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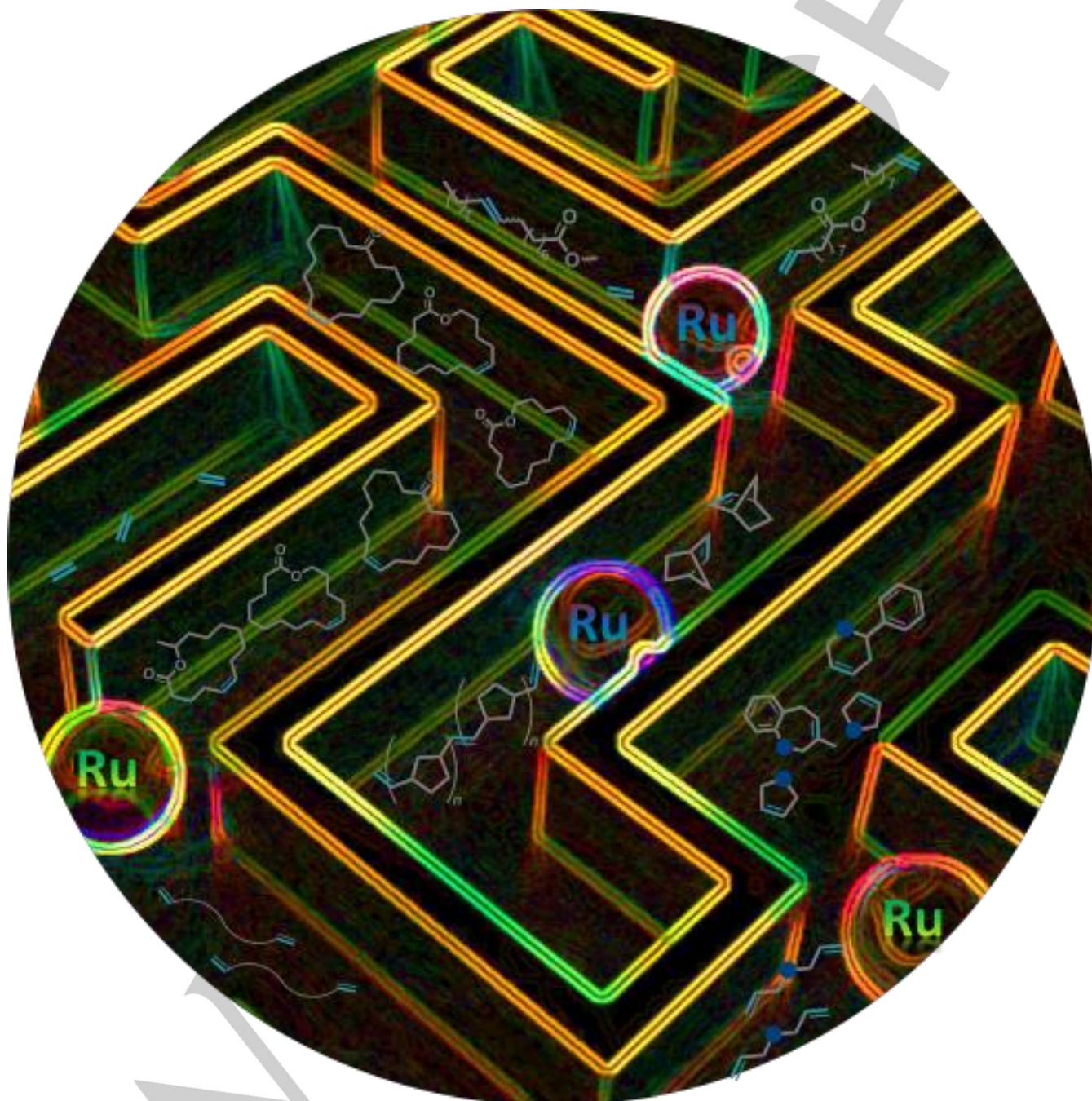
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Challenges Arising from Continuous Flow Olefin Metathesis

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and Marc Mauduit^{*,[a]}



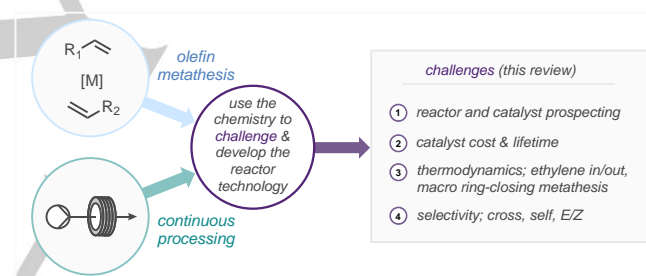
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Abstract: The versatility of olefin metathesis is evident from its successful applications ranging from natural product synthesis to the valorization of renewable feedstocks. On the other side, flow chemistry has recently gained particular interest among the synthetic community, offering valuable alternatives to classic batch chemistry and paving the way to the development of new transformations. The application of continuous flow to olefin metathesis represents one of the most promising evolutions in the field at the interface of industrially relevant synthesis and reactor engineering, significantly improving some of the typical problems such as undesired self-reactions and ethylene-mediated catalyst de-activation. This review aims to provide a small survey covering the major aspects of those techniques which we hope may be of interest for the chemical community, but also those interested in catalysis, continuous processing, enabling technologies and reactor design.

Introduction

Olefin metathesis has revolutionized the way that synthetic chemists plan and implement the construction of molecules, including natural products, fragrances, polymers and the valorization of waste streams. With the discovery of ever more active catalysts, the selective formation/cleavage of C–C bonds can be achieved in the presence of ppm levels of metal. Continuous flow processing represents a promising technology for the rapid delivery, at scale, of the molecules now accessible by alkene metathesis. Over the last 10-15 years these two fields have developed together, with the chemistry of olefin metathesis serving as a challenge to drive the exploration, creativity and miniaturization of innovative flow chemical reactor designs (Scheme 1).^[1,2] As part of this development there have been interesting dead-ends and detours *en route* to meet the challenges posed by this exciting chemistry. This review takes a look at the current state-of-the-art and retrospectively identifies the key challenges that have emerged from the collection of literature. To date, the key challenges are 1) establishing that continuous flow processing can be used for olefin metathesis by prospecting the pros and cons of different reactor designs; 2) Cost of catalyst – can continuous processing permit effective immobilization so that a single ‘shot’ of catalyst can be effectively used to turnover more material than a batch reactor? 3) Thermodynamics – metathesis is an equilibrium process which can be driven to the favorable end point, this is typically achieved by either removal/introduction of ethylene; a key challenge here lies in macro-cyclic ring closing metathesis (RCM); 4) Selectivity –

there are several selectivity issues that may arise, including cross-, self- and ring closing as well as controlling *E/Z* alkene geometry. This review will briefly describe progress thus far at the intersection of these fields. We have broken the review down into the aforementioned challenges, not following necessarily the chronological representation of the literature reports, whereby typically the complexity of the reactor systems, and to some extent, the catalyst increases. It is noteworthy that many of the papers cited here represent collaborative efforts between organic chemists (methodologists, catalyst designers) and flow chemists or reactor engineers.



Scheme 1. exploring the synergistic development of continuous processing reactor technologies for olefin metathesis.

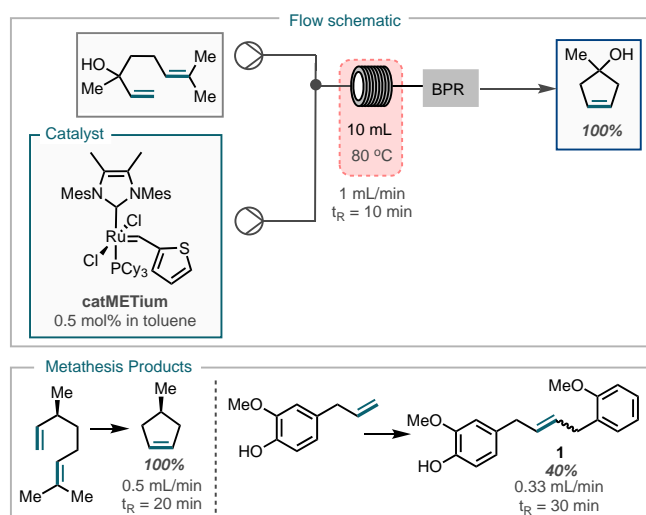
1. Challenge One - Demonstrating Continuous Flow Metathesis

Early efforts at the interface of olefin metathesis and continuous flow processing looked to establish that simple cross metathesis (CM) or small-ring closing metathesis (RCM) was feasible. To this end, a rudimentary flow system would bring together a flowing stream of reagents and a catalyst at a mixing-tee prior to proceeding through a residence coil or reactor chip. Heating of the chip may be used to increase reaction rates and reduce residence times.

1.1. Residence coil and reactor chip systems

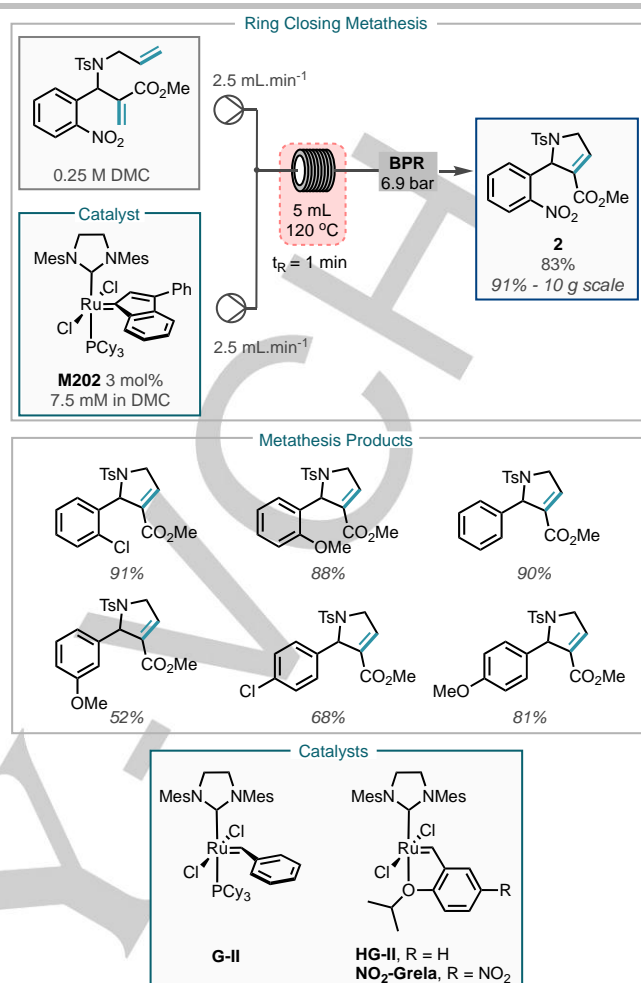
In 2016 Leadbeater and coworkers developed a simple flow procedure for the RCM of linalool and citronellene using two pumps, a coiled tubular reactor and a back-pressure regulator.^[3] After optimization in batch conditions, it was found that a solution of the linalool and 0.5 mol% of catMETium® in toluene were passed through a 10 mL coil heated at 80 °C with a flow rate of

1 mL/min (residence time, t_R , of 10 minutes) providing the cyclization product in quantitative yields, with release of isobutene as byproduct. A t_R of 20 minutes was necessary for the RCM on citronellene. On the other hand, a more challenging self-metathesis (SM) of eugenol provided **1** with 40% conversion even when increasing the t_R to 30 minutes, likely due to the formation of ethylene by-product, which is known to inhibit the catalytic process (Scheme 2).



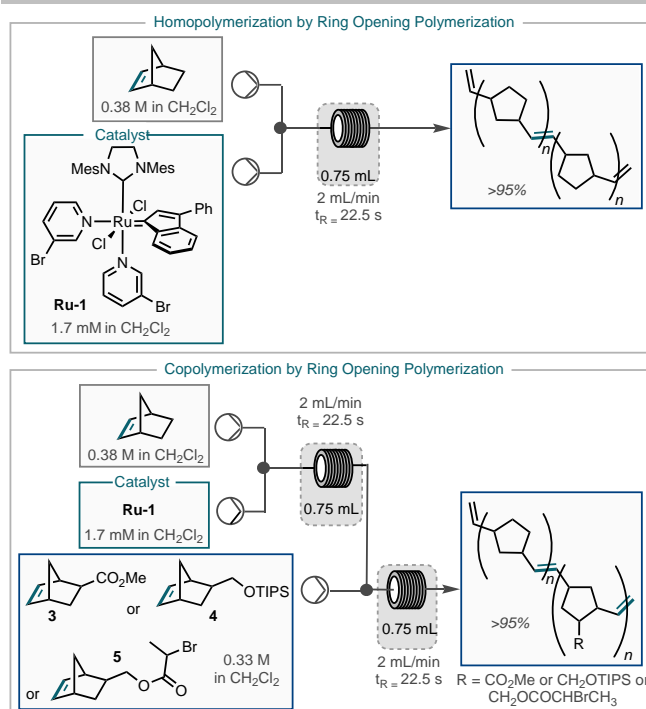
Scheme 2. continuous flow RCM and SM on linalool, citronellene and eugenol.

In 2017 the group of Lamaty reported a flow RCM protocol for the preparation of 2,5-dihydro-1H-pyrrole-3-carboxylates, a family of versatile building blocks for the synthesis of biologically active compounds.^[4] For this purpose, a solution of the diallyl substrate and catalyst were injected at a flow rate of 2.5 mL/min⁻¹ through a T-shaped mixer and then through a 5 mL PTFE coil reactor heated at 120 °C with a t_R of 1 minute. The corresponding cyclized product **2** could be obtained in 83% yield. Notably this process employed dimethyl carbonate (DMC) as solvent, which is classified as non-toxic for the industrial synthesis of APIs.^[5] Among the catalysts screened, the catalyst **M202** proved most promising against **G-II**, **HG-II** and **NO₂-Grela**, assuring quantitative conversions with lower catalytic loading and residence times. The robustness of the method could be demonstrated with the preparation of differently substituted derivatives. Additionally, scaling up the protocol to 10 gram scale, keeping the same t_R of 1 minute, delivered **2** with 91% yield (Scheme 3).^[6]



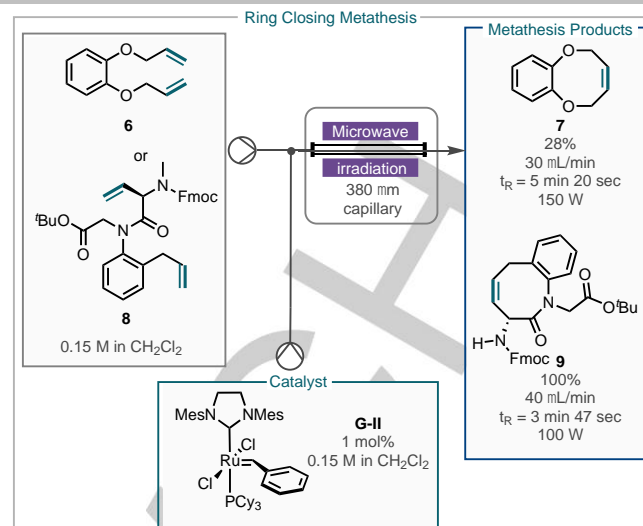
Scheme 3. synthesis of pyrrole derivatives via continuous flow RCM.

An example of how flow techniques can be applied to the ROMP (Ring-Opening-Metathesis Polymerization) was reported by Hobbs and coworkers in 2019.^[7] The authors developed a method for the homo and co-polymerization of monomers via ROMP under flow conditions, by means of a PTFE tubing system. After the initially encountered problems of viscosity, the homo-polymerization of norbornene could be carried out with quantitative conversion in the presence of a modified Grubbs 3rd generation catalyst **Ru-1**. ROMP of the protected species **3**, **4** and **5** led to higher dispersions and lower yield, especially for the polymerization of **5**, presumably due to the coordination of oxygen to the ruthenium. The problem was partially overcome by increasing the flow rate, leading to a reduction of the retention time (t_R). With the addition of another T-piece the system could be implemented for the preparation of block copolymers, allowing the sequential injection of norbornene and the other monomers at different concentrations (Scheme 4).



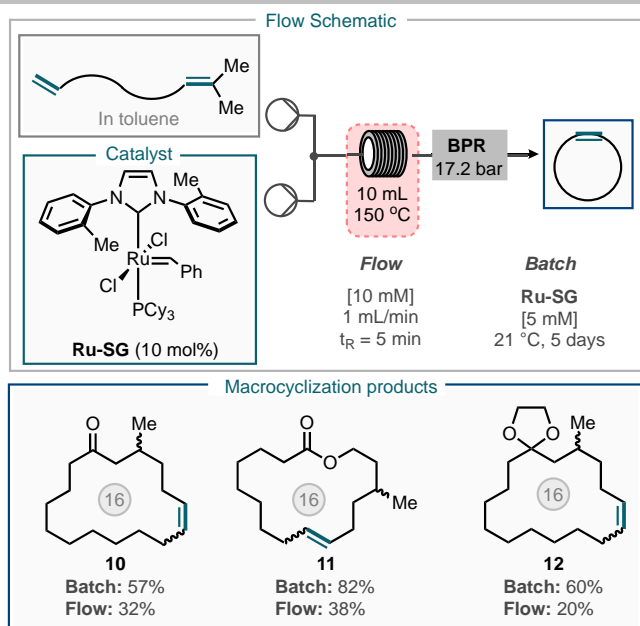
Scheme 4. continuous flow for homo and copolymerization of norbornene derivatives via ROMP.

Microchannel reactors, also called “lab-on-a-chip” microreactors, consist of a “credit-card”-sized series of interconnecting channels, typically of a diameter ranging from 50 to 500 μm constituted of glass or other materials.^[8] Such devices can be coupled with other technologies such as microwave (MW) apparatus in order to enhance the efficiency of some chemical processes. As further demonstrated by Mauduit, Grela and Couve-Bonnaire, MW irradiation represents also a clever escamotage to enhance the catalytic performances for challenging olefin metathesis transformation.^[9,10] The group of Organ developed a pioneering RCM procedure based on a microwave assisted-microreactor flow procedure. Under these conditions, 28% of substrate **6** could be converted, in the presence of 1 mol % of **G-II** catalyst, into the corresponding cyclic product **7** in 5 minutes and 20 seconds, against the 16 hours normally required for a batch approach. Reacting amide substrate **8** under the same conditions led to full conversion to the desired ring closed product **9** within 3 minutes and 47 seconds only, showing a clear improvement compared to the batch conditions, were the reaction conducted for the same time, provided only 30% conversion (Scheme 5).^[11]



Scheme 5. “Lab-on-a-chip” approach for RCM.

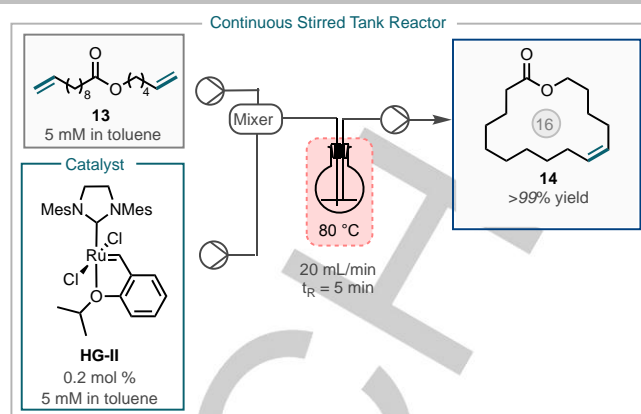
The group of Collins explored the macrocyclization of long-chain dienes for the synthesis of macrocyclic musks, a highly demanded class of compounds in the fragrance industry.^[12] Under optimized batch conditions involving 3 mol % of the Stewart-Grubbs catalyst (**Ru-SG**), the product of macrocyclization **10** could be obtained in 57% isolated yield, after 17 hours (Scheme 6). A translation to continuous flow was investigated. For this purpose, separate streams of the macrocyclic precursors and catalyst were pumped at a flow rate of 1 mL/min into a T-shaped mixer before flowing through a 10 mL ($t_R = 5$ minutes) heated stainless-steel coil reactor at 150 $^{\circ}\text{C}$, providing **10** with 32% isolated yield. Terminal olefins and acetal-derivatives did not demonstrate higher reactivity and the respective macrocyclization products **11** and **12** were obtained with 38% and 20% yield respectively. Notably here, the challenge of thermodynamics of the macro-RCM chemistry was not met with a reactor design to support the removal of ethylene gas. Without sufficient removal of ethylene gas there is increased potential for the catalyst to degrade, which can be expedited at higher reaction temperatures. This is an important demonstration at the interface of metathesis and flow as it identifies a challenge.



Scheme 6. continuous-flow synthesis of Macrocyclic Musk derivatives.

1.2. Continuous Stirred Tank Reactor (CSTR)

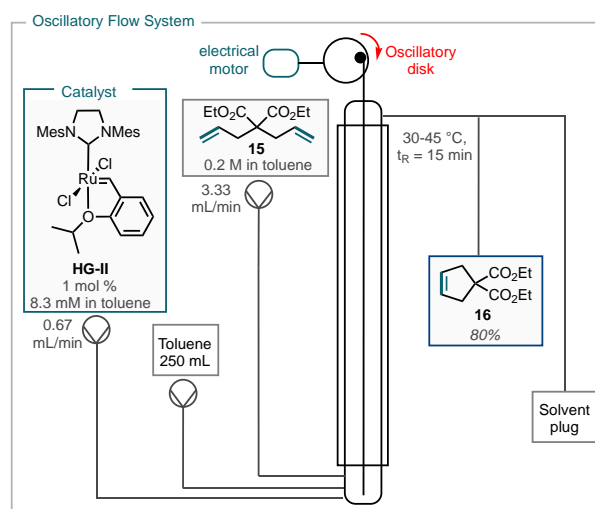
In 2010 the group of Fogg applied the use of a Continuous-Stirred-tank-Reactor (CSTR) for the RCM of macrocycles.^[13] From a practical point of view, the apparatus consists of two input reservoirs containing solutions of the substrate and the catalyst respectively, these are pumped through a micromixer into a reactor which is continuously flushed with argon to keep a low concentration of ethylene. Finally, the mixture can be transferred out and quenched, typically such systems are continuously fed with material at the same rate that they are drained and in such a way to maintain a steady-state process within the CSTR. Notably, in this particular case, it was possible to work at a higher concentration (20 mM) for a macrocyclization process, whilst maintaining good selectivity of RCM over SM. Under this protocol, macrocyclic precursor substrate **13** could be cyclized quantitatively into the Exaltolide fragrance intermediate **14** in the presence of 0.2 mol % of HG-II. The reactant solutions were flowed at a rate of 5 mL/min through a Teflon® tube connected to a micromixer, prior to collection into the stirring tank, held at 80 °C. A second pump forces out the solution into a collecting flask containing a quenching solution. This second transfer occurs through another Teflon® tube, with a flow rate of 40 mL/min, ensuring a constant volume of 5 mL into the tank. The hybrid methodology showed superiority compared to both a more traditional batch approach and a plug-flow reactor, being able to provide the macrocyclization product with lower catalytic loading (Scheme 7).



Scheme 7. continuous-Stirred-tank-Reactor (CSTR) technology for the RCM of macrocycles.

1.3. Oscillatory flow system

In 2011 the group of Bjørsvik introduced the Multijet Oscillating Disk Reactor (MJODR) for meso scale flow processes.^[14] A key advantage of working with oscillatory reactors is the intense mixing, which is provided by the presence of oscillating baffles. The movement of such an oscillating reactor can be likened to a piston. As a consequence, it is possible to increase the t_R without modifying the flow rate. When the mixture is pumped into the reactor, the naturally occurring vortex mixing is amplified by the activity of the oscillating disk, which moves along the longitudinal section of the reactor. A system of valves avoid the mixtures to come back to the reservoirs ("back-kick"). In this way, the mixing remains efficient, as demonstrated by the quantitative conversion of diethyldiallylmalonate **15** into the corresponding cyclopentene product **16**. The RCM was performed by separating the solutions of substrate and the HG-II catalyst (1 mol % loading) into different reservoirs, pumped at different rates into the reactor (3.33 and 0.67 mL·min⁻¹ respectively), which was heated to 30 °C, while the oscillation system was run at 1.6 Hz. The product could be obtained with 80% yield with a t_R of 15 minutes (Scheme 8).



Scheme 8. oscillatory flow system for RCM.

2. Challenge two – Getting More From the catalyst

Having described contributions that establish that continuous processing can be used for metathesis chemistry we now focus on those systems that have tried to address immobilisation of the catalyst. One of the key drivers for exploring alternative techniques and reactors is the potential to reduce costs and intensity of a process, both from the perspective of manual handling steps but also input materials.

2.1. Supported Heterogeneous catalysts

The great advantage of using heterogeneous systems resides in the opportunity to filter off the catalyst and eventually re-use it for further runs. In this regard, packing the catalyst in a fixed bed or cartridge and flowing the desired substrates through to get the final product, may be seen as a natural evolution from traditional batch heterogeneous catalysis. One particular problem with preparing a heterogeneous catalyst bed is ensuring homogenous packing and ensuring that the bed doesn't crack under pressure of the flowing solution, this is relatively easy to achieve on meso-scale but can be more of a challenge on much larger packed-bed. Cracked packed-bed reactors can lead to 'channeling' where the material passes through the reactor without sufficient and intended exposure time to the catalyst. In addition, the recovery of undesired traces of metal in the collected fractions (leaching) represents a notable problem that has been explored by a number of methods, including the development of more efficient immobilization techniques, playing on catalyst modification and/or type of support and inline scavenging. For olefin metathesis some highly active catalysts also require access to precious metals and ligands. In the previous section the idea of increasing reaction temperatures in pressurised flow systems has been explored to increase TON. This section will describe progress in this area. Supported catalysts offer great promise both for recycling of catalysts (especially precious metals and ligands) and simplified purification of reaction mixtures.^[15] However, realising this promise is a difficult task and has been met with many creative avenues for exploration. The key issues are immobilising the catalyst, monitoring leaching and avoiding/minimising poisoning of the catalyst. Indeed, failure to meet some of these challenges can result in a process resembling an over-elaborate homogenous approach, but nonetheless, exploring these hypotheses and ideas is part of the broader scientific endeavour. Immobilisation of ligated metathesis catalysts generally falls into two strategies. Strategy one features covalently binding the ligand to the support and then introducing the metal, this can be achieved by either incorporating suitable ligand fragments into the fabrication of the support material itself, or by post-modification of the support material to append a ligand structure. This strategy may well result in supported catalyst materials that are less likely to leach, but could be more difficult to synthesise and less flexible for performing effective catalysis. Strategy two features immobilisation through non-covalent interactions such as by ion pairing, typically this strategy is easier to achieve and may lead to more active catalysis but may also result in increased leaching as competing ionic materials or impurities can cause ion exchange and release of the non-covalently bound species (Figure 1).

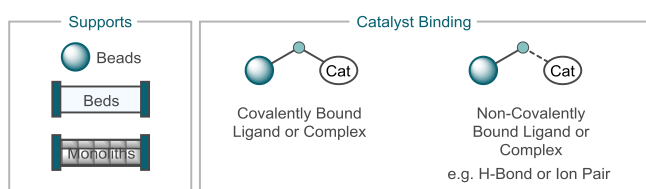
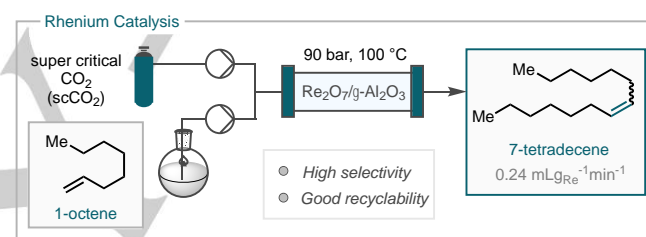


Figure 1. catalyst binding and supports.

2.1.1. Alumina Support

In 2012, Maschmeyer and co-workers developed a continuous flow procedure for the self-metathesis of 1-octene in the presence of Re_2O_7 impregnated on $\gamma\text{-Al}_2\text{O}_3$ using super critical CO_2 (scCO_2) as a carrier (Scheme 9).^[16] After optimisation of flow parameters, the reaction proceeded with very good self-metathesis selectivity (>90%) and an average productivity of 7-tetradecene of $0.24 \text{ mLg}_{\text{Re}}^{-1}\text{min}^{-1}$. The authors note that the catalyst was completely deactivated after the first 100-150 min of processing, likely due to slow poisoning of the rhenium catalyst due to build-up of oligomers as well as the reductive elimination of a metallacyclobutane intermediate, the system could be recycled for at least five subsequent runs without the loss of performance. Interestingly the use of scCO_2 was shown to be superior to conventional liquid carriers such as toluene or hexane and considerably extends catalyst life by improving and restoring catalyst performance.



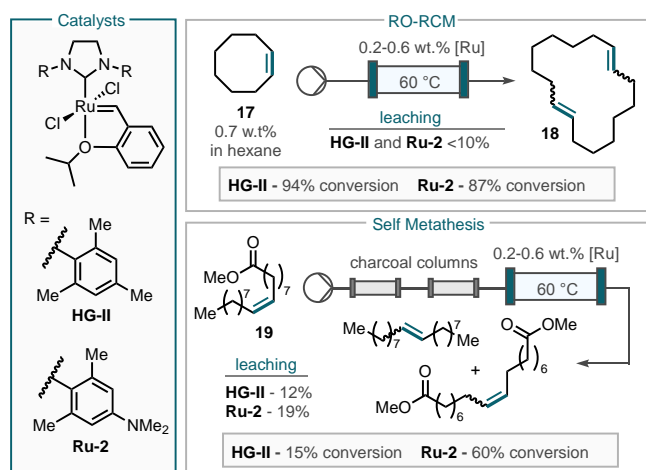
Scheme 9. rhenium Catalyzed Cross Metathesis.

2.1.2. Silica supports

2.1.2.a. Non-functionalized Supports

In 2012 Limbach and co-workers, prepared a range of heterogenized olefin-metathesis catalysts consisting of ruthenium complexes adsorbed onto a silica support (Scheme 10).^[17] Inductively coupled plasma-mass spectrometry (ICP-MS) analysis revealed that all but one of the complexes showed very strong affinity to 60A-Acros silica (<1% of initial Ru content was detectable in the filtrate) and were immobilized by simple mixing and removal of solvent. Split tests were also performed to ensure the catalysts acted as truly heterogeneous species and catalysis was not due to homogenous species that had desorbed from the silica support. The evaluation of the catalyst's potential was determined using the RO-RCM of *cis*-cyclooctene (**17**) which represents one of the shortest routes to macrocyclic skeletons (**18**).^[18] A solution of 0.7 wt.% **17** in cyclohexane was pumped at 60 °C through a cylindrical steel reactor that was charged with the Ru-impregnated silica materials (0.2-0.6 wt.%) as well as a benchmark material derived from the **HG-II** complex and a classical heterogeneous metathesis catalyst, $\text{Re}_2\text{O}_7/\text{B}_2\text{O}_3$ on silica. In terms of lifetime and activity, material **HG-II** and material **Ru-2**, which contained an analogous complex with an $\text{H}_2\text{I}^+\text{Tap}$ ligand, showed the best performance (94% and 87% conversion respectively). The authors note that leaching of <10% was determined by ICP-MS. **HG-II** and **Ru-6** were further studied in the self-metathesis of methyl oleate **19**, a more polar substrate with greater potential of leaching. Guard beds contain-

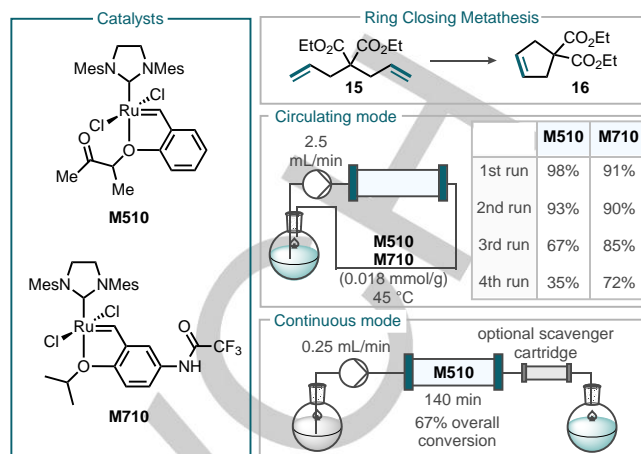
ing charcoal (2 x 20 g, Norit A Supra) were installed to absorb trace peroxide impurities from the commercially available starting material which could act as catalyst poisons. Both materials, **HG-II** and **Ru-2** showed significant leaching (12% and 19% respectively). Despite the greater leaching, the catalytic activity of **Ru-2** over 24 h was significantly higher than **HG-II**, 60% and 15% conversion respectively. Finally, all the materials derived from an organometallic pre-complex performed substantially better than the classical state-of-the-art heterogeneous Re_2O_7 catalyst in both the RO-RCM of **17** as well as self-metathesis of methyl oleate **19**.



Scheme 10. silica immobilised Catalysts for Ring-Opening Ring-Closing Metathesis and Self Metathesis.

In 2013 Kirschning and co-workers developed a procedure utilizing silica immobilized Hoveyda type pre-catalysts for batch and continuous flow olefin metathesis.^[19] Two pre-catalysts, Umicore **M510** and Umicore **M710** (Scheme 11) were studied in detail, both containing a chelating aryloxide alkylidene unit previously shown to have an affinity to silica. Both catalysts, immobilized by physisorption by simply shaking with silica, showed good activity in model batch reactions for RCM, cross (CM) and enyne metathesis (99% conversions, >96% yields). The application to flow chemistry was then demonstrated by loading the immobilized catalyst into a flow reactor (loading of **M510** or **M710** = 0.018 mmol/g) and a solution of diethyl diallylmalonate **15** in hexane was pumped through in a circulating mode at a flow rate of 2.5 mL/min and heated to 45 °C. Both catalysts showed good activity across multiple runs. Pre-catalyst **M510** gave 98% and 93% conversion after 1 hour for the first two runs respectively, 67% for the 3rd run but only moderate activity for the 4th run. The more robust pre-catalyst **M710** gave conversions of 91-72% over the first four runs. The performance of pre-catalyst **M510** was then tested without recirculation. High initial conversions (90% at 0.5 mL/min and 98% at 0.25 mL/min) were observed which steadily decreased over time due to deactivation and catalyst leaching. Ruthenium contamination was therefore examined in the metathesis products. For RCM, leaching of ruthenium under continuous flow conditions was negligible (<0.01%) when the process is performed in hexane due to the metathesis process occurring on the surface of the silica. For enyne metathesis, where more polar solvents are needed such as toluene, substantial contamination of enyne products occurred (320 ppm). However, the use of a QuadraSil AP scavenger cartridge (a packed silica column grafted with aminopropyl

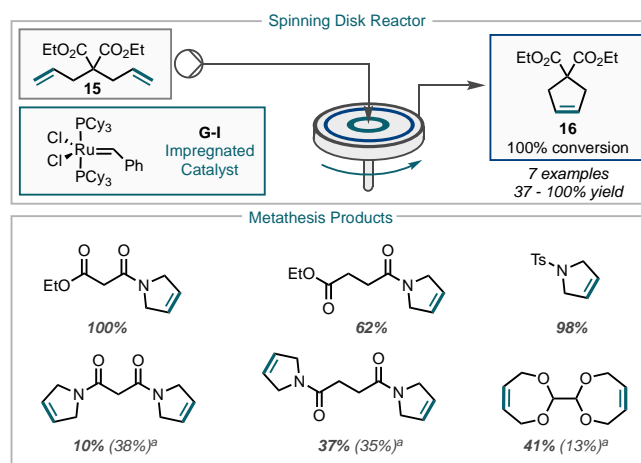
groups) was found to be effective in reducing the contamination to 0.26 ppm.



Scheme 11. silica-supported Hoveyda Type Pre-Catalysts in Flow.

The spinning disk reactor (SDR) was first developed in the 1930's by Kenneth Hickman.^[20-22] SDRs are mainly used in process intensification technology for polymer and particle chemistry, where they generate a sheared liquid film (ca. 10-200 nm) by applying a liquid to the centre of a heated disk which spins at around 1000 rpm. The centrifugal force thins the liquid as it flows over the rotating surface and permits both rapid mixing of reagents (including gasses), and short residence times (typically 1-5 seconds) and significantly improved mass and heat transfer.^[23]

Looking to harness these attributes for a continuous metathesis process Hearn and co-workers developed an SDR which uses a glass disk loaded with porous silica which was impregnated with **G-I** catalyst to perform ring closing metathesis when the reactants flow across the surface (Scheme 12).^[24] In addition, the reaction products could be easily and concomitantly separated by simple *in situ* solvent elution methods. Good to excellent yields were observed for all examples with mixtures of both single and double metathesis products shown for examples with two bis-allyl groups. This solvent-lean process permitted easy separation of starting materials and products by using the inherent polarities of each compound. Leaching from the silica hosted support material was also reported to be avoided with the use of this modified SDR system.

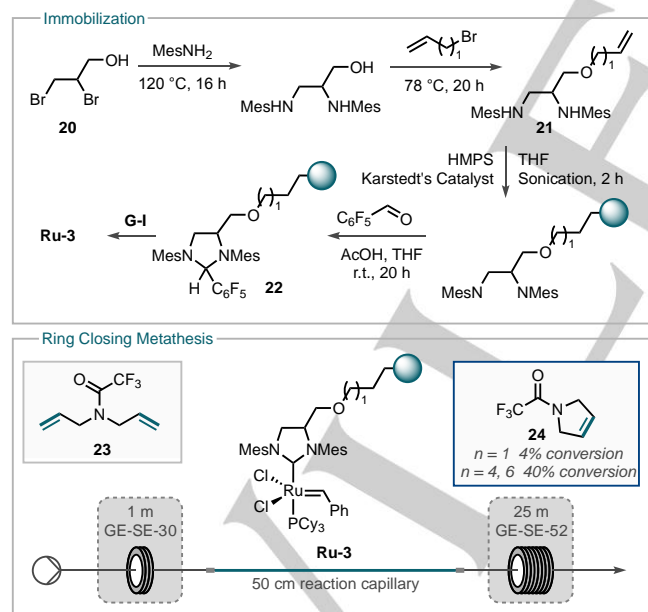


^a single metathesis products

Scheme 12. ring closing metathesis using Spinning-Disk technology.

2.1.2.b. Functionalised Supports

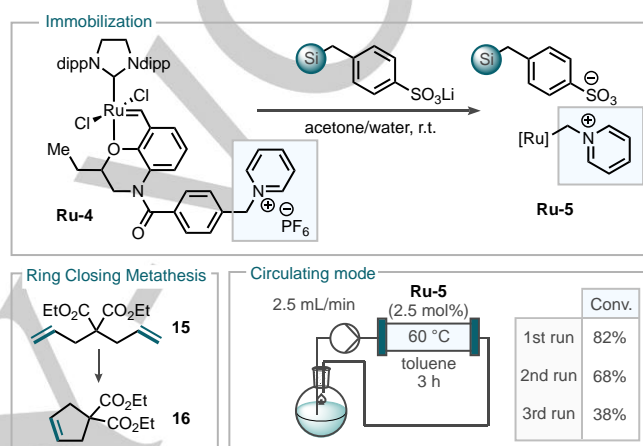
In 2014 Trapp and co-workers developed an advanced synthetic protocol for the covalent immobilization of **G-II** catalyst onto the inner surface of fused silica capillaries.^[25] This offered the opportunity for kinetic characterization of catalytic reactions, in particular for NHC-carbene ligands, which often require many synthetic steps to prepare enough material for classical reaction screening. A robust synthetic procedure was developed to produce the silica fused immobilized precursor from commercially available 2,3-dibromo-1-propanol (**20**) (Scheme 13). After reaction with 2,4,6-trimethylaniline and an ω -bromoalkene the resulting modified amine **21** was reacted with hydridomethyl dimethyl polysiloxane (HMPS) using Karstedt's catalyst. This could then be loaded onto a fused silica capillary and flushed with pentafluorobenzaldehyde to give the imidazolidine **22**, which could be flushed with **G-I** to undergo ligand exchange to obtain the immobilized catalyst (**Ru-3**). With the immobilized catalyst in hand, the influence of the linker length was investigated by studying the metathesis reaction of *N,N*-diallyltrifluoroacetamide (**23**). The catalytically active 50 cm column was installed between a pre-separation and a separation column in the GC/MS allowing for *in situ* reaction monitoring of the RCM reaction. Linker lengths of $n = 1, 4$ and 6 were examined at increasing temperatures and a maximum of 40% conversion into **24** was observed at 80 °C with $n = 4$ and at 60 °C with $n = 6$. In contrast, poor conversions of less than 5% were observed when $n = 1$. Stable reaction measurements over a period of 24 h were reported as well as a wide temperature range of up to 150 °C. Quantifying the amount of leaching of the catalyst from the silica capillary was not reported.



Scheme 13. immobilised Grubbs II Catalyst in Flow-Through Devices.

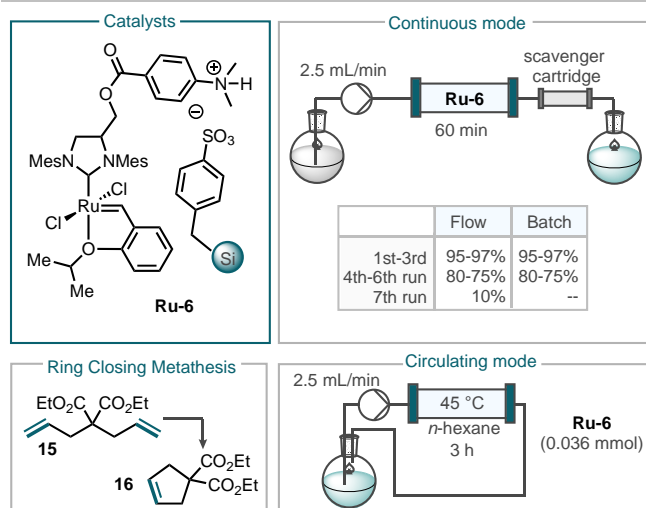
In 2012 Mauduit, Kirschning and co-workers designed and anchored a new pyridinium-tagged Ru complex onto sulfonated silica, creating a highly active and robust olefin metathesis precursor for use under both batch and flow conditions.^[26] Ru complex **Ru-4** (dipp = 1,6-diisopropylphenyl) was designed to incorporate a pyridinium motif and was synthesised on large scale over 5 steps prior to immobilisation by ion exchange yielding pre-catalyst **Ru-5** as a dark green powder with a loading of 0.009 mmol/gram (Scheme 14). A circulating flow process was

devised as catalyst **Ru-5** demonstrated good reactivity and reusability when tested with RCM, CM and enyne substrates in batch (70 – 88% yields). For flow, a solution of diallylmalonate **15** in hexane was circulated at a high flow rate of 2.5 mL/min through a reactor packed with **Ru-5** (111 mg, 2.5 mol%) at 45 °C. Unfortunately, the RCM efficiency could not match batch conditions with a conversion of 68% into **16** observed after 6 hours. Varying the solvent to CH_2Cl_2 decreased conversion, however toluene showed an increased conversion of 82% after three hours, 68% on a second run and 38% on a third. Furthermore, the flow conditions showed similar ruthenium leaching to batch conditions with the first run giving the highest levels of ruthenium contamination, hence it was deemed that the recyclability of precatalyst **Ru-5** was insufficient for continuous flow processing.



Scheme 14. immobilised Pyridinium Tagged Ru-Complex.

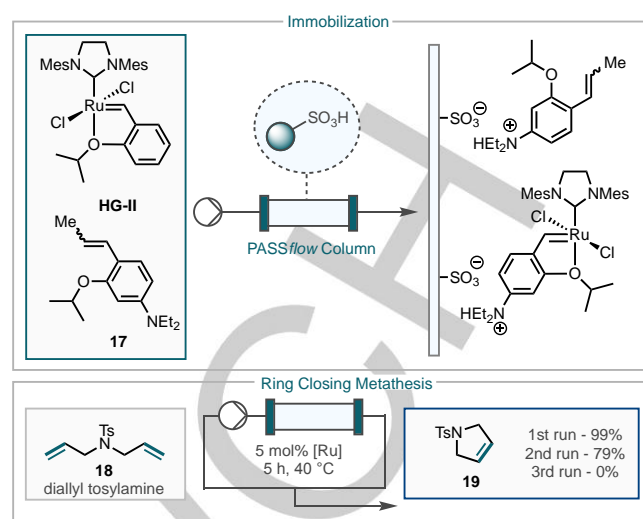
The concept of silica-immobilized catalysts was recently revised by Grela, Kirschning and Kajetanowicz with the modification of alkoxy derivative of HG-II catalyst (**Ru-6**) with neutral Brønsted basic tags (Scheme 15). The straightforward functionalization with silica gel modified with *p*-toluenesulfonic acid allowed efficient metathetic reactions under batch and flow conditions.^[27] Experiments under batch conditions in the presence of 1 mol% of catalysts **Ru-6** showed high reactivity at 45 °C for the conversion of **15** into the corresponding cyclized product **16** (94 and 96% isolated yield respectively). Additionally, the catalyst reusability was proven to be possible over 6 runs without any significant effect on the final yield. ICP-MS and split tests provided evidence of reduced leaching. Encouraged by these results, flow experiments were further performed using a loop set-up. The heterogeneous catalyst **Ru-6** (100 mg, 2.5 mol%) was placed inside the flow-reactor (glass column, internal dimensions 100 x 2.5 mm) and a solution of diethyl diallylmalonate in *n*-hexane was pumped through the reactor and heated to 45 °C in a circulating mode with a flow rate of 2.5 mL/min. After three consecutive runs, where catalyst **Ru-6** showed higher activity and stability, the corresponding cyclization product could be observed with conversions from 95-97%. From the 4th run, 80, 70 and 57% conversion were detected while the 7th run provided only 10% of the desired product. ICP-MS analyses of the different runs evidenced low presence of [Ru] (from 0.39 ppm to 0.08 ppm from the first to the last run). For continuous flow experiments, 0.036 mmol of **12** was loaded into a flow reactor, made of a glass column with internal sizes of 100 x 2.5 mm. A solution of **15** (0.15M in *n*-hexane) was pushed through a preheated reactor with a flow rate of 2.5 mL/min. The mixture was circulated for three hours providing almost quantitative conversion.



Scheme 15. silica-immobilised catalysts for continuous and circulating mode RCM.

One of the downfalls of the ruthenium catalyst family for olefin metathesis is that they can create undesirable ruthenium by-products which prove difficult to remove from the reaction products. Several protocols to remove these impurities have been proposed, including various scavengers,^[28–30] biphasic extractions,^[31] and silica gel chromatography.^[32] In 2001, Kirschning and coworkers developed a reactor system that was termed the PASSflow technique (Polymer Assisted Solution-phase Synthesis in the Flow-through mode).^[33] This reactor system consisted of a highly porous monolithic glass/polymer composite material. Embedding this material in a suitable casing created a flow-through microreactor with a high polymer surface area.

In 2006 Grela, Kirschning and co-workers described a strategy for the noncovalent immobilisation of **HG-II** that relies on electrostatic binding.^[34] A tailor-made sulfonated polystyrene support synthesised in the presence of a monolithic glass rod yielded a 'megaporous' glass-polymer composite material which could be loaded into a PASSflow reactor. The catalyst was immobilised by circulating a solution of the **HG-II** and an excess of aniline derivative **25** (1:19) in CH₂Cl₂ through the reactor allowing simultaneous immobilisation and saturation of all SO₃H groups (Scheme 16). This was achieved by protonation of the aniline to form an ammonium ion complex with the sulfonate support, prior to then capturing the Ru-material *via* a metathesis reaction on to the supported ammonium. Following this immobilization, diene **26** was circulated at 2 mL/min at 40 °C for five hours through the catalytically active reactor (5 mol% of Ru) which quantitatively afforded RCM product cyclopentene **27**. To test the levels of leaching and deactivation, the column was reused under identical conditions after washing with CH₂Cl₂. The second run afforded product **27** in 79% yield, while a third run did not yield the desired product demonstrating deactivation of the reactor column. However, the column could be reactivated through a system of acid and base washes and reloading of **HG-II** and ligand **25** as described above. Impressively, under batch conditions using Raschig rings as the monolith for immobilisation of the catalyst, the reaction could be run for up to 6 runs before deactivation (1st run >99%, 2nd run 88%, 3rd run 56%, 4th run 68%, 5th run 38% and 6th run 10%). Despite more pronounced catalyst deactivation than the above batch method, this work demonstrated for the first time that olefin metathesis is possible under PASSflow continuous flow conditions.

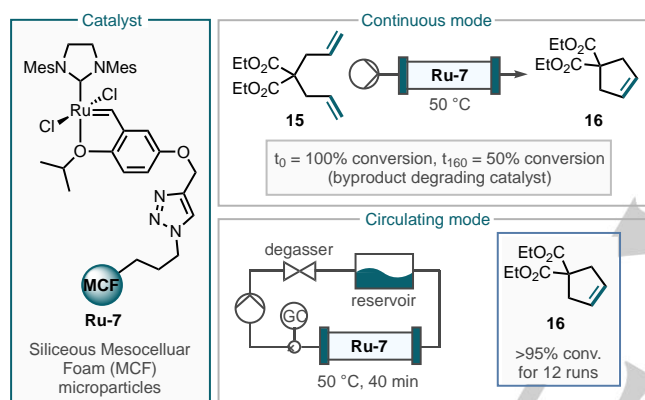


Scheme 16. ring closing metathesis using PASSflow technology

2.1.3. Mesoporous Support

Limbach and co-workers studied the effect of pore size of a variety of porous support materials on a challenging RO-RCM process. Starting with *cis*-cyclooctene as input substrate there are myriad of products derivable from reaction steps involving ring-opening, cross metathesis, isomerisation, oligomerisation and ring-closing metathesis.^[35] The authors note that the selectivity for a targeted RO-RCM process was significantly increased by conducting the reaction in flow using mesoporous supported **HG** complexes. By tuning several critical parameters including the pore diameter, substrate concentration, reaction temperature and mean residence time a maximum selectivity of 35% for the cyclic dimer derived from RO-RCM was obtained, an impressive result considering all potential pathways of this reaction process. Notably, 'split' experiments were used to characterise the activity of any leached materials, such an experiment consists of splitting the collected liquid phase at 50% conversion, quenching any leached catalyst in one portion with ethyl-vinylethyl and analysing yield. For the remaining portion, quenching is delayed for 4 hours prior to quenching and analysis. In the instances where the conversions remain equal between the splits the reaction is presumed heterogenous, whereas if the later quenched split shows subsequent conversion it indicates that there is a catalytically active species in the liquid phase. This type of experiment really serves to benchmark and highlight the performance of supported metathesis catalysts. Lee, Ying & Lim used click chemistry to immobilize **HG-II** on Siliceous Mesocellular Foam (MCF) (Scheme 17).^[36] MCF is characterised as a stable mesoporous silica with ultralarge cell-like pores.^[37–41] The material has a large surface area (561 m²/g) as measured by BET and large pore volume (2.1 cm³/g). Following preparation of the supported **HG-II** material (**Ru-7**), elemental analysis demonstrated metal loading of 0.16 mmol/g and ligand density of 0.19 mmol/g, implying >80% of the immobilized ligand was loaded with ruthenium. Catalyst recyclability tests in batch demonstrated mixed outcomes, dependant on the specific substrate examined. Promising examples were further explored and exemplified in flow. Preliminary reactor design featured a packed bed of catalyst and 0.5 mL/min flow rate at 50 °C in dichloro-

methane. It was found that conversion of **15** into the corresponding product of cyclization **16** decreased sharply against operation time and it was hypothesised that the ethylene byproduct deactivated the supported catalyst.^[42] Alternatively, 'channelling' or 'cracking' of the catalyst bed over time could also account for this observation (such changes in the catalyst bed would lead to reduced exposure time to the catalyst and lower conversions). The second iteration of the reactor design featured a recirculating flow device where the substrate was passed through the catalyst bed but also a degasser and open reservoir so as to minimize catalyst deactivation by removal of ethylene, and represents a useful way to address this key challenge. The recirculation was maintained for 40 minutes whereby GC analysis confirmed complete conversion. In this manner the same catalyst bed could be re-exposed on multiple runs leading to >95% conversion into **16** across 12 runs. With regards to leaching of ruthenium from the support material in the recirculating flow device, it was found, by ICP-MS, that an average of 8.4 ppm was leached to the reaction mixture for the first 4 runs, and 2.9 ppm for the following 8 runs.

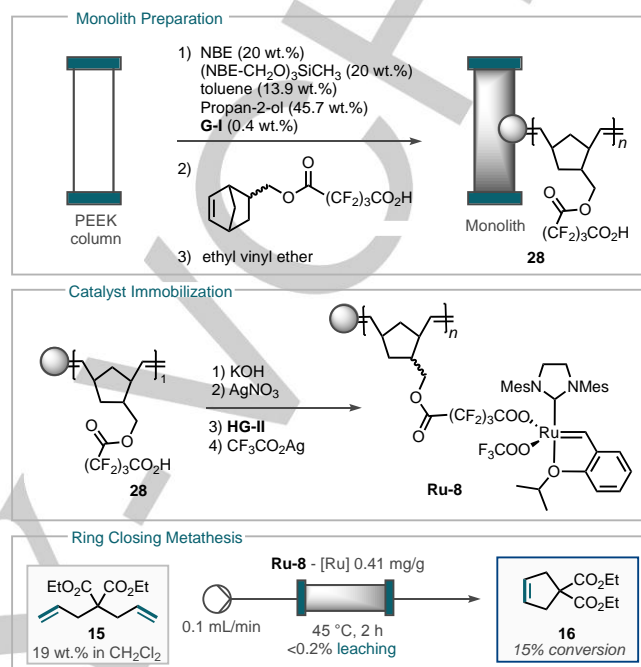


Scheme 17. MCF Supported Catalysts for Ring Closing Metathesis.

2.1.4. Monolithic Support

Monolithic materials, prepared by radical polymerization have been known since the 1970s,^[43,44] and have been further developed by the likes of Fréchet and Svéc.^[45,46] The main advantage of monolithic media is the comparatively fast mass transfer between the support and liquid phase due to their high surface area and pore size distribution. In 2001, Buchmeiser and co-workers developed a new high performance monolithic support for covalently immobilized metathesis catalyst.^[47] In 2003, the group further developed these supports for continuous flow metathesis.^[48] The monolith (**28**) was made in a PEEK column by the ROMP of norbornene (NBE) with **G-I** and (NBE-CH₂O)₃SiCH₃, in a suitable mixture of porogens (Scheme 18). This process is conducted in a stoppered column, following the initial ROMP to prepare the monolith, the perfluorinated NBE material was added to the column mixture allowing the grafting of ligating sites to the monolith backbone. Following monolith preparation the porogen and catalyst can be washed out by flushing with ethyl vinyl ether and water. Catalyst immobilization began with flushing the column with KOH which resulted in the potassium carboxylate salt which could be converted to the silver salt using aqueous AgNO₃. After the reaction with **HG-II**, CF₃CO₂Ag was added to substitute the second chlorine ligand to give **Ru-8** with a metal loading of 0.41 mg/g, corresponding to

2.5 mg of catalyst per gram of support. The RCM of diallylmalonate **15** was used to evaluate the monolith. Substrate **15** (19 wt. %) in DCM was passed across the monolith at 0.1 mL/min at 45 °C. After 2 h, a 15% conversion into **16** was observed with no side products present. Leaching was also extremely low (<0.2%) resulting in product of contamination with Ru and Ag of 1.8 and 0.01 ppm respectively.

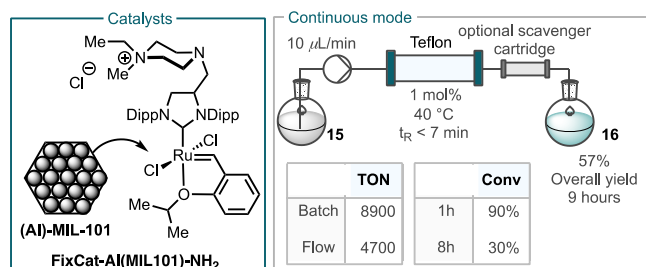


Scheme 18. monolith Supported Catalysts for Ring Closing Metathesis.

2.1.5. Metal-Organic Framework (MOF) immobilized catalysts

Alternative immobilization strategies based on physical interactions between catalyst and support (physisorption) have also been reported. In 2016 Chmielewski and Grela developed a batch and flow protocol for RCM in the presence of MOFs (Metal-Organic-Framework) impregnated with a modified **HG-II** catalyst bearing an ammonium-tagged NHC ligand (Scheme 19).^[49] Based on its peculiar stability and spacious pores, (**AI**)MIL-101-NH₂ was prepared and used for the sorption of a series of catalysts. The sorption of **FixCat™** on (**AI**)MIL-101-NH₂ provided the best performing heterogeneous system. The robustness of physisorption was harnessed by static and dynamic desorption experiments, the respective supernatants were analyzed by UV to reveal low leaching values. Studies in batch conditions demonstrated that pretreatment of **FixCat-AI(MIL101)-NH₂** with HCl solution in ether, could provide the full conversion of **15** into the corresponding cyclized **16** product after 24 hours, performing the reaction at room temperature in the presence of 2 μmol catalyst (2% w/w of [Ru] approximatively) (TON up to 6400). Encouraged by this result, a protocol for continuous flow was designed, consisting of a Teflon tube of 1.5 mm internal diameter, filled with 27 mg of the activated **FixCat-AI(MIL101)-NH₂ HCl**, containing 1% of ruthenium catalyst, able to form a solid deposit of approximately 5 cm. A 0.5 M solution of **15** was pumped through the reactor containing the packed catalyst at 40 °C with a flow rate of 10 μL/min for 8 hours (t_R<7 minutes). The conversion resulted in more than 90% after one hour, decreasing to 30% after 8 hours, with an overall average yield

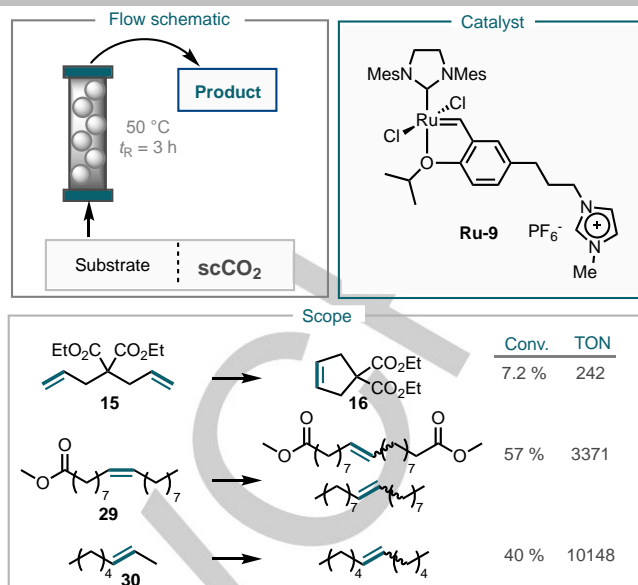
value of 57% (TON 4700). Further ICP-MS analyses revealed less 0.02 ppm of ruthenium in the collected solution.



Scheme 19. Ru@MOFs catalyzed RCM in continuous flow.

2.1.6. Supported Ionic Liquid Phase (SILP)

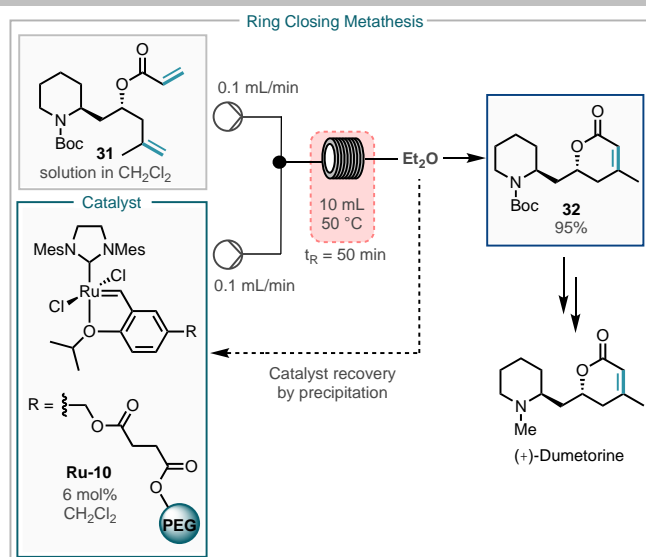
In 2011 the groups of Nolan, Mauduit and Cole-Hamilton developed a heterogeneous system for a continuous flow alkene metathesis based on the Supported Ionic Liquid Phase (SILP) concept, where the ruthenium catalyst, opportunely functionalized with an imidazolium-based ionic liquid, is ionically anchored on silica (Scheme 20).^[50] The nature of such interaction, makes the catalyst immobilized in a thin film of ionic liquid, allowing the formal solubilization of the reagents and catalysts at the surface of the support. Supercritical CO₂ was employed as the flowing medium, (SILP-SCF). Due to the low solubility of both ionic liquids and reagents in SC-CO₂, leaching events are greatly reduced. From a practical point of view, **Ru-9** was prepared upon reacting **G-II** catalyst in a solution of dichloromethane containing 1-butyl-3-methylimidazolium bistrifluoromethanesulfonamide (BMIM-NTf₂) and silica.^[51] Further evaporation allowed the immobilization of the catalyst, which was loaded with the reagents into a stainless steel tubular reactor with a volume of 8.8 mL,^[52] stabilized at the desired temperature before CO₂ flow. All reactions were carried out with the tubular reactor held vertical and with the flow being from bottom to top. The resulting material was collected and analysed by inductively coupled plasma optical emission spectroscopy (ICP-OES) to determine the ruthenium content while ¹H and ¹⁹F NMR spectroscopy to eventually detect the leached BMIM-NTf₂. Initial experiments focused on the cyclization of diethyldiallylmalonate **15** as the benchmark reaction. Good catalytic performances could be measured over the first hour (TON from 242 to 564 h⁻¹ depending on stream rate, temperature and catalyst loading), followed by a steady decline in performance, probably due to catalyst degradation. Considerably higher TON was reached for the CM of 2-octene **30** (3371 h⁻¹) after 5 hours, demonstrated an enhanced stability of the catalyst. Finally the protocol was applied on the self-metathesis of methyl oleate **29**, where a TON of 10148 h⁻¹ could be observed after a 9 hour run. Using a flow rate of 0.05 mL/min at 23 °C (CO₂ flow pressure of 100 bar) with a catalyst loading of 77 ppm of Ru on SiO₂, up to 57% conversion was obtained over the first 2 hours.



Scheme 20. SILP for RCM and CM of **15**, **27** and **29**.

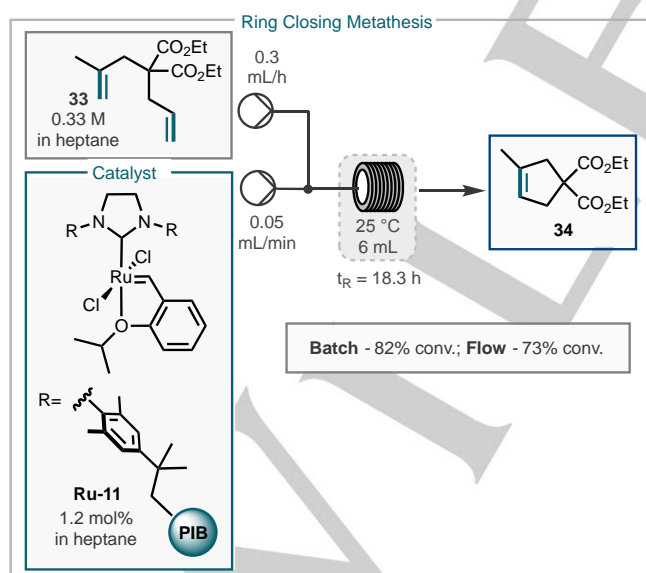
2.1.7. Soluble Supported catalysts

The separation and reusability of a catalyst represents one of the major issues for the industrial application of catalytic transformations. In this perspective, heterogeneous chemistry plays a pivotal role, being successfully applied to a series of reactions, including olefin metathesis. Early attempts on the preparation of supported ruthenium catalysts and the subsequent application were made.^[53] Unfortunately only limited success was found due to the lower activity compared to homogeneous systems and loss of activity after each reaction cycle. To overcome these drawbacks, in the early 2000's, Yao developed a strategy based on the functionalization of **HG-I** with poly(ethylene glycol) support (PEG). In such systems, the catalyst could retain its efficacy for homogeneous RCM, and following reaction could be precipitated and reused for further cycles without loss of activity.^[54] In 2011 Martinelli and coworkers exploited this strategy for the flow synthesis of (+)-Dumetorine, a 2-piperidynil alkaloid isolated from tubers of *Discorea dumetorum* Pax showing biological activity.^[55] In this particular case PEG-immobilized **HG-II** catalyst was prepared (**Ru-10**), showing excellent performance in RCM and almost quantitative recovery and reused up to six times without significant loss of activity (Scheme 21). A stream containing the solution of ester **31** in DCM and a second stream of **Ru-10** supported catalyst (6 mol% in Ru) were pumped at a flow rate of 0.1 mL/min, mixed at a T-piece and pumped through a PTFE loop reactor heated at 70 °C, with a t_R of 50 minutes. At the exit of the reaction mixture, the catalyst was precipitated with diethyl ether and filtered off prior to reuse. The strategy allowed the almost quantitative cyclization of the desired substrate, leading to the formation of the corresponding intermediate **32** which could be further functionalized.^[56]



Scheme 21. soluble PEG-Hoveyda catalyst for continuous flow synthesis of **31**.

Analogously, in 2016 Bergbreiter and coworkers could prepare a polyisobutylene (PIB)-supported **HG-II** catalyst for RCM (**Ru-11**) (Scheme 22). Two distinct solutions of **Ru-11** and **33** in heptane were pumped into the system using a HPLC pump and syringe pump, regulated at a flow rate of 0.05 mL/min and 0.3 mL/h respectively. The coil was maintained at room temperature with a t_R of 18.3 h, leading to the cyclized product **34** in 73% yield. The lower conversion compared to the batch conditions (82%) was attributed to the inactivation of the catalyst caused by the ethylene byproduct. ICP-MS analyses revealed a leach of 6.1% of the charged catalyst into the product phase.^[57]

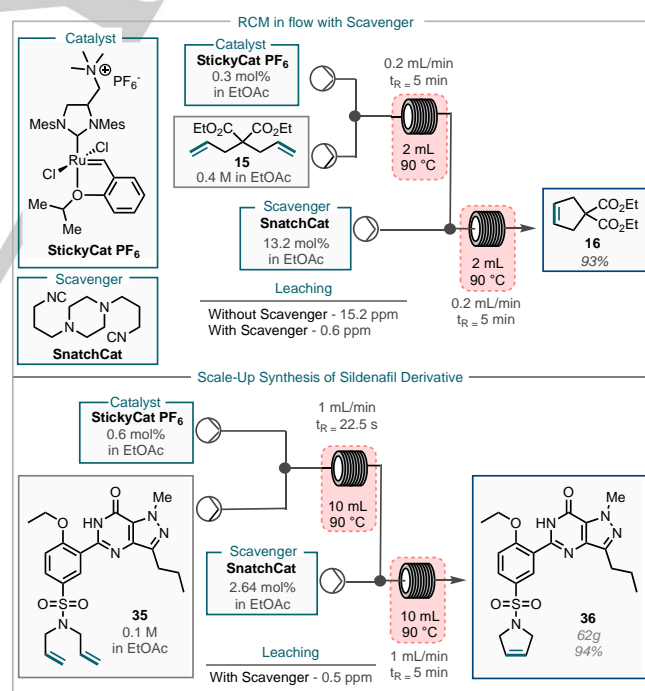


Scheme 22. Ru-11 catalyst for continuous flow synthesis of **34**.

2.2. Non-supported Heterogeneous catalysts

In recent work Grela, Wu and Kajetanowicz proposed a protocol for a RCM process in flow performed in the presence of **StickyCat**[®]PF₆, a modified **HG-II** catalyst bearing an ammonium

functionality on the NHC moiety (Scheme 23).^[58] The reaction was conducted using HPFA (high-purity filter aids) and optimized with **15** as a benchmark substrate. A stream of 0.4 M solution of substrate in ethylacetate and **StickyCat**[®]PF₆ (0.3 mol% in ethylacetate) were pumped through the coiled reactor, heated to 90 °C with a t_R of 2.5 min. The resulting product of cyclization could be achieved with 94% (NMR yield) but further ICP-MS analyses of the product mixture revealed the presence of 15.2 ppm of ruthenium. To reduce the metal concentration at the end of the process, the flowing reaction stream of **15** and catalyst was intercepted with a stream of **SnatchCat**[®] an passed through a second HPFA coil. The co-elution with such soluble metal scavenger (13.2 mol%) for a t_{R1} of 5 minutes, permitted significantly lower levels of ruthenium (down to 0.6 ppm) after a final filtration of the mixture through a silica pad. Notably, the employment of a soluble scavenger in combination with a polar-tagged catalyst resulted in a robust strategy for RCM in flow with potential applications to multigram-scale production. Flowing two separate solutions of substrate **35** (0.1M in ethylacetate) and **StickyCat**[®]PF₆ (0.006M in ethylacetate) through a first 10 mL HPFA coil with a rate of 1.0 mL/min, then through a second coil co-eluted with a solution of **SnatchCat**[®] (0.0026M in ethylacetate) with the same t_R (5 minutes for each coil) at 90 °C afforded the corresponding Sildenafil analogue **36** with 94% yield. The protocol was also demonstrated feasible for a continuous production over 24 h, leading to the preparation of 62 g of **36** (Scheme 23) with a measured concentration of 0.5 ppm of ruthenium.



Scheme 23. continuous flow RCM with scavenger.

3. Challenge Three – Working with Thermodynamics

3.1. Removing Ethylene from the reaction stream

Although metathesis processes in which ethylene is not produced were efficiently converted from batch to continuous flow mode, ethylene evolution in a continuous flow reactor tends to significantly decrease the performance of the transformation (one exception reported).^[11] The production of ethylene as a by-product, when the reaction is pursued in a closed system with a limited headspace, prevents the shift of the equilibrium of the metathesis reaction, leading to the early degradation of the ruthenium-based catalyst. Methylidene species formed with excess of ethylene are usually more susceptible to decomposition thus decreasing the overall efficiency of the process.^[59,60]

3.1.1. Tube-in-tube flow reactor

In 2010 the group of Ley developed an alternative technology able to support gas-liquid transformations in continuous flow mode.^[61] The system is composed of 2 tubes nested one inside the other, the external tube is fabricated from PTFE whereas the internal tube is an amorphous, permeable copolymer of tetrafluoroethylene and 87% of perfluorodioxolane (Figure 2). The tube-in-tube (TiT) manifold displays high permeability to a range of different gases (H_2 , CO, CO_2 , O_2 , O_3 , C_2H_4), retaining the liquid components (except fluorinated) and is resistance to various solvents and corrosives.^[62] This continuous flow reactor design enabled several chemical transformations such as ozonolysis, hydrogenations, carboxylations, Heck couplings and oxidations, with homogeneous or heterogeneous catalytic systems.^[63]

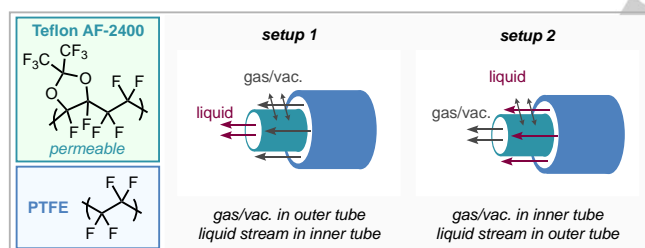
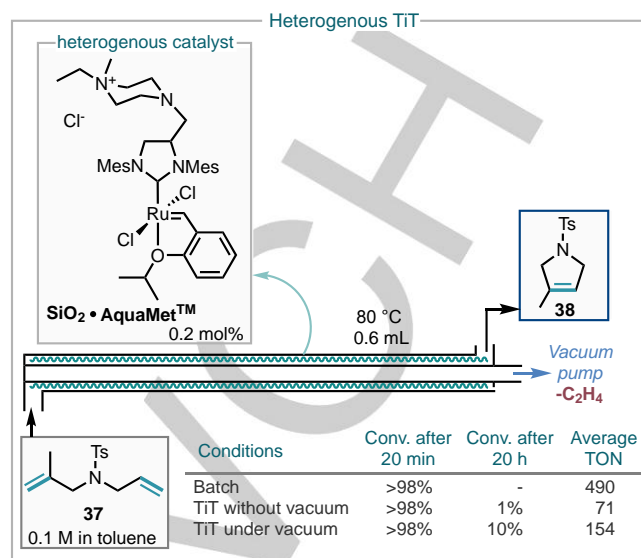


Figure 2. section of Tube-in-tube reactor.

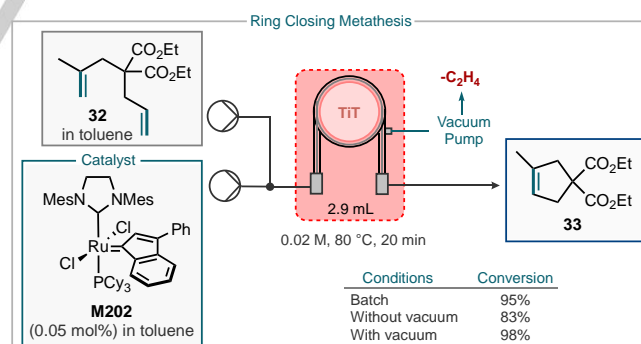
Skowerski and co-workers were the first to apply the TiT technology for metathesis reactions. The system, connected to a vacuum line, showed a significant increase in the conversions for RCM and CM reactions (Scheme 24). This process allowed a continuous removal of the ethylene by-product^[64] thus increasing the life of the supported catalyst $SiO_2 \cdot AquaMet^{TM}$.^[65] No conversion could be observed in the absence of vacuum after 20 h of continuous reaction, clearly indicating the involvement of ethylene in catalyst deactivation. The reaction was initially investigated under heterogenous conditions, where catalyst $AquaMet^{TM}$ was deposited on commercially available silica ($SiO_2 \cdot AquaMet^{TM}$). The reaction performed comparatively with batch and TiT. Under batch conditions, the catalysis was performed in presence of 0.2 mol% of catalyst, providing quantitative conversion of **37** into the substrate **38** with a TON of 490. The conversion performances were then studied using the TiT system with and without vacuum. The catalyst on $SiO_2 \cdot AquaMet^{TM}$ was loaded into the space between the inner and the outer tube within the TiT reactor as a suspension while a solution containing the substrate. The conversion after 20 hours resulted extremely low (1%) since the protocol was performed without a vacuum system able to purge the generated ethylene. Connecting the outlets of the inner tube to a vacuum pump,

provided an increased conversion (24%) with a turnover number of 154 (Scheme 21).



Scheme 24. RCM reactions in Tube-in-tube reactor with heterogeneous catalytic system.

The TiT reactor system has been more commonly studied for homogeneous metathesis reactions, where RCM was performed using 0.05 mol% of **M202** catalyst. Under batch conditions, heating of a 0.02 M solution of substrate **39** in toluene at 80 °C, ethylene could be more dissolved, providing a quantitative conversion into **40** within 20 minutes. Analogous results were observed by performing the reaction in a TiT reactor, heated to 80 °C and connected to a vacuum pump. When no vacuum is applied, the resulting conversion was slightly lower (83%) pointing again to the detrimental effects of ethylene to the catalysis (Scheme 25).

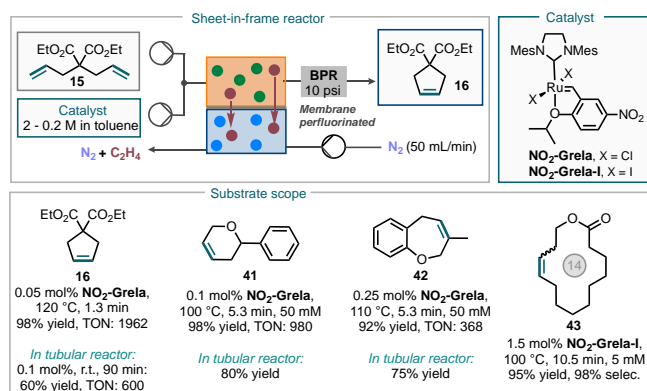


Scheme 25. RCM reactions in Tube-in-tube reactor with homogeneous catalytic system.

3.1.2. Membrane sheet-in-frame reactor

In 2020 Bio, Jamison and co-workers designed a continuous flow system incorporating a semi-permeable membrane, consisting of a perfluorinated polymer coated on a chemically resistant microporous layer that selectively permeates the ethylene by-product formed during RCM reactions (Scheme 26).^[66] The technology was developed by Compact Membrane Systems Inc. (CMS) and originally used for drying *tert*-butyl hydroperoxide.^[67] After optimisation of reaction conditions (temperature, back pressure, N_2 flow rate and residence time t_R) for the RCM of

diethyldiallylmalonate **15**, the authors underlined the benefits of this reactor design compared to a sealed stainless-steel tubular reactor across six examples (four reported). With identical reaction conditions, both yields and TON were higher when the membrane sheet-in-frame reactor is used (92 to 98% yields). By decreasing the concentration of the substrate, 6- and more challenging 7- and 14-membered rings (**41**, **42** and **43**) were obtained with excellent yields (75 to 95%) and selectivity (for **38**, 98% cyclization instead of oligomerization). To gain in efficiency and minimize the t_R , the transformations were performed at higher temperatures (above 90 °C).



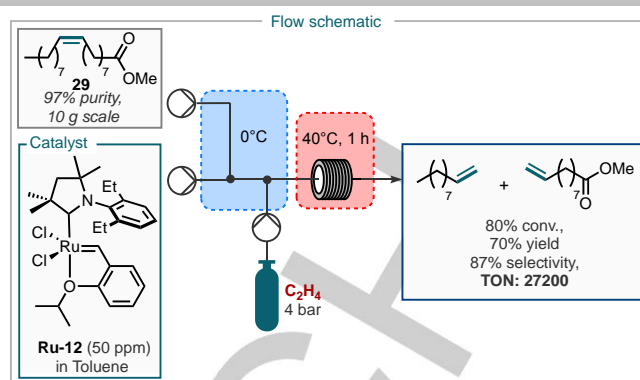
Scheme 26. membrane *sheet-in-frame* reactor with pervaporation membrane for RCM and mRCM reactions.

3.2. Addition of ethylene into the reaction stream

The manipulation of reactive gases to pursue heterogeneous gas-liquid reactions requires controlled, (sometimes) restricted and well equipped environments to fulfill safety protocols. Due to the low interfacial mixing, such transformations need a large excess of gas thus impacting on the overall pressure inside the reactor, demanding for precautional monitoring to prevent leakages, especially on higher scales. On the other hand, continuous flow technology allows precise and controlled introduction/ventilation of gas, limiting further exposure and significantly de-risking the working conditions. At the same time, it warrants a higher interfacial mixing with beneficial effects on the kinetics and the efficiency of the overall process.^[68,69]

3.2.1. Microreactor

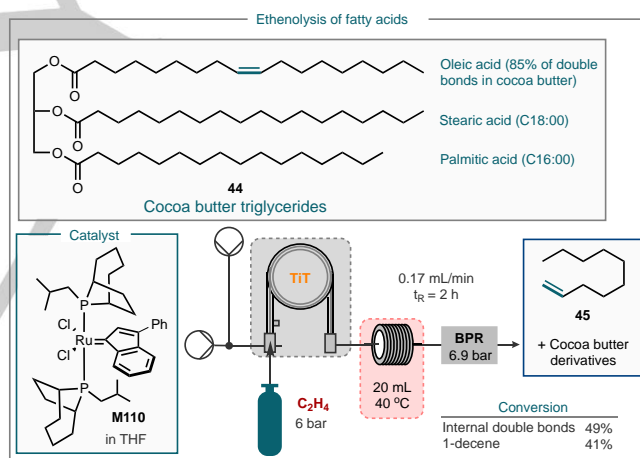
In 2011 Grubbs and co-workers reported the fast and efficient ethenolysis of methyl oleate under microfluidic conditions. A solution containing the CAAC-Ru based metal catalyst **Ru-12** (50 ppm in toluene) and **29** were pumped through a first T-junction (1 $\mu\text{L}/\text{min}$ and 5.7 $\mu\text{L}/\text{min}$ respectively) at 0 °C before being saturated with ethylene. The reaction was initiated in the microfluidic reactor, made up of a polydimethylsiloxane capillary tube with an internal diameter of 0.5 mm and 450 cm length, preheated to 40 °C. The desired product could be obtained with 80% conversion and 70% yield when the t_R was extended to 1 hour. Analogous results could be obtained using traditional batch conditions, where ethenolysis is performed under 10 bar of ethylene gas. The microfluidic approach allowed to work with lower gas pressure (4 bar), impacting significantly on the safety of the procedure (Scheme 27).^[70]



Scheme 27. ethenolysis of methyl oleate under microfluidic conditions.

3.2.2. Tube-in-tube continuous flow reactor

In 2015 Browne, Lapkin and co-workers used the TiT manifold for CM between ethylene and triglycerides derived from raw cocoa butter (**44**), a food industry waste, to provide 1-decene (**45**) as the major lower weight alkene product.^[71] In batch mode, optimized conditions could provide 49% conversion after 16 h at r.t., in presence of the *bis*-phosphine indenylidene complex **M110** (1 mol%) and 2 bar of ethylene. After optimisation of the reaction conditions (temperature, pressure, flow rate and t_R), the same conversion was reached by combining a TiT and tubular reactor (Scheme 28).

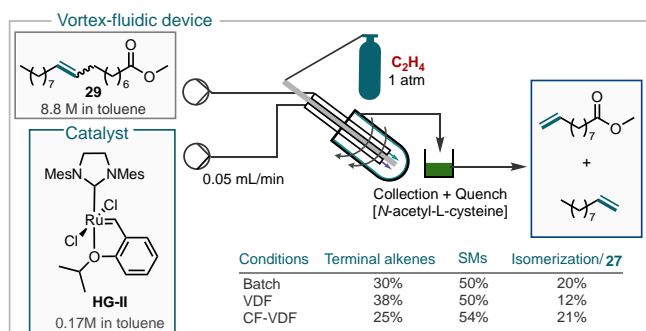


Scheme 28. ethenolysis of cocoa butter triglycerides in TiT reactor.

3.2.3. Vortex-fluidic device (VFD)

As an alternative to the *tube-in-tube* technology, Raston and coworkers developed a meso-scale flow process for the ethenolysis of methyl oleate **29** in a vortex-fluidic device (VFD). Such a device features a rapidly rotating tube able to impart a vortex of liquid to the base of the tube, this increases the gas-liquid contact, in this case the gas being ethylene. The catalysis, performed in presence of **G-I**, **G-II** and **HG-II** resulted in a process with similar efficiencies to batch conditions, where the terminal alkene, isomerization (mixed with starting **29**) and homometathesis (SMs) products could be observed within 30, 20 and 50%. For VFD, solutions of **29** and **HG-II** catalyst were fed using separate jet feeds providing 38% conversion into terminal alkene products, within 10% isomerization (mixed with **29**) and 50% homometathesis products (SM). The outcome of the reaction was not significantly affected by continuous-flow

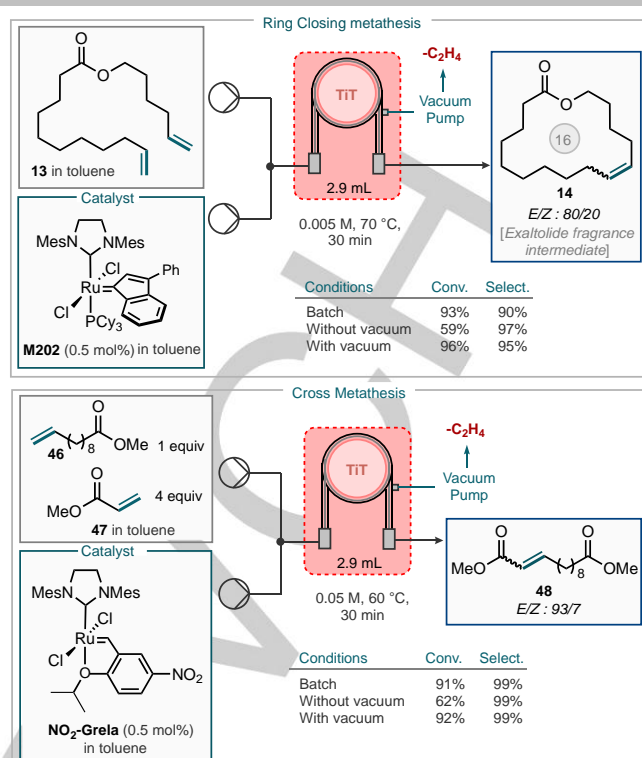
VDF. Maintaining an atmosphere of ethylene, a solution of **29** (79.2 mM in 9 mL toluene) and **HG-II** (1.59 mM in 9 mL) were delivered to the base of the VDF tube using separate jet feeds with flow rates of 0.05 mL/min with an overall t_R of 20 minutes (Scheme 29). At the end of the process, quenching was performed by using a solution of *N*-acetyl-L-cysteine. Terminal alkene products could be identified as 25%, while 54% as homometathesis products (SM). In this case, 21% of isomerization product could be observed. the VFD is unable to support higher pressures. As consequence, the ethenolysis can be advantageously performed in presence of atmospheric pressures of ethylene gas instead.^[72]



Scheme 29. continuous flow VDF process for ethenolysis of methyl oleate **27**.

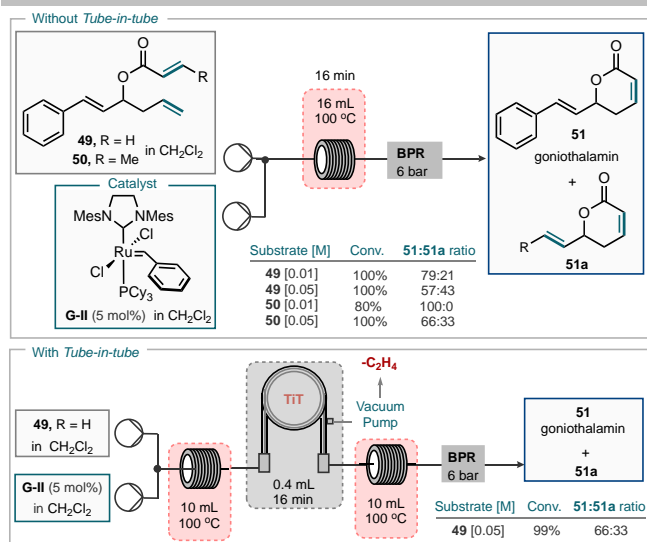
4. Challenge Four – combining reactor and catalyst design to support reaction selectivity

As part of the work described in the previous section, Skowerski and coworkers also developed a TiT protocol for the homogeneous macro-RCM and CM with methyl acrylate.^[65] In this case, products **14** and **48** could be accessed in similar excellent conversions from **13**, **46** and **47** respectively (from 91 to 96%) within 30 minutes, in both a batch reactor and TiT (vacuum on) flow conditions connected. As evidenced by their results, the efficiency of the transformation drops when ethylene could not be adequately removed from the system (59% yield for **14** with no vacuum; Scheme 30). Moreover, for the synthesis of an exaltolide fragrance precursor **14**, the selectivity of the reaction toward isomerization instead of cross-metathesis resulted in slightly higher when performed in continuous flow mode (90% batch vs 95% or 97% in flow).



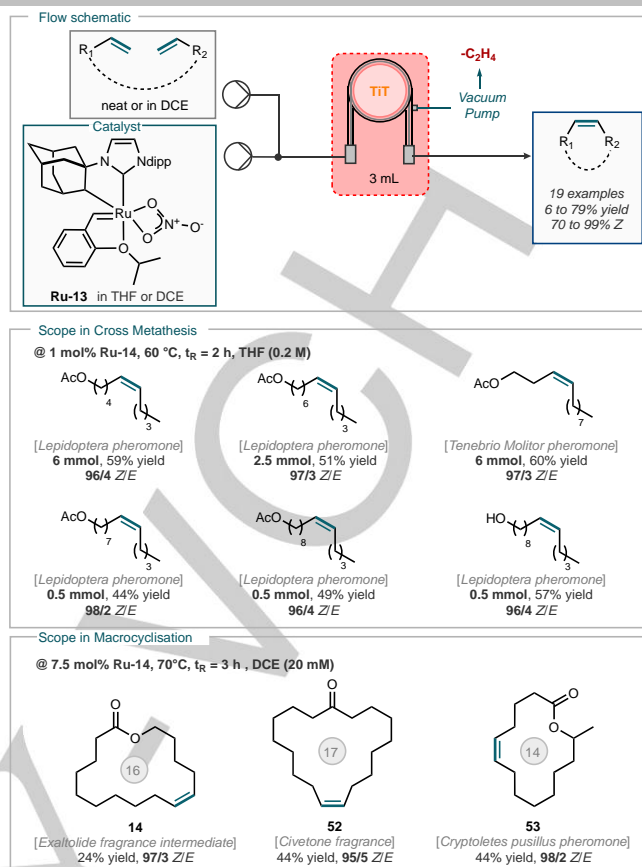
Scheme 30. RCM and CM reactions in TiT reactor with homogeneous catalytic systems.

In 2020 Pilli, Ley and co-workers achieved the synthesis of goniotalamin **51** through a RCM at the last step to form the 6-membered α,β -unsaturated lactone from **49** and **50**.^[73] In both the batch and the flow conditions, high dilutions were required to favour the cyclization vs the dimerization of the starting triene. Even though full conversion could be obtained in a short t_R (16 min) from **49**, under continuous flow conditions, the entrapment of ethylene was deleterious to the final yield and selectivity of the process, even in the presence of high catalytic loading (5 mol% of **HG-II**). In a non-permeable traditional flow system, the evolving gases underwent olefin cross-metathesis reaction with the styryl moiety of goniotalamin **51** affording the lactone **51a**. Unfortunately, with a concentration of 0.05 M, the use of a TiT manifold did not significantly improve the selectivity towards the desired compound **51** (Scheme 31). In a similar manner, the use of a sacrificial olefin for ethylene trapping was unsuccessful. Finally, in non-permeable PTFE coil, a modification of the substrate (**50**) consisting of replacement of the terminal olefin with an internal double bond, enabled an increase in selectivity at low dilution (0.01 M) at the cost of incomplete conversion (80%).



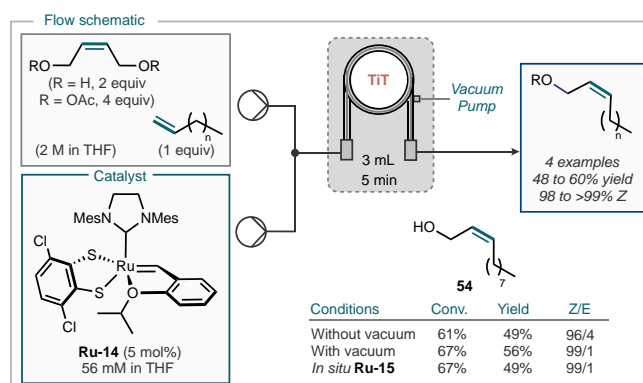
Scheme 31. late-stage flow RCM for the synthesis of goniotalamin.

During the last decade, a significant challenge in the catalyst design was achieved for the selective formation of *Z*-alkene by olefin metathesis.^[74] Two main Ru-based catalyst classes could be developed, consisting of cyclometalated Ru-catalysts^[75] and dithiolate catalyts.^[76] Whereas the former has proven to be highly *Z*-stereoselective in the presence of terminal olefins (up to >99:1), the latter is able to efficiently promote the transformation of *Z*-olefins into corresponding *Z*-products by retaining the stereochemical information (up to >99:1) (Scheme 32). In 2021 the groups of Mauduit and Browne described the first *Z*-selective olefin metathesis by continuous flow, exploiting the TiT reactor technology to overcome the instability of both classes of Ru-based *Z*-selective complexes towards air, moisture and ethylene.^[77] After a brief screening of cyclometalated Ru complexes and optimisation of reaction conditions, a series of *Z*-internal olefins could be obtained by SM, CM and *macro*RCM in the presence of **Ru-13**,^[78] with moderate to good yields (32 to 75%) and good to excellent selectivity. (80 to 99% *Z/E*). This approach was exemplified with the preparation of 7 pheromones and 3 macrocyclic fragrances or their intermediates (**14**, **52** and **53**) (Scheme 29).



Scheme 32. *Z*-selective cross-metathesis and macrocyclization in TiT reactor.

The TiT reactor manifold also proved beneficial for the production of *Z*-allylic alcohols in the presence of *Z*-stereoretentive catechodithiolate **Ru-14** catalyst, providing very high *Z/E* ratio (above 98/2) and moderate yields (48-60%, Scheme 33), whereas the former **Ru-13** suffered a lack of selectivity for these compounds under these conditions. Notably, the *in situ* generation of catalyst **Ru-14** directly in the flowing stream,^[79] led to product **54** with the same efficiency as that with isolated catalyst, while avoiding the use of a glove-box for catalyst preparation.



Scheme 33. *Z*-retentive cross-metathesis and macrocyclization in TiT reactor with catechodithiolate **Ru-16**.

Conclusion and Future Outlook

The aim of this review is to highlight the wide range of creative and innovative methods that have been explored to translate key metathetic transformations from batch methods to continuous processes. This has been achieved by the intense synergistic collaboration of the scientific community, bringing together appropriate skills in catalyst- and reactor-design.

By showing these results as conceptual challenges we hope to stimulate the community to see where their ideas would place within this framework, or indeed, provide a similar framework for collaborative fields in areas other than metathesis, trying to explore alternative reactor technologies to leverage important chemical transformations. It is tempting to conclude that targeting the most ambitious challenge is the only way to move forward. However, challenges are built on the foundations and, contributions to the foundations certainly support a clearer path forward. With regards to the future outlook of continuous flow metathesis, it is clear that the issue of catalyst recycling is not yet solved. There are examples of non-covalently supported catalysts that demonstrate high TON but also high leaching; and, covalently supported catalysts that exhibit low leaching but relatively poor activity. On the other hand, given the problems related to the efficient management of reaction byproducts (e.g. ethylene), further studies in catalyst- and reactor design are required for successful continuous processes on industrial scale-up applications. Metathetic transformations represent an ideal chemistry platform to challenge the existing reactor platforms, setting the stage for the development of new technologies, eventually extendible to other challenging transformations. It is perhaps fair to say that until this point, the chemistry has largely driven the development of appropriate flow reactor solutions by challenging the reactor design with tasks that can already be met by traditional batch protocols and this has been driven by the ideology of more streamlined scalability and potential for catalyst immobilization. The future in this collaborative field is exciting, some of the flow designs presented herein could become amenable to multistep processing, automated purification, automated reaction optimization, catalyst screening (including other metals) and the use of machine learning to reconfigure reactors as well as reactions (including asymmetric transformations) and deliver new understanding of metathetic processes.

Acknowledgements

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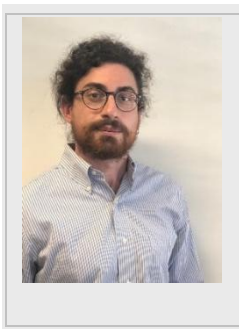
Keywords: Olefin Metathesis • Ruthenium • Continuous Flow • Reactor Design • Heterogeneous/Homogeneous Catalysis

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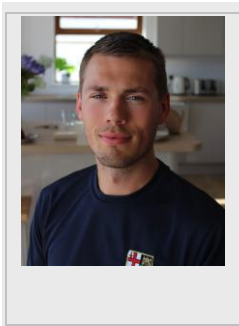
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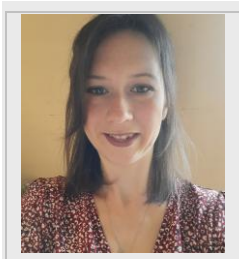
Antonio Del Vecchio obtained the MSc degree in Chemistry and Pharmaceutical Technologies at University of Ferrara (Italy). In October 2016, he joined the Service de Chimie Bioorthogonale et de Marquage (SCBM) at CEA-Saclay (French Atomic Energy Commission) under the supervision of Dr. Davide Audisio and Dr. Frédéric Taran. Here, he received his Ph.D. working on new synthetic methodologies involving CO₂, and carbon radio-labeling. From 2019 to 2021, he joined the Prof. Dr. Ackermann group at the Georg-August-Universität Göttingen (Germany) as postdoctoral researcher, working on metalla-electrocatalyzed C–H activations. Since September 2021 he is working as postdoctoral researcher in the Dr. Mauduit group at the Organometallic Chemistry Department at Ecole Nationale Supérieure de Rennes on the development of metathesis processes in continuous flow.



Harry R. Smallman obtained his MChem degree from Cardiff University in 2019, undertaking his masters project with Prof. Thomas Wirth exploring the synthesis of a natural product in flow. He moved to UCL (University College London) in November 2019 and has since been a PhD student in the Browne group. The focus of his research is on reactive intermediates in flow and mechanochemical synthesis.



Jennifer Morvan obtained her MSc and engineering degrees in Molecular chemistry in 2018 at Ecole Nationale Supérieure de Chimie de Rennes (ENSCR, France). She joined then Organometallic, Material and Catalysis department of ENSCR for her PhD supervised by Dr M. Mauduit and Dr C. Crévisy. Her work focused on the development of new ruthenium based complexes for stereoselective olefin metathesis in batch and continuous flow mode. In 2022, she receives the Henri Kagan thesis award of the French Chemical Society (SCF). In september she will join Janssen Pharmaceuticals (Belgium) as postdoctoral researcher.



Tom McBride obtained his MChem from Cardiff University in 2017, under the supervision of Duncan L. Browne. In the same year, he started his PhD in the Browne research group at Cardiff and is currently writing his thesis. The main focus of his research has been designing flow systems for organic synthesis with a strong interest in reactive intermediates (such as acyl ketenes), telescoped reaction processes and reactor design.

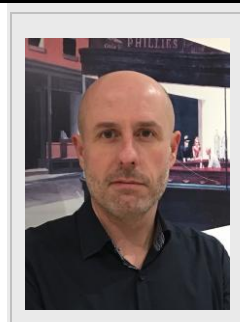


Duncan L. Browne obtained his MChem degree from the University of Sheffield (one year intern at GSK, Stevenage, UK). In 2009 he was awarded a Ph.D. in organic synthesis under the supervision of Prof. Joseph P. A. Harrity (Syngenta, CASE). This was followed with a one year Doctoral Prize Fellowship from the EPSRC before moving in 2010 to the University of Cambridge for Postdoctoral studies with Professor Steven V. Ley FRS CBE. In September

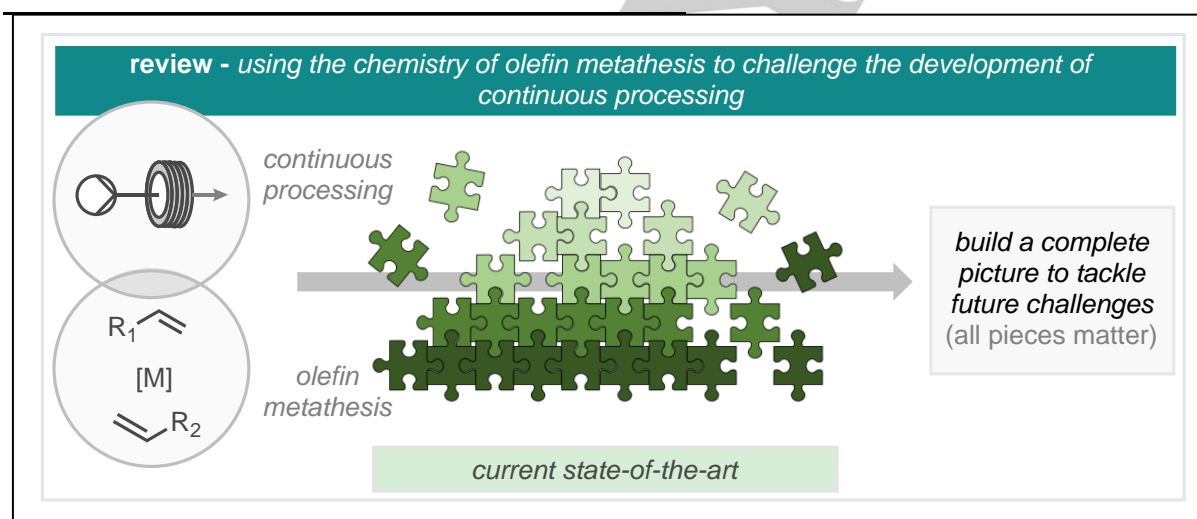
2014, Duncan established his independent research group at Cardiff University focussing on the use of enabling technologies for synthesis and catalysis. In 2019 he was recognised by both Green Chemistry and Reaction Chemistry and Engineering as an 'Emerging Investigator' and was a recipient of a Thieme Chemistry Journal Award. In 2019, Duncan was appointed as Associate Professor of Organic Synthesis and Drug Discovery at UCL (University College London).



Marc Mauduit obtained his Ph.D. degree in 1999 from the University of Paris-Sud Orsay (France) under the supervision of Professor Y. Langlois. After postdoctoral studies with Professor S. Hanessian at Montreal University (Canada), he was appointed CNRS Research Fellow in 2001 at Ecole Nationale Supérieure de Chimie de Rennes (UMR CNRS 6226 «*Institut des Sciences Chimiques de Rennes*»). In 2010, he was appointed as CNRS Research Director and co-founded the DEMETA SAS company.



His main research interests are the development of N-heterocyclic carbenes (NHCs) and cyclic(amino)(alkyl)carbenes (CAACs) for homogeneous (asymmetric) catalysis.



This mini-review aims to provide a survey of the symbiotic developments of flow chemistry and olefin metathesis. Looking at the current state-of-the-art, key challenges have been retrospectively identified with both catalyst & flow reactor design and development which together paint an intriguing outlook for the future development at this interface.

Institute and/or researcher Twitter usernames: @EnscrOmc; @chimie_ISCR; @BrowneGroup