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Green Chemistry

Cite this: DOI: 10.1039/x0xx00000x

Received 00th August 2016, Accepted 00th September 2016

DOI: 10.1039/x0xx00000x

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Design of a heterogeneous catalytic process for continuous and direct synthesis of lactide from lactic acid

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We present a continuous one-step reaction pathway for optically pure lactide under atmospheric condition based on a novel SnO_2 -SiO₂ nanocomposite catalyst. The new heterogeneous catalytic system gave a record high lactide yield of 94% with almost 100% enantioselectivity and long-term stability (>2,500 h) from L-lactic acid.

Today, owing to concerns about the shortage of fossil fuel resources and climate change, much attention has been paid to finding substitutes for petroleum-based plastics¹⁻³ and fuels^{4,5}. Polylactic acid (PLA) is regarded as a representative bio-based biodegradable polymer that has many potential applications in packaging, fibres, coatings, and biomedical fields^{6,7}. The global PLA market is expected to grow to one million tonnes per year by 2020⁸.

Industrially, PLA with a molecular weight (Mw) greater than 10⁵ g mol⁻¹ is made from lactide (LT), a six-membered dimeric cyclic ester of (usually L-) lactic acid (LA), using the ring-opening polymerization technique^{6,9}. In this method, LT is produced using a so-called a prepolymer process. In this process, L-LA is first polymerized at ~180 °C to form L-LA oligomer (Mw < 3000), and then depolymerized at ~210 °C to give L-LT via a back-biting mechanism using a Sn-based catalyst, such as SnCl2¹⁰⁻¹² (red path in Fig. 1). However, it is difficult to produce optically pure L-LT with high yields using this prepolymer route because it requires a long residence time (>10 h) at a high reaction temperature and the chemical stability of L-LT is very low¹³. In addition, the whole process should be conducted under high vacuum to separate L-LT rapidly from the reaction system; otherwise, the produced L-LT is degraded easily to L-LA oligomer or meso-LT (M-LT) through reactions with impurities, such as water, LA and catalyst^{10,14}. Another drawback of this process is the production of heavy oligomeric waste (Mw > 5000) that contains Sn metal, which is toxic. Sn is very difficult to recover after the reaction because it is dissolved completely in the oligomer.

Recently, Dusselier et al. reported a new process in which LT could be synthesized with 85% yield from aqueous LA in a batch reactor using H-beta zeolite and toluene^{15,16}. They also proposed that LT (purity > 98%) could be separated from a mixture of toluene, LA, LT, oligomer, and zeolite catalyst by successive filtration, extraction with water, and distillation. However, considering that the LT yield in the commercialized prepolymer process is higher than $90\%^{10}$, the LT yield obtained using this catalytic reaction is not satisfactory, despite using the toxic solvent toluene¹⁷. In addition, the zeolite catalyst must be reactivated after the reaction to remove LA and the oligomer before reuse.

In the early 1990s, DuPont and Biopak patented a one-step continuous process for LT synthesis from LA. In this process, aqueous LA is first converted into vapour, which is passed through a fixed-bed reactor with an Al₂O₃ or SiO₂/Al₂O₃ catalyst to produce $LT^{18,19}$. Compared with the prepolymer route, this simple reaction pathway appears favourable because LA is converted directly to LT without formation of the oligomer intermediate, and the entire process can be operated at atmospheric pressure. Unfortunately, this technology has not been commercialized as it suffers from low LT yield (<40%) owing to poor activity of the conventional acid-type catalysts. Hence, it is necessary to develop a more efficient catalytic system for this technology to be comparable with the conventional prepolymer process.

It should be noted that LA self-oligomerizes in the absence of an acid catalyst because a condensation reaction between the carboxyl and alcohol groups can proceed with ease²⁰⁻²³. LA is first condensed to LA dimer (L₂A) by dehydration (Fig. 2a). L₂A can then be converted to LT by dehydration; however, most L₂A gives LA trimer (L₃A) via a second condensation reaction, especially at long residence times. Thus, to increase LT selectivity, a short residence time is desirable, but a loss of LA conversion is inevitable at this reaction condition. In addition, because LT is transformed easily to L₃A when exposed to LA or M-LT at high temperatures, LT should be desorbed rapidly from the reaction system to prevent its degradation. Considering this reaction mechanism for LA dehydration, it would not be easy to find a reaction system that

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satisfies both high LA conversion and high LT selectivity without an effective catalyst. Here, we report novel heterogeneous catalysis for continuous and direct synthesis of optically pure LT using a SnO_2 -SiO₂ nanocomposite catalyst under atmospheric conditions (blue path in Fig. 1).

First, we investigated the catalytic activities of conventional acidic metal oxides as heterogeneous catalysts for one-step continuous LT synthesis. The LA dehydration reaction was performed in a fixed-bed reactor with continuous flow of aqueous L-LA (75 wt%). Typically, the reaction temperature was maintained at 240 °C with a weight hourly space velocity (WHSV) of 1.0 h⁻¹ under N₂ carrier gas (Fig. S1). The catalytic results for various catalysts are summarized in Fig. 2b (for analysis, see Fig.S2, S3, Tables S1 and S2). SiO₂ gave a very low L-LT yield (13%) at 27% LA conversion, which was almost the same as the result of the blank test (no catalyst). ZSM-5 (Si/Al = 23) zeolite gave a much higher LA conversion (67%), but a L-LT yield of only 25% was obtained because of the high oligomer yield (39%). When the Si/Al ratio of ZSM-5 was increased to 50, the LA conversion was not much changed, but the L-LT yield was greatly improved to 59%. However, when the Si/Al ratio of ZSM-5 was further increased to 280, the L-LT yield decreased considerably to 29%, although the L-LT selectivity was not much affected. These results indicate that the acidity of the catalyst has a positive effect on LA conversion owing to dehydration of LA, but a negative effect on L-LT selectivity owing to successive oligomerization of L2A and L-LT. We also investigated beta zeolite (Si/Al = 25), a shape selective zeolite catalyst¹⁵, in a liquid-phase reaction, which showed similar catalytic activity to ZSM-5 (Si/Al = 280). Therefore, there is a limitation on the yield of L-LT obtained from L-LA using Brønsted acidic catalysts due to unselective acid-catalysed condensation of LA to oligomer.

To overcome the limitations of conventional Brønsted acidictype materials, we designed novel SnO₂-based nanocomposites as heterogeneous catalysts because LA adsorption and LT desorption by SnO_2 is more favourable than that by TiO_2 and Al_2O_3 , according to our thermodynamic calculation (Fig. 3). Using grand canonical Monte Carlo (GCMC) calculations, we found that hydrogen bonding of LA to SnO₂ was more abundant than that to TiO₂ and Al₂O₃, while hydrogen bonding of LT to SnO2 was not observed (Fig. S4 and Fig. S5). The higher adsorption energy of LA for SnO₂ resulted from a strong Coulombic interaction between LA and the bridging oxygen. This particular electrostatic interaction caused adsorption of LA on SnO₂ to be favoured, regardless of the weak van der Waals interaction. However, when LA was transformed into LT, this characteristic interaction disappeared and a slightly smaller total adsorption energy was observed for SnO₂ than for the other substrates (Table S3). We prepared SnO₂-SiO₂ nanocomposites by simple precipitation-deposition of aqueous SnCl₄ on colloidal SiO₂ particles in NaOH, similar to our previously developed method^{24,25}. The Sn content, confirmed by inductively coupled plasma spectrometry, was almost identical to the theoretical loading (Table S4).

Increasing the SnO₂ loading from 40 to 80 wt% in the SnO₂–SiO₂ nanocomposite resulted in an increase of the LA conversion from 79% to 94%, and the L-LT yield was also increased from 63% to 93%. However, further increasing the SnO₂ loading to 90% resulted in decrease of the LA conversion to 93% and L-LT yield to

91%. The lower surface area of $\text{SnO}_2(90)$ -SiO₂ (134 m²/g) might be a main reason of the lower catalytic activity than $\text{SnO}_2(80)$ -SiO₂ (180 m²/g). Interestingly, compared with ZSM-5, crystalline SnO₂ also gave a good LA conversion of 80% and L-LT yield of 69%.

product distribution The determined using liquid chromatography clearly illustrates that the SnO₂(80)-SiO₂ nanocomposite (SSO-80) produces LT selectively, even at high LA conversion, whereas the production of LT by ZSM-5 (Si/Al = 23) is not selective, with a huge amount of oligomers formed (Fig. 4a). The selective formation of LT on SSO-80 was also confirmed by Operando-IR spectroscopy (Fig. 4b). The LT concentration on the SSO-80 surface was highest when the cell temperature was maintained at 250 °C (Fig. S6). However, SiO₂, which had very low LA conversion, only showed a peak corresponding to LA. ZSM-5, which had high LA conversion and low LT yield, showed peaks corresponding to LA oligomer and a negligible LA peak.

To determine the origin of the high catalytic activity of SSO-80, we investigated its physicochemical properties using various techniques. Most Sn was converted to a tetragonal SnO₂ phase after calcination in all SnO₂–SiO₂ composites with different Sn loadings, as confirmed by X-ray diffraction (XRD) patterns (Fig. 4c). The Sn oxidation state of SSO-80 was identified as Sn⁴⁺ by Sn 3d X-ray photoelectron spectroscopy (XPS) (Fig. 4d). From the XRD and XPS results, it is clear that tetragonal SnO₂ species are highly dispersed on the SiO₂ surface, even for loadings as high as 80 wt%^{26,27}. The IR spectra of pyridine chemisorption (Fig. 4e) and NH₃ desorption experiments (Fig. 4f) confirmed that weak Lewis acid sites are dominant on SSO-80, while Brønsted acid sites and strong Lewis acid sites are dominant on ZSM-5.

The morphology and particle size distribution of SSO-80 was analysed using scanning electron microscopy (SEM) (Fig. S7), and uniform particles with sizes smaller than 100 nm were observed. The distribution and size of the SnO_2 particles were measured using transmission electron microscopy (TEM) (Fig. S8). Most of the SnO_2 nanoparticles were spherical in shape without mutual aggregation. The nanoparticles were monodisperse and the average particle size was 2 nm, which corresponds to the crystallite size calculated from the XRD patterns. In high-resolution TEM images, uniform fringes with an interval of 3.34 Å, corresponding to the (110) lattice spacing of the cassiterite phase, were observed over the entire region of the SnO_2 nanoparticle.

The BET surface areas of the SnO_2 -SiO₂ nanocomposites were much higher than that of the crystalline SnO_2 (Table S5). It is thought that the good dispersion of SnO_2 nanoparticles on the SiO₂ surface is responsible for the high surface area, even at high SnO_2 loading. The nitrogen physisorption isotherms of SSO-80 showed characteristic type IV shapes, indicating that SSO-80 has mesoporosity (Fig. S9).

Based on this structural information, we performed density functional theory (DFT) calculations to investigate possible reaction paths converting LA to L_2A or LT over SnO₂ surface. First, consistent with the GCMC results, the DFT results further support the strong interaction between LA and the SnO₂ surface ($\Delta G_{B,LA} = -0.67 \text{ eV}$) owing to both the hydrogen bond between the surface oxygen of SnO₂ and the hydrogen of the LA carboxylic group, and the Lewis acid-base interaction between surface Sn⁴⁺ of SnO₂ and O=C of the LA carboxylic group. For intermolecular dehydration, the OH group of another LA molecule is required to be adjacent to

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the COOH group of the first LA molecule adsorbed on the SnO₂ surface. To retain this local atomistic arrangement, two distinct reaction paths were proposed based on DFT energetics, as shown in Fig. 5. The L_2A formation path (blue in Fig. 5) proceeds via a linear configuration of $(LA)_2^*$, which is thermodynamically more favourable by 0.26 eV, but the second dehydration required for L_2A formation proceeds via a highly unstable conformation of L_2A on the SnO₂ surface (by losing a key COOH–SnO₂ interaction), and is thereby kinetically unfavourable. In contract, the *LT formation path* (red in Fig. 5) proceeds via a cyclic configuration of $(LA)_2^*$, where the COOH and OH groups of both LA molecules are positioned in opposite directions, which is thermodynamically less preferred during the initial stage, but involves no significantly unstable states.

For continuous heterogeneous catalysis, the catalyst stability is vital, together with high activity. It is notable that high LA conversion, as well as high L-LT selectivity, was maintained over SSO-80 at the optimized reaction conditions for more than 2,500 h without a notable loss in activity (Fig. S10). The XRD pattern of the used catalyst was very similar to that of the fresh catalyst, with a tetragonal SnO₂ phase present in both XRD patterns. The TEM analysis confirmed that the used catalyst had well-dispersed SnO₂ nanoparticles with sizes smaller than 5 nm, similar to the fresh catalyst (Fig. S11). The TGA analysis showed almost identical profiles for the fresh and used catalyst, except below 100 °C, which indicates that coke deposition is negligible over the SSO-80 catalyst (Fig. S12). In addition, no decomposition products, such as CO and CO₂, were detected, as confirmed by analysis of the gaseous products using a TCD detector.

After the catalytic reaction using SSO-80, the crude LT crystal was separated from the aqueous solution by filtration. The ¹H NMR spectrum of the crude LT sample had two strong characteristic peaks at 1.68 and 5.05 ppm, corresponding to the methyl (–CH₃) and methine (–CH) groups, respectively, together with weak LA and H₂O-related peaks (Fig. S13).

Conclusions

We designed a novel heterogeneous catalyst for continuous and direct synthesis of optically pure L-LT from L-LA under atmospheric conditions based on SnO_2 -SnO_2 nanocomposites with the average crystallite size of 2 nm, based on GCMC and DFT calculations. The new catalytic system gave a record high LT yield of 94% with almost 100% enantioselectivity and excellent long-term stability (>2,500 h) at a WHSV of 1.0 h⁻¹. By adopting this green process, optically pure lactide can be produced easily from aqueous lactic acid with a high yield and no waste.

Acknowledgements

This work was supported by the R&D Program of Institutional Research Program of KRICT [KK-1601-C00].

Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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Figure 1. Lactide production routes from biomass-derived lactic acid. Conventional two-step batch homogeneous catalysis under vacuum (red) vs. one-step continuous heterogeneous catalysis under atmospheric pressure (blue).

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Figure 2. Reaction pathways and catalyst performance. a) Reaction pathways for lactic acid dehydration to lactide via lactic acid dimer. b) Comparison of catalytic activity over various metal oxide catalysts (reaction conditions: 101.3 kPa, 240 °C, WHSV: 1.0 h⁻¹, N₂ flow rate: 250 mL min⁻¹, time-on-stream: 50 h).

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Figure 3. Adsorption isotherms with respect to fugacity at 544 K for L-lactic acid (a) and L-lactide (b). The confidence limits of the data are smaller than the symbols. The number of adsorbed molecules was divided by the surface area of each catalyst, and then multiplied by a factor, i.e. 1000, which is similar to the area of the catalysts, for the clear view



Figure 4. Product distributions with catalyst and characterization of SnO_2 -SiO₂ nanocomposites. a) HPLC product profiles. b) Operando-IR spectra. c) XRD patterns. d) Sn 3d XPS patterns. e) FTIR spectra of pyridine chemisorption (pretreatment at 400 °C for 2 h; adsorption at 20 °C; desorption at 100 °C for 1 h). f) NH₃ desorption spectra (pretreatment at 600 °C for 2 h; adsorption at 100 °C).



Figure 5. DFT calculated free energy changes of the reaction paths for L_2A formation (blue) and LT formation (red), where green, red, grey, and white balls represent Sn, O, C, and H atoms, respectively, and black dashed lines represent hydrogen bonds