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Supporting Information

Rapid Chemical Reaction Monitoring by Digital Microfluidics-NMR: Proof of Principle Towards an Automated Synthetic Discovery Platform

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Supplementary Information

Experimental Section

DMF-NMR Device:

Figure 1b shows the integration of the NMR microcoil as it has been described in detail previously[1]. Briefly the coil has an I.D. of 500 µm with 4 turns with of copper 30 µm wide, spaced at 30 µm giving an O.D. of 0.98 mm. The microcoil is set into a copper plate (coated with 200 nm of Parylene), which acts as a ground electrode for the DMF device (top-plate). The top-plate was coated with FluoroPel[1]. The bottom plate contained 20 square DMF driving electrodes (2.25 × 2.25 mm), two reservoir electrodes (6.6 × 16 mm) and two dispensing electrodes (2.25× 4.1 mm) and was coated with Parylene and then FluoroPel. The assembly is shown in Fig. S1 and described in detail in our previous work with a hardware setup.[1]

The device and electrical connections are mounted to a standard MIC-05 imaging probe, and then loaded into a 11.7 T (500 MHz) Bruker Avance III spectrometer. Once inside the NMR spectrometer the DropBot^{TM} control system permits real time capacitance measurements between the actuation-electrode and ground-electrode to distinguish between filler (air) and fluid (sample).[2] This allows the location of all the droplets to be monitored in realtime. This is very important for the study outlined here as once loaded into the NMR it is not possible to physically see the DMF-NMR device.

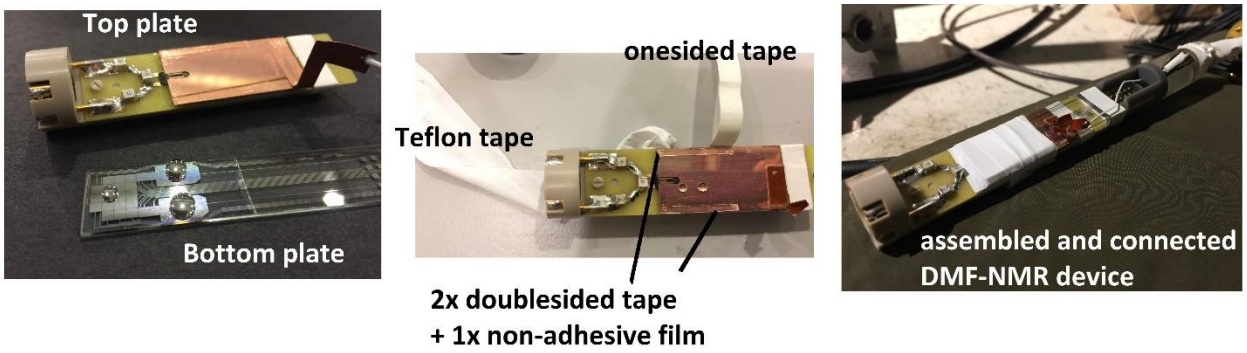


Figure S1: Photographs of the NMR-DMF-assembly. Two strips of two layers of double-sided tape were placed on the long sides of the DMF device, they were additionally covered with a thin, non-adhesive film. These triple layer strips served as a ~180micron spacer between top and bottom-plate. To hold bottom and top plates in the correct relative position after their assembly, a small strip of one-sided adhesive tape was used. Additional non-adhesive Teflon tape was used to provide mechanical stability against sheer and torque forces, which couldn't be provided by the tape adhesive tape alone. Assembly and disassembly doesn't induce any stress to the components, because only the (small) one-sided adhesive tape provides a bonding, while the other tapes were only providing tight fit.

NMR Experimental:

DMF-NMR experiments were performed using a Bruker Avance III HD 11.7 T instrument equipped with a MIC-5 probe (DMF-NMR assembly: 1mm planar spiral coil coupled with 26 electrodes DMF chips, further details can be found in Swyer et al.[1, 3] Measurements were carried out at 293 K (20 ^{o}C). All the 1D ^{1}H NMR experiments were performed using single 90^{o} excitation pulse sequence. The microcoil required 0.1W to generate a 90^{o} RF pulse of 5 µs. Due to the extremely low power required heating effects were not observed and NMR peaks did not drift, even with the absence of a spectrometer lock (as an example see Figure S7 (right panel)).

For hydrolysis reaction, the typical acquisition parameters were as follows: 1) 16k acquisition points; 2) 4.2s recycle delay; 3) 1 scan; 4) 10 kHz spectral width. For the tandem Knoevenagel condensation and Michael addition, the typical acquisition parameters are following: 1) 16k acquisition points; 2) 2s recycle delay; 3) 64 scans; 4) 10kHz spectral width.

The ^{1}H DOSY (Diffusion Ordered Spectroscopy) experiment was performed using the pulsed-field gradient (PFG) stimulated-echo (STE) sequence with phase cycling of radio frequency pulses and a spoil gradient to suppress artifacts. A total of 16 increments were collected for the DOSY dimension with 32 transients collected for each increment. The gradient was ramped in a linear fashion from 2 to 98% of the full gradient strength 30G/cm/A. Two sine shaped gradient pulses of 1.1 ms duration was used for both coding and decoding. Typical acquisition parameters were as follows: 1) 8k acquisition points 2) 2.0s recycle delay and 80ms diffusion time 3) 10kHz spectral width.

All data with the exception of the ^{1}H-^{1}H TOCSY were collected with the DMF-NMR system.

To support the spectral assignments ^{1}H-^{1}H TOSCY (total correlation spectroscopy) data were performed on a Bruker Avance III HD 11.7T NMR spectrometer equipped with a ^{1}H-^{13}C-^{15}N TCI Prodigy^{TM} cryoprobe. A homonuclear Hartman-Hahn transfer using a MLEV17 spinlock for mixing was used. Typical acquisition parameter are as following: 1) 2k acquisition points 2) 1.0 s recycle delay and 256 increments 3) 7.6 kHz spectra width 4) 80 ms mixing time. Data were processed using a sine-squared function shifted by $\pi/2$ in both dimensions and a zero filling factor of 2.

Organic Reactions:

For the racemic cyclohexene carbonate (CHC) hydrolysis, two droplets were combined to start the reaction. For the 4M concentration experiment, the first droplet contained 8 M cyclohexene carbonate (CHC) and 8 M water in dimethylformamide-d_7. While the second droplet contained 1.6 M 2-propanol (IPA), 8 M water and 1.6 M triazabicyclodencene (TBD) in dimethylformamide-d_7. The ratio between these chemicals was also confirmed by NMR. For reactions involving other concentration of CHC, the concentration of other chemicals in dimethylformamide-d_7 was scaled down accordingly.

In tandem Knoevenagel condensation and Michael addition, two solutions were mixed on chip inside the NMR. The first solution was 0.1 M benzaldehyde (BA) in 10%H_2O+40% D_2O+50% MeOD-d_4. While the second solution was 0.05 M 5,5-Dimethylcyclohexane-1,3-dione (DIM) in 10%H_2O+50% D_2O+50% MeOD-d_4.

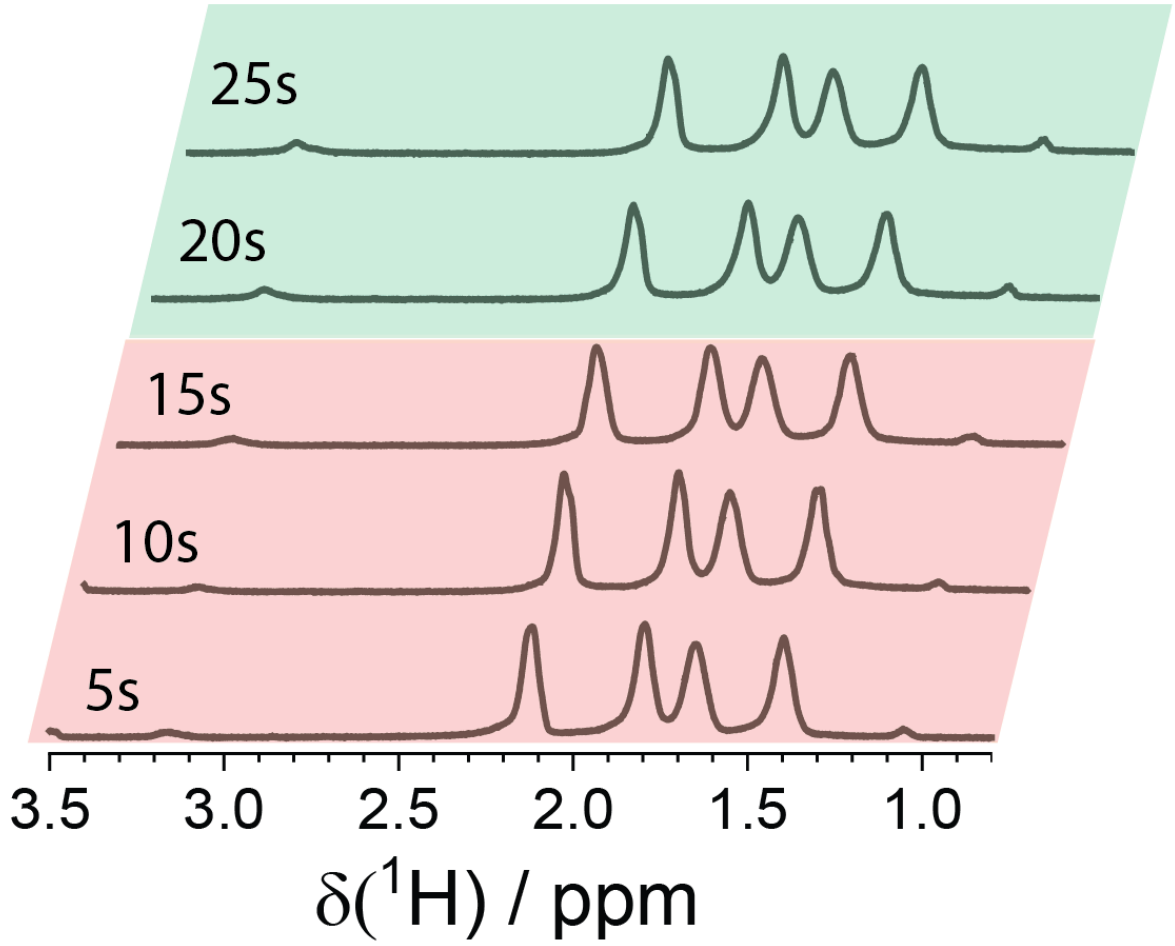
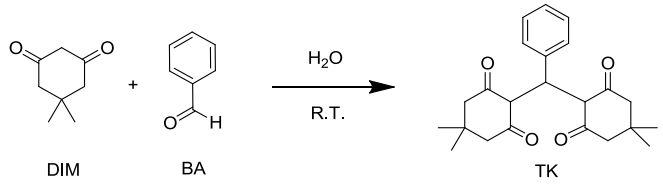


Figure S2. In the first 15 seconds the signals (red zone) are less stable due to the active mixing of the droplets. However, NMR data can still be collected adequately during this period if very fast reactions need to be captured. After 20s the droplets have settled and the data are highly reproducible (see Figure 2 in the main paper).



Scheme S1. TBD-catalyzed hydrolysis of racemic cyclohexene carbonate (rac-CHC) to cis-1,2-cyclohexanediol (c-CHDO).

NMR Spectra:

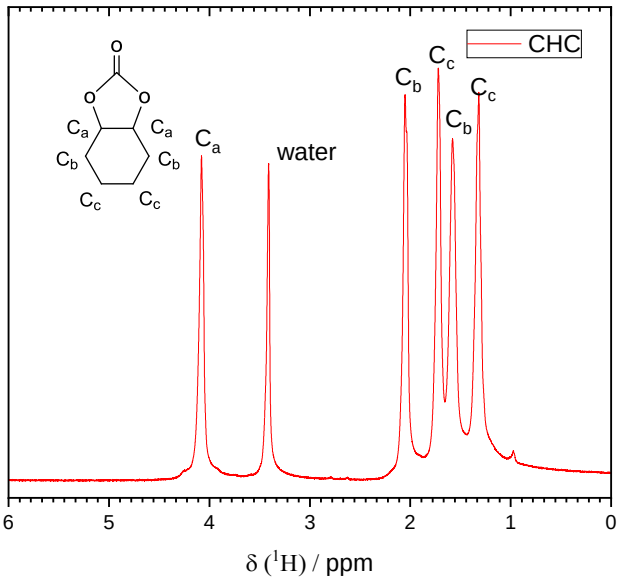


Figure S3. ^{1}H DMF-NMR spectrum of rac-CHC and its assignment.

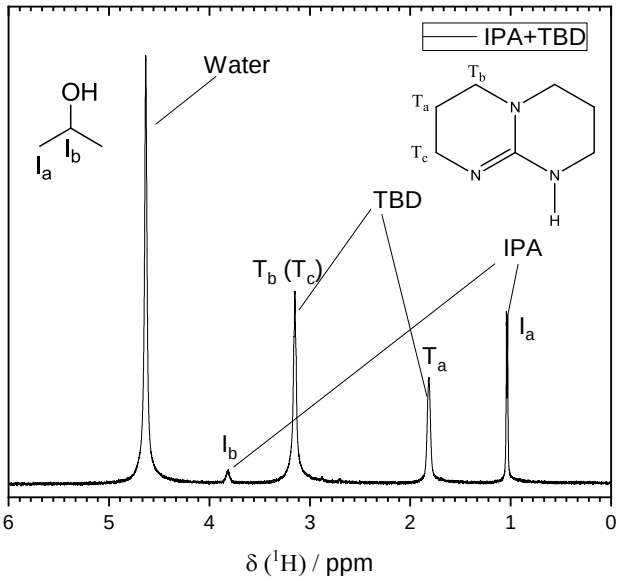


Figure S4. ^{1}H DMF-NMR spectrum of IPA+TBD and its assignment.

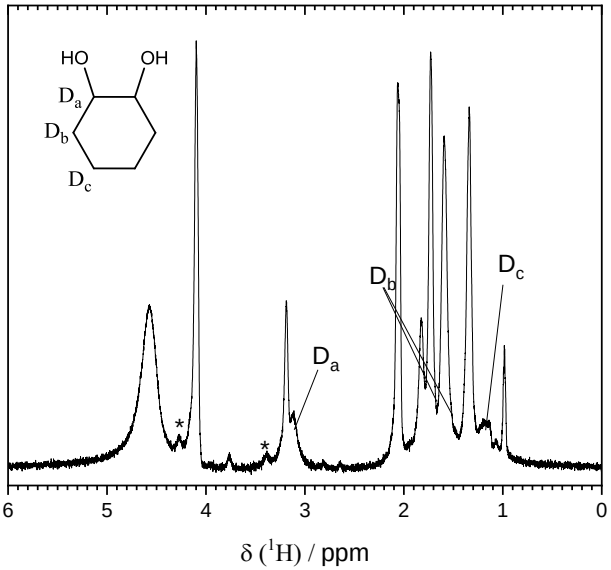


Figure S5. ^{1}H DMF-NMR spectrum of all reactants in the cyclichexdiene carbonate hydrolysis one hour after mixing. The product cyclic (* is trace-amount of oligomer peak for ring-opening polymerization of rac-CHC)

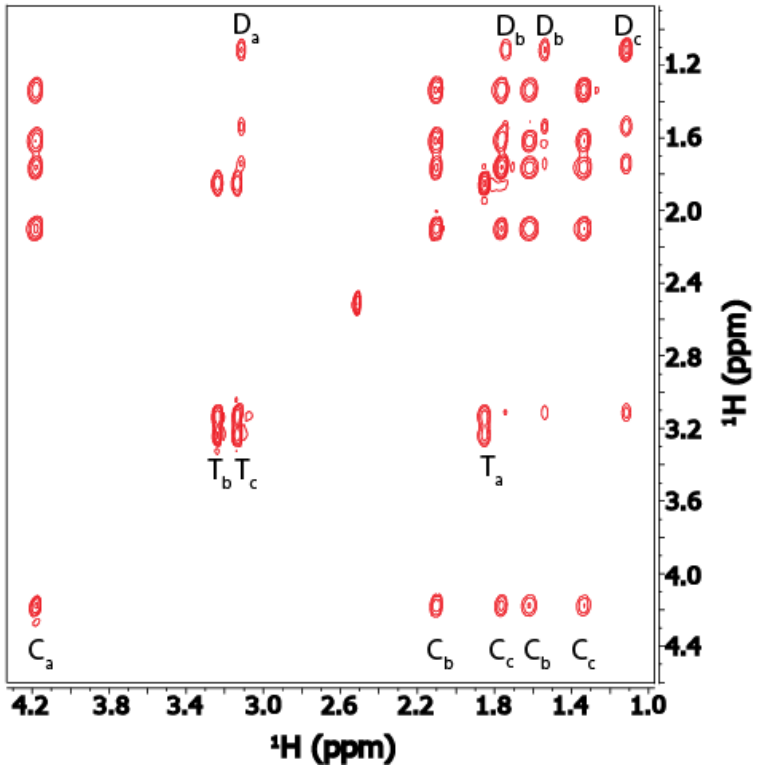


Figure S6, ^{1}H-^{1}H TOCSY spectrum of the reaction solution (I) after one hour collected in a 5mm tube using a cryoprobe, and the corresponding assignments.

Diffusion coefficients for all the chemicals measured by DOSY experiments.

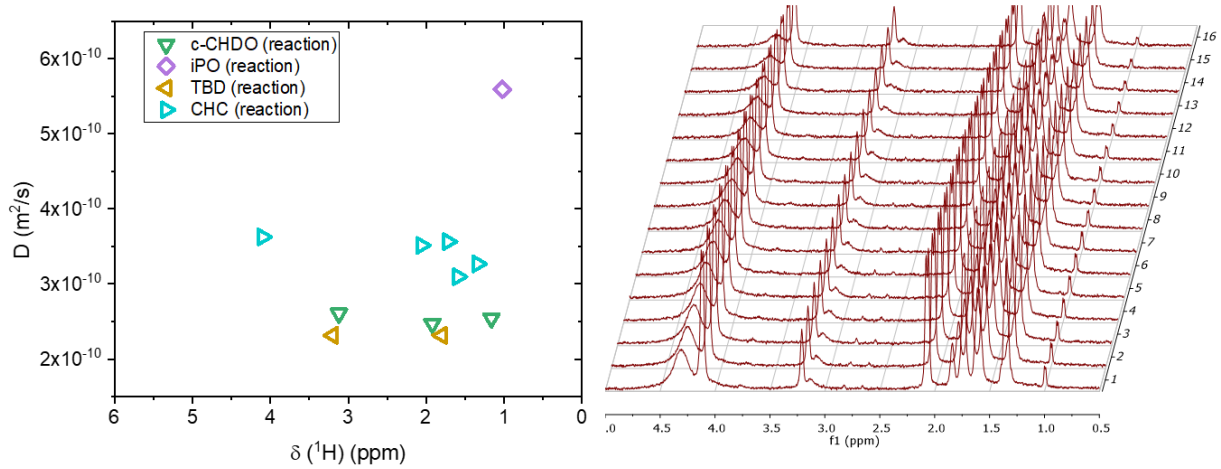


Figure S7, ^{1}H DOSY-NMR measurement of the cyclichexdiene carbonate hydrolysis reagents 1 hr after mixing. DOSY NMR is included to demonstrate that complex pulse programs can be performed on the NMR microcoil. DOSY is a powerful technique that has key applications for the separation of products from reactants in organic chemistry[4] and for the study of non-covalent molecular interactions[5]. Here the slower diffusion of c-CHDO relative to CHC is likely caused due to its interaction with TBD.

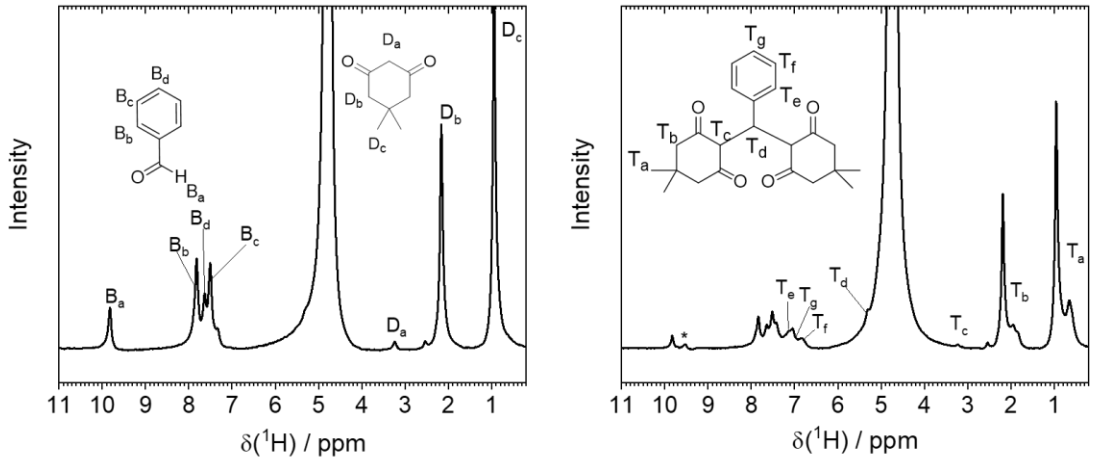


Figure S8. ^{1}H DMF-NMR spectrum of BP and DIM at the beginning (left), and after 20min (right) of reaction II and the corresponding assignments of BA, DIM and the product tetraketone (TK).

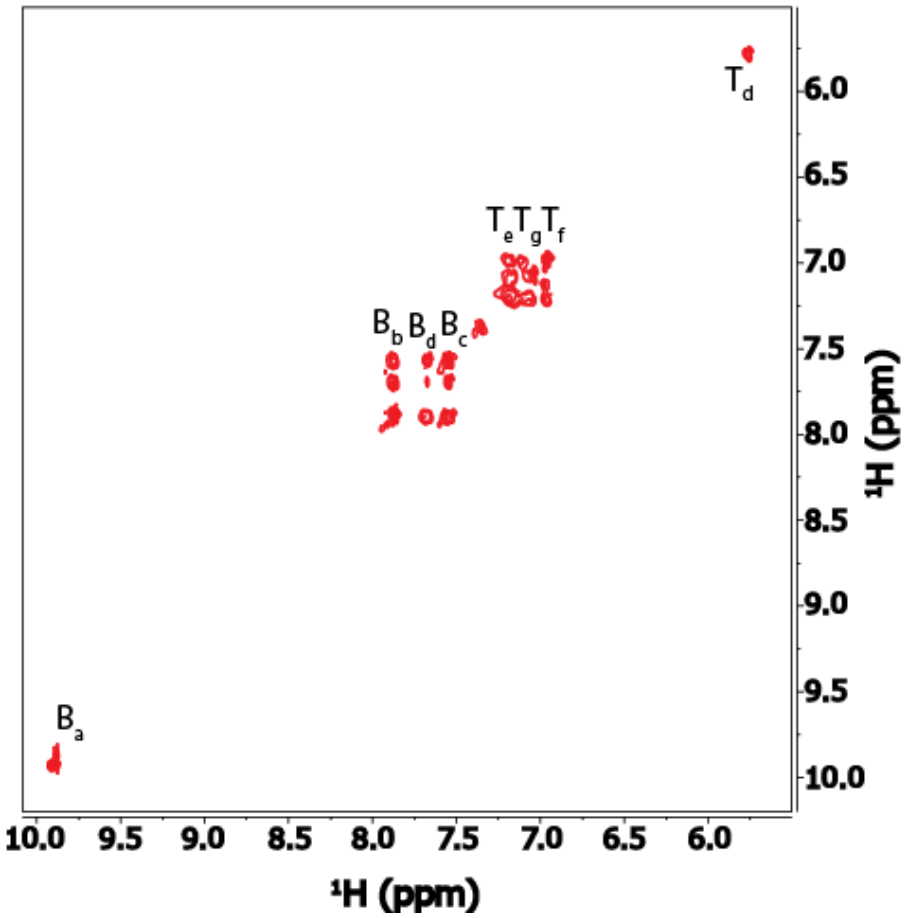


Figure S9 ^{1}H-^{1}H TOCSY spectrum of reaction solution (II) after one hour collected in a 5mm tube using a cryoprobe, and the corresponding assignments.

References:

[1] I. Swyer, S. von der Ecken, B. Wu, A. Jenne, R. Soong, F. Vincent, D. Schmidig, T. Frei, F. Busse, H. J. Stronks, A. J. Simpson, A. R. Wheeler, *Lab on a chip* **2019**, *19*, 641-653.

[2] R. Fobel, C. Fobel, A. R. Wheeler, *Appl Phys Lett* **2013**, *102*.

[3] I. Swyer, R. Soong, M. D. M. Dryden, M. Fey, W. E. Maas, A. Simpson, A. R. Wheeler, *Lab on a chip* **2016**, *16*, 4424-4435.

[4] J. S. Kavakka, I. Kilpelainen, S. Heikkinen, *Organic letters* **2009**, *11*, 1349-1352.

[5] Y. Cohen, L. Avram, L. Frish, *Angew Chem Int Edit* **2005**, *44*, 520-554.