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Conformational control of tetrahydropyran-based hybrid dipeptide catalysts improves activity and stereoselectivity

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Dedicated to Professor Victor S. Martín on the occasion of his 65th birthday.

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Abstract. Herein, we introduce and demonstrate how carbohydrates can be used as conformational control units of organocatalysts to tune their catalytic properties. New hybrid dipeptide-like organocatalysts based on ζ-sugar aminoacids and proline were prepared and tested for the asymmetric Michael addition of aldehydes to β-nitrostyrenes. Taking full advantage of the modular nature of the carbohydrate motif, both reactivity and stereoselectivity were significantly improved. By simple structural changes, such as the elimination of the methoxy group in the C4 position of the tetrahydropyran ring, we obtained two complementary catalysts that allow access to both enantiomers of the γ-nitroaldehydes with excellent yields, diastereoselectivity, and enantiomeric excesses between 97 and 99%, using a catalytic load even below 1 mol%.

Keywords: organocatalysis; asymmetric catalysis; Michael addition; noncovalent interactions; peptides

Conformation plays a fundamental role in the biological properties of numerous molecules, and its control in flexible systems is both a goal and a great challenge for chemists. The importance of conformational control also extends to organocatalysis, where several studies have pointed out the undeniable correlation between conformation and catalytic properties.[1] Especially noteworthy are those performed by Miller and co-workers with small peptides,[2] by Jacobsen and co-workers with the pyrrolidinoamido-thioureas[3] and by Wennemers and co-workers with the tripeptides Pro-Pro/Pip-Glu.[4] Therefore, the search for new strategies to control the conformational equilibria is desirable, and the incorporation of new molecular scaffolds into organocatalysts bears great potential to modulate their conformation and function.

On this point, we consider that sugar amino acids (SAAs) display several advantageous features for catalyst design, such as the controllable and partially predictable conformational restriction, and the possibility to precisely modulate their chemical functionality and stereochemistry. Diverse types of furanoid and pyranoid α-, β-, γ- and δ-SAAs have been described as peptide building blocks and used as conformationally constrained scaffolds.[5] Previous work by our group showed that the tetrahydropyran units linked through C2 and C3 positions display inherent conformational preferences in some macrooligolides and chiral receptors,[6] and this structural topology was extended to the synthesis of cyclopeptides with well-defined conformations. In this case, the conformation of the cyclodipeptides depends significantly on the presence or lack of the methoxy group at the C4 position of the tetrahydropyran. The crystal structures showed a folded structure when the methoxy group is present, and unfolded when it is absent (Figure 1a).[7] These conformations are adopted mainly due to the internal network of noncovalent interactions. A similar result was also observed in solution, with a predominance of these conformations in aprotic solvents. In order to check the influence of the methoxy group, NMR and FT-IR studies were performed in model compounds without the macrocycle constraints (Figure 1b). In the model with the methoxy group, the amide proton displays a large vicinal coupling constant with the proton at the C3 position of the tetrahydropyran ($^3J_{NH\text{-}C3H}$ = 10.1 Hz), which corresponds to an antiperiplanar arrangement (H-N-C3-H ≈ ±172°). This indicates that the N-H is located equidistantly between the tetrahydropyran oxygen and the methoxy group at the C4 position. However, the model without the methoxy group displays a lower vicinal coupling constant of $^3J_{NH\text{-}C3H}$ = 8.3 Hz, which corresponds to a dihedral angle of H-N-C3-H ≈ ±151°, indicating that the N-H is directed

towards the tetrahydropyran oxygen. Therefore, the role of the methoxy group is to control the rotation of the N-C3 bond.[7]

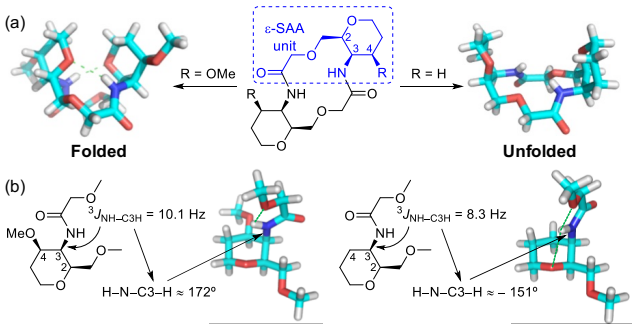


Figure 1. (a) Crystal structures of cyclodipeptides based on ε-SAAs. (b) Structures, vicinal coupling constants ($^3J_{NH-C3H}$) and dihedral angles (H-N-C3-H) in $CDCl_3$ (7 mM) for the model compounds without the macrocycle constraints.

Recently, we found that hybrid dipeptides based on ε- or ζ-sugar amino acids (SAAs) and proline efficiently catalyze the Michael addition of aldehydes to β-nitrostyrenes.[8] This reaction has found widespread use as a benchmark reaction to explore the potential of new orgonocatalysts. Among the most efficient systems for this asymmetric Michael addition[9,10] are the tripeptidic catalysts (Pro-Pro/Pip-Asp/Glu) found by Wennemers and coworkers.[11] Small peptides have emerged as organocatalysts because they offer many sites for structural and functional diversity, compared to a single amino acid, providing fine-tuning of their catalytic properties.[2,12] These tripeptidic catalysts work without any additives, without the formation of side products, and using catalytic loads even below 1 mol% (Figure 2a).[4,11] The success of these bifunctional catalysts is due to a well-defined β-turn conformation induced by the D-Pro-Pro/Pip motifs, which provide an optimal arrangement between the *N*-terminus pyrrolidine (for enamine formation) and the *C*-terminus carboxylic acid (for the protonation of the iminium nitronate intermediate). In contrast, in our hybrid catalysts the carbohydrate motifs are embedded in the ε- or ζ-amino acids, thus providing similar arrangements between the carboxylic acid and the pyrrolidine as the D-Pro-Pro/Pip motifs of the Wennemers catalysts. Hereby we combined two highly modular building blocks: carbohydrates and amino acids. Our initially envisioned structure had a methoxy group at the C4 equatorial position of the tetrahydropyran ring to stabilize its chair conformation (Figure 2b, R = OMe).[8] However, taking into account the conformational behavior found in the cyclodipeptides and the model compounds (Figure 1), we decided to remove the methoxy group from our dipeptidic catalysts. Our expectation was that a similar conformational change would take place in the intermediate enamine, and this could result in better reactivity and selectivity.

Herein, we report how a simple change in the carbohydrate motif of these hybrid dipeptides dramatically improved the catalytic activity and stereoselectivity in the Michael addition of aldehydes to β-nitrostyrenes (Figure 2b, R = H).

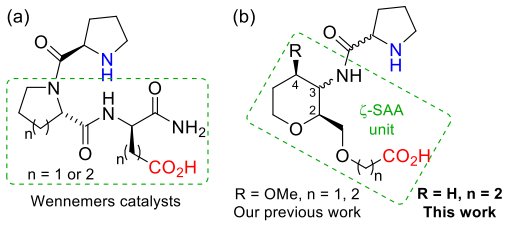
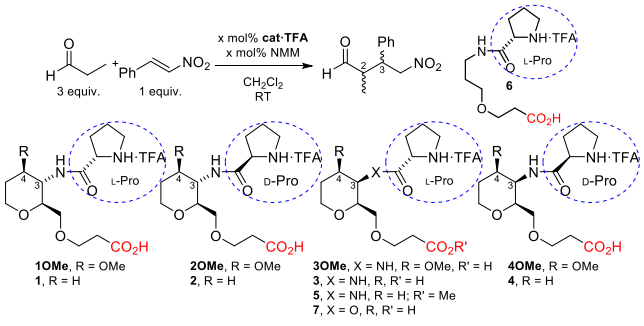


Figure 2. (a) Tripeptidic catalysts (Pro-Pro/Pip-Asp/Glu) found by Wen-nemers. (b) Dipeptidic catalysts based on SAAs.

Therefore, four new catalysts **1-4** were prepared without the methoxy group at the C4 position of the tetrahydropyran, by changing the stereochemistries of the proline and the C3 in the tetrahydropyran.[13] Their catalytic properties were compared with catalysts bearing the methoxy group **1OMe-4OMe**. As a proof of concept, we chose the Michael addition of aldehydes to nitrostyrenes, and more specifically, the addition of propanal to *trans*-β-nitrostyrene (Table 1). All reactions were performed at room temperature with the trifluoroacetic acid (TFA) salts of the dipeptides, the corresponding equivalent of *N*-methylmorpholine (NMM) to neutralize the ammonium salt, and 3 equivalents of propanal for each equivalent of *trans*-β-nitrostyrene in CH_2Cl_2 (0.1M).[14] In general, better results were observed with the catalysts without the methoxy group. The best enantiomeric excesses were obtained with catalysts **2** and **3** (Table 1, entries 4 and 6), although the diastereomeric ratios were modest. It should be noted that these two catalysts are complementary, one of them gives an enantiomer, while the other provides the opposite enantiomer with a similar enantiomeric excess. Catalyst **3** was very reactive and this allowed us to reduce the catalytic load to 3 or 1 mol%, thus improving diastereoselectivity and enantioselectivity and upholding the excellent conversion (Table 1, entries 9 and 10).

Table 1. Catalyst screening and optimization of reaction conditions.



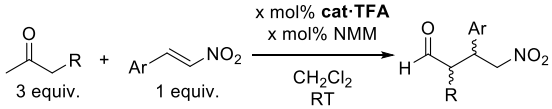
Entry[a]	Cat.	mol%	Time [h]	Conv. [%][b]	*syn*:*anti*[b]	*ee* (%)[c]
1	**1OMe**	5	22	74	6:1	85 (2*R*,3*S*)
2	**1**	5	22	90	7:1	89 (2*R*,3*S*)
3[d]	**2OMe**	5	22	quant.	7:1	93 (2*S*,3*R*)
4	**2**	5	22	quant.	4:1	97 (2*S*,3*R*)
5[d]	**3OMe**	5	20	quant.	7:1	92 (2*R*,3*S*)
6	**3**	5	4	quant.	2:1	97 (2*R*,3*S*)
7	**4OMe**	5	48	76	4:1	66 (2*S*,3*R*)
8	**4**	5	48	98	4:1	71 (2*S*,3*R*)
9	**3**	3	4	99	7:1	97 (2*R*,3*S*)
10	**3**	1	10	97	21:1	98 (2*R*,3*S*)
11[e,f]	**3**	1	9	99	56:1	99 (2*R*,3*S*)
12[e,g]	**3**	1	9	99	70:1	98 (2*R*,3*S*)
13[e,h]	**3**	1	9	95	56:1	97 (2*R*,3*S*)
14	**5**	1	67	11	6:1	-
15	**6**	1	18	76	6:1	91 (2*R*,3*S*)
16	**7**	5	2	quant.	2:1	86 (2*R*,3*S*)

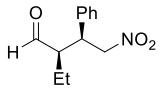
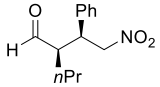
[a] All reactions were carried out at 0.1 mmol scale in dry CH_2Cl_2 at 0.1M.
[b] Determined by ^1H NMR spectroscopy of the reaction mixture.
[c] Determined by chiral HPLC, Chiralpak IC-3, *n*-hexane:*i*-PrOH (7:3).
[d] Data taken from ref [8].
[e] In this case, *n*-butanal was used.
[f] at 0.1 M.
[g] at 0.2 M.
[h] at 0.5 M.

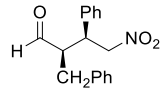
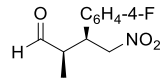
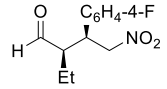
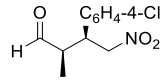
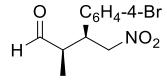
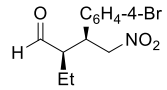
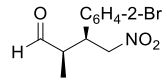
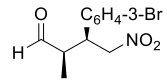
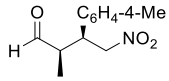
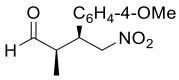
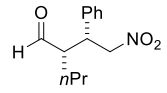
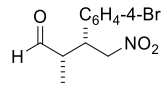
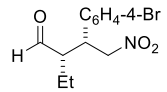
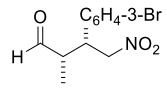
The concentration of the reactions was also studied, verifying that the best results were obtained at 0.1 M (Table 1, entries 11-13). Furthermore, we confirmed that the carboxylic acid is necessary for the reaction to take place, since when catalyst **3** was converted to the methyl ester **5** the reaction failed (Table 1, entry 14). This supports the idea of the bifunctional nature of these catalysts, where the carboxylic acid moiety is placed in an appropriate position to activate the nitrostyrene and acts as a proton donor to the iminium nitronate intermediate. To check the influence of the carbohydrate moiety, a model catalyst **6** that lacks the tetrahydropyran ring was synthesized. Catalyst **6** showed worse enantioselectivity than catalysts **2** and **3**, confirming that the tetrahydropyran ring contributes to the stereochemical course of the reaction (Table 1, entry 15). In addition, a decrease in enantioselectivity was also observed with catalyst **7**, which is the same as catalyst **3** but possessing an ester instead of an amide (Table 1, entry 16). This indicates the importance of the amide group in the conformational control of the catalyst. Clearly, the stereochemistry of the final product depends on the proline fragment used. However, the high enantiomeric excesses observed depend on a suitable configuration of the tetrahydropyran ring and the conformation adopted by the entire system.[15]

Once we established the catalytic load (1 mol%) providing the best diastereo- and enantioselectivity, the next step was to evaluate the scope of catalyst **3**. This was tested using several *trans*-β-nitrostyrenes and aldehydes, from the most activated *trans*-β-nitrostyrenes, such as those with electron-poor aromatic moieties (Table 2, entries 7-15), to the least reactive ones with electron-rich aromatic moieties, such as *p*-methoxy- or *p*-methyl-*trans*-β-nitrostyrenes (Table 2, entries 16 and 17). In all cases, the desired γ-nitroaldehyde products were obtained with excellent conversions and yields, and enantiomeric excesses between 97 and 99% (Table 2). The diastereomeric and enantiomeric ratios were better when longer-chain aldehydes such as *n*-butanal or *n*-pentanal were used. Catalyst **3MeO**, which bears the methoxy group, was examined under the same reaction conditions and with the same catalytic load (1 mol%), obtaining worse results in terms of yields, and diastereo- and enantioselectivity (Table 2, entries 4, 11 and 13). Considering the high efficiency of catalyst **3**, it was also possible to reduce the catalytic load to 0.5 mol% and even to 0.2 mol%, without loss of enantiomeric excess (Table 2, entries 2 and 3). We also had the advantage of having a complementary catalyst available, catalyst **2**, that allows accessing the opposite enantiomers with excellent yields, diastereoselectivities and enantioselectivities (between 97 and 99% *ee*) using 1 mol% of catalytic load (Table 2, entries 18, 19, 21 and 23). It should be noted that these two catalysts **2** and **3** are diastereoisomers and behave as pseudoenantiomeric catalysts. Again, catalyst **2**, which lacks the methoxy group, displays better results in terms of yields, and enantio- and diastereoselectivity than its analog catalyst **2MeO**, previously reported by our group (Table 2, entries 20, 22 and 24), even using lower catalytic loads.[8]

Table 2. Substrate scope of conjugate addition reactions between aldehydes and trans-β-nitrostyrenes catalyzed by dipeptides **2**, **2OMe**, **3** and **3OMe**.

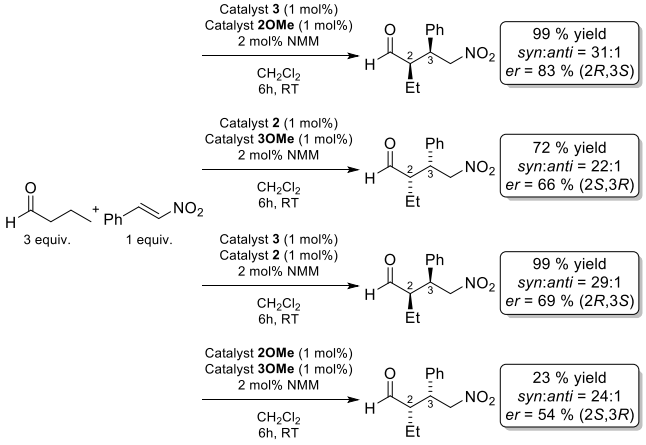


Entry[a]	Product	Catalyst (x mol%)	Time (h)	Yield (%)[b]	dr[c]	*ee* (%)[d]
1		**3** (1)	9	98	56:1	99
2		**3** (0.5)	24	94	55:1	99
3[e]		**3** (0.2)	48	85	51:1	99
4		**3OMe** (1)	50	46	61:1	89
5		**3** (1)	12	98	58:1	99

6		**3** (1)	19	quant.	44:1	98
7		**3** (1)	16	97	15:1	98
8		**3** (1)	16	98	38:1	99
9		**3** (1)	10	quant.	23:1	98
10		**3** (1)	10	quant.	25:1	99
11		**3OMe** (1)	50	80	29:1	86
12		**3** (1)	10	quant.	50:1	99
13		**3OMe** (1)	50	61	39:1	90
14		**3** (1)	24	92	17:1	97
15		**3** (1)	12	98	28:1	98
16		**3** (1)	24	96	16:1	98
17		**3** (1)	24	93	21:1	98
18		**2** (1)	24	91	42:1	99
19		**2** (1)	24	98	23:1	97
20[f]		**2MeO** (5)	6	95	9:1	92
21		**2** (1)	24	quant.	38:1	98
22[f]		**2MeO** (5)	22	97	24:1	96
23		**2** (1)	24	98	14:1	98
24[f]		**2MeO** (5)	16	98	5:1	93

[a] All reactions were carried out at 0.1 mmol scale in dry CH_2Cl_2 at 0.1M.
[b] Isolated yield.
[c] Determined by ^1H NMR spectroscopy of the reaction mixture.
[d] Determined by chiral HPLC, Chiralpak IC-3.
[e] In this case, 1.5 equivalents of *trans*-β-nitrostyrene and 1 equivalent of *n*-butanal was used.
[f] Data taken from ref [8].

Since the catalysts with the methoxy group (**2OMe** and **3OMe**) and without the methoxy group (**2** and **3**) give the same enantiomers of the final product, they cannot be directly compared. However, this can be achieved indirectly, by comparing the enantiomeric efficiency of the catalysts that provide the opposite enantiomers of the final product. In order to allow for comparison, the following assumptions were made: 1) the stereoisomer 2*S*,3*R* of the γ-nitroaldehyde is exclusively formed by the catalysts **2** and **2OMe**, while stereoisomer 2*R*,3*S* is formed by the catalysts **3** and **3OMe**, and 2) catalyst aggregation is negligible under the reaction conditions.[16] Therefore, we performed a series of competition experiments between catalysts **3** vs **2OMe**, **2** vs **3OMe**, **3** vs **2**, and **2OMe** vs **3OMe** (Scheme 1). All reactions were performed using 1 mol% of each catalyst, *n*-butanal (3 equiv.) and β-nitrostyrene (1 equiv.) in CH_2Cl_2 (0.1M) at room temperature during 6h. The competition experiment between catalysts **3** (that provides the 2*R*,3*S* γ-nitroaldehyde) and **2OMe** (that provides the 2*S*,3*R* γ-nitroaldehyde) afforded the γ-nitroaldehyde in almost quantitative yield with 83% *er* (2*R*,3*S*). This result indicates that catalyst **3** is 4.8 times more efficient than catalyst **2OMe**. The competition experiment between catalysts **2** (that provides the 2*S*,3*R* γ-nitroaldehyde) and **3OMe** (that provides the 2*R*,3*S* γ-nitroaldehyde) gave the γ-nitroaldehyde in 72% yield with 66% *er* (2*S*,3*R*), showing that catalyst **2** is almost twice as efficient as catalyst **3OMe**. The competition experiment between catalysts **3** and **2** provided the γ-nitroaldehyde in quantitative yield with 69% *er* (2*R*,3*S*). Therefore, we can assume that catalyst **3** is 2.3 times more efficient than catalyst **2**. Finally, the competition experiment between catalysts **2OMe** and **3OMe** provided the γ-nitroaldehyde in 23% yield with 54% *er* (2*S*,3*R*), hence catalyst **2OMe** is 1.2 times more efficient than catalyst **3OMe**. Taking these results into account, we can state that removing the methoxy group from the catalyst (from **3OMe** to **3**) improves the catalytic efficiency 5.0 ± 0.9 times. Something similar occurs when the catalyst **2OMe** is compared with its analogue without the methoxy group, namely catalyst **2**: the catalytic efficiency was found to increase by a factor of 1.9 ± 0.3.



Scheme 1. Catalyst competition experiments.

In conclusion, through a rational design, new hybrid dipeptide catalysts based on sugar amino acids have

been developed using as starting point Wennemers tripeptides. These dipeptides were able to catalyze asymmetric 1,4-additions of aldehydes to β-nitrostyrenes. Such catalysts combine two highly-modular building blocks: amino acids and carbohydrates. The carbohydrate motif is embedded in the ζ-aminoacids, which are coupled with a proline to obtain the dipeptide. The bifunctional nature of these organocatalysts and the significance of the tetrahydropyran unit in their reactivity and stereoselectivity were also demonstrated. The present work also emphasizes the modular nature of the carbohydrate unit that facilitates tuning of the dipeptide catalytic properties. By simple structural changes, such as the elimination of the methoxy group at the C4 position of the tetrahydropyran ring, a significant improvement in the catalytic performance was achieved. We also benefit from two complementary catalysts that allow accessing both enantiomers of the γ-nitroaldehydes, with similar yields, and diastereo- and enantioselectivity, using catalytic loads even below 1 mol%. It should be noted that these catalysts work in a single solvent system, at room temperature and without the use of additives. Additionally, using competition experiments between catalysts that provide opposite enantiomers, we were able to quantify the improvement of the catalytic efficiency. The structural design of these organocatalysts offers enormous possibilities of modulation by changing substituents or stereochemistry in the carbohydrate unit. In this way, they could be adapted and extended to different types of reactions. Current work is ongoing in this direction and our progress will be published in due time.

Experimental Section

For detailed experimental information and the characterization of compounds, see the supporting information.

General Procedure

The β-nitrostyrene (1.0 equiv) and the aldehyde (3.0 equiv) were added to a solution of dipeptide (0.01 equiv) and *N*-methylmorpholine (0.01 equiv) in dichloromethane at room temperature. The reaction mixture was stirred until TLC showed the end of the reaction. The solvents were removed under vacuum and the crude was purified by a chromatography column with silica gel using mixtures of hexanes and ethyl acetate as eluent.

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[13] For details of catalyst synthesis see the Supporting information.

[14] Optimal conditions (solvent, concentration, temperature) were previously established for those catalysts bearing methoxy group **1OMe-4OMe**, see reference 8, and applied for the new catalysts without the methoxy group.

[15] At this point of the study the question remains whether the improve in reactivity and selectivity observed upon elimination of the methoxy group is exclusively associated to conformational factors, as possible electronic effects cannot be ruled out.

[16] The formation of dimers or aggregates between the catalysts is unlikely because of very low catalyst concentration (0.001 M). In addition, in Table 1 (entries 11, 12 and 13) where the catalyst concentration were 0.001, 0.002 and 0.005 M respectively, the results obtained did not show significant variation in terms of yield, diastereomeric ratio and enantiomeric excess.

Conformational control of tetrahydropyran-based hybrid dipeptide catalysts improves activity and stereoselectivity

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