Electronic Supplementary Material (ESI) for Analyst.
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Supporting information

Implementing reactive secondary electrospray ionization based on gas-droplet reactions for VOCs analysis

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MS^n spectra of the reaction-related ions in reactive SESI-MS analysis of propionaldehyde

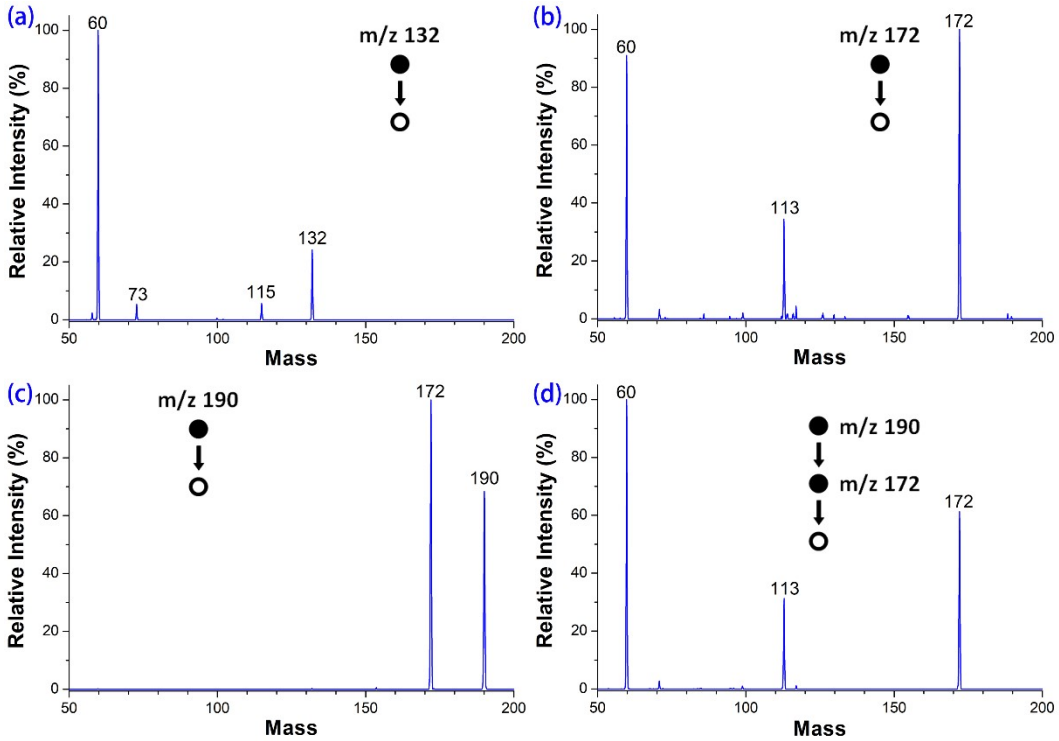

Fig. S1. MS^2 spectra of (a) Girard T ion (m/z 132), (b) product ion (m/z 172), and (c) intermediate ion (m/z 190). (d) MS^3 spectrum of the fragmentation ion (m/z 172) from CID of the intermediate ion (m/z 190), which has the same ion composition with the reaction product ion (m/z 172). As a characteristic functional group of Girard T, protonated trimethylamine ion (m/z 60) is observed in the three compounds, indicating that both the intermediate and product ions are derived from Girard T.

Influence of some experimental parameters on the reaction efficiency

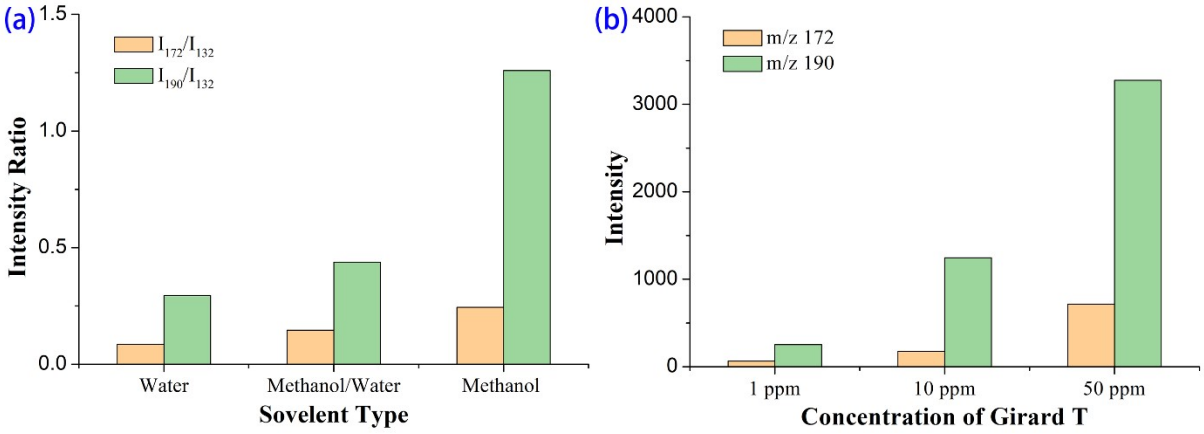

Fig. S2. (a) The intensity ratio of the reactant (Girard T, m/z 132) ion and the reaction product ions (m/z 172, m/z 190) obtained using different types of solvent (water, methanol/water (1:1) mixture, and methanol). (b) Intensities of the reaction intermediate ion (m/z 190) and product ion (m/z 172) acquired using different concentrations (1 ppm, 10 ppm and 50 ppm) of Girard T solutions.

Reactive SESI-MS analysis of formaldehyde with different derivatization reagents

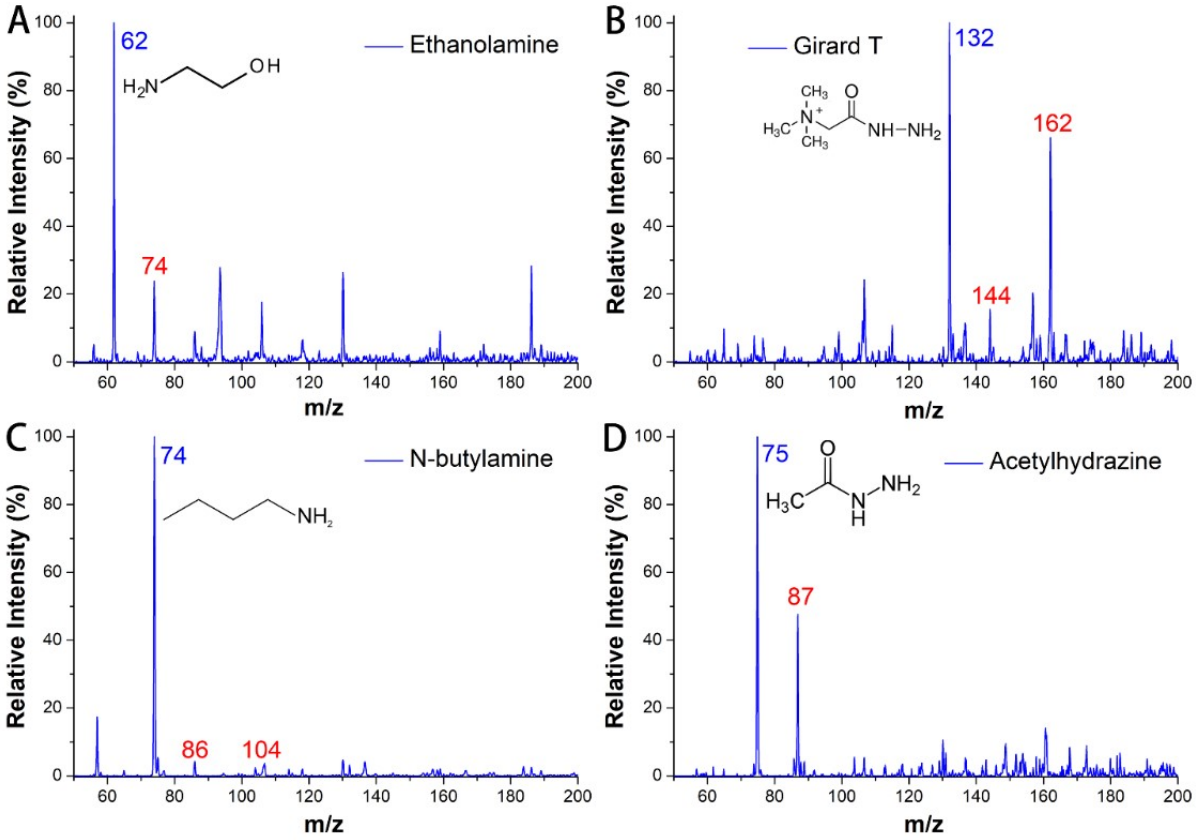

Fig. S3. Reactive SESI-MS spectra of formaldehyde using (A) ethanolamine, (B) Girard T, (C) N-butylamine, and (D) acetylhydrazide as the derivatization reagents. Online derivatization of formaldehyde (marked as F, molecular mass 29) can be induced using a variety of reagents (marked as R), such as ethanolamine (*m/z* 62), Girard T (*m/z* 132), n-butylamine (*m/z* 74), and acetylhydrazide (*m/z* 75). The reactions between formaldehyde and these additives generally take place through the Schiff base formation mechanism, namely, an initial addition reaction and then a dehydration process. The product ions of Schiff base formation $[R+F-H_2O+H]^+$ or the intermediate ions $[R+F+H]^+$ can be found in all spectra. Since the generation of those derivative ions is related to formaldehyde in the samples, they can be used as markers to indicate the content of formaldehyde.

Reactive SESI-MS analysis of butanone and butyraldehyde by Girard T solution

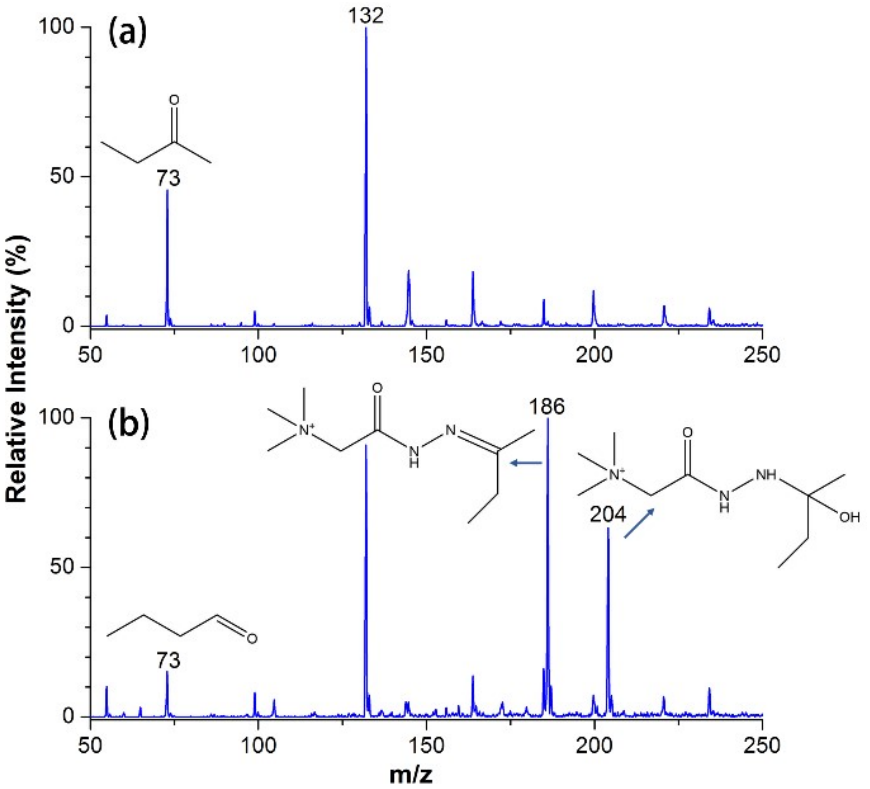

Fig. S4. Reactive SESI mass spectra of (a) butanone, and (b) butyraldehyde, in which Girard T was used as the derivatization reagent. Ketones have one more alkyl group nearing the carbonyl structure that pushes electrons to the neighboring electrophilic center, leading to less electrophilic and reactive nucleophilic addition. Moreover, since the reaction starts with nucleophile attacking the carbon in the carbonyl group, more hydrogen atoms in ketones will produce more steric hindrance for nucleophile approaching. In the SESI process, the addition reaction of Girard T and butanone rarely occurred, so no obvious product ions were observed. In contrast, a certain amount of addition products, including the hydrazine ion (*m/z* 204) and its dehydration ion (*m/z* 186), were produced from the online derivatization of butyraldehyde. Girard T carries a formal charge on the nitrogen atom, thus transforming aldehydes into products with charged (quaternary ammonium) and easily ionizable (secondary amine for positive-ion mode) groups which improve mass spectrometric response.

Silver-containing complex ions in exhaled breath of cultured non-diabetic and diabetic mice

Table S1 The Ag-containing complex ions detected in the exhaled breath from the cultured nondiabetic and diabetic mice using reactive SESI-MS. The most proposed molecular formula, signal intensity, and mass error were also given. The types of these ions are roughly determined from their signal changes in EIC. Specifically, ions detected in the mouse with diabetes have significantly higher intensities than that in the normal mouse are classified as potential biomarkers for diabetes. Ions have fewer differences in signal intensities between the two samples are classified as suspect biomarkers. Additionally, the remaining ion pairs can be divided into two other categories: air or solvent background. Thereinto, the ion intensity of the former does not change with sample injection, while the intensity change of the latter corresponds to the injection process, but is independent of the mouse type.

Type	Measured m/z value	Mass error (ppm)	Molecular formula	Intensity (nondiabetic)	Intensity (diabetic)
Silver ion	106.9050	4.26	Ag	248587	272442
	108.9050	7.28		232747	251268
Potential biomarkers	164.9464	-0.06	C_3H_6OAg	171	2595
	166.9456	-2.83		147	2349
	347.0168	-0.26	$C_{12}H_{12}N_6Ag$	1	1231
	349.0161	-1.30		1	1344
Suspected biomarkers	222.9882	-0.33	$C_6H_{12}O_2Ag$	1421	1979
	224.9877	-1.05		1036	2049
	281.0297	-1.6	$C_9H_{18}O_3Ag$	9074	17097
	283.0293	-1.77		7908	14607
	306.0015	-0.26	$C_{10}H_{15}O_4Ag$	1111	1318
	308.0006	-2.08		998	1075
Sample background	288.9747	3.51	$C_8H_{10}O_3N_2Ag$	26907	34974
	290.9742	2.92		25720	31012
	289.9783	-1.83	$C_4H_7ON_8Ag$	1582	957
	291.9777	-2.70		807	1182
	306.9853	-0.94	$C_9H_8N_6Ag$	73032	121939
	308.9850	-0.82		67328	110815
	307.9887	2.10	$C_3H_{13}O_6N_4Ag$	4246	7513
	309.9883	1.88		3889	6575
	330.0013	-0.84	$C_{12}H_{15}O_4Ag$	144918	209241
	332.0009	-1.03		133592	189842
	331.0048	-1.74	$C_6H_{10}ON_9Ag$	11503	189842
	333.0044	-1.93		10980	15321
Air or solvent background	123.9312	0.86	H_3NAg	2206	1212
	125.9309	1.14		2310	1265
	124.9152	0.73	H_2OAg	3906	4794
	126.9149	0.73		4133	3891
	147.9309	-1.31	C_2H_3NAg	465888	564490
	149.9307	-0.38		449845	536517
	165.9415	-0.95	C_2H_5ONAg	27772	37494
	167.9413	-0.13		25721	35892
	188.9575	-0.76	$C_4H_6N_2Ag$	152811	177229
	190.9572	-0.55		139122	169552

189.9610	-9.411	CH_9O_3NAg	5558	6576
191.9606	-9.641		5284	5759
212.9675	-0.18	$C_4H_{10}O_3Ag$	833	1128
214.9669	-1.40		800	1092
223.9833	-0.99	$C_5H_{11}O_2NAg$	4372	2185
225.9829	0.50		3555	2021
269.0298	-1.26	$C_8H_{18}O_3Ag$	10523	11214
271.0294	-1.48		9976	10208
301.0712	-1.36	$C_{13}H_{22}OAg$	6636	5502
303.0708	-1.56		6665	5277
311.0402	-1.62	$C_{10}H_{20}O_4Ag$	9195	9738
313.0398	-1.81		8101	7419
333.0972	-1.88	$C_{14}H_{26}O_2Ag$	1925	1876
335.0969	-1.75		1740	1704
355.1179	-1.86	$C_{17}H_{28}OAg$	6403	5479
357.1177	-1.47		6071	5513
361.1285	-1.73	$C_{16}H_{30}O_2Ag$	9136	9676
363.1281	-1.89		8189	8815
389.1595	1.07	$C_{16}H_{32}ON_3Ag$	1768	1579
391.1593	1.42		1361	1607