

Supporting Information

Accelerated Microdroplet Synthesis of Benzimidazoles by Nucleophilic Addition to Protonated Carboxylic Acids

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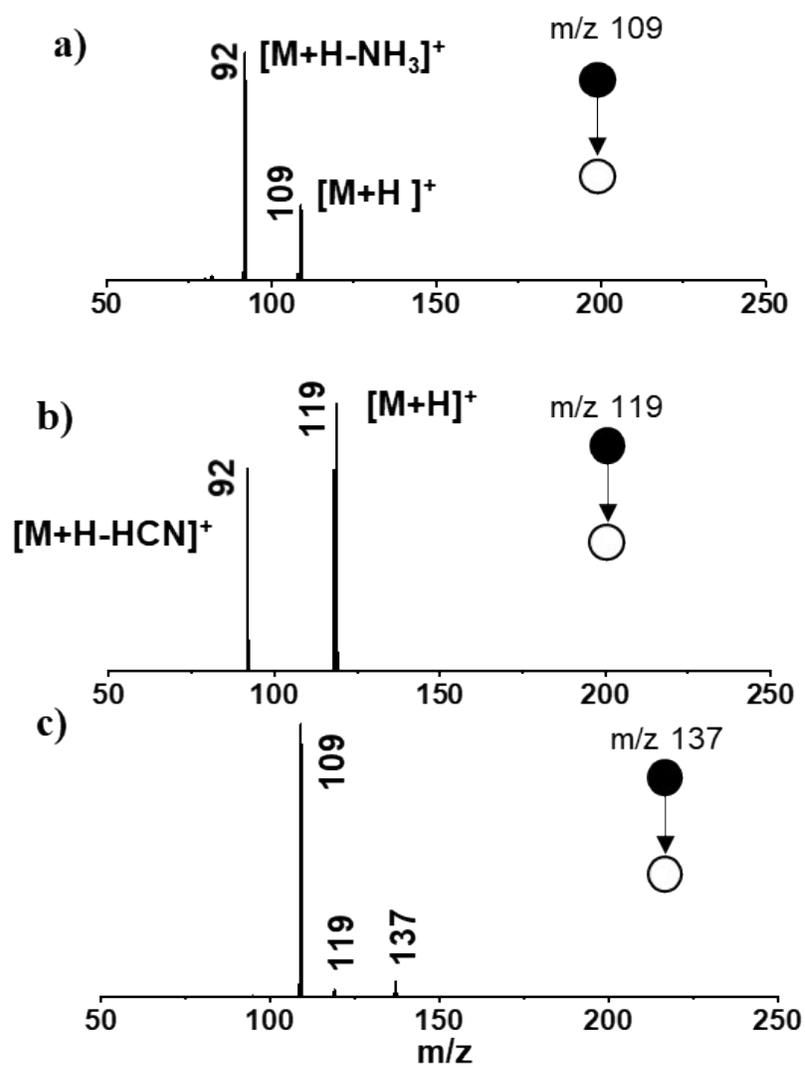


Figure S1. MS/MS spectra of (a) reagent peak at m/z 109, (b) product peak at m/z 119, and (c) intermediate peak at m/z 137 for nESI microdroplet synthesis in methanol.

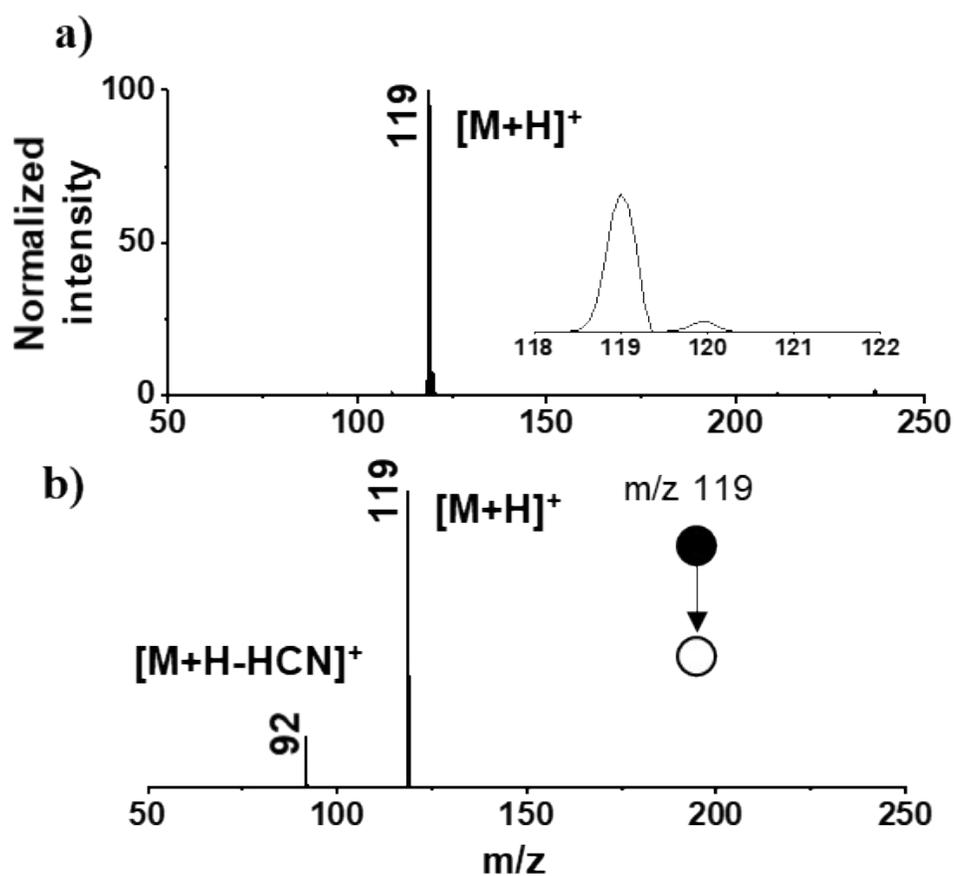


Figure S2. Mass spectra of benzimidazole standard. (a) Mass spectrum of 1 mM solution of benzimidazole in methanol. Inset shows the isotopic distribution of the peak. (b) MS/MS spectrum of protonated benzimidazole at m/z 119.

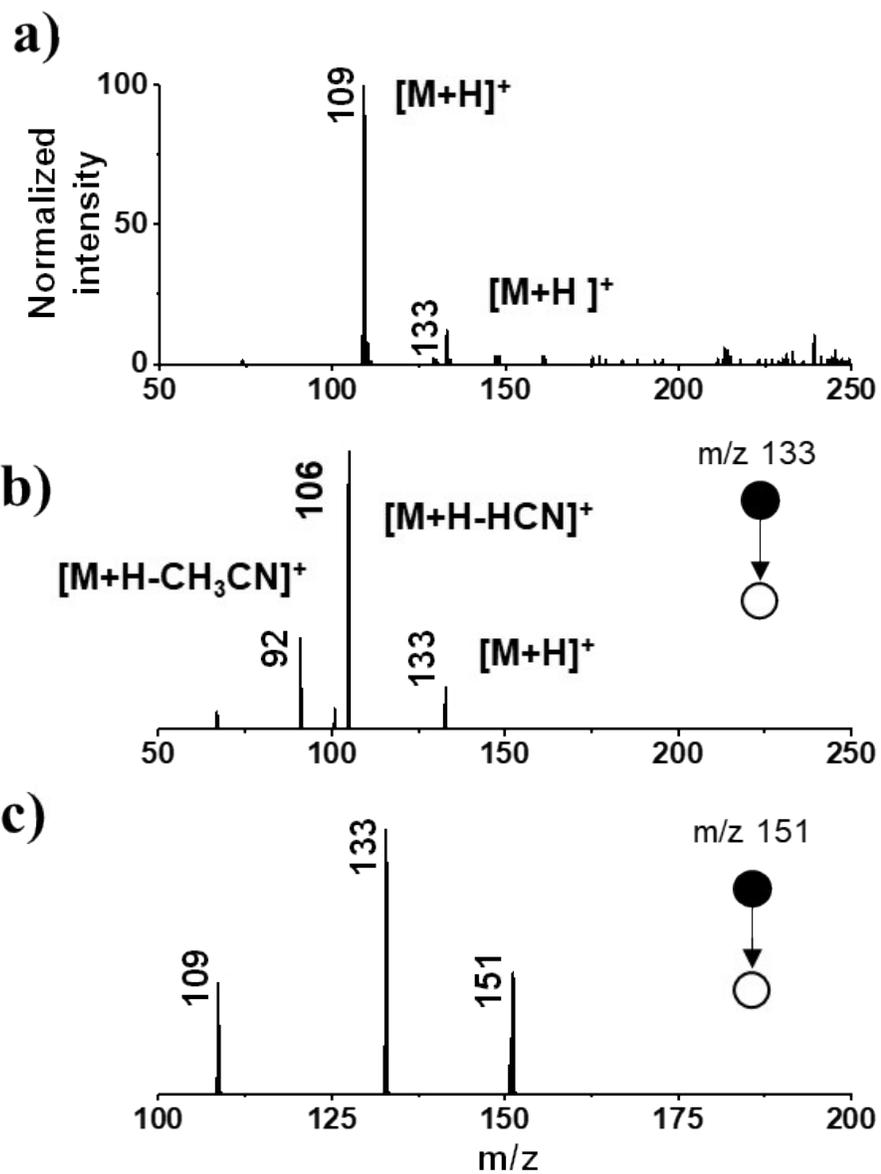


Figure S3. Microdroplet synthesis of 2-methylbenzimidazole. (a) Mass spectrum of the reaction mixture containing phenylenediamine (PDA) and acetic acid in methanol. The final concentration of the individual reagents is 8 mM. (b) MS/MS spectrum of the product at m/z 133 (c) MS/MS spectrum of intermediate at m/z 151.

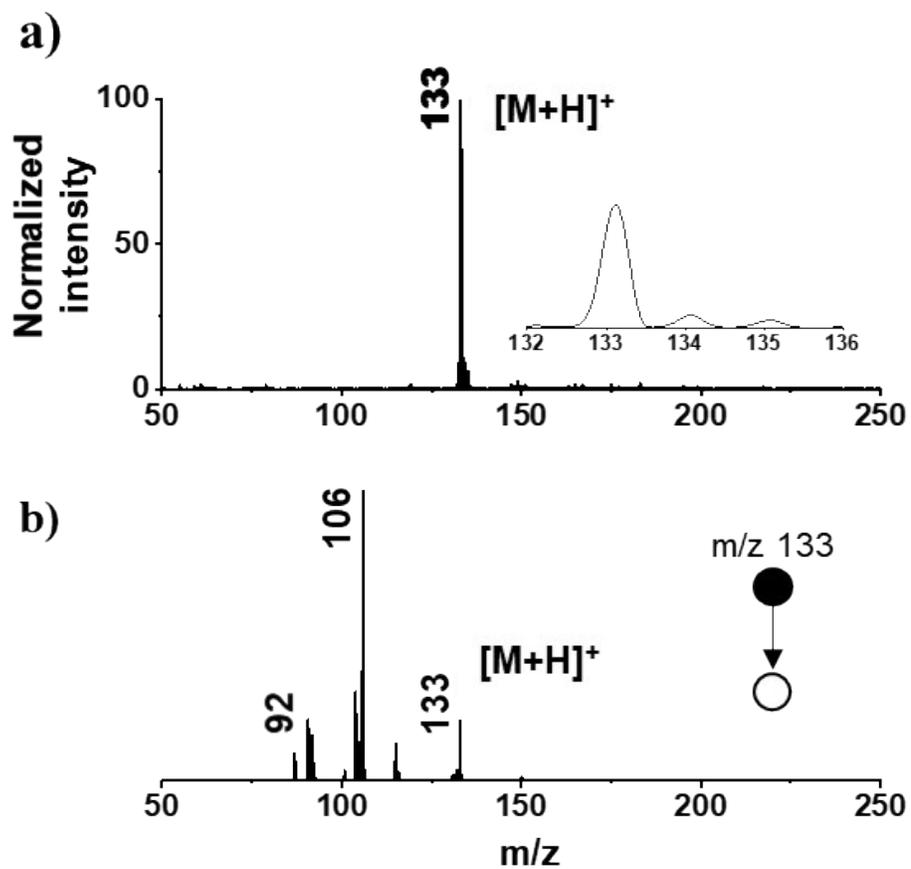


Figure S4. Mass spectra of 2-methylbenzimidazole standard. (a) Mass spectrum of 1 mM solution of 2-methylbenzimidazole in methanol. Inset shows the isotopic distribution. (b) MS/MS spectrum of protonated 2-methylbenzimidazole at m/z 133.

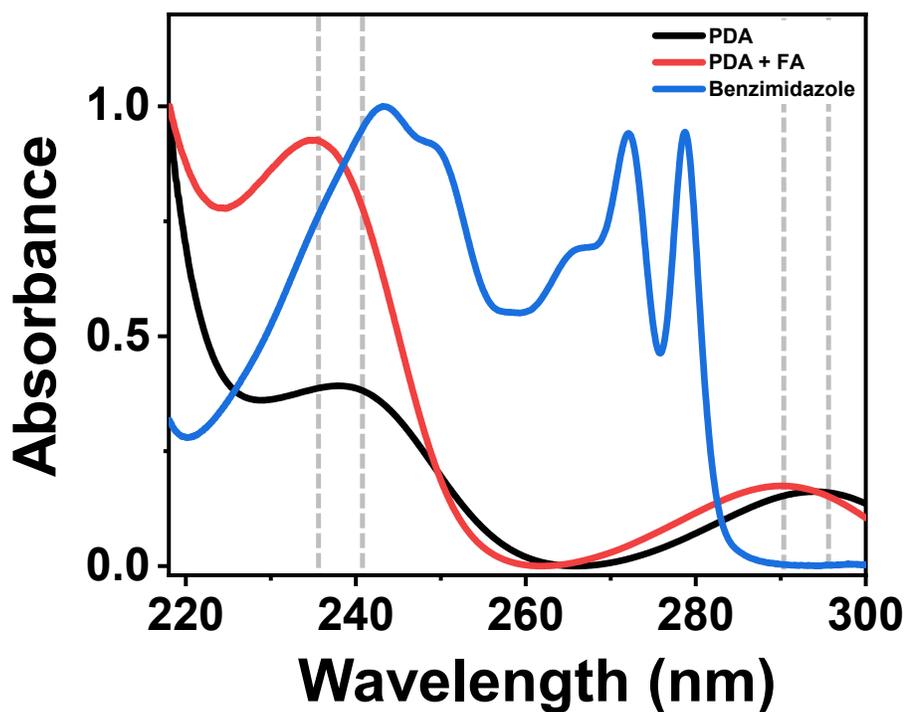


Figure S5. UV-vis spectra of *o*-phenylenediamine (black), reaction mixture for the synthesis of benzimidazole (red) and standard product (blue), all in methanol. The shift in the UV-vis spectra, as indicated by dotted lines, is due to the addition of formic acid and corresponds to Brønsted acid formation in solution by addition of a proton.

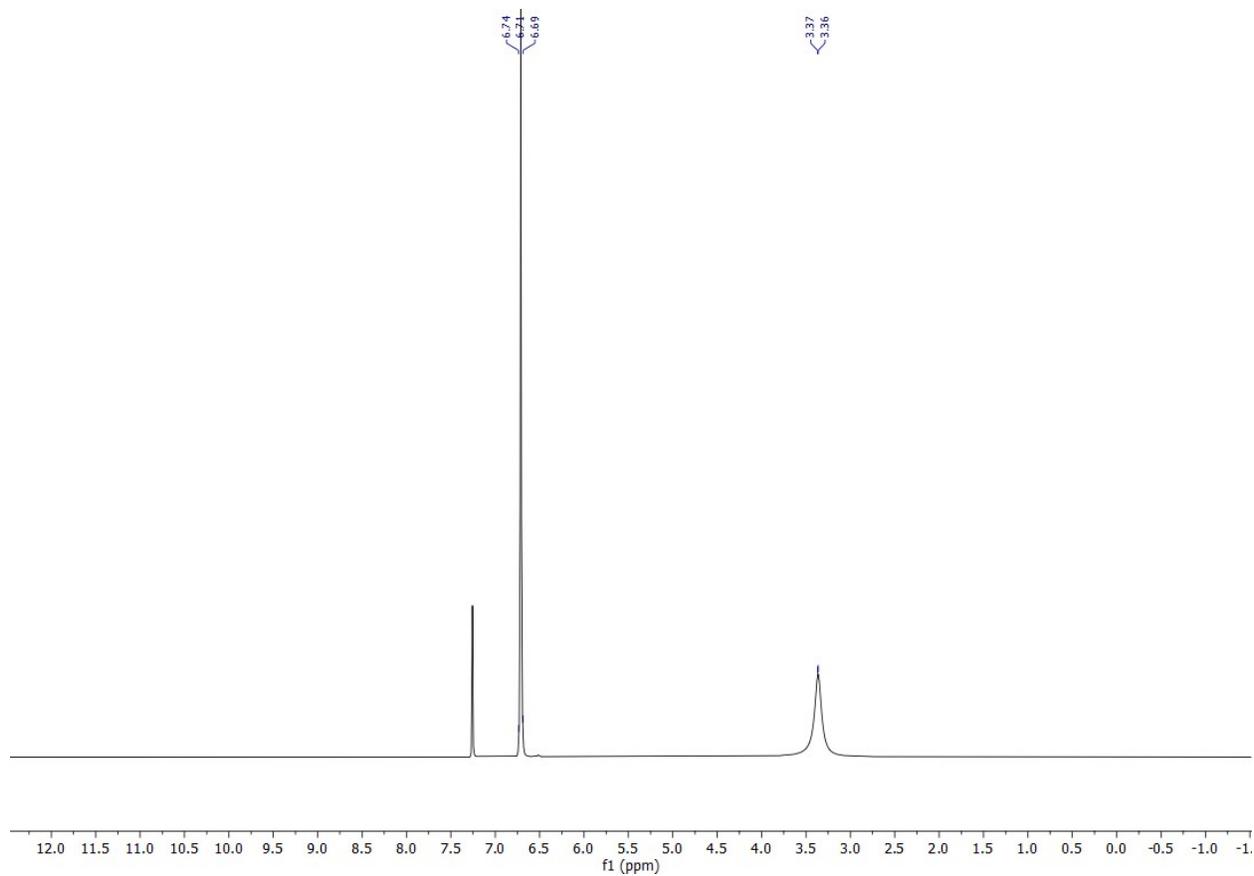


Figure S6. ¹H NMR data (400 MHz, CDCl₃) for *o*-phenylenediamine in CDCl₃. (· δ 6.71 (s, 1H), 3.49 – 3.23 (m, 1H). Solvent peak is observed at 7.26 ppm.

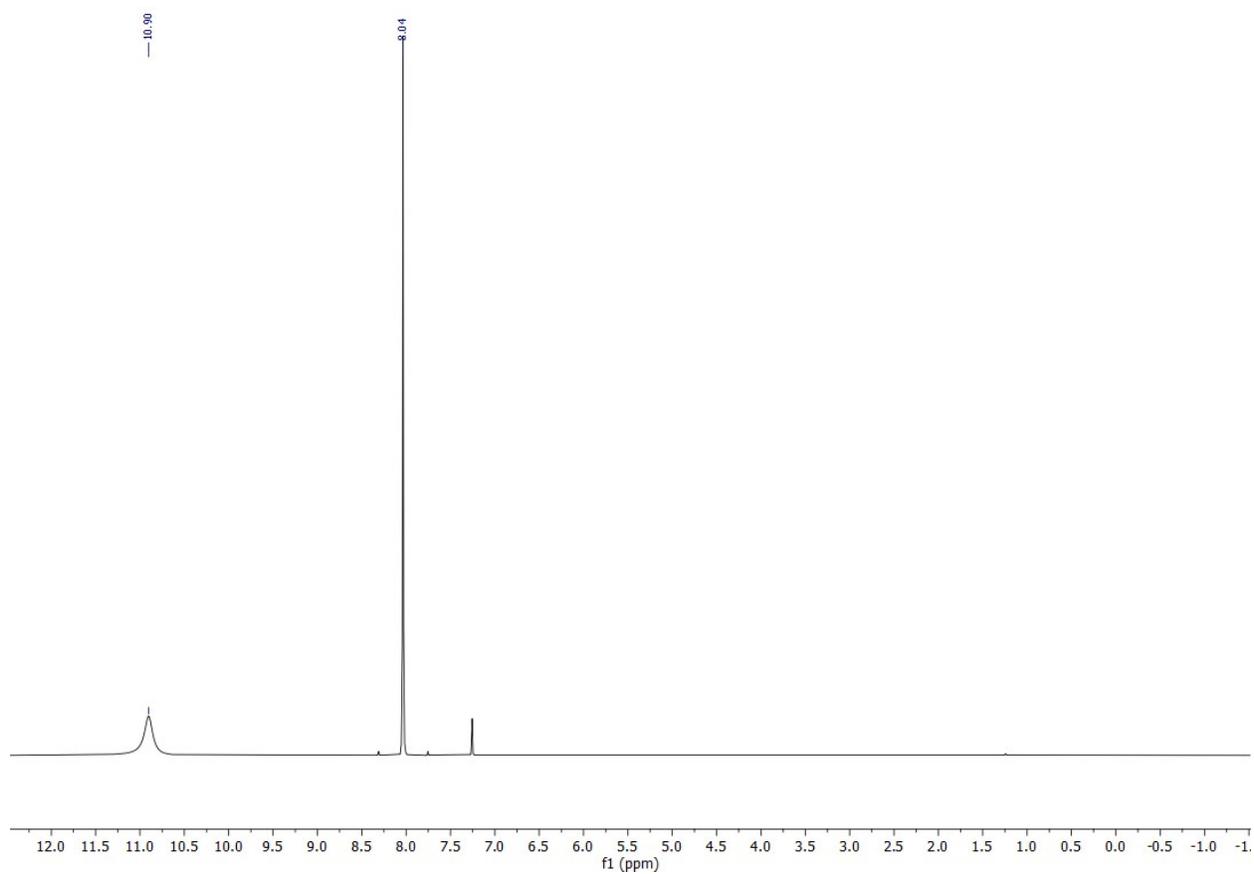


Figure S7. ^1H NMR data (400 MHz, CDCl_3) for formic acid. δ 10.90 (s, 1H), 8.04 (s, 1H). Solvent peak is observed at 7.26 ppm.

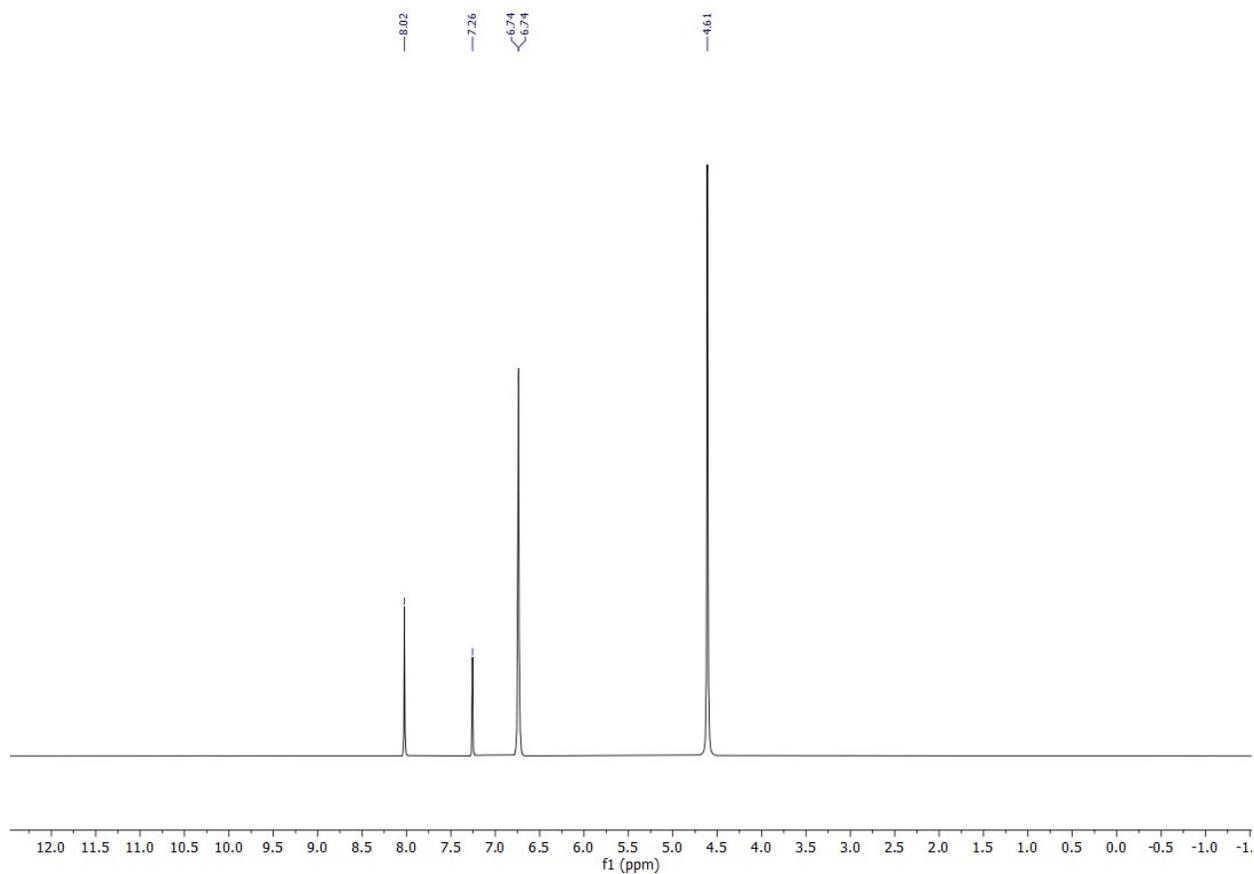


Figure S8. ¹H NMR data (400 MHz, CDCl₃) for a mixture of *o*-phenylenediamine and formic acid. δ 8.02 (s, 1H), 6.79 – 6.69 (m, 5H), 4.61 (s, 7H). Solvent peak is observed at 7.26 ppm.

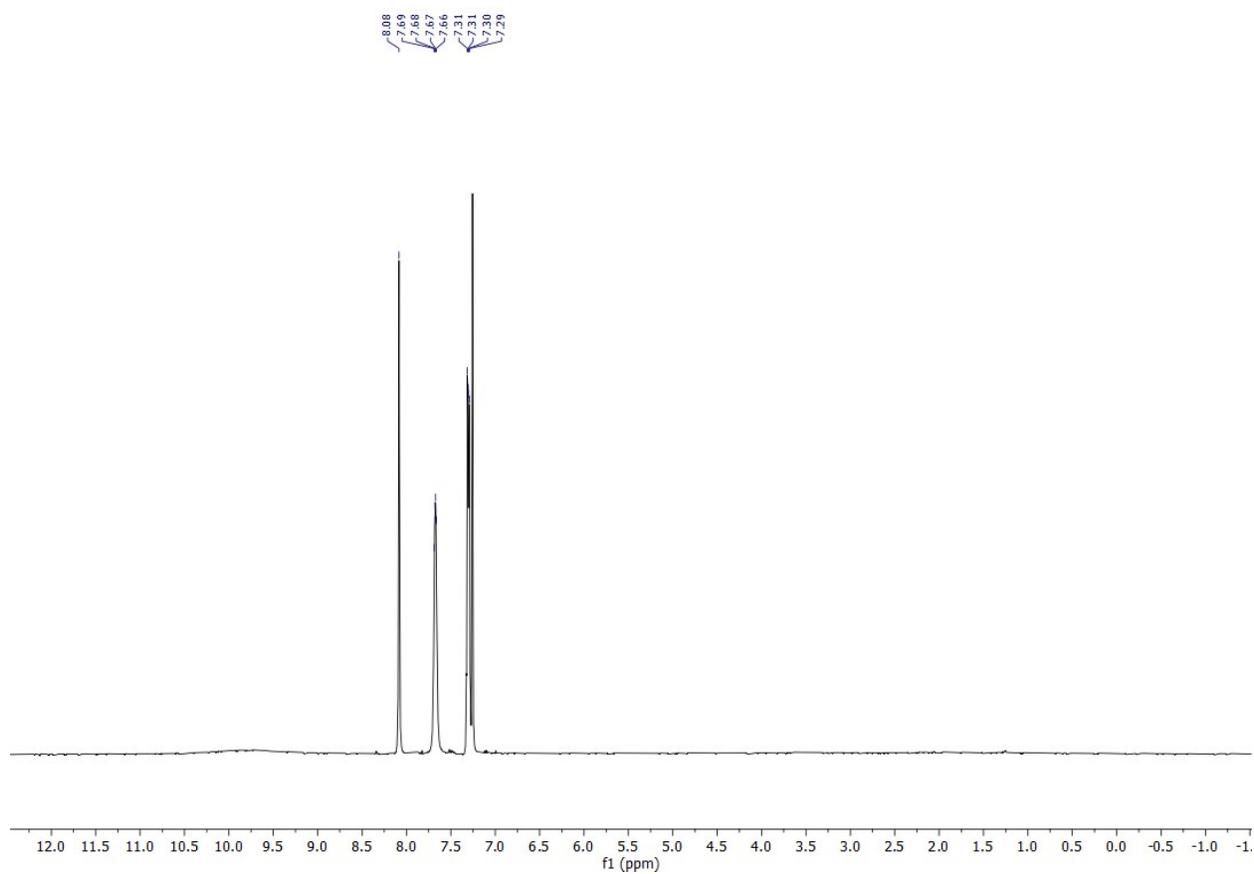


Figure S9. ¹H NMR data (400 MHz, CDCl₃) for benzimidazole standard. δ 8.08 (s, 1H), 7.71 – 7.64 (m, 2H), 7.31 (dt, J = 6.1, 3.6 Hz, 2H). Solvent peak is observed at 7.26 ppm.

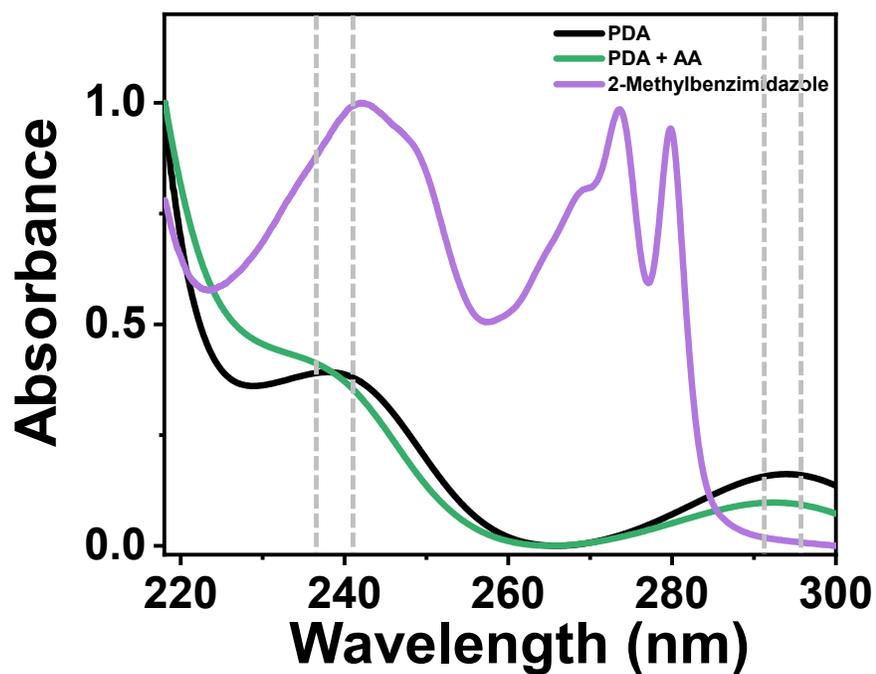


Figure S10. UV-vis spectra of *o*-phenylenediamine (black), its mixture with acetic acid (green) and standard 2-methylbenzimidazole (violet) in methanol.

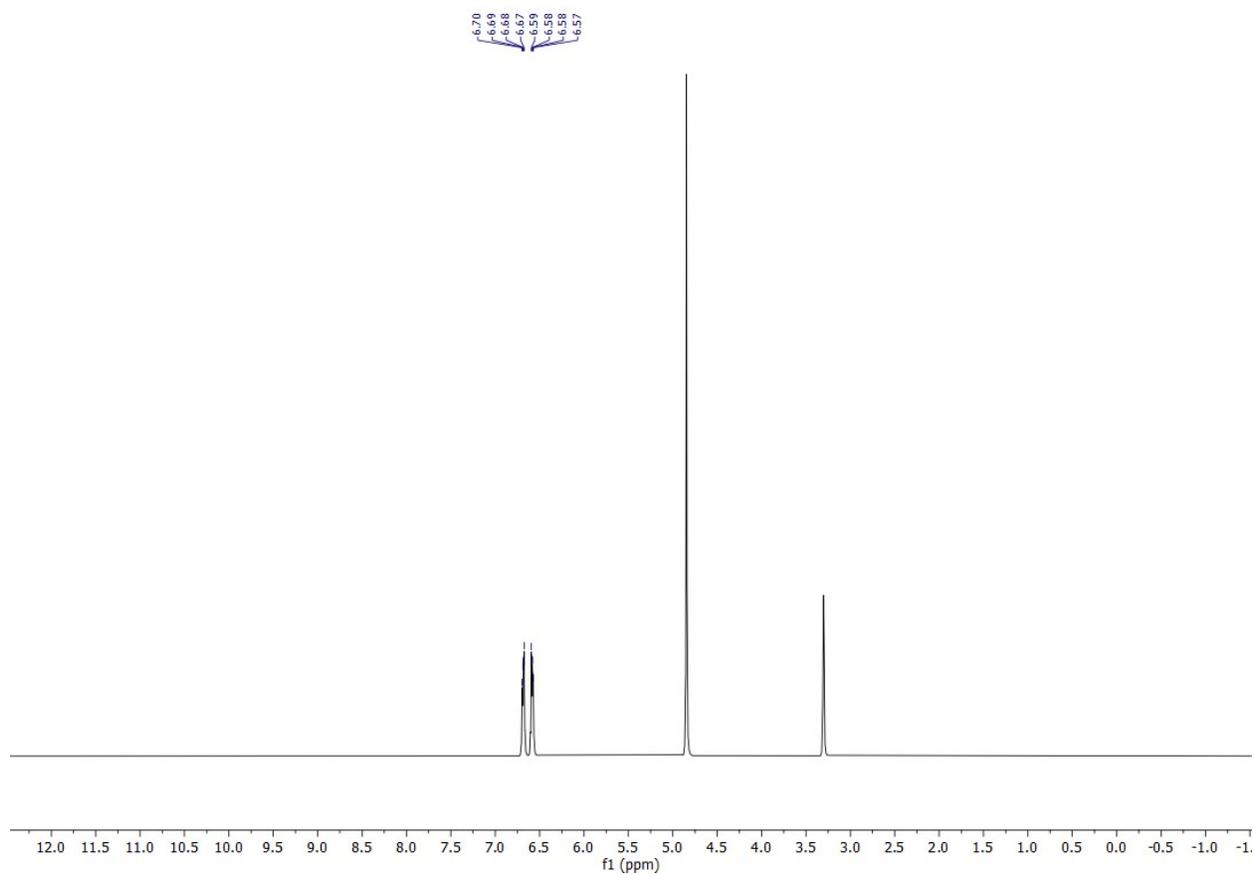


Figure S11. ¹H NMR data (400 MHz, CDCl₃) for *o*-phenylenediamine standard. δ 6.69 (dd, J = 5.7, 3.5 Hz, 1H), 6.58 (dd, J = 5.8, 3.4 Hz, 1H).

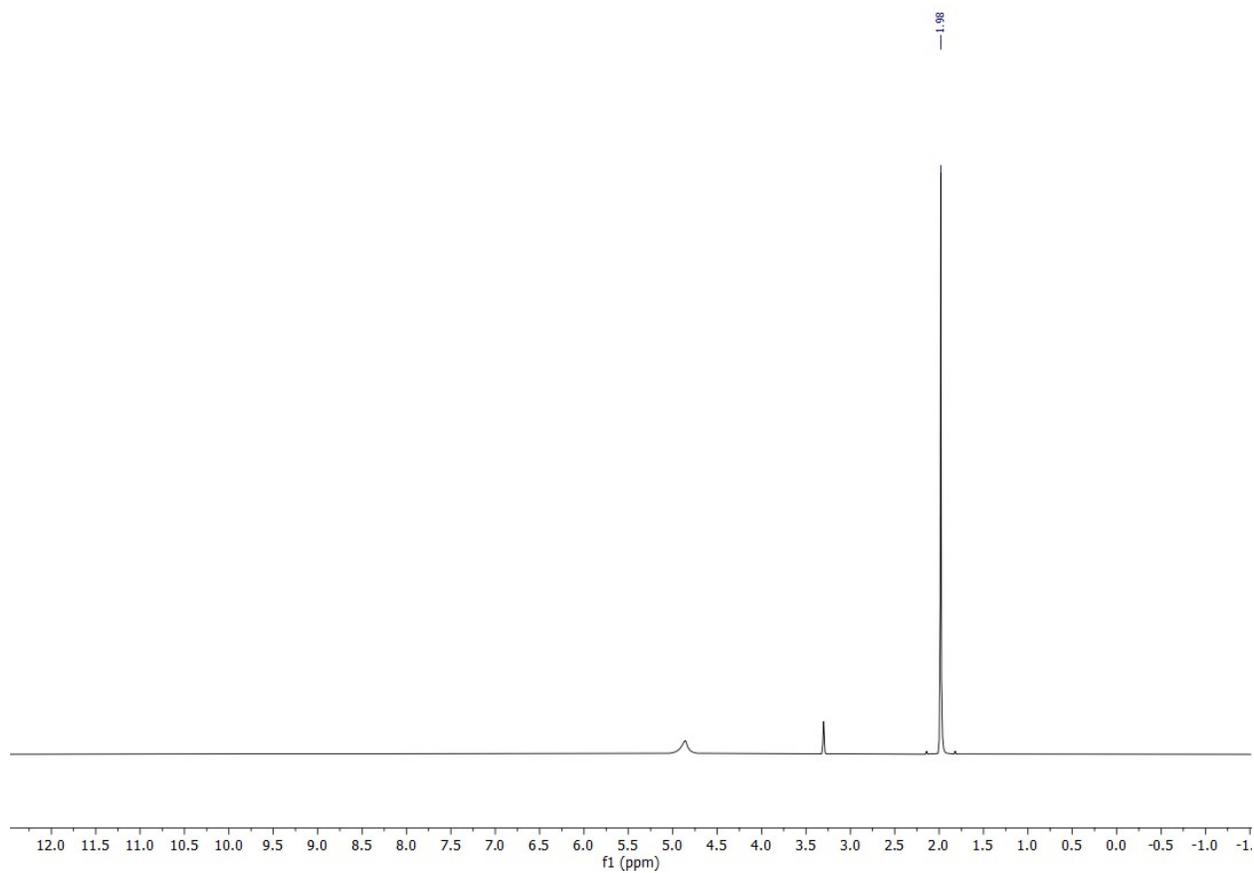


Figure S12. ^1H NMR data for acetic acid(400 MHz, MeOD) δ 1.98 (s, 1H). Peaks at 4.85 ppm and 3.30 ppm are solvent peaks.

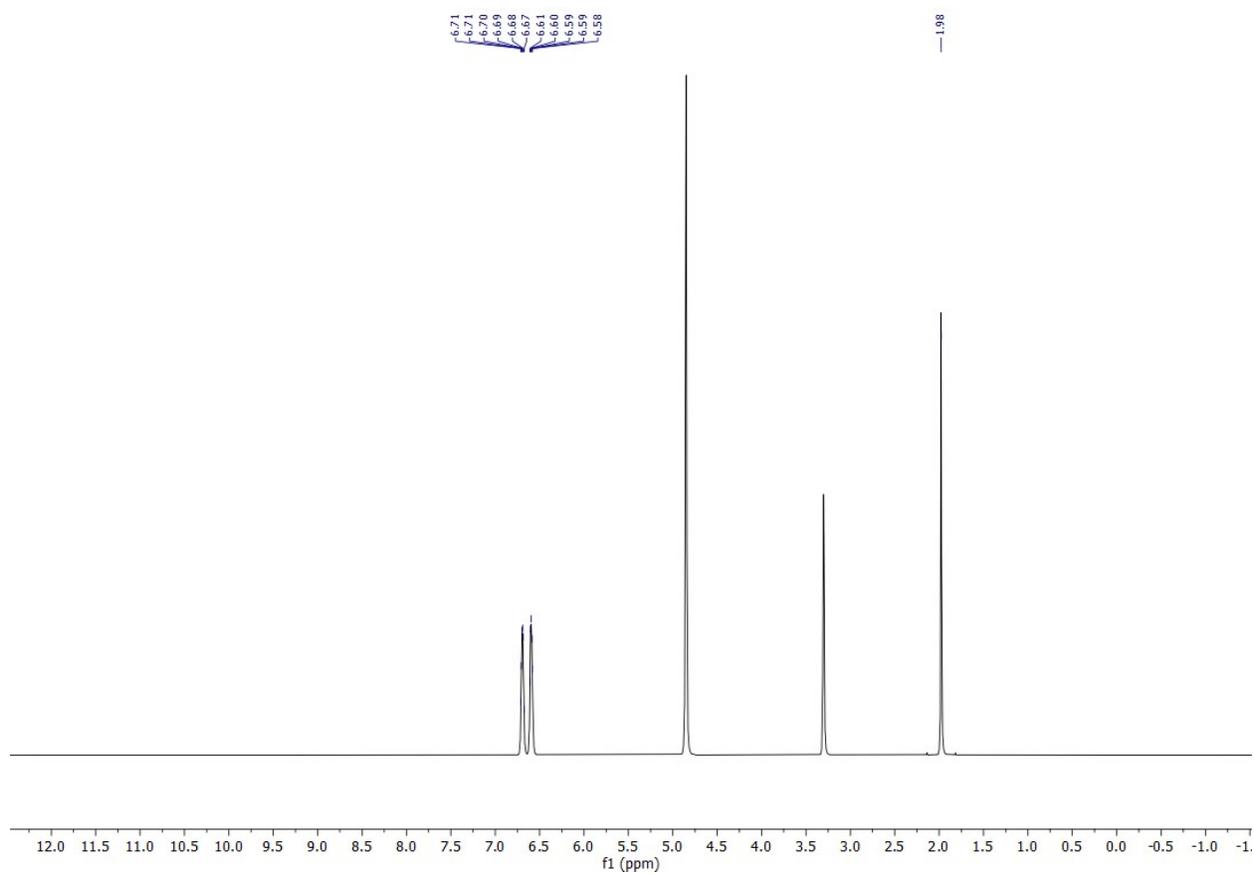


Figure S13. ¹H NMR data for mixture of *o*-phenylenediamine and acetic acid (400 MHz, MeOD) δ 6.69 (dq, $J = 6.4, 3.6, 3.0$ Hz, 1H), 6.59 (dt, $J = 5.8, 2.8$ Hz, 1H), 1.98 (s, 1H). Peaks at 4.85 ppm and 3.30 ppm are due to solvent.

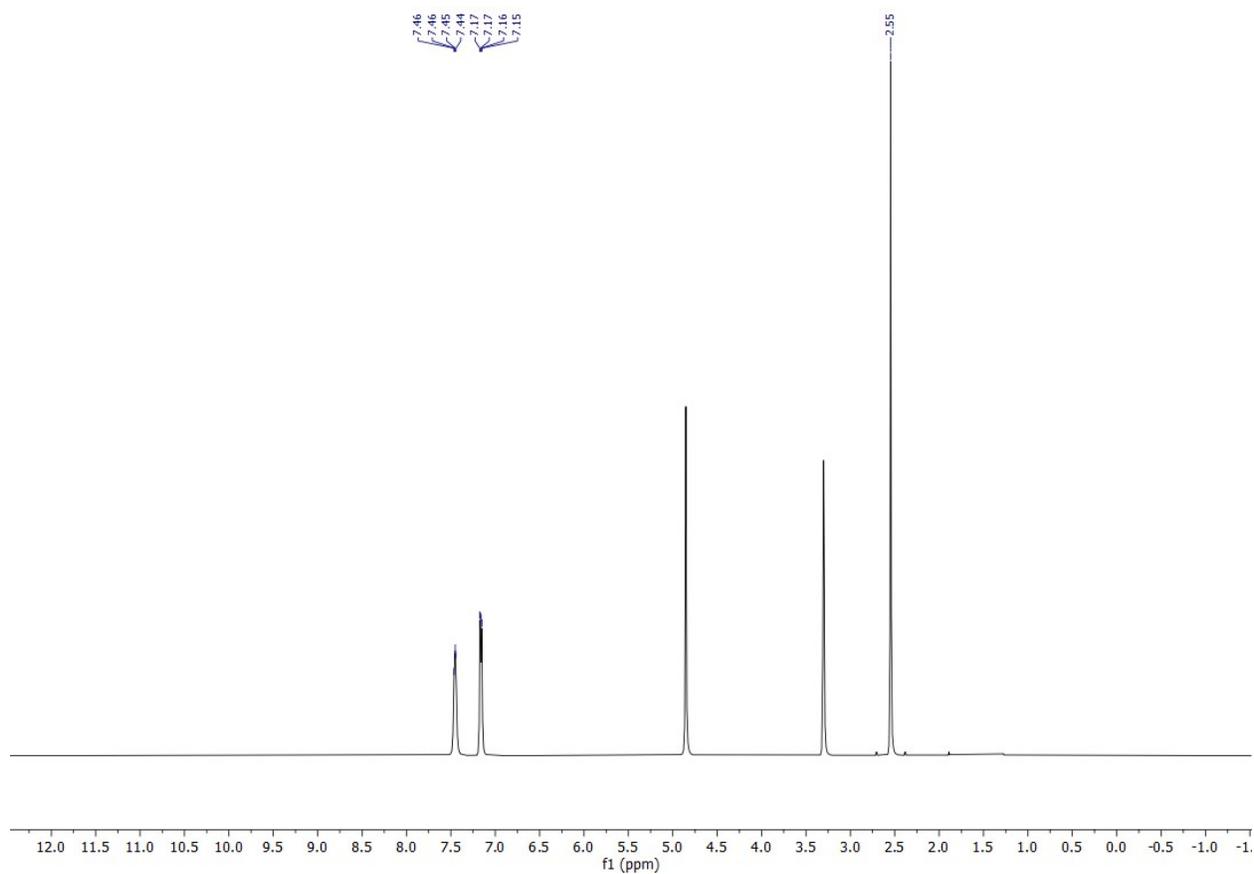


Figure S14. ^1H NMR data (400 MHz, MeOD) for 2-methylbenzimidazole standard. δ 7.51 – 7.37 (m, 1H), 7.16 (dd, $J = 6.0, 3.2$ Hz, 1H), 2.55 (s, 2H). Peaks at 4.85 ppm and 3.30 ppm are due to solvent.

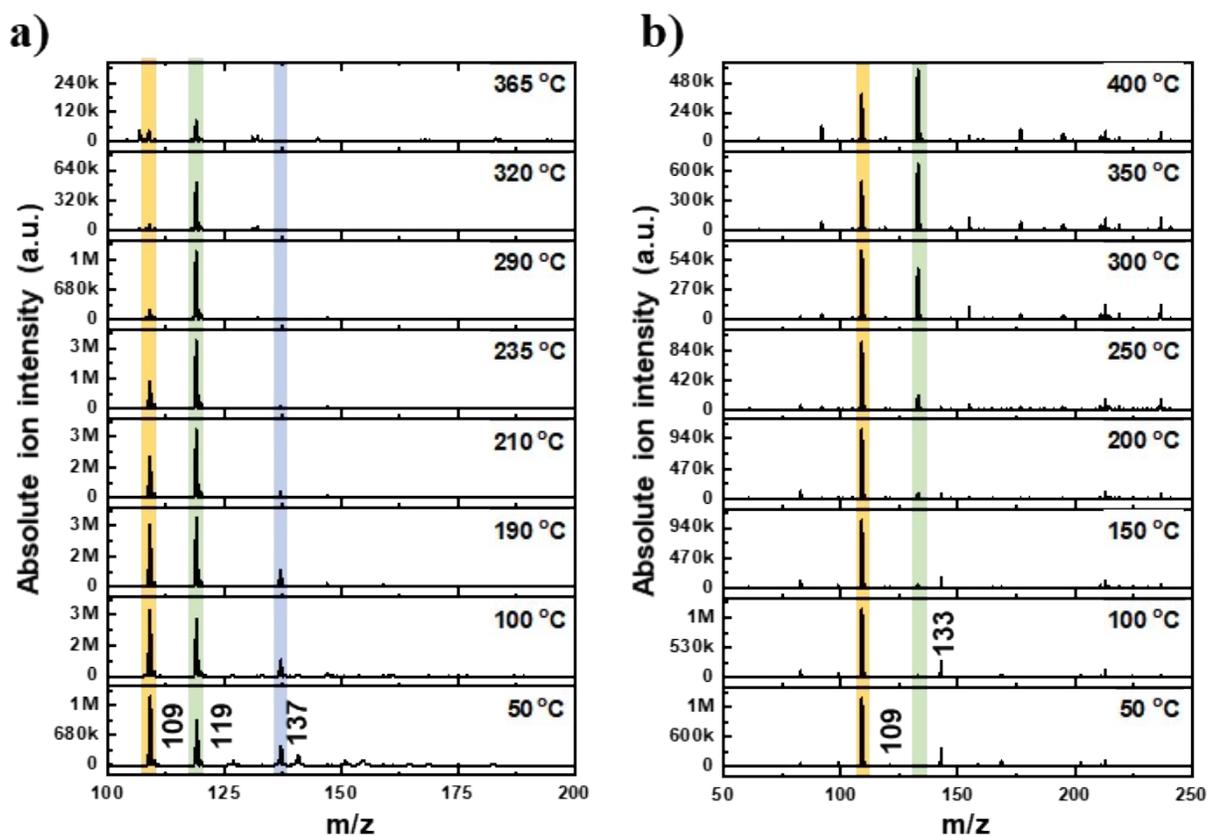


Figure S15. Temperature dependent mass spectra for microdroplet synthesis in methanol of a) benzimidazole and b) 2-methylbenzimidazole. The reagent peak at m/z 109, as indicated by yellow shading, decreases with increasing temperature, whereas, the product peaks at m/z 119 and m/z 133, as indicated by green shading, increase with increasing temperature.

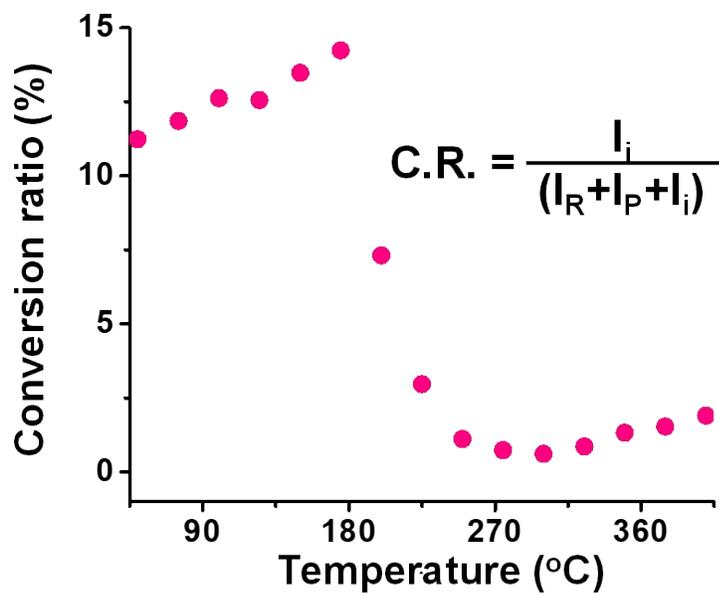


Figure S16. Conversion ratio versus temperature plot for the intermediate (m/z 137) in benzimidazole synthesis in methanol microdroplets. Inset shows the equation for conversion ratio.

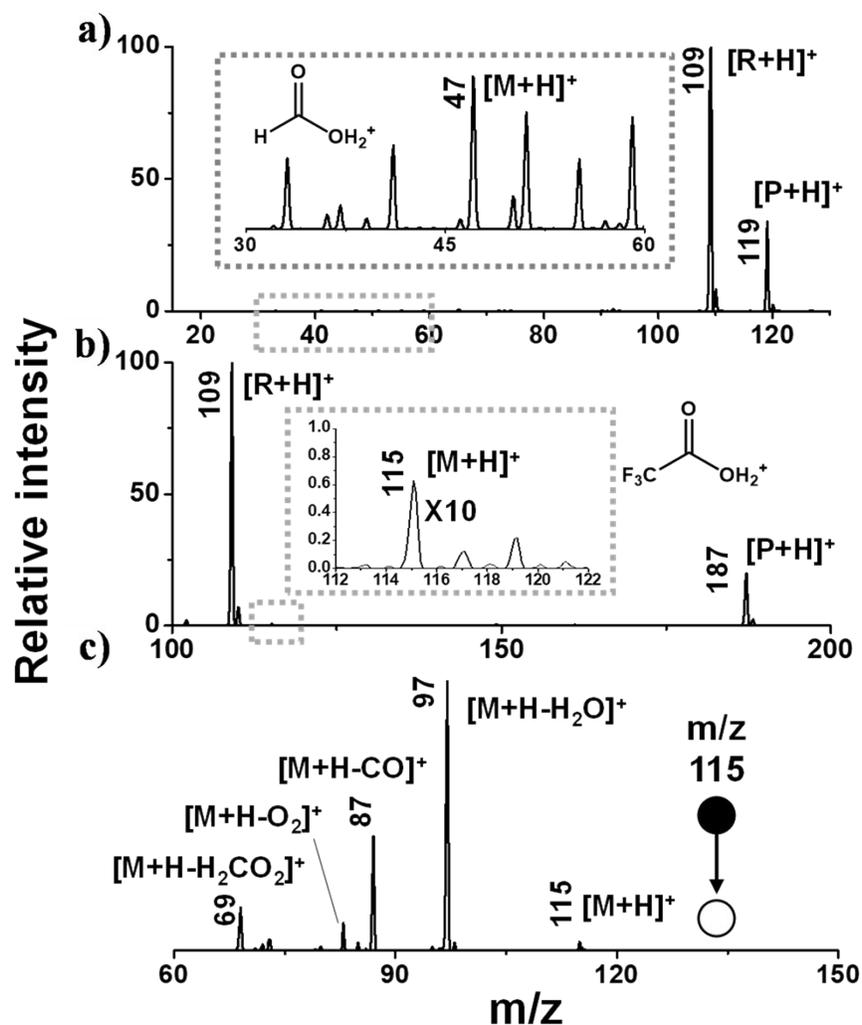


Figure S17. Mass spectra of reaction mixtures containing (a) o-phenylenediamine and formic acid (b) trifluoroacetic acid and (c) MS/MS spectrum of protonated trifluoroacetic acid. Zoom-in view of selected mass ranges in (a) and (b) showing peaks corresponding to protonated formic acid and trifluoroacetic acid. The solutions were prepared in HPLC grade methanol at 8 mM concentration.

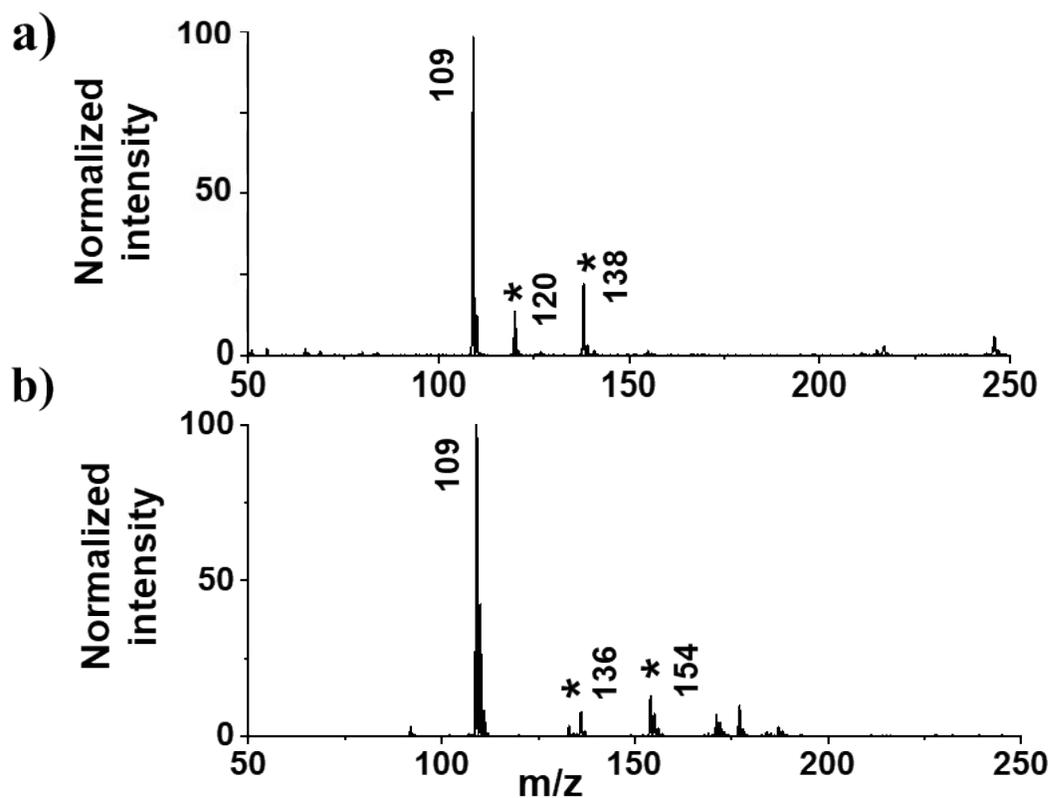


Figure S18. Isotope labeling experiments. Mass spectra showing reaction mixture for microdroplet reaction of phenylenediamine with (a) deuterated formic acid (DCOOH) and (b) acetic acid (CD₃COOH). The isotopically labeled product peaks are indicated with stars. The solvent used for the reaction is deuterated methanol. The temperature of the inlet was set to 50 °C for these experiments.

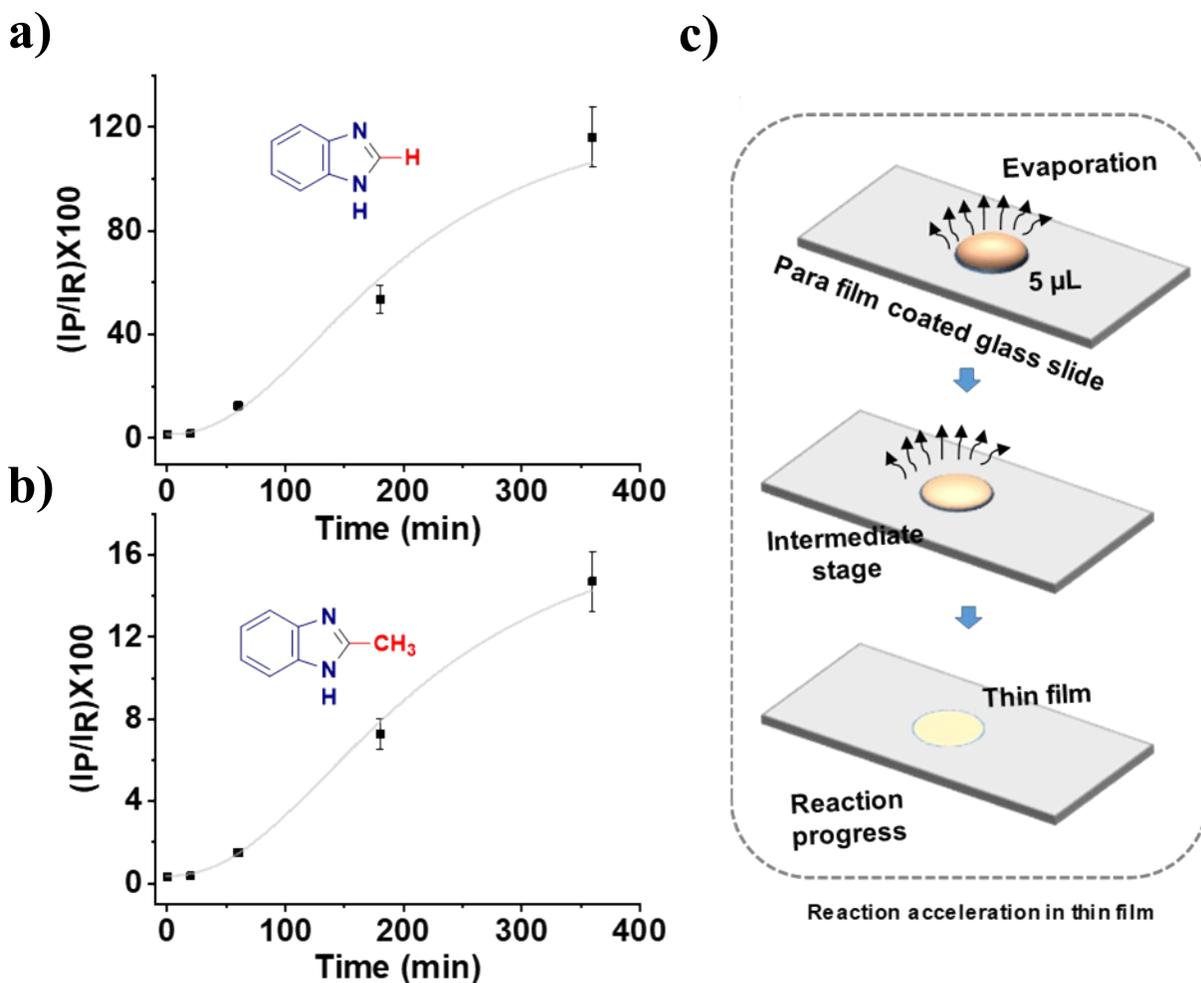


Figure S19. Ratio of product ion to reagent ion intensity for ambient thin film synthesis in methanol containing traces of *p*-toluenesulfonic acid to increase the lifetime of the fluid state for (a) benzimidazole and (b) 2-methylbenzimidazole. c) Schematic illustration of the thin film experiments from Z. Wei, M. Wleklinski, C. Ferreira and R. G. Cooks, *Angewandte Chemie International Edition*, 2017, **56**, 9386-9390. Note the induction period of some minutes while the methanol evaporates.

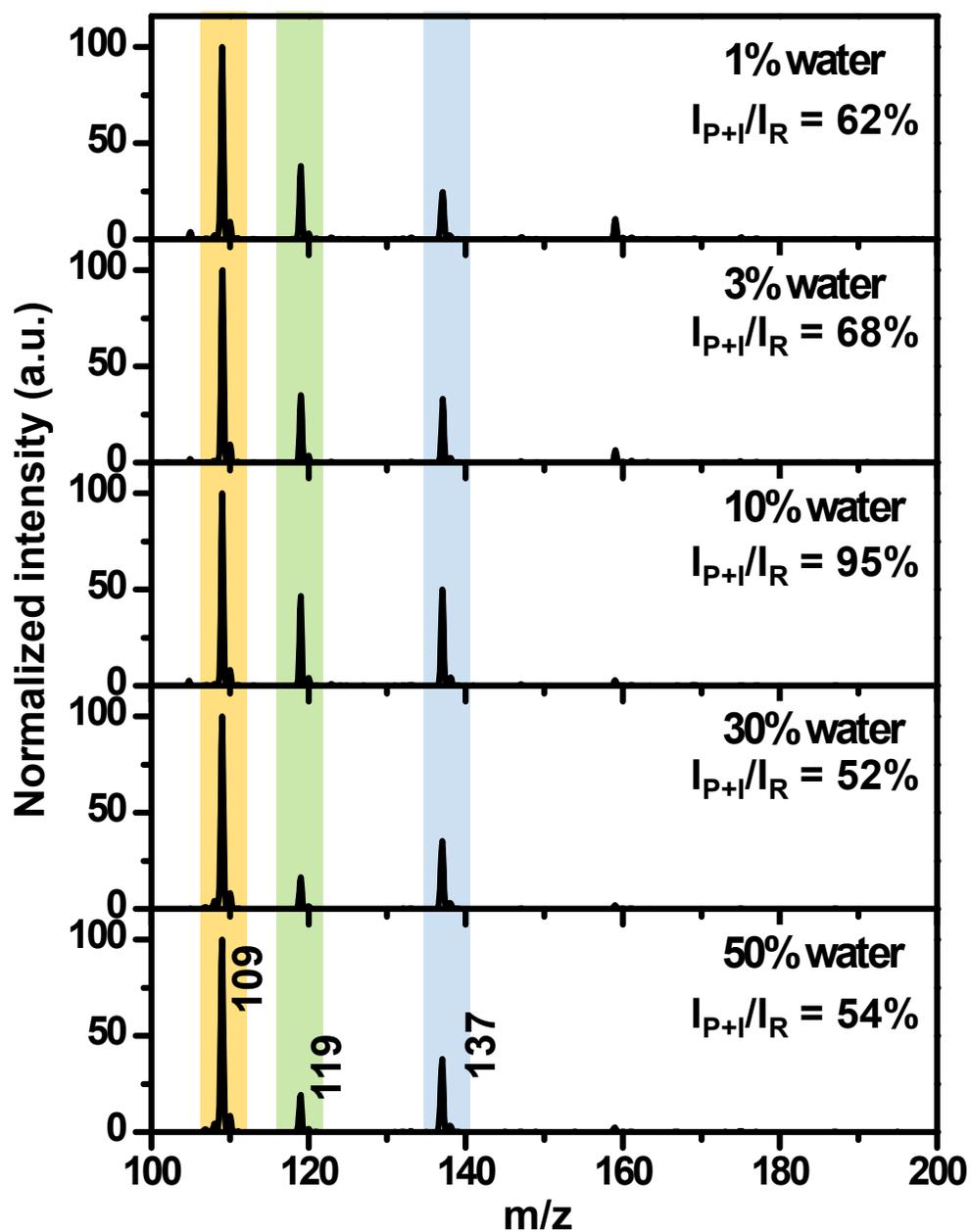


Figure S20. Benzimidazole reaction in presence of macroscopic amounts of water in methanol monitored by relative intensity of the product ion m/z 117 plus the intermediate ion m/z 137 vs. that of the reagent ion m/z 109. As the water concentration is increased up to 10%, we see increased product and intermediate formation. Above this concentration the relative product and intermediate intensities fall.

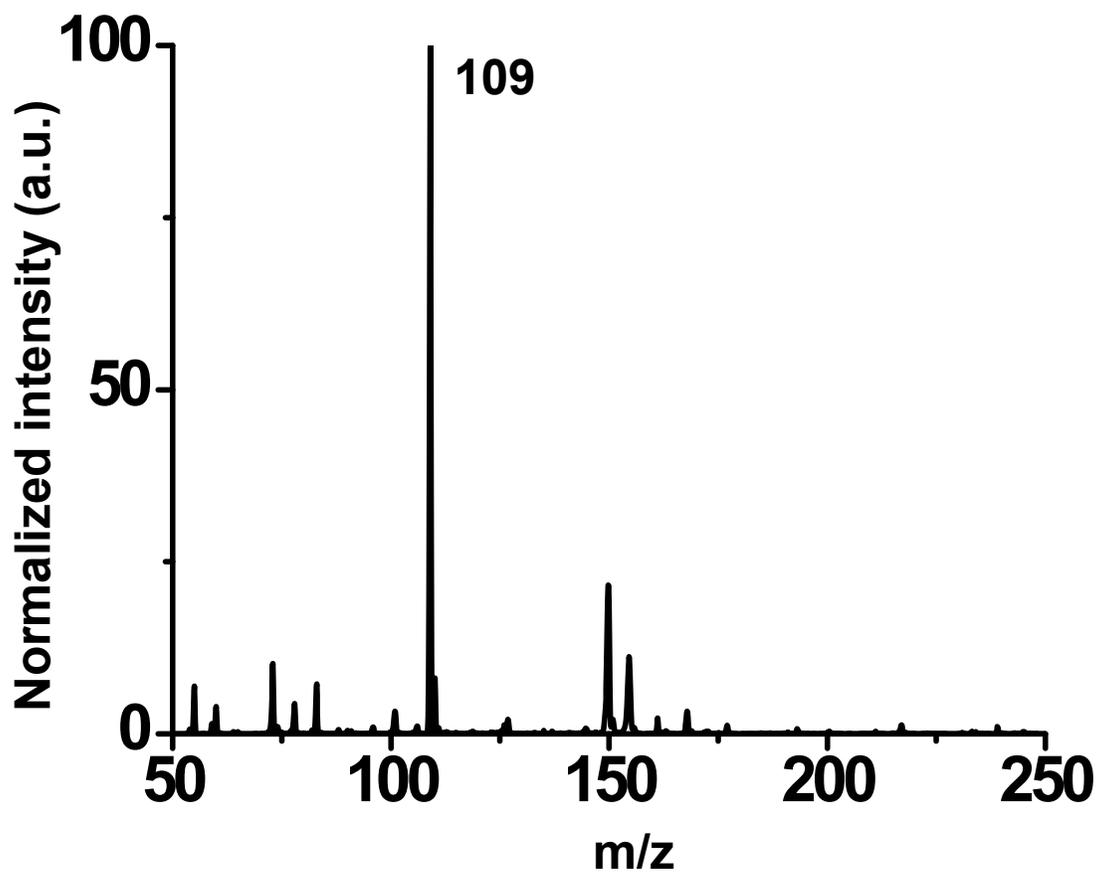


Figure S21. Benzimidazole reaction in dry ACN. Note the low signal (noise) and the absence of both product and intermediate ion signals. Other than the reagent signal, the peaks seen in the mass spectrum are from background.

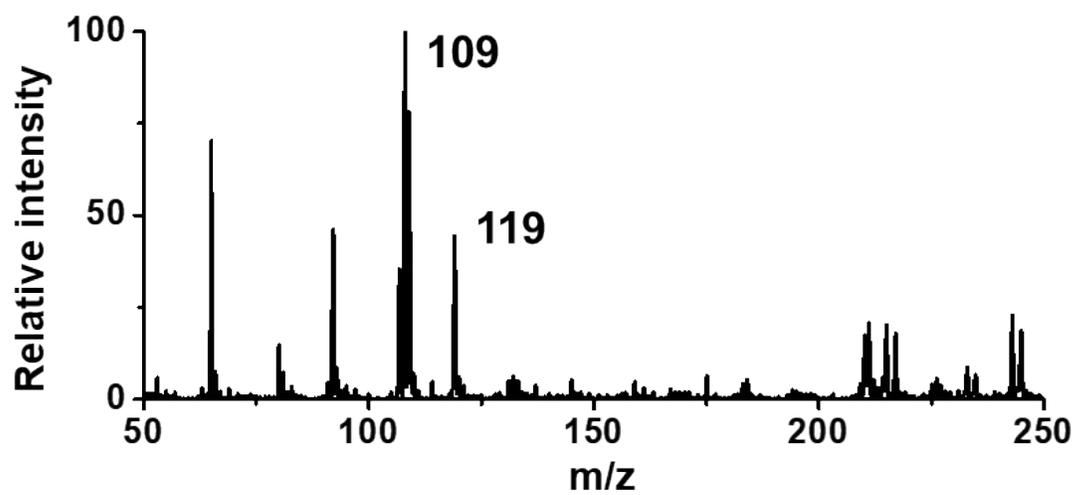


Figure S22. Mass spectrum of o-phenylenediamine/formic acid mixture in methanol in the presence of HCl. Concentrations of reactants and of HCl were 8 mM. Similar CRs were observed with and without HCl.

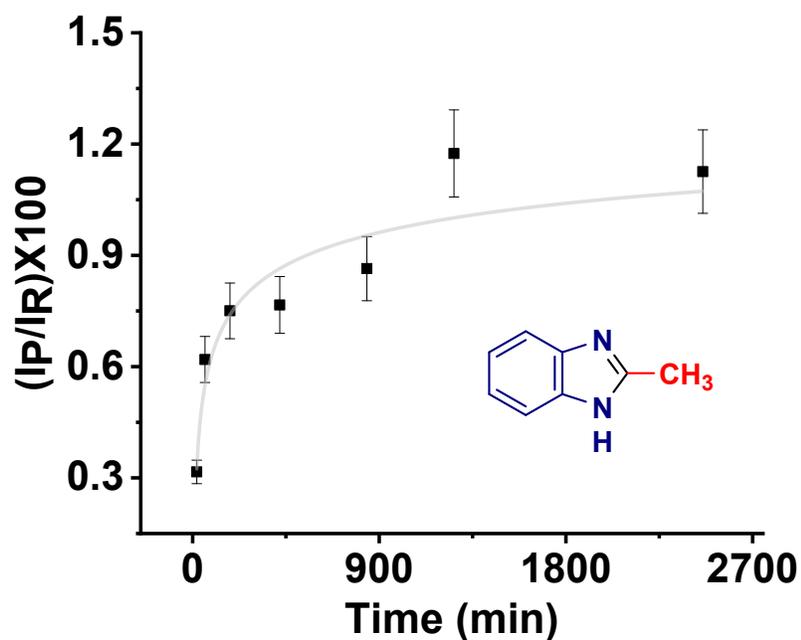


Figure S23. Product to reagent ion intensity ratio for the bulk reaction in methanol under ambient conditions for 2-methylbenzimidazole synthesis. Inset shows the molecular structure of the product. The starting concentration of each reagent in methanol was e 8 mM. The reaction was performed in a closed 500 mL round bottom flask and MS analysis was done using 50 °C inlet temperature to avoid reaction acceleration during bulk product analysis.

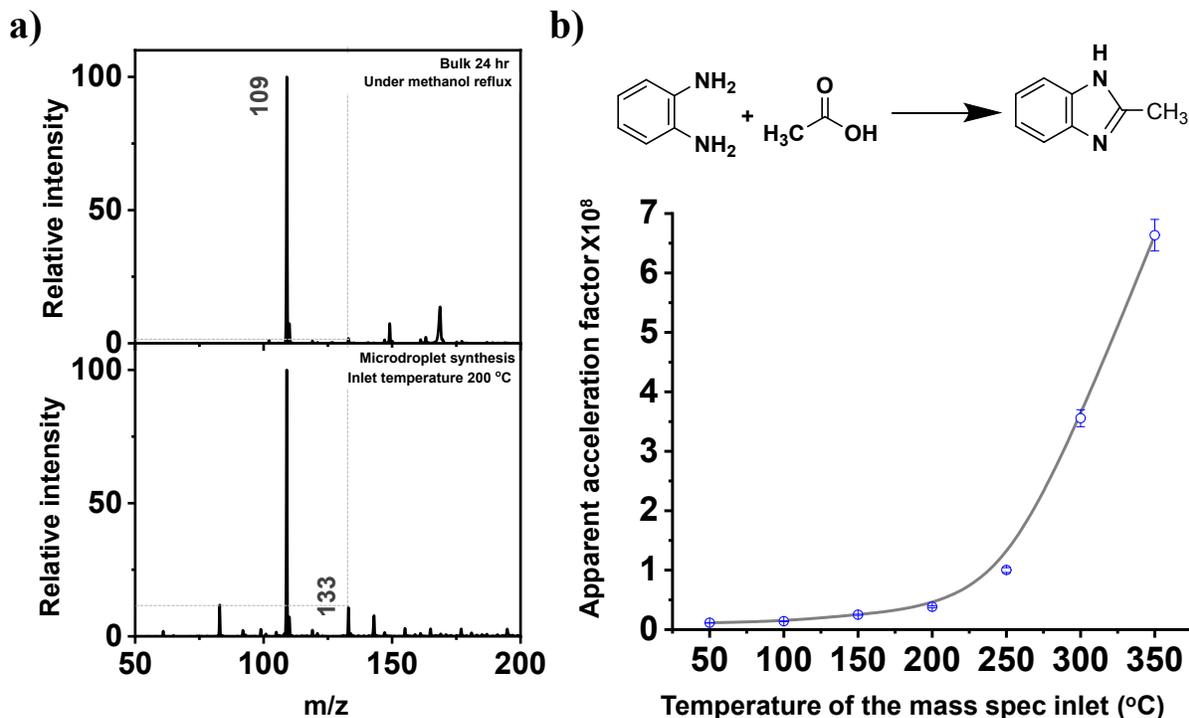


Figure S24. Effect of inlet temperature on accelerated formation of 2-methylbenzimidazole (m/z 133) from phenylenediamine (m/z 109). (a) Comparison of mass spectrum of bulk reaction mixture after 24 h under methanol reflux with that for microdroplet synthesis at 200 °C inlet temperature. (b) Temperature of MS inlet vs. apparent reaction rate acceleration factor. Inset shows the reaction scheme. Apparent acceleration factor considered the difference in reaction time of the droplet and bulk reactions. Note that the bulk reaction analysis was performed at constant 50 °C inlet temperature to avoid reaction acceleration during the analysis.

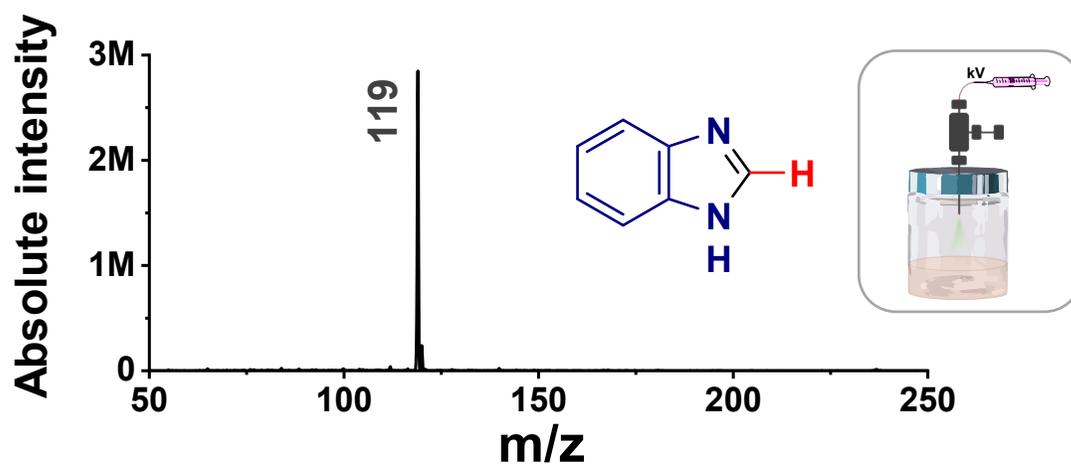


Figure S25. Mass spectrum of the isolated product after benzimidazole synthesis in methanol by spray deposition with a diagram that depicts the spray deposition reaction setup. The crude mixture was separated using flash column chromatography. Yield was determined to be about 72%.

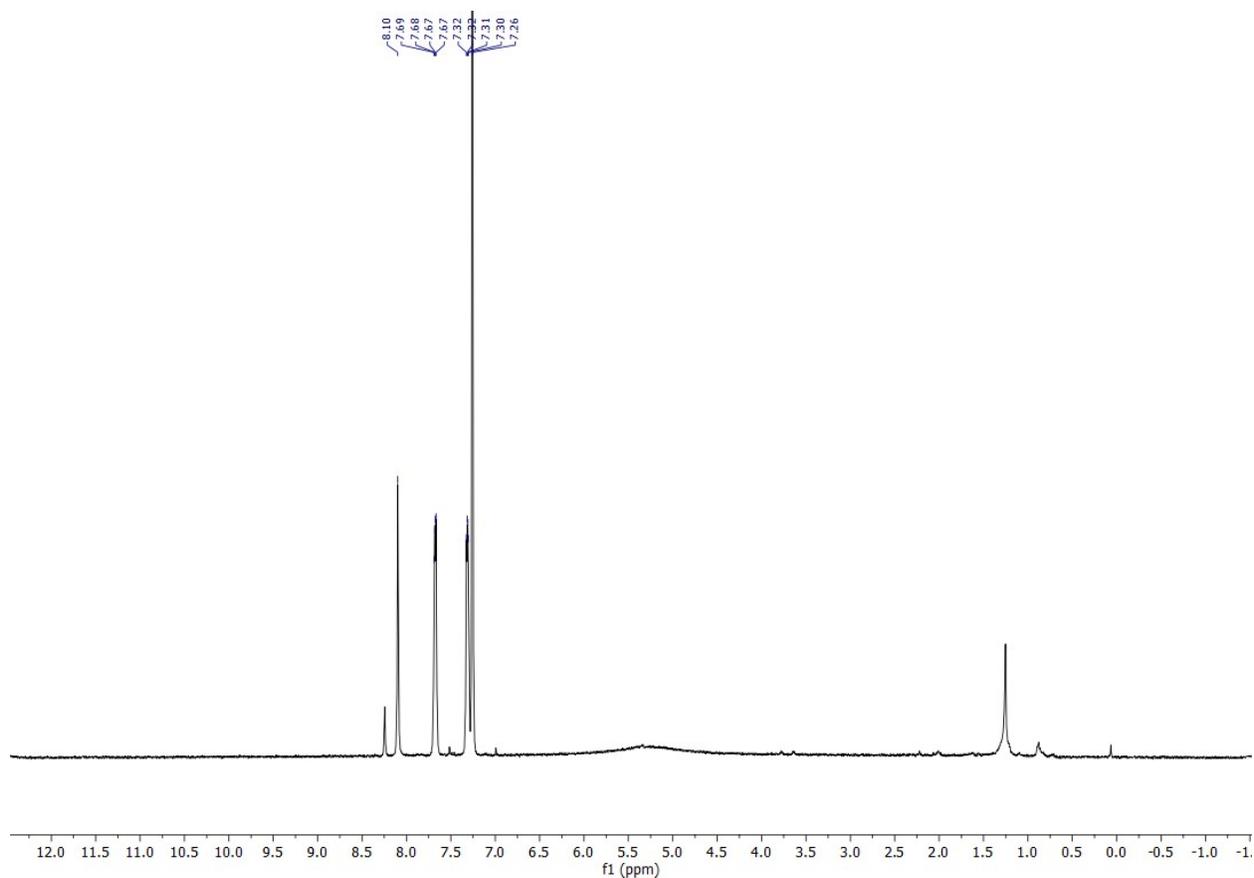


Figure S26. ^1H NMR (400 MHz, CDCl_3) of the isolated product from the deposited sample in benzimidazole spray deposition synthesis. δ 8.24 (s, 1H), 8.10 (s, 6H), 7.68 (dd, $J = 6.1, 3.2$ Hz, 11H), 7.31 (dd, $J = 6.1, 3.2$ Hz, 11H), 7.26 (s, 18H), 1.25 (s, 5H). Peak at 7.26ppm is the solvent peak and 8.24ppm peak is an impurity.

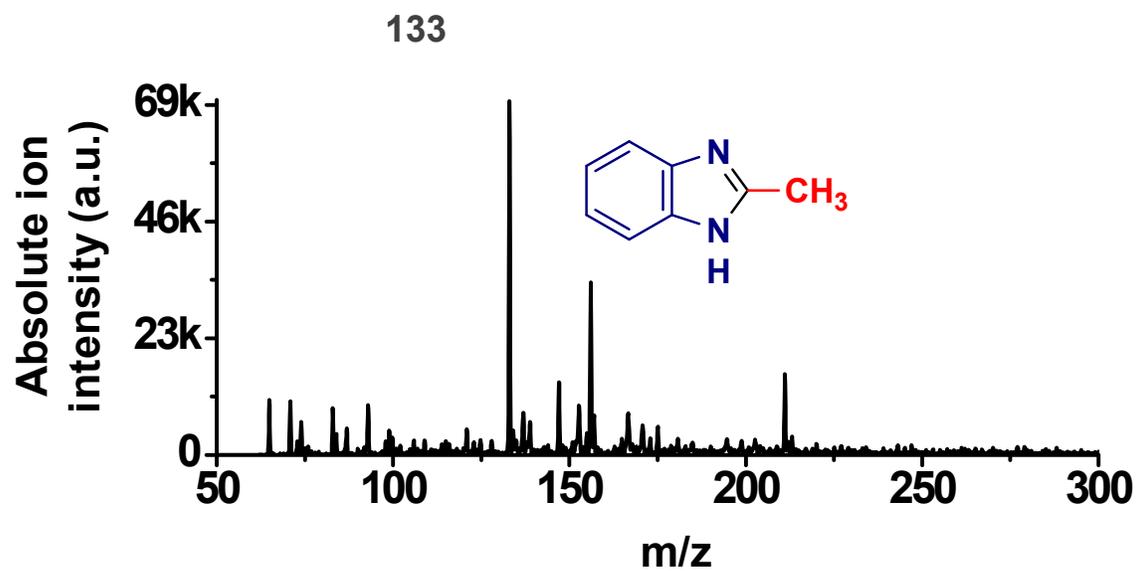


Figure S27. Mass spectrum of the isolated product of the deposited sample for the 2-benzimidazole spray synthesis. Low isolated yield resulted in noise in the mass spectrum.

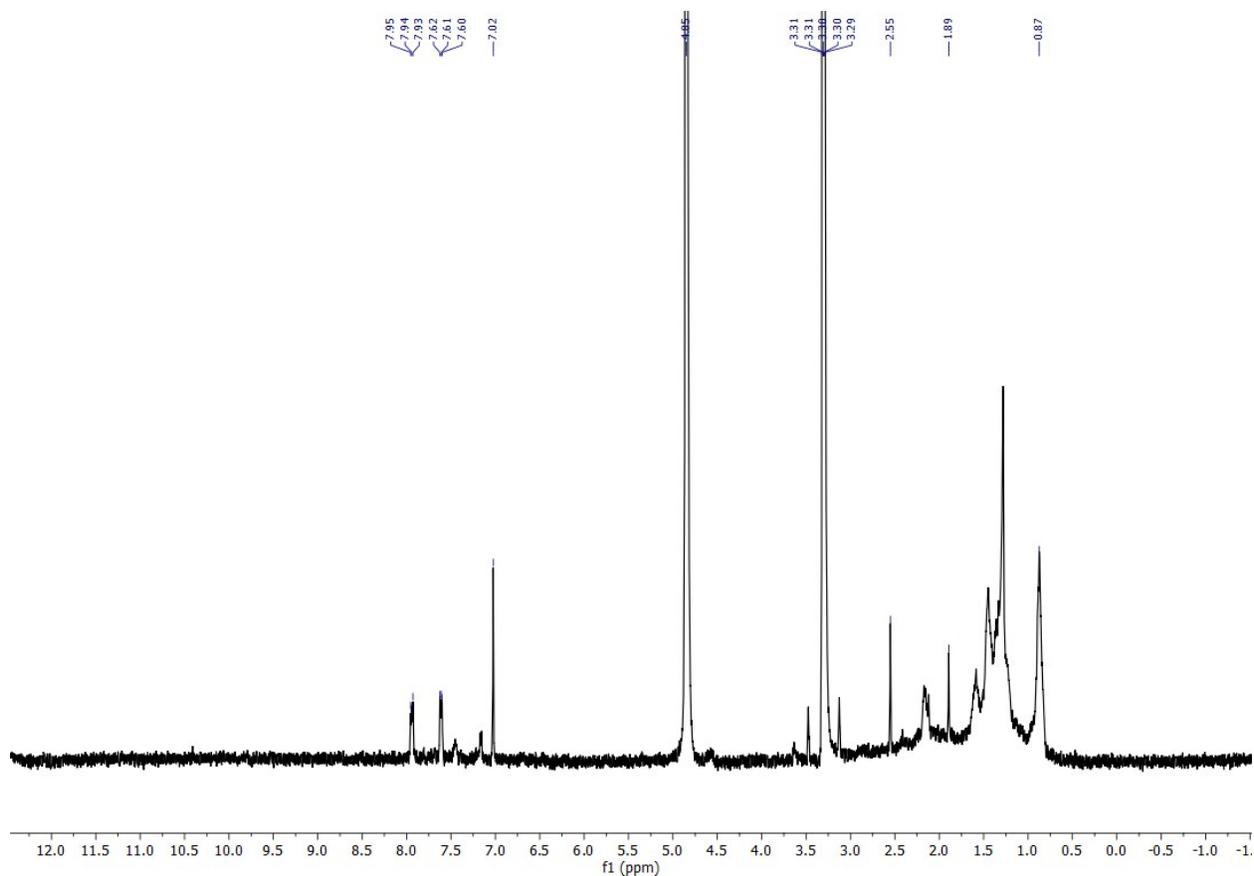


Figure S28. ¹H NMR (400 MHz, MeOD) for the isolated product of the deposited sample from the 2-methylbenzimidazole spray synthesis. δ 7.96 – 7.91 (m, 2H), 7.65 – 7.58 (m, 1H), 7.02 (s, 2H), 2.55 (s, 1H). Peaks at 4.85 and 3.29-3.31 ppm are solvent peaks while other minor peaks are from impurities.

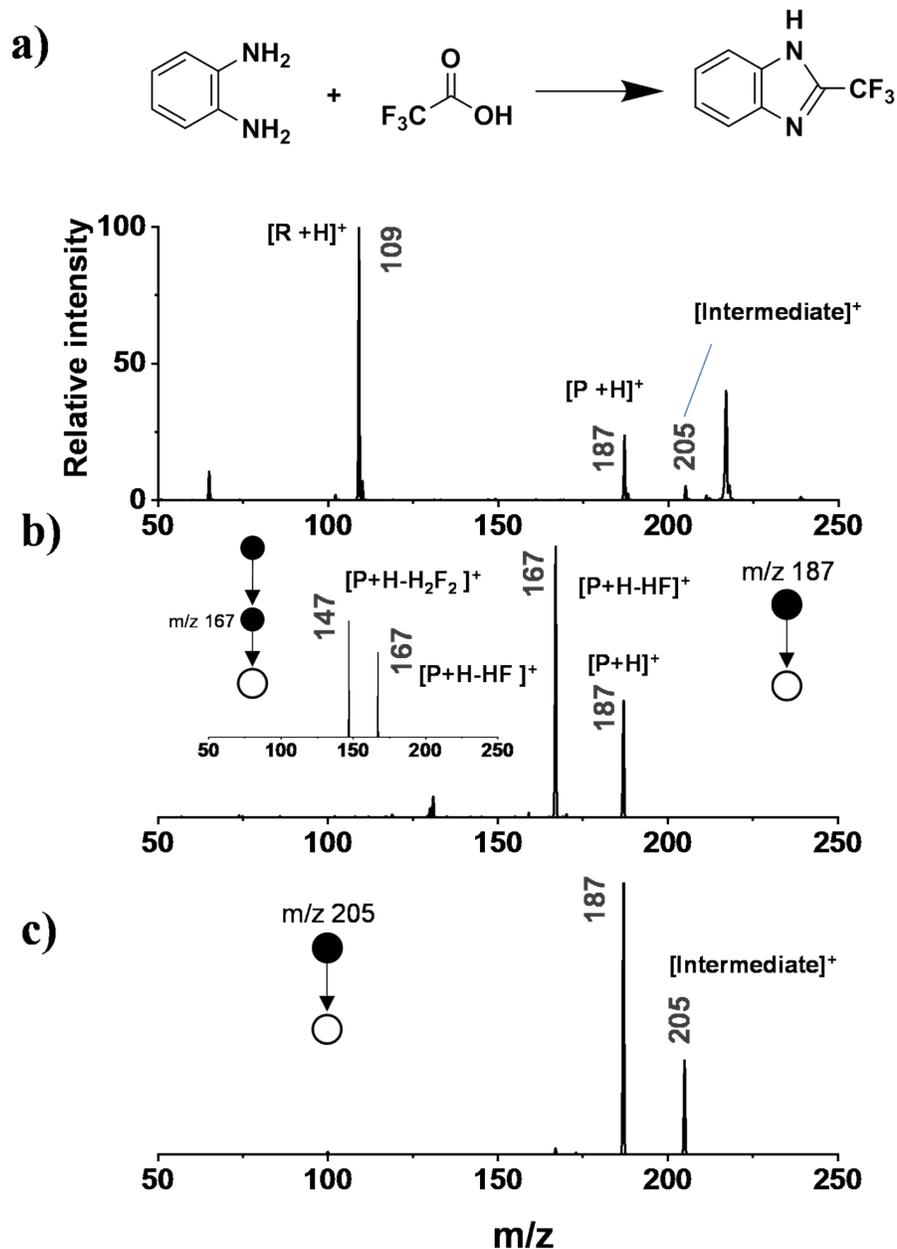


Figure S29. (a) Online mass spectrum of microdroplet reaction between *o*-phenylenediamine and trifluoroacetic acid in methanol at 50 °C inlet temperature. The MS/MS spectrum of the (b) product and (c) intermediate are shown. The reagent and the product are denoted as R and P.

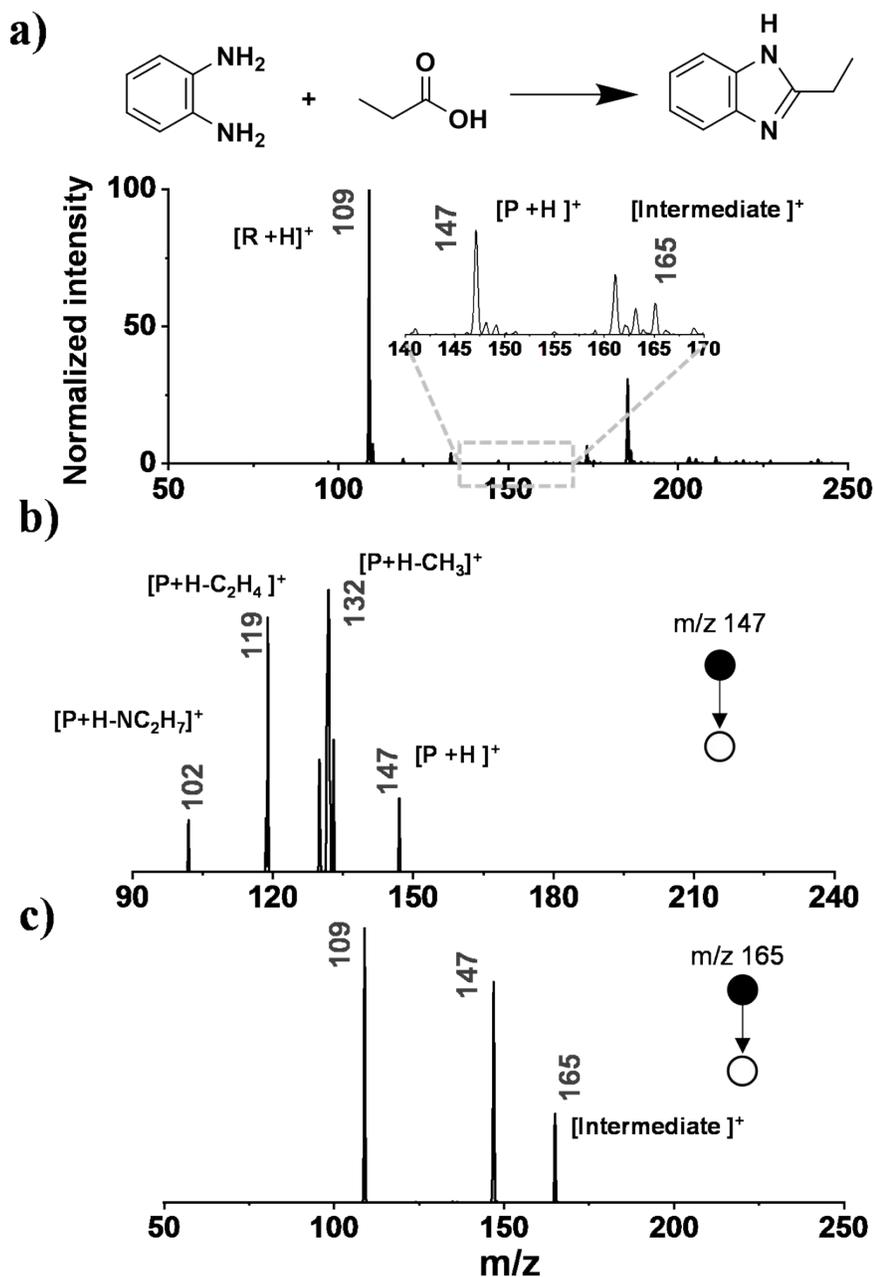


Figure S30. a) Online MS of microdroplet reaction between *o*-phenylenediamine and propanoic acid in methanol at 50 °C inlet temperature. The MS/MS spectrum of the (b) product and (c) intermediate are shown. The reagent and the product are denoted as R and P.

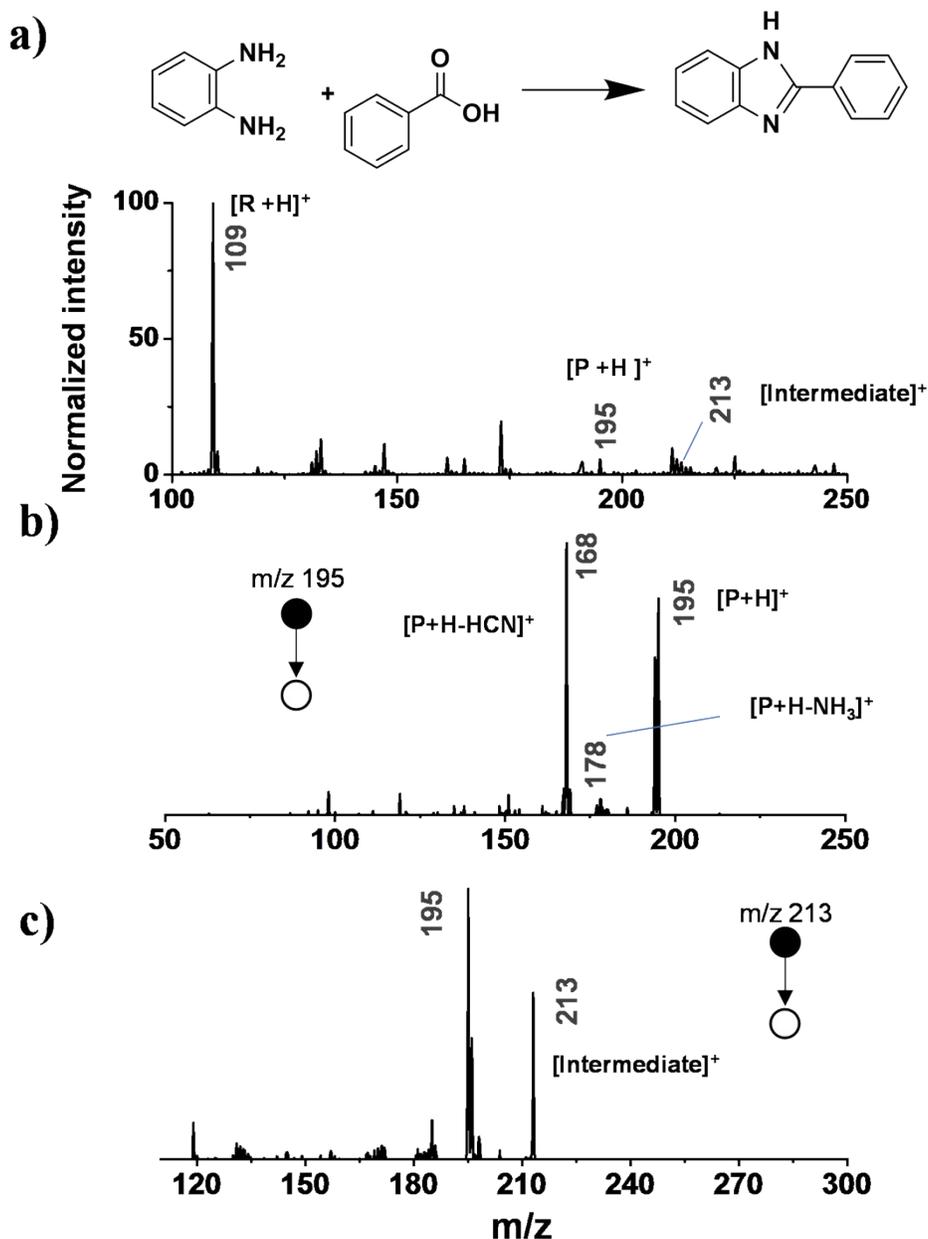


Figure S31. (a) Online MS of microdroplet reaction between *o*-phenylenediamine and benzoic acid in methanol at 50 °C inlet temperature. The MS/MS spectrum of (b) product and (c) intermediate are shown. The reagent and the product are denoted as R and P.

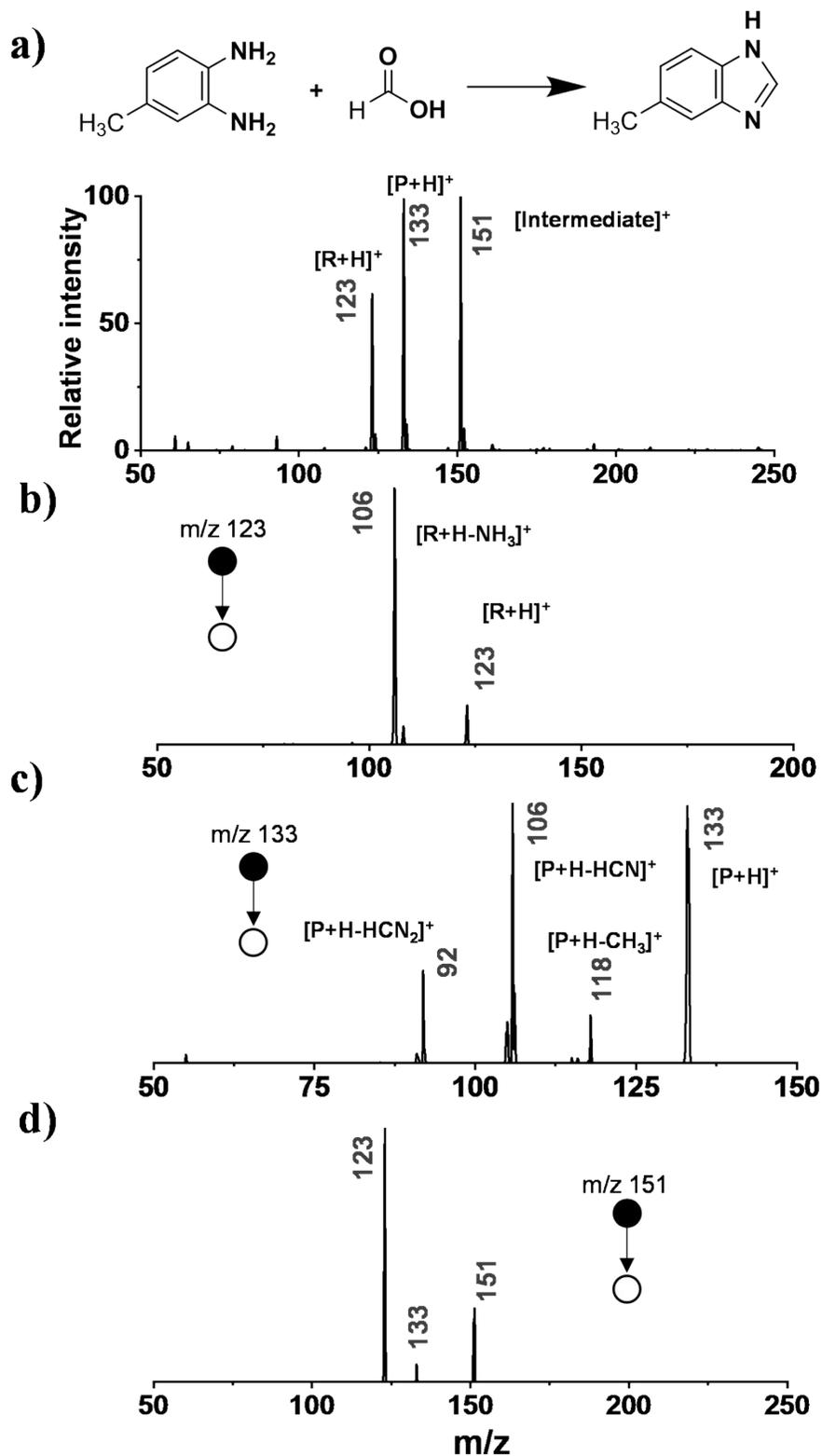


Figure S32. (a) Online MS of microdroplet reaction between 4-methyl-1,2-phenylenediamine and formic acid in methanol at 50 °C inlet temperature. MS/MS spectrum of the (b) reagent, (c) product, and (d) intermediate. The reagent and the product are denoted as R and P.

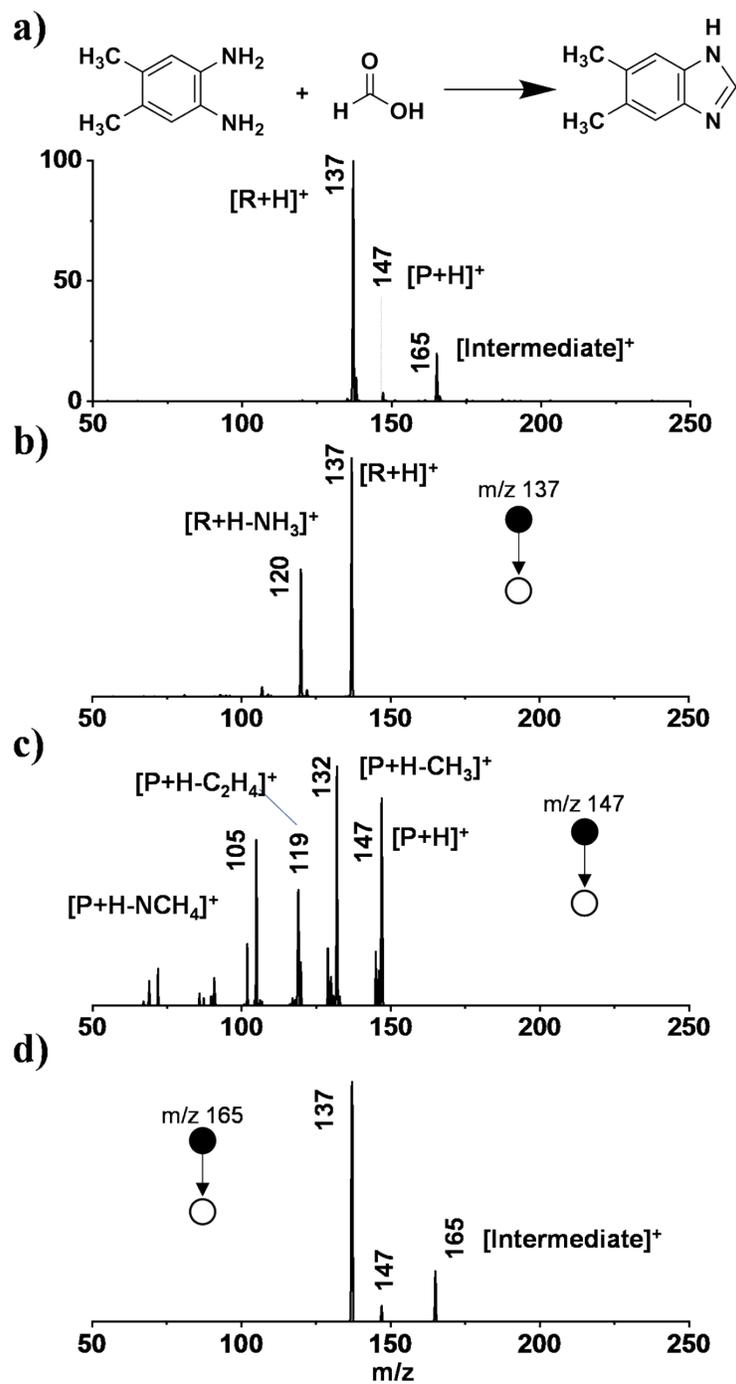


Figure S33. (a) Online MS of microdroplet reaction between 4,5-dimethylo-phenylenediamine and formic acid in methanol at 50 °C inlet temperature. MS/MS spectra of the (b) reagent (c) product and (d) intermediate. The reagent and the product are denoted as R and P.

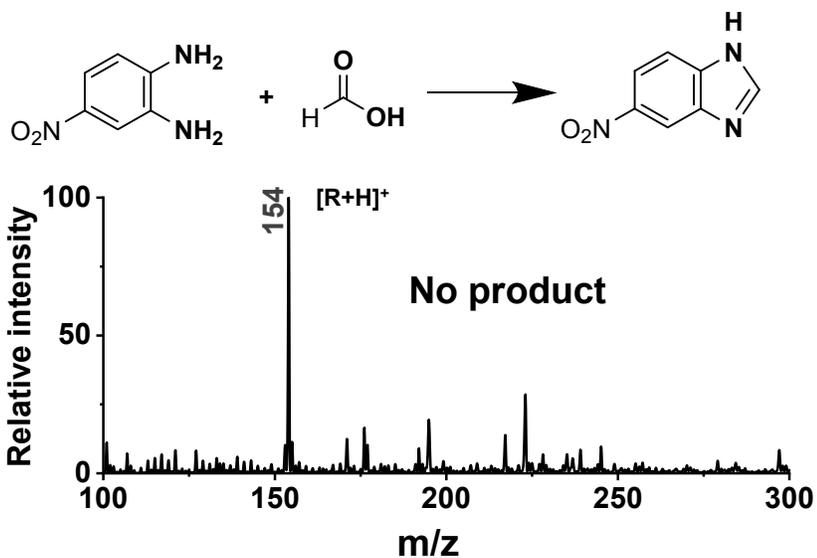


Figure S34. Online MS of microdroplet reaction between 4-nitro-1,2-phenylenediamine and formic acid in methanol at 50 °C inlet temperature. No product formation observed. The reagent is denoted as R.

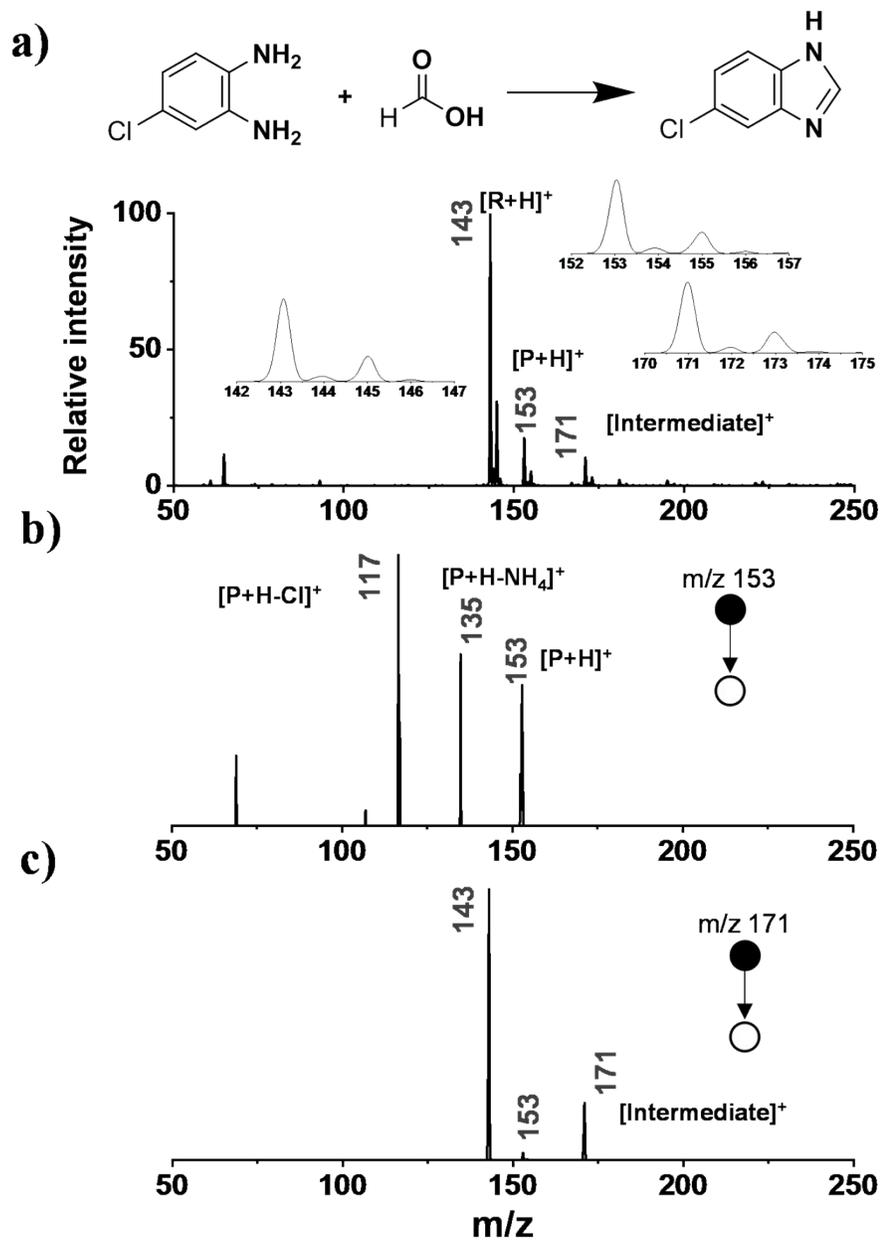


Figure S35. (a) Online MS of microdroplet reaction between 4-chloro-1,2-phenylenediamine and formic acid in methanol at 50 °C inlet temperature. MS/MS spectrum of (b) product and (c) intermediate. The reagent and the product are denoted as R and P.

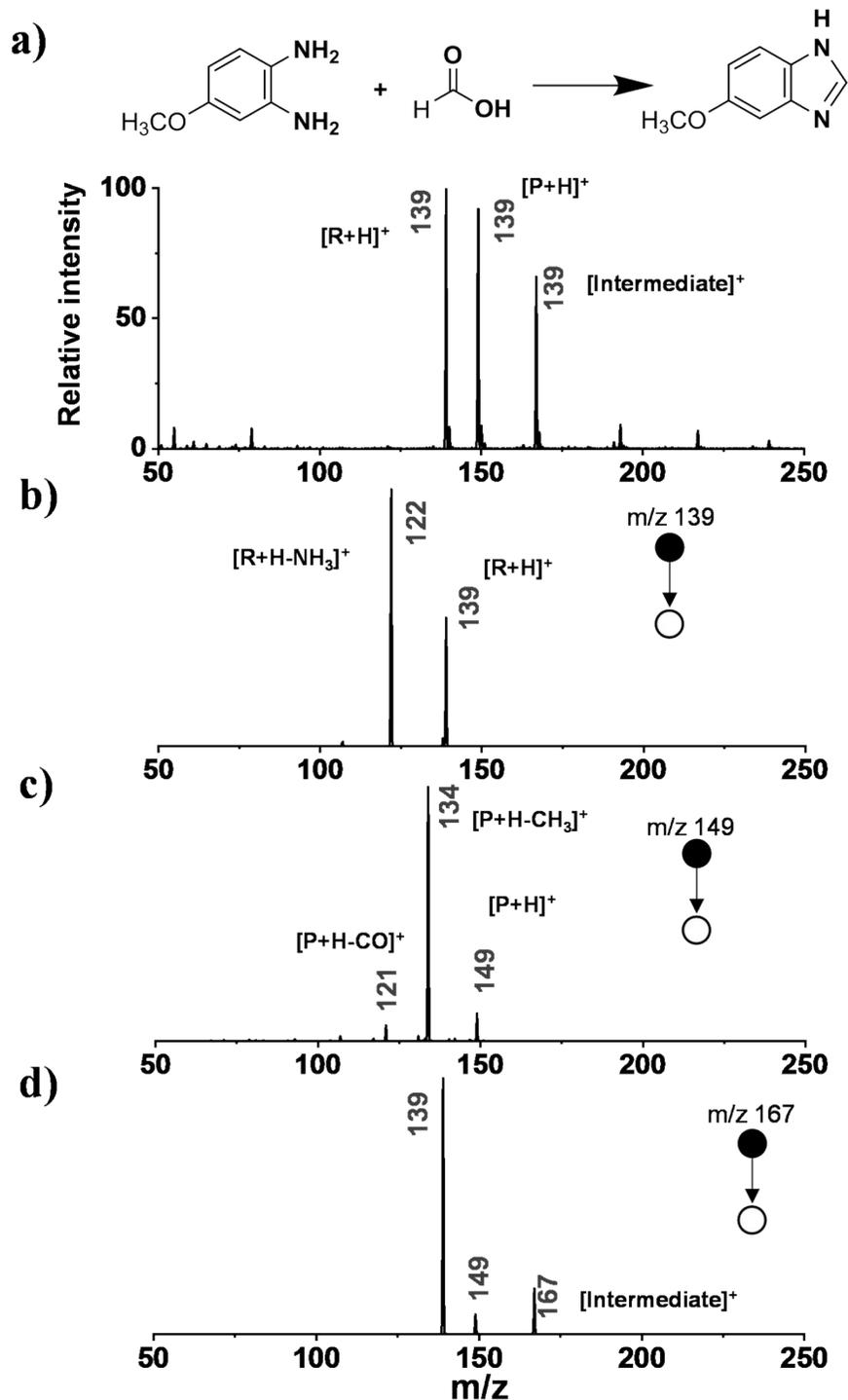


Figure S36. (a) Online MS of microdroplet reaction between 4-methoxy-1,2-phenylenediamine and formic acid in methanol at 50 °C inlet temperature. The fragmentation pattern of (b) reagent (c) product and (d) intermediate. The reagent and the product are denoted as R and P.

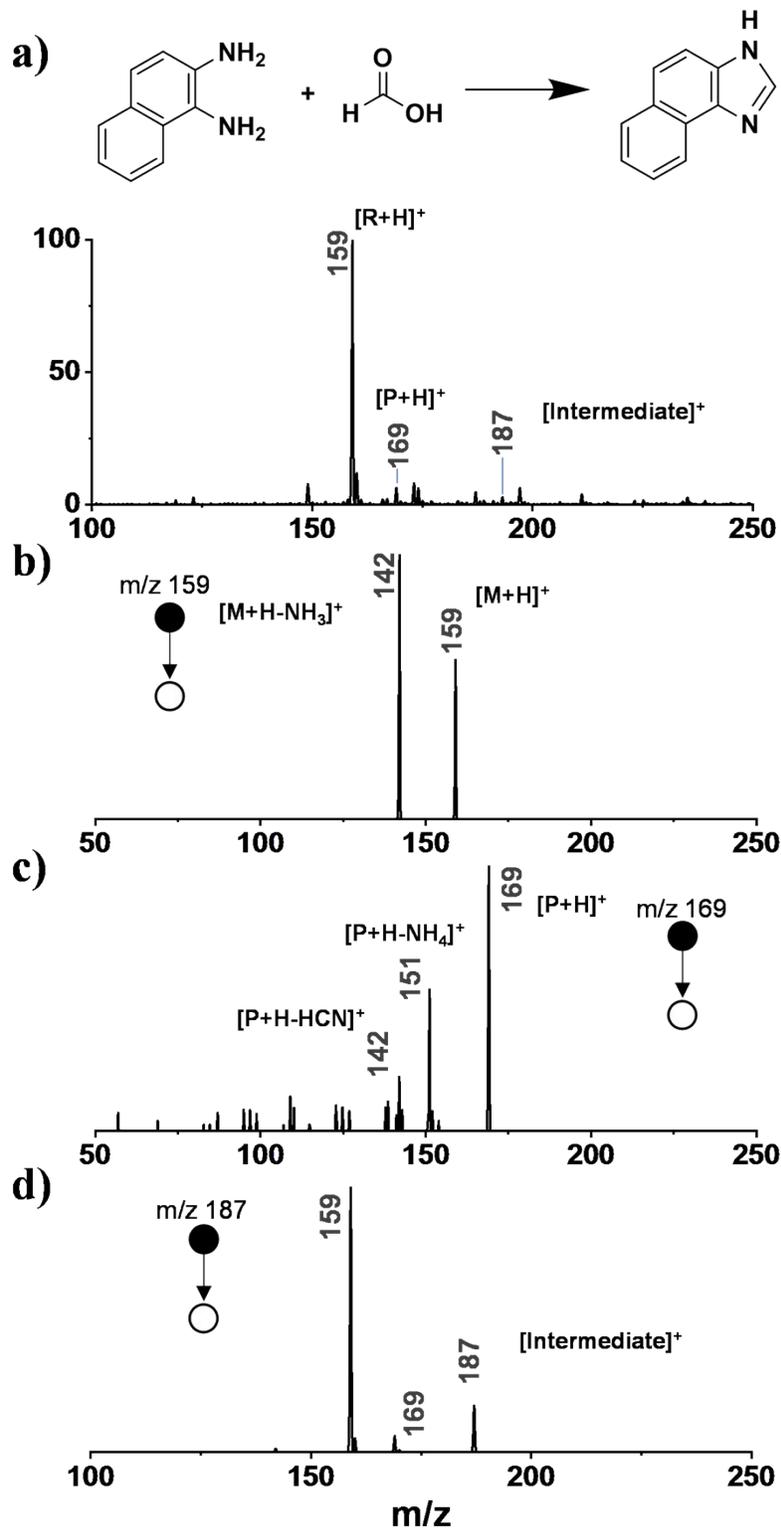


Figure S37. (a) Online MS of microdroplet reaction between 1,2-diaminonaphthalene and formic acid in methanol at 50 °C inlet temperature. The MS/MS spectra of (b) reagent (c) product and (d) intermediate. The reagent and the product are denoted as R and P.

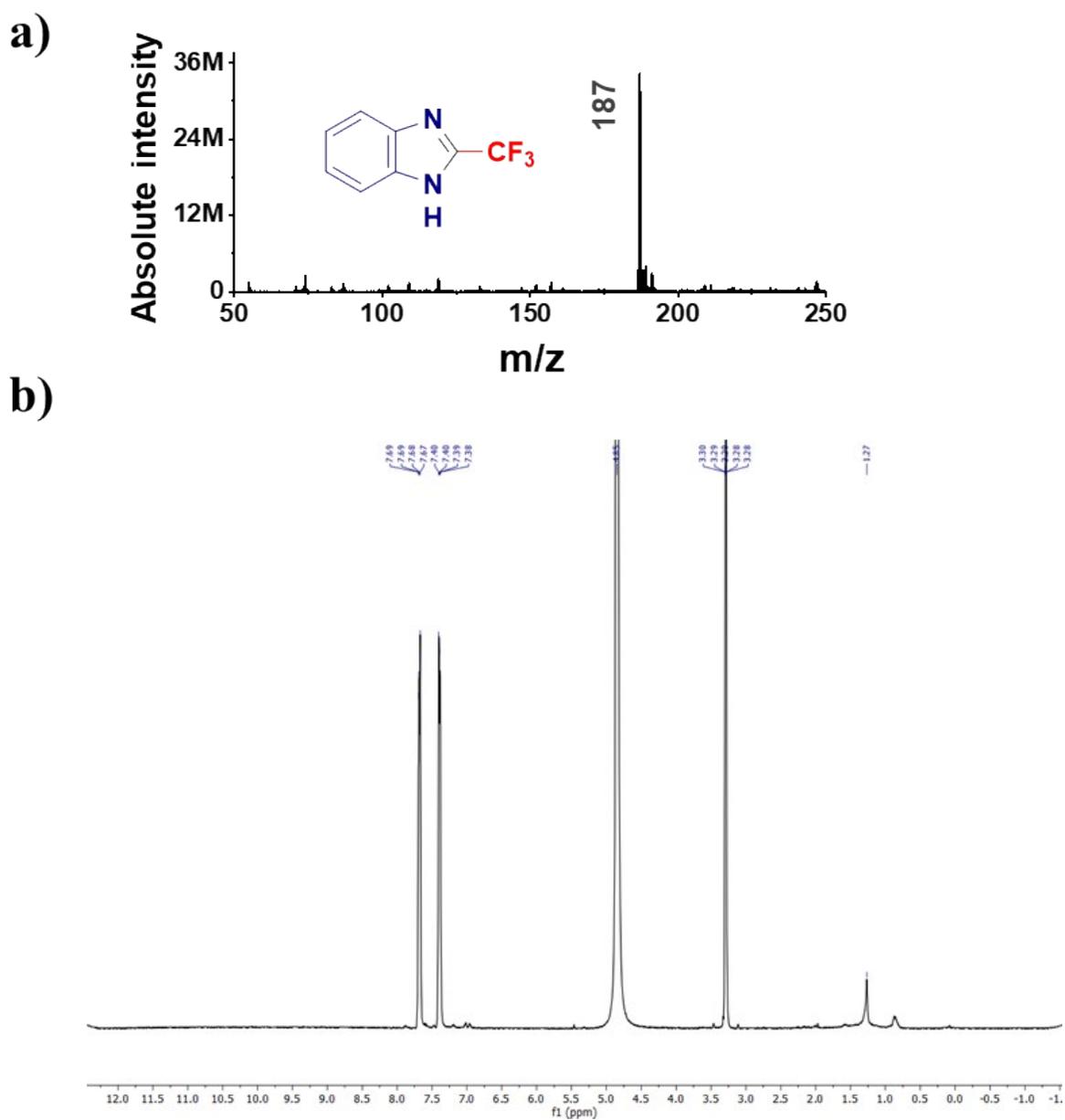


Figure S38. Characterization of isolated product of spray deposition reaction between trifluoroacetic acid and *o*-phenylenediamine. (a) Mass spectrum and (b) ¹H NMR (400 MHz, MeOD) of the product. δ 7.69 (dd, J = 6.2, 3.2 Hz, 1H), 7.40 (dd, J = 6.3, 3.2 Hz, 1H). Peaks 4.85ppm and 3.28-3.30ppm are solvent peaks.

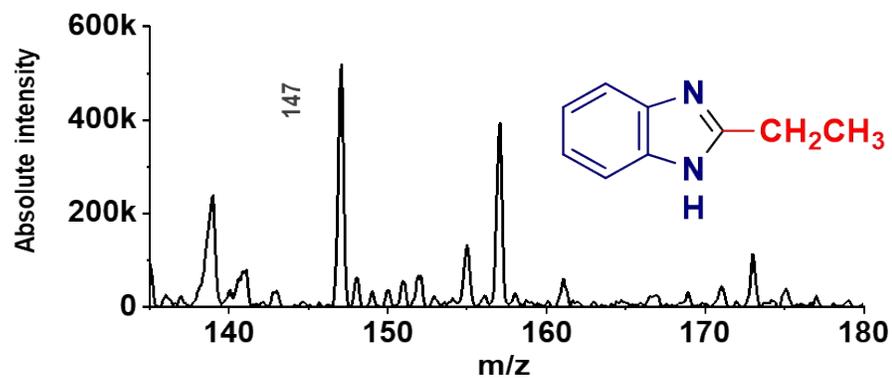


Figure S39. Characterization of isolated product of the spray deposition reaction between propanoic acid and *o*-phenylenediamine in methanol. Due to poor separation, an NMR of the isolated product was not obtained.

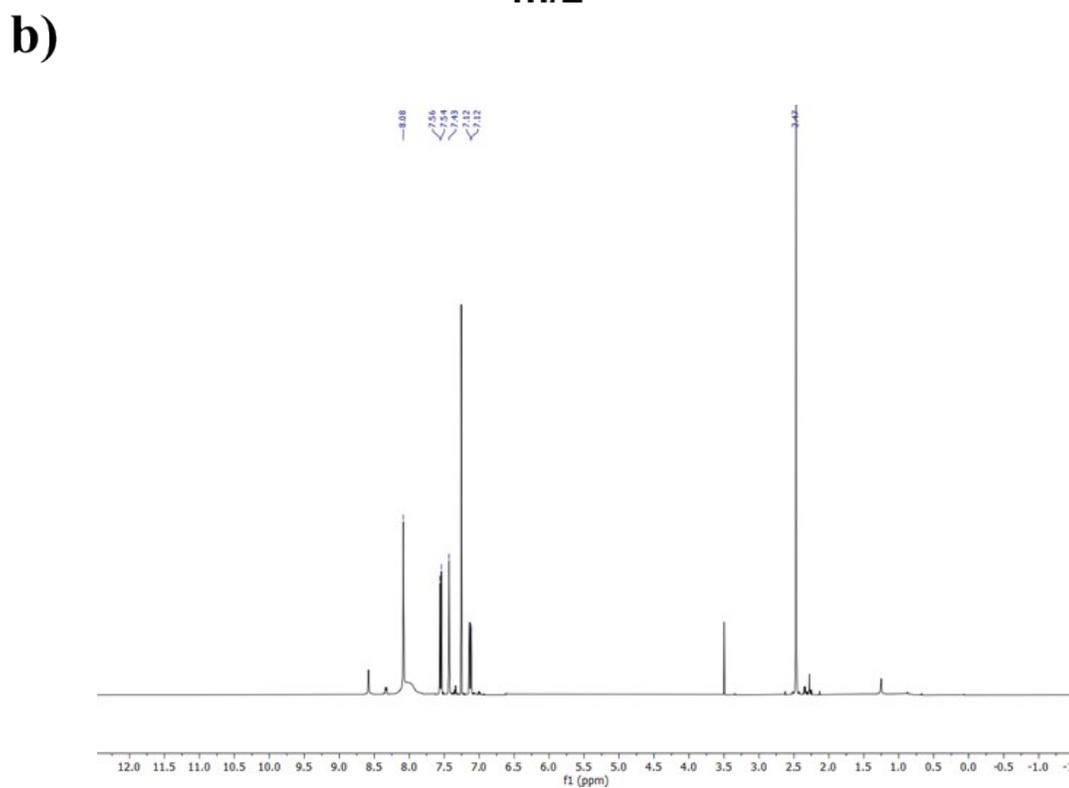
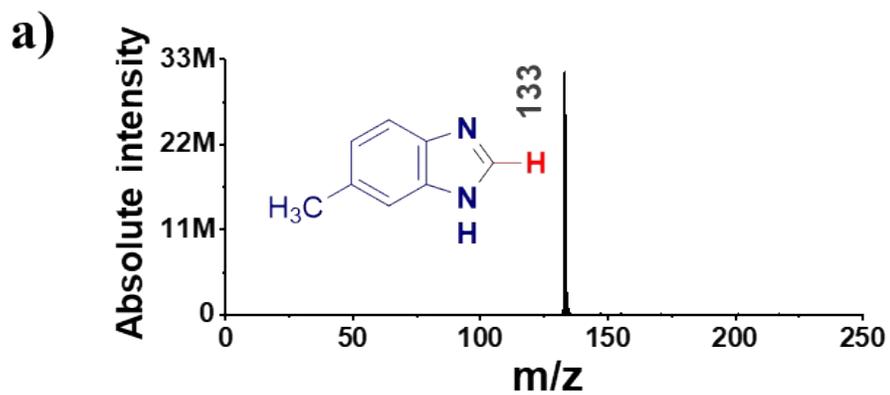


Figure S40. Characterization of isolated product of spray deposition reaction between formic acid and 4-methyl-1,2-phenylenediamine. (a) Mass spectrum and (b) ¹H NMR (400 MHz, CDCl₃) spectrum of the product. δ 8.08 (s, 1H), 7.55 (d, J = 8.3 Hz, 1H), 2.47 (s, 3H). Peak in 7.26ppm region is the solvent peak. Other peaks are due to artifacts or by-products.

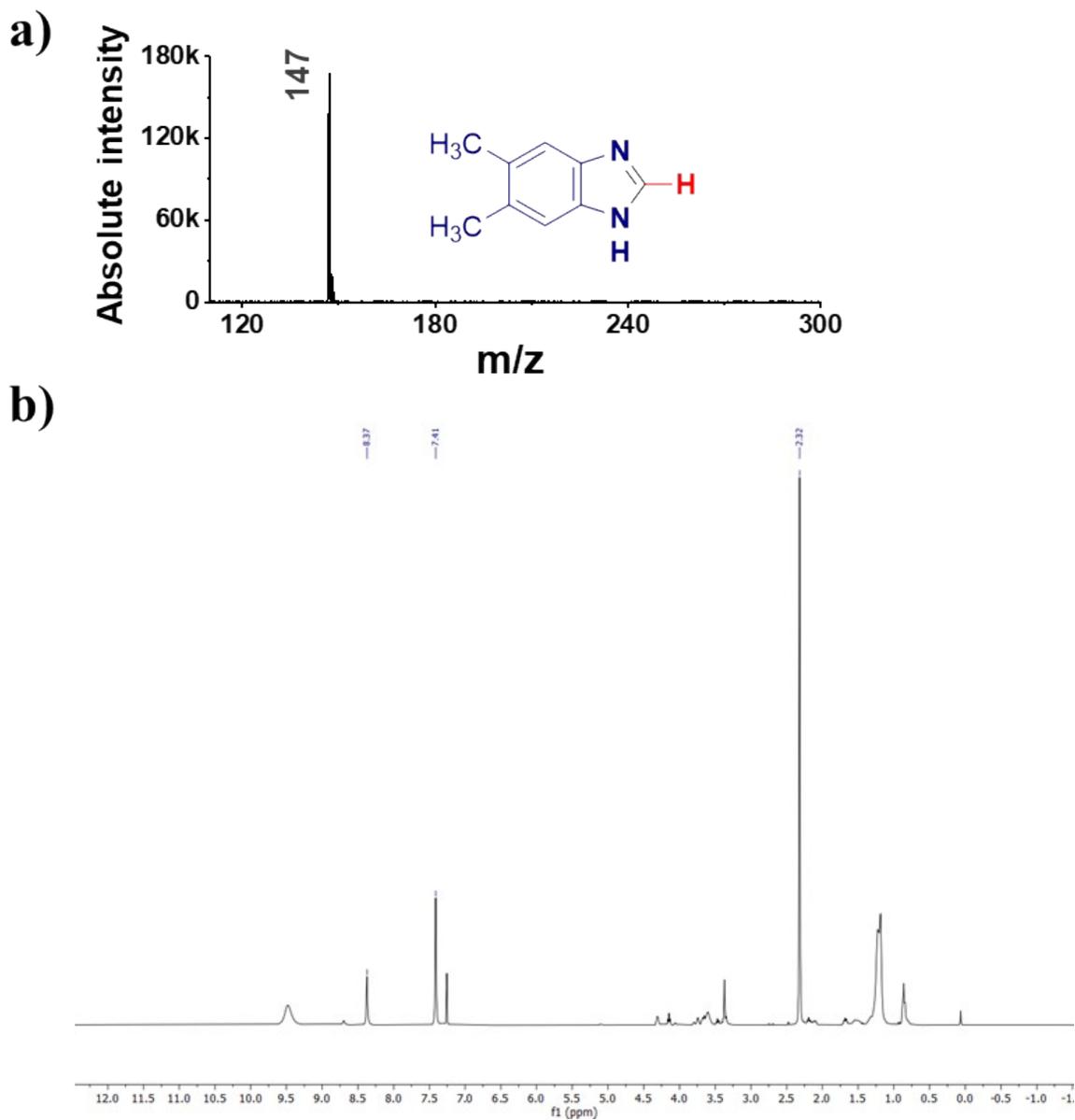


Figure S41. Characterization of the isolated product of spray deposition reaction between formic acid and 4,5-dimethyl-1,2-phenylenediamine in methanol. a) Mass spectrum and b) ^1H NMR (400 MHz, CDCl_3) δ 8.37 (s, 1H), 7.41 (s, 2H), 2.32 (s, 6H). Peak in 7.26 ppm region is the solvent peak. Unlabeled peaks represent minor reaction products.

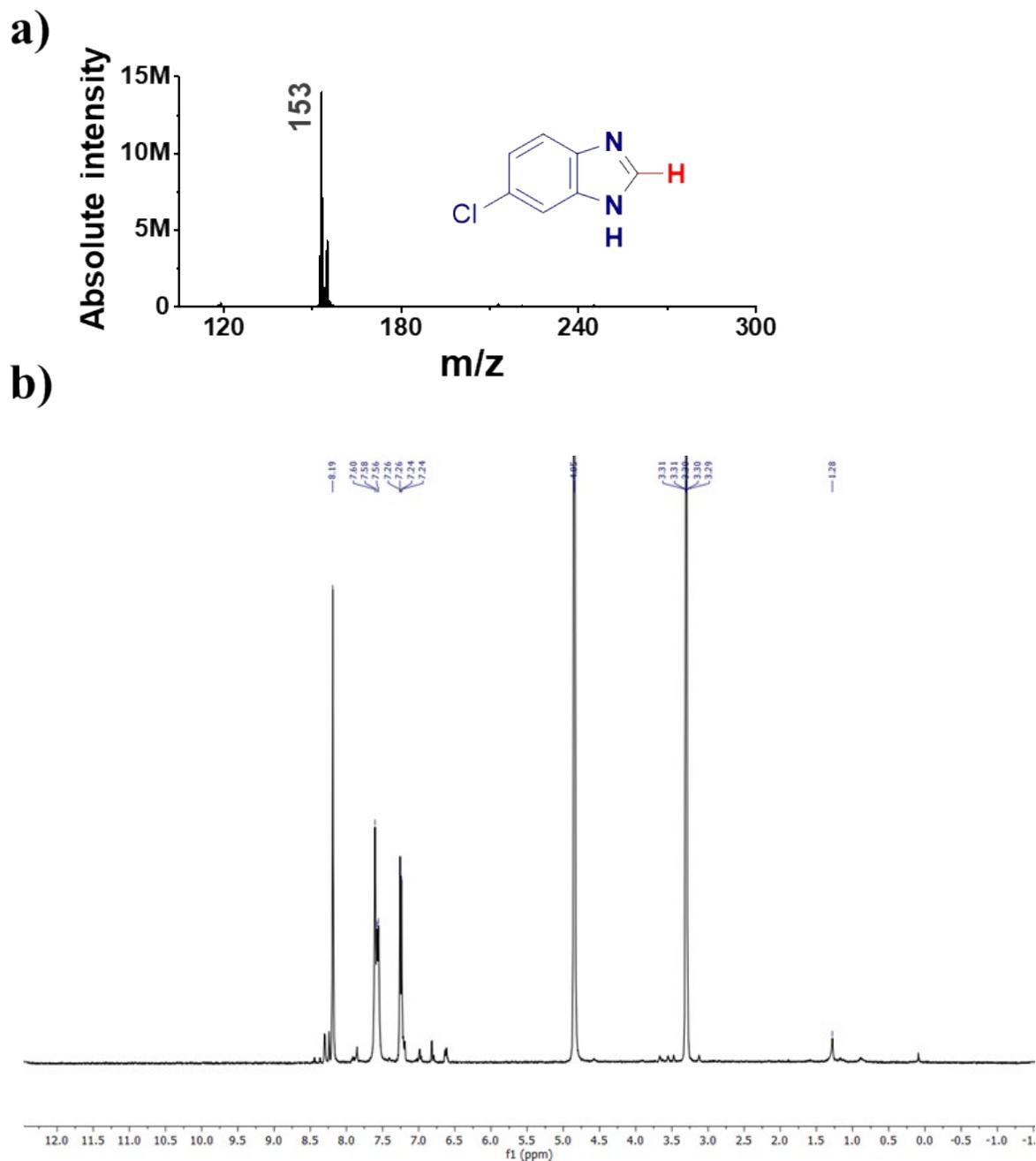


Figure S42. Characterization of isolated product of spray deposition reaction between formic acid and 4-chloro-1,2-phenylenediamine in methanol. (a) Mass spectrum and (b) ¹H NMR (400 MHz, MeOD). δ 8.19 (s, 1H), 7.60 (s, 1H), 7.57 (d, $J = 8.7$ Hz, 1H), 7.25 (dd, $J = 8.5, 2.0$ Hz, 1H). Peaks 4.85 ppm and 3.29-3.31 ppm are solvent peaks.

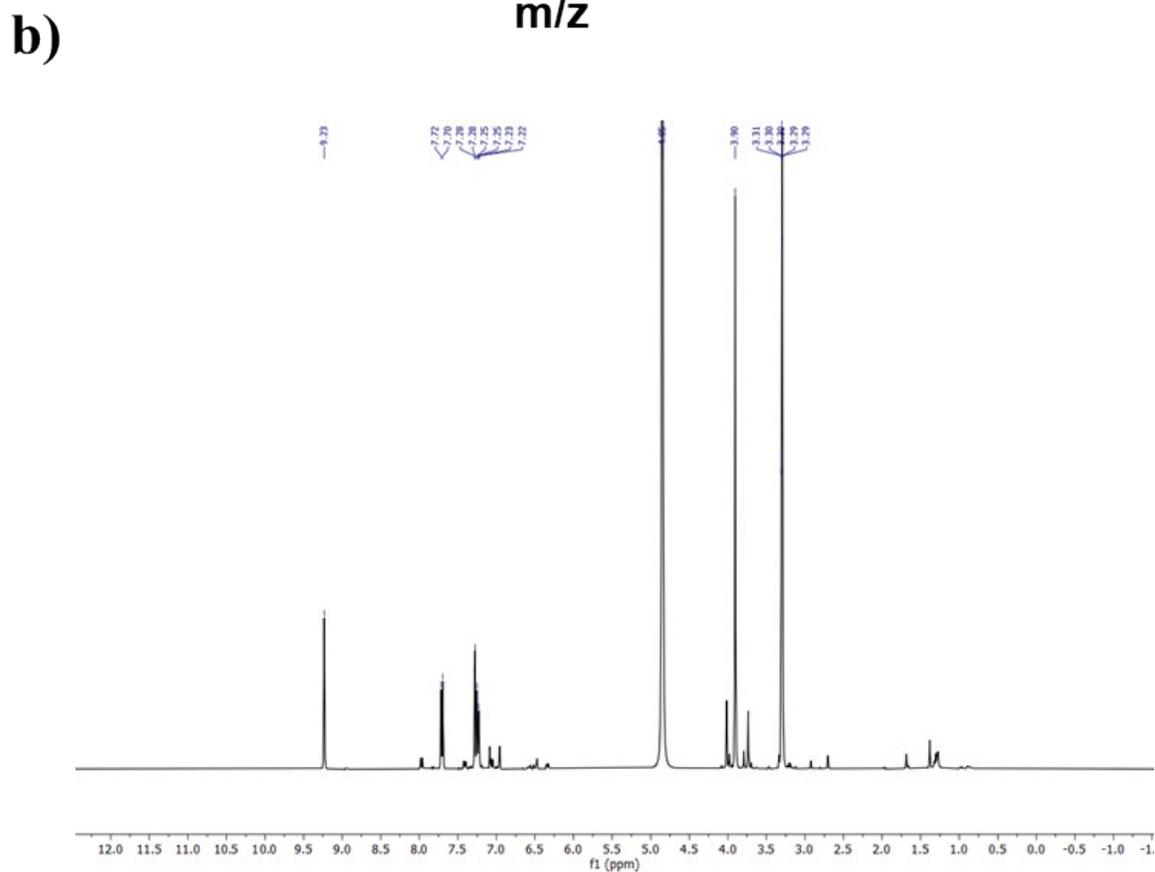
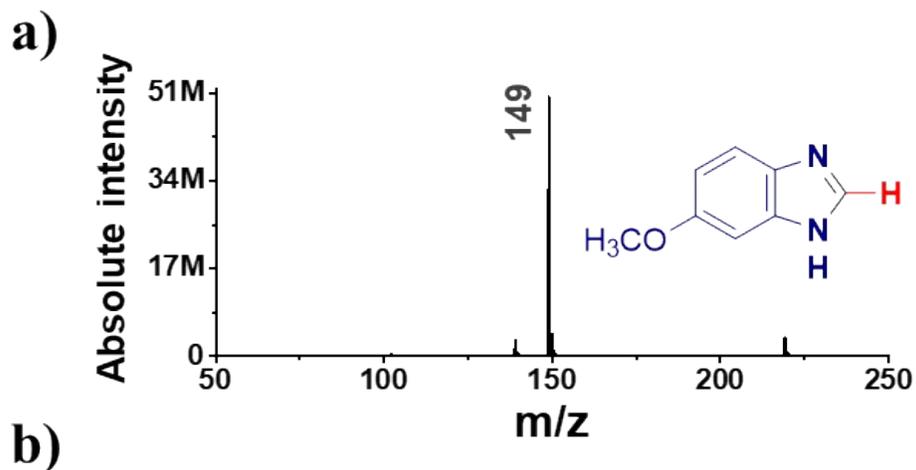


Figure S43. Characterization of isolated product of spray deposition reaction between formic acid and 4-methoxy-1,2-phenylenediamine in methanol. a) Mass spectrum and b) ¹H NMR (400 MHz, MeOD). δ 9.24 (s, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.31 – 7.17 (m, 2H), 3.91 (s, 3H). Peaks 4.85ppm and 3.29-3.31ppm are solvent peaks.

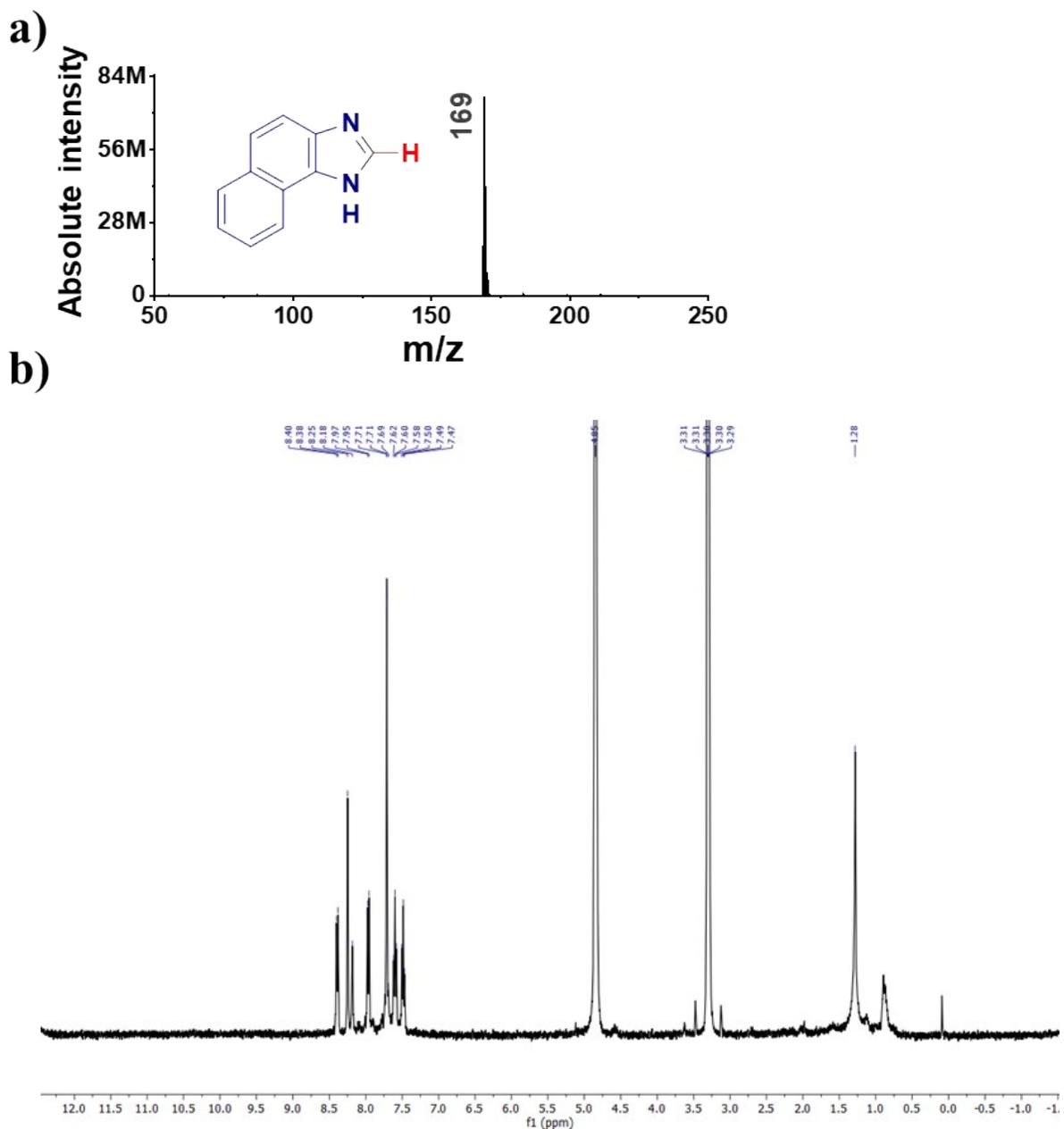


Figure S44. Characterization of isolated product of spray deposition reaction between formic acid and 1,2-diaminonaphthalene in methanol. (a) Mass spectrum and (b) ^1H NMR (400 MHz, MeOD). δ 8.39 (d, $J = 8.2$ Hz, 1H), 8.25 (s, 1H), 8.18 (s, 1H), 7.96 (d, $J = 8.2$ Hz, 1H), 7.71 (d, $J = 1.5$ Hz, 2H), 7.60 (t, $J = 7.7$ Hz, 1H), 7.49 (t, $J = 7.6$ Hz, 1H). Peaks 4.85ppm and 3.29-3.31ppm are solvent peaks.

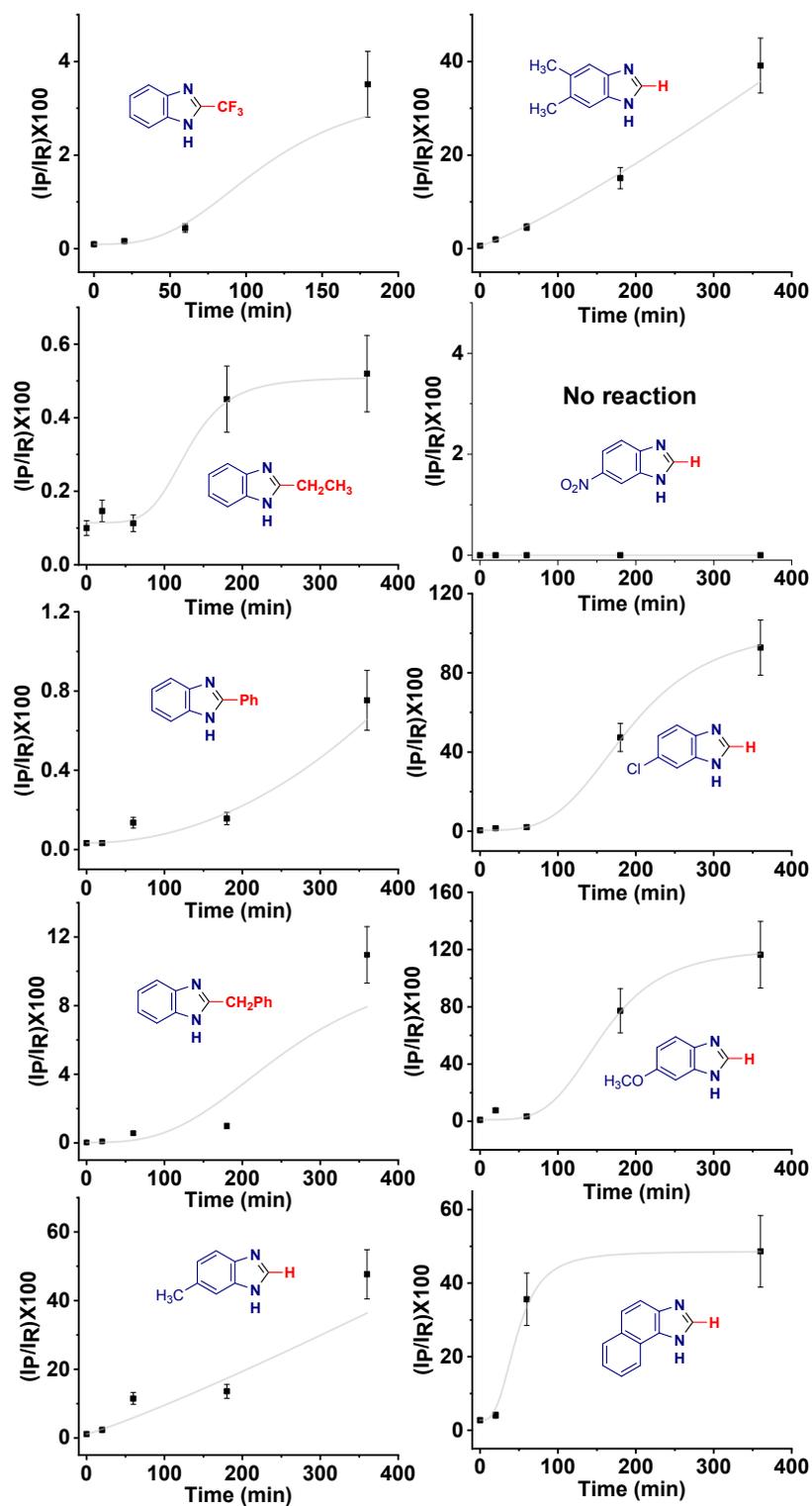


Figure S45. Kinetics data for thin film reactions. Reactions were done for 6 h in methanol under ambient conditions. Lines are drawn only as guides.

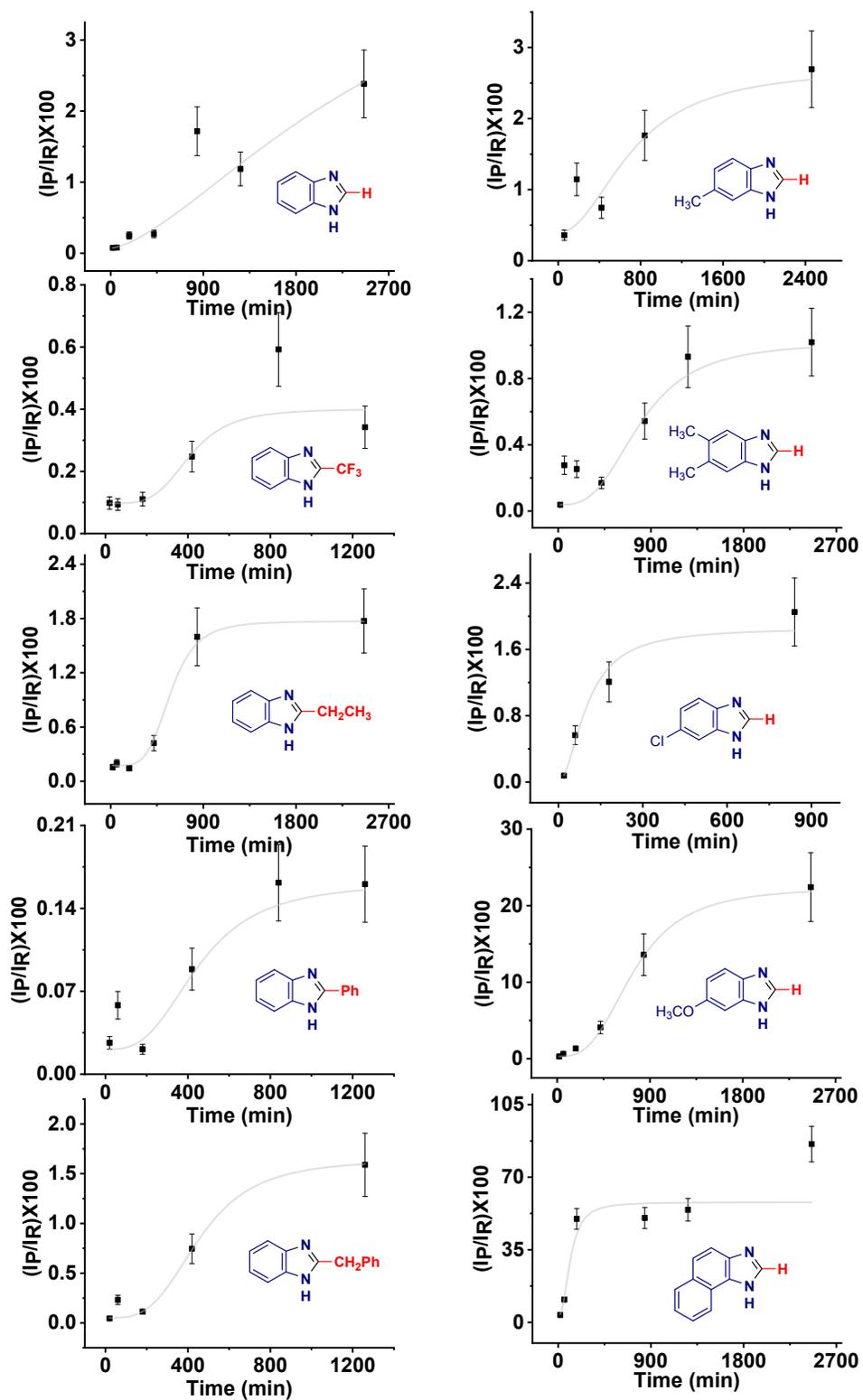


Figure S46. Kinetics data for bulk reactions. Reactions were done for 41 h in methanol under ambient conditions. Lines are drawn only as guides.