# Rapid investigation of the effect of binary and ternary solvent gradient mixtures on reaction outcomes using a continuous flow system

Dawid Drelinkiewicz, Tom J. A. Corrie, and Richard J. Whitby

# Supporting Information

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# 1. Materials and methods

## 1. 1. Materials

Anhydrous DMSO was obtained by stirring the DMSO with $CaH_2$ overnight, followed by a vacuum distillation, and was then stored under $N_2$, with a freshly dried 3 Å molecular sieves. *N,N*-Dimethylphenylene-1,4-diamine was distilled directly prior to use (Kugelrohr, 115 °C, 4.0 mbar), then stored in a light protected container at -25 °C under $N_2$. All other commercially available reagents were used as received. Following solvents were used as received:

*Table S 1Purity of used solvents and their water content.*

| Solvent (abbreviation) | Purity | Water content | Manufacturer |
|---|---|---|---|
| Acetonitrile (MeCN) | HPLC Grade, ≥99.9% | ≤0.004% | Fisher Scientific |
| Acetone | ACS Reagent Grade, ≥99.5% | ≤0.2% | Sigma-Aldrich |
| Benzonitrile (PhCN) | ≥99% | n/a | Lancaster |
| *tert*-Butanol (tBuOH) | ACS Reagent Grade, ≥99% | n/a | Sigma-Aldrich |
| Chlorobenzene (PhCl) | HPLC Grade, ≥99.85% | n/a | Thermo Scientific Acros |
| Chloroform | ≥99% | ≤0.1% | Fisher Scientific |
| 1-Chloronaphthalene | Technical, 85% (remainder 2-Chloronaphthalene) | n/a | Thermo Scientific Acros |
| Cyclohexanone | ACS Reagent Grade, ≥99% | ≤0.05% | Sigma Aldrich |
| 1,2-Dichlorobenzene (*o*DCB) | ≥99% | n/a | Thermo Scientific Acros |
| 1,2-Dichloroethane (DCE) | ≥99% | n/a | Thermo Scientific Alfa Aesar |
| Dichloromethane (DCM) | ≥99% | ≤0.05% | Fisher Scientific |
| *N,N*-Dimethylacetamide (DMA) | ≥99% | ≤0.1% | Thermo Scientific Acros |
| | ≥99.8% | n/a | Thermo Scientific Alfa Aesar |
| *N,N*Dimethylformamide (DMF) | ≥99% | ≤0.2% | Fisher Scientific |
| Dimethylsulfoxide (DMSO) | ≥99.9% | ≤0.012% | Fisher Scientific |
| 1,4-Dioxane | ≥99% | ≤0.2% | Fisher Scientific |
| Ethanediol | ≥99% | ≤0.5% | Fisher Scientific |
| Ethanol (EtOH) | Absolute, ≥99.8% | n/a | Fisher Scientific |
| Ethyl acetate (AcOEt) | ≥99.0% | ≤0.05% | Fisher Scientific |
| Ethyl formate | ≥98% | n/a | Thermo Scientific Acros |
| *n*-Hexane | HPLC Grade, ≥95% | ≤0.004% | Fisher Scientific |
| Methanol (MeOH) | HPLC Grade, ≥99.8 | ≤0.01% | Fisher Scientific |
| Methyl *tert*-butyl ether (MTBE) | ≥98.5% | ≤0.01% | Thermo Scientific Acros |
| *N*-Methylpyrrolidinone (NMP) | ≥99% | n/a | Thermo Scientific Alfa Aesar |
| (-)-β-Pinene | technical | n/a | Koch-Light Laboratories Ltd |
| *iso*-Propanol (IPA) | ≥99.5% | ≤0.2% | Fisher Scientific |
| Propylene Carbonate | ≥99.9% | n/a | Thermo Scientific Alfa Aesar |

| | | | |
|---|---|---|---|
| Tetrahydrofuran (THF) | Extra pure, ≥99.5% | n/a | Fisher Chemical |
| Toluene (tol) | Low in sulfur, 100% | n/a | Fisher Scientific |
| Triethylene glycol dimethyl ether (triglyme) | ≥99% | n/a | Sigma Aldrich |

## 1. 2. Methods

NMR spectra were obtained on a Bruker DPX400 or Bruker AvanceCore AVII 400 spectrometers. $^{1}H$ chemical shifts are reported as values in ppm referenced to residual $CHCl_3$ in $CDCl_3$. $^{13}C$ chemical shifts are reported as values in ppm referenced to the main peak of deuterated solvent and are proton decoupled. Positive/negative ion electrospray ionisation mass spectra were recorded using a MaXis (Bruker Daltonics, Bremen, Germany) time of flight (TOF) mass spectrometer. Samples were introduced to the mass spectrometer via a Dionex Ultimate 3000 autosampler and uHPLC pump. Ultrahigh performance liquid chromatography was performed using a Waters, Acquity UPLC BEH C18 (50 mm x 2.1 mm 1.7um) column. Gradient elution from 5% acetonitrile (0.2% formic acid) to 100% acetonitrile (0.2% formic acid ) was performed in five minutes at 0.6 mL/min.

GC measurements were performed on a Hewlett Packard HP 6890 series GC system, using a HP-5 (cross-linked 5% Ph Me siloxane) 30 m column, with a film thickness of 0.25 µm and 0.32 mm internal diameter. The carrier gas was helium and the flow rate was 2.7 mL·min-1. The injector was maintained at 300 °C with 1.0 µL injection. The run started at 80 °C with a gradient of 25 °C/min until 275 °C which was held for 4 min.

Infrared spectra were run as neat films on a Thermo Nicolet 380 FT-IR spectrometer with a Smart Orbit Goldengate ATR attachment.

UV-Vis measurements were recorded with the Ocean Optics DH-2000-BAL light source and USB 2000+ fiber optic spectrometer at room temperature using SpectraSuite Software. All flow in situ UV-Vis measurements were performed with a Type 583-F Starna® fluorimeter flow cell (path length 0.100, 0.010, or 0.001 cm). The other UV-Vis measurements were run with UV Fused Quartz cuvette (path length 1 cm). The wavelengths are given in nanometres and the corresponding extinction coefficients in $M^{-1}\cdot cm^{-1}$.

Molar extinction coefficients were determined by plotting absorption vs concentration multiplied by path length graph and using Beer-Lambert law, accordingly to the equation below, by fitting a linear function to the obtained data.

$$A=\varepsilon\cdot c\cdot l$$

Where: A – absorption [a.u.]
ε – molar extinction coefficient [$M^{-1}\cdot cm^{-1}$]
c – sample concentration [M]
l – path length [cm]

Melting points were recorded on a Stuart SMP20 melting point apparatus and are uncorrected.

Thin-layer chromatography was carried out on Merck silica gel plates, which were visualised under UV irradiation of 254 nm and/or by staining with aqueous KMnO4, methanolic H2SO4, PMA or iodine. Column chromatography was performed with Merck silica gel 60 using solvent ratios as volumes before mixing described in the method.

The Vapourtec® R series Integrated Flow Chemistry System (R2+) was the platform used for the flow experiments. When python scripts designed to control the Vapourtec hardware are presented in this document, note that the commands responsible for hardware control have been redacted, due to the confidentiality disclosure. If needed, contact Vapourtec Ltd for details of the serial command protocol.

Grant Optima™ TXF200 heated oil bath with high-temperature silicone oil was used for precise reaction temperature control.

Matlab® R2022b (9.13.0.2049777) was used in analysis of experimental data. Matlab® R2022b (9.13.0.2049777) and Origin 2021b SR2 9.8.5.212 were used for plotting of the obtained experimental results.

# 2. Solvents mixture studies methodology, flow setup, and crucial parameters

## 2. 1. General procedure for the solvent studies experiments

Note that procedure for investigating effects of binary solvents mixture on reaction outcome **consists of two complementary experiments**, namely first experiment in which solvent A is used, and second experiment in which solvent B is used for dissolving the reagents, respectively.

### 2. 1. 1. Flow setup

Solvent A and Solvent B were connected to the flow streams of two independent pumps and their flow rates were set to X and Y mL·min$^{-1}$, respectively. Stock solution(s) of reagents in Solvent A was connected to the subsequent pump(s) flow stream(s), and the desired flow rate(s) was set (Z mL·min$^{-1}$). All streams were then joined, directed subsequently to the mixer, flow reactor, and back-pressure regulator. Flow stream was then directed to the in-line monitoring cell and/or to the fraction collector for off-line analysis (Figure S 1.).

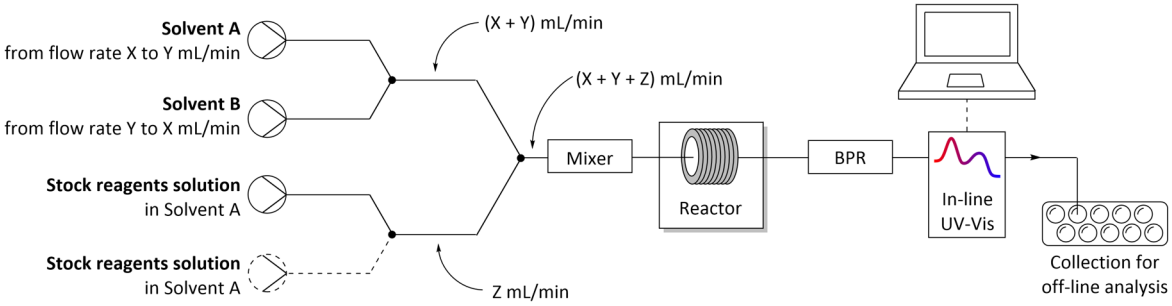



*Figure S 1. General flow system used for studying solvents mixtures effects.*

### 2. 1. 2. Experimental procedure

Before starting the experiment, flow system was allowed to stabilise by injecting only solvents into the flow system. Once the system was stable, the feeding valve(s) of the pump(s) delivering stock reagents solution(s) was switched and reagents solution(s) was injected into the flow system. When the first reaction steady state was achieved, flow rates of pumps delivering Solvent A and Solvent B were changed stepwise from X to Y and from Y to X mL·min$^{-1}$, respectively, while keeping the total flow rate constant and equal to X + Y mL·min$^{-1}$. After reaching boundary flow rates (Y and X mL·min$^{-1}$ for pumps delivering Solvent A and Solvent B, respectively) no change in the flow system was made, which allowed for reaching the second steady state. Flow rates of the pumps delivering solvents were then switched back to initial values (X and Y mL·min$^{-1}$ for pumps delivering Solvent A and Solvent B, respectively), allowing for reaching the third steady state (which should give the same outcome as the

first steady state). Afterwards, pump(s) feeding valves delivering stock reagents solution(s) was switched back to Solvent A and remaining reaction mixture was eluted from the reactor.

Alternatively, after reaching the second steady state the feeding valve(s) can be switched back to deliver Solvent A, which would reduce experimental time and material consumption, however the third steady state wouldn't be achieved, which often serves a diagnostic purpose.

The whole procedure was then repeated, only this time the solvents A and B were swapped (including in the stock reagents solution(s)).

Figure S 2. presents each step of the performed experiments as visualised from in-line monitoring, with information on solvents composition for each step. The transitional period during which solvents composition change affecting the reaction outcome is marked with a dotted box.

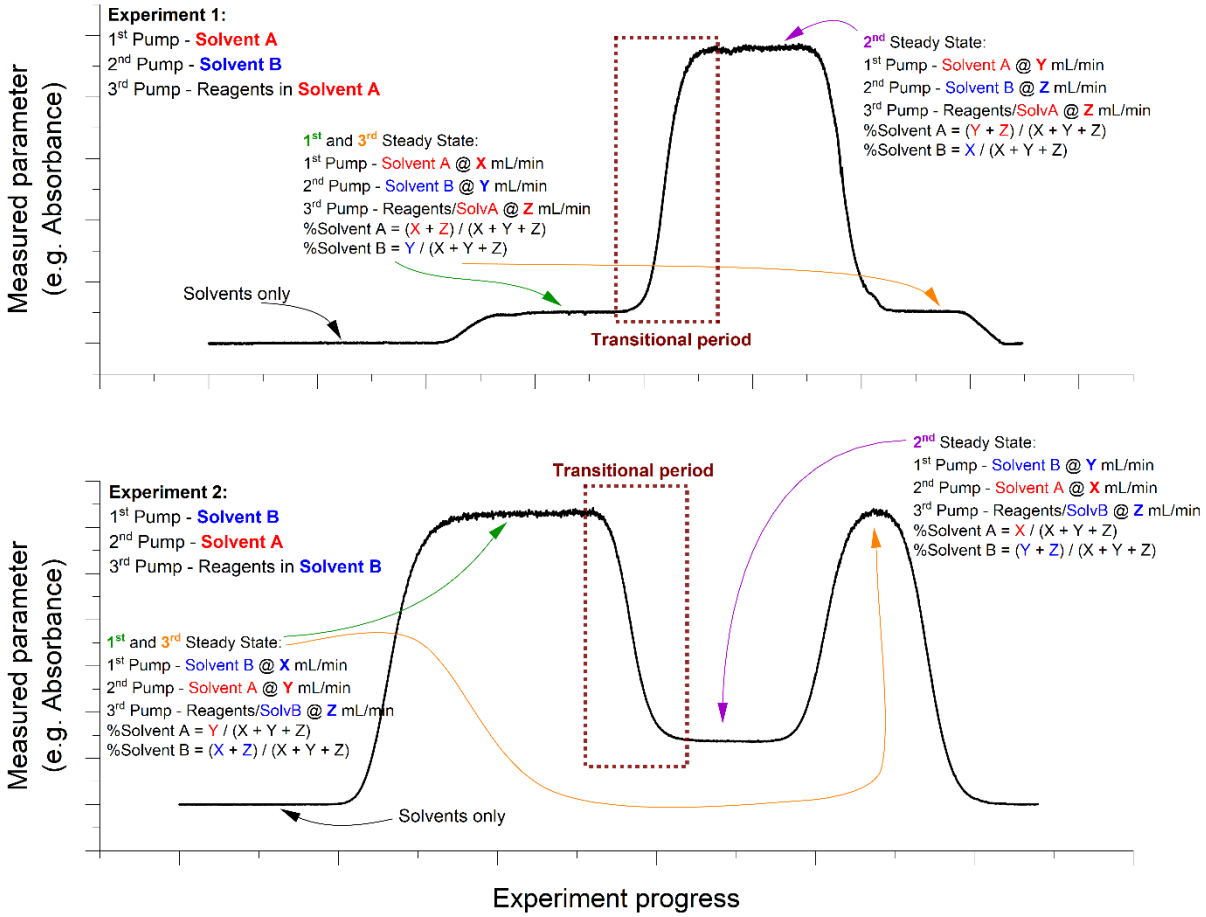



*Figure S 2. Visualisation of the solvents mixtures studies methodology using in-line monitoring.*

### 2. 1. 3. Analysis of results obtained from *in situ* UV-Vis monitoring

Analysis of UV-Vis data obtained flow solvent studies was performed using Matlab® script, that allowed for automation of analysis and delivered consistent results with the same layout. The whole experiment-analysis routine can be graphically represented (Figure S 3. Solvent studies routine, including actions performed in Matlab script. Green-blue rectangles are experimental protocols, violet-blue rectangles are manual data post-processing, and blue rectangles are incorporated into Matlab® analysis script.) as a simple step-by-step process:


*Figure S 3. Solvent studies routine, including actions performed in Matlab script. Green-blue rectangles are experimental protocols, violet-blue rectangles are manual data post-processing, and blue rectangles are incorporated into Matlab® analysis script.*

Exact Matlab® scripts used for studies of solvents mixtures reported herein, can be found in the sections 3. 3. Analysis script for the $S_NAr$ solvent studies experimentsand 4. 3. Analysis script for the imine formation solvent studies experiments of this document.

## 2. 2. Importance of efficient mixing

Proper mixing of solvents and other reaction components is crucial in studies of solvent effects in flow systems. Initial methodology development was performed in a simple flow system (Figure S 4.) in which all flow streams were connected with a T-connectors, then directed to the reactor and monitoring cell.

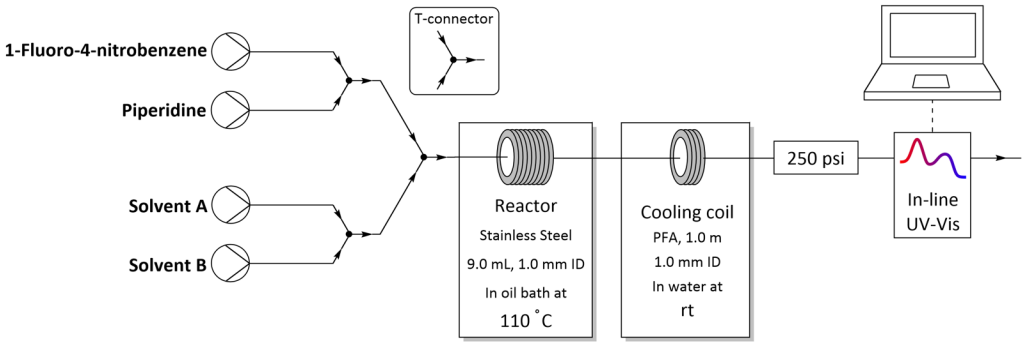



*Figure S 4. Initial flow system used for solvents mixtures studies.*

Analysis of the results obtained showed that the complementary experiments did not overlap in the region of common solvents mixture composition. Examples of results obtained from DMF/EtOH, and DMF/THF mixtures with inefficient mixing are presented below (Figure S 5.).

Afterwards, incorporation of the micromixer chip resulted in improved mixing efficiency and generation of desired experimental results that were unaffected by the error caused by the inefficient mixing. Additional incorporation of the HPLC-type mixer showed no effect, proving that the mixing was efficient when using only micromixer chip, however it was decided to keep the HPLC-type mixer in the flow system for subsequent investigation of solvents effects. Results of the solvent effects on the $S_NAr$ reaction with micromixer chip and HPLC-type mixer incorporated into the flow system (Figure S 6.).

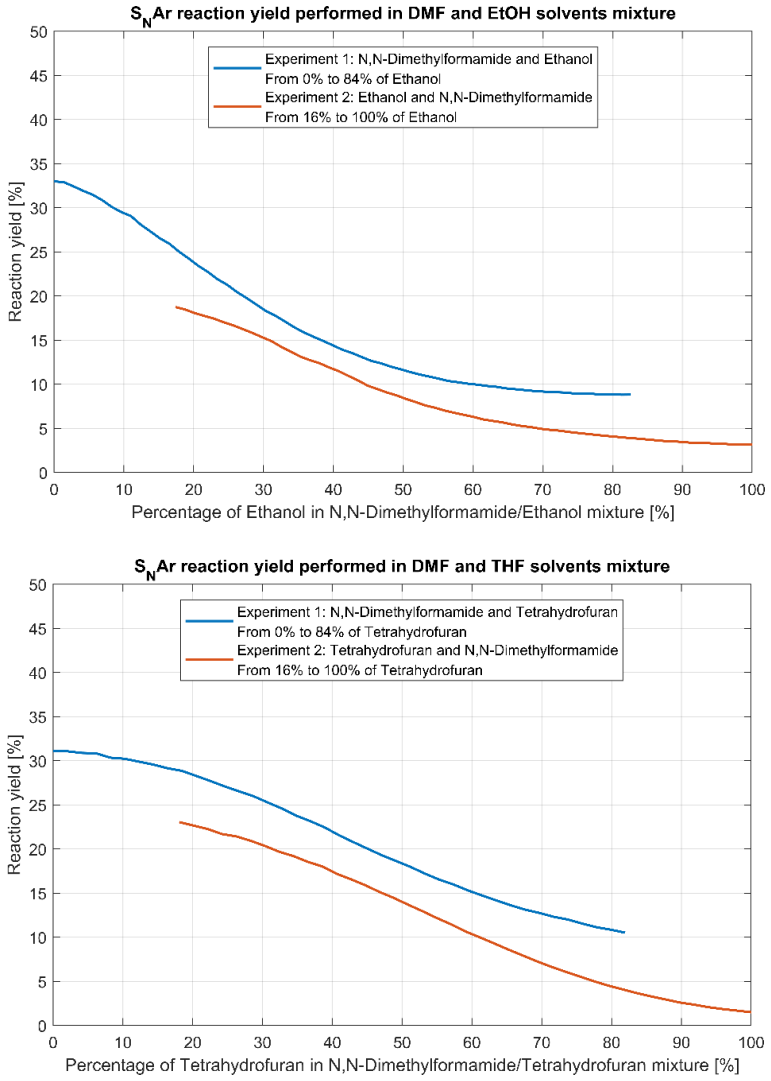



*Figure S 5. Initial results obtained from a flow system with inefficient mixing using DMF/EtOH (top) and DMF/THF (bottom).*

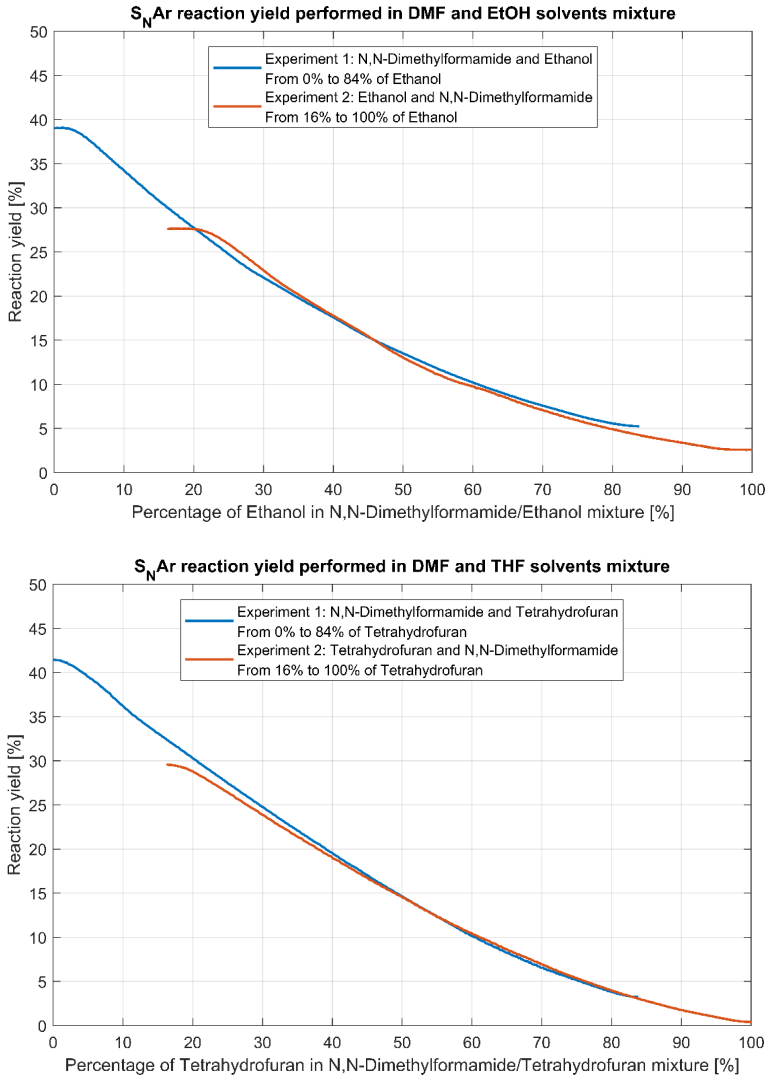



*Figure S 6. Results of solvents mixtures studies in a system with efficient mixing using DMF/EtOH (top) and DMF/THF (bottom).*

## 2. 3. Corrections for various physical phenomena

### 2. 3. 1. Correction for solvatochromic effects

It is well known that a molecule absorption maxima position (wavelength) and intensity (molar extinction coefficient (referred to as MEC) to be more precise) is influenced by the phase in which the molecule is dissolved,[1,2] which has been termed by Hantzsch as solvatochromism.[3] In experiments performed *ibid.*, the solvents composition (the phase) is changing throughout the experiment, thus affecting the absorption maximum wavelength and molar extinction coefficients, which in turn affects the calculated concentration of the monitored species (accordingly with Beer-Lamber law). Correction for the solvatochromic effects was performed in following steps:

1. Precise determination of the MEC of the monitored reaction species in the primary solvent, using series of dilution method, which was used in respective solvent effect studies:
   i. 1-(4-nitrophenyl)piperidine **3** in *N,N*-dimethylformamide, see Chapter 3. 1. 1. Determination of molar extinction coefficient in DMF;
   ii. (E)-*N,N*-dimethyl-4-((4-nitrobenzylidene)amino)aniline **6** in 1,2-dichloroethane, see Chapter 4. 1. 1. Determination of molar extinction coefficient in 1,2-DCE;

2. Measurement of the absorption spectra of the monitored reaction species in the secondary solvents at known concentration. Measurements were performed 3 times for each solvent and averaged absorbance values have been used in calculation of MEC values.
    i. 1-(4-nitrophenyl)piperidine **3**, see Chapter 3. 1. 2. Determination of molar extinction coefficient of 1-(4-nitrophenyl)piperidine in various solvents;
    ii. (E)-*N,N*-dimethyl-4-((4-nitrobenzylidene)amino)aniline **6**, see Chapter 4. 1. 2. Determination of molar extinction coefficients in solvents used in various solvents;
3. MEC values for used solvents mixtures have been calculated with the assumption that the change of the coefficient is linear with the change of the liquid medium. This, however imperfect solution, allows for approximate correction of the effect of the medium on the calculated concentration (and yield) of the monitored species. The correction has been applied in the Matlab® scripts used for automated analysis of the experimental results and consists of following steps:
    i. Generation of the linear model of MEC values against the mixture composition using the MEC values for pure solvents A and B (obtained in points 1. and 2.).
    ii. Calculation of the solvents mixture composition for each point in the analysed region.
    iii. Calculation of the corrected MEC values for different solvents mixture compositions generated *in situ*.

### 2. 3. 2. Corrections for liquids volumetric expansion/contraction

Another important aspects to address, are that when two liquids are mixed a volumetric contraction or expansion can occur, due to chemical reactivity or intermolecular forces between the liquid molecules, and that when the liquid medium is heated, for example during a thermal reaction, it undergoes thermal expansion. Both phenomena result in change of the liquid volume, thus affecting the actual residence times in the flow systems.

In the studies performed herein, no corrections for these effects were applied, as they are out of scope of the studies, and due to the fact that both of the abovementioned phenomena exhibit non-linear relationships for binary solvents mixtures, thus requiring laborious and extensive studies, whereas the effect of applying such corrections would be minimal.

## 2. 4. Determination of start- and endpoint of the gradient information

Determination of the start and endpoint of the region containing gradient information data can be performed mathematically, by knowing the total volume of the flow system and flow rates used, however such method can be inaccurate due to the need to include dead volumes of various flow elements (such as BPRs, mixers, etc.) in calculations, which are not always known. Moreover, when experiments are performed using high temperatures, thermal expansion of solvents occurs which is another factor that needs to be incorporated into calculations. This affects the effective position of start- and endpoints of the gradient region, however this effect is usually small and sometimes can be omitted.

A second method would be to experimentally determine the start and endpoints of gradient region by execution of an experiment in which no reagents are used, instead an indicator can be added into the secondary solvent and its absorbance can be followed by using in-line monitoring. Moreover, a mixture of two solvents which differ in the maximum of absorption wavelength can be used without the need for indicator, when using UV-Vis monitoring. We found this method to be the more efficient, as it eliminates possible inaccuracies of the theoretical flow system volume calculations (e.g. dead volumes of flow system components or thermal solvents expansion), and it also eliminates possible chemical interactions of the indicator with the solvents or physical interactions with the flow system itself (e.g. re- and adsorption on the stainless steel reactor).

Additionally, both start- and endpoints of the gradient information can be determined manually, by determination of the derivative of the measured reaction signal (e.g. absorbance). Start point of the region containing gradient information can then be determined as a point during which the derivative starts to change, indicating transition from first reaction steady state into the transient region, and endpoint can be determined as the point after which the derivative remains constant, indicating transition from the transient region into second reaction steady state. This method however may not work well, when the difference in the reaction output generated by studied solvent effects is small, thus making the derivative values unrecognizable from the signal noise.

In studies performed herein, the approximate position of the gradient boundaries was determined by performing the initial experiment with solvents that differ in absorption spectra. Obtained information was then used in analysis of each solvent effects experiment, however manual adjustments were allowed if needed.

## 2. 5. Averaging of reaction signal at the 'ends' of the experimental data

When using the mesoscale Vapourtec flow systems with a standard tubing (internal diameter of 1.0 mm) and flow rates in a range of 0.1 and 20.0 mL·min$^{-1}$ a laminar flow occurs (Reynolds number < 2000), and significant Taylor dispersion is expected, which results in smoothing out the concentration gradient along the tubing. Additionally, in a curved tubes such as reactor coils a secondary flow movement known as Dean circulation occurs resulting in an enhanced mixing of liquid across the tube, thus reducing the Taylor dispersion in the parts of flow system with curved coils. We observed that the influence of the dispersion is insignificant except at the beginning and end of the region containing gradient information. This results in 'flattening' of the experimental results at both ends of the respective experiments. As an example, the $S_NAr$ reaction between **1** and **2** when using DMF and ethyl acetate solvents mixture in our studies shows small deviations at the beginning and the end of the plot of reaction yield *vs*. solvents mixture composition (Figure S7). It should be noted that the amount of dispersion is likely to change with the solvent mixture and the above shows that this will not significantly affect the results obtained.

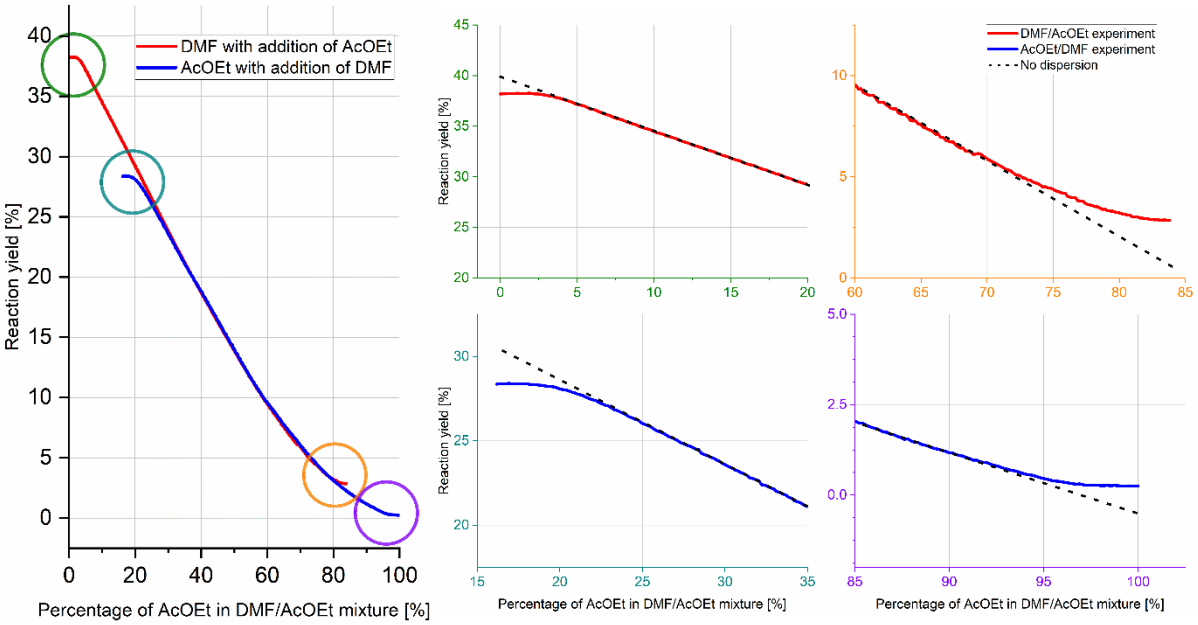



*Figure S 7. Effects of dispersion on the beginning and the end of the data obtained from the transient region of the solvent studies experiment, visualised on the example of $S_NAr$ reaction and DMF/AcOEt solvents mixture.*

# 3. Solvent effects studies in $S_NAr$ reaction between 1-fluoro-4-nitrobenzene and piperidine

## 3. 1. Determination of molar extinction coefficient of 1-(4-nitrophenyl)piperidine

### 3. 1. 1. Determination of molar extinction coefficient in DMF

A stock solution of 1-(4-nitrophenyl)piperidine (205.68 mg, 1.00 mmol) in *N,N*-dimethylformamide (50.0 mL) was prepared. Pure *N,N*-dimethylformamide was measured as a background. 1-(4-Nitrophenyl)piperidine sample was then obtained by diluting the stock solution 300 times, 1.5 mL of the sample was added to the quartz UV-Vis cuvette, and the absorbance of the sample was measured. *N,N*-Dimethylformamide (0.1 mL) was added, resulting solution was mixed, and the absorbance was measured once again. Procedure was repeated until filling the UV-Vis cuvette. Results are presented in the table below (Table S 2.).

*Table S 2. Values obtained from determination of MEC of 1-(4-nitrophenyl)piperidine.*

| Measurement | Moles of 1-(4-nitrophenyl) piperidine [mol] | Sample volume [mL] | Concentration of 1-(4-nitrophenyl) piperidine [M] | Absorbance at 402 nm [a.u.] |
|---|---|---|---|---|
| 1 | $9.97 \cdot 10^{-8}$ | 1.5 | $6.65 \cdot 10^{-5}$ | 1.40 |
| 2 | | 1.6 | $6.23 \cdot 10^{-5}$ | 1.31 |
| 3 | | 1.7 | $5.87 \cdot 10^{-5}$ | 1.24 |
| 4 | | 1.8 | $5.54 \cdot 10^{-5}$ | 1.18 |
| 5 | | 1.9 | $5.25 \cdot 10^{-5}$ | 1.12 |
| 6 | | 2.0 | $4.99 \cdot 10^{-5}$ | 1.07 |
| 7 | | 2.1 | $4.75 \cdot 10^{-5}$ | 1.02 |
| 8 | | 2.2 | $4.53 \cdot 10^{-5}$ | 0.977 |
| 9 | | 2.3 | $4.34 \cdot 10^{-5}$ | 0.938 |
| 10 | | 2.4 | $4.16 \cdot 10^{-5}$ | 0.904 |
| 11 | | 2.5 | $3.99 \cdot 10^{-5}$ | 0.864 |
| 12 | | 2.6 | $3.84 \cdot 10^{-5}$ | 0.834 |
| 13 | | 2.7 | $3.69 \cdot 10^{-5}$ | 0.804 |
| 14 | | 2.8 | $3.56 \cdot 10^{-5}$ | 0.776 |
| 15 | | 2.9 | $3.44 \cdot 10^{-5}$ | 0.748 |
| 16 | | 3.0 | $3.32 \cdot 10^{-5}$ | 0.728 |
| 17 | | 3.1 | $3.22 \cdot 10^{-5}$ | 0.704 |
| 18 | | 3.2 | $3.12 \cdot 10^{-5}$ | 0.684 |
| 19 | | 3.3 | $3.02 \cdot 10^{-5}$ | 0.662 |
| 20 | | 3.4 | $2.93 \cdot 10^{-5}$ | 0.647 |
| 21 | | 3.5 | $2.85 \cdot 10^{-5}$ | 0.628 |
| 22 | | 3.6 | $2.77 \cdot 10^{-5}$ | 0.614 |
| 23 | | 3.7 | $2.70 \cdot 10^{-5}$ | 0.600 |
| 24 | | 3.8 | $2.62 \cdot 10^{-5}$ | 0.581 |
| 25 | | 3.9 | $2.56 \cdot 10^{-5}$ | 0.562 |

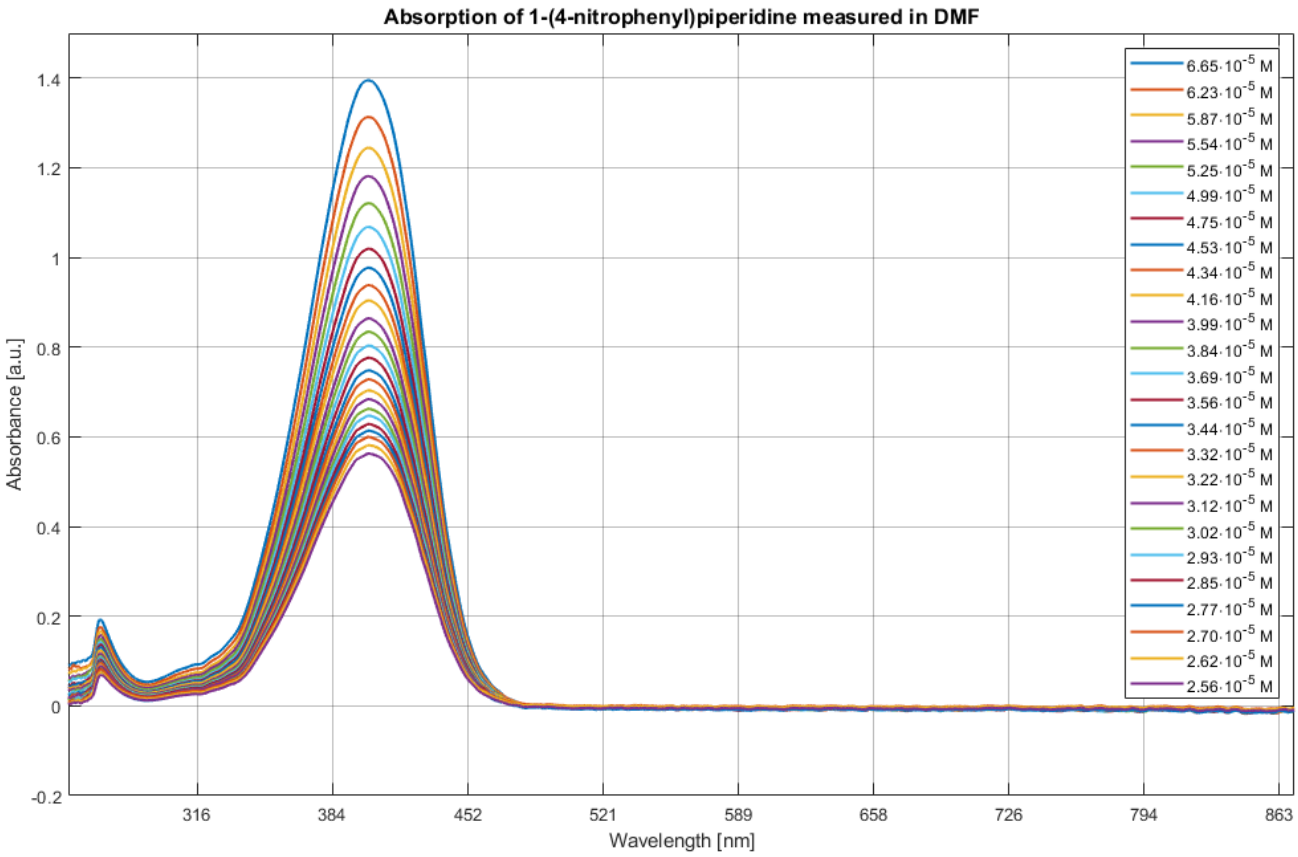



*Figure S 8. Absorbance of 1-(4-nitrophenyl)piperidine in DMF.*

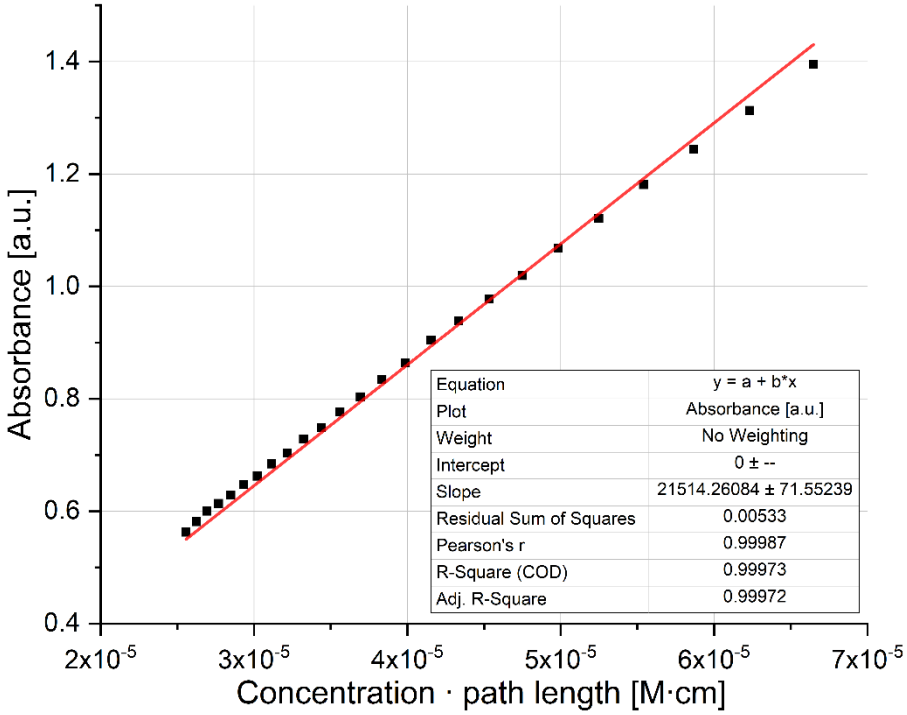



*Figure S 9. Absorbance at 402 nm vs (concentration · path length) graph of 1-(4-nitrophenyl)piperidine in DMF.*

Determined molar extinction coefficient of 1-(4-nitrophenyl)piperidine at 402 nm in DMF is:

$$\varepsilon_{DMF}^{402\,nm} = 21514 \pm 72\ [M^{-1}cm^{-1}]$$

### 3. 1. 2. Determination of molar extinction coefficient of 1-(4-nitrophenyl)piperidine in various solvents

Samples of 1-(4-nitrophenyl)piperidine in various solvents were prepared accordingly to the table below (Table S 3.). Prepared samples were then injected into the flow UV-Vis cell and absorbance measurements were performed 3 times for each sample. Prior to each measurement, pure solvent used in the measured sample was injected into the flow UV-Vis cell for background correction. Averaged absorbances were then used for determination of molar extinction coefficient of 1-(4-nitrophenyl)piperidine in various solvents.

*Table S 3. Combined results of MEC determination of 1-(4-nitrophenyl)piperidine in various solvents.*

| Sample | Solvent | Solvent abbreviation | Sample volume [mL] | 1-(4-Nitrophenyl) piperidine concentration [M] | Maximum of absorption [nm] | Absorbance at maximum of absorption [a.u.] | Molar extinction coefficient at maximum of absorption [$M^{-1}cm^{-1}$] | Absorbance at 402 nm [a.u.] | Molar extinction coefficient at 402 nm [$M^{-1}cm^{-1}$] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | *N,N*-Dimethylformamide | DMF | 20.0 | $4.99 \cdot 10^{-3}$ | 402 | 1.04 | 20731 | 1.04 | 20731 |
| 2 | Dimethylsulfoxide | DMSO | 20.0 | $4.87 \cdot 10^{-3}$ | 409 | 1.04 | 21261 | 1.01 | 20748 |
| 3 | *N*-Methylpyrrolidinone | NMP | 20.0 | $4.92 \cdot 10^{-3}$ | 404 | 1.03 | 20858 | 1.03 | 20828 |
| 4 | Ethanol | EtOH | 20.1 | $5.23 \cdot 10^{-3}$ | 389 | 0.975 | 18633 | 0.879 | 16796 |
| 5 | Acetonitrile | MeCN | 20.0 | $4.92 \cdot 10^{-3}$ | 397 | 0.985 | 20009 | 0.97 | 19707 |
| 6 | Ethyl acetate | AcOEt | 20.0 | $5.02 \cdot 10^{-3}$ | 383 | 1.06 | 21176 | 0.776 | 15455 |
| 7 | Propylene Carbonate | PC | 20.2 | $4.92 \cdot 10^{-3}$ | 404 | 0.939 | 19087 | 0.938 | 19063 |
| 8 | *tert*-Butanol | *t*BuOH | 20.0 | $5.07 \cdot 10^{-3}$ | 388 | 0.975 | 19237 | 0.847 | 16719 |
| 9 | Acetone | Acetone | 20.0 | $5.19 \cdot 10^{-3}$ | 393 | 1.12 | 21537 | 1.05 | 20143 |
| 10 | 1,4-Dioxane | Diox | 10.1 | $5.14 \cdot 10^{-3}$ | 383 | 1.03 | 20091 | 0.765 | 14899 |
| 11 | Triethylene glycol dimethyl ether | triglyme | 10.0 | $4.61 \cdot 10^{-3}$ | 392 | 0.933 | 20247 | 0.843 | 18303 |
| 12 | 1,2-Dichloroethane | 1,2-DCE / DCE | 10.0 | $5.28 \cdot 10^{-3}$ | 396 | 1.12 | 21186 | 1.09 | 20643 |
| 13 | Toluene | tol | 10.0 | $4.90 \cdot 10^{-3}$ | 380 | 0.942 | 19239 | 0.615 | 12550 |
| 14 | Tetrahydrofuran | THF | 10.0 | $4.80 \cdot 10^{-3}$ | 388 | 1.06 | 22048 | 0.843 | 17554 |
| 15 | Methanol | MeOH | 10.0 | $5.38 \cdot 10^{-3}$ | 393 | 1.06 | 19640 | 1.00 | 18636 |
| 16 | *iso*-Propanol | IPA | 5.0 | $4.86 \cdot 10^{-3}$ | 388 | 0.92 | 18930 | 0.811 | 16700 |
| 17 | Dichloromethane | DCM | 5.0 | $5.63 \cdot 10^{-3}$ | 397 | 1.25 | 22127 | 1.22 | 21672 |
| 18 | Chloroform | $CHCl_3$ | 5.0 | $5.03 \cdot 10^{-3}$ | 395 | 1.09 | 21737 | 1.05 | 20903 |
| 19 | Methyl *tert*-butyl ether | MTBE | 5.0 | $5.26 \cdot 10^{-3}$ | 372 | 1.12 | 21316 | 0.483 | 9192 |
| 20 | *N,N*-Dimethylacetamide | DMA | 10.0 | $4.78 \cdot 10^{-3}$ | 400 | 0.982 | 20547 | 0.981 | 20511 |
| 21 | 5% water in DMF | 5% $H_2O$ in DMF | 20.0 | $5.16 \cdot 10^{-3}$ | 404 | 1.13 | 21954 | 1.13 | 21883 |
| 22 | 10% water in DMF | 10% $H_2O$ in DMF | 10.0 | $4.02 \cdot 10^{-3}$ | 406 | 0.864 | 21464 | 0.857 | 21292 |
| 23 | 15% water in DMF | 15% $H_2O$ in DMF | 20.0 | $5.07 \cdot 10^{-3}$ | 408 | 1.12 | 22138 | 1.1 | 21743 |
| 24 | 20% water in DMF | 20% $H_2O$ in DMF | 20.0 | $2.13 \cdot 10^{-3}$ | 410 | 0.472 | 22142 | 0.458 | 21465 |
| 25 | 25% water in DMF | 25% $H_2O$ in DMF | 20.0 | $5.09 \cdot 10^{-3}$ | 411 | 1.06 | 20886 | 1.02 | 20107 |
| 26 | 30% water in DMF | 30% $H_2O$ in DMF | 50.0 | $1.75 \cdot 10^{-3}$ | 413 | 0.371 | 21257 | 0.35 | 20075 |
| 27 | 35% water in DMF | 35% $H_2O$ in DMF | 50.0 | $1.81 \cdot 10^{-3}$ | 415 | 0.391 | 21573 | 0.364 | 20060 |
| 28 | 40% water in DMF | 40% $H_2O$ in DMF | 5.0 | $6.12 \cdot 10^{-3}$ | 416 | 1.13 | 18527 | 1.13 | 18467 |
| 29 | 50% water in DMF | 50% $H_2O$ in DMF | 100.0 | $4.85 \cdot 10^{-4}$ | 418 | 0.0776 | 16007 | 0.0676 | 13937 |

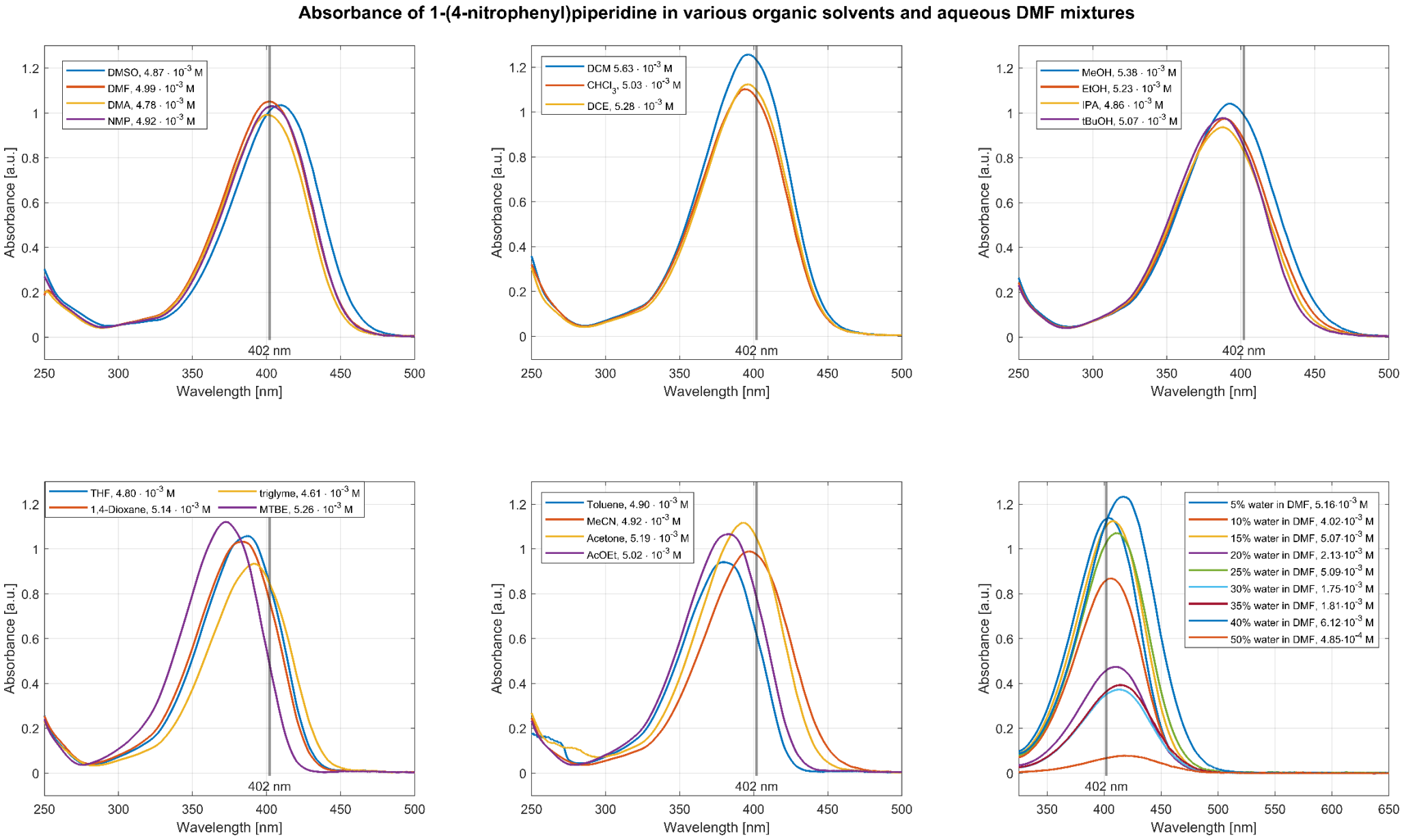



*Figure S 10. Absorbance of 1-(4-nitrophenyl)piperidine in various solvents.*

## 3. 2. Solvent effects studies in $S_NAr$ reaction

### 3. 2. 1. Experimental procedure

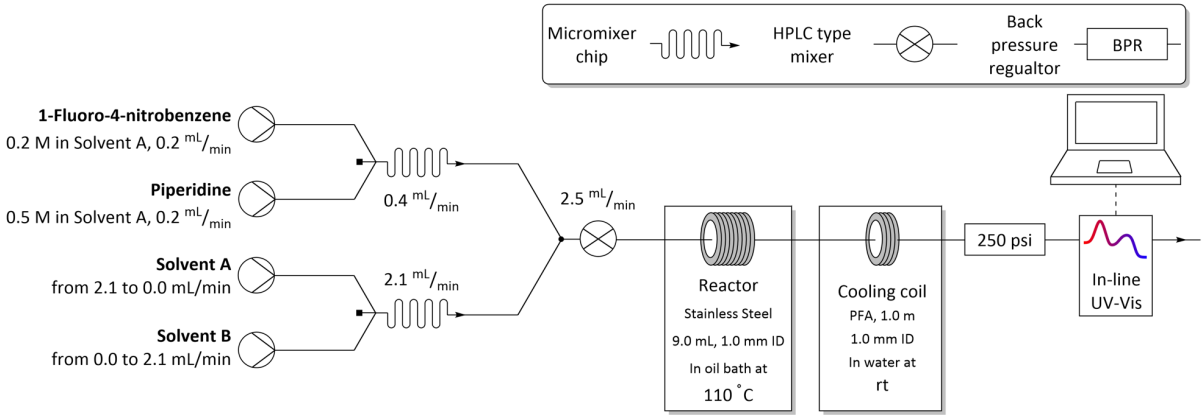



*Figure S 11.Flow setup used for solvents mixture studies in $S_NAr$ reaction.*

A 0.20 M solution of 1-fluoro-4-nitrobenzene (564.4 mg, 424.4 µL, 4.0 mmol, 1.0 eq. in 20.0 mL (35.4 vol.) of Solvent A) was connected to the first flow reagent line. A 0.50 M solution of piperidine (851.5 mg, 987.8 µL, 10.0 mmol, 2.5 eq. in 20.0 mL (23.5 vol.) of Solvent A) was connected to the second flow reagent line. Solvent A was connected to the first, second, and third flow solvents lines. Solvent B was connected to the fourth flow solvent line. Flow rates were set to 0.20, 0.20, 2.10, and 0.00 mL·min$^{-1}$ for the flow streams, respectively. First and second flow streams were directed to the first channel of dolomite mixer, third and fourth flow streams were directed to the second channel of dolomite mixer, and then both mixer outlets were combined, directed to the HPLC mixer, and reactor (stainless steel, 9.0 mL, 1.0 mm I.D., 1.6 mm O.D., submersed in high-precision oil bath set to 110 °C). Flow stream was then directed via a cooling coil (PFA, 1.0 mm ID, 1.6 mm OD, submersed in water at rt) and BPR (250 psi) to the UV-Vis flow cell.

Vapourtec R2 units were controlled using python script (see below), following the procedural steps described below:

1. Flow rates of 0.20, 0.20, 2.10, and 0.00 mL·min$^{-1}$ were set for each pump respectively, pumps were turned on, and system was allowed to equilibrate for 90 seconds.
2. First and second flow streams were switched to reagents position and a wait period of 540 seconds was scheduled, after which first reaction steady state was observed.
3. Gradient of solvents composition was generated by stepwise change of third and fourth flow streams with a two second interval:
    i. Third flow stream flow rate was decreased by 0.01 mL·min$^{-1}$.
    ii. Fourth flow stream flow rate was increased by 0.01 mL·min$^{-1}$.
    iii. Two second interval was scheduled.

    Points i. to iii. were repeated until flow rate of third flow stream reached 0.00 mL·min$^{-1}$ and flow rate of fourth flow stream reached 2.10 mL·min$^{-1}$.
4. System waited for 120 seconds, during which a second steady state was observed.
5. First and second flow streams were switched back to solvents positions and system waited for additional 120 seconds.
6. Third and fourth streams flow rates were instantly changed to 2.10 and 0.00 mL·min$^{-1}$, respectively.
7. A wait period of 600 seconds was scheduled, during which remaining reaction mixture was eluted from the reactor.

The whole procedure was then repeated, with the only change being the substitution of the solvent A with solvent B, and solvent B with solvent A.

Note that in the python script below, the *time.sleep* command executed during the generation of solvents gradient is set only to 1.5 second. This is due to the fact, that when changing the flow rate of any pump (using the *Vtec_PumpX(port,flow)* command), additional period of 250 ms of wait time is incorporated into the command (as defined in *def VTec_PumpX* command definition), to maintain the serial connection stability. Note that the commands responsible for hardware control have been redacted, due to the confidentiality disclosure. If needed, contact Vapourtec Ltd for details of the serial command protocol.

```
import serial
import time
import os

def cls():
          os.system('cls' if os.name == 'nt' else 'clear')

def Vtec_On(port):
          """Define turn on command"""
          port.write('▒▒▒▒▒▒▒'.encode())
          time.sleep(0.5)
          port.readline()
          port.write('▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.5)
          port.readline()
def Vtec_Off(port):
          """Define turn off command"""
          port.write('▒▒▒▒▒▒▒'.encode())
          time.sleep(0.5)
          port.readline()
          port.write('▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.5)
          port.readline()

def Vtec_PumpA(port,flow):
          """Define flow of A pump"""
          flow1_uL = flow1 * 1000
          port.write('▒▒▒▒▒'.encode() + str(flow1_uL).encode() + '▒▒▒▒'.encode())
          time.sleep(0.25)
          port.readline()
def Vtec_PumpB(port,flow):
          """Define flow of B pump"""
          flow2_ul = flow2 * 1000
          port.write('▒▒▒▒▒'.encode() + str(flow2_ul).encode() + '▒▒▒▒'.encode())
          time.sleep(0.25)
          port.readline()
def Vtec_PumpC(port,flow):
          flow3_uL = flow3 * 1000
          port.write('▒▒▒▒▒▒▒▒'.encode() + str(flow3_uL).encode() + '▒▒▒▒'.encode())
          time.sleep(0.25)
          port.readline()
def Vtec_PumpD(port,flow):
          flow4_uL = flow4 * 1000
          port.write('▒▒▒▒▒▒▒▒'.encode() + str(flow4_uL).encode() + '▒▒▒▒'.encode())
          time.sleep(0.25)
          port.readline()

def PumpASolv(port):
          port.write('▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)
def PumpAReagent(port):
          port.write('▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)
def PumpBSolv(port):
          port.write('▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)
def PumpBReagent(port):
          port.write('▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)
def PumpCSolv(port):
          port.write('▒▒▒▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)
def PumpCReagent(port):
          port.write('▒▒▒▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)
def PumpDSolv(port):
```

```
          port.write('▒▒▒▒▒▒▒▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)
def PumpDReagent(port):
          port.write('▒▒▒▒▒▒▒▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)

ser = serial.Serial(
          port = "COM" + str(8),
          baudrate = 19200,
          parity = serial.PARITY_NONE,
          stopbits = serial.STOPBITS_ONE,
          bytesize = serial.EIGHTBITS,
          )

flow1 = 0.2
flow2 = 0.2
flow3 = 2.1
flow4 = 0.0

cls()
Vtec_PumpA(ser,flow1)
Vtec_PumpB(ser,flow2)
Vtec_PumpC(ser,flow3)
Vtec_PumpD(ser,flow4)

PumpASolv(ser)
PumpBSolv(ser)
PumpCSolv(ser)
PumpDSolv(ser)

print('#######################################')
print('# VTec 90s stabilization - system on! #')
print('#######################################')
print(' ')

Vtec_On(ser)
time.sleep(85)
print('5 sec')
time.sleep(1)
print('4 sec')
time.sleep(1)
print('3 sec')
time.sleep(1)
print('2 sec')
time.sleep(1)
print('1 sec')
time.sleep(1)
PumpAReagent(ser)
PumpBReagent(ser)
print('Pumps 1 and 2 switched to reagents!')
print('Experiment start! UV-Vis acquisition on!')
print(' ')

time.sleep(540)
print('First steady state reached!')
print('Generating gradient of solvents composition!')
print('(0.01 mL/min change, 2 seconds interval)')
print(' ')

flowA = flow3
flowB = flow4
i = 1
while (flowA > 0.01):
          flowA = flowA - 0.01
          flowA = round(flowA, 2)
          flow3 = flowA
          flowB = flowB + 0.01
          flowB = round(flowB, 2)
          flow4 = flowB
          Vtec_PumpC(ser,flow3)
          Vtec_PumpD(ser,flow4)
          time.sleep(1.5)
          print('Iteration #', i, ', flow3/C =', flow3, ' and flow4/D =', flow4)
          i = i + 1

flow3 = 0.0
flow4 = 2.1
Vtec_PumpC(ser,flow3)
Vtec_PumpD(ser,flow4)

print(' ')
print('Gradient done. Holding steady state for 4 minutes.')
time.sleep(120)
PumpASolv(ser)
PumpBSolv(ser)
```

```
print('Switched pumps 1 and 2 back to solvents.')
time.sleep(120)

print(' ')
print('Switching flow rates of pumps 3 and 4 to initial flow rates.')
flow3 = 2.1
flow4 = 0.0
Vtec_PumpC(ser,flow3)
Vtec_PumpD(ser,flow4)
print('Reaction mixture elution and system cleanup for 10 min')
time.sleep(600)

Vtec_Off(ser)
print('################################')
print('# VTec Off! End of experiment! #')
print('################################')
```

## 3. 2. 2. Results of solvent effects studies in $S_NAr$ reaction

### 3. 2. 2. 1. DMF and DMSO solvents mixture:

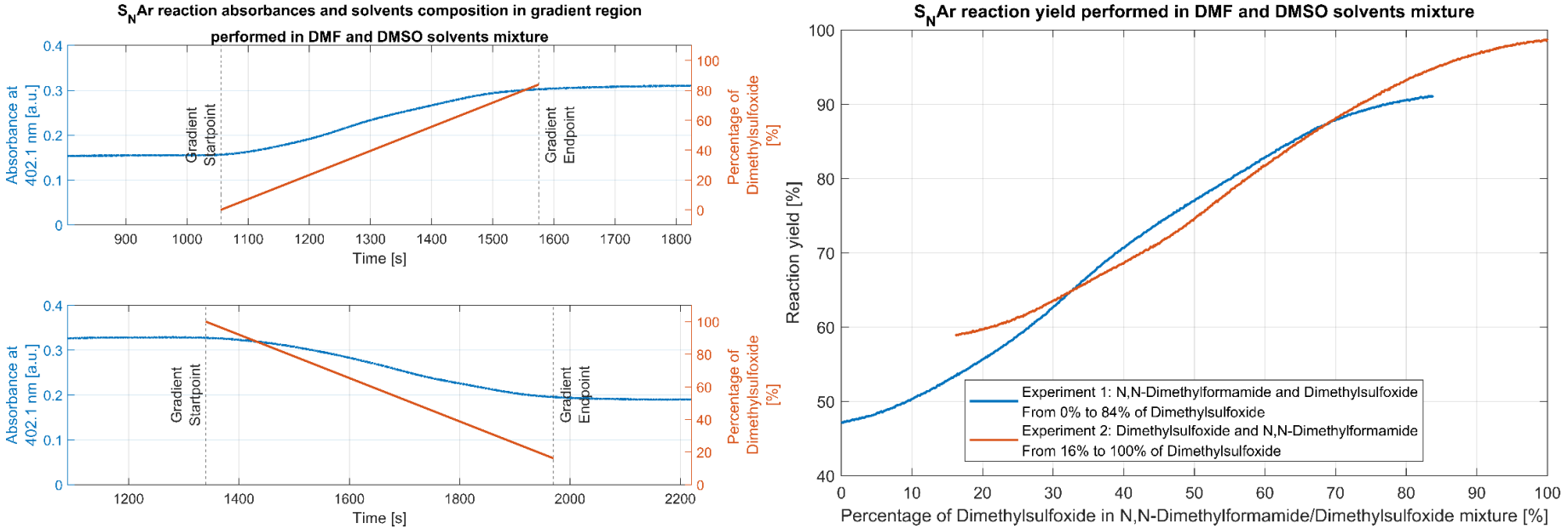



*Figure S 12. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/DMSO mixtures as reaction medium.*

### 3. 2. 2. 2. DMF and NMP solvents mixture:

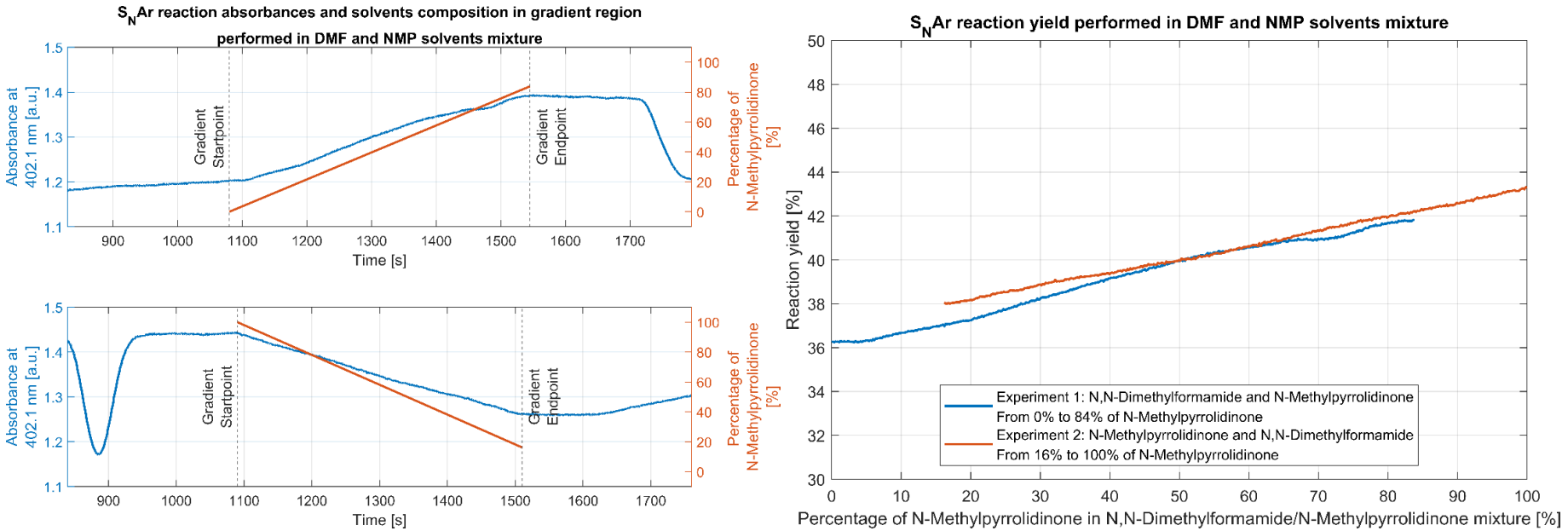



*Figure S 13. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/NMP mixtures as reaction medium.*

### 3. 2. 2. 3. DMF and MeOH solvents mixture:

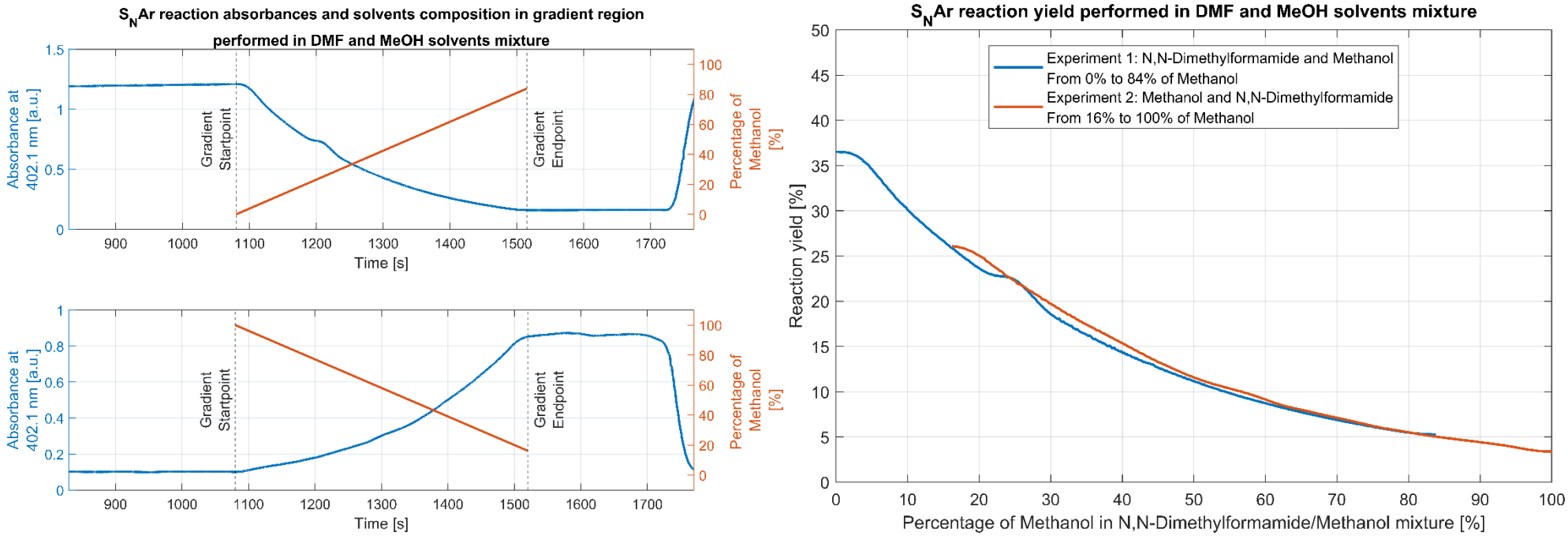



*Figure S 14. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/MeOH mixtures as reaction medium.*

### 3. 2. 2. 4. DMF and EtOH solvents mixture:

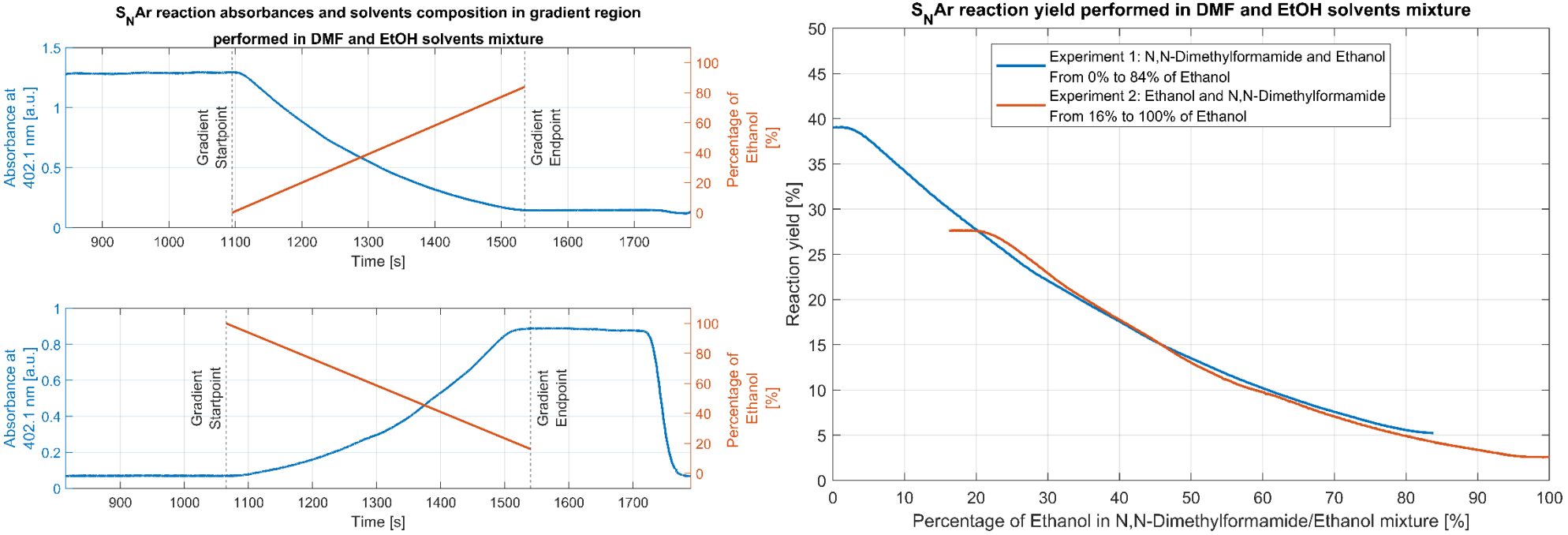



*Figure S 15. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/EtOH mixtures as reaction medium.*

### 3. 2. 2. 5. DMF and *t*BuOH solvents mixture:

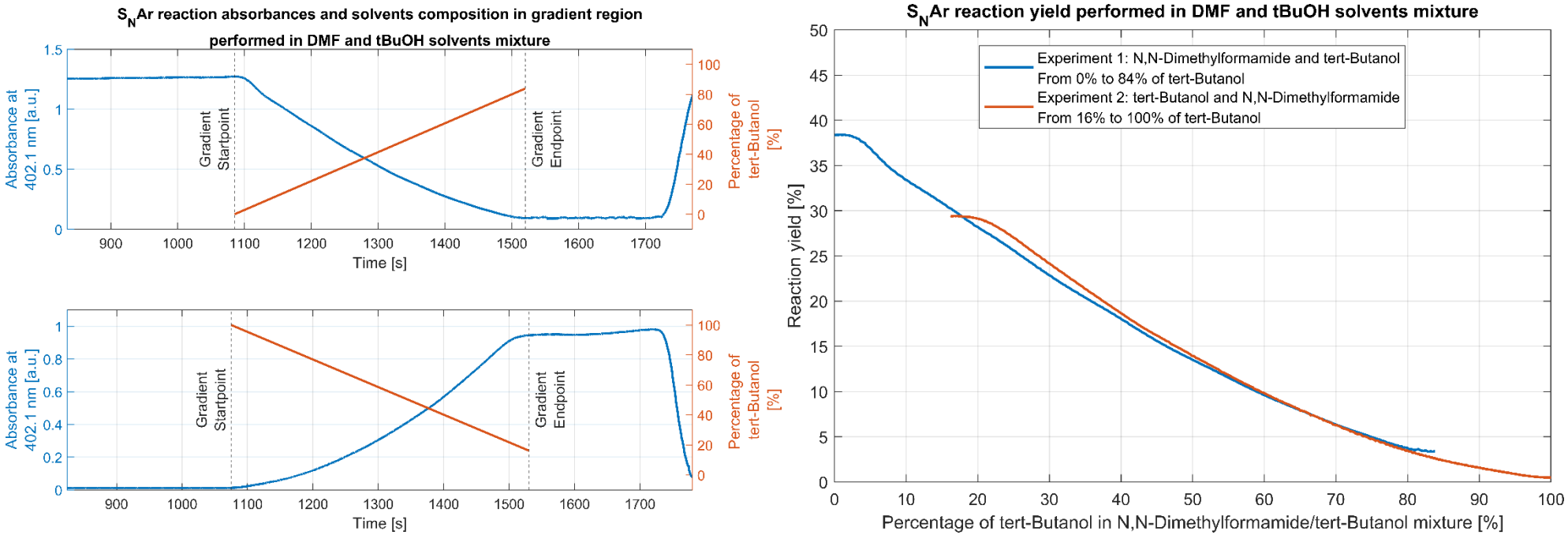



*Figure S 16. . Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/tBuOH mixtures as reaction medium.*

### 3. 2. 2. 6. DMF and toluene solvents mixture:

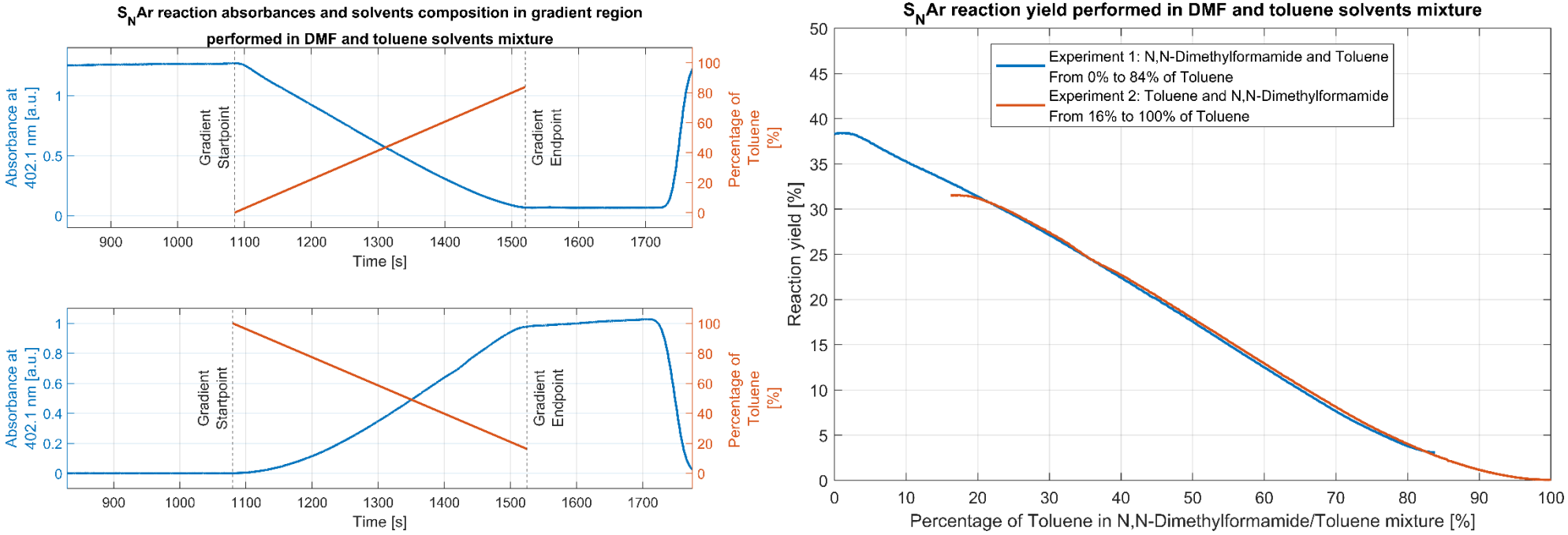



*Figure S 17. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/toluene mixtures as reaction medium.*

### 3. 2. 2. 7. DMF and THF solvents mixture:

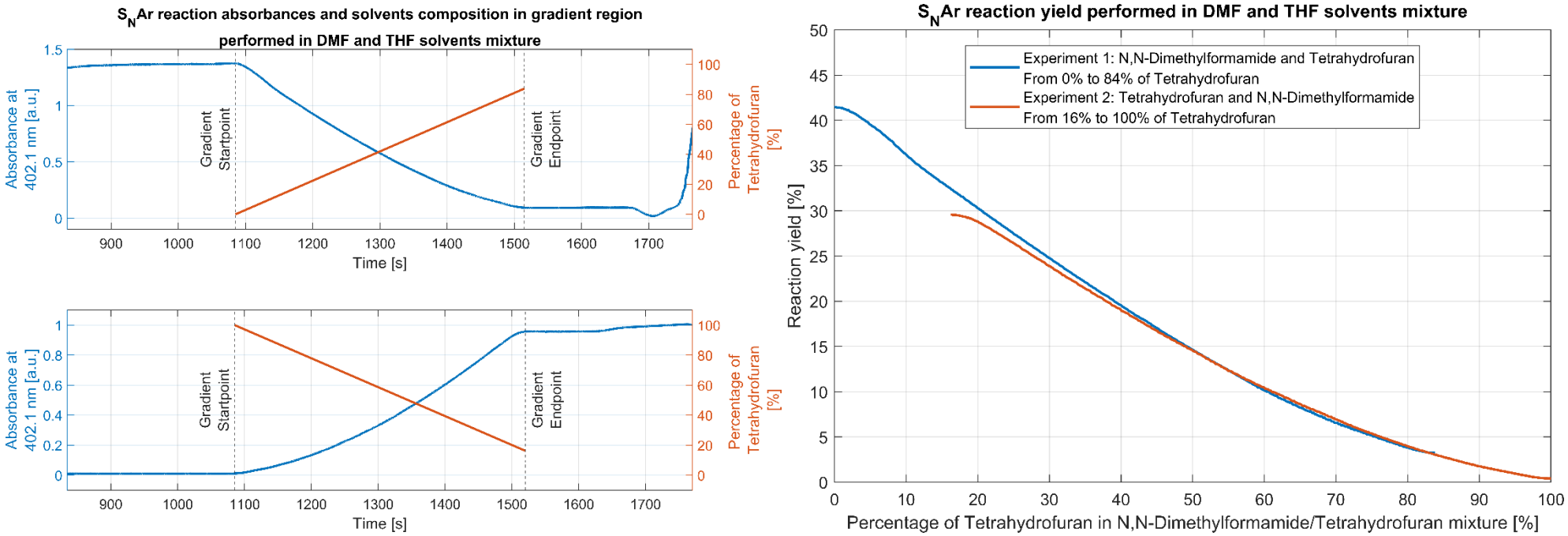



*Figure S 18. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/THF mixtures as reaction medium.*

### 3. 2. 2. 8. DMF and AcOEt solvents mixture:

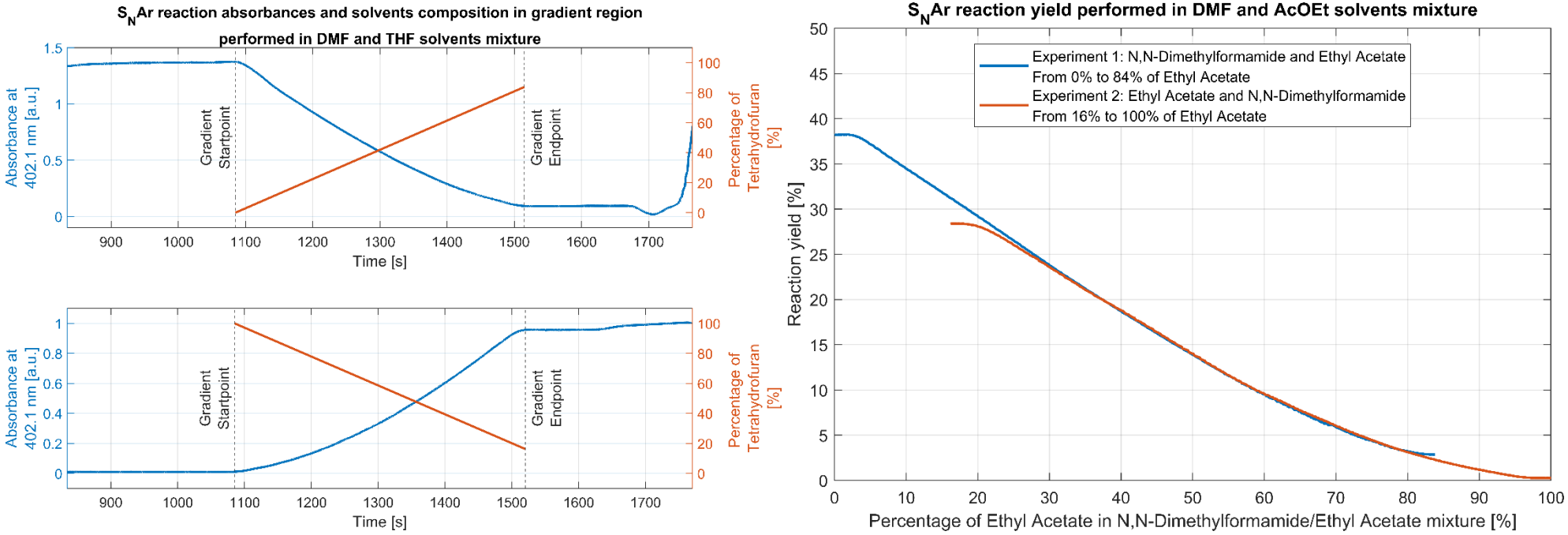



*Figure S 19. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/AcOEt mixtures as reaction medium.*

### 3. 2. 2. 9. DMF and MeCN solvents mixture:

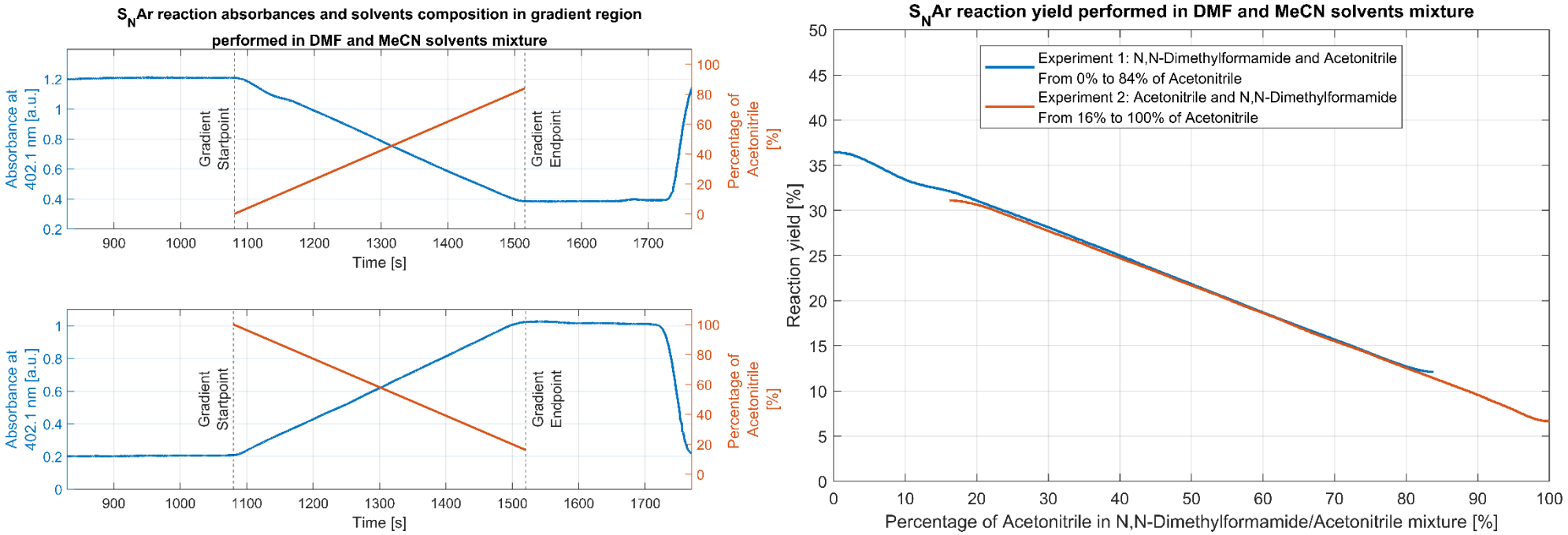



*Figure S 20. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/MeCN mixtures as reaction medium.*

### 3. 2. 2. 10. DMF and triglyme solvents mixture:

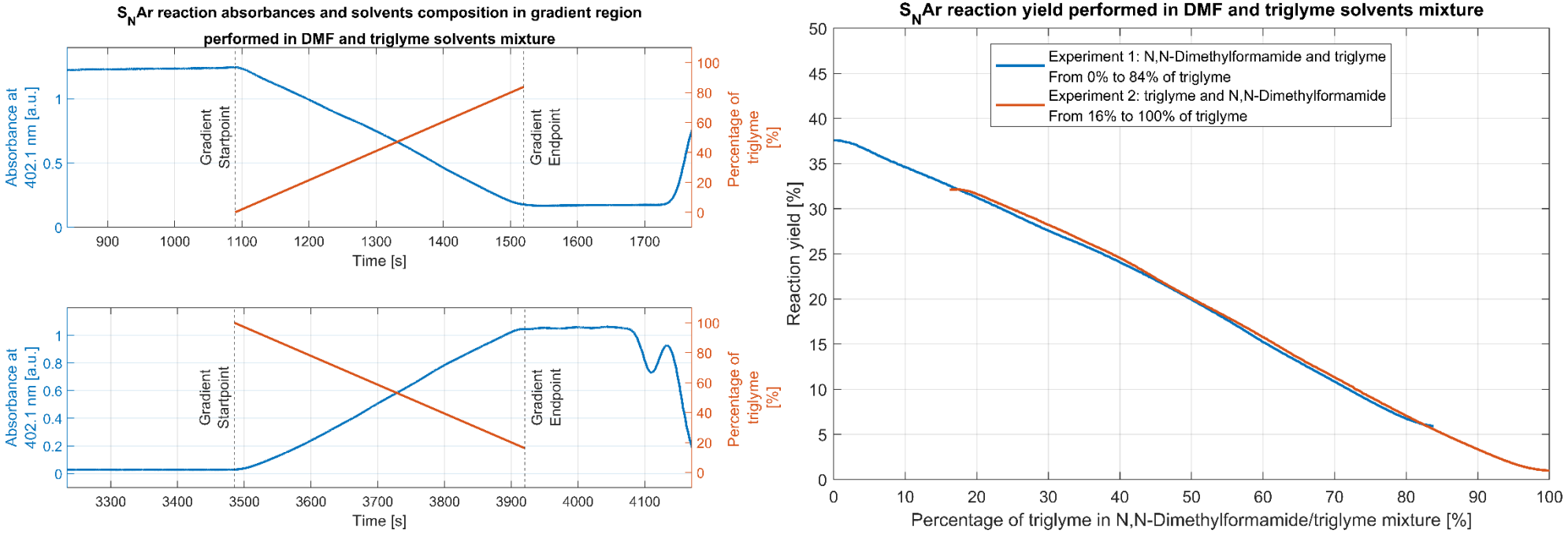



*Figure S 21. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/triglyme mixtures as reaction medium.*

### 3. 2. 2. 11. DMF and acetone solvents mixture:

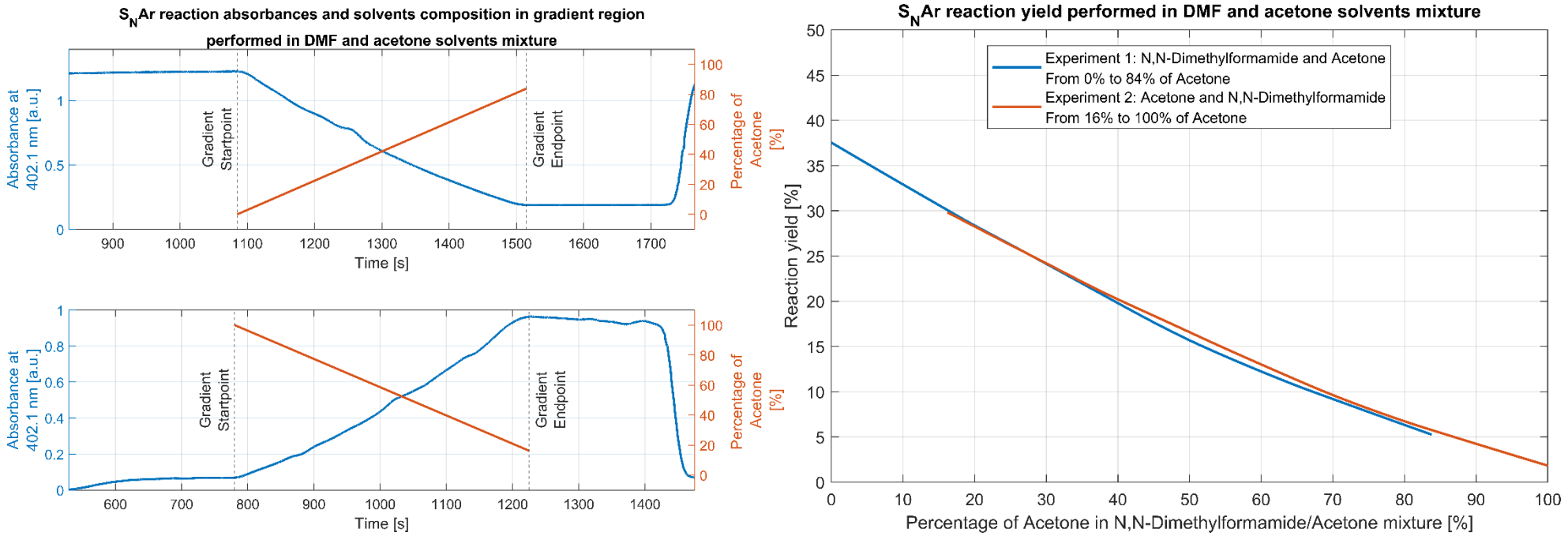



*Figure S 22. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/acetone mixtures as reaction medium. Graph of reaction yield against solvent composition has been smoothed.*

### 3. 2. 2. 12. DMF and 1,2-DCE solvents mixture:

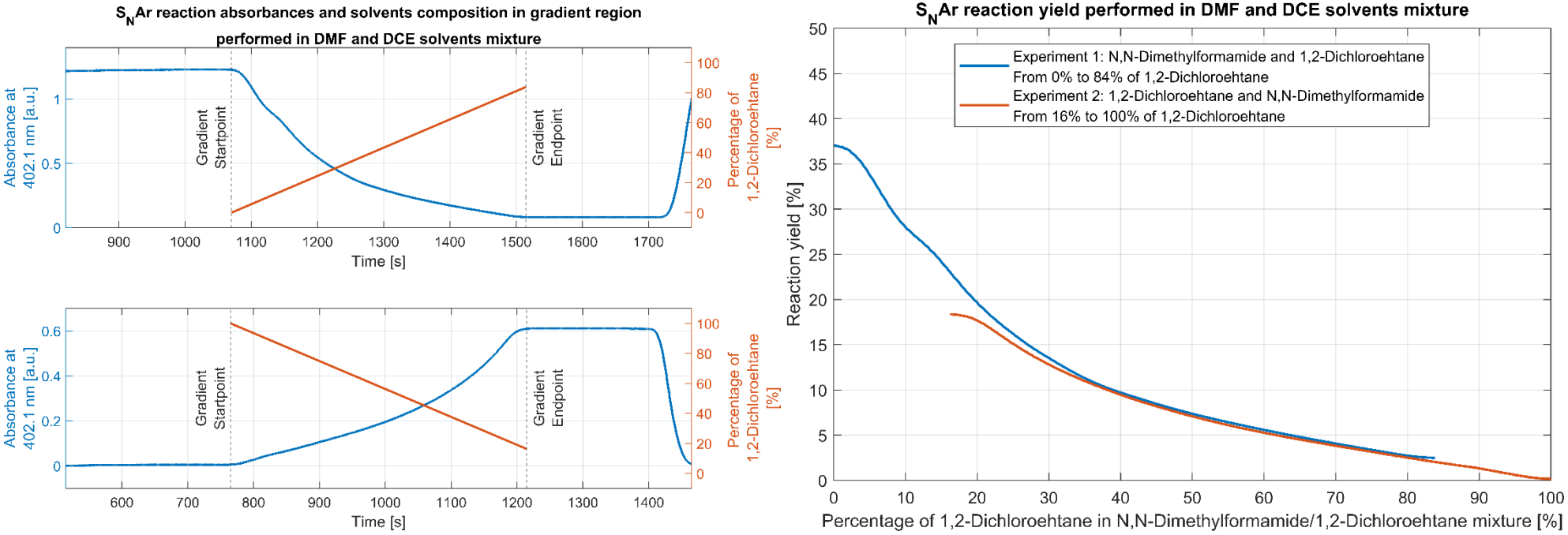



*Figure S 23. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/DCE mixtures as reaction medium.*

### 3. 2. 2. 13. DMF and DCM solvents mixture:

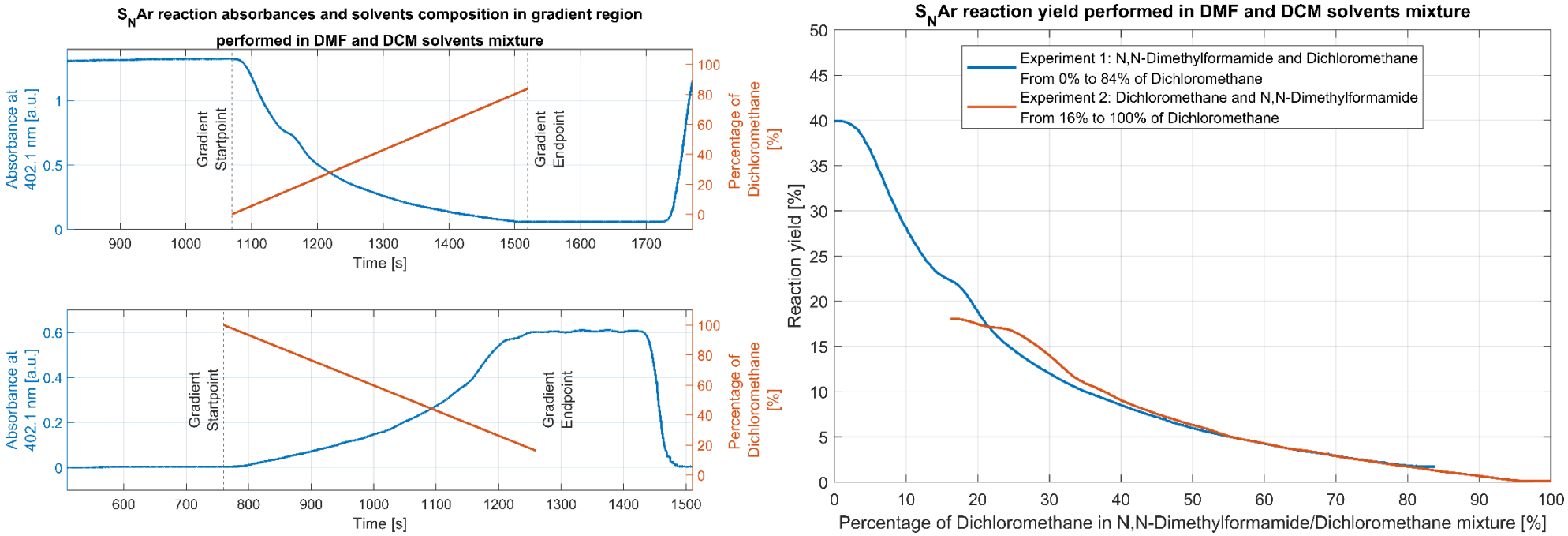



*Figure S 24. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/DCM mixtures as reaction medium.*

### 3. 2. 2. 14. DMF and $CHCl_3$ solvents mixture:

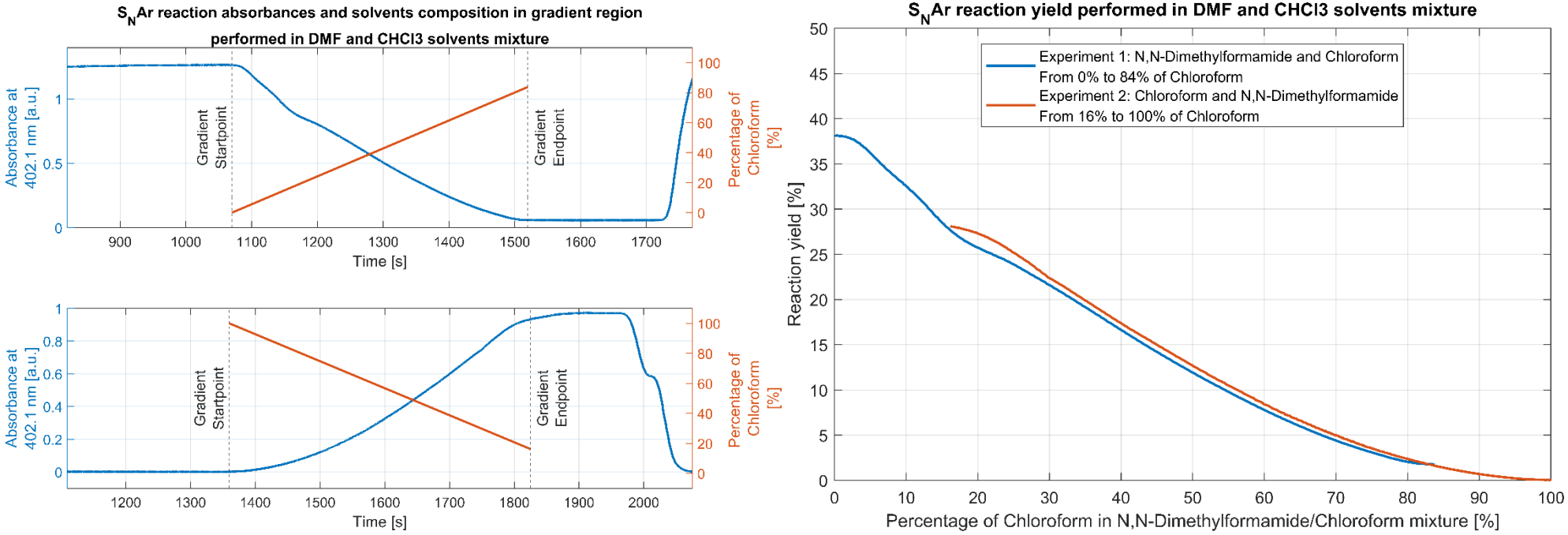



*Figure S 25. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/$CHCl_3$ mixtures as reaction medium.*

### 3. 2. 2. 15. DMF and 1,4-dioxane solvents mixture:

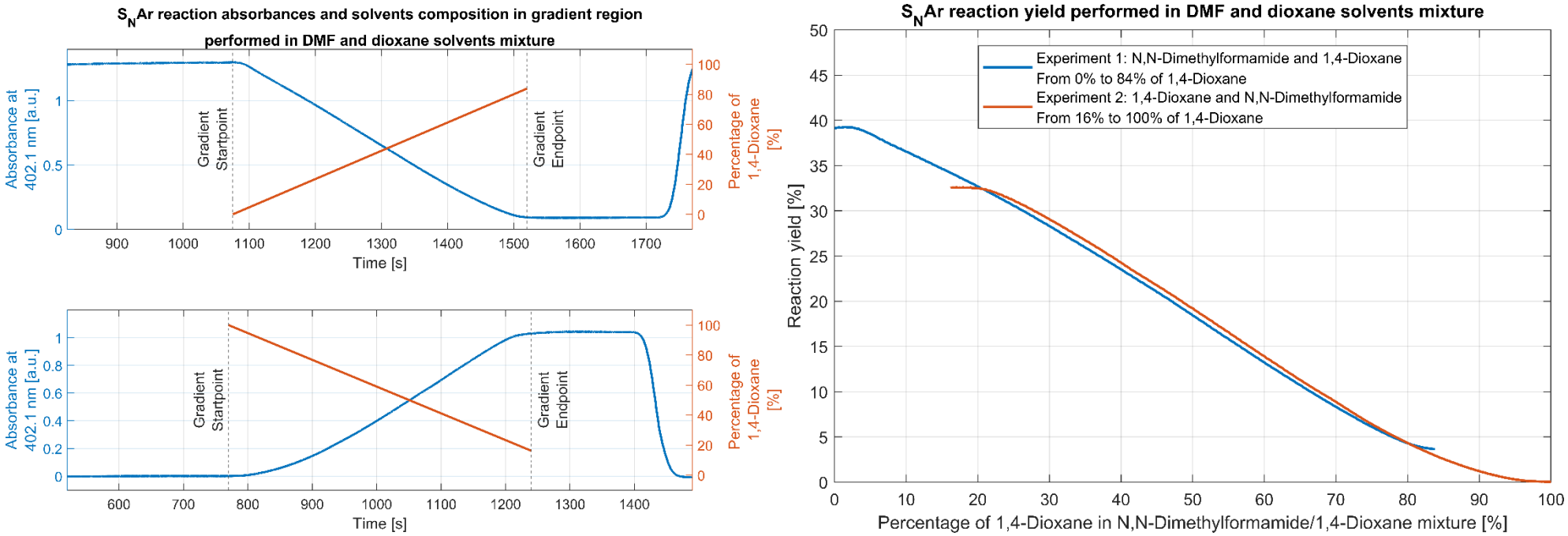



*Figure S 26. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/1,4-dioxane mixtures as reaction medium.*

### 3. 2. 2. 16. DMF and MTBE solvents mixture:

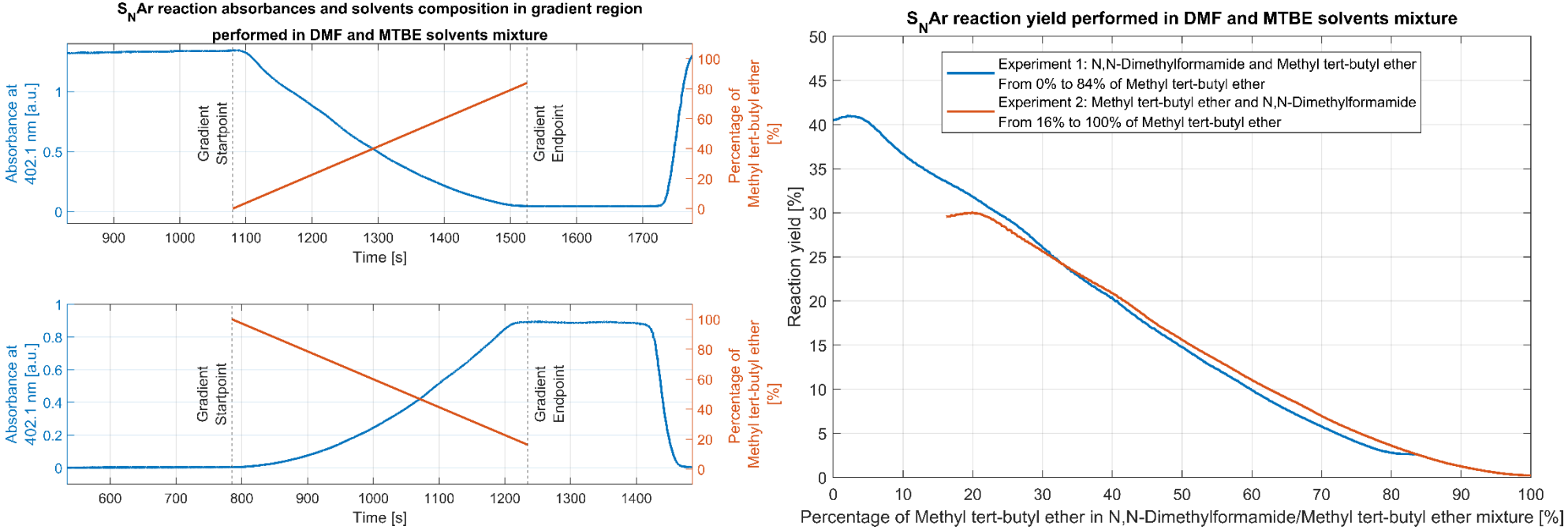



*Figure S 27. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/MTBE mixtures as reaction medium.*

### 3. 2. 2. 17. DMF and DMA solvents mixture:

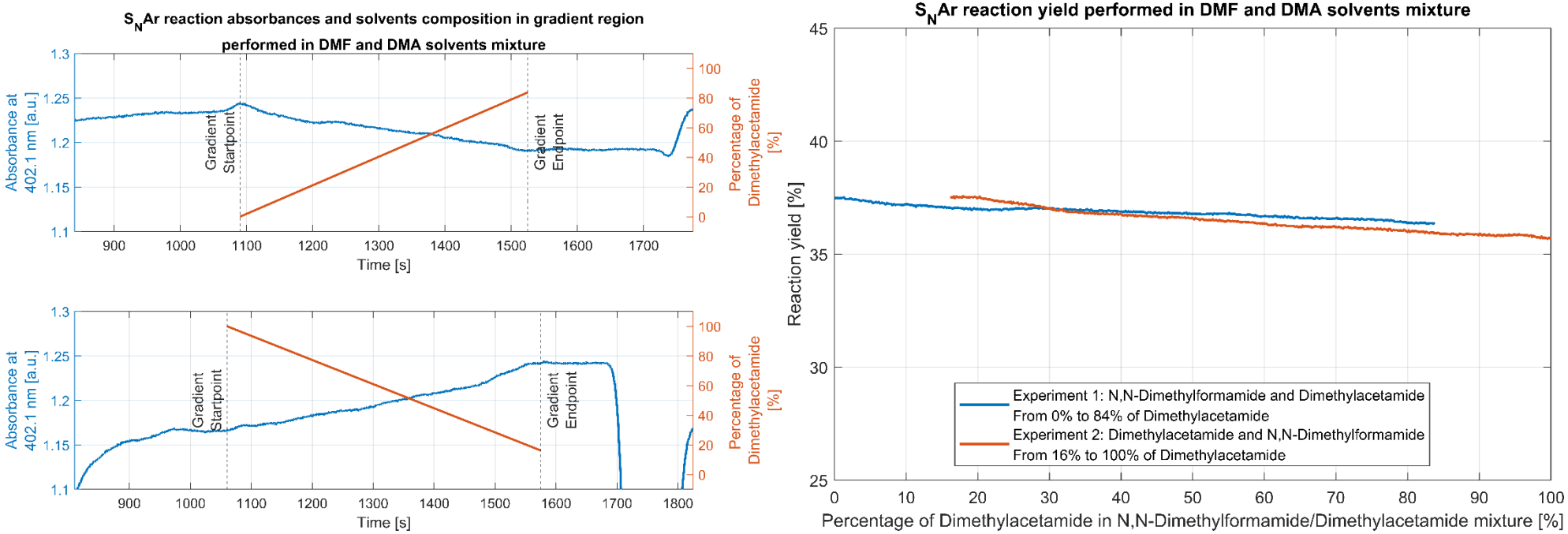



*Figure S 28. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated DMF/DMA mixtures as reaction medium.*

### 3. 2. 2. 18. DMF and IPA solvents mixture:

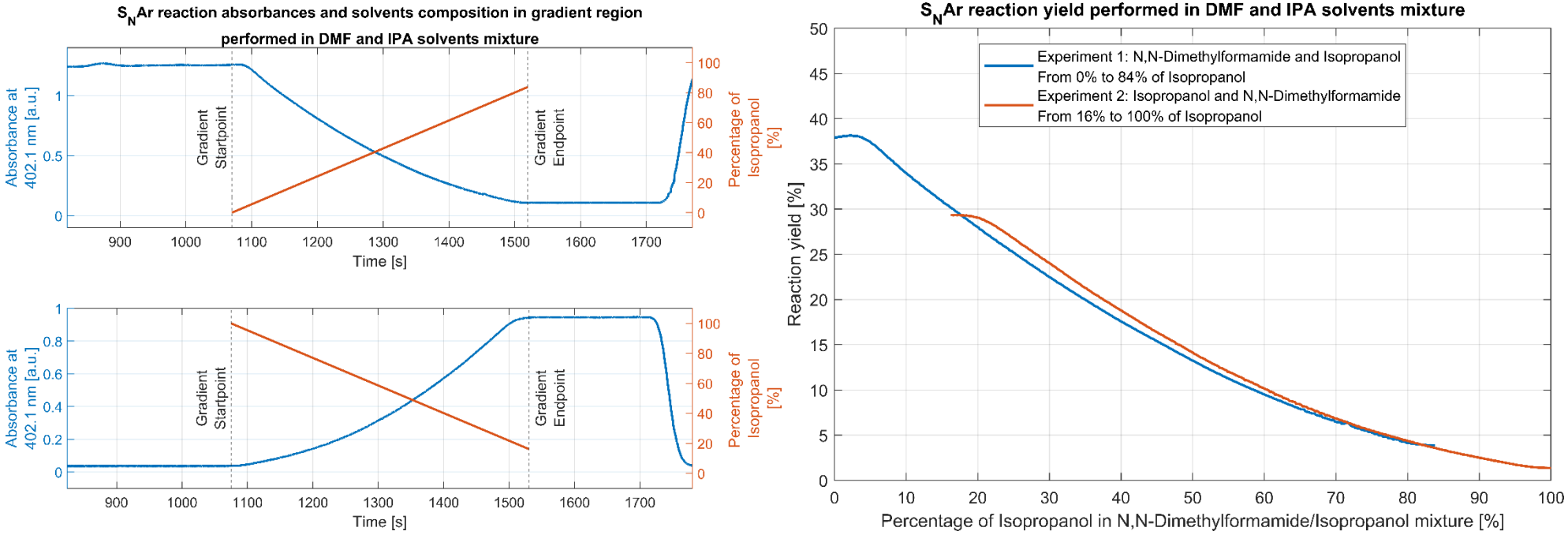



*Figure S 29. Results of flow solvents mixture studies in SNAr reaction using in situ generated DMF/IPA mixtures as reaction medium.*

### 3. 2. 2. 19. Summary of all solvent mixtures of DMF with secondary solvent tested:

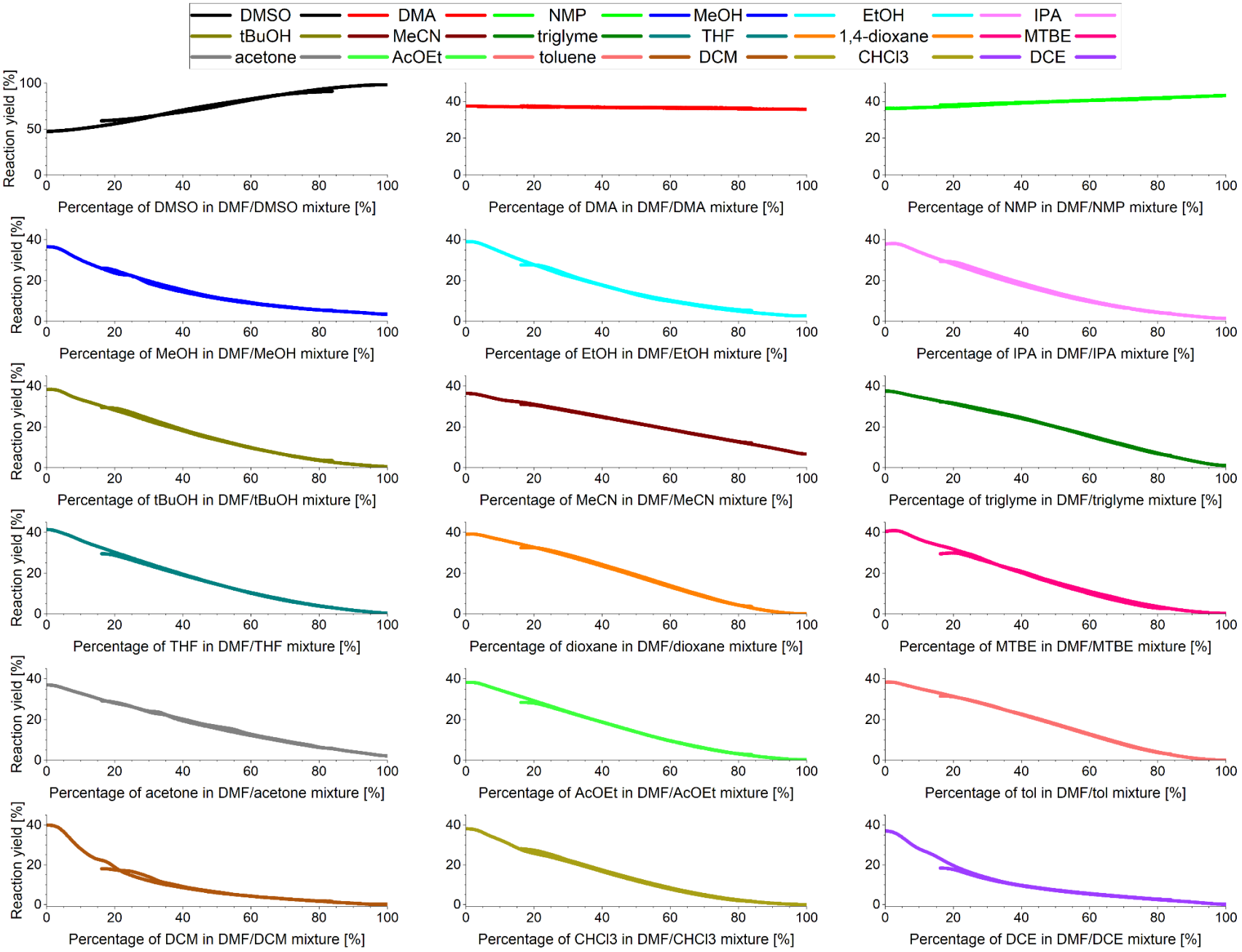



*Figure S 30. Results of flow solvents mixture studies in $S_NAr$ reaction using in situ generated solvents mixtures as reaction medium.*

## 3. 3. Analysis script for the $S_NAr$ solvent studies experiments

Matlab® script used for analysis of solvent effects in $S_NAr$ reaction experiments:

```
clear
close all

% Suppress warning associated with saving Matlab workspaces with embedded figures
warning('off','MATLAB:Figure:FigureSavedToMATFile');

% Table below contains values of the molar extinction coefficient of
% 1-(4-nitrophenly)piperidine for various solvents at 402.1 nm
solvents_table = ["1: Row" "2: Name" "3: Abbrv" "4: MEC@402.1nm"
    "2" "N,N-Dimethylformamide","DMF",20731.3
    "3" "Dimethylsulfoxide","DMSO",20747.6
    "4" "N-Methylpyrrolidinone","NMP",20827.7
    "5" "Ethanol","EtOH",16796.1
    "6" "Acetonitrile","MeCN",19706.7
    "7" "Propylene Carbonate","PropCarb",19063.3
    "8" "tert-Butanol","tBuOH",16718.7
    "9" "Acetone","acetone",20142.6
    "10" "1,4-Dioxane","dioxane",14898.8
    "11" "triglyme","triglyme",18303.0
    "12" "1,2-Dichloroehtane","DCE",20643.4
    "13" "Toluene","toluene",12549.6
    "14" "Tetrahydrofuran","THF",17553.7
    "15" "Methanol","MeOH",18636.4
    "16" "20% H_2O in DMF","20%water",21465.1
    "17" "40% H_2O in DMF","40%water",18377.4
    "18" "Ethyl Acetate","AcOEt",15455.4
    "19" "Isopropanol","IPA",16700.3
    "20" "Dichloromethane","DCM",21591.8
    "21" "Chloroform","CHCl3",20833.1
    "22" "Methyl tert-butyl ether","MTBE",9188.7
    "23" "Dimethylacetamide","DMA",20412.2
    "24" "10% H_2O in DMF","10%water",21292.1];
disp(solvents_table);

solvent_1 = input('1st solvent is?','s'); % Determine 1st used solvent
solvent_2 = input('2nd solvent is?','s'); % Determine 2nd used solvent

% If statement below extracts the desired MEC value for 1st solvent
if solvent_1 == "DMF"
    MEC_solvent_1 = solvents_table(2,4);
elseif solvent_1 == "DMSO"
    MEC_solvent_1 = solvents_table(3,4);
elseif solvent_1 == "NMP"
    MEC_solvent_1 = solvents_table(4,4);
elseif solvent_1 == "EtOH"
    MEC_solvent_1 = solvents_table(5,4);
elseif solvent_1 == "MeCN"
    MEC_solvent_1 = solvents_table(6,4);
elseif solvent_1 == "PropCarb"
    MEC_solvent_1 = solvents_table(7,4);
elseif solvent_1 == "tBuOH"
    MEC_solvent_1 = solvents_table(8,4);
elseif solvent_1 == "acetone"
    MEC_solvent_1 = solvents_table(9,4);
elseif solvent_1 == "dioxane"
    MEC_solvent_1 = solvents_table(10,4);
elseif solvent_1 == "triglyme"
    MEC_solvent_1 = solvents_table(11,4);
elseif solvent_1 == "DCE"
    MEC_solvent_1 = solvents_table(12,4);
elseif solvent_1 == "toluene"
    MEC_solvent_1 = solvents_table(13,4);
elseif solvent_1 == "THF"
    MEC_solvent_1 = solvents_table(14,4);
elseif solvent_1 == "MeOH"
    MEC_solvent_1 = solvents_table(15,4);
elseif solvent_1 == "20%water"
    MEC_solvent_1 = solvents_table(16,4);
elseif solvent_1 == "40%water"
    MEC_solvent_1 = solvents_table(17,4);
elseif solvent_1 == "AcOEt"
    MEC_solvent_1 = solvents_table(18,4);
elseif solvent_1 == "IPA"
    MEC_solvent_1 = solvents_table(19,4);
elseif solvent_1 == "DCM"
    MEC_solvent_1 = solvents_table(20,4);
elseif solvent_1 == "CHCl3"
    MEC_solvent_1 = solvents_table(21,4);
elseif solvent_1 == "MTBE"
```

```
    MEC_solvent_1 = solvents_table(22,4);
elseif solvent_1 == "DMA"
    MEC_solvent_1 = solvents_table(23,4);
elseif solvent_1 == "10%water"
    MEC_solvent_1 = solvents_table(24,4);
else
    disp('Wrong solvent abbreviation used for solvent 1!')
    return
end

% If statement below extracts the desired MEC value for 2nd solvent
if solvent_2 == "DMF"
    MEC_solvent_2 = solvents_table(2,4);
elseif solvent_2 == "DMSO"
    MEC_solvent_2 = solvents_table(3,4);
elseif solvent_2 == "NMP"
    MEC_solvent_2 = solvents_table(4,4);
elseif solvent_2 == "EtOH"
    MEC_solvent_2 = solvents_table(5,4);
elseif solvent_2 == "MeCN"
    MEC_solvent_2 = solvents_table(6,4);
elseif solvent_2 == "PropCarb"
    MEC_solvent_2 = solvents_table(7,4);
elseif solvent_2 == "tBuOH"
    MEC_solvent_2 = solvents_table(8,4);
elseif solvent_2 == "acetone"
    MEC_solvent_2 = solvents_table(9,4);
elseif solvent_2 == "dioxane"
    MEC_solvent_2 = solvents_table(10,4);
elseif solvent_2 == "triglyme"
    MEC_solvent_2 = solvents_table(11,4);
elseif solvent_2 == "DCE"
    MEC_solvent_2 = solvents_table(12,4);
elseif solvent_2 == "toluene"
    MEC_solvent_2 = solvents_table(13,4);
elseif solvent_2 == "THF"
    MEC_solvent_2 = solvents_table(14,4);
elseif solvent_2 == "MeOH"
    MEC_solvent_2 = solvents_table(15,4);
elseif solvent_2 == "20%water"
    MEC_solvent_2 = solvents_table(16,4);
elseif solvent_2 == "40%water"
    MEC_solvent_2 = solvents_table(17,4);
elseif solvent_2 == "AcOEt"
    MEC_solvent_2 = solvents_table(18,4);
elseif solvent_2 == "IPA"
    MEC_solvent_2 = solvents_table(19,4);
elseif solvent_2 == "DCM"
    MEC_solvent_2 = solvents_table(20,4);
elseif solvent_2 == "CHCl3"
    MEC_solvent_2 = solvents_table(21,4);
elseif solvent_2 == "MTBE"
    MEC_solvent_2 = solvents_table(22,4);
elseif solvent_2 == "DMA"
    MEC_solvent_2 = solvents_table(23,4);
elseif solvent_2 == "10%water"
    MEC_solvent_2 = solvents_table(24,4);
else
    disp('Wrong solvent abbreviation used for solvent 2!')
    return
end

% Determine full name of solvents for graphs labelling
if solvent_1 == "DMF"
    solvent_1_name = solvents_table(2,2);
elseif solvent_1 == "DMSO"
    solvent_1_name = solvents_table(3,2);
elseif solvent_1 == "NMP"
    solvent_1_name = solvents_table(4,2);
elseif solvent_1 == "EtOH"
    solvent_1_name = solvents_table(5,2);
elseif solvent_1 == "MeCN"
    solvent_1_name = solvents_table(6,2);
elseif solvent_1 == "PropCarb"
    solvent_1_name = solvents_table(7,2);
elseif solvent_1 == "tBuOH"
    solvent_1_name = solvents_table(8,2);
elseif solvent_1 == "acetone"
    solvent_1_name = solvents_table(9,2);
elseif solvent_1 == "dioxane"
    solvent_1_name = solvents_table(10,2);
elseif solvent_1 == "triglyme"
    solvent_1_name = solvents_table(11,2);
elseif solvent_1 == "DCE"
    solvent_1_name = solvents_table(12,2);
```

```
elseif solvent_1 == "toluene"
    solvent_1_name = solvents_table(13,2);
elseif solvent_1 == "THF"
    solvent_1_name = solvents_table(14,2);
elseif solvent_1 == "MeOH"
    solvent_1_name = solvents_table(15,2);
elseif solvent_1 == "20%water"
    solvent_1_name = solvents_table(16,2);
elseif solvent_1 == "40%water"
    solvent_1_name = solvents_table(17,2);
elseif solvent_1 == "AcOEt"
    solvent_1_name = solvents_table(18,2);
elseif solvent_1 == "IPA"
    solvent_1_name = solvents_table(19,2);
elseif solvent_1 == "DCM"
    solvent_1_name = solvents_table(20,2);
elseif solvent_1 == "CHCl3"
    solvent_1_name = solvents_table(21,2);
elseif solvent_1 == "MTBE"
    solvent_1_name = solvents_table(22,2);
elseif solvent_1 == "DMA"
    solvent_1_name = solvents_table(23,2);
elseif solvent_1 == "10%water"
    solvent_1_name = solvents_table(24,2);
end

if solvent_2 == "DMF"
    solvent_2_name = solvents_table(2,2);
elseif solvent_2 == "DMSO"
    solvent_2_name = solvents_table(3,2);
elseif solvent_2 == "NMP"
    solvent_2_name = solvents_table(4,2);
elseif solvent_2 == "EtOH"
    solvent_2_name = solvents_table(5,2);
elseif solvent_2 == "MeCN"
    solvent_2_name = solvents_table(6,2);
elseif solvent_2 == "PropCarb"
    solvent_2_name = solvents_table(7,2);
elseif solvent_2 == "tBuOH"
    solvent_2_name = solvents_table(8,2);
elseif solvent_2 == "acetone"
    solvent_2_name = solvents_table(9,2);
elseif solvent_2 == "dioxane"
    solvent_2_name = solvents_table(10,2);
elseif solvent_2 == "triglyme"
    solvent_2_name = solvents_table(11,2);
elseif solvent_2 == "DCE"
    solvent_2_name = solvents_table(12,2);
elseif solvent_2 == "toluene"
    solvent_2_name = solvents_table(13,2);
elseif solvent_2 == "THF"
    solvent_2_name = solvents_table(14,2);
elseif solvent_2 == "MeOH"
    solvent_2_name = solvents_table(15,2);
elseif solvent_2 == "20%water"
    solvent_2_name = solvents_table(16,2);
elseif solvent_2 == "40%water"
    solvent_2_name = solvents_table(17,2);
elseif solvent_2 == "AcOEt"
    solvent_2_name = solvents_table(18,2);
elseif solvent_2 == "IPA"
    solvent_2_name = solvents_table(19,2);
elseif solvent_2 == "DCM"
    solvent_2_name = solvents_table(20,2);
elseif solvent_2 == "CHCl3"
    solvent_2_name = solvents_table(21,2);
elseif solvent_2 == "MTBE"
    solvent_2_name = solvents_table(22,2);
elseif solvent_2 == "DMA"
    solvent_2_name = solvents_table(23,2);
elseif solvent_2 == "10%water"
    solvent_2_name = solvents_table(24,2);
end

% Convert MECs from string to numerical values
MEC_solvent_1 = str2double(MEC_solvent_1);
MEC_solvent_2 = str2double(MEC_solvent_2);

% Generate linear model for MEC behaviour in selected solvents
MEC_mat_x = [0 100]; %X axis for MEC calculation - from 0 to 100% of solvent 2
MEC_mat_y = [MEC_solvent_1 MEC_solvent_2]; %Y axis for MEC calculation - from MEC in Solvent1 to EMC in
solvent2
MEC_linear_model = fitlm(MEC_mat_x,MEC_mat_y); %Create a linear function for values above
MEC_alpha = table2array(MEC_linear_model.Coefficients(2,1)); %Extract alpha value from linear function (y =
alpha*x + beta)
```

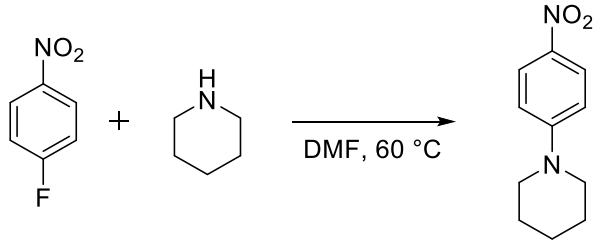
```
MEC_beta = table2array(MEC_linear_model.Coefficients(1,1)); %Extract beta value from linear function (y =
alpha*x + beta)

% Read raw absorbance data (.spc format)
data_1 = tgspcread('./d1.spc');
data_2 = tgspcread('./d2.spc');

% Generate absorbance data at 402.1 nm (row 653 in spc files)
calc_1(:,1) = data_1.Y(653,:);
calc_2(:,1) = data_2.Y(653,:);

% Plot absorption data to determine start and endpoints
disp(' ')
disp('Generating Figure 1: Absorbances at 402.1 nm for both experiments!')
fig1_label_yaxis_1 = 'Absorbance at';
fig1_label_yaxis_2 = '402.1 nm [a.u.]';
figure(1),
subplot(2,1,1),yyaxis left,plot(calc_1(:,1)),axis tight,grid on,
ylabel({fig1_label_yaxis_1,fig1_label_yaxis_2},'color','#0072BD'),xlabel('Time [s]'),
subplot(2,1,2),yyaxis left,plot(calc_2(:,1)),axis tight,grid on,
ylabel({fig1_label_yaxis_1,fig1_label_yaxis_2},'color','#0072BD'),xlabel('Time [s]'),
f1 = figure(1);
u1 = f1.Position;
f1.Position = [300 450 1250 500];

% Generate start and endpoints of gradient data
disp(' ')
startpoint_d1 = input('Provide the strating point of gradient from experiment d1!');
endpoint_d1 = input('Provide the ending point of gradient from experiment d1!');
startpoint_d2 = input('Provide the strating point of gradient from experiment d2!');
endpoint_d2 = input('Provide the ending point of gradient from experiment d2!');

% Provide flow rates for solvents and concentrations calculations [mL/min]
flow_1 = 0.2;
flow_2 = 0.2;
flow_3and4 = 2.1;
flow_total = flow_1 + flow_2 + flow_3and4;

% Generate linear solvent composition for the d1 experiment
gradient_d1_steps = (endpoint_d1+1) - (startpoint_d1-1);
gradient_d1_solv2_max = flow_3and4/flow_total;
gradient_d1_solv2_min = 0;

gradient_d1_x = [1 gradient_d1_steps];
gradient_d1_y = [gradient_d1_solv2_min gradient_d1_solv2_max];
gradient_d1_linear_model = fitlm(gradient_d1_x,gradient_d1_y);
gradient_d1_alpha = table2array(gradient_d1_linear_model.Coefficients(2,1));
gradient_d1_beta = table2array(gradient_d1_linear_model.Coefficients(1,1));
gradient_d1_index = 1;
while gradient_d1_index < gradient_d1_steps
    calc_1((startpoint_d1-1)+gradient_d1_index,2) =
((gradient_d1_alpha.*gradient_d1_index+gradient_d1_beta).*100);
    gradient_d1_index = gradient_d1_index + 1;
end

% Generate linear solvent composition for the d2 experiment
gradient_d2_steps = (endpoint_d2+1) - (startpoint_d2-1);
gradient_d2_solv2_max = 1;
gradient_d2_solv2_min = (flow_1+flow_2)/flow_total;

gradient_d2_x = [1 gradient_d2_steps];
gradient_d2_y = [gradient_d2_solv2_max gradient_d2_solv2_min];
gradient_d2_linear_model = fitlm(gradient_d2_x,gradient_d2_y);
gradient_d2_alpha = table2array(gradient_d2_linear_model.Coefficients(2,1));
gradient_d2_beta = table2array(gradient_d2_linear_model.Coefficients(1,1));
gradient_d2_index = 1;
while gradient_d2_index < gradient_d2_steps
    calc_2((startpoint_d2-1)+gradient_d2_index,2) =
((gradient_d2_alpha.*gradient_d2_index+gradient_d2_beta).*100);
    gradient_d2_index = gradient_d2_index + 1;
end

%  Generate new column in which change the 0% values into NaN values, so they won't show on graph
calc_1(1:startpoint_d1-1,6) = NaN;
calc_1(startpoint_d1:endpoint_d1,6) = calc_1(startpoint_d1:endpoint_d1,2);
calc_1(endpoint_d1+1:end,6) = NaN;
calc_2(1:startpoint_d2-1,6) = NaN;
calc_2(startpoint_d2:endpoint_d2,6) = calc_2(startpoint_d2:endpoint_d2,2);
calc_2(endpoint_d2+1:end,6) = NaN;

% Plot the solvents composition data to figure(1)
fig1_label_yyaxis_1 = ['Percentage of ',solvent_2_name,'[%]'];
fig1_label_yyaxis_2 = ['Percentage of ',solvent_2_name,'[%]'];
disp(' ')
disp('Adding solvent compositions data to figure 1!')
```

```
figure(1),
subplot(2,1,1),yyaxis right,plot(calc_1(:,6)),ylabel(fig1_label_yyaxis_1),ylim([-10 110]),
xline(startpoint_d1,'--
',{'Gradient','Startpoint'},'LabelHorizontalAlignment','left','LabelVerticalAlignment','middle');
xline(endpoint_d1,'--',{'Gradient','Endpoint'},'LabelVerticalAlignment','middle');
fig1_title = string(['S_NAr reaction absorbances and solvents composition in gradient region performed in
',solvent_1,' and ',solvent_2,' solvents mixture']);
title(fig1_title);
subplot(2,1,2),yyaxis right,plot(calc_2(:,6)),ylabel(fig1_label_yyaxis_2),ylim([-10 110]),
xline(startpoint_d2,'--
',{'Gradient','Startpoint'},'LabelHorizontalAlignment','left','LabelVerticalAlignment','middle');
xline(endpoint_d2,'--',{'Gradient','Endpoint'},'LabelVerticalAlignment','middle');

% Calculate MEC values for the variable solvents composition range
calc_1(:,3) = ((MEC_alpha.*calc_1(:,2))+MEC_beta);
calc_2(:,3) = ((MEC_alpha.*calc_2(:,2))+MEC_beta);

% Control plot of MEC values for used solvents composition
% disp(' ')
% disp('Generating Figure 2: MEC values for used solvent combination!')
% fig2_label_xaxis_1 = ['Percentage of ',solvent_2_name,' [%]'];
% figure(2),
% plot(calc_1(startpoint_d1:endpoint_d1,2),calc_1(startpoint_d1:endpoint_d1,3)),hold on,
% plot(calc_2(startpoint_d2:endpoint_d2,2),calc_2(startpoint_d2:endpoint_d2,3)),hold off,
% legend ({'Exp d1','Exp d2'}), grid on,
% grid on,ylabel('MEC value'),xlabel(char(fig2_label_xaxis_1));
% ax = gca;
% ax.YAxis.Exponent = 0;

% Calculate the concentration of the product from absorbance data
path_length_1 = 0.01; % [cm]
path_length_2 = path_length_1; % in case two experiments were done with different UV-Vis cells
calc_1(:,4) = (calc_1(:,1)./(calc_1(:,3).*path_length_1));
calc_2(:,4) = (calc_2(:,1)./(calc_2(:,3).*path_length_2));

% Calculate the maximum reaction yield
initial_concentration = 0.2; % concentration of the limiting reagent [M]
max_concentration =
initial_concentration*(flow_1/(flow_1+flow_2))*((flow_1+flow_2)/(flow_1+flow_2+flow_3and4));

% Calculate the in situ reaction yield
calc_1(:,5) = calc_1(:,4)/max_concentration*100;
calc_2(:,5) = calc_2(:,4)/max_concentration*100;

% Control plot of calculated concentrations and yields
% disp(' ')
% disp('Generating Figure 3: Calculated concentration and yields!')
% figure(3),subplot(3,1,[1,2]),
% plot(calc_1(:,4),'-.'),hold on,plot(calc_2(:,4),'-.'),hold off,
% xlabel('Time [s]'),ylabel('Product concentration [M]'),grid on,axis tight,
% yyaxis right,plot(calc_1(:,5),'-','color','#0072BD'),hold on,plot(calc_2(:,5),'-','color','#D95319'),hold
off,
% ylabel('Reaction yield [%]'),ylim([-10 110]),set(gca,'ycolor','k'),
% legend({'Exp d1: Concentration','Exp d2: Concentration','Exp d1: Yield','Exp d2: Yield'}),
% subplot(3,1,3),
% plot(calc_1(:,1)),hold on,plot(calc_2(:,1)),hold off,
% xlabel('Time [s]'),ylabel('Absorbance [a.u.]'),grid on, axis tight,
% f3 = figure(3);
% u3 = f3.Position;
% f3.Position = [500 350 900 500];

% Plot reaction yield vs solvent composition data
disp(' ')
disp('Generating Figure 4: Reaction yield vs solvents composition used!')
disp(' ')
fig4_label_xaxis_1 = ['Percentage of ',convertStringsToChars(solvent_2_name),' in
',convertStringsToChars(solvent_1_name),'/',convertStringsToChars(solvent_2_name),' mixture [%]'];
figure(4),
plot(calc_1(startpoint_d1:endpoint_d1,2),calc_1(startpoint_d1:endpoint_d1,5)),hold on,
plot(calc_2(startpoint_d2:endpoint_d2,2),calc_2(startpoint_d2:endpoint_d2,5)),hold off,
%plot(calc_1(startpoint_d1:endpoint_d1,2),smoothdata(calc_1(startpoint_d1:endpoint_d1,5),'lowess')),hold
on,
%plot(calc_2(startpoint_d2:endpoint_d2,2),smoothdata(calc_2(startpoint_d2:endpoint_d2,5),'lowess')),hold
off,
xlabel(fig4_label_xaxis_1),ylabel('Reaction yield [%]'),grid on,xlim([-0 100])
figure_4_y_max_lim = input('Determine maximum yield boudnary for figure 4 (reaction yield vs solvent
composition)!');
ylim([0 figure_4_y_max_lim]),
fig4_legend_entry_1 = string(['Experiment 1: ',convertStringsToChars(solvent_1_name),' and
',convertStringsToChars(solvent_2_name),'\newlineFrom ',num2str(round(gradient_d1_solv2_min*100,2)),'% to
',num2str(round(gradient_d1_solv2_max*100,2)),'% of ',convertStringsToChars(solvent_2_name)]);
fig4_legend_entry_2 = string(['Experiment 2: ',convertStringsToChars(solvent_2_name),' and
',convertStringsToChars(solvent_1_name),'\newlineFrom ',num2str(round(gradient_d2_solv2_min*100,2)),'% to
',num2str(round(gradient_d2_solv2_max*100,2)),'% of ',convertStringsToChars(solvent_2_name)]);
legend({fig4_legend_entry_1,fig4_legend_entry_2},'location','best');
```

```
fig4_title = string(['S_NAr reaction yield performed in ',solvent_1,' and ',solvent_2,' solvents
mixture']);
title(fig4_title);
f4 = figure(4);
u4 = f4.Position;
f4.Position = [1000 400 750 450];

% Save calculated data if the results are satisfactory
decision_save = input('Save all calculated data ? 1 = yes, anything else = no!','s');
disp(' ')
if decision_save == "1"

    % Create figure with zoomed data from fig(1)
    figure(6),
    subplot(2,1,1),yyaxis left,plot(calc_1(:,1)),axis tight,grid on,
    ylabel({fig1_label_yaxis_1,fig1_label_yaxis_2},'color','#0072BD'),xlabel('Time [s]'),ylim([0 inf]);
    subplot(2,1,2),yyaxis left,plot(calc_2(:,1)),axis tight,grid on,
    ylabel({fig1_label_yaxis_1,fig1_label_yaxis_2},'color','#0072BD'),xlabel('Time [s]'),ylim([0 inf]);
    subplot(2,1,1),yyaxis right,plot(calc_1(:,6)),ylabel(fig1_label_yyaxis_1),ylim([-10 110]);
    xline(startpoint_d1,'--
',{'Gradient','Startpoint'},'LabelHorizontalAlignment','left','LabelVerticalAlignment','middle');
    xline(endpoint_d1,'--',{'Gradient','Endpoint'},'LabelVerticalAlignment','middle');
    fig6_title_1 = "S_NAr reaction absorbances and solvents composition in gradient region";
    fig6_title_2 = string(['performed in ',solvent_1,' and ',solvent_2,' solvents mixture']);
    title({fig6_title_1,fig6_title_2}),xlim([startpoint_d1-250 endpoint_d1+250]);
    subplot(2,1,2),yyaxis right,plot(calc_2(:,6)),ylabel(fig1_label_yyaxis_2),ylim([-10
110]),xlim([startpoint_d2-250 endpoint_d2+250]);
    xline(startpoint_d2,'--
',{'Gradient','Startpoint'},'LabelHorizontalAlignment','left','LabelVerticalAlignment','middle');
    xline(endpoint_d2,'--',{'Gradient','Endpoint'},'LabelVerticalAlignment','middle');
    f6 = figure(6);
    u6 = f6.Position;
    f6.Position = [300 450 750 500];

    calculation_information = input('Provide information on date and experiment number!','s');
    disp(' ')
    results_xlsx = {'Analysis information','',string(calculation_information),'','','';
        'Solvent 1 used:',string(solvent_1_name),' ','Solvent 2 used:',string(solvent_2_name),'';
        'Gradient startpoint of exp d1:',startpoint_d1,'','Gradient endpoint of exp d1:',endpoint_d1,'';
        'Gradient startpoint of exp d2:',startpoint_d2,'','Gradient endpoint of exp d2:',endpoint_d2,'';
        'Reagents concentration:','1-Fluoro-4-nitrobenzene:',initial_concentration,'[M]','','';
        '','Piperidine:',(2.5*initial_concentration),'[M]','','';
        'Flow rates:',flow_1,flow_2,flow_3and4,'(1st, 2nd, and 3rd+4th streams respectively','[mL/min]';
        'Path length:','Experiment d1:',path_length_1,'Experiment d2',path_length_2,'[cm]';
        'Results of experiment d1:','','','','','';
        '','','','','Reaction yield [%]:',calc_1(startpoint_d1:endpoint_d1,2);
        '','','','',fig4_label_xaxis_1,calc_1(startpoint_d1:endpoint_d1,5);
        'Results of experiment d2:','','','','','';
        '','','','','Reaction yield [%]:',calc_2(startpoint_d2:endpoint_d2,2);
        '','','','',fig4_label_xaxis_1,calc_2(startpoint_d2:endpoint_d2,5);};

    filename = input('Provide filename for calculation results!','s');
    disp(' ')

    filename1 = string(filename + " 01 Abs and solvents composition");
    filename2 = string(filename + " 02 MEC values used");
    filename3 = string(filename + " 03 Calculated concentration and yield");
    filename4 = string(filename + " 04 Reaction yield vs solvents composition");
    filename5 = string(filename + " 05 Caulcation information and results");
    filename6 = string(filename + " 06 Gradient region");

    saveas(figure(1),filename1,'fig');
    exportgraphics(figure(1),filename1+'.tiff','Resolution',1200);
    print(figure(1),filename1,'-dsvg','-r1200');

    % saveas(figure(2),filename2,'fig');
    % exportgraphics(figure(2),filename2+'.tiff','Resolution',1200);
    % print(figure(2),filename2,'-dsvg','-r1200');

    % saveas(figure(3),filename3,'fig');
    % exportgraphics(figure(3),filename3+'.tiff','Resolution',1200);
    % print(figure(3),filename3,'-dsvg','-r1200');

    saveas(figure(4),filename4,'fig');
    exportgraphics(figure(4),filename4+'.tiff','Resolution',1200);
    print(figure(4),filename4,'-dsvg','-r1200');

    saveas(figure(6),filename6,'fig');
    exportgraphics(figure(6),filename6+'.tiff','Resolution',1200);
    print(figure(6),filename6,'-dsvg','-r1200');

    writecell(results_xlsx,filename5+'.xlsx');

    % Save MATLAB workspace
    filename7 = string(filename + " 07 MatlabWorkspace");
```

```
    save(filename7)
end

disp('######################')
disp('## Script finished! ##')
disp('######################')
```

## 3. 4. Synthesis and characterisation data of 1-(4-nitrophenyl)piperidine




*Scheme S 1. $S_NAr$ reaction between 1-fluoro-4-nitrobenzene and piperidine.*

1-Fluoro-4-nitrobenzene (0.75 g, 0.56 ml, 5.32 mmol, 1.00 eq.) and piperidine (1.13 g, 1.31 ml, 13.29 mol, 2.5 eq.) were added to DMF (22.5 ml, 30.0 vol) and the reaction was heated to 60 °C for 1h. Reaction mixture was then poured into water (200.0 ml), precipitate was collected, and remaining solution was extracted with DCM (5x50.0 ml). Organic layers were then combined, concentrated, poured into water, and the precipitate was filtered off. Combined solids were preadsorbed onto silica and purified by flash chromatography ($SiO_2$, 20% *n*-hexane in chloroform). Organic layers were combined, dried over $Na_2SO_4$, and solvent was distilled off. 1-(4-Nitrophenyl)piperidine was obtained as a yellow solid (1.02 g, 79% yield). NMR data was in agreement with literature.[4]

**Mp.** 105.2 – 105.8 °C, Lit. 104.0 – 105.0 °C.[4] **$^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) =** 8.10 (m, 2H), 6.80 (m, 2H), 3.47 – 3.40 (m, 4H), 1.73 – 1.65 (m, 6H). **$^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm) =** 155.0 (C), 137.7 (C), 126.3 (CH), 112.6 (CH), 48.6 ($CH_2$), 25.4 ($CH_2$), 24.4 ($CH_2$). **UV-Vis $\lambda_{max}$[nm] (ε[$M^{-1}cm^{-1}$]) MeCN:** 397 (20009); **Acetone:** 393 (21537); ***tert*-Butanol:** 388 (19237); **$CHCl_3$:** 395 (21737); **1,2-DCE:** 396 (21186); **DCM:** 397 (22127); **DMA:** 4001 (20547); **DMF:** 402 (21514 ± 72); **DMSO:** 409 (21261); **1,4-Dioxane:** 383 (20091); **EtOH:** 389 (18633); **AcOEt:** 383 (21176); **MeOH:** 393 (19640); **MTBE:** 372 (21316); **NMP:** 404 (20858); **IPA:** 388 (18930); **Propylene Carbonate:** 404 (19087); **THF:** 388 (22048); **Toluene:** 380 (19239); **triglyme:** 392 (20247); **5% $H_2O$ in DMF:** 404 (21954); **10% $H_2O$ in DMF:** 406 (21464) ; **15% $H_2O$ in DMF:** 408 (22138) ; **20% $H_2O$ in DMF:** 410 (22142) ; **25% $H_2O$ in DMF:** 411 (20886); **30% $H_2O$ in DMF:** 413 (21257); **35% $H_2O$ in DMF:** 415 (21573); **40% $H_2O$ in DMF:** 416 (20036); **50% $H_2O$ in DMF:** 418 (n/a). **FT-ATR-IR ν ($cm^{-1}$) =** 2943, 2839, 1595, 1579, 1506, 1473, 1451, 1304, 1244, 1224, 1199, 1133, 1104, 1069, 1020, 990, 950, 913, 858, 816, 753, 731, 689, 644, 629, 538. **LRMS (ESI+) m/z =** 207.2 (M + $H^+$).

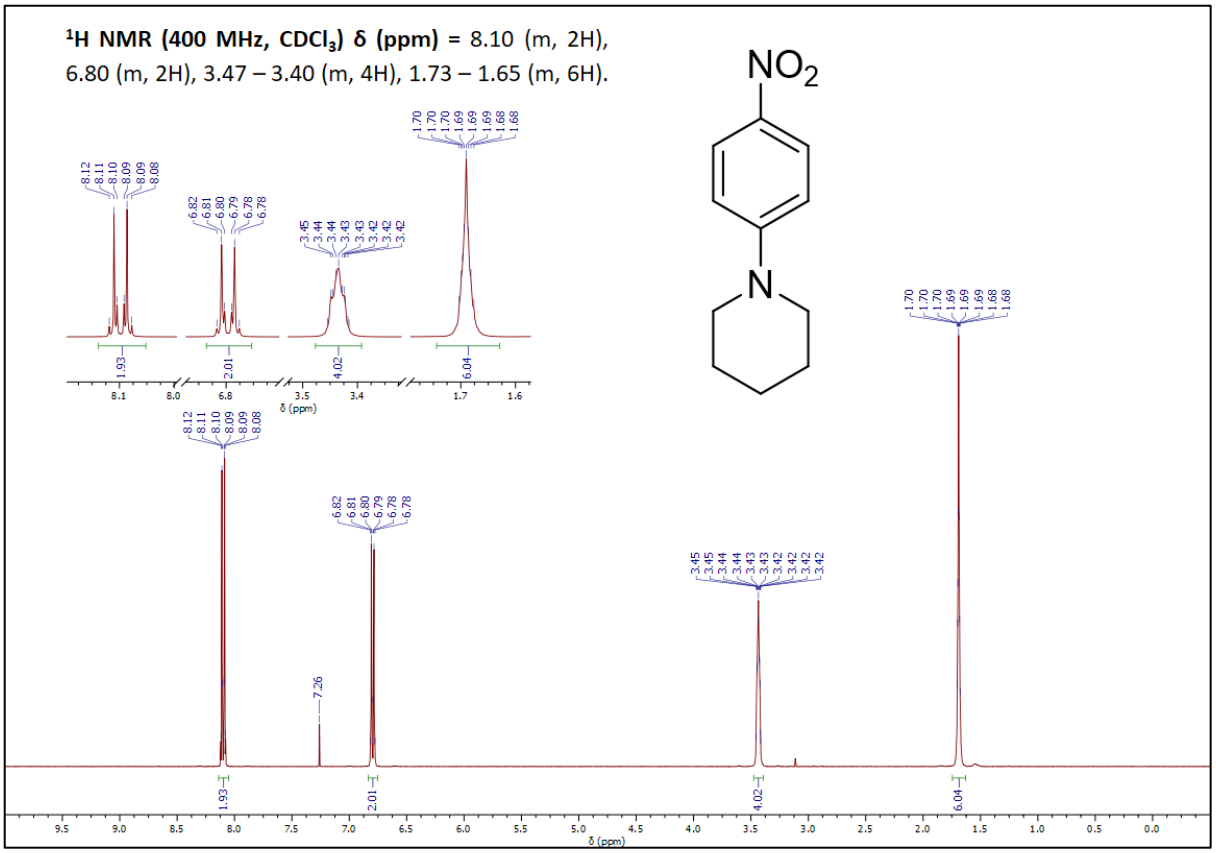



*Figure S 31. $^{1}H$ NMR spectrum of 1-(4-nitrophenyl)piperidine in $CDCl_3$.*

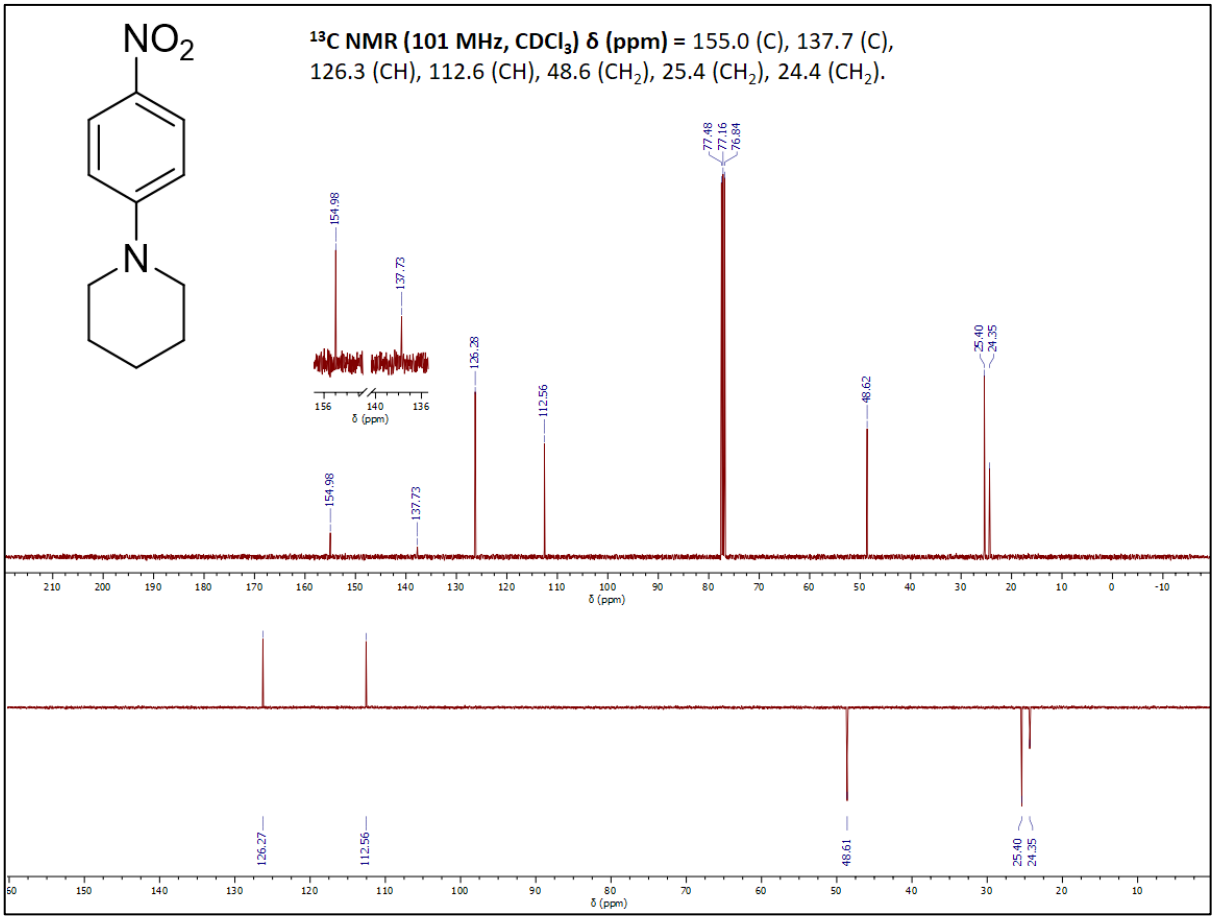



*Figure S 32. $^{13}C$ and DEPT-135 NMR spectra of 1-(4-nitrophenyl)piperidine in $CDCl_3$.*

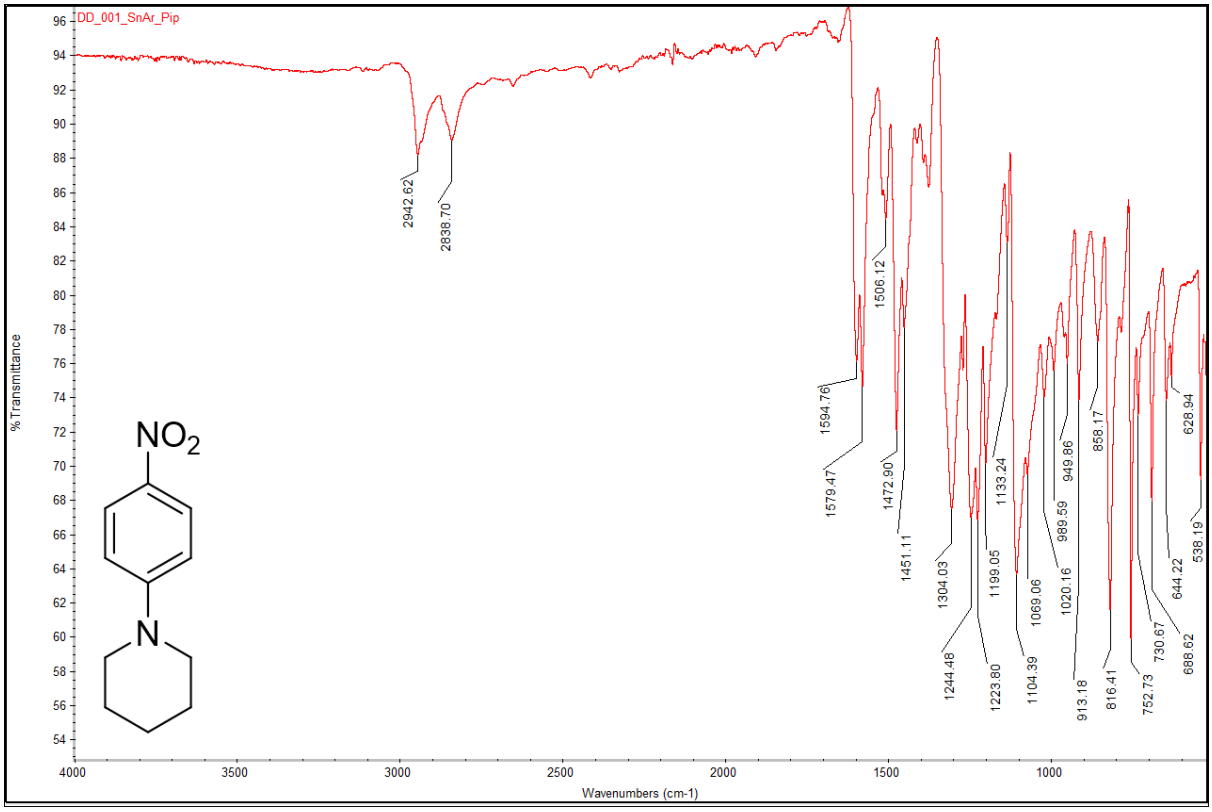



*Figure S 33. FT-ATR-IR spectrum of 1-(4-nitrophenyl)piperidine.*

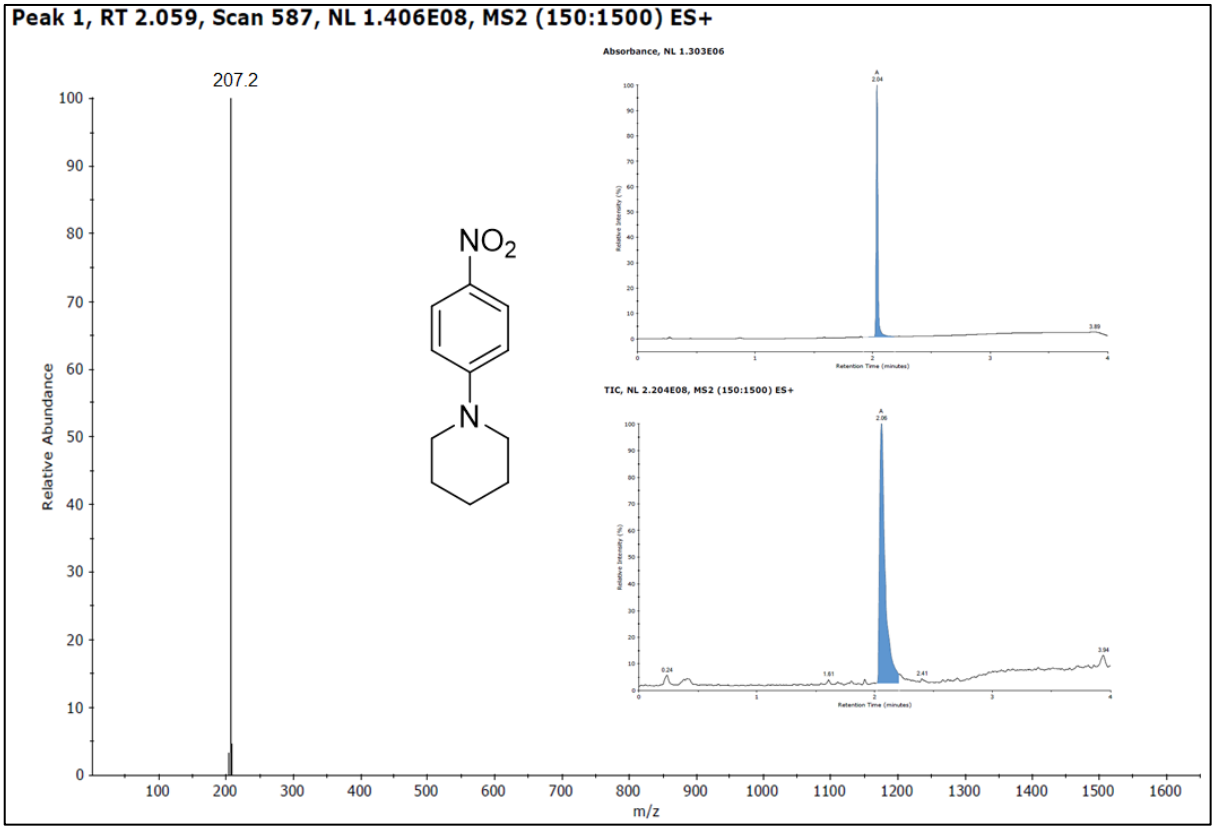



*Figure S 34. Positive electrospray ionisation mass spectrum of 1-(4-nitrophenyl)piperidine.*

## 3. 5. Validation of Solvent Studies in $S_NAr$ reaction

Validation of results obtained from the flow studies of solvent effects on $S_NAr$ reaction was performed in a series of batch experiments with various solvents mixtures.

### 3. 5. 1. Calibration of GC-FID for monitoring of batch SNAr reactions between 1-fluoro-4-nitrobenzene and piperidine

Samples containing 1-fluoro-4-nitrobenzene **1**, 1-(4-nitrophenyl)piperidine **3**, and veratrole (IS) were prepared according to the Table S 4. and were then measured using GC-FID. Obtained results were used for plotting of the calibration curve (Figure S 35. GC-FID calibration curves for 1-fluoro-4-nitrobenzene (black) and 1-(4-nitropehnyl)piperidine (red).).

*Table S 4. Molar and area ratios of samples used for calibration of GC-FID.*

| Sample | Molar ratio of 1:IS:3 | Area **1** | Area IS | Area **3** | Area ratio **1**:IS | Area ratio **3**:IS |
|---|---|---|---|---|---|---|
| S1 | 2.00:1.00:2.00 | 150.0582 | 82.6634 | 302.6851 | 1.8153 | 3.6617 |
| S2 | 1.00:1.00:1.00 | 129.8634 | 139.4952 | 291.6948 | 0.9310 | 2.0911 |
| S3 | 0.75:1.00:0.75 | 116.4323 | 166.9059 | 255.5241 | 0.6976 | 1.5309 |
| S4 | 0.50:1.00:0.50 | 127.4809 | 277.3445 | 274.4141 | 0.4596 | 0.9894 |
| S5 | 0.10:1.00:0.10 | 25.8286 | 408.0157 | 57.1832 | 0.0633 | 0.1401 |
| S6 | 0.05:1.00:0.05 | 32.2461 | 858.1626 | 66.0772 | 0.0376 | 0.0770 |
| S7 | 0.01:1.00:0.01 | 15.0479 | 2010.059 | 25.2933 | 0.0075 | 0.0126 |

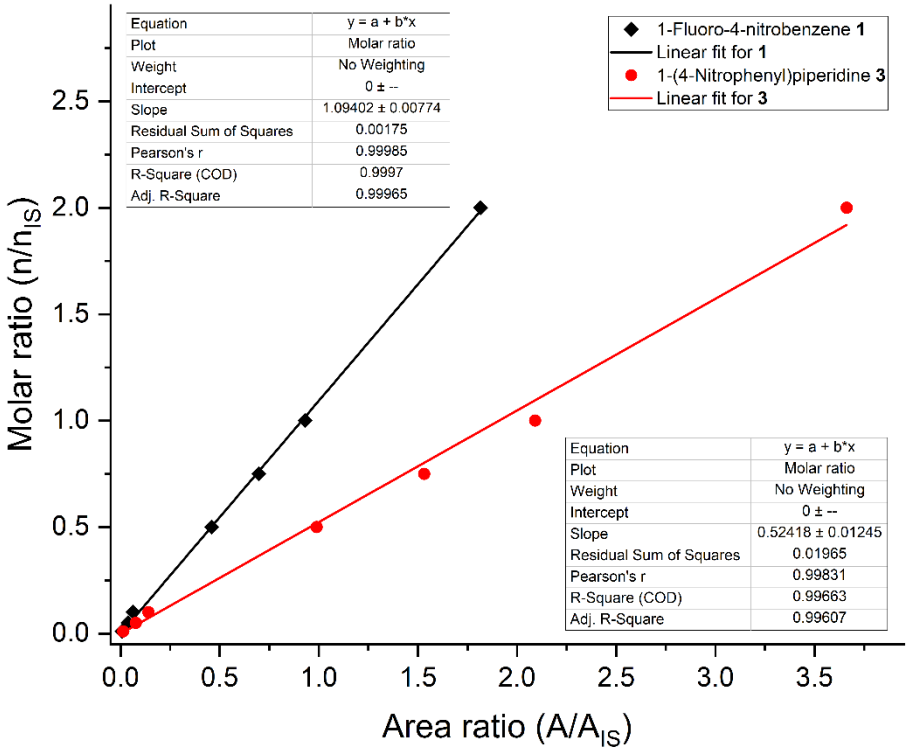



*Figure S 35. GC-FID calibration curves for 1-fluoro-4-nitrobenzene (black) and 1-(4-nitropehnyl)piperidine (red).*

### 3. 5. 2. Experimental procedure for batch validation of solvent effects in $S_NAr$ reaction

Batch reactions were performed using Gilson GX-271 React Array automated batch reactor and following procedure:

To the reaction vessels placed in a heating block, Solvent A and Solvent B in desired ratio were added (total of 20.0 mL, 283.3 vol.), stirring (1000 rpm) was turned on and reaction temperature was set to

25 °C. After temperature stabilisation, 1-fluoro-4-nitrobenzene (53.0 µL, 70.6 mg, 0.50 mmol, 1.0 eq., 25.0 mM solution), piperidine (123.5 µL, 106.4 mg, 1.25 mmol, 2.5 eq., 62.5 mM solution), and veratrole (IS, 100.0 µL, 108.0 mg, 0.78 mmol, 1.56 eq., 39.0 mM solution) were added and reaction was stirred for 2 hours. Sample of reaction mixture (0.5 mL) was acquired, diluted with acetone (1.0 mL), and measured using calibrated GC-FID.

### 3. 5. 3. Results of batch validation of solvent effects in $S_NAr$ reaction

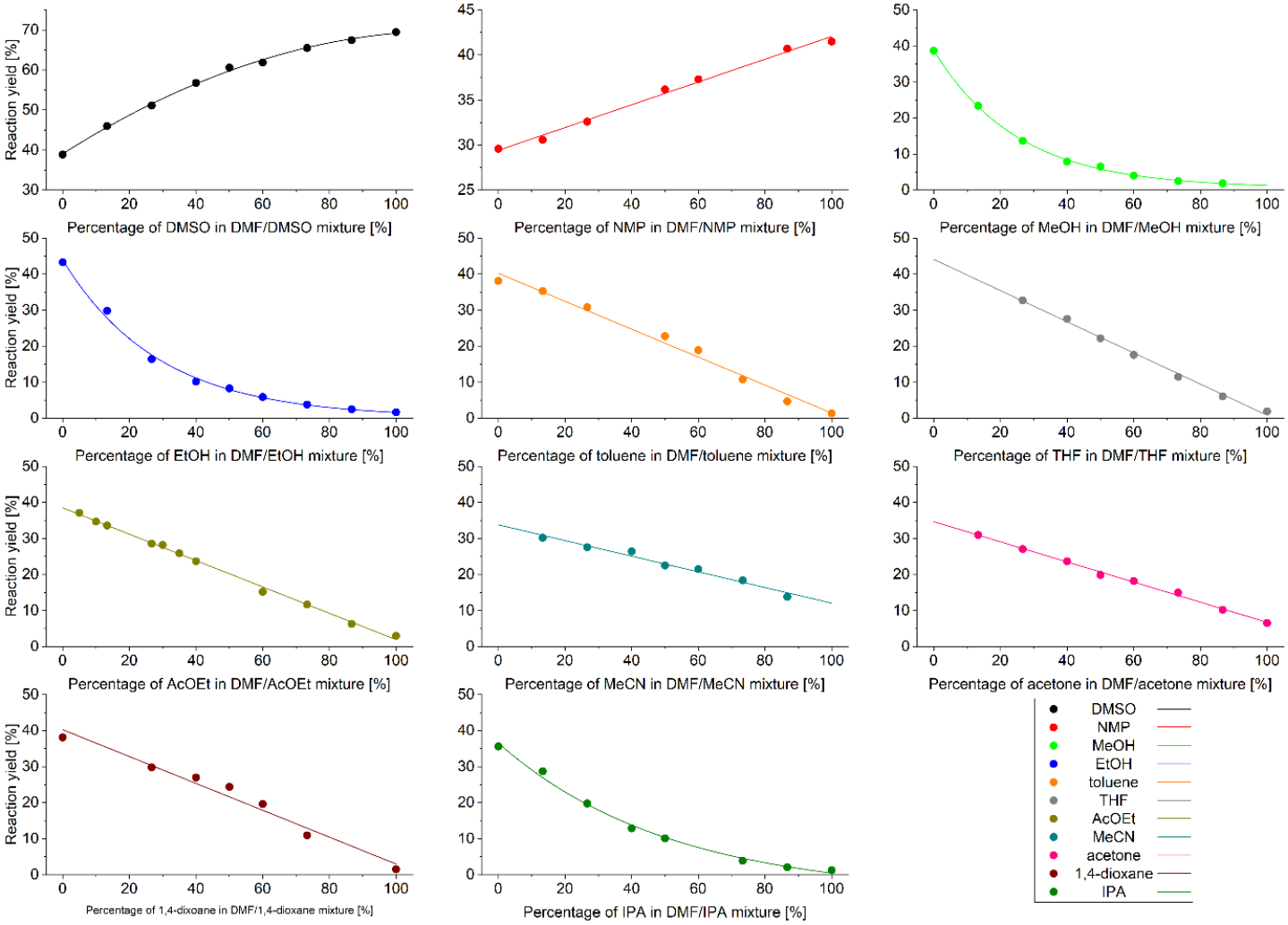



*Figure S 36. Reaction yields of $S_NAr$ reaction between **1** and **2** in various solvents mixtures performed in a series of automated batch experiments.*

# 4. Solvent effects studies in imine formation reaction between 4-nitrobenzaldehyde and *N,N*-dimethylphenylene-1,4-diamine

## 4. 1. Determination of molar extinction coefficient of *N,N*-dimethyl-4-((4-nitrobenzylidene)amino)aniline

### 4. 1. 1. Determination of molar extinction coefficient in 1,2-DCE

A stock solution of (E)-*N,N*-dimethyl-4-((4-nitrobenzylidene)amino)aniline (18.70 mg, 0.0695 mmol) in 1,2-dichloroethane (20.0 mL) was prepared and was used for further samples preparation by series of dilution, as described in the table below (Table S 5. Table of measured samples of imine in 1,2-DCE and their respective absorbance.). Prior to each measurement, pure 1,2-dichloroethane was injected into the flow UV-Vis cell for background correction. Prepared samples were then injected into the UV-

Vis cell and absorbance measurements were performed 3 times for each sample. Averaged absorbances were then used for determination of molar extinction coefficient.

*Table S 5. Table of measured samples of imine in 1,2-DCE and their respective absorbance.*

| Sample | Dilution factor wrt to stock solution | Concentration [M] | Concentration times path length [M · cm] | Absorbance [a.u.] | | Average Absorbance [a.u.] | |
|---|---|---|---|---|---|---|---|
| | | | | 446 nm | 281 nm | 446 nm | 281 nm |
| 1 | Stock solution | $3.47 \cdot 10^{-3}$ | $3.47 \cdot 10^{-5}$ | 0.602 | 0.654 | 0.598 | 0.655 |
| | | | | 0.589 | 0.654 | | |
| | | | | 0.602 | 0.656 | | |
| 2 | 2x | $1.74 \cdot 10^{-3}$ | $1.74 \cdot 10^{-5}$ | 0.307 | 0.338 | 0.306 | 0.336 |
| | | | | 0.303 | 0.334 | | |
| | | | | 0.307 | 0.336 | | |
| 3 | 4x | $8.69 \cdot 10^{-4}$ | $8.69 \cdot 10^{-6}$ | 0.155 | 0.172 | 0.155 | 0.172 |
| | | | | 0.155 | 0.172 | | |
| | | | | 0.154 | 0.171 | | |
| 4 | 8x | $4.34 \cdot 10^{-4}$ | $4.34 \cdot 10^{-6}$ | 0.079 | 0.089 | 0.079 | 0.088 |
| | | | | 0.079 | 0.088 | | |
| | | | | 0.078 | 0.088 | | |
| 5 | 16x | $2.17 \cdot 10^{-4}$ | $2.17 \cdot 10^{-6}$ | 0.040 | 0.046 | 0.040 | 0.046 |
| | | | | 0.039 | 0.046 | | |
| | | | | 0.040 | 0.046 | | |
| 6 | 5x | $6.95 \cdot 10^{-4}$ | $6.95 \cdot 10^{-6}$ | 0.124 | 0.138 | 0.124 | 0.138 |
| | | | | 0.125 | 0.138 | | |
| | | | | 0.123 | 0.137 | | |
| 7 | 10x | $3.47 \cdot 10^{-4}$ | $3.47 \cdot 10^{-6}$ | 0.062 | 0.070 | 0.063 | 0.071 |
| | | | | 0.063 | 0.071 | | |
| | | | | 0.063 | 0.071 | | |
| 8 | 25x | $1.39 \cdot 10^{-4}$ | $1.39 \cdot 10^{-6}$ | 0.026 | 0.030 | 0.026 | 0.030 |
| | | | | 0.025 | 0.030 | | |
| | | | | 0.026 | 0.031 | | |
| 9 | 3x | $1.16 \cdot 10^{-3}$ | $1.16 \cdot 10^{-5}$ | 0.208 | 0.231 | 0.208 | 0.230 |
| | | | | 0.207 | 0.230 | | |
| | | | | 0.208 | 0.229 | | |
| 10 | 1.5x | $2.32 \cdot 10^{-3}$ | $2.32 \cdot 10^{-5}$ | 0.409 | 0.449 | 0.410 | 0.450 |
| | | | | 0.410 | 0.450 | | |
| | | | | 0.410 | 0.450 | | |

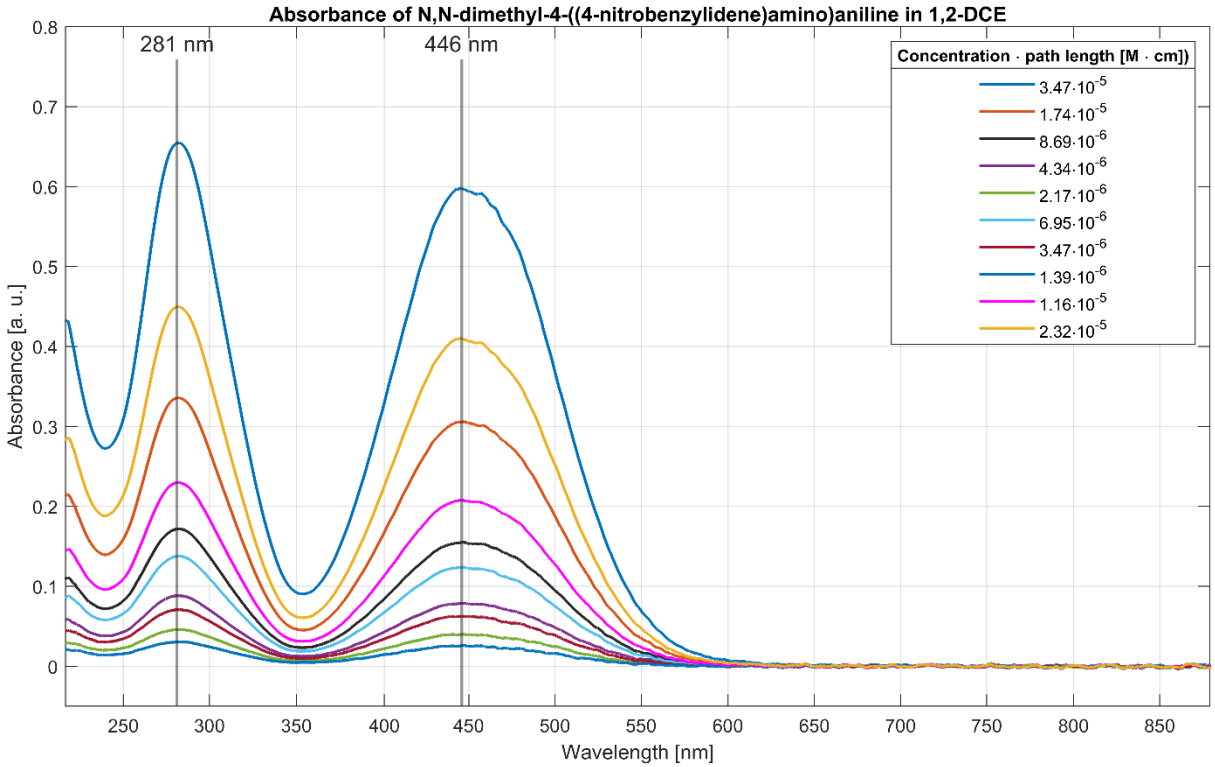



*Figure S 37. Absorbance of N,N-dimethyl-4-((4-nitrobenzylidene)amino)aniline in 1,2-DCE.*

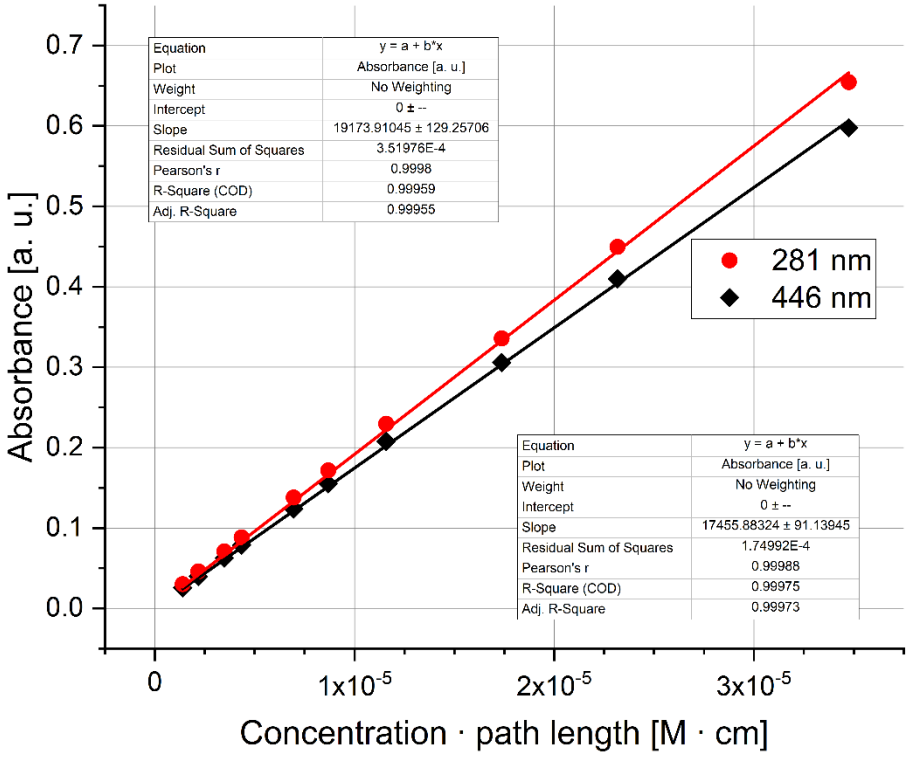



*Figure S 38. Absorbance at 281 nm (red) and 446 nm (black) vs (concentration · path length) graph of N,N-dimethyl-4-((4-nitrobenzylidene)amino)aniline in 1,2-DCE.*

Determined molar extinction coefficients of *N,N*-dimethyl-4-((4-nitrobenzylidene)amino)aniline in 1,2-DCE at 281 nm and 446 nm are:

$$\varepsilon_{1,2-DCE}^{281\,nm} = 19174 \pm 129\ [M^{-1}cm^{-1}]$$

$$\varepsilon_{1,2-DCE}^{446\,nm} = 17456 \pm 91\ [M^{-1}cm^{-1}]$$

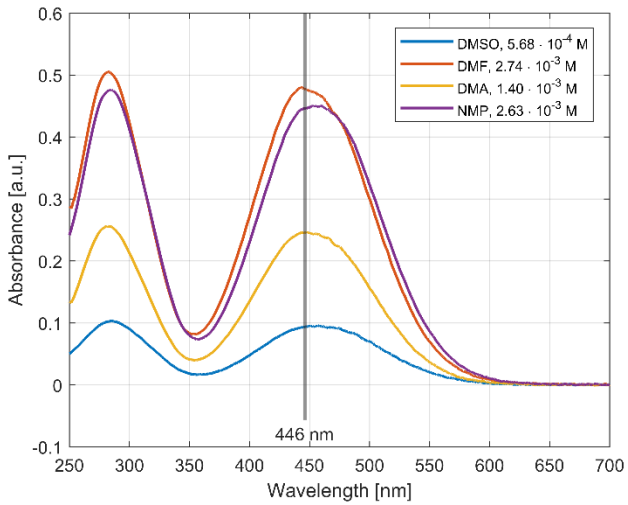
### 4. 1. 2. Determination of molar extinction coefficients in solvents used in various solvents

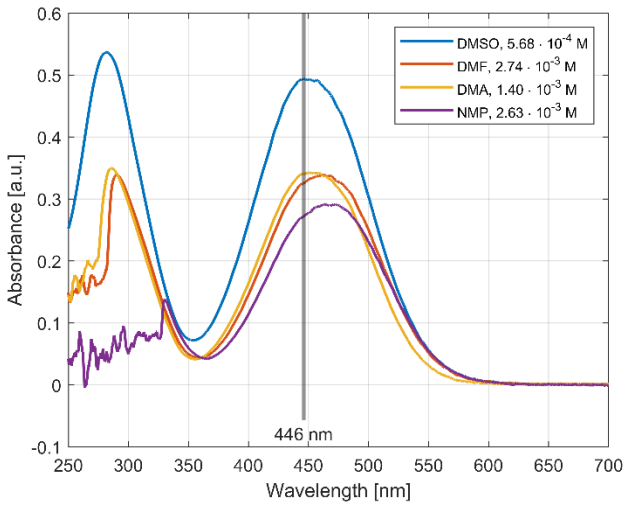
Samples of *N,N*-dimethyl-4-((4-nitrobenzylidene)amino)aniline in various solvents were prepared accordingly to the table below (Table S 6. ). Prepared samples were then injected into the flow UV-Vis cell and absorbance measurements were performed. Prior to each measurement, pure solvent was injected into the flow UV-Vis cell for background correction. Obtained absorbance values were then used for determination of molar extinction coefficient of *N,N*-dimethyl-4-((4-nitrobenzylidene)amino)aniline in different solvents.

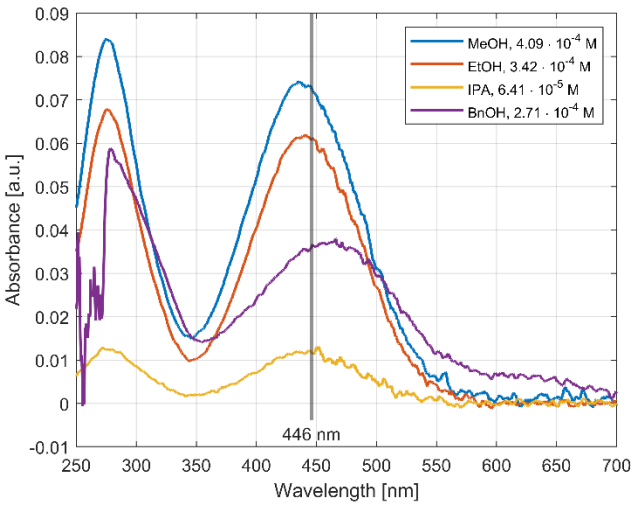
*Table S 6. Combined results of MEC determination of (E)-N,N-dimethyl-4-((4-nitrobenzylidene)amino)aniline in various solvents.*

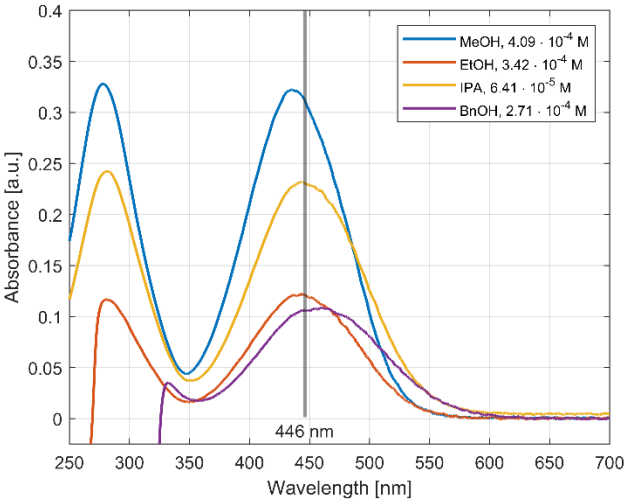
| Sample | Solvent | Solvent abbreviation | Sample volume [mL] | *N,N*-dimethyl -4-((4-nitrobenzylidene) amino)aniline concentration [M] | Maxima of absorption [nm] | Absorbance at maxima of absorption [a.u.] | Molar extinction coefficient at maxima of absorption [$M^{-1}cm^{-1}$] | Absorbance at 446 nm [a.u.] | Molar extinction coefficient at 446 nm [$M^{-1}cm^{-1}$] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | *N,N*-Dimethylformamide | DMF | 20.0 | $2.74 \cdot 10^{-3}$ | 282, 443 | 0.505, 0.480 | 18449, 17539 | 0.478 | 17448 |
| 2 | Dimethylsulfoxide | DMSO | 100.0 | $5.68 \cdot 10^{-4}$ | 286, 455 | 0.103, 0.0946 | 18123, 16665 | 0.0937 | 16497 |
| 3 | *N*-Methylpyrrolidinone | NMP | 20.0 | $2.65 \cdot 10^{-3}$ | 284, 453 | 0.476, 0.450 | 17991, 16990 | 0.447 | 16876 |
| 4 | Acetonitrile | MeCN | 20.0 | $1.42 \cdot 10^{-3}$ | 279, 438 | 0.258, 0.241 | 18217, 17051 | 0.236 | 16670 |
| 5 | Propylene Carbonate | PC | 25.0 | $1.25 \cdot 10^{-3}$ | 282, 450 | 0.216, 0.208 | 17215, 16606 | 0.207 | 16491 |
| 6 | Ethyl acetate | AcOEt | 50.0 | $1.52 \cdot 10^{-3}$ | 277, 436 | 0.330, 0.314 | 21738, 20742 | 0.306 | 20153 |
| 7 | 1,4-Dioxane | Diox | 20.0 | $1.56 \cdot 10^{-3}$ | 278, 435 | 0.328, 0.321 | 20991, 20592 | 0.312 | 19964 |
| 8 | Methanol | MeOH | 50.0 | $4.09 \cdot 10^{-4}$ | 275, 435 | 0.0843, 0.0779 | 20614, 19051 | 0.0728 | 17816 |
| 9 | Ethanol | EtOH | 50.0 | $3.42 \cdot 10^{-4}$ | 275, 438 | 0.0673, 0.0613 | 19697, 17940 | 0.0603 | 17636 |
| 10 | Benzonitrile | PhCN | 20.0 | $1.27 \cdot 10^{-3}$ | 460 | 0.218 | 17180 | 0.214 | 16847 |
| 11 | *orto*-Dichlorobenzene | *o*DCB | 20.0 | $2.01 \cdot 10^{-3}$ | 461 | 0.338 | 16856 | 0.325 | 16180 |
| 12 | Chlorobenzene | PhCl | 20.0 | $2.06 \cdot 10^{-3}$ | 456 | 0.343 | 16611 | 0.340 | 16499 |
| 13 | β-Pinene | β-Pin | 100.0 | $1.97 \cdot 10^{-4}$ | 440 | 0.0349 | 17738 | 0.0340 | 17247 |
| 14 | *iso*-Propanol | IPA | 500.0 | $6.41 \cdot 10^{-5}$ | 277, 448 | 0.0122, 0.0119 | 19043, 18498 | 0.0118 | 18363 |
| 15 | 1-Chloronaphthalene | ClNaphth | 25.0 | $1.81 \cdot 10^{-3}$ | 466 | 0.291 | 16033 | 0.272 | 14987 |
| 16 | 5% Water in DMSO | 5% $H_2O$ in DMSO | 50.0 | $7.10 \cdot 10^{-4}$ | 460 | 0.108 | 15161 | 0.106 | 14916 |
| 17 | Cyclohexanone | cHexOne | 20.0 | $2.06 \cdot 10^{-3}$ | 445 | 0.349 | 16954 | 0.349 | 16927 |
| 18 | Ethyl formate | EtForm | 25.0 | $1.60 \cdot 10^{-3}$ | 277, 435 | 0.299, 0.292 | 18721, 18260 | 0.284 | 17745 |
| 19 | Tetrahydrofuran | THF | 25.0 | $6.94 \cdot 10^{-4}$ | 443 | 0.122 | 17504 | 0.120 | 17331 |
| 20 | Triethylene glycol dimethyl ether | triglyme | 25.0 | $1.32 \cdot 10^{-3}$ | 281, 443 | 0.240, 0.230 | 18216, 17454 | 0.229 | 17348 |
| 21 | *N,N*-Dimethylacetamide | DMA | 20.0 | $1.40 \cdot 10^{-3}$ | 283, 445 | 0.256, 0.246 | 18219, 17509 | 0.245 | 17463 |
| 22 | Benzyl alcohol | BnOH | 100.0 | $2.71 \cdot 10^{-4}$ | 466 | 0.0380 | 14005 | 0.0362 | 13332 |

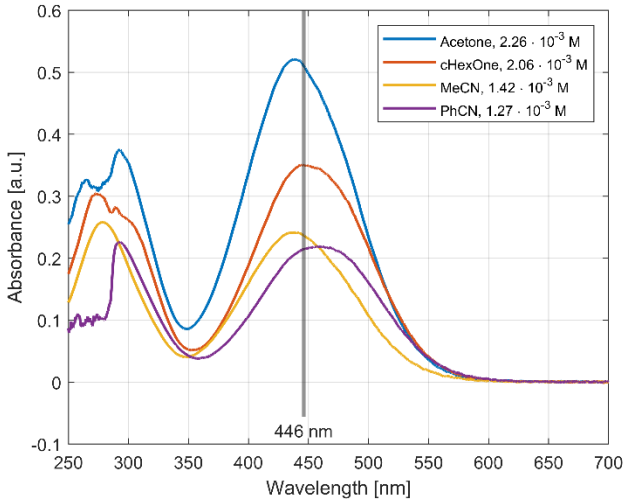
**Absorbance of (E)-N,N-dimethyl-4-((4-nitrobenzylidene)amino)aniline in various organic solvents**



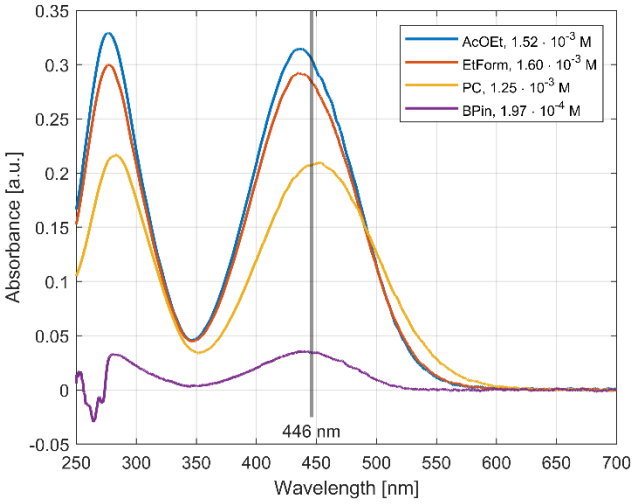




*Figure S 39.*

## 4. 2. Effects of addition of acid on imine absorbance spectrum

The dependency of the imine absorbance on the presence of TFA is another variable that can alter the results obtained in the solvent studies, as possible interactions between imine and trifluoroacetic acid could lead to formation of protonated species, which can result in overall change of imine absorbance during the experiments. To investigate such effects, various equivalents of imine and TFA were injected into the flow system used for solvents studies with in-line monitoring of the UV-Vis spectrum (XXX).

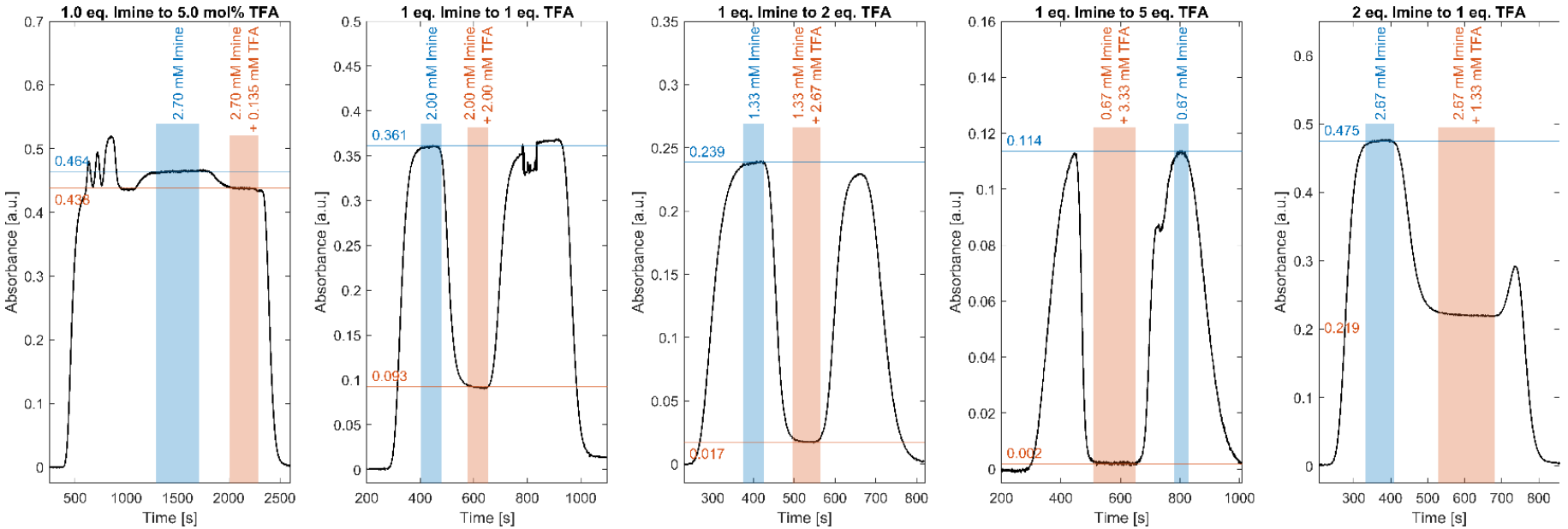



*Figure S 40. Investigation into imine **6** absorbance in presence of trifluoroacetic acid. Blue regions correspond to the measurement of pure imine **6**, and orange regions correspond to the measurement of imine **6** in presence of TFA.*

Obtained UV-Vis spectra were then analysed, average absorbances of the datapoints associated with pure imine and imine with addition of TFA were collected and percentage absorbance ratio was calculated as the ratio of absorbance of imine with addition of TFA to absorbance of pure imine. Obtained values are presented in table below.

*Table S 7. Experiments stoichiometry and measurements absorbances obtained from investigations of effects of addition of acid on imine **6** absorption.*

| Concentration | | Stoichiometry | | Absorbance of free imine [a.u.] | Absorbance of imine and TFA [a.u.] | Percentage absorbance ratio [%] |
|---|---|---|---|---|---|---|
| Imine [mM] | TFA [mM] | Imine [eq.] | TFA [eq.] | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2.70 | 0.14 | 1.00 | 0.05 | 0.464 | 0.438 | 94.4 |
| 2.67 | 1.33 | 1.00 | 0.50 | 0.475 | 0.219 | 46.1 |
| 2.00 | 2.00 | 1.00 | 1.00 | 0.361 | 0.093 | 25.8 |
| 1.33 | 2.67 | 1.00 | 2.00 | 0.239 | 0.017 | 7.1 |
| 0.67 | 3.33 | 1.00 | 5.00 | 0.114 | 0.002 | 1.8 |

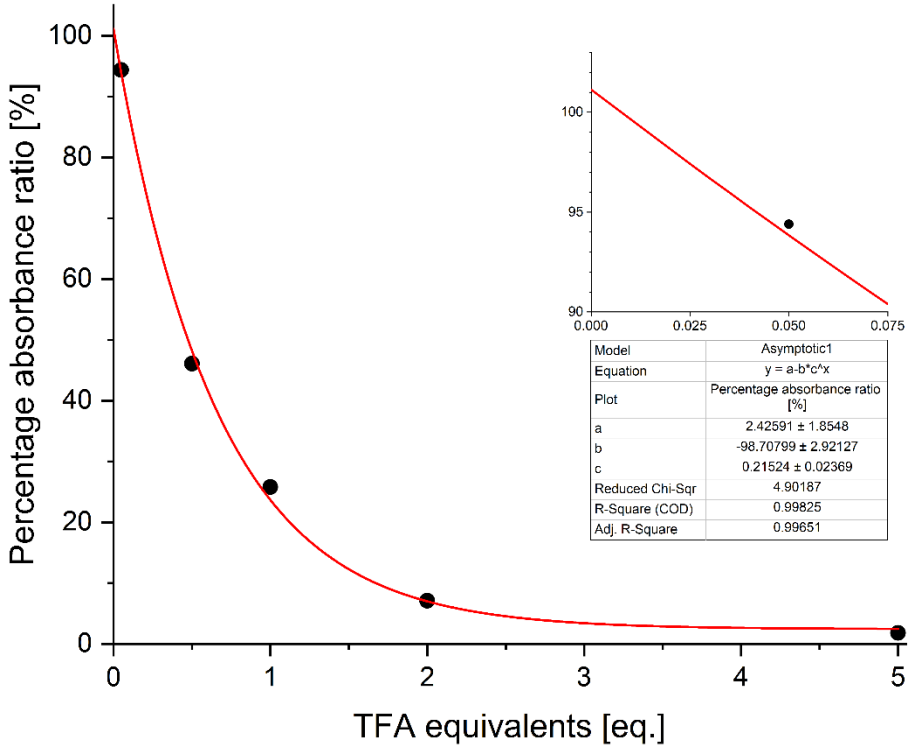



*Figure S 41. Percentage change of imine absorbance in presence of various equivalents of TFA.*

The absorbance change of imine in presence of TFA is significant when compared to absorbance of pure imine, however in studies performed *ibid.* only 5.0 mol% of TFA is used, which resulted in maximum change of 5.6% of imine absorption. Moreover, not all TFA will be available to 'react' with imine and affect its absorbance as it is catalysing the imine formation reaction, thus the overall change would be negligible and no correction for that effect was applied in studies performed herein.

## 4. 3. Analysis script for the imine formation solvent studies experiments

```
clear
close all

% Suppress warning associated with saving Matlab workspaces with embedded figures
warning('off','MATLAB:Figure:FigureSavedToMATFile');

% Table below contains values of the molar extinction coefficient
% (abbrv. MEC) of (E)-N,N-dimethyl-4-((4-nitrobenzylidene)amino)aniline
% in various solvents at 446 nm:
solvents_table = ["1: Row" "2: Name" "3: Abbrv" "4: Imine MEC @ 446 nm"
    "2" "N,N-Dimethylformamide","DMF",17448
    "3" "Dimethylsulfoxide","DMSO",17947
    "4" "N-Methylpyrrolidinone","NMP",16876
    "5" "Ethanol","EtOH",17636
    "6" "Acetonitrile","MeCN",16670
    "7" "Propylene Carbonate","PropCarb",16491
    "8" "Acetone","acetone",
    "9" "1,4-Dioxane","dioxane",19964
    "10" "1,2-Dichloroethane","DCE",17456
    "11" "Tetrahydrofuran","THF",17331
    "12" "Methanol","MeOH",17816
    "13" "Ethyl Acetate","AcOEt",20153
    "14" "Isopropanol","IPA",20365
    "15" "Dimethylacetamide","DMA",17463
    "16" "(-)-\beta-Pinene","BPinene",17247
    "17" "Benzyl Alcohol","BnOH",13332
    "18" "Triethylene glycol dimethyl ether","triglyme",17348
    "19" "2-Chloronaphthalene","ClNaphth",14987
    "20" "1,2-Dichlorobenzene","oDCB",16180
    "21" "Chlorobenzene","PhCl",16499
    "22" "Ethyl formate","EtForm",17745
    "23" "Cyclohexanone","cHexOne",16927
    "24" "Benzonitrile","PhCN",16847
    "25" "5% Water in DMSO","5%",14916];

disp(solvents_table);

solvent_1 = input('1st solvent is?','s'); % Determine 1st used solvent
solvent_2 = input('2nd solvent is?','s'); % Determine 2nd used solvent

% If statement below extracts the desired MEC value for 1st solvent
if solvent_1 == "DMF"
    MEC_solvent_1 = solvents_table(2,4);
elseif solvent_1 == "DMSO"
    MEC_solvent_1 = solvents_table(3,4);
elseif solvent_1 == "NMP"
    MEC_solvent_1 = solvents_table(4,4);
elseif solvent_1 == "EtOH"
    MEC_solvent_1 = solvents_table(5,4);
elseif solvent_1 == "MeCN"
    MEC_solvent_1 = solvents_table(6,4);
elseif solvent_1 == "PropCarb"
    MEC_solvent_1 = solvents_table(7,4);
elseif solvent_1 == "acetone"
    MEC_solvent_1 = solvents_table(8,4);
elseif solvent_1 == "dioxane"
    MEC_solvent_1 = solvents_table(9,4);
elseif solvent_1 == "DCE"
    MEC_solvent_1 = solvents_table(10,4);
elseif solvent_1 == "THF"
    MEC_solvent_1 = solvents_table(11,4);
elseif solvent_1 == "MeOH"
    MEC_solvent_1 = solvents_table(12,4);
elseif solvent_1 == "AcOEt"
    MEC_solvent_1 = solvents_table(13,4);
elseif solvent_1 == "IPA"
    MEC_solvent_1 = solvents_table(14,4);
elseif solvent_1 == "DMA"
    MEC_solvent_1 = solvents_table(15,4);
elseif solvent_1 == "BPinene"
    MEC_solvent_1 = solvents_table(16,4);
elseif solvent_1 == "BnOH"
    MEC_solvent_1 = solvents_table(17,4);
elseif solvent_1 == "triglyme"
    MEC_solvent_1 = solvents_table(18,4);
elseif solvent_1 == "ClNaphth"
    MEC_solvent_1 = solvents_table(19,4);
elseif solvent_1 == "oDCB"
    MEC_solvent_1 = solvents_table(20,4);
```

```
elseif solvent_1 == "PhCl"
    MEC_solvent_1 = solvents_table(21,4);
elseif solvent_1 == "EtForm"
    MEC_solvent_1 = solvents_table(22,4);
elseif solvent_1 == "cHexOne"
    MEC_solvent_1 = solvents_table(23,4);
elseif solvent_1 == "PhCN"
    MEC_solvent_1 = solvents_table(24,4);
elseif solvent_1 == "5%"
    MEC_solvent_1 = solvents_table(25,4);
else
    disp('Wrong solvent abbreviation used for solvent 1!')
    return
end

% If statement below extracts the desired MEC value for 2nd solvent
if solvent_2 == "DMF"
    MEC_solvent_2 = solvents_table(2,4);
elseif solvent_2 == "DMSO"
    MEC_solvent_2 = solvents_table(3,4);
elseif solvent_2 == "NMP"
    MEC_solvent_2 = solvents_table(4,4);
elseif solvent_2 == "EtOH"
    MEC_solvent_2 = solvents_table(5,4);
elseif solvent_2 == "MeCN"
    MEC_solvent_2 = solvents_table(6,4);
elseif solvent_2 == "PropCarb"
    MEC_solvent_2 = solvents_table(7,4);
elseif solvent_2 == "acetone"
    MEC_solvent_2 = solvents_table(8,4);
elseif solvent_2 == "dioxane"
    MEC_solvent_2 = solvents_table(9,4);
elseif solvent_2 == "DCE"
    MEC_solvent_2 = solvents_table(10,4);
elseif solvent_2 == "THF"
    MEC_solvent_2 = solvents_table(11,4);
elseif solvent_2 == "MeOH"
    MEC_solvent_2 = solvents_table(12,4);
elseif solvent_2 == "AcOEt"
    MEC_solvent_2 = solvents_table(13,4);
elseif solvent_2 == "IPA"
    MEC_solvent_2 = solvents_table(14,4);
elseif solvent_2 == "DMA"
    MEC_solvent_2 = solvents_table(15,4);
elseif solvent_2 == "BPinene"
    MEC_solvent_2 = solvents_table(16,4);
elseif solvent_2 == "BnOH"
    MEC_solvent_2 = solvents_table(17,4);
elseif solvent_2 == "triglyme"
    MEC_solvent_2 = solvents_table(18,4);
elseif solvent_2 == "ClNaphth"
    MEC_solvent_2 = solvents_table(19,4);
elseif solvent_2 == "oDCB"
    MEC_solvent_2 = solvents_table(20,4);
elseif solvent_2 == "PhCl"
    MEC_solvent_2 = solvents_table(21,4);
elseif solvent_2 == "EtForm"
    MEC_solvent_2 = solvents_table(22,4);
elseif solvent_2 == "cHexOne"
    MEC_solvent_2 = solvents_table(23,4);
elseif solvent_2 == "PhCN"
    MEC_solvent_2 = solvents_table(24,4);
elseif solvent_2 == "5%"
    MEC_solvent_2 = solvents_table(25,4);
else
    disp('Wrong solvent abbreviation used for solvent 2!')
    return
end

% Determine full name of solvents for graphs labelling
if solvent_1 == "DMF"
    solvent_1_name = solvents_table(2,2);
elseif solvent_1 == "DMSO"
    solvent_1_name = solvents_table(3,2);
elseif solvent_1 == "NMP"
    solvent_1_name = solvents_table(4,2);
elseif solvent_1 == "EtOH"
    solvent_1_name = solvents_table(5,2);
elseif solvent_1 == "MeCN"
    solvent_1_name = solvents_table(6,2);
elseif solvent_1 == "PropCarb"
    solvent_1_name = solvents_table(7,2);
elseif solvent_1 == "acetone"
    solvent_1_name = solvents_table(8,2);
elseif solvent_1 == "dioxane"
```

```
    solvent_1_name = solvents_table(9,2);
elseif solvent_1 == "DCE"
    solvent_1_name = solvents_table(10,2);
elseif solvent_1 == "THF"
    solvent_1_name = solvents_table(11,2);
elseif solvent_1 == "MeOH"
    solvent_1_name = solvents_table(12,2);
elseif solvent_1 == "AcOEt"
    solvent_1_name = solvents_table(13,2);
elseif solvent_1 == "IPA"
    solvent_1_name = solvents_table(14,2);
elseif solvent_1 == "DMA"
    solvent_1_name = solvents_table(15,2);
elseif solvent_1 == "BPinene"
    solvent_1_name = solvents_table(16,2);
elseif solvent_1 == "BnOH"
    solvent_1_name = solvents_table(17,2);
elseif solvent_1 == "triglyme"
    solvent_1_name = solvents_table(18,2);
elseif solvent_1 == "ClNaphth"
    solvent_1_name = solvents_table(19,2);
elseif solvent_1 == "oDCB"
    solvent_1_name = solvents_table(20,2);
elseif solvent_1 == "PhCl"
    solvent_1_name = solvents_table(21,2);
elseif solvent_1 == "EtForm"
    solvent_1_name = solvents_table(22,2);
elseif solvent_1 == "cHexOne"
    solvent_1_name = solvents_table(23,2);
elseif solvent_1 == "PhCN"
    solvent_1_name = solvents_table(24,2);
elseif solvent_1 == "5%"
    solvent_1_name = solvents_table(25,2);
end

if solvent_2 == "DMF"
    solvent_2_name = solvents_table(2,2);
elseif solvent_2 == "DMSO"
    solvent_2_name = solvents_table(3,2);
elseif solvent_2 == "NMP"
    solvent_2_name = solvents_table(4,2);
elseif solvent_2 == "EtOH"
    solvent_2_name = solvents_table(5,2);
elseif solvent_2 == "MeCN"
    solvent_2_name = solvents_table(6,2);
elseif solvent_2 == "PropCarb"
    solvent_2_name = solvents_table(7,2);
elseif solvent_2 == "acetone"
    solvent_2_name = solvents_table(8,2);
elseif solvent_2 == "dioxane"
    solvent_2_name = solvents_table(9,2);
elseif solvent_2 == "DCE"
    solvent_2_name = solvents_table(10,2);
elseif solvent_2 == "THF"
    solvent_2_name = solvents_table(11,2);
elseif solvent_2 == "MeOH"
    solvent_2_name = solvents_table(12,2);
elseif solvent_2 == "AcOEt"
    solvent_2_name = solvents_table(13,2);
elseif solvent_2 == "IPA"
    solvent_2_name = solvents_table(14,2);
elseif solvent_2 == "DMA"
    solvent_2_name = solvents_table(15,2);
elseif solvent_2 == "BPinene"
    solvent_2_name = solvents_table(16,2);
elseif solvent_2 == "BnOH"
    solvent_2_name = solvents_table(17,2);
elseif solvent_2 == "triglyme"
    solvent_2_name = solvents_table(18,2);
elseif solvent_2 == "ClNaphth"
    solvent_2_name = solvents_table(19,2);
elseif solvent_2 == "oDCB"
    solvent_2_name = solvents_table(20,2);
elseif solvent_2 == "PhCl"
    solvent_2_name = solvents_table(21,2);
elseif solvent_2 == "EtForm"
    solvent_2_name = solvents_table(22,2);
elseif solvent_2 == "cHexOne"
    solvent_2_name = solvents_table(23,2);
elseif solvent_2 == "PhCN"
    solvent_2_name = solvents_table(24,2);
elseif solvent_2 == "5%"
    solvent_2_name = solvents_table(25,2);
end
```

```
% Convert MECs from string to numerical values
MEC_solvent_1 = str2double(MEC_solvent_1);
MEC_solvent_2 = str2double(MEC_solvent_2);

% Generate linear model for MEC behaviour in selected solvents
MEC_mat_x = [0 100]; %X axis for MEC calculation - from 0 to 100% of solvent 2
MEC_mat_y = [MEC_solvent_1 MEC_solvent_2]; %Y axis for MEC calculation - from MEC in Solvent1 to MEC in
solvent2
MEC_linear_model = fitlm(MEC_mat_x,MEC_mat_y); %Create a linear function for values above
MEC_alpha = table2array(MEC_linear_model.Coefficients(2,1)); %Extract alpha value from linear function (y =
alpha*x + beta)
MEC_beta = table2array(MEC_linear_model.Coefficients(1,1)); %Extract beta value from linear function (y =
alpha*x + beta)

% Read raw absorbance data (.spc format)
data_1 = tgspcread('./d1.spc');
data_2 = tgspcread('./d2.spc');

% Generate absorbance data at 446 nm (row 781 in spc files)
calc_1(:,1) = data_1.Y(781,:);
calc_2(:,1) = data_2.Y(781,:);

% Plot absorption data to determine start and endpoints
disp(' ')
disp('Generating Figure 1: Absorbances at 446 nm for both experiments!')
fig1_label_yaxis_1 = 'Absorbance at';
fig1_label_yaxis_2 = '446 nm [a.u.]';
figure(1),
subplot(2,1,1),yyaxis left,plot(calc_1(:,1),'LineWidth',1.5),axis tight,grid on,
ylabel({fig1_label_yaxis_1,fig1_label_yaxis_2},'color','#0072BD'),xlabel('Time [s]'),
subplot(2,1,2),yyaxis left,plot(calc_2(:,1),'LineWidth',1.5),axis tight,grid on,%ylim([0 0.37]),
ylabel({fig1_label_yaxis_1,fig1_label_yaxis_2},'color','#0072BD'),xlabel('Time [s]'),
f1 = figure(1);
u1 = f1.Position;
f1.Position = [300 450 1250 500];

% Generate start and endpoints of gradient data
disp(' ')
startpoint_d1 = input('Provide the strating point of gradient from experiment d1!');
endpoint_d1 = input('Provide the ending point of gradient from experiment d1!');
startpoint_d2 = input('Provide the strating point of gradient from experiment d2!');
endpoint_d2 = input('Provide the ending point of gradient from experiment d2!');
% startpoint_d1 = 790;
% endpoint_d1 = 950;
% startpoint_d2 = 790;
% endpoint_d2 = 950;

% Provide flow rates for solvents and concentrations calculations [mL/min]
flow_1 = 0.3;
flow_2 = 0.3;
flow_3and4 = 1.4;
flow_5 = 0.25;
flow_total = flow_1 + flow_2 + flow_3and4 + flow_5;

% Generate linear solvent composition for the d1 experiment
gradient_d1_steps = ((endpoint_d1+1) - (startpoint_d1-1));
gradient_d1_solv2_max = (flow_3and4/flow_total);
gradient_d1_solv2_min = 0;
% display_gradient_d1 = ['Gradient data for Experiment d1: Solvent 2 (',string(solvent_2_name),'): from
',num2str(round(gradient_d1_solv2_min*100),3),'% to ',num2str(round(gradient_d1_solv2_max*100),3),'%.'];
% disp(' ')
% disp(display_gradient_d1)

gradient_d1_x = [1 gradient_d1_steps];
gradient_d1_y = [gradient_d1_solv2_min gradient_d1_solv2_max];
gradient_d1_linear_model = fitlm(gradient_d1_x,gradient_d1_y);
gradient_d1_alpha = table2array(gradient_d1_linear_model.Coefficients(2,1));
gradient_d1_beta = table2array(gradient_d1_linear_model.Coefficients(1,1));
gradient_d1_index = 1;
while gradient_d1_index < gradient_d1_steps
    calc_1((startpoint_d1-1)+gradient_d1_index,2) =
((gradient_d1_alpha.*gradient_d1_index+gradient_d1_beta).*100);
    gradient_d1_index = gradient_d1_index + 1;
end

% Generate linear solvent composition for the d2 experiment
gradient_d2_steps = (endpoint_d2+1) - (startpoint_d2-1);
gradient_d2_solv2_max = ((flow_1+flow_2+flow_3and4)/flow_total);
gradient_d2_solv2_min = ((flow_1+flow_2)/flow_total);
% display_gradient_d2 = ['Gradient data for Experiment d2: Solvent 2 (',solvent_2_name,'): from
',num2str(round(gradient_d2_solv2_min*100),3),'% to ',num2str(round(gradient_d2_solv2_max*100),3),'%.'];
% disp(' ')
% disp(display_gradient_d2)

gradient_d2_x = [1 gradient_d2_steps];
```

```
gradient_d2_y = [gradient_d2_solv2_max gradient_d2_solv2_min];
gradient_d2_linear_model = fitlm(gradient_d2_x,gradient_d2_y);
gradient_d2_alpha = table2array(gradient_d2_linear_model.Coefficients(2,1));
gradient_d2_beta = table2array(gradient_d2_linear_model.Coefficients(1,1));
gradient_d2_index = 1;
while gradient_d2_index < gradient_d2_steps
    calc_2((startpoint_d2-1)+gradient_d2_index,2) =
((gradient_d2_alpha.*gradient_d2_index+gradient_d2_beta).*100);
    gradient_d2_index = gradient_d2_index + 1;
end

%  Generate new column in which change the 0% values into NaN values, so they won't show on graph
calc_1(1:startpoint_d1-1,6) = NaN;
calc_1(startpoint_d1:endpoint_d1,6) = calc_1(startpoint_d1:endpoint_d1,2);
calc_1(endpoint_d1+1:end,6) = NaN;
calc_2(1:startpoint_d2-1,6) = NaN;
calc_2(startpoint_d2:endpoint_d2,6) = calc_2(startpoint_d2:endpoint_d2,2);
calc_2(endpoint_d2+1:end,6) = NaN;

% Plot the solvents composition data to figure(1)
fig1_label_yyaxis_1 = ['Percentage of ',solvent_2_name,'[%]'];
fig1_label_yyaxis_2 = ['Percentage of ',solvent_2_name,'[%]'];
disp(' ')
disp('Adding solvent compositions data to figure 1!')
figure(1),
subplot(2,1,1),yyaxis right,plot(calc_1(:,6),'LineWidth',1.5),ylabel(fig1_label_yyaxis_1),ylim([-10 110]),
xline(startpoint_d1,'--
',{'Gradient','Startpoint'},'LabelHorizontalAlignment','left','LabelVerticalAlignment','middle');
xline(endpoint_d1,'--',{'Gradient','Endpoint'},'LabelVerticalAlignment','middle');
yline(0.00,'Alpha',0.35,'LabelVerticalAlignment','middle','LabelOrientation','horizontal','LineWidth',1,'La
bel',{'0.00%'});
yline(62.22,'Alpha',0.35,'LabelVerticalAlignment','middle','LabelOrientation','horizontal','LineWidth',1,'L
abel',{'62.22%'});
fig1_title = string(['Absorabnce of imine and solvents composition in gradient region performed in
',solvent_1,' and ',solvent_2,' solvents mixture']);
title(fig1_title);
subplot(2,1,2),yyaxis right,plot(calc_2(:,6),'LineWidth',1.5),ylabel(fig1_label_yyaxis_2),ylim([-10 110]),
xline(startpoint_d2,'--
',{'Gradient','Startpoint'},'LabelHorizontalAlignment','left','LabelVerticalAlignment','middle');
xline(endpoint_d2,'--',{'Gradient','Endpoint'},'LabelVerticalAlignment','middle');
yline(26.67,'Alpha',0.35,'LabelVerticalAlignment','middle','LabelOrientation','horizontal','LineWidth',1,'L
abel',{'26.67%'});
yline(88.89,'Alpha',0.35,'LabelVerticalAlignment','middle','LabelOrientation','horizontal','LineWidth',1,'L
abel',{'88.89%'});

% Calculate MEC values for the variable solvents composition range
calc_1(:,3) = ((MEC_alpha.*calc_1(:,2))+MEC_beta);
calc_2(:,3) = ((MEC_alpha.*calc_2(:,2))+MEC_beta);

% Control plot of MEC values for used solvents composition
disp(' ')
disp('Generating Figure 2: MEC values for used solvent combination!')
fig2_label_xaxis_1 = ['Percentage of ',solvent_2_name,' [%]'];
figure(2),
plot(calc_1(startpoint_d1:endpoint_d1,2),calc_1(startpoint_d1:endpoint_d1,3)),hold on,
plot(calc_2(startpoint_d2:endpoint_d2,2),calc_2(startpoint_d2:endpoint_d2,3)),hold off,
legend ({'Exp d1','Exp d2'}), grid on,
grid on,ylabel('MEC value'),xlabel(char(fig2_label_xaxis_1));
ax = gca;
ax.YAxis.Exponent = 0;

% Calculate the concentration of the product from absorbance data
path_length_1 = 0.01; % [cm]
path_length_2 = path_length_1; % in case two experiments were done with different UV-Vis cells
calc_1(:,4) = (calc_1(:,1)./(calc_1(:,3).*path_length_1));
calc_2(:,4) = (calc_2(:,1)./(calc_2(:,3).*path_length_2));

% Calculate the maximum reaction yield
initial_concentration = 0.025; % concentration of the limiting reagent [M]
max_concentration =
initial_concentration*(flow_1/(flow_1+flow_2))*((flow_1+flow_2)/(flow_1+flow_2+flow_3and4+flow_5));

% Calculate the in situ reaction yield
calc_1(:,5) = calc_1(:,4)/max_concentration*100;
calc_2(:,5) = calc_2(:,4)/max_concentration*100;

% Control plot of calculated concentrations and yields
disp(' ')
disp('Generating Figure 3: Calculated concentration and yields!')
figure(3),subplot(3,1,[1,2]),
plot(calc_1(:,4),'-.'),hold on,plot(calc_2(:,4),'-.'),hold off,
xlabel('Time [s]'),ylabel('Product concentration [M]'),grid on,axis tight,
yyaxis right,plot(calc_1(:,5),'-','color','#0072BD'),hold on,plot(calc_2(:,5),'-','color','#D95319'),hold
off,
ylabel('Reaction yield [%]'),ylim([-10 110]),set(gca,'ycolor','k'),
```

```
legend({'Exp d1: Concentration','Exp d2: Concentration','Exp d1: Yield','Exp d2: Yield'}),
subplot(3,1,3),
plot(calc_1(:,1)),hold on,plot(calc_2(:,1)),hold off,
xlabel('Time [s]'),ylabel('Absorbance [a.u.]'),grid on, axis tight,
f3 = figure(3);
u3 = f3.Position;
f3.Position = [500 350 900 500];

% Plot reaction yield vs solvent composition data
disp(' ')
disp('Generating Figure 4: Reaction yield vs solvents composition used!')
disp(' ')
fig4_label_xaxis_1 = ['Percentage of ',convertStringsToChars(solvent_2_name),' in
',convertStringsToChars(solvent_1_name),'/',convertStringsToChars(solvent_2_name),' mixture [%]'];
figure(4),
plot(calc_1(startpoint_d1:endpoint_d1,2),calc_1(startpoint_d1:endpoint_d1,5),'LineWidth',1.5),hold on,
plot(calc_2(startpoint_d2:endpoint_d2,2),calc_2(startpoint_d2:endpoint_d2,5),'LineWidth',1.5),hold off,
%plot(calc_1(startpoint_d1:endpoint_d1,2),smoothdata(calc_1(startpoint_d1:endpoint_d1,5),'lowess')),hold
on,
%plot(calc_2(startpoint_d2:endpoint_d2,2),smoothdata(calc_2(startpoint_d2:endpoint_d2,5),'lowess')),hold
off,
xlabel(fig4_label_xaxis_1),ylabel('Reaction yield [%]'),grid on,xlim([-0 100])
figure_4_y_max_lim = input('Determine maximum yield boudnary for figure 4 (reaction yield vs solvent
composition)!');
ylim([0 figure_4_y_max_lim]),
fig4_legend_entry_1 = string(['Experiment 1: ',convertStringsToChars(solvent_1_name),' and
',convertStringsToChars(solvent_2_name),'\newlineFrom ',num2str(round(gradient_d1_solv2_min*100,2)),'% to
',num2str(round(gradient_d1_solv2_max*100,2)),'% of ',convertStringsToChars(solvent_2_name)]);
fig4_legend_entry_2 = string(['Experiment 2: ',convertStringsToChars(solvent_2_name),' and
',convertStringsToChars(solvent_1_name),'\newlineFrom ',num2str(round(gradient_d2_solv2_min*100,2)),'% to
',num2str(round(gradient_d2_solv2_max*100,2)),'% of ',convertStringsToChars(solvent_2_name)]);
legend({fig4_legend_entry_1,fig4_legend_entry_2},'location','best');
fig4_title = string(['Imine formation reaction yield performed in ',solvent_1,' and ',solvent_2,' solvents
mixture']);
title(fig4_title);
f4 = figure(4);
u4 = f4.Position;
f4.Position = [1000 400 750 450];

% Save calculated data if the results are satisfactory
decision_save = input('Save all calculated data ? 1 = yes, anything else = no!','s');
disp(' ')
if decision_save == "1"

    % Create figure with zoomed data from fig(1)
    figure(6),
    subplot(2,1,1),yyaxis left,plot(calc_1(:,1),'LineWidth',1.5),axis tight,grid on,
    ylabel({fig1_label_yaxis_1,fig1_label_yaxis_2},'color','#0072BD'),xlabel('Time
[s]'),ylim("tickaligned");
    subplot(2,1,2),yyaxis left,plot(calc_2(:,1),'LineWidth',1.5),axis tight,grid on,
    ylabel({fig1_label_yaxis_1,fig1_label_yaxis_2},'color','#0072BD'),xlabel('Time
[s]'),ylim("tickaligned");
    subplot(2,1,1),yyaxis right,plot(calc_1(:,6),'LineWidth',1.5),ylabel(fig1_label_yyaxis_1),ylim([-10
110]);
    xline(startpoint_d1,'--
',{'Gradient','Startpoint'},'LabelHorizontalAlignment','left','LabelVerticalAlignment','middle');
    xline(endpoint_d1,'--',{'Gradient','Endpoint'},'LabelVerticalAlignment','middle');

yline(0.00,'Alpha',0.35,'LabelVerticalAlignment','middle','LabelOrientation','horizontal','LineWidth',1,'La
bel',{'0.00%'});

yline(62.22,'Alpha',0.35,'LabelVerticalAlignment','middle','LabelOrientation','horizontal','LineWidth',1,'L
abel',{'62.22%'});
    fig6_title_1 = "Imine 4 absorbance and solvents composition in gradient region";
    fig6_title_2 = string(['performed in ',solvent_1,' and ',solvent_2,' solvents mixture']);
    title({fig6_title_1,fig6_title_2}),xlim([startpoint_d1-100 endpoint_d1+100]);
    subplot(2,1,2),yyaxis right,plot(calc_2(:,6),'LineWidth',1.5),ylabel(fig1_label_yyaxis_2),ylim([-10
110]),xlim([startpoint_d2-100 endpoint_d2+100]);
    xline(startpoint_d2,'--
',{'Gradient','Startpoint'},'LabelHorizontalAlignment','left','LabelVerticalAlignment','middle');
    xline(endpoint_d2,'--',{'Gradient','Endpoint'},'LabelVerticalAlignment','middle');

yline(26.67,'Alpha',0.35,'LabelVerticalAlignment','middle','LabelOrientation','horizontal','LineWidth',1,'L
abel',{'26.67%'});

yline(88.89,'Alpha',0.35,'LabelVerticalAlignment','middle','LabelOrientation','horizontal','LineWidth',1,'L
abel',{'88.89%'});
    f6 = figure(6);
    u6 = f6.Position;
    f6.Position = [300 450 750 500];

    calculation_information = input('Provide information on date and experiment number!','s');
    disp(' ')
    results_xlsx = {'Analysis information','',string(calculation_information),'','','';
        'Solvent 1 used:',string(solvent_1_name),' ','Solvent 2 used:',string(solvent_2_name),'';
```

```
        'Gradient startpoint of exp d1:',startpoint_d1,'','Gradient endpoint of exp d1:',endpoint_d1,'';
        'Gradient startpoint of exp d2:',startpoint_d2,'','Gradient endpoint of exp d2:',endpoint_d2,'';
        'Reagents concentration:','1-Fluoro-4-nitrobenzene:',initial_concentration,'[M]','','';
        '','Piperidine:',(2.5*initial_concentration),'[M]','','';
        'Flow rates:',flow_1,flow_2,flow_3and4,'(1st, 2nd, and 3rd+4th streams respectively','[mL/min]';
        'Path length:','Experiment d1:',path_length_1,'Experiment d2',path_length_2,'[cm]';
        'Results of experiment d1:','','','','','';
        '','','','','Reaction yield [%]:',calc_1(startpoint_d1:endpoint_d1,2);
        '','','','',fig4_label_xaxis_1,calc_1(startpoint_d1:endpoint_d1,5);
        'Results of experiment d2:','','','','','';
        '','','','','Reaction yield [%]:',calc_2(startpoint_d2:endpoint_d2,2);
        '','','','',fig4_label_xaxis_1,calc_2(startpoint_d2:endpoint_d2,5);};

    filename = input('Provide filename for calculation results!','s');
    disp(' ')

    filename1 = string(filename + " 01 Abs and solvents composition");
    filename2 = string(filename + " 02 MEC values used");
    filename3 = string(filename + " 03 Calculated concentration and yield");
    filename4 = string(filename + " 04 Reaction yield vs solvents composition");
    filename5 = string(filename + " 05 Caulcation information and results");
    filename6 = string(filename + " 06 Gradient region");

    saveas(figure(1),filename1,'fig');
    exportgraphics(figure(1),filename1+'.tiff','Resolution',1200);
    print(figure(1),filename1,'-dsvg','-r1200');

    % saveas(figure(2),filename2,'fig');
    % exportgraphics(figure(2),filename2+'.tiff','Resolution',1200);
    % print(figure(2),filename2,'-dsvg','-r1200');

    % saveas(figure(3),filename3,'fig');
    % exportgraphics(figure(3),filename3+'.tiff','Resolution',1200);
    % print(figure(3),filename3,'-dsvg','-r1200');

    saveas(figure(4),filename4,'fig');
    exportgraphics(figure(4),filename4+'.tiff','Resolution',1200);
    print(figure(4),filename4,'-dsvg','-r1200');

    saveas(figure(6),filename6,'fig');
    exportgraphics(figure(6),filename6+'.tiff','Resolution',1200);
    print(figure(6),filename6,'-dsvg','-r1200');

    writecell(results_xlsx,filename5+'.xlsx');

    % Save MATLAB workspace
    filename7 = string(filename + " 07 MatlabWorkspace");
    save(filename7)
end

disp('######################')
disp('## Script finished! ##')
disp('######################')
```

## 4. 4. Solvent effects studies in imine formation reaction

### 4. 4. 1. Experimental procedure

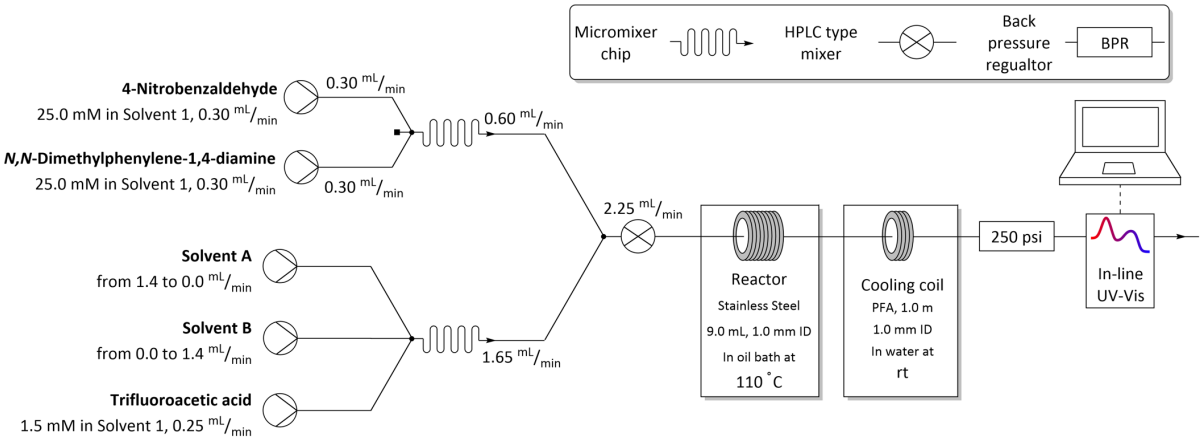



*Figure S 42. Flow setup used in imine formation reaction solvents mixtures studies.*

A 25.0 mM solution of 4-nitrobenzaldehyde (75.6 mg, 0.5 mmol, 1.0 eq. in 20.0 mL (293.7 vol.) of Solvent A) was connected to the first flow reagent line. A 25.0 mM solution of *N,N*-dimethylphenylene-

1,4-diamine (68.1 mg, 0.5 mmol, 1.0 eq. in 20.0 mL (293.7 vol.) of Solvent A) was connected to the second flow reagent line. Solvent A was connected to the first, second, and third flow solvents lines. Solvent B was connected to the fourth flow solvent line. A 1.5 mM solution of trifluoroacetic acid (42.8 mg, 0.38 mmol, 0.05 eq. in 250 mL (5841.1 vol.) of 1,2-dichloroethane) was connected to the fifth flow solvent line. Flow rates were set to 0.30, 0.30, 1.40, 0.00, and 0.25 $mL \cdot min^{-1}$ for the flow streams, respectively. First and second flow streams were directed to the first channel of dolomite mixer, third, fourth, and fifth flow streams were directed to the second channel of dolomite mixer, and then both mixer outlets were combined, directed to the HPLC mixer, and reactor (stainless steel, 9.0 mL, 1.0 mm I.D., 1.6 mm O.D., submersed in high-precision oil bath set to 110 °C). Flow stream was then directed via a cooling coil (PFA, 1.0 mm ID, 1.6 mm OD, submersed in water at rt) and BPR (250 psi) to the UV-Vis flow cell.

Vapourtec R2 units were controlled using python script (see below), following the procedural steps described below:

1. Flow rates of 0.30, 0.30, 1.40, 0.00, and 0.25 $mL \cdot min^{-1}$ were set for each pump respectively, pumps were turned on, and system was allowed to equilibrate for 60 seconds.
2. First and second flow streams were switched to reagents position and a wait period of 540 seconds was scheduled, after which first reaction steady state was observed.
3. Gradient of solvents composition was generated by stepwise change of third and fourth flow streams with a one second interval:
    i. Third flow stream flow rate was decreased by 0.01 $mL \cdot min^{-1}$.
    ii. Fourth flow stream flow rate was increased by 0.01 $mL \cdot min^{-1}$.
    iii. One second interval was scheduled.

    Points i. to iii. were repeated until flow rate of third flow stream reached 0.00 $mL \cdot min^{-1}$ and flow rate of fourth flow stream reached 1.40 $mL \cdot min^{-1}$.
4. System waited for 180 seconds, during which a second steady state was observed.
5. First and second flow streams were switched back to solvents positions, third and fourth flow streams flow rates were instantly changed to 1.40 and 0.00 $mL \cdot min^{-1}$, respectively.
6. A wait period of 700 seconds was scheduled, during which remaining reaction mixture was eluted from the reactor.

The whole procedure was then repeated, with the only change being the substitution of the solvent A with solvent B, and solvent B with solvent A.

Note that in the python script below, the *time.sleep* command executed during the generation of solvents gradient is set only to 0.5 second. This is due to the fact, that when changing the flow rate of any pump (using the *Vtec_PumpX(port,flow)* command), additional period of 250 ms of wait time is incorporated into the command (as defined in *def VTec_PumpX* command definition), to maintain the serial connection stability. Note that the commands responsible for hardware control have been redacted, due to the confidentiality disclosure. If needed, contact Vapourtec Ltd for details of the serial command protocol.

```
import serial
import time
import os

def cls():
         os.system('cls' if os.name == 'nt' else 'clear')

def Vtec_On(port):
          """Define turn on command"""
          port.write('▒▒▒▒▒▒▒'.encode())
          time.sleep(0.5)
          port.readline()
          port.write('▒▒▒▒▒▒▒▒'.encode())
```

```
          time.sleep(0.5)
          port.readline()
def Vtec_Off(port):
          """Define turn off command"""
          port.write('▒▒▒▒▒▒'.encode())
          time.sleep(0.5)
          port.readline()
          port.write('▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.5)
          port.readline()

def Vtec_PumpA(port,flow):
          """Define flow of A pump"""
          flow1_uL = flow1 * 1000
          port.write('▒▒▒▒▒▒'.encode() + str(flow1_uL).encode() + '▒▒▒▒'.encode())
          time.sleep(0.25)
          port.readline()
def Vtec_PumpB(port,flow):
          """Define flow of B pump"""
          flow2_ul = flow2 * 1000
          port.write('▒▒▒▒▒▒'.encode() + str(flow2_ul).encode() + '▒▒▒▒'.encode())
          time.sleep(0.25)
          port.readline()
def Vtec_PumpC(port,flow):
          flow3_uL = flow3 * 1000
          port.write('▒▒▒▒▒▒▒▒'.encode() + str(flow3_uL).encode() + '▒▒▒▒'.encode())
          time.sleep(0.25)
          port.readline()
def Vtec_PumpD(port,flow):
          flow4_uL = flow4 * 1000
          port.write('▒▒▒▒▒▒▒▒'.encode() + str(flow4_uL).encode() + '▒▒▒▒'.encode())
          time.sleep(0.25)
          port.readline()
def Vtec_PumpE(port,flow):
          """Define flow of A pump"""
          flow5_uL = flow5 * 1000
          port.write('▒▒▒▒▒▒'.encode() + str(flow5_uL).encode() + '▒▒▒▒'.encode())
          time.sleep(0.25)
          port.readline()
def Vtec_PumpF(port,flow):
          """Define flow of B pump"""
          flow6_ul = flow6 * 1000
          port.write('▒▒▒▒▒▒'.encode() + str(flow6_ul).encode() + '▒▒▒▒'.encode())
          time.sleep(0.25)
          port.readline()

def PumpASolv(port):
          port.write('▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)
def PumpAReagent(port):
          port.write('▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)
def PumpBSolv(port):
          port.write('▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)
def PumpBReagent(port):
          port.write('▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)
def PumpCSolv(port):
          port.write('▒▒▒▒▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)
def PumpCReagent(port):
          port.write('▒▒▒▒▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)
def PumpDSolv(port):
          port.write('▒▒▒▒▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)
def PumpDReagent(port):
          port.write('▒▒▒▒▒▒▒▒▒▒▒▒'.encode())
          time.sleep(0.25)

ser1 = serial.Serial(
          port = "COM" + str(7),
          baudrate = 19200,
          parity = serial.PARITY_NONE,
          stopbits = serial.STOPBITS_ONE,
          bytesize = serial.EIGHTBITS,
          )

ser2 = serial.Serial(
          port = "COM" + str(12),
          baudrate = 19200,
          parity = serial.PARITY_NONE,
          stopbits = serial.STOPBITS_ONE,
          bytesize = serial.EIGHTBITS,
```

```
         )

flow1 = 0.3
flow2 = 0.3
flow3 = 1.4
flow4 = 0.0
flow5 = 0.25
flow6 = 0.0
Vtec_PumpA(ser1,flow1)
Vtec_PumpB(ser1,flow2)
Vtec_PumpC(ser1,flow3)
Vtec_PumpD(ser1,flow4)
Vtec_PumpE(ser2,flow5)
Vtec_PumpF(ser2,flow6)

PumpASolv(ser1)
PumpBSolv(ser1)
PumpCSolv(ser1)
PumpDSolv(ser1)
PumpAReagent(ser2)
PumpBReagent(ser2)

Vtec_On(ser1)
Vtec_On(ser2)

cls()
print('####################################')
print('VTec 60s stabilization - system on!')
print('####################################')
time.sleep(30)
print('-30 sec')
time.sleep(25)
print('-5 sec')
time.sleep(1)
print('-4 sec')
time.sleep(1)
print('-3 sec')
time.sleep(1)
print('-2 sec')
time.sleep(1)
print('-1 sec')
time.sleep(1)

print(' ')
print('Experiment start! UV-Vis acquisition on!')
PumpAReagent(ser1)
PumpBReagent(ser1)
print(' ')
time.sleep(540)
print('First steady state reached!')
print('Generating gradient of solvents composition!')
print('(0.01 mL/min change, 1 second interval)')
print(' ')

flowA = flow3
flowB = flow4
i = 1
while (flowA > 0.01):
         flowA = flowA - 0.01
         flowA = round(flowA, 2)
         flow3 = flowA
         flowB = flowB + 0.01
         flowB = round(flowB, 2)
         flow4 = flowB
         Vtec_PumpC(ser1,flow3)
         Vtec_PumpD(ser1,flow4)
         time.sleep(0.5)
         print('Iteration #', i, ', flow3/C =', flow3, ' and flow4/D =', flow4)
         i = i + 1

flow3 = 0.0
flow4 = 1.4
Vtec_PumpC(ser1,flow3)
Vtec_PumpD(ser1,flow4)
print(' ')
print('Gradient applied!')

print('Holding steady state for 180 sec!')
time.sleep(120)
print('60 sec of steady state left!')
time.sleep(60)
print(' ')

print('Setting up end conditions. Switching back to solvents and initial flow rates!')
PumpASolv(ser1)
```

```
PumpBSolv(ser1)
flow3 = 1.4
flow4 = 0.0
Vtec_PumpC(ser1,flow3)
Vtec_PumpD(ser1,flow4)
print('Flow system cleanup!')
time.sleep(700)

Vtec_Off(ser1)
Vtec_Off(ser2)
print('##############################')
print('VTec Off! End of experiment!')
print('##############################')
```

## 4. 4. 2. Results of solvent effects studies in imine formation reaction

### 4. 4. 2. 1. DCE and DMSO solvents mixture:

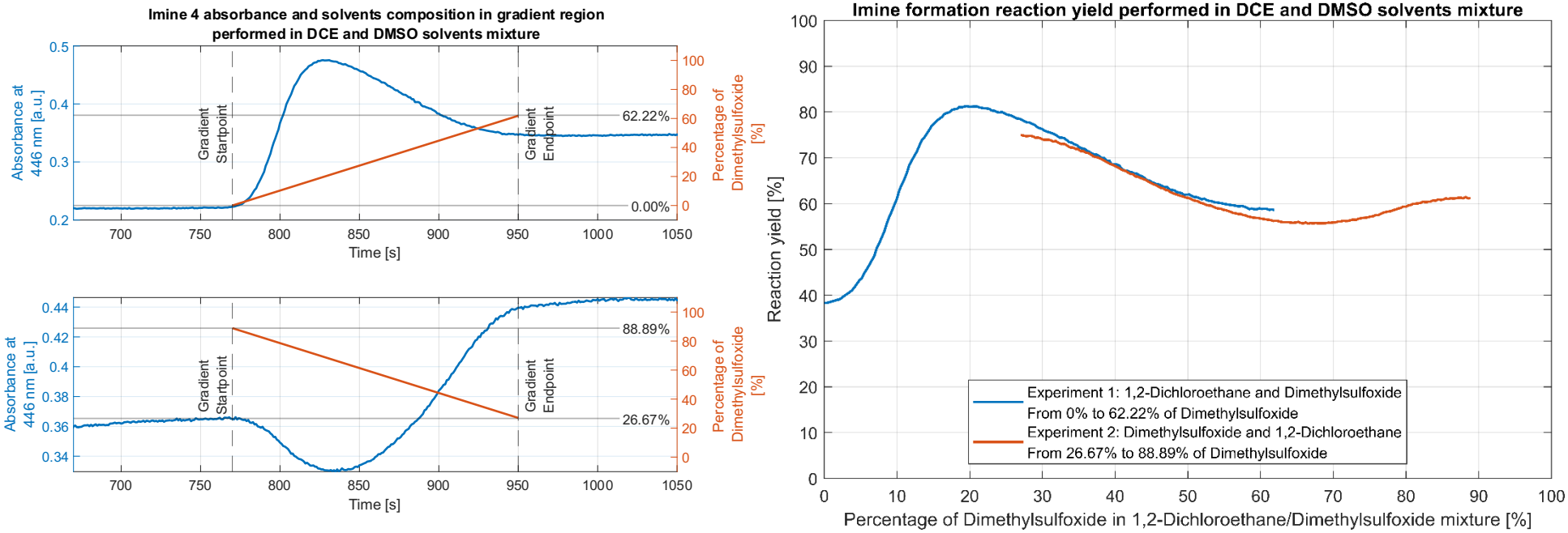



*Figure S 43. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/DMSO mixtures as reaction medium.*

### 4. 4. 2. 2. DCE and DMF solvents mixture:

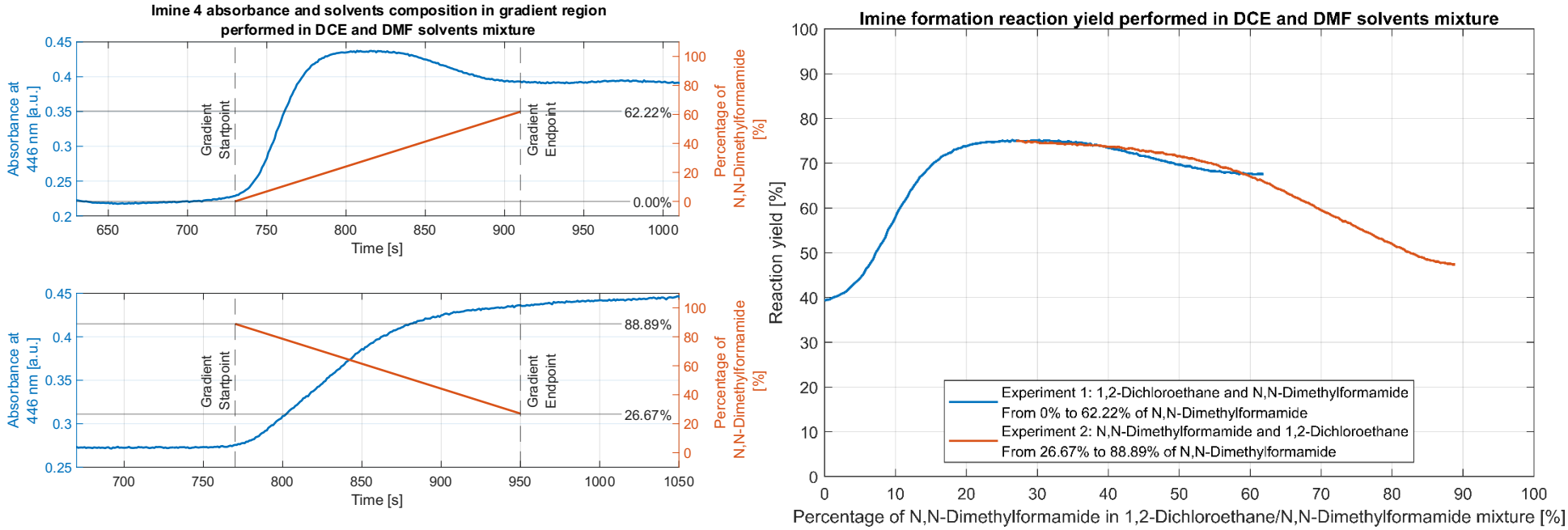



*Figure S 44. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/DMF mixtures as reaction medium.*

### 4. 4. 2. 3. DCE and MeOH solvents mixture:

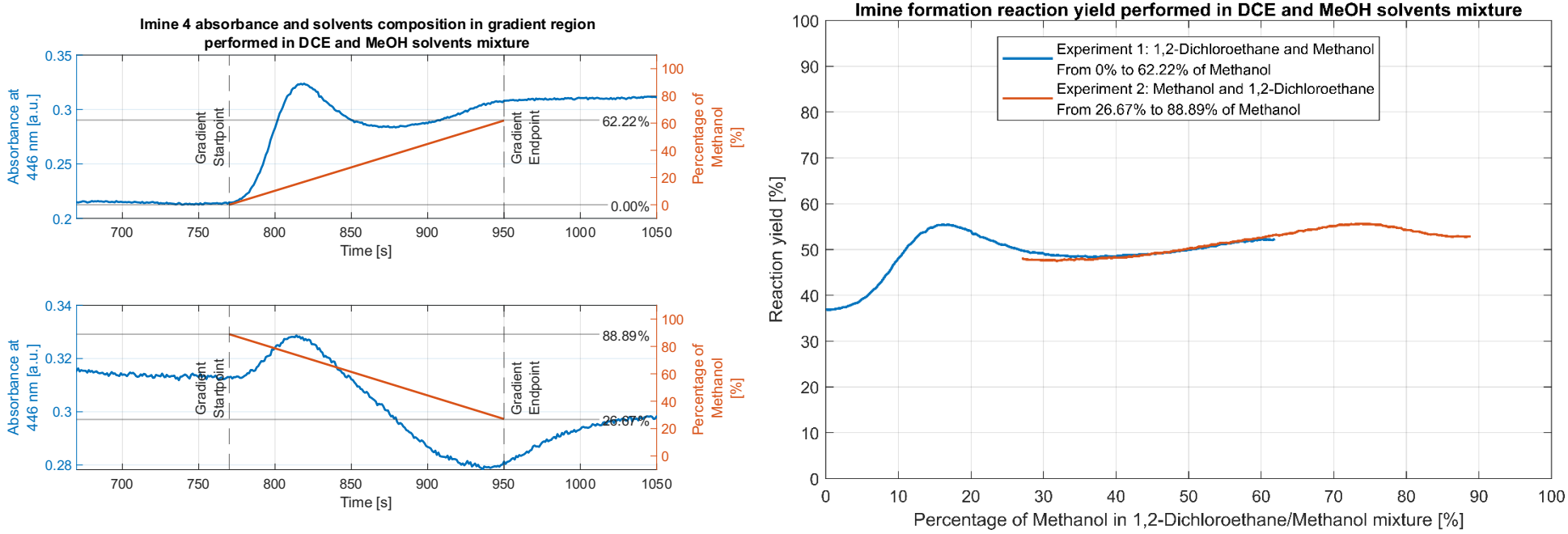



*Figure S 45. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/MeOH mixtures as reaction medium.*

### 4. 4. 2. 4. DCE and EtOH solvents mixture:

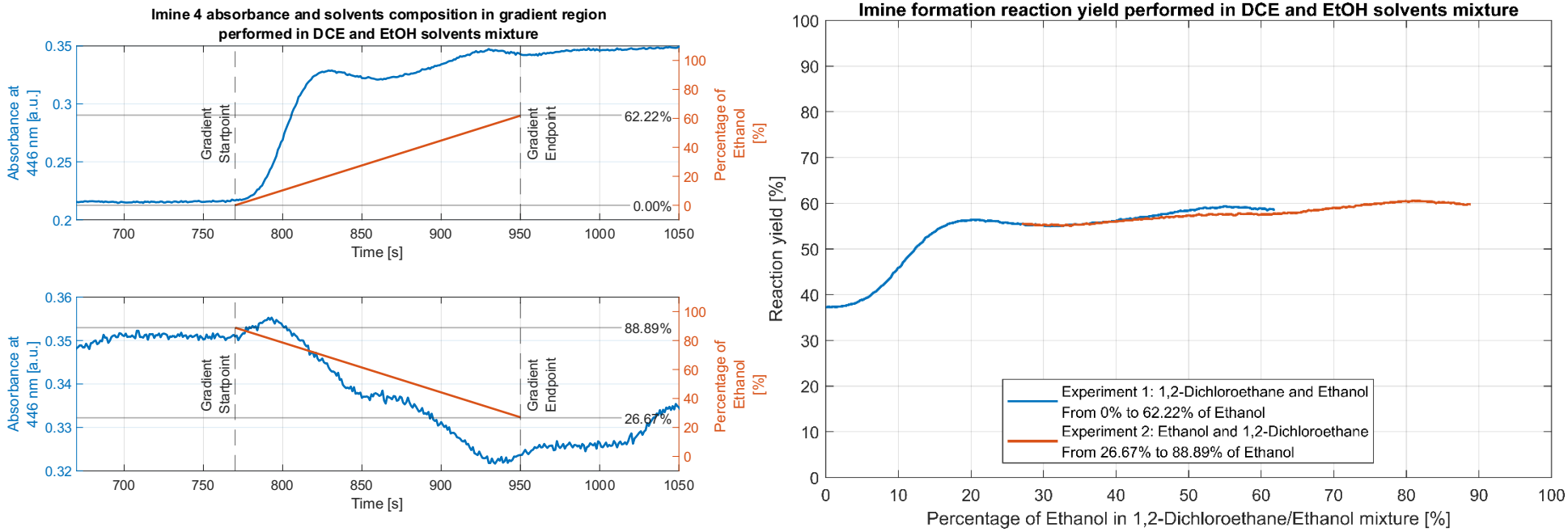



*Figure S 46. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/EtOH mixtures as reaction medium.*

### 4. 4. 2. 5. DCE and IPA solvents mixture:

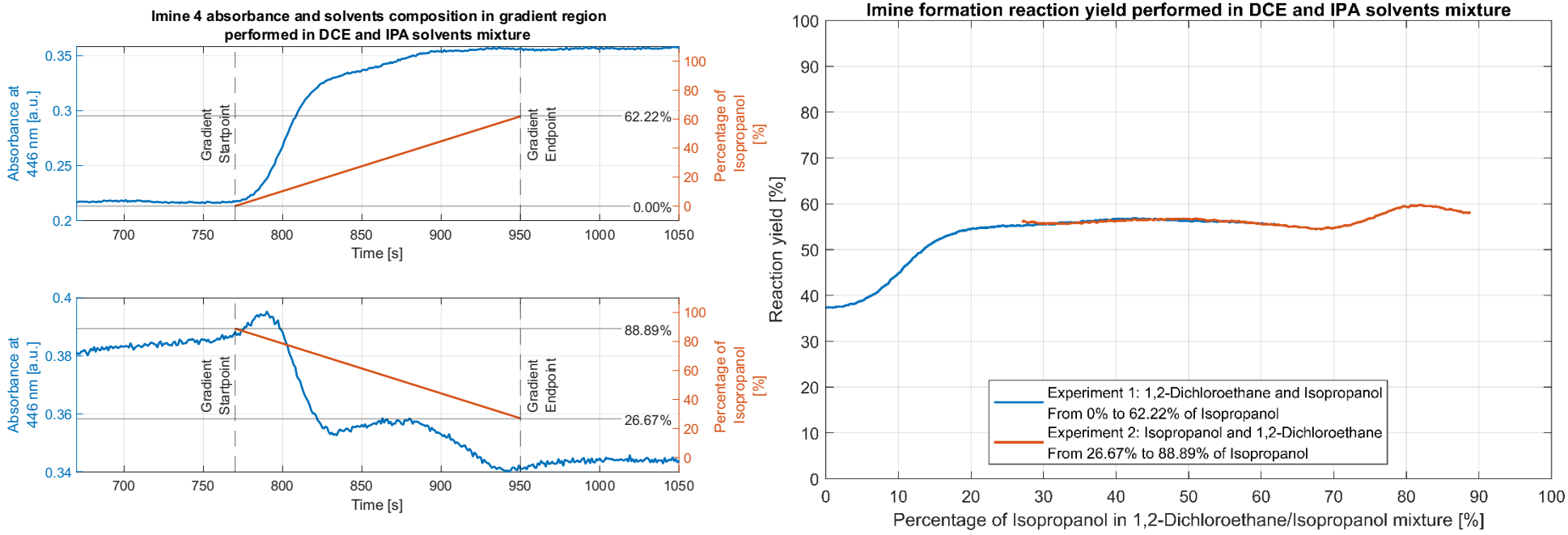



*Figure S 47. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/IPA mixtures as reaction medium.*

### 4. 4. 2. 6. DCE and AcOEt solvents mixture:

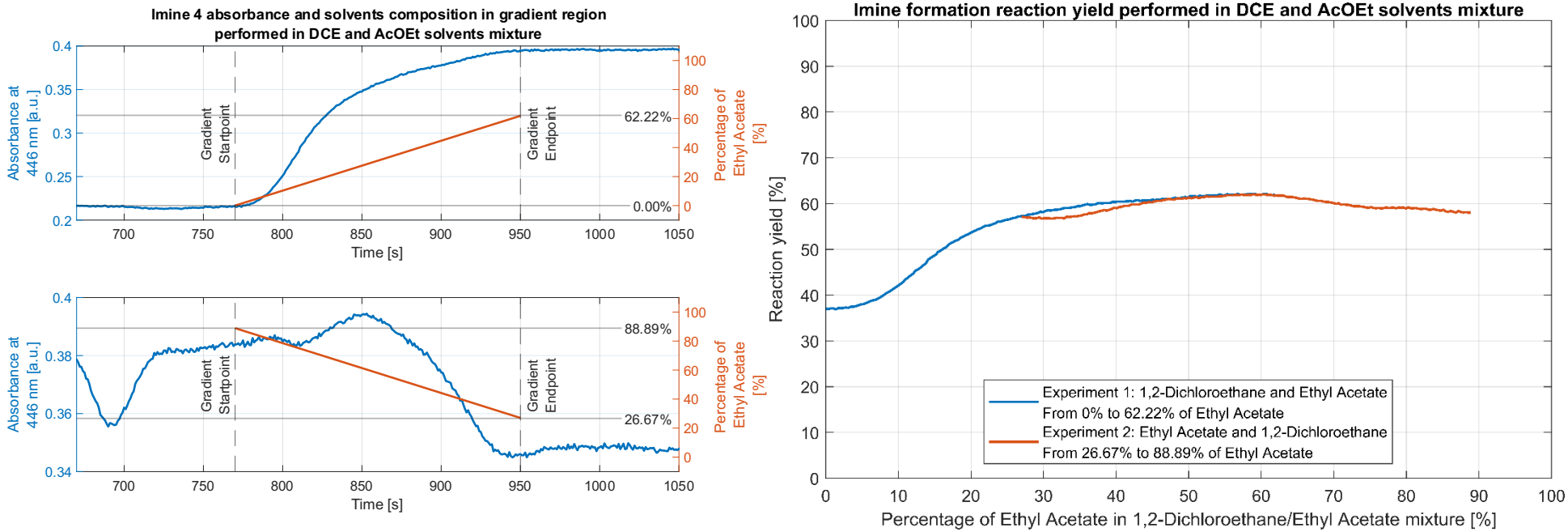



*Figure S 48. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/AcOEt mixtures as reaction medium.*

### 4. 4. 2. 7. DCE and NMP solvents mixture:

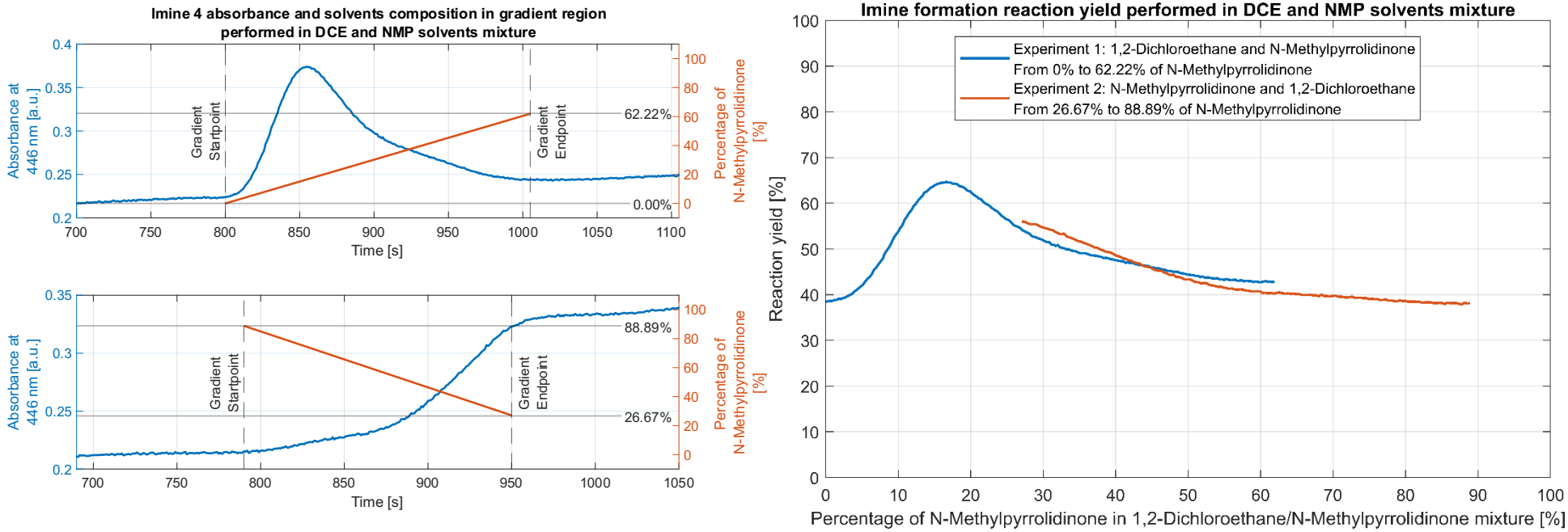



*Figure S 49. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/NMP mixtures as reaction medium.*

### 4. 4. 2. 8. DCE and MeCN solvents mixture:

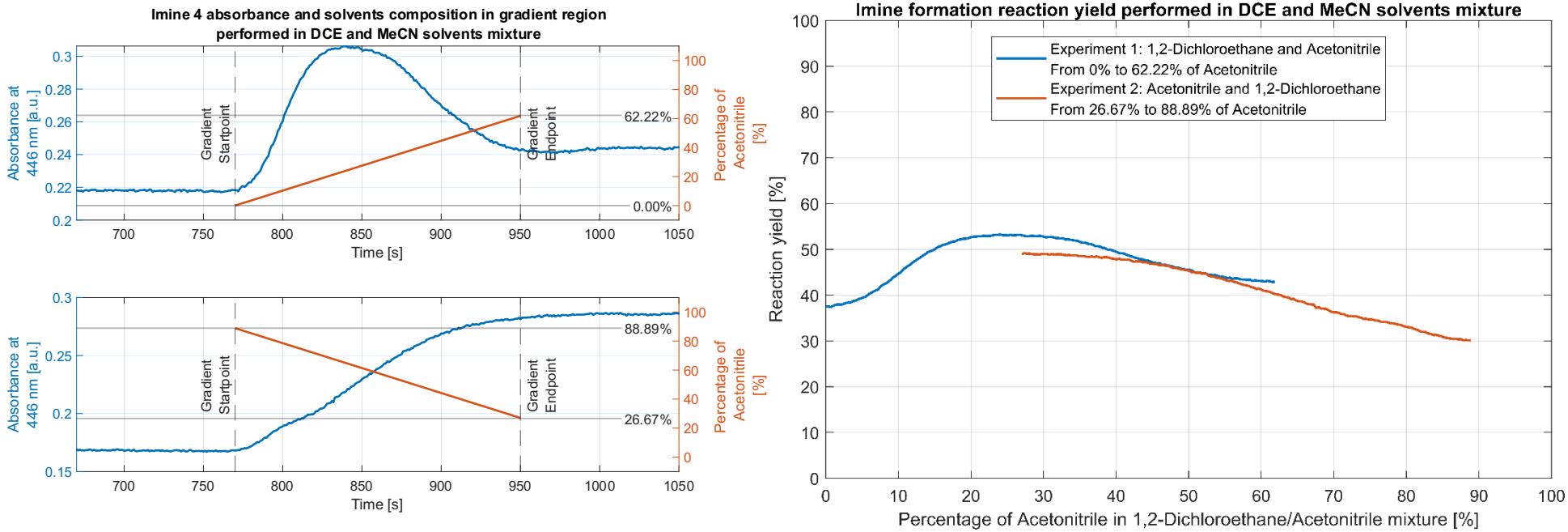



*Figure S 50. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/MeCN mixtures as reaction medium.*

### 4. 4. 2. 9. DCE and 1,4-dioxane solvents mixture:

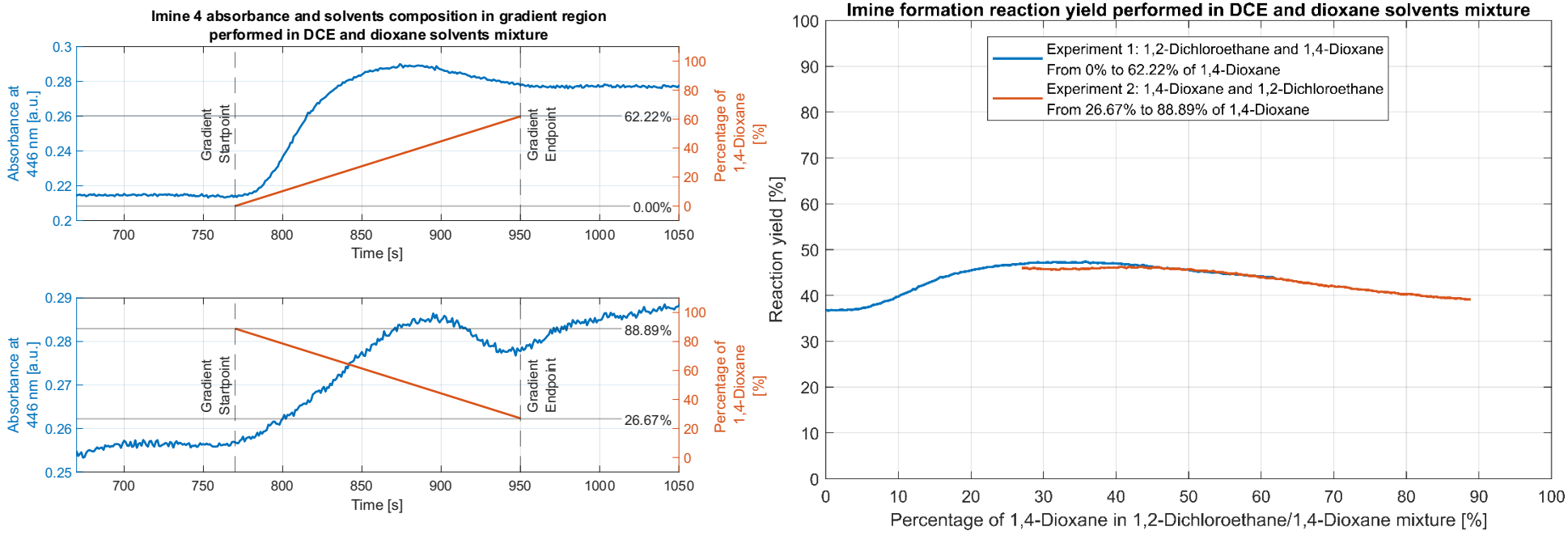



*Figure S 51. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/1,4-dioxane mixtures as reaction medium.*

### 4. 4. 2. 10. DCE and propylene carbonate solvents mixture:

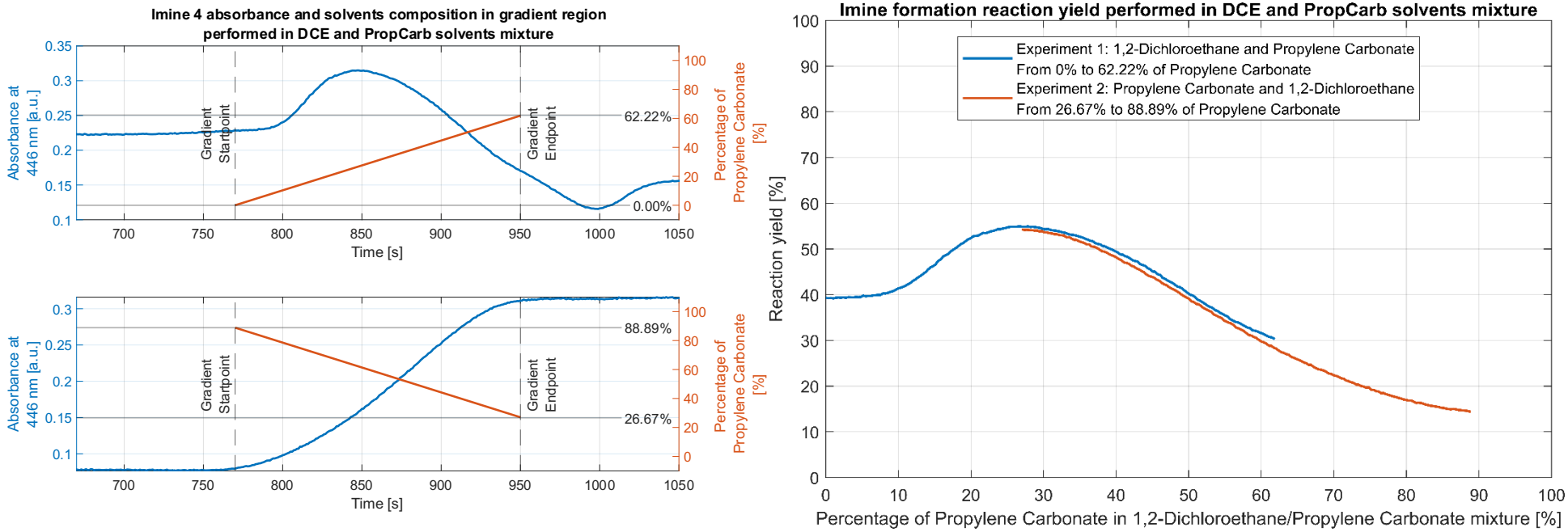



*Figure S 52. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/PC mixtures as reaction medium.*

### 4. 4. 2. 11. DCE and chlorobenzene solvents mixture:

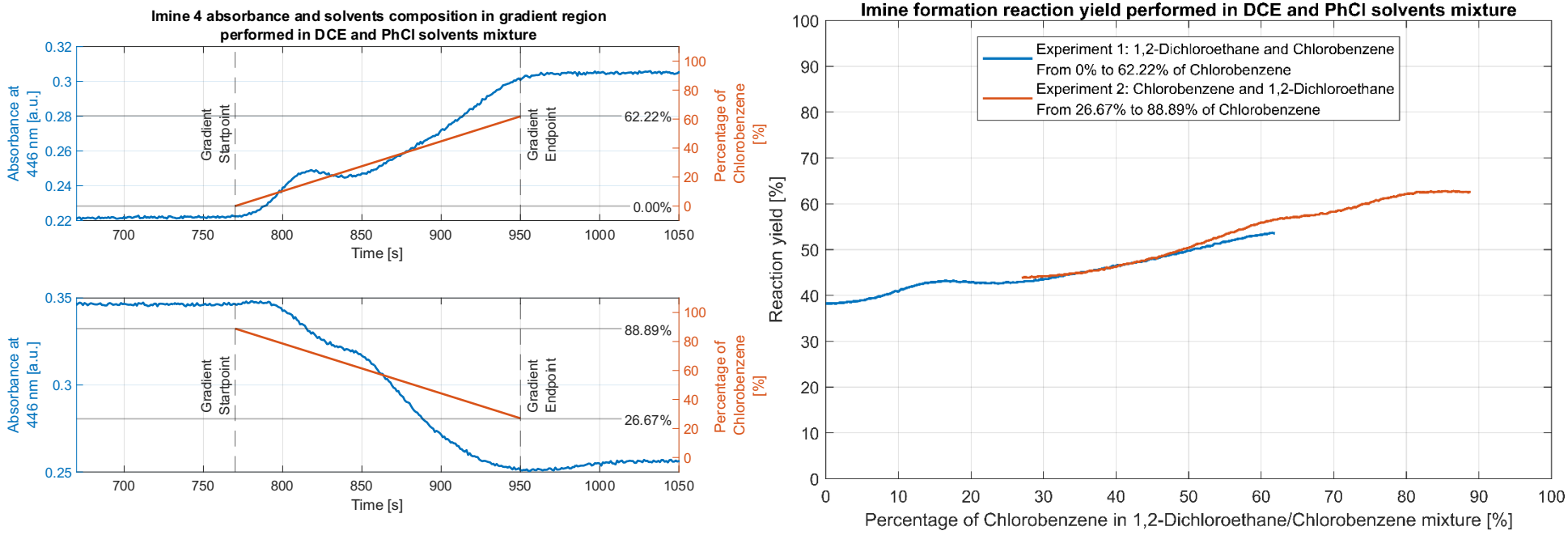



*Figure S 53. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/chlorobenzene mixtures as reaction medium.*

### 4. 4. 2. 12. DCE and *orto*-dichlorobenzene solvents mixture:

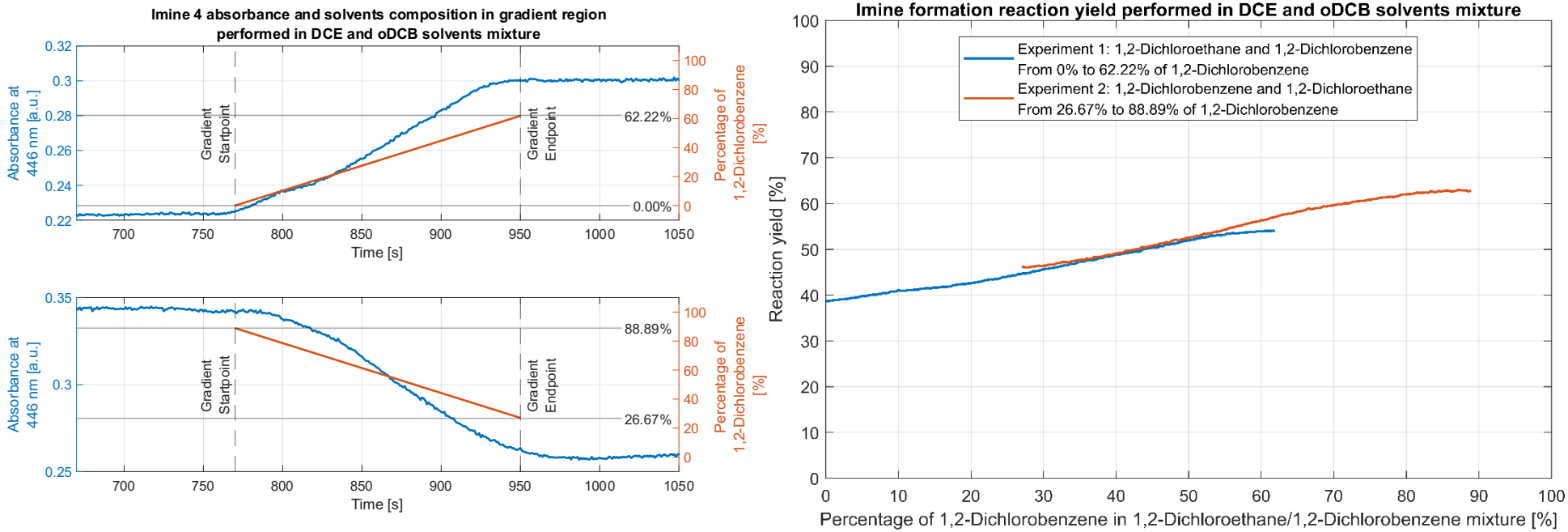



*Figure S 54. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/oDCB mixtures as reaction medium.*

### 4. 4. 2. 13. DCE and triglyme solvents mixture:

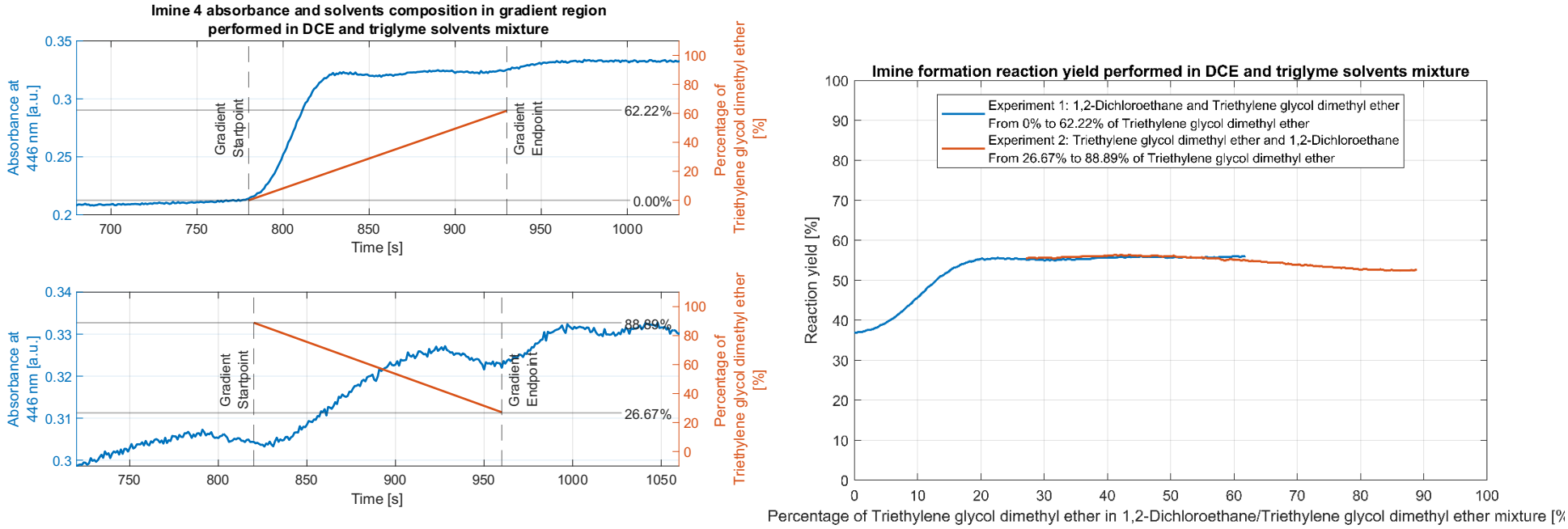



*Figure S 55. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/triglyme mixtures as reaction medium.*

## 4. 4. 2. 14. DCE and DMA solvents mixture:

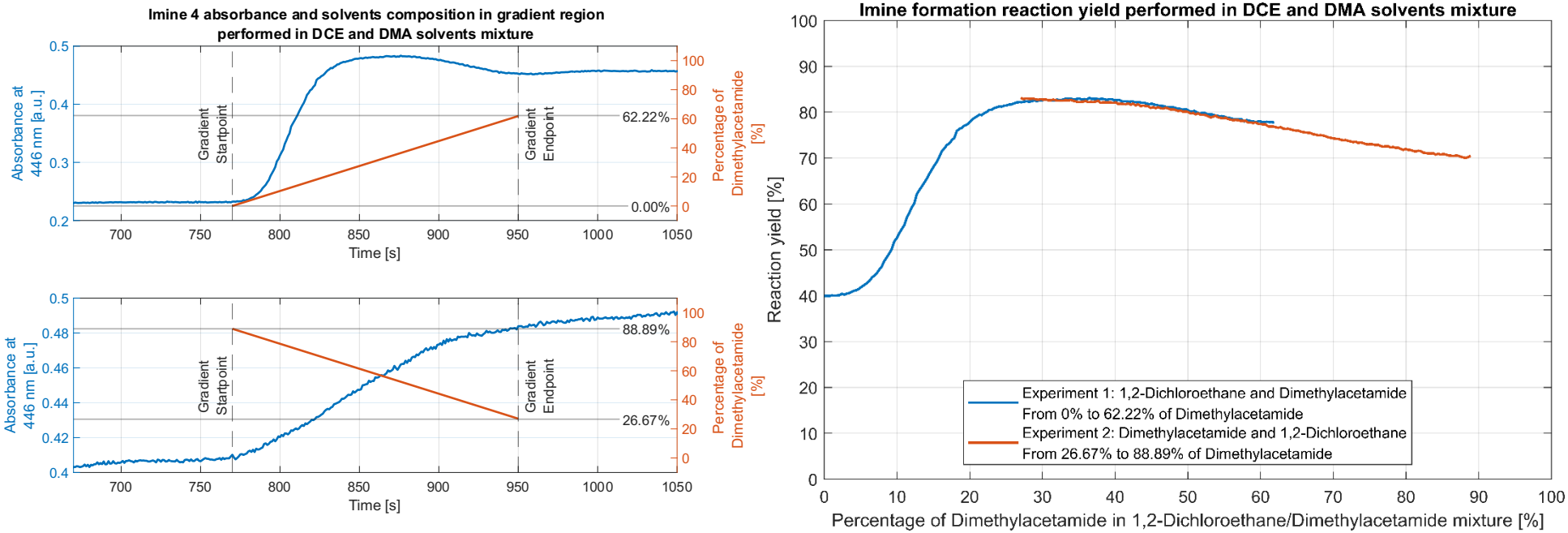



*Figure S 56. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/DMA mixtures as reaction medium.*

4. 4. 2. 15. Summary of all solvent mixtures of DCE with secondary solvent tested:

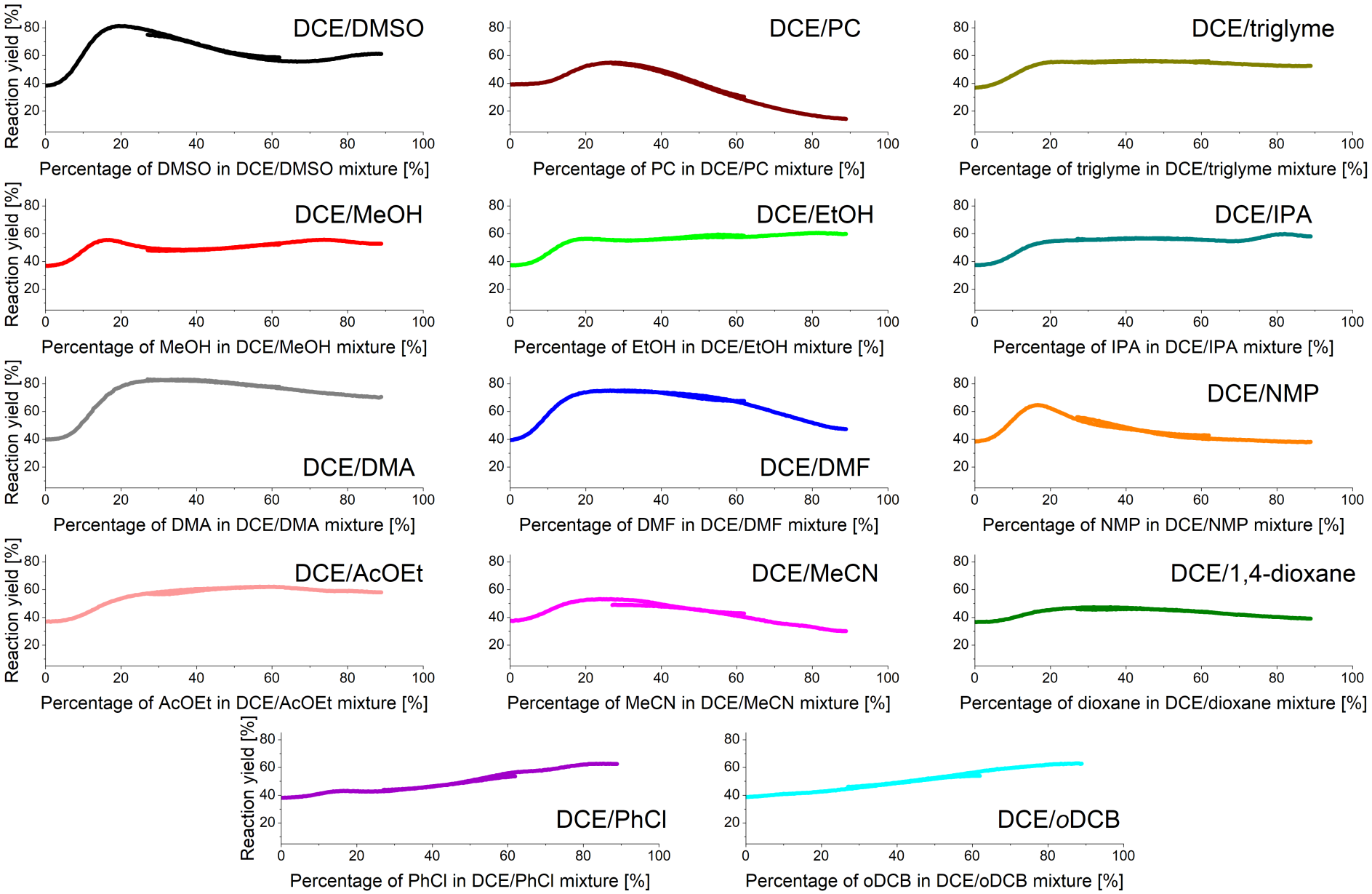
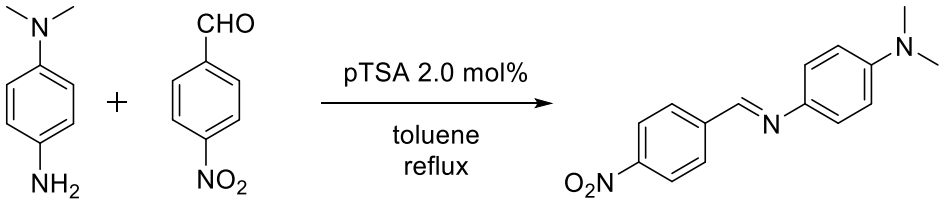



*Figure S 57. Results of flow solvents mixture studies in imine formation reaction using in situ generated solvents mixtures as reaction medium.*

## 4. 5. Synthesis of (E)-*N,N*-dimethyl-4-((4-nitrobenzylidene)amino)aniline




*Scheme S 2. Synthesis of imine from N,N-dimethylphenylene-1,4-diamine and 4-nitrobenzaldehyde.*

*N,N*-Dimethylphenylene-1,4-diamine (1.00 g, 7.34 mmol, 1.0 eq.) was dissolved in toluene (30.0 mL, 30.0 vol.). 4-Nitrobenzaldehyde (1.01 g, 6.68 mmol, 0.91 eq.) and *para*-toluenesulfonic acid (27.9 mg, 0.15 mmol, 0.02 eq.) were then added and the mixture was heated to reflux in a system equipped with Dean-Stark apparatus. After 4 hours, the mixture was cooled down to rt, toluene was removed, and obtained residue was washed with ice-cold *n*-hexane. Desired (E)-*N,N*-dimethyl-4-((4-nitrobenzylidene)amino)aniline was obtained as a shiny, dark burgundy solid (1.703 g, 86% yield). $^{1}$H NMR was in agreement with the literature.[5]

**Mp.** 221.3 – 222.1 °C, Lit. 224 °C.[5] **$^{1}$H NMR (400 MHz, $CDCl_3$) δ (ppm) =** 8.60 (s, 1H), 8.29 (m, 2H), 8.03 (m, 2H), 7.34 (m, 2H), 6.76 (m, 2H), 3.02 (s, 6H). **$^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm) =** 151.7, 150.5, 148.7, 142.8, 139.4, 128.8, 124.1, 123.1, 112.7, 40.7. **UV-Vis $\lambda_{max}$[nm] (ε[$M^{-1}cm^{-1}$]) Acetonitrile:** 279 (18217), 438 (17051); **Benzonitrile**: 460 (17180); **Benzyl alcohol:** 466 (14005); **Chlorobenzene:** 456 (16611); **Cyclohexanone:** 445 (16954)**;** ***ortho*-Dichlorobenzene:** 461 (16856); **1,2-Dichloroethane:** 281 (19174), 446 (17456); ***N,N*-Dimethylacetamide:** 283 (18219), 445 (17509); ***N,N*-Dimethylformamide:** 282 (18449), 443 (17539); **Dimethylsulfoxide:** 286 (18123), 455 (16665); **1,4-Dioxane**: 278 (20991), 435 (20592); **Ethanol**: 275 (20614), 438 (17940); **Ethyl acetate:** 277 (21738), 436 (20742); **Ethyl formate:** 277 (18721), 435 (18260); **Methanol:** 275 (20614), 435 (19051); ***N*-Methylpyrrolidinone:** 284 (17991), 453 (16990); **(-)-β-Pinene:** 440 (17738); ***iso*-Propanol:** 277 (19043), 448 (18498); **Propylene Carbonate:** 282 (17215), 450 (16606); **Tetrahydrofuran:** 443 (17504); **Triethylene glycol dimethyl ether:** 281 (18216), 443 (17454); **5% Water in DMSO v/v:** 460 (15161). **FT-ATR-IR ν ($cm^{-1}$) =** 2900, 2817, 1598, 1567, 1501, 1454, 1327, 1227, 1164, 1122, 1096, 1062, 1035, 1011, 938, 850, 819.8, 751, 724, 687, 641, 569, 537. **LRMS (EI) m/z =** 269.2 ($M^{+\cdot}$), 254.2 ($M^{+\cdot}$ - $CH_3$), 239.2 ($M^{+\cdot}$ - $C_2H_6$), 223.2 ($M^{+\cdot}$ – $NO_2$), 208.2, 195.2, 180.2, 167.2, 152.2, 145.2, 118.2, 111.2, 104.1, 89.9 ($C_7H_5^{+\cdot}$), 77.1 ($C_6H_5^{+\cdot}$), 63.1, 51.1 ($C_4H_3^{+\cdot}$), 42.2.

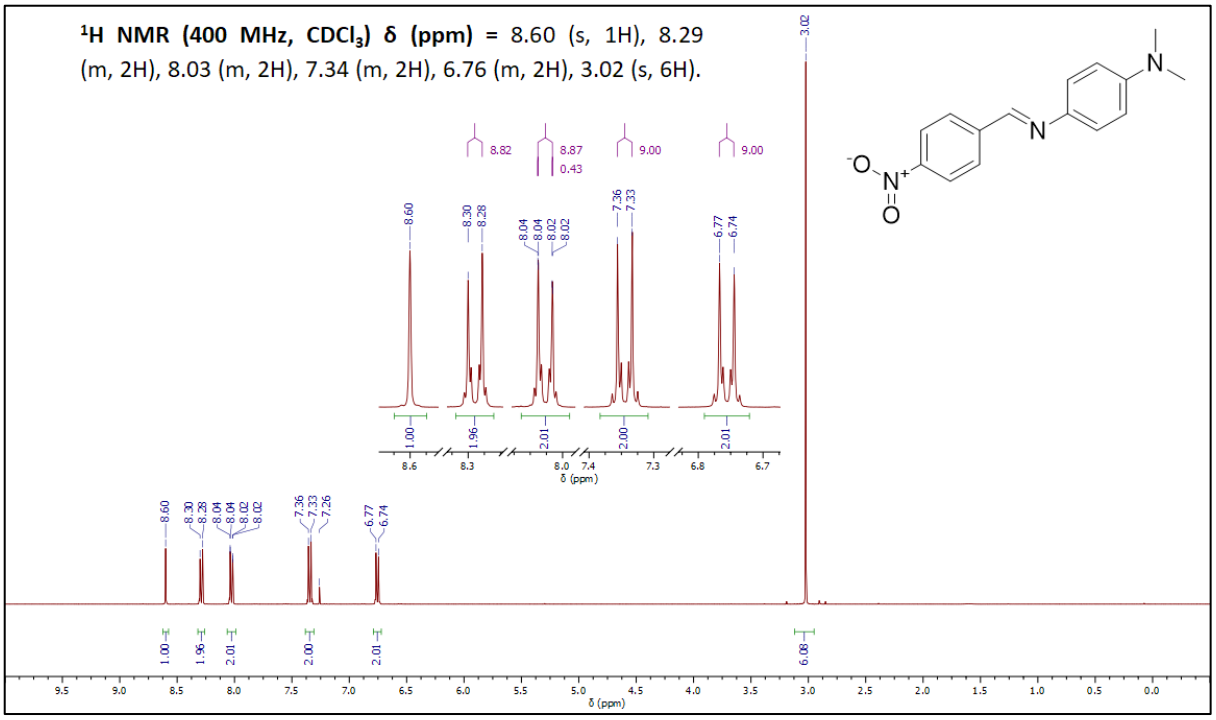



*Figure S 58. [1]H NMR spectrum of (E)-N,N-dimethyl-4-((4-nitrobenzylidene)amino)aniline.*

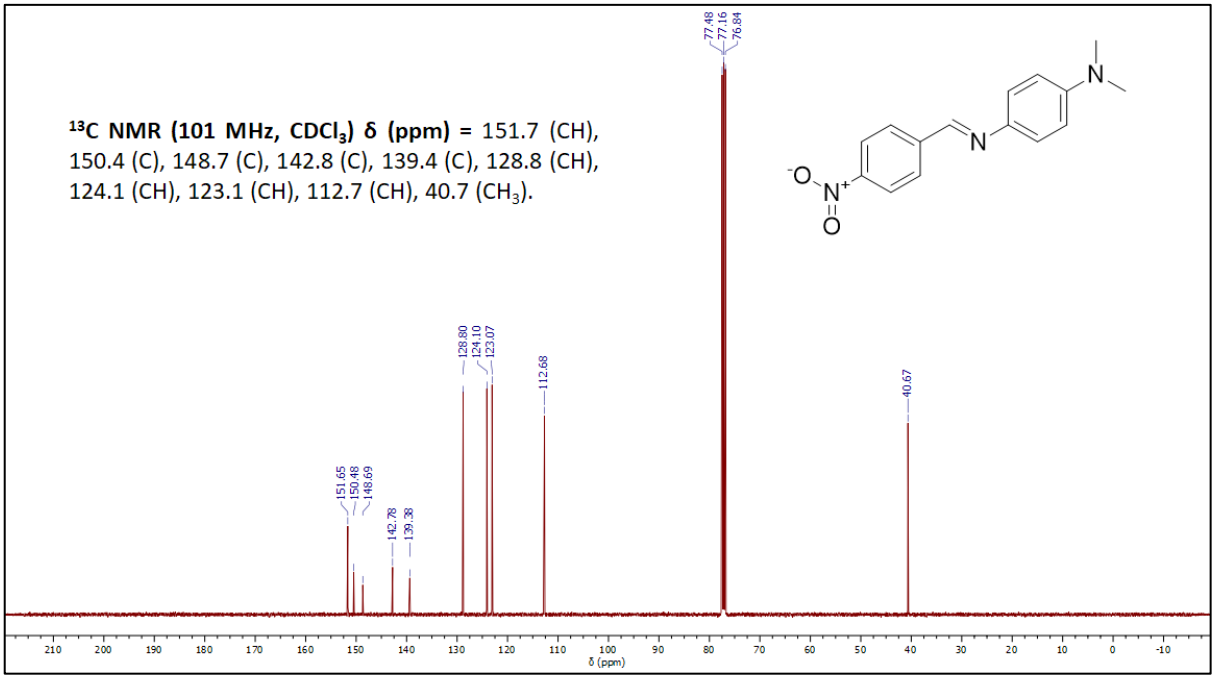



*Figure S 59. [13]C NMR spectrum of (E)-N,N-dimethyl-4-((4-nitrobenzylidene)amino)aniline.*

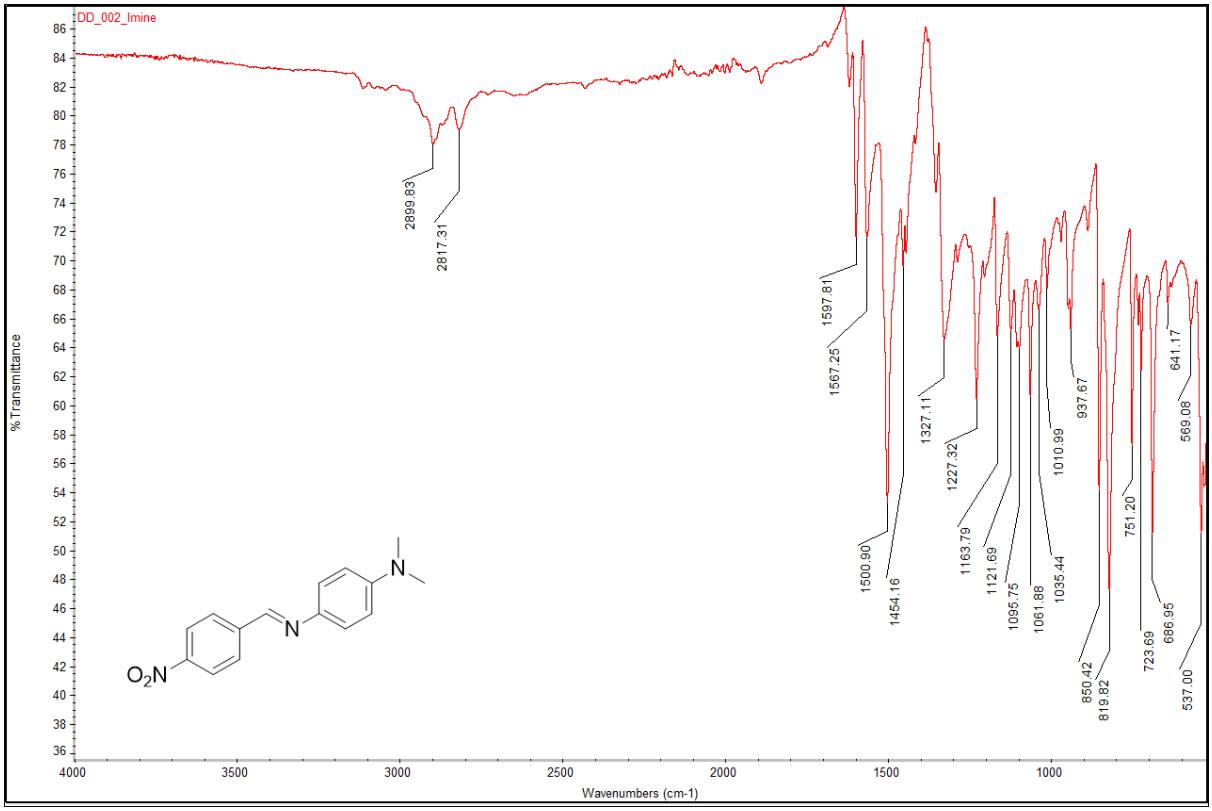



*Figure S 60. FT-ATR-IR spectrum of (E)-N,N-dimethyl-4-((4-nitrobenzylidene)amino)aniline.*

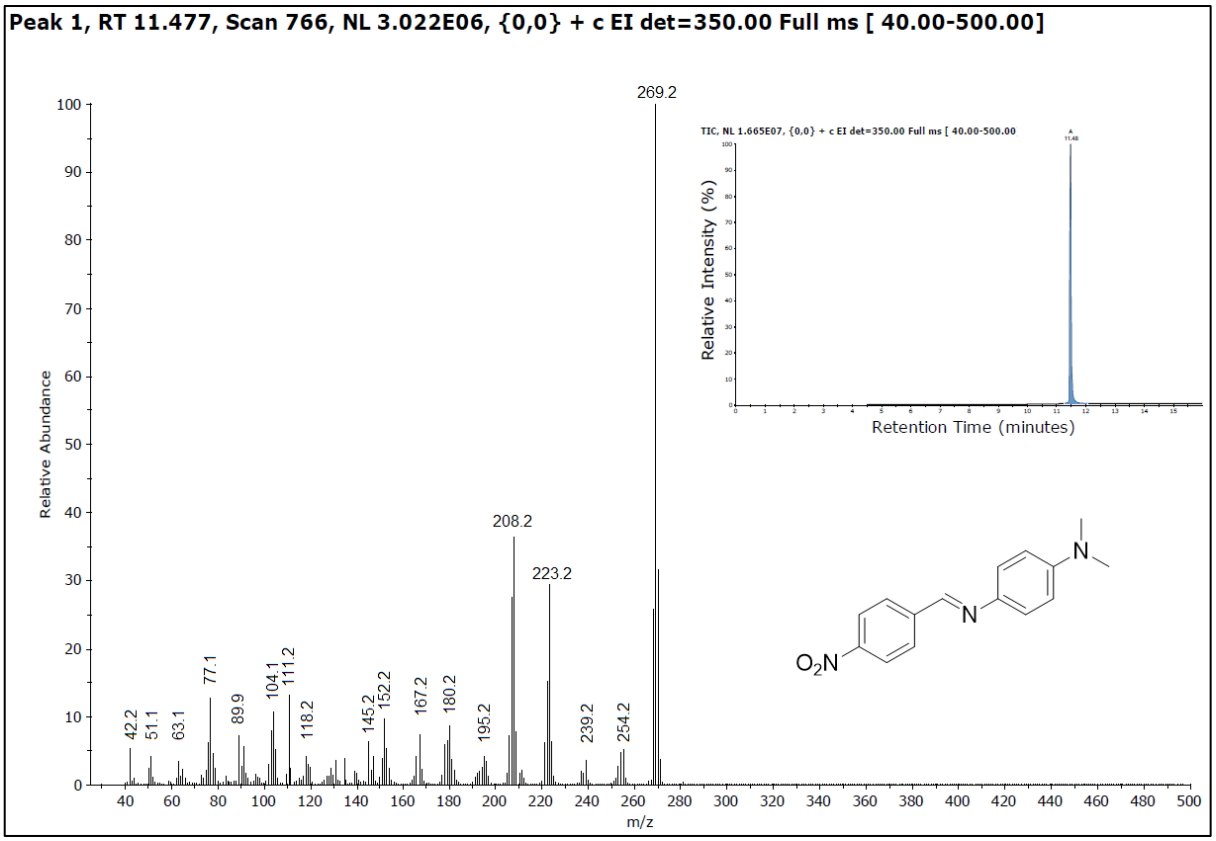



*Figure S 61. Electron ionisation mass spectrum of (E)-N,N-dimethyl-4-((4-nitrobenzylidene)amino)aniline.*

## 4. 6. Validation of Solvent Studies in imine formation reaction by performing steady state reactions in flow

Validation of results obtained from the flow studies of solvent effects in imine formation reaction was performed in a series of steady state flow experiments in which pre-mixed solvents mixtures were used for reagents dissolution and solvents mixture delivery, as described below. Validation was performed using the same flow system that was used for solvents mixtures studies experiments.

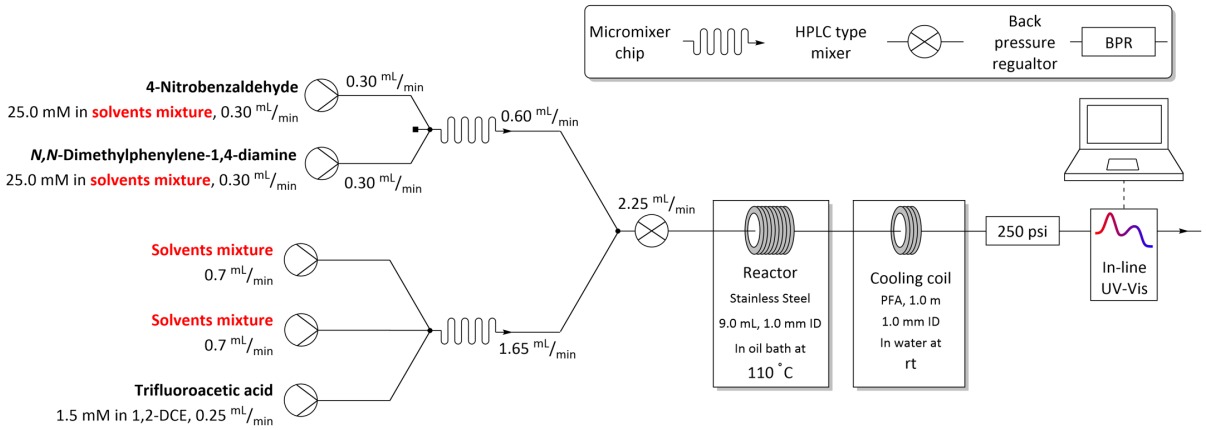



*Figure S 62. Flow setup used for validation solvents mixtures studies in imine formation reaction.*

A 25.0 mM solution of 4-nitrobenzaldehyde (75.6 mg, 0.5 mmol, 1.0 eq. in 20.0 mL (293.7 vol.) of indicated solvents mixture) was connected to the first flow reagent line. A 25.0 mM solution of *N,N*-dimethylphenylene-1,4-diamine (68.1 mg, 0.5 mmol, 1.0 eq. in 20.0 mL (293.7 vol.) of indicated solvents mixture) was connected to the second flow reagent line. Indicated solvents mixture was connected to the first, second, third, and fourth flow solvents lines. A 1.5 mM solution of trifluoroacetic acid (42.8 mg, 0.38 mmol, 0.05 eq. in 250 mL (5841.1 vol.) of 1,2-dichloroethane) was connected to the fifth flow solvent line. Flow rates were set to 0.30, 0.30, 0.7, 0.7, and 0.25 mL·min$^{-1}$ for each pump respectively. First and second flow streams were directed to the first channel of dolomite mixer, third, fourth, and fifth flow streams were directed to the second channel of dolomite mixer, and then both mixer outlets were combined, directed to the HPLC mixer, and reactor (stainless steel, 9.0 mL, 1.0 mm I.D., 1.6 mm O.D., submersed in high-precision oil bath set to 110 °C). Flow stream was then directed via a cooling coil (PFA, 1.0 mm ID, 1.6 mm OD, submersed in water at rt) and BPR (250 psi) to the UV-Vis flow cell. Pumps were turned on, only reaction medium was injected for 60 seconds allowing for system equilibration, then first and second flow streams were switched to reagents line. After 33.33 minutes, first and second flow stream were switched back to solvents line. After fully eluting remining reaction mixture from the flow system, the pumps were turned off.

Collected reaction mixture was then worked up, depending on the reaction medium used:

- For 1,2-DCE/DMSO mixture, reaction was poured into water, extracted with DCM (4x), organic layers were combined, washed with water, and the solvent was removed. Obtained residue was washed with ice-cold hexane (3x) and then dried *in vacuo*.
- For 1,2-DCE/MeOH mixture, solvent was removed from collected reaction mixture and obtained residue was washed with ice-cold *n*-hexane (3x) and then dried *in vacuo*.

*Table S 8. Solvents mixtures used as pre-mixed reaction medium and results of validation of solvents mixtures studies in imine formation reaction.*

| Experiment number | Indicated pre-mixed solvents mixture | Percentage of secondary solvent after mixing of all components in used flow system [%] | *In situ* UV-Vis yield [%] | Isolated yield [%] |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Val_01 | 100% 1,2-DCE | 0 | 39.5 | 38.5 |
| Val_02 | 11.25% DMSO in 1,2-DCE | 10 | 73.7 | 71.5 |
| Val_03 | 22.50% DMSO in 1,2-DCE | 20 | 78.8 | 77.9 |
| Val_04 | 33.75% DMSO in 1,2-DCE | 30 | 71.2 | 71.5 |
| Val_05 | 45.00% DMSO in 1,2-DCE | 40 | 62.8 | 62.6 |
| Val_06 | 56.25% DMSO in 1,2-DCE | 50 | 58.4 | 57.8 |
| Val_07 | 67.50% DMSO in 1,2-DCE | 60 | 55.0 | 54.7 |
| Val_08 | 74.25% DMSO in 1,2-DCE | 66 | 51.1 | 52.3 |
| Val_09 | 78.75% DMSO in 1,2-DCE | 70 | 53.5 | 52.9 |
| Val_10 | 90.00% DMSO in 1,2-DCE | 80 | 54.5 | 55.3 |
| Val_11 | 100% DMSO | 89 | 60.2 | 59.6 |
| Val_12 | 5.63% MeOH in 1,2-DCE | 5 | 46.2 | 44.7 |
| Val_13 | 11.25% MeOH in 1,2-DCE | 10 | 48.6 | 48.1 |
| Val_14 | 18.23% MeOH in 1,2-DCE | 16.2 | 51.1 | 51.0 |
| Val_15 | 22.50% MeOH in 1,2-DCE | 20 | 49.7 | 49.8 |
| Val_16 | 33.75% MeOH in 1,2-DCE | 30 | 47.1 | 46.7 |
| Val_17 | 45.00% MeOH in 1,2-DCE | 40 | 47.3 | 48.1 |
| Val_18 | 56.25% MeOH in 1,2-DCE | 50 | 51.1 | 50.8 |
| Val_19 | 67.50% MeOH in 1,2-DCE | 60 | 52.7 | 51.9 |
| Val_20 | 78.75% MeOH in 1,2-DCE | 70 | 53.9 | 52.5 |
| Val_21 | 82.69% MeOH in 1,2-DCE | 73.5 | 55.0 | 54.4 |
| Val_22 | 90.00% MeOH in 1,2-DCE | 80 | 54.4 | 53.6 |
| Val_23 | 100% MeOH | 89 | 51.5 | 50.8 |

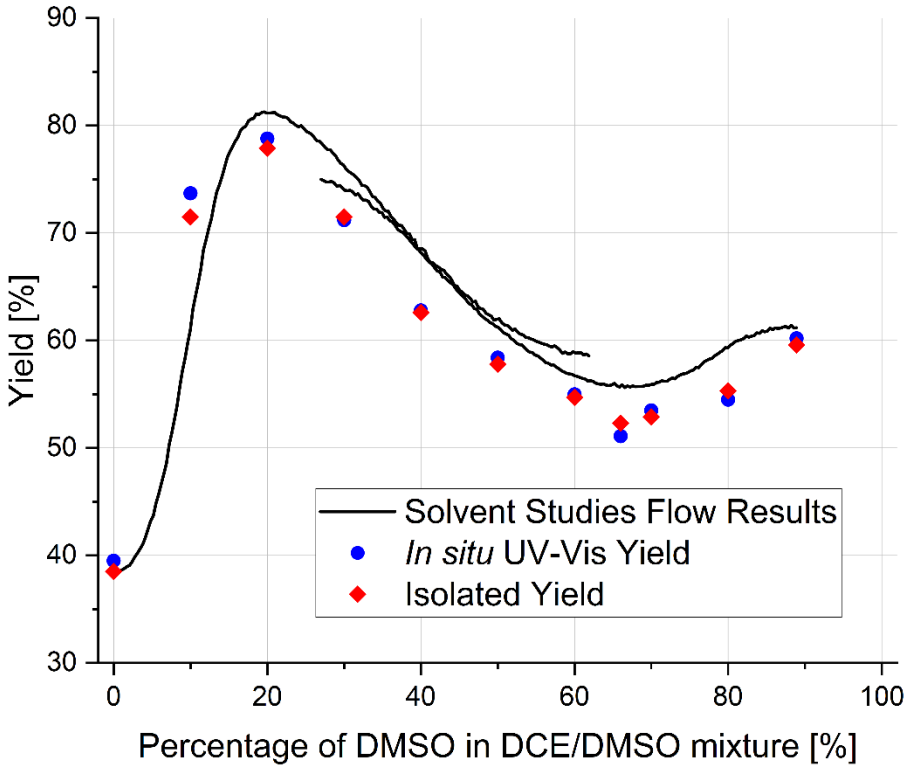



*Figure S 63. Comparison of experiments obtained from flow solvents mixtures studies (black line) with validation results (blue and red points) using 1,2-DCE/DMSO mixtures.*

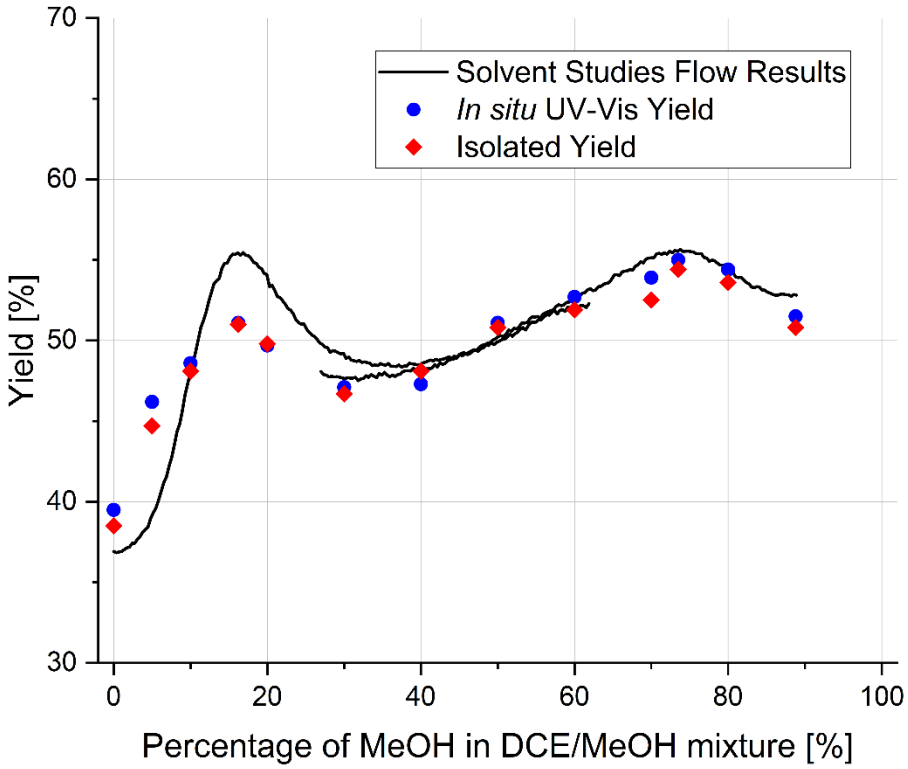



*Figure S 64. Comparison of experiments obtained from flow solvents mixtures studies (black line) with validation results (blue and red points) using 1,2-DCE/MeOH mixtures.*

# 5. Solvent effects studies in imine formation reaction using for screening of ternary solvents mixtures

## 5. 1. Flow setup and experiment design

Developed methodology for creation of solvents composition gradient was extended to ternary solvents mixtures. Flow setup in Figure S 65. was used for studies of ternary solvents mixtures. Two series of experiments were designed, first in which binary solvents mixtures were used for investigation of boundary regions of the ternary mixtures and second series used to investigate the inner region of the ternary mixture, in which constant amount of one solvent was introduced into the working reaction stream, while two other solvents composition was varied throughout the experiment, accordingly to the table below:

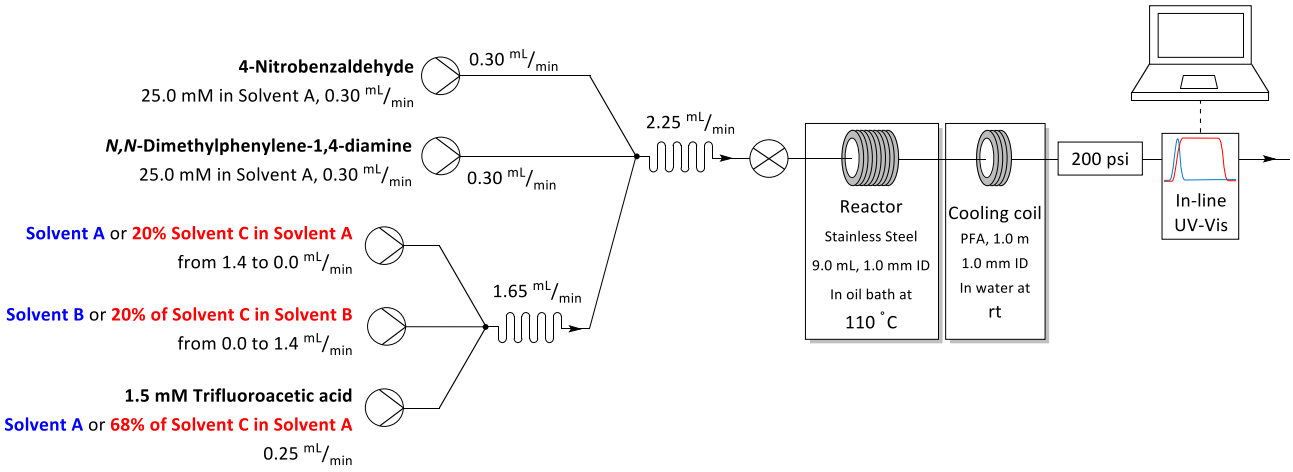



*Figure S 65.Flow setup used in studies of ternary solvents mixtures. Conditions in blue colours were used for studies of boundary region of ternary mixtures (first series of experiments) and conditions in red were used for studies of inner region of ternary mixture (second series of experiments).*

*Table S 9. Experiments performed in studies of solvent effects using ternary solvents mixtures of DCE/DMSO/MeOH and oDCB/DMF/AcOEt in imine formation reaction.*

| Experiment number | Ternary mixture of DCE/DMSO/MeOH | | | | | |
|---|---|---|---|---|---|---|
| | First series of experiments – boundary region of ternary mixture | | | | Range of screened mixture | |
| | Solvents system | | TFA in | | From | To |
| Ternary_A_01 | MeOH/DMSO | | MeOH | | 0% DMSO<br>100% MeOH | 62.2% DMSO<br>37.8% MeOH |
| Ternary_A_02 | DMSO/MeOH | | MeOH | | 88.9% DMSO<br>11.1% MeOH | 26.7% DMSO<br>73.3% MeOH |
| Ternary_A_03 | DCE/MeOH | | DCE | | 0% MeOH<br>100% DCE | 62.2% MeOH<br>37.8% DCE |
| Ternary_A_04 | MeOH/DCE | | MeOH | | 100% MeOH<br>0% DCE | 37.8% MeOH<br>62.2% DCE |
| Ternary_A_05 | DCE/DMSO | | DCE | | 0% DMSO<br>100% DCE | 62.2% DMSO<br>37.8% DCE |
| Ternary_A_06 | DMSO/DCE | | DCE | | 88.9% DMSO<br>11.1% DCE | 26.7% DMSO<br>73.3% DCE |
| | Second series of experiments – inner region of ternary mixture | | | | Range of screened mixture | |
| | Solvents system | Varied solvents | Constant solvent [%] | TFA in | From | To |
| Ternary_A_07 | DCE/DMF/MeOH | DCE/MeOH | 20% DMSO | 68% DMSO in DCE | 80% DCE<br>20% DMSO<br>0% MeOH | 30.2% DCE<br>20% DMSO<br>49.8% MeOH |
| Ternary_A_08 | | MeOH/DCE | 20% DMSO | 68% DMSO in MeOH | 0% DCE<br>20% DMSO<br>80% MeOH | 49.8% DCE<br>20% DMSO<br>30.2% MeOH |
| Ternary_A_09 | | MeOH/DMSO | 20% DCE | 68% DCE in MeOH | 20% DCE<br>0% DMSO<br>80% MeOH | 20% DCE<br>49.8% DMSO<br>30.2% MeOH |
| Ternary_A_10 | | DMSO/MeOH | 20% DCE | 68% DCE in DMSO | 20% DCE<br>80% DMSO<br>0% MeOH | 20% DCE<br>30.2% DMSO<br>49.8% MeOH |
| Ternary_A_11 | | DCE/DMSO | 20% MeOH | 68% MeOH in DCE | 80% DCE<br>0% DMSO<br>20% MeOH | 30.2% DCE<br>49.8% DMSO<br>20% MeOH |
| Ternary_A_12 | | DMSO/DCE | 20% MeOH | 68% MeOH in DMSO | 0% DCE<br>80% DMSO<br>20% MEOH | 49.8% DCE<br>30.2% DMSO<br>20% MeOH |

| | Ternary mixture of *o*DCB/DMF/AcOEt | | | | | |
|---|---|---|---|---|---|---|
| | First series of experiments – boundary region of ternary mixture | | | | Range of screened mixture | |
| | Solvents system | | TFA in | | From | To |
| Ternary_B_01 | AcOEt/DMF | | AcOEt | | 0% DMF<br>100% AcOEt | 62.2% DMF<br>37.8% AcOEt |
| Ternary_B_02 | DMF/AcOEt | | AcOEt | | 88.9% DMF<br>11.1% AcOEt | 26.7% DMF<br>73.3% AcOEt |
| Ternary_B_03 | oDCB/DMF | | oDCB | | 0% DMF<br>100% *o*DCB | 62.2% DMF<br>37.8% *o*DCB |
| Ternary_B_04 | DMF/oDCB | | oDCB | | 88.9% DMF<br>11.1% *o*DCB | 26.7% DMF<br>73.3% *o*DCB |
| Ternary_B_05 | oDCB/AcOEt | | oDCB | | 0% AcOEt<br>100% *o*DCB | 62.2% AcOEt<br>37.8% *o*DCB |
| Ternary_B_06 | AcOEt/oDCB | | AcOEt | | 100% AcOEt<br>0% *o*DCB | 37.8% AcOEt<br>62.2% *o*DCB |
| | Second series of experiments – inner region of ternary mixture | | | | Range of screened mixture | |
| | Solvents system | Varied solvents | Constant solvent [%] | TFA in | From | To |
| Ternary_B_07 | *o*DCB/DMF/AcOEt | AcOEt/DMF | 20% *o*DCB | 68% *o*DCB in AcOEt | 20% *o*DCB<br>80% AcOEt<br>0% DMF | 20% *o*DCB<br>30.2% AcOEt<br>49.8% DMF |
| Ternary_B_08 | | DMF/AcOEt | 20% *o*DCB | 68% *o*DCB in DMF | 20% *o*DCB<br>0% AcOEt<br>80% DMF | 20% *o*DCB<br>49.8% AcOEt<br>30.2% DMF |
| Ternary_B_09 | | *o*DCB/AcOEt | 20% DMF | 68% DMF in *o*DCB | 80% *o*DCB<br>0% AcOEt<br>20% DMF | 30.2% *o*DCB<br>49.8% AcOEt<br>20% DMF |
| Ternary_B_10 | | AcOEt/*o*DCB | 20% DMF | 68% DMF in AcOEt | 0% *o*DCB<br>80% AcOEt<br>20% DMF | 49.8% *o*DCB<br>30.2% AcOEt<br>20% DMF |
| Ternary_B_11 | | *o*DCB/DMF | 20% AcOEt | 68% AcOEt in *o*DCB | 80% *o*DCB<br>20% AcOEt<br>00% DMF | 30.2% *o*DCB<br>20% AcOEt<br>49.80% DMF |
| Ternary_B_12 | | DMF/*o*DCB | 20% AcOEt | 68% AcOEt in DMF | 0% *o*DCB<br>20% AcOEt<br>80% DMF | 49.80% *o*DCB<br>20% AcOEt<br>30.2% DMF |

Overall datapoints distribution from experiments performed accordingly to the table above, can be presented as in Figure S 66. Distribution of datapoints in used methodology for studies ternary solvents mixtures. For visual clarity, only 25% of the datapoints is displayed.:

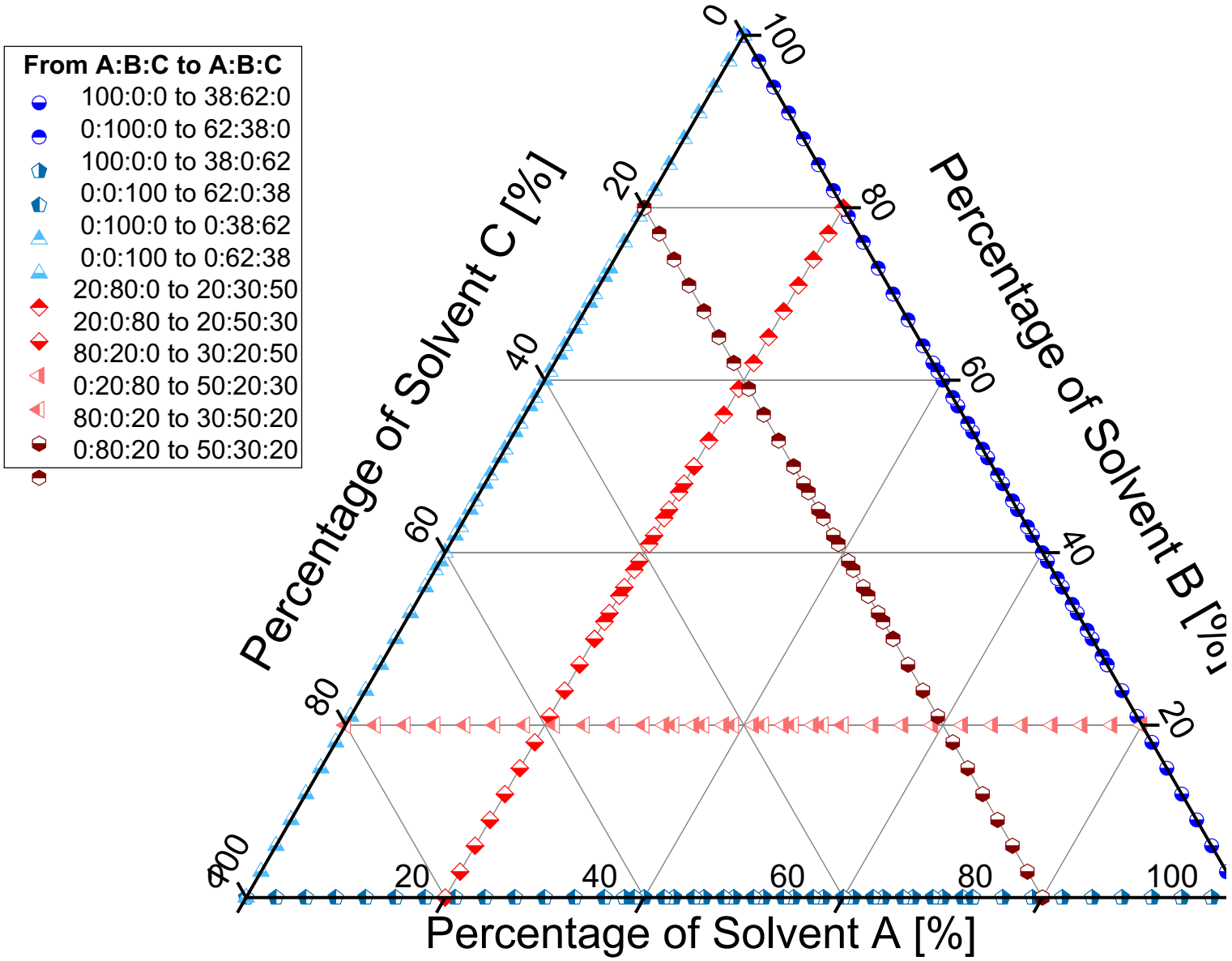



*Figure S 66. Distribution of datapoints in used methodology for studies ternary solvents mixtures. For visual clarity, only 25% of the datapoints is displayed.*

As mentioned in the article, the TFA can react with some solvents (such as DMSO or DMF), thus for the first series of experiments it was always dissolved in non-reactive solvent, in this case DCE, MeOH, *o*DCB, or AcOEt. In second series of experiments the TFA was dissolved in a mixture of two solvents, however we found that even when DMSO or DMF were the main component of the mixture (e.g. 68% DMSO in DCE), the experimental results were still overlapping in the common region of two performed experiments, thus no flow setup correction was needed in this case.

Analysis of the obtained results was performed in the same manner as for studies of binary mixtures, however the correction for molar extinction coefficient values for various solvents mixtures was still applied in the linear approximation, thus the MEC values in ternary mixtures were calculated as weighted average, accordingly to the equations below:

$$MEC^{ternary}_{DCE/DMSO/MeOH} = \frac{\%DCE \cdot MEC_{DCE} + \%DMSO \cdot MEC_{DMSO} + \%MeOH \cdot MEC_{MeOH}}{\%DCE + \%DMSO + \%MeOH}$$

or

$$MEC^{ternary}_{oDCB/DMF/AcOEt} = \frac{\%oDCB \cdot MEC_{oDCB} + \%DMF \cdot MEC_{DMF} + \%AcOEt \cdot MEC_{AcOEt}}{\%oDCB + \%DMF + \%AcOEt}$$

where: %X – percentage of solvent X in mixture
$MEC_X$ – molar extinction coefficient value in pure solvent X

## 5. 2. Results of solvent effects studies using ternary DCE/DMSO/MeOH mixture

### 5. 2. 1. Results of individual experiments for DCE/DMSO/MeOH mixture

Results of solvent effects in DCE/DMSO and DCE/MeOH mixtures are presented on Figure S 43. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/DMSO mixtures as reaction medium. and Figure S 45. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/MeOH mixtures as reaction medium., respectively.

#### 5. 2. 2. 1. MeOH and DMSO solvents mixture:

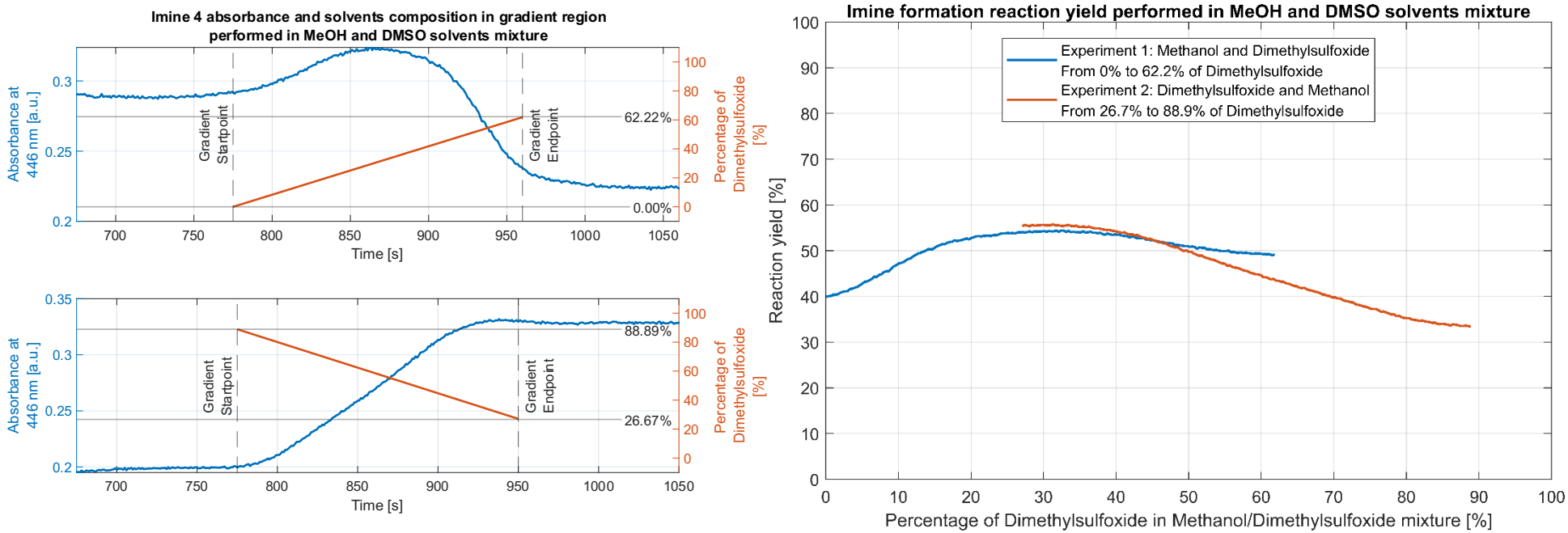



*Figure S 67. Results of flow solvents mixture studies in imine formation reaction using in situ generated MeOH/DMSO mixtures as reaction medium.*

### 5. 2. 2. 2. MeOH and DMSO mixture with constant 20% DCE:

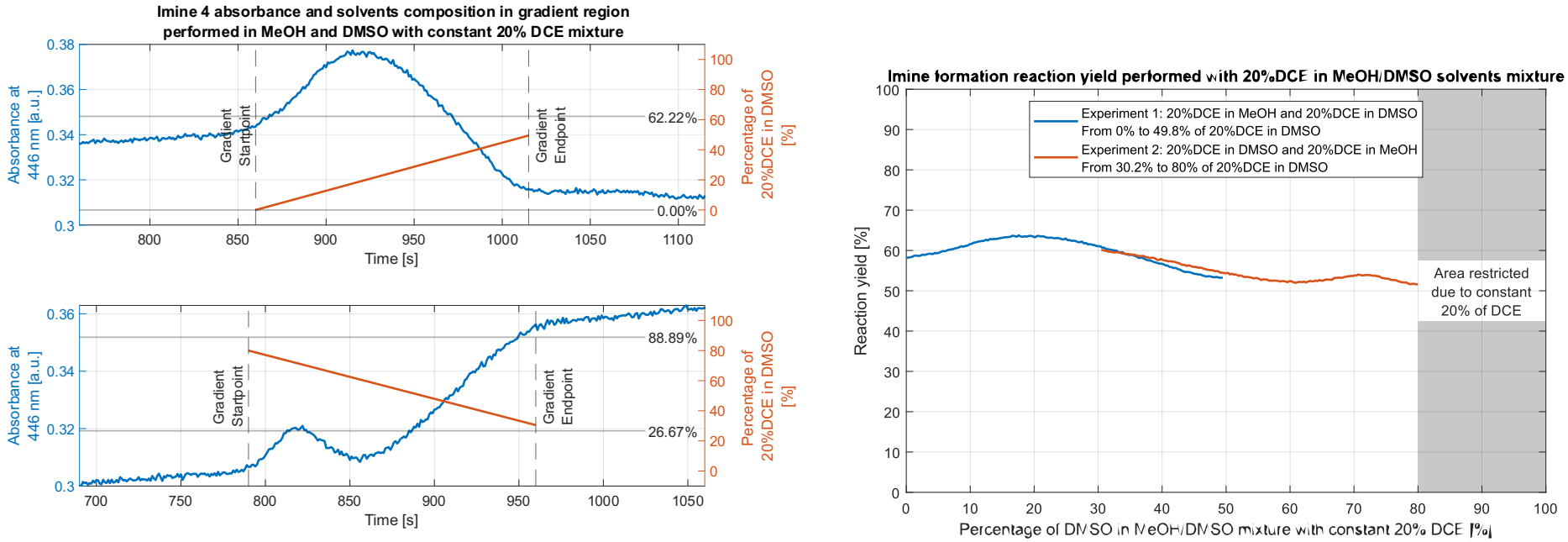



*Figure S 68. Results of flow solvents mixture studies in imine formation reaction using in situ generated MeOH/DMSO mixtures with constant 20% DCE as reaction medium.*

### 5. 2. 2. 3. DCE and MeOH mixture with constant 20% DMSO:

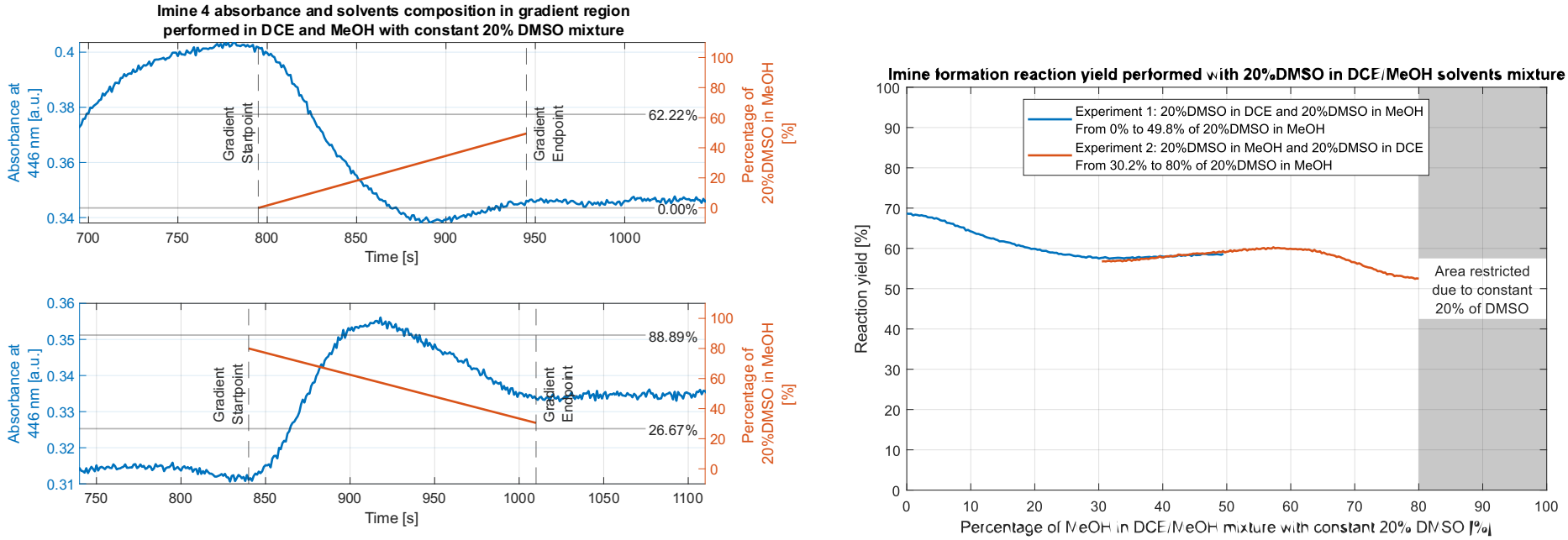



*Figure S 69. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/MeOH mixtures with constant 20% DMSO as reaction medium.*

### 5. 2. 2. 4. DCE and DMSO mixture with constant 20% MeOH:

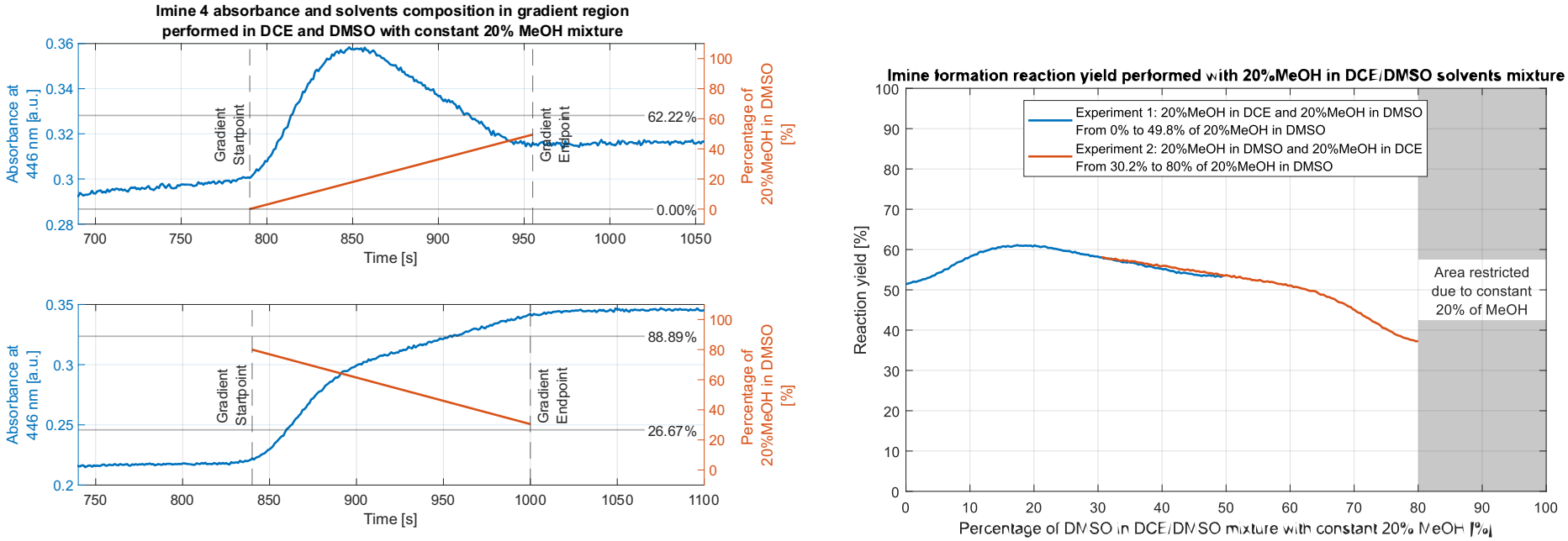



*Figure S 70. Results of flow solvents mixture studies in imine formation reaction using in situ generated DCE/DMSO mixtures with constant 20% MeOH as reaction medium.*

### 5. 2. 2. Ternary plot for DCE/DMSO/MeOH mixture

Obtained data was then combined and ternary plot was generated using Origin 2021b, following few steps:

- Delaunay triangulation – all datapoints are connected to create as equiangular triangle mesh as possible, with no two triangles to intersect.
- Linear interpolation – during which intersection points for contour lines are determined.
- Drawing of contour lines – by tracing of characteristic points on the triangular mesh.
- Smoothing (additionally) – can be applied to smooth the lines connecting the characteristic points.

For more details on the plotting procedure see Origin Help, section 8. 10. 2. Creating Contour Graphs [accessed on 29.06.2023].

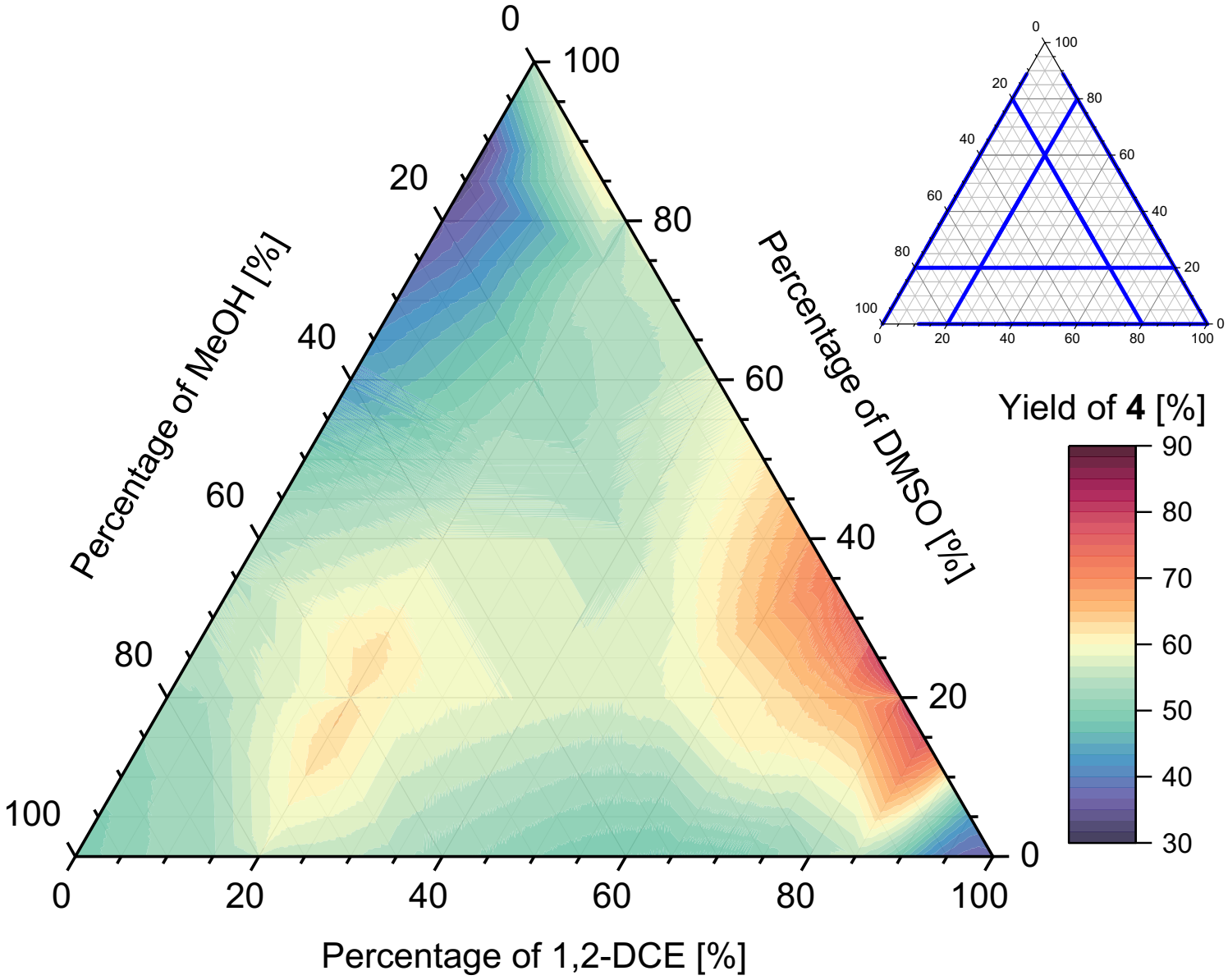



*Figure S 71. Ternary plot of imine **4** yield against composition of ternary DCE/DMSO/MeOH solvent system.*

## 5. 3. Results of solvent effects studies using ternary *o*DCB/DMF/AcOEt mixture

### 5. 3. 1. Results of individual experiments for *o*DCB/DMF/AcOEt mixture

#### 5. 3. 1. 1. AcOEt and DMF solvents mixture:

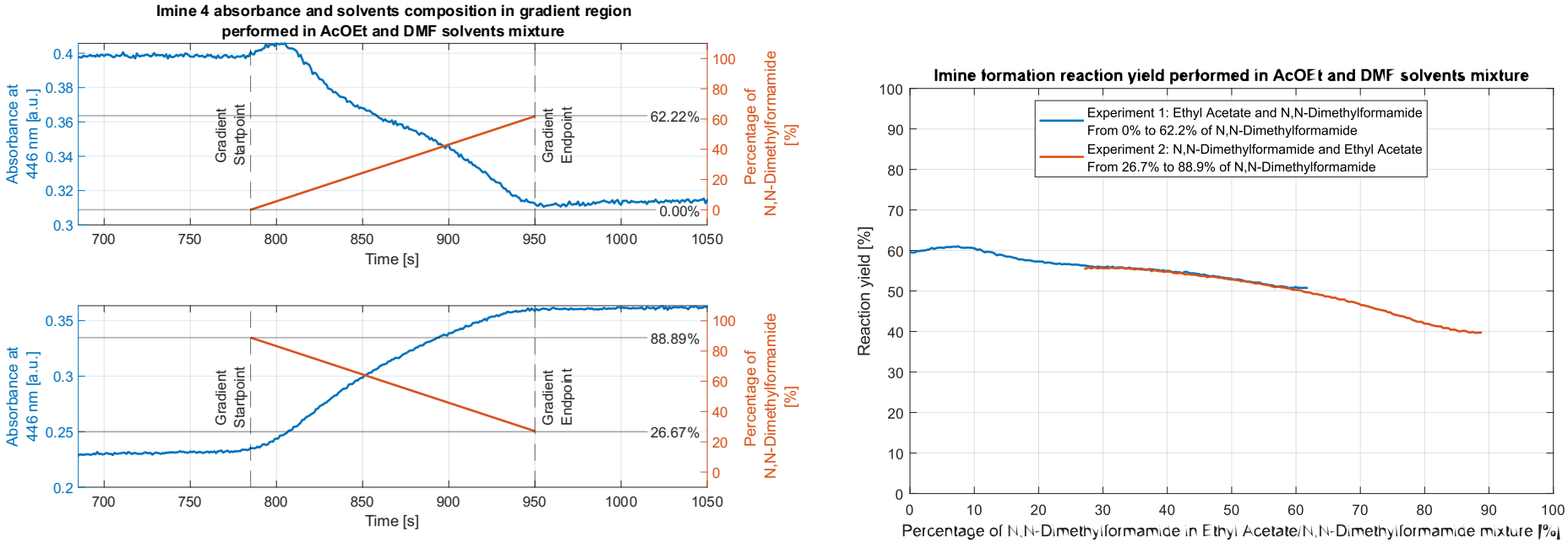



*Figure S 72. Results of flow solvents mixture studies in imine formation reaction using in situ generated AcOEt/DMF mixtures as reaction medium.*

### 5. 3. 1. 2. *o*DCB and AcOEt solvents mixture:

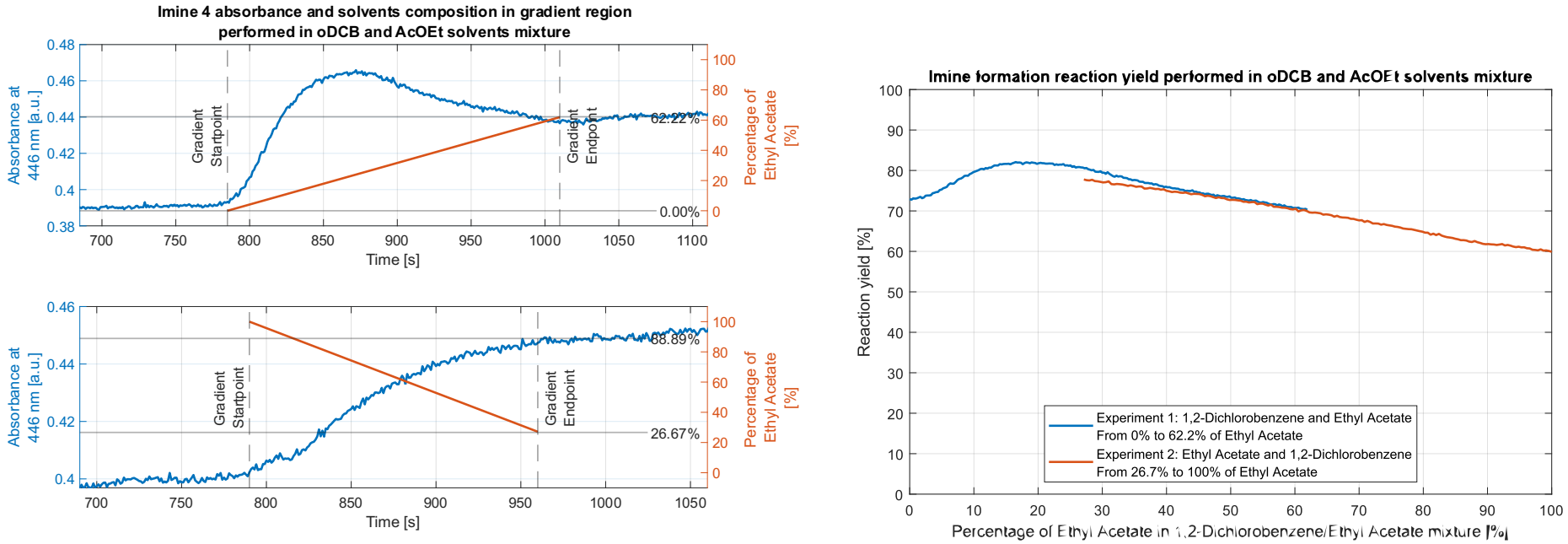



*Figure S 73. Results of flow solvents mixture studies in imine formation reaction using in situ generated oDCB/AcOEt mixtures as reaction medium.*

### 5. 3. 1. 3. *o*DCB and DMF solvents mixture:

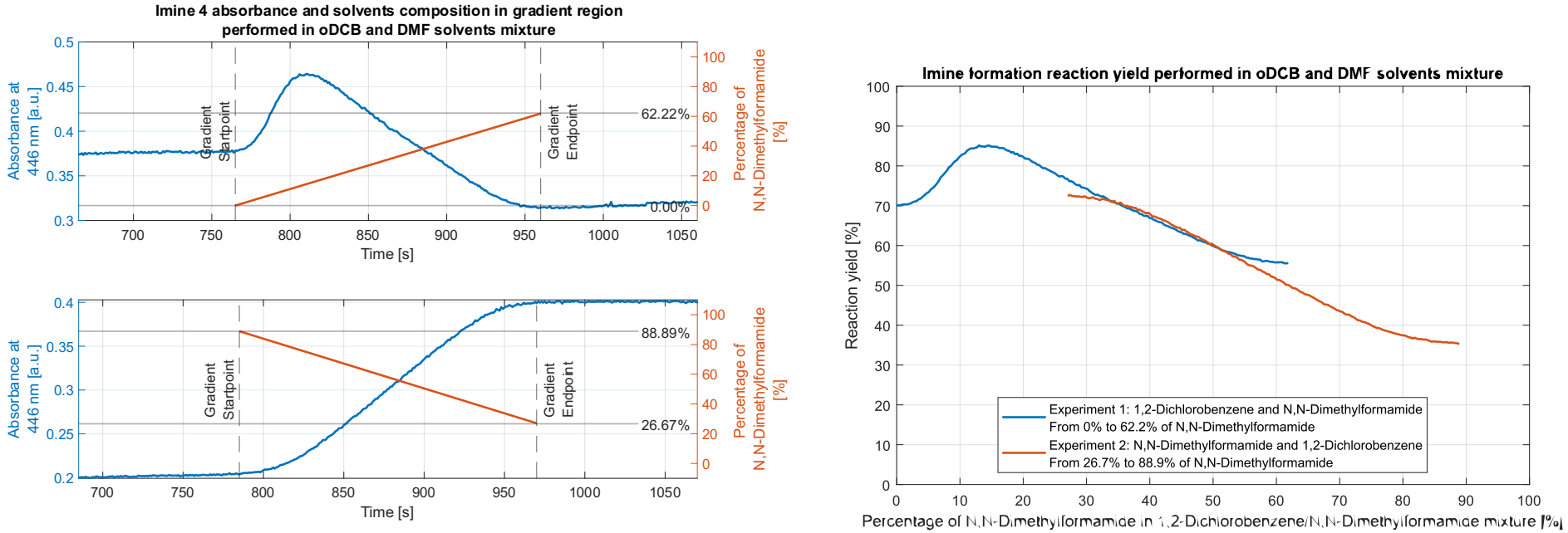



*Figure S 74. Results of flow solvents mixture studies in imine formation reaction using in situ generated oDCB/DMF mixtures as reaction medium.*

### 5. 3. 1. 4. *o*DCB and DMF mixture with constant 20% AcOEt:

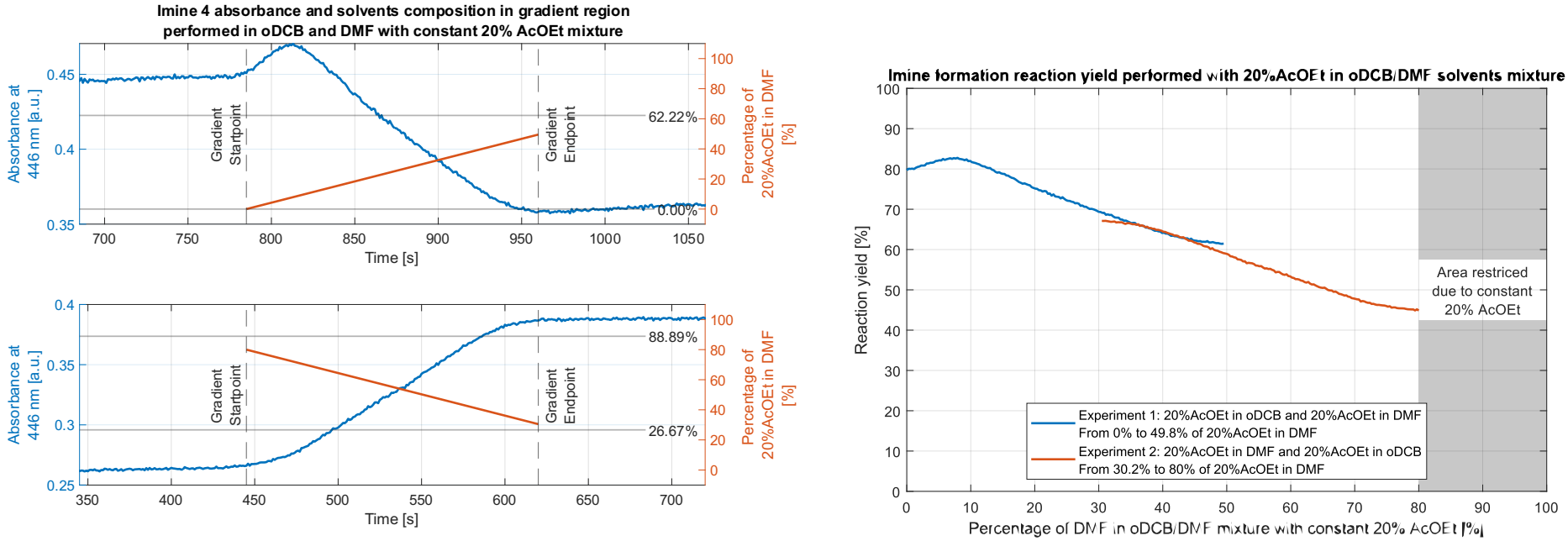



*Figure S 75. Results of flow solvents mixture studies in imine formation reaction using in situ generated oDCB/DMF mixtures with constant 20% AcOEt as reaction medium.*

### 5. 3. 1. 5. *o*DCB and AcOEt mixture with constant 20% DMF:

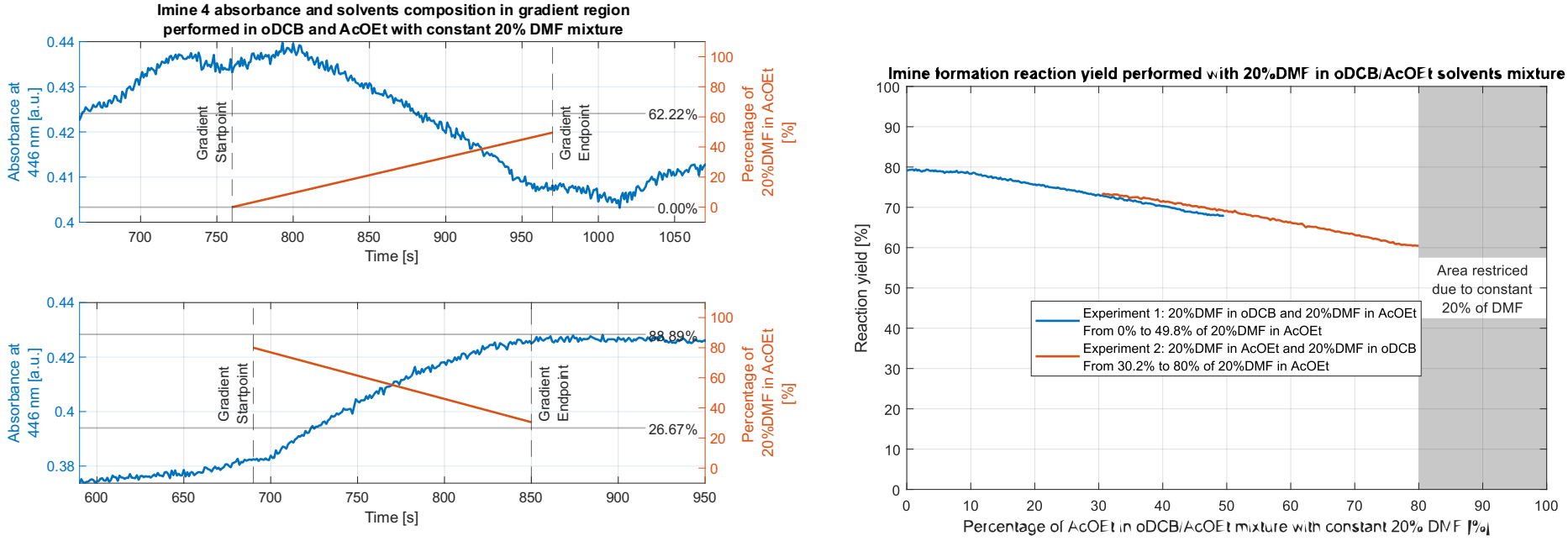



*Figure S 76. Results of flow solvents mixture studies in imine formation reaction using in situ generated oDCB/AcOEt mixtures with constant 20% DMF as reaction medium.*

### 5. 3. 1. 6. AcOEt and DMF mixture with constant 20% DCE:

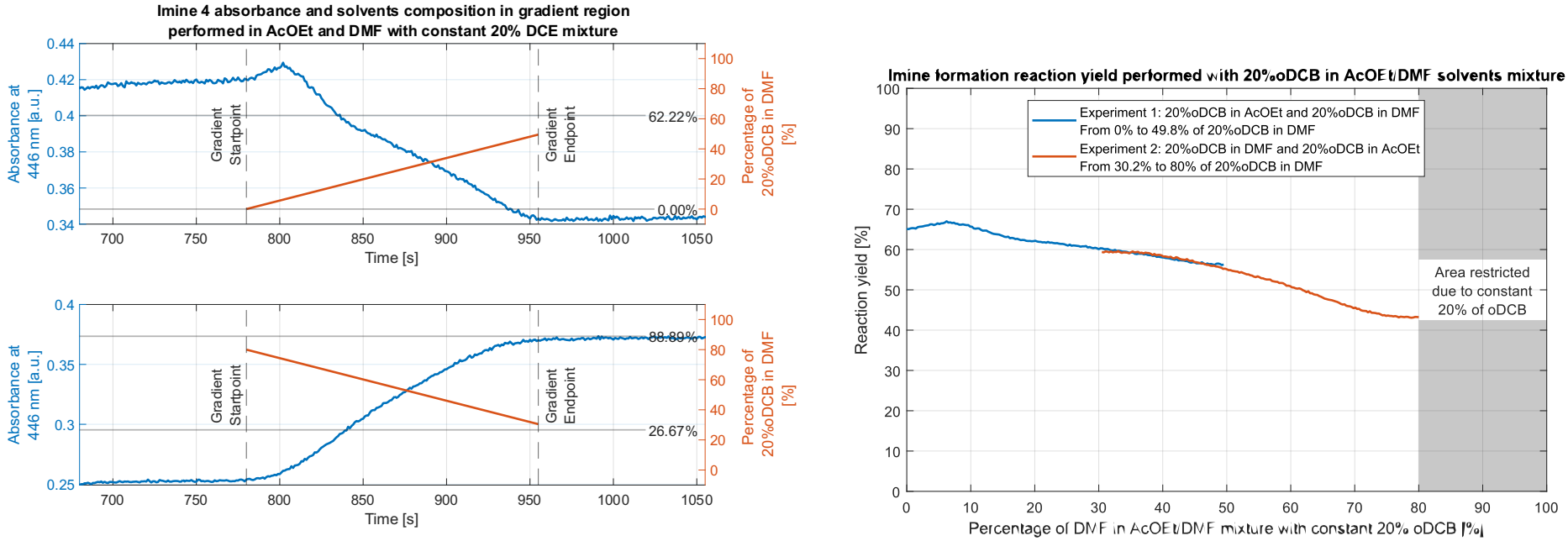



*Figure S 77. Results of flow solvents mixture studies in imine formation reaction using in situ generated AcOEt/DMF mixtures with constant 20% oDCB as reaction medium.*

### 5. 3. 2. Ternary plot for *o*DCB/DMF/AcOEt mixture

Obtained data was then combined and ternary plot was generated, as described in section 5. 2. 2. Ternary plot for DCE/DMSO/MeOH mixture of this document.

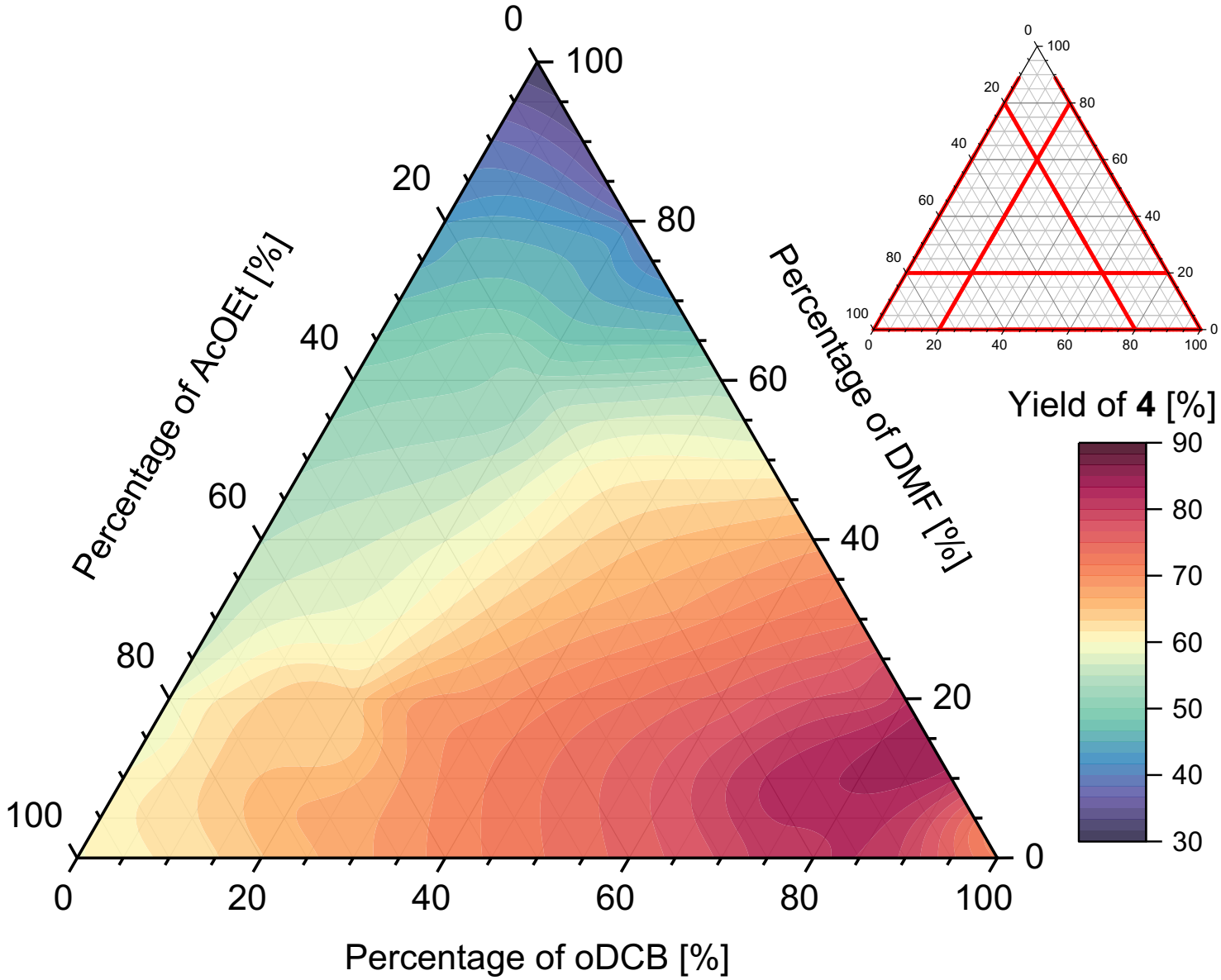



*Figure S 78. Ternary plot of imine **4** yield against composition of ternary oDCB/DMF/AcOEt solvent system.*

## 6. References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