Continuous Flow Z-Stereoselective Olefin Metathesis: Development and Applications in the Synthesis of Pheromones and Macrocyclic Odorant Molecules**

Jennifer Morvan, Tom McBride, Idriss Curbet, Sophie Colombel-Rouen, Thierry Roisnel, Christophe Cr visy, Duncan L. Browne,* and Marc Mauduit*

Abstract: The first continuous flow Z-selective olefin meta-thesis process is reported. Key to realizing this process was the adequate choice of stereoselective catalysts combined with the design of an appropriate continuous reactor setup. The designed continuous process permits various self-, cross- and macro-ring-closing-metathesis reactions, delivering products in high selectivity and short residence times. This technique is exemplified by direct application to the preparation of a range of pheromones and macrocyclic odorant molecules and culminates in a telescoped Z-selective cross-metathesis/ Dieckmann cyclisation sequence to access (Z)-Civetone, incorporating a serial array of continually stirred tank reactors.

Olefin metathesis[1] has emerged as a powerful synthetic tool to construct carbon-carbon double bonds. The versatility of olefin metathesis is evident from its successful application to natural product synthesis,[2] the valorisation of renewable feedstocks[3] or the preparation of new materials such as polymers.[4] The gamut of applications is largely due to the development of efficient, well-defined, air stable and easy to handle catalysts, such as the ruthenium-arylidene complexes which demonstrate high tolerance towards various organic functionalities.[1] A significant challenge for catalyst design has been the selective formation of Z-alkenes. As numerous highly valuable molecules feature a Z-alkene moiety, special attention has recently been focused on the development of a new class of Ru-based complexes to enable high selectively towards Z-olefins (Figure 1).[5] Cyclometalated Ru-catalyst

Ru-1 (Grubbs)[6] and monothiolate Ru-catalyst Ru-2

(Jensen)[7] have proved to be highly Z-stereoselective in cross-metathesis (CM) of terminal olefins (up to > 99:1) while stereoretentive dithiolate catalyst Ru-3 (Hoveyda)[8] effi-ciently promoted the transformation of Z-olefins into corre-sponding Z-products by retaining the stereochemical infor-mation (up to > 99:1). Recently, we described the synthesis of

a cost-effective Z-selective cyclometalated Ru-catalyst Ru-4[9] featuring an unsymmetrical unsaturated N-heterocyclic car-bene (U$_2$-NHC) ligand accessible through a multicomponent process.[10] Apart from its high versatility and excellent Z-selectivity demonstrated in self-, cross- and ring-opening-polymerization metathesis, the novel cyclometalated catalyst Ru-4 showed impressive robustness in reactive media afford-ing good fidelity of high Z-selectivity over time, surpassing previously described Ru-catalysts. This sought-after feature led us to focus our attention on the development of a continuous flow Z-selective process. Over the last decade, continuous flow olefin metathesis has been well studied; with specific emphasis on the Ru-catalysts employed (both hetero-and homogeneous), and a variety of reactor designs, with

[*] J. Morvan, Dr. I. Curbet, Dr. S. Colombel-Rouen, Dr. T. Roisnel, Dr. C. Cr visy, Dr. M. Mauduit
Univ Rennes, Ecole Nationale Sup rieure de Chimie de Rennes CNRS, ISCR UMR 6226
35000 Rennes (France)
E-mail: marc.mauduit@ensc-rennes.fr

T. McBride
Cardiff Catalysis Institute, School of Chemistry, Cardiff University Main Building, Park Place, Cardiff, CF10 3AT (UK)

Dr. D. L. Browne
UCL School of Pharmacy (Room 210)
29–39 Brunswick Square, London, WC1 1AX (UK)
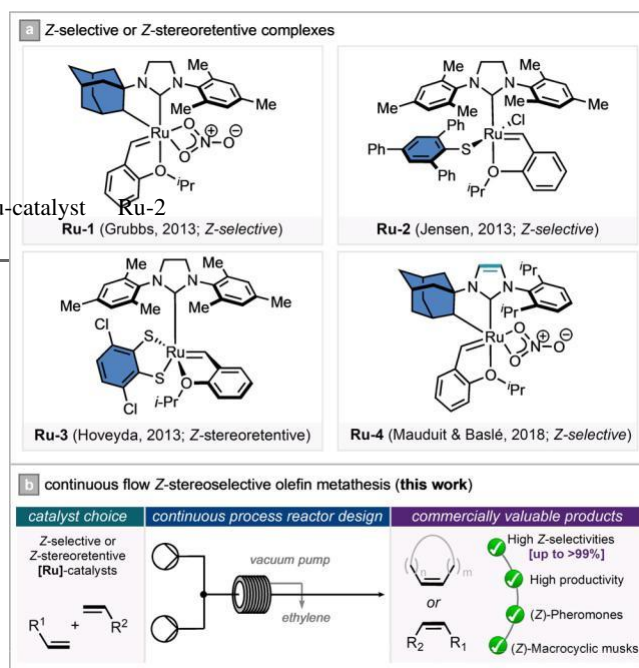E-mail: duncan.browne@ucl.ac.uk

Figure 1. a) Previously described Z-stereoselective catalysts (Ru-1, -2 and -4) and stereoretentive catalysts (Ru-3). b) Z-stereoselective con-tinuous flow olefin metathesis (this work).
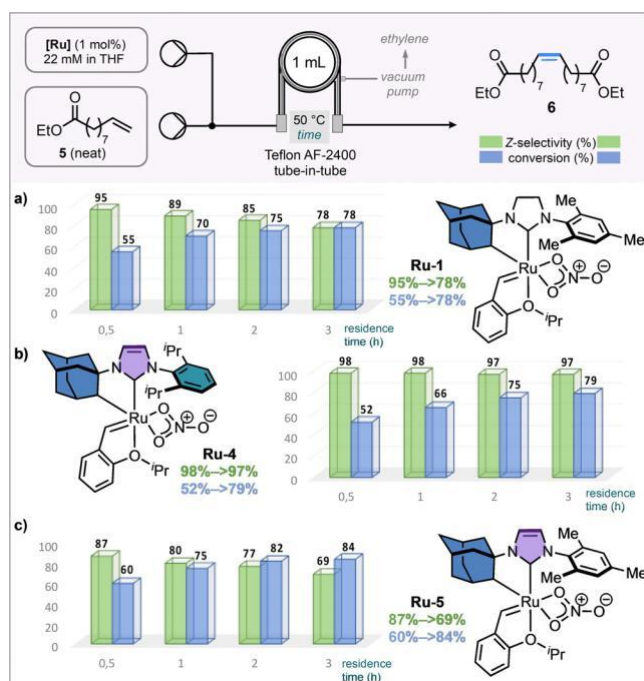
varying degrees of success.[11] A key criteria in reactor design is to enable efficient mass transfer thus allowing the removal of ethylene gas, this is especially key at larger scales.

Typically, gas-to-liquid-phase mass transfer in batch vessels become less efficient as scale increases owing to diminishing returns on surface area to volume ratios. Indeed, in 2014 Skowerski and co-workers demonstrated efficient mass transfer removal of ethylene gas with the application of a vacuum across a tube-in-tube permeable membrane reac-tor.[11k] Recent studies from Jamison, Bio and co-workers elegantly demonstrated an alternative perevaporation approach ("blowing" a stream of N2 gas across a permeable membrane to carry the ethylene gas out of the liquid phase) as an effective strategy for the mass transfer removal of ethylene gas.[11o] Despite these key developments in reactor design, a general approach to continuous flow Z-selective metathesis remains elusive. In order to realise an effective continuous process, careful attention must be given to both the catalyst choice and the continuous reactor design (Figure 1 b) but success in this area paves the way to the continuous preparation of a variety of pheromone and odorant mole-cules.

We initiated our study by investigating the application of a Teflon AF-2400 tube-in-tube semi-permeable membrane reactor[12] to the Z-selective process, preliminary results highlighted that application of a "vacuum-on" across the membrane for ethylene removal, versus "vacuum-off" deliv-ered a clear benefit in terms of yield (See Supplementary Information (SI); Table S4 entry 5). Taking this further, the self-metathesis (SM) of ethyl 9-decenoate under continuous flow condition using a 1 mL Teflon AF-2400 tube-in-tube reactor was explored in more detail against a focused collection of catalysts Ru-1, Ru-4 and Ru-5 (Scheme 1. For the gram-scale synthesis of Ru-4, -5 and X-ray character-isation of Ru-5,[13] see SI, Scheme S1 and Figure S5). Despite an excellent 95/5 Z/E ratio observed with Ru-1 within 0.5 h, the selectivity dropped gradually as the conversion increased reaching 78 % after 3 h of residence time (Scheme 1 a).[14] Interestingly, 2,6-diisopropylphenyl (DIPP)-containing cyclo-metalated Ru-4 demonstrated excellent catalytic perfor-mance in the flow reactor affording the desired internal olefin with 78 % conversion and very high 97 % Z-selectivity after 3 hours of residence time (Scheme 1 b).

The novel Ru-5 catalyst, which is a structural link between Ru-1 and Ru-4, deserved to be examined. Unfortunately, a lower range of Z-selectivity over time (87 to 69 %) was observed, although the resulting diester 6 was produced in a higher yield (84 %, Scheme 1 c).[14, 15] Consequently, the DIPP group appears to be the key structural moiety to deliver the highest selectivity. It is worth underlining that continuous flow metathesis can be conducted outside a glovebox while batch conditions require an open vessel inside the glovebox to efficiently remove the ethylene and reach high conversions.[16]
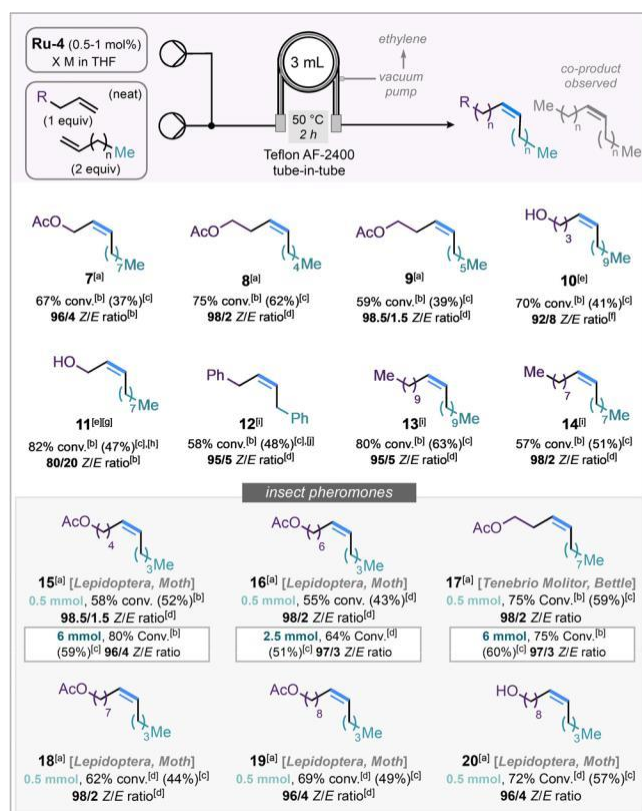
Having identified the combination of Ru-4 and a Teflon AF-2400 vacuum-on tube-in-tube design as the most efficient combination to achieve continuous Z-selective catalysis, a range of several cross- and self-metathesis transformations were explored in a larger 3 mL reactor (Scheme 2). Initially running a range of substrates through the reactor with a two-

Scheme 1. Catalytic performances of cyclometalated Ru-complexes Ru-1, -4, and -5 in continuous flow self-metathesis of ethyl 9-decenoate 5.

hour residence time and 1 mol % catalyst loading led to moderate to good conversions and yields. Notably, all CM products were formed in excellent Z-selectivity, ranging from 94 to 98.5 %, with the exception of allylic alcohol 11 which afforded a Z/E ratio of 80/20[17] Furthermore, a 0.5 mol %, Ru-4 loading was sufficient to promote the self-metathesis of allyl-benzene and other unfunctionalized linear terminal alkenes furnishing, after 2 hours, the corresponding internal Z-olefins 12–14 in excellent selectivity (up to 98 %) and moderate to good isolated yields. Using the designed flow reactor rig, highly valuable semiochemicals 15–20,[18] acting as potential bio-pesticides against Lepidoptera (moth) and Tenebrio Molitor (beetle), were efficiently produced with excellent Z-selectivity (96–98.5 %). Noticeable, a similar efficiency was observed at 6 mmol scale (12 times the standard substrate scope scale) with a slight alteration of Z-selectivity (96–97 %).

We next turned our attention to the macro ring-closing metathesis (RCM) reaction of terminal olefins. Typically, macro-RCM requires higher dilution than CM so as to minimise the competitive oligomerization reaction; reaction concentration therefore becomes a variable.[14] As depicted in Table 1 entries 1 and 2, similar catalytic performances were observed with Ru-1 and Ru-5 in the formation of the 16-membered macrocycle 22 when the reaction was run at 20 mM[19] in 1,2-dichloroethane (70 8C, 3 hours residence time, 70 % and 75 % isolated yield, respectively). Never-theless, the Z-selectivity still remained moderate reaching 86 % and 82 % respectively. To our delight, Ru-4 showed an impressive 97/3 Z/E ratio although a significantly lower yield was observed (24 % isolated yield, Table 1, entry 3).[20] By increasing the residence time to 4.5 h (entry 4), the yield could be slightly improved without any alteration of Z-

Scheme 2. Scope of continuous flow cross- and self-metathesis catalysed by Ru-4. [a] Catalyst loading: 1 mol % (14–23 mM in THF). [b] Determined by ^{1}H NMR spectroscopy with mesitylene as internal standard. [c] Isolated Yield. [d] Determined by GC analysis. [e] Residence time: 4 h. [f] Determined by quantitative ^{13}C NMR spectroscopy. [g] Catalyst loading: 2 mol % (40 mM in THF). [h] 13 % of SM-product were detected by ^{1}H NMR spectroscopy. [i] Catalyst loading: 0.5 mol % (10–17 mM in THF). [j] 5 % of isomerized by-product from allylbenzene were detected by ^{1}H NMR spectroscopy.

Table 1: Catalytic performances of cyclometalated Ru-complexes Ru-1,4,5 in continuous flow macro-RCM.

Entry	Catalyst	Time (h)	conc. @ tee (mM)	conv. (%)[a]	Yield[b]	Z:E ratio[c]
1	Ru-1	3	20	80	70	86:14
2	Ru-5	3	20	80	75	82:18
3	Ru-4	3	20	25	24	97:3
4	Ru-4	4.5	20	42	29	96:4
5	Ru-4	3	50	77	30[d]	95:5

[a] Determined by ^{1}H NMR spectroscopy using mesitylene as internal standard. [b] Isolated yield. [c] Z/E molar ratio were monitored by GC analysis. [d] Oligomers were also detected. [e] ^{1}H NMR yield. Nd: not determined.

Scheme 3. Catalytic performances of stereoretentive Ru-3 in continuous flow CM and mRCM. [a] 2 equiv of cis-butenediol were used (1.9 M in THF). [b] 4 equiv of cis-1,3-diacetoxy-2-butene were used (neat). [c] Determined by ^{1}H NMR spectroscopy with mesitylene as internal standard. [d] Isolated yield. [e] Determined by GC analysis. [f] Catalyst loading: 6 mol % (2.4 mM in THF); diene (40 mM in THF), 70 8C, 3 h. [g] Some amounts of dimer by-product were also detected.

selectivity demonstrating again the excellent stability of Ru-4. At a higher concentration (50 mM), similar isolated yield and Z-selectivity were observed but a competitive oligomeriza-tion occurred (entry 5). Applying these conditions for Ru-4 and Ru-5 (Table 1 entries 2 and 3) in the context of highly desirable macrocyclic odorant molecules or pheromones, cyclometalated Ru-4 surpassed Ru-5 in the mRCM (at 20 mM) providing (Z)-civetone 23[21] and Cryptoletes pusillus (rac)-(Z)-24,[22] which were isolated in 44 % yield and excellent 95–98 % Z-selectivity, respectively. Surprisingly, Ru-4 was inefficient toward (Z)-yuzu lactone 25,[23] where a higher yield was reached with the parent Ru-5 (32 % isolated yield) but the Z/E ratio remained moderate (82/18).

Given the deficiencies found in our efforts towards continuous flow Z-selective metathesis, namely moderate Z/ E ratios observed in CM involving allylic alcohols (product 11, Scheme 2) and moderate performance in mRCM reac-tions, we in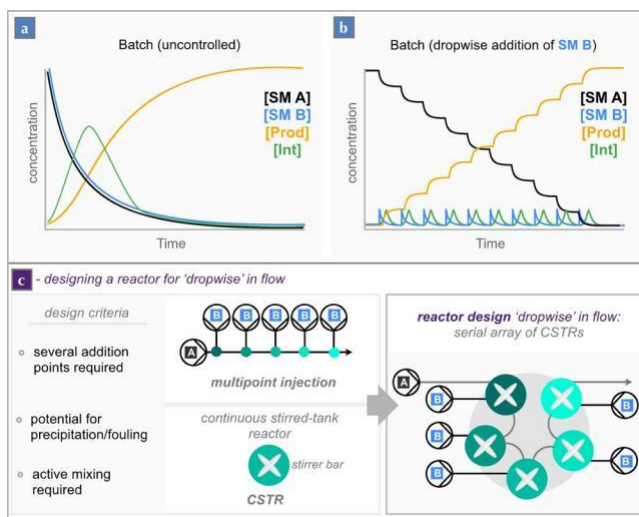vestigated the catalytic performance of the stereoretentive catecholdithiolate catalyst Ru-3[24] (Scheme 3). To our delight, the rapid reaction (within 5 min.) between cis-butenediol and 1-undecene led to the desired internal olefin 11 with a remarkable 99 % Z-selectiv-

ity and a moderate 56 % yield. It is worth noting that without vacuum, a slightly lower productivity and selectivity were observed despite the limited production of ethylene observed here. Interestingly, the in situ generated Ru-3, which avoids the requirement of a glove-box led to 11 with the same efficiency (see SI for details).[25] Furthermore, the stereo-retentive Ru-3 catalyst was also able to produce internal olefins 7, 26 and 27 with moderate to good yields and

excellent Z/E ratios (up to > 99/1). Unfortunately, Ru-3 was inefficient towards the mRCM leading to (Z)-yuzu lactone 25, delivering a low 7 % yield despite a prolonged residence time and higher reaction temperature. As some amounts of dimer by-product were also detected, we suspect that the semi-permeable membrane reactor is unable to efficiently remove the 1-butene co-product.

At last, due to the dilution condition (20 mM) required to produce Z-civetone 23 via macro-RCM (Table 1), we envis-aged an alternative synthetic route that involves a macro-cyclisation via a Dieckmann reaction of the Z-diester 6.[21b,c] Such a proposed route sets a challenge for continuous flow reactor design. Similarly to mRCM, macro-Dieckmann cyclisations also require careful control over the reactive intermediate concentration, so as to favour cyclisation over oligomerization. Reactions of this type are controlled in batch by dropwise addition of one of the components to keep the concentration of intermediate low, favouring cyclisation (Scheme 4 b).[21] Design of a reactor to achieve this in flow requires multiple injection points along the length of the reactor, where, at each point a portion of one component is introduced via a mixer to the flowing stream. Depending on the rate of reaction there may need to be a maturing period for the reaction prior to the next "injection" or "drop" of material.
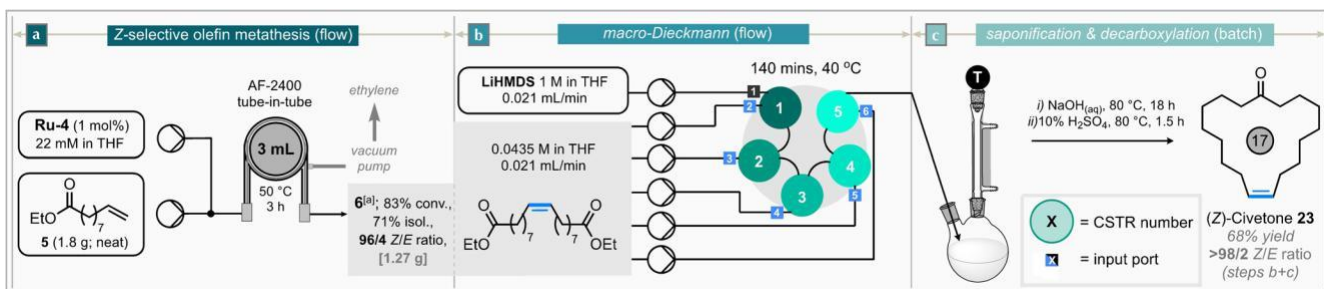
This can be achieved using a continuous stirred-tank reactor design (CSTR), which can also accommodate active stirring (Scheme 4 c). The use of multiple injection points and CSTRs is also a good reactor design if there is the risk of fouling, bridging or precipitation in the reactor. Deprotona-tions, or reactions incorporating organometallic reagents can encounter fouling or precipitation issues. Preliminary exper-imentation with a flow system which simply combined lithium bis(trimethylsilyl)amide (LiHMDS) with a full equivalent of diester 6 at a tee-piece, highlighted the propensity to form a precipitate and block the reactor. With this in mind we opted for a reactor design consisting of a serial array of CSTRs.[26] Incorporating this into a semi-continuous process targeting Civetone, we began with a larger scale self-meta-thesis of the bio-sourced ethyl 9-decenoate 5 catalyzed by cyclometalated Ru-4. Pleasingly, after 3 hours inside the 3 mL tube-in-tube reactor, 6 was isolated in good yield (71 %; 1.27 g) and excellent 96 % Z-selectivity (Scheme 5 a). Diester 6 was then diluted in THF and split across 5 input feeds. The base, LiHMDS, was used in large excess; such pseudo-first order conditions in base favour macrocyclization. LiHMDS

Scheme 4. Reactor design considerations for the continuous macro-Dieckmann cyclisation reaction.

was introduced into the serial CSTR reactor through input port 1 where it met the first portion of diester in tank 1 of the reactor and progressed through the reactor cascade to meet a total of 5 portions of diester before exiting to a batch collection flask (Scheme 5 b). The flowing output was col-lected into a stirring RBF and a solution of aqueous sodium hydroxide was added and heating commenced to saponify the cyclized ester intermediate (Scheme 5 c). Treatment of the b-keto acid with sulfuric acid induced decarboxylation and furnished (Z)-Civetone in 62 % yield, which is a comparable yield for the batch preparation of this material via a Dieck-mann cyclisation approach.

In summary, we have developed the first continuous flow Z-stereoselective olefin metathesis. Key to achieving this was finding the right combination of catalyst and reactor design. Among a selection of Z-stereoselective Ru-complexes, cyclo-metalated Ru-4 as well as dithiolated Ru-3 catalysts have proven to be the most efficient toward the formation of Z-internal olefins. Moderate to good yields and remarkable Z-selectivity (up to > 99 %) were obtained in various CM and mRCM allowing for the production of highly valuable pheromones and macrocyclic odorant molecules. Addition-ally, the continuous flow synthesis of (Z)-Civetone was successfully achieved in > 98 % Z-selectivity and 48 % yield over 3 steps from a biosourced raw material via a Z-selective

Scheme 5. Reactor design for the telescoped continuous Z-selective cross-metathesis/Dieckmann cyclisation approach to (Z)-Civetone 23.

CM followed by a Dieckmann cyclisation involving serial array of CSTRs.

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

Keywords: (Z)-Civetone · continuous flow · olefin metathesis · pheromones · Z-selectivity

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