Electronic Supplementary Material (ESI) for Chemical Science.

Accelerated Hantzsch Electrospray Synthesis with Temporal Control of Reaction Intermediates

Supplementary Information

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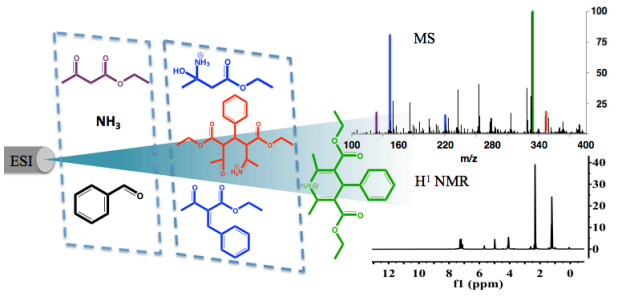
Graphical Abstract



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Importance of the Hantzsch synthesis

The distinctive DHP class of molecules is of interest for pharmaceutical,[1] biological,[2] and microbial applications.[3] Nifedipine[4-6] (and analogs including amlodipine,[7] azelnidipine,[8] efonidipine,[9] lercanidipine,[10] manidipine,[11] and nicardipine[12]) is used as a calcium channel blocker for the treatment of hypertension and other cardiovascular diseases.[13,14]

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9 T. Yotsumoto, Y. Masuda, C. Shudo, H. Sugita, T. Yamashita, and S. Tanaka, *Gen. Pharmacol.*, 1995, **26**, 333–7.

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11 K. Mizuno, H. Haga, M. Takahashi, and S. Fukuchi, *Curr. Ther. Res.*, 1992, **52**, 248–53.

12 R. I. Huang, P. Patel, P. Walinsky, D. L. Fischman, J. D. Ogilby, M. Awar, C. Frankil, and M. P. Savage, *Catheter. Cardiovasc. Interv.*, 2006, **68**, 671–6.

13 U. Pleiss, *J. Label. Compd. Radiopharm.*, 2007, **50**, 818–30.

14 J.-G. Wang, *Vasc. Health Risk Manag.*, 2009, **5**, 593–605.

Table S1 Bulk reaction conditions, time required and yields

Phenylboronic acid catalyst with reflux		Phenylboronic acid catalyst w/o reflux		No catalysis or reflux	
Time (hours)	Percent Yield[a]	Time (hours)	Percent Yield[a]	Time (hours)	Percent Yield[a]
2	39	2	-	2	-
4	83	4	7	4	3
8	94	8	23	8	7
16	96	16	49	16	13
32	-	32	61	32	24
64	-	64	82	64	37

[a]Percent yield based on UV-Vis data collected at λ=378 nm using molar absorbtivity of 5.2 x 10^3 L/mol*cm[48]

Figure S1 NMR spectra

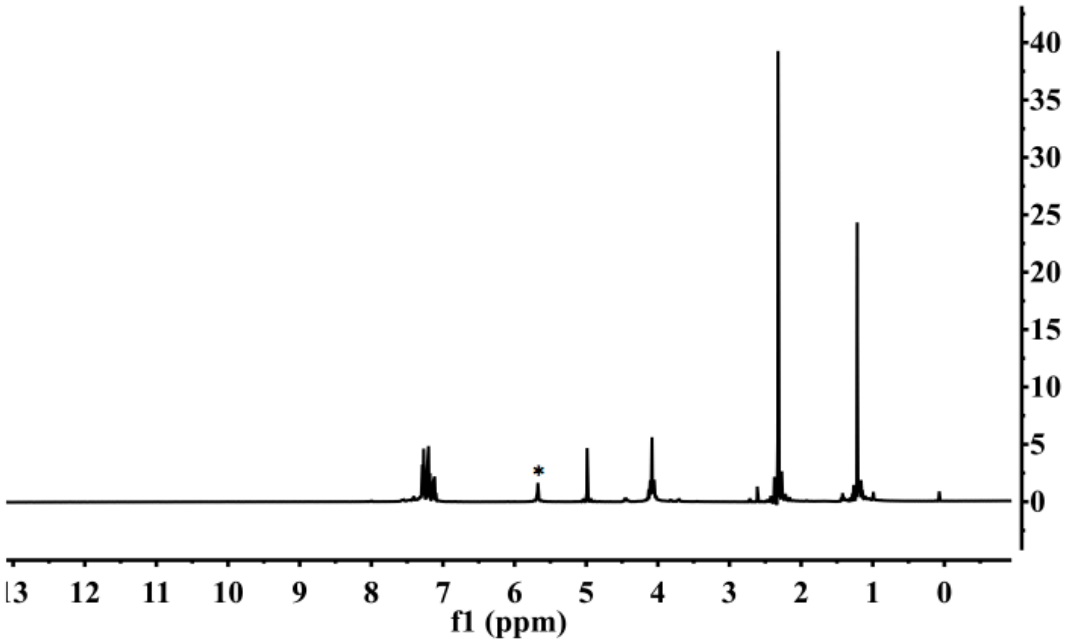


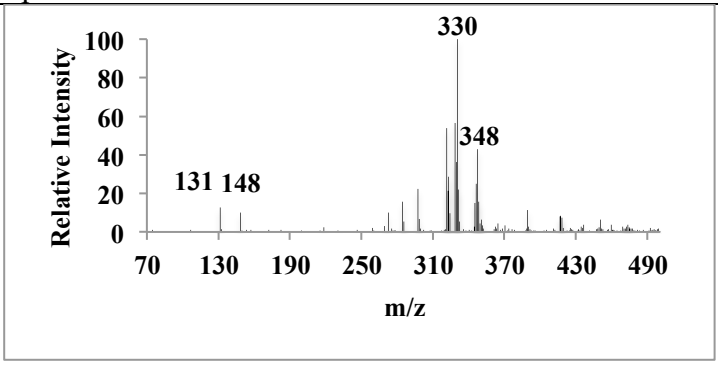
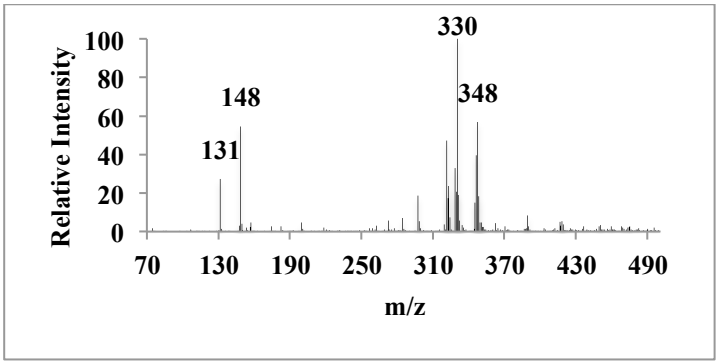
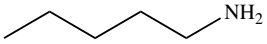
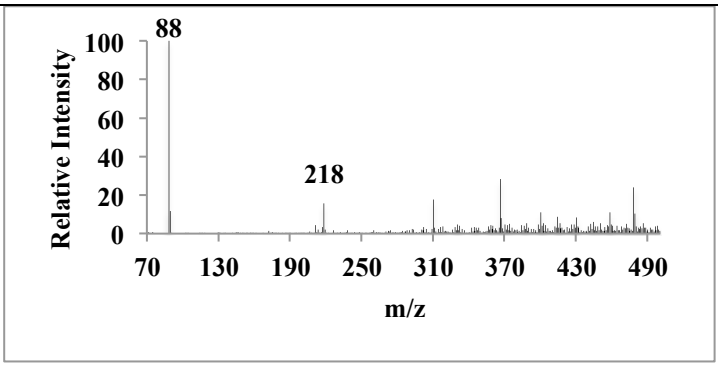
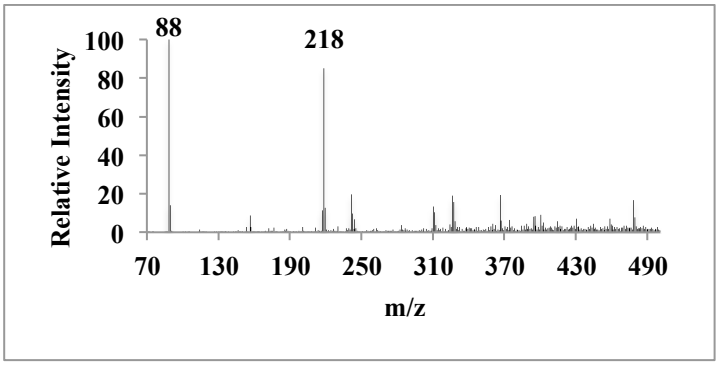
Figure S1 NMR of product from spray after recrystallization in chloroform-d which is in agreement with bulk phase experiments and literature. * denotes solvent peak.

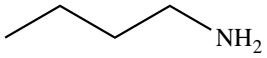
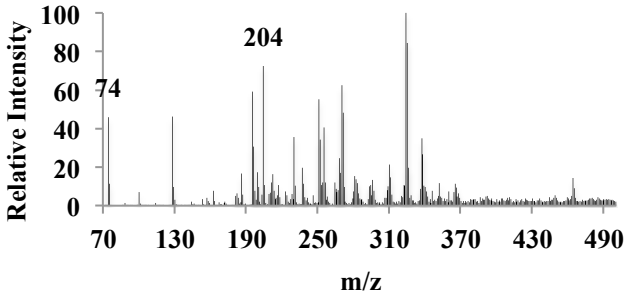
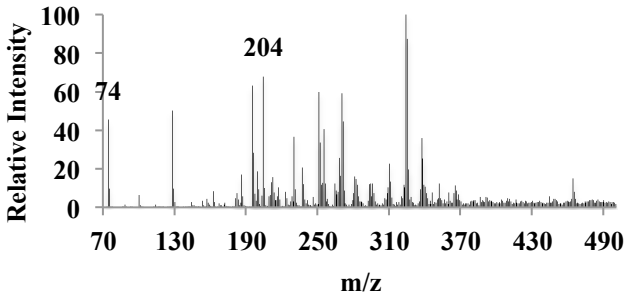
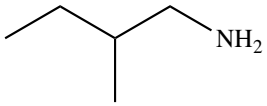
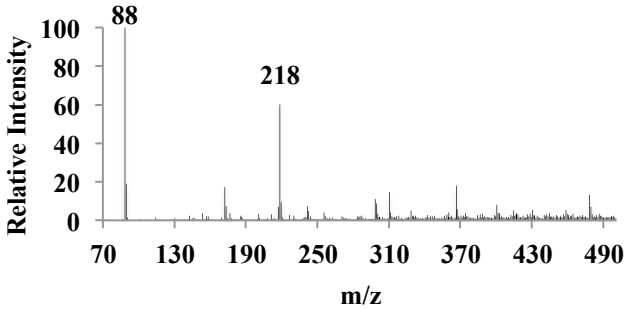
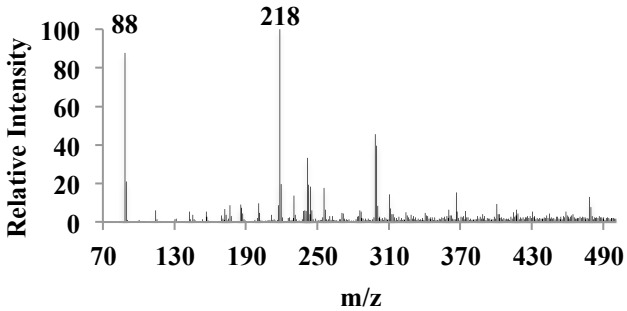
Table S2 Amine reactions in spray and bulk modes

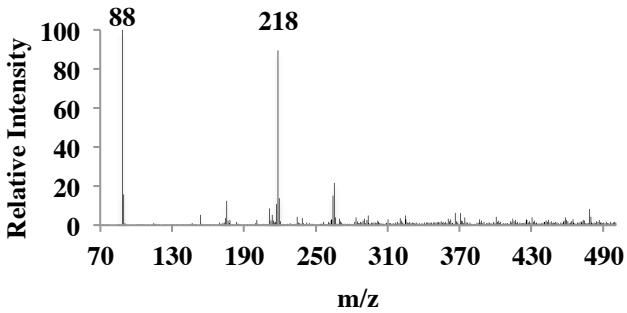
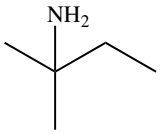
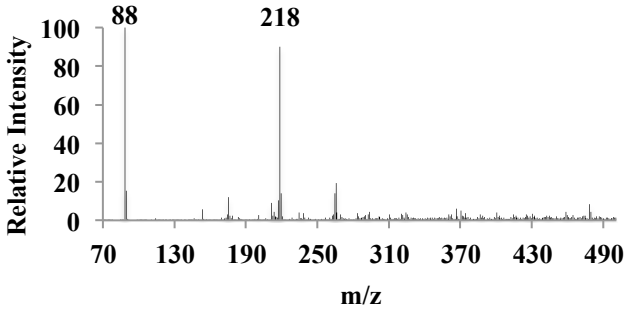
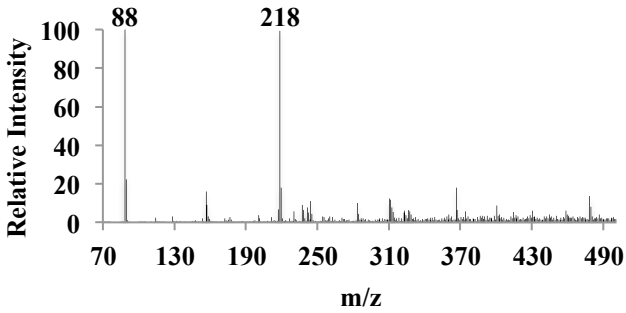
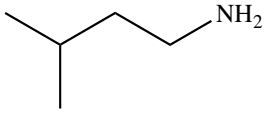
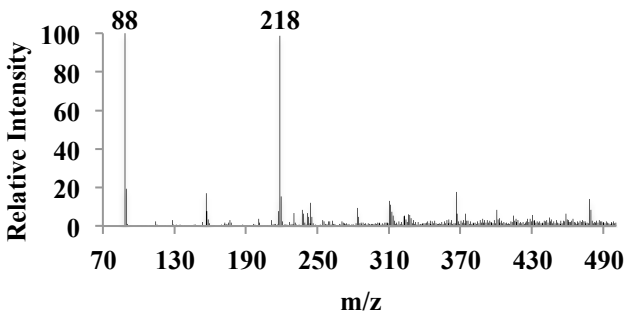
	2		**Amine**		**5**		**7**		**9**	
	S	*B*	*S*	*B*	*S*	*B*	*S*	*B*	*S*	*B*
ammonia	x	x	-	-	x	x	x	x	x	x
pentan-1-amine	x	x	x	x	x	x	-	-	-	-
butan-1-amine	x	x	x	x	x	x	-	-	-	-
2-methylbutan-1-amine	x	x	x	x	x	x	-	-	-	-
2-methylbutan-2-amine	x	x	x	x	x	x	-	-	-	-
3-methylbutan-1-amine	x	x	x	x	x	x	-	-	-	-
2-methylpropan-2-amine	x	x	x	x	x	x	-	-	-	-
dibutylamine	x	x	x	x	x	x	-	-	-	-
tributylamine	x	x	x	x	-	-	-	-	-	-

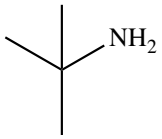
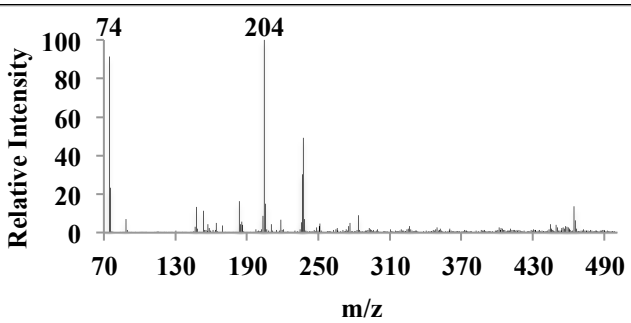
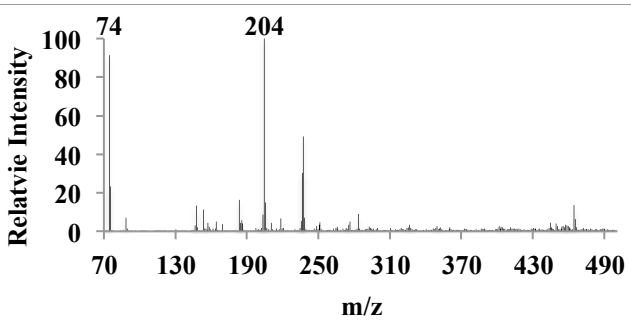
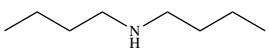
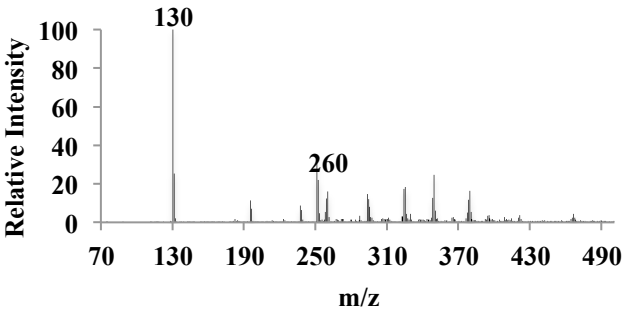
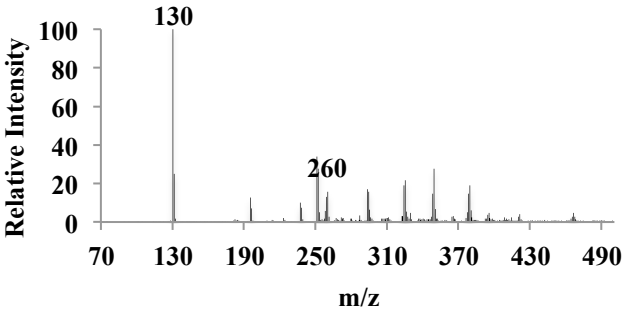
S denotes sprayed reaction mixture. B denontes bulk phase reactions. Due to ion suppression some identifications were performed in MS^2.

Table S3 Amine substituent effects

Nitrogen Source	Spectral Details	Spectra
ammonium acetate (Product m/z = 330) (Intermediates **5**,**7** m/z = 148, 348)	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	
pentan-1-amine (Intermediate **5** m/z = 218) (Starting Material m/z = 88) 	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	

butan-1-amine (Intermediate **5** m/z = 204) (Starting material m/z = 74) 	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	
2-methylbutan-1-amine (Intermediate **5** m/z = 218) (Starting material m/z = 88) 	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	

2-methylbutan-2-amine (Intermediate **5** m/z = 218) (Starting material m/z = 88)	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	
3-methylbutan-1-amine (Intermediate **5** m/z = 218) (Starting material m/z = 88)	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	

2-methylpropan-2-amine (Intermediate **5** m/z = 204) (Starting material m/z = 74) 	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	
dibutylamine (Starting material m/z = 130) (Intermediate **5** m/z= 260 	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	

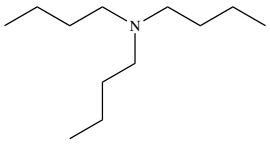
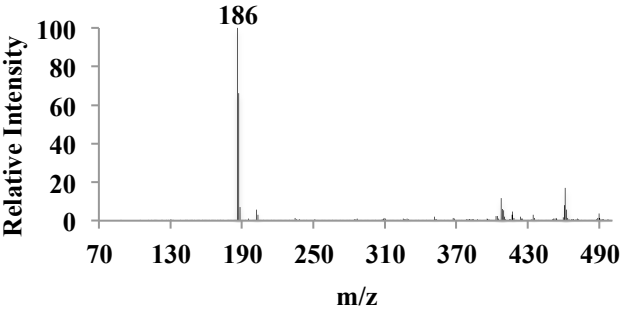
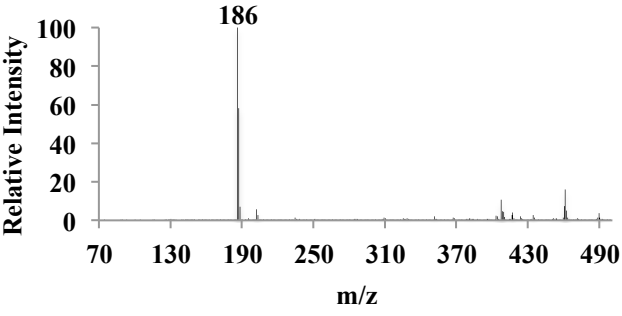
tributylamine (Starting material m/z =186) 	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	

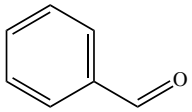
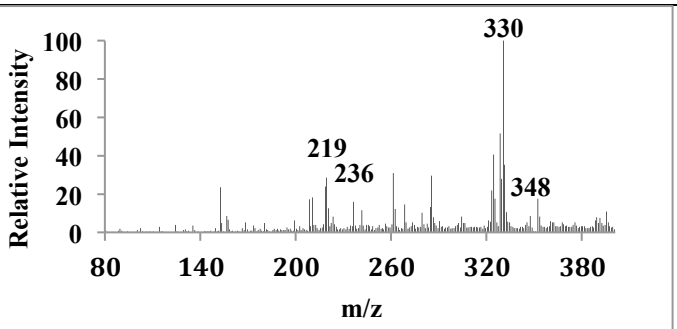
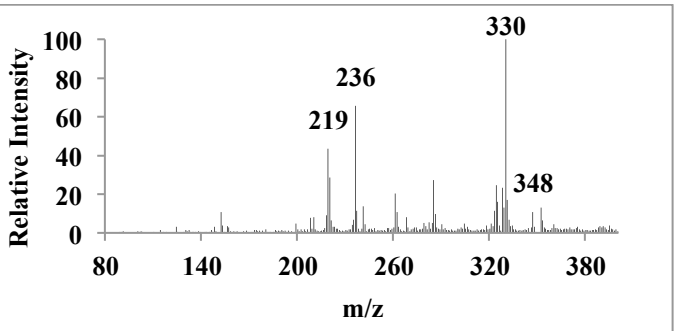
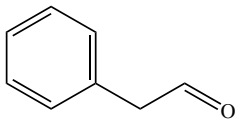
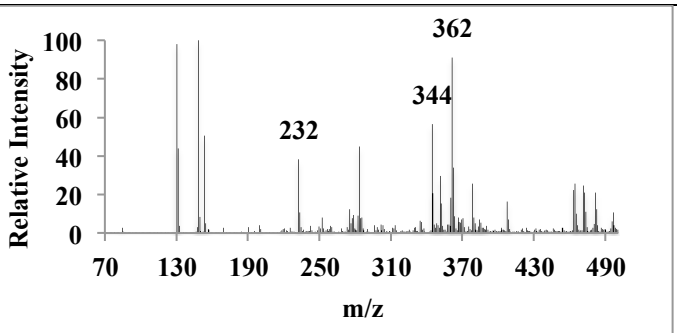
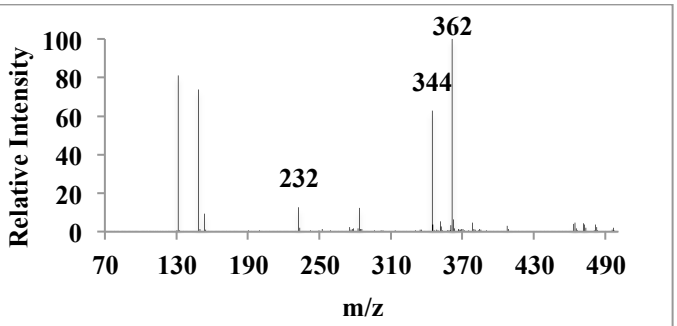
Table S3 A compilation of spectra supporting Table S2. Shows the similarity and differences between the spectra from the bulk phase product as well as the ESI synthesis.

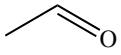
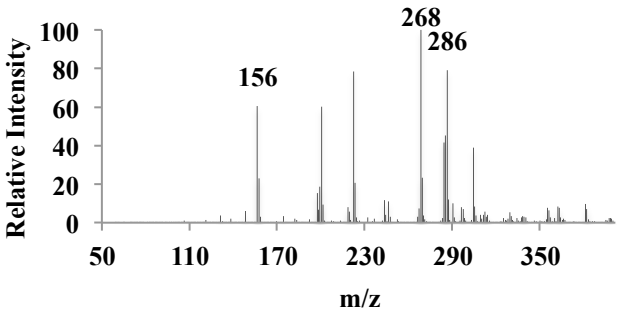
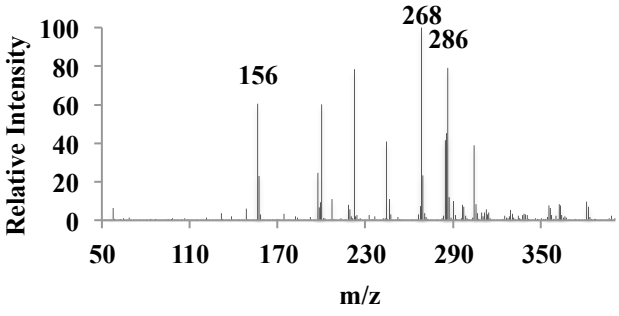
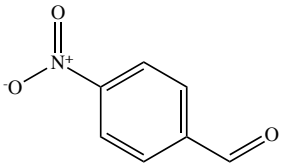
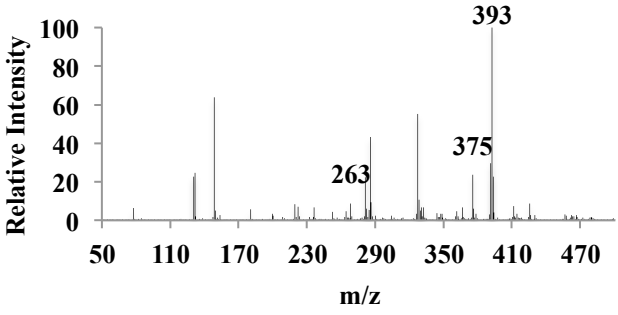
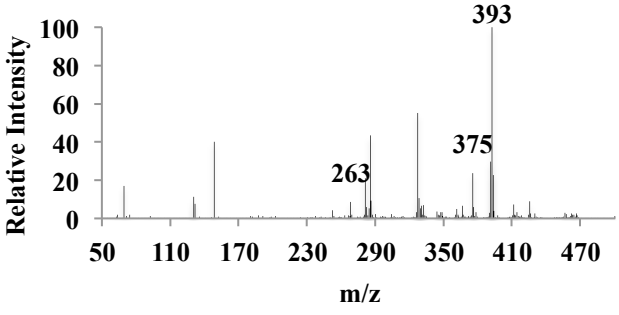
Table S4 Aldehyde effect summary

	2		**3**		**4**		**7**		**9**	
	S	*B*	*S*	*B*	*S*	*B*	*S*	*B*	*S*	*B*
benzaldehyde	-	-	x	x	x	x	x	x	x	x
2-phenylacetaldehyde	-	-	x	x	x	x	x	x	x	x
acetaldehyde	-	-	x	x	x	x	x	x	x	x
4-nitrobenzaldehyde	-	-	x	x	x	x	x	x	x	x
anthracene-9-carbaldehyde	x	x	-	-	-	-	-	-	-	-
dodecanal	-	-	x	x	x	x	x	x	x	x

S denotes sprayed reaction mixture. B denotes bulk phase reactions. Due to ion suppression some identifications were performed in MS^2.

Table S5 Aldehyde substituent effects

Aldehyde	Spectral Details	Spectra
benzaldehyde (Product m/z = 330) 	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	
2-phenylacetaldehyde (Product m/z = 344) 	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	

acetaldehyde (Product m/z = 268) 	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	
4-nitrobenzaldehyde (Product m/z = 375) 	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	

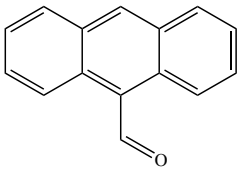
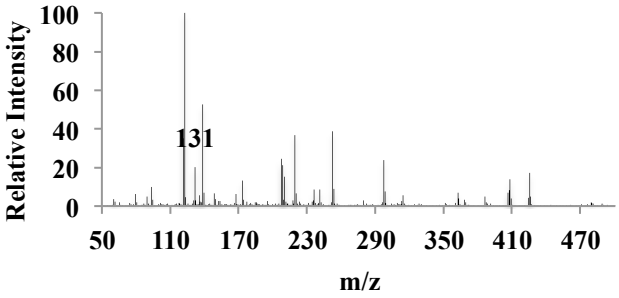
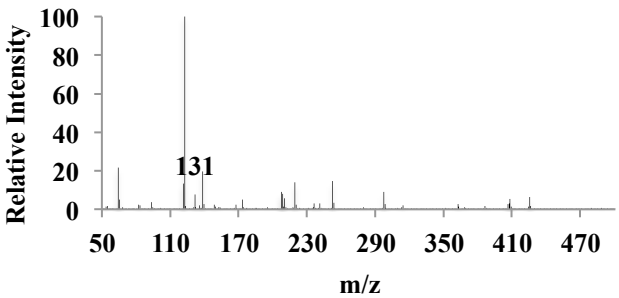
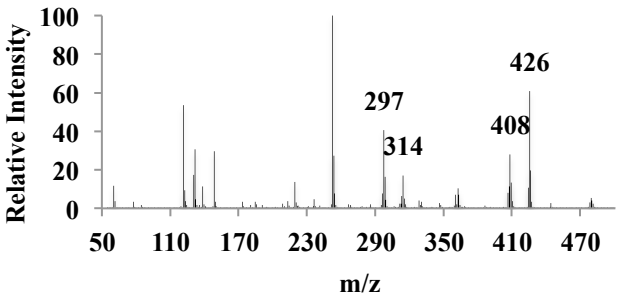
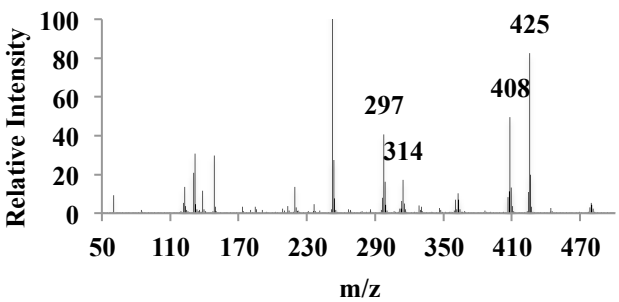
anthracene-9-carbaldehyde (Product m/z = 430*) * not seen 	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	
dodecanal (Product m/z = 408) 	ESI synthesis (75 cm, 200°C inlet temperature)	
	Sprayed bulk phase (2 cm, 100°C inlet temperature)	

Table S5 A compilation of spectra supporting Table S4. Shows the similarity and differences between the spectra from the bulk phase product as well as the ESI synthesis.

Figure S2 On-line distance

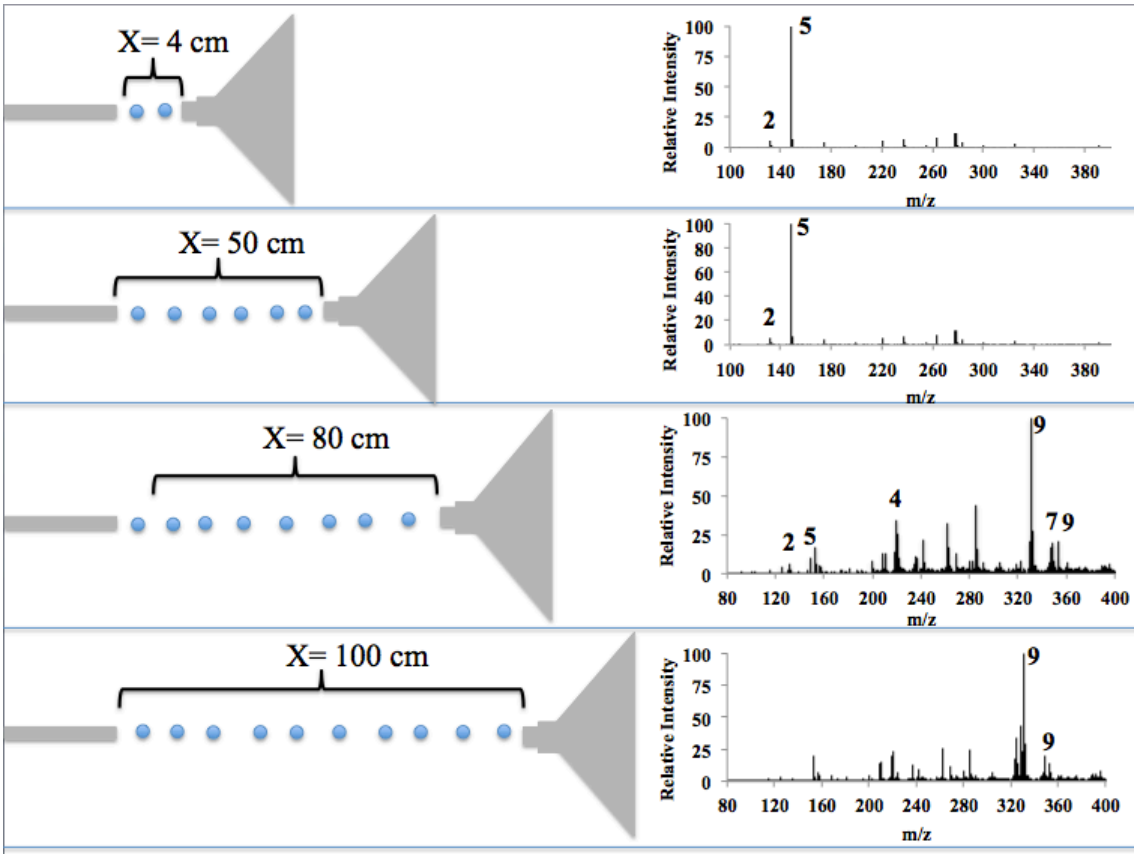
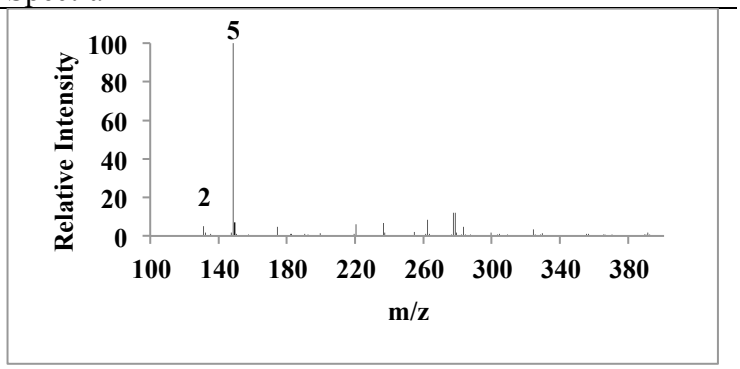
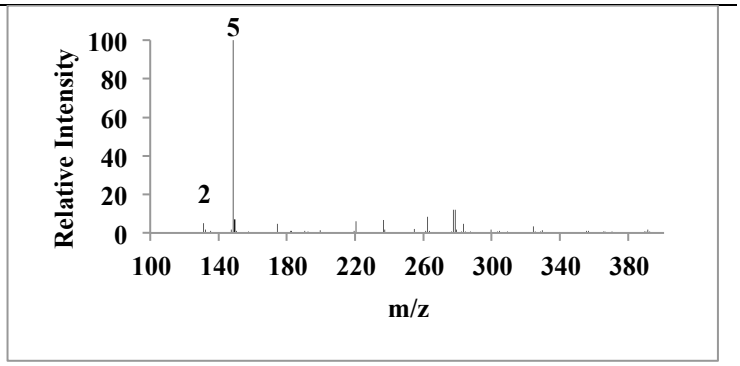
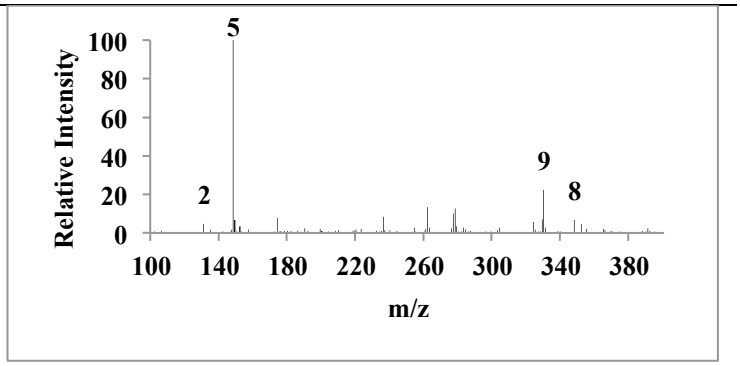
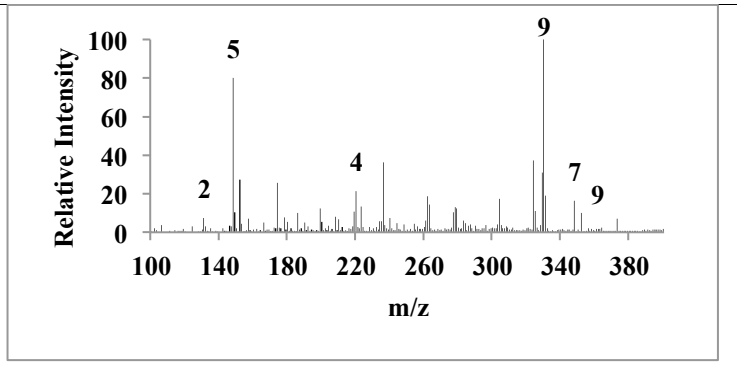


Figure S2 Stages of reaction completeness in the droplets traveling between the MS inlet and the sprayer as a function of distance (x).

Table S6 On-line distance

Distance (cm)	Spectra
4 cm	
50 cm	
60 cm	
70 cm	

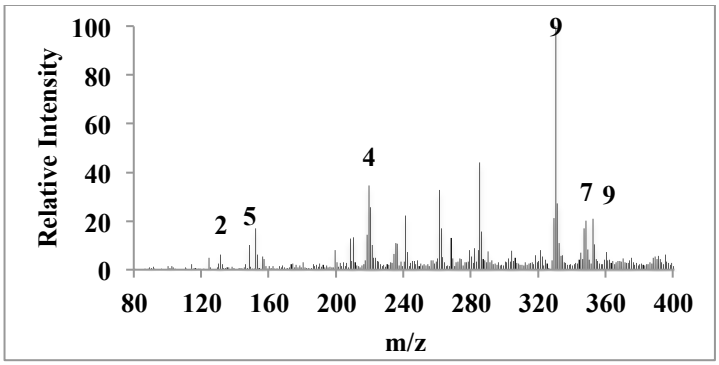
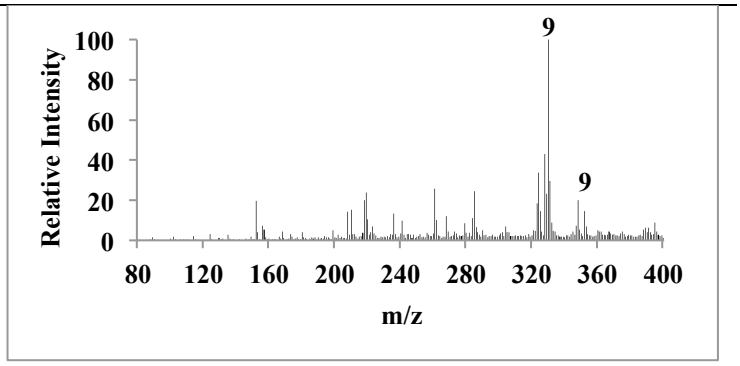
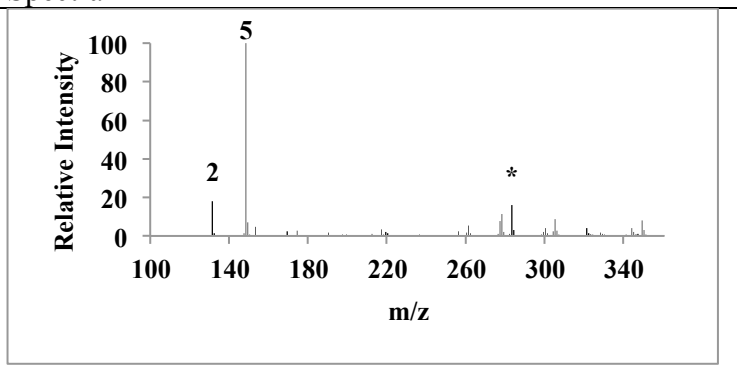
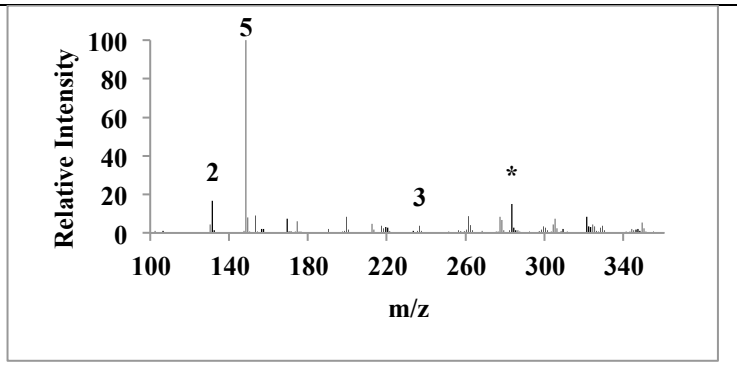
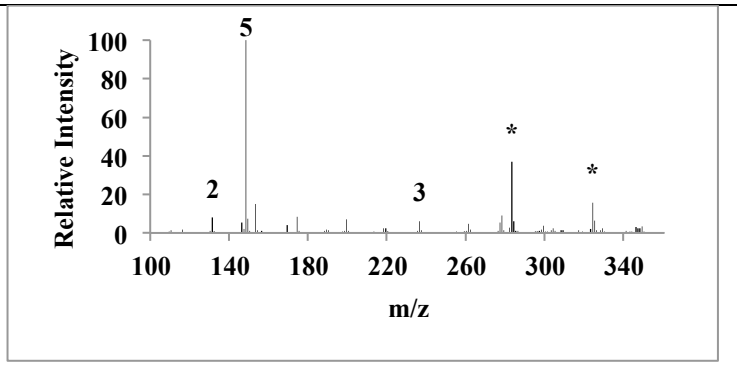
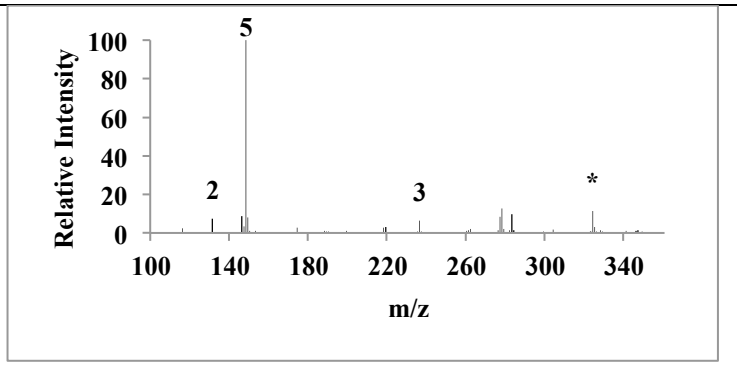
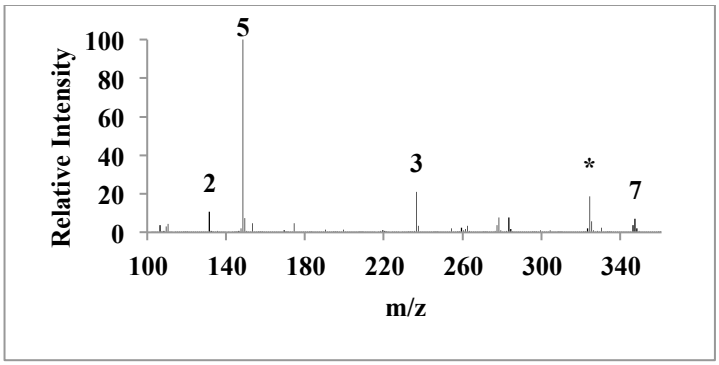
80 cm	
100 cm	

Table S6 Collected spectra for distances between the ion transfer capillary and the spray source. Capillary temperature 150°C with a total flow rate of 50 μL/min and a nitrogen gas pressure of 125 psi. Other variables are consistent with Table S1.

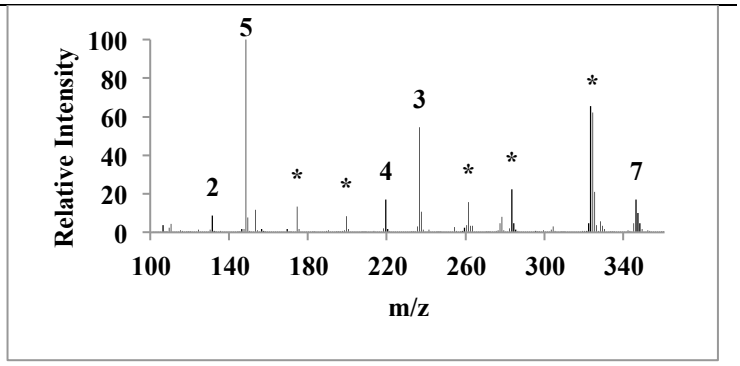
Table S7 On-line distance with tube

Tube length (cm)	Spectra
20 cm	
30 cm	
40 cm	
50 cm	

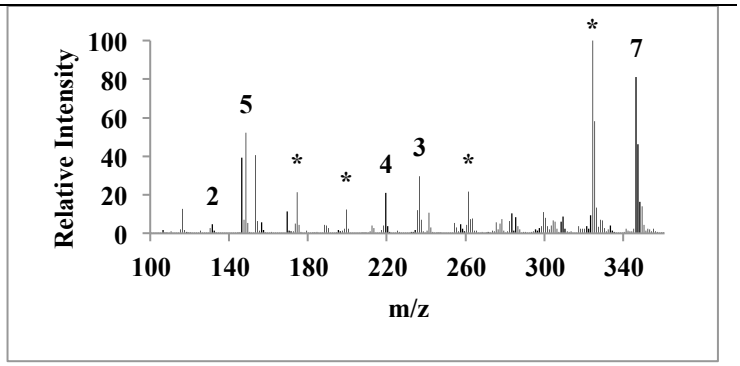
55 cm



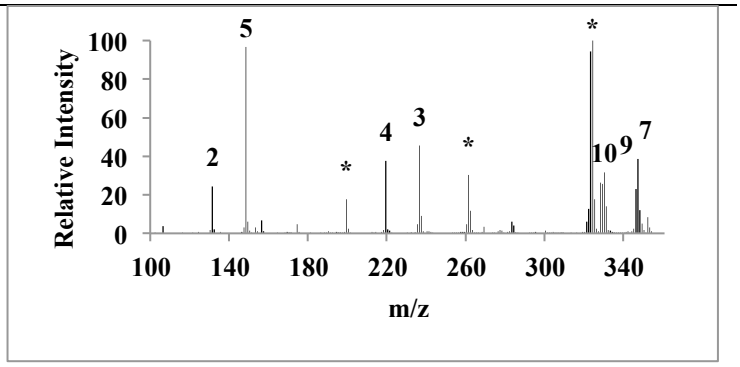
60 cm

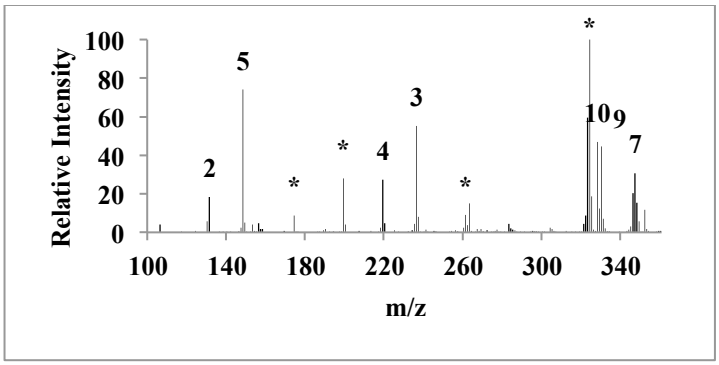
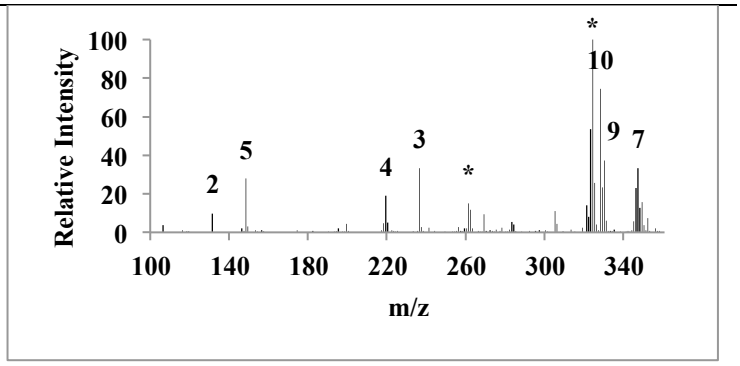
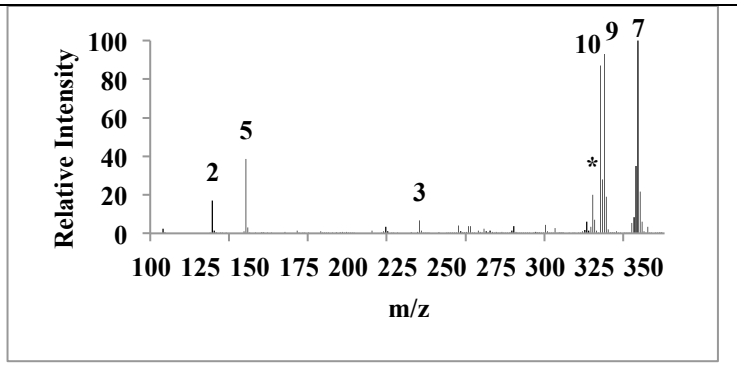
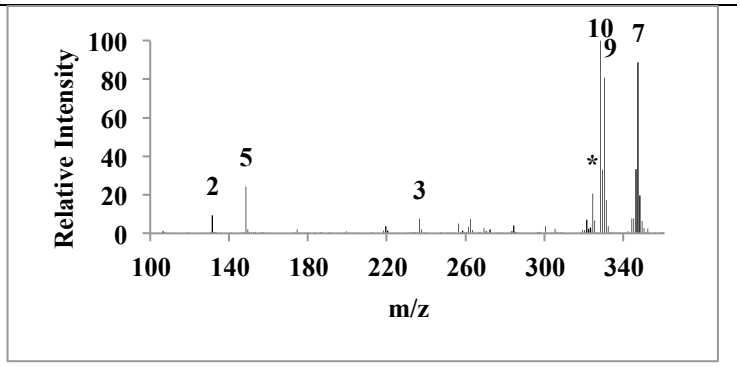


65 cm



70 cm



75 cm	
80 cm	
85 cm	
90 cm	

95 cm

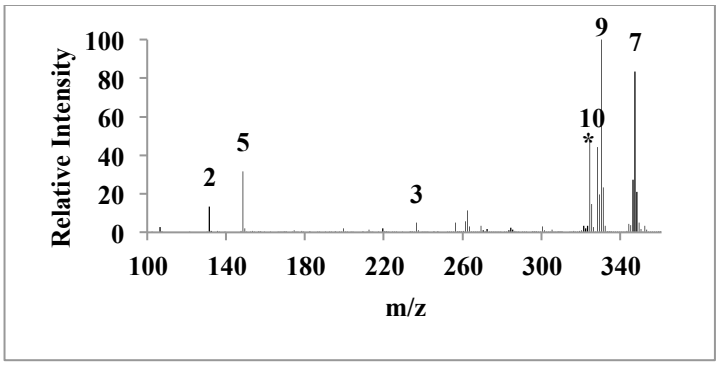
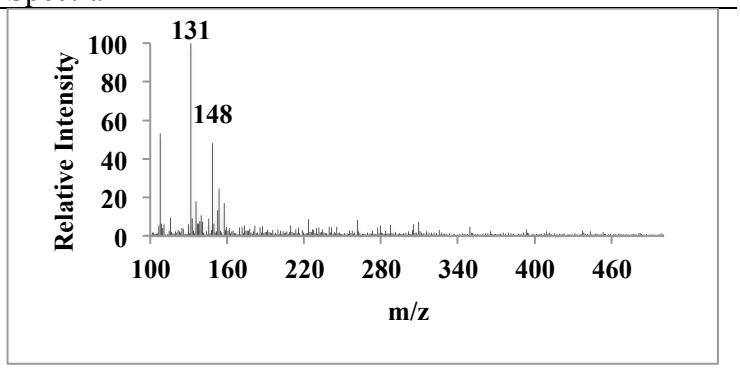
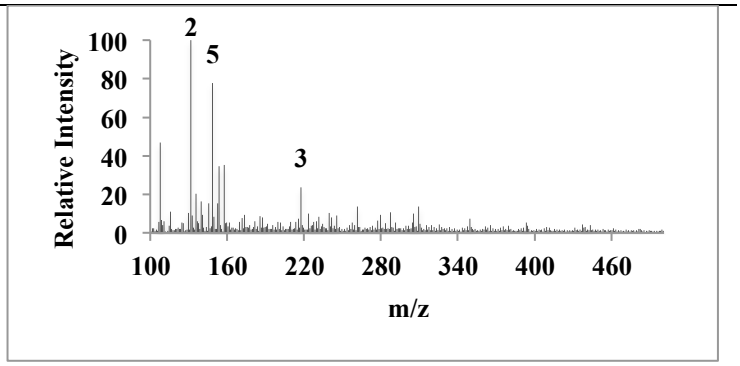
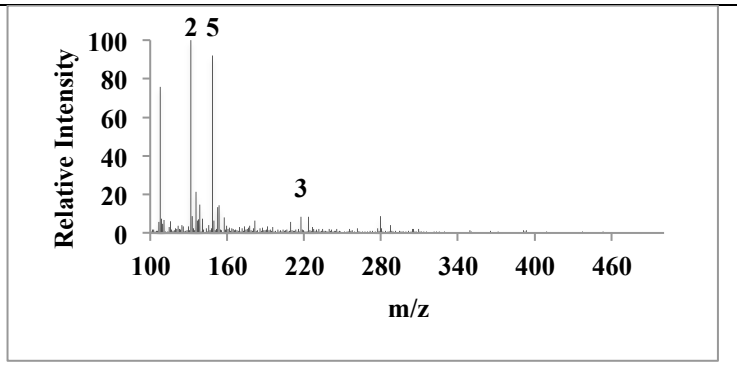
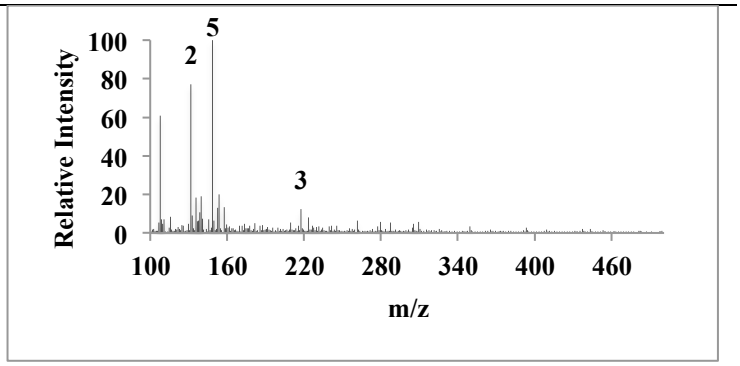


Table S7 Collected spectra for distances between the ion transfer capillary and the spray source with a stainless steel tube of length (x) in between. 5 cm were between the tube and the MS. Capillary temperature 150°C with a total flow rate of 50 μL/min and a nitrogen gas pressure of 125 psi. Other variables are consistent with Table S1.

Table S8 Off-line distance with cold collection

Distance	Spectra
4 cm	
25 cm	
50 cm	
60 cm	

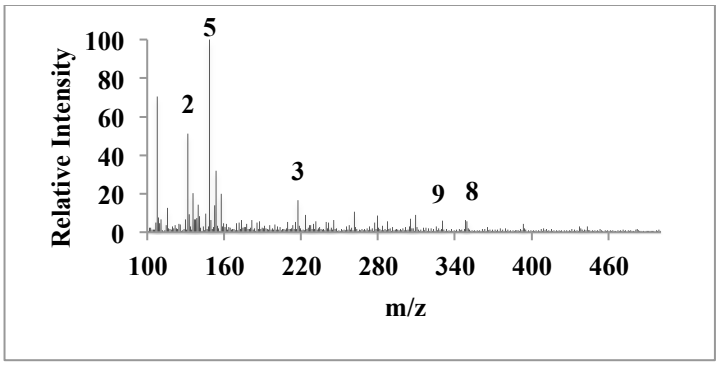
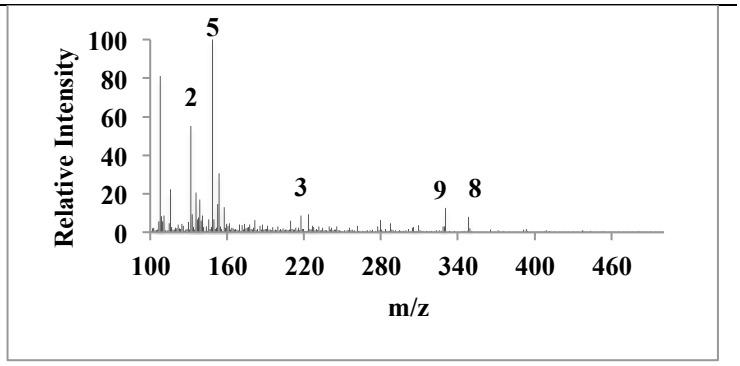
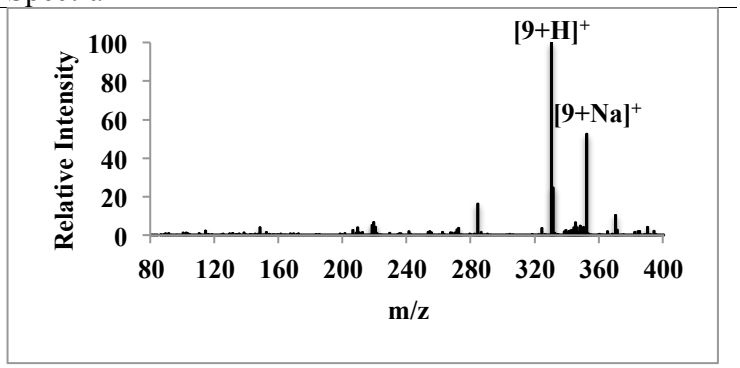
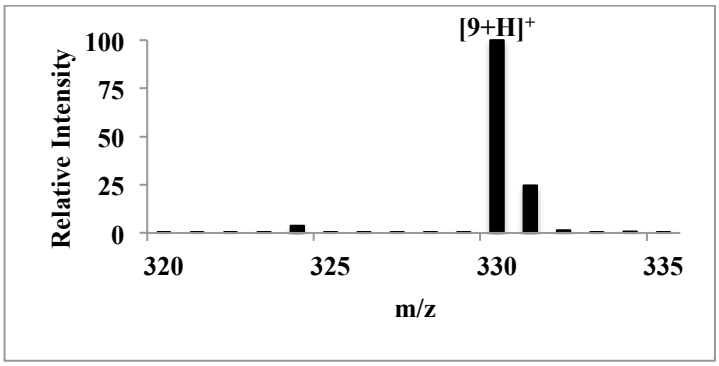
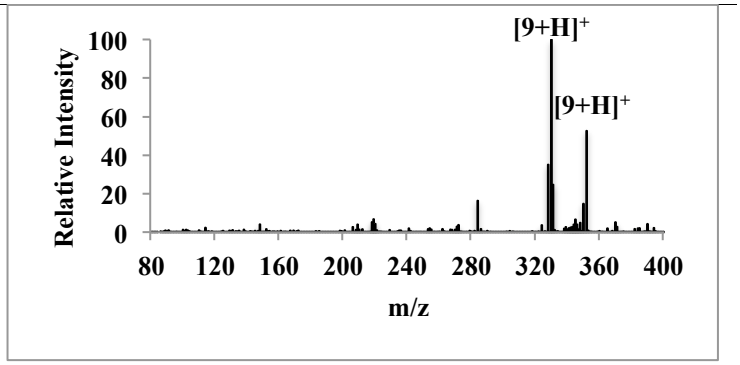
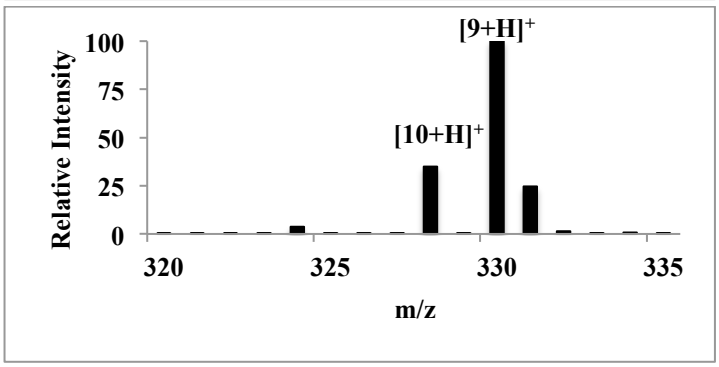
80 cm	
100 cm	

Table S8 Collected spectra from a distance study with collection on a surface kept at ~-77°C by a dry-ice/IPA bath. Total flow rate of 50 μL/min and a nitrogen gas pressure of 125 psi. Other variables are consistent with Table S1.

Table S9 Ion transfer capillary temperature

Capillary Temperature (˚C)	Spectra
150˚C	
	
250˚C	
	

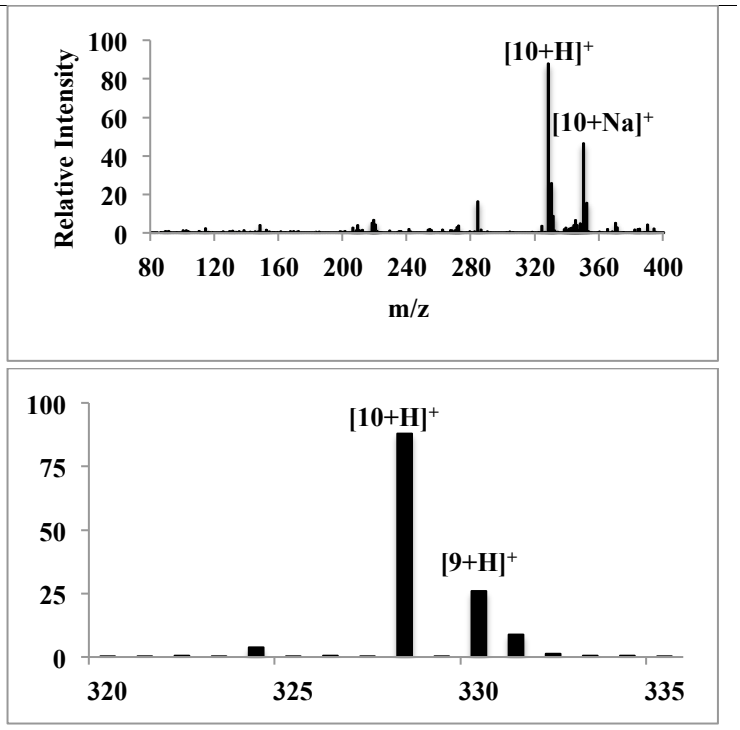
350˚C	

Table S9 Ion transfer capillary temperature varied with a constant distant of 100 cm between the MS and the spray source. A total flow rate of 50 μL/min and a nitrogen gas pressure of 125 psi was used throughout. Other variables are available in Table S1.

Table S10 Spray source variable

Variable		Value
Capillary length (in source)	*Inner (silica)*	50 mm
	Outer (stainless)	100 mm
Capillary diameter (ID)	*Inner (silica)*	100 μm
	Outer (stainless)	~500 μm
Flow rate	*Reagent*	5 - 100 μL/min
	Gas	50 - 125 psi
Mixing methods		Upchurch static mixing T
Spray geometry	*Angle*	45˚
	Distance	5 cm
Voltage		+/- 5 kV
Concentration sprayed		0.1-100 mM
Collection surface		Beaker & colander

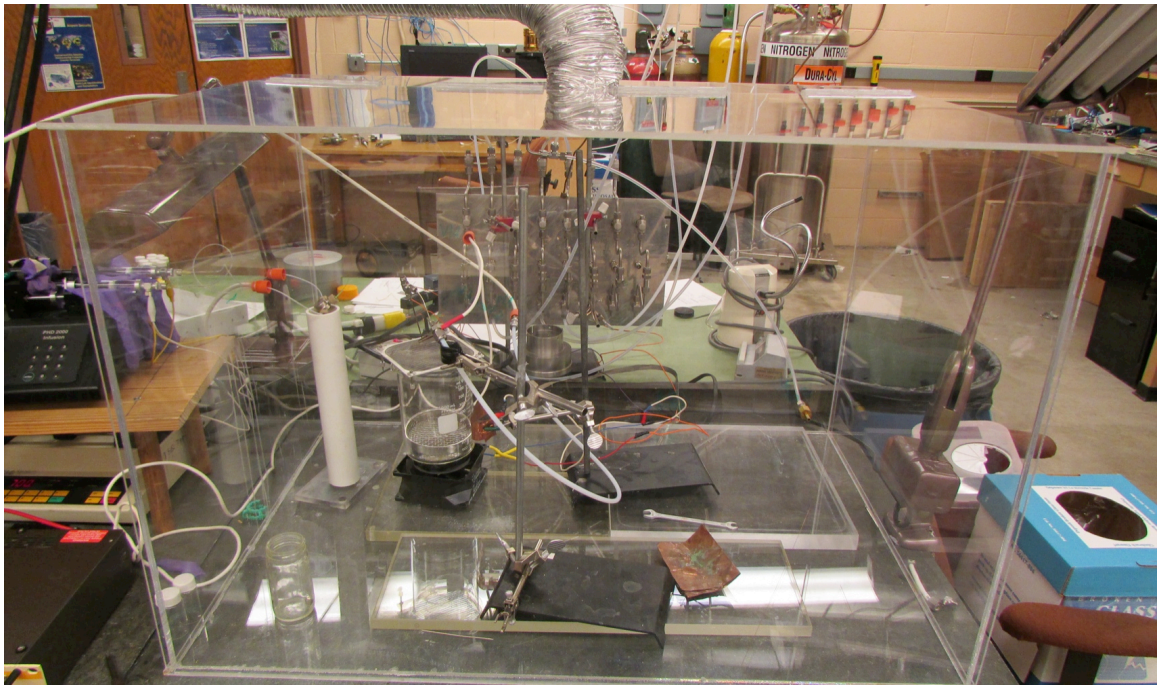
Optimized ESI and collection variables used throughout unless otherwise noted.

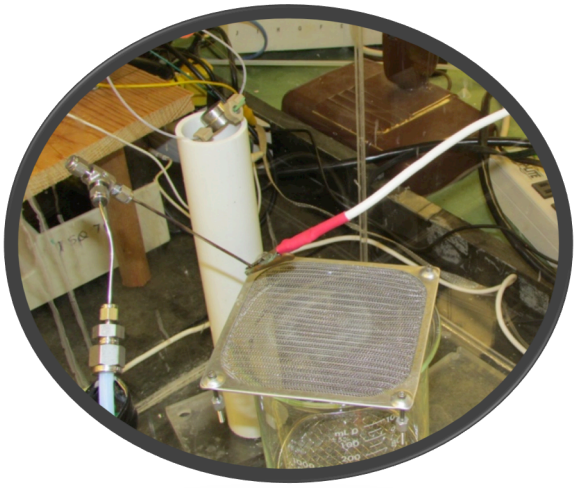
250 mg/hr experimental design

In order to achieve product formation at 250 mg/hr 85 mM solutions of benzaldehyde, ethyl acetoacetate, and ammonium acetate were used. The benzaldehyde and ammonium acetate were loaded into 10.0 mL Hamilton gas-tight syringes fitted with luer-locks. Since the ethyl acetoacetate is needed in a 2 molar equivalent, 20.0 mL were loaded into a 25.0 mL syringe. Flow rates of 166 µL/min for benzaldehyde and ammonium acetate and 332 µL/min for ethyl acetoacetate (or 664 µL/min at the sprayer) were used for maximum yield experiments. Desolvation was also aided by 125 psi of nitrogen gas supplied by a liquid nitrogen tank. The optimized spray surface of a grounded steel colander sitting on a rotating beaker was rinsed with 100 mL of ethanol as a diluent. A total dilution of 4 L was done in series. This experimental procedure allowed for optimization because ~90% yield was ~1 Abs unit for UV-Vis analysis.

Recovery experiments were also performed where synthesized **9** was sprayed at 85 mM and recovered on the collection surface. This showed an average percent recovery of 95%. Surfaces can greatly affect the percent recovery as well as the percent yield due to the high pressure of sheath gas.

Off-line Apparatus Photos





Cold Collection Photos