

Electronic Supplementary Information

**Ultrafast C–C and C–N Bond Formation Reactions in Water
Microdroplets Facilitated by the Spontaneous Generation of
Carbocations**

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Table of Contents

1. Experimental Section	3
1.1. Chemicals and Materials.	3
1.2. The emitter fabrication and characterization.....	3
1.3. Mass spectrometry.....	3
1.4 Offline collection and analysis of the sprayed reaction mixture.....	4
1.5 Gas chromatography-mass spectrometry (GC-MS)	4
2. Figures	5
Figure S1. A photograph of the experimental setup for the online microdroplet reaction....	5
Figure S2. Mass spectrum of the aqueous solution of 1a obtained without voltage.....	5
Figure S3. SEM images of bare emitters	6
Figure S4. Mass spectra obtained using bare emitters with different diameters	6
Figure S5. Mass spectra obtained using different reaction distances	7
Figure S6. Tandem mass spectra of products 2a , 2b , and 2c	8
Figure S7. Mass spectra obtained from aqueous solution of different pH.....	9
Figure S8. Tandem mass spectrum of 4a	10
Figure S9. Tandem mass spectrum of 4b	10
Figure S10. Mass spectrometric analysis of the spontaneous dehydrative C–N couplings in water microdroplets	11
Figure S11. Tandem mass spectra of products 6a , 6b , 8a and 8b	12
Figure S12. A photograph of the experimental setup for the offline collection of the sprayed microdroplets.....	13
Figure S13. GC-MS chromatogram for 1a and 3a/3b mixture solutions.....	14
Figure S14. GC-MS chromatogram for 1b and 3c/3d mixture solutions.....	15
Figure S15. GC-MS chromatogram for 1c and 3d/3c mixture solutions.....	16
Figure S16. ¹ H NMR spectra for 1a and 3a/3b mixture solutions.....	17
Figure S17. ¹ H NMR spectra for 1b and 3c/3d mixture solutions.....	18

Figure S18. ^1H NMR spectra for **1c** and **3d/3c** mixture solutions.....19

1. Experimental Section

1.1 Chemicals and reagents

4,4'-difluorobenzhydrol, 3-methylindole, Sodium chloride were purchased from Aladdin (Shanghai, China), diphenylmethanol and piperazine were purchased from Macklin (Shanghai, China), 4,4'-dimethoxybenzhydrol, 1,3,5-trimethoxybenzene and pyrazole were purchased from Bidepharm (Shanghai, China), HPLC grade acetonitrile (MeCN) was purchased from Perimed AB (Beijing, China), pure water was purchased from Wahaha Company (Jiangsu, China). All chemicals were used without further purification.

The compounds 4,4'-dimethoxybenzhydrol, diphenylmethanol, 4,4'-difluorobenzhydrol, 1,3,5-trimethoxybenzene, 3-methylindole, pyrazole, and piperazine were each dissolved in acetonitrile to prepare highly concentrated solutions of 100 mM. These solutions were subsequently diluted with water to achieve the necessary concentrations for ensuing experiments. Using **1a** as a case in point, we diluted 100 mM **1a** into 1 mL of water to obtain the experimental concentration of 100 μ M. This process results in an acetonitrile volume ratio of approximately 0.1%, a quantity so small that it is essentially negligible.

1.2 The emitter fabrication and characterization

A bare emitter about 5 cm was fabricated from a borosilicate capillary (BF100-58-10, Sutter Instrument) using a laser-based P-2000 (Sutter Instrument Co., Novato, CA, USA). See support information for typical parameters for fabricating four emitters with the opening of \sim 400, 800, 1200, and 2400 nm, respectively.

Typical parameters for fabricating a bare emitter with an opening of \sim 400 nm were:

- Line 1: HEAT=300, FIL=2, VEL=25, DEL=128, PUL=70;
- Line 2: HEAT=300, FIL=2, VEL=25, DEL=130, PUL=80;
- Line 3: HEAT=300, FIL=2, VEL=25, DEL=130, PUL=110.

Typical parameters for fabricating a bare emitter with an opening of \sim 800 nm were:

- Line 1: HEAT=288, FIL=2, VEL=25, DEL=128, PUL=65;
- Line 2: HEAT=288, FIL=2, VEL=25, DEL=130, PUL=80;
- Line 3: HEAT=288, FIL=2, VEL=25, DEL=130, PUL=110.

Typical parameters for fabricating a bare emitter with an opening of \sim 1200 nm were:

- Line 1: HEAT=275, FIL=2, VEL=25, DEL=128, PUL=60;
- Line 2: HEAT=275, FIL=2, VEL=25, DEL=130, PUL=75;
- Line 3: HEAT=275, FIL=2, VEL=25, DEL=130, PUL=110.

Typical parameters for fabricating a bare emitter with an opening of \sim 2400 nm were:

- Line 1: HEAT=266, FIL=2, VEL=25, DEL=128, PUL=50;
- Line 2: HEAT=266, FIL=2, VEL=25, DEL=130, PUL=70;
- Line 3: HEAT=266, FIL=2, VEL=25, DEL=130, PUL=95.

A scanning electron microscope (SEM, SM-7800F, JEOL Ltd., Japan) was used

for characterizing the hollow structure of the four emitters, with a thin layer of Au (~5 nm) sputtered (**Figure S3**).

1.3 Mass spectrometry

The Q-TOF mass spectrometer (6530B, Agilent Technologies, Inc., Santa Clara, U.S.A.) was operated in positive ion mode for all MS measurements. The emitter was placed in front of the MS inlet at a distance of ~15 mm. Except as noted, the instrument parameters were as follows: gas temp = 300 °C, drying gas = 1.5 L/min, nebulizer = 0 psi. For MS/MS settings, 5 to 15 eV collision energy was used, and the isolation window was 1.3 Da.

1.4 Offline collection and analysis of the sprayed reaction mixture

The offline collection of sprayed microdroplets was carried out using the experimental setup shown in **Figure S12**. A 10 mL mixed solution (10 mM diarylmethanol and 10 mM nucleophiles) in 2:1 water/acetonitrile (v/v) was aerosolized using a syringe pump through a fused silica capillary (50 μm i.d., 150 μm o.d.) that sits inside a larger coaxial capillary (200 μm i.d., 365 μm o.d.) through which high-pressure N_2 sheath gas with an 80 psi back pressure flows. The solution flow rate was maintained at 30 $\mu\text{L}/\text{min}$. The spray source was fitted to a two-neck round bottom flask. To reduce the product loss, one condenser (cooled by cold water circulation, 0 °C) was connected to the other neck of the flask. The inside bottom of the flask was grounded using conductive tape. A 10 mL solution was sprayed using a +5 kV spray potential (applied to the syringe needle). After 5.5 h, the offline collection of the sprayed reaction mixture was redissolved in 5 mL ethyl acetate, followed by aliquoting 1 mL for GC-MS analysis and the remaining volume for the 1H NMR study. The GC-MS analysis was directly performed with the crude reaction product collected in the ethyl acetate (1 mL). The NMR experiment was performed by evaporation and the addition of CDCl_3 to the remaining mixture.

1.5 Gas chromatography-mass spectrometry (GC-MS)

The GC-MS analysis was performed using a gas chromatograph (Agilent Technologies, Model 7890B) coupled with an ion trap mass spectrometer (Agilent Technologies, Model 5977B). Agilent J&W GC capillary column (30 m length, 0.25 mm i.d., 0.25 μm film thickness) was utilized. Helium was used as a carrier gas (99.99% purity) and maintained at a constant flow rate of 1.6 mL/min. The GC column temperature program was as follows: initial temperature of 50 °C for 1 min, then 50 to 280 °C at 20 °C/min temperature ramp, and finally kept at 280 C for 7.5 min. The MS conditions were as follows: electron ionization (EI) mode at ionization energy of 70 eV, emission current of 250 μA , ion source, and transfer line temperature were maintained at 230 and 250 °C, respectively.

2. Figures

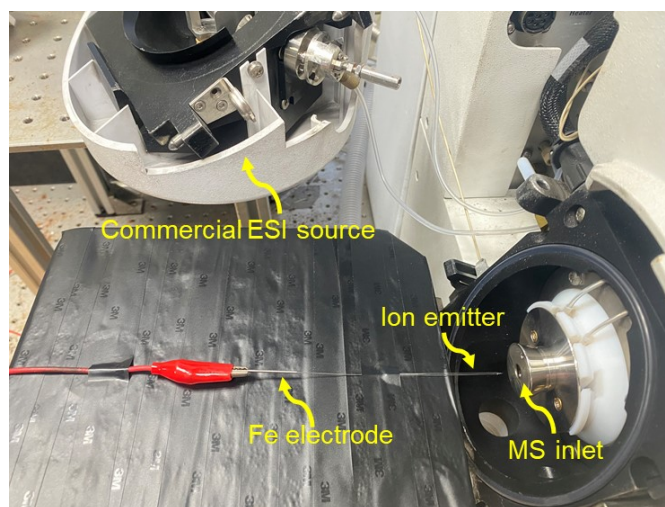


Figure S1. A photograph of the experimental setup for the online MS monitoring of the microdroplet reactions. Note the commercial ESI source was removed to enable the use of our nESI source.

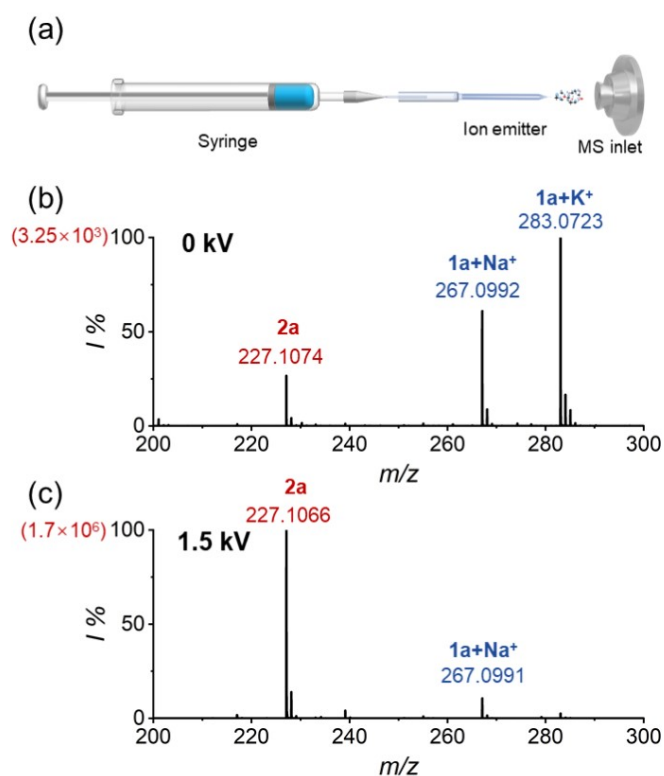


Figure S2. (a) A schematic illustration of the experimental setup for online reaction without voltage; Mass spectrum of the aqueous solution of 4,4'-dimethoxybenzhydrol (**1a**, 100 μM) at (b) 0 kV potential and (c) 1.5 kV potential. The spray source was operated with a 50 $\mu\text{L}/\text{min}$ solution flow rate.

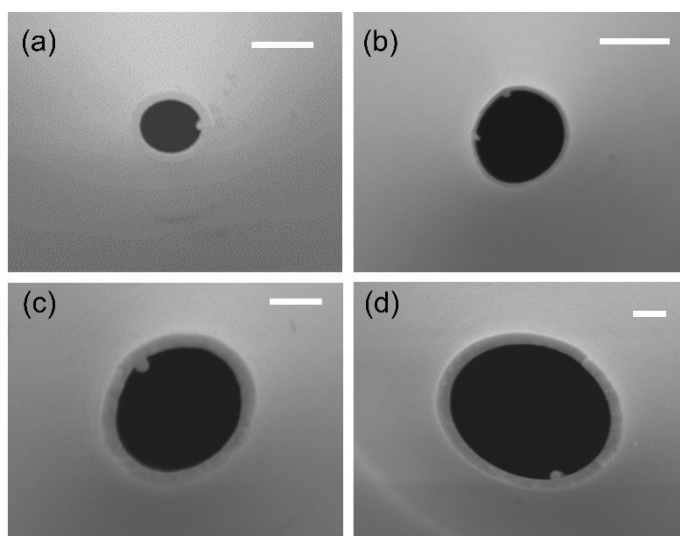


Figure S3. SEM images of bare emitters with the inner diameter of (a) 400 nm, (b) 800 nm, (c) 1200 nm, and (d) 2400 nm. Scale bar: 500 nm

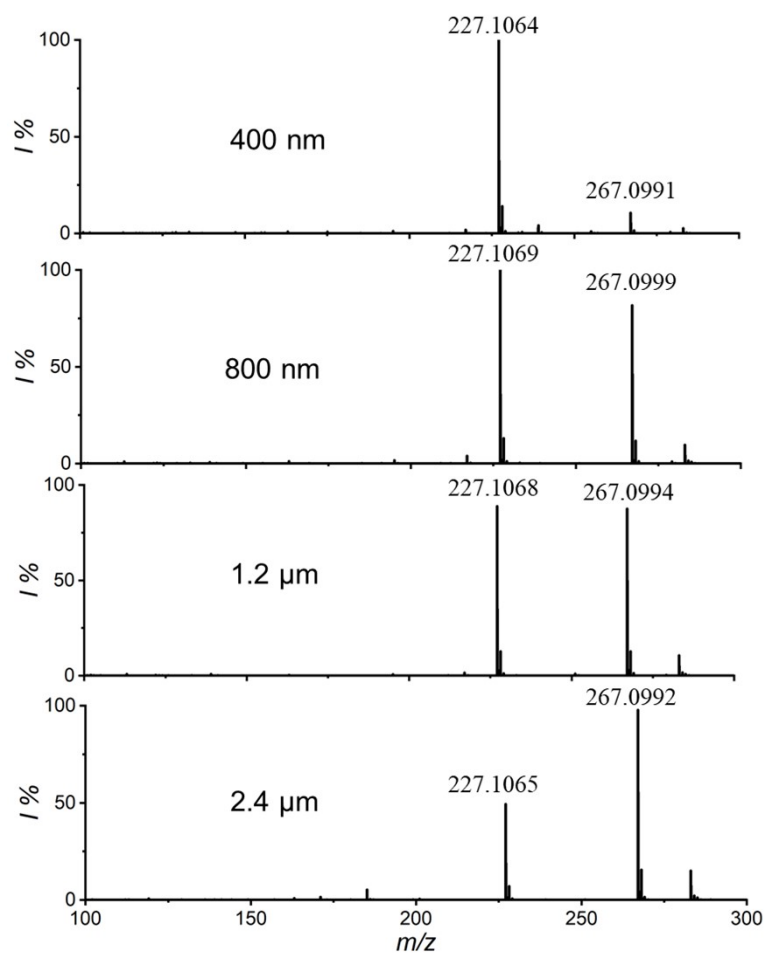


Figure S4. Mass spectrum showing the conversion was decreased when increasing the inner diameter of the injector from 400 mm to 2400 mm. The spray distance was kept at 15 mm.

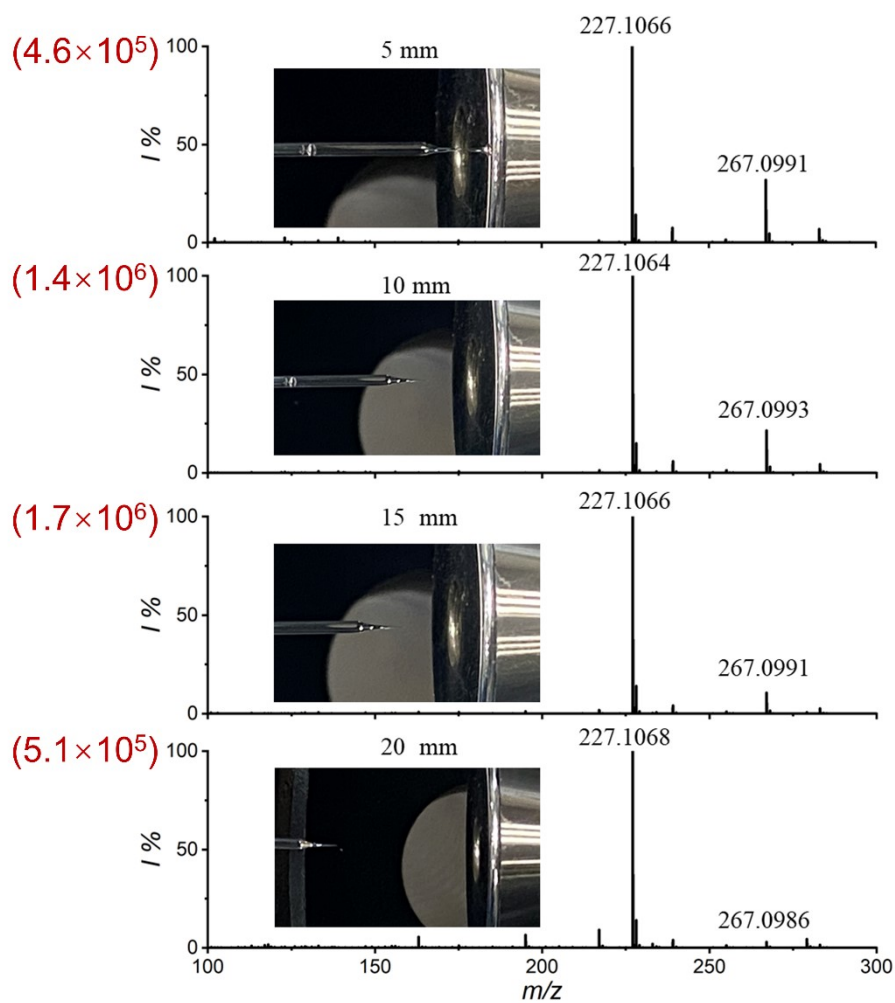


Figure S5. Mass spectrum showing the conversion was increased when increasing spray distance from 5 mm to 20 mm. The spray distance of 15mm was chosen as the experimental condition to maximize the cation signal. The inner diameter of the emitter was ~ 400 nm.

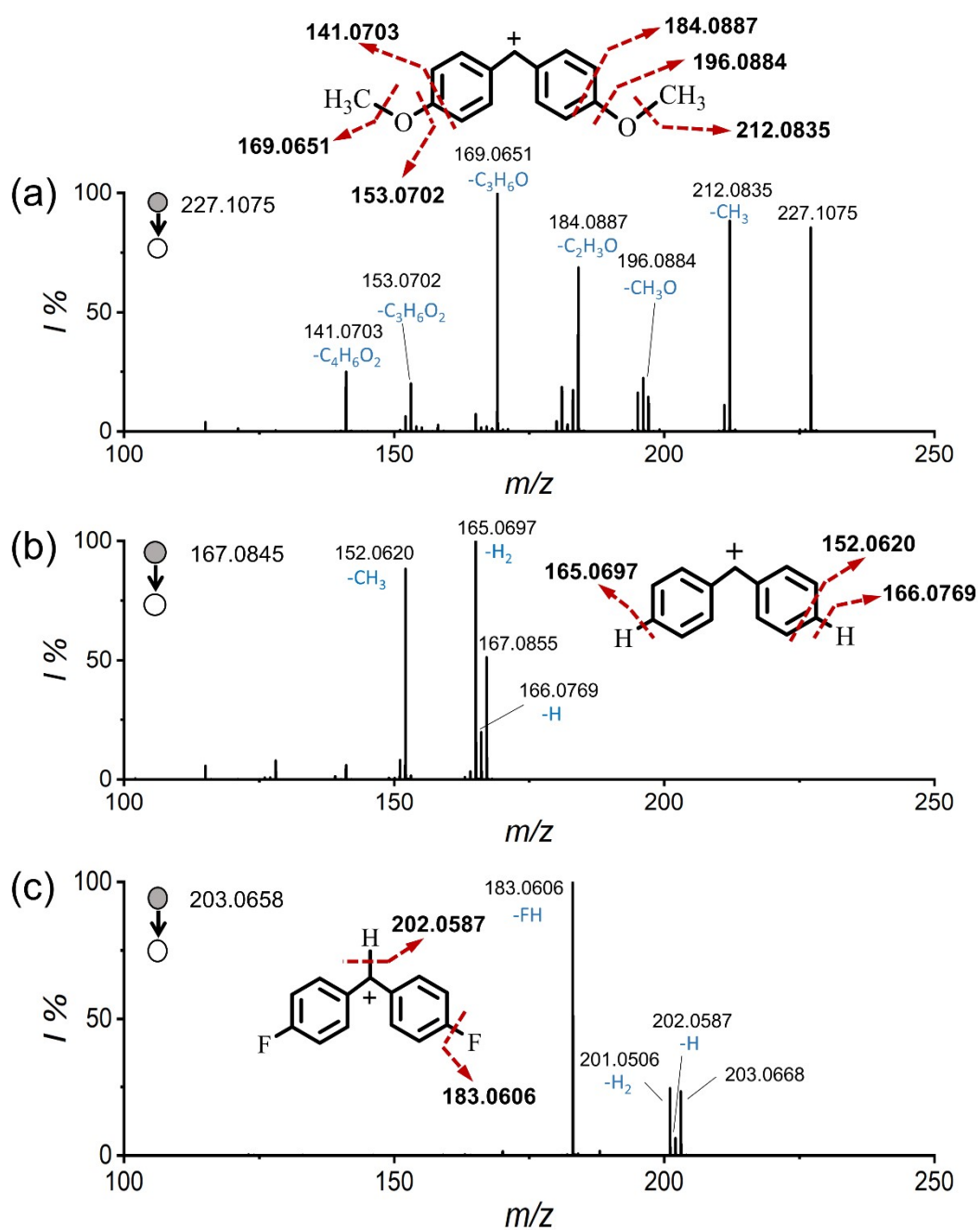


Figure S6. Tandem mass spectrum of (a) **2a**, (b) **2b**, and (c) **2c**. CID energy: 10 eV

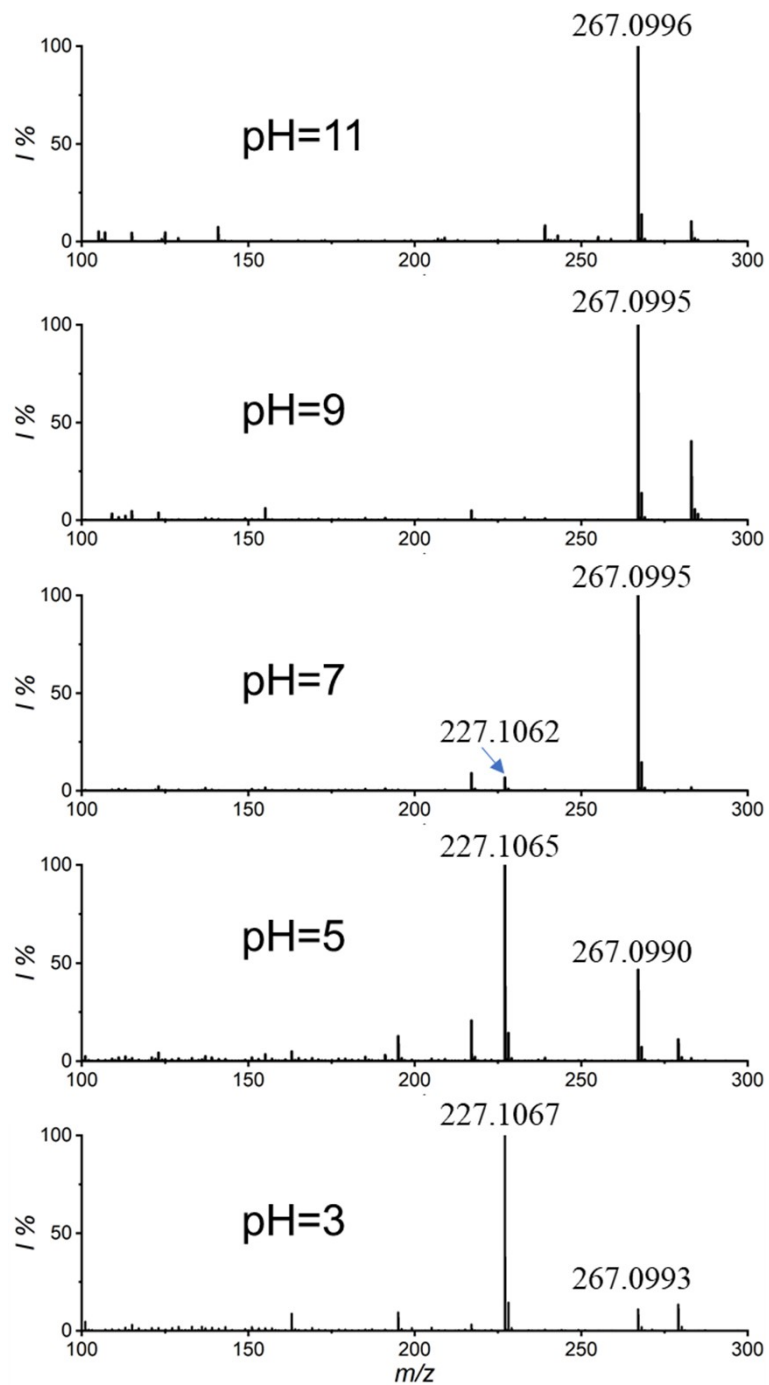


Figure S7. Mass spectrum showing the conversion was increased when decreasing the pH of the aqueous solution from 11 to 3. The spray distance was kept at 15 mm. The inner diameter of the emitter was ~400 nm.

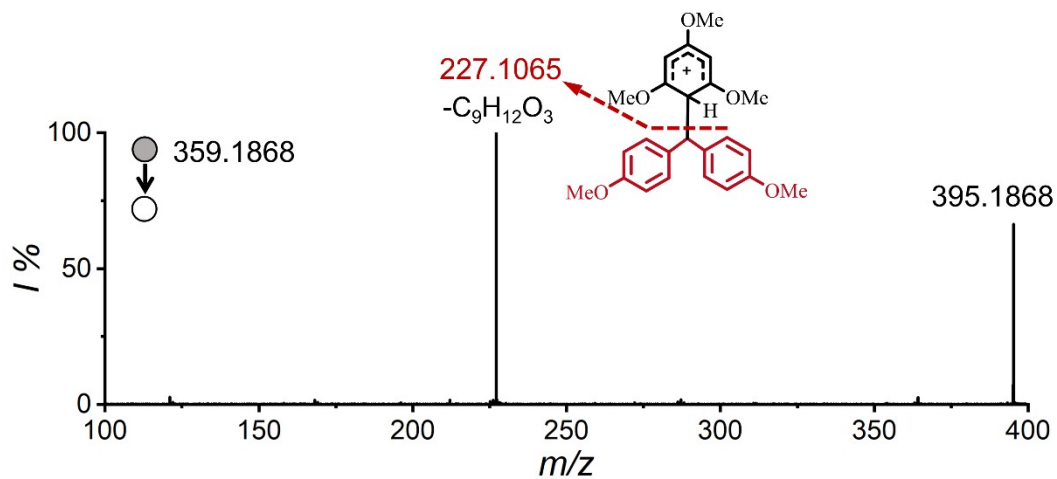


Figure S8. Tandem mass spectra of **4a**. CID energy: 10 eV

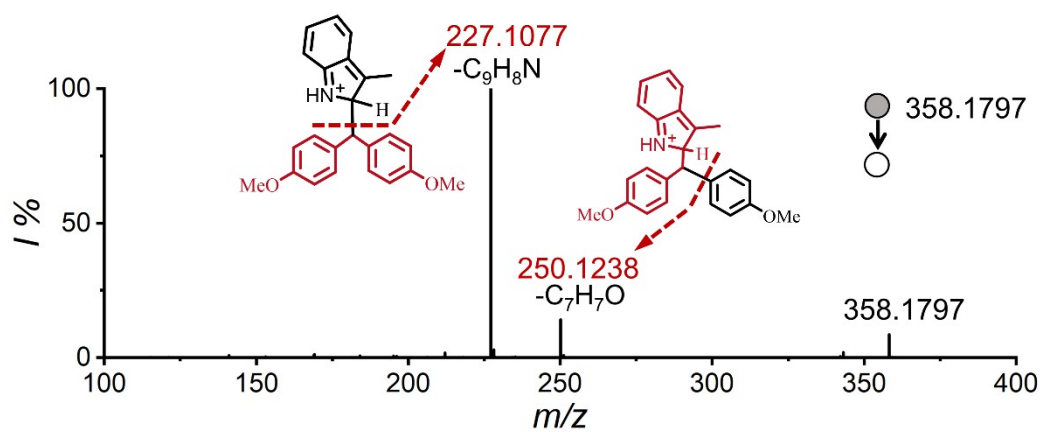


Figure S9. Tandem mass spectra of **4b**. CID energy: 10 eV

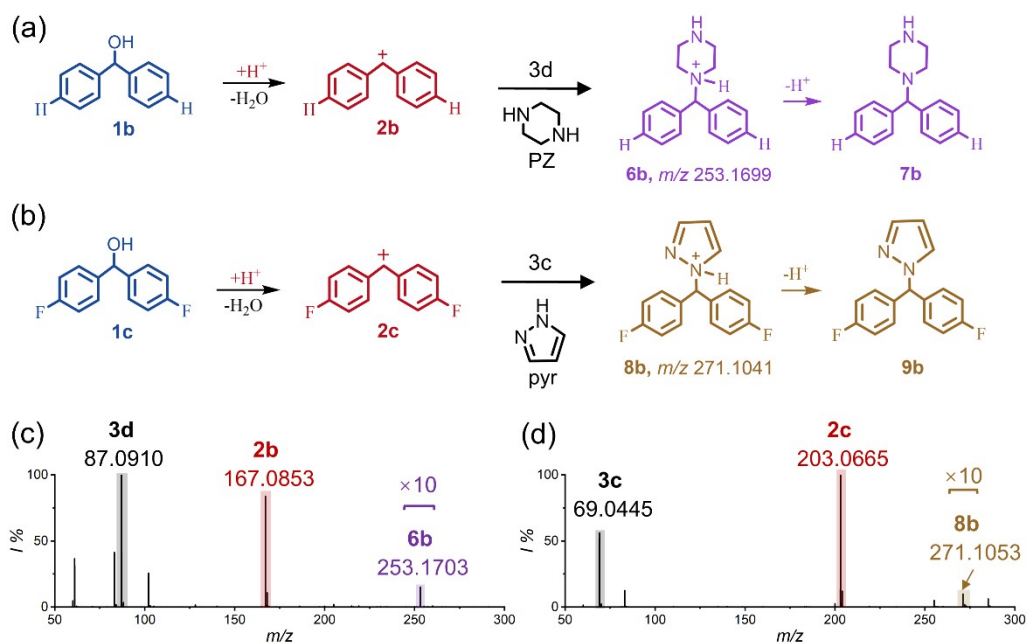


Figure S10. Mass spectrometric analysis of the spontaneous dehydrative C–N coupling in water microdroplets. (a) Proposed reaction mechanism for the spontaneous dehydrative C–N coupling between **1b** and **3d** in water microdroplets. (b) Proposed reaction mechanism for the spontaneous dehydrative C–N coupling between **1c** and **3c** in water microdroplets. (c) Mass spectrum showing the spontaneous dehydrative C–N coupling products when spraying aqueous solution containing **1b** and **3d**. (d) Mass spectrum showing the spontaneous dehydrative C–N coupling products when spraying aqueous solution containing **1c** and **3c**.

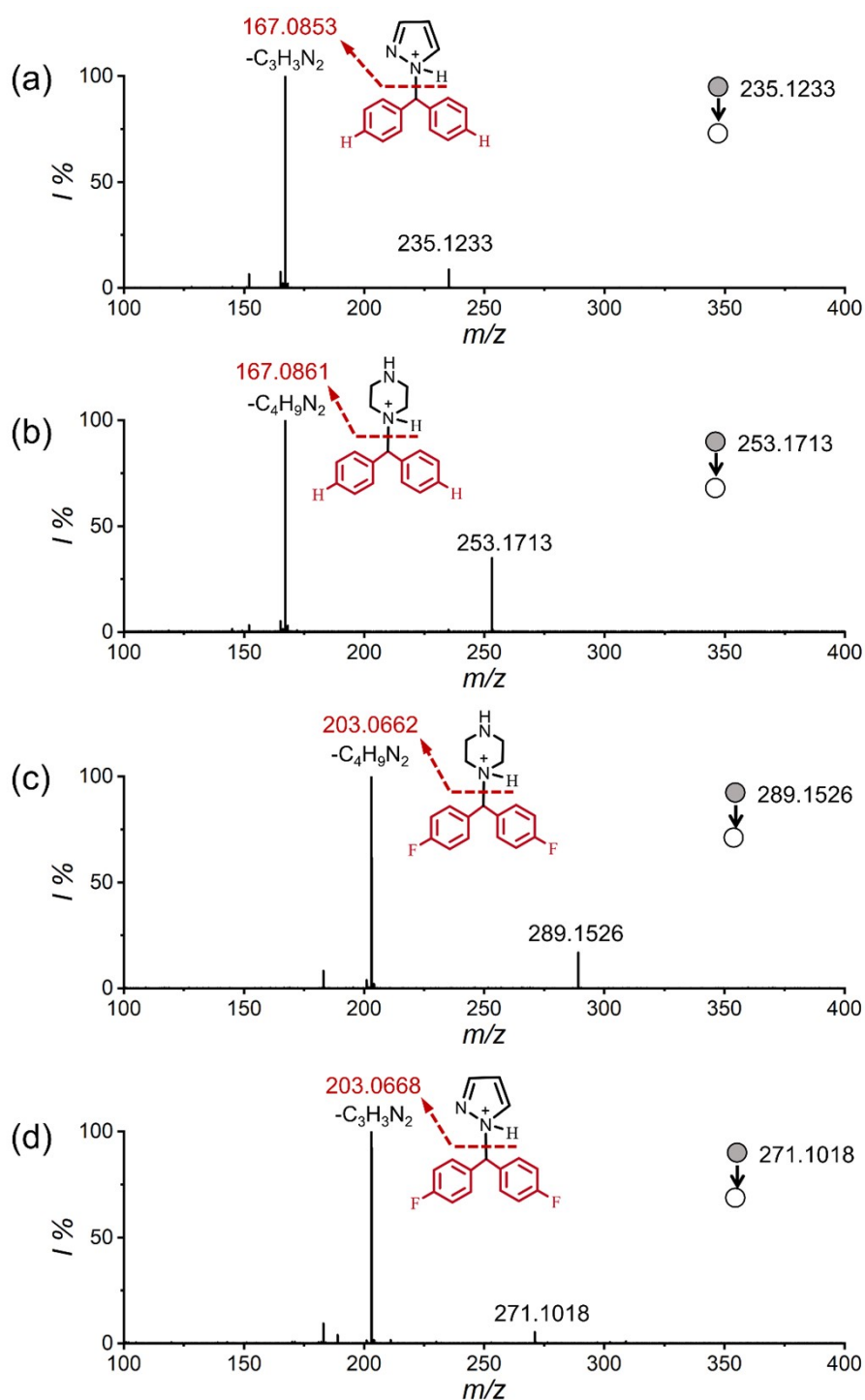


Figure S11. Tandem mass spectra of the (product+H)⁺ ions formed via the in-droplet reaction between (a) **1b** and pyz; (b) **1b** and PZ; (c) **1c** and PZ and (d) **1c** and pyz. CID energy: 10 eV.

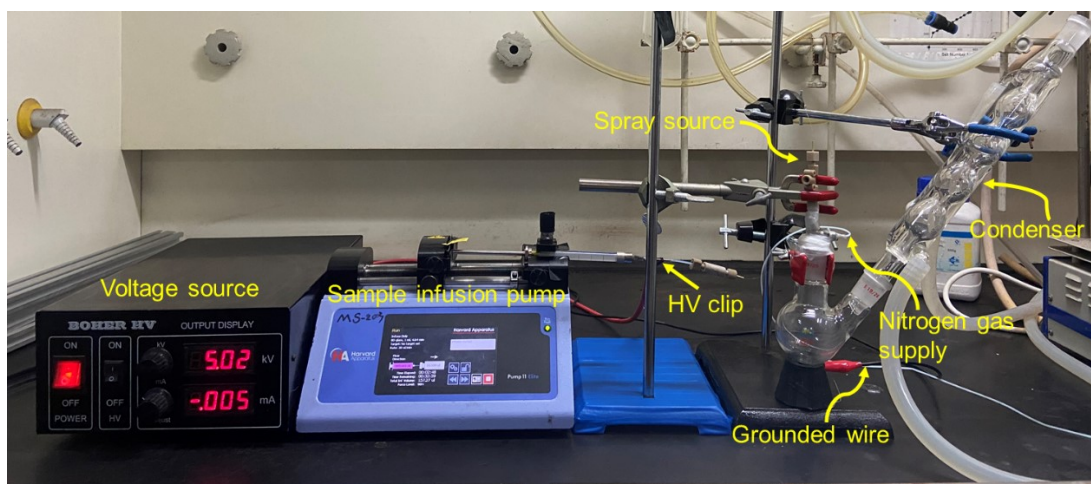


Figure S12. A photograph of the experimental setup for the offline collection of the sprayed microdroplets in a round bottom flask (50 mL) connected to a condenser. The spray source was operated with 5 kV voltage, 30 $\mu\text{L}/\text{min}$ solution flow rate and 80 psi back pressure.

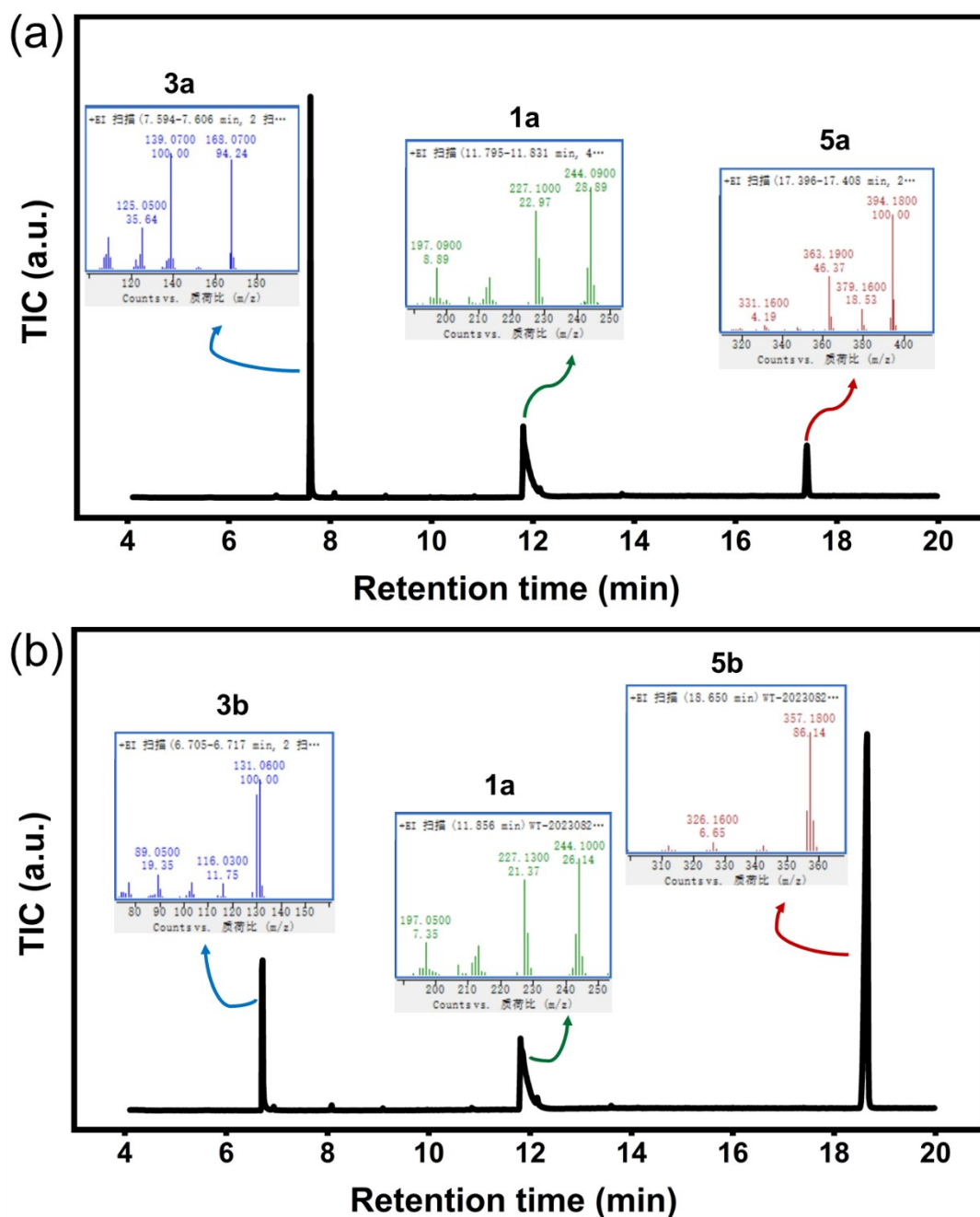


Figure S13. GC-MS chromatogram of the reaction mixture collected from the offline spraying of (a) 10 mM **1a** and 10 mM **3a**, (b) 10 mM **1a** and 10 mM **3b**. The inset of each chromatogram exhibits the electron ionization mass spectral data of the associated GC peak.

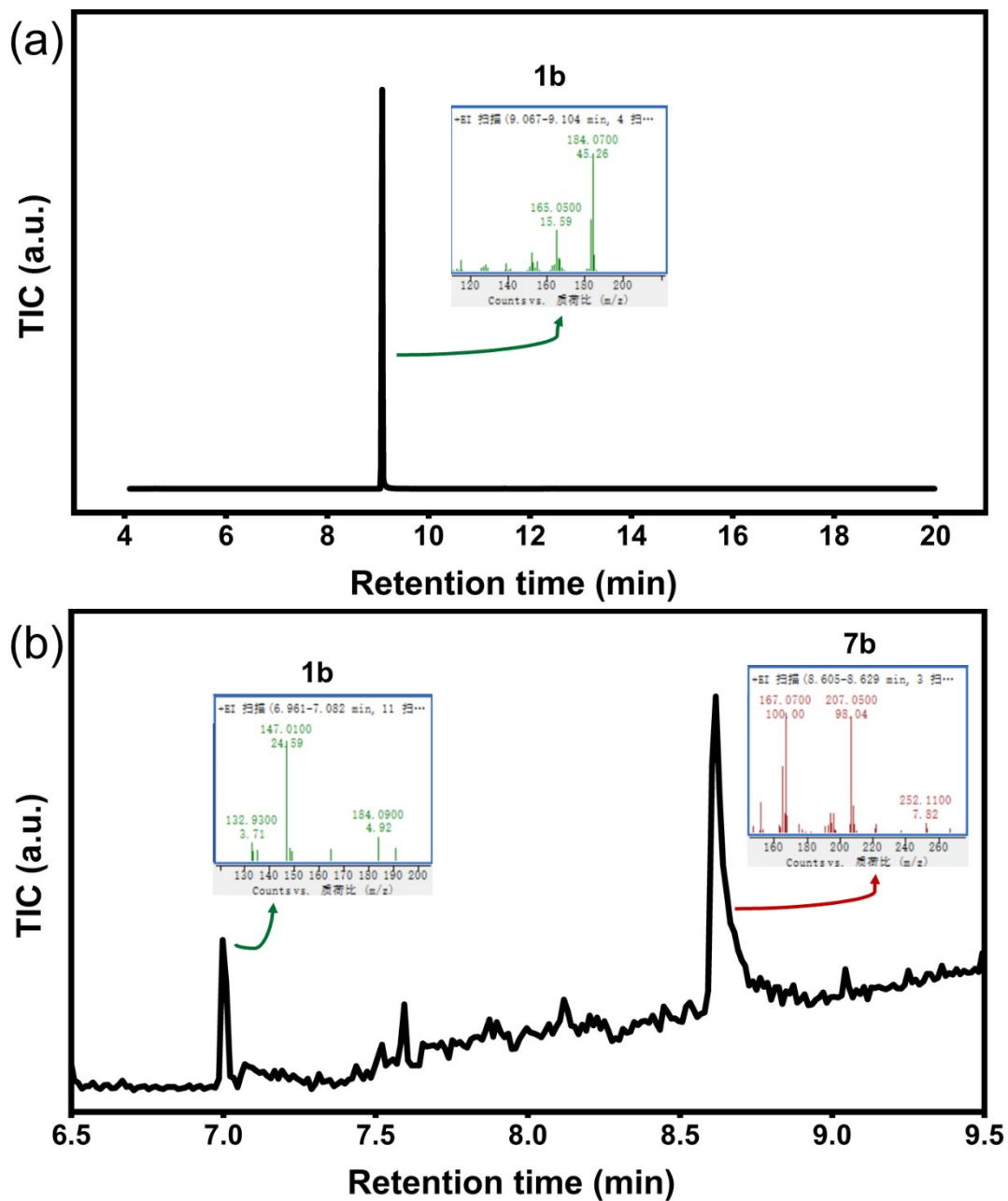


Figure S14. GC-MS chromatogram of the reaction mixture collected from the offline spraying of (a) 10 mM **1b** and 10 mM **3c**, (b) 10 mM **1b** and 10 mM **3d**. The inset of each chromatogram exhibits the electron ionization mass spectral data of the associated GC peak.

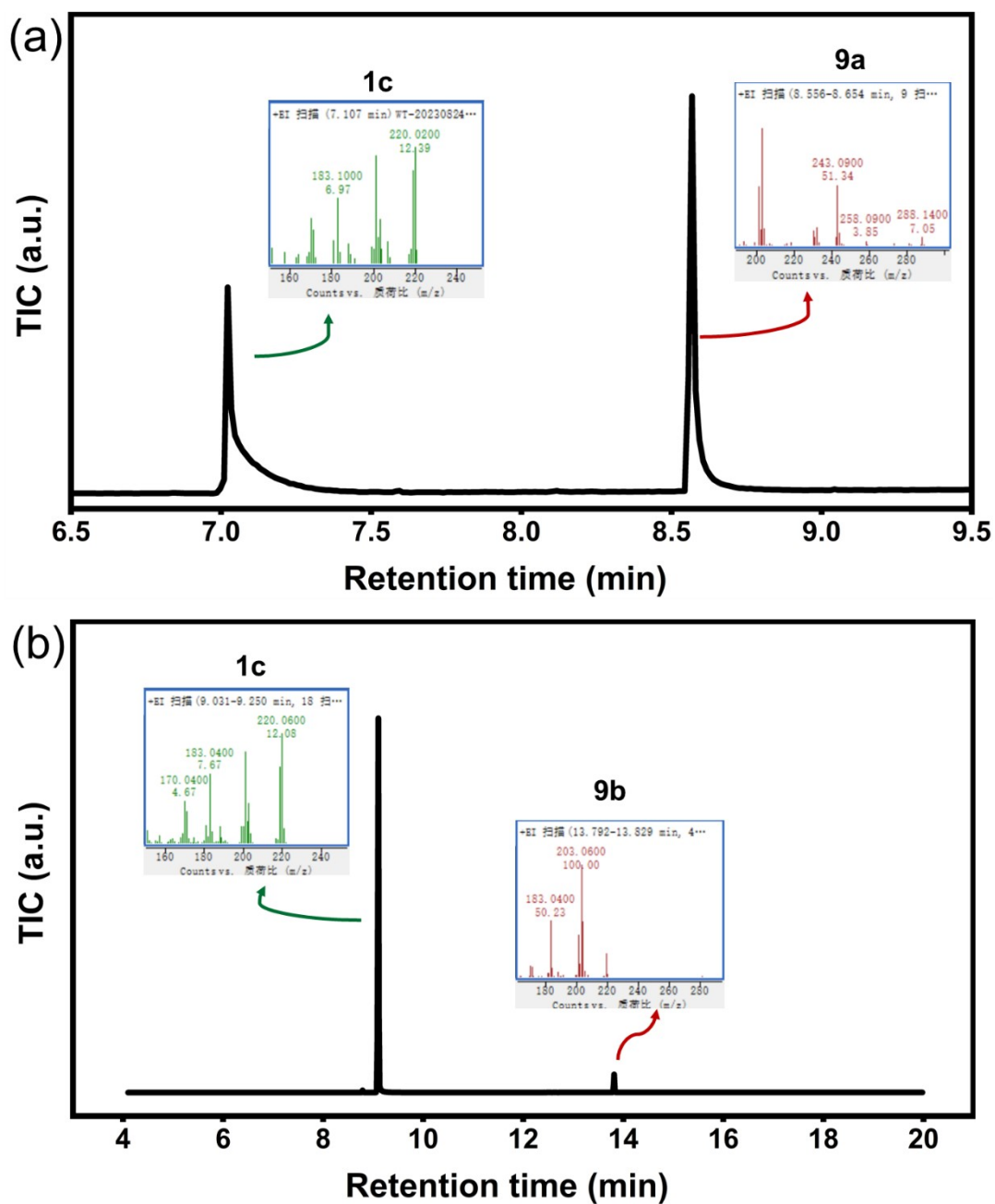


Figure S15. GC-MS chromatogram of the reaction mixture collected from the offline spraying of (a) 10 mM **1c** and 10 mM **3d**, (b) 10 mM **1c** and 10 mM **3c**. The inset of each chromatogram exhibits the electron ionization mass spectral data of the associated GC peak.

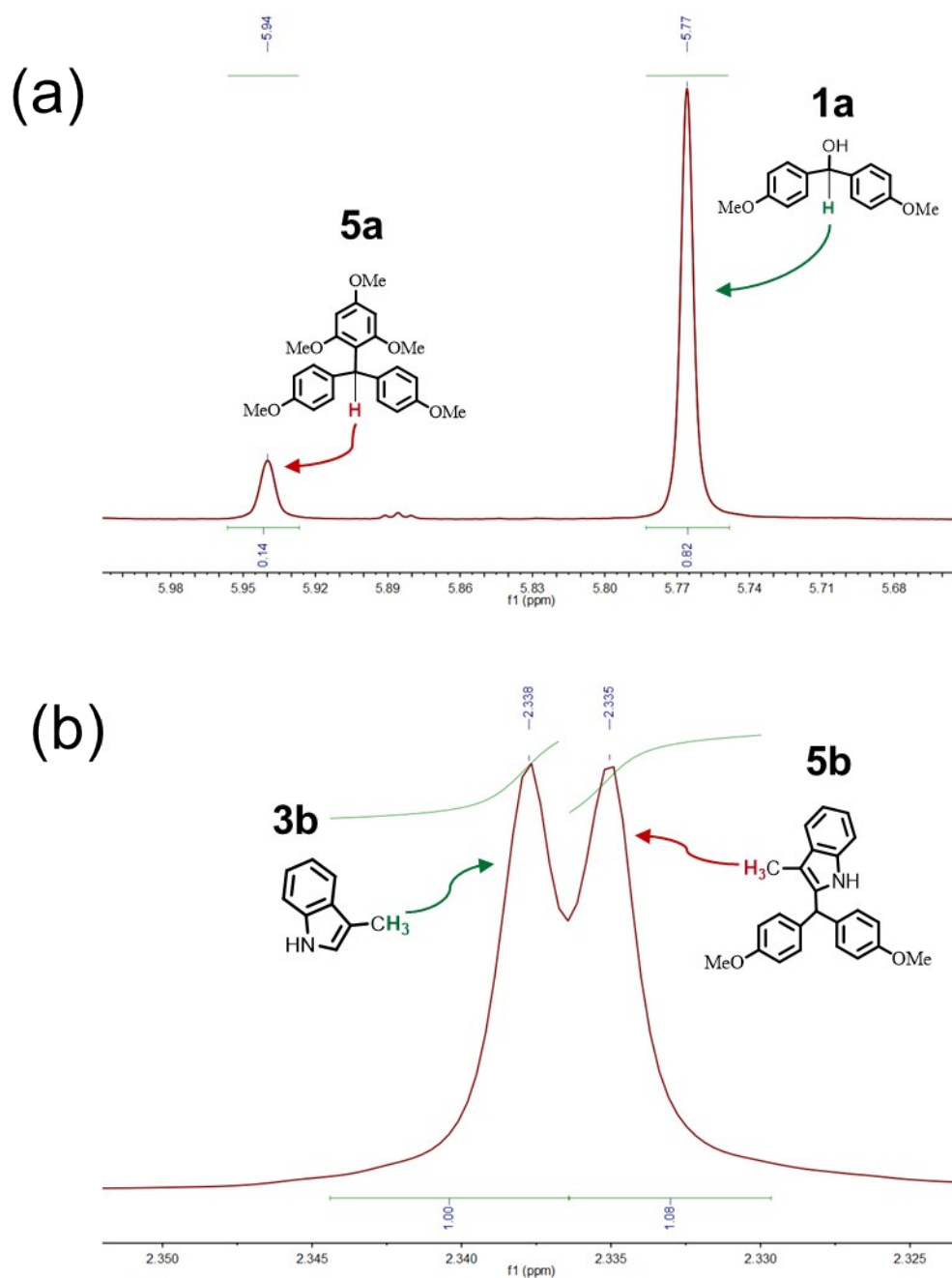


Figure S16. ^1H NMR spectra of the CDCl_3 extract of the reaction mixture collected from the offline spraying of (a) 10 mM **1a** and 10 mM **3a**, (b) 10 mM **1a** and 10 mM **3b**. The ratio of proton in **1a** (Ar-CH) to **5a** (Ar-CH) reveals a conversion rate of nearly 15% to form **5a** in microdroplets. The ratio of proton in **3b** (- CH_3) to **5b** (- CH_3) reveals a conversion rate of nearly 52% to form **5b** in microdroplets.

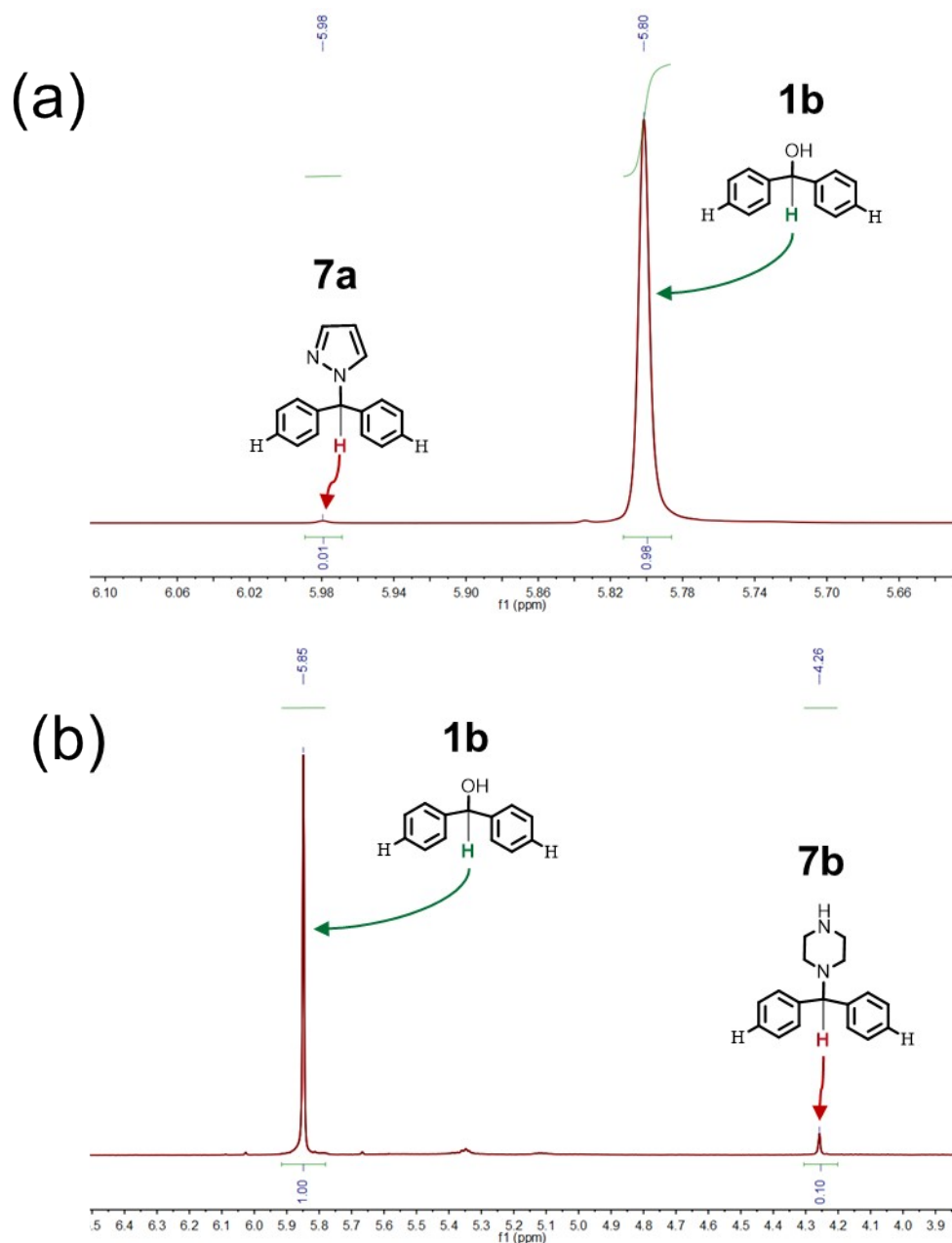


Figure S17. ^1H NMR spectra of the CDCl_3 extract of the reaction mixture collected from the offline spraying of (a) 10 mM **1b** and 10 mM **3c**, (b) 10 mM **1b** and 10 mM **3d**. The ratio of proton in **1b** (Ar-CH) to **7a** (Ar-CH) reveals a conversion rate of nearly 1% to form **7a** in microdroplets. The ratio of proton in **1b** (Ar-CH) to **7b** (Ar-CH) reveals a conversion rate of nearly 9% to form **7b** in microdroplets.

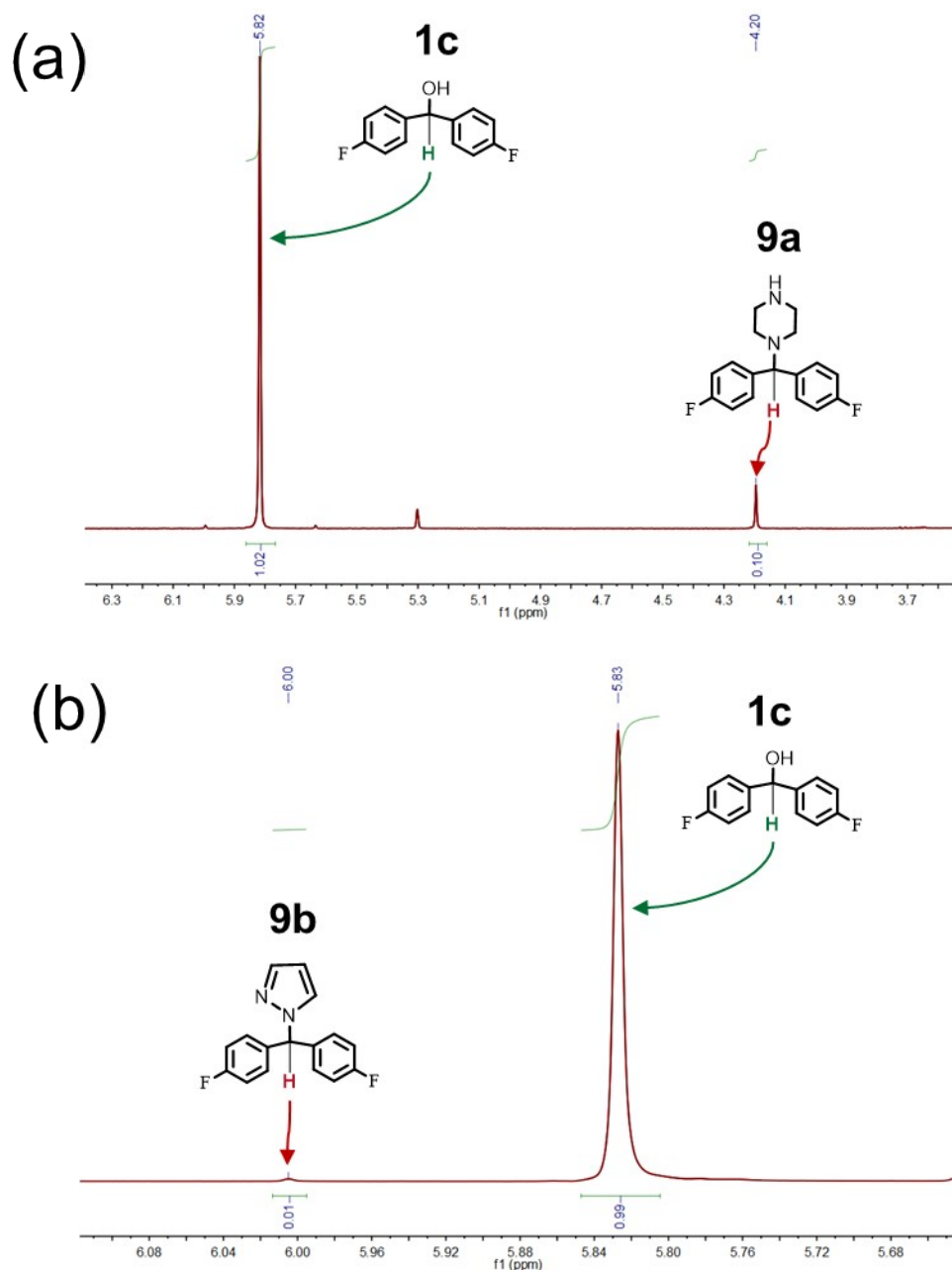


Figure S18. ^1H NMR spectra of the CDCl_3 extract of the reaction mixture collected from the offline spraying of (a) 10 mM **1c** and 10 mM **3d**, (b) 10 mM **1c** and 10 mM **3c**. The ratio of proton in **1c** (Ar-CH) to **9a** (Ar-CH) reveals a conversion rate of nearly 9% to form **9a** in microdroplets. The ratio of proton in **1c** (Ar-CH) to **9b** (Ar-CH) reveals a conversion rate of nearly 1% to form **9b** in microdroplets.