# Electronic Supplementary Information (ESI)

# Nanocellulose Enriches Enantiomers in Asymmetric Aldol Reactions

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# 1. Characterization of TEMPO-oxidized cellulose nanofibers (TOCNFs)

### 1.1. TEM image of TOCNFs

Transmission electron microscopy (TEM) observation was performed using a JEM-2100HCKM microscope (JEOL, Tokyo, Japan), operated at an accelerating voltage of 200 kV, at the Ultramicroscopy Research Center, Kyushu University. A TOCNF dispersion (0.005% w/w, 5  $\mu$ L) was deposited on a glow-discharged carbon-coated Cu grid. Excess liquid was absorbed with filter paper after 5 min, and a negative staining reagent (1% sodium phosphotungstate, 5  $\mu$ L) was dropped onto the sample. After allowing to stand for 5 min, excess liquid was absorbed with filter paper. Deionized water (5  $\mu$ L) was then added dropwise, and removed with filter paper after 3 min. After air-drying, the coated grid was observed using the TEM apparatus in bright-field mode.



Fig. S1. TEM image of TOCNFs supplied by Nippon Paper Industries Co., Ltd. (Tokyo, Japan).

### 1.2. X-Ray diffraction pattern of TOCNFs

The XRD pattern was recorded using a Rigaku SmartLab diffractometer (Rigaku Corporation, Tokyo, Japan) with Ni-filtered Cu K $\alpha$  radiation ( $\lambda$ = 0.15418 nm) at 40 kV and 20 mA. Scanning was performed at 0.5° min<sup>-1</sup> with 0.05° intervals. Freeze-dried TOCNF samples were pressed to make a pellet. The crystallinity index (CrI) was calculated according to the method reported by Segal and co-workers<sup>1</sup>:

CrI (%) = 
$$[(I_{200}-I_{am})/I_{200}] \times 100$$
 (1)

where  $I_{200}$  represents the intensity at  $2\theta = 22.5^{\circ}$  and  $I_{am}$  at  $2\theta = 18.7^{\circ}$ . The sample crystallite dimension ( $D_{200}$ ) was calculated using the Scherrer equation:

$$D_{200} = 0.9\lambda/\beta \cos\theta \tag{2}$$

where  $\beta$  is the line broadening at the full width at half maximum (FWHM) after subtracting the instrumental line broadening, in radians. The CrI of TOCNFs was 72% and the crystallite dimension  $D_{200}$  was 2.6 nm.



**Fig. S2.** XRD pattern of TOCNFs supplied by Nippon Paper Industries Co., Ltd. (Tokyo, Japan). CrI = 72% and  $D_{200} = 2.6$  nm.

#### Reference

 Segal, L., Creely, J. J., Martin, A. E. & Conrad, C. M. An Empirical Method for Estimating the Degree of Crystallinity of Native Cellulose Using the X-Ray Diffractometer. *Text. Res. J.* 29, 786–794 (1959).

#### 1.3. AFM image of TOCNFs

The morphology of TOCNFs was analyzed by atomic force microscopy (AFM) with a Dimension Icon SPM apparatus (Bruker Japan Co. Ltd., Tokyo, Japan). The topographic image of the nanocellulose sample was acquired by dropping a water suspension of nanocellulose (0.001% w/w, 3 µL) onto a freshly exfoliated mica plate, followed by being dried in a desiccator at room temperature. As-prepared specimen was measured in a tapping mode using a SCANASYST-AIR probe (k = 0.4 N m<sup>-1</sup>,  $F_0 = 70$  kHz, Bruker Japan Co. Ltd., Tokyo, Japan) with a scan size of 2 µm × 2 µm. The digital data were analyzed with a NanoScope Analysis software (version 1.8).



**Fig. S3.** Topographic image of TOCNFs supplied by Nippon Paper Industries Co., Ltd. (Tokyo, Japan). Average height of each fiber =  $2.62 \pm 0.60$  nm (n = 40).

# 2. Comparison of <sup>1</sup>H NMR spectra for reactions with or without TOCNFs



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**Fig. S4.** Enlargements of <sup>1</sup>H NMR spectra (400 MHz, CDCl<sub>3</sub>) shown in Figs. S5 and S6, which represent the crude mixture from the aldol reaction between 4-nitrobenzaldehyde (300 mg, 2 mmol) and cyclopentanone (10 mL) catalyzed by (*S*)-proline (0.3 mmol) after stirring at 0 °C for 24 h. The singlet at 4.95 ppm was attributed to dibromomethane, used as an internal standard. Top spectrum, with TOCNFs; bottom spectrum, without TOCNFs. Each spectrum was recorded from the combined organic layers dried *in vacuo* after the extraction process and before column chromatography purification.



**Fig. S5.** <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>) of the crude mixture from the aldol reaction without TOCNFs.



**Fig. S6.** <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>) of the crude mixture from the aldol reaction with TOCNFs.

# 3. <sup>1</sup>H NMR spectra of aldol products



**Fig. S7.** <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>) of (R)-2-((R)-hydroxy(4-nitrophenyl)methyl) cyclopentan-1-one.



**Fig. S8.** <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>) of (R)-2-((R)-hydroxy(4-bromophenyl)methyl) cyclopentan-1-one.



**Fig. S9.** <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>) of (R)-2-((R)-hydroxy(4-chlorophenyl)methyl) cyclopentan-1-one.



**Fig. S10.** <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>) of (*R*)-2-((*R*)-hydroxy(naphthalen-2-yl)methyl) cyclopentan-1-one.

### 4. Supercritical fluid chromatography profiles

Each product is described with a set of racemic and asymmetric SFC profiles. The vertical axis corresponds to the absorbance in atomic units (AU) and the horizontal axis is the retention time in minutes (min).



Fig. S11. SFC profile of (R)-2-((R)-hydroxy(4-nitrophenyl)methyl)cyclopentan-1-one. Daicel

Chiralpak IB-3, CO<sub>2</sub>/2-propanol = 95:5, flow = 1.0 mL min<sup>-1</sup>, 30 °C,  $\lambda$  = 264 nm, t<sub>r</sub>(minor) = 3.7 min, t<sub>r</sub>(major) = 3.9 min, *er* (*syn*) = 95:5.



**Fig. S12.** SFC profile of (*R*)-2-((*R*)-hydroxy(4-bromophenyl)methyl)cyclopentan-1-one. Daicel Chiralpak IB-3, CO<sub>2</sub>/2-propanol = 97:3, flow = 1.0 mL min<sup>-1</sup>, 30 °C,  $\lambda$  = 220 nm, t<sub>r</sub>(major) = 2.9 min, t<sub>r</sub>(minor) = 3.4 min, *er* (*anti*) = 94:6.



**Fig. S13.** SFC profile of (*R*)-2-((*R*)-hydroxy(4-chlorophenyl)methyl)cyclopentan-1-one. Daicel Chiralpak IB-3, CO<sub>2</sub>/2-propanol = 97:3, flow = 1.0 mL min<sup>-1</sup>, 30 °C,  $\lambda$  = 220 nm, t<sub>r</sub>(major) = 2.2 min, t<sub>r</sub>(minor) = 2.6 min, *er* (*anti*) = 94:6.



**Fig. S14.** SFC profile of (*R*)-2-((*R*)-hydroxy(naphthalen-2-yl)methyl)cyclopentan-1-one. Daicel Chiralpak IB-3, CO<sub>2</sub>/2-propanol = 97:3, flow = 1.0 mL min<sup>-1</sup>, 30 °C,  $\lambda$  = 220 nm, t<sub>r</sub>(major) = 2.8 min, t<sub>r</sub>(minor) = 3.3 min, *er* (*anti*) = 94:6.

#### 5. Time course of the TOCNFs-enhanced aldol reaction

The reaction conditions are the same as the representative aldol reaction procedure. TOCNFs (300 mg) treated by precipitation in DMF were dispersed in the reaction solvent (DMF, 40 mL) using a double-cylinder-type homogenizer. To the suspension were added 4-nitrobenzaldehyde (300 mg, 2 mmol), cyclopentanone (10 mL), and (*S*)-proline (0.2 mmol), and the resultant mixture was stirred at 0 °C for 24 h. The reaction was aliquoted at an interval of 3 h and analyzed by SFC (Daicel Chiralpak IB-3, CO<sub>2</sub>/2-propanol = 95:5, flow = 1.0 mL min<sup>-1</sup>, 30 °C,  $\lambda$  = 264 nm). Each SFC sample was constituted of an aliquot of the filtered crude mixture diluted in IPA. In overall, the diastereoselectivity and enantioselectivity were constant throughout the reaction (Fig. S15). Slight discrepancies in *ee* were due to the limit of detection of the SFC machine, especially for the minor *anti* enantiomer whose peak intensity was relatively small for accurate quantification (see SFC profiles in Figs. S16–S23).



**Fig. S15.** Left graph: change in the *syn/anti* ratios overtime. Right graph: *ee* change overtime, the blue line with square symbols is the *anti ee* and the orange line with triangle symbols is the *syn ee*.



**Fig. S16.** SFC profile of the crude mixture of the aldol reaction between cyclopentanone and 4-nitrobenzaldehyde after the 3-h reaction.



**Fig. S17.** SFC profile of the crude mixture of the aldol reaction between cyclopentanone and 4nitrobenzaldehyde after the 6-h reaction.



**Fig. S18.** SFC profile of the crude mixture of the aldol reaction between cyclopentanone and 4nitrobenzaldehyde after the 9-h reaction.



**Fig. S19.** SFC profile of the crude mixture of the aldol reaction between cyclopentanone and 4nitrobenzaldehyde after the 12-h reaction.



**Fig. S20.** SFC profile of the crude mixture of the aldol reaction between cyclopentanone and 4nitrobenzaldehyde after the 15-h reaction.



**Fig. S21.** SFC profile of the crude mixture of the aldol reaction between cyclopentanone and 4nitrobenzaldehyde after the 18-h reaction.



**Fig. S22.** SFC profile of the crude mixture of the aldol reaction between cyclopentanone and 4nitrobenzaldehyde after the 21-h reaction.



**Fig. S23.** SFC profile of the crude mixture of the aldol reaction between cyclopentanone and 4nitrobenzaldehyde after the 24-h reaction.

### 6. Molecular models for computational simulation



**Fig. S24.** Slice and side views of a CNF model with a hexagonal shape (19-chains of 10-mers in a  $3 \times 4 \times 5 \times 4 \times 3$  cellulose chain arrangement).



**Fig. S25.** Schematic representation of quantum mechanics (QM) and molecular mechanics (MM) regions for molecular dynamics (MD) simulation of the aldol reaction on the CNF surface shown in Fig. S24.

```
QM/MM-MD simulation for 100 ps
&cntrl
 imin = 0, irest = 1, ntx = 5, ifqnt = 1,
 ntb = 2, ntp = 1, taup = 1.0, pres0 = 1.0, iwrap = 0,
 ntt = 3, gamma_ln = 2.0, tempi = 300.0, temp0 = 300.0,
 cut = 12.0, ntf = 2, ntc = 2, ig = -1, infe = 1,
 nstlim = 200000, dt = 0.0005, ntpr = 200, ntwx = 200, ntwr = 200,
&end
&qmmm
 qmmask = '(:246,268)'
 qmcharge = 0,
 qmshake = 0,
 qm_theory = 'DFTB2',
 dftb_3rd_order = 'PA',
writepdb = 1,
&end
&smd
 output_file = 'smd_work.dat'
output_freq = 500
 cv_file = 'cv.file'
&end
```

**Fig. S26.** Input file for SANDER of AMBER program package using DFTB/MM-MD simulation. All MD calculations were conducted using the SANDER and PMEMD.CUDA modules of the Amber 18 package with the NVIDIA Kepler GPU system (See #53–55 in Notes and references). MD trajectory analysis was performed using the CPPTRAJ module of AmberTools 19 (See #56 in Notes and references).