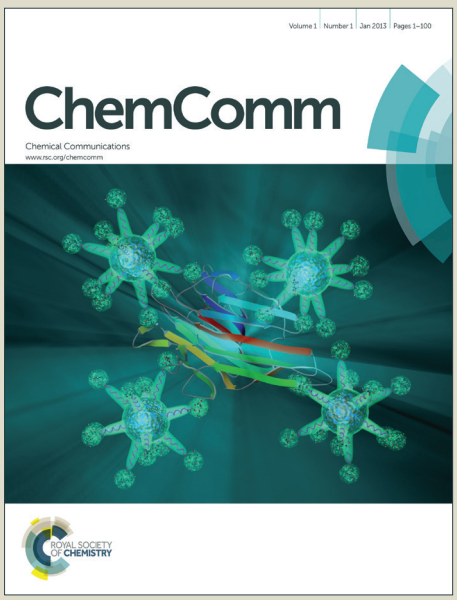
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

The utilization of copper flow reactors in organic synthesis

Jennifer Bao[a] and Geoffrey K. Tranmer[a,b]*

DOI: 10.1039/b000000x [DO NOT ALTER/DELETE THIS TEXT]

The use of flow chemistry techniques has flourished over the past decade, with the field expanding to include the use of copper flow reactors in bench-top organic synthesis in recent years. These reactors are available in a variety of forms and possess a number of advantages over their batch reaction counterparts, in terms of both safety and yield. This review will highlight the current research employing copper flow reactors, such as 1,3 dipolar cycloadditions ('click' chemistry), macrocyclizations (via 'click' chemistry), Sonogashira C-C couplings, Ullmann couplings, decarboxylations, and other reported findings.

Introduction

Due to its many advantages over batch reaction processes, flow chemistry has become an emerging field in organic synthesis[1], and has recently been employed in laboratory settings to enhance the selectivity, safety, and efficiency of chemical syntheses, including the rapid synthesis of natural products[2] and pharmaceuticals[3]. In its simplest form, flow chemistry reactions operate in a continuous stream where the reagents are pumped through some form of flow reactor, as opposed to batch reaction processes which are carried out in fixed volume reaction flasks. Typically, solution-phase flow chemistry reactions are performed using tubular reactors which are made of a variety of materials, such as stainless steel, polytetrafluoroethylene (PTFE), perfluoroalkoxy copolymers (PFA) or copper, while column reactors packed with reagents/catalysts, or microfluidic chips, may also be employed[4]. The reagents engaged in the flow reaction are introduced into the reaction system via a pumping mechanism and are performed using bespoke or commercially available flow chemistry systems[5] which allow control over residence time, temperature, pressure and flow rate of each reagent. Some of the advantages of flow chemistry reactions include: the efficient mixing of reagents; the ability to control and perform reactions in harsh conditions, such as high temperatures and pressures; control of residence time and exothermic reactions; greater surface area to volume ratios, allowing for better contact between the reagents; ease of scale up; and safer handling of hazardous reagents and intermediates[6]. Automation is also a significant advantage employed within flow chemistry reactions, as it allows for better control over time-sensitive synthetic reactions and easier and more rapid reaction optimization[7], including in-situ reaction monitoring[8].

While flow chemistry has become a burgeoning field in organic synthesis, the utilization of tubular flow reactors made of copper has only been reported in the past several years. Reactions that have been reported include: 1,3-dipolar cycloadditions ('click' chemistry[9]), macrocyclizations[10] (via 'click' chemistry), Sonogashira couplings[11], Ullmann-type reactions[12] and decarboxylations[13]. This review will outline the utilization of copper flow reactors in the performance of these reactions,

and the incorporation of other technology within the copper reactor, as well as, reported findings. It is expected that the use of copper flow reactors will greatly increase in the near future as a result of these recent findings, as researchers look to take advantage of the many benefits of copper flow reactors, such as: ease of incorporation, (i.e. commercial availability); the ease of replacing copper reagents with copper-metal flow reactors; the ability to rapidly heat and cool reactions (increased thermal conductivity); the ability of copper-metal reactors to mediate reactions; and the many benefits inherent to flow chemistry, *vide infra*. For the purposes of this review, the authors have focused on the use of 'copper-metal flow reactors' in bench-top organic synthesis, (i.e. any flow reactor which uses copper metal to perform a chemical transformation, such as copper powder/turnings, or copper tubing/wire) and will reserve the description of Cu-catalyzed reactions in flow[14] for a potential future review, and have excluded a single patent which describes the production of cyclopropane derivatives using copper metal or copper oxide in a continuous process[15].

Review: Reactions involving the use of copper-based flow reactors

1. 1,3-Dipolar cycloadditions ('click' chemistry)

To the best of our knowledge, the first reported utilization of a tubular copper flow reactor for mesoscale organic synthesis, was performed by Bogdan and James (2009) for the continuous synthesis of 1,4-disubstituted-1,2,3 triazoles[16]. 1,2,3-triazoles have been of interest in the field of drug discovery due to their biological applications and use in therapeutic agents[17]. Traditionally they can be synthesized via the 'click' reaction between an organic azide and acetylenes[18]. Specifically, the authors reacted organic azides, generated *in situ* from alkyl halides and sodium azide with acetylene via a copper-catalysed Huisgen 1,3-dipolar cycloaddition (see figure 1)

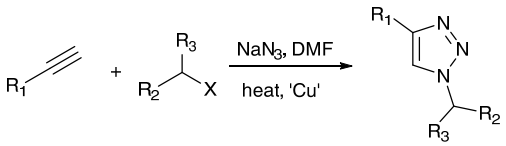


Figure 1. The one-pot click methodology, developed by Bogdan et al. (2009) to form 1,4 disubstituted 1,2,3 triazoles.

A Conjure™ flow reactor was used, with a reactor diskette made of copper, adopting a segmented flow approach which would minimize material consumption and limit reaction size, as well as, allow for maximum efficiency. When the reaction segments containing sodium azide, alkyl halide and acetylene in DMF was passed through the copper flow reactor, high conversions were obtained in 5 minutes. The authors then proceeded to optimize their one-pot 'click' methodology using 4-ethynyl toluene, 2-bromoethanol, sodium azide and DMF. Optimal reaction conditions were obtained by varying residence time, reaction temperature and equivalents of alkyl azides, and 30 triazoles were synthesized in hours with modest to excellent yields under flow conditions. Aliphatic and aromatic acetylenes, and primary and secondary alkyl halides were also used successfully in the one-pot 'click' methodology.

Due to safety concerns as a result of this reaction generating highly reactive and dangerous intermediates (organic azides which can violently decompose and are

difficult to handle safely on scale), batch processes would not be suitable. Performing the reaction in flow reduces this danger since the scale-up is a function of time and flow rate, and eliminates the need to handle the azides, creating a much safer reaction.

A study performed by Ceylan et al. (2010) also utilized inductively heated copper flow reactors in the synthesis of 1,2,3 triazoles[19]. The authors proposed that their set up would contain several features, such as a simple set up, having copper as the only initial source of heat inside the reactor, as well as, having the heated metal serve as the sole catalytic source for activation, allowing copper to heat above 220ºC and minimizing copper leaching. To minimize the effects of leaching, a metal scavenger cartridge charged with Quadrapur™ TU was employed. As well, the authors had found that the copper wire was able to heat up rapidly and efficiently above 220ºC, no matter which solvent was used. At around 180ºC however, the authors found that oxidation would occur on the Cu surface that they attributed to dissolved oxygen, which could be avoided if degassed solvents were used. The efficiency of the inductive heating depends on several factors, such as the design of the inductor and the reactor, and the magnitude of temperature change required. However, in comparison to batch processes where heat is applied using a source external to the reactor, and energy can be more easily lost to the surroundings, inductive heating of a source internal to the reactor can be considered a more efficient process.

Similar to Bogdan et al., the authors had also performed the 'click' reaction *in situ*, forming organic azides from alkyl halides at high temperatures, and reacting these immediately with acetylenes[19]. The one pot click methodology was performed using phenyl acetylene, 2-bromoethanol and sodium azide in a DMF/water mixture. The authors also reacted organobromides with either 5-hexynol or phenyl acetylenes. The benzyl bromides were smoothly converted to triazoles with high yields, however, non-benzylic bromides/iodides, while still providing the desired product, required slower flow rates due to their lower nucleophilicity. More functionalized, as well as, chiral bromides also provided the expected products. No conversions were seen however when the reactions were performed in a flask. The authors proposed that higher temperatures are easily achieved via induction inside the Cu wire compared to global temperatures measured, which could result in the generation of an active catalytic species on the surface of the copper, or its release into solution. This form of activation would not occur under conventional methods in batch.

A study performed by the same group, Kupracz et al. (2011), had also demonstrated successful synthesis of 1,2,3 triazoles, in flow using a copper reactor, but involves the Huisgen-type cycloaddition between vinyl azides and alkynes, which at the time had not yet been reported[20]. Optimization conditions were performed using 2-(1-azidovinyl)naphthalene and phenylacetylene as reaction partner, with the temperature measured using an IR pyrometer. The authors determined that copper turnings gave complete conversion and good yields, which could be attributed to a larger surface area. Flow rates that were equal to or higher than 0.05ml/min lead to very low or no conversion, while increasing the temperature above 80ºC lead to decomposition of reactants. DMF was found to be the best solvent of choice. With these conditions optimized, the authors then synthesized 12 aryl/alkyl substituted triazoles (figure 2).

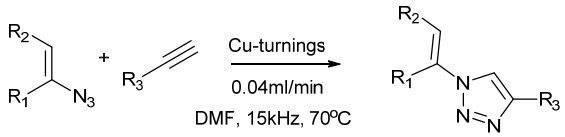


Figure 2. Scheme for the synthesis of 1,2,3 triazoles, using previously prepared vinyl azides and inductively heated copper turnings, in a packed column bed, performed in flow.

Following azido iodination, a route was devised by the authors that allowed a cycloaddition to occur, followed by an elimination step. However, this route had experienced difficulties, with cycloaddition not being achieved in DCM, and transformation leading to low yields.

While copper tubing has been used as the primary catalyst in flow, Otvos et al. (2013) performed alkyne-azide cycloadditions with copper powder in a high-pressure continuous flow reactor (CF)[21]. Copper powder was available as the cheapest source of Cu(I), with copper flow reactions performed in a replaceable, stainless cartridge on a catalyst bed. This allowed high pressure and temperature conditions to be safely employed for unstable reactions, preventing explosion as the reactants are exposed to the harsh reaction conditions for a safe, limited and controllable amount of time. To determine optimum conditions, a 1,3-dipolar cycloaddition was performed between benzyl azide (1 equiv.) and phenylacetylene (1.5 equiv.) (see figure 3). A 0.085M concentration of the azide was found to be best, as any concentration higher than this led to precipitation of the triazole product in the reactor. The conditions for the reactor were set at an increased pressure from atmospheric to 1 bar, room temperature, with a flow rate of 0.5ml/min and CH_2Cl_2 as the solvent. It was found that increasing the pressure, increased the rate of triazole formation, and allowed for higher temperatures to be utilized without the solvent boiling over. As temperature was increased, conversion also increased as well, with 90% conversion achieved at 50ºC and quantitative conversion seen at 100ºC. Decreasing the residence time and increasing the flow rate however was shown to result in a dramatic decrease in conversion. At 1ml/min, 31% conversion was achieved, while at 3ml/min, 10% conversion was observed[21].

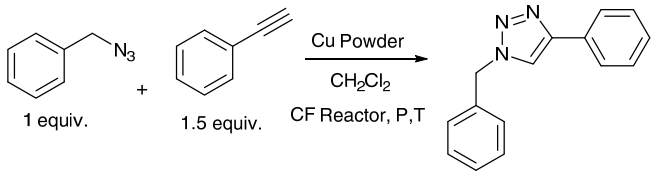


Figure 3. The 1,3 dipolar cycloaddition, using benzyl azide and phenylacetylene in determining optimal reaction conditions for the CF reactor.

The addition of amines as a basic additive can also enhance the reactivity of the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, as it serves as ligand, coordinating with the Cu(I), liberating it from the matrix thereby promoting the formation of the Cu-alkyne complex with the authors choosing *N*,*N*-diisopropylethylamine (DIPEA) and acetic acid (HOAc) as the basic and acid additives. When no additives were used at room temperature, with a flow rate of 0.5ml/min, only 34% conversion was seen. However when HOAc was added, 56% conversion was seen, while a 96% conversion was seen with DIPEA. Quantitative conversion was seen when both additives were used in combination, 1.0 eq. each.

The authors performed a scale up of the CuAAC reaction between benzyl azide and phenyl acetylene under two different set of copper flow conditions (CFA & CFB). With CFA, conditions were set at 100 bar, 100ºC at 0.5ml/min while CFB conditions were set at 100 bar, room temperature at 0.5ml/min with DIPEA (0.04 equiv.) and HOAc (0.04 equiv.). When 75ml of the mixture was pumped through in 150 minutes, a 99% yield of triazole was obtained under both conditions.

To determine the applicability of the CF conditions the authors outlined, they proceeded to perform a number of reactions under condition CFA and CFB using phenylacetylene and various azides (see figure 4). Aliphatic and aromatic azides were found to be excellent substrates for the CF CuAAC and with the aromatic azides, electron-withdrawing and electron donating groups present on the phenyl rings did not affect yields. CFB conditions, containing additives, were found to yield better results in azide scope and gave higher yields compared to CFA conditions.

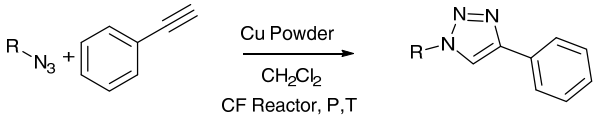


Figure 4. The reaction between various azides and phenylacetylene.

In the scope of alkynes however, the CFA and CFB conditions performed equally well. The authors also performed the reaction between various alkynes and benzyl azide. Non-aromatic alkynes, as well as the non-terminal alkyne diethyl acetylenedicarboxylate performed well under CFA conditions. The authors also decided to test the reaction between benzyl azide and ethynyl ferrocene, due to the importance of ferrocene as a labeling agent for biomolecules in medicinal chemistry[21]. The ferrocenyl triazole was synthesized in high yield (99%).

An interesting study performed by Tu et al. (2012) highlights the use of an ultrasound (US) assisted click reaction in continuous flow[22]. The advantage in using ultrasound is that it is able to enhance product yield via a high energy input for both heterogeneous and homogeneous processes in conventional round bottom flasks. The initial reaction optimization conditions were performed using alkyne 1,2 bromoethanol and sodium azide in DMA under both US and heating conditions (figure 5). The desired 1-pot click reaction product was obtained in good yield (55%) by varying residence time, reactor temperature, US intensity and US time. The product was prepared in under 8 minutes of US irradiation and with a residence time of 8 minutes at 75ºC.

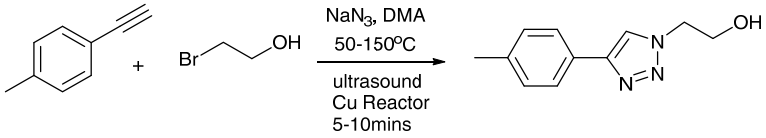


Figure 5. Reaction between alkyne, 1,2 bromoethanol and sodium azide in DMA to determine optimal reaction conditions.

Otvos et al. (2013) also investigated the synthesis of highly functionalized Cispentacin derivatives. Cispentacin is a natural carbocyclic β-amino acid with anti-fungal properties, and when batch reactions were performed between phenylacetylene and azido esters, figure 6, the desired triazole derivatives were not obtained[21]. However triazole-cispentancin in the presence of CuI in MeCN, reflux

for 12hrs led to a 69% yield and 73% yield, respectively. These yields in batch were comparable to CFA conditions. However, under conditions CFB, 99% yields were obtained, without the need for any work up.

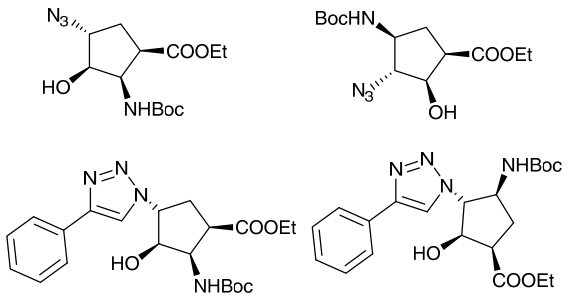


Figure 6. Azido Esters, triazole derivatives.

The azido-substituted Cispentacin derivatives were then subjected to a dipolar cycloaddition with ethynyl ferrocene in batch, containing CuI in MeCN, however, no transformation was observed. A 51% and 69%, figure 7, batch yield was obtained when CuI was changed to $CuSO_4$/ascorbic acid over 14hrs. Under CFA and CFB conditions, 99% yields were obtained. Based on the comparisons between the batch and CF conditions (CFA and CFB), it is illustrated that CF methods are more efficient due to shorter reaction times, higher yields, and ease of product isolation. Specifically, CFB conditions were found to be best[21].

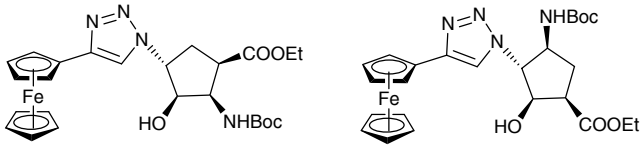


Figure 7. Ferronycyl triazole derivatives.

It should be added that due to safety concerns as a result of this reaction generating highly reactive and dangerous intermediates (organic azides which can violently decompose and are difficult to handle safely on scale), batch processes would not be suitable. Performing the reaction in flow reduces this danger since the production of large amounts of product (scale-up) is a function of time and flow rate, and eliminates the need to handle the azides, creating a much safer reaction[23], as smaller amounts of azides are generated at any given time point.

In a similar study by Otvos et al. (2013), a series of 1,2,3-triazole-substituted β-aminocyclohexane carboxylates were synthesized in flow utilizing copper powder as a readily accessible Cu(I) source[24]. Initially, the reactions were performed under high-pressure and high-temperature conditions (100 bar, 100˚C, 0.5 mL/min) resulting in 12 examples with yields ranging from 33 to 98 percent. However, through the use of both basic and acidic additives (0.04 eq. DIPEA, 0.04 eq. AcOH), the authors were able to perform the reactions at room temperature and greatly improve yields (a 76-98% range), as well as, achieve excellent yields when the additives were used in combination with high-temperature and pressure, all yields >92% (100 bar, 100˚C, 0.5 mL/min, 0.04 eq. DIPEA/0.04 eq. AcOH). One example was used to highlight the increased safety realized via flow chemistry where a

0.085M solution of azide was pumped at 0.5 mL/min for 100 minutes, producing over 2 grams of product at room temperature in 96% yield, a result that would be difficult to obtain under batch conditions, figure 8.

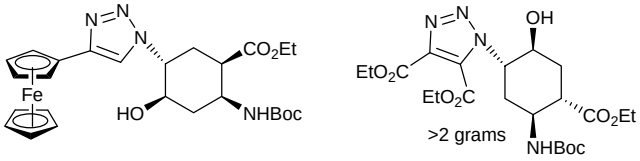


Figure 8. Continuous flow synthesis of 1,2,3-triazole-substituted β-aminocyclohexane carboxylates using copper powder and basic/acidic additives.

A copper on iron bimetallic system has also been employed to perform continuous-flow azide-alkyne cycloadditions by the same group, using iron powder as a copper scavenger, reducing the level of copper impurities. Once again, the authors employed basic/acidic additives at room temperature and 100 bar pressure to produce a 94% yield, although in this case, two stainless steel columns were used, one charged with Cu/Fe catalyst and the other, a scavenger column filled with Fe powder[25]. In this case, the Cu/Fe catalyst was observed to offer comparable yields and results to copper powder.

2. Macrocyclizations (via 'click' reactions)

Macrocycles have been of interest in the regulation of protein-protein interactions due to their conformational constraints present intrinsically, as well as their lower rotatable bond count that allows these compounds to retain improved physicochemical, pharmacological, and pharmacokinetic properties in comparison to their acyclic counterparts. Protein-protein interactions are crucial in molecular activities, such as in cellular signalling pathways. As such, macrocyclization has been of interest in the field of drug discovery.

Due to their importance, Bogdan and James then proceeded to construct drug like macrocycles, developing methodologies that could be applied to drug discovery programs. As indicated earlier, Cu(I) catalysed azide-acetylene cycloaddition (CuACC) reactions could be carried out under flow conditions to yield 1,2,3 triazoles[26]. Macrocyclization, under conventional conditions is inefficient, due to problems including high dilution of product, slow reaction times and high consumption of solvent, but can be minimized or prevented when performed in flow. Bogdan and James (2010) proposed that in a flow reaction, a reactive copper-acetylide species could be generated at or near the copper [coil] surface at a high temperature, which could favour macrocyclization via an intramolecular reaction, rather than yielding a dimer. Comparing their optimized flow parameters with other reaction conditions, Bogdan and James illustrated that only the flow protocol resulted in a high ratio between the macrocycle and dimer product. When the reaction was performed under reflux in ethanol with copper turnings, no detectable product was shown after 5 minutes, and only trace amounts of product were detected after 90mins. Addition of soluble CuI resulted in a low yield of product and only a 1:1 ratio between macrocycle and product. The reaction was then tested in a sealed tube, at 150°C for 5 minutes in an oil bath with CuI, copper turnings or copper powder, which yielded 52, 17 and 50% of product, respectively. Using the optimized conditions determined from this protocol, the authors then examined a number of

azidoalkyne substrates and their macrocyclization rates, and prepared to synthesize 12-22 membered macrocycles, all generated in modest to excellent yield.

There are a number of reasons that Bogdan and James attribute to the high ratio of product to dimer ratio, achieved when the reaction was run in flow. First, the reaction is occurring at or near the copper surface, which is in line with elemental analysis results and reactions conducted with soluble copper[26]. Second, a pseudodilution effect may be present in which there is a possible interaction between the cyclization precursor with the surface bound reagent, which occurs at a distance that prevents intermolecular reactions[26]. The control experiments that involved the use of copper turnings or copper powder, in an oil bath failed to produce the high macrocycle to dimer ratio obtained using flow. It would also be impractical and hazardous to perform at 150°C in a batch process. Likewise, the experiment could not be replicated using a microwave heater, as it does not contain an internal temperature sensor needed to measure and precisely control the temperature of the metal surface inside the microwave reactor[26].

In another experiment, Bogdan and James (2011) had also examined and employed a new macrocyclization strategy to synthesize 12-31 membered 5-iodo-1,2,3 triazole containing macrocycles. Because the presence of the iodotriazole moiety would allow for facile library development, via the palladium-catalyzed cross couplings, the authors had examined the use of this reaction in the synthesis of drug-like macrocycles[27]. It was anticipated that the 1-iodoalkynes instead of terminal alkynes would lead to similarly high yields for cycloaddition using the copper tubing as a catalyst. The reaction performed to determine optimal conditions is illustrated in figure 9 and found to be 10 minutes at 100ºC with 10mol% tris-((1-*tert*-butyl-1*H*-1,2,3-triazoyl)methyl)amine (TTTA) and 2.0 equiv. of DIPEA for macrocyclization. Temperatures above 100ºC resulted in decomposition of the starting materials[4].

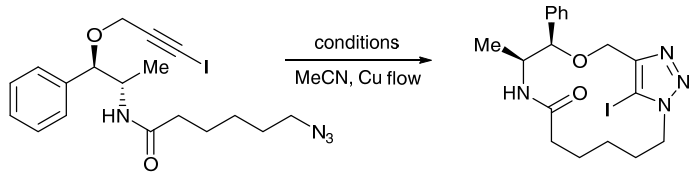


Figure 9. Reaction performed to determine optimal conditions for macrocyclization.

Bogdan and James illustrated that larger macrocyclic rings exhibited a significant amount of deiodination, yielding amounts of the proteotriazole, which could result from competition between the rate of deiodination and slower rate of macrocyclization for larger rings. As well, differing levels of atropisomerism were observed dependent upon the ring size and strain within the larger macrocycles, with smaller, more strained macrocycles, resulted in a single product, due to the triazole ring's inability to freely rotate within the macrocycle. A mix of atropisomers was observed for slightly larger macrocycles, while 22 membered rings showed no atropisomerism, due to little conformational strain. Both triazole conformers are formed, and at room temperature readily interconvert.

To illustrate the diversity of 5-iodo-1,2,3 triazoles in library synthesis, Bogdan and James also subjected three of the macrocycle products to palladium catalysed cross coupling reactions. This reaction is the first example of a macrocyclization strategy that allows for the synthesis of a regiocontrolled trisubtituted triazole ring[27]. 1,2,5-trisubstituted-1,2,3 triazole macrocycles were obtained in high yields (68, 83 and

77%).

Bogdan et al. (2011) had also investigated the effects of ring size on the synthesis of strained cyclophane macrocycles, as well as their structure[28]. Macrocyclizations are usually performed under high dilution conditions (<1mM), and hence are inefficient due to high consumptions of solvent and long reaction times[10]. The synthesis of these drug-like macrocycles was performed via an intramolecular CuAAC reaction under flow, in Cu-tubing. This protocol allows for macrocycles to be prepared in good yields under reasonable dilution conditions, and has been successful in the synthesis of macrocycles as large as 29-membered rings. Similar to previous studies, this reaction will generate a 1,4-disubstituted 1,2,3 triazoles. The authors investigated macrocycles containing 10-14 membered rings in terms of their structural properties, as well as lower limit of the macrocycle ring size that is accessible using this methodology. The authors presume that the lower limit would depend on the substitution pattern of the ring, which would be incumbent on the strain present in the macrocycle, at which the strain is great enough to reduce macrocyclization rates compared to dimerization[28].

Most of the macrocycles synthesized were based on the homochiral (1*R*, 2*S*) ephedrine fragment. The scheme used for synthesis is illustrated in figure 10. The only deviations the authors had made were in which 10-membered system synthesized had the azido group introduced at the last step. The synthesis of an 11-membered system required a diazo-transfer system due to problems with β-elimination. The authors used X-ray crystallography for structure determination and revealed that an increased level of distortion within the structure resulted in an increase in strain energy.

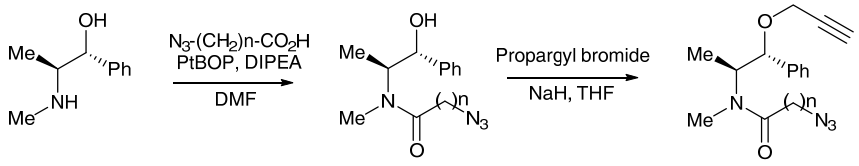


Figure 10. The synthetic route for macrocycle precursors (excluding 10-membered and 11-membered system).

The authors had explored the impact of ring size, stereochemistry, conformational constraint and macrocyclization efficiency on the yields of the macrocycles. With regards to ring size, a 90% yield was obtained for norephedrine macrocycle-1, representing a low strain system, in which both the triazole ring and amide bond are planar. The ephedrine derived 14 membered macrocycle was synthesized in 80% yield. The 11-membered macrocycle, representing a more strained system, was only synthesized with 20% yield, under more dilute conditions. The structure of each macrocycle is illustrated in figure 11. The calculated strain energy was found to be 7 kcal/mol greater compared to the 14-membered homologue. X-ray structure data revealed a 43˚ deviation from planarity in order to adjust to the higher strain. This molecule is the first the authors note to have been reported, containing the 1,4 disubstituted 1,2,3 triazole. The formation of a 10-membered macrocycle however proved unsuccessful, with strain energy calculated to be 25kcal/mol greater compared to the 14-membered homologue. The alkyne-azido substrates proceeded in a fashion, whereby less strained products were yielded[28].

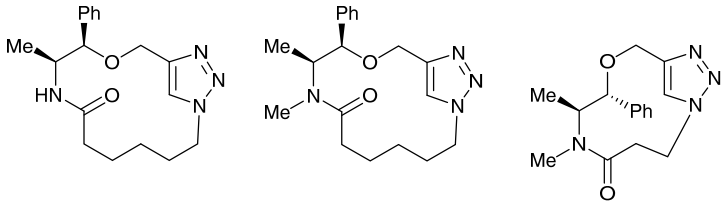


Figure 11. Macrocycles.

The authors explored the impact of stereochemistry by changing the configuration at a stereogenic center containing a methyl group, in a 12-membered ephedrine macrocycle (73% yield). Pseudopherdine macrocycle was synthesized in lower yields compared to its analogue (40%), figure 12.

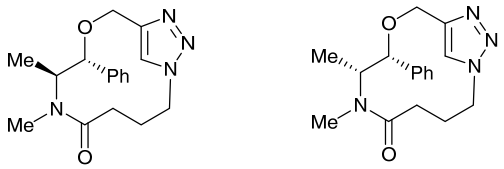


Figure 12. Ephedrine macrocycle and Pseudoephedrine macrocycle.

Given that the strain energy of the 12-membered macrocycle is low, the authors attributed the lower yield of pseudoephedrine macrocycle to a kinetic effect, in which the arrangement of the methyl, phenyl, azido, and alkynyl substituents in the linear precursor is less favorable in the formation of this macrocycle, compared to the ephedrine macrocycle.

In order to explore the impact of conformational constraint, the authors synthesized an additional macrocycle, with an *o*-(azidomethyl)benzoyl substituent in place of the azido alkynoyl moiety, as the macrocyclization precursor. This macrocycle was generated in lower yield compared to ephedrine macrocycle (nonbenzo-fused system), but did not appear more strained. X-ray structures illustrated that incorporating the ortho-benzene fused ring did not impact the macrocycle ring structure. However, incorporation of a *m*-bridged benzene did impact the ring structure greatly, as the *m*-(Azidomethyl)benzoyl macrocycle represents a 13-membered macrocycle, which was generated in low yield (35%).

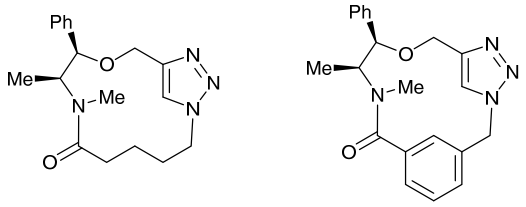


Figure 13. Macrocycles.

The average strain energy for *m*-(Azidomethyl)benzoyl macrocycle was found to be 7 kcal/mol higher compared to ephedrine macrocycle (66% yield), its non-bridged counterpart. The *m*-bridged macrocycle was found to have a large of amount of distortion in both the triazole ring and amide bond (>30^{o} deviation from planarity), as well as a lack of conjugation between the amide carbonyl and benzene ring, due

to rotation around (aryl)-C-(CO)C bond[28].

To determine the efficiency of macrocyclization, both the product-to-dimer ratios, observed using UV spectroscopy, as well as isolated yields obtained after chromatography. The authors found a correlation with average strain energy and structural distortion, which played a large factor in reaction outcome. Higher strain energy within the product and transition state results in the reaction proceeding along an intermolecular pathway, to form oligomer and dimer products. The authors determined that formation of cyclophane macrocycles via CuAAC macrocyclization would not likely proceed if strain energy of the product approached ~21 kcal/mol. In summary, strain energy was found to be highly correlated with yield[28].

3. Sonogashira C-C coupling

Zhang et al. (2010) published the first example of a Sonogashira coupling reaction using a copper flow reactor, without the use or need for palladium[29]. During the course of implementing this flow based reaction using the heated copper tube flow reactor (CTFR) without palladium, it was determined that solvent choice was an important factor in flow. DMF was found to be most appropriate, while CH_3CN, THF, EtOAc and EtOH resulted in precipitation and blockage within the system during the reaction. The authors then developed a protocol to synthesize arylalkynes (figure 14), which were synthesized in good yields (78-94%). However, when less reactive substrates such as bromobenzene or trimethylsilyl acetylene were used, catalytic amounts of palladium were still required.

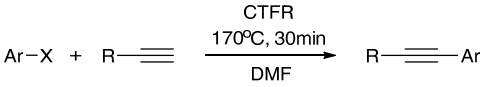


Figure 14. The synthesis of Arylalkynes.

A study by Tan et al. (2013) utilized a palladium-coated tubular reactor in conjunction with copper tubing to perform a Sonogashira C-C coupling reaction[30]. The advantages the authors outlined for their method are that the setup is easy to carry out, promoters are not required, only the leached amount of palladium is needed, and that any palladium that is leached can be removed with the copper reactor and metal scavenging resins present at the back end of the flow set up. After a number of catalytic cycles, performance is also maintained.

The reported Pd-Cu reactor was shown to utilize only a minimum amount of palladium, while providing easy access to a range of Sonogashira coupling products, with moderate to good yields under ambient conditions. Good conversions were shown with the initial set up when palladium catalyst was used with the copper reactor, with efficiency maintained at low catalyst loading. When the reaction was carried out with a palladium tubular reactor (i.e. No homogeneous palladium), only a 47% yield of product was obtained, which prompted the authors to place the palladium reactor in line with the copper reactor, in which the palladium reactor would provide enough leached palladium (3785ppb) to catalyze the Sonogashira reaction and afford quantitative conversions of product[30]. The sequence of the copper in the Pd-Cu dual reactor was important as low conversions were obtained when the order had been reversed, or when copper was absent. The authors proposed that the proximity between Pd and copper during transmetalation helps the palladium redeposit on the copper tubing.

The authors then proceeded with this methodology with a variety of iodobenzenes (see figure 15). It was determined that substrates with both electron-withdrawing and electron donating groups were able to afford diarylalkynes when coupled with terminal alkynes, with 40-98% yields. However substrates with electron-withdrawing groups were able to yield higher conversions, as it is easier for these substrates to undergo oxidative addition. The performance of the Pd-Cu dual reactor was maintained after 10 cycles.

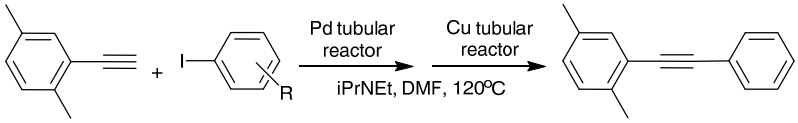


Figure 15. Reaction between iodobenzene derivatives and terminal alkynes to form diarylalkynes.

4. Ullmann couplings

Besides the click reaction and triazole synthesis, other reactions have illustrated the use of copper tubing as a reactor. Zhang et al. (2010) has reported the use of the copper tube flow reactor for both Ullmann and Sonogashira couplings (vide supra), as well as high temperature protiodecarboxylation reactions, in a single publication[29]. The Ullmann couplings were performed using several aryl halides and amines to form aryl/biaryl -N- containing compounds (see figure 16). These reactions were conducted in a copper tube flow reactor (CTFR), treated via circulated air to 150ºC using the Vapourtec R4 module[29]. With traditional methods, these reactions require high copper loading as well as long reaction times. Performing these reactions in flow eliminates these problems, with the added advantage of eliminating the need for additional catalysts and the Ullman couplings required no added ligands, when performed in flow. The authors first investigated the coupling of iodobenzene and benzylamine, which was achieved in the copper tube flow reactor without the addition of any catalysts or ligands, when tetra-n-butylammonium acetate (TBAA) was used as a base, and acetonitrile as a solvent. No product however was observed when a perfluoroalkoxyalkane (PFA) tube reactor was utilized, suggesting that copper was responsible for the catalysis of the reaction. The authors proceeded to apply the above protocol in the coupling of aryl halides and amines (figure 16) and utilized a 250psi backpressure regulator to ensure that acetonitrile could be heated above its boiling point safely, as well as, Quadrapure Thiourea (QP-TU) to remove trace amounts of copper that had leached from the reactor. It was found that TBAA, an organic ionic base was more effective compared to other commonly used bases. The coupling was illustrated to be successful as illustrated by the high conversion (82-100%) and yield (53-95%).

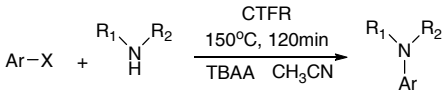


Figure 16. The synthesis of Arylamines

5. Decarboxylations

Use of the CTFR in protiodecarboxylation reactions of aromatic and heteroaromatic substrates was achieved at 250ºC without the addition of any catalyst, ligands or additives[29] (see figure 17), simply by passing the starting material through the

copper reactor. With these reactions, the formation of CO_2 at high temperatures raises safety concerns, especially when performed in batch. However performing the reaction in flow lowers these concerns as there is more control over the reaction, and smaller amounts of gas are generated.

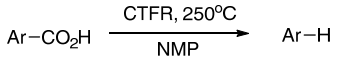


Figure 17. Protiodecarboxylation Reactions.

In order to illustrate the applicability of the copper flow system, Ceylan et al. (2010) also explored the catalytic decarboxylation of 2-alkynoic acids, as well as C-O coupling[19]. Continuous copper-catalysed decarboxylation of propargylic acids were found to progress smoothly with full conversion and very high isolated yields, >90%. In addition, the authors described a single example for the intramolecular copper-catalysed C-O coupling between a tethered arylbromide and benzoic acid to yield a benzopyranone in 95% isolated yield. It was found that when the reactions were performed in batch, no conversions were obtained. However when the reaction was run in the presence of equimolar copper(I)chloride and sodium carbonate in a flask, full conversion was found[19].

Conclusion

The utilization of copper flow reactors in 1,3 dipolar cycloadditions ('click' chemistry), macrocyclizations (via 'click' chemistry), Sonogashira C-C couplings, Ullmann couplings and decarboxylations has been successfully demonstrated. Performing these reactions in flow illustrates a number of advantages in comparison to their batch counterparts, in terms of both safety and reported yields. Although possible in batch, the flow reactions have shown to be vastly superior to their batch reaction counterparts, while some of the results have been shown to be possible only when performed in flow, through the ability to control reaction conditions such as flow rate, pressure and temperature. Copper flow reactors have also been proven to be versatile, as they can be utilized in different forms (ex. copper powder/turnings, copper tubing), as well as, be used in conjunction with other technologies available in organic synthesis (ex. ligands, 'Pd'). Mechanistically, the debate continues whether these reactions can best be described as being mediated via dissolved copper (homogeneous), or occurring on the surface of the copper metal (heterogeneous). It is clear, however, that copper must be present for these reactions to occur and a certain degree of leaching (dissolved copper) is observed as a by-product of these reactions. One publication in particular has addressed this question and concluded that for flow-based CuAAC reactions, when Cu/C catalyst is used, a homogeneous mechanism is likely in operation, while a heterogeneous mechanism involving surface layer Cu_2O is in operation when a zerovalent copper metal flow reactor are used[31]. In summary, copper flow reactors have become an efficient and effective tool in organic synthesis, and have been shown to be especially useful for 'click' chemistry reactions (CuAAC), among other reactions cited herein.

References

[a] *Address, Faculty of Pharmacy, University of Manitoba, Winnipeg, MB, Canada, R3E 0T5. Fax: 01 204 789 3744; Tel: 01 289 474 8358; E-mail:geoffrey.tranmer@umanitoba.ca*

[b] *Address, (Adjunct) Department of Chemistry, University of Manitoba, Winnipeg, MB, Canada, R3T 2N2.*

1 J. Wegner, S. Ceylan, A. Kirschning. *Adv. Synth. Catal.*, 2012, **354**, 17; T. Rodrigues, P. Schneider, G. Schneider. *Angew. Chem. Int. Ed.*, 2014, **53**, 5750; J.-I. Yoshida, A. Nagaki, D. Yamada. *Drug Discov. Today Technol.*, 2013, **10**, e53; and references cited therein.
2 I. R. Baxendale, J. Deeley, C. M. Griffiths-Jones, S. V. Ley, S. Saaby, G. K. Tranmer. *Chem. Commun.*, 2006, 2566; J. C. Pastre, D. L. Browne, S. V. Ley. *Chem. Soc. Rev.*, 2013, **42**, 8849.
3 C. Wiles, P. Watts. *Future Med. Chem.*, 2009, **1**, 1593; L. Matel-Sanz, F. Susanne. *J. Med. Chem.*, 2012, **55**, 4062; F. Levesque, P. H. Seeberger, *Angew. Chem. Int. Ed.*, 2013, **51**, 1706.
4 C. Wiles, P. Watts, *Green Chem.*, 2012, **14**, 38; D. Webb, T. F. Jamison, *Chem. Sci.*, 2010, **1**, 675; R. C. Wheeler, O. Benali, M. Deal, E. Farrant, S. J. F. MacDonald, B. H. Warrington. *Org. Process Res. Dev.*, 2007, **11**, 704.
5 For examples of commercially available flow chemistry systems, see: www.vapourtec.co.uk, www.uniqsis.com, www.thalesnano.com, www.syrris.com.
6 S. G. Newman, K. F. Jensen, *Green Chem.*, 2013, **15**, 1456.
7 J. Gerhard, A. Kirschning, *Chem. Eur. J.*, 2003, **9**, 5708.
8 C. F. Carter, H. Lange, S. V. Ley, I. R. Baxendale, B. Wittkamp, J. G. Goode, N. L. Gaunt. *Org. Process. Res. Dev.*, 2010, **14**, 393.
9 J. E. Moses, A. D. Moorhouse. *Chem. Soc. Rev.*, 2007, **36**, 1249; H. C. Kolb, K. B. Sharpless. *Drug Discov. Today*. 2003, **8**, 1128.
10 C. J. White, A. K. Yudin. *Nat. Chem.*, 2011, **3**, 509.
11 R. Chinchilla, C. Najera. *Chem. Soc. Rev.*, 2011, **40**, 5084.
12 J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire. *Chem. Rev.*, 2002, **102**, 1359; K. Kunz, U. Scholz, D. Ganzer. *Synlett*, 2003, 2428.
13 W. I. Dzik, P. P. Lange, L. J. Gooben. *Chem. Sci.*, 2012, **3**, 2671; J. Cornella, I. Larrosa. *Synthesis*, 2012, **44**, 653.
14 Examples such as: C. A. Correia, D. T. McQuade, P. H. Seeberger. *Adv. Synth. Catal.*, 2013, **355**, 3517.
15 M. Thathagar, P. Poechlauer, S. Braune. *PCT Int. appl.*, **2010**, WO/2010/055106.
16 A. R. Bogdan, N. W. Sach. *Adv. Synth. Catal.*, 2009, **351**, 849.
17 S. G. Agalave, S. R. Maujan, V. S. Pore. *Chem. Asian J.*, 2011, **6**, 2696; S. K. Mamidyala, M. G. Finn. *Chem. Soc. Rev.*, 2010, **39**, 1252.
18 G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba, A. A. Genazzani. *Med. Res. Rev.*, 2008, **28**, 278, and original references cited therein.
19 S. Ceylan, T. Klande, C. Vogt, C. Friese, A. Kirschning. *Synlett*, 2010, 2009.
20 L. Kupracz, J. Hartwig, J. Wegner, S. Ceylan, A. Kirschning. *Beilstein J. Org. Chem.*, 2011, **7**, 1441.
21 S. B. Otvos, I. M. Mandity, L. Kiss, F. Fulop. *Chem. Asian J.*, 2013, **8**, 800.
22 N. P. Tu, J. E. Hochlowski, S. W. Djuric. *Mol. Divers.*, 2012, **16**, 53.
23 M. M. E. Delville, P. J. Nieuwland, P. Janssen, K. Koch, J. C. M. van Hest, F. P. J. T. Rutjes. *Chem. Eng. J.*, 2011, **167**, 556; B. Gutmann, D. Obermayer, J.-P. Rodiut, D. M. Roberge, C. O. Kappe. *J. Flow Chem.*, 2012, **2**, 8.
24 S. B. Otvos, A. Georgiades, I. M. Mandity, L. Kiss, F. Fulop. *Beilstein J. Org. Chem.*, 2013, **9**, 1508.
25 S. B. Otvos, G. Hatoss, A. Georgiades, S. Kovacs, I. M. Mandity, Z. Novak, F. Fulop. *RSC Adv.*, 2014, **4**, 46666.
26 A. R. Bogdan, K. James. *Chem. Eur. J.*, 2010, **16**, 14506.
27 A. R. Bogdan, K. James. *Org. Lett.*, 2011, **13**, 4060.
28 A. R. Bogdan, S. V. Jerome, K. N. Houk, K. James. *J. Am. Chem. Soc.*, 2012, **134**, 2127.
29 Y. Zhang, T. F. Jamison, S. Patel, N. Mainolfi. *Org. Lett.*, 2011, **13**, 280.
30 L. Tan, Z. Sem, W. Chong, X. Liu, Hendra, W. L. Kwan, C-L. K. Lee. *Org. Lett.*, 2013, **15**, 65.
31 M. Fuchs, W. Goessler, C. Pilger, C. O. Kappe. *Adv. Synth. Catal.*, 2010, **352**, 323.