# **Supplementary Information:**

# Making diazomethane accessible for R&D and industry: Generation and direct conversion in a continuous micro-reactor set-up

Michael Struempel,<sup>a</sup> Bernd Ondruschka<sup>a</sup>, Ralf Daute<sup>b</sup> and Annegret Stark<sup>\*a</sup>

## Analytics

Since the liberation of diazomethane from the precursor Diazald<sup>®</sup> and successive reaction with carboxylic acid is an <sup>10</sup> established quantitative method,<sup>1</sup> the yield of benzoic acid methyl ester is directly proportional to the yield of diazomethane.

Quantitative analyses were conducted on a Hewlett Packard 6890 Series GS-System (Chrompak HP5, 30 m; 0.25  $\mu$ m) with FID against an external calibration with benzoic acid methyl ester. The 15 total error was determined to be  $\pm 5$  %.

### Experimental

*Note: Diazomethane is highly toxic, explosive and should therefore only be handled according to recommended procedures.*<sup>2,3</sup>

All chemicals and solvents were used as received: Diazald<sup>®</sup> 99 % (Sigma Aldrich); KOH 95 % (Merck); Carbitol (Fluka) 98 %; diethyldiglycol (Fluka) 98 %; 2-propanol 95 % (Merk); benzoic acid 99.9 % (Merck); benzoic acid methyl ester 99 % (Sigma Aldrich).

#### 25 Batch experiments

All batch experiments were carried out in a fume-hood under particular safety precautions: In a 4 ml vial with magnetic stirrer, Diazald<sup>®</sup> was dissolved in the solvent specified. The vial was closed by a cap with septum. A capillary to another 10 ml vial filled <sup>30</sup> with 30 % acetic acid solution is used to avoid over-pressure and to safely destroy all gaseous diazomethane developed. The solution of KOH is added to the Diazald<sup>®</sup> solution *via* syringe. The reaction is subsequently quenched with a solution of benzoic acid, and analysed by GC.

#### 35 Micro-reactor experiments

The working mechanism of the continuous micro-reactor set-up was shown in Scheme 3. The precursor Diazald<sup>®</sup> and KOH are brought together in the first part of either the Y-shaped micro-reactor (see Supplementary Figure 3, residence time  $t_{R1}$ ) or a

- <sup>40</sup> capillary to generate diazomethane. In the second part, benzoic acid is added to yield benzoic acid methyl ester (residence time  $t_{R2}$ ). To ensure safety, all fluid-containing components of the set-up are placed in a fume-hood and immersed in an acetic acid bath to quench any diazomethane released in case of leakage. The second <sup>45</sup> function of the bath is to control the temperature of the set-up.
- Additionally, the set-up is equipped with temperature (Typ K, Conatex Dipl.-Ing. L. Colbus GmbH, St.Wendel, Germany) and

pressure sensors (26pc, Honeywell, Offenbach, Germany) programmed for shut-down if the internal pressure reaches 7 bar.

- As reaction device, a commercially available micro-reactor (see Supplementary Figure 3, Little Things Factory GmbH, Ilmenau, Germany, type "ST MI018", 0.12 ml internal volume) was used. This reactor consists of four layers providing 32 mixing elements distributed over the length of the reactors. These twist the product stream by 90° each. For comparison, and only when explicitly stated, a PTFE-capillary (Upchurch Scientific, Oak Harbor, USA, inner diameter of 1.55 mm, no mixing elements) was used. The fluid streams were generated by a micro-dosing syringe pump "MDSP3f, i-14" (Micro Mechatronic Technologies GmbH, MMT,
- <sup>60</sup> Siegen, Germany). The set-up was centrally controlled with a computer, for which a control and automation programme was developed with the visual programming software HP-VEE 5.0.

All continuous experiments were carried out using the parameters specified in the Supplementary Table below at a ratio of <sup>65</sup> Diazald<sup>®</sup> : KOH : benzoic acid = 1.0 : 1.5 : 4.0, at T = 28 °C, except entry 5 (T= 0-85°C).

The conditions for the continuous reaction set-up carried out either in the micro-reactor or the capillary set-up are listed in the Supplementary Table.

<sup>70</sup> Entry 1 refers to a comparison experiment showing that if the base feed contains water, the yield of benzoic acid ethyl ester is low (5 %), as was found in the batch experiments. Entry 2 shows the parameters used for optimising the system. Entries 3 and 4 refer to reactions performed using a capillary to investigate the effect of  $t_{R1}$  and total flow rate. Entries 5 and 6 detail the conditions under which the effect of temperature and long-term stability testing were investigated.

### References

- 80 1 E. K. Marshall and S. F. Acree, *Ber. Chem. Ges.*, 1910, **10**, 2323.
  - 2 Th. J. de Boer and H. J. Backer, Org. Synth., 1963, Coll. Vol. 4, 250.
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**Supplementary Fig 1.** Dependency of the yield of benzoic acid methyl ester (relative to Diazald<sup>®</sup>) on the temperature (for experimental conditions see Supplementary Table, entry 5).



**Supplementary Fig 2.** Stability of the yield of benzoic acid methyl ester (relative to Diazald<sup>®</sup>) during the continuous operation of the set-up (experimental conditions see Supplementary Table, entry 6).

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Supplementary Table Experimental conditions for the continuous processes

Entry	Diazald®		КОН		Benzoic acid		v <sup>a</sup>	$\mathbf{t}_{\mathrm{R1}}^{b}$	$t_{R2}^{b}$
		[mol/l]	] [	mol/l	]	[mol/l	] [ml/h]	[s]	[s]
1	$CH_2Cl_2$	0.5	water	1.0	CH <sub>2</sub> Cl <sub>2</sub>	1.0	20-1050	287-6	340-7
2	carbitol	0.4	2-propanol	1.5	carbitol	1.5	30-840	120-4	267-10
3 <sup><i>d</i></sup>	carbitol	0.4	2-propanol	1.5	carbitol	2.0	60-600	48-5	43-4
$4^d$	carbitol	0.4	2-propanol	1.5	carbitol	1.5	30-840	920-33	56-2
5 <sup>e</sup>	carbitol	0.4	2-propanol	1.5	carbitol	1.5	240	19	36
6	carbitol	0.4	2-propanol	1.5	carbitol	1.5	240	19	3
<sup><i>a</i></sup> total flow rate, <sup><i>b</i></sup> partial residence times, <sup><i>c</i></sup> carbitol = di(ethylene glycol) ethyl ether, <sup><i>d</i></sup> capillary without mixing elements, <sup><i>c</i></sup> temperatures varied between 0 and 85°C.									



**Supplementary Fig. 3.** ST MI018-micro-reactor (left) and the mixing elements contained in the channels (right) from Little Things Factory <sup>105</sup> GmbH, Ilmenau, Germany.

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