Supporting Information

2. Gelatin and Collagen Proteins-mediated Reactions

2.2 Gelatin Protein-mediated Direct Aldol Reaction

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Note: A description of the most important features of both gelatin and collagen can be found in the Supporting Information of our previous work focused on the nitroaldol (Henry) reaction catalyzed by these proteins.[1]

1. Preliminary optimization experiments

Table S1. Screening of cyclohexanone equivalents.[a]

Entry	Cyclohexanone (2, eq.)	Time (d)	Temperature (°C)	Yield 3a (%)[b]
1	5	7	37	38
2	10	7	37	62
3	20	7	37	64

[a] Reaction conditions: 4-nitrobenzaldehyde (**1a**, 15.1 mg, 0.1 mmol), DMSO (0.5 mL), PSTA gelatin (10 mg); [b] ^{1}H NMR yield was determined with diphenylmethane as internal standard. Standard deviation, STDV = ± 2%.

Table S2. Screening of catalyst loading.[a]

Entry	Solvent	Temperature (° C)	Time (d)	Catalyst loading (mg)	Yield 3a (%)[b]
1	DMSO	25	14	0	38
2	DMSO	25	18	5	62
3	DMSO	25	14	10	64
4	H_2O	25	21	0	2
5	H_2O	37	7	0	7
6	H_2O/TBAB	37	7	0	5
7	H_2O	25	21	5	2
8	H_2O	37	7	10	14

[a] Reaction conditions: 4-Nitrobenzaldehyde (**1a**, 0.1 mmol), cyclohexanone (**2**, 2.0 mmol), DMSO (0.5 mL); [8] ^{1}H NMR yield was determined with diphenylmethane as internal standard. Standard deviation, STDV = ± 2%. Note: The use of more than 10 mg of PSTA makes the work-up of the reaction more laborious.

2. Selected ^{1}H NMR spectra

Relative configurations were assigned by comparison with ^{1}H NMR data reported in the literature.[2] Dimethylacetamide was used as internal standard for recording NMR spectra.

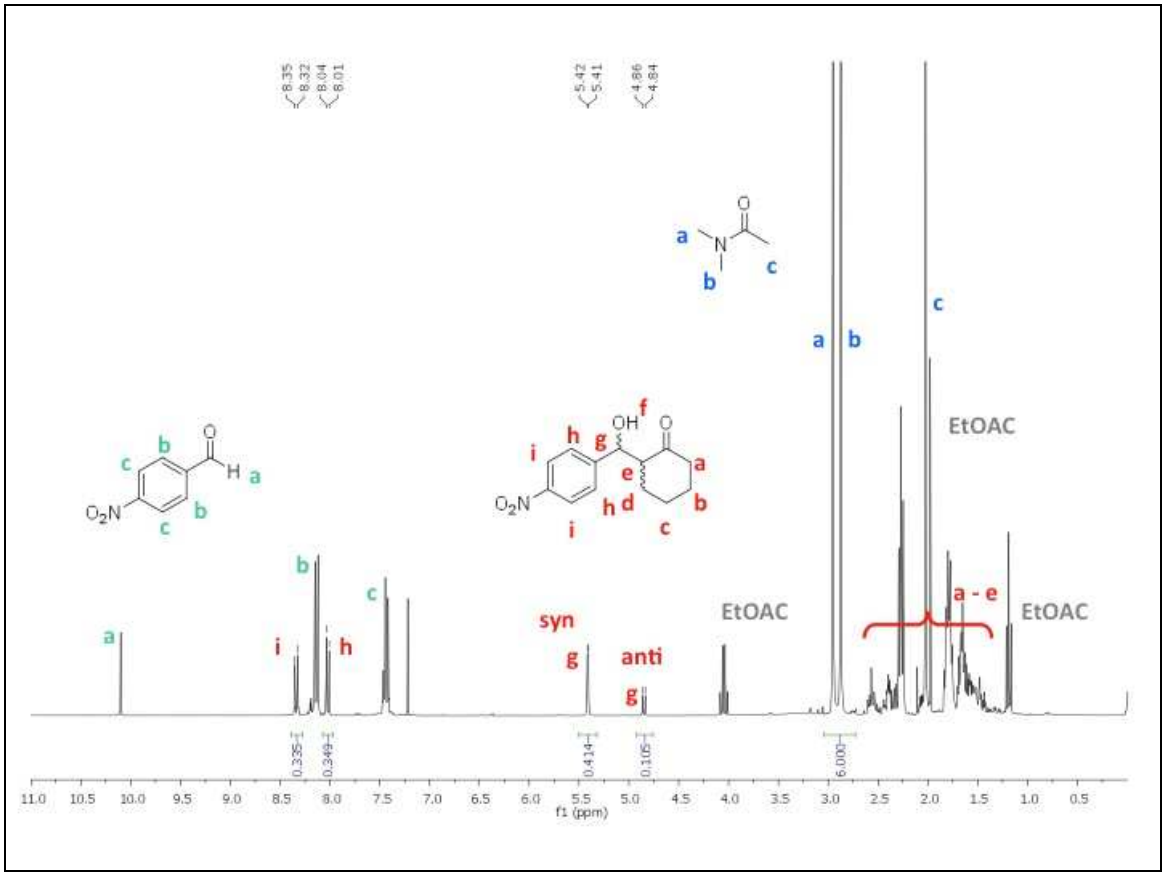

Figure S1. ^{1}H NMR spectrum of the reaction crude obtained from the gelatin-catalyzed aldol reaction between 4-nitrobenzaldehyde and cyclohexanone. Reaction conditions: 4-nitrobenzaldehyde (**1a**, 0.1 mmol), cyclohexanone (**2**, 1.0 mmol), PSTA (10 mg), solvent (0.5 mL), 37 ºC, 7 days at 250 rpm.

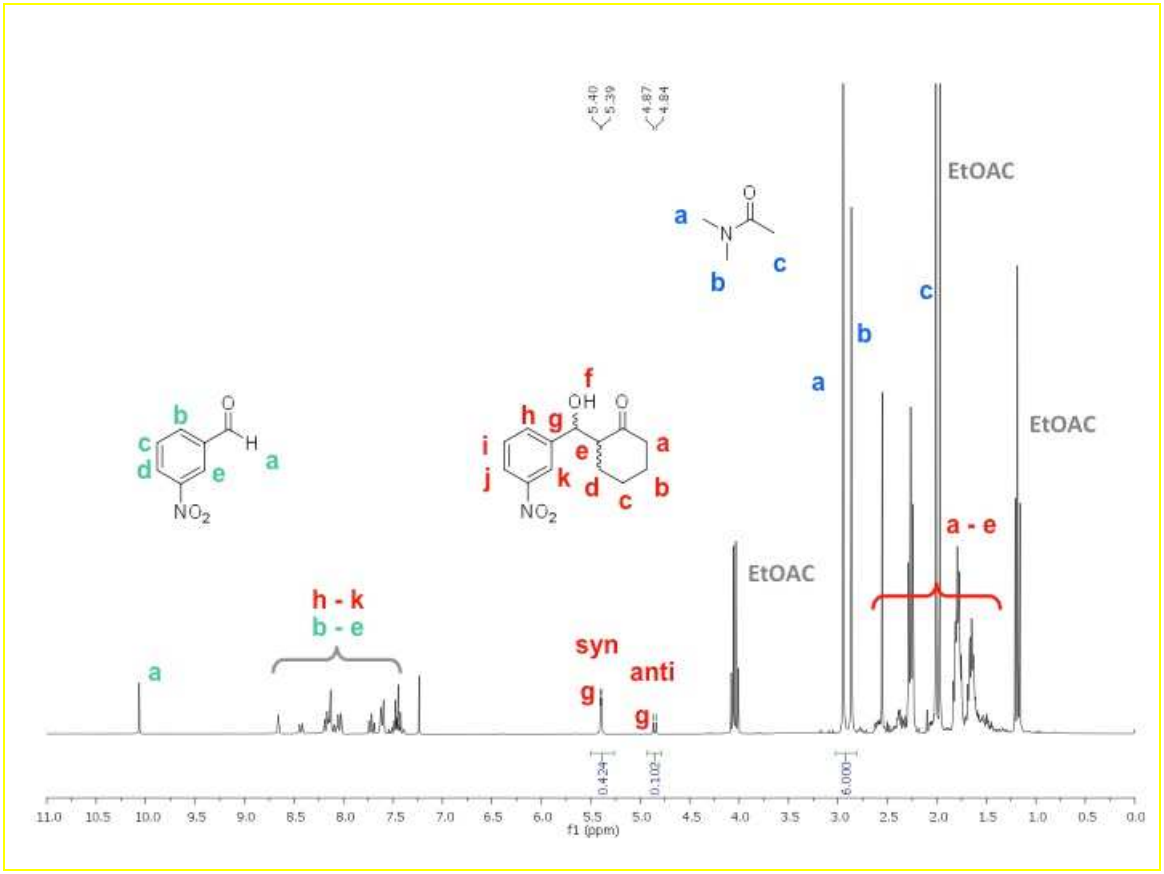

Figure S2. ^{1}H NMR spectrum of the reaction crude obtained from the gelatin-catalyzed aldol reaction between 3-nitrobenzaldehyde and cyclohexanone. Reaction conditions: 3-nitrobenzaldehyde (**1b**, 0.1 mmol), cyclohexanone (**2**, 1.0 mmol), PSTA (10 mg), solvent (0.5 mL), 37 ºC, 7 days at 250 rpm.

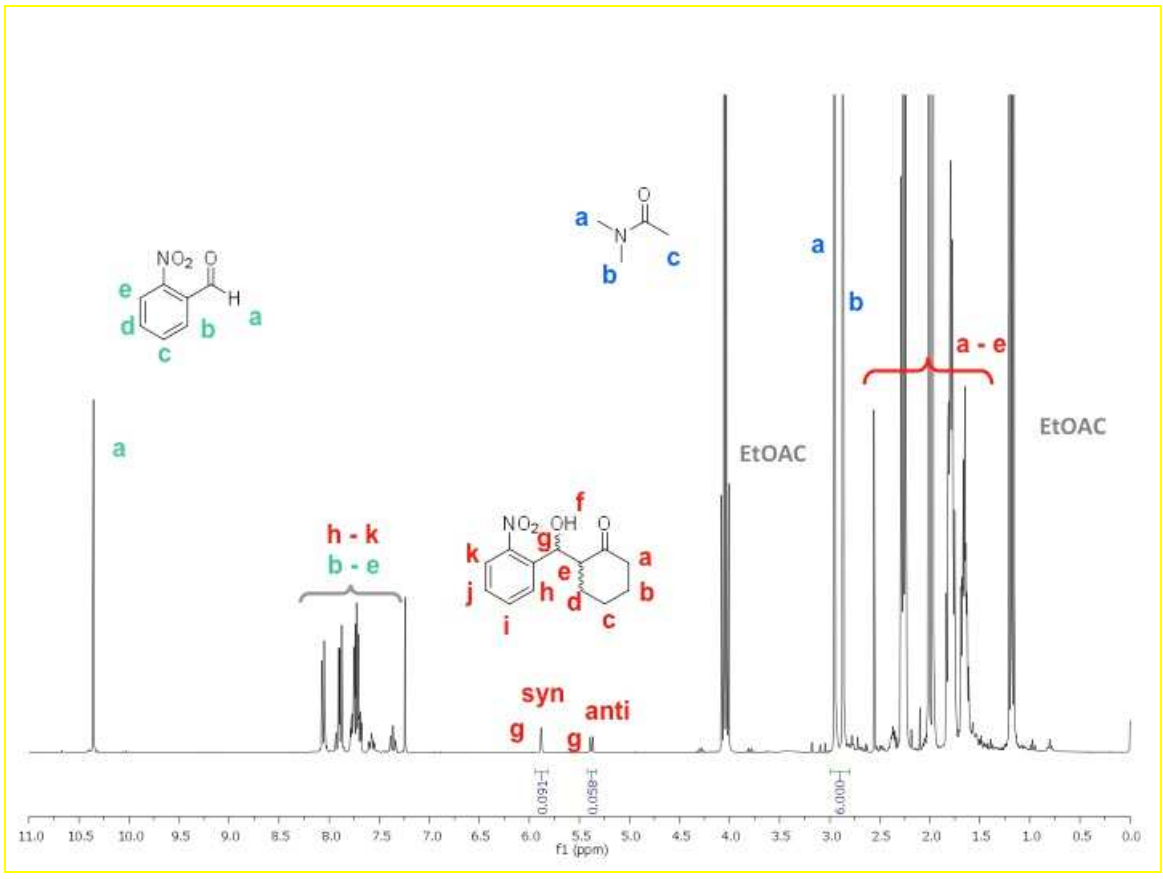

Figure S3. ^{1}H NMR spectrum of the reaction crude obtained from the gelatin-catalyzed aldol reaction between 2-nitrobenzaldehyde and cyclohexanone. Reaction conditions: 2-nitrobenzaldehyde (**1c**, 0.1 mmol), cyclohexanone (**2**, 1.0 mmol), PSTA (10 mg), solvent (0.5 mL), 37 ºC, 7 days at 250 rpm.

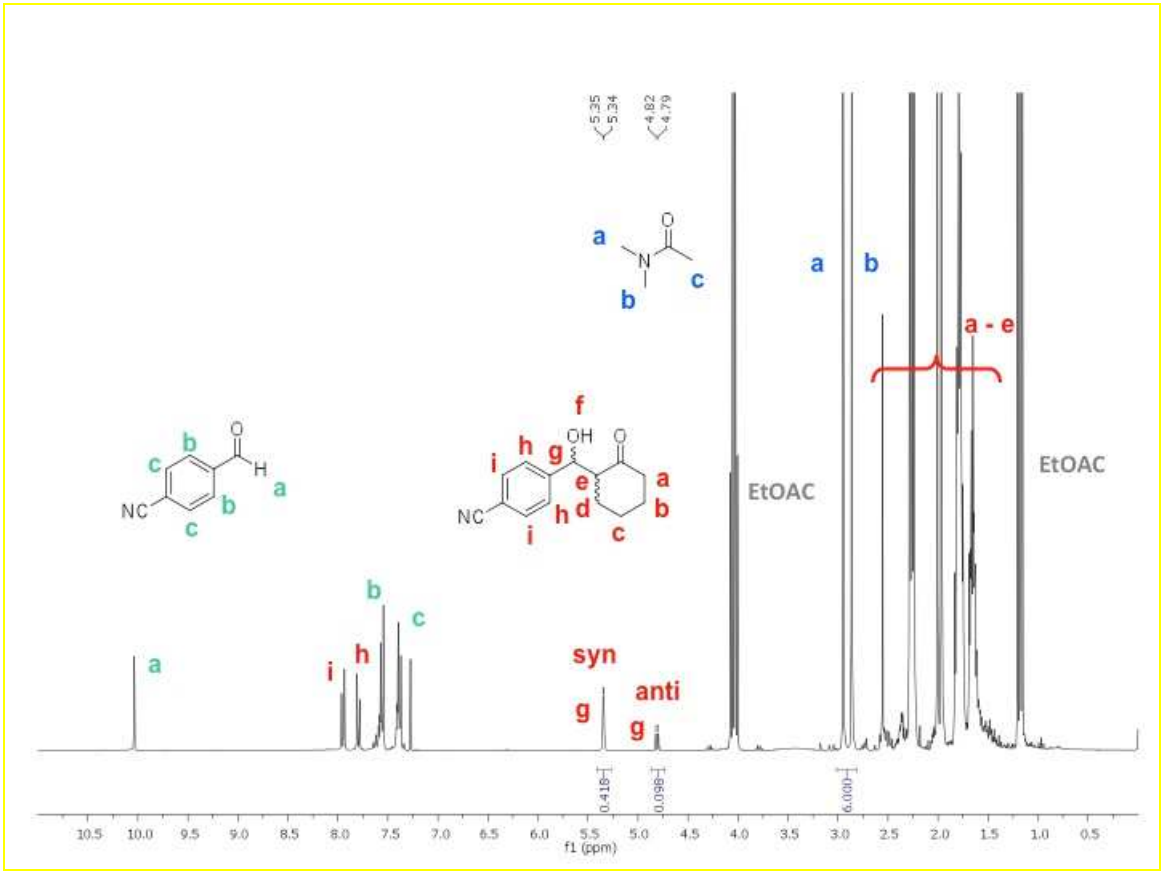

Figure S4. ^{1}H NMR spectrum of the reaction crude obtained from the gelatin-catalyzed aldol reaction between 4-cyanobenzaldehyde and cyclohexanone. Reaction conditions: 4-cyanobenzaldehyde (**1d**, 0.1 mmol), cyclohexanone (**2**, 1.0 mmol), PSTA (10 mg), solvent (0.5 mL), 37 ºC, 7 days at 250 rpm.

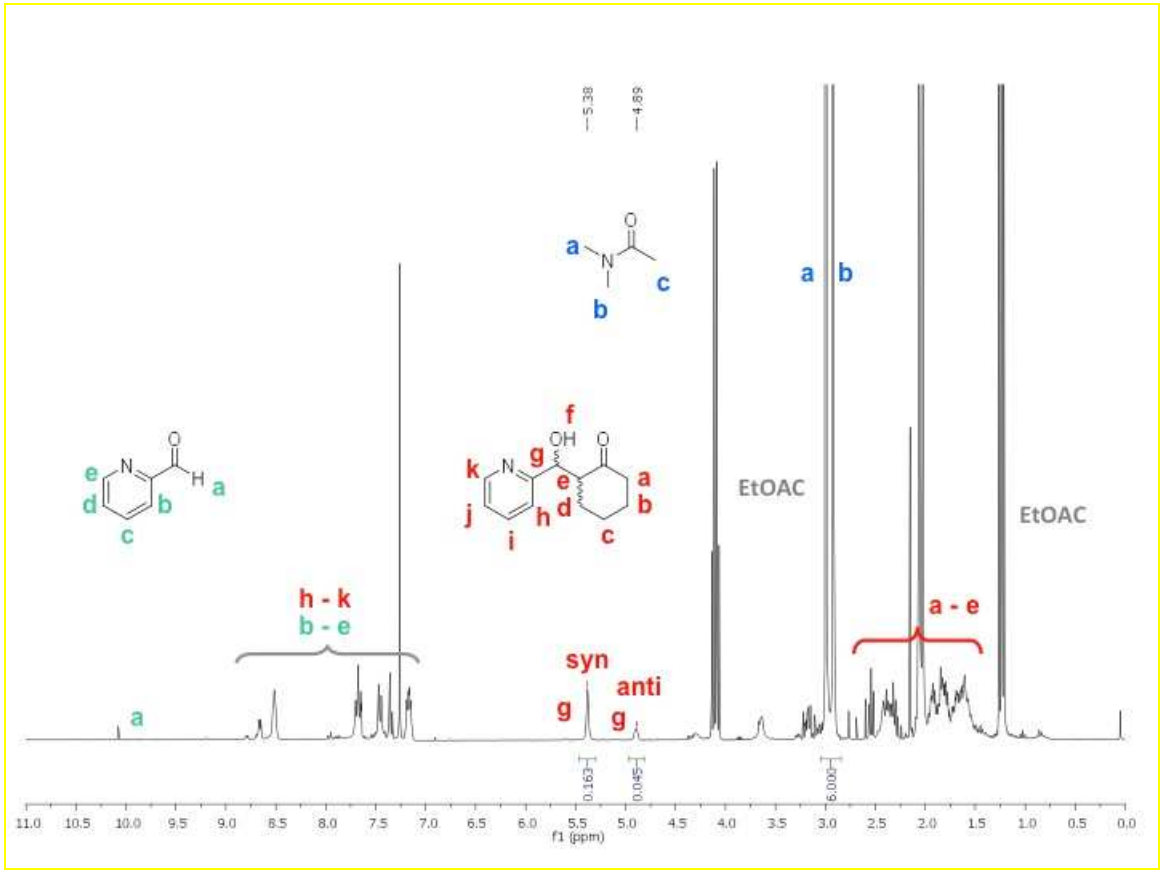

Figure S5. ^{1}H NMR spectrum of the reaction crude obtained from the gelatin-catalyzed aldol reaction between 2-pyridinecarbaldehyde and cyclohexanone. Reaction conditions: 2-pyridinecarbaldehyde (**1f**, 0.1 mmol), cyclohexanone (**2**, 1.0 mmol), PSTA (10 mg), solvent (0.5 mL), 37 ºC, 7 days at 250 rpm.

3. FT-IR spectra

Gelatin could be recovered and reused in at least two consecutive runs with virtual maintenance of catalyst activity. A nearly quantitative recovering of the catalyst (wt.%) was obtained after each run. However, a major detriment in the product yield was observed in the third cycle. An evident yellow coloring and clogging of the catalyst after successive runs suggest an inefficient molecular desorption from the surface rather than a decomposition process. Indeed, the characteristic IR absorption peaks of the gelatin are preserved after each cycle. Slightly broadening of these peaks as well as the presence of additional small peaks supports certain molecular absorption even after washing/drying the catalyst (Figure S6).

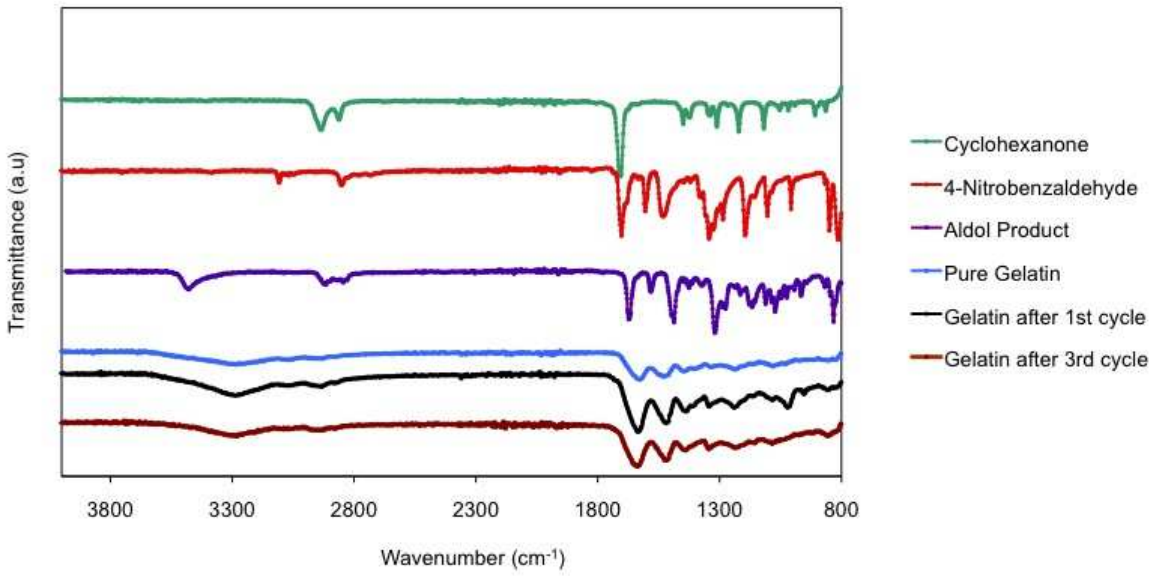

Figure S6. Comparative FT-IR spectra of reactants, reaction product and catalysts. The spectra of the gelatin after 1st and 3rd cycle correspond to washed and dried material after the reaction.

4. Additional FESEM images

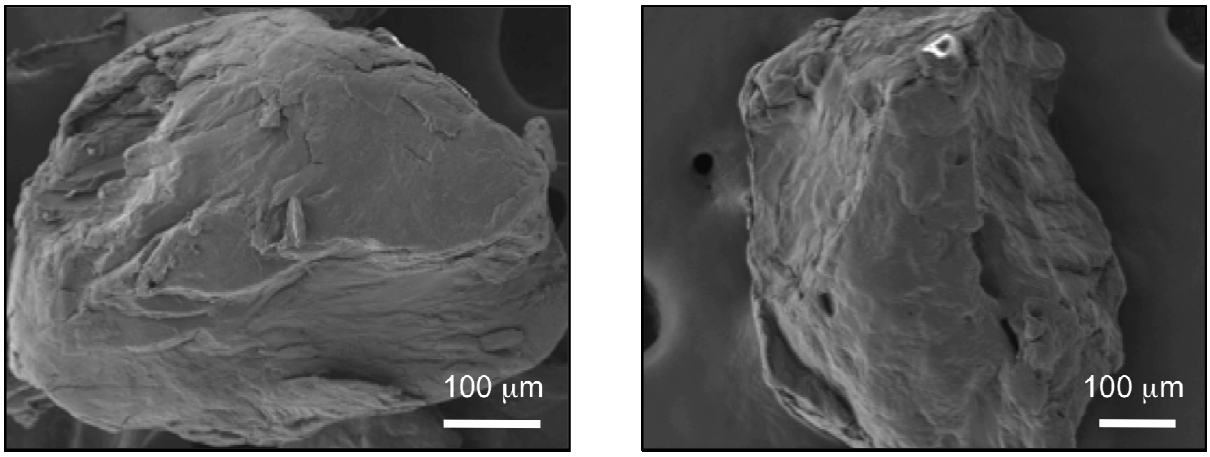

Figure S7. Additional FESEM images of commercial powdered gelatin protein.

5. References

[1] D. Kühbeck, B. B. Dhar, E.-M. Schön, C. Cativiela, V. Gotor-Fernández, D. D. Díaz, *Beilstein J. Org. Chem.* **2013**, *9*, 1111-1118.

[2] a) R. Pedrosa, J. M. Andrés, R. Manzano, P. Rodríguez, *Eur. J. Org. Chem.* **2010**, 5310-5319; b) A. Ricci, L. Bernardi, C. Gioia, S. Vierucci, M. Robitzer, F. Quignard, *Chem. Commun.* **2010**, *46*, 6288-6290; c) S. Paladhi, J. Das, P. K. Mishra, J. Dash, *Adv. Synth. Catal.* **2013**, *355*, 274-280; d) Z.-B. Xie, N. Wang, G.-F. Jiang, X.-Q. Yu, *Tetrahedron Lett.* **2013**, *54*, 945-948.