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Supporting Information

Nonlinear Effects at Soft Interface of an Emulsion in List-Lerner-Barbas Aldol Reaction

Jyoti Dutta, NutanWakdikar and Shraeddha Tiwari*

Department of Chemistry, Institute of Chemical Technology, Mumbai 400019

*Corresponding Author

Email: ss.tiwari@ictmumbai.edu.in

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1. Materials & Methods:

Commercially available cyclohexanone and *p*-nitrobenzaldehyde were used without further purification. All experiments were carried out using high purity or spectroscopic grade solvents and distilled water. Amphiphillic catalysts, 4-(decanoyloxy)pyrrolidine-2-carboxylic acid (4) and 4-(dodecanoyloxy)pyrrolidine-2-carboxylic acid (5), were synthesized from D- and L- isomers of proline as per the reported procedure ¹and characterized by ¹H NMR.

2. Synthesis of amphiphillic catalyst:

Typical experimental procedure for the synthesis¹ of catalysts 4



Scheme 1: General synthesis of proline-derived amphiphilic catalysts 4

(2S,4R)-4-(decanoyloxy)pyrrolidine-2-carboxylic acid (4)

trans-4-hydroxy-L-proline (7.6 mmol, 1g) was dissolved in trifluoroacetic acid (4.3mL) and was stirred at room temperature for 15 min. The solution was cooled below room temperature in an ice bath, removed from the bath and lauroyl chloride (15.2mmol, 3.53mL) was added in one portion (mildly exothermic). The solution was further stirred at room temperature for 2h. Solution under cooling in an ice bath was precipitated by addition of diethyl ether (14.8mL).

Precipitate obtained was vacuum-filtered, washed with diethyl ether and dried under vacuum for 42h to give (*2S*, *4R*)-4-(decanoyloxy)pyrrolidine-2-carboxylic acid hydrochloride as a fine white powder. All the hydrochloride salt was dissolved in ethanol by heating. The solution was cooled in ice bath and was crystallized after addition of propylene oxide (1.27mL). After drying the product was obtained as white flat needles (yield 70%).

¹**H NMR (400 MHz, CDCl₃)** δ 5.37 – 5.29 (m, 1H), 4.34 – 4.26 (m, 1H), 3.69 (m, 1H), 3.40 (d, 1H), 2.44 (m, 1H), 2.32 (m, 3H), 1.64 – 1.57 (m, 2H), 1.26 (s, 16H), 0.88 (t, 3H)

3. General Experimental Procedure

Direct LLB–A reaction of cyclohexanone and *p*-nitrobenzaldehyde carried out in presence of water and amphiphillic catalyst **4** at controlled temperature of 298 K (±0.1 K) was used as a model aldol reaction for the study (Scheme 2). For a typical reaction run, cyclohexanone (5mL, 48mmol) was added to proline-based catalyst (0.19 mmol) and stirred, followed by addition of water (17.5mL) resulting into suspension. *p*-Nitrobenzaldehyde (189mg, 1.25mmol) was added to the suspension and stirred for 24 h. Progress of reaction was monitored by thin layer chromatography (TLC). The reaction was quenched using saturated NH₄Cl solution and product was extracted in ethyl acetate. The extracted product was analyzed using HPLC. Purified products were characterized by ¹H NMR and the %ee was determined using HPLC analysis.



Scheme 2: Reaction of cyclohexanone with *p*-nitrobenzaldehyde in presence of modified proline surfactant catalyst

¹**H** NMR (400 MHz, CDCl₃) δ 8.21 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 4.90 (d, 1H), 4.09 (s, 1H), 2.66 – 2.55 (m, 1H), 2.50 (d, *J* = 13.7 Hz, 1H), 2.37 (m, *J* = 13.4, 6.1 Hz, 1H), 2.18 (s, 1H), 2.16 – 2.08 (m, 1H), 1.83 (d, *J* = 12.5 Hz, 1H), 1.74 – 1.49 (m, 2H), 1.45 – 1.22 (m, 1H).

Control reactions were performed for these sets using only proline and proline with sodium dodecysulphate (SDS); no product was obtained for these reactions.

4. HPLC Analysis

HPLC was carried out on an Agilent 1200 series instrument equipped with UV detector and manual injector using Chiralpak Kromasil 5-AmyCoat column (250x4.6mm i.d.) and the HPLC conditions were as per previous reports.² For injection, samples were dissolved in hexane-isopropanol (IPA) mixture (1:1) to a final concentration of 1mg/mL and 10 μ L was injected in to the column. The separation was realized in an isocratic mode with a mobile phase composition of hexane-isopropanol 80:20 (v/v) and flow rate 0.5mL, λ =254nm. The method was standardized by a racemic standard product in order to establish HPLC conditions (hex:IPA 80:20(v/v), flow rate 0.5mL, λ =254nm), t_{R(anti)}= 35.09 min; major isomer: t_{R(anti)}= 26.24min; minor isomer and t_{R(syn)}= 24.15min; major isomer: t_{R(syn)}=22.05min; minor isomer.



Figure 1. Typical HPLC chromatogram for LLB-A product (45% enantiomeric excess)

Entry	% ee of Catalyst	Ratio of area under peak (<i>anti</i> major: <i>anti</i> minor)	% <i>ee</i> of product ^a	Normalized % <i>ee</i> of product ^b					
LLB-A reaction in homogeneous conditions (DMSO as solvent)									
1	0	1.09:1	4	0					
2	20	1.46:1	19	16					
3	40	2.27:1	39	38					
4	60	3.18:1	52	52					
5	80	4.26:1	62	62					
6	100	67.3:1	97	100					
LLB-A reaction under biphasic / emulsifying conditions (with equilibration)									
1	0	1.05:1	2	0					
2	10	2.56:1	44	44					
3	20	2.54:1	44	44					
4	30	2.90:1	49	49					
5	40	2.95:1	49	50					
6	50	2.64:1	45	45					
7	60	2.58:1	44	44					
8	70	2.93:1	49	50					
9	80	4.24:1	62	63					

Table 1. HPLC data for LLB-A reaction catalyzed by 4

10	90	5.88:1	71	73				
11	100	55.0:1	96	100				
LLB-A reaction under biphasic / emulsifying conditions (without equilibration)								
1	0	1.01:1	1	0				
2	10	1.23:1	10	10				
3	20	1.51:1	20	21				
4	30	1.32:1	14	14				
5	40	1.44:1	18	18				
6	50	1.35:1	15	15				
7	60	1.56:1	22	22				
8	70	2.03:1	34	35				
9	80	2.72:1	46	48				
10	90	8.22:1	78	81				
11	100	59.8:1	97	100				

a. Enantiomeric excess of product calculated using ratio of peak area as ((*anti* major-*anti* minor)/ (*anti* major + *anti* minor))*100

b. Normalized % *ee* of product calculated as ((% ee of product-c)/(d+c))*100 where c = % *ee* of product corresponding to 0% *ee* of catalyst and d = % *ee* of product corresponding to 100% *ee* of catalyst

5. Preparation of catalyst emulsions for CD spectroscopy

0.19 mmol of proline based catalyst was dissolved in 5mL of cyclohexanone (catalyst and cyclohexanone mixture was heated in a hot water bath at 340K to ensure complete dissolution of catalyst in cyclohexanone). The catalyst cyclohexanone mixture was added to water (17.5mL) with constant stirring. The cyclohexanone was added in small fraction (20μ L) care was taken to add second fraction only after dissolution of first. A maximum of 1.3mL of catalyst cyclohexanone mixture can be added to obtain a homogeneous emulsion. A homogeneous emulsion formed by dissolving 1.3mL of catalyst cyclohexanone solution in 17.5mL of water was used for further analysis with Congo Red.



Figure 2. Emulsions with different scalemic composition of catalyst 4



6. Representative UV Spectra of CR-4 aggregate

Figure2. Representative UV spectra of CR-4 aggregate



7. Representative CD Spectra of CR-4 aggregate

Figure 3. Representative CD spectra of CR-4 aggregate

8. References

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