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## Continuous amination of aryl/heteroaryl halides using aqueous ammonia in a Teflon AF-2400 tube-in-tube micro-flow reactor†

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The annual production of primary (hetero)arylamines has exceeded 6 million tons and has been extensively employed in the pharmaceutical, agrochemical, and materials industries. Catalyst-free and protecting group-free nucleophilic amination using ammonia represents a green and atom-economical method. However, due to the innate reactivity, chemical compatibility issue and the safety hazardous properties of ammonia gas, such transformation is still underused. By implementing a gas-permeable Teflon AF-2400 tube-in-tube system, diffusion of NH<sub>3</sub> from aqueous ammonia to a reaction mixture for amination can be achieved in a continuous flow fashion. In this communication, we herein report the use of aqueous ammonia as the NH<sub>3</sub> source in the amination of heteroaryl chlorides to generate primary heteroaryl amines, providing a protocol that is green, economical and safe.

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Primary (hetero)arylamines represent one of the most important chemical motifs which have been extensively employed in the pharmaceutical, agrochemical, and materials industries.<sup>1</sup> Transformation *via* nucleophilic amination of (hetero)arylhalides is increasingly important to synthesize these amines, and ammonia represents the most atom-economical nitrogen source. Despite its high abundance (100 million tons per year) and low-cost nature, ammonia is less frequently utilized as the amination reagent, especially in research laboratories for several reasons. First, concentrated anhydrous ammonia (both gas and liquid) is explosive and toxic; the extremely corrosive nature of ammonia gas means that it may be fatal when inhaled, which promotes users to seek safer alternatives. Secondly, the nucleophilicity of ammonia is much weaker than those of other amines. Common strategies to overcome its low reactivity include the use of transition-metal catalysis or the use of more nucleophilic ammonia surrogates<sup>2</sup> which result in low atom- or

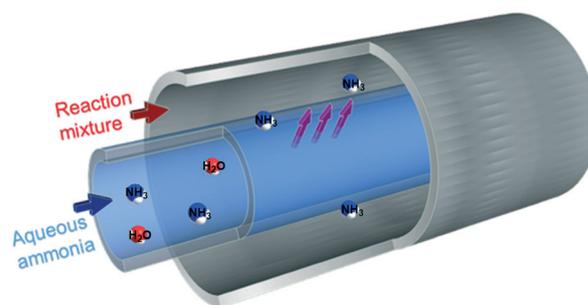


Fig. 1 Utilization of aqueous ammonia in tube-in-tube micro-flow reactors.

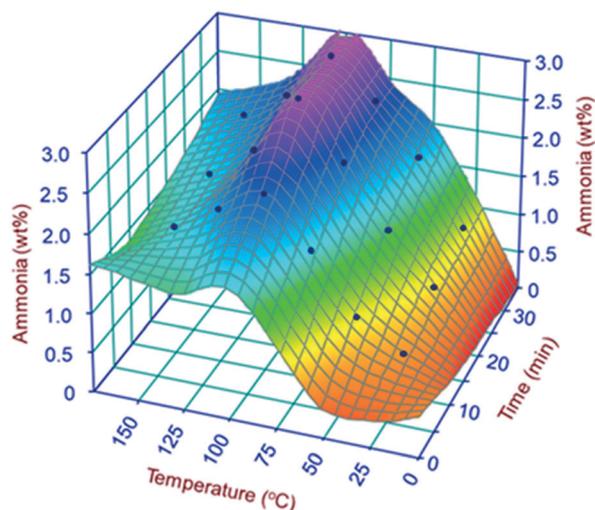


Fig. 2 Plots of ammonia concentration in DMSO against time and temperature in the tube-in-tube flow reactor.

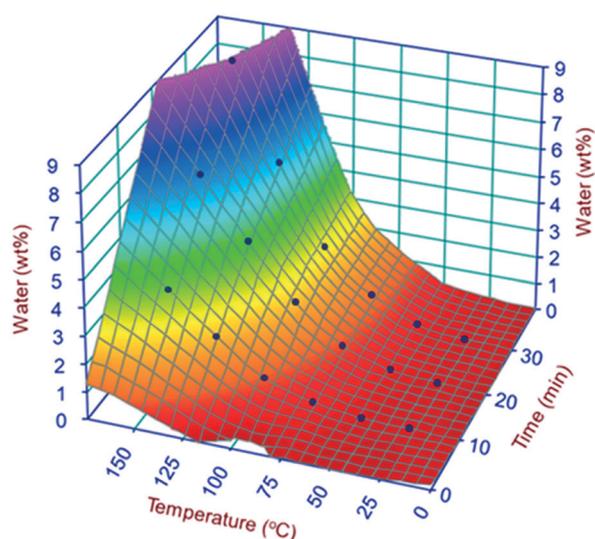


Fig. 3 Plots of water concentration in DMSO against time and temperature.

step-economy, formation of extra waste, and redundant purification. On the other hand, aqueous ammonia serves as a convenient, low-cost and safe  $\text{NH}_3$  source, however, the presence of excess water is often detrimental to most organic transformations.

Continuous-flow reactors possess many processing advantages compared to stirred reactor vessels, including improved thermal management, enhanced mixing control, and access to larger operating windows.<sup>3</sup> When biphasic gas-liquid reactions are conducted in flow reactors, specific surface areas can greatly exceed those attained in conventional batch reactors due to flow pattern effects.<sup>4</sup> This also minimises process associated risks, such as high-temperature, high-pressure, toxic or explosive reagents/intermediates. The consistency of gas/liquid reactions was further improved through the use of the tube-in-tube reactor developed by Ley's group.<sup>5</sup> In the reactor design, a gas-permeable membrane Teflon AF-2400 has been employed to allow a gaseous reactant to diffuse out, but to keep the liquid within the tube. The successful use of a tube-in-tube flow reactor has been demonstrated in a range of organic transformations employing commonly used reactive gases.<sup>6</sup> Notably, this technology has been exploited to provide anhydrous diazomethane, in which, the generation, separation, and chemical transformations of this explosive gaseous reagent were integrated into one reactor system.<sup>7</sup> Inspired by this prominent work, we hypothesized that ammonia can diffuse through the AF-2400 tubing at elevated temperature from readily available and safe aqueous ammonia and can be directly used in amination reactions in flow (Fig. 1).

To validate our hypothesis, a tube-in-tube reactor was assembled in accordance with Ley's protocol,<sup>5a</sup> with an inner gas-permeable AF-2400 tubing containing ammonia water and an outer stainless-steel tubing containing the reaction solution. Zaiput back-pressure regulators were placed at the terminus of the flow system to achieve tunable pressure control.<sup>8</sup> Next, we investigated the concentration of ammonia in

Table 1 Optimization of amination using aqueous  $\text{NH}_3$  in the tube-in-tube reactor

Entry	Solvent	$R_t$ [min]	$T$ [°C]	$P$ (inner/outer) [psi]	Yield <sup>a</sup> [%]
1	DMSO	30	150	100/100	57
2	DMSO	30	150	350/300	93
3	DMSO	60	150	350/300	100
4	DMSO	30	100	350/300	29
5	NMP	30	150	350/300	82
6	ACN	30	150	350/300	9
7	MeOH	30	150	350/300	62
8	DMF	30	150	350/300	0

<sup>a</sup> Isolated yields.

**Table 2** Evaluation of substrate scope and productivity of amination using aqueous ammonia in the tube-in-tube reactor<sup>a</sup>

Entry	Aryl halide	Product	Conv. <sup>b</sup> [%]	Yield <sup>c</sup> [%]	Productivity <sup>g</sup> [mg mL <sup>-1</sup> per 10 h]
1			95	93	1402
2			94	90	854
3			60	55	417
4			87	84	637
5			100	97	1261
6 <sup>d</sup>			100	82	582
7 <sup>f</sup>			100	83	913
8			100	97	967
9			77	70	1055
10			83	80	1078
11			56	52	879
12			94	90	955
13			79	71	759
14			97	94	1345
15 <sup>d</sup>			95	92	903
16 <sup>d</sup>			100	65	683
17 <sup>e</sup>			94	91	1023
18 <sup>e</sup>			100	62	769

<sup>a</sup> Reactions were all conducted under the conditions shown in Table 1 entry 2. Steady state was achieved after equilibration for 80 mins for all entries. <sup>b</sup> Conversions were determined by analysis of the <sup>1</sup>H NMR spectra of the crude reaction mixture. <sup>c</sup> Isolated yields. <sup>d</sup> At 0.2 M. <sup>e</sup> At 0.15 M. <sup>f</sup> Fluoride is permeable in the Teflon® AF-2400 membrane. <sup>g</sup> With the 1 mL tube-in-tube reactor.

DMSO by varying the residence time and temperature in the absence of a reactant *via* in-line colorimetric flow titration.<sup>6b</sup> Both inner and outer tubes were adjusted to 100 psi. As illustrated in Fig. 2, the ammonia concentration in DMSO exhibits a bell shape against temperature and reaches a peak at 100 °C. Next, we evaluated the amount of water that diffuses

into the tube-in-tube system under the same conditions. This measurement was done under an inert atmosphere and determined using Karl Fischer titration. As shown in Fig. 3, the permeation of water is negligible when reaction is below 50 °C, however, an increasing amount of water is detected at increased residence time and temperature.

After establishing the criteria for efficient ammonia uptake in the tube-in-tube continuous micro-reactor with aqueous ammonia, we started to evaluate the amination reaction using 2-chloro-8-nitroquinoline **1a** as the model haloarene substrate (Table 1). The nucleophilic substitution in the tube-in-tube reactor (inner/outer ID: 0.04"/0.08") afforded moderate conversion at 150 °C in DMSO with 30 min residence time at 100/100 psi inlet/outlet pressure (entry 1). We anticipated that an increased pressure of ammonia might improve the reaction conversion. It is important to note that the advantage of using aqueous ammonia as the ammonia source in the tube-in-tube reactor is that a high pressure reaction system can be easily achieved whereas reaction pressure is restricted to 8 bar (~116 psi) when directly using an ammonia gas cylinder. Increasing the inlet/outlet pressure to 350/300 psi significantly improved the yield (entry 2). The measured ammonia concentration and water concentration were 4.6 wt% and 20.7 wt%, respectively, under this condition. The reaction yield could be further improved with longer residence time (entry 3). Lowering the temperature to 100 °C significantly reduced the product conversion (entry 4). DMSO appeared to be the optimal solvent among the solvents investigated (entries 5–8). In contrast, when **1a** and aqueous ammonia in DMSO were subjected to a microwave reactor at 150 °C for 30 min, the reaction proceeded sluggishly to afford **1b** in 13% yield. In addition, the reaction was problematic as high pressure built up (>300 psi) and NH<sub>3</sub> escaped violently when the microwave reactor was vented to release the pressurized vial.

The substrate scope was evaluated at 30 min retention time, and the amination of a remarkable broad scope of heteroaryl fluorides and chlorides proceeded effectively in the tube-in-tube reactor under the optimized amination conditions to afford primary heteroaryl amines (Table 2). Chloro-heteroaryl compounds including pyridine (**2a**), pyrazine (**3a**), pyridazine (**4a–6a**), thiazole (**8a**), quinolone (**9a–11a**), benzimidazole (**12a**), benzoxazole (**13a**), and phthalazine (**14a**) were all good candidates for this transformation. We were pleased to find that this methodology was applicable towards more complex substrates such as **15a–18a**, yielding the desired amines with high yield and good productivity. These amines are advanced intermediates in the pharmaceutical industry and it is crucial to generate them in a green and safe manner. Chloride was selectively converted to amine in the presence of bromide functionality (**17a**).

Diamination was viable using highly electron-deficient heteroarenes (**6a**), otherwise the transformation would preferentially stop at mono-amination (**14a** and **16a**). Even though the nucleophilic substitution of aryl fluoride proceeded much faster than that of aryl chloride to obtain full conversion without by-product formation, only 83% of product **6b** was isolated. This was probably due to the permeability of the fluoride compound through the Teflon AF-2400 tube, as the aqueous stream became bright yellow after the transformation. The residence time in the system for each substrate (from the injection tee mixer to the outlet tee mixer) was 30

min, translating into a scalability of 0.8 mmol per hour. A 10 hour collection was performed for each substrate at the steady state for yield calculation. The merit of this tube-in-tube system resides in its ability to perform gas–liquid transformation in a safe and controlled fashion. The risk of explosion and the use of a cumbersome high-pressure gas tank are avoided, and the tube-in-tube system can exceed the 8 bar limitation of using the ammonia tank by replacing it with aqueous ammonia. Due to the difficulty of scaling up the membrane-type micro-flow reactor,<sup>5b</sup> a numbering-up strategy can be employed when larger quantity of material is required.

In conclusion, we have demonstrated that aqueous ammonia can be applied as the ammonia source in the continuous amination of aromatic and heteroaromatic halides assisted by a Teflon AF-2400 tube-in-tube reactor. A wide range of densely substituted aryl/heteroaryl amines can be generated in high yields with this safe, simple, scalable method with no additional optimization. With an understanding of ammonia/water distribution in the tube-in-tube reactor under various conditions, this technique may allow a plethora of synthetic reactions utilizing aqueous ammonia as the ammonia source in a safe and effective manner.

## Experimental section

A 50 mL round bottom flask was charged with aryl halide (9.6 mmol) and DMSO (0.4 M, 24 mL), which was stirred under vacuum for 5 min, then backfilled and protected with nitrogen. Another 50 mL round bottom flask was charged with 25% aqueous ammonia (24 mL) and protected with nitrogen. Both solutions were taken up in an Asian pump and introduced into the tube-in-tube reactor (both flow rates at 33.2 μL min<sup>-1</sup>), and the oil bath was heated to 150 °C. After 80 min of equilibration, the reaction mixture was collected for 10 h in a vial protected under a nitrogen atmosphere.

Saturated NaHCO<sub>3</sub> solution was then added to the reaction mixture and extracted with ethyl acetate 3 times. The combined organic layers were dried using MgSO<sub>4</sub>, concentrated, and subjected to flash column chromatography using DCM/MeOH 50:1 to 10:1 as the eluent.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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