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FULL PAPER

High-pressure asymmetric hydrogenation in a customized flow reactor and its application in multi-step flow synthesis of chiral drugs

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Abstract

Asymmetric homogeneous hydrogenation under high pressure in continuous flow was achieved with a slug flow reactor. High hydrogen pressure enabled iridium-catalyzed asymmetric hydrogenation of acetophenone with a turn-over-frequency (TOF) of up to 274,000 h^{-1}. An *operando* infrared tool was used to provide in-situ monitoring of the reaction. The effect of gas-liquid ratio and speed of slug flow in the microchannel were studied. The multi-step flow synthesis of active pharmaceutical ingredients, in which asymmetric hydrogenation is a key step, was successfully demonstrated, with subsequent reactions carried out under longer residence times within a cascade of CSTRs.

Keywords Asymmetric hydrogenation · High pressure · Slug flow reactor · Multi-step synthesis · Chiral drug

Introduction

The end-to-end continuous-flow production of active pharmaceutical ingredients (APIs) is based on multi-step telescoped flow reactors that enable high efficiency and automated chemical synthesis. [1–7] However, current processes rarely involve catalytic enantioselective transformations. [8–12] Asymmetric hydrogenation (AH) is one of the most powerful synthetic tools to obtain chiral molecules in pharmaceutical industry. [13] However, practical homogeneous hydrogenation with a low catalyst loading typically requires a long reaction time (more than 24 h), which poses challenges for continuous operation. [14, 15] Immobilization of the catalyst for homogeneous hydrogenation has been demonstrated as a practical strategy, in which the catalyst loading can be reduced to 0.02 mol% (e.g. H-cube hydrogenation reactor). [16–21] But homogenous AH is still an underdeveloped area. To the best of our knowledge, there has been only one report of the application of AH as the key step in a multi-step flow synthesis of chiral molecules, in which the 2.5 mol% catalyst loading was far from ideal. [22–24]

Continuous microfluidic reactors can benefit hydrogenations for several reasons. Firstly, capable of handling bi- or multi- phasic systems, they can facilitate reactions with their high surface area-to-volume ratio and efficient mixing. [25–28] Secondly, hydrogen gas is highly flammable and forms an explosive mixture in air; the lower gas inventory and improved control can reduce this hazard. [29] Thirdly, the use of excess hydrogen under high pressure can accelerate the reaction and give high conversion, avoiding the need for further purification, and making processes suitable for integrated multi-step flow synthesis. [5]

Existing reactors for homogeneous AH are summarized in Fig. 1. These include the micro-structured mesh reactor, [30] the helicoidal single channel falling film micro-reactor, [31] the tube-in-tube reactor, [24] and *f*Reactor. [32] The pressure rating of these reactors is typically less than 25 bar and the catalyst loading were relatively high (e.g. 1–2.5 mol%). Eli Lilly developed an industrial coiled reactor for asymmetric hydrogenation. [33] This resulted in a fully continuous process with 73 L reactor volume achieving the same production

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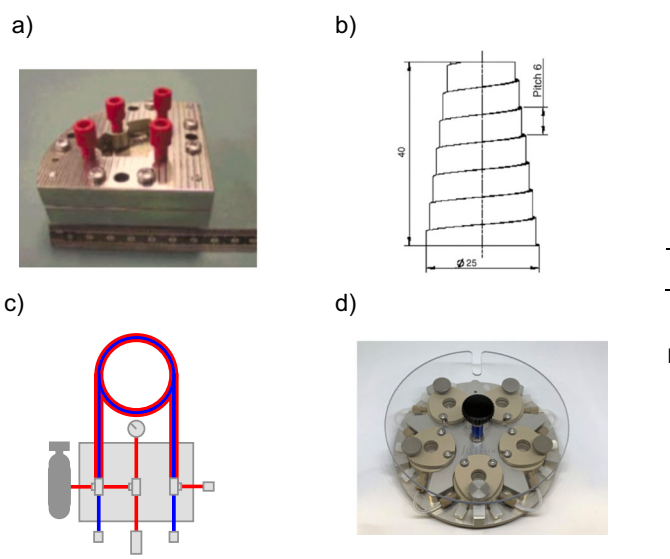


	a	b	c	d	This Work
Catalyst Loading (mol%)	1	1	2.5	1	0.0025
Reactor Pressure Rate (bar)	11	10	25	10	100
Productivity (mmol h^{-1})	0.42	0.07	0.1	0.56	55.2
Space-time yield ($kg{\cdot}L^{-1}{\cdot}h^{-1}$)	460	730	0.00275	4.8	910
TOF (h^{-1})	6000	2000	60	93	274000

Fig. 1 Representative Continuous Reactor Systems for Homogeneous Asymmetric Hydrogenation

capacity as a 400 L batch reactor. This group also reported an industrial vertical Pipe-in-Series flow reactor [34, 35] using a bubble and segmented gas-liquid flow regime with an operating pressure of 55 bar H_2/CO and had a minimum catalyst loading of 0.074 mol%. [34] However, a research scale flow reactor capable of handling inert conditions, gaseous reactants, variable temperature, and elevated pressure is still needed.

Herein we report AH performed in a high-pressure segmented flow reactor system incorporating an in-line infrared (IR) probe. The conditions required to form stable slug flow under high pressure in a microchannel reactor were studied and the effect of mass transfer on the reaction was clarified. Asymmetric synthesis of ezetimibe and eslicarbazepine acetate was achieved by high pressure hydrogenation then telescoped with downstream flow processes to give products with both high efficiency and optical purity.

Results and discussion

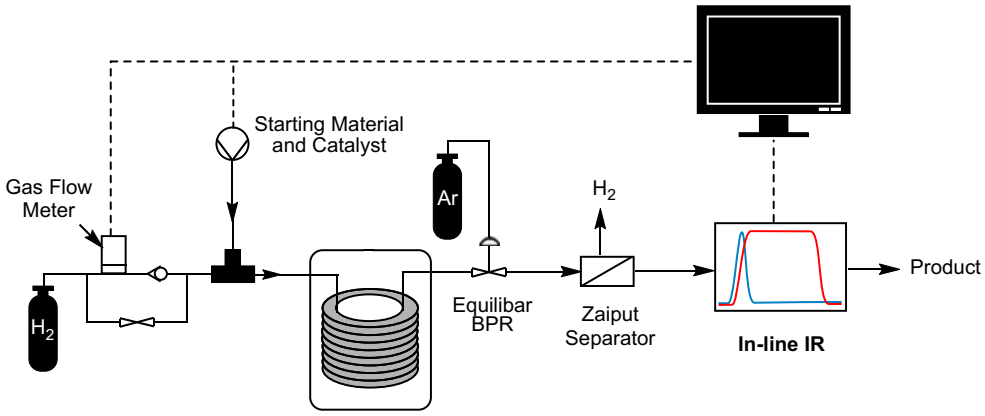
High-pressure continuous flow equipment

High pressure and high temperature can increase the TOF in a catalytic reaction and therefore shorten the reaction time, making a microreactor suitable for carrying out AH. According to our investigation, the commercially available reactors do not meet the requirements for hydrogenation with high efficiency (residence time around 10 min and extreme pressure). The system we designed was able to work under high pressure (60 ~ 150 bar) and temperature (80 ~ 150 °C), is suitable for screening catalysts and conditions, can deliver products quickly and safely and be applied in multi-step flow synthesis. The customized set-up is shown in Scheme 1. To accommodate the anticipated pressures, all components of reactor system were made of 316 SS with valve and fittings of >500 bar pressure rating. [36]

The HPLC pump was rated to 150 bar, [37] and the gas flow meter was a customized high-pressure unit (outlet pressure rating: 400 bar). [38] To generate a stable gas liquid flow, a diaphragm-type back pressure regulator was used. [39] The segmented flow pattern was generated by a T-junction with a liquid and gas inlet. The reactor outflow passed through a hydrophobic membrane-based gas-liquid separator, [40] and the reaction solution passed across an *in-line* IR probe. A remote-control application (code in supporting information) was developed to realize safe automated operation, able to vary pump speed affecting the residence time and gas-liquid ratio.

Batch hydrogenation reactors classically provide hydrogen by stirring and bubbling, and reaction rates are usually gas-liquid mass transfer limited. When implemented in a microchannel-reactor, in our case 1/16-in. OD 316 SS tube, the reaction medium containing catalyst, substrate and base is mixed with hydrogen in T-junction and pumped through the reactor. The catalyst elutes with the product from the end of the reactor. Different flow regimes are possible: bubbly, slug, churn, slug-annular and annular. [41–44] The type of flow has a significant effect on reaction conversion. [45, 46] Among them, gas-liquid slug flow is beneficial as the frictional forces create Taylor flow micromixing, illustrated in Fig. 2 giving more reproducible results with good mass transfer and narrower residence time distribution. [47] It is characterized by a series of equi-volume elongated bubbles, separated from each other by liquid slugs and surrounded by liquid film, which results in surface-area-to-volume ratios of 40~230 cm^{-1}. [48, 49] A stable slug flow with relatively long residence time, linear velocity of 7.3 cm/s and gas liquid ratio of 1.5 were selected as the starting point of optimization. The gas

Scheme 1 Process Diagram of Slug Flow Reactor. BPR, back pressure regulator



volume rate in a microreactor was calculated by non-ideal gas law, which was explained in SI.

The concept of AH in high-pressure slug flow was verified with an iridium catalyzed ketone reduction. Our original tridentate ligands *f*-amphox [50, 51] was selected, as the tridentate complex with iridium is more stable than Noyori's ruthenium/bisphosphine-diamine catalysts that are prone to loss of reactivity by dissociation of diamine ligand. The benchmark substrate, acetophenone, gave full conversion to the alcohol in 99% ee with 0.0025 mol% catalyst loading and residence time of 8.75 min, giving a remarkably high TOF of 274,000 h^{-1} (Fig. 2c, for details see supporting information). The reactor volume was 7.4 mL and the space-time yield was calculated to be 910 $kg{\cdot}L^{-1}{\cdot}h^{-1}$. This result demonstrates the efficiency of AH in a high-pressure slug flow reactor.

Application of continuous-flow hydrogenation in late-stage synthesis of ezetimibe

Our study on the synthesis of APIs in continuous flow commenced by producing ezetimibe, a blockbuster drug used to lower cholesterol level in blood. [52] A dilemma was encountered at the start: reactant **3** was soluble in toluene but less so in ^{i}PrOH, while the product **4** was soluble in ^{i}PrOH but less so in toluene. To avoid blocking, the microreactor, 0.5 M **3** in toluene/^{i}PrOH (1:1) was adopted. With better solubility in the reaction medium, CsOH, rather than Cs_2CO_3, was chosen as the base. A batch reaction suggested that after 4 h, 85% conversion and 95% de was achieved with 0.02 mol% catalyst and 2% CsOH at room temperature and hydrogen at 60 bar. This was transferred to the continuous reactor with an increased pressure of 80 bar and temperature of 90 °C.

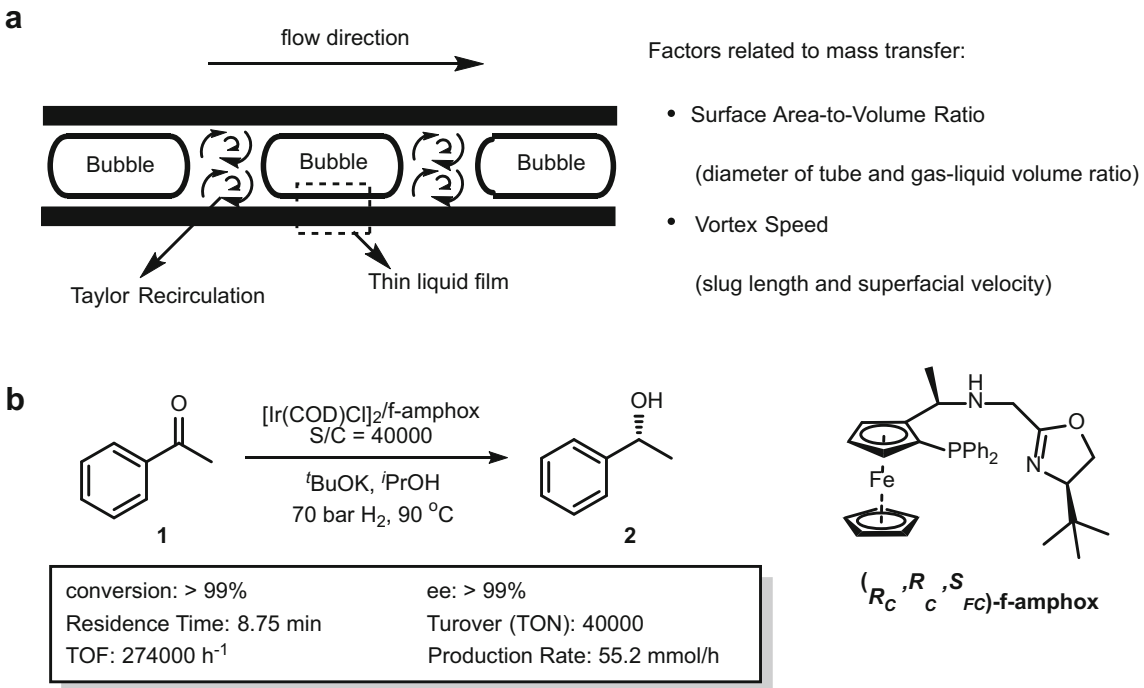


Fig. 2 (**a**) liquid slug showing Taylor flow mixing; (**b**) high TON in asymmetric reduction of acetophenone

Table 1 Asymmetric hydrogenation of 3 in flow [a]

entry	S/C	P (bar)	T (°C)	linear velocity (cm/s)	residence time (min)	conv. (%)	de (%)
1[b]	5000	80	90	7.3	5.2	51	95
2[b]	5000	80	90	3.6	10.4	2	N.A.
3[c]	5000	80	40	7.3	6.5	40	95
4[c]	5000	80	60	7.3	6.5	84	95
5[c]	5000	80	80	7.3	6.5	59	95
6[c]	5000	80	100	7.3	6.5	46	95
7[c]	5000	100	60	7.3	6.5	94	95
8[c]	2500	100	60	7.3	6.5	99	95

[a] substrate concentration: 0.5 M; Toluene/^{i}PrOH = 1:1; CsOH: 2 mol%; liquid flow rate and gas flow rate for 2, it was 0.23 mL/min and 0.33 mL/min, while for other Entries are 0.46 mL/min and 0.68 mL/min; conversion and de (diastereomeric excess) values were determined by HPLC via semi-quantitative analysis. [b] reactor volume: 5.9 mL; [c] reactor volume: 7.4 mL.

Normally, in batch, elongating reaction time causes a higher conversion, however, it was interesting to find that when the residence time was prolonged from 5.2 to 10.4 min (Table 1, entries 1 and 2) by decreasing gas and liquid flow rate, the conversion dropped to 2%. This was probably caused by reduced Taylor flow mixing, [53] that slowed catalyst activation; the coordinating cyclooctadiene needs to be hydrogenated to start the catalytic cycle. [54] The influence of temperature was studied (entries 3–6). A temperature of 40 °C resulted in 40% conversion which increased at 60 °C to 84% but fell thereafter to 46% at 100 °C. This decreased conversion might be caused by the decomposition of the catalyst. Increasing the pressure from 80 to 100 bar allowed 94% conversion, (entry 7), and when the catalyst loading was doubled, 99% conversion and 95% de were obtained (entry 8).

It has been demonstrated that Taylor flow mixing increases with the superficial velocity of the fluids, [45] with short, fast-moving slugs preferred.[53] Fig. 3a shows a flow-regime universal map of linear velocity and gas-liquid volume ratio in a microchannel at 15 bar gas pressure (for details, see supporting information) and the findings are similar to those of Jensen and co-workers done under ambient conditions. [43, 55] It was found that at low linear velocity, the liquid slug is longer than 5 cm, and leads to a slower Taylor mixing. When the velocity and gas liquid ratio are high, the pulse of back pressure equipment can turn the slug flow into intermittent, unstable, annular flow (videos and pictures can be found in supporting information). Stable slug flow is achieved in the area shown in red. The area along the dashed line is the

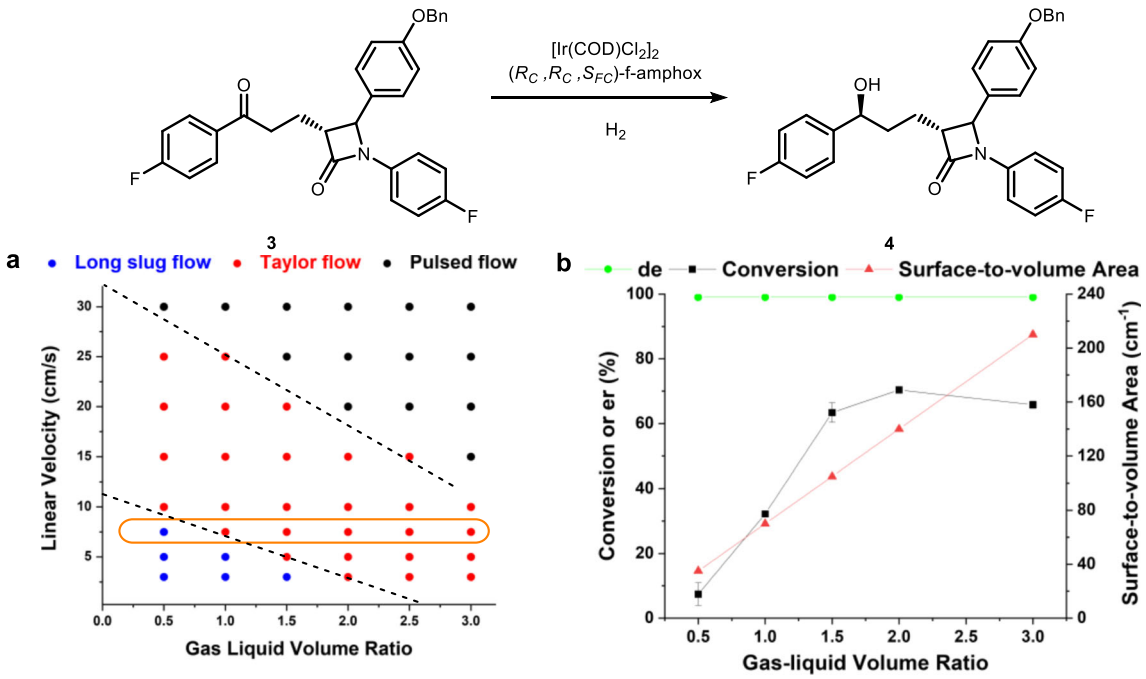
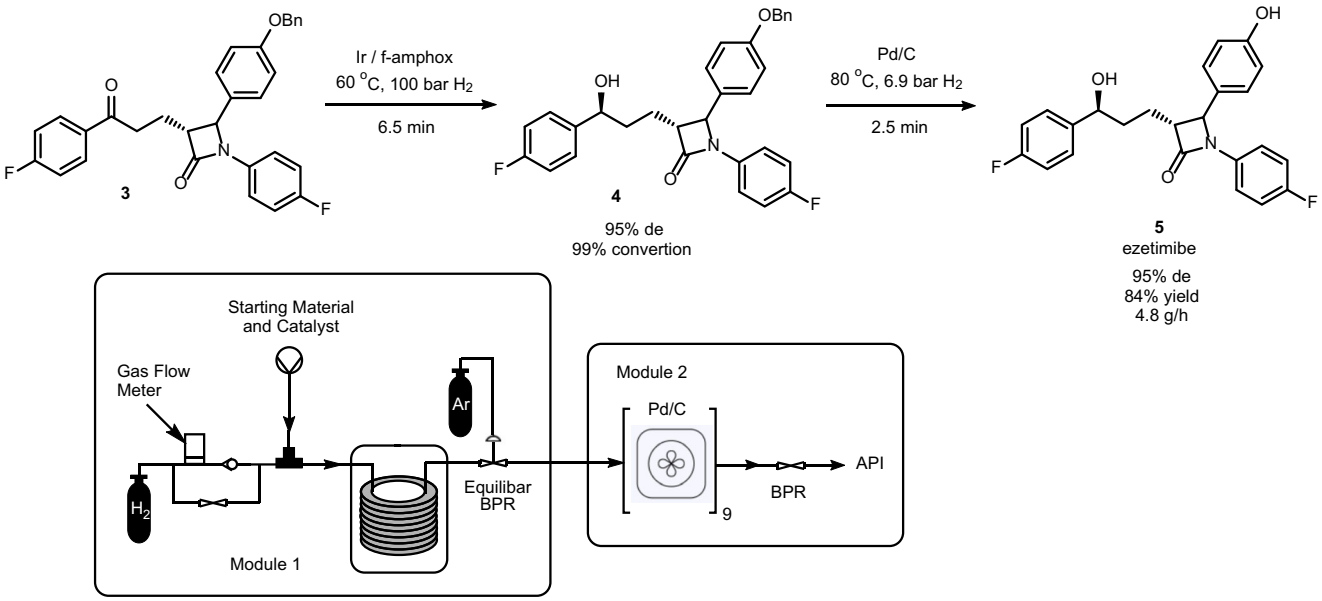


Fig. 3. (**a**) a universal map of gas-liquid flow in microchannel under 15 bar; (**b**) the effect of gas-liquid volume ratio on conversion of 3 to 4



Scheme 2 Late-stage flow synthesis of ezetimibe using hydrogenation

transient area. The effect of the gas-liquid volume ratio was studied (for details, see supporting information) over 0.5 to 3.0 in a 7.4 mL reactor with 6.5 mins residence time. Flow regimes altered from long slug flow to short slug flow, indicated by the orange box, under 15 bar in Fig. 3(a). A similar change in flow, along with gas-liquid ratio, might also be observed under 80 bar. As shown in Fig. 3, the surface area to volume increased from 40 to 210 cm^{-1} giving an increase in mass transfer explained by the following equation:

$$a = \frac{4r}{d} \tag{1}$$

where a is the surface area to volume ratio (cm^{-1}), d the inner tube diameter (0.057 cm in this case) and r the gas-liquid volume ratio (for the derivation of eq. 1, see supporting information). The conversion increased from 8% to 64% when the gas-liquid ratio was increased from 0.5 to 1.5, and is explained by improved mass transfer. When the ratio was increased further to 2 or 3, the conversion remained similar (~ 67%), showing the gas-liquid ratio, hence mass transfer, was no longer rate limiting. A gas-liquid ratio of 1.5 was adopted for all reactions.

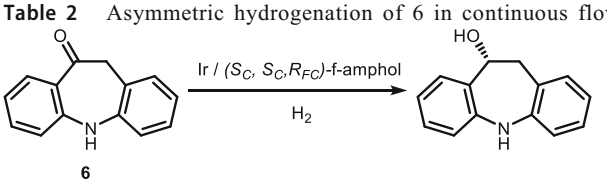
In the synthetic route shown in Scheme 2, debenzylation of intermediate **4** is required to yield ezetimibe **5** and relies on hydrogenation with palladium on activated charcoal. This heterogeneous triphasic reaction relies on good mixing for high efficiency. Miniature cascade CSTRs, *f*Reactor, that incorporate active mixing, even at low flow rates allowing for long residence times, were adopted for carrying out the downstream reaction. [32] These have the potential to broaden the range of reactions that can be performed during multi-step flow synthesis. [56]

The reaction medium of module 1 was delivered directly to module 2. Nine *f*Reactors were filled with 750 mg 10% Pd/C in total, using a frit-in-ferrule installed before the BPR to hold the solid catalyst in each of the reactors, and heated to 80 °C with a two-step residence time of 9 min. The yield of ezetimibe over both steps was 84% with 95% de and the production rate was 4.8 g/h.

Inline analysis by in situ FTIR

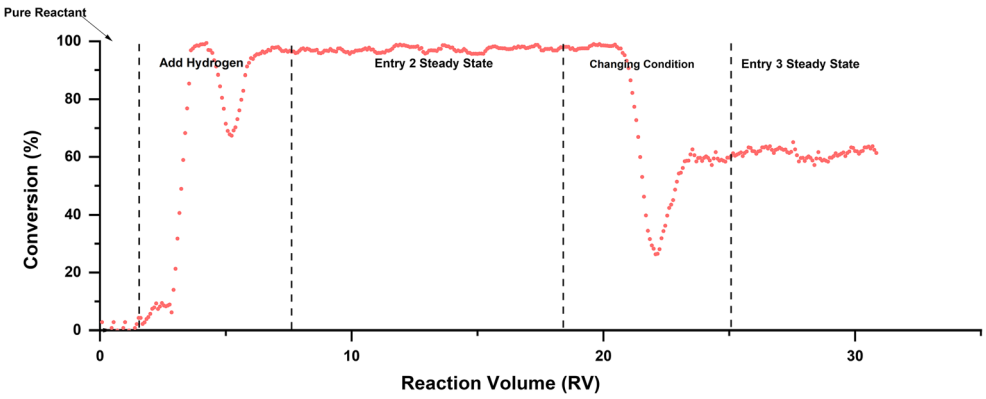
AH of dibenzazepinone **6** [57] was the key step in the synthesis of eslicarbazepine acetate **9**, an anticonvulsant for the treatment of partial onset seizures. [58] In a batch reaction with 0.1 mol% Ir/f-amphol/ catalyst and 5 mol% ^{t}BuONa in mixed solvent DCM/^{i}PrOH (1:1, *v*/v) at ambient temperature under 60 bar

Table 2 Asymmetric hydrogenation of 6 in continuous flow [a]



Entry	S/C	T (°C)	conv. (%)[b]	ee (%)[c]
1	1000	60	98	98
2	2500	60	98	98
3	2500	40	61	98
4	5000	60	22	98
5	5000	80	77	98
6	5000	100	43	97

[a] substrate concentration: 0.5 M; DCM/^{i}PrOH = 1:1; ^{t}BuONa: 5 mol%; reactor volume: 7.4 mL; pressure: 90 bar. [b] conversion was determined by inline IR. [c] ee was determined by HPLC.

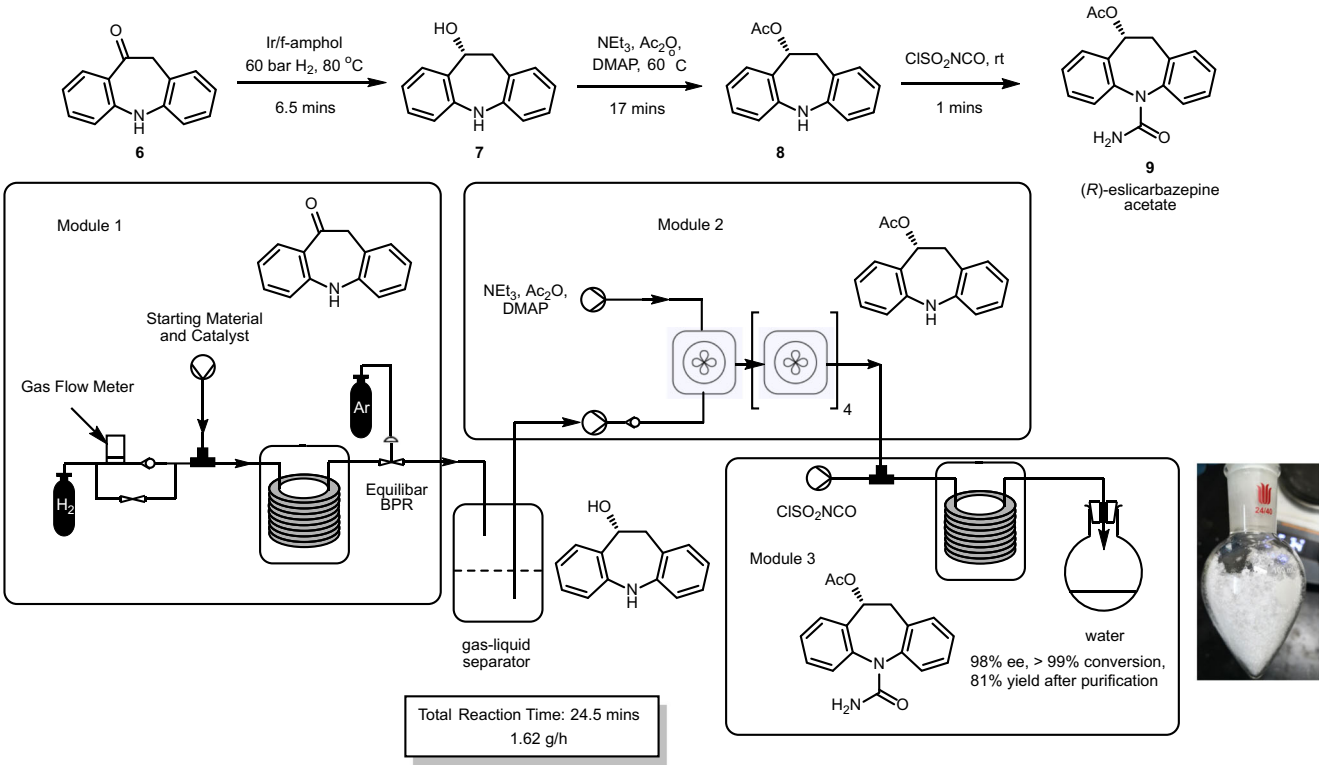


Scheme 3 In-line analysis by in-situ FTIR for the condition optimization

hydrogen, >99% conversion and 98% ee were achieved in 24 h. AH in continuous flow provides short reaction times that facilitate fast screening of conditions. To assist this, inline AFT-FTIR was incorporated at the outflow to give real-time data on the concentration of components in the reaction mixture using the Lambert-Beer law and calibration. The carbonyl group of **6** absorbing at 1661 cm^{-1} was selected as a strong and unique signal to measure conversion. Table 2 shows the results of testing different reaction conditions and Scheme 3 an example of the IR trace recorded (Entry 2 and 3). 98% conversion and 98% ee were achieved at 60 °C and 90 bar hydrogen, at gas liquid ratio 1.5 and residence time of 6.5 mins, with catalyst loadings of 0.1 mol% and 0.04 mol% (entries 1 and 2). However, the conversion decreased markedly to 22% with a catalyst loading of 0.02 mol% (entry 4) but recovered to 77% when the temperature was increased to 80 °C (entry 5), equating to a TOF of 37,000 h^{-1}. At 100 °C the conversion decreased to 43% and this may reflect a decrease in catalyst stability (entry 6).

Multi-step synthesis of (*R*)-eslicarbazepine acetate in continuous flow

The asymmetric synthesis route of (*R*)-eslicarbazepine acetate is shown in Scheme 4. [59] Given the poor solubility of urea compounds, this step was placed last in the sequence. In module 1, ketone **6** was hydrogenated to alcohol **7** under 90 bar hydrogen and 80 °C with a TON of 1000, which afforded the product with 98% conversion and 98% ee. The reactor was a 7.4 mL tube



Scheme 4 Multi-step synthesis of (*R*)-eslicarbazepine acetate

giving a residence time of 6.5 min. After steady state was achieved, the outlet stream was collected in a gas liquid separator (Schlenk flask) and the hydrogen was discharged through a tube filled with argon. The resulting alcohol **7** was pumped into a *f*Reactor at 0.23 mL/min, set for a reaction temperature of 60 °C, and mixed with a stream containing NEt_3, Ac_2O and DMAP (0.26 mL/min) before flowing through another four *f*Reactors to give a residence time of 17 min for full conversion. The acetylated product was pumped through a 1 m cooling coil and mixed with a stream (0.069 mL/min) of neat chlorosulfonyl isocyanate. In batch, intermediate **8** was fully consumed in 1 min so the flow process was designed with the same residence time. The resulting mixture was collected in a round-bottom-flask with water quench during which chlorosulfonyl group was hydrolyzed. After flash chromatographic purification, **9** was obtained in 81% yield and 98% ee. The total reaction time was 24.5 mins and 2.7 g pure API could be produced in 100 min.

Conclusion

Two multi-step asymmetric flow syntheses of ezetimibe and eslicarbazepine acetate are reported. This was enabled by asymmetric hydrogenation in a continuous slug flow reactor able to operate at pressures up to ~ 150 bar and temperature ~ 100 °C and real-time quantitative analysis was performed by in-situ IR spectroscopy followed by a longer residence time reaction within the *f*Reactor CSTR cascade. A remarkably high TOF of 274,000 h^{-1} was observed in hydrogenation of acetophenone. Two optically active APIs, ezetimibe and eslicarbazepine acetate, were successfully synthesized by the multi-step flow system with high efficiency (4.8 g/h for ezetimibe and 1.62 g/h for eslicarbazepine acetate) and enantioselectivity. It was found that changing of flow regime can have a significant effect on the reaction conversion in the slug flow reactor with optimal gas-liquid flow rate and ratio determined. Continuous flow asymmetric hydrogenation is usually quantitative, with no by-product and few impurities, so requires no purification before carrying though to the next reaction. Continuous flow asymmetric hydrogenation with low catalyst loading will become an important tool in end-to-end enantioselective flow synthesis of chiral compounds.

Appendix

Experimental

High TON AH of acetophenone in flow

To a 5-mL vial was added the catalyst precursor $[Ir(COD)Cl]_2$ (1.4 mg, 0.002 mmol), f-amphox (2.3 mg, 0.0042 mmol) and anhydrous ^{i}PrOH (1.0 mL) in an argon-filled glovebox. This vial was sealed and mixed for 2 h at room temperature. ^{t}BuOK (89.8 mg, 0.8 mmol) was dissolved in 10 mL anhydrous ^{i}PrOH. 0.5 mL catalyst solution was firstly mixed with 10 mL base solution and then acetophenone (9.6 g, 9.4 mL, 80 mmol). The resulting mixture was filtered and the filtrate was added into a flask.

The process diagram was shown in Fig. S7 and Scheme S1. Fig. S8 showed the remote control app and real time IR analysis. The process was washed by anhydrous and degassed ^{i}PrOH at a liquid flow rate of 4 mL/min and gas flow rate of 5 sccm (avoid back flow of liquid to gas flow meter) for 5 min and then pressurized the BPR. After the reactor was pressurized to 70 bar and heated to 90 °C, the aforehand reaction medium was pumped instead of solvent. Liquid flow rate was set at 0.23 mL/min and gas flow rate 0.9 mL/min (45 sccm). The reactor system could achieve steady state in 5 reaction volumes. Samples were collected every 15 min in an empty vial. The conversion and ee were analyzed by NMR and HPLC. When reaction finished, system was depressurized by releasing the gas of Equilibar BPR slowly, and washed the whole system by pumping ^{i}PrOH for 10 min.

Multi-step flow synthesis of 5

To a 20-mL vial was added the catalyst precursor $[Ir(COD)Cl]_2$ (16.8 mg, 0.025 mmol), f-amphox (31.0 mg, 0.055 mmol) and anhydrous ^{i}PrOH (10.0 mL) in an argon-filled glovebox. The solution was mixed for 2 h under room temperature. $CsOH{\bullet}H_2O$ (83.5 mg, 0.5 mmol) was dissolved in 10.0 mL anhydrous ^{i}PrOH. 10.0 mL catalyst solution was sequentially mixed with 10.0 mL base solution and **3** (12.5 g, 25 mmol) in 25.0 mL toluene. The resulting mixture was filtrated and clear solution was added into a 50-mL volumetric flask. Then, 5.0 mL ^{i}PrOH was added to prepare a 50.0 mL reaction solution.

Deprotection module consisting of 9 *f*Reactors (15.3 mL) were installed after the high-pressure slug flow reactor. The *f*Reactors were filled with 750 mg 10% Pd/C in total. The frit-in-ferrule was installed before the BPR to hold the solid catalyst in the reactor. The hydrogenation module with a residence time of 6.5 min was pressurized to 100 bars and heated to 60 °C. After it reached steady state, the gas liquid flow was directed to the deprotection module without separation. The *f*Reactor module was heated to 80 °C. Two step yield of ezetimibe was 84%. 272 mg product was obtained in 15 min with 95% de.

Multi-step flow synthesis of (*R*)-9

Medium for module 1 To a 20.0 mL vial was added the catalyst precursor $[Ir(COD)Cl]_2$ (16.8 mg, 0.025 mmol), f-amphol (38.0 mg, 0.055 mmol) and anhydrous ^{i}PrOH (10.0 mL) in the argon-filled glovebox. The medium was mixed for 2 h under room temperature. ^{t}BuONa (120.0 mg,

1.25 mmol) was dissolved in 5.0 mL catalyst medium. The resulting medium was mixed with **6** (5.2 g, 25 mmol) in anhydrous and degassed 25.0 mL DCM. The resulting medium was filtrated by filter paper and added into a 50 mL volumetric flask. Then, 15.0 mL ^{i}PrOH was added to prepare a 50 mL reaction medium.

Medium for module 2 37.5 mL acetic anhydride and 12.5 mL NEt_3 were mixed in a 100 mL volumetric flask. 133.0 mg DMAP was dissolved in the medium.

Medium for module 3 Was neat $ClSO_2NCO$.

The module 1 was washed by anhydrous and degassed ^{i}PrOH by a liquid flow rate of 4 mL/min and gas flow rate of 5 sccm (avoid back flow of liquid to gas flow meter) for 5 min and then pressurized the BPR. After the pressure and temperature was elevated to 90 bar and 80 °C, the aforehand reaction medium was pumped instead of solvent. Liquid flow rate was 0.46 mL/mins and gas flow rate was 44 sccm. The reaction was monitored by TLC analysis. After it reached steady state with full conversion, the product medium was collected in the gas liquid separator (Schlenk tube in this process). Module 2 consisting of 5 *f*Reactors (8.5 mL) was installed and filled with dry DCM. The medium for module 2 was taken by a 50 mL syringe that was installed on a PhD Ultra syringe pump. Then it was pumped by a flow rate of 0.26 mL/min. The liquid in gas liquid separator was pumped into module 2 by a flow rate of 0.23 mL/min. The hotplate was heated to 70 °C to have a liquid temperature of 60 °C. The residence time of module 2 was 17 mins. The reaction was monitored by TLC analysis. After it reached steady state with full conversion, the outlet was connected to cooling part of the module 3. Neat $ClSO_2NCO$ was pumped by a flow rate of 0.069 mL/min and mixed with medium from module 2 in a T-junction. Tubes of module 3 were in a room temperature water bath. The final product was connected in a beaker that has 20 mL water to quench the solution. There was HCl gas generated in module 3. Thus, the calculated residence time was 2.7 min that was longer than batch reaction time that was 1 min. The biphasic medium was left stirring for 1 h. Organic phase was separated. 5 ml DCM was added to wash the aqueous phase for two times. Organic layer was combined and washed with water (5 mL). The solvent was evaporated at 40 °C under reduced pressure. The crude materials were purified by column chromatography. (60 mL 50% ethyl acetate in petroleum ether, then 100 mL 80% ethyl acetate in petroleum ether). In the first run, 320.0 mg eslicarbazepine acetate with 76% yield and 98% ee in 13 min. In the second run, 2.7 g eslicarbazepine acetate with 81% yield and 98% ee in 100 min.

More experimental details could be found in the supplementary information.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41981-021-00143-8.

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