

Catalyst-Free Decarboxylative Amination of Carboxylic Acids in Water Microdroplets

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ABSTRACT: Previous studies have shown that hydroxyl radicals can be formed at the water–gas surface of water microdroplets. We report the use of *in situ* generated hydroxyl radicals to carry out an organic transformation in one step, namely, the formation of anilines from aryl acids as well as both ammonia and primary/secondary amines via decarboxylation. Benzoic acids and amines are dissolved in water, and the solution is sprayed to form microdroplets whose chemical contents are analyzed mass spectrometrically. All intermediates and products are determined using mass spectrometry (MS) as well as in some cases tandem mass spectrometry (MS²). These results support the following reaction mechanism: NR₂OH, formed via reaction of the amine with •OH, reacts with benzoic acid to form an isocyanate via a Lossen rearrangement. Hydrolysis followed by liberation of CO₂ then delivers the aniline product. Notably, the scope of this transformation includes a variety of amines and aromatic acids and enables their conversion into aniline and *N*-substituted anilines, all in a single step. Additionally, this reaction occurs at room temperature and does not require metal catalysts or organic solvents.

The C–N bond formation products and their derivatives are useful building blocks for the synthesis of pharmaceuticals, agrochemicals, textile products, and other valuable organic compounds.^{1,2} As a result, numerous methods have been developed to synthesize secondary and tertiary aryl amines, such as the Pd-catalyzed Buchwald–Hartwig coupling from aryl boronic acid and amines to obtain the substituted aryl amines.³ Another route is Chan–Lam coupling in which copper-catalyzed reactions between aryl boronic acids and amines yield the substituted amines.^{4,5} Additionally, Cu- or Pd-catalyzed Ullmann-type coupling offers a wide range of coupling products.^{6,7} Aniline and *N*-substituted anilines have been synthesized from different starting materials, such as metal-catalyzed chlorobenzene to aniline (Sandmeyer reaction) and base-mediated Hoffmann rearrangement which affords the products from aromatic amides.⁸ Interestingly, in one step it is possible to reduce nitrobenzene to aniline, in the presence of Sn/HCl.⁹ Recently, developed copper-catalyzed decarboxylative C–N coupling has been developed to generate amines by photolysis, and in addition, nickel-catalyzed direct decarbonylative amination offers C–N bond formation products.^{10,11} To the best of our knowledge, however, there are no reports available on the direct, catalyst-free transformation of benzoic acid to aniline in water.

Researches from our group and others have shown that water microdroplets exhibit unusual reaction properties that are not observed in bulk water or other organic solvents.^{12–18} One possible reason for the unique properties of water microdroplets is the large amount of hydroxyl radicals at the water–gas interface produced by a strong electric field^{19–21} and by contact electrification.²² Taking advantage of this feature, our group and others have shown that hydrogen peroxide forms in water microdroplets.^{22–24} The hydrogen peroxide originates from the recombination of two hydroxyl

radicals at the surface of the water microdroplet. A limited number of examples exist for the utilization of hydrogen peroxide generated *in situ* from water microdroplets to conduct organic transformations. Two examples are the use of hydrogen peroxide formed in water microdroplets for the Bayer–Villiger and Dakin oxidation reactions²⁵ and the conversion of aryl boronic acid to useful phenol derivatives.²³ Recently, our group synthesized formic acid from water microdroplets via the hydroxyl radical and also utilized the microdroplet technique to oxidize the aldehyde to obtain the acid.²⁶ We also developed direct C(sp³)–N bond formation between toluene and amine in water.²⁷ Similarly, we tried to cause a direct reaction between benzene and amine but unfortunately failed to find the product. In sharp contrast, we observed the direct formation of aniline from benzoic acid in water via decarboxylation under mild conditions. Utilization of *in situ* generated hydroxyl radical from water to convert useful organic transformations is still underexplored. Herein, we describe the one-step synthesis of aniline from benzoic acid in water via decarboxylation under mild conditions.

Figure 1 shows a schematic diagram of the microdroplet experimental setup. Benzoic acid and amines are dissolved in water to make a mixed solution. The solution is injected into the droplet sprayer with a syringe (5 μL/min) from a fused silica capillary (i.d. 75 μm, o.d. 350 μm). Water microdroplets containing benzoic acid and ammonia are generated by the

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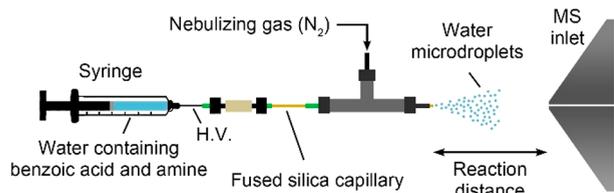


Figure 1. Schematic diagram of the experimental setup using sprayed water microdroplets in which benzoic acid and amine have been dissolved.

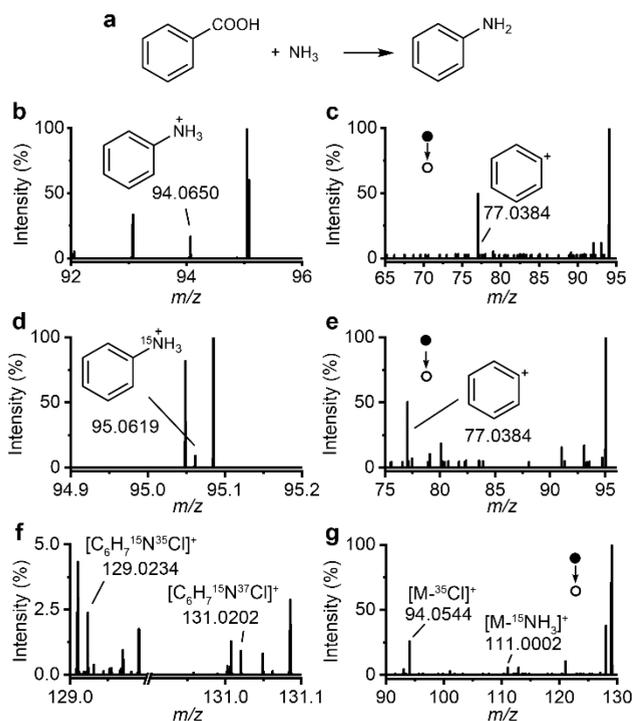


Figure 2. (a) Synthesis of aniline from benzoic acid and ammonia in water microdroplets. (b) Mass spectrum of the water microdroplets containing both ammonia and benzoic acid. (c) MS² spectrum of the peak of m/z at 94.0650 shown in panel b. (d) Mass spectrum of the microdroplets containing benzoic acid and ¹⁵NH₃. (e) MS² spectrum of the peak at m/z 95.0619 shown in panel d. (f) Mass spectrum of the microdroplets containing 4-Cl-benzoic acid and ¹⁵NH₃. (g) MS² spectrum of the peak at m/z 129.0234 shown in panel f.

sprayer using N₂ (120 psi) as the nebulizing gas. A positive voltage (4 kV) is applied to the sprayer to obtain a higher electric field at the water–gas interface of the microdroplets. The detailed optimization of the applied voltage is shown in Figure S1. Our previous study has shown that hydroxyl radicals are able to form without any external voltage.^{23,26} The aim of applying a high voltage here is to obtain a higher electric field at the water–gas surface and accelerate the reaction. The ions produced by the microdroplets are directly detected by a high-resolution mass spectrometer (Orbitrap Velos Pro, Thermo Fisher Scientific, Waltham, MA). The distance between the sprayer and the MS inlet is considered as the reaction distance of the microdroplets. In this experiment, the distance is set to 10 mm. Considering that the jet velocity of the microdroplets by the sprayer is about 83 m/s, which has been shown in our previous study,²⁸ the reaction time can be calculated to be about 120 μs.

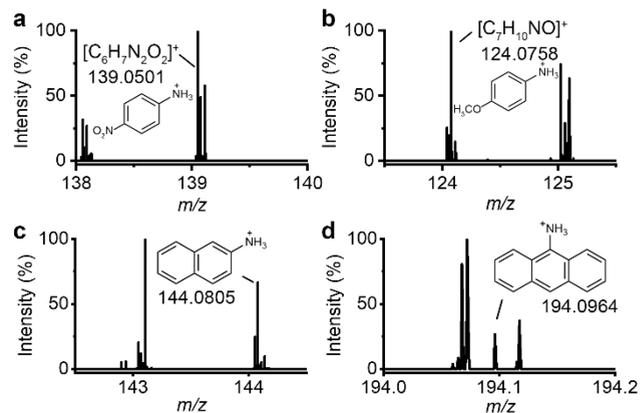


Figure 3. (a) Mass spectrum of the microdroplets containing 4-nitrobenzoic acid and NH₃. (b) Mass spectrum of the microdroplets containing 4-methoxybenzoic acid and NH₃. (c) Mass spectrum of the microdroplets containing 2-naphthoic acid and NH₃. (d) Mass spectrum of the microdroplets containing 9-anthracenecarboxylic acid and NH₃.

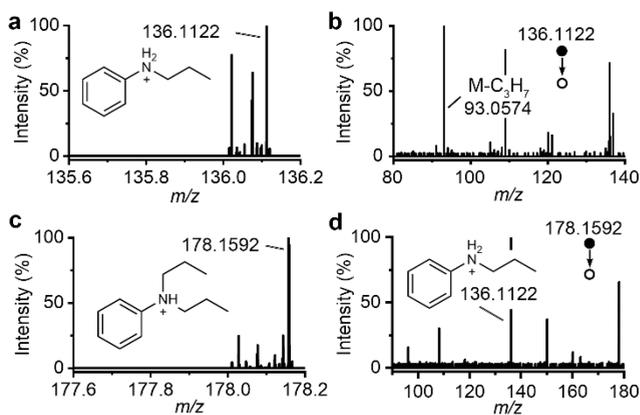


Figure 4. Formation of aniline derivatives between benzoic acid and primary amine and secondary amine. (a) Mass spectrum of the water microdroplets containing benzoic acid and propylamine. (b) MS² spectrum of the selected peak at m/z 136.1122 shown in panel a. (c) Mass spectrum of the water microdroplets containing benzoic acid and dipropylamine. (d) MS² spectrum of the selected peak at m/z 178.1592 shown in panel c.

Figure 2a shows the formation of aniline from benzoic acid and ammonium hydroxide in a water microdroplet. We dissolved benzoic acid (100 μM) into ammonium hydroxide solution (28% ammonia in water solution) directly. By using MS, the chemical contents in the microdroplets generated by the sprayer can be precisely detected. Figure 2b shows the mass spectrum of the water microdroplets containing benzoic acid and ammonia. A peak of mass-to-charge ratio (m/z) at 94.0650 can be clearly observed. This peak is identified as protonated aniline (C₆H₈N⁺), whose exact m/z is 94.0652. To further confirm the molecular structure, MS² analysis was carried out on the selected peak of m/z at 94.0650 in Figure 2b. As shown in Figure 2c, from the MS² spectrum, we can observe the peak of m/z at 77.0384, which is C₆H₅⁺, a fragment from the collision-induced dissociation (CID) of C₆H₈N⁺. Additionally, the product peak is not observed in the control group, that is, only benzoic acid in water or only ammonia in water (Figure S2). By calculating with the standard addition method of aniline, the product yield is about

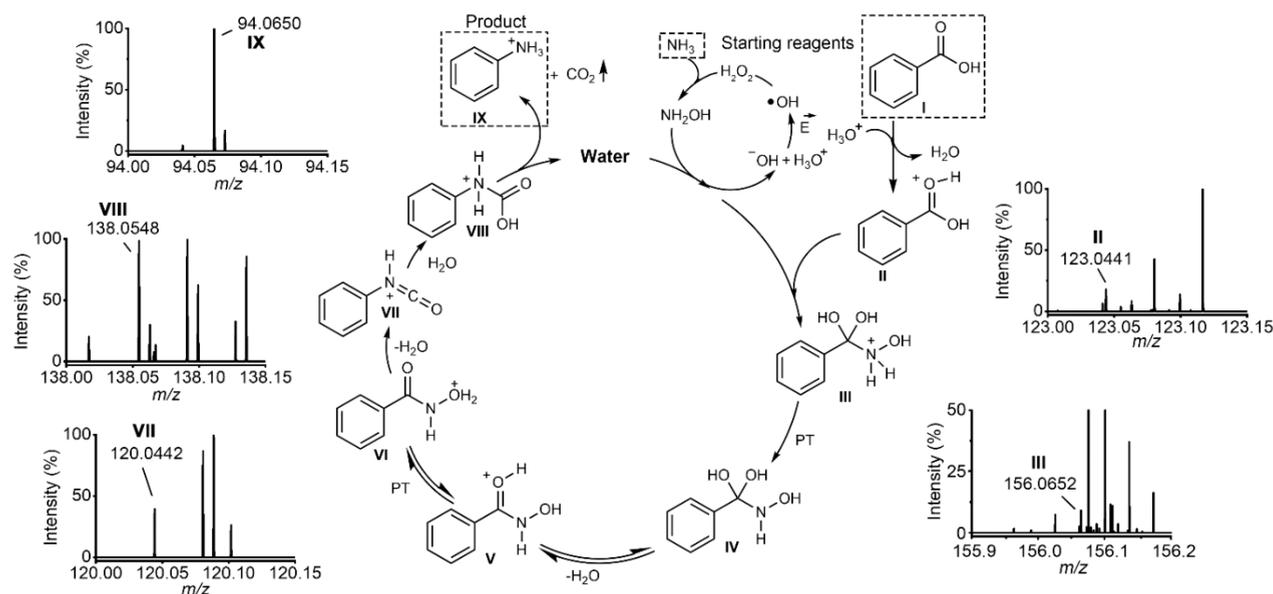


Figure 5. Proposed mechanism and MS verification for aniline formation from benzoic acid and ammonia in water microdroplets.

1.4% (Figure S3). The evaporation of aniline from microdroplets may account, in part, for the poor yield.

^{15}N -ammonium hydroxide solution ($^{15}\text{NH}_4\text{OH}$) is used to trace the origin of N atoms in the aniline product. Similar with the experiments showed above, benzoic acid is dissolved in $^{15}\text{NH}_4\text{OH}$ (28% water solution). Figure 2d shows the signals obtained in the *in situ* MS, which indicate the formation of the protonated aniline- ^{15}N (m/z at 95.0619) and show that the only source of nitrogen is from NH_4OH . Figure 2e presents the MS^2 spectrum of the product, which shows the same fragments of C_6H_5^+ at m/z 77.0384. We also carried out the microdroplet experiment with *p*-chlorobenzoic acid and $^{15}\text{NH}_4\text{OH}$. As shown in Figure 2f, the peaks at m/z 129.0234 and m/z 131.0202 are considered to be protonated 4-chloroaniline. The intensity ratio of the two peaks is about 3:1, which is expected for the isotope ratio of ^{35}Cl to ^{37}Cl . Figure 2g shows the MS^2 spectrum of the peak at m/z 129.0234, which demonstrates two different dissociation paths from the parent molecule, fragmentation of ^{35}Cl and $^{15}\text{NH}_3$. This result clearly indicates the product formation. Because aniline derivative mass spectra are well-known, we matched ours with the literature data.^{29,30} This comparison proves the formation of aniline from benzoic acid and ammonia in a charged water microdroplet.

Further, the scope of the reaction has been expanded to electron-rich and electron-deficient groups containing aromatic acids. Both 4-nitrobenzoic acid and 4-methoxybenzoic acids afforded the corresponding aromatic amines such as 4-nitroaniline and *p*-anisidine, respectively. The formations of protonated 4-nitroaniline and protonated *p*-anisidine were observed with MS (Figure 3a,b). In addition, the structure was further confirmed with MS^2 (Figures S4 and S5). We also extended the reaction of benzoic acid and ammonia to other substrates (2-naphthoic and 9-anthracenecarboxylic acid). As shown in Figure 3c, the injection of 2-naphthoic acid and ammonia offers the protonated 2-naphthylamine peak at m/z 144.0805. The MS^2 spectrum is shown in Figure S6. The fragment peak of $\text{C}_{10}\text{H}_7^+$ can be observed at m/z 127.0541. Similarly, the sprayed microdroplets between 9-anthracenecarboxylic acid and ammonia produced 9-aminoanthracene at

m/z 194.0964 ($[\text{M} + \text{H}]^+$). Moreover, the fragment peaks for the aryl cation observed ($\text{C}_{14}\text{H}_9^+$) at m/z 177.0695 are also observed (Figure 3d and Figure S7).

In addition to ammonia, we also carried out the reaction between benzoic acid and primary and secondary amines to obtain various aniline *N*-alkyl derivatives. First, benzoic acid and propylamine were dissolved in water, whose concentrations were both 100 μM . When spraying the solution into the MS, the peak of $\text{C}_9\text{H}_{14}\text{N}^+$ at m/z 136.1122 can be observed in the generated microdroplets, as shown in Figure 4a. This is considered to be the decarboxylation product from the reaction between benzoic acid and propylamine. Figure 4b shows the MS^2 spectrum of the selected peak at m/z 136.1122 shown in Figure 4a. The fragment of $[\text{M} - \text{C}_3\text{H}_7]^+$ at m/z 93.0574 further proves the formation of the *N*-propylaniline in water microdroplets. The synthesis of *N,N*-dipropylaniline is also carried out with dipropylamine and benzoic acid by the same method. Figure 4c shows the protonated product ($\text{C}_{12}\text{H}_{20}\text{N}^+$) at m/z 178.1592, and the MS^2 spectrum is shown in Figure 4d. By using a standard addition method, we have calculated the yield of *N,N*-dipropylaniline to be about 4.7% (Figure S8), which is slightly higher than the aniline. These experimental results indicate that aniline derivatives can also form from benzoic acid and the corresponding amines in water microdroplets at room temperature.

Based on these observations, we propose the mechanism shown in Figure 5 for the synthesis of aniline from benzoic acid I. The water dissociates into hydronium cation and hydroxide anion, followed by the formation of hydroxyl radical at the air-water interface. Where the electron from OH^- goes has not been completely established, but experiments have shown that the walls of the sprayer become negatively charged through contact electrification.²² The *in situ* generated $\bullet\text{OH}$ radicals recombine to form HOOH that then reacts with ammonia to form hydroxylamine (NH_2OH) and water. Because the m/z of NH_2OH is only 33, which is below the detection range of our mass spectrometer, we are not able to see this intermediate. However, we have successfully trapped *N*-propylhydroxylamine, which is generated from the propylamine in the same way (Figure S9). This result proves that the formation of

hydroxylamine is an important step in the proposed mechanism for the microdroplet reaction. Further, the hydroxylamine attacks protonated benzoic acid **II** to form the intermediate **III**, which loses a proton to provide the acetal derivative **IV**. Owing to the instability of the acetal derivative, it releases water to form **V**, which undergoes a proton transfer to give **VI**. The intermediate **VI** further releases water via a Lossen rearrangement to produce protonated isocyanate **VII**. Hydrolysis of this isocyanate generates an unstable carbamic acid (**VIII**), which undergoes spontaneous decarboxylation to yield the aniline product **IX**. As shown in the Figure 5, most of the intermediates and the product were observed by us with high-resolution MS. Some of the stable intermediates can also be detected with MS² (Figure S10). Table S1 lists all the observed and reference *m/z* values of the ions in this work. Thus, we are confident that the mechanism shown is correct.

In summary, we report the one-step decarboxylative C(sp²)-N coupling reaction between benzoic acid and aliphatic amines in water microdroplets via decarboxylation to form aniline and aromatic amine derivatives. To determine the reaction mechanism, the intermediates were detected using *in situ* high-resolution MS and MS². The ¹⁵N labeling experiment clearly delineates the source of nitrogen and further supports the mechanism of the reaction. The scope of this transformation was extended to electron-rich, electron-deficient, and polyaromatic acids to obtain corresponding amines. Also, the scope of the nucleophile has been expanded to both primary and secondary amines. This simple method provides a green approach for the one-step synthesis of aniline and *N*-substituted anilines from aromatic carboxylic acids and amines at room temperature, without any metal catalysts and without any organic solvents.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.2c12236>.

Voltage optimization, MS² spectra data, calculation of product conversion rate, and exact/observed *m/z* of the ions in this work (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Amini, B.; Lowenkron, S. Aniline and its derivatives. In *Kirk-Othmer Encyclopedia of Chemical Technology*; John Wiley & Sons, Ltd, 2000; pp 783–806. DOI: 10.1002/0471238961.0114091201130914.a01.pub2.
- (2) Kahl, T.; Schröder, K.-W.; Lawrence, F. R.; Marshall, W. J.; Höke, H.; Jäckh, R. Aniline. In *Ullmann's Encyclopedia of Industrial Chemistry*; John Wiley & Sons, Ltd, 2011, pp 1–15. DOI: 10.1002/14356007.a02_303.
- (3) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C-N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116* (19), 12564–12649.
- (4) Wang, C.; Zhang, H.; Wells, L. A.; Liu, T.; Meng, T.; Liu, Q.; Walsh, P. J.; Kozłowski, M. C.; Jia, T. Autocatalytic photoredox Chan-Lam coupling of free diaryl sulfoximines with arylboronic acids. *Nat. Commun.* **2021**, *12* (1), 932.
- (5) West, M. J.; Fyfe, J. W. B.; Vantourout, J. C.; Watson, A. J. B. Mechanistic Development and Recent Applications of the Chan-Lam Amination. *Chem. Rev.* **2019**, *119* (24), 12491–12523.
- (6) Khan, F.; Dlugosch, M.; Liu, X.; Banwell, M. G. The Palladium-Catalyzed Ullmann Cross-Coupling Reaction: A Modern Variant on a Time-Honored Process. *Acc. Chem. Res.* **2018**, *51* (8), 1784–1795.
- (7) Yang, Q.; Zhao, Y.; Ma, D. Cu-Mediated Ullmann-Type Cross-Coupling and Industrial Applications in Route Design, Process Development, and Scale-up of Pharmaceutical and Agrochemical Processes. *Org. Process Res. Dev.* **2022**, *26* (6), 1690–1750.
- (8) Hartwig, J. F.; Shekhar, S.; Shen, Q.; Barrios-Landeros, F. Synthesis of Anilines. In *PATAI'S Chemistry of Functional Groups*; John Wiley & Sons, Ltd, 2009; pp 1–82. DOI: 10.1002/9780470682531.pat0391.
- (9) Yamabe, S.; Yamazaki, S. A DFT study of reduction of nitrobenzene to aniline with SnCl₂ and hydrochloric acid. *J. Phys. Org. Chem.* **2016**, *29* (7), 361–367.
- (10) Zhao, W.; Wurz, R. P.; Peters, J. C.; Fu, G. C. Photoinduced, Copper-Catalyzed Decarboxylative C-N Coupling to Generate Protected Amines: An Alternative to the Curtius Rearrangement. *J. Am. Chem. Soc.* **2017**, *139* (35), 12153–12156.
- (11) Malapit, C. A.; Borrell, M.; Milbauer, M. W.; Brigham, C. E.; Sanford, M. S. Nickel-Catalyzed Decarbonylative Amination of Carboxylic Acid Esters. *J. Am. Chem. Soc.* **2020**, *142* (13), 5918–5923.
- (12) Xing, D.; Meng, Y.; Yuan, X.; Jin, S.; Song, X.; Zare, R. N.; Zhang, X. Capture of Hydroxyl Radicals by Hydronium Cations in Water Microdroplets. *Angew. Chem., Int. Ed.* **2022**, *61* (33), No. e202207587.
- (13) Huang, K.-H.; Wei, Z.; Cooks, R. G. Accelerated reactions of amines with carbon dioxide driven by superacid at the microdroplet interface. *Chem. Sci.* **2021**, *12* (6), 2242–2250.
- (14) Gong, C.; Li, D.; Li, X.; Zhang, D.; Xing, D.; Zhao, L.; Yuan, X.; Zhang, X. Spontaneous Reduction-Induced Degradation of Viologen Compounds in Water Microdroplets and Its Inhibition by Host-Guest Complexation. *J. Am. Chem. Soc.* **2022**, *144* (8), 3510–3516.
- (15) Qiu, L.; Cooks, R. G. Simultaneous and Spontaneous Oxidation and Reduction in Microdroplets by the Water Radical Cation/Anion Pair. *Angew. Chem., Int. Ed.* **2022**, *61* (41), No. e202210765.
- (16) Kumar, A.; Mondal, S.; Sandeep; Venugopalan, P.; Kumar, A.; Banerjee, S. Destabilized Carbocations Caged in Water Micro-

droplets: Isolation and Real-Time Detection of α -Carbonyl Cation Intermediates. *J. Am. Chem. Soc.* **2022**, *144* (8), 3347–3352.

(17) Zhao, P.; Gunawardena, H. P.; Zhong, X.; Zare, R. N.; Chen, H. Microdroplet Ultrafast Reactions Speed Antibody Characterization. *Anal. Chem.* **2021**, *93* (8), 3997–4005.

(18) Zhang, D.; Yuan, X.; Gong, C.; Zhang, X. High Electric Field on Water Microdroplets Catalyzes Spontaneous and Ultrafast Oxidative C-H/N-H Cross-Coupling. *J. Am. Chem. Soc.* **2022**, *144* (35), 16184–16190.

(19) Chamberlayne, C. F.; Zare, R. N. Simple model for the electric field and spatial distribution of ions in a microdroplet. *J. Chem. Phys.* **2020**, *152* (18), 184702.

(20) Xiong, H.; Lee, J. K.; Zare, R. N.; Min, W. Strong Electric Field Observed at the Interface of Aqueous Microdroplets. *J. Phys. Chem. Lett.* **2020**, *11* (17), 7423–7428.

(21) Hao, H.; Leven, I.; Head-Gordon, T. Can electric fields drive chemistry for an aqueous microdroplet? *Nat. Commun.* **2022**, *13* (1), 280.

(22) Chen, B.; Xia, Y.; He, R.; Sang, H.; Zhang, W.; Li, J.; Chen, L.; Wang, P.; Guo, S.; Yin, Y.; Hu, L.; Song, M.; Liang, Y.; Wang, Y.; Jiang, G.; Zare, R. N. Water-solid contact electrification causes hydrogen peroxide production from hydroxyl radical recombination in sprayed microdroplets. *Proc. Natl. Acad. Sci. U.S.A.* **2022**, *119* (32), No. e2209056119.

(23) Lee, J. K.; Walker, K. L.; Han, H. S.; Kang, J.; Prinz, F. B.; Waymouth, R. M.; Nam, H. G.; Zare, R. N. Spontaneous generation of hydrogen peroxide from aqueous microdroplets. *Proc. Natl. Acad. Sci. U.S.A.* **2019**, *116* (39), 19294–19298.

(24) Mehrgardi, M. A.; Mofidfar, M.; Zare, R. N. Sprayed Water Microdroplets Are Able to Generate Hydrogen Peroxide Spontaneously. *J. Am. Chem. Soc.* **2022**, *144* (17), 7606–7609.

(25) Gao, D.; Jin, F.; Lee, J. K.; Zare, R. N. Aqueous microdroplets containing only ketones or aldehydes undergo Dakin and Baeyer-Villiger reactions. *Chem. Sci.* **2019**, *10* (48), 10974–10978.

(26) (a) Song, X.; Meng, Y.; Zare, R. N. Spraying Water Microdroplets Containing 1,2,3-Triazole Converts Carbon Dioxide into Formic Acid. *J. Am. Chem. Soc.* **2022**, *144* (37), 16744–16748.

(b) Yan, X.; Lai, Y.-H.; Zare, R. N. Preparative Microdroplet Synthesis of Carboxylic Acids from Aerobic Oxidation of Aldehydes. *Chem. Sci.* **2018**, *9*, 5207–5211.

(27) Meng, Y.; Gnanamani, E.; Zare, R. N. Direct C(sp³)-N Bond Formation between Toluene and Amine in Water Microdroplets. *J. Am. Chem. Soc.* **2022**, *144* (43), 19709–19713.

(28) Lee, J. K.; Kim, S.; Nam, H. G.; Zare, R. N. Microdroplet fusion mass spectrometry for fast reaction kinetics. *Proc. Natl. Acad. Sci. U.S.A.* **2015**, *112* (13), 3898–3903.

(29) Zhang, X.; Pei, M.; Wu, D.; Yang, S.; Le, Z. Real-time monitoring of the reaction between aniline and acetonylacetone using extractive electrospray ionization tandem mass spectrometry. *Sci. Rep.* **2019**, *9* (1), 19279.

(30) Lalli, P. M.; Iglesias, B. A.; Toma, H. E.; de Sa, G. F.; Daroda, R. J.; Silva Filho, J. C.; Szulejko, J. E.; Araki, K.; Eberlin, M. N. Protomers: formation, separation and characterization via travelling wave ion mobility mass spectrometry. *J. Mass Spectrom.* **2012**, *47* (6), 712–719.