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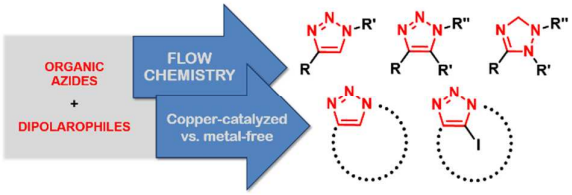

This review surveys the continuous-flow strategies for the synthesis of triazoles by means of copper-catalyzed and catalyst-free cycloadditions between azides and various dipolarophiles.

Flow chemistry as a versatile tool for the synthesis of triazoles

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ABSTRACT

Continuous-flow processing offers unprecedented opportunities to accelerate, integrate, simplify, scale-up and automatize chemical reactions, in combination with an inherently safer and 'greener' nature over traditional batch-based syntheses. Triazoles are amongst the most important and most intensively studied heterocycles, thanks to their diverse biological activities and the incredible number of their applications in the labeling, modification and synthesis of various biomolecules, polymers and supramolecular assemblies. Many research groups have demonstrated that both copper-catalyzed and catalyst-free cycloadditions between azides and various dipolarophiles leading to triazoles or triazole-based structures can be greatly facilitated through the beneficial features of continuous-flow processing. The present review therefore surveys the flow chemistry-based approaches for the synthesis of triazoles, covering the most important catalytic and catalyst-free strategies in continuously operated systems published during the past decade.

1. Introduction

Triazoles are aromatic five-membered heterocycles with one pyrrole-like and two pyridine-like N-atoms in the 1,2,3- or 1,2,4-positions. They have emerged as among the most exploited structures in contemporary heterocyclic chemistry.[1, 2] This is due in part to the fact that triazoles are key structural motifs in products with a variety of biological properties, including antiviral, analgesic, anti-inflammatory, anticonvulsant, antimicrobial, antiproliferative and anticancer effects.[3] Relevant pharmaceuticals based on the triazole core include, for example, the broad-spectrum cephalosporin antibiotic Cefatrizine, the antifungal Fluconazole, the penicillin-derived antibiotic Tazobactam and the antiepileptic Rufinamide, which is one of the best-selling five-membered heterocyclic medicaments of recent years (Figure 1).[4, 5] The 1,2,3- and 1,2,4-triazole cores are frequently used in drug discovery for the modification of known bioactive molecules and pharmaceuticals.[5, 6] As examples, 1,2,3-triazole analogs of the well-known antiviral cyclic amino acid derivatives oseltamivir and zanamivir have recently been

reported,[7, 8] and the triazole skeleton is a constituent part of many modified nucleosides, nucleotides and oligonucleotides which display various biological effects.[9]

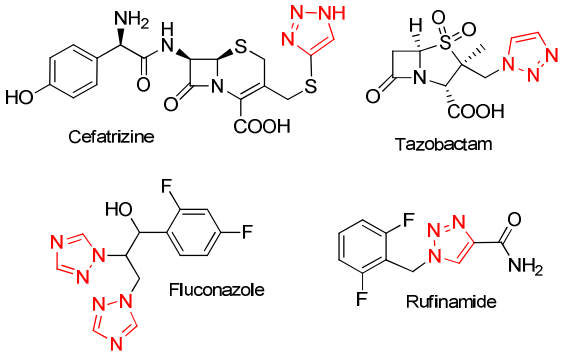

Figure 1. Examples of pharmaceuticals based on the 1,2,3- and 1,2,4-triazole cores.

Triazole chemistry has recently received a significant impulse from the pioneering works of Sharpless and Meldal on Cu(I)-catalyzed alkyne–azide cycloaddition (CuAAC).[10, 11] Thanks to its excellent fidelity and compatibility,[12, 13] CuAAC has become the definition of the "click chemistry" concept,[14] and has paved the way for triazole chemistry to achieve an incredible number of applications. For example, CuAAC is frequently utilized for the labeling of biomolecules,[15-20] or for the synthesis and modification of various polymers, surfaces and supramolecular assemblies.[21-23] Moreover, as an excellent bioisostere for the amide bond, the 1,2,3-triazole moiety is increasingly found in peptidomimetic chemistry, e.g. for the ligation of peptide fragments, for peptide cyclizations, or for backbone modifications.[24-26]

The progress toward increased sustainability requires developments and novel approaches that involve improved performance and value in association with a reduced environmental impact.[27] These requirements have opened up new routes in synthetic organic chemistry,[28] and continuous-flow manufacturing has recently emerged as a novel alternative to conventional batch-based synthetic techniques.[29] _ENREF_22 As outlined in excellent recent reviews, the flow chemistry concept furnishes an increased parameter space for chemical intensification,[30-34] and allows reactions to be performed with an unprecedented level of control due to the greatly enhanced heat and mass transfer and improved mixing properties.[35-38] This implies not only higher reaction rates, but an inherently safer and greener chemistry.[39-42]

Over the past few years, it has been demonstrated that flow chemistry and catalysis are an ideal match for the synthesis of a variety of useful products.[29, 36] Among continuous-flow catalytic techniques, packed-bed systems are especially popular.[43] This is not merely due to the ease of use of such heterogeneous materials, but in loaded catalyst columns the continuous

stream of the reactants interacts with a superstoichiometric amount of catalyst molecules, which makes unprecedented reaction rates possible, and if catalyst deactivation can be ruled out, the scale of production becomes a direct function of the process time.[44] Moreover, the contact time between the reactants and the active reactor zone (i.e. a catalyst column or a heated reaction coil) can easily be fine-tuned via the flow rate. With such precise control over the residence time, the optimization of conversion and throughput becomes simple and safe.[45]

From the aspects of triazole synthesis, the improved safety profile of continuous-flow processing is particularly appealing, considering that organic azides are known to be highly energetic and unstable substances.[46] A further benefit is that the ability to combine multistep reactions into integrated continuous-flow sequences permits a rapid and safe access to target molecules, as hazardous reaction partners (such as azides) can be generated and consumed *in situ* without the need for isolation and work-up.[47-51] These features, in association with the excellent transferability between bench-top flow chemistry and industrial-scale production,[52, 53] have rendered continuous-flow processing an enabling tool for the catalytic and catalyst-free synthesis of triazoles. The advances made in this field during the past decade are reviewed herein.

2. Synthesis of 1,2,3-triazoles via copper-catalyzed alkyne–azide cycloadditions in flow systems

The [3+2] cycloaddition of organic azides with terminal alkynes as dipolarophiles is known as the most direct way for the synthesis of 1,2,3-triazoles.[13] The classical thermally induced Huisgen reaction results in a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazoles,[54, 55] and because of the high activation energy barrier, these reactions are often very slow, even at elevated temperatures.[1] In contrast, the application of Cu(I) catalysis affords an efficient access to the 1,4-disubstituted 1,2,3-triazole regioisomer under milder reaction conditions.[10, 11] Accordingly, most continuous-flow approaches for the synthesis of triazoles rely on various heterogeneous or homogeneous copper sources.

2.1. Alkyne–azide cycloadditions with a polymer-bound copper catalyst

The first example of CuAAC in a continuous-flow system was demonstrated by Ley and co-workers.[56] A modular flow reactor was constructed that relied on the combination of a polymer-bound copper catalyst and various scavenger resins in glass columns (Figure 2). CuI

was immobilized in a complex form on a dimethylaminomethyl-grafted polystyrene resin,[57] which also served as a heterogeneous nitrogen base to improve the reactivity in the cycloaddition.[58] The copper catalyst was expected to leach from the resin due to the weak coordinative forces, and a subsequent in line scavenging step was therefore necessary, a thiourea resin being used to remove the copper contamination from the solution phase. The azide was employed in excess to drive the reaction to completion within a single pass at ambient temperature. To obtain the corresponding 1,4-disubstituted 1,2,3-triazole products in pure form, the unreacted azide was removed in-line over a phosphine resin, the azide being captured onto the solid phase as an iminophosphorane via a Staudinger reaction.[59] _ENREF_52 As a result of the study, the triazole products were obtained in short process times, in high yields (up to 93%) and without the need for further purification steps, and gram-scale production was also successfully implemented.

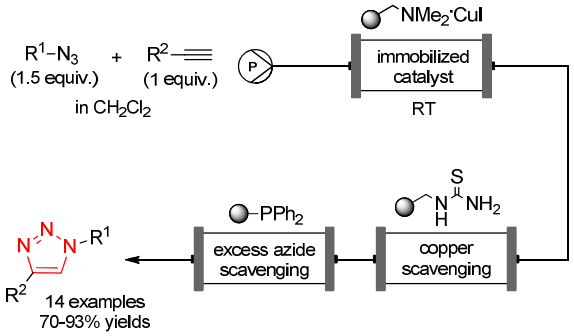

Figure 2. Continuous-flow synthesis of 1,2,3-triazoles with a polymer-bound copper catalyst and various scavenger resins.[56] (P = pump, RT = room temperature.)

In a subsequent contribution, Ley and co-workers demonstrated an elegant application of their continuous-flow CuAAC concept. The syntheses of various amides and guanidines were investigated with phosphine reagents in a modular flow reactor.[60] Complete removal from the reaction mixture of the phosphine oxide generated continuously as by-product is very difficult by means of chromatography. To facilitate the work-up and purification steps, a terminal alkyne-functionalized phosphine was used as starting material and the corresponding phosphine oxide contaminant was removed in line by means of a CuAAC mediated by immobilized CuI as catalyst (Figure 3a). A carboxylic acid-functionalized azide was employed as reaction partner, and the acidic 1,2,3-triazole formed *in situ* could therefore easily be captured with resin-bound Na_2CO_3. The authors also suggested an alternative possibility for continuous phosphine oxide removal by using a polymer-supported azide and catalytic amounts of CuI together with *N*,*N*-diisopropylethylamine (DIEA) as a nitrogen base to bind the contaminant to the solid phase as a 1,2,3-triazole (Figure 3b)

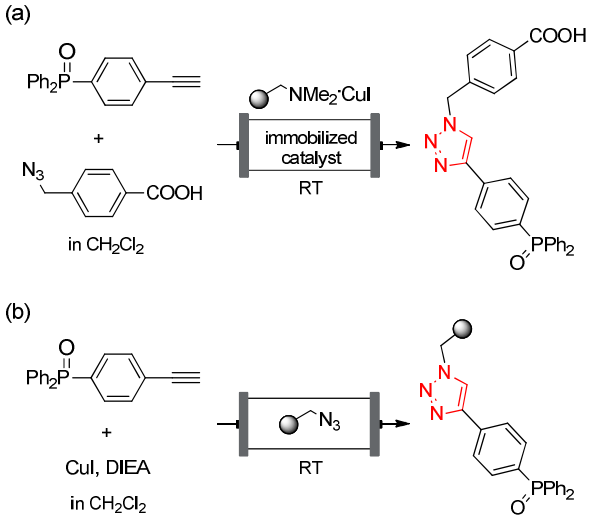

Figure 3. In line removal of a phosphine oxide contaminant by means of continuous-flow CuAAC: (a) formation of a carboxylic acid-functionalized 1,2,3-triazole, which can be captured with resin-bound Na_2CO_3, (b) binding of the contaminant onto the solid phase as a 1,2,3-triazole.[60]

With the aim of achieving multistep chemical transformations in continuous reaction sequences, the Ley-group combined continuous-flow alkyne–azide cycloadditions with the *in situ* generation of the alkyne component from various aldehydes and the Bestmann–Ohira (BO) reagent.[61] A modular flow system was designed which consisted of a heated coil reactor and several glass columns loaded with immobilized reagents and scavengers (Figure 4). The mixture of an appropriate aldehyde and the BO reagent together with an organic azide in MeCN was introduced as stream 1, which was then combined with a MeOH solution of KO*t*Bu through a T-piece as stream 2. The alkyne component was formed during the passage through the heated reaction coil (100 °C, residence time ~35 min), and the resulting mixture was next directed through a series of scavenger columns. A benzylamine resin was used to capture the excess aldehyde at 70 °C, and a subsequent column filled with sulfonic acid resin that effectively neutralized the base and protonated the remaining reagent, which was cleaned up on a dimethylamine resin. The resulting stream, which contained the pure acetylene product and the azide component, was next passed through a catalyst cartridge containing coordinatively immobilized CuI (similarly as in an earlier study),[56] and a subsequent thiourea-based resin finally removed any leached copper species from the solution phase to yield 1,2,3-triazoles without the need for conventional work-up procedures. To overcome difficulties with the handling of aldehydes as starting materials (e.g. hydrate formation and polymerization), the system was extended with an integrated heterogeneous oxidation step to obtain 1,2,3-triazoles directly from alcohols.[62]

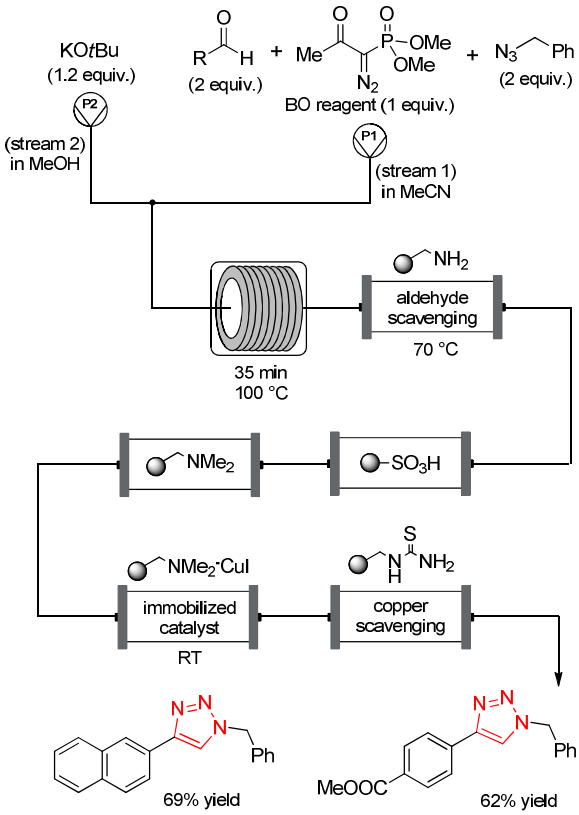

Figure 4. A continuous reaction sequence for the expeditious synthesis of 1,2,3-triazoles with the *in situ* generation of the alkyne component. To obtain 1,2,3-triazole products without conventional work-up procedures, the alkyne synthesis and the subsequent CuAAc were followed by in line purification on various immobilized scavengers.[61]

2.2. Alkyne–azide cycloadditions with copper metal as catalytic source

Bogdan and Sach introduced an experimentally convenient approach for azide–alkyne cycloadditions by developing an on-demand flow reactor made of copper without the need for any additional copper catalyst or additives (e.g. an oxidant).[63] It was later shown that the catalytic activity of the zerovalent metal actually originates from the surface layers of different oxides, including Cu_2O.[64] In order to minimize reaction size and to facilitate rapid library development, a segmented flow approach was utilized, the reaction segments being separated by an immiscible fluorous spacer. The reactive organic azides were generated *in situ* from NaN_3 and the corresponding alkyl halides,[65] and were reacted immediately with the acetylene component in DMF as solvent (Figure 5). This one-pot click methodology was highly beneficial, as even potentially explosive low molecular weight azides, such as azidoethane, could be handled safely. The temperature, the reaction stoichiometry and the residence time were simultaneously optimized by means of statistical experimental design.[66, 67] _ENREF_56 _ENREF_56 _ENREF_57The use of a temperature of 150 °C and excess alkyl

azide proved favorable together with a residence time of 5 min, which allowed high throughput. A library of 30 1,4-disubstituted 1,2,3-triazoles were prepared in a matter of hours through the use of six different alkynes, six different alkyl halides and NaN_3, each triazole segment being collected in a 96-well plate containing a scavenger resin to remove any leached copper species. The preparative capability of the continuous system was also investigated, and a theoretical throughput of >10 g triazole/day was found.

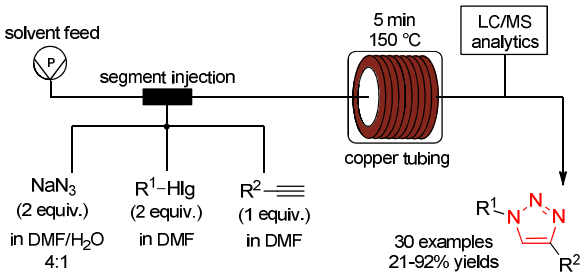

Figure 5. Synthesis of 1,2,3-triazoles with a copper coil flow reactor. The organic azides as reaction partners were generated *in situ* from NaN_3 and the corresponding alkyl halides.[63] (Hlg = Br, Cl or I.)

The application of ultrasound in chemical reactions provides specific activation based on acoustic cavitation.[68] Moreover, cavitation increases the mixing efficiency and improves the mass transfer in narrow reaction channels.[69] Tu et al. therefore investigated the effects of ultrasound promotion on alkyne–azide cycloadditions, utilizing the same heated copper coil reactor as in the Bogdan and Sach study in combination with a custom sonication piezoelectric transducer.[63, 70] _ENREF_54It was demonstrated that ultrasound promotion can reduce the need for harsh reaction conditions, and 1,2,3-triazoles were obtained in acceptable yields at temperatures in the range 35–50 °C. In contrast, much lower reaction rates were found without irradiation. For example, at 35 °C with the same residence time, only trace amounts of the corresponding triazoles were obtained.

Macrocyclic systems offer a wide range of pharmaceutical applications, but their conventional synthesis is inefficient, mainly because of the extremely high-dilution conditions required (even with concentrations in the submillimolar range) to direct the reactions toward macrocyclization from competing oligomerization.[71] The scope of the copper coil flow reactions was therefore extended by Bogdan and James to the synthesis of drug-like macrocycles based on 1,2,3-triazoles obtained via intramolecular click reactions (Figure 6).[72] Azidoalkynes, readily synthetized from chiral, bifunctional compounds such as amino alcohols and hydroxy acids were employed as starting materials. The setup of the continuous system was basically the same as detailed above. The addition of a tris-(triazolyl) ligand and

DIEA as nitrogen base was necessary for the macrocyclizations to take place in an adequately short residence time of 5 min at 150 °C. Interestingly, the presence of the additives (ligand and base) not only accelerated the reaction, but also exerted a positive effect on the macrocycle product to dimer ratio. As a result of the study, the synthesis of a diverse set of 12- to 22-membered triazole-linked macrocycles was achieved under flow conditions without the need for extreme dilutions, and with the competing dimerization successfully minimized. It was later shown through the use of a combination of X-ray crystallographic, spectroscopic and computational approaches that the main limitation of the above intramolecular cycloadditions is related to the strain energy in the macrocyclic products.[73] A reduction of the macrocycle size progressively increased the ring strain, which involved a decrease in the rate of macrocyclization and therefore a low yield of the triazole-linked macrocycle as compared with the less strained oligomerization product. The smallest ring size successfully prepared was an 11-membered cyclophane containing a triazole bridge, which established a limit to the ring strain that can be generated through the use of this synthesis technology.

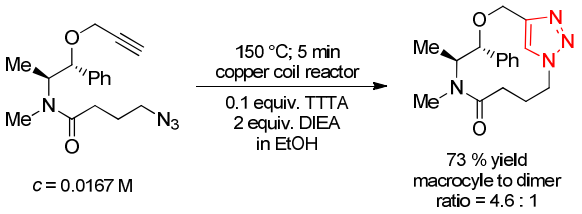

Figure 6. An example of the synthesis of 1,2,3-triazole-bridged drug-like macrocycles in a copper coil flow reactor.[72] (TTTA = tris[(1-*tert*-butyl-1*H*-1,2,3-triazolyl)methyl]amine.)

An interesting extension of the continuous-flow click macrocyclization strategy was reported later by Bogdan and James utilizing disubstituted acetylenes as starting materials instead of terminal alkynes.[74] It is known that Cu(I)-catalyzed cycloadditions between internal alkynes and azides can lead to 1,4,5-trisubstituted 1,2,3-triazoles, though the scope of this transformation is mostly limited to electron-deficient acetylenes.[75] Intramolecular cycloadditions of 1-iodo-substituted azidoalkynes were therefore investigated in a copper coil reactor under conditions similar to those in the previous studies (Figure 7). To avoid decomposition of the starting material, the reactor temperature was reduced to 100 °C, but the residence time was doubled (10 min). A small library of trisubstituted triazole-containing macrocycles was generated, and some of them were further transformed via various palladium-catalyzed cross-couplings to demonstrate the potential of the 5-iodo-1,2,3-triazole moiety as a point of diversification (Figure 7).

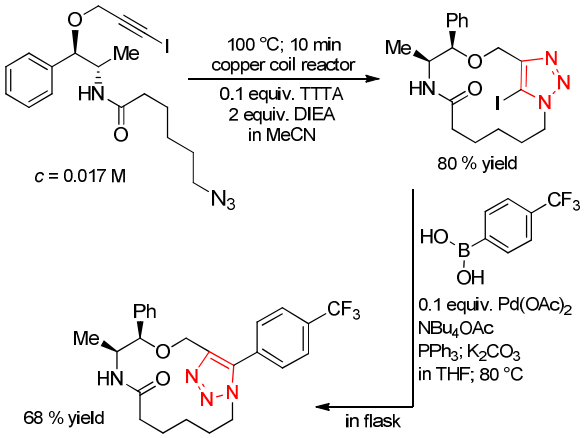

Figure 7. Intramolecular cycloaddition of a 1-iodo-substituted azidoalkyne in a copper coil flow reactor, and the subsequent modification of the resulting macrocycle via palladium-mediated Suzuki coupling.[74]

Most recently, Kappe and co-workers employed a similar flow chemistry-based strategy for the click macrocyclization of linear peptoids obtained via continuous-flow multistep Ugi four-component reactions.[76] They confirmed that the nature of the linear precursor and the resulting ring strain strongly affect the outcome of the intramolecular cycloadditions, yielding either a dimeric or a monomeric form of the cyclic product.

Jamison and co-workers reported the continuous-flow total synthesis of the antiepileptic drug Rufinamide,[4] _ENREF_23 featuring a copper coil-mediated alkyne–azide cycloaddition as the key step (Figure 8).[77] The cycloaddition precursors were generated continuously from readily available starting materials, and were combined into one flow without the isolation of any intermediate, thereby achieving improved process safety. 2,6-Difluorobenzyl azide was obtained from the corresponding bromide in reaction with NaN_3 in DMSO during passage through a reaction coil within a residence time of 1 min at ambient temperature. The otherwise costly and unstable propiolamide was generated from neat methyl propiolate with ammonium hydroxide at 0 °C in order to avoid unwanted polymerization (the residence time was 5 min). In this step, the utilization of pressure proved crucial to attain the optimal dissolution of NH_3, and to prevent gas generation. For the CuAAC to take place, the two reaction streams were mixed together and directed through a copper coil, at 110 °C to achieve sufficient reaction rates and at the same time to avoid decomposition of the azide. Under the optimized conditions, Rufinamide was isolated in a yield of 92% within an overall residence time of 11 min.

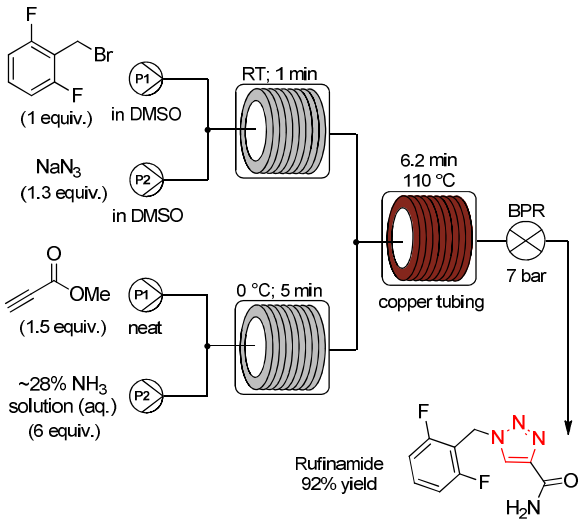

Figure 8. Continuous-flow total synthesis of an antiepileptic drug, Rufinamide, with the *in situ* generation of 2,6-difluorobenzyl azide and propiolamide as cycloaddition precursors.[77] (BPR = backpressure regulator.)

Tu and co-workers recently introduced the practical combination of a copper coil flow reactor and an exchangeable reaction column to carry out the synthesis and modification of 1,2,3-triazoles as an integrated process (Figure 9).[78] 1-Bromo-4-ethynylbenzene as dipolarophile was combined with various azides generated *in situ* from NaN_3 and the corresponding alkyl halides in well-defined reaction segments. The resulting triazole was immediately reacted with a boronic acid in a subsequent reaction column filled with an immobilized palladium catalyst (Siliacat DPP-Pd) to yield the desired tandem CuAAC–Suzuki products.[79] The system was combined with in line HPLC analytics, and a second coil was therefore built in after the catalyst column to ensure the integrity of the reaction segments to be analyzed. A small library of highly functionalized 1,2,3-triazoles were synthetized, but only moderate yields were obtained (27–37%), possibly because of the low residence time on the catalyst bed containing the immobilized palladium species.

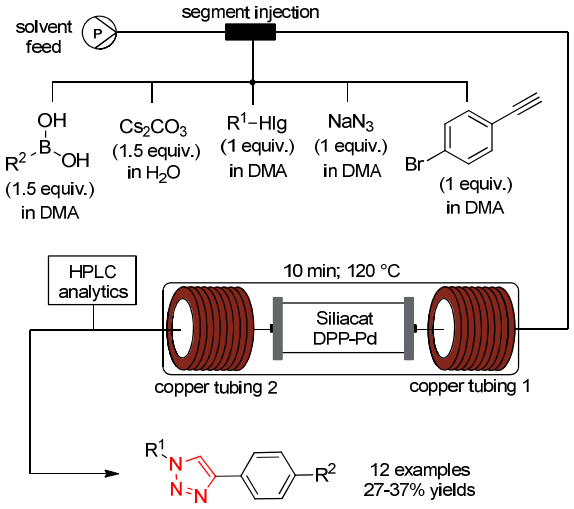

Figure 9. CuAAC–Suzuki tandem reactions in continuous-flow with heated copper coils and an immobilized palladium catalyst. Tubing 2 serves only for the reassembly of the reaction segments to be analyzed.[78] (Hlg = Br or I; DMA = dimethylacetamide.)

Kirschning and co-workers suggested electromagnetic induction as a resourceful novel way for the introduction of thermal energy into chemical reactions,[80] and proposed that conductive metals such as copper are able to serve as a direct heating medium in an electromagnetic field.[81] An inductively heated copper flow reactor was therefore built for the synthesis of triazoles, which consisted of a glass column filled with copper turnings and a medium-frequency (10–25 kHz) inductor to heat the metal directly and instantly with electromagnetic induction (Figure 10).[82] With this setup, the system could be heated up very rapidly to even above 200 °C, and inside the copper turnings much higher temperatures were presumably generated, which was expected to assist the formation of active Cu(I) species on the surface of the metal without a further catalytic source. A one-pot click methodology allowed the safe *in situ* generation of organic azides, and the system was equipped with a thiourea cartridge to remove copper contamination in line. After optimization of the most important reaction conditions (residence time, reactor temperature, concentration and reaction stoichiometry), 1,2,3-triazoles were obtained in quantitative conversion and in good yields. The authors also pointed out through a subsequent batch experiment that this extent of reactivity is not attainable with conventionally heated copper catalysts.

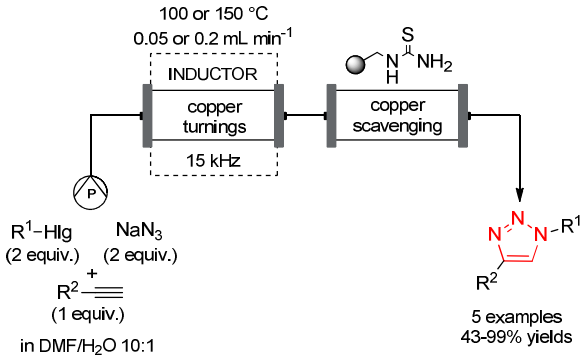

Figure 10. Synthesis of 1,2,3-triazoles with an inductively heated flow reactor filled with copper turnings.[82] (Hlg = Br or I.)

An inductively heated copper flow reactor was later applied for the effective synthesis of a small library of vinyl triazoles.[83] Vinyl azide intermediates were prepared prior to the CuAAC reaction in a telescoped two-step flow process, utilizing immobilized regents (Figure 11a). A resin-bound iodine azide transfer reagent served to carry out the 1,2-functionalization of the alkene starting materials, thereby practically eliminating the generation of the highly explosive iodine azide.[84] The intermediate 2-iodo azides were next subjected to an immobilized base-mediated elimination step, leading to vinyl azides in moderate to excellent yields. The vinyl azides were then combined with various alkynes as reaction partners in an inductively heated reactor loaded with copper turnings (Figure 11b). The reactor temperature was kept at 70 °C to prevent decomposition of the vinyl azides, and a moderate flow rate of 0.04 mL min^{-1} was maintained to achieve sufficiently high yields in a single pass.

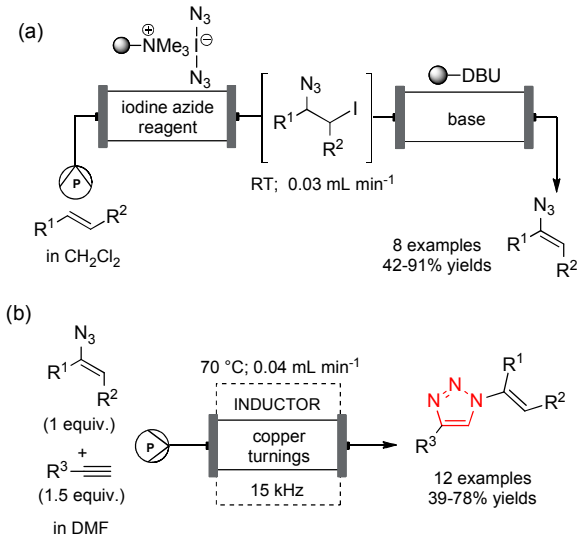

Figure 11. (a) Synthesis of vinyl azides in a multistep flow process utilizing resin-bound regents, and (b) preparation of vinyl triazoles from vinyl azides and various alkynes in an inductively heated copper flow reactor.[83] (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.)

The present authors utilized copper powder charged into a stainless steel column for the continuous-flow synthesis of various 1,2,3-triazoles (Figure 12).[85] Similarly to the copper tubings and copper turnings employed by other research groups,[63, 82] copper powder can act as a readily available source for catalytically active Cu(I) species, due to the surface copper oxide layers.[64] Thanks to its larger surface area, fine-grained copper powder (with an average particle size of 200 μm) acted as an outstandingly active catalyst for alkyne–azide cycloadditions. The reaction was found very sensitive to the temperature and the residence time, and the role of pressure was not only to allow the overheating of CH_2Cl_2 as solvent, but also to enhance triazole formation. Complete conversion was reached in the benzyl azide–phenylacetylene model reaction at 100 bar, 100 °C and a flow rate of 0.5 mL min^{-1}, which corresponded to a short residence time of 90 s. Subsequently, it was demonstrated that the harsh reaction conditions can be avoided through the joint use of substoichiometric amounts of DIEA and glacial acetic acid (AcOH) as additives, the continuous reaction thereby being accomplished with improved operational safety at ambient temperature. The applicability of the flow methodology was found considerably wide for different azides and alkynes, and excellent yields were obtained in most of the cases (72–99%) when either high-pressure/high-temperature conditions or additives at RT were applied.

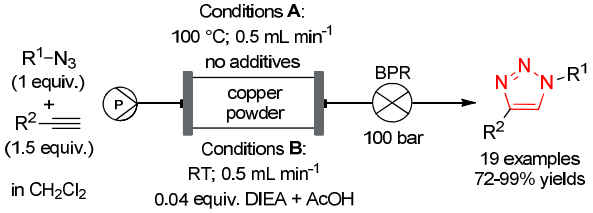

Figure 12. Continuous-flow triazole synthesis with copper powder as catalytic source under either conditions **A** or **B**.[85]

Alicyclic β-amino acids have attracted considerable attention in the past twenty years, as a consequence of their pharmacological potential and diverse synthetic applications.[86] The scope of the copper powder-mediated flow process has been extended to the synthesis of 1,2,3-triazole-substituted alicyclic β-amino acid derivatives as novel potentially bioactive compounds.[85, 87] Various azido-substituted β-aminocyclopentane- and β-aminocyclohexanecarboxylates were reacted with phenylacetylene, diethyl acetylenedicarboxylate or ethynyl ferrocene as dipolarophiles.[88] The flow reactions were conducted under high-pressure/high-temperature conditions, and also at RT with additives, as described above. A library of 16 triazole-modified β-amino acids were prepared, each of them

in a yield of ≥93% with DIEA and AcOH added (Figure 13). In comparison, the use of harsh reaction conditions without additives resulted in lower yields in some of the cases. The analytical data on the as-prepared products showed that the leaching of copper from the catalyst bed was not significant, but the presence of the additives did increase the copper content of the crude triazoles. Scale-up was implemented simply and safely as a function of the process time: >2 g of a chosen triazole-substituted β-aminocyclohexanecarboxylate was prepared in 100 min.

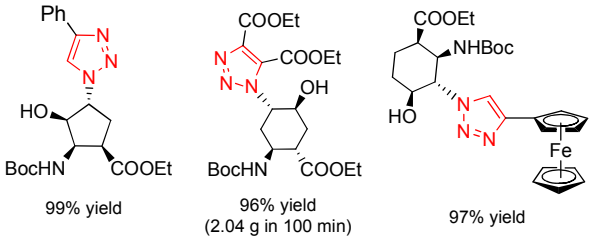

Figure 13. Examples of 1,2,3-triazole-substituted alicyclic β-amino acid derivatives prepared in flow with copper powder as catalytic source utilizing under **B** as shown in Figure 11.[85, 87]

2.3. Alkyne–azide cycloadditions with further heterogeneous copper catalysts

Copper-in-charcoal (Cu/C) was utilized as a heterogeneous Cu(I) source by Kappe and co-workers in a dedicated high-pressure/high-temperature flow reactor (X-Cube®) to obtain important mechanistic insights on continuous CuAAC reactions.[64] The Cu/C system was originally developed by Lipshutz and co-workers as an inexpensive self-stable catalyst, suggested as different types of copper oxides, including Cu_2O, bound within the charcoal matrix.[89, 90] _ENREF_82 Optimization of the benzyl azide–phenylacetylene model reaction in acetone as solvent rapidly resulted in quantitative conversion and yield at 170 °C, 20 bar and a flow rate of 1.5 mL min^{-1}, corresponding to a markedly short residence time of ~12 s. The authors established that the catalysis in the course of the continuous process predominantly operated in the homogeneous phase, due to leaching of the catalytically active copper species from the heterogeneous Cu/C. It was identified that mainly the azide component and the triazole product were responsible for the leaching of copper, as both of them forming quite stable complexes with Cu(I/II) ions. Effective in line copper scavenging was achieved on a smaller scale by using thiourea resin (as previously reported by other groups), and also with activated charcoal as a less costly alternative. It was additionally pointed out that the lifetime of the catalyst was strongly limited by the leaching of copper, and an off line extractive work-up with ethylenediaminetetraacetic acid (EDTA) was more straightforward on a larger scale.

A recent study by Buckley et al. gave additional insights into the leaching phenomena observed with Cu/C.[91] It was shown that catalyst preparation by the method of Lipshutz et al. (from activated carbon and an aqueous solution of $Cu(NO_3)_2$ through the use of sonication, followed by the removal of water by distillation, and azeotropic drying with toluene) does not afford Cu_2O and CuO immobilized within the charcoal matrix.[89, 90] _ENREF_83 Instead, a distinct Cu(II)-containing precatalyst ($Cu_2(OH)_3NO_3$) is formed which is not bound to the carbon support. These observations rationalize the severe leaching reported by the Kappe-group.[64]

After deposition of copper nanoparticles onto an iron surface, copper-on-iron (Cu/Fe) bimetallic system was employed as catalyst in continuous-flow triazole synthesis (Figure 14).[92] The activity of the Cu/Fe system proved sufficient under high-pressure/high-temperature conditions (100 bar and 100 °C), though the authors set out to avoid heating so as to achieve maximum operational safety. In accordance with the observation of Tu et al.,[70] ultrasound promotion (at 150 W) greatly improved the rate of triazole formation at ambient temperature. However, the joint use of DIEA and AcOH as basic and acidic additives proved to be an ultimate choice, allowing excellent reaction rates without heating. The methodology proved widely applicable, as not only terminal alkynes, but also various electron-deficient disubstituted acetylenes were well tolerated as dipolarophiles yielding useful 1,4,5-trisubstituted 1,2,3-triazoles. It emerged that simple iron powder can act as a cheap and effective in line scavenger for leached copper species, and that the scavenger used can be recycled effectively as a freshly generated portion of Cu/Fe catalyst.

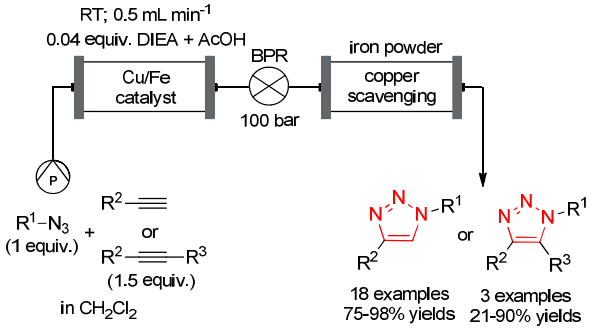

Figure 14. Synthesis of 1,4-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles with Cu/Fe as heterogeneous catalyst and iron powder as copper scavenger.[92]

Psaro et al. immobilized copper nanoparticles by metal vapor synthesis (MVS) on 3-aminopropyl-functionalized silica ($APSiO_2$), and utilized the resulting material as a heterogeneous catalyst in continuous-flow alkyne–azide cycloadditions (Figure 15).[93] The analytical data showed that the MVS allowed the deposition of very small copper particles

(<5 nm), which were readily oxidized into Cu(I/II) species after being exposed to air. The primary amine groups on the support served not only as a stabilizer of copper nanoparticles, but also as a heterogeneous base enhancing the reactivity in the CuAAC. Besides the alkyne and azide components, the reaction feed also contained phenyl hydrazine as a reducing agent to increase the population of the catalytically active Cu(I) species in the Cu/APSiO$_2$-loaded catalyst bed. A low flow rate of 50 µL min^{-1} was applied to achieve high conversions at ambient temperature. Upon successive reuse of the heterogeneous system, continuous loss of activity was observed, though regeneration was possible by flushing with a phenyl hydrazine stream. The most alluring feature of the methodology was that only a negligibly low copper contamination of <9 ppm was detected in the crude triazole products, thereby eliminating the need for purification steps.

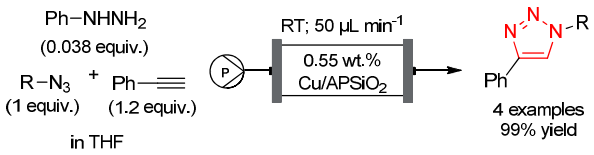

Figure 15. Continuous-flow alkyne–azide cycloadditions with Cu/APSiO$_2$ as heterogeneous catalyst. (Phenyl hydrazine is added to activate the catalyst bed.)[93]

A copper-containing layered double hydroxide (LDH) was recently employed as heterogeneous catalyst by the Fülöp-group for the synthesis of triazoles in a high-pressure/high-temperature continuous-flow reactor (Figure 16).[94] _ENREF_87 The LDH catalyst was readily obtained by controlled co-precipitiation from Cu(NO$_3$)$_2$·3H$_2$O and Fe(NO$_3$)$_3$·9H$_2$O at alkaline pH.[95] The as-prepared Cu(II)Fe(III)-LDH exhibited excellent reactivity in CuAAC reactions, in spite of the fact that the presence of Cu(I) was not traceable in the catalyst matrix. The authors proved that oxidative homocoupling of the alkyne component activates the LDH prior to the cycloaddition, and the resulting Cu(I)-containing lattice defects are responsible for the observed activity.[96] It was also proposed that some of the primordial structural features of the LDH material (such as the well-defined hydroxide layers and the inherent polynuclear nature) cooperatively add to the outstanding catalytic properties. A library of 24 1,2,3-triazoles were synthetized at 100 °C and 100 bar in CH$_2$Cl$_2$ as solvent, with a residence time on the catalyst bed of only 100 s. The Cu(II)Fe(III)-LDH was proven to be a highly robust catalytic system, as no loss of activity and no destruction of the layered structure were noted after a 10-h gram-scale synthesis.

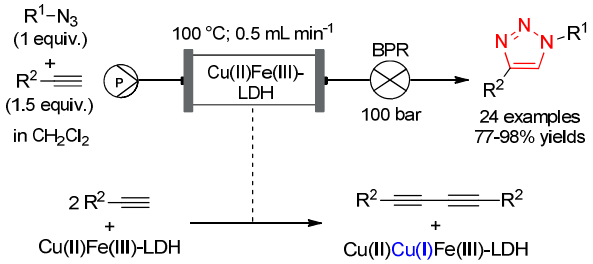

Figure 16. Continuous-flow synthesis of 1,2,3-triazoles with Cu(II)Fe(III)-LDH as heterogeneous catalyst. The oxidative homocoupling of the alkyne component activates the LDH toward cycloaddition.[94]

Reichert and co-workers recently reported the development of a continuous-flow microfluidic device incorporating an immobilized Cu(I) catalyst for 1,2,3-triazole-based bioconjugations (Figure 17).[97] The microreactor was made out of polydimethylsiloxane (PDMS) and glass with a special dotted inner surface to improve the catalyst loading and to reduce the diffusion time of the reactants. A novel water-soluble tris-(benzyltriazolylmethyl)amine (TBTA)-derived ligand was synthetized and covalently immobilized onto the reactor surface. The TBTA-functionalized reactor walls were next activated by pumping a solution of $CuSO_4$/sodium ascorbate, catalytically active Cu(I) being captured by means of chelation with the ligand. CuAAC between a highly functionalized azide and propargylamine was studied to evaluate the applicability of the activated on-chip device. Residence times of 15, 30 and 50 min were screened at 37 °C, leading to the corresponding 1,2,3-triazole conjugate in yields of 55, 76 and 83%, respectively. Upon continuous reuse, the activated microreactor slowly lost its activity, possibly due to the leaching of copper and detachment of the ligand from the surface, but repeated regenerations with Cu(I) solution prolonged its lifetime. The methodology was employed successfully for the CuAAC between an alkyne-terminated biomolecule and an azido-modified cyclic peptide, which predicts possible applications in further bioconjugation reactions.[98]

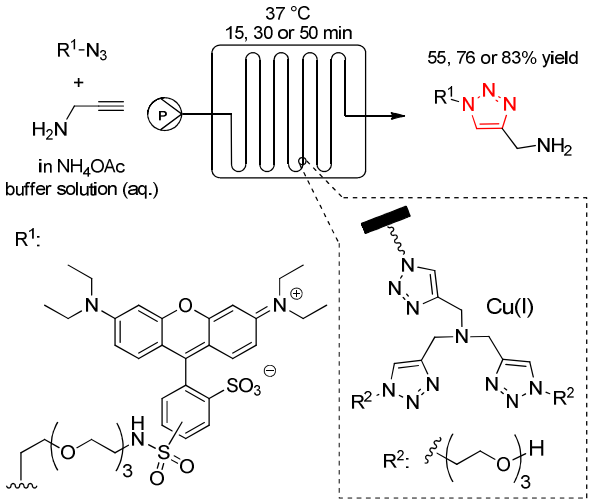

Figure 17. Synthesis of a highly functionalized 1,2,3-triazole in a ligand-functionalized microreactor where Cu(I) is immobilized via chelation.[97]

2.4. Alkyne–azide cycloadditions with homogeneous copper catalysts

Although the most popular sources of Cu(I) in continuous-flow azide–alkyne cycloadditions are heterogeneous approaches, Hessel et al. employed a homogeneous copper complex as catalyst in a microreactor for triazole synthesis (Figure 18).[99] The model reaction between phenylacetylene and phenylazide was studied in *N*-methyl-2-pyrrolidone (NMP) as solvent. After a short screening study, $[Cu(phen)(PPh_3)_2]NO_3$ (phen=phenanthroline) was selected as a soluble copper catalyst.[100] To obtain sufficient reaction rates and to avoid catalyst or azide decomposition simultaneously, 180 °C was selected as optimal temperature. The authors utilized a low catalyst loading of 0.01 equiv. and a short residence time of 10 min, and the corresponding 1,2,3-triazole was isolated in a yield of 88%. To allow a direct comparison, the continuous-flow reaction was repeated under similar conditions in a copper coil reactor, as seen in the study of Bogdan and Sach.[63] The yield of the homogeneous copper complex-mediated reaction was higher, but the remaining catalyst severely contaminated the final product. To overcome this limitation, the authors employed microfluidic extraction with aqueous EDTA solution and removed the copper impurities in line from the triazole product.[99, 101]

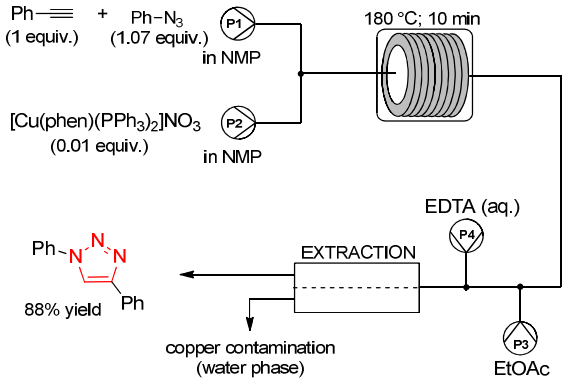

Figure 18. 1,2,3-Triazole synthesis in a microreactor with a homogeneous copper catalyst, and removal of the copper contamination by microfluidic extraction.[99]

In an intriguing study, Jung and co-workers described a glass microreactor with β-cyclodextrin-functionalized inner walls for CuAAC reactions of aromatic azides.[102] The cyclodextrin rings were attached to the silane-modified reactor surface through 1,2,3-triazole linkers. The solution of the azide and the alkyne (in *t*BuOH) and a $CuSO_4$/sodium ascorbate mixture (in H_2O) as catalytic source were pumped into the microreactor through separate

inlets (Figure 19). 1,2,3-Triazoles were obtained in excellent yields (97–99%) from various aromatic azides and aromatic or aliphatic alkynes at ambient temperature utilizing a relatively low flow rate of 5 μL min^{-1}. A series of control experiments with variously functionalized or unmodified reactor surfaces revealed that the β-cyclodextrin moiety serves as an efficient phase-transfer catalyst and markedly boosts the rates of the CuAAC by forming inclusion complexes with the aromatic azides or acetylenes. As an example, a yield of only 31% was achieved in the benzyl azide–phenylacetylene test reaction when the cyclodextrin moieties of the reactor coating were exchanged for phenyl groups, and in the case of a non-functionalized reactor surface the yield was merely 24%. However, a significant limitation of the methodology is that aliphatic azides as starting materials were poorly tolerated, possibly because of the characteristics of the cyclodextrin host.

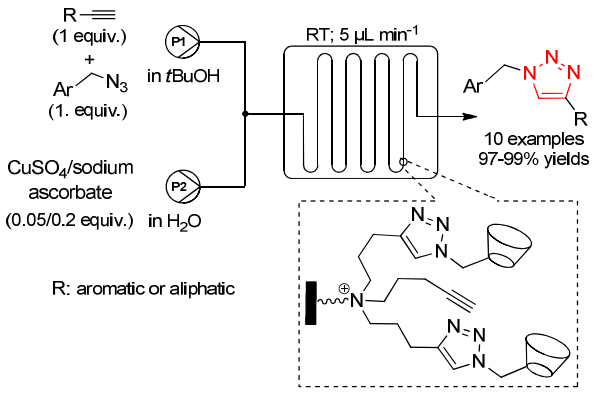

Figure 19. Reactions of aromatic azides and alkynes in a β-cyclodextrin-functionalized microreactor with $CuSO_4$/sodium ascorbate as catalytic Cu(I) source.[102]

Bédard and Collins recently reported an improved strategy for the 1,2,3-triazole-based macrocyclization of 1-iodo-substituted azidoalkynes.[103] As discussed previously, the main limitation of the synthesis of such macrocycles is the extremely high degree of dilution needed to slow the competing oligomerization.[71] _ENREF_66 An aggregated mixture of poly(ethylene) $glycol_{400}$ (PEG_{400})/MeOH (1:1) was employed to control dilution effects.[104] In such a reaction medium, the lipophilic PEG aggregates preferentially solubilize organic substrates, and the slow diffusion into the MeOH co-solvent practically mimics high-dilution conditions, allowing efficient macrocyclizations at concentrations as high as 0.03 M. With the phase separation strategy in hand, the authors exploited continuous processing to achieve gram-scale macrocycle synthesis, using CuI as catalyst in combination with *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA) as ligand at 80 °C (Figure 20). The corresponding 1,2,3-triazole-macrocycle was obtained in a yield of 83%, which is almost identical to that of

the subsequent batch reaction, but the batch-wise synthesis took almost three times longer than the continuous process on the same scale.

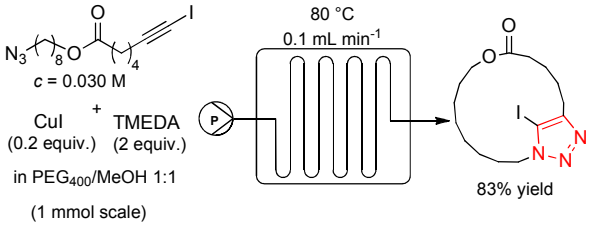

Figure 20. Large-scale synthesis of a triazole-macrocycle with phase separation strategy.[103]

3. Copper-free synthesis of triazoles in flow systems

3.1. Copper-free alkyne–azide cycloadditions

Without any catalytic metal sources, the thermally induced Huisgen reaction gives a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazoles from terminal alkynes and organic azides,[54, 55] however these cycloadditions are mostly very slow, even at high temperatures.[1] _ENREF_47 In an early example, Savin et al. therefore investigated the effects of microwave irradiation on the rates of various copper-free azide–alkyne cycloadditions.[105] Although a substantial rate enhancement was found when the reactions were run in a microwave oven as compared with conventional heating, different reaction conditions (e.g. temperature and concentration) had only moderate effects on the regioselectivity of triazole formation. To achieve large-scale production, the reaction of a disubstituted alkyne (diethyl acetylenedicarboxylate) and benzyl azide was transferred to a continuous-flow microwave reactor. The simple flow-through system allowed a 6-mmol-scale synthesis of the desired 1,4,5-trisubstituted cycloadduct in toluene at 110 °C within a residence time of 10 min, affording a yield of 70%.

It was established that triazole formation can be accelerated tremendously with the azide and alkyne reaction partners being held together in a close proximity, and click chemistry was therefore recognized as an excellent tool for the identification of high-affinity protein ligands by assembling azide and acetylene building blocks *in situ*, i.e. inside the binding pockets of a target enzyme via 1,3-dipolar cycloadditions.[106] The *in situ* click cycloadditions are typically conducted by using 96-well plates, which requires significant amounts of the target proteins and reagents and limits screening throughput and efficacy.[107] These drawbacks led Tseng and co-workers to develop an integrated microfluidic reactor for the parallel screening of an *in situ* click chemistry library (Figure 21), which reduces the consumption of the target protein

and reagents and allows rapid and automated screening.[108] Bovine carbonic anhydrase II (bCAII) was employed in a proof-of-concept study as a target protein, with acetylenic benzenesulfonamide as a reactive scaffold (it binds the target with high affinity) to capture complementary azide reagents and to form 1,2,3-triazole-based bCAII inhibitors *in situ*. The microfluidic instrument relied on a stopped-flow profile rather than continuous operation, the reaction components being introduced, mixed together and then loaded into 32 individual microvessels by a sequence of pumps. The actual cycloadditions took place in the microvessels through an incubation period of 40 h at 37 °C, from where the resulting mixtures were eluted for analysis. After the screening of 20 different azides, 10 triazoles were identified as hits via enzyme-induced reactions, and all of them were obtained with high 1,4-regioselectivity in spite of the lack of a copper source. The process clearly proved enzyme-dependent, as thermal cycloadditions performed as control reactions under identical conditions but in the absence of bCAII resulted in no hits.

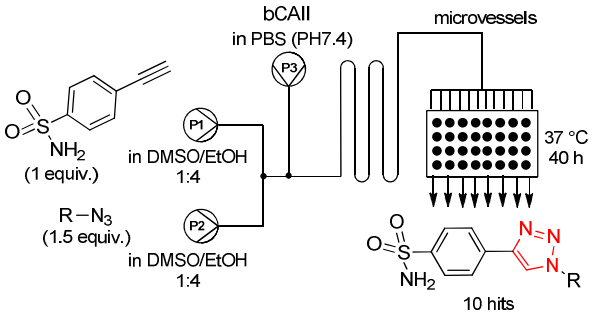

Figure 21. Parallel screening of 20 different azides with acetylenic benzenesulfonamide as a reactive scaffold for the identification of 1,2,3-triazole-based bCAII inhibitors in an integrated microfluidic reactor.[108] (PBS = phosphate-buffered saline.)

Hessel and co-workers investigated the copper-free synthesis of the methyl ester precursor of Rufinamide in a high-pressure/high-temperature environment to achieve chemical intensification and to direct the selectivity.[109] The cycloaddition of 2,6-difluorobenzyl azide and methyl propiolate was explored in an autoclave batch reactor, specialized for the kilobar pressure range, and in a continuous-flow system equipped with a 400-bar BPR (Figure 22). The desired 1,4-cycloadduct was achieved in the flow reactor with a yield of 48% and with moderate 1,4-regioselectivity at atmospheric pressure and 90 °C. Pressurizing to 400 bar increased the yield to 58%, however the product distribution was only slightly enhanced. The yield was further increased at higher concentrations, but the use of high-temperature conditions was found to have the greatest impact on the rate of the continuous reaction. 140 °C was established as the optimal temperature, furnishing the target 1,4-disubstituted triazole in a yield of 80%, which compared well with the results obtained in catalytic control

experiments. In the batch autoclave, pressurizing improved the yield appreciably, and at a maximum pressure of 1800 bar, the preference for the formation of the 1,4-regioisomer was also greatly enhanced. In spite of this, the continuous process proved more efficient, as a 48-fold increase of the reaction time was necessary in the batch autoclave to obtain similar yields as in the flow reactor within 30 min.

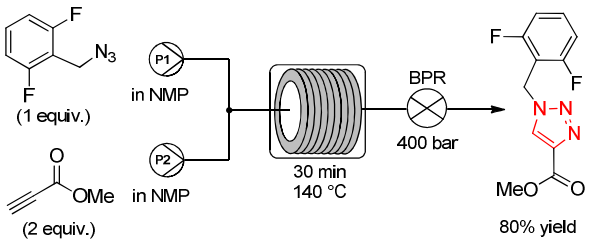

Figure 22. Catalyst-free synthesis of a Rufinamide precursor in a high-pressure/high-temperature flow reactor.[109]

3.2. Copper-free cycloadditions of azides and non-alkyne dipolarophiles

Although alkynes are most frequently employed as reaction partners to yield triazoles with organic azides, the use of different further dipolarophiles can be highly advantageous or even essential from many synthetic aspects.[1, 2] For example, the scope of Cu(I)-catalyzed and thermally induced cycloadditions between azides and disubstituted acetylenes as dipolarophiles, leading to 1,4,5-trisubstituted 1,2,3-triazoles, is mostly limited to activated substrates, such as electron-deficient and strained internal alkynes.[75, 110-113] This is mainly due to the fact that the activation toward cycloaddition via coordination of Cu(I) with the alkyne component involves a significantly higher energetic barrier in the case of disubstituted acetylenes than with terminal ones.[114] While the emergence of ruthenium- and (most recently) iridium-based catalytic systems has addressed this challenge to some extent,[115-117] various strategies involving non-alkyne dipolarophiles in combination with metal-free continuous-flow conditions can be highly attractive for the synthesis of diversely substituted triazoles.

For example, Storz et al. exploited the benefits of continuous processing for the synthesis of an N^1-alkylated 5-amino-1,2,3-triazole carboxamide (Figure 23),[118] the only reported batch process claimed for this important building block sufferring from low yield, structural ambiguity and considerable safety concerns.[119] Cyanoacetamide was used as dipolarophile, in combination with NaOH as base and with β-azidoethyl phenyl sulfide as a synthon of ethyl azide to reduce the explosion hazard. An elaborate optimization study suggested a complex coherence between the reaction conditions. As an example, at higher temperatures (such as 95 °C) the base induced the decomposition of cyanoacetamide in a concentration-dependent manner, leading to the formation of by-products. Nevertheless, the authors succeeded in

identifying an optimal set of conditions (65 °C, 2 min residence time, 1.5 equiv. of NaOH), which allowed the high-yielding gram-scale synthesis of the trisubstituted cycloadduct as one regioisomer. The desired N^1-ethyl triazole building block was finally achieved via RaNi-mediated desulfurization. Another research group has recently integrated the above methodology with the one-pot generation of the azide component, and reported the continuous synthesis of an N^1-benzyl-substituted triazolopyrimidine as the core structure of the antiplatelet agent Brilinta®.[120]

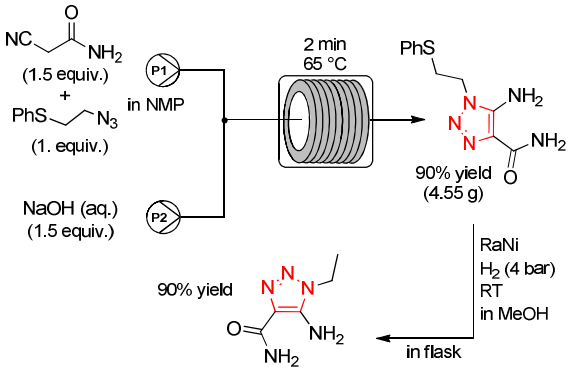

Figure 23. Gram-scale continuous-flow synthesis of an N^1-alkylated 5-amino-1,2,3-triazole carboxamide with subsequent batch desulfurization.[118]

Bacchi and co-workers reported a telescoped two-step procedure for the continuous synthesis of N^1-arylated 1,4,5-trisubstituted 1,2,3-triazoles from anilines as starting materials without isolation of the corresponding azides as reactive intermediates (Figure 24).[121] In the first step, a mixture of a substituted aniline and azidotrimethylsilane ($TMSN_3$) were combined in a T-piece with a solution of *tert*-butyl nitrite (*t*BuONO), and passed through a heated reaction coil (50 °C, residence time 20 or 30 min).[122] The resulting stream containing the aryl azide intermediate was mixed with a solution of an enolate dipolarophile, generated *in situ* from various β-ketoesters in the presence of DBU, and directed through a second coil at 80 °C (residence time 13 or 19 min) where the 1,3-dipolar cycloaddition took place. N^1-Arylated 1,4,5-trisubstituted 1,2,3-triazole products were obtained in short process times and in good yields (up to 79%).

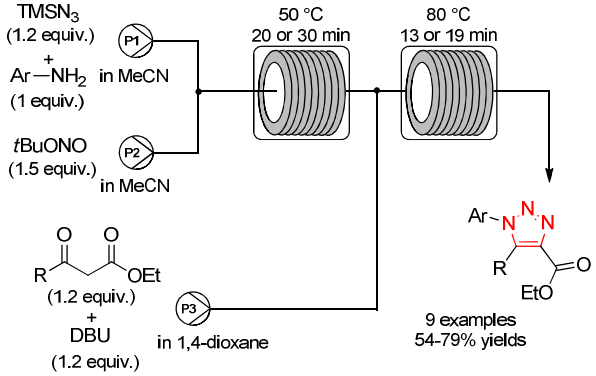

Figure 24. Continuous-flow synthesis of N^1-arylated 1,4,5-trisubstituted 1,2,3-triazoles with *in situ* generation of the azide reaction partner. Enolates as dipolarophiles were generated from various β-ketoesters with DBU.[121]

An improved approach was later demonstrated by Baxendale and co-workers for cycloadditions of *in situ* generated azides to yield a series of biologically interesting 5-amino-4-cyano-1,2,3-triazoles in pure form.[123] Similarly as in the study by Bacchi et al.,[121] $TMSN_3$ in combination with *t*BuONO was used to generate azides from the corresponding anilines.[124] However, to retain unreacted toxic anilines and $TMSN_3$, the crude azide stream was purified in line through the use of immobilized scavengers (Figure 25). A sulfonic acid resin was applied to trap the remaining aniline and at the same time to convert any unreacted $TMSN_3$ to hydrazoic acid, which was next cleaned up on a dimethylamine resin. Instead of the introduction of a third stream containing a base and malononitrile as a dipolarophile, the purified azide stream was passed through a reaction column filled with a basic resin-supported malononitrile. Before collection of the final stream, a washing step was introduced with a solution of malononitrile to release any triazole products captured on the malononitrile-functionalized resin, which also had the benefit of column regeneration. To achieve fully automated production, the multistep flow system was combined with a series of valves and reagent loops, and was linked to control software. The automated system allowed the expeditious synthesis of a small library of 5-amino-4-cyano-1,2,3-triazoles in high yields.

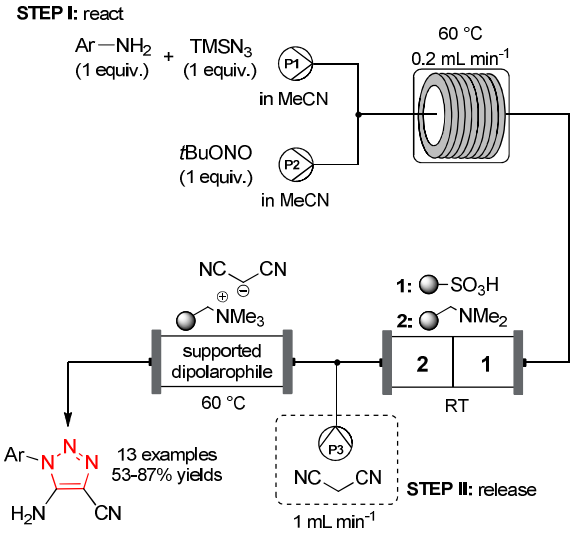

Figure 25. Synthesis of 5-amino-4-cyano-1,2,3-triazoles in a multistep flow system through the use of a series of resin-supported scavengers and reagents. Triazole products retained on the malononitrile-functionalized reaction column were released in a subsequent washing step.[123]

A recent study by Hessel and co-workers nicely exemplified that a switch to an alternative non-alkyne dipolarophile in combination with the merits of continuous-flow reaction technology can considerably enhance the catalyst-free production of a pharmaceutically relevant 1,2,3-triazole.[125] The synthesis of the methyl ester precursor of Rufinamide was investigated with (*E*)-methyl 3-methoxyacrylate as a nontoxic and inexpensive dipolarophile. It was previously shown that the thermal cycloaddition of (*E*)-methyl 3-methoxyacrylate to 2,6-difluorobenzyl azide, resulting in a trisubstituted 4,5-dihydro-1,2,3-triazole, is immediately followed by the elimination of methanol, leading to perfect regioselectivity toward the desired 1,4-cycloadduct.[126] However, the preceding batch experiment raised serious safety issues in view of the instability of the azide component, as the reaction required 28 h of heating at 135 °C without solvent. To meet the requirements of industry, a safer and intensified solvent-free continuous-flow methodology was developed (Figure 26). To ensure the complete homogeneity of the reaction mixture, the entire reactor coil was heated above the melting point of the product. A reactor temperature of 210 °C accompanied by a residence time of 10 min was found optimal for high reaction rates without decomposition of the azide component. The isolation of the product was simple and easy, as a stream of MeCN or MeOH was introduced, from which the analytically pure product precipitated in the collection tank after passing through a cooling zone. The optimized procedure allowed the production of 4.2 g (83% yield) of the desired Rufinamide precursor in 30 min.

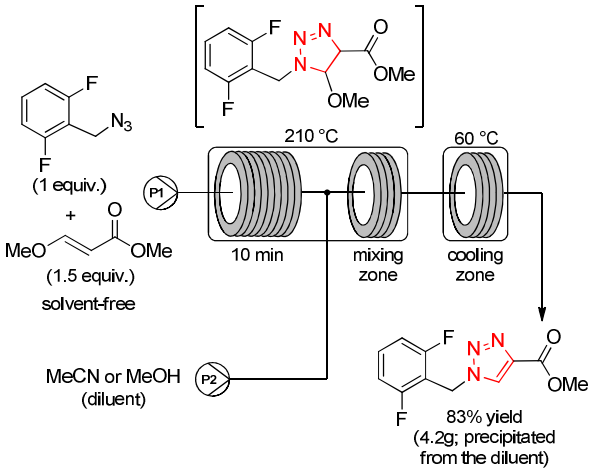

Figure 26. Solvent- and catalyst-free synthesis of a 1,2,3-triazole ester, a key intermediate for the production of Rufinamide with (*E*)-methyl 3-methoxyacrylate as dipolarophile.[125]

Kirschning and co-workers investigated the photochemical activation of vinyl azides and the trapping of the corresponding nitrile ylide intermediates by different dipolarophiles via [3+2] cycloadditions in a continuous-flow manner.[127] The authors demonstrated that, with the use of azodicarboxylates as dipolarophiles, trisubstituted 2,3-dihydro-1,2,4-triazoles become directly accessible from the corresponding vinyl azides by means of the simple and scalable photoinduced flow methodology. Most recently, Baxendale and co-workers have also reported a continuous system for the synthesis of 1,2,4-triazoles, although no azide component was involved in the reaction.[128] In the telescoped process, ethyl isocyanoacetate and various aryl diazonium species were generated *in situ* and mixed together subsequently. The cycloaddition took place after the resulting stream was combined with an aqueous feed of potassium carbonate, affording 1,3-disubstituted 1,2,4-triazoles in high yields.

4. Summary and outlook

Flow chemistry, in combination with heterogeneous and homogeneous copper sources and also with various copper-free strategies, has been shown as a versatile tool for the synthesis of triazoles via 1,3-dipolar cycloadditions of organic azides with different dipolarophiles. Heterogeneous catalytic systems (such as polymer-bound CuI, Cu/C, Cu/Fe, Cu/APSiO$_2$, copper-containing LDH, copper-functionalized reactor walls and even copper metal) have the benefits of facile reuse, robustness and simplified work-up procedures, while the leaching of copper species, typically occurring at higher temperatures or in the presence of bases and stabilizing ligands, can be successfully minimized in line through the use of cheap and readily available solid-phase scavengers (such as thiourea-based resins, activated charcoal and simple

iron powder). Homogeneous catalytic approaches afford higher reaction rates in some cases, but subsequent catalyst removal is necessary to obtain pure products. To overcome this limitation, an example has been given for in line copper removal by employing a microfluidic extraction process. Copper-free cycloadditions between azides and terminal alkynes typically require substantial chemical intensification (such as very high pressure or microwave irradiation), for which continuous processing can be highly advantageous. However, the lack of control over the regioselectivity in the absence of the catalytic metal remains a significant drawback. Catalyst-free continuous-flow reactions between azides and further dipolarophiles nicely complement the copper-catalyzed transformations and have proved convenient for the synthesis of diversely substituted triazoles.

The safety aspects associated with the handling of azides, as hazardous species, have been recognized as one of the most important driving forces behind the advent of continuous-flow processes for triazole synthesis. Better heat-transfer characteristics and increased mixing efficiency can be accounted for an improved safety profile, and as well as for the elimination of common by-products of alkyne–azide cycloadditions, such as diacetylenes and bis-triazoles. The routine use of pressure valves allows the safe overheating of common solvents, thereby achieving excellent reaction rates at temperatures which are normally inaccessible with conventional systems (such as >200 °C). It has also been demonstrated that sufficiently high pressures can not only result in overheating, but also enhance triazole formation. Many examples have proved that flow chemistry is an ideal technology for integrated multistep syntheses, where azides can be generated and consumed *in situ*, thereby minimizing the risks associated with the accumulation of hazardous species. Additionally, telescoped approaches in combination with solid supported reagents and scavengers allow the synthesis of diversely functionalized triazoles without the need for conventional work-up and purification procedures. Such continuous methodologies permit not only the production of ready-to-use building blocks, but also the effective syntheses of complex biologically and pharmacologically relevant structures (such as drug-like macrocycles, triazole-modified β-amino acid derivatives, a peptide–triazole conjugate, a triazole-based enzyme inhibitor and a triazole-containing antiepileptic drug).

Although many synthetic challenges in triazole chemistry have already been addressed or at least simplified by the toolbox of continuous-flow chemistry and catalysis, and alternative continuous-flow cyclization strategies have also emerged for the synthesis of various biologically relevant triazoles,[129, 130] but numerous gaps still remain. For example, there is a

compelling need for ruthenium- and iridium-based heterogeneous catalytic systems in association with complementary flow chemistry-based synthetic techniques to facilitate the selective production of novel 1,5-disubstituted and 1,4,5-trisubstituted triazoles.[115-117] However, currently the most important task in continuous-flow triazole chemistry is undoubtedly to outstrip bench-top syntheses and achieve practical industrial-scale production in a sustainable manner.

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Keywords

azides; continuous-flow processing; cycloadditions; microreactors; triazoles

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