Electronic Supplementary Information

Bayesian based reaction optimization for complex continuous gas-liquid-solid reactions

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1. Analysis method

The sample is analyzed offline utilizing gas chromatography (Agilent, GC-8860) with an FID detector and an Agilent HP-5 column (length: 30 m, diameter: 0.32 mm, film thickness: 0.25 μm). The samples are diluted with methanol (molar ratio: 1:5) and measured under the following conditions: the injection temperature, 280 °C; the column temperature, 50 ~ 110 °C, 20 °C/min, 110 ~ 150 °C, 10 °C/min, 150 °C, 4 min, 150 ~ 250 °C, 20 °C/min; the detector temperature, 280 °C. The sample volume for all analysis was 1 μL. Based on these analytical conditions, the retention times of the reactants and products are as following: aniline: 3.6 min, nitrobenzene: 4.7 min, dichloroaniline: 5.8 min; 3,4-dichloronitrobenzene: 7.8 min; 3,4-dichloroaniline: 8.5 min; 5-aminotetrahydroisoquinoline: 11.5 min, 5-aminoisoquinoline: 12.2 min, 5-nitroisoquinoline: 12.5 min, azoxy compound (hydrogenation of 3,4-dichloronitrobenzene): 13.3 min, azoxy compound (hydrogenation of 5-nitroisoquinoline): 16.2 min.

2. Sample chromatograms for the hydrogenation

The sample chromatograms for the hydrogenation of nitrobenzene, 3,4-

chloronitrobenzene and 5-nitroisoquinoline are shown in Figure S1, Figure S2 and Figure S3 respectively.

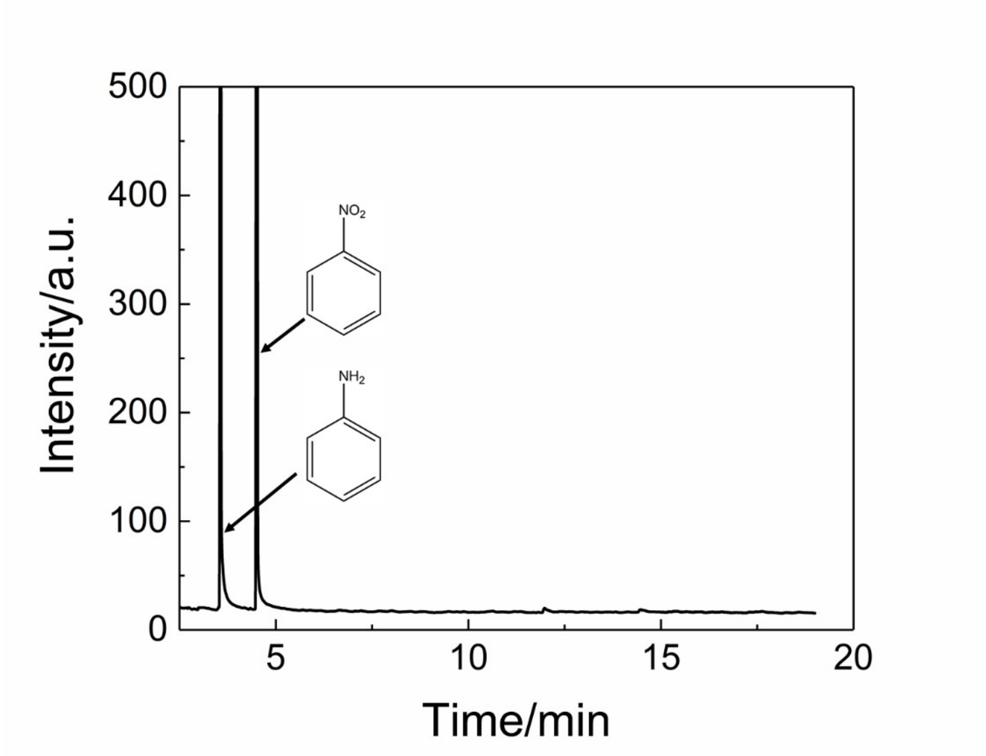


Figure S1 The sample chromatography for the hydrogenation of nitrobenzene.

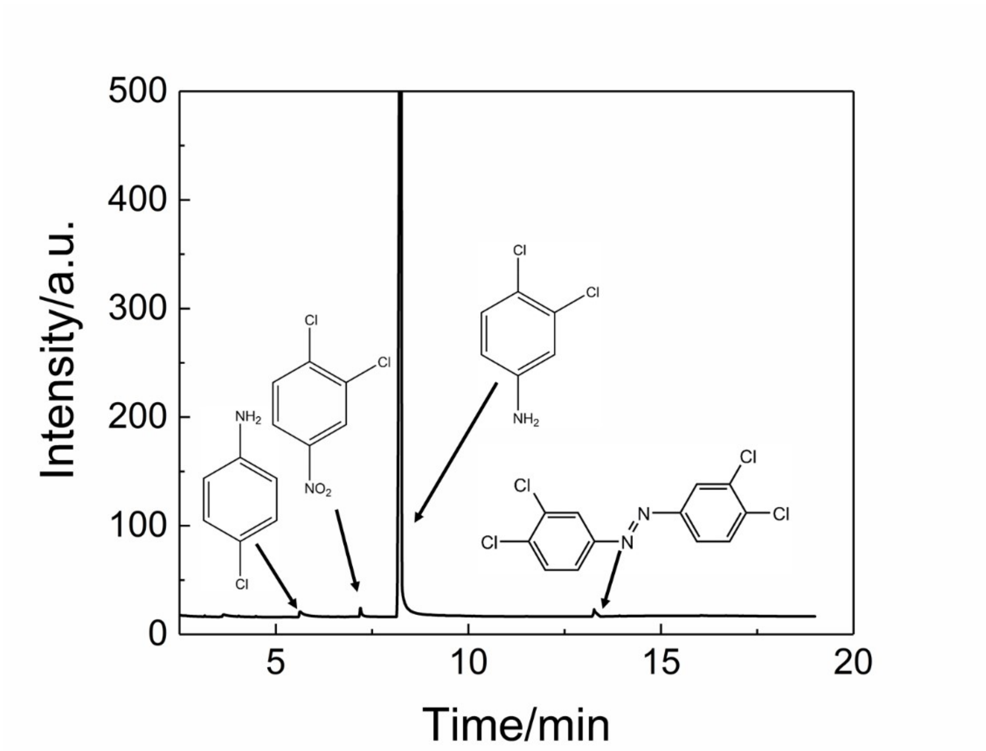


Figure S2 The sample chromatography for the hydrogenation of 3,4-dichloronitrobenzene

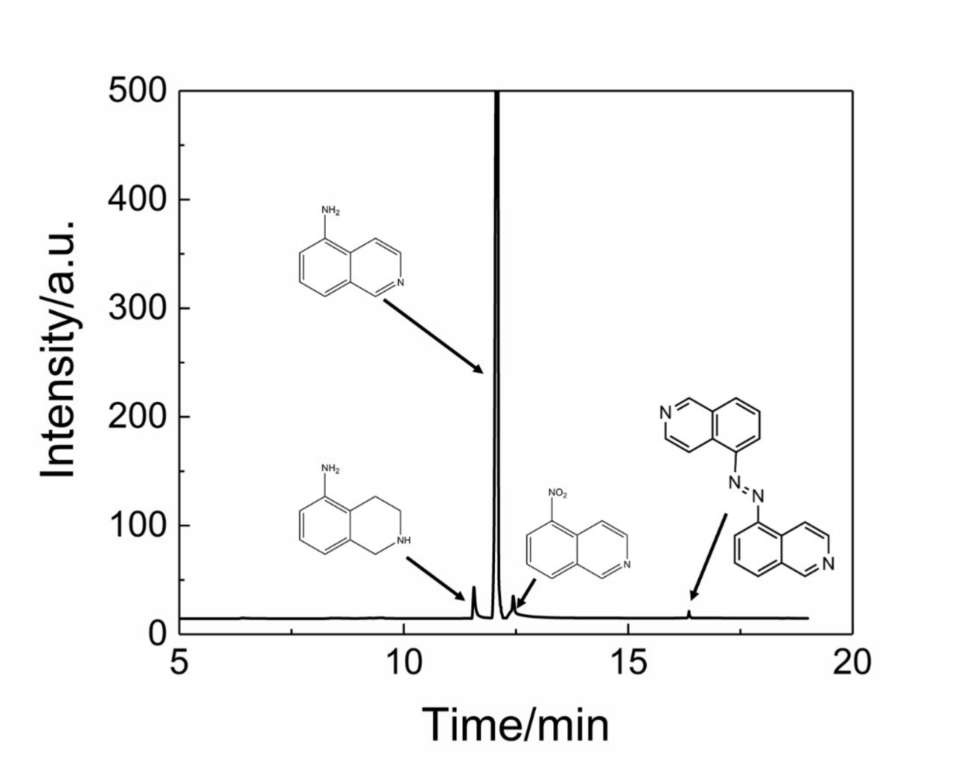
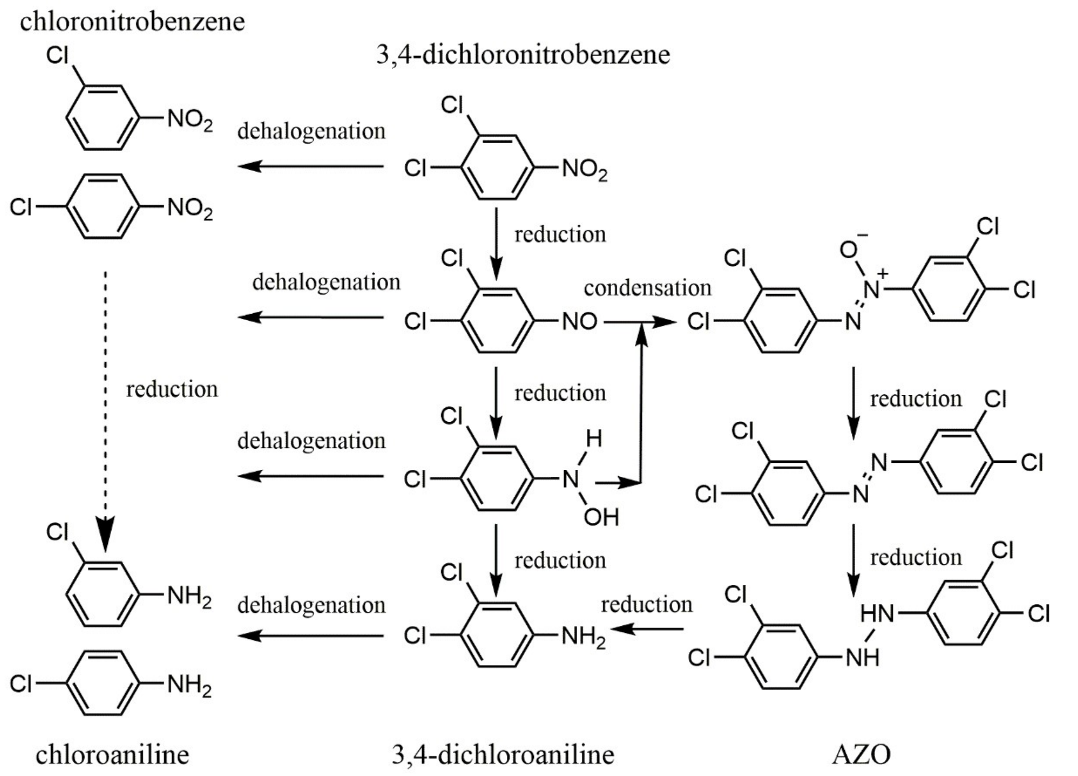


Figure S3 The sample chromatography for the hydrogenation of 5-nitroisoquinoline

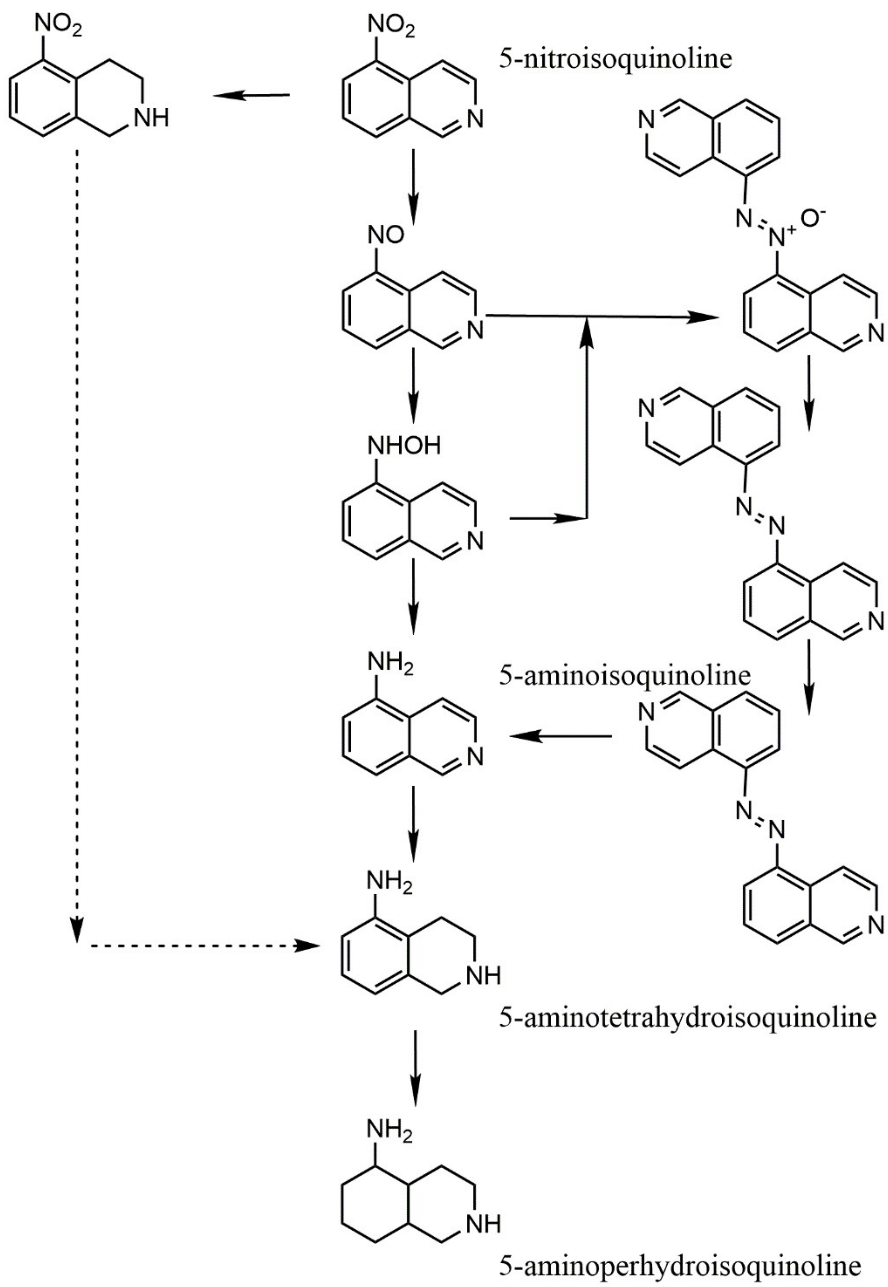
3. Reaction pathways for the hydrogenation

For the hydrogenation of 3,4-dichloronitrobenzene, the reduction of 3,4-dichloronitrobenzene proceeds via the nitroso compound and hydroxylamine to 3,4-dichloroaniline. Dehalogenation of the nitro raw material is possible to occur at any step during the reaction pathway, but the dehalogenation of the more electron-rich product (3,4-dichloroaniline) is commonly faster. Another pathway can accrue from condensation of these intermediates. For instance, nitroso and hydroxylamine intermediates can condense to form azoxy compounds. Besides, nitroso intermediate can also react with 3,4-dichloroaniline to form diazo compound. These compounds could be reduced to 3,4-dichloroaniline through a hydrazo intermediate, and the complex reaction pathways are depicted in Scheme S1.



Scheme S1 The reaction pathway for the hydrogenation of 3,4-dichloronitrobenzene

While for the synthesis of 5-aminoisoquinoline, the over hydrogenation of pyridine may also appear during the reaction process except for the similar pathway described in the hydrogenation of 3,4-dichloronitrobenzene, and the reaction mechanism of 5-nitroisoquinoline is depicted as Scheme S2.



Scheme S2 The reaction pathway for the hydrogenation of 5-nitroisoquinoline

4. Optimization routes of OVAT and Bayesian optimization for the hydrogenation

Optimization routes proposed by OVAT and Bayesian optimization of the hydrogenation of nitrobenzene, 3,4-dichloronitrobenzene and 5-nitroisoquinoline are listed in Table S1 – S6, respectively.

Table S1 The OVAT optimization route for the hydrogenation of nitrobenzene

Experiment number	Temperature /°C	Hydrogen pressure /MPa	Liquid flow rate /mL/min	Conversion /%	Selectivity of aniline /%	Yield of aniline /%
1	30.0	1.0	1.4	51.2	100.0	51.2
2	35.0	1.0	1.4	58.5	100.0	58.5
3	40.0	1.0	1.4	66.6	100.0	66.6
4	45.0	1.0	1.4	69.1	100.0	69.1
5	50.0	1.0	1.4	74.5	100.0	74.5
6	40.0	1.0	0.6	91.9	100.0	91.9
7	40.0	1.0	0.8	85.7	100.0	85.7
8	40.0	1.0	1.0	77.4	100.0	77.4
9	40.0	1.0	1.2	71.8	100.0	71.8
10	40.0	1.0	1.4	64.7	100.0	64.7
11	40.0	0.5	1.0	55.4	100.0	55.4
12	40.0	1.0	1.0	75.4	100.0	75.4
13	40.0	1.5	1.0	90.4	100.0	90.4
14	40.0	2.0	1.0	94.5	100.0	94.5
15	40.0	2.5	1.0	98.5	100.0	98.5

Reaction conditions: initial concentration: 0.2 mol/L, solvent: methanol, gas flow rate: 20 mL/min, catalyst: 0.5 wt% Pd/Al_2O_3, catalyst loading: 0.34 g (diluted by 1.36 g Al_2O_3).

Table S2 Bayesian optimization route for the hydrogenation of nitrobenzene

Experiment number	Temperature /°C	Hydrogen pressure /MPa	Liquid flow rate /mL/min	Conversion /%	Selectivity of aniline /%	Yield of aniline /%
1	30.0	1.0	1.0	68.1	100.0	68.1
2	40.0	1.0	1.0	75.4	100.0	75.4
3	50.0	1.0	1.0	85.5	100.0	85.5
4	40.0	0.5	1.0	55.4	100.0	55.4
5	40.0	2.5	1.0	98.5	100.0	98.5
6	40.0	1.0	0.6	91.9	100.0	91.9
7	40.0	1.0	1.6	61.0	100.0	61.0
8	44.8	2.5	0.6	99.8	99.1	98.9
9	35.1	2.5	0.6	99.7	100.0	99.7

Reaction conditions: initial concentration: 0.2 mol/L, solvent: methanol, gas flow rate: 20 mL/min, catalyst: 0.5 wt% Pd/Al_2O_3, catalyst loading: 0.34 g (diluted by 1.36 g Al_2O_3).

Table S3 The proposed Bayesian based optimization route for the hydrogenation of nitrobenzene

	Experiment number	Temperature/ ℃	Hydrogen pressure /MPa	Liquid flow rate /mL/min	Conversion /%	Selectivity of aniline /%	Yield of aniline /%
Initial simplex	1	40.0	1.0	1.0	77.4	100.0	77.4
	2	44.0	1.0	1.0	92.2	100.0	92.2
	3	40.0	1.5	1.0	90.4	100.0	90.4
	4	40.0	1.0	1.2	71.8	100.0	71.8
Local optimization	5	42.7	1.3	0.8	99.1	100.0	99.1
	6	44.1	1.4	0.6	99.6	100.0	99.6
	7	45.4	1.6	0.7	99.7	100.0	99.7

Reaction conditions: initial concentration: 0.2 mol/L, solvent: methanol, gas flow rate: 20 mL/min, catalyst: 0.5 wt% Pd/Al_2O_3, catalyst loading: 0.34 g (diluted by 1.36 g Al_2O_3).

Table S4 The OVAT optimization route for the hydrogenation of 3,4-dichloronitrobenzene

Experiment number	Temperature /°C	Hydrogen pressure /MPa	Liquid flow rate /mL/min	Conversion /%	Selectivity /%	Yield of 3,4-dichloroaniline /%
1	40.0	2.0	0.30	74.7	92.0	68.7
2	50.0	2.0	0.30	96.1	94.6	90.9
3	60.0	2.0	0.30	100.0	94.9	94.9
4	70.0	2.0	0.30	100.0	97.4	96.4
5	80.0	2.0	0.30	100.0	93.0	93.0
6	60.0	2.0	0.20	100.0	96.7	96.7
7	60.0	2.0	0.25	100.0	98.6	98.6
8	60.0	2.0	0.30	94.3	96.8	91.3
9	60.0	2.0	0.35	69.8	96.1	67.1
10	60.0	2.0	0.40	56.4	92.2	52.0
11	60.0	1.0	0.30	89.8	93.3	83.8
12	60.0	1.5	0.30	90.7	93.9	85.2
13	60.0	2.0	0.30	96.5	98.1	94.7
14	60.0	2.5	0.30	97.4	98.0	95.5
15	60.0	3.0	0.30	100.0	96.8	96.8

Reaction conditions: initial concentration: 0.39 mol/L, solvent: methanol, gas flow rate: 20 mL/min, catalyst: 20 wt% Ni/SiO_2, catalyst loading: 1.88 g.

Table S5 Bayesian optimization route for the hydrogenation of 3,4-dichloronitrobenzene

Experiment number	Temperature /°C	Hydrogen pressure /MPa	Liquid flow rate /mL/min	Conversion /%	Selectivity /%	Yield of 3,4-dichloroaniline /%
1	40.0	2.0	0.30	74.7	92.0	68.7
2	60.0	2.0	0.30	100.0	94.9	94.9
3	80.0	2.0	0.30	100.0	93.0	93.0
4	60.0	2.0	0.20	100.0	96.7	96.7
5	60.0	2.0	0.40	56.4	92.2	52.0
6	60.0	1.0	0.30	89.8	93.3	83.8
7	60.0	3.0	0.30	100.0	96.8	96.8
8	60.0	2.5	0.20	100.0	93.6	93.6
9	59.6	2.8	0.20	100.0	92.4	92.4
10	59.5	2.2	0.20	100.0	94.3	94.3
11	53.3	1.7	0.23	99.7	98.5	98.2
12	52.3	1.5	0.25	99.5	96.6	96.1
13	75.4	2.9	0.30	100.0	83.0	83.0
14	52.8	1.4	0.34	99.3	91.6	91.0
15	52.7	1.9	0.22	100.0	98.3	98.3
16	53.2	2.3	0.40	90.8	97.4	88.4
17	59.5	1.4	0.30	99.5	97.9	97.4
18	59.0	1.7	0.34	100.0	98.0	98.0

Reaction conditions: initial concentration: 0.39 mol/L, solvent: methanol, gas flow rate: 20 mL/min, catalyst: 20 wt% Ni/SiO_2, catalyst loading: 1.88 g.

Table S6 The proposed Bayesian based optimization route for the hydrogenation of 3,4-dichloronitrobenzene

	Experiment number	Temperature /℃	Hydrogen pressure /MPa	Liquid flow rate /mL/min	Conversion /%	Selectivity /%	Yield of 3,4-dichloroaniline /%
Initial simplex	1	60.0	2.0	0.30	100	94.8	94.8
	2	70.0	2.0	0.30	100	97.4	97.4
	3	60.0	2.0	0.35	69.8	96.1	67.1
	4	60.0	2.5	0.30	100	95.5	95.5
Local optimization	5	66.7	2.3	0.25	100	95.6	95.6
	6	71.1	2.5	0.27	100	93.6	93.6
	7	62.8	2.1	0.29	100	94.6	94.6
	8	68.3	2.4	0.28	100	92.4	92.4
	9	64.2	2.2	0.29	100	94.1	94.1
Global optimization	10	40.0	1.0	0.20	73.8	95.5	70.5
	11	80.0	1.0	0.20	100	96.7	96.7
	12	80.0	3.0	0.40	100	97.3	97.3
	13	80.0	3.0	0.20	100	94.7	94.7
	14	60.4	2.2	0.20	100	98.9	98.9

15	70.5	2.5	0.22	100	99.1	99.1
16	70.7	1.8	0.40	99.8	98.4	98.2
17	67.5	2.6	0.20	100	97.9	97.9
18	80.0	2.0	0.31	100	99.1	99.1

Reaction conditions: initial concentration: 0.39 mol/L, solvent: methanol, gas flow rate: 20 mL/min, catalyst: 20 wt% Ni/SiO_2, catalyst loading: 1.88 g.

Table S7 The OVAT optimization route for the hydrogenation of 5-nitroisoquinoline

Experiment number	Temperature /°C	Hydrogen pressure /MPa	Liquid flow rate /mL/min	Gas flow rate /mL/min	Conversion /%	Selectivity /%	Yield of 5-aminoisoquinoline /%
1	40.0	2.0	0.30	20.0	98.1	99.1	97.2
2	50.0	2.0	0.30	20.0	99.0	93.5	92.6
3	60.0	2.0	0.30	20.0	99.6	87.4	87.1
4	70.0	2.0	0.30	20.0	100.0	81.6	81.6
5	80.0	2.0	0.30	20.0	100.0	76.3	76.3
6	60.0	2.0	0.20	20.0	99.6	92.4	92.1
7	60.0	2.0	0.30	20.0	99.8	93.7	93.4
8	60.0	2.0	0.40	20.0	100.0	95.3	95.3
9	60.0	2.0	0.50	20.0	100.0	96.5	96.5
10	60.0	2.0	0.60	20.0	100.0	97.6	97.6

11	60.0	2.0	0.70	20.0	99.2	98.2	97.5
12	60.0	2.0	0.80	20.0	99.6	98.6	98.2
13	60.0	2.0	0.90	20.0	100.0	98.9	98.9
14	60.0	2.0	1.00	20.0	98.3	99.3	97.5
15	60.0	2.0	1.10	20.0	96.8	99.2	96.1
16	60.0	1.0	0.30	20.0	98.0	97.8	95.9
17	60.0	1.5	0.30	20.0	98.0	97.0	95.1
18	60.0	2.0	0.30	20.0	100.0	94.8	94.8
19	60.0	2.5	0.30	20.0	100.0	94.1	94.1
20	60.0	3.0	0.30	20.0	100.0	93.2	93.2
21	60.0	2.0	0.30	15.0	100.0	94.5	94.5
22	60.0	2.0	0.30	20.0	99.3	93.5	92.8
23	60.0	2.0	0.30	25.0	99.4	93.8	93.3
24	60.0	2.0	0.30	30.0	99.4	94.1	93.5

Reaction conditions: initial concentration: 0.18 mol/L, solvent: tetrahydrofuran, catalyst: 5 wt% Pt/C, catalyst loading: 0.8 g.

Table S8 Bayesian optimization route for the hydrogenation of 5-nitroisoquinoline

Experiment number	Temperature /°C	Hydrogen pressure /MPa	Liquid flow rate /mL/min	Gas flow rate /mL/min	Conversion /%	Selectivity /%	Yield of 5-aminoisoquinoline /%
1	40.0	2.0	0.30	20.0	99.3	97.9	97.2

2	60.0	2.0	0.30	20.0	100.0	93.4	93.4
3	60.0	2.0	0.60	20.0	100.0	97.6	97.6
4	80.0	2.0	0.30	20.0	100.0	76.3	76.3
5	60.0	1.0	0.30	20.0	100.0	95.9	95.9
6	60.0	3.0	0.30	20.0	100.0	93.2	93.2
7	60.0	2.0	0.20	20.0	100.0	92.1	92.1
8	60.0	2.0	1.20	20.0	98.3	94.7	93.1
9	60.0	2.0	0.30	15.0	100.0	94.5	94.5
10	60.0	2.0	0.30	30.0	100.0	93.5	93.5
11	48.0	1.0	1.20	15.0	94.2	92.4	87.0
12	60.0	1.5	0.70	20.0	100.0	94.8	94.8
13	40.0	2.8	0.20	27.0	99.1	98.4	97.5
14	47.0	1.0	1.20	30.0	97.2	92.9	90.3
15	40.0	2.4	0.30	26.0	99.6	98.8	98.4
16	40.0	2.9	1.10	23.0	93.6	90.2	84.4
17	40.0	2.9	0.20	26.0	100.0	95.9	95.9
18	41.0	2.1	0.40	27.0	100.0	96.8	96.8
19	40.0	1.9	0.70	27.0	100.0	97.0	97.0
20	40.0	1.2	0.20	26.0	100.0	95.3	95.3

Reaction conditions: initial concentration: 0.18 mol/L, solvent: tetrahydrofuran, catalyst: 5 wt% Pt/C, catalyst loading: 0.8 g.

Table S9 The proposed Bayesian based optimization route for the hydrogenation of 5-nitroisoquinoline

	Experiment number	Temperature /°C	Hydrogen pressure /MPa	Liquid flow rate /mL/min	Gas flow rate /mL/min	Conversion /%	Selectivity /%	Yield of 5-aminoisoquinoline /%
Initial simplex	1	60.0	2.0	0.60	20.0	100.0	97.6	97.6
	2	70.0	2.0	0.60	20.0	100.0	95.2	95.2
	3	60.0	2.4	0.60	20.0	100.0	98.4	98.4
	4	60.0	2.0	0.80	20.0	100.0	98.2	98.2
	5	60.0	2.0	0.60	25.0	100.0	98.5	98.5
Local optimization	6	50.0	2.2	0.70	22.5	100.0	99.4	99.4
	7	40.0	2.3	0.75	23.8	99.5	99.5	99.0
	8	55.0	2.3	0.75	23.8	100.0	99.5	99.5
	9	52.5	2.5	0.83	25.7	100.0	99.5	99.5
	10	52.5	2.5	0.53	25.7	100.0	98.2	98.2
	11	54.4	2.4	0.60	24.3	100.0	98.4	98.4
Global optimization	12	40.0	1.8	0.42	15.2	99.7	99.2	98.9
	13	40.0	2.8	1.04	29.9	99.2	98.4	97.6
	14	40.2	1.3	0.57	15.4	100.0	99.4	99.4
	15	43.2	2.7	1.17	15.1	100.0	99.3	99.3

Reaction conditions: initial concentration: 0.18 mol/L, solvent: tetrahydrofuran, catalyst: 5 wt% Pt/C, catalyst loading: 0.8 g.