Electronic Supplementary Material (ESI) for Chemical Science.

Supplementary Information

An Integrated Mass Spectrometry Platform Enables Picomole-Scale Real-time Electrosynthetic Reaction Screening and Discovery

Qiongqiong Wan, Suming Chen & Abraham K. Badu-Tawiah*

Department of Chemistry and Biochemistry, The Ohio State University, Columbus, OH 43210, United States.
Correspondence should be addressed to A.B-T. (badu-tawiah.1@osu.edu).

Material and apparatus

N,N-Dimethylaniline (DMA), aniline, *β*-carboline, 1,2,3,4-tetrahydroisoquinoline, 4-iodoanisole, copper (I) iodide, potassium phosphate tribasic, isopropyl alcohol, ethylene glycol, 8-methyl-1,2,3,4-tetrahydroquinoline, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), tetraethylammonium perchloride, acetonitrile-d_3 (CD_3CN), methanol-d_4 (CD_3OD), deuterium oxide (D_2O) and HPLC grade acetonitrile (CH_3CN) were purchased from Sigma-Aldrich.

A Velos Pro ion trap mass spectrometer (Thermo Scientific, San Jose, CA, USA) was used for studying the electrochemical reactions, operated in the full mass spectrum mode. High resolution electrospray ionization mass spectra (HR-ESI-MS) were recorded on LTQ Orbitrap mass spectrometer (FINNIGAN LTQ, Thermo Scientific, San Jose, CA, USA). The Xcalibur software (Thermo Scientific, version 2.2) was used for control of the MS system and data acquisition. The temperature of the MS inlet capillary was 150 °C. The nano-electrospray ionization (nESI) capillaries were pulled from borosilicate glass capillaries with filament (Sutter Instrument, USA) using a micropipette puller (Model P-97, Sutter Instrument Co., Novato. CA, USA). For the nESI MS experiment, the distance between the tip of capillary and MS inlet was ~ 8 mm, full MS mass range: 50-1000 Da; maximum ion injection time: 100 ms, microscan time: 3 μs. All the experiments were conducted in positive ion mode. Bulk electrochemical reactions were proceeded with BK Precision 1666 Direct Current (DC) Regulated Power Supply (40V, 5A, Tequipment, NG, USA) with two platinum electrodes (dimeter 0.7 mm). X-ray photoelectron spectroscopy (XPS) of the platinum electrodes surface were analyzed on a Kratos Axis Ultra spectrometer (Kratos analytical, UK). ^{1}H NMR and ^{13}C NMR (using carbon proton decoupling method) were measured on a Bruker DMX-400 spectrometer.

Methods

X-ray Photoelectron Spectroscopy (XPS)

The Pt surface was characterized by an XPS measurements carried out with a Kratos Axis Ultra spectrometer, using focused monochromatized Al Kα radiation (*hv* = 1486.6 eV). The analyzed area of the samples was set to 110 μm of X-ray spot size. Peaks were recorded with a constant pass energy of 80 eV for survey (Figure S1a) and 20 eV for Pt_{4f} (Figure S1b). The pressure in the analysis chamber was ~5×10^{-8} Pa. The binding energy scale was calibrated from hydrocarbon contamination using the C1s peak at 285.0 eV. Pt electrode sample was prepared by spraying acetonitrile from the n-ESI method for 100 h using voltage of 2 kV. A new Pt wire was used as control. For XPS measurement of each electrode sample, several XPS analyses were performed at different positions to make the results statistically reliable.

Real-time electrochemical reaction screening

For electrochemical reaction screening, CH_3CN solutions (1-10 μL) containing reagents (10 μM) were transferred into the nESI emitter, which were equivalent to quantities of 10-100 pmol reagents in the test. Furthermore, we inferred that lower concentration of reagents (such as 1 μM) could also be selectively used in the screening platform because of the high sensitivity of mass spectrometers. Therefore, the new nESI combining real time electrosynthetic screening platform is effective in picomole-scale scope. Pt wire (0.2 mm) was used as electrode for application of DC potential throughout the screening process with a spray voltage of 2 kV.

The progress of the electrooxidative reactions of *N,N*-dimethylaniline, aniline, *β*-carboline, 1,2,3,4-tetrahydroisoquinoline, 8-methyl-1,2,3,4-tetrahydroquinoline and 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline were monitored on the electrochemical reaction screening platform. Reactions were thoroughly studied by continuously spraying the sample solution (10 μM reagents in CH_3CN at 25 ^{o}C under air) within 5 min. For example, 0 min and 1.5 min in Figure 1e (in the text) represent MS spectra recorded after continuously

spraying the sample, and the corresponding spectra were selected and zoomed in between the time of 0.00-0.03 min and 1.50-1.53 min, respectively.

The progress of the TEMPO-mediated electrooxidative dehydrogenation reaction were studied on the electrochemical reaction screening platform. Reactions were thoroughly studied through continuous application of 2 kV spray voltage to the sample solution (10 μM reagent and 1 μM TEMPO in CH_3CN) for 5 min.

Undivided electrolytic cell for bulk synthesis

General note: The power supply device used in this work was a precision 40V/5A Switching Direct Current (D.C.) power supply. The output plug was connected to the positive and negative output wires. These wires were connected directly to the reaction anode and cathode (alligator clips soldered onto the ends of the wires to facilitate connection to the reaction electrodes). Note that the positive terminal of the power supply is connected to the reaction anode and the negative terminal of the power supply is connected to the reaction cathode.

General procedure of electrolysis. An undivided electrolytic cell was assembled from a tube (5 mL) and two platinum electrodes (diameter: 0.7 mm). Current (2 V, 40 mA) was passed through a solution of the *N*-heterocycles (100 μM) in CH_3CN-H_2O (7:3, 1.5 mL), and the reaction solution was gently stirred at room temperature. The progress of the reaction was studied by extracting samples (100 μM, 10 μL) in a selected time period. Samples were diluted with CH_3CN to 10 μM, and then detected with sonic spray mass spectrometry (voltage: 0 kV) driven by nitrogen gas (100 psi) and syringe pump (velocity: 5 μL/min).

General procedure of TEMPO catalyzed electrolysis. An undivided electrolytic cell was assembled from a tube (5 mL) and two platinum electrodes (diameter: 0.7 mm). Current (2 V, 40 mA) was passed through a solution of the *N*-heterocycles (100 μM) and TEMPO (10 μM) in CH_3CN-H_2O (7:3, 1.5 mL), and the reaction solution was gently stirred at room temperature. The progress of the reaction was studied by extracting samples (100 μM, 10 μL) in a selected period of time. Samples were diluted with CH_3CN to 10 μM, and then detected with sonic spray mass spectrometry (voltage: 0 kV) driven by nitrogen gas (100 psi) and syringe pump (velocity: 5 μL/min).

Preparation of 8,8'-dimethyl-3,4-dihydro-2H-1,6'-biquinoline

An undivided electrolytic cell was assembled from a glass vial (25 mL) and two platinum electrodes (diameter: 0.7 mm). Current (2 V, 40 mA) was passed through a solution of 8-methyl-1,2,3,4-tetrahydroquinoline (100 mg, 0.68 mmol) in CH_3CN-H_2O (7:3, 6 mL), and the reaction solution was gently stirred at room temperature for 24 h until starting material was mostly consumed. The reaction was concentrated and chromatographed on silica gel (dichloromethane / mehanol = 50:1) to afford product 8,8'-dimethyl-3,4-dihydro-2H-1,6'-biquinoline **16** as yellow oil (35 mg, 36% yield). HR-ESI-MS (*m/z*): $[M+H]^+$ calculated for $C_{20}H_{21}N_2^+$, 289.1705; measured, 289.1700.

Preparation of 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline

Copper (I) iodide (38 mg, 0.2 mmol) and potassium phosphate tribasic (531 mg, 2.5 mmol) were put into a Schlenk tube. The tube was evacuated and back filled with nitrogen. 2-Propanol (5.0 mL), ethylene glycol (0.5 mL), 1,2,3,4-tetrahydroisoquinoline (266 mg, 2.0 mmol) and *p*-iodoanisole (351 mg, 1.5 mmol) were added successively by micro-syringe at room temperature. The reaction mixture was heated at 90 °C and kept for 24 h and then allowed to cool to room temperature. Dichloromethane (20 mL) and water (20 mL) were then added to the reaction mixture. The organic layer was extracted by dichloromethane (2 × 20 mL). The combined organic phases were washed with brine and dried over sodium sulfate. The solvent was removed by rotary evaporation and purified by column chromatography on silica gel (hexane/ethyl acetate=20:1), give the desired product 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **19** 162 mg with 45 % isolated yields. HR-ESI-MS (*m/z*): $[M+H]^+$ calcd. for $C_{16}H_{18}NO^+$, 240.1388; found, 240.1384.

Preparation of 3,4-dihydroisoquinoline

An undivided electrolytic cell was assembled from a tube (5 mL) and two platinum electrodes (diameter: 0.7 mm). Current (2 V, 40 mA) was passed through a solution of tetrahydroisoquinoline (1.35 mg, 0.01 mmol) and TEMPO (0.16 mg, 0.001 mmol) in CD_3OD-H_2O (7:3, 800 μL), and the reaction solution was gently stirred at room temperature for 10 h. ^1H NMR showed that the starting material was completely transferred to the product 3,4-dihydroisoquinoline. HR-ESI-MS (*m/z*): $[M+H]^+$ calcd. for $C_9H_{10}N^+$, 132.0813; found, 132.0804.

Preparation of 2-(4-methoxyphenyl)-3, 4-dihydroisoquinolinium

An undivided electrolytic cell was assembled from a tube (5 mL) and two platinum electrodes (diameter: 0.7 mm). Current (2 V, 40 mA) was passed through a solution of 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (2 mg, 0.008 mmol) and TEMPO (0.12 mg, 0.8 μmol) in CH_3CN-H_2O (7:3, 800 μL), and the reaction solution was gently stirred at room temperature for 10 h. After the solvent was removed by dry nitrogen gas. ^1H NMR showed that the starting material was completely transferred to the product 2-(4-methoxyphenyl)-3, 4-dihydroisoquinolinium. HR-ESI-MS (*m/z*): $[M]^+$ calcd. for $C_{16}H_{16}NO^+$, 238.1226; found, 238.1226.

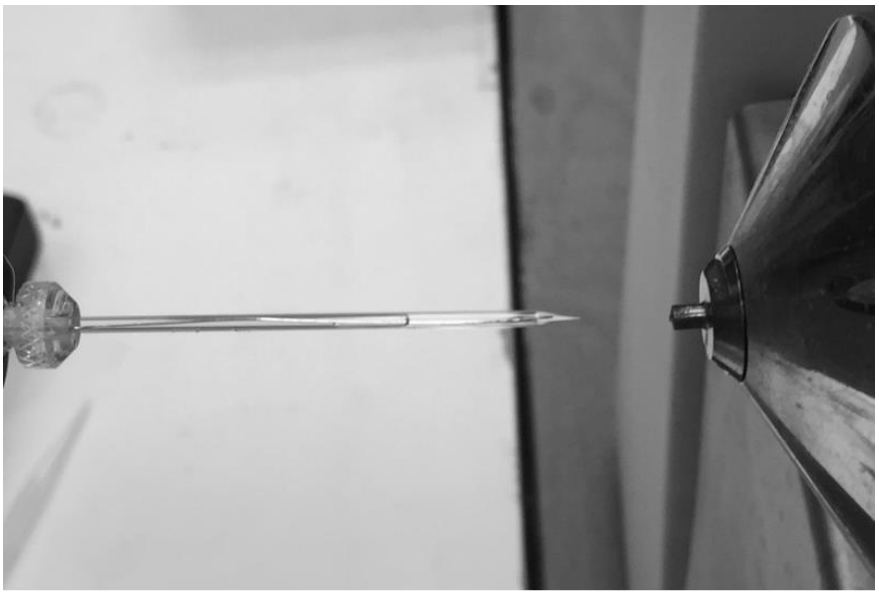

Figure S1. Experimental setup of the real time electrochemical reaction platform. The borosilicate glass capillary is used with O.D. = 1.5 mm and I.D. = 0.86 mm. The distance of Pt electrode away from the capillary tip is ~ 2 mm. 10 μL sample was transferred into the capillary, the distance of sample liquid level to the capillary tip is about 1.6 cm. The distance between the capillary tip and MS inlet was kept at 0.8 cm. The diameter of Pt electrode is 0.2 mm.

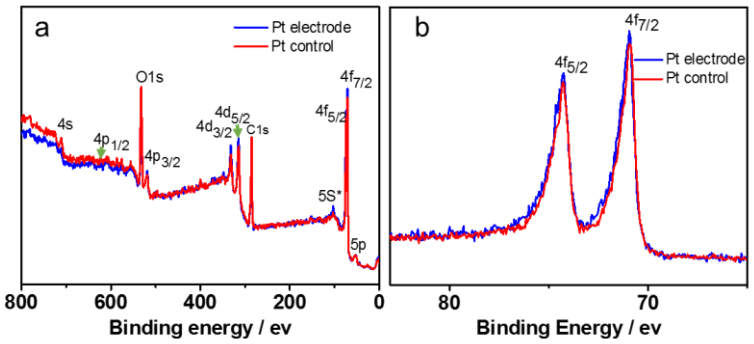

Figure S2. Comparison of the XPS spectrum for Pt electrode (using 100 h) and new Pt wire. **a**, Comparison of XPS survey spectra. The two spectra of used Pt electrode and new one match very well, the corresponding peak of Pt_{4s} (725 eV), $4p_{1/2}$ (609 eV), $4p_{3/2}$ (520 eV), $4d_{3/2}$ (332 eV), $4d_{5/2}$ (315 eV), 5S* (103 eV), $4f_{5/2}$ (74 eV), $4f_{7/2}$ (71 eV) and 5p (52 eV) are consistent with previous report. The spectra recorded at the pass energy of 80 eV. **b**, Comparison of Pt_{4f} spectra. The corresponding binding energies are $4f_{5/2}$ (74 eV) $4f_{7/2}$ (71 eV) for used platinum electrode and $4f_{5/2}$ (74 eV) $4f_{7/2}$ (71 eV) for new one. The spectra recorded at the pass energy of 20 eV.

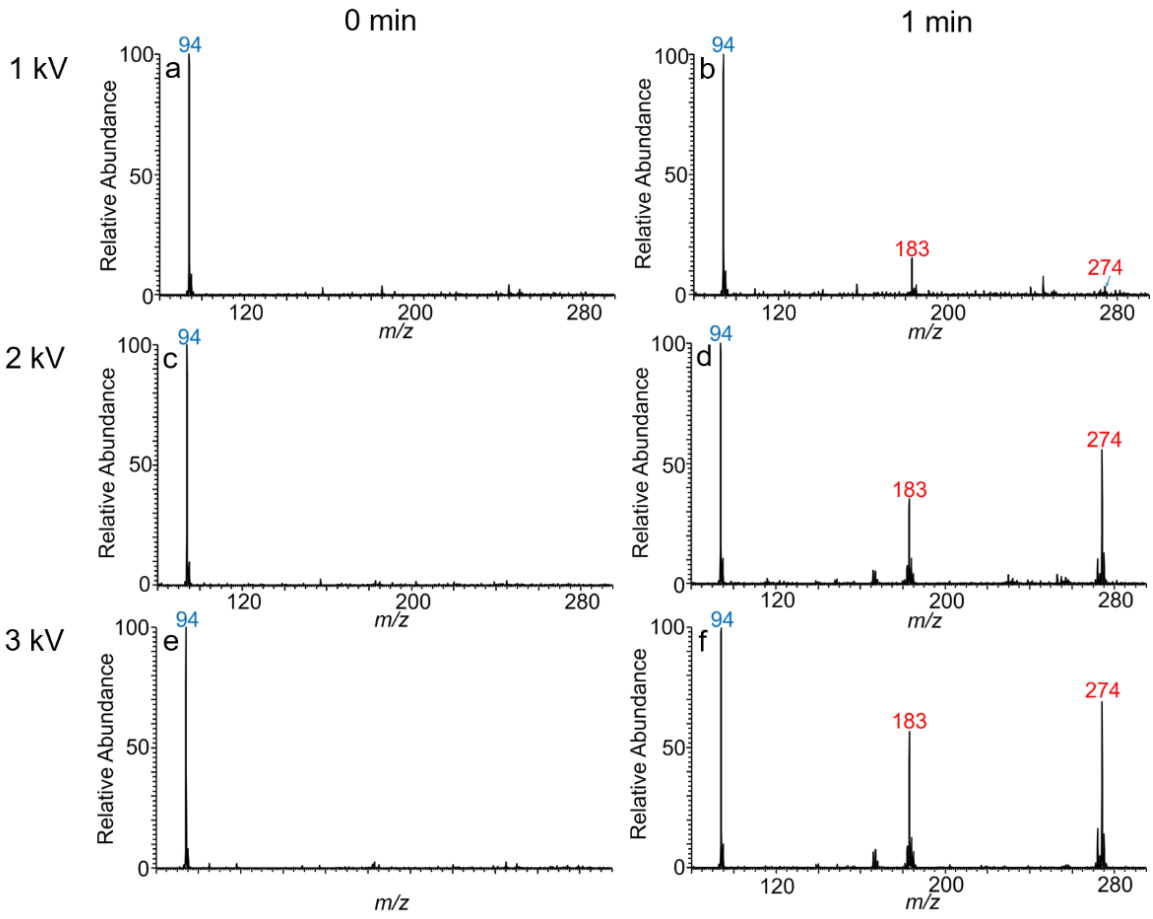

Figure S3. The impact of different voltages on the electrochemical reaction of aniline in nESI. The peaks of *m/z* 94, 183 and 274 on the mass spectra denote the aniline (*MW* 93 g/mol), dimeric intermediate (*MW* 182 g/mol) and trimeric product (*MW* 273 g/mol), respectively. Reactions were thoroughly studied by continuously spraying the aniline solution (10 μM reagents in CH_3CN) at direct current voltage of 1 kV, 2 kV and 3 kV. Mass spectra were recorded at 0 min (**a**, **c**, **e**) and 1 min (**b**, **d**, **f**), respectively. The distance of Pt electrode away from the capillary tip is 2 mm.

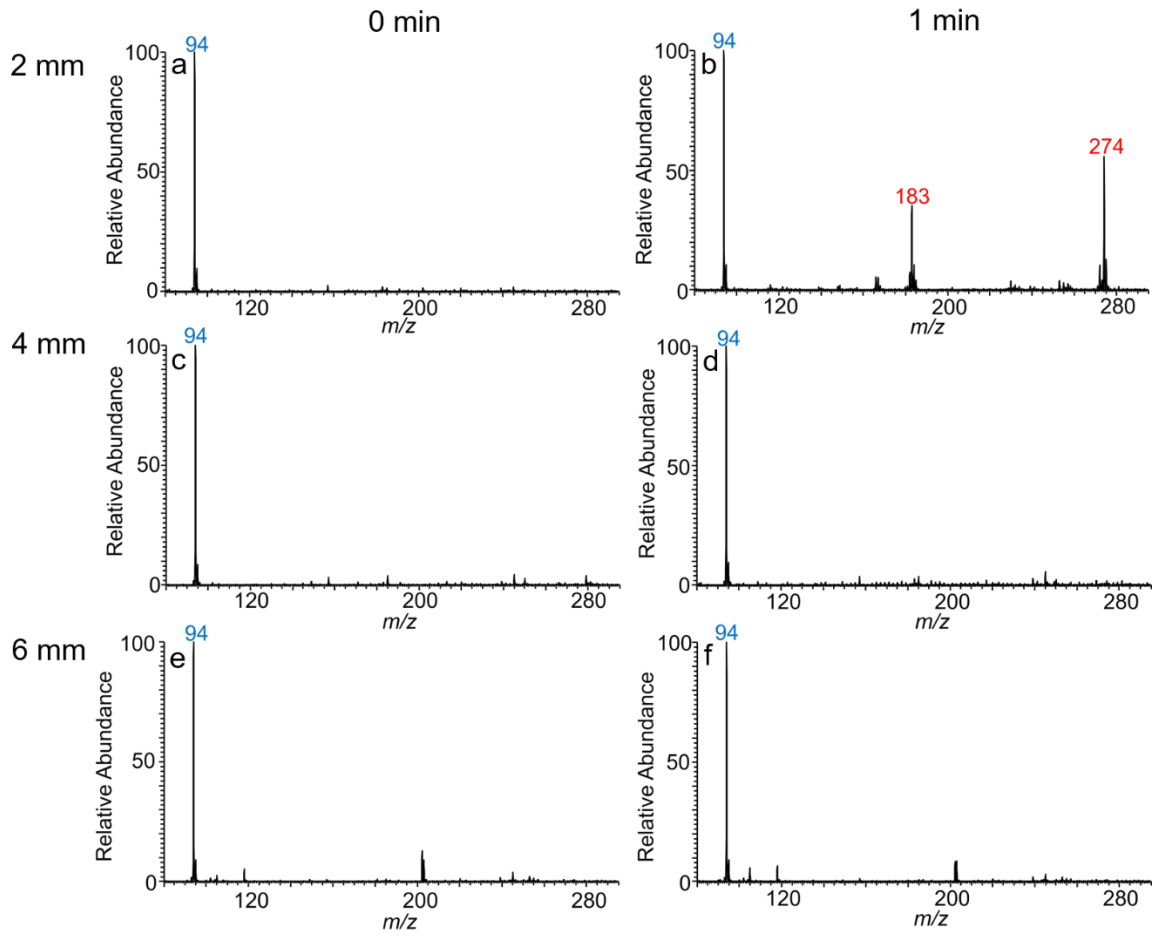

Figure S4. The impact of different electrode tip positions on the electrochemical reaction of aniline in nESI. The peaks of *m/z* 94, 183 and 274 on the mass spectra denote the aniline (*MW* 93 g/mol), dimeric intermediate (*MW* 182 g/mol) and trimeric product (*MW* 273 g/mol), respectively. Reactions were thoroughly studied by continuously spraying the aniline solution (10 μM reagents in CH_3CN) at different distances of electrode away from the capillary tip (2 mm, 4 mm and 6 mm). Mass spectra were recorded at 0 min (**a**, **c**, **e**) and 1 min (**b**, **d**, **f**), respectively. Direct current voltage is 2 kV.

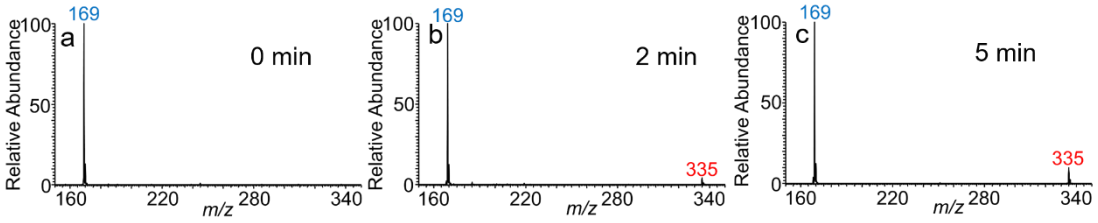

Figure S5. Use of the electrochemical reaction screening platform to monitor the progress of electrocatalytic oxidation of *β*-carboline (*MW* 168 g/mol) to the corresponding product (*MW* 334 g/mol). Reactions were thoroughly studied by continuously spraying the *β*-carboline (10 *μ*M) and tetraethylammonium perchloride (10 *μ*M) solution in CH_3CN. Mass spectra were recorded at 0 min (**a**), 2 min (**b**), and 5 min (**c**), respectively. The distance of Pt electrode away from the capillary tip is 2.0 mm. Direct current voltage is 2 kV.

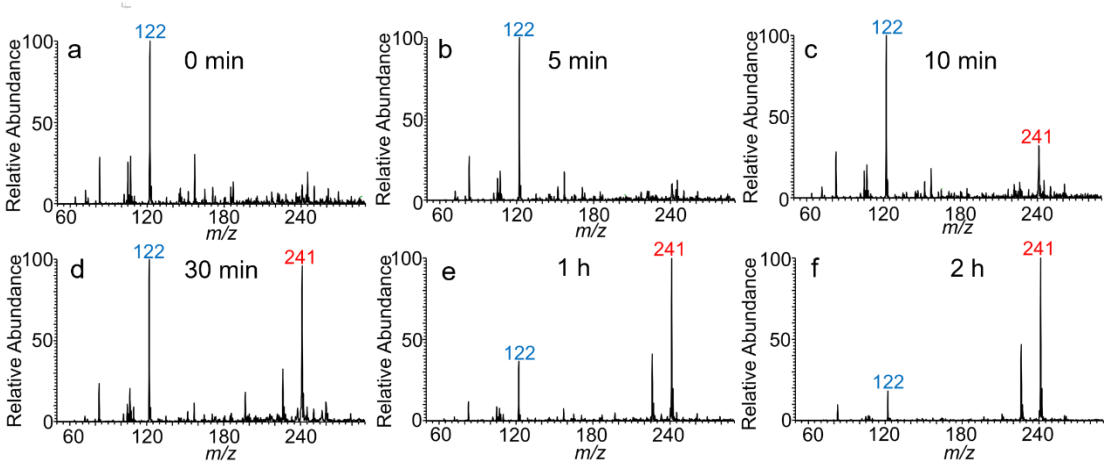

Figure S6. Use of the classical undivided electrolytic cell and mass spectrometry to monitor the progress of electrocatalytic oxidation of DMA (*MW* 121 g/mol) to *N,N,N',N'*-tetramethylbenzidine (TMB, *MW* 240 g/mol). Direct current 2 V was continuously applied to electrolyte (100 *μ*M) for 0 min (**a**), 5 min (**b**), 10 min (**c**), 30 min (**d**), 60 min (**e**) and 120 min (**f**), respectively.

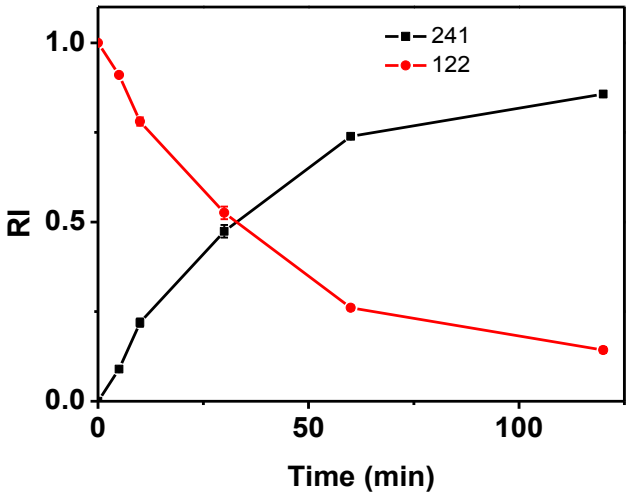

Figure S7. Calculated relative ion intensity (RI) of the reagent DMA (*MW* 121 g/mol) to TMB (*MW* 240 g/mol) with time in the classical undivided electrolytic cell (see Figure S6 for the detailed information). RI was measured as the intensity of a specific ion (reactant or product) relative to the sum of intensities of product, reactant and intermediates derived from this reactant.

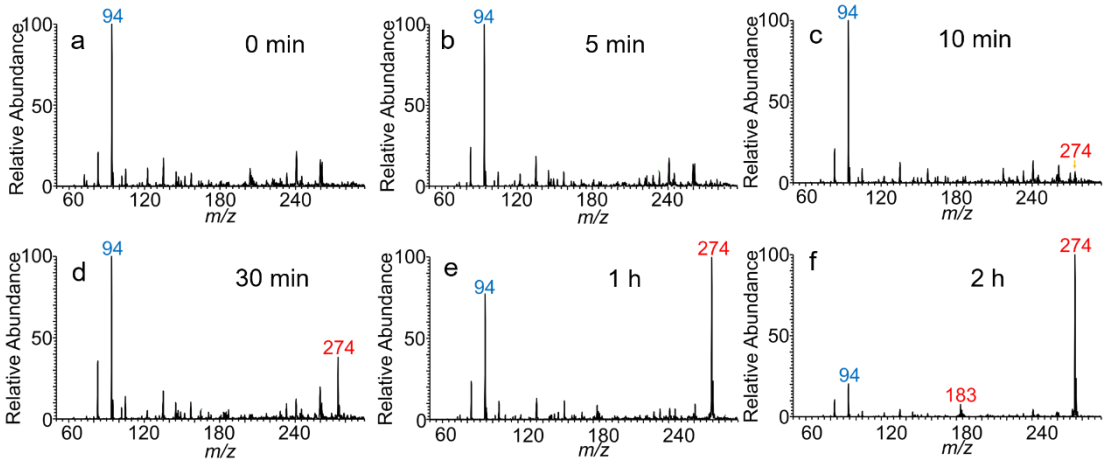

Figure S8. Use of the classical undivided electrolytic cell and mass spectrometry to monitor the progress of electrocatalytic oxidation of aniline (*MW* 93 g/mol) to dimeric intermediate **5** (*MW* 182 g/mol) and trimeric product **6** (*MW* 273 g/mol). Direct current 2 V was continuously applied to electrolyte (100 μM) for 0 min (**a**), 5 min (**b**), 10 min (**c**), 30 min (**d**), 60 min (**e**) and 120 min (**f**), respectively.

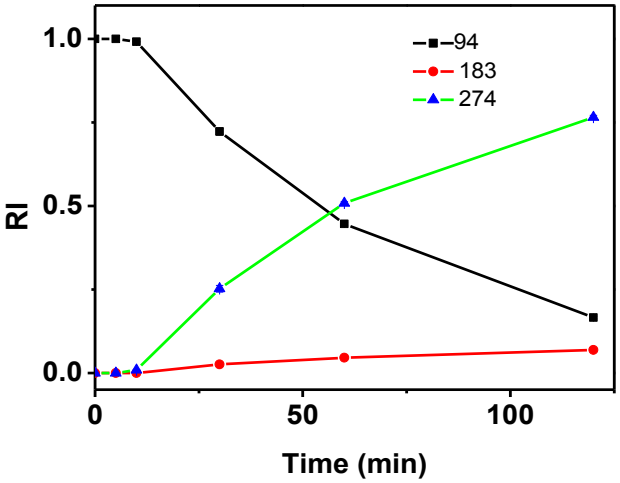

Figure S9. Calculated relative ion intensity (RI) of the reagent aniline (*MW* 93 g/mol) to dimeric intermediate **5** (*MW* 182 g/mol) and trimeric product **6** (*MW* 273 g/mol) with time in the classical undivided electrolytic cell (see Figure S8 for the detailed information).

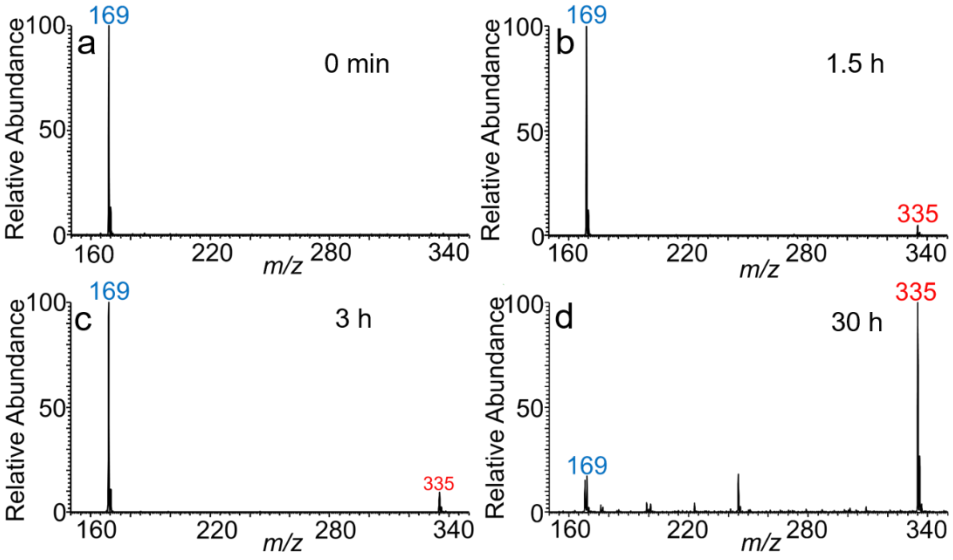

Figure S10. Use of the classical undivided electrolytic cell and mass spectrometry to monitor the progress of electrocatalytic oxidation of *β*-carbolines (*MW* 168 g/mol) to its product **8** (*MW* 334 g/mol). Direct current 2 V was continuously applied to *β*-carbolines (100 *μ*M) and tetraethylammonium perchloride (100 *μ*M) solution for 0 min (**a**), 1.5 h (**b**), 3 h (**c**) and 30 h (**d**), respectively.

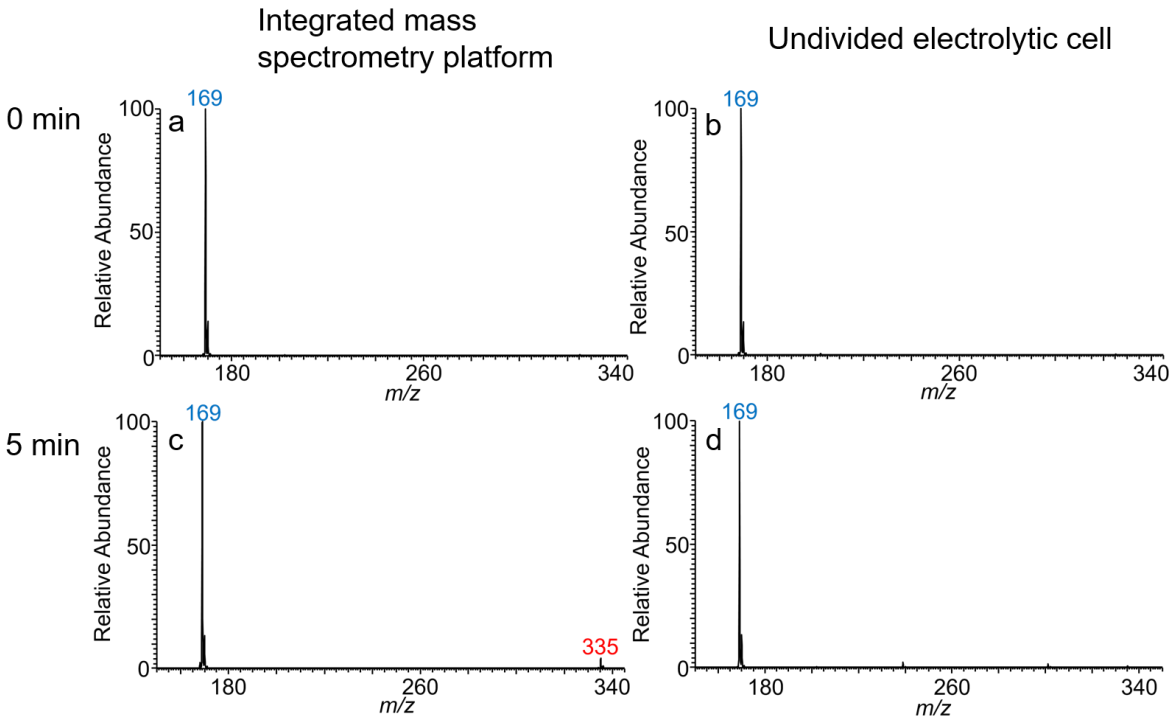

Figure S11. Comparison of the electrocatalytic oxidation of *β*-carbolines (100 *μ*M) between the integrated mass spectrometry platform and undivided electrolytic cell. The reaction was studied by continuous spraying the *β*-carbolines in tetraethylammonium perchloride solution (100 *μ*M) for 5 min on the integrated mass spectrometry platform, and mass spectra were recorded at 0 min (**a**) and 5 min (**c**). The reaction was also studied by continuous applying direct current (2 V) to the *β*-carbolines and tetraethylammonium perchloride solution by using undivided electrolyte cell for 0 min (**b**) and 5 min (**d**), respectively.

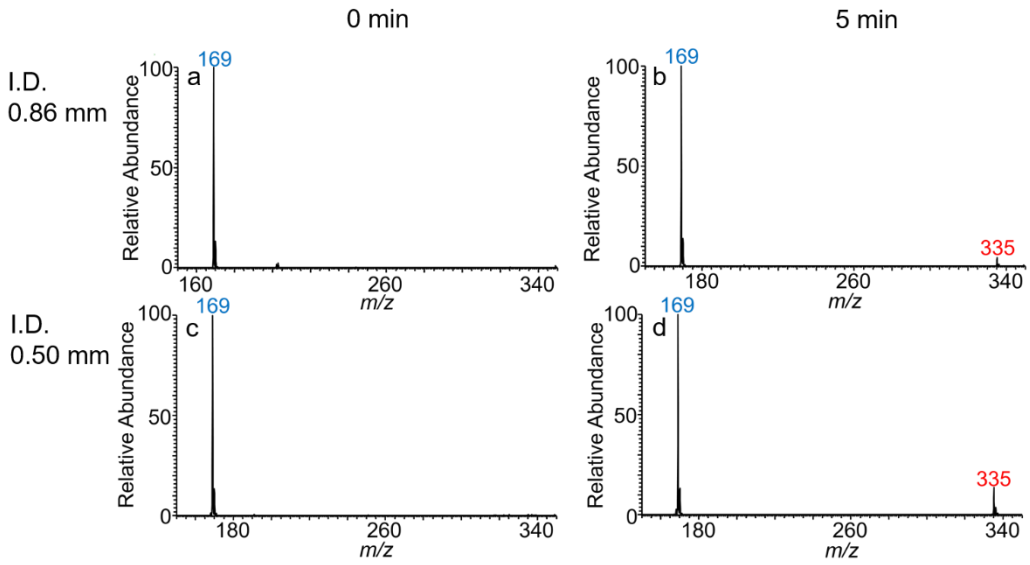

Figure S12. Comparison of the electrooxidation of *β*-carbolines (100 *μ*M) in different size of borosilicate glass capillary. The reaction was studied by continuous spraying the *β*-carbolines in tetraethylammonium perchloride (100 *μ*M) solution for 0 min (**a, c**) 5 min (**b, d**) on the integrated mass spectrometry platform. The O.D. and I.D. of borosilicate glass capillary for **a** and **b** are 1.5 mm and 0.86 mm, respectively. The O.D. and I.D. of borosilicate glass capillary for **c** and **d** are 1.0 mm and 0.50 mm, respectively. The distance of Pt electrode away from the capillary tip is ~ 2 mm. The length of the liquid in the capillary is about 1.6 cm. The diameter of Pt electrode is 0.2 mm.

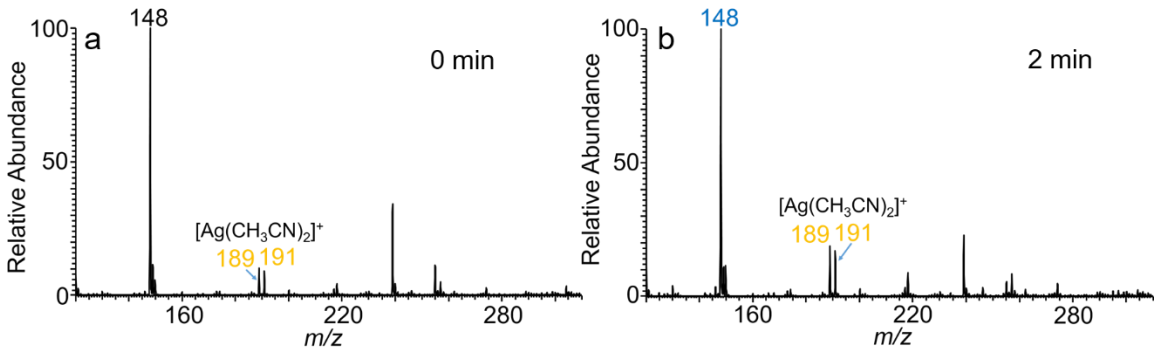

Figure S13. nESI MS spectra of 8-methyl-1,2,3,4-tetrahydroquinoline (**9)** at the times a) 0 min and b) 2 min. The peak at *m/z* 148 correspond to compounds **9** (*MW* 147 g/mol). The peaks at *m/z* 189 and *m/z* 191 are the characteristic isotopic peaks of $[Ag(CH_3CN)_2]^+$. The reaction was conducted with **9** (10 μM) in acetonitrile. Electrospray voltage is 2.0 kV with Ag anode (Outer diameter: 0.2 mm, the distance of Ag electrode away from the capillary tip is 2.0 mm).

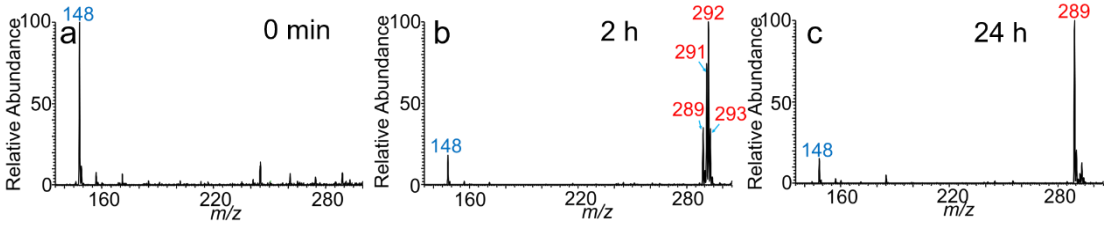

Figure S14. Use of the classical undivided electrolytic cell and mass spectrometry to monitor the progress of electrocatalytic oxidation of 8-methyl-1,2,3,4-tetrahydroquinoline (*MW* 147 g/mol) to the dimeric intermediates **12** (*MW* 293 g/mol), **13** (*MW* 292 g/mol), **14** and **15** (*MW* 290 g/mol) and final product **16** (*MW* 288 g/mol). Direct current 2 V was continuously applied to electrolyte (100 μM) for 0 min (**a**), 2 h (**b**) and 24 h (**c**), respectively.

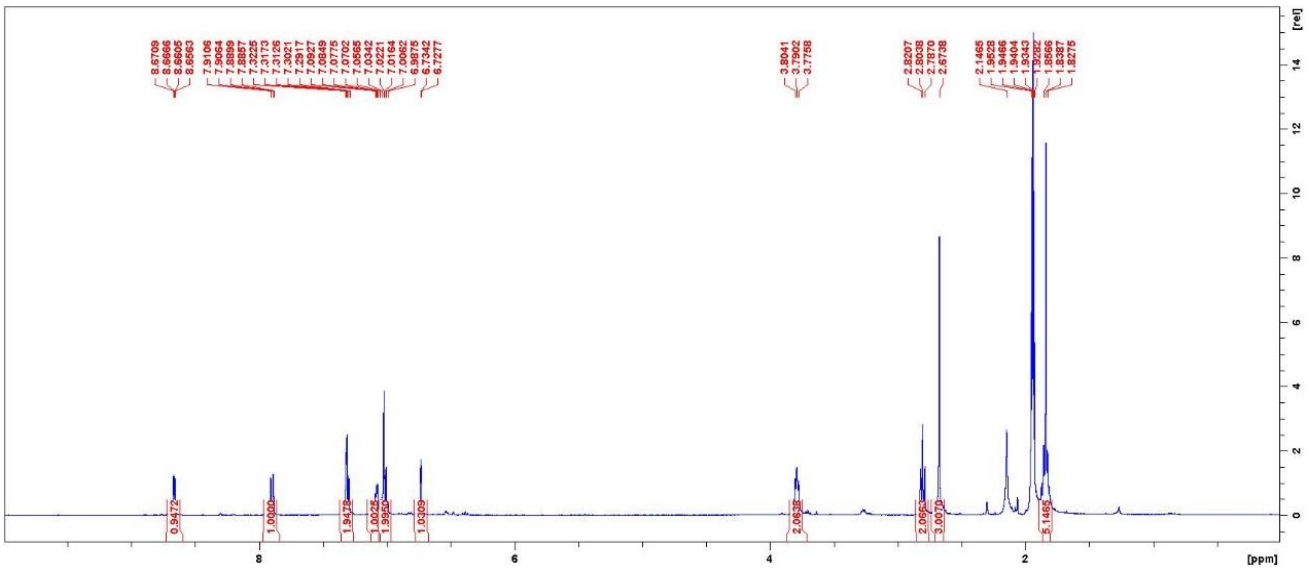

Figure S15. [1] H NMR of dimeric product **16** (CD_3CN, 400 M, 300.2 K): δ 8.67 (m, 1H), 7.91 (m, 1H), 7.32 (m, 2H), 7.09 (m, 1H), 7.01 (m, 2H), 6.73 (d, *J* = 2.6 Hz, 1H), 3.80 (t, *J* = 5.6 Hz, 2H), 2.82 (t, *J* = 6.8, 2H) 2.67 (s, 3H), 1.86 (m, 5H).

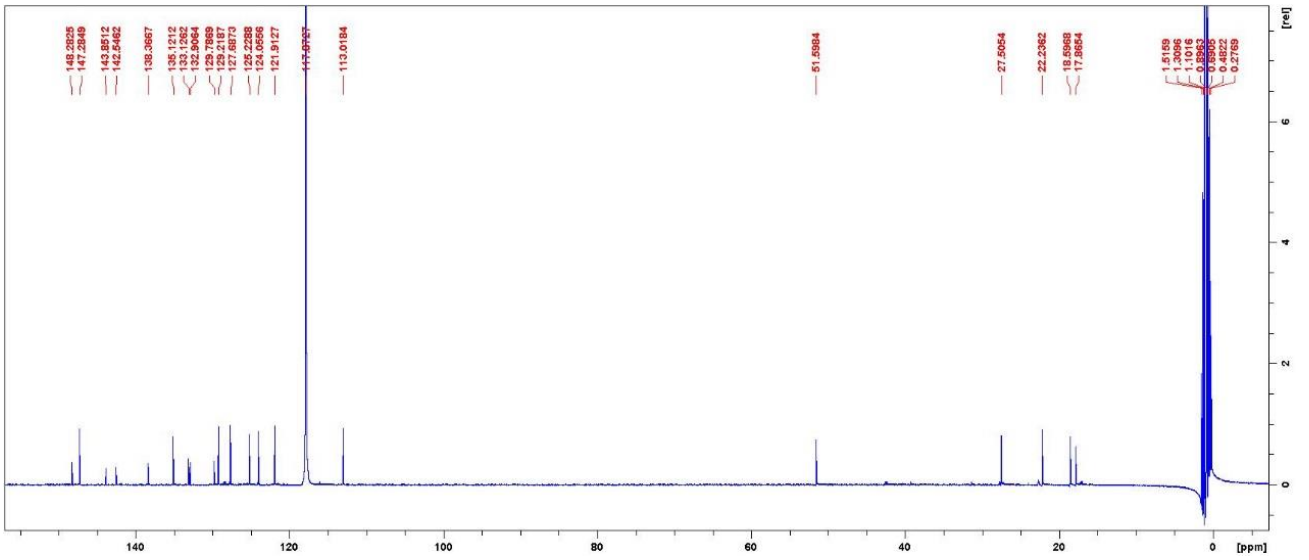

Figure S16. [13]C NMR of dimeric product **16** (CD_3CN, 400 M, 300.2 K): δ 148.3, 147.3, 143.8, 142.5, 138.4, 135.1, 133.1, 132.9, 129.8, 129.2, 127.7, 125.2, 124.1, 121.9, 113.0, 51.6, 27.5, 22.2, 18.6, 17.9.

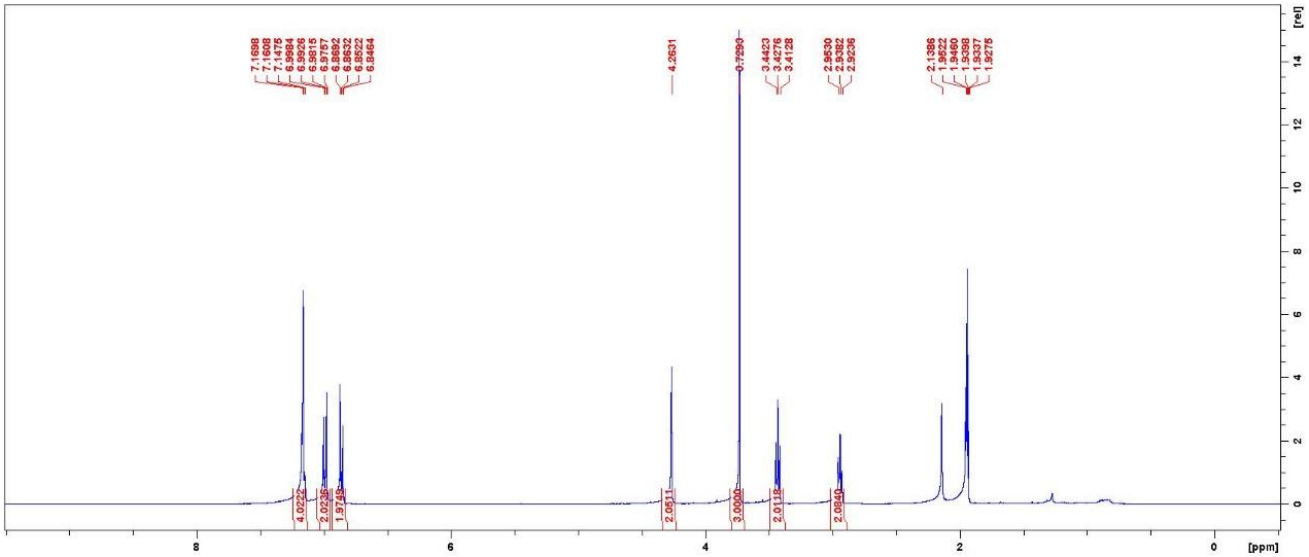

Figure S17. [1] H NMR of 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (CD_3CN, 400 M, 300.2 K): δ 7.17 (m, 4H), 7.00 (m, 2HH), 6.87 (m, 2H), 4.26 (s, 2H), 3.73 (s, 3H), 3.44 (t, *J* = 5.9 Hz, 2H), 2.95 (t, *J* = 5.9 Hz, 2H).

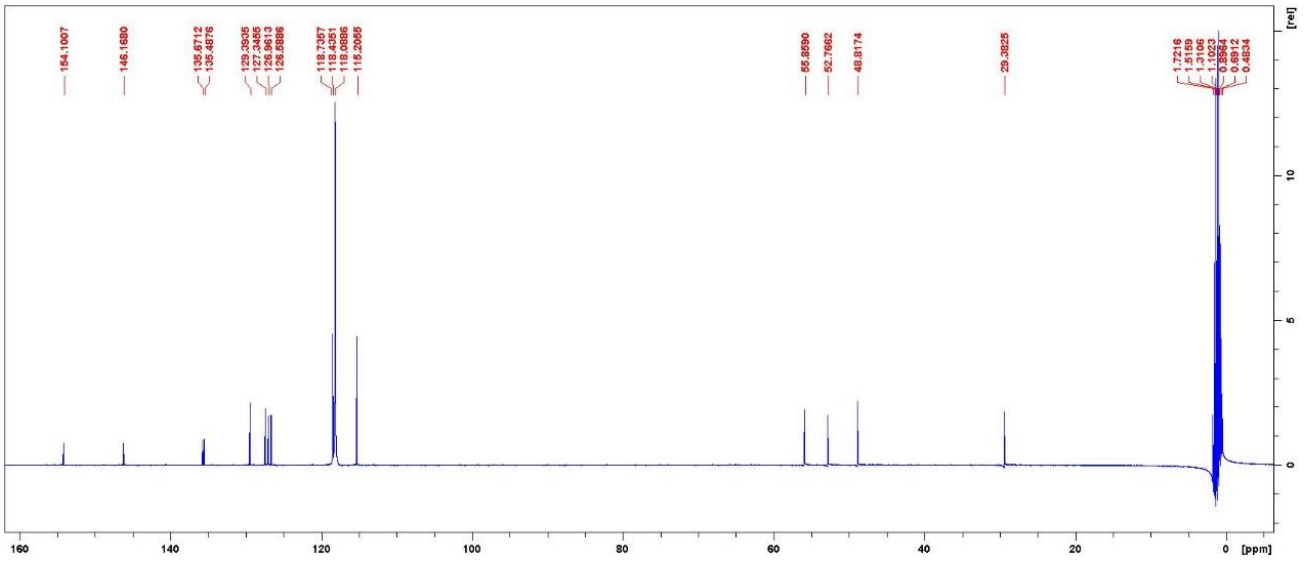

Figure S18. [13]C NMR of 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (CD_3CN, 400 M, 300.2 K): δ 154.1, 146.2, 135.7, 135.5, 129.4, 127.3, 127.0, 126.6, 118.7, 115.2, 55.9, 52.8, 48.8, 29.4.

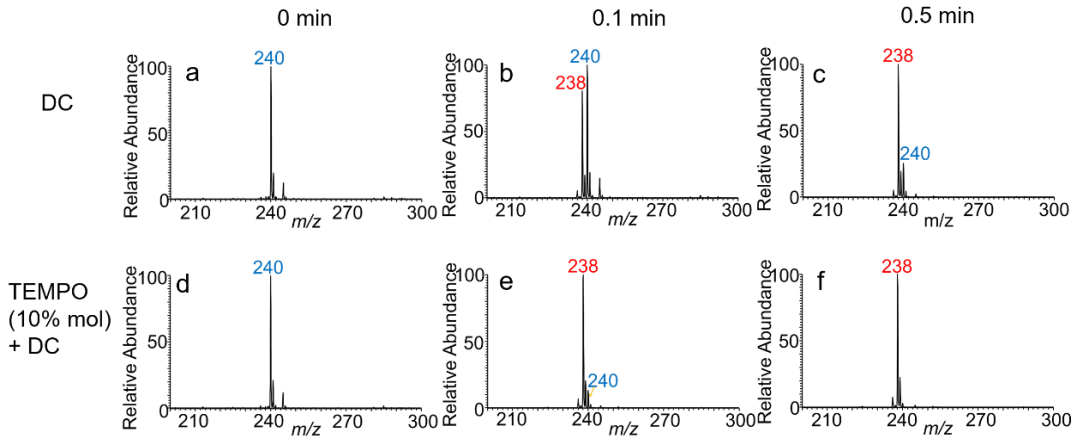

Figure S19. Use of the electrochemical reaction screening platform to monitor the progress of electrocatalytic oxidation of 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**19**, *MW* 239 g/mol) to corresponding product **20** (*MW* 238 g/mol) without (**a**, **b**, **c**) or with (**d**, **e**, **f**) TEMPO. Mass spectra were recorded at 0 min (**a, d**), 0.1 min (**b, e**) and 0.5 min (**c, f**), respectively.

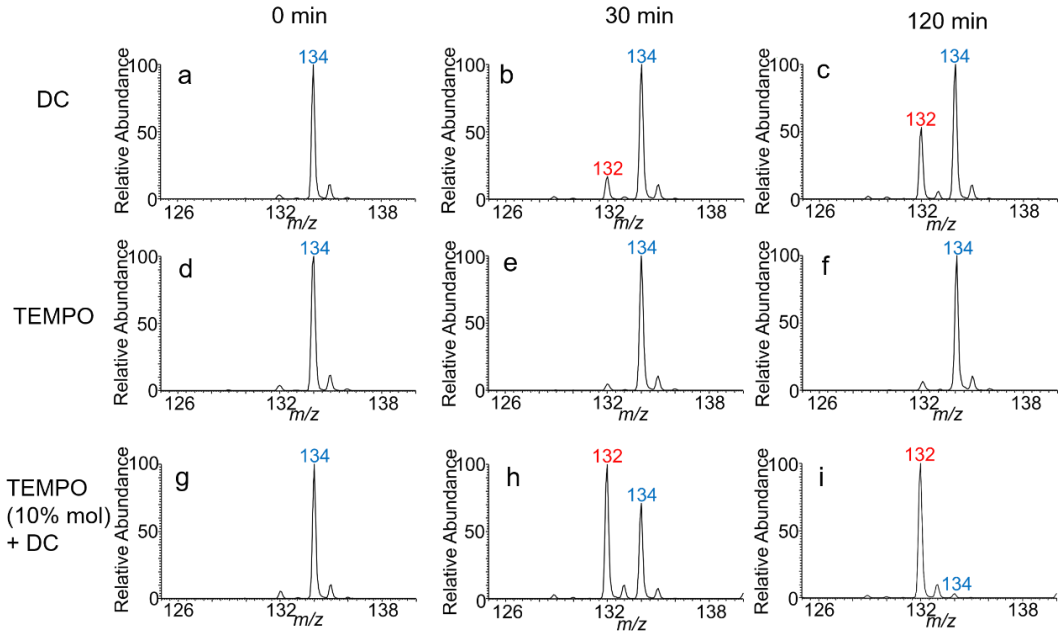

Figure S20. Electrooxidative dehydrogenation of 1,2,3,4-tetrahydroisoquinoline. The first row, direct current of 2 V was continuously acted on the solution of 1,2,3,4-tetrahydroquinoline (100 μM) in acetonitrile-water. The second row, the solution of 1,2,3,4-tetrahydroisoquinoline (100 μM) and TEMPO (10 μM) in acetonitrile-water without current. The third row, direct current of 2 V was continuously acted on the solution of 1,2,3,4-tetrahydroquinoline (100 μM) and TEMPO (10 μM) in acetonitrile-water. Mass spectra were recorded at reaction times of 0 min (**a, d, g**), 30 min (**b, e, h**) and 120 min (**c, f, g**), respectively.

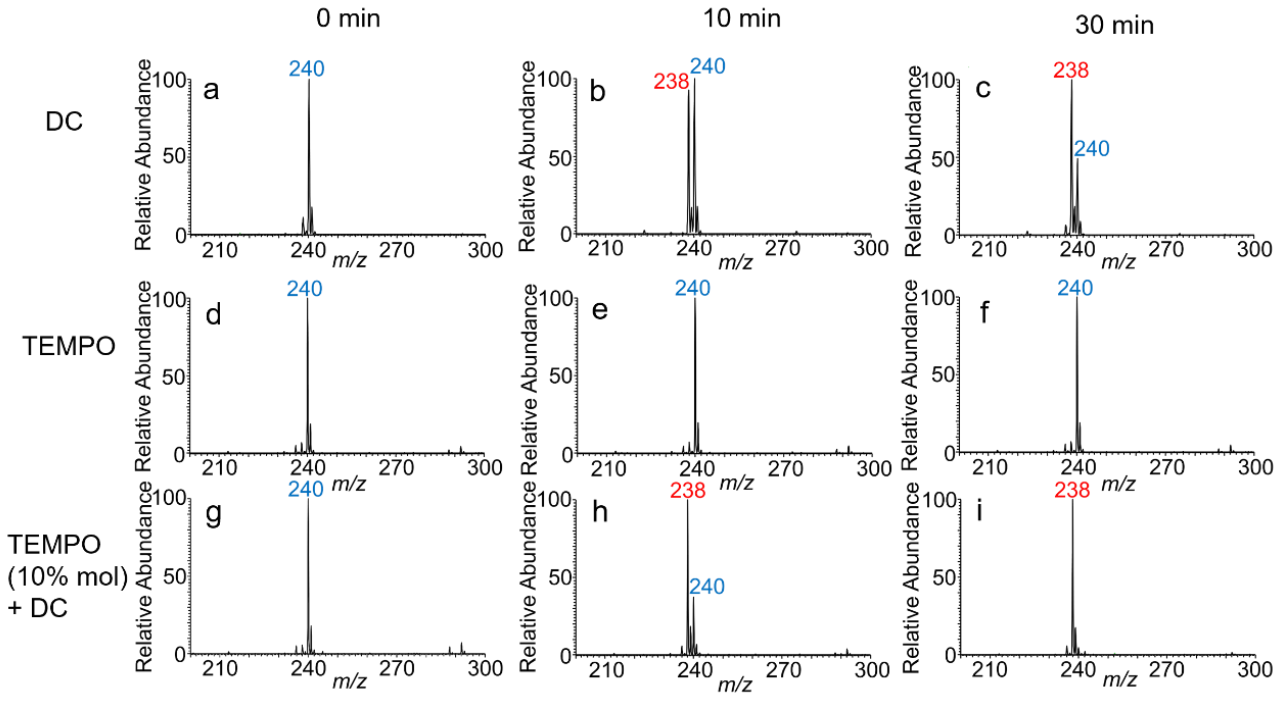

Figure S21. Electrooxidative dehydrogenation of 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline. The first row, direct current of 2 V was continuously acted on the solution of 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (100 μM) in acetonitrile-water. The second row, the solution of 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (100 μM) and TEMPO (10 μM) in acetonitrile-water without current. The third row, direct current of 2 V was continuously acted on the solution of 2-(4-methoxyphenyl)-1, 2, 3, 4-tetrahydroisoquinoline (100 μM) and TEMPO (10 μM) in acetonitrile-water. Mass spectra were recorded at reaction times of 0 min (**a, d, g**), 30 min (**b, e, h**) and 120 min (**c, f, g**), respectively.

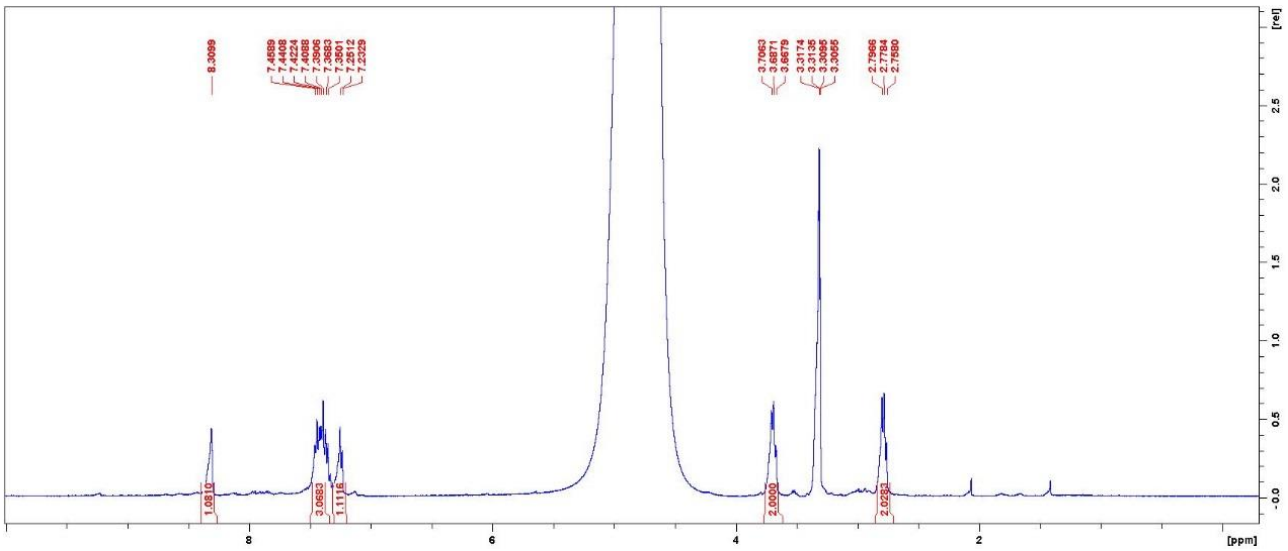

Figure S22. ^{1}H NMR of 3,4-dihydroisoquinoline (CD_3OD and D_2O, 400 M, 300.2 K): δ 8.31 (s, 1H), 7.46 (m, 3H), 7.25 (d, *J* = 7.3 Hz, 1H), 3.71 (t, *J* = 7.7 Hz, 2H), 2.80 (t, *J* = 7.3 Hz, 2H).

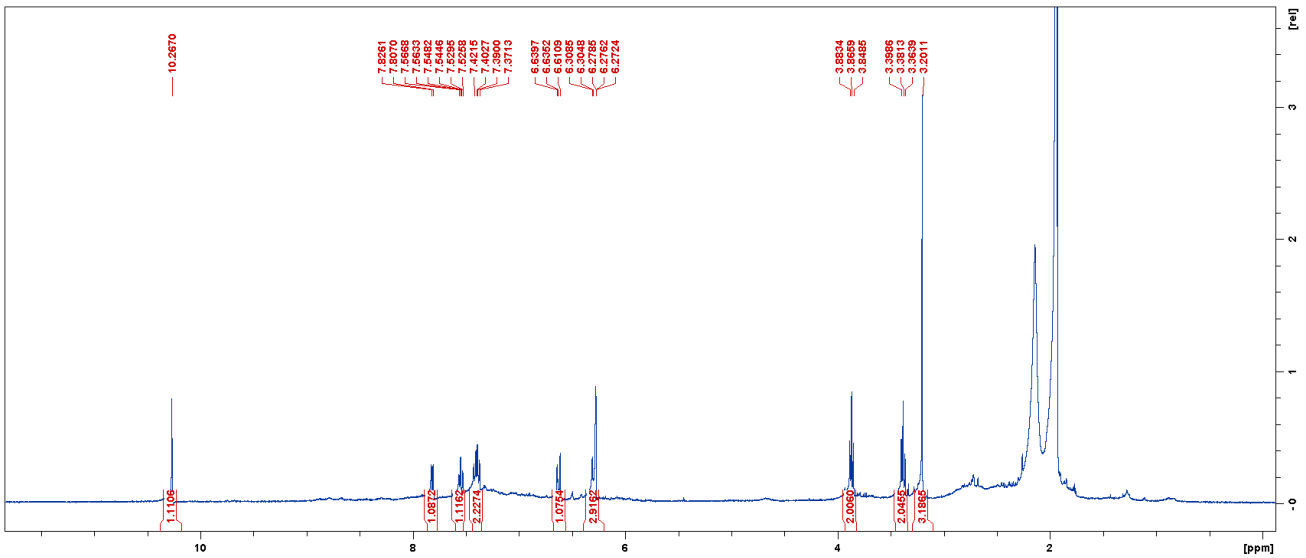

Figure S23. ^{1}H NMR of 2-(4-methoxyphenyl)-3,4-dihydroisoquinolinium (CD_3CN, 400 M, 300.2 K): δ 10.27 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.57 (m, 1H), 7.42 (m, 2H), 6.64 (m, 1H), 6.31 (m, 3H), 3.88 (t, *J* = 7.0 Hz, 2H), 3.40 (t, *J* = 6.9 Hz, 2H), 3.20 (s, 3H).

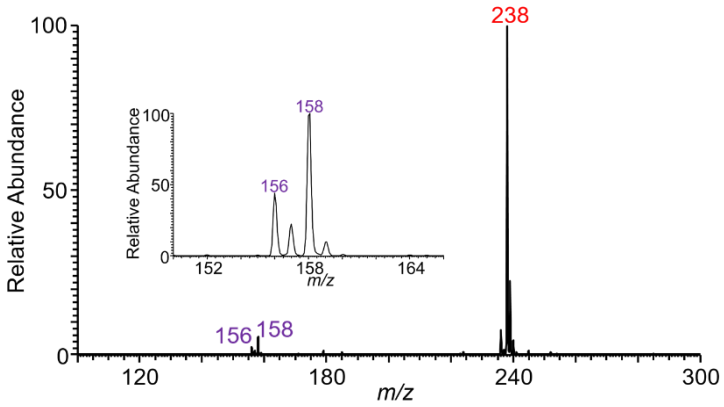

Figure S24. The nESI MS mass spectrum of the electrooxidation of 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (10 μM in ACN) with TEMPO (10 mol%) at 0.5 min. Inset is the enlarged mass spectrum in the range of *m/z* 150 to 166.