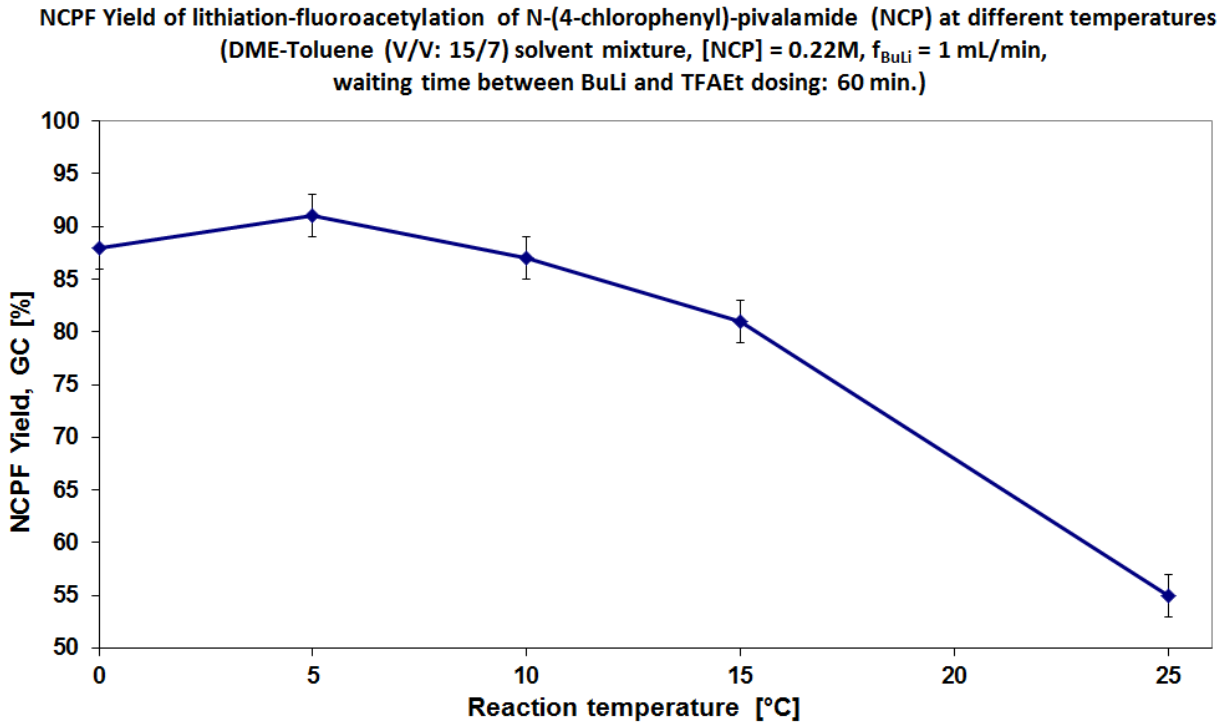
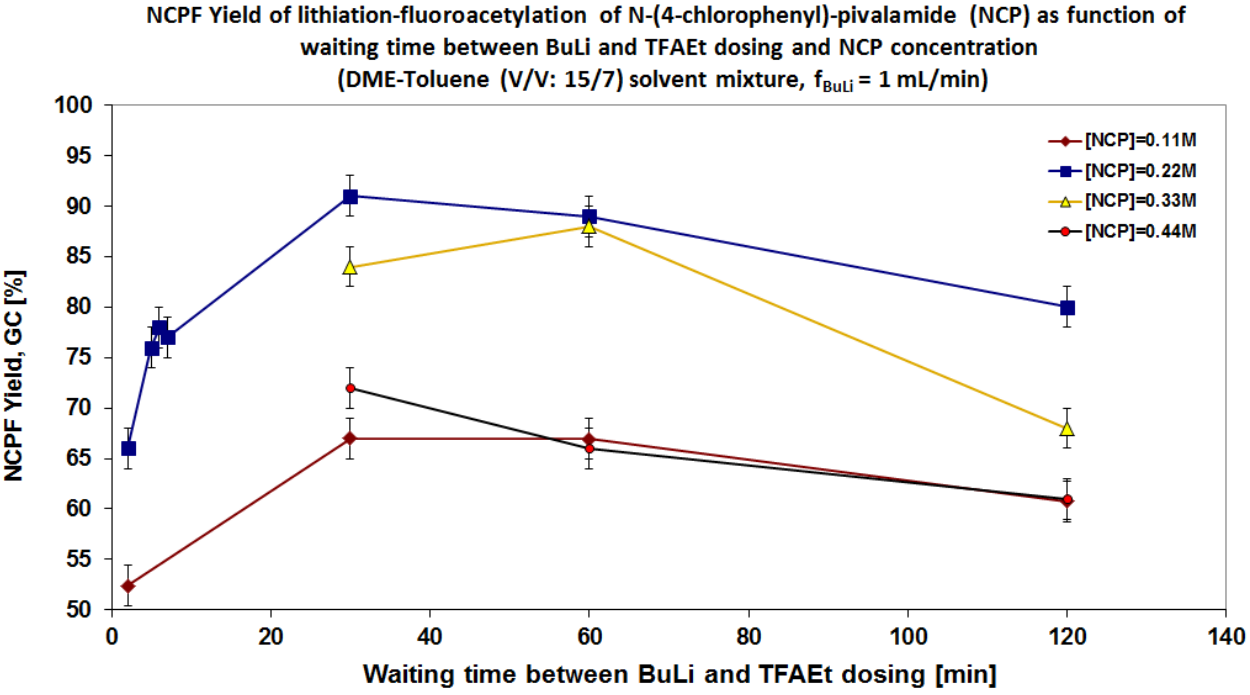
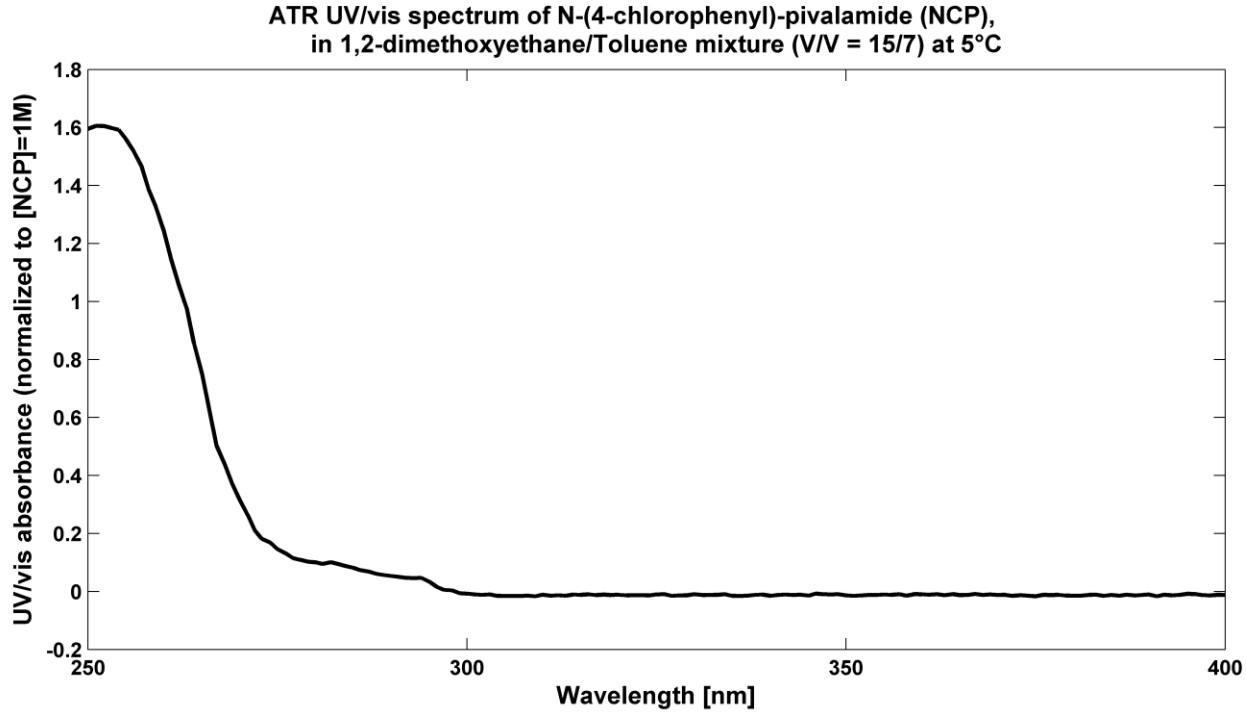
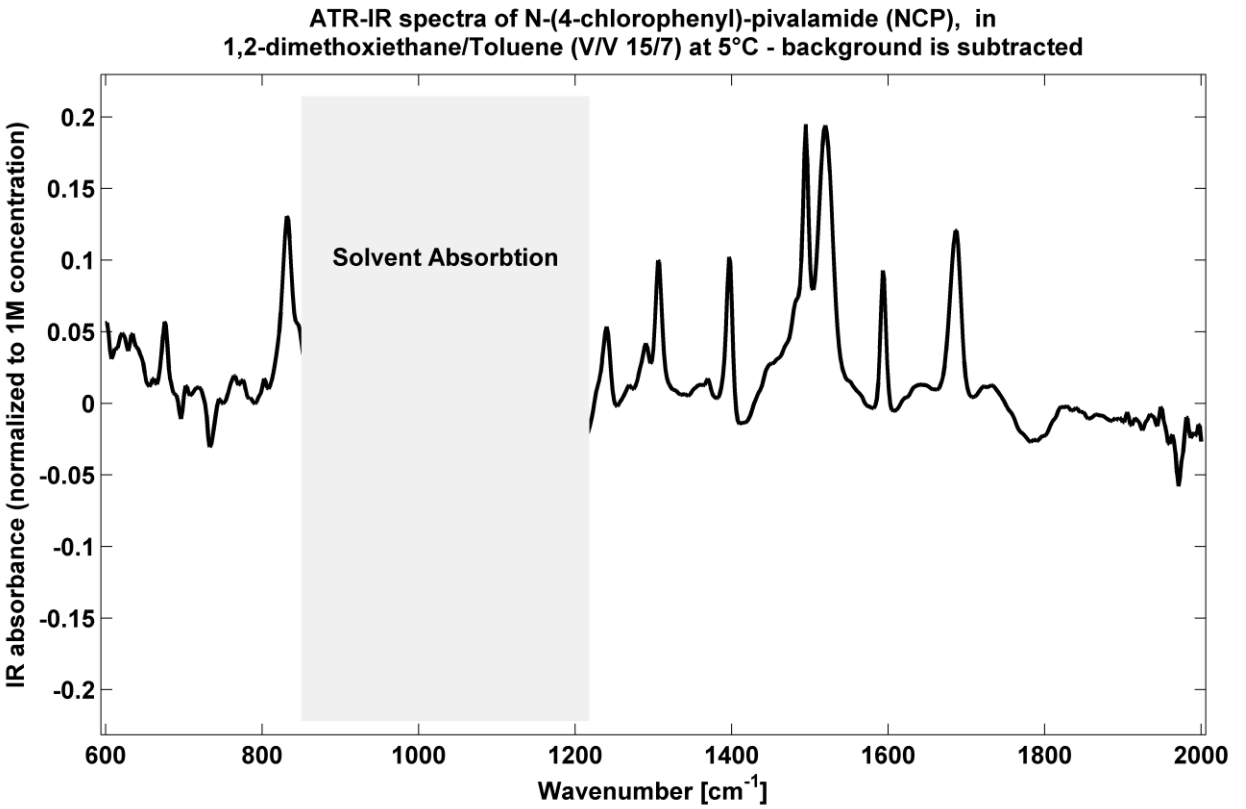
S.1 Optimization results

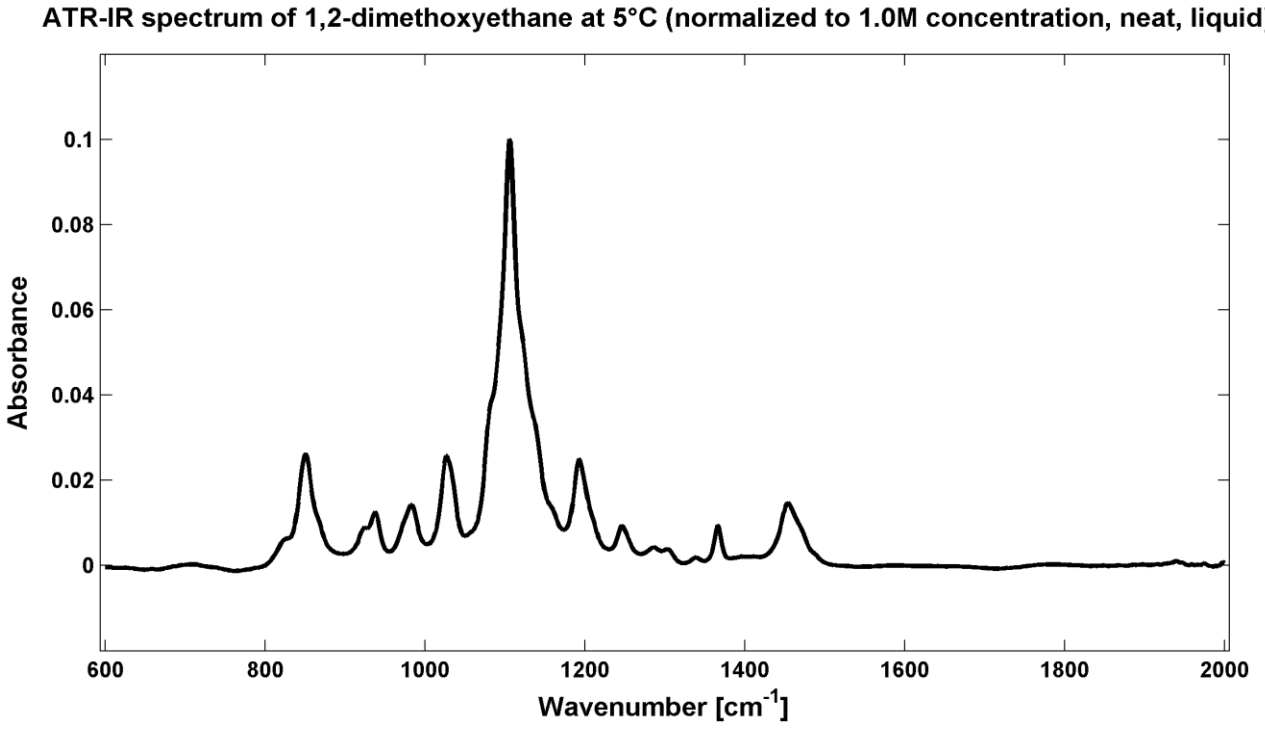


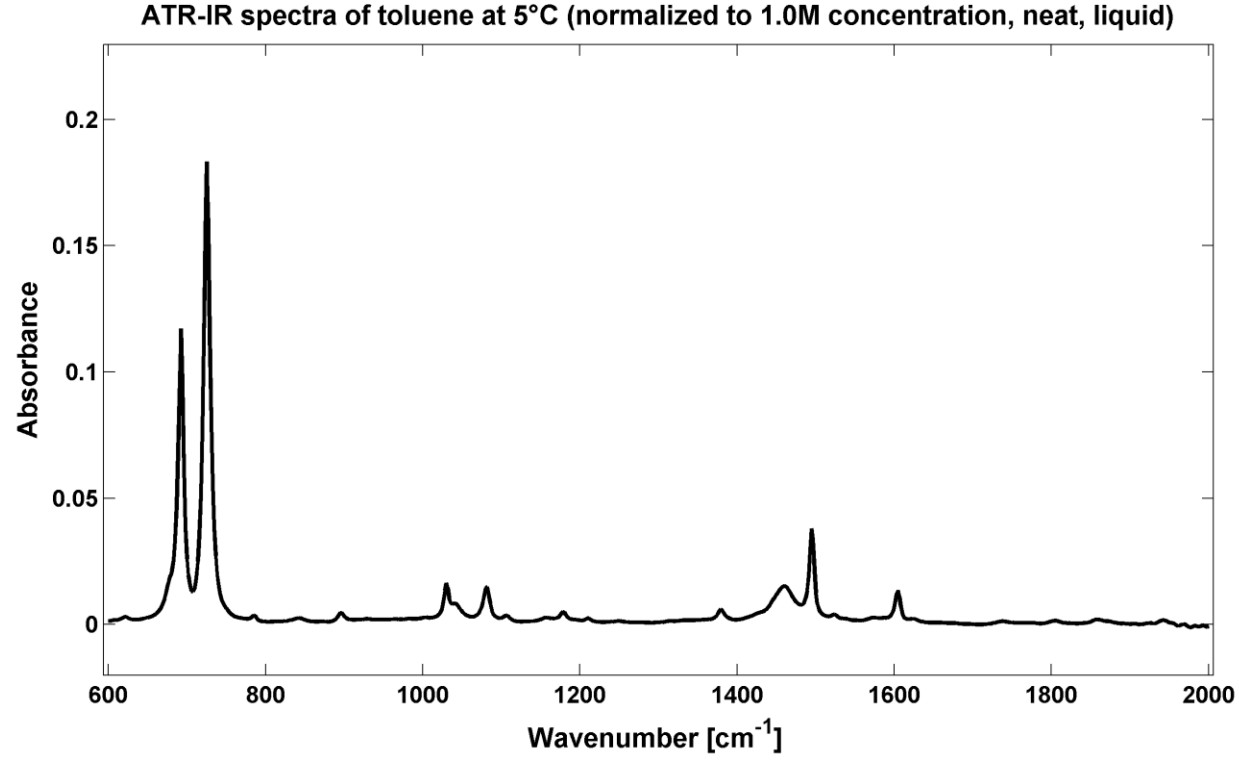


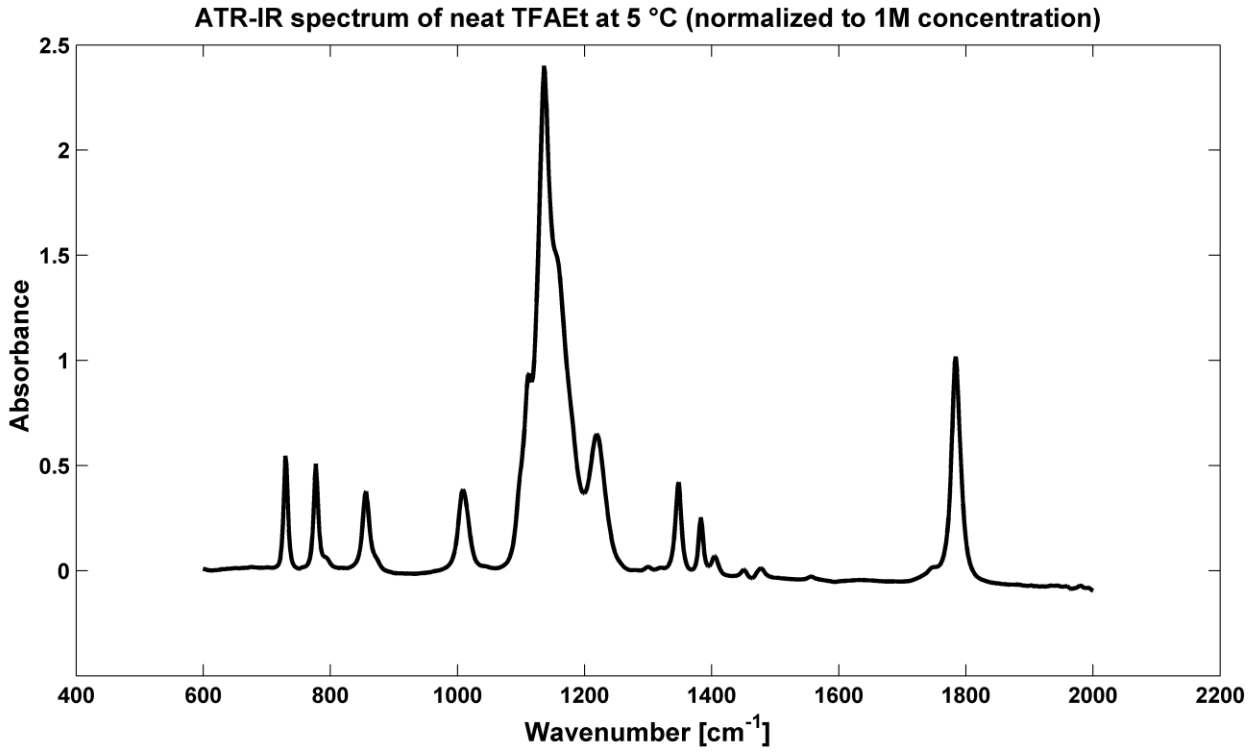
S.2: reference spectra



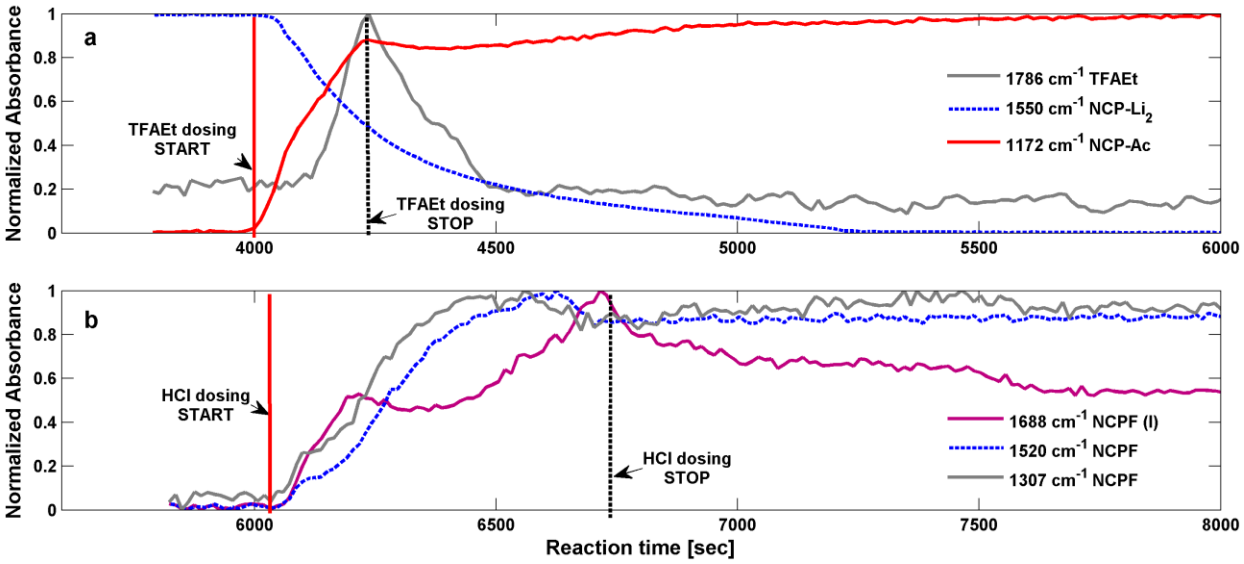



ATR-IR spectrum of 1,2-dimethoxyethane at 5°C (normalized to 1.0M concentration, neat, liquid)
Absorbance
0.1
0.08
0.06
0.04
0.02
0
600
800
1000
1200
1400
1600
1800
2000
Wavenumber [cm-1]


ATR-IR spectra of toluene at 5°C (normalized to 1.0M concentration, neat, liquid)
Absorbance
0.2
0.15
0.1
0.05
0
600
800
1000
1200
1400
1600
1800
2000
Wavenumber [cm-1]



S.3 IR absorbance profiles recorded during fluoroacetylation (a) and hydrolysis (b) latter indicating the NCPF product formation:



S.4 Sample Matlab code for fitting first order reaction model for the fluoroacetylation step:

Model:

$$\left[\text{NCP-Li}_2\right]=\left[\text{NCP-Li}_2\right]_0 \cdot e^{-k \cdot t} \Rightarrow \text{Abs}_{\text{NCP-Li}_2} = (\text{baseline}) + \text{Abs}_{\text{NCP-Li}_2,0} \cdot e^{-k \cdot t}$$

Where:

- k is the apparent rate constant
- $\left[\text{NCP-Li}_2\right]$ is the NCP-Li_2 concentration at t seconds after the start of TFAEt dosing,
- $\left[\text{NCP-Li}_2\right]_0$ is the (initial) NCP-Li_2 concentration, at the start of TFAEt dosing,
- $\text{Abs}_{\text{NCP-Li}_2}$ is the absorbance related to NCP-Li_2, measured at time t at IR-bands IIb, III, V, VI and IX (Table 1)
- $\text{Abs}_{\text{NCP-Li}_2,0}$ is the (initial) absorbance related to NCP-Li_2, measured at IR-bands IIb, III, V, VI and IX (Table 1), at the start of TFAEt dosing,

Matlab:

1. Define objective function:

```
function ObjectiveFunction = fit_simp(x,X,Y)
A=x(1);
B=x(2);
C=x(3);

ObjectiveFunction = A + B.*exp(C.*X) - Y;
```

2. Fit and visualize data:

```
% Initialize coefficients of the function fit_simp:

X0=[mean(irmat2(i,:)) (max(irmat2(i,:))-min(irmat2(i,:))) -
2/(max(t) - min(t))]';

% Calculate the new coefficients using LSQNONLIN:
options = optimset('Largescale','off');
x=lsqnonlin(@fit_simp,X0,[],[],options,X,Y);

% Plot the original and experimental data.
y_new=fit_simp(x,X,Y)+Y;
plot(X,Y,'or',X,y_new,'b')

%Apparent first order rate constant:

k=-x(3);
```

S.5 Yield calculation from the GC/FID data via internal standard method

Five standard solutions of NCP and NCPF in 10 mL DME/Toluene (V/V=15/7) mixture were measured using GC/FID for calibration, the solutions were:

	Solution #1		Solution #2		Solution #3	
	mass [mg]*	Area (GC) [pA·s]	mass [mg]*	Area (GC) [pA·s]	mass [mg]*	Area (GC) [pA·s]
NCP	174	6784	520	16762	345	11408
NCPF	503	10501	200	4219	331	6955
Dibenzyl	104	5284	41	2106	19	948

	Solution #4		Solution #5	
	mass [mg]*	Area (GC) [pA·s]	mass [mg]*	Area (GC) [pA·s]
NCP	0	1334	489	15581
NCPF	497	10950	0	0
Dibenzyl	49.8	2659	23	1172

* added weight, the NCPF standard contains about 10% NCP

S.5/a determination of NCP content of the NCPF standard via standard addition.

As seen from the GC/FID results for solution #4 (no added NCP), the NCPF standard contains a significant amount of NCP. Therefore the amount of NCP impurity has to be determined, based on the standard addition method (equations 1.1 - 1.3).

For a choosen solution “i”:

$$\frac{A_{NCP,\,i}}{A_{NCPF,\,i}} = \frac{y_{NCP}}{y_{NCPF}} \cdot \frac{c_{NCP,\,i}}{c_{NCPF,\,i}} = y_{rel} \cdot \frac{M_{NCPF} \cdot m_{NCP,\,i}^{total}}{M_{NCP} \cdot m_{NCPF,\,i}^{total}} = y_{rel} \cdot \frac{M_{NCPF} \cdot (m_{NCP,\,i} + r \cdot m_{NCPF,\,i})}{M_{NCP} \cdot m_{NCPF,\,i}(1\text{-}r)} \quad 1.1$$

For an other choosen solution “j”:

$$\frac{A_{NCP,\,j}}{A_{NCPF,\,j}} = y_{rel} \cdot \frac{M_{NCPF} \cdot (m_{NCP,\,j} + r \cdot m_{NCPF,\,j})}{M_{NCP} \cdot m_{NCPF,\,j}(1\text{-}r)} \quad 1.2$$

Where:

- A_{xxx} is the corresponding area measured with GC
- m_{xxx}^{total} is the total weight of the corresponding species in the solution
- m_{xxx} is the added weight of the corresponding species
- M_{xxx} is the molecular weight of the corresponding species
- y_{xxx} is the sensitivity of the GC system to the corresponding species
- y_{rel} is the relative sensitivity of the GC system to NCP versus NCPF
- r is the weight percentage of NCP in the NCPF standard

If $L = \frac{A_{NCP,\,i}}{A_{NCPF,\,i}} \cdot \frac{A_{NCPF,\,j}}{A_{NCP,\,j}}$, after division of equation 1.1 by equation 1.2:

$$r = \frac{m_{NCP,\,i} \cdot m_{NCPF,\,j} - L \cdot m_{NCPF,\,i} \cdot m_{NCP,\,j}}{L \cdot m_{NCPF,\,i} \cdot m_{NCPF,\,j} - m_{NCPF,\,i} \cdot m_{NCPF,\,j}} \qquad 1.3$$

Considering all the $\binom{5}{2} = 10$ combinations, we received that there is $100 \cdot r$ = **8.3 ± 1 % w/w NCP content in the NCPF standard** (68% confidence level). Since there are no other significant impurities, purity of the NCPF used for internal standard calibration is $100 \cdot (1-r)$ = 91.7 ± 1 %.

S.5/b Determination of the response factor y* of NCPF and NCP versus dibenzyl for the internal standard calibration

For a choosen solution "i":

$$\frac{A_{S,\,i}}{A_{DB,\,i}} = y_S \cdot \frac{M_{DB} \cdot m_{S,\,i}}{M_S \cdot m_{DB,\,i}} \qquad 1.4$$

Where:

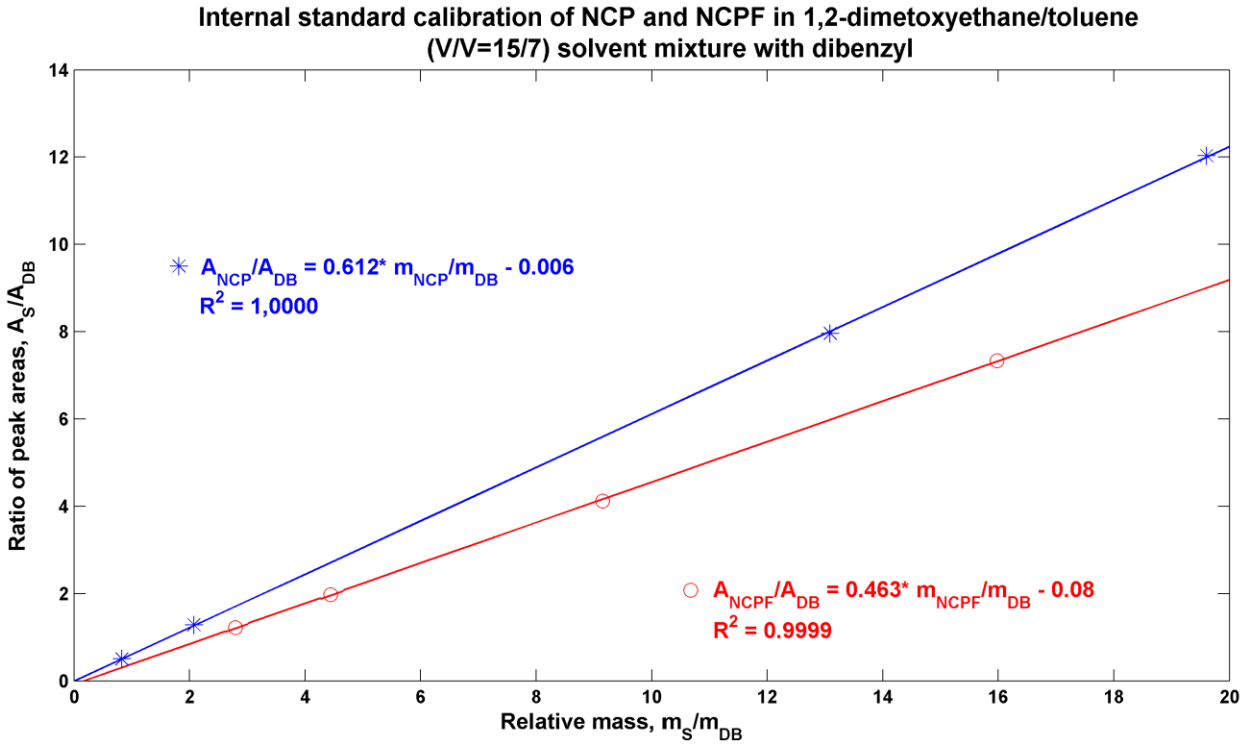
- y_S is the response factor of species S (NCPF or NCP) versus dibenzyl
- A_{DB} is the peak area corresponding to dibenzyl
- M_{DB} is the molecular weight of dibenzyl
- M_{DB} is the molecular weight of species S (NCPF or NCP)
- m_S is the total weight of species S in the solution (in case of NCPF $m_{NCPF,\,total} = (1-r) \cdot m_{NCPF}$, in case of NCP, $m_{NCP,\,total} = m_{NCP} + r \cdot m_{NCPF}$)

For convenience, we incorporate the molecular weights into the response factor, thus we can calculate with weights:

$$y_S^* = y_S \cdot \frac{M_{DB}}{M_S} \qquad 1.5$$

As shown below, y_S^* values can be determined as slopes of the $A_S/A_{DB} = y_S^* mS/m_{DB} + b$ functions. The corresponding values to NCP and NCPF:

$y_{NCPF}^* = 0.463$ and $y_{NCP}^* = 0.612$



S.5/c Calculation of the yield and the remaining NCP content

The mass of species S (NCP or NCPF) in the reaction mixture, after hydrolysis and neutralization:

$$m_S = \frac{A_S \cdot m_{DB}}{y_S^* A_{DB}} \qquad 1.6$$

Example GC result:

Measurement ID: GT_110310, measurement date: 11.03.2010

Conditions: reagent amounts BuLi/BuLi/TFAET/HCl = 2.15/0.15/1.3/2.25 NCP equivalents, [NCP] = 0.22M, solvent: DME/Toluene (V/V = 15/7), waiting times after dosing steps: 60/10/30/10 min, $f_{BuLi}/f_{TFAEt}/f_{HCl}$ = 1.0/0.2/0.2 mL/min, T_{react} = 5 °C, stirrer speed: 600 rpm.

Species	Retention time [min]	Area [pA*s]	Weight [mg]	Y (mol/mol initial NCP)
Dibenzyl	8.852	1527	100.6	
NCPF	9.294	10422	**1483***	**96.45**
NCP	9.71	308	**33.2***	**3.13**

* calculated according to equation 1.6