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Synthesis of Crizotinib Intermediate via Highly Efficient Catalytic Hydrogenation in Continuous-Flow

Feng Xu,[†] Jianli Chen,[†] Xiaoxuan Xie,[†] Pengfei Cheng,[†] Zhiqun Yu,[*†] Weike Su[*‡]

[†] *National Engineering Research Center for Process Development of Active Pharmaceutical Ingredients, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, P.R. China*

[‡] *Key Laboratory for Green Pharmaceutical Technologies and Related Equipment of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P.R. China*

[*] Correspondent. Tel: (+86)57188871038. E-mail: yzq@zjut.edu.cn.

[*] Correspondent. Tel: (+86)57188320899. E-mail: pharmlab@zjut.edu.cn.

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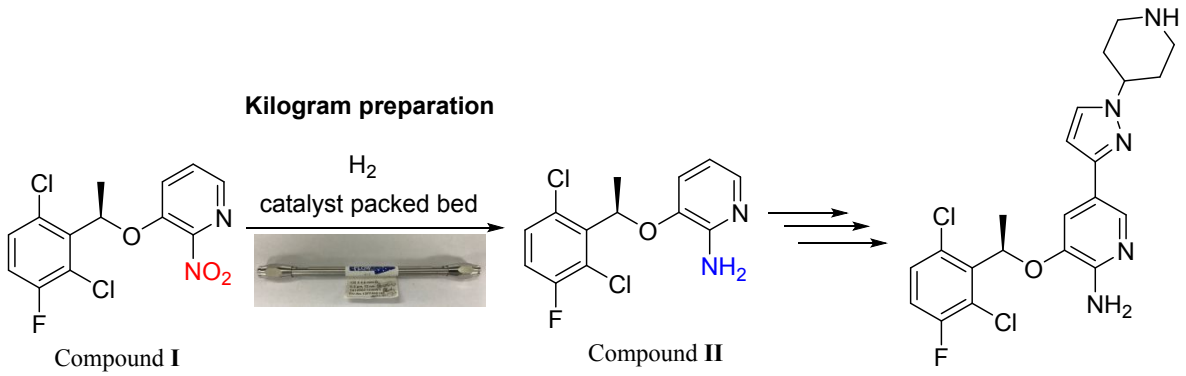


Yield >99%, product free of catalyst, no post processing

Abstract:

A kilogram scale highly selective catalytic hydrogenation of aryl nitro group in the intermediate of Crizotinib has been developed which adopted continuous-flow technology with pre-passivated Raney Ni as catalyst under room temperature. According to the reaction condition optimizing, side reactions like dehalogenation, debenzylation and reduction of other unsaturated functional groups were inhibited eminently. Moreover, catalytic hydrogenation of (*R*)-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-2-nitropyridine (compound **I**) afforded the desired product (*R*)-3-[1-(2,6-dichloro-3-fluorophenyl)ethoxy]pyridin-2-amine (compound **II**) with high selectivity (99.9%) and high conversion (99.5%). Finally, the high quality Crizotinib was synthesized from the intermediate **II**.

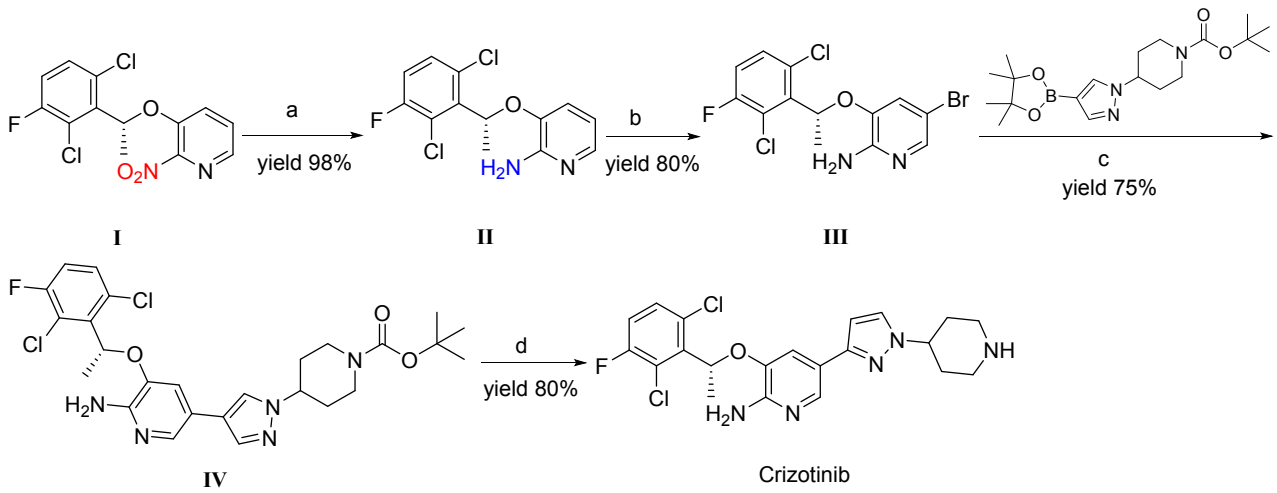
Key Words: Chemoselectivity, continuous-flow, catalyst, hydrogenation, Crizotinib.

Introduction

Crizotinib is an ATP competitive multi-target protein kinase and a small molecular inhibitor of ALK/c-MET/ROS. It is currently considered as the best treatment for advanced Anaplastic Lymphoma Kinase (ALK)-Positive non-small cell lung cancer (NSCLC).[1] According to the literatures, compound **II** was obtained by catalytic hydrogenation of compound **I** (scheme 1), which was a key intermediate of Crizotinib.[1]

Among them, the researchers tried to use Fe or Ni as the catalyst to reduce compound **I** to compound **II**.[1-3] However, two major problems need to be overcome in the synthesis of compound **II**: ① Debenzylation and dehalogenation reactions were carried out during catalytic nitro reduction. In fact, it was found that the dehalogenated and debenzylated impurities were very difficult to remove in the product. ② Catalytic hydrogenation was flammable and explosive, and the catalyst filtration was difficult and dangerous. Therefore, development of an inherent safety and

environmentally friendly nitro reduction process should be explored.



(a) H_2, sponge-nickel, MeOH, 20-50 °C; **(b)** (i) NBS, MeCN/CH_2Cl_2, -15 to -10 °C; (ii) $Na_2S_2O_5$, KOH, CH_2Cl_2/water; **(c)** $PdCl_2$(dppf) CH_2Cl_2, Cs_2CO_3, Bu_4NBr, toluene/water, 70 °C; **(d)** HCl, EtOH/EtOAc/CH_2Cl_2, 0-5 °C, over 2 h.

Scheme 1. Synthesis of Crizotinib involving intermediate II

In general, the catalytic hydrogenation of aromatic nitro compounds containing functional groups, such as halogens, benzyl, *etc*., with high selectivity ($\geqslant$ 99%) is one of the challenge. According to the reports, the results can be divided into two categories based on class of catalysts: adopting precious metal catalysts and using novel catalysts with yields in the range of 63%-100%.[4-15] However, batch process for catalytic hydrogenation have some safety issues, such as normally tedious post-processing and poor controllability of product dynamics.

Above all, the research in this field focused on the exploration of catalysts and application of continuous-flow technology for obtaining highly chemoselective hydrogenations of aromatic nitro compounds in the last decade.[16] Continuous-flow technology had some certain advantages compared to batch mode, such as inherent safety, high efficiency, good mass and heat transfer.[17-19] A key feature of this enabling technology was the straightforward implementation of heterogeneous catalysis in a continuous-flow transformation, since the catalyst could be easily immobilized in a specific region of the flow path.[20-26] Although the above reports involved continuous flow reduction of nitro compounds, the continuous-flow catalytic hydrogenation of compounds containing halogen

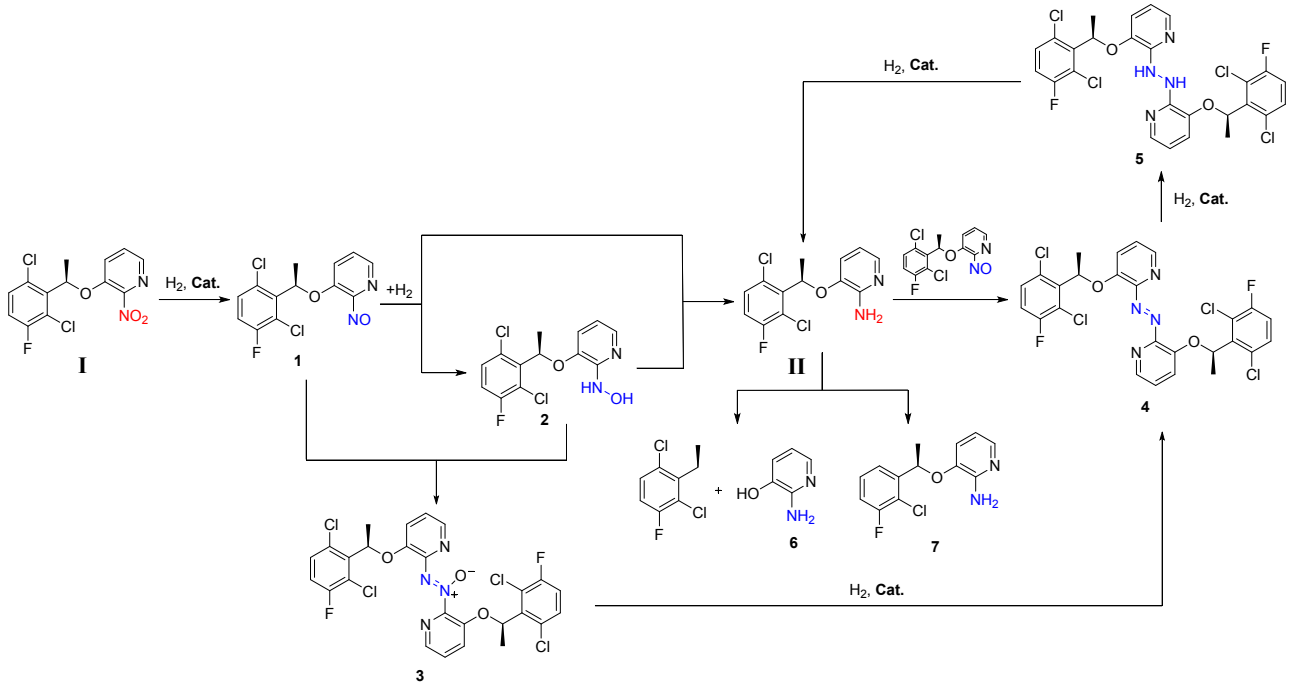
and benzyl with high selectivity and high conversion has not been reported.

During the past decade, our group had put continuous efforts on applying continuous-flow technology to hazardous reactions, and in this paper a continuous-flow hydrogenation process for the preparation of compound **II** from compound **I** was explored with high selectivity (99.5%) and high conversion (99.9%).

Results and Discussions

Reaction process analysis

According to study on the mechanism of nitro-catalyzed hydrogenation in the references, the direction of catalyst design and the improvement of reaction selectivity and conversion were indicated.[27-33,34] We speculated that there might have two pathways for the reduction of compound **I** to compound **II** (Scheme 2).



Scheme 2. Proposal reaction process and main by-products

In this work, the application of the packed-bed continuous flow reaction technology was consisted of three parts: ① The performance of the catalyst was evaluated and investigated in the

hydrogenation reactor to check its availability in continuous flow reaction. ② The catalyst was immobilized on continuous flow reactor to obtain a suitable packed-bed continuous flow reactor through preliminary design and improvement. ③ After the continuous flow reaction system was setup, the preparation of intermediate **II** was well explored, including reaction temperature, reaction time, residence time, solvent, pressure and recovery of catalyst.

Catalyst performance evaluation

Raney-Ni was selected as catalyst with the characteristics of low cost and high efficiency. Purchased Raney-Ni was pre-passivated by immersion in an ammonia water solution, and then applied to the catalytic hydrogenation of compound **I**. In consideration of the better catalytic activity of Ni than that of Fe, the hydrogenation reaction was firstly conducted at low temperature. According to the literatures, reaction rate of catalytic hydrogenation of aryl nitro group was influenced by solvents, and ethanol has been reported as the best solvent.[35,36] In our case, THF was selected as the solvent due to the poor solubility of compound **I** in alcohol. After that, passivation reagents of catalyst were further investigated. As shown in Table 1, aqueous ammonia had the best effect with the selectivity reaching over 75.8%. The reaction selectivity of unpassivated Raney-Ni catalyst was only 6.2%, 65.1% for benzylamine passivation and 4.3% for ethylenediamine passivation, respectively.

Dechlorination (Scheme 2, Comp.**7**) and dibenzyl (Scheme 2, Comp.**6**) byproducts were the main impurities in the reaction adopting unpassivated catalyst. Moreover, when the catalyst was passivated by using ethylenediamine, benzylamine or aqueous ammonia, the azoxybenzene (Scheme 2, Comp.**3**) and debenzylated (Scheme 2, Comp.**6**) byproducts were the main impurities.

Table 1. Screening of catalyst

Entry	Passivation solution	Conversion (%)	Selectivity (%)

1	None	100	6.2
2	Aqueous ammonia	100	75.8
3	Ethylenediamine	100	4.3
4	Benzylamine	100	65.1

Condition: Concentration of compound **I** is 100 g/L. THF as solvent, temperature at 30 °C, reaction time is 1.5 h, pressure is 2.5 MPa. Selectivity (%) = amount of amine substance/(amount of raw material substance - amount of raw material remaining substance) ×100%.

After that, the reaction time was further investigated to confirm whether it was suitable for continuous-flow reaction. Expected product was obtained and the conversion was higher than 88.0%. However, the selectivity was poor (65.4%) and main byproducts were confirmed as debenzylated (Comp.**6**) and azoxybenzene (Comp.**3**) byproducts. It was found that when the reaction temperature was increased to 25 °C and the reaction time was set for 10 min, a slight lower conversion rate of 84.0% was obtained with an improved selectivity of 74.2%, main impurity was (*R)*-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-2-nitrosopyridine (Comp.**1**). When reaction time was extended to 20 min, the conversion was increased to over 94.7% with a better selectivity of 80.0%. Further prolonging the reaction time to 30 min resulted in decreased selectivity of 78.0% (Table 2). It was clearly illustrated that the reaction time significantly influences the conversion rate and selectivity of the reaction, which indicated that such method was not suitable for large-scale production. Meanwhile, the side reaction was difficult to restrain.

Table 2. Evaluation of catalyst activity

Entry	Conditions	Conversion (%)	Selectivity (%)
1	-8℃，20 h	88.0	65.4
2	25℃，10 min	84.0	74.2
3	25℃，20 min	94.7	80.0

4	25℃，30 min	95.3	78.0
5	25℃，40 min	100	75.8

Condition: Concentration of compound **I** is 100 g/L. THF as solvent, pressure is 1.0 MPa. Selectivity (%) = amount of amine substance/(amount of raw material substance - amount of raw material remaining substance) ×100%.

Based on the characteristics and advantages of continuous flow reaction technology, both the conversion rate and selectivity of reaction might be improved: 1) The conversion rate of the reaction can be improved by increasing the effective usage of catalyst. 2) The selectivity of reaction can be improved by avoiding backmixing of materials. Therefore, it was expected that the catalyst could be suitable for the development of continuous flow reaction technology in packed-bed for the preparation of intermediate **II**.

Continuous flow process

According to the results of trials in batch mode, continuous-flow was applied to avoid side reactions. Figure 1 was the set of tubular reaction system. Reaction conditions were optimized, THF as solvent, at room temperature, back pressure was set to 44 psi, total residence time was 4 s, result with conversion of 96.3%, selectivity of 89.8% acquired. Side reactions were inhibited eminently, and efficiency also improved. However, there were three unsolved problems: ① Catalyst flows with reaction mixture to collecting vessel, filtration separation of catalyst and reaction solution was tedious. The usage of catalyst was also higher than in batch. ② The catalyst and the material were pressurized into the reactor by high-pressure nitrogen gas， which were uniformly stirred in the autoclave. Yet, solid-liquid mixing and feeding device was not convenient in lab-scale or large-scale manufactory. ③ There was a problem that the catalyst could clog the back pressure valve with the increasing of the reaction concentration and catalyst dosage.

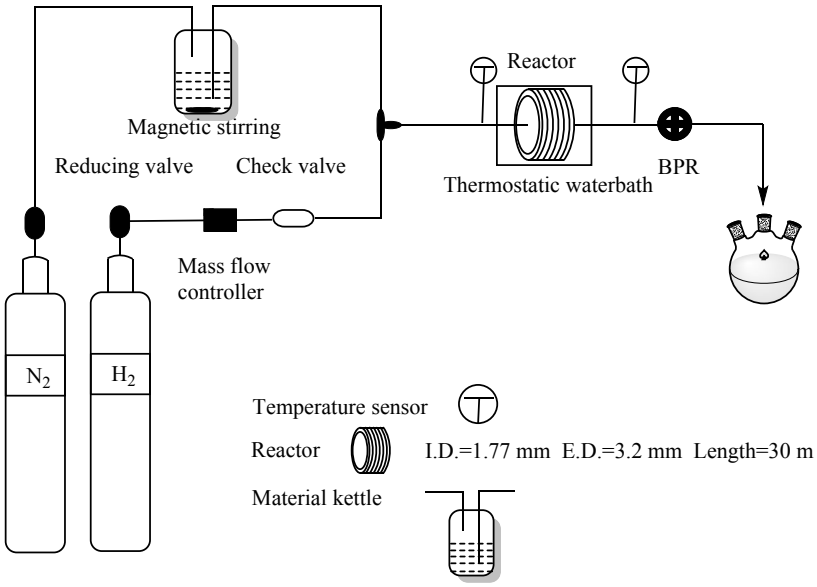


Figure 1. Original continuous-flow reaction system

Condition: Concentration of compound **I** is 4 g/L. THF as solvent, at room temperature, back pressure is set to 44 psi, total flow rate is 10 mL/min, samples are tested by HPLC.

An upgraded continuous-flow system that filled catalyst up in reaction tube was adopted in order to solve these problems (Figure 2). Autoclave was replaced by normal pressure vessel, high pressure N_2 removed, and materials were pumped into reaction tube. Pre-passivated catalyst filled in reaction tube and thermostat was added to control reaction temperature.

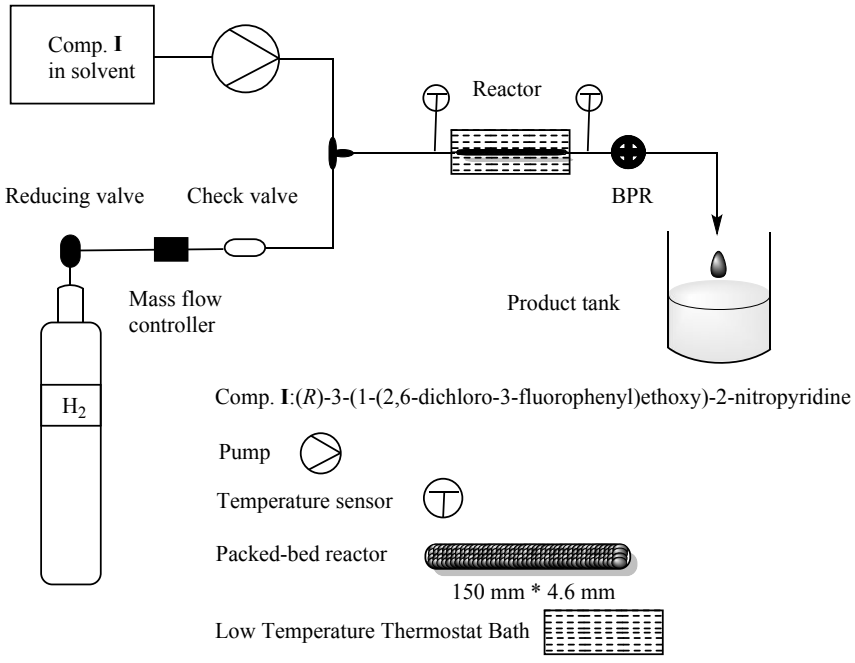


Figure 2. Upgrade continuous-flow reaction system

Condition: Concentration of compound **I** is 4 g/L. THF as solvent, at room temperature, back pressure is set to 44 psi, total residence time is 4 s, samples are tested by HPLC.

Influence of reaction solvent

To make the process conditions milder, the original reaction temperature is set to 25 °C, and concentration of compound **I** is 4 g/L, passivated Raney-Ni as catalyst. The length of the packed-bed reactor is 150 mm and the diameter is 4.6 mm. Moreover, the selectivity and conversion of the reaction in various solvents have been systematically studied (As shown in Ref. 1, methanol were not examined because of its poor solubility at room temperature.) The results showed that the conversion rates of compound **I** in ethyl acetate, tetrahydrofuran reached more than 99% (Figure 3). However, selectivity in more polar solvents was poor, and main byproducts were the dechlorination product (Comp.**7**) and 2-aminopyridin-3-ol (Comp.**6**). The reaction with *n*-hexane as solvents had a low conversion rate of 35.5% and a poor selectivity of 5.0%. The reaction with tetrahydrofuran as solvents had a high conversion rate of 99.1% and a poor selectivity of 32.9%. On the other hand, the reaction has an excellent conversion rate of over 99.0% and a selectivity of 97.9% by using less polar solvent dichloromethane. Only small amounts of 2-aminopyridin-3-ol (Comp.**6** is 0.02%) and azoxybenzene (Comp.**3** is 0.7%) byproducts were detected. It should be noted that the solvent was crucial for catalytic hydrogenation of aryl nitro group, not only affect reaction rate, but also related to the formation of debenzylated side products (decreased to 0.2%).

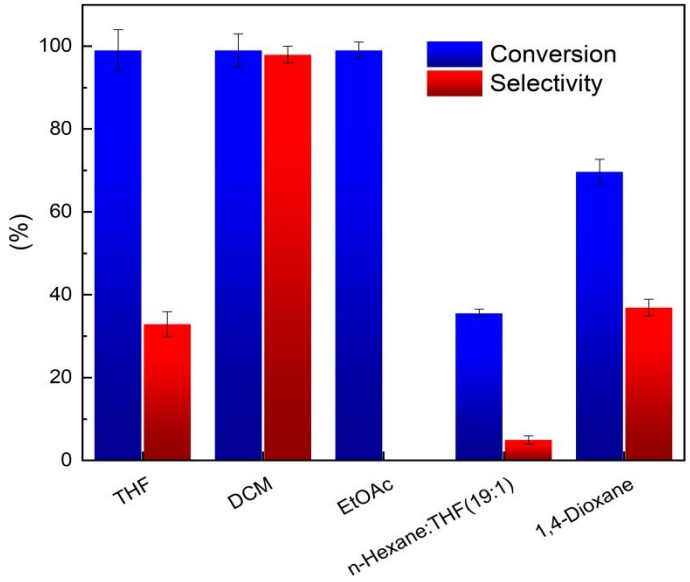


Figure 3. Influence of solvent polarity on reaction

Condition: Concentration of compound **I** is 4 g/L. At room temperature, back pressure is set to 44 psi, total residence time is 4 s, samples are tested by HPLC.

Influence of reaction temperature

In order to accelerate the reaction rate and increase the productivity, using dichelоromethane as the reaction solvent, the selectivity and conversion of the reaction at different temperatures were systematically studied. As the reaction temperature increasing, conversion and selectivity increased at first reaching to the maximum, which was conversion of 99.9% and selectivity of 97.9% at 25 ^{o}C, and then selectivity declined (Figure 4). When the reaction temperature was higher than 25 ^{o}C, side reactions were accelerated, resulting in a remarkable decline of selectivity, which contained the dehalogenated (0.8%) and debenzylated (0.6% and 0.4%) side products. According to optimized the reaction temperature, the reaction conversion rate could reach to 99.9% and had a better selectivity (97.9%).

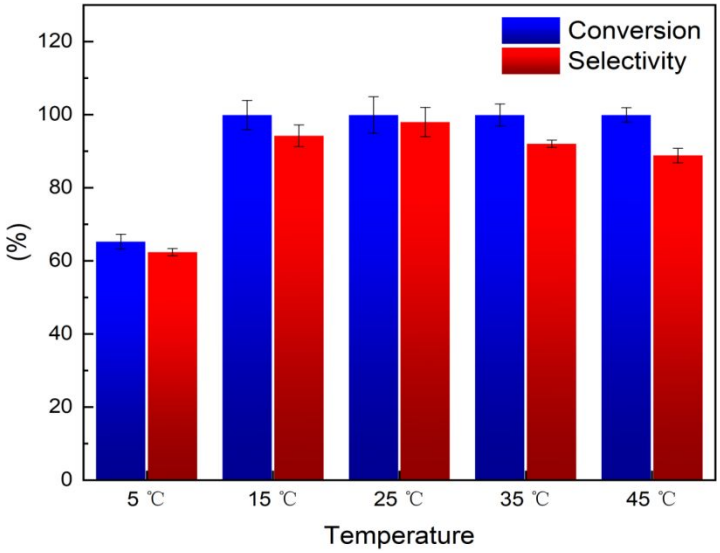


Figure 4. Influence of temperature on reaction

Condition: Concentration of compound **I** is 4 g/L. DCM as solvent, back pressure is set to 44 psi, total residence time is 4 s, samples are tested by HPLC.

Influence of pressure

While running time was prolonged, a new problem came out: Pressure in plunger pump was increasing over time (excess than 600 psi, the pump's automatically shut down value), meanwhile, selectivity and conversion were decreasing. According to further research, the higher the pressure in the reaction tube, the faster the reaction system was shuted down. The results showed that the high pressure could crush the physical structure of catalyst, reduced active center and the effective surface area, therefore the efficiency of reaction reduced. Plus, crushed catalyst increased pressure-drop of reactor, worsening catalytic efficiency and caused reaction system shut down eventually. It was respectively the state before and after the use of catalyst (Figure S1). Obviously, catalyst physical structure was crushed. To deal with this problem, a pressure sensor was added before the reaction tube to explore a suitable inlet pressure of reactor pressure (Figure 5). Finally, under conditions of outlet pressure of reactor (back pressure) $\leqslant$ 30 psi and inlet pressure of reactor pressure < 95 psi, physical structure of catalyst could maintain a long time.

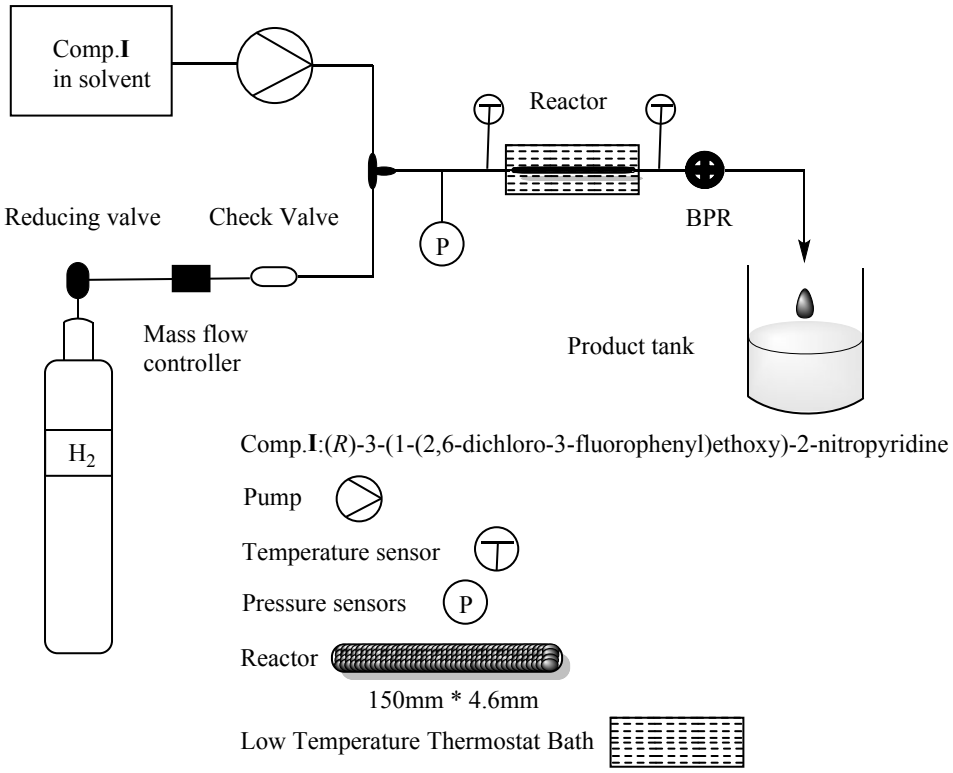


Figure 5. Advanced packed-bed continuous flow reactor

Condition: Concentration of compound **I** is 4 g/L. DCM as solvent, at 25 °C, back pressure was set to 30 psi, total residence time was 4 s, Samples are tested by HPLC.

The relationship between reaction pressure, reaction selectivity and conversion rate were studied under outlet pressure of reactor pressure < 95 psi at 25 °C, dichloromethane (DCM) as solvent. When the reaction pressure was in range of 0 to 60 psi, the conversion rate reached more than 99.9% (Figure 6). However, reaction pressure had great influence on selectivity of catalytic hydrogenation. As the pressure increasing, selectivity first increases and then decreases. The reason may be that when the reaction pressure was greater than 30 psi, the high pressure hydrogen greatly increased the amount of active hydrogen on the surface of the catalyst, the product was overreacted to form by-products such as dehalogenation (0.7%) and debenzylation (0.5%). When the reaction pressure was less than 30 psi, the product was rapidly desorbed from the catalyst surface, and even some of the material was desorbed from the catalyst surface in the intermediate state. As the solution flowed into the collector, there was an intermediate in the product. Finally, when the pressure was set to 30 psi using DCM as solvent at 25 °C, the reaction has the best result with a conversion 99.9%

and a selectivity of 98.1%.

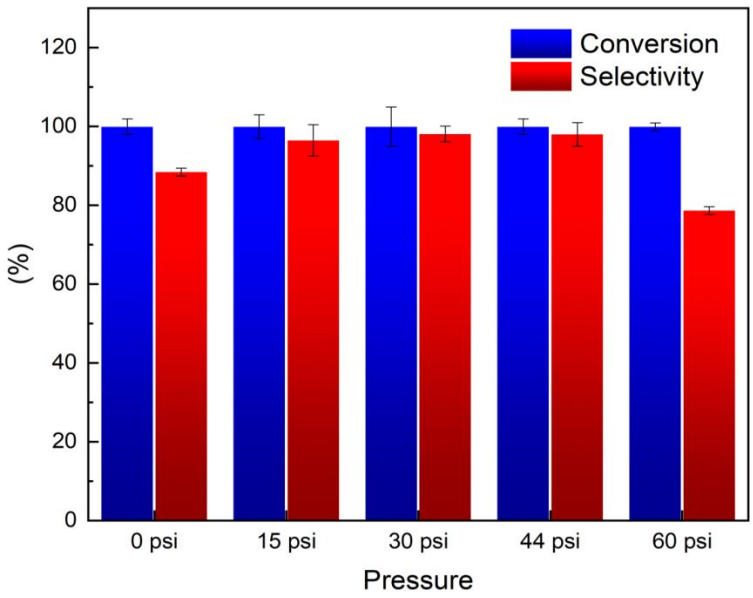


Figure 6. Influence of reaction pressure on the reaction

Condition: Concentration of compound **I** is 4 g/L. DCM as solvent, at 25 °C, total residence time is 4 s, samples are tested by HPLC.

Influence of concentration

The concentration of raw materials was related to the industrialization feasibility of the process, and the relationship between concentration, conversion and selectivity was studied. At concentrations of 80 g/L, 100 g/L and 120 g/L, the selectivity and conversion rates of the intermediates were 99.8%, 100%, 0.2% (intermediate); 99.5%, 100%, 0.5% (intermediate); 99.4%, 100%, 0.6% (intermediate) all achieved the desired results (Figure 7). Under the existing conditions, with the increase of concentration, the selectivity gradually decreases (mainly due to the increase of intermediates) and the conversion rate gradually decreases. When the concentration reached 150 g/L, both selectivity and conversion rate decreased, indicating that the amount of raw material exceeded the upper limit of the conversion amount. Therefore, the optimal reaction concentration was 120 g/L, which was close to the kettle reaction[1]. Surprisingly, keeping the residence time unchanged, the substrate concentration was actually increased by 30 times. Presumably in a unit volume of the

catalyst active sites more than the amount of substrate, and catalytic reaction is completed quickly.

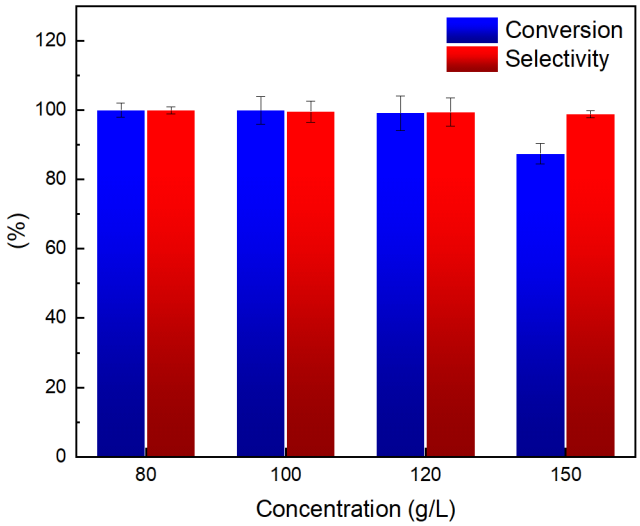


Figure 7. Influence of concentration on the reaction

Condition: DCM as solvent, at 25 °C, back pressure is set to 30 psi, total residence time is 4 s, samples are tested by HPLC.

Influence of the residence time

When the reaction residence time was less than 6 s, it was found that the catalyst could not completely catalytically hydrogenate the raw material on the surface of the catalyst (Figure 8). Meanwhile, the azoxybenzene were detected in the product with 6.6% (residence time is 2 s). When the residence time was more than 6 s, the competitive reaction rapidly appeared, substituents such as halogen and benzyloxy were substituted to produce by-products such as dehalogenation and debenzylation. Best result, 99.9% conversion and 99.5% selectivity were achieved without complicated post-processing in the condition of reaction temperature of 25 °C, DCM as solvent, 30 psi back pressure and 6 s residence time, in which azoxybenzene, dehalogenation and debenzylation impurities were reduced to 0.01%.

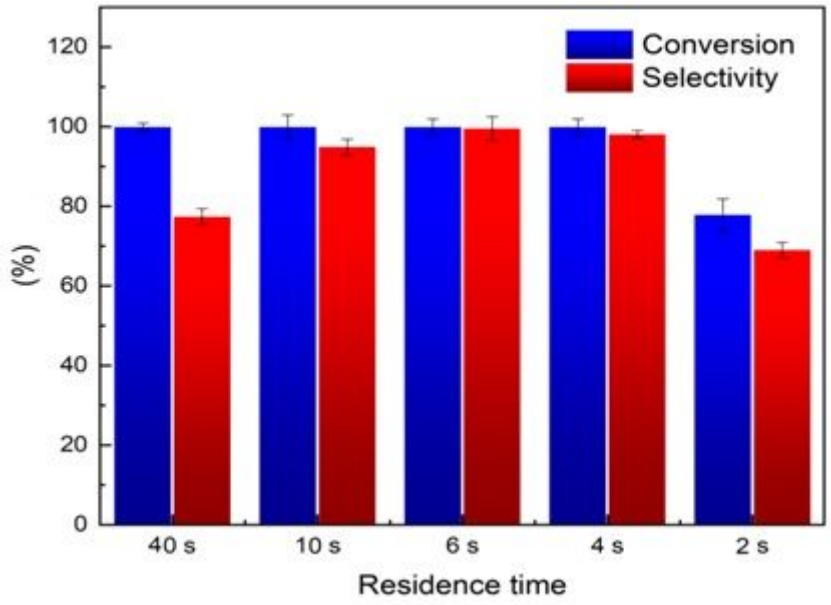


Figure 8. The influence of the residence time on the reaction

Condition: Concentration of compound **I** is 120 g/L. DCM as solvent, at 25 °C, back pressure is set to 30 psi, samples are tested by HPLC.

Reuse of catalyst

The life cycle of the catalyst was investigated and reached nearly 281h after 3 cycles. The selectivity was maintained above 99% according to the standard, and the conversion rate should not be less than 96%. The specific data were shown in Table 3. It was found that the selectivity remains unchanged, only the conversion rate decreases with the extension of time, and can be recovered after washing, which should be the inactivation caused by the covering of the product on the catalyst surface. Until, the pressure increased eminently and physical form of catalyst was destroyed.

Table 3. Catalyst reuse

Number of runs	Duration (h)	Conversion (%)	Selectivity (%)
NO.1	0→98 h	99.9→98.3	>99.0
NO.2	0→93 h	99.6→97.5	>99.0
NO.3	0→90h	99.7→96.6	>99.0

Comparison of batch and continuous-flow process

Compared to batch process, packed-bed continuous-flow process has some advantages (Table 4). (1) Based on green chemistry principles and inherent safety conception, it was noted that the packed-bed technology was intensified, and reaction time was shortened. (2) The catalyst post processing was simplified in packed-bed, which did not need to filter the discharge, post processing is simplified, and the reduction reaction solution can be directly used in subsequent synthesis without post-treatment. According to the method of literature,[1] the subsequent synthesis process was verified and qualified high-quality Crizotinib was obtained (specific operation and data were shown in the supporting information).

Table 4. Comparison of batch experiment and continuous-flow process

Reaction attribute	Batch[a]	Advance continuous-flow
Reaction yield (%)	95~98	＞99.0
Reaction time	>90 min	6 s
Temperature (°C)	25→50	25
Pressure (MPa)	0.35	0.20
Post-treatment	complexity	None
Catalyst consumption (wt %)	5.99	0.016

[a] Crizotinib intermediate **II** was obtained using batch reaction from reference 1.

Conclusions

Pre-passivated catalyst was prepared and packed in a reaction tube to build a packed-bed continuous-flow reaction system. Economic H_2 was chose as the hydrogen source, studying on reaction temperature, solvent, concentration, residence time, back pressure to optimize reaction. At

room temperature, DCM as solvent, concentration 120 g/L, back pressure of 30 psi, residence time of 6 s, reaction has 99.9% or above and conversion rate 99.5% or above selectivity. The dehalogenation and debenzylation impurities are less than 0.01%, and the reduction reaction solution can be directly used in subsequent synthesis without post-treatment. Moreover, product can be treated by following process to obtain high quality Crizotinib.

Experimental section

All chemicals were purchased from commercial sources and used without purification. HPLC analysis was performed a FULI 2200 high-performance liquid chromatography. HPLC conditions: C18 chromatographic column; HPLC acetonitrile and 0.1% phosphoric as mobile phase, mobile phase acetonitrile stayed at 35% for 3 min, from 35% to 45% for 17 min, stayed at 45% for 5 min, from 45% to 85% for 3 min, stayed at 85% for 2 min, from 85% to 35% for 2 min, and at 35% for 3min; flow rate of mobile phase 1.0 mL/min; detection wavelength at 254 nm.

1. Prepared of catalyst

From the catalyst-containing bottle, weigh 20 g of the type DLAW-Ⅴ (Deqing Donglai Chemical co. LTD) Raney Ni catalyst (Catalyst particle size is 400-500 mesh), put it in a clean jar, and wash it with 30 mL of deionized water for 1 min, then use Pasteur dropper to remove deionized water. Add 30 mL of deionized water again and oscillating washing for 1 min, then remove the deionized water with a Pasteur dropper, until the deionized water is tested as neutral with a pH test paper. 20 mL of concentrated ammonia water was added, and the mixture was placed in an environment of 35-50 ^{o}C. The mixture was stirred for 30 min and then stored in a static state for 24 h. The nickel was passivated and ready for use. When the catalyst is reactivated, ethyl acetate is pumped into the reactor, and the catalyst is continuously washed for about 5 h. Then ammonia is

slowly pumped into the reactor and circulated for 24 h.

2. General batch reaction procedure

Take a clean 25 mL high pressure autoclave and weigh 2 g 3-[[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethyl]oxy]-2-nitropyridine in it, 0.01 g of pre-passivated catalyst was added, 20 mL of tetrahydrofuran was added, and magnetons were added and sealed. Pump vacuum, then filled with nitrogen, vacuum again, repeat three times, try to replace the air in the reactor with nitrogen. Thereafter, the mixture was stirred in a 38 °C water bath for 30 min. After the completion of the mixing, the reactor was placed in an ice machine pre-frozen to -10 °C and cooled to -8.0 °C. At low temperature, fill hydrogen to pressure of 0.3 MPa, release hydrogen to atmospheric pressure, and repeat three times. Finally, the hydrogen pressure was filled to 2.5 MPa, sealed, and the reaction was stirred at a temperature of 30 °C at a speed of 700 - 800 rpm to keep the reaction pressure constant. After about 1.5 h of reaction, the progress of the reaction was monitored by HPLC until the reaction was completed.

3. Continuous-flow reaction procedure

3.1 Loading of reaction column

A clean internal HPLC column with a diameter of 4.6 mm and a length of 150 mm is taken. One end is sealed with a sieve plate, and the passivated catalyst solid 4.1 g is gradually added from the other end, and the unconfined end is sleeved with a high pressure vacuum tube, and the compacted catalyst is continuously blown with nitrogen gas, and the pressure of nitrogen gas reaches 0.5 MPa. After the catalyst is compacted, a void is generated in the reaction column, and the passivated catalyst is continuously filled, and the nitrogen compaction process is repeated until the reaction column is completely filled, and both ends are sealed with a sealing nut for use.

3.2 Reaction process

1000g of compound **I** was weighed and placed in a flask, and 8.34 L of dichloromethane was added. Solution, seal the bottle mouth with plastic wrap to prevent solvent evaporation, insert the pipette of the plunger pump below the level of the raw material, and place the packed-bed reactor in a 25 °C water bath. The back pressure valve creates a back pressure of 30 psi, the pressure sensor and temperature sensor were ready for power. The mass flow meter in the hydrogen line was connected to the power supply, and the check valve was ready. Open the plunger pump, set the residence time to 6 s, maintain the hydrogen pressure at 0.72 - 0.83 MPa (amount of H_2: amount of comp. **1** was about 5 : 1), maintain the plunger pump pressure at 75 - 81 psi, sample test by HPLC, the conversion rate was over 99.0%, and the selectivity was over 99.0%. (*R*)-3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-2-amine: Light yellow solid, m.p.:108-109 °C (ref.[1], mp: 109 °C) ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm 7.57 (dd, J = 9.0, 5.0 Hz, 1H), 7.54-7.41 (m, 2H), 6.72-6.59 (m, 1H), 6.41 (dd, J = 7.8, 5.0 Hz, 1H), 5.98 (q, J = 6.6 Hz, 1H), 5.69 (s, 2H), 1.79 (d, J = 6.6 Hz, 3H). HR-MS[ESI]: $C_{13}H_{11}Cl_2FN_2O$ for $[M+H]^+$, Calculated 301.0232, found 301.0233.

Supporting Information

Experimental procedures for Crizotinib and copies of ^{1}HNMRand MS spectra for all compounds and HPLC of compound **II.**

Acknowledgment

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