



# Continuous preparation and reaction of nonafllyl azide (NfN<sub>3</sub>) for the synthesis of organic azides and 1,2,3-triazoles

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## Abstract

Organic azides are widely used in organic synthesis. Continuous flow processing can be used to bypass their isolation, and can therefore be useful in mitigating the hazards associated with these potentially toxic and explosive reagents. Nonafllyl azide has been reported as an effective, bench-stable, and relatively safe diazo transfer reagent that can be useful in the preparation of azides from amines and so avoid the use of alkyl halides. Here we demonstrate the synthesis and purification of nonafllyl azide in continuous flow with isolation of the neat, pure reagent by membrane filtration. The neat reagent was used in the preparation of organic azides from primary amines, and then applied to the synthesis of triazoles. A variety of triazoles, including the antiseizure drug Rufinamide, were prepared from primary amines and alkynes via the CuAAC click reaction in a semi-batch parallel array without isolation of alkyl azide intermediates. A telescoped two-stage continuous flow process was also designed and demonstrated to form triazoles via the same CuAAC reaction, which avoids the handling of the intermediate reactive azides.

**Keywords** Azide · Triazole · Copper click reaction · Continuous flow · Semi-batch array

## Introduction

Azides are an important class of reactive intermediates that are widely used for organic synthesis [1, 2]. Organic azides are well-known for their facile reduction to amines, formation of iminophosphoranes via the Staudinger reaction [3–6], and as a component of the copper azide-alkyne cycloaddition (CuAAC) ‘click reaction’ [7–10]. The CuAAC click reaction in particular has been frequently applied to late-stage

coupling and conjugation strategies [11]. Furthermore, the product triazoles provide medicinally-relevant heterocycles [12–14], and bioisosteres of amide bonds [15].

Despite thousands of examples of the broad synthetic utility of azide compounds, they are often avoided on a process scale because of their toxicity, instability and potentially explosive behaviour [16–22]. Additionally, low molecular weight azides can prove volatile and explosive and be inadvertently isolated during purification steps [23–27]. Methods which limit handling of organic azides are therefore highly desirable to allow access to efficient synthetic routes using azides whilst alleviating safety concerns.

Strategies to mitigate the hazards of azides include avoiding their isolation and/or maintaining low concentration solutions in order to minimise the risks of processing neat material [28–32]. Continuous flow chemistry is now an established technology for the safer in situ generation and use of hazardous materials [33, 34]. The higher surface-area-to-volume ratio of flow reactors, compared to batch reactors, typically results in superior thermal control [35] and efficient dissipation of heat from potential exotherms. A range of flow chemistry approaches have therefore been applied to the preparation and reaction of azides, and related diazo and

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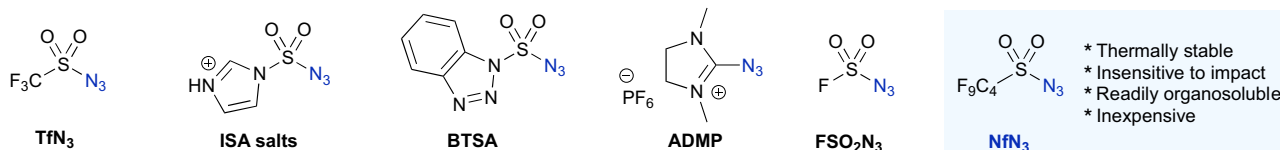
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diazonium compounds [36–42]. A notable report by Jamison described a two-step continuous flow route to rufinamide, an antiepileptic agent, involving a reaction of a sodium azide with the corresponding benzyl bromide, with subsequent reaction of the benzylazide to form a triazole [43].

An attractive method generate azides is diazo transfer to primary amines, allowing the application of amines as common building blocks and intermediates in medicinal chemistry. Moreover, this approach provides precursors with much reduced toxicity compared to common alkyl halide alkylating agents. Diazo transfer reagents (DTRs) are electron-poor azides that are capable of efficiently transferring an  $N_2$  group to an appropriate acceptor to prepare organic azides or diazo compounds [44]. A subset of reactive diazo transfer reagents have been used to prepare azides from amines (Fig. 1a).

The explosive nature of some diazo compounds means that it is imperative to consider their safety profile [16, 45–47]. An early breakthrough was the use of triflyl azide ( $TfN_3$ ) [48–50], that was later improved by using catalytic amounts of  $Cu^{II}$  or  $Zn^{II}$  [51, 52]. The explosive hazards associated with triflyl azide has led efforts to find safer DTRs suitable for azide formation. Imidazole-1-sulfonyl azide (ISA) salts [53] were effective but unfortunately were found to be impact sensitive, hygroscopic [54] and to generate toxic and explosive hydrazoic acid gas upon reaction with water [55]. Their synthesis requires strict precautions to avoid hydrazoic acid formation, addition of sodium azide to sulfonyl chloride (which risks forming explosive sulfonyl diazide byproduct), and processing solutions of ISA which is sensitive if isolated [53–55].

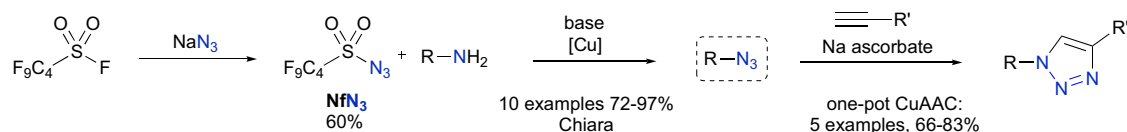
#### a) Diazo transfer reagents effective for primary amines:



#### b) Batch synthesis of nonafllyl azide, diazo transfer to primary amines and subsequent CuAAC:

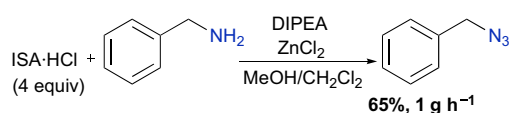
Zhu, 1994

updated by Chiara, 2010

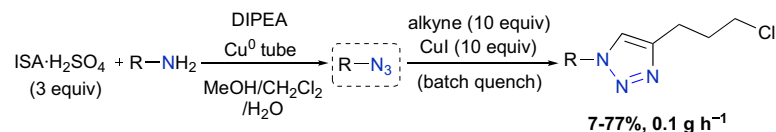


#### c) Previous examples of flow diazo transfer or CuAAC:

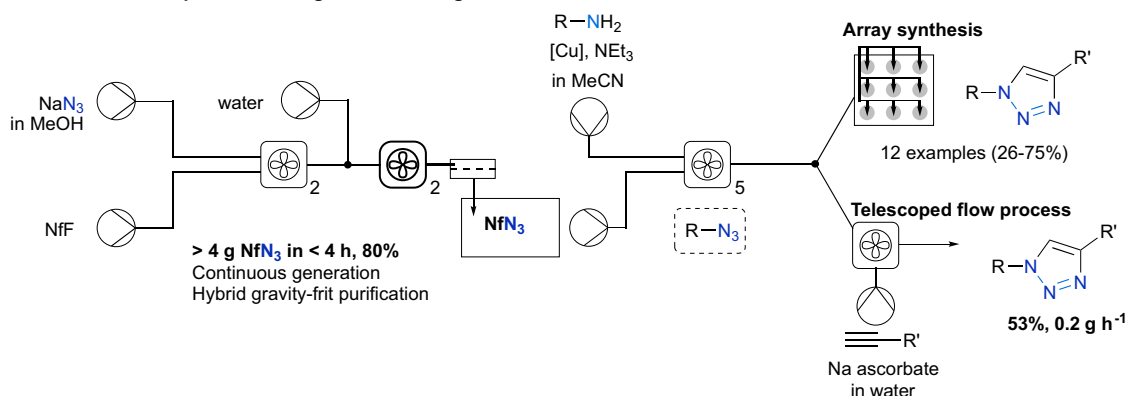
Rutjes, 2011: flow diazo transfer



de Borggraeve, 2015: flow diazo transfer & batch CuAAC



#### d) This Work: Flow sequence avoiding isolation of organic azide intermediates



**Fig. 1** A) Examples of diazo transfer reagents suitable for diazo transfer to amines. B) Preparation of nonafllyl azide and a one-pot diazo transfer/CuAAC reaction to afford triazoles as reported by Zhu [65] and Chiara [66, 67]. c) Diazo transfer reactions to primary amines

reported in continuous flow [68, 69]. D) This work to develop a three-step flow preparation of nonafllyl azide, diazo transfer to primary amines and subsequent CuAAC formation of triazoles

Benzotriazole-1-yl-sulfonyl azide (BTSA) [56] is similarly unstable and potentially explosive [57]. 2-Azido-1,3-dimethylimidazolium hexafluorophosphate (ADMP) is a shelf-stable and commercially available alternative to sulfonyl azide reagents, with subtly different reactivity [58–62]. Researchers at Bristol-Meyers-Squibb (BMS) recently reported that it suffers from limited commercial supply and a short shelf-life.<sup>10c</sup> Most recently, fluorosulfonyl azide ( $\text{FSO}_2\text{N}_3$ ) was reported as a fast and effective base-free and catalyst-free DTR [63]. Unfortunately, similar to triflyl azide, it is volatile (and therefore may inadvertently isolate around the tops of vessels) and likely to be explosive.

During our investigations into the thermal stability of diazo transfer reagents and diazo compounds [16], we were intrigued by reports of nonafluorobutanesulfonyl azide (nonafl azide,  $\text{NfN}_3$ ) as an effective, shelf-stable, and relatively safe reagent (Fig. 1a) [64].  $\text{NfN}_3$  was originally prepared by Zhu [65], and then elaborated upon by Chiara for the synthesis of diazo compounds [66], azides and triazoles (Fig. 1b) [67]. We previously reported differential scanning calorimetry (DSC) data for  $\text{NfN}_3$  in direct comparison to other diazotransfer reagents, which indicated an exotherm initiation temperature of 102 °C (136 °C onset temperature) and an average decomposition enthalpy of  $-189 \text{ kJ mol}^{-1}$  [16].

Only a few examples of diazo transfer to primary amines in flow have been reported to date (Fig. 1c). Rutjes and co-workers used batch-prepared  $\text{ISA}\bullet\text{HCl}$  with  $N,N$ -diisopropylethylamine (DIPEA) and zinc chloride in a microreactor to optimise conversion of benzylamine to benzyl azide, followed by a scaled synthesis of 1.36 g in 95 min with a 10 min residence time [68]. In 2015, de Borggraeve and co-workers used a coil of copper tubing as a flow reactor to convert several amines to azides using batch-prepared  $\text{ISA}\bullet\text{H}_2\text{SO}_4$  with DIPEA, achieving good yields with a 5 min residence time [69]. Recently, Maguire and co-workers have developed a flow synthesis of triflyl azide [70, 71]. There are numerous examples of  $\text{CuAAC}$  following  $\text{S}_\text{N}2$  with azide salts, often using  $\text{Cu(0)}$  [72–74] which risks the formation of explosive copper azide from any leftover azide anions. Maintaining solubility of  $\text{Cu}^\text{I}$  salts (or  $\text{Cu}^\text{II}$  with a reductant) in a solvent compatible with the azide synthesis is a key challenge [75]. Additionally, the preparation of aryl azides for this purpose is often attempted via a diazonium salt leaving group [76], with the accompanying explosive hazard [77].

Telescoping aqueous solutions of sodium azide into subsequent organic phases, typically required for DTRs, can be a challenge due to the formation of two-phases with limited mixing in flow. One approach is to use organosoluble azide sources, however, resultant by-products can interfere with subsequent steps and are difficult to remove [42], posing a safety risk if unreacted ionic azide is present in the isolated crude product.

We considered that  $\text{NfN}_3$  could be ideally suited to continuous flow synthesis and subsequent diazo transfer

processes. The facile separation of neat  $\text{NfN}_3$  from the sodium azide precursor avoids contamination in subsequent steps while also delivering high productivity of pure DTR on demand. As a liquid reagent, this could be directly fed into a flow reactor for continuous synthesis of azides or diazo compounds.

Herein we demonstrate the continuous synthesis and purification of  $\text{NfN}_3$  using fReactor modules, a series of small-volume continuous stirred reactors that can overcome the limitations of mixing of multi-phase systems encountered by conventional tubular flow reactors. The integration of either a continuous membrane separator or gravity-frit separator can be used to facilitate the isolation of neat  $\text{NfN}_3$  that can be used directly without further purification. We also demonstrate the direct use of  $\text{NfN}_3$  in the synthesis and reaction of organic azides, both in the application of this process to array chemistry, achieving the synthesis of several triazoles with limited handling of the organic azides, and in a telescoped two-stage continuous process avoiding isolation of hazardous reagents and removing the risks of downstream contamination with sodium azide (Fig. 1d).

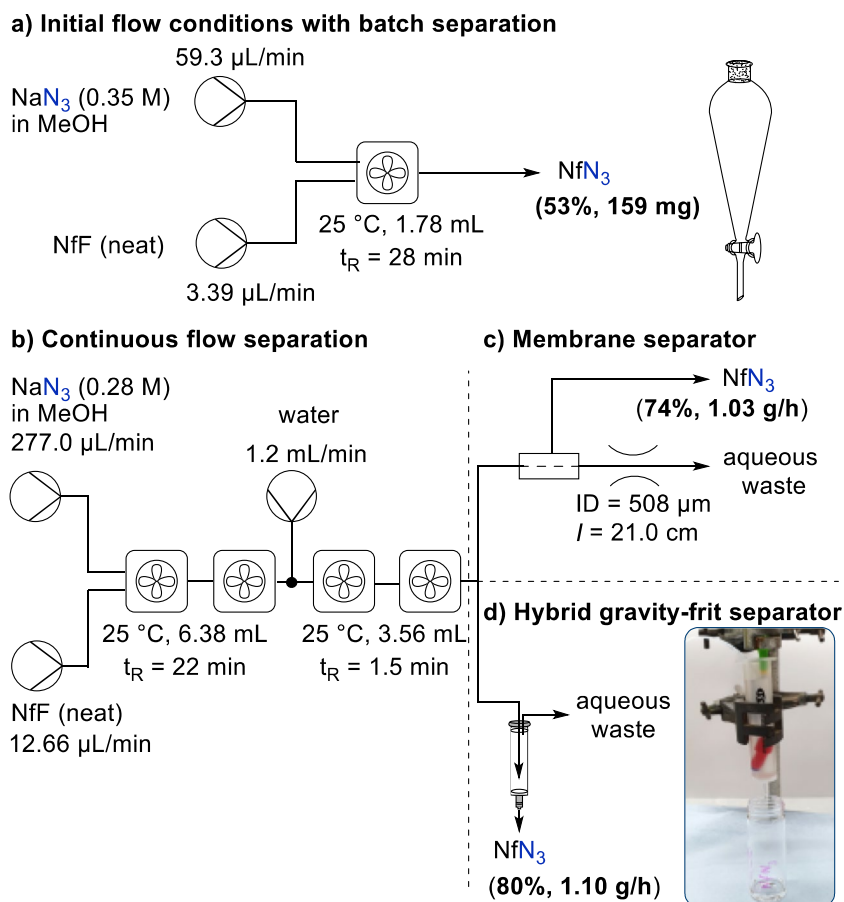
## Results and discussion

### Continuous flow preparation of nonafl azide

Preliminary investigations of the batch preparation of  $\text{NfN}_3$  as reported by Chiara (1.1 equiv. of sodium azide in methanol 0.5 M, 25 °C, 24 h) produced 89% analytical yield by  $^{19}\text{F}$  NMR, with no trace of remaining starting material.<sup>1</sup> Chiara and co-workers reported an isolated yield of 60% under these conditions. We found the reaction time could be reduced to 2 h with a modest improvement in isolated yield to 65%. Chiara's conditions proceed as a slurry, which inhibited direct translation to flow. Attempts to solubilise the feed solutions initially focused on preparing a solution of sodium azide, as nonafl fluoride could be pumped directly into the reactor as a neat liquid to maintain high reaction concentrations. Reactions using aqueous sodium azide solutions resulted in only trace amounts of  $\text{NfN}_3$  due to the immiscibility of water and nonafl fluoride. Solutions of sodium azide in methanol were then investigated and concentrations of up to 0.35 M could be prepared at ambient temperature. However, nonafl fluoride was not fully miscible with methanol at this concentration. Rather than diluting the nonafl fluoride feed solution and decrease the concentration of the reaction further, efforts turned to reactor design to accomplish more efficient mixing of the reactor streams.

<sup>1</sup> ‡ Nonafl fluoride is supplied as 95% purity, with cyclic perfluoro-sulfolane from its production the most likely identity of the ca. 7% impurity detected.

**Scheme 1** a) Continuous flow synthesis and conventional separation of nonafllyl azide. b) Further optimised flow synthesis. c) Continuous separation using a membrane separator or; d) a hybrid gravity-frit separator



The initial flow experiments used traditional tubular (ID 1.0 mm) flow reactors, which limited turbulent mixing of reagent streams and resulted in blockages from precipitation of sodium fluoride by-product. To better handle precipitates and to ensure adequate mixing of the neat nonafllyl fluoride starting material in the reaction mixture, modular continuous stirred-tank reactors (CSTRs) ‘fReactors’ were used [78]. Using the fReactor under flow conditions with  $t_R$  28 min, full conversion of nonafllyl fluoride was achieved (determined by quantitative  $^{19}\text{F}$  NMR), although lower isolated yields of 53% were obtained due to inefficient separation on a small scale using a batch separation with a separating funnel (Scheme 1a). The literature preparation of nonafllyl azide reported an aqueous work-up in which a large quantity of ice water was added to the crude mixture, and the nonafllyl azide product was separated as a neat fluoruous phase [79]. In our hands, and on the smaller scale batch reaction the settling of the product fluoruous phase in the separating funnel remained incomplete with droplets of product dispersed throughout the aqueous phase and appears to adhere to the sides of the glass separating funnel. The yield of nonafllyl azide was therefore limited by the isolation of the product.

To overcome these separation inefficiencies a continuous flow membrane separator [80, 81] with hydrophobic pores

was investigated. Unlike the traditional separation of two solvent phases of approximately equal volumes, this unusual separation of neat liquid product from reaction solvent would have a large volume disparity of separated phases (approx. 13  $\mu\text{L}$  of neat product for every 1 mL of aqueous phase). Typical commercial separators are unlikely to work under these circumstances, as they use the output phase to modulate the back pressure and affect the separation [82]. Using the porous tubing membrane separator previously reported by de Mello and co-workers [83, 84], the separation was optimised to 0.28 M sodium azide in methanol, with water injected after the reaction to induce the separation (Scheme 1b and 1c, see Sect. 2.3 of the ESI for further details on membrane separation optimisation). These conditions afforded 74% yield, and 1 g/h of NfN<sub>3</sub>, a substantial increase on the previous batch separation.

Despite the yield improvements membrane separation offered, it was found that there was a narrow window of optimum backpressure where only one phase can cross the membrane, likely due to the methanol content of the aqueous phase increasing the similarity between phases (ca. 19% MeOH). Despite the higher isolated yields, the sensitivity of this separator to changes in system pressure, the expense of the membrane material and its fragility made it impractical for long-term use.

A hybrid gravity/membrane approach was then developed (Scheme 1d), analogous to continuous gravity separators [85, 86]. The reservoir was a commercially available solid-phase extraction (SPE) cartridge, with a hydrophobic frit at the bottom (20  $\mu\text{m}$  polyethylene), while a pump was used to continuously remove aqueous waste. Any fluorine phase would settle under gravity due to the high density ( $1.7 \text{ g mL}^{-1}$  for  $\text{NfN}_3$ ) and selectively pass through the frit. Pleasingly, this separation was both effective and robust, and afforded over 4 g of pure  $\text{NfN}_3$  in under 4 h, in 80% isolated yield ( $1.1 \text{ g h}^{-1}$ ), offering a continuous supply of the DTR.

### Synthesis of azides from amines in batch and flow

Following the optimised preparation of  $\text{NfN}_3$  in continuous flow, we proceeded to investigate its use for the diazo transfer to amines. As a starting point we used conditions reported by Chiara for diazo transfer in batch: addition of sodium bicarbonate (4 equiv),  $\text{CuSO}_4 \cdot \text{H}_2\text{O}$  (10 mol%) and  $\text{NfN}_3$  (1.5 equiv) in solvent mixture  $\text{H}_2\text{O}/\text{Et}_2\text{O}/\text{MeOH}$  1:1.5:2.75. Two main changes were required from Chiara's conditions for diazo transfer: 1) use of a homogeneous solution (instead of a slurry of inorganic  $\text{NaHCO}_3$  base, copper sulfate catalyst and solvent) and, 2) a decrease in reaction time from 6 h. We first tested homogeneous batch conditions in acetonitrile with triethylamine as base and a benzylamine substrate. Copper sulfate, though effective, was only soluble once mixed with both the substrate and DTR. A screen of several copper sources (see SI for more details) found both heterogeneous copper<sup>0</sup> metal and homogeneous copper<sup>II</sup> acetate were equally effective and were more amenable to flow than copper sulfate. Both copper acetate and copper metal were therefore taken forward to develop homogeneous and heterogeneous flow conditions respectively. A series of

control reactions were performed under batch conditions to investigate the role of each component (see Table 1 for summary and Table S4 for full details).

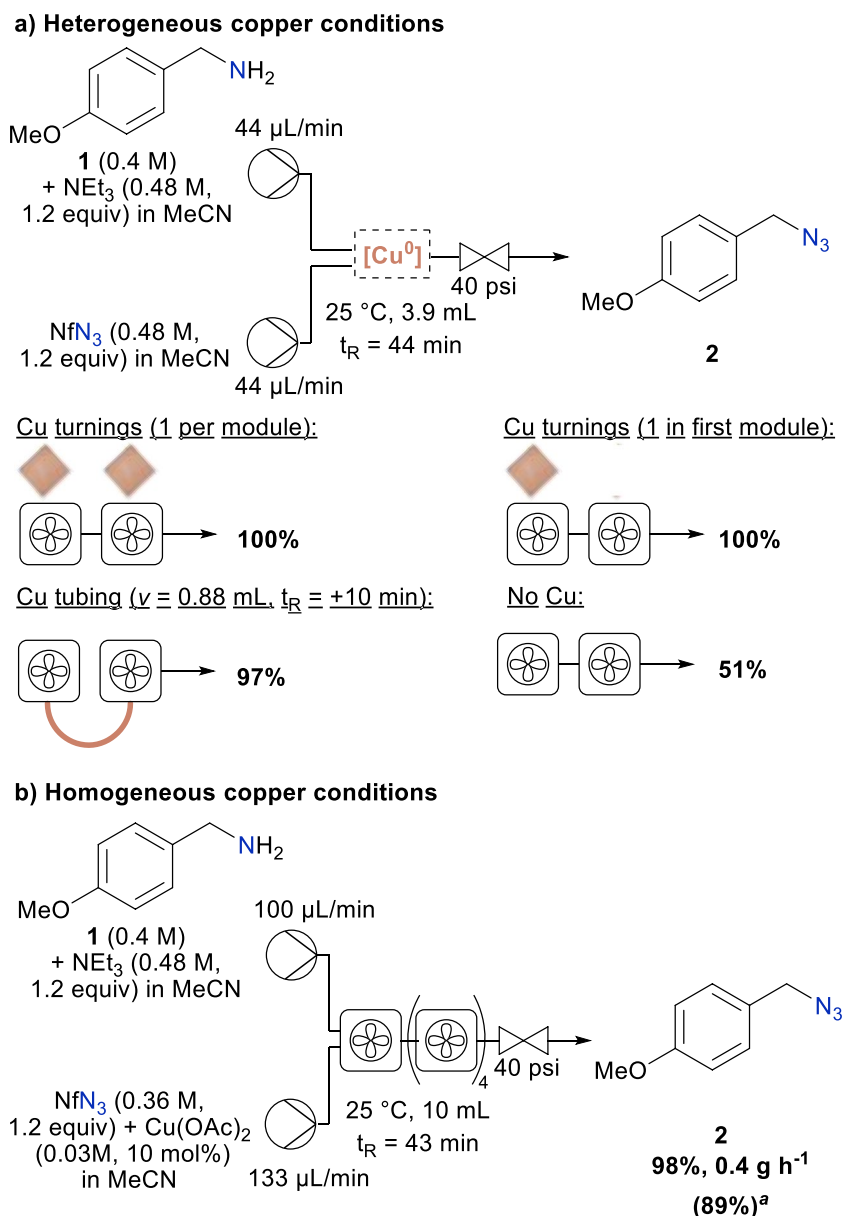
Quantitative conversion was achieved for all the tested amines when using the standard conditions (Table 1). Good isolated yields were obtained using benzylamines 1 and 3 when both copper source and triethylamine were included (Table 1, entries 1 and 3). For these substrates, there was a relatively small reduction in conversion on the omission of triethylamine and/or copper sources (entries 1 to 6). Quantitative conversion was also achieved with aniline 5 under the full reaction conditions (entry 7). Yields were slightly reduced when copper was omitted and markedly reduced to 33% for the aniline substrate when no copper source or triethylamine were used (entries 8 to 10). Under the optimised conditions benzylamine 7 and an amine with a longer alkyl chain 9 also gave full conversion to the corresponding azides along with high isolated yields. These conditions providing full conversion were then progressed into the flow chemistry regime.

The diazo transfer conditions were readily adapted to flow using both a heterogeneous copper source and homogeneous copper acetate conditions (Scheme 2). For the heterogeneous method, copper turnings were placed inside the fReactor modules, with a  $t_R$  of 44 min (Scheme 2a). Under these conditions, an increased concentration of amine was suitable, along with a solution of  $\text{NfN}_3$  in MeCN (both solutions 0.48 M). Quantitative conversion was achieved for 4-methoxybenzylamine 1 with one or two copper turnings. High conversions (97%) were also achieved using copper tubing to connect the two modules. Conducting the reaction in the absence of any copper source decreased the yield to 51%. Under homogenous conditions, a solution of  $\text{NfN}_3$  at 0.36 M was used at a slightly lower concentration to ensure

**Table 1** Impact of copper(II) and base on yield of azide under batch conditions.

| Entry | Amine | Change in conditions                               | Yield (%) <sup>a</sup> | Azide |
|-------|-------|----------------------------------------------------|------------------------|-------|
| 1     | 1     | None                                               | 100 (99)               | 2     |
| 2     | 1     | No $\text{NEt}_3$ , no $\text{Cu}(\text{OAc})_2$   | 80                     | 2     |
| 3     | 3     | None                                               | 100 (73)               | 4     |
| 4     | 3     | No $\text{NEt}_3$                                  | 86                     | 4     |
| 5     | 3     | No $\text{Cu}(\text{OAc})_2$                       | 88                     | 4     |
| 6     | 3     | No $\text{NEt}_3$ , no $\text{Cu}(\text{OAc})_2$   | 87                     | 4     |
| 7     | 5     | None                                               | 100 (62)               | 6     |
| 8     | 5     | No $\text{NEt}_3$                                  | 97                     | 6     |
| 9     | 5     | No $\text{Cu}(\text{OAc})_2$                       | 83                     | 6     |
| 10    | 5     | No $\text{NEt}_3$ , no $\text{Cu}(\text{OAc})_2$   | 33                     | 6     |
| 11    | 5     | $\text{Cu}^0$ instead of $\text{Cu}(\text{OAc})_2$ | 80                     | 6     |
| 12    | 7     | None                                               | 100 (93)               | 8     |
| 13    | 9     | None                                               | 100 (78)               | 10    |

**Scheme 2** a) Heterogeneous copper catalysed diazo transfer conditions in continuous flow to amine **1**. b) Diazo transfer using homogeneous copper catalysis in flow. Yields given as an average of at least three consecutive 30 min samples of flow output, determined by  $^1\text{H}$  NMR using 1,3,5-trimethoxybenzene as an internal standard with a 22 s relaxation time. <sup>a</sup>Isolated yield in parentheses, reactor output collected for 30 min, 1 mmol scale



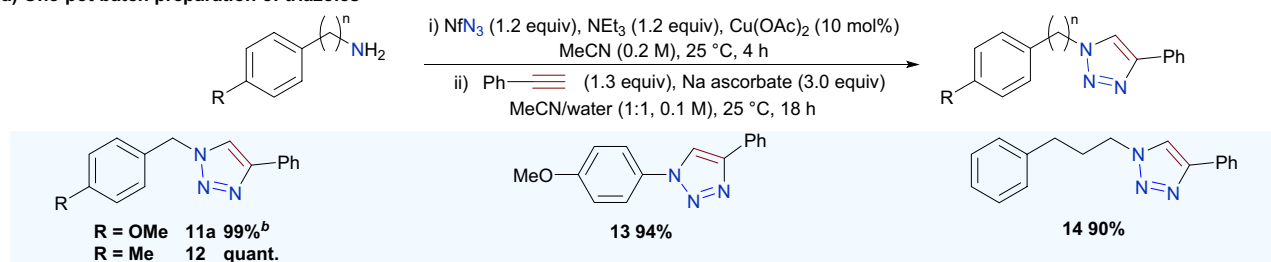
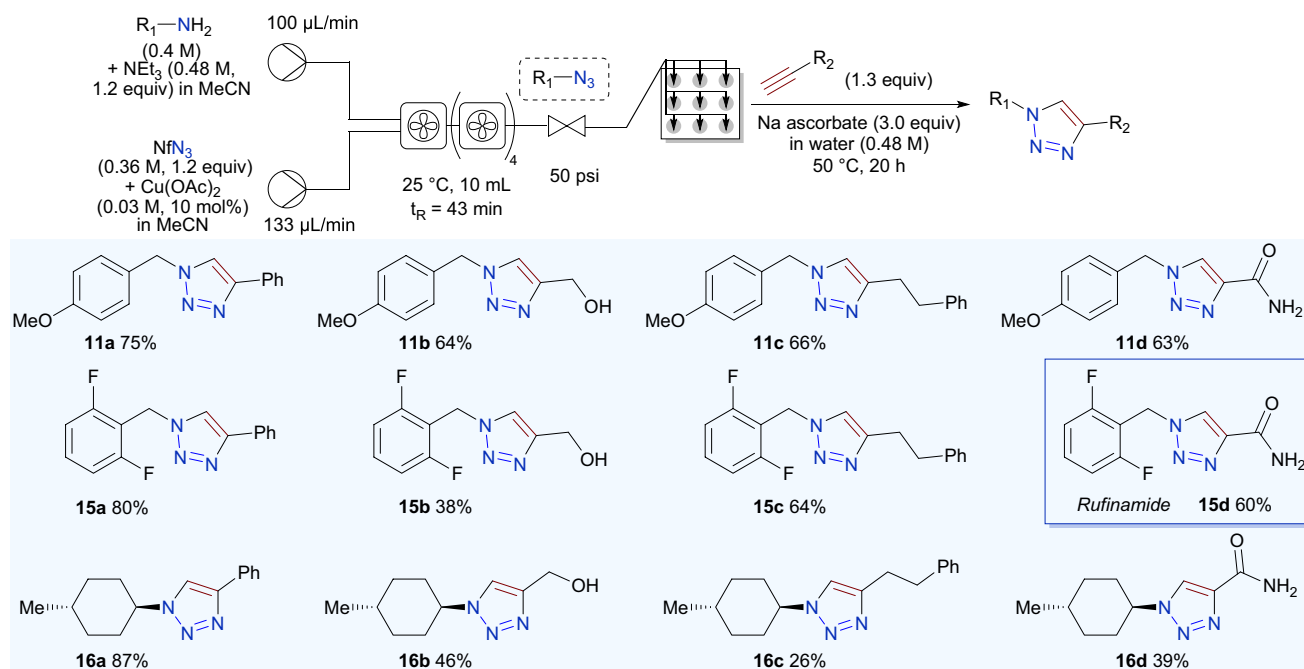
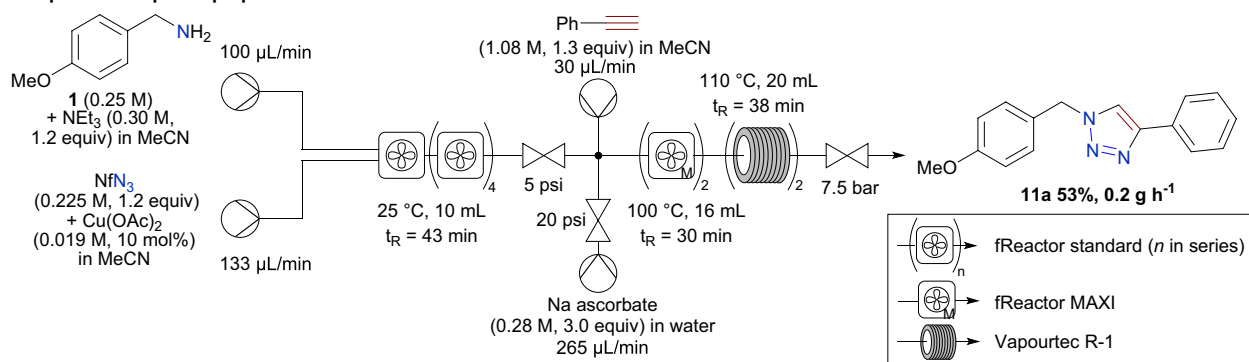
the solubility of copper acetate in in the same acetonitrile solution. The homogenous conditions were applied on a larger scale using five fReactor modules, achieving near quantitative conversions and an output of  $0.4 \text{ g h}^{-1}$  azide product **2** (Scheme 2a).

### Telescoped diazo transfer and CuAAC ‘Click’ reactions

The continuous synthesis of organic azides from amines was applied to the synthesis of triazoles using the CuAAC ‘Click’ reaction. Reactions were initially optimised in batch under homogenous catalysed conditions, wherein Chiara reported a slurry formation [67] which is unsuitable for flow. Under our batch conditions, adding an aqueous sodium

ascorbate solution along with the neat alkyne gave a substantial improvement in solubility and yield (for full optimisation, see SI). The optimised one-pot conditions gave > 90% isolated yield of several triazoles from the corresponding primary amines (Scheme 3a).

Increased temperatures were investigated to improve triazole yield, decrease reaction time to be more suitable for flow, and to consume any residual azide present.  $50^\circ\text{C}$  was found to be the optimum temperature for formation of triazole **4** (see SI table S6 for details). A semi-batch array synthesis of triazoles was then undertaken using the flow diazo transfer conditions for azide synthesis, with the output directed into different vessels containing various alkynes with aqueous ascorbate solution (Scheme 3b). The elevated temperature of  $50^\circ\text{C}$  and 20 h reaction time was used to

a) One-pot batch preparation of triazoles<sup>a</sup>b) Semi-batch array preparation of triazoles<sup>c</sup>c) Telescoped two-step flow preparation of triazoles<sup>d</sup>

**Scheme 3** Two-step telescoped preparation of triazoles by **a**) one-pot batch procedure, **b**) semi-batch array and **c**) a fully continuous flow process. <sup>a</sup>Reactions run on 0.2 mmol scale. Isolated yields reported. <sup>b</sup>Reaction time was 2 h, reaction temperature was 70 °C. <sup>c</sup>Output of the flow reactor was collected for 5 min per sample, 0.2 mmol azide equivalent, into vials containing a mixture of the desired alkyne

(0.26 mmol, 1.3 equiv) and sodium ascorbate (0.6 mmol) in water (1 mL). Isolated yields reported. <sup>d</sup>Yields given as an average of three consecutive 30 min samples of flow output, determined by <sup>1</sup>H NMR with respect to input of **1** during this time using 1,3,5-trimethoxybenzene as an internal standard and a 22 s relaxation time

ensure maximum conversion to the triazole. This method obtained four triazole compounds per amine. Alkynes with a range of functionalities were tolerated in the reaction,

forming triazoles with aryl (**11a**, **15a**, and **16a**), primary alcohol (**11b**, **15b**, and **16b**) alkyl (**11c**, **15c**, and **16c**), and primary amide (**11d**, **15d**, and **16d**), reacting successfully

with the corresponding benzylamines and cyclohexylamine. Using alkynes with alcohol and primary amide groups enabled the formation of triazoles with handles for further derivatization. Of the tested amines, phenylacetylene gave the highest yields of triazoles (11a to 11d, 63–75%). Pleasingly, the antiseizure drug Rufinamide (15d) was synthesized in good yield using this two-step array process from commercial reagents, a complementary synthesis to a previous continuous flow approach by Jamison forming the azide from sodium azide and a benzyl bromide [43]. Whilst the yields for *trans*-methylcyclohexylamine were more varied across the scope of alkynes (16a to 16d, 26% to 87%), good quantities of material were made with retention of relative stereochemistry in what otherwise might have been a challenging synthesis, or one which necessitated the isolation of the organic azide.

Finally, we developed the fully telescoped flow reaction to form triazole 11a from amine 1 (Scheme 3c). Using solutions of amine and  $\text{NfN}_3$  of the same concentration as in Scheme 3b was not possible due to blockages from precipitation during the triazole formation step. The feed solutions were therefore diluted to reduce reaction concentration while maintaining stoichiometry. On doing so, gas evolution was observed in the first two, azide forming fReactor modules, however, adjusting the final back pressure regulator to maintain a system pressure of 7.5 bar suppressed this gas formation. A combination of fReactors and tubular reactors were then used for the triazole formation reaction: two fReactor MAXI modules to maintain efficient mixing, then Vapourtec R-1 tubular reactors to achieve superior heat transfer to the reaction mixture and to extend the residence time. We therefore reached a stable process achieving 53% conversion to triazole 11a from the amine.

## Conclusions

In summary, we report a three-stage flow process, forming first the thermally stable diazo transfer agent  $\text{NfN}_3$ . This was prepared through continuous synthesis and purification in flow, using membrane separators to produce the pure, neat product. A hybrid gravity frit separation method proved to be a very effective way of isolating neat  $\text{NfN}_3$  for further reaction.  $\text{NfN}_3$  was an effective diazo transfer reagent for the formation of several organic azides from amines using the flow fReactor modular system, with either copper<sup>II</sup> or copper<sup>0</sup>. A semi-batch array CuAAC process was developed using the azide output of this flow reaction to facilitate a series of batch reactions in parallel to rapidly generate a diverse array of triazole products without isolating the potentially hazardous organic azide. We envisage that such combined flow and parallel synthesis platforms will find wider applications with low barriers to automated parallel synthesis. Furthermore,

we demonstrate a successful two-step telescoped flow process to form a triazole from a primary amine and nonafllyl azide, using a combination of fReactors and Vapourtec R-1 tubular reactors to achieve efficient heating of the CuAAC reaction. The additional safety aspect of generating the intermediate nonafllyl azide does however come at a cost of atom economy, and we are therefore currently exploring ways of improving the sustainability of this process by recycling the unwanted fluororous by-products.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s41981-024-00327-y>.

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**Data Availability** The data that support the findings of this study are available on request from the corresponding authors PM and JB.

## Declarations

**Conflicts of interest** There are no conflicts to declare.

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