Research Square

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Chemically Etched Silicon Powder-Supported Platinum as a Durable and Selective Catalyst for Continuous-Flow Reductive N-Alkylation

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Abstract

The continuous-flow reductive *N*-alkylation of amines with carbonyl compounds over supported transition-metal catalysts provides an attractive approach to the synthesis of secondary and tertiary amines. However, maintaining long-term catalytic activity while suppressing metal aggregation and leaching remains a major challenge. Additionally, the competitive hydrogenation of carbonyl compounds to yield the corresponding alcohols can compromise product selectivity. Herein, a durable and selective platinum catalyst supported on chemically etched silicon powder is reported for application in continuous-flow reductive *N*-alkylation. When integrated into a packed-bed reactor, the catalyst enabled the continuous synthesis of a range of secondary and tertiary amines from various amines and carbonyl compounds in a single reactor. Notably, this catalytic system was successfully applied to the synthesis of lomerizine, affording a high product selectivity by effectively suppressing the undesired hydrogenation of 2,3,4-trimethoxybenzaldehyde. This work demonstrates the potential of chemically etched silicon powder as a support for platinum catalysts in continuous-flow synthesis and provides a promising strategy for enhancing catalyst durability and product selectivity while improving resource efficiency in amine synthesis.

1. Introduction

The immobilization of heterogeneous catalysts in column-type reactors for continuous-flow synthesis has emerged as an attractive strategy for improving the efficiency and practicality of fine chemical production compared with conventional batch processes [1–7]. This approach enables continuous product collection at the reactor outlet, thereby facilitating catalyst–product separation and eliminating the requirement for catalyst recovery after each reaction cycle. Furthermore, a single immobilized catalyst can be employed to synthesize different products simply by changing the reactants, provided that the catalyst is compatible with the corresponding transformations. These advantages can improve catalyst utilization and potentially reduce the consumption of expensive transition metals.

Despite these benefits, the application of immobilized transition-metal catalysts in continuous-flow organic synthesis remains challenging. For example, metal aggregation or sintering and metal leaching can compromise catalytic activity, product selectivity, and long-term operational stability [8–11]. To address these challenges, various catalyst-design strategies have been developed. These include enhancing electronic interactions between metal species and support materials to improve metal stabilization, as well as engineering support structures that spatially isolate metal species and suppress their aggregation [12–15].

The hydrogenation of unsaturated organic compounds, such as alkenes [16–18], alkynes [19–22], imines [23–25], nitriles [26–29], and nitro compounds [30–34], represents an important process for synthesizing valuable chemicals and intermediates in both laboratory and industrial settings. In continuous-flow hydrogenation systems, gas–liquid–solid three-phase reactions must proceed within relatively short residence times, typically on the order of minutes. Accordingly, the development of highly

active and selective immobilized metal catalysts is essential, particularly for hydrogenation reactions involving substrates prone to competing side reactions. These requirements are especially important in reductive *N*-alkylation, which provides an attractive route to *N*-alkylated and *N*-arylated amines. In general, this transformation involves the condensation of amines with carbonyl compounds to form imine intermediates, followed by their subsequent hydrogenation over heterogeneous metal catalysts [35–39]. However, nitrogen-containing compounds can coordinate strongly with metal centers, potentially inhibiting catalytic activity [40–42]. Furthermore, the competing hydrogenation of carbonyl compounds to alcohols can reduce the selectivity toward the desired amine products and thereby lower the overall reaction efficiency [43–45].

Several groups have explored strategies to improve the catalytic performance of these systems. For example, Kobayashi et al. demonstrated the reductive *N*-alkylation of primary and secondary amines under continuous-flow conditions using molecular hydrogen and activated-carbon-supported platinum as the catalyst [35]. These reactions were conducted in toluene at temperatures ranging from 80 to 140 °C. More recently, the same group reported a mild continuous-flow protocol for the reductive *N*-alkylation of amines with ketones at 25–50 °C using activated-carbon-supported dimethylpolysilane-palladium as the catalyst [36]. Although these catalytic systems enabled the continuous synthesis of various secondary and tertiary amines, the sequential synthesis of different amine products using a single reactor was not investigated. In a separate study, an etched silicon powder-supported Pd catalyst (ESi-Pd) was developed by our group for the continuous-flow reductive *N*-alkylation of amines with carbonyl compounds [39]. Etching of the Si powder improved its porous structure, facilitating the immobilization and stabilization of Pd species. This catalyst enabled the sequential synthesis of 16 different amine products using a single reactor in the presence of only 0.025 mmol of Pd. However, the competing reduction of carbonyl compounds to the corresponding alcohols remained difficult to suppress. Consequently, an excess of the carbonyl compound (1.6 molar equivalents relative to the amine) was required to achieve the desired transformations.

In this work, an etched Si powder-supported Pt catalyst (ESi-Pt) was developed that exhibits improved selectivity for the reductive *N*-alkylation of amines with carbonyl compounds while effectively suppressing the undesired reduction of carbonyl compounds (Fig. 1). The enhanced selectivity enabled the use of an elevated amine substrate concentration of 0.3 M, which represents a 12-fold increase compared with the 0.025 M concentration typically employed in ESi-Pd catalytic systems [39], thereby significantly improving productivity. Notably, consistent with our practical synthetic approach, the newly developed catalyst also enabled the sequential synthesis of various aromatic and aliphatic amines, including a pharmaceutical compound, under continuous-flow conditions without noticeable catalyst deactivation.

2. Results and Discussion

2.1 Preparation and characterizaion of the ESi-Pt catalyst

The etched Si powder was prepared according to a previously reported method [39]. Specifically, an aqueous solution of K_2PtCl_4 (5.6 mM) was introduced as the Pt precursor, and subsequently reduced by the pre-installed Si–H surface groups on the Si powder, affording ESi-Pt as a black powder (Fig. 1). Using inductively coupled plasma (ICP) emission spectrometry, the Pt loading was determined to be 1.09 wt%.

The Brunauer–Emmett–Teller (BET) surface areas of the original Si powder, the etched Si powder, and the prepared catalyst were analyzed using Kr adsorption isotherm data. The results revealed specific surface areas of 0.65 and 6.41 m^2/g for the original and etched Si powders, respectively. Following the immobilization of Pt species on the Si powder, the specific surface area decreased to 1.80 m^2/g (Supplementary Fig. 1). These results suggest that Pt species may be immobilized within the pore structures formed during the etching treatment of the Si powder. The dispersion of Pt species on the Si powder was then examined using scanning electron microscopy (SEM) observation coupled with energy-dispersive X-ray spectroscopy (EDS) analysis (Supplementary Fig. 2). The particle size of Pt was investigated by transmission electron microscopy (TEM), which revealed the formation of Pt nanoparticles on the Si powder, with an average particle diameter of 31.0 ± 6.5 nm (Figs. 2a and 2b). The structure of the Pt species was investigated by X-ray absorption fine structure (XAFS) measurements of ESi-Pt, using Pt foil, PtO_2, and K_2PtCl_4 as reference materials. The Pt L_3-edge X-ray absorption near edge structure (XANES) spectrum of ESi-Pt (red line) closely resembles that of Pt foil (black line), suggesting that Pt is predominatnely present in the zero-valent state on ESi (Fig. 2c). To further clarify the oxidation states, linear combination fitting of the XANES spectra was performed for the ESi-Pt catalyst over the energy range of 11.546–11.596 keV (50 eV), using K_2PtCl_4 and PtO_2 as references. The results indicated that the conribution of metallic Pt (Pt foil) to the fitted spectrum was 0.942. Additionally, the Fourier-transformed extended X-ray absorption fine structure (FT-EXAFS) spectrum of ESi-Pt exhibited a peak at ~2.5 Å, which can be assigned to Pt–Pt coordination (Fig. 2d) [46–48]. In contrast, the peak at ~1.9 Å, corresponding to Pt–Cl coordination in K_2PtCl_4 (green line), was substantially diminished in the FT-EXAFS spectrum of ESi-Pt. These results indicate that the K_2PtCl_4 percusor was reduced to form zero-valent Pt nanoparticles on ESi, without requiring additional reducing agents or further treatment steps.

2.2 Continuous-flow reductive *N*-alkylation using the ESi-Pt catalyst

The synthesis of the pharmaceutical compound lomerizine (**3aa**) [49] under continuous-flow reductive *N*-alkylation conditions was selected as a model reaction (Fig. 3). Specifically, the freshly prepared ESi-Pt catalyst (603 mg, 0.034 mmol Pt) was mixed with glass beads (603 mg) and packed into a column-type reactor. The two substrates, 1-(4,4'-difluorodiphenylmethyl)piperazine (**1a**) and 2,3,4-trimethoxybenzaldehyde (**2a**), were separately dissolved in the desired organic solvent at concentrations of 25 and 30 mM, respectively. The resulting solutions were independently pumped into the flow system at a flow rate of 0.1 mL/min and mixed with hydrogen gas in a micromixer. The hydrogen pressure was maintained at 0.7 MPa, and the gas flow rate was controlled at 3.0 mL/min using a mass flow controller (Supplementary Fig. 4). Before entering the reactor, the gas–liquid mixture was preheated to 70 °C in a coiled tube. Under these conditions, the residence time was determined to be 4.15 min. The reaction

effluent was collected over a period of 3 h and analyzed by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy.

Initially, the reaction was conducted at a reactor temperature of 115 °C and toluene was employed as the solvent, affording the target product **3aa** in 44% yield (Fig. 3, entry 1). The effects of other solvents, including 2-propanol and *N*,*N*-dimethylformamide (DMF), were subsequently investigated (Fig. 3, entries 2 and 3). However, 2-propanol resulted in a low reactivity during the reductive *N*-alkylation reaction, whereas no product was detected when DMF was used. When the ESi-Pt catalyst was replaced with ESi-Pd (0.025 mmol Pd), **3aa** was obtained in 39% yield, together with 41% of **2aa**, the alcohol formed by the reduction of aldehyde **2a** (Fig. 3, entry 1). These results suggest that the Pt catalyst favors the hydrogenation of the imine intermediate over the direct reduction of the aldehyde, consistent with a previous report [35].

Following optimization of the reaction conditions, the catalyst loading was increased to 1.2 g (0.067 mmol Pt), mixed with 1.2 g glass beads, and packed into a column-type reactor measuring ~5.5 cm in length. The hydrogen gas flow rate was set to 5.0 mL/min, while the reaction temperature was increased to 140 °C, resulting in a residence time of 3.4 min. Under these conditions, ^{1}H NMR analysis confirmed the formation of **3aa** in >99% yield, with no appreciable formation of **2aa** (Fig. 3, entry 5). To further evaluate the operational stability of the ESi-Pt catalyst, the reaction was continued for an additional 7 h, and the reaction effluent was collected and analyzed every 3 h. During the 3–6 and 7–10 h periods, the catalyst maintained its activity, affording **3aa** in isolated yields of 94% (197.4 mg) and 96% (201.3 mg), respectively. Furthermore, Pt leaching was evaluated by ICP–mass spectrometry (ICP-MS) using the reaction effluent collected during the 6–7 h period. The Pt concentration was below the detection limit, indicating the high stability of the ESi-Pt catalyst under continuous-flow reaction conditions.

To further investigate the applicability and stability of ESi-Pt under continuous-flow reductive *N*-alkylation conditions, a series of reactions were conducted using the same reactor while sequentially varying the substrate, as shown in Fig. 4. Specifically, solutions of amine compounds (300 mM) and carbonyl compounds (360 mM) in toluene were prepared and pumped into the reactor at a flow rate of 0.1 mL/min, with hydrogen gas supplied at a flow rate of 7.0 mL/min. Each reaction was conducted for 3 h, after which the reactor was washed with pure toluene for 2 h before introducing the next substrate solution into the reactor. In total, eight different substrate combinations were tested sequentially over a 24 h reaction period. Notably, aniline was efficiently alkylated with various aryl aldehydes bearing electron-donating or electron-withdrawing groups, continuously affording the corresponding products **3bb**, **3bc**, **3bd**, and **3be** in yields ranging from 77% to 92%. The reaction of 4-*tert*-butylaniline with benzaldehyde also gave **3cb** in 88%. Additionally, the reactions of primary alkyl amines with benzaldehyde proceeded smoothly, affording the corresponding secondary amines **3db**, **3eb**, and **3fb** in yields of 80%, 84%, and 76%, respectively. These findings demonstrate the potential of the ESi-Pt catalyst for the sequential synthesis of various amine compounds over extended continuous-flow operation.

Conclusion

In this study, a novel catalyst was developed by immobilizing Pt nanoparticles on chemically etched silicon powder as a support. The Pt precursor, K_2PtCl_4, was directly reduced by the pre-installed Si–H surface groups on the Si powder, without the requirement for additional reducing agents or further treatment procedures. The resulting catalyst selectively promoted the reductive *N*-alkylation of amines with carbonyl compounds rather than the direct reduction of the carbonyl compounds. Notably, this chemoselectivity was also demonstrated during the continuous-flow synthesis of lomerizine. Furthermore, the catalytic system was successfully applied to the sequential synthesis of multiple amine compounds, highlighting its potential for broader synthetic applications. Therefore, the synthesis of value-added products, such as pharmaceuticals and organic functional materials, is expected to be further expanded in future studies.

Methods

Preparation of the ESi-Pt catalyst

Silicon powder (Si powder, 10 g, particle size: 40–75 μm) was first immersed in a mixture of concentrated H_2SO_4 (95%) and H_2O_2 (30%) (3:1, v/v, 40 mL) for 15 min. The powder was subsequently treated with 5% aqueous HF (10 mL) for 3 min, followed by thorough washing with deionized water. The pretreated Si powder was then stirred in a mixture of 5 M HF and 10 mM $AgNO_3$ for 5 min and washed with deionized water. The resulting Ag-treated Si powder was etched in a mixture of 5 M HF and 2% H_2O_2 (100 mL) at 50 °C for 2 h. After etching, the powder was thoroughly washed with deionized water. The etched Si powder was then treated twice with 50% aqueous HNO_3 (30 mL) for 3 min per treatment, followed by washing with deionized water to obtain the etched silicon powder.

For Pt deposition, the obtained ESi was dispersed in 0.1 M aqueous HF (100 mL), followed by the addition of 5.6 mM aqueous K_2PtCl_4. The resulting suspension was stirred for 10 min. The solid was sequentially washed with deionized water, acetone, and ethanol, and dried under vacuum at room temperature overnight to afford the ESi-Pt catalyst.

Continuous-flow reductive *N*-alkylation

ESi-Pt (0.067 mmol Pt; Pt loading: 1.09 wt%) was mixed with glass beads (1.2 g) in a vial using a vortex mixer (Vortex-Genie 2, KENIS Ltd.) at 1000 rpm for 5 min. The resulting mixture was packed into a glass column (6 mm in diameter), with polytetrafluoroethylene filters installed at both the top and bottom of the column. The packed catalyst bed had an approximate length of 5.5 cm. The column was then placed in the heating unit of the continuous-flow reactor.

Typically, a solution containing an amine (300 mM) and a carbonyl compound (360 mM) in toluene was prepared in a 50 mL flask. Molecular sieve 3A (MS3A, 3 g) was also added into the flask. The prepared solution and H_2 gas were then injected into the flow system. The liquid feed and H_2 gas were introduced

into a micromixer at flow rates of 0.1 and 7.0 mL/min, respectively. The resulting gas–liquid mixture was preheated to 70 °C in a coiled tube before entering the reactor. The reaction mixtures were collected in separate vials every 1 h during the reaction. The products were subsequently purified by silica gel column chromatography to obtain the corresponding pure compounds.

Declarations

Data availability

All data generated during this study (experimental methods, compound characterization, ^{1}H NMR spectra and ^{13}C NMR spectra) are provided in the Supplementary Information file (PDF).

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Author contributions

Y.M.A.Y. directed the project. H.B. and Z.Z. conducted the experiments. Z.Z. and Y.M.A.Y. wrote and revised the manuscript. All authors have approved the final version of the manuscript.

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Additional information

Supplementary information is available.

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Trial registration

Not applicable. This study is not a clinical trial.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Figures

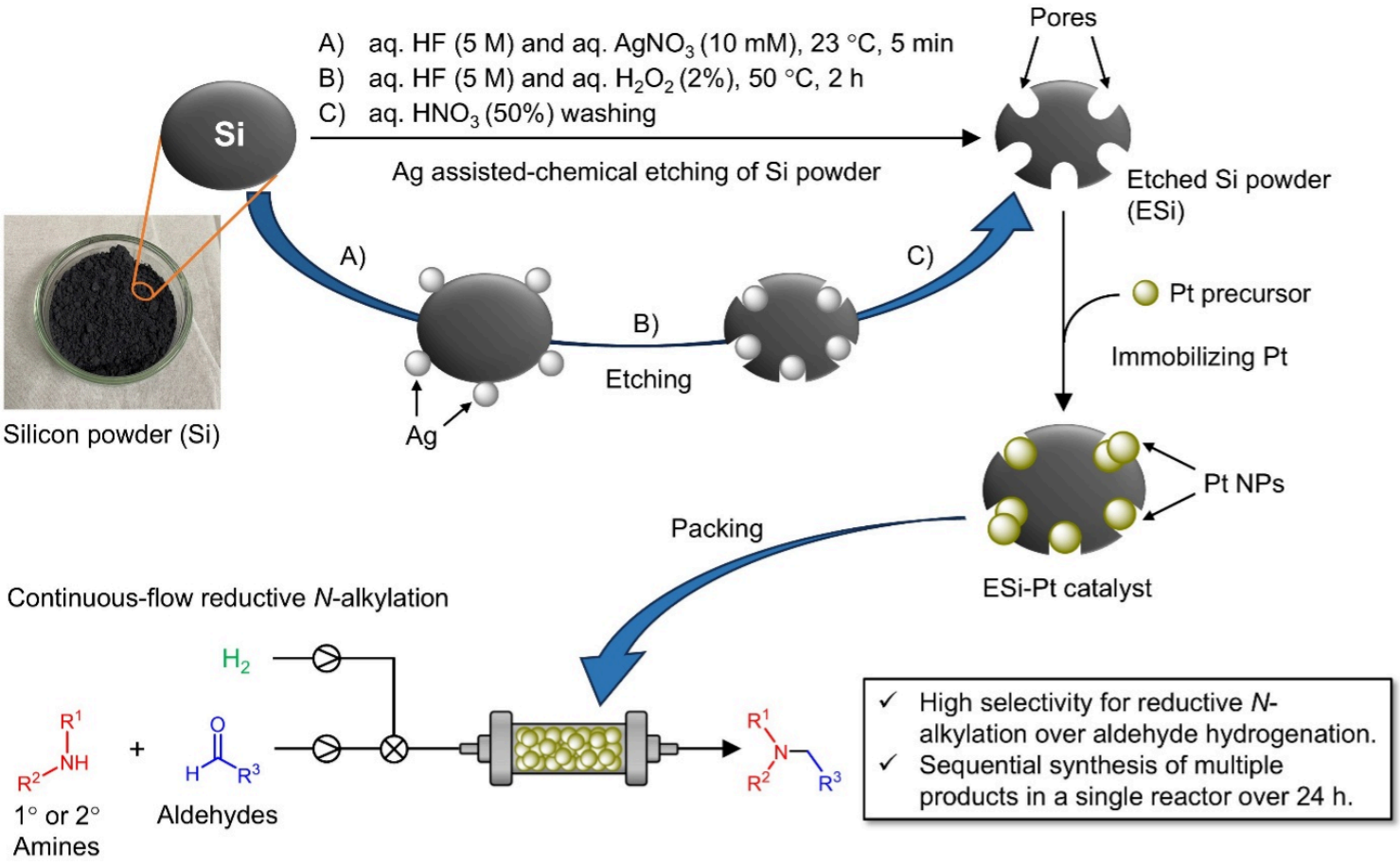


Figure 1

Preparation of the ESi-Pt catalyst and the continuous-flow reductive *N*-alkylation process developed herein

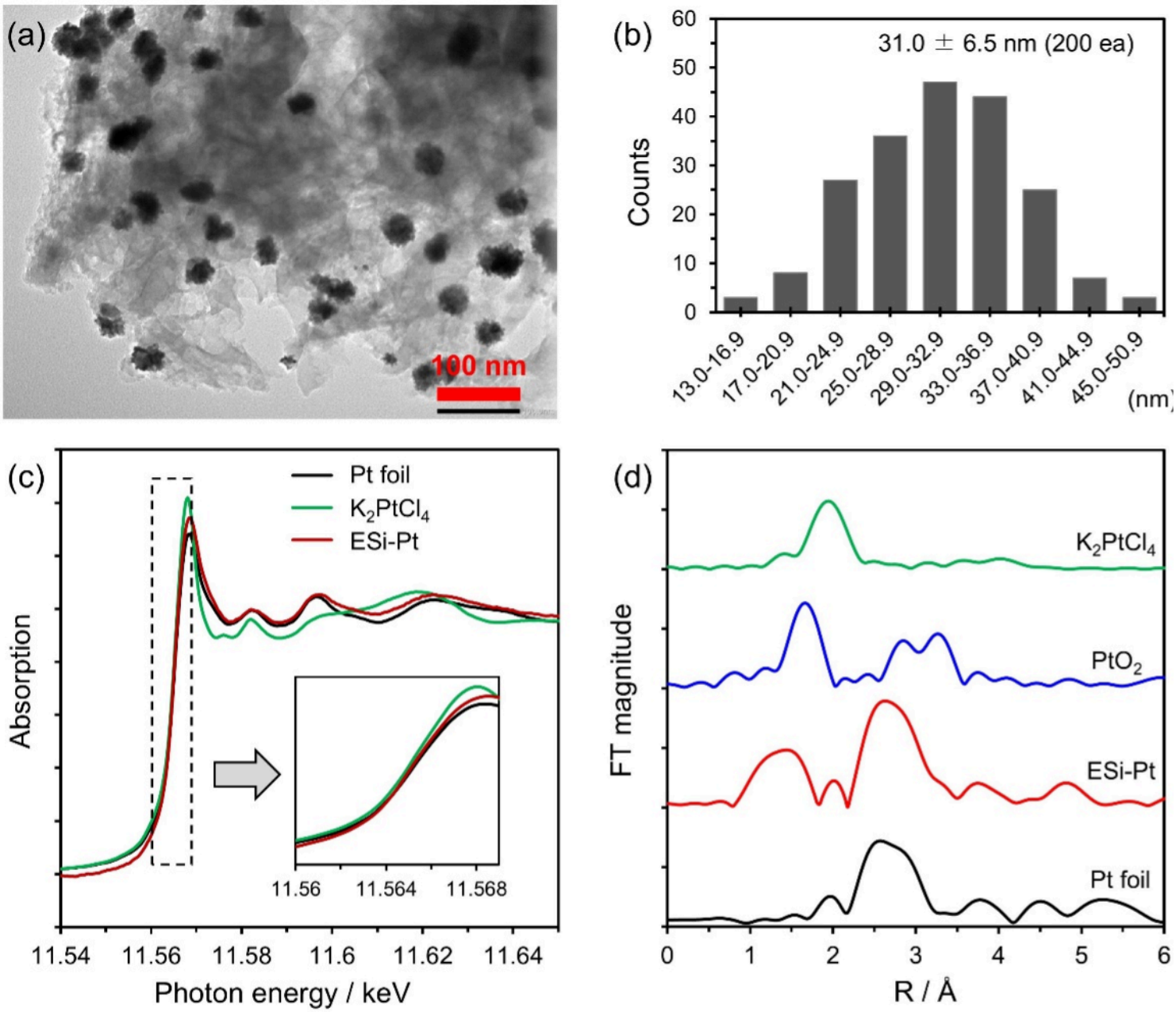
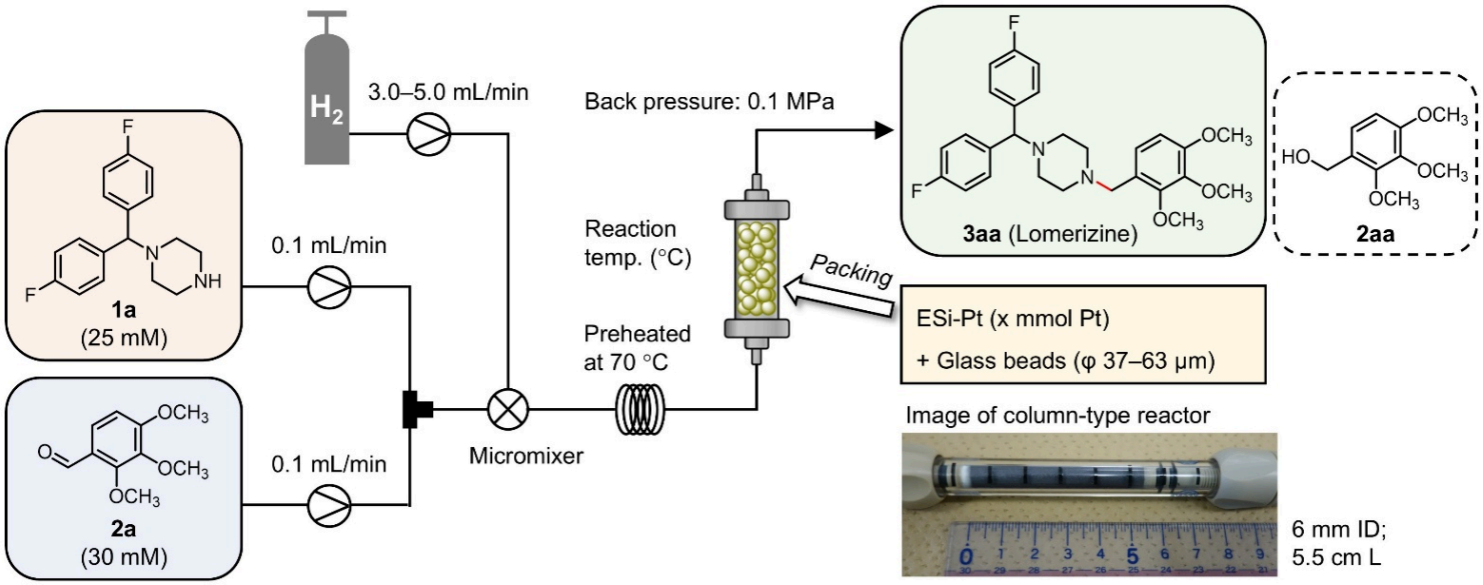


Figure 2

Characterization of the ESi-Pt catalyst: (a) TEM image, (b) particle size and size distribution of Pt, cC) Pt L_3-edge XANES spectra of Pt foil, K_2PtCl_4, and ESi-Pt, and (d) Fourier-transforms of the k^3-weighted Pt L_3-edge EXAFS spectra (k = 3–12 $Å^{-1}$)



Entry	Catalyst	Solvent	Collection time (h)	Temp. (°C)	Yield of **3aa** (%)[a]	Yield of **2aa** (%)[a]
1	ESi-Pt (0.034 mmol Pt)	Toluene	0–3	115	44	<1
2	ESi-Pt (0.034 mmol Pt)	2-Propanol	0–3	115	15	<1
3	ESi-Pt (0.034 mmol Pt)	DMF	0–3	115	n.d.	n.d.
4	ESi-Pd (0.025 mmol Pd)	Toluene	0–3	115	39	41
5	ESi-Pt (0.067 mmol Pt)	Toluene	0–3	140	>99	<1
			3–6	140	98 (94)	<1
			7–10[b]	140	>99 (96)	<1

Figure 3

Continuous-flow synthesis of lomerizine (3aa). [a]The yields of 3aa and 2aa were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybezene as an internal standard. The values in parentheses represent the isolated yields of 3aa. [b]The reaction mixture collected during the 6–7 h period was used for ICP-MS analysis

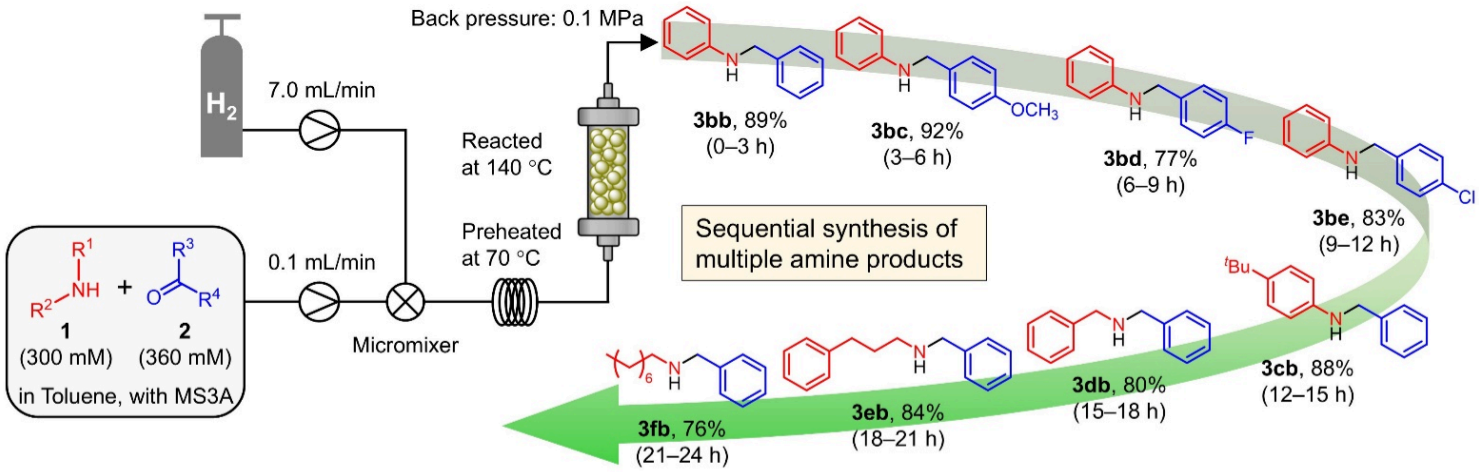


Figure 4

Substrate scope of the ESi-Pt-catalyzed continuous-flow reductive *N*-alkylation protocol. [a]Each substrate solution was reacted for 3 h, after which time the reactor was washed with pure toluene for 2 h before injection of the subsequent substrate solution

Supplementary Files

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- 20261107SupplementaryInformation.pdf