.7, 80.4, 74.1, 70.5, 67.7, 65.8, 56.2, 20.8 ppm.³⁵

Methyl 3-O-Acetyl-4,6-O-benzylidene- β -D-glucopyranoside (6b). Procedure 1. Methyl 4,6-O-benzylidene- β -D-glucopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac₂O (112.6 mg, 105 μ L, 1.1 mmol, 1.1 equiv), and 10 mL of DCM were used to obtain **6b** after column chromatography (*n*-hexane/EtOAc 1:1) in 121.0 mg (0.37 mmol, 37%) yield as a colorless solid. R_f = 0.29 (*n*-hexane/EtOAc 1:1). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.37 (s, 5H), 5.62 (d, *J* = 5.5 Hz, 1H), 5.59 (s, 1H), 5.05 (t, *J* = 9.4 Hz, 1H), 4.42 (d, *J* = 7.6 Hz, 1H), 4.24 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.74 (t, *J* = 10.1 Hz, 1H), 3.64 (t, *J* = 9.5 Hz, 1H), 3.54 (td, *J* = 9.7, 4.9 Hz, 1H), 3.43 (s, 3H), 3.33–3.26 (m, 2H), 2.03 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 169.6, 137.4, 128.8, 128.1, 126.0, 104.2, 100.2, 77.9, 73.6, 71.8, 67.8, 65.5, 56.5, 20.8 ppm.³⁶

Methyl 2,3-O-Diacetyl-4,6-O-benzylidene- β -D-glucopyranoside (6c). Procedure 1. Methyl 4,6-O-benzylidene- β -D-glucopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac₂O (112.6 mg, 105 μ L, 1.1 mmol, 1.1 equiv), and 10 mL of DCM were used to obtain **6c** after column chromatography (*n*-hexane/EtOAc 1:1) in 66.1 mg (0.18 mmol, 18%) yield as a colorless solid. R_f = 0.62 (*n*-hexane/EtOAc 1:1). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.37 (s, 5H), 5.63 (s, 1H), 5.29 (t, *J* = 9.4 Hz, 1H), 4.81 (dd, *J* = 9.2, 7.9 Hz, 1H), 4.74 (d, *J* = 7.9 Hz, 1H), 4.27 (dd, *J* = 9.9, 4.7 Hz, 1H), 3.82 (t, *J* = 9.6 Hz, 1H), 3.79 (t, *J* = 9.6 Hz, 1H), 3.70 (td, *J* = 9.7, 4.7 Hz, 1H), 3.39 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆): δ 169.5, 169.1, 137.2, 128.9, 128.1, 126.1, 101.0, 100.3, 77.5, 71.7, 71.4, 67.5, 65.4, 56.5, 20.4, 20.4 ppm.³⁷

4-Methylphenyl 2-O-Acetyl-4,6-O-benzylidene-1-thio- β -D-glucopyranoside (7a). Procedure 1. 4-Methylphenyl 4,6-O-benzylidene-1-thio- β -D-glucopyranoside (480.0 mg, 1.3 mmol, 1.0 equiv), DMAP (15.7 mg, 0.13 mmol, 0.1 equiv), Ac₂O (169.9 mg, 170 μ L, 1.7 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain a mixture of **7a** and **7b** after column chromatography (*n*-hexane/EtOAc 2:1) as a colorless solid. Analytical amounts of the mixture were subsequently separated by HPLC. R_f = 0.36 (*n*-hexane/EtOAc 2:1). Retention time = 9.25 min (Eurospher II CN column, eluent: 15% EtOAc/*n*-hexane, 0.477 CV/min, UV-detector λ = 254 nm). ¹H NMR (400 MHz, CDCl₃): δ 7.51–7.43 (m, 2H), 7.42–7.33 (m, 5H), 7.14 (d, *J* = 7.8 Hz, 2H), 5.53 (s, 1H), 4.91 (dd, *J* = 10.0, 8.8 Hz, 1H), 4.68 (d, *J* = 10.0 Hz, 1H), 4.38 (dd, *J* = 10.5, 4.7 Hz, 1H), 3.91 (td, *J* = 8.8, 2.3 Hz, 1H), 3.78 (dd, *J* = 10.5, 9.5 Hz, 1H), 3.58–3.45 (m, 2H), 2.50 (d, *J* = 3.2 Hz, 1H), 2.35 (s, 3H), 2.19 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 170.2, 138.8, 137.0, 133.7, 129.5, 128.5, 128.2, 126.4, 102.1, 86.9, 80.8, 73.8, 72.6, 70.4, 68.7, 21.3, 21.2 ppm.⁴⁰

4-Methylphenyl 3-O-Acetyl-4,6-O-benzylidene-1-thio- β -D-glucopyranoside (7b). Procedure 1. 4-Methylphenyl 4,6-O-benzylidene-1-thio- β -D-glucopyranoside (480.0 mg, 1.3 mmol, 1.0 equiv), DMAP (15.7 mg, 0.13 mmol, 0.1 equiv), Ac₂O (169.9 mg, 170 μ L, 1.7 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain a mixture of **7a** and **7b** after column chromatography (*n*-hexane/EtOAc 2:1) as a colorless solid. Analytical amounts of the mixture were subsequently separated by HPLC. R_f = 0.37 (*n*-hexane/EtOAc 2:1). Retention time = 8.14 min (Eurospher II CN column, eluent: 15% EtOAc/*n*-hexane, 0.477 CV/min, UV-detector λ = 254 nm). ¹H NMR (400 MHz, CDCl₃): δ 7.49–7.39 (m, 4H), 7.39–7.31 (m, 3H), 7.16 (d, *J* = 7.6 Hz, 2H), 5.48 (s, 1H), 5.23 (t, *J* = 9.0 Hz, 1H), 4.62 (d, *J* = 9.6 Hz, 1H), 4.38 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.77 (dd, *J* = 10.6, 9.4 Hz, 1H), 3.62–3.46 (m, 3H), 2.73 (s, 1H), 2.37 (s, 3H), 2.11 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 171.1, 139.1, 139.0, 134.0, 130.1, 129.3, 128.4, 127.2, 126.3, 101.6, 89.5, 78.4, 74.9, 74.9, 71.6, 71.0, 68.7, 21.3, 21.1. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₂H₂₄O₈SnNa, 439.1186; found, 439.1188. IR (ATR) ν /cm⁻¹: 3387, 2866, 1743, 1716, 1494, 1453, 1366, 1311, 1237, 1076, 1028, 964, 808, 741, 695.

4-Methylphenyl 2,3-O-Diacetyl-4,6-O-benzylidene-1-thio- β -D-glucopyranoside (7c). Procedure 1. 4-Methylphenyl 4,6-O-benzylidene-1-thio- β -D-glucopyranoside (480.0 mg, 1.3 mmol, 1.0 equiv), DMAP (15.7 mg, 0.13 mmol, 0.1 equiv), Ac₂O (169.9 mg, 170 μ L, 1.7 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain **7c** after column chromatography (*n*-hexane/EtOAc 2:1) in 154.0 mg

(0.34 mmol, 26%) yield as a colorless solid. R_f = 0.56 (*n*-hexane/EtOAc 2:1). ¹H NMR (400 MHz, CDCl₃): δ 7.47–7.32 (m, 7H), 7.15 (d, *J* = 7.9 Hz, 2H), 5.49 (s, 1H), 5.33 (t, *J* = 9.3 Hz, 1H), 4.97 (dd, *J* = 10.0, 8.9 Hz, 1H), 4.74 (d, *J* = 10.0 Hz, 1H), 4.38 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.78 (t, *J* = 10.2 Hz, 1H), 3.64 (t, *J* = 9.5 Hz, 1H), 3.55 (td, *J* = 9.6, 4.9 Hz, 1H), 2.36 (s, 3H), 2.11 (s, 3H), 2.03 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 170.1, 169.5, 138.8, 136.8, 133.7, 129.8, 129.2, 128.3, 127.7, 126.2, 101.5, 86.8, 78.1, 73.0, 70.8, 70.7, 68.5, 21.2, 20.9, 20.8 ppm.⁴¹

Methyl 4,6-O-Benzylidene-2-O-isobutyryl- α -D-glucopyranoside (8a). Procedure 1. Methyl 4,6-O-benzylidene- α -D-glucopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), isobutyric anhydride (205.6 mg, 215 μ L, 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain **8a** after column chromatography (*n*-hexane/EtOAc 3:1) in 101.4 mg (0.29 mmol, 29%) yield as a colorless solid. R_f = 0.14 (*n*-hexane/EtOAc 3:1). ¹H NMR (400 MHz, acetone-*d*₆): δ 7.53–7.46 (m, 2H), 7.37 (m, 3H), 5.63 (s, 1H), 4.88 (d, *J* = 3.8 Hz, 1H), 4.70 (dd, *J* = 9.6, 3.8 Hz, 1H), 4.27–4.19 (m, 1H), 4.09–4.01 (m, 1H), 3.83–3.72 (m, 2H), 3.65–3.54 (m, 1H), 3.39 (s, 3H), 2.59 (sept, *J* = 7.0 Hz, 1H), 1.15 (dd, *J* = 7.0, 3.8 Hz, 6H) ppm. ¹³C{¹H} NMR (100 MHz, acetone-*d*₆): δ 176.9, 139.1, 129.6, 128.8, 127.3, 102.4, 98.7, 82.6, 74.6, 69.4, 69.1, 69.0, 63.4, 55.6, 34.5, 29.8, 19.3, 19.1 ppm.⁴²

Methyl 4,6-O-Benzylidene-3-O-isobutyryl- α -D-glucopyranoside (8b). Procedure 1. Methyl 4,6-O-benzylidene- α -D-glucopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), isobutyric anhydride (205.6 mg, 215 μ L, 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain **8b** after column chromatography (*n*-hexane/EtOAc 3:1) in 100.4 mg (0.28 mmol, 28%) yield as a colorless solid. R_f = 0.19 (*n*-hexane/EtOAc 3:1). ¹H NMR (400 MHz, acetone-*d*₆): δ 7.46–7.40 (m, 2H), 7.38–7.31 (m, 3H), 5.60 (s, 1H), 5.30 (t, *J* = 9.6 Hz, 1H), 4.80 (d, *J* = 3.7 Hz, 1H), 4.31–4.21 (m, 1H), 3.89–3.75 (m, 2H), 3.73–3.62 (m, 2H), 3.45 (s, 3H), 2.82 (bs, 1H), 2.56 (sept, *J* = 7.0 Hz, 1H), 1.12 (dd, *J* = 7.0, 2.6 Hz, 6H) ppm. ¹³C{¹H} NMR (100 MHz, acetone-*d*₆): δ 176.7, 138.9, 129.5, 128.8, 127.0, 101.9, 101.7, 80.2, 72.7, 72.1, 69.5, 63.7, 55.8, 34.7, 19.5, 19.2 ppm.⁴³

Methyl 4,6-O-Benzylidene-2,3-O-diisobutyryl- α -D-glucopyranoside (8c). Procedure 1. Methyl 4,6-O-benzylidene- α -D-glucopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), isobutyric anhydride (205.6 mg, 215 μ L, 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain **8c** after column chromatography (*n*-hexane/EtOAc 3:1) in 98.1 mg (0.23 mmol, 23%) yield as a colorless solid. R_f = 0.50 (*n*-hexane/EtOAc 3:1). ¹H NMR (400 MHz, acetone-*d*₆): δ 7.47–7.41 (m, 2H), 7.39–7.30 (m, 3H), 5.66 (s, 1H), 5.57–5.50 (m, 1H), 4.96 (d, *J* = 3.7 Hz, 1H), 4.90 (dd, *J* = 9.9, 3.7 Hz, 1H), 4.34–4.23 (m, 1H), 3.91–3.80 (m, 3H), 3.44 (s, 3H), 2.54 (sept, *J* = 7.0 Hz, 1H), 2.53 (sept, *J* = 7.0 Hz, 1H), 1.13–1.08 (m, 12H) ppm. ¹³C{¹H} NMR (100 MHz, acetone-*d*₆): δ 176.4, 176.2, 138.7, 129.6, 128.8, 127.0, 102.0, 98.7, 80.0, 72.04, 69.5, 69.3, 63.6, 55.8, 34.6, 34.5, 19.4, 19.2, 19.2, 19.1 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₂H₃₀O₈Na, 455.1835; found, 455.1833. IR (ATR) ν /cm⁻¹: 2973, 2931, 1745, 1738, 1454, 1370, 1342, 1257, 1184, 1147, 1121, 1093, 1049, 1026, 1004, 989, 923, 750, 699.

Methyl 4,6-O-Methylidene-2-O-isobutyryl- α -D-glucopyranoside (9a). Procedure 1. Methyl 4,6-O-methylidene- α -D-glucopyranoside (206.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), isobutyric anhydride (205.6 mg, 215 μ L, 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain **9a** after column chromatography (*n*-hexane/EtOAc 2:1) in 65.4 mg (0.24 mmol, 24%) yield as a colorless solid. R_f = 0.22 (*n*-hexane/EtOAc 2:1). ¹H NMR (400 MHz, CDCl₃): δ 5.22 (t, *J* = 9.7 Hz, 1H), 5.03 (d, *J* = 6.2 Hz, 1H), 4.75 (d, *J* = 3.8 Hz, 1H), 4.56 (d, *J* = 6.3 Hz, 1H), 4.16 (dd, *J* = 10.1, 5.0 Hz, 1H), 3.74 (td, *J* = 10.0, 4.9 Hz, 1H), 3.61 (dd, *J* = 9.6, 3.9 Hz, 1H), 3.45 (t, *J* = 10.3 Hz, 1H), 3.45 (s, 3H), 3.30 (t, *J* = 9.6 Hz, 1H), 2.62 (sept, *J* = 7.0 Hz, 1H), 2.09 (s, 1H), 1.19 (dd, *J* = 7.0, 5.0 Hz, 6H) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 177.4, 100.2, 100.1, 93.8, 79.0, 72.1, 71.9, 68.8, 63.0, 55.7, 34.2, 19.1, 19.1 ppm.⁴⁶

Methyl 4,6-O-Methylidene-3-O-isobutyryl- α ,D-glucopyranoside (9b). Procedure 1. Methyl 4,6-O-methylidene- α ,D-glucopyranoside (206.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), isobutyric anhydride (205.6 mg, 215 μ L, 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain 9b after column chromatography (*n*-hexane/EtOAc 2:1) in 69.2 mg (0.25 mmol, 25%) yield as a colorless solid. R_f = 0.23 (*n*-hexane/EtOAc 2:1). ^1H NMR (400 MHz, CDCl_3): δ 5.22 (t, J = 9.7 Hz, 1H), 5.03 (d, J = 6.2 Hz, 1H), 4.75 (d, J = 3.8 Hz, 1H), 4.56 (d, J = 6.3 Hz, 1H), 4.16 (dd, J = 10.1, 5.0 Hz, 1H), 3.74 (td, J = 10.0, 4.9 Hz, 1H), 3.61 (dd, J = 9.6, 3.9 Hz, 1H), 3.45 (t, J = 10.3 Hz, 1H), 3.45 (s, 3H), 3.30 (t, J = 9.6 Hz, 1H), 2.62 (sept, J = 7.0 Hz, 1H), 2.09 (s, 1H), 1.19 (dd, J = 7.0, 5.0 Hz, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 177.4, 100.2, 100.1, 93.8, 79.0, 72.1, 71.9, 68.8, 63.0, 55.7, 34.2, 19.1, 19.1 ppm.⁸⁵

Methyl 4,6-O-Methylidene-2,3-O-diisobutyryl- α ,D-glucopyranoside (9c). Procedure 1. Methyl 4,6-O-methylidene- α ,D-glucopyranoside (206.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), isobutyric anhydride (205.6 mg, 215 μ L, 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain 9c after column chromatography (*n*-hexane/EtOAc 2:1) in 89.1 mg (0.26 mmol, 26%) yield as a colorless solid. R_f = 0.57 (*n*-hexane/EtOAc 2:1). ^1H NMR (400 MHz, CDCl_3): δ 5.52 (t, J = 9.7 Hz, 1H), 5.04 (d, J = 6.2 Hz, 1H), 4.89 (d, J = 3.8 Hz, 1H), 4.85 (dd, J = 9.7, 3.8 Hz, 1H), 4.57 (d, J = 6.2 Hz, 1H), 4.17 (dd, J = 10.3, 4.9 Hz, 1H), 3.82 (td, J = 9.9, 4.9 Hz, 1H), 3.48 (t, J = 10.3 Hz, 1H), 3.38 (s, 3H), 3.36 (t, J = 9.7 Hz, 1H), 2.54 (dp, J = 8.1, 7.0 Hz, 2H), 1.13 (t, J = 6.9 Hz, 12H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 176.6, 176.1, 97.7, 93.9, 79.6, 71.3, 68.8, 68.7, 62.6, 55.6, 34.1, 33.9, 19.1, 19.0, 18.9 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{36}\text{O}_8\text{Na}$, 369.1520; found, 369.1523 IR (ATR) ν/cm^{-1} : 2976, 2878, 1735, 1471, 1389, 1352, 1232, 1191, 1149, 1122, 1107, 1073, 1047, 1021, 991, 971, 921, 849.

Methyl 2-O-Acetyl-4,6-O-benzylidene- α ,D-mannopyranoside (10a). Procedure 1. Methyl 4,6-O-benzylidene- α ,D-mannopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac_2O (113.4 mg, 105 μ L, 1.1 mmol, 1.1 equiv), and 10 mL of DCM were used to obtain 10a after column chromatography (*n*-hexane/EtOAc 2:1) in 48.0 mg (0.15 mmol, 15%) yield as a colorless solid. R_f = 0.45 (*n*-hexane/EtOAc 2:1). ^1H NMR (400 MHz, $\text{MeOH-}d_4$): δ 7.53–7.46 (m, 2H), 7.38–7.31 (m, 3H), 5.64 (s, 1H), 5.10 (dd, J = 3.7, 1.5 Hz, 1H), 4.67 (d, J = 1.6 Hz, 1H), 4.22 (dd, J = 9.7, 4.4 Hz, 1H), 4.12–4.06 (m, 1H), 3.91 (dd, J = 10.0, 9.0 Hz, 1H), 3.86–3.80 (m, 1H), 3.79–3.72 (m, 1H), 3.40 (s, 3H), 2.13 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{MeOH-}d_4$): δ 172.0, 139.2, 129.9, 129.3, 129.0, 127.8, 127.5, 103.3, 100.9, 80.2, 74.0, 69.7, 67.9, 65.0, 55.5, 20.8 ppm.⁴²

Methyl 3-O-Acetyl-4,6-O-benzylidene- α ,D-mannopyranoside (10b). Procedure 1. Methyl 4,6-O-benzylidene- α ,D-mannopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac_2O (113.4 mg, 105 μ L, 1.1 mmol, 1.1 equiv), and 10 mL of DCM were used to obtain 10b after column chromatography (*n*-hexane/EtOAc 2:1) in 224.5 mg (0.69 mmol, 69%) yield as a colorless solid. R_f = 0.29 (*n*-hexane/EtOAc 2:1). ^1H NMR (400 MHz, $\text{MeOH-}d_4$): δ 7.47–7.39 (m, 2H), 7.39–7.30 (m, 3H), 5.59 (s, 1H), 5.13 (dd, J = 10.3, 3.4 Hz, 1H), 4.69 (d, J = 1.6 Hz, 1H), 4.28–4.17 (m, 1H), 4.17–4.08 (m, 1H), 4.06 (dd, J = 3.7, 1.9 Hz, 1H), 3.90–3.77 (m, 2H), 3.41 (s, 3H), 2.07 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{MeOH-}d_4$): δ 172.3, 139.0, 130.0, 129.1, 127.5, 103.6, 103.3, 77.3, 72.4, 70.1, 69.8, 65.3, 55.4, 20.9, 20.9 ppm.⁴³

Methyl 2,3-O-Diacetyl-4,6-O-benzylidene- α ,D-mannopyranoside (10c). Procedure 1. Methyl 4,6-O-benzylidene- α ,D-mannopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac_2O (113.4 mg, 105 μ L, 1.1 mmol, 1.1 equiv), and 10 mL of DCM were used to obtain 10c after column chromatography (*n*-hexane/EtOAc 2:1) in 43.9 mg (0.12 mmol, 12%) yield as a colorless solid. R_f = 0.59 (*n*-hexane/EtOAc 2:1). ^1H NMR (400 MHz, $\text{MeOH-}d_4$): δ 7.48–7.40 (m, 2H), 7.37–7.30 (m, 3H), 5.63 (s, 1H), 5.31–5.25 (m, 2H), 4.72 (d, J = 1.3 Hz, 1H), 4.31–4.20 (m, 1H), 4.15–4.08 (m, 1H), 3.94–3.82 (m, 2H), 3.43 (s, 3H), 2.14 (s, 3H), 1.97 (s,

3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{MeOH-}d_4$): δ 171.8, 171.6, 138.9, 130.1, 129.1, 127.5, 103.3, 101.0, 77.3, 71.1, 70.0, 69.7, 65.2, 55.6, 20.9, 20.6, 20.6 ppm.⁴⁴

Methyl 2-O-Acetyl-4,6-O-methylidene- α ,D-mannopyranoside (11a). Procedure 1. Methyl 4,6-O-methylidene- α ,D-mannopyranoside (128.0 mg, 0.62 mmol, 1.0 equiv), DMAP (8.0 mg, 0.06 mmol, 0.1 equiv), Ac_2O (82.0 mg, 76 μ L, 0.81 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain 11a after column chromatography (*n*-hexane/EtOAc 1:1) in 30.0 mg (0.12 mmol, 12%) yield as a colorless solid. R_f = 0.24 (*n*-hexane/EtOAc 1:1). ^1H NMR (400 MHz, $\text{MeOH-}d_4$): δ 5.07–5.03 (m, 1H), 4.97 (d, J = 6.3 Hz, 1H), 4.65 (d, J = 6.3 Hz, 1H), 4.63 (dd, J = 5.8, 1.6 Hz, 1H), 4.09–4.06 (m, 1H), 4.01 (dd, J = 3.4, 1.7 Hz, 1H), 3.87–3.81 (m, 1H), 3.74–3.67 (m, 1H), 3.60–3.52 (m, 2H), 3.39 (s, 3H), 2.08 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{MeOH-}d_4$): δ 172.2, 103.5, 95.0, 77.3, 72.3, 70.2, 69.5, 65.4, 55.4, 20.9 ppm.¹⁴

Methyl 3-O-Acetyl-4,6-O-methylidene- α ,D-mannopyranoside (11b). Procedure 1. Methyl 4,6-O-methylidene- α ,D-mannopyranoside (128.0 mg, 0.62 mmol, 1.0 equiv), DMAP (8.0 mg, 0.06 mmol, 0.1 equiv), Ac_2O (82.0 mg, 76 μ L, 0.81 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain 11b after column chromatography (*n*-hexane/EtOAc 1:1) in 3.1 mg (0.01 mmol, 2%) yield as a colorless solid. R_f = 0.08 (*n*-hexane/EtOAc 1:1). ^1H NMR (400 MHz, $\text{MeOH-}d_4$): δ 5.13 (d, J = 0.8 Hz, 1H), 4.97–4.95 (m, 1H), 4.93–4.92 (m, 1H), 4.39 (dd, J = 11.9, 2.3 Hz, 1H), 4.17 (dd, J = 11.8, 6.4 Hz, 1H), 4.11–4.07 (m, 1H), 3.86 (dd, J = 5.6, 0.8 Hz, 1H), 3.70 (dddd, J = 10.4, 6.4, 2.3, 0.6 Hz, 1H), 3.44 (dd, J = 10.4, 7.4 Hz, 1H), 3.39 (s, 3H), 2.06 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{MeOH-}d_4$): δ 172.7, 99.4, 95.6, 79.3, 77.6, 69.1, 67.9, 64.8, 55.2, 20.7 ppm.¹⁴

Methyl 2,3-O-Diacetyl-4,6-O-methylidene- α ,D-mannopyranoside (11c). Procedure 1. Methyl 4,6-O-methylidene- α ,D-mannopyranoside (128.0 mg, 0.62 mmol, 1.0 equiv), DMAP (8.0 mg, 0.06 mmol, 0.1 equiv), Ac_2O (82.0 mg, 76 μ L, 0.81 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain 11c after column chromatography (*n*-hexane/EtOAc 1:1) in 82.0 mg (0.10 mmol, 17%) yield as a colorless solid. R_f = 0.51 (*n*-hexane/EtOAc 1:1). ^1H NMR (400 MHz, $\text{MeOH-}d_4$): δ 5.24 (dd, J = 3.6, 1.6 Hz, 1H), 5.22–5.17 (m, 1H), 5.00–4.95 (m, 1H), 4.69 (d, J = 6.3 Hz, 1H), 4.67 (d, J = 1.6 Hz, 1H), 4.14–4.07 (m, 1H), 3.84–3.74 (m, 2H), 3.57 (t, J = 10.1 Hz, 1H), 3.41 (s, 3H), 2.12 (s, 3H), 1.98 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{MeOH-}d_4$): δ 171.7, 171.5, 100.9, 95.0, 77.3, 71.1, 69.9, 69.3, 65.3, 55.6, 20.6, 20.6 ppm.¹⁴

Methyl 2-O-Acetyl-4,6-O-(2-naphthylidene)- α ,D-mannopyranoside (12a). Procedure 1. Methyl 4,6-O-naphthylidene- α ,D-mannopyranoside (169.0 mg, 0.51 mmol, 1.0 equiv), DMAP (6.1 mg, 0.05 mmol, 0.1 equiv), Ac_2O (66.4 mg, 61 μ L, 0.66 mmol, 1.3 equiv), and 5 mL of DCM were used to obtain 12a after column chromatography (*n*-hexane/EtOAc 1:2) in 110.0 mg (0.29 mmol, 58%) yield as a colorless solid. R_f = 0.50 (*n*-hexane/EtOAc 1:2). ^1H NMR (400 MHz, $\text{MeOH-}d_4$): δ 7.99 (s, 1H), 7.89–7.82 (m, 3H), 7.62 (dd, J = 8.5, 1.7 Hz, 1H), 7.52–7.46 (m, 2H), 5.80 (s, 1H), 5.13 (dd, J = 3.7, 1.6 Hz, 1H), 4.69 (d, J = 1.5 Hz, 1H), 4.28 (dd, J = 9.8, 4.5 Hz, 1H), 4.13 (dd, J = 10.0, 3.7 Hz, 1H), 3.98 (dd, J = 10.1, 9.0 Hz, 1H), 3.92–3.85 (m, 1H), 3.84–3.77 (m, 1H), 3.41 (s, 3H), 2.15 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{MeOH-}d_4$): δ 172.0, 136.5, 135.1, 134.3, 129.3, 128.8, 128.7, 127.5, 127.2, 126.8, 125.2, 103.4, 100.9, 80.3, 74.0, 69.8, 68.0, 65.1, 55.5, 20.8 ppm.¹⁴

Methyl 3-O-Acetyl-4,6-O-(2-naphthylidene)- α ,D-mannopyranoside (12b). Procedure 1. Methyl 4,6-O-naphthylidene- α ,D-mannopyranoside (169.0 mg, 0.51 mmol, 1.0 equiv), DMAP (6.1 mg, 0.05 mmol, 0.1 equiv), Ac_2O (66.4 mg, 61 μ L, 0.66 mmol, 1.3 equiv), and 5 mL of DCM were used to obtain 12b after column chromatography (*n*-hexane/EtOAc 1:2) in 33.1 mg (0.09 mmol, 17%) yield as a colorless solid. R_f = 0.69 (*n*-hexane/EtOAc 1:2). ^1H NMR (400 MHz, $\text{MeOH-}d_4$): δ 7.92–7.88 (m, 1H), 7.86–7.79 (m, 3H), 7.54 (dd, J = 8.5, 1.7 Hz, 1H), 7.48–7.43 (m, 2H), 5.72 (s, 1H), 5.19 (dd, J = 10.3, 3.3 Hz, 1H), 4.71 (d, J = 1.7 Hz, 1H), 4.33–4.18 (m, 2H), 4.10 (dd, J = 3.4, 1.6 Hz, 1H), 3.95–3.85 (m, 2H), 3.39 (s, 3H), 2.06 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{MeOH-}d_4$): δ 172.2, 136.3, 135.0,

134.2, 129.3, 128.9, 128.7, 127.5, 127.2, 126.8, 125.0, 103.5, 103.4, 77.4, 72.4, 70.1, 69.8, 65.3, 55.4, 20.9 ppm.¹⁴

Methyl 2,3-O-Diacetyl-4,6-O-(2-naphthylidene)- α , β -mannopyranoside (12c). Procedure 1. Methyl 4,6-O-naphthylidene- α , β -mannopyranoside (169.0 mg, 0.51 mmol, 1.0 equiv), DMAP (6.1 mg, 0.05 mmol, 0.1 equiv), Ac₂O (66.4 mg, 61 μ L, 0.66 mmol, 1.3 equiv), and 5 mL of DCM were used to obtain 12c after column chromatography (*n*-hexane/EtOAc 1:2) in 44.0 mg (0.11 mmol, 21%) yield as a colorless solid. *R*_f = 0.79 (*n*-hexane/EtOAc 1:2). ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.92 (s, 1H), 7.89–7.82 (m, 3H), 7.56 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.51–7.46 (m, 2H), 5.80 (s, 1H), 5.34–5.28 (m, 2H), 4.74 (d, *J* = 1.3 Hz, 1H), 4.34–4.27 (m, 1H), 4.20–4.13 (m, 1H), 3.98–3.90 (m, 2H), 3.45 (s, 3H), 2.15 (s, 3H), 1.97 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, MeOH-*d*₄): δ 171.9, 171.6, 136.2, 135.2, 134.3, 129.3, 128.9, 128.7, 127.5, 127.3, 126.9, 125.0, 103.4, 101.0, 77.4, 71.1, 70.1, 69.7, 65.2, 55.6, 20.7, 20.6 ppm.¹⁴

Methyl 2-O-Acetyl-4,6-O-benzylidene- α , β -galactopyranoside (13a). Procedure 1. Methyl 4,6-O-benzylidene- α , β -mannopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac₂O (113.4 mg, 105 μ L, 1.1 mmol, 1.1 equiv), and 10 mL of DCM were used to obtain 13a after column chromatography (*n*-hexane/EtOAc 1:2) in 115.3 mg (0.36 mmol, 36%) yield as a colorless solid. *R*_f = 0.29 (*n*-hexane/EtOAc 1:2). ¹H NMR (400 MHz, CDCl₃): δ 7.56–7.46 (m, 2H), 7.43–7.32 (m, 3H), 5.56 (s, 1H), 5.15 (dd, *J* = 10.3, 3.5 Hz, 1H), 4.98 (d, *J* = 3.5 Hz, 1H), 4.30 (dd, *J* = 4.9, 1.4 Hz, 1H), 4.28 (dd, *J* = 3.8, 1.4 Hz, 1H), 4.14–4.04 (m, 2H), 3.73 (q, *J* = 1.6 Hz, 1H), 3.42 (s, 3H), 2.14 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 171.2, 137.5, 129.4, 128.4, 126.5, 101.5, 98.3, 76.2, 71.4, 69.3, 67.4, 62.5, 55.7, 21.2 ppm.^{18c}

Methyl 3-O-Acetyl-4,6-O-benzylidene- α , β -galactopyranoside (13b). Procedure 1. Methyl 4,6-O-benzylidene- α , β -mannopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac₂O (113.4 mg, 105 μ L, 1.1 mmol, 1.1 equiv), and 10 mL of DCM were used to obtain 13b after column chromatography (*n*-hexane/EtOAc 1:2) in 151.7 mg (0.48 mmol, 48%) yield as a colorless solid. *R*_f = 0.38 (*n*-hexane/EtOAc 1:2). ¹H NMR (400 MHz, CDCl₃): δ 7.55–7.45 (m, 2H), 7.41–7.30 (m, 3H), 5.51 (s, 1H), 5.12 (dd, *J* = 10.4, 3.4 Hz, 1H), 4.95 (d, *J* = 3.7 Hz, 1H), 4.37 (dd, *J* = 3.6, 1.2 Hz, 1H), 4.27 (dd, *J* = 12.5, 1.6 Hz, 1H), 4.17 (dd, *J* = 10.4, 3.8 Hz, 1H), 4.06 (dd, *J* = 12.5, 1.8 Hz, 1H), 3.72 (q, *J* = 1.7 Hz, 1H), 3.47 (s, 3H), 2.14 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 171.5, 137.8, 129.1, 128.3, 126.3, 100.9, 100.4, 77.5, 77.2, 76.8, 74.4, 71.8, 69.3, 66.9, 62.7, 55.8, 21.2 ppm.^{18c}

Methyl 2,3-O-Diacetyl-4,6-O-benzylidene- α , β -galactopyranoside (13c). Procedure 1. Methyl 4,6-O-benzylidene- α , β -mannopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), Ac₂O (113.4 mg, 105 μ L, 1.1 mmol, 1.1 equiv), and 10 mL of DCM were used to obtain 13c after column chromatography (*n*-hexane/EtOAc 1:2) in 50.4 mg (0.15 mmol, 15%) yield as a colorless solid. *R*_f = 0.65 (*n*-hexane/EtOAc 1:2). ¹H NMR (400 MHz, CDCl₃): δ 7.54–7.47 (m, 2H), 7.41–7.32 (m, 3H), 5.51 (s, 1H), 5.39–5.29 (m, 2H), 5.08 (d, *J* = 3.0 Hz, 1H), 4.46 (dd, *J* = 3.2, 1.2 Hz, 1H), 4.28 (dd, *J* = 12.5, 1.6 Hz, 1H), 4.06 (dd, *J* = 12.6, 1.8 Hz, 1H), 3.75 (q, *J* = 1.6 Hz, 1H), 3.42 (s, 3H), 2.08 (s, 3H), 2.08 (s, 3H) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 170.8, 170.4, 137.7, 129.2, 128.3, 126.4, 101.0, 97.9, 74.1, 69.2, 68.7, 68.3, 62.2, 55.7, 21.1, 21.0 ppm.⁴⁵

Methyl 2-O-Isobutyryl-4,6-O-benzylidene- α , β -mannopyranoside (18a). Procedure 1. Methyl 4,6-O-benzylidene- α , β -mannopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), isobutyric anhydride (206 mg, 217 μ L, 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain 18a after column chromatography (*n*-hexane/EtOAc 3:1) in 43.7 mg (0.12 mmol, 12%) yield as a colorless solid. *R*_f = 0.29 (*n*-hexane/EtOAc 3:1). ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.56–7.47 (m, 2H), 7.39–7.29 (m, 3H), 5.64 (s, 1H), 5.09 (dd, *J* = 3.7, 1.6 Hz, 1H), 4.63 (d, *J* = 1.6 Hz, 1H), 4.23 (dd, *J* = 9.5, 4.1 Hz, 1H), 4.11 (dd, *J* = 10.0, 3.7 Hz, 1H), 3.91 (t, *J* = 9.4 Hz, 1H), 3.87–3.72 (m, 2H), 3.41 (s, 3H), 2.67 (hept, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 7.0 Hz, 7H) ppm. ¹³C{¹H} NMR (100 MHz, MeOH-*d*₄): δ 178.0, 139.2, 129.9, 129.0, 127.5, 103.4, 101.0, 80.3, 73.8, 69.8, 68.0, 65.0, 55.6, 35.2, 19.4, 19.2 ppm. HRMS (ESI-

TOF) *m/z*: [M + Na]⁺ calcd for C₁₈H₂₄O₇Na, 375.1414; found, 375.1415 IR (ATR) ν /cm⁻¹: 3468, 2974, 2935, 1736, 1456, 1386, 1316, 1255, 1199, 1158, 1130, 1097, 1069, 1026, 969, 924, 883, 795, 751, 699.

Methyl 3-O-Isobutyryl-4,6-O-benzylidene- α , β -mannopyranoside (18b). Procedure 1. Methyl 4,6-O-benzylidene- α , β -mannopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), isobutyric anhydride (206 mg, 217 μ L, 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain 18b after column chromatography (*n*-hexane/EtOAc 3:1) in 207.0 mg (0.59 mmol, 59%) yield as a colorless solid. *R*_f = 0.12 (*n*-hexane/EtOAc 3:1). ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.46–7.39 (m, 2H), 7.37–7.28 (m, 3H), 5.60 (s, 1H), 5.16 (dd, *J* = 10.4, 3.4 Hz, 1H), 4.68 (d, *J* = 1.7 Hz, 1H), 4.26–4.20 (m, 1H), 4.18–4.10 (m, 1H), 4.03 (dd, *J* = 3.5, 1.7 Hz, 1H), 3.90–3.78 (m, 2H), 3.42 (s, 3H), 2.62 (hept, *J* = 7.0 Hz, 1H), 1.15 (dd, *J* = 7.0, 4.6 Hz, 6H) ppm. ¹³C{¹H} NMR (100 MHz, MeOH-*d*₄): δ 178.3, 139.1, 129.9, 129.0, 127.3, 103.8, 103.1, 77.5, 72.0, 70.3, 69.8, 65.3, 55.4, 35.2, 19.5, 19.1 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₁₈H₂₄O₇Na, 375.1414; found, 375.1416 IR (ATR) ν /cm⁻¹: 3521, 2968, 2932, 1721, 1469, 1451, 1369, 1317, 1205, 1161, 1119, 1097, 1060, 1024, 970, 911, 800, 747, 697.

Methyl 2,3-O-Isobutyryl-4,6-O-benzylidene- α , β -mannopyranoside (18c). Procedure 1. Methyl 4,6-O-benzylidene- α , β -mannopyranoside (282.0 mg, 1.0 mmol, 1.0 equiv), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv), isobutyric anhydride (206 mg, 217 μ L, 1.3 mmol, 1.3 equiv), and 10 mL of DCM were used to obtain 18c after column chromatography (*n*-hexane/EtOAc 3:1) in 125.0 mg (0.29 mmol, 29%) yield as a colorless solid. *R*_f = 0.45 (*n*-hexane/EtOAc 3:1). ¹H NMR (400 MHz, MeOH-*d*₄): δ 7.49–7.40 (m, 2H), 7.40–7.32 (m, 3H), 5.67 (s, 1H), 5.36–5.29 (m, 2H), 4.71 (s, 1H), 4.33–4.24 (m, 1H), 4.16–4.07 (m, 1H), 3.95–3.85 (m, 2H), 3.46 (s, 3H), 2.69 (hept, *J* = 6.9 Hz, 1H), 2.50 (hept, *J* = 7.0 Hz, 1H), 1.24 (dd, *J* = 14.2, 7.0 Hz, 6H), 1.11 (dd, *J* = 7.0, 1.5 Hz, 6H) ppm. ¹³C{¹H} NMR (100 MHz, MeOH-*d*₄): δ 177.6, 177.3, 138.9, 130.0, 129.1, 127.3, 103.1, 101.1, 77.7, 70.9, 70.0, 69.7, 65.2, 55.6, 35.2, 19.5, 19.2, 19.2, 19.1 ppm. HRMS (ESI-TOF) *m/z*: [M + Na]⁺ calcd for C₂₂H₃₀O₈Na, 445.1833; found, 445.1834 IR (ATR) ν /cm⁻¹: 2975, 2936, 1741, 1469, 1387, 1283, 1251, 1195, 1128, 1073, 1012, 967, 914, 892, 750, 698.

Catalysts. Boc-*L*-Pmh-^AGly-*L*-Cha-*L*-Phe-*OMe* (1). The synthesis and characterization data for 1 can be found in the literature.¹⁶

Boc-*D*-Pmh-^AGly-*L*-Val-*L*-Phe-*OMe* (2). Procedure 2. The coupling of H-*L*-Phe-*OMe*-HCl and Boc-*L*-Val-OH was performed on a 5.0 mmol scale to obtain 1.90 g (5.0 mmol, quant.) of Boc-*L*-Val-*L*-Phe-*OMe* as a colorless solid. Procedure 3: 5.0 mmol of Boc-*L*-Val-*L*-Phe-*OMe* was deprotected and directly used for the next coupling. Procedure 2: The coupling of H-*L*-Val-*L*-Phe-*OMe*-HCl and Boc-^AGly-OH was performed on a 5.0 mmol scale to obtain 2.83 g (5.0 mmol, quant.) of Boc-^AGly-*L*-Val-*L*-Phe-*OMe* as a colorless solid. Procedure 3: 2.1 mmol Boc-^AGly-*L*-Val-*L*-Phe-*OMe* was deprotected and directly used for the next coupling. Procedure 4: The coupling of H-^AGly-*L*-Val-*L*-Phe-*OMe*-HCl and Boc-*D*-Pmh-OH was performed on a 2.1 mmol scale to obtain 0.82 g (1.16 mmol, 55%) of 2 after column chromatography (CH₂Cl₂/MeOH 10:1) as a colorless solid. *R*_f = 0.38. (CH₂Cl₂/MeOH 10:1). ¹H NMR (400 MHz, CDCl₃): δ 7.30 (s, 1H), 7.23–7.12 (m, 3H), 7.09–7.04 (m, 2H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.76 (s, 1H), 6.39 (s, 1H), 6.23 (d, *J* = 8.5 Hz, 1H), 5.29 (d, *J* = 8.5 Hz, 1H), 4.76 (td, *J* = 7.5, 5.8 Hz, 1H), 4.23 (dd, *J* = 8.5, 6.4 Hz, 2H), 3.62 (s, 3H), 3.44 (s, 3H), 3.09 (dd, *J* = 14.0, 5.9 Hz, 1H), 2.98 (dd, *J* = 14.0, 7.4 Hz, 1H), 2.90 (d, *J* = 6.8 Hz, 2H), 2.21–2.04 (m, 4H), 2.01–1.80 (m, 2H), 1.77–1.49 (m, 9H), 1.35 (s, 9H), 0.80 (t, *J* = 7.1 Hz, 6H) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 176.4, 171.8, 171.2, 169.8, 155.5, 138.2, 136.1, 129.2, 128.8, 128.8, 128.5, 127.2, 80.4, 57.7, 54.2, 53.6, 53.4, 52.4, 52.4, 42.8, 40.1, 38.7, 38.2, 37.8, 35.2, 31.8, 31.5, 29.3, 29.2, 28.4, 27.5, 19.2, 18.2 ppm.^{17d}

Boc-*L*-Pmh-*OMe* (15). The synthesis and characterization data for 15 can be found in the literature.^{17d}

H-^AGly-*OMe*-HCl (19). 6 mL of dry methanol was cooled to 0 °C, and thionyl chloride (0.83 g, 0.50 mL, 7.0 mmol, 3.5 equiv) was added. The solution was stirred at 0 °C for 30 min, then Boc-^AGly-

OH (0.59 g, 2.0 mmol, 1.0 equiv) was added. The solution was stirred at rt for 20 h. The solvent was removed under reduced pressure to afford **19** in 0.49 g (2.0 mmol, quant.) yield as a colorless solid. ^1H NMR (400 MHz, CDCl_3): δ 8.46 (s, 3H), 3.63 (s, 3H), 2.31–2.23 (m, 2H), 2.18 (s, 2H), 2.08–1.96 (m, 4H), 1.92–1.77 (m, 4H), 1.73–1.60 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 175.9, 53.2, 52.0, 42.6, 41.5, 39.7, 37.3, 34.4, 28.8 ppm.¹⁶

Boc-L-Pmh^AGly-OMe (16). Procedure 4. The coupling of H^AGly-OMe-HCl and Boc-L-Pmh-OH was performed on a 0.20 mmol scale to obtain 0.049 g (0.11 mmol, 53%) of **16** after column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) as a colorless solid. $R_f = 0.31$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). ^1H NMR (400 MHz, CDCl_3): δ 7.46 (s, 1H), 6.80 (2, 1H), 5.90 (s, 1H), 5.20 (d, $J = 8.2$ Hz, 1H), 4.16–4.05 (m, 1H), 3.58 (s, 3H), 3.56 (s, 3H), 2.93 (d, $J = 6.8$ Hz, 2H), 2.14–2.08 (m, 2H), 2.06–1.96 (m, 2H), 1.91–1.69 (m, 8H), 1.61–1.52 (m, 2H), 1.37 (s, 9H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 176.9, 169.7, 155.5, 138.1, 127.8, 127.4, 80.6, 52.4, 51.9, 42.7, 42.2, 40.6, 40.5, 37.9, 35.3, 31.9, 29.1, 28.4, 27.0 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{36}\text{N}_4\text{O}_5\text{H}$, 461.2758; found, 461.2762, $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{36}\text{N}_4\text{O}_5\text{Na}$, 483.2578; found, 483.2580. IR (ATR) ν/cm^{-1} : 3308, 2911, 2857, 1796, 1712, 1661, 1506, 1454, 1391, 1365, 1343, 1241, 1164, 1125, 1106, 1050, 977, 928, 856, 833, 771, 662.

Boc-L-Pmh^AGly-L-Cha-OMe (17). Procedure 2. The coupling of H-L-Cha-OMe-HCl and Boc^AGly-OH was performed on a 0.50 mmol scale to obtain 0.26 g (0.50 mmol, quant.) of Boc-L-Cha^AGly-OMe as a colorless solid. Procedure 3: 0.50 mmol of Boc-L-Cha^AGly-OMe was deprotected and directly used for the next coupling. Procedure 4: The coupling of H-L-Cha^AGly-OMe-HCl and Boc-L-Pmh-OH was performed on a 0.50 mmol scale to obtain 0.12 g (0.19 mmol, 38%) of **17** after column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) as a colorless solid. $R_f = 0.35$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). ^1H NMR (400 MHz, CDCl_3): δ 7.75 (s, 1H), 6.93 (s, 1H), 6.22 (s, 1H), 6.00 (d, $J = 8.2$ Hz, 1H), 5.34 (d, $J = 8.3$ Hz, 1H), 4.62 (td, $J = 8.7, 5.5$ Hz, 1H), 4.31–4.19 (m, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.01 (d, $J = 6.8$ Hz, 2H), 2.26–2.16 (m, 2H), 2.10–2.00 (m, 2H), 2.00–1.86 (m, 4H), 1.86–1.57 (m, 12H), 1.53 (ddd, $J = 14.2, 9.0, 5.9$ Hz, 1H), 1.43 (s, 9H), 1.29–1.10 (m, 4H), 1.01–0.82 (m, 2H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 176.3, 173.9, 169.6, 137.5, 128.2, 80.4, 52.5, 52.3, 49.9, 42.5, 42.2, 40.4, 40.0, 38.2, 38.1, 35.2, 34.3, 33.4, 32.6, 32.1, 29.1, 29.1, 28.3, 27.1, 26.4, 26.2, 26.0 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{51}\text{N}_5\text{O}_6\text{H}$, 614.3912; found, 614.3904, $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{33}\text{H}_{51}\text{N}_5\text{O}_6\text{Na}$, 636.3732; found, 636.3730. IR (ATR) ν/cm^{-1} : 3307, 2924, 2851, 1795, 1699, 1507, 1450, 1389, 1377, 1286, 1255, 1229, 1179, 1166, 1146, 1081, 976, 947, 928, 912, 899, 855, 834, 768, 753, 733, 718, 667.

Boc-D-Pmh-OMe (20). Procedure 4. The esterification of methanol and Boc-D-Pmh-OH was performed on a 2.0 mmol scale to obtain 0.42 g (1.5 mmol, 75%) of **20** after column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) as a colorless solid. $R_f = 0.40$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). ^1H NMR (400 MHz, CDCl_3): δ 7.43 (s, 1H), 6.78 (s, 1H), 5.20 (d, $J = 7.8$ Hz, 1H), 4.53 (q, $J = 6.4$ Hz, 1H), 3.73 (s, 3H), 3.58 (s, 3H), 3.09 (qd, $J = 15.4, 5.9$ Hz, 2H), 1.41 (s, 9H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 171.8, 154.7, 140.0, 129.6, 126.7, 80.4, 53.1, 52.7, 31.5, 28.9, 27.0 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{21}\text{N}_3\text{O}_4\text{H}$, 284.1605; found, 284.1600, $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{21}\text{N}_3\text{O}_4\text{Na}$, 306.1424; found, 306.1423. IR (ATR) ν/cm^{-1} : 3155, 2979, 2011, 1733, 1694, 1535, 1509, 1451, 1437, 1420, 1390, 1365, 1322, 1289, 1258, 1243, 1219, 1200, 1163, 1110, 1073, 1053, 1038, 990, 934, 814, 752, 663.

Boc^AGly-L-Pmh-OMe (21). The synthesis and characterization data for **21** can be found in the literature.²⁴

3,5-Bis(trifluoromethyl)phenylthiourea^AGly-L-Pmh-OMe (22). The synthesis and characterization data for **22** can be found in the literature.²⁴

Boc-D-Val^AGly-L-Pmh-OMe (23). The synthesis and characterization data for **23** can be found in the literature.²⁴

Boc-L-Cha^AGly-L-Pmh-OMe (24). The synthesis and characterization data for **24** can be found in the literature.²⁴

Boc-L-Trp^AGly-L-Pmh-OMe (25). The synthesis and characterization data for **25** can be found in the literature.²⁴

Boc-L-Phe^AGly-L-Pmh-OMe (26). The synthesis and characterization data for **26** can be found in the literature.²⁴

Boc-D-Pmh^AGly-OMe (27). Procedure 4. The coupling of H^AGly-OMe-HCl and Boc-D-Pmh-OH was performed on a 0.20 mmol scale to obtain 0.056 g (0.12 mmol, 61%) of **27** after column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) as a colorless solid. $R_f = 0.33$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). ^1H NMR (400 MHz, CDCl_3): δ 7.35 (s, 1H), 6.78 (s, 1H), 5.78 (s, 1H), 5.18 (d, $J = 8.3$ Hz, 1H), 4.15–4.02 (m, 1H), 3.58 (s, 3H), 3.54 (s, 3H), 2.98–2.86 (m, 2H), 2.08–2.13 (m, 2H), 2.07–1.95 (m, 2H), 1.90–1.66 (m, 8H), 1.53–1.57 (m, 2H), 1.37 (s, 9H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 176.9, 169.8, 155.5, 138.4, 128.3, 127.4, 80.5, 54.6, 52.3, 51.9, 42.6, 42.2, 40.6, 40.5, 37.9, 35.3, 31.7, 29.1, 28.4, 26.9 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{36}\text{N}_4\text{O}_5\text{H}$, 461.2758; found, 461.2761, $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{24}\text{H}_{36}\text{N}_4\text{O}_5\text{Na}$, 483.2578; found, 483.2575. IR (ATR) ν/cm^{-1} : 3305, 2912, 2858, 1711, 1661, 1505, 1454, 1435, 1391, 1365, 1342, 1320, 1239, 1164, 1124, 1105, 1053, 929, 873, 816, 778, 757, 661.

Boc-L-Pmh^AGly-L-Val-OMe (28). Procedure 2. The coupling of H-L-Val-OMe-HCl and Boc^AGly-OH was performed on a 0.30 mmol scale to obtain 0.13 g (0.30 mmol, quant.) of Boc^AGly-L-Val-OMe as a colorless solid. Procedure 3: 0.30 mmol Boc^AGly-L-Val-OMe was deprotected and directly used for the next coupling. Procedure 4: The coupling of H^AGly-L-Val-OMe-HCl and Boc-L-Pmh-OH was performed on a 0.30 mmol scale to obtain 0.064 g (0.12 mmol, 40%) of **28** after column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) as a colorless solid. $R_f = 0.25$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). ^1H NMR (400 MHz, CDCl_3): δ 7.56 (s, 1H), 6.87 (s, 1H), 6.07 (d, $J = 8.5$ Hz, 1H), 6.01 (s, 1H), 5.27 (d, $J = 8.2$ Hz, 1H), 4.53 (dd, $J = 8.6, 5.0$ Hz, 1H), 4.25–4.14 (m, 1H), 3.73 (s, 3H), 3.63 (s, 3H), 3.05–2.94 (m, 2H), 2.25–2.18 (m, 2H), 2.18–2.09 (m, 1H), 2.03 (s, 2H), 1.99–1.74 (m, 8H), 1.71–1.56 (m, 2H), 1.43 (s, 9H), 0.90 (t, $J = 6.9$ Hz, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 176.4, 172.9, 169.7, 155.0, 138.1, 127.8, 127.3, 80.6, 56.8, 52.5, 52.3, 42.9, 42.5, 40.5, 40.4, 38.4, 38.3, 35.3, 31.9, 31.5, 29.3, 28.4, 27.0, 19.1, 18.1 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{45}\text{N}_5\text{O}_6\text{H}$, 560.3443; found, 560.3443, $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{29}\text{H}_{45}\text{N}_5\text{O}_6\text{Na}$, 582.3262; found, 582.3261. IR (ATR) ν/cm^{-1} : 3308, 2910, 2855, 1795, 1699, 1652, 1506, 1453, 1390, 1365, 1286, 1248, 1230, 1165, 1110, 1082, 976, 928, 855, 833, 768, 664.

Boc-D-Pmh^AGly-L-Val-OMe (29). Procedure 2. The coupling of H-L-Val-OMe-HCl and Boc^AGly-OH was performed on a 0.30 mmol scale to obtain 0.13 g (0.30 mmol, quant.) of Boc^AGly-L-Val-OMe as a colorless solid. Procedure 3: 0.30 mmol Boc^AGly-L-Val-OMe was deprotected and directly used for the next coupling. Procedure 4: The coupling of H^AGly-L-Val-OMe-HCl and Boc-D-Pmh-OH was performed on a 0.30 mmol scale to obtain 0.059 g (0.11 mmol, 35%) of **29** after column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) as a colorless solid. $R_f = 0.25$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). ^1H NMR (400 MHz, CDCl_3): δ 7.54 (s, 1H), 6.86 (s, 1H), 6.07 (d, $J = 8.6$ Hz, 1H), 5.99 (s, 1H), 5.26 (d, $J = 8.3$ Hz, 1H), 4.53 (dd, $J = 8.5, 5.0$ Hz, 1H), 4.25–4.14 (m, 1H), 3.73 (s, 3H), 3.62 (s, 3H), 3.05–2.94 (m, 2H), 2.24–2.18 (m, 2H), 2.18–2.09 (m, 1H), 2.06–1.99 (m, 2H), 1.97–1.75 (m, 8H), 1.69–1.57 (m, 2H), 1.42 (s, 9H), 0.90 (t, $J = 6.9$ Hz, 6H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): δ 176.4, 172.9, 169.8, 155.5, 138.1, 127.8, 127.4, 80.6, 56.8, 52.5, 52.3, 42.8, 42.5, 40.5, 40.5, 38.4, 38.3, 35.3, 31.9, 31.5, 29.3, 28.4, 27.0, 19.1, 18.1 ppm. HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{45}\text{N}_5\text{O}_6\text{H}$, 560.3443; found, 560.3445, $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{29}\text{H}_{45}\text{N}_5\text{O}_6\text{Na}$, 582.3262; found, 582.3256. IR (ATR) ν/cm^{-1} : 3307, 2911, 2857, 1652, 1506, 1454, 1391, 1365, 1245, 1207, 1162, 1110, 1050, 1020, 929, 815, 661.

Boc-L-Pmh^AGly-L-Phe-OMe (30). The synthesis and characterization data for **30** can be found in the literature.²²

Boc-D-Pmh^AGly-L-Cha-L-Phe-OMe (31). Procedure 2. The coupling of H-L-Phe-OMe-HCl and Boc-L-Cha-OH-DCHA was performed on a 0.82 mmol scale to obtain 0.29 g (0.66 mmol, 80%) of Boc-L-Cha-L-Phe-OMe as a colorless solid. Procedure 3: 0.66 mmol of Boc-L-Cha-L-Phe-OMe was deprotected and directly used for the next

coupling. Procedure 2: The coupling of H-L-Cha-L-Phe-OMe-HCl and Boc-^AGly-OH was performed on a 0.66 mmol scale to obtain 0.40 g (0.65 mmol, 99%) of Boc-^AGly-L-Cha-L-Phe-OMe as a colorless solid. Procedure 3: 0.65 mmol Boc-^AGly-L-Cha-L-Phe-OMe was deprotected and directly used for the next coupling. Procedure 4: The coupling of H-^AGly-L-Cha-L-Phe-OMe-HCl and Boc-D-Pmh-OH was performed on a 0.65 mmol scale to obtain 0.29 g (0.38 mmol, 59%) of **31** after column chromatography (CH₂Cl₂/MeOH 10:1) as a colorless solid. *R*_f = 0.42. (CH₂Cl₂/MeOH 10:1). ¹H NMR (400 MHz, CDCl₃): δ 7.38 (s, 1H), 7.30–7.19 (m, 3H), 7.13–7.08 (m, 2H), 6.83 (s, 1H), 6.77 (d, *J* = 7.9 Hz, 1H), 6.13–6.02 (m, 2H), 5.27 (d, *J* = 8.4 Hz, 1H), 4.83–4.75 (m, 1H), 4.47 (td, *J* = 8.3, 6.2 Hz, 1H), 4.26–4.14 (m, 1H), 3.69 (s, 3H), 3.54 (s, 3H), 3.13 (dd, *J* = 14.0, 5.8 Hz, 1H), 3.04 (dd, *J* = 14.0, 6.9 Hz, 1H), 2.96 (d, *J* = 6.9 Hz, 2H), 2.22–2.16 (m, 2H), 2.03–1.93 (m, 3H), 1.93–1.80 (m, 3H), 1.77–1.55 (m, 12H), 1.49–1.39 (m, 1H), 1.41 (s, 9H), 1.28–1.06 (m, 4H), 0.96–0.77 (m, 2H) ppm. ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 176.4, 172.1, 171.8, 169.8, 155.5, 138.3, 136.1, 129.3, 128.7, 128.4, 127.3, 127.2, 80.5, 53.4, 52.5, 52.4, 50.8, 42.7, 42.5, 40.4, 40.3, 39.9, 38.4, 38.2, 37.9, 35.3, 34.3, 33.6, 32.9, 31.6, 29.3, 29.2, 28.5, 28.5, 27.2, 26.5, 26.3, 26.2 ppm. HRMS (ESI-TOF) *m/z*: [M + H]⁺ calcd for C₄₂H₆₀N₆O₈H, 761.4596; found, 761.4594, [M + Na]⁺ calcd for C₄₂H₆₀N₆O₈Na, 783.4416; found, 783.4418. IR (ATR) ν /cm⁻¹: 3298, 2918, 2852, 1745, 1659, 1505, 1449, 1391, 1365, 1282, 1245, 1215, 1166, 1110, 1050, 1021, 929, 890, 814, 747, 700, 670, 665, 542, 495, 439.

Boc-L-Pmh-^AGly-L-Val-L-Phe-OMe (32). The synthesis and characterization data for **32** can be found in the literature.¹⁵

Boc-D-Pmh-^AGly-D-Val-L-Phe-OMe (33). The synthesis and characterization data for **33** can be found in the literature.^{17d}

Boc-L-Pmh-^AGly-^AGly-L-Phe-OMe (34). The synthesis and characterization data for **34** can be found in the literature.¹⁵

Methyl 4,6-O-Benzylidene- α -D-glucopyranoside (3). 194.2 mg (1.00 mmol, 1.00 equiv) of methyl α -D-glucopyranoside, 152.2 mg (150.7 μ L, 1.00 mmol, 1.00 equiv) of benzaldehyde dimethyl acetal, 0.3 mg (0.001 mmol, 0.001 equiv) of camphor sulfonic acid, and 5000 mg 4 Å were suspended in 100 mL of dry toluene and refluxed for 3 h. It was then filtered and concentrated under reduced pressure. The crude product was purified via column chromatography (EtOAc) to obtain 68.2 mg (0.24 mmol, 24%) of product as a colorless solid. *R*_f = 0.30 (EtOAc).

Procedure for the One-Pot Protection and Acetylation. 194.2 mg (1.00 mmol, 1.00 equiv) of methyl α -D-glucopyranoside, 152.2 mg (150.7 μ L, 1.00 mmol, 1.00 equiv) of benzaldehyde dimethyl acetal, 0.3 mg (0.001 mmol, 0.001 equiv) of camphor sulfonic acid, and 5000 mg 4 Å were suspended in 100 mL of dry toluene and refluxed for 3 h. After cooling to rt, 35.5 mg (0.05 mmol, 0.05 equiv) of peptide catalyst **2** and 132.7 mg (122.9 μ L, 1.30 mmol, 1.3 equiv) of acetic anhydride were added and stirred for 18 h. It was then filtered, quenched with 1 mL methanol, and concentrated under reduced pressure. The crude product was purified via column chromatography (*n*-hexane/EtOAc 4:1 \rightarrow 1:1) to obtain 15.3 mg (0.04 mmol, 4%) of **3c**, 70.0 mg (0.22 mmol, 22%) of **3a**, and 16.8 mg (0.05 mmol, 5%) of **3b**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.0c02772>.

Additional results, superimposed ¹H NMR spectra, catalyst screening and DoE, and NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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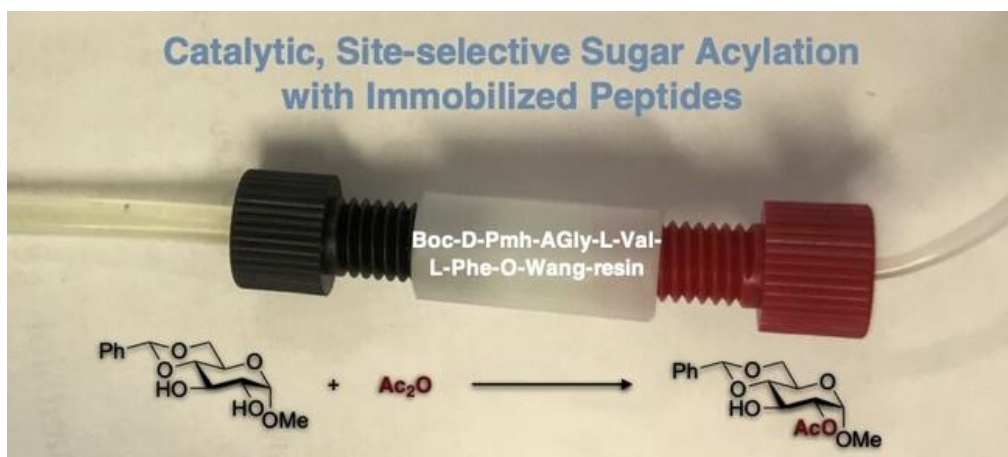
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2.2 Site-Selective Acylation of Pyranosides with Immobilized Oligopeptide Catalysts in Flow



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.”

Reference

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

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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

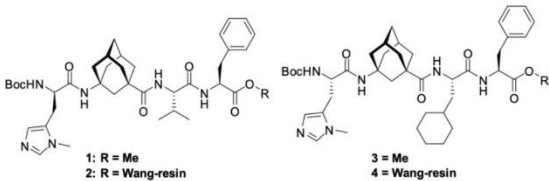
We commenced our investigation by immobilizing highly active catalyst 1 (Table 1)^[15,44] on Wang-resin using solid-phase peptide synthesis (SPPS) without cleaving the catalyst from the resin, and performed the acetylation of methyl-4,6-*O*-benzylidene- α -D-glucopyranoside (5). Although this catalyst 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-

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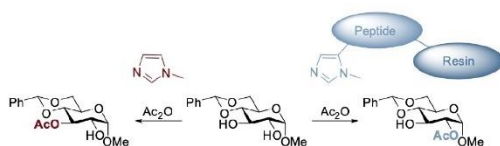
This manuscript is part of a joint special collection on Mechanisms and Selectivities of Organic Reactions – In Celebration of Prof. Kendall N. Houk's 80th birthday.

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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	5 a [%]	5 b [%]	5 c [%]	C (%)	Selectivity [%] ^[d]
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] $x = 5a / (5a + 5b + 5c) \times 100$; Product ratios and conversions determined via ¹H NMR spectroscopy.

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

tion 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-glu-

copyranoside (**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 occurring 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,

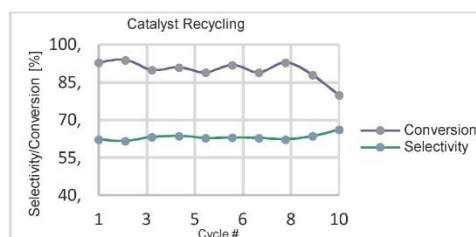
**Figure 2.** Using immobilized catalyst **2** in up to ten reaction cycles.

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

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

[a] $x = \text{Xa}/(\text{Xa} + \text{Xb} + \text{Xc}) \times 100$; Product ratios and conversions determined via ¹H NMR spectroscopy.

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

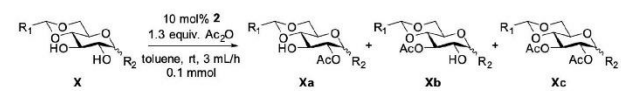
In the first experiment we used the standard conditions (0.1 mmol of starting material, 10 mL toluene, 1.3 equiv. acetic anhydride) and a flow of 2 mL h⁻¹. Unfortunately, the starting material did not dissolve completely and some of it had to be filtered off before running the experiment. Still, we were 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

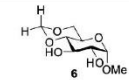
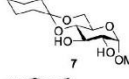
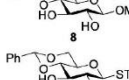
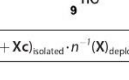
product (Table 3, Entry 1), compared to the experiments in a flask (Table 1, Entry 3). Similar results were achieved by conducting the reaction at 3 mL h⁻¹ (Table 3, Entry 2) but at 4 mL h⁻¹ the amount of isolated material compared to deployed material dropped and less diacetylated product 5c as well 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.

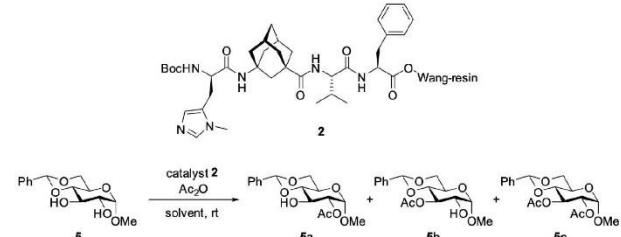
Entry	Flow/mL h ⁻¹	Volume/mL (solvent)					C [%]	IM [%] ^[a]
			5a [%]	5b [%]	5c [%]	C [%]		
1	2	10 (toluene)	57	29	12	98	80	
2	3	10 (toluene)	58	28	13	99	85	
3	4	10 (toluene)	57	28	11	96	66	
4	4	10 (DCM)	23	12	–	35	97	
5	4	15 (toluene)	57	27	6	90	94	
6	6	15 (toluene)	55	25	6	86	77	

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

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


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

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

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


Entry	Flow/mL h ⁻¹	Solvent	Reaction Scale [mmol]	Equiv. Ac ₂ O	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 ^[d]	20 ^[d]	7 ^[d]	–	–	66
5 ^[e]	4	Toluene/DCM (10:1)	1.7	2.0	54 ^[e]	23 ^[e]	6 ^[e]	–	–	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 ^[f]	19 ^[f]	4 ^[f]	–	–	68
8 ^[h]	4	Toluene/DCM (10:1)	4.4	2.0	56 ^[h]	24 ^[h]	6 ^[h]	–	–	65

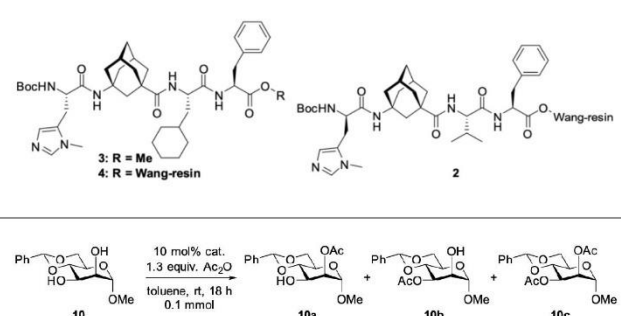
[a] IM = $n(5 + 5a + 5b + 5c)_{\text{isolated}} \cdot n^{-1}(5)_{\text{deployed}}$; [b] $x = 5a / (5a + 5b + 5c) \times 100$; [c] Yield of isolated product; [d] 96 h flow time; [e] 72 h flow time; [f] 7 was used as starting material; [g] 24 h flow time; [h] 184 h flow time; Product ratios and conversions determined via ¹H 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	10 a [%]	10 b [%]	10 c [%]	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. Ac₂O; [c] reaction performed in flow: 4 mL h⁻¹; [d] IM = $n(10 + 10a + 10b + 10c)_{\text{isolated}} \cdot n^{-1}(10)_{\text{deployed}}$; [e] $x = 10a/(10a + 10b + 10c) \times 100$; Product ratios and conversions determined via ¹H 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 \times 3 mL), DCM (5 \times 3 mL), and DMF (5 \times 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 μ L, 1.2 mmol, 4.0 equiv.) in 2.5 mL DMF. After washing with DMF (5 \times 3 mL), DCM (5 \times 3 mL), and DMF (5 \times 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-^AGly-OH (2 \times 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 \times 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 \times 3 mL), EtOAc (5 \times 3 mL), and Et₂O (5 \times 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/Et₃N/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 ¹H 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.

Keywords: acylation · immobilization · monosaccharides · non-covalent interactions · organocatalysis

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3 Appendix

3.1 List of Publications in Peer Reviewed Journals

R. C. Wende, A. Seitz, D. Niedek, S. M. M. Schuler, C. Hofmann, J. Becker, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2016**, 55, 2719.

D. Niedek, S. M. M. Schuler, C. Eschmann, R.C. Wende, A. Seitz, F. Keul, P. R. Schreiner, *Synthesis* **2017**; 49 (02), 371.

D. Niedek, F. R. Erb, C. Topp, A. Seitz, R. C. Wende, A. K. Eckhardt, J. Kind, D. Herold, C. M. Thiele, P. R. Schreiner *J. Org. Chem.* **2020**, 85 (4), 1835.

A. Seitz, R. C. Wende, E. Roesner, D. Niedek, C. Topp, A. C. Colgan, E. M. McGarrigle, P. R. Schreiner, *J. Org. Chem.* **2021**, 86, 5, 3907.

A. Seitz, R. C. Wende, P. R. Schreiner, *Chem. Eur. J.* **2023**, 29, e202203002.

4 Conclusion and Outlook

During our investigations we showed that the applied oligopeptide catalyst, bearing PMH as the catalytic motif, can perform a site-selective acetylation reaction of different pyranosides. The catalysts were used in solution but could also be used immobilized onto Wang-resin without a significant loss in selectivity and reactivity. Additionally, initial experiments performed in our studies showed that an application of the peptide catalysts in a one pot multistep reaction is possible. Those results show that the first reaction of the sequence shown in Figure 15 is feasible.

Investigations performed by McGarrigle *et al.* show that thiourea catalyst **82** can perform α -selective glycosylation reactions, with pre-protected pyranosides that are very similar to the ones we investigated in our studies, to yield disaccharides **84**.⁶⁶ This indicates that the second reaction sequence is theoretically also possible. In future studies, it would be interesting to combine those two reactions in a single reaction. This can be done using the oligopeptide and the thiourea in a one pot reaction, although my initial studies show that the two catalysts might interfere with each other. Another option is to perform the initial site-selective acetylation reaction in continuous flow and have the two catalysts physically separated from each other. An additional possibility is to develop a catalyst that carries both catalytic motifs, such as **83**.

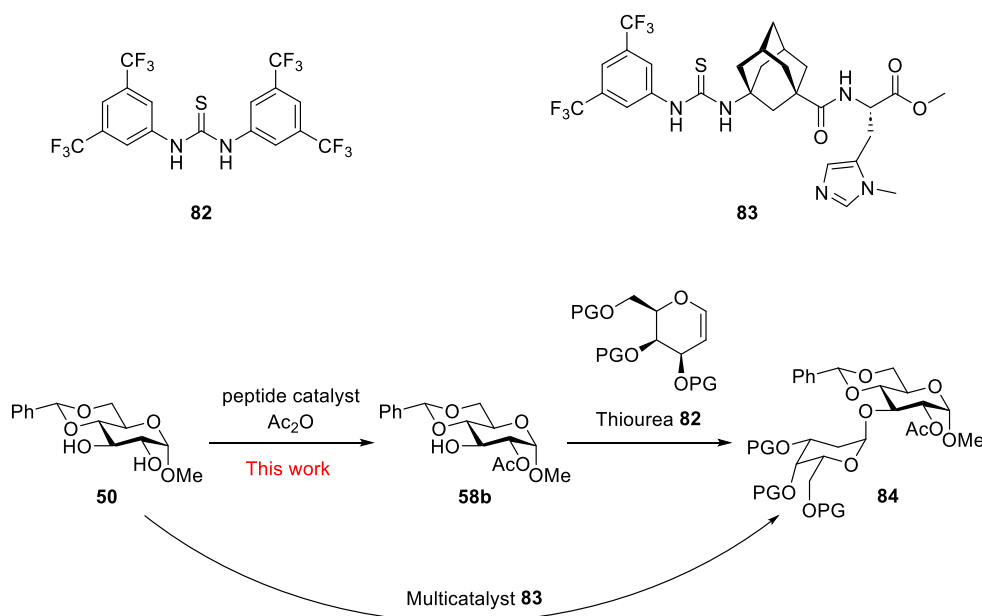


Figure 15 Application of the investigated site-selective acetylation of pyranosides using peptide catalysts in a proposed multistep reaction sequence, also showing a subsequent glycosylation reaction using thiourea **82**. A potential multistep catalyst **83**, which can theoretically catalyze both reaction steps, is also shown.

5 Abbreviations

Ac	acetyl
AcCl	acetyl chloride
Ac ₂ O	acetic anhydride
Aib	2-Aminoisobutyric acid
Asp	aspartic acid
Bn	benzyl
BOC	<i>tert</i> -butyloxycarbonyl
BTM	benzotetramisole
<i>n</i> -Bu	<i>n</i> -butyl
Bz	benzoyl
CF	continuous flow
CHCl ₃	chloroform
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DOE	design of experiments
<i>ee</i>	enantiomeric excess
Et	ethyl
Et ₃ N	triethylamine
et al.	et alli
Glu	glutamic acid
Gly	glycine
HCN	hydrogen cyanide
<i>i</i> -Pr	<i>iso</i> -propyl
<i>n</i> -Pr	<i>n</i> -propyl
mCPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
NaBH ₄	sodium borohydride
NMI	<i>N</i> -methylimidazole
PG	protecting group
Ph	phenyl
PhCH ₃	toluene
Phe	phenylalanine
PMH	π -methyl-histidine
PPY	4-pyrrolidinopyridine
Pro	proline
PS	polystyrene

Abbreviations

quant.	quantitative
rac	racemic
RT	room temperature
SPPS	solid-phase peptide synthesis
<i>t</i> -Bu	<i>tert</i> -butyl
TBS	<i>tert</i> -butyldimethylsilyl ethers
TBSCN	<i>tert</i> -butyldimethylsilylcyanid
TFAA	trifluoroacetic anhydride
TG	TentaGel
THF	tetrahydrofuran
TON	turnover number
Trt	trityl
Ts	tosyl
Val	valine

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