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COMMUNICATION

Azide-Alkyne Cycloadditions in a Vortex Fluidic Device: Enhanced “On Water” Effects and Catalysis in Flow

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The Vortex Fluidic Device is a flow reactor that processes reactions in thin films. Running the metal-free azide-alkyne cycloaddition in this reactor revealed a dramatic enhancement of the “on water” effect. For the copper-catalyzed azide-alkyne cycloaddition, stainless steel or copper jet feeds were effective reservoirs of active copper catalyst.

The azide-alkyne cycloaddition is a mainstay in the chemical, biological, and material sciences.¹⁻³ Indeed, the widespread use of both the copper-catalyzed^{4,5} and uncatalyzed⁶ variants of this transformation position it as a model example in the click chemistry philosophy.⁷ Yet, even with the broad utility of these reactions, there is intense interest in delivering more versatile and reactive catalysts,⁸ as well as safe processing methods for the handling of azides.^{9,10} In this study, we examined these issues in the context of flow chemistry. Specifically, we explored both the copper-catalyzed and uncatalyzed azide-alkyne cycloaddition in a unique reactor: the Vortex Fluidic Device (VFD, Figure 1 and S5).¹¹⁻¹³ In this reactor, reagents are added to a rapidly spinning tube and react in a thin film. In the confined mode, the reaction mixture remains in the tube. In continuous mode the products exit the top of the tube while more reagents are delivered through feed jets under the control of a syringe pump. We hypothesized that the thin film processing in the VFD might impart some advantage to the azide-alkyne cycloaddition, potentially enhancing “on water” effects when hydrophobic starting materials are reacted in aqueous media.¹⁴⁻¹⁶ This hypothesis relates to the fluid flow in the VFD that promotes high surface area contact between immiscible liquids and the centrifugal force that layers liquids of different density. Additionally, for azide-alkyne cycloadditions that proceed at elevated temperature, continuous processing in the VFD was anticipated to increase

the safety profile because the local scale of the reaction would be small with scalability a matter of continuous or parallel processing. Finally, we wanted to explore new strategies in catalysis for this reaction and report a method that integrates a copper jet feed and a photoredox process to generate the active catalyst in flow.

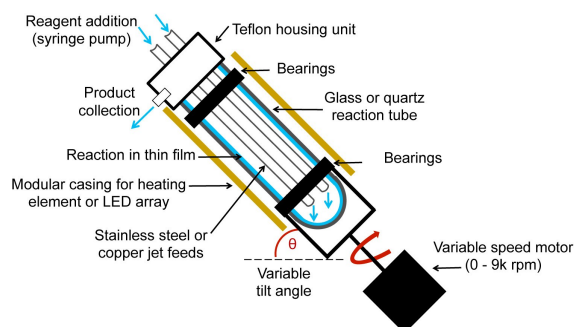


Figure 1. A schematic representation of the Vortex Fluidic Device (VFD). Digital images of the reactor are provided in the Electronic Supplementary Information.

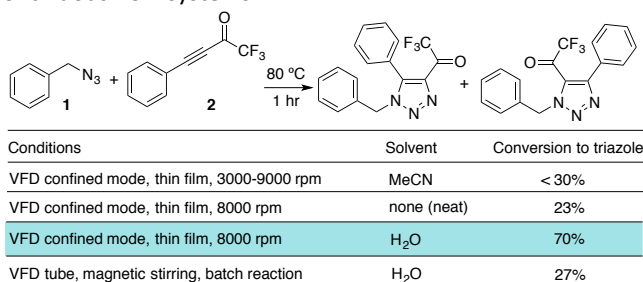
The uncatalyzed reaction between benzyl azide (**1**) and disubstituted alkyne **2** was studied first to determine any advantages of the VFD and the effect of water on the reaction. While the tilt angle of the rotating tube in the VFD can be varied (θ , Fig. 1), the optimal value for a diversity of applications is 45° ,¹¹⁻¹³ so this angle was used in this study. When the reaction between **1** and **2** was run in confined mode in the VFD at 80°C in acetonitrile, the conversion to triazole never exceeded 30%, even at a range of rotational speeds (Scheme 1 and S6). Similarly, conversion to the triazole was a mere 23% when the reaction was run neat, with no solvent (Scheme 1 and S10). However, when water was present in the reaction under otherwise identical conditions, reaction conversions increased up to 70%, as determined by ^1H NMR spectroscopic analysis of the reaction mixture (Scheme 1 and S11). The conversion also correlated with the rotational speed of the tube, with 8000 rpm identified as optimal for this reaction (S6). Importantly, the conversion to triazole in water was always higher in the VFD than when the azide and alkyne were simply stirred in the glass reaction tube at 80°C (a

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“batch” reaction, S4 and S7). For example, while the reaction of **1** and **2** reached 70% conversion in the VFD, the corresponding batch reaction only reached 27%. We attribute this difference to an enhanced “on water” effect for this reaction in the VFD in comparison to batch processing. “On water” azide-alkyne cycloadditions have been previously described¹⁵ and we attribute the enhancement of this effect in the VFD to the aforementioned high proportion of reagents at the organic-water phase boundary. In contrast to running the reaction in a thin film, traditional batch processing has a much smaller proportion of the reagents at this interface so the “on water” effect is less pronounced. Similar conclusions were made by Huck and co-workers¹⁷ and also Song and co-workers¹⁸ for other “on water” reactions in biphasic, continuous flow systems.



Scheme 1. Thin film processing in the VFD enhances the “on water” effect for the azide-alkyne cycloaddition. 0.25 mmol azide, 0.30 mmol alkyne and 0.5 mL solvent were used in all reactions, except for the neat reaction in which no solvent was used. The tilt angle for all VFD reactions was 45°. Conversions, determined by ¹H NMR spectroscopy, are the average of triplicate experiments.

This phenomenon was observed for a range of azides and alkynes (Table 1). Notably, this enhanced “on water” effect provided excellent conversions where the same transformations in other solvents were previously reported to require high pressures and far higher temperatures to achieve comparable results.¹⁹ In fact, the reaction between benzyl azide and methyl propiolate even occurred at room temperature in water in the confined mode of the VFD, with up to 49% conversion observed in a mere 2.5 hours (S16-S17). No reaction was observed at room temperature under batch conditions for this reaction, illustrating the dramatic rate enhancement enabled by the thin film processing in the VFD. The “on water” effect was also apparent for the reaction of benzyl azide with dimethyl acetylenedicarboxylate, which was run at room temperature, with batch processing providing 53% conversion and VFD processing resulting in an 87% isolated yield. Additionally, the last four entries in Table 1 indicated that confined mode processing could be used on a preparative scale, with 300-500 mg of triazole obtained in excellent isolated yields (S18-S24). It was also shown that the azide in these reactions could be generated *in situ* in the VFD followed by direct reaction with the alkyne (S19-S24). The “on water” effect was still observed under such conditions and the water could extract the salts, facilitating clean isolation of the product triazole.

In scaling up reactions in the VFD, continuous mode is required. In this setting, the azide and alkyne are added to the rotating reaction tube via two separate syringe pumps,

entering the tube through stainless steel jet feeds. For these experiments, mixtures of water and acetonitrile were used so that homogenous solutions of the reagents could be delivered in a controlled fashion. Under such conditions we did not expect to observe the “on water” effect, but the homogenous conditions were helpful in controlling stoichiometry when using the syringe pump. In the first experiments (run at 80 °C, Table 2), no copper was added to the reaction and the result was a surprise: near quantitative conversion to the triazole was observed with the exclusive formation of the 1,4-isomer.

Table 1. Comparison of VFD processing and batch processing in the azide-alkyne cycloaddition. All reactions were run at 80 °C for 1 h using 0.25 mmol azide, 0.30 mmol alkyne and 0.5 mL water (unless otherwise specified). VFD processing was carried out at 8000 rpm in confined mode at a 45° tilt angle. Batch reactions were run in the same glass reaction tube with magnetic stirring. VFD conversions are reported as the average of triplicate experiments. Isolated yields are reported in the bottom four examples.

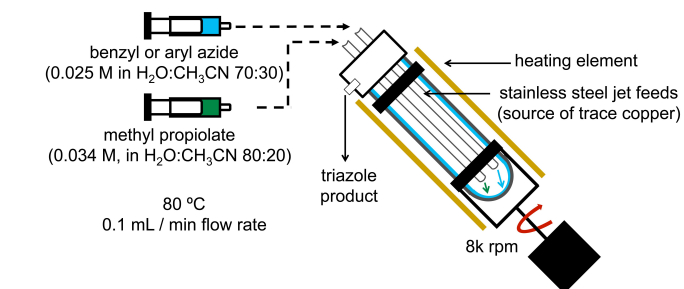
Azide	Alkyne	Product ^[a]	Batch ^[b]	VFD
Ph-CH ₂ -N ₃	MeO ₂ C-C≡C-CO ₂ Me	Ph-CH ₂ -1,2,4-triazole-5-carboxylate	50%	91 ± 2% ^[b]
Ph-N ₃	MeO ₂ C-C≡C-CO ₂ Me	Ph-1,2,4-triazole-5-carboxylate	14%	82 ± 1% ^[b]
2,6-difluorophenyl-CH ₂ -N ₃	MeO ₂ C-C≡C-CO ₂ Me	2,6-difluorophenyl-CH ₂ -1,2,4-triazole-5-carboxylate	41%	82 ± 3% ^[b]
2,6-difluorophenyl-N ₃	MeO ₂ C-C≡C-CO ₂ Me	2,6-difluorophenyl-1,2,4-triazole-5-carboxylate	31%	42 ± 2% ^[b]
Ph-CH ₂ -N ₃ [c]	MeO ₂ C-C≡C-CO ₂ Me	Ph-CH ₂ -1,2,4-triazole-5-carboxylate	53%	87% ^[d]
Ph-CH ₂ -N ₃ [c,e]	MeO ₂ C-C≡C-CO ₂ Me	Ph-CH ₂ -1,2,4-triazole-5-carboxylate	-	82% ^[d]
Ph-CH ₂ -N ₃	^t BuO ₂ C-C≡C-CO ₂ ^t Bu	Ph-CH ₂ -1,2,4-triazole-5-carboxylate	-	90% ^[d]
Ph-CH ₂ -N ₃ [e]	^t BuO ₂ C-C≡C-CO ₂ ^t Bu	Ph-CH ₂ -1,2,4-triazole-5-carboxylate	-	83% ^[d]

[a] Only one regioisomer is shown for asymmetric alkynes [b] Conversions based on ¹H NMR spectroscopy. [c] Reaction run at 20 °C [d] Isolated yield for VFD processing with reaction scale >300 mg. [e] Azide generated *in situ* in the VFD by reaction of benzyl bromide and sodium azide in water.

The exquisite regioselectivity strongly suggested that a copper contaminant was present and indeed ICP-MS indicated 9 ppb copper in the product solution. We suspect that the trace copper was leaching from the stainless steel jet feed. The Milli-Q water used in the reaction did not contain sufficient copper to account for these results because the confined mode resulted in a mixture of regioisomers (S27). The same reaction run in continuous mode at room temperature resulted in no reaction. This result suggests that catalyst leaching from the stainless steel required elevated temperature. The results in

Table 2 are remarkable because of the very low copper levels required to catalyze this reaction. The low levels of copper will also help meet heavy metal regulatory limits when, for instance, these reactions are used in the preparation of active pharmaceutical ingredients. Furthermore, using the jet feed as a reservoir for the copper is a convenient and technically simple method for delivering catalyst to the reaction.

Table 2. Continuous mode operation of the VFD provided full conversion to a single regioisomer. Trace copper was leached from the steel jet feeds, resulting in a final concentration of 9 ppb.



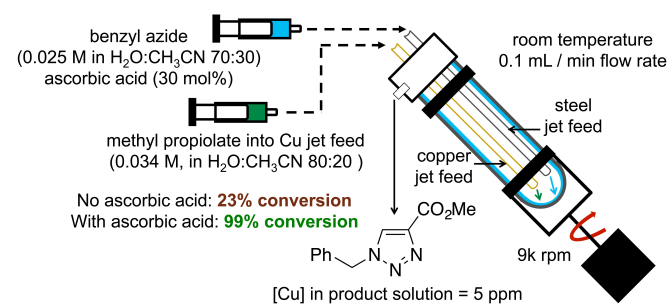
Azide	Alkyne	Product ^[a]	Conversion ^[b]
<chem>c1ccc(cc1)C#N</chem>	<chem>COC(=O)C#C</chem>	<chem>COC(=O)C1=NC(=CN1)Cc2ccccc2</chem>	99%
<chem>c1ccc(cc1)C#N</chem>	<chem>COC(=O)C#C</chem>	<chem>COC(=O)C1=NC(=CN1)Cc2ccccc2</chem>	99%
<chem>Fc1ccc(cc1)C#N</chem>	<chem>COC(=O)C#C</chem>	<chem>COC(=O)C1=NC(=CN1)Cc2cc(F)c(F)cc2</chem>	99%

[a] A single regioisomer was produced in these reactions [b] Conversions based on ¹H NMR spectroscopy

Inspired by the results above, it occurred to us that using a copper jet feed might be a useful reservoir of catalyst, especially for reactions that might require catalyst loading higher than low ppb levels generated from the stainless steel.²⁰ Additionally, the higher copper concentration might allow the reactions to proceed at room temperature—a capability not realized using the stainless steel jet feeds. Control experiments indicated that copper was easily leached from the copper jet feed, as determined by ICP-MS of the solvent flow through (S30). Water alone provided copper in a concentration of 75 ppb in the outflow, while mixtures of water and acetonitrile consistently provided copper concentrations of 2–7 ppm copper (S30–S31). Unfortunately, the conversion for the reaction of benzyl azide and methyl propiolate were relatively low in continuous mode, never exceeding 23% (Table 3, top). In contrast to recent reports where sufficient active catalyst was leached into solution from a copper reaction tube in flow,²¹ we suspected that the leached copper in our system might not be in the right oxidation state. Therefore, we simply included ascorbic acid in the azide solution. In doing so, quantitative conversion to the triazole was observed in continuous mode where the azide and ascorbic acid were delivered to the tube through a stainless

steel jet feed and methyl propiolate was delivered to the reaction tube through the copper jet feed. The reaction occurred at room temperature and the flow rate was 0.1 mL/min, which corresponds to a residence time of 11.7 minutes. Analysis of the product solution under these conditions revealed a copper concentration of 4.4 ppm (S34). Notably, these conditions consistently provided higher conversions of the triazole than when copper sulfate and ascorbic acid were used as the catalyst in confined mode (S30). This finding suggests that the catalyst generated from the copper jet feed is highly active. We also note that this method is distinct from other flow chemistry reports in which the reaction occurs in a copper tube.¹⁰ In the VFD setup in Table 3, the copper jet feed is a reservoir for catalyst, which is leached into the reaction zone in the glass tube.

Table 3. A copper jet feed leaches sufficient metal to catalyze the azide-alkyne cycloaddition in flow at room temperature. Ascorbic acid is required for high conversions. The tabulated results were all run on >200 mg scale.



Azide	Alkyne	Product	Isolated yield
<chem>c1ccc(cc1)C#N</chem>	<chem>COC(=O)C#C</chem>	<chem>COC(=O)C1=NC(=CN1)Cc2ccccc2</chem>	80%
<chem>c1ccc(cc1)C#N</chem>	<chem>CCOC(=O)C#C</chem>	<chem>CCOC(=O)C1=NC(=CN1)Cc2ccccc2</chem>	82%
<chem>c1ccc(cc1)C#N</chem>	<chem>COC(=O)C#C</chem>	<chem>COC(=O)C1=NC(=CN1)Cc2ccccc2</chem>	90%
<chem>COc1ccc(cc1)C#N</chem>	<chem>COC(=O)C#C</chem>	<chem>COC(=O)C1=NC(=CN1)Cc2ccc(OC)cc2</chem>	93%
<chem>COc1ccc(cc1)C#N</chem>	<chem>OC#C</chem>	<chem>OC#CC1=NC(=CN1)Cc2ccc(OC)cc2</chem>	82%
<chem>COc1ccc(cc1)C#N</chem>	<chem>COC(=O)C#C</chem>	<chem>COC(=O)C1=NC(=CN1)Cc2ccc(OC)cc2</chem>	73%

This protocol was also adapted to a preparative scale in which the methyl propiolate and benzyl azide solutions were delivered into the VFD at 80 °C at a 10 fold higher

concentration and increased flow rate (1.0 mL/min). The reaction resulted in complete consumption of starting materials and could provide gram-scale quantities of triazole per hour of continuous processing (S37). To further assess the scope of this method, several additional azide-alkyne cycloadditions were processed in flow (Table 3). All reactions were run on at least 200 mg in scale and isolated yields were good to excellent. Notably, these reactions using the copper tubing as the catalyst reservoir have been reproducible for at least 30 experiments, indicating the leaching process consistently provided active catalyst.

The requirement of ascorbic acid in generating the active catalyst led us to explore other methods of copper reduction in the VFD. Taking advantage of the transparent reaction tube, we considered photochemical reduction of the leached copper. In the event, eosin Y was used as a photoredox catalyst at a loading of 0.15 mol%.²² The eosin was delivered to the rotating tube in the same solution as the benzyl azide through a stainless steel jet feed while methyl propiolate was added through the copper jet feed, all at room temperature. Green LEDs (525 nm) were positioned around the outside of the reaction tube (see pages S53-S54 for details including a digital image and schematic of the equipment). Running in continuous mode at a flow rate of 0.1 mL/min resulted in quantitative conversion to the triazole. The full conversion was consistent in the product outflow over a total run time of 3.5 hours. If eosin Y was not contained in the reaction, the conversion dropped to 21%. If the LEDs were not used, the conversion dropped to 33% (S53). And while there have been reports of photochemically promoted copper-catalyzed azide-alkyne cycloadditions,²²⁻²⁴ our method is a simple way to deliver and maintain an active copper catalyst in flow. Furthermore, the transparent tube and the thin film in the VFD reactor helps ensure efficient irradiation of the reaction mixture.²⁵

The azide-alkyne cycloaddition was explored in a unique flow reactor: the Vortex Fluidic Device. The thin film processing led to an enhanced "on water" effect for copper-free cycloadditions. This is an important new addition to other advantages imparted by thin film processing in the VFD such as efficient heat dissipation,^{26, 27} rapid gas exchange and mass transfer,²⁷ and accelerated multi-phase reactions.²⁷ In continuous mode, the metallic jet feeds served as a convenient reservoir of catalyst in the copper-catalyzed azide-alkyne cycloadditions. To maintain the active copper catalyst, a reducing agent such as ascorbic acid was required for efficient reactions at room temperature. Alternatively, reducing conditions could be maintained photochemically using eosin Y and green LEDs, which promoted a highly efficient copper-catalyzed azide-alkyne cycloaddition in flow. Together, these results illustrate how novel processing techniques can reveal interesting chemical phenomena and new strategies in catalysis. Furthermore, the integration of azide-alkyne cycloaddition into flow chemistry platforms^{10, 28, 29} is an important capability as this reaction continues to be adopted in industrial and pharmaceutical endeavors.^{2,20}

Conflicts of interest

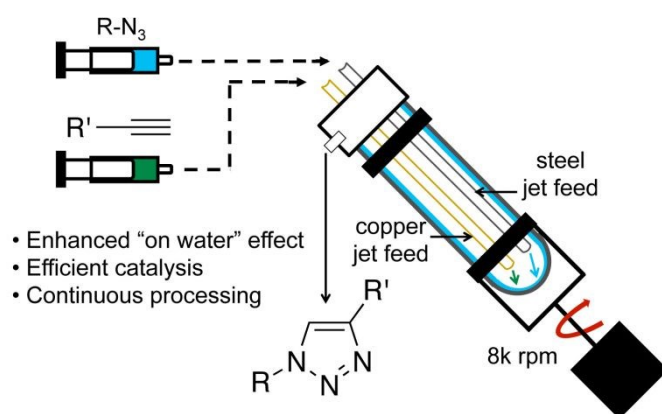
There are no conflicts to declare.

Notes and references

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TOC Graphic:



Azide-alkyne cycloadditions in a Vortex Fluidic Device benefit from enhanced “on water” effects and copper jet feeds provide a convenient method of highly active catalyst delivery for flow chemistry.