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FULL PAPER

Self-assembled polydiacetylene nanoribbons for semi-heterogeneous and enantioselective organocatalysis of aldol reactions in water

Minh-Duc Hoang,[a] Ramar Arun Kumar,[a,b] David A. Buisson,[a] Wai Li Ling,[c] Edmond Gravel,*[a] Eric Doris*[a]

Abstract: We report the synthesis, characterization, and supra-molecular assembly of novel diacetylene amphiphilic units bearing a chiral proline-derived head group. In water, these amphiphiles self-assemble into twisted ribbons that are photo-polymerized to afford stable nanostructures. The nanoribbons were valorized in the semi-heterogeneous and enantioselective catalysis of aldol reactions in water. The system is active on a variety of substrates, operates under sustainable conditions (room temperature, air atmosphere, low catalyst loading), provides access to the target compounds with high enantiomeric excess, and the organocatalyst can be recycled over several runs with no loss in activity.

Introduction

Catalytic enantioselective reactions are central in the synthesis of many valuable organic compounds.[1] The ideal catalytic system should combine several pivotal features that include simple preparation, mild conditions of use, moderate loadings, easy recycling, high efficiency (yield/enantioselectivity), and compatibility with environment-friendly solvents such as water.[2] In fact, efforts have been devoted, over the last decades, to the development of water-compatible chemical processes that take advantage of the peculiar and beneficial features of this solvent such as cost, safety, waste management, and overall green aspect of aqueous chemistry.[3] Among key enantioselective reactions, the aldol reaction stands out,[4] as the β-hydroxycarbonyl motif is present in the structure of many biologically active compounds.[5] Whilst in nature specific enzymes, namely aldolases, efficiently promote aqueous enantioselective aldol reactions, synthetically carrying out such transformations in water remains tricky.[6] As an example, organocatalytic asymmetric aldol reactions promoted by proline are usually performed in organic solvents, although the addition of a small amount of water is likely to accelerate reaction rates and/or improve enantioselectivities.[7] However, the use of fully aqueous conditions usually results in low yields and poor selectivities.[8] This has led to the development of new proline-derived organocatalysts[9] such as the one implemented by Barbas and co-workers[10] that is active and selective under aqueous conditions. In their approach, proline-surfactants were designed in such a way to encapsulate hydrophobic reactants and isolate the transition state from water. Yet, the catalytic system could not be recycled.

With these results in mind and as part of our longstanding interest in the supra-molecular chemistry of diacetylene-based amphiphiles[11] and catalytic systems,[12] we report here the development of a semi-heterogeneous polydiacetylene organocatalyst. Under specific conditions, diacetylene amphiphiles self-organize into bilayered structures such as ribbons, spirals, and tubes that can be further stabilized by photo-polymerization under UV light.[13] We conceived that self-supported organocatalysts, applied to enantioselective aldol reactions, could be assembled starting from a specifically designed amphiphile combining an “active” proline center together with a “structuring” diacetylene lipophilic chain. The resulting nanostructured material (ribbon) is expected to offer beneficial features such as a hydrophobic environment for the reactants in water and the possibility of recycling the catalyst thanks to the semi-heterogeneous nature of the nanoribbons.

Results and Discussion

To this end, we combined, in a single amphiphilic unit hereafter referred to as DAPro (**1**), a diacetylene hydrophobic C_{25} chain with a proline-derived polar head group. DAPro (**1**) was readily synthesized from pentacosa-10,12-diynoic acid (**2**) that was first activated into the corresponding *N*-hydroxysuccinimidyl ester, before being reacted with ethylene diamine (Scheme 1). The resulting primary amine-terminated intermediate compound **3** was then coupled to *N*-Boc-L-proline, followed by deprotection of the amino group under acidic conditions. The target DAPro amphiphile (**1**) was obtained in overall 66% yield.

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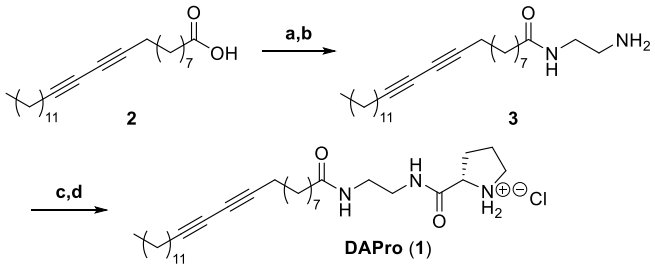


Scheme 1. Synthesis of the DAPro (**1**) amphiphile. a) NHS, EDCI-HCl, CH_2Cl_2, 90%; b) ethylenediamine, CH_2Cl_2, 95%; c) Boc-L-Proline, NEt_3, HOBt, EDCI, CH_2Cl_2, 96%; d) HCl, dioxane, 80%.

With the DAPro amphiphile **1** in hands, we next looked at its supra-molecular self-assembly properties (Figure 1a and 1b).[14] A suspension of **1** in water (10 mg mL^{-1}) was sonicated for 30 min. The clear solution was kept at room temperature for 4 h and stored at 5 °C for additional 20 h. This led to the formation of an opaque gel-like milky suspension (Figure S1a) that was subjected to UV irradiation at 254 nm for 2 min. The resulting dark-blue suspension was then bath-sonicated for 1 h to disperse the aggregates. This treatment induced a blue to red transition,[15] with the concomitant formation of stable small crimson red nanostructures corresponding to the final polymerized DAPro material (*i.e.* pDAPro, Figure 1c).

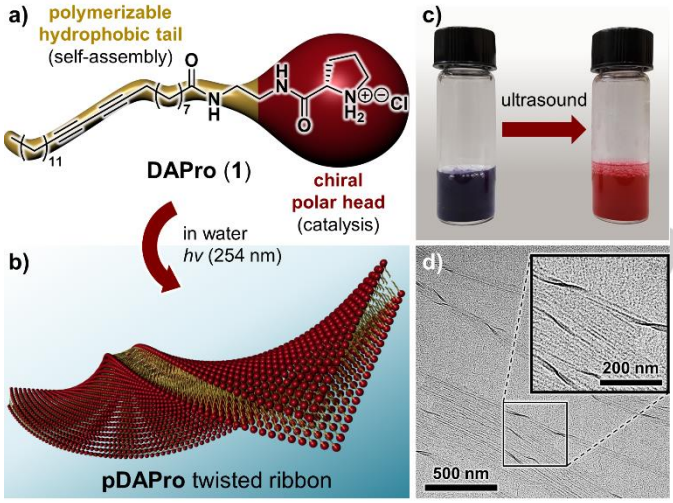
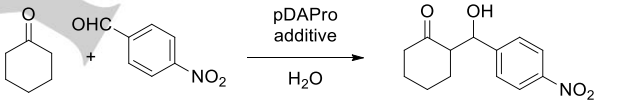


Figure 1. Catalyst synthesis and characterization: a) Schematic representation of the DAPro amphiphile and b) its assembly into pDAPro ribbons; c) Color change upon bath sonication; d) TEM image of pDAPro.

Morphological characterization of the pDAPro assembly was performed by transmission electron microscopy (TEM) operating at 200 kV. Close inspection of the TEM images revealed a dense network of nanostructures made of twisted ribbons with a homogeneous width of *ca.* 18 nm (Figure 1d). In fact, these ribbons are made of a bilayered structure, resulting from tail-to-tail assembly of DAPro and further polymerization.[16] While the lipophilic part of amphiphile **1** is positioned at the interface of the bilayer and creates a hydrophobic domain, the chiral L-proline polar head is pointing towards the aqueous medium, thus making the nanoribbons partly dispersible in water. The assembly was also investigated by circular dichroism (CD) which revealed a characteristic positive peak at the largest UV-vis absorption (at *ca.* 545 nm, see Figure S2). This CD signal is attributed to the conjugated polydiacetylene backbone[17] and suggests that the PDA region establishes a supramolecular chiral environment leading to the twisted conformation observed for the nanoribbons.

The pDAPro catalyst was then evaluated in a model enantioselective aldol reaction between cyclohexanone (**4a**) and *p*-nitrobenzaldehyde (**5a**) (Table 1). Water was selected as the only solvent, the catalyst loading was set at 5 mol%, and the reactions were run at room temperature. Under these conditions, the aldol reaction reached 95% conversion after 24 h (Entry 1). The *anti*/*syn* diastereomeric ratio (*dr*) was 9:1 and enantiomeric excess (*ee*) 68%. Increasing the reaction time to 48 h only had a slight effect on the conversion (Entry 2). In order to improve the overall efficacy of the transformation, some additives were selected as activators, since it has been demonstrated by others that carboxylic acids, in sub-stoichiometric amounts, have beneficial impacts on the outcome of stereoselective aldol reactions.[18]

Table 1. Conditions investigated for the enantioselective aldol reaction.[a]



4a 5a 6aa

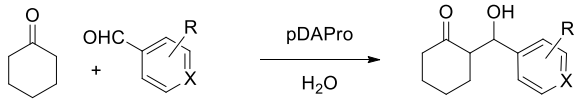
Entry	Additive	Time (h)	Conv. (%)	*dr* *anti*/*syn*[b]	*ee*[c] (%)
1	-	24	95	90:10	68
2	-	48	99	90:10	68
3	TFA (5 mol%)	24	75	90:10	88
4	AcOH (5 mol%)	24	99	87:13	64
5	HCO_2H (5 mol%)	24	99	92:8	74
6	$PhCO_2H$ (5 mol%)	24	99	93:7	89

[a] Conditions: pDAPro catalyst (0.00625 mmol, 5 mol%), additive (if used, 0.00625 mmol, 5 mol%), **4a** (1.25 mmol), and **5a** (0.125 mmol) in water (1.0 mL) at room temperature. [b] Dete+rmined by ^{1}H-NMR of the crude product. [c] Determined by chiral-phase HPLC analysis for *anti*-product.

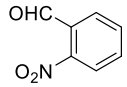
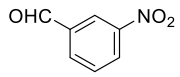
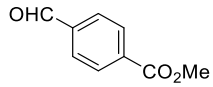
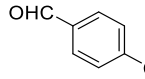
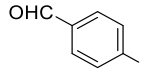
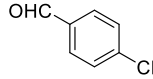
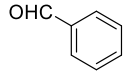
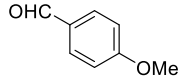
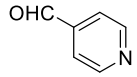
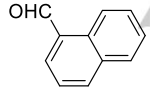
The use of 5 mol% of trifluoroacetic acid (TFA) decreased the conversion rate of the reaction (Entry 3) but significantly improved the *ee* to 88%. On the contrary, the use of acetic acid (Entry 4) proved beneficial on the reaction rate but detrimental to the enantioselectivity of the transformation. The same comment holds true for the use of formic acid (Entry 5). The best compromise between conversion rate and selectivity was found to be the addition of 5 mol% of benzoic acid (Entry 6) which allowed nearly full conversion into **6aa** within 24 h with *dr* and *ee* values of 93:7 and 89%, respectively.

To demonstrate the heterogeneous nature of the organocatalyzed transformation, that is that the catalytic process actually takes place at the surface of the nanostructures and is not promoted by "contaminating" free standing proline-based amphiphiles in solution, a simple aldol reaction was set under the conditions of Table 1, Entry 6. The only difference here was that the pDAPro catalyst suspension was filtered over a 0.2 µm membrane to remove the solid catalyst prior to the addition of the reagents. Under these conditions, the reaction rate was significantly decreased as only 30% conversion was observed after 24 h, and the aldol products were obtained as racemates.

Table 2. Scope of the pDAPro-catalyzed aldol reaction between cyclohexanone **4a** and various aldehydes.[a]



4a **5** **6ax**

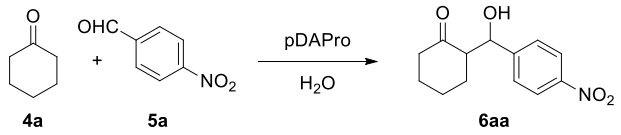
Entry	Aldehyde	**5**	Time (h)	Conv. (%)	*dr*[b] *anti*/*syn*	*ee*[c] (%)
1		**5b**	24	94	87:13	80
2		**5c**	24	99	91:09	86
3		**5d**	24	95	91:09	86
4		**5e**	24	88	87:13	84
5		**5f**	24	92	84:16	80
6		**5g**	24	99	81:19	82
7		**5h**	72	34	90:10	88
8		**5i**	72	12	86:14	82
9		**5j**	24	99	82:18	80
10		**5k**	192	84	87:13	76

[a] Conditions: pDAPro catalyst (0.00625 mmol, 5 mol%), benzoic acid (0.00625 mmol, 5 mol%), **4a** (1.25 mmol), and **5** (0.125 mmol) in water (1 mL) at room temperature. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral-phase HPLC analysis of the *anti*-product.

To evaluate the scope of the system, the efficacy of the pDAPro catalyst **1** was tested on a variety of substrates (Table 2) under the optimized reaction conditions, *i.e.* 5 mol% pDAPro and 5 mol% phenylacetic acid additive, room temperature in water. We first investigated the reaction of cyclohexanone with variously substituted aromatic aldehydes. The system proved very efficient with electron-deficient aldehydes, both in terms of conversion and selectivity. In addition to *para*-nitro benzaldehyde **5a**, *ortho*- (**5b**, Entry 1) and *meta*-nitro benzaldehydes (**5c**, Entry 2) were also both well converted (94% and 99% conversion, respectively) with good selectivity (*dr* = 87:13 and 91:9, *ee* = 80% and 86%, respectively). Methyl ester substituted **5d** (Entry 3) was cleanly transformed (95% conversion) along with very good *dr* (91:9) and *ee* (86%). Halogenated substrates, namely *p*-chloro (**5e**, Entry 4) and *p*-bromo benzaldehyde (**5f**, Entry 5), also underwent smooth (88% and 92% conversion, respectively) and selective reaction (*dr* = 87:13 and 84:16, *ee* = 84 and 80%, respectively). Similarly, *para*-cyano benzaldehyde (**5g**, Entry 6) was quantitatively transformed (*dr* = 81:19, *ee* = 82%). Unfortunately, simple benzaldehyde (**5h**, Entry 7) was poorly reactive under the pDAPro-catalyzed reaction conditions, leading only to 34% conversion yet with good selectivity (*dr* = 90:10, *ee* = 88%). In a similar fashion, electron-rich *para*-methoxy benzaldehyde (**5i**, Entry 8) did not afford better than 12% conversion after 72 h, even though selectivity was satisfactory (*dr* = 86:14, *ee* = 82%). The efficacy of the system was also tested on other aromatic aldehydes including isonicotinaldehyde (**5j**, Entry 9) which was fully converted within 24 h (*dr* = 82:18, *ee* = 80%), as well as 1-naphthaldehyde (**5k**, Entry 10) which was smoothly (84%) and selectively (*dr* = 87:13, *ee* = 76%) converted. It is to be noted that the kinetics of the latter reaction was rather slow (8 days of reaction).

An important feature of (semi)-heterogeneous catalysis is the possibility of recovering the catalyst and recycling it for subsequent reactions. In an ideal case, the recovery step should be as simple as possible, and reusability should not rely on any treatment or reactivation of the catalytic species. For our nano-ribbon pDAPro catalyst, a very simple in-flask recovery protocol was used. After completion of the reaction, the aldol product was extracted from the aqueous layer with ethyl acetate, leaving the catalyst in water ready to be used in the next run. We carried out five consecutive aldol reactions between **4a** and **5a** with the same sample of pDAPro catalyst using this recycling protocol and we were pleased to observe that neither conversion nor selectivity were affected over the course of the experiments (Table 3, Entries 1-5). Aldol products were obtained consistently in all cases with 99% conversion, and 93:7 *dr* / 89% *ee*. These results emphasize the robustness of the catalytic nanoribbon system that remained equally active over several cycles.

Table 3. Recycling of the pDAPro nanoribbon catalyst **1**.[a]



4a **5a** **6aa**

Entry	Catalyst	Time (h)	Conv. (%)	*dr anti/syn*[b]	*ee*[c] (%)
1	Fresh	24	99	93:7	89
2	1st recycle	24	99	93:7	89
3	2nd recycle	24	99	93:7	89
4	3rd recycle	24	99	93:7	89
5	4th recycle	24	99	93:7	89

[a] Conditions: pDAPro catalyst (0.00625 mmol, 5 mol%), benzoic acid (0.00625 mmol), **4a** (1.25 mmol), and **5a** (0.125 mmol) in water (1 mL) at room temperature. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral-phase HPLC analysis of the *anti*-product.

The overall performances of our catalyst in water can be rationalized by the peculiar structure of the nanoribbons which offers, in addition to the active proline center, a hydrophobic domain located at the interface of the lipophilic chains. This domain is likely to accommodate the hydrophobic reagents involved in the aldol reaction in such a way that it behaves as a nanoreactor favoring aqueous dispersion of the reagents and their concentration at the vicinity of the active sites of the catalyst. At the same time, the hydrophobic domain sequester the transition state from water, thus minimizing interference of the aqueous medium on the outcome of the transformation, especially as regards its selectivity.

Conclusions

Novel amphiphiles bearing a proline-derived polar head group and a diacetylene lipophilic chain were synthesized, self-assembled in aqueous medium, and further photopolymerized to afford twisted nanoribbons. The supra-molecular material was investigated for the promotion of semi-heterogeneous and enantioselective aldol reactions. The L-proline-based catalyst was shown to be effective on a variety of substrates in water without addition of any organic solvents. The assembly acted as a nano-reactor in which organocatalysis take place and contributed favorably to the overall process by allowing, i) dispersion of the reagents in water, ii) their concentration close to the catalyst active sites, and iii) sequestration of the transition states from the aqueous environment, thus minimizing solvent interference. The system demonstrated excellent reactivity, diastereo- and enantioselectivities, and was found to be operative under sustainable conditions (room temperature, air atmosphere, low catalyst loading, water as unique solvent). In addition, the catalyst could be recycled over several runs with no loss of activity. From the above perspectives, it appears that the nanoribbon catalyst favors compartmentalization of the reagents which leads to unique selectivities, in a manner similar to that of enzymatic systems such as aldolases.

Experimental Section

General procedure for the asymmetric aldol reaction: At room temperature, to a suspension of pDAPro (0.00625 mmol, 5 mol%) in water (1 mL) was added benzoic acid (0.00625 mmol, 5 mol%) and ketone **4** (1.25 mmol). The reaction mixture was stirred for 15 min, before aldehyde **5** (0.125 mmol) was added. The reaction mixture was vigorously stirred for the indicated time and worked-up by extraction twice with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc) to afford pure aldol products. All aldol products are known compounds, and their spectroscopic data are in accordance with literature. Diastereomeric ratios were assessed by ^{1}H-NMR analysis of the crude reaction mixture and enantiomeric excesses were measured by chiral HPLC analysis.

Recycling procedure: At room temperature, to a suspension of pDAPro (0.00625 mmol, 5 mol%)) in water (1 mL) was added benzoic acid (0.00625 mmol, 5 mol%) and cyclohexanone **4a** (1.25 mmol). The reaction mixture was stirred for 15 min, before 4-nitrobenzaldehyde **5a** (0.125 mmol) was added. The reaction mixture was vigorously stirred for 24 h. The mixture was then extracted twice with EtOAc, the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc, 85:15) to afford pure aldol product **6aa**. The remaining aqueous phase was reused to carry out further reactions, by simple addition of 5 mol% of benzoic acid, cyclohexanone **4a** (1.25 mmol) and 4-nitrobenzaldehyde **5a** (0.125 mmol) for each additional run.

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Keywords: Aldol • organocatalysis • enantioselective • polydiacetylene • self-assembly

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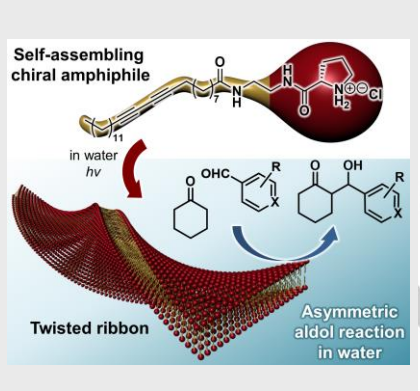
Nano-ribbons bearing proline groups were valorized in the semi-heterogeneous and enantioselective catalysis of aldol reactions in water.



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Self-assembled polydiacetylene nanoribbons for semi-heterogeneous and enantioselective organocatalysis of aldol reactions in water