A Facile Optimization of Diazotization and Phase Transfer Catalyzed Azo-Coupling Reactions in Microreactors

Faith M. Akwi, Coos Bosma and Paul Watts*

InnoVenton: NMMU Institute for Chemical Technology, Nelson Mandela Metropolitan University, University Way, Port Elizabeth 6031, South Africa

Received: 18 January 2016; accepted: 14 March 2016

Herein, we illustrate how microreactor technology can be used as a tool for reaction screening and optimization, in addition to improving the reaction chemistry. We report the in-situ generation of azo compounds by reactive quenching of diazonium intermediates in microreactors. This involves an electrophilic aromatic substitution reaction, namely, an azo-coupling reaction performed in continuous-flow systems in the presence of a phase transfer catalyst with great emphasis on compounds that do not easily couple. Capitalizing on the benefits of a large surface area and the short molecular diffusion distances observed in microreactors, in-situ phase transfer catalyzed azo-coupling reaction of diphenylamine to *p*-nitroaniline was investigated. A rapid and easy optimization protocol was established which yielded a 99%, 22%, and 33% conversion of diphenylamine, carbazole, and triphenylamine, respectively, in approximately 2.4 min.

Keywords: diazotization, azo-coupling, phase transfer catalysis, microreactors

1. Introduction

Azo compounds are important groups of compounds synthesized using diazonium salts as intermediates. They have a plethora of applications in pharmaceutical [1], food [2], textile [3], and printing [4] as well as the cosmetic industries [5]. Despite the fact that there are numerous applications for these compounds, the large amount of waste generated in their manufacturing process has a detrimental effect on the environment [6, 7] in addition to largely increasing the cost of production.

Azo compounds are synthesized by a two-step reaction, i.e., diazotization of a primary amine **1** to form diazonium salt **2** and azo-coupling of **2** with **3** to the form azo compound **4** (Scheme 1).

Diazonium compounds are prepared by direct diazotization, indirect diazotization, or by the method of Witt, Griess, or Knoevenagel [8–12]. The most critical aspect in the synthesis of diazonium salts is the reaction temperature. For example, a number of salts derived from primary aromatic amines are quite stable if the reaction temperature is maintained between 0 and 5 °C whereas those derived from aliphatic primary amines decompose to their corresponding phenols even at this temperature. Furthermore, isolation of these compounds is not advisable since they are potentially explosive.

Azo-coupling is the second step in the synthesis of azo compounds. It is an electrophilic substitution reaction between a diazonium cation and a coupling agent, e.g., hydroxylated and aminated aromatic systems [13].

The pH is of utmost importance for the azo-coupling reaction but critically depends on the kind of coupling compound being used [14]. For example, it has been established that phenols are successfully coupled in alkaline conditions. In these conditions, a phenolate ion is formed, which in addition is more soluble in water than the phenol itself. This in turn readily provides the desired electron releasing group, thus, facilitating the electrophilic substitution reaction to afford the azo compound. However, highly alkaline conditions are usually avoided as they lead to diazonium salt decomposition.

On the other hand, when aromatic secondary or tertiary amines are used as coupling agents, the azo-coupling reaction is carried out in mildly acidic conditions. The reason for this is to avail a water-soluble protonated version of the aromatic amine. Like the phenolate ion formed in regards to azo-coupling of phenols, this protonated aromatic amine is far more reactive than when it is in its ordinary form. Clearly, the protonation also renders the aromatic ring less nucleophilic; therefore, it is imperative to optimise the pH in order to balance both of these effects.

Phase transfer catalysis, commonly abbreviated as "PTC", is a term that was coined to define the movement of a reactant between two immiscible phases with the aid of a phase transfer catalyst. This unique technique of contacting otherwise inaccessible reactants in reaction media has already proven to be quite useful in many an organic synthesis such as nucleophilic reactions [15]. For example the cyanation of an aryl halide in dimethylsulfoxide, where a tremendous increase in reaction yield was seen, it increased selectivity in the synthesis of polycarbonate from phosgenation of bisphenol-A, minimizing the quantity of waste generated and occurrence of undesired products in these two reactions, respectively [16]. Phase transfer catalysts are divided into two categories [17]: soluble and insoluble phase transfer catalysts with examples such as open chain polyethers, macrocyclic polyethers, onium (phosphonium and quaternary ammonium) salts, and aza-macrobicyclic ethers. The reaction systems in which these catalysts are employed are further divided into liquid–liquid, gas–liquid, and solid–liquid reactions systems. In this PTC cycle, the catalyst transfers the reacting ion into the organic phase from the aqueous phase in the form of an ion pair where the actual reaction takes place [18].

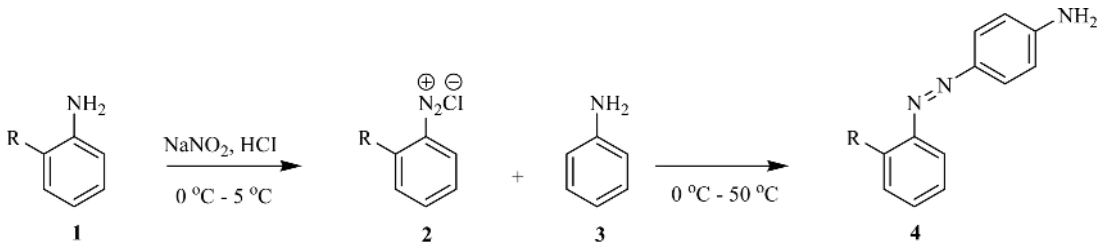
According to the above diazo-coupling mechanism, the diazonium ion exchanges with the PTC ion and this newly formed ion pair solubilizes into the organic phase where the reaction takes place to form the product (Figure 1).

Phase transfer catalysis has already been established to greatly improve reaction yields in azo-coupling reactions [19, 20]. Although a few early pioneering papers were published by Wootton and coworkers [21, 22] on diazonium synthesis in microreactors, these did not address phase transfer catalysis, where a search of this literature only provided Hisamoto et al. [23] who actually did not employ a phase transfer catalyst, but rather the principle to increase reaction selectivity in the diazo-coupling of 5-methyl resorcinol to *p*-nitrobenzene diazonium tetrafloroborate in a biphasic laminar flow reaction system. Due to the large specific interfacial area and short molecular

* Author for correspondence: E-mail: Paul.Watts@nmmu.ac.za

DOI: 10.1556/1846.2016.00003

Scheme 1. Illustrative scheme showing diazotization and azo-coupling reactions



diffusion distances provided by the microchip, the group was able to achieve higher conversion with the elimination of the undesired second bisazo-coupling reaction as compared to the batch synthesis.

In this study, we utilized a phase transfer catalyst in a liquid–liquid Taylor droplet flow reaction system for the in-situ reactive quench of diazonium salts. In this type of flow, the plugs or slugs formed in these reactor systems improve the mixing and mass transfer [24] of reactants involved due to added internal circulation within these fluidic formations as is illustrated below (Figure 2).

These plugs or slugs act as mini microreactors existing in a microchannel of a microreactor being employed for the synthesis. For the formation of plugs, surface tension between the aqueous phase and disperse phase should be lower than that between the microchannel wall and aqueous phase; basically, the surface chemistry at the liquid–liquid interface plays a huge role in their formation. On the other hand, the formation of slugs is influenced by the surface chemistry between the microchannel wall and the continuous phase, as well as that between the disperse phase and the latter.

Furthermore, microreactors with microchannels having bends and twists to effect chaotic advection have also been found to further intensify mixing [25, 26] in these systems, thus, having the potential to improve reaction output.

Looking at the diazotization reaction, instances of decomposition of diazonium salts subsequently causing explosions [27] have been reported. This clearly indicates the adverse effect of this reaction in industry and justifies the need for the generation and in-situ use of these compounds so as to avoid their isolation.

The cost of production and quality of the product cannot be overlooked in the synthesis of azo dyes and pigments [28]. This investigative research involved the synthesis of two azo pigments (yellow and red pigments) in microreactors where it was demonstrated that scaling out in the microreactors provided better and consistent quality of the pigments as compared to scale up in the batch vessels. A comparison of the scaled out microreactor lab and pilot plants also showed consistent quality in the pigments.

Similarly, yellow pigment 12 was also synthesized by using a micromixer apparatus [29]. Comparison of the results with the batch synthesis of the said pigment affirmed the notion that mixing is an essential unit operation in the synthesis of azo pigments. The said pigment synthesized in a micromixer (25 μm channel width) at a flow rate of 30 mL/min had smaller pigment size distribution compared to the batch synthesized pigment. The fast mixing in the micromixer was noted to be responsible for the improvement of glossiness (73%) and tinctorial strength (66%) of the yellow pigment thus yielding a good quality product.

It is also of note that, in our preliminary experiments prior to this study [30], we established that when the diazotization reaction was performed in a batch manner, the results attained could not be reproduced owing probably to the decomposition of the diazonium compound in solution and/or incomplete diazotization, which in turn affected the output of the azo-coupling reaction.

This is particularly a problem encountered in syntheses involving diazonium compounds in addition to the safety concern with regard to the explosive nature of these compounds. Performing both the diazotization and azo-coupling reaction in microreactors enables immediate use of the diazonium intermediate as is formed, thus, eliminating these concerns.

Equipped with the knowledge of the benefits of microreactor technology and phase transfer catalysis, we postulated that the synergy created by the combination of microreactor technology and phase transfer catalysis is bound to be a powerful tool in improving reaction output in this organic synthesis. We were thus driven to look at the diazotization as well as the phase transfer catalyzed azo-coupling reaction of these compounds in microreactors. In addition, a comparison of this reaction in microreactors to that in batch reactors was also worth investigating.

In this paper, we therefore report the optimization of diazotization of *p*-nitroaniline and phase transfer catalyzed azo-coupling reactions of highly hydrophobic aromatic amines, i.e., diphenylamine **5** in microreactors. We also look into the diazotization of a related primary aromatic amine and its in-situ coupling to triphenylamine **6**, 9-ethylcarbazole **7**, and carbazole **8** (Figure 3).

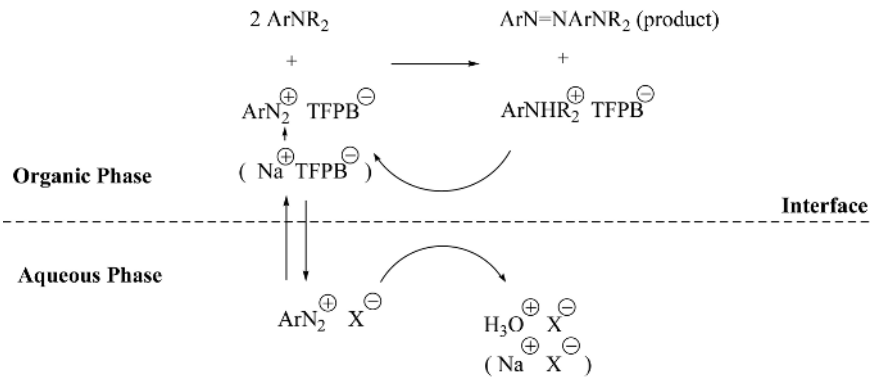


Figure 1. Iwamoto's proposed PTC diazo-coupling mechanism

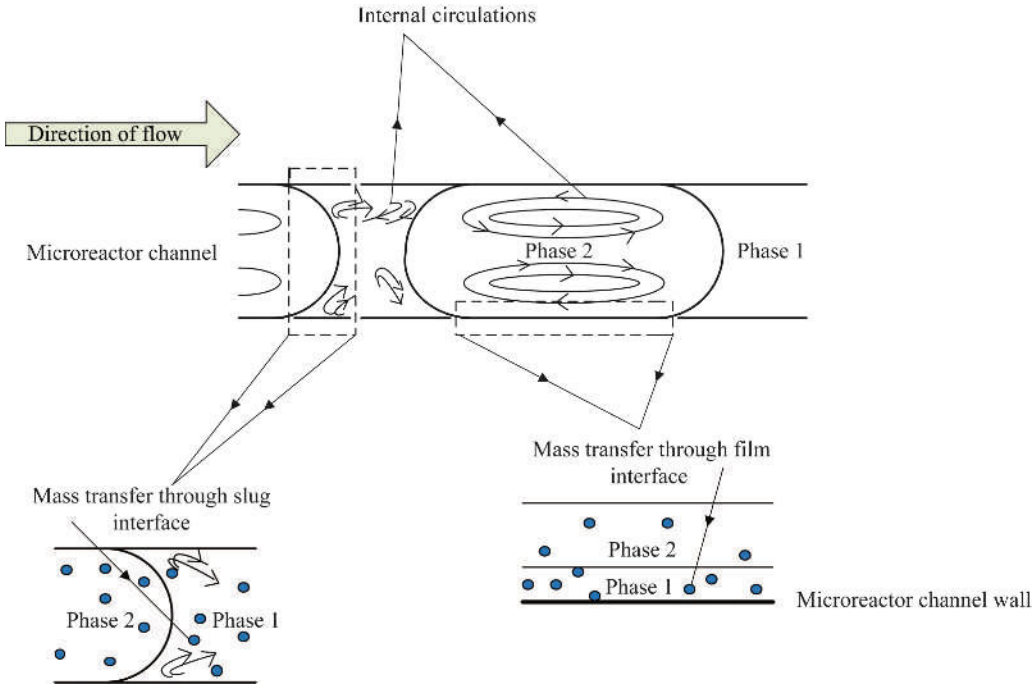


Figure 2. Mixing phenomena in biphasic microfluidic slug flow patterns

These coupling compounds **5**, **6**, **7**, and **8** are hardly soluble in aqueous solutions, and their azo-coupling reactions can only be efficiently effected with the use of organic solvents. Even then, the reaction is slow and an increase in reaction temperature only leads to the decomposition of the diazonium compound. However, in the presence of a phase transfer catalyst, the yield of the azo-coupling reactions of such compounds in batch reactors has been reported to have improved [19].

From literature, the reaction parameters that govern/control the diazotization and azo-coupling reactions under investigation in this study are quite palpable, i.e., reaction temperature, amount of phase transfer catalyst, and the flow of the reactants [13, 19, 23]. Our task was therefore to manipulate these parameters to attain an optimum reaction output which in our case was the conversion of the coupler. In addition, we were also interested in determining the robustness of the found optimum parameters to different and/or similar chemical substrates.

It is an objective of this paper to demonstrate the ease with which reaction optimization can be performed using continuous-flow microreactor technology. We also aim at highlighting how the effect of the combination of this technology and phase transfer catalysis will improve the synthesis of these rather very useful compounds. Furthermore, we benchmark the synthesis of these compounds in flow reactors.

2. Experimental Procedures

All chemicals and solvents used were of analytical grade.

2.1. Microreactor Setup. Using three (1 mL) SGE glass syringes and PTFE tubing, reactant solutions A (amine+HCl solution), B (sodium nitrite solution), and C (coupler+PTC solution) were fed into two T-mixers (Chemtrix T-mixer 3023; reactor volume: 10 μL, width channel size: 300 μm, depth channel: 60 μm, and quench volume: 1.5 μL) joined by PEEK tubing (ID 125 μm). Each T-mixer was equipped with a temperature controller unit. The delivery of the reactants was enabled by three Chemyx Fusion 100 syringe pumps (Figure 4).

2.2. Preparation of Reactant Solutions. Solution A (amine +HCl solution): *p*-Nitroaniline (0.056 g) was dissolved in hot concentrated HCl (15 mL, 0.067 M), and acetonitrile (30 mL) was added to this, after which the solution was made up to a volume of 100 mL with distilled water.

Solution B (sodium nitrite solution): Sodium nitrite (0.0603 g) was dissolved in distilled water (50 mL).

Solution C (coupler+PTC solution): Diphenylamine (0.035 g) and PTC (sodium dioctyl sulfosuccinate equivalent to primary aryl amine used) were dissolved in chloroform (50 mL).

2.2.1. Microreactor Diazotization and Consequent Phase Transfer Catalyzed Azo-Coupling Reactions. A central composite experimental design with a total of 54 experiments was used for this optimization study, where the diazotization of *p*-nitroaniline and its in-situ phase transfer catalyzed azo-coupling to diphenylamine was used as a general reaction. The experiments were performed in a randomized manner. The temperature of the diazotization reaction was kept constant at 0 °C while that of the phase transfer catalyzed azo-coupling reaction was varied (Table 1).

2.3. Sample Preparation. The microreactor setup was stabilized for 10 min between each experiment. In order to obtain substantial amount of samples for analysis, they were collected

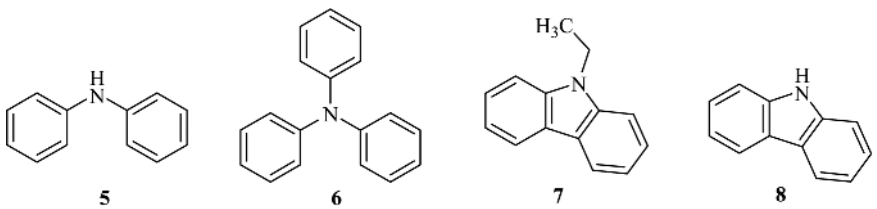


Figure 3. Azo-coupling compounds

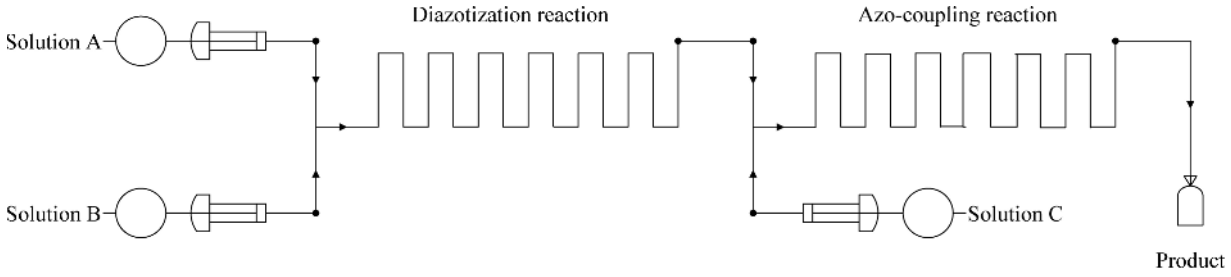


Figure 4. Schematic representation of the microreactor setup

for a period of 15 min each in a sample vial containing aqueous NaOH (0.2 mL of 2 M). The mixture was then diluted with methanol.

2.4. Batch Reactor Diazotization and Phase Transfer Catalyzed Azo-Coupling Reactions. Into a 50-mL one neck round bottomed flask, the diazonium salt solution was prepared by simple addition of solution A to solution B following a volumetric ratio obtained from the optimized microreactor synthesis. This was kept at 0 °C and stirred until potassium starch iodide paper test was positive (characteristic blue color indicating the formation of nitrous acid). A known volume of azo-coupling component solution C also obtained from the optimized microreactor conditions was thereafter added, and the mixture was subsequently heated via a water bath maintained at 50 °C. The setup was then mounted on a magnetic hot plate stirrer, and a magnetic stirrer bar of length 1 cm was employed to effect mixing at 700 rpm. Samples were taken periodically into sample vials containing aqueous NaOH (0.2 mL of 2 M). The mixture was then diluted with methanol.

2.5. Sample Analysis. Off-line reversed phase high-performance liquid chromatography (HPLC) using a Phenomenex Luna 5 μ C18 100A (250×4.60 mm×5 μm) column under the following conditions: flow rate of 1.2 mL/min and mobile phase (acetonitrile 0.1% formic acid (80:20)) equipped with a variable wavelength detector, was used for sample analysis. The external standard calibration HPLC method was used to quantify the amount of coupler utilized in the reaction. The wavelengths used for quantification of the couplers were as follows: diphenylamine — 285 nm, carbazole — 326 nm, triphenylamine — 324 nm, 9-ethylcarbazole — 310 nm, *n*-methylaniline — 300 nm, *N*,*N*-dimethylaniline — 292 nm and *m*-phenylenediamine — 300 nm.

2.6. Data Analysis. The total volume of samples collected ($tvs_{collected}$) was calculated by multiplying the total flow rate of the reactant solutions (tfr_{ABC}) by the total sample collection time ($t_{collection}$). The reaction time was calculated by dividing the total reaction space volume, i.e., the total volume of the two T-mixers, the PEEK tubing used to join the two mixers and also that leading to the final outlet: the point of sample collection by the total flow rate of reactant solutions (tfr_{ABC}). The total length of tubing that was used was 106.9 cm.

It was assumed that the actual flow rates as well as azo-coupling temperature were identical to the set values. For purposes of data as well as statistical analysis, all flow rates were converted to liters/minute.

3. Results and Discussion

3.1. Microreactor System. A Logit model was fitted onto the resultant calculated conversions of the diphenylamine as obtained from reversed phase HPLC analysis output (see Supporting Information for data analysis and modeling results). Statistica 12 Statsoft program was thereafter used to validate the model fitted. Using Solver-Excel program (2007), the optimum values for the reaction parameters were varied then determined and found to be as shown in Table 2.

The result of statistical multivariate regression analysis of the observed data is presented here in form of simple profile plots. These plots are based on the optimal reaction parameter values found. The Solver–Excel program also predicted a conversion of 99.12% at these optimal reaction parameter values.

3.1.1. Reaction Parameters Investigated

3.1.1.1. Phase Transfer Catalyst Equivalents with Respect to Diazotizable Primary Aromatic Amine. As is seen in Figure 5, the amount of phase transfer catalyst employed for the azo-coupling reaction clearly has an effect on the conversion of the azo-coupling compound with a gradual increase in conversion observed between 0.01 and 0.2 eq. of PTC. Beyond 0.2 eq. of PTC up to 0.5 eq., there appears to be almost no visible increase in the conversion. It is known that the use of anionic surfactants as phase transfer catalysts to increase the rate of chemical reactions in two phase media not only utilize their ability to increase the interfacial area [23] between the two phases by lowering the interfacial surface tension but also through micellar catalysis [31]. The effect of the latter phenomena on the rate of a chemical reaction can be confirmed by the behavioral trend of the rate of the reaction around the critical micelle concentration (CMC) of the surfactant employed.

Based on our predicted trend of the reaction conversion with increasing amount or concentration of surfactant in reactant solution, we suspect that a combination of lowered interfacial surface tension and micellar catalysis played a role in increasing the reaction conversion; more so that between PTC eq. of 0.01 and 0.2, the concentration of sodium dioctyl sulfosuccinate (NaDOSS) in the organic phase is lower than its CMC

Table 1. Experimental domain

Reaction parameters	Minimum	Maximum
HCl+amine (μL/min)	9	30
Sodium nitrite (μL/min)	1	5
Coupler (μL/min)	1	12
Temperature (°C)	0	50
PTC eq.	0.01	0.5

Table 2. Optimal reaction parameters

Reaction parameters	Optimal values
HCl+amine (μL/min)	9
Sodium nitrite (μL/min)	3.73
Coupler (μL/min)	5.06
Temperature (°C)	50
PTC eq.	0.418

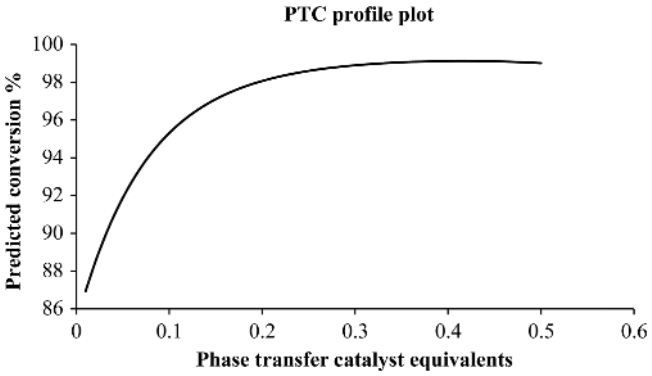


Figure 5. Phase transfer catalyst profile plot

(approximately 6.8×10^{-3} M) [32]. It can also be seen from the PTC profile plot (Figure 5) that, at these surfactant concentrations, there is a linear relationship between PTC eq. and conversion whereas, near the CMC, the reaction conversion is almost constant. This trend indicates that, for this particular reaction using DOSS and under the aforementioned experimental domain, no micellar catalysis inhibition is likely to be observed.

From the PTC profile plot in Figure 5, it can also be seen that the amount of PTC eq. in the azo-coupler solution that would provide highest predicted conversion is in the range of 0.25–0.5 eq. In summary, within this experimental domain, any increase in the amount of PTC beyond 0.25 eq. in the coupler solution does not enhance its ability to transport the diazonium ion across the interface into the organic phase where the azo-coupling reaction actually takes place. It must also be remembered that, since the PTC was dissolved in the organic phase, i.e., solution C: coupler solution, the rate of addition of this solution to the in-situ formed diazonium salt solution will have an effect on the reaction conversion as is explained in the next section.

3.1.1.2. Flow Rate of Coupling Solution. Looking at the coupler flow rate profile plot, it is predicted that a drop in the conversion of coupling compound is expected at higher flow rates. This is due to insufficient time of contact of the two reactants, i.e., diazonium compound and the coupling compound solutions or the very short residence times resulting from the high flow rates although the azo-coupling reaction in itself is regarded to be a relatively fast reaction. From Figure 6, the preferred flow rate of azo-coupler solution was predicted to be in the range of 2–8 μL/min.

3.1.1.3. Flow Rate of Sodium Nitrite Solution. The amount of sodium nitrite is crucial in the direct diazotization of primary aryl amines since it is the source of the nitronium ions that in turn are involved in the in-situ formation of nitrous acid. In this study, the optimum concentration of the nitrosating agent (sodium nitrite) employed was not investigated. Following literature, a stoichiometric equimolar amount or a slight excess is usually used in the diazotization reaction. A sodium nitrite concentration of 0.017 M, a slight excess, was chosen for the study (Figure 7).

Using our predictive model, it was shown that, at high flow rates of sodium nitrite in the range of 2–5 μL/min, conversions higher than 98 % should be expected. This is because the rate of addition of sodium nitrite to the hydrochloride solution of the primary aryl amine is also important in the diazotization reaction. The sodium nitrite should be added at such a rate that there is no excess of nitrous acid formed in the reaction solution.

3.1.1.4. Temperature of Coupling Reaction. The predictive model shows that, as the temperature increases, the conversion of the coupler increases nonlinearly. This can be explained by the fact that an increase in temperature also reduces the surface tension between the two phases, thus, facilitating the transfer of reactants across the liquid interface (Figure 8).

To this end, a confirmatory experiment was carried out in the microreactors at the found optimal values of the investigated reaction parameters. The level of reproducibility can clearly be seen (Table 3) from the experiments performed at the said optimal parameters values.

The optimal reaction parameters were therefore used to affect both the diazotization of *p*-nitroaniline and 2-chloro-4-nitroaniline with their subsequent azo-coupling to aromatic amines triphenylamine, 9-ethylcarbazole, and carbazole with the aim of investigating the substituent effect of the diazotizable primary aromatic amine as well as coupler on conversion. The findings of this investigation are summarized in Table 4.

3.1.2. Microreactor Chip versus the Round Bottomed Flask. A simple comparison of the efficiency of the microreactor system to the batch reactor system showed the superiority of microreactor technology in combination with phase transfer catalysis in the synthesis of azo dyes from highly hydrophobic aromatic amines as azo-coupling components.

From the above summary of the results, we see that the in-situ phase transfer catalyzed azo-coupling reactions of the aforementioned couplers in the microreactor system give comparable conversions and slightly shorter residence times as compared to that seen in the batch reactor system used in this study. Taking any of the above runs involving carbazole **8** and 9-ethylcarbazole **7** as an example, in an approximate total residence time of 2.4 min for both diazotization and azo-coupling reactions in the microreactor setup, higher conversions were attained whereas the azo-coupling reaction in the batch reactor system in 3 min provided comparable conversions. However, it is important to remember that the diazotization

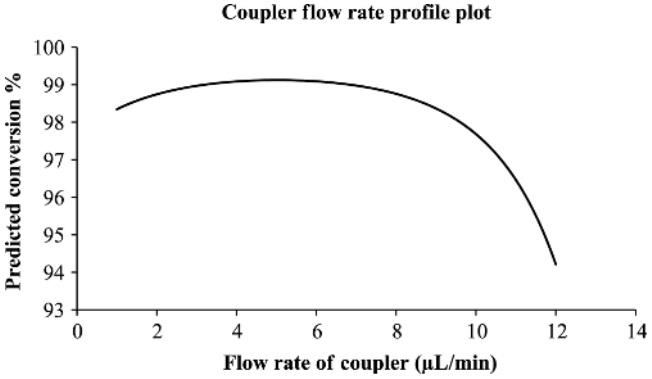


Figure 6. Profile plot describing the effect of the coupler flow rate on the predicted conversion of coupler

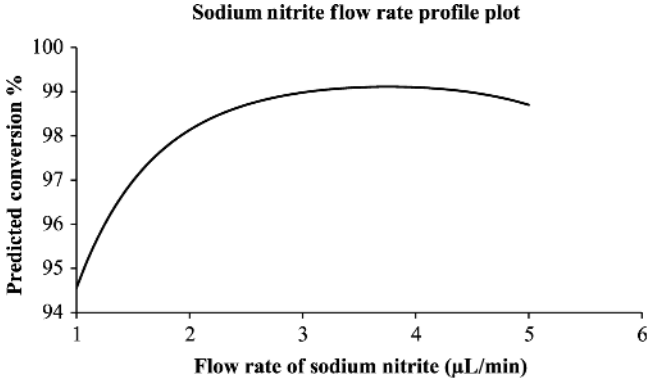


Figure 7. Profile plot showing the effect of the flow rate of sodium nitrite on the predicted conversion of coupler

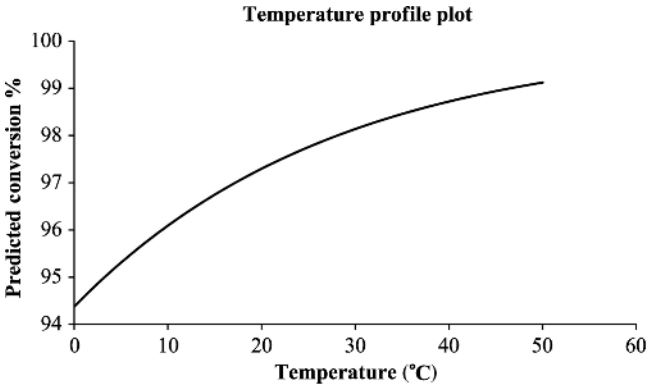


Figure 8. Profile plot showing the effect of temperature on coupler conversion

reaction was carried out separately in this system as opposed to the microreactor system where both reactions were performed in microreactor chips.

Substituent effects were also observed in our investigation. These were evident in the conversions obtained (Table 4). Comparing reactions that involved carbazole **8** and 9-ethylcarbazole **7** as couplers, this effect is seen with the latter coupler seeming more difficult to couple than the former. A closer look at the substituent effect on the diazotizable primary aromatic amine seems to suggest that the more substituted the amine, the higher the conversion especially for carbazole **8** and 9-ethylcarbazole **7**. This could probably be ascribed to the increase in electron withdrawing ability of the attached halogen group on the benzene ring of the diazotizable primary aromatic amine thus increasing its electrophilicity.

Since the optimal reaction parameters used herein were specific to the diazotization of *p*-nitroaniline and its in-situ phase transfer catalyzed azo-coupling to diphenylamine, it is an obvious inkling that an increase in the residence time either by reducing the flow rate of the reagents or by addition of residence microreactor chips to the setup will improve the reaction conversion especially in the in-situ azo-coupling reactions involving carbazole **8** and 9-ethylcarbazole **7**. Clearly, the products produced in lower conversion could be further optimized by following this procedure.

We also found that the addition of a solvent to the hydrochloride solution of the diazotizable primary aromatic amine reduced the chances of blockages by avoiding the precipitation of the amine from solution. This can also be circumvented by the use of very dilute solutions during reaction screening and optimization stages; better still, reaction tailored microreactor chips can be also employed. The choice is left to the chemist; nonetheless, useful information can be attained with which ever approach is chosen to combat particulate formation that eventually leads to blockages in these microfluidic systems.

A major drawback of the batch reactor systems is their inability to facilitate the use of solvents above their boiling points and this was in fact affirmed in this study. The batch synthesis of these compounds at the optimal microreactor reaction temperature (50 °C) was problematic owing to the fact that one of the solvents employed in the synthesis has a boiling point lower than this (dichloromethane boiling point: 40 °C).

Table 3. Experiments at optimal reaction parameter values

Run	Amine[a] (μL/min)	Nitrite[b] (μL/min)	Coupler[c] (μL/min)	Temperature (°C)	PTC[d] eq.	Conversion (%)
1	9	3.7	5.1	50	0.42	99.95
2	9	3.7	5.1	50	0.42	99.95
3	9	3.7	5.1	50	0.42	99.94
4	9	3.7	5.1	50	0.42	99.96
5	9	3.7	5.1	50	0.42	99.96

[a] Amine — flow rate of HCl+amine (*p*-nitroaniline) solution.
[b] Nitrite — flow rate of sodium nitrite solution.
[c] Coupler — flow rate of coupler (diphenylamine) solution.
[d] PTC eq. — phase transfer catalyst equivalents.

Table 4. Comparison of microreactor and batch reaction output

Run	Diazotizable amine	Coupler	Conversion (%)	
			Microreactor[RT1]	Batch[RT2]
1[a]	*p*-Nitroaniline	Diphenylamine[1]	99	94
2[b]	*p*-Nitroaniline	*m*-Phenylenediamine[1]	99	99
3[b]	*p*-Nitroaniline	*n*-Methylaniline[1]	99	100
4[b]	*p*-Nitroaniline	*N*,*N*-dimethylaniline[1]	99	100
5[a]	*p*-Nitroaniline	Triphenylamine[1]	33	89
6[a]	*p*-Nitroaniline	Carbazole[2]	22	20
7[a]	*p*-Nitroaniline	9-Ethylcarbazole[3]	27	21
8[a]	2-Chloro-4-nitroaniline	Diphenylamine[1]	93	96
9[a]	2-Chloro-4-nitroaniline	Carbazole[2]	72	63
10[a]	2-Chloro-4-nitroaniline	Triphenylamine[1]	69	96
11[a]	2-Chloro-4-nitroaniline	9-Ethylcarbazole[3]	35	23

[a] 2 moles of diazotizable amine : 1 mole of coupler, [b] 1 mole of diazotizable amine : 1 mole of coupler. [RT1] Reaction time approx. 2.4 min. [RT2] Reaction time approx. 3 min. Aprotic nonpolar solvent used: [1] (chloroform), [2] (dichloromethane), [3] (1,2-dichloroethane).

4. Conclusion

Microreactor technology, as has been shown here, first and foremost, reduces the time needed for reaction parameter screening. The combination of phase transfer catalysis and microreactor technology in the azo-coupling of nonbasic aromatic amines greatly improves the reaction output and slightly shortens reaction times. These findings will definitely be of great importance to the synthesis of azo compounds with more of the highly hydrophobic aromatic amines utilized as azo-coupling components. Although the reaction times are similar to batch, clearly, it is important to emphasize that this approach also provides enhanced safety, scalability, environmental advantages, ease of work up, and collection. We can confidently state that the combination of these two ways of performing this organic synthesis will add the "green" to azo chemistry.

Acknowledgements. We would like to thank the South African National Research Foundation, InnoVenton, and Nelson Mandela Metropolitan University for the financial support.

Supporting Information

Electronic Supplementary Material (ESM) is available in the online version at doi: 10.1556/1846.2016.00003.

References

1. Wainwright, M. *Dyes Pigm.* **2008,** *76,* 582.
2. Baltac, T.; Vlad, G.; Sebe, I. *Rev. Chim. (Bucharest)* **2012,** *63*, 18–21.
3. Antoine, C.; Anton, A.; Urs, L.; Anthanassios, T. Azo dyes, a process for their preparation and their use in the production of coloured plastics or polymeric colour particles and in dyeing or printing of hydrophobic fibre materials. (October 17, 2007). EP 1 366 122 B1, 2007.
4. Baur, R.; Macholdt, H.-T.; Nickel, U.; Unverdorben, L.; Wille, C. Preparation of azo colourants in microreactor and their use in electrophotographic toners and developers, ink jet inks and electronic medias (December 18, 2007). US 7,309,389 B2, 2007.
5. Giancola, G.; Schlossman, M. L. In *Cosmeceuticals and Active Cosmetics*, 3rd ed.; CRC Press: Florida, 2015; pp. 191–220.
6. Chung, K. *J. Environ. Sci Health, Part C: Environ. Carcinog. Ecotoxicol Rev.* **2000,** *18*, 51–74.
7. Wang, C.; Yediler, A.; Lienert, D.; Wang, Z.; Kettrup, A. *Chemosphere* **2002**, *46,* 339–344.
8. Godovikova, T. I.; Rakitin, O. A.; Khmel, L. I. *Russ. Chem. Rev.* **1983,** *52*, 440–445.
9. Hunger, K. *Industrial Dyes: Chemistry, Properties, Applications,* 2nd ed.; Wiley-VCH: Weinheim, 2003; pp. 115–124.
10. Saunders, K. H. *The Aromatic Diazo-Compounds and Their Technical Applications*, 2nd ed.; E. Anorld: London, 1949; pp. 3–20.
11. Cain, J. C. *The Chemistry of Diazo-Compounds*; E. Arnold: London, 1908; pp. 6–11.
12. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Texbook of Practical Organic Chemistry*, 5th ed.; Longman: England, 1989; pp. 920–922.
13. Christie, R. M. *Colour Chemistry*; The Royal Society of Chemistry: Cambridge, 2001; pp. 56–58.
14. Finar, I. L. *Organic Chemistry Volume One: The Fundamental Principles*, 3rd ed.; Longmans: London, 1956; pp. 589–591.
15. Jovanovic, S.; Vico-Stevanovic, M.; Ugljesic-Kilibarda, D.; Popadic, D.; Simic, S.; Dzeletovic, D. J. *Serb. Chem. Soc.* **2006,** *71,* 867–887.
16. Halpern, M. *Ind. Phase Transfer Catal.* **2007,** *19,* 1.
17. Yadav, G. D. *Top. Catal.* **2004,** *29,* 145–161.
18. Iwamoto, H.; Yoshimura, M.; Sonoda, T. *Bull. Chem. Soc. Jpn.* **1983,** *56,* 796–801.
19. Ellewood, M.; Gregory, P.; Griffiths, J. Azo dyestuff preparation by phase transfer catalysed coupling in a two-phase medium (May 13, 1981). EP 0 028 464 A1.
20. Ellewood, M.; Griffiths, J.; Gregory, P. *J. Chem. Soc. Chem. Commun.* **1980,** 181–183.
21. Wootton, R. C. R.; Fortt, R.; De Mello, A. J. *Lab. Chip* **2002,** 5–7.
22. Fortt, R.; Wootton, R. C. R.; De Mello, A. J. *Org. Process Res. Dev.* **2003,** *7,* 762–768.
23. Hisamoto, H.; Saito, T.; Tokeshi, M.; Hibara, A.; Kitamori, T. *Chem. Commun.* **2001,** 2662–2663.
24. Zhao, C.-X.; Middelberg, A. P. J. *Chem. Eng. Sci.* **2011,** *66,* 1394–1411.
25. Song, H.; Tice, J. D.; Ismagilov, R. F. *Angew. Chem., Int. Ed.* **2003,** *115*, 792–796.
26. Gunther, A.; Jhunjhunwala, M.; Thalmann, M.; Schmidt.; M. A.; Jensen, K. F. *Langmuir* **2005,** *21,* 1547–1555.
27. Partington, S.; Waldram, S. *Process Saf. Environ.* **2002,** *80,* 33–39.
28. Wille, C.; Gabski, H.; Haller, T.; Kim, H.; Unverdorben, L.; Winter, R. *Chem. Eng. J.* **2004,** *101,* 179–185.
29. Pennemann, H.; Forster, S.; Kinkel, J.; Hessel, V.; Lowe, H.; Wu, L. *Org. Process Res. Dev.* **2005,** *9,* 188–192.
30. Akwi, F. M. *Scalable Chemistry Involving Diazonium Compounds,* PhD thesis, Nelson Mandela Metropolitan University, 2016.
31. Doronin, S. Y.; Chernova, R. K. *Russ. J. Gen. Chem.* **2008,** *78,* 2019–2024.
32. Myers, D. *Surfactant Science and Technology*, 3rd ed.; Wiley: New Jersey, 2005; p. 137.