Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting Information

Selectivity Engineering of Diazotization Reaction in Continuous Flow Reactor

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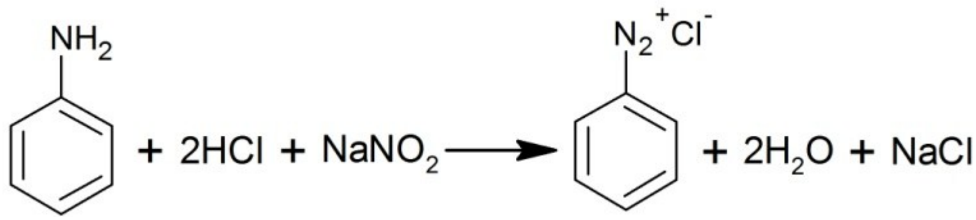
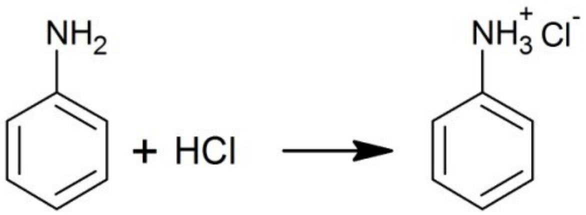
Contents

1. Reaction Schemes

Typical sequence of reactions that take place in the synthesis of diazonium salts are given in Schemes S2 - S4 and the decomposition of the salt is given in Scheme S5. The overall diazotization reaction is given in Scheme S1. The reaction occurs in three stages (Schemes S2 - S4). In the first step, aniline and hydrochloric acid react to give anilinium chloride salt (Scheme S2), which is soluble in the water available in the reaction mass along with excess hydrochloric acid. This reaction usually goes to completion in the presence of excess hydrochloric acid. In the second step, reaction of this solution containing anilinium chloride salt and excess hydrochloric acid with the aqueous sodium nitrite solution that generates nitrous acid in-situ (Scheme S3), which in the last step reacts with the anilinium chloride salt to give benzene diazonium salt (Scheme S4). NaCl gets generated along with nitrous acid and can remain undissolved depending on the water concentration and the operating temperature. In general, diazotization is carried out under highly acidic conditions and the literature reports it to be a third order reaction.[1, 2] Diazonium salt decomposes above 5°C (Scheme S5). The decomposition reaction is first order with respect to diazonium salt.[3] Unreacted aniline can also react with diazonium salt (Scheme S6) to form waste dye product.



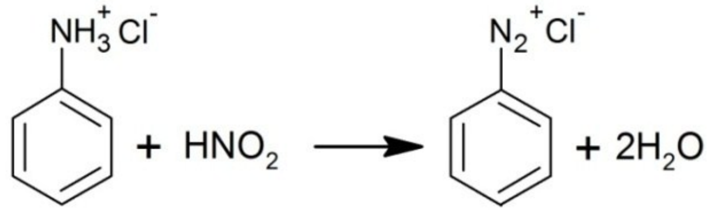
Scheme S1 Overall diazotization reaction of aniline



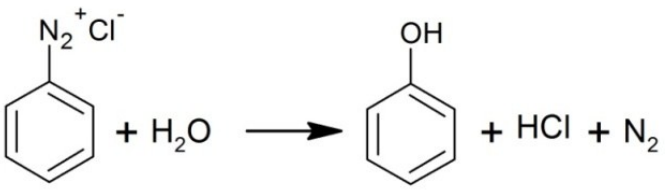
Scheme S2 Formation of anilinium chloride salt

$$NaNO_2 + HCl \rightleftharpoons HNO_2 + NaCl$$

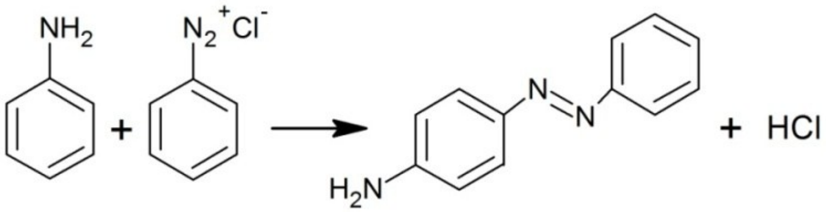
Scheme S3 In-situ generation of nitrous acid



Scheme S4 Simplified reaction for our model



Scheme S5 Decomposition of diazonium salt



Scheme S6 Diazocoupling reaction forming aniline yellow dye

2. Experimental

2.1 Residence Time Distribution (RTD)

RTD experiments were performed to get the model parameters (*Pe*) for the axial dispersion model. Salt solution of 20 mg/mL concentration and pure water were filled in different syringe pumps. This salt solution was used for step input at the inlet of the reactor and the conductivity of the solution was monitored at the outlet of reactor using a pre-calibrated conductivity meter to get the concentration vs. time data. Initially experiments were performed for residence time of 5 s-35 s for different reactors (straight tube, coiled tube, pinched tube and AmAR3 reactor). Similar experiments were carried out for residence time of 45 s- 230 s for straight tube reactor and 30 s - 150 s for coiled tube reactor. Fig. S1 shows the experimental setup for RTD experiments in a straight tube reactor. For the analysis of the data, closed-closed boundary condition approach was used. Every experiment was repeated three times to ensure the reproducibility.

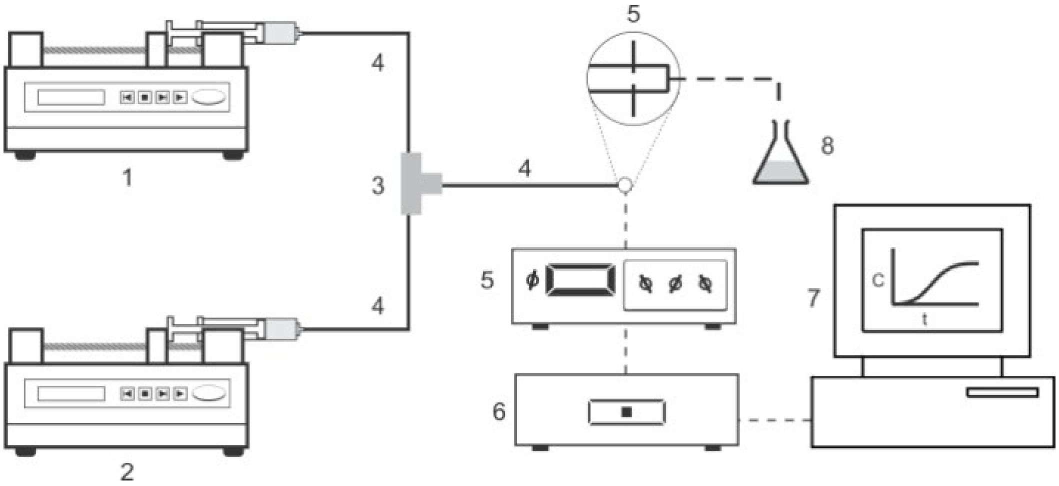


Fig. S1 Schematic for the RTD setup, (1) Syringe pump for salt solution, (2) Syringe pump for water, (3) T-mixer, (4) SS316, 1/8 in. tube, (5) Conductivity meter with probes, (6) Data Acquisition System, (7) Computer, and (8) Flask for waste brine collection.

2.2 Diazotization Reactions in Continuous Flow Reactors

The overall diazotization reaction is given by Scheme S1. Aniline (1 equiv) was mixed with 11.64 M HCl solution (3.25 equiv). This results in the formation of anilinium chloride salt (Scheme S2). Water is added to this solution to completely dissolve the anilinium chloride salt. The resulting solution was stirred using glass rod or magnetic needle for a few minutes to get a uniform solution with molar concentrations of HCl and aniline 3.9 M and 1.2 M respectively. 1.5 M $NaNO_2$ solution was prepared by mixing $NaNO_2$ (1.2 equiv) in water. Both the solutions were pumped using syringe pumps (Longer Pump, China). In order to stabilize the diazonium salt synthesized in the reaction, the reaction mixture at the outlet of the reactor was collected in aqueous solution containing β-Naphthol (0.45 M) and NaOH (1.53 M).The reaction was quenched in several sampling vials having 2-10 mL β-Naphthol solution and collection was done over a period of 15 s - 30 s to meet the stoichiometry and give Sudan-I dye. This dye was insoluble in the solution and hence it precipitates. Sufficient amount of ethanol (95% v/v) was added to this quenched solution to get a homogeneous dye solution which was further diluted with additional ethanol (dilution ratio 1:10 by volume) and analyzed (λ_{max} = 481 nm) using UV-vis spectrophotometer (Cary 8454 Agilent Technologies). The reaction temperature was maintained using a constant temperature bath (Julabo, Germany).The reaction was carried out in different flow reactors (straight tube, coiled tube, pinched tube and AmAR3 reactor). Fig. S2 shows the experimental setup for reaction for straight tube reactor. Every experiment was repeated three times to ensure the reproducibility.

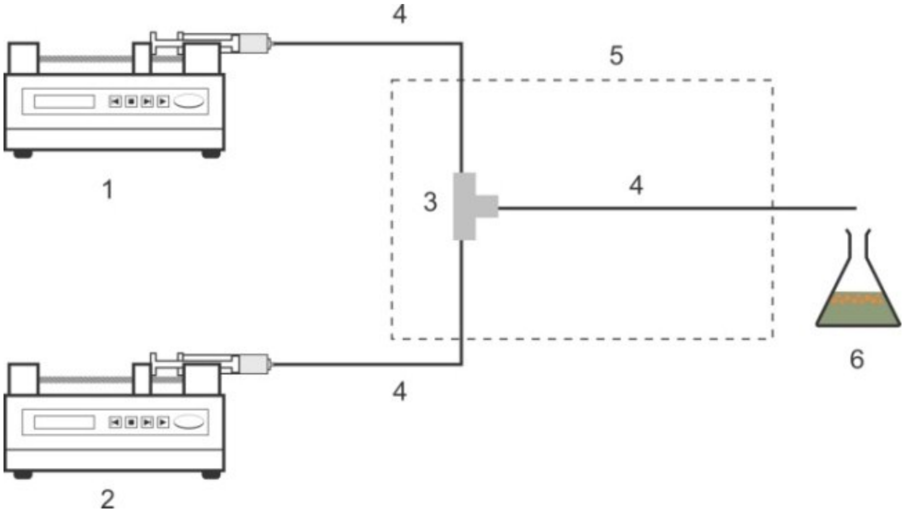
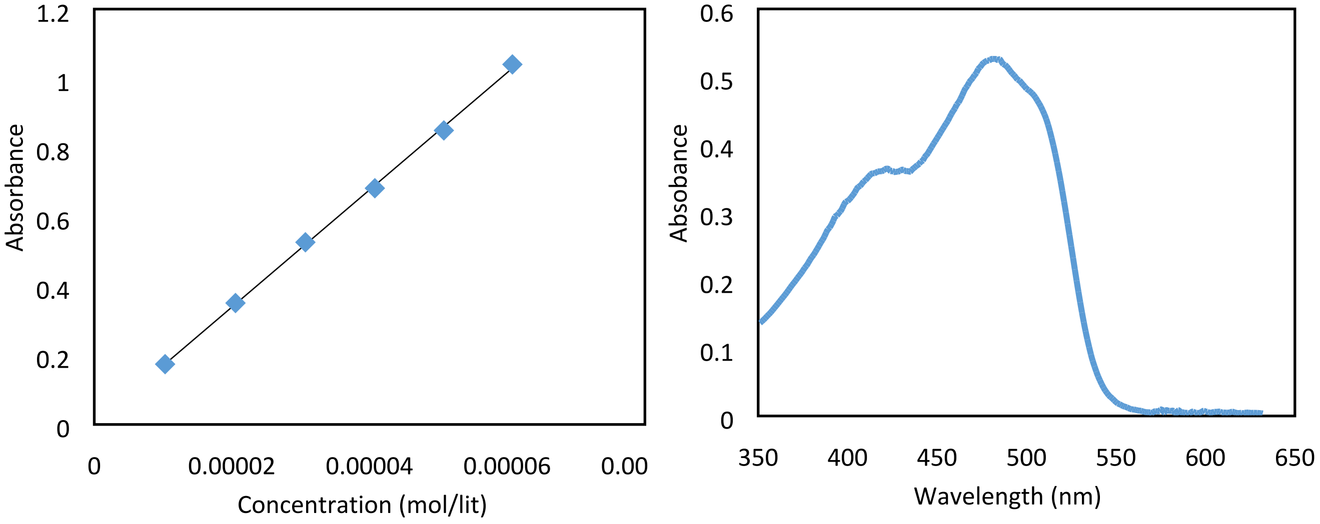


Fig. S2 Schematic for diazotization reaction, (1) Syringe pump for Aniline-HCl solution, (2) Syringe pump for $NaNO_2$ solution, (3) T-mixer, (4) SS316, 1/8 in. tube, (5) Constant temperature bath and (6) Quenching and sample collection

3. Calibration of Sudan I dye

UV-vis spectrophotometer (Cary 8454 Agilent Technologies) was used to quantify Sudan I dye. Fig. S3 (A-B) shows the calibration chart and uv-vis spectrum of Sudan I dye.



A B

Fig. S3 (A) Calibration chart and (B) UV-vis spectrum for Sudan I dye

4. Reproducibility of the RTD experiments

RTD experiments were repeated 3 times to check the reproducibility. Fig. S4 shows the E-Curves for coiled reactor (4.5 mL) with total flow rate 1.8 ml/min.

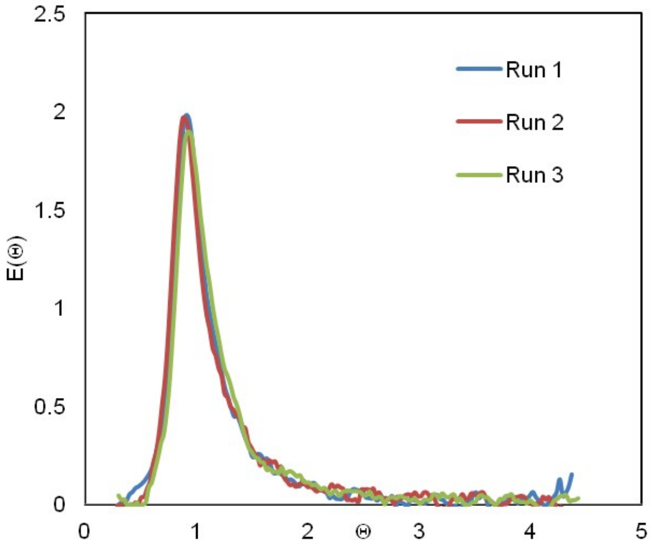


Fig. S4 RTD experiments to check reproducibility

5. Heat transfer coefficient, friction factor and optimization of Peclet Number

The heat transfer coefficient was calculated by using Gnielinski's correlation given in Equations (S1), wherein the friction factor was estimated using Equation (S2).[34]

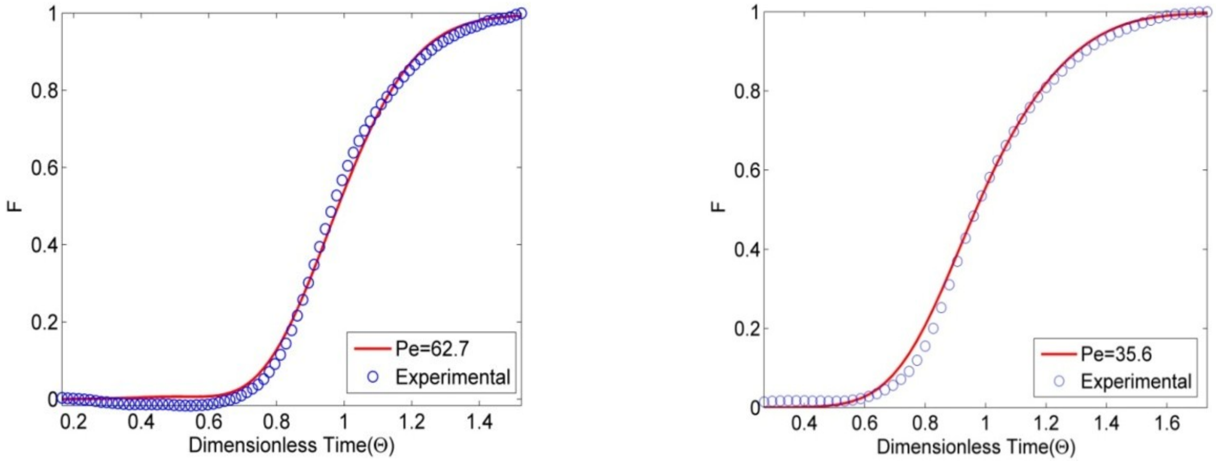
$$Nu = \left[\left(\frac{f}{8}\right)(Re - 1000)Pr\right] \Big/ \left[1 + 12.7\sqrt{f/8}\,(Pr^{0.66} - 1)\right] \qquad (S1)$$

$$f = \frac{1}{(1.82\log Re - 1.64)^2} \qquad (S2)$$

Analytical solution of open-open boundary conditions given by equation (S3) provides a good approximation for closed-closed system.[4] The model parameters were estimated and optimized by least square technique using $\Sigma(F_{exp}-F_{Model})^2$. The model F-curve was obtained by numerically integrating equation (S3) and the corresponding *Pe* for closed-closed condition was obtained using equation (S4).[4, 5] Fig. 54 shows the experimental and model F-curves. The Peclet number fitted in Fig. S5 is the optimized Peclet number.

$$E(\Theta) = \sqrt{\frac{Pe}{4\pi\Theta^3}}\,exp\left(-Pe\frac{(1-\Theta)^2}{4\Theta}\right) \qquad (S3)$$

$$Pe_{cc} = 0.7Pe_{oo}^{1.073} \qquad (S4)$$



A

B

Fig. S5 Optimization of Peclet Number, (A) 0.56 ml/min in Straight Tube Reactor and (B) 1.8 ml/min in Coiled Reactor

6. Time Scales

The reaction time and mixing time was calculated using equation (S3) and (S4) respectively whereas Da_M is obtained by fitting. Table S1 shows different time scales for diazotization reaction in different flow reactors.

$$\tau_R = \frac{1}{kC_0^2} \qquad (S3)$$

$$Da_M = \frac{\tau}{t_m} \qquad (S4)$$

Table S1. Time scales for different reactor types studied in this work

Experiment No.	Temperature (°C)	Residence Time(s)	Pe_M (Experimental)	Da_M (fitted)	Reaction Time(s)	Mixing Time(s)
Straight Tube Reactor (1.78 mL, 1.75 mm ID)						
1	1.46	5	26.54	0.76	0.00718	6.57
2	1.46	15	63.78	1.2	0.00718	12.5
3	1.46	25	26.53	1.8	0.00718	13.88
4	1.46	35	61.97	2.5	0.00718	14
5	1.46	45	45.44	4.5	0.00718	10
6	1.46	72.9	54.11	4.2	0.00718	17.35
7	1.46	202.9	60.70	5	0.00718	40.58
8	5	5	26.54	1.01	0.0058	4.95
9	5	15	63.78	1.4	0.0058	10.71
10	5	25	26.53	2.6	0.0058	9.61
11	5	35	61.97	3.1	0.0058	11.29
12	5	45	45.44	4.5	0.0058	10
13	5	137.5	76.07	5.5	0.0058	25

14	5	230	23.41	5.5	0.0058	41.8
Pinched Tube (1.78 mL, 1.75 mm inlet diameter)						
15	5	5	3.81	0.67	0.0058	7.46
16	5	15	4.76	1.2	0.0058	12.5
17	5	25	8.61	1.55	0.0058	16.12
18	5	35	6.11	3	0.0058	11.66
Coiled Tube (1.78 mL, 1.75 mm ID)						
19	5	5	20.28	0.88	0.0058	5.68
20	5	15	15.47	0.92	0.0058	16.30
21	5	35	10.66	2.2	0.0058	15.90
AmAR3 reactor (4 mL, 1 mm inlet diameter)						
22	5	5	78.21	2.4	0.0058	2.03
23	5	15	8.81	60	0.0058	0.25
24	5	25	14	90	0.0058	0.27
25	5	35	10.4	90	0.0058	0.38

7. Central Composite Design (CCD) Model Fitting and Validation

Equation (S5) represents the fitted regression model (R^2 = 0.8063). Table S2 shows the comparison between the experimental and predicted yield.

$$Yield(\%) = 102.1 + 0.2T - 0.03\tau - 0.237T^2 + 0.0067T \times \tau + 0.0000196\tau^2 \qquad (S5)$$

where, T is Temperature (^{0}C) and τ is the residence time (s)

Table S2. CCD Experimental Matrix with experimental and predicted yield

Experimental Run	Type	Temperature (⁰C)	Residence Time (s)	Experimental Yield	Predicted Yield	% Error
1	Central	5	137.5	95.11	98.0	-2.94
2	Central	5	137.5	98.84	98.0	0.86
3	Central	5	137.5	97.11	98.0	-0.9.
4	Axial	5	45	98.04	97.4	0.69
5	Axial	5	230	99.44	99.0	0.54
6	Central	5	137.5	99.68	98.0	1.73
7	Central	5	137.5	99.06	98.0	1.09
8	Factorial	8.54	202.91	92.96	92.9	0.19
9	Factorial	8.54	72.9	51.08	88.6	-42.4
10	Factorial	1.46	72.9	97.14	100	-3.32
11	Factorial	1.46	202.91	97.26	98.5	-1.23
12	Axial	10	137.5	85.55	85.9	-3.90
13	Axial	0	137.5	99.86	98.3	1.63

The experimental data obtained with the aid of Central Composite Design (CCD) was fitted using MATLAB surface fitting tool to get contour plot shown by Fig. S6. This contour plot can be used to find optimum and robust operating region. It indicates that operating the reactor between below 5 ⁰C would always result in higher yields. The results indicate that for a constant temperature (above 5 ⁰C) the yield of diazonium salt will increase with increasing residence time. The difference in the nature of contour lines of the dispersion model contour and CCD contour plots is obvious because dispersion contour plot is obtained by a mechanistic model (based on first principle) whereas CCD contour is obtained by empirical model (regression model). However the deviation in yield is not more than 3%. It needs to be noted that the CCD model can only be used for interpolation within a set of operating conditions where as the dispersion model being a mechanistic model can be extrapolated which is more useful for scale up. The nature of the contour lines of Fig. S6 indicate that for T > 5 ^{0}C the yield will continue to increase for $\tau > 230$ s. However, this is not practically possible as once the aniline is completely consumed diazotization reaction will stop and only decomposition reaction will progress to decrease the yield of diazonium salt. This strongly indicates that CCD model is not reliable for extrapolation.

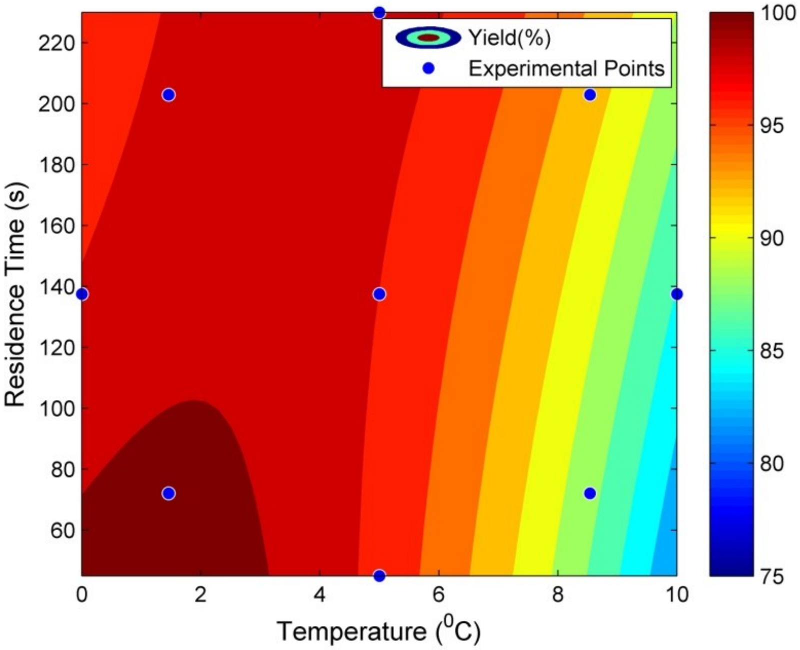


Fig. S6 Contour plot obtained by Central Composite Design

8. Sensitivity analysis

8.1 Sensitivity analysis towards kinetics

For extremely fast reactions, the measured kinetic parameters can be lumped with transport limitations and hence can be scale sensitive. In view of this it was thought desirable to check the sensitivity of the kinetic parameters on the performance of diazotization reaction before using model for pilot or plant scale prediction. This was done by imposing ±30% error on the rate constant (i.e. also the Da_R) and compared the predicted conversion with the reference value for a range of Peclet numbers (10-100). Simulations were performed by imposing ±30% error on Da_R for Peclet number range from 10 to 100. Da_M was set as 10^{10} in order to solve model in kinetically controlled regime. However it was observed that the predicted conversion even after imposing 30% error on Da_R was deviating by not more than 0.3 % from the reference value (also obtained from simulations) for the given set of parameters. Hence it was decided to compare the % unreacted aniline instead of conversion. Fig. S7 shows the variation in % unreacted aniline for various model parameters. The % relative error varies from 13-16% and is within the acceptable limits considering prediction of unreacted aniline.

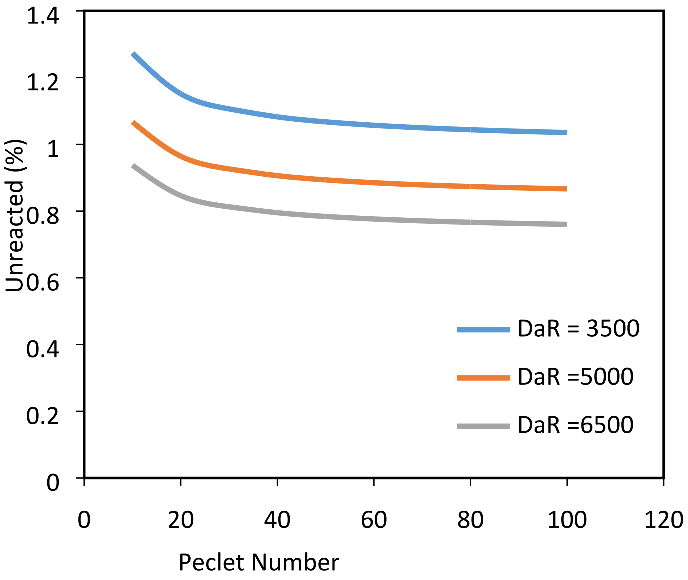


Fig. S7 Sensitivity analysis towards kinetics. Here Da_R = 5000 is the reference value where as Da_R = 3500 and 6500 are obtained after imposing ±30% error on reference value. $Da_M = 10^{10}$ for the all isothermal simulations

8.2 Sensitivity analysis towards mixing

The mixing process in flow reactors is controlled by convection and diffusion. Rate of convection will depend on Reynolds number whereas rate of diffusion depends on characteristic length scale, concentration gradients, fluid properties and to some extent temperature (for non-isothermal case). Thus different initial concentrations under same hydrodynamic condition will lead to different mixing times as concentration gradients can significantly affect the diffusion rate.[6] In view of this it was decided to do sensitivity analysis for mixing time (i.e. also the Da_M). The approach is similar to the kinetics sensitivity analysis discussed earlier. ±30% error was imposed in the value of Da_M and compared the predicted conversion with the reference value. Simulations were done for Peclet number range of 10-100 and $Da_R=10^{10}$.The results are shown in Fig. S8. The % conversion varies by 0.62-3.9% from the reference value. The % error in conversion is acceptable.. For higher Da_M the percent deviation in conversion will decrease for the given imposed error.

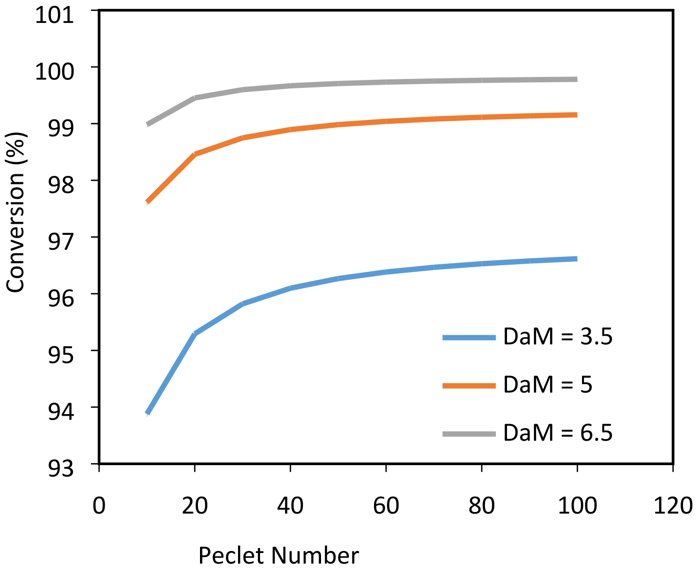


Fig. S8 Sensitivity analysis towards mixing. Here $Da_M = 5$ is the reference value where as $Da_M = 3.5$ and 6.5 are obtained after imposing ±30% error on reference value. $Da_R = 10^{10}$ for all the isothermal simulations

9. RTD of AmAR3 reactor (Scale- up Experiment)

RTD experiments for an AmAR3 reactor (volume ~35 mL) were performed by giving a pulse of saturated sodium chloride solution. The conductivity of the solution was monitored at the outlet of reactor using a pre-calibrated conductivity meter to get the concentration vs. time data. Fig. S9 shows a typical E-curve for AmAR3 reactor. Experiment was repeated three times to ensure the reproducibility.

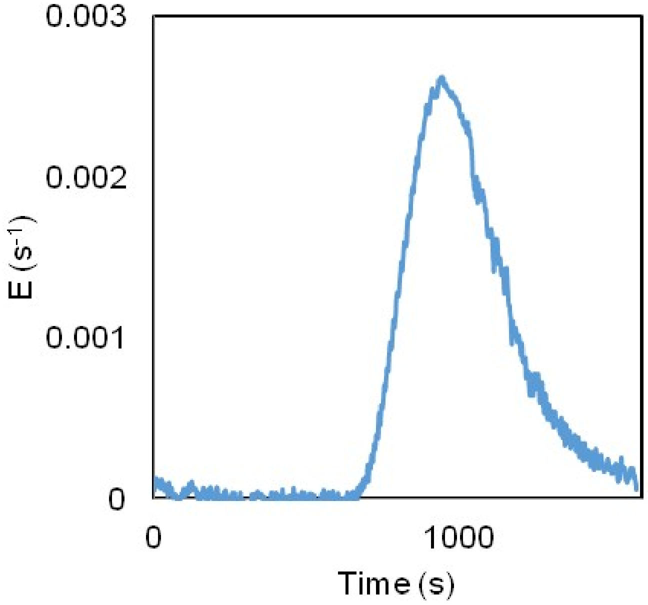


Fig. S9 E-Curve for AmAR3 reactor (~35 mL volume)

10. Scale up methodology for pilot and production scale

At lab scale it is relatively easy to maintain near isothermal conditions. The main challenge in the scale-up diazotization is the temperature control and lower yield which is as a result of decomposition or coupling with the unreacted aniline. Both these issues can be addressed by operating strictly below 5 ^{0}C and in lesser dispersion region. Initial concentration, physical properties like heat capacity or density and other operating conditions can strongly influence the temperature profile inside the reactor. Following three examples will demonstrate the effects of these variables on temperature profile for a tubular reactor having 20 mm inner diameter and 10 m length at a residence time of 45 s. The flow regime is in the transition and turbulent regimes. Dispersion coefficients were estimated using correlation charts for dispersion in pipes.[7] Before we discuss the observations, we bring out a few important issues related to keeping the reaction mixture homogeneous.

10.1 Effect of solvents on Adiabatic Temperature Rise

The extent of deviation in the yield of diazonium salt is directly related to the adiabatic temperature rise in the reactor. Consider the reaction mixture having initial concentration of reactants as mentioned previously. This concentration can be achieved by using fixed volume of solvent. By using different solvents in the same amount (by volume) one can achieve same initial concentration but different average heat capacity and average density of the reaction mixture. The non-isothermal model was used to predict adiabatic temperature rise by setting $\hat{Q}$= 0. This exercise was performed for different solvents. The results are shown in Fig. S10. Water has the minimum adiabatic temperature rise as compared to other organic solvents due to its higher heat capacity. The organic solvent having least adiabatic temperature rise (DSMO, 18.26 ^{0}C) is still higher than water (9.85^{0}C). Hence one should prefer to carry out diazotization in aqueous medium wherever possible.

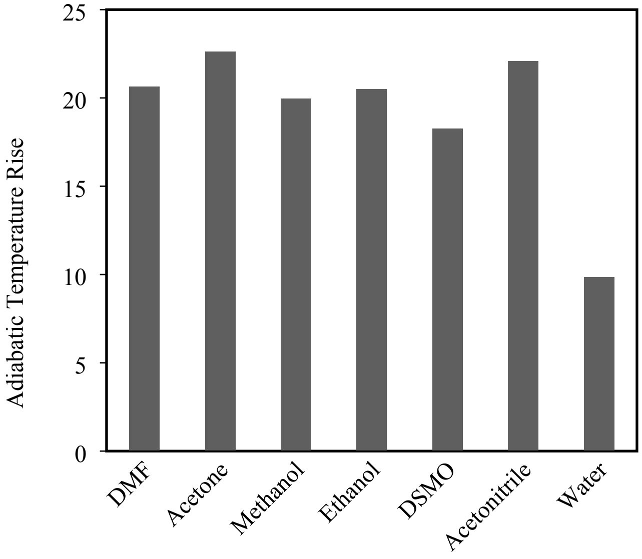


Fig. S10 Adiabatic temperature rise for various solvents; $\Delta H = -65$kJ/mol, $\hat{Q}$ = 0, d=0.02m, L=10m, $\gamma = 16.3$, Pe_M= 33.3

10.2 Effect of water-solvent mixtures on Temperature Profile/ Hot Spots

In many practical cases the aniline substrate may not be soluble in water. In such cases one should prefer to use a water-solvent mixture instead of using pure organic solvent to reduce the probability of hot spots. Consider initial aniline concentration 0.3 mol/lit which can be obtained by water-acetone mixture with different volume percent of water and acetone. Fig. S11 shows the concentration and temperature profile for different water-acetone mixtures. It was observed that as water concentration increases the hot spot temperature decreases. This is because water has higher density and heat capacity than acetone. The productivity of diazonium salt for 100% water and 75% water-acetone mixture is 82.74 ton/year. For other cases the productivity will decrease due to decomposition reaction as temperature is above 5 ^{0}C. It can also increase temperature further ultimately leading to runaway reaction. In reality one should do some solubility experiments to choose appropriate mixture of water and solvent right in the beginning of process development stage to avoid decomposition at the larger scale.

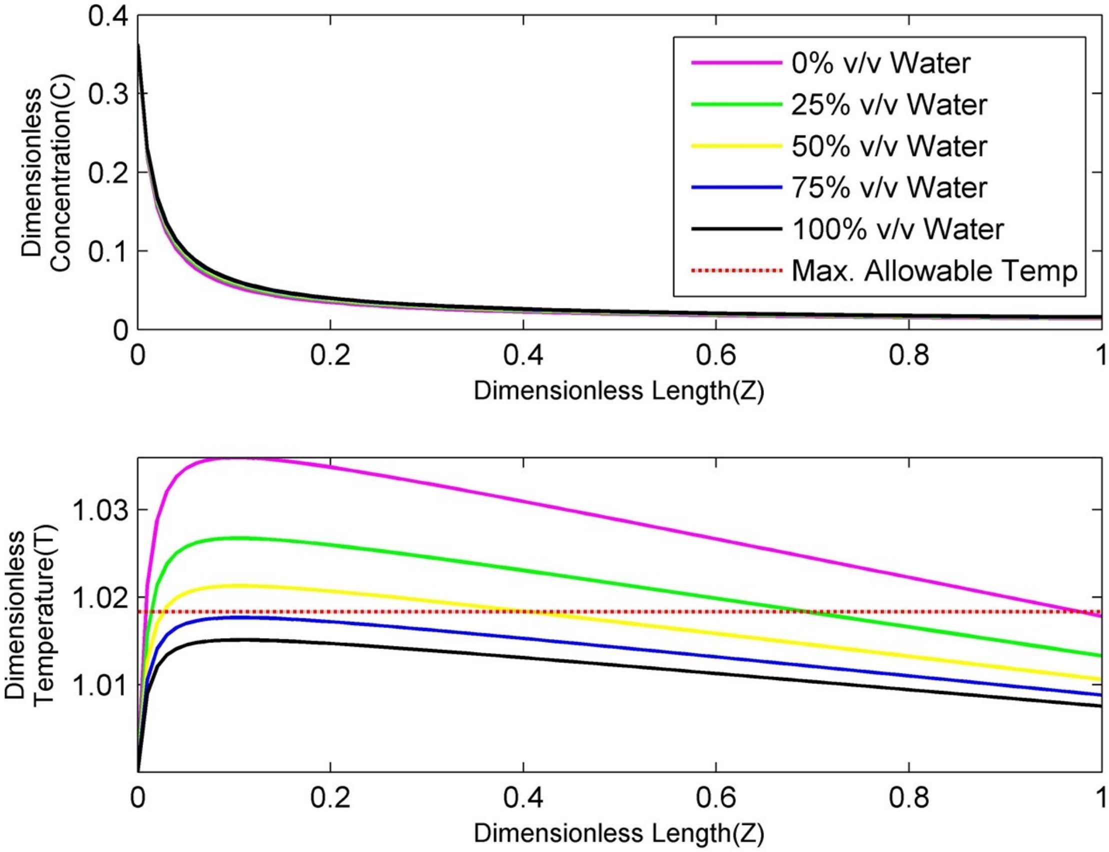


Fig. S11 Concentration and temperature profile in the tubular reactor for different water-acetone solvent mixtures; C_0=0.3 mol/min, $\Delta H = -65$ kJ/mol, h=767 W/m^{2}K, d=0.02 m, L=10 m, T_W=263 K, T_0=273 K, $\gamma = 16.3$, Pe_M= 33.3, Da= 9.88×10^9 and Re=3000-8914

10.3 Effect of Initial Concentration on the Temperature Profile/ Hot Spots

By increasing the concentrations of the substrates to increase the production rate for a fixed cooling capacity can be detrimental.[8] Here we have quantified the effect of different initial concentrations of aniline on the performance of the reactor while the inlet temperature is maintained at 0 ^{0}C. The concentration and temperature profiles for different initial concentrations are given in Fig. S12. It is clearly seen that higher concentration will lead to more conversion but it will also have higher hot spot temperature. Hence one can do some simulations for different initial concentrations to see its effect on hot spot temperature and thus avoid any accident or decomposition of the diazonium salt at pilot or plant scale. For higher inlet temperature the hot spot temperature will also be higher. Thus, for 0.3 mol/lit of inlet concentration, the productivity will be 82.74 tons/year. Productivity can be further increased by increasing the L/D ratio and by maintaining the same residence time.

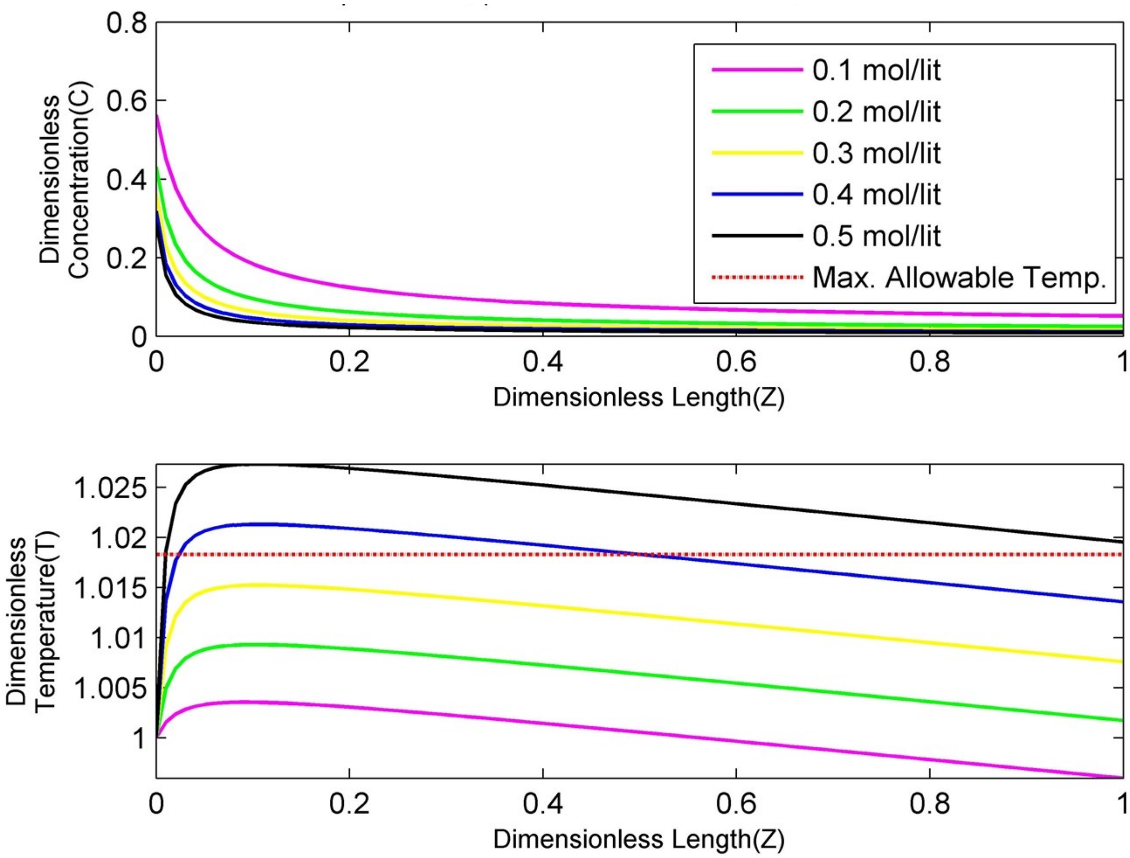
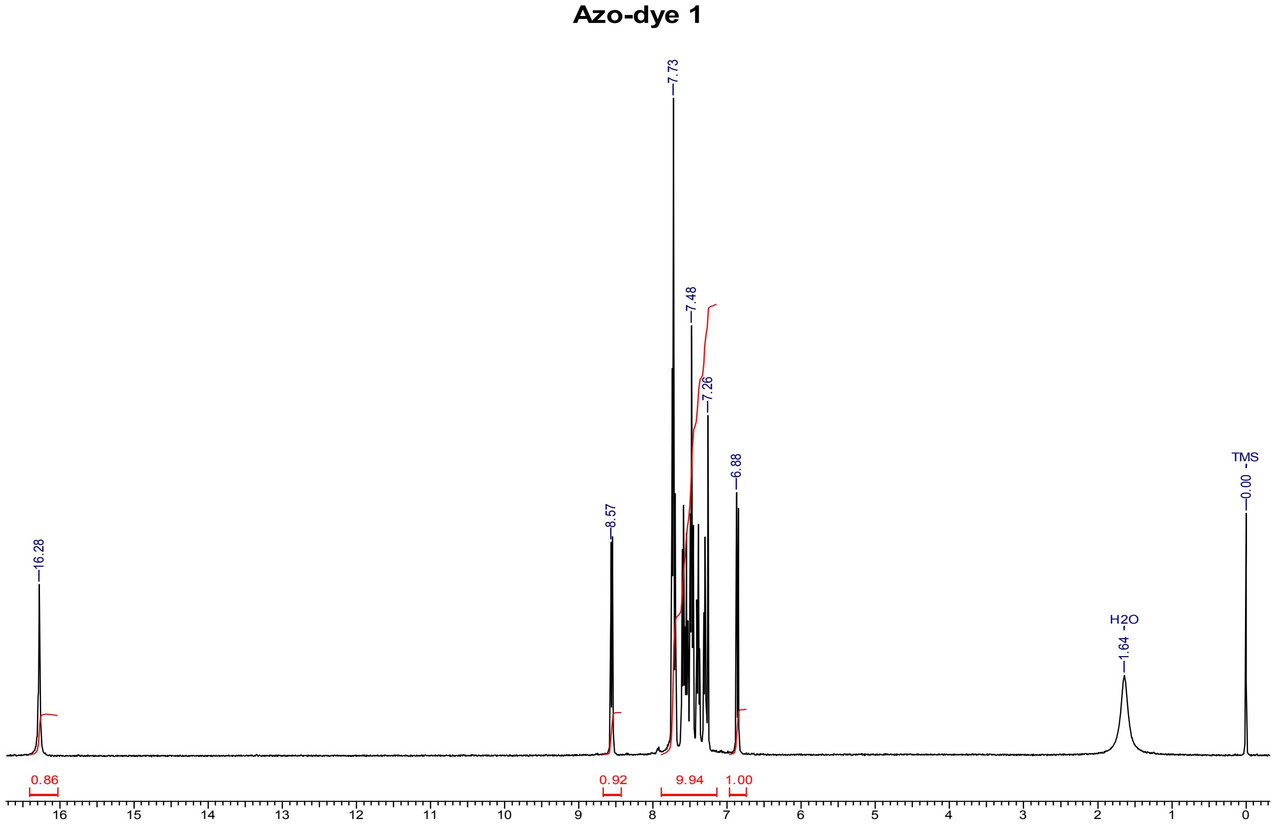
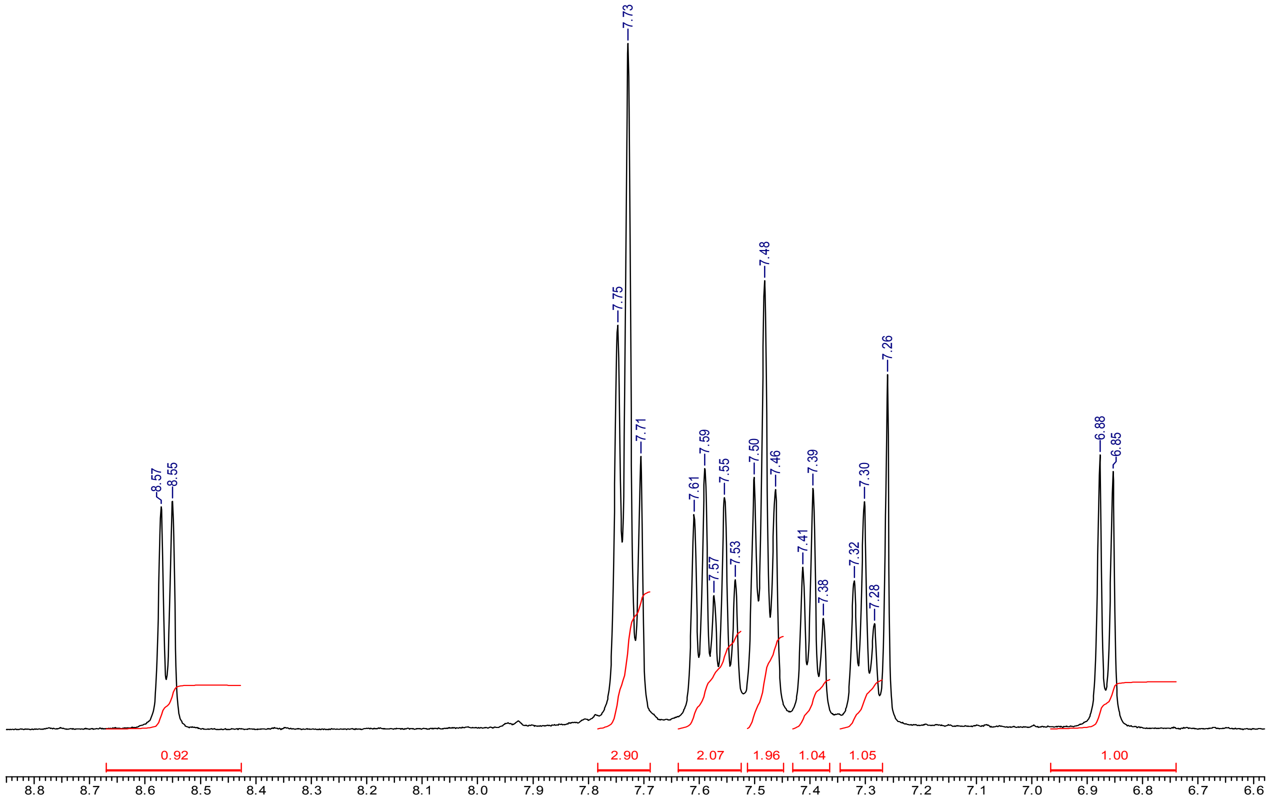


Fig. S12 Concentration and temperature profile in the tubular reactor for initial concentrations in aqueous medium; $\Delta H = -65$ kJ/mol, h=767 W/m^{2}K, d=0.02 m, L=10 m, T_W=263 K, T_0=273 K, $\gamma = 16.3$, Pe_M= 33.3 and Re=3000

11. NMR Spectra for Sudan I dye (1-[(*E*)-phenyldiazenyl]naphthalen-2-ol)



Azo-dye 1



8.57
8.55
7.75
7.73
7.71
7.61
7.59
7.57
7.55
7.53
7.50
7.48
7.46
7.41
7.39
7.38
7.32
7.30
7.28
7.26
6.88
6.85
0.92
2.90
2.07
1.96
1.04
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8.8
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7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6

12. Effect of temperature on yield of diazonium salt for T < 5 ^{0}C

In order to verify the suitability of the model for estimation of the yield of diazonium salt, the yield was observed as a function of temperature for various residence times in a straight tube reactor. In the observations shown in Figure S13 the dashed lines and symbols correspond to model predictions and experimental data respectively while the solid lines (yellow and red) corresponds to kinetically controlled reaction. The simulations for kinetically controlled conditions were obtained by solving the model with $Da_M = 10^{20}$ ($t_m=5\times10^{-20}$ s) and the corresponding Da_R and Pe_M. The results indicate that the experimental yield is always low compared to the yield obtained if the reaction were kinetically controlled. This implies that the diazotization reaction is always controlled by mixing in the straight tube reactor.

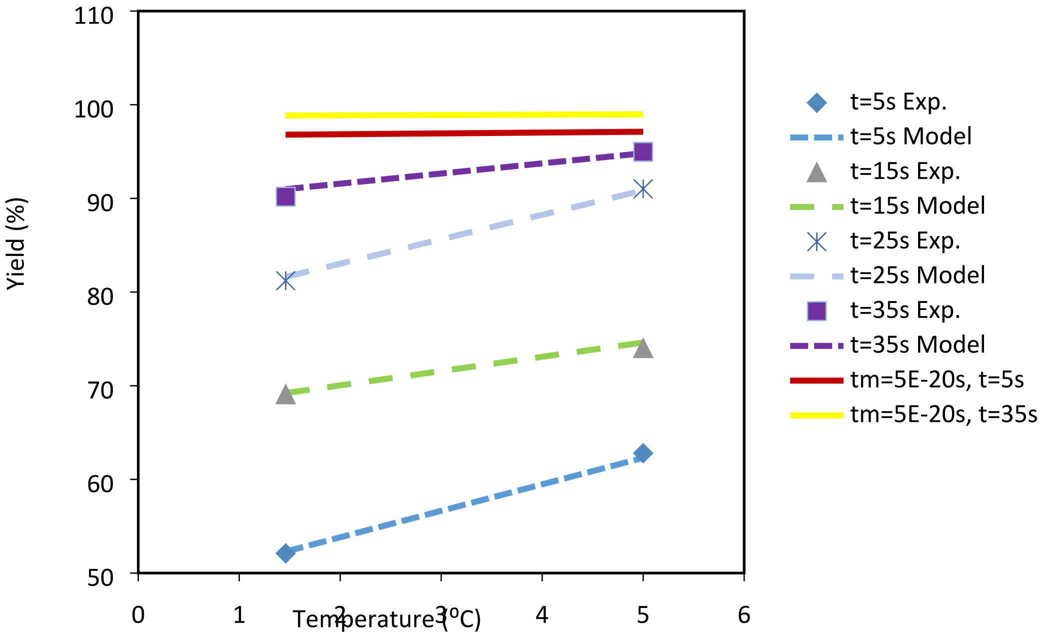

Fig.S13: Yield vs. Temperature in straight tube reactor, t = residence time in s

13. References

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