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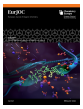

Asymmetric Organocatalysis Accelerated via Self-Assembled Minimal Structures

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Self-assembling minimalistic peptides embedded with an organocatalytic moiety were designed. By controlling the formation of fibrils via external intervention, it was shown that the activation is accelerated when the organocatalyst is in its supramolecular state. The effect of the accelerated catalysis was demonstrated in a Michael benchmark reaction.

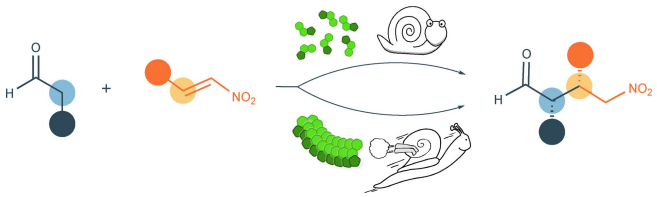
Over the last two decades asymmetric organocatalysts gained a prominent role in modern research;[1–3] its often low turnover may be tackled by immobilization, recycle, engineering highly active catalysts,[4] or combining different types of catalysts synergistically.[5] On a more complex level, molecular machines have been used in organocatalysis.[6] On the other hand, self-assembling short peptides have attracted great interest;[7] derivatives of the dipeptide Phe-Phe stand out, thanks to the high propensity towards fibrillization in a variety of solvents, giving scope for chemical diversity of the building blocks.[8–10]

Combining self-assembly of short peptides and organocatalysis, we embarked in a proof of concept to accelerate organocatalysis. We surmised that self-assembling minimalistic peptides embedded with an organocatalytic moiety could be designed. Creating a lipophilic pocket and excluding water from its structure, an easily prepared peptide could function as an enhanced organocatalyst in its supramolecular assembly; it might also provide a cooperative interaction of different functions of the structure, or its activity be switched on and off, or from one type of catalysis to another.[8,11] There are examples, albeit limited, of simple catalytic activity with self-assembled structures.[12,13]

Proline and its derivatives have a prominent role in organocatalysis. Proline-containing amphiphiles in Mannich reactions,[14] proline derivatives self-assembling with other organocatalysts,[15] and a self-assembling lipopeptide featuring proline residues were previously reported.[16] However, all these examples rely on moderately complex structures.[17] Simpler catalysts, such as tripeptides, are attractive alternatives.[18] We reasoned that combining the privileged proline with the self-assembling propensity of Phe-Phe would provide supramolecular catalysts showing higher activity.

Herein, we report the first proof of concept of supramolecular fibril organocatalysts, composed solely of a tripeptide, that exhibit higher activity than their non-self-assembled structures in the Michael reaction of aldehydes to nitroalkenes (Scheme 1).

D-Pro-L-Phe-L-Phe (^{D}**PFF**) was, therefore, selected to promote aminocatalysis in aqueous media. The stereoconfiguration was chosen based on a recent study on Pro-Phe-Phe isomers which, above a critical concentration, formed macroscopic hydrogels.[19] Our rationale was that a high-ordered



Scheme 1. Enhancement of catalytic activity in a Michael reaction via a self-assembled organocatalyst.

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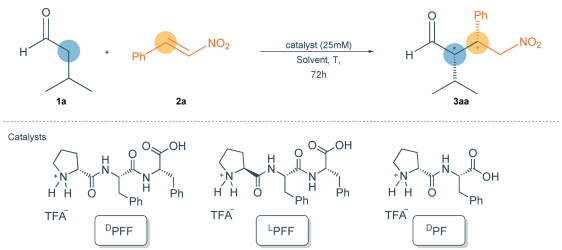
supramolecular structure is capable of creating a more organized lipophilic pocket and cooperative interactions to accelerate the catalysis. As previously reported, ^{D}**PFF** fibrils self-assembled in HFIP/H_2O and in a phosphate buffer saline solution (PBS), whereas homochiral analogue ^{L}**PFF** and the ^{D}**PF** derivative only yielded amorphous aggregates (see ESI).[19,20]

The Michael addition of isovaleraldehyde to β-nitrostyrene was chosen as a benchmark reaction to test the proof of concept of the effect on the catalytic activity of the tripeptide fibrils.[21] The aldehyde partner was chosen for its limited reactivity[22] to appreciate better the enhancement in catalysis *via* fibrils.

The reaction catalyzed by ^{D}**PFF** when no fibrils are formed (Table 1, entry 1) was compared with solvent mixtures where the peptide self-assembles (entries 2–3). HFIP/H_2O provided poor results, but a very encouraging improvement was observed in PBS (entry 3 vs 1). The lack of conversion in the uncatalyzed reaction (entry 4) proved that the PBS alone had no effect. These results were the first indication that organocatalysis could be enhanced in fibrils. The epimer peptide ^{L}**PFF** forms agglomerates and it showed only a small increase in conversion in PBS (entries 5 and 6). The best results were obtained with 5% catalyst loading (entries 3, 7–8); note that a lower catalyst loading at the same catalyst concentration means a higher reagent concentration. Increasing the temperature and the equivalents of **1a** improved the conversion without significantly affecting the ee (entries 3 vs 9–10). The outcome of ^{D}**PFF** in water and with the non-self-assembling ^{L}**PFF** in PBS at 35 °C confirmed the acceleration on catalysis imparted by fibrils (74% vs 41% and 56% conversion, entries 10–12). A further set of experiments ruled out the effect of PBS alone on the catalysis and proved that the supramolecular assembly improved the conversion rate, underpinning the initial concept that we set out to prove. In fact, comparing ^{D}**PFF** and ^{L}**PFF** is not entirely correct; experiments with ^{D}**PF**, the inferior analogue of ^{D}**PFF** that does not form fibrils, showed a negligible increase in conversion (entries 13–14).

Table 1. Optimization of reaction conditions for the addition of isovaleraldehyde **1a** to β-nitrostyrene **2a**.[a]



Entry	Cat	Cat [%]	Solvent	Conv. [%][b]	*ee* [%][c,d]
1	^{D}**PFF**	5	H_2O	17	69
2	^{D}**PFF**	5	HFIP/H_2O	7	53
3	^{D}**PFF**	5	PBS	51	72
4	–	–	PBS	<1	n.d.
5	^{L}**PFF**	5	H_2O	22	−43
6	^{L}**PFF**	5	PBS	33	−48
7	^{D}**PFF**	10	PBS	49	71
8	^{D}**PFF**	15	PBS	44	71
9[e]	^{D}**PFF**	5	PBS	64	69
10[e,f]	^{D}**PFF**	5	PBS	74	66
11[e,f]	^{D}**PFF**	5	H_2O	41	69
12[e,f]	^{L}**PFF**	5	PBS	56	−50
13[e,f]	^{D}**PF**	5	H_2O	8	70
14[e,f]	^{D}**PF**	5	PBS	12	71

[a] Reaction conditions: isovaleraldehyde **1a** (0.34 mmol, 1 equiv.), β-nitrostyrene **2a** (0.34 mmol, 1 equiv.), d.r. > 94:6 syn/anti in all cases; [b] Conversion was determined by ^{1}H NMR spectroscopy; [c] ee reported of syn (major) diastereomer; [d] The *ee* value was determined by HPLC on a chiral stationary phase; [e] Reaction performed at 35 °C; [f] Reaction performed with 2 equiv. of **1a**.

Plotting the conversion vs time, the reaction catalyzed in the presence of fibrils is clearly faster over the 24 h observed (Figure 1).

The effect on the organocatalytic addition of aldehydes **1a–g** to nitroalkenes **2a–i** was evaluated over 24 h. The catalysis promoted by the organocatalyst in its supramolecular assembly is faster and the acceleration imparted by the supramolecular assemblies is evident in all cases, proving an enhanced catalysis in fibrils (11% to 74% increments in conversion, Table 2). Aldehyde **1b**, probably thanks to its smaller size, proved to be the one that benefitted the most from the fibrils (entry 2), whereas **1g** showed the smallest enhancement (entry 7), supposedly because of its steric hindrance hampering the penetration in the fibrils. In general, the acceleration of the reaction is comparable for all nitroalkenes, regardless of whether they are aromatic with electron-withdrawing or electron-donating groups (entries 3, 8–12), or aliphatic (entries 13–15).

Having established that supramolecular ^{D}**PFF** accelerates the catalysis of the Michael reaction, we evaluated the scope of the organocatalytic reaction between aldehydes **1a–g** and nitroalkenes **2a–i** (Table 3). Less steric hindered aldehydes provided higher yields and conversions (e.g., entries 1–3). Yields of aromatic nitroalkenes with electron-withdrawing groups (entries 8–9) were lower than the ones with electron-donating groups (entries 10–11). Aliphatic nitroalkenes proved to be less reactive. In general, all isolated yields are in good agreement with the conversion.

In conclusion, we report the first proof of concept of a simple tripeptide, featuring proline and able to self-assemble into fibrils, that accelerates organocatalysis in its supramolecular state. This approach opens interesting options to explore to accelerate organocatalysis. The nature of the self-assembling

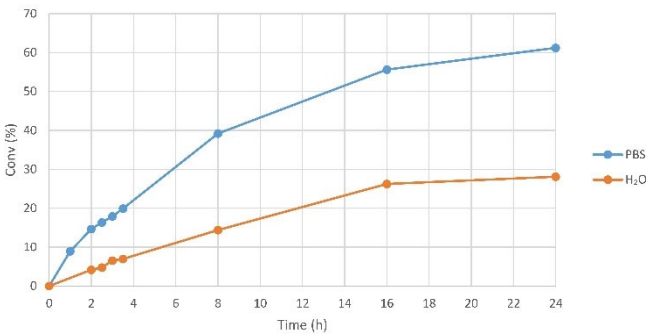
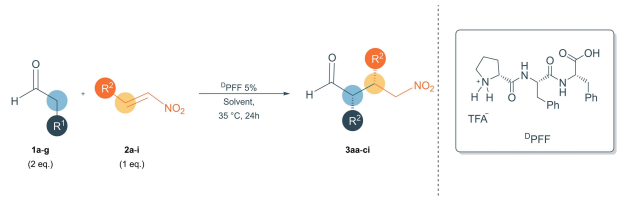


Figure 1. Comparison of the conversion to **3aa** in reactions catalyzed by ^{D}**PFF**, in PBS and H_2O over 24 h.

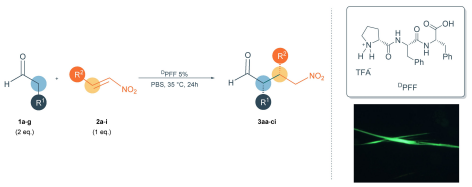
Table 2. Enhanced catalysis of fibril organocatalyst ^{D}**PFF** in the reaction of aldehydes **1a–g** with β-nitroalkenes **2a–i**.[a]



Entry	R^1	R^2	Product	Conv. [%] H_2O	Conv. [%] PBS
1	^{i}Pr	Ph	**3aa**	**28**	**61**
2	Me	Ph	**3ba**	**26**	**>95**
3	Et	Ph	**3ca**	**56**	**93**
4	Pr	Ph	**3da**	**51**	**93**
5	Bu	Ph	**3ea**	**53**	**92**
6	Ept	Ph	**3fa**	**36**	**81**
7	Bn	Ph	**3ga**	**73**	**84**
8	Et	4-ClC_6H_4	**3cb**	**49**	**>95**
9	Et	4-$NO_2C_6H_4$	**3cc**	**17**	**61**
10	Et	4-$MeOC_6H_4$	**3cd**	**33**	**74**
11	Et	4-$^{i}PrC_6H_4$	**3ce**	**24**	**61**
12	Et	2-Fur	**3cf**	**74**	**>95**
13	Et	^{i}Bu	**3cg**	**22**	**62**
14	Et	Pr	**3ch**	**27**	**61**
15	Et	$-CH_2CH_2Ph$	**3ci**	**56**	**>95**

[a] Reaction conditions: aldehyde **1a–g** (0.68 mmol, 2 equiv.), nitroalkenes **2a–i** (0.34 mmol, 1 equiv.), H_2O or PBS, ^{D}**PFF** (25 mM), 5 mol%; Conversion was determined by ^{1}H NMR spectroscopy.

Table 3. Scope of the Catalytic asymmetric Michael addition in fibrils of aldehydes **1a–g** to β-nitroalkenes **2a–i**.[a]



Entry	R^1	R^2	Product	Yield [conv.] [%]	dr	ee [%]
1[b]	^{i}Pr	Ph	**3aa**	71 (74)	98:2	66
2	Me	Ph	**3ba**	98 (>95)	90:10	71
3	Et	Ph	**3ca**	92 (93)	96:4	72
4	Pr	Ph	**3da**	87 (93)	95:5	70
5	Bu	Ph	**3ea**	86 (92)	96:4	73
6	Ept	Ph	**3fa**	78 (81)	96:4	74
7	Bn	Ph	**3ga**	83 (84)	95:5	74
8[b]	Et	4-ClC_6H_4	**3cb**	71 (>95)	95:5	68
9[b]	Et	4-$NO_2C_6H_4$	**3cc**	52[c] (62)	92:8	43
10[b]	Et	4-$MeOC_6H_4$	**3cd**	93 (>95)	95:5	70
11[b]	Et	4-$^{i}PrC_6H_4$	**3ce**	85 (>95)	94:6	70
12	Et	2-Fur	**3cf**	75 (>95)	94:6	69
13[b]	Et	^{i}Bu	**3cg**	61 (76[d])	84:16	73
14[b]	Et	Pr	**3ch**	40 (65[d])	83:17	70
15	Et	$-CH_2CH_2Ph$	**3ci**	74 (>95)	83:17	73

[a] Reaction conditions: aldehyde **1a–g** (0.68 mmol, 2 equiv.), nitroalkenes **2a–i** (0.34 mmol, 1 equiv.), PBS, ^{D}**PFF** (25 mM), 5 mol%; conversion was determined by ^{1}H NMR spectroscopy; dr determined by ^{1}H NMR analysis of the crude reaction mixture; the *ee* value was determined by HPLC on a chiral stationary phase; the *ee* values reported are for the syn diastereomer, see SI for the further data; [b] t = 72 h; [c] Yield calculated *via* qNMR; [d] Yield calculated *via* qNMR, in place of conversion, due to high volatility.

organocatalyst makes it modular and a range of amino acids can be chosen to affect the formation of fibrils. Further work is underway for the development of different organocatalytic fibrils that would deploy a range of activations based on their constituents, and it will be reported in due course.

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Conflict of Interest

The authors declare no conflict of interest.

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