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A large-scale continuous-flow process for the production of adipic acid *via* catalytic oxidation of cyclohexene with H_2O_2 [†]

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The demand for a clean production process of adipic acid (AA) can be achieved by developing a synthetic route using H_2O_2 as the oxidant. In this paper, a green process with a recyclable catalyst system consisting of H_2WO_4 , H_2SO_4 and H_3PO_4 was developed for the production of AA *via* catalytic oxidation of cyclohexene. A continuous-flow reactor was set up for the optimization of the reaction parameters and developing the industrial operation of this green process. The mixture of H_2SO_4 and H_3PO_4 as acidic promoter displays a significant improvement in the activity of catalyst and the stability of H_2O_2 . The catalyst could be recovered and reused 20 times, and no significant loss of catalytic performance can be observed. The effect of Fe³⁺ ion as a possible contaminant has no serious negative effect on this reaction, and the 316L stainless steel and glass-lined steel were selected as appropriate equipment material. Calorimetry and the scale-up in batch reactor demonstrate that the reaction could be operated safely on scale. The process was scaled up in a continuous-flow pilot plant, with excellent yield (94.7%) and purity (99.0%). Some advantages such as the solvent-, phase-transfer-catalyst-, and organic additive-free and low-cost light up the application of this process in the industrial production of AA.

Introduction

Adipic acid (AA) is the main raw material for manufacturing nylon 6,6 and many other products,^{1,2} with a global annual production over 3.50 million tons. Currently, there are two commercial processes for the production of AA (Fig. 1).² The traditional process developed by DuPont for the production of AA (Fig. 1a) involves the hydrogenation of benzene to cyclohexane, the oxidation of cyclohexane to KA oil (the mixture of cyclohexanol and cyclohexanone) with air as oxidant, and the oxidation of KA oil to AA with HNO₃. The application of selective hydrogenation of benzene to cyclohexene has provided a novel way to product abundant and cheap cyclohexene, which was used for the industrial synthesis of AA.³⁻⁶ The improved process developed by Asahi Kasei (Fig. 1b) involves the selective hydrogenation of benzene to cyclohexene, the hydration of cyclohexene to cyclohexanol, and the oxidation of cyclohexanol to AA with HNO₃. Due to removing the procedure of cyclohexane oxidation with air, the Asahi Kasei process improves the operational safety and the utilization of carbon atom significantly. It is noteworthy that both of the above two processes produce a large amount of N₂O, an environmentally harmful greenhouse gas.^{7,8} A supplementary catalytic reactor must be employed for conversion of N2O into

 N_2 and O_2 . Therefore, several environmentally benign methods for the synthesis of AA have been designed and investigated, such as the oxidative cleavage of 1,2-diol by HNO_3 ,⁹ the oxidation of 1,2-diol or cycloalkanones by hydrogen peroxide,^{10–12} the synthesis from D-glucose or muconic acid,^{13,14} the oxidation of cyclohexane by dioxygen,^{15–20} and the bishydroformylation of 1,3-butadiene.²¹ Nevertheless, novel environmentally benign methods are still needed for the industrial production of AA.

One-step oxidative cleavage of cyclohexene to adipic acid with H_2O_2 has been considered to be one of the green synthetic processes with most potential up to date.¹ H_2O_2 is a cheap and



Fig. 1 (a, b) Current industrial processes and (c) green processes for production of AA.

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environmentally benign oxidant with water as the only byproduct, and thus it has played an important role in environmentally benign methods in the chemical industry.^{22,23} Currently, H_2O_2 is produced on an industrial scale by the anthraquinone oxidation process.²³ The cost of manufacturing H₂O₂ has continued to decrease by the progress of process technology and the increasing economies of scale. New promising methods for H₂O₂ production, such as synthesis from CO/O₂/H₂O mixtures, direct synthesis from O₂/H₂, photocatalytic synthesis and bioinspired production, will make this key reagent of green chemistry even cheaper.^{22,23} In 1998, Noyori had obtained a historic breakthrough in the green production of AA via one-step oxidative cleavage of cyclohexene to AA with H_2O_2 (Fig. 1c).¹ In Novori's system, the homogeneous tungstic catalysts showed excellent catalytic activity for oxidation of cyclohexene to AA.^{1,24-33} In order to accelerate the reaction, quaternary ammonium salt was employed as phase-transfer catalyst.^{1,24} The phase-transfer catalyst can be replaced by organic ligands, which coordinate onto peroxotungstate.²⁵⁻²⁸ Surfactant-type peroxotungstate had also been synthesized and used in this organic solvent-free catalytic synthesis of AA.²⁹ Na₂WO₄ in acidic ionic liquids and Dawson polyoxotungstate also were reported as effective catalysts.^{30,31} The microwave reactor and PVDF flat membranes as contactors for direct solvent-free biphasic oxidation of cyclohexene to AA have been researched.^{32,33} The zeolite, mesoporous material or heteropolyacid supported on metal oxide also showed somewhat activity in synthesis of AA with H₂O₂.³⁴⁻³⁹ However, owing to the difficulty in recycling catalyst, ^{1,34,35,38} these attractive methods for the synthesis of AA via green oxidation of cyclohexene have not been industrialized. Hence, this oxidation reaction requires further improvements with particular focus on the recycle of catalyst, as well as the effective utilization of H₂O₂ by avoiding the unproductive decomposition.

Compared to batch operation, the continuous-flow techniques has significant processing advantages.⁴⁰ A particularly attractive feature of continuous-flow process is the ease with which reaction conditions can be scaled up to achieve production scale. In previous works, process development and theoretical studies of the green oxidation of cyclohexene to AA with catalyst system of peroxotungstate have been carried out for several years in our laboratory.^{41–46}

Herein, we report a large-scale continuous-flow process for green production of AA *via* catalytic oxidation of cyclohexene with H_2O_2 as oxidant using H_2WO_4 , H_2SO_4 and H_3PO_4 as catalyst precursor. The present method possesses the following advantages: (1) no N_2O produced; (2) organic-solvent- and quaternary-ammonium-free system; (3) high yield and purity for AA; (4) the catalyst can be reused and possesses excellent stability; and (5) simple, inexpensive and safe.

Results and discussion

A recyclable catalyst system

In order to solve the problem of recycling tungstate catalyst, our group explored a recyclable catalyst system. As a starting point, the effect of different acidic promoters on the yield of AA and the stability of H_2O_2 in the green oxidation of cyclohexene to

AA with H₂O₂ using peroxotungstate formed in situ as catalysts in the absence of organic solvents and phase-transfer catalyst were investigated and compared (Table S1, ESI[†]). With H₂SO₄ as acidic promoters, the highest yield of AA was obtained. The vield of AA increased with the increase of acidity of acidic promoters except HCl and HNO3, which was similar to the results in previous reports.^{24,27,46} Although HCl is very strong in acidity, the yield of AA is low with HCl as acidic promoters. The reason is that the volatility of the HCl (or HNO_3), decrease actual acid concentration in heated liquid phase that leads to the decrease of catalyst activity. The stability of H₂O₂ in the presence of different acidic promoters was also investigated (Table S1, ESI^{\dagger}). The results demonstrate that H₂O₂ is more stable in the presence of H_3PO_4 or 5-sulfosalicylic acid. The reason is that H₃PO₄ and 5-sulfosalicylic acid can sequester many transition metals, reduce their catalytic activity for unproductive decomposition of H₂O₂, and stop H₂O₂ decomposition as radical scavenger.47

 H_2SO_4 was selected as the primary promoter for the oxidation of cyclohexene to AA, and H_3PO_4 was used as assistant promoter to improve the stability of H_2O_2 , because they are much more inexpensive and stable than 5-sulfosalicylic acid. Thereby a system consisting of H_2WO_4 , H_2SO_4 and H_3PO_4 was chosen as catalyst precursor. The influence of addition amount of H_2SO_4 and H_3PO_4 on the yield of AA and the stability of H_2O_2 were studied and the results are shown in Fig. 2. As shown in Fig. 2a,



Fig. 2 The effect of (a) H_2SO_4 and (b) H_3PO_4 on AA yield and H_2O_2 decomposition. Reaction conditions: (a) H_2WO_4 , H_3PO_4 , cyclohexene and H_2O_2 in a molar ratio of 1:0.5:50:220 (all other conditions were given in the Experimental section). (b) H_2WO_4 , H_2SO_4 , cyclohexene and H_2O_2 in a molar ratio of 1:1.04:50:220 (all other conditions were unchanged).

the ratio of H₂SO₄ in catalyst system has clear effect on the catalytic performances. Based on the experimental data of production yield, the simulated curve about the effect of sulfuric acid on AA yield was given via cubic Spline function fitting. The simulated curve showed that the suitable molar ratio of H₂SO₄ to H₂WO₄ was 1.04, which was also validated by experiment. When the molar ratio of H_2SO_4 to H_2WO_4 was 2.2, the byproducts (such as glutaric acid and succinic acid) in the reaction solution were increased over 3%. It indicates that the excessive H₂SO₄ caused oxidative degradation of intermediate and reduced reaction selectivity.⁴⁶ In addition, H₂SO₄ caused the increase of H₂O₂ decomposition, especially when the molar ratio of H_2SO_4 to H_2WO_4 was above 1.2. It could be seen in Fig. 2b that the suitable molar ratio of H_3PO_4 to H_2WO_4 was 0.56, and the highest AA yield up to 92.3% was obtained. When the molar ratio of H₃PO₄ to H₂WO₄ increases over 0.56, the yield of AA decreases with the further increase of H_3PO_4 , although the decomposition of H_2O_2 decreased slightly. Thus a catalyst precursor system consisting of H₂WO₄, H₂SO₄ and H₃PO₄ in a molar ratio of 1.00: 1.04: 0.56 was employed, and excellent results (92.3% product yield and 7.1% H₂O₂ decomposition) were obtained under the optimized catalyst precursor.

Fig. 3 shows the reuse results of the catalyst. This catalyst could be recycled easily. After the AA crystal was separated from the oxidation reaction mixture, the filtrate was condensed

70

60

50

40

30

Ú,H

(a) 100

90 %

80

70

60

AA yield



Fig. 3 The reuse of catalyst (a) in the present of H_3PO_4 and (b) in the absence of H₃PO₄. Reaction conditions: (a) H₂WO₄, H₂SO₄, H₃PO₄ cyclohexene and H₂O₂ in a molar ratio of 1:1.04:0.56:50:220 (all other conditions were given in the Experimental section). (b) H_2WO_4 , H_2SO_4 cyclohexene and H_2O_2 in a molar ratio of 1:1.04:50:220, without H₃PO₄ (all other conditions were unchanged).

and reused in the next run. This recycled catalyst (H₂WO₄, H₂SO₄ and H₃PO₄ as precursor) could be reused for twenty cycles in the oxidation of cyclohexene to AA without significant loss of catalytic activity (Fig. 3a). The average yield in twenty cycles was over 93%, and only slight increase of unproductive decomposition of H₂O₂ was observed. At the end of the reaction, the recovery efficiency of the catalyst was about 90 wt%. In contrast, the catalyst system with tungstatic acid and sulfuric acid as catalyst precursor rapidly deactivated (Fig. 3b).

The active structure of this catalyst system (with H₂WO₄, H_2SO_4 and H_3PO_4 as precursor) is $\{PO_4[WO(O_2)_2]_4\}^{3-}$ synthesized *in situ*. $^{48-53}$ According to previous experiments and the reaction pathway proposed by Noyori,^{1,46} this reaction should include the organic-water heterogeneous reaction stage (stage A in Fig. S1, ESI⁺) and the homogeneous reaction stage (stage B in Fig. S1, ESI[†]). The experimental results show that, with the consumption of H₂O₂ in reaction, the catalyst system is converted into soluble H₃PW₁₂O₄₀ (Fig. S2a and S3a, ESI[†]), which is a commonly used catalyst for oxidation using H₂O₂ as the oxygen donor and can rapidly form $\{PO_4[WO(O_2)_2]_4\}^{3-}$ in moderate concentration of H₂O₂ solution.^{11,50} Even in low concentration of H₂O₂ solution (5%), the catalyst system can retain catalytic activity for the oxidation of 1,2-cyclohexanediol to AA (Table S3, ESI[†]), which is the main reaction in the homogeneous reaction stage. In the next run, when H₂O₂ is added into the reaction system, $H_3PW_{12}O_{40}$ is reconverted into $\{PO_4[WO(O_2)_2]_4\}^3$ as active catalyst of oxidation reaction. 10,50 Therefore, the catalyst can be recycled without significant loss in catalytic activity. Comparatively, the colloidal tungstic acid is formed in the absence of H₃PO₄ with the concentration of H₂O₂ decreasing (Fig. S2b and S3b, ESI⁺), which leads the leaching of tungsten and the deactivation of catalyst (Table S3, ESI⁺). Thus, the H₃PO₄ in catalyst system, not only restrains the decomposition of H₂O₂, but also retains the active structure of catalyst in low concentration of H₂O₂ solution.

According to our experiments for verifying the promoting action of H_2SO_4 and H_3PO_4 on this reaction (Table S2, ESI^{\dagger}), in the organic-water heterogeneous reaction stage, the TOF of cyclohexene and the yield of 1,2-cyclohexanediol decreased significantly from 25.7 h^{-1} to 4.1 h^{-1} , and 54.0% to 4.0%, respectively, while the yield of 1,2-epoxycyclohexane increased from 0.0% to 6.1%, after adding Na₂CO₃ into the reaction system to adjust the pH value of aqueous phase of to 7. Finally, the yield and purity of AA decreased significantly from 90.2% to 8.5%, and 98.0% to 77.6%, respectively, concurrently with the increase of the unproductive decomposition of H_2O_2 to H_2O and O_2 from 7.2% to 35.8%. Even using 1,2-cyclohexanediol as substrate, the yield and purity of AA were as low as 25.1% and 88.7% respectively, concurrent with a highly unproductive decomposition of H_2O_2 (30.3%). H_2SO_4 gives higher TOF of cyclohexene and yield of AA than H₃PO₄, while H₃PO₄ gives a lower unproductive decomposition of H₂O₂ than H₂SO₄ by sequestering transition metals and scavenging radical which cause decomposition of H₂O₂.⁴⁷ The results demonstrate that a highly acidic system is efficient in the increase of the utilization rate of H2O2, and more significantly in the acceleration of the acid-catalyzed hydrolysis of 1,2-epoxycyclohexane to 1,2-cyclohexanediol and adipic anhydride to AA. In combination with the stabilizing effect of H₃PO₄ on catalyst system and H₂O₂ during the recycling

reaction, this formulation of catalyst system leads to the effective oxidation of cyclohexene to AA with $\rm H_2O_2.$

Process development and scale-up

In order to reasonably design the continuous-flow reactor, the catalytic oxidation of cyclohexene with this catalyst system was monitored (Fig. 4). The conversion of cyclohexene, the formation of 1,2-cyclohexandiol and the formation of AA versus time are shown in Fig. 4a. No 1,2-epoxycyclohexane was detected in this reaction system, because of the rapid hydrolysis of 1,2-epoxycyclohexane to 1,2-cyclohexandiol in the presence of strong acid. Hence, the irreversible inactivation of catalytic system ($\{PO_4[WO(O_2)_2]_4\}^{3-}$) at high concentrations of epoxide is avoided.⁵⁰ 1,2-Cyclohexandiol produced in stage A is rapidly converted to other intermediates and AA in the first hour of stage B. Interestingly, the conversion of cyclohexene is an accelerated process. Because cyclohexene is insoluble in water, the turnover rate of cyclohexene is limited by organic-aqueous mass transfer at first. With the increase of soluble organics such as 1,2-cyclohexandiol, the solubility of cyclohexene in aqueous phase improves, so the turnover rate of cyclohexene increases. Hence, the high conversion and turnover rate of cyclohexene can be simultaneously achieved in one continuous-flow reactor. The

100 100 (a) 80 80 Conversion (%) 60 60 Yield (% ---- Cyclohexene 40 40 - Cyclohexandiol ---- Adipic acid 20 20 0 0 2 3 4 5 6 8 0 Time (h) 96 - (b) 92 Yield (%) 88 84 AA yield Simulation curve 80 120 130 140 150 160 170 180 Residence time (min)

Fig. 4 The effect of (a) reaction time in batch reactor and (b) residence time in continuous-flow reaction device. Reaction conditions: (a) H_2WO_4 7.57 mmol, H_2SO_4 7.88 mmol, H_3PO_4 4.24 mmol, cyclohexene 380 mmol, and H_2O_2 1.67 mol (all other conditions were given in the Experimental section). (b) The reactants and catalyst were fed continuously into the continuous-flow reactor (all other conditions were given in the Experimental section).



Fig. 5 The simplified process flow diagram. Abbreviations: CR, crystallizer; P, pump; R, reactor; RC, reflux condenser; T, tank; TE, thermo element, TS, thermo sensor; V, valve.

formation of AA increases rapidly in the first hour of stage B with rising reaction temperature and then increases slowly because of the decrease of H_2O_2 and 1,2-cyclohexandiol. Therefore, multiple continuous flow reactors in series should be employed for high yield of AA in the stage B.

To the best of our knowledge, a relatively small number of reactors in series required in the reaction were usually chosen to avoid excessive complication.^{54,55} A continuous-flow reaction device consisting of four continuous stirred-tank reactors (CSTR) in series was designed and employed to examine the feasibility of the continuous-flow process and optimize process condition, and the simplified process flow diagram of scale-up reaction is shown in Fig. 5 (the reaction device of laboratory scale is shown in Fig. S4, ESI[†]). The effects of residence time (τ) in continuous-flow reactor on the oxidation of cyclohexene to AA with H₂O₂ were investigated (Fig. 4b). The results indicate that the optimal retention time in the continuous-flow reaction device is 588 min (optimization *via* cubic Spline function fitting), and the actual yield (94.1%) is slightly lower than the yield of simulated result.

The effect of reaction temperature on the AA yield in the continuous-flow device was studied, and the results are listed in Table 1. As shown in Table 1, with the increase of reaction temperature in the first reactor of the continuous-flow reaction device, the yield of AA increased remarkably. Due to the limitation of the boiling point of water–cyclohexene mixture (70.9 °C), 73 °C was selected as the reaction temperature in the first reactor. In the subsequent reactors, the highest yield of AA was obtained at 90 °C. Because the oxidation of 1,2-cyclohexanediol and other intermediates produce more byproducts at higher temperature, and at lower temperature, incomplete oxidation of 1,2-cyclohexanediol results in low AA yield.⁴⁶

Hydrogen peroxide can decompose to oxygen and water with iron ion as catalyst. If some Fe^{3+} leach from the material of reactor and pipeline, this possible side reaction would decrease the utilization of H_2O_2 . The influence of Fe^{3+} ion on decomposition of H_2O_2 during the catalytic reaction was investigated. The results are shown in Fig. 6a. The decomposition of H_2O_2 distinctively increases with the increase of the Fe^{3+} concentration, and the decomposition ratio of H_2O_2 is 14.2%, even if the concentration of Fe^{3+} is up to 10.0 ppm. The results demonstrate that this reaction system can tolerate a certain concentration of Fe^{3+} , because phosphoric acid, 1,2-cyclohexandiol,

 Table 1
 The AA yield at various reaction temperatures in CSTRs⁴

Tempera	ture (°C)			
R1	R2	R3	R4	Yield of AA (%)
73	90	90	90	94.1
68	90	90	90	85.4
63	90	90	90	78.5
73	95	95	95	91.4
73	85	85	85	80.9

^{*a*} Reaction conditions: H_2WO_4 , H_2SO_4 , H_3PO_4 , cyclohexene and H_2O_2 in a molar ratio of 1:1.04:0.56:50:220, the total retention time in CSTRs was 580–590 min (all other conditions were given in the Experimental section).



Fig. 6 (a) The influence of Fe^{3+} and (b) various materials on AA yield and H_2O_2 decomposition. Reaction conditions: (a) H_2WO_4 , H_2SO_4 , H_3PO_4 , cyclohexene and H_2O_2 in a molar ratio of 1:1.04:0.56:50:220, the total retention time in CSTRs was 580–590 min (all other conditions were given in Experimental section). (b) The surface area of material for test is 0.01 m² per kg reaction mixture and the time over test is 100 h (all other conditions were unchanged).

2-hydroxycyclohexanone and AA could sequester Fe^{3+} and quench the chain mechanism of H_2O_2 decomposition as radical scavengers.⁴⁷ Furthermore, the test of gas explosion indicates that the gas mixture in the reactor headspace is outside the explosion limits and thus the oxidation processes can be handled safely.

The influence of various materials (such as glass-lined steel, graphite, 316L and 304 stainless steels) for manufacturing reactor and pipeline on the reaction was investigated (Fig. 6b). The results demonstrate that glass-lined steel and 316L stainless steel are suitable material of the equipment for this green oxidation. The glass and 316L stainless steel can resist the corrosion of this reaction system, and the increase of the concentration of metal ions (such as Fe, Cr, Mn, Co, Ni, and Mo) due to leaching from the reactor material in mother liquor is under the detection limit. Therefore, the glass-lined steel was selected as the chemical tanks material and the 316L stainless steel was used as the material of pipelines and mechanical parts of reactor.

With the optimized reaction conditions, we paid attention to the scale-up. Safety assessment on the oxidation reaction was conducted by calorimetry in continuous-flow reactor (Fig. 7a) and batch reactor (Fig. 7b). Fig. 7a shows the heat release rate of the reaction in each reactor of CSTRs on steady-state conditions. The maximum heat release rate of 93.9 W kg⁻¹ observed at the second reactor, indicating the rapid oxidation of 1,2-cyclohexandiol to AA. Thus, the transfer of heat *via* cooling system is



Fig. 7 The calorimetric profiles in (a) CSTRs and (b) batch reactor. Reaction conditions: (a) H_2WO_4 15.14 mmol, H_2SO_4 15.76 mmol, H_3PO_4 8.48 mmol, cyclohexene 760 mmol, and H_2O_2 3.34 mol (all other conditions were given in the Experimental section). (b) Reaction in 4×1 L CSTRs (all other conditions were given in the Experimental section).

Table 2The continuous-flow reaction and batch reaction on a large $scale^a$

Reactor	Volume of reactor (L)	Yield of AA (%)	Purity of crude product (%)
Batch	5	93.0	98.0
Batch	100	89.5	99.1
Batch	2000	96.3	98.9
Batch	5000	95.8	99.2
CSTRs	4×0.5	94.1	98.8
CSTRs	4×100	92.0	98.7
CSTRs	4×5000	94.7	99.0

^{*a*} Reaction conditions: H_2WO_4 , H_2SO_4 , H_3PO_4 , cyclohexene, and H_2O_2 in a molar ratio of 1 : 1.04 : 0.56 : 50: 220, at 73 °C (all other conditions were given in the Experimental section).

essential in scale-up reactor. The results demonstrate that no uncontrollable heat accumulation occurred in the continuousflow reactor and the reaction could be operated safely on scale. Fig. 7b shows the representative heat output with reaction time in this oxidation. Oxidation of cyclohexene was marked by a mild exothermal event devoid of significant thermal activity until the system was converted to homogeneous phase. A significant exothermic event took place upon the second hour since the beginning of reaction, with a maximum heat release rate of 220.2 W kg⁻¹ observed at about 123 min, indicating the formation of AA, and then the heat release rate decreased and a subsiding of heat release was observed, which indicated that the reaction rate decreased because of the decrease of H₂O₂ and 1.2cyclohexandiol. In comparison with the reaction in batch reactor, excellent thermal management was obtained within continuousflow reactor. At first scale-up was carried out in batch reactors, and the results shown in Table 2 demonstrate that the reaction heat of large-scale reaction is controllable and the reaction system can be operated safely on large scale. The results of an experiment to validate reproducibility of scale-up are shown in Table S4 in the ESI,† indicating that the reactions of scale-up were reproducible.

Scale-up and pilot-scale continuous-flow reactions were performed in a reaction device consisting of four 100 L continuous stirred-tank reactors in series (4×100 L CSTRs) and reaction device consisting of four 5000 L continuous stirred-tank reactors in series (4×5000 L CSTRs), representing a 200-fold scale-up and 10 000-fold scale-up from the laboratory-scale reaction. The product was sampled and analyzed every 10 h by HPLC to monitor constancy of the reaction. The results were shown in Fig. S5 in ESI,† indicating that the large-scale continuous-flow reactions were constant. In the pilot plant, the reaction was successfully run for 350 h, and both AA yield (94.7%) and product purity (99.0%, crystalline solid without recrystallization) were excellent. The results indicate that the optimized laboratory process was successfully scaled up 10 000-fold in the pilot plant, giving good agreement between both product yield (94.7% in pilot plant and 94.1% in the laboratory) and product purity (99.0% in pilot plant and 98.8% in the laboratory).

Compared with the current industrial processes, this green process is environmentally benign and more simple. From cyclohexene (or cyclohexane) to crude product, the current industrial processes require five units (Fig. 1a) for reaction, separation and waste gas treatment, the DuPont process consists of five units, such as cyclohexane oxidation, distillation separation of KA oil, oxidation of KA oil, crystallization separation and waste gas treatment, and the Asahi Kasei process consists of five units (Fig. 1b), such as cyclohexene hydration, distillation separation of cyclohexanol, oxidation of cyclohexanol, crystallization separation and waste gas treatment. As an improvement, this green continuous-flow process requires only two units consisting of cyclohexene oxidation with H_2O_2 and crystallization separation. The simplification of process increases the production efficiency of AA and reduces the cost of chemical plant.

Conclusions

In conclusion, the oxidation of cyclohexene to AA with H_2O_2 has been studied using a catalyst system synthesized in situ by H_2WO_4 , H_2SO_4 and H_3PO_4 in H_2O_2 , under the solvent-, phasetransfer-catalyst- and organic additive-free conditions. A continuous-flow reactor was set up for the industrial operation of this green process and the optimization of the reaction parameter. The activity and stability of the catalyst depended strongly on the acidic promoters. Under the optimal experimental conditions, the catalyst system exhibits an excellent catalytic performance and can be reused for twenty cycles with an average yield over 93% in batch reactor. A green and efficient continuous-flow process for AA production has been developed using this recyclable catalyst system. The laboratory-scale reaction was successfully scaled up 10 000-fold in the pilot plant. Both the product yield (94.7% in pilot plant and 94.1% in laboratory) and the purity of crude product (99.0% in pilot plant and 98.8% in laboratory) are excellent. The results of calorimetry, scale-up and pilot-scale continuous-flow reaction indicate that the industrialization of this green synthesis is safe and feasible. It will be an alternative for the current industrial process.

Experimental

Materials and apparatus

All materials were used as received except 30% H₂O₂ was diluted to 27.5%. Optimization of catalyst and process development experiments in lab were performed using glass flasks (0.5 L), and a continuous-flow reaction device consisting of four

0.5 L continuous stirred-tank reactors in series (4 \times 0.5 L CSTRs). The scale-up experiments of batch operation were performed using glass reactor (5 L) and glass-lined reactors (100–5000 L) of geometric similarity equipped with heating jacket, agitator and reflux condenser. Calorimetric experiments for safety assessment were performed using Mettler-Toledo RC1 reaction calorimeter equipped with a 1 L jacketed glass vessel, a teflon straight blade agitator and a reflux condenser. The scale-up and pilot-scale of continuous process were performed using four 100 L continuous stirred-tank reactors in series (4 \times 100 L CSTRs, glass-lined) and four 5000 L continuous stirred-tank reactors in series (4 \times 5000 L CSTRs, glass-lined).

General analytical methods

For the determination of catalysts composition, inorganic acids were analyzed by ion chromatography (IC) using a Dionex ICS-2100 equipped with an electrical conductivity detector. Reaction process and soluble organics were evaluated by HPLC, using a Hewlett-Packard Series 1100 HPLC equipped with a UV detector and a differential refraction detector. The cyclohexene conversion was monitored by internal standard method using a Techcomp 7890 GC equipped with OV-1701 capillary column and a FID detector. The gas from the reaction system was monitored by an Albright gas analyzer. The test of gas explosion was carried out in a detonation reactor.

Catalytic oxidation

Typical procedure of catalytic oxidation in batch reactor. A batch reactor was charged with H₂WO₄, H₂SO₄, H₃PO₄, cyclohexene and aqueous H_2O_2 in a molar ratio of 1:1.04:0.56:50:220. For lab-scale reaction, the oil-water mixture was heated to 73 °C and refluxed for 2 h with violent stirring. After the organic phase was consumed the homogeneous reaction mixture was heated to 90 °C with the rate of 1 °C min⁻¹. For large-scale reaction, the oil-water mixture was heated to 73 °C by steam-heating unit, and then heat exchange system was switched to water-cooling unit to remove the reaction heat. After the organic phase was consumed the water-cooling unit was turned up with the temperature rising of reaction system to avoid temperature runaway. The homogeneous reaction continued at 90 °C for 6 h. Meanwhile, the gas from the reaction system was monitored by an Albright gas analyzer to evaluate the decomposition of H_2O_2 and performed by the test of gas explosion. After completion of the reaction, the reaction solution was kept at 0 °C for 12 h, and the resulting white crystals was separated by filtration and dried in vacuum at 60 °C. The reaction solution and product were determined by HPLC. After the AA crystal was filtered, the filtrate was condensed and reused for the next run (for large-scale reaction, the filtrate was treated by acid resin-bed before concentration).

Typical procedure for lab-scale catalytic oxidation in continuous-flow device. The continuous-flow reaction device is shown in Fig. S4, ESI.[†] This device was made up of CSTRs, equipped with Teflon agitator and reflux condenser, peristaltic pump, reagent container, temperature controller and thermo element. The reagent containers, CSTRs and pumps were connected with pipe of viton. The system was filled with mother liquor of batch reaction at first. After temperature stabilization (the reaction temperature in R1 reactor of CSTRs is 73 °C, and in other reactor is 90 °C), the reactants and catalyst consisting of cyclohexene, aqueous H2O2, H2WO4, H2SO4 and H3PO4 in a molar ratio of 1:1.04:0.56:50:220 were fed into the reactor continuously from the reagent container by peristaltic pump, with a total retention time in CSTRs was 580-590 min. (The residence time τ was calculated according to the equation: τ [min] = reactor volume [mL]/total flow rate [mL min⁻¹].) Product collection began two residence times (20 h) later, and the previously produced material was rejected. The consistency of the flow rate was verified by measuring the consumed volume of starting material in a certain interval. The product was sampled and analyzed every 10 h by HPLC to monitor constancy of the reaction. After the crystallization separation of AA, the filtrate was condensed by rotary evaporator and reused as catalyst in the next run.

Typical procedure for large-scale catalytic oxidation in continuous-flow device. The process flow diagram of continuousflow reaction is shown in Fig. 5. This device was made up of CSTRs, equipped with dual-impeller agitator and reflux condenser, diaphragm metering pump, reagent vessels, temperature controller, heat exchange system consist of steam-heating and watercooling. The reagent vessels, CSTRs and pumps were connected with pipe of 316L stainless steel. The system was filled with the mother liquor of the batch reaction at first. Initially, the steamheating unit was used to heat the reaction mixture, and then the water-cooling unit was turned up to remove the reaction heat. After temperature stabilization (the reaction temperature in R1 reactor of CSTRs is 73 °C, and in other reactor is 90 °C), the reactants and catalyst consisting of cyclohexene, aqueous H2O2, H2WO4, H2SO4 and H3PO4 in a molar ratio of 1:1.04:0.56:50:220 were fed into the reactor continuously from the reagent vessels by diaphragm metering pump, with a total retention time in CSTRs was 580-590 min. Product collection began two residence times (20 h) later, and the consistency of the flow rate was verified by measuring the consumed volume of starting material in a certain interval. The product was sampled and analyzed every 10 h by HPLC to monitor constancy of the reaction. The reaction solution was fed into batch operated crystallizer for the crystallization of AA from mother liquor. After separation of AA by centrifugal filtration, the filtrate was treated by acid resin-bed, condensed by vacuum evaporator and reused as catalyst in the next run.⁴⁰

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