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Nanocellulose enriches enantiomers in asymmetric aldol reactions†

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Cellulose nanofibers obtained from wood pulp by TEMPO-mediated oxidation acted as a chiral enhancer in direct aldol reactions of 4-nitrobenzaldehyde and cyclopentanone with (*S*)-proline as an organocatalyst. Surprisingly, catalytically inactive TEMPO-oxidized cellulose nanofibers enriched the (*R,R*)-enantiomer in this reaction, affording 89% ee in the *syn* form with a very high yield (99%). Conversely, nanocellulose-free (*S*)-proline catalysis resulted in poor selectivity (64% ee, *syn* form) with a low yield (18%). Green organocatalysis occurring on nanocellulose solid surfaces bearing regularly aligned chiral carbons on hydrophobic crystalline facets will provide new insight into asymmetric synthesis strategies for interfacial catalysis.

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Introduction

Nanocellulose has emerged as a cutting-edge sustainable nanomaterial in the last two decades.^{1–3} Native cellulose, found mainly in phytomass such as trees and plants, is a homopolymer of β -1,4-linked D-glucopyranose.⁴ Biologically synthesized cellulose molecules assemble and then crystallize into nanometer-width fibers during biosynthesis, in which dozens of cellulose chains are regularly packed in parallel.³ Various methods to isolate this naturally occurring nanofiber, known as nanocellulose, have been developed to date, including mechanical, chemical, and enzymatic treatments.^{5–7} The highly crystalline nature of thin nanocellulose provides steel-level mechanical strength, quartz-level thermal stability, and glass-level transparency. Owing to its superior physicochemical properties, accompanied by huge abundance and carbon-neutral renewability, a wide range of studies are currently underway to develop composite fillers,⁸ gas-barrier films,⁹ heat insulators,¹⁰ and solid emulsifiers for foods and cosmetics.^{11,12}

Despite being a developing field, the use of nanocellulose in catalysis is among its most fascinating applications owing to the high demand for green molecular transformations in fine chemical industries. Metal nanoparticle catalysts immobilized

on nanocellulose have been widely studied and demonstrated to have excellent catalytic performance.^{13,14} The high specific surface area and structural rigidity of nanocellulose are key to enhancing catalytic efficiency in heterogeneous reactions.¹⁵ Although nanocellulose has only been reported as a solid support in immobilized catalysts to date, the direct contribution of nanocellulose to heterogeneous catalysis¹⁶ will attract much attention in academia and industry because such novel catalytic systems would expand the potential practical applications of nanocellulose and will open up new horizons in nanocellulose engineering and catalysis science. We have recently reported that typical nanocellulose, especially 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)-oxidized cellulose nanofibers (TOCNFs),¹⁷ significantly accelerate catalytic carbon-carbon bond-forming reactions. We discovered that the simple addition of TOCNFs to the reaction media drastically improved the catalytic efficiency of proline, a low-performance organocatalyst, in a direct aldol reaction¹⁸ and Michael addition.¹⁹ The striking effects of the nanofibrillation and crystallinity of nanocellulose on catalytic performance have clearly indicated that this unique interfacial nanoarchitecture plays an indispensable role in catalytic enhancement.

Some studies have reported that nanosized cellulose materials affect enantioselectivity in catalytic processes. Serizawa and coworkers reported that the hydrolysis of chiral peptides for several days showed different reaction rates for each enantiomer when the hydrolytic reaction was directly catalysed by cellulose nanowhiskers.²⁰ Furthermore, Kaushik and coworkers showed that the hydrogenation of ketones catalyzed by palladium nanoparticles supported on cellulose nanowhiskers afforded the products with some enantioselectivity.²¹ Although the reaction selectivities were insufficient from the viewpoint of asymmetric synthesis, these two reports clearly indicated that

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RSC Adv., 2020, 10, 37064–37071 | 37065

Table 1 Optimization of reaction conditions^a

Entry	Solvent	Temperature	TOCNFs	Yield ^b (%)	<i>syn/anti</i> ^c	ee ^d (% <i>syn/anti</i>)
1	DMSO	rt	—	9	77 : 23	39/54
2 ^e	DMSO	rt	Precipitate	—	—	—
3	DMSO	rt	Precipitate	55	65 : 35	84/71
4	DMF	0 °C	—	18	80 : 20	64/68
5	DMF	0 °C	Precipitate	>99	78 : 22	89/87
6	DMF	0 °C	Gel	86	78 : 22	90/86
7	DMF	rt	Gel	85	71 : 29	60/79

^a Conditions: **1** (2 mmol), **2** (10 mL), (*S*)-proline (0.2 mmol), TOCNFs (300 mg, when used), solvent (40 mL). ^b Isolated yield. ^c Determined by ¹H-NMR (400 MHz, CDCl₃). ^d Determined by chiral-phase SFC. ^e Without (*S*)-proline.

Several reports on proline-catalyzed aldol reactions showed that despite having complex kinetics, the reaction is often reversible, especially at high catalyst concentrations (>30 mol%) and long reaction times (several days). Albeit the reversibility, a critical control on the transition states can grant higher enantioselectivity within relatively short reaction time.^{35,36} Fortunately, TOCNFs enabled faster reaction completion and the use of a lower concentration of (*S*)-proline. Furthermore, upon following the diastereoselectivity determined by SFC analysis until full conversion, no epimerization was detected as the dr stayed constant throughout the reaction (Fig. S15†). As the same was applied to the enantioselectivity, there was no erosion of the ee. Therefore, although there is a possibility for numerous hydroxy and carboxylic acid groups to potentially interact with reaction species, the planar rigid TOCNFs surface probably allowed the stabilization of key transition states as the reaction is kinetically controlled in the presence of the nanocellulose in DMF at 0 °C.

Substrate scope

Different aldehyde substrates were tested in the TOCNF/(*S*)-proline catalyzed aldol reaction (Table 2). The main diastereomer had a *syn*-configuration (Fig. S7–S14†). Surprisingly, all substrates resulted in enhanced enantioselectivity in the *anti*-product. The reaction yields gradually decreased with increasing strength of the electron-withdrawing groups on the aldehyde (entries 1 to 3). The bulky naphthaldehyde yielded the *anti*-product in a low yield with high enantiopurity (entry 4). This effect might be attributed to both electrophilic interaction and steric hindrance between the substrates and the TOCNF solid surface bearing carboxylate groups,³⁹ although a detailed mechanism remains to be determined.

Amino acid scope

Several amino acids were also tested to determine whether they benefitted from the assistance of TOCNFs (Table 3). Excluding

(*S*)-proline, no reaction occurred during the screening time period when using amino acids alone. However, when paired with TOCNFs, an appreciable amount of product was formed within 24 h (entries 2, 4, and 6). In general, the ee of the *anti*-product was high, similar to the case of TOCNFs combined with proline (Table 2). Aliphatic amino acids proved to be a good match with TOCNFs (entries 1–6), while aromatic (*S*)-phenylalanine and (*S*)-tyrosine failed to catalyze the reaction (entries 7–10). This was probably due to both hydrophobic catalysts and substrates being competitively adsorbed on the hydrophobic facets of the TOCNF crystals.

Molecular dynamics simulation

The adsorption of substrates and intermediates onto TOCNFs was probably a key step in these asymmetric aldol reactions. The three-dimensional structure of the product was speculated to be determined by the enantioselective mechanism occurring on the TOCNF surface, rather than asymmetric induction by the

Table 2 Stereoselective aldol reaction in the presence of protonated TOCNFs as a matrix using (*S*)-proline as organocatalyst^a

Entry	R	Yield ^b (%)	<i>syn/anti</i> ^c	<i>syn</i> ee ^d (%)	<i>anti</i> ee ^d (%)
1	4-NO ₂ -C ₆ H ₄	>99	78 : 22	89	87
2	4-Br-C ₆ H ₄	60	63 : 37	53	88
3	4-Cl-C ₆ H ₄	55	64 : 36	55	88
4	2-Naphthyl	24	64 : 36	51	87

^a Conditions: arylaldehyde (2 mmol), cyclopentanone (10 mL), (*S*)-proline (0.2 mmol), precipitated TOCNFs (300 mg), DMF (40 mL). Each product structure conformed to previous reports.^{37,38} ^b Isolated yield. ^c Determined by ¹H-NMR (400 MHz, CDCl₃). ^d Determined by chiral-phase SFC.



Table 3 Scope of amino acids for cooperative catalysis in aldol reaction^a

Entry	Amino acid	TOCNFs	Yield ^b (%)	syn/anti ^c	ee ^d (% syn/anti)
1	(S)-Alanine	—	Trace	—	—
2		+	60	51 : 49	48/89
3	(S)-Valine	—	Trace	—	—
4		+	65	49 : 51	40/91
5	(S)-Lysine	—	Trace	—	—
6		+	54	69 : 31	36/82
7	(S)-Phenylalanine	—	Trace	—	—
8		+	Trace	—	—
9	(S)-Tyrosine	—	Trace	—	—
10		+	Trace	—	—

^a Conditions: **1** (2 mmol), **2** (10 mL), (S)-proline (0.2 mmol), TOCNFs (300 mg, when used), DMF (40 mL). ^b Isolated yield. ^c Determined by ¹H-NMR (400 MHz, CDCl₃). ^d Determined by chiral-phase SFC.

catalyst molecule as a unique chiral source. Attempts on the modelization of hexagonal crystals of TOCNFs for the QM/MM-SMD were unfruitful, probably due to the electronegative carboxylate moiety at the C6 position, which may cause the unstable architecture of cellulose chain assembly. On the other hand, the (100)/(200) planes of TOCNF and CNF crystals are regarded as being both hydrophobic.^{40,41} The adsorption of key intermediates in the TOCNFs-enhanced aldol reaction is expected to occur on the same lattice plane. Despite being less selective, precipitated CNFs devoid of carboxylate groups on their surface also improved the outcome of the reaction with the same conditions as precipitated TOCNFs (90% yield, 54 : 46 dr, 76/68 ee). Therefore, the adsorption behavior of the substrate and enamine intermediate was evaluated on the CNF surface in DMF solution using conventional molecular dynamics (MD) calculations. The substrate (4-nitrobenzaldehyde) was reversibly adsorbed on the hydrophobic surface of CNF of the (100)/(200) lattice planes of cellulose Iβ (Movie 1†). In particular, the molecular axis of 4-nitrobenzaldehyde preferred being perpendicular to the fiber axis of the cellulose chains, with the aromatic plane of the substrate parallel to the pyranose plane. Fig. 2 shows the distribution of substrate and intermediate on the surface of the CNF model for 2 μs, with the clear distribution of 4-nitrobenzaldehyde obtained by reflecting the aromatic ring.

The regular and homogeneous high-density distribution of the substrate exclusively appeared over the cellobiose unit, reflecting the two-fold helical symmetry of a cellulose chain, which suggested that the orientation of the substrate was restricted by the surface topology of the CNF. Conversely, the enamine intermediate showed an obscure distribution, indicating less specific adsorption behavior, albeit with a tendency to be located around the substituted groups of the adsorbed substrate. Therefore, substrate 4-nitrobenzaldehyde on the CNF

surface was especially constrained by carbohydrate–aromatic CH/π and hydrophobic interactions, which possibly led to nucleophilic attack by the enamine intermediate at the aldehyde group of the adsorbed substrate from a specific direction.

This MD simulation successfully provided pictorial elucidation of the enantioselectivity in the presence of CNF observed in the present aldol reaction. Our next target was to verify whether the asymmetric aldol reaction proceeded on the substrate adsorbed on the CNF surface in the manner proposed by the MD simulation. A quantum mechanics (QM)/molecular mechanics (MM)-steered molecular dynamics (SMD) simulation was conducted to evaluate the aldol reaction on the CNF

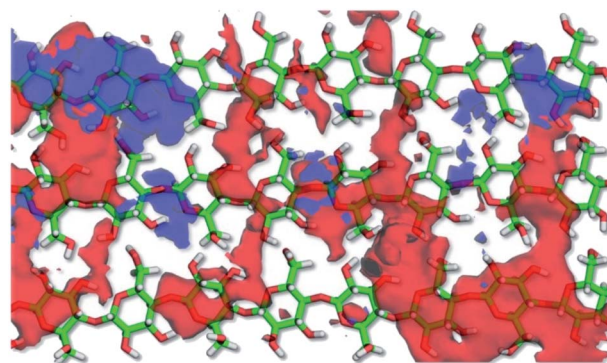


Fig. 2 Isocounter surfaces of the substrate and intermediate density relative to the structures of the CNF model calculated from the MD trajectories. Red and blue surfaces indicate 0.38 mol L⁻¹ (corresponding to twice the bulk density) for 4-nitrobenzaldehyde and the enamine intermediate, respectively. The density was calculated for a 0.5 × 0.5 × 0.5 Å grid as the number of hits in 2 000 000 frames. Molecular graphics with isocontour map were analyzed and drawn using PyMOL 1.7.1 (<http://www.pymol.org>).





Fig. 3 C_{α} - C_{δ} bond forming reaction progression on CNF surface observed by QM/MM-SMD simulation. All structure diagrams were generated using PyMOL 1.7.1 (<http://www.pymol.org>).



Fig. 4 Work distribution and potential mean force (PMF) obtained for the forced approach between the substrate (C_{δ}) and enamine intermediate (C_{α}) in DMF solvents, displayed for 0.01 Å ps^{-1} for 1000 trajectories in an SMD pulling simulation.

surface in a DMF solution. The QM region consisted of the aldehyde substrate and the enamine intermediate involved in the reaction. The MM region included the CNF model, DMF solvent and the surrounding substrates/intermediates that are not directly taking part in the new bond formation (Fig. S25†).

The QM/MM-SMD method showed that C-C bond formation was selected as the reaction coordinate leading to

enantioselectivity, such that the enamine intermediate carbon (C_{α}) was pulled toward the carbonyl carbon (C_{δ}) of the substrate, giving the (*R,R*)-product. As shown in Fig. 3 and Movie 2† (2a and 2b are the same in different drawings), proton transfer occurred from the carboxy group of the enamine intermediate to the carbonyl oxygen of the substrate, accompanied by C_{α} - C_{δ} bond formation. Fig. 4 shows the nonequilibrium work and potential of mean force (PMF) for the reaction coordinate of the C_{α} - C_{δ} distance. The C-C bond forming reaction pathway of the present aldol reaction was exothermic ($\Delta G_r = -10.0 \text{ kcal mol}^{-1}$) and involved the transition state at a C_{α} - C_{δ} distance of 1.95–2.00 Å, in which the eight-membered ring structure with half-chair form contributed to stabilizing the transition state structure.^{42–44} The activation energy (ΔG^{\ddagger}) was estimated to be $3.7 \text{ kcal mol}^{-1}$. Therefore, the asymmetric aldol reaction was reasonably concluded to proceed on the CNF surface. Subsequent hydrolysis provided the reaction products, accompanied by recovery of the (*S*)-proline catalyst (Fig. 5).

Conclusions

In conclusion, green natural nanofibers obtained from wood pulp by aqueous TEMPO-mediated oxidation substantially enriched enantiomers and enhanced catalytic efficiency in direct asymmetric aldol reactions. The proposed catalytic pathway for enantioselective asymmetric aldol reactions occurring on nanocellulose surfaces is shown in Fig. 5. TOCNFs drastically suppressed oxazolidinone formation, which indicates effective prevention of proline decarboxylation in the reaction media and avoidance of undesirable side polymerization reactions among substrates and/or products. MD calculations proved that the aldehyde substrate orientation was controlled by carbohydrate–aromatic CH/ π and hydrophobic interactions on the CNF surfaces. The interfacial interaction was assumed to exert considerable enantiocontrol on the aldol reaction. Furthermore, the reaction proceeded in the direct vicinity of the cellulose surface, as suggested by QM/MM-SMD



Fig. 5 Proposed catalytic pathway for enantioselective asymmetric aldol reactions occurring on nanocellulose surfaces in this study.



calculation results and proposed in Fig. 1. This extraordinary development of highly efficient, enantioselective, and stereo-regulated organocatalysis *via* nanocellulose provides a new direction for green sustainable chemistry and industry.

Experimental

Materials

TEMPO-oxidized cellulose nanofiber (TOCNFs; crystallinity index 72%, crystallite size 2.6 nm, carboxylate content = 1.45 mmol g^{-1}) was kindly supplied by Nippon Paper Industries Co., Ltd. (Tokyo, Japan). 4-Nitrobenzaldehyde and (*S*)-proline were purchased from Sigma-Aldrich Japan Ltd. (Tokyo, Japan) and used as received. Other chemicals and organic solvents were purchased from Sigma-Aldrich Japan Ltd. (Tokyo, Japan), Wako Pure Chemical Industries, Ltd. (Osaka, Japan), and Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), and used as received. Water used in this study was purified using an Arium Ultrapure Water System (Sartorius Co., Ltd., Tokyo, Japan). The water content of the precipitated TOCNFs was measured by Karl Fischer titration method on an MKH-700 titrator (Kyoto Electronics Manufacturing Co., Ltd., Kyoto, Japan). Reaction progress was monitored by thin-layer chromatography (TLC) on glass-backed plates precoated with silica gel (silica gel 60 GF254, 0.25 mm Merck, Tokyo, Japan). Purification by column chromatography was performed using an automated flash chromatography system (Smart Flash EPCLC-AI-580S, Yamazen, Osaka, Japan). All product structures were in agreement with previously reported data from nuclear magnetic resonance (NMR) analysis.^{37,38} ^1H -NMR spectra were recorded on a JNM-ECZ400 spectrometer (JEOL, Tokyo, Japan) at the Center of Advanced Instrumental Analysis, Kyushu University. The enantioselectivity and diastereomeric ratios of products were measured by supercritical fluid chromatography (SFC; ACQUITY UPC2, Waters, Tokyo, Japan) using chiral stationary phases.

Methods

Preparation of TOCNF precipitate. A water suspension of TOCNFs in the sodium carboxylate form (2.01 wt%, 300 mg of dried cellulose) was mixed with 0.1 M aqueous HCl solution (25 mL), shaken several times, and then centrifuged ($12\,000 \times g$, 10 min). The supernatant was then renewed with deionized water (25 mL) and the mixture was centrifuged again. This washing cycle was repeated until the supernatant pH reached 4.5 (3 times). To remove water, the protonated TOCNFs were washed with the type of solvent to be used in the respective aldol reaction using the same centrifugation procedure ($12\,000 \times g$, 10 min, 7 cycles). After the last cycle, the solvent was removed, and the TOCNF precipitate was recovered and used in reactions. Each sample had less than 1.2 wt% (15 eq. of aldehyde 1) water content upon Karl Fischer titration of the dispersed nanomaterial as a reaction solvent.

Preparation of TOCNF organogel. TOCNFs dispersion (0.5% w/v, 100 mg of dried cellulose) was poured into a mold (6 cm \times 5 cm \times 1 cm in size) and covered with a nylon sheet (20 μm

mesh). A 0.1 M aqueous HCl solution (10 mL) was spread over the nylon sheet and the mold was allowed to stand overnight. The resulting stiff gel was cut into cubes (1 cm \times 1 cm \times 1 cm) and shaken gently in 0.01 M aqueous HCl overnight (30 mL). The as-prepared hydrogel cubes were immersed in DMF (30 mL) and shaken gently, renewing the solvent every 8 h (five times), to afford the TOCNF organogel of DMF with less than 1.2 wt% water content (15 eq. of aldehyde 1). Organogel samples of other solvents were prepared using the same procedure.^{45,46}

Representative aldol reaction procedure. Cubes of the TOCNF organogel of DMF or precipitates (300 mg) were dispersed in 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 $^\circ\text{C}$ for 24 h. The reaction was then quenched with water and extracted with CH_2Cl_2 . After drying over MgSO_4 and concentrating, the residue was purified by silica gel column chromatography to afford the product as a colorless oil. The diastereomeric ratio and enantioselectivity were determined using SFC (Chiralpak IB-3; IPA/ CO_2 , 95 : 5; 40 $^\circ\text{C}$; 264 nm).

Molecular dynamics simulation. A CNF model with a hexagonal shape consisting of 19 chains of 10-mers in a $3 \times 4 \times 5 \times 4 \times 3$ cellulose chain arrangement was built based on the crystallographic structural data of cellulose I β (Fig. S24 †).⁴⁷ The DMF suspension system around the CNF model was constructed, including 50 molecules of either 4-nitrobenzaldehyde or the enamine intermediate equivalent to a concentration of 0.19 mol L^{-1} . The latter was an intermediate of the reaction of cyclopentanone with (*S*)-proline in DMF solution (Fig. 5). Conventional molecular dynamics (MD) calculations were performed for the system at constant temperature (300 K) and pressure (1 bar) for 2 μs . The adsorption distribution of 4-nitrobenzaldehyde and the enamine intermediate on the CNF surface was evaluated by analyzing the obtained MD trajectory.

Furthermore, a multiscale simulation combining quantum mechanics (QM) and molecular mechanics (MM) was conducted to reproduce the aldol reaction on the CNF surface. The substrate was appropriately arranged on the CNF model based on the results obtained by MD calculation. The substrate and enamine intermediate involved in the aldol reaction were included as the QM region, and the rest of the system was treated as the MM region (Fig. S25 †). The enamine intermediate was pulled toward 4-nitrobenzaldehyde arranged on the CNF model by an external force of $1000 \text{ kcal mol}^{-1} \text{ \AA}^{-2}$ using a steered molecular dynamics (SMD) method.⁴⁸ The potential of mean force (PMF) of the reaction process was estimated from the exponential Boltzmann-weighted ensemble average of nonequilibrium works obtained from 1000 SMD runs under ambient conditions (300 K and 1 bar) for 100 ps.

The CNF model was described by the GLYCAM06 force field.⁴⁹ 4-Nitrobenzaldehyde, the enamine intermediate, and DMF solvent were modeled using the GAFF force field.⁵⁰ The QM/MM simulation was conducted using the SCC-DFTB-PA method with mio-1-1 parameters (Fig. S26 †).^{51,52} The particle mesh Ewald algorithm was adopted for long-range interactions, and the cutoff for nonbonding interactions in the coordinate



space was fixed at 12 Å. All MD and DFTB/MM-MD calculations were conducted using the SANDER and PMEMD. CUDA modules of the Amber 18 package with the NVIDIA Kepler GPU system.^{53–55} MD trajectory analysis was performed using the CPPTRAJ module of AmberTools 19.⁵⁶

Conflicts of interest

There are no conflicts to declare.

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