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Controlled Transformations of Aryl Halides in a Flow System: Selective Synthesis of Aryl Azides and Aniline Derivatives

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Abstract. Copper-mediated nitrogenation of aryl halides with sodium azide can result in either aryl azides or aniline derivatives. The selectivity of the transformation is highly dependent on reaction time and temperature, which led to contradictory literature results with respect to product selectivity and the conditions applied. The advantages of a strictly controlled flow reactor environment were exploited in order to facilitate selective haloarene transformations. Reaction conditions were carefully investigated to understand their role on product selectivity.

Aryl azides and aryl amines were successfully prepared from the same starting materials using the same auxiliaries by means of precise control over residence time and reaction temperature, thereby ensuring time-, cost- and atom-efficient syntheses.

Keywords: aryl halides, aryl azides, aniline derivatives, copper catalysis, flow chemistry, residence time

Introduction

Aryl azides and aryl amines play prominent roles in synthetic and pharmaceutical chemistry. Both can be transformed into a wide range of valuable chemical structures (Scheme 1)[1] and they are essential in the construction of various *N*-heterocycles.[1a, 2] As a consequence of their significant importance in click reactions, azides are popular coupling partners in bioorthogonal chemistry.[3] The azide function is an isosteric substituent of numerous functional groups including isocyanate, methylsulfonyl and aminosulfonyl groups. In addition, azide derivatives of pharmaceutically active compounds can exhibit increased biological activity.[4]

In the most important synthetic pathways towards aryl amines, nitro compounds,[5] aryl halides[6] and arylboronic acids may be utilized as starting materials.[7] Catalytic reduction of nitro compounds is quite well-established; however, in some cases, it requires various transition metal catalysts, expensive ligands and/or harsh reaction conditions.[5b,5c] The price and low availability of arylboronic acids also constitute a reasonable limit for practical applications. For the convenient synthesis of aniline derivatives and aryl azides, copper-mediated reactions of aryl halides with sodium azide were also demonstrated.[8]
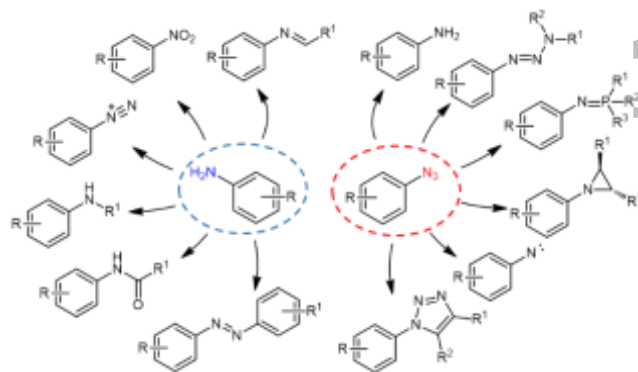
Scheme 1. Examples for the transformation of aryl amines and aryl azides.[1a, 2]

As a consequence of the price and easy availability of common copper salts and haloarene starting materials, these reactions have recently come into the focus of interest. On the other hand, the selectivity of these transformations strongly depends not only on the materials (i.e. solvent, catalyst and different auxiliaries) but also on the conditions (i.e. temperature and reaction time) applied (Scheme 2). For example, Ma and Zhu synthesized aryl azides by reacting aryl halides with sodium azide catalyzed by CuI/L-proline under relatively mild conditions (40–70 °C, 5–24 h reaction time).[8] Similar results were achieved later in the presence of a porous copper metal catalyst and L-

proline as ligand.[9] It was also shown that the reaction time could significantly be reduced in the presence of Na ascorbate and various diamine ligands.[10] Additionally, azidation of aryl halides was also performed at somewhat higher temperatures (>100 °C) applying heterogeneous CuFeO₂ as catalyst in the presence of L-proline and NaOH as auxiliaries.[11] Interestingly, very similar conditions were reported for the copper-catalyzed synthesis of aniline derivatives from aryl halides, using sodium azide as the amine source.[12] For instance, Helquist and co-workers achieved direct amination of aryl halides applying various Cu(I) salts with L-proline or N,N'-dimethylethylenediamine (DMEDA) as ligand at 100 °C.[12c] Copper metal and CuSO₄·5H₂O in combination with ascorbic acid (or Na ascorbate) and various ligands were also successfully utilized in the synthesis of substituted anilines from haloarenes at temperatures of 60–100 °C.[12b, 12d]
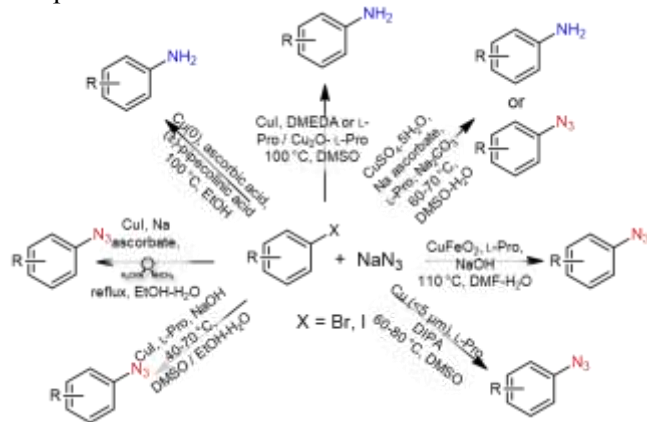
Scheme 2. Copper-catalyzed reactions between aryl halides and sodium azide.[8-12]

It is clearly visible that in spite of the efforts having made in copper-catalyzed aryl halide transformations, the exact effects of reaction conditions are still unclear. The confusing literature results, with respect to whether the products are aryl azides or amines, may be explained by facile azide reduction/decomposition.[12b-d] With strict control over the important reaction conditions, the contradictions in product formation may be resolved, and selective and reproducible synthesis of both aryl azides and aniline derivatives would possibly be accomplished.

On the basis of the above findings, we envisioned that the application of flow chemistry may be a practical strategy for the controlled transformations of aryl halides.[13] In order to realize a diversity-oriented synthesis method,[14] we aimed to selectively synthesize both classes of valuable products from the same haloarenes as starting materials using the same auxiliaries and changing only reaction conditions. The residence time in the active reactor zone can precisely be regulated by the fluid flow rate,[15] which can affect the chemo- and even the stereoselectivity of the reaction.[16] Another point is that the transfer of thermal energy in flow reactors occurs in a highly controlled manner,[17] which contributes to homogeneous temperature distribution thereby hindering side-reactions.[18] We therefore set out to regulate the azide–amine equilibrium and hence the chemoselectivity of the reactions on demand by using strategic control over both residence time and reaction temperature.

Thus, we are presenting our results on a selective continuous-flow approach for the copper-mediated synthesis of aryl azides and aryl amines using the corresponding halides as practical starting materials.

Results and Discussion

At the beginning of our investigation, we assembled a simple continuous-flow apparatus. Because of its low price, non-toxicity and easy availability, we envisioned that copper metal may act as a practical source for catalytically active species.[19] Copper powder was therefore loaded into stainless steel columns (internal dimensions: 4.6×50 mm or 4.6×100 mm) serving as packed-bed reactors. The catalyst bed was immersed into an oil bath for heating purposes and a 50-bar backpressure regulator (BPR) was also installed in order to overheat solvents.[20]

On the basis of literature data, NaN₃ was selected as a source for azide anions together with L-proline and N,N-diisopropylethylamine (DIEA) serving as ligand and base, respectively.[8, 11, 12b, 12c, 12e] 4-Iodoanisole was chosen as a model substrate for an initial optimization study (Scheme 3).

Scheme 3. Copper-catalyzed nitrogenation of 4-iodoanisole with NaN₃ as nitrogen source in a continuous-flow reactor.

Because of the differences in solubility of the starting materials (i.e. the haloarene, NaN₃, L-proline and DIEA), a careful solvent compatibility test was carried out in order to prevent precipitation during reactions and the concomitant blockage in the reactor channels. The solvent mixtures MeCN/H₂O 3:1, EtOH/H₂O 7:3 and DMSO/H₂O 4:1 proved to be suitable and offered a homogeneous reaction medium when 4-iodoanisole was applied in a reasonable concentration of 0.1 M in the presence of 2 equivalents of NaN₃ along with 30 mol% of L-proline and 30 mol% of DIEA as auxiliaries. The effect of the above solvent systems was next investigated under continuous-flow conditions at 120 °C utilizing a residence time of 7 min (0.1 mL min⁻¹ flow rate) on a 50-mm long copper column as catalytic source (4.6×50 mm stainless steel column charged with 2 g of copper powder). As results in Figure 1 indicate, the solvents applied had a significant effect on both conversion and selectivity. MeCN/H₂O and EtOH/H₂O performed far below optimal with conversions of <40%. In DMSO/H₂O, in

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turn, almost full conversion was measured and the corresponding azide was detected as the main product with an azide/amine ratio of 71:29.
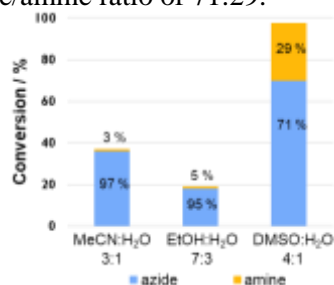

Figure 1. Solvent effects on the continuous-flow nitrogenation of 4-iodoanisole with NaN_3 as nitrogen source (Scheme 3). Conditions: 1 equivalent 4-iodoanisole (c= 0.1 M), 2 equivalents NaN_3, 30 mol% L-proline, 30 mol% DIEA, 120 °C, 50 bar, 0.1 mL min^{-1} flow rate (7 min residence time), 4.6×50 mm copper column as catalytic source. (Product selectivity is marked with blue/orange column components.)

Having established DMSO/H_2O 4:1 as a suitable reaction medium, the effects of reaction temperature were next investigated on a fixed residence time of 7 min (0.1 mL min^{-1} flow rate). As expected, the temperature had crucial effects on both conversion and product selectivity (Figure 2). Heating the reaction zone from 75 °C to 120 °C resulted in a significant increases in conversion (from 47% to 98%). However, higher temperatures led to significant amine formation; for example, to an extent of 28% at 120 °C. Interestingly, elevation of the reaction temperature from 120 to 150 °C did not exert any substantial change in product selectivity, the amine/azide product ratio remained constant around 30:70.
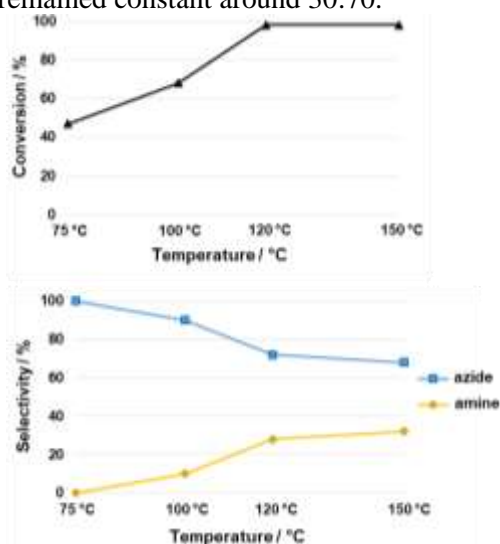

Figure 2. The effect of temperature in the 4-iodoanisole–NaN_3 model reaction (Scheme 3) using a 4.6×50 mm copper column as catalytic source. Conditions: 1 equivalent 4-iodoanisole (c= 0.1 M), 2 equivalents NaN_3, 30 mol% L-proline, 30 mol% DIEA, DMSO/H_2O 4:1 as solvent, 50 bar, 0.1 mL min^{-1} flow rate (7 min residence time).

The examination of the effects of the auxiliaries led to the conclusion that the ligand is essential for the reaction: only trace amounts of products were detected without added proline, even at a temperature as high as 150 °C (Table 1, entry 1 vs entry 2). In contrast to previous literature findings[8, 11, 12e], DIEA as base could be omitted without measurable change in the reaction rate (entry 3). Upon reducing the amount of the ligand to 15 mol%, conversion decreased significantly (entry 4). Gratifyingly, however, the excess of NaN_3 could be reduced to 1.5 equivalents without any loss in conversion (entry 5).

Table 1. The effect of auxiliaries in the 4-iodoanisole–NaN_3 model reaction (Scheme 3) using a 4.6×50 mm copper column as catalytic source.[a]

Entry	L-Pro (mol%)	DIEA (mol%)	NaN_3 (equiv.)	Conv.[a] (%)	Azide/amine ratio[b]
1	30	30	2	98	72:28
2[c]	0	30	2	9	50:50
3	30	0	2	94	70:30
4	15	0	2	72	72:28
5	30	0	1.5	92	74:26

[a] Conditions: 1 equivalent 4-iodoanisole (c= 0.1 M), DMSO/H_2O 4:1 as solvent, 120 °C, 50 bar, 0.1 mL min^{-1} flow rate (7 min residence time). [b] Determined by ^1H NMR spectroscopy of the crude material. [c] 150 °C reaction temperature.

Figure 3. The effect of residence time in the 4-iodoanisole–NaN_3 model reaction (Scheme 3) using a 4.6×50 mm copper column as catalytic source. Conditions: 1 equivalent 4-iodoanisole (c= 0.1 M), 1.5 equivalents NaN_3, 30 mol% L-proline, DMSO/H_2O 4:1 as solvent, 120 or 150 °C, 50 bar.

The effect of residence time was next investigated at various temperatures (Figure 3). At 120 °C, conversions decreased sharply from 97% to 63% upon decreasing the residence time from 25 to 3.5 min. Product selectivity, in turn, was only slightly affected: the azide ratio remained around 70–80% at each flow

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rate applied. It is significant that at 150 °C, product selectivity could practically be inverted with the residence time, while the conversion remained in the range of 86–100%. Specifically, at a residence time of 25 min (corresponding to 0.03 mL min⁻¹ flow rate), the azide/amine ratio was 21:79 (100% conversion). In contrast, upon reducing the residence time to 3.5 min (corresponding to a flow rate of 0.2 mL min⁻¹), the azide/amine product selectivity changed to 78:22 at 86% conversion.

Beyond a certain limit, the simultaneous control of conversion and selectivity cannot be achieved through the sole modification of the fluid flow rate, therefore the volume of the catalyst bed also needs to be increased.[15a] In order to achieve a more detailed picture with respect to the effects of residence time and reaction temperature, we selected a longer copper column as catalytic source (4.6×100 mm stainless steel column charged with 3.5 g of copper powder) and carried out some additional optimization. Initially, the flow rate was fixed at 0.1 mL min⁻¹ (corresponding to 10.5 min residence time), and the temperature was increased step-wise from 75 to 150 °C. This resulted in a sharp increase in conversion, similar to that observed previously with the shorter copper column (Figure 4 vs. Figure 2). Moreover, we were delighted to find higher selectivities towards azide formation in the 75–120 °C temperature range. The best results were found at 100 °C with a conversion of 83% and an azide/amine ratio of 94:6 (Figure 4). In order to achieve the selective synthesis of the desired amine as well, the effects of the residence time were next examined at a fixed temperature of 150 °C (Figure 5). Gratifyingly, the amount of azide decreased strongly with decreasing flow rates. The corresponding amine was formed with an excellent selectivity of 98% at complete conversion using a residence time of 35 min (equal to 0.03 mL min⁻¹ flow rate).

Figure 4. The effect of temperature in the 4-iodoanisole–NaN₃ model reaction (Scheme 3) using a 4.6×100 mm copper column as catalytic source. Conditions: 1 equivalent 4-iodoanisole (c= 0.1 M), 1.5 equivalents NaN₃, 30 mol% L-proline, DMSO/H₂O 4:1 as solvent, 50 bar, 0.1 mL min⁻¹ flow rate (10.5 min residence time).
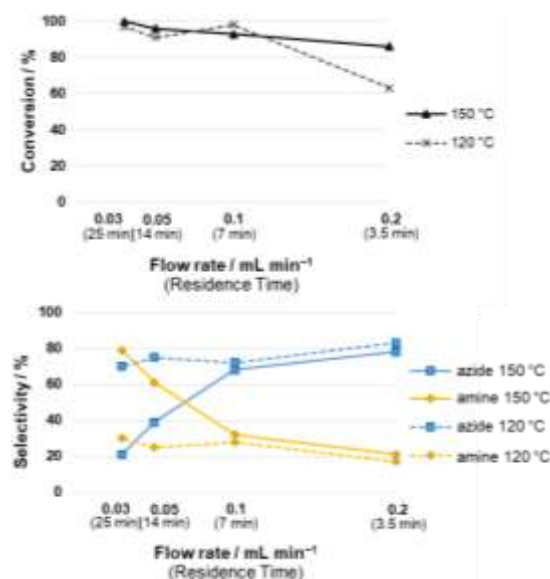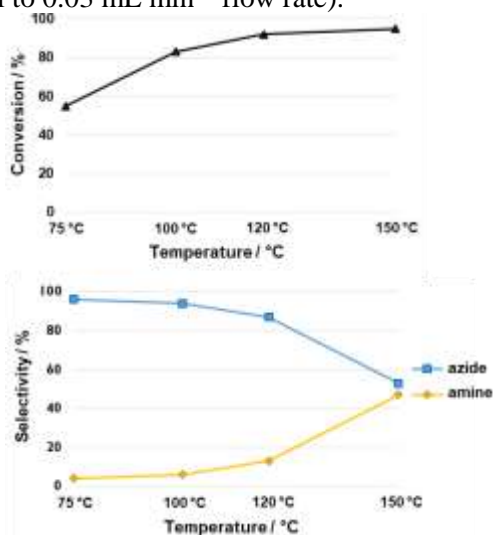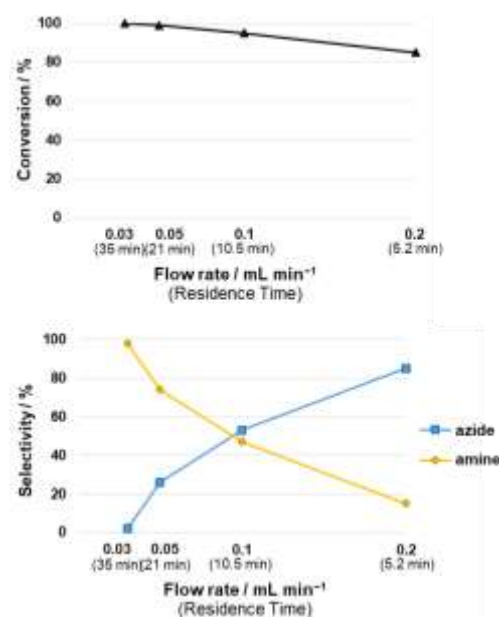

Figure 5. The effect of residence time in the 4-iodoanisole–NaN₃ model reaction (Scheme 3) using a 4.6×100 mm copper column as catalytic source. Conditions: 1 equivalent 4-iodoanisole (c= 0.1 M), 1.5 equivalents NaN₃, 30 mol% L-proline, DMSO/H₂O 4:1 as solvent, 150 °C, 50 bar.

On the basis of the above observations, we had two distinct sets of parameters in hand for the selective synthesis of either 1-azido-4-methoxybenzene or 4-methoxyaniline using the corresponding aryl iodide as starting material (Figure 6). We managed to obtain both products by using precise control over reaction temperature and residence time without changing the quality or the quantity of the materials applied. The data obtained clearly suggest that the sensitive reaction system of copper-mediated azidation and azide reduction/decomposition is strongly affected not only by the nature of the materials applied but also by the reaction time and temperature. Such precise control over the reaction parameters is not available in conventional batch reactions, which may explain the inconsistency of earlier literature observations. It should also be noted that the increased temperature and pressure ranges in combination with the high local catalyst concentration offered a marked chemical intensification over previous batch reactions,[8, 10-11, 12b-e, 21] and ensured time- and atom-efficient syntheses.
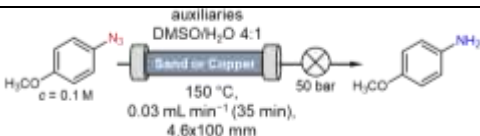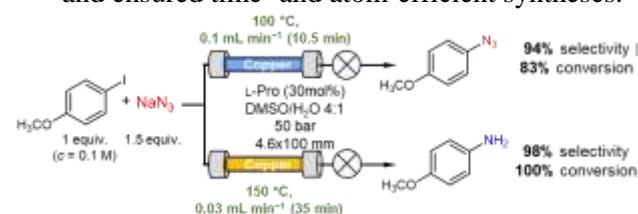

Figure 6. Optimal reaction parameters for the diversity-oriented synthesis of 4-methoxyaniline and 1-azido-4-methoxybenzene from 4-iodoanisole as starting material.

Table 2. Investigation of the nature of the azide–amine transformation in the case of 1-azido-4-methoxybenzene in a continuous-flow reactor.

Entry	Column packing	L-Pro (mol%)	NaN$_3$ (equiv.)	Azide/amine ratio[a]
1	Quartz sand	-	-	100:0
2	Quartz sand	-	1.5	52:48
3	Copper powder	-	-	0:100
4[b]	Copper powder	-	-	84:16
5[b]	Copper powder	30	-	70:30

[a] Determined by ^{1}H NMR spectroscopy of the crude material. [b] 75 °C temperature

It is quite clear that after copper-mediated azidation, subsequent azide reduction/decomposition is of crucial importance for product selectivity.[12b-d] However, the nature of this step is still ambiguous: the thermal decomposition of azides has been known from the literature from a long time.[22] There are examples for copper-mediated azide decomposition/reduction,[23] and there are a few previous reports in which azide anions (from NaN$_3$) are suggested to operate as the reducing agent.[12c, 24] To obtain additional mechanistic insights, the thermal stability of the preformed azide was investigated on a 4.6×100 mm inert column (packed with quartz sand). Utilizing the optimal temperature and residence time developed previously for the selective aryl amine synthesis (150 °C and 35 min), no amine formation was detected, and 1-azido-4-methoxybenzene was quantitatively recovered after the experiment (Table 2, entry 1). Interestingly, when the experiment was repeated in the presence of 1.5 equivalents of NaN$_3$ (under otherwise identical conditions), significant amine formation occurred and an azide/amine ratio of 1:1 was measured in the crude product mixture (entry 2). Next, preformed 1-azido-4-methoxybenzene was pumped through a 4.6×100 mm copper column under the previously set conditions (150 °C and 35 min residence time). In this case, quantitative amine formation was detected (entry 3). Upon changing the reactor temperature to 75 °C, amine formation decreased to a mere 16% (entry 4). However, the amount of the amine could be increased to 30% in the presence of L-proline (entry 5). These experimental results indicate that the azide–amine transformation is not a purely thermal process. Rather, it is strongly dependent on both the catalytic metal and the auxiliaries present. According to earlier reports,[23a, 25] it seems feasible that copper-induced decomposition of the initially formed aryl azide leads to an aryl

nitrene intermediate (possibly complexed with copper), which then evolves into the final amine. In view of the data in Table 2, entry 2, it can be surmised that NaN$_3$ also contributes somewhat to the decomposition of the organic azide, while L-proline works as a ligand making the catalyst more accessible.

Table 3. Continuous-flow synthesis of various aryl amines from aryl halides as starting materials.

Entry	Starting material	Product	Conv.[a] (%)	Select.[a] (%)
1			100 (90)[b]	98
2			94	100
3			100	100
4			100	100
5			100 (93)[b]	100
6			100	95
7			98	100
8			100 (92)[b]	100
9			91	89
10			100	100
11			60	100
12			88 (79)[b]	100
13			100	90
14			81	100

[a] Determined by ^{1}H NMR spectroscopy of the crude material. [b] Isolated yield.

Finally, the scope and limits of the methodology were explored. The conditions developed for the selective haloarene–aryl amine transformation (150 °C and 35 min residence time on a 100-mm long copper column) worked very well with diversely substituted aryl iodides. Both electron-donating and electron-withdrawing substituents were nicely tolerated, and the corresponding substituted anilines were formed in excellent conversion (94–100%) and, in most cases, with perfect chemoselectivity (Table 3, entries 1–8). Note that isolated yields were also determined in a few representative cases. The reactivity of aryl bromides was also investigated (entries 9–14). Both *para*- and *meta*-substituted substrates gave excellent selectivities (between 89 and 100%) and high conversions similar to those of iodo derivatives (entries 9, 10 and 13).

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ortho-Substituted aryl bromides (entries 11, 12, 14), in turn, were less reactive (conversions of 60–88%), possibly because of steric hindrance. Nevertheless, the desired aromatic amines formed exclusively under the conditions investigated. It is important to point out that the flow methodology nicely tolerated various aryl halides decorated with readily convertible functional groups (see entries 8, 12, 13 and 14). These findings are of high importance as concerns further transformations of the anilines obtained.

Because of the sensitivity of azide reduction/decomposition, the selective aryl azide syntheses proved more challenging. The temperature and residence time (100 °C, 10.5 min), optimized previously for the 4-iodoanisole–NaN₃ model reaction, had to be modified for each substrate to obtain satisfactory conversions and selectivities (Table 4). In a few cases, only minor changes in the substitution pattern of the starting material led to significant changes in the reaction outcome. For example, 1-iodo-4-methylbenzene and 1-iodo-4-ethylbenzene were transformed to the corresponding azides with only poor selectivities (11 and 36%, respectively) under the conditions applied earlier for 4-iodoanisole (see entries 2 and 6 vs. entry 1). Gratifyingly, elevating the reaction temperature from 100 to 120 °C and at the same time reducing the residence time to 5.2 min resulted in an impressive increase in azide selectivity (to 90 and 82%, respectively) while maintaining high conversions (entries 3–5 and 7). In the case of 1-(*tert*-butyl)-4-iodobenzene, a similar temperature increase and residence time decrease were necessary to improve the conversion to 90%, while maintaining a good azide selectivity (entries 8–12). Similar good conversion and azide selectivity were achieved at 80 °C by using a residence time of 21 min (entry 13). Interestingly, in the 4-iodoaniline–NaN₃ reaction, extending the residence time from 10.5 to 21 min at 100 °C had no effects on the otherwise perfect azide selectivity, but enhanced the conversion from 62% to a decent level of 86% (entries 14 and 15).

Table 4. Continuous-flow synthesis of various aryl azides from aryl halides as starting materials.

Entry	Starting material	Product	Conditions	Conv.[a] (%)	Select.[a] (%)
1			100 °C, 0.1 mL min⁻¹ (10.5 min)	83 (69)[c]	94
2			100 °C, 0.1 mL min⁻¹ (10.5 min)	89	11
3			120 °C, 0.15 mL min⁻¹ (7.8 min)	87	65
4			120 °C, 0.2 mL min⁻¹ (5.2 min)	78	90
5			140 °C, 0.15 mL min⁻¹ (7.8 min)	96	16
6			100 °C, 0.1 mL min⁻¹ (10.5 min)	70	36
7			120 °C, 0.2 mL min⁻¹ (5.2 min)	82	82
8			100 °C, 0.1 mL min⁻¹ (10.5 min)	77	79
9			100 °C, 0.15 mL min⁻¹ (7.8 min)	65	80
10			120 °C, 0.2 mL min⁻¹ (5.2 min)	90	71
11			120 °C, 0.25 mL min⁻¹ (4 min)	71	85
12			140 °C, 0.25 mL min⁻¹ (4 min)	88	61
13			80 °C, 0.05 mL min⁻¹ (21 min)	80	75
14[b]			100 °C, 0.1 mL min⁻¹ (10.5 min)	62	100
15[b]			100 °C, 0.05 mL min⁻¹ (21 min)	86 (76)[c]	100

[a] Determined by ¹H NMR spectroscopy of the crude material. [b] Due to solubility issues DMSO/H₂O 5:1 was used as solvent. [c] Isolated yield.

Conclusion

Selective synthesis of aryl azides and aniline derivatives was achieved in a continuous-flow system using the corresponding aryl halides as practical starting materials. Copper powder packed into a stainless steel column served as a readily available catalytic source, and the role of temperature and residence time was carefully examined in order to understand their effects on product selectivity. It was established that after copper-mediated halogen–azide substitution, the azide decomposition/reduction, leading to the amine product, is also dependent on the presence of the catalytic metal. Consequently, a very precise control over reaction conditions is necessary to obtain adequate product selectivity. In the 4-iodoanisole–NaN₃ model reaction, we managed to selectively synthesize both 1-azido-4-methoxybenzene and 4-methoxyaniline by strategic control over the reaction temperature and residence time without the necessity to change the quality or the quantity of the materials and auxiliaries applied. Reaction conditions developed for the model reaction were subsequently utilized for the synthesis of a

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diverse set of aromatic amines. Notably, even *ortho*-substituted aryl bromides were successfully transformed into the desired derivatives. After further optimization of the temperature and residence time, synthetically more challenging aryl azides could also prepared selectively. Our results nicely demonstrate the synthetic usefulness of strategic reaction parameter control available in continuous-flow reactors

Experimental Section

General Information

Reagents and materials were commercially available and were used as received. Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 plates and flash column chromatography on Merck silica gel 60. Compounds were visualized by means of UV or KMnO₄. NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer, in CDCl₃ as solvent, with TMS as internal standard, at 400.1 and 100.6 MHz, respectively. GC-MS analyses were carried out with a Thermofisher Scientific DSQ II Single Quadrupole GC/MS, on a 30 m×0.25 mm×0.25 µm TG-5SILMS capillary column (Thermo Scientific). The measurement parameters: column oven temperature: 30 °C (0–2 min), 30 to 250 °C at 10 °C min⁻¹ (2–24 min), and 250°C (24–26 min); injection temperature: 240 °C; ion source temperature: 200 °C; EI: 70 eV; carrier gas: He, at 1.5 mL min⁻¹; injection volume: 2 µl; split ratio: 1:50; and mass range: 50–500 m/z.

General Procedure for the Flow Reactions

Reactions were carried out in a home-made flow reactor consisting of an HPLC pump (JASCO PU-880), stainless steel HPLC columns as catalyst bed (internal dimensions: 4.6×50 mm or 4.6×100 mm), a stainless steel preheating coil (1 mL, 254 µm internal diameter) and a commercially available 50-bar BPR (IDEX P-455 BPR Assembly 750, PEEK). The parts of the system were connected with stainless steel and PEEK capillary tubing (254 µm internal diameter). The column was charged with copper powder (<425 µm particle size, 2 or 3.5 g depending on the length of the column) purchased from Sigma Aldrich and was sealed with compatible frits (2 µm pore size). The filled catalyst bed and the preheating coil were immersed in a heated oil bath.

The appropriate haloarene (0.5 mmol, 1 equivalent), L-proline (0.15 mmol, 30 mol%) and NaN₃ (0.75 mmol, 1.5 equivalents) were dissolved in 5 mL DMSO/H₂O 4:1 as solvent. The solution was carefully homogenized and pumped through the reactor under the selected conditions. EtOAc (20 mL) and ethylenediaminetetraacetic acid (EDTA, 0.1 M, 20 mL) were added to the collected mixture and the aqueous phase was extracted with 30 mL of EtOAc three times. The combined organic phases were dried on Na₂SO₄ and concentrated *in vacuo*. Column chromatography purification, when necessary, was carried out with mixtures of *n*-hexane/EtOAc as eluent. Between two experiments, the system was washed for at least 10-10-10 min with DMSO-MeOH-DMSO, respectively, at a flow rate of 1 mL min⁻¹.

For the mechanistic experiments either an inert column (internal dimensions: 4.6×100 mm, packed with 2.5 g of quartz sand) or a copper column (internal dimensions: 4.6×100 mm, packed with 3.5 g of copper powder) was used. 1-Azido-4-methoxybenzene (0.5 mmol, 1 equivalent) was dissolved in 5 mL DMSO/H₂O 4:1 as solvent. When necessary, NaN₃ (0.75 mmol, 1.5 equivalent) or L-proline (0.15 mmol, 30 mol%) was also added. The solution was carefully homogenized and pumped through the reactor under the selected conditions. The crude material was worked up as detailed above.

To determine the residence time on the catalyst bed, a solution of a dye was pumped through the filled catalyst column. The elapsed time between the first contact of the dye with the cartridge and the moment when the colored solution appeared at the outlet was measured.

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FULL PAPER

Controlled Transformations of Aryl Halides in a Flow System: Selective Synthesis of Aryl Azides and Aniline Derivatives

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