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Continuous flow synthesis of 1,4-disubstituted 1,2,3-triazoles *via* consecutive β-azidation of α,β-unsaturated carbonyl compounds and CuAAC reactions†

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We herein report a multi-step flow protocol for the synthesis of 1,4-disubstituted 1,2,3-triazoles starting from α,β-unsaturated carbonyls. Best results, both in terms of chemical productivity and sustainability, were obtained using a sequential combination of two flow reactors: one packed with a tailor-made **POLITAG-F** organocatalytic system and a copper tube apparatus. Moreover, the use of aqueous acetonitrile azeotrope led to excellent catalytic performances in both the developed processes while affording a waste-minimized multi-step protocol. Indeed, the azide intermediates subsequently reacted without the need for an additional purification step, and the aqueous acetonitrile azeotrope could be largely recovered/reused at the end of the process. 1,4-disubstituted β-keto 1,2,3- triazoles were obtained with high yields, which can be associated with low E-factor values. Finally, the green metrics evaluation of the process is also given to quantify the advantages associated with the use of our flow strategy.

Introduction

Modern synthetic chemistry aims to meet the urgent need for a shift toward more sustainable industrial production by designing efficient and benign chemical processes.[1] In this context, different principles of green chemistry are fulfilled by click chemistry. This approach was introduced in 2001 by Sharpless as a novel organic synthesis strategy to obtain complex molecules by employing simple reaction conditions that produce innocuous by-products.[2] Among click chemistry reactions, Copper-Catalyzed Azide–Alkyne Cycloaddition (CuAAC), which was developed independently by the groups of Sharpless[3] and Meldal[4] in 2002, is the simplest method for generating architecturally complex functional organic molecules.

The widespread utilization of the CuAAC strategy in different fields for the synthesis of valuable molecules has been acknowledged by the Nobel prize in Chemistry 2022.[5]

The Cu(I)-catalyzed cycloaddition of organic azides and alkynes leads to the formation of 1,2,3-triazoles with exclusive selectivity to the 1,4-disubstituted isomer. This class of compounds has gained increasing interest as they show anti-HIV, antibiotic, antiviral and antibacterial activities.[6]

Although the CuAAC reaction is a benign synthetic approach, different strategies have been developed to improve the sustainability of the protocol by further reducing the waste production.[7]

Particular attention has been paid to the recovery and reuse of both the catalytic system and reaction media,[7a,b] as well as the implementation of continuous flow techniques to improve large-scale production.[8]

In the context of heterogeneous copper catalysis under continuous flow conditions, using copper tubes (Cu-tubes), which are generally referred to as copper tube flow reactors (CTFRs), is a solid option. They are commercially available and can easily be incorporated into a flow line while allowing rapid heating and cooling owing to their highly increased thermal conductivity.[9] This kind of reactor has been widely used in different transformations.[9,10] Thanks to the above-mentioned advantages, different groups have exploited Cu-Tubes in the CuAAC reaction for the assembly of high-value products, such as macrocycles, peptoids and API rufinamide, with high yields.[11]

Despite the ready availability of alkynes, most organic azides are not commercially available and difficult to manipulate due to their explosive character and instability. Moreover,

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organic azides are usually obtained using a combination of sodium azide and strong acid as hydrazoic sources, which render unsuitable conditions for the safety of the process.[12] For this purpose, different approaches have been developed for the synthesis of 1,2,3-triazoles, such as the utilization of multicomponent reactions[13] and multi-step flow protocols.[11c,14]

Flow chemistry has become a key tool to enhance the selectivity, safety, and efficiency of synthetic chemical processes.[15] Indeed, the shift from batch to flow ensures easy scale-up[16] and safer handling of hazardous reagents and intermediates.[17] Moreover, the flow technology allows better control of reaction parameters, even for gas phase reagents,[18] by providing a high area-to-volume ratio, which increases thermal contact and mass transfer.[19] The automation of the flow process is also responsible for enhanced reproducibility.[20] Other advantages are the facilitated work-up procedure along with a decrease in environmental footprint.[21]

Herein, we report a waste-minimized multi-step flow protocol for the synthesis of 1,4-disubstituted β-keto triazoles from enones. The two-step protocol consists of the azido-Michael reaction of α,β-unsaturated carbonyl compounds to yield the corresponding β-azidocarbonyl products, which are readily converted to β-keto triazoles *via* the CuAAC reaction.[12b,c]

Trimethylsilyl azide ($TMSN_3$) has been selected as a safer N_3^- source in comparison with hydrazoic acid and sodium azide.[9,22] $TMSN_3$ is widely applied in the synthesis of organic azides in combination with metal-based catalysts[23] and under metal-free conditions,[24] and in a catalyst-free protocol for the azidation of perfluoroalkyl α,β-unsaturated ketones.[25]

However, some procedures report the use of $TMSN_3$ under acidic conditions to generate HN_3 *in situ*.[24d–f] Due to the high toxicity and explosive character of hydrazoic acid, it is necessary to minimize its formation. In this context, it has been demonstrated that the combination of a fluoride-based catalyst with $TMSN_3$ shows a safer profile compared with both these procedures and the use of other azido sources, such as sodium azide.[22a] Although a holistic evaluation has revealed that the preparation of $TMSN_3$ from trimethylsilyl chloride and sodium azide[12a] is disadvantageous, and the presence of the trimethylsilyl group certainly affects the Atom Economy (AE) of the process and the mass of byproduct formed (trimethylsilanol), in comparison with NaN_3, the use of additives can be avoided when $TMSN_3$ is used as the azido source. Moreover, considering the risks associated with the use of $TMSN_3$ and the lack of data regarding its hazardous attributes, such as explosive power and occupational exposure limits, the global environmental impact and safety profile are lower when $TMSN_3$ is used.[22a]

POLITAG-F is an organocatalytic system,[26] wherein F refers to the fluoride counter anion of the ionic resin, has been chosen as the catalyst for the first step as fluoride is known to effectively interact with silicon in $TMSN_3$, activating the Si–N bond and thereby the nucleophilic ability of the azido ion.[27]

Therefore, in our strategy, α,β-unsaturated carbonyl compounds and $TMSN_3$ are flowed through the first **POLITAG-F**-packed reactor to yield the corresponding azides, which without purification undergo the CuAAC reaction in the flow when mixed with an alkyne substrate in the Cu-tube. While this strategy can effectively pave the way to a waste-minimized green route for the synthesis of the target 1,4-disubstituted β-keto 1,2,3-triazoles, it requires the delicate tuning of the two separate reactors and flows to achieve the highest chemical efficiency.

For the minimization of waste, in this process, we have focused on the use of an aqueous acetonitrile azeotropic mixture as the medium as it brings the benefits of both aqueous and organic media, while it can also be efficiently recovered and reused.[28]

A final comparison of the different green metrics (Atom Economy (AE), Mass Recovery Parameter (MRP), Reaction Mass Efficiency (RME), Stochiometric Factor (1/SF) and E-factor) highlights the advantages of the flow protocol developed herein, compared to batch, as it features a low environmental footprint for the telescoped synthesis of 1,4-disubstituted β-keto 1,2,3-triazoles with minimal metal contamination.

Results and discussion

POLITAG-F has previously shown superior results in the cyanosilylation of aldehydes compared with commercially available F-based catalysts of both homogeneous and heterogeneous nature.[26] In addition, the "SPACER"-type polymeric support has shown enhanced stability and better recyclability in comparison with commercially available chloromethylated resins.[26,28b] For these reasons, we began our investigation with the polymer-supported bis-imidazolium pincer ligand, POLITAG, which contained fluoride as the counterion[26] and SPACER as the cross-linker of the polymeric support[29] (Fig. 1).

The loading of the fluoride organocatalyst (1.26 mmol g^{-1}), as per the previously reported procedure,[26] was calculated by elemental analysis based on the number of bis-imidazolium units (see ESI for further details†).

The consecutive batch protocol

A preliminary optimization for the definition of our synthetic strategy, including the study of the consecutive protocol, was performed under batch conditions.

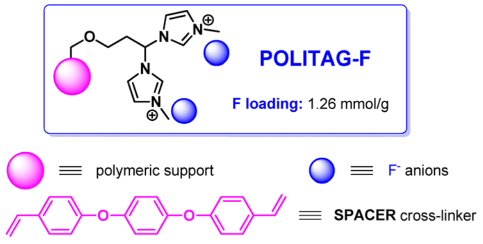


Fig. 1 Representation of **POLITAG-F** organocatalyst.

Initially, the **POLITAG-F** catalyst was tested in the β-azidation reaction of (*E*)-3-hepten-2-one (**1a**) in different reaction media (Table 1).

With the intention to develop a waste-minimized process, we started by performing the reaction under solvent-free conditions (SolFC). However, in these conditions, the conversion to product **2a** was poor even after 8 h reaction time (entry 1, Table 1).

By employing cyclopentylmethylether (CPME) and *tert*-amyl methyl ether (TAME) as reaction media, only small amounts of the desired product could be detected (entries 7 and 8, Table 1). On the contrary, when dichloromethane, acetonitrile and 2-methyl tetrahydrofuran (2-MeTHF) were used, more efficient conversion was observed in a short time (2.5 h).

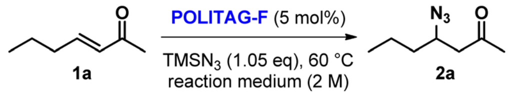
The use of an aqueous acetonitrile azeotropic mixture gave the best results in terms of conversion and yield (entry 4, Table 1). Indeed, in comparison with the reaction performed in acetonitrile, the process in aqueous acetonitrile azeotrope presented enhanced catalytic performance.

When the reaction medium amount was reduced to increase the mixture concentration from 2 M to 5 M, a complete conversion of **1a** was detected in 3 h. Comparable results were also obtained at 10 M concentration. However, under batch conditions, for better mixing of the reaction mixture in the presence of the heterogeneous catalytic system, we selected 5 M concentration as the best to balance efficiency and waste minimization.

With these optimized conditions, we proceeded with the study of the consecutive CuAAC reaction by reacting intermediate **2a** with phenylacetylene **3a** in aqueous acetonitrile azeotrope for testing the possibility of avoiding the intermediate purification step.

After the completion of the first β-azidation step, **POLITAG-F** was recovered by filtration and washed with aqueous acetonitrile azeotrope. To the resulting mixture, copper rods (10 mol%) and **3a** (1 eq.) were added, and the reaction mixture was heated at 60 °C for 24 h.

Table 1 Reaction medium optimization for the β-azidation reaction of (*E*)-3-hepten-2-one (**1a**) using the **POLITAG-F** catalyst[a]



Entry	Reaction medium	*T* (h)	Conv.[b] (%)
1	SolFC	8	35
2	CH_2Cl_2	2.5	48
3	CH_3CN	2.5	53
4	$CH_3CN : H_2O_{Az.}$[c]	2.5	86
5[d]	$CH_3CN : H_2O_{Az.}$[c]	3	>99
6[e]	$CH_3CN : H_2O_{Az.}$[c]	3	>99
7	CPME	2.5	32
8	TAME	7	23
9	2-MeTHF	2.5	56

[a] Reaction conditions: **1a** (1 mmol), $TMSN_3$ (1.05 eq.), **POLITAG-F** (5 mol%), reaction medium (0.5 mL), 60 °C. [b] Conversion determined by GC analysis, the remaining material was unreacted **1a**. [c] $CH_3CN : H_2O$ 83.7: 16.3% w/w. [d] Reaction medium (0.2 mL, 5M). [e] Reaction medium (0.1 mL, 10 M).

With the use of a metallic copper catalyst, we could avoid the utilization of additional additives that are generally needed in homogeneous catalytic conditions. Indeed, the CuAAC reaction performed using homogenous Cu(II) salts required the use of reductive agents to generate the catalytically active species Cu(I).

By adding specific amounts of the azeotropic mixture when washing the first mixture after the first azidation step, different concentrations were screened to select the best condition for the consecutive process (Table 2).

The reaction showed quantitative conversion in the concentration range from 4M to 1M, while a drop in the formation of 1,4-disubstituted β-keto 1,2,3-triazole **4aa** was observed at 0.5M concentration.

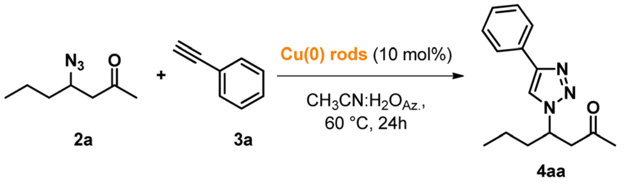
At the end of the process, the metallic copper rods were filtered and washed with 2 mL of the aqueous azeotrope. The overall reaction medium was then recovered by distillation (89%), and the obtained crude product was washed with additional cold azeotrope (0.5 mL) to afford pure product **4aa**. Even at this stage, it could be noticed that the protocol is promising for overall waste minimization.

Depending on the concentration used, we observed important differences in the isolated yields. Indeed, partial precipitation of the product in the reaction mixture at high concentrations (entries 1 and 2, Table 2) led to lower yields in comparison with the reaction performed using 1 mL $mmol^{-1}$ (1M) azeotropic mixture (entry 3, Table 2), which led to the isolation of product **4aa** with an excellent overall yield of 94%.

The multi-step protocol in flow

At this stage, we focused our attention on using these preliminary data obtained in the batch protocol for the definition of a multi-step continuous-flow protocol for the synthesis of β-keto 1,2,3-triazoles starting from enones, without the isolation and manipulation of the azide intermediates.

Table 2 CuAAC in $CH_3CN:H_2O_{Az.}$ catalysed by heterogenous Cu(0) rods[a]



Entry	Concentration (M)	Conv.[b] (%)	Yield[c] (%)
1	4	>99	55
2	2	>99	70
3	1	>99	94
4	0.5	52	—

[a] Reaction conditions: **2a** (1 mmol), **3a** (1 eq.), $CH_3CN : H_2O_{Az.}$, 60 °C, 24 h. [b] Determined by GC analysis, the remaining materials were unreacted **2a** and **3a**. [c] Isolated yield obtained with optimized work-up.

The first step was optimized by packing a PTFE coil reactor with the heterogenous organocatalyst **POLITAG-F** blended with quartz powder to guarantee a homogenous flow and pressure in the reactor. Several parameters were varied to achieve the complete conversion of **1a** to the desired azide **2a** before proceeding to the optimization of the consecutive CuAAC process.

The adoption of a 10-atm back pressure regulator (BPR) was crucial. Indeed, in the process performed with a BPR at 6 atm, only a trace amount of product **2a** was detected (entry 1, Table 3).

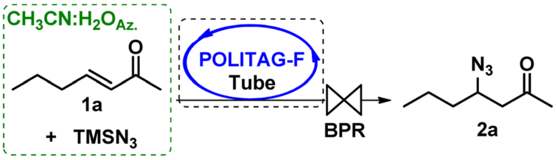
A positive effect was observed by setting the flow rate at 0.1 mL min^{-1} and the aqueous acetonitrile azeotrope concentration at 5M. Conversion to product **2a** gradually increased depending on the reactor length (entries 5 and 6, Table 3) rather than on the catalyst amount (entries 6 and 11, Table 3). Increasing the temperature to 75 °C showed a negligible effect on the process (entry 8, Table 3).

Complete conversion of **1a** was obtained by using a PTFE tube reactor with a length of 3.2 m and an internal diameter of 1/8″ packed with 2.0 g of the **POLITAG-F** organocatalyst.

After this preliminary set-up of the first part of the flow apparatus, we connected the second reactor for the optimization of the consecutive CuAAC process. Notably, the employment of a consecutive flow protocol required further optimization to combine the two single processes (see Table ESI-1 in ESI†). We selected **1a** ketone and phenylacetylene **3a** as model substrates for the optimization of the continuous-flow synthesis of 1,4-disubstituted 1,2,3-triazoles.

The metallic copper heterogeneous catalyst used under batch condition was replaced with a Cu tube, which is commercially available and largely used for setting up gas lines and other general purposes, with an internal diameter of 1/32″ and a length of 10 m, providing a volume of 2 mL.

Table 3 Optimization of the continuous-flow β-azidation reaction[a]



Entry	Length (m)	POLITAG-F (g)	Conc. (M)	Flow rate (mL min^{-1})	T (°C)	Conv.[b] (%)
1[c]	0.25	0.4	10	0.25	60	Traces
2	0.25	0.4	10	0.25	60	12
3	0.25	0.4	10	0.05	60	20
4	0.25	0.8	5	0.05	60	22
5	0.25	0.8	5	0.10	60	28
6	0.50	1.6	5	0.10	60	38
7	0.50	1.6	10	0.10	60	30
8	0.50	1.6	10	0.10	75	26
9	0.50	1.6	10	0.20	60	10
10[d]	1.60	1.0	1	0.10	60	35
11[d]	1.60	1.0	5	0.10	60	63
12[d]	3.20	2.0	5	0.10	60	>99
13[d,e]	3.20	2.0	5	0.10	60	>99

[a] Reaction conditions: **1a** (5 mmol), $TMSN_3$ (1.05 eq.), reactor diameter (4.5 mm), BPR (10 atm). [b] Conversion determined by GC analysis, the remaining material was unreacted **1a**. [c] BPR 6 atm. [d] Reactor inner diameter: 1/8″. [e] Reaction performed with $TMSN_3$ (1.02 eq.).

The two different lines equipped with two HPLC pumps were connected using a T joint, and the resultant mixture flowed through the Cu tube. The reactors were thermostated in two different isolated boxes: the PTFE-packed reactor with **POLITAG-F** at 60 °C and the Cu tube at 100 °C. In this modified configuration, the BPR was placed at the end of the Cu-tube.

Due to the pressure generated in the second copper tube reactor, we started the optimization using a single BPR at 6 atm (Table ESI-1†). To allow the efficacious combination and mixing of the two reaction mixtures, the flow rate of line A was slowed down to 0.05 mL min^{-1}, and the line B flow was set at 0.1 mL min^{-1} (entry 1, Table ESI-1†). However, these flow rates were insufficient for the mixture to properly flow through the reactors. Even after increasing these values to 0.25 mL min^{-1}, unsuccessful results were obtained (entries 2 and 3, Table ESI-1†). Optimal conditions were obtained by setting both lines at 0.1 mL min^{-1} (entry 4, Table ESI-1†). However, due to the poor yield of **4aa** even after varying the concentration and an excess of **3a** (entries 5 and 6, Table ESI-1†), different conditions were evidently needed.

Particularly, unreacted $TMSN_3$ and excess **3a** led to the rapid deactivation of the copper tube. This phenomenon was clearly visible as a greenish solution was recovered at the end of these optimization experiments. Anyway, we confirmed that the Cu-tube could be regenerated[8f] by using 5 mL of H_2O_2. To minimize this deactivation effect, $TMSN_3$ was reduced to 1.02 eq., which in combination with the optimal flow rates used, achieved very high efficiency in the first azidation process (entry 13, Table 3).

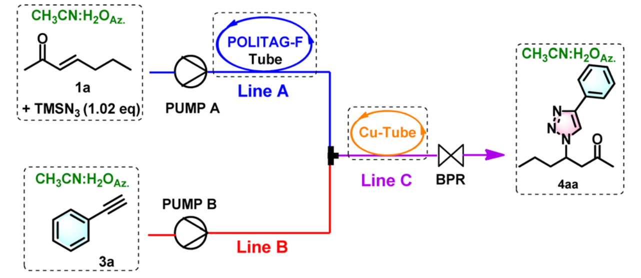
However, for the consecutive process, the 6 atm BPR was inadequate to achieve a satisfactory result (entry 1, Table 4). Indeed, only 34% of product **4aa** was detected at the flow outlet; the remaining material was a 2 : 1 mixture of unreacted ketone **1a** and the azide intermediate **2a**.

At this stage, a change of the first reactor was needed, and different polymer-supported fluoride-based catalysts were used to achieve the best performance (entries 7–9, Table ESI-1†). Although high catalyst loading showed beneficial effects in the single process,[24c] in the consecutive azidation-CuAAC protocol, poor results were obtained. For this reason, we proceeded with further optimization of the **POLITAG-F** catalyst (Table 4).

Since under batch conditions, both processes were sensitive to the mixture concentration in aqueous acetonitrile azeotrope, we investigated this effect in the combined consecutive flow protocol using a BPR at 10 atm (entries 2–4, Table 4).

Performing the reaction with both reactants at low concentrations led to only 42% product **4aa** in the final mixture (entry 2, Table 4). Further, when the concentration was increased in both lines to achieve a final concentration of 2.5M in line **C**, the high-density mixture also displayed a lower conversion of azide **2a** to the desired product, affording a low yield of **4aa** (entry 4, Table 4).

Table 4 Optimization of the reaction conditions in the continuous flow mode[a]



Entry	BPR	Conc. A[b] (M)	Conc. B[c] (M)	Conc. C[b] (M)	4aa[d] (%)
1	6 atm	5	1.2	0.83	34[e]
2	10 atm	1	1.2	0.5	42[f]
3	10 atm	5	1.2	0.83	>99
4	10 atm	5	6	2.5	57[g]

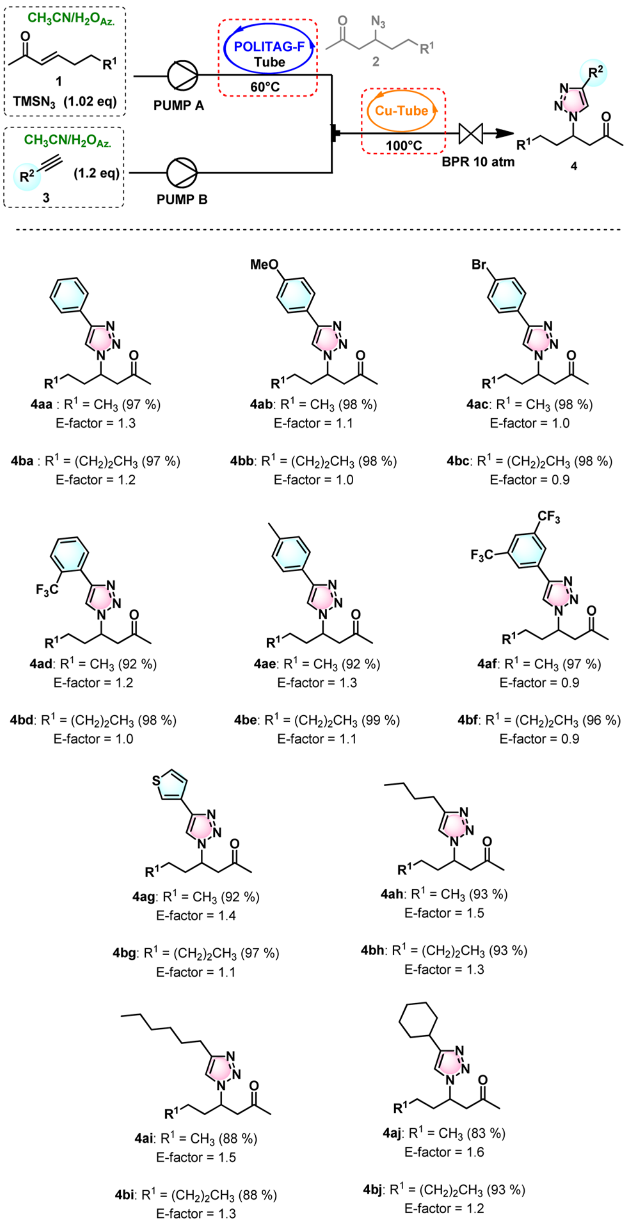
[a] Line A: **1a** (5 mmol), $TMSN_3$ (1.02 eq.), $CH_3CN:H_2O_{Az.}$; line B: **3a** (1.2 eq.) and $CH_3CN:H_2O_{Az.}$; flow rate 0.1 mL min^{-1}; 1st reactor (**POLITAG-F**, loading: 1.26 mmol g^{-1}) thermostated at 60 °C; Cu-tube thermostated at 100 °C. [b] Referred to **1a**. [c] Referred to **3a**. [d] Determined by GC analysis. [e] The remaining material was a 2 : 1 mixture of **1a** and **2a**. [f] The remaining material was a 1 : 1 mixture of **1a** and **2a**. [g] The remaining material was unreacted **2a**.

The use of 5M concentration in the aqueous acetonitrile azeotrope in line **A** and 1.2M in line **B** boosted the quantitative conversion of (*E*)-3-hepten-2-one to the desired triazole **4aa** (entry 3, Table 4). Furthermore, we also attempted to reduce the Cu-tube length from 10 m to 5 m (entries 10 and 11, Table ESI-1†), which also led to poor results. Indeed, even when the BPR was increased to 17 atm, the product yield did not exceed 70% (entry 11, Table ESI-1†).

The optimized consecutive protocol (entry 3, Table 4) afforded **4aa** at 1.5 mmol h^{-1}. The reaction time in flow was also drastically reduced compared with the small-scale batch protocol. Remarkably, under continuous flow conditions, it is possible to keep the heterogeneous catalyst **POLITAG-F** safely in the reactor and reuse it efficiently, as proven by our test. On the contrary, its recovery under batch conditions proved to be more complicated due to the crushing of the material to a finely dispersed powder under the classic stirring conditions.

Once the pumping of the reagents was stopped, and the reaction mixture was completely eluted, the lines and reactors were washed with 15 mL of the $CH_3CN:H_2O$ azeotropic mixture, which could mostly be recovered (94%) by distillation and reused.

After the removal and recovery of the azeotropic mixture, the desired product **4aa** was collected as a pure solid product (97% yield) without further purification. Furthermore, copper leaching reduced from 87.7 ppm in the batch process to 2.4 ppm under flow conditions (after 20 mmol conversion), thus avoiding the additional purification of the product. The product isolated from the flow protocol featured minimal copper contamination (41.1 μg g^{-1}), which is below the limits permitted in drug production.[30] To give more insights into the long-term stability of the consecutive flow protocol, we further stressed the system by pumping the reagent mixtures for a longer time (see Figure ESI-1 in ESI†). After the steady state was reached, 60 mmol of α,β-unsaturated ketones (**1**) were efficiently converted to the desired triazoles. After 40 h, copper leaching increased to 19 ppm accompanied by a drop in the conversion of the azides **2** to 45%, and then, a further increase in leaching up to 45 ppm was measured. At this point, the Cu-tube was treated with H_2O_2, and the initial efficiency along with the low Cu leaching (3.0 ppm) could be regenerated. This approach was preventively employed after every 60 mmol reac-



Scheme 1 The 1,4-disubstituted β-keto-1,2,3-triazoles synthesized from β-azido-ketones and functionalized alkynes in continuous flow. The isolated yields are given in parentheses.

tant was processed to keep the efficiency of the system constant (Figure ESI-1†).

These optimized conditions were then extended to the consecutive β-azidation of α,β-unsaturated carbonyls (**1a–b**) followed by the CuAAC reaction with different terminal alkynes (**3b–j**). The substrates tested showed good isolated yields in the range of 83% to 99% (Scheme 1).

Up to 185 mmol α,β-unsaturated carbonyl compounds were efficiently converted to various functionalized 1,4-disubstituted 1,2,3-triazoles with the optimized flow apparatus.

The high efficiency of this consecutive flow protocol and the recovery of the reaction medium led to the fast and waste-minimized synthesis of triazoles associated with very low E-factor values (0.9–1.6) (see ESI for further details†). These values are extremely low compared with those of other previously developed waste-minimized CuAAC protocols.[7b,c]

To better comprehend the main factors that led to the reduced generation of waste, we performed a green metrics assessment by evaluating AE, RME, MRP, 1/SF and the E-factor distribution profile (see Fig. 1 and ESI for further details†).[31]

The advantages of the flow protocol not only include the reduction of reaction time but also the easy manipulation of the reaction mixture, which allows the avoidance of any additional steps and materials necessary to separate the heterogeneous catalyst from the reaction mixture. Moreover, the flow protocol led to an enhancement of the sustainability of the process, as visualized and quantified by the comparison of the radial polygons in Fig. 2. When the reaction is scaled up from batch to flow, the red line (right panel) fits the ideal situation better (green line). MRP and RME are doubled in the flow protocol (see ESI for further details†) mainly due to the high recovery of the selected azeotropic mixture.

This improvement is also reflected in the E-factor value, which was reduced by 60% when the protocol was switched from batch to flow (Fig. 2).

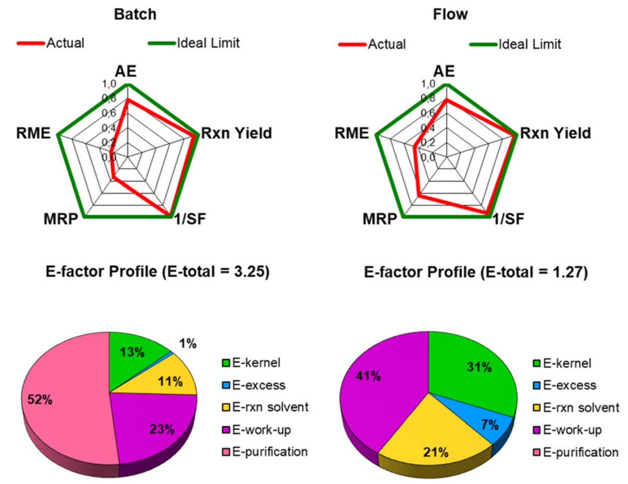


Fig. 2 A comparison of the green metrics (AE: Atom economy; MRP: Mass recovery parameter, RME: Reaction mass efficiency, SF: Stochiometric factor; E-factor: Environmental factor) between the batch and consecutive-flow β-azidation/CuAAC reaction protocols.

The main contribution that influenced the E-factor of the batch protocol was the final purification step, which contributed 52% to the total waste generation. Thanks to the high efficiency of the flow protocol and low Cu contamination, this step is avoided.

Moreover, the kernel contribution to the total E-factor values increased up to 31% in the flow protocol compared with 13% in the batch process (Fig. 2). Indeed, with all the auxiliary substances in the kernel E-factor excluded from the calculation,[31] the enhanced E-factor profile further confirms the waste minimization of the optimized consecutive protocol.

Conclusions

With the consecutive use of **POLITAG-F** as a heterogeneous organocatalyst for the β-azidation of α,β-unsaturated carbonyls and the use of Cu-tube as a heterogenous metallic copper catalyst for the CuAAC reaction, we have defined a very efficient protocol for the preparation of 1,4-disubstituted β-keto 1,2,3-triazoles. After a preliminary optimization of the batch protocol, we developed a consecutive flow protocol performed in a CH_3CN/H_2O azeotropic mixture, featuring significant waste reduction.

The developed two-step consecutive protocol in flow allows for a drastic reduction in reaction time compared with the batch mode, while also allowing safe and complete recovery and reuse of the catalytic system, and affording a productivity of 1.5 mmol h^{-1}.

The high efficiency of the telescoped flow synthesis method avoids purification steps while maintaining the copper contamination level below the permitted limit for pharmaceutical compounds. This is reflected in the minimization of the environmental footprint in comparison with the batch process, as demonstrated by the different green metrics (AE, RME, MRP, 1/SF, and E-factor).

Starting from different α,β-unsaturated carbonyls, high isolated yields of various 1,4-disubstituted 1,2,3-triazoles were obtained, resulting in very low E-factor values (0.9–1.6).

Conflicts of interest

There are no conflicts to declare.

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