DOI: 10.1002/cssc.201300829



## Tube-In-Tube Reactor as a Useful Tool for Homo- and Heterogeneous Olefin Metathesis under Continuous Flow Mode

Krzysztof Skowerski,\*<sup>[a]</sup> Stefan J. Czarnocki,<sup>[a]</sup> and Paweł Knapkiewicz<sup>[b]</sup>

A tube-in-tube reactor was successfully applied in homo- and heterogeneous olefin metathesis reactions under continuous flow mode. It was shown that the efficient removal of ethylene facilitated by connection of the reactor with a vacuum pump significantly improves the outcome of metathesis reactions. The beneficial aspects of this approach are most apparent in reactions performed at low concentration, such as macrocyclization reactions. The established system allows achievement of both improved yield and selectivity, and is ideal for industrial applications.

tion of renewable raw materials or the introduction of catalysts

that are effective at low loading.<sup>[3]</sup> There is, however, another

direction that remains underdeveloped. This is the application

### Introduction

Over the past decades, olefin metathesis has been repeatedly proved to be an efficient method of C–C double bond formation.<sup>[1]</sup> Both the industrial and academic success of this approach was breach was breach by

proach was largely caused by the development of stable and active ruthenium catalysts, such as 1-3 (Figure 1). Today, a vast array of commercially available complexes allows chemists to optimize conditions of nearly any metathetic transformation. This is of crucial importance, as it has been proved that no single catalyst outperforms

tions.<sup>[2]</sup> Although great advances have been made, some issues in the field of olefin metathesis remain. Probably the most significant, especially for industrial applications, is a need for the development of more efficient and sustainable metathesis processes. To achieve this, research is widely underway into the utiliza-

others in all metathesis reac-



Figure 1. Classical metathesis catalysts 1–3 and complexes 4, 5 used in flow mode metathesis (Mes = 2,4,6-trime-thylphenyl).

[a]	K. Skowerski, Dr. S. J. Czarnocki
	Apeiron Catalysts
	Duńska 9, 54-427 Wrocław (Poland)
	E-mail: krzysztof.skowerski@apeiron-catalysts.com
[b]	Dr. P. Knapkiewicz
	Division of Microengineering and Photovoltaics
	Faculty of Microsystem Electronics and Photonics
	Wrocław University of Technology
	Janiszewskiego 11/17, 50-372 Wrocław (Poland)
	Supporting Information for this article is available on the WWW under
	http://dx.doi.org/10.1002/cssc.201300829

of well-defined catalysts to conduct metathetic processes in continuous flow (CF) mode.<sup>[4]</sup> The potential of this methodology was demonstrated in pioneering works reported by Buchmeiser et al.,<sup>[5]</sup> in which the heterogeneous catalyst **4** gave a turnover number (TON) of 480 in the CF cyclization of diethyl diallylmalonate.

Further detailed studies revealed that the efficiency observed for both the homogeneous and heterogeneous catalysts usually applied in batch reactors (BR), tends to decrease

## CHEMSUSCHEM Full papers

significantly in continuous or circulating flow processes.<sup>[6]</sup> For example, in the ring-closing metathesis (RCM) of diethyl diallylmalonate, the TON observed for heterogeneous catalyst 5 decreased from 968 in BR to 75 in a circulating flow reactor.[6b] This problem is strongly connected to the evolution throughout the metathesis reaction of ethylene, which is not efficiently removed in typical CF-conducted processes. The decomposition studies of metathesis catalysts reported by Grubbs and co-workers proved that, in contact with ethylene, unstable ruthenium methylidene species are formed that are susceptible to degradation, thus decreasing the overall efficiency.<sup>[7]</sup> Moreover, it was shown that pretreatment of 1 a with ethylene prior to metathesis in a CF mode negatively impacts its performance.<sup>[8,9]</sup> An additional confirmation of the negative influence of ethylene is the observation that high TON values (up to 10000) were obtained in continuous flow processes in which ethylene is not produced, such as ring-opening ring-closing metathesis, ring-opening metathesis polymerization, and selfmetathesis.<sup>[10]</sup> To the best of our knowledge, only two setups were developed to solve the problems related to ethylene evolution in metathesis under flow mode. Although very successful, both solutions suffer from some limitations. The use of a degassing module, as proposed by Ying et al., <sup>[6e]</sup> is not applicable in the classical CF reactors, and the continuous stirred tank reactor (CSTR) used by Fogg et al. is not appropriate for reactions promoted by heterogeneous catalysts.<sup>[6f]</sup> This in-

spired our research focused on finding a better, more universal solution that would give researchers the opportunity to move processes from batch to CF systems without losing catalyst efficiency, a task that has proved to be extremely difficult so far.

## **Results and Discussion**

We present herein our efforts towards the development of more efficient homo- and heterogeneous olefin metathesis processes proceeding in CF mode with the evolution of ethylene. We performed a series of CF experiments in tube-in-tube reactors,<sup>[11]</sup> widely utilized in other areas of organic synthesis. The benefit of such systems is strongly related to the process efficiency that they provide, which is crucial, especially in industrial applications. The very high throughput that can be provided by flow reactors, combined with no scale-up effects, makes this technology ideal for large-scale production. These characteristics motivated us to study the possible applications of metathesis in such systems, which, to the best of our knowledge, has not been examined before.

The reactor utilized in the present study was constructed from two tubes. The outer tube was made from fine Teflon and the inner tube was made from porous material. During our initial search for the best semipermeable material we turned our attention to siloxane-based materials such as polydimethoxysiloxane (PDMS) as well as poly(1-trimethylsilyl-1propyne) (PTMSP), which are characterized by very good permeability for ethylene. Unfortunately, both these materials swell significantly in contact with organic solvents; moreover, PTMSP undergoes significant physical aging. Therefore, we decided to use tubes made from Teflon AF2400, a commercially available semipermeable material that was previously applied in tube-in-tube reactors.<sup>[12]</sup> The efficient removal of the ethylene evolved within the reaction progress was facilitated by connection of the inner tube to a vacuum pump. The driving force for the removal of ethylene is a great pressure difference on both sides of the internal tube. As a result, migration of ethylene through the Teflon AF2400 tube is possible, thus diminishing its negative impact on the metathesis outcome. The schematic presentation of this new plug flow reactor-vacuum (PFR-V) is pictured in Figure 2.







We decided to test this system by performing both hetero- and homogenous metathesis. The former, which in CF-mode can be even more challenging than the latter, was promoted by catalyst **6**, which was synthesized in our laboratory<sup>[13]</sup> and deposited on commercially available silica gel. Heterogeneous **6-SiO**<sub>2</sub> was used in the

RCM of **7** in toluene at 80 °C (Table 1 and Figure 3).

For comparative purposes, all reactions were performed in three modes: batch (BR), tube-in-tube reactor in which the

Table 1. Results of	of RCM of 7 promoted by h	eterogeneous <b>6</b> -SiO <sub>2</sub> .
Mode	TON	Ru content [ppm]
BR PFR PFR-V	490 71 154	3.2 1.5 3.0



Figure 3. Results of the RCM of 7 promoted by heterogeneous  $6-SiO_2$ : a) in BR mode; b) in CF mode.

outlets of inner tube were closed (PFR), and the new combination in which the inner tube was connected to a vacuum pump (PFR-V). The reaction in BR mode promoted by 6-SiO<sub>2</sub> (0.2 mol%) provided the tri-substituted product 8 in almost quantitative yield, which corresponds to a TON of 490. Because we needed to know the overall conversion for the calculation of TON, it was important to check that metathesis does not occur outside the reactor. Therefore, we performed split tests that proved the heterogeneity of the catalytic system in both batch and CF reactor (see the Supporting Information for details). As the outcome of heterogeneous olefin metathesis in flow mode depends on many factors, it was crucial to ensure that conditions for reactions in PFR and PFR-V are identical so that the influence on catalyst efficiency of ethylene removal alone could be observed. The catalyst, 6-SiO<sub>2</sub> was loaded into the space between the inner and the outer tube and the reaction was run at relatively low concentration of 7 (0.1 M) with low flow rate of 40  $\mu$ L min<sup>-1</sup> to minimize the influence of ethylene evolution on residence time in PFR. These conditions could, to some extent, negatively affect the efficiency of 6-SiO<sub>2</sub> in CF mode. However, it should be noted that the aim of this study was to prove the compatibility of PFR-V with heterogeneous metathesis, not to optimize the conditions of such transformations. The overall result of 6-SiO2-promoted RCM leading to 8 in PFR (TON=71) was found out to be nearly seven times less efficient than the same reaction in BR mode (TON=490). Ring-closing metathesis in PFR-V was over two times more productive (TON = 154) than in PFR and the catalyst retained some activity even after 20 h. The efficiency of 6-SiO<sub>2</sub> in this approach is obviously insufficient for practical applications. Nevertheless, the benefits originating from removal of ethylene in PFR-V are evident. Importantly, in all reactor types, ruthenium content in the product was very low, as determined by inductively coupled plasma mass spectrometry (ICP-MS).

To check whether the positive effect of application of PFR-V is also evident in homogeneous metathesis, we conducted RCM of **9** promoted by only 0.05 mol% of **3** (Table 2).

The initial experiment was performed in toluene heated to  $80 \,^{\circ}$ C with 0.2 M concentration of **9** and showed only minor efficiency differences between the three types of tested reactors. Therefore, we decided to explore the same reaction performed at an olefin concentration of  $0.02 \,\text{M}$ , at which the molar ratio



<sup>© 2014</sup> Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

of dissolved ethylene to catalyst should be higher. The positive effect of ethylene removal was more pronounced at lower reaction concentrations. In BR and PFR-V mode, maximum conversion was observed after 20 min.<sup>[14]</sup> In PFR-V mode, catalyst 3 not only provided higher conversion than in PFR mode, but also initiated faster and remained active two times longer, surpassing the results obtained by utilization of BR.<sup>[15]</sup> Importantly, even at a relatively high concentration of 0.2 m, we observed almost the same conversion in BR and in PFR-V, proving that diffusion of ethylene through Teflon AF2400 does not limit the efficiency of our reactor. The results obtained at 0.2 M and 0.02 M in CF mode suggest that the negative effect of ethylene can be limited by performing the reaction at high concentration. However, there are some metathetical transformations that are preferably performed at low concentration. Seeing the benefit of our system in conditions of low concentration, we decided to continue our research in this direction.

We examined the PFR-V system in the homogeneous ringclosing metathesis of **11** and **12** (Table 3). Metathetic macrocyclization is one of the reactions requiring high dilution con-



ditions (5 mm or lower) in order to avoid formation of oligomeric byproducts, so we presumed a significant advantage of PFR-V over PFR.<sup>[16]</sup> The results of RCM leading to **13** and **14** are summarized in Table 3.

In all cases, both the conversion and selectivity varied from good to excellent. Both PFR-V and PFR ensured higher selectivity than BR; this was most apparent in RCM of **11**, a precursor of a musk-scented fragrance ingredient.<sup>[16b]</sup> A decrease in yield of **13** and **14** was observed when the reaction was conducted in PFR instead of BR. On the other hand, yields in PFR-V were noticeably higher than in BR. This suggests that, at low concentrations, removal of ethylene in PFR-V is even better than in the open batch reactor, a finding that was not anticipated by us. Interestingly, in all cases, the selectivity of reaction was affected by isomerization and ring contraction, not by substrate oligomerization.

The most important observation was that the yield noted in CF setup, when ethylene was removed, was 50-60% higher (57 vs. 90% yield). Having obtained these promising results, further optimization was undertaken. RCM of 11 run in PFR-V with 0.25 mol% of 3 resulted in the formation of 13 in 60% yield [as determined by gas chromatography (GC)], corresponding to a TON of 240 [turnover frequency (TOF) of  $0.2 \text{ s}^{-1}$ ],<sup>[17]</sup> which was over two times higher than observed for reaction in PFR, but remained unsatisfactory. The general conclusion from these experiments is that PFR-V is especially suitable for macrocyclization reactions that have to be performed at low concentration, because it ensures better conversion and selectivity. In addition, with appropriate construction of the whole setup (for example, application of continuous removal of solvent from post reaction mixture), the use of PFR-V can avoid the need for large volumes of solvents.

Searching for further applications of the PFR-V system, we turned to utilization of renewable resources. Long chain diesters and aminoesters are valuable monomers for the synthesis of polymers, thus their production in CF mode should be of interest for the industry if high throughput can be achieved.<sup>[18]</sup> Recently, it has been shown that cross metathesis (CM) of renewable unsaturated esters with methyl acrylate or acrylonitrile can be an attractive way to synthesize such compound-s.<sup>[3a-e]</sup> To test the compatibility of our setup with CM we reacted methyl undecenoate (**15**) with 4 equivalents of methyl acrylate (**16**) in the presence of 0.5 mol% of fast initiator **2**′ (Table 4).<sup>[19]</sup>

Table 4	CM of methyl undecenoate with methyl acrylate. $(-1)^{0}$ $(-1)^$	0-
Mode	Conversion [%]	t <sub>end</sub> [min]
BR	91	30
PFR	62	10
PFR-V	92	30

Again, a significant decrease in conversion of the substrate was observed when reaction was conducted in PFR instead of BR. Results of the process in BR and PFR-V modes were similar. Directly comparing PFR and PFR-V, the reaction proceeded with significantly higher conversion and the catalyst remained active three times longer when ethylene is removed. Notably, in all cases, only traces of the dimer of 15 (<1%) were observed. Attempts to conduct this transformation at higher concentrations revealed differences in results that were not strongly pronounced. A minor difference in conversion in PFR and PFR-V was observed at 0.2 m reaction concentration (86% and 93%, respectively). Nevertheless, conversion in PFR-V was very close to that observed in BR (95%), proving again that removal of ethylene in PFR-V is effective even at high concentration. As in the case of RCM, high concentration in CM limited the negative effect of ethylene observed in PFR. This is also

<sup>© 2014</sup> Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

the reason that the advantage of PFR-V over PFR is more apparent at low concentration.

During the experiments, an interesting observation was made. The conversion in BR and PFR-V always grows as the reaction time increases (up to maximum conversion). In the PFR mode, on the other hand, an inconsistency was observed (Figure 4). The maximum conversions for CM in PFR were observed after 5 min (89%) and 10 min (62%) at 0.2 M and 0.02 M



Figure 4. CM of 15 and 16 at 0.02 M concentration.

concentration, respectively. After slightly longer reaction times, conversion dropped and then again started to increase when reactions were performed for a longer period. This suggests that, after accumulation of some critical amount of ethylene, the reverse reaction – ethenolysis – may occur. However, limited mixing efficiency in the presence of ethylene bubbles could be responsible for these unusual results as well. Thus, PFR-V can also serve as a useful tool for fast optimization of reaction conditions for batch processes, as results obtained in these reactors are generally in good agreement.

## Conclusions

We have shown that the problems associated with ethylene presence in CF olefin metathesis processes catalyzed by ruthenium complexes can be easily circumvented by a new approach: utilization of a tube-in-tube reactor. This work presents the compatibility of the PFR-V system with both hetero- and homogeneous metathesis reactions. A significant increase in heterogeneous catalyst efficiency is observed in PFR-V when compared to a simple continuous flow reactor (PFR). Results of homogeneous RCM and CM reactions run at low concentrations in PFR-V mode also clearly proved the beneficial aspects of ethylene removal under CF mode. In addition, the results obtained using the developed technique are similar or better than those obtained in batchwise mode, even at concentration as high as 0.2 m, and the technique is free from scale-up issues. It seems that material which would allow better diffusion of ethylene could potentially provide further improvement, namely higher substrate conversions in CF setup than in batch setup, as was observed for reactions run at very low concentration. Work is on-going in our laboratory to explore the enormous potential of the PFR-V reactor in olefin metathesis, including on-line removal of residual ruthenium or modification of the reactor to allow for the portionwise addition of ruthenium complex, which is known to be beneficial in metathetic transformations.

### **Experimental Section**

#### Materials

Toluene (Sigma–Aldrich) was dried by distillation over Na, transferred under argon and stored over MS 4A molecular sieves (Alfa Aesar). Indenylidene  $2^{nd}$  generation catalyst (**3**, Stream) as well as nitro-substituted Hoveyda catalyst (**2**', Apeiron Catalysts) and catalyst **6** (Apeiron Catalysts) were commercially available. Teflon AF2400 tube was purchased from Biogeneral. Teflon impermeable tubes were purchased from Postnova. Column chromatography: Merck silica gel 60 (230–400 mesh).

#### **Analytical methods**

NMR spectroscopy: Spectra were recorded on a Bruker Avance 300 MHz spectrometer in CDCl<sub>3</sub>; chemical shifts ( $\delta$ ) are given in parts per million (ppm) downfield from trimethylsilane as referenced to residual protio solvent peaks; coupling constants (J) are given in Hz. GC: Trace GC Ultra, Thermo Electron Corporation, HP-5 column; inlet temperature 250°C; detector temperature 300°C. Method parameters for RCM of 7: initial temperature 170°C, initial time 1 min, ramp 12°Cmin<sup>-1</sup>, final temperature 240°C, final time 1 min. Retention times: substrate 6.161 min, product 8 6.750 min. Method parameters for RCM of 9: initial temperature 160°C, initial time 1 min, ramp 10  $^{\circ}\text{C\,min^{-1}}$ , final temperature 220  $^{\circ}\text{C}$ , final time 1 min. Retention times: substrate 3.471 min, product 10 3.065 min. Method parameters for RCM of 11: initial temperature 172 °C, initial time 0.1 min, ramp 6.5 °C min<sup>-1</sup>, final temperature 210 °C, final time 1.0 min. Retention times: substrate 5.801 min, product 13 [(E)isomer 5.728 min, (Z)-isomer 5.876 min], dodecane 1.840 min. Method parameters for RCM of 12: initial temperature 160°C, initial time 0.1 min, ramp 6°Cmin<sup>-1</sup>, final temperature 210°C, final time 1.0 min. Retention times: substrate 5.023 min, product 14 [(E)isomer 4.943 min, (Z)-isomer 5.105 min], dodecane 2.062 min. Method parameters for CM of 15 with 16: initial temperature 170°C, initial time 0.1 min, ramp 8°C min<sup>-1</sup>, second temperature 195 °C, second time 0.1 min, ramp 50 °C min<sup>-1</sup>, final temperature 295 °C, final time 4 min. Retention times: substrate 15 2.501 min, product 17 [(E)-isomer 4.370 min, (Z)-isomer 4.175 min], dimer of 15 6.400 min. Retention times were confirmed with samples authenticated by NMR analysis. Residual ruthenium was measured using ICP-MS.

#### Equipment for CF experiments with heterogeneous catalyst

Tube-in-tube reactor: length 40 cm; outer tube (fine Teflon) with inner diameter (ID) of 1.57 mm and outer diameter (OD) of 3.15 mm; inner tube (Teflon AF2400) with ID of 0.8 mm and OD of 1 mm. A solution of **7** was driven through the system with the use of a PN 1610 syringe dosing system (Postnova) with a flow rate of 40  $\mu$ Lmin<sup>-1</sup>. The tube-in-tube reactor in which the internal tube was connected to a vacuum pump is denoted as PFR-V. The same reactor in which the outlets of internal tube were closed is denoted as PFR.

<sup>© 2014</sup> Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

#### Equipment for CF experiments with homogeneous catalyst

Tube-in-tube reactor: length 2 m; outer tube (Teflon) with ID of 1.57 mm and OD of 3.15 mm; inner tube (Teflon AF2400) with ID of 0.8 mm and OD of 1 mm. No special mixer was used for mixing the substrate(s) and catalyst streams. Solutions of substrate(s) and catalyst were driven through the system with the use of an AP23 double syringe pump (Ascor). The tube-in-tube reactor in which the internal tube was connected with a vacuum pump is denoted as PFR-V. The same reactor in which the outlets of internal tube were closed is denoted as PFR.

#### Preparation of 6-SiO<sub>2</sub>

Complex **6** (6 mg, 7.46  $\mu$ mol) was dissolved in DCM (4 mL) and silica gel (234 mg) was added. The resultant suspension was stirred at room temperature for 2 min. Next, solvent was removed on a rotavapor, resulting in **6-SiO**<sub>2</sub> (240 mg) which was dried at high vacuum for 10 min prior to use.

#### RCM of 7 in BR

A solution of **7** in dry, degassed toluene (0.1 m, 38 mL, 3.80 mmol of **7**) was stabilized at 80 °C and **6-SiO**<sub>2</sub> (240 mg, 7.60  $\mu$ mol of **6**, 0.2 mol%) was added in one portion and reaction was stirred at 700 rpm. The reaction progress was monitored by means of gas chromatography with flame ionization detector (GC-FID) (100  $\mu$ L of reaction mixture was removed periodically, filtered through cotton, and diluted with 450  $\mu$ L of toluene).

#### Split test for RCM of 7 in BR

RCM of **7** promoted by **6-SiO**<sub>2</sub> was performed as described above. After 3 min of reaction, half of each reaction mixture was filtered through a piece of cotton (under argon) into a new flask that was filled with argon and placed in an oil bath heated to 80 °C. A sample from the filtered mixture was quenched with ethyl vinyl ether and analyzed by means of GC-FID in order to determine the conversion at the split time. After 30 min, conversion in filtered and non-filtered reaction mixtures was determined by means of GC-FID.

#### RCM of 7 in PFR

6-SiO<sub>2</sub> (240 mg, 7,60 µmol of 6) was loaded into a tube-in-tube reactor (in which both outlets of inner tube were closed; PFR) as a suspension in dry, degassed toluene, and an additional 4 mL of solvent was passed through the reactor. Next, the reactor was connected to a tube that delivered a solution of substrate (the tube was previously filled with a 0.1 M solution of 7) and placed in an oil bath heated to 80°C. A solution of 7 (70 mL) was placed in a round bottomed, two-necked flask from which it was transferred into the reactor with the use of a syringe dosing system with a flow rate of 40  $\mu L\,min^{-1}$  via the tube (ID 1.0 mm, OD 1.57 mm) placed in the oil bath heated to 80 °C. Periodically, samples of reaction mixture (40  $\mu$ L) were collected, diluted with toluene (200  $\mu$ L) and analyzed by means of GC-FID to determine the conversion. After 20 h, all samples collected for GC analysis were combined with the main fraction and overall conversion was determined by means of GC-FID.

#### RCM of 7 in PFR-V

**6-SiO**<sub>2</sub> (240 mg, 7.60  $\mu$ mol of **6**) was loaded into the tube-in-tube reactor (in which both outlets of the inner tube were connected to a vacuum pump; the vacuum pressure was in the range of 0.05–0.07 mbar; PFR-V) as a suspension in dry, degassed toluene, and an additional 4 mL of solvent was passed through the reactor. From this point, the procedure was identical to that for reaction in PFR. After 20 h, all samples collected for GC analysis and the sample from the split test were combined with the main fraction and overall conversion was determined by means of GC.

#### Split test for RCM of 7 in PFR-V

RCM of **7** was run as described above and after 160 min, a sample of reaction mixture (200  $\mu$ L) was collected in a 5 mL flask prefilled with argon; 40  $\mu$ L of this mixture was transferred to GC vial, quenched with ethyl vinyl ether (4  $\mu$ L), diluted with toluene (200  $\mu$ L), and analyzed by means of GC-FID to determine conversion. The rest of the sample was gently stirred at 80 °C for an additional 200 min. After that, the sample was prepared and analyzed by means of GC.

## Construction of time profile for homogeneous reactions in PFR and PFR-V

Reaction times were varied by controlling the flow rates through the system; each data-point in the rate curves thus corresponds to a separate experiment. Flow rates were in the range of 4– 48 mL h<sup>-1</sup>. For each, a 1 min interval was allowed for the new flow rate to stabilize, followed by purging for a period of double the reaction time, and then collection of the samples for analysis. Samples for GC were collected into vials containing ethyl vinyl ether to ensure immediate quenching of the reaction.

#### Representative procedure of homogeneous reaction in BR

A solution of **11** and dodecane (1 equiv) in dry, degassed toluene (0.01  $\mu$ , 18 mL, 1.8 mmol) was placed in dry flask and diluted with dry, degassed toluene (18 mL). Next, 150  $\mu$ L of this solution was removed and analyzed by GC-FID to establish the initial ratio of the substrate to dodecane at  $t_0$  (0% conversion). The remaining solution of substrate (0.005  $\mu$ ) was stabilized at 70 °C and stock solution of complex **3** in dry, degassed toluene (86  $\mu$ L, 0.5 mol%) was added. Reaction progress was monitored by GC-FID (200  $\mu$ L of reaction mixture was removed periodically, quenched with 4  $\mu$ L of ethyl vinyl ether, and analyzed at this concentration).

#### Representative procedure of homogeneous reaction in PFR

A syringe was filled with a solution of **11** and dodecane (0.01 M, 25 mL) and installed in a syringe pump. Stock solution of complex **3** (119  $\mu$ L, 0.5 mol %) was placed in a dry flask and diluted with dry, degassed toluene (24.9 mL). A syringe was filled with the resultant solution and installed in syringe pump. Solutions were pumped with the same speed (to generate the final substrate concentration of 0.005 M) into the PFR placed in oil bath heated to 70 °C. Solution of **11** was delivered through the tube placed in the same oil bath. Reaction progress was monitored by means of GC-FID (200  $\mu$ L of reaction mixture was collected, quenched with 4  $\mu$ L of ethyl vinyl ether, and analyzed at this concentration). The initial ratio of sub-

<sup>© 2014</sup> Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

strate to dodecane determined for the experiment in BR was used for calculations in this experiment.

# Representative procedure of homogeneous reaction in PFR-V

The reaction was performed and monitored as described for PFR except that, in PFR-V, the internal tube was connected to a vacuum pump (pressure was in the range of 0.05–0.07 mbar).

**Keywords:** continuous flow · ethylene removal · heterogeneous catalysis · homogeneous catalysis · metathesis

- [1] a) R. H. Grubbs, Handbook of Metathesis, Wiley-VCH, Weinheim, Germany, 2003; b) M. Michalak, Ł. Gułajski, K. Grela, Alkene Metathesis. In Science of Synthesis: Houben-Weyl Methods of Molecular Transformations, Vol. 47a (Alkenes), Thieme, Stuttgart, 2010, pp. 327–438.
- [2] M. Bieniek, A. Michrowska, D. L. Usanov, K. Grela, Chem. Eur. J. 2008, 14, 806–818.
- [3] For application of renewables, see: a) A. Nickel, T. Ung, G. Mkrtumyan, J. Uy, Ch. W. Lee, D. Stoianova, J. Papazian, W.-H. Wei, A. Mallari, Y. Schrodi, R. L. Pederson, Top. Catal. 2012, 55, 518-523; b) E. Borré, T. H. Dinh, F. Caijo, Ch. Crevisy, M. Mauduit, Synthesis 2011, 13, 2125-2130; c) X. Miao, C. Fischmeister, C. Bruneau, P. H. Dixneuf, J.-L. Dubois, J.-L. Couturier, ChemSusChem 2012, 5, 1410-1414; d) X. Miao, R. Malacea, C. Fischmeister, C. Bruneau, P. H. Dixneuf, Green Chem. 2011, 13, 2911-2919; e) X. Miao, A. Blokhin, A. Pasynskii, S. Nefedov, S. N. Osipov, T. Roisnel, C. Bruneau, P. H. Dixneuf, Organometallics 2010, 29, 5257-5262; for development of catalysts efficient at low loading, see: f) K. M. Kuhn, T. M. Champagne, S. H. Hong, W.-H. Wei, A. Nickel, C. W. Lee, S. C. Virgil, R. H. Grubbs, R. L. Pederson, Org. Lett. 2010, 12, 984-987; g) V. Sashuk, L. H. Peeck, H. Plenio, Chem. Eur. J. 2010, 16, 3983-3993; h) X. Bantreil, R. A. M. Randall, A. M. Z. Slawin, S. P. Nolan, Organometallics 2010, 29, 3007-3011; i) O. Songis, A. M. Z. Slawin, C. S. J. Cazin, Chem. Commun. 2012, 48, 1266-1268; j) L. H. Peeck, R. D. Savka, H. Plenio, Chem. Eur. J. 2012, 18, 12845-12853; k) R. Kadyrov, Chem. Eur. J. 2013, 19, 1002-1012.
- [4] For a review discussing the advantages of CF processes, see: a) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* 2007, 107, 2300–2318; b) D. M. Roberge, L. Ducry, N. Bieler, P. Cretton, B. Zimmermann, *Chem. Eng. Technol.* 2005, 28, 318–323.
- [5] a) M. Mayr, B. Mayr, M. R. Buchmeiser, Angew. Chem. 2001, 113, 3957–3960; Angew. Chem. Int. Ed. 2001, 40, 3839–3842; b) J. O. Krause, S. H. Lubbad, O. Nuyken, M. R. Buchmeiser, Macromol. Rapid Commun. 2003, 24, 875–878; for similar work see: c) L. Yang, M. Mayr, K. Wurst, M. R. Buchmeiser, Chem. Eur. J. 2004, 10, 5761–5770.
- [6] a) A. Michrowska, K. Mennecke, U. Kunz, A. Kirsching, K. Grela, J. Am. Chem. Soc. 2006, 128, 13261-13267; b) E. Borré, M. Rouen, I. Laurent, M. Magrez, F. Caijo, Ch. Crvisy, W. Solodenko, L. Toupet, R. Frankfurter, C. Vogt, A. Kirschning, M. Mauduit, Chem. Eur. J. 2012, 18, 16369-16382; c) D. Schoeps, K. Buhr, M. Dijkstra, K. Ebert, H. Plenio, Chem. Eur. J. 2009, 15, 2960-2965; d) A. Kajetanowicz, J. Czaban, G. R. Krishnan, M. Malińska, K. Woźniak, H. Siddique, L. G. Peeva, A. G. Livingston, K. Grela, ChemSusChem 2013, 6, 182-192; e) Ying et al. used degasser to removed ethylene from circulating flow reactor, see: J. Lim, S. S. Lee, J. Y. Ying, Chem. Commun. 2010, 46, 806-808; f) Fogg et al. used continuous stirred tank reactor (CSTR), that allow for ethylene removal by means of flushing with inert gas, see: S. Monfette, M. Eyholzer, D. M. Roberge, D. E. Fogg, Chem. Eur. J. 2010, 16, 11720-11725; g) B. Autenrieth, W. Frey, M. R. Buchmeiser, Chem. Eur. J. 2012, 18, 14069-14078; h) for example where 1b was more efficient in CF reactor (without re-

moval of ethylene) than in batch, see: E. Comer, M. G. Organ, J. Am. Chem. Soc. 2005, 127, 8160-8167.

- [7] a) S. H. Hong, M. W. Day, R. H. Grubbs, J. Am. Chem. Soc. 2004, 126, 7414–7415; b) S. H. Hong, A. G. Wenzel, M. W. Day, R. H. Grubbs, J. Am. Chem. Soc. 2007, 129, 7961–7968.
- [8] Z. Lysenko, B. R. Maughon, T. Mokhtar-Zadeh, M. L. Tulchinsky, J. Organomet. Chem. 2006, 691, 5197–5203.
- [9] It should be noted that batchwise processes are also negatively influenced by the presence of ethylene, especially at large scale and when molecules prone to cross metathesis with ethylene (ethenolysis) are present in reaction mixture. For more information, see: a) T. Nicola, M. Brenner, K. Donsbach, P. Kreye, Org. Process Res. Dev. 2005, 9, 513–515; b) N. K. Yee, V. Farina, I. N. Houpis, N. Haddad, R. P. Frutos, F. Gallou, X. Wang, X. Wei, R. D. Simpson, X. Feng, V. Fuchs, Y. Xu, J. Tan, L. Zhang, J. Xu, L. L. Smith-Keenan, J. Vitous, M. D. Ridges, E. M. Spinelli, M. Johnson, J. Org. Chem. 2006, 71, 7133–7145; c) P. Winter, W. Hiller, M. Christmann, Angew. Chem. 2012, 124, 3452–3456; Angew. Chem. Int. Ed. 2012, 51, 3396–3400.
- [10] a) B. van Berlo, K. Houthoofd, B. F. Sels, P. A. Jacobs, Adv. Synth. Catal. 2008, 350, 1949–1953; b) J. Cabrera, R. Padilla, M. Bru, R. Lindner, T. Kageyama, K. Wilckens, S. L. Balof, H.-J. Schanz, R. Dehn, J. H. Teles, W. Deuerlein, K. Müller, F. Rominger, M. Limbach, Chem. Eur. J. 2012, 18, 14717–14724; c) R. Duque, E. Öchsner, H. Clavier, F. Caijo, S. P. Nolan, M. Mauduit, D. J. Cole-Hamilton, Green Chem. 2011, 13, 1187–1195.
- [11] Tube-in-tube reactors were recently successfully used in heterogeneous gas-liquid non-metathetical transformations: a) P. B. Cranwell, M. O'Brien, D. L. Browne, P. Koos, A. Polyzos, M. Peña-López, S. V. Ley, Org. Biomol. Chem. 2012, 10, 5774–5779; b) T. P. Petersen, A. Polyzos, M. O'Brien, T. Ulven, I. R. Baxendale, S. V. Ley, ChemSusChem 2012, 5, 274–277; c) A. Polyzos, M. O'Brien, T. P. Petersen, I. R. Baxendale, S. V. Ley, Angew. Chem. 2011, 123, 1222–1225; Angew. Chem. Int. Ed. 2011, 50, 1190–1193; 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, 2648–2651; e) M. A. Mercadante, N. E. Leadbeater, Org. Biomol. Chem. 2011, 9, 6575–6578; f) S. L. Bourne, P. Koos, M. O'Brien, B. Martin, B. Schenkel, I. R. Baxendale, S. V. Ley, Synlett 2011, 18, 2643–2647; g) M. O'Brien, I. R. Baxendale, S. V. Ley, Org. Lett. 2010, 12, 1596–1598.
- [12] a) I. Pinnau, L. G. Toy, *J. Membr. Sci.* **1996**, *109*, 125–133; b) A. Y. Alentiev, V. P. Shantarovich, T. C. Merkel, V. I. Bondar, B. D. Freeman, Y. P. Yampolskii, *Macromolecules* **2002**, *35*, 9513–9522; c) T. C. Merkel, V. Bondar, K. Nagai, B. D. Freeman, Y. P. Yampolskii, *Macromolecules* **1999**, *32*, 8427– 8440.
- [13] K. Skowerski, G. Szczepaniak, C. Wierzbicka, Ł. Gułajski, M. Bieniek, K. Grela, Catal. Sci. Technol. 2012, 2, 2424–2427.
- [14] For homogeneous reactions in CF mode, reaction time was determined by the coil volume divided by the flow rate.
- [15] So far, the highest efficiency of homogeneous Ru-based metathesis catalyst in reaction in flow mode was reported by Buchmeiser et al., who observed a TON of 900 in RCM of *N*,*N*-diallyl trifluoroacetamide, see: ref. 6 g.
- [16] a) R. Hamasaki, S. Funakoshi, T. Misaki, Y. Tanabe, *Tetrahedron* 2000, *56*, 7423–7425; b) A. Fürstner, K. Langemann, *J. Org. Chem.* 1996, *61*, 3942–3943; c) ref. 6 f.
- [17] Reaction time 20 min; TOF calculated after 20 min.
- [18] J.-L. Couturier, J.-L. Dubois, X. Miao, C. Fischmeister, C. Bruneau, P. H. Dixneuf, Brevet: FR 2959742A120111111; PCT Int. Appl., WO 2011138051A1 20111110, **2011**.
- [19] It is known that phosphine free catalysts are more appropriate for CM with electron deficient partners; see: ref. 3 d.

Received: August 7, 2013 Published online on October 24, 2013