

Acylation

Site-Selective Acylations with Tailor-Made Catalysts

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Abstract: The acylation of alcohols catalyzed by *N,N*-dimethylamino pyridine (DMAP) is, despite its widespread use, sometimes confronted with substrate-specific problems: For example, target compounds with multiple hydroxy groups may show insufficient selectivity for one hydroxyl, and the resulting product mixtures are hardly separable. Here we describe a concept that aims at tailor-made catalysts for the site-specific acylation. To this end, we introduce a catalyst library where each entry is constructed by connecting a variable and readily tuned peptide scaffold with a catalytically active unit based on DMAP. For selected examples, we demonstrate how library screening leads to the identification of optimized catalysts, and the substrates of interest can be converted with a markedly enhanced site-selectivity compared with only DMAP. Furthermore, substrate-optimized catalysts of this type can be used to selectively convert “their” substrate in the presence of structurally similar compounds, an important requisite for reactions with mixtures of substances.

Enzymes are the standard catalysts of nature: With their variably shaped proteinogenic framework, they possess an unrivaled specificity for one substrate, optimized through multiple rounds of evolution. Enzymes are capable of fulfilling their function in a highly selective manner, and structurally similar substances in the biological system are not problematic. From a synthetic chemist's point of view, the arguably most astonishing feature is that this way nature can avoid less economic pathways as, for example, protecting group manipulations one might find in numerous synthetic organic strategies.^[1,2]

The purpose of homogeneous catalysts as used in synthetic chemistry is completely different: These catalysts are optimized for an average substrate and the goal is to have a broadly applicable catalyst that is competent enough to convert a maxi-

imum number of compounds of a certain class (i.e., “broad-spectrum catalysts”). Although recently it became accepted that the development of catalytic methods should involve the assessment of the robustness to various functional groups,^[3] current research endeavors typically do not aim to find the one catalyst that is tailor-made for one substrate. As a result, only a quite small number of concepts exist to identify substrate-optimized catalysts by mimicking natural evolution, that is, the selection from diversity, in the laboratory.^[4]

In the context of our recent studies on the defunctionalization of polyhydroxylated compounds, we became interested in the site-selective benzylation of those compounds. However, our benzylation results with DMAP as the catalyst were consistently disappointing, and product mixtures were obtained that were mostly inseparable. For example, the catalyzed benzylation of ouabagenin-derived acetone **1** led to a hardly useful 3:1:1 mixture of the benzoates **2a** and **2b** and the dibenzoylated compound **2c** (Figure 1a).^[5,6] We then developed the concept to boost the site-selectivity by connecting DMAP with a peptide scaffold. The DMAP unit of the new system should still be accountable for catalyzing the acylation^[7] while the peptidic chain was expected to influence the selectivity, ultimately affording substrate-optimized catalysts (i.e., “narrow-scope catalysts”, Figure 1b).

In quite a range of inspiring studies, Miller and co-workers demonstrated that low-molecular weight peptides are highly selective and readily tuned catalysts for a number of transformations.^[8,9] In particular, the site-selectivities obtained with polyfunctional targets underline the potential of short peptidic sequences to create high degrees of selectivity and substrate specificity, even in comparison with full grown proteins.^[10] Our idea was not to use the peptide by itself as the catalyst but to attach a catalytically active unit to the peptide core. Thus, we set out to discover DMAP-based small-molecule peptides that could convert specific substrates with a significantly higher site-selectivity than one would achieve by using mere DMAP as the acylation catalyst.

It was planned to connect the DMAP unit through chemoselective alkyne–azide cycloaddition^[11] to the peptide. To this end, pyridine **3** bearing an azide group was constructed as summarized in Figure 2a. The Fmoc-protected amino acid **4** with an additional alkyne moiety was the designed point of attachment; the synthesis of Fmoc-**4** is outlined in Figure 2b.^[12] We then created a random peptide library using automated solid-phase synthesis with Fmoc chemistry.^[13] To start the project with a reasonable number of variants, each member of the library contained between five and eight amino acids with one amino acid being **4** (Figure 2c, see Supporting Information for further details). Regarding the other amino acids, we decided

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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.201600790>.

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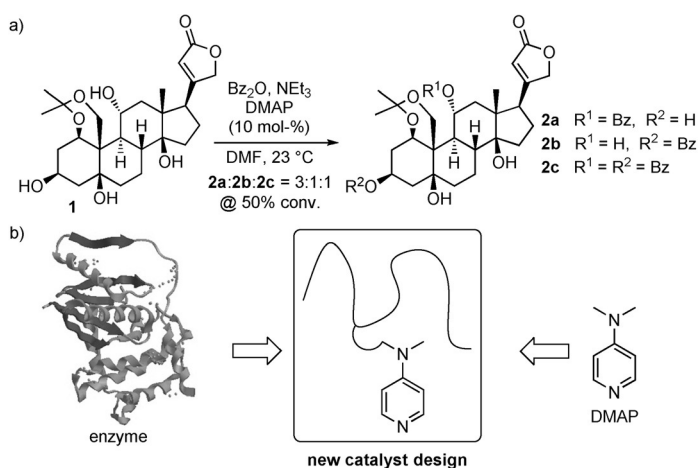


Figure 1. a) Insufficient selectivity in the DMAP catalyzed benzoylation of ouabagenin-derived **1**. b) Catalyst design consisting of peptide scaffold and DMAP unit.

to focus on a selection of 11 amino acids, Ala, Val, Leu, Pro, Phe, Thr, Ser, Gln, Asp, His, and Lys; this selection should cover the most important characteristics of the side chains, and the conceivable diversity should be suitable for a proof of concept. Of note, the peptide structures we generated possessed an acetyl group at the *N*-terminus and the *C*-terminus was the amide instead of the free carboxylic acid. While still attached to the solid-phase, the small peptides were connected with DMAP derivative **3** under standard copper-catalyzed cycloaddition conditions, thus forming the artificial amino acid **5**. Upon cleavage from the solid support, the stage was set for the activity screening of our DMAP-peptide conjugates (Figure 2 d).

For a start, it was verified that all 154 DMAP-containing peptides of our library catalyzed the acetylation of 1-phenyl-

ethanol with Ac₂O and NEt₃ in CH₂Cl₂ at room temperature. On the other hand, the peptides with amino acid **4** (i.e., no DMAP attached) showed no catalytic activity, and ester formation was typically not observed when attempting the acetylation of 1-phenylethanol. If otherwise, those sequences were not considered any further.

We then began to study whether it is possible to optimize the DMAP-catalyzed acylation of dihydroxylated substrates with regard to the site-selectivity (Figure 3). The sample reactions were typically run with almost equimolar amounts of the acylating agent and were stopped before full conversion was reached. The benzoylation of glucose-derived diol **6**, for example, gave only a poor selectivity with DMAP (**7a/7b** = 2.8:1), and significant amounts of the di-benzoylated product were found. Our library was then screened for the reaction, and we were able to obtain a strikingly higher selectivity (**7a/7b** = 28:1)

when employing 10 mol% of Ac-Val-Pro-Phe-5-Leu-Asp-NH₂; the dibenzoylated product was hardly found under the reaction conditions.^[14] Since the selective modification of sugar derivatives is of great interest, and a range of valuable strategies were developed to achieve this goal,^[15,16,17] we continued to review the performance of our screening concept in this realm. When optimizing the benzoylation of diol **8**, a compound closely similar to **6** but with an additional nitro group, Ac-Ala-Thr-5-Val-Pro-Ser-Asp-NH₂ was found to be the best hit (Figure 3 b). This result highlights how subtle changes in substrate structure can influence the screening outcome. The screening also led to optimized catalysts for the benzoylation of manno- and galactose-derived substrates. For example, mannoside **10** was monobenzoylated with a selectivity up to 5:1 for the C3-hydroxyl using Ac-Val-5-Val-Phe-Val-His-Lys-NH₂. Remarkably, the screening also revealed a catalyst (i.e., Ac-Pro-5-Asp-Val-Ser-Asp-Gln-NH₂) that gave the inversed selectivity (**11a/11b** = 2:1), albeit with low conversion. In the case of galactose-derived diol **12**, we were capable of boosting the site-selectivity of the acetylation to a ratio of 15.5 to 1 by using Ac-Ala-Thr-5-Val-Pro-Ser-Asp-NH₂, a ten-fold increase in comparison to DMAP (Figure 3 d). The optimization of the benzoylation of rhamnoside **14** was also successful: An excellent selectivity for the benzoylation of the C3-hydroxyl was found with 10 mol% of Ac-Asp-Ser-Ala-Pro-Phe-5-Pro-NH₂. Last of all, we turned back to our starting question of how to improve the benzoylation of ouabagenin-derived acetonide **1** (Figure 3 f). To our delight, we could significantly raise the ratio between the benzoates **2a** and **2b** from 3:1 to 33.3:1 by applying our concept. It was found through screening of the library of DMAP-peptide conjugates that the catalyst of choice was Ac-Val-5-Phe-Pro-Ala-Leu-Lys-NH₂, in this case.

We then questioned whether our screening hits were also suited to make preparative scale acylations possible. To this end, several substrates were examined, and the respective acylation reactions were run until complete conversion, in the presence of 10 mol% of the optimized catalysts that were identified from the screening. We were pleased to find that

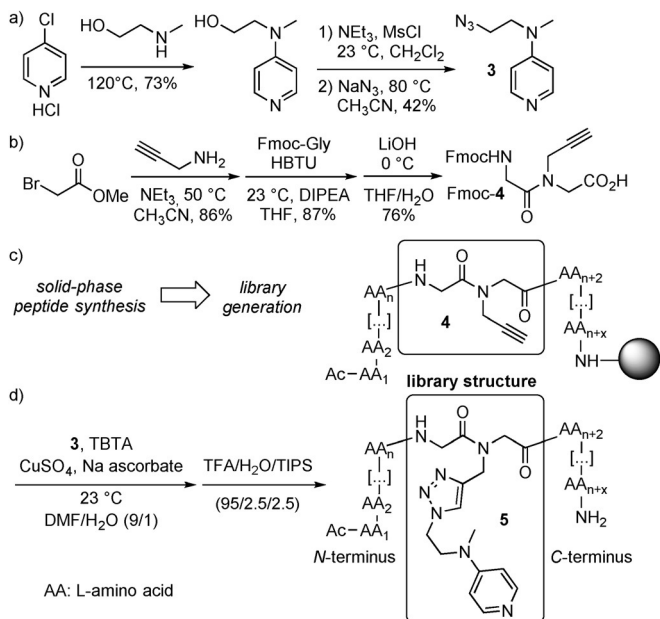


Figure 2. a) Synthesis of **3**. b) Synthesis of Fmoc-**4**. c) Creation of peptide libraries through Fmoc-SPPS. d) Synthesis of DMAP-peptide conjugates.

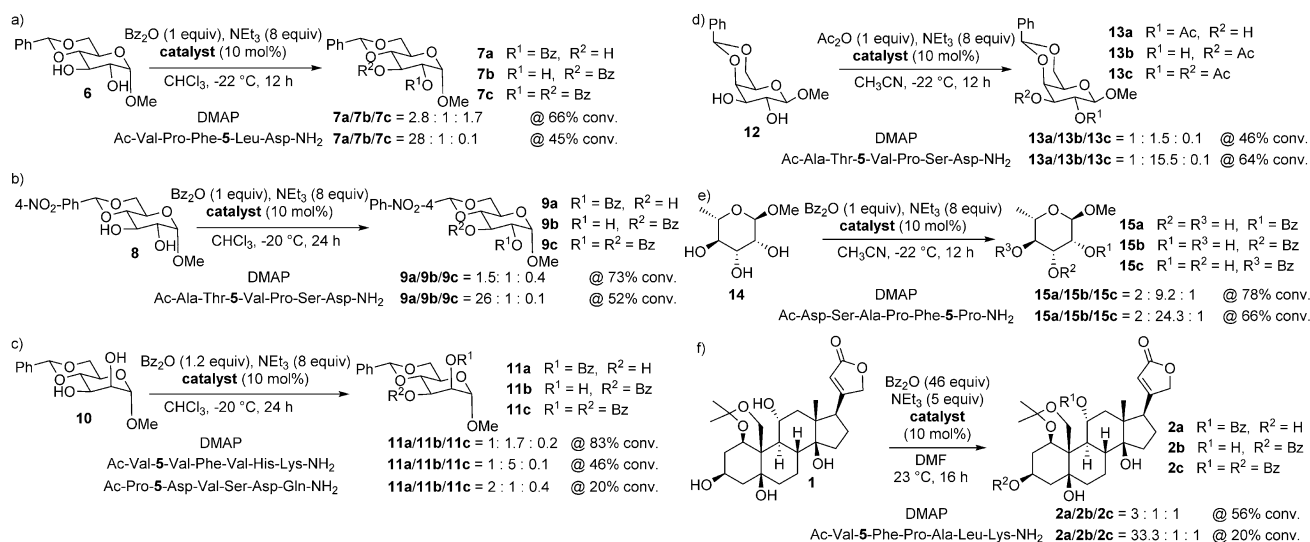
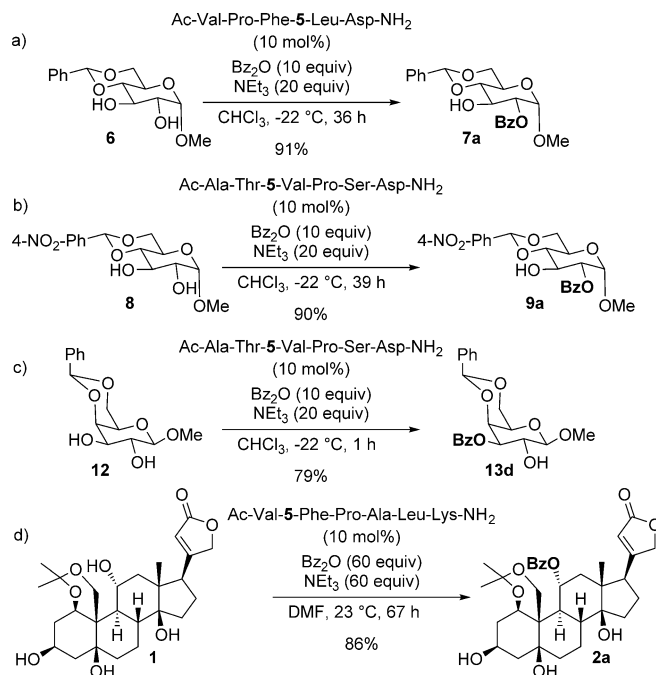


Figure 3. Selected examples for the optimization of the site-selectivity of acylations by use of DMAP-peptide conjugates. Product ratios were determined as detailed in the supporting information.

the selected catalysts performed their specific tasks properly with high isolated yields for the desired products (Scheme 1). For example, benzoate **7a** was obtained in 91% yield from diol **6**; Ac-Val-Pro-Phe-5-Leu-Asp-NH₂ was tailor-made for this transformation. Despite the huge excess of Bz₂O and elongated reaction times, the formation of the dibenzoylated product **7c** was not observed. Other substrates (e.g., **8** and **12**) reacted equally well with their optimized catalysts. Of particular importance to us was the reaction of ouabagenin-derived acetonide **1** that gave benzoate **2a** in excellent 86% yield by use of 10 mol% of Ac-Val-5-Phe-Pro-Ala-Leu-Lys-NH₂.

Notably, at the outset of the study, we were unclear as to whether our screening concept can produce a substrate-specific hit with markedly better performance than DMAP as our random library was, admittedly, rather small (154 entries). This lack of diversity was a particular concern since we had deliberately abstained from any models and assumptions on what peptide sequences would be optimal. Therefore, we were delighted to find that efficient catalysts, superior to DMAP in terms of site-selectivity, were identified for all the challenges where the concept was put to test.^[18]

We briefly demonstrated that the library screening can also produce substrate-optimized catalysts that can be used to selectively convert one substrate in the presence of structurally similar compounds (Figure 4).^[19] For example, an equimolar mixture of glucose-derived diol **6** and the analogous mannose derivative **10** yielded a hardly separable mixture of the benzoates **7a**, **7b**, **11a** and **11b** when treated with Bz₂O and catalytic amounts of DMAP. On the contrary, our best hit from the library was Ac-Lys-Leu-Leu-Gln-Ala-Pro-5-NH₂, which gave an excellent selectivity for the formation of the benzoylated glucoside **7a** while leaving mannoside **10** mostly untouched (Figure 4a). On a preparative scale, we were able to isolate **7a** in 91% yield, and 52% of the starting compound **10** could be recovered under the reaction conditions: **6** (1 equiv), **10**



Scheme 1. Isolated yields for selected acylations by use of tailor-made DMAP-peptide conjugates.

(1 equiv), Ac-Lys-Leu-Leu-Gln-Ala-Pro-5-NH₂ (10 mol%), Bz₂O (5 equiv), NEt₃ (15 equiv), -15°C , 38 h, CHCl_3 . Although most of the substrates we tested so far were derived from carbohydrates, our concept is not restricted to this class of substrates. As shown in Figure 4b, we were able to selectively convert deoxycholic acid (**16**) into its acetate **18**; with Ac-Asp-Thr-Lys-5-Ser-Asp-His-Leu-NH₂ as the catalyst of choice, the present cholesterol (**17**) remained mainly unreacted, even after 12 h of reaction and with an excess of Ac₂O. Under the same set of

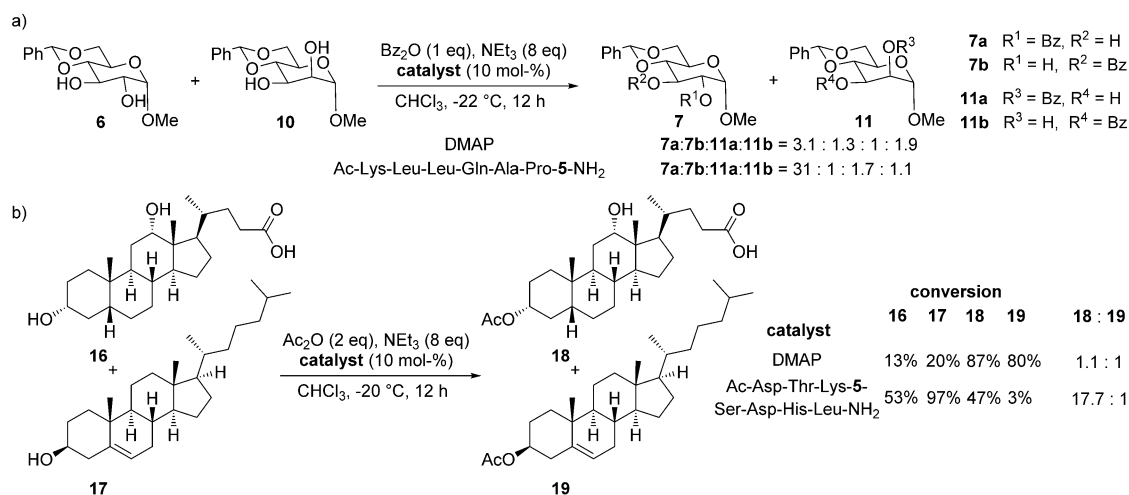


Figure 4. Selective acylations with mixtures of substrates.

conditions, DMAP gave an almost 1:1 mixture of acetates **18** and **19**.

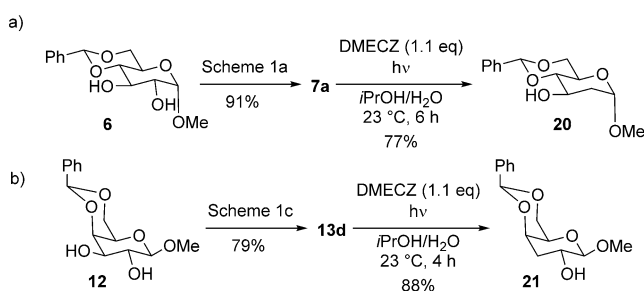
Finally, we intend to highlight how the site-selective benzylation can be used to rapidly produce deoxygenated molecules if the benzoates are fully removed through photosensitized deoxygenation with, for example, 3,6-dimethyl-9-ethylcarbazole (DMECZ) as the photosensitizer.^[20] As outlined in Scheme 2, the combination of the two methodologies, that is, the catalyzed benzylation followed by the photosensitized deoxygenation, has potential to streamline synthetic sequences by reducing the need for protecting groups. Glucopyranoside **6** was converted into the 2-deoxy compound **20** in a highly straightforward manner with this two-step sequence (70% yield over two steps). Galactopyranoside **12** was deoxygenated in 70% yield using the same sequence. Further applications will be reported in due course.

to the selection of catalysts tailor-made for the site-selective acylation of the target molecules. We have also shown that this concept has potential in optimizing the reactions of compound mixtures, where the desired acylation of one compound is to be paired with the other compound remaining unreactive.

Acknowledgements

We gratefully acknowledge the experimental works by M.Sc. Arik Möller on the ouabagenin defunctionalization.

Keywords: acylations · catalysis · libraries · peptides · regioselectivity



Scheme 2. Site-selective deoxygenations via benzoate intermediates.

In summary, we have presented a concept where catalytically active units were combined with a library of small molecule peptides with the goal to identify optimized catalysts through library screening. Although, in general, every type of catalytically active unit may be attached to the peptide core, and other catalyst-peptide conjugates will be described in the future by us, this paper focused solely on DMAP-based acylation catalysts: It was demonstrated how library screening led

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Received: February 19, 2016

Published online on March 10, 2016