A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

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

Authors: Jennifer Morvan, Tom McBride, Idriss Curbet, Sophie Colombel-Rouen, Thierry Roisnel, Christophe Crévisy, Duncan L Browne, and Marc Mauduit

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202106410

Link to VoR: https://doi.org/10.1002/anie.202106410

WILEY-VCH

10.1002/anie.202106410

WILEY-VCH

COMMUNICATION

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

Jennifer Morvan,[a] Tom McBride,[b] Idriss Curbet, [a] Sophie Colombel-Rouen, [a] Thierry Roisnel,[a] Christophe Crévisy, [a] Duncan L. Browne*[c] and Marc Mauduit*[a]

Dedication ((optional))

[a] J. Morvan, Dr. I. Curbet, Dr. S. Colombel-Rouen, Dr. T. Roisnel, Dr. C. Crévisy, Dr. M. Mauduit
Univ Rennes, Ecole Nationale Supérieure de Chimie de Rennes, CNRS, ISCR UMR 6226, F-35000 Rennes, France
E-mail: marc.mauduit@ensc-rennes.fr
[b] T. McBride
Cardiff Catalysis Institute, School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff, CF10 3AT, UK
[c] 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

Supporting information for this article is given via a link at the end of the document

Abstract: *The first continuous flow Z-selective olefin metathesis 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] efficiently promoted the transformation of *Z*-olefins into corresponding *Z*-products by retaining the stereochemical information (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 NHC (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 affording 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 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.

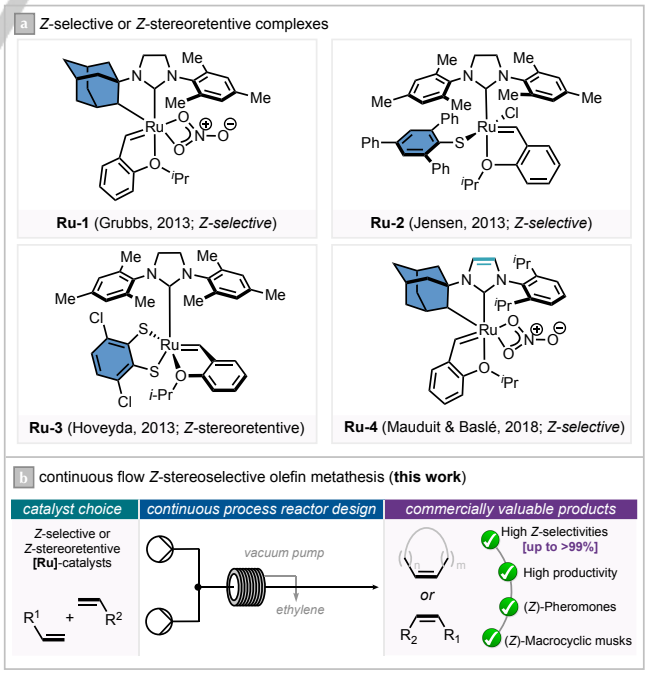


Figure 1 a) Previously described *Z*-stereoselective catalysts (**Ru-1**,-**2** and -**4**) and stereoretentive catalysts (**Ru-3**). b) *Z*-stereoselective continuous flow olefin metathesis (**this work**).

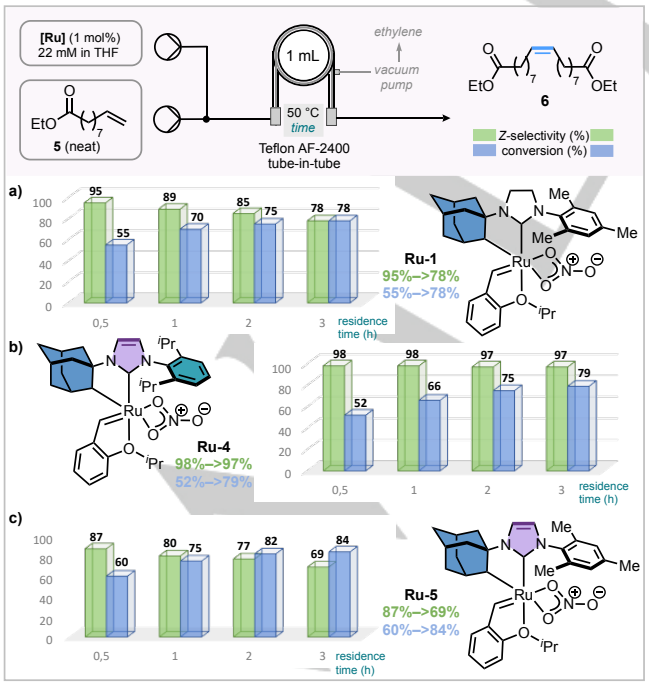
10.1002/anie.202106410

WILEY-VCH

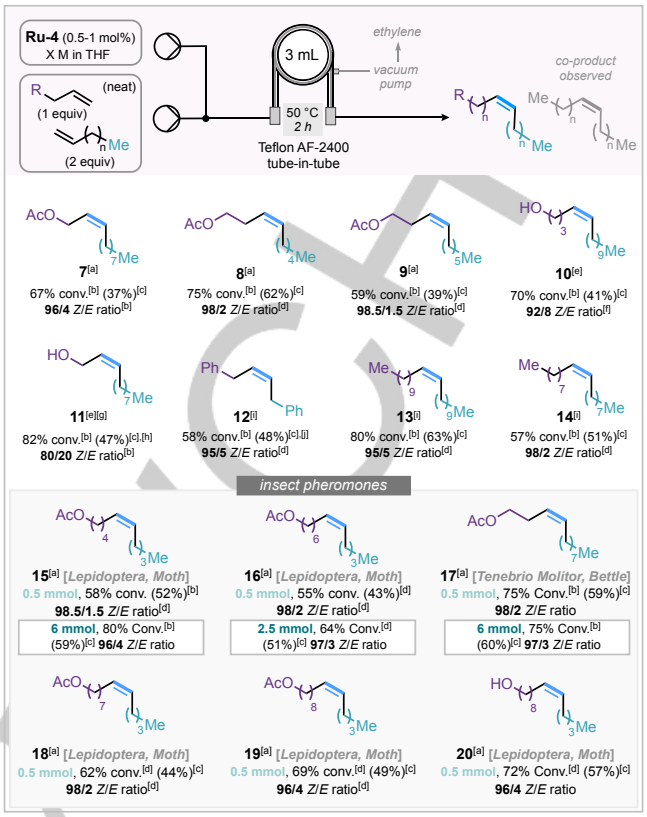
COMMUNICATION

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 reactor.[11k] Recent studies from Jamison, Bio and coworkers elegantly demonstrated an alternative perevaporation approach ('blowing' a stream of N_2 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 molecules.

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' delivered a clear benefit in terms of yield (See Supplementary Information (SI); table S4 entry 5). Taking this further, the self-metathesis 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 characterisation 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, DIPP-containing cyclometalated **Ru-4** demonstrated excellent catalytic performance 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).



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



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 with mesitylene as internal standard. [c] Isolated Yield. [d] Determined by GC. [e] Residence time: 4 h. [f] Determined by quantitative ^{13}C NMR. [g] Catalyst loading: 2 mol% (40 mM in THF). [h] 13% of SM-product were detected by ^{1}H NMR. [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.

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-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*

10.1002/anie.202106410

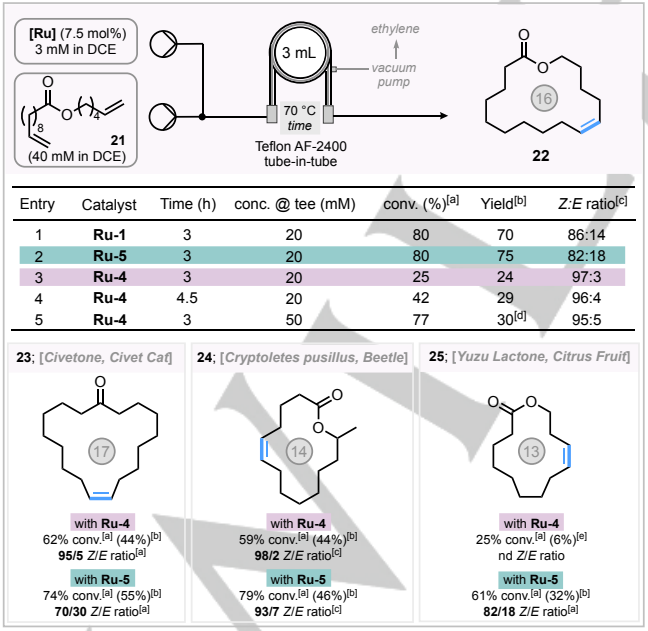
WILEY-VCH

COMMUNICATION

(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%).

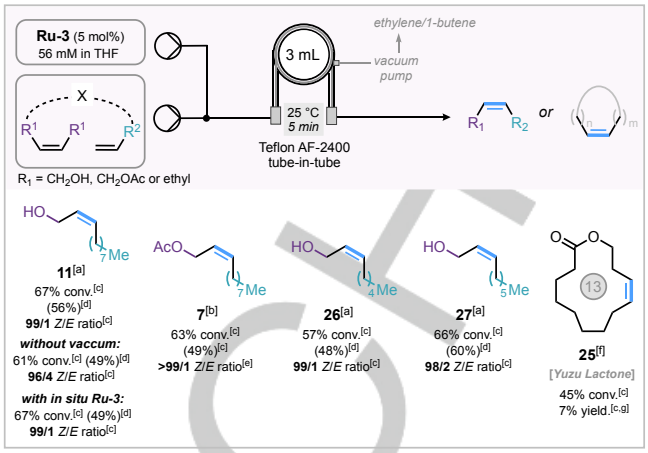
We next turned our attention to the macro-RCM reaction of terminal olefins. Typically, macro-RCM requires higher dilution than CM so as to minimise the competitive oligomerization reaction; reaction concentration therefore becomes a variable.[14] As depicted in Table 1 entries 1 and 2, similar catalytic 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 °C, 3 hours residence time, 70% and 75% isolated yield respectively). Nevertheless, 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*-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 oligomerization 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).

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

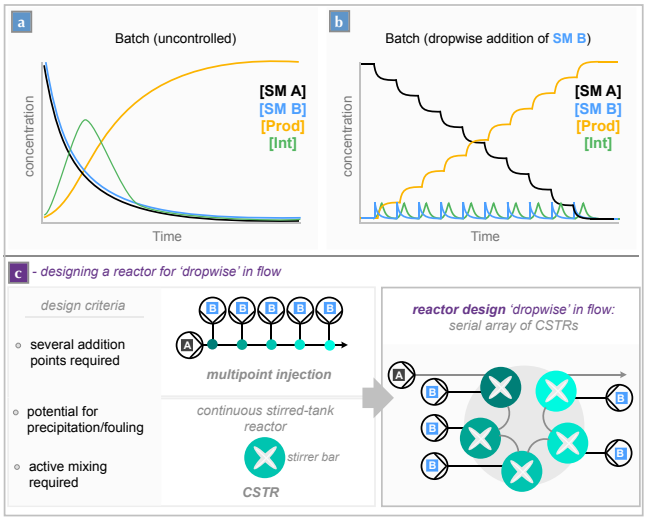


Scheme 3. Catalytic performances of stereoretentive **Ru-3** in continuous flow CM and mRCM. [a] 2 equiv of *cis*-butenediol were used (1.9 M in THF). [b] 4 equiv of *cis*-1,3-diacetoxy-2-butene were used (neat). [c] Determined by ^{1}H NMR with mesitylene as internal standard. [d] Isolated yield. [e]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

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 reactions, we investigated 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*-selectivity 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 stereoretentive **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 envisaged an alternative synthetic route that involves a macrocyclisation *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 requires careful control over the reactive intermediate concentration, so as to favor 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, favoring 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.

10.1002/anie.202106410



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

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. Deprotonations, or reactions incorporating organometallic reagents can encounter fouling or precipitation issues. Preliminary experimentation with a flow system which simply combined 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-metathesis 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, lithium bis(trimethylsilyl)amide (LiHMDS), was used in large excess; such pseudo-first order conditions in base favour macrocyclization. LiHMDS 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 collected 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 β-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 Dieckmann 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, cyclometalated **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. Additionally, 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 CM followed by a Dieckmann cyclisation involving serial array of CSTRs.

Acknowledgements

We are grateful to the CNRS and the Ecole Nationale Supérieure de Chimie de Rennes. This work was supported by the region Bretagne (ARED 2018 N° 601 – BIOMETA; grant to JM) and the FASO (grant to IC). TM thanks Cardiff University and EPSRC for a studentship (EP/N509449/1). Umicore AG & Co is acknowledged for a generous gift of Ru-complexes. We are grateful to Elsa Caytan and the PRISM core facility (Biogenouest©, UMS, Biosit, Université de Rennes 1) for NMR experiences.

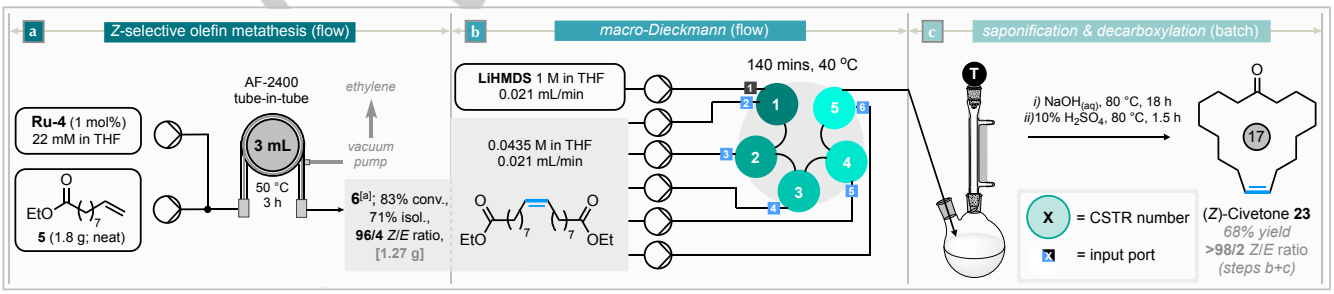
Keywords: Olefin metathesis • *Z*-selectivity • Continuous Flow • Pheromones • (*Z*)-Civetone

[1] a) *Handbook of Metathesis, 2nd Edition* (Eds.: R. H. Grubbs, A. G. Wenzel, D. J. O'Leary, E. Khosravi); Wiley-VCH: Weinheim, Germany, **2015**; b) *Olefin Metathesis: Theory and Pratice* (Ed: K. Grela), John Wiley & Sons: Hoboken, N. J., **2014;** c) O. M. Ogba, N. C. Warner, D. J. O'Leary, R. H. Grubbs, *Chem. Soc. Rev.* **2018**, *47*, 4510.

[2] Metathesis in Natural Product Synthesis: Strategies, Substrates, and Catalysts (Eds: Cossy, J.; Arseniyadis, S.; Meyer, C.) Wiley-VCH: Weinheim, Germany, **2010**.

[3] C. Bruneau, C. Fischmeister in *Alkene Metathesis for Transformations of Renewables* in Organometallics for Green Catalysis (Eds: P. Dixneuf, J. F. Soulé) Topics in Organometallic Chemistry, vol 63. Springer, **2018**.

[4] a) C. Slugovc in *Olefin Metathesis: Theory and Practice* (Ed: K. Grela) John Wiley & Sons: Hoboken, N. J., **2014**, pp. 329; b) S. Kovacic, C. Slugovc, *Mater. Chem. Front.*, **2020**, *4*, 2235.



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

[5] For selected reviews on stereoselective and stereoretentive metathesis, see: a) A. H. Hoveyda, *J. Org. Chem.* **2014**, *79*, 4763; b) M. H. Herbert, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2015**, *54*, 5018; c) T. P. Montgomery, T. S. Ahmed, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2017**, *56*, 11024; d) T. P. Montgomery, A. M. Johns, R. H. Grubbs, *Catalysts* **2017**, *7*, 87. e) D. S. Müller, O. Baslé, M. Mauduit, *Beilstein J. Org. Chem*. **2018**, *14*, 2999.

[6] a) B. K. Keitz, K. Endo, P. R. Patel, M. B. Herbert, R. H. Grubbs, *J. Am. Chem. Soc.* **2012**, *134*, 693; For recent developments, see: b) Y. Xu, J. J. Wong, A. E. Samkian, J. Hoon Ko, S. Chen, K. N. Houk, R. H. Grubbs, *J. Am. Chem. Soc.* **2020**, *142*, 20987.

[7] a) G. Occhipinti, F. R. Hansen, K. W. Törnroos, V. R. Jensen, *J. Am. Chem. Soc.* **2013**, *135*, 3331; For recent developments, see: b) W. Smit, J. B. Ekeli, G. Occhipinti, B. Woźniak, K. W. Törnroos, V. R. Jensen, *Organometallics* **2020** *39*, 397.

[8] a) R. K. M. Khan, S. Torker, A. H. Hoveyda, *J. Am. Chem. Soc.* **2013**, *135*, 10258; For recent developments, see: b) Z. Liu, C. Xu, J. del Pozo, S. Torker, A. H. Hoveyda, *J. Am. Chem. Soc.* **2019**, *141*, 7137.

[9] A. Dumas, R. Tarrieu, T. Vives, T. Roisnel, V. Dorcet, O. Baslé, M. Mauduit, *ACS Catal.* **2018**, *8*, 3257.

[10] a) P. Queval, C. Jahier, M. Rouen, I. Artur, J.-C. Legeay, L. Falivene, L. Toupet, C. Crévisy, L. Cavallo, O. Baslé, M. Mauduit, *Angew. Chem. Int. Ed.* **2013**, *52*, 14103; b) R. Tarrieu, A. Dumas, J. Thongpaen, T. Vives, T. Roisnel, V. Dorcet, C. Crévisy, O. Baslé, M. Mauduit, *J. Org. Chem.* **2017**, *82*, 1880.

[11] a) A. Michrowska, K. Mennecke, U. Kunz, A. Kirschning, K. Grela, *J. Am. Chem. Soc.*, **2006**, *128*, 13261; b) S. Monfette, M. Eyholzer, D. M. Roberge, D. E. Fogg, *Chem. Eur. J.* **2010**, *16*, 11720; c) E. Riva, A. Rencurosi, S. Gagliardi, D. Passarella, M. Martinelli, *Chem. Eur. J.*, **2011**, *17*, 6221; d) R. Duque, E. Ochsner, H. Clavier, F. Caijo, S. P. Nolan, M. Mauduit, D. J. Cole-Hamilton, *Green Chem.*, **2011**, *13*, 1187; e) E. Borré, M. Rouen, I. Laurent, M. Magrez, F. Caijo, C. Crévisy, W. Solodenko, L. Toupet, R. Frankfurter, C. Vogt, A. Kirschning, M. Mauduit, *Chem. Eur. J.*, **2012**, *18*, 16369; f) K. Skowerski, C. Wierzbicka, K. Grela, *Curr. Org. Chem.*, **2013**, *17*, 2740; g) W. Solodenko, A. Doppiu, R. Frankfurter, C. Vogt, A. Kirschning, *Aust. J. Chem.*, **2013**, *66*, 183; h) R. Munirathinam, J. Huskens, W. Verboom, *Adv. Synth. Catal.*, **2015**, *357*, 1093; i) M. Bru, R. Dehn, J. H. Teles, S. Deuerlein, M. Danz, I. B. Müller, M. Limbach, *Chem. Eur. J.*, **2013**, *19*, 11661; j) E. J. O'Neal, K. F. Jensen, *ChemCatChem*, **2014**, 6, 3004; k) K. Skowerski, S. J. Czarnocki, P. Knapkiewicz, *ChemSusChem*, **2014**, *7*, 536; l) C. Schotten, D. Plaza, S. Manzini, S. P. Nolan, S. V. Ley, D. L. Browne, A. Lapkin, *ACS Sustainable Chem. Eng.*, **2015**, *3*, 1453; m) M. Drop, X. Bantreil, K. Grychowska, G. U. Mahoro, E. Colacino, M. Pawłowski, J. Martinez, G. Subra, P. Zajdel, F. Lamaty, *Green Chem*. **2017**, *19*, 1647; n) É. Morin, J. Sosoe, M. Raymond, B. Amorelli, R. M. Boden, S. K. Collins, *Org. Process Res. Dev*. **2019**, *23*, 283; o) C. P. Breen, C. Parrish, N. Shangguan, S. Majumdar, H. Murnen, T. F. Jamison, M. M. Bio, *Org. Process Res. Dev*. **2020**, 24, 2298.

[12] For previous developments with tube-in-tube reactors, see for instance, ref 11k and: a) M. O'Brien, I. R. Baxendale, S. V. Ley, *Org. Lett.* **2010**, *12*, 1596; b) S. L. Bourne, P. Koos, M. O'Brien, B. Martin, B. Schenkel, I. R. Baxendale, S. V. Ley, *Synlett* **2011**, *18*, 2643; c) M. A. Mercadante, N. E. Leadbeater, *Org. Biomol. Chem*. **2011**, *9*, 6575; d) S. Kasinathan, S. L. Bourne, P. Tolstoy, P. Koos, M. O'Brien, R. W. Bates, I. R. Baxendale, S. V. Ley, *Synlett* **2011**, *18*, 2648; e) A. Polyzos, M. O'Brien, T. P. Petersen, I. R. Baxendale, S. V. Ley, *Angew. Chem. Int. Ed.* **2011**, *50*, 1190; f) T. P. Petersen, A. Polyzos, M. O'Brien, T. Ulven, I. R. Baxendale, S. V. Ley, *ChemSusChem* **2012**, *5*, 274; g) P. B. Cranwell, M. O'Brien, D. L. Browne, P. Koos, A. Polyzos, M. Pena-Lopez, S. V. Ley, *Org. Biomol. Chem.* **2012**, *10*, 5774. For prior use of Teflon AF2400 in tube-in-tube reactors, see for instance: h) I. Pinnau, L. G. Toy, *J. Membr. Sci.* **1996**,*109*, 125; i) A. Y. Alentiev, V. P. Shantarovich, T. C. Merkel, V. I. Bondar, B. D. Freeman, Y. P. Yampolskii, *Macromolecules* **2002**, *35*, 9513; j) T. C. Merkel, V. Bondar, K. Nagai, B. D. Freeman, Y. P. Yampolskii, *Macromolecules* **1999**, *32*, 8427; k) S. L. Bourne, M. O'Brien, S. Kasinathan, P. Koos, P. Tolstoy, D. X. Hu, R. W. Bates, B. Martin, B. Schenkel, S. V. Ley, *ChemCatChem* **2013**, *5*, 159. l) M. Brzozowski, M. O'Brien, S. V. Ley, A. Polyzos, *Acc. Chem. Res.* **2015**, *48*, 349; m) P. B. Cranwell, M. O'Brien, D. L. Browne, P. Koos, A. Polyzos, M. Peña-Lopez, S. V. Ley, *Org. Biomol. Chem.* **2012**, *10*, 5774; n) D. L. Browne, M. O'Brien, P. Koos, P. B. Cranwell, A. Polyzos, S. V. Ley, *Synlett*, **2012**, *23*, 1402; o) J. C. Pastre, D. L. Browne, M. O'Brien, S. V. Ley, *Org. Process Res. Dev.* **2013**, *17*, 1183; p) F. Mastronardi, B. Gutmann, C. O. Kappe, *Org. Lett.* **2013**, *15*, 5590; q) L. Kupracz, A. Kirschning, *Adv. Synth. Catal.* **2013**, *355*, 3375.

[13] Cambridge Crystallographic Data Center (CCDC 2079754 and 2072389).

[14] We suspect catalyst decomposition over time. For decomposition pathways for *Z*-selective catalysts, see: M. B. Herbert, Y. Lan, B. K. Keitz, P. Liu, K. Endo, M. W. Day, K. N. Houk, R. H. Grubbs, *J. Am. Chem. Soc*. **2012**, *134*, 7861.

[15] These catalytic behaviours are in full accordance with results observed in self-metathesis reactions conducted under batch conditions (see SI, table S1).

[16] For a recent review on the ethylene effect on efficiency and stereocontrol, see: A. H. Hoveyda, Z. Liu, C. Qin, T. Koengeter, Y. Mu, *Angew. Chem. Int. Ed.* **2020**, *59*, 22324.

[17] As this lower selectivity was also observed in batch conditions (affording **11** in a 65/35 *Z*/*E* ratio, see SI, p S32), a level of incompatibility of the allylic alcohol functionality is suspected.

[18] For an interesting review dealing with the synthesis of semiochemicals via olefin metathesis, see: a) G. Turczel, E. Kovacs, G. Merza, P. Coish, P. T. Anastas, R. Tuba, *ACS Sustainable Chem. Eng*. **2019**, *7*, 33; for previous synthesis of pheromones: for **15**-**16**, see: b) V. I. Bykov, T. A. Butenko, E. V Egupova, E. S. Finkelshtein, Russ. Chem. Bull. 2000, 49, 1301; for **17**, see ref. 9; for **18**, see ref. 6a; for **19**, see: c) K. M. Wampler, P. Meinhold, P. Coelho, V. Bui, L. Ondi, H. Mehdi. US Patent 2017/0137365 A1, **2017**; for **20**, see: d) M. B. Herbert, V. M. Marx, R. L. Pederson, R. H. Grubbs *Angew. Chem. Int. Ed.* **2013**, *52*, 310.

[19] Skowerski and co-workers reported the non Z-selective continuous flow synthesis of macrocyclic **22** at higher dilution (5 mM), see ref. 11k

[20] This lower productivity was also observed in batch conditions that affords **22** in a 32% yield (see SI, Table S7, entry 2).

[21] For previous stereoselective synthesis of (*Z*)-Civetone, see: a) A. Fürstner, G. Seidel, *J. Organomet. Chem.* **2002**, *606*, 75; b) Y. Tanabe, A. Makita, S. Funakoshi, R. Hamasaki, T. Kawakusu T. *Adv. Synth. Catal.* **2002**, *344*, 507; c) H. Hagiwara, T. Adachi, T. Nakamura, T. Hoshi, T. Suzuki, *Natural Product Communications*, **2012**, *7*, 913.

[22] a) For previous enantioselective synthesis of (*S*)-**24**, see: T. Hamada, K. Daikai, R. Irie, T. Katsuki, *Synlett* **1995,** 407-408*;* b) For previous synthesis of (*rac*)-**24** by (non *Z*-selective) olefin metathesis, see: A. Fürstner, K. Langemann, *Synthesis* **1997**, 792

[23] a) R. P. Doss, S. J. Gould, K. J. R. Johnson, R. A. Flath, R. L. Kohnert, *Phytochemistry* **1989**, *28*, 3311; b) L. Rodefeld, W. Tochtermann, *Tetrahedron* **1998**, *54*, 5893.

[24] We used a home-made **Ru-3** following a modified procedure, see SI.

[25] The *in situ* formation of dithiolated catalysts is advantageous as it avoids the use of a glove-box for weighing the air-sensitive catalyst **Ru-3**, see: D. S. Müller, I. Curbet, Y. Raoul, J. Le Nôtre, O. Baslé, M. Mauduit, *Org. Lett.* **2018,** *20,* 6822.

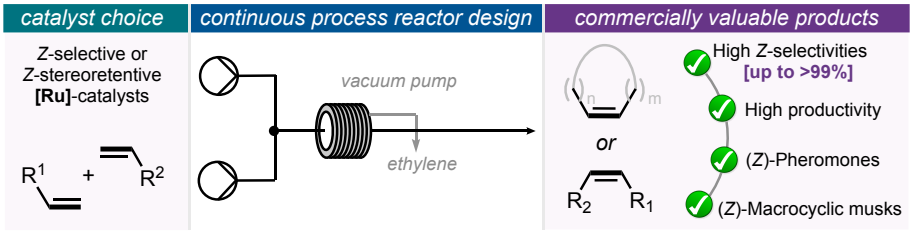
[26] In this work we have used the *f*Reactor, see: a) M. R. Chapman, M. H. T. Kwan, G. King, K. E. Jolley, M. Hussain, S. Hussain, I. E. Salama, C. G. Niño, L. A. Thompson, M. E. Bayana, A. D. Clayton, B. N. Nguyen, N. J. Turner, N. Kapur, A. J. Blacker, *Org. Process Res. Dev*. **2017**, *21*, 1294; b) K. E. Jolley, M. R. Chapman, A. J. Blacker, *Beilstein J. Org. Chem.* **2018**, *14*, 2220; c) M. R. Chapman, S. C. Cosgrove, N. J. Turner, N. Kapur, A. J. Blacker, *Angew. Chem. Int. Ed.* **2018**, *57*, 10535.

10.1002/anie.202106410

WILEY-VCH

COMMUNICATION

Entry for the Table of Contents



The first continuous flow *Z*-stereoselective olefin metathesis was described with a set of *Z*-stereoselective Ru-catalysts. Good productivity and excellent *Z*-selectivity (up to >99%) were obtained in the formation of various internal olefins including highly desirable pheromones and macrocyclic odorant molecules. A telescoped Z-selective cross-metathesis/Dieckmann cyclisation sequence to access (*Z*)-Civetone, incorporating a serial array of continually stirred tank reactors was also reported.

Institute and/or researcher Twitter usernames: ((optional))