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Angled vortex fluidic mediated multicomponent photocatalytic and transition metal-catalysed reactions

Louisa A. Ho,[a] Colin L. Raston[b] and Keith A. Stubbs*[a]

Abstract: The dynamic thin film which is formed in an angled rapidly rotating tube in a vortex fluidic device (VFD) is effective in facilitating multicomponent reactions (MCRs) as photocatalytic or metal-mediated processes. Here we demonstrate the utility of the VFD using two known MCRs, an Ugi-type three component and A^3-coupling reactions. The Ugi-type reaction can be done in either confined or continuous flow modes of operation of the microfluidic platform whereas the A^3-coupling reaction was optimised for the confined mode of operation. The examples tested gave excellent yields with short reaction times.

Introduction

At the heart of organic chemistry is the development of new methodologies to prepare molecules, not only new bond-forming reactions but also developing more efficient and scalable preparation techniques. Two aspects of these concepts, which are receiving increasing attention, are the use of mulitcomponent reactions (MCRs)[1-6] and flow chemistry[7-14] to gain access to new molecules and facilitate chemical transformations, respectively.

MCRs are a useful method of preparing new synthetic molecules where typically three or more components are combined in a single pot and through a series of chemical reactions new compounds can be produced which are dependent only on the starting materials used.[15] Flow chemistry on the other hand has seen a rapid increase in its use to prepare a wide variety of molecules both in academia and industry.[7-14] The advancement of flow chemistry in the literature has been greatly aided by the development of smaller-sized reactors that allow for their use in laboratory settings[16-18] and to this end the use of a number of microfluidic platforms with synthetic capabilities have been discussed.[19-30] The increased interest in flow chemistry stems from the ability to use it to efficiently control a variety of factors important to the success of a chemical reaction, for example reagent quantities, surface area of reaction and temperature.[18] Of interest is that the flow device based on angled vortex driven dynamic thin films, called the vortex fluidic device (VFD) (Figure 1A),[25] has not been rigorously investigated in regards to its ability to be used as a processing platform for MCRs, even though its design characteristics,[25] which have been reviewed recently,[31] are favoured as such.[25]

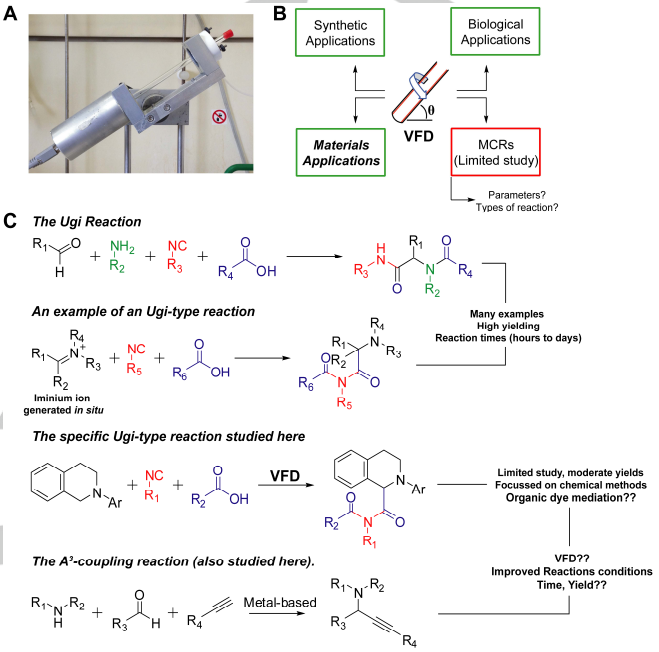

Figure 1. (A) Photograph of a VFD shown operating in the confined mode (heating block/ photochemical apparatus removed for clarity). The device features a tube, being rotated at a specific angle at high speed to generate a thin film. (B) Overall utility of the VFD in terms of applications noting that MCRs are well suited for this microfluidic platform. (C) Examples of the MCRs and those being studied here.

An important advantage of the VFD over other microfluidic platforms is the ability of the device to form a dynamic thin film, where the chemistry of interest takes place. The film is formed by the rapid rotation of a tube with the thickness of the film controlled by varying the speed of rotation and the tilt angle.[25, 31] Using a film confers a number of advantages in synthesis including rapid heat transfer and uniform mixing with no concentration gradients. Numerous applications have been studied utilizing these features (Figure 1B)[31] with optimizing rotational speeds enhancement of both organic and enzymatic reactions arising from pressure waves being achieved.[32] In addition, the VFD works in two modes of operation, depending on the chemistry being conducted, the confined mode for a finite

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volume of liquid and the continuous flow mode, where the reaction is conducted within the tube and the mixture collected as it leaves the system.[25, 31]

To explore the utility of the VFD as a device to mediate MCRs we chose two examples of MCRs, the Ugi-type three-component and the A^3-coupling reactions. Classically the Ugi reaction employs an aldehyde, amine, a carboxylic acid and an isocyanide[33] (Figure 1C) but recent advances have shown that variations of reaction are possible to give Ugi-type reaction processes where the iminium ion intermediate needed for a successful reaction is generated *in situ* from non-classical precursors using, for example, chemical oxidative[34-36] or photochemical processes,[37] allowing for the formation of a variety of different types of molecules.[1, 38-40] The A^3-coupling reaction involves the coupling of an aldehyde, alkyne and amine through C-H bond activation.[41] This type of reaction has gained wide attention as the propargylamine products formed in these reactions have been used in the preparation of a wide variety of nitrogen containing heterocycles.[42] Typically the reaction is catalysed by metals and these materials include ionic salts and ligand-based compounds, in high yields and in reasonable reaction times.[41, 43, 44]

Overall, here we demonstrate the potential utility of the VFD as a simple flow reactor in being able to mediate MCRs as part of developing new efficient synthetic protocols for organic reactions, which can be translated easily between laboratories.

Results and Discussion

The type of MCR we first investigated with the VFD was a specific Ugi-type three-component reaction involving sp^3 C-H bond activation of a tetrahydroisoquinoline with a carboxylic acid and an isocyanide which can be photocatalytically-mediated through the use of metals,[45] and more recently using diethyl diazodicarboxylate[46] (Figure 1C). Organic dyes represent an excellent substitute for the use of metal-based systems in photocatalytic reactions with many examples of reactions involving such dyes reviewed in the literature.[47-51] We hypothesised that the dynamic thin film in the VFD with tuneable fluid dynamics could facilitate the use of organic dyes in simplifying the application of MCRs in synthesis.

Initially, we used the confined mode of operation of the VFD, a strategy which has served well in studying a number of processes before taking them to continuous flow processing.[31] This involves optimising the unique operational parameters of the device, namely the rotational speed of the tube and its tilt angle. Studies were conducted using a 10 mm OD borosilicate glass tube (NMR grade) for *N*-phenyltetrahydroisoquinoline, acetic acid and cyclohexyl isocyanide in the presence of an amount of Rose Bengal and solvent. The choice of solvent and organic dye loading was based on successful literature photocatalytic reactions.[45, 52-55] Interestingly, the reaction proceeded smoothly and was deemed complete after only 30 minutes across all parameters, but 5000 rpm rotational speed and 45° tilt angle produced the highest conversion, at 88% yield (Figure 2). This is highly commensurate with literature reactions

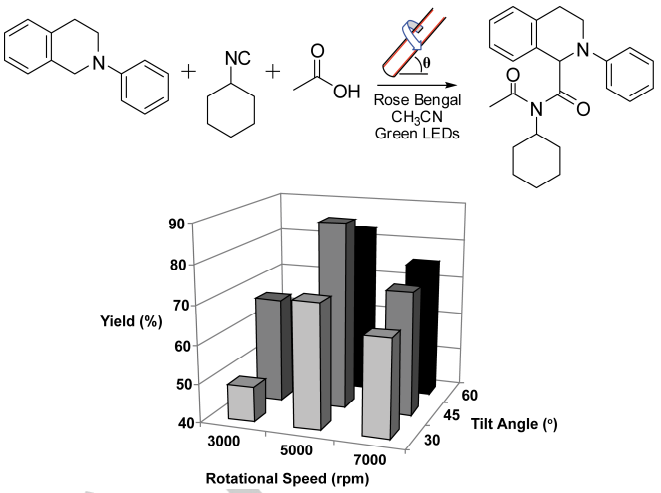


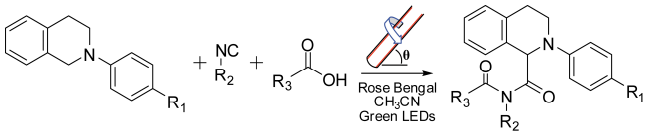
Figure 2. Variation in isolated yield for the test MCR reaction between *N*-phenyltetrahydroisoquinoline, acetic acid and cyclohexyl isocyanide as a function of rotational speed and tilt angle of the VFD tube, as factors which affect the film thickness. The optimisation procedure used acetonitrile with Rose Bengal (1 mol%) for 30 minutes. All reactions were conducted in triplicate with the average Errors were within ±2%.

for the preparation of this molecule where reactions are typically conducted for many hours with lower yields. We established that under similar reaction conditions that Eosin Y, another commonly used organic dye in photocatalytic reactions, gave a lower yield (60%).

Further investigation into the amount of Rose Bengal required to facilitate the process also demonstrated the utility of the VFD of being able to establish a thin film (ca 250 nm at 5000 rpm and 45° tilt angle)[25] which is important in generating a large surface area for the reaction. This allows for more uniform irradiation as the liquid moves along the tube, in moving towards all molecules being treated in the same way, and thus more effective and homogenous reaction conditions. Interestingly the amount of Rose Bengal needed to complete the reaction within the same time frame could be reduced significantly (See Supporting Figure 1). Of particular note is a ~10-fold reduction in the amount of organic dye that is normally used to facilitate photocatalytic reactions reported in the literature. In addition, the optimal 5000 rpm speed and 45° tilt has been established for a number of reactions and processes for the 10 mm OD tube, including protein folding,[56] highlighting special fluid dynamic effects which are currently under investigation in a number of research laboratories.

With suitable reaction conditions established for the confined mode of operation of the VFD, we expanded the set of substrates to demonstrate that the reaction has general utility (Table 1). In all cases the yields were comparable to literature preparations of the respective compounds but they are achieved in a considerably shorter time, as well as with greatly reduced catalytic loading. We then expanded the method to using continuous flow operation of the VFD, noting that a 30 minute reaction time in the confined mode is highly commensurate with

Table 1. Synthesis of various compounds using the VFD operating at 5000 rpm rotational speed and 45° tilt angle in confined mode at room temperature for 30 minutes, in the presence of Rose Bengal (0.1 mol%). All reactions were conducted in triplicate with the average shown. Errors were within ±2%. Literature yields for known compounds are shown in brackets.



Entry	Substrate 1	Substrate 2	Substrate 3[a]	Product Yield (Lit. Yield)
	R_1	R_2	R_3	
1	H	C_6H_{11}	CH_3	88(86)[45]
2	H	CH_2Ph	CH_3	79(60)[46]
3	H	C_4H_9	CH_3	73
4	H	CH_2CO_2Me	CH_3	79
5	H	CH_2Ts	CH_3	71(85)[46]
6	H	MeOPh	CH_3	71
7	OMe	C_6H_{11}	CH_3	93(95)[45]
8	OMe	CH_2Ph	CH_3	79(92)[45]
9	OMe	C_4H_9	CH_3	83
10	OMe	CH_2CO_2Me	CH_3	73
11	OMe	MeOPh	CH_3	80(80)[45]
12	Br	C_6H_{11}	CH_3	84(91)[45]
13	Br	CH_2Ph	CH_3	81
14	Br	C_4H_9	CH_3	78
15	Br	CH_2CO_2Me	CH_3	83
16	Br	MeOPh	CH_3	74
17	H	C_6H_{11}	MCA	71
18	H	C_6H_{11}	$C_6H_4OCH_2$	81
19	H	C_6H_{11}	Ph	78
20	H	C_6H_{11}	C_3H_7	79
21	H	C_6H_{11}	3-BrPh	79
22	H	C_6H_{11}	4-NO_2Ph	83

[a] MCA = 4-$MeOC_6H_4CHCH$

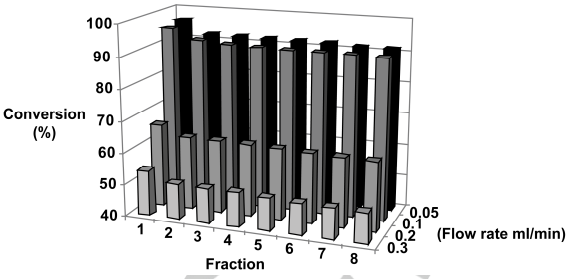


Figure 3. Synthesis of *N*-acetyl-*N*-cyclohexyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (Table 1, Entry 1) using the VFD in the continuous flow mode. The parameters used were those that were optimised in the confined mode (5000 rpm and 45° tilt angle) at room temperature. Fractions (2 mL) were collected in a continuous fashion from when the reaction mixture begun to elute from the device. The components of all materials in the reaction mixture were as for the optimised confined mode reactions. All reactions were conducted in triplicate with the average conversion shown (errors within ±3%) as determined using ^{1}H NMR.

the residence time for liquid entering the tube and exiting at the top for a flow rate of 0.1 mL/min.[25, 31] Again we used a working solution of phenyltetrahydroisoquinoline, acetic acid and cyclohexyl isocyanide to investigate the utility of the continuous flow mode in the preparation of the targeted coupled product (Table 1, Entry 1) and found that fractions collected contained an excellent conversion of product (Figure 3). Consistent with that observed previously[57] initial fractions had a higher conversion than fractions collected later, implying steady state conversion needs to be achieved during the processing. Higher than optimal flow rates reduced the conversion, which is consistent with a reduction in residence time for the reaction under continuous flow.

With these successful results in hand we next turned our attention to the other model MCR reaction, the A^3-coupling reaction. We felt that the VFD was well suited to using this

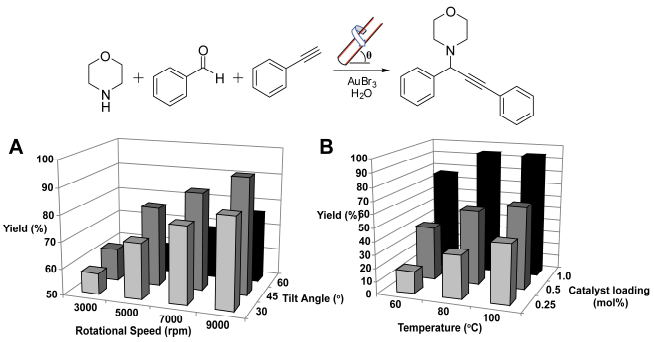
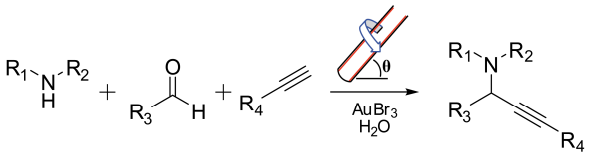


Figure 4. (A) Variation in isolated yield for the MCR reaction between morpholine, benzaldehyde and phenylacetylene in water at 100°C with $AuBr_3$ (1 mol%) for 2 hours. (B) Variation in isolated yield for the MCR reaction between morpholine, benzaldehyde and phenylacetylene in water with varying catalyst loading and temperature using optimised VFD parameters (9000 rpm, maximum capability of the VFD, 45° tilt angle) for 2 hours. All reactions were conducted in triplicate with the average shown. Errors were within ±2%.

Table 2. Synthesis of various A^3-coupling products using the VFD operating at 9000 rpm (maximum rotational speed) and 45° tilt angle in confined mode at 80°C with $AuBr_3$ (1.0 mol%) for 2 hours. All reactions were conducted in triplicate with the average shown. Errors were within ±2%. Literature yields for known compounds are shown in brackets.



Entry	Amine		Aldehyde	Alkyne	Product Yield (Lit. Yield)
	R_1	R_2	R_3	R_4	
1	-$(CH_2)_2O(CH_2)_2$-		Ph	Ph	94(59)[58]
2	-$(CH_2)_5$-		Ph	Ph	83(75)[59]
3	-$(CH_2)_4$-		Ph	Ph	85(88)[60]
4	-$(CH_2)_6$-		Ph	Ph	82
5	C_4H_9	C_4H_9	Ph	Ph	72(61)[61]
6	-$(CH_2)_2O(CH_2)_2$-		4-MeOPh	Ph	88(90)[62]
7	-$(CH_2)_5$-		4-MeOPh	Ph	81(61)[63]
8	-$(CH_2)_4$-		4-MeOPh	Ph	84(87)[60]
9	-$(CH_2)_2O(CH_2)_2$-		C_6H_{11}	Ph	90(90)[60]
10	-$(CH_2)_5$-		C_6H_{11}	Ph	92(99)[63]
11	-$(CH_2)_4$-		C_6H_{11}	Ph	92(98)[58]
12	-$(CH_2)_2O(CH_2)_2$-		4-MePh	Ph	87
13	-$(CH_2)_5$-		4-MePh	Ph	82
14	-$(CH_2)_4$-		4-MePh	Ph	84(86)[60]
15	-$(CH_2)_2O(CH_2)_2$-		Ph	3-MeOPh	88

strategy that allowed for the application of this reaction. Again, to demonstrate whether the VFD could be used in conjunction with a suitable transition metal salt for such MCRs we used the confined mode of operation. $AuBr_3$ was the choice of metal salt, which is simple and has been demonstrated to be useful in mediating A^3-couplings.[64]

Studies were conducted using morpholine, benzaldehyde and phenylacetylene in water with dissolved $AuBr_3$ (1 mol%) at 5000 rpm rotational speed and 45° tilt angle (VFD parameters used in the initial MCR, Figure 4A). Interestingly, the reaction proceeded smoothly and was deemed complete after only 2 hours at 100°C (yield 80%). With a basis for optimisation in hand we varied the speed and found the yield was increased at higher speeds with 9000 rpm being optimal (94%). After optimising the VFD operating parameters, we investigated the loading of the catalyst and the temperature of the reaction (Figure 3B). Disappointingly, the catalyst loading could not be reduced without a significant loss of yield (0.5 mol%, 63% yield). On the other hand, the temperature could be reduced to 80°C without a reduction in yield.

With suitable reaction conditions established, we expanded the set of substrates to demonstrate general utility (Table 2). In all cases the yields were comparable to literature preparations of the respective compound but nevertheless, they were also achieved in a considerably shorter time. We note that the tilt angle is optimal at 45° (Figure 4A), with the optimal speed ≥ 9000 rpm, which is limited by the operational limits of the in-house constructed VFD.[25] Clearly the 45° tilt angle is a common thread for all reactions herein, and for a number of other reactions and processes studied in the VFD.[25, 31] While the reactions studied herein are in a 10 mm OD tube in the VFD, in recent studies a 20 mm OD tube has been utilised, but the optimal tilt remains at 45°, and thus the choice of tube diameter is not a limiting design feature of the VFD.

Conclusions

We have demonstrated that the VFD, a user-friendly plug-and-play device (relative to most other microfluidic flow devices), can be used efficiently to facilitate MCRs in high yield. The MCRs demonstrated are photocatalytic and metal-mediated in nature which demonstrates the overall flexibility of chemical reactions which are able to be conducted in the VFD. As has been previously described[25, 31] the rotational speed and tilt can be optimised for a particular reaction, akin to optimising reagents, solvents and temperature when finding ideal conditions for a new chemical transformation using traditional batch processing. The optimised tilt angle of 45° is noteworthy, where the effect of gravity on the dynamic thin film is the greatest, at least judged as the maximum cross vector of gravity with centrifugal force. The utility of the VFD lies in this point as two more parameters can be added to the optimisation protocol. The thin films generated by the VFD allow for efficient heat and mass transfer, uniform mixing and no concentration gradients which are important considerations in chemical synthesis. The presence of rotational speed dependent introduced pressure waves,[31, 32] is likely to be in play for the optimal 5000 rpm for the MCR reaction between *N*-phenyltetrahydroisoquinoline, acetic acid and cyclohexyl isocyanide. This speed is optimal for a number of other reactions using 10 mm diameter glass tubes in the VFD, in contrast to close to 7000 rpm for a number of reactions in 20 mm glass tubes.[31, 32] Radial dependent processing in the VFD is now a major current research program underway. We note that the VFD has two different operating methodologies, namely confined and continuous flow, reactions for which the conditions are appropriate can be easily upscaled for increased output. We envisage that the VFD can be readily adapted to other MCRs which will add to the utility of the VFD as a device which controls chemical reactivity and selectivity.

Experimental Section

General

Details of the in-house construction of the 10 mm VFD powered by a Faulhaber 4490 H 024 B motor have been previously reported.[25] ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance IIIHD 500 (500 MHz for ^{1}H and 125.8 MHz for ^{13}C) or Bruker Avance IIIHD 600 spectrometer (600 MHz for ^{1}H and 150.9 MHz for ^{13}C). The solvent used for NMR was deuteriochloroform ($CDCl_3$) and were calibrated for ^{1}H at δ 7.26 ppm and ^{13}C at δ 77.16 ppm. High resolution mass spectra (HR-MS) were obtained on a Waters LCT Premier XE spectrometer, run in W-mode, using the electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI) method with CH_3CN:0.1% HCOOH (9:1) as a matrix. Infrared spectra were obtained on a PerkinElmer spectrum one FTIR spectrometer fitted with a PerkinElmer Universal ATR sampling accessory. Samples were analysed as neat samples and recorded in wave numbers (cm^{-1}). Flash chromatography was performed on Merck silica gel using the specified solvents. Thin layer chromatography (TLC) was effected on Merck silica gel 60 F254 aluminium-backed plates that were visualised using a UV lamp.

Optimisation of VFD reaction conditions for the coupling of *N*-phenyltetrahydroisoquinoline, acetic acid and cyclohexyl isocyanide with Rose Bengal

A 10 mm NMR tube was charged with *N*-phenyltetrahydroisoquinoline (52 mg, 0.25 mmol), acetic acid (17 μL, 0.3 mmol), cyclohexyl isocyanide (37 μL, 0.3 mmol) Rose Bengal (2 mg, 1 mol%) and acetonitrile (2 mL). The tube was then capped tightly then rotated in the VFD at 3000, 5000 or 7000 rpm with a tilt angle of 15, 45 or 75° for 30 minutes in the presence of green LEDs (~530 nm - 2.7 mW/cm^2) at a distance of 3 cm. The mixture was then diluted with EtOAc (2-3 mL) transferred to a round bottom flask and evaporated to dryness. The residue was then redissolved in EtOAc and adsorbed onto silica gel and subsequent flash chromatography (EtOAc:hexanes, 1:9) was conducted and gave the desired compound.

General procedure for photoredox coupling of *N*-aryltetrahydroisoquinoline, carboxylic acids and isocyanides with Rose Bengal

A 10 mm NMR tube was charged with the appropriate tetrahydroisoquinoline (0.25 mmol), carboxylic acid (0.3 mmol), isocyanide (0.3 mmol), Rose Bengal (0.2 mg, 0.1 mol%) and acetonitrile (2 mL). The tube was capped tightly and then rotated in the VFD at 5000 rpm with a tilt angle of 45° for 30 minutes in the presence of green LEDs (~530 nm - 2.7 mW/cm^2) at a distance of 3 cm. The mixture was then diluted with EtOAc (2-3 mL) and transferred to a round bottom flask and evaporated to dryness. The residue was then redissolved in EtOAc and adsorbed onto silica gel and subsequent flash chromatography (EtOAc:hexanes, 1:9-1:4) gave the desired compounds.

***N*-acetyl-*N*-cyclohexyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (Table 1, Entry 1)**

N-Phenyltetrahydroisoquinoline[65] (50 mg), acetic acid (17 μL) and cyclohexyl isocyanide (37 μL) was used to obtain the title compound (82 mg, 88%). R_f 0.28 (EtOAc:hexanes 1:9). ^{1}H NMR and ^{13}C NMR were consistent with literature values.[45] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38-7.33 (m,1H), 7.30-7.20 (m, 4H), 7.17-7.14 (m, 1H), 7.00-6.95 (m, [app d], 2H), 6.86-6.83 (m, [app t], 1H), 6.16 (s, 1H), 3.71-3.64 (m, 1H), 3.59-3.51 (m, 2H), 3.03-2.95 (m, 1H), 2.94-2.86 m, 1H), 2.18 (s, 3H), 2.01-1.89 (m, 1H), 1.84-1.65 (m, 3H), 1.57-1.43 (m, 2H), 1.20-0.95 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.2, 174.5, 148.6, 135.5, 132.5, 129.2, 128.4, 127.7, 126.3, 119.1, 115.3, 63.3, 59.1, 44.7, 30.7, 29.4, 27.4, 26.4, 25.6, 25.0.

Experimental details for the other compounds listed in Table 1 are provided in the Supporting Information.

Optimisation of reaction conditions for the coupling of morpholine, benzaldehyde and phenylacetylene with $AuBr_3$

A 10 mm NMR tube was charged with morpholine (100 μl, 1.1 mmol), benzaldehyde (100 μl, 1.0 mmol) and phenylacetylene (160 μl, 1.5 mmol), $AuBr_3$ (4 mg, 1 mol%) in water (1 mL). The tube was capped tightly and then rotated in the VFD at 3000, 5000, 7000 or 9000 rpm at a tilt angle of 15, 45 or 75° for 2 hours at 100°C. The mixture was then transferred to a round bottom flask and evaporated to dryness. The residue was then then redissolved in EtOAc and adsorbed onto silica gel and subsequent flash chromatography (EtOAc:hexanes) gave the desired compound.

Optimisation of reaction conditions (catalyst loading and temperature) for the coupling of morpholine, benzaldehyde and phenylacetylene with $AuBr_3$

A 10 mm NMR tube was charged with morpholine (100 μL, 1.1 mmol), benzaldehyde (100 μL, 1.0 mmol) and phenylacetylene (160 μL, 1.5 mmol), $AuBr_3$ (0.25-1 mol%) in water (1 mL). The tube was capped tightly then rotated in the VFD at 9000 rpm at a tilt angle of 45° for 2 hours at 60, 80 and 100°C. The mixture was then transferred to a round bottom flask and evaporated to dryness. The residue was then redissolved in EtOAc and adsorbed onto silica gel and subsequent flash chromatography (EtOAc:hexanes) gave the desired compound.

General procedure for A^3-coupling of an amine, aldehyde and alkyne with $AuBr_3$

A 10 mm NMR tube was charged with the appropriate amine (1.1 mmol) aldehyde (1.0 mmol) and acetylene (1.5 mmol), $AuBr_3$ (1 mol%) in water (1 mL). The tube was capped tightly then rotated in the VFD at 9000 rpm with a tilt angle of 45° for 2 hours at 80°C. The mixture was then transferred to a round bottom flask and evaporated to dryness. The residue was then redissolved in EtOAc and adsorbed onto silica gel and subsequent flash chromatography (EtOAc:hexanes) gave the desired compound.

4-(1,3-Diphenylprop-2-yn-1-yl)morpholine (Table 2, Entry 1)

Morpholine (100 μL), benzaldehyde (100 μL) and phenylacetylene (160 μL) was used to obtain the title compound (260 mg, 94%). R_f 0.24 (EtOAc:hexanes 1:9). ^{1}H NMR and ^{13}C NMR were consistent with literature values.[58] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68-7.63 (m, [app d], 2H), 7.56-7.50 (m, 2H), 7.42-7.29 (m, 6H), 4.80 (s, 1H), 3.80-3.70 (m, 4H), 2.70-2.60(m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.8, 131.8, 128.5, 128.3, 128.2, 128.2, 127.7, 122.9, 88.4, 85.0, 67.1, 62.0, 49.9.

Experimental details for the other compounds listed in Table 2 are provided in the Supporting Information.

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Keywords: Thin film microfluidics • photocatalysis • vortex fluidics • multicomponent reactions • A^3 coupling

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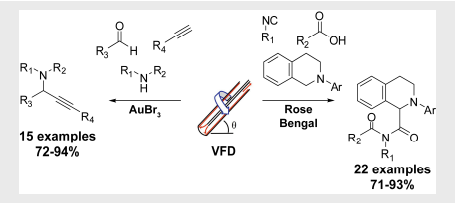

The VFD microfluidic device, has been used in multicomponent reactions (MCRs) involving photocatalytic or metal-mediated processes. These reactions give excellent yields with short reaction times.

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Angled vortex fluidic mediated multicomponent photocatalytic and transition metal-catalysed reactions